The Pennsylvania State University

The Graduate School

Department of Chmeistry

APPLICATION OF MODERN PUMMERER METHODOLOGY IN MODEL STUDIES TOWARD THETOTAL SYNTHESIS OF PALAU'AMINE

A Thesis in

Chemistry

by

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ABSTRACT

A route leading to two key Pummerer substrates which bear a *syn* or *trans* cyclopentane moiety was designed, developed and completed as a model study toward the total synthesis of palau'amine. The Pummerer cyclization of the *syn* substrate was performed. The structure of the cyclized products was characterized and their stereochemistry was tentatively demonstrated base on the nOe effect. The Pummerer cyclization of the *trans* substrate was performed but a better way to isolate and characterize the product is needed. A route leading to two key Pummerer substrates which bear a cyclohexane/cyclohexene moiety and their cyclization is still under exploration.

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Dedicated to my family

(For all the love)

Chapter 1

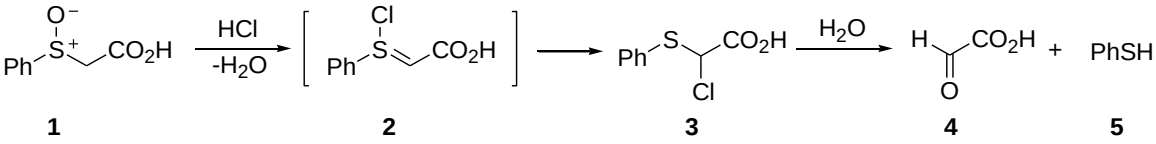
Introduction

1.1 The Pummerer Reaction

1.1.1 History/Discovery

The Pummerer reaction was named after Rudolph Pummerer because of his seminal report on the consequences of treating sulfinyl acetic acid (**1**) with HCl (Scheme **1**).[1] In this report, Pummerer characterized the product distribution from this reaction, which included the aldehyde **4** and thiophenol (**5**). In addition, he proposed the intermediacy of the sulfurane **2** and its formal 1,2-chloride shift product, sulfide **3**. He rationalized the formation of the products by employing a sulfurane intermediate **2**, which is a close counterpart of the currently adopted thionium ion intermediate, Ph(+)S=CH-. As a result, the name "Pummerer" was extended to any reaction involving treatment of a sulfoxide with an acid anhydride. Nowadays, the Pummerer reaction describes the formation of a

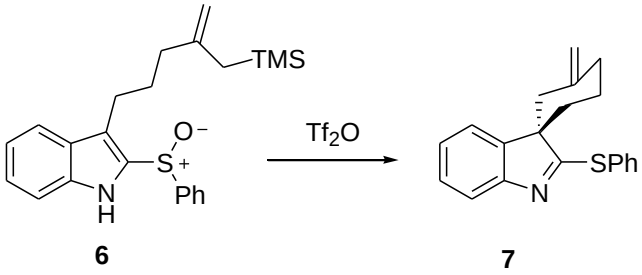
thionium ion from oxidation of a sulfide, and the addition of a nucleophile to that thionium ion intermediate. The reaction has gained remarkable attention as a robust synthetic strategy.



Scheme 1 An early example of a Pummerer reaction.

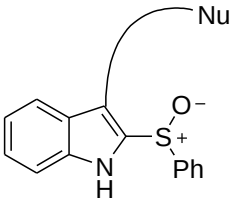
1.1.2 Pummerer Chemistry Developed in the Feldman Group

The first successful Pummerer reaction developed in the Feldman group was aimed toward the synthesis of 3,3-spiro substituted indole derivatives.[2] Several shortcomings of the previous methods for oxidative cyclization onto C3 of the indole nucleus were low yields, inadequate control of regiochemistry, and product over-oxidation. In order to avoid undesired over-oxidation products, Pummerer methodology was employed, as this process restricts oxidation to the sulfur atom. Thus, a regioselective cyclization of 3-substituted-2-(phenylsulfinyl) indole **6** was initiated by Tf_2O activation to furnish the 3,3-spirocyclic-2-(phenylthio)indolenine product **7** (Scheme **2**). A representative mechanism via either a vinylogous or additive pathway is illustrated below.



6 **7**

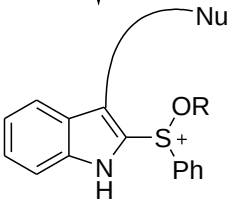
Representative mechanism:



8

Activator

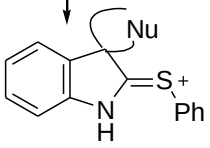
R—X



9

Path B:
additive Pummerer

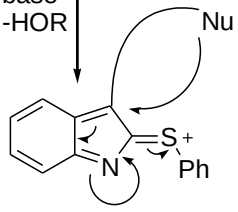
direct S_N2'-like displacement



10

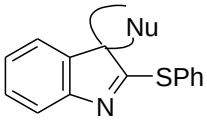
Path A:
vinylogous Pummerer

base
-HOR



11

base
$-H^+$



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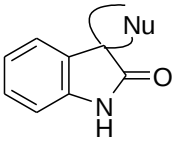
hydrolysis



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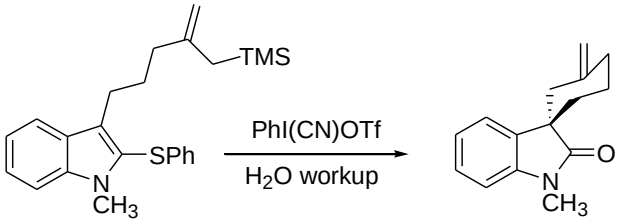
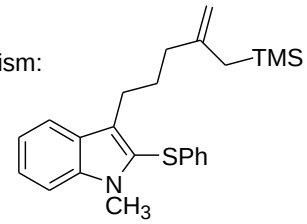
Scheme 2 Feldman's Pummerer-based Approach to 3,3-spirocyclic-2-(phenylthio)indolenines.

The Feldman group not only used a classical Pummer activator (Tf_2O) on the sulfoxide precursors, but also developed a new activator for a Pummerer-like cyclization on sulfide precursors.[3] Where as the hypervalent iodide species $PhI(OAc)_2$ and $PhI(OTFA)_2$ failed to initiate the spirocyclization, Stang's reagent, PhI(CN)OTf, with a diminished oxidative power and a softened iodonium center, successfully promoted the spirocyclization. Thus, treatment of the aryl sulfide substrate **14** with Stang's reagent in the presence of base gave the desired cyclizion product **15** via a vinylogous or additive pathway (Scheme **3**).



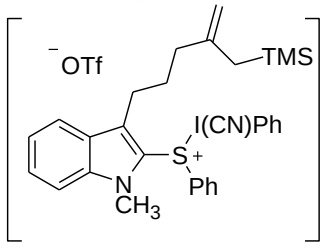
14 **15**

Representative mechanism:



15

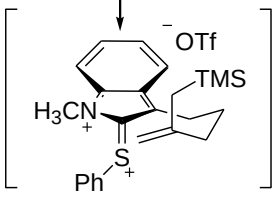
PhI(CN)OTf



16

Path A:
vinylogous Pummerer

-PhI
-CN-



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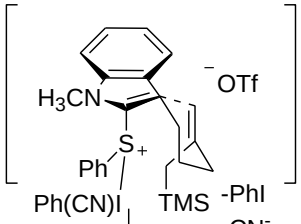

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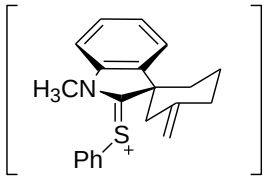
-PhI
-CN-
-TMSOTf

Path B:
additive Pummerer

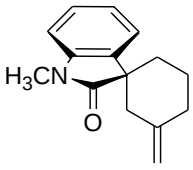
direct S_N2'-like
displacement

-TMSOTf



18

H_2O



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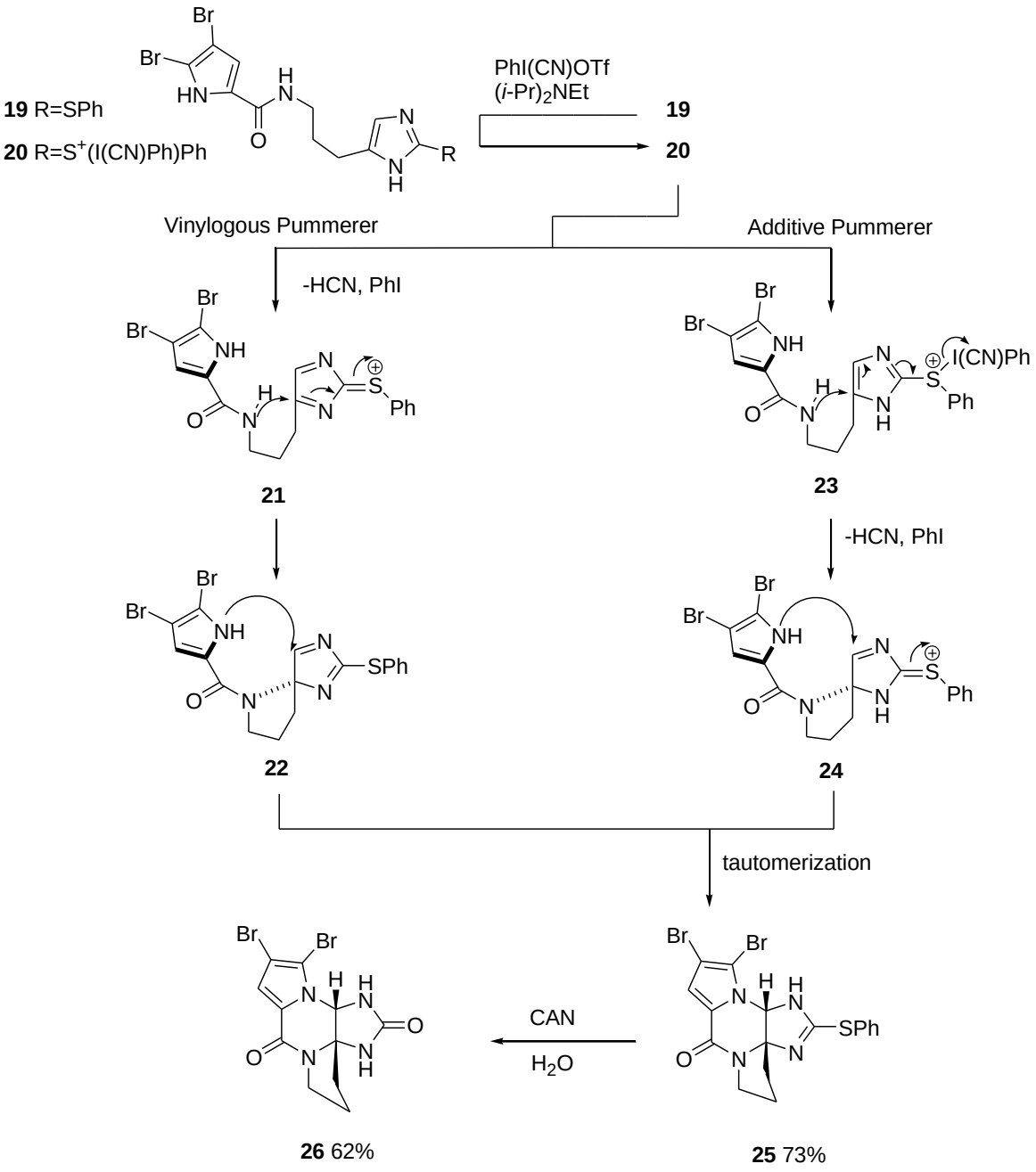
Scheme 3 Feldman's Pummerer based strategy for the syntheses of 3,3-spirocyclic-2-(phenylthio)indolenines

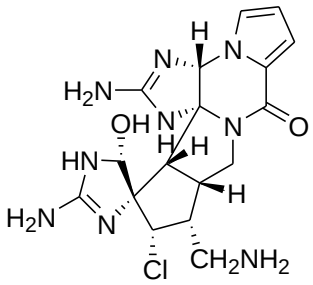
The value of this new initiator for the Pummerer reaction is illustrated in a biomimetic total synthesis of the sponge alkaloid dibromophakellstatin (**26**), which extended aromatic heterocycle oxidative cyclization methodology to the imidazole nucleus (Scheme **4**).[4] The treatment of sulfide **19** with PhI(CN)OTf likely gave rise to a sulfonium species **20**. This intermediate went through either a vinylogous or an additive pathway to give tetracyclic product **25** which could be hydrolyzed to furnish dibromophakellstatin (**26**). This Pummerer strategy will also be widely appled to the palau'amine syntheis work.



Scheme 4 A PhI(CN)OTf-mediated Pummerer cyclization on an imidazole sulfide substrate.

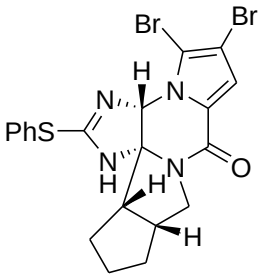
1.2 Palau'amine

Palau'amine, a hexacyclic bisguanidine originally assigned the structure **27** (figure **1**), was extracted from the sponge *Stylotella agminata* from the Western Caroline Islands in the Western Pacific Ocean.[5] The aqueous extract has substantial activity against gram-negative and gram-positive bacteria (*Staphylococcus aureus* and *Bacillus subtilis* at 10 μg /disk). In addition, palau'amine showed remarkable resistance to fungal growth on prolonged storage (*Penicillium notatum* at 50 μg / disk). It is reasonably nontoxic (LD_{50}=13 mg/kg), yet quite active against P-388 and A-549 cell lines (0.1 μg/mL for P-388 and 0.2 μg/mL for A-549). Palau' amine is quite stable in acid but decomposes rapidly at pH > 6.5. This instability, and the hexacyclic structural complexity of palau'amine, makes this marine alkaloid a daunting target for the synthetic community.[6] In our model studies toward this alkaloid, pentacyclic derivatives **28** and **29** are important targets because of their identical pentacyclic core structure for the natural product dibromopalau'amine.

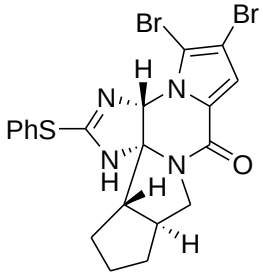


27

(orginal structural assignment)



28



29

Figure 1 Palau'amine originally assigned structure (**14**) and related model compounds **15** and **16**

Very recently, *Crube et al*. solved the structure of a new palau'amine congener tetrabromostyloguanidine (**30**) by using spectroscopic and computational methods.[7] The relative configuration at the stereogenic centers C12 and C17 turned out to be different than the currently accepted structure **31** (Figure **2**). Their methods and data also strongly suggest a revised relative configuration of palau'amine as shown in **32**.

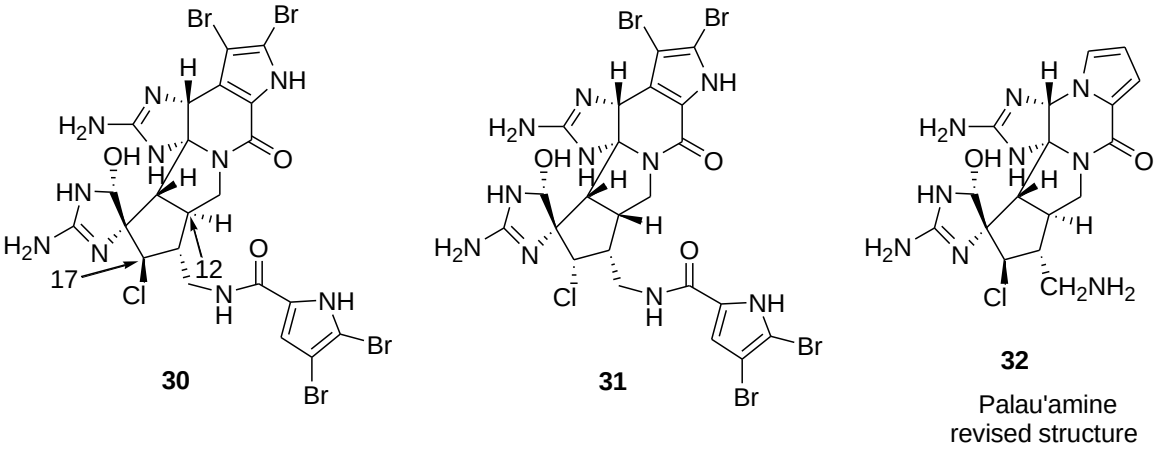
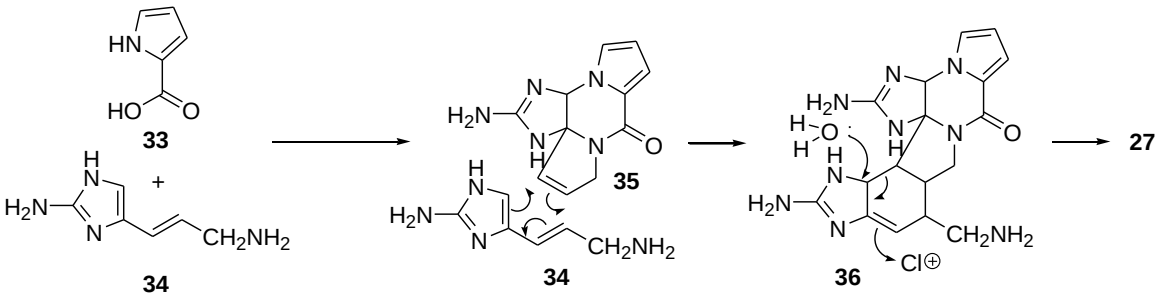


Figure 2 Reassigned tetrabromostyloguanidine (**31**) and palau'amine (**32**).

