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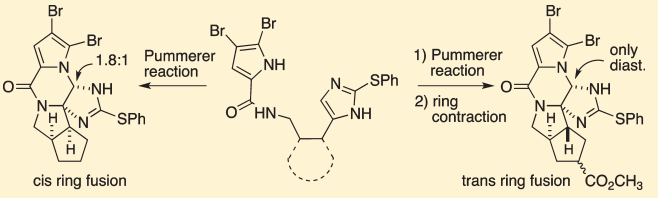
# Extending Pummerer Reaction Chemistry: Studies in the Palau'amine Synthesis Area

Ken S. Feldman,* Ahmed Yimam Nuriye, and Jianfeng Li

Department of Chemistry, The Pennsylvania State University, University Park, Pennsylvania 16802, United States

Supporting Information

**ABSTRACT:** Exploratory oxidative cyclization studies on cyclopentanelated and cyclohexenelated oroidin derivatives utilized Pummerer chemistry to generate pentacyclic structures related to the palau'amine family of sponge metabolites. Stereochemical issues were paramount, and appropriate choice of annelated ring size led to formation of the pentacyclic framework with complete diastereoselectivity for all of the core bonds.




## INTRODUCTION

The pyrrole-imidazole alkaloids (PIA's) comprise a large and growing family of sponge secondary metabolites whose biosynthesis origins have been a matter of much speculation.[1] The simple linear species oroidin (**1a**), hymenidin (**1b**), and clathrodin (**1c**) are invariably cited as the genesis for the more structurally complex PIA's through various sequences of oxidations, cyclizations, and rearrangements. The polycyclic monomers, dimers, and tetramers presumably so derived are offered as evidence for either Nature's bounty or Nature's parsimony, depending upon perspective. These species are isolated from sponges in several genera (*Stylotella, Stylissa, Agelas, Axinella, Acanthella, Cymbastella, Phakellia,* and *Hymeniacidon*), but their precise point of origin in all cases remains to be discovered. Microflora can account for a large proportion of a sponge's dry weight, and there is much evidence that at least some (non-PIA) sponge metabolites are produced by these symbionts.[2] Thus, the role of the sponges themselves vs their microbial consortia in PIA biosynthesis is an open question.

One prominent subset of the PIA's feature the (formal) dimers, which number >30 at present, Figure 1. Examples include the palau'amines (**2a**−**2c**),[1a] which have been isolated in all of the brominated versions related to **1a**−**1c**, respectively, and the konbuacidins (**2d**−**2e**),[3] which may serve as biosynthesis precursors to the palau'amines by simple hydrolysis of their pyrrole carboxamide unit. Of particular note is the fact that the original structural assignment of palau'amine was incorrect and a later revision required inversion of the stereochemistry at C(11) and C(17) (cf. **2**).[4] Thus, the palau'amine architecture features a highly strained trans azabicyclo[3.3.0]octane nucleus. The structurally related styloguanidines (**3a**−**3c**)[5] (primary amine) and cateramine A[4b] (**3d**, pyrrole amide) possess an "inverted" bonding pattern at the connection point of the pyrrole with the fused guanidine (formerly 2-aminoimidazole) unit compared with the palau'amines; C(4) → C(6) attachment for **3** rather than N(1) → C(6) attachment for **2**. The axinellamines (**4a**−**4d**)[6] contain the same chlorocyclopentane/spiro-2-aminoimidazoline core as do the palau'amines and styloguanidines, but the peripheral (oxidative) cyclizations to formulate the remaining rings differ. Now, the (former) 2-aminoimidazoles have linked up to form diastereomeric tricyclic ring systems, and the pyrrole carboxamide units remain intact and unperturbed. The methyl ethers **4c** and **4d** may be artifacts of methanol extraction upon initial isolation. Finally, massadine (**5**)[7] appears to fall out from the axinellamine biosynthesis tree by virtue of the familiar cyclopentane/spiroimidazoline core, but now the two (former) 2-aminoimidazole rings are linked by an intervening oxygen and not directly as in **4**.

Al Mourabit and Potier were the first to speculate that the polycyclized PIA structures all could emerge through judicious reliance on tautomerizations to activate the 2-aminoimidazole unit for both nucleophilic and electrophilic additions to complementary reaction partners.[1b] For the dimeric alkaloids of Figure 1, this line of thinking involved a dimerization/oxidation (chlorination) sequence to convert the linear species **1** (bromine count unspecified) into a linear dimer of the general structure **6**, Scheme 1. Cyclization of the nucleophilic enamine into the electrophilic imine within **6** was postulated to lead to a series of tautomeric/conformational isomers of a chlorocyclopentane core bearing spiro-2-aminoimidazoline and pendant 2-aminoimidazole rings, as exemplified by the imidazole-containing isomer **8**. Interestingly, Köck and Baran arrived at a similar intermediate in their biosynthesis thinking through an alternative pathway from **1** that relied upon the intermediacy of the natural product ageliferin (or ageliferin-type structures **7**, depending upon the bromine count on the pyrrole ring). The focal point of this chemistry is a pinacol-like ring contraction that condenses the cyclohexene ring into a cyclopentane ring with appropriate positioning of the Cl. Oxidation of the 2-aminoimidazole ring within **8** (or one of its imidazole ring tautomers) then is suggested to produce the pivotal intermediate(s) in both the Al Mourabit/Potier and Köck/Baran biosynthesis landscape, the

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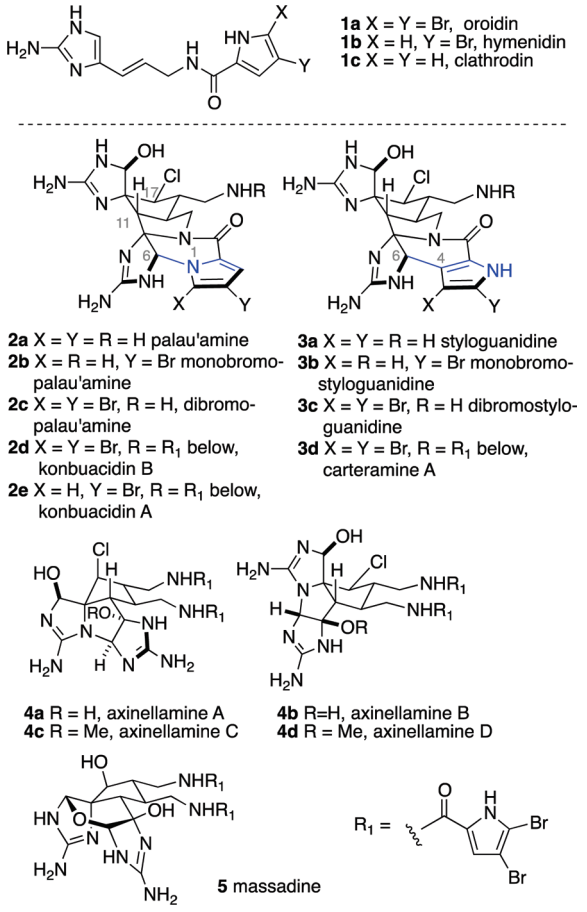


**Figure 1.** Sponge metabolites based upon formal oroidin, clathrodin, or hymenidin oxidative dimerization.

highly electrophilic triazafulvene iminium ion **9**, depicted as a rapidly equilibrating mixture of rotamers **9a**/**9b** that only differ in the dihedral angle about the C(9)/C(11) bond, Scheme 1. Al Mourabit/Potier do not explicitly cite this construct, whereas Köck/Baran indicate that this species (dubbed "preaxinellamine"), in equilibrium with its hydration product at C(9), is the central palau'amine/axinellamine branch point. In this hypothesis, the hydration product is shown as the precursor of the axinellamines whereas the triazafulvene species **9** is placed on the path toward the palau'amine family of dimeric PIA's. In any event, the hydration details notwithstanding, an intermediate of the type **9** is described as the key divergence point in the biosynthesis of all of the dimeric PIA's displayed in Figure 1.

Although not explicitly detailed by either set of authors, some logical progressions can be invoked to connect "preaxinellamine" **9** with the eventual dimeric alkaloid isolates. To further elaborate this biosynthesis speculation, it is necessary to focus on the distinct chemical options available to the two presumably rapidly equilibrating conformers of **9**, **9a** and **9b**. For example, the phakellin portion of the palau'amine structure **2** might derive from two successive cyclizations of proximal nucleophilic nitrogens into the two electrophilic carbons on the triazafulvene moiety of **9b**. Similar reaction through **9a** would not give the palau'amine stereochemistry. Initial 5-exotrig addition of N(14) into C(9) within **9b** (red arrow) would generate the strained trans azabicyclo[3.3.0]octane core of **10**, and then a subsequent addition of N(1) of the pyrrole unit into C(5) of putative intermediate **10** would deliver the skeleton of the palau'amine family of dimeric PIA's. Alternatively, the formation of this strained azabicyclo[3.3.0]octane core might be avoided by first closing N(1) into C(5) within **9b** (blue arrow) to give a macrocyclic construct **11** that is very similar to Baran's "macro-palau'amine" intermediate from his successful synthesis of **2a**.[8] The intermediacy of such a macrocycle in palau'amine biosynthesis might be anticipated perhaps by Al Mourabit/Potier's original biosynthesis speculation for the simpler phakellins.[1b] This species, featuring 5 (or 6, depending upon tautomer involved) $sp^2$ atoms in a nine-membered ring is likely to be quite strained as well, and Baran's landmark synthesis already has demonstrated that it readily undergoes transannular cyclization to forge the N(14)/C(9) bond of the final product palau'amine. A priori, there is no compelling reason to favor one sequence over another, as both rely on formation of highly strained intermediates, but in a substrate related to the much simpler monomeric oroidin case (i.e., no cyclopentane ring appended to the imidazole/pyrrole tether), cyclization from N(14) is observed when N(1) is blocked.[9] This observation provides no more than circumstantial evidence that initial N(1) (macro)cyclization is not required for formation of a phakellin structure from an oroidin-type monomer. The styloguanidine **3** family of dimeric PIA's can extend from **9b** as well, with C(4) → C(5) cyclization replacing N(1) → C(5) bond formation in both sequences.

The origins of the axinellamines (**4**) can be traced to this same common intermediate **9** according to this biosynthesis speculation. The significance of the rotational isomers **9a**/**9b** now becomes apparent; **9b** is aligned to promote facile N(23)/C(5) bond formation through a 5-exotrig pathway (green arrow) to generate the tetracyclic syn-fused diastereomer **12**, from which hydration on the convex face of the triazabicyclo[3.3.0]octane unit will deliver axinellamine B (**4b**). Similarly, conformer **9a** juxtaposes N(23) with the diastereotopic face of C(5) compared with **9b**, and so the diastereomer **13** should emerge from bond formation. Once again, hydration from the convex face will product axinellamine A (**4a**). The Köck/Baran biosynthesis blueprint cites hydration before cyclization, a sequence supported by chemistry exposed during Baran's synthesis of the axinellamines[10] However, the in vivo sequence of events is unknown, and the ordering of these two steps is not consequential in any event (vide infra). This biosynthesis plan also accommodates the formation of massadine (**5**); cyclization of the C(20) secondary alcohol of **9a** into C(5) followed by C(9) hydration (or the reverse sequence) will form this tetracyclic PIA.

All of this biosynthesis speculation has implicit in it an overriding theme; a desire for chemical economy that encourages identification of an early common intermediate which can serve as the genesis point for a myriad of structures. In the above scenario, preaxinellamine **9** serves this function. However, this almost compulsory focus on simplification may be misleading. Specifically, it is curious that an electrophilic intermediate like **9**, when faced with the three choices of N(23) → C(5) cyclization (–> axinellamines), N(14) → C(9) cyclization (→ palau'amines) and N(1) → C5) cyclization (→ palau'amines also), "picks" what are likely to be higher energy options and makes the palau'amine skeleton. This assessment is based upon the strain inherent in the palau'amine intermediates **10** and **11** compared to **12**/**13**, and the expectation that at least some of that strain energy is "felt" in the transition states for cyclization leading up to these species. Specifically, model systems for the isomeric structures **10**–**13**, in which


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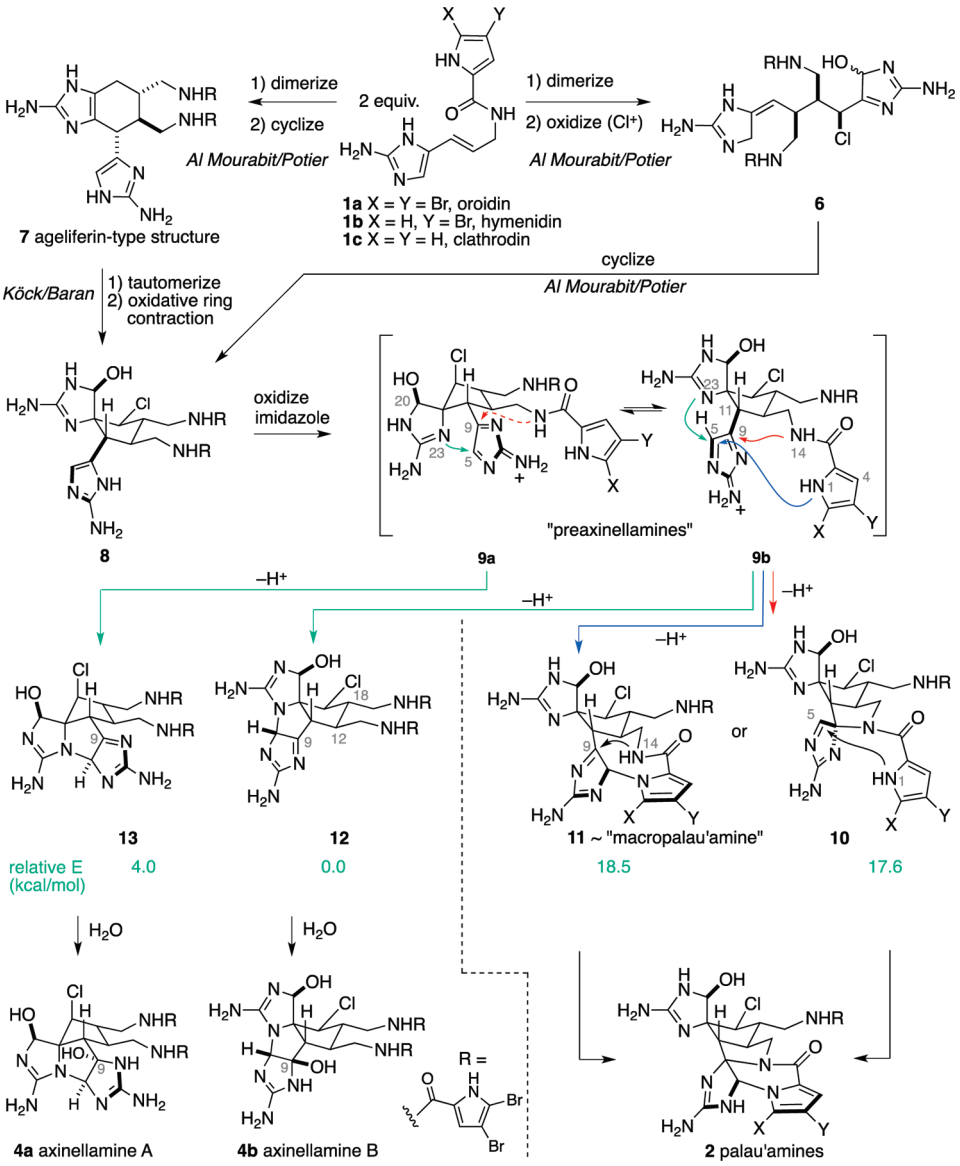
**Scheme 1. Consolidated Biosynthesis Proposal for the Dimeric PIA's Axinellamines and Palau'amines Adapted from Seminal Hypotheses of Al Mourabit/Potier[1b] and Köck/Baran[1d]**




the C(18) "$CH_2NHR$" unit in each case was replaced with a simple methyl group, were examined computationally first with Molecular Mechanics calculations to identify the low-energy conformer about the remaining rotatable bonds (i.e., the $CH_2NHCO$pyrrole unit extending from C(12)), and then those structures were subjected to a density functional calculation (PB3LYP/6-31G**).[11] The resulting energies are illustrated in Scheme 1. Even given all of the uncertainties that attend this type of calculational analysis, it is striking that the axinellamine precursor cyclization products **12** and **13** are calculated to be over 12 kcal/mol more stable than the palau'amine precursor cyclization products **10** and **11**.

