

Synthesis of [2.2.2]-Diazabicyclic Alkaloids: Diels-Alder Reactions of a C2-Carboxy Pyrazinone/Intermolecular Diels-Alder Reaction of a Proline Derived Pyrazinone with Symmetric Dienophiles

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Department of Chemistry

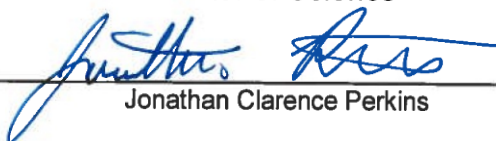
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August, 2017



## APPROVAL PAGE

This thesis is submitted in partial fulfillment of  
the requirements for the degree of

Master of Science



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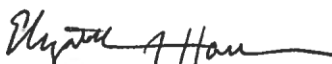
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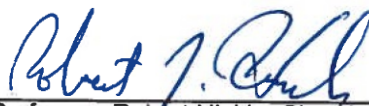
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## ABSTRACT

[2.2.2]-Diazabicyclic alkaloids are a natural product family with diverse biological activities. The development of a synthetic methods towards the synthesis of [2.2.2]-diazabicyclic alkaloids is described.

### I: Diels-Alder Reactions of a C2-Carboxy Pyrazinone

Using an N-heterocyclic carbene catalyzed arylation of a proline 3,5-dichloropyrazinone, a synthetic route to C2-carboxy pyrazinones was developed to study the intermolecular and intramolecular Diels-Alder reactions of these compounds to form the bicyclo[2.2.2]diazaoctane core. Studies showed that having oxidation present  $\alpha$  to the pyrazinone ring did not provide any significant increase in reactivity or selectivity as compared to pyrazinones without oxidation  $\alpha$  to the ring. In some cases, the oxidation completely hindered reactivity.

### II: Intermolecular Diels-Alder Reaction of a Proline Derived Pyrazinone with Symmetric Dienophiles

The intermolecular Diels-Alder reaction of a proline derived pyrazinone with maleic anhydride allows for selective access the *anti*-C19 isomer of the [2.2.2]-diazabicyclic alkaloid. Selective opening of the resulting anhydride cycloadduct followed by radical excision of the C18 carboxy group provides a known intermediate in the Williams' synthesis of Brevianamide B. The overall route provides the desired *anti*-C19 isomer of the methyl ester product in 6 steps and 12% overall yield from the proline derived pyrazinone. This route constitutes a 15 step formal synthesis of Brevianamide B.

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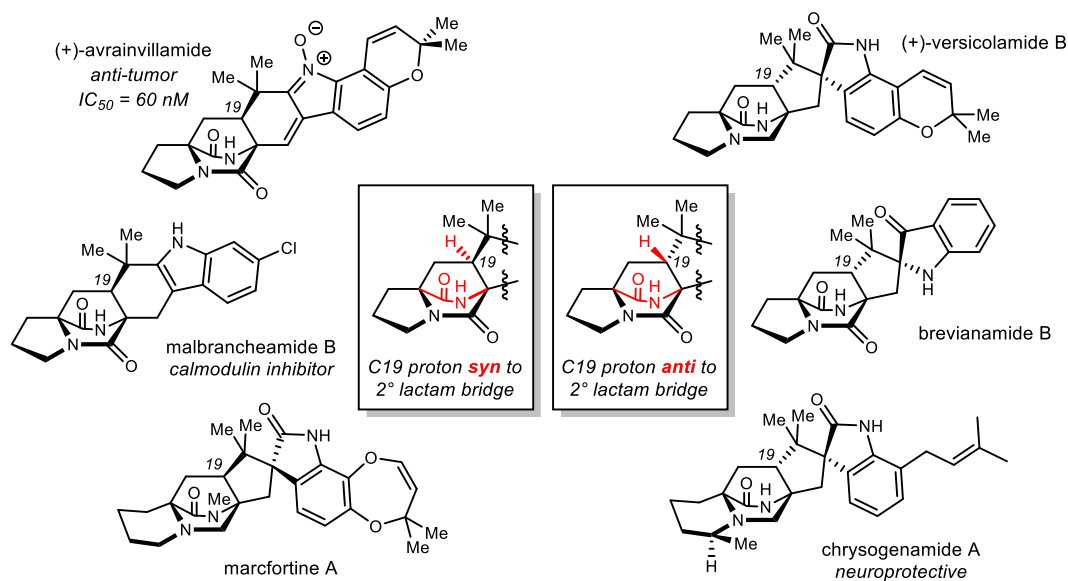
I would like to thank my parents David and Karen for their unyielding support throughout my entire life. They have provided me with more love and opportunities than I can even imagine. Finally, I would like to thank my fiancé Peter Booth for his love and affection. He gives me the motivation and support to get up and to go to work every morning and provides an even better reason to want to come home at the end of the day. I cannot wait to move with him to Ann Arbor, Michigan and begin the next chapter of our life together.

This thesis is dedicated to my parents Karen and David and my fiancé Peter Booth. Without their unending support and love, I would not be where I am today.

