STUDIES TOWARDS THE TOTAL SYNTHESIS OF IMIDAZOLE-CONTAINING NATURAL PRODUCTS

by

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Abstract

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The University of Texas at Arlington, 2018

Supervising Professor: Carl J. Lovely

Nature has inspired man in all aspects of life, chemistry included. The first antibiotic ever discovered came from nature, and since then, chemists have been probing nature for insights to guide drug discovery and development. Alkaloids are a class of naturally occurring molecules which contain nitrogen atoms and can be found in all forms of life. Imidazole is common structural unit found in many natural molecules, from the simple amino acid histamine to more complex structures like the marine sponge derived alkaloid palau'amine. Many imidazole-containing natural products are biologically active, such as inhibiting the growth of tumors, possessing

antibacterial properties, and influencing signaling pathways of cells like an inflammatory response. Access to large quantities of these molecules would aid medical science in drug discovery and design, potentially impacting the overall quality of life for all. It is therefore essential for the chemical community to pursue the synthesis of natural products not only to gain more knowledge in the overall science, allowing for better isolation, characterization, and synthesis of molecules, but also to better the quality of life and health as a whole.

Chapter 1 of this dissertation describes the isolation and characterization of spiroleucettadine and terrazoanthines A-C. It further describes, in detail, the unsuccessful attempts to synthesis spiroleucettadine, which prompted its structural revision, and the only reported synthesis of the revised structure.

Chapter 2 focuses on our approach to the total synthesis of spiroleucettadine. Initially our strategy centered on employing a novel reaction discovered in our lab to help facilitate the construction of the spirocyclic center. However, we later found this route to not be viable, leading to a significant revision in our strategy.

In chapter 3 describe our approach to total synthesis of terrazoanthines A-C. Besides its purification and structural assignment, there are no reports pertaining to this molecule in the literature. Of the 3 molecules, only one of them possesses multiple stereochemical centers.

However, upon further examination of the core structure we proposed a concise synthetic route leading to not only all 3 molecule, all possible stereoisomers through the construction of a key symmetric intermediate.

In chapter 4 we discuss the oxidative chemistry of tetrahydrobenzimidazole. The two oxidants used were dimethyldioxarine and oxaziridine. The results show the choice of oxidant, *N*-protecting group, and the functionalization at the C2-position can greatly affect the outcome of the reactionss, leading to additions, cyclizations, and ring openings.

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Chapter 1

INTRODUCTION TO THE HISTORY OF SPIROLEUCETTADINE

1.1 Imidazole-Containing Natural Products (Spiroleucettadine)

Imidazole-containing molecules make up a significant percentage of natural products, being isolated from marine life, land floras, and animals such as scorpions.[1-6] Many of these compounds are biologically active and therefore are of interest to the medicinal community, having antibiotic, antitumor, and anti-inflammatory properties which can be explored as possible treatments for disease.[7-11] Also, some of these compounds contain intriguing structural motifs, making them excellent, as well as challenging, synthetic targets. Often new techniques or reactions are discovered in efforts to complete the total synthesis of complex molecules, adding to the *richness* of the science.

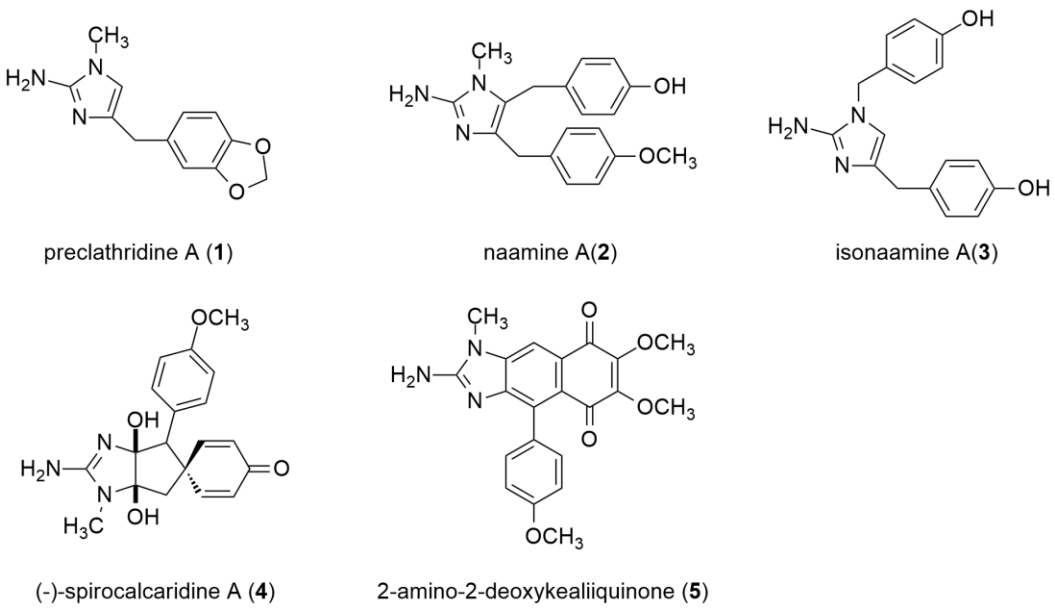


Figure 1.1 Common structural motifs from Leucetta sponge.

The *Leucetta* genus of marine sponges has yielded many compounds, of which most may be placed into five classes based on general core structures.[12-14] These classes are characterized by the lead compound in each of the groups: preclathridine A (**1**), naamine A (**2**), isonaamine A (**3**), (-)spirocalcaridine A (**4**), and 2-amino-2-deoxykealiiquinone (**5**).[14]

All of these cores incorporate an imidazole motif. Devising a sound synthetic route utilizing imidazole, then systematically functionalizing its core to achieve the desired molecule makes these compounds excellent targets for synthesis. A molecule of high interest to our lab from this family is (-)-spiroleucettadine (**6**). Over the past decade (-)-spiroleucettadine has been investigated by several groups and has initiated much debate over its original structural assignment.[15-17] The compound was isolated and characterized originally in 2004 by Phillip Crews.[18] The Crews lab utilized methanol

extraction of animal material, then solvent partitioning, followed by reverse-phase HPLC for isolation and purification. The structure of the molecule was probed using a combination of HR-ESI-MS, ^{1}H and ^{13}C NMR spectroscopy, along with 2D NMR techniques including HMBC and ROESY. When these data were brought together and analyzed, Crews and coworkers finalized the proposed structure **6**.

First assignment (-)-spiroleucettadine (**6**) Revised assignment (-)-spiroleucettadine (**7**)

Figure 1.2 Proposed and revised structures of spiroleucettadine.

One of the most intriguing features of the structure proposed by Crews is a *trans*-fused [3.3.0] bicyclic core, which is relatively rare in nature.[19-21] This unique structure motivated synthetic chemists to attempt the total synthesis of spiroleucettadine. In 2005, Danishefsky and coworkers from Columbia University made one of the first synthetic attempts toward spiroleucettadine.[15] The group employed three different synthetic strategies but to no avail(for details see schemes 1.3, 1.4, and1.5). It was noted that two of the attempts' final product was the ring opened isomer of spiroleucettadine, with the opening occurring at what would be the bicyclic bridge. It was this failure to construct the *trans*-bicyclic bridge that prompted Danishefsky to suggest there was too much intrinsic stain in the system, and perhaps the initial structure was assigned incorrectly. Other teams in the synthetic community made attempts towards the synthesis of

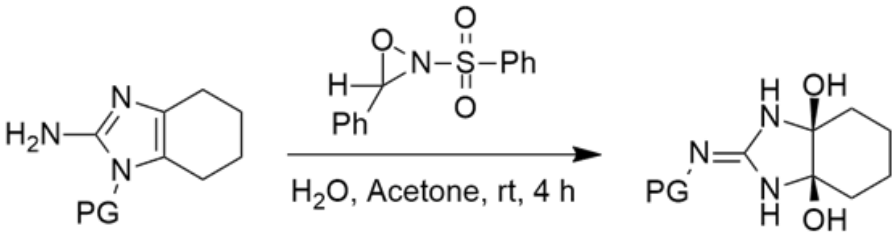
spiroleucettadine, such as the Ciufolini group, but all efforts proved futile.[16] Some researchers chose to interrogate the molecule using computer calculations and spectroscopic methods. The Watson group from Australia also attempted a total synthesis of **6**. However, their most significant contributions came from using density functional theory calculations to predict ^{13}C NMR chemical shifts, along with reevaluating some of the original NMR data, in an attempt to elucidate other possible structural assignments.[17] When they compared their findings to Crews', Watson found discrepancies in the proposed structural assignment.

In 2008, prompted by the speculation in the synthetic community based on their previous efforts, Crews decided to reevaluate his proposed structure of spiroleucettadine. The group reanalyzed the NMR data and were also able to grow a crystal suitable for synchrotron crystallographic analysis. In this reexamination, Crews found that indeed the originally proposed structure was incorrect. With all the new data collected, Crews revised the structure to **7**, to which there have been no objections thus far. Crews partially attributed the mistake to the H/C ratio being less than one for the core structure, increasing the difficulty of analyzing NMR spectra.[22]

Until recently, the literature was absent of any reports pertaining to the total synthesis of spiroleucettadine.[23] Having this compound in hand would yield additional data to confirm the structure. While a crystal structure has been obtained, this method is not without flaws. Calculated parameters, such as R, standard deviation, wrong atom assignments due to similar electron densities, and bond lengths, can be miscalculated due to the convention of the process.[24] In 2006 a group had to retract five structures due to an

error that arose from calculations.[25] Since significant speculation has surrounded this compound, total synthesis can advocate for or against the revised structure.

Second, in 2007 our lab discovered a novel oxidative addition reaction involving imidazole derivatives.[26] This reaction was found inadvertently in the course of efforts to synthesize a different molecule. The discovery showed when electron poor imidazole derivatives were subjected to reaction conditions with *N*-sulfonyloxaziridines, oxidative addition occurs across the C-4 and C-5 carbons (Scheme 1.1). Potentially this unique reaction could be utilized as a key step in the synthesis of spiroleucettadine; offering an excellent opportunity to showcase novel chemistry previously developed by our lab.

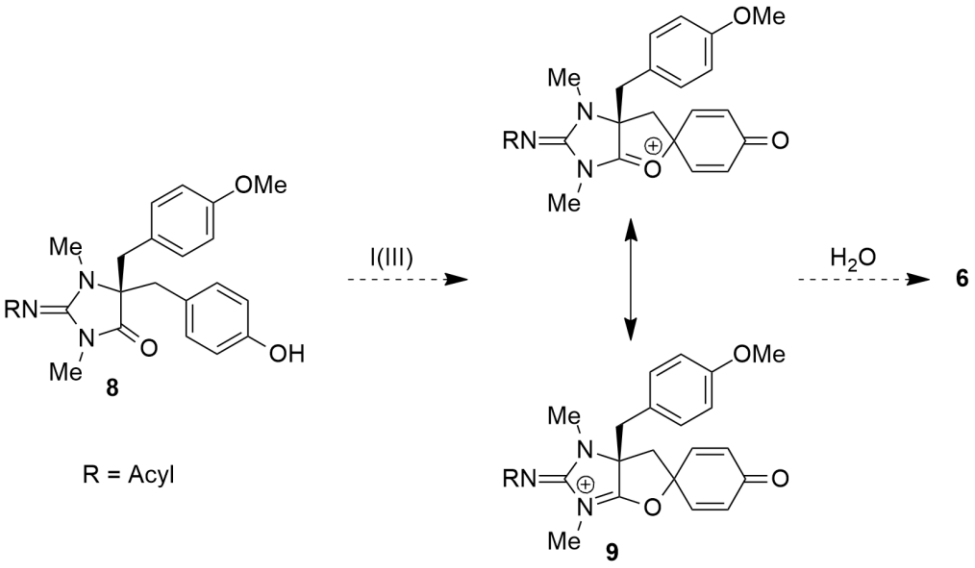


Scheme 1.1 Oxidative addition

Finally, spiroleucettadine did show promising biological activity. In an inhibition study performed against *Enterococcus durans*, spiroleucettadine had a minimum inhibitory concentration (MIC) of 6.25 µg/mL. As a positive control, penicillin displayed a MIC of 12.5 µg/mL.[18] Further studies on the antibacterial, anticancer, and potentially other biological properties of the compound could be carried out if greater quantities were made available from synthesis.

1.2 Danishefsky's Synthetic Attempt

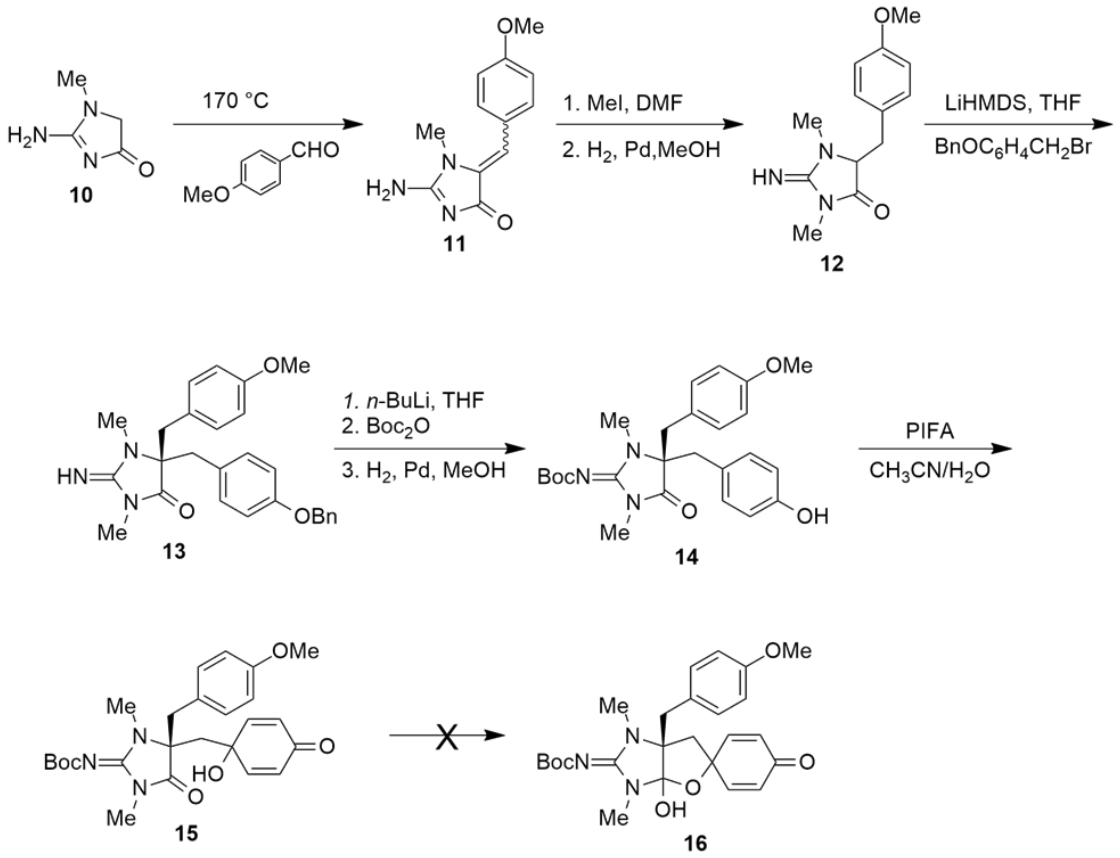
One of the first extensive synthetic attempts reported for the initial assignment of spiroleucettadine, compound **6**, was by Danishefsky and co-workers in 2005.[15] They envisioned being able to synthesize spirocyclic compound **9** by utilizing hypervalent iodine oxidation of phenol **8** followed by an intramolecular nucleophilic attack of the resulting alcohol on neighboring amide (Scheme 1.2). A selective hydration of **9** would then yield the desired molecule **6**.



Scheme 1.2 Hypervalent iodine oxidation of key phenol.

Danishefsky began the synthesis with creatinine (**10**), which was subjected to Knoevenagel condensation conditions to form alkene **11** (Scheme 1.3). N-Methylation and hydrogenation provided **15**. Next, LiHMDS-mediated alkylation, followed by Boc protection of the nitrogen, then palladium catalyzed reduction to remove the benzyl

group yield the key intermediate, phenol **14**. However, when the phenol was subjected to hypervalent iodine oxidation conditions, it did not afford the desired spirocycle **16**. Instead, the ring-opened isomer **15** was isolated with a 56% yield. Additional attempts to cyclize alcohol **15** to **16** failed, with no evidence of spirocyclization detected.



Scheme 1.3 Danishefsky and co-worker's first synthetic

In a second attempt, Danishefsky and co-workers envisioned completing the synthesis with a ring closing reaction of lactone **17** (Figure 1.3). This endeavor commenced with ester **19** (Scheme 1.4). After two alkylations, Boc protection of the amine, and removal of the benzyl group by reduction, they had compound **21** in hand and were ready to attempt hypervalent iodine oxidation to provide spirocycle **16**.

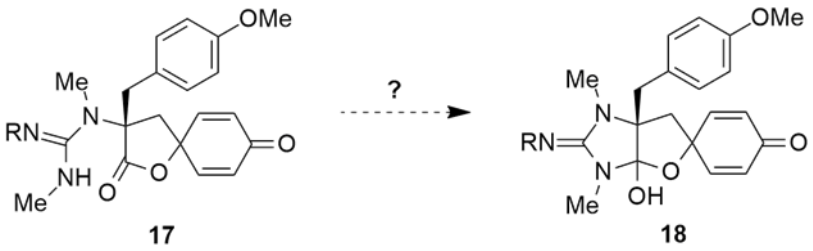
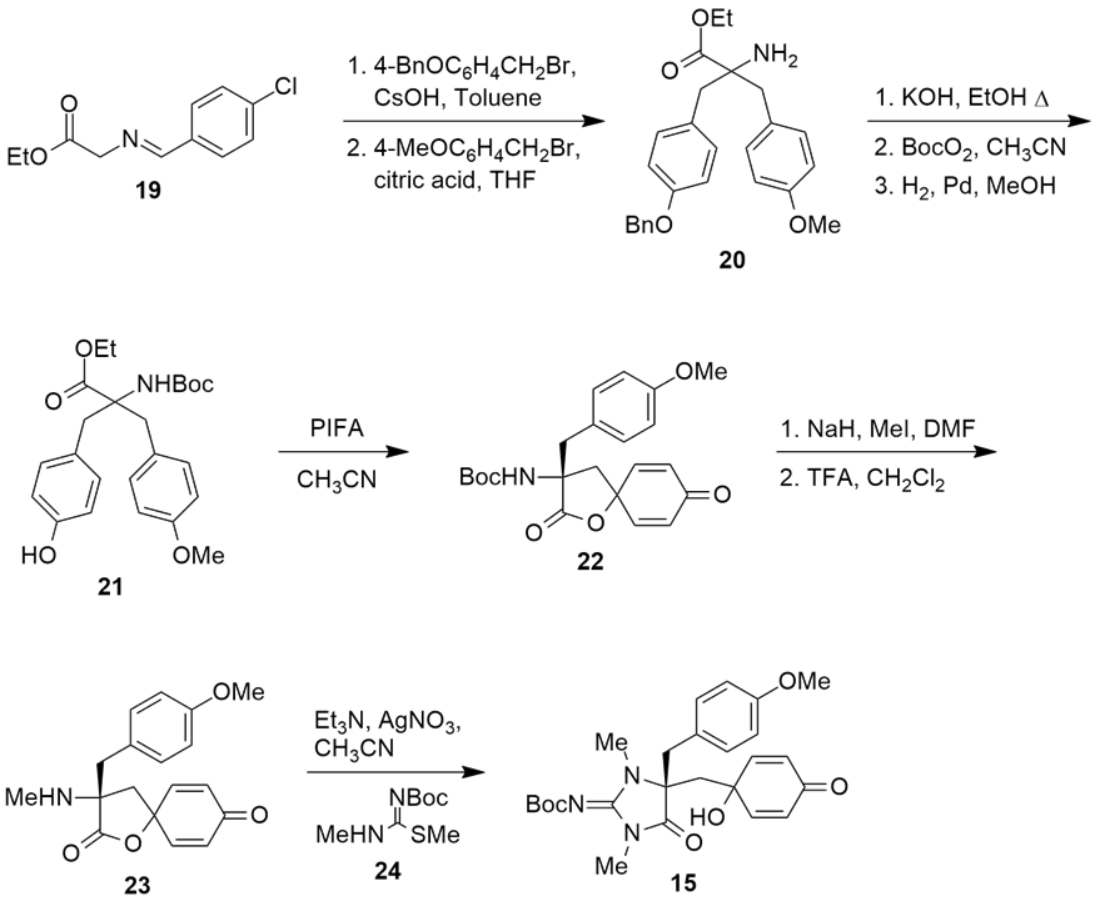


Figure 1.3 Key intermediate of second route.

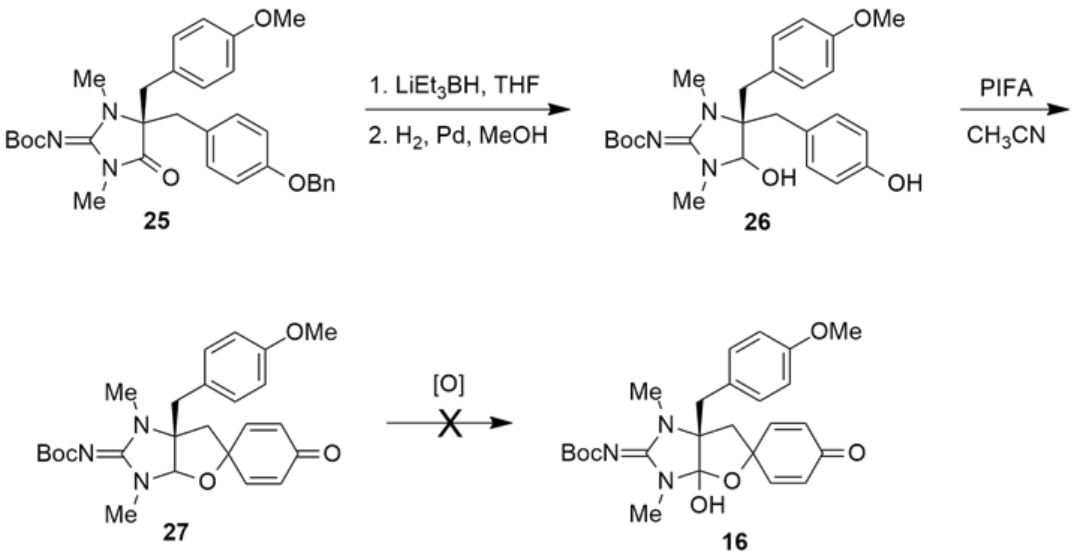
In this effort, spirocyclization was indeed successful in allowing the group to focus on guanidine cyclization. After several failed attempts at guanylation, positive results were achieved under conditions using isothiourea **24**. While these conditions provided the guanidine cyclization, it occurred due to acyl transfer from the spirocycle, deconstructing that portion of the molecule to provide compound **15** again.



Scheme 1.4 Danishefsky and co-worker's second synthetic route.

The group made one final attempt to complete the synthesis. Hypothesizing the cause of **8** not undergoing the desired spirocyclization resolve this issue. Performing a Boc protection on amine **13** furnished compound **25**, followed by reduction of the carbonyl of **25** using $LiEt_3BH_3$ and removal of the benzyl ether yielded phenol **26** (Scheme 1.5). Upon exposing **26** to PIFA oxidation conditions, spirocyclic compound **27** was afforded in 75% yield. However, all attempts to oxidize **27** to give **16** were unsuccessful. It was this fact which prompted Danishefsky to suggest spirocycle **27** showed the *cis* configuration to be stable and permissible, but the *trans* arrangement was likely to be

prohibitively strained and “invited caution” as to the validity of Crew’s structural assignment of spiroleucettidine.



Scheme 1.5 Danishefsky and co-worker’s final synthetic route.

1.3 Ciufolini’s Synthetic Attempt

During Ciufolini’s investigation, many of the same observations were made as in Danishefsky’s studies. However, while Danishefsky did consider stereocontrol in his strategy for total synthesis of proposed structure **6**, Ciufolini admitted to focusing on answering structural questions in his approach, such as stability, and ignoring absolute configuration. To accomplish this goal, the group proposed possible precursors to **6**, constructed key compounds in route to **6** and the speculated precursors, and used NMR spectroscopy to make comparisons to these structures and the data for **6** reported by Crews.