Furthermore, the taxonomies of the end products lend little support to the thesis that a preaxinellamine-like common axinellamine/palau'amine intermediate is obligate in the biosynthesis. Thus, there is no evidence that the sole reported sources of the axinellamines, seven *Axinella* species from Australian waters, produce any of the palau'amines.[6] In addition, the reported sources of the palau'amines and related styloguanidines/konbuacidins (*Stylotella aurantium* from the Coral Sea,[1a] *Hymeniacidon sp.* from Japanese waters,[3] *Stylissa carteri* from Japanese waters,[4b] *Stylissa flabellata* from Australian waters,[3b] *Axinella verrucosa* from the Mediterranean Sea[12]) are not described as containing axinellamines. One complication to this "either/or" scenario is the observation that dibromopalau'amine (and konbu'acidin B) and massadine (possibly an axinellamine-channel species) are all isolated from *Stylissa flabellata*.[3b] Two other massadine-producing sponges (*Stylissa caribica* from the Caribbean Sea[13] and *Styllisa* aff. *masa* from Japanese waters[7]) are not reported to contain any palau'amine-type PIA's. The significance of these dimeric PIA isolation observations should not be overinterpreted, given the ambiguity in identifying the actual producing organism (sponge or microbe?, vide supra) and the possibility that some of the "crossover" species might be present but simply have evaded detection as a consequence of the particular isolation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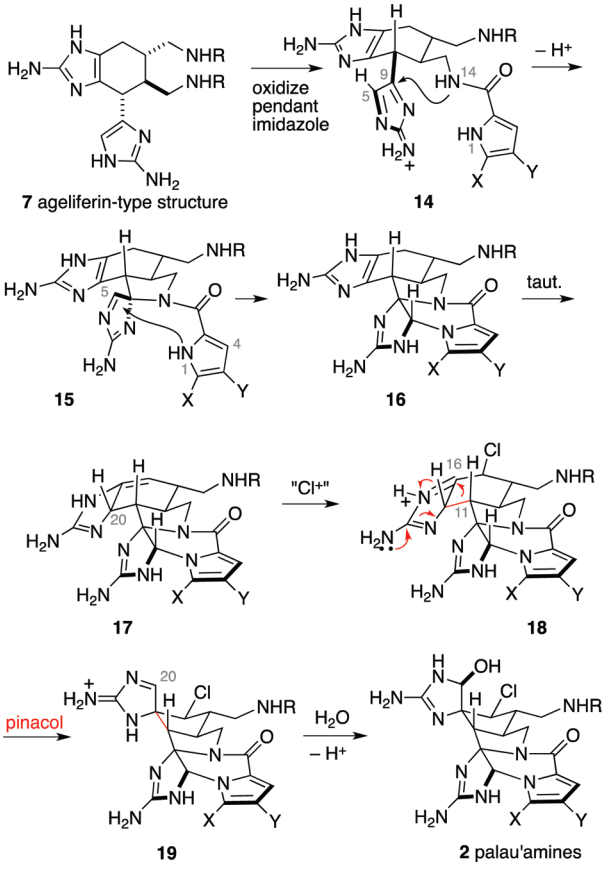
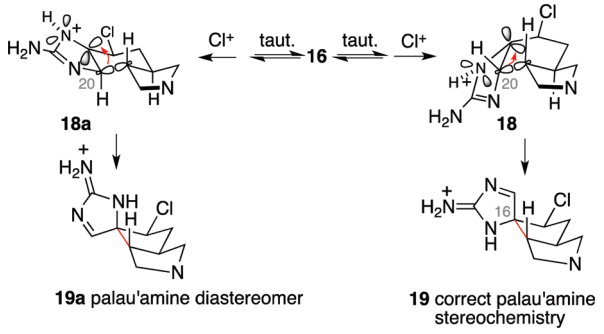
**Scheme 2. Alternative Biosynthesis Hypothesis for Formation of the Palau'amines from Ageliferin-type Progenitors**




**Scheme 3. Stereochemical Subtlety in the Pinacol Rearrangement of Chlorocyclohexane 18**




procedures used. Nevertheless, the lack of "positive" evidence, with the possible exception of the *Stylissa flabellata* data, does not lend any support to the preaxinellamine common intermediate hypothesis. Perhaps an alternative explanation deserves consideration.

Specifically, what if the turning point toward the palau'amine-type PIA's occurred much earlier in the family tree, perhaps at the ageliferin level (Scheme 2)? In this circumstance, the key electrophilic intermediate **14** will extend from a six-membered ring, and so N(14) to C(9) closure will form a much less strained trans 6−5 ring system as illustrated in **15**. Further cyclization of N(1) to C(5) within **15** will furnish the "homopalau'amine" structure **16**. Variations on this general ageliferin-based bicyclization theme, like C(4) to C(5) cyclization within **15** to form the styloguanidine skeleton, or N(1) to C(5) cyclization within **14** followed by transannular N(14) to C(9) closure, can be accommodated as well. Formation of "homopalau'amine" **16** now permits entry into familiar territory; this species (stereochemistry notwithstanding) is just the intermediate originally proposed by Kinnel and Scheuer as part of their seminal palau'amine biosynthesis speculation.[1a] The later stereochemical correction of palau'amine rendered that original proposal untenable, and so biosynthesis conjecture moved in a different direction. However, perhaps a re-examination is indicated. The stereochemistry of an ageliferin-type structure **7** is perfectly poised to deliver the correct stereochemistry of the palau'amines, provided certain mechanistic exigencies are met (vide infra). The central tenet of the Kinnel/Scheuer hypothesis is an oxidative (chlorinative) ring contraction of a 2-aminoimidazoline-cyclohexene unit that converts the six-membered ring of the precursor to the five-membered ring of palau'amine. In the present case, this chemistry is expressed as a chlorination of the alkene of **17**, formed by tautomerization of **16**, to initiate a pinacol-like 1,2-shift of C(11) to form an attachment to the electrophilic carbon C(16), as illustrated in **18** −> **19**. Hydration of the C(20) imine then will deliver the palau'amine structure **2**. The pivotal pinacol-mediated ring contraction has much precedent in related model systems at various levels of complexity, as reported independently by Romo,[14] Lovely,[15] Baran,[16] and Chen.[17] This conceptualization of the dimeric PIA biosynthesis problem (the Kinnel/Scheuer hypothesis; ageliferin and not preaxinellamine as a precursor to the palau'amines) may inform synthesis efforts in this area, and earlier we had reported preliminary results with a model system for both the oxidative bicyclization with a cyclohexene core and for the subsequent ring contraction of the 6−5 ring system to the trans fused 5−5 ring system of the palau'amines.[18] Independent of our studies, Chen recently has arrived at the same biosynthesis speculation (the Kinnel/Scheuer hypothesis on an ageliferin-type substrate), and his group has demonstrated the feasibility of the oxidative bicyclization on an advanced cyclohexene-based intermediate.[19]

The tautomerization of **16** into **17** sets up the eventual stereochemical outcome for the pinacol-mediated ring contraction. Acquisition of palau'amine's relative stereochemistry requires that the hydrogen at C(20) attaches to the "upper" face of the ring system, as shown in **18** and elaborated in Scheme 3. From this configuration, appropriate stereoelectronic alignment between $\sigma_{C-C}$ of the shifting bond and the "lower" face lobe of the iminium ion LUMO can be maintained. In this arrangement, the requisite stereochemistry at the spiro center C(16) will emerge, as illustrated in the **18** → **19** conversion below. On the other hand, formation of the "lower" face C(20) hydrogen tautomer **18a** sets the stage for a pinacol-like contraction wherein now the best alignment is between the migrating bond's $\sigma_{C-C}$ orbital and the "top" face lobe of the imine's LUMO; in this arrangement, formation of a C(16) diastereomer **19a** to the palau'amine stereochemistry would be indicated.

The palau'amine model system synthesis work described herein originated as an extension of our earlier efforts to develop Pummerer reaction chemistry as a means to conduct oxidative cyclizations onto aromatic heterocycles.[9,20] In the imidazole case, the potential to develop a tractable alternative to the putative biosynthesis intermediate triazafulvene **26** presented as a real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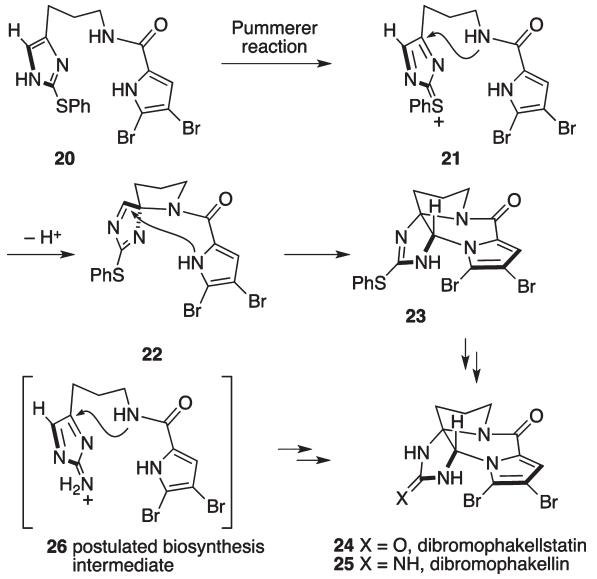
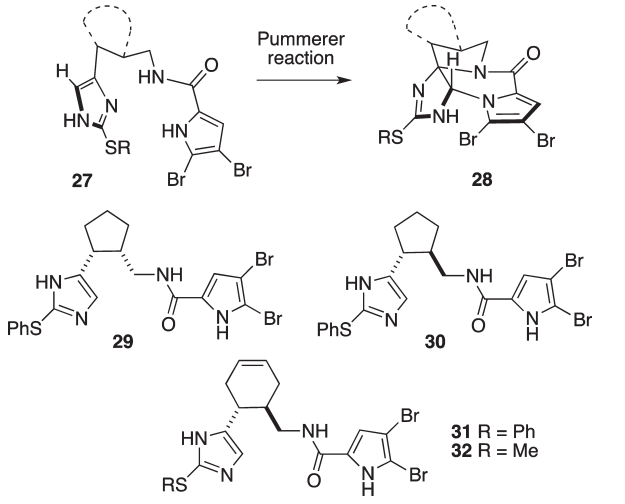
**Scheme 4. Earlier Pummerer Reaction-based Biomimetic Syntheses of Dibromophakellstatin and Dibromophakellin**




**Scheme 5. Scope of the Dibromopalau'amine Model System Work**




opportunity to advance the synthesis of the phakellin alkaloids, Scheme 4. Büchi and later Horne have documented the success of bromonium ion mediated bicyclizations of dihydrooroidin (cf. **1a**, without the alkene) as part of their biomimetic syntheses of the phakellin alkaloids,[21] and more recently Chen has introduced $PhI(OAc)_2$ as a useful oxidant for this bicyclization.[22] As an alternative to these oxidants, we envisioned that Pummerer reaction-mediated oxidative activation of the imidazole nucleus for this type of chemistry would benefit from (1) completely localizing the site of oxidation to the imidazole moiety, and (2) removing product (over)oxidation from the realm of possible yield-limiting competitive reactions. Whereas these features of Pummerer chemistry may not translate to significant advantages in the simple and unfunctionalized phakellin-type substrates (**20** → **21** → **23**), they might prove useful for promoting relatively clean cyclizations in the more heavily functionalized and sensitive palau'amine (and related) series.

In this full accounting of our model system work, we describe the results of studies to effect Pummerer-reaction mediated oxidative bicyclization of three ring systems relevant to the palau'amine architecture; a cis cyclopentane substrate **29**, a trans cyclopentane substrate **30**, and a pair of trans cyclohexene substrates, **31** and **32**, Scheme 5. Substrate syntheses will be detailed, the results of optimization studies for the key Pummerer-based bicyclization will be discussed, and a ring contraction protocol extending from the cyclohexene-based polycycle derived from **31**, which delivers the correct relative stereochemistry of the pentacyclic palau'amine system, will be presented.

## RESULTS AND DISCUSSION

The inception of this project predated the palau'amine structural revision, and so the initial synthesis target was the model system **29** that featured the (incorrect) cis cyclopentane core. While these studies were ongoing, the stereochemical correction to the trans cyclopentane core was reported, and so the complementary trans cyclopentane substrate **30** later became the focus of the initial model system work. Concerns about the prospects of accomplishing a bicyclization to fashion a trans azabicyclo[3.3.0]octane unit in acceptable yield, as well as a rethinking of the possible palau'amine biosynthesis pathways that might lead to a feasible approach to this core moiety (vide supra), prompted us to consider an alternative cyclization substrate based upon a six-membered ring core, **31**/**32**, as well. The development of reliable routes to these Pummerer cyclization substrates is discussed below.