## Chapter 1: An Introduction to [2.2.2]-Diazabicyclic Alkaloids

### Overview of [2.2.2]-diazabicyclic Alkaloids

Prenylated indole alkaloids containing a bicyclo[2.2.2]-diazaoctane core were first isolated in the late 1960's as secondary metabolites from a number of fungal species.<sup>1,2,3,4</sup> The family now contains more than 10 different subgroups comprised of over 100 distinct members (Scheme 1). Many [2.2.2]-diazabicyclic alkaloids possess desirable biological activities including calmodulin inhibition, cytotoxicity, anthelmintic, and neuroprotection making them ideal natural product targets for synthetic chemists.<sup>1,5,6</sup> The unique structure and diverse range of biological activities of [2.2.2]-diazabicyclic alkaloids have made them the subject of intense investigation since their discovery.<sup>7</sup>



**Scheme 1.** Examples of various [2.2.2]-diazabicyclic natural products.

Structurally, members of the family are formed of three parts: the eponymous bicyclo[2.2.2]-diazaoctane core, an amino acid derived cyclic portion, and a tryptophan moiety.<sup>1,7</sup> The core piece is quite standard among most members of the family with the only variation being that some members possess a reduced monoketopiperazine core instead of the more common diketopiperazine form. The cyclic portion is most commonly a five-membered proline derived ring, however the marcfortine family of natural products

(including chrysogenamide A) possess a unique six-membered ring derived from pipercolic acid. Finally, the pendant tryptophan moiety is where the most variety exists between family members. Some contain halogenation (e.g. malbrancheamide B), while others have various prenyl derived substitution (e.g. stephacidin A and veriscolamide B).

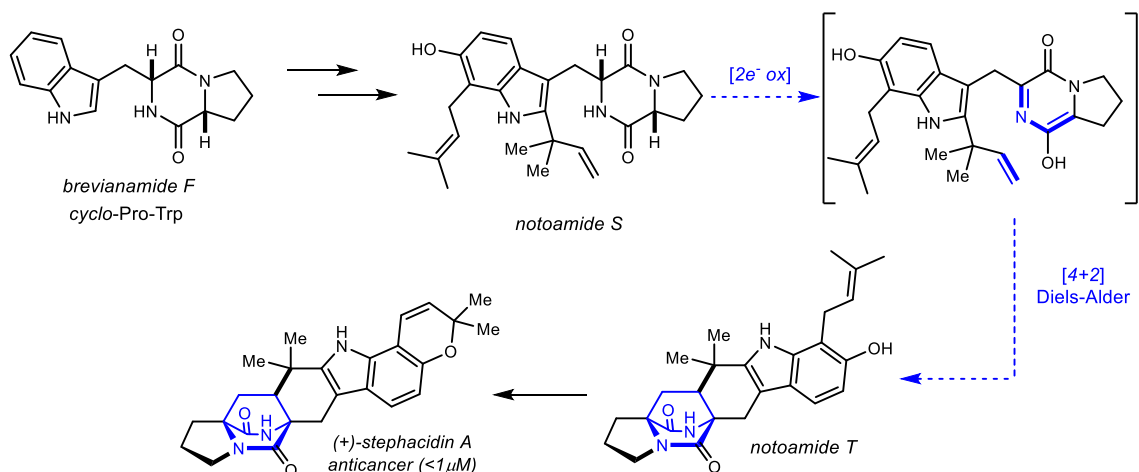
Members of the family can be further classified by the relative stereochemistry at C19 (brevianamide numbering) on the core. Namely, the hydrogen at this position possess either a *syn*- or *anti*-configuration with respect to the secondary lactam bridge.<sup>1</sup> The less common *anti*-configuration has only been found in the breavianamide family and two other metabolites: chrysogenamide A and veriscolamide B.<sup>1</sup>

### **Isolation and Biosynthesis**

The breavianamides were isolated by Birch and Wright in 1969 from *Penicillium brevicopactum* and were the first family of fungal secondary metabolites found to contain the bicyclo[2.2.2]-diazaoctane core.<sup>2</sup> Since that first isolation, over 100 distinct alkaloids have been isolated containing the bicyclo[2.2.2]-diazaoctane core. Interestingly, it has been discovered that different fungal species can produce different enantiomers of the metabolites. For example, the marine fungus *Aspergillus sp. MF297-2* produces (-)-stephacidin A, whereas the terrestrial fungus *Aspergillus versicolor* produces its enantiomer (+)-stephacidin A.<sup>1, 8, 9, 10</sup>