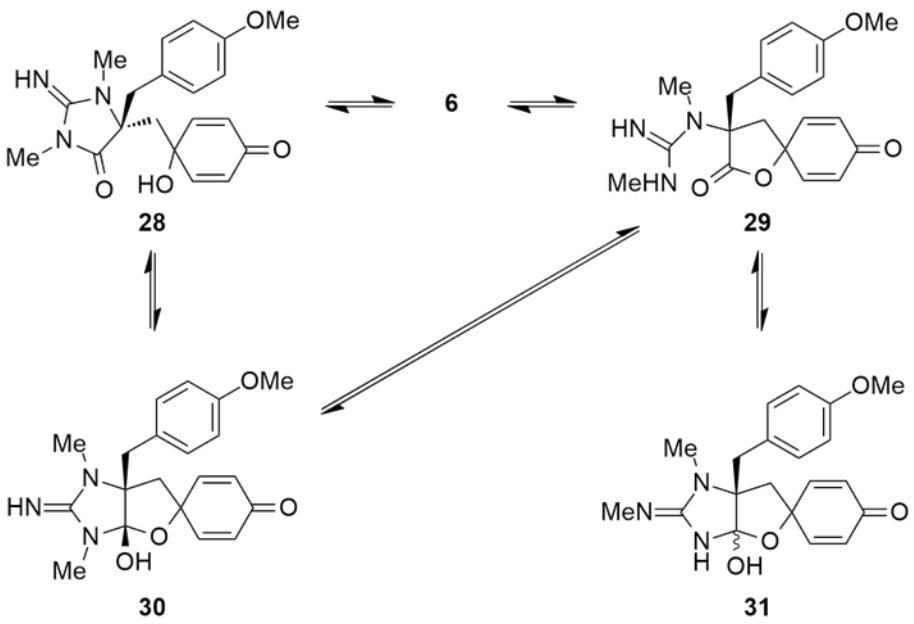
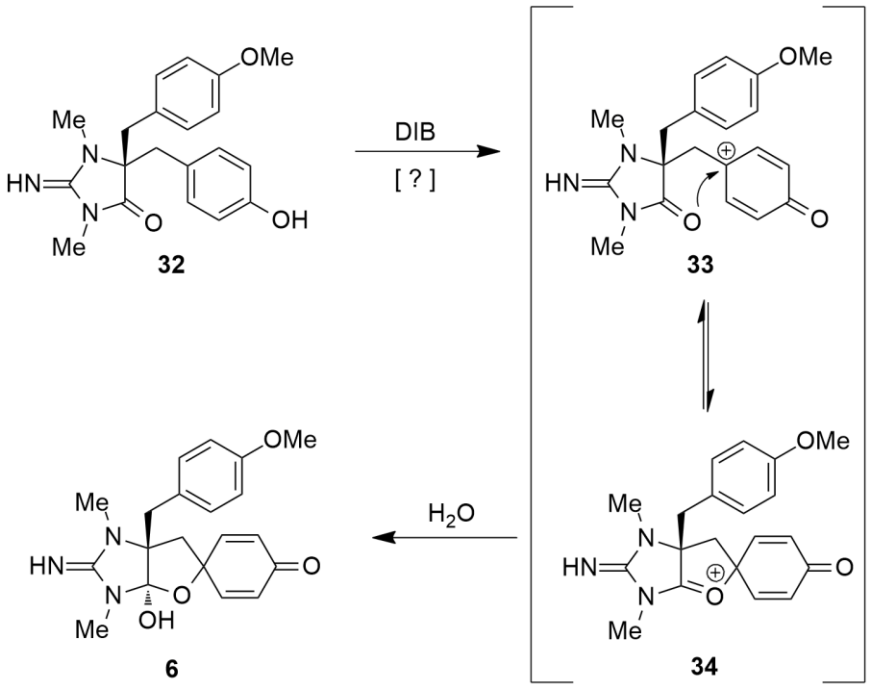


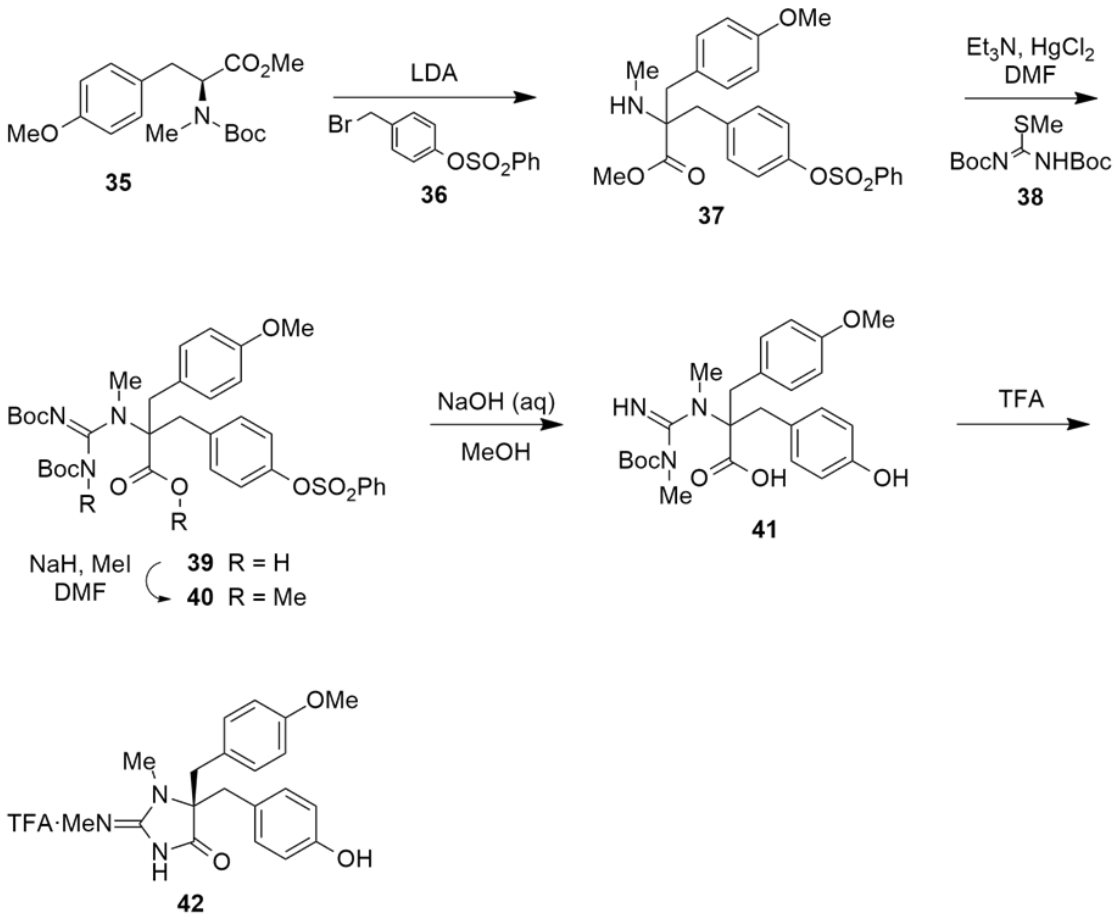
Figure 1.4 Possible isomerization pathways for 6.

Ciufolini and co-workers began their investigation by calculating the energy difference of the [3.3.0] *trans*-fused system to that the *cis* analog. Utilizing computer modeling, they concluded the *trans*-bicyclic core was no less than 14 kcal/mol higher in energy due to strain than *cis* isomer. Next, they proposed five logical isomers which could exist in equilibrium with **6**, two of which directly with spiroleucettadine, compounds **28** and **29**, and the remaining three in equilibrium with the latter two (Figure 1.4). The group further proposed the orthoamide type functionality should “promote facile equilibration” between spiroleucettadine and compounds **28** or **29**, from cleavage of the C-O or C-N bond, respectively. Furthermore, they speculated once the rings were opened, thermodynamics would dictate recyclization should give the lower energy *cis*-bicyclic isomers. It was noted, however, the spectral data showed only one compound in solution, signifying the existence of only one molecule, presumably **6**.



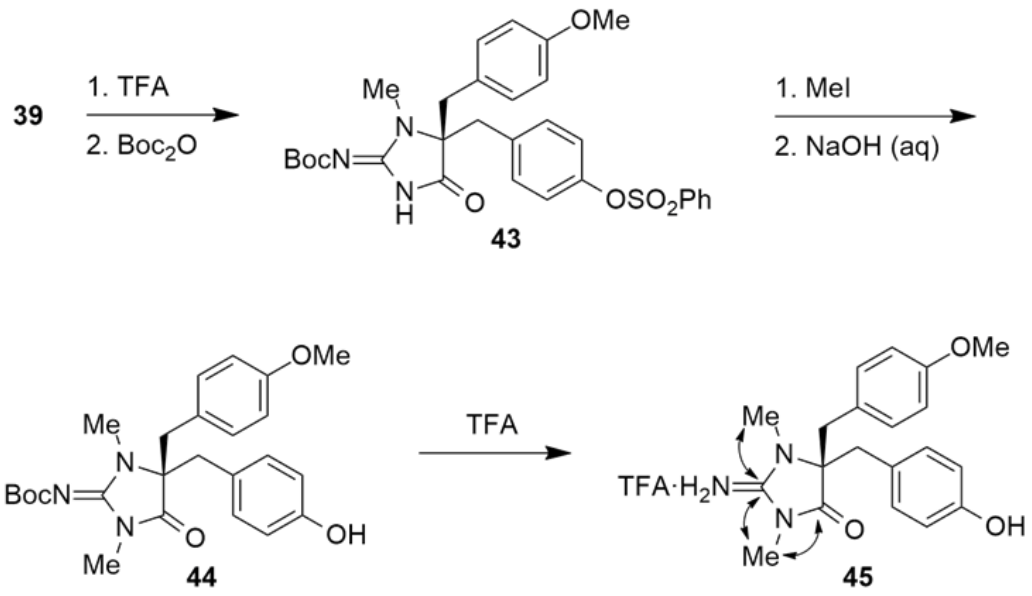
Scheme 1.6 Ciufolini's strategy for spirocyclization.

Similar to Danishefsky's approach, Ciufolini's strategy envisioned a hypervalent iodine oxidation of **32**, followed by hydration of **34** to complete the synthesis (Scheme 1.6). Their effort initiated with the construction of a precursor to compound **31**. Utilizing α-deprotonation of L-tyrosine derived **35** with LDA to generate the corresponding enolate, followed by addition of benzyl bromide **36**, gave rise to an intermediate ester, which was Boc deprotected to furnish 2° amine **37** (Scheme 1.7). Next, **37** was reacted with isothiourea **38** providing acid **39**. It was noted saponification of the ester was likely due to traces of water, but was inconsequential, as **39** was treated with excess NaH and MeI reforming the ester and installing the required N-methyl substituent furnishing compound **40**.



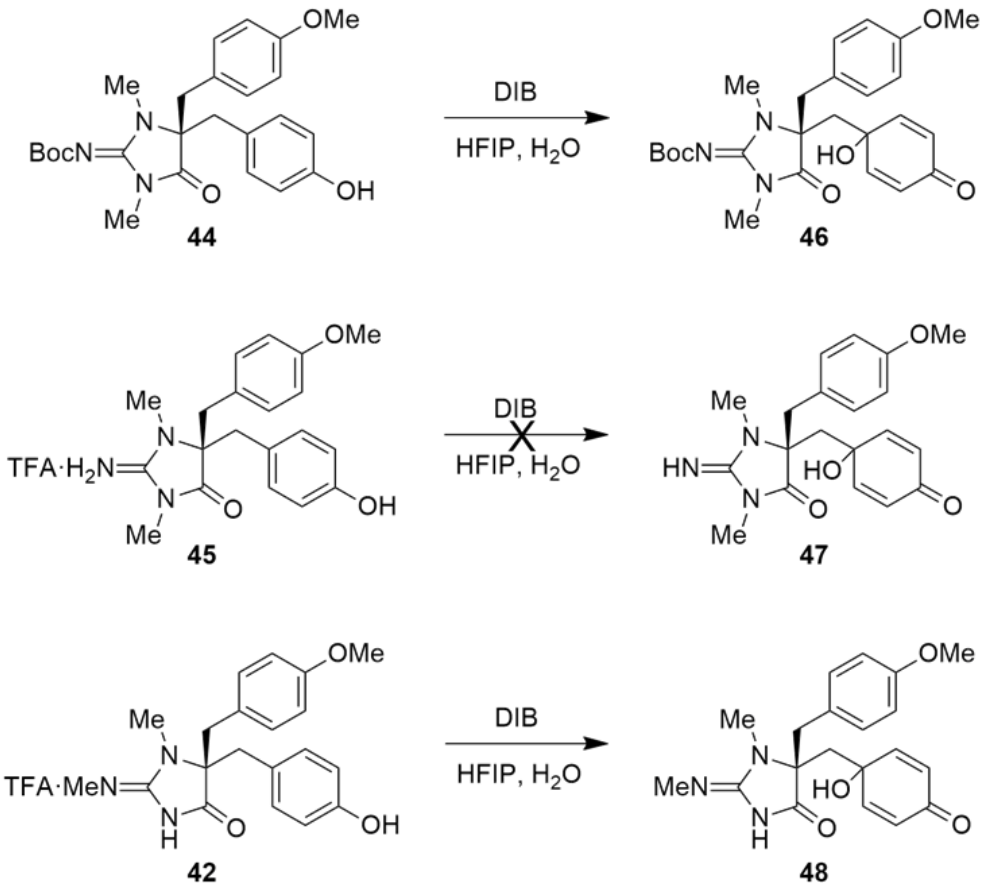
Scheme 1.7 Synthesis of precursor for compound 31.

Exposing **40** to aqueous NaOH again saponified the ester to the acid, as well as selectively deprotecting the sp^2 nitrogen, and cleaving the sulfonyl group resulting in the formation of phenol **41**. Subjecting this phenol to neat TFA induced the loss of the remaining Boc group and initiated cyclization to the dimethyl creatinine moiety, making heterocyclic salt **42**. The assignment of this structure was based on the presence of strong correlations from the H atoms on the N-methyl substituents with the guanidine carbon, and the absence of a correlation with the carbonyl carbon.



Scheme 1.8 Synthesis of precursor for compound 32.

Next, the team focused on the preparation of the “correct” isomer of the dimethyl creatinine (Scheme 1.8). Complete Boc deprotection and cyclization of previously synthesized compound **39** were carried out in one pot via treatment with TFA, which was followed by selective reprotection of the sp^2 nitrogen with Boc_2O providing heterocycle **43**. This intermediate was *N*-methylated with MeI and the sulfonyl group cleaved with aqueous NaOH to furnish phenol **44**. Finally, **44** was treated with neat TFA providing the amine salt **45**. Again, structural assignments rest on HMBC correlations, indicated by the double-headed curved arrows (Scheme 1.8).



Scheme 1.9 Results of hypervalent iodine oxidation.

With **45** in hand, Ciufolini and co-workers proceeded with hypervalent iodine oxidation conditions using DIB in HFIP (Scheme 1.9). As with Danishefsky, oxidation furnished an intractable mixture of products. Identical observations were made when **44** and **42** were subjected to the same conditions. However, when **44** was subjected to DIB oxidation in aqueous HFIP **46** was isolated in 8% yield. When subjected to analysis by NMR spectroscopy the illustrated tautomer existed exclusively in solution. Analysis of the ^{13}C spectrum of **46** revealed a resonance at 174.4 ppm, which corresponds to the carbonyl group of the creatinine segment. This signal was also observed in the ^{13}C spectrum of the precursor **44** at 175.7 ppm, suggesting the carbonyl was still intact after oxidation

and spirocyclization was not successful. As well, a new signal at 187.3 ppm was detected in **46**, which is attributable to the dienone carbonyl carbon. This implies oxidation of the phenol ring was successful. Finally, in the ^{13}C spectrum of spiroleucettadine, a signal appears at 102 ppm for the orthoamide carbon. In the spectrum for **46** this single was absent. In fact, the spectrum was void of any signals between 113.9 and 79.9 ppm, reaffirming the absence of an orthoamide carbon.

Encouraged by the successful oxidation of **44** utilizing aqueous HFPI, Ciufolini subjected **45** to analogous reaction conditions in hopes of the formation of **6** or its open tautomeric form. Again, this resulted in an inseparable mixture of products. It was noted the mixture was subjected to ESI mass spectrometry. While there was a signal detected for the *m/z* = 370, corresponding to the mass of $[M+H]^+$, all attempts to isolate the perceived product failed.

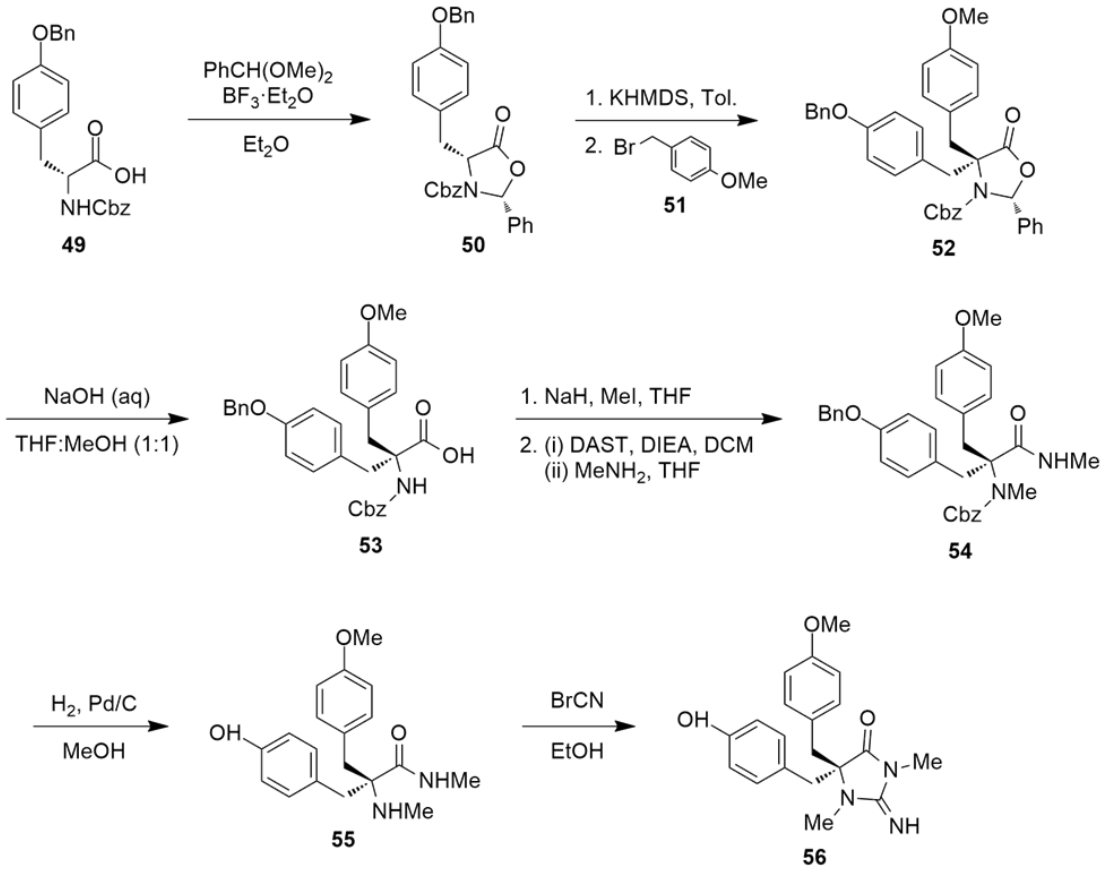
In a final attempt to construct **31**, the amine salt **42** was subjected to DIB oxidation in aqueous HFIP. In contrary to the previous two compounds, the oxidation of **31** occurred with a high yield of 95%. But similarly to the oxidation of **44**, the resulting product, **48**, was not the desired spirocyclic molecule, but again the intact creatinine hydroxydienone motif as confirmed by ^{13}C spectroscopy.

In Ciufolini's final notes, he speculated the apparent instability of the assumed hydroxydienone produced from the oxidation of **45** brings into question the viability of intermediates related to the proposed precursor **28**. In fact, Ciufolini cites his previous efforts towards synthesis of cylindricines, stating **28** is analogous to the *N*-unprotected dienones intermediates encountered during those efforts, which were predisposed to polymerization. This likely accounts for the inability to isolate products from the

oxidation of **45**.[27] Cuifolini concludes the current investigation shows the orthoamide is intrinsically unstable, concurring with Danishefsky that the current structural assignment is likely incorrect.

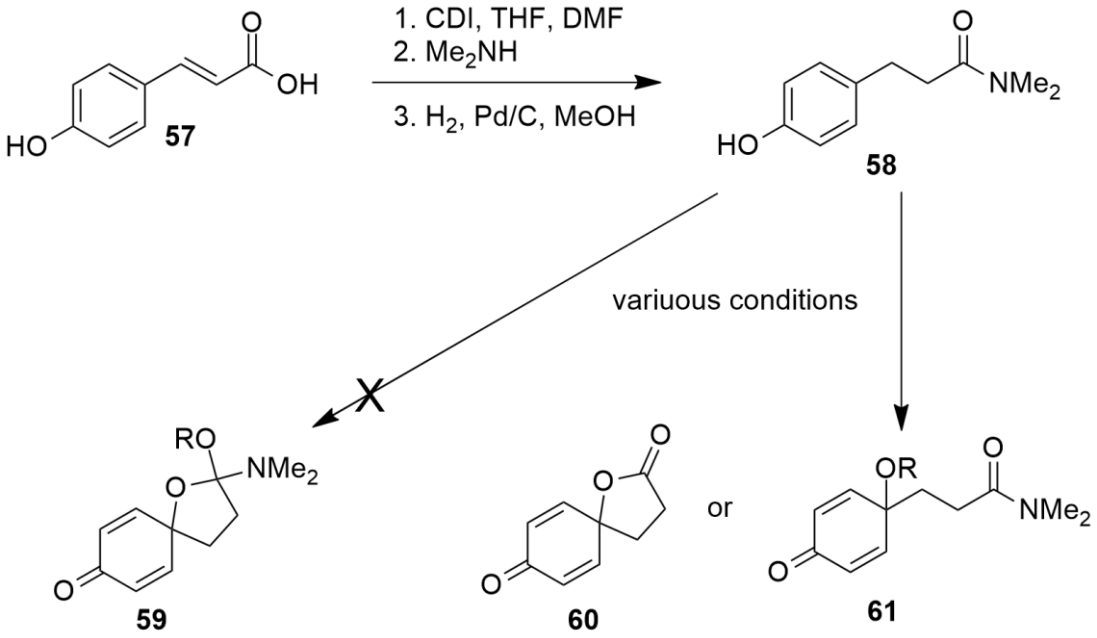
1.4 Watson's Synthetic Attempt

When Watson and co-workers began their investigation of spiroleucettadine, total synthesis was the initial goal. However, the more significant contributions made by the group came from the results of a model study focusing on the feasibility of the oxidative spirocyclization reaction, and computational studies utilizing DFT to predict NMR chemical shifts, comparing them to the experimental data collected by Crews.



Scheme 1.10 Synthesis of chiral precursor.

Watson's sequence commenced with D-tyrosine derivative **49** which was reacted with benzaldehyde dimethyl acetal to furnish the 5-oxazolidinone **50** (Scheme 1.10). Alkylation with **51** proceeded smoothly producing **52** with the desired configuration. Aqueous NaOH was used to facilitate ring opening of the 5-oxazolidinone affording compound **53**. The formation of **54** was initiated with N-methylation of **53**, followed by the addition of excess methylamine to yield the amino-amide. Simultaneous removal of the benzyl and carboxybenzyl groups was achieved via palladium catalyzed hydrogenation to furnish compound **55**, which when treated with cyanogen bromide cyclized the desired precursor **56**.



Scheme 1.11 Model system for spirocyclization

All efforts to induce the oxidative spirocyclization of **56** were unsuccessful. Aware of the similar failed attempts of Danishefsky and Ciufolini, Watson proceeded by constructing a model system free of ring-strain due to the *trans*-fused [5,5] system found in spiroleucettadine (Scheme 1.11). The model aimed to determine if an amino-ketal **59** (R = alkyl) would provide more stability to the spirocyclic system than the required hemiketal **59** (R = H). Compound **58** served as the model for this experiment and was constructed from *p*-hydroxycinnamic acid **57** in two steps. Amide **58** was subjected to multiple attempts of hypervalent iodine oxidation under various conditions. However, only compounds **60**, **61**, or mixtures of both, were isolated. These findings only further support Ciufolini's concerns of the viability of such oxidative reactions on the orthoamide-type moiety and of the group's instability.

Prompted by the results of the model experiments, Watson decided to examine the available spectroscopic data collected by Crews for spiroleucettadine in greater detail. During this inspection, Waston found the assignments of C-4 and C-5 to be of great concern, which were based on ^{13}C chemical shift, HMBC, and ROESY data. Also, Crews stated there was an HMBC correlation observed between the two H-8 protons and the C-6 carbon. However, Watson believed this was a coincidental correlation between H-8 and the ^{13}C resonance of methanol, the solvent in which the NMR data was collected, implying there is no correlation between C-6 and C-8 at all. Based on this evidence, Watson suggested C-6 and the oxygen in the oxolane ring could be reversed to compound **62** (Figure 1.5).

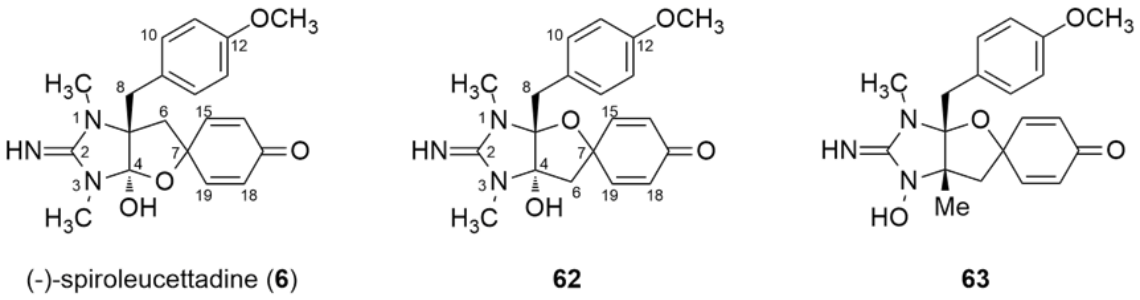


Figure 1.5 Possible revisions for

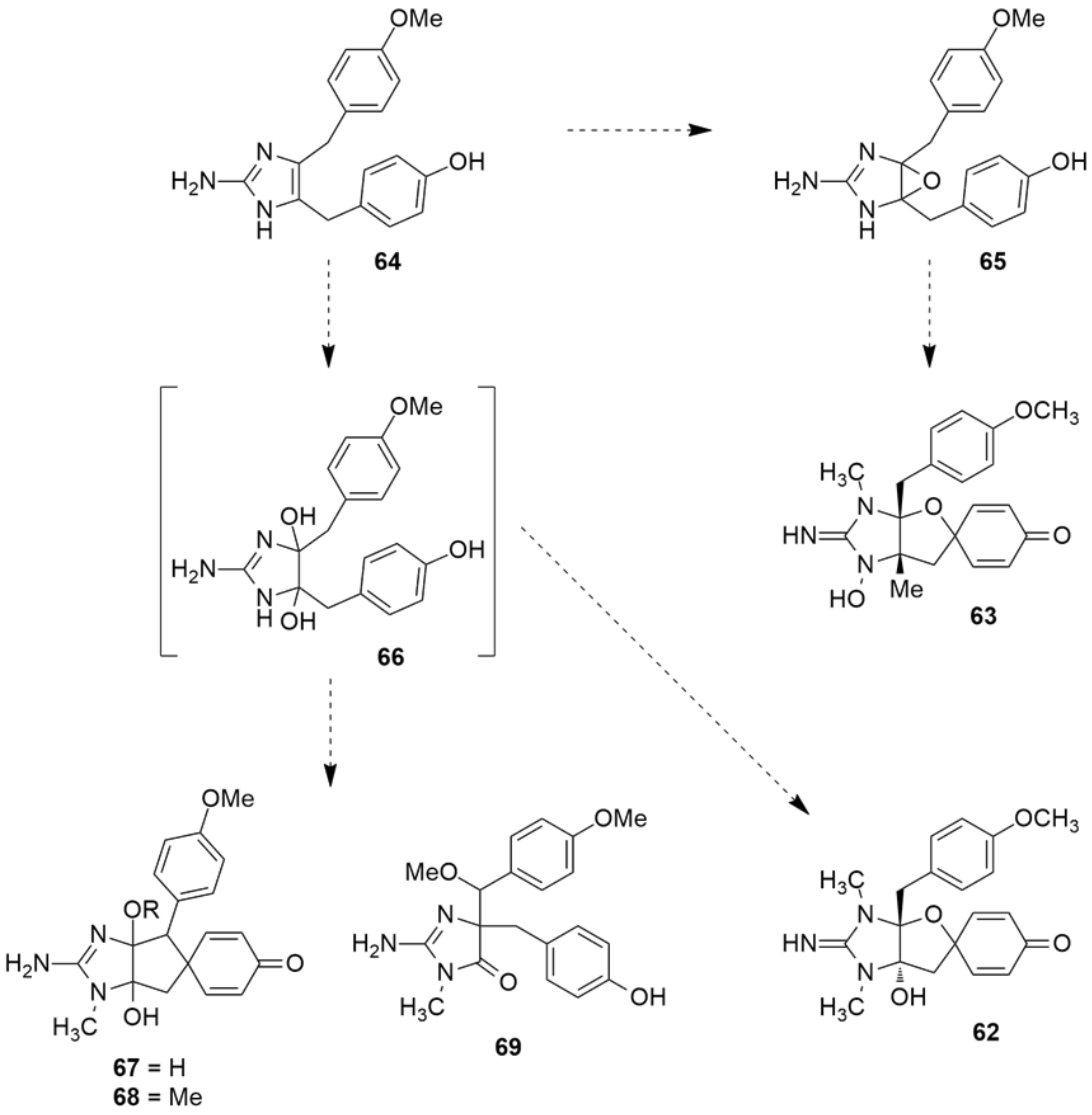
Watson also believed this revision better matched the observed resonances for C-4 and C-5, which were reported as 102.5 and 82.5,

respectively.

