APPLICATION OF MODERN PUMMERER METHODOLOGY IN MODEL STUDIES TOWARD THE TOTAL SYNTHESIS OF PALAU’AMINE

A Thesis in
Chemistry

by
Jianfeng Li

© 2009 Jianfeng Li

Submitted in Partial Fulfillment of the Requirements for the Degree of

Master of Science

May 2009
The thesis of Jianfeng Li was reviewed and approved* by the following:

Kenneth Feldman  
Professor of Chemistry  
Thesis Advisor  

Raymond Funk  
Professor of Chemistry  

Harry Allcock  
Professor of Chemistry  

Sen Ayusman  
Professor of Chemistry  
Head of the Department of Chemistry  

*Signatures are on file in the Graduate School
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.
# TABLE OF CONTENTS

LIST OF SCHEMES ........................................................................................................ iv
LIST OF FIGURES ........................................................................................................ vi
LIST OF TABLES ........................................................................................................ vii
ACKNOWLEDGEMENTS ............................................................................................... viii

## Chapter 1  Introduction ............................................................................................ 1

1.1 The Pummerer Reaction ......................................................................................... 1

1.1.1 History/Discovery .............................................................................................. 1

1.1.2 Pummerer Chemistry Developed in the Feldman Group .................................... 2

1.2 Palau’amine ........................................................................................................... 8

1.3 Palau’amine model system chemistry .................................................................... 15

## Chapter 2  Synthesis of the syn and anti Five-Membered and the anti Six-
Membered Ring Cyclization Precursors and Their Cyclization Trials ..................... 21

2.1 The Syn Five-Membered Cyclization Precursor and its Cyclization ..................... 21

2.2 The Anti Fve-Membered Ring Cyclization Precursor and its Cyclization ............. 29

2.3 The Anti Six-Membered Cyclization Precursors .................................................. 32

## Chapter 3  Experimental ........................................................................................ 37

Bibliography ................................................................................................................. 71
LIST OF SCHEMES

Scheme 1 An early example of a Pummerer reaction ........................................... 2

Scheme 2 Feldman’s Pummerer-based Approach to 3,3-spiro cyclic-2-(phenylthio) indolenines ................................................................. 4

Scheme 3 Feldman’s Pummerer based strategy for the syntheses of 3,3-spiro cyclic-2-(phenylthio) indolenines ........................................................................................................... 6

Scheme 4 A PhI(CN)OTf-mediated Pummerer cyclization on an imidazole sulfide substrate .................................................................................................................. 7

Scheme 5 Proposed biosynthesis of the original structure of palau’amine (27) ....... 10

Scheme 6 Romo’s synthesis toward a palau’amine-like spirocyclic core structure 45 ......................................................................................................................... 11

Scheme 7 Conversion of intermediate 46 into diastereomeric palau’amine derivatives 62 and 63 ................................................................................................................. 14

Scheme 8 Conversion of sceptrin 64 into ageliferin 65 ................................................. 14

Scheme 9 Sceptrin 64 as a biosynthetic precursor to palau’amine 30 ................. 15

Scheme 10 A mechanistic outline for the synthesis of pentacyclic derivative 28/75 ................................................................................................................................. 17

Scheme 11 Parallel syntheses of pentacyclic derivative 28/75, 77, 79, and 81 ....... 19

Scheme 12 .................................................................................................................. 20

Scheme 13 Preparation and reduction of disubstituted cyclopentenes 97, 98, and 99 ......................................................................................................................... 22

Scheme 14 Opening of epoxide 100 under basic conditions ..................................... 23

Scheme 15 Direct Heck coupling between cyclopentanone (102) and halogenide 105 and 106 .................................................................................................................. 24

Scheme 16 Stille coupling between 2-Chlorocyclopentanone (107) and stannane 92 ......................................................................................................................... 24

Scheme 17 Ireland Claisen approach to from methylene cyclopentane 114 ........... 25
Scheme 18 A precedent from Kato et al. and its application to form cyclopentanone 117. 26