## SUBSTRATE SYNTHESES

The addition of organometallic reagents to α-chloroketones has been advanced as a method for formal α-vinylation of ketones.[23] This chemistry might map into the problem of **29** synthesis if a 5-lithioimidazole could be substituted for the vinyl(alkynyl) organometallic species that were reported in the precedents, Scheme 6. Fortunately, the generation of 5-lithioimidazoles is facile with an appropriate protecting group on N(1). And so, combination of the 5-lithioimidazole, formed by deprotonation of the SEM-protected 2-(phenylthio)indole **33**,[24] with 2-chlorocyclopentanone (**34**) did proceed to the desired 2-imidazoyl cyclopentanone **35**, but the yield was never better than ~16% despite some optimization efforts. The unrearranged direct carbonyl 1,2-addition product was a major isolate, and starting imidazole **33** was recovered in significant amounts as well. Switching to either the magnesiate or cuprate reagent derived from the 5-lithioimidazole did not lead to any improvement. Nevertheless, the ready availability of the starting materials **33** and **34** allowed us to forge ahead with the intent of returning to yield optimization studies if the ultimate Pummerer chemistry with **29** panned out. As it transpired, the palau'amine stereochemical revision abrogated those plans. Methylenation of the ketone within **35** was best accomplished with the Petasis reagent.[25] Alternative methylenation approaches, such as the original Tebbe procedure (~5% of **36**) or Wittig chemistry (→ endocyclic alkene product) were not competitive. Hydroboration of the methylene unit of **36** with 9-BBN afforded the expected alcohol, following oxidative workup, as a 4:1 mixture of diastereomers favoring the desired species **37**.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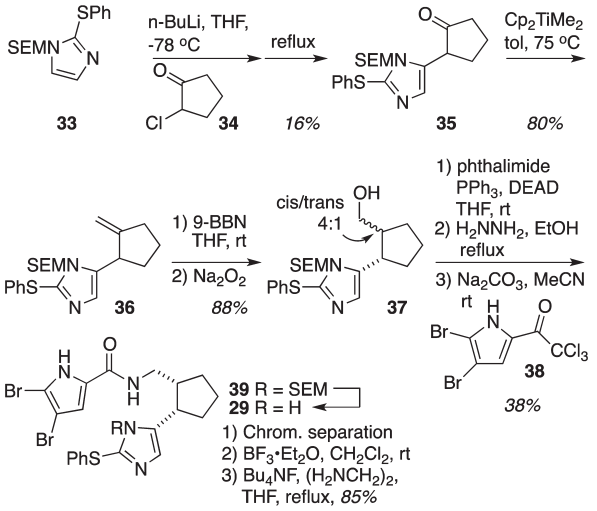
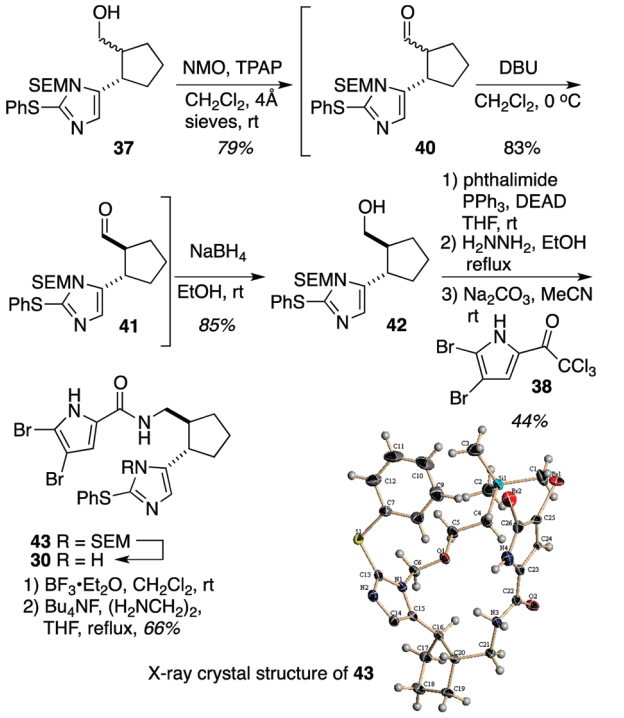
**Scheme 6. Synthesis of Cis-fused Cyclopentyl Pummerer Cyclization Substrate 29**




**Scheme 7. Synthesis of Trans-fused Cyclopentyl Pummerer Cyclization Substrate 30**




The stereochemistry of the major isomer was difficult to assign at this point due to overlap of signals in the $^1$H NMR spectrum, and so we proceeded with a provisional cis assignment based simply on mechanistic reasoning. Eventual stereochemical assignment within this series of compounds was based upon a process of elimination; X-ray crystallographic analysis of the diastereomer of **39** secured the relative stereochemistry of that alternative isomer (cf. **43**, see Scheme 7). These diastereomeric alcohols were difficult to separate at this stage, and so the mixture was processed on to the dibromopyrrole adduct **39**, where chromatographic separation was easy. The nitrogen-for-oxygen swap within **37** was accomplished via Mitsunobu chemistry, and acylation of the primary amine with the commercially available 2,3-dibromo-5-(trichloroacetyl)-1*H*-pyrrole (**38**) then provided the intact cis fused cyclopentane core model system. SEM removal from **39** proceeded smoothly via a two-step protocol[9,26] to deliver the cis-fused cyclopentane Pummerer oxidative cyclization substrate **29**.

We next turned our attention to the trans cyclopentane cyclization substrate **30**, which features the correct stereochemistry for the palau'amine family of natural products (Scheme 7). The chemistry that was developed for the synthesis of **29** could be incorporated, at least in part, in this effort. Thus, the mixture of alcohols **37** favoring the cis stereochemistry could be oxidized to an analogous mixture of aldehydes **40**, which, upon exposure to the base DBU,[27] completely isomerized to afford exclusively the trans imidazole aldehyde **41**. This aldehyde was prone to decomposition, and so as a practical matter, it was immediately reduced to alcohol **42**. Acquisition of alcohol **42** sets the stage for completion of trans model system **30** by following essentially the same chemistry already developed for the cis isomer **29**. The stereochemistry of compounds within this series was established unambiguously by single crystal X-ray analysis of the intermediate amide **43**.[28]

The alternate plan for construction of the pentacyclic architecture of the palau'amines passed through a six-membered ring core as a concession to the perceived difficulty of accomplishing azabicyclo[3.3.0]octane synthesis via an acyclic closure approach. Thus, this "ageliferin"-centered strategy required a cyclohexene platform to both facilitate Pummerer-mediated bicyclization, and to provide functionality conducive to executing the necessary 6 → 5 ring contraction. Diels–Alder chemistry seemed like the obvious choice for forming a cyclohexene ring-based substrate that satisfied both of these requirements. The various dienophiles examined in this transformation were synthesized as illustrated in Scheme 8. Compounds in the BOM series (**45b**, **46b**, and **49b**) were described in a preliminary account of this work.[18] The 2-(phenylthio)imidazole aldehydes **45a**–**45c** were prepared by following the Lipshutz double metalation protocol on the parent protected imidazoles **44a**–**44c**, respectively.[24] Simple Emmons-Horner methylenation with diethyl(carbamoylmethyl) phosphonate then provided the exclusively (*E*)-enamides **46a**–**46c** in excellent yields. The synthesis of the methylthio analogue **48** required a bit of a detour, as initial metalation of the intermediate SEM-protected 2-(methylthio)imidazole led to loss of the MeS group. In this instance, regiospecific bromination of the SEM-protected 2-(methylthio)imidazole provided the 5-bromo product, which could be cleanly metalated and then the intermediate 5-lithio species formylated without event to give aldehyde **47**. Chain extension as above provided the final Diels–Alder dienophile **48**.

Synthesis of the cyclohexene-based Pummerer bicyclization substrates commenced with a Diels–Alder cycloaddition between the various protected 2-thio-5-enamides **46a**–**46c** and **48** and butadiene under forcing conditions, Scheme 9. Optimization studies revealed that both the presence of hydroquinone as a radical inhibitor and the high temperature were required to advance material even in the modest yields reported. The Diels–Alder reaction was not particularly responsive to the nature of the N(1) protecting group or the thioether substituent. Surprisingly, all attempts to extend this Diels–Alder reaction to 2-(methoxy)butadiene, 2-(trimethylsilyloxy)butadiene, or 1-methoxy-3-(trimethylsilyloxy)butadiene (Danishefsky's diene) were not fruitful. In all cases, either starting dienophile was returned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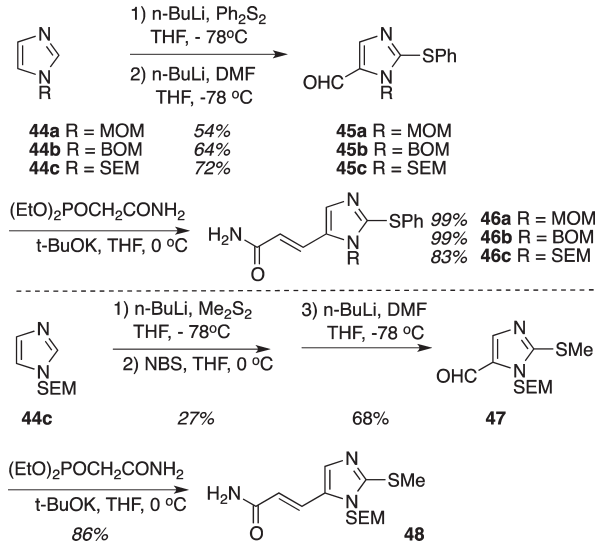
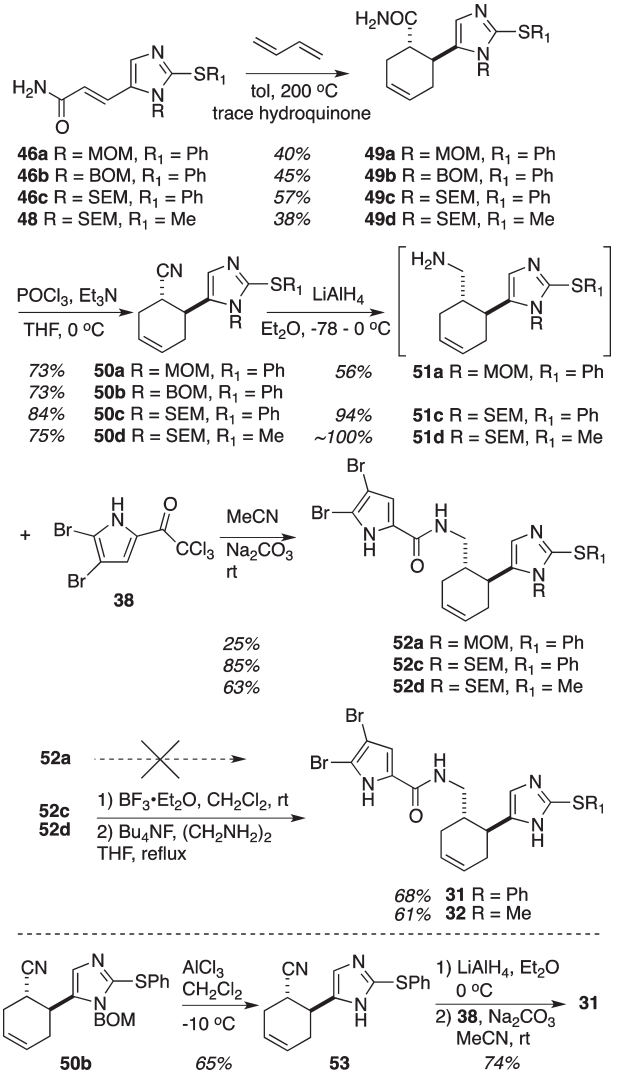
**Scheme 8. Synthesis of 2-Thio-imidazole-based Dienophiles**




or decomposition to uncharacterized products was observed. In addition to thermal studies, attempts to promote Diels–Alder reaction with these oxygenated dienes extended to mediation by either (a) various Lewis acids ($SnCl_4$, $TiCl_4$, $Cu(OTf)_2$, $LiClO_4$, $EtAlCl_2$), or (b) high pressure (12 kbar); nothing promising was observed. Nevertheless, the successful Diels–Alder reactions of **46a**–**46c**/**48** did provide sufficient material to complete the synthesis of the cyclohexene-based cyclization substrates. Reduction of the primary amides of **49a**–**49d** to primary amines was required next, but all attempts with hydride reagents ($LiAlH_4$, $LiBH_4$, $BH_3$) at elevated temperatures led to reductive removal of the SR unit to various extents — low-temperature attempts just returned starting material with the thio group intact. A workaround that proceeded at lower temperatures was needed. The primary amides **49a**–**49d** were dehydrated with $POCl_3$ to give the nitriles **50a**–**50d**, respectively. These nitriles, with the exception of the BOM-protected species **50b**, then could be reduced cleanly to the primary amines **51a**, **c**–**d** at <0 °C, conditions that preserved the thio substituent. We did not anticipate that the BOM-protected species **50b** would present a problem for this 2-stage reduction sequence; rather, we had concerns that eventual BOM deprotection might be incompatible with the pyrrole bromides in **31**. Therefore, we elected to remove the BOM group at the stage of nitrile **50b** and then reduce the CN function to the primary amine as above, **50b**→ **53** → **31**. The primary amines **51a**, **51c**–**d** then were acylated with 2,3-dibromo-5-(trichloroacetyl)-1*H*-pyrrole (**38**) in variable yields to give the protected Pummerer cyclization substrates **52a**, **c**–**d**. Deprotection of the MOM-containing species **52a** failed under all protocols examined, and so that approach appeared to be a dead end. Fortunately, the SEM-protected substrates **52c** and **52d** could be deprotected via the 2-step procedure used earlier with **39** and **43** to deliver the corresponding free imidazole-pyrrole species **31** and **32**, respectively, ready for Pummerer mediated bicyclization studies. The phenylthio substrate **31** also could be derived from the BOM-protected species **50b** in good yield, as indicated in Scheme 9.

Earlier success with Pummerer-mediated oxidative bicyclizations using the simpler phakellin species provided direction for optimization studies with the more complex substrates in the palau'amine series. Thus, Stang's reagent, PhI(CN)OTf,[29] in the

**Scheme 9. Diels–Alder Cycloaddition of Butadiene with Imidazole-based Dienophiles, and Subsequent Pummerer Cyclization Substrate 31/32 Synthesis**




presence of Hunig's base defined the starting point for these studies. The cis substituted cyclopentane substrate **29** was the initial species examined, as at that point in time, the palau'amine structural revision had not yet been reported. We were pleased to find that, in fact, this substrate could be cyclized through this procedure to give two pentacyclic compounds whose spectral data supported the gross structural assignments shown as **57a** and **57b** (Scheme 10). Well-defined singlets for H(3) and H(6) in the $^1$H NMR spectrum of both **57a** ($\delta$6.99 and 5.68, respectively) and **57b** ($\delta$6.98 and 5.70, respectively) corresponded closely to the related signals in the $^1$H NMR spectrum of the simpler phakellin-like Pummerer cyclization product **23** ($\delta$6.92 and 5.87, respectively, see Scheme 11). Yields of these cyclized products were never high, but could be optimized to ~30% overall by incorporation of a little methanol in the reaction medium to help with solubility. Key NOE correlations that permitted tentative assignment of relative stereochemistry are shown on the product structures. The formation of two diastereomers of the cyclized product can be rationalized by citing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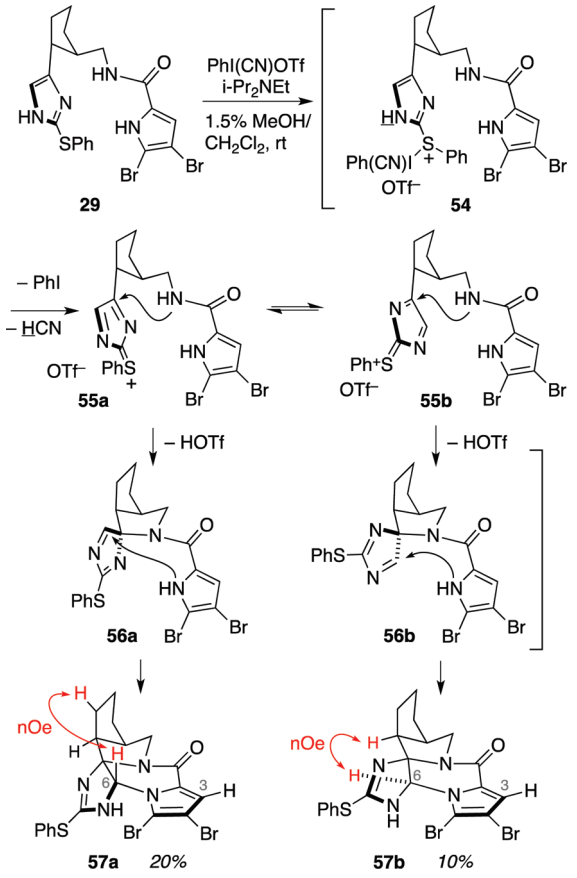
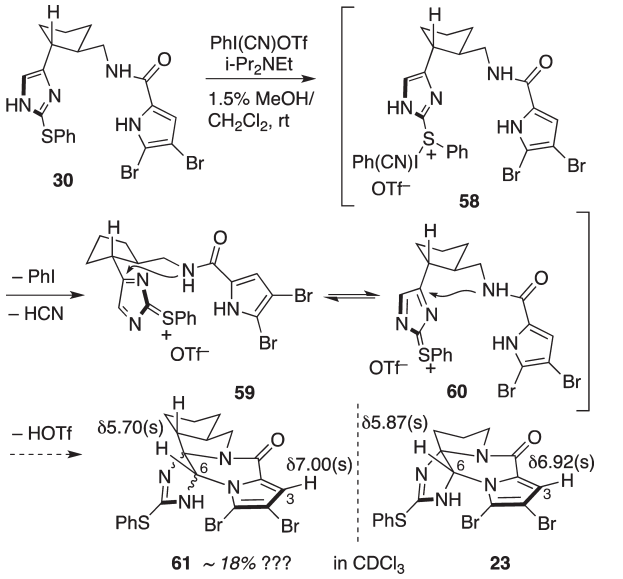
**Scheme 10. Pummerer-Mediated Bicyclization of the Cis Cyclopentyl Substrate 29**




**Scheme 11. Attempted Pummerer-mediated Bicyclization of the Trans Cyclopentyl Substrate 30**




rotational isomers **55a** and **55b** as key intermediates. The orientation of the electrophilic imidazole moiety in these species determines the ultimate stereochemistry of product formation. The rotamer **55a** translates into the diastereomer **57a** as shown, whereas the alternative rotamer **55b** precedes **57b**. By this analysis, there appears to be little energetic discrimination between the two channels. The lack of preference for the "natural" palau'amine stereochemistry was concerning and called into question the entire biomimetic foundation of this synthesis endeavor. However, at this juncture, the palau'amine stereochemical revision was announced, and so this entire point became moot; perhaps the biosynthesis analysis as we envisioned it had received a reprieve.