Next, Watson and his colleagues utilized DFT calculations to predict ^{13}C chemical shifts of **6** and propose structures which better fit the experimental data reported by Crews. Calculations were first made for the reported structure of spiroleucettadine and then compared to the observed data. When the two sets were compared, the mean absolute error (MAE) was found to be 4.3 ppm. Next, chemical shifts were calculated for **62**, showing an MAE of only 3.4 ppm. Watson then focused on the carbons located at the fused-ring junction, C-4 and C-5, and the spiro-carbon C-7. Analysis of the chemical shifts for C-4 and C-5 predicts one of them should be connected to three carbons and one nitrogen, while the other should be connected to two carbons, one nitrogen, and one oxygen. When C-7 calculations were examined, the data implied its chemical shift is likely due to a *cis*-fused system, as opposed to the *trans* system. With the previous requirements in mind, further structures were proposed within these parameters. After DFT calculations were performed on these structures, it was found compound **63** best fit the requirements with the lowest MAE value of 2.2

ppm. Watson then evaluated **62** and **63** in a biosynthetic manner, speculating **62** could originate from a dihydroxylation of a naamine-type skeleton **64**, followed intramolecular spirocyclization and subsequent methylations (Scheme 1.12). He further suggested the intermediate **66** could be a precursor to spirocalcaridines A and B, **67** and **68**, respectively, and via a pinacol-type rearrangement, produce the carbon structure of calcaridine **69**. Structure **63** could originate from the epoxidation of **64**, followed by ring opening of epoxide **65** by methylation, and then an intramolecular spirocyclization.

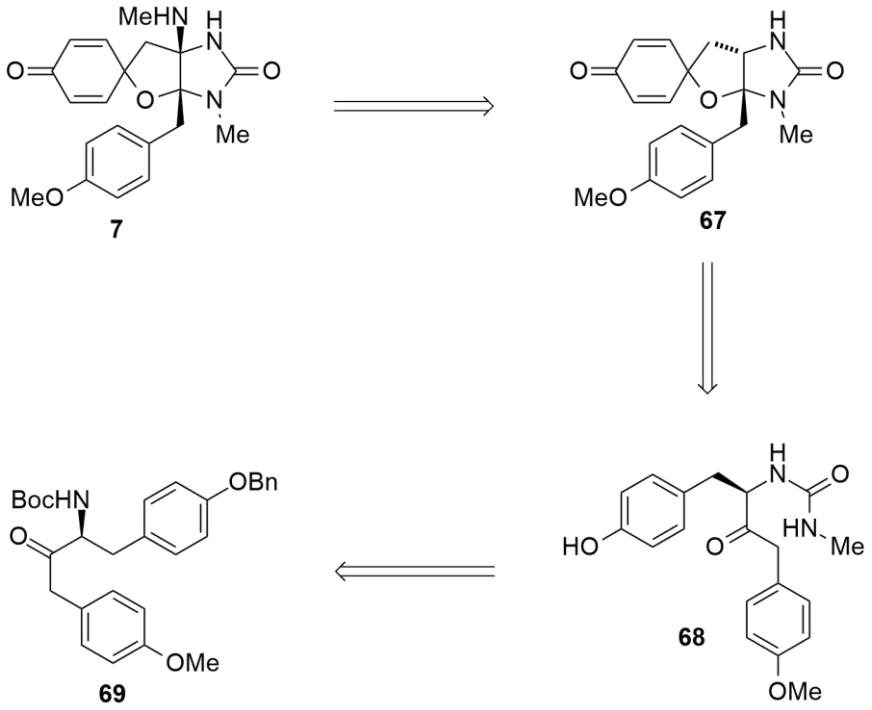
After analyzing the data acquired in this investigation, along with the cumulative evidence from Danishefsky and Ciufolini, Watson believed the structure assigned to spiroleucettadine was indeed incorrect. In reference to the proposed structures arising from the DFT calculations, Watson stated **62** is the most feasible from a biosynthetic perspective, while **63** best fit the calculations, with his group's future work focusing on providing synthetic evidence for these structures.



Scheme 1.12 Possible biosynthetic pathway for 62 and 63.

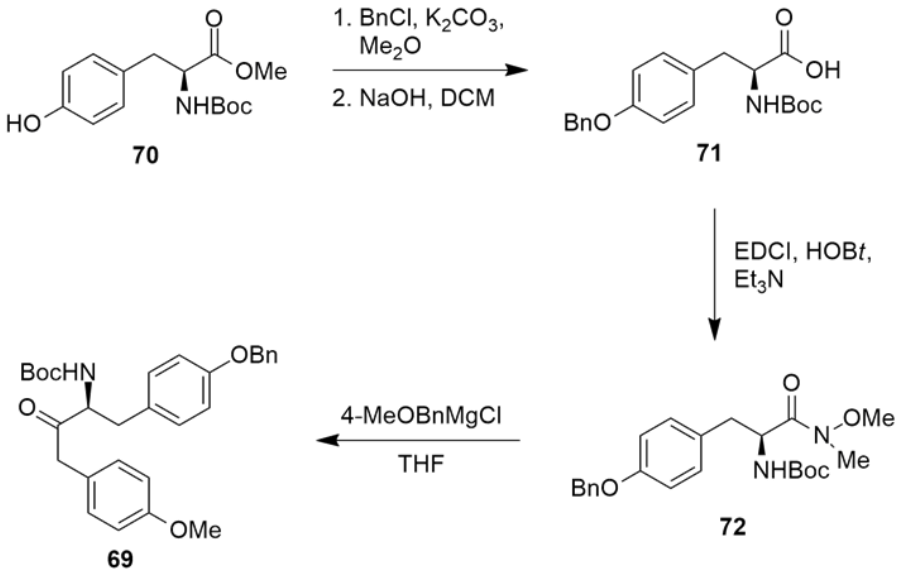
1.5 Hawkins' Total Synthesis of Spiroleucettadine

The first and to date only reported total synthesis of spiroleucettadine was published in 2017 by the New Zealand group of Hawkins.[23] The New Zealand group used a biomimetically inspired strategy, starting with a derivative of the amino acid tyrosine, as opposed to methods similar to ours which relies on the elaboration of an imidazole core (Scheme 1.12).[28-30]



Scheme 1.12 Hawkins retro synthesis for spiroleucettadine.

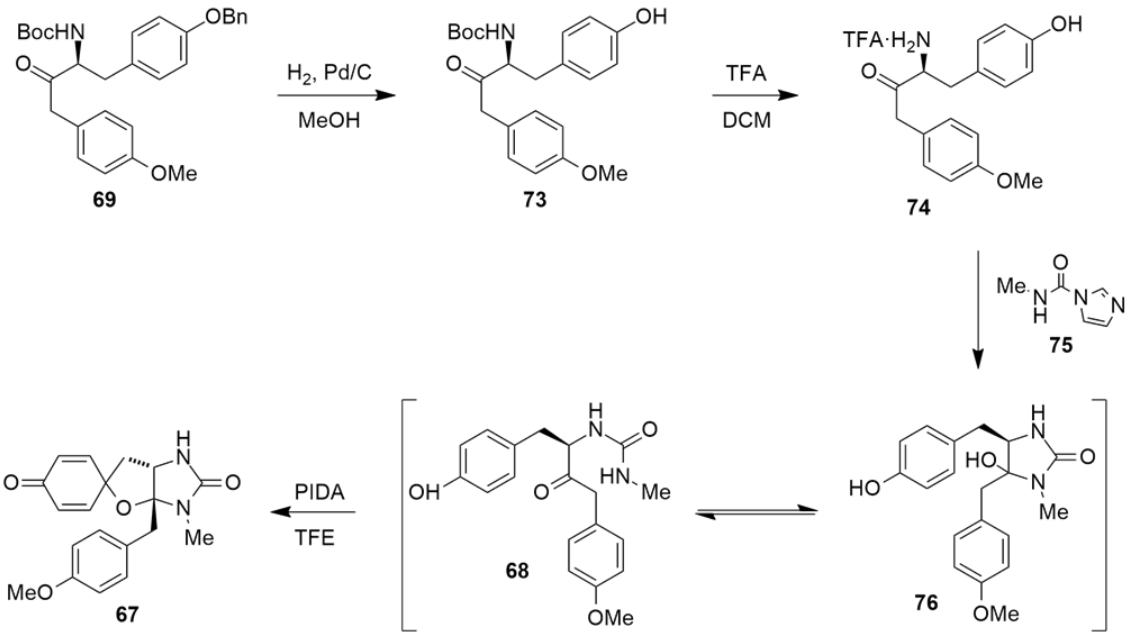
Hawkins' strategy began with the *N*-Boc protected methyl ester of L-tyrosine **70** (Scheme 1.13). The tyrosine derivative's phenol was benzyl protected, then the ester was hydrolyzed to give the acid **71**. Conversion of **77** the Weinreb amide was achieved with the use of EDCI and HOBT; the amide was then reacted with freshly prepared 4-methoxybenzylmagnesium chloride to yield ketone **69**.



Scheme 1.13 Ketone intermediate for spiroleucettadine.

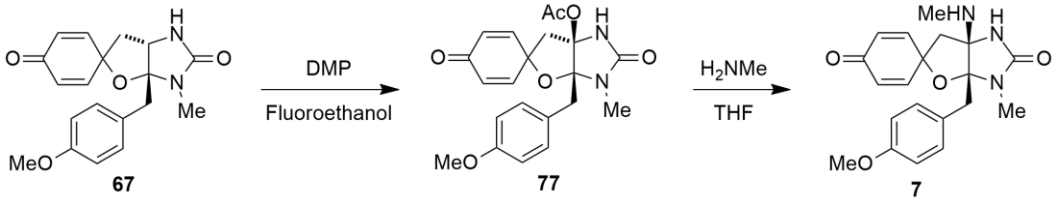
Next, the phenol of **69** was debenzylated using H_2 and palladium, followed by Boc deprotection with TFA and isolated as the amine salt **74** (Scheme 1.14). The amine was then reacted with *N*-methyl carbamoylimidazole to furnish both compounds **68** and **76** which were not isolated and carried through to the next reaction with no further purification. This mixture was then subjected to hypervalent iodine oxidation via PIDA in 2,2,2-trifluoroethanol, which yielded spirocycle **67** in 17% yield over the two steps.

With key intermediate **67** in hand, Hawkins only needed to install the N-methyl amino moiety to complete their synthesis of spiroleucettadine. To achieve this, the group first installed an acetate group by oxidizing **67** using Dess-Martin periodinane giving compound **77** (Scheme 1.15).



Scheme 1.14 Synthesis of spirocycle intermediate.

Treatment of **77** with methylamine hydrochloride and trimethylamine in THF afforded (-)-spiroleucettadine in 91% yield. This strategy utilized ten steps starting from **70**, with an overall yield of 3.8%. The spectral data and specific rotation for synthesized **7** matched the data reported by Crews in the revision paper, ensuring that the revised assignment was indeed correct.



Scheme 1.15 Methylamine installation.

1.6 Imidazole-Containing Natural Products (Terrazoanthine)

Another group of marine invertebrates under synthetic consideration is from the order Zoantharia. These animals are found all throughout the world, especially in the Indo-Pacific oceans, typically in coral reef systems.[31] A variety of molecules, some with biological activity, have been harvested from this group.[32-36] Of particular interest is the species *Terrazoanthus onoi*, which was isolated off the coast of Ecuador in 2010.[37] To date only one chemical study has been performed on this species. In 2017, a family of 2-aminoimidazole compounds, terrazoanthines A-C (**78-80**) were isolated and characterized by the Thomas group (Figure 1.3).[38] Terrazoanthine A and B feature a 6-(imidazol-5-yl)benzo[d]imidazole not found in other relatives of the T. *onoi* species.

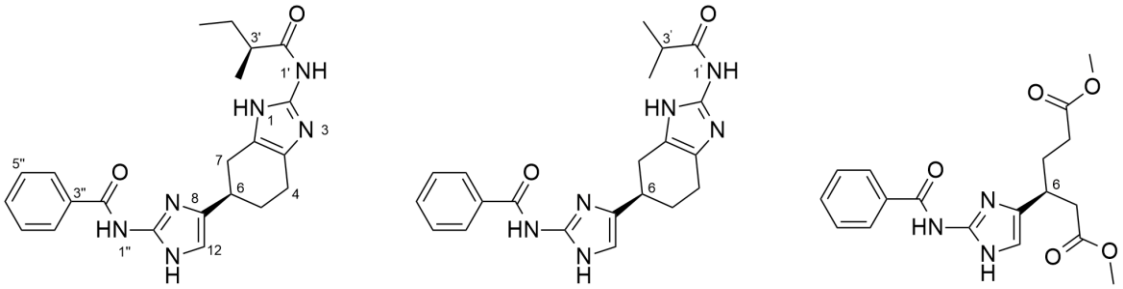


Figure 1.3 Proposed structures of terrazoanthine A-C.

The molecules were extracted in the methanol fraction and were further purified via reverse-phase HPLC. The masses of terrazoanthines A, B, and C were determined by use of (+)-HRESIMS, with Δ's of -0.7 ppm, 2.3 ppm, and 0.2 ppm, respectively. All molecules were interrogated via ^{1}H, ^{13}C, COSY, HMBC, HSQC, and ROESY NMR spectroscopy. However, no crystal structure was obtained for any of the isolated molecules, with all absolute configurations based on comparing experimental data to

computational theoretical data. The configuration of C-6 was established using experimental ECD spectra and comparing it to the theoretical TDDFT data of the two possible enantiomers of terrazoanthine A only. Because theoretical ECD TDDFT could not be used to assign the configuration at C-3', the investigators utilized a different theoretical method based on using PD4 probability. This was a unique method developed by Smith and Goodman to assign absolute configuration. The method is based on using a single set of experimental NMR chemical shifts and is compared to chemical shifts generated by single-point calculations on molecular mechanics geometries.[39] While this technique provided the investigators with an 81.8% confidence value, a further examination of the full data sets could leave one to call into question the accuracy of the assignment of *R* to the configuration at the C-3' position.

While the stereochemical assignments match the theoretical data reasonably well, there is a significant chance the assignments are wrong. Synthesis of the proposed structures would elucidate the true structure of all three of the terrazoanthines.

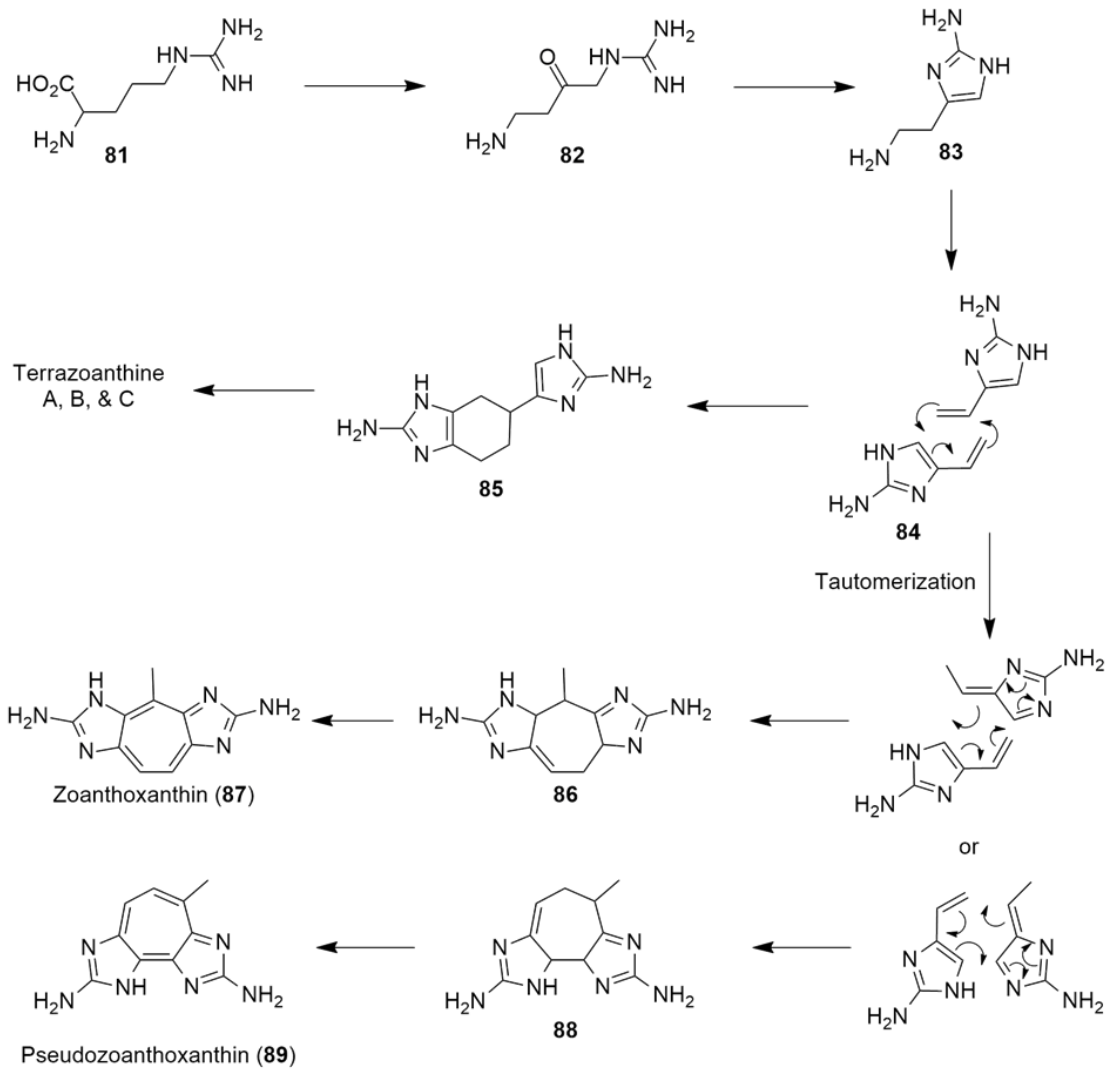
While a simple synthetic route could be used to produce each of the desired molecules, an ideal synthesis would streamline the beginning of all three molecules and diverge at a strategic step to produce not only the three intended compounds but also be capable of producing all possible stereoisomers. It is our belief our proposed synthetic route is capable of achieving this goal.

All three compounds were tested for antibacterial activity against *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*, and cell growth inhibition of human liver tumor cell line (HepG2). Unfortunately, they showed no activity at concentrations up to 96 µg/mL. However, this result is surprising given the

activity of many other 2-aminoimidazoles. As well, this is a small selection of bacterial and tumor cell lines. With larger quantities of the terrazoanthines the sample size to test against could be greatly increased. Also, it can be tested for other biological applications such as inhibition of acetylcholine esterase, since compounds closely related to terrazoanthines, like zoanthoxanthin derivatives, have shown to be potent inhibitors.

1.7 Proposed Biosynthesis of Terrazoanthine

To date, there have been no reported synthetic attempts, nor a total synthesis towards terrazoanthine A, B, or C. There is a proposed biosynthetic pathway, which is based on the pathway proposed by Büchi and coworkers in the 1970's for zoanthoxanthin (**86**) and pseudozoanthoxanthin (**88**) (Scheme 1.16).[40,41] This route suggests terrazoanthine originates from the amino acid arginine **81**. Decarboxylation of the acid followed by oxidation beta to the guanidine would give **82**. A condensation would then furnish **83**, followed by deamination would yield the 2-aminoimidazole **84**. Then two of **84** would engage in a Diels-Alder type [4+2] cycloaddition to furnish the core of terrazoanthines A and B. It is then suggested C would arise from hydrolysis of the guanidine from the tetrahydrobenzimidazole, leading to the formation of a 1,2-dione, which is then cleaved by oxidation to the dicarboxylic acid, followed by esterification to the methyl esters. However, if this pathway is correct, caution should be exercised in reference to their esterification. These compounds were extracted in the methanolic fractions. It is therefore possible it was during this process that the dicarboxylic acids esterified, and the true structure of terrazoanthine C is that of a diacid and not esters.



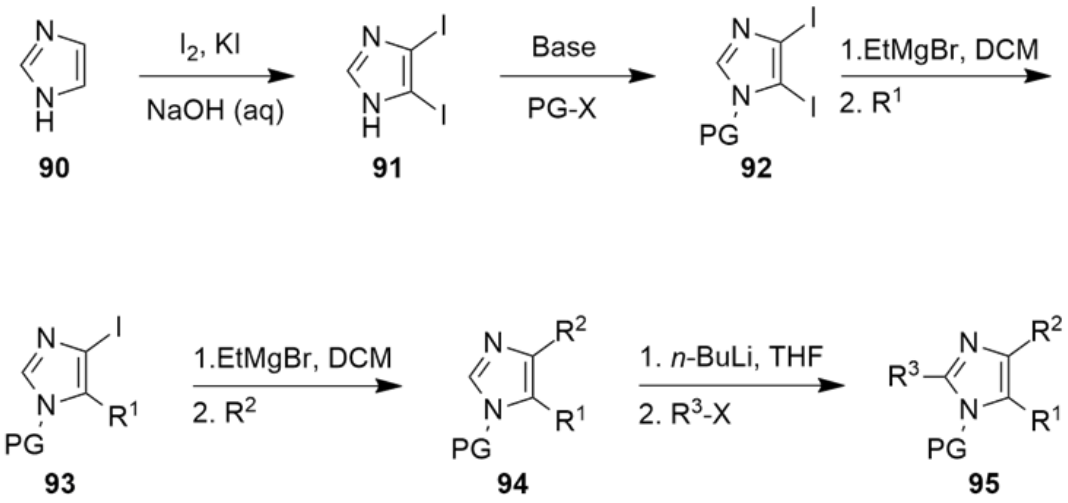
Scheme 1.16 Proposed biosynthetic pathway for terrazoanthines A-C and related zoanthoxanthins.

Chapter 2

Synthetic Efforts Towards Spiroleucettadine

2.1 Our Approach to Spiroleucettadine

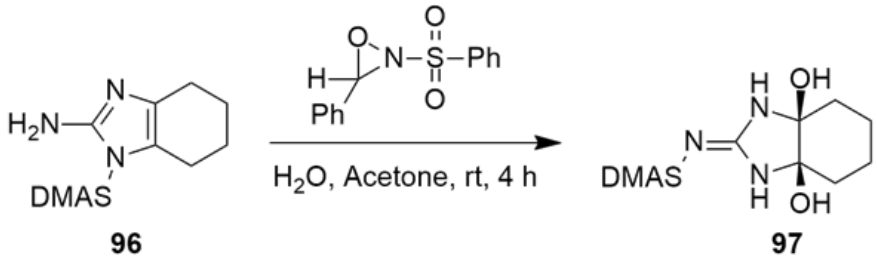
The general approach employed in our lab when synthesizing imidazole-containing alkaloids is the stepwise functionalization of the imidazole initially reported in 1997 by Lindell and co-workers.42 This strategy commences with the diiodination of imidazole to give 91 (Scheme 2.1).



Scheme 2.1 General procedure for imidazole functionalization.

It is then typically followed by *N*-protection with a suitable protecting group for the chosen strategy, giving rise to general compound **92**. Next, if **92** reacted with one equivalent of a 1° Grignard reagent, metalation will occur exclusively at the C-5 carbon. This transformation allows the imidazole to engage in a nucleophilic attack on an appropriate substrate, such as an aldehyde, ketone, or 1° and 2° halides, yielding a

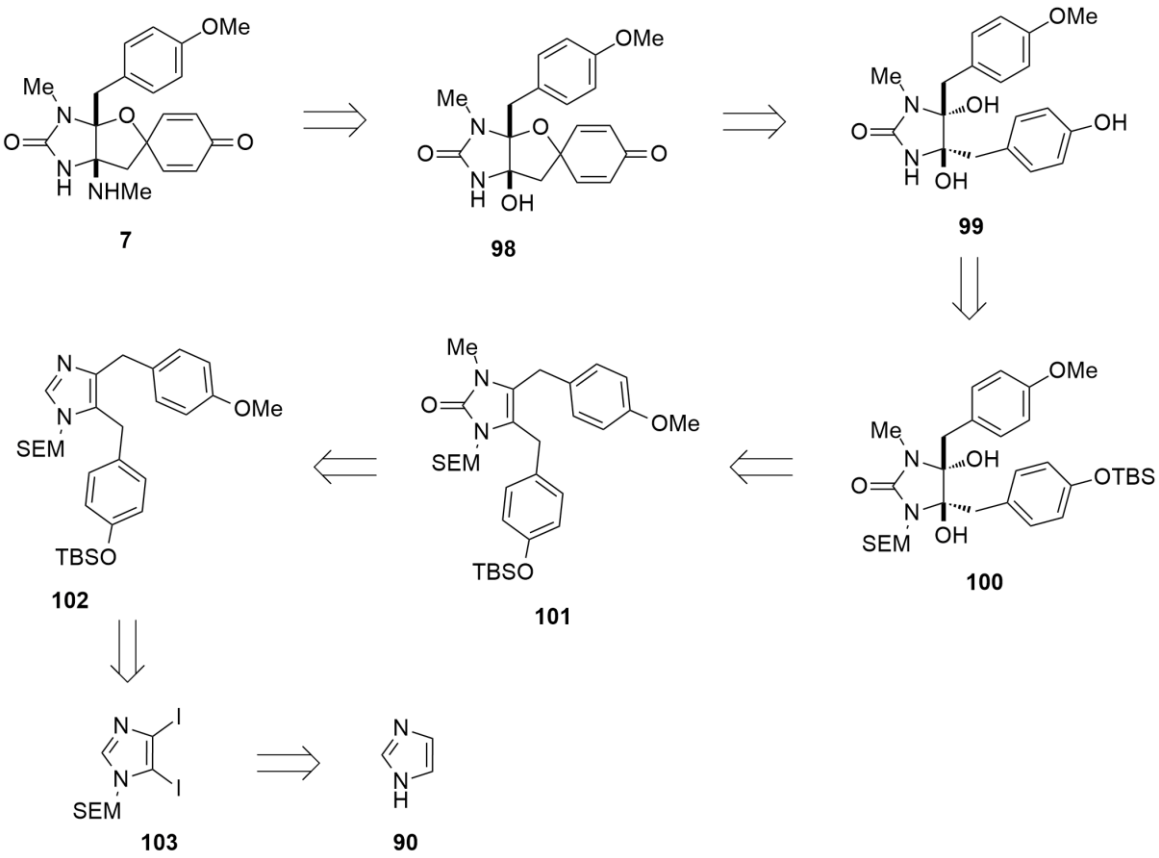
substitution at the C-5 position, furnishing **93**. This same process can be repeated to form **94**, substituting at the C-4 position. The C2 carbon is next in the series to be functionalized. In most scenarios the C2 carbon is deprotonated via a strong base, such as *n*-BuLi or *tert*-BuLi, again making the molecule a suitable nucleophile to react with an electron-deficient reagent giving **95**. While this is perhaps the most common means of C-2 functionalization, there are other milder conditions which can be utilized enact C-2 transformations, such as halogenations and oxidations.[42]



Scheme 2.2 Oxidative addition.