Scheme 19 The preparation of syn five-membered cyclization precursor 71. 27

Scheme 20 The cyclization of syn five-membered precursor 71. 28

Scheme 21 The preparation of anti five-membered cyclization precursor 76. 30

Scheme 22 The cyclization of the anti five-membered precursor 76. 31

Scheme 23 The preparation of dienes and dienophiles for the test of Diels-Alder reaction. 34

Scheme 24 The best result of the Diels-Alder reaction chemistry. 35

Scheme 25 The preparation of anti six-membered cyclization precursor 139. 36

Scheme 26 The hydrogenation and functional group manipulation of 136. 36
LIST OF FIGURES

**Figure 1** Palau’amine originally assigned structure (14) and related model compounds 15 and 16 ................................................................. 9

**Figure 2** Reassigned tetrabromostyloguanidine (31) and palau’amine (32). ........ 9

**Figure 3** nOe effect in compounds 28 and 75. ......................................................... 29

**Figure 4** The energy difference between the syn and anti pentacyclic system. .... 32

**Figure 5** The energy difference between the syn and anti pentacyclic system. .... 33
LIST OF TABLES

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

.................................................................35
ACKNOWLEDGEMENTS

First at all, I would like to address my gratefulness to Dr. Kenneth Feldman, my supervisor, whose constructive instructions and constant support accompanied me throughout my graduate study. Also I would like to address particular thanks to my committee members, Dr. Harry Allcock, Dr. Raymond, Funk and Dr. Squire Booker for reading my reports and guilding my study.

Many thanks for technical support received from Li Zhang and James Miller (mass spectroscopy), Alan Benesi (NMR), Evelyn Bradley (IT support), Vince Musumeci (stock room).

Thank you to everyone who worked with me in the Feldman Group. Working with your guys made the lab days so joyful.

I would like to say “thank you” to everyone working for the Chemistry Graduate Program and Chemistry Department for all the academic and social events we have shared.

Finally, I would like to address my sincere thanks to all my friends in State College.

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). 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(+)=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.

\[ \text{PhS}^+\text{CO}_2\text{H} \xrightarrow{\text{HCl}, \text{H}_2\text{O}} \begin{array}{c} \text{PhS}^-\text{CO}_2\text{H} \\ \text{PhS}^+\text{SO}_2\text{H} \end{array} \xrightarrow{\text{H}_2\text{O}} \text{PhS}^+\text{SO}_2\text{H} \xrightarrow{\text{HCO}_2\text{H}} \text{PhS}^+\text{SO}_2\text{H} \]

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. 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$_2$O activation to furnish the 3,3-spiro cyclic-2-
(phenylthio)indolenine product 7 (Scheme 2). A representative mechanism via
either a vinylogous or additive pathway is illustrated below.
Representative mechanism:

Path B: additive Pummerer
- direct $S_N2'$-like displacement

Path A: vinylogous Pummerer
- base-HOR

Hydrolysis
Scheme 2 Feldman’s Pummerer-based Approach to 3,3-spiroyclic-2-(phenylthio)indolenines.

The Feldman group not only used a classical Pummer activator (Tf₂O) 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 cyclization product 15 via a vinylogous or additive pathway (Scheme 3).
Representative mechanism:

Path A: vinylogous Pummerer

Path B: additive Pummerer
direct $S_N^{2'}$-like displacement
Scheme 3  Feldman’s Pummerer based strategy for the syntheses of 3,3-spiro cyclic-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). 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 applied to the palau’amine synthesis 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. 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. 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.
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. 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). 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). This synthesis started with perbenzylation of imidazolone 37. Then, a DIBAl-H reduction of the ester and MnO₂ 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 °C 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 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.
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). He also proposed that sceptrin might be a potential biosynthetic precursor to other complex pyrrole-imidazole alkaloids including palau’amine because of its extremely high concentration in organisms that produce this family of natural products.

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). 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 pentacyclic 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 \textit{79/81} compared to the trans 5-5 bicyclic core of \textit{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). However, reduction of the tetrasubstituted double bonds in 97, 98 and 99 was not successful under various conditions including Crabtree catalytic hydrogenation, diimine-mediated hydrogenation, hydroboration/protonolysis, and ordinary catalytic hydrogenation procedures.
Attempts to open epoxide (100) with organometallic reagents were also pursued as a strategy to connect the cyclopentene moiety and imidazole nucleus.\textsuperscript{18} The result in all instances was the recovery of starting material.

1) -78 °C to 25 °C  
2) BF\textsubscript{3} Et\textsubscript{2}O, -78 °C to 25 °C  
3) CuCN, -78 °C to 25 °C  
4) (-) Sparteine, BF\textsubscript{3} Et\textsubscript{2}O, -78 °C to 25 °C  

No reaction

\textbf{Scheme 13} Preparation and reduction of disubstituted cyclopentenes 97, 98, and 99.
**Scheme 14** Opening of epoxide 100 under basic conditions.

Inspired by a successful direct Heck coupling between cyclopentanone (102) and 2-bromoiodobenzene (103), a similar approach was employed to connect cyclopentanone (102) with the imidazole moiety. Bromide 105 and iodide 106 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).
Scheme 15 Direct Heck coupling between cyclopentanone (102) and halogenide 105 and 106.

\[
\begin{align*}
\text{Condition 1: LiCl, CuCl, Pd(PPh}_3)_4, \\
\text{DMSO, Cs}_2\text{CO}_3, 2\text{h.} \\
\text{Condition 2: Pd(PPh}_3)_2\text{Cl}_2, \text{DMF, 70 }^\circ\text{C, 16 h.} \\
\text{Decomposition}
\end{align*}
\]

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. In order to explore this route to access methylenecyclopentane 114, several procedures were employed to generate ketene acetal 113 (Scheme 5). Carboxylic acid 108 was prepared from imidazole 91 and was coupled with alcohol 110 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). 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.

Methylene cyclopentane 119 was prepared from 118 by using the Tebbe-Petasis reagent (Cp₂TiMe₂) 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 methylene cyclopentane 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 NH₂NH₂ 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 BF₃·Et₂O followed by overnight heating with 1M Bu₄NF 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 Pummerer 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, $H_a$ 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, $H_c$ 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 Five-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, DBU-catalyzed isomerization and NaBH₄ 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 SiO₂ column run at -78 °C. 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.

![Diagram of the cyclization of the *anti* five-membered precursor 76.](image)

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

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.
A Diels-Alder reaction 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 shown 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).
Starting Materials | Conditions | Result
--- | --- | ---
134 + 132 | 200 °C, Toluene, 48 h | No Reaction
134 + 132 | Microwave, 200 W, 30 mins. | Decomposition
134 + 132 | Lewis Acid: BF₃, InCl₃, Sc(OTf)₃, MeAlCl₂ | No Reaction
134 + 82 | 200 °C, Toluene, 48 h | No Reaction
134 + 82 | Microwave, 200 W, 30 mins. | Decomposition
134 + 82 | Lewis Acid: MeAlCl₂ | No Reaction
135 + 82 | 200 °C, 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](image)

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 LiAlH₄ (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
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 °C for 30 min, warmed up to 25 °C, and then SEMCl (1.60 mL, 8.80 mmol) was added drop-wise 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 NH₄Cl solution (20 mL) and water (10 mL) were added to quench the excess n-BuLi and then the solution was extracted with Et₂O (3×100 mL). The organic layers were combined, dried over MgSO₄, and evaporated under reduced pressure to give a yellow oil. The yellow oil was purified by SiO₂ 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
2-[2-Phenylsulfanyl-3-(2-trimethylsilanyloxyethyl)-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 °C 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 °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 SiO₂ 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, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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 [C₂₀H₂₉N₂O₂SiS]⁺, 389.1719; found, 389.1704.
5-(2-Methylene-cyclopentyl)-2-phenylsulfanyl-1-(2-trimethylsilyl-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 (Cp₂TiMe₂, 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 SiO₂ flash column chromatography (hexane, 10 % Et₂O/hexane as eluent) to give 119 (0.57 g, 80%) as a yellow oil: IR (thin film) 1650 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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 [C₂₁H₃₁N₂OSiS]⁺, 387.1926; found, 387.1905.
{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 °C and the reaction mixture was held at 25 °C for 10 h. A solution of Na2O2 (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 Et2O and water and the aqueous layer was extracted with Et2O (3×20 mL). The organic layers were combined, dried over Na2SO4, and concentrated in vacuo to give a yellow oil. The yellow oil was purified by SiO2 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, CDCl3) 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); ¹³C NMR (major isomer, 75 MHz, CDCl3) 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 [C21H33N2O2SiS]⁺, 405.2032; found, 405.2051.
2-{2-[2-Phenylsulfanyl-3-(2-trimethylsilanyloxyethyl)-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 Ph₃P (0.0610 g, 0.233 mmol) in THF (3 mL) at 0 °C 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 °C 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 °C for 10 h. After reaction was determined to be complete by TLC, the reaction solution was partitioned between Et₂O and water and the aqueous layer was extracted with Et₂O (3×10 mL). The organic layers were combined, dried over Na₂SO₄, and concentrated in vacuo to give a colorless oil. The colorless oil was purified by SiO₂ 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, CDCl₃) 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); ¹³C NMR (major, isomer, 75 MHz, CDCl₃) 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_{3}O_{3}SiS]^+, 534.2247; found, 534.2261
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 °C 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 Et₂O and water and the aqueous layer was extracted with Et₂O (3×10 mL). The organic layers were combined, dried over Na₂SO₄, 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 Na₂CO₃ (0.0192 g, 0.179 mmol) were added to this solution at 25 °C and the reaction mixture was held at 25 °C for 20 h. After removal of the solvent, the organic residue was partitioned between CH₂Cl₂ and water and the aqueous layer was extracted with CH₂Cl₂ (3×10 mL). The organic layers were combined, dried over Na₂SO₄, and concentrated in vacuo to give a colorless oil. The colorless oil was purified by flash column chromatography (CH₂Cl₂ then 10-20% Et₂O/CH₂Cl₂ as eluent) to give 123 (0.064 g, 55%) as a colorless oil: IR (thin film) 3116, 1631 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) 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$_3$) $\delta$ 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$_2$N$_4$O$_2$SiS]$^+$, 653.0617; found, 653.0644.
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, BF₃·Et₂O (0.111 mL, 0.882 mmol) was added slowly into a solution of 123 (0.144 g, 0.220 mmol) in CH₂Cl₂ (10 mL) at 0 °C and the reaction mixture was warmed to 25 °C 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 Na₂SO₄, 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 Bu₄NF solution in THF (1M, 2.25 mL, 2.25 mmol) were sequentially added into this solution at 25 °C 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 Na₂SO₄, and concentrated in vacuo to give a yellow solid. The yellow solid was purified by SiO₂ flash column chromatography (CH₂Cl₂ then 10-30% Et₂O/ CH₂Cl₂ as eluent) to give 71 (0.098 g, 85%) as a white solid. m.p. = 207-209 °C (decomposition); IR (thin film) 3117, 1623 cm⁻¹; ¹H NMR (300 MHz, CD₃OD) 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$_3$OD) $\delta$ 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$_2$Br$_2$N$_4$OS]$^+$, 522.9803; found, 522.9796.
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 CH₂Cl₂ (20 mL) at 25 °C. 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 CH₂Cl₂ (3×20 mL). The organic layers were combined and concentrated under reduced pressure to give a yellow oil. The yellow oil was purified by SiO₂ flash column chromatography (10-30% EtOAc/hexane as eluent) to give 124 (0.66 g, 79%) as a yellow oil. The crude product was carried on to the next step.
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 CH₂Cl₂ (15 mL) at 0 °C 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 CH₂Cl₂ (3×15 mL). The organic layers were combined, dried over Na₂SO₄, 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. ¹H NMR (300 MHz, CDCl₃) 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.
[2-[2-Phenylsulfanyl-3-(2-trimethylsilanyl-ethoxymethyl)-3H-imidazol-4-yl]-cyclopentyl]-methanol (126). In a 50 mL round-bottom flask, NaBH₄ (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 °C 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 Et₂O and partitioned between Et₂O and water. The aqueous layer was extracted with Et₂O (3×15 mL) and the organic fractions were combined, dried over Na₂SO₄ and concentrated under reduced pressure to give a colorless oil. The colorless oil was purified by SiO₂ 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, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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 [C₂₁H₃₃N₂O₂SiS]⁺, 405.2032; found, 405.2034.
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 Ph₃P (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 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 °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 the reaction was determined to be complete by TLC, the reaction solution was partitioned between Et₂O and water and the aqueous layer was extracted with Et₂O (3×10 mL). The organic layers were combined, dried over Na₂SO₄, and concentrated under reduced pressure to give a colorless oil. The colorless oil was purified by SiO₂ 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, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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_{3}O_{3}SiS]^+, 534.2247; found, 534.2242.
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 °C 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 Et₂O and water and the aqueous layer was extracted with Et₂O (3×10 mL). The organic layers were combined, dried over Na₂SO₄, 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 Na₂CO₃ (0.043 g, 0.40 mmol) were added into this solution at 25 °C 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 CH₂Cl₂ and water and the aqueous layer was extracted with CH₂Cl₂ (3×10 mL). The organic layers were combined, dried over Na₂SO₄, and concentrated under reduced pressure to give a colorless oil. The colorless oil was purified by SiO₂ flash column chromatography (CH₂Cl₂ then 10-30% Et₂O/CH₂Cl₂ 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$_3$) $\delta$ 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$_{33}$Br$_2$N$_4$O$_2$SiS]$^+$, 653.0617; found, 653.0606. One carbon signal was not observed due to overlap with another signal in the aromatic range.
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, BF₃·Et₂O (0.0360 mL, 0.289 mmol) was added slowly to a solution of 129 (0.0472 g, 0.0721 mmol) in CH₂Cl₂ (3 mL) at 0 °C and the reaction mixture was warmed to 25 °C 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 Na₂SO₄, 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 Bu₄NF solution in THF (1M, 100 mL, 1.00 mmol) were sequentially added to this solution at 25 °C 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 Na₂SO₄, and concentrated under reduced pressure to give a yellow solid. The yellow solid was purified by flash column chromatography (CH₂Cl₂ then 10-30% Et₂O/ CH₂Cl₂ as eluent) to give 76 (0.025 g, 66%) as a white solid. m.p. = 216-218 °C (Decomposition); IR (thin film) 3095, 1602 cm⁻¹; ¹H NMR (300 MHz, CD₃OD) 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$_3$OD) $\delta$ 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$_2$N$_4$OS]$^+$, 522.9803; found, 522.9793. One hydrogen signal was not observed due to overlap with the MeOH peak.
Pummerer Pentacycles 28 and 75. In a 25 mL round-bottom flask, (i-Pr)\textsubscript{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\textsubscript{3}OH/CH\textsubscript{2}Cl\textsubscript{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)\textsubscript{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\textsubscript{2}Cl\textsubscript{2} and water and the aqueous layer was extracted with CH\textsubscript{2}Cl\textsubscript{2} (3×10 mL). The organic layers were combined, dried over Na\textsubscript{2}SO\textsubscript{4}, and concentrated under reduced pressure to give a colorless oil. The colorless oil was purified by SiO\textsubscript{2} flash column chromatography (CH\textsubscript{2}Cl\textsubscript{2} then 10-30% Et\textsubscript{2}O/ CH\textsubscript{2}Cl\textsubscript{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\textsuperscript{-1}; \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) \textsuperscript{δ} 7.51-7.40 (m, 5H), 6.98 (s, 1H), 5.70 (s, 1H), 5.46 (s, 1H), 4.26 (dd, \textit{J} = 11.9, 9.2 Hz, 1H), 3.32 (dd, \textit{J} = 11.8, 6.9 Hz, 1H), 2.96 (m, 1H), 2.79 (m, 1H), 1.79-1.21 (m, 6H); \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}) \textsuperscript{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\textsuperscript{+}); HRMS (ESI) m/z calcd for [C\textsubscript{20}H\textsubscript{19}Br\textsubscript{2}N\textsubscript{4}OS]\textsuperscript{+}, 520.9646; found, 520.9624.
75, IR (thin film) 3201, 1654 cm\(^{-1}\); \(^1\)H 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\(_2\)N\(_4\)OS]\(^+\), 520.9646; found, 520.9662.
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, 76.1 mmol) 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 °C 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 NaHCO₃ (150 mL) was added and the aqueous layer was extracted with Et₂O (3 × 200 mL). The organic layers were combined, dried over Na₂SO₄, 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 °C 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 °C, held at that temperature for 30 min, and then cooled to -40 °C. 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 °C for 1 h, warmed to 25 °C 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 Et₂O and water and the aqueous layer was extracted with Et₂O (3 × 300 mL). The organic layers were combined, dried over Na₂SO₄, and evaporated under reduced pressure to give a
brown oil which was purified by SiO\textsubscript{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\textsuperscript{-1}; \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) \(\delta\) 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); \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}) \(\delta\) 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\textsuperscript{+}); HRMS (ESI) m/z calcd for [C\textsubscript{18}H\textsubscript{26}N\textsubscript{3}O\textsubscript{2}SiS]\textsuperscript{+}, 376.1515; found, 376.1503.
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 °C for 120 hours. The autoclave was cooled to 25 °C 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 Na₂SO₄, and evaporated under reduced pressure to give a yellow solid which was purified by SiO₂ 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 °C; IR (thin film) 3318, 3176, 1672, 1480 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) 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 = 10.7 Hz, 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); ¹³C NMR (75 MHz, CDCl₃) 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 [C₂₂H₃₂N₃O₂SiS]⁺, 430.1985; found, 430.1974. One carbon signal was not observed in the aromatic range due to overlap with another signal.
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 POCl₃ (0.0870 mL, 0.931 mmol) in CH₃CN (2.5 mL) was cooled to 0 °C and Et₃N (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 °C 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 CH₃CN (3×5 mL). The organic fractions were combined and concentrated under reduced pressure. The organic residue was dissolved in CHCl₃ and partitioned between CHCl₃ and aqueous NaHCO₃ solution. The aqueous layers were combined and extracted with CHCl₃ (3×5 mL). The combined organic phases were dried over Na₂SO₄ and evaporated under reduced pressure to give a colorless oil which was purified by SiO₂ flash column chromatography (10-40 % Et₂O/hexane as eluent) to give 137 (0.038 g, 80%) as a colorless oil. IR (thin film) 2210 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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_{3}OSiS]^⁺, 412.1879; found, 412.1865.
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$_2$O (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$_2$O/THF (15 mL) at 0 °C 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$_2$SO$_4$ 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$_2$CO$_3$ (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$_2$Cl$_2$ and water and the aqueous layer was extracted with CH$_2$Cl$_2$ (3×10 mL). The organic layers were combined, dried over Na$_2$SO$_4$, and
concentrated under reduced pressure to give a colorless oil. This oil was purified by SiO₂
flash column chromatography (CH₂Cl₂ then 40% Et₂O/ CH₂Cl₂ 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, CDCl₃) 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); ¹³C NMR
(75 MHz, CDCl₃) 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 [C₂₇H₃₅Br₂N₄O₂Si]⁺, 665.0617; found, 665.0617. One carbon signal was not observed in
the aromatic range due to overlap with another signal.
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$_2$SO$_4$ 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 °C; IR (thin film) 3296, 1676 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 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$_3$) $\delta$ 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_{3}O_{2}SiS]⁺, 432.2141; found, 432.2112.
2-[2-Phenylsulfanyl-3-(2-trimethylsilanyl-ethoxymethyl)-3H-imidazol-4-yl]-cyclohexanecarbonitrile (141). In a 50 mL flame-dried Schlenk flask, a solution of POCl₃ (0.232 mL, 2.49 mmol) in CH₃CN (25 mL) was cooled to 0 °C and Et₃N (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 °C 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 CH₃CN (3x20 mL). The organic fractions were combined and concentrated under reduced pressure. The organic residue was dissolved in CHCl₃ and partitioned between CHCl₃ and aqueous NaHCO₃ solution. The aqueous layers were combined, extracted with CHCl₃ (3x20 mL), dried over Na₂SO₄, and evaporated under reduced pressure to give a colorless oil which was purified by SiO₂ flash column chromatography (20-40 % Et₂O/hexane as eluent) to give 141 (0.070 g, 55%) as a colorless oil IR (thin film) 2215 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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.
Bibliography