Pyrrole-2-carboxylic acid **33** and 3-amino-1-(2-aminoimidazolyl)prop-1-ene (AAPE) **34**, were proposed as the biogenetic source of the orginal paula'amine structure by Kinnel *et al.*(Scheme **5**).[8] In this proposal, 11,12-dehydrophakellin **35**, derived from one equivalent of **33** and **34**, and a second equivalent of AAPE undergo a Diels-Alder reaction to give a hexacyclic adduct **36**. Next, a

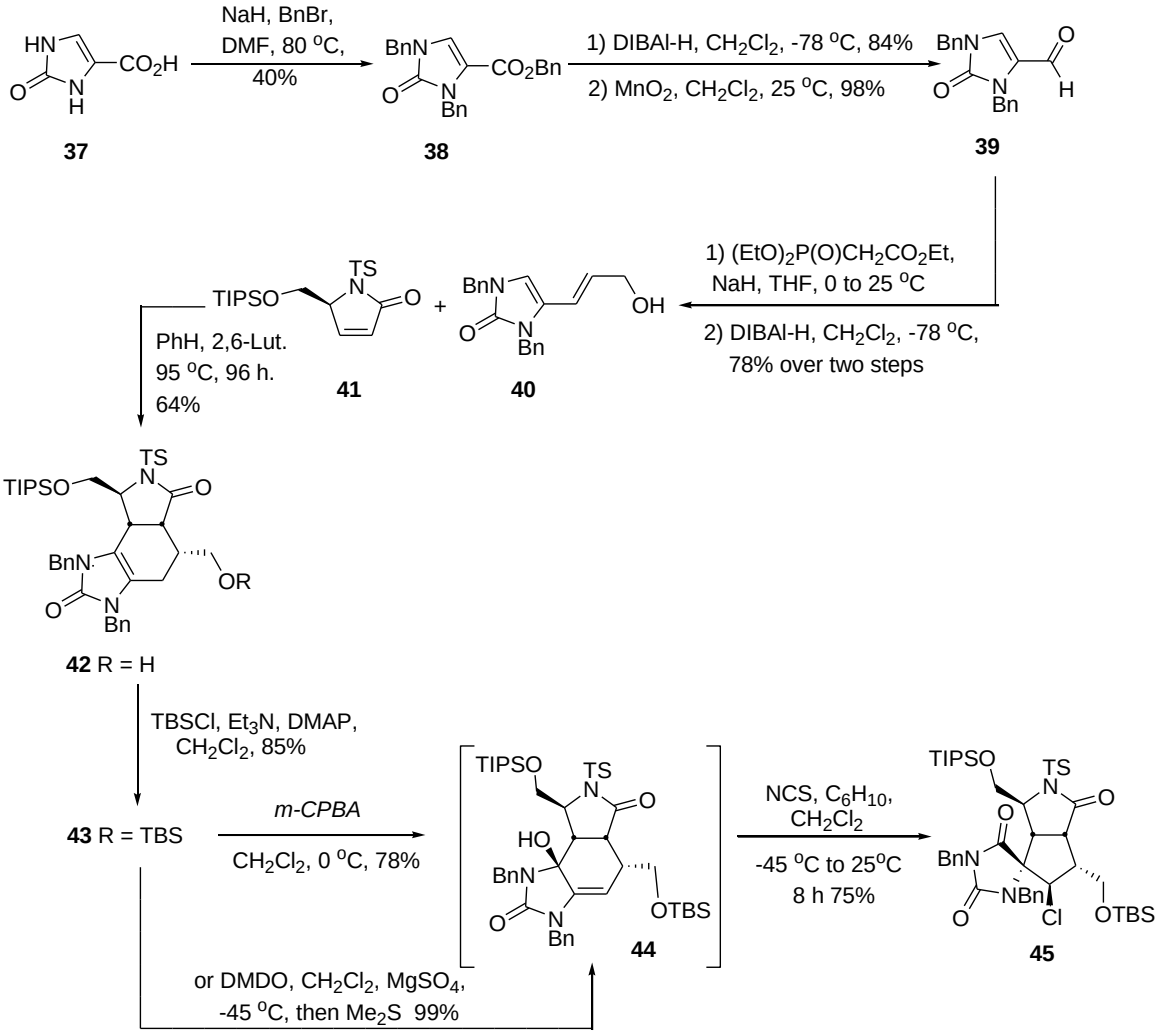
chloroperoxidase-initiated chlorination, subsequent bond migration, and hydration is proposed to afford the natural product.



Scheme 5 Proposed biosynthesis of the original structure of palau'amine (**27**)

This biosynthetic route was examined by Romo *et al*. to furnish a palau'amine-like spirocyclic core structure **45** (Scheme **6**).[9] This synthesis started with perbenzylation of imidazolone **37**. Then, a DIBAl-H reduction of the ester and MnO_2 oxidation of the desired alcohol delivered the corresponding aldehyde **38**. A subsequent olefination followed by another DIBAl-H reduction furnished alcohol **40**. A Diels-Alder reaction was performed by heating dienophile **41** and diene **40** in a sealed tube at 95 ℃ for 96 h to give cycloadduct **42** in 64% yield. After silyl protection of the alcohol in **42**, initial epoxidation of alkene **43** with *m*-CPBA or DMDO followed by epoxide ring opening via presumed iminium ion formation and deprotonation gave carbinol **44**. Finally, treatment of carbinol **44** with *N*-chlorosuccinimide (NCS) in the presence of cyclohexene delivered the chlorinated spirocyclic core product **45**. Although this proposal limits the two ring fusion hydrogen atoms to be on the same face of the molecule and can not be

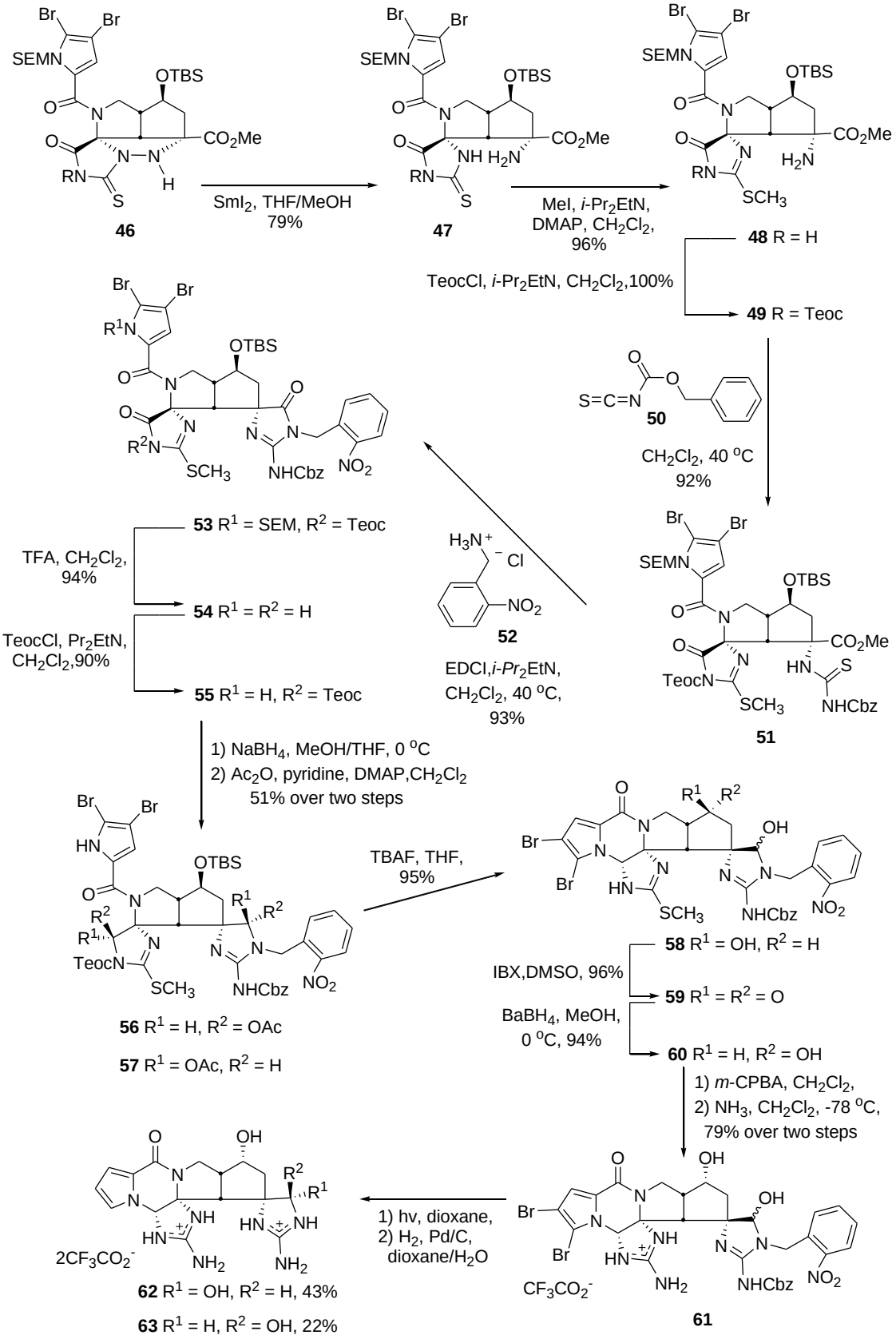
applied to the revised structure of palau' amine, the ring contraction strategy may still be a valid approach to the 5-membered ring of **32** if the appropriate *trans* fused precursor was available.



Scheme 6 Romo's synthesis toward a palau'amine-like spirocyclic core structure **45**

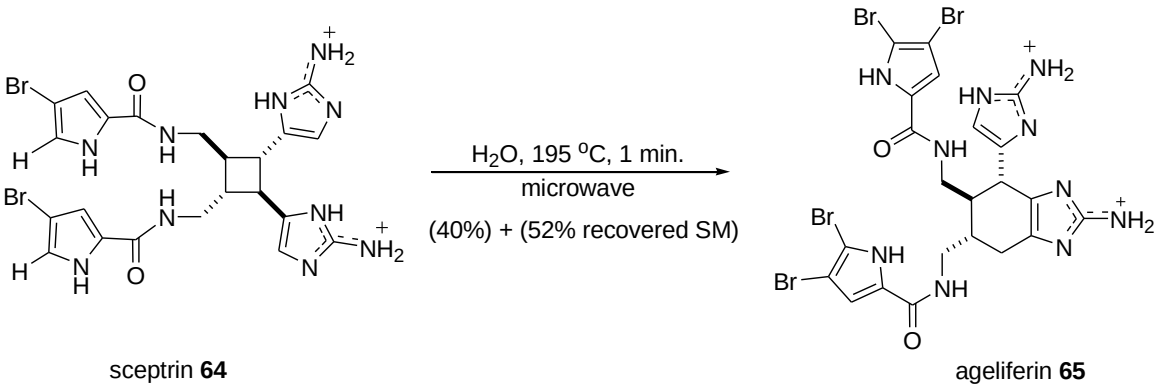
Overman *et al.* developed a synthetic route for the conversion of a intermediate triazatriquinane **46**[10] into hexacyclic palau'amine derivatives **62/63**, which have the same

relative configuration at their stereogenic centers as the originally proposed construct **27** of palau'amine (Scheme **7**).[11] This chemistry is the first synthesis of hexacyclic palau'amine congeners that incorporates both guanidine functional groups. The comparison of NMR data of **62/63** with data from natural extracted palau'amine strongly favored the revised structure **32** of palau'amine.


SmI2, THF/MeOH
79%
MeI, i-Pr2EtN,
DMAP, CH2Cl2,
96%
TeocCl, i-Pr2EtN, CH2Cl2,100%
CH2Cl2, 40 °C
92%
TFA, CH2Cl2,
94%
TeocCl, Pr2EtN,
CH2Cl2,90%
EDCI,i-Pr2EtN,
CH2Cl2, 40 °C,
93%
1) NaBH4, MeOH/THF, 0 °C
2) Ac2O, pyridine, DMAP,CH2Cl2
51% over two steps
TBAF, THF,
95%
IBX,DMSO, 96%
BaBH4, MeOH,
0 °C, 94%
1) m-CPBA, CH2Cl2,
2) NH3, CH2Cl2, -78 °C,
79% over two steps
1) hv, dioxane,
2) H2, Pd/C,
dioxane/H2O
46
47
48 R = H
49 R = Teoc
50
51
52
53 R1 = SEM, R2 = Teoc
54 R1 = R2 = H
55 R1 = H, R2 = Teoc
56 R1 = H, R2 = OAc
57 R1 = OAc, R2 = H
58 R1 = OH, R2 = H
59 R1 = R2 = O
60 R1 = H, R2 = OH
61
62 R1 = OH, R2 = H, 43%
63 R1 = H, R2 = OH, 22%

Scheme 7 Conversion of intermediate **46** into diastereomeric palau'amine derivatives **62** and **63**.

