APPLICATION OF THE PUMMERER REACTION IN A STUDY DIRECTED
TOWARD THE TOTAL SYNTHESIS OF DIBROMOPALAU’AMINE

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by
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ABSTRACT

The utility of the imidazole-based Pummerer cyclization reaction for the construction of the pentacyclic core of the marine alkaloid dibromopalau’amine is discussed. The polycyclic bisguanidine natural product palau’amine exhibits remarkable biological activity including its immunosuppression at IC_{50} < 18 ng/mL in a mixed lymphocyte assay. However, the molecule’s unusual and highly strained 5,5-trans fused azabicyclo[3.3.0]octane ring system has been a major challenge in wide-reaching attempts for its total synthesis. The assembly of the pentacyclic core of dibromopalau'amine employing the Pummerer oxidative cyclization initiated by PhI(CN)OTf and a subsequent photochemical Wolff rearrangement (ring contraction) sequences is reported.
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Chapter 1

Palau’amine and Pyrrole-Imidazole Alkaloids

1.1 Introduction to Pyrrole-Imidazole Alkaloids

Marine sponges are a rich source of diverse natural products\(^1,2\) with more than 3300\(^3\) secondary metabolites reported to date. Among these species are the pyrrole-imidazole (P-I) alkaloids whose number is growing every year. The isolation of the first P-I natural product, oroidin (1),\(^4\) from the sponge *Agelas oroides* in 1971 marked the beginning of the discovery of a large number of structurally novel and biologically active P-I alkaloids (Figure 1.1). Hundreds of these P-I natural products now have been identified; some with simple structures, such as oroidin (1), hyminidin (2), sventrin (3), and keramadine (4), and others featuring complex and novel backbones, such as the phakellin alkaloids (8 - 10), the axinellamines (11), palau’amine (12 - 14),\(^5,6\) konbu’acidin (15)\(^7\) and the styloguanidines (16 - 18).\(^8,9\) These metabolites are thought to provide the sponges that produce them with defense against predators.\(^10-12\)
Figure 1. Some examples of P-I alkaloids.

Oroidin (1) and its analogs are believed to serve as precursors for the more complex monomeric, dimeric and higher-order P-I sponge alkaloids. On the topic of the origin of 1 itself, Al-Mourabit and Travert have proposed a possible biosynthetic pathway involving the coupling of proline and guanidine (Figure 1.2). In this proposed pathway,
two equivalents of proline and one equivalent of guanidine are coupled in a peptide
synthesis reaction to give 21. This sequence is followed by oxidation of one of the proline
units in step 1 to a pyrrole (22) and oxidative rearrangement of the proline-guanidine
moiety in step 2 to give 2-aminoimidazole 23.

In order to validate the viability of their proposed work, Al-Mourabit and Travert
have shown that step 2 does furnish 2-aminoimidazoles under oxidative conditions
(requiring aerobic media) (26 \(\rightarrow\) 27 and 28, Figure 1.3). Note that under anaerobic
conditions, the reaction did not deliver 27 and 28, indicating the involvement of an
oxidative transformation. Compounds 27 and 28 were subsequently converted to the
natural product dispacamide A (30) by bromination of the pyrrole unit (Br\(_2\), AcOH),
deprotection of the Boc groups and then acid-mediated dehydration. These observations
have led Al-Mourabit and Travert to speculate not only that oroidin (1) is synthesized via
proline-guanidine coupling but also that dispacamide A (30) may be a precursor for the
biosynthesis of 1 itself.\(^\text{10}\)
Figure 1.3. Synthesis of dispacamide A via oxidative rearrangement a proline-guanidine system.

Some of the less complex P-I marine alkaloids trace their origin to simple dimerization (and isomerization) of oroidin (1) and its derivatives. For instance, sceptrin (5) and dibromosceptrin (6) are formal [2+2] adducts of two hymnidine (2) units and two oroidin (1) units, respectively, while ageliferin (7) is a formal [4+2] cyclization product of two hymnidine (2) molecules (Figure 1.4). On the other hand, the more complex molecules of this family of marine alkaloids pose significant challenges both in understanding their biosynthesis and also in designing a chemical synthesis due to their non-trivial structures and dimerization patterns. Palau’amine (12) and its congeners fall into this category. Many attempts at the biomimetic (and chemical) total syntheses of these natural products have met unresolved obstacles.
1.2 Introduction to Palau’amine and Congeners

Palau’amine (12)\(^5\) (Figure 1.5) was first isolated by Scheuer and coworkers in 1993 from the sponge *Stylorella agminata*, collected near the islands of Palau. The compound was found to occur along with the known alkaloids sceptrin (5), hymnidine (2), oroidin (1), dibromophakellin (9) as well as mono- and dibrominated derivates of the parent compound (13 and 14, Figure 1.1). This bis-guanidine, hexacyclic P-I alkaloid and its congeners contain at least nine nitrogen atoms, eight contiguous stereogenic centers and reactive (hemi)-aminal functional groups. Palau’amine and congeners also contains a 5,5-*trans-* ring fused system which is unique to this family of natural products. The molecule is extremely polar and sensitive to basic conditions but it was found to be stable in acidic media.\(^5\) Palau’amine exhibits remarkable biological activity including its...
immunosuppression (IC$_{50}$ < 18 ng/mL in mixed lymphocyte assay). The molecule also was found to be relatively nontoxic (LD$_{50}$ 13 mg/kg (i.p. mice). With the exception of a recent report by Baran and coworkers,$^{13}$ the total synthesis of palau’amine has remained elusive presumably due to challenges posed by its daunting structural features.

![Figure 1.5. Palau’amine – original and revised structures.](image)

### 1.3 Palau’amine Structural Revision

NMR analysis, computational calculations and comparison of the palau’amine framework to related marine alkaloids (styloguanidines, 16 – 18, Figure 1.1), has led at least three different research groups$^{9,14,15}$ to question the validity of the original stereochemical assignment by Scheuer and Kinnel. These data suggest that the endo-disposed C17 chloro group and the C12 cis-fused ring junction in the originally proposed structure 31 instead exist as its C12, C17 epimers (Figure 1.5).

Palau’amine contains a very rare trans-fused azabicyclo[3.3.0]-octane skeleton. The original structure of palau’amine proposed by Scheuer and Kinnel featured a 5,5-cis fused ring system. The cis stereochemistry at the ring junction was assigned based on the coupling constant between H11 and H12 (palau’amine numbering, see Figure 1.5), which
was found to be 14.1 Hz. The authors compared this coupling constant to the spirolactone leucodrine (32)\textsuperscript{16} (Figure 1.6) where the H4/H3 \textit{cis} protons were assigned a coupling constant of 12.4 Hz. Note that the 12.4 Hz coupling constant in 32 was assigned for the \textit{cis} H4/H3 because the known \textit{trans} H8/H9 pair had a coupling constant of 8.3 Hz. By analogy, the \textit{trans} disposed H4/H3’ pair were assigned the lowest coupling constant of 7.8 Hz. At the time, Scheuer and coworkers acknowledged that the 14.1 Hz coupling constant was too high, although due to lack of any further information the assignment was let to stand.

Figure 1.6. Leucodrine; the reference molecule used to assign the H11-H12 \textit{cis} stereochemistry in palau’amine by Scheuer and Kinnel.

The \textit{cis} stereochemistry between H11 and H12 in palau’amine (31) was accepted for more than a decade until it came into question as a result of the characterization of palau’amine congeners dibromostyloguanidine (18)\textsuperscript{14} and konu’acidin B (15).\textsuperscript{15} In these newly characterized natural products, the C17 and C12 configurations are inverted from the original palau’amine structure, thus giving the \textit{trans} configuration for the H11/H12 relative stereochemistry. Computational studies by Grube and Köck\textsuperscript{14} have suggested that the coupling constant between H11/H12 protons amounts to 13.1 Hz for a \textit{trans}
relationship, but the *cis* configuration would be 1.5 Hz lower. Given the 14.1 – 14.5 Hz coupling constants observed for palau’amine and congeners, Baran and coworkers and others have concluded that the observed coupling constants arise from the *trans* configuration.\(^\text{17}\)

1.4 Biosynthetic Consideration for Palau’amine and Congeners

1.4.1 Scheuer et al. Biosynthetic Proposal to Palau’amine

The earliest hypothesis for the biogenesis of palau’amine (31) was proposed by Scheuer and Kinnel in 1998 (Figure 1.7)\(^6\). In this proposal, a key Diels-Alder cycloaddition reaction between a phakellin-type dienophile (33) and a 3-amino-1-(2-aminoimidazoyl)-prop-1-ene (34) diene gives cyclohexene intermediate 35. Electrophilic chlorine-initiated ring contraction and hydration then furnishes the palau’amine framework 31. This proposal predates the structural revision of palau’amine and thus it was designed to account for the *cis* stereochemical relationship at the 5,5- ring fusion assigned to the original skeleton. Based upon the revision to a *trans* ring fusion, the Diels-Alder cycloaddition as depicted below (Figure 1.7) is not a likely step. The ring contraction process on the other hand has later been hypothesized by Baran et al.\(^17\) as well as Romo et al.\(^18\) to be a plausible course in the biosynthesis of other P-I alkaloids (*vide infra*).
The structural relationships among the P-I alkaloids has ignited tremendous interest in the nature of their origin and whether one or a few universal precursors can be identified. In 2001 Al-Mourabit and Potier\textsuperscript{19} put forth a biosynthesis proposal (Figure 1.8) based on the observation that 2-aminoimidazoles (36 – 38) possess ambivalent reactivities (both nucleophilic and electrophilic properties at C4/C5) as a result of tautomerization. A potential precursor for the biosynthesis of various P-I alkaloids was identified by Al-Mourabit’s group to be 3-amino-1-(2-aminoimidazolyl)-prop-1-ene (39) which has multiple reactive sites as depicted below (species 40 – 46, Figure 1.9). Different dimerizations and cyclizations of these precursors are thought to lead to the structural diversity and complexity of P-I alkaloids.
In the context of the biosynthesis of palau’amine and congeners (Figure 1.10), C7-C7 dimerization of the given tautomers of 3-amino-1-(2-aminoimidazolyl)-prop-1-ene, 39a and 39b, leads to an intermediate species 47 (path b), which can be transformed directly to sceptrin (5) and its derivatives via path c. Imine/enamine tautomerization of intermediate 47 also gives two more reactive intermediates 48 and 49 (path d, and path e). The cyclization of 47 via path d leads to the formation of ageliferin (7) and its derivatives. Chlorination of one of the exocyclic double bonds 49 and hydration of the imine moiety of the imidazole unit of 49 (“chlorohydroxylation”) gives intermediate 50 that cyclizes to give a key precursor 51. The authors believe that 51 serves as the
common starting point for the biosynthesis of the palau’amines, styloguanidines and axinellamines as outlined below.

Oxidation of 51, N1-C4 cyclization, followed by annulation of the amide nitrogen to C5 leads to the palau’amines 12 (path f). On the other hand, oxidation, C3-C4 cyclization, and annelation of amide nitrogen to C5 would furnish the styloguanidines 16 (path g). Intermediate 51 is also amenable to the biosynthesis of the axinellamines via tautomerization and rotation (51 → 52 → 53, path h) as depicted to give 53 followed by oxidation and N1-C3 cyclization (Figure 1.10). Note that Al-Muorabit and Potier’s proposal does not take stereochemical issues into consideration, perhaps assuming the mediation of enzymes in the process.
Figure 1.10. Al-Mourabit and Potier’s unified biosynthetic proposal for P-I alkaloids.
1.4.3 Baran’s Proposal for the Biosynthesis of P-I Alkaloids

Baran, et al.\textsuperscript{17} have proposed a biosynthetic pathway very similar to the one put forth by Al-Mourabit and Potier.\textsuperscript{19} In this proposal, a key biosynthetic intermediate dubbed “pre-axinellamine” (63, Figure 1.11) is thought to furnish a plethora of P-I alkaloids in a stereocontrolled fashion. The biogenetic route to 63 itself follows Al-Mourabit and Potier’s proposal (\textit{vide supra}) starting from oroidin (1). In addition, sceptrin (5) and ageliferin (7) are also implicated in the biosynthetic pathway as possible intermediates (Scheme 1.11).

The authors reason that the presence of sceptrin (5) in very high concentration in organisms from which ageliferin (7)\textsuperscript{20} was isolated suggests that 5 may be the precursor for the more complex class of this family of natural products. As depicted in Figure 1.11, it can be reasoned that 5 undergoes a ring expansion to generate a carbocation intermediate 58, which can trap a chloride nucleophile via the intermediacy of an aziridine species 59, to give 60. A formal oxidation of the remaining imidazole unit in 60 provides the desired “pre-axinellamine” species 63.

A third pathway to “pre-axinellamine” was proposed using ageliferin (7) as the starting material. In this case, Baran’s route is based on Scheuer and Kinnel’s\textsuperscript{6} biosynthetic proposal for palau’amine although the two proposals differ in the actual ring contraction precursor (35 vs. 61). Imine/enamine tautomerization followed by electrophilic chlorine initiated ring contraction, hydration and subsequent oxidation leads to “pre-axinellamine”. Evidence in support of this third hypothesis has been reported by
Baran and coworkers, in which a species bearing an ageliferin-like skeleton delivered axinellamine-like structures when subjected to ring contraction conditions (not shown).\textsuperscript{21}

Figure 1.11. Baran’s biosynthetic proposal for pre-axinellamine.
Baran and coworkers’ biosynthesis hypothesis for the dimeric P-I alkaloids starting from “pre-axinellamine” (63) is depicted in Figure 1.12. In path A, the authors suggest that the nitrogen of the spiro-imidazole unit in 63 cyclizes onto the imine-containing aminoimidazole to give the axinellamines 65. Both syn diastereomers (axinellamine A and B) are expected from this reaction pathway because the two diastereomers have similar energies based on molecular modeling calculations. In path B, the proximal pyrrole C3 of 64 cyclizes onto C4 of the oxidized electrophilic 2-aminoimidazole and annulation of the amide nitrogen atom onto C5 of the 2-aminoimidazole leads to the isophakellin framework found in tetrabromostyloguanide (66), which, upon amide hydrolysis gives styloguanidine (17) and derivates. Similarly, in path C the proximal pyrrole N1 of 64 cyclizes onto C4 of the activated 2-aminoimidazole and annulation of the amide nitrogen atom onto C5 of the 2-aminoimidazole leads to the phakellin skeleton found in conbu’acidin A (15). Amide hydrolysis of 15 gives palau’amine (12) and derivatives.

Ring closure of the hemiaminal oxygen atom of 63 onto the imine of the 2-aminoimidazole unit (path D) furnishes massadine chloride (67). Baran and coworkers have suggested, based on molecular modeling, that the chloride in 67 might be susceptible to intramolecular aziridination to form 68 dubbed as “massadine aziridine”. Ring opening of the aziridine in 68 by water leads to massadine (69). Although no direct evidence is found for the existence of 68, massadine chloride has been isolated by Baran et al in22 their effort to synthesize massadine (69). Coupling of 69 and massadine aziridine 68 can also lead to the styllassadines 70 and 71.
Figure 1.12. Unified biosynthetic pathways to P-I alkaloids from “pre-axinellamines” (63).
1.4.4 Feldman’s Biosynthesis Proposal for Palau’amine and the Axinellamines

The biosynthesis proposal by Feldman (unpublished data) is a modification to Al-Mourabit and Potier’s hypothesis\textsuperscript{19} and begins with the dimeric 2-aminoimidazole substrate 72 (Figure 1.13). In this proposal, selective oxidation of one of the imidazoles and subsequent tautomerization of the remaining imidazole generates reactive species 73 which can adopt either of the two equilibrating confirmations 73 and 74. Species 73 has an electronically favorable conformation in which the electrophilic imidazolium moiety and the nucleophilic alkylidene imidazole functionality are parallel with each other. Species 74 on the other hand has adopted an A\textsuperscript{1,3} favored conformation but the electronics in this species are not well suited. If conformation 73 reacts, as expected (and as is necessary for the correct stereochemical outcome), then it will generate spirocyclic intermediate 75 after hydration of the imine of the ensuing species (not shown).

The spirocycle 75, which is similar to the intermediate named “pre-axinellamine” (63) (cf. Figure 1.12) in Baran’s biosynthetic proposal, can be oxidized to generate two equilibrating reactive species 76 and 77, creating a branching point for palau’amine and axinellamine synthesis. Cyclization of the amide nitrogen atom of 76 onto C10 forms intermediate 78 (\textit{path A}), followed by a second cyclization of the pyrrole nitrogen of 78 onto C5 to deliver dibromopalau’amine (14) with a \textit{trans}-azabicyclo[3,3,0]octane ring system. On the other hand, cyclization of N23 of 76 onto C5 followed by hydration of the resulting imine (\textit{path B}) would form axinellamine A (54) with a \textit{cis}-bicyclo[3,3,0]octane ring system. Reactive intermediate 77 arises from a ring-flip of the cyclopentane unit of
76 and rotation about the cyclopentane-imidazole bond. Cyclization of N23 of 77 onto C5 in this conformation (path C) will give axinellamine B (79).

![Diagram of axinellamine biosynthesis]

Figure 1.13. Feldman’s modification of the biosynthetic proposal by Al-Mourabit.

It is noteworthy that computational study by Feldman (molecular mechanics (MM) calculations) shows that conformer 77 is 4.4 kcal/mole more stable than conformer 76. Axinellamine B is slightly favored in the natural isolate over axinellamine A (1.3:1), in qualitative agreement with the calculated energetic bias of 76 relative to 77. Feldman also notes that none of the sponges from which the axinellamines were isolated contain palau’amine and vice versa. This observation may suggest that the two alkaloids may not
share a similar biological origin despite the popular speculation about common intermediates.

1.5 Conclusion

Pyrrole-imidazole alkaloids, most notably palau’amine (12) and congeners have captivated the attention of synthetic and physical organic chemists alike due to their intriguing and unprecedented structural complexity as well as their potential biological significance. The numerous studies conducted to understand this family of natural products have led to important developments including the many biosynthetic proposals, computational and biological studies, new reactions discovered, and of course, the milestone set by Baran and coworkers in the first total synthesis of palau’amine (vide infra).
Chapter 2
Efforts toward the Total Synthesis of Palau’amine

2.1 Background

In addition to the intricate skeleton of palau’amine (12), its striking immunosuppressive activity (IC$_{50}$ < 18 ng/mL) coupled with its low toxicity (LD$_{50}$ 13 mg/kg, mice) have made it a favorite synthesis target since its isolation almost two decades ago. Despite the many attempts, there is only one total synthesis of the molecule, reported by Baran and coworkers (vide infra). This account will review some of the most notable studies toward the total synthesis of palau’amine. Much of the chemistry in this review and most efforts to date have focused on the densely functionalized cyclopentane ring structure. Also, the majority of work has occurred prior to the structural revision of palau’amine (vide supra) and this account will review efforts toward both the original and the revised palau’amine structures.

2.2 Overman and Coworkers’ 1,3-Dipolar Cycloaddition Strategy

Overman and coworkers’ effort was directed toward the total synthesis of the unrevised structure of palau’amine (31) (Figure 2.1). The plan employed a clever intramolecular azomethine imine 1,3-dipolar cycloaddition reaction to construct triazacyclopenta[cd]pentalenes (81), featuring a cis fused aza-[3,3,0]-bicyclooctane system.
A summary of Overman and coworker’s synthesis attempt is shown in Figure 2.2 below. The secondary amine 85 was prepared from commercial compound 84 in seven steps. Initial attempts at acylation of amine 85 to produce 87 proved to be challenging. After some experimentation, a procedure for the acylation of this sterically demanding amine was found using 86, BOPCl and Hunig’s base in acetonitrile to give the desired compound 87. The PMB protecting group in 87 was then oxidatively removed and the free alcohol 88 was oxidized to an aldehyde by exposure to Dess-Martin periodinane. A Horner-Wadsworth-Emmons reaction of the aldehyde with phosphonate A to install the TBS enol ether (compound 89) and subsequent hydrolysis of this moiety gave the α-ketoester 90. Subjecting compound 90 to a ring closing metathesis reaction (RCM) gave the desired precursor 91 for the intramolecular azomethine imine 1,3-dipolar cycloaddition reaction. Heating an ethanolic solution of 91 and B in a sealed tube at 110
°C led to the cycloadduct 92 in good yields (69 – 71%). Compound 92 features a 5,5-cis fused ring system and a spirocyclic imidazole unit resembling the core structure of the unrevised palau’amine (31) skeleton.
Figure 2.2. Summary of Overman and coworkers’ synthesis of the cis-5,5-azabicyclo-[3,3,0]-octane core of the unrevised structure of palau'amine by an azomethine imine 1,3-dipolar cycloaddition reaction.
As far as the total synthesis of palau’amine was concerned, this advanced intermediate (92) was the last molecule to be reported by Overman and coworkers. However, after the palau’amine structural revision surfaced, the above intermediate (92) was transformed to analogs of the unrevised palau’amine structure (93 and 94) (Figure 2.2). Comparison of the spectral data of 93 and 94 with that of palau’amine as well as computational calculations performed by the Overman group provided additional support for the revised structure.

2.3 Enantioselective Strategy to the Spirocyclic Core of Palau’amine by Romo and Coworkers

Romo and coworkers’s initial effort also was directed at the original palau’amine structure, 31. They subsequently reworked their route to prepare the correct trans-fused bicyclic core (*vide infra*). Romo’s group tackled the challenge of constructing the 5,5-*cis* fused ring system by making use of a modified version of Kinnel and Scheuer’s biosynthetic proposal (*vide supra*). As depicted in their retrosynthetic analysis for the synthesis of the core structure of palau’amine (Figure 2.3), a Diels-Alder cycloaddition between 98 and 99 was envisioned to furnish the tricyclic intermediate 97 which in turn would give the spirocyclic compounds 95 and 96 upon electrophilic chlorine-mediated ring contraction (pinacol-like 1,2-alkyl shift) followed by hydration of the resulting iminium ion intermediate.
Figure 2.3. Romo and coworkers’ retrosynthetic analysis of the spirocyclic core of palau’amine.