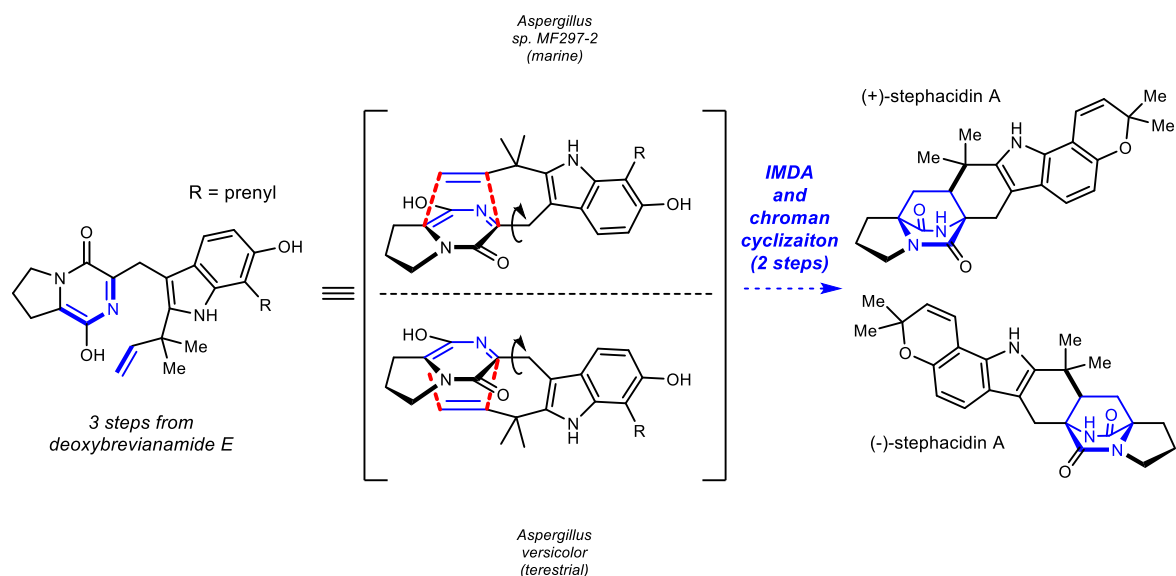
After isolating the breavianamides in 1969, Birch and co-workers conducting <sup>13</sup>C-labeled incorporation studies to investigate the biosynthetic pathways of the breavianamides.<sup>1,4</sup> These studies initially revealed that breavianamide A is derived from L-proline and L-tryptophan residues. Further analysis showed that the residues undergo a condensation to form *cyclo*-L-Trp-L-Pro which they called breavianamide F followed by a C2 reverse prenylation of the indole to give deoxybreavianamide E. Birch proposed that a subsequent oxidation and cyclization of deoxybreavianamide E would lead to breavianamide B. Using similar tracer incorporation studies, Williams and co-workers found that

deoxybrevianamide E does in fact undergo a stereoselective indole oxidation.<sup>9,10</sup> This is followed by another  $2e^-$  oxidation, intramolecular Diels-Alder (IMDA), and pinacol rearrangement to give brevianamide. Despite extensive efforts, the exact order of last three steps in the biosynthetic pathway has not been revealed.



**Scheme 2.** Proposed biosynthetic pathway for the notoamides and stephacidins.

Significant effort has been devoted by Williams and Sherman to investigating the biosynthetic pathways of the notoamides and stephacidins in different fungal species because of the discovery that different species produce different enantiomers.<sup>9,10</sup> Genome sequencing and bioinformatic mining studies by Sherman isolated several gene clusters in the biosynthesis of the notoamides and stephacidins.<sup>9</sup> Combined with biochemical studies, this enabled the development of an extensive biosynthetic pathway (Scheme 2).<sup>10</sup> They confirmed that the unique enantioselectivity observed in different fungal species was derived from an enantioselective IMDA reaction of an achiral pyrazinone precursor (Scheme 3).<sup>1</sup> Although, the so-called Diels-Alderase enzyme has not been isolated all other evidence still supports that the entioselectivity is derived from a selective Diels-Alder reaction.



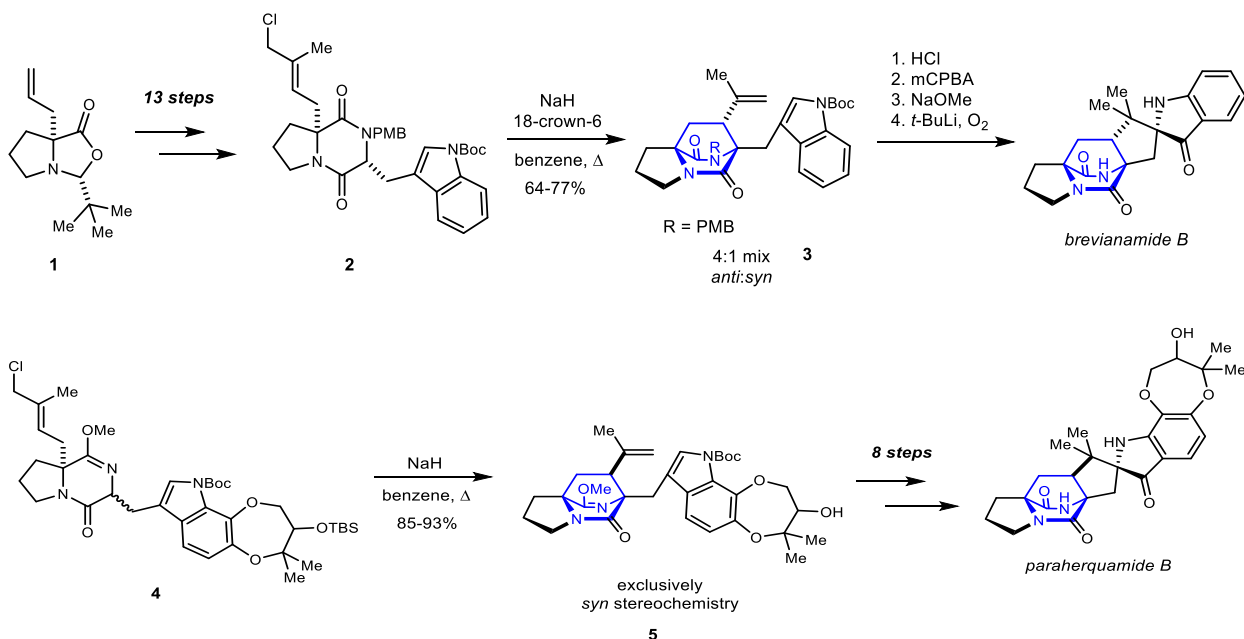
**Scheme 3.** Enantioselective IMDA in the biosynthesis of stephacidin A.