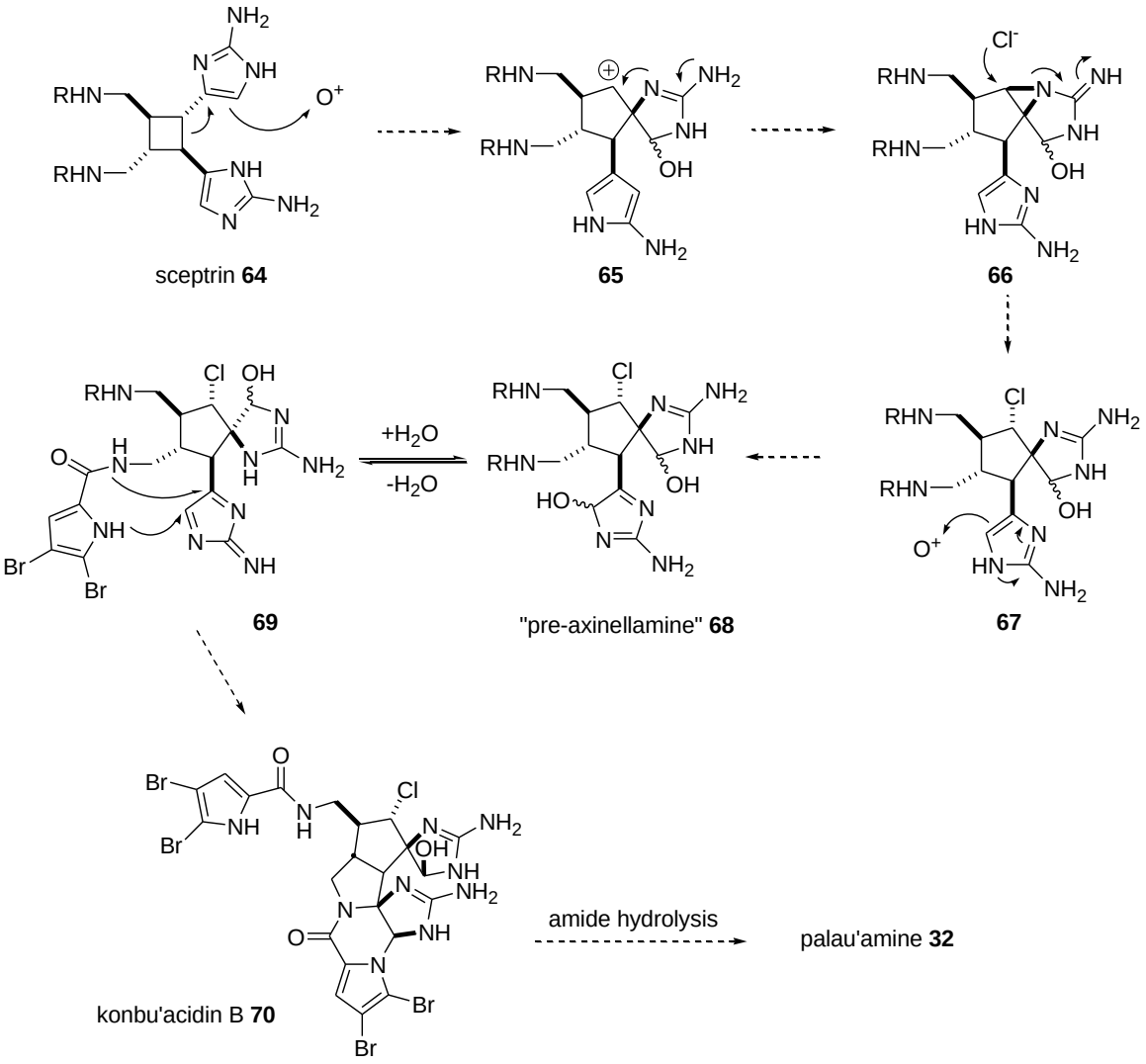
In 2004, Baran *et al.* reported the first total synthesis of ageliferin (**65**) from sceptrin (**64**) (Scheme **8**).[12] He also proposed that sceptrin might be a potential biosynthetic precursor to other complex pyrrole-imidazole alkaloids incuding palau'amine because of its extremely high concentration in organisms that produce this family of natural products.



sceptrin **64** ageliferin **65**

Scheme 8 Conversion of sceptrin **64** into ageliferin **65**.

In this biosynthesis hypothesis, pre-axinnellamines **68** and **69**, which could be accessed by a ring expansion of sceptrin (**64**), were proposed as the hypothetical central intermediates for the entire pyrrole-imidazole alkaloid family including palau'amine **32** (Scheme **9**).[13] The *anti* stereochemistry of the cyclobutane ring in sceptrin was kept throughout the process which guarantees the delivery of the *trans* ring fusion within revised palau'amine structure **32**.

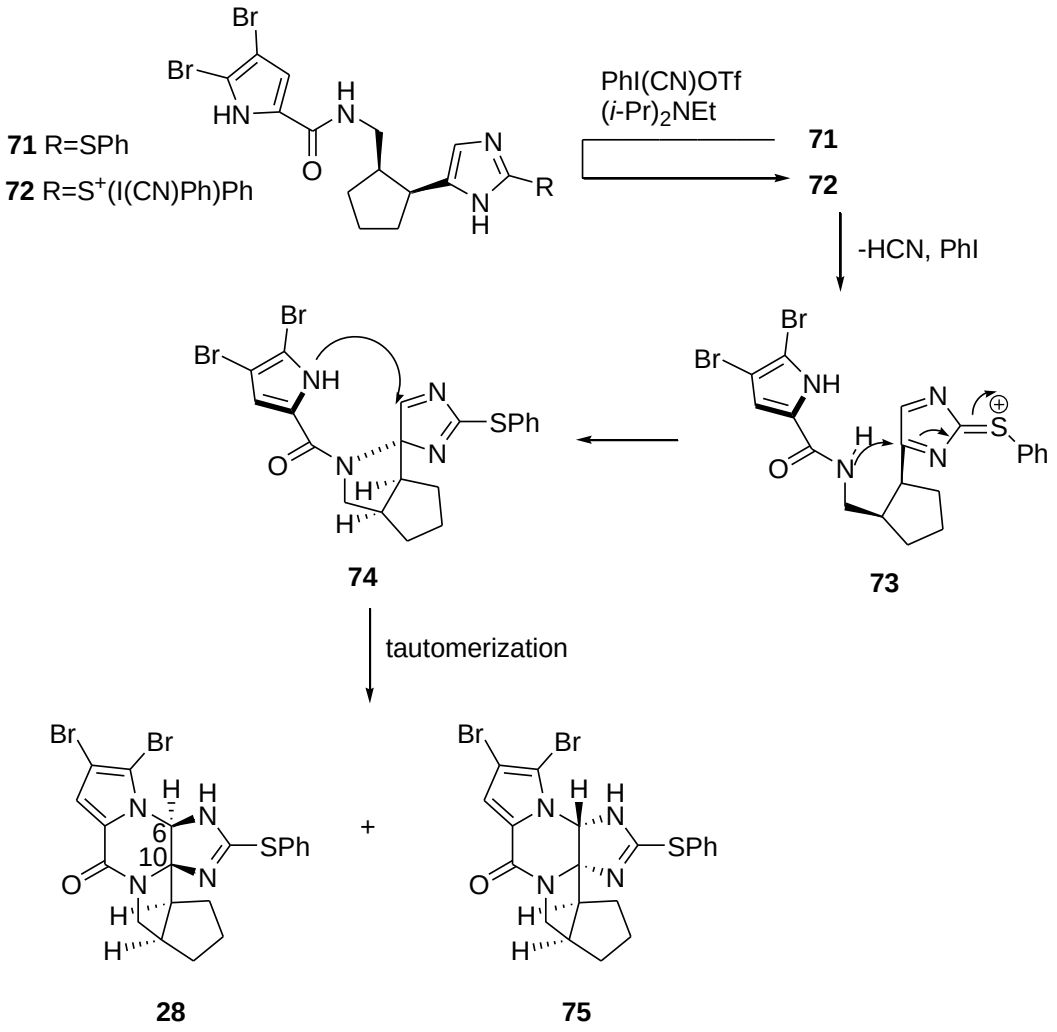


Scheme 9 Sceptrin 64 as a biosynthetic precursor to palau'amine **30**.

1.3 Palau'amine model system chemistry

Prior to disclosure of the the revised structure of palau'amine, a model study focusing on the incorrect *cis*-fused palau'amine core **28** was initiated (Scheme **10**). The important question probed here is the relative stereochemistry at C6 and

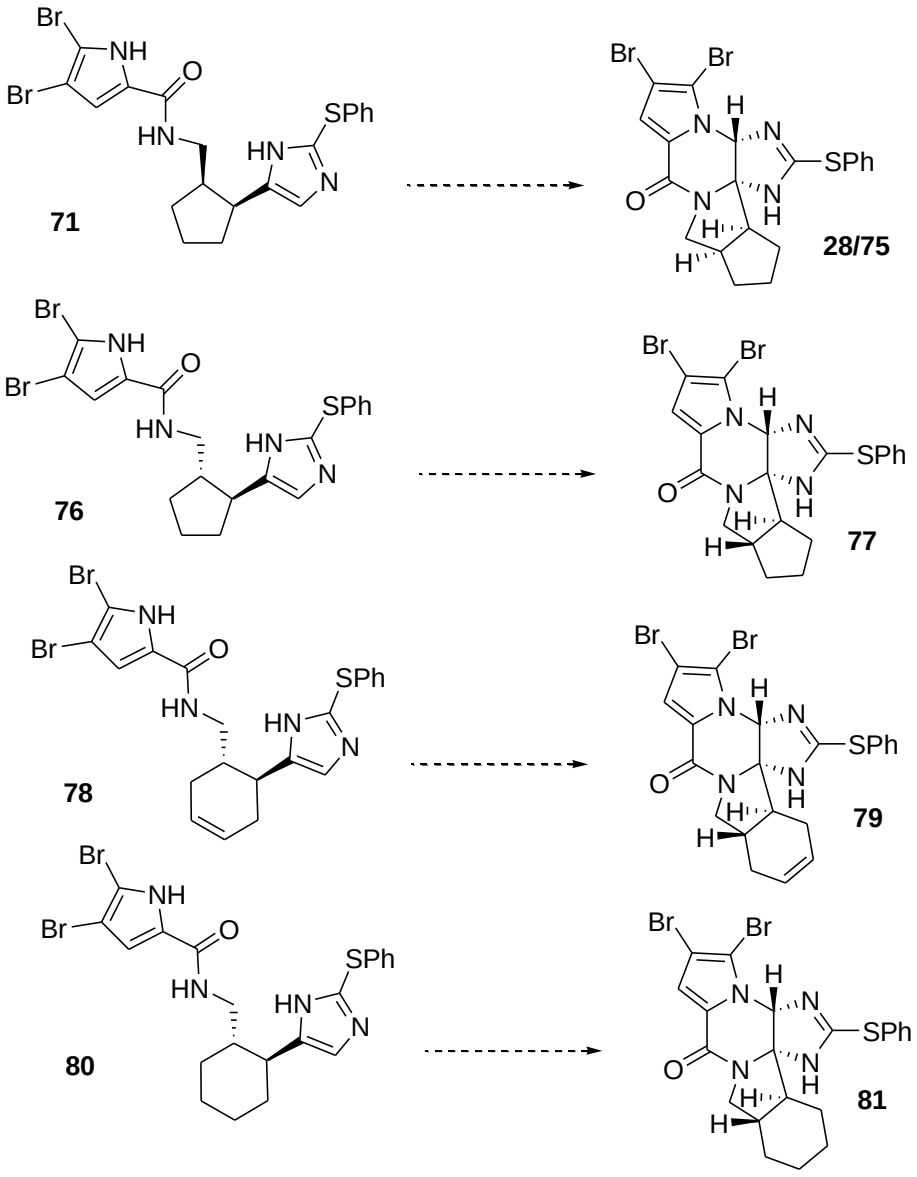
C10 vs. the ring fusion positions. Two possibilities exist, illustrated as **28** and **75**. The relative stereochemistry in **28** was desired at the outset. Based on the previously mentioned regioselective access to dibromophakellin (**26**) via the Pummerer strategy developed in the Feldman group, a similar route is proposed for the synthesis of these species. In this route, Stang's reagent (PhI(CN)OTf) will be employed as an initiator for the Pummerer sequence to carry out an oxidative cyclization on **71** and give the pentacyclic products, hopefully with some sterochemical bias. The relative stereochemistry of the ring fusion in pentacyclic products **28** and **75** is controlled by the *syn*-disubstituted cyclopentane **71**. This constraint also ensures that the two new N-C bonds are formed on the same face of the imidazole ring, but whether **28**'s relative stereochemistry or that shown in **5** will emerge, is an open question at present.



Scheme 10 A mechanistic outline for the synthesis of pentacyclic derivative **28/75**

Once the revision of palau'amine's stereochemistry was disclosed, our synthesis target changed to the *trans*-fused species **77**, **79** and **81**. If the previously mentioned route can prepare pentacylic product **28/75** from *syn*-disubstituted cyclopentane **71**, the pentacyclic product **77** might be accessible from *anti*-disubstituted cyclopentane **76** via a similar Pummerer sequence. Due to the ready accessibly of the six-membered ring platforms illustrated in **78** and **80**, these

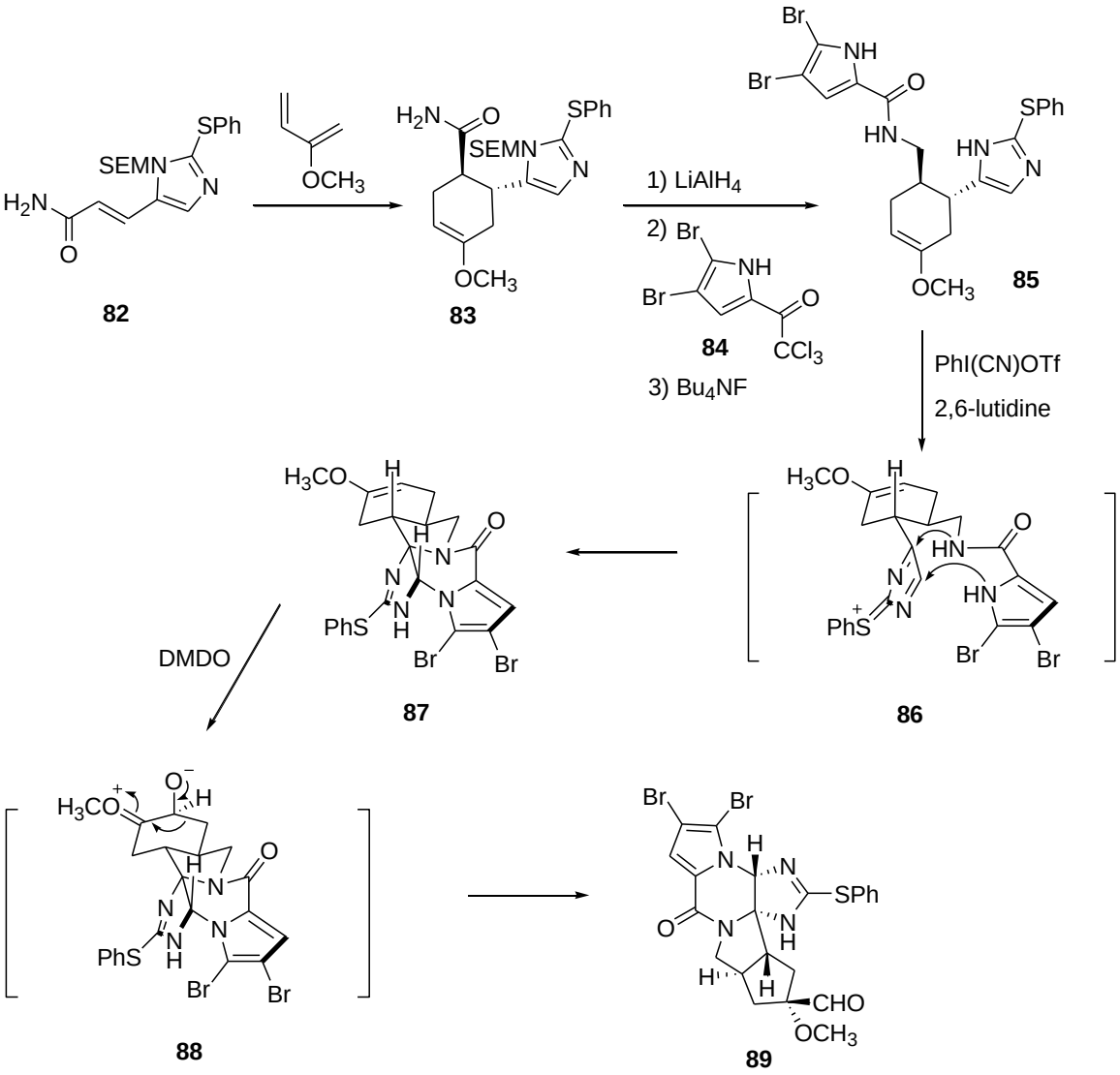
species will be tested as protential Pummerer substrates also (Scheme **11**). The appeal of these latter two substrates stems from (1) the presumed lower ring strain attending a *trans* 6-5 bicyclic core as in **79**/**81** compared to the *trans* 5-5 bicyclic core of **78**, and (2) the potential for conversion of the 6-5 ring system into the desired *trans* 5-5 species via Romo-like ring contraction methodologies.



Scheme 11 Parallel syntheses of pentacyclic derivative **28/75**, **77**, **79**, and **81**.

For example, Pummerer chemistry on the thioimidazole in **85** is expected to deliver the oxidized and electrophilic imidazolone equivalent in **86** followed by bicyclization to furnished the desired *anti* 6-5 ring system of the pentacyclic product **87**. Then, a pinacol-like ring contraction strategy would generate **89** via an intermediate **88** (Scheme **12**). The

anti stereochemistry of two bridgehead hydrogen atoms is controlled by the Diels-Alders reaction and would be kept intact throughout the whole process to furnish the correct product **89**.