The researchers began their synthesis by heating substrates 99 and 100 in benzene at 95 °C in the presence of 2,6-lutidine (adventitious H⁺ scavenger). The Diels-Alder adduct 101 was obtained after four days in 64% along with the other expected regioisomer 102 isolated in 15% yield. The structure of the major isomer was secured by nOe analysis (Figure 2.4). Note that the two compounds (101 and 102) possess an imidazolone skeleton (double bond in the imidazole unit) instead of the direct cycloaddition product due to double bond isomerization during the DA reaction. In a later study, the researchers were able to switch off the formation of the second regioisomer 102 by modifying the electronics of the diene. This advance was accomplished by changing the protecting group on N1 of 106 from the electron-releasing benzyl to the electron-withdrawing tosylvinyl (Tsv) group (see DA TS 107 in Figure 2.4). The protecting group switch gave a 75% yield of the desired cycloadduct 108 as the only isolated isomer.

Protection of the primary alcohol in 101 using TBSCl and DMDO oxidation of the imidazolone unit led to alcohol 104 with the new double bond at the right location for electrophilic chlorine-promoted ring contraction. This task was accomplished by treating
with N-chlorosuccinimide (NCS) in the presence of cyclohexene in methylene chloride to give the 1,2-alkyl shift product 105 in 75% yield. The stereochemistry illustrated in 105 was determined by NOESY spectral analysis.

Figure 2.4. Construction of the spirocyclic core of the original structure of palau’amine (31).

**2.4 Romo’s Synthesis of 5,5-Trans-fused Bicyclic Core of Palau’amine**

Romo and coworkers’ hypothesized that the phakellin core of palau’amine and other P-I alkaloids can be synthesized by a sequence they used in their synthesis of (+)-
phakellin (111) from L-prolinol (109) (Figure 2.5). Therefore, Romo’s group sought to prepare compound 112 that encompasses the L-prolinol unit and the trans-fused bicyclic structure of palau’amine (12).

![Chemical structures](image)

Figure 2.5. Romo and coworkers' synthesis of (+)-phakellin and a plan for the total synthesis of palau’amine.

Romo’s latest synthesis of the trans-fused bicyclic core of palau’amine (12) began with cis-fused bicyclic compound 105 (Figure 2.6) which they prepared in their earlier attempt at the total synthesis of the original structure of palau’amine (31) (vide infra). Selective deprotection of the TIPS group in 105 to give 113 followed by sodium methoxide initiated ring opening and epimerization of the resulting secondary ester gave the methyl ester 114. Ester 114 was then reduced and the resulting primary alcohol 116 was submitted to the Mitsunobu conditions (DIAD, PPh₃) to furnish the trans-fused bicyclic compound 117 in good yield. The formation of 117 by this acyclic ring closure is remarkable because of the high degree of strain in the transition state through which 116 must pass during cyclization. The installation of the phakellin unit to 117 via the method the authors described in their (+)-phakellin (111) synthesis remains to be reported.
2.5 Carreira and Coworkers’ Synthesis of the Cyclopentane Core of Axinellamines/Palau’amine Framework

The synthesis of a fully functionalized cyclopentane core of axinellamine (and palau’amine) by Carreira and coworkers\(^\text{28}\) was one of the first synthesis attempts (another by Overman, \textit{vide supra}) at the total synthesis of this family of natural products. Carreira and coworkers recognized that desymmetrization of the Diels-Alder cycloadduct bicyclo[2.2.1]hept-5-ene \(121\) (Figure 2.7) will deliver the substituted cyclopentane ring found in palau’amine and congeners. An account of this strategy is discussed below.

The key Diels-Alder reaction between \(118\) and \(119\) (Figure 2.7) proceeded at 0 °C to give a 1:1 mixture of two endo diastereomeric bicyclo[2.2.1]hept-5-enes, the undesired \(120\) and the desired compound \(121\). It was found that heating \(120\) in chlorobenzene at reflux gives a 1:1 mixture of \(120\) and \(121\). Three cycles of this process furnished the
desired diastereomer 121 in 74% overall yield. This product was further transformed to anhydride 122, a precursor for the key desymmetrization reaction. When 122 was treated with methanol in the presence of 1.1 equivalents of quinine in carbon tetrachloride and toluene (a method reported by Bolm et al.),29 the methyl ester-acid 123 was obtained in quantitative yield and 93% ee. Selective epimerization of the ester to the corresponding trans ester-acid 124 using LDA (73% yield) and further functional group manipulation gave the bicyclo[2.2.1]hept-5-ene 125, setting the stage to unmask the cyclopentane ring by oxidative cleavage of the alkene.

Ozonolysis of 125 followed by a reductive workup (K₂CO₃ or PPh₃) gave the trans aldehyde 127 with simultaneous epimerization as shown (Figure 2.7). Note that although the cis aldehyde 126 was observed in solution when 1.0 equivalent PPh₃ was used for workup, this compound was never isolated. The remaining task was the installation of the chloride atom. To accomplish the task, the researchers selectively protected the indicated aldehyde to the corresponding acetal 128 (reason for selectivity unknown), and oxidation of the remaining aldehyde to the acid 129 was accomplished by treatment with KMnO₄ in a 2:1 mixture of t-BuOH and water. Finally, Barton decarboxylation in carbon tetrachloride gave the chlorinated cyclopentane 130 in 76% yield (>10:1 dr) after homolytic cleavage of the Barton ester and abstraction of chlorine from the solvent.
Figure 2.7. Carreira and coworkers’ synthesis of a fully functionalized cyclopentane core of palau’amine/axinellamine.

2.6 Carreira and Coworkers’ Synthesis of a Fully functionalized Cyclopentane Core of Massadine

A follow-up report on a study directed toward the total synthesis of massadine (69) was published by Carreira and coworkers in 2008 (Figure 2.8). In this work, a key Diels-Alder reaction between cyclopentadiene 131 and di(−)-menthylfumarate furnished cycloadduct 132 that was transformed to bridged ketone 133 in 6 subsequent steps. Aminocyanation of this ketone installed the desired amine functionality a nitrile group in
134 in 95% yield and high diastereoselectivity (95:5 dr.). At this stage all necessary carbon and nitrogen atoms are in place. Further functional group manipulations on 134 delivered 135 which underwent ozonolysis in the presence of methanol to give ester 136 in high yield and good regioselectivity. The basis for regioselectivity of this transformation is not well understood but Carreira and coworkers point out the possible participation of the proximal –OBn group in the ester formation step. The remaining steps in the synthesis involved functional group swapping (conversion of the aldehyde group to an alcohol and the –OBn groups to azides) to give 137 and epimerization of the secondary ester unit to give the correct trans disposition between substituents at C1 and C2 in 138 (massadine numbering, Figure 2.8). This new route is advantageous over the one reported earlier (cf. Section 2.5) in that the synthesis involved high yielding steps (average of 90% yield, 8% overall). Also, the aldehyde functionality in 136 can serve as a handle for the installation of a chloride group found in palau’amine and the axinellamines by decarboxylative chlorination of a 136-derived Barton ester.
2.7 Gleason and Coworkers’ Effort toward the Cyclopentane Core of Palau’amine

Gleason and coworkers identified that 2-silyloxy substituted 5-alkyl cyclopentadienes are resistant toward 1,5-hydrogen shift compared to simple 5-alkyl-cyclopentadienes. This discovery enabled them to employ cyclopentadiene 139 in a study directed toward the synthesis of the carbocyclic core of the original structure of palau’amine (31) (Figure 2.9). In this study, diene 139 was allowed to react with chloromethyleneoxazolone 140 in a Diels-Alder reaction to furnish a 1:1 mixture of endo/exo products 141 and 142. These silyl enol ether compounds were unstable on silica gel, therefore, the crude mixture was oxidized with DMDO to the α-hydroxy ketones and the oxazolone unit was subjected to methanolsysis to give 143 and 144 in 52% overall
yield. Oxidative cleavage of the \(\alpha\)-hydroxy ketone 144 with \(\text{Pb(OAc)}_4\) in methanol led to the all-cis carbocyclic core of the original structure of palau’amine (31) as shown in 145.

![Diagram of chemical reactions]

Figure 2.9. Gleason’s synthesis of a fully substituted all-cis carbocycle present in the original structure of palau’amine.

### 2.8 Haran and Coworkers’ Spiro Cycloisomerization of Tethered Alkylidene Glycocyamidines

Harran and coworkers\(^{30}\) approach to the total synthesis of palau’amine was based on their biosynthetic hypothesis for palau’amine and congeners, which is drawn from Al-Mourabit and Potier’s proposal (Figure 2.10).\(^{19}\) In this approach, species referred to as alkylidene glycocyamidines (cyclic anhydrides of \(\alpha\)-guanidino carboxylic acids) such as 149 are the key substrates participating in spirocyclization upon initiation with electrophilic chlorine. The stereochemical outcome of this spirocyclization is thought to be controlled by (among other factors) the conformations the activated species can adopt.
as illustrated by species 150 and 151. Carbon-carbon bond formation in the given “stacked” conformations would lead to addition of the electrophilic chlorine from a defined trajectory, reminiscent of the chlorine-promoted annulation of 1,5-cyclooctadiene (152) to give the bicyclooctane 153 (152 → 153, Figure 2.10).31 Harran and coworkers’ synthesis of a spirocyclic compound resembling the core structure of palau’amine (31) based on this idea is described below.

Figure 2.10. Harran and coworkers’ retrosynthetic analysis of palau’amine.
In their synthesis effort, the researchers soon learned that alkylidene glycocyamidine 155 (Figure 2.11) does not participate in spirocyclization upon exposure to tert-butyl hypochlorite due to a presumed intermolecular network of hydrogen bonding that favors bimolecular association. They chose to prepare compound 159 as a substitute for 155 because compound 159 is less likely to participate in intermolecular hydrogen bonding. This compound was prepared by coupling the bis-amino acid 157 with thioimidate 156 to form 158 in which both N2 and N3 of the imidazole unit are tied in a 2,4-benzodiazepine framework (Figure 2.11).

Upon treatment of compound 158 with DBU in DMF at 35 °C, a 1:2.8 $E/Z$ mixture of spirocyclic compound 160 was formed in 90% yield instead of the alkylidene glycocyamidine 159. NMR and additional studies using a non-symmetrical mono-sulfonamide substrate (not shown) suggested that the bis-alkylidene glycocyamidine 159 might be a transient species in the transformation. It is believed that the bis-alkylidene species undergoes spirocyclization promoted by the salt DBU-H⁺·PhSO₂⁻. However, at which stage this salt is involved is unclear.
Figure 2.11. Spirocyclization of bis-alkylidene glycocymidine 159 promoted by $H^+$. 

In a subsequent study, Harran and coworkers prepared a more elaborate alkylidene surrogate 162 (Figure 2.12) by oxidative enolate coupling of the monomer 161. Compound 162 was subjected to hydrosilylation conditions (Rh cat. 166, PhMe$_2$Si-H) to reduce the alkenes. Treatment of the hydrosilylation product 163 with the phosphorus base proazaphosphatrane 167 accomplished cleavage of the N-N bonds in 163 to deliver bis-alkylidene glycocyamidine 164. Also, base 167 cleaved two pyrrole bromines in the process (undesired but inconsequential outcome). Note that the exact nature of aryl-bromide bond cleavage is not understood.

Electrophilic chlorine initiated cyclization of bis-alkylidene compound 164 gave the desired spirocycle 165 in good yields and the correct relative stereochemistry at C12, C17 and C18 centers (Figure 2.12). However, Harran and coworkers have yet to disclose
the stereochemistry of the compound at the spirocenter. Although this biomimetic transformation has its appeal, stereocontrol at the spirocenter needs to be addressed before it can be used in total synthesis.

![Chemical structures and reactions](image)

Figure 2.12. Harran and coworkers' chlorinative cyclization of akylidine glycocyanamide precursors.
2.9 A Ring Contraction Strategy towards Axinellamine and Massadine (and Palau’amine) by Lovely and Coworkers

In Lovely et al.’s approach, the researchers identified a common intermediate 168 (Figure 2.13) for the synthesis of axinellamine and massadine (which, although not explicitly stated, could equally be applicable to palau’amine).\textsuperscript{35-38} Lovely and coworkers’ endeavor for the synthesis of 168 involves an intramolecular Diels-Alder cycloaddition of tethered \textit{bis}-vinylimidazoles to prepare an ageliferin-type substrate 170. This intermediate is expected to undergo chlorination and oxidative ring contraction to give 168. This approach bears some resemblance to the method reported by Romo and coworkers\textsuperscript{27} as well as Baran’s\textsuperscript{17} biosynthetic proposal for P-I alkaloids (\textit{vide supra}).
The key intramolecular Diels-Alder cycloaddition reaction of bis-vinylimidazole 172 (Figure 2.14) proceeded at 145 – 150 °C to give both the desired “normal” cycloadduct 173 (84%) and the inverse electron demand cycloadduct 173 (10%). The cycloadducts were isolated with the double bond isomerized under the reaction conditions (compare 170 vs. 173). The stereochemistry assignment was accomplished using the $^1$H NMR coupling constants for the bridgehead proton $H_a$ with $H_b$ ($J = 10 \text{ Hz})$ and $H_c$ ($J = 11 – 12 \text{ Hz}$), which indicated that the tetrahydrobenzimidazole cycloadduct possessed trans stereochemistry at the ring junction. Further derivatization of similar
cycloadducts and X-ray crystallographic analysis (not shown) also supported these assignments.

Figure 2.14. Diels-Alder cycloaddition of tethered bis-vinylimidazole 172.

The double bond isomerization in the DA reaction hindered the original plan to chlorinate the DA adduct prior to ring contraction. With the Diels-Alder product 173 in hand, two routes were explored for the synthesis of spirocycle 177 (Figure 2.15). In the first case, 173 was subjected to oxidative ring contraction conditions using N-sulfonyloxaziridine 179 to give a single spiro-fused 5-imidazolone compound 176 in 71% yield. This transformation was followed by reduction of the imine (NaBH₄) and reductive cleavage of the N-O linkage of the hydroxamate using SmI₂ to give the hydroxamide product 177.
Figure 2.15. The synthesis of epimeric spirocyclic core of axinellamine and massadine by Lovely and coworkers.

In a second route, the hydroxamate N-O linkage 173 (Figure 2.15) was first reduced to yield 175 and then the oxidative ring contraction was effected to give 178. Reduction of the C=N bond using sodium borohydride furnished the same compound 177. The all \textit{trans} stereochemistry depicted in the final product was verified by X-ray crystallography. Note that the stereochemistry at the spiro center is epimeric to that found in axinellamine and massadine (as well as palau’amine). Therefore, whereas the method
highlights important concepts concerning the utility of the Diels-Alder reaction and the oxidative rearrangement protocol in constructing the core structure of palau’amine and congeners, the lack of stereocontrol limits its use in total synthesis.

2.10 Pauson–Khand Cyclization Strategy for the Synthesis of the Deschloro Carbocyclic Core of Palau’amine by Austin and Coworkers

Austin and coworkers’ interest in palau’amine stems from their desire to make analogs of the alkaloid for biological testing.\(^{39}\) Their strategy for the synthesis of the deschloro cyclopentane core of palau’amine involves a key Pauson-Khand cyclization\(^{39,41}\) of an N-O linked substrate 184 to form cyclopentene 183 (Figure 2.16). The researchers theorized that carbocycle 183 would be amenable to functional group manipulations to give the syn cyclopentane core of the original palau’amine structure 182. Compound 182 then might be converted to deschloro palau’amine 180 by late stage installation of the bis-guanidine moieties through intermediate 181.
Figure 2.16. Austin and coworkers’ retrosynthetic analysis of palau’amine (original structure).

The key Pauson-Khand substrate 187 was prepared by coupling bromide 185 and amine 186 (NaH, DMF) and subsequent removal of the TMS protecting group using potassium carbonate (K$_2$CO$_3$) in methanol (83%, 2 steps) (Figure 2.17). The Pauson-Khand cyclization proceeded to deliver a 4:1 mixture of cyclopentenones 188 and 189 in 69% overall yield. The stereochemistry of the major isomer was assigned from nOe studies on compound 190 after hydrogenation of the alkene (H$_2$, Pd/C, 95%) in 188. Lithium borohydride reduction of the ketone and samarium iodide (or sodium-mercury amalgam)-promoted reductive cleavage of the N-O linkage furnished tetrasubstituted cyclopentane core of palau’amine 192, albeit with the wrong stereochemistry at the indicated site (Figure 2.17).
Figure 2.17. Pauson-Khand cyclization for the synthesis of the cyclopentane core of deschloro palau’amine.

2.11 [3,3]-Sigmatropic Rearrangement of a Bridged Tricyclodecadiene by Gin and Coworkers

Like many other synthesis strategies discussed (vide supra), Gin and coworkers came to the conclusion that the fully substituted and chlorine-containing five-membered ring system would be the most challenging task in the synthesis of palau’amine. Thus, the researchers directed their attention to the synthesis 193 (Figure 2.18). They theorized that 193 can come from bicyclo[2.2.1]heptene 193. The bicyclo[2.2.1]heptene system can be prepared by a [4+2] cycloaddition between a chlorinated cyclopentadiene 195 and an appropriately substituted dienophile 196.
Due to its susceptibility to 1,5-hydrogen shift, the diene component 195 could not be used in a direct [4+2] cycloaddition. Therefore, the task of chlorination was postponed until after the Diels-Alder reaction. This approach was made possible by key [3,3]-sigmatropic rearrangement of a bridged tricyclodecadiene 199 (originally observed by Woodward and Katz\textsuperscript{43}) to give 200 (Figure 2.19). The synthesis began with a Diels-Alder cycloaddition between cyclopentadiene 197 and benzoquinone 198 to produce the sigmatropic rearrangement precursor 199 in a few steps. It was found that enoate 199 and the sigmatropic rearranged product 200 equilibrate to a 78:22 isomeric ratio. Selective Meerwein–Verley-Pondorf reduction of the bridgehead ketone in 200 gave the alcohol, and conversion of that alcohol to the chloride with overall retention of configuration gave the bridgehead chloride 201 (97% yield over two steps). The relative stereochemistry of 201 was determined by an nOe correlation study as depicted in Figure 2.19.
Figure 2.19. The key [3,3]-sigmatropic rearrangement in Gin et al.’s palau’amine strategy.

At this point, all but a single nitrogen substituent are in place around the cyclopentane ring system 201. To install the remaining nitrogen, compound 201 was transformed to the ketone 202 in 3 steps (ester hydrolysis, acyl azide formation, Curtius rearrangement and hydrolysis – not shown) and this ketone was converted to the corresponding oxime (Figure 2.20). Thionyl chloride-initiated Beckmann ring expansion of this oxime gave amide 203 (56%, 2 steps), which then was converted to N-Boc compound 204. At this point, the alkene in Boc amide 204 was cleaved using OsO₄ and the resulting secondary aldehyde was epimerized by exposure to silica gel in the presence of triethylamine (86% yield) to give trans aldehyde 205.

An alternative and more elaborate procedure also was employed (Figure 2.20) that involved ozonolysis of the alkene 204. The resulting aldehydes then were reduced and the proximal alcohol was lactonized on to the amide (alcoholysis of the amide). Protection of the free alcohol with TIPSCI finally generated compound 206. At this point the benzyl protecting group was removed by hydrogenolysis and both the newly liberated alcohol
and the NHBoc groups were protected as the five-membered carbamate 175. Hydrolysis of the lactone, methyl ester formation and oxidation of the primary alcohol gave an aldehyde that was epimerized using silica gel and triethylamine to give a fully and correctly functionalized cyclopentane compound 208. The stereochemistry of both compound 205 and 208 were determined by extensive nOe analysis.

This chemistry by Gin and coworkers offers a creative approach to the cyclopentane core of palau’amine and congeners. Most of the steps involved are high yielding, which makes it an attractive method for total synthesis. However, the feasibility of an acyclic ring closure forming the highly strained trans-fused azabicyclo[3,3,0]octane ring system remains to be seen although Romo’s recent work lends precedent for the task (cf. Section 2.4). It is also important to consider whether the chloride in 205 and 208 will survive conditions necessary to transform these molecules into the natural product.
2.12 Total Synthesis of Palau’amine by Baran and Coworkers

The first and only total synthesis of palau’amine to date was reported by Baran and coworkers in 2010. This synthesis is the culmination of over a decade long quest by synthetic organic chemists around the world for the total synthesis of palau’amine (12). Baran and coworkers’ success relied on their experience in synthesizing other P-I alkaloids such as the axinellamines and massadine. Their retrosynthetic analysis for palau’amine is depicted in Figure 2.21.
The researchers hypothesized that a N14-C10 transannular cyclization of a highly strained cyclononane structure 210, which is dubbed “macro-palau’amine”, would furnish the natural product. Macro-palau’amine 210 is believed to exist in a dynamic equilibrium with an amidine tautomer 209 that is capable of transannular cyclization. Macro-palau’amine was envisioned to come from the intramolecular coupling between the pyrrole carboxylic acid and the proximal primary amine moieties in 211. Compound 211 will arise from coupling bromoimidazole 212 with pyrrole carboxylic acid in an aromatic substitution reaction. A versatile and fully functionalized spirocyclic
intermediate 213, which was utilized by Baran and coworkers as a key starting material in the total synthesis of the axinellamines and the massadines, serves as the precursor for bromopyrrole 212. The synthesis of the key spirocycle 213 and its conversion to 1,9-dideoxy-axinellamine\textsuperscript{44}, the axinellamines,\textsuperscript{45} massadine\textsuperscript{46} and finally to the revered P-I alkaloid palau’amine\textsuperscript{13} is examined below.