Retrosynthetic analysis of spiroleucettadine concluded our general approach was a suitable strategy to use for synthesis of the molecule. It was also theorized the oxidative reaction previous discovered by Rasapalli and co-workers could be employed (Scheme 2.2). With this in mind, the retrosynthetic approach envisioned **7** furnished from a methylamine substitution of **98** (Scheme 2.3). The spirocyclic compound **98** could be synthesized from **99** using hypervalent iodine oxidation. Next, **99** would be realized from **100** via N-deprotection. Then the oxidative addition of **101** with oxaziridine would yield diol **100**. **101** could be achieved from **102** via C-2 oxidation and N-methylation with MeI. Two sequential metalations of **103** with the appropriate benzaldehyde derivatives followed by reduction of the resulting alcohols would afford **102**. And **103** would be

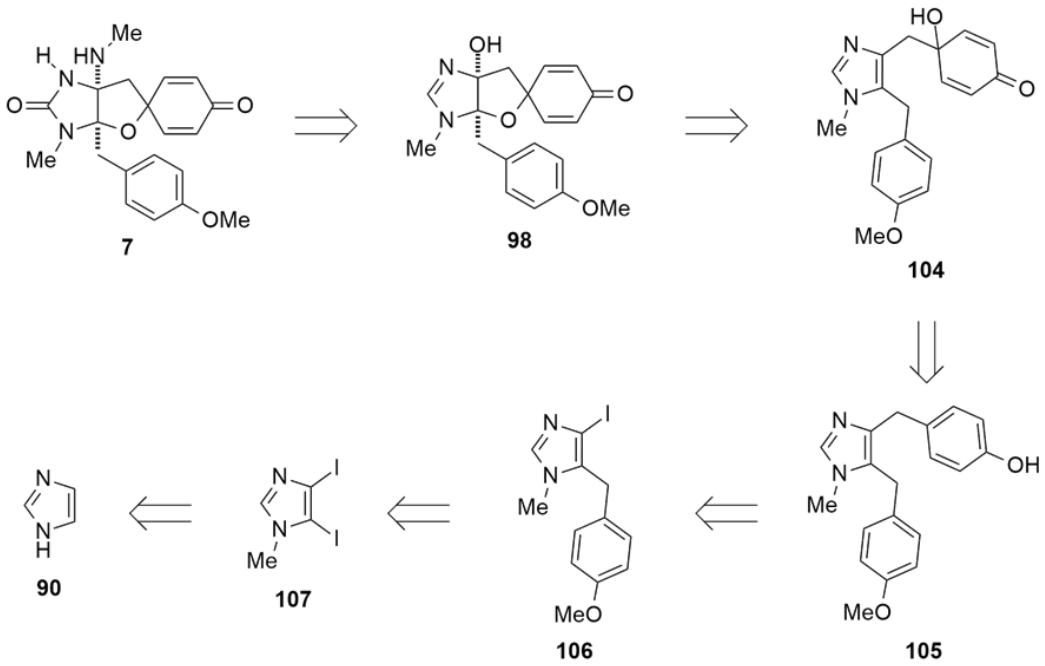
yielded from diiodination followed by SEM (2-(trimethylsilyl)ethoxymethyl) protection of imidazole.



Scheme 2.3 First retrosynthetic analysis for spiroleucettadine.

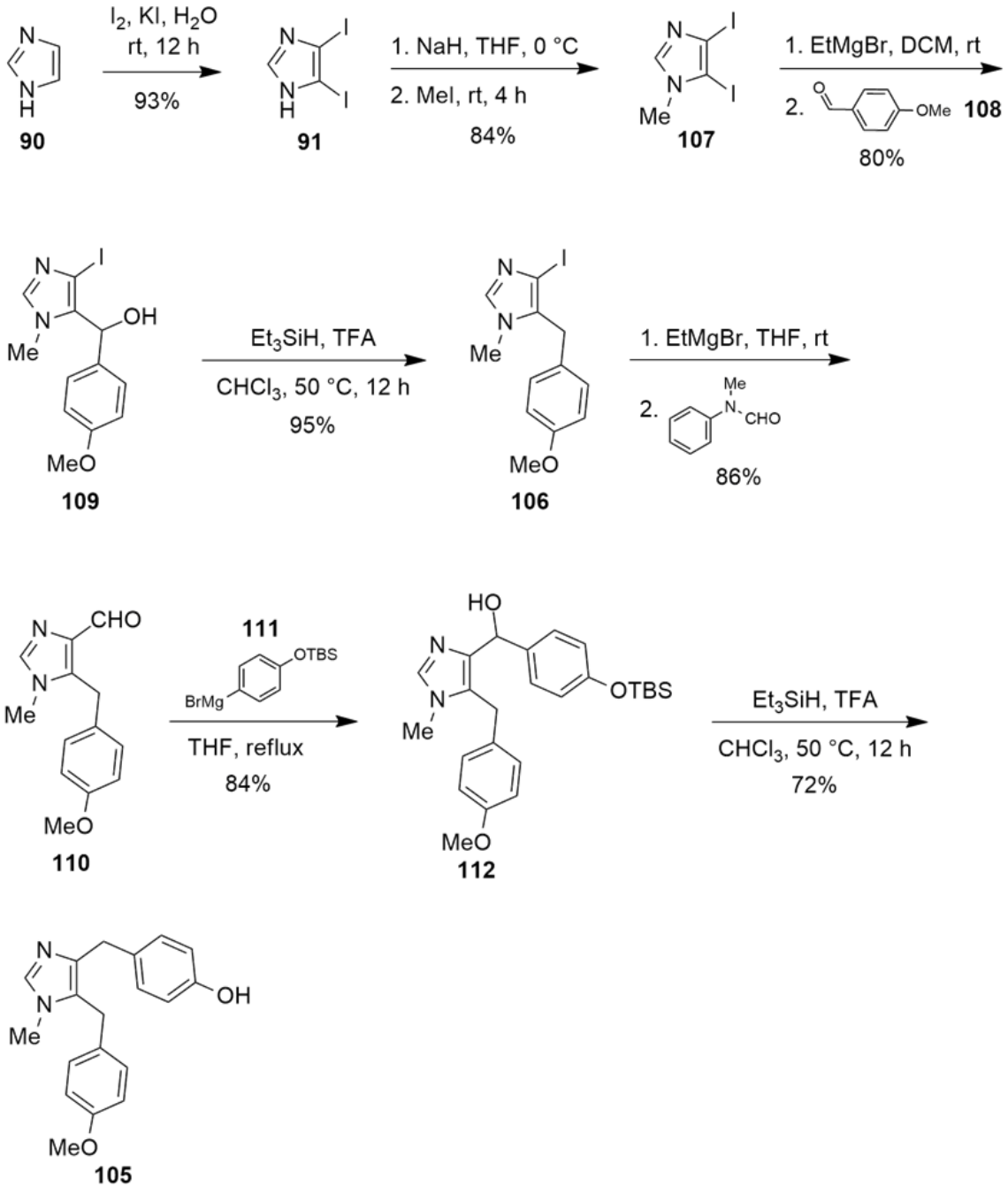
Before synthesis of spiroleucettadine began, model systems were employed to assess the viability of key intermediates along the synthetic route. The intermediate which received a large amount of our attention was **101**, having concerns centered on its oxidation to the diol. When this oxidation was initially discovered, the substrate was 2-amino-1-dimethylaminosulfonyl-4,5,6,7-tetrahydrobenzimidazole, compound **96** (Scheme 2.2). It was hypothesized an electron-withdrawing protecting group was

required in order for this transformation to take place, as electron-donating groups were typically shown to yield the 5-imidazolone via a pinacol-type rearrangement.[26,43] However, we were aware the DMAS (dimethylaminosulfonyl) group could not be removed at this stage, and therefore not a viable protecting group for the synthesis. This deficiency prompted the investigation of different protecting groups with similar electronic effects. The SEM protecting group was chosen due to its electron-withdrawing characteristics and ease of removal with fluoride reagents such as TBAF. Again, THB was used for the model to test the viability of the C2-oxidation of the SEM protected derivative, as well as other variables. Unfortunately, the outcome from these investigations showed SEM to be an unsuitable protecting group to effect the desired transformation, with no reaction occurring when subjected to oxidative conditions. These findings prompted not only a reexamination of the protecting group, but of the synthetic strategy as a whole.



Scheme 2.3 Second retrosynthetic analysis for spiroleucettadine.

In our second approach to spiroleucettadine, the same stepwise functionalization of imidazole was employed, while omitting the need for a protecting group and the use of the problematic C2-oxidation. Again, we anticipated spiroleucettadine could be prepared by substitution of the alcohol of spirocyclic compound **98** with methylamine (Scheme 2.4). Epoxidation of **104** followed by spirocyclization would yield **98**. Hypervalent iodine oxidation of **105** would afford **104**. Two series of metalations of **107** with appropriate benzyl derivatives would furnish **105**. Finally, **107** would be derived from diiodination of imidazole, followed by N-methylation.



Scheme 2.4 Synthesis of spiroleucettadine intermediate 105.

Synthesis commenced with diiodination of commercially available imidazole in basic-aqueous solution to provide its diiodo derivative **91** in 93% yield. N-methylation with MeI proceeded smoothly to furnish **107** in good yield (Scheme 2.4). Treatment of **107** with

EtMgBr followed by the addition of benzaldehyde **108** afforded alcohol **109** with 80% yield. Ionic reduction of the alcohol was achieved using Et_3SiH and TFA, conditions which had previously been reported by Ohta and co-workers, providing **106**.[44] Formylation of **106** proceeded by metalation with EtMgBr, followed by addition of *N*-methylformanilide, furnishing the corresponding aldehyde **110** in 86% yield. The reaction of **110** with the freshly prepared Grignard reagent **111**, derived from the TBS-protected 4-Bromophenol resulted in the formation of alcohol **112**, which was again reduced via ionic reduction, which also conveniently promoted desilylation of the phenol, providing **105** in 72% yield.

Unfortunately, it was at this step during our synthesis Hawkins and co-workers reported their successful total synthesis of spiroleucettadine, ending this project in our lab for the time being.

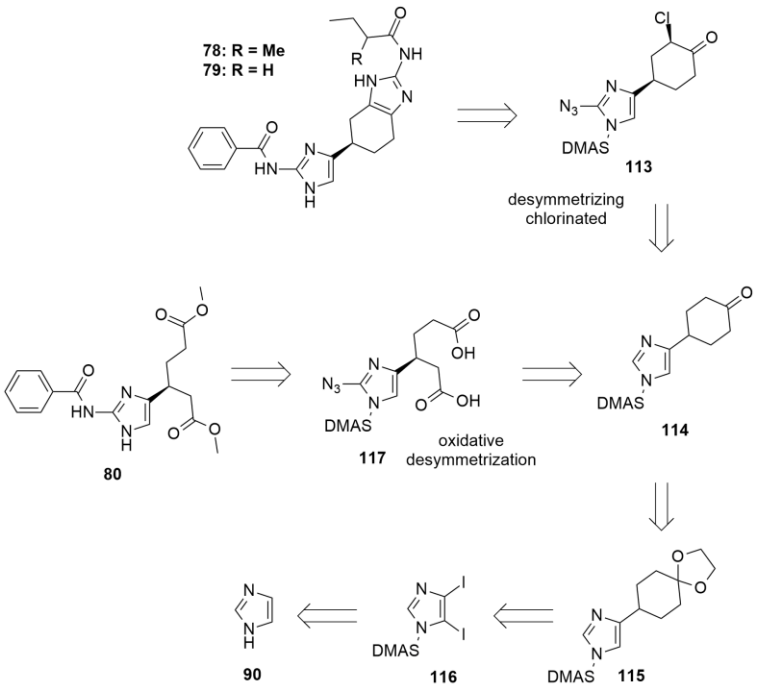
In conclusion, while there are some aspects of our synthesis which are similar to Hawkins, contributions to the synthetic community can be made from the synthesis of spiroleucettadine in our lab. Perhaps a way can be found to reincorporate the oxidative addition back into the synthetic strategy with the use of a Boc protecting group instead of the DMAS, allowing for deprotection of the nitrogen. Or perhaps even new aspects or applications of the oxidation will be discovered should we resume our efforts.

Chapter 3

Synthetic Efforts Towards Terrazoanthines A-C

3.1 Our Approach to Terrazoanthines A-C

Our approach to the terrazoanthine family incorporates three key aspects. First, we will use the stepwise functionalization of imidazole to construct the majority of the molecule. Next, we envision a strategy which streamlines the synthesis of all three species of molecules and diverges at a key intermediate to lead to both terrazoanthine A and B in one path of the route, and to C in the other. Finally, we will take advantage of symmetry in the initial steps of our synthesis until the key intermediate, where symmetry will be broken with an asymmetric reaction. It is the goal of this strategy to not only produce the configurations claimed in the isolation paper, but all stereoisomers of these compounds. In a retrosynthetic analysis of our approach to terrazoanthine A, we envisioned the amide installation as the final steps of the synthesis **78** (Scheme 3.1). In this transformation, we chose to utilize two different functional groups to allow for selective amidation of **113**, allowing flexibility of order and timing of these reactions. Compound **113** could be realized via guanylation of α-halide **114**, which could be derived from **115**, in two possible routes after ketal removal.

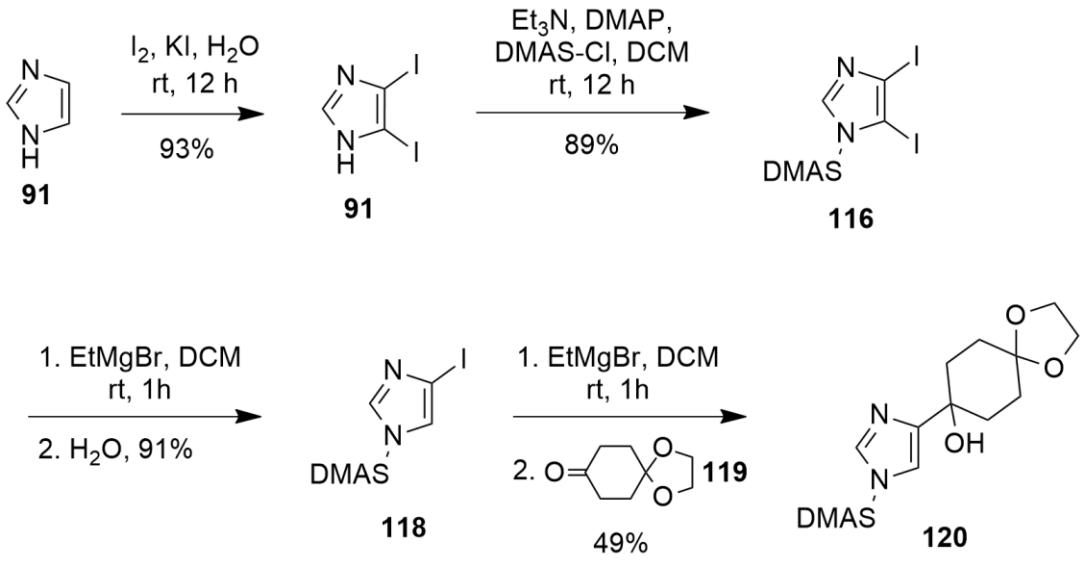


Scheme 3.1 Retrosynthesis of terrazoanthine A.

First, a directed asymmetric alpha halogenation of the ketone, or via asymmetric deprotonation and trapping the resulting enolate to form a silyl enol ether, followed by halogenation. Metalation of **116** with EtMgBr, then quenching with water, followed by a second metalation and reaction with cyclohexadione ketal would furnish **115.** Finally, diiodination and protection of **90** would afford **115**.

Synthesis was initiated with commercially available imidazole which was subjected to iodination in a basic aqueous solution to yield diiodoimidazole **91** in 93% (Scheme 3.2). DMAS protection of the amine proceeded smoothly furnishing **116** with 89% yield. The N-protected diiodoImidazole **116** was reacted with EtMgBr then quenched with water providing 4-iodoimidazole **118** in high yield. The monoiodoimidazole was subjected to the same metalation conditions as **116**, followed

by the addition of dione **119** to give alcohol **120**. However, upon purification of the residue, the calculated yield of alcohol **120** was only 36%.



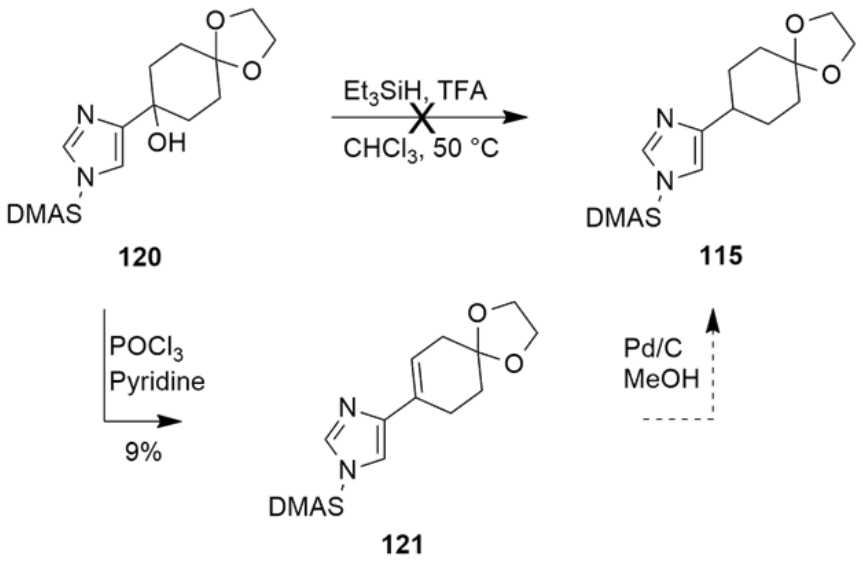
Scheme 3.2 Synthesis of Alcohol.

Analysis of the ^{1}H NMR spectrum of the crude reaction mixture showed the majority of the mixture was the desired alcohol, unreacted dione, and DMAS-protected imidazole, which was produced from the quenching of metallated imidazole. This suggested the iodoimidazole successfully underwent metalation but did not completely react with the dione.

Attempts to optimize the yield via increased time, temperature, and equivalents of **119** only gave moderate results of 49% yield. Further efforts were made to increase yield by using additives in the hope to promote the desired addition reaction. Employing a procedure reported by Imamoto and co-workers, $CeCl_3$ was added to the reaction.[45] Applying the method developed by authors, as well as two variations in the order of addition of the salt developed by our lab, the experiments were carried out and the

results examined. Unfortunately, no improvements were observed, giving either a decrease in yield or no change at all. Willing to accept the modest yield this earlier in the sequence, for the time being, we focused our attention on the removal of the alcohol.

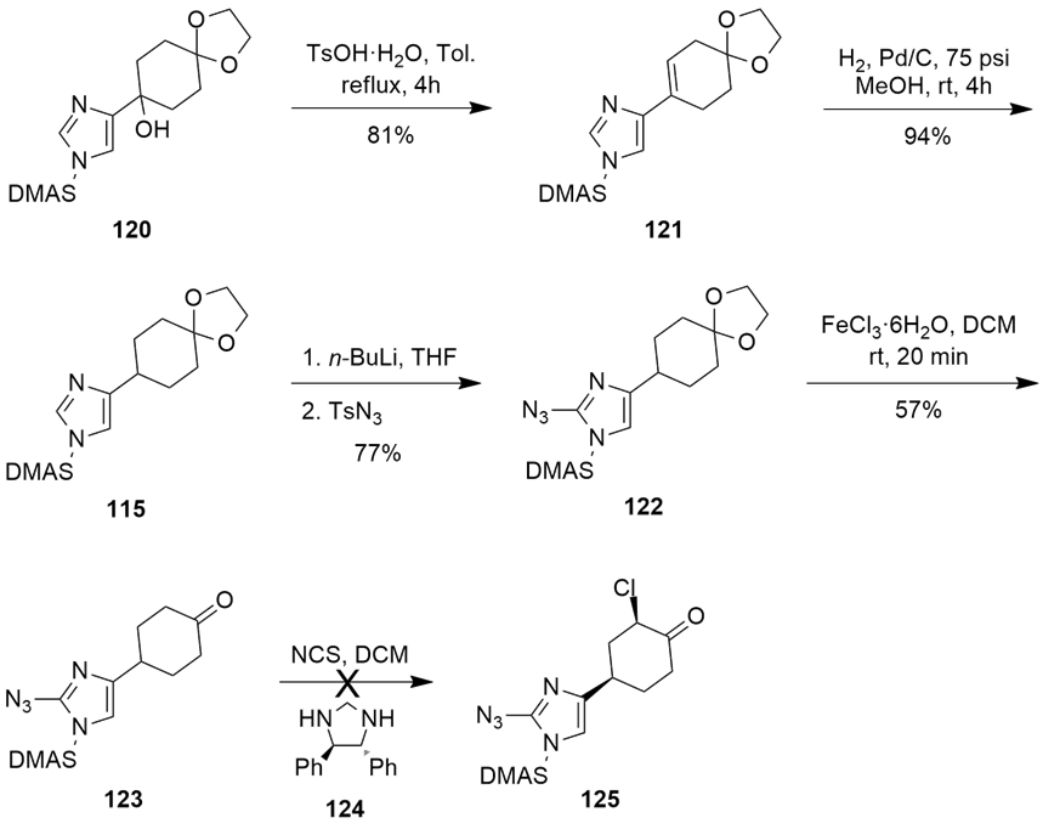
Initially, we attempted an ionic reduction of the alcohol using Et_3SiH and TFA.[44] We previously used this reaction with good results in our efforts with spiroleucettadine. We were aware of the probable cleavage of the ketal due to the use of TFA but proceeded in hopes of avoiding the route of elimination followed by reduction, reducing the step count of the synthesis. However, spectroscopic analysis of the crude reaction mixture confirmed cleavage of the ketal had occurred, with no detection of the ethylene protons in the range of 3.90-3.95 ppm (Scheme 3.3).



Scheme 3.3 Initial dehydration attempts.

After the attempts of reduction were unsuccessful, we modified our approach to dehydration of the alcohol, followed by reduction of the resulting alkene. In our first attempt, we utilized phosphoryl chloride to facilitate the reaction. Surprisingly, this well-known reaction did not work as we expected. While there was some product formation, the resulting reaction mixture was complex, and upon purification, only 9-10% of the desired product was isolated. After several attempts of trying to improve this reaction did not succeed, it was decided to abandon phosphoryl chloride as a reagent and explore other possibilities.

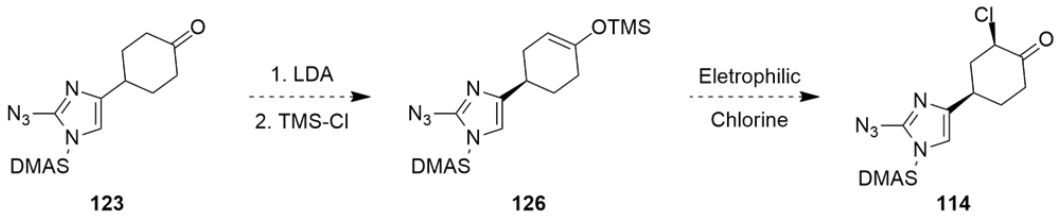
Reymond and co-workers had shown that benzylic-tertiary alcohols could be dehydrated using TsOH in the presence of a ketal moiety.[46] It was decided to employ this chemistry with caution due to our previous attempt which utilized an acid. Gratifyingly, the reaction worked well with only slight modification, furnishing alkene **121** in 81% yield (Scheme 3.4). With the alkene in hand, we proceeded with a standard method of reduction using 10% Pd/C in methanol under gaseous hydrogen which gave **115** in excellent yield. We then considered to whether to stay with the original synthetic route, requiring removal of the ketal, or if this juncture was a more appropriate time for the installation of the 2-azido group, which originally was to be added in the final steps of the synthesis. We concluded now was a better time to introduce the azide, since it is performed under relatively harsh conditions and all labile functional groups on the molecule were protected.



Scheme 3.3 Synthesis of ketone.

The lithiation was carried out with n-BuLi at -78 °C, followed by the addition of TsN_3 to provide azide **122** in good yield. With **122** in hand, we examined the removal of the ketal. This transformation is typically carried out in a polar solvent, and catalyzed with strong aqueous acids.[47-49] However, the DMAS-protecting group is sensitive to acidic solutions and can be removed by small quantities acid, such as aqueous HCl.[50,51] In hopes of avoiding this dilemma, a Lewis acid was used in lieu of a protic acid, as well as a relatively nonpolar aprotic solvent. To our delight, when **122** was subjected to $FeCl_3$ in DCM, the corresponding ketone **123** was furnished in an acceptable 57% yield.[52] It hypothesized the lower yield is likely due to the catalyst dying at 20 minutes. By filtering out the ferric chloride at 15 minutes and adding a fresh equivalent of the catalyst, it is

possible the yield would improve. With ketone **123** in hand, we were ready to attempt the asymmetric chlorination. Ketone **123** was reacted with NCS in the presence of chiral catalyst **124**, the reaction quenched and then worked up. The crude reaction mixture was then subjected to ^{1}H NMR spectroscopy. Analysis of the data suggested the chlorination occurred at the C-5 position of the imidazole instead of alpha to the ketone. This conclusion was reached due to the absence of the resonance signal for C-5 proton of imidazole, which is located at 6.84 pmm for ketone **123**. Unfortunately, the product was not isolated to confirm this speculation via full characterization of the molecule. While the first attempt at this reaction did not work, future investigation is warranted to determine if indeed the 5-chloroimidazole was the true product. As well, the reaction needs to be duplicated to confirm this conclusion and also to see if slight modification could induce the desired chlorination. If indeed the envisioned transformation cannot be achieved, then a reaction sequence leading to the formation of a silyl enol ether intermediate is a viable alternative route to accessing the alpha halogenated species (Scheme 3.4).



Scheme 3.4 Plausible future

In conclusion, terrazoanthines A, B, and C are half way through to total synthesis. While the key chlorination failed on the first attempt, there is no reason to believe the synthetic

strategy will require any major revisions, as the reaction itself still needs further investigation. As well, if direct chlorination proves unviable, then a secondary route is already in place to be tested.