Scheme 12

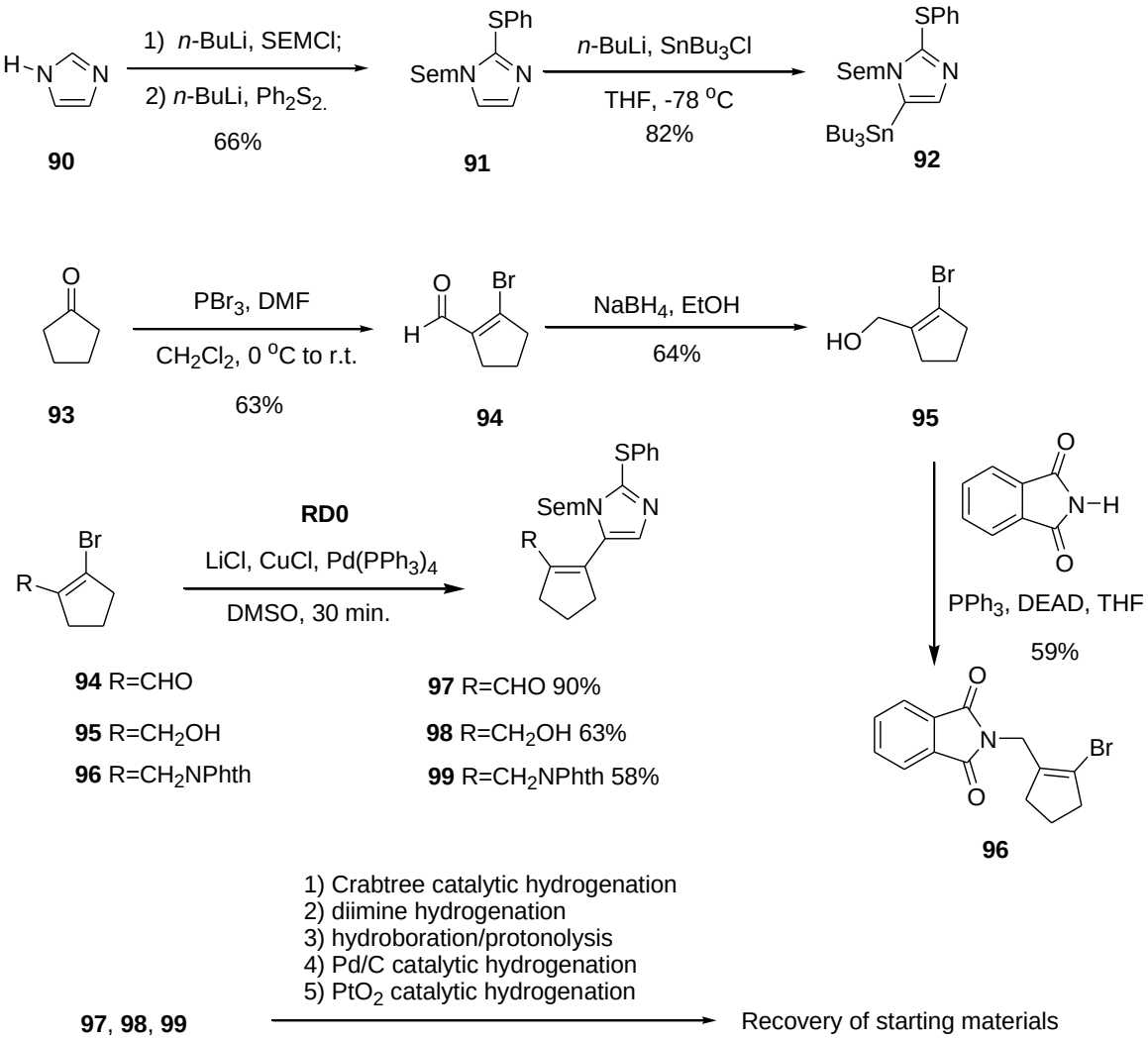
Exploration of a model cyclization/ring-contraction route for palau'amine synthesis.

Chapter 2:

Synthesis of the *syn* and *anti* Five-Membered and the *anti* Six-Membered Ring Cyclization Precursors and Their Cyclization Trials

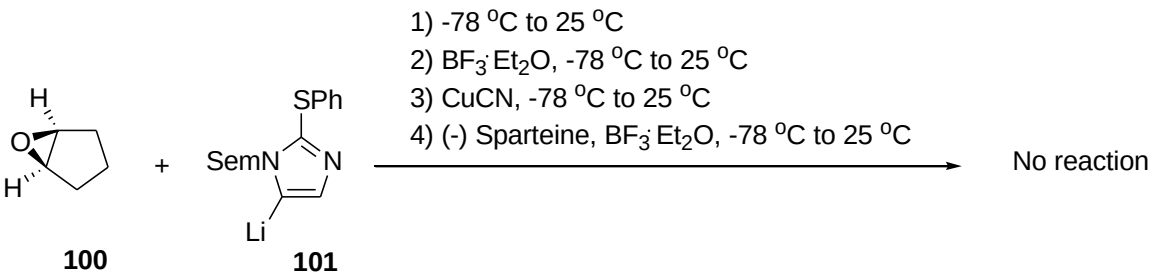
2.1 The *Syn* Five-Membered Cyclization Precursor and its Cyclization

Disubstituted cyclopentenes **97**, **98** and **99** were prepared through Stille coupling of cyclopentenyl bromides **94**, **95**, and **96** with stannane **92** by following the procedures developed by Dr. Skoumbourdis in the Feldman Group (Scheme **1**).[14] However, reduction of the tetrasubstituted double bonds in **97**, **98** and **99** was not successful under various conditions including Crabtree catalytic hydrogenation,[15] diimine-mediated hydrogenation, [16] hydroboration/protonolysis, [17] and ordinary catalytic hydrogenation procedures.



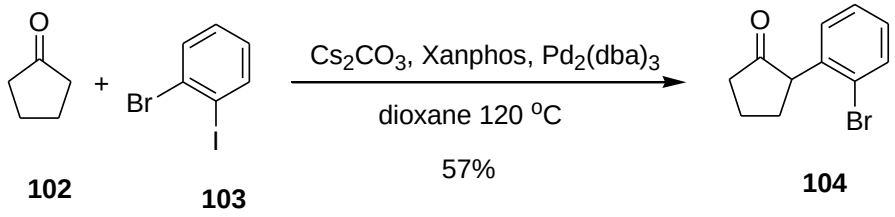
Scheme 13 Preparation and reduction of disubstituted cyclopentenes **97**, **98**, and **99**.

Attempts to open epoxide (**100**) with organometallic reagents were also pursued as a strategy to connect the cyclopentane moiety and imidazole nucleus.[18] The result in all instances was the recovery of starting material.

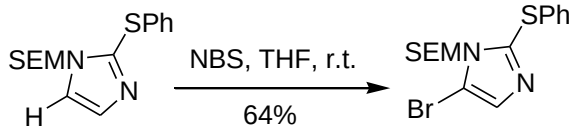


Scheme 14 Opening of epoxide **100** under basic conditions.

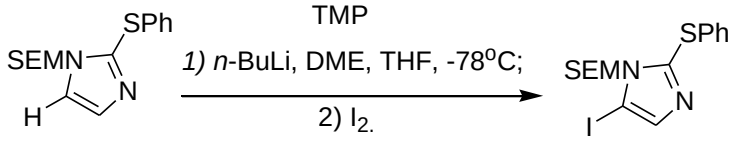
Inspired by a successful direct Heck coupling between cyclopentanone (**102)** and 2-bromoiodobenzene (**103)**,[19] a similar approach was employed to connect cyclopentanone (**102**) with the imidazole moiety. Bromide **105** and iodide **106**[20] were prepared from imidazole **91**. Reaction of both these species (**105** and **106**) with cyclopentanone (**102**) under identical conditions as those used with **103** did not lead to any coupling products (Scheme **3**). In addition, the Stille coupling between 2-chlorocyclopentanone (**107**) and stannane **92** was also carried out, but only decomposition of starting materials occurred (Scheme **4**).



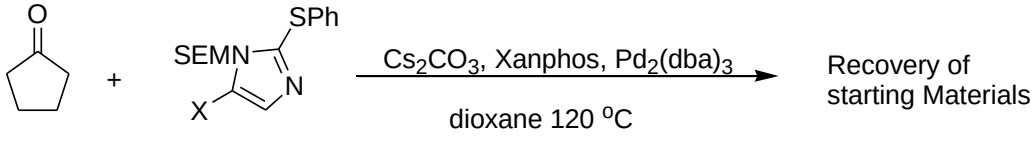
102 **103** **104**



91 **105**

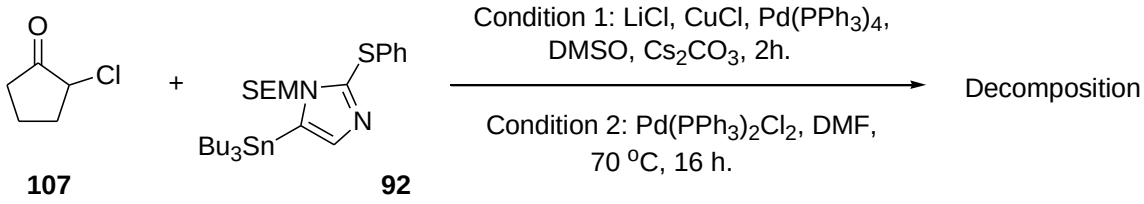


91 **106**



102 **105** X=Br, **106** X=I

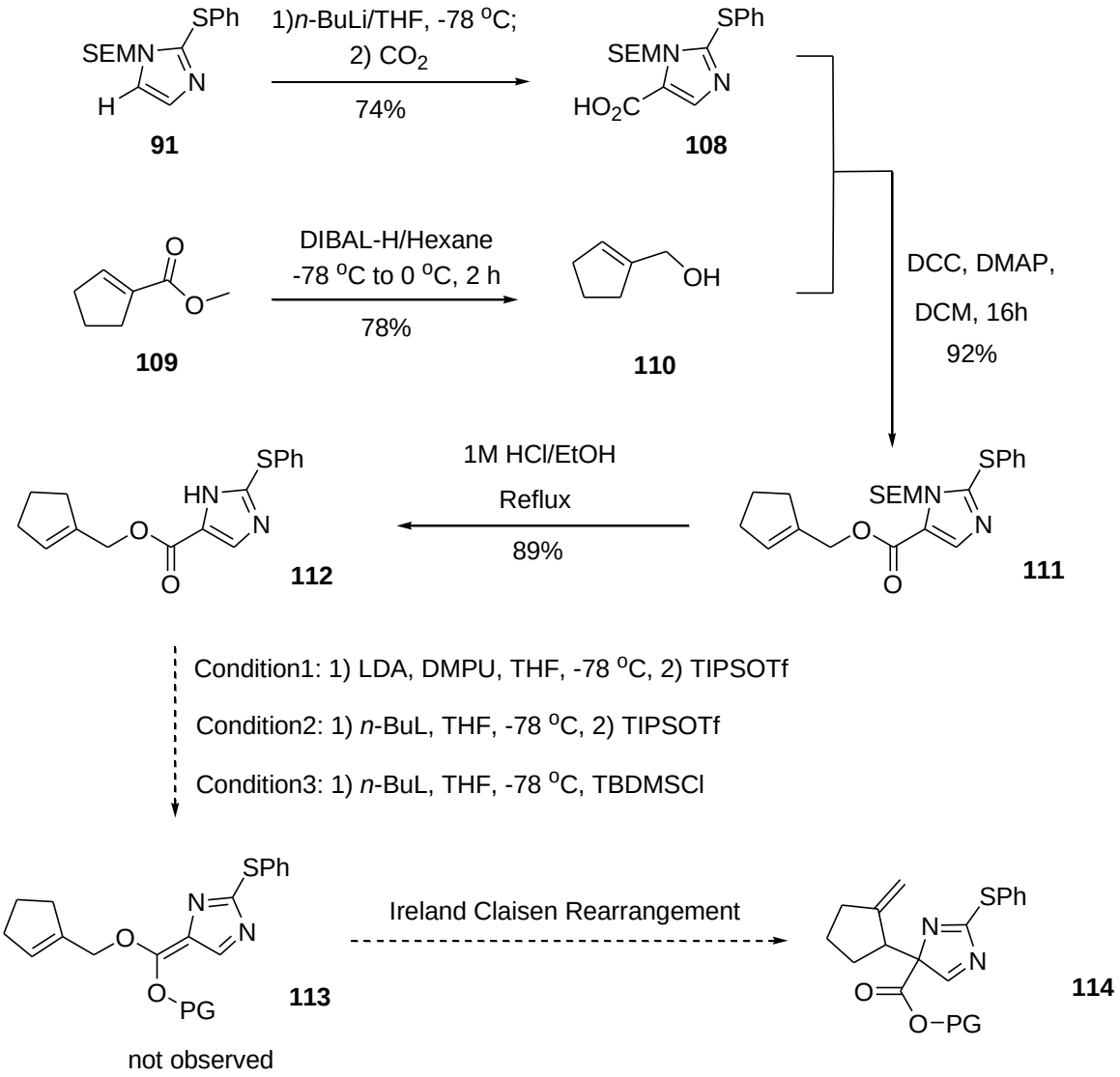
Scheme 15 Direct Heck coupling between cyclopentanone (**102**) and halogenide **105** and **106**.



107 **92**

Scheme 16 Stille coupling between 2-Chlorocyclopentanone (**107**) and stannane **92**.

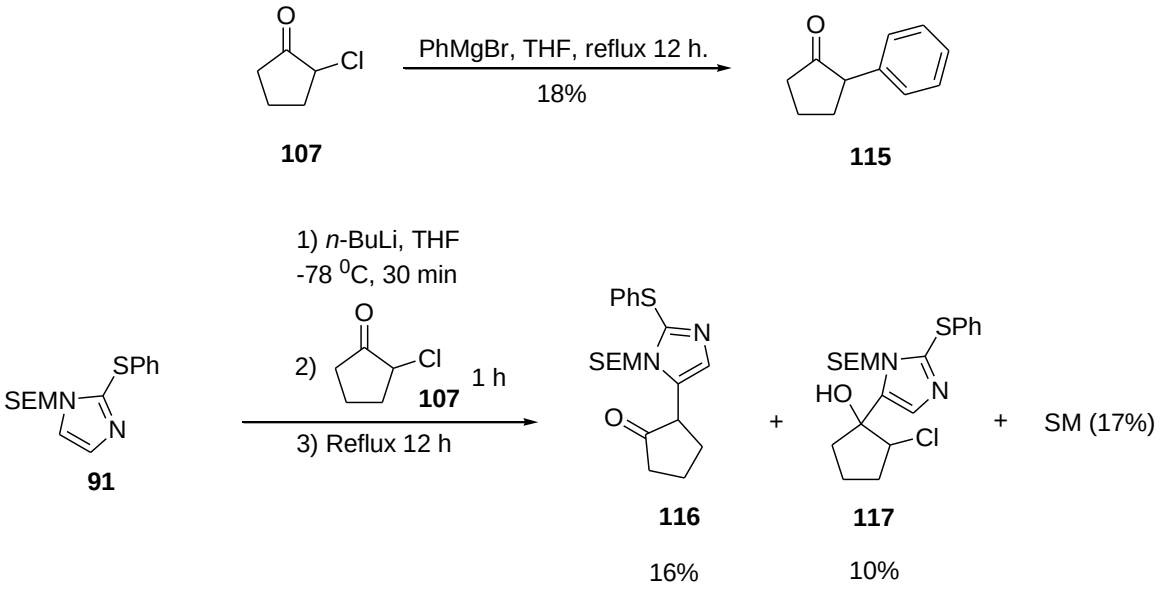
The Ireland Claisen rearrangement is a useful method to construct carbon-carbon bonds involving aromatic rings. [21] In order to explore this route to access methylenecyclopentane **114**, several procedures were employed to generate ketene acetal **113** (Scheme **5**).[22] Carboxylic acid **108** was prepared from imidazole **91** and was coupled with alcohol **110**[23] to afford ester **111**. Deprotection of the SEM group led to imidazole **112**. Unfortunately, ketene acetal **113** was not formed when imidazole **112** was treated with various bases and several silylating agents.