2.12.1 Synthesis of the Common Spirocyclic Intermediate 213

The synthesis of spirocycle 213 began with a Diels-Alder cycloaddition reaction between dimethyl fumarate and diene 214 that set three of the five stereocenters, shown in 215 (Figure 2.22). Further functional group manipulations to substitute the methyl esters for azides (64%, 5 steps) and swapping the TIPS protecting group for PMB gave compound 217. Compound 217 underwent ozonolytic cleavage of the tetrasubstituted alkene to give the \textit{bis} methyl ketone 218 (85%, 2 steps). Enolization of the \textit{bis} ketone with Hunig’s base and TMSOTf, bromination of the enol ethers with NBS, and dry silica gel-promoted aldol cyclization gave the cyclopentane 219 (57%, 2 steps).
Selective substitution of the α-bromo moiety in 219 with a chloride (LiCl) followed by removal of the PMB group (TFA, 78%, 2 steps) created a reactivity differential between the two halide groups in 220. Elimination of the β-hydroxy group in 220 proved challenging and required the development of a sulfuryl chloride initiated...
cascade elimination-chlorination sequence to give chloride 223 (38 – 43% yield). To complete the synthesis of spirocycle 213, a Luche reduction of the carbonyl group in 223 to the corresponding alcohol and chemoselective alkylation of the bromide with N,N’-bis-Boc guanidine gave cyclopentene 225. A cascade oxidation-conjugate addition sequence was initiated with IBX to give the desired spirocycle 213 in 70% yield as a 1.3:1 diastereomeric ratio slightly favoring 213. The evolution of spirocycle 213 to the different P-I alkaloids are briefly described in the next sections.

2.12.2 Transformation of Spirocycle 213 to 1,9-Dideoxy-preaxinellamine

Prior to their synthesis of the axinellamines, Baran and coworkers converted spirocycle 213 to the 1,9-dideoxy-preaxinellamine 227 by the following sequence (Figure 2.23). To install the second imidazole unit found in the axinellamines and palau’amine, spirocycle 213 was allowed to react with mono-Boc guanidine followed by Boc protection of the imidazole nitrogen to give the bis-imidazole compound 226 in 33% yield over two steps. Reduction of the azide units to the free amines was accomplished by treating 226 with triphenylphosphine, and the free amines were then coupled with dibromopyrrole carboxylic (228) acid to deliver 1,9-dideoxy-preaxinellamine 227 after removal of the Boc groups with TFA.
2.12.3 Conversion of Spirocycle 213 to Axinellamine A and B

The 1,9-dideoxy-pre-axinellamine 227 prepared above was not used in axinellamine total synthesis due to concern that the amide and pyrrole nitrogen atoms in 227 might interfere with the formation of the tetracyclic core of the axinellamines (via palau’amine type ring formation). Therefore, the tetracyclic core was constructed as follows. Initially, the second imidazole unit was installed the same way as in the synthesis of 1,9-dideoxy-pre-axinellamine from spirocycle 213 (vide supra) to give 229 after removal of the Boc groups with TFA (Figure 2.24). Product 229 was oxidized using DMDO to provide the bis-hemiaminal 230 in situ, which, upon treatment with TFA, cyclized to deliver tetracycle 232, presumably though imine intermediate 231.
The selective oxidation at C1 of the indicated imidazole in compound \( \text{232} \) (Figure 2.24) with silver (II) picolinate\(^{47,48} \) in water was achieved in a reasonable yield (40\%, 3:1 dr) to give \( \text{233} \) in one of the hallmark reactions of this total synthesis effort. It is noteworthy that this oxidation is a significant discovery in the oxidation of imidazoles given its tolerance of functional groups such as the free amines and the reactive hemiaminal present in \( \text{232} \). The remaining tasks of azide reduction (1,3-propanedithiol) and acylation with the bromopyrrole \( \text{234} \) are accomplished to generate both axinellamine A (34) (45\% from diamine) and axinellamine B (79) (24\% from diamine). This outstanding feat in the total synthesis of these P-I alkaloids, set the stage for the later synthesis of palau'amine (*vide infra*).
2.12.4 The Total Synthesis of Massadine from Spirocycle 213

The total synthesis of massadine (240) began with spirocycle 213 (Figure 2.25). This compound was alkylated with NaN(CHO)$_2$ and the Boc groups were then removed by treatment with TFA to give 235. The resulting intermediate 235 was oxidized at C1 using the silver (II) picolinate protocol to furnish the amino alcohol 236 after deformylation of the -N(CHO)$_2$ group under the reaction conditions. The free amine 236 was allowed to react with cyanamide to install the second imidazole unit, which gave two compounds; one with intact chloride, 237 (32%), and another with a hydroxyl group substituted for the chloride with retention of configuration, 238 (24%). The chloride
compound 237 was eventually converted to massadine chloride (not shown) while compound 238 served as a precursor for massadine (240) synthesis (see Figure 2.26).

Figure 2.25. Synthesis of the massadine precursor 238 and massadine chloride precursor 237.

Exposure of 238 to DMDO (pH control was important to suppress axinellamine type N-cyclization) and treatment with neat TFA gave the tetracyclic core of massadine 239 in 65% as a 1:1.9 diastereomeric ratio favoring the unnatural 3,7-epi-massadine skeleton 241 (Figure 2.26). Hydrogenation of the azides using Pt₂O catalyst and acylation of the resulting free amines with dibromopyrrole 242 resulted in synthetic massadine 240 (40%) and 3,7-epi-massadine 241 (40%).
2.12.5 Total Synthesis of Palau’amine from Spirocyle 213

The versatility of spirocycle 213 in the synthesis of P-1 alkaloids was demonstrated by its conversion to palau’amine (12) with relatively few manipulations (Figure 2.27 and 2.28).13 The α-chloroketone functionality in spirocycle 213 was selectively alkylated with N-formylformamide sodium salt. This transformation is followed by in situ removal of the Boc groups and deformylation using 50% aqueous TFA to give protonated α-amino ketone 243. This species was then oxidized using the silver (II)-picolinate protocol to furnish the alcohol 236 in 64% yield along with 17% of unoxidized amine 243. The amino alcohol 236 was then allowed to react with cyanamide to install the second imidazole unit to give 237. Bromination of this imidazole using molecular bromine yielded the desired aryl bromide 244 in 54% yield. The above sequence set the stage for aromatic substitution of the bromide in 244 with pyrrole carboxylic acid as outlined in the retrosynthetic analysis. However, this reaction failed. As a result, the researchers assembled the pyrrole unit by the sequence delineated in Figure 2.27 (244 → 248).
Hydrogenolysis of the azide groups in 248 led to the corresponding bis amine 249 and in situ intramolecular EDC coupling of the pyrrole carboxylic acid moiety and the proximal amine gave a highly strained macrolactone 210 known as “macro-palau’amine” (Figure 2.28). This species underwent transannular cyclization when the crude substance was heated at 70 °C in TFA to produce the venerated natural product palau’amine (12) (17% yield from azide 248). The final annulation is believed to commence through an amidine tautomer 209, but the exact nature of the reactive intermediates is not clear. Baran and co-workers accomplished the first and only total synthesis of palau’amine in 25 steps from commercial starting material in 0.015% overall yield. This total synthesis is
a direct result of knowledge the researchers acquired during their earlier studies toward the axinellamines, massadines, ageliferin and other related natural products.

Figure 2.28. Trans-annular cyclization of “macro-palau’amine” to deliver palau’amine.

2.13 Conclusion

Since palau’amine’s isolation from the sponge *Stylotella agminata* by Scheuer and Kinnel in 1993, there have been numerous attempts at its total synthesis. Although only one total synthesis has been achieved by Baran and coworkers so far, the many attempts toward have contributed tremendously to our knowledge of P-I alkaloids. Reactions such as Overman’s intramolecular azomethine imine 1,3-dipolar cycloaddition, Romo and Lovely’s Diels-Alder cycloaddition-ring contraction sequences, and Harran’s
spiroisomerization of alkylidene glycocyamidine all have advanced the field of P-I alkaloid synthesis.
Chapter 3
Modern Pummerer-Type Oxidative Cyclizations

3.1 Introduction

The Pummerer reaction was named after chemist Rudolf Pummerer (1882-1973, Germany), who was first to explain the reaction mechanistically.\textsuperscript{49,50} Although it was Smythe\textsuperscript{51} who first published experimental results that resembled the Pummerer reaction in 1909, he provided no explanation for his results. In Smythe’s report, dibenzyl sulfoxide 250 (Figure 3.1) gave a series of compounds (251 - 255) when it was heated in the presence of acetic anhydride and HCl. Both aldehyde 251 and the 251-derived thioacetal 253 now are acknowledged to be products of the Pummerer transformation.

![Figure 3.1. The original Pummerer-type reaction published by Smythe.](image-url)
The first report from Pummerer came that same year on the synthesis of α-chlorosulfide 258 (Figure 3.2) from the reaction of sulfinyl acetic acid 256 with HCl. Pummerer cited the involvement of sulfuryl chloride 257 to explain the formal oxidation state at carbon, which upon 1,2-chloride shift gave α-chlorosulfide 258. The transient species proposed by Pummerer (257) is very similar to the thionium ion 262 (Figure 3.3) that is generally accepted to be an intermediate in modern Pummerer chemistry. Pummerer’s contribution in this sense is noteworthy because modern Pummerer chemistry has become a valuable way to transform sulfoxides to α-substituted sulfides.52-57

![Figure 3.2. Pummerer’s first report on his namesake reaction.](image)

![Figure 3.3. Conventional acetic anhydride-initiated Pummerer reaction mechanism.](image)

### 3.2 Pummerer Reactions in Indole-Based Systems

Since its discovery almost a century ago, the Pummerer reaction has found numerous applications in organic synthesis.52-57 The relevance of the methodology to indole based substrates is enormous because of its potential as a synthetic tool for
preparation of indole alkaloids that are abundant in nature. A useful variation of the reaction developed at Penn State\textsuperscript{58-62} furnishes 3,3-spirocyclic indolenines by *ipso* attack of a pendant nucleophile at C3 of indole-2-sulfoxides (Figure 3.4). When sulfoxide representatives such as \textit{264} are activated using a Pummerer initiator (Tf\textsubscript{2}O, Ac\textsubscript{2}O, TFAA etc.), 3,3-spiro indolenines the likes of \textit{266} are obtained with excellent regioselectivity. Note that in the general outline depicted in Figure 3.4, nucleophilic attack at the C2 and C4 positions of intermediate \textit{265} are possibilities. However, regioselective addition to the C3 position is assured because of the increased electrophilicity of the C3 position brought about by the conjugated oxidized sulfur. In addition, nucleophilic attack at C3 allows aromaticity to be restored in the product (see Section 3.3 for mechanism).

![Figure 3.4. A general outline for indole-based Pummerer reactions.](image)

### 3.3 Mechanism Highlights

Indole-2-sulfoxides can participate in the Pummerer reaction through two distinct mechanistic sequences. These mechanistic pathways are termed vinylogous\textsuperscript{63-69} and additive.\textsuperscript{70-74} The difference between the two mechanisms lies in the order in which the nucleophile attacks the activated indole core. The details of these mechanisms are given
below as they are applied to indole-based sulfoxide substrates (cf. Section 3.6 for an imidazole-based Pummerer reaction mechanism).

3.3.1 Indole-2-Sulfoxides in the Pummerer Reaction

Both the vinylogous and additive pathways begin when the sulfoxide 264 (Figure 3.5) is activated by an electrophile to form the leaving group –OR in sulfonium intermediate 267. In the vinylogous mechanism, a base removes the proton on the activated indole nitrogen of 267 which leads to the expulsion of the leaving group to give the thionium species 268. The pendant nucleophile attacks at C3 to form a ring and deliver spirocycle 266. This process resembles an $S_{N1}$-like sequence. By contrast, the additive mechanism involves attack of the pendant nucleophile on C3 in intermediate 267, which then expels the leaving group in an $S_{N2}'$-like reaction to generate the thionium species 269. Removal of the proton on the indole nitrogen by a base then restores neutrality in 266.
3.4 Activation of Indole-2-Sulfides for a Pummerer-like Reaction

Sulfides have been shown to undergo a Pummerer-type cyclization promoted by hypervalent iodine initiators such as PhI(CN)OTf\(^6\) (Stang’s reagent), PhI(OTFA)\(_2\),\(^7\) PhI(OAc)\(_2\) and tol-IF\(_2\).\(^7\) Possible mechanistic courses of this process are presented below (Figure 3.6). The lone pair on the sulfur atom in 270 acts as a nucleophile to attack the
hypervalent iodine, which activates the substrate for the Pummerer reaction ($270 \rightarrow 271$). The activated sulfonium species $271$ then forms the spiro indolenine $266$ by either the additive or vinylogous pathways as shown in Figure 3.6. Note that aside from the formal sulfide oxidation ($270 \rightarrow 271$), the steps described for sulfoxides apply here too.

Figure 3.6. Hypervalent iodine (Stang’s reagent) promoted Pummerer cyclization.
3.4 Synthesis of 3,3-Spiro Indolenines by the Pummerer Oxidative Cyclizations

Initial studies in the synthesis simple 3,3-spiro indolenines focused on the scope of nucleophiles that participated in the cyclization event. In this effort tethered carboxylate groups (not shown), allylsilanes, silyl enol ethers, and silyl ketene iminal nucleophiles were found to cyclize in the Pummerer reaction. For instance, when allylsilane 272 (Figure 3.7) and silyl enol ether 274 were activated with Tf₂O under optimized cyclization conditions (CH₂Cl₂, 2,6-lutidine, -75 °C), 3,3-spiro indolenine 273 and 275 were obtained in very good yields and complete regioselectivity.

In addition, sulfoxide silyl ketene iminal 276 was cyclized by the Tf₂O-mediated Pummerer reaction to give 3,3-spiro indolenine 278 in high yield. The reaction proceeded with complete regioselectivity as in the previous cases and in good diastereoselectivity (6.8:1) for the shown diastereomer (Figure 3.7). A sulfide version of the silyl ketene iminal, 277, was also found to furnish the desired spirocycle 278 in moderate yields when subjected to Stang’s reagenet (PhI(CNOTf) (Figure 3.7).
Figure 3.7. Cyclization of activated alkenes in the Pummerer reaction.

The successful synthesis of 3,3-spiro indolenines 273, 275 and 278 via the recently developed Pummerer-type cyclization sparked an interest in expanding the scope of the reaction to include the synthesis of 3,3-spiro indolenines with an adjacent quaternary center. This interest stemmed from the recognition that the core structure of a considerable number of natural products including crassanine (279), 77 tabernoxidine (280), 78 koumine (281), 79 maremcyin, 80 communesin B (283), 81 and E (282), 80 and perophoramidine (284) 82 exhibit a 3,3-spirocyclic indole-derived center and an adjacent
quaternary carbon (Figure 3.8). Although a number of methods have been utilized to construct this core structural motif, there is no general and reliable method to accomplish the task. The assembly of all-carbon quaternary centers remains a challenging problem in organic synthesis because it requires the formation of a new C-C bond at a hindered site. The presence of an adjacent quaternary center makes the job all the more demanding.

![Chemical Structures](image)

Figure 3.8. Natural products with a 3,3-spirocyclic indole-derived center and a vicinal quaternary stereocenter.

Among the methods utilized to assemble this structural motif are: oxidative rearrangements, transition metal mediated reductive alkylation, intramolecular cyclopropanation reactions, base-promoted alkylation, palladium catalyzed trimethylenemethane-[3+2]-cycloadditions, intramolecular Heck coupling, and intramolecular S_N2 reactions. A methodology based upon the Pummerer oxidative
cyclization for the synthesis of 3,3-spiro indolenines featuring an adjacent quaternary stereocenter is described below.

### 3.5 Synthesis of 3,3-Spiro Indolenines with an Adjacent Quaternary Stereocenter by the Pummerer Oxidative Cyclization Protocol

We have developed an extension of the Pummerer oxidative cyclization protocol to prepare 3,3-spiro indolenines with an adjacent all-carbon quaternary center (Figure 3.9).\textsuperscript{93,94} In this methodology, silyl enol ethers such as 286 are cyclized to furnish all-carbon 3,3-spiro indolenines 285 (R = Me or Ph). The success of this effort relied on facile access to the silyl enol ether nucleophiles. Preparation of these Pummerer precursors by base-promoted deprotonation of the corresponding ketones (287 $\rightarrow$ 286) proved unproductive in our laboratory. However, silyl enol ethers would be generated by hydrosilylation of $\alpha$,$\beta$-unsaturated ketones catalyzed by RhCl(PPh$_3$)$_3$ (Wilkinson’s catalyst) (288 $\rightarrow$ 286), a process first reported by Ojima in 1982.\textsuperscript{95}
Silyl enol ether 291 was accessed by conjugate reduction of the corresponding enone 290 using RhCl(PPh₃)₃ and dimethylphenylsilane in 78% (Figure 3.10). Similar experiments performed using tert-butyldimethylsilane and triisopropylsilane as the hydride donors were unsuccessful. The triflic anhydride promoted Pummerer cyclization of silyl enol ether 291 proceeded smoothly to furnish 3,3-spiro cyclic indol enine 292 in 79% yield.
Silyl enol ether 294 was prepared in a similar fashion by conjugate reduction of enone 293 using Wilkinson’s catalyst and dimethylphenylsilane in 77% (Figure 3.11). In principle, this conjugate addition reaction could give both the Z and E geometric isomers of the silyl enol ether. However, the E-alkene was the only compound observed as elucidated by nuclear Overhauser enhancement (nOe) experiments. Silyl enol ether 294 was cyclized in the Pummerer reaction using triflic anhydride to furnish 3,3-spiro cyclic indolenine 295 in a modest 41% yield. The Pummerer cyclization gave only a single stereoisomer of compound 295. Structural assignment was made based on $^{1}$H and $^{13}$C NMR spectroscopy and the relative stereochemistry shown was secured by a single crystal X-ray structural analysis of the molecule (Figure 3.12).

Figure 3.11. Tf$_2$O initiated Pummerer cyclization of silyl enol ethers.
Figure 3.12. Single crystal X-ray structure of Pummerer cyclization product 295.

Spirocycle 295 was formed as a single diastereomer featuring equatorial Ph substituent and an axially disposed aryl ring of indolenine core. The observed diastereoselectivity of the Pummerer cyclization is believed to be the result of sterically favorable organization of reacting sites depicted by transition state structure 297 (Figure 3.13, vinylogous Pummerer shown for clarity). It is apparent from the result of the reaction that the transition state depicted by 296 is unfavorable (compound 298 not observed), presumably due to the steric clash between the indole core and the methyl group on the incipient six-membered ring.
In this effort, Stang’s reagent (PhI(CN)OTf) mediated a Pummerer-like cyclization on Pummerer shown for simplicity).

Attempts were made to prepare the Z-silyl enol ether in order to probe the stereochemical consequence of silyl enol ether geometry on the Pummerer cyclized product. Our efforts focused on the generation of the thermodynamic Z-enolate by base-promoted deprotonation of a ketone precursor (not shown) and trapping of the resulting enolate with different silylating groups. These efforts, however, were not successful.

3.6 Hypervalent Iodine Reagent (PhI(CN)OTf) Promoted Pummerer Cyclization

In a related work, we explored a variant of the Pummerer initiator methodology. In this effort, Stang’s reagent (PhI(CN)OTf) mediation of a Pummerer-like cyclization on a sulfide silyl enol ether 300 prepared by hydrosilylation delivered spirocycle product
albeit in inferior yield (28%) compared to the Tf$_2$O mediated Pummerer cyclization results (Figure 3.14). Attempts to improve the yield of this reaction were unsuccessful. It is clear from this result that the Pummerer cyclization is possible with the iodine activator although it is not yet as effective as the triflic anhydride promoted Pummerer chemistry in this particular system.

![Figure 3.14. Hypervalent iodine (PhI(CN)OTf) initiated Pummerer cyclization sequence.](image)

Overall, this work showed the feasibility of using triflic anhydride promoted Pummerer oxidative cyclization for the efficient construction of 3,3-spiro indolenines with adjacent bis-quaternary centers on all-carbon substrates.

**3.7 The Pummerer Reaction in Imidazole-based Systems**

The Pummerer cyclization methodology introduced above for indoles has also been extended to imidazole systems in our laboratory. The significance of the methodology to imidazole based substrates is underscored by its enormous potential as a synthetic tool for PI alkaloids (see Chapter 1). In this methodology a dihydrooroidin derivative imidazole-2-sulfide 301 (Figure 3.15) is activated by the hypervalent iodine Pummerer initiator PhI(CN)OTf to give intermediate 302. At this stage, both the amide and pyrrole nitrogen atoms cyclize in sequence onto the activated imidazole core to give
tetracycle \textit{307} as depicted in Figure 3.15 below. Note that this cyclization event closely resembles the suggested biosynthetic pathways to PI alkaloids (\textit{vide supra}). The tetracycle \textit{307} characterizes the phakellin core of many of the dimeric and higher-order P-I alkaloids including palau’amine and its derivatives.

As discussed for the case of indole-based Pummerer reactions (\textit{vide supra}), the imidazole-based Pummerer cyclization reaction can take either the additive\textsuperscript{70-74} or the vinylogous mechanistic\textsuperscript{63-69} pathways depicted below (Figure 3.15), similar to situation discussed for indole-based Pummerer cyclization. A major advantage of this Pummerer cyclization reaction is its ability to confine oxidation to the sulfur atom and thus avoid destructive oxidation side reactions of the electron-rich imidazole core.
It is noteworthy that, in principle, the sulfoxide analog of 301 can participate in a Tf$_2$O initiated Pummerer cyclization sequence to give the tetracycle 307. However, such transformations on test substrates have so far produced inconsistent results. This technology has been a valuable instrument in our laboratory for construction of the phakellin alkaloids dibromophallstatin (313) and dibromophakellin (315) (vide infra). These preceding results in this area are reviewed below.
3.8 Application of the Imidazole-Based Pummerer Cyclization for the Total Synthesis of Dibromophakellstatin and Dibromophakellin

The utility of the imidazole-based Pummerer reaction was highlighted with the total synthesis of dibromophakellstatin (313) (Figure 3.16). In this synthesis, imidazole was functionalized using standard imidazole chemistry\(^\text{97}\) to give amino sulfide 309, which was acylated with dibromopyrrole 310 to give the dihydrooroidin derivative Pummerer cyclization precursor 311. As anticipated, the Pummerer cyclization resulted in tetracycle 312 in 56% yield when treated with Stang’s reagent (PhI(CN)OTf). Oxidative hydrolysis of the thioimidate functionality in 312 delivered the natural product (±)-dibromophakellstatin (313) in 62% yield. This synthesis set the stage for the preparation of the related alkaloid dibromophakellin.