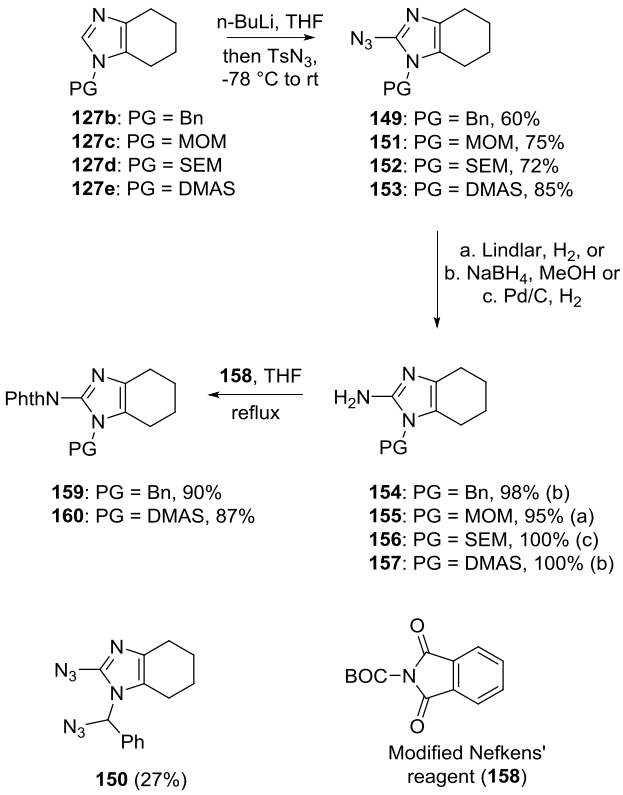
Chapter 4

4.1 Oxidative Reactions of Reactions of Tetrahydrobenzimidazole

When we first constructed our retrosynthetic approach to spiroleucettadine we planned to incorporate chemistry developed in our lab (Scheme 2.2). Knowing the DMAS-protected imidazole was not feasible in our strategy due to the inability to deprotect the sulfonyl urea caused by C-2 amino-functionalization, we initially wanted to examine the viability of the SEM protecting group. In a previous study we examined the effect of only the protecting groups on converting imidazoles into imidazolones via rearrangement (Table 4.1). Using SEM-protected tetrahydrobenzimidazole as the model for a 4,5-disubstituted imidazole we examined the effects of varying a nitrogen substituent on the C2-carbon, primarily azides and amines. Upon obtaining surprising results after just a few oxidative reactions, what started as a protect group evaluation for total synthesis quickly turned into a comprehensive investigation of the oxidation chemistry of tetrahydrobenzimidazole.

We first considered our options for an oxidizing reagent, with dimethyldioxirane (DMDO) emerging as the reagent of choice as it is reactive, neutral and produces acetone as an innocuous byproduct.[53] Next, a synthetic approach to 2-aza substituted imidazoles **154**-**157** was developed through metalation of the parent tetrahydrobenzimidazole with *n*-BuLi and trapping with tosyl azide to deliver the corresponding 2-azido derivatives (Scheme 4.1).[54,55] The presence of an electron withdrawing and, in the cases of the MOM and SEM derivatives a chelating protecting group presumably should facilitate this chemistry. In addition we decided to establish the utility of the benzyl protected tetrahydrobenzimidazole in this reaction. Interestingly,

the benzyl-protected congener **149** could be prepared through this metalation/trapping sequence but required the rapid addition of tosyl azide. Furthermore, the corresponding bis azide **150** resulting from lateral metallation of the benzylic cation and trapping was isolated as a major byproduct (Scheme 4.1).[56] The 2-azido derivatives **149**, **151**-**153** were converted into the 2-amino derivatives **154-157** by reduction[57] and in the case of the benzyl- and DMAS-derivatives were converted to the phthalimides **159-160** upon treatment with modified Nefkin's reagent.[58]

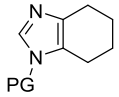
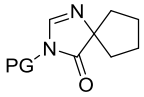
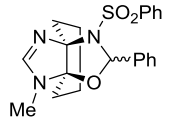
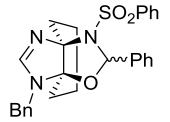
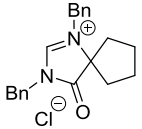
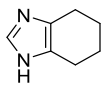
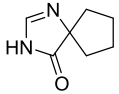
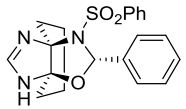
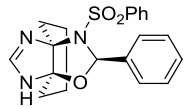


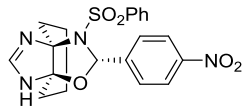
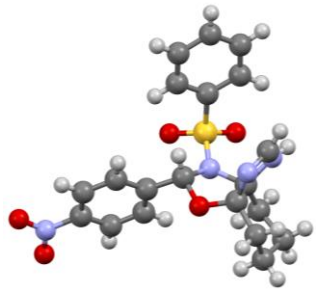
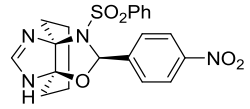
Scheme 4.1: Synthesis of 2-aminosubstituted tetrahydrobenzimidazoles

The azides were subjected to oxidation with DMDO and it was found that three of the substrates **149**, **151**-**152** underwent rearrangement to deliver 5-imidazolones (Table 2, entries 4-5, 7), the DMAS-protected derivative **153** was unreactive under these conditions (Table 2, entry 9). Interestingly, one of the imidazolones contained a

surprise in that the azido moiety was no longer present, but had undergone cyclization to provide the tetrazole valence tautomer **161** (Table 1, entry 4). This assignment was supported through the lack of an azide stretch in the IR spectrum and ultimately through X-ray crystallography. This valence tautomerism of azomethine azides to the corresponding tetrazole is well-known in literature,{Cubero, 1998 #73}[59-63] but there are only limited examples of 2-azidoimidazole derivatives favoring the tetrazole form.[64,65] Indeed, both experiment and theoretical calculations suggest that electron-donating groups favor the tetrazole form, whereas electron withdrawing substituents favor the azide, results that are mirrored in our systems. Although there appears to be a subtle balance however, as the precursor **149** appears to be exclusively in the azido form. The 2-amino derivatives **154-157** were also evaluated, but none of the these substrates engaged in productive reaction, however, the *N*-phthaloyl derivative **159** did undergo rearrangement leading to the formation of the anticipated imidazolone in good yield (entry 17, Table 2) , on the other hand the DMAS-protected phthalimide congener **160** did not.

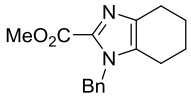
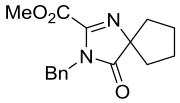
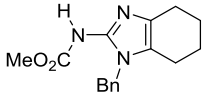
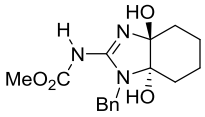
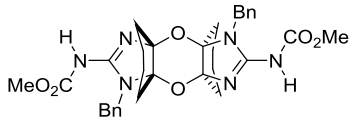
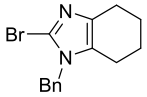
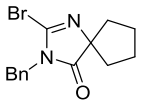
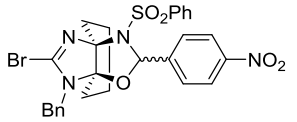
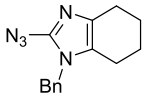
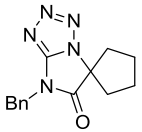
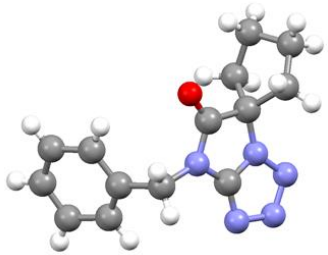
Table 4.1: Influence of nitrogen-protecting group on oxidative rearrangement

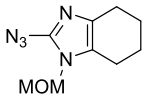
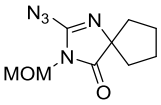
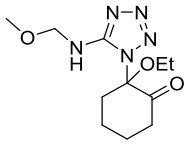
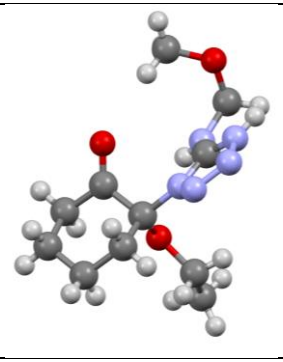
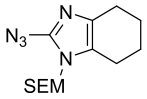
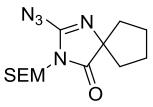
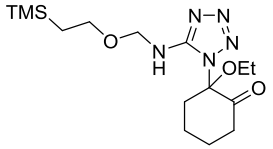
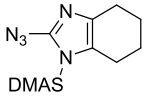
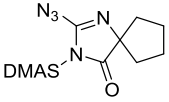
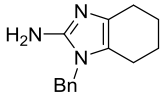
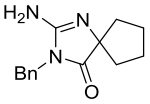
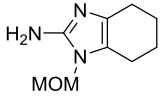
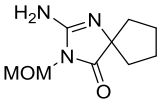
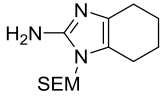
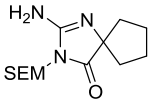
Entry	Substrate	Product	PG	$\delta_{c=o}$	$\delta_{c\text{-}spiro}$	DMDO (Yield/%)	Oxaziridine (Yield/%)	Byproduct[a]
								
1	**127a**	**128a**	Me	185.6	77.7	70	82	 **129**
2	**127b**	**128b**	Bn	185.2	78.0	73	80	 **130**
3	**127c**	**128c**	MOM	185.4	78.2	60	50	
4	**127d**	**128d**	SEM	185.3	78.2	43	64	
5	**127e**	**128e**	DMAS			0	0	
6	**127f**	**128f**	Ts			0	-	
7	**127g**	**128g**	Tr			0	-	
8	 **131**	 **134**				0	0	
9	 **133**	 **134**				0	 **135**	 **136**

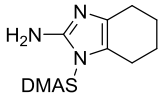
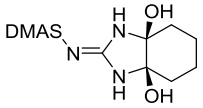
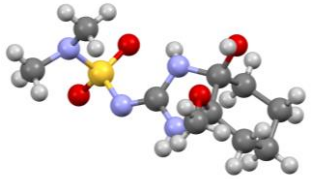
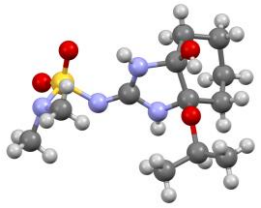
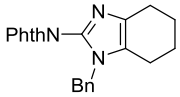
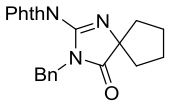
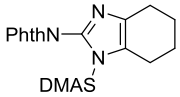
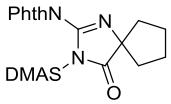
10	**133**	**134**				0	 **137** 	 **138**

These byproducts were obtained in ~2-3% yield in the oxaziridine-mediated oxidation reactions only.

Table 4.2: Oxidative reactions of 2-substituted tetrahydrobenzimidazoles

Entry	Substrate	Product	δc-spiro	δc-spiro	DMDO (Yield/%)	Oxaziridine (Yield/%)	
1	 **139**	 **144**	185.9	78.2	56	55	
2	 **142**	 **145**			70	17	 98 (15)
3	 **143**[66]	 **147**			0		 **148**
4	 **149**	 **161**	177.1	74.6	80	65	

5	 **151**	 **162**	177.5	74.6	40	 **163** 45	
	 **152**	 **164**					
6	MeOH	R = Me				**165a** 69	
7	EtOH	R = Et			18	**165b** 63	
8	i-PrOH	R = i-Pr				**165c** 56	
9	 **153**	 **166**			NP	0	
10	 **154**	 **167**	181.2	71.9	NR	59	
11	 **107**	 **168**			NR	NR	
12	 **156**	 **169**			NR	NR	

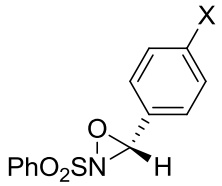
	 **157**						
13	MeOH	**170a**: R = Me				68	
14	EtOH	**170b**: R = Et				54	
15	i-PrOH	**170c**: R = i-Pr				40	
16	H_2O	**170d**: R = H				65	
17	 **159**	 **171**	184.4	79.0	60	40	
18	 **160**	 **172**			-	0	

One of the continuing issues that has hindered this study was the need for the preparation of isolated DMDO solutions. Attempts to effect this chemistry through the *in situ* formation of the oxidant were to of no avail; we suspect that this is due to the formation of protonated imidazolium salt which then does not participate in the rearrangement chemistry (*cf.* **131**, entry 8, Table 1). The preparation of the reagent was tedious, was variable in active oxidant concentration and in water content, all of which rendered this reagent less attractive for scouting experiments. Although it is important to note that for synthetic applications, the use of DMDO is preferable as the subsequent work-up and product purification is simplified substantially.

Accordingly, we began to consider other potential oxidants, many of the usual suspects were investigated without much success until *N*-sulfonyloxaziridines (Davis reagents)[67,68] were evaluated.[69,70] These strained three-membered ring compounds possess many of the same characteristics of dioxiranes but they have the added advantage of being relatively stable and storable in the freezer for many months. Gratifyingly, we found that either the phenyl- or 4-nitrophenyl-derivative **173** or **174(**NOTE: We ultimately settled on the use of the p-nitrophenyl substituted derivative as it is slightly more reactive**.)** effected the rearrangement of the same group of electron rich tetrahydrobenzimidazole

substrates as DMDO (Table 1, entries 1-4) but generally have used **174** because of its enhanced reactivity. For effective rates, these reactions required heating at 45-55 °C in either dichloromethane or chloroform for several hours, typically with two equivalents of the oxidant. Other solvents can be used, including acetonitrile and alcohols, which clearly adds value to the chemistry.

A further advantage of these reagents is their use in scouting and “NMR-tube” experiments useful for quickly establishing the viability of a particular transformation. While the rates were generally lower compared to DMDO, the chemical yields were similar for the simple tetrahydrobenzimidazoles; thus if a rearrangement occurs with a Davis reagent, it will also occur with DMDO.



173: X = H
174: X = NO_2

Figure 4.1: N-sulfonyloxaziridines

Initial experiments were performed using the N-Me and N-Bn THB-derivatives, systems that performed well in the DMDO version of the reactions. On treatment with **173**, both systems delivered the corresponding 5-imidazolone **128a-b** in excellent yield (Table 1, entries 1-2).

Interestingly, minor byproducts **129** and **130** were obtained which derive from the net [3+2] cycloaddition of the oxaziridine across the 4,5-bond of the imidazole reminiscent of the adducts described by Dmitrienko on reactions of indoles with oxaziridines[71] and bearing a resemblance to cycloadducts obtained by Yoon and coworkers through the copper- or iron-catalyzed addition of *N*-sulfonyloxaziridines to alkenes.[72-75] We also found that the non-substituted parent tetrahydrobenzimidazole **133** reacted with either oxaziridine giving rise to a pair of diastereomeric [3+2] addition products **135**/**136** and **137**/**138** (Table 1, entries 9-10). We were able to obtain an X-ray crystal structure on the major isomer **137** derived from the 4-nitrophenyl derivative which not only confirmed the connectivity but allowed us to assign the relative stereochemistry of it and by analogy the other related derivatives which have been prepared subsequently. We subjected all of the tetrahydrobenzimidazole derivatives we had in hand, including those obtained via DA chemistry, to reaction with oxaziridine **174** and determined the outcomes, which were similar in terms of isolated

products and selectivities to DMDO (Tables 1-2). The yields were sometimes lower, but this was attributed to purification issues being more challenging than with DMDO. A notable group of exceptions emerged with substrates containing an electron withdrawing nitrogen protecting group and either a 2-azido group or a 2-amino group that led to formation of unanticipated products on reaction with Davis reagents (Table 1). The only exception to this was the 2-amino-N-benzyl protected system **154** which underwent oxidative rearrangement on exposure to the 5-imidazolone **167** (Table 2, entry10), although to achieve this result, the reaction was conducted in methanol rather than the more usual chloroform. Encouragingly, this latter result points to the tolerance of the free NH_2 group which is pivotal in our total synthesis endeavors as this rearrangement can be employed in the end stages.

The first unexpected observation occurred when the MOM- or SEM-protected 2-azido-THB derivatives **151** and **152** were subjected to oxidation with Davis reagent, while reaction with DMDO delivered the anticipated imidazolones in modest to low yields, oxidation with **174** in chloroform led to a totally unexpected product in which a deep seated rearrangement and incorporation of ethanol was observed affording the tetrazoles **163** (Table 2, entry 5). X-ray crystallography unambiguously revealed the structure of the rearranged product as **163**. The source of

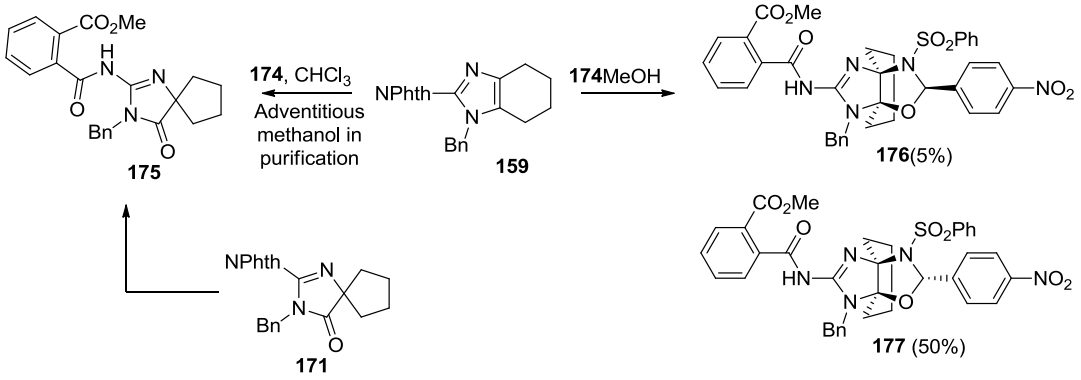
the EtOH was quickly identified as the stabilizing agent in the chloroform that was employed, we typically used HPLC grade solvent that was devoid of this stabilizer but in initial experiments “normal” chloroform was employed. When the reaction was performed in pure ethanol, the tetrazole rearrangement product was obtained in good yield as the only product. A similar outcome was observed with the SEM-protected congener affording tetrazole **165b** (Table 2, entry7)**;** this rearrangement was not limited to ethanol as when other alcohols were evaluated (methanol and isopropanol) similar tetrazoles **165a, 165c** were obtained (Table 2, entries 6,8).

One final set of products were obtained when the reaction of 2-amino derivatives **150** containing the DMAS-protecting group with Davis reagent **174** was explored (Table 2, entries 13-15). It was anticipated that these substrates would not participate in oxidative chemistry but surprisingly, these substrates underwent reaction in alcoholic solvents via oxidative addition-rearrangement wherein the oxygen of the nucleophilic solvent as well as the oxygen from the oxaziridine added across the 4,5-double bond of the imidazole to produce carbinolamines **170a-d**. X-ray structures were obtained on two of these derivatives **170a** and **170c** revealing both the relative stereochemistry of the two oxygen-containing substituents, in addition to the unexpected location of the DMAS group which was now on

nominally the C2-amino group (see Scheme 4.4 for putative mechanism – akin to the Dimroth rearrangement).

In addition to these unusual rearrangements, one interesting observation emerged during experiments with the N-benzyl-N'-phthaloyl substrate **159** in the presence of methanol (Scheme10). In initial rearrangement experiments performed in $CHCl_3$ we isolated an imidazolone product **175** resulting from methanolysis of the phthaloyl moiety – this was quite remarkable given that methanol had not been explicitly used in either the reaction or the purification (Scheme 4.2). Eventually, we tracked this down to contamination of the ethyl acetate used in chromatography with a small amount of methanol. Upon purification with unadulterated ethyl acetate the expected *N*-phthaloyl-protected imidazolone was obtained in 40% yield (Table 2, entry 17). Remarkably, when the reaction is conducted in pure methanol different products are obtained altogether, specifically two [3+2] adducts-methanolysis derivatives **176** and **177** were isolated of which one was produced in significant excess. The relative configuration of this material was assigned by analogy to the parent systems and the chemical shift of the C# signal in the ^{1}H NMR spectrum.

The regioselectivity of the cycloaddition was assigned on the basis of the isolation of only 5-imidazolones in these rearrangements, which indicated that oxygen transfer occurred to this position.

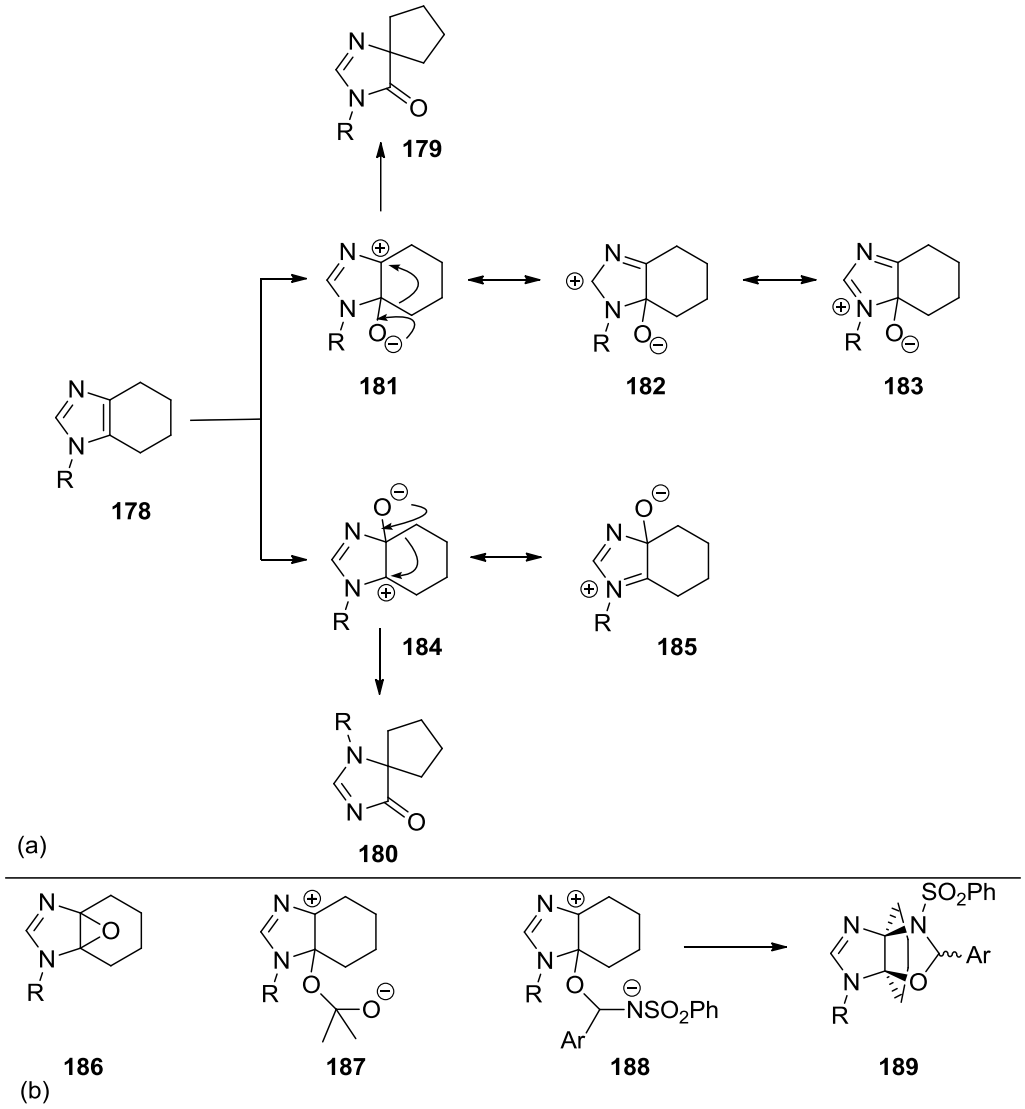


Scheme 4.2: Some alternative reaction pathways for N-phthaloyl-protected derivative 159

4.2 Mechanism

No detailed mechanistic or kinetic studies have been performed to elucidate the mechanisms of these reactions, but the general processes can be articulated on the basis of a pinacol type rearrangement in analogy to the rearrangements of N-acyl indoles.[76-78] Basically there are three outcomes of the reaction of DMDO or the *N*-sulfonyloxaziridine with imidazoles leading to the formation of a 5-imidazolone, a solvent-addition product or a [3+2] cycloaddition product. The formation of the 5-

imidazolone can be understood in terms of the participation of the zwitterionic intermediate **181** or **184** in a pinacol-like rearrangement (Scheme 4.3a). Whether this zwitterionic intermediate is formed directly or arises from other intermediates, e.g., **186-188** (Scheme 4.3b), is unclear and may in fact depend upon the identity of the substrate, the solvent and the nature of the oxidant. In the case of the oxaziridine, at least some portion of the reaction must proceed via an adduct related to **188** (Scheme 4.3b), which then can fragment to the zwitterion or undergo ring closure to produce the cycloadduct.