Scheme 17 Ireland Claisen approach to from methylenecyclopentane **114**.

Kato *et al.* reported that the nucleophilic addition of phenyl lithium to 2-chlorocyclopentanone (**107**) led to a 1,2-shift and provided 2-phenylcyclopentanone (**115**).[24] This chemistry was a potential method to connect the cyclopentane fragment and the imidazole ring (Scheme **6**). Imidazole **91** was treated with *n*-BuLi and 2-chlorocyclopentanone (**107**) to give 2-imidazolylcyclopentanone **116** in 16% yield along

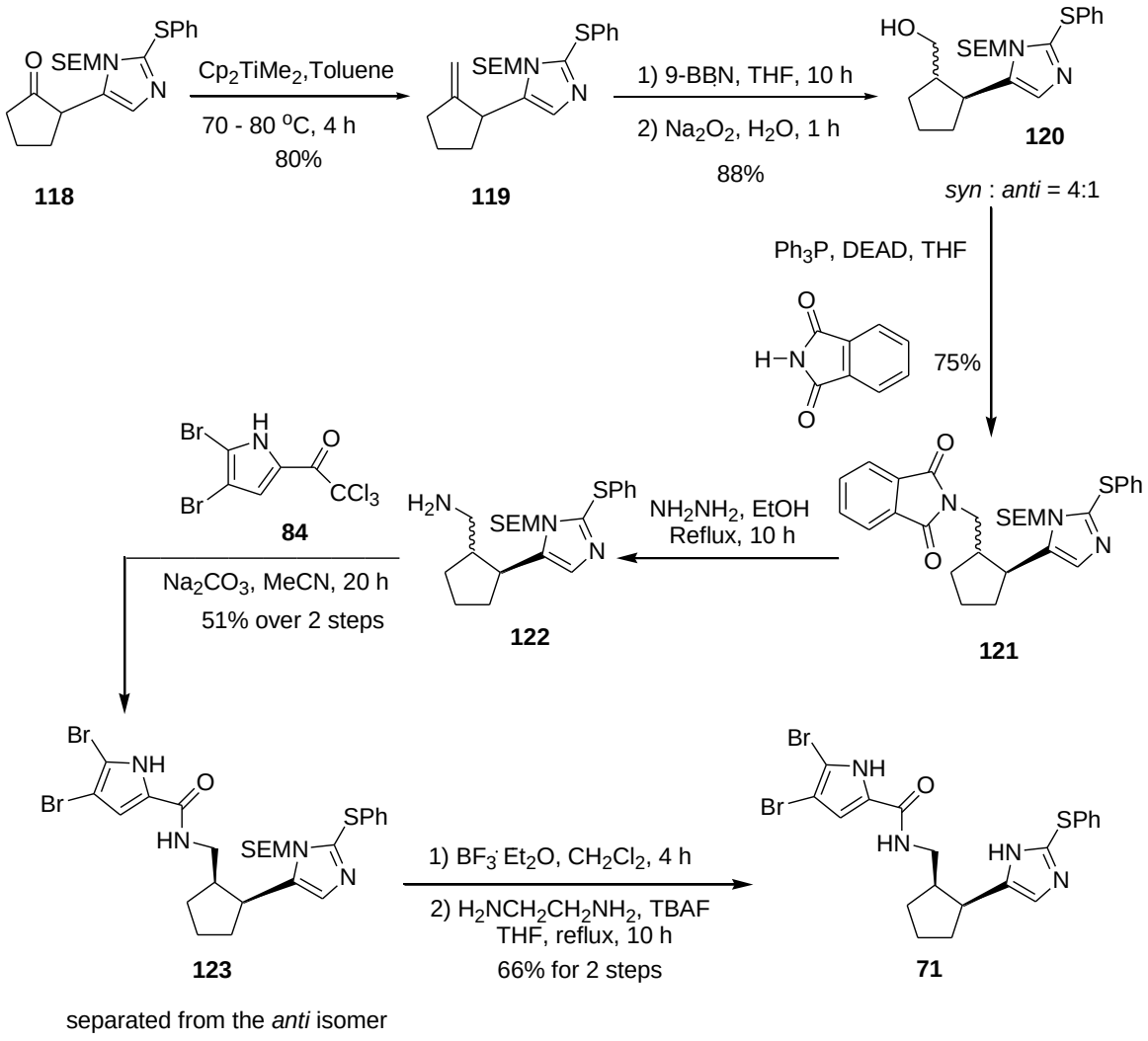
with alcohol **117** and recovered starting material. Other organometallic reagents such as the cuprate and magnesium species also were employed under identical conditions but none of these alternative metals gave better results than the lithium reagent. A more efficient coupling strategy is highly desired to improve the yield.



Scheme 18 A precedent from Kato *et al*. and its application to form cyclopentanone **117**.

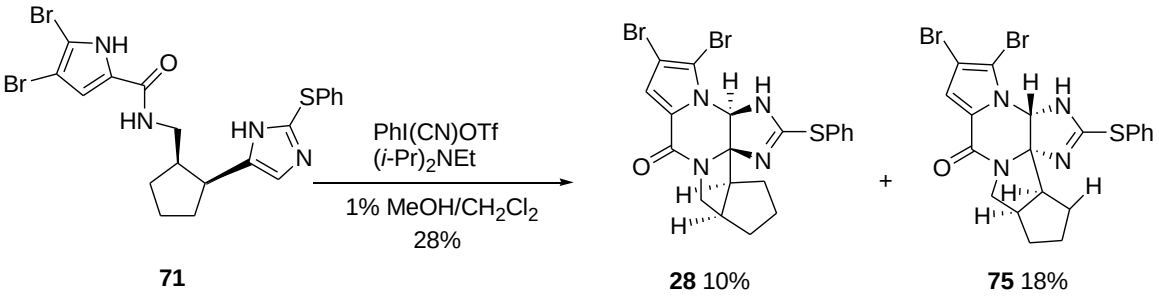
Methylenecylcopentane **119** was prepared from **118** by using the Tebbe-Petasis reagent (Cp_2TiMe_2) in good yield (Scheme **7**).[25] Wittig conditions resulted in the formation of an isomeric product with an endocyclic double bond. The standard Tebbe reagent delivered methylenecyclopentane **119** in very low yield (5%). Hydroboration of the alkene **119** using 9-BBN and an oxidative work up produced alcohol **120** as a 4:1 mixture of *syn* and *anti* isomers, respectively, in 88% overall yield. A Mitsunobo reaction introduced the phthalamide group under mild conditions. The phthalamide of **121** was removed by NH_2NH_2 in refluxing EtOH to give the free amine **122**, which was

coupled with pyrrole **84** to afford pyrrole-imidazole **123** in 51% over 2 steps. Finally, the SEM group was removed in 85% by a two-step procedure; treatment with $BF_3 \cdot Et_2O$ followed by overnight heating with 1M Bu_4NF at refluxing temperature in the presence of ethylenediamine. The most common deprotection method for the SEM group, refluxing with dilute HCl, caused a side reaction (nucleophilic aromatic substitution of Cl on the pyrrole ring) and formed several chloro-substituted pyrrole-imidazole derivatives.



Scheme 19 The preparation of *syn* five-membered cyclization precursor **71**.

With the pyrrole-imidazole **71** in hand, the stage is now set for the key Pummmer reaction (Scheme **8**). To our surprise, when pyrrole-imidazole **71** was treated with Stang's reagent in the presence of Hunig's base, two compounds were separated and found to have similar ^{1}H NMR spectra. Their relative stereochemistry was tentatively assigned as indicated below based on their NOSEY spectrums. When the ^{1}HNMR of **28** and **25** was compared, $H_{\mathbf{a}}$ was observed at $\delta = 5.46$ which is a similar shift to H_e in **25** ($\delta = 5.87$). The nOe effect observed between H_a and H_b ($\delta = 2.95$) indicated that they are on the same face of compound **28** as drawn below. When the ^{1}H NMR spectra of **75** and **25** were compared, $H_{\mathbf{c}}$ was observed at $\delta = 5.54$ which is a similar value as that observed for H_e in **25** ($\delta = 5.87$). The nOe effect observed between H_c and H_d ($\delta = 1.77$) suggested that these protons are on the same face of compound **75** as drawn below (Figure **1**).



Scheme 20. The cyclization of *syn* five-membered precursor **71**.

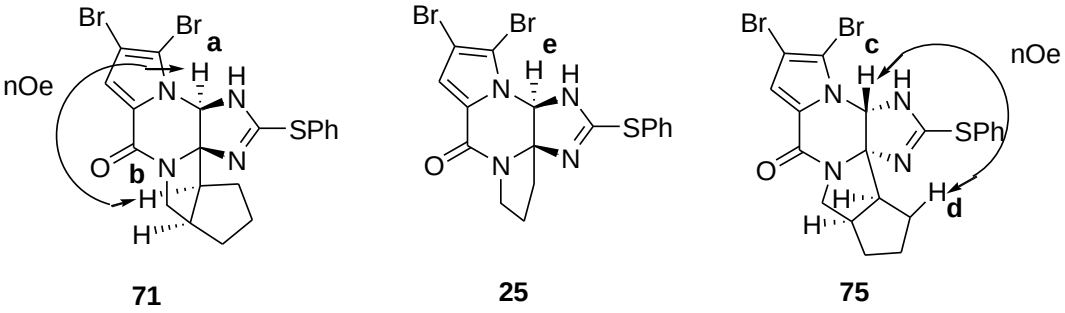
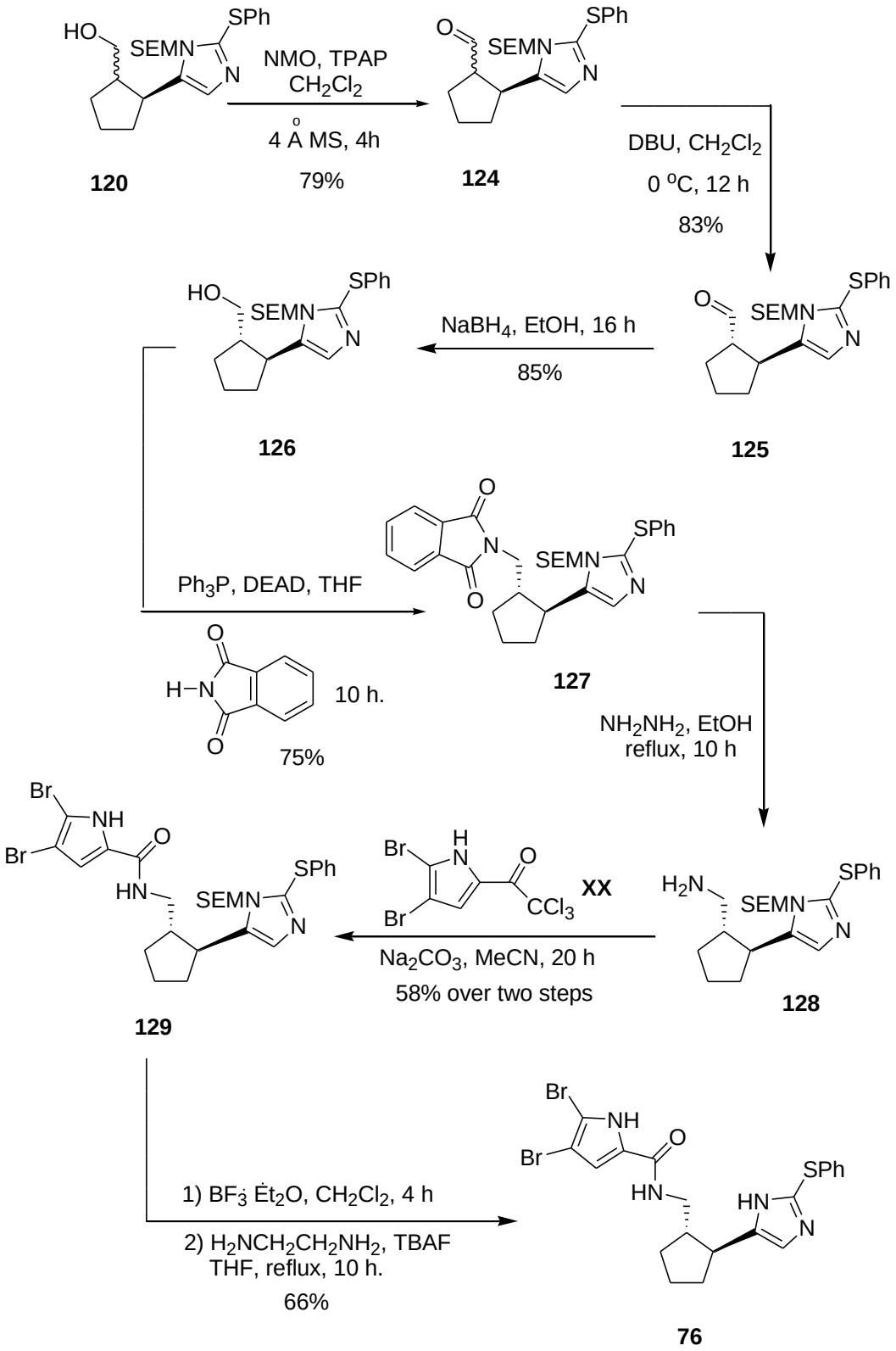


Figure 3 nOe effect in compounds **28** and **75.**

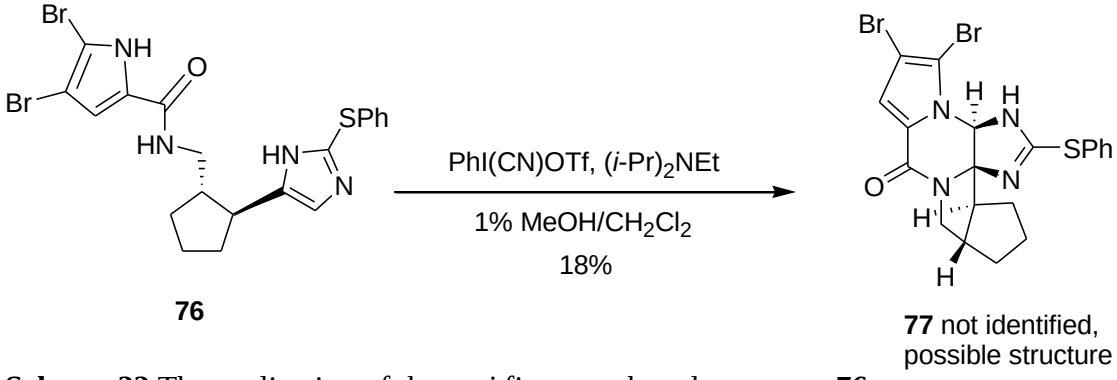
2.2 The *Anti* Fve-Membered Ring Cyclization Precursor and its Cyclization

In order to access the *anti* five-membered cyclization precursor **76**, a convenient conversion process was carried out to afford the *anti*-disubstituted cyclopentane **126** from *syn*-cyclopentane **120** via a NMO-TPAP oxidation,[26] DBU-catalyzed isomerization[27] and $NaBH_4$ reduction to deliver the *anti* alcohol **126** (Scheme **9**). The NMO-TPAP oxidation product was a 4:1 mixture of *syn* and *anti* aldehydes that was prone to decomposition and was carried on to the next step immediately. The DBU-catalyzed isomerization gave a more than 10:1 mixture of *anti* to *syn* aldehydes. Then, following the same procedure for the *syn* five-membered precursor, the *anti* five-membered precursor **76** was delivered in 5 steps.



Scheme 21 The preparation of *anti* five-membered cyclization precursor **76**.

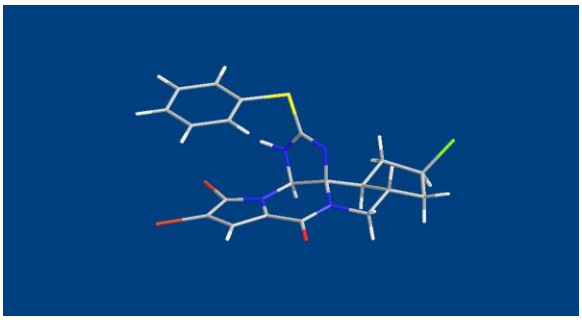
Now the stage is set to test the key Pummerer methodology on the *anti* precursor **76** (Scheme **10**). Based upon the recent stereochemical revision of palau'amine, this substrate should afford a product consistent with the correct structure of the natural product. The reaction gave only a single product as shown by TLC. This compound was isolated via an SiO_2 column run at -78 ℃. Mass spectral analysis showed a hit for the desired exact mass. However, due to the thermal instability of this product, additional spectral data could not be acquired. Future efforts to isolate and stabilize this product are currently being explored.