![Figure 3.16. Total synthesis of dibromophakellstatin.](image-url)
The conversion of dibromophakellstatin (313) to dibromophakellin (315) is illustrated in Figure 3.17 below. Initial attempts at direct displacement of either the –SPh moiety in 312 or an oxidized version of it (not shown) by nitrogen nucleophiles (NH₃, N₃, BnNH₂) failed to give the desired guanidine natural product 315. After much experimentation, a protocol for the conversion of the urea in 313 was developed (Figure 3.17). This procedure involved formation of 3-ethoxymidine 314 from 313 by treatment with Meerwein’s salt. This activated imine then underwent guanidine formation when heated with ammonium propionate⁹⁸ to give the natural product dibromophakellin (315).

![Figure 3.17. Conversion of dibromophakellstatin to dibromophakellin.](image)

3.9 Conclusion

The Pummerer oxidative cyclization protocol for the synthesis of 3,3-spiro indolenines from tethered silyl enol ether indole-2-sulfides and indole-2-sulfoxides was demonstrated. The utility of this reaction also was extended to include the synthesis 3,3-spiro indolenines with an adjacent quaternary stereocenter (cf. compounds 292 and 295). In addition, the imidazole-based Pummerer cyclization has proved to be a robust method for the synthesis of P-I alkaloids as evidenced by the successful total synthesis the phakellin alkaloids dibromophakellstatin (313) and dibromophakellin (315). Application
of this imidazole Pummerer reaction in a model study toward the more complex alkaloid dibromopalu’amine (14) will be discussed shortly.
Chapter 4

The Modern Pummerer Reaction in a Study toward Palau’amine Total Synthesis

4.1 Work Toward the Original Structure of Palau’amine (by Mr. J. Li)

The initial effort in the palau’amine total synthesis project was directed toward the originally assigned structure of the natural product, \(31\). Model system \(327\) was chosen as the target for this preliminary study (Figure 4.1). Note that this compound features a 5,5-cis fused azabicyclooctane system as per the original structure of palau’amine (\(31\)). Compound \(327\) was projected to come from substrate \(328\) by the imidazole-based Pummerer oxidative cyclization\(^{96,58,99}\) protocol, which has been a successful tool for the construction of the phakellin alkaloids dibromophakellstatin (\(324\)) and dibromophakellin (\(326\)) in our laboratory (\textit{vide supra}). This model system study was conducted by Mr. Jianfeng Li in the Feldman lab.

![Figure 4.1. Retrosynthetic analysis for model system \(327\) based on the original structure of palau'amine (\(31\)).](image_url)
The synthesis of cyclization precursor 328 began with the preparation of ketone 330 (Figure 4.2) from 329 by standard imidazole metalation chemistry (not shown). Ketone 330 was converted to alcohol 331 by a two step sequence involving Tebbe olefination\(^{100}\) and a regioselective hydroboration-oxidation reaction of the derived alkene product (4:1 syn/anti mixture). Alcohol 331 was transformed to the primary amine 332 by (1) a phthalimide-based Mitsunobu reaction, and (2) deprotection of the phthalimide group with hydrazine. Acylation of the primary amine 332 with bromopyrrrole 333 followed by removal of the SEM protecting group furnished the desired Pummerer cyclization precursor 328. When compound 328 was submitted to the Pummerer cyclization condition (PhI(CN)OTf, \(i\)-Pr\(_2\)NEt), a 2:1 mixture of two cyclization products 334 and 335 was isolated in 28% combined yield favoring the undesired diastereomer 335. Note that the relative stereochemistry shown was assigned based on nOe studies as indicated in Figure 4.2. Despite poor diastereoselectivity and yield, the reaction proved capable of producing the 5,5-cis-fused ring system in 334 and 335.
4.2 Efforts toward the Total Synthesis of the Revised Structure of Palau’amine

While the synthesis work of Figure 4.2 was proceeding, the revised structure of palau’amine (12) was proposed by several research groups (*vide supra*). This new structure contains a highly strained 5,5-*trans* fused azabicyclo[3.3.0]octane moiety instead of the cis-fused system in 31. As a result of this development, the trans-fused model system, 336 (Figure 4.3) was now targeted. Pentacycle 336 should arise from 337 by the Pummerer cyclization reaction.
Until this point, the Pummerer cyclization reaction was untested in the construction of strained 5,5-trans fused ring systems. It should be noted that the calculated (MM) strain energy difference between a 5,5-cis and a trans palau’amine structure is ~7.4 kcal/mol. The proposed Pummerer cyclization must overcome a similar energy barrier to deliver the desired trans bicyclization product.

In order to test the feasibility of this cyclization, precursor 337 was prepared by Mr. J. Li from 331 by the sequence outlined in Figure 4.4. Compound 331 was oxidized to the aldehyde, which was then epimerized by treatment with DBU to give the trans-substituted cyclopentanecarboxaldehyde. Reduction of the aldehyde back to the alcohol delivered compound 338. Alcohol 338 was converted to amide 337 by the same four-step sequence outlined for the synthesis of 328 in Figure 4.2. Pummerer cyclization attempts using the substrate 337 failed to furnish the desired pentacyclic ring structure, most likely due to the high degree of strain at the transition state. This failure necessitated yet another revision in the retrosynthetic analysis.
Figure 4.4. Attempted Pummerer cyclization of trans-substituted cyclopentane precursor 337.

A Pummerer cyclization was expected to proceed smoothly if the strain energy associated with the formation of a 5,5-trans ring fusion can be alleviated. This strain reduction can be achieved by substituting a 6-membered ring system for the 5-membered ring in the original cyclization precursor 337. Molecular Mechanics (MM) calculations on trans-6,5 system 340 (Figure 4.5) (where R₁ = Ph) indicates that 340 is only 0.8 kcal/mol more strained than its cis counterpart. Based on this analysis, a new strategy was proposed which is summarized in a revised retrosynthetic plan in Figure 4.5.
The cyclopentane ring in 339 is projected to arise from a ring contraction process (see Figure 4.6 below for an outline of ring contraction strategies). Pentacycle 340 should emerge from the Pummerer cyclization of sulfide 341. The cyclization precursor 341 can be prepared from elementary substrate 343 by a Diels-Alder cycloaddition reaction with an appropriate diene and further functional group manipulations.

Two distinct strategies are outlined in Figure 4.6 for the construction of the cyclopentane ring in the model system 339 from the cyclohexene-containing Pummerer product 339. The first strategy (Figure 4.6, top) employs an oxidative ring contraction of an alkoxy epoxide 345 by a mechanism similar to the pinacol rearrangement. For this strategy to work, the Diels-Alder reaction would require a 2-alkoxy butadiene (such as 2-methoxy butadiene) as the diene component. The second method (Figure 4.6, bottom)
would employ a Wolff rearrangement of an $\alpha$-diazoketone 348. The Wolff rearrangement’s utility in forming strained ring systems from cyclic $\alpha$-diazoketones is well documented.$^{103-106}$ The substrate for the Wolff rearrangement 348 can be prepared from 347 by a sequence involving hydroboration-oxidation (or oxymercuriation-reduction), alcohol oxidation and a diazo transfer reaction. It is projected also that the carboxylic acid (or derivative) in 339 can serve as a handle for the installation of the chloride group at that position in palau’amine (12) through a Barton-type chlorinative decarboxylation (cf. Romo et. al., section 2.3).

Figure 4.6. Ring contraction strategies to prepare the cyclopentane core of model system 339.

4.3 Synthesis Attempts Using $N$-Dimethyl Sulfamoyl Imidazole Substrates

In order to set the $trans$ stereochemistry at the 5,5-ring junction found in palau’amine (12), a Diels-Alder cycloaddition between a $trans$-substituted imidazole-
containing alkene (of the type 343, Figure 4.5) and an appropriate diene was required. Initially, an \( N,N' \)-dimethyl sulfamoyl protected imidazole dienophile 354 was chosen (Figure 4.7). The sulfonamide protecting group was selected because it is inexpensive and easily deprotected by treatment with aqueous acid. This electron-withdrawing protecting group also has the added benefit of activating the dienophile toward the cycloaddition reaction.

The synthesis of dienophile 354 commenced by reacting imidazole with dimethyl sulfamoyl chloride in toluene in the presence of triethylamine to give the known \( N \)-sulfonamide imidazole 350 (Figure 4.7).\(^{107}\) Exploiting the differential acidities of the imidazole C2 and C5 protons,\(^{97}\) substrate 350 was sequentially lithiated with \( n \)-butyllithium at the 2-position and that anion was quenched with dimethyl disulfide to install the sulfur group in sulfide 351. This species then was formylated at the 5-position to give aldehyde 352. A Horner-Wadsworth-Emmons olefination\(^{108-110}\) of aldehyde 352 with 353-derived ylide\(^{111}\) furnished the desired dienophile 354 in nearly quantitative yield.
Figure 4.7. Preparation $N$-DMSA dienophile for a Diels-Alder cycloaddition reaction.

It soon became evident that dienophile 354 was not capable of furnishing the desired Diels-Alder adduct (Figure 4.8). Submission of compound 354 to Diels-Alder reaction conditions with a variety of dienes (1,3-butadiene, 2-methoxy-1,3-butadiene$^{112,113}$ and Danishefsky's diene$^{114}$) all led to either unreacted starting materials (100 – 160 °C) or decomposition of the diene and/or the dienophile when heated at 160 – 210 °C. The reaction was also found to be unproductive under catalytic conditions$^{115,116}$ (AlCl$_3$, Cu(OTf)$_2$, etc). A series of dienophiles ($\alpha,\beta$-unsaturated nitrile 356$^{117}$, esters 357 and 358$^{118}$, and aldehyde 359$^{7,119,120}$) were prepared and submitted to the Diels-Alder reaction conditions both under heat and catalytic conditions without success (Figure 4.9).
Figure 4.8. Attempted Diels-Alder cycloaddition of dienophile 354 with various butadiene partners

Figure 4.9. Preparation and attempted Diels-Alder reactions of $N$-sulfonamide imidazole dienophiles.

This outcome was surprising given the initial assumption that the electron-withdrawing sulfonamide protecting group would make the dienophile more electron-
deficient, thus facilitating cycloaddition. A careful examination of the chemical literature suggested that alkyl protecting groups such as methoxymethyl (MOM), benzyloxymethyl (BOM) and 2-(trimethylsilyl)ethoxymethyl (SEM) may favor the Diels-Alder reaction of the imidazole-derived dienophile. Our findings using these alternate protecting groups in the effort to assemble the pentacyclic core of palau’amine (12) are discussed below.

4.4 Synthesis Using N-MOM-Protected Imidazoles

The preparation of a MOM-protected dienophile was accomplished using a modification of the method reported by Ohta and coworkers. The synthesis commenced with treatment of a THF solution of imidazole with n-butyllithium at -78 °C followed by alkylation of the resulting lithium amide with methoxymethyl chloride to give the N-MOM imidazole 361 in 55% yield (Figure 4.1). This substrate was sequentially lithiated with n-butyllithium first at the 2-position to install the sulfur group (Ph₂S₂), 54% yield) and then at the 5-position to affix the formyl moiety (DMF, 100% yield) in one pot to give aldehyde 363. Note that the phenylsulfide imidazole compounds were prepared because these compounds were found to be better behaved in the metalation chemistry than their methylsulfide analogues.

The Horner-Wadsworth-Emmons reaction of aldehyde 363 with an ylide derived from 353 gave the desired N-MOM-2-thiophenyl imidazole dienophile 364 in 99% yield. The dienophile was obtained exclusively as the E-alkene, an assignment made based upon the coupling constants for the alkene protons (15.5 Hz). In this instance, the key Diels-Alder cycloaddition proceeded smoothly to deliver the cycloadduct 365 upon heating of a toluene solution of dienophile 364 and 1,3-butadiene at 200 °C in a sealed
tube in the presence of hydroquinone. The structure of 365 was elucidated by $^1$H and $^{13}$C NMR spectral data analysis. Diagnostic signals in the molecule’s $^1$H NMR spectrum include a multiplet at 5.72 ppm corresponding to the alkene protons. Note that the $^1$H NMR signals for H11 and H12 both appear as multiplets, which hindered calculation of the coupling constants for these protons. As a result, the relative stereochemistry in 365, which is assumed to be trans based on the trans alkene dienophile 364, could not be confirmed at this point.

![Diagram](image_url)

Figure 4.10. Preparation of N-MOM dienophile 364 and its successful Diels-Alder cycloaddition reaction to give cycloadduct 365.

With the Diels-Alder adduct 365 in hand, we needed to reduce the amide functionality in this molecule to the corresponding primary amine in order to install the pyrrole unit. Direct reduction of the amide functionality in 365 with hydride sources such
as LiAlH₄ and BH₃ led to the isolation of starting material at low temperatures (-78 to 0 °C) (Figure 4.11). When the reaction was performed at higher temperatures, loss of the thiophenyl group became unavoidable. This disappointing outcome prompted the use of a two-step procedure where the amide 365 was first dehydrated to the nitrile 366, using phosphorus oxychloride, in 73% yield. Nitrile 366 then was reduced by treatment with LiAlH₄ in a 1:1 mixture of diethyl ether and THF at 0 °C to give the amine 367, which was used crude in the next step.

![Diagram of synthetic pathway]

**Figure 4.11.** Synthesis of amide 368 and attempted N-MOM deprotection.
Crude amine 367 from above was allowed to react with dibromopyrrole 234 in the presence of three equivalents of sodium bicarbonate to deliver amide 368 in unoptimized 28% yield (Figure 4.11). With the amide in hand, the remaining task before the crucial Pummerer cyclization could be attempted was removal of the MOM protecting group from 368. To our disappointment, the usual MOM deprotection methods (aqueous or concentrated protic acids) returned unreacted material. Attempts to remove the protecting group using Lewis acids such as boron trichloride and aluminum trichloride gave no useful quantities of the desired product 369. Most of these reactions led to decomposition of the starting material at elevated temperatures or unreacted starting material at low temperatures. This setback led us to screen other alkyl protecting groups that can be removed with relative ease. Although the inability to remove the MOM group hampered our pursuit of the pentacyclic core of dibromopalau’amine (14), identification of reaction conditions for effecting the Diels-Alder reaction set the stage for subsequent more successful studies (vide infra).

4.5 Synthesis with N-BOM-2-Thiophenyl Imidazole Substrates

The synthesis of the N-BOM compounds began with the reaction of imidazole (329) with benzyloxymethyl chloride (BOM-Cl) in acetonitrile in the presence of a large excess of potassium carbonate (K$_2$CO$_3$) at room temperature to give the N-BOM imidazole 370 (Figure 4.12). This reaction was found to form the bis-BOM imidazole salt when excess BOM-Cl was used. The low yield of the reaction could also be attributed to competing salt formation. An attempt to prepare 370 by forming the lithium amide of
imidazole using \(n\)-butyllithium followed by alkylation with BOM-Cl led to a mixture of unidentified compounds.

The crude \(N\)-BOM imidazole 370 then was treated with \(n\)-butyllithium at -78 °C and the resulting lithiated imidazole was allowed to react with diphenyl disulphide to attach the S-phenyl moiety in 371 (Figure 4.12). Note that chromatographic purification of 370 prior to this reaction made no difference in the yield of the S-phenyl product 371. Formylation of imidazole 371 with \(n\)-butyllithium and DMF yielded the corresponding aldehyde 372 in excellent yield. Aldehyde 372 was subjected to Horner-Wadsworth-Emmons reaction with an ylide derived from 353 to give the desired \(N\)-BOM dienophile 373 in nearly quantitative yield. The compound was obtained exclusively as the \(E\)-alkene based on \(^1\)H coupling constants for the alkene protons (15.6 Hz).
As expected, dienophile 373 furnished cycloadduct 374 when it was allowed to react with 1,3-butadiene in a Diels-Alder reaction (Figure 4.12). The structure of compound 374 was elucidated based on $^1$H, $^{13}$C NMR spectral data and molecular weight confirmation by mass spectrometry. The $^1$H NMR spectrum of cycloadduct 374 contains a multiplet signal at 5.74 ppm corresponding to the two vinylic protons. The relative stereochemistry in 374 is assumed to be trans based on the trans alkene 373, although this could not be verified by spectral means at this point due to inability to calculate coupling constants for H11 and H12 as both signals appear as multiplets.
All attempts to reduce the amide group in 374 directly to the primary amine again failed. Therefore, we resorted to the two-step protocol used in the N-MOM imidazole series (vide supra). Accordingly, amide 374 was dehydrated using phosphorus oxychloride to give the corresponding nitrile 375 in very good yield. At this point, instead of reducing nitrile 375 to the corresponding amine as was done in the case of the MOM-protected imidazole series, we sought to remove the BOM group in order to avoid potential complications in a late-stage deprotection. Upon examination of the chemical literature, we came across AlCl$_3^{122,123}$ as a safe reagent for the removal of this protecting group. To our delight, a brief (15 min) exposure of N-BOM substrate 375 to a suspension of aluminum chloride in dichloromethane gave the desired N-H imidazole product 376 in good yield (Figure 4.12).

The remaining tasks needed in order to obtain the Pummerer precursor 369 (Figure 4.13) included reduction of nitrile 376 to amine 377 and acylation of this amine with dibromopyrrole 234. The reduction of nitrile 376 was accomplished with lithium aluminum hydride at 0 °C to give the primary amine 377 in excellent yield. The reduction proceeded cleanly in two hours and did not require any purification of the crude material. The amine obtained from this reaction was then acylated with dibromopyrrole 234 in acetonitrile (10% DMF was necessary to aid with solubility) in the presence of sodium carbonate (Na$_2$CO$_3$) to give the desired amide 369 in 74% yield. It is noteworthy that the naked imidazole nitrogen atom does not compete with the primary amine for the acyl electrophile as evidenced by TLC and spectroscopic data of the crude reaction mixture.
Figure 4.13. Synthesis of the Pummerer cyclization precursor amide 369.

4.6 Synthesis with N-SEM-2-Thiophenyl Imidazole Substrates

In parallel with the N-BOM substrate synthesis, an N-SEM imidazole series was also explored for the synthesis of the Pummerer cyclization precursor 369. The SEM protecting group not only offers the alkyl substitution on the imidazole nitrogen required for the Diels-Alder cycloaddition reaction (*vide supra*), but also deprotection of this unit under relatively mild conditions is well established. However, compared to MOM-Cl and BOM-Cl, SEM-Cl is significantly more expensive.

In this effort, imidazole (329) was treated with *n*-butyllithium at -78 °C and the resulting lithium amide was alkylated with SEM-Cl at room temperature (Figure 4.14). The SEM-protected imidazole 378 then was lithiated *in situ* at the 2-position with *n*-butyllithium at -78 °C and the resulting carbanion was treated with diphenyl disulphide to give the S-phenyl imidazole 379 in 72% over two steps. Formylation of S-phenyl imidazole 379 by treatment with *n*-butyllithium and DMF furnished aldehyde 380 in
quantitative yield. Aldehyde 380 was carried on crude in a Horner-Wadsworth-Emmons reaction with phosphonate 353 to give the desired N-SEM dienophile 359. Heating a mixture of this dienophile and 1,3-butadiene at 200 °C for 44 hours delivered the Diels-Alder cycloadduct 382 in 53% yield (Scheme 4.11). The amide group in this product was converted to the primary amine in two steps; dehydration of the amide to the nitrile 383 using phosphorus oxychloride (76% yield) and then reduction of the nitrile to the amine using lithium aluminum hydride (94% yield).

![Chemical structures](image_url)

Figure 4.14. Synthesis of N-SEM substrates.

Amine 384 was acylated with dibromopyrrole 234 using an optimized protocol to deliver amide 385 in 74% yield (Figure 4.15). Before this compound could be used in the Pummerer cyclization, the imidazole nitrogen atom had to be freed from the SEM
protecting group. This task was accomplished by using a two-step sequence as outlined in Figure 4.15. First the ethylsilyl group was cleaved using boron trifluoride etherate. Then, deformylation of the product’s N-methylene hydroxy group using a mixture of TBAF and ethylene diamine in refluxing THF gave the desired Pummerer precursor 369 in 68% overall yield. The successful synthesis of this same Pummerer precursor by both N-BOM and N-SEM protecting group chemistry set the stage for the oxidative Pummerer cyclization trials described below.

Figure 4.15. Synthesis of Pummerer precursor 369 by N-SEM imidazole chemistry.

The Pummerer cyclization sequence was initiated by treating 369 with the hypervalent iodine reagent Phl(CN)OTf in acetonitrile at 0 °C in the presence of 2,6-lutidine to give the pentacyclic product 387 as a single diastereomer (55% yield; ~75% yield per C-N bond formed, Figure 4.16). Pentacycle 387 features a trans-6,5 ring fusion reminiscent of the trans-5,5 ring fusion found in palau’amine (12). It also contains the correct relative stereochemistry found in the natural product at all four contiguous
stereogenic centers. The structure and relative stereochemistry of pentacycle 387 was suggested by spectroscopic methods and confirmed by single crystal X-ray crystallographic analysis (Figure 4.17). Diagnostic $^1$H NMR signals for this molecule include a singlet at 5.37 ppm corresponding to H6 (palau’amine numbering). The $^{13}$C signal for C6 was observed at 71.8 ppm and C10 appeared at 92.6 ppm, both of which are indicative of N-C bond formation by the Pummerer cyclization.