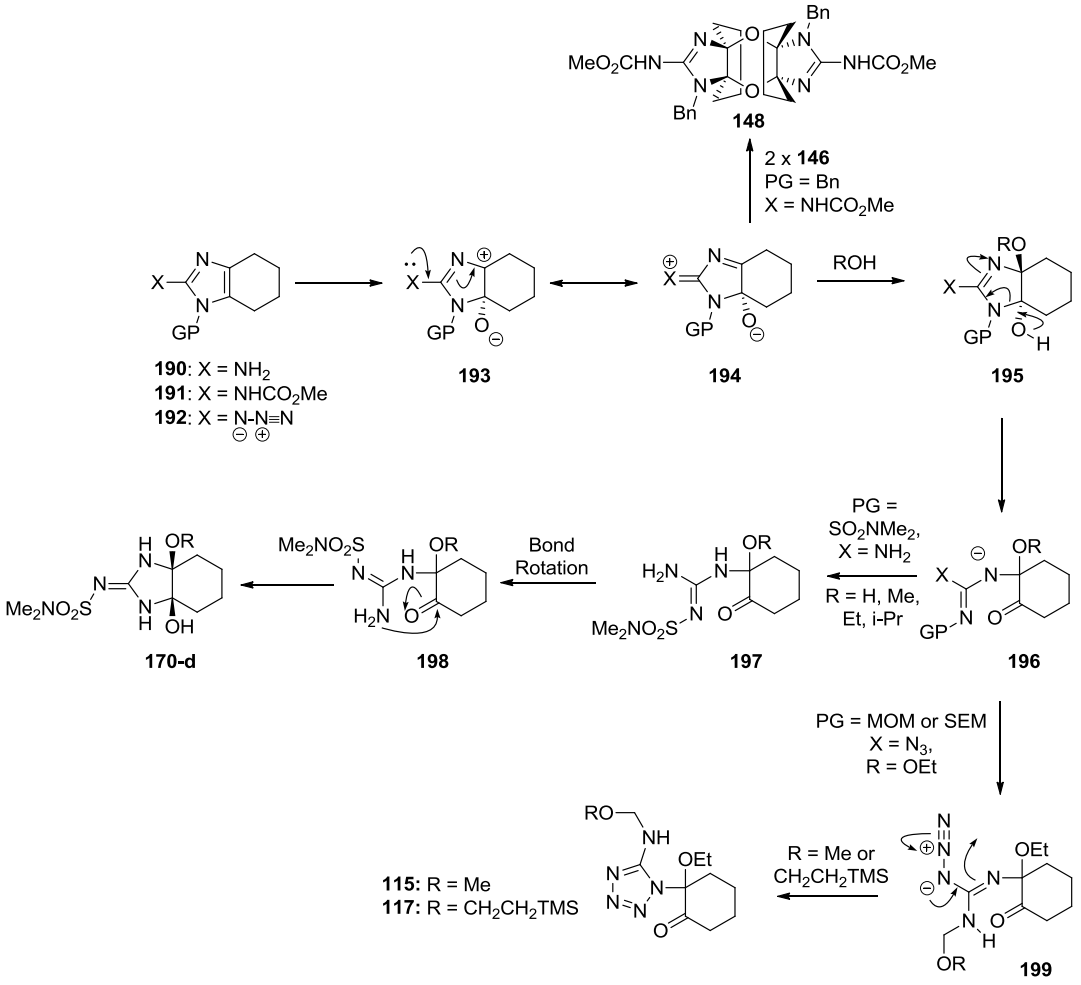
Scheme 4.3: Plausible mechanistic pathway for imidazolone formation

4.3 Outcomes

We have conducted well-over 30 examples of this oxidative rearrangement and, without exception, the 5-imidazolone is obtained as

the sole product.**(**NOTE: While the vast majority of examples that we have explored are derivatives of tetrahydrobenzimidazoles, we have explored the rearrangement of a few 4,5-dibenzyl substituted imidazoles; these too lead to the formation of the 5-imidazolones.**)** Clearly, without additional experimental support for a definitive mechanism the explanation of this selectivity has to be considered working hypothesis, but by analogy to the case of indoles, the formation of the zwitterionic species **181** and **184** is product determining (Scheme 4.3a). If the same driving force pertains in the rearrangement of imidazoles, then when the corresponding isomeric zwitterions **181** and **184** are compared, the one leading to the observed product is more stable. In the very simplest terms, more resonance structures can be drawn in the case of **181** than **184** and it is presumably this stability difference that leads to the observed selectivity. It is important to note that the participation of intermediates like the epoxide **186**, the alkoxide **187** (DMDO) or the carbinolamine **188** (Davis reagent) cannot be ruled out. In particular, adduct **188** is a presumptive adduct en route to the [3+2] adduct (the concerted addition of the oxaziridine to the π–bond cannot be ruled out)[71] and so direct rearrangement of this material may contribute to the formation of the imidazolone. Resubjection of **189** to the reaction conditions does not lead to the formation of an imidazolone and appears to constitute a dead end. The intermediacy of

these species **186-188** still mandates the formation of the same type of carbocations as in Scheme 4.3a and thus the same stabilizing factors are at play.



Scheme 4.4: Plausible mechanistic origins of addition-rearrangement products

4.4 Rearrangement vs addition:

The vast majority of substrates which undergo rearrangement are relatively electron rich, that is they either have an electron donating substituent or a weakly electron with drawing *N*-substituent, those with a more strongly electron withdrawing group do not undergo reaction. Presumably, the presence of electron donating groups favors stabilization of resonance structure **181**(and **184**) and the rearrangement pathway. However, there is a subset of substrates which contain a 2-amino group or a 2-azido group **and** an electron-withdrawing group on the imidazole nitrogen which undergo addition and in most cases rearrangement. It is not clear what the driving force behind this change is, but clearly there is a subtle interplay between the electronic characteristics of the two substituents that permits the initial oxygen transfer process to occur. Presumably the electron donating nature of the 2-substituent is sufficient to provide additional stabilization to the carbocation intermediate which then traps out water (or an alcohol). It should be noted that the azido group is a π–electron donor (σ_{p+} = -0.57) and thus even in this case stabilizes the incipient positive charge via resonance structure **194** (Scheme 4.4).[79] Presumably, in the case of the benzyl derivative the intermediate may be sufficiently long-lived to undergo dimerization and deliver compound **148**.

We hypothesize that nucleophilic attack occurs via axial addition leading to the formation of the *trans* adduct **194** (note when PG = Bn, X = $NHCO_2Me$ and R = H ≡ **145**); this intermediate is somewhat unstable in the case of the DMAS, MOM and SEM derivatives, which can fragment to **197** (after proton transfer) followed by bond rotation (**197**→**198**) and recyclization via the 2-amino nitrogen thus forming the observed addition products **170a-d** after proton transfer. This latter process bears a close resemblance to the classical Dimroth rearrangement.[80] In the case of the 2-azido compounds, the fragmented intermediate **199** undergoes recyclization via an electrocyclization pathway involving the azide, leading to the formation of the tetrazoles **163** and **165b** (Scheme 4.4). The initial fragmentation is favored by the electron withdrawing characteristics of these three nitrogen protecting groups, whereas this stabilization of the fragmented intermediate is not feasible when the nitrogen protecting group is benzyl and thus the reaction stops at this stage.

In summary, we have discovered a variety of methods for functionalizing tetrahydrobenzimidazoles oxidatively providing either oxidative rearrangement products (5-imidazolones) or net oxidative addition products (either [3+2] or electrophilic addition), the latter two pathways occurring predominantly with Davis oxaziridines that are practical and shelf stable compared to DMDO. Rearrangement tends to be favored by

electron rich tetrahydrobenzimidazoles whereas addition can result if the imidazole is protected with an electron withdrawing group and there is an electron donating group at C2. A third pathway involving solvent addition and rearrangement of the 2-azido moiety to form a tetrazole was observed. The first two of these pathways have potential applications in approaches to several alkaloids containing a 2-aminoimidazole fragment.

Chapter 5

Experimental Section

5.1 General Procedures

All reagents were purchased from commercial suppliers and used without purification unless otherwise specified. All reactions involving moisture sensitive reagents were conducted in flame-dried glassware under a dry nitrogen atmosphere. All solvents used in moisture sensitive reactions were purified by Innovative Technology's Pure-Solve solvent purification system.

NMR spectra were recorded on JEOL ECX 300 MHz and Eclipse+ 500 MHz spectrometers. ^{1}H NMR spectra were recorded in $CDCl_3$ (unless otherwise indicated) at a spectrometer frequency of 300.53 MHz or 500.13 MHz using residual $CHCl_3$ (δ = 7.26 ppm) as an internal reference. For spectra recorded in other solvents, residual MeOH (δ = 3.31 ppm) or DMSO (δ = 2.50 ppm) were used as internal references. 13C NMR spectra were recorded in $CDCl_3$ (unless otherwise indicated) at a spectrometer frequency of 75.57 MHz or 125.76 MHz using residual $CHCl_3$ (δ = 77.2 ppm) as an internal reference. For spectra recorded in other solvents, residual MeOH (δ = 39.5 ppm) or DMSO (δ = 49.0 ppm) were used as internal references.

Melting points were recorded on a Laboratory Devices Inc. Mel Temp apparatus and are uncorrected. Infrared (IR) spectra were obtained on a Bruker ALPHA FT-IR Spectrometer using neat samples (ATR spectroscopy); all absorptions are reported in cm^{-1}.

High resolution mass spectra (HRMS) were performed by the Shimadzu Center for Advanced Analytical Chemistry by electrospray ionization (ESI) unless otherwise indicated. All mass spectral data are reported as m/z (relative intensity).

Analytical thin layer chromatography (TLC) was performed on Sorbent Technologies Silica G TLC aluminum backed plates (200 μm thickness). Liquid chromatography was performed using Sorbent Technologies Standard Grade Silica Gel (230 x 400 mesh).

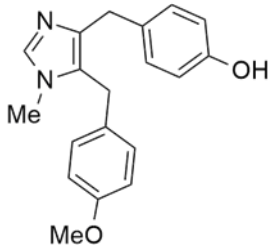
5.2 Synthesis

4,5-Diiodoimidazole (91) : was prepared starting from imidazole in 1 step following literature report.[81]

4,5-Diiodo -1-methyl -1H-Imidazole (107): was prepared starting from imidazole in 2 steps following literature report.[81]

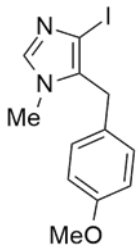
(4-Iodo-1-methyl-1H-imidazol-5-yl)(4-methoxyphenyl)methanol (109): was prepared starting from imidazole in 3 steps following literature report.

4-((5-(4-methoxybenzyl)-1-methyl-1H-imidazol-4-yl)methyl)phenol (105):



To a flame-dried RBF and stir bar was added 109 (2.50 g, 5.70 mmol) and dissolved in $CHCl_3$ (30 mL). Once mixture was partially dissolved TFA (3.90 g, 34.2 mmol, 2.62mL) was added followed by Et_3SiH (4.79 g, 28.5 mmol, 6.51 mL). The reaction was stirred at 50 °C for 48 h. The reaction was quenched with saturated $NaHCO_3$ (10 mL) 3x until gas evolution stopped. The mixture was filtered with vacuum filtration. The product was washed with DCM and H_2O. The organic layer was extracted, washed with saturated NaCl and dried with Na_2SO4. The solution was then filtered and evaporated under vacuum to dryness. The compound was a dark yellow solid (1.26 g, 72%). mp: 230-232 ˚C; ^{1}H NMR (DMSO-d_6): δ = 9.18 (s, 11H), 7.37 (s, 9H), 7.06 (d, J = 9.5 Hz, 13H), 6.80 – 6.72 (m, 77H), 6.59 (s, 15H), 3.29 (s, 31H). ^{13}C NMR: δ = 157.2, 155.5, 137.3, 136.4, 133.3, 129.3, 129.0, 128.9, 125.9, 115.1, 113.4, 54.9, 32.0, 31.1, 27.3; IR (neat, cm^{-1})3116, 2995, 2934, 2919, 2834, 2725, 2663, 2559, 1609, 1507, 1240, 1034

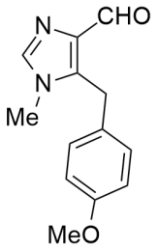
4-iodo-5-4(methoxybenzyl)-1-methyl-1*H*-imidazole (106):



To a flame dried RBF and stir bar was added 109 (12.5 g, 36.2 mmol) and dissolved in $CHCl_3$ (180 mL). Once mixture was partially dissolved TFA (24.9 g, 217 mmol, 16.7mL) was added followed by Et_3SiH (30.2 g, 181 mmol, 41.5 mL). The reaction was stirred at 50 °C for 48 h. The reaction was quenched with saturated $NaHCO_3$ (3x 30 mL) until gas evolution stopped. The mixture was filtered with vacuum filtration. The product was washed with DCM and H_2O. The organic layer was extracted, washed with saturated NaCl and dried with Na_2SO4. The solution was then filtered and evaporated under vacuum to dryness. The compound was a colorless solid (11.3 g, 95%). mp: 178-180 ˚C; ^{1}H NMR(DMSO-d_6): δ = 7.58 (s 1H), 7.17 (d, *J* = 9.5, 2H), 6.93 (d, *J* = 9.5, 2H), 6.22(d, *J* = 4.0, 1H), 5.80(d, *J* = 4.0, 1H), 3.72(s, 3H), 3.37(s, 3H); ^{13}C NMR: δ = 158.20, 141.32, 134.85, 133.79, 126.37, 113.64, 85.15, 65.92, 55.04, 32.59; IR (neat, cm^{-1}) = 3395, 3151, 3110, 3003, 2964, 2841, 1661, 1637, 1508, 1357, 1332, 1239. 1030.

5-(4-methoxybenzyl)-1-methyl-1H-imidazole-4-carbaldehyde (110):

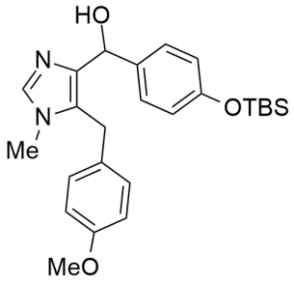
To a flame-dried RBF and stir bar was added 106 (8.75 g, 22.7 mmol) and



dissolved in THF (250 mL). EtMgBr (11.6 mL, 34.7 mmol) was added to the reaction and stirred at room temperature for 15 min. Next *N*-methylformanilide (4.68 g, 34.7 mmol, 4.28 mL) was added and stirred for 2 h. The reaction was quenched with half saturated NH_4Cl (30 mL). The aqueous layer was extracted with DCM until organic layer was colorless. The organic fractions were combined, washed with NaCl, and dried with Na_2SO_4. The product was then evaporated under vacuum to dryness. The product was then purified with column chromatography (Hexane/EtOAc 3:7). The compound was a pale yellow solid (5.27 mg, 86%). mp: 110-112 ˚C; ^{1}H NMR: δ = 9.99 (s, 1H), 7.41 (s, 1H), 7.04 (d, *J* = 10 Hz 2H), 6.70 (d *J* = 10 Hz, 2H), 4.32 (s, 2H), 3.73 (s, 3H) 3.45 (s, 3H) ^{13}C NMR: δ = 187.6, 158.6, 138.8, 138.3, 137.9, 129.4, 128.5, 114.4, 55.4, 31.6, 28.5; IR (neat, cm^{-1}) = 3107, 3024, 2957, 2911, 2888, 2838, 2818, 2771, 2741, 1739, 1667, 1550, 1509, 1278, 1237, 1231, 1021.

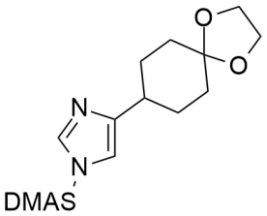
(4-((tert-butyldimethylsilyl)oxy)phenyl)(5-(4-methoxybenzyl)-1-methyl-1H-imidazol-4-yl)methanol (112):

To a flame dried 3 neck RBF, condenser, and stir bar was added Mg (833 mg) and THF (15 mL). A few drops of drops of **111** dissolved in THF (30 mL) was added to the mixture along with 1 to 2 crystals of I_2 and heated to 45 °C under nitrogen until the color of I_2 faded. Next, the remainder of the **111** (9.98 g) was added dropwise over 5 to 10 min and refluxed for 1 h. The solution was cooled to room temperature. Then 700 mg **110** was dissolved in THF (7 mL) and was added dropwise to reaction mixture and refluxed for overnight. The reaction was then cooled with an ice bath and ¾ saturated NH4Cl was added slowly. The aqueous solution was extracted with EtOAc (3X). The organic fractions were combined and dried with Na2SO4. The product was purified with column chromatography (hexane/EtOAc 1:9). The compound was a colorless solid (910 mg, 84%). mp: 110-112 ˚C; ^{1}H NMR: δ = 7.35 (s, 1H), 7.34 (d *J* = 8.5, 2H) , 7.32 (d, *J* = 6.5, 2H), 6.83 (d, *J* = 6.5, 2H), 6.82 (d, *J* = 8.5, 2H), 6.82 (s, 1H), 6.80 (s, 2H), 6.70 (s, 2H), 5.75 (s, 3H), 3.82, 3.76 (s, 9H), 0.96 (s, 6H),. ^{13}C NMR: δ = 157.28, 155.59, 137.38, 136.47, 133.34, 129.36, 129.03, 128.91, 125.93, 115.17, 113.42, 54.97, 32.09, 31.14, 27.30; IR (neat, cm^{-1}) =



3117, 3.57, 2996, 2949, 2928, 2896, 2856, 2833, 2715, 1604, 1582, 1505, 1469, 1242, 1053.

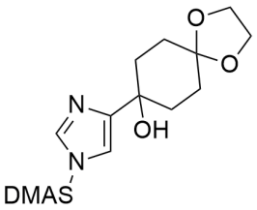
***N,N*-Dimethyl-4-(1,4-dioxaspiro[4.5]decan-8-yl)-1H-imidazole-1-sulfonamide (115):**



To a high-pressure reaction vessel was added N,N-dimethyl-4-(1,4-dioxaspiro[4.5]dec-7-en-8-yl)-1H-imidazole-1-sulfonamide (4.69 g, 15.0 mmol) and MeOH (100 mL). Then 10% Pd/C (1.59 g, 1.50 mmol) to the vessel and the vessel was sealed and purged 3x with H_2 (100 psi) and stirred for 4 h at rt. The mixtre was then filtered through Celite and the Celite was washed 2x with MeOH (50 mL). The solvent was removed via rotary evaporation and then placed under Hi-Vac. No further purification was required. The compound was a colorless solid (4.46 g, 94%). mp: 112-115 ˚C; ^{1}H NMR: δ 7.81 (d, J = 1.2 Hz, 1H), 7.07 (s, 1H), 6.48 (dt, J = 4.0, 2.5 Hz, 1H), 4.00 (s, 4H), 2.83 (s, 6H), 2.54 (ddt, J = 6.5, 4.4, 1.8 Hz, 2H), 2.47 – 2.44 (m, 2H), 1.90 (t, J = 6.6 Hz, 2H) = ^{13}C NMR: δ = 148.61, 136.21, 112.14, 108.57, 64.35, 38.28, 35.93, 34.40, 29.44; IR (neat, cm^{-1}) 3165, 3112, 2979, 2943, 2928, 2879, 1687, 1610, 1477, 1454, 1382, 1333, 1172, 1081, 950, 923, 846,

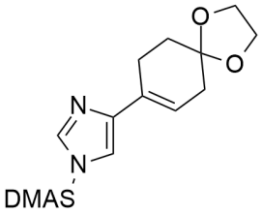
723, 598; HR-ESIMS (*m/z*): Calcd for $C_{13}H_{22}N_3O_4S$ $[M+H]^+$ 316.1327, found 316.1326.

4-(8-hydroxy-1,4-dioxaspiro[4.5]decan-8-yl)-*N,N*-dimethyl-1*H*-imidazole-1-sulfonamide (120):



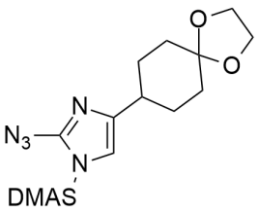
To a flame-dried round-bottom flask and stir bar was added 1-DMAS-4-iodoimidazole (12.12 g, 40.24 mmol) and dry DCM (130 mL) under argon. EtMgBr (3.0 M, 14.8 mL, 44 mmol) was added dropwise and stirred for 1 h. In a separate flame-dried round-bottom flask was added 1,4-Cyclohexanedione monoethylene ketal (6.92 g, 44.3 mmol) under argon and was dissolved in dry DCM (20 mL). This mixture was then added dropwise to the flask containing the imidazole Grignard and stirred overnight. The reaction mixture was quenched with half saturated NH_4Cl. The solutions were separated and the aqueous solution was extraxted 2x with DCM. The organic solutions were combined and dried with Na_2SO_4. The solvent was then removed by a rotary evaporator. The residue was then purified with flash chromatography using 3.5/3.5/3 hexanes/acetone/DCM. The compound was a colorless solid (6.57 g, 49%). mp: 119-121 ˚C

***N,N*-dimethyl-4-(1,4-dioxaspiro[4.5]dec-7-en-8-yl)-1H-imidazole-1-sulfonamide (121):**



To a round-bottom flask of toluene (30 mL) under nitrogen was added tosylic acid monohydrate (110 mg, 0.577 mmol) and was heated to reflux and held there overnight. In the morning 4-(8-hydroxy-1,4-dioxaspiro[4.5]decan-8-yl)-N,N-dimethyl-1H-imidazole-1-sulfonamide (1.91 g, 5.77 mmol) was added to the mixture and refluxed for 4 h. The mixture was removed from heat and the solvent removed via a rotary evaporator. The resulting residue was dissolved in EtOAc and washed 3x with saturated $NaHCO_3$, then with saturated NaCl, and then dried with Na_2SO_4. The sovent was removed by a rotary evaporator. The resulting residue was purified via flash chromatography 4:1 EtOAc/hexanes. The compound was a colorless solid (3.45 g, 81%). mp: 144-146 ˚C

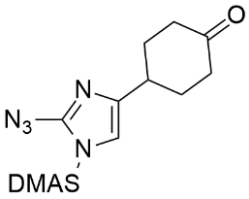
2-Azido-*N,N*-dimethyl-4-(1,4-dioxaspiro[4.5]decan-8-yl)-1H-imidazole-1-sulfonamide (122):



To a solution a N,N-dimethyl-4-(1,4-dioxaspiro[4.5]decan-8-yl)-1H-imidazole-1-sulfonamide (1.00 g, 3.17 mmol) under argon in dry THF (16.0 mL) at -78 °C was added *n*-BuLi (2.5 M, 1.39 mL, 3.49 mmol) solution (5.2 ml, 0.31

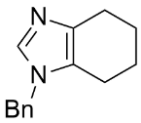
mmol) and stirred at -78 °C for 30 min. Next, TsN_3 (720 mg, 3.65 mmol) was added dropwise and stirred for 1 h. The mixture was then allowed to warm to 0 °C, then quenched with saturated NH_4Cl. The THF was removed by rotary evaporation and the aqueous mixture was extracted 3x with DCM. The organic solutions were combined, then wash with saturated NaCl and dried with Na_2SO_4. The solvent was removed by a rotary evaporator. The resulting residue was purified via flash chromatography 2:3 EtOAc/Hexanes.. The compound was a colorless solid (838 mg, 74%).

2-Azido-*N,N*-dimethyl-4-(4-oxocyclohexyl)-1H-imidazole-1-sulfonamide (123):



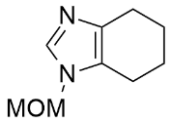
To a solution of 2-Azido-N,N-dimethyl-4-(1,4-dioxaspiro[4.5]decan-8-yl)-1H-imidazole-1-sulfonamide (770 mg, 2.16 mmol) dissolved in DCM (36.0 mL) was added $FeCl_3 \cdot 6H_2O$ (2.04 g, 7.56 mmol) and stirred at rt for 20 min. The reaction was quenched with saturated $NaHCO_3$ (10 mL). The two layers were separated and the aqueous solution was extracted 2x with DCM. The organic solutions were combined and washed with saturated NaCl, then dried with Na_2SO_4. The solvent was removed by a rotary evaporator. The resulting residue was purified via flash chromatography 3:2 EtOAc/Hexanes.. The compound was a yellow solid (386 mg, 57%). mp: 78-81 ˚C

1-Benzyl-4,5,6,7-tetrahydro-1H-benzimidazole (127b):



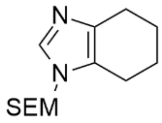
Sodium hydride (60% oil dispersion, 648 mg, 16.2 mmol, 1.1 equiv) was added in portions to a stirred solution of tetrahydrobenzimidazole (1.80 g, 14.7 mmol, 1 equiv) in dry DMF (30 mL) with cooling (ice/water). After 10 min, the reaction mixture was allowed to warm to rt and stirred for 1.5 h. The gray solution was then re-cooled (ice/water) and benzyl chloride (1.86 mL, 16.2 mmol, 1.1 equiv) was added dropwise. The reaction mixture was stirred overnight at rt and then quenched with a small amount of water. The solvent was removed by vacuum distillation. The residue was partitioned between water and EtOAc. The aqueous layer was extracted with EtOAc (2x). The organic extracts were dried (Na_2SO_4), and concentrated to give the solid product which was washed with hexanes to provide pure **127b** (2.71 g, 87%) as a colorless solid. m.p. 129-130 °C [Lit. 123.5-124 °C]. ^{1}H NMR: δ = 7.38 (s, 1H), 7.34-7.28 (m, 3H), 7.07-7.06 (m, 2H), 4.98 (s, 2H), 2.61-2.59 (m, 2H), 2.35-2.32 (m, 2H), 1.78-1.74 (m, 4H); ^{13}C NMR: δ = 137.3, 136.7, 135.5, 128.9, 127.9, 126.9, 125.8, 48.4, 24.5, 23.3, 23.0, 20.7; FT-IR (KBr, cm^{-1}): 2920, 2844, 1490; EI-MS (m/z): 213.6 (M^++1, 80%), 212.4 (M^+, 100%), 185.2 (64%), 183.7 (60%), 156.3 (11%), 91.2 (6%). Anal. Calcd. for $C_{14}H_{16}N_2$: C, 79.21; H, 7.60; N, 13.20. Found: C, 78.88; H, 7.53; N, 13.13.

1-(Methoxymethyl)-4,5,6,7-tetrahydro-1H-benzimidazole (127c):



Following the general procedure, tetrahydrobenzimidazole (2.00 g, 16.3 mmol, 1 equiv.) and chloromethyl methyl ether (1.40 mL, 18.4 mmol, 1.1 equiv.) provided **127c** (2.19 g, 81%) as a light brown solid. m.p. 75-76 °C. ^{1}H NMR: δ = 7.39 (s, 1H), 5.08 (s, 2H), 3.22 (s, 3H), 2.60-2.55 (m, 2H), 2.55-2.50 (m, 2H), 1.80-1.75 (m, 4H); ^{13}C NMR: δ = 137.7, 135.9, 125.7, 75.6, 55.7, 24.3, 23.3, 22.9, 20.4; FT-IR (neat, cm^{-1}): 2934, 2850, 1654, 1601, 1496, 1445, 1370, 1214, 1188, 1098, 1039, 921; EI-MS (m/z): 166.2 (M^{+}, 100%), 135.2 (26%), 123.1 (9%), 108.1 (26%), 94.1 (9%), 67.0 (7%), 52.9 (5%). Anal. Calcd. for $C_9H_{14}N_2O$: C, 65.03; H, 8.49; N, 16.85. Found: C, 64.96; H, 8.34; N, 16.72.

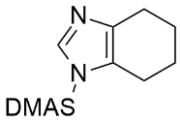
1-Trimethylsilylethoxymethyl-4,5,6,7-tetrahydro-1H-benzimidazole (127d):



Following the general procedure using tetrahydrobenzimidazole (2.00 g, 16.4 mmol) and SEMCl (3.50 mL, 19.7 mmol) provided **127d** (2.78 g, 71%) as a pale yellow oil after purification by chromatography (EtOAc/hexane, 3:7): ^{1}H NMR: δ = 7.43 (s, 1H), 5.13 (s, 2H), 3.46 (t, *J* = 8.2 Hz, 2 H), 2.60 (m, 4H), 1.80 (m, 4H), 0.89 (t, *J* = 8.2 Hz, 2 H), -0.03 (s, 9H); 13C NMR δ = 137.5, 135.8,

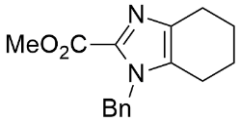
125.7, 73.8, 65.8, 24.3, 23.3, 22.9, 20.5, 17.7, -1.3; IR (neat, cm^{-1}): = 3374, 2931, 2853, 1680, 1494, 1447, 1248, 1090, 859, 836. HR-ESIMS: Calcd. for $C_{13}H_{24}N_2NaOSi$ $[M+Na]^+$ 275.1550, found 275.1549.