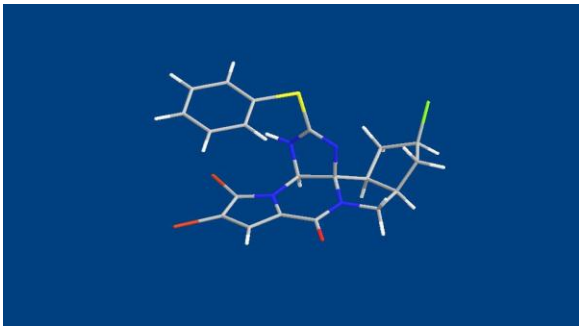
Scheme 22 The cyclization of the *anti* five-membered precursor **76**.

Calculations done using Macromodel with the MMFF force field predict that the *syn* pentacyclic system is more stable than the *anti* system by 9.4 kcal/mol (Figure **2**). This difference in energy might be an explanation for the instability of the *anti* product.

Rel E (kcal/mol)



anti 9.4

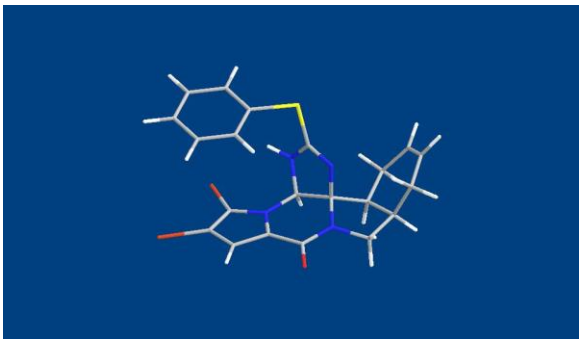


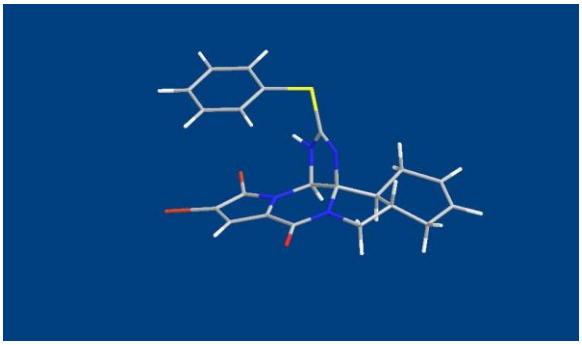
syn 0.0

Figure 4 The energy difference between the *syn* and *anti* pentacyclic system.

2.3 The *Anti* Six-Membered Cyclization Precursors

The replacement of five-membered ring by a six-membered ring in **76** might permit the *anti*-type cyclization to occur with greater facility, and might lead to a more stable product. In order to probe this point, calculations were carried out by using the Macromodel/MMFF software on both *anti* and *syn* pentacyclic systems bearing six-membered rings. For the six-membered ring cyclization, the *anti* product is more stable than the *syn* product by 2.0 kcal/mol (Figure **3**). This energy difference encourages attempts to make the six-membered ring precursors and test our Pummerer methodology.

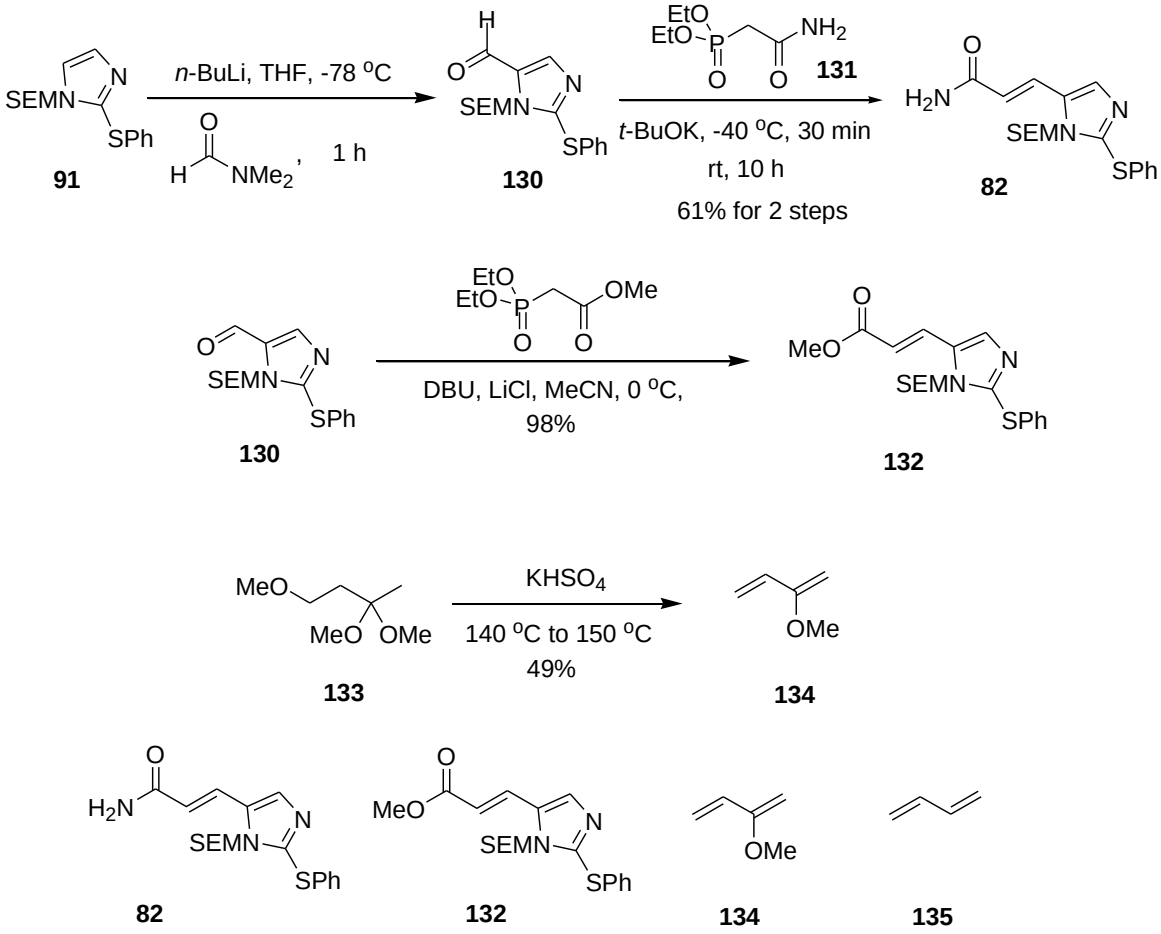




	Rel E (kcal/mol)
syn	2.0
anti	0.0

Figure 5 The energy difference between the *syn* and *anti* pentacyclic system.

A Diels-Alder reation was selected to build the cyclohexane moiety. The synthesis of the dienophile started with the generation of the lithiate of **91** and followed with a dimethylformamide quench to give aldehyde **130**. A Horner-Wadsworth-Emmons reaction between aldehyde **130** and phosphonate **131** delivered α,β-unsaturated amide **82** in 61% over 2 steps. Then, α,β-unsaturated ester **132** was prepared following similar chemistry. Dienes **134** and **135** were obtained and tested under various Diels-Alder reaction conditions to construct the key cyclohexane-imidazole moiety (Scheme **11**).

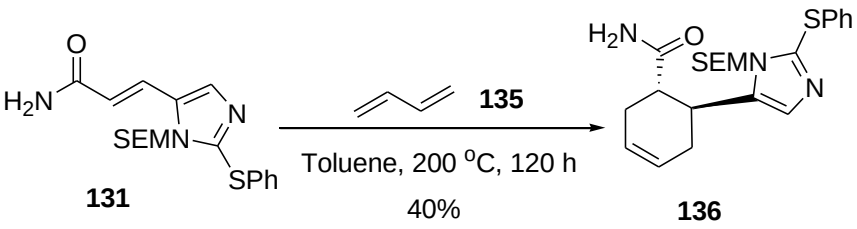


Scheme 23 The preparation of dienes and dienophiles for the test of Diels-Alder reaction.

As show in the Table below (Table **1**), a variety of Diels-Alder conditions were tried between dienes **134** and **135** and dienophiles **132** and **82**. In the best case, the thermal Diels-Alder reaction between **131** and **135** gave **136** in 40% after 120 h (Scheme **12**).[28]

Starting Materials	Conditions	Result
134 + **132**	200 ℃, Toluene, 48 h	No Reaction
134 + **132**	Microwave, 200 W, 30 mins.	Decomposition
134 + **132**	Lewis Acid:BF_3, $InCl_3$,$Sc(OTf)_3$, $MeAlCl_2$	No Reaction
134 + **82**	200 ℃, Toluene, 48 h	No Reaction
134 + **82**	Microwave, 200 W, 30 mins.	Decomposition
134 + **82**	Lewis Acid: $MeAlCl_2$	No Reaction
135 + **82**	200 ℃, Toluene, 48 h	21% 48 h; 40% 120h
135 + **82**	Microwave, 200 W, 30 mins.	**RD12** leaking
135 + **82**	Lewis Acid:$Sc(OTf)_3$	No Reaction

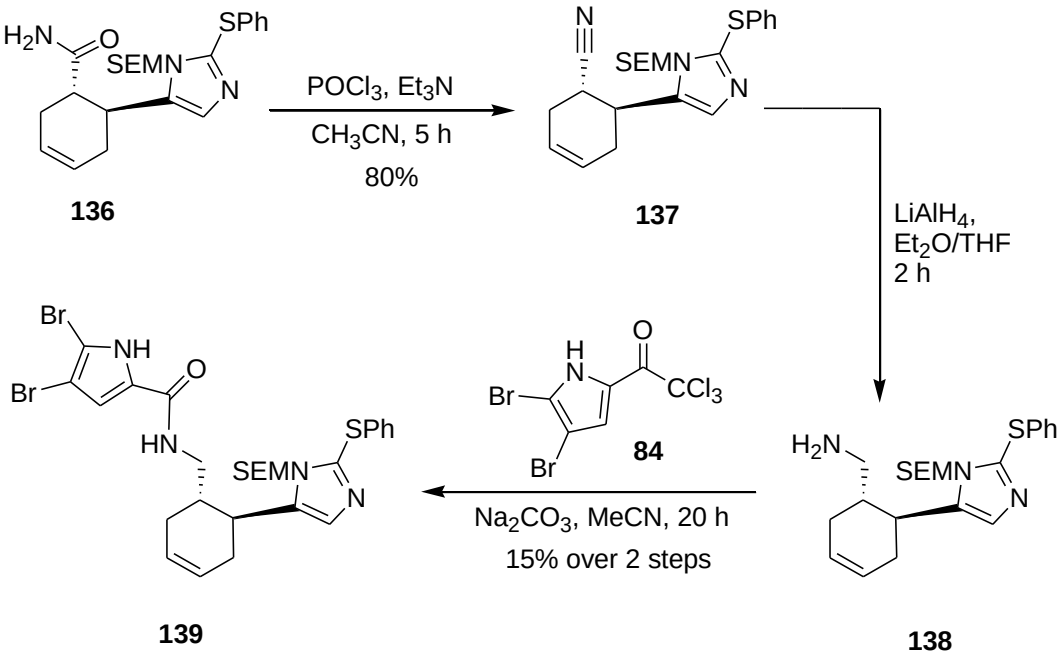
Table 1 Test of different Diels-Alder reaction conditions for dienes and dienophiles.



Scheme 24 The best result of the Diels-Alder reaction chemistry.

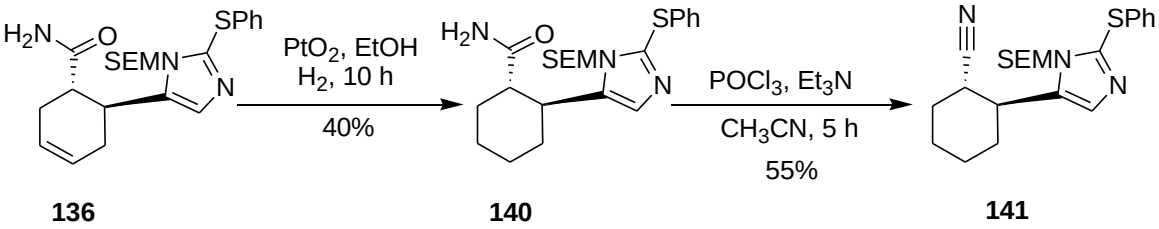
Although various reductive conditions were tested, none of them accomplished a direct reduction of amide **136** to give a primary amine. Instead, this conversion was completed by transformation of amide **136** to nitrile **137** in 80%[29] followed by reduction of the

nitrile by $LiAlH_4$ (Scheme **13**). The resulting amine **138** was coupled with the pyrrole moiety to give pyrrole-imidazole **139**. Deprotection of the SEM protecting group will afford the precursor for the six-membered ring cyclization.



Scheme 25 The preparation of *anti* six-membered cyclization precursor **139**

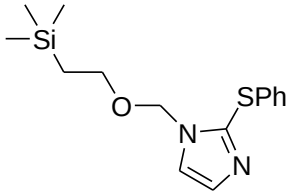
Adam's catalyst was found to hydrogenate the cyclohexene double bond to give amide **140**, which was converted to nitrile **141**. This compound will be coupled with the pyrrole moiety and used to test the key Pummerer methodology as well (Scheme **14**).



Scheme 26 The hydrogenation and functional group manipulation of **136**

Chapter 3

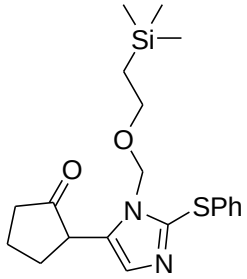
Experimental



91

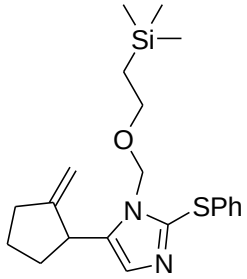
2-Phenylsulfanyl-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazole (91). In a 100 mL flame-dried Schlenk flask, a solution of imidazole (0.508 g, 7.30 mmol) in THF (25 ml) was cooled to -78 °C and a solution of *n*-BuLi in hexane (2.28 M, 3.50 mL, 8.00 mmol) was added drop-wise to the reaction solution. The reaction mixture was stirred at -78 ℃ for 30 min, warmed up to 25 ℃, and then SEMCl (1.60 mL, 8.80 mmol) was added drop-wise by syringe. The reaction mixture was stirred at 25 ℃ for 20 min then cooled to -78 ℃. 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 ℃ 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 ℃ for 1 h and then warmed to 25 ℃ 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 **91** as a yellow oil (1.6 g, 71%). Spectral data matched those reported by Lipshutz.[xxx]



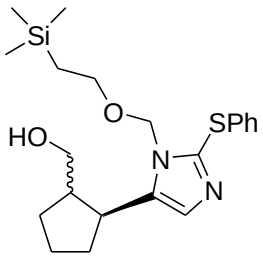
118

2-[2-Phenylsulfanyl-3-(2-trimethylsilanyl-ethoxymethyl)-3H-imidazol-4-yl]-cyclopentanone (118). In a 500 mL flame-dried Schlenk flask, a solution of **91** (3.84 g, 12.5 mmol) in THF (125 mL) was cooled to -78 ℃ and a *n*-BuLi solution in hexane (2.50 M, 5.47 mL, 13.7 mmol) was added drop-wise to the reaction solution. After 30 min, 2-chlorocyclopentanone (**107**) (1.16 mL 11.4 mmol) was added and the reaction mixture was held at -78 ℃ for 1 h, warmed up 25 ℃ 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 **118** (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.