The cyclization process is believed to proceed via the $^{1,3}$-favored transition state 386 depicted in Figure 4.16 (vinylogous Pummerer intermediate shown for clarity) that unambiguously explains the observed stereochemical outcome of the reaction. This cyclization to form the trans-6,5 ring system is noteworthy not only for the efficient construction of the polycyclic system 387, but also for its mimicry of the proposed biosynthetic pathways for palau’amine (12) (and other P-I alkaloids) by both Baran and Al-Mourabit (vide supra).

![Figure 4.16. Pummerer cyclization to form the pentacyclic core of palau'amine.](image_url)


4.7 N-SEM-2-Thiomethyl Imidazole Substrates

Alongside the S-phenyl substrates described above, S-methyl analogues also were prepared using a similar sequence of transformations (Figure 4.18). This route was explored because the S-methyl substrates greatly simplify the NMR spectra for these compounds. In addition, the S-methyl group is reported to be readily substituted for a nitrogen species to make the guanidine unit found in palau’amine (12). The preparation of the S-methyl analogues began with protection of imidazole (329) with a SEM group and addition of the S-methyl moiety in situ using n-BuLi and dimethyl disulfide to give the N-SEM 2-thiomethyl substrate 388 in 38% yield over two steps.

Direct formylation at the 5-position of imidazole 388 using various bases (n-BuLi, LDA, LiTMP, etc) all failed to give the desired aldehyde. In all cases, the S-methyl group was found to be too labile and it was cleaved under the reaction conditions. In addition, mixtures of mono- and bis-formylated compounds were recovered. As a result, alternative methods for the installation of the aldehyde unit were pursued. Bromination at the 5-position of N-SEM imidazole 388 using NBS gave the 5-bromo imidazole compound 389, albeit in unsatisfactory and inconsistent yields (Figure 4.18). With bromoimidazole 389 in hand, Heck coupling reactions were attempted using different
activated alkenes, but these reactions failed to deliver the desired α,β-unsaturated compound 390.

Figure 4.18. Substrate synthesis in the S-methyl series.

However, a facile lithium-bromine exchange was effected by treating bromide 389 with n-butyllithium to generate the 5-lithioimidazole (not shown), which was formylated with DMF to give the desired aldehyde 391 in a good yield (Figure 4.19). Then, aldehyde 391 was converted to α,β-unsaturated amide 392 by the Hornner-Wadsworth-Emmons olefination in excellent yield. Subsequently, the Diels-Alder reaction between amide 392 and butadiene gave the cycloadduct 393 in 38% yield upon heating in toluene at 200 °C. Coupling constants for H11 and H12 could not be calculated from 1H NMR data of 393. Therefore, the trans stereochemistry in 393 is assigned tentatively based on the trans dienophile 392. The alkene protons for 393 were observed at 6.02 ppm in 1H NMR spectrum as a broad singlet, a typical observation among this type of molecules (cf. Sections 4.4 and 4.5).
Figure 4.19. Lithium-bromine exchange for C5 formylation of imidazole 389 and subsequent Diels-Alder cycloaddition reaction to prepare 393.

We then proceeded to synthesize the Pummerer cyclization precursor 397 (Figure 4.20) once the Diels-Alder product was obtained. The amide functionality in 393 was reduced to amine 395 by the two-step process used in the S-phenyl series (POCl₃; LiAlH₄). Acylation of crude amine 395 with dibromopyrrole 234 was achieved with Na₂CO₃ in acetonitrile to give amide 396 in 63% yield over two steps from nitrile 394. The SEM protecting group in compound 396 was removed by the two-step protocol used in the S-phenyl series (BF₃•Et₂O; TBAF) to give the N-H imidazole 397 in 61% yield over 2 steps.
Figure 4.20. Preparation of S-methyl Pummerer cyclization precursor 397.

The S-methyl Pummerer cyclization precursor 397 gave the desired cyclization product 398 in 40% yield when subjected to the hypervalent iodine reagent PhI(CN)OTf in acetonitrile (Scheme 4.21). The compound was tentatively assigned the stereochemistry shown by spectral data comparison with the S-phenyl Pummerer product 387 (structure secured by X-ray crystallographic analysis). Diagnostic $^1$H NMR signals for the bicyclization 398 include a singlet at 5.57 ppm corresponding to the aminal proton H6. The $^{13}$C NMR signals for C6 and C10 were observed at 72.2 and 92.1 ppm, respectively (cf. 71.8 and 92.6 for compound 387). Despite the advantages of using the S-methyl substrate (see earlier discussion), the lower overall yields of this series and unpredictability of some of the transformations involved (including the imidazole
bromination step) discouraged us from using this route in synthesizing the desired palau’amine model compound 399 (Figure 4.22).

![Chemical structure](image)

Figure 4.21. Pummerer cyclization of S-methyl substrate 397 to give pentacycle 398.

### 4.8 Wolff Rearrangement to Construct the Cyclopentane Core

Through the successful synthesis of the pentacyclic ring systems 387 and 398, we demonstrated the potential utility of the imidazole-based Pummerer reaction in the total synthesis of the palau’amine (12) framework. With the pentacycle 387 in hand, the conversion of this system to our more advanced model 399 (Figure 4.22) that contains a trans-5,5 ring fusion was pursued. This task was envisioned to be accomplished via a Wolff rearrangement of an α-diazo ketone derived from compound 402. This plan necessitated the transformation of the alkene functionality in 387 to a ketone 402 from which the desired α-diazo ketone can be prepared. The description of this effort in the synthesis of the trans-5,5 model system is discussed below.
Initial efforts to prepare ketones 402/403 focused on the conversion of the alkene moiety in 387 to the corresponding alcohols 400/401 (Figure 4.23) via the well established Brown hydroboration-oxidation protocol\textsuperscript{128-130}. However, attempts at hydroboration-oxidation of the alkene in pentacycle 387 met with failure. Treatment of alkene 387 with stoichiometric amount-to-large excess of boranes (such as BH\textsubscript{3}•DMS,\textsuperscript{114} BH\textsubscript{3}•THF, 9-BBN, etc.) all led to the isolation of unreacted starting material along with trace amounts of alcohol-containing product that was detectable only by mass spectrometry. The reason why this reaction failed is unclear.\textsuperscript{131} This setback prompted us to look for alternative methods to prepare the required ketone substrate. One of the methods tried was a Wacker oxidation protocol.
Wacker oxidation is a popular transformation that oxidizes terminal alkenes to the corresponding methyl ketones under mild conditions using palladium catalysis\textsuperscript{132-134}. Although this method is applied in the synthesis of methyl ketones from terminal olefins, many examples exist in the chemical literature that involve the preparation of cyclic ketones from internal cycloalkenes\textsuperscript{135-137}. We sought to implement such direct oxidation of the alkene in pentacycle \textbf{387} to the corresponding ketones \textbf{402/403} (Figure 4.23). Unfortunately, none of the conditions tried in our laboratory gave the desired ketones; all efforts led to decomposition or complex mixtures of products.

Having failed to prepare the desired ketones by the aforementioned methods, we resorted to a classic technology for the hydration of alkenes, namely, the oxymercurcation-demercuration protocol\textsuperscript{138-140}. Although the process of oxymercurcation-demercuration reaction has its disadvantages because of the toxicity of the mercury byproduct, it is a reliable procedure for the Markovnikov addition of water to olefins. The method proved
to be compatible with the current system and produced the desired alcohols (400 and 401) from 387 albeit in consistently low yields (Figure 4.24). Treatment of pentacycle 387 with either mercuric acetate (Hg(OAc)$_2$) or mercuric trifluoroacetate (Hg(OTf)$_2$) in a mixture of THF and water at room temperature gave the organo-mercury salt (not shown) as a white precipitate in a few hours. In this step, the use of a catalytic amount of acid (HClO$_4$) was important for accelerating the oxymercuration reaction that otherwise took an extended reaction time.$^{141,70}$

The mercury adduct was reduced in situ with a solution of sodium borohydride in 3.0 M sodium hydroxide to furnish a mixture of four alcohols (400 and 401) in 40% yield along with 30% of the alkene starting material 387. The recovered starting material is due to an elimination side reaction which is a well documented problem in the reduction step of oxymercuration-demercuration reactions.$^{141}$ Attempts to suppress this unproductive side reaction by using diethyl ether$^{141}$ as the solvent in place of THF resulted in lowered yields. The alcohols 400 and 401 were oxidized to ketones 402 and 403 using Dess-Martin periodinane (DMP) in 72% yield. The ketones were obtained as a 3:1 mixture of regioisomers. The regiochemistry of the major isomer is tentatively assigned as 403 based on the HMBC correlation indicated in Figure 4.24. The most diagnostic spectral feature of compound 403 includes the carbonyl carbon that was observed at 208.8 ppm in the $^{13}$C NMR spectrum. Also significant was the disappearance of the alkene protons at $\sim$6 ppm from the $^1$H NMR spectrum of 403 (cf. 5.62 ppm, brs for 387).
Figure 4.24. Oxymercuration-demercuration followed by Dess-Martin oxidation to synthesize ketones 402/403.

The next step in the synthesis of model system 399 necessitated the generation of an α-diazoketone substrate for the crucial Wolff rearrangement (ring contraction) protocol. α-Diazoketones are prepared commonly by diazo transfer\textsuperscript{142,143} reactions where a ketone enolate reacts with sulfonyl azides to give the α-diazo compounds. Whereas highly stabilized β-dicarbonyl enolates are capable of direct diazo transfer reactions, the synthesis of α-diazoketones from unactivated ketones requires a two step protocol known as a deformylative diazo transfer reaction.\textsuperscript{135,142,144} In this procedure, unactivated ketones are first converted to β-dicarbonyl compounds by a Claisen condensation. Diazo transfer from a sulfonyl azide followed by deformylation of the second carbonyl group (appended by the Claisen reaction) finally affords the desired α-diazoketone.
Figure 4.25. Synthesis of cyclopentane methyl ester 407 by a Wolff rearrangement of α-diazoketone 406.

The initial Claisen condensation in this deformylative diazo transfer strategy was effected by treating the mixture of ketones 402/403 with lithium bis-(trimethylsilyl)amide followed by reaction of the resulting enolates with 2,2,2-trifluoroethyl 2,2,2-trifluoroacetate to give the desired β-dicarbonyls 404 and 405. The reaction furnished 39% of the major regioisomer 404 exclusively as the enol tautomer (structure elucidated by HMBC correlation studies, see Figure 4.25). Also isolated was 34% of a ~1.5:1.5:7
(by $^1$H NMR) inseparable mixture of three other regioisomers, also entirely as the enol tautomers. The other major regioisomer in the mixture is assumed to be the $\beta$-dicarbonyl 405 which arises from the ketone 402. Dicarbonyls 404 and 405 are believed to arise from deprotonation of ketones 403 and 402 each from the sterically less encumbered side. Diagnostic $^1$H NMR features for 404 includes a singlet at 15.2 ppm corresponding to the enol proton. On the other hand, the carbonyl carbon for the trifluoromethyl ketone moiety in 404 was observed at 180.3 ppm in the $^{13}$C NMR spectrum as a quartet with a $^2J$ C-F coupling constant of 34.1 ppm, which is a typical splitting pattern for such systems.$^{145}$

Dicarbonyl 404 was transformed to the corresponding $\alpha$-diazoketone 406 by treatment with mesyl azide in acetonitrile in the presence of triethylamine and water at room temperature (Figure 4.25). Repeated attempts to isolate and characterize 406 failed due to the compound’s sensitivity to silica gel. However, when the crude material was irradiated at 300 nm in methanol, the Wolff rearrangement$^{103,146-148}$ occurred to deliver the cyclopentane methyl ester 407 as the sole isolable regioisomer in 41% yield over 2 steps from 404. The methyl ester was obtained as a ~1:1 mixture of two diastereomers.

Note that irradiation of a crude mixture of all four possible $\alpha$-diazoketones derived from ketones 402/403 delivered the cyclopentane methyl ester 407 as the sole isolable regioisomer in 37% yield over 3 steps (>70% average yield per transformation, 1:1 mixture of diastereomers). On the other hand, the Wolff rearrangement reaction performed using $\alpha$-diazoketones in the presence of water (instead of methanol) failed to give the corresponding cyclopentane carboxylic acid product both under heat and photochemical conditions. The reason for this failure is not yet clear.
The mechanism for the photochemical Wolff rearrangement is outlined in Figure 4.26. The widely accepted sequence under photochemical conditions involves the expulsion of nitrogen gas from the diazoketone 406 to generate a carbene 408. The carbene can follow one of two possible courses of reaction. The first one is a simple O-H insertion of methanol to give 409, which has the same molecular weight as methyl ester 407. On the other hand carbene 408 can participate in a 1,2-alkyl shift and electronic rearrangement to give a ketene intermediate 410 that is trapped with the solvent (in this case methanol) to give cyclopentane methyl ester 407 after tautomerization of enol 411 (note also that 1,2-alkyl shift and expulsion of N2 can occur in a concerted fashion to furnish ketene 410). Compound 409 is excluded as a possible product based on 1H and 13C NMR and HMQC data analyses. For instance no 13C signal was observed for the ketone group in 409 at ~200 ppm (cf. ~175 ppm for 407).

Figure 4.26. Mechanism for the photochemical Wolff rearrangement reaction.
A summary of notable $^1$H and $^{13}$C NMR signals for 407 is found in Table 4.1 along with the corresponding NMR data found in the palau’amine isolation report. Diagnostic signals in the $^1$H NMR spectrum of the methyl ester 407 include two singlets belonging to the methoxy groups at 3.73 and 3.70 (diastereomers) each integrating to 3H. The $^{13}$C signal for the same methoxy groups appear at 52.1 and 52.0 whereas the carbonyl carbon of this methyl ester group appears at 176.3 and 175.5 ppm. The 5,5-ring junction proton H11 (palau’amine numbering) was observed at 2.31 and 2.14 ppm as doublets of a triplet. The signal for H12 was observed at 2.78 and 2.69 ppm as multiplets.

A direct comparison between the chemical shifts for methyl ester 407 and palau’amine (12) cannot be made, of course, because of the difference in the substitution patterns for the two molecules. Also, the NMR data for 407 was obtained in CDCl$_3$ while D$_2$O was used in the case of 12. However, it is important to note that the $^1$H-$^1$H coupling constant for H11 was found to be 13.3 Hz for methyl ester 407 (in CDCl$_3$) compared to 14.1 Hz for the same proton in both Baran’s synthetic palau’amine and Scheuer’s isolation report (in D$_2$O). The lower coupling constant for 407 may be a result of the relative ease in the movements of the ring system in 407 (twist, flip)$^{149}$ compared to 12 which should be more rigid than 407 due to dense substitution around the cyclopentane ring. Nevertheless, this new entry to the trans-fused azabicyclo[3.3.0]octane systems should give some perspective on the NMR properties of these scarce trans-fused bicyclooctane rings. An extensive HMBC correlation in support of the given regioisomer is shown in Figure 4.27.
<table>
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<td>$^1$H ($J$ in Hz)</td>
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<td>6.37, s</td>
<td>69</td>
</tr>
<tr>
<td>10</td>
<td>---</td>
<td>80.8</td>
</tr>
<tr>
<td>11</td>
<td>3.11, dd, 14.1</td>
<td>56.3</td>
</tr>
<tr>
<td>12</td>
<td>2.52, m</td>
<td>41.9</td>
</tr>
</tbody>
</table>

Table 1. Comparison table of some significant $^1$H and $^{13}$C NMR signals for palau'amine (Scheuer) and cyclopentane methyl ester 407.

Figure 4.27. HMBC correlations for cyclopentane methyl ester 385 as supporting evidence for the regiochemical assignment.
4.9 Other Ring Contraction Attempts

Alternative and potentially more expedient ring contraction procedures were attempted. Among the methods tried was hypervalent iodine promoted ring contraction\(^{150}\) of the cyclohexene \(\text{387}\) to the corresponding cyclopentanecarboxaldehyde \(\text{412}\) (Figure 4.28). A limited number of literature precedents exist on the ring contraction of cyclohexenes to the corresponding cyclopentanes promoted by I(III) (e.g., \(\text{413} \rightarrow \text{416}\), Figure 4.28).\(^{150-152}\) All attempts with this chemistry on alkene \(\text{387}\) (using hypervalent iodine sources such as PhIO•BF\(_3\)^{151}, \text{PhI(OAc)}_{2}^{152}, \text{etc}) failed to give the desired ring contraction product.

![Figure 4.28. Hypervalent iodine-promoted ring contraction attempts.](image)

Rearrangements of epoxide-containing carbocycles to give smaller ring systems are a well-documented phenomena (e.g., \(\text{420} \rightarrow \text{422}\), Figure 4.29).\(^{153-156}\) Most literature
precedents involve tri- or tetra-substituted oxiranes or simple, minimally strained carbocycles such as cyclohexane oxide although precedents exist on steroidal systems as well (not shown).\textsuperscript{157,158} Nevertheless, these rearrangements appear to be robust and high yielding on the systems reported. In order to attempt such an epoxide ring contraction process, alkene 387 was oxidized to the corresponding epoxide 418 by treatment with \textit{m}CPBA.

Note that during this oxidation the thioimidate functionality in 387 was hydrolyzed to the urea, a process occurring most likely through a sulfoxide intermediate. Careful addition of the oxidant and control of the reaction time revealed that thioimidate hydrolysis proceeded first to give the urea 417. Attempted ring contractions of epoxide 418 using reagents such as alumina-supported LiBr\textsuperscript{155} and LiBr in the presence of HMPA\textsuperscript{159} gave none of the rearrangement product. In both cases, the starting material was recovered unchanged. Note that epoxy urea 418 is currently being studied for biological activity. Preliminary results show that both epoxide 418 and sulfide 387 possess potent 20S proteosome inhibitory activity.\textsuperscript{160} The results of these tests will be reported in due course.
4.10 Conclusion

The synthesis of the \textit{trans}-6,5 pentacyclic core of dibromopalau’amine was accomplished using Pummerer oxidative cyclization chemistry as the key bond forming reaction (compounds 387 and 398). The success of this diastereoselective reaction demonstrated the potential utility of this method for the total synthesis of palau’amine. Subsequent ring contraction of the cyclohexene moiety in 387 to a cyclopentane ring system featuring a 5,5-trans-fused system (compound 407) was also achieved by a Wolff rearrangement. In addition, initial results on the biological activity of pentacycles 387 and epoxy urea 418 are encouraging.
Chapter 5

Experimental Procedures

5.1 General Experimental

All air and moisture sensitive reactions were carried out in flame-dried glassware under an argon or nitrogen atmosphere. All reaction solvents were purified by passage through activated alumina columns (Glass Contour - glasscontoursolventsystems.com). All reagents were used as purchased. Reactions were monitored by thin-layer chromatography when possible. Flash column chromatography was performed using 32 – 63 µm silica gel columns. In the indicated cases, silica gel was deactivated by thoroughly mixing water (20% wt) and silica. All melting points are uncorrected. Low and high-resolution mass spectra were obtained according to the specified technique and were performed at The Huck Institute of the Life Sciences – Proteomics and Mass Spectrometry Core Facility at The Pennsylvania State University, University Park, PA. X-ray data were obtained from the Protein X-ray Crystallography Core Facility, hosted by the Department of Biochemistry and Molecular Biology, at The Pennsylvania State University, University Park, PA.

5.2 General Methods

General Procedure 1: N-MOM and N-SEM Protection of Imidazole. To a solution of imidazole (1.0 equiv) in THF (0.5 M) at -78 °C was added a solution of 2.5 M n-BuLi in hexanes (1.2 equiv) and the reaction mixture was warmed to 0 °C and stirred
for 30 min.\textsuperscript{121} To this reaction mixture at 0 °C was added 1.2 equiv chloromethyl methyl ether (MOM-Cl) or 1.2 equiv (2-(chloromethoxy)ethyl)trimethylsilane (SEM-Cl) dropwise over 5 min and the resulting solution was stirred for 30 min at rt. Then, a saturated solution of NH\textsubscript{4}Cl was added and the organic layer was separated. The aqueous layer was extracted with Et\textsubscript{2}O. The organic layers were combined, dried over anhydrous Na\textsubscript{2}SO\textsubscript{4}, filtered and concentrated \textit{in vacuo} to give the desired N-MOM or N-SEM imidazole. The crude material was purified by silica gel column chromatography using the indicated solvent system.

**General Procedure 2: Preparation of C2 Thiophenyl and Thiomethyl Imidazoles.** To the appropriate N-protected imidazole dissolved in THF (0.1 M) was added a solution of 2.5 mL \textit{n}-BuLi in hexanes (1.2 equiv) at -78 °C, dropwise over 5 min and the reaction mixture was stirred at that temp for 30 min more. A solution of diphenyl disulfide or dimethyl disulfide (1.2 equiv) in THF (1.0 M) then was added at -78 °C, dropwise, over 5 min. After stirring the reaction mixture for 1 h at -78 °C, a saturated aqueous solution of NH\textsubscript{4}Cl was added and the mixture was warmed up to rt. The organic layer was separated and the aqueous layer was extracted with Et\textsubscript{2}O. The combined organic layers were dried over anhydrous Na\textsubscript{2}SO\textsubscript{4}, filtered and concentrated \textit{in vacuo}. The crude material was purified by silica gel column chromatography using the indicated solvent system.

**General Procedure 3: C5 Formylation of Imidazole Substrates.** To a solution of the appropriate N-protected imidazole (1.0 equiv) in THF (0.15 M) at -78 °C was added \textit{n}-BuLi (1.2 equiv) dropwise over 5 min and the resulting solution was stirred for
15 min at that temperature. To this solution was added neat DMF (1.2 equiv) over 5 min via syringe and the resulting solution was stirred at that temperature for 30 min. A saturated aqueous NH₄Cl solution was added and the reaction mixture was warmed up to rt. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated *in vacuo* to give the desired aldehyde. The crude material was purified by the indicated method.