The important question then became, "Is Pummerer-mediated bicyclization from a trans cyclopentane substrate feasible?" To probe this issue, the trans cyclopentane species **30** was subjected to the standard Pummerer conditions, Stang's reagent in the presence of Hunig's base, Scheme 11. Chromatographic analysis (TLC) indicated consumption of starting material and formation of a single new product spot higher in $R_f$ than the uncyclized material and also higher in $R_f$ than both **57a** and **57b**. Chromatographic purification of this spot proved problematic, but rapid $SiO_2$ chromatography at −78 °C (jacketed column) led to recovery of a small amount of material (ca. 18% yield) corresponding to this spot. Examination of this purified sample by both $^1$H NMR spectroscopy and mass spectrometry provided promising preliminary data supporting formation of a single pentacyclic structure; mass spectrometry, $m/z$ at 521 compared with the (unoxidized) cyclization precursor **30** ($m/z$ at 523) and the (oxidized) cyclized cis-fused species **57a**/**57b** ($m/z$ at 521); $^1$H NMR ($CDCl_3$), singlets at $\delta$7.00 (tentatively assigned as H(3)) and 5.70 (tentatively assigned as H(6)), cf. **23** in Scheme 11. Unfortunately, the compound was so unstable in $CDCl_3$ or $CD_3OD$ that a clean $^{13}$C NMR spectrum could not be obtained. Furthermore, this first-formed product decomposed upon standing at −20 °C over the course of 24 h. So, in the final analysis, we did not obtain any conclusive evidence that confirmed the formation of **61**. Once again, our initial biosynthesis-inspired strategy was called into question, and perhaps it was time to consider alternative approaches to securing the palau'amine skeleton.

This line of reasoning led to a reevaluation of the orthodoxy in palau'amine biosynthesis, and eventually we were attracted to the alternative conceptualization that featured an ageliferin-type intermediate and not a preaxinellamine-type intermediate as the direct oxidative cyclization precursor to a "palau'amine" pentacycle, as discussed above with Schemes 2 and 3. Reducing this hypothesis to a discrete experimental test involved preparing the trans cyclohexene-based Pummerer substrates **31** and **32**, and exposing them to the standard Stang reagent conditions, Scheme 12. We were pleased to observe that in each case, oxidative cyclization did indeed occur to furnish the pentacyclic cyclohexenyl homologues of the palau'amine pentacycle, **65a** and **65b**, respectively, as single diastereomers. The gross structural assignment and stereochemical definition of **65a** was provided by a single-crystal X-ray analysis;[28] the assignment in the methylthio series **65b** was made by comparison of its spectral data to those of **65a**. Comparison of the H(3) and H(6) $^1$H NMR signals for these trans cyclohexene products (H(3): $\delta$6.80 for **65a**, 6.97 for **65b**, and H(6) 5.76 for **65a**, 5.94 for **65b**) with the same protons in the unstable mystery compound formed from Pummerer cyclization of the trans cyclopentane substrate **30** (H(3) $\delta$7.00, H(6) 5.70) lends further support to its provisional assignment as a pentacyclic oxidative cyclization product, as suggested by the structure **61**.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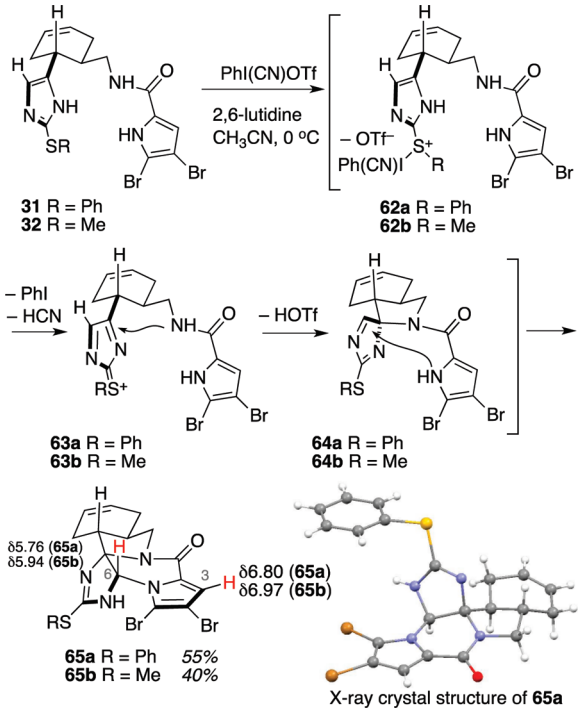
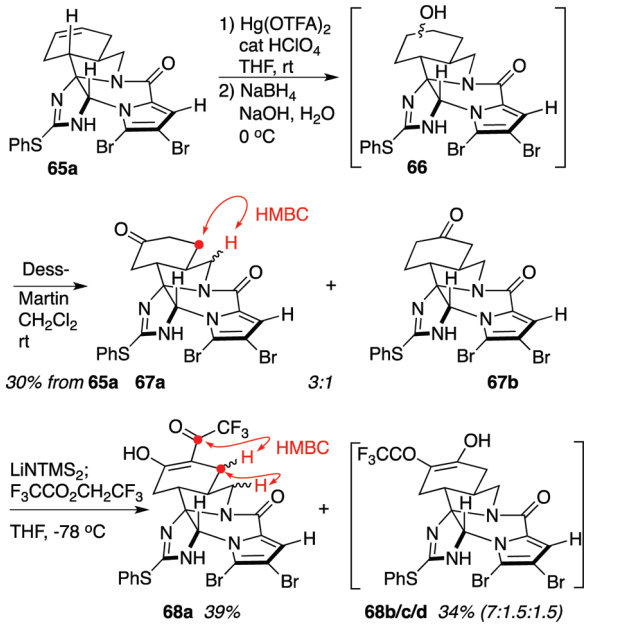
**Scheme 12. Pummerer-mediated Bicyclization of the Trans Cyclohexenyl Substrates 31/32**




**Scheme 13. Formation of the α-Diazoketone Precursors 68a−d**




The successful cyclization of **31** and **32** to give single, diastereomerically pure pentacycles attested to the feasibility of one-half of the "ageliferin-based" synthesis strategy for assembling the palau'amine skeleton. The second half of this approach requires execution of a ring contraction sequence to deliver the trans azabicyclo[3.3.0]octane core of the palau'amines. The simple alkene of **65a** is not set up to participate in a halogenative ring contraction as per the Kinnel-Scheuer biosynthesis hypothesis and the early studies of Romo and Lovely,[14,15] and so we had to consider other options. One attractive possibility is the Wolff rearrangement of α-diazoketones, which has documented utility in ring contraction sequences that deliver highly strained small ring products.[30] Thus, to explore this chemistry, we set out to convert the alkene function of **65a** into an α-diazoketone Wolff rearrangement precursor, Scheme 13. These efforts began inauspiciously with the failure of common protocols for alkene hydroxylation/oxidation; both hydroboration/oxidation or Wacker-type oxidation proved fruitless with **65a**, as only returned starting alkene or uncharacterized decomposition products resulted. We fared better with oxymercuration procedures, but even that chemistry was not without its problems in this complex functionally rich substrate. Initial oxymercuration proceeded smoothly and with complete consumption of starting alkene with either $Hg(OAc)_2$ or $Hg(OTFA)_2$ in the presence of a catalytic amount of $HClO_4$.[31] However, the $NaBH_4$-mediated demercuration step was complicated by an elimination process[31] that regenerated the parent alkene **65a** (~24%) in addition to the desired alcohol products **66** as a mixture of four regio- and stereoisomers. These alcohols were not separated, but rather oxidized as the crude mixture to give two ketone products **67a** and **67b** in a ~3:1 ratio. The regiochemical assignment rested on the HMBC correlation illustrated in **67a**. Since both ketones, in principle, can converge to the same Wolff rearrangement product eventually, we did not separate these species. Introduction of the α-diazo function necessitated activating these ketones as their trifluoroacetyl derivatives **68a**−**68d** via Claisen condensation.[32] These species were strictly enolic, and the major isomer **68a** was isolated as a pure species by column chromatography. The regiochemical assignment of this pure isomer was based upon the HMBC correlations indicated. The remaining three isomers were not separable. We presume that the major species within this mixture would be the one derived from the most (kinetically) accessible enolate available from **67b**, and that tentative assignment is shown in brackets.

The synthesis and Wolff rearrangement study of the α-diazoketone **69** continues in Scheme 14. Treatment of pure enol **68a** with the diazo transfer reagent $MsN_3$ furnished the desired α-diazoketone **69** in good crude yield, but as a sensitive material that resisted all attempts at purification. Thus, this unpurified material was subjected to irradiation in MeOH immediately after preparation, and from this sequence a single ester-bearing structure emerged, as a 1:1 mixture of diastereomers. Spectroscopic analysis supported the assigned structure as **71**, featuring the intact azabicyclo[3.3.0]octane core as part of the pentacyclic framework of the palau'amines. Connectivities were established via the HMBC correlations shown in Scheme 14, and the $^1H$ NMR signals for key H(3) and H(6) protons (δ6.97, 5.88/5.87, respectively) match well with those for the thiophenylphakellin systems discussed earlier (cf. **65a**, **65b**, and **23**). The critical coupling constant between the protons at the ring fusion of the azabicyclooctane core, H(11) and H(12), is 13.3 Hz for both isomers, a value similar to dibromopalau'amine itself (13.9 Hz),[1a] and distinct from the H(11)/H(12) coupling in two cis-fused analogues of palau'amine (12 and 10.7 Hz).[33] In an independent experiment, treatment of the mixture of enol isomers **68a**−**68d** collectively with $MsN_3$, and then irradiation (MeOH) of the resulting crude mixture of α-diazoketones, led to the same mixture of methyl esters **71**, now in an overall 37% yield.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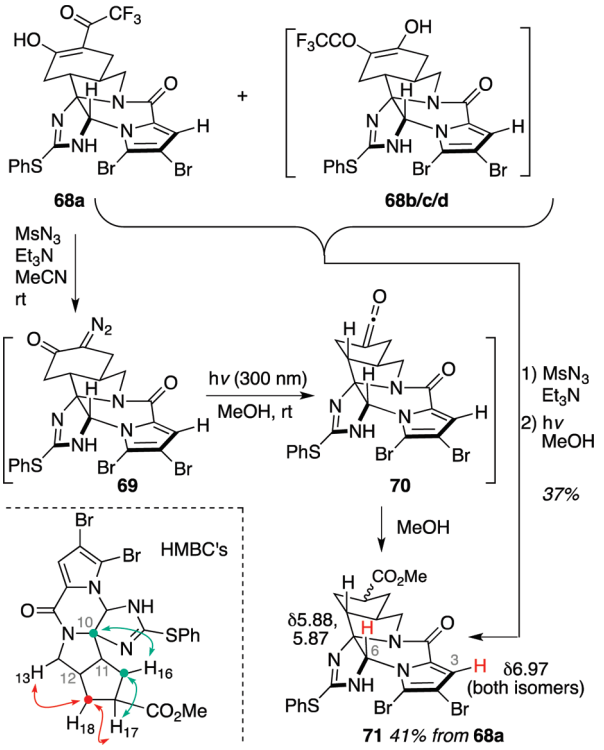
**Scheme 14. Wolff Rearrangement-Mediated Ring Contraction of 69, with Spectral Data Correlation for the Product 71**

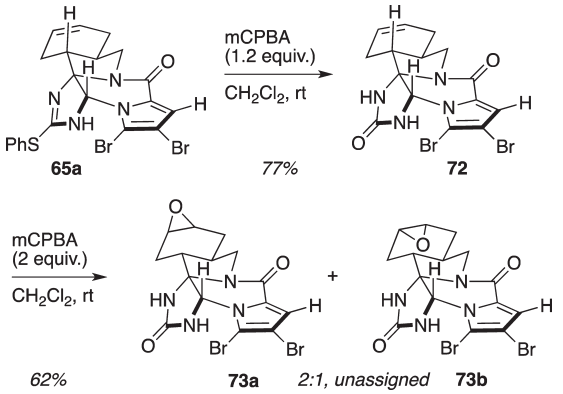



Among the failed attempts at functionalization/ring contraction of the cyclohexene unit of **65a** was an approach based upon initial oxidation of the alkene to an epoxide. This chemistry led first to the urea **72**, which could be isolated when only a slight excess of mCPBA was used, Scheme 15. Presumably, sulfur oxidation within the phenylthioamidine moiety is more rapid than alkene epoxidation, and the derived sulfoxide is readily hydrolyzed upon aqueous workup. The alkene within this urea-containing pentacycle could be epoxidized by treatment with more mCPBA to deliver the expected oxiranes **73a** and **73b** as an approximately 2:1 mixture of diastereomers. No stereochemical assignments were made. All attempts to effect ring contraction from the epoxides **73a**/**73b** met with failure.

## CONCLUSIONS

The value of the Pummerer reaction in promoting oxidative bicyclization of oroidin analogues bearing fused rings has been demonstrated. The products of this transformation feature an annelated dibromophakellin core, and the tolerated rings include a cis-fused cyclopentane and a trans fused cyclohexene. The latter species serves as the entry into a proof-of-concept synthesis thrust in the palau'amine area, as Wolff rearrangement-mediated ring contraction delivers the trans azabicyclo[3.3.0]octane core of these sponge metabolites. From a larger perspective, the results reported herein provide some insight into open biosynthesis questions in the dimeric PIA area. Specifically, the successful biomimetic oxidative cyclization/ring contraction sequence that delivers the trans azabicyclo[3.3.0]octane core of the palau'amines speaks to the feasibility of biosynthesis hypotheses promoting (1) an early divergence in the construction of

**Scheme 15. Formation of an Epoxyurea Derivative of Pentacycle 65a**




palau'amine and axinellamines structures, and (2) an ageliferin-based route to the palau'amines related to the original conceptualization of Kinnel and Scheuer.