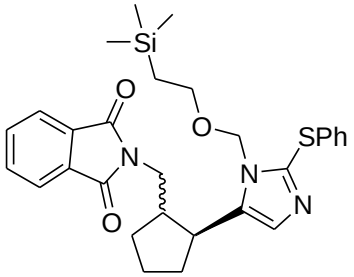
119

5-(2-Methylene-cyclopentyl)-2-phenylsulfanyl-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazole (119). In a 100 mL flame-dried Schlenk flask, a solution of **118** (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 ℃. 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 **119** (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.



120

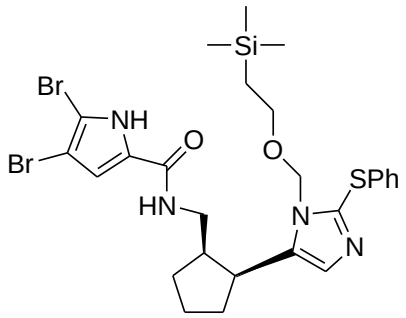
{2-[2-Phenylsulfanyl-3-(2-trimethylsilanyl-ethoxymethyl)-3H-imidazol-4-yl]-cyclopentyl}-methanol (120). In a 50 mL flame-dried Schlenk flask, a solution of 9-BBN in THF (0.5 mL, 5.55mL, 2.78 mmol) was added drop-wise into a solution of **119** (0.358 g, 0.925 mmol) in THF (10 mL) at 25 ℃ and the reaction mixture was held at 25 ℃ 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 **120** (0.33 g, 88%, a 4:1 mixture of *syn* and *anti* product) as a yellow oil: IR (thin film) 3305 cm^{-1}; ^1H NMR (mixture of two isomers, 300 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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.



121

2-{2-[2-Phenylsulfanyl-3-(2-trimethylsilanyl-ethoxymethyl)-3H-imidazol-4-yl]-cyclopentylmethyl}-isoindole-1, 3-dione (121). 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 drop-wise into a solution of Ph_3P (0.0610 g, 0.233 mmol) in THF (3 mL) at 0 ℃ and the reaction mixture was stirred at this temperature for 15 min. A solution of **120** (4:1 syn/anti, 0.0786 g, 0.194 mmol) in THF (3 mL) was added to the reaction mixture and held at 25 ℃ for 20 min after which time solid phthalimide (0.0320g, 0.214 mmol) was added in one portion and the reaction mixture was stirred at 25 ℃ for 10 h. After reaction was determined to be complete by TLC, 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 **121** (0.078 g, 75%, mixture of *syn* and *anti* products) as a colorless oil: IR (thin film) 1713 cm^{-1}; ^1H NMR (major isomer, 300 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 168.7, 138.6, 136.3, 135.6, 132.3, 129.6, 129.4, 128.1, 128.0, 126.9, 123.5,

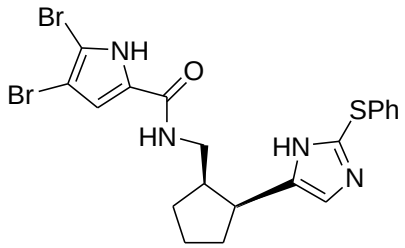
74.1, 66.5, 40.2, 39.7, 38.8, 30.4, 29.6, 22.8, 18.2, -1.1; LRMS (ESI) m/z (relative intensity) 534.2 (100%, M + H^+); HRMS (ESI) m/z calcd for $[C_{29}H_{36}N_3O_3SiS]^+$, 534.2247; found, 534. 2261



123

4,5-Dibromo-1H-pyrrole-2-carboxylic acid {2-[2-phenylsulfanyl-3-(2-trimethylsilanyl-ethoxymethyl)-3H-imidazol-4-yl]-cyclopentylmethyl}-amide (123). In a 25 mL round-bottom flask, hydrazine monohydrate (1.00 mL, 21.4 mmol) was added drop-wise to a solution of **121** (4:1 syn/anti, 0.0954 g, 0.179 mmol) in EtOH (3 mL) at 25 ℃ and the reaction mixture was heated at reflux for 10 h. After the reaction was determined to be complete by TLC, 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. This colorless oil was transferred into a 25 mL round-bottom flask with MeCN (5 mL) via cannula and pyrrole **84** (0.0666 g, 0.179 mmol) and Na_2CO_3 (0.0192 g, 0.179 mmol) were added to this solution at 25 ℃ and the reaction mixture was held at 25 ℃ for 20 h. After removal of the solvent, 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 in vacuo to give a colorless oil. The colorless oil was purified by flash column chromatography (CH_2Cl_2 then 10-20% Et2O/ CH_2Cl_2 as eluent) to give **123** (0.064 g, 55%) as a colorless oil: IR (thin film) 3116, 1631 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 11.73 (bs, 1H), 7.27-7.16 (m, 5H), 7.06 (s, 1H),

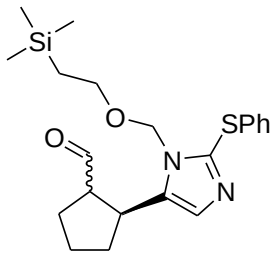
6.41 (s, 1H), 6.21 (t, *J* = 5.3 Hz, 1H), 5.41 (d, *J* = 10.5 Hz, 1H), 5.28 (d, *J* = 10.4 Hz, 1H), 3.53-3.42 (m, 2H), 3.38-3.21 (m, 2H), 2.94 (m, 1H), 2.60 (m, 1H), 2.09-1.81 (m, 4H), 1.67 (m, 1H), 1.53 (m, 1H), 0.89-0.80 (m, 2H), -0.06 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.9, 139.1, 136.9, 134.9, 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.



71

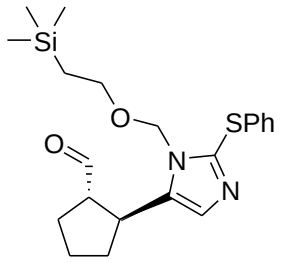
4,5-Dibromo-1H-pyrrole-2-carboxylic acid [2-(2-phenylsulfanyl-3H-imidazol-4-yl)-cyclopentylmethyl]-amide (71). In a 25 mL round-bottom flask, BF_3 Et_2O (0.111 mL, 0.882 mmol) was added slowly into a solution of **123** (0.144 g, 0.220 mmol) in CH_2Cl_2 (10 mL) at 0 ℃ and the reaction mixture was warmed to 25 ℃ and held at this temperature for 4 h. After the reaction was determined to be complete by TLC, the reaction solution was partitioned between EtOAc and water and the aqueous layer was extracted with EtOAc (3×20 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated in vacuo to give a yellow solid. This yellow solid was transferred into a 25 mL round-bottom flask with THF (5 mL) via cannula, ethylenediamine (0.0540 ml, 0.451 mmol, 2.00 equiv) and a Bu_4NF solution in THF (1M, 2.25 mL, 2.25 mmol) were sequentially added into this solution at 25 ℃ and the reaction mixture was heated at reflux for 10 h. After reaction was determined to be complete by TLC, the reaction solution was partitioned between EtOAc and water and the aqueous layer was extracted with EtOAc (3×20 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated in vacuo to give a yellow solid. The yellow solid was purified by SiO_2 flash column chromatography (CH_2Cl_2 then 10-30% Et_2O/ CH_2Cl_2 as eluent) to give **71** (0.098 g, 85%) as a white solid. m.p. = 207-209 ℃ (decomposition); IR (thin film) 3117, 1623 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 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) δ 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.



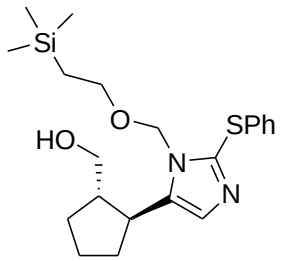
124

2-[2-Phenylsulfanyl-3-(2-trimethylsilanyl-ethoxymethyl)-3H-imidazol-4-yl]-cyclopentanecarbaldehyde (124). 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 **120** (0.838 g, 2.07 mmol) in CH_2Cl_2 (20 mL) at 25 ℃. Tetra-n-propylammonium pertuthenate (TPAP, 0.728 g, 0.207 mmol) was added quickly to the reaction solution and the reaction mixture was stirred for 4 h. After the reaction was determined to be complete by TLC, 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 elunet) to give **124** (0.66 g, 79%) as a yellow oil. The crude product was carried on to the next step.



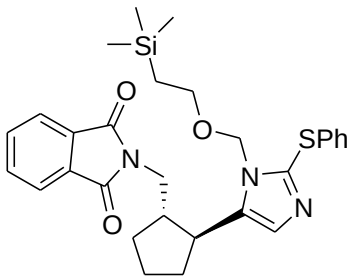
125

2-[2-Phenylsulfanyl-3-(2-trimethylsilanyl-ethoxymethyl)-3H-imidazol-4-yl]-cyclopentanecarbaldehyde (125). In a 50 mL round-bottom flask, DBU (0.017 mL, 0.112 mmol) was added drop-wise into a solution of **124** (0.451 g, 1.12 mmol) in CH_2Cl_2 (15 mL) at 0 ℃ and the reaction mixture was stirred at that temperature for 1 h. After the reaction was determined to be complete by TLC, 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 **125** (0.38 g, 83%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 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.



126

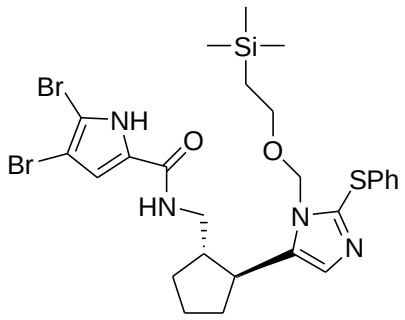
{2-[2-Phenylsulfanyl-3-(2-trimethylsilanyl-ethoxymethyl)-3H-imidazol-4-yl]-cyclopentyl}-methanol (126). In a 50 mL round-bottom flask, $NaBH_4$ (0.0380 g, 0.100 mmol) was added in one portion to a solution of **125** (0.137 g, 0.339 mmol) in EtOH (15 mL) at 25 ℃ and the reaction mixture was held at the same temperature for 10 h. After the reaction was determined to be complete by TLC, 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 **126** (0.12 g, 85%) as a colorless oil : IR (thin film) 3325 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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.



127

2-{2-[2-Phenylsulfanyl-3-(2-trimethylsilanyl-ethoxymethyl)-3H-imidazol-4-yl]-cyclopentylmethyl}-isoindole-1,3-dione (127). In a 25 mL flame-dried Schlenk flask, a solution of DEAD in toluene (40 wt%, 0.119 mL,0.265 mmol) was added drop-wise into a solution of Ph_3P (0.0759 g, 0.289 mmol) in THF (3 mL) at 0 ℃ and the reaction mixture was held at 0 ℃ for 15 min and then a solution of **126** (0.0974 g, 0.241 mmol) in THF (4 mL) was added and the reaction mixture was stirred at 25 ℃ for an additional 20 min. After that time, solid phthalimide (0.0390g, 0.265 mmol) was added in one portion and the reaction mixture was stirred at 25 ℃ for 10 h. After the reaction was determined to be complete by TLC, 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. The colorless oil was purified by SiO_2 flash column chromatography (20-40% EtOAc/hexane as eluent) to give **127** (0.10 g, 79%) as a colorless oil: IR (thin film) 1710 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 168.9, 139.7, 137.5,

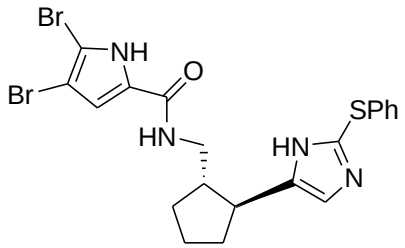
135.6, 134.3, 132.2, 129.6, 128.2, 127.0, 126.9, 123.5, 73.8, 66.2, 44.1, 42.1, 40.7, 35.3, 30.4, 23.8, 18.3, -1.1; LRMS (ESI) m/z (relative intensity) 534.2 (100%, M + H^+); HRMS (ESI) m/z calcd for $[C_{29}H_{36}N_3O_3SiS]^+$, 534.2247; found, 534. 2242.



129

4,5-Dibromo-1H-pyrrole-2-carboxylic acid {2-[2-phenylsulfanyl-3-(2-trimethylsilanyl-ethoxymethyl)-3H-imidazol-4-yl]-cyclopentylmethyl}-amide (129). In a 50 mL round-bottom flask, hydrazine monohydrate (3.00 mL, 61.8 mmol) was added drop-wise to a solution of **127** (0.251 g, 0.471 mmol) in EtOH (15 mL) at 25 ℃ and the reaction mixture was heated at reflux for 10 h. After the reaction was determined to be complete by TLC, 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 **84** (0.150 g, 0.405 mmol) and Na_2CO_3 (0.043 g, 0.40 mmol) were added into this solution at 25 ℃ and 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. 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 **129** (0.18 g, 58%) as a colorless oil: IR (thin film) 3095, 1635 cm^{-1}; ^1H NMR (300

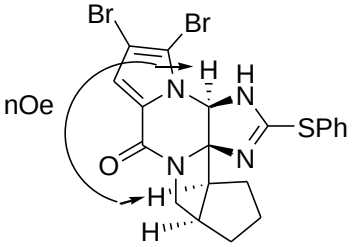
MHz, $CDCl_3$) δ 11.07 (bs, 1H), 7.26-7.16 (m, 5H), 7.04 (s, 1H), 6.93 (t, *J* = 5.2 Hz, 1H), 6.57 (s, 1H), 5.55 (d, *J* = 11.1 Hz, 1H), 5.49 (d, *J* = 11.2 Hz, 1H), 3.57 (m, 1H), 3.52-3.44 (m, 2H), 3.32 (m, 1H), 2.91 (m, 1H), 2.32-2.16 (m, 2H),1.99 (m, 1H), 1.84-1.70 (m, 3H), 1.48 (m, 1H), 0.97-0.79 (m, 2H), -0.05 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 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



76

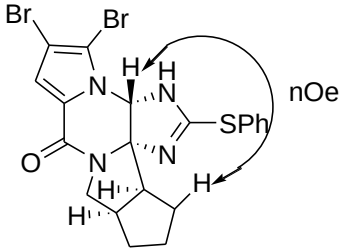
4,5-Dibromo-1H-pyrrole-2-carboxylic acid [2-(2-phenylsulfanyl-3H-imidazol-4-yl)-cyclopentylmethyl]-amide (76). In a 10 mL round-bottom flask, BF_3 Ɛt$_2$O (0.0360 mL, 0.289 mmol) was added slowly to a solution of **129** (0.0472 g, 0.0721 mmol) in CH_2Cl_2 (3 mL) at 0 ℃ and the reaction mixture was warmed to 25 ℃ and stirred for 4 h. After the reaction was determined to be complete by TLC, the reaction solution was partitioned between EtOAc and water and the aqueous layer was extracted with EtOAc (3×5 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated under reduced pressure to give a yellow solid. Then, this yellow solid was transferred into a 10 mL round-bottom flask with THF (3 mL) via cannula and ethylenediamine (0.0230 ml, 0.192 mmol) and a Bu_4NF solution in THF (1M, 100 mL, 1.00 mmol) were sequentially added to this solution at 25 ℃ and the reaction mixture was heated at reflux for 10 h. After the reaction was determined to be complete by TLC, the reaction solution was partitioned between EtOAc and water and the aqueous layer was extracted with EtOAc (3×10 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated under reduced pressure to give a yellow solid. The yellow solid was purified by flash column chromatography (CH_2Cl_2 then 10-30% Et$_2$O/ CH_2Cl_2 as eluent) to give **76** (0.025 g, 66%) as a white solid. m.p. = 216-218 ℃ (Decomposition); IR (thin film) 3095, 1602 cm^{-1}; ^{1}H NMR (300 MHz, CD_3OD) δ 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) δ 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.



28

and

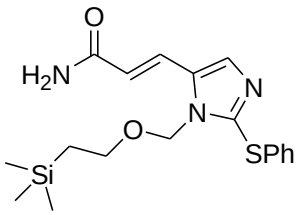


75

Pummerer Pentacycles 28 and **75**. In a 25 mL round-bottom flask, (*i*-Pr)$_2$NEt (0.0400 mL, 0.228 mmol) was added drop-wise to a solution of **71** (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*-Pr)$_2$NEt (4.00 equiv) were added over 6 hours, 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 **28** (0.0060 g, 10%) and **75** (0.012 g, 18%) as colorless oils.