**General Procedure 4: Horner-Wadsworth-Emmons Olefination of Aldehydes.** To a solution of diethyl 2-amino-2-oxoethylphosphonate (1.0 equiv) in THF (0.35 M) at 0 °C was added t-BuOK (1.0 equiv) and the mixture was stirred at that temperature for 30 min. To the resulting ylide at 0 °C was added a solution of the appropriate aldehyde (1.2 equiv) in THF (0.5 M) dropwise over 5 min and the reaction mixture was stirred until TLC showed complete consumption of the aldehyde. The reaction solution was then diluted with water and the THF layer was removed *in vacuo*. The aqueous layer was extracted with EtOAc and the combined organic layers were dried over anhydrous Na₂SO₄, filtered and the solvent was removed *in vacuo*. The resulting crude residue was purified by the indicated methods to give the desired α,β-unsaturated amide dienophile.

**General Procedure 5: Diels-Alder Cycloaddition Reactions.** The appropriate α,β-unsaturated amide dienophile (1 equiv), 1,3-butadiene (14 equiv) and hydroquinone (0.1 equiv) were mixed in toluene (0.5 M in amide) at -78 °C in a sealed tube or a stainless steel autoclave under air atmosphere and warmed to rt. The reaction mixture was
then heated at 200 °C for 36 hrs and then cooled to rt. The crude mixture was transferred directly to a silica gel column and chromatographed using the indicated solvent system to yield the desired Diels-Alder adduct.

**General Procedure 6: Dehydration of Amides to Nitriles.** To a solution of phosphorus oxychloride (8.0 equiv) in THF (0.6 M) at 0 °C was added Et₃N (12 equiv) dropwise over 2 min and the mixture was stirred for 30 min. This solution was cannulated into a solution of the appropriate amide (1 equiv) in CH₃CN (0.15 M) dropwise over 5 min at 0 °C and stirred at that temperature until TLC showed complete consumption of the starting amide. The reaction mixture was then filtered through a thin pad of Celite®, washing with CH₃CN, and the filtrate was concentrated under reduced pressure. The residue was chromatographed directly on a silica gel column using the indicated solvent system as the eluent to give the pure nitrile.

**General Procedure 7: Reduction of Nitriles to Primary Amines.** To a solution of the appropriate nitrile (1.0 equiv) in Et₂O (0.03 M) at -78 °C was added a solution of 1.0 M LiAlH₄ in Et₂O (2.0 equiv) dropwise over 5 min. The resulting cloudy suspension was warmed up to 0 °C over 30 min and stirred until TLC showed complete consumption of the nitrile. The reaction mixture then was diluted with THF and water (x mL of water per x gram of LiAlH₄) was added at 0 °C dropwise followed by a 3.0 M aqueous NaOH solution (x mL) and more water (3x mL), and then the mixture was warmed up to rt. Anhydrous MgSO₄ was added to remove residual water, and the solution was filtered and concentrated *in vacuo* to give the desired amine product, requiring no further purification.
**General Procedure 8: Acylation of Amines with 2,2,2-Trichloro-1-(4,5-
dibromo-1H-pyrrol-2-yl)ethanone.** To a solution of the appropriate amine (1.0 equiv) in CH$_3$CN (0.1 M) at rt was added 2,2,2-trichloro-1-(4,5-dibromo-1H-pyrrol-2-yl)ethanone (1.1 equiv) followed by granular anhydrous Na$_2$CO$_3$ (3.0 equiv). The reaction mixture was stirred at rt until TLC showed complete consumption of the amine. The mixture was then diluted with water and the CH$_3$CN layer was removed under reduced pressure. The aqueous layer was extracted with EtOAc and the combined organic layers were dried over anhydrous Na$_2$SO$_4$, filtered and concentrated in vacuo. The resulting residue was purified by silica gel column chromatography using the indicated eluent system to give the desired amide.

**General Procedure 9: Deprotection of N-SEM Imidazoles.** To a solution of the appropriate N-SEM protected imidazole in CH$_2$Cl$_2$ (0.025 M) at 0 °C was added BF$_3$•Et$_2$O (5.0 equiv) and the solution was warmed up to rt. The reaction mixture was stirred for 3 h at that temperature and diluted with water. The mixture was then extracted with EtOAc and the combined organic layers were dried over anhydrous Na$_2$SO$_4$, filtered and concentrated in vacuo. The resulting off-white solid was dissolved in THF (0.025 M) and ethylenediamine (3.0 equiv) was added at rt followed by a 1.0 M solution of Bu$_4$NF (10 equiv) in THF. The reaction mixture was heated at reflux for 16 h, cooled to rt, diluted with water and EtOAc, and the organic layer was separated. The aqueous layer was extracted with EtOAc and the combined organic layers were dried over anhydrous Na$_2$SO$_4$, filtered and concentrated in vacuo. The crude residue was chromatographed on a silica gel column using the indicated eluent to give the desired N-H imidazole product.
General Procedure 10: PhI(CN)OTf Initiated Pummerer Cyclization of Sulfide Substrates to Pentacycles. The appropriate N-H imidazole substrate was dissolved in CH$_3$CN (0.005 M) and cooled to 0 °C. To this reaction mixture was added 2,6-lutidine (4 equiv) followed by PhI(CN)OTf (3 equiv) portionwise over 30 min. The resulting solution was stirred for an additional 30 min and the reaction mixture was diluted with water and EtOAc. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic extracts were dried over anhydrous Na$_2$SO$_4$ and concentrated *in vacuo*. The crude material was purified by the indicated method.
5.3 Preparations for N-MOM-2-Thiophenyl Imidazole Substrates

![Chemical Structure]

1-(Methoxymethyl)-2-(phenylthio)-1H-imidazole (362). Following general procedure 1, imidazole (10.0 g, 147 mmol) was converted into 9.11 g (55%, crude) of N-MOM imidazole 361, which was obtained as a pale yellow oil. The crude oil was used in the next step without purification.

Following general procedure 2, the crude N-MOM imidazole 361 (5.85 g, 52.2 mmol) was converted to 6.20 g (54%) of N-MOM-S-phenylimidazole 362, which was obtained as a pale yellow oil following purification of the crude material by silica gel column chromatography using 15 – 30% EtOAc in hexanes as the eluent: IR (thin film) 2932 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.25 – 7.14 (m, 7H), 5.30 (s, 2H), 3.14 (s, 3H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 138.4, 134.3, 130.6, 129.0, 128.3, 126.7, 122.2, 77.1, 56.1; LRMS (ESI+) \(m/z\) (relative intensity) 221.4 (M+H\(^+\), 100%).
1-(Methoxymethyl)-2-(phenylthio)-1H-imidazole-5-carbaldehyde (363).

Following general procedure 3, 1-(methoxymethyl)-2-(phenylthio)-1H-imidazole (362) (3.00 g, 13.6 mmol) was converted into 3.37 g aldehyde 363, which was obtained as a yellow tacky solid (100% crude): IR (thin film) 1670 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 9.66 (s, 1H), 7.77 (s, 1H), 7.53 – 7.51 (m, 2H), 7.40 – 7.36 (m, 3H), 5.77 (s, 2H), 3.34 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 178.1, 152.1, 144.0, 132.8 (2), 129.4, 129.1, 128.9, 75.4, 56.4; LRMS (ESI+) $m/z$ (relative intensity) 248.1 (M+H$^+$, 100%).

(E)-3-(1-(Methoxymethyl)-2-(phenylthio)-1H-imidazol-5-yl)acrylamide (364).

Following general procedure 4, $N$-MOM aldehyde 363 (2.50 g, 10.1 mmol) was converted into $\alpha$,$\beta$-unsaturated amide 364. The crude off-white solid was purified by trituration with Et$_2$O to give 2.90 g (99%) of the desired $\alpha$,$\beta$-unsaturated amide 364 as a white solid: mp 136 – 137 ºC; IR (thin film) 3331, 3179, 1672 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.53 (d, $J = 15.5$ Hz, 1H), 7.51 (s, 1H), 7.27 – 7.22 (m, 5H), 6.70 (brs, 1H),
6.49 (d, \( J = 15.5 \) Hz, 1H), 6.45 (brs, 1H), 5.44 (s, 2H), 3.18 (s, 3H); \(^{13}\text{C NMR (75 MHz, CDCl}_3\) \(\delta\) 167.6, 142.3, 133.1, 131.7, 131.6, 129.3, 129.1, 127.4, 126.7, 120.4, 74.9, 56.0; LRMS (ESI\(^+\)) \(m/z\) (relative intensity) 307.2 (M+H\(^+\), 100%); HRMS (ESI) \(m/z\) calcd for [C\(_{14}\)H\(_{16}\)N\(_3\)O\(_2\)S]\(^+\), 290.0964; found, 290.0963.

![Chemical Structure](image)

**6-(1-(methoxymethyl)-2-(phenylthio)-1H-imidazol-5-yl)cyclohex-3-enecarboxamide (365).** Following general procedure 5, (E)-3-(1-(methoxymethyl)-2-(phenylthio)-1H-imidazol-5-yl)acrylamide (364) (2.28 g, 7.88 mmol) was converted into Diels-Alder adduct 365 (1.08 g, 40%), which was obtained as a pale yellow solid following purification of the crude material by silica gel column chromatography using 50 – 100% EtOAc in hexanes as the eluent: mp 132 - 133 °C; IR (thin film) 3319, 3179, 2909, 1668, 1096 cm\(^{-1}\); \(^1\text{H NMR (300 MHz, CDCl}_3\) \(\delta\) 7.24 – 7.16 (m, 3H), 7.09 – 7.06 (m, 2H), 7.04 (s, 1H), 5.98 (brs, 1H), 5.73 – 5.72 (m, 2H), 5.54 (brs, 1H), 5.27 – 5.19 (m, 2H), 3.15 (s, 3H), 3.06 – 2.99 (m, 1H), 2.92 – 2.83 (m, 1H), 2.54 – 2.43 (m, 2H), 2.28 – 2.17 (m, 2H); \(^{13}\text{C NMR (75 MHz, CDCl}_3\) \(\delta\) 177.8, 145.8, 137.3, 135.2, 129.1, 127.6, 126.6, 125.8, 125.1, 119.8, 77.2, 56.3, 45.6, 35.9, 32.0, 28.7; LRMS (ESI\(^+\)) \(m/z\) (relative intensity) 344.2 (M+H\(^+\), 100%); HRMS (ESI) \(m/z\) calcd for [C\(_{18}\)H\(_{22}\)N\(_3\)O\(_2\)S]\(^+\), 344.1429; found, 344.1433.
6-(1-(Methoxymethyl)-2-(phenylthio)-1H-imidazol-5-yl)cyclohex-3-enecarbonitrile (366). Following general procedure 6, amide 365 (0.770 g, 2.24 mmol) was converted into nitrile 366 (0.534 g, 73%), which was obtained as a pale yellow oil following silica gel column chromatography using 20% EtOAc in hexanes as the eluent: IR (thin film) 2226 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.26 – 7.14 (m, 6H), 5.81 – 5.60 (m, 2H), 5.30 (s, 2H), 3.27 – 3.21 (m, 1H), 3.16 (s, 3H), 3.15 – 3.10 (m, 1H), 2.56 – 2.46 (m, 4H); ¹³C NMR (75 MHz, CDCl₃) δ 144.0, 138.0, 134.7, 129.1, 127.5, 126.5, 126.4, 123.1, 121.7, 119.6, 77.3, 56.2, 35.7, 30.7, 30.0, 28.3; LRMS (ESI+) m/z (relative intensity) 326.4 (M+H⁺ 100%); HRMS (ESI) m/z calcd for [C₁₈H₂₀Br₂N₃OS]⁺, 326.1315; found, 326.1327.
4,5-Dibromo-N-((6-(1-(methoxymethyl)-2-(phenylthio)-1H-imidazol-5-yl)cyclohex-3-enyl)methyl)-1H-pyrrole-2-carboxamide (368). Following general procedure 7, nitrile 366 (0.300 g, 0.922 mmol) was converted into 0.171 g (56%) of the corresponding amine, which was obtained as a clear and colorless oil. This product was used crude in the next step.

Following general procedure 8, the crude amine from above (0.171 g, 0.519 mmol) was converted into 76.0 mg (25%) of amide 368, which was obtained as a white solid following silica gel column chromatography using 30 – 40% EtOAc in hexanes as the eluent: mp 75 – 76 °C; IR (thin film) 3295, 3119, 1634 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 11.5 (brs, 1H), 7.58 (brs, 1H), 7.19 – 7.06 (m, 5H), 6.90 (s, 1H), 6.43 (s, 1H), 5.61 (brs, 2H), 5.20 (s, 2H), 3.67 – 3.61 (m, 1H), 3.11 (s, 3H), 2.94 – 2.90 (m, 1H), 2.74 – 2.67 (m, 1H), 2.3 – 2.25 (m, 2H), 2.1 – 2.07 (m, 1H), 2.01 – 1.97 (m, 1H), 1.91 – 1.87 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 159.6, 146.8, 138.8, 133.6, 129.3 (2), 127.4, 126.6, 125.8, 118.1, 112.5 (2), 104.9, 99.3, 77.2, 56.4, 42.2, 40.6, 37.0, 31.3, 30.5; LRMS (ESI⁺) m/z (relative intensity) 579.0 (M+H⁺ 100); HRMS (ESI) m/z calcd for [C₂₃H₂₅Br₂N₄O₂S]⁺, 579.0062; found, 579.0065.
5.4 Methods for the Preparations of N-BOM-2-Thiophenyl Imidazole Substrates

1-(Benzyloxymethyl)-1H-imidazole (370). To a suspension of imidazole (20.0 g, 294 mmol) in CH$_3$CN at rt was added K$_2$CO$_3$ (122 g, 882 mmol), followed by a dropwise addition of benzyloxymethyl chloride (BOM-Cl) (45.0 mL, 323 mmol) over 30 min. The reaction mixture then was stirred at rt for 16 h. The K$_2$CO$_3$ was filtered off and the CH$_3$CN layer was removed under reduced pressure. The residue was re-suspended in CH$_2$Cl$_2$ and washed with water (2 x 250 mL) and brine (100 mL). The organic layer was dried over anhydrous MgSO$_4$, filtered, and concentrated in vacuo to give 35.1 g (64%, crude) of the known N-BOM imidazole 370 as yellow oil. Analytical data matched literature values:\textsuperscript{161} IR (thin film) 2932 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.38 (app s, 1H), 7.17 – 7.04 (m, 5H), 6.91 (app s, 1H), 6.85 (s, 1H), 5.10 (s, 2H), 4.21 (s, 2H); LRMS (ESI+) $m/z$ (relative intensity) 189.3 (M+H$^+$, 100).
1-(Benzyloxymethyl)-2-(phenylthio)-1H-imidazole (371). Following general procedure 2, N-BOM imidazole (370) (24.0 g, 128 mmol) was converted into 24.0 g (64%) of 2-thiophenyl imidazole 371, which was obtained as a yellow oil following purification of the crude material by silica gel column chromatography using 10 – 50% EtOAc in hexanes as the eluent. Spectral data for 371 matched literature values:\textsuperscript{107} IR (thin film) 2932 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) \(\delta\) 7.34 – 7.18 (m, 12H), 5.46 (s, 2H), 4.36 (s, 2H); LRMS (ESI+) \(m/z\) (relative intensity) 297.3 (M+H\textsuperscript{+}, 100).

\begin{figure}
\centering
\includegraphics[width=0.5\textwidth]{structure1.png}
\caption{1-(Benzyloxymethyl)-2-(phenylthio)-1H-imidazole (371).}
\end{figure}

1-(Benzyloxymethyl)-2-(phenylthio)-1H-imidazole-5-carbaldehyde (372). Following general procedure 3, 1-(benzyloxymethyl)-2-(phenylthio)-1H-imidazole (371) (24.0 g, 81.0 mmol) was converted into 26.3 g (100%) of aldehyde 372, which was obtained as a yellow solid: mp 104 – 105 °C; IR (thin film) 1670 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) \(\delta\) 9.66 (s, 1H), 7.74 (s, 1H), 7.55 – 7.51 (m, 2H), 7.39 – 7.29 (m, 8H), 5.92 (s, 2H), 4.61 (s, 2H); \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}) \(\delta\) 178.2, 144.2, 139.7, 136.7, 132.9, 132.8, 129.5, 129.3, 129.1, 128.4, 127.9, 127.6, 74.1, 71.1; LRMS (ESI+) \(m/z\) (relative
intensity) 325.3 (M+H⁺, 100%); HRMS (ESI) m/z calced for [C₁₈H₁₇N₂O₂S]⁺, 325.1005; found, 325.1011.

(E)-3-(1-(Benzyloxymethyl)-2-(phenylthio)-1H-imidazol-5-yl)acrylamide (373). Following general procedure 4, aldehyde 372 (17.0 g, 52.4 mmol) was converted into 19.0 g (99%) of α,β-unsaturated amide 373, which was obtained as a white solid following purification of the crude material by trituration with Et₂O: mp 73 – 74 °C; IR (thin film) 3319, 3176, 1671 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.50 (d, J = 15.6 Hz, 1H), 7.44 (brs, 1H), 7.23 – 7.00 (m, 10H), 6.36 (d, J = 15.6 Hz, 1H), 6.02 (brs, 2H), 5.46 (s, 2H), 4.33 (s, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 167.0, 142.6, 136.3, 133.2, 132.0, 131.8, 129.4, 129.2, 128.4, 128.0, 127.6, 127.5, 127.2, 120.1, 73.2, 70.5; LRMS (ESI⁺) m/z (relative intensity) 366.1 (M+H⁺, 100%); HRMS (ESI⁺) m/z calcd for [C₂₀H₂₀N₃O₂S]⁺, 366.1270; found, 366.1276.
6-(1-(Benzyloxymethyl)-2-(phenylthio)-1H-imidazol-5-yl)cyclohex-3-ene carboxamide (374). Following general procedure 5, α,β-unsaturated amide 373 (10.0 g, 27.4 mmol) was converted into 6.25 g (54%) of Diels-Alder adduct 374, which was obtained as a brown solid following purification of the crude material by silica gel column and chromatography using 10 – 100% EtOAc in hexanes as the eluent: mp 132 – 133 °C; IR (thin film) 3319, 3180, 1668 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.35 – 7.30 (m, 3H), 7.24 – 7.06 (m, 8H), 5.78 – 5.70 (m, 2H), 5.61 (brs, 1H), 5.38 (d, \(J = 10.5\) Hz, 1H), 5.32 (d, \(J = 10.5\) Hz, 1H), 5.09 (brs, 1H), 4.36 (s, 2H), 3.04 (dt, \(J = 7.6, 5.3\) Hz, 1H), 2.88 (dt, \(J = 7.6, 5.3\) Hz, 1H), 2.57 – 2.46 (m, 2H), 2.30 – 2.28 (m, 1H), 2.25 – 2.23 (m, 1H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 177.6, 145.9, 137.4, 136.4, 135.3, 129.2, 128.5, 128.1, 127.7 (2), 126.7, 125.9, 125.1, 120.0, 75.1, 70.5, 45.6, 36.0, 32.1, 28.7; LRMS (ESI+) \(m/z\) (relative intensity) 420.0 (M+H\(^+\), 100%); HRMS (ESI) \(m/z\) calcd for \([C_{24}H_{26}N_{3}O_{2}S]^+\), 420.1754; found, 420.1746.
6-(1-(Benzylxomethyl)-2-(phenylthio)-1H-imidazol-5-yl)cyclohex-3-enecarbonitrile (375). Following general procedure 6, amide 374 (4.40 g, 10.5 mmol) was converted into 3.07 g (73%) of nitrile 375, which was obtained as a pale yellow oil following silica gel column chromatography using 20% EtOAc in hexanes as the eluent: IR (thin film) 2239 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.26 – 7.05 (m, 11H), 5.76 – 5.71 (m, 1H), 5.60 – 5.56 (m, 1H), 5.31 (s, 2H), 4.27 (d, J = 11.3 Hz, 1H), 4.22 (d, J = 11.3 Hz, 1H), 3.21 – 3.12 (m, 1H), 3.06 – 2.98 (m, 1H), 2.48 – 2.32 (m, 4H); ¹³C NMR (75 MHz, CDCl₃) δ 144.1, 137.9, 136.3, 134.8, 129.2, 128.4, 128.0, 127.7, 127.5, 126.6, 126.4, 123.1, 121.7, 119.7, 75.2, 70.4, 35.7, 30.7, 29.9, 28.3; LRMS (ESI⁺) m/z (relative intensity) 402.2 (M+H⁺, 100%); HRMS (ESI) m/z calcd for [C₂₄H₂₄N₃OS]⁺, 402.1642; found, 402.1640.
Aluminum trichloride\(^{122}\) (8.70 g, 65.3 mmol) was suspended in CH\(_2\)Cl\(_2\) (450 mL) and cooled to -10 °C (ice, acetone). To this suspension was added a solution of N-BOM imidazole 375 (2.62 g, 6.53 mmol) in CH\(_2\)Cl\(_2\) (200 mL) via cannula, dropwise over 10 min. The reaction mixture was stirred at -10 °C for 15 min at which time TLC showed complete consumption of nitrile 375. Water (150 mL) was added and the organic layer was separated. The aqueous layer was extracted with CH\(_2\)Cl\(_2\) (2 x 100 mL) and the combined organic layers were dried over anhydrous MgSO\(_4\), filtered and concentrated \textit{in vacuo}. The crude residue was purified by silica gel column chromatography using 20 – 50% EtOAc in hexanes as the eluent to give 1.20 (65%) of the desired N-H imidazole 376 as a pale yellow solid: mp 54 – 55 °C; IR (thin film) 3060, 3033, 2240 cm\(^{-1}\); \textsuperscript{1}H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.20 – 7.08 (m, 3H), 7.07 – 6.98 (m, 2H), 6.88 (s, 1H), 5.69 – 5.65 (m, 1H), 5.56 – 5.53 (m, 1H), 3.10 – 2.95 (m, 2H), 2.45 – 2.25 (m, 4H); \textsuperscript{13}C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 143.2, 136.2, 135.2, 129.1, 127.7, 126.4, 126.2, 123.0, 121.7, 117.7, 35.2, 30.8, 30.1, 28.1; LRMS (ESI+) \(m/z\) (relative intensity) 282.2 (M+H\(^+\), 100%).
Following general procedure 7, nitrile 376 (1.20 g, 4.26 mmol) was converted into 1.22 g (100%) of pure amine 377, which was obtained as a clear and colorless oil without any purification: IR (thin film) 3060, 3022 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.21 – 7.06 (m, 5H), 6.79 (s, 1H), 5.70 – 5.62 (m, 2H), 2.74 (dd, \(J = 15.9, 9.1\) Hz, 1H), 2.59 (dd, \(J = 12.9, 3.3\) Hz, 1H), 2.44 (dd, \(J = 12.9, 5.9\) Hz, 1H), 2.30 – 2.15 (m, 2H), 2.15 – 1.95 (m, 1H), 1.92 – 1.70 (m, 2H); \(^13\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 143.0, 136.2, 134.8, 128.8, 127.2, 125.9 (2), 125.7, 120.3, 45.0, 40.5, 35.2, 31.5, 28.7; LRMS (ESI+) \(m/z\) (relative intensity) 286.1 (M+H\(^+\), 100%).
4,5-Dibromo-N-((6-(2-phenylthio)-1H-imidazol-5-yl)cyclohex-3-enyl)methyl)-1H-pyrrole-2-carboxamide (369). Following general procedure 8, amino imidazole 377 (1.22 g, 4.27 mmol) was converted into 1.69 g (74%) of N-H imidazole 369, which was obtained as a white solid following purification of the crude material by silica gel column chromatography using 30 – 50% EtOAc in hexanes as the eluent: mp 161 – 162 °C; IR (thin film) 3117, 3060, 1632 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\), TFA salt) \(\delta\) 15.0 (brs, 1H), 13.0 (brs, 1H), 11.1 (s, 1H), 7.79 (s, 1H), 7.50 – 7.33 (m, 5H), 7.03 (s, 1H), 6.82 (s, 1H), 5.67 (brs, 2H), 3.60 – 3.50 (m, 1H), 3.15 – 3.10 (m, 1H), 2.95 (dd, \(J = 14, 8.1\) Hz, 1H), 2.37 – 2.20 (m, 3H), 2.12 – 2.02 (m, 1H), 1.94 – 1.85 (m, 1H); \(^1^3\)C NMR (75 MHz, CD\(_2\)Cl\(_2\)) \(\delta\) 162.4, 140.8, 139.6, 134.2, 131.1, 130.7, 126.7, 126.3, 125.9, 124.8, 117.8, 115.9, 106.8, 100.6, 43.3, 37.4, 34.0, 29.9, 28.6; LRMS (ESI\(^+\)) \(m/z\) (relative intensity) 535.1(M+\(H^+\) 100%); HRMS (ESI) \(m/z\) calcd for [C\(_{21}\)H\(_{21}\)Br\(_2\)N\(_3\)OS]\(^+\), 534.9782; found, 534.9803.
5.5 Preparations for N-SEM-2-Thiophenyl Imidazole Substrates