## EXPERIMENTAL SECTION

**General Procedure 1: Preparation of C2 Thiophenyl and Thiomethyl Imidazoles.** To the appropriate *N*-protected, C(2)-thiophenyl imidazole dissolved in THF (0.1 M) was added a solution of 2.5 mL *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 $NH_4Cl$ was added and the mixture was warmed up to rt. The organic layer was separated and the aqueous layer was extracted with $Et_2O$. The combined organic layers were dried over anhydrous $Na_2SO_4$, filtered and concentrated *in vacuo*. The crude material was purified by silica gel column chromatography using the indicated solvent system.

**General Procedure 2: C5 Formylation of Imidazole Substrates.** To a solution of the appropriate *N*-protected 2-(thiophenyl)-imidazole (1.0 equiv) in THF (0.15 M) at −78 °C was added *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 $NH_4Cl$ 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 $Na_2SO_4$, filtered, and concentrated *in vacuo* to give the desired aldehyde. The crude material was purified by the indicated method.

**General Procedure 3: Horner−Wadsworth−Emmons Olefination of Aldehydes.** To a solution of diethyl(carbamoylmethyl) phosphonate (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 anion 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 $Na_2SO_4$, 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.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**General Procedure 4: 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 h 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 5: Dehydration of Amides to Nitriles.** To a solution of phosphorus oxychloride (8.0 equiv) in THF (0.6 M) at 0 °C was added $Et_3N$ (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 $CH_3CN$ (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 $CH_3CN$, and the filtrate was concentrated under reduced pressure. The residue was chromatographed on a silica gel column using the indicated solvent system as the eluent to give the pure nitrile.

**General Procedure 6: Reduction of Nitriles to Primary Amines.** To a solution of the appropriate nitrile (1.0 equiv) in $Et_2O$ (0.03 M) at −78 °C was added a solution of 1.0 M $LiAlH_4$ in $Et_2O$ (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 $LiAlH_4$) at 0 °C followed by addition of a 3.0 M aqueous NaOH solution (*x* mL) and more water (3*x* mL), and then the mixture was warmed up to rt. Anhydrous $MgSO_4$ 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 7: Acylation of Amines with 2,3-Dibromo-5-(trichloroacetyl)-1*H*-pyrrole.** To a solution of the appropriate amine (1.0 equiv) in $CH_3CN$ (0.1 M) at rt was added 2,3-dibromo-5-(trichloroacetyl)-1*H*-pyrrole (1.1 equiv) followed by granular anhydrous $Na_2CO_3$ (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 $CH_3CN$ layer was removed under reduced pressure. The aqueous layer was extracted with EtOAc and the combined organic layers were dried over anhydrous $Na_2SO_4$, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography using the indicated eluent system to give the desired amide.

**General Procedure 8: Deprotection of *N*-SEM Imidazoles.** To a solution of the appropriate *N*-SEM protected imidazole in $CH_2Cl_2$ (0.025 M) at 0 °C was added $BF_3 \cdot Et_2O$ (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 $Na_2SO_4$, 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 $Bu_4NF$ (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 $Na_2SO_4$, 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 9: PhI(CN)OTf Initiated Pummerer Cyclization of Sulfide Substrates to Pentacycles.** The appropriate *N*-H imidazole substrate was dissolved in $CH_3CN$ (0.005 M) and cooled to 0 °C. To this solution 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 $Na_2SO_4$ and concentrated *in vacuo*. The crude material was purified by the indicated method.

**2-Phenylsulfanyl-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-imidazole (33)[24].** In a 100 mL flame-dried Schlenk flask, a solution of imidazole (0.508 g, 7.30 mmol) in THF (25 mL) was cooled to −78 °C and a solution of *n*-BuLi in hexane (2.28 M, 3.50 mL, 8.00 mmol) was added dropwise to the reaction solution. The reaction mixture was stirred at −78 °C for 30 min, warmed up to 25 °C, and then SEMCl (1.60 mL, 8.80 mmol) was added dropwise by syringe. The reaction mixture was stirred at 25 °C for 20 min then cooled to −78 °C. A second portion of *n*-BuLi solution in hexane (2.28 M, 3.50 mL, 8.00 mmol) was added and the resulting mixture was stirred at −78 °C for 30 min after which time a solution of phenyl disulfide (1.90 g, 8.80 mmol) in THF (5 mL) was added via cannula. The reaction mixture was stirred at −78 °C for 1 h and then warmed to 25 °C and stirred for an additional 4 h. Saturated aqueous $NH_4Cl$ solution (20 mL) and water (10 mL) were added to quench the excess *n*-BuLi and then the solution was extracted with $Et_2O$ (3 × 100 mL). The organic layers were combined, dried over $MgSO_4$, and evaporated under reduced pressure to give a yellow oil. The yellow oil was purified by $SiO_2$ flash column chromatography (10−20% EtOAc/hexane as eluent) to give the known imidazole **33** as a yellow oil (1.6 g, 71%).

**2-[2-Phenylsulfanyl-3-(2-trimethylsilanyl-ethoxymethyl)-3*H*-imidazol-4-yl]-cyclopentanone (35).** In a 500 mL flame-dried Schlenk flask, a solution of **33** (3.84 g, 12.5 mmol) in THF (125 mL) was cooled to −78 °C and a *n*-BuLi solution in hexane (2.50 M, 5.47 mL, 13.7 mmol) was added dropwise to the reaction solution. After 30 min, 2-chlorocyclopentanone (**34**) (1.16 mL 11.4 mmol) was added and the reaction mixture was held at −78 °C for 1 h, warmed up 25 °C over 30 min, and then heated overnight at reflux for 10 h. At that time, the solution was cooled to room temperature and the solvent was evaporated in vacuo to give a black oil which was purified by $SiO_2$ flash column chromatography (10−40% EtOAc/hexane as eluent) to give **35** (0.73 g, 16%) as a yellow oil: IR (thin film) 1743 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.28−7.12 (m, 5H), 7.01 (s, 1H), 5.47 (d, *J* = 11.0 Hz, 1H), 5.62 (d, *J* = 11.0 Hz, 1H), 3.67 (dd, *J* = 11.0, 8.5 Hz, 1H), 3.40−3.24 (m, 2H), 2.52−2.26 (m, 3H), 2.23−2.09 (m, 2H), 1.94 (m, 1H), 0.90−0.69 (m, 2H), −0.10 (s, 9H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 215.6, 139.2, 135.3, 132.7, 129.7, 128.6, 128.2, 127.1, 74.7, 66.3, 45.9, 38.0, 29.4, 21.3, 18.3, −1.0; LRMS (ESI) *m*/*z* (relative intensity) 389.2 (100%, M + $H^+$); HRMS (ESI) *m*/*z* calcd for $[C_{20}H_{29}N_2O_2SiS]^+$, 389.1719; found, 389.1704.

**5-(2-Methylene-cyclopentyl)-2-phenylsulfanyl-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-imidazole (36).** In a 100 mL flame-dried Schlenk flask, a solution of **35** (0.708 g, 1.82 mmol) in toluene (5 mL) was transferred via cannula into a solution of Petasis reagent ($Cp_2TiMe_2$, 5.71 wt %, 24.6 g, 6.67 mmol) in toluene (11 mL) and the reaction mixture was heated for 4 h at 70−80 °C. After reaction was determined to be complete by TLC, the solvent was evaporated under reduced pressure to give a brown oil which was purified by $SiO_2$ flash column chromatography (hexane, 10% $Et_2O$/hexane as eluent) to give **36** (0.57 g, 80%) as a yellow oil: IR (thin film) 1650 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.23−7.08 (m, 5H), 6.98 (s, 1H), 5.38 (s, 2H), 4.95 (d, *J* = 2.1 Hz, 1H), 4.66 (d, *J* = 2.1 Hz, 1H), 3.73 (td, *J* = 7.4, 1.7 Hz, 1H), 3.39−3.34 (m, 2H), 2.49−2.44 (m, 2H), 2.14 (m, 1H), 1.89−1.59 (m, 3H), 0.80−0.75 (m, 2H), −0.10 (s, 9H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 153.6, 139.0, 137.7, 136.3, 129.5, 128.7, 128.0, 126.9, 107.8, 73.7, 66.3, 41.3, 34.6, 33.0, 24.6, 18.3, −1.0; LRMS (ESI) *m*/*z* (relative intensity) 387.2 (100%, M + $H^+$); HRMS (ESI) *m*/*z* calcd for $[C_{21}H_{31}N_2OSiS]^+$, 387.1926; found, 387. 1905.

**{2-[2-Phenylsulfanyl-3-(2-trimethylsilanyl-ethoxymethyl)-3*H*-imidazol-4-yl]-cyclopentyl}-methanol (37).** In a 50 mL


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flame-dried Schlenk flask, a solution of 9-BBN in THF (0.5 mL, 5.55 mL, 2.78 mmol) was added dropwise into a solution of **36** (0.358 g, 0.925 mmol) in THF (10 mL) at 25 °C and the reaction mixture was held at 25 °C for 10 h. A solution of $Na_2O_2$ (0.721 g, 9.25 mmol) in water (10 mL) was slowly added to the reaction mixture and stirring was continued for 1 h. The reaction mixture was partitioned between $Et_2O$ and water and the aqueous layer was extracted with $Et_2O$ (3 × 20 mL). The organic layers were combined, dried over $Na_2SO_4$, and concentrated in vacuo to give a yellow oil. The yellow oil was purified by $SiO_2$ flash column chromatography (20−60% EtOAc/hexane as eluent) to give **37** (0.33 g, 88%, a 4:1 mixture of cis and trans products) as a yellow oil: IR (thin film) 3305 $cm^{-1}$; $^1H$ NMR (mixture of two isomers, 300 MHz, $CDCl_3$) $\delta$ 7.22−7.09 (m, 5H), 6.91 (s, 1H), 5.47 (d, $J$ = 8.1 Hz, 1H), 5.35 (d, $J$ = 8.0 Hz, 1H), 3.46−1.16 (m, 15H), 0.79−0.74 (m, 2H), −0.09 (s, 9H); $^{13}C$ NMR (major isomer, 75 MHz, $CDCl_3$) $\delta$ 137.7, 137.5, 135.9, 129.6, 128.8, 127.8, 126.9, 73.7, 66.7, 63.7, 45.3, 37.7, 31.8, 28.4, 23.8, 18.2, −1.0; LRMS (ESI) $m/z$ (relative intensity) 405.2 (100%, M + $H^+$); HRMS (ESI) $m/z$ calcd for $[C_{21}H_{33}N_2O_2SiS]^+$, 405.2032; found, 405. 2051.

**4,5-Dibromo-1*H*-pyrrole-2-carboxylic Acid {2-[2-Phenylsulfanyl-3-(2-trimethylsilanyl-ethoxymethyl)-3*H*-imidazol-4-yl]-cyclopentylmethyl}-amide (39).** In a 25 mL flame-dried Schlenk flask, a solution of diethyl azodicarboxylate (DEAD) in toluene (40 wt %, 0.096 mL, 0.214 mmol) was added dropwise into a solution of $Ph_3P$ (0.0610 g, 0.233 mmol) in THF (3 mL) at 0 °C and the reaction mixture was stirred at that temperature for 15 min. A solution of **37** (4:1 cis/trans, 0.0786 g, 0.194 mmol) in THF (3 mL) was added to the reaction mixture and held at 25 °C for 20 min after which time solid phthalimide (0.0320 g, 0.214 mmol) was added in one portion and the reaction mixture was stirred at 25 °C for 10 h. After TLC indicated the complete consumption of starting alcohol, the reaction solution was partitioned between $Et_2O$ and water and the aqueous layer was extracted with $Et_2O$ (3 × 10 mL). The organic layers were combined, dried over $Na_2SO_4$, and concentrated in vacuo to give a colorless oil. The colorless oil was purified by $SiO_2$ flash column chromatography (20−40% EtOAc/hexane as eluent) to give 2-{2-[2-phenylsulfanyl-3-(2-trimethylsilanyl-ethoxymethyl)-3H-imidazol-4-yl]-cyclopentylmethyl}-isoindole-1, 3-dione (0.078 g, 75%, mixture of cis and trans products) as a colorless oil: IR (thin film) 1713 $cm^{-1}$; $^1H$ NMR (major isomer, 300 MHz, $CDCl_3$) $\delta$ 7.83−7.80 (m, 2H), 7.72−7.69 (m, 2H), 7.25−7.14 (m, 5H), 7.11 (s, 1H), 5.56 (s, 2H), 3.50−3.32 (m, 4H), 3.08 (m, 1H), 2.82 (m, 1H), 2.22−1.61 (m, 6H), 0.91−0.81 (m, 2H), −0.06 (s, 9H); $^{13}C$ NMR (major, isomer, 75 MHz, $CDCl_3$) $\delta$ 168.7, 138.6, 136.3, 135.6, 132.3, 129.6, 129.4, 128.1, 128.0, 126.9, 123.5, 74.1, 66.5, 40.2, 39.7, 38.8, 30.4, 29.6, 22.8, 18.2, −1.1; LRMS (ESI) $m/z$ (relative intensity) 534.2 (100%, M + $H^+$); HRMS (ESI) $m/z$ calcd for $[C_{29}H_{36}N_3O_3SiS]^+$, 534.2247; found, 534. 2261.

In a 25 mL round-bottom flask, hydrazine monohydrate (1.00 mL, 21.4 mmol) was added dropwise to a solution of this phthalimide (4:1 cis/trans, 0.0954 g, 0.179 mmol) in EtOH (3 mL) at 25 °C and the reaction mixture was heated at reflux for 10 h. After TLC indicated the complete consumption of starting phthalimide, the reaction solution was partitioned between $Et_2O$ and water and the aqueous layer was extracted with $Et_2O$ (3 × 10 mL). The organic layers were combined, dried over $Na_2SO_4$, and concentrated in vacuo to give the primary amine product as a colorless oil.

Following General Procedure 7, this crude amine, pyrrole **38** (0.0666 g, 0.179 mmol) and $Na_2CO_3$ (0.0192 g, 0.179 mmol) were combined to give a colorless oil. The oil was purified by flash column chromatography ($CH_2Cl_2$ then 10−20% Et2O/$CH_2Cl_2$ as eluent) to give **39** (0.064 g, 55%) as a colorless oil: IR (thin film) 3116, 1631 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 11.73 (bs, 1H), 7.27−7.16 (m, 5H), 7.06 (s, 1H), 6.41 (s, 1H), 6.21 (t, $J$ = 5.3 Hz, 1H), 5.41 (d, $J$ = 10.5 Hz, 1H), 5.28 (d, $J$ = 10.4 Hz, 1H), 3.53−3.42 (m, 2H), 3.38−3.21 (m, 2H), 2.94 (m, 1H), 2.60 (m, 1H), 2.09−1.81 (m, 4H), 1.67 (m, 1H), 1.53 (m, 1H), 0.89−0.80 (m, 2H), −0.06 (s, 9H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 159.9, 139.1, 136.9, 134.9, 129.7, 128.8, 128.7, 127.3, 127.3, 112.8., 106.0, 99.8, 73.4, 67.0, 42.1, 42.0, 38.5, 30.6, 30.4, 23.4, 18.3, −1.5; LRMS (ESI) $m/z$ (relative intensity) 653.1 (100%, M + $H^+$); HRMS (ESI) $m/z$ calcd for $[C_{26}H_{35}Br_2N_4O_2SiS]^+$, 653.0617; found, 653. 0644.