1-Dimethylsulfamoyl-4,5,6,7-tetrahydro-1H-benzimidazole (127e):



Following the general procedure, tetrahydrobenzimidazole (2.00 g, 16.3 mmol, 1 equiv) and dimethylsulfamoyl chloride (1.90 mL, 17.7 mmol, 1.1 equiv) provided **127e** as a colorless solid (2.44 g, 65%). m.p. 85-86 °C. ^{1}H NMR: δ = 7.75 (s, 1H), 2.85 (s, 6H), 2.72-2.69 (m, 2H), 2.59-2.55 (m, 2H), 1.82-1.74 (m, 4H); ^{13}C NMR: δ = 139.0, 136.3, 125.5, 38.1, 24.4, 22.9, 22.7, 22.2; FT-IR (KBr, cm^{-1}): 2928, 2859, 1594; EI-MS (*m/z*): 229.1 (M^+, 30%), 121.1 (60%), 108.0 (68%), 94.1 (74%), 67.0 (100%), 57.0 (96%), 53.0 (69%). Anal. Calcd. for $C_9H_{15}N_3O_2S$: C, 47.14; H, 6.59; N, 18.33. Found: C, 47.34; H, 6.64; N, 18.23.

1-Benzyl-4,5,6,7-tetrahydro-1H-benzimidazole-2-carboxylic acid methyl ester (139):

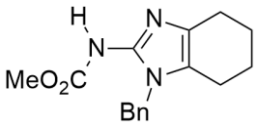


127b (300 mg, 1.41 mmol, 1 equiv.) and Et_3N (0.39 mL, 2.82 mmol, 2 equiv.) were dissolved in dry CH_3CN (1.5 mL). The mixture was cooled to –15 °C followed by careful addition of methyl chloroformate (freshly distilled, 0.22 mL, 2.82 mmol, 2 equiv.). The

reaction mixture was allowed to warm up to rt slowly and then stirred for 12 h. After re-cooling to –15 °C, Et_3N (0.39 mL, 2.82 mmol, 2 equiv.) and methyl chloroformate (distilled, 0.22 mL, 2.82 mmol, 2 equiv.) were added to the reaction mixture, which was then allowed to warm up to rt and stirred for additional 12 h. The same addition and stirring process was repeated three times. Water was added to the reaction and stirred for several hours, then extracted by EtOAc (3x). The organic extracts were dried, concentrated and purified by column chromatography (EtOAc) to provide the ester **139** (213 mg, 56%), unreacted **127b** (81 mg, 27%) and bisimidazolyl ketone (53 mg, 6%). Characterization data for ester **139**: A colorless solid. m.p. 134-135 °C. ^{1}H NMR: δ = 7.27-7.20 (m, 3H), 7.01-6.99 (m, 2H), 5.54 (s, 2H), 3.84 (s, 3H), 2.63-2.61 (m, 2H), 2.42-2.41 (m, 2H), 1.78-1.76 (m, 4H); ^{13}C NMR: δ = 159.8, 138.9, 136.6, 134.0, 132.7, 128.8, 127.6, 126.5, 52.1, 48.5, 24.4, 23.1, 22.6, 21.5; FT-IR (KBr, cm^{-1}): 2937, 1706, 1469, 1265, 1102; EI-MS (*m/z*): 270.2 (M^+, 8%), 91.1 (100%), 64.9 (45%), 55.0 (79%). Anal. Calcd. for $C_{16}H_{18}N_2O_2$: C, 71.09; H, 6.71; N, 10.36; Found: C, 71.03; H, 6.71; N, 10.34.

Bis(1-benzyl-4,5,6,7-tetrahydro-1H-benzimidazol-2-yl)methanone: A light-brown solid. m.p. 211–213 °C. ^{1}H NMR: δ = 7.27-7.19 (m, 3H), 7.10-7.08 (m, 2H), 5.51 (s, 2H), 2.73-2.71 (m, 2H), 2.41-2.39 (m, 2H), 1.78-1.75 (m, 4H); ^{13}C NMR: δ = 173.9, 142.2, 139.7, 136.9, 133.2, 128.7, 127.5, 126.9, 48.6, 24.8, 23.2, 22.6, 21.4; FT-IR (KBr, cm^{-1}): 3028, 2925, 2851, 1623, 1557, 1477, 1403, 1344, 1262, 1217, 1152, 1020, 934, 911, 790, 722, 710, 644; EI-MS (*m/z*): 449.9 (M+, 68%), 358.7 (93%), 210.6 (82%), 89.8 (100%).

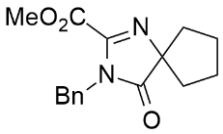
1-Benzyl-4,5,6,7-tetrahydro-1H-benzimidazol-2-yl-carbamic acid methyl ester (142):



The carbonyl azide **141** (150 mg, 0.53 mmol, 1 equiv.) was dissolved in anhydrous benzene (5 mL) and heated at 60 °C for 1 h. Anhydrous MeOH (2 mL) was added and the mixture was heated at reflux for 10 h. The solvent was removed and the crude oil was purified by chromatography (EtOAc/hexanes: 2/1) to provide the product **142** (129 mg, 85%) as a colorless solid and the methyl ester **139** (16 mg, 11%). m.p. 132 – 133.5 °C. ^{1}H NMR: δ = 10.80 (brs, 1H), 7.30–7.19 (m, 3H), 7.19-7.17 (m, 2H), 5.00 (s, 2H), 3.71 (s, 3H), 2.42–2.39 (m, 2H), 2.24–2.22 (m, 2H), 1.78–1.72 (m, 4H); ^{13}C NMR: δ = 164.2,

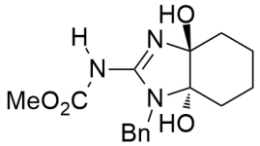
151.0, 136.6, 128.7, 127.7, 127.3, 120.5, 119.0, 52.3, 45.2, 22.2, 22.1, 20.8, 19.9; FT-IR (KBr, cm^{-1}): 2940, 2852, 1732, 1613, 1590; EI-MS (*m/z*): 285.3 (M^+, 44%), 253.2 (100%), 194.3 (30%), 162.2 (20%), 135.2 (12%), 91.1 (85%), 65.0 (20%), 59.0 (22%). Anal. Calcd. for $C_{10}H_{19}N_3O_2$: C, 67.35; H, 6.71; N, 14.73; Found: C, 67.13; H, 6.77; N, 14.62.

3-Benzyl-2-methoxycarbonyl-1,3-diazaspiro[4.4]non-1-en-4-one (144):



Following the general rearrangement procedure, ester **39** (200 mg, 0.74 mmol, 1 eq.) and DMDO (25 mL, 1.50 mmol, 2 equiv.) at rt for 6 h provided the product **144** (118 mg, 56%) as a colorless solid after purification though a short plug of silica gel (EtOAc). m.p. 56-59 °C. ^{1}H NMR: δ = 7.31-7.24 (m, 3H), 7.21-7.19 (m, 2H), 5.01 (s, 2H), 3.85 (s. 3H), 2.08-2.00 (m, 4H), 1.99-1.95 (m, 2H), 1.94-1.88 (m, 2H); ^{13}C NMR: δ = 185.9, 159.4, 151.3, 136.9, 128.8, 127.8, 127.6, 78.4, 53.5, 44.9, 37.7, 26.3; FT-IR (KBr, cm^{-1}): 3202, 3090, 2950, 1690, 1420, 1373, 1354, 1313, 1187; EI-MS (*m/z*): 286.3 (M^+, 46%), 257.3 (27%), 195.3 (30%), 153.3 (18%), 91.2 (100%), 65.1 (29%). Anal. Calcd. for $C_{16}H_{18}N_2O_3$: C, 67.12; H, 6.34; N, 9.78. Found: C, 67.06; H, 6.26; N, 9.97.

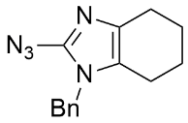
Methyl 2-(1-Benzyl-3a,7a-dihydroxy-3a,4,5,6,7,7a-hexahydro-1*H*-benzoimidazolyl)carbamate (145):



To a solution of carbamate **142** (60 mg, 0.21 mmol) in anhydrous CH_2Cl_2 (1.2 mL) at 0 °C was added DMDO (0.05 M, 3 mL, 0.15 mmol) dropwise and then stirred at 0 °C for 1 h. An additional amount of DMDO (0.05 M, 3 mL, 0.15 mmol) was added and then the reaction was allowed to warm up to rt within 1 h. The solvent was removed under vacuum (water bath <30 °C). The resulting crude sample was purified by PTLC (hexane/EtOAc: 1/1) to provide **145** (50 mg, 80%) and **146** (9 mg, 15%). Data for bis carbinolamine **145**: A colorless solid. ^{1}H NMR: δ = 8.20 (s, 1H), 7.38 (appr d, *J* = 7.1 Hz, 2H), 7.27-7.22 (m, 3H), 4.64 (d, *J* = 15.4 Hz, 1H), 4.46 (d, *J* = 15.4 Hz, 1H), 3.70 (s, 3H), 1.90-1.81 (m, 3H), 1.58-1.45 (m, 2H), 1.40-1.35 (m, 1H), 1.30-1.26 (m, 1H), 1.24-1.18 (m, 1H); ^{1}H NMR (DMSO-d_6): δ = 8.12 (s, 1H), 7.34 (appr d, *J* = 7.5 Hz, 2H), 7.28 (appr t, J = 7.5 Hz, 2H), 7.20 (appr t, J = 7.5 Hz,1H), 5.84 (brs, 1H), 5.74 (brs, 1H), 4.54 (d, *J* = 15.8 Hz, 1H), 4.19 (d, *J* = 15.8 Hz, 1H), 3.48 (s, 3H), 1.78-1.74 (m, 2H), 1.73-1.66 (m, 1H), 1.41-1.37 (m, 2H), 1.26-1.12 (m, 2H), 1.04-0.98 (m, 1H); ^{13}C NMR (DMSO-d_6): δ = 164.1, 161.4, 139.9, 128.6, 128.1, 127.2, 88.6, 86.4, 52.0, 42.4, 34.4, 33.4, 21.2, 20.6. FT-IR (KBr, cm^{-1}): 3353, 2947, 2866, 1655, 1593, 1255, 1194, 1105, 1050,; EI-MS (*m/z*): 301.1 (5%), 207.2 (100%), 176.1 (32%), 106.1 (61%),

91.0 (80%). Elemental Analysis: found: C, 58.79; H, 6.05; N, 12.57. Data for dimer #: A colorless solid. m.p. = 148-150 °C. ^{1}H NMR: δ = 9.56 (s, 1H), 7.43-7.41 (m, 2H), 7.29-7.21 (m, 8H), 4.99 (d, *J* = 16.0 Hz, 1H), 4.86 (d, *J* = 15.6 Hz, 1H), 4.40 (d, *J* = 15.6 Hz, 1H), 4.21 (d, *J* = 16.0 Hz, 1H), 3.79 (s, 3H), 3.78 (s, 3H). 2.10 (appr dt, *J* = 14.2, 4.8 Hz, 1H), 2.02 (dt, *J* = 14.2, 4.8 Hz, 1H), 1.91-1.78 (m, 4H), 1.73-1.64 (m, 3H), 1.58-1.51 (m, 2H), 1.48-1.43 (m, 1H), 1.38-1.28 (m, 3H), 1.11-1.06 (m, 2H), 0.77-0.69 (m, 1H); ^{13}C NMR: δ = 164.5, 162.0, 161.0, 156.6, 137.92, 137.89, 128.63, 128.56, 127.9, 127.7, 127.6, 127.4, 105.0, 98.8, 87.9, 79.6, 60.5, 53.2, 52.6, 44.3, 43.5, 34.7, 31.9, 28.7, 27.5, 19.4, 19.1, 15.6, 15.6, 15.1, 14.3. HR-MS (*m/z*): calcd. for $[M+H]^+$ $C_{32}H_{39}N_6O_6$ 603.2925, found 603.2916.

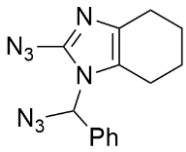
2-Azido-1-benzyl-4,5,6,7-tetrahydro-1H-benzimidazole (149):



n-BuLi (8 mL, 16 mmol, 2 M solution in cyclohexane) was added dropwise to a pre-cooled (-78 °C) solution of **127b** (3.15 g, 14.8 mmol) in anhydrous THF (60 mL) and the reaction mixture was allowed to stir for 1.5 h at that temperature. Tosyl azide (3.34 g, 17.0 mmol) was added at -78 °C to the resulting reaction mixture. The suspension was stirred for 2 h at -78 °C and gradually allowed to reach room temperature (cooling bath removed) and stirred for additional 2 h. Saturated aqueous solution of NH_4Cl was added to the reaction and

extracted with EtOAc (3x 50 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and the solvent was removed *in vacuo*. The residue was purified over silica gel using 20% EtOAc in hexanes to give **101** (2.27 g, 60%) as a colorless oil and **150** (1.17 g, 27%) resulting from lateral lithiation of the benzylic position. Characterization data for **149** ^{1}H NMR: δ = 7.32 (t, *J* = 7.3 Hz, 2H), 7.28 (d, *J* = 7.3 Hz, 1H), 7.08 (d, *J* = 7.3 Hz, 2H), 4.82 (s, 2H), 2.54 (m, 2H), 2.33 (m, 2H), 1.75 (m, 4H); ^{13}C NMR δ = 138.8, 136.5, 134.6, 128.9, 127.8, 126.8, 125.0, 46.2, 24.2, 23.3, 22.8, 20.8; IR (neat, cm^{-1}): 2932, 2851, 2132; HR-ESIMS: Calcd. for $C_{14}H_{16}N_5$ $[M+H]^+$ 254.1400, found 254.1399; Calcd. for $C_{14}H_{16}N_2$ $[M-N_3+H]^+$ 226.1339, found 226.1335.

2-azido-1-(azidophenylmethyl)-4,5,6,7-tetrahydro-1H-benzimidazole (**150**):

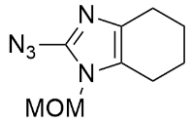


Dark brown solid: m.p. 90-93 °C; ^{1}H NMR δ = 7.37-7.32 (m, 3H), 7.25-7.21 (m , 2H), 6.72 (s, 1H), 2.52-2.49 (m, 2H), 2.37-2.28 (m, 1H), 1.75-1.57 (m, 5H); ^{13}C NMR: δ = 138.9, 136.0, 135.0, 129.1, 128.8, 126.1, 124.5, 70.9, 24.2, 22.9, 22.8, 21.8; DEPT (135): δ = 129.1 (CH), 128.8 (CH), 126.1 (CH), 70.7 (CH), 24.2 (CH_2), 22.9 (CH_2), 22.7 (CH_2), 21.8 (CH_2); IR (KBr, cm^{-1}) = 3317, 3051,

3030, 2934, 2852, 2147, 2103; HRMS (*m/z*): Calcd. for $C_{14}H_{15}N_8$ $[M+H]^+$ 295.1414, found 295.1414.

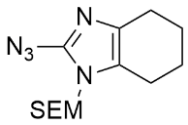
2-Azido-1-(methoxymethyl)-4,5,6,7-tetrahydro-1H-benzimidazole (151):

To MOM-protected tetrahydrobenzimidazole **127c** (670 mg, 4.03 mmol) in anhydrous THF (16 mL) at –78 °C was added n-BuLi (1.1 M solution in hexane, 4.03 mL, 4.43 mmol) and stirred at –78 °C for 20 min. A solution of TsN_3 (874 mg, 4.43 mmol) in anhydrous THF (8 mL) was added dropwise, and stirred for 30 min at –78 °C. Then the reaction temperature was allowed to warm up slowly to rt and quenched by careful addition of sat. NH_4Cl solution (40 mL). The aqueous layer was extracted with CH_2Cl_2 (3x). Combined organics were dried (Na_2SO_4) and concentrated. The crude oil was purified by chromatography (hexane/EtOAc: 2/5) to provide



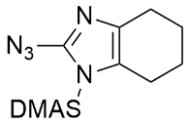
the title compound **151** (627 mg, 75%) as a colorless oil. ^1H NMR: δ = 4.87 (s, 2H), 3.19 (s, 3H), 2.45-2.41 (m, 4H), 1.77-1.68 (m, 4H); ^{13}C NMR: δ = 139.1, 134.8, 125.0, 73.0, 56.1, 24.0, 22.6, 23.2, 20.4; FT-IR (neat, cm^{-1}): 2941, 2853, 2156, 2132, 1612; HR-ESIMS (*m/z*): Calcd for $C_9H_{14}N_3O$ $[M-N_2+H]^+$ 180.1137, found 180.1089.

2-Azido-1-trimethylsilylethoxymethyl-4,5,6,7-tetrahydro-1*H*-benzimidazole (152):



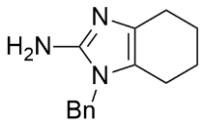
To a flame dried round-bottom flask under argon was added SEM-protected tetrahydrobenzimidazole **127d** (3.52 g, 14.0 mmol), dissolved with anhydrous THF (100 mL) and chilled to -78 °C. Next, *n-BuLi* (8.4 mL, 21 mmol, 2.5 M in hexanes) was added dropwise and stirred for 40 min at -78 °C. Then, tosyl azide (3.30 g, 16.4 mmol) was added dropwise at -78 °C and stirred for 40 min. The mixture was warmed to rt, then quenched with saturated NH_4Cl (20 mL). The aqueous and organic solutions were separated, and the aqueous solution was extracted (3x 20) with dichloromethane. The organic solutions were combined and the solvent was removed by rotary evaporation. The resulting mixture was purified using flash chromatography using 1:9 EtOAc/hexanes. The compound was a yellow oil (2.94 g, 72%). ^{1}H NMR: δ = 4.97 (s, 1H), 3.48 (t, *J* = 8.5, 2H), 2.51 (m, 4H), 1.76 (m, 4H), 0.89 (t, *J* = 8.5, 2H) -0.01 (s, 9H); ^{13}C NMR: δ = 139.0, 134.8, 125.1, 71.2, 66.1, 24.1, 23.3, 22.8, 21.6, 17.8, -1.30; IR (neat, cm^{-1}) 2935, 2895, 2854, 2142, 2121, 1268; HR-ESIMS (*m/z*): Calcd for $C_{13}H_{24}N_3OSi$ $[M-N_2+H]^+$ 266.1689, found 266.1687.

2-Azido-1-dimethylaminosulfonyl-4,5,6,7-tetrahydrobenzimidazole (153):



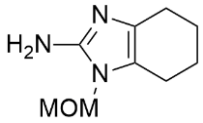
n-BuLi (7.3 mL, 11 mmol of 1.5 M solution in hexanes) was added dropwise to a pre-cooled (-78 °C) solution of **127e** (2.29 g, 10.0 mmol) in anhydrous THF (50 mL), followed by stirring for 1.5 h at that temperature. Tosyl azide (2.35 g, 12.0 mmol) was added in one portion at -78 °C to the reaction mixture. The suspension was stirred for 2 h at -78 °C and gradually allowed to reach room temperature and stirred for additional 2 h. The reaction mixture was quenched with dilute NH_4Cl (15 mL) and water (50 mL) was added, followed by extraction with CH_2Cl_2 (2x50 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* below 30 °C. The resulting crude residue was purified by column chromatography (hexane/ethyl acetate, 1:9) to yield **153** as a yellow solid (2.30 g, 85%): m.p. 101-103 °C; ^{1}H NMR δ = 2.97 (s, 6H), 2.71-2.69 (m, 2H), 2.50-2.48 (m, 2H), 1.78-1.76 (s, 4H), ^{13}C NMR: δ = 139.2, 135.0, 126.8, 38.4, 24.3, 23.4, 22.9, 22.5; IR (KBr, cm^{-1}): 2940, 2857, 2149, 1609; HR-ESIMS (*m/z*): Calcd for $C_9H_{15}N_6O_2S$ $[M+H]^+$ 271.0972, found 271.0972; Calcd for $C_9H_{15}N_4O_2S$ $[M+H-2N]^+$ 243.0910, found 243.0889.

2-Amino-1-benzyl-4,5,6,7-tetrahydro-1H-benzimidazole (154):



$NaBH_4$ (519 mg, 13.4 mmol, 2.1 equiv.) was added portionwise to a solution of **149** (1.62 g, 6.39 mmol, 1 equiv.) in anhydrous MeOH (50 mL) with cooling (ice/water). The mixture was stirred 10 min at the same temperature, at which time TLC analysis indicated the completion of the starting material. The reaction was quenched by adding saturated NH_4Cl (20 mL) and the aqueous layer was extracted with CH_2Cl_2 (3x30 mL), combined layer was dried (Na_2SO_4) and concentrated to isolate **154** (1.45 g, 100%) as a pale yellow solid: m.p. 134-137 °C; ^1H NMR: δ = 7.53- 7.26 (m, 3H), 7.10-7.08 (m, 2H), 4.84 (s, 2H), 3.77 (br, 2H), 2.49 (m, 2H), 2.37 (m, 2H), 1.80- 1.78 (m, 4H); ^{13}C NMR δ = 146.6, 136.7, 131.2, 129.1, 127.8, 126.4, 121.6, 45.9, 24.0, 23.5, 23.1, 20.7; IR (KBr, cm^{-1}): 3363, 3290, 3087 (brd) 2942, 2917, 2854, 1643; HR-ESIMS (*m/z*): Calcd for $C_{14}H_{18}N_3$ $[M+H]^+$ 228.1495, found 228.1511.

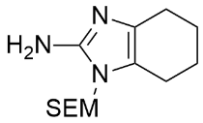
2-Amino-1-(methoxymethyl)-4,5,6,7-tetrahydro-1*H*-benzimidazole (155):



To azide **151** (625 mg, 3.02 mmol) in EtOH (30 mL) was added 5% Pd on barium sulfate (321 mg, 0.15 mmol, 5 mol%) and stirred at r.t. under a H_2 balloon overnight. The catalyst was filtered and the solvent was removed and further dried under high vacuum

to provide the title compound **155** (567 mg, 100%) as a dark-brown semi-solid, which was used without further purification. ^{1}H NMR: δ = 4.88 (s, 2H), 4.32 (brs, 2H), 3.21 (s, 3H), 2.37 (m, 4H), 1.74-1.68 (m, 4H); ^{13}C NMR: δ = 147.9, 131.3, 120.8, 73.5, 55.6, 23.9, 23.4, 23.0, 20.5. HR-ESIMS (*m/z*): Calcd for $C_9H_{15}N_3O$ $[M+H]^+$ 182.1288, found 182.1281.

2-Amino-1-trimethylsilylethoxymethyl-4,5,6,7-tetrahydro-1*H*-benzimidazole (156):

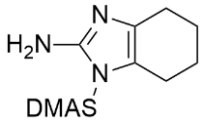


To a high-pressure reaction vessel was added 2-azido-1-trimethylsilylethoxymethyl-4,5,6,7-tetrahydro-1*H*-benzimidazole **152** (2.94 g, 10.0 mmol), Pd/C (10% by mass, 533 mg, 0.501 mmol), and methanol (100 mL). The vessel was flushed with H_2 4x, pressurized to 150 psi with H_2, heated to 100 °C, then stirred overnight. The next day the vessel was allowed to cool to rt and slowly depressurized. The solution was vacuum filtered through celite and washed 3x with methanol. The solvent was then removed by rotary evaporation to give the final product. The compound **156** was a thick, orange oil (2.64 g, 99%). ^{1}H NMR: δ = 4.95 (s, 2H), 4.10 (bs, 2H) 3.48 (t, *J* = 8.3 2H), 2.42 (m, 4H), 1.77 (m, 4H), 0.87 (t, *J* = 8.3 2H), -0.02 (s, 9H); ^{13}C NMR: δ = 147.7, 131.4, 120.9, 71.8, 65.7, 24.0, 23.5, 23.1, 20.7, 17.9, -1.3; IR (neat, cm^{-1})3380, 3305, 3149, 2950, 2920, 2896, 2850, 1674,

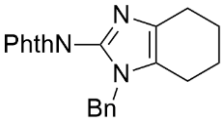
1550, 1229, 1062; HR-ESIMS (*m/*z): Calcd for $C_{13}H_{26}N_3OSi$ $[M+H]^+$ 268.1845, found 268.1800.

2-Amino-1-dimethylaminosulfonyl-4,5,6,7-tetrahydro-1H-benzimidazole (157):

Following the above procedure, $NaBH_4$ (204 mg, 5.27 mmol, 2.1 equiv.) and **153** (0.68 g, 2.51 mmol, 1 equiv.) were used to produce **157** (0.62 g, 100%) as a pale yellow solid: m.p. 192-195 °C; ^{1}H NMR: δ = 5.20 (br, 2H), 2.92 (s, 6H), 2.62-2.58 (m, 2H), 2.41-2.37 (m, 2H), 1.78-1.70 (m, 4H); ^{13}C NMR δ =148.2, 133.6, 120.3, 38.4, 24.2, 23.2, 23.0, 22.8; IR (neat, cm^{-1}): = 3423, 3282, 3122, 2932, 2855, 1638, 1562, 1454, 1377, 1185, 1163, 1055, 969, 724; HR-ESIMS (*m/z*): Calcd. for $C_9H_{17}N_4O_2S$ $[M+H]^+$ 248.1072, found 245.1062.

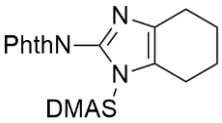


1-Benzyl-2-phthalimidoyl-4,5,6,7-tetrahydro-1H-benzimidazole (159):



The amine **154** (1.36 g, 6.0 mmol), potassium carbonate (1.65 g, 12.0 mmol) and the modified Nefkens' reagent **158** (2.97 g, 12.0 mmol) were added simultaneously to dichloromethane (75 mL) and the reaction mixture was allowed to stir at rt. for 24 h. The

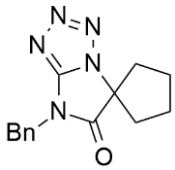
reaction mixture was washed with 10% $NaHCO_3$ solution and the organic layer was separated. The aqueous phase was further extracted with CH_2Cl_2 (25 mL). The combined organic extracts were washed with brine and dried (Na_2SO_4). The organic solution was concentrated by rotary evaporation and the residue was purified by column chromatography (hexane/ethyl acetate, 7:3) to obtain the product **111** (1.92 g, 90%) as a solid: m.p. 174-175 °C ; ^{1}H NMR: δ = 7.93-7.89 (dd, *J* = 3.0, 5.5 Hz, 2H), 7.80-7.75 (dd, *J* = 3.0, 5.5 Hz, 2H), 7.27-7.19 (m, 3H), 7.08-7.06 (m, 2H), 4.91 (s, 2H), 2.66 (m, 2H), 2.35 (m, 2,H), 1.80 (m, 4H); ^{13}C NMR δ = 166.9, 136.6, 135.5, 134.8, 131.6, 130.5, 128.9, 127.9, 127.7, 126.9, 124.2, 47.5, 24.2, 23.1, 22.8, 21.2; IR (neat, cm^{-1}): = 2933, 2850, 1731; HRESIMS: Calcd. for $C_{22}H_{20}N_3O_2$ $[M+H]^+$ 358.1550, found 358.1529.