![Chemical Structure Image]

**2-(Phenylthio)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazole** \( (379) \)

Following general procedure 1, imidazole (4.35 g, 63.9 mmol) was converted into N-SEM imidazole \( 378 \). Following general procedure 2, the crude N-SEM imidazole \( 378 \) from above then was converted, \textit{in situ}, into 14.1 g (72%, 2 steps) of sulfide \( 379 \), which was obtained as a yellow oil following purification of the crude material by silica gel column chromatography using 10 – 20% EtOAc in hexanes as the eluent: IR (thin film) 2952 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 7.31 – 7.26 (m, 7H), 5.43 (s, 2H), 3.42 (t, \( J = 8.2 \) Hz, 2H), 0.87 (t, \( J = 8.2 \) Hz, 2H), 0.011 (s, 9H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \( \delta \) 138.2, 134.6, 130.7, 129.1, 128.2, 126.7, 122.2, 75.5, 66.3, 17.6, -1.58; LRMS (ESI+) \( m/z \) (relative intensity) 290.2 (M+H\(^+\), 100%).
2-(Phenylthio)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazole-5-carbaldehyde (380). Following general procedure 3, 2-(phenylthio)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazole (379) (10.4 g, 33.9 mmol) was converted into 11.3 g (100%) of aldehyde 380, which was obtained crude as a tacky yellow solid: IR (thin film) 1673 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 9.65 (s, 1H), 7.75 (s, 1H), 7.54-7.51 (m, 2H), 7.38-7.36 (m, 3H), 5.80 (s, 2H), 3.58 (t, \(J = 7.5, 1.2 \text{ Hz, 2H})\), 0.90 (t, \(J = 7.5, 1.1 \text{ Hz, 2H})\), -0.02 (s, 9H); \(^13\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 187.1, 152.1, 144.1, 132.8 (2), 129.5 (2), 129.0, 73.8, 66.6, 17.7, -1.5; LRMS (ESI+) \(m/z\) (relative intensity) 335.1 (M+H\(^+\), 100%); HRMS (ESI) \(m/z\) calcd for [C\(_{16}\)H\(_{23}\)N\(_2\)O\(_2\)Si]\(^+\), 335.1248; found, 335.1250.
(E)-3-(2-(Phenylthio)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-5-yl)acrylamide (381). Following general procedure 4, aldehyde 380 (11.3 g, 33.9 mmol) was converted into 10.7 g (83%) of α,β-unsaturated amide 381, which was obtained as a white solid following purification of the crude material by trituration with Et₂O: mp 121 – 122 °C; IR (thin film) 3325, 3180, 1672 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.61 (d, J = 15.7 Hz, 1H), 7.56 (s, 1H), 7.33 – 7.28 (m, 5H), 6.52 (d, J = 15.7 Hz, 1H), 6.35 (brs, 2H), 5.52 (s, 2H), 3.47 (t, J = 8.2 Hz, 2H), 0.87 (t, J = 8.2 Hz, 2H), -0.03 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 167.5, 142.2, 133.3, 131.8 (2), 129.3, 129.0, 127.3, 127.2, 120.1, 73.3, 66.3, 17.7, -1.6; LRMS (ESI⁺) m/z (relative intensity) 376.1 (M+H⁺, 100%); HRMS (ESI) m/z calcd for [C₁₈H₂₆N₃O₂SSi]⁺, 376.1511; found, 376.1515.
6-(2-(Phenylthio)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-5-yl)cyclohex-3-enecarboxamide (382). Following general procedure 5, α,β-unsaturated amide 381 (10.5 g, 28.0 mmol), was converted into 6.80 g (57%) of Diels-Alder adduct 382, which was obtained as a pale yellow solid following silica gel column chromatography using 50 – 100% EtOAc in hexanes as the eluent: mp 42 – 43 °C; IR (thin film) 3331, 3182, 2900, 1668, 1089 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.34 – 7.11 (m, 6H), 5.98 (brs, 1H), 5.80 (s, 2H), 5.45 (brs, 1H), 5.38 (d, \(J = 10.5\) Hz, 1H), 5.30 (d, \(J = 10.5\) Hz, 1H), 3.45 – 3.39 (m, 2H), 3.11 – 3.08 (m, 1H), 3.00 – 2.95 (m, 1H), 2.61 – 2.51 (m, 2H), 2.36 – 2.29 (m, 1H), 2.12 – 2.10 (m, 1H) 0.88 – 0.83 (m, 2H), 0.00 (s, 9H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 177.7, 145.8, 137.0, 135.4, 129.1, 127.5, 126.5, 125.8, 125.1, 119.8, 75.5, 66.4, 45.5, 35.9, 32.1, 28.7, 17.6, -1.53; LRMS (ESI+) \(m/z\) (relative intensity) 430.2 (M+H\(^+\), 100%); HRMS (ESI) \(m/z\) calcd for [C\(_{22}\)H\(_{32}\)N\(_3\)O\(_2\)SSi]\(^+\), 430.1996; found, 430.1985.
6-(2-(Phenylthio)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-5-yl)cyclohex-3-enecarbonitrile (383). Following general procedure 6, amide 382 (1.29 g, 3.00 mmol) was converted into 1.03 g (84%) of nitrile 383, which was obtained as a clear and colorless oil following purification of the crude material by silica gel column chromatography using 20% ethyl acetate in hexanes as the eluent. Note: this reaction consistently gives higher yields when performed in 1.0 g batches: IR (thin film) 2260 cm⁻¹; ¹H NMR (300 MHz, acetone-d₆) δ 7.41 (s, 1H), 7.29 – 7.15 (m, 5H), 5.85 – 5.75 (m, 1H), 5.70 – 5.62 (m, 1H), 5.41 (s, 2H), 3.46 – 3.40 (m, 2H), 3.22 – 3.19 (m, 1H), 3.11 – 3.08 (m, 1H), 2.47 – 2.38 (m, 4H), 0.77 (t, J = 8.1 Hz, 2H), -0.08 (s, 9H); ¹³C NMR (75 MHz, acetone-d₆) δ 145.0, 137.6, 136.4, 129.9, 128.2, 127.1 (2), 124.2, 122.3, 121.2, 76.2, 66.6, 36.4, 31.3, 31.1, 29.1, 18.1, -1.4; LRMS (ESI⁺) m/z (relative intensity) 412.1 (M+H⁺ 100%); HRMS (ESI) m/z calcd for [C₂₂H₃₀N₃OSSi]⁺, 412.1879; found, 412.1879.
(6-(2-(Phenylthio)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-5-yl)cyclohex-3-enyl)methanamine (384). Following general procedure 7, N-SEM nitrile 383 (1.55 g, 3.78 mmol) was converted to 1.48 g (94% yield) of crude N-SEM amine 384, which was obtained as a clear and colorless oil: IR (thin film) 3376, 3295 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.22 – 7.20 (m, 2H), 7.13 – 7.09 (m, 3H), 6.97 (s, 1H), 5.69 (brs, 2H), 5.27 (s, 2H), 3.29 (t, $J =$ 8.2 Hz, 2H), 2.81 – 2.73 (m, 1H), 2.62 (dd, $J =$ 12.9, 3.8 Hz, 1H), 2.49 (dd, $J =$ 12.9, 6.4 Hz, 1H), 2.42 – 2.33 (m, 1H), 2.39 – 2.27 (m, 1H), 2.16 – 2.09 (m, 1H), 2.02 – 1.89 (m, 2H), 1.32 (brs, 2H), 0.75 (t, $J =$ 8.2 Hz, 2H), -0.11 (s, 9H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 147.4, 136.6, 135.3, 129.1, 127.4, 126.4, 126.1, 125.9, 118.5, 75.4, 66.1, 45.4, 40.8, 36.2, 31.3, 28.4, 17.6, -1.6; LRMS (ESI+) $m/z$ (relative intensity) 416.2 (M+H$^+$ 100).
4,5-Dibromo-N-((6-(2-(phenylthio)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-5-yl)cyclohex-3-enyl)methyl)-1H-pyrrole-2-carboxamide (385). Following general procedure 8, N-SEM amine 384 (1.00 g, 2.41 mmol) was converted into 1.37 g (85%) of amide 385, which was obtained as a white solid following purification of the crude material by silica gel column chromatography using 30 – 50% EtOAc in hexanes as the eluent: mp 175 – 176 °C; IR (thin film) 3295, 3113, 2951, 1634 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 11.7 (s, 1H), 7.77 (dd, \(J = 7.9, 4.2\) Hz, 1H), 7.33 – 7.25 (m, 4H), 7.21 – 7.15 (m, 1H), 7.03 (s, 1H), 6.56 (d, \(J = 2.7\) Hz, 1H), 5.75 (brs, 2H), 5.34 (s, 2H), 3.84 – 3.75 (m, 1H), 3.44 (t, \(J = 8.2\) Hz, 2H), 3.03 (td, \(J = 14.7, 4.1\) Hz, 1H), 2.89 – 2.80 (m, 1H), 2.50 – 2.24 (m, 2H), 2.23 – 2.08 (m, 2H), 2.03 – 1.96 (m, 1H), 0.88 (t, \(J = 8.2\) Hz, 2H), 0.00 (s, 9H); \(^1^3\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 159.6, 146.7, 138.5, 133.8, 129.3, 129.2, 127.4, 127.3, 126.7, 125.8, 118.0, 112.4, 104.9, 99.3, 75.5, 66.4, 42.1, 40.8, 37.0, 31.3, 30.6, 17.7, -1.5; LRMS (ESI+) \(m/z\) (relative intensity) 665.0611 (M+H\(^+\) 100).
4,5-Dibromo-N-((6-(2-(phenylthio)-1H-imidazol-5-yl)cyclohex-3-enyl)methyl)-1H-pyrrole-2-carboxamide (369). Following general procedure 9, N-SEM imidazole 385 (1.36 g, 2.04 mmol) was converted into 740 mg (68%) of N-H imidazole 369, which was obtained as a white solid following purification of the crude material by silica gel column chromatography using 30-50% EtOAc in hexanes as the eluent. Analytical data matched those reported for compound 369 which was prepared from 377.
5.6 Methods for the Preparation of N-SEM-2-Thiomethyl Substrates

2-(Methylthio)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazole (388).

Following general procedure 1, imidazole (3.21 g, 47.1 mmol) was converted into N-SEM imidazole 378. Following general procedure 2, the crude N-SEM imidazole 378 then was converted, in situ, into 6.80 g (59%, 2 steps) of sulfide 388, which was obtained as pale yellow oil following purification of the crude material by silica gel column chromatography using 20% EtOAc in hexanes as the eluent: IR (thin film) 2939 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.03 (d, \(J = 1.4\) Hz, 1H), 7.01 (d, \(J = 1.4\) Hz, 1H), 5.21 (s, 2H), 3.46 (t, \(J = 8.22\) Hz, 2H), 2.56 (s, 3H), 0.87 (t, \(J = 8.22\) Hz, 2H), -0.06 (s, 9H); \(^13\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 143.5, 129.5, 121.0, 74.7, 66.1, 17.6, 16.1, -1.6; LRMS (ESI+) \(m/z\) (relative intensity) 245.3 (M+H\(^+\), 100%).
**5-Bromo-2-(methylthio)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazole** (389). To a solution of N-SEM 2-thiomethyl imidazole 388 (1.21 g, 4.95 mmol) in THF (15 mL) at 0 °C was added a solution of freshly recrystallized N-bromosuccinimide (975 mg, 5.45 mmol) in THF (5 mL) dropwise over 5 min. The reaction mixture was stirred for 30 additional min at which time TLC showed complete consumption of imidazole 388. The reaction mixture was then diluted with water (25 mL) and EtOAc (50 mL) and the organic layer was separated. The aqueous layer was extracted with EtOAc (2 x 25 mL) and the combined organic extracts were dried over anhydrous Na$_2$SO$_4$, filtered and concentrated *in vacuo*. The crude material was purified by silica gel column chromatography using 10 – 20% EtOAc in hexanes to give 734 mg (46% yield) of 5-bromo imidazole 389 as a pale yellow oil: IR (thin film) 2951 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 6.98 (s, 1H), 5.16 (s, 2H), 3.50 – 3.44 (m, 2H), 2.97 (s, 3H), 0.87 (t, $J$ = 8.2 Hz, 2H), -0.06 (s, 9H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 143.8, 119.9, 115.2, 74.9, 66.5, 17.5, 16.1, -1.54; LRMS (ESI+) $m/z$ (relative intensity) 323.3 (M+H$^+$, 100%); HRMS (ESI) $m/z$ calcd for [C$_{10}$H$_{20}$BrN$_2$OSSi]$^+$, 323.0257; found, 323.0249.
2-(Methylthio)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazole-5-carbaldehyde (391). A solution of 5-bromo imidazole 389 (2.90 g, 8.97 mmol) in THF (10 mL) at -78 °C was treated with a solution of n-BuLi in hexanes (3.66 mL, 8.97 mmol). The reaction mixture was stirred at that temperature for 15 minutes and DMF (695 µL, 8.97 mmol) was added neat, dropwise over 2 min. After stirring for an additional 30 min, a saturated aqueous solution of NH₄Cl was added and the reaction mixture was brought to rt. The organic layer was separated and the aqueous layer was extracted with EtOAc (2 x 50 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The crude product was purified by silica gel column chromatography using 10 – 20% EtOAc in hexanes as the eluent to give 1.67 g (68% yield) of aldehyde 391 as a yellow oil: IR (thin film) 1668 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 9.57 (s, 1H), 7.71 (s, 1H), 5.64 (s, 2H), 3.55 (t, J = 8.3 Hz, 2H), 2.68 (s, 3H), 0.88 (t, J = 8.3 Hz, 2H), 0.08 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 177.6, 155.4, 144.1, 132.9, 73.5, 66.5, 17.7, 14.5, -1.56; LRMS (ESI⁺) m/z (relative intensity) 273.2 (M+H⁺, 100%); HRMS (ESI) m/z calcd for [C₁₁H₂₁N₂O₂SSi]⁺, 273.1088; found, 273.1093.
(E)-3-(2-(Methylthio)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-5-yl)acrylamide (392). Following general procedure 4, aldehyde 391 (1.67 g, 6.13 mmol) was converted into 1.66 g (86%) of \( \alpha,\beta \)-unsaturated amide 392, which was obtained as a white solid following purification of the crude material by a silica gel column chromatography using 20% EtOAc in hexanes as the eluent: mp 126 – 127 °C; IR (thin film) 3322, 3179, 2952, 1666 cm\(^{-1}\); \(^1\)H NMR (400 MHz, MeOD) \( \delta \) 7.52 (d, \( J = 15.6 \) Hz, 1H), 7.41 (s, 1H), 6.35 (d, \( J = 15.6 \) Hz, 1H), 5.77 (brs, 2H), 5.32 (s, 2H), 3.56 (t, \( J = 8.1 \) Hz, 2H), 2.65 (s, 3H), 0.91 (t, \( J = 8.1 \) Hz, 2H), 0.02 (s, 9H); \(^{13}\)C NMR (75 MHz, MeOD) \( \delta \) 170.4, 149.0, 132.4, 131.3, 127.8, 120.6, 74.1, 67.4, 18.5, 16.5, -1.35; LRMS (ESI+) \( m/z \) (relative intensity) 314.2 (M+H\(^+\), 100%); HRMS (ESI) \( m/z \) calcd for [C\(_{13}\)H\(_{24}\)N\(_3\)O\(_2\)SSi]\(^+\), 314.1364; found, 314.1359.
6-(2-(Methylthio)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-5-yl)cyclohex-3-enecarboxamide (393). Following general procedure 5, α,β-unsaturated amide 392 (501 mg, 1.65 mmol) was converted into 230 mg (38%) of Diels-Alder adduct 393, which was obtained as a brown solid following purification of the crude material by silica gel column chromatography using 30 – 50% EtOAc in hexanes as the eluent: mp 61 – 62 °C; IR (thin film) 3337, 3190, 2925, 1668 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 6.82 (s, 1H), 6.02 (brs, 1H), 5.69 (s, 2H), 5.65 (brs, 1H), 5.21 (d, J = 10.7 Hz, 1H), 5.15 (d, J = 10.7 Hz, 1H), 3.45 (t, J = 8.0 Hz, 2H), 2.95 – 2.87 (m, 1H), 2.86 – 2.78 (m, 1H), 2.50 – 2.38 (m, 5H), 2.20 (m, 2H), 0.86 (t, J = 8.1 Hz, 2H), 0.05 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 177.9, 144.6, 142.1, 125.8, 125.1, 118.2, 74.9, 66.1, 45.4, 36.7, 31.9, 28.5, 17.6, 17.5, -1.52; LRMS (ESI+) m/z (relative intensity) 368.1 (M+H⁺, 100%); HRMS (ESI) m/z calcd for [C₁₇H₃₀N₃O₂SSi]⁺, 368.1823; found, 368.1828.
6-(2-(Methylthio)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-5-yl)cyclohex-3-enecarbonitrile (394). Following general procedure 6, amide 393 (230 mg, 0.626 mmol) was converted into 164 mg (75%) of nitrile 394, which was obtained as a clear and colorless oil following purification of the crude material by silica gel column chromatography using 20% EtOAc in hexanes as the eluent: IR (thin film) 2240 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 6.93 (s, 1H), 5.80 – 5.77 (m, 1H), 5.64 – 5.60 (m, 1H), 5.30 – 5.15 (m, 2H), 3.49 (t, \(J = 8.16\) Hz, 2H), 3.17 – 3.05 (m, 2H), 2.54 (s, 3H), 2.50 – 2.32 (m, 4H), 0.90 (t, \(J = 8.16\) Hz, 2H), -0.027 (s, 9H); \(^13\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 143.0, 142.9, 126.4, 123.0, 121.9, 118.0, 74.9, 66.2, 35.4, 30.3, 29.6, 28.0, 17.6, 17.1, -1.50; LRMS (ESI\(^+\)) \(m/z\) (relative intensity) 350.2 (M+H\(^+\), 100%).
4,5-Dibromo-N-((6-(2-(methylthio))-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-5-yl)cyclohex-3-enyl)methyl)-1H-pyrrole-2-carboxamide (396). Following general procedure 7, nitrile 394 (65.0 mg, 0.186 mmol) was converted into 65.0 mg (100%) of the corresponding N-SEM amine, which was obtained as a clear and colorless oil. The product was used in the acylation reaction without purification.