**4,5-Dibromo-1*H*-pyrrole-2-carboxylic acid [2-(2-phenylsulfanyl-3*H*-imidazol-4-yl)-cyclopentylmethyl]-amide (29).** Following General Procedure 8, SEM protected imidazole **39** (0.144 g, 0.220 mmol) was converted to the free NH imidazole **29** (0.098 g, 85%) as a white solid, mp 207−209 °C (decomposition); IR (thin film) 3117, 1623 $cm^{-1}$; $^1H$ NMR (300 MHz, $CD_3OD$) $\delta$ 7.26−7.11 (m, 5H), 6.97 (s, 1H), 6.73 (s, 1H), 3.26 (dt, $J$ = 7.5, 7.3 Hz, 1H), 3.07 (dd, $J$ = 13.4, 8.6 Hz, 1H), 2.92 (dd, $J$ = 13.4, 6.7 Hz, 1H), 2.42 (m, 1H), 2.03 (m, 1H), 1.91−1.81 (m, 3H), 1.67 (m, 1H), 1.51 (m, 1H); $^{13}C$ NMR (75 MHz, $CD_3OD$) $\delta$ 161.5, 142.8, 137.1, 136.7, 130.3, 129.2, 128.8, 127.8, 121.9, 114.2., 105.8, 99.9, 44.4, 41.8, 41.3, 31.8, 30.2, 24.1; LRMS (ESI) $m/z$ (relative intensity) 523.0 (100%, M + $H^+$); HRMS (ESI) $m/z$ calcd for $[C_{20}H_{21}Br_2N_4OS]^+$, 522.9803; found, 522. 9796.

**{2-[2-Phenylsulfanyl-3-(2-trimethylsilanyl-ethoxymethyl)-3*H*-imidazol-4-yl]-cyclopentyl}-methanol (42).** In a 50 mL round-bottom flask, *N*-methylmorpholine-*N*-oxide (NMO, 0.486 g, 4.14 mmol) and 4 Å molecular sieves (1.45 g) were added in one portion to a solution of **37** (0.838 g, 2.07 mmol) in $CH_2Cl_2$ (20 mL) at 25 °C. Tetra-*n*-propylammonium peruthenate (TPAP, 0.728 g, 0.207 mmol) was added quickly to the reaction solution and the reaction mixture was stirred for 4 h. After TLC indicated the complete consumption of starting alcohol, the reaction solution was filtered through a pad of Celite, eluting with $CH_2Cl_2$ (3 × 20 mL). The organic layers were combined and concentrated under reduced pressure to give a yellow oil. The yellow oil was purified by $SiO_2$ flash column chromatography (10−30% EtOAc/hexane as eluent) to give aldehyde **40** (0.66 g, 79%) as a yellow oil. This crude product was carried on to the next step.

In a 50 mL round-bottom flask, DBU (0.017 mL, 0.112 mmol) was added dropwise into a solution of aldehyde **40** (0.451 g, 1.12 mmol) in $CH_2Cl_2$ (15 mL) at 0 °C and the reaction mixture was stirred at that temperature for 1 h. After TLC indicated the complete consumption of starting material, the reaction solution was mixed with a pH 7 buffer (30 mL) and the aqueous layer was extracted with $CH_2Cl_2$ (3 × 15 mL). The organic layers were combined, dried over $Na_2SO_4$, and concentrated under reduced pressure to give a yellow oil. The yellow oil was purified by flash column chromatography (10% EtOAc/hexane as eluent) to give aldehyde **41** (0.38 g, 83%) as a yellow oil. $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 9.69 (d, $J$ = 1.7 Hz, 1H), 7.37−7.17 (m, 5H), 7.06 (s, 1H), 5.49 (d, $J$ = 10.8 Hz, 1H), 5.41 (d, $J$ = 10.8 Hz, 1H), 3.54−3.52 (m, 1H), 3.39−3.33 (m, 2H), 3.02−2.98 (m, 1H), 2.25−1.68 (m, 6H), 0.83−0.77 (m, 2H), −0.06 (s, 9H). This aldehyde was prone to decomposition and so it was carried on to the next step immediately.

In a 50 mL round-bottom flask, $NaBH_4$ (0.0380 g, 0.100 mmol) was added in one portion to a solution of aldehyde **41** (0.137 g, 0.339 mmol) in EtOH (15 mL) at 25 °C and the reaction mixture was held at the same temperature for 10 h. After TLC indicated the complete consumption of starting aldehyde, the solvent was removed under reduced pressure and the organic residue was dissolved in $Et_2O$ and partitioned between $Et_2O$ and water. The aqueous layer was extracted with $Et_2O$ (3 × 15 mL) and the organic fractions were combined, dried over $Na_2SO_4$ and concentrated under reduced pressure to give a colorless oil. The colorless oil was purified by $SiO_2$ flash column chromatography (20−60% EtOAc/hexane as eluent) to give alcohol **42** (0.12 g, 85%) as a colorless oil: IR (thin film) 3325 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.30−7.18 (m, 5H), 7.07 (s, 1H), 5.52 (d, $J$ = 8.2 Hz, 1H), 5.40 (d, $J$ = 8.2 Hz, 1H), 3.56 (m, 2H), 3.48−3.37 (m, 2H), 2.99 (dt, $J$ = 6.1, 6.0 Hz, 1H), 2.41 (bs, 1H), 2.23−2.15 (m, 2H), 1.93 (m, 1H), 1.85 (m, 1H), 1.76−1.68 (m, 2H), 1.58 (m, 1H), 0.79−0.74 (m, 2H), −0.05 (s, 9H); $^{13}C$ NMR

(75 MHz, $CDCl_3$) $\delta$ 140.6, 137.3, 135.7, 129.6, 128.1, 127.5, 127.0, 73.3, 66.8, 64.6, 50.5, 37.8, 35.0, 28.4, 24.4, 18.3, −1.1; LRMS (ESI) $m/z$ (relative intensity) 405.2 (100%, M + $H^+$); HRMS (ESI) $m/z$ calcd for $[C_{21}H_{33}N_2O_2SiS]^+$, 405.2032; found, 405.2034.

**4,5-Dibromo-1*H*-pyrrole-2-carboxylic Acid {2-[2Phenylsulfanyl-3-(2-trimethylsilanyl-ethoxymethyl)-3*H*-imidazol-4-yl]-cyclopentylmethyl}-amide (43).** In a 25 mL flame-dried Schlenk flask, a solution of DEAD in toluene (40 wt %, 0.119 mL, 0.265 mmol) was added dropwise into a solution of $Ph_3P$ (0.0759 g, 0.289 mmol) in THF (3 mL) at 0 °C and the reaction mixture was held at 0 °C for 15 min. A solution of alcohol **42** (0.0974 g, 0.241 mmol) in THF (4 mL) was added and the reaction mixture was stirred at 25 °C for an additional 20 min. After that time, solid phthalimide (0.0390 g, 0.265 mmol) was added in one portion and the reaction mixture was stirred at 25 °C for 10 h. After TLC indicated the complete consumption of starting alcohol, the reaction solution was partitioned between $Et_2O$ and water and the aqueous layer was extracted with $Et_2O$ (3 × 10 mL). The organic layers were combined, dried over $Na_2SO_4$, and concentrated under reduced pressure to give a colorless oil. This oil was purified by $SiO_2$ flash column chromatography (20−40% EtOAc/hexane as eluent) to give 2-{2-[2-phenylsulfanyl-3-(2-trimethylsilanyl-ethoxymethyl)-3H-imidazol-4-yl]-cyclopentylmethyl}-isoindole-1,3-dione (0.10 g, 79%) as a colorless oil: IR (thin film) 1710 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.77−7.74 (m, 2H), 7.70−7.67 (m, 2H), 7.26−7.12 (m, 5H), 6.99 (s, 1H), 5.42 (s, 2H), 3.77−3.74 (m, 2H), 3.30−3.14 (m, 2H), 2.96 (m, 1H), 2.67 (m, 1H), 2.26 (m, 1H), 2.01 (m, 1H), 1.83−1.73 (m, 2H), 1.62−1.47 (m, 2H), 0.79−0.72 (m, 2H), −0.10 (s, 9H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 168.9, 139.7, 137.5, 135.6, 134.3, 132.2, 129.6, 128.2, 127.0, 126.9, 123.5, 73.8, 66.2, 44.1, 42.1, 40.7, 35.3, 30.4, 23.8, 18.3, −1.1; LRMS (ESI) $m/z$ (relative intensity) 534.2 (100%, M + $H^+$); HRMS (ESI) $m/z$ calcd for $[C_{29}H_{36}N_3O_3SiS]^+$, 534.2247; found, 534. 2242.

In a 50 mL round-bottom flask, hydrazine monohydrate (3.00 mL, 61.8 mmol) was added dropwise to a solution of this phthalimide (0.251 g, 0.471 mmol) in EtOH (15 mL) at 25 °C and the reaction mixture was heated at reflux for 10 h. After TLC indicated the complete consumption of starting phthalimide, the reaction solution was partitioned between $Et_2O$ and water and the aqueous layer was extracted with $Et_2O$ (3 × 10 mL). The organic layers were combined, dried over $Na_2SO_4$, and concentrated under reduced pressure to give a colorless oil (0.163 g).

This colorless oil (0.163 g, 0.405 mmol) was transferred into a 25 mL round-bottom flask with MeCN (8 mL) via cannula, and pyrrole **38** (0.150 g, 0.405 mmol) and $Na_2CO_3$ (0.043 g, 0.40 mmol) were added to this solution at 25 °C. The reaction mixture was stirred at this temperature for 20 h. After removal of the solvent in vacuo, the organic residue was partitioned between $CH_2Cl_2$ and water and the aqueous layer was extracted with $CH_2Cl_2$ (3 × 10 mL). The organic layers were combined, dried over $Na_2SO_4$, and concentrated under reduced pressure to give a colorless oil. This oil was purified by $SiO_2$ flash column chromatography ($CH_2Cl_2$ then 10−30% $Et_2O/CH_2Cl_2$ as eluent) to give **43** (0.18 g, 58%) as a colorless oil. An X-ray crystallography quality crystal of **43** was grown via slow evaporation of a 1:1 $CH_2Cl_2/CHCl_3$ solution; mp 158−159 °C. IR (thin film) 3095, 1635 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 11.07 (bs, 1H), 7.26−7.16 (m, 5H), 7.04 (s, 1H), 6.93 (t, $J$ = 5.2 Hz, 1H), 6.57 (s, 1H), 5.55 (d, $J$ = 11.1 Hz, 1H), 5.49 (d, $J$ = 11.2 Hz, 1H), 3.57 (m, 1H), 3.52−3.44 (m, 2H), 3.32 (m, 1H), 2.91 (m, 1H), 2.32−2.16 (m, 2H), 1.99 (m, 1H), 1.84−1.70 (m, 3H), 1.48 (m, 1H), 0.97−0.79 (m, 2H), −0.05 (s, 9H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 160.2, 140.3, 138.1, 135.1, 129.8, 128.4, 127.5, 127.3, 112.7, 105.8, 99.9, 73.2, 66.9, 47.5, 42.7, 39.5, 34.6, 29.8, 24.0, 18.4, −1.2; LRMS (ESI) $m/z$ (relative intensity) 653.1 (100%, M + $H^+$); HRMS (ESI) $m/z$ calcd for $[C_{26}H_{35}Br_2N_4O_2SiS]^+$, 653.0617; found, 653.0606. One carbon signal was not observed due to overlap with another signal in the aromatic range.

**4,5-Dibromo-1*H*-pyrrole-2-carboxylic Acid [2-(2-Phenylsulfanyl-3*H*-imidazol-4-yl)-cyclopentylmethyl]-amide (30).** Following General Procedure 8, SEM protected pyrrole **43** (0.0472 g, 0.0721 mmol) was converted to the free NH pyrrole **30** (0.025 g, 66%) as a white solid; mp 216−218 °C (decomposition); IR (thin film) 3095, 1602 $cm^{-1}$; $^1H$ NMR (300 MHz, $CD_3OD$) $\delta$ 7.19−7.03 (m, 5H), 6.90 (s, 1H), 6.68 (s, 1H), 2.70 (q, $J$ = 7.7 Hz, 1H), 2.18 (q, $J$ = 7.6 Hz, 1H), 2.02 (m, 1H), 1.78−1.56 (m, 3H), 1.39 (m, 1H), 1.18 (m, 1H); $^{13}C$ NMR (75 MHz, $CD_3OD$) $\delta$ 160.8, 142.1, 137.2, 132.1, 130.3, 130.0, 128.6, 127.7, 118.9, 113.1, 105.1, 99.0, 46.2, 43.0, 41.5, 33.7, 30.1, 23.9; LRMS (ESI) $m/z$ (relative intensity) 523.0 (100%, M + $H^+$); HRMS (ESI) $m/z$ calcd for $[C_{20}H_{21}Br_2N_4OS]^+$, 522.9803; found, 522. 9793. One hydrogen signal was not observed due to overlap with the MeOH peak.

**1-(Methoxymethyl)-2-(phenylthio)-1*H*-imidazole-5-carbaldehyde (45a).** Following General Procedure 1 with diphenyl disulfide, *N*-MOM imidazole (**44a**) (5.85 g, 52.2 mmol) was converted to 6.20 g (54%) of *N*-MOM-2-thiophenylimidazole, 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 $cm^{-1}$; $^1H$ 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%).

Following General Procedure 2, 1-(methoxymethyl)-2-(phenylthio)-1H-imidazole (3.00 g, 13.6 mmol) was converted into 3.37 g of aldehyde 45a, which was obtained as a yellow tacky solid (100% crude): IR (thin film) 1670 $cm^{-1}$; $^1H$ 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)-1*H*-imidazol-5-yl)-acrylamide (46a).** Following General Procedure 3, *N*-MOM aldehyde **45a** (2.50 g, 10.1 mmol) was converted into $\alpha,\beta$-unsaturated amide **46a**. The crude off-white solid was purified by trituration with $Et_2O$ to give 2.90 g (99%) of the desired $\alpha,\beta$-unsaturated amide **46a** as a white solid: mp 136−137 °C; IR (thin film) 3331, 3179, 1672 $cm^{-1}$; $^1H$ 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); $^{13}C$ 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 $[C_{14}H_{16}N_3O_2S]^+$, 290.0964; found, 290.0963.

**1-(Benzyloxymethyl)-2-(phenylthio)-1*H*-imidazole-5-carbaldehyde (45b).** Following General Procedure 1 with diphenyl disulfide, *N*-BOM imidazole (24.0 g, 128 mmol) was converted into 24.0 g (64%) of 1-(benzyloxymethyl)-2-(phenylthio)-1H-imidazole,[24] 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. IR (thin film) 2932 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.34 − 7.18 (m, 12H), 5.46 (s, 2H), 4.36 (s, 2H); LRMS (ESI+) $m/z$ (relative intensity) 297.3 (M + $H^+$, 100).

Following General Procedure 2, 1-(benzyloxymethyl)-2-(phenylthio)-1H-imidazole (24.0 g, 81.0 mmol) was converted into 26.0 g (99%) of aldehyde **45b**, which was obtained as a yellow solid: mp 104 − 105 °C; IR (thin film) 1670 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 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); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 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) $m/z$ calcd for $[C_{18}H_{17}N_2O_2S]^+$, 325.1005; found, 325.1011.

**(*E*)-3-(1-(Benzyloxymethyl)-2-(phenylthio)-1*H*-imidazol-5-yl)acrylamide (46b).** Following general procedure 3, aldehyde **45b**

(17.0 g, 52.4 mmol) was converted into 19.0 g (99%) of α,β-unsaturated amide **46b**, which was obtained as a white solid following purification of the crude material by trituration with $Et_2O$: mp 73−74 °C; IR (thin film) 3319, 3176, 1671 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) 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); $^{13}C$ NMR (75 MHz, $CDCl_3$) 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 $[C_{20}H_{20}N_3O_2S]^+$, 366.1270; found, 366.1276.