2-Phthalimidoyl-1-dimethylaminosulfonyl-4,5,6,-7-tetrahydro-1H-benzlimidazole (160): 

Amine **157** (732 mg, 3.0 mmol), potassium carbonate (0.826 g, 6.0 mmol) and the modified Nefkens' reagent **158** (1.485 g, 6.0 mmol) (45 mL) were stirred in dichloromethane, following the above procedure to obtain the product **160** (1.12 g, 100%) as a pale yellow solid after the purification by column chromatography (hexane/ethyl acetate, 7:3): m.p. 197-200 °C; ^{1}H NMR: δ = 7.95 (dd, *J* = 3.0, 5.5 Hz, 2H, 2H), 7.81 (dd, *J* = 3.0, 5.5 Hz, 2H, 2H),

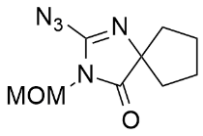
2.88 (s, 6H), 2.76 (m, 2H), 2.64 (m, 2H), 1.86 (m, 4H);); ^{13}C NMR δ = 166.8, 137.1, 134.9, 131.8,131.0, 128.4, 124.3, 38.1, 24.1, 22.9, 22.7, 22.5; IR (neat, cm^{-1}): 2941, 2856, 1735, 1721, 1526; HR-ESIMS (*m/z*): Calcd. for $C_{34}H_{36}N_8NaO_8S_2$ $[2M+Na]^+$ 771.1990, found 771.1919.

2-Azido-3-benzyl-1,3-diazaspiro[4.4]non-2-ene-4-one (161):



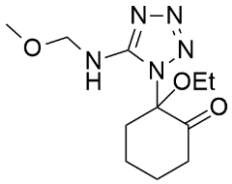
Oxaziridine **126** (765 mg, 2.50 mmol, 2.5 equiv.) was added to a solution of **149** (253 mg, 1.0 mmol) in $CHCl_3$ (15 mL) at room temperature. The reaction mixture was heated at 35 °C for 4 h, at which time TLC analysis indicated the completion of the reaction. The solvent was removed under vacuum at room temperature, and the residue was purified through a silica gel column (hexane/ethyl acetate, 8:2) to afford **161** (175 mg, 70%) as a pale yellow solid: m.p. 83-85 °C. ^{1}H NMR: δ = 7.46-7.44 (m, 2H), 7.36-7.25 (m, 3H), 4.97 (2H, s), 2.36-2.28 (m, 2H), 2.24-2.13 (m, 2H), 2.13-2.03 (m, 4H); ^{13}C NMR: 177.1, 156.7, 134.2, 129.2, 128.84, 128.80, 74.6, 45.6, 37, 6, 25.5; IR (KBr, cm^{-1}): = 2968, 2937, 1750, 1591, 1501, 1437, 1343, 1220, 1120, 747, 704, 627; HR-ESIMS (*m/z*): Calcd. for $C_{14}H_{16}N_5O$ $[M+H]^+$ 270.1349, found 270.1346.

2-Azido-3-methoxymethyl-1,3-diazaspiro[4.4]non-1-en-4-one (162):



Following the general rearrangement procedure, **151** (36 mg, 0.17 mmol, 1 equiv.) and DMDO (3.6 mL, 0.06 M, 0.22 mmol, 1.3 equiv.) in CH_2Cl_2 (0.8 mL) at 0 °C for 2 h provided the oily product **162** (15 mg, 40%) after chromatography (hexane/EtOAc: 3/1). ^{1}H NMR: δ = 5.22 (s, 2H), 3.45 (s, 3H), 2.37-2.32 (m, 2H), 2.24-2.13 (m, 4H), 2.11-2.06 (m, 2H); ^{13}C NMR: δ = 177.5, 156.3, 74.6, 72.8, 58.1, 37.8, 25.5; FT-IR (neat, cm^{-1}): 2968, 2883, 2156, 1780, 1594; HR-MS (*m/z*): calcd. for $[M+H]^+$ $C_9H_{14}N_5O_2$ 224.1142, found 224.1146.

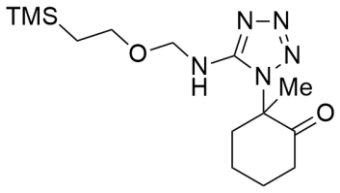
2-Ethoxy-2-(5-((methoxymethyl)amino)-1H-tetrazol-1-yl)cyclohexanone (163):



To a solution of 2-azido-1-(methoxymethyl)-4,5,6,7-tetrahydro-1*H*-benzimidazole **151** (50 mg, 0.24 mmol) dissolved in absolute ethanol (15 mL) was added *p*-nitrophenyloxaziridine **174** (148 mg, 0.482 mmol) and stirred at rt. The reaction progress was monitored by thin-layer chromatography. When no starting material was visible on the plate (4 h), the solvent was removed by rotary evaporation. The resulting mixture was purified by flash chromatography using 6.5:3.5 EtOAc/hexanes. The compound **115** was a colorless solid (29 mg, 45%). mp: 116-118 ˚C; ^{1}H NMR: δ = 5.52 (t, *J* = 6.9

Hz, 1H), 4.89 (dd, *J* = 7.1, 3.4 Hz, 2H), 3.75 (dq, *J* = 8.9, 7.0 Hz, 1H), 3.36 (s, 3H), 3.16 (dq, *J* = 8.9, 7.0 Hz, 1H), 2.88 (ddd, *J* = 13.5, 12.3, 6.1 Hz, 1H), 2.84 – 2.74 (m, 1H), 2.71 – 2.59 (m, 1H), 2.47 (dtd, *J* = 13.5, 4.3, 1.4 Hz, 1H), 2.16 – 2.04 (m, 1H), 2.01 – 1.93 (m, 1H), 1.92 – 1.70 (m, 2H), 1.25 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR: δ = 200.4, 156.1, 93.8, 76.2, 58.9, 56.1, 38.6, 33.3, 26.8, 20.7, 14.8; IR (neat, cm^{-1}) 3337, 2978, 2956, 2933, 2871, 2850, 1733, 1583, 1390, 1058, 1040; HR-ESIMS (*m/z*): Calcd for $C_{11}H_{19}N_5NaO_3$ $[M+Na]^+$ 292.1380, found 292.1167.

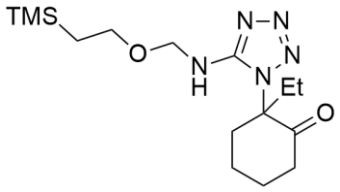
2-Methoxy-2-(5-(((2-(trimethylsilyl)ethoxy)methyl)amino)-1H-tetrazol-1-yl)cyclohexanone (165a):



To a solution 2-azido-1-trimethylsilylethoxymethyl-4,5,6,7-tetrahydro-1H-benzimidazole (60 mg, 0.20 mmol) dissolved in methanol (10 mL) was added *p*-nitrophenyloxaziridine (125 mg, 0.408 mmol) and stirred at rt. The reaction progress was monitored by thin-layer chromatography. When no starting material was visible on the plate (4 h), the solvent was removed by rotary evaporation. . The resulting mixture was purified by flash chromatography using a gradient starting at 3:7 EtOAc/hexanes then switching to 1:1 EtOAc/hexanes after removing the residual oxaziridine, then washed with NaOH(aq) to remove traces of

sulfonyl amide. The resulting compound was a pale yellow oil (40 mg, 69%). ^{1}H NMR: δ = 5.46 (t, *J* = 6.9 Hz, 1H), 4.92 (dd, *J* = 7.0, 1.3 Hz, 2H), 3.60 (qt, *J* = 9.5, 6.7 Hz, 2H), 3.26 (s, 3H), 2.83 (ddd, *J* = 13.4, 11.9, 6.0 Hz, 1H), 2.76 (dtd, *J* = 15.2, 4.6, 2.4 Hz, 1H), 2.68 (ddd, *J* = 15.3, 11.5, 4.0 Hz, 1H), 2.46 (dtd, *J* = 13.5, 4.4, 1.2 Hz, 1H), 2.13 – 2.04 (m, 1H), 1.99 (dt, *J* = 13.1, 4.0 Hz, 1H), 1.92 – 1.72 (m, 2H), 0.91 (ddd, *J* = 11.1, 6.1, 3.8 Hz, 2H), -0.04 (s, 9H); ^{13}C NMR: δ =200.2, 156.1, 93.8, 74.3, 65.7, 50.3, 38.6, 32.7, 26.8, 20.6, 18.0, -1.3; IR (neat, cm^{-1}) 3369, 2951, 2894, 2869, 1739, 1589, 1504, 1449, 1379, 1248, 1166, 1070, 1045, 858, 831; HR-ESIMS (*m/*z): Calcd for $C_{14}H_{27}N_5NaO_3Si$ [M+Na]$^{+}$ 364.1775, found 364.1784.

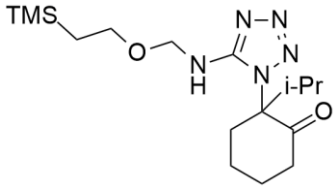
2-Ethoxy-2-(5-(((2-(trimethylsilyl)ethoxy)methyl)amino)-1H-tetrazol-1-yl)cyclohexanone (165b):



To a solution 2-azido-1-Trimethylsilylethoxymethyl-4,5,6,7-tetrahydro-1H-benzimidazole (60 mg, 0.20 mmol) dissolved in absolute ethanol (10 mL) was added *p*-nitrophenyloxaziridine (125 mg, 0.408 mmol) and stirred at rt. The reaction progress was monitored by thin-layer chromatography. When no starting material was visible on the plate (4 h), the solvent was removed by rotary evaporation. . The resulting mixture was purified by flash chromatography using 3:7 EtOAc/hexanes,

then washed with NaOH(aq) to remove traces of sulfonyl amide. The resulting compound was a pale yellow oil (38 mg, 63%). ^{1}H NMR: δ =5.44 (t, *J* = 6.9 Hz, 1H), 4.94 (d, *J* = 7.0 Hz, 2H), 3.74 (dq, *J* = 8.8, 7.0 Hz, 1H), 3.67 – 3.55 (m, 2H), 3.16 (dq, *J* = 8.8, 7.0 Hz, 1H), 2.88 (ddd, *J* = 13.4, 12.1, 6.1 Hz, 1H), 2.79 (dddd, *J* = 15.2, 4.6, 3.5, 2.5 Hz, 2H), 2.68 (ddd, *J* = 15.4, 11.8, 4.0 Hz, 1H), 2.47 (dtd, *J* = 13.5, 4.3, 1.3 Hz, 1H), 2.14 – 2.05 (m, 1H), 2.03 – 1.96 (m, 1H), 1.94 – 1.70 (m, 2H), 1.26 (t, *J* = 7.0 Hz, 3H), 0.92 (ddd, *J* = 9.1, 7.3, 1.6 Hz, 2H), -0.02 (s, 9H) ; ^{13}C NMR: δ = 200.3, 156.2, 93.7, 74.4, 65.8, 58.8, 38.6, 33.4, 26.8, 20.8, 18.1, 14.8, -1.3; IR (neat, cm^{-1}) 3379, 2952, 2895, 2871, 2247, 1738, 1590, 1508, 1447, 1395, 1378, 1249, 1164, 1070, 1040, 833, 728; HR-ESIMS (*m/*z): Calcd for $C_{15}H_{29}N_5O_3NaSi$ [M+Na]+ 378.1932, found 378.1940.

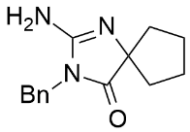
2-Isopropoxy-2-(5-(((2-(trimethylsilyl)ethoxy)methyl)amino)-1H-tetrazol-1-yl)cyclohexanone (165c):



To a solution 2-azido-1-trimethylsilylethoxymethyl-4,5,6,7-tetrahydro-1H-benzimidazole (50 mg, 0.17 mmol) dissolved in isopropanol (4 mL) was added *p*-nitrophenyloxaziridine (104 mg, 0.341 mmol) and stirred overnight at rt. The reaction progress was monitored by thin-layer chromatography. When no starting material was visible on the

plate, the solvent was removed by rotary evaporation. . The mixture was purified by flash chromatography using a gradient starting with 1:4 EtOAc/hexanes, with a gradual increase to 3:7 EtOAc/hexanes after the residual oxaziridine was removed, and then washed with NaOH(aq) to remove traces of sulfonyl amide. The resulting compound was a colorless solid (35 mg, 56%). m.p.: 113-116 °C; ^{1}H NMR: δ = 5.34 (t, *J* = 6.6 Hz, 1H), 4.93 (d, *J* = 6.9 Hz, 2H), 4.12 (dt, *J* = 12.2, 6.1 Hz, 1H), 3.66 – 3.58 (m, 2H), 3.05 – 2.68 (m, 3H), 2.44 – 2.37 (m, 1H), 2.21 – 1.99 (m, 2H), 1.96 – 1.70 (m, 3H), 1.30 (d, *J* = 6.1 Hz, 2H), 0.95 – 0.90 (t, *J* = 8.4 Hz, 2H), 0.89 (d, *J* = 6.1 Hz, 3H), -0.02 (s, 9H); ^{13}C NMR: δ = 200.3, 156.2, 93.7, 74.4, 65.8, 58.8, 38.6, 33.4, 26.8, 20.8, 18.1, 14.8, -1.3; IR (neat, cm^{-1}) 3379, 2952, 2895, 2871, 2247, 1738, 1590, 1508, 1447, 1395, 1378, 1249, 1164, 1070, 1040, 833, 728; HR-ESIMS (*m/z*): Calcd for $C_{16}H_{31}N_5NaO_3Si$ [M+Na]+ 392.2088, found 392.2081.

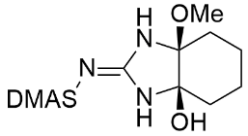
2-Amino-3-benzyl-1,3-diazaspiro[4.4]non-2-ene-4-one (167):



Oxaziridine **174** (522 mg, 2.00 mmol, 2 equiv.) was added to **154** (227 mg, 1.0 mmol) in MeOH (30 mL) followed by stirring at room temperature for 4 h. The solvent was removed by rotary evaporation and the residue was purified through a short plug of silica gel (EtOAc/Hexanes, 1:1→EtOAc→MeOH/EtOAc, 0.5:9.5) to isolate **167** (143

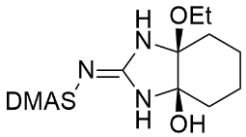
mg, 59%) as a pale yellow solid: m.p. 106-108 °C; ^{1}H NMR: δ = 7.35-7.32 (m, 2H), 7.30-7.28 (d, 1H), 7.27-7.23 (m, 2H), 4.70 (s, 2H), 4.65 (br, 2H), 2.10-2.05 (m, 2H), 1.90-1.73 (m, 6H); ^{13}C NMR δ = 181.2, 155.5, 135.5, 129.0,128.1, 127.2, 71.9, 42.7, 38.1, 25.6. IR (neat, cm^{-1}): = 3364, 3032, 2958, 1665, 1455, 1353, 1074, 754, 666; HR-ESIMS: Calcd. for $C_{14}H_{18}N_3O$ $[M+H]^+$ 244.1444, found 244.1463.

2-Dimethylaminosulfonylimino-3a-hydroxy-7a-



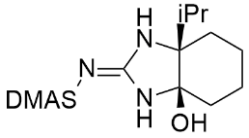
methoxyoctahydrobenzimidazole (170a): Oxaziridine **126** (615 mg, 2.00 mmol, 2.0 equiv.) was added to a stirred solution of **157** (245 mg, 1.0 mmol) in anhydrous MeOH (15 mL) at room temperature and it was stirred for 4 h. The solvent was removed *in vacuo* and the crude product was purified by a short plug of silica gel using (EtOAc/hexanes = 6/4) to provide a white solid which was recrystallized from dichloromethane to isolate **170a** as a colorless crystalline solid (198 mg, 68%): m.p. 149-151 °C; ^{1}H NMR (DMSO-d_6): δ = 8.16 (s, 1H), 7.71 (s, 1H), 5.51 (s, 1H), 3.19 (s, 3H), 2.53 (s, 6H), 2.05-1.93 (m, 2H), 1.53-1.17 (m, 6H); ^{13}C NMR: δ = 157.8, 89.0, 87.8, 50.1, 38.8, 36.9, 29.1, 21.2, 19.9; IR (KBr, cm^{-1}): 3463, 3350, 3251 (brd), 2956, 2866, 1611; HR-ESIMS (*m/z*): Calcd. for $C_{20}H_{40}N_8NaO_8S_2$ $[2M+Na]^+$ 607.2303, found 607.2286.

2-Dimethylaminosulfonylimino-3a-hydroxy-7a-ethoxyoctahydrobenzimidazole (170b):



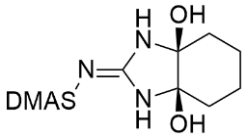
To 2-amino-1-dimethylaminosulfonyl-4,5,6,7-tetrahydrobenzimidazole **157** (244 mg, 1.00 mmol) was added *p*-nitrophenyloxaziridine (613 mg, 2.00 mmol) in EtOH (20 mL) and stirred at rt. The reaction progress was monitored by thin-layer chromatography (7:3 EtOAc/hexanes). When no starting material was visible on the plate (4 h), the solvent was removed by rotary evaporation. The resulting mixture was purified by flash chromatography using a gradient starting with 3:7 EtOAc/hexanes with a gradual increase to 7:3 EtOAc/hexanes after the residual oxaziridine was removed. The compound **170b** was a colorless solid (164 mg, 54%). mp: 122-125 ˚C; ^{1}H NMR (DMSO-d_6): δ = 8.11 (s, 1H), 7.71 (s, 1H), 5.35 (s, 1H), 3.53 (m, 1H), 3.45 (m, 1H), 2.53 (s, 6H), 1.94 (m, 2H), 1.50 (m, 2H), 1.42-1.15 (m, 4H), 1.03 (t, *J* = 6.7, 3H); ^{13}C NMR (DMSO-d_6): δ = 157.3, 88.4, 87.2, 57.3, 38.2, 36.1, 29.3, 20.5, 19.3, 15.7; IR (neat, cm^{-1}) 3436, 3359, 3167, 2951, 2869, 2836, 1598, 1465, 1146, 1039; HR-ESIMS (*m/*z): Calcd for $C_{11}H_{22}N_4NaO_4S$ $[M+Na]^+$ 307.1435, found 307.1430.

2-Dimethylaminosulfonylimino-3a-hydroxy-7a-isopropoxyoctahydrobenzimidazole (170c):



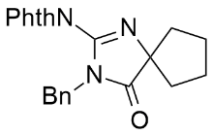
To 2-amino-1-dimethylaminosulfonyl-4,5,6,7-tetrahydrobenzimidazole **157** (500 mg, 2.05 mmol) was added *p*-nitrophenyloxaziridine (1.25 g, 4.09 mmol) in *i*-PrOH (50 mL) and stirred at rt. The reaction progress was monitored by thin-layer chromatography (7:3 EtOAc/hexanes). When no starting material was visible on the plate (4 h) the solvent was removed by rotary evaporation. The resulting mixture was purified by flash chromatography using a gradient starting with 3:7 EtOAc/hexanes with a gradual increase to 7:3 EtOAc/hexanes after the residual oxaziridine was removed. The compound **170c** was a colorless solid (260 mg, 40%). mp: 131-133 ˚C; ^{1}H NMR (DMSO-d_6): δ = 8.18 (s, 1H), 7.70 (s, 1H), 5.15 (s, 1H), 4.04 (sep, *J* = 6.3 Hz, 1H), 2.55 (s, 6H), 2.06-2.03 (m, 1H), 1.96-1.92 (m, 1H), 1.54-1.16 (m, 6H), 1.90 (d, *J* = 4.0 Hz, 3H), 1.08 (d, *J* = 4.0 Hz, 3H); ^{13}C NMR (DMSO-d_6): δ = 157.3, 88.4, 87.5, 64.4, 35.6, 29.9, 24.5, 24.3, 20.6, 19.5; IR (neat, cm^{-1}) 3448, 3411, 3366, 3329, 3185, 2965, 2950, 2873, 1607, 1453, 1143, 866, 595; HR-ESIMS (*m/z*): Calcd for $C_{12}H_{24}N_4NaO_4S$ $[M+Na]^+$ 343.1410, found 343.1401.

2-Dimethylaminosulfonylimino-3a,7a-



dihydroxyhexahydrobenzimidazole (170d): Oxaziridine **-173/174** (366 mg, 1.2 mmol, 1.1 equiv.) was added to a stirred solution of **157** (270 mg, 1.1 mmol) in an acetone-water (2:1) mixture (15 mL) followed by stirring for 2 h. The solvent was removed *in vacuo* and the crude product was purified by a short plug of silica gel using (acetone/hexanes = 3/7) to isolate a white solid, which was recrystallized using a methanol-acetone mixture to give **170d** as a colorless crystalline solid (199 mg, 65%): m.p. =100-103 °C; ^{1}H NMR (DMSO-d_6): δ = 7.60 (s, 2H), 5.61 (s, 2H), 2.52 (s, 6H), 1.80-1.55 (m, 4H), 1.40-1.20 (m, 4H); ^{13}C NMR: δ = 157.9, 86.5, 38.8, 34.3, 20.8; IR (KBr, cm^{-1}) = 3417, 3364, 3348, 3258, 2942, 2868, 1611, 1465, 1298, 1202, 1146, 1049, 953, 874,859, 717 ; HR-ESIMS (*m/z*): Calcd for $C_9H_{19}N_4O_4S$ $[M+H]^+$, 279.1121, found 279.1135; Calcd for $C_9H_{18}N_4NaO_4S$ $[M+Na]^+$ 301.0940, found 301.0949.

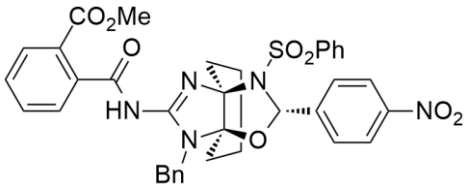
2-Phthalimidoyl-3-benzyl-1,3-diazaspiro[4.4]non-2-ene-4-one (171):



To a solution of 1-benzyl-2-phthalimidoyl-4,5,6,7-tetrahydro-1*H*-benzimidazole (50 mg, 0.14 mmol) dissolved in dichloromethane (2.0 mL) was added DMDO solution in acetone (4.7 mL, 0.28 mmol) and stirred at rt. Consumption of starting

material was monitored via thin-layer chromatography. After 30 minutes starting material was still visible, so an additional portion of DMDO (2.3 ml, 0.14 mmol) was added to the solution. The reaction mixture was checked 30 min later, visualizing complete consumption of starting material consumption. The solvent was removed rotary evaporation. The resulting mixture was purified via flash chromatography 45:55 EtOAc/Hexanes. The compound was a colorless solid (31 mg, 60%). Alternatively, oxaziridine **174** (1.11 g, 3.64 mmol, 2 equiv.) was added to a stirred solution of **159** (651 mg, 1.8 mmol) in anhydrous chloroform (27 mL) at 40 °C, and it was stirred for 12 h. The solvent was removed *in vacuo* and the crude product was purified by a short plug of silica gel using (EtOAc/Hexanes = 15/85) to provide **171** as a pale yellow solid (269 mg, 40%): m.p. 159.5-162.5 ˚C; ^{1}H NMR: δ = 7.83-7.79 (m, 2H), 7.79-7.75 (m, 2H), 7.08-7.04 (m, 3H), 7.98-7.95 (m, 2H), 4.68 (s, 2H), 2.19-2.16 (m, 2H), 2.04-2.01 (m, 6H); ^{13}C NMR: δ = 184.4, 164.5, 146.5, 135.0, 131.3, 128.8, 127.9, 127.0, 124.3, 79.0, 44.3, 37.8, 26.0; IR (neat, cm^{-1}) = 2965, 1733, 1635; HRMS (*m/z*): Calcd. for $C_{22}H_{20}N_3O_3$ $[M+H]^+$ 374.1491, found 374.1491.

(1*R,6*S**,8*R**)- and (1*R**,6*S**,8*S**)-*N*-[9-Benzenesulfonyl-12-benzyl-8-(4-nitrophenyl)-7-oxa-9,10,12-triaza-tricyclo[4.3.3.0]dodec-10-en-11-yl]phthalamic acid methyl ester (176) and (177):**



Oxaziridine **174**(320 mg, 1.04 mmol, 2 equiv) was added to **159** (187 mg, 0.5 mmol) in MeOH (8 mL) followed by stirring at 40 °C for 17 h. The solvent was removed by rotary evaporation and the residue was purified through a short plug of silica gel (EtOAc/Hexanes, 1:4) providing two diastereomeric products. Minor Adduct **176**, pale yellow solid (22 mg, 6%): m.p. 90-93 °C; ^{1}H NMR: δ = 9.72 (s, 1H), 8.05 (m, 1H), 7.93 (m, 1H), 7.84 (d, *J* = 8.8 Hz, 2H), 7.57-7.39 (m, 8H), 7.34 (m, 2H), 7.27-7.28 (m, 4H), 6.18 (s, 1H), 4.64 (d, *J* = 15.1 Hz, 1H), 4.09 (d, *J* = 15.1 Hz, 1H), 3.88 (s, 3H), 2.81 (m, 1H), 2.14 (m, 1H), 1.89-1.84 (m, 1H), 1.66-1.49 (m, 3H), 1.38 (m, 2H); ^{13}C NMR: δ = 178.7, 170.5, 160.1, 148.2, 142.2, 140.4, 137.8, 137.6, 133.8, 133.2, 130.6, 130.1, 129.8, 129.2, 129.0, 128.7, 128.6, 127.9,127.2, 126.5, 123.2, 98.4, 89.6, 82.9, 52.6, 43.7, 30.9, 30.4, 18.3, 17.3; IR (neat, cm^{-1}): 3335 (brd), 3064, 2951, 2852, 1729, 1614, 1561; HR-ESIMS (*m/z*): Calcd. for $C_{36}H_{34}N_5O_8S$ $[M+H]^+$ 696.2122, found 696.2114. Major adduct **177** as a pale yellow solid (182 mg, 50%): m.p. 79-82 °C; ^{1}H NMR: δ = 9.24 (s, 1H), 8.33 (d, *J* = 8.8 Hz, 2H), 8.13 (d, *J* = 8.3 Hz, 2H), 8.00 (d, *J* = 8.8 Hz, 2H), 7.91-7.76 (m, 4H), 7.71-7.53 (m, 4H), 7.51-7.47 (m, 4H), 7.47 (d, *J* = 7.2 Hz, 2H), 7.05 (s, 1H), 4.92 (d, *J* = 15.1 Hz, 1H), 4.60 (d, *J* = 15.1 Hz, 1H), 4.06 (s, 3H), 2.48-2.41 (m, 1H), 2.28-2.23 (m, 1H), 1.92-1.80 (m, 2H),

1.66-1.14 (m, 4H); ^{13}C NMR: δ = 178.4, 170.3, 159.8, 148.1, 144.6, 141.1, 137.9, 137.2, 133.9, 133.3, 130.5, 130.0, 129.8, 129.5, 128.8, 128.5, 127.8, 127.7, 127.1, 126.9, 123.5, 98.7, 90.2, 84.3, 52.4, 42.8, 28.2, 25.0, 15.3, 14.1 ; IR (neat, cm^{-1}): 3335 (brd), 3054, 2951, 2836, 1729, 1601, 1561; HR-ESIMS (*m/z*): Calcd. for $C_{36}H_{34}N_5O_8S$ [M+H]+ 696.2122, found 696.2120.

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