Following general procedure 8, crude amine from above (56.0 mg, 0.186 mmol) was converted into 70.0 mg (63%) of amide 396, which was obtained as a tacky solid. Following purification of the crude substance by silica gel column chromatography using 50% Et₂O in hexanes as the eluent: IR (thin film) 3304, 3113, 1634 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 11.8 (s, 1H), 7.90 (brs, 1H), 6.82 (s, 1H), 6.73 (s, 1H), 5.68 (brs, 2H), 5.18 (s, 2H), 3.79 – 3.67 (m, 1H), 3.50 (t, J = 8.10 Hz, 2H), 3.08 – 2.96 (m, 1H), 2.82 – 2.68 (m, 1H), 2.58 (brs, 3H), 2.35 – 2.25 (m, 2H), 2.21 – 2.01 (m, 3H), 1.95 – 1.80 (m, 1H), 0.90 (t, J = 8.07 Hz, 2H), -0.02 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 159.6, 145.8, 143.0, 127.7, 126.7, 126.0, 117.1, 112.1, 105.0, 99.2, 74.9, 66.4, 42.1, 41.0, 37.1, 31.4, 30.7, 17.6, 16.6, -1.45; LRMS (ESI⁺) m/z (relative intensity) 603.1 (M+H⁺, 100%).
4,5-Dibromo-N-((6-(2-(methylthio)-1H-imidazol-5-yl)cyclohex-3-enyl)methyl)-1H-pyrrole-2-carboxamide (397). Following general procedure 9, N-SEM imidazole 396 (60.0 mg, 0.099 mmol) was converted into 29.0 mg (61%) of N-H imidazole 397, which was obtained as a clear and colorless film following purification of the crude residue by silica gel column chromatography using 30 – 50% EtOAc in hexanes as the eluent: IR (thin film) 3114, 1626 cm⁻¹;¹H NMR (300 MHz, MeOD) δ 7.32 (s, 1H), 6.73 (s, 1H), 5.74 (brs, 2H), 3.36 – 3.31 (m, 1H), 3.10 (dd, J = 13.8, 6.3 Hz, 1H), 2.92 – 2.84 (m, 1H), 2.67 (s, 3H), 2.42 – 2.18 (m, 4H), 1.98 – 1.89 (m, 1H);¹³C NMR (75 MHz, MeOD) δ 161.5, 143.8, 139.8, 128.5, 126.9, 125.9, 118.4, 114.2, 106.2, 100.0, 44.1, 38.5, 35.8, 31.9, 30.0, 16.3; LRMS (ESI+) m/z (relative intensity) 473.0 (M+H⁺, 100%); HRMS (ESI) m/z calcd for [C₁₆H₁₉Br₂N₄OS]⁺, 472.9635; found, 472.9646.
5.7 Experimental for Pummerer Cyclization and Ring Contraction Protocols

Thiophenyl Pentacycle (387). Following general procedure 10, \(N\)-H imidazole 369 (1.68 g, 3.13 mmol) was converted into 918 mg (55%) of pentacycle 387, which was obtained as a brown solid following purification of the crude residue by silica gel column chromatography using 30 – 50% EtOAc in hexanes as the eluent: mp 189 – 190 °C; IR (thin film) 3224, 1644 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CD\(_3\)OD) \(\delta\) 7.38 – 7.21 (m, 5H), 6.80 (s, 1H), 5.76 (s, 1H), 5.62 (bbr, 2H), 5.37 (s, 1H), 3.90 – 3.87 (m, 1H), 3.13 – 3.07 (m, 1H), 2.31 – 2.26 (m, 1H), 2.16 – 2.11 (m, 1H), 2.11 – 2.04 (m, 2H), 1.91 – 1.83 (m, 2H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 161.8, 154.7, 134.9, 130.5, 130.2, 126.6, 126.4, 126.2, 125.3, 115.0, 103.3, 102.7, 92.6, 71.8, 51.5, 49.8, 34.3, 30.0, 23.4; LRMS (ESI+) \(m/z\) (relative intensity) 533.0 (M+\(H^+\), 100%); HRMS (ESI) \(m/z\) calcd for [C\(_{21}\)H\(_{19}\)Br\(_2\)N\(_4\)OS]\(^+\), 532.9641; found, 532.9646. A single crystal X-ray structure was obtained (CCDC 782151) to confirm the assigned structure.
X-Ray data for tetracycle 387 (CCDC 782151). The appropriate crystals were obtained by the vapor diffusion technique using acetone and hexanes as the solvents. A colorless rod shaped crystal of pentacycle 387 \((\text{C}_{21}\text{H}_{18}\text{Br}_{2}\text{N}_{4}\text{OS})\) with approximate dimensions 0.07 x 0.08 x 0.15 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured at 108(2) K, cooled by Rigaku-MSC X-Stream 2000, on a Bruker SMART APEX CCD area detector system equipped with a graphite monochromator and a MoK\(\alpha\) fine-focus sealed tube \((\lambda = 0.71073\text{Å})\) operated at 1600 watts power (50 kV, 32 mA). The detector was placed at a distance of 5.8 cm from the crystal.

A total of 1850 frames were collected with a scan width of 0.3° in \(\omega\) and an exposure time of 20 seconds/frame. The total data collection time was about 14 hours. The frames were integrated with the Bruker SAINT software package using a narrow-frame integration algorithm. The integration of the data using a Triclinic unit cell yielded a total of 8131 reflections to a maximum \(\theta\) angle of 28.29° (0.90 Å resolution), of which 4905 were independent, completeness = 97.3%, \(R_{\text{int}} = 0.0140\), \(R_{\text{sig}} = 0.0336\) and 3787 were greater than 2\(\sigma\)(I). The final cell constants: \(a = 7.630(2)\text{Å}, b = 11.254(3)\text{Å}, c = 12.992(4)\text{Å}, \alpha = 104.415(5)^{\circ}, \beta = 104.272(5)^{\circ}, \gamma = 99.480(5)^{\circ}\), volume = 1016.3(5)Å³,
are based upon the refinement of the XYZ-centroids of 3632 reflections above 20\(\sigma(1)\) with 2.835° < \(\theta\) < 27.911°. Analysis of the data showed negligible decay during data collection. Data were corrected for absorption effects using the multiscan technique (SADABS). The ratio of minimum to maximum apparent transmission was 0.1660.

The structure was solved and refined using the Bruker SHELXTL (Version 6.1) Software Package, using the space group P-1, with \(Z = 2\) for the formula unit, C21 H18 Br2 N4 O S. The final anisotropic full-matrix least-squares refinement on \(F^2\) with 262 variables converged at \(R1 = 7.07\%\), for the observed data and \(wR2 = 17.20\%\) for all data. The goodness-of-fit was 1.041. The largest peak on the final difference map was 2.413 e\(^{-}\)/Å\(^3\) and the largest hole was -1.623 e\(^{-}/Å\(^3\). Based on the final model, the calculated density of the crystal is 1.746 g/cm\(^3\) and \(F(000)\) amounts to 532 electrons.
**Thiomethyl pentacyle (398).** Following general procedure 10, N-H imidazole 397 (10.0 mg, 0.021 mmol) was converted into 4.0 mg (40%) of pentacyle 398, which was obtained as a pale yellow film following purification of the crude residue by spherical silica gel column chromatography using 50% EtOAc in hexanes as the eluent: IR (thin film) 3401, 1643 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 6.97 (s, 1H), 5.94 (brs, 1H), 5.68 (brs, 2H), 5.57 (s, 1H), 4.17 (dd, $J = 11.5, 8.4$ Hz, 1H), 3.35 – 3.24 (m, 1H), 2.49 – 2.42 (m, 2H), 2.46 (s, 3H), 2.19 – 2.13 (m, 1H), 2.02 – 1.86 (m, 3H); $^{13}$C NMR (75 MHz, CD$_3$OD) $\delta$ 161.0, 158.0, 128.0, 127.3 (2), 116.7 (2), 104.0, 92.1, 72.2, 51.9, 43.6, 36.1, 31.5, 25.5, 14.5; LRMS (ESI+) $m/z$ (relative intensity) 470.9 (M+H$^+$, 100%); HRMS (ESI) $m/z$ calcd for [C$_{16}$H$_{17}$Br$_2$N$_4$OS]$^+$, 470.9491; found, 470.9490.
Pentacyclic Ketones (402/403). To a solution of mercuric trifluoroacetate (287 mg, 0.674 mmol) in water (0.25 mL) at rt was added a solution of cyclic alkene 387 (96 mg, 0.18 mmol) in THF (2.0 mL). To the resulting yellow solution was added a drop of 70% aqueous perchloric acid. The resulting mixture was stirred at rt for 16 h at which time a white precipitate formed and TLC showed complete consumption of the alkene. The reaction mixture was then cooled to 0 °C, basified with the addition of 3 M aqueous solution of NaOH (0.25 mL), and the solution was stirred for 10 min at that temperature. A solution of NaBH₄ (40.0 mg, 1.06 mmol) in 3.0 M aqueous NaOH (0.5 mL) was added to the mixture and the resulting solution was brought to rt. The reaction mixture turned grey and deposition of metallic mercury was observed. After stirring this mixture at rt for 1 h, the mercury was coagulated by rapid addition of a large excess of solid NaCl. The solid was then filtered off over a pad of Celite®, rinsing with THF (20 mL), and the filtrate was diluted with EtOAc (25 mL) and water (25 mL). The organic phase was separated and the aqueous layer was extracted with EtOAc (2 x 10 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to
give a mixture of four alcohols as a white solid (88.0 mg, 92% crude) that was used without purification.

The mixture of crude alcohols from above (88.0 mg, 0.159 mmol) was suspended in CH$_2$Cl$_2$ (2.0 mL), and Dess-Martin periodinane (203 mg, 0.478 mmol) was added in one portion at rt. The reaction mixture was stirred at rt for 16 h at which time TLC showed complete consumption of the alcohols. The reaction mixture was then diluted with a saturated aqueous solution of Na$_2$S$_2$O$_3$ (5 mL) and with CH$_2$Cl$_2$ (5 mL). The mixture then was stirred for an additional 1 h. The organic layer was separated and the aqueous layer was extracted with CH$_2$Cl$_2$ (10 mL) and EtOAc (10 mL). The combined organic layers were dried over anhydrous MgSO$_4$, filtered and concentrated in vacuo. The crude product was purified by silica gel column chromatography using 50 – 100% EtOAc in hexanes as the eluent to give 26.0 mg (30% over 2 steps) of ketone 402/403 as a 3:1 mixture of two regioisomers as a clear and colorless film along with 23.0 mg of the alkene 387: IR (thin film) 3252, 1716, 1650, 1565 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$, major isomer) δ 7.57 – 7.35 (m, 5H), 6.96 (s, 1H), 5.84 (brs, 1H), 5.41 (s, 1H), 4.18 (dd, J = 11.4, 8.4 Hz, 1H), 3.30 – 3.20 (m, 1H), 2.75 – 2.68 (m, 1H), 2.55 – 2.12 (m, 6H), 1.62 – 1.54 (m, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$, major isomer) δ 208.8, 162.9, 154.6, 135.1, 130.7, 130.2, 126.1 (x2), 115.2 (x2), 102.8, 92.1, 71.2, 55.1, 48.5, 44.6, 40.1, 37.2, 27.2; LRMS (ESI+) m/z (relative intensity) 548.9 (M+H$^+$, 100%); HRMS (ESI) m/z calcd for [C$_{21}$H$_{19}$Br$_2$N$_4$O$_2$S]$^+$, 548.9609; found, 548.9595.
Trifluoroacetyl Cyclohexanone (404). A solution of regioisomeric pentacyclic ketones 402/403 (16.0 mg, 0.029 mmol) in THF (1 mL) was cooled at -78 °C and a 1.0 M solution of LiHMDS (71.0 µL, 0.064 mmol) in THF was added dropwise over 5 min. The reaction mixture was stirred at that temperature for 30 min and 2,2,2-trifluoroethyl trifluoroacetate (9.3 µL, 0.070 mmol) was added in one portion via syringe. The resulting mixture was stirred for 15 min and then poured into a separatory funnel containing ethyl acetate (5 mL) and 5% aqueous HCl solution (5 mL). The organic layer was separated and the aqueous phase was extracted with ethyl acetate (2 × 5 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. Analytical quality samples were obtained via purification by silica gel column chromatography using 10 – 50% ethyl acetate in hexanes as the eluent to give 7.4 mg (39%) of the major regioisomer of the desired β-diketone 404 as a clear and colorless film and exclusively as the enol tautomer. Also isolated was 6.4 mg (34%) of a ~1.5:1.5:7 (¹H NMR) mixture of three other isomers also exclusively as the enol tautomers: IR (thin film, major isomer) 1658, 1651, 1644, 1634 cm⁻¹; ¹H NMR (300 MHz, CDCl₃, major
isomer) δ 15.2 (s, 1H), 7.56 – 7.44 (m, 5H), 6.99 (s, 1H), 5.50 (s, 1H), 4.20 (t, J = 9.7 Hz, 1H), 3.35 (t, J = 10.4 Hz, 1H), 2.97 (d, J = 13.8 Hz, 1H), 2.72 – 2.64 (m, 1H), 2.58 – 2.50 (m, 1H), 2.48 – 2.36 (m, 1H), 2.29 (t, J = 13.1 Hz, 1H), 2.23 – 2.14 (m, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$, major regioisomer) δ 187.2, 180.3 (q, J = 34.1 Hz), 164.1, 154.6, 135.2, 131.0, 130.4, 125.9, 125.7, 115.6, 103.9, 103.4, 103.1, 91.6, 71.5, 49.5, 49.0, 34.6, 30.4, 25.5; LRMS (ESI+) $m/z$ (relative intensity) 646.9 (M+H$^+$, 100%).
Cyclopentane methyl esters (407). β-Diketone 404 (7.0 mg, 0.011 mmol) was dissolved in CH$_3$CN (1.0 mL) and water (4 µL, 0.22 mmol), and Et$_3$N (45 µL, 0.33 mmol) was added at rt. To the resulting yellow reaction mixture was added a 1.0 M solution of MsN$_3$ (33 µL, 0.033 mmol) in CH$_3$CN dropwise over 15 min. After stirring for an additional 2.5 h, the CH$_3$CN layer was removed under reduced pressure and the residue was diluted in EtOAc (5 mL) and water (5 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (2 x 5 mL). The combined organic layers were dried over anhydrous Na$_2$SO$_4$, filtered and concentrated in vacuo to give the desired α-diazoketone as a pale yellow film which was used immediately in the next step without purification.

The crude α-diazoketone was dissolved in methanol (2 mL) and irradiated at 300 nm in a quartz vessel for 1 h. The solvent then was removed and the residue was re-suspended in EtOAc (5 mL) and water (5 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (2 x 5 mL). The combined organic layers were dried over anhydrous Na$_2$SO$_4$, filtered and concentrated in vacuo. The crude product was
purified by a silica gel column chromatography using 30 – 50% EtOAc in hexanes as the eluent to give 2.6 mg (41%, 2 steps) of the cyclopentane methyl ester 407 as a clear and colorless film and nearly a 1:1 mixture of diastereomers: IR (thin film) 3225, 1726, 1650 cm\(^{-1}\); \(^1\)H NMR (600 MHz with CryoProbe, CDCl\(_3\), \(~1:1\) mixture of two diastereomers) \(\delta\) 7.51 – 7.42 (m, 10H), 6.97 (s, 2H), 5.88 (s, 1H), 5.87 (s, 1H), 5.43 (s, 1H), 5.40 (s, 1H), 4.09 (dd, \(J = 10.6, 7.62\) Hz, 2H), 3.73 (s, 3H), 3.70 (s, 3H), 3.39 – 3.36 (m, 2H), 3.17 (t, \(J = 11.0\) Hz, 1H), 3.13 (t, \(J = 11.0\) Hz, 1H), 2.79 – 2.73 (m, 1H), 2.70 – 2.65 (m, 1H), 2.31 (dt, \(J = 13.3\) Hz, 1H), 2.27 – 2.24 (m, 2H), 2.14 (dt, \(J = 13.3\) Hz, 1H), 2.03 – 2.00 (m, 1H), 1.99 – 1.97 (m, 1H), 1.64 – 1.54 (m, 4H); \(^{13}\)C NMR (600 MHz with CryoProbe, CDCl\(_3\), \(~1:1\) mixture of two diastereomers) \(\delta\) 176.3, 175.5, 162.4, 162.3, 155.2 (2), 135.0, 134.9, 130.6, 130.5, 130.2 (2), 126.7, 126.6, 126.5, 126.3, 115.1 (2), 103.5, 103.4, 102.7 (2), 89.5 (2), 72.2, 72.1, 61.1, 60.4, 52.1, 52.0, 46.9, 46.8, 46.3, 46.2, 44.7, 44.1, 30.0, 28.6, 25.0, 24.0; LRMS (ESI+) \(m/z\) (relative intensity) 578.8 (M+H\(^{+}\), 100%); HRMS (ESI) \(m/z\) calcd for \([C_{22}H_{21}Br_{2}N_{4}O_{3}S]^{+}\), 578.9684; found, 578.9701.
Epoxy Urea (418). To a solution of pentacycle 387 (11.0 mg, 0.021 mmol) in CH$_2$Cl$_2$ (2.0 mL) at 0 °C was added mCPBA (70%, 6.1 mg, 0.25 mmol) in one portion. The reaction mixture was stirred at that temperature until TLC showed complete consumption of 387 (4 h) and then a 10% aqueous solution of Na$_2$S$_2$O$_3$ (10 mL) was added and the mixture was stirred for 10 min more at rt. The organic layer was separated and the aqueous layer was extracted with CH$_2$Cl$_2$ (2 x 5 mL). The organic layers were combined and dried over anhydrous MgSO$_4$, filtered and concentrated in vacuo to give the urea 417 (7.0 mg, 77%, crude) as a clear and colorless film: IR (thin film) 1766, 1690 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) δ 7.03 (s, 1H), 6.44 (brs, 1H), 6.39 (brs, 1H), 5.76 – 5.72 (m, 2H), 5.68 (s, 1H), 4.10 – 4.00 (m, 1H), 3.22 – 3.15 (m, 1H), 2.52 – 2.44 (m, 1H), 2.44 – 2.23 (m, 2H), 2.17 – 2.20 (m, 3H); LRMS (ESI+) m/z (relative intensity) 443.0 (M+H$^+$, 100%).

The crude alkene 417 (7.0 mg, 0.016 mmol) was dissolved in CH$_2$Cl$_2$ (1.0 mL) and treated with mCPBA (70%, 6.0 mg, 0.035 mmol) at rt. The reaction mixture was stirred at that temp until TLC showed complete consumption of the starting material (12 h) and then a 10% aqueous solution of Na$_2$S$_2$O$_3$ (5 mL) was added and the mixture was stirred for 10 min more at rt. The organic layer was separated and the aqueous layer was extracted with CH$_2$Cl$_2$ (2 x 5 mL). The organic layers were combined and dried over
anhydrous MgSO₄, filtered and concentrated \textit{in vacuo}. The crude substance was purified by silica gel column chromatography using 100% EtOAc – 5% MeOH in EtOAc to give a 2:1 diastereomeric mixture of the epoxy urea \textbf{418} (4.7 mg, 62%) as a clear and colorless film: IR (thin film) 1766, 1692 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl₃, 2:1 mixture of diastereomers) \(\delta\) 7.07 (brs, 1H), 7.00 (s, 2H), 6.63 (brs, 1H), 6.32 (brs, 1H), 6.24 (brs, 1H), 5.62 (s, 1H), 5.59 (s, 1H), 3.97 – 3.94 (m, 2H), 3.35 – 3.30 (m, 1H), 3.29 – 3.25 (m, 1H), 3.25 – 3.21 (m, 2H), 3.10 (t, \(J = 10.0\) Hz, 1H), 2.98 (t, \(J = 10.7\) Hz, 1H), 2.57 – 2.40 (m, 3H), 2.25 – 2.33 (m, 1H), 2.20 – 2.04 (m, 2H), 1.92 – 1.84 (m, 2H), 1.81 – 1.72 (m, 2H), 1.64 – 1.57 (2H); \(^{13}\)C NMR (600 MHz with CryoProbe, CDCl₃, 2:1 mixture of diastereomers) \(\delta\) 157.9 (2), 154.9, 154.8, 125.0 (2), 116.3, 116.2, 105.0, 104.9, 103.3 (2), 79.3 (2), 68.9, 68.8, 53.1, 53.0, 50.9, 50.1, 49.9, 49.4, 48.5, 47.1, 32.9, 31.9, 29.0, 27.9, 23.8, 22.7; LRMS (ESI+) \(m/z\) (relative intensity) 459.1 (M+H\(^{+}\), 100%).
Bibliography

VITA

AHMED YIMAM NURIYE

Ahmed was born in 1981 in Ethiopia where he obtained his elementary and part of his secondary education. He then moved to Hong Kong on a United World Colleges scholarship to finish his high school education at Li Po Chun United World College. After obtaining his International Baccalaureate Diploma in 2001, he moved to the United State where he completed his BS degree in chemistry in 2005 at the State University of New York College at Brockport on a Distinguished Scholars in Residence scholarship. At Brockport, Ahmed worked with the mentorship of Professor Margaret Logan on the synthesis of novel diaryl- and aryltelluride antioxidants. After graduating from Brockport, he moved to Penn State and joined Professor Ken Feldman’s laboratory where he worked on the development of novel Pummerer-based reactions in indole-based systems and on the total synthesis of dibromopalau’amine. Ahmed will join the faculty at Neumann University to start his independent career as an assistant professor of chemistry.

SELECT PUBLICATIONS


SELECT AWARDS AND HONORS

1. Dalalian Graduate Fellowship Award in Organic Chemistry, Penn State University, 2009-2010
2. Dan H. Waugh Memorial Teaching Award, Penn State University, 2008-2009
3. Rochester Section of the American Chemical Society Achievement Award, 2005