**2-(Phenylthio)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazole-5-carbaldehyde (45c).** Following General Procedure 1 with diphenyl disulfide, *N*-SEM imidazole **44c** (12.5 g) was converted, into 14.1 g (72%) of 2-(phenylthio)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazole, 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 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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%).

Following General Procedure 2, 2-(phenylthio)-1-((2-(trimethylsilyl)-ethoxy)methyl)-1*H*-imidazole (10.4 g, 33.9 mmol) was converted into 11.3 g (100%) of aldehyde **45c**, which was obtained as a tacky yellow solid: IR (thin film) 1673 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 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 Hz, 2H), 0.90 (t, *J* = 7.5, 1.1 Hz, 2H), −0.02 (s, 9H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 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 $[C_{16}H_{23}N_2O_2SSi]^+$, 335.1248; found, 335.1250.

**(*E*)-3-(2-(Phenylthio)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-5-yl)acrylamide (46c).** Following General Procedure 3, aldehyde **45c** (11.3 g, 33.9 mmol) was converted into 10.7 g (83%) of α,β-unsaturated amide **46c**, which was obtained as a white solid following purification of the crude material by trituration with $Et_2O$: mp 121−122 °C; IR (thin film) 3325, 3180, 1672 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) 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); $^{13}C$ NMR (75 MHz, $CDCl_3$) 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 $[C_{18}H_{26}N_3O_2SSi]^+$, 376.1511; found, 376.1515.

**2-(Methylthio)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazole-5-carbaldehyde (47).** Following General Procedure 1 with dimethyl disulfide, *N*-SEM imidazole **44c** (9.4 g) was converted into 6.80 g (59%) of 2-(methylthio)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazole, 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 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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%).

To a solution of *N*-SEM 2-thiomethyl imidazole (1.21 g, 4.95 mmol) from above 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 an additional 30 min at which time TLC showed complete consumption of the imidazole. 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 × 25 mL) and the combined organic extracts were dried over anhydrous $Na_2SO_4$, 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-2-(methylthio)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazole as a pale-yellow oil: IR (thin film) 2951 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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 $[C_{10}H_{20}BrN_2OSSi]^+$, 323.0257; found, 323.0249.

A solution of 5-bromo-2-(methylthio)-1-((2-(trimethylsilyl)ethoxy)-methyl)-1*H*-imidazole (2.90 g, 8.97 mmol) from above 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 min 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 $NH_4Cl$ was added and the reaction mixture was brought to rt. The organic layer was separated and the aqueous layer was extracted with EtOAc (2 × 50 mL). The combined organic layers were dried over anhydrous $Na_2SO_4$, 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 **47** as a yellow oil: IR (thin film) 1668 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) 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); $^{13}C$ NMR (75 MHz, $CDCl_3$) 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 $[C_{11}H_{21}N_2O_2SSi]^+$, 273.1088; found, 273.1093.

**(*E*)-3-(2-(Methylthio)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-5-yl)acrylamide (48).** Following General Procedure 3, aldehyde **47** (1.67 g, 6.13 mmol) was converted into 1.66 g (86%) of α,β-unsaturated amide **48**, 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 $cm^{-1}$; $^1H$ NMR (400 MHz, MeOD) δ 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) δ 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 $[C_{13}H_{24}N_3O_2SSi]^+$, 314.1364; found, 314.1359.

**6-(1-(Methoxymethyl)-2-(phenylthio)-1*H*-imidazol-5-yl)cyclohex-3-enecarboxamide (49a).** Following General Procedure 4, (*E*)-3-(1-(methoxymethyl)-2-(phenylthio)-1*H*-imidazol-5-yl)acrylamide (**46a**) (2.28 g, 7.88 mmol) was converted into Diels−Alder adduct **49a** (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 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 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); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 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 $[C_{18}H_{22}N_3O_2S]^+$, 344.1429; found, 344.1433.

**6-(1-(Methoxymethyl)-2-(phenylthio)-1*H*-imidazol-5-yl)-cyclohex-3-enecarbonitrile (50a).** Following General Procedure 5, amide **49a** (0.770 g, 2.24 mmol) was converted into nitrile **50a** (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, $CDCl_3$) 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); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 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 $[C_{18}H_{20}N_3OS]^+$, 326.1315; found, 326.1327.

**4,5-Dibromo-*N*-((6-(1-(methoxymethyl)-2-(phenylthio)-1*H*-imidazol-5-yl)cyclohex-3-enyl)methyl)-1*H*-pyrrole-2-carboxamide (52a).** Following General Procedure 6, nitrile **50a** (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 without further purification in the next step.

Following General Procedure 7, the crude amine from above (0.171 g, 0.519 mmol) was converted into 76.0 mg (25%) of amide **52a**, 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$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 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); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 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 $[C_{23}H_{25}Br_2N_4O_2S]^+$, 579.0062; found, 579.0065.

**6-(1-(Benzyloxymethyl)-2-(phenylthio)-1*H*-imidazol-5-yl)-cyclohex-3-enecarboxamide (49b).** Following General Procedure 4, $\alpha,\beta$-unsaturated amide **46b** (10.0 g, 27.4 mmol) was converted into 6.25 g (54%) of Diels−Alder adduct **49b**, which was obtained as a brown solid following purification of the crude material by silica gel column 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 $[C_{24}H_{26}N_3O_2S]^+$, 420.1754; found, 420.1746.

**6-(1-(Benzyloxymethyl)-2-(phenylthio)-1*H*-imidazol-5-yl)-cyclohex-3-enecarbonitrile (50b).** Following General Procedure 5, amide **49b** (4.40 g, 10.5 mmol) was converted into 2.99 g (71%) of nitrile **50b**, 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$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 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); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 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 $[C_{24}H_{24}N_3OS]^+$, 402.1642; found, 402.1640.

**6-(2-(Phenylthio)-1*H*-imidazol-5-yl)cyclohex-3-enecarbonitrile (53).** Aluminum trichloride[34] (8.70 g, 65.3 mmol) was suspended in $CH_2Cl_2$ (450 mL) and cooled to −10 °C (ice, acetone). To this suspension was added a solution of *N*-BOM imidazole **50b** (2.62 g, 6.53 mmol) in $CH_2Cl_2$ (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. Water (150 mL) was added and the organic layer was separated. The aqueous layer was extracted with $CH_2Cl_2$ (2 × 100 mL) and the combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The 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 **53** as a pale-yellow solid: mp 54−55 °C; IR (thin film) 3060, 3033, 2240 cm$^{-1}$; $^1$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); $^{13}$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%).

**4,5-Dibromo-*N*-((6-(2-(phenylthio)-1*H*-imidazol-5-yl)cyclohex-3-enyl)methyl)-1*H*-pyrrole-2-carboxamide (31).** Following General Procedure 6, nitrile **53** (1.20 g, 4.26 mmol) was converted into 1.22 g (100%) of 6-(2-(phenylthio)-1*H*-imidazol-5-yl)cyclohex-3-enyl)methanamine, which, without any further purification, was obtained as a clear and colorless oil: 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%).

Following General Procedure 7, 6-(2-(phenylthio)-1*H*-imidazol-5-yl)cyclohex-3-enyl)methanamine (1.22 g, 4.27 mmol) was converted into 1.69 g (74%) of *N*-H imidazole **31**, 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); $^{13}$C NMR (75 MHz, $CD_2Cl_2$) $\delta$ 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 $[C_{21}H_{21}Br_2N_4OS]^+$, 534.9782; found, 534.9803.

**6-(2-Phenylthio)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-5-yl)cyclohex-3-enecarboxamide (49c).** Following General Procedure 4, $\alpha,\beta$-unsaturated amide **46c** (10.5 g, 28.0 mmol) was converted into 6.80 g (57%) of Diels−Alder adduct **49c**, 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. Twenty-nine (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 $[C_{22}H_{32}N_3O_2SSi]^+$, 430.1996; found, 430.1985.

**6-(2-(Phenylthio)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-5-yl)cyclohex-3-enecarbonitrile (50c).** Following General Procedure 5, amide **49c** (1.29 g, 3.00 mmol) was converted into 1.03 g (84%) of nitrile **50c**, 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. Note: this reaction consistently gives higher yields when performed in 1.0 g batches: IR (thin film) 2260 cm$^{-1}$; $^1$H NMR (300 MHz, acetone-$d_6$) $\delta$ 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); $^{13}$C NMR

(75 MHz, acetone-$d_6$) $\delta$ 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 $[C_{22}H_{30}N_3OSSi]^+$, 412.1879; found, 412.1879.

**4,5-Dibromo-*N*-((6-(2-(phenylthio)-1-((2-(trimethylsilyl)-ethoxy)methyl)-1*H*-imidazol-5-yl)cyclohex-3-enyl)methyl)-1*H*-pyrrole-2-carboxamide (52c).** Following General Procedure 6, *N*-SEM nitrile **50c** (1.55 g, 3.78 mmol) was converted to 1.48 g (94% yield) of crude *N*-SEM amine **51c**, which was obtained as a clear and colorless oil: IR (thin film) 3376, 3295 $cm^{-1}$; $^1H$ 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).

Following General Procedure 7, *N*-SEM amine **51c** (1.00 g, 2.41 mmol) from above was converted into 1.37 g (85%) of amide **52c**, 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 $cm^{-1}$; $^1H$ 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); $^{13}C$ 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)-1*H*-imidazol-5-yl)-cyclohex-3-enyl)methyl)-1*H*-pyrrole-2-carboxamide (31).** Following general procedure 8, *N*-SEM imidazole **52c** (1.36 g, 2.04 mmol) was converted into 740 mg (68%) of N−H imidazole **31**, 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. Spectroscopic data for this product matched those reported for compound **31** that was prepared from **53**.

**6-(2-(Methylthio)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-5-yl)cyclohex-3-enecarboxamide (49d).** Following General Procedure 4, $\alpha,\beta$-unsaturated amide **48** (501 mg, 1.65 mmol) was converted into 230 mg (38%) of Diels−Alder adduct **49d**, 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, $CDCl_3$) $\delta$ 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); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 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 $[C_{17}H_{30}N_3O_2SSi]^+$, 368.1823; found, 368.1828.

**6-(2-(Methylthio)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-5-yl)cyclohex-3-enecarbonitrile (50d).** Following General Procedure 5, amide **49d** (230 mg, 0.626 mmol) was converted into 164 mg (75%) of nitrile **50d**, 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 $cm^{-1}$; $^1H$ 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)-1*H*-imidazol-5-yl)cyclohex-3-enyl)methyl)-1*H*-pyrrole-2-carboxamide (52d). Following General Procedure 6, nitrile 50d (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 further purification.

Following General Procedure 7, the crude amine from above (56.0 mg, 0.186 mmol) was converted into 70.0 mg (63%) of amide **52d**, which was obtained as a tacky solid following purification of the crude substance by silica gel column chromatography using 50% $Et_2O$ in hexanes as the eluent: IR (thin film) 3304, 3113, 1634 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 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); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 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)-1*H*-imidazol-5-yl)-cyclohex-3-enyl)methyl)-1*H*-pyrrole-2-carboxamide (32).** Following General Procedure 8, *N*-SEM imidazole **52d** (60.0 mg, 0.099 mmol) was converted into 29.0 mg (61%) of *N*-H imidazole **32**, 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) $\delta$ 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); $^{13}C$ NMR (75 MHz, MeOD) $\delta$ 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 $[C_{16}H_{19}Br_2N_4OS]^+$, 472.9635; found, 472.9646.

**Pummerer Reaction-Derived Pentacycles 57a and 57b.** In a 25 mL round-bottom flask, $(i\text{-Pr})_2NEt$ (0.0400 mL, 0.228 mmol) was added dropwise to a solution of **29** (0.0598 g, 0.114 mmol) in 1.5% $CH_3OH/CH_2Cl_2$ (10 mL) at 25 °C. Stang's reagent (PhI(CN)OTf, 0.0220 g 0.0570 mmol) was added to the reaction solution. Additional portions of PhI(CN)OTf (total of 4.00 equiv) and $(i\text{-Pr})_2NEt$ (4.00 equiv) were added over 6 h, at which time the starting material was determined by TLC to be completely consumed. At that time, the reaction solution was partitioned between $CH_2Cl_2$ and water and the aqueous layer was extracted with $CH_2Cl_2$ (3 × 10 mL). The organic layers were combined, dried over $Na_2SO_4$, and concentrated under reduced pressure to give a colorless oil. The colorless oil was purified by $SiO_2$ flash column chromatography ($CH_2Cl_2$ then 10−30% $Et_2O/CH_2Cl_2$ as eluent) to give **57a** (0.012 g, 20%) and **57b** (0.0060 g, 10%) as colorless oils.

**57a**: IR (thin film) 3201, 1654 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.53−7.41 (m, 5H), 6.99 (s, 1H), 5.68 (s, 1H), 5.54 (s, 1H), 3.98 (dd, $J$ = 12.0, 9.5 Hz, 1H), 3.59 (dd, $J$ = 12.1, 4.4 Hz, 1H), 3.04 (m, 1H), 2.56 (q, $J$ = 8.4 Hz, 1H), 2.06 (m, 1H), 1.91 (m, 1H), 1.78 (m, 1H), 1.59−1.50 (m, 2H), 1.35 (m, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 160.9, 155.5, 135.2, 130.8, 130.5, 127.3, 126.3, 115.3., 104.1, 103.0, 96.0, 70.4, 55.5, 51.2, 39.2, 33.8, 29.7, 26.3; LRMS (ESI) $m/z$ (relative intensity) 521.0 (100%, M + $H^+$); HRMS (ESI) $m/z$ calcd for $[C_{20}H_{19}Br_2N_4OS]^+$, 520.9646; found, 520. 9662.

**57b**: IR (thin film) 3568, 1654 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.51−7.40 (m, 5H), 6.98 (s, 1H), 5.70 (s, 1H), 5.46 (s, 1H), 4.26 (dd, $J$ = 11.9, 9.2 Hz, 1H), 3.32 (dd, $J$ = 11.8, 6.9 Hz, 1H), 2.96 (m, 1H), 2.79

(m, 1H), 1.79−1.21 (m, 6H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 161.2, 154.8, 135.2, 130.7, 130.3, 127.3, 126.3, 115.2., 103.8, 102.8, 93.6, 73.8, 57.2, 49.7, 41.4, 32.0, 28.2, 26.6; LRMS (ESI) $m/z$ (relative intensity) 521.0 (100%, M + H$^+$); HRMS (ESI) $m/z$ calcd for $[C_{20}H_{19}Br_2N_4OS]^+$, 520.9646; found, 520. 9624.

**Pummerer Reaction-Derived Pentacycle 65a.** Following General Procedure 9, *N*-H imidazole **31** (1.68 g, 3.13 mmol) was converted into 918 mg (55%) of pentacycle **65a**, 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. A crystal suitable for X-ray analysis was grown via vapor diffusion using acetone and hexane. IR (thin film) 3224, 1644 cm$^{-1}$; $^1$H NMR (300 MHz, $CD_3OD$) $\delta$ 7.38−7.21 (m, 5H), 6.80 (s, 1H), 5.76 (s, 1H), 5.62 (brs, 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 $[C_{21}H_{19}Br_2N_4OS]^+$, 532.9641; found, 532.9646.

**Pummerer Reaction-Derived Pentacycle 65b.** Following General Procedure 9, *N*-H imidazole **32** (10.0 mg, 0.021 mmol) was converted into 4.0 mg (40%) of pentacycle **65b**, 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, $CD_3OD$) $\delta$ 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 $[C_{16}H_{17}Br_2N_4OS]^+$, 470.9491; found, 470.9490.