28: IR (thin film) 3568, 1654 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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.

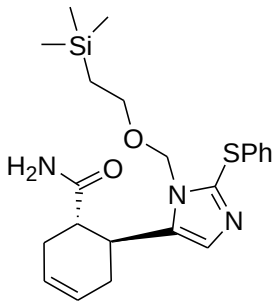
75, IR (thin film) 3201, 1654 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53-7.41 (m, 5H), 6.99 (s, 1H), 5.68 (s, 1H), 5.54 (s, 1H), 3.98 (dd, *J* = 12.0, 9.5 Hz, 1H), 3.59 (dd, *J* = 12.1, 4.4 Hz, 1H), 3.04 (m, 1H), 2.56 (q, *J* = 8.4 Hz, 1H), 2.06 (m, 1H), 1.91 (m, 1H), 1.78 (m, 1H), 1.59-1.50 (m, 2H), 1.35 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 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.



82

3-[2-Phenylsulfanyl-3-(2-trimethylsilanyl-ethoxymethyl)-3H-imidazol-4-yl]-acrylamide (82). In a 1 L flame-dried Schlenk flask, a solution of imidazole **91** (23.3 g, 76.1mmol) in THF (300 ml) was cooled to -78 °C and a solution of *n*-BuLi in hexane (2.50 M, 39.5 mL, 98.9 mmol) was added drop-wise to the reaction solution. The reaction mixture was stirred at -78 ℃ for 1 h and then DMF (7.07 mL, 91.3 mmol) was added drop-wise at the same temperature. After 1 h, saturated aqueous $NaHCO_3$ (150 mL) was added and the aqueous layer was extracted with Et_2O (3 × 200 mL). The organic layers were combined, dried over Na_2SO_4, and evaporated under reduced pressure to give **130** as a brown oil (25.9 g, >100%). In a 1 L flame-dried Schlenk flask, a solution of phosphite **131** (16.6 g, 85.2 mmol) in THF (150 mL) was cooled to -40 ℃ and a solution of *t*-BuOK (17.56 g, 156.5 mmol) in THF (50 mL) was transferred to the reaction solution via cannula. The reaction mixture was warmed to 0 ℃, held at that temperature for 30 min, and then cooled to -40 ℃. A solution of crude aldehyde **130** (25.9 g, 77.4 mmol) in THF (200 mL) was transferred into the reaction solution and the reaction mixture was held at -78 ℃ for 1 h, warmed to 25 ℃ over 1 h, and then stirred for 10 h. After the reaction was determined to be complete by TLC, the reaction solution was concentrated under reduced pressure and the residue was partitioned between Et_2O and water and the aqueous layer was extracted with Et_2O (3×300 mL). The organic layers were combined, dried over Na_2SO_4, and evaporated under reduced pressure to give a

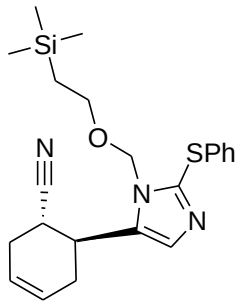
brown oil which was purified by SiO_2 flash column chromatography (40% EtOAc/hexane then EtOAc as eluent) to give **82** (18 g, 61%) as a brown oil: IR (thin film) 3325, 3181, 1672, 1607 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.59 (d, *J* =15.7 Hz, 1H), 7.54 (s, 1H), 7.30-7.17 (m, 5H), 6.47 (d, *J* = 15.6 Hz, 1H), 6.13 (s, 2H), 5.50 (s, 2H), 3.48-3.42 (m, 2H), 0.88-0.82 (m, 2H), -0.04 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.9, 142.8, 133.8, 132.5, 132.3, 129.9, 129.6, 128.8, 127.9, 120.4, 73.8, 66.9, 18.2, -1.0; LRMS (ESI) m/z (relative intensity) 376.2 (100%, M + H^+); HRMS (ESI) m/z calcd for $[C_{18}H_{26}N_3O_2SiS]^+$, 376.1515; found, 376.1503.



136

6-[2-Phenylsulfanyl-3-(2-trimethylsilanyl-ethoxymethyl)-3H-imidazol-4-yl]-cyclohex-3-enecarboxylic acid amide (136). In a 200 mL autoclave, a solution of **131** (5.00 g, 13.3 mmol) in toluene (100 mL) was mixed with liquid 1,3-butadiene (10.0 g, 185 mmol, 14.0 equiv) and hydroquinone (0.140 g, 1.27 mmol) and heated at 200 ℃ for 120 hours. The autoclave was cooled to 25 ℃ and the solution was concentrated under reduced pressure. The concentrated solution was partitioned between EtOAc and water and the aqueous layer was extracted with EtOAc (3×100 mL). The organic layers were combined, dried over Na_2SO_4, and evaporated under reduced pressure to give a yellow solid which was purified by SiO_2 flash column chromatography (40% EtOAc/hexane then EtOAc as eluent) to give **136** (2.3 g, 40%) as a white solid. m.p. = 152-153 ℃; IR (thin film) 3318, 3176, 1672, 1480 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.26-7.13 (m, 5H), 7.05 (s, 1H), 5.91 (s, 1H), 5.77 (s, 2H), 5.55 (d, *J* = 10.7 Hz, 1H), 5.47 (d, *J* = 10.7Hz, 1H), 5.16 (s, 1H), 3.37 (dd, *J* = 16.8, 10.2 Hz, 2H), 3.27 (m, 1H), 2.61 (m, 1H), 2.47-2.43 (m, 2H), 2.35-2.18 (m, 2H), 0.87-0.71 (m, 2H), -0.06 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.0, 139.5, 136.6, 135.3, 129.1, 127.3, 126.4, 125.4, 125.2, 73.3, 65.8, 46.8, 32.6, 32.3, 29.5, 17.8, -1.6; LRMS (ESI) m/z (relative intensity) 430.3 (100%, M +

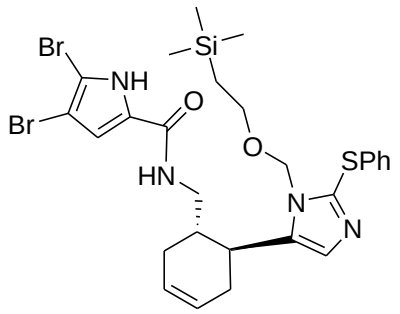
H^+); HRMS (ESI) m/z calcd for $[C_{22}H_{32}N_3O_2SiS]^+$, 430.1985; found, 430.1974. One carbon signal was not observed in the aromatic range due to overlap with another signal.



137 .

6-[2-Phenylsulfanyl-3-(2-trimethylsilanyl-ethoxymethyl)-3H-imidazol-4-yl]-cyclohex-3-enecarbonitrile (137). In a 25 mL flame-dried Schlenk flask, a solution of $POCl_3$ (0.0870 mL, 0.931 mmol) in CH_3CN (2.5 mL) was cooled to 0 ℃ and Et_3N (0.195 mL, 1.40 mmol) was added drop-wise by syringe into the reaction solution. After 1 h, solid **136** (0.0500 g, 0.116 mmol) was added to the reaction mixture, which then was warmed to 25 ℃ and stirred for 5 h. After the reaction was determined to be complete by TLC, the reaction solution was filtered through a pad of Celite, eluting with CH_3CN (3×5 mL). The organic fractions were combined and concentrated under reduced pressure. The organic residue was dissolved in $CHCl_3$ and partitioned between $CHCl_3$ and aqueous $NaHCO_3$ solution. The aqueous layers were combined and extracted with $CHCl_3$ (3×5 mL). The combined organic phases were dried over Na_2SO_4 and evaporated under reduced pressure to give a colorless oil which was purified by SiO_2 flash column chromatography (10-40 % Et_2O/hexane as eluent) to give **137** (0.038 g, 80%) as a colorless oil. IR (thin film) 2210 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.25-7.15 (m, 6H), 5.84 (m, 1H), 5.75 (m, 1H), 5.54 (d, *J* = 11.2 Hz, 1H), 5.49 (d, *J* = 11.3 Hz, 1H), 3.47-3.34 (m, 3H), 3.02 (m, 1H), 2.62 (m, 1H), 2.51 (s, 2H), 2.32 (m, 1H), 0.91-0.78 (m, 2H), -0.04 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.4, 136.3, 134.7, 129.2, 128.7, 127.7,

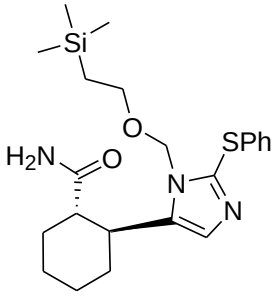
126.6, 125.9, 123.4, 121.0, 73.4, 66.1, 32.4, 31.0, 30.8, 28.2, 17.8, -1.6; LRMS (ESI) m/z (relative intensity) 412.2 (100%, M + H^+); HRMS (ESI) m/z calcd for $[C_{22}H_{30}N_3OSiS]^+$, 412.1879; found, 412.1865.



139

4,5-Dibromo-1H-pyrrole-2-carboxylic acid {6-[2-phenylsulfanyl-3-(2-trimethylsilanyl-ethoxymethyl)-3H-imidazol-4-yl]-cyclohex-3-enylmethyl}-amide (139): In a 50 mL round-bottom flask, a solution of $LiAlH_4$ in Et_2O (1M, 0.943 mL, 0.943 mmol) was slowly added into a solution of **137** (0.203 g, 0.472 mmol) in 1:1 Et_2O/THF (15 mL) at 0 ℃ and the reaction mixture was held at this temperature for 2 h. After the reaction was determined to be complete by TLC, water (5 mL) was cautiously added followed by 30% aqueous NaOH (5 mL) and additional water (5 mL). The reaction mixture was partitioned between EtOAc and water and the aqueous layer was extracted with EtOAc (3×20 mL). 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 (EtOAc then 20% MeOH/EtOAc) to give a yellow oil. This yellow oil (0.184 g, 0.443 mmol, 1 equiv) was transferred into a 50 mL round-bottom flask with MeCN (15 mL) via cannula, and pyrrole **84** (0.328 g, 0.886 mmol) and Na_2CO_3 (0.0940 g, 0.886 mmol) were added to the solution and the reaction mixture was stirred at room 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

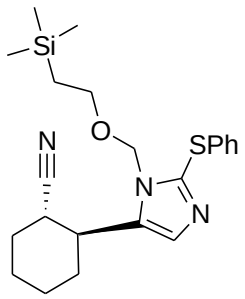
concentrated under reduced pressure to give a colorless oil. This oil was purified by SiO_2 flash column chromatography (CH_2Cl_2 then 40% Et_2O/ CH_2Cl_2 as eluent) to give **139** (0.045 g, 15%) as a colorless oil: IR (thin film) 3119, 2943, 1631 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.84 (bs, 1H), 7.30-7.18 (m, 5H), 7.13 (s, 1H), 6.67 (t, *J* = 6.4 Hz, 1H), 6.60 (s, 1H) 5.73 (m, 2H), 5.57 (d, *J* = 11.3 Hz, 1H), 5.41 (d, *J* = 11.3 Hz, 1H), 3.70 (m, 1H), 3.60-3.49 (m, 2H), 3.18 (m, 1H), 2.90 (m, 1H), 2.44-2.14 (m, 4H), 2.05 (m, 1H), 0.98 (td, *J* = 12.3, 5.5 Hz, 1H), 0.83 (td, *J* = 12.7, 5.4 Hz, 1H), -0.05 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.3, 139.8, 135.2, 129.8, 128.7, 128.3, 127.4, 127.3, 126.7, 125.4, 112.6, 105.8, 99.9, 72.8, 67.1, 42.0, 39.3, 33.9, 33.0, 28.7, 18.4, -1.2; LRMS (ESI) m/z (relative intensity) 665.2 (100%, M + H^+); HRMS (ESI) m/z calcd for $[C_{27}H_{35}Br_2N_4O_2SiS]^+$, 665.0617; found, 665.0617. One carbon signal was not observed in the aromatic range due to overlap with another signal.



140

2-[2-Phenylsulfanyl-3-(2-trimethylsilanyl-ethoxymethyl)-3H-imidazol-4-yl]-cyclohexanecarboxylic acid amide (140). In a 25 mL round-bottom flask, PtO_2 (0.0530 g, 0.233 mmol) was added in one portion to a solution of **136** (0.0500 g, 0.116 mmol) in EtOH (5 mL) and the reaction mixture was stirred under a H_2 balloon for 10 h. After the reaction was determined to be complete by TLC, the reaction mixture was filtered through a pad of Celite, eluting with EtOH (2×5 mL). The solvent was removed under reduced pressure and the organic residue was dissolved in EtOAc and partitioned between EtOAc and water. The aqueous layer was extracted with EtOAc (3×5 mL) and the organic fractions 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 (40% EtOAc/hexane then EtOAc as eluent) to give **140** (0.020 g, 40%) as a white solid. m.p. = 170-172 ℃; IR (thin film) 3296, 1676 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.26-7.06 (m, 5H), 7.00 (s, 1H), 6.01 (s, 1H), 5.51 (d, *J* = 10.6 Hz, 1H), 5.45 (d, *J* = 9.5 Hz, 1H), 5.12 (s, 1H), 3.40-3.33 (m, 2H), 3.02 (m, 1H), 2.32 (t, *J* = 10.6 Hz, 1H), 2.00-1.98 (m, 2H), 1.86-1.83 (m, 2H), 1.64 (q, *J* = 12.3 Hz, 1H), 1.48-1.28 (m, 3H), 0.81-0.77 (m, 2H), -0.06 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.4, 140.4, 137.2, 135.9, 129.6, 128.0, 127.6, 126.9, 73.7, 66.3, 51.9, 36.4, 34.1, 30.9, 26.3, 25.6, 18.3, -1.1;

LRMS (ESI) m/z (relative intensity) 432.3 (100%, M + H^+); HRMS (ESI) m/z calcd for $[C_{22}H_{34}N_3O_2SiS]^+$, 432.2141; found, 432.2112.



141

2-[2-Phenylsulfanyl-3-(2-trimethylsilanyl-ethoxymethyl)-3H-imidazol-4-yl]-cyclohexanecarbonitrile (141). In a 50 mL flame-dried Schlenk flask, a solution of $POCl_3$ (0.232 mL, 2.49 mmol) in CH_3CN (25 mL) was cooled to 0 ℃ and Et_3N (0.520 mL, 3.74 mmol) was added drop-wise to the reaction solution. After 1 h, solid **140** (0.134 g, 0.311 mmol) was added to the reaction mixture, which then was warmed to 25 ℃ and stirred for 5 h. After the reaction was determined to be complete by TLC, the reaction solution was filtered through a pad of Celite, eluting with CH_3CN (3×20 mL). The organic fractions were combined and concentrated under reduced pressure. The organic residue was dissolved in $CHCl_3$ and partitioned between $CHCl_3$ and aqueous $NaHCO_3$ solution. The aqueous layers were combined, extracted with $CHCl_3$ (3×20 mL), dried over Na_2SO_4, and evaporated under reduced pressure to give a colorless oil which was purified by SiO_2 flash column chromatography (20-40 % Et_2O/hexane as eluent) to give **141** (0.070 g, 55%) as a colorless oil IR (thin film) 2215 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.26-7.13 (m, 6H), 5.35 (d, *J* = 12.9 Hz, 1H), 5.32 (d, *J* = 12.9 Hz, 1H), .3.31-3.11 (m, 2H), 2.98 (td, *J* = 11.6, 3.5 Hz, 1H), 2.80 (td, *J* = 11.2, 3.5 Hz, 1H), 2.22 (d, *J* = 13.4 Hz, 1H), 2.00 (m, 1H), 1.86-1.65 (m, 4H), 1.46-1.32 (m, 2H), 0.83-0.79 (m, 2H), -0.05 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.4, 137.8, 135.6, 129.7, 127.7, 126.9,

122.5, 119.6, 76.1, 66.9, 40.6, 34.7, 32.4, 30.3, 25.5, 25.0, 18.2, -1.1; LRMS (ESI) m/z (relative intensity) 414.3 (100%, M + H^+); HRMS (ESI) m/z calcd for $[C_{22}H_{32}N_3OSiS]^+$, 414.2035; found, 414.2012.

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