### Synthetic Strategies Towards the Bicyclo[2.2.2]-diazaoctane Core

Several synthetic strategies have been developed to make the bicyclo[2.2.2]-diazaoctane core *en route* to various natural products in the family including: (1) intramolecular  $S_N2'$  cyclization<sup>11,12</sup> (2) biomimetic intramolecular Diels-Alder (IMDA) reaction<sup>7,13</sup>, (3) radical cyclization<sup>14</sup>, (4) oxidative enolate coupling<sup>15</sup>, (5) cationic cyclization cascade<sup>16,17,18</sup>, (6) Dieckmann condensation<sup>19</sup>, and (7) oxidative aza-Prins cyclization<sup>20</sup>.

The intramolecular  $S_N2'$  cyclization was developed by the Williams research group as a key method for the synthesis of a number of different prenylated indole alkaloid.<sup>7</sup> Its first use in the synthesis of a [2.2.2]-diazabicyclic alkaloid came during the Williams groups' synthesis of brevianamide B and again during their subsequent syntheses of paraherquamide B and stephacidin A (Scheme 4).<sup>11,12</sup> During the synthesis of brevianamide B, synthesis of the key allylic chloride  $S_N2'$  cyclization precursor **2** from known allylated proline derivative **1** was followed by reaction with NaH in hot benzene with 18-crown-6 added provided the desired epimer **3** of the [2.2.2]-diazabicyclic core with *anti*-

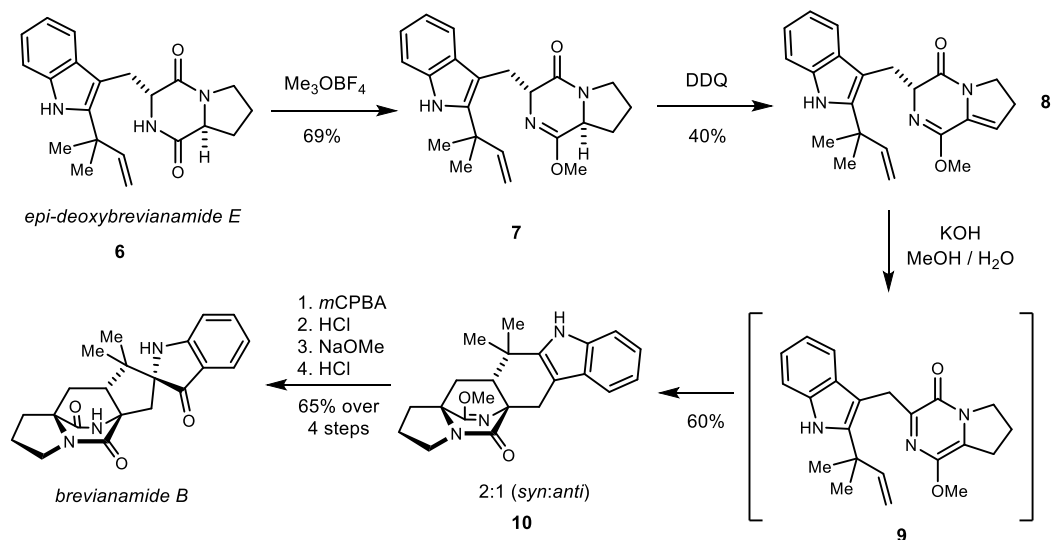
stereochemistry at C19 in a 4:1 ratio with the undesired *syn*-C19 epimer. **3** was then carried forward in 4 steps to give brevianamide B. A similar allylic chloride precursor **4** was used in the synthesis of paraherquamide B. Reaction of **4** with NaH in hot benzene without addition of 18-crown-6 provided the core scaffold **5** with exclusively *syn*-C19 stereochemistry, as desired. **5** was then moved forward to paraherquamide B in 8 additional steps.



**Scheme 4.** Williams' synthesis of brevianamide B and paraherquamide B featuring an intramolecular S<sub>N</sub>2' cyclization.

After developing the intramolecular S<sub>N</sub>2' cyclization method, the Williams group moved on to develop the biomimetic IMDA reaction to make the bicyclo[2.2.2]-diazaoctane core. The IMDA method was first used in the Williams groups' biomimetic total synthesis of brevianamide B from biologically isolated *epi*-deoxybrevianamide E **6** in an effort to provide evidence for their proposed biosynthesis involving a biogenic Diels-Alder reaction (Scheme 5).<sup>13</sup> Reaction of **6** with Me<sub>3</sub>OBF<sub>4</sub> provided the lactim ether **7** which was then oxidized to the exocyclic unsaturated Diels-Alder precursor **8** upon reaction with DDQ. Treatment of **8** with aqueous KOH caused tautomerization to the pyrazinone azadiene **9**,

which immediately underwent an IMDA to give 2:1 mix of diastereomers **10**. Brevianamide B was synthesized by oxidation, pinacol rearrangement, and lactam hydrolysis of the minor isomer. Since its initial use, the IMDA method has been used in a number of racemic and asymmetric total syntheses of [2.2.2]-diazabicylic natural products.<sup>7</sup>

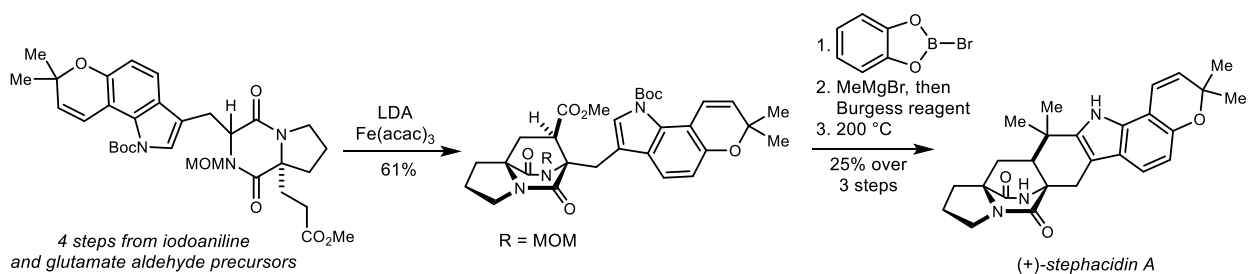


**Scheme 5.** Williams' synthesis of brevianamide B featuring a biomimetic IMDA reaction.

While the biomimetic IMDA reaction developed by Williams and co-workers has arguably been the most widely used method for synthesis of the bicyclo[2.2.2]diazaoctane core, a number of other methods to synthesize the core have been developed in subsequent years.

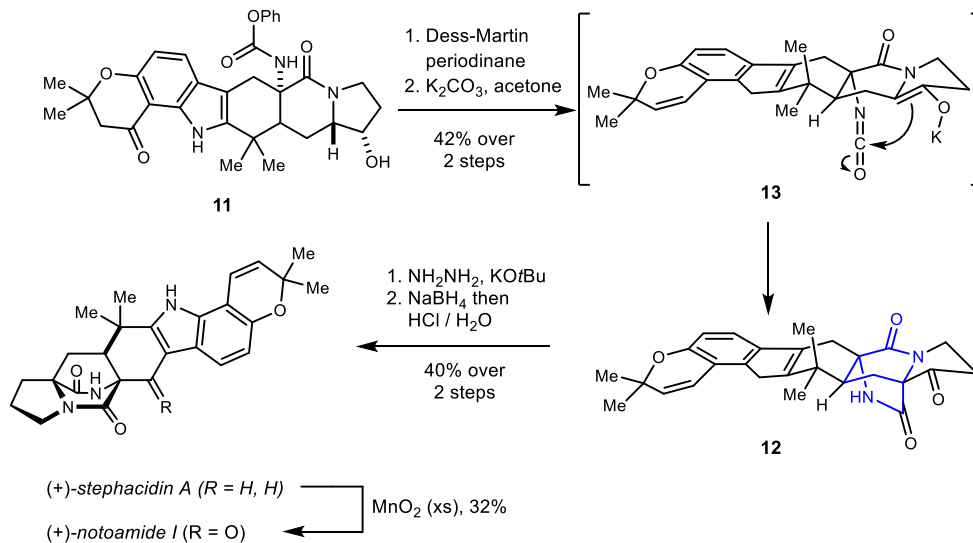
In their pursuit of stephacidin A, Myers and co-workers used a radical iminium cyclization to form the [2.2.2]-diazabicyclic core.<sup>14</sup> Baran and co-workers developed an oxidative enolate coupling promoted by  $\text{Fe}(\text{acac})_3$  to form the core during their synthesis of stephacidin A (Scheme 6).<sup>15</sup> The cationic cyclization cascade was developed by Simpkins and co-workers in their asymmetric synthesis of (–)-malbrancheamide B.<sup>16</sup> Their key precursor was a proline DKP with pendent indole and prenyl groups. Treatment of the precursor with TMS-OTf initially cleaves the Boc group from the indole nitrogen and subsequently promotes cyclization of the indole onto the prenyl group which then cyclizes

onto the DKP ring to establish both the bicyclo[2.2.2]-diazaoctane core and cyclohexene ring adjacent to the indole nucleus.



**Scheme 6.** Asymmetric synthesis of stephacidin A by Baran and co-workers featuring an oxidative enolate coupling.

More recently, the Sarpong group published their asymmetric synthesis of (+)-stephacidin A (Scheme 7).<sup>19</sup> Starting from precursor **11**, the [2.2.2]-diazabicyclic core **12** was established from a Dieckmann condensation of the isocyanate-enolate intermediate **13** formed from treatment of **11** with Dess-Martin periodinane followed by reaction with  $K_2CO_3$ . Wolff-Kishner reduction of the ketone group followed by reduction of the chromanone carbonyl group afforded (+)-stephacidin A. Additionally, they demonstrated that treatment of (+)-stephacidin A with excess  $MnO_2$  gave (+)-notoamide I which possesses a carbonyl at C10, adjacent to the [2.2.2]diazabicyclic core. In 2016, notoamide I was the target of a synthesis by Sun, Li, and co-workers who established the core through an oxidative aza-Prins cyclization.<sup>20</sup> This synthesis will be discussed in more detail in chapter 2 of this thesis.



**Scheme 7.** Synthesis of (+)-stephacidin A and (+)-notoamide I by Sarpong and co-workers featuring

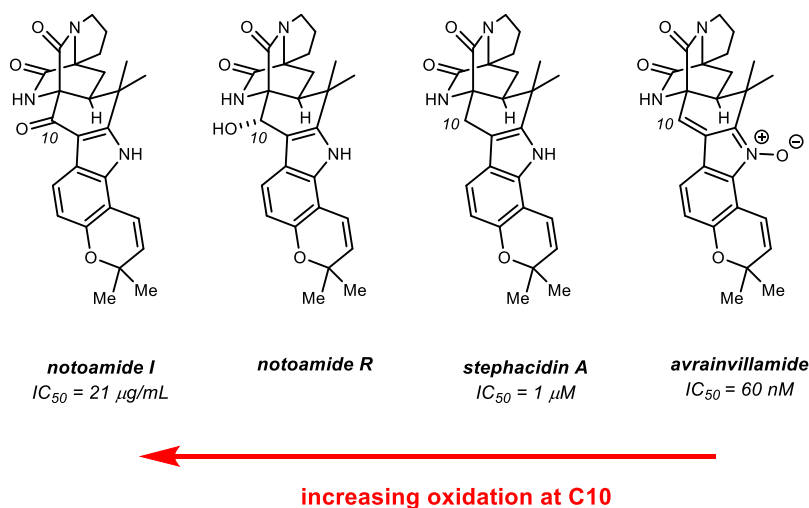
## Conclusions

[2.2.2]-Diazabicyclic alkaloids represent a distinct class of natural products with a unique structural motif and diverse biological activities. Since the initial isolation of the brevianamides by Birch and Wright in 1969, a wide array of synthetic methods have been developed for the synthesis of the bicyclo[2.2.2]-diazaoctane core. Much room still exists to explore the use of Diels-Alder reactions to establish the [2.2.2]-diazabicyclic core and improve the stereoselectivity of such reactions.

## Chapter 2: Diels-Alder Reactions of a C2-Carboxy Pyrazinone

### Introduction

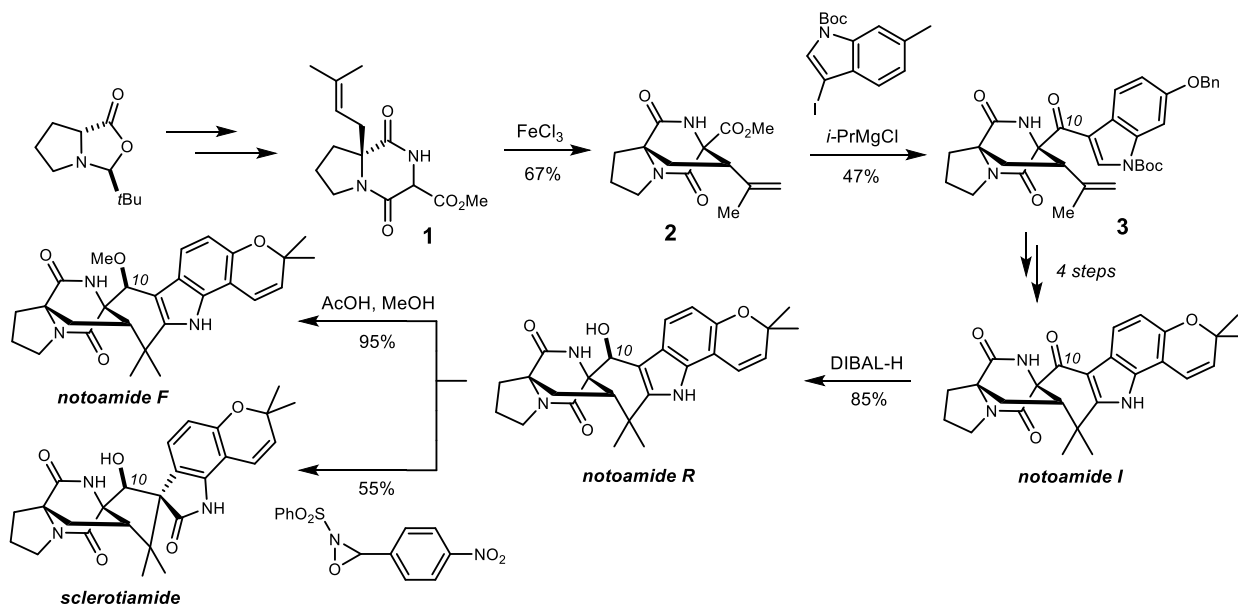
Between 2008 and 2010, Tsukamoto and co-workers published several articles on the isolation of several new prenylated indole alkaloids from the marine derived fungus *Aspergillus sp.* that possessed unique oxygenation at C10 (Scheme 1).<sup>21,22</sup> These metabolites are members of the notoamide family of [2.2.2]-diazabicyclic alkaloids and are related to the previously isolated alkaloid stephacidin A. It was later shown that notoamides F-H and notoamide R are downstream oxygenated metabolites of stephacidin A.<sup>1</sup> For example, notoamides R possess a hydroxyl group at C10 and notoamide I is further oxidized possessing a carbonyl at C10. Alternatively, Stephacidin A and avrainvillamide are less oxidized at C10. Bioactivity assays conducted on the newly isolated metabolites showed that notoamide I is cytotoxic towards HeLa cells with an  $IC_{50}$  value of 21  $\mu\text{g/mL}$ .<sup>21</sup> While this value is not as impressive as those of stephacidin A or the structurally related avrainvillamide which both possess impressive  $IC_{50}$  values of 1  $\mu\text{M}$  and 60 nM, respectively



**Scheme 1.** Examples of [2.2.2]-diazabicyclic alkaloids with oxidation at C10.

In 2016, Sun, Li, and co-workers published their synthesis of notoamides F, I, and R as well as the related spirocyclized alkaloid sclerotiamide (Scheme 2).<sup>20</sup> To date, it

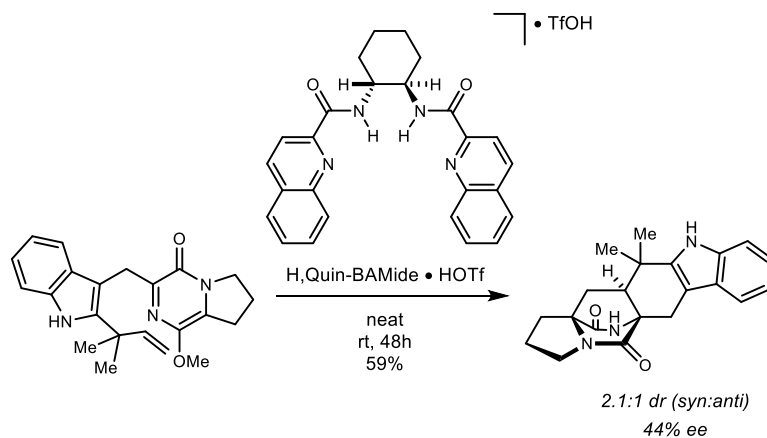
remains the only published method for synthesis of these oxidized [2.2.2]-diazabicyclic alkaloids. Their retrosynthetic plan was targeted at synthesizing notoamide I as it is the most oxidized at C10. They comment that their initial efforts to follow a similar pathway to the tandem radical cyclization methods developed by Simpkins and co-workers were met without success due to the unique C10 oxidation. This led them to develop a new method whereby the [2.2.2]-diazabicyclic core **2** is formed through an oxidative aza-Prins cyclization of DKP **1**. The indole moiety was introduced using a Grignard reaction to give **3**. Cobalt-catalyzed radical cyclization of the indole onto the pendant isoprenyl group establishes the main scaffold followed by deprotection of the benzyl group on the indole with hydrogenation, copper-catalyzed propargylation and heating to afford notoamide I. Reduction of notoamide I with DIBAL-H gave (+)-notoamide R as a single stereoisomer followed by either acid catalyzed methanolysis to give (+)-notoamide F or pinacol rearrangement to give (-)-sclerotiamide.<sup>20</sup>



**Scheme 2.** Sun, Li, and co-workers' synthesis of notoamides I, R, and F and the spirocyclized sclerotiamide.

Our work related to the synthesis of C10 oxidized [2.2.2]-diazabicyclic alkaloids, which began before Sun, Li, and co-workers had published their synthesis, was focused

on establishing the [2.2.2]-diazabicyclic core through the IMDA cyclization of a C2-carboxy DKP-azadiene with a pendant reverse prenyl dienophile. Our first goal was to develop a reliable synthetic path to the C2-carboxy DKP-azadiene IMDA precursor in order to evaluate if there is any inherent diastereoselectivity of the Diels-Alder when the C2-carbonyl is present. After studying the intrinsic reactivity and selectivity of the C2-carboxy substrates, we hoped that having a carbonyl  $\alpha$  to the DKP-azadiene would provide a handle to introduce some form of enantioselective catalysis to the Diels-Alder. In particular, Johnston and co-workers showed that their bis(amidine) (BAM) catalytic system was capable of inducing some control over enantioselectivity during the IMDA step of Williams' synthesis of breviramide (Scheme 3).<sup>23</sup> We proposed that the additional C2-carboxy group could provide a more attractive alternative binding site for the BAM catalyst. With these goals in mind, we began work on the synthesis of the desired C2-carboxy DKP-azadiene IMDA precursor.

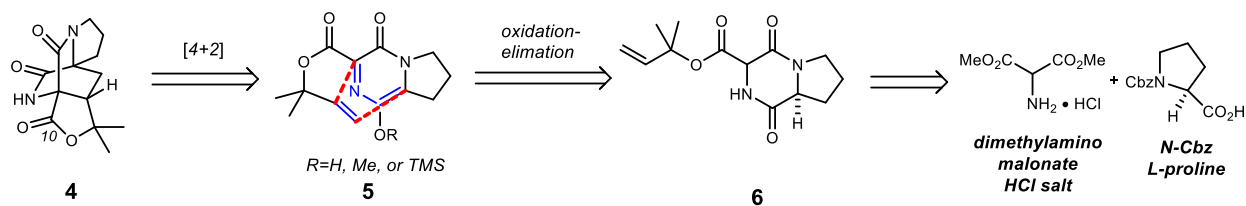


**Scheme 3.** Enantioselective formation of the bicyclo[2.2.2]diazaoctane core of breviramide by Johnston and co-workers using their H,Quin-BAMide catalyst.

### Retrosynthetic Plan

Cycloadduct **4** would provide a key scaffold which could be used in the synthesis of a number of [2.2.2]-diazabicyclic natural products. We proposed that **4** could arise through the IMDA of pyrazinone (DKP-azadiene) **5**. In turn, pyrazinone **5** would be derived

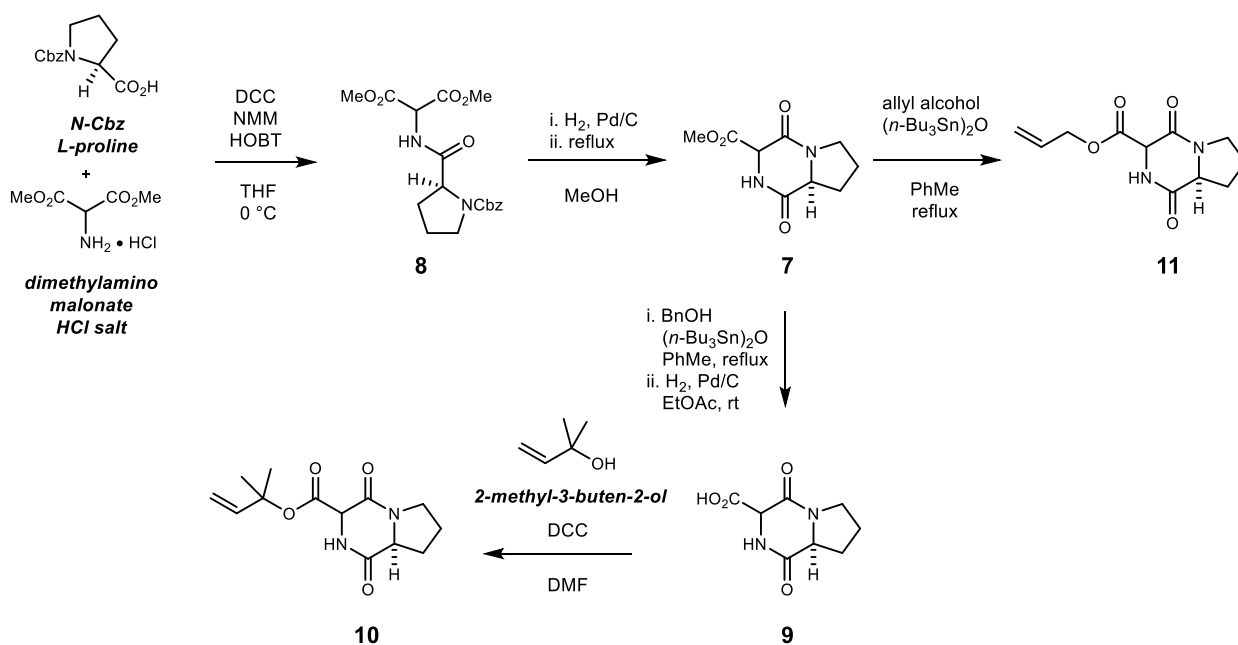
from an oxidation/elimination cascade of C2-carbomethoxy DKP **6** which is synthesized from CBZ protected L-proline and dimethylaminomalonate (Scheme 4).<sup>24</sup>



**Scheme 4.** Retrosynthetic plan for the synthesis of C10 oxidized cycloadduct **4**.

### Synthesis of C2-carboxy Diketopiperazines