**Pentacyclic Ketones 67a/67b.** 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 **65a** (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 $NaBH_4$ (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 gray 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 × 10 mL). The combined organic layers were dried over anhydrous $Na_2SO_4$, filtered and concentrated *in vacuo* to give a mixture of four alcohols as a white solid (88.0 mg) that was contaminated by alkene **65a**. This mixture was used without further purification.

The mixture of crude alcohols (+ alkene **65a**) from above (88.0 mg) was suspended in $CH_2Cl_2$ (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 $Na_2S_2O_3$ (5 mL) and with $CH_2Cl_2$ (5 mL). The mixture then was stirred for an additional 1 h. The organic layer was separated and the aqueous layer was extracted with $CH_2Cl_2$ (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 ketones **67a**/**67b** (3:1 mixture) as a clear and colorless film along with 23.0 mg of the alkene **65a** (24% recovery): IR (thin film) 3252, 1716, 1650, 1565 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$, major isomer) $\delta$ 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) $\delta$ 208.8, 162.9, 154.6, 135.1, 130.7, 130.2, 126.1 (×2), 115.2 (×2), 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 $[C_{21}H_{19}Br_2N_4O_2S]^+$, 548.9609; found, 548.9595.

**Trifluoroacetyl Cyclohexanones 68a−68d.** A solution of regioisomeric pentacyclic ketones **67a**/**67b** (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 $\mu$L, 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 $\mu$L, 0.070 mmol) was added in one portion via syringe. The resulting mixture was stirred for 15 min and then poured into a solution of EtOAc (5 mL) and 5% aqueous HCl solution (5 mL). The organic layer was separated and the aqueous phase was extracted with EtOAc (2 × 5 mL). The combined organic layers were dried over anhydrous $Na_2SO_4$, filtered and concentrated *in vacuo*. Analytical quality samples were obtained via purification by silica gel column chromatography using 10−50% EtOAc in hexanes as the eluent to give 7.4 mg (39%) of the major regioisomer of the desired $\beta$-diketone **67a** 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 ($^1$H NMR) mixture of three other isomers also exclusively as the enol tautomers.

**67a**: IR (thin film) 1658, 1651, 1644, 1634 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 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, H), 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, $CDCl_3$) $\delta$ 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 71.** $\beta$-Diketone **67a** (7.0 mg, 0.011 mmol) was dissolved in $CH_3CN$ (1.0 mL) and water (4 $\mu$L, 0.22 mmol) and $Et_3N$ (45 $\mu$L, 0.33 mmol) were added at rt. To the resulting yellow reaction mixture was added a 1.0 M solution of $MsN_3$ (33 $\mu$L, 0.033 mmol) in $CH_3CN$ dropwise over 15 min. After stirring for an additional 2.5 h, the $CH_3CN$ layer was removed under reduced pressure and the residue was poured into EtOAc (5 mL) and water (5 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (2 × 5 mL). The combined organic layers were dried over anhydrous $Na_2SO_4$, filtered and concentrated *in vacuo* to give the desired α-diazoketone as a pale yellow film that 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 resuspended in EtOAc (5 mL) and water (5 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (2 × 5 mL). The combined organic layers were dried over anhydrous $Na_2SO_4$, 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 esters **71** as a clear and colorless film (∼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 $[C_{22}H_{21}Br_2N_4O_3S]^+$, 578.9684; found, 578.9701.

**Epoxy Ureas 73a/73b.** To a solution of pentacycle **65a** (11.0 mg, 0.021 mmol) in $CH_2Cl_2$ (2.0 mL) at 0 °C was added mCPBA (70%, 6.1 mg, 0.025 mmol) in one portion. The reaction mixture was stirred at that temperature until TLC showed complete consumption of **65a** (4 h) and then a 10% aqueous solution of $Na_2S_2O_3$ (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 $CH_2Cl_2$ (2 × 5 mL). The organic layers were combined and dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give the urea **72** (7.0 mg, 77%, crude) as a clear and colorless film: IR (thin film) 1766, 1690 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 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%).

This crude alkene urea **72** (7.0 mg, 0.016 mmol) was dissolved in $CH_2Cl_2$ (1.0 mL) and treated with *m*CPBA (70%, 6.0 mg, 0.024 mmol) at rt. The reaction mixture was stirred at that temperature until TLC showed complete consumption of the starting material (12 h) and then a 10% aqueous solution of $Na_2S_2O_3$ (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 $CH_2Cl_2$ (2 × 5 mL). The organic layers were combined and dried over anhydrous $MgSO_4$, filtered and concentrated *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 ureas **73a**/**73b** (4.7 mg, 62%) as a clear and colorless film: IR (thin film) 1766, 1692 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$, 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, $CDCl_3$, 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%); HRMS of a sample in DMSO (ESI) $m/z$ calcd for $M^+$+DMSO $[C_{17}H_{21}Br_2N_4O_4S]^+$, 534.9650; found, 534.9662.

## ■ ASSOCIATED CONTENT

**Supporting Information.** Copies of $^1H$ NMR and $^{13}C$ NMR spectra for **29**, **31**, **32**, **35**−**37**, **39**, **42**, **43**, **45a**−**c**, **46a**−**c**, **47**, **48**, **49a**−**b**, **49d**, **50a**−**d**, **52a**, **52c**−**d**, **53**, **57a**−**b**, **65a**−**b**, **67a** and **67b**, **71**, and **73a** and **73b**; X-ray crystallographic data in CIF format for **43** and **65a**. This material is available free of charge via the Internet at http://pubs.acs.org.

## ■ AUTHOR INFORMATION

**Corresponding Author**
*E-mail: ksf@chem.psu.edu.

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## ■ REFERENCES

(1) (a) Kinnel, R. B.; Gehrken, H.-P.; Swali, R.; Skoropowski, G.; Scheuer, P. J. *J. Org. Chem.* **1998**, *63*, 3281–3286. (b) Al Mourabit, A.; Potier, P. *Eur. J. Org. Chem.* **2001**, 237–243. (c) Dransfield, P. J.; Dilley, A. S.; Wang, S.; Romo, D. *Tetrahedron* **2006**, *62*, 5223–5247. (d) Köck, M.; Grube, A.; Seiple, I. B.; Baran, P. S. *Angew. Chem., Int. Ed.* **2007**, *46*, 6586–6594. (e) Vergne, C.; Appenzeller, J.; Ratinaud, C.; Martin, M.-T.; Debitus, C.; Zaparucha, A.; Al-Mourabit, A. *Org. Lett.* **2008**, *10*, 493–496. (f) Li, Q.; Hurley, P.; Ding, H.; Roberts, A. G.; Akella, R.; Harran, P. G. *J. Org. Chem.* **2009**, *74*, 5909–5919.

(2) (a) Lee, Y. K.; Lee, J.-H.; Lee, H. K. *J. Microbiol.* **2001**, *39*, 254–264. (b) Piel, J. *Nat. Prod. Rep.* **2004**, *21*, 519–538. (c) Simmons, T. L.; Andrianasolo, E.; McPhail, K.; Flatt, P.; Gerwick, W. H. *Mol. Cancer Ther.* **2005**, *4*, 333–342. (d) Taylor, M. W.; Hill, R. T.; Piel, J.; Thacker, R. W.; Hentschel, U. *ISME J.* **2007**, *1*, 187–190.

(3) (a) Kobayashi, J.; Suzuki, M.; Tsuda, M. *Tetrahedron* **1997**, *53*, 15681–15684. (b) Buchanan, M. S.; Carroll, A. R.; Addepalli, R.; Avery, V. M.; Hooper, J. N. A.; Quinn, R. J. *J. Org. Chem.* **2007**, *72*, 2309–2317.

(4) (a) Grube, A.; Köck, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 2320–2324. (b) Kobayashi, H.; Kitamura, K.; Nagai, K.; Nakao, Y.; Fusetani, N.; van Soest, R. W. M.; Matsunaga, S. *Tetrahedron Lett.* **2007**, *48*, 2127–2129. (c) Buchanan, M. S.; Carroll, A. R.; Quinn, R. J. *Tetrahedron Lett.* **2007**, *48*, 4573–4574.

(5) Kato, T.; Shizuri, Y.; Izumida, H.; Yokoyama, A.; Endo, M. *Tetrahedron Lett.* **1995**, *36*, 2133–2136.

(6) Urban, S.; de Almeida Leone, P.; Carroll, A. R.; Fechner, G. A.; Smith, J.; Hooper, J. N. A.; Quinn, R. J. *J. Org. Chem.* **1999**, *64*, 731–735.

(7) Nishimura, S.; Matsunaga, S.; Shibazaki, M.; Suzuki, K.; Furihata, K.; van Soest, R. W. M.; Fusetani, N. *Org. Lett.* **2003**, *5*, 2255–2257.

(8) Seiple, I. B.; Su, S.; Young, I. S.; Lewis, C. A.; Yamaguchi, J.; Baran, P. S. *Angew. Chem., Int. Ed.* **2010**, *49*, 1095–1098.

(9) Feldman, K. S.; Fodor, M. D. *J. Org. Chem.* **2009**, *74*, 3449–3461.

(10) O'Malley, D. P.; Yamaguchi, J.; Young, I. S.; Seiple, I. B.; Baran, P. S. *Angew. Chem., Int. Ed.* **2008**, *47*, 3581–3583.

(11) The Molecular Mechanics calculations were performed with the MMFF force field using Macromodel9.0. The Monte Carlo conformational search algorithm was employed in order to explore conformational space about all rotatable bonds as part of a 10,000-step search. In the case of the macrocycle model for **11**, the ring conformation was explored as well, in a 20,000-step search. The lowest energy geometry that emerged from these searches was subjected to a density functional calculation using the PB3LYP/6-31G** routine in Spartan04. The energies of all calculations converged.

(12) (a) Aiello, A.; D'Esposito, M.; Fattorusso, E.; Menna, M.; Müller, W. E. G.; Perović-Ottstadt, S.; Schröder, H. C. *Bioorg. Med. Chem.* **2006**, *14*, 17–24. (b) Haber, M.; Carbone, M.; Ilan, M.; Gavagnin, M. *ARKIVOC* **2010**, 233–239.

(13) Grube, A.; Köck, M. *Org. Lett.* **2006**, *8*, 4675–4678.

(14) (a) Dilley, A. S.; Romo, D. *Org. Lett.* **2001**, *3*, 1535–1538. (b) Dransfield, P. J.; Wang, S.; Dilley, A.; Romo, D. *Org. Lett.* **2005**, *7*, 1679–1682. (c) Wang, S.; Dilley, A. S.; Poullennec, K. G.; Romo, D. *Tetrahedron* **2006**, *62*, 7155–7161. (d) Dransfield, P. J.; Dilley, A. S.; Wang, S.; Romo, D. *Tetrahedron* **2006**, *62*, 5223–5247.

(15) (a) Lovely, C. J.; Du, H.; He, Y.; Rasika Dias, H. V. *Org. Lett.* **2004**, *6*, 735–738. (b) Sivappa, R.; Hernandez, N. M.; He, Y.; Lovely, C. J. *Org. Lett.* **2007**, *9*, 3861–3864. (c) Sivappa, R.; Mukherjee, S.; Rasika Dias, H. V.; Lovely, C. J. *Org. Biomol. Chem.* **2009**, *7*, 3215–3218.

(16) O'Malley, D. P.; Li, K.; Maue, M.; Zografos, A. L.; Baran, P. S. *J. Am. Chem. Soc.* **2007**, *129*, 4762–4775.

(17) Tan, X.; Chen, C. *Angew. Chem., Int. Ed.* **2006**, *45*, 4345–4348.

(18) Feldman, K. S.; Nuriye, A. Y. *Org. Lett.* **2010**, *12*, 4532–4535.

(19) Ma, Z.; Lu, J.; Wang, X.; Chen, C. *J. Chem. Soc., Chem. Commun.* **2011**, *47*, 427–429.

(20) (a) Feldman, K. S.; Vidulova, D. B. *Org. Lett.* **2004**, *6*, 1869–1871. (b) Feldman, K. S.; Vidulova, D. B. *Tetrahedron Lett.* **2004**, *45*, 5035–5037. (c) Feldman, K. S.; Karatjas, A. G. *Org. Lett.* **2004**,

*6*, 2849–2852. (d) Feldman, K. S.; Skoumbourdis, A. P. *Org. Lett.* **2005**, *7*, 929–931. (e) Feldman, K. S.; Vidulova, D. B.; Karatjas, A. G. *J. Org. Chem.* **2005**, *70*, 6429–6440. (f) Feldman, K. S.; Karatjas, A. G. *Org. Lett.* **2006**, *8*, 4137–4140. (g) Feldman, K. S.; Skoumbourdis, A. P.; Fodor, M. D. *J. Org. Chem.* **2007**, *72*, 8076–8086. (h) Feldman, K. S.; Fodor, M. D. *J. Am. Chem. Soc.* **2008**, *130*, 14964–14965. (i) Feldman, K. S.; Fodor, M. D.; Skoumbourdis, A. P. *Synthesis* **2009**, 3162–3173. (j) Feldman, K. S.; Nuriye, A. Y. *Tetrahedron Lett.* **2009**, *50*, 1914–1916.(k)

(21) (a) Foley, L. H.; Büchi, G. *J. Am. Chem. Soc.* **1982**, *104*, 1776–1777. (b) Wiese, K. J.; Yakushijin, K.; Horne, D. A. *Tetrahedron Lett.* **2002**, *43*, 5135–5136.

(22) Lu, J.; Tan, X.; Chen, C. *J. Am. Chem. Soc.* **2007**, *129*, 7768–7769.

(23) (a) Kato, T.; Kondo, H.; Nishino, M.; Tanaka, M.; Hata, G.; Miyake, A. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 2958–2961. (b) Wender, P. A.; Holt, D. A.; Sieburth, S. M. *J. Am. Chem. Soc.* **1983**, *105*, 3348–3350.

(24) Lipshutz, B. H.; Huff, B.; Hagen, W. *Tetrahedron Lett.* **1988**, *29*, 3411–3414.

(25) Petasis, N. A.; Bzowej, E. I. *J. Am. Chem. Soc.* **1990**, *112*, 6392–6394.

(26) (a) Muchowski, J. M.; Solas, D. R. *J. Org. Chem.* **1984**, *49*, 203–205.(b)

(27) Hayashi, Y.; Gotoh, H.; Tamura, T.; Yamaguchi, H.; Masui, R.; Shoji, M. *J. Am. Chem. Soc.* **2005**, *127*, 16028–16029.

(28) Cambridge Crystallographic Data Centre deposition numbers: **43**: CCDC 815251, **65a**: CCDC 782151. The data can be obtained free from Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif.

(29) Zhdankin, V. V.; Crittell, C. M.; Stang, P. J.; Zefirov, N. S. *Tetrahedron Lett.* **1990**, *31*, 4821–4824.

(30) Kirmse, W. *Carbene Chemistry*; Academic Press: New York, 1971; pp 484−487.

(31) Jerkunica, J. M.; Traylor, T. G. *Org. Syn.* **1988**, *50*−*9*, 766–768.

(32) Danheiser, R. L.; Miller, R. F.; Brisbois, R. G.; Park, S. Z. *J. Org. Chem.* **1990**, *55*, 1959–1964.

(33) Lanman, B. A.; Overman, L. E.; Paulini, R.; White, N. S. *J. Am. Chem. Soc.* **2007**, *129*, 12896–12900.

(34) Meketa, M. L.; Weinreb, S. M. *Tetrahedron* **2007**, *63*, 9112–9119.

## ■ NOTE ADDED AFTER ASAP PUBLICATION

Scheme 14 contained an error in the version published ASAP May 16, 2011; the correct version reposted June 10, 2011.