DISSERTATION

THE SYNTHESIS OF THE PENTACYCLIC CARBON FRAMEWORK OF THE PF1270 FAMILY OF NATURAL PRODUCTS

Submitted by

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ABSTRACT

SYNTHESIS OF THE PENTACYCLIC CARBON FRAMWORK OF THE PF1270 FAMILY OF NATURAL PRODUCTS

The PF1270 family of natural products contains novel indole alkaloids that display interesting biological activity; the synthesis of these natural products and their analogs could lead to the discovery of novel therapeutics. Discussed herein is the synthesis of the complete pentacyclic carbon framework of the PF1270s, accomplished through a key intermolecular Diels-Alder reaction. Other highlights of the synthesis include an acid catalyzed opening lactim ether at a late stage, and a particularly difficult decarboxylation promoted by diphenylphosphoryl azide.

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Chapter 1: Introduction to the PF1270s and Related Natural Products

1.1 PF1270 Family of Natural Products

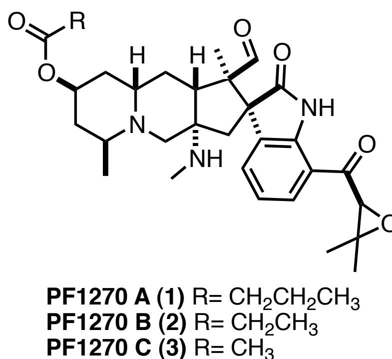


Figure 1: Structures of PF1270 A, B, and C.

Histamine is a biogenic amine that has a number of physiological functions and is found in several types of mammalian tissue. In 1983, Arrang *et al.* identified histamine receptors (H3Rs) in the brain and peripheral tissue.[1] It was later determined that H3Rs in the brain act as autoreceptors, controlling the synthesis and release of histamine, and as heteroreceptors, controlling the release of the neurotransmitters serotonin, noradrenalin and dopamine.[2,3,4] Developing a novel synthesis of selective H3R inhibitors and their analogs could lead to the development of therapeutic agents for diabetes, obesity, cognitive disorders, depression, epilepsy and sleeping disorders. Three H3R inhibitors, PF1270 A, B, and C (Figure 1), were isolated from the broth of a *Penicillium waksmanii* strain, found in a soil sample from Shimane Prefecture, Japan in 2007 by Kushida *et al.* PF1270 A, B, and C have EC_{50} values of 0.12, 0.15 and 0.20 μM, respectively.[5] To date there is no record of any biosynthetic studies and as a result little is known about the biosynthetic origin of PF1270 A, B, and C. Also, to date no total or

partial synthesis has been reported. Herein we will discuss the isolation, structural characterization and biological activity of the PF1270 family of natural products.

1.1.1 Isolation

Three novel compounds, PF1270 A (**1**), B (**2**) and C (**3**), were isolated and characterized by Kushida *et al.* in 2007 from fungal strain PF1270. The PF1270 strain was isolated from a soil sample collected in Shimane Prefecture, Japan and was identified to be *Penicillium waksmanii* by morphological characteristics.[5]

Fifteen 100 mL Erlenmeyer flasks which each contained a solution of seed medium was sterilized and then used. The medium consisted of glucose (1.0%), soluble starch (2.0%), yeast extract (0.3%), polypeptone (0.5%), soybean meal (0.2%), wheat germ (0.6%), and $CaCO_3$ (0.2%) in deionized water. The aqueous solution was adjusted to pH 7.0 by addition of NaOH. After sterilization a slant culture of the PF1270 strain was used to inoculate the fifteen Erlenmeyer flasks. These flasks were then incubated at 25°C for 72 hours with shaking at 220 rpm. After the allotted time period, 3.0 mL of the seed culture was transferred to 500 mL Erlenmeyer flasks (100) which contained soybean meal (2.5%) and 100 grams of rice that was soaked in water. Each flask was stirred once and then kept static at 25°C for an additional 14 days. Once finished, the resulting 10 kg portion was then extracted with 20 liters of aqueous acetone (67%). The filtrate was concentrated to remove the acetone and then the pH raised to 7.0 with 1N NaOH. The aqueous solution was then run on a DIAON HP-20 column. The column was rinsed with 3 liters of water, 3 liters aqueous acetone, and then 3 liters acetone sequentially. To the resulting acetone eluent was added an

additional 3 liters of water and the resulting solution was then concentrated under reduced pressure. Finally, the resulting aqueous solution was basified to a pH of 9 with 1N NaOH. The aqueous was then extracted with an equal amount of ethyl acetate and the organic phase was concentrated under reduced pressure to afford 3.7 grams of crude extract. This extract was purified further by silica gel column chromatography. Three different columns were run on the crude extract. The first two were eluted with hexanes and EtOAc and the final column was eluted with chloroform and methanol. The fractions that contained PF1270 A, B and C were then purified using both preparative TLC and preparative HPLC. After purification 70.2 mg of A (**1**), 17.0 mg of B (**2**) and 6.0 mg of C (**3**) were isolated.[5]

1.1.2 Structural Characterization

Kushida and coworkers used standard spectroscopic analysis and X-ray crystallographic data to establish the relative stereochemistry and to elucidate the structure of the PF1270s. PF1270 A (**1**) was characterized by ^{1}H-NMR, ^{13}C-NMR, ^{1}H-COSY, HSQC, and HMBC. The molecular formula was established as $C_{32}H_{43}N_3O_6$ by HR-FAB-MS. Also, the relative configuration was established by X-ray crystallographic analysis. PF1270 B (**2**) and C (**3**) were characterized by ^{1}H-NMR, and ^{13}C-NMR. The molecular formulas were established as $C_{31}H_{41}N_3O_6$ and $C_{30}H_{39}N_3O_6$ respectively by HR-FAB-MS. These three natural products possess the same pentacyclic spirooxidole framework, and each posses the unique epoxycarbonyl side chain. The only difference in the structure is located on the acyl side chain of the pipecolic acid moiety. A (**1**)

possess a propyl group, B (**2**) possesses a ethyl group and C (**3**) possesses a methyl group.[5]

1.1.3 Biological Activity

In addition to their interesting molecular framework, the PF1270 natural products possess interesting biological activity. This family of natural products does not exhibit any antimicrobial activities. All three natural products displayed high affinity for both rat and human H3Rs. Like naturally occurring histamine, most H3R ligands possess an imidazole ring. This correlation to structure activity relationship is present in both agonist and antagonist ligands. Therefore, it is surprising that **1**, **2** and **3** are all H3R agonists. As shown in Table 1, the *Ki* values for rat H3R were 0.058, 0.17, and 0.19 μM, respectively. The *Ki* values for human H3R were 0.047, 0.12, and 0.22 μM, respectively. All of these compounds acted as potent agonists with EC_{50} values of 0.12, 0.15 and 0.20 μM, respectively.[5]

Table 1: Binding affinity (*Ki*) and potency (EC_{50}) of **1**, **2**, and **3**.

Compound	Rat H3R *Ki* (μM)	Human H3R *Ki* (μM)	Human H3R EC_{50} (μM)
1	0.058	0.047	0.12
2	0.17	0.12	0.15
3	0.19	0.22	0.20

1.2 Citrinadins

Citrinadin A (**4**) and B (**5**) bear a striking structural resemblance to the PF1270 family. In 2004, Kobayashi and coworkers isolated citrinadin A (**4**) from *Penicillium citrinum,* which was cultured from marine red alga *Actinotrichia fragilis*.[6] Then in 2005, Kobayashi and coworkers isolated citrinadin B (**5**) in a similar fashion.[7] It should be

noted that after the synthesis of citrinadin B by Wood *et al.*[8] and the synthesis of citrinadin A by Martin *et al.*[9] the original stereochemical structure was revised. The revised stereochemical configuration now aligns with the PF1270s and is shown in Figure 2.

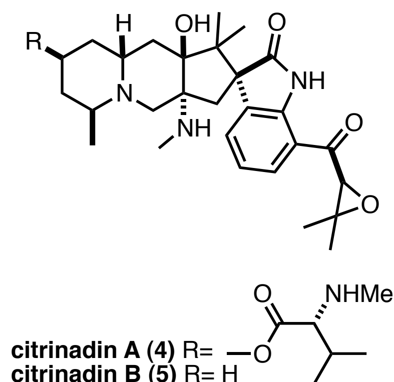


Figure 2: Structures of citrinadin A (**4**) and citrinadin B (**5**).

Noticeably, the citrinadins contain the same pentacyclic sprioxindole core and the same epoxycarbonyl side chain as the PF1270s. The citrinadins also possess noteworthy biological activity. Both **4** and **5** demonstrated activity against epidermoid carcinoma KB cells (IC_{50} 10 μg/mL), and against murine leukemia L1210 cells (IC_{50} 6.2 μg/mL and 10 μg/mL respectively).[6,7] Although structurally similar, **1-3** have not been tested for analogous cytotoxic activity. Which may be due to the fact that only way to access these natural products is by isolation because no total synthesis has been reported. Natural product isolation is notoriously difficult and can only provide small quantities of **1-3** for biological testing.

1.3 Other Structurally Related Natural Products

Many other natural products containing the spirooxindole moiety have been previously isolated. Such secondary metabolites include the brevianamides[10-12],

paraherquamides[13-17], the notoamides[18-20] and the marcfortines[21-23], which have been isolated from various *Penicillium* and *Aspergillus* fungi. (Figure 3) These natural metabolites encompass a broad range of bioactivities including insecticidal, antitumor, anthelmintic, antiparasitic and antibacterial properties. While the biosynthesis of the PF1270s remains a mystery, extensive research has been done on the synthesis and biosynthesis of these natural products.[24-25] Furthermore, copious research has been done by Williams *et al.* to elucidate the biosynthesis of the paraherquamides.[26-28] The complex amino acid structure found in these natural products is comprised of tryptophan unit, a cyclic amino acid unit, and one or two isoprene units.

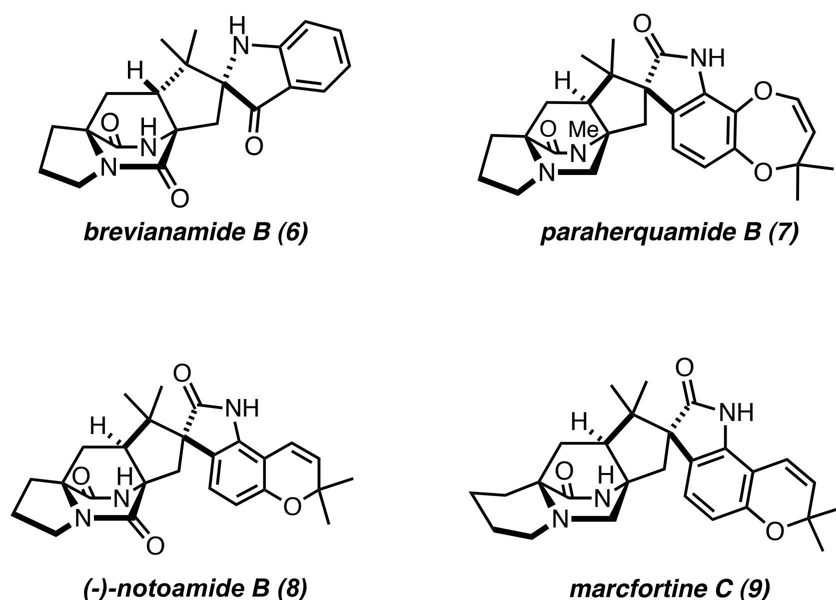


Figure 3: Structures of members of the brevianamide, paraherquamide, notoamide and marcfortine families of indole alkaloids.

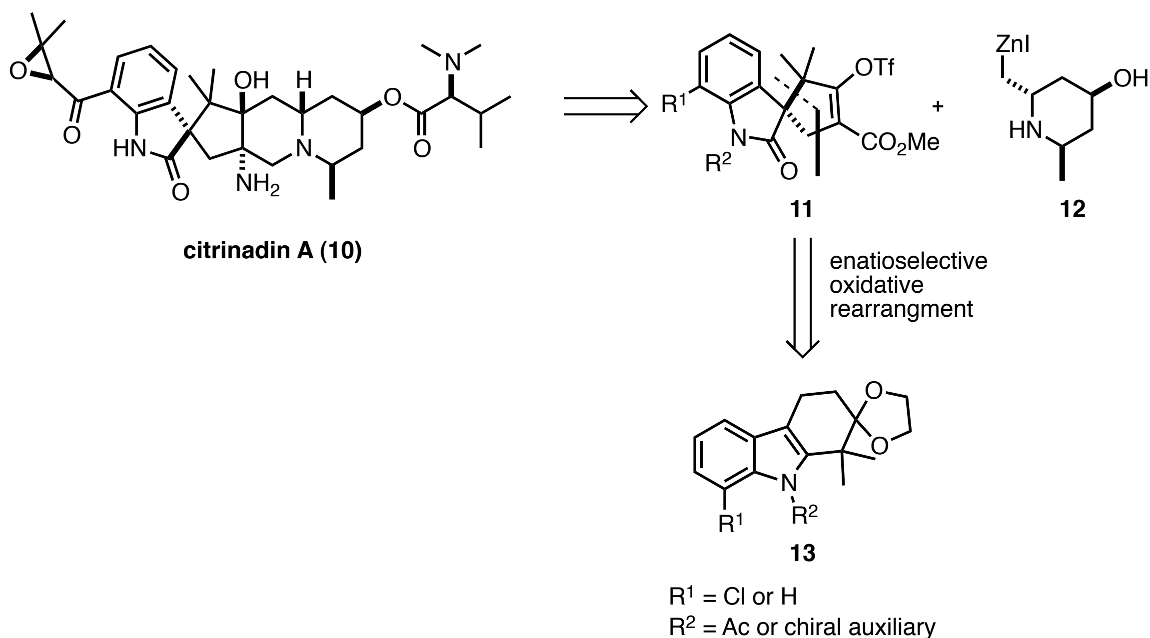
Chapter 2: Previous Synthetic Efforts

2.1 Introduction

To date, no total synthesis of the PF1270s has been reported. Both the PF1270s and citrinadins have been the focus of interest in the synthetic community due to their interesting molecular scaffold, as well as their interesting biological activities. Since the isolation of the PF1270s and citrinadins, there have been a number of different synthetic studies towards the pentacyclic core present in both of these natural products. In addition, the first total synthesis of both citrinadin A and citrinadin B were recently reported. Below is a discussion on the relevant syntheses that have been reported to date.

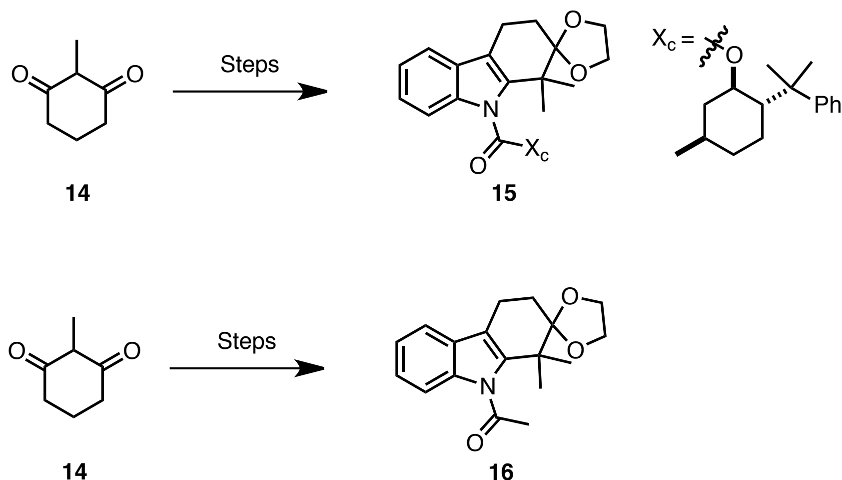
2.2 Martin Group Spirooxindole Synthesis

Martin *et al.*[28] envisioned the spirooxindole moiety arising from an enantioselective oxidative rearrangement, initially reporting the synthesis prior to reassignment of the citrinadin A stereochemistry.[29] They hypothesized that citrinadin A could arise from a Negishi coupling of triflate **11** with pipecolinic **12**, in which they envisioned that **11** could arise from a key enantioselective oxidation rearrangement of indole **13**. The enantioselectivity of the spirooxindole was proposed to arise from either epoxidation of indole **13** with a chiral dioxirane, or through facial selectivity that would arise from the use of a chiral auxiliary (R^2) attached to the indole nitrogen. (Scheme 1)



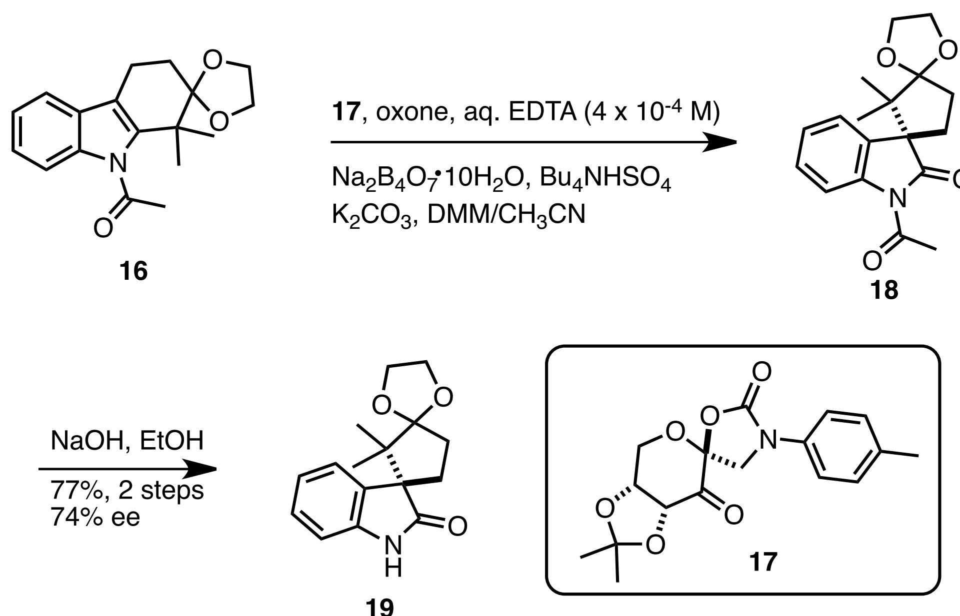
Scheme 1: Martin's retrosynthetic approach to citrinadin A (**10**).

To test this hypothesis **15** and **16** were synthesized in five steps from diketone **14**. Intermediate **16** was used to test the asymmetric epoxidation approach, while **15** was used to test the chiral auxiliary approach. Both of these intermediates were then used to screen conditions for the enantioselective oxidative rearrangement.



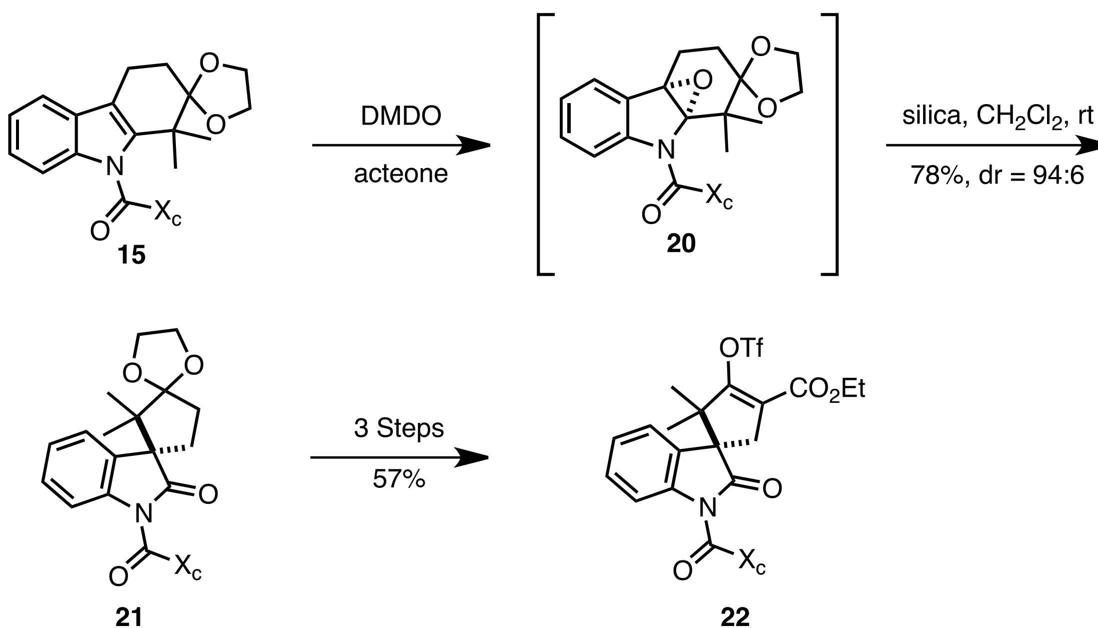
Scheme 2: Preparation of intermediates **15** and **16** for oxidation.

First, intermediate **16** was submitted to standard Shi asymmetric epoxidation conditions.[30-32] Initial treatment of **16** with D-epoxone was low yielding and showed no asymmetric induction; however, treatment of **16** with related *N*-aryloxazolidinone,[33] followed by deprotection of the *N*-acetyl, gave **19** in 77% yield over both steps and 74% ee. (Scheme 3)



Scheme 3: Enantioselective oxidative rearrangement of **16**.

A concurrent approach utilizing a chiral auxiliary was also investigated. To start, intermediate **15** was treated with DMDO in acetone. Upon purification of epoxide **20** using column chromatography, small amounts of spirooxindole **21** were observed. The authors used this to their advantage, and upon stirring epoxide **20** over silica using DCM as the solvent, they observed full conversion to **21**. The authors confirmed that absolute stereochemistry of the spirocenter matched **10** by X-ray crystallography. Finally, **21** was readily converted to **22** in 3 steps and 57% yield. (Scheme 4)



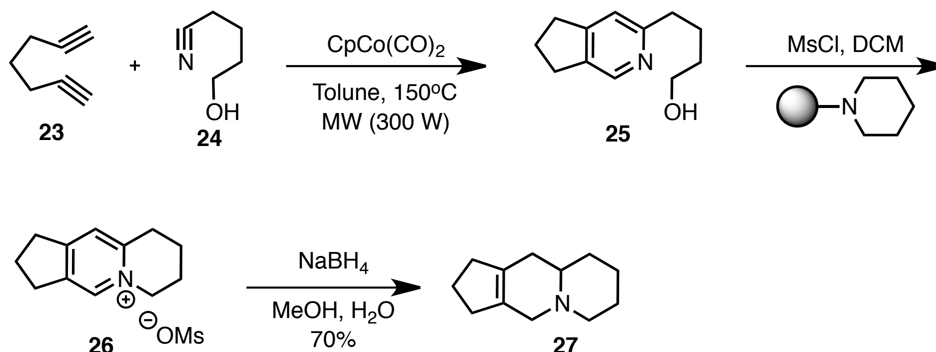
Scheme 4: Diastereoselective oxidation of **15**.

Martin and co-workers were the first to devise a synthesis for the citrinadin family of natural products. They achieved the first reported enantioselective oxidative rearrangement of an indole intermediate to a spirooxindole. Furthermore, they were the first group to develop and report the synthesis of the spirocenter present in citrinadin A.

2.3 Deiters Group Synthesis of the Tricyclic Core

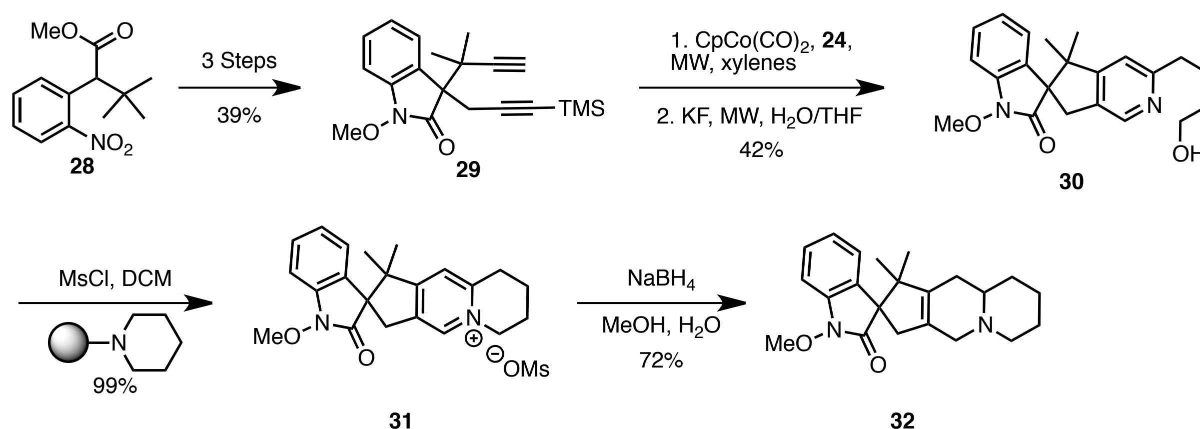
In 2010, Deiters and co-workers[34] developed a two-step [2 + 2 + 2] cyclotrimerization-substitution reaction that was used to synthesize the pentacyclic core of the citrinadins and the PF1270s. First, using commercially available starting materials, they screened reaction conditions. They started by submitting diyenes **23** and **24** to cyclotrimerization conditions. With the use of $CpCo(CO)_2$ catalyst in toluene under microwave irradiation alcohol **25** was synthesized, and immediately converted to the desired mesylate **26**. To accomplish this transformation with out the need of purification, they used MsCl in DCM and a polymer bound piperidine base. Finally, **26** was readily

converted to **27** by treatment with $NaBH_4$ in MeOH and H_2O in excellent yields. (Scheme 5)



Scheme 5: Two-step [2 + 2 + 2] cyclotrimerization-substitution reaction. Followed by reduction to form tricyclic **27**.

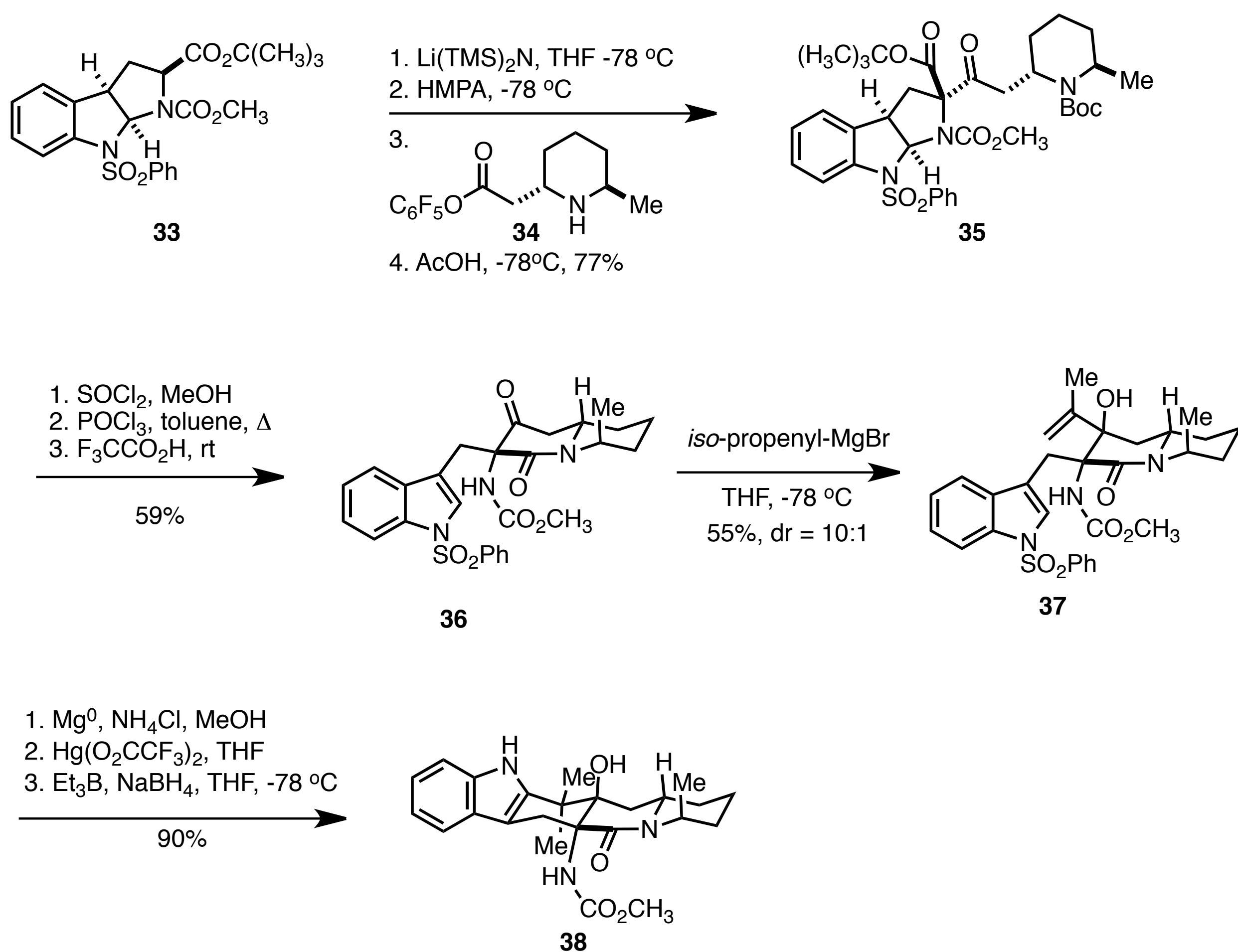
Deiters and co-workers then synthesized the pentacyclic core of the citrinadins and the PF1270s using the optimized conditions. In three steps and 39% yield **29** was synthesized from known **28**. With desired **29** in-hand, they effected the cyclotrimerization reaction by treatment with $CpCo(CO)_2$ catalyst under microwave conditions in the presence of **24**. While most of the TMS moiety was cleaved to form **30** under the initial microwave irradiation, a small amount of the silylated intermediate remained. In order to remove the remaining TMS moiety, the reaction was treated with KF under microwave irradiation. Substrate **30** was then mesylated and eliminated using the previously described conditions to form pyridinium compound **31**. Reduction of **31** with $NaBH_4$ provided the desired pentacyclic core (**32**) in good yields. Deiters *et al.* were able to construct the complex pentacyclic core (**32**) in a 30% yield from the diyne **29**. (Scheme 6)



Scheme 6: Synthesis of the racemic pentacyclic core **32**.

2.4 Sorensen Group Synthesis of the Citrinadin Core

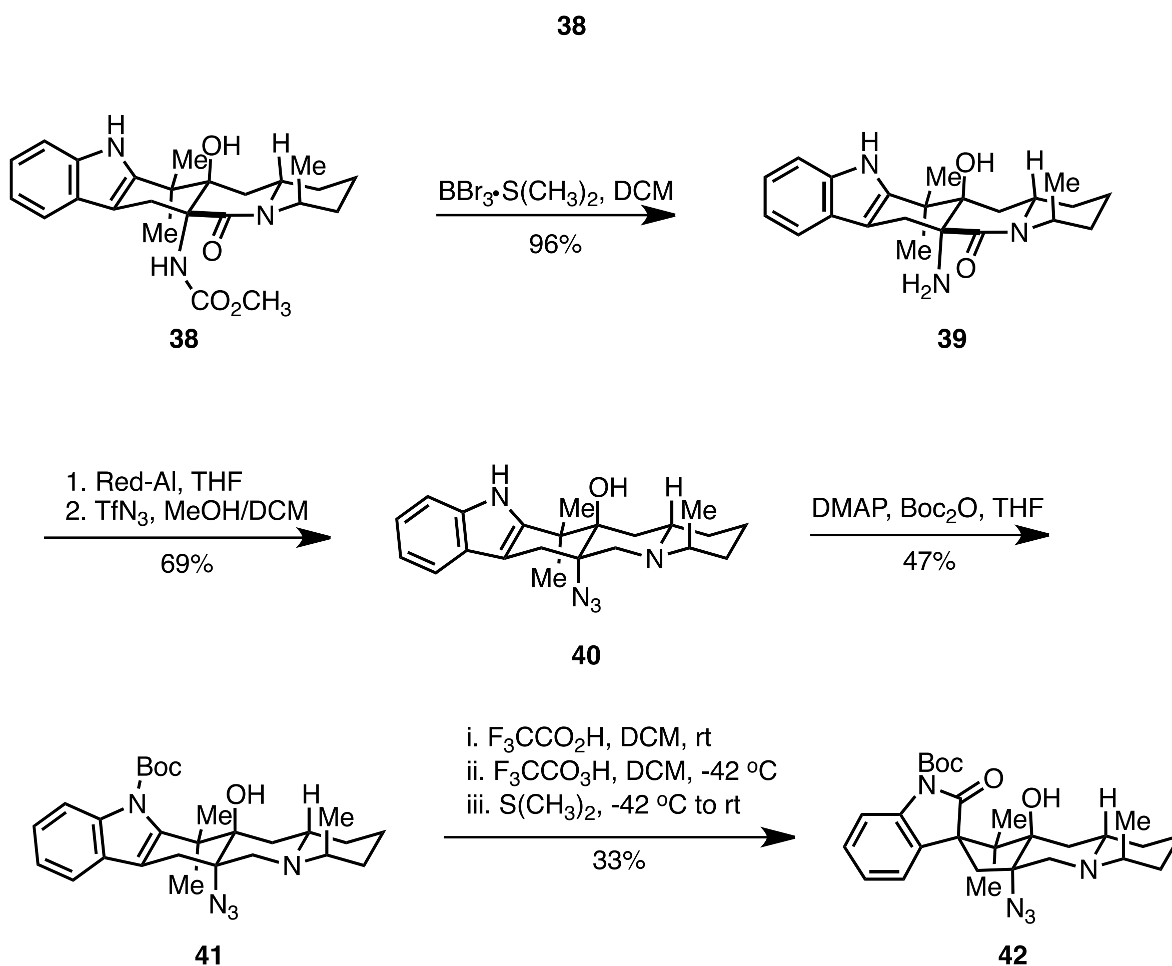
In 2011, Sorensen *et al.*[35] synthesized a highly functionalized pentacyclic core of the citrinadins. The synthesis started with a mixed Claisen acylation of tryptophan **33** with pipecolic ester **34** to afford substrate **35** with high yields and good diastereoselectivity. The β-keto ester **35** was then treated with $SOCl_2$ to remove the Boc group. The resulting residue was then treated with excess $POCl_3$ and heated at reflux. The reaction mixture was concentrated, treated with neat TFA, and stirred for two days to afford the desired lactam **36**. Substrate **36** was then treated with *iso*-propenylmagnesium bromide to selectively install the central isoprene. The favorable diastereoselectivity (10:1) was induced by lower reaction temperatures and afforded **37**. Indole **37** was subsequently deprotected using Mg powder. The free indole then underwent cycloisomerization in the presence of $Hg(O_2CCF_3)_2$ followed by reductive demercuration to afford pentacycle **38**. (Scheme 7)



Scheme 7: Sorensen synthesis of **38**.

Sorensen's previous unpublished studies showed problems with protecting group liability during the oxidative rearrangement to the spirooxindole. To alleviate any possible problems, they planned a protecting group swap prior to the oxidative rearrangement. The methyl carbamate **38** was first removed with excess BBr_3•$S(CH_3)_2$, furnishing **39** in excellent yield. The resulting lactam was subsequently reduced in the presence of Red-Al, and the primary amine was then converted to azide **40** by treatment with TfN_3. Prior to the oxidative rearrangement, the indole nitrogen was Boc protected using Boc_2O and DMAP in THF to afford substrate **41**. Oxidative rearrangement

conditions previously described in their group, as well as work by Petrini and co-workers,[36] was used to convert **41** to **42**. First, **41** was treated with TFA to protonate the tertiary amine, which was followed by the addition of an excess amount of exogenously generated trifluoroperacetic acid. Finally, the reaction was quenched with dimethyl sulfide to afford **42** in a 33% yield. The Sorensen group was then first to synthesize the highly functionalized pentacyclic core of the citrinadins. (Scheme 8)

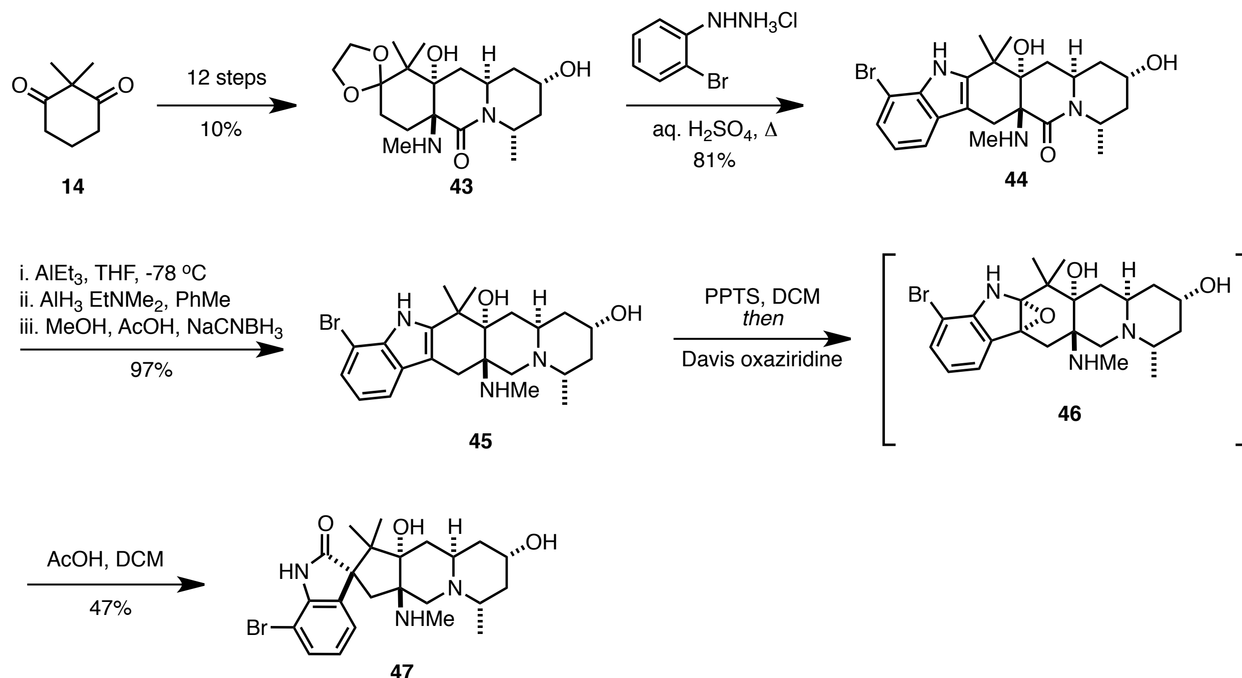


Scheme 8: Sorensen synthesis of the citrinadin pentacyclic core **42**.

2.5 Martin Group Total Synthesis of (-)-citrinadin A

Recently Martin *et al.*[37] reported the first total synthesis of citrinadin A. Their synthesis highlights an asymmetric vinylogous Mannich reaction and a substrate controlled oxidative rearrangement. In addition, the synthesis was completed in 20 steps from commercially available starting materials and resulted in the revision of the citrinadin A structure.

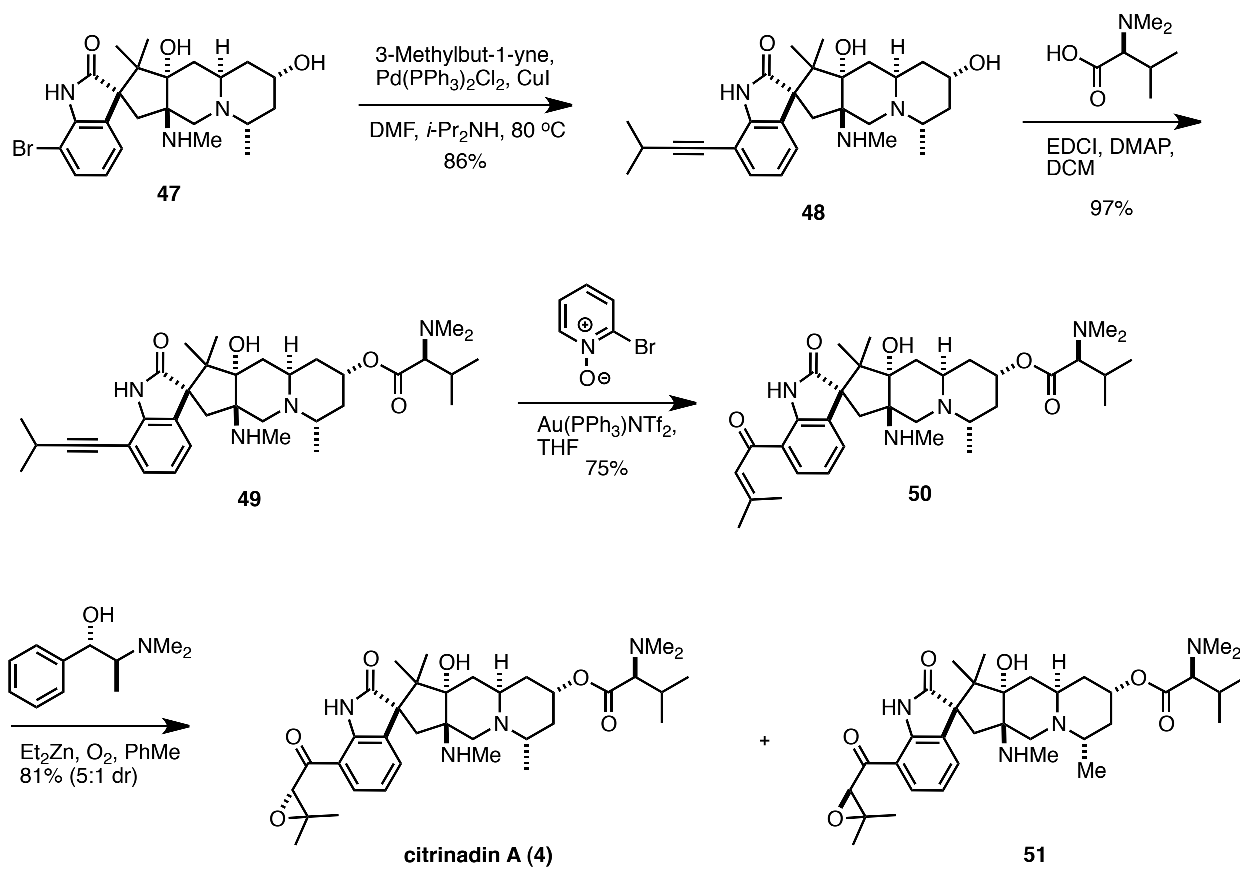
Their synthesis commenced from commercially available dione **14**, the same dione they used in their previously described synthesis of the spirooxindole.[28] Dione **14** was converted to amino alcohol **43** in 12 steps, which included an asymmetric vinylogous Mannich reaction. With the amino alcohol in-hand, they next turned their attention to constructing the pentacyclic core. First, **43** was heated in the presence of acid and *o*-bromophenyl hydrazine hydrochloride to afford indole **44** in excellent yields. Normal reduction conditions of the amide, using only alane, provided moderate yields of the desired product **45**; however, treatment with alane followed by $NaCNBH_3$ gave excellent yields.[38,39] They initially screened a number of different conditions for the formation of the spirooxindole moiety, yet all of their initial attempts failed. Formation of the spirooxindole was finally achieved by using conditions previously described by Williams and co-workers.[40-42] First, indole **45** was treated with PPTS to protect the amino groups from oxidation via protonation, and then treated with Davis' oxaziridine to form epoxide **46**. Epoxide **46** was then treated with AcOH to furnish spirooxindole **47** in moderate yields. (Scheme 9)



Scheme 9: Martin's synthesis of spirooxindole **47**.

In order to install the requisite side chains, **47** was first treated with a Sonogashira coupling with 3-methylbut-1-yne to furnish alkyne **48**, which was then acylated with *N,N*-dimethyl-L-valine, EDCI and DMAP to provide **49**. Enone **50** was synthesized from a gold catalyzed oxidation of **49**.[43] Finally, the epoxide was installed using a diastereoselective epoxidation method that was established by Enders *et al.*[44] Treatment of **50** under these conditions furnished **4** and **51** as a separable (5:1) mixture. (Scheme 10)

The CD spectrum of **4** was identical to that reported for citrinadin A whereas, the CD spectrum of **51** was not a match. Furthermore, ^{1}H and ^{13}C data of **4** also matched the reported data provided by Kobayashi. Thus they strongly suggest that the correct structure for citrinadin A is **4** and not **10**.



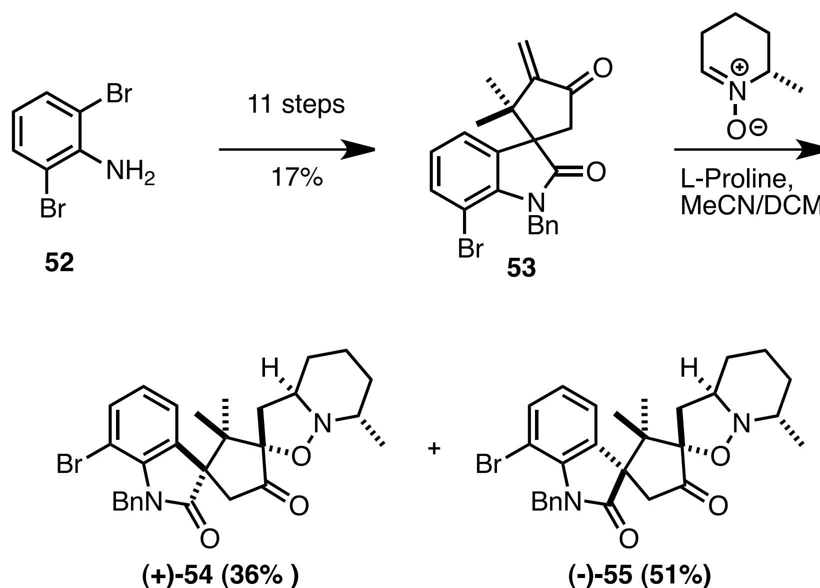
Scheme 10: Martin's total synthesis of citrinadin A.

2.6 Wood Group Total Synthesis of (+)-citrinadin B

Concurrent to Martin's synthesis of citrinadin A, the Wood group[45] published the first reported synthesis of citrinadin B. The Wood group utilized a key stereoselective intermolecular nitrone cycloaddition as the key step in their synthesis. After the completion of their synthesis, they revised the stereochemistry of citrinadin B.

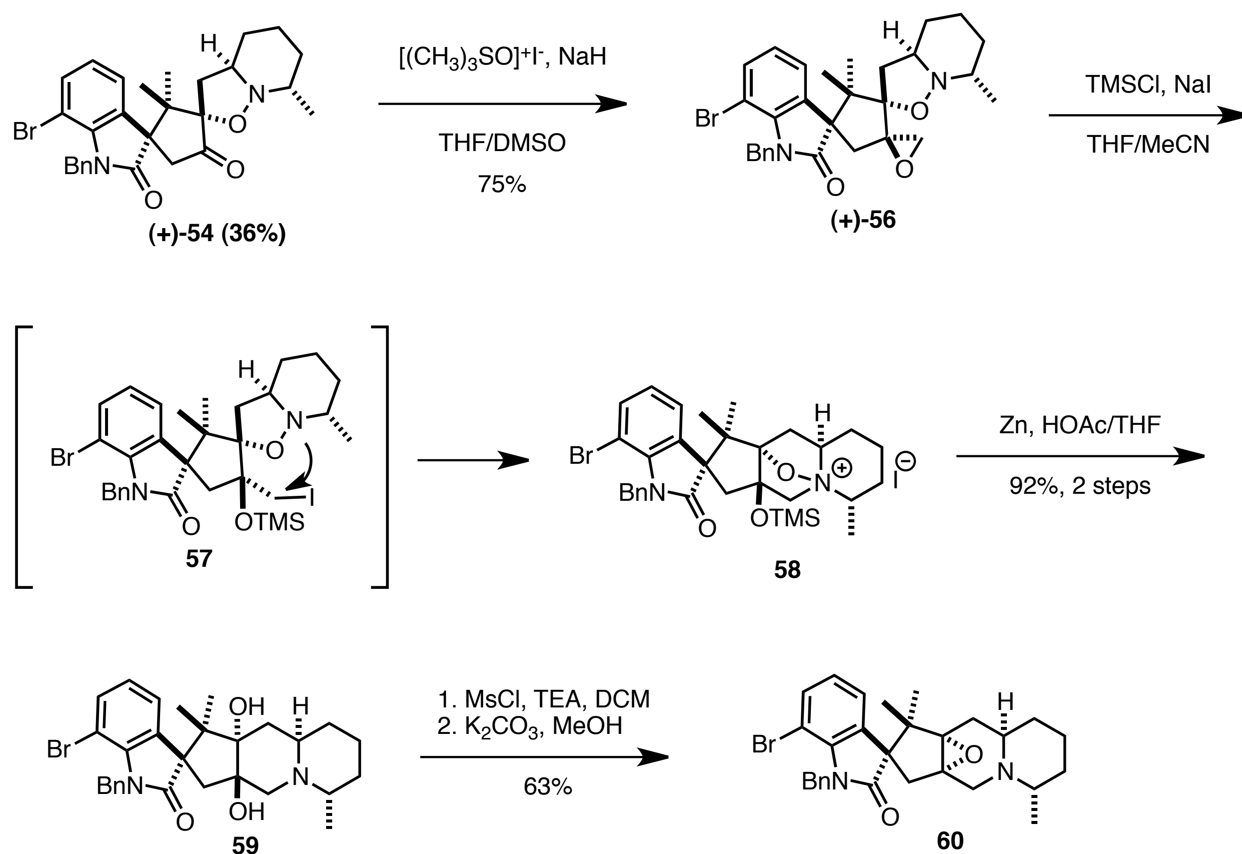
Wood and co-workers started with commercially available dibromo aniline **52,** which was converted to **53** in 11 steps and 17% yield. Intermediate **53** was then used in the critical [3 + 2] cycloaddition. While a variety of diastereo- and regioisometric products were anticipated to result from this reaction, they were pleasantly surprised to observe two diastereometric cycloaddition products (+)-**54** and (-)-**55**. After considerable

studies to determine the stereochemical configuration, they determined that the two products differed at the spirooxindole center. Unfortunately, the minor product contained the same stereochemical configuration found in the natural product. (Scheme 11)



Scheme 11: Synthesis of cycloaddition products **54** and **55**.

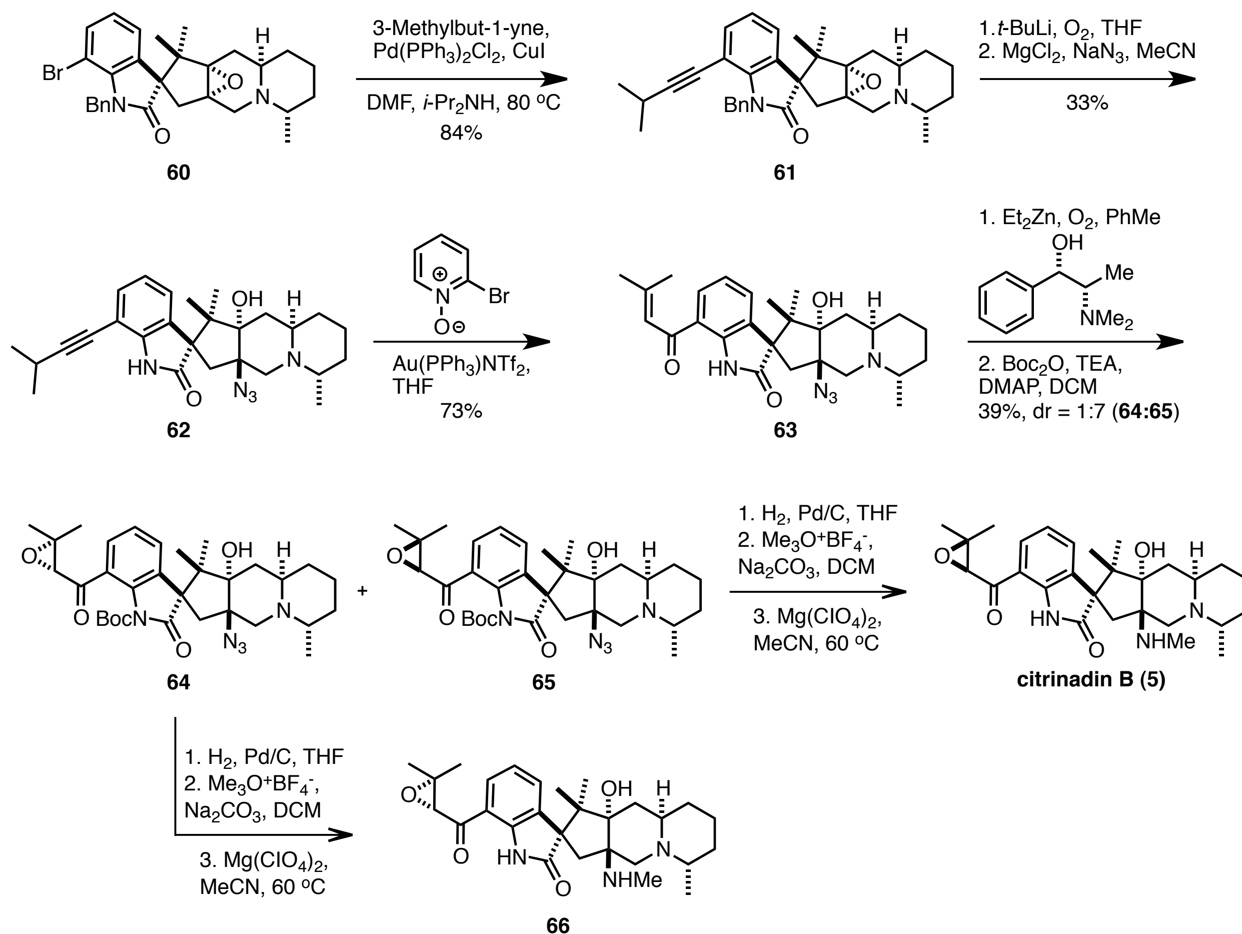
With the correct enone in-hand, a Corey-Chaykovsky epoxidation of **54** provided spiroepoxide **56** as a single diastereomer;[46] however, all attempts to promote intermolecular opening of **56** failed. Thus, they treated **56** to *in situ* generated TMSI and were able isolate ammonium salt **58** through proposed intermediate **57**. Diol **59** was formed via a Zn mediated N-O bond cleavage of **58**. Substrate **59** was then treated with mesyl chloride, and the resulting mesylate was eliminated to form epoxide **60**. (Scheme 12)



Scheme 12: Formation of the epoxide **60**.

With the desired pentacyclic core intact, all that remained was to attach the requisite side chain and install the methylamine functionality. Conditions used for the instillation of the desired epoxiketone side chain mirrored those of Martin.[37] Epoxide **60** was coupled to 3-methyl-1-butyne under Sonogashira conditions to provide alkyne **61**, which was subsequently benzyl deprotected and treated with $MgCl_2$/NaN_3 to form azide **62**. Using gold mediated oxidation conditions, azide **62** was converted to azido alcohol **63**,[43] which was subsequently submitted to epoxidation conditions developed by Enders,[44] Boc protection then afforded **64** and **65** in a mixture (1:7) of separable isomers. It should be noted that the initial epoxidation step led to a mixture of inseparable isomers. Both **64** and **65** were separately converted to the desired

methylamines using the same reaction sequence. First, the azide was reduced to the amine via treatment with Pd/C, and the resulting free amine was monomethylated using methyl Meerwein salt. Finally, the indole was deprotected by treatment with $Mg(ClO_4)_2$ to afford substrates **66** and **5**. (Scheme 13)



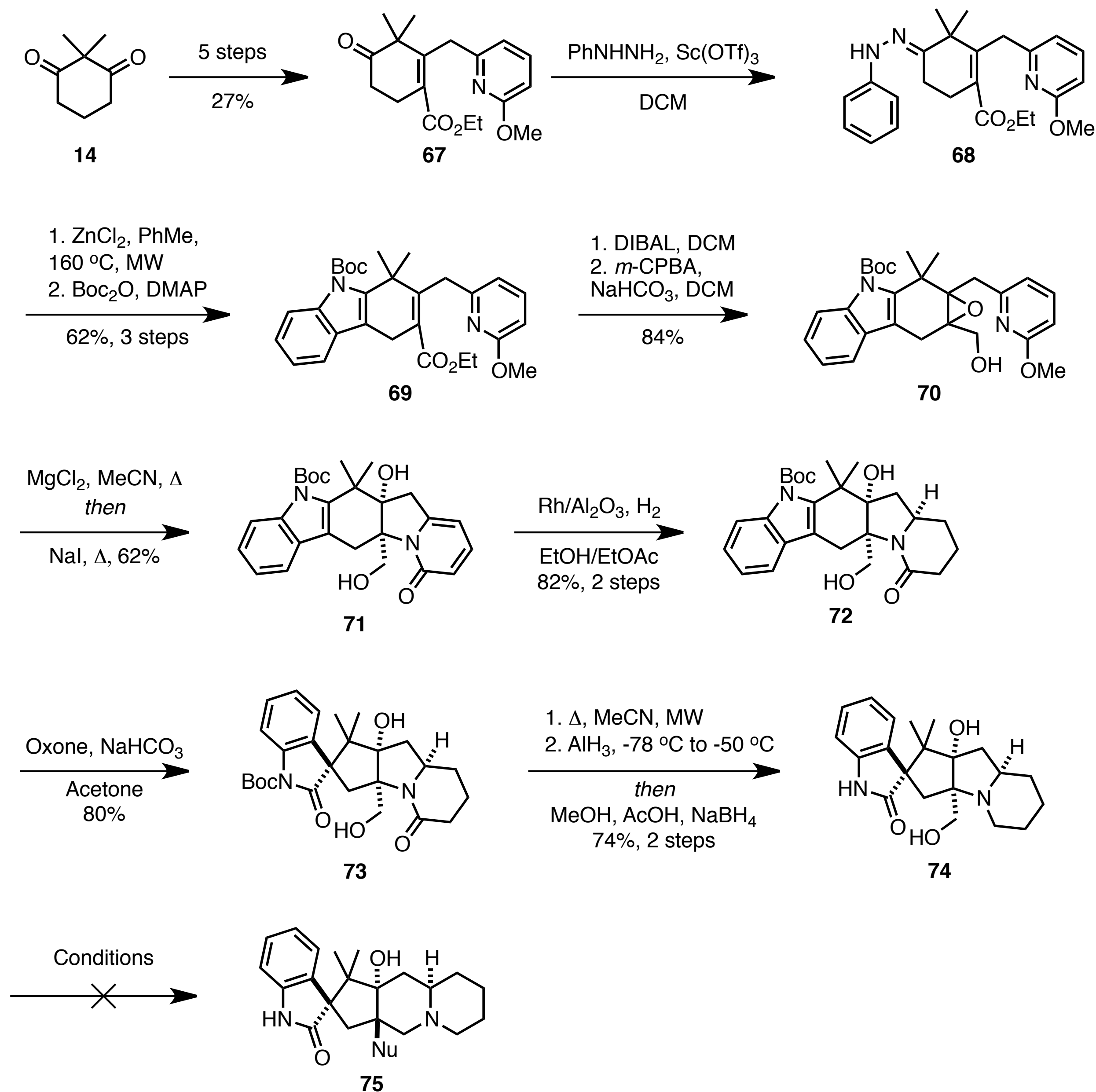
Scheme 13: Synthesis of citrinadin B (**5**).

After comparing the spectral data for both **66** and **5** to the spectral data obtained for the natural product, the structure of citrinadin B was reassigned. While Kobayashi originally proposed the structure of citrinadin B as **66**, Wood *et al.* determined that the correct structure is actually **5**. This aligns with reassignment of citrinadin A proposed by Martin *et al.*[38]

2.7 Sarpong Group synthesis of the citrinadin core

In 2013 Sarpong *et al.*[47] reported a synthesis of the citrinadin core. Their synthesis shares some synthetic strategies found in both the Martin and Wood synthesis.

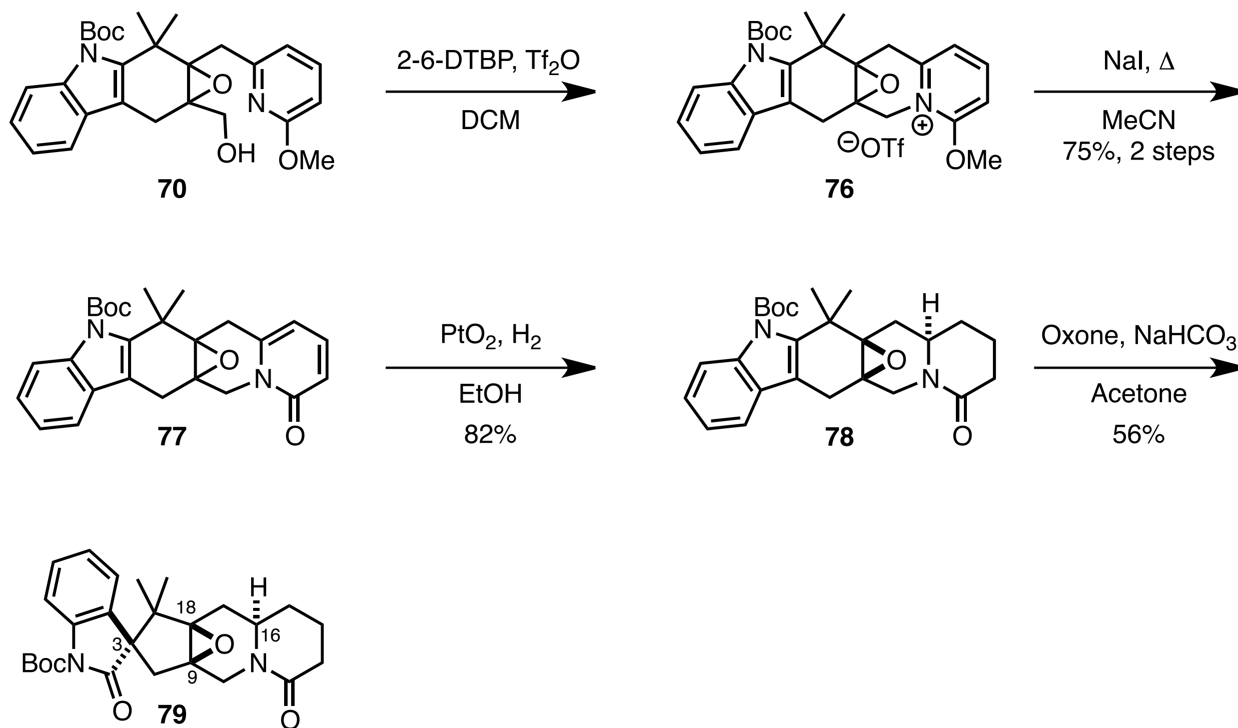
Sarpong starts with the same commercially available dione **14** that Martin used, which was converted to ketone **67** in five steps and 27% yield. Fisher indole conditions[48] were utilized to first form dihydrocarbazole **68**, followed by formation of indole **69**. Treatment of indole **69** with DIBAL reduced the ethylester to the corresponding alcohol. Subsequent epoxidation furnished **70**, which was treated with $MgCl_2$ and then NaI to afford substrate **71**. Diastereoselective hydrogenation of pyridine **71** afforded pentacycle **72** in excellent yields. The structure of **72** was confirmed by X-ray crystallography. Indole **72** was then treated with oxone in acetone to afford spirooxindole **73**. This oxidation also proceeded with high levels of diastereoselectivity, which they attributed to both the oxidation at the more accessible convex face and directed oxidation for the primary alcohol. Subsequent Boc deprotection, followed by amide reduction provided intermediate **74**. Unfortunately, despite screening a number of different conditions they were unable to convert **74** to **75**. (Scheme 14)



Scheme 14: Synthesis of diol **74**.

After attempting numerous conditions, they decided upon an alternative strategy for the synthesis of the desired carbon skeleton. Using a strategy similar to what Wood used in his synthesis of citrinadin B,[45] epoxide **70** was treated with Tf_2O and 2,6-DTBP providing pyridinium salt **76**. Without purification, salt **76** was treated with NaI in refluxing MeCN to afford pyridone **77**. Next, catalytic hydrogenation afforded **78** with

excellent diastereoselectivity. Finally, indole **78** was oxidized to spirooxindole **79** using the previously described conditions, and the structure was confirmed using X-ray analysis. (Scheme 15)



Scheme 15: Alternative route to pentacyclic **79**.

While the relative stereochemistry at C-3 and C-16 are correct, Sarpong and coworkers note that the relative stereochemistry at C-18 will require inversion. Ongoing studies in their group are addressing both the stereochemical inversion as well as nucleophilic opening of the epoxide group. Although work still remains on this project, they were able to access the pentacyclic carbon framework of the citrinadins and the PF1270s.

2.8 Conclusion

While there have been a number of different synthetic strategies reported to synthetize the pentacyclic core of the PF1270s, a total synthesis remains to be reported. The recent elegant syntheses reported by Martin[37] and Wood[45] remain the only syntheses of the citrinadins, and the need for other convergent and elegant synthetic approaches remains evident.

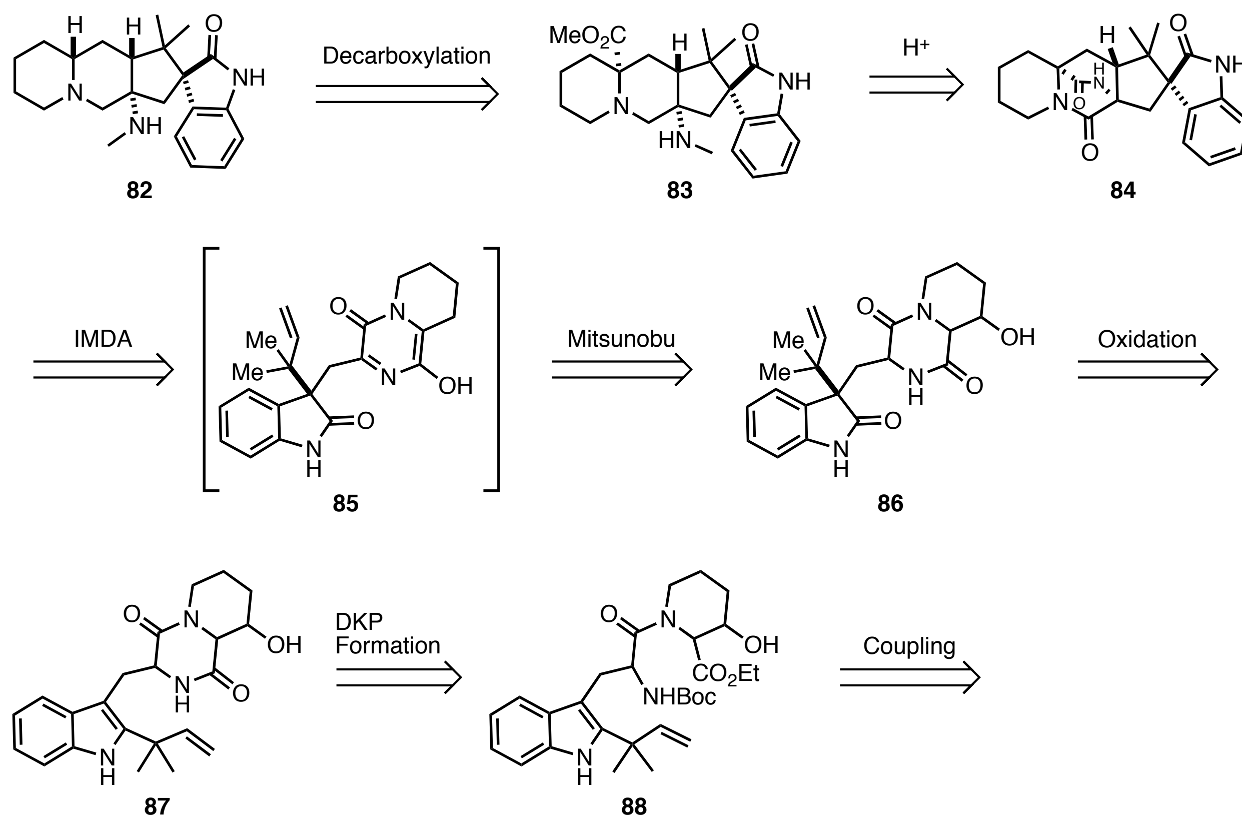
Chapter 3: Current Work

3.1 General Synthetic Strategy

To date, no total synthesis of the PF1270s has been reported. As previously described, the pentacyclic core of the PF1270s and citrinadins has been synthesized;[34,35,47] there have also been two recently reported total syntheses of the citrinadins.[37,45] With all of the previous synthetic routes in mind, we designed a completely novel synthesis for the construction of the pentacyclic core. Our plan centered on previously developed Williams group chemistry in the total synthesis of similar spriooxindole alkaloids, such as the paraherquamides[39,49] and marcfortines[41,50]. Both of these natural products were synthesized utilizing a key Diels-Alder reaction to set the stereochemistry of the bicyclo[2.2.2.]diazaoctane core. Utilizing a similar Diels-Alder reaction, we hypothesized that we could rapidly access the desired pentacyclic core, which could further be elaborated into the exact carbon framework of the PF1270s. Furthermore, after successfully synthesizing the pentacyclic core, we planned on employing the same synthetic strategy to complete the first reported total synthesis of **1**.

3.2 Retrosynthetic Plan

As such, we proposed a retrosynthetic plan for the synthesis of the pentacyclic core starting from reverse prenylated tryptophan **80** and hydroxypipecolic acid derivative **81** (Scheme 16).



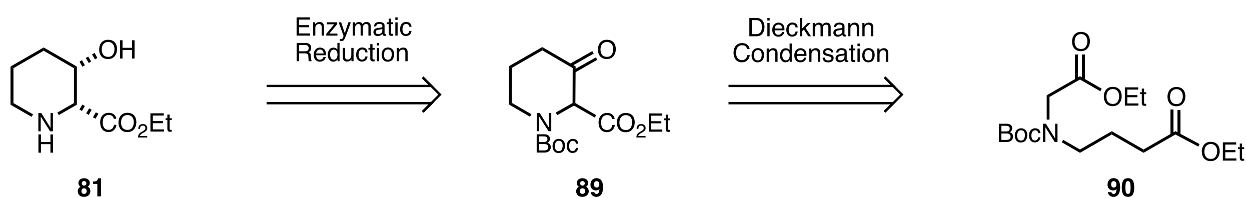
Scheme 16: First generation retrosynthetic plan.

We envisioned forming the complete pentacyclic core of PF1270 (**82**) by decarboxylation of **83**, which could be synthesized via acid catalyzed cleavage of the bridging amide present in **84**. A significant precedence for acid catalyzed cleavage of the bridging amides can be found in the literature.[51] We envisioned forming the bridged pentacycle **84** through our previously developed intermolecular Diels-Alder (IMDA) reaction. The IMDA reaction would be utilized to set the stereochemistry of the bridging amide as the desired *anti*-diastereomer. In the synthesis of (-)-versicolamide B, our group has shown that the IMDA reaction on spirooxindole intermediates provided exclusively the *anti*-diastereomer;[52] this synthesis provided experimental support for the theoretical calculations of Domingo and co-workers.[53-55] Consequently, we decided to

form the sprirooxindole prior to the IMDA reaction. The required azadiene precursor (**85**) could be formed by submitting spirooxindole **86** to Mitsunobu conditions followed by treatment of the resulting enamide with base. An oxidative rearrangement of **87** would then give rise to the spirooxindole intermediate **86**. Precursor **88** could be synthesized through a peptide coupling and subsequent deprotection/cyclization to give DKP **87** (Scheme 16).

3.2.1 Synthesis of the Pipecolic Acid Derivative

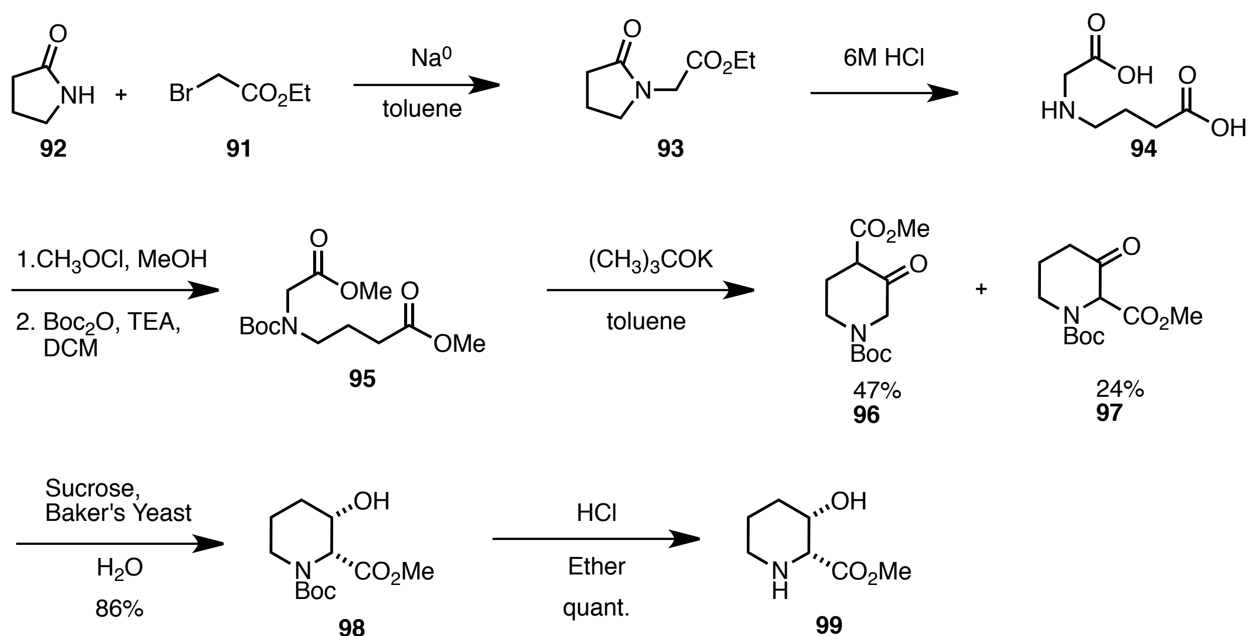
To start the synthesis of the pentacyclic core, a route to readily synthesize the desired pipecolic acid derivative in large quantities was needed. We chose a synthetic plan based on work previously described by Knight and co-workers.[56] This group synthesized the desired pipecolic acid derivative (**81**) via an enzymatic reduction of ketone **89** which was formed through a Dieckmann condensation of diester **90** (Scheme 17).



Scheme 17: First generation retrosynthesis of pipecolic acid derivative.

Our synthesis of the diester **90** was achieved via the route shown in Scheme 18. A nucleophilic substitution of ethyl bromoacetate (**91**) with 2-pyrrolidinone (**92**) in the presence of sodium metal provided **93**, which was then treated with HCl to afford free amine diacid **94**. Subsequent Boc protection followed by esterification of **94** afforded diester **95** in excellent yields. Finally, treatment with potassium tert-butoxide afforded a

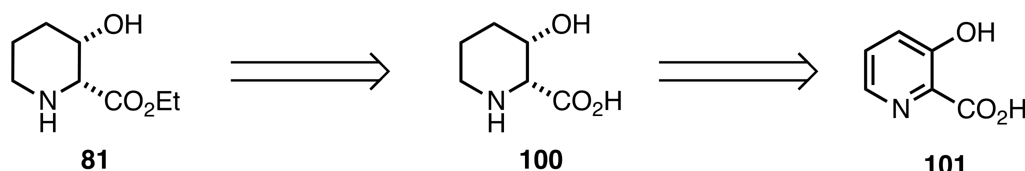
mixture of two products (**96** and **97**) of which, the undesired product **96** was the major product. A number of different reaction conditions were screened in an effort to produce the desired product in higher yields, however, all the conditions we screened failed. The desired product **97** was then submitted to the enzymatic reduction in the presence of baker's yeast to produce **98**. On a small scale, after some optimization, the reduction proceeded with excellent yields. The subsequent deprotection and conversion to desired free amine **99** was completed smoothly. However, on large scale the baker's yeast reduction was low-yielding and proved to be more problematic. When carried out on a large scale the amount of baker's yeast required for the reduction formed a thick paste that made extraction extremely difficult. This resulted in only a twenty percent recovery of the desired product from the aqueous paste. As this synthetic plan contained both a low-yielding Dieckmann condensation and a low-yielding baker's yeast reduction, a new route was devised.



Scheme 18: First generation synthesis of the pipecolic acid derivative.

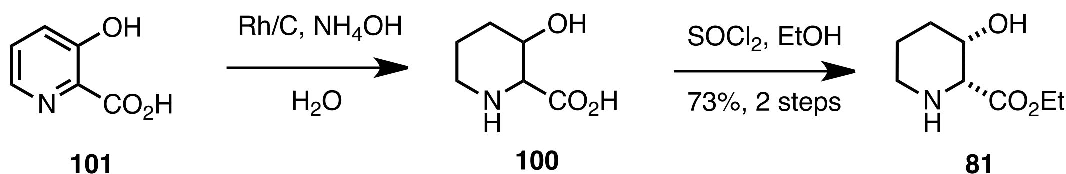
3.2.2 Second Generation Pipecolic Acid Synthesis

We believed that we could access the desired pipecolic acid ester **81** by esterification of acid **100**. (Scheme 19) Desired acid **100** could arise from a reduction of commercially available 3-hydroxypicolinic acid **101**.



Scheme 19: Second generation retrosynthesis for pipecolic acid derivative.

Following a literature procedure, catalytic hydrogenation of **101** gave only trace amounts of product.[57] Increasing both the pressure and the duration of the reaction allowed for a substantial product recovery. With our desired acid in-hand, the esterification was carried out in the presence of thionyl chloride and EtOH at reflux providing **81** in good yield over 2 steps. (Scheme 20) More importantly, this reaction sequence was scalable and allowed us to access large amounts of the desired acid. With pipecolic acid derivative **81** in-hand, we turned our attention to the synthesis of reverse prenylated indole **80**.

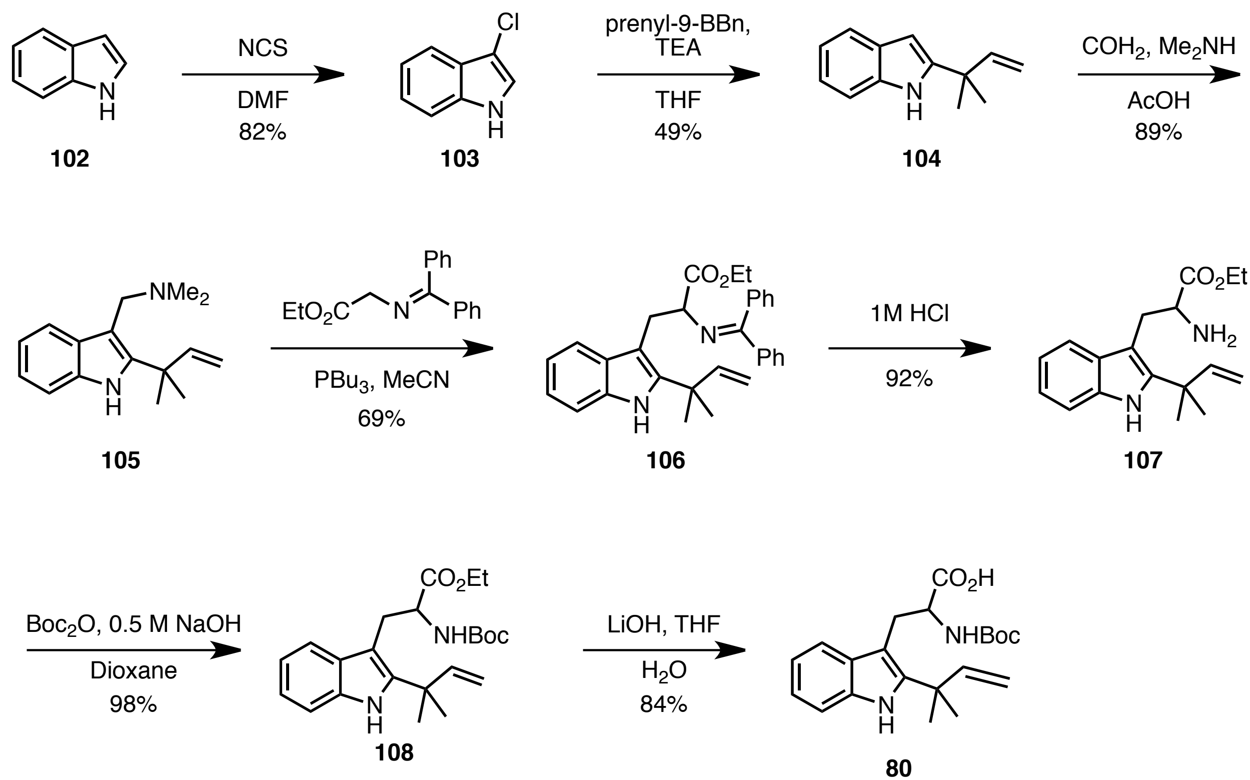


Scheme 20: Synthesis of the desired pipecolic acid derivative.

3.2.3 Synthesis of the Tryptophan Derivative

The synthesis of the reverse prenylated tryptophan precursor **80** is shown below. (Scheme 21) Commercially available indole (**102**) was chlorinated in good yield using N-

chlorosuccinimide to provide **103**, which was treated with prenyl-9-BBN to provide the C-2 reverse prenylated indole **104** in 78% yield. Next, a Mannich reaction afforded gramine **105**, which was coupled with glycine benzophenone imine to afford tryptophan derivative **106** in good yield. Cleavage of the benzophenone imine with aqueous HCl afforded free amine **107**, which was subsequently Boc-protected to provide **108**. Finally, ester **108** was saponified with LiOH to provide acid **80**. With both the desired pipecolic acid and reverse prenylated tryptophan in-hand, we turned our attention to the IMDA reaction.



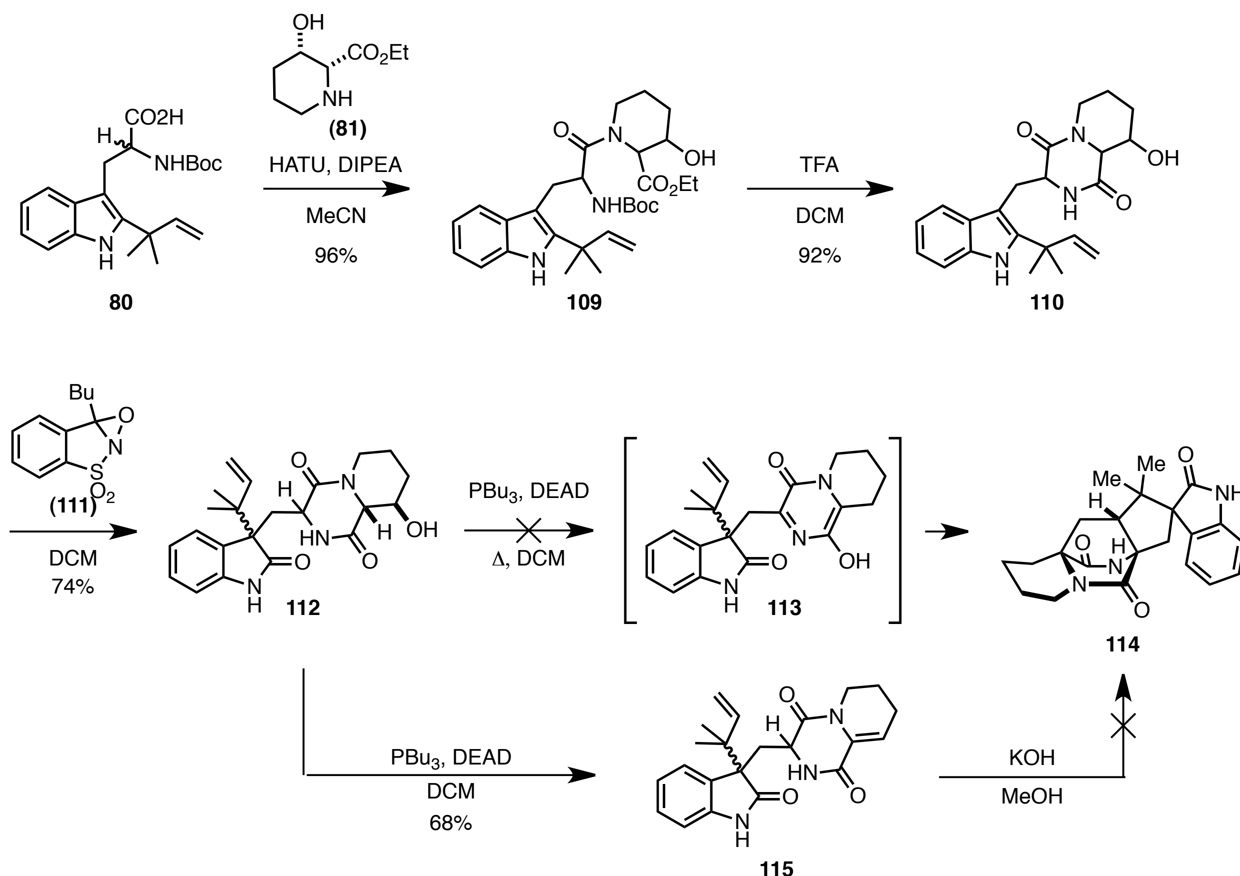
Scheme 21: Synthesis of the reverse prenylated indole derivative.

3.2.4 Initial IMDA Attempt

The coupling of pipecolic acid **81** to **80** in the presence of HATU afforded **109** in 96% yield. This dipeptide was then treated with TFA to remove the Boc group, providing

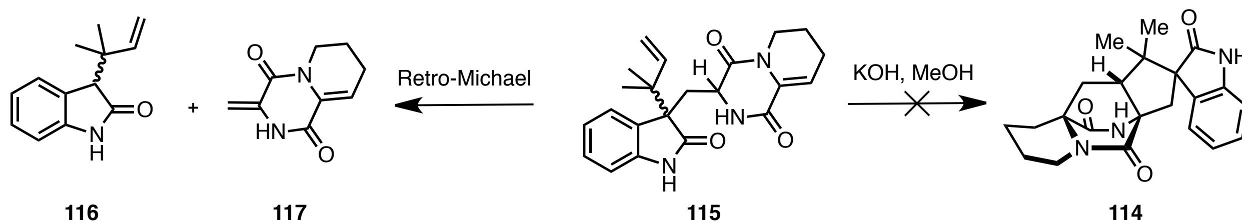
the free amine which, upon basic work up, cyclized to diketopiperazine **110** in 92% yield. Treatment of **110** with Davis' oxaziridine (**111**) formed the desired spirooxindole **112** in 74% yield.

Our group previously showed a one pot cycloaddition of a similar spirooxindole.[50] However, heating **112** in the presence of excess PBu_3 and DEAD did not afford the expected cycloaddition product **114**. Since the one-pot elimination Diels-Alder addition failed, we turned to a known two-step procedure[58-60]. Starting from alcohol **112**, a Mitsunobu-type elimination afforded enamide **115** in moderate yields. Nevertheless, when enamide **115** was treated with KOH/MeOH none of the desired cycloadduct **114** was detected.



Scheme 22: First attempted IMDA reaction.

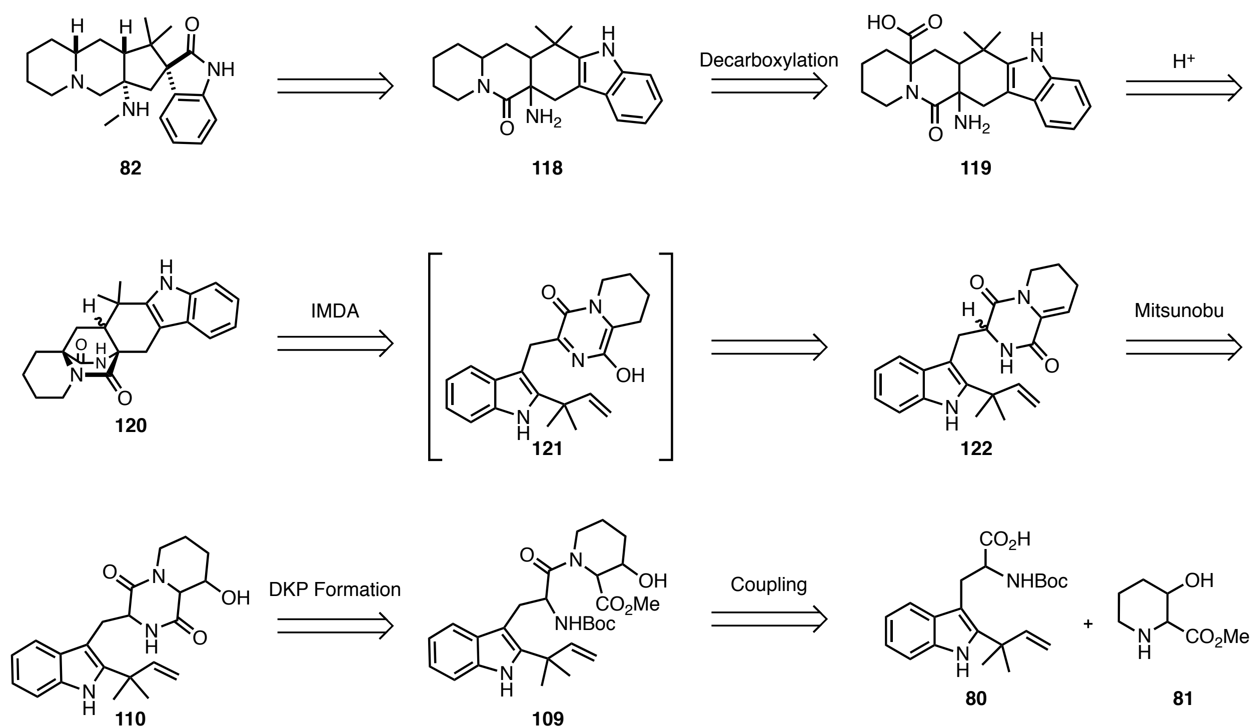
Unfortunately, all attempts to synthesize the cycloadduct from both the *R*- and *S*-oxidole moieties failed. We believe that there is a competing retro-Michael reaction that is more facile than the desired IMDA reaction (Scheme 23). This retro-Michael reaction was first reported in our group by Dr. Kathleen Halligan in her synthesis of the brevianamides,[61] and also by Dr. Jennifer Finefield in her synthesis of (-)-versicoleamide B.[62] The undesired side reaction could be easily avoided by forming the Diels-Alder adduct prior to the oxidation to the spirooxindole.[62]



Scheme 23: Probable retro-Michael reaction.

3.3 Second Retrosynthetic Plan

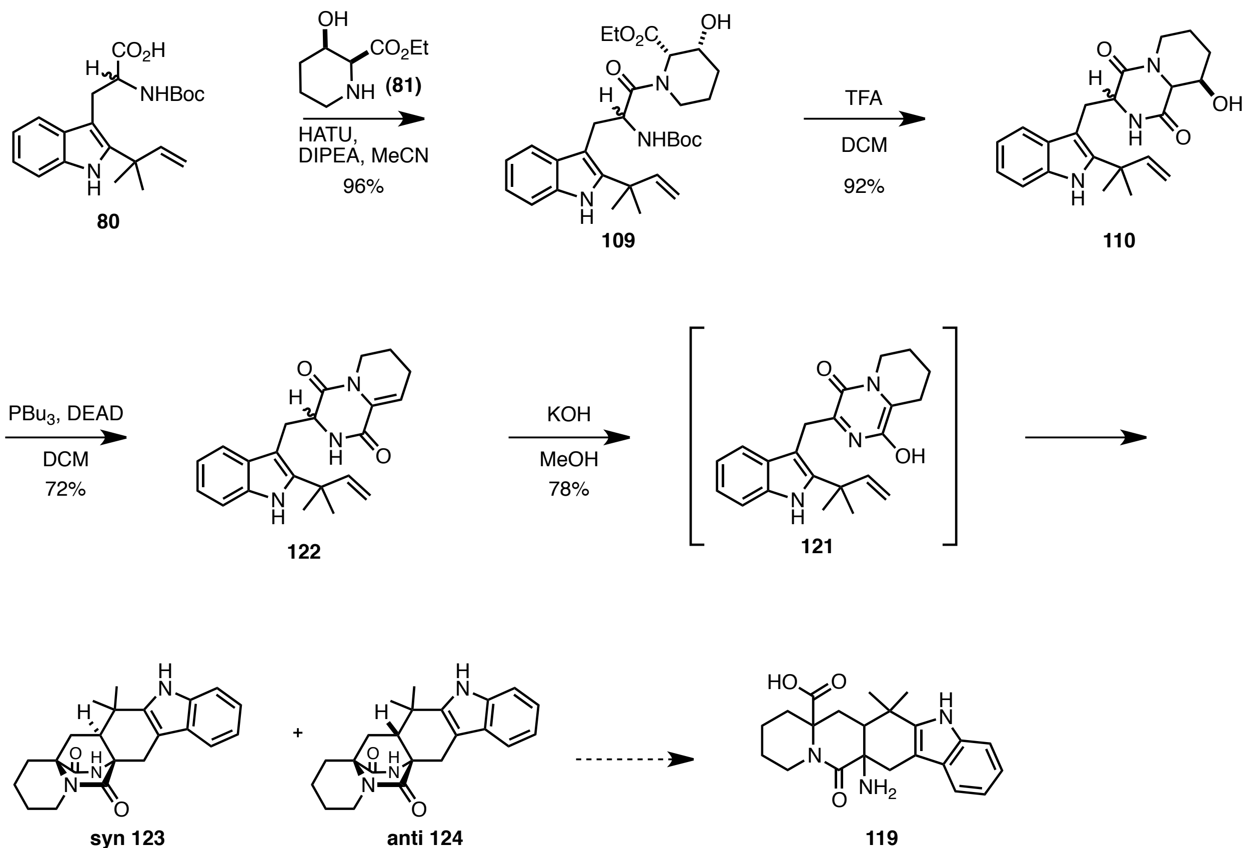
Since the desired cycloadduct could not be synthesized as originally planned, an alternative route was devised. We envisioned the complete pentacyclic core of the PF1270 family coming from a late stage decarboxylation of acid **118** and subsequent oxidation to the spirooxindole. Acid **118** could arise from the same proposed acid catalyzed cleavage of the bridging amide **120**. Amide **120** would come from the IMDA reaction of azadiene **121**. The azadiene precursor **122** could be formed by submitting DKP **110** to Mitsunobu conditions, followed by treatment of the resulting enamide with base. Finally, DKP **110** could arise from the same previously described coupling and then cyclization (Scheme 24).



Scheme 24: Second generation retrosynthetic analysis.

3.3.1 Synthesis of the Diels-Alder Product

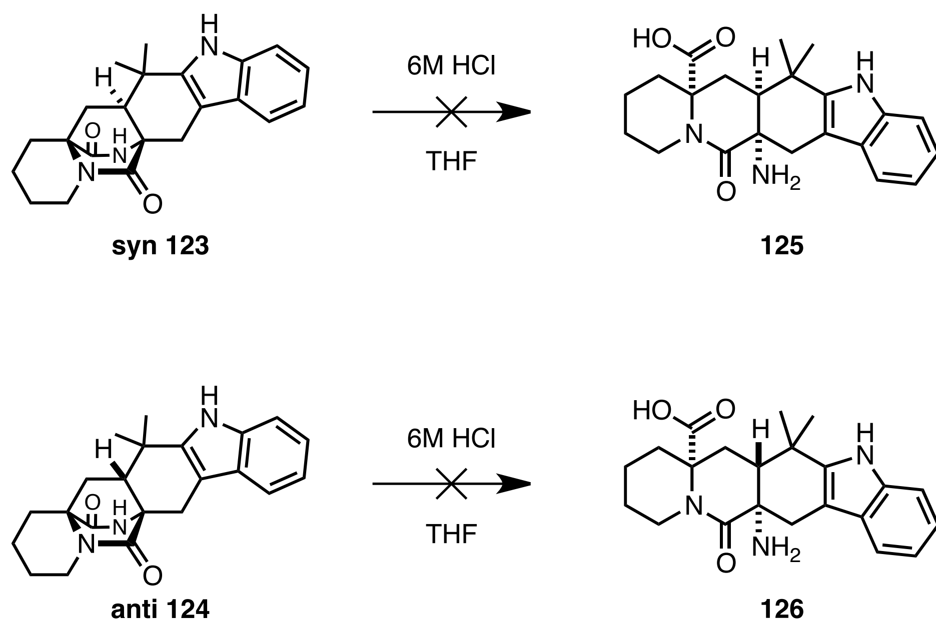
As previously described, DKP **110** was formed by first coupling tryptophan **80** with pipecolic acid **81,** followed by deprotection/cyclization. Enamide **122** was formed in 72% yield by Mitsunobu-type elimination of alcohol **110**. Treatment of enamide **122** with KOH and MeOH gave cycloadducts **123** and **124** in a 1.5:1 ratio. It is important to note that this is a bottleneck of the synthesis as this IMDA reaction provides the desired *anti*-adduct as the minor product. However, with a route to the desired cycloadduct in-hand, we turned our attention to the bridging amide. (Scheme 25)



Scheme 25: Synthesis of the IDMA cycloadducts **123** and**124**.

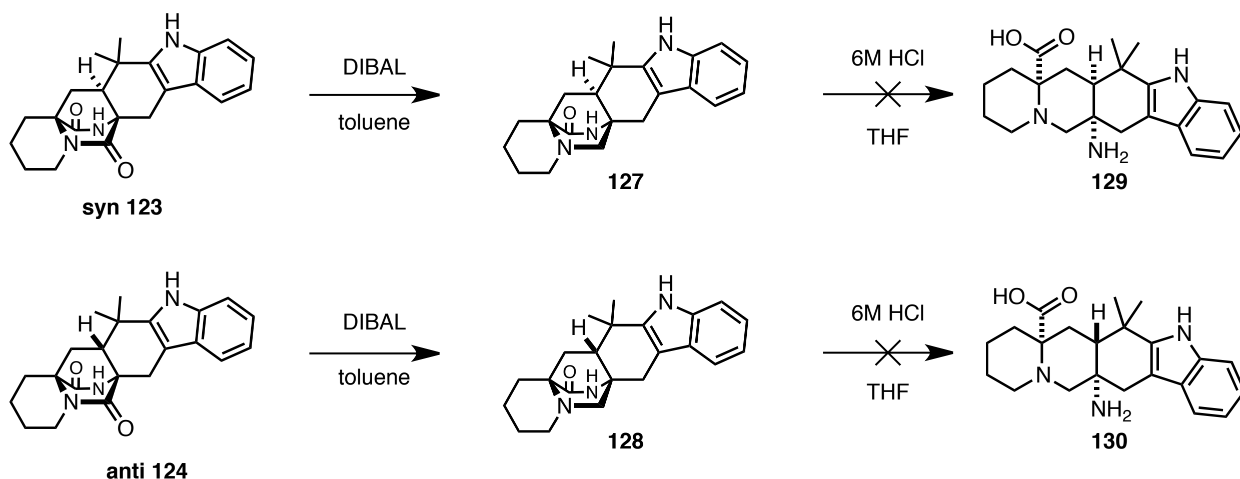
3.3.2 Opening of the Bridging Amide

Initially we believed that opening the bridging amide would proceed smoothly, but it turned out to be quite challenging. First we attempted to hydrolyze **123** and **124** to the corresponding acids (**125** and **126**) using 6M HCl.[63-66] (Scheme 26) At room temperature for 24 hours, we only recovered starting material. Next, the reaction was refluxed for days, and under these forcing conditions we only observed decomposition.



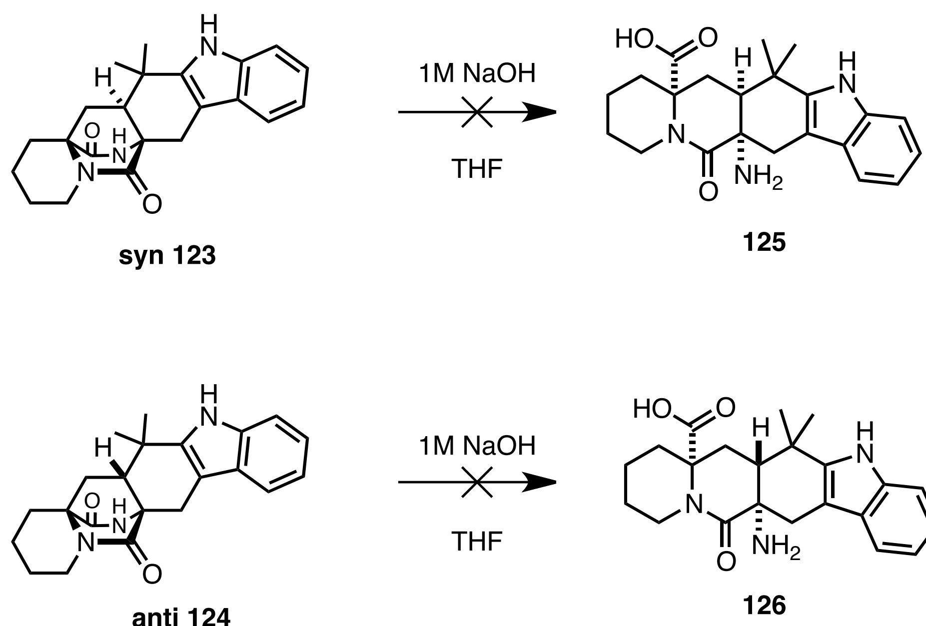
Scheme 26: Attempted hydrolysis of bridging amide.

Next we reduced the tertiary amide hoping that its reduction would change the reactivity of the system thereby allowing the bridging amide to be hydrolyzed. Treatment of both the *syn* **123** and *anti* **124** cycloadducts with DIBAL in toluene provided cycloadducts **127** and **128**. Nevertheless, treatment of both **127** and **128** with 6M HCl failed to afford acids **129** and **130**. (Scheme 27)



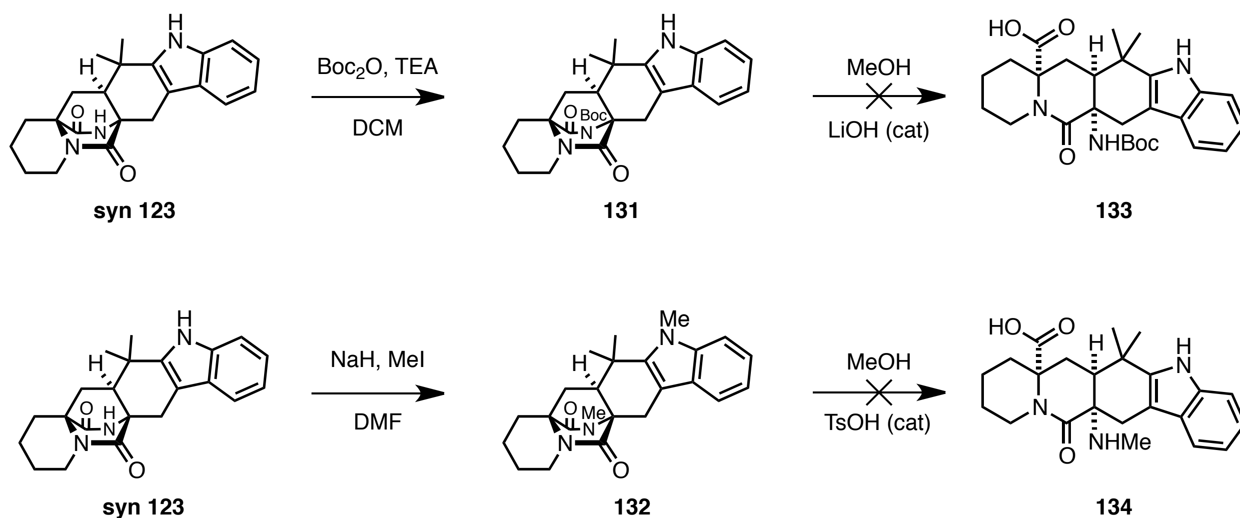
Scheme 27: Formation of **127** and **128** followed by attempted hydrolysis.

Under acidic conditions we failed to open the bridging amide; consequently we decided to attempt the opening under basic conditions.[67-70] Again, treatment of both **123** and **124** with 1M NaOH at room temperature yielded only starting material, while treatment with 1M NaOH at reflux resulted in decomposition. Under basic conditions we were still unable to produce acids **125** and **126**. (Scheme 27)



Scheme 27: Attempted ring opening under basic conditions.

Because attempts at hydrolysis under both basic and acid conditions were unsuccessful, we hypothesized that increasing the amide's reactivity might allow us to open the bridging amide.[71-74] Therefore, amide **123** was first converted to protected amide **131** by treatment with Boc_2O and TEA in DCM. Next, we converted amide **123** to methyl amide **132** by treatment with NaH and MeI in DMF. However, all attempts to open the bridging amide in both **133** and **134** were unsuccessful.



Scheme 28: Attempted opening of the amide to the ester.

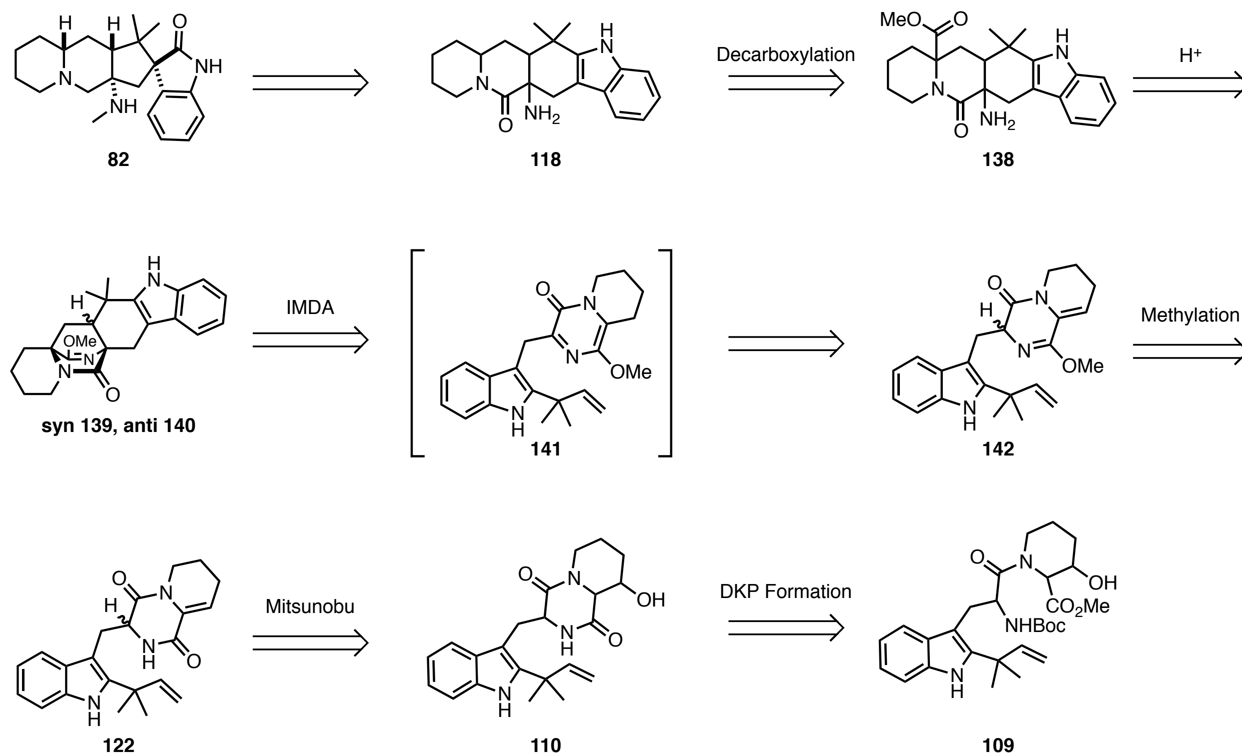
Unfortunately, all of the screened conditions were unsuccessful. The opening of the bridging amide proved to be more problematic than we had originally anticipated, and we were forced to devise another alternative route.

3.4 Third Retrosynthetic Plan

In this new plan, the early stages of the synthesis remained the same and only the later stages changed. Our new plan was based on previous chemistry done in the group. In the synthesis of the stephacidin A and notoamide B, we observed the ring open conformer during deprotection the lactim ether (Scheme 29).[75,59] In these examples, only the *syn* conformer stayed open and the *anti*-conformer was isolated as the bridging amide.

Scheme 29: Previous synthesis of stephacidin A and notoamide B.

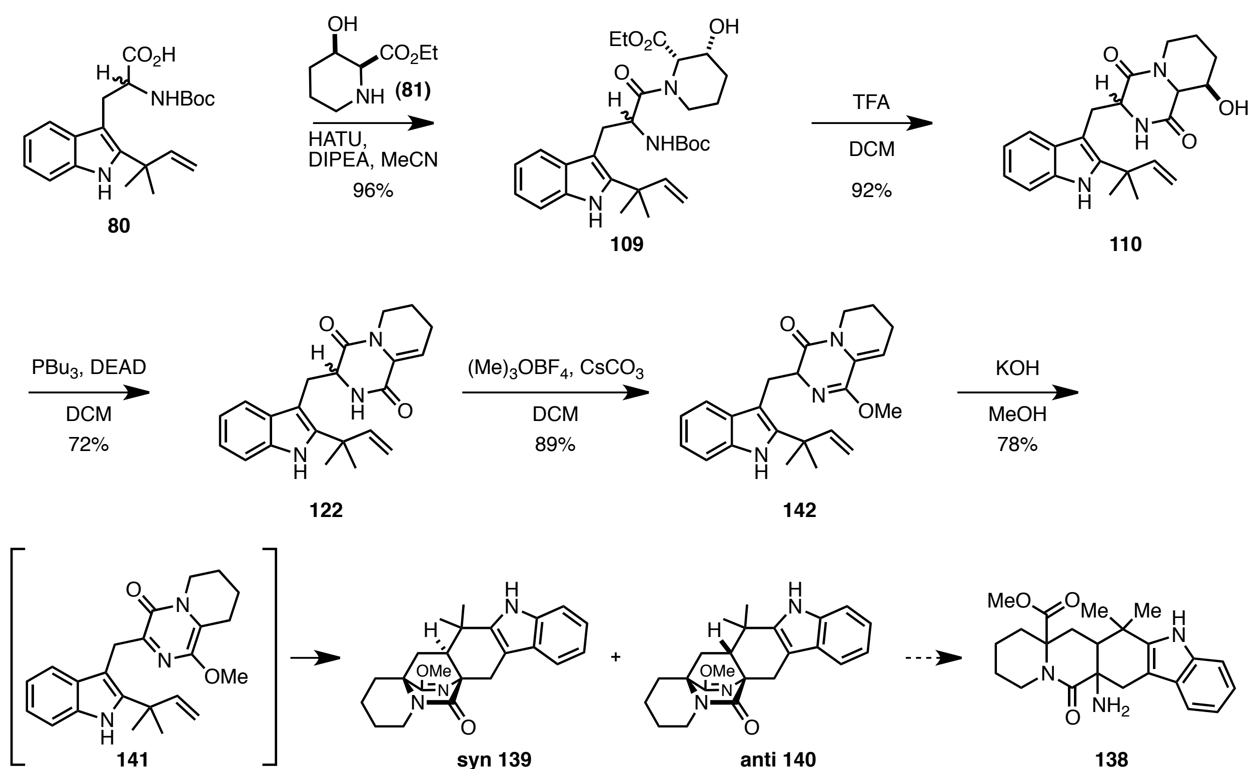
We believed that after reaction optimization, we would be able to isolate both ring open conformers (**138**). In order to test our theory, we first had to synthesize the required lactim ether intermediates. The desired lactim ethers **139** and **140** could come from the IMDA reaction of azadiene **141**. The azadiene would come form lactim ether **142**, which could in turn arise from a methylation of the previously synthesized enamide **122**. Enamide **122** could come from the same reaction sequence as previously discussed. (Scheme 30)



Scheme 30: Third generation retrosynthesis.

3.4.1 Third Generation Synthesis

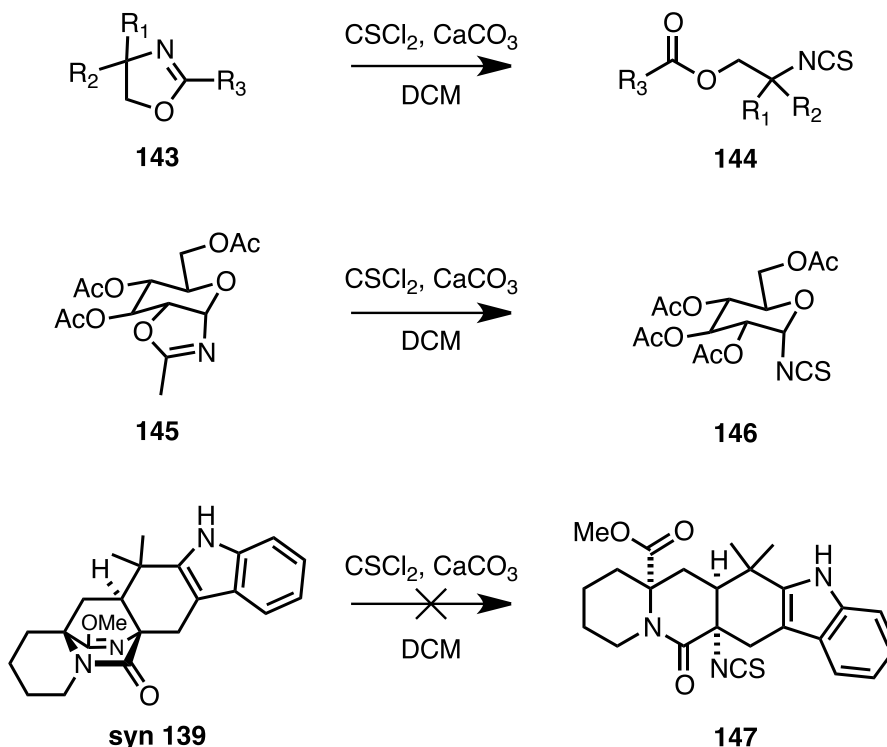
This synthesis begins as before with a HATU coupling of indole **80** to pipecolic acid **81** affording dipeptide **109**. Dipeptide **109** was then treated with TFA to afford the free amine which, upon basic workup, provided the cyclized DKP **110**. DKP **110** was then treated with PBu_3 and DEAD to provide enamide **122**. Enamide **122** was then treated with Meerwein's salt to afford lactim ether **142**, which was then treated to KOH in MeOH to provide the IMDA cycloadducts *syn* **139** and *anti* **140**. (Scheme 31) With the desired substrates in-hand, we turned our attention to conditions for opening of the bridging lactim ether.



Scheme 31: Third generation synthesis.

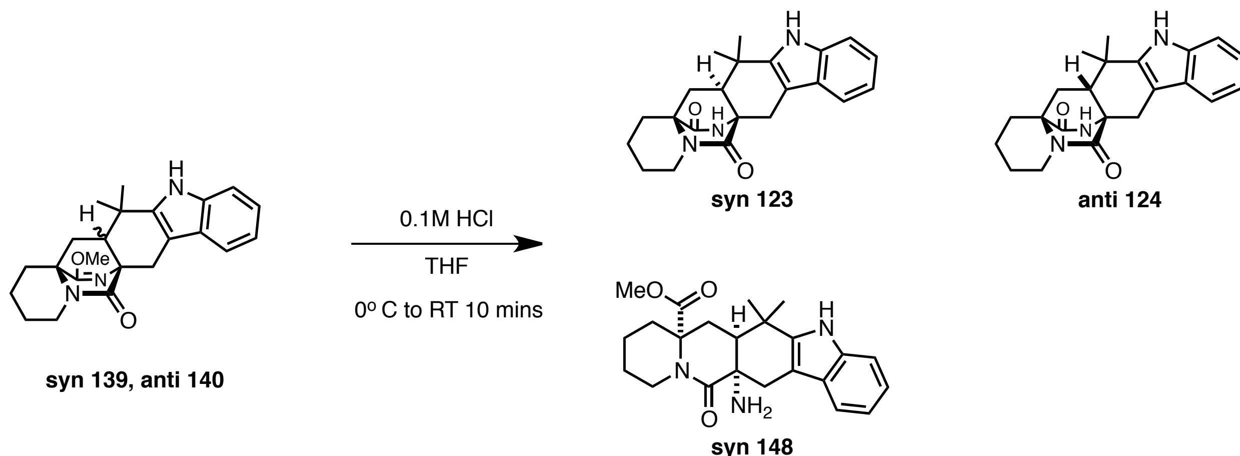
3.4.2 Opening of the Bridging Amide

Mikler and co-workers showed that treatment of nitrogen-containing heterocycles **143** with $CSCl_2$, $CaCO_3$ in DCM afforded isothiocyanate **144**.[76,77] Also, Fernandez and co-workers utilized identical reaction conditions to convert **145** to isothiocyanate **146**.[78] Using the aforementioned conditions, we submitted **139** to $CSCl_2$ and $CaCO_3$ in DCM for 5 hours or overnight. Unfortunately, we never observed the desired isothiocyanate **147** and only isolated starting material. (Scheme 32)



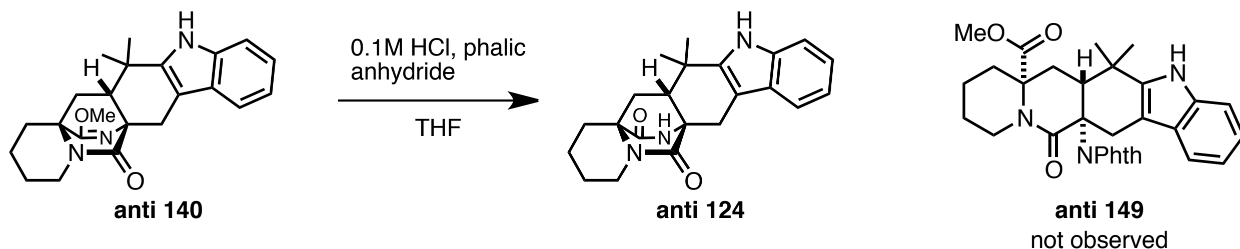
Scheme 32: Synthesis of isothiocyanates **144, 146** and attempted synthesis of **147**.

Next, we decided to attempt opening the lactim ether using the conditions that were previously described in our group. Thus we followed the exact procedures found in the synthesis of stephacidin A. [75,59] A mixture of *syn* **139** and *anti* **140** cycloadducts was cooled to 0 °C in THF and 0.1M HCl was added dropwise. The reaction was then allowed to warm to room temperature and was quenched with $NaHCO_3$. Under these reaction conditions, we isolated a mixture of both open and closed conformers. *Anti* **124** was isolated, unfortunately none of the desired ring open compound was observed. The *syn* isomer was isolated as both the ring open conformer **148** and the bridging amide **124** in small amounts. (Scheme 33)



Scheme 33: First attempt at opening the lactim ether.

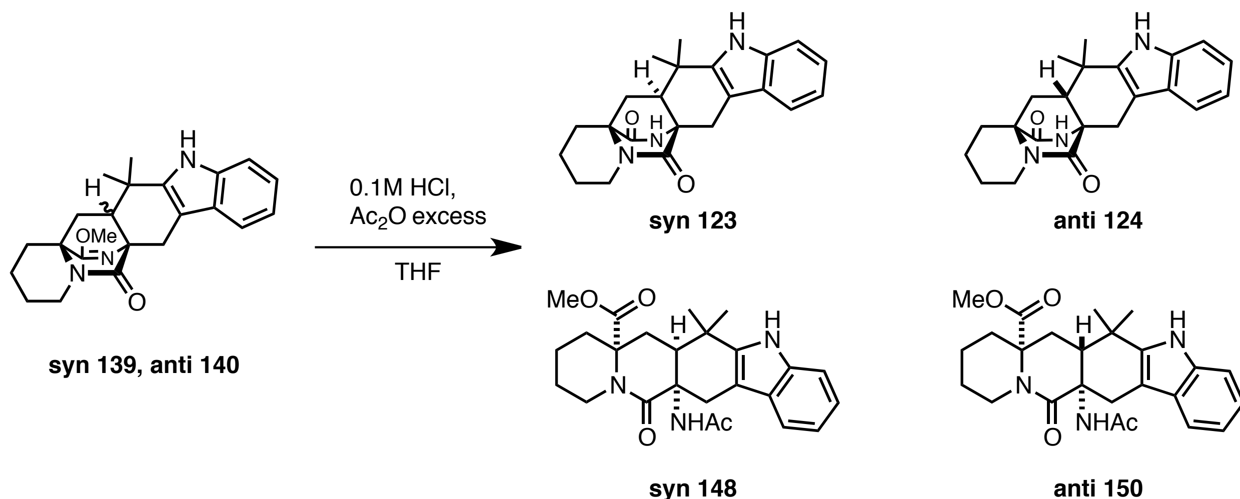
As we knew that this reaction must proceed via the ring open conformer, we postulated that we could prevent intramolecular cyclization by trapping the free amine. First, we attempted to trap the free amine as the phthalimide protected amine.[79] However, treatment of **140** with HCl in the presence of phthalic anhydride only provided **124** and we did not observe **149**. (Scheme 34)



Scheme 34: Attempted phthalimide protection.

Although our initial attempt at trapping the free amine was unsuccessful, we decided to try an alternative method to trap the amine.[80] Lactim ethers **139** and **140** were first dissolved in THF and 20 equivalents of Ac_2O were added. Then 0.1M HCl was added dropwise over five minutes at 0 °C. The reaction was allowed to stir at 4 ^{o}C overnight. Under these conditions, we isolated four different products, including both the

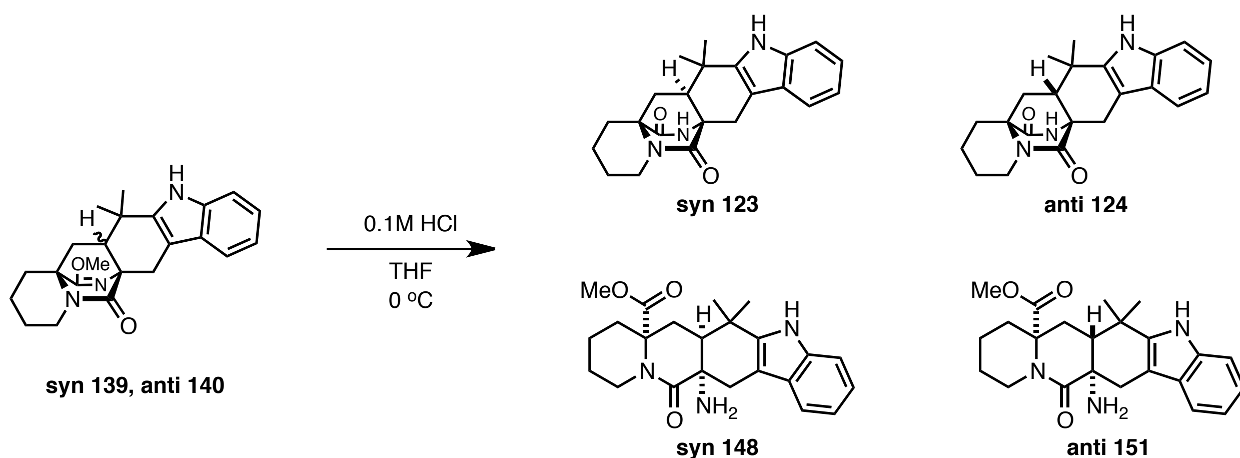
syn **148** and *anti* **150** open products, but the major products were still the bridging amides **123** and **124**. (Scheme 35) Every attempt to optimize the reaction was unsuccessful. We were never able to exclusively form the desired acetate protected amines (**148** and **150**) without the formation of the undesired side products (**123** and **124**). We decided that this reaction sequence would not provide us with enough material to complete the PF1270 synthesis.



Scheme 35: Trapping of the free amine with acetic anhydride.

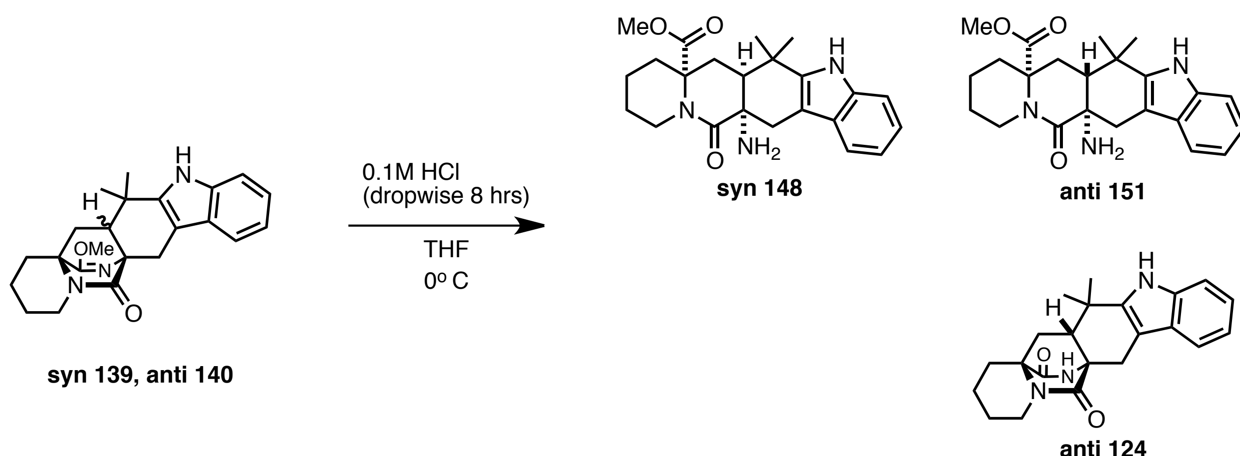
Since the ring open conformers remained the minor products of the reaction, we turned our attention to the acid catalyzed hydrolysis of the lactim ether. We hoped that by further optimizing these reaction conditions, we would be able to isolate the ring open conformers as the major products. As previously stated, we needed to disfavor the intramolecular cyclization. As quenching with $NaHCO_3$ would only promote the cyclization, we decided to quench with a pH 7 buffer instead. Also, we hoped that controlling the reaction temperature would allow us to isolate more of the desired product. Instead of allowing the reaction to warm to room temperature, we decided to

keep the reaction at 0 °C. We submitted **139** and **140** to these reaction conditions and were pleasantly surprised. We observed a small amount of the ring open *anti* adduct **151**. Unfortunately, **151** remained a minor product of the reaction, and the intramolecular cyclization product **124** remained the major product of the reaction. (Scheme 36)



Scheme 36: Formation of *anti* **150**.

Next, we hoped to increase the quantity of **148** and **151** by slowing the addition of acid. To a mixture of **139** and **140** dissolved in THF was added 0.1M HCl dropwise over 8 hours, making sure to keep the reaction at 0 °C for the entire addition. Once the addition was complete, we placed the reaction in a cold room for another 8 hours. TLC analysis showed that starting material was consumed and only two products were observed. The reaction was worked up by quenching with pH 7 buffer and extracting into ether. Three products were isolated: **148** and **151** as the major products, and **124** as a minor product. (Scheme 37)



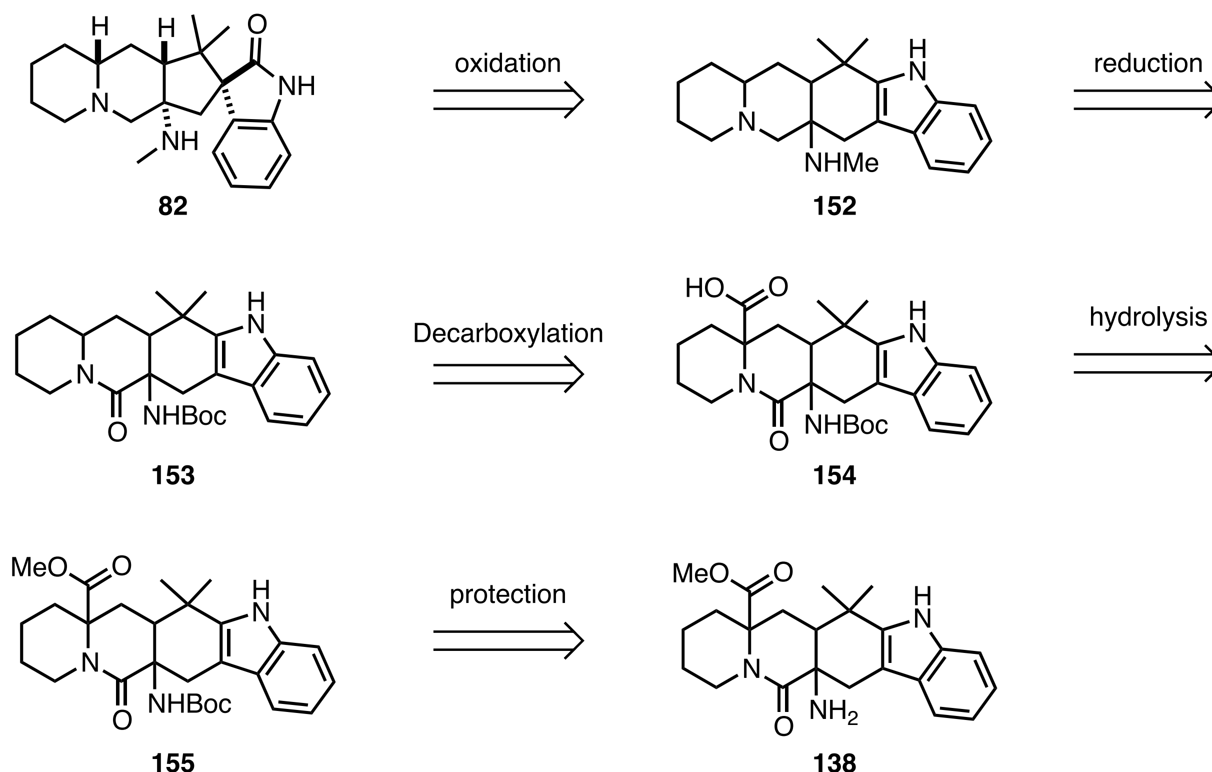
Scheme 37: Formation of **148** and **151** as major products.

Bridging amide **124** was not observed prior to workup, but was isolated after workup. We believed that during the workup, the reaction was warmed to room temperature thereby promoting the intermolecular reaction. In order to test this hypothesis, we submitted **140** to the same reaction conditions, but we were careful not to allow the aqueous and organic phases to warm to room temperature during workup. To our surprise we were able to isolate **151** as the aole product by TLC. It should also be noted that the free amine is not stable and in solution it will spontaneously form **124**. Free amine **151** was so unstable in solution that obtaining an NMR was difficult; consequently, the free amine must be taken directly on to the next step. Next we turned our attention to amine protection. This step also proved problematic.

3.5 Late Stage Retrosynthetic Plan

After considering many different protecting groups we decided on carbamate protection in order to functionalize the carbamate later in the synthesis. We believed that we could readily access the desired core (**82**) via a late stage oxidation to form the desired spirooxindole moiety. Precursor **152** could arise from a LAH reduction of amide

153 which at the same time would provide the desired methylamine **152**.[81] Amide **153** would come from a decarboxylation of acid **154** which could arise from a two-step protection of **138** followed by hydrolysis of methylester **155**. (Scheme 38)

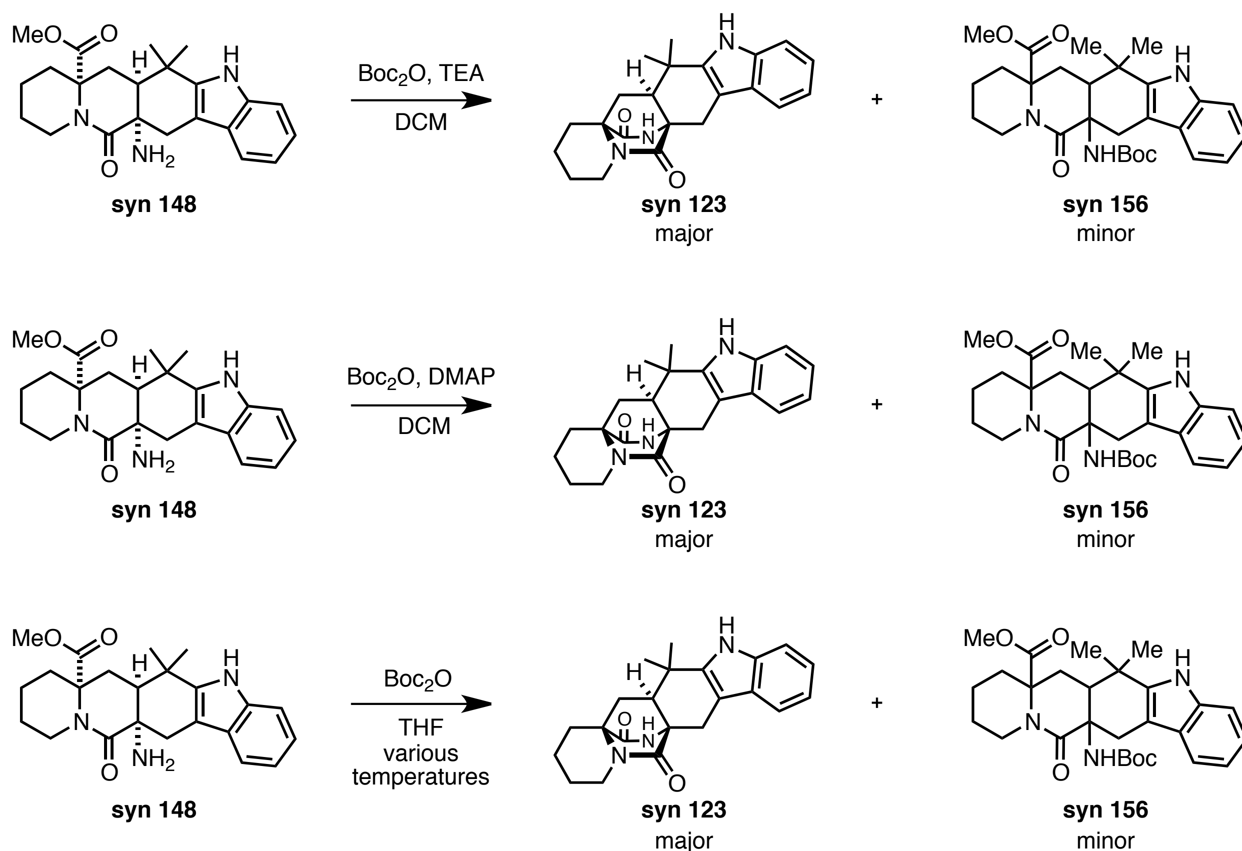


Scheme 38: Late stage retrosynthetic plan.

3.5.1 Boc Protection of the Free Amine

Numerous attempts were made to form the desired Boc protected precursor from *syn* **148**. However, all attempts resulted in the formation of undesired bridging amide **123** as the major product. During our initial screening, we started with traditional conditions for Boc protection. Boc_2O, with TEA in DCM yielded **123** as the major product.[82] We also tried adding DMAP to the above mentioned reaction conditions and saw no change in the ratio of products. Finally, we decided to omit the base completely and attempt the protection using solely Boc_2O in THF at various temperatures. When

this reaction was kept at 0 °C the reaction was slow, and no products formed. At room temperature for days small amounts of both products were formed. Finally, at reflux, the reaction went to completion overnight, albeit with **123** as the major product. (Scheme 39)

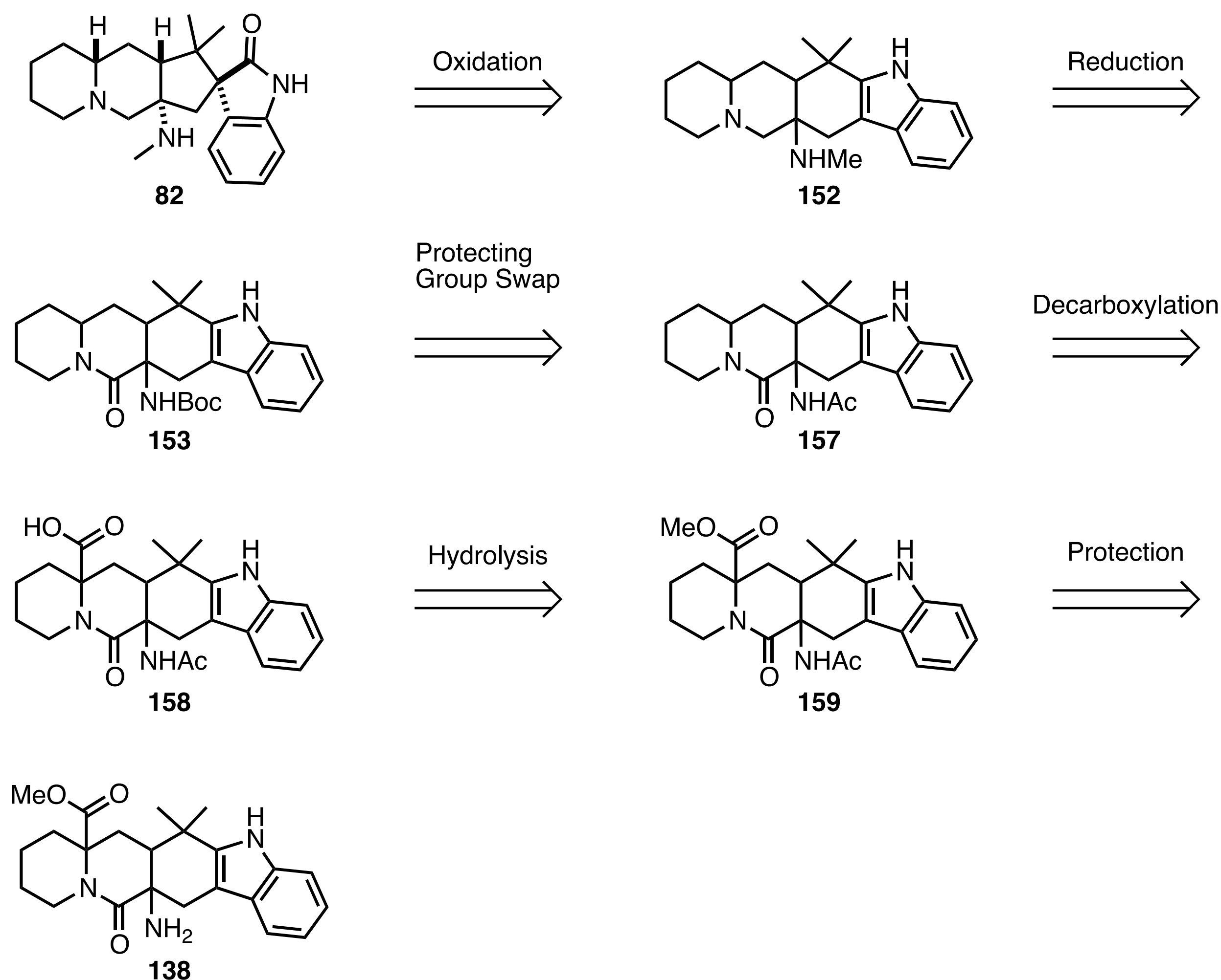


Scheme 39: Attempt to form adduct **156**.

3.6 Late Stage Retrosynthesis, Revised

Since all attempts to protect the free amine as the carbamate were unsuccessful an alternate route was devised. After careful consideration we decided on acetate protection. The late stage synthesis remained the same in that we planned on accessing the desired core **82** via a reduction of protected amine **153,** followed by an oxidation of **152** to install the spirooxindole. We believed that we could access **153**

through a protecting group swap on **157**. The protecting group swap would allow for a one-pot reduction/methylation. Otherwise, a two step methylation and then deprotection of the acetate group would be required prior to the reduction of the amide moiety. Substrate **157** could arise from a decarboxylation of acid **158**. Acid **158** could arise from an acetate protection of **138** followed by hydrolysis of ester **159**. (Scheme 40)

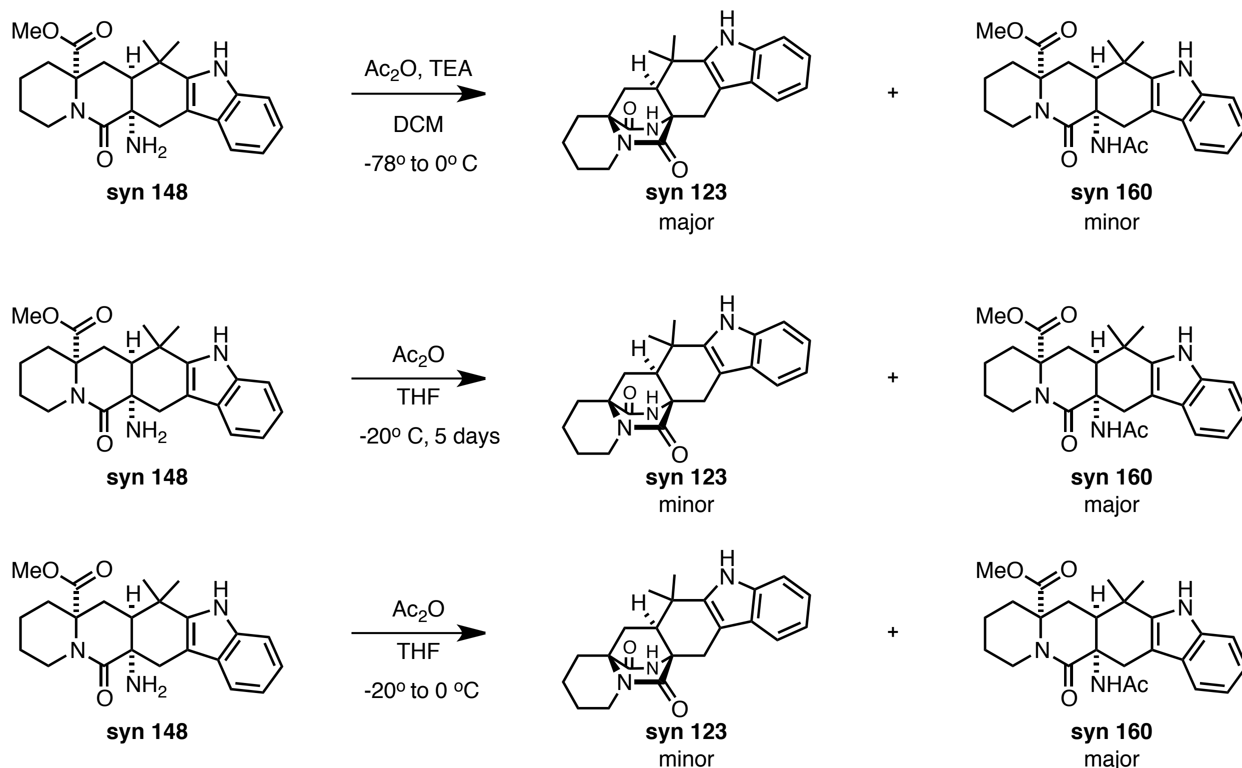


Scheme 40: Late stage retrosynthesis revised

3.6.1 Acetate Protection of the Free Amine

The initial reaction screening was done on the *syn* adduct in an effort preserve the *anti* material for future use. In the initial screening, we decided to lower the reaction

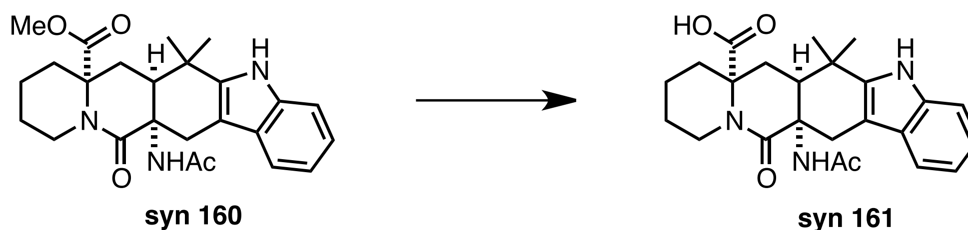
temperature in hopes of slowing the intermolecular reaction. To test if the added base would promote the intermolecular reaction, we tried the reaction with the addition of base. Amine **148** was dissolved in THF and cooled to -78 °C and Ac_2O was added, followed by TEA. The reaction was then allowed to warm to -15 °C and stirred overnight. As expected, the major product was **123,** and **160** was the minor product. After careful consideration we decided to omit the base and retry the reaction. We repeated the reaction only adding the Ac_2O at -20 °C and kept the reaction at -20 °C. The reaction was very slow and took days to go to completion at this temperature. Thus the reaction was allowed to slowly warm to 0 °C overnight in hopes of speeding up the reaction time. Under these conditions, the reaction went to completion and provided us with the desired acetate protected amine **160** as the major product. With the desired product in-hand we could move forward with the synthesis.



Scheme 40: Acetate protection of the free amine.

3.6.2 Conversation of the Ester to the Acid

With **160** in-hand, we turned our efforts to the synthesis of decarboxylation precursor **161**. By all accounts, the conversion of ester **160** to the desired acid **161** looked to be straightforward. (Scheme 41)



Scheme 41: Conversation of ester **160** to desired acid **161**.

This conversion, proved to be quite challenging. (Conditions summarized in Table 2) We submitted ester **160** to 1M LiOH in THF for days at room temperature;[83,84] these

conditions resulted in complete recovery of starting material, so the reaction was refluxed for 3 days, leading to decomposition. Next, we tried to effect the same conversion by treating **160** with Me_3SnOH.[85,86] Attempts at different temperatures and durations resulted in no reaction. Treatment of the ester with LiCl using microwave conditions resulted in a 15% yield of **161**;[87] due to the low yield of this reaction alternative conditions were considered.

We postulated that all of the above conditions were failing due to the steric interactions. Both the ester and protected amine are on the same face of the hydrocarbon framework, causing the steric bulk of the protected amine to block the ester from nucleophilic addition. In an effort to test this theory, we used a reagent designed for the conversion of sterically hindered methyl esters to acids. This reagent was developed by Corey *et al.*, and was utilized in their synthesis of salinosporamide.[88,89] The desired methyltellurate reagent was synthesized by refluxing tellurium powder and $(Me_3Al)_2$ in toluene. The resulting 0.8 M solution was then added to ester **160** in DCM and stirred at room temperature for 6 hours. When the reaction was complete, it was quenched with 1 M HCl and stirred vigorously for several hours. Under these reaction conditions we produced the desired acid in very high yields. With the desired free acid in-hand we turned our attention to the key decarboxylation.

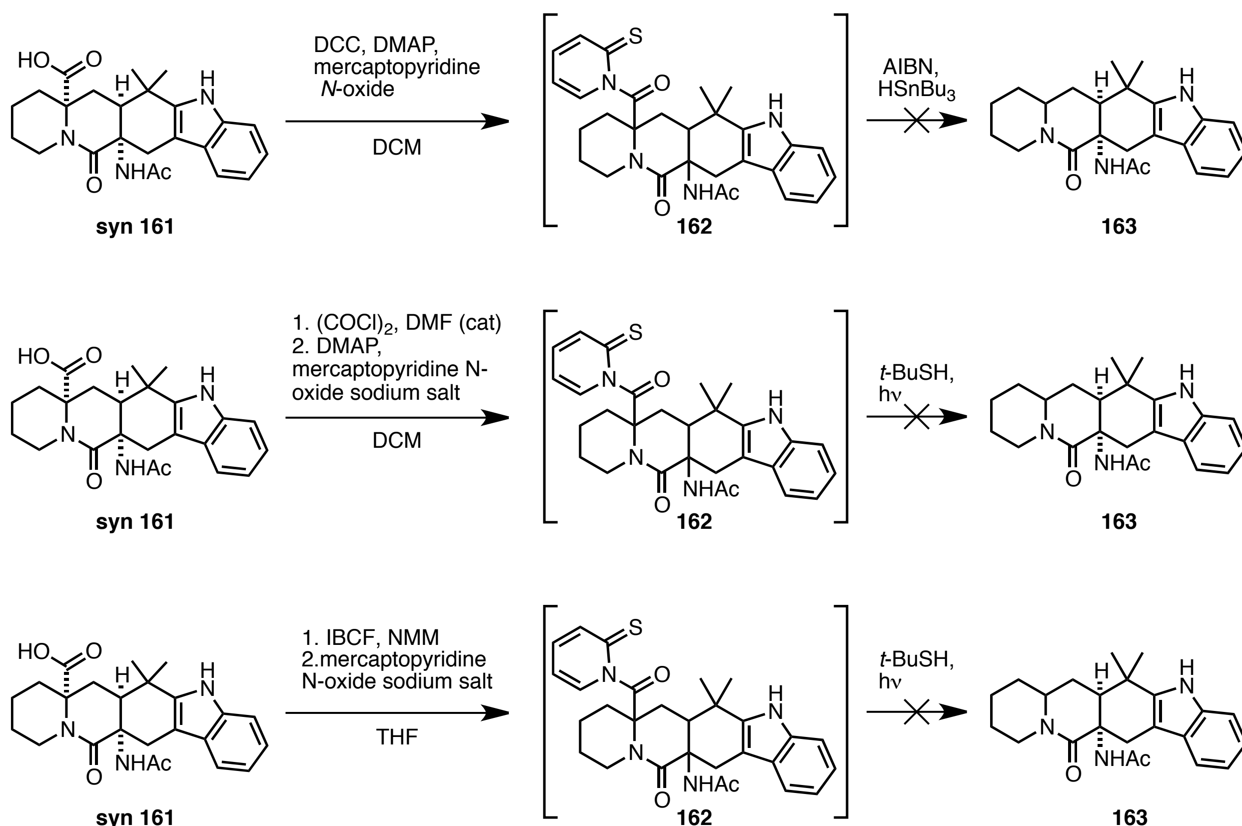
Table 2: Conditions screened for the conversion of methyl ester to desired acid.

Reagent	Solvent	Time	Temperature	Results
LiOH	THF	16 hr	24 °C	No reaction
LiOH	THF	72 hr	100 °C	Decomposition
Me_3SnOH	DCE	24 hrs	60 °C	No Reaction
Me_3SnOH	DCE	72 hrs	90 °C	No Reaction
LiCl	DMF	10 mins	Microwave	15% yield
$(Me_2AlTeMe)_2$	**DCM**	**6 hrs**	**24 °C**	**85% yield**

3.6.3 Barton Decarboxylation

After an extensive literature search, we decided to try Barton decarboxylation conditions first. Barton decarboxylations have been used extensively in total synthesis, and remain one of the top methods for decarboxylation.[90-95] These conditions call for the conversation of the carboxylic acid to the thiohydroxamate ester. The ester is then warmed in the presence of a hydrogen donor resulting in reductive decarboxylation.[96,97] There are many different conditions that can be used to form the thiohydroxamate and also a number of different conditions can be used to promote the radical decarboxylation.[98,99] We attempted a number of different Barton decarboxylations using various conditions. (Scheme 42) The first Barton reaction we tried utilized a DCC coupling to afford thiohydroxamate ester **162**, which was then treated with AIBN and

$HSnBu_3$. Attempts were also made to convert acid **161** to the corresponding acid chloride, which was then used in situ to form the desired thiohydroxamate ester **162**. The ester was then treated with *t*-BuSH and irradiated with a desk lamp. Finally, we attempted the formation of the mixed anhydride, which was then used to form thiohydroxamate ester **162**. This ester was then treated with *t*-BuSH and irradiated with a desk lamp. Unfortunately all of these reactions resulted in a complex mixture of products from which we were never able to isolate our desired product.



Scheme 42: Attempted decarboxylation of **160**.

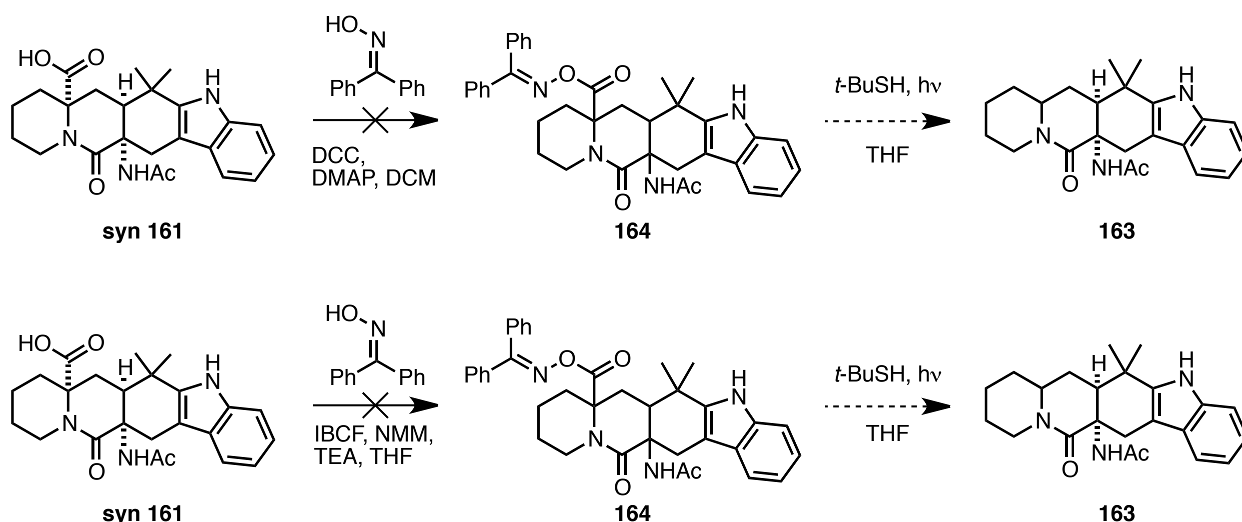
It should be noted that thiohydroxamate esters produced under these reaction conditions were not isolated because of their high reactivity. These esters are extremely sensitive to light and heat making their isolation difficult. Due to their low stability,

purification of such esters is rarely attempted. These conditions presented us with a difficult problem. The reactions were clearly failing, but it was nearly impossible to pinpoint where the failure was occurring. In an effort to identify the step in which the problem arose, we decided to employ different reaction conditions.

3.6.4 Modified Barton Decarboxylations

A few different Barton modifications have been published.[100] We decided to use a modification developed by Hasebe and co-workers in which benzophenone oxime esters are employed in the place of thiohydroxamate esters.[101] Unlike thiohydroxamate esters, benzophenone oxime esters can be isolated, purified and stored under ambient temperatures for months at a time.[102] If we were able to isolate the desired benzophenone oxime ester, then we would be able to screen a number of different decarboxylation conditions.

The desired benzophenone oxime **164** could be synthesized in one step from acid **161**. First, we tried to couple acid **161** with benzophenone imine using DCC and DMAP. Secondly, we tried to form the mixed anhydride of **161** followed by treatment with benzophenone imine. However, both attempts to form **164** failed. (Scheme 43)



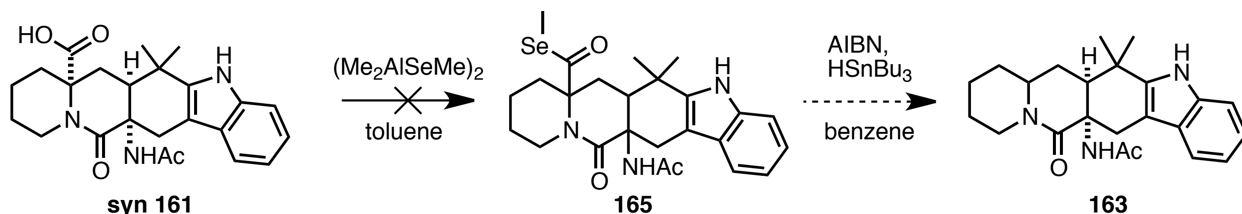
Scheme 43: Attempted formation of benzophenone oxime ester **164**.

We believe that the formation of both esters **162** and **164** was unsuccessful because of steric interactions. Ester **160** was unreactive, and conversation to acid **161** required a special reagent used in hindered systems. Although we only screened a few reaction conditions for the formation of **162** and **164**, we believed that screening alternative conditions would result in the same outcome. Due to the steric constraints of both the Barton reagent and the benzophenone imine, we believed that coupling of either reagent would be impossible, and we decided to screen other known decarboxylation conditions.

3.6.5 Other Decarboxylations

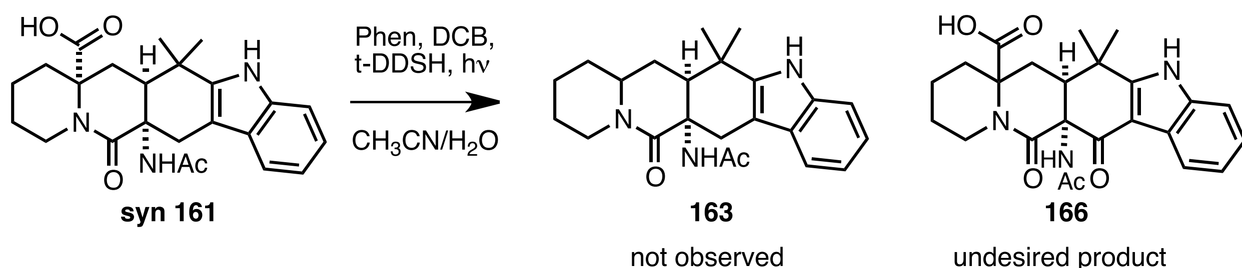
Since we had been successful at converting the ester **160** to acid **161** using a methyltellurate reagent, we believed that we might be able to access a selenoester using similar reaction conditions.[103-105] We made the corresponding dimethyl aluminum selenide reagent and added it to acid **161** in DCM at room temperature. After stirring at room temperature the starting material was still present, so the reaction was then

warmed to 30 °C overnight. Unfortunately, even under these conditions no desired product was isolated. (Scheme 44) Since these conditions were not working we decided to try a less conventional method of decarboxylation.



Scheme 44: Attempted formation of selenoester **165**.

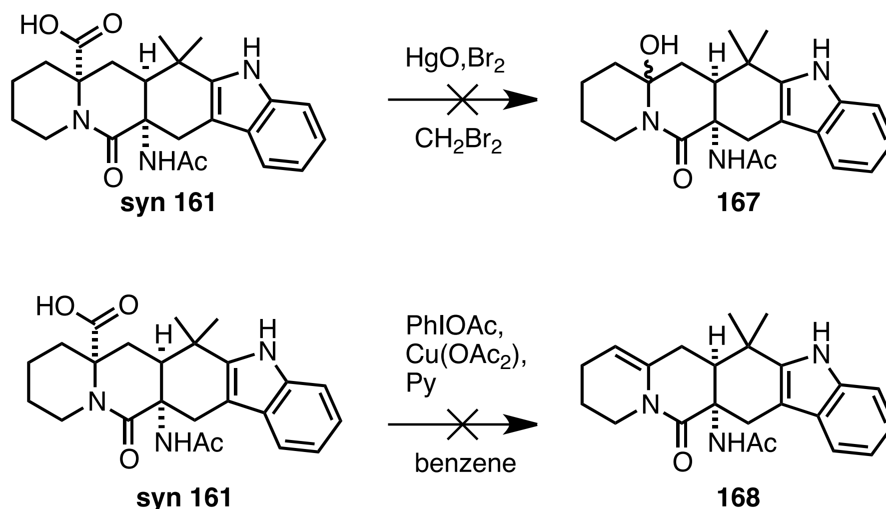
In the next attempt, we wanted to try decarboxylation using photogenerated cation radical chemistry developed by Hatanaka and co-workers.[106] Acid **161** was treated with Phen, DCB, *t*-DDSH in MeCN and H_2O. The resulting solution was then irradiated with a 400W high-pressure mercury lamp for 24 hours. (Scheme 45) Unfortunately, none of the desired decarboxylated product **163** was isolated. We did, however, recover an undesired side product **166**.



Scheme 45: Attempted formation of **163** using photogenerated radical conditions.

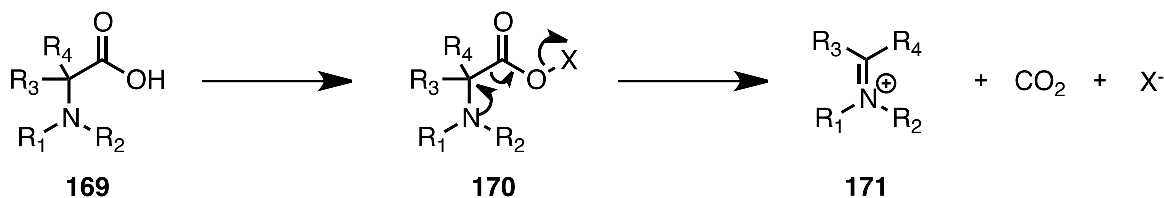
Since all of the previous decarboxylations failed, alternative conditions were proposed. The classic Hunsdiecker reaction involves treatment of a carboxylic acid with silver oxide to form the corresponding silver salt. The silver salt is then treated with one equivalent of a halogen, providing the desired alkyl halide.[107,108] A major problem with

the Hunsdiecker reaction is that the silver salt must be very pure and dry. To avoid this problem, we decided to try both the Cristol-Firth modification[109] and the Suarez modification.[110] First, we treated acid **161** with HgO and Br_2 in dibromomethane but never observed any of the desired product (**167**). Next, we treated acid **161** with $PhI(OAc)_2$, $Cu(OAc)_2$ and pyridine in benzene. Under these conditions we were also unable to isolate any of our desired product (**168**). (Scheme 46)



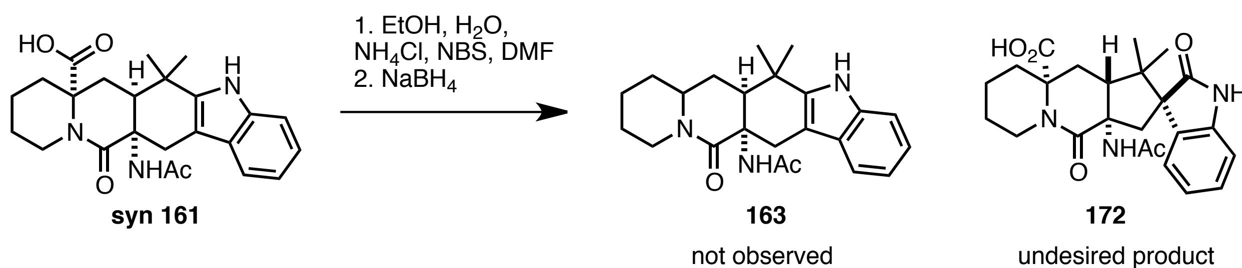
Scheme 46: Attempted modified Hunsdiecker reactions.

Given that all of these attempts at the decarboxylation were unsuccessful, we decided to look at the problem from a different perspective. Up until this point, we had attempted decarboxylation using various radical conditions on our acid moiety. Treatment of our system as an amino acid, rather than an independent carboxylic acid, presented alternative decarboxylation conditions which we believed would be more successful. It has been previously demonstrated that tertiary α-amino acid derivatives such as **169** can undergo clean decarboxylations by activation of the carboxylic acid moiety (**170**). (Scheme 47)



Scheme 47: Activation and decarboxylation of α-amino acids derivatives.

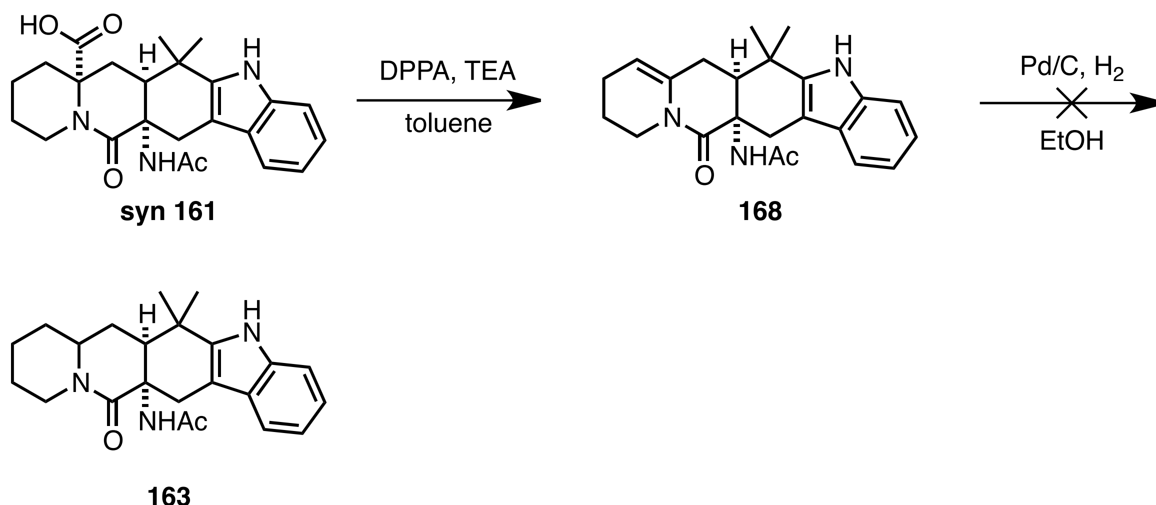
There are a number of different ways to activate the carboxylic acid moiety.[111-115] One such method was used by Golding and co-workers.[116] Using these conditions, we treated acid **161** with NBS in hopes of promoting the decarboxylated imine, which we then tried to reduce by treatment with excess $NaBH_4$. We did not see any of our desired product (**163**). We did, however, isolate the undesired spirooxindole **172**. (Scheme 48)



Scheme 48: Attempted decarboxylation of **161**.

Although our initial attempts failed, we still wanted to screen conditions for the decarboxylation of α-amino acids. After searching the literature, we chose conditions used by Bermejo-Gonzalez and co-workers in their synthesis of indolizidine alkaloids.[117,118] We treated acid **161** with DPPA and TEA in toluene. The reaction was then warmed to 100 °C for 16 hours. After workup we isolated our decarboxylated alkene **168** in a 41% yield. With the desired alkene in-hand, we turned our attention to reduction of alkene **168** to **163**. (Scheme 49) However, all of the conditions that we have currently tried have not provided **163**. Since the decarboxylation proved to be very

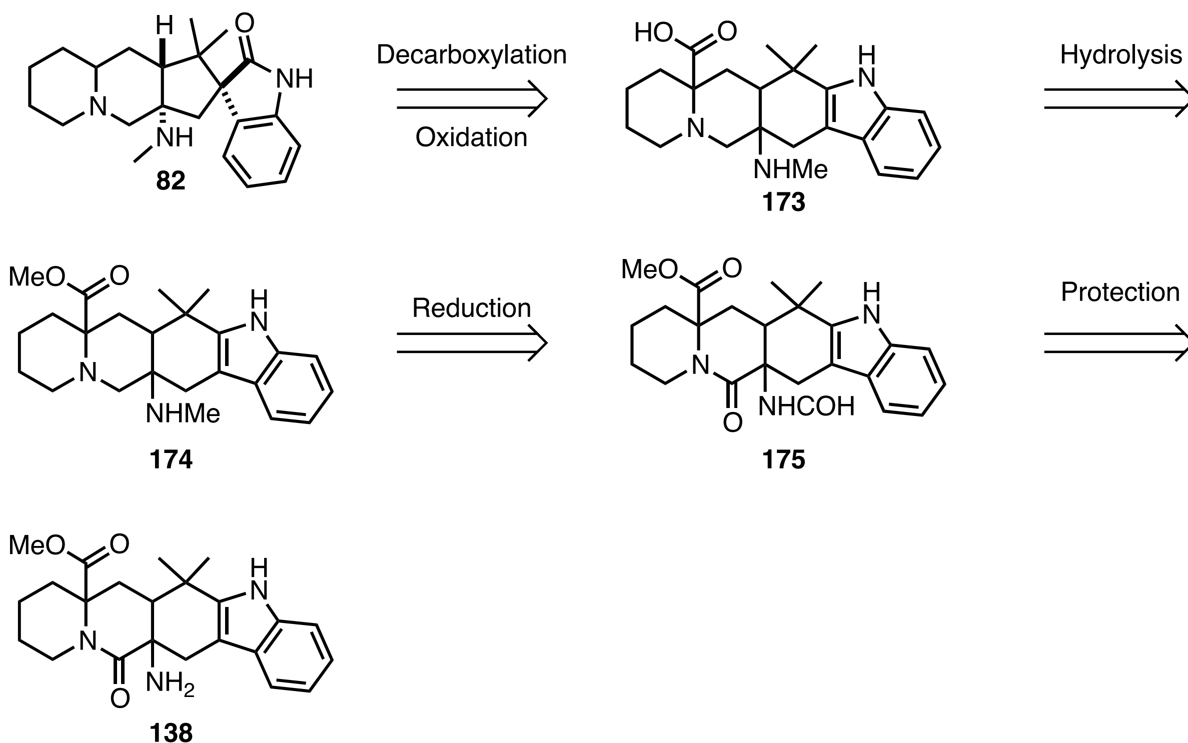
difficult, we were working on a concurrent plan that might allow us to readily decarboxylate.



Scheme 49: Decarboxylation of **161** with DPPA to afford **168**.

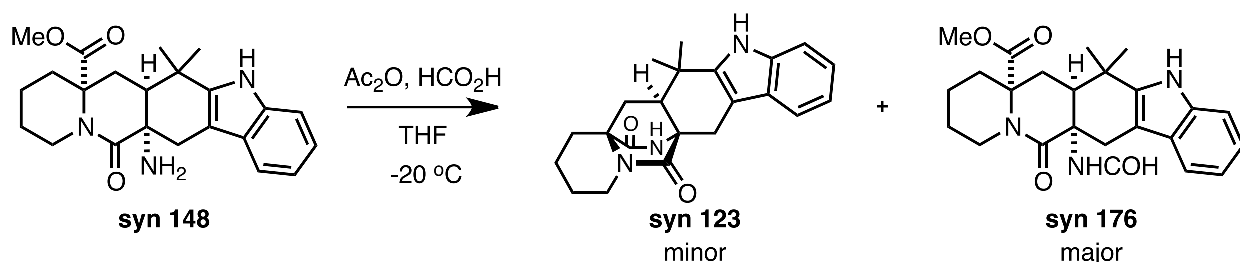
3.7 Concurrent Route for Decarboxylation

We proposed that the decarboxylation was difficult because of sterics found in the pentacyclic ring system. We believed that changing the protecting group on the amine would reduce steric strain, thereby allowing us readily decarboxylate. We decided to revisit the retrosynthetic analysis shown in Scheme 50. We believed that we could access the exact pentacyclic core **82** via a decarboxylation, followed by an oxidative rearrangement of **173**. Next, we could access acid **173** via hydrolysis of ester **174**. Although traditional hydrolysis conditions were unsuccessful in previous studies, we believed that reducing the size of the substituent on the amine would make the acid more accessible. The desired ester could come from a one-pot reduction of both the amide and formate moieties present in intermediate **175**. We believed that we could access formate **175** via a protection of the previously described free amine **138**.



Scheme 50: Revised late stage retrosynthetic analysis.

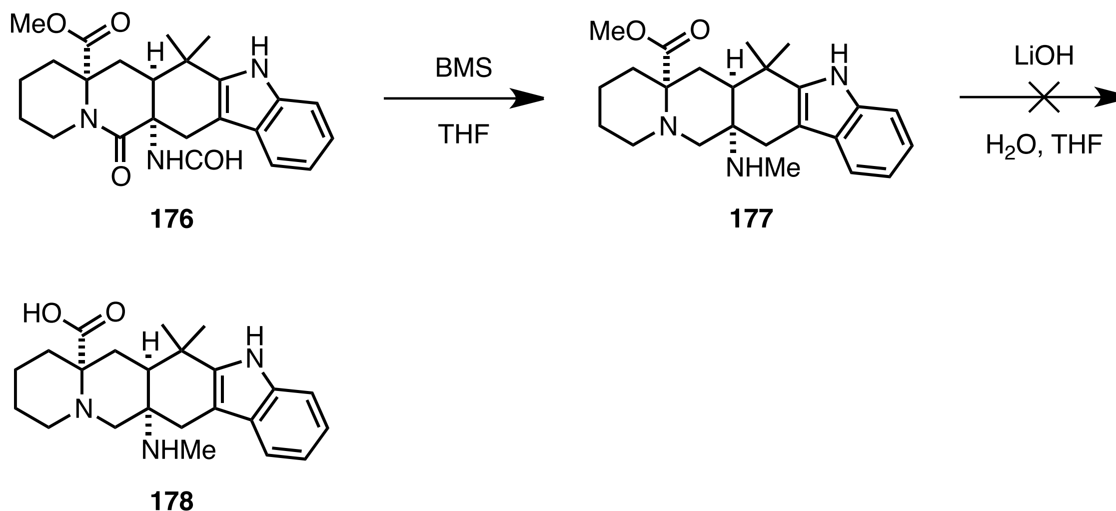
In the forward direction, the synthesis starts with protection of the free amine as the formate. After optimization we were able to get the desired formate as the major product by keeping the reaction at -20 °C for 5 hours.[119-121] (Scheme 51)



Scheme 51: Formation of formate **176**.

With the desired formate in-hand, we needed to reduce **176** to the methylamine **177**. We found that treatment of **176** with BMS in THF at ambient temperature for 16 hours resulted in the formation of **177** in excellent yields.[122,123] However, treatment of **177** with

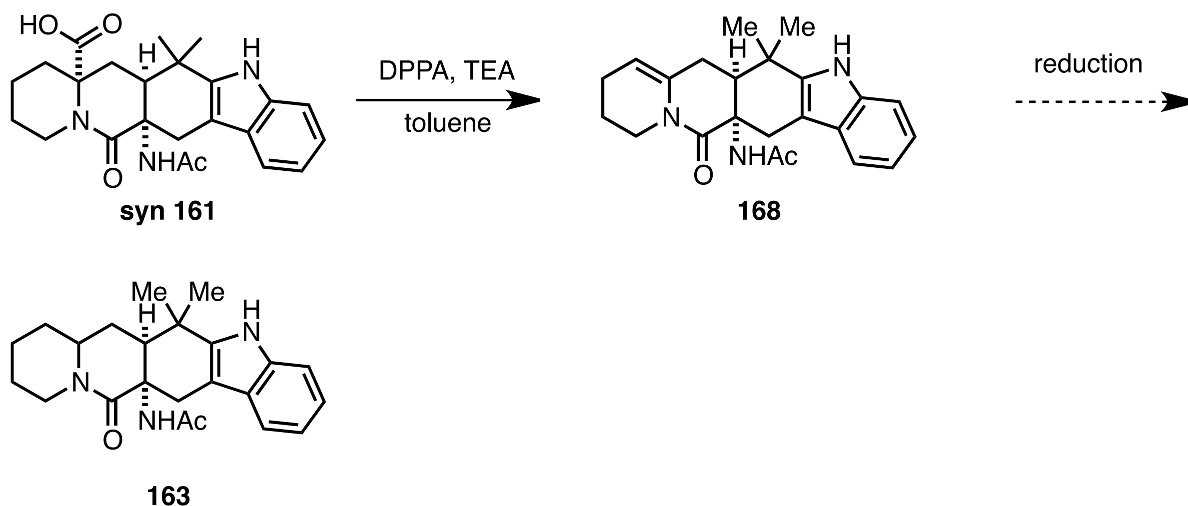
LiOH and THF at reflux did not result in the formation of acid **178**. This suggests that even after the reduction of the formate, the ester remains hindered and is unable to undergo hydrolysis. (Scheme 52)



Scheme 52: Attempted synthesis of acid **178**.

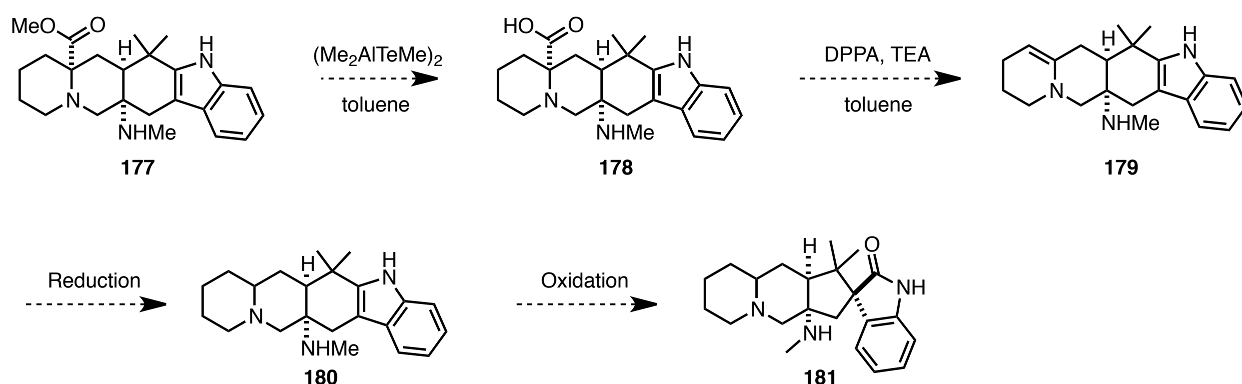
3.8 Future Directions

Although we were able to form the desired decarboxylated intermediate **168**, many questions remain unanswered. In our first synthetic route, the reduction of alkene **168** to **163** remains a top priority. We plan on screening a number of different conditions in hopes of accomplishing the desired reduction product. (Scheme 53)



Scheme 53: Future plans for the late stage synthesis of intermediate **163**.

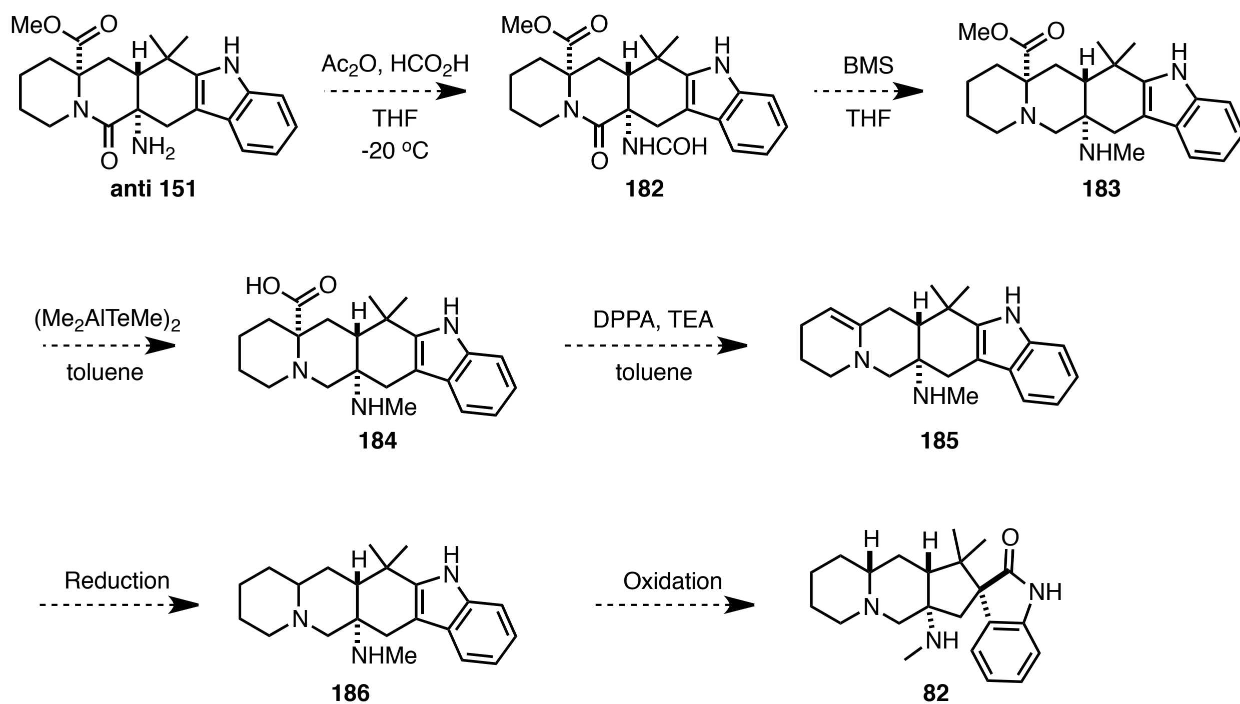
We hope to combine both of our late stage synthetic approaches to access the desired pentacyclic core **181**. Treatment of **177** with the methyltellurate reagent would provide us with acid **178**. Using the previously described decarboxylation conditions, we could access alkene **179**. Reduction of the double bond could provide intermediate **180**. Finally, oxidation of intermediate **180** could provide the desired spirooxindole **181**. (Scheme 54)



Scheme 54: Future work for the formation of **181**.

It should be noted, that until the late stage synthesis has been established, we plan on carrying out the synthesis on the *syn* product in an effort to save the *anti*

product. In our final synthetic efforts, we plan on utilizing the same synthetic strategy to convert *anti* **151** to the pentacyclic **82** framework of the PF1270s and the citrinadins. (Scheme 55)



Scheme 55: Proposed synthesis of pentacyclic **82** from **151**.

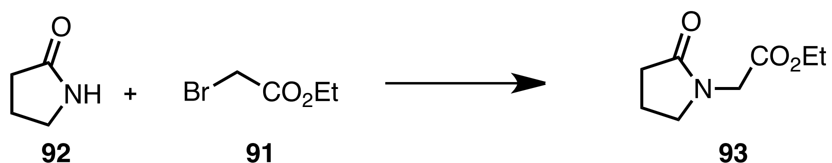
Chapter 4: Experimental

4.1 General Synthetic Considerations

All reagents were commercial grade and used without further purification unless otherwise noted. Unless otherwise noted, all reactions were run under an argon atmosphere in flame or oven-dried glassware. Reactions were monitored by thin layer silica gel chromatography (TLC) using 0.25 mm silica gel 60 F plates with fluorescent indicator (Merck). Products were purified via either flash column chromatography using silica gel grade 60 (230-400 mesh) purchased from Sorbent Technologies or preparative thin layer chromatography (1000 mm). Acetonitrile (CH_3CN), dichloromethane (CH_2Cl_2), diethyl ether (Et_2O), *N*,*N*-dimethylformamide (DMF), methanol (MeOH), tetrahydrofuran (THF), toluene (PhMe), and triethylamine (Et_3N) were all degassed with argon and passed through a solvent purification system containing alumina or molecular sieves. ^{1}H-NMR spectra and ^{13}C-NMR spectra were obtained on ROBOT Varian 300, 400, or 500 MHz NMR spectrometers. NMR spectra were taken n $CDCl_3$ (^{1}H, 7.26 ppm; ^{13}C, 77.0 ppm), CD_3OD (^{1}H, 3.31 ppm, 49.15 ppm), d_6-DMSO (^{1}H, 2.50 ppm, ^{13}C, 39.51 ppm) and D_2O (^{1}H, 4.79 ppm) obtained from Cambridge Isotope Labs. Mass spectra were obtained on Fisons VG Autospec using a high/low resolution magnetic sector.

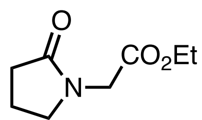
4.2 Experimental Procedures

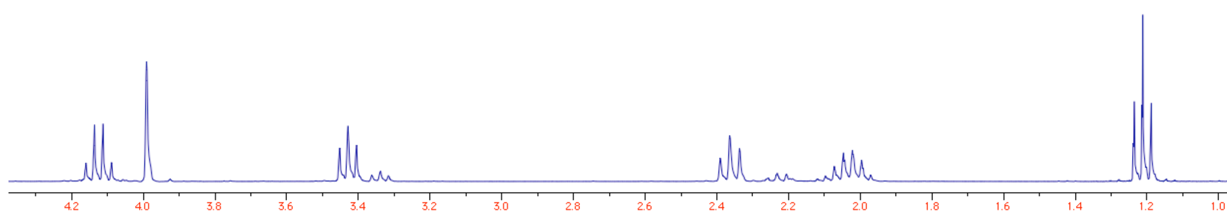
ethyl 2-(2-oxopyrrolidin-1-yl)acetate (93):



To a solution of Na (0.540 g, 23.5 mmol) refluxing in toluene (15 mL) was added 2-pyrrolidinone **92** (2 g, 23.5 mmol) dropwise. The reaction mixture was stirred at reflux for one hour after the addition was complete. An additional 10 mL of toluene was added so that the slurry could be stirred. Ethyl bromoacetate **91** (3.92 g, 23.5 mmol) was added dropwise for 20 minutes and the reaction mixture was stirred for an additional hour. The reaction was then cooled to room temperature and filtered. The solvents were evaporated under reduced pressure. The desired product was purified by distillation (literature bp 108-113 °C at 1-2 mmHg) to afford a colorless oil (3.75 g, 93%).

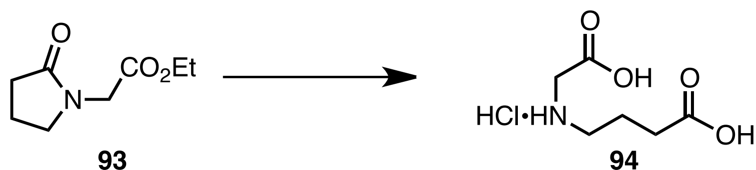
^{1}H NMR (300 MHz, $CDCl_3$) δ 4.13 (q, *J* = 7.2 Hz, 2H), 3.99 (s, 2H), 3.42 (t, *J* = 6.9 Hz, 2H), 2.36 (t, *J* = 7.8 2H), 2.09- 1.97 (m, 2H), 1.21 (t, *J* = 6.9 Hz, 3H).





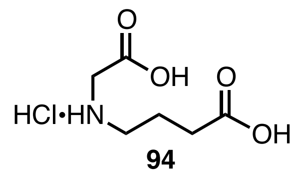
^{1}H NMR, 300 MHz, $CDCl_3$, filename: ms228fr5

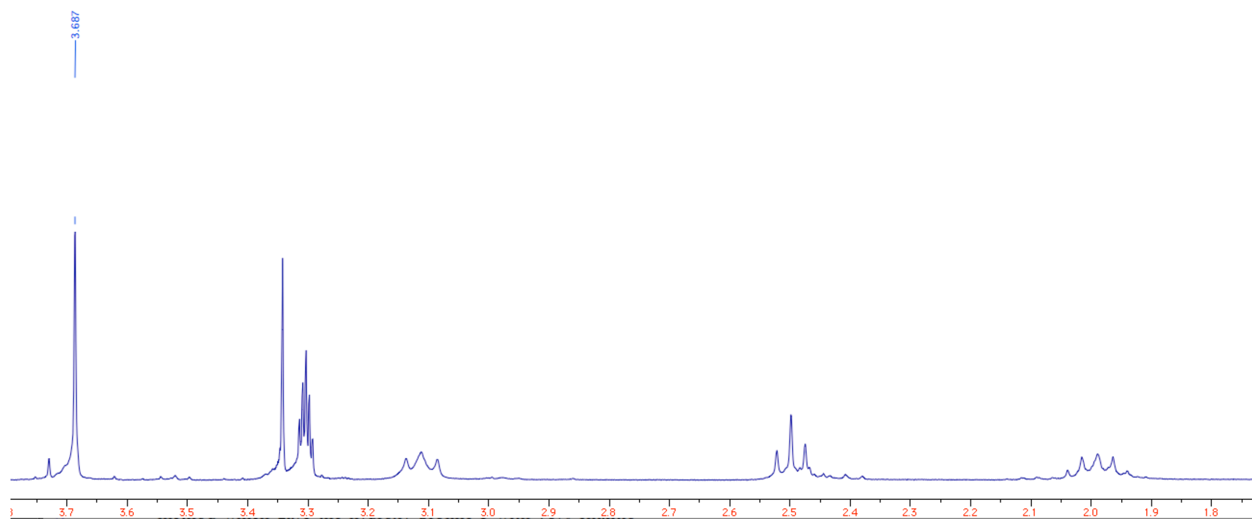
3-azaheptane-1,7-dioic acid hydrochloride (94):



A solution of pyrrolidinone **93** (1.33 g, 7.78 mmol) was dissolved in 6 M HCl (10 mL). The solution was then refluxed for 48 hours. The solution was then cooled to room temperature and concentrated. The residue was then dissolved in MeOH (5 mL) and concentrated three times. The off white solid (1.24g, 98%) was then taken on without any further purification.

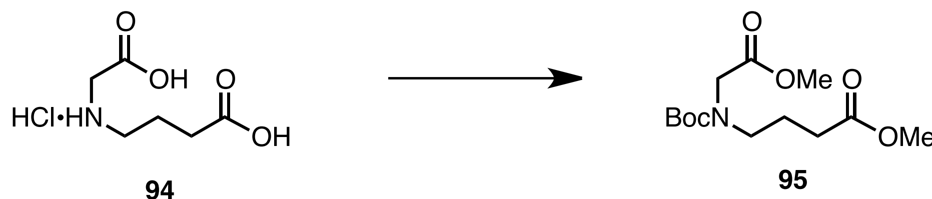
^{1}H NMR (300 MHz, D_2O) δ 3.68 (s, 2H), 3.11 (t, J = 7.7 2H), 2.498 (t, *J* = 7.2 Hz, 2H), 2.01-1.95 (m, 2H), 2.04 (m, 2H), 1.21 (t, *J* = 6.9 Hz, 3H).





^{1}H NMR, 300 MHz, D_2O, filename: ms224crude

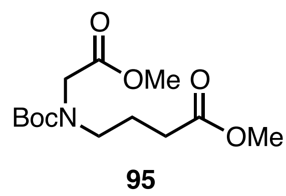
methyl 4-((*tert*-butoxycarbonyl)(2-methoxy-2-oxoethyl)amino)butanoate (95):

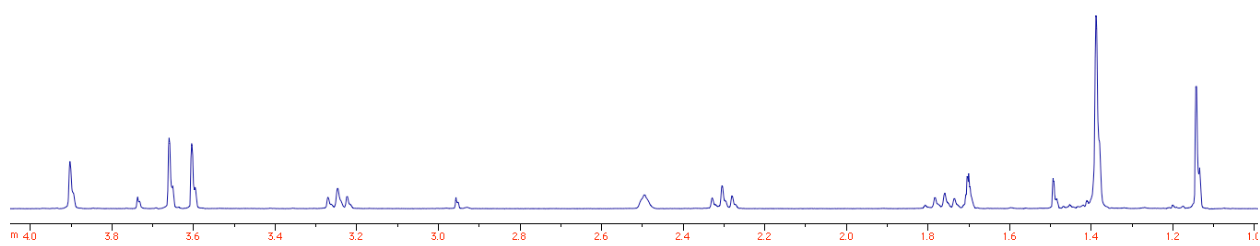


Acetyl chloride (1.17 mL) was added to MeOH (10 mL) and the solution was stirred for 15 minutes at room temperature. The diacid **94** (1.9 g, 9.6 mmol) was then added and the reaction mixture was refluxed for five hours. The resulting solution was then cooled to room temperature and concentrated under reduced pressure. The crude clear oil was then taken on without further purification.

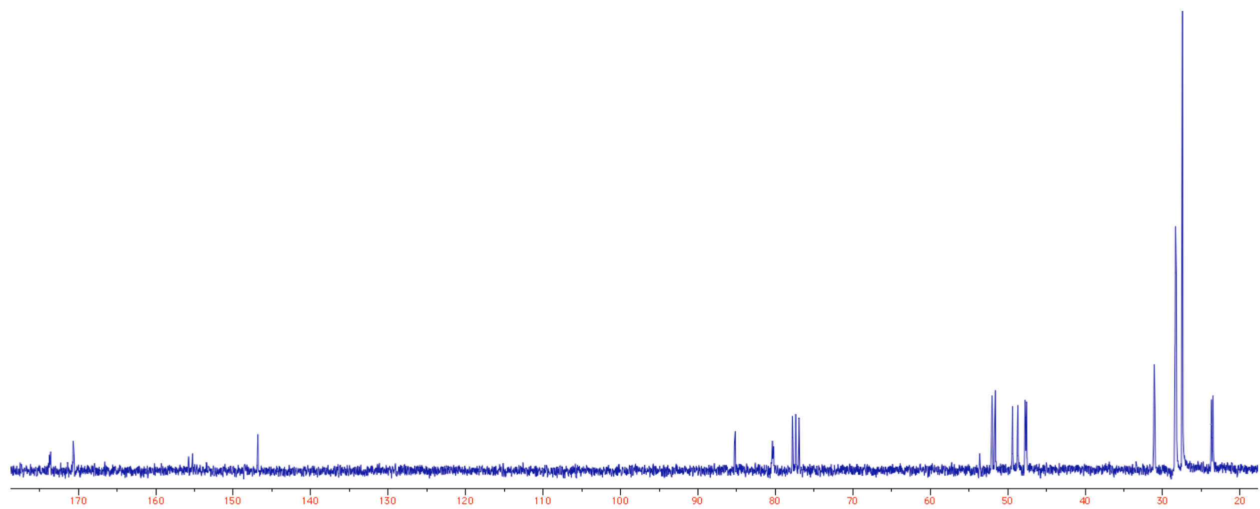
Boc_2O (3.43 g, 15.4 mmol) in DCM (3.2 mL) was added dropwise to a solution of TEA (2.31 mL, 15.4 mmol) and diester (2.24 g, 11.8 mmol) in 28.8 mL of DCM. The reaction mixture was then stirred at ambient temperature for 16 hours. The reaction mixture was then diluted with DCM (50 mL) and was washed with 2 M aqueous citric acid two times. The organic phase was then washed with brine then dried over Na_2SO_4, filtered and concentrated to half volume. The organic phase was ran through a bed of silica gel and evaporated to yield a colorless oil (67% over 2 steps).

^{1}H NMR (300 MHz, $(CD_3)_2SO$) δ 3.90 (bs, 2H), 3.66 (s, 3H), 3.60 (s, 3H), 3.24 (t, *J* = 7.2 2H), 2.3 (t, *J* = 7.2 Hz, 2H), 1.76-1.69 (m, 2H), 1.38 (s, 6H), 1.14 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.7, 170.6, 155.2, 80.3, 51.6, 49.3, 47.5, 31.0 27.9, 23.6, 23.6.



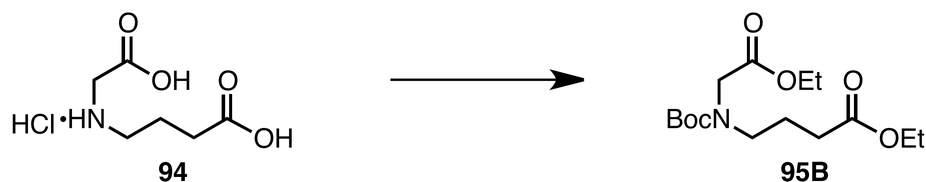


^{1}H NMR, 300 MHz, $(CD_3)_2SO$, filename: ms236ht



^{13}C NMR, 75 MHz, $CDCl_3$, filename: ms236carbon

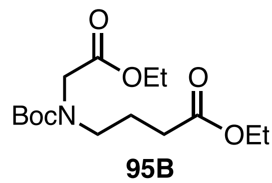
ethyl 4-((*tert*-butoxycarbonyl)(2-ethoxy-2-oxoethyl)amino)butanoate (95B):

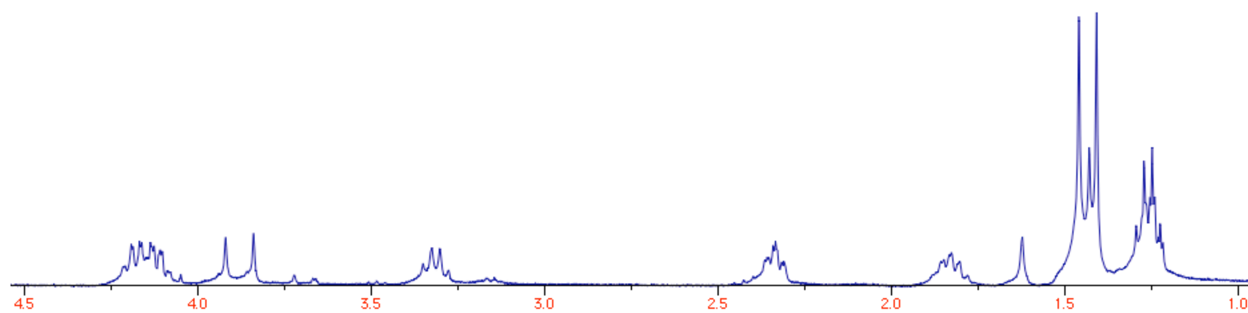


Acetyl chloride (1.63 mL) was added to EtOH (14.6 mL) and the solution was stirred for 15 minutes at room temperature. The diacid **94** (2.62 g, 13.3 mmol) was then added and the reaction mixture was refluxed for five hours. The resulting solution was then cooled to room temperature, and concentrated under reduced pressure. The crude clear oil was then taken on without further purification.

Boc_2O (3.38 g, 14.6 mmol) in DCM (3.2 mL) was added dropwise to a solution of TEA (2.21 mL, 14.6 mmol) and diester (2.65 g, 12.2 mmol) in 32 mL of DCM. The reaction mixture was then stirred at ambient temperature for 16 hours. The reaction mixture was then diluted with DCM (50 mL) and was washed with 2 M aqueous citric acid two times. The organic phase was then washed with brine then dried over Na_2SO_4, filtered and concentrated to half volume. The organic phase was ran through a bed of silica gel and evaporated to yield a colorless oil (87% over 2 steps).

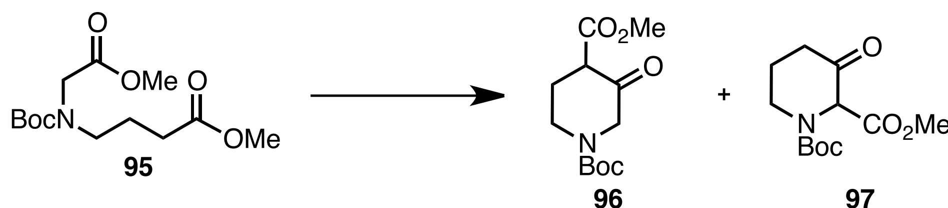
^{1}H NMR (300 MHz, $CDCl_3$) δ 4.20-4.07 (m, 4H), 3.91 (s, 1H), 3.83 (s, 1H), 3.31 (q, J = 14.4, 7.8 Hz, 2H), 2.33 (t, J = 8.7 Hz, 2H), 1.87-1.77 (m, 2H), 1.45, 1.42, 1.40 (all singlets, total 9H), 1.29-1.22 (m, 6H).





^{1}H NMR, 300MHz, $CDCl_3$, filename: ms241sp2

1-*tert*-butyl 4-methyl 3-oxopiperidine-1,4-dicarboxylate (96) and 1-*tert*-butyl 2-methyl 3-oxopiperidine-1,2-dicarboxylate (97) :



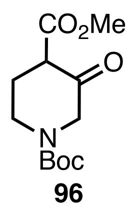
Potassium *tert*-butoxide (176 mg, 1.58 mmol) was added over 10 minutes to an ice-cooled, stirred solution of Boc diester **95** (500 mg, 1.58 mmol) in dry toluene (4 mL). After an additional 20 minutes, the reaction was acidified to pH 3 using 2 M aqueous citric acid and the organic layer was separated. The aqueous phase was extracted with DCM and the combined organic phases were washed with washed with brine, dried over Na_2SO_4, filtered and concentrated. The crude oil was purified via flash column chromatography (5% EtOAc/Hex to 25% EtOAc/Hex).

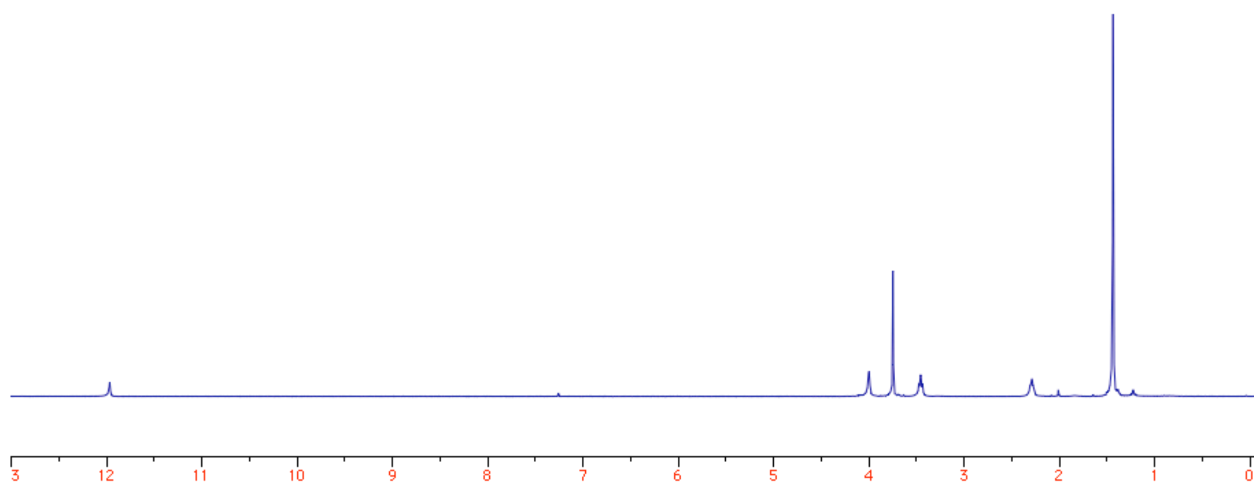
1-*tert*-butyl 4-methyl 3-oxopiperidine-1,4-dicarboxylate (96):

^{1}H NMR (300 MHz, ($CDCl_3$) δ 11.96 (s, 1H), 3.99 (s, 2H), 3.74 (s, 3H), 3.45 (t, 2H), 2.30-2.27 (m, 2H), 1.43 (s, 9H). (47%)

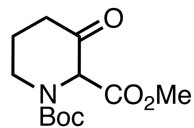
1-*tert*-butyl 2-methyl 3-oxopiperidine-1,2-dicarboxylate (97):

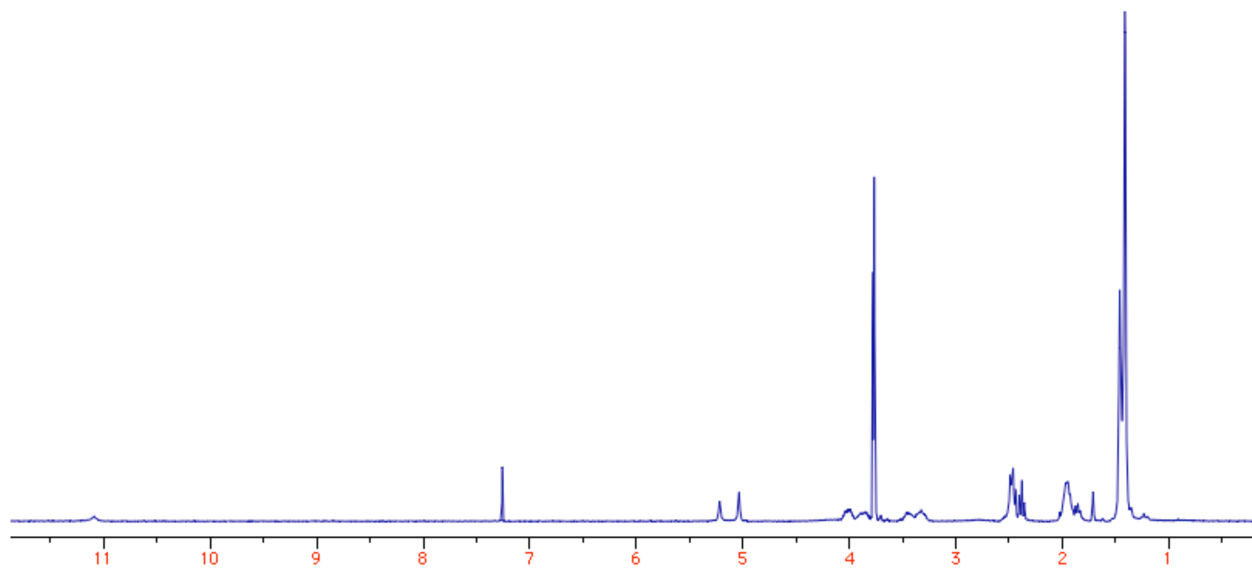
^{1}H NMR (300 MHz, ($CDCl_3$) δ 11.09 (s, 1H), 5.21 and 5.22 (both bs, total 1H), 4.05-3.83 (m, 1H), 3.76 (s, 3H), 3.48-3.28 (m, 1H), 2.48-2.35 (m, 2H), 1.96-1.83 (m, 2H), 1.44 (d, J = 14.4 Hz, 9H). (27%)





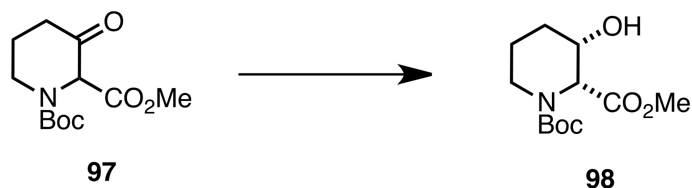
^{1}H NMR, 300 MHz, $CDCl_3$, filename: ms240sp1





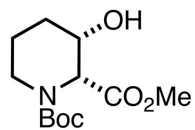
^{1}H NMR, 300 MHz, $CDCl_3$, filename: ms240sp2

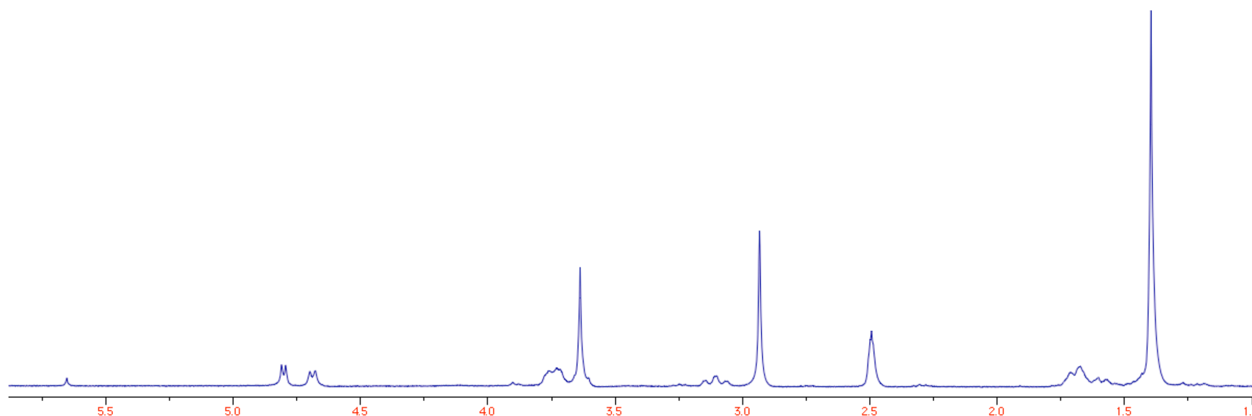
(2*R*,3*S*)-1-*tert*-butyl 2-methyl 3-hydroxypiperidine-1,2-dicarboxylate (98):



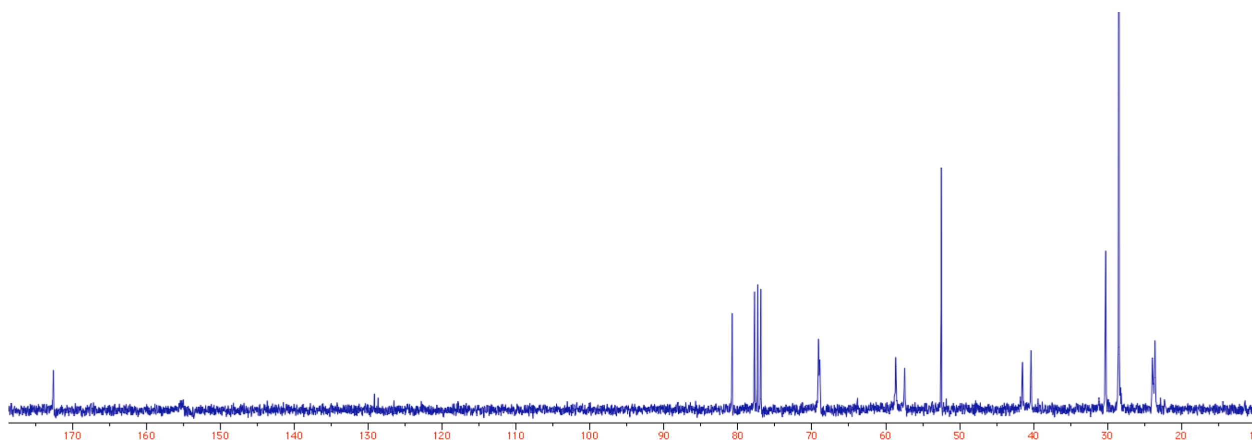
To a stirred, fermenting suspension of dried bakers' yeast (288 mg) and sucrose (960 mg) in tap water (9 mL) was added Boc ketone **97** (96 mg, 0.373 mmol). The reaction mixture was gently warmed to 30-32 °C. After 24 hours, the mixture was vacuum filtrated and re-filtered through Celite. The filtrate was then extracted with DCM 5 times. The combined extracts were washed with brine and then dried, filtered, and concentrated to give an oil (83 mg, 86%).

^{1}H NMR (300 MHz, $(CD_3)_2SO$, 300K) δ 4.87 (d, *J* = 4.8 Hz, 1H), 4.68 (d, *J* = 6.6 Hz, 1H), 3.76-3.71 (m, 2H), 3.63 (s, 3H), 3.10 (dt, *J* = 12.6 Hz, 1H), 1.71-1.56 (m, 4H), 1.39 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.6, 155.4, 80.7, 68.9, 58.6, 57.4, 52.4, 41.4, 40.3, 30.2, 28.4, 23.9, 23.5.



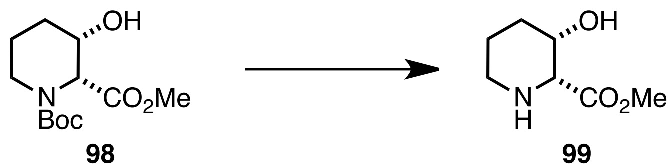


^{1}H NMR, 300 MHz, $(CD_3)_2SO$, 300K , filename: ms291ht



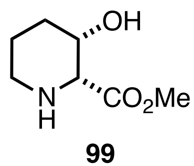
^{13}C NMR, 75 MHz, $CDCl_3$, filename: ms291carbon

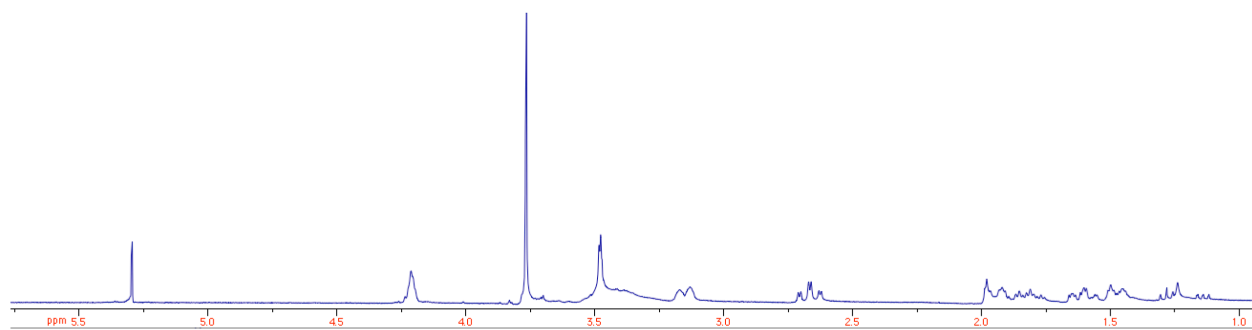
(2*R*,3*S*)-methyl 3-hydroxypiperidine-2-carboxylate (99):



To a stirred solution of Boc amine **98** (80.6 mg) in DCM (3 mL) at 0 °C was added TFA (230 µL). The reaction was warmed to ambient temperature and was stirred for an additional 5 hours. The reaction mixture was then concentrated under reduced pressure. The residue was then dissolved in EtOAc and quenched with $NaHCO_3$ (pH 9). The organic phase was then separated and the aqueous was then extracted with EtOAc. The combined extracts were dried, filtered over Na_2SO_4, and concentrated under reduced pressure.

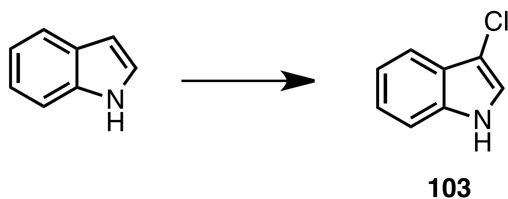
^{1}H NMR (300 MHz, ($CDCl_3$) δ 4.20 (bs, 1H), 3.76 (s, 3H), 3.15 (d, *J* = 12.1 Hz, 1H), 2.66 (td, *J* = 3.0, 12 Hz 1H), 1.98-1.88 (m, 2H), 1.75-1.66 (m, 2H), 1.30-1.11 (m 2H).





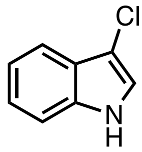
^{1}H NMR, 300 MHz, $CDCl_3$, filename: ms285p

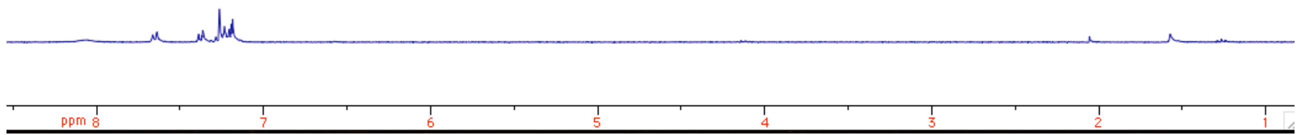
3-chloro-1H-indole (103):



To a solution of indole (5 g, 42.68 mmol) in 100 mL of DMF stirring at 0 °C was added N-Chlorosuccinimide (5.69 g, 42.68 mmol). The yellow solution was stirred at room temperature in an inert atmosphere overnight resulting in brown solution. This was then quenched with a saturated solution of brine and extracted with ether. The combined organic phases were then washed with water, dried over magnesium sulfate and concentrated under reduced pressure. The resulting brown solid was purified via flash column chromatography (5% ETOAc/hexanes) to afford a white crystalline solid (5.70 g, 88%).

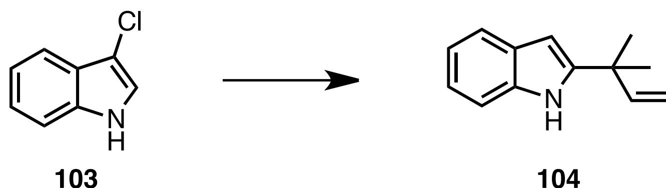
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (bs, 1H), 7.65 (d, J = 8.4 Hz, 1H), 7.37 (d, J = 8.7 Hz, 1H), 7.29-7.18 (m, 3H); HRMS (ESI/APCI) calcd for C_8H_8N (M+H) 118.0651, found 118.0654.





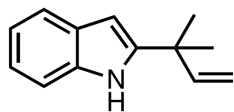
^{1}H NMR, 300 MHz, $CDCl_3$, filename: ms296pure

2-(2-methylbut-3-en-2-yl)-1H-indole (104):

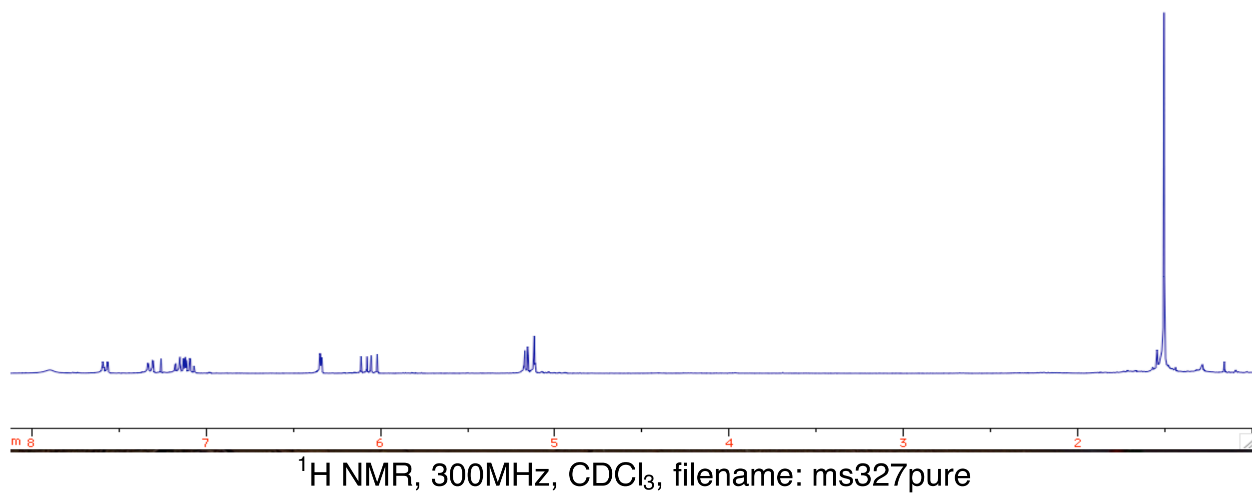


To a solution of prenyl-9-BBN (0.5M) at room temperature was added TEA (9.58 mL, 71.59 mmol) and then solid chloroindole **103** (3.34 g, 22.03 mmol). The yellow solution was then stirred for an additional 3 hours at room temperature. This reaction was then quenched with saturated $NaHCO_3$ and then extracted with ether. The combined organic phases were then washed with H_2O, brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude yellow oil was then purified via flash column chromatography (EtOAc/hexanes 2:8) to afford a pale yellow foam (3.45 g, 84%).

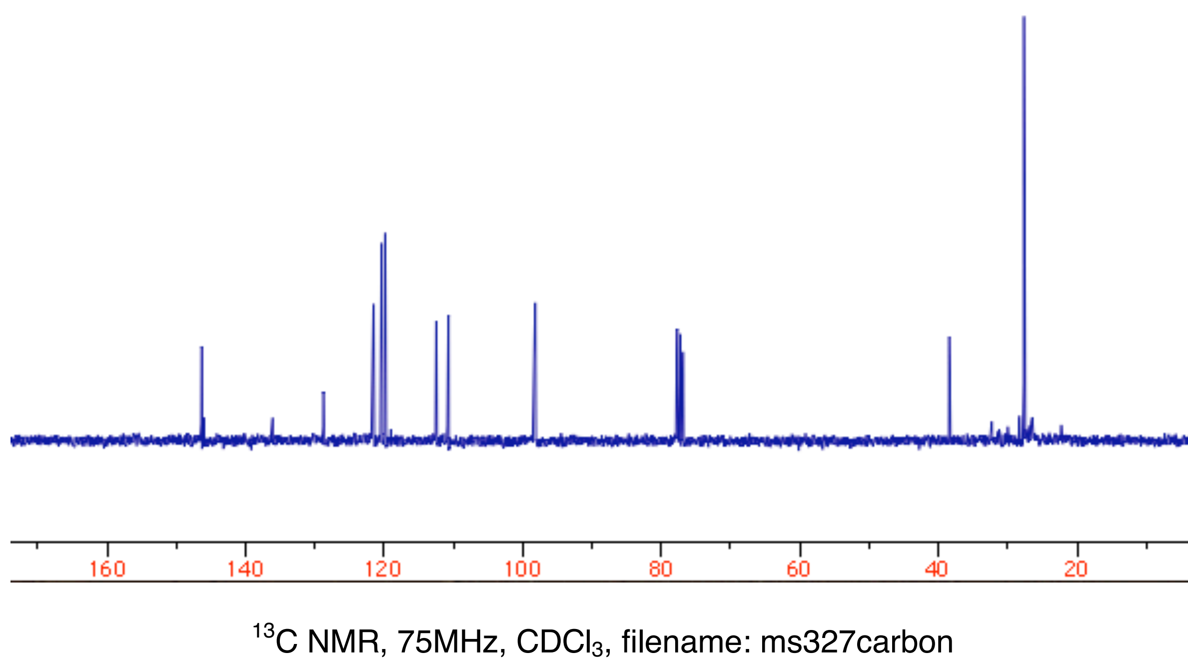
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (bs, 1H), 7.57 (d, J = 8.1 Hz, 1H), 7.34 (d, J = 8.1 Hz, 1H), 7.19-7.05 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.3, 136.1, 128.7, 121.5, 120.3, 119.8, 112.4, 110.7, 98.1, 38.4, 27.6; HRMS (ESI/APCI) calcd for C_8H_8N (M+H) 186.1284, found 186.1281.



104

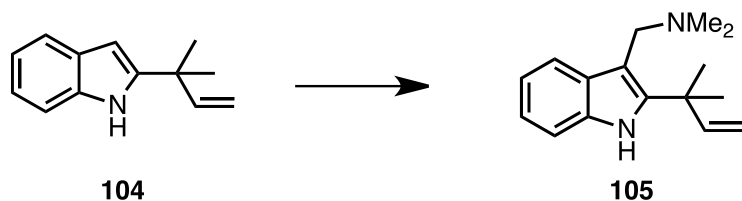


^1H NMR, 300MHz, $CDCl_3$, filename: ms327pure



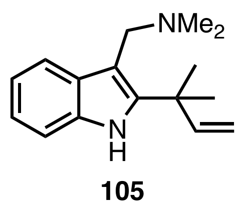
^{13}C NMR, 75MHz, $CDCl_3$, filename: ms327carbon

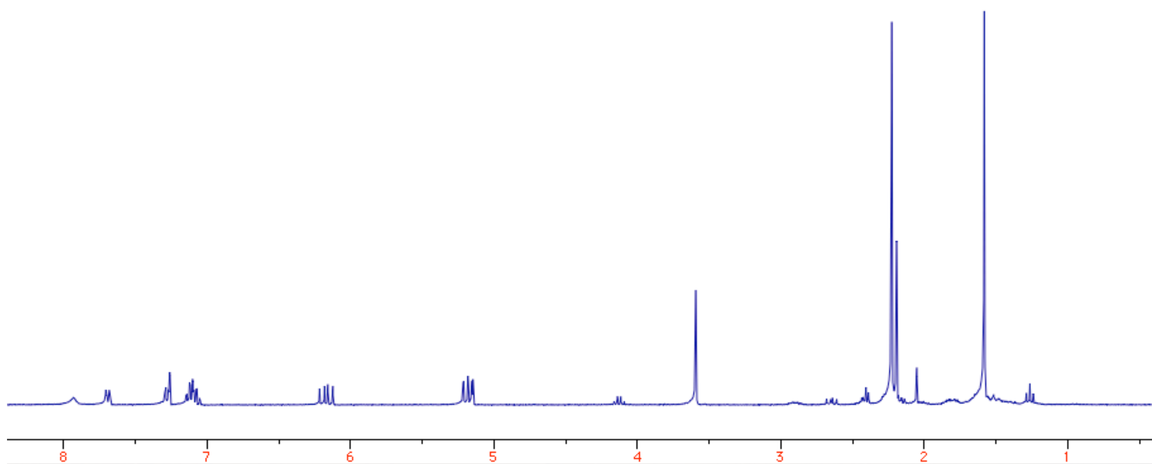
N, N-dimethyl-1-(2-(2-methylbut-3-en-2-yl)-1H-indol-3-yl)methanamine (105):



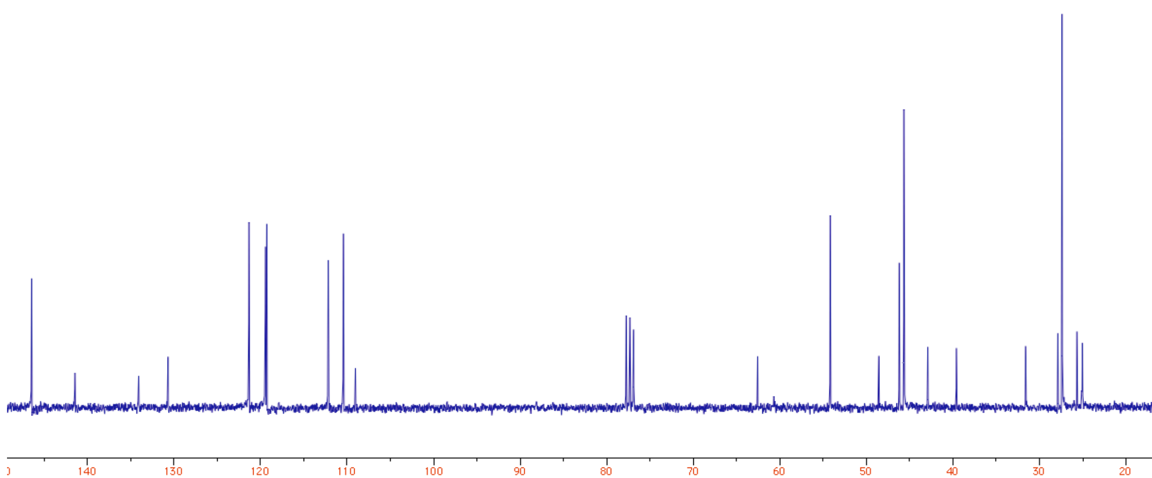
To formaldehyde (4.04 mL, 54.29) in 100 mL AcOH was added diethylamine (25.85 mL, 45.08) dropwise. The resulting solution was then stirred at room temperature for 10 minutes. Reverse prenylated indole **104** (6.67 g, 36.6 mmol) dissolved in 20 mL of AcOH was then added and the resulting mixture was stirred overnight. The reaction mixture was then quenched with 2 M NaOH (pH of at least 10) and extracted with ether. The combined ether extracts were then dried over magnesium sulfate, filtered and concentrated under reduced pressure. The resulting yellow oil (6.66 g, 74%) was then taken on without further purification.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (bs, 1H), 7.69 (d, *J* = 8.1 Hz, 1H), 7.29-7.25 (m, 1H), 7.14-7.05 (m, 2H), 6.17 (dd, *J* = 17.4, 10.5Hz, 1H), 5.18 (dd, *J* = 9.1, 1.3 Hz, 1H), 5.18 (q, *J* = 1.4, 1.1 Hz), 3.59 (s, 2H), 2.27 (s 6H), 1.58 (s 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.4, 141.4, 134.0, 130.6, 121.3, 119.4, 112.1, 110.4, 109.0, 62.5, 54.1, 45.6, 39.5, 27.3; HRMS (ESI/APCI) calcd for C_8H_8N (M+H) 186.1284, found 186.1281.



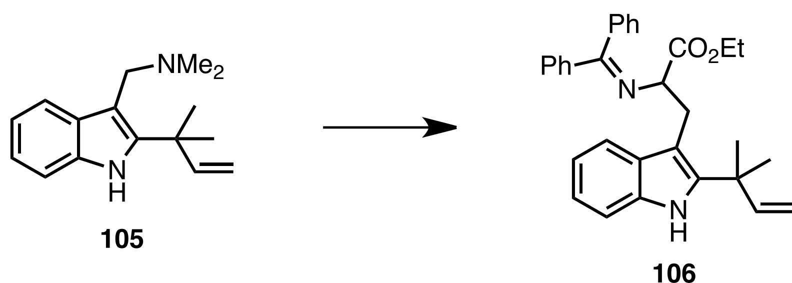


^{1}H NMR, 300 MHz, $CDCl_3$, filename: ms328p



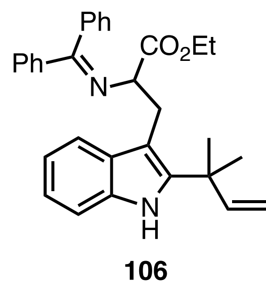
^{13}C NMR, 75 MHz, $CDCl_3$, filename: ms328carbon

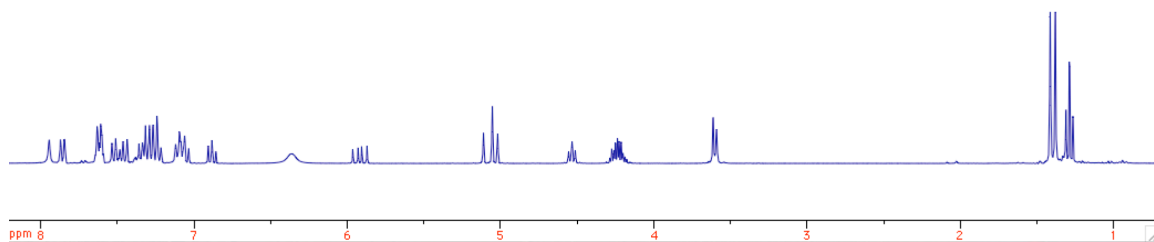
ethyl-2-((diphenylmethylene)amino)-3-(2-(2-methylbut-3-en-2-yl)-1H-indol-3-yl)propanoate (106):



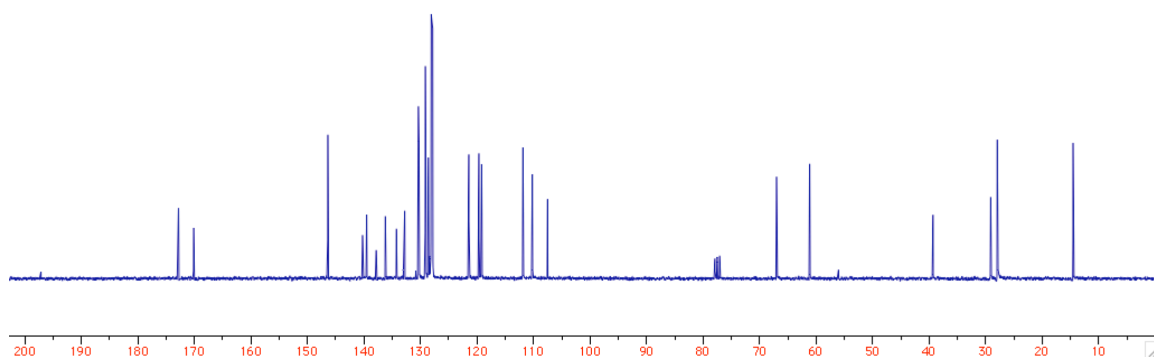
The crude gramine **105** (3.33 g, 13.74 mmol) and benzophenone imine (4.04 g, 15.11 mmol) were dissolved in 60 mL of MeCN. Then PBu_3 was added to the reaction mixture at room temperature. The resulting solution was refluxed overnight at 110 °C. This mixture was then concentrated under reduced pressure. The crude brown oil was then purified via flash column chromatography (EtOAc/hexanes 1:9) to afford a pale yellow foam (3.99 g, 63%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94-6.856 (m, 14H), 7.69 (bs, 1H), 5.91 (dd, *J* = 17.4, 10.5 Hz, 1H), 5.14- 5.01 (m, 2H), 4.53 (t, *J* = 13.2, 1H), 4.25-4.22 (m, 2H), 3.60 (d, *J* = 6.9, 2H), 1.41 (s, 3H), 1.38 (s, 3H), 1.29 (t, *J* = 6.9, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.8, 170.1, 146.3, 139.5, 137.8, 136.2, 134.2, 132.7, 130.3, 130.2, 129.1, 128.6, 128.1, 128.0, 127.8, 121.4, 119.6, 119.1, 111.8, 110.2, 107.5, 66.9, 61.1, 39.3, 29.0, 27.9, 27.8, 14.5; HRMS (ESI/APCI) calcd for $C_{31}H_{33}N_2O_2$ (M+H) 465.2537, found 465.2543.



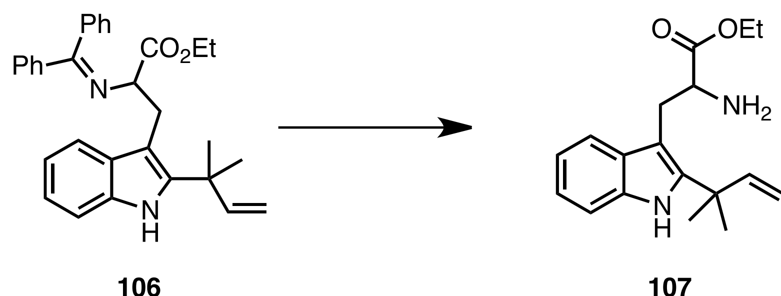


^{1}H NMR, 300 MHz, $CDCl_3$, filename: ms329pure



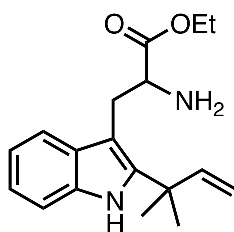
^{13}C NMR, 75 MHz, $CDCl_3$, filename: ms329purecarbon

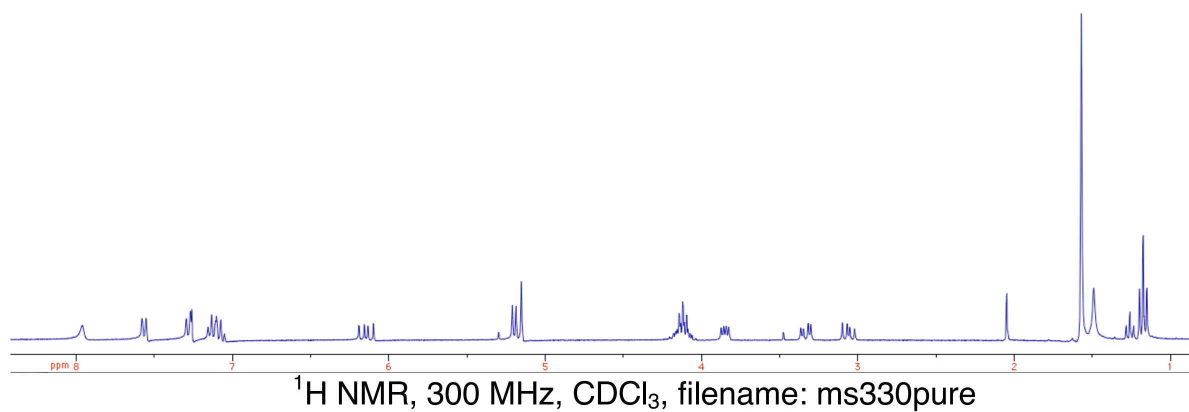
ethyl 2-amino-3-(2-(2-methylbut-3-en-2-yl)-1*H*-indol-3-yl)propanoate (107):



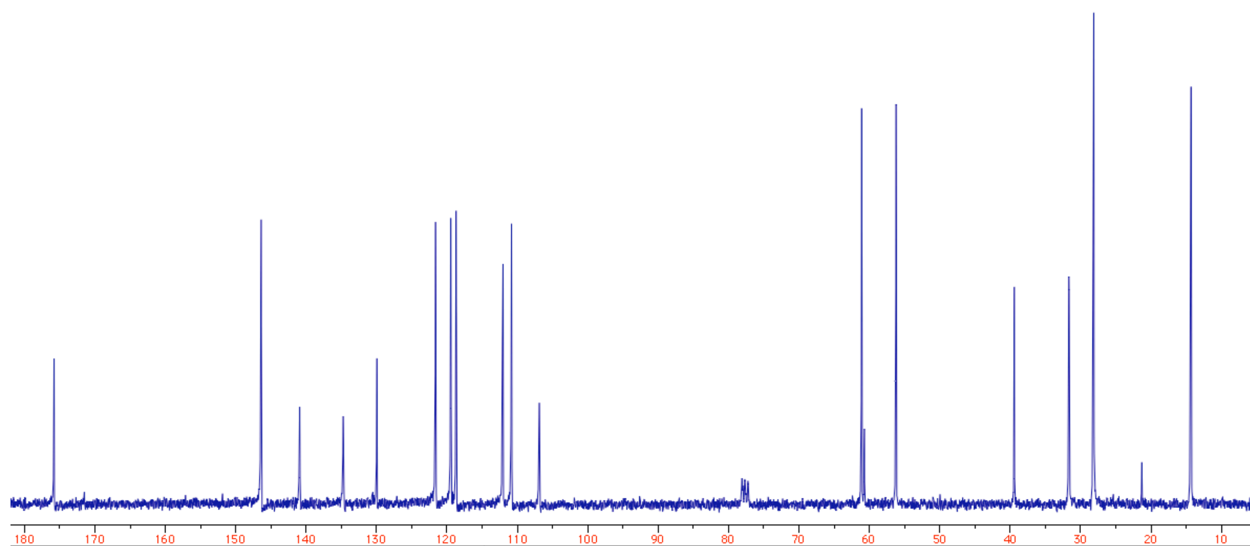
To imine **106** (6.38 g, 13.7 mmol) was dissolved in THF (100 mL) and cooled to 0 °C. Then 2 M HCl (6.87 mL) was slowly added to the reaction mixture. The reaction mixture turned bright red and was allowed to warm to ambient temperature over 20 minutes. The THF was then evaporated under reduced pressure. The resulting aqueous layer was then basified with $NaHCO_3$ and extracted with DCM. The pale yellow oil (2.52 g, 62%) was then purified via column chromatography (EtOAc/Hex 1:1 to MeOH/DCM 1:9).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (bs, 1H), 7.56 (d, *J* = 7.5 Hz, 1H), 7.29-7.26 (m, 1H), 7.15-7.05 (m, 2H), 6.13 (dd, *J* = 17.4, 10.5 Hz, 1H), 5.21- 5.15 (m, 2H), 4.18-4.05 (m, 3H), 3.36-3.30 (m, 1H), 3.10-3.01 (m, 1H), 1.57 (s, 6H), 1.17 (t, *J* = 14.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.7, 146.3, 140.9, 134.7, 129.9, 121.6,119.4, 118.6, 112.0, 110.8, 106.8, 61.1, 56.2, 39.4, 31.6, 28.2, 28.1, 14.3; HRMS (ESI/APCI) calcd for $C_{18}H_{24}N_2O_2$ (M+H) 300.1838, found 301.1906.



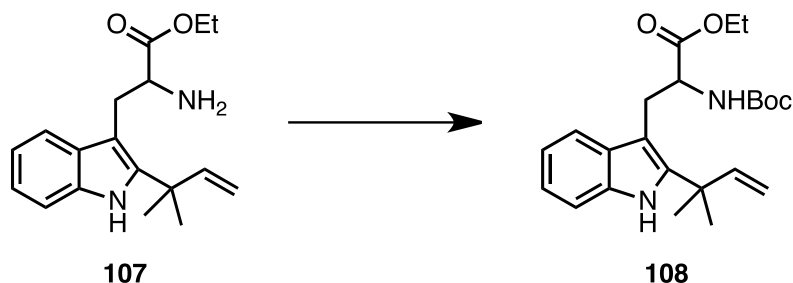


^{1}H NMR, 300 MHz, $CDCl_3$, filename: ms330pure



^{13}C NMR, 75M Hz, $CDCl_3$, filename: ms330purecarbon

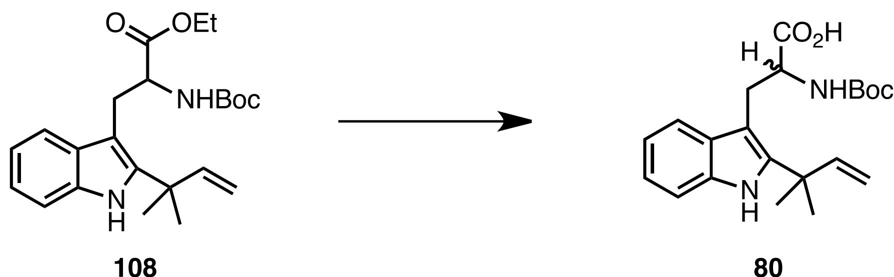
ethyl 2-((*tert*-butoxycarbonyl)amino)-3-(2-(2-methylbut-3-en-2-yl)-1*H*-indol-3-yl)propanoate (108):



To amine (0.4 g, 1.33 mmol) dissolved in dioxanes was added Boc_2O (0.30g, 1.39 mmol) followed by 1 M NaOH (1.33 mL). The reaction mixture was stirred at ambient temperature for 3 hours, then was quenched with saturated citric acid. The reaction was then extracted with EtOAc and dried, filtered, and concentrated under reduced pressure. The pale yellow foam was purified via column chromatography (EtOAc/Hexanes 2:8) to provide a pale yellow foam (0.501 g, 94%).

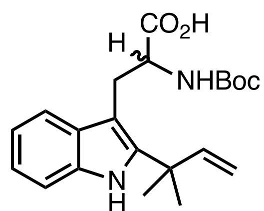
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (bs, 1H), 7.50 (d, *J* = 7.5 Hz, 1H), 7.26 (d, *J* = 8.1 Hz, 1H), 7.14-7.04 (m, 2H), 6.14 (dd, *J* = 17.4, 10.5 Hz, 1H), 4.16-3.88 (m, 2H), 3.34- 3.18 (m, 2H) 1.56(d, *J* = 3.3 Hz, 6H) 1.52 (s, 2H), 1.33 (s, 7H).

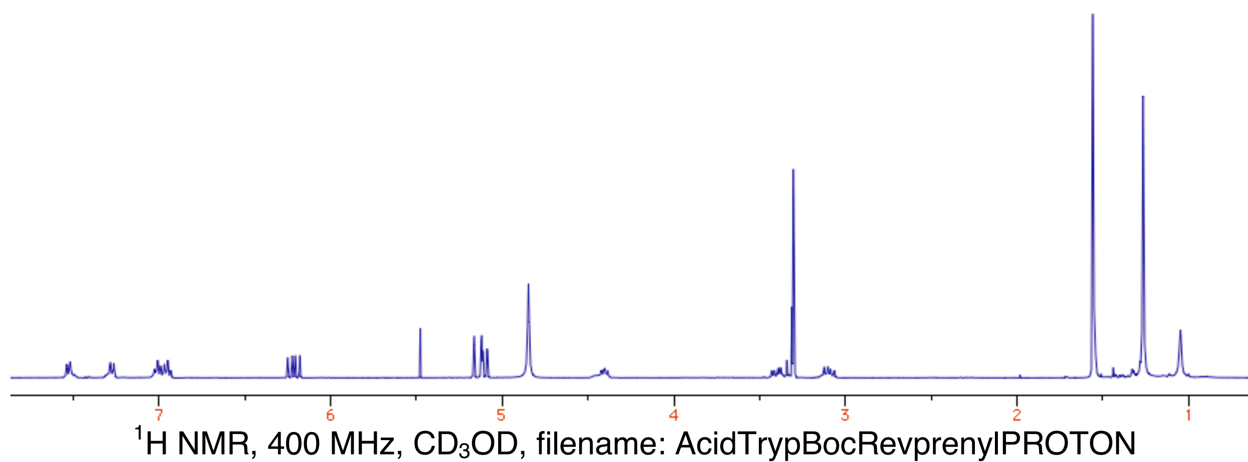
2-((*tert*-butoxycarbonyl)amino)-3-(2-(2-methylbut-3-en-2-yl)-1*H*-indol-3-yl)propanoic acid (80):



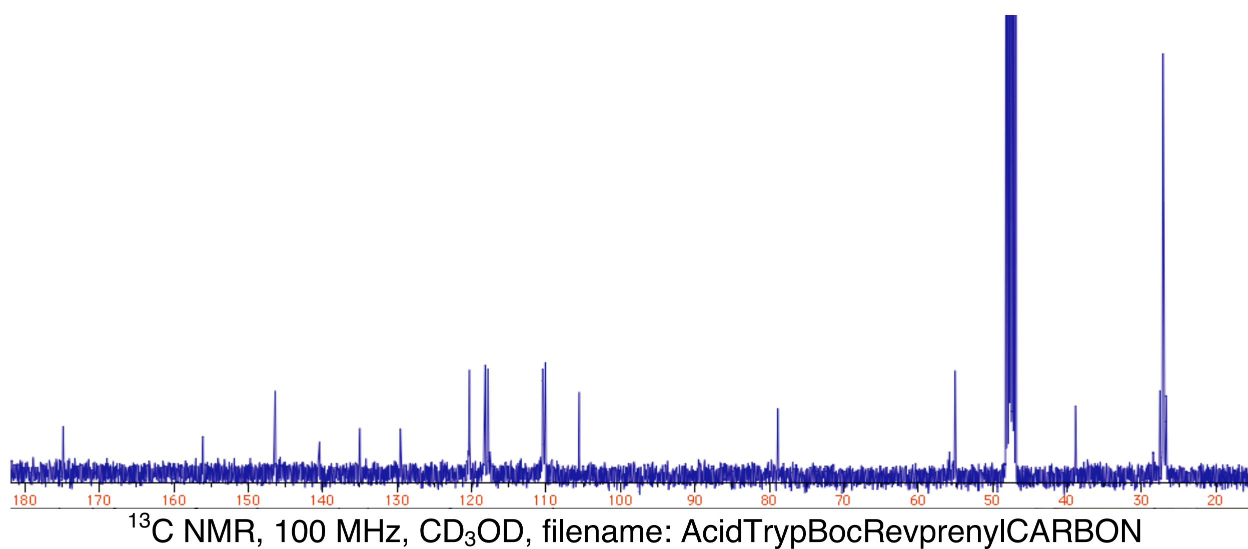
To ester **108** (2.94 g, 6.16 mmol) dissolved in 2:1 H_2O: THF (41:20 mL) was added LiOH (2.85 g, 61.6 mmol). The resulting solution was stirred overnight at ambient temperature. The biphasic reaction mixture was then concentrated under reduced pressure. The resulting solution was then quenched with 1 M $KHSO_4$ to pH 2. The aqueous was then extracted 5 times with EtOAc, dried over Na_2SO_4, filtered and concentrated under reduced pressure to provide a pale white solid (2.15 g, 93%).

^{1}H NMR (300 MHz, CD_3OD) δ 7.52 (d, *J* = 7.6 Hz, 1H), 7.27 (d, *J* = 8 Hz, 1H), 7.02-6.93 (m, 2H), 6.21 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.16- 5.08 (m, 2H), 4.39 (t, *J* = 8.8 Hz, 1H), 3.40 (dd, *J* = 14.8, 6 Hz, 1H), 3.09 (dd, *J* = 14.4, 8.8 Hz, 1H), 1.56 (s, 6H), 1.26 (s, 6H) 1.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.86, 156.09, 146.37, 140.41, 135.01, 129.56, 120.28, 118.15, 117.79, 110.44, 110.09, 105.54, 78.86, 55.05. 38.88. 27.54, 27.12, 26.71.



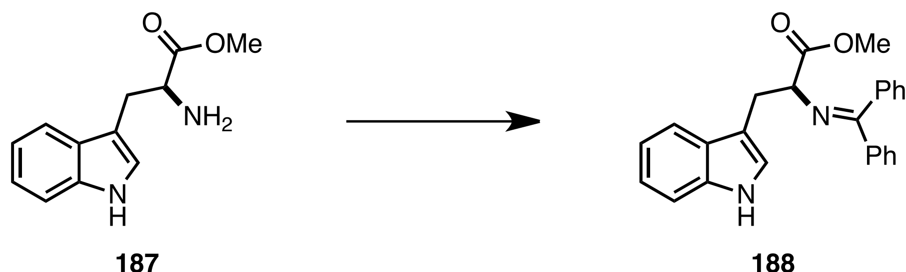


^{1}H NMR, 400 MHz, CD_3OD, filename: AcidTrypBocRevprenylPROTON



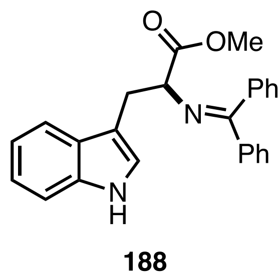
^{13}C NMR, 100 MHz, CD_3OD, filename: AcidTrypBocRevprenylCARBON

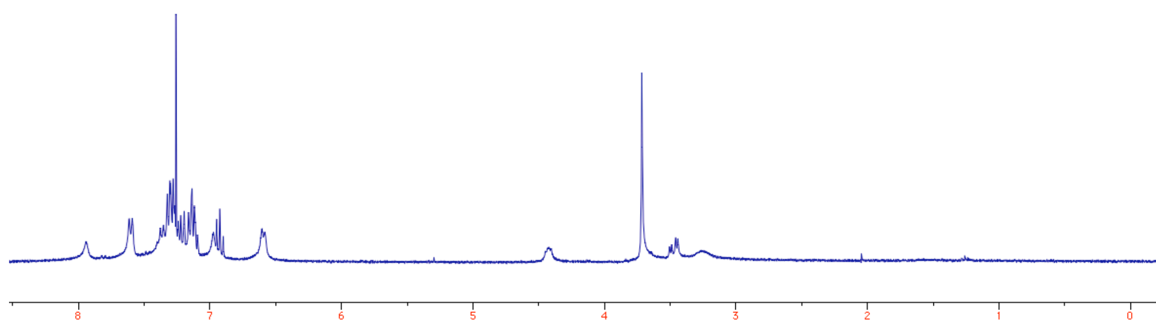
(S)-methyl 2-((diphenylmethylene)amino)-3-(1H-indol-3-yl)propanoate (188):



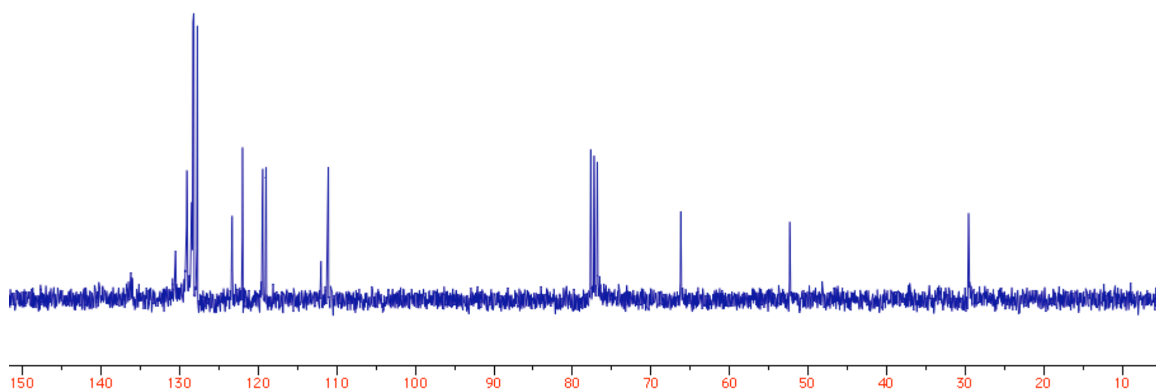
Tryptophan **187** (30 g, 117.78 mmol) was taken up in 471 mL of DCM. To this solution, benzophenone imine (19.33 mL 117.78 mmol) was added. The resulting solution was stirred at room temperature for 24 hours under argon. The reaction mixture was filtered to remove NH_4Cl and evaporated to dryness on a rotary evaporator. The residue was taken up in 100 mL of ether, filtered, washed with 50 mL of water, and dried with Na-$_2SO_4$. The white solid was purified via recrystallization from hexane/ethylacetate.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (bs, 1H), 7.69 (d, J = 6.9, 2H), 7.40-7.09 (m, 14H), 6.97-6.89 (m, 1H), 4.55-4.40 (m, 1H), 3.71 (s, 3H), 1.38 (s, 3H), 3.50-3.44 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 129.0, 128.3, 127.7, 123.3, 122.0, 119.4, 118.9, 112.0, 111.0, 66.21, 52.3, 29.5.



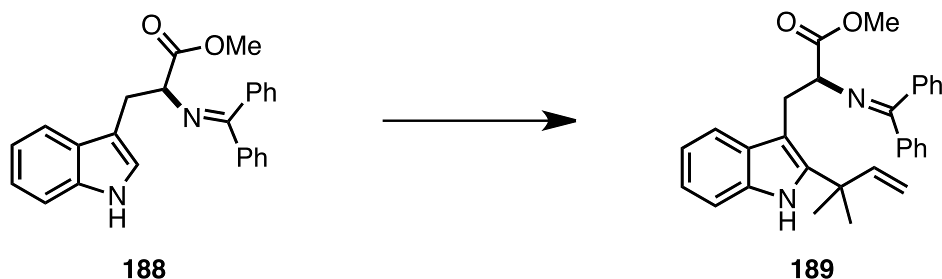


^{1}H NMR, 300 MHz, $CDCl_3$, filename: ms686p



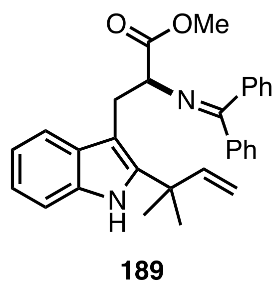
^{13}C NMR, 75M Hz, $CDCl_3$, filename: ms686pcarbon

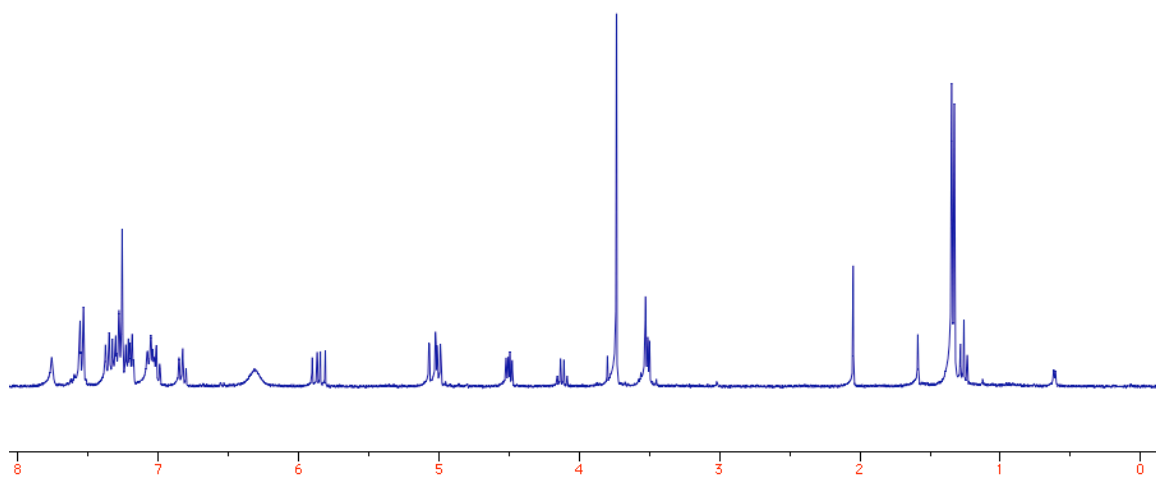
(S)-methyl 2-((diphenylmethylene)amino)-3-(2-(2-methylbut-3-en-2-yl)-1H-indol-3-yl)propanoate (189):



To a cold (-78 °C) solution of tryptophan **188** (1.99 g, 5.70 mmol) and TEA (0.95 mL, 6.84 mmol) in 20 mL of THF was added tert-butyl hypochlorite (0.83 mL, 6.84 mmol). After the solution was stirred for 0.5 h at -78 °C, a 1.0 M solution of prenyl-9-BBN (11.4 mL, 11.4 mmol) in THF was added dropwise. The solution was allowed to warm slowly over 6 h to ambient temperature, after which 5 mL of a saturated solution of K_2CO_3 (aq) was added. The layers were separated, and the aqueous layer was extracted with ethyl acetate (3x10 mL). The organics were combined, dried ($MgSO_4$), filtered, and concentrated in vacuum.

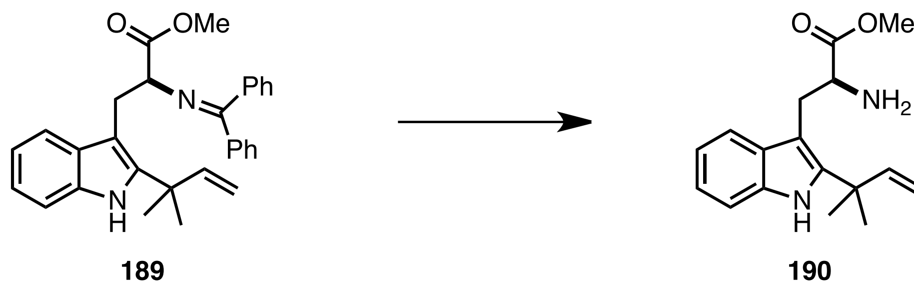
^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.93 (s, 1H), 7.68 (m, 2H), 7.60 (m, 2H), 7.26 (d, J = 7.9 Hz, 1H), 7.12 (d, J = 8.1 Hz, 1H), 6.9 (t, J = 7.1 Hz, 1H), 6.71 (t, J = 7.1 Hz, 1H), 6.19 (dd, J = 10.5, 17.5 Hz, 1H), 5.18 (m, 3H), 3.87 (dd, J = 3.8, 15.2 Hz, 1H), 3.77 (s, 3 H), 3.67 (dd, J = 11.3, 15.2 Hz, 1H), 1.57 (s, 6H); HRMS (ESI/APCI) calcd for $C_{25}H_{24}N_2O_4$ (M+H) 416.1736, found 416.1733.





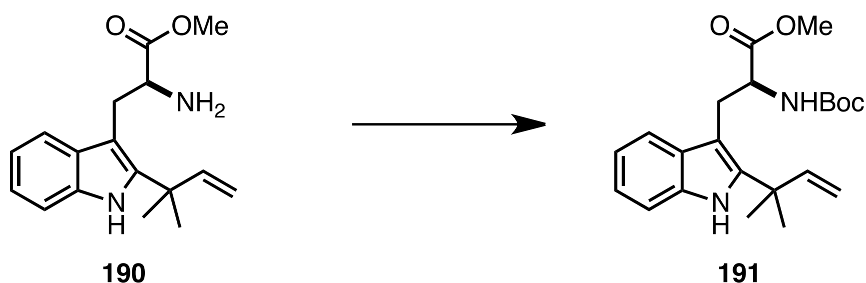
^{1}H NMR, 300 MHz, $CDCl_3$, filename: ms538p

(S)-methyl 2-amino-3-(2-(2-methylbut-3-en-2-yl)-1H-indol-3-yl)propanoate (190):



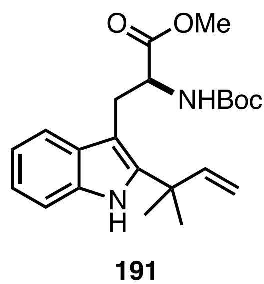
Benzophenone **189** (2.19 g, 5.01 mmol) was dissolved in a THF (37 mL) and then cooled to 0 °C. Then 1 M HCl (12.5 mL) was added and the reaction mixture was stirred at 0 °C for an additional 15 minutes. The reaction was then warmed to room temperature and then stirred for an additional 30 minutes. The solvent was then evaporated, saturated $NaHCO_3$ was added, and the aqueous solution was extracted three times with EtOAC. The combined organic phases were then dried over anhydrous Na_2SO_4, filtered and then concentrated under reduced pressure. The crude amine was then taken on without further purification to the next step.

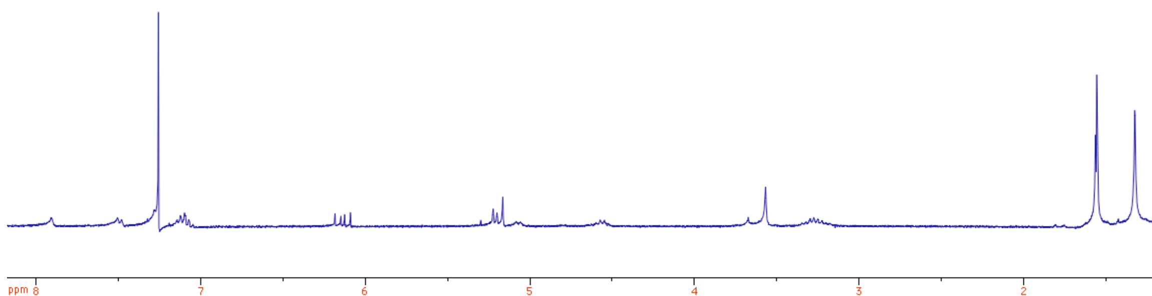
(S)-methyl 2-((tert-butoxycarbonyl)amino)-3-(2-(2-methylbut-3-en-2-yl)-1H-indol-3-yl)propanoate (191):



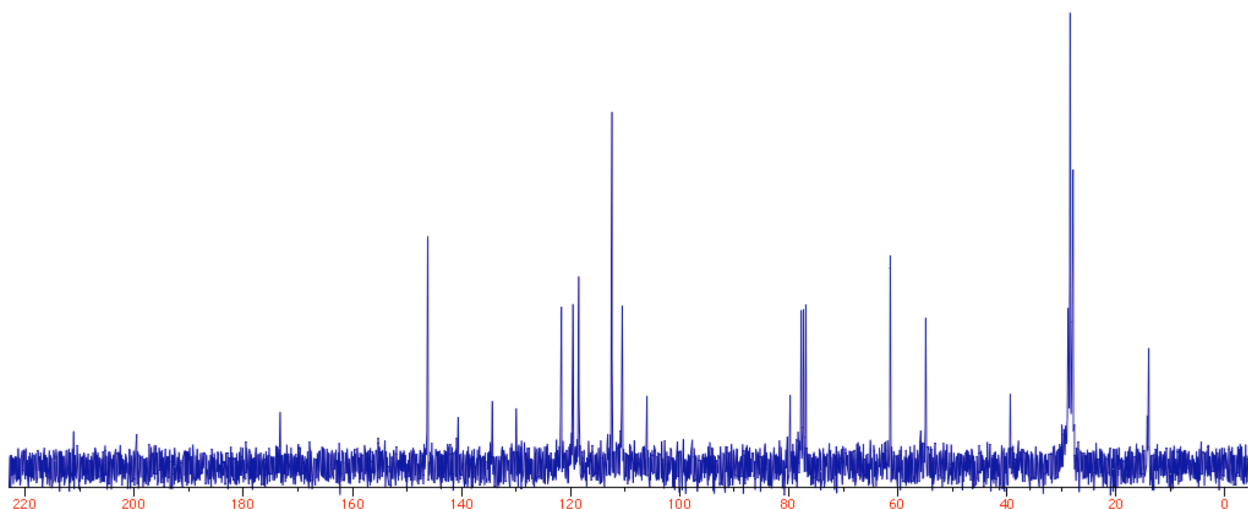
To a solution of free amine (1.74 g, 6.4 mmol) dissolved in dioxanes (32.5 mL) at room temperature was added di-tert-butylcarbonate (1.48 g, 6.8 mmol) and 1M NaOH (3.25 mL). The mixture was stirred at room temperature for 2.5 hours. The solvent was then evaporated, saturated $KHSO_4$ was added and the aqueous solution was then extracted three times with ethyl acetate. The combined organics were then dried over Na_2SO_4 and concentrated. The crude product was then purified by means of silica gel chromatography, using EtOAc/hexanes (1:9) as the eluent to yield 2.49 g of pure protected amine (25%, over 3 steps).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.93 (bs, 1H), 7.50 (d, J = 7.8 Hz, 1H), 7.19-7.04 (m, 2H), 6.14 (dd, J = 10.5, 17.5 Hz, 1H), 5.20 (m, 3H), 4.60-4.50 (m, 1H), 3.56 (s, 3H), 3.34-3.17 (m, 2H), 1.57 (s, 6H), 1.32 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.1, 199.5, 173.2, 146.2, 140.6, 134.3, 129.9, 121.6, 119.5, 118.5, 112.4, 110.5, 106.0, 79.7, 77.3, 76.8, 61.3, 54.9, 39.4, 28.4, 27.9, 14.0.



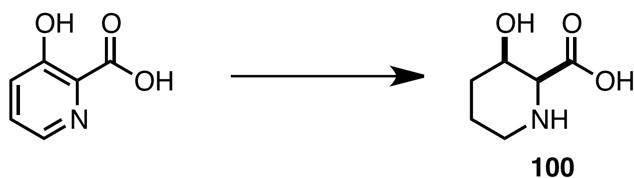


^{1}H NMR, 300 MHz, $CDCl_3$, filename: ms541p



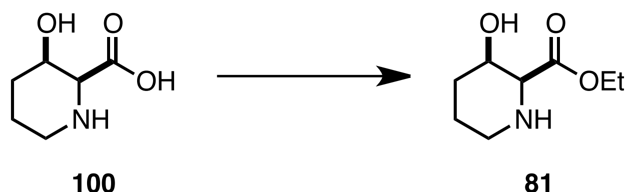
^{13}C NMR, 75 MHz, $CDCl_3$, filename: m2315pcarbon

cis-3-hydroxypiperidine-2-carboxylic acid (100):



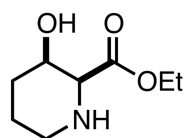
In a high-pressure vessel, the acid (6 g, 43.1 mmol) was dissolved in 90 mL of H_2O and then degassed with argon for 15 minutes. To this solution, NH_4OH (12 mL) was added followed by Rh/C (2.5 g, 4% mass eq.). The solution was then pressurized to 80 psi with H_2 and stirred for 72 hours. The mixture was then filtered through a bed of Celite, rinsed with EtOAc, concentrated and then lyophilized overnight. The pale pink powder (5.34 g, 85%) was then taken on crude to form the ester.

cis-ethyl 3-hydroxypiperidine-2-carboxylate (81):

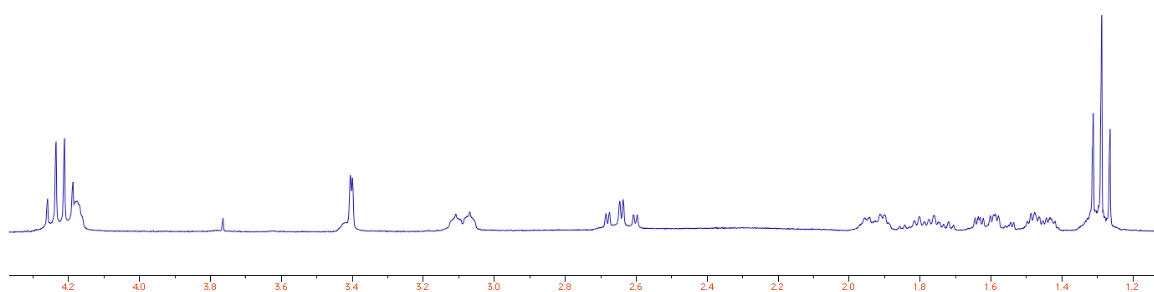


To EtOH (116 mL) at 0 °C was added $SOCl_2$ (6.33 mL, 87.2 mmol). The resulting solution was then stirred for 15 minutes at ambient temperature. After which, the pipecolic acid **100** (4.22g, 29.0 mmol) was then added to the reaction flask. The reaction mixture was stirred at 80 °C for 24 hours. The reaction was then cooled to room temperature and concentrated under reduced pressure. The resulting white solid was then dissolved in EtOH and concentrated again. This was repeated three more times. The resulting white solid was then treated with $NaHCO_3$ (pH of 10) and extracted with DCM. The organics were then combined, dried over $NaSO_4$, filtered and then concentrated. The crude oil product was then purified by means of silica gel chromatography, using DCM-MeOH (9:1) as the eluent to yield 3.67 g of pure protected amine (73%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.25-4.10 (m, 3H), 3.40 (d, *J* = 1.5), 3.07 (d, *J* = 11.7 Hz, 1H), 2.65 (td, *J* = 11.7, 3 Hz, 1H), 1.96-1.41 (m, 5H), 1.28 (t, *J* = 7.2 Hz, 3H).

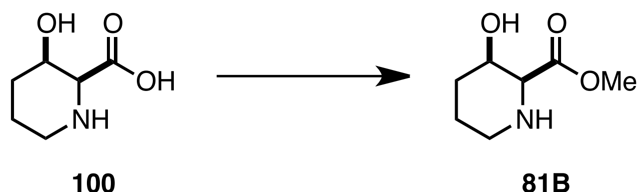


81



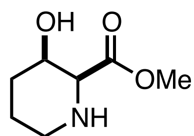
^{1}H NMR, 300 MHz, $CDCl_3$, filename: mspipA

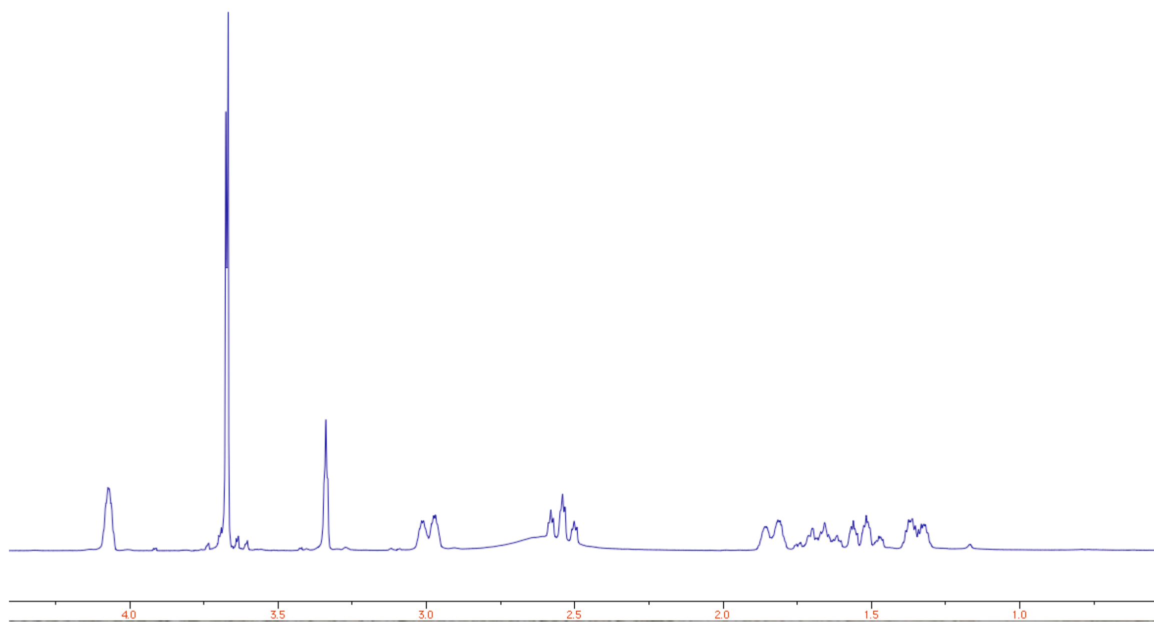
(2S,3R)-methyl 3-hydroxypiperidine-2-carboxylate (81B)



To MeOH (60 mL) at 0 °C was added $SOCl_2$ (3.14 mL, 43.1 mmol). The resulting solution was then stirred for 15 minutes at ambient temperature. After which, the pipecolic acid **100** (2.0 g, 14.3 mmol) was then added to the reaction flask. The reaction mixture was stirred at 80 °C for 24 hours. The reaction was then cooled to room temperature and concentrated under reduced pressure. The resulting white solid was then dissolved in MeOH and concentrated again. This was repeated three more times. The resulting white solid was then treated with $NaHCO_3$ (pH of 10) and extracted with DCM. The organics were then combined, dried over $NaSO_4$, filtered and then concentrated. The crude oil product was then purified by means of silica gel chromatography, using DCM-MeOH (9:1) as the eluent to yield 1.97 g of pure protected amine (73%).

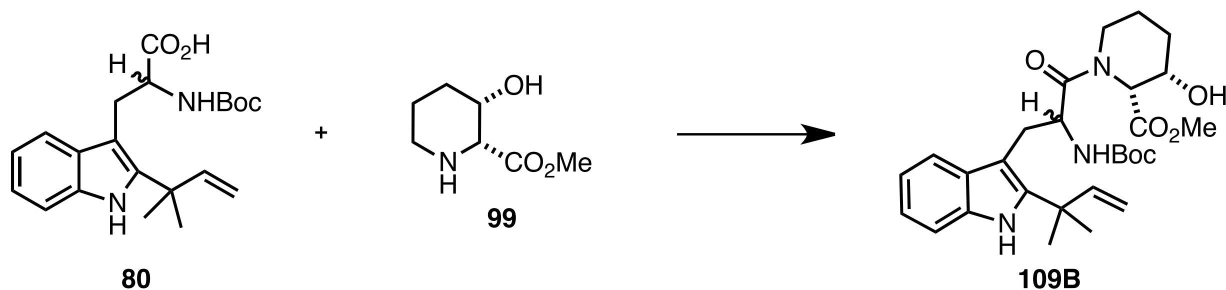
^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.06 (s, 1H), 3.66 (s, 1H), 3.33 (s, 1H), 3.00 (d, *J* = 2.65 Hz, 1H), 2.54 (t, *J* = 11.7, 1H), 1.86-1.31 (m, 4H).





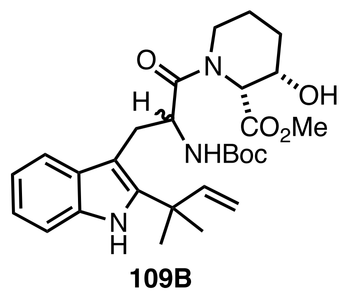
^{1}H NMR, 300 MHz, $CDCl_3$, filename: mspipA

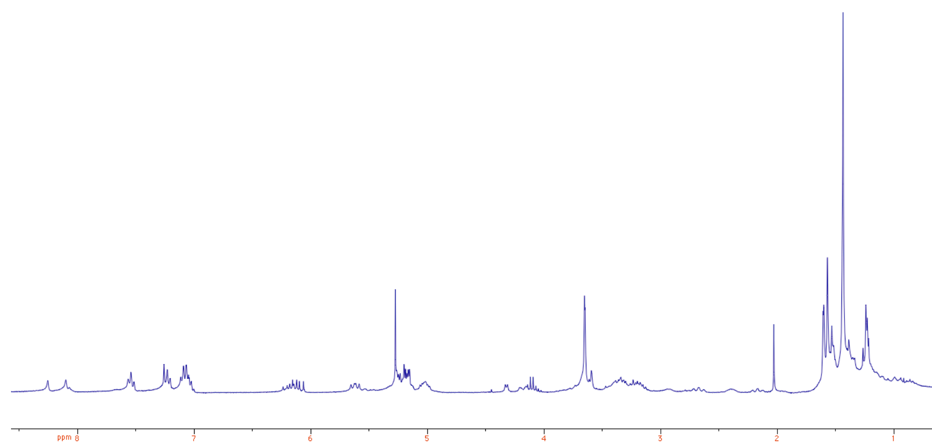
(2R,3S)-methyl 1-(2-((tert-butoxycarbonyl)amino)-3-(2-(2-methylbut-3-en-2-yl)-1H-indol-3-yl)propanoyl)-3-hydroxypiperidine-2-carboxylate (109B):



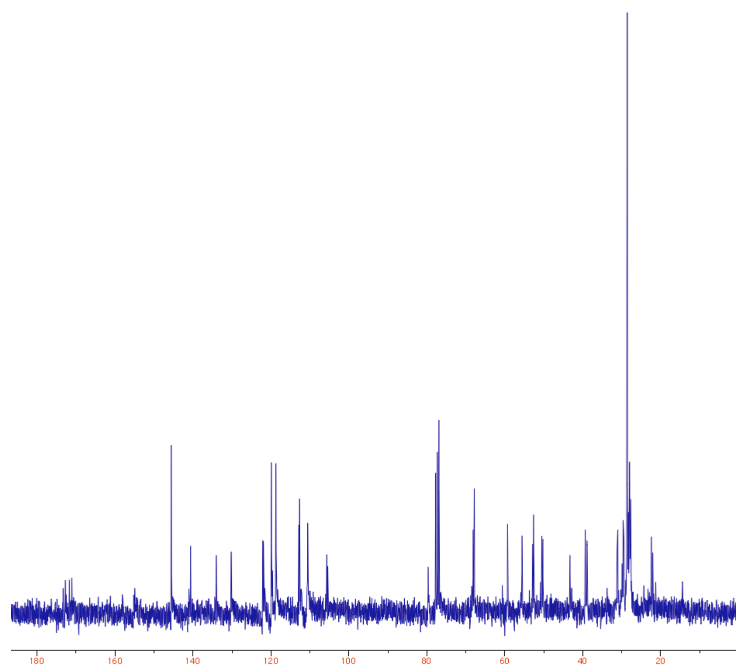
To a solution of acid **80** (1.22 g, 3.29 mmol) and methyl ester **99** (0.570 g, 3.29 mmol) in MeCN at 0 °C was added HATU (1.87 g, 4.94 mmol), then DIPEA (2.29 mL, 13.16 mmol). The mixture was stirred overnight at room temperature and concentrated under reduced pressure. The residue was then purified by means of silica gel chromatography, using EtOAc/hexanes (2:8) as the eluent to yield 1.02 g of pure yellow foam (63%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.25 (bs, 1H), 8.09 (bs, 1H), 7.54 (t, J = 7.2 Hz, 1H), 7.25-7.02 (m, 3H), 6.23-6.06 (m, 1H), 5.61 (m, 1H), 5.26-5.15 (m, 2H), 5.02 (bs, 1H), 4.32 (d, J = 5.4 Hz, 1H), 3.65 (s, 3H), 3.40-3.12 (m, 4H), 2.66 (m, 1H), 2.39 (bs, 1H), 2.21 (m, 1H), 1.59 (m, 6H), 1.43 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.7, 171.7, 171.0, 145.5, 140.6, 134.0, 130.1, 122.0, 121.9, 119.8, 118.7, 112.8, 112.6, 110.6, 110.5, 105.6, 105.4, 79.6, 79.4, 68.1, 67.8, 59.2, 55.5, 52.8, 52.6, 50.4, 50.2, 43.2, 39.3, 39.3, 31.1, 31.0, 29.6, 29.4, 28.5, 28.0, 27.9, 22.3, 22.0; HRMS (ESI/APCI) calcd for $C_{28}H_{39}N_3O_6$ (M+H) 513.2839, found 514.2909.



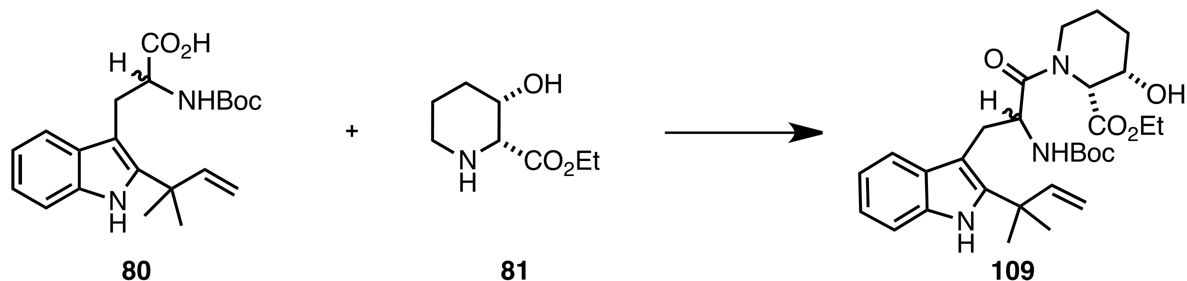


^1H NMR, 300 MHz, CD_3OD, filename: ms316pure



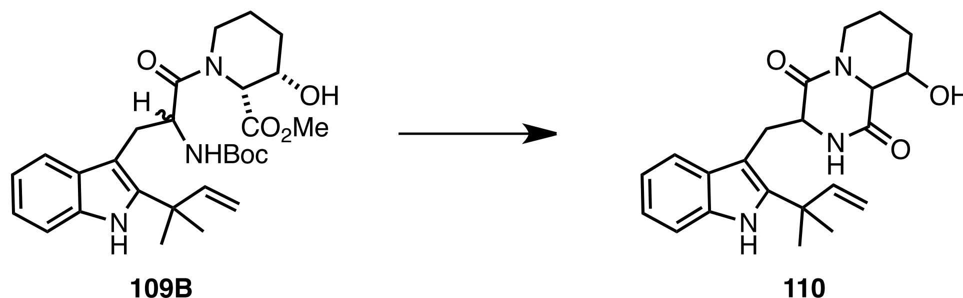
^1H NMR, 300 MHz, $CDCl_3$, filename: ms316pcarbon

(2R,3S)-ethyl 1-(2-((tert-butoxycarbonyl)amino)-3-(2-(2-methylbut-3-en-2-yl)-1H-indol-3-yl)propanoyl)-3-hydroxypiperidine-2-carboxylate (109):



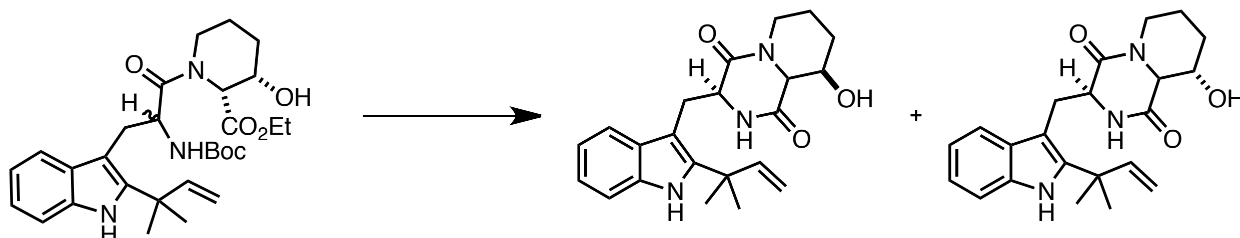
To a solution of acid **80** (841 mg, 2.25 mmol) and methyl ester **81** (391 mg, 2.25 mmol) in MeCN at 0 °C was added HATU (1.29 g, 3.38 mmol), then DIPEA (1.57 mL, 9.03 mmol). The mixture was stirred overnight at room temperature and concentrated under reduced pressure. The residue was then purified by means of silica gel chromatography, using EtOAc/hexanes (2:8) as the eluent to yield 1.09 g of pure yellow foam (91%).

9-hydroxy-3-((2-(2-methylbut-3-en-2-yl)-1H-indol-3-yl)methyl)hexahydro-1H-pyrido[1,2-a]pyrazine-1,4(6H)-dione (110):



To a solution of protected amine **109B** (970 mg, 1.83 mmol) in 3 mL of DCM at 0 °C was added 3 mL of TFA. This was then stirred for 1 hour at room temperature. The resulting brown solution was then concentrated to dryness and the residue was treated with a saturated solution of $NaHCO_3$. The solution was stirred for 60 minutes at room temperature and then extracted with DCM. The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and then concentrated to dryness. The residue was then purified by means of silica gel chromatography, using MeOH/DCM (1:19) as the eluent to yield 632 mg of pure yellow foam (90%).

9-hydroxy-3-((2-(2-methylbut-3-en-2-yl)-1H-indol-3-yl)methyl)hexahydro-1H-pyrido[1,2-a]pyrazine-1,4(6H)-dione (110)

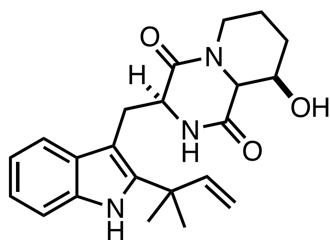


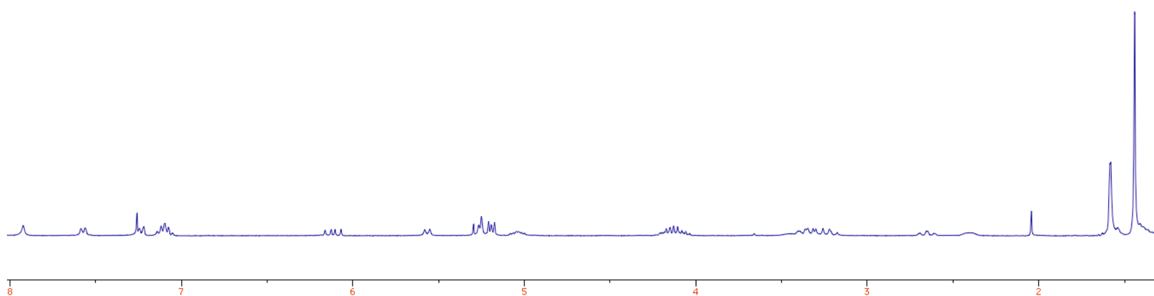
To a solution of protected amine **109** (970 mg, 1.83 mmol) in 3 mL of DCM at 0 °C was added 3 mL of TFA. This was stirred for 1 hour at room temperature. The resulting brown solution was then concentrated to dryness and the residue was treated with a saturated solution of $NaHCO_3$. The solution was then stirred for 60 minutes at room temperature and extracted with DCM. The combined organic phases were then washed with brine, dried over Na_2SO_4, filtered and then concentrated to dryness. The residue was then purified by means of silica gel chromatography, using MeOH/DCM (1:19) as the eluent to yield 632 mg of pure yellow foam (67%).

Trans: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.92 (bs, 1H), 8.09 (bs, 1H), 7.57 (d, *J* = 7.2 Hz, 1H), 7.24 (d, *J* = 7.5 Hz, 1H), 7.14-7.05 (m, 2H), 6.15 (dd, *J* = 17.4, 10.5 Hz, 1H), 5.58 (d, *J* = 8.7 Hz, 1H), 5.26-5.17 (m, 3H), 5.03 (m, 1H), 4.23-4.03 (m, 3H), 3.40-3.17 (m, 4H), 2.64 (t, *J* = 13.2 Hz 1H), 2.39 (bs, 1H), 1.44 (s, 6H).

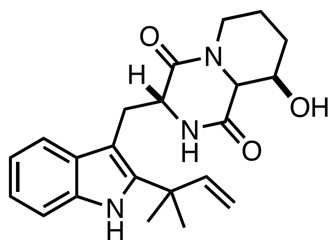
Cis: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.04 (bs, 1H), 7.54 (d, *J* = 7.2 Hz, 1H), 7.24 (m, 1H), 7.14-7.02 (m, 2H), 6.20 (dd, *J* = 17.4, 10.5 Hz, 1H), 5.67 (d, *J* = 8.7 Hz, 1H), 5.22-5.15 (m, 2H), 5.06 (m, 1H), 4.28 (d, *J* = 5.4 Hz, 1H), 4.21-4.05 (m, 3H), 3.41-3.12 (m, 3H), 2.13 (t, *J* = 27 Hz, 1H), 1.45 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.2, 170.6, 154.8,

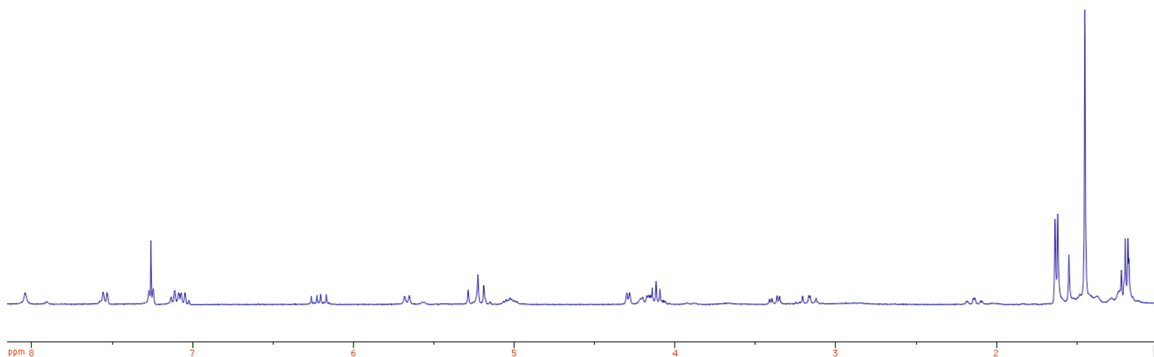
145.6, 141.0, 133.9, 130.2, 121.9, 119.9, 118.7, 112.9, 110.6, 105.4, 79.4, 68.1, 62.0, 59.1, 50.3, 38.9, 31.3, 29.5, 28.5, 28.0, 27.5, 22.06, 14.0; HRMS (ESI/APCI) calcd for $C_{22}H_{27}N_3O_3$ (M+H) 381.4681, found 381.4692.



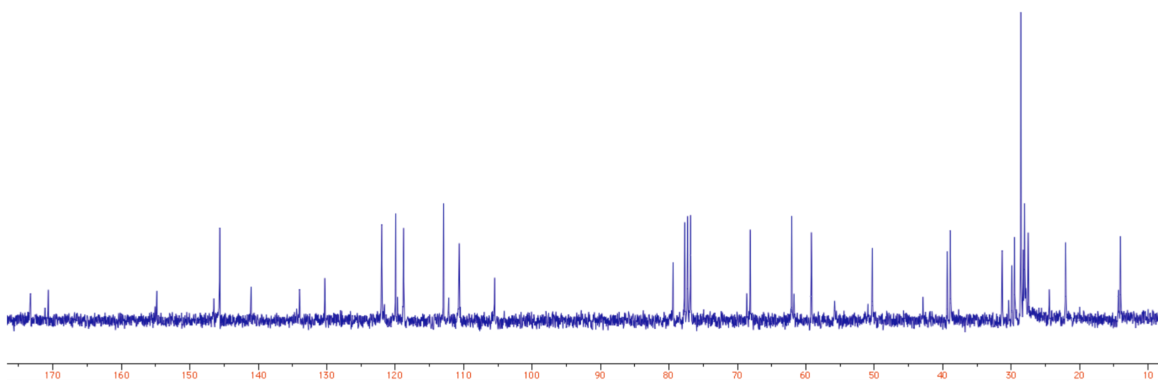


^{1}H NMR, 300 MHz, $CDCl_3$, filename: mscoupledTS1



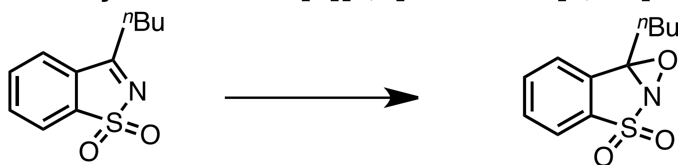


^{1}H NMR, 300 MHz, $CDCl_3$, filename: mscoupledBS



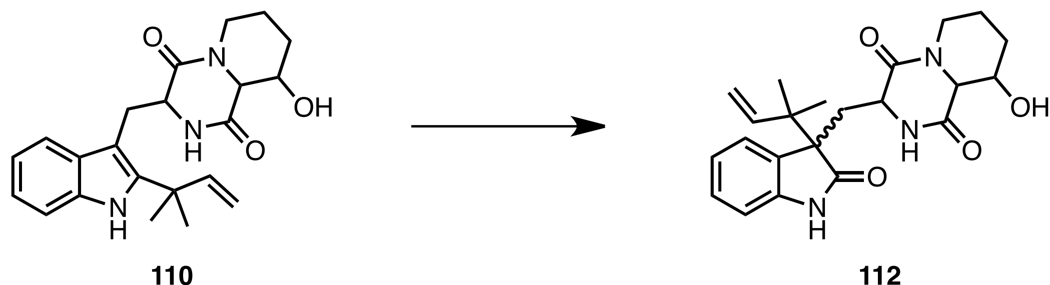
^{13}C NMR, 75 MHz, $CDCl_3$, filename: ms358carbon

7b-butyl-7b*H*-benzo[*d*][1,2]oxazireno[2,3-*b*]isothiazole 3,3-dioxide (111):



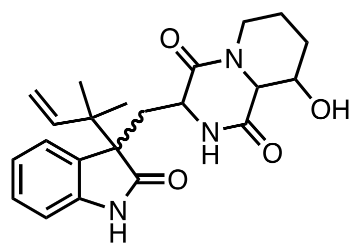
In a three neck round bottom fitted with an addition funnel was added imine (0.5 g, 2.20 mmol), 30 mL of DCM and 30 mL of saturated K_2CO_3 solution. The addition funnel was then charged with m-CPBA (0.58 g, 3.35 mmol) in 20 mL of DCM. The *m*-CPBA was added dropwise over 30 minutes at room temperature. Once the addition was finished the reaction mixture was stirred for an additional 30 minutes at room temperature. The organic phase was then separated from the aqueous phase using a separatory funnel. The organic phase was then washed with saturated Na_2SO_3, saturated $NaHCO_3$, and brine. Finally the organic phase was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude material was then purified via column chromatography (DCM/Hexanes 4/6) to provide a white solid (0.4 g, 78%).

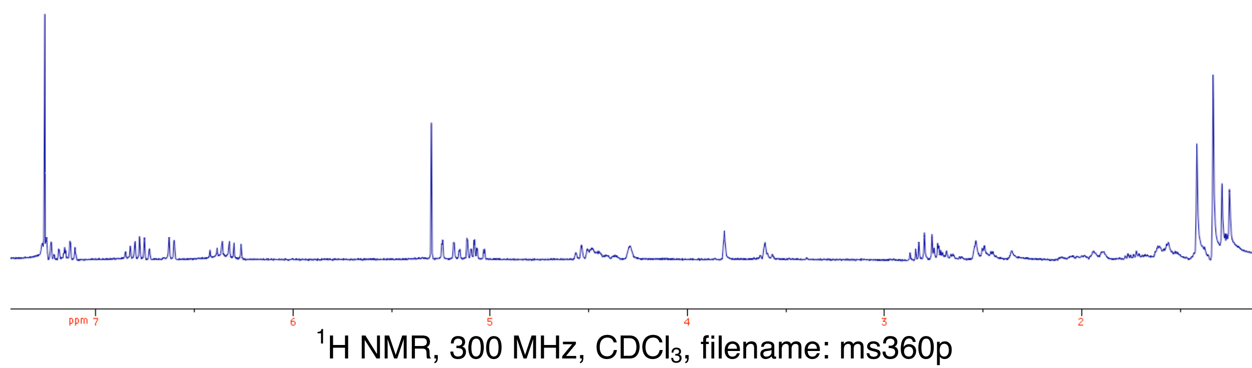
(3*S*,9*S*,9a*R*)-9-hydroxy-3-((3-(2-methylbut-3-en-2-yl)-2-oxoindolin-3 yl)methyl)hexahydro-1*H*-pyrido[1,2-*a*]pyrazine-1,4(6*H*)-dione (112):



To a solution of DKP **110** (70.6 mg, 0.185 mmol) dissolved in 3.7 mL of DCM at ambient temperature, was added oxaziridine (88.5 mg, 0.370 mmol). The reaction mixture was allowed to stir at ambient temperature for 48 hours and then was concentrated. The crude oil was then purified via column chromatography (MeOH/DCM 3/97) to afford a pale yellow foam (44.5, 61%).

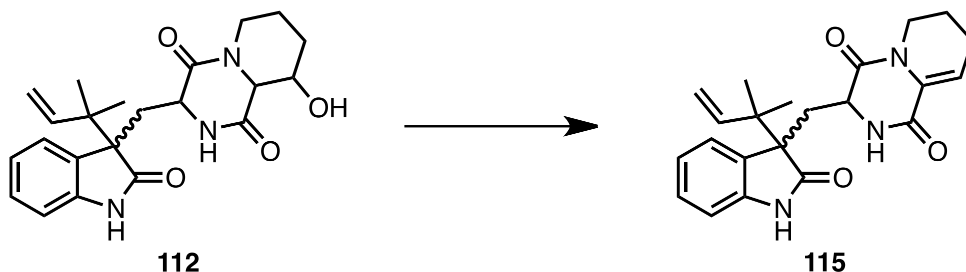
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22-7.10 (m, 1H), 6.85-6.72 (m, 0.7H), 6.61 (d, J = 7.8 Hz, 0.3H), 6.42-6.26 (m, 1H), 5.241-5.028(m, 1H), 4.56-4.28 (m, 1H), 3.81 (bs, 0.3H), 3.63-3.56 (m, 0.5H), 2.87-2.60 (m, 1H), 2.53-2.44 (m, 1H), 2.102-1,89 (m, 1H), 1.81-1.51 (m, 1H), 1.45 (s, 1.17H), 1.33 (s, 1.87H), 1.26 (d, J = 11.1 Hz, 2H); HRMS (ESI/APCI) calcd for $C_{22}H_{27}N_3O_4$ (M+H) 398.2002, found 398.2076.





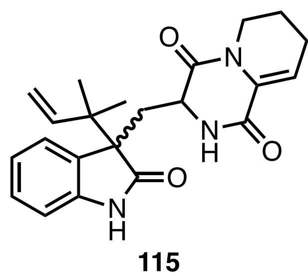
^{1}H NMR, 300 MHz, $CDCl_3$, filename: ms360p

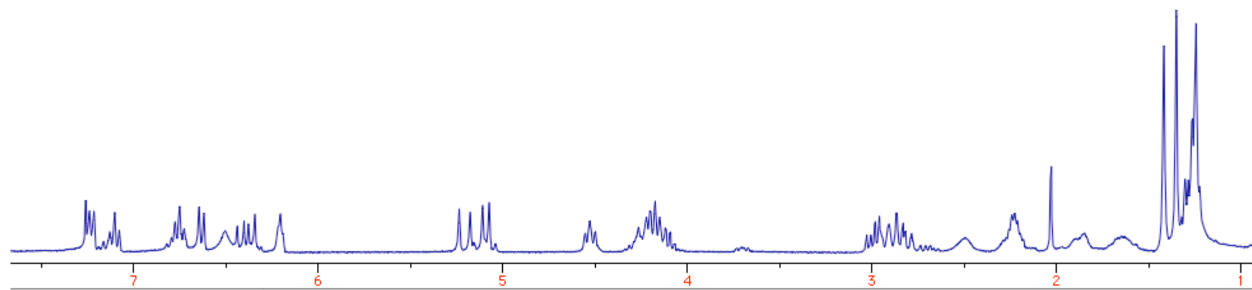
3-((3-(2-methylbut-3-en-2-yl)-2-oxoindolin-3-yl)methyl)-2,3,7,8-tetrahydro-1*H*-pyrido[1,2-*a*]pyrazine-1,4(6*H*)-dione (115):



The alcohol **112** (129.2 mg, 0.325 mmol) was dissolved in 7 mL of DCM under argon. To the reaction was added DEAD (0.15 mL, 0.975mmol) and PBu_3 (0.24 mL, 0.975 mmol). The mixture was then stirred at room temperature for 16 hours and was concentrated to afford a brown oil. The crude oil was then submitted to purification via column chromatography (MeOH/DCM 3/97) and provided a pale yellow foam (59.7 mg, 48%).

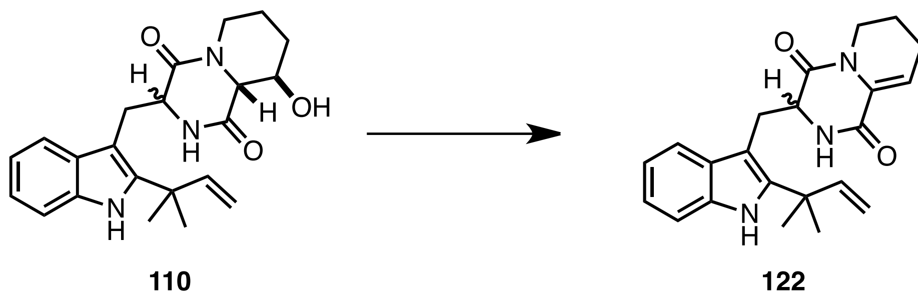
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26.7.25 (m, 2H), 6.81-6.72 (m, 2H), 6.61 (bs, 1H), 6.37 (q, *J* = 17.7, 10.8 Hz, 1H), 6.20 (bs, 1H), 5.13 (q, *J* = 17.7, 10.8 Hz, 2H), 4.52 (t, *J* = 7.5 Hz, 1H), 4.31-4.07 (m, 4H), 3.03-2.78 (m, 3H), 2.28-2.17 (m, 2H), 1.91-1.83 (m, 1H), 1.41 (s, 3H), 1.35 (s, 3H).





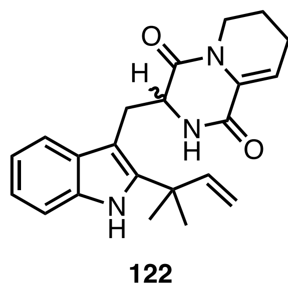
^{1}H NMR, 300 MHz, $CDCl_3$, filename: ms426ts

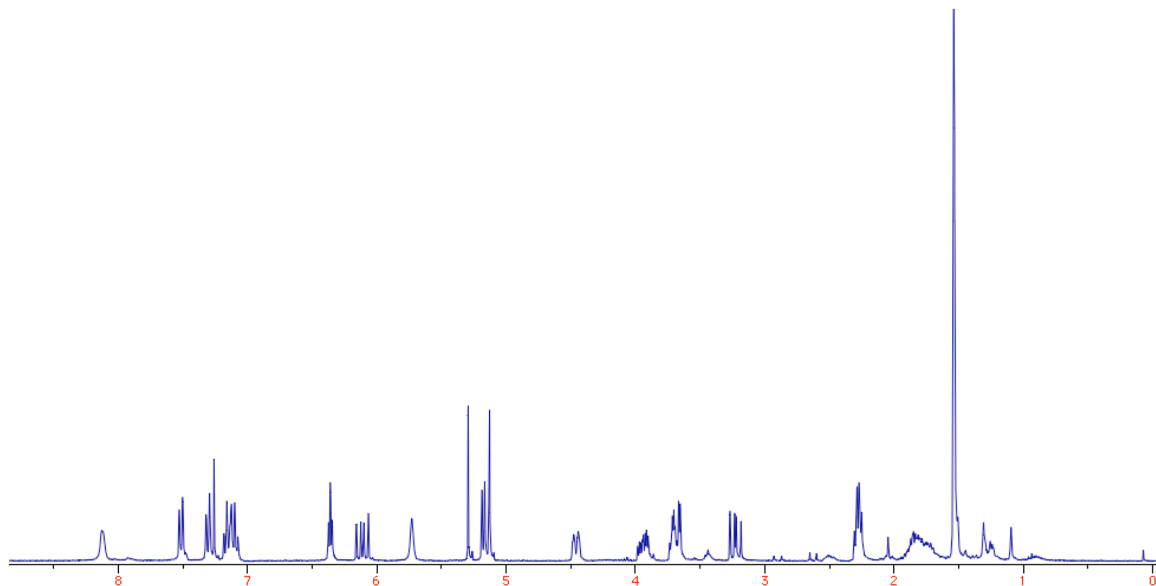
3-((2-(2-methylbut-3-en-2-yl)-1H-indol-3-yl)methyl)-2,3,7,8-tetrahydro-1H-pyrido[1,2-a]pyrazine-1,4(6H)-dione (122)



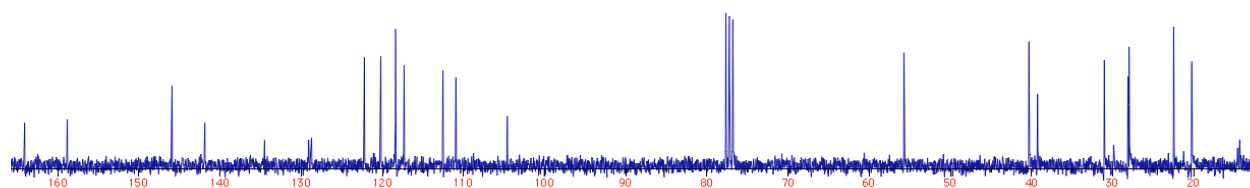
To a flame dried flask fitted with a reflux condenser was added alcohol derivative **110** (470 mg, 1.232 mmol) and 24.6 mL of MeCN. Then DEAD (0.582 mL, 3.69 mmol) was added and the mixture was stirred for 15 minutes at room temperature. PBu_3 (0.923 mL, 3.69 mmol) was added to the reaction flask and the resulting solution was refluxed at 90 °C overnight. The solution was then allowed to cool to room temperature and then concentrated to afford a crude brownish oil. The residue was purified by means of silica gel chromatography, using EtOAc/hexanes (4:1) as the eluent to yield 447 mg of pure white foam (89%).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.12 (bs, 1H), 7.51 (d, J = 7.8 Hz, 1H), 7.30 (d, J = 8.1 Hz, 1H), 7.18-7.07 (m, 2H), 6.36 (t, J = 4.2 Hz, 1H), 6.15 (dd, J = 17.4, 10.2 Hz, 1H), 5.73 (bs, 1H), 5.18-5.12 (m, 2H), 4.45 (d, J = 10.2 Hz, 1H), 3.99-3.90 (m, 1H), 3.73-3.65 (m, 2H), 3.26-3.18 (m, 1H), 2.30-2.25 (m, 2H), 1.91-1.69 (m, 3H), 2.39 (bs, 1H), 1.53 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 164.0, 158.8, 145.9, 141.8, 134.5, 129.0, 128.7, 122.2, 120.2, 118.3, 117.3, 112.5, 110.9, 104.6, 55.7, 40.3, 39.2, 31.0, 27.9, 22.4, 20.2; HRMS (ESI/APCI) calcd for $C_{22}H_{25}N_3O_2$ (M+H) 363.1947, found 364.2022.



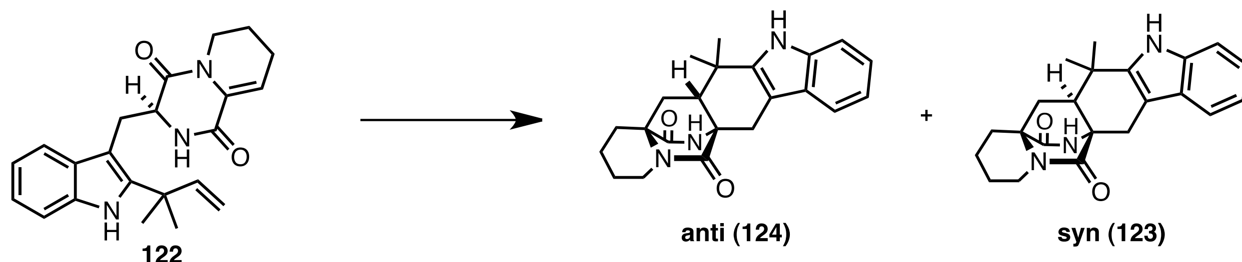


^{1}H NMR, 300 MHz, $CDCl_3$, filename: ms771p



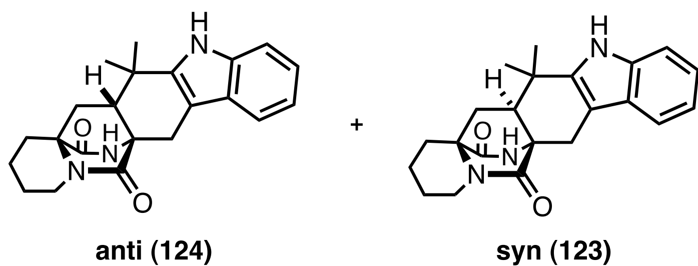
^{13}C NMR, 75 MHz, $CDCl_3$, filename: ms389pcarbon

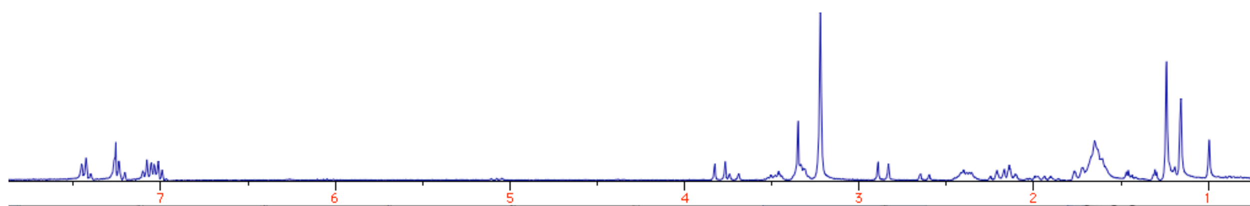
Diels-Alder Cycloadducts (124 and 123):



To a solution of enamide **122** (463.6 mg, 1.127 mmol) in MeOH (102 mL) at 0 °C, was added 20% aqueous KOH (25.5 mL). The resulting reaction mixture was stirred at room temperature for 5 hours. The MeOH was evaporated under reduced pressure and the resulting residue was diluted with DCM, and quenched saturated aqueous NH_4Cl. The organic layer was separated from the aqueous layer using a separatory funnel. The aqueous layer was then extracted 5 times with DCM (25 mL). The combined organic extracts were dried over Na_2SO_4, filtered and then concentrated. Total combined yield 400.2 mg, 86% yield. syn: 236.9 mg anti: 163.3 mg (1.5:1).

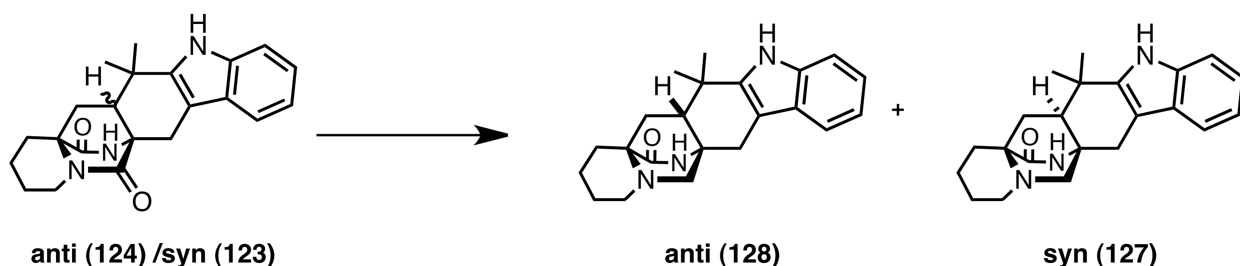
Mixture: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45-7.740 (m, 2H), 7.26-7.20 (m 2H), 7.10 (m, 4H), 3.79 (d, J = 17.4 Hz, 1H), 3.70 (d, J = 12.9 Hz, 0.5H), 3.50-3.44 (m, 1H), 2.87 (d, J = 17.7 Hz, 1H), 2.63 (d, J = 15.3 Hz, 0.5H), 2.41-2.35 (m, 2H), 2.24-2.10 (m, 2H), 2.04-1.85 (m, 1H), 1.23 (s, 1H), 1.15 (s, 1H); HRMS (ESI/APCI) calcd for $C_{22}H_{25}N_3O_2$ (M+H) 363.1947, found 363.2013.





^{1}H NMR, 300 MHz, $CDCl_3$, filename: ms404pure

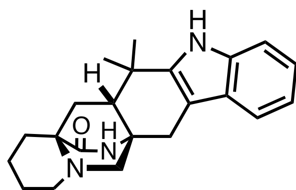
(6a*R*,7a*S*,13a*S*)-6,6-dimethyl-5,6,6a,7,8,9,10,11,13,14-decahydro-13a,7a-(epiminomethano)quinolizino[2,3-*b*]carbazol-16-one (127) and (6a*S*,7a*S*,13a*S*)-6,6-dimethyl-5,6,6a,7,8,9,10,11,13,14-decahydro-13a,7a-(epiminomethano)quinolizino[2,3-*b*]carbazol-16-one (128)



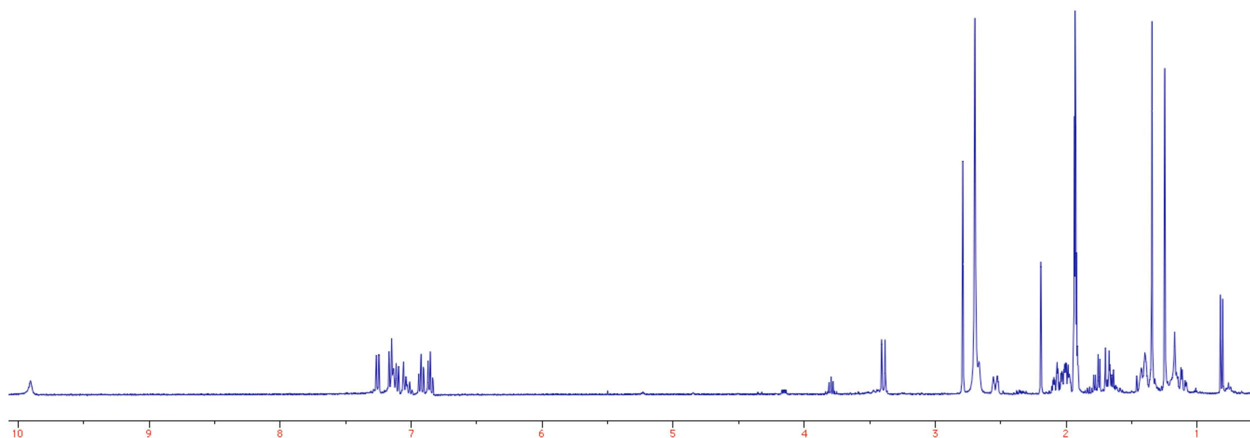
To a mixture of amides **124** and **123** (82.5 mg, 0.225 mmol) in toluene (45 mL) at 0 °C, was added DIBAL (4.5 mL) dropwise. The reaction mixture was then stirred at room temperature overnight. Solid Na_2SO_4-$9H_2O$ was added and stirred for 60 minutes. The solids were filtered off and rinsed with EtOAc. The filtrate was concentrated under reduced pressure to afford a crude pale yellow solid. The crude solid was purified via column chromatography (MeOH/ DCM 1/99) to afford a white solid (63.5 mg, 80%).

Anti: ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 9.90 (bs, 1H), 7.26-6.83 (m, 4H), 3.83-3.75 (m, 1H), 3.39 (d, J = 10.4, Hz, 1H), 2.19 (s, 1H), 2.09-1.97 (m, 4H), 1.79-1.74 (m, 1H), 2.16 (m, 2H), 1.42-1.38 (m, 3H), 1.34 (s, 3H), 1.24 (s, 3H), 1.17-1.08 (m, 3H); ^{13}C NMR (100 MHz, $(CD_3)_2CO$) δ 173.0, 128.8, 120.8, 118.4, 117.4, 110.5, 104.6, 103.9, 60.9, 55.2, 54.7, 46.9, 34.4, 31.2, 30.1, 25.8, 23.5, 21.3, 18.2; HRMS (ESI/APCI) calcd for $C_{22}H_{27}N_3O$ (M+H) 350.2154, found 350.2165.

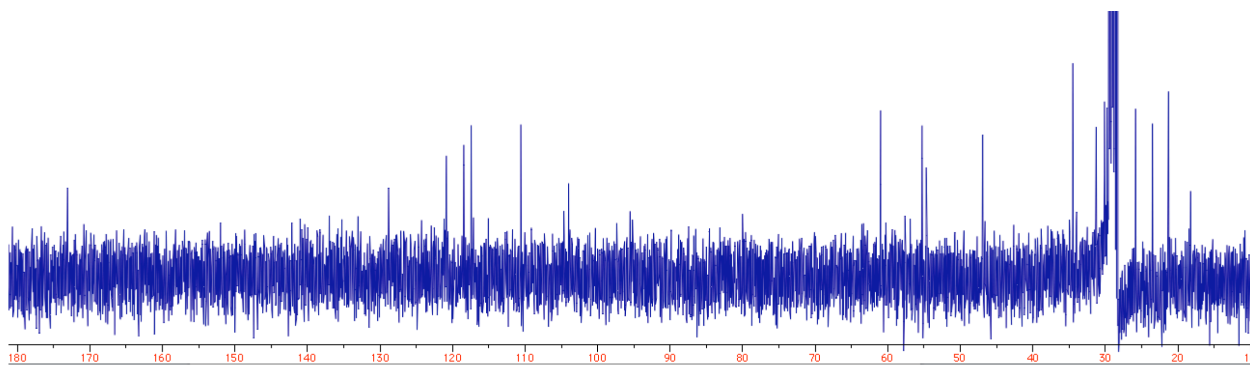
Syn: ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 9.84 (bs, 1H), 7.22 (d, J = 8.0 Hz, 1H), 7.14 (d, J = 8.0 Hz, 1H), 6.93-6.81 (m, 2H), 3.50-3.35 (m, 1H), 3.11 (d, J = 13.2 Hz, 1H), 2.57-2.53 (m, 1H), 2.27-2.20 (m, 2H), 1.74-1.67 (m, 1H), 1.60-1.53 (m, 1H), 1.40-1.35 (m, 3H), 1.16 (s, 3H), 1.16-1.05 (m, 4H); ^{13}C NMR (100 MHz, $(CD_3)_2CO$) δ 173.3, 141.6, 136.9, 120.7, 118.3, 117.6, 110.5, 103.4, 98.3, 64.3, 58.0, 54.2, 54.0, 46.7, 34.5, 34.0, 30.7, 27.9, 25.9, 23.4, 20.9; HRMS (ESI/APCI) calcd for $C_{22}H_{27}N_3O$ (M+H) 350.2154, found 350.2165.



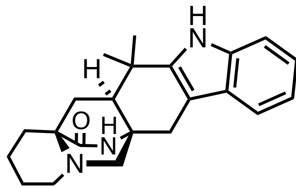
anti



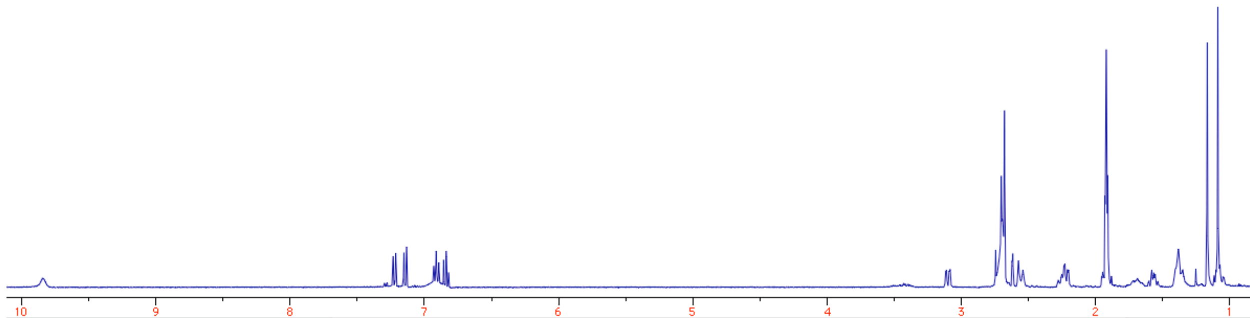
^{1}H NMR, 400 MHz, $(CD_3)_2CO$, filename: ms411ts/PROTON_001



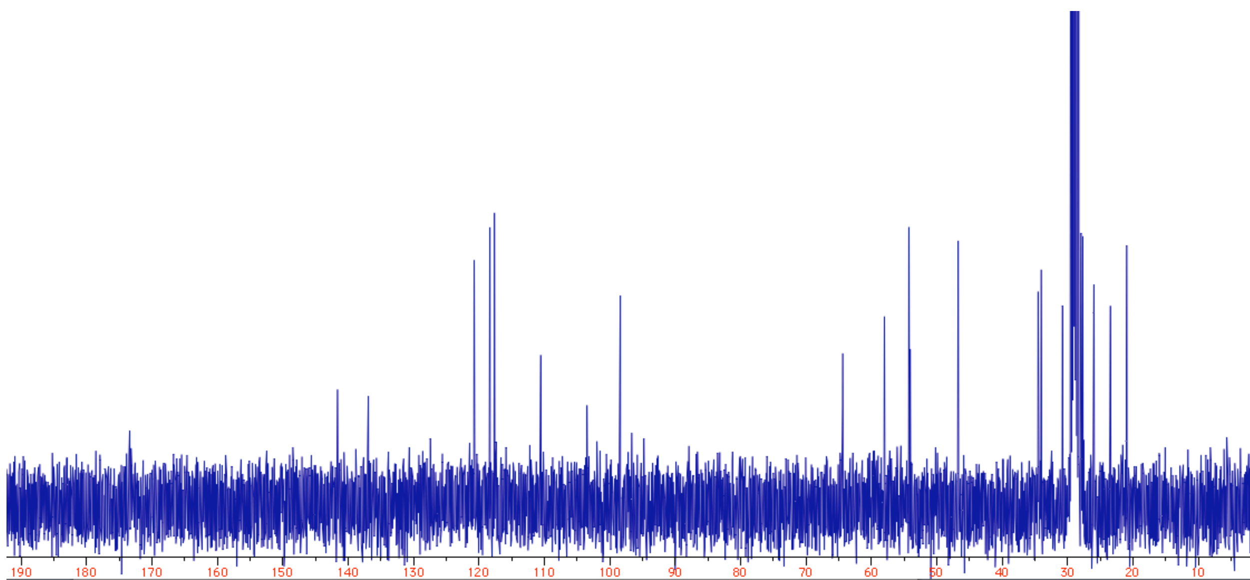
^{13}C NMR, 75 MHz, $(CD_3)_2CO$, filename: ms566pcarbon



syn

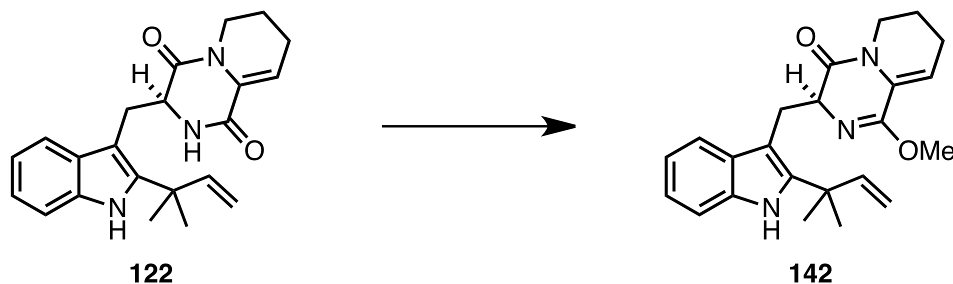


^{1}H NMR, 400 MHz, $(CD_3)_2CO$, filename: ms411Bs/PROTON_001



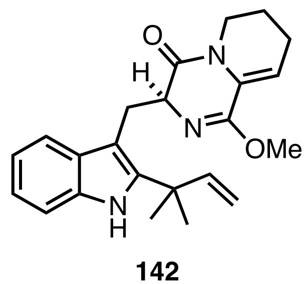
^{13}C NMR, 100 MHz, $(CD_3)_2CO$, filename: ms411Bs

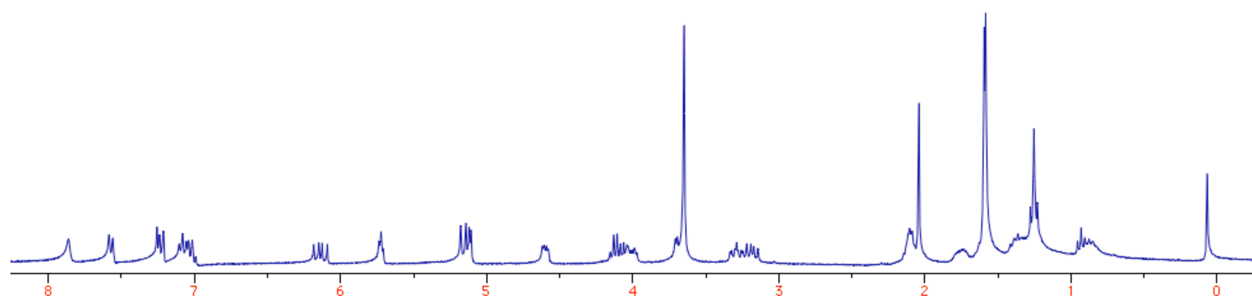
(S)-1-methoxy-3-((2-(2-methylbut-3-en-2-yl)-1H-indol-3-yl)methyl)-7,8-dihydro-3H-pyrido[1,2-a]pyrazin-4(6H)-one (142)



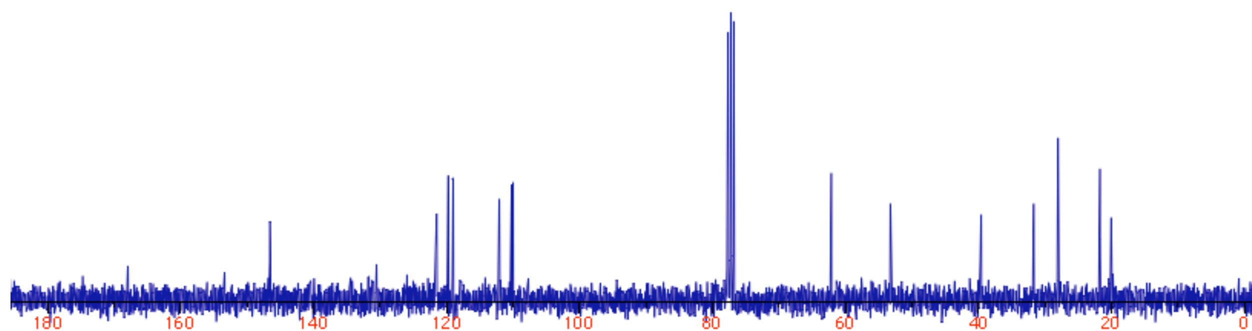
To a solution of enamide **122** (830 mg, 2.28 mmol), and $CsCO_3$ (3.72 g, 11.40 mmol) in DCM (22.8 mL) at ambient temperature, was added $(CH_3)_3OBF_4$ (1.012 g, 6.84 mmol). The reaction mixture was stirred for an additional 6 hours, quenched with ice and extracted with DCM. The combined organic phases were dried over Na_2SO_4, filtered and then concentrated.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (bs, 1H), 7.57 (d, *J* = 8.1 Hz, 1H), 7.34 (m, 1H), 7.10-6.99 (m, 2H), 6.13 (q, *J* = 17.4, 8.1 Hz, 1H), 5.73 (t, *J* = 3.9 Hz, 1H), 5.12 (q, *J* = 20.4, 13.5 Hz, 2H), 4.60 (q, *J* = 8.4, 4.2 Hz, 1H), 4.043-3.97 (m, 1H), 3.64 (s, 3H), 3.33-3.14 (m, 3H), 2.14-2.07 (m, 2H), 1.79-1.71 (m 2H), 1.59 (d, *J* = 3.3 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.9, 146.5, 121.4, 119.7, 119.0, 112.0, 110.2, 110.0, 62.1, 53.2. 39.6, 31.7, 21.7, 20.0; HRMS (ESI/APCI) calcd for $C_{23}H_{27}N_3O_2$ (M+H) 378.2103, found 378.2181.



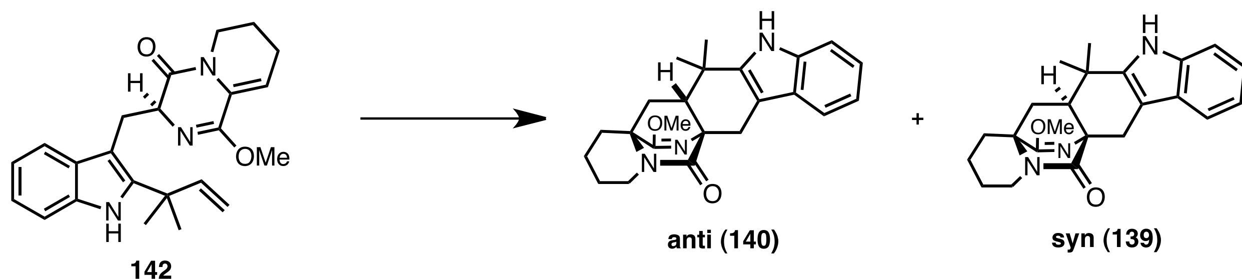


^{1}H NMR, 300 MHz, $CDCl_3$, filename: ms426ts



^{13}C NMR, 75M Hz, $CDCl_3$, filename: ms566pcarbon

Diels-Alder Cycloadducts (139 and 140):

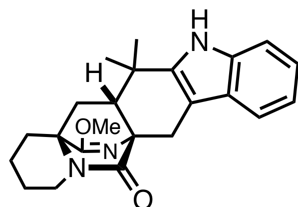


To a solution of lactim ether **142** (600 mg, 1.589 mmol) in MeOH (127 mL) at 0°C, was added 20% aqueous KOH (37 mL). The mixture was then refluxed for 3 hours. The solution was then cooled to room temperature and concentrated. The resulting residue was then neutralized to pH 7 with KH_2PO_4, diluted with H_2O and extracted with DCM. The combined organic extracts were dried over Na_2SO_4, filtered and then concentrated (Anti 1 to syn 1.20).

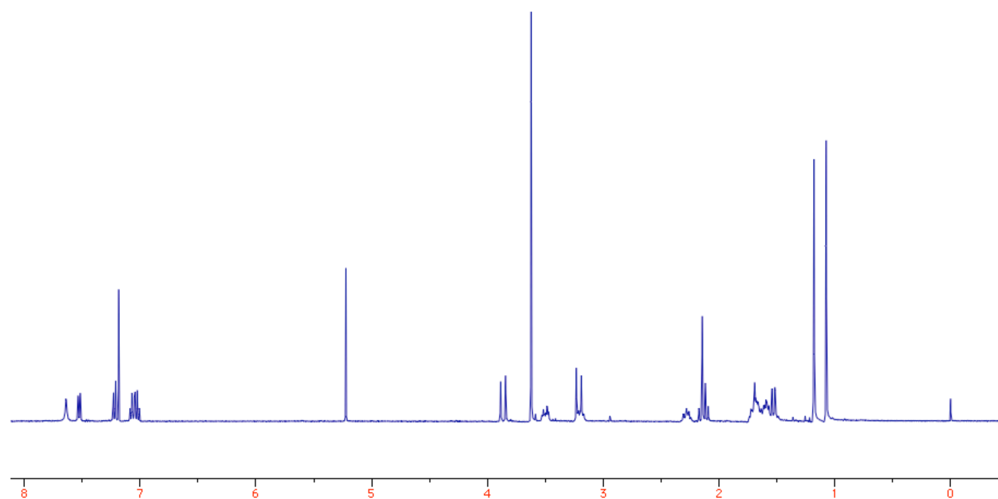
Anti: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (bs, 1H), 7.52 (d, *J* = 7.6 Hz, 1H), 7.22 (d, *J* = 7.6 Hz, 1H), 7.09-7.00 (m, 2H), 3.86 (d, *J* = 16.8 Hz, 1H), 3.62 (s, 3H), 3.20 (d, *J* = 16.8 Hz, 1H), 2.30-2.24 (m, 1H), 2.24-2.09 (m, 2H), 1.74-1.57 (m, 6H), 1.52 (d, *J* = 9.6 Hz, 1H), 1.18 (s, 3H), 1.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.9, 170.3, 139.6, 136.3, 128.0, 121.4, 119.1, 118.8, 110.2, 106.3, 65.2, 57.3, 24.0, 44.8, 39.3, 34.8, 33.7, 28.5, 26.5, 25.2, 22.0, 18.2; HRMS (ESI/APCI) calcd for $C_{23}H_{27}N_3O_2$ (M+H) 378.2103, found 378.2171.

Syn: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (bs, 1H), 7.53 (d, *J* = 7.2 Hz, 1H), 7.15-7.04 (m, 3H), 4.02 (d, *J* = 16.0 Hz, 1H), 3.79 (s, 3H), 3.09 (d, *J* = 16.0 Hz, 1H), 2.52-2.41 (m, 1H),

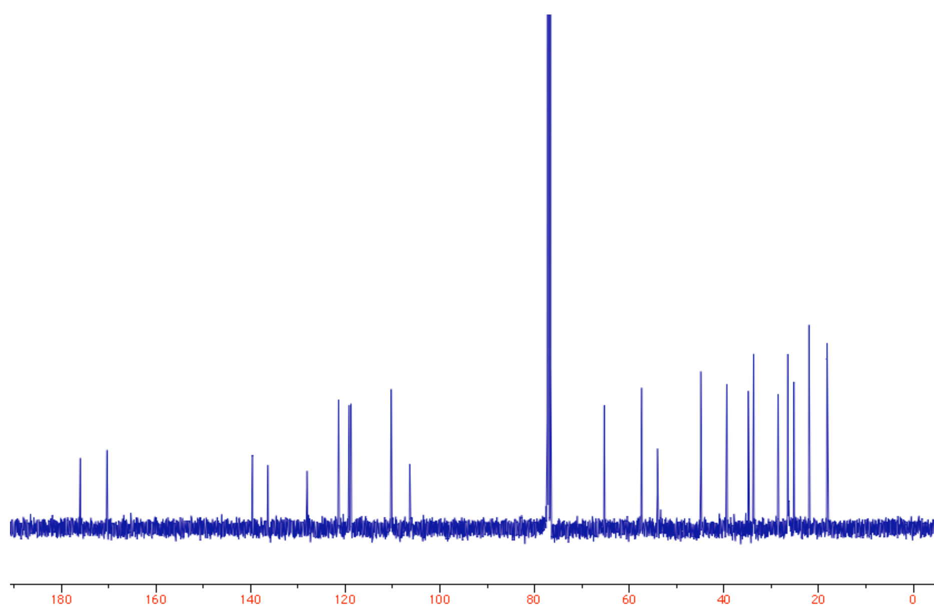
2.39-2.34 (m, 1H), 2.16 (q, J = 10.4, 5.2 Hz, 1H), 1.52 (dd, J = 12.8, 5.2 Hz, 1H), 1.78-1.66 (m, 6H), 1.44 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.9, 170.3, 139.6, 136.3, 128.0, 121.4, 119.1, 118.8, 110.2, 106.3, 65.2, 57.3, 24.0, 44.8, 39.3, 34.8, 33.7, 28.5, 26.5, 25.2, 22.0, 18.2; HRMS (ESI/APCI) calcd for $C_{23}H_{27}N_3O_2$ (M+H) 378.2103, found 378.2171.



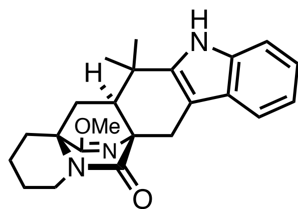
anti (140)



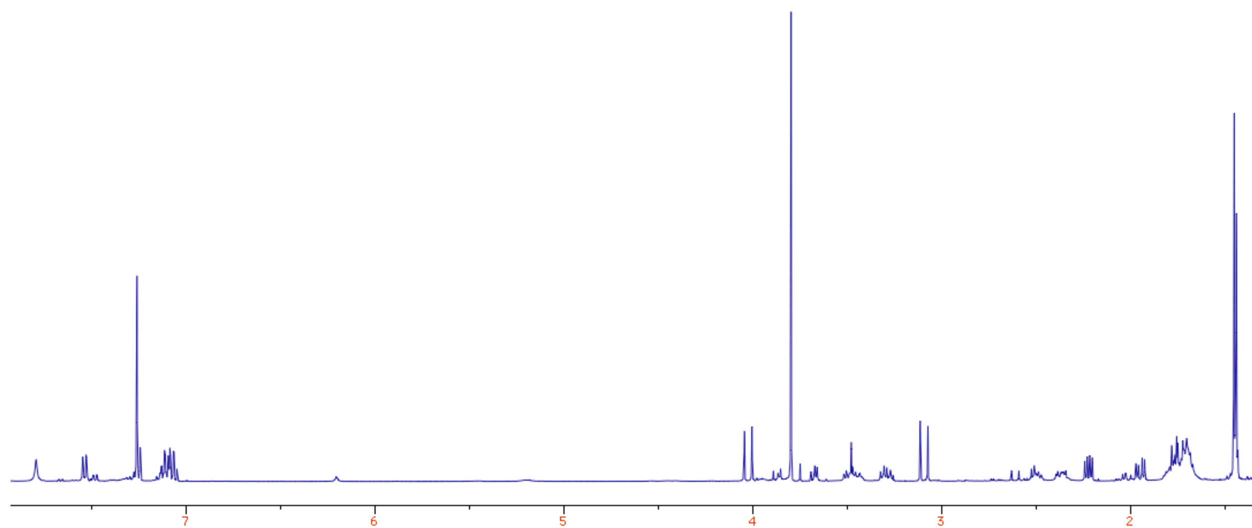
^{1}H NMR, 400 MHz, $CDCl_3$, filename: msLacEthAnti



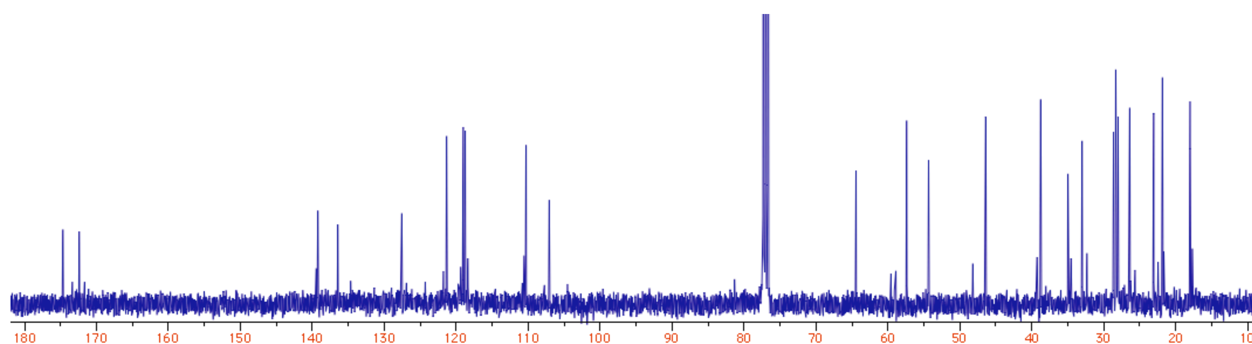
^{13}C NMR, 100 MHz, $CDCl_3$, filename: msLacEthAnticarbon



syn (139)

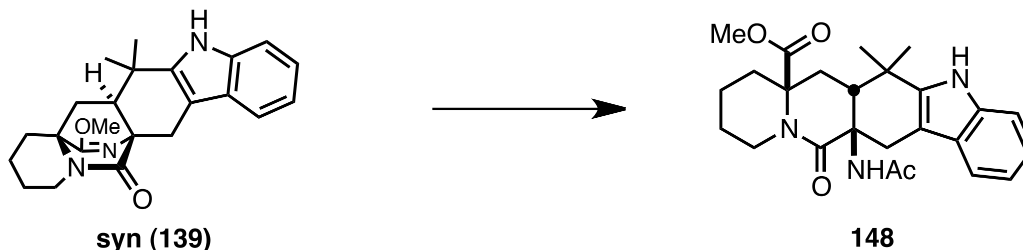


^{1}H NMR, 400 MHz, $CDCl_3$, filename: LacEtherSynProton



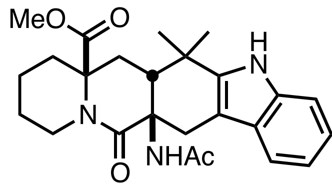
^{13}C NMR, 100 MHz, $CDCl_3$, filename:LacEtherSynCARBON

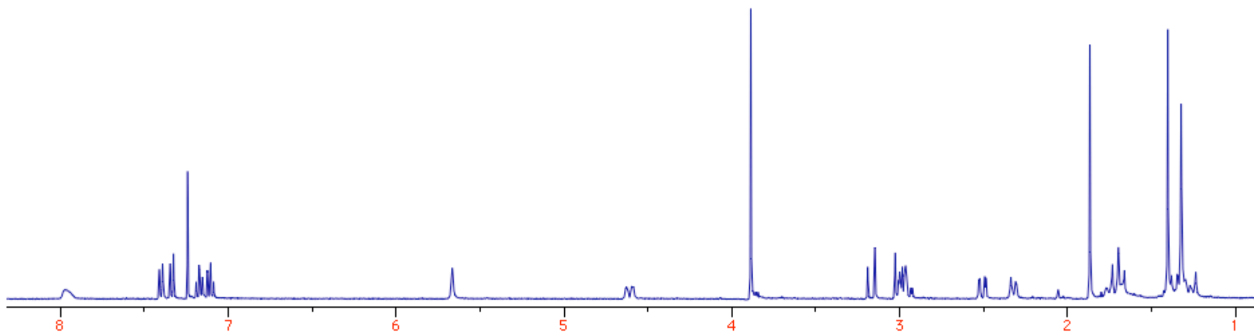
(7aR,13aR)-methyl 13a-acetamido-6,6-dimethyl-13-oxo-5,6,6a,7,7a,8,9,10,11,13,13a,14-dodecahydroquinolizino[2,3-b]carbazole-7a-carboxylate (148)



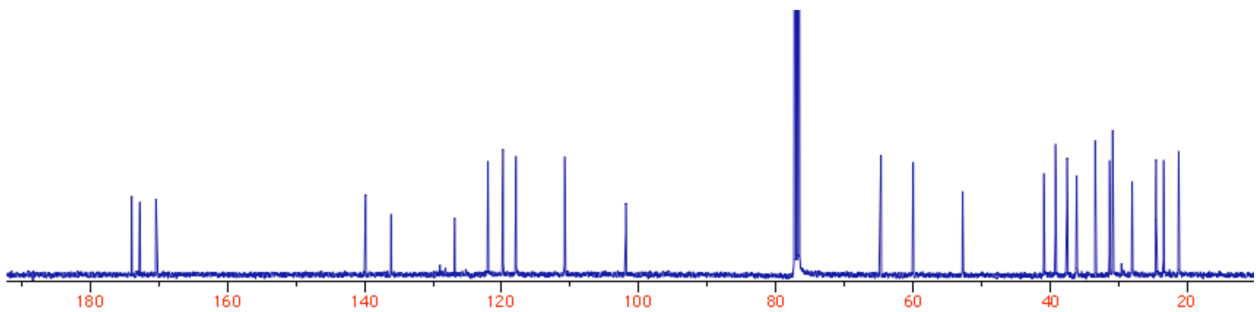
To a solution of bicyclo adduct **139** (29.4 mg, 0.00779 mmol) in THF (0.779 mL) at 0 °C was added Ac_2O (.147mL) and then 0.1 M aqueous HCl (0.779mL). The reaction was then stirred overnight in the cold room (4 °C). The reaction was then quenched with a saturated solution of $NaHCO_3$ and extracted with EtOAc. The combined organic phases were dried over Na_2SO_4, filtered and then concentrated under reduced pressure. The desired product was the minor product and therefore different conditions were utilized.

^{1}H NMR (400 MHz, ($CDCl_3$) δ 7.96 (bs, 1H), 7.40 (d, J = 8.0 Hz, 1H), 7.33 (d, J = 8.0 Hz, 1H), 7.19-7.08 (m, 2H), 5.66 (bs, 1H), 4.60 (d, J = 14 Hz, 1H), 3.88 (s, 3H), 3.15 (d, J = 17.2 Hz, 1H), 3.02-2.92 (m, 3H), 2.50 (dd, J = 14, 2.8 Hz, 1H), 2. 31 (d, J = 11.2 Hz, 1H), 1.86 (s, 3H), 1.76-1.66 (m, 3H), 1.40 (s, 3H), 1.32 (s, 3H), 1.32-1.23 (m, 2H); ^{13}C NMR (100 MHz, ($CDCl_3$) δ 173.9, 172.7, 170.3, 139.8, 136.1, 126.8, 122.0, 119.8, 117.9, 110.8, 101.8, 64.7, 60.0, 52.7, 40.9, 39.2, 37.5, 36.1, 33.4, 31.3, 30.9, 28.0, 24.6, 23.5, 21.3; HRMS (ESI/APCI) calcd for $C_{25}H_{31}N_3O_4$ (M+H) 438.2315, found 438.2389.



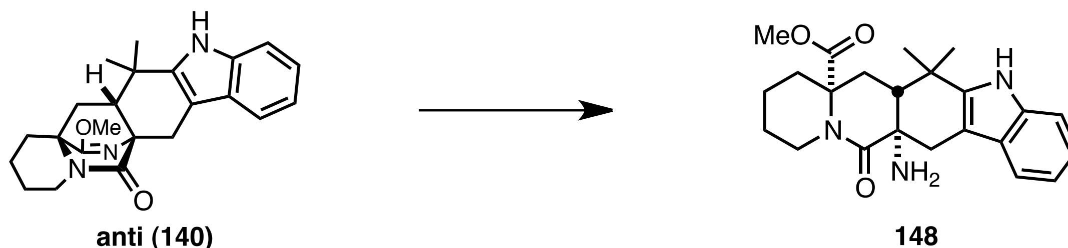


^{1}H NMR, 400 MHz, $CDCl_3$, filename: ms904p/PROTON_01



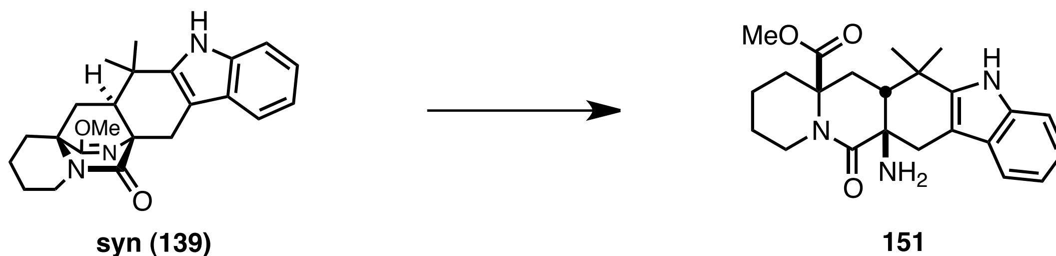
^{13}C NMR, 100 MHz, $CDCl_3$, filename: ms904p/CARBON_01

(7a*S*,13a*S*)-methyl 13a-amino-6,6-dimethyl-13-oxo-5,6,6a,7,7a,8,9,10,11,13,13a,14-dodecahydroquinolizino[2,3-*b*]carbazole-7a-carboxylate (148):



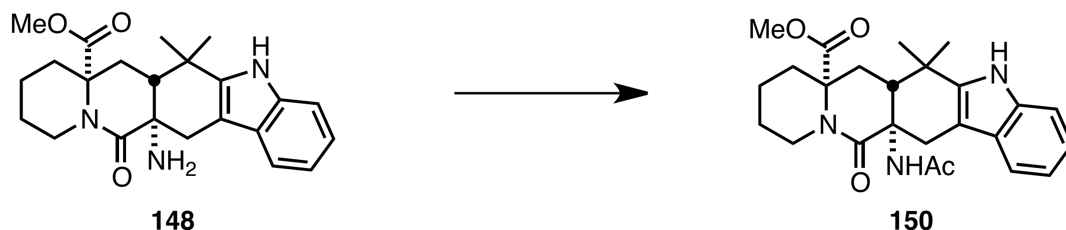
To a solution of bicyclo adduct **140** (7.7mg, 0.02 mmol) in THF (204 µL) at 0 °C was added 0.1 M HCl (204 µL) dropwise over 8 hours. The solution was then stirred at 0 °C for 2.5 hours. The mixture was then moved to the cold room (4 °C) and stirred for an additional 18 hrs. While still cold the solution was then quenched with a phosphate buffer (7.3 pH) and quickly extracted with Et_2O. The combined organic phases were dried over Na_2SO_4, filtered and then concentrated under reduced pressure. The crude amine was taken directly on without purification.

(7a*R*,13a*R*)-methyl 13a-amino-6,6-dimethyl-13-oxo-5,6,6a,7,7a,8,9,10,11,13,13a,14-dodecahydroquinolizino[2,3-*b*]carbazole-7a-carboxylate (151):



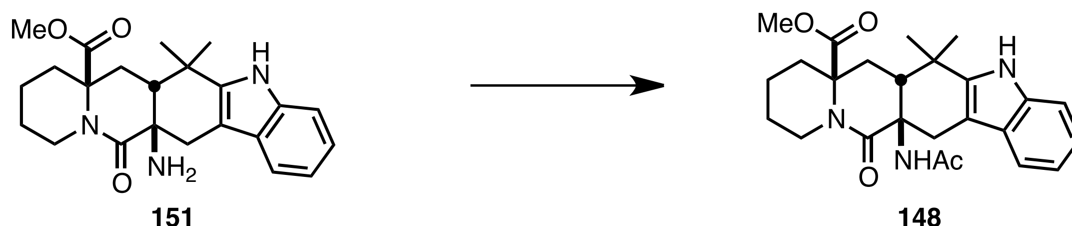
To a solution of bicyclo adduct **139** (32.2mg, 0.087 mmol) in THF (0.879 mL) at 0 °C was added 0.1 M HCl (0.879 mL) dropwise over 4 hours. The mixture was then moved to the cold room (4 °C) and stirred for an additional 18 hrs. While still cold the solution was then quenched with a phosphate buffer (7.3 pH) and quickly extracted with Et_2O. The combined organic phases were dried over Na_2SO_4, filtered and then concentrated under reduced pressure. The crude amine was taken directly on without purification.

(7a*S*,13a*S*)-methyl 13a-acetamido-6,6-dimethyl-13-oxo-5,6,6a,7,7a,8,9,10,11,13,13a,14-dodecahydroquinolizino[2,3-*b*]carbazole-7a-carboxylate (150):



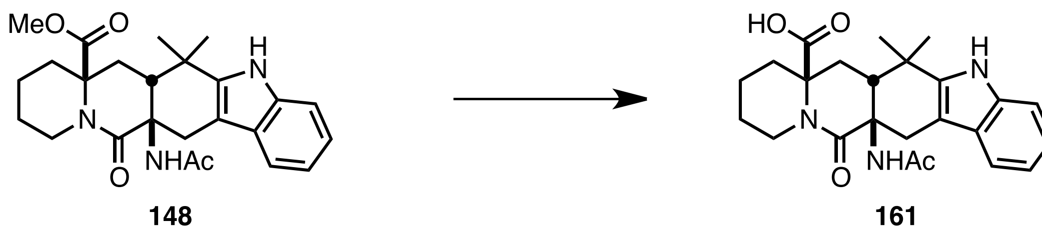
The crude amine **148** (275.2 mg, 0.696 mmol) was then dissolved in THF (6.9 mL) and cooled to -15 °C. To this was then added Ac_2O (109 mL, 2.9 mmol) and subsequently the reaction was then slowly allowed to warm to 0 °C and stirred for 48 hours. The reaction mixture was quenched with NH_4Cl and extracted with EtOAC. The combined organics were then dried over Na_2SO_4, filtered and then concentrated under reduced pressure. The crude pale yellow solid was purified via column chromatography (MeOH/DCM 3/97) to afford a pale yellow foam (122.4 mg, 40%).

(7a*R*,13a*R*)-methyl 13a-acetamido-6,6-dimethyl-13-oxo-5,6,6a,7,7a,8,9,10,11,13,13a,14-dodecahydroquinolizino[2,3-*b*]carbazole-7a-carboxylate (148):



The crude amine **148** (0.879 mmol) was then dissolved in THF (0.879 mL) and cooled to 0 °C. To this reaction mixture, was added Ac_2O (24.9 µL, 0.263 mmol). The resulting solution was then moved to the cold room (4 °C) and stirred for 24 hours. The reaction mixture was quenched with NH_4Cl and then extracted with EtOAC. The combined organics were then dried over Na_2SO_4, filtered, and then concentrated under reduced pressure. The crude pale yellow solid was purified via column chromatography (MeOH/DCM 3/97) to afford a pale yellow foam (10.7 mg, 27%).

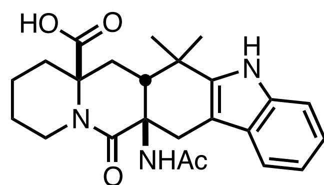
(7a*S*,13a*S*)-13a-acetamido-6,6-dimethyl-13-oxo-5,6,6a,7,7a,8,9,10,11,13,13a,14-dodecahydroquinolizino[2,3-*b*]carbazole-7a-carboxylic acid (161):



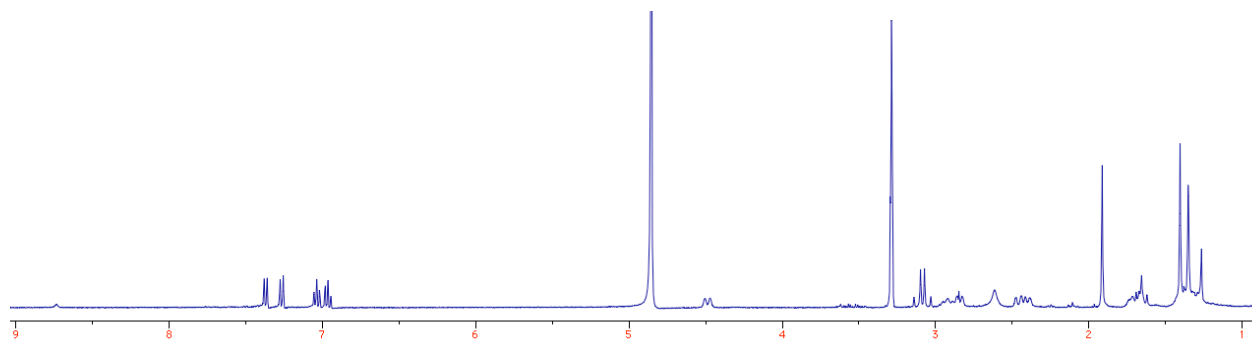
To a stirred suspension of tellurium powder (0.355 mg) in dry degassed toluene (1.25 mL), was added 2 M $(Me_3Al)_2$ (1.25 mL). The resulting solution was stirred at 112 °C for 6 hours. The resulting 0.8 M solution of methyltellurolate (117 µL, 0.0937 mmol) was then added in one portion to a stirred solution of methylester (4.1 mg, 0.00937 mmol) in DCM (12.3 µL) at ambient temperature. The resulting orange solution was stirred for 6 hours and then diluted with ethylacetate. The resulting solution was treated with 2 M solution of HCl and stirred for 2 hours. Aqueous was then separated from the organic phase and then extracted with EtOAc. The combine organic phases were then washed three times with brine, dried over Na_2SO_4, filtered and then concentrated under reduced pressure. The crude product was purified via column chromatography (MeOH/DCM 1/9) to accord a pale yellow solid (2.8 mg, 72%).

Syn: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, *J* = 8.1 Hz, 1H), 7.26 (d, *J* = 8.1 Hz, 1H), 7.05- 6.94 (m, 1H), 4.48 (d, *J* = 12.8 Hz, 1H), 3.08 (q, *J* = 16.8, 26.8 Hz, 2H), 2.95- 2.82 (m, 2H), 2.61 (bs, 1H), 2.42 (q, *J* = 15.2, 24.4 Hz 2H), 1.91 (s, 3H), 1.74-1.62 (m, 3H), 1.40 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.7, 139.2, 136.8, 126.9,

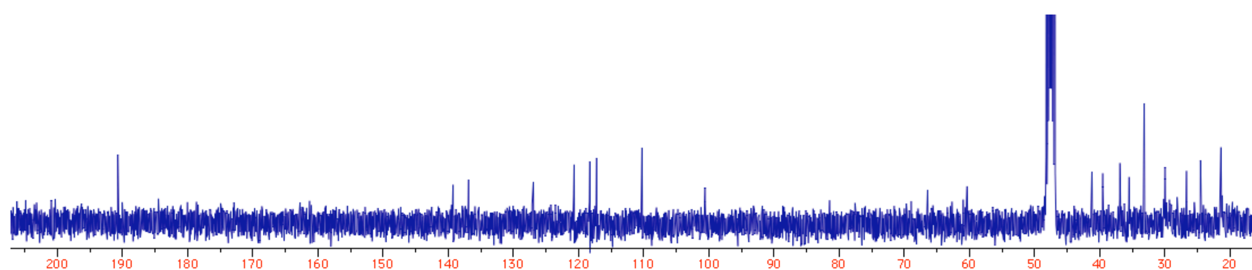
120.6, 118.2, 117.2, 110.2, 100.5, 81.4, 66.4, 61.2, 60.3, 56.0, 41.2, 39.5, 36.9, 35.5, 33.1, 30.1, 29.9, 26.6, 24.5, 21.5, 21.4.



syn

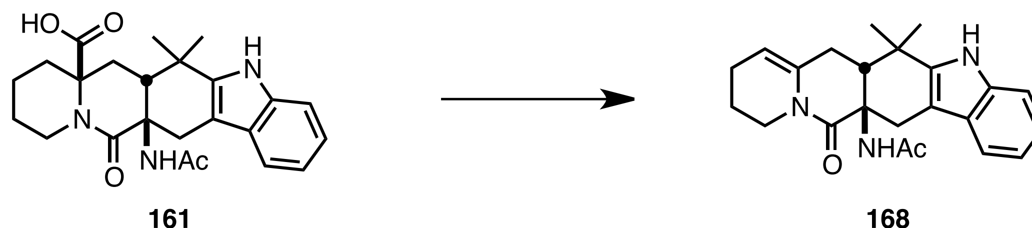


^{1}H NMR, 400 MHz, CD_3OD, filename: ms931p_proton



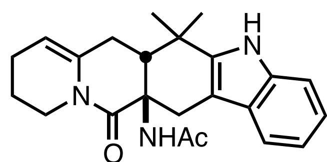
^{13}C NMR, 75 MHz, CD_3OD, filename: ms931p_carbon

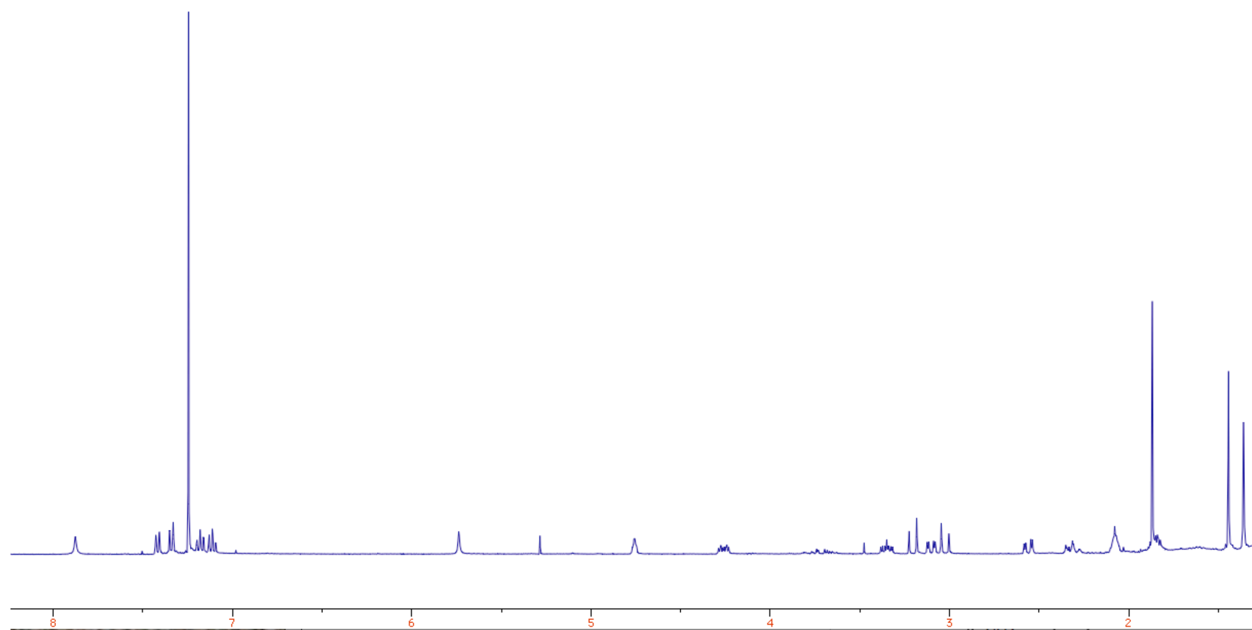
***N*-((13a*S*)-6,6-dimethyl-13-oxo-5,6,6a,7,9,10,11,13,13a,14-decahydroquinolizino[2,3-*b*]carbazol-13a-yl)acetamide (168):**



To acid (3 mg, 7.08x^{-6} mol) in toluene (83 µL), TEA (2.9 µL, 21.03x^{-6} mol) and DPPA (4.4 µL, 20.8x^{-6} mol) were added. The reaction was stirred at room temperature for 10 minutes and then warmed to 100 °C for 16 hours. The reaction was then diluted with EtOAc and quenched with NH_4Cl. The aqueous was separated from the organic and then extracted with EtOAc. The organics were combined, dried over Na_2SO_4, filtered, and then concentrated. The crude yellow product was purified using column chromatography (MeOH/DCM 1/19) to afford a white film (1.1 mg, 42%).

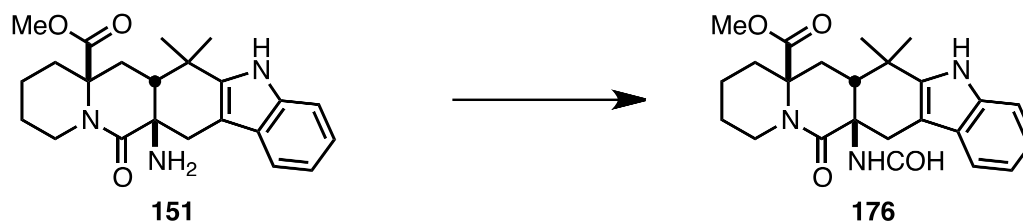
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (bs, 1H) 7.41 (d, *J* = 8 Hz, 1H) 7.34 (d, *J* = 8 Hz, 1H) 7.20-7.09 (m, 3H) 5.73 (bs, 1H) 4.75 (bs, 1H) 4.28-4.23 (m, 1H) 3.76- 3.64 (m, 1H) 3.38-3.31 (m 1H) 3.20 (d, *J* = 16.8 Hz, 1H) 3.10 (dd, *J* = 14.4, 3.6 Hz, 1H) 2.56 (dd *J* = 14.8, 3.6 Hz, 1H) 2.351-2.266 (m, 1H) 2.101-2.041 (m, 2H) 1.89 (s, 3H) 1.44 (s, 3H) 2.58 (s, 3H); HRMS (ESI/APCI) calcd for $C_{23}H_{27}N_3O_2$ (M+H) X, found X.





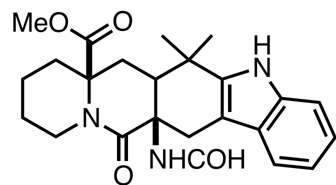
^{1}H NMR, 400MHz, $CDCl_3$, filename:ms1210p

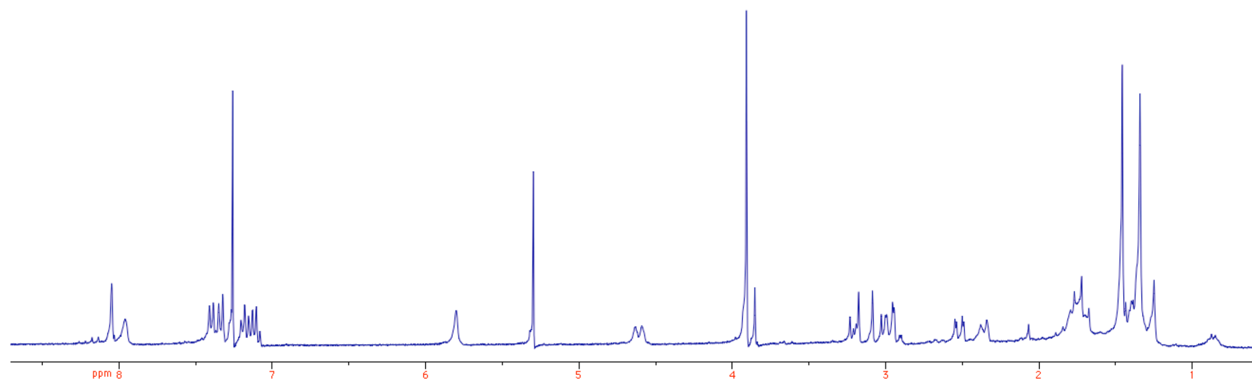
(7a*R*,13a*R*)-methyl 13a-formamido-6,6-dimethyl-13-oxo-5,6,6a,7,7a,8,9,10,11,13,13a,14-dodecahydroquinolizino[2,3-*b*]carbazole-7a-carboxylate (176):



Ac_2O (15.9 µL, 0.168 mmol) and formic acid (7.8 µL, 0.207 mmol) were stirred together at 50 °C for 2 hours. The solution was then cooled to -20 °C and then was added amine **151** (25.6 mg, 0.649 mmol) in THF (20.4 µL). The resulting solution was then stirred for an additional 4 hours at -20 °C. The reaction was then concentrated under reduced pressure and then purified via column chromatography (MeOH/DCM 3/97) to afford a white solid.

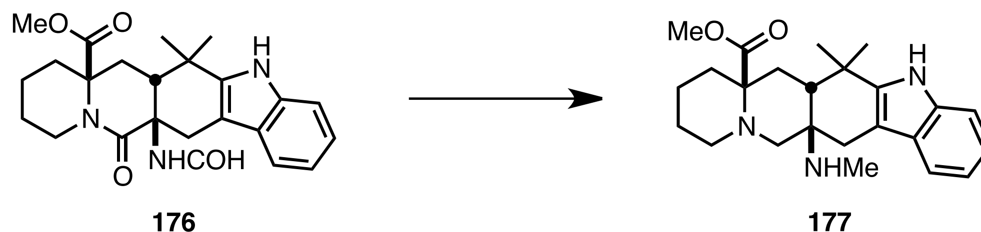
^{1}H NMR (300 MHz, ($CDCl_3$) δ 8.04 (bs, 1H), 7.95 (bs, 1H), 7.41-7.32 (m, 2H), 7.20 (m, 2H), 7.19-7.08 (m, 2H), 5.80 (bs, 1H), 4.60 (d, *J* = 14 Hz, 1H), 3.90 (s, 3H), 3.23-3.17 (m, 1H), 3.08-2.89 (m, 4H), 2.50 (dd, *J* = 14, 2.8 Hz, 1H), 2.31 (d, *J* = 11.2 Hz, 1H), 1.84-1.67 (m, 4H), 1.47 (s, 3H), 1.34 (s, 3H).





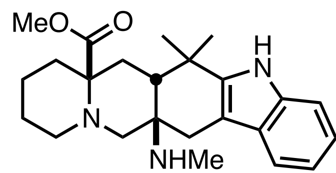
^{1}H NMR, 300MHz, $CDCl_3$, filename: ms1072BS

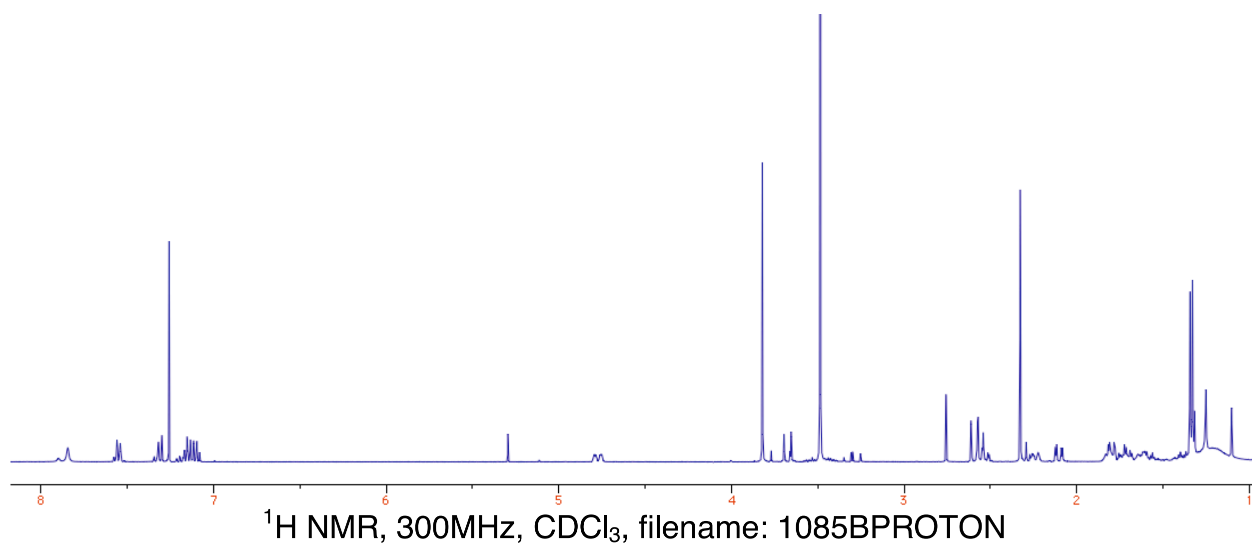
(7a*R*,13a*R*)-methyl 6,6-dimethyl-13a-(methylamino)-5,6,6a,7,7a,8,9,10,11,13,13a,14-dodecahydroquinolizino[2,3-*b*]carbazole-7a-carboxylate (177):



To formaldehyde **176** (7.1 mg, 0.0167 mmol) cooled to 0 °C and was added BMS solution (20.9 µL, 0.0419 mmols). After stirring at an additional 10 minutes at 0 °C, the reaction was warmed to ambient temperature and stirred for an additional 10 hours. The reaction was then quenched with 50 µL of MeOH and stirred for 10 minutes followed by the slow addition of saturated $NaHCO_3$. The reaction was then extracted with EtOAc and combined organics were dried over Na_2SO_4, filtered, and then concentrated. The crude reaction was purified via preparatory thin layer chromatography (MeOH/DCM, 2/98) to afford a white solid (4 mg, 61%).

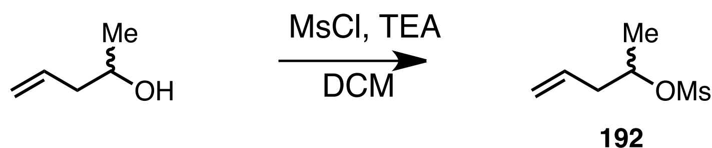
^{1}H NMR (300 MHz, ($CDCl_3$) δ 7.84 (bs, 1H), 7.95 (bs, 1H), 7.455 (d, *J* = 7.6 Hz, 1H) 7.318 (d, *J* = 8 Hz, 1H), 7.17- 7.07 (m, 2H), 4.76 (d, *J* = 13.6 Hz, 1H), 3.82 (s, 3H), 3.67 (d, *J* = 16.4 Hz, 1H), 2.75 (s, 1H), 2.61-2.54 (m, 3H), 2.32 (s, 3H), 2.27-2.23 (m, 1H), 2.10 (dd, *J* = 13.6, 2.8 Hz, 1H), 1.81-1.56 (m, 6H), 1.33 (d, *J* = 5.6 Hz, 6H).





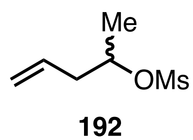
^{1}H NMR, 300MHz, $CDCl_3$, filename: 1085BPROTON

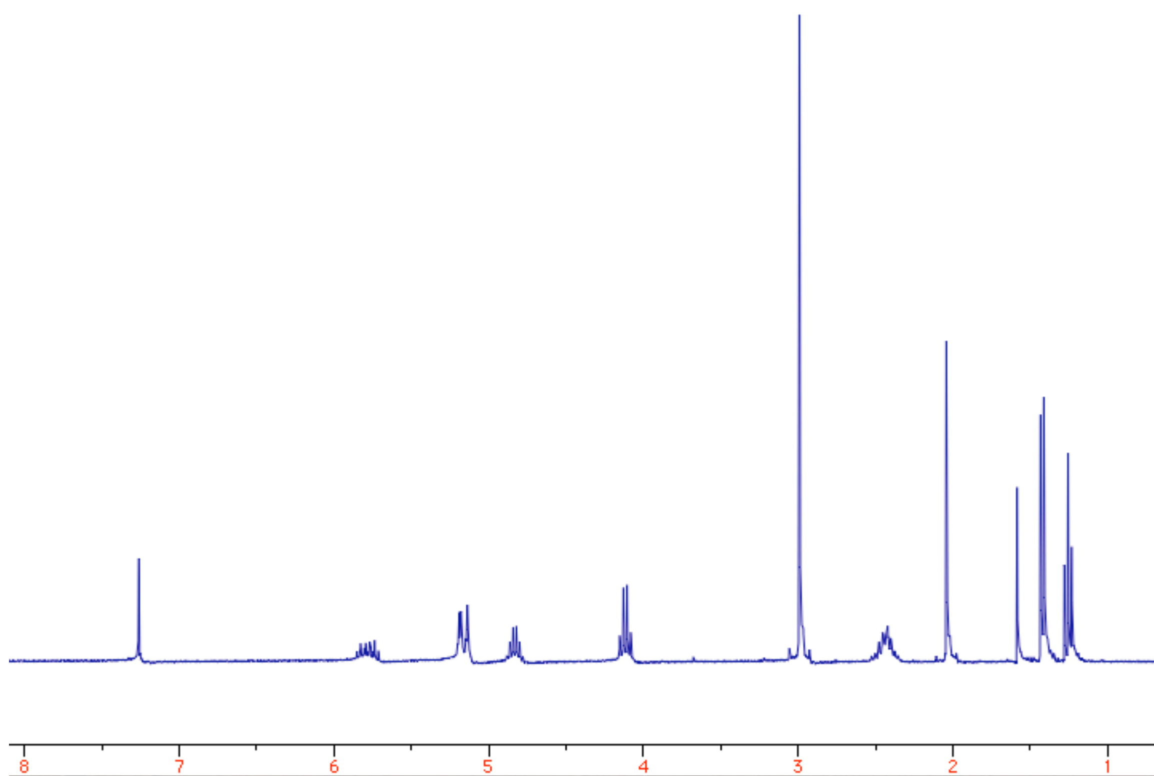
pent-4-en-2-yl methanesulfonate (192):



A solution of 4-penten-2-ol (1 g, 11.6 mmol) and CH_3SO_2Cl (1.16 mL, 15.09 mmol) in 10 mL of DCM was cooled to -50 °C, and then TEA (2.42 mL, 17.4 mmol) was added dropwise. The solution was allowed to warm to 10 °C and after 5 min was re-cooled to 0 °C. Cold water was then added, and the mixture was rapidly transferred to a separatory funnel using Et_2O. The ether extract was washed with cold dilute HCl solution, $NaHCO_3$ solution, and saturated NaCl solution, and dried over $MgSO_4$. After filtration, the solvents were removed using a rotary evaporator to give the crude mesylate as a pale brown oil. The mesylate was then purified by flash column chromatography (9:1 Hexanes/Ethyl Acetate) to give a colorless oil (1.65 g, 86%).

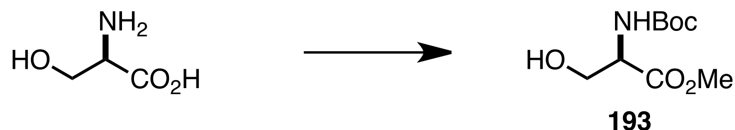
^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.79 (m, 1H), 5.18 (m, 1H), 5.16 (m, 1H), 4.83 (m, 1H), 3.00 (s, 3H), 2.47 (m, 1H), 2.41 (m, 1H), 1.43 (d, J = 6.3 Hz, 3H).





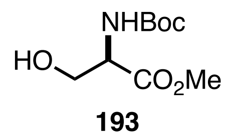
^{1}H NMR, 300 MHz, $CDCl_3$, filename: ms607p

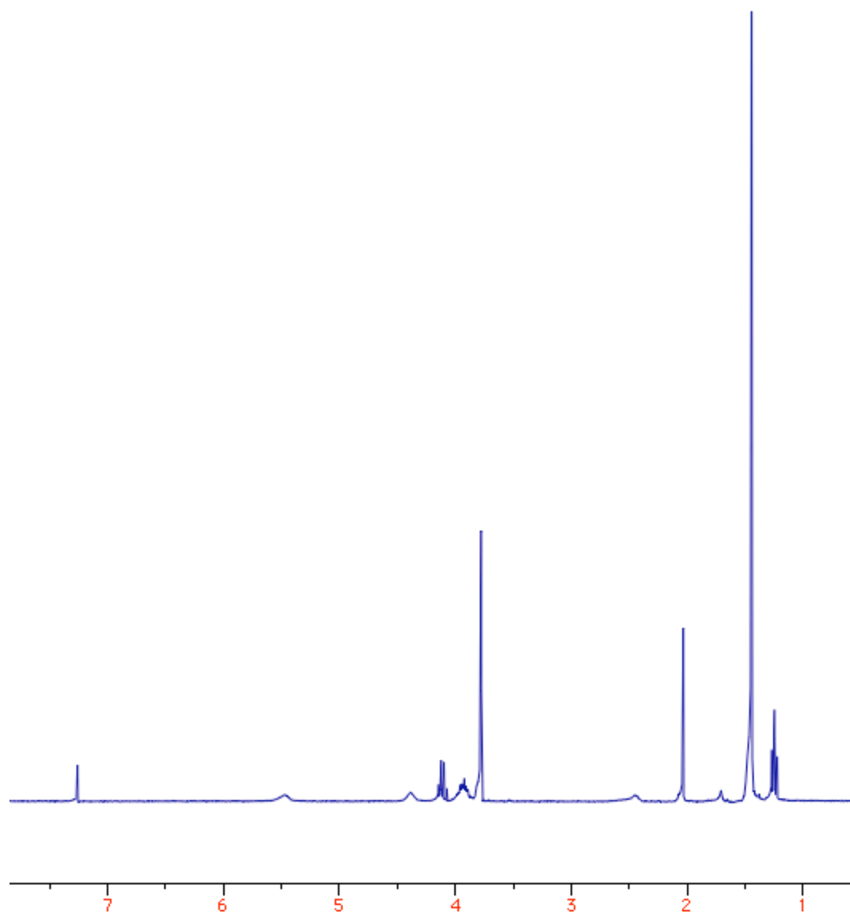
(R)-methyl 2-((tert-butoxycarbonyl)amino)-3-hydroxypropanoate (193):



L-serine (20 g, 19.0 mmol) was refluxed in 250 mL of anhydrous methanol with AcCl (37.89 mL, 53.28 mmol) for 2 hours. The methanol was removed under reduced pressure. The residue was then dissolved in 633 mL of THF and added TEA (50.28 mL, 36.01 mmol). The solution was then cooled to 0 °C and di-tert-butylcarbonate (37.05 g, 16.97 mmol) in 282 mL of THF was added dropwise over 1 hour. The resulting solution was then warmed to room temperature and stirred overnight. The solvents were removed under reduced pressure and the residue was diluted with ether, and washed with $NaHCO_3$. The aqueous layer was separated from the organic and then extracted three more times with ether. After drying over anhydrous $MgSO_4$, the solvent was removed in vacuo and the product was purified by flash column chromatography (EtOAC/ hexanes 2:8) to give a clear oil (31.2g, 84% from L-ser).

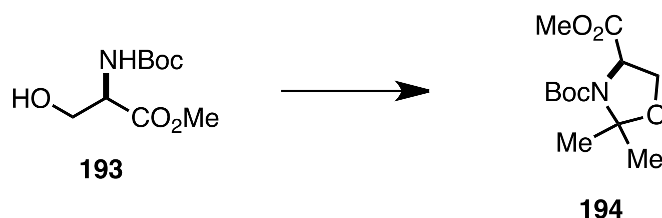
^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.51 (bs, 1H), 4.34 (bs, 1H), 3.97-3.8 (m, 2H), 3.75 (s, 3H), 1.43 (s, 9H).





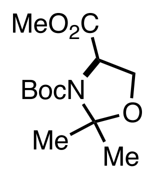
^{1}H NMR, 300 MHz, $CDCl_3$, filename: ms609p

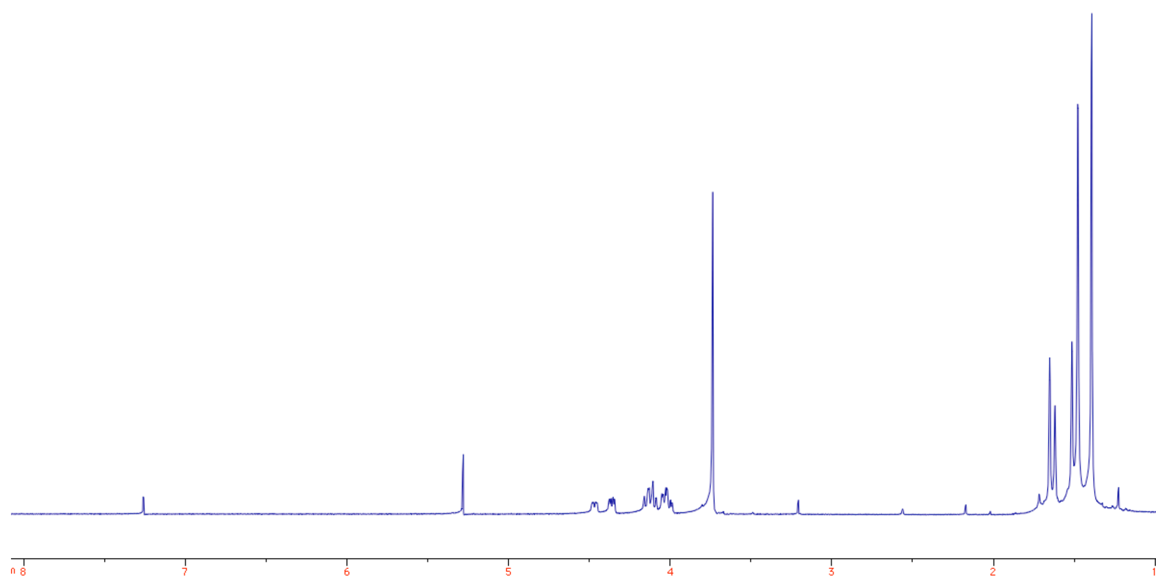
(R)-3-tert-butyl 4-methyl 2,2-dimethyloxazolidine-3,4-dicarboxylate (194):



Ester **193** (18 g, 82.2 mmol) was dissolved in 303 mL of dry acetone. Dimethoxypropane (74.96 mL, 71.9 mmol) and boron trifluoride diethyl etherate (0.617 mL, 5.0 mmol) were added sequentially. The reaction mixture was then stirred at room temperature for an additional 2.5 hours. The orange solution was then quenched with TEA (2 mL), stirred for an additional 15 minutes and then concentrated under reduced pressure. Saturated $NaHCO_3$ was added to the residue and then solution was extracted three times with Et_2O. The organic phases were combined, dried over $NaSO_4$, filtered, and then concentrated reduced pressure. The resulting bright yellow oil was purified via flash column chromatography (EtOAC/Hexanes 1:9) to provide a pale yellow oil (18.8 g, 88.8%).

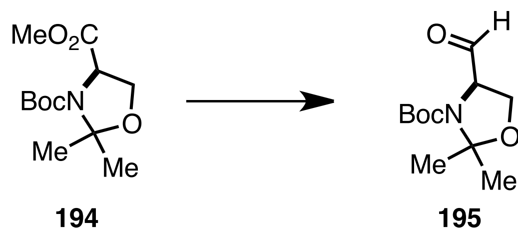
^1H NMR ($CDCl_3$, 300 MHz) δ 4.48 and 4.37 (bd, total 1H), 4.15-3.99 (m, 2H), 3.73 (s, 3H), 1.63 (d, J = 9.9 Hz, 3H), 1.49 (d, J = 10.8 Hz, 7H), 1.39 (s, 5H).





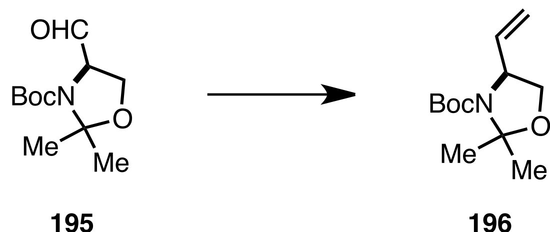
^{1}H NMR, 300 MHz, $CDCl_3$, filename: ms647p

Garner Aldehyde (195):



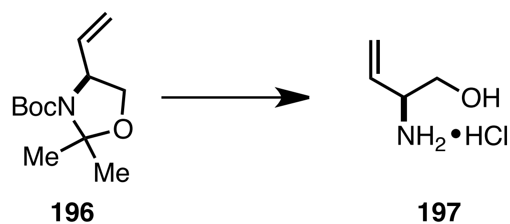
To a stirring solution of ester **194** (22.99 g, 88.66 mmol) in 185 mL of dry toluene at -78 °C under an inert atmosphere, DIBAL-H (150 mL, 150 mmol) was added dropwise over 1 hour. The solution was then stirred an additional 2 hours at -78 °C, then was slowly warmed to -20 °C and quenched with 34.1 mL dry MeOH. Next, a saturated solution of Rochell's Salt (591 mL) was added and the reaction was stirred for an additional 2 hours. The solids were filtered and washed with Et_2O. The organic phase was separated from the aqueous, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The crude aldehyde was then taken on without further purification.

(S)-tert-butyl 2,2-dimethyl-4-vinyloxazolidine-3-carboxylate (196):



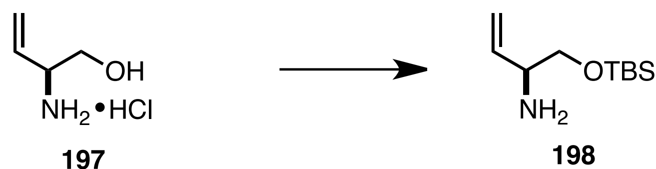
To a solution of Ph_3PCH_3Br (18.32 g, 51.29 mmol) in 434 mL of THF at room temperature, KHMDS (98.4 mL, 49.2 mmol) was added dropwise. The solution was then stirred for an additional hour at room temperature. The resulting bright yellow solution was then cooled to -78 °C and a solution of garners aldehyde **195** (6.72 g, 29.3 mmol) in 88 mL of THF was added dropwise. When the addition was complete, the solution was slowly warmed to room temperature and stirred for an additional 2 hours. The solution was added to 50 mL of dry MeOH and then poured into a 1:1 mixture of saturated Rochell's salt and water. The aqueous phase was then extracted with diethyl ether, dried over magnesium sulfate, filtered, and then concentrated. The product was purified via flash column chromatography (10% ethyl acetate/hexanes) to provide alkene as a clear oil (5.63 g, 84%).

(*S*)-2-aminobut-3-en-1-ol hydrochloride (197):



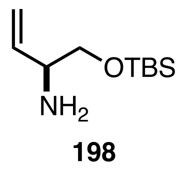
Protected oxazolidine **196** (3.70 g, 16.2 mmol) was stirred in 6 M HCl (12.0 mL) for 30 minutes. The solution was then concentrated under reduced pressure. The white solid was further dried at 70 °C under a vacuum for 24 hours. The white solid (1.98, 98.4%) was then taken on without further purification.

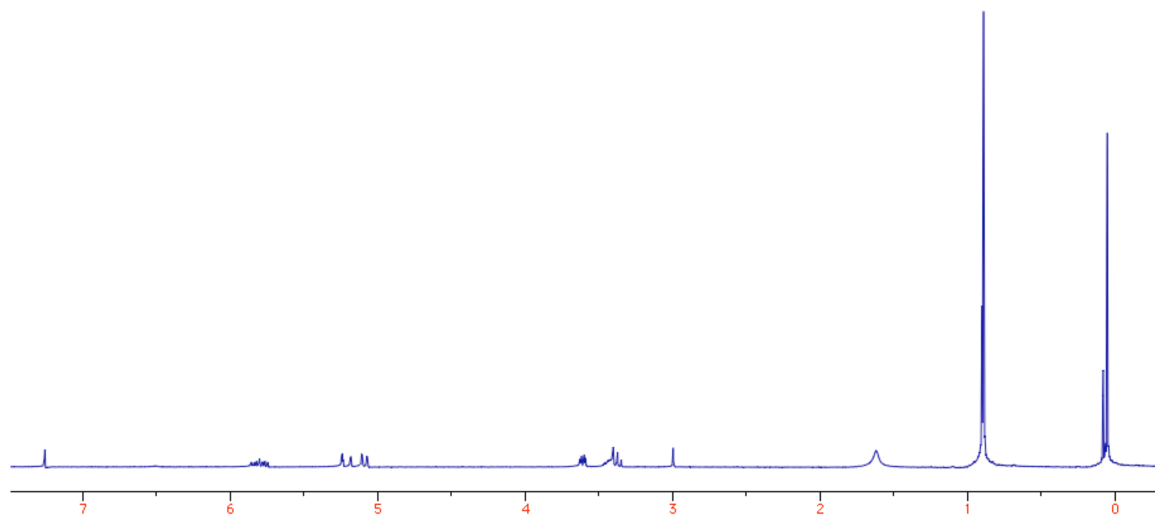
(S)-1-((tert-butyldimethylsilyl)oxy)but-3-en-2-amine (198):



To HCl salt **197** (728.4 mg, 5.89 mmol) in DCM, was added TEA (1.79 mL, 12.08 mmol), DMAP (72.84 mg, 0.1 wt%), and TBSCl (967 mg, 6.42 mmol), sequentially. The mixture was then stirred overnight at room temperature. The reaction was quenched with H_2O for 10 minutes. The phases were separated, the organic phase was washed with brine, dried over Na_2SO_4, and filtered. The organic phase was then concentrated under reduced pressure to afford a clear oil (1.02 g, 86%) that was then taken on crude.

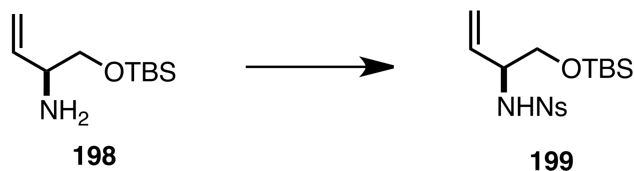
^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.85-5.74 (m, 1H), 5.21 (d, *J* = 17.4 Hz, 1H), 5.09 (d, *J* = 10.5 Hz, 1H), 3.63-3.859 (m, 1H), 3.46-3.34 (m, 2H), 1.62 (bs, 2H), 0.89 (s, 9H) 053 (s, 6H).





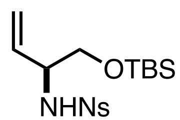
^{1}H NMR, 300 MHz, $CDCl_3$, filename: ms636c

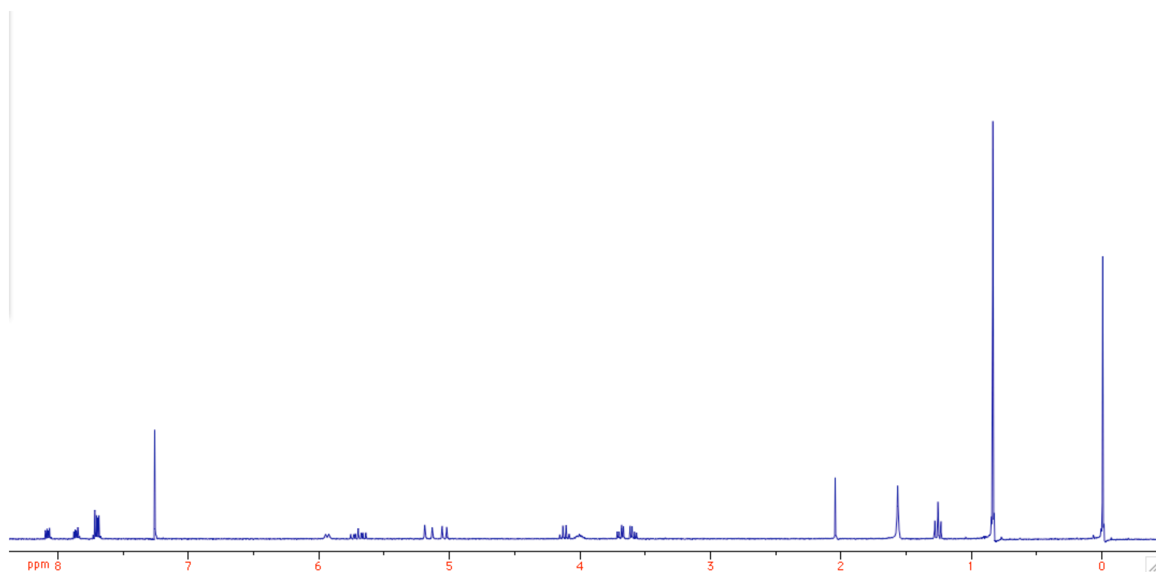
(S)-N-(1-((tert-butyldimethylsilyl)oxy)but-3-en-2-yl)-2-nitrobenzenesulfonamide (199)



To amine **198** (50 mg, 0.2482 mmol) in DCM at room temperature, was added TEA (38 µL, 0.273 mmol) and then 2-nitrobenzenesulfonyl chloride (60.5 mg, 0.273 mmol. The solution was then stirred at room temperature overnight. Saturated NH_4Cl was added and phases were separated. The aqueous phase was then extracted with DCM. The combined organic phases were washed with brine, dried over Na_2SO_4, filtered, and then concentrated under reduced pressure. The resulting brown oil was then purified via flash column chromatography (ETOAc/hexanes 2:8) to afford a pale yellow oil (92.9 mg, 96%).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.10-8.05 (m, 1H), 7.88-7.83 (m, 1H), 7.73-7.67 (m, 2H), 5.92 (d, *J* = 7.2 Hz, 1H), 5.75-5.64 (m, 1H), 5.15 (d, *J* = 17.1 Hz, 1H), 5.04 (d, *J* = 10.5 Hz, 1H), 3.97-3.96 (m, 1H), 3.71-3.56 (m, 2H), 0.83 (s, 9H) 0.01 (s, 6H).





^{1}H NMR, 300 MHz, $CDCl_3$, filename: ms644p

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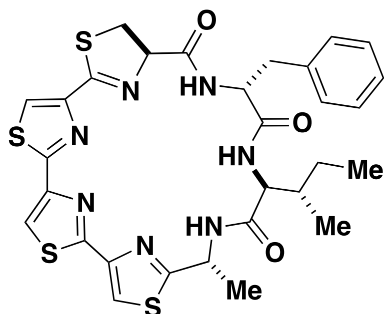
Appendix 1: Research Proposal

Total Synthesis of Marthiapeptide A, an Anti-infective and Cytotoxic Polythiazole Cyclopeptide and the Synthesis of a Several Unnatural Analogs.

Abstract/Specific Aims

Abstract:

The aim of this proposal is to develop a convergent synthetic plan for the total synthesis Marthiapeptide A[1] (**1**, Figure 4) utilizing synthetic methods that are accessible to undergraduate researchers. Marthiapeptide A, a cyclopeptide isolated from sea sediment off the southern China coast, has shown antibacterial activity and strong cytotoxic activity making it an interesting prospect for potential therapeutics. It exhibited MIC values ranging from 2.0 to 8.0 µg/mL, and IC50 values ranging from 0.38 to 0.52 µM.[1] The unique trithiazole-thiazoline moiety make Marthapeptide A an ideal lead compound for drug discovery. Discussed herein will be the synthetic design of Marthiapeptide A and other potential antibacterial and cytotoxic therapeutics.



Marthapeptide A (1)

Figure 4: Natural Product Marthapeptide A.

Specific Aims for this proposal:

1. To Develop a convergent synthetic plan for the total synthesis Marthiapeptide A (1, Figure 4).
2. To confirm the correct structure of Marthiapeptide A.
3. To synthesize multiple analogs by systematically changing the amino acid framework of Marthiapeptide A.
4. To conduct initial structure-activity relationship (SAR) analysis on these analogs.

Background and Significance:

Antimicrobial Resistance is an emerging problem in modern medicine. Drug resistant organisms are extending hospital stays and increasing mortality rates all over the world. The discovery and development of new antibiotics is necessary for effective treatment of these drug resistant super bugs.[2] In the United States cancer is the second most common cause of death among adults. The discovery and development of novel cancer therapeutics could help half a million Americans each year alone.[3] *Therefore, there is a critical unmet need to develop new antibiotics and cancer therapeutics*.

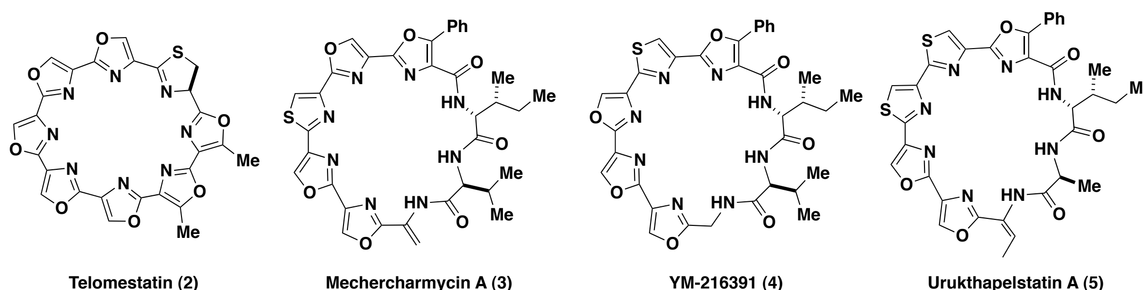


Figure 5: Members of the cyclic polyazole family of natural products.

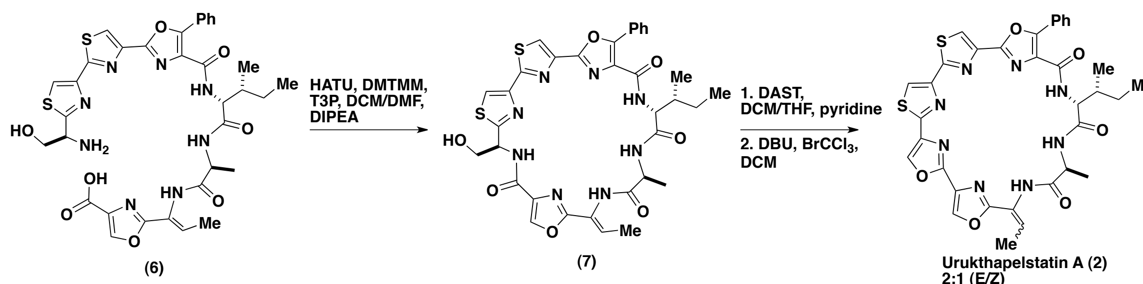
Marthapeptide A belongs to a new and emerging family of natural products that contain four or more sequential 2,4-disubstituted oxazoles/oxazolines and thiazoles/thiazolines. Other members of this family include Telomestatin[4] (**2**),

Mechercharmycin A[5] (**3**), YM-216391[6,7] (**4**), and Urukthapelstatin A[8] (**5**) (Figure 5). Members of this cyclic polyazole family of natural products show a diverse array of biological activities. While Telomestatin is a known Telemersase inhibitor,[9,10] the specific mode of action for the other members in this family remains unknown. Furthermore, understanding how Marthapeptide A acts in the cell, may also shed light what gives the other members of this family its cytotoxic properties. *A deeper understanding about the SAR has the potential to identify new antibacterial and cytotoxic therapeutics*. The unique trithiazole-thiazoline moiety make Marthapeptide A an ideal lead compound for drug discovery. In order to conduct preliminary SAR studies, first the total synthesis must be completed and the proposed structure must be verified. To date no total synthesizes have been reported.

Previous macrocyclizations:

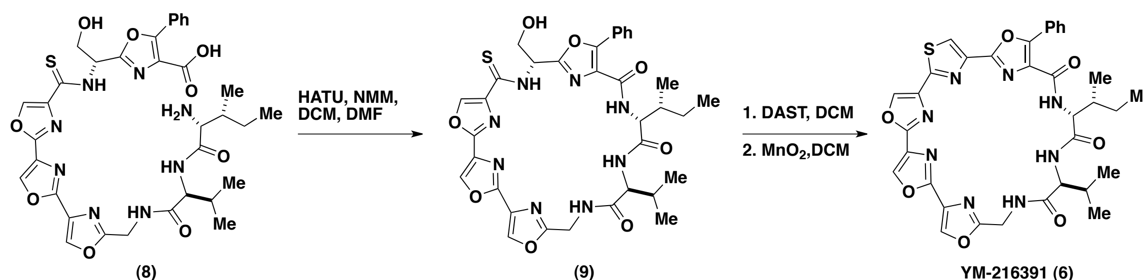
The design and synthesis of cyclic polyazole natural products has been subject to study over the last decade. The synthesizes of Telomestatin[11] (**2**), Mechercharmycin A[12] (**3**), YM-216391[13,14] (**4**), and Urukthapelstatin A[15] (**5**) have all been reported. Macrocyclization has been a synthetic challenge for members of this family.[16,17] It has been hypothesized, the problem arises due to the rigidity of the consecutive heterocycle backbone.[17] To overcome this synthetic challenge macrocyclization must be completed prior to the formation of the rigid heterocyclic backbone. As shown in Scheme 56, in the total synthesis of Urkthapelstatin A[15](**5**), macrocyclization was achieved by treatment of intermediate **6** with 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate (HATU), 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-

methylmorpholinium chloride (DMTMM) , 2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphorinane-2,4,6-trioxide (T3P), and *N*,*N*-diisopropylethylamine (DIPEA). The resulting macrolide (**7**) was then converted to Urkthapelstatin A (**5**) as 2:1 mixture of E/Z inseparable isomers by a two step oxazole formation.



Scheme 56: The macrocyclic formation of Urukthapelstatin A.

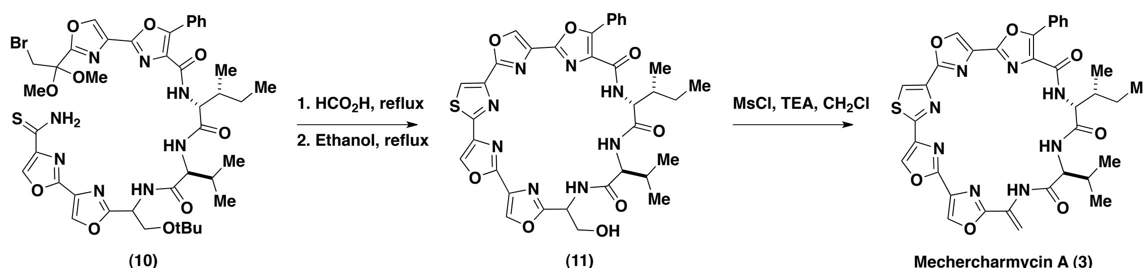
In the synthesis YM-216391[14], the macrocyclization shown in Scheme 57, is achieved by treatment of intermedia **8** with HATU and 4-methylmorpholine (NMM) in dicloromethane (DCM) and dimethylformamide (DMF). The thioazole unit was then constructed by treatment of thioamide **9** with (diethylamino)sulfur trifluoride (DAST) and then manganese (IV) oxide (Mn_2O).



Scheme 57: The macrocyclic formation of YM-216391.

In same way also, Alvarez and coworkers[12] first form the macrocycle and then subsequently form the thiazole moiety in their synthesis Mechercharmycin A (Scheme 58). Substrate **10** was first refluxed in formic acid providing them with the free alcohol

and bromoketone. Then resulting the bromoketone is then condensed on to the thioamide by refluxing in ethanol to afforded thiazole **11**. The free alcohol was then converted to mesylate and eliminated to afford Mechercharmycin (**3**).



Scheme 58: The macrocyclic formation of Merchercharmycin A.

Previous SAR studies:

While little is known about the specific mode of action that renders this family of natural products of cytotoxic, some initial SAR studies have been conducted. These previous studies can be used to gain valuable insight which we can apply to our own SAR analysis of Marthapeptide A. During these studies, key structural features have been identified to directly correlate to biological activity. We plan on implementing and incorporating these key structural features when we synthesize our own library of compounds.

Perhaps the most important structural feature pertains to rigidity of the macrocycles. When the ring open conformers were submitted for biological testing there was a sharp decrease in cytotoxic activities. [5,12] . Mechercharmycin B (**12**) and the ring open analog **13**, shown in Figure 6, are two such examples. It has then been reasoned that the biological activity arises from the macrocycles rigid conformation. Therefore the only analogs that we will submit to SAR studies will contain a macrocycle.

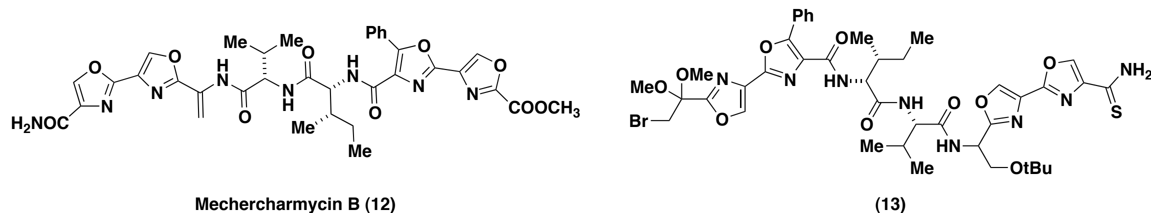


Figure 6: Examples of biologically inactive conformers.

Also, it should be noted that substituting the thiazole moiety for the oxazole moiety (**14)** in the Mechercharmycin A framework results in loss of biological activity[18] (Figure 7). Thus suggesting that the thiazole moiety is key for cytotoxic activity. Since Marthiapeptide A contains three thiazole rings, it may be possible to systematically exchange each for an oxazole and determine if the location if the thiazole ring is important for biological activity. Also, converting the thiazoline moiety to a thiazole would result in a sequential tetrathiazole analog, which could possibly lead to increased biological activity.

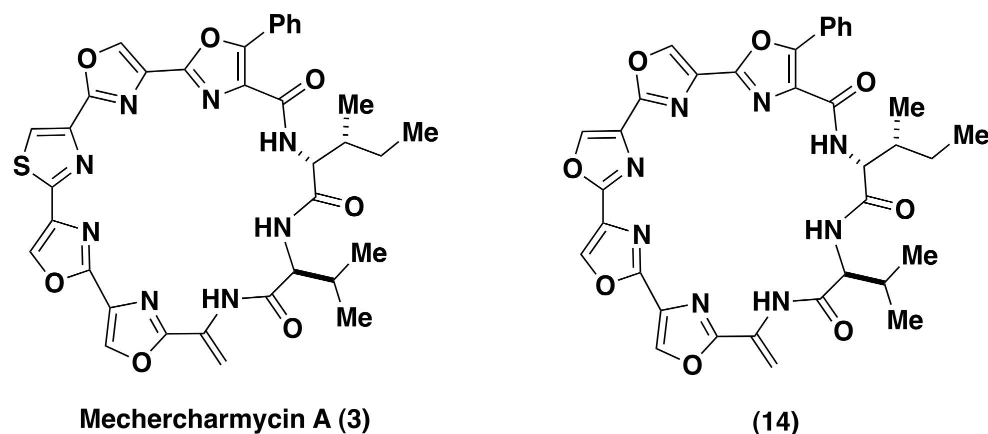
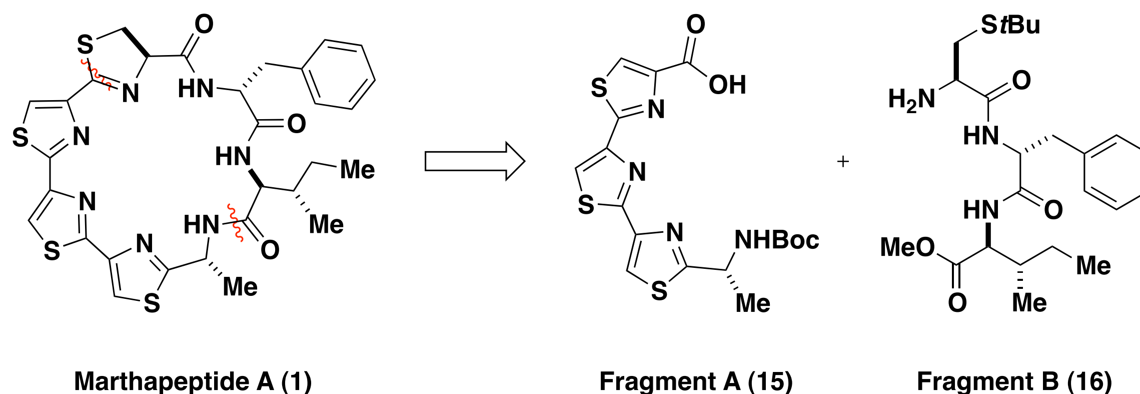


Figure 7: Penta-oxazole analog of Mechercharmycin A.

Research and Design Methods:

We believe we can access Marthiapeptide A (1) via a coupling of Fragment A (**15**) and Fragment B (**16**). As previously stated the macrocyclization of these polyzole

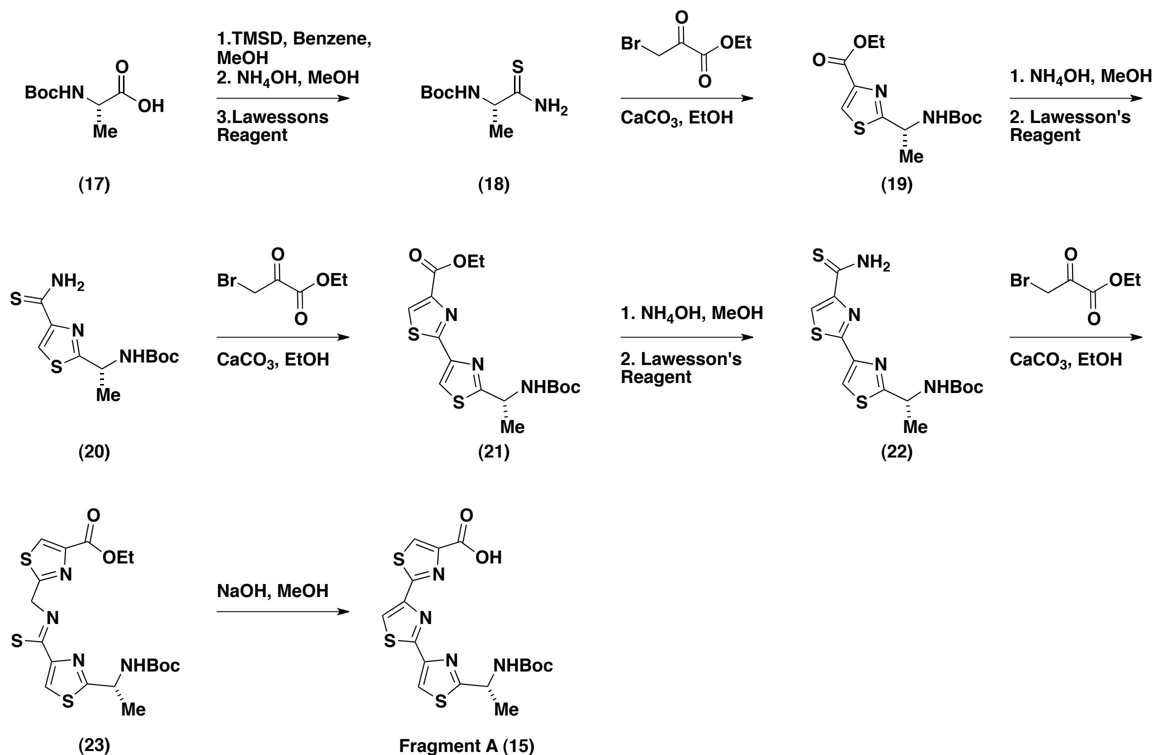
natural products must prior to the formation of the rigid heterocyclic backbone. Therefore, after the initial coupling and macrocyclization we will install the thiazole moiety.



Scheme 59: Retrosynthetic analysis of Marthiapeptide A.

Synthesis of Fragment A

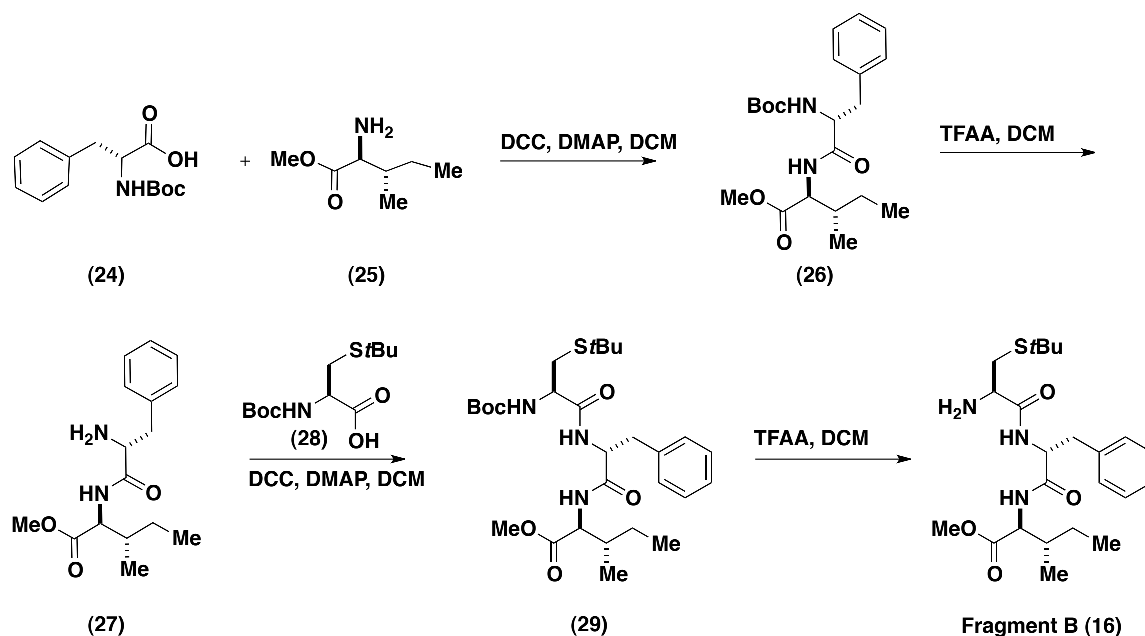
We envision the synthesis of Fragment A, shown in Scheme 60, starting with commercially available Boc-L-alanine (**17**). The acid will be converted to the methyl ester by treatment with trimethylsilsydiazomethane (TMSD). The resulting ester will then be converted to the amide by stirring in ammonium hydroxide and methanol. Finally, thioamide **18** can be accessed by treatment with Lawesson's reagent. Condensation of the thioamide **18** with ethyl bromopyruvate in the presence of calcium carbonate and ethanol will provide thiazole **19**. Treatment of thiazole **19** with ammonium hydroxide in methanol and then Lawesson's reagent sequentially with provide us with thioamide **20**. The resulting thioamide will then be condensed with ethyl bromopyruvate to afford dithiazole **21**. These steps can then be repeated again to provide first thioamide **22** and then trithiazole ester **23**. The resulting ester will then be stirred with lithium hydroxide and tertahyrofuran in water to provide Fragment A (**15**).



Scheme 60: Proposed synthesis of Fragment A.

Synthesis of Fragment B

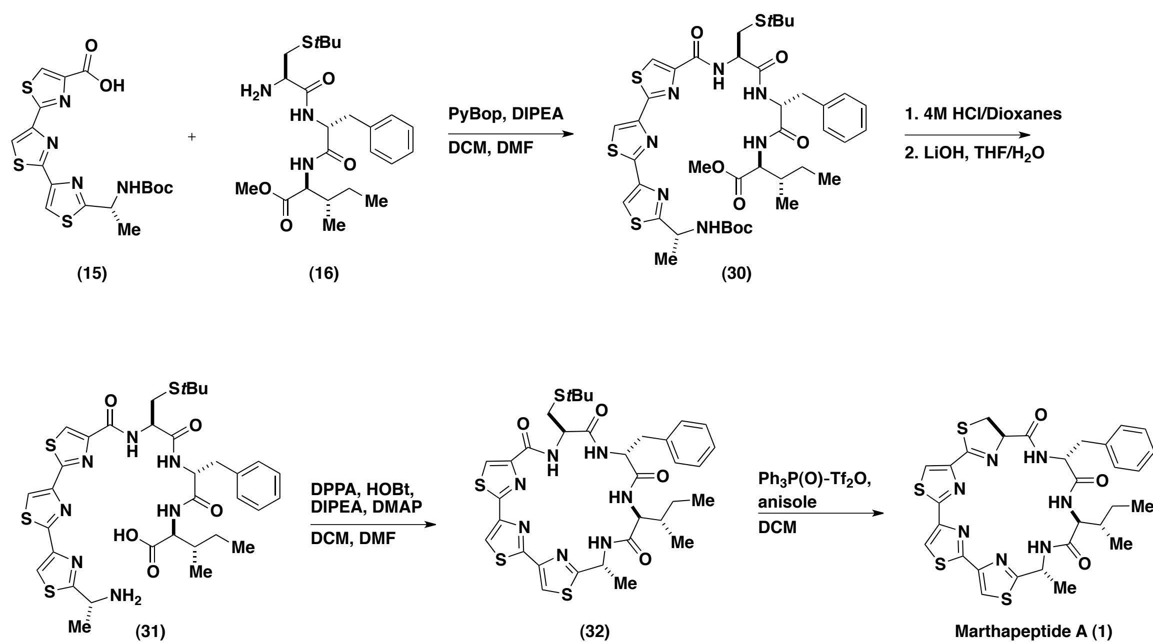
The synthesis of Fragment B will start by coupling Boc-D-phenylalanine **24**, with L-isoleucine methyl ester **25** using dicyclohexylcarbodiimide (DCC) and 4-(dimethylamino)pyridine (DMAP). The resulting dipeptide **26** will then be deprotected using trifluoroacetic anhydride (TFAA) in DCM to afford free amine **27**. This amine will then be coupled with cysteine derivative **28** yielding substrate **29**. The protected amine will be subsequently deprotected to provide Fragment B (**16**).



Scheme 61: Proposed synthesis of Fragment B.

Macrocyclization:

To complete the synthesis Fragment A (**15**) and Fragment B (**16**) will then be coupled together providing us with peptide **30**. Subsequent deprotection of both the Boc group and the ester will provide us with the desired macrocyclic precursor **31**. The macrocyclization will be carried out using DPPA, HOBt, DMAP and DIPEA. With macrolide **32** in-hand we plan on installing the thiazoline moiety using Kelly's[19] method. Deprotection and the cyclocondensation will be achieved by treatment with $Ph_3P(O)$-Tf_2-anisole in DCM to furnish us with Marthiapeptide A. With Marthiapeptide A in hand we will verify the proposed structure.



Scheme 62: Proposed late stage synthesis of Marthapeptide A.

Synthesis of Analogs

A number of different analogs can be readily accessed following our convergent synthesis of Marthiapeptide A. Each one of these analogs will be synthesized in 10-20 mg quantities and will be used in our initial SAR studies. Or goal is to synthesize a large number of candidates for biological testing in the next 3 years. Analogs that will be submitted for testing include the enantiomer (**33**) and diastereomers (**34-37**) of Marthiapeptide A. We do not plan on testing any of the open chain intermediates since they have been reported to have diminished biologically active.

Comparing the peptide framework of Marthiapeptide A with the other members of the family, allows us to envision other possible analogs. Both Mechercharmycin A (**3**), YM-216391 (**4**) contain L-valine moieties that are not present in Marthiapeptide A. To learn more about the SAR we will synthesize macrocycles that contain the

Marthiapeptide A backbone and that contain L-valine in the place of the L-alaine moiety (**38**).

It has already been shown that the thiazole moiety is important for biological activity; However no studies have been conducted to determine the importance of the thiazoline ring system. Thus we plan on synthesizing an analog that contains concatenated tetrathiazole ring system (**39**). This analog can be easily be synthesized from a one step oxidation of the Marthiapeptide A. [20,21]

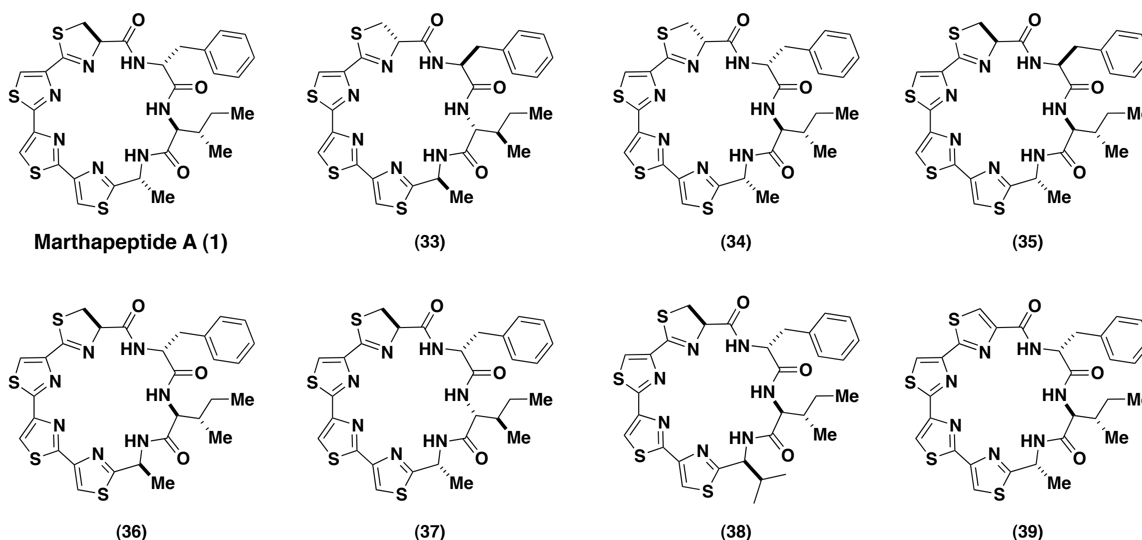


Figure 8: Some of the analogs for initial SAR studies.

Potential Limitations and Difficulties:

Difficulties, anticipated and not, are always part of every research program. Below are listed the anticipated difficulties and how we plan to overcome said difficulties should they arise.

1. It is possible that proposed structure of Marthiapeptide A is not correct. If this is the case we will try to identify the correct structure by looking for discrepancies in

the spectrometric data. Using these discrepancies we should be able to determine if there is an incorrect assignment of one or more stereogenic centers.

2. It is possible that the proposed macrocyclization will be unsuccessful. If this is the case, there are a number of different coupling reagents and conditions that will be investigated. Also if all these conditions fail we can redesign the retro synthetic plan allowing for the macrocyclization at another place in the molecule.
3. It is possible that the different analogs synthesized may not lead to increased potency and biological activity. If this is the case we will investigate analogs that also differ substantially from the Marthiapeptide A. We will introduce different heterocycles in place of the trithiazole ring system and we will investigate different heterocycles in place of the thiazoline moiety.

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List of Abbreviations

Ac	acetyl
Ac_2O	acetic anhydride
AcOH	acetic acid
AIBN	2,2-azo *bis*isobutyronitrile
BBN (9-BBN)	9-borabicyclo[3.3.1]nonane
Bn	benzyl
Boc	*tert*-butoxycarbonyl
Boc_2O	di-*tert*-butyl dicarbonate
BOP reagent	benzotriazol-1-yloxytris(dimthylamino) phosphonium hexafluorophosphate
Bz	benzoyl
BuLi	butyllithium
BMS	borane dimethylsulfide
Cbz	benzyloxycarbonyl
CoA	co-enzyme A
Collidine	2,4,6-trimethylpyridine
18-crown-6	1,4,7,10,13,16-hexaoxacyclooctadecane
CSA	camphorsulfonic acid
DA	Diels-Alder
DABCO	1,4-diazabicyclo[2.2.2]octane

DBU	1,8-diazabicycol[5.4.0]undec-7-ene
DCB	1,4-dicyanobenzene
DCM	dichloromethane
DCC	dicyclohexylcarbodimide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethyl azocarboxylate
DIBAL	diisobutylaluminum hydride
DIPEA	diisopropylethylamine
DKP	diketopiperazine
DMAP	4-(dimethylamino)pyridine
DMDO	dimethyldioxirane
DMF	dimethylformamide
DMS	dimethylsulfide
DMSO	dimethylsulfoxide
DPPA	diphenylphosphoryl azide
2,6-DTBP	2,6-di-*tert*-butylpyridine
EC_{50}	half maximal effective concentration
EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hyrdochloride
Et	ethyl
EtOAc	ethyl acetate
Et_2O	diethyl ether

EtOH	ethanol
Fmoc	fluorenylmethyloxycarbonyl
HATU	*O*-(7-Azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate
H3R	histamine 3 receptor
Im	imidazole
IMDA	intermolecular Diels-Alder
IPP	isopenylpyrophosphate
KF	potassium fluoride
KHMDS	potassium (bis)trimethylsilyl amide
K*i*	inhibitor constant
LAH	lithium aluminum hydride
LDA	lithium diisopropylamine
LHMDS (or LiHMDS)	lithium (bis)trimethylsilyl amide
LiOH	lithium hydroxide
2,6-lutidine	2,6-dimethylpyridine
*m*CPBA	*meta*-chloroperbenzoic acid
Me	methyl
MeCN	acetonitrile
MeI	methyl iodide
MeOH	methanol
$MgCl_2$	magnesium chloride

Ms	methanesulfonyl (mesylate)
MsCl	methanesulfonyl chloride
$NaCNBH_4$	sodium cyanoborohydride
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimde
NHMDS (or NaHMDS)	sodium (bis)trimethylsilyl amide
NMM	*N*-methyl morpholine
Phen	phenanthrene
PMB	*p*-methoxybenzyl
PPTS	pyridinium *p*-toluenesulfonate
PTLC	preparative thin layer chromatography
i-Pr	isopropyl
Py. or Pyr	pyridine
Red-Al	sodium bis(2-methoxyethoxy)-aluminum hydride
TBAF	tetrabutylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TBSCl	*tert*-butyldimethylsilyl chloride
t-DDSH	*tert*-dodecanethiol
t-BuOK	potassium *tert*-butoxide
TEA	triethylamine
TFA	trifluoroacetic acid

TFAA — trifluoroacetic anhydride

TfN_3 — trifluoromethanesulfonyl azide

Tf_3O — trifluoromethanesulfonic anhydride

THF — tetrahydrofuran

TLC — thin layer chromatography

TMS — trimethylsilyl

TMSI — trimethylsilyl iodide

TMSCl — trimethylsilyl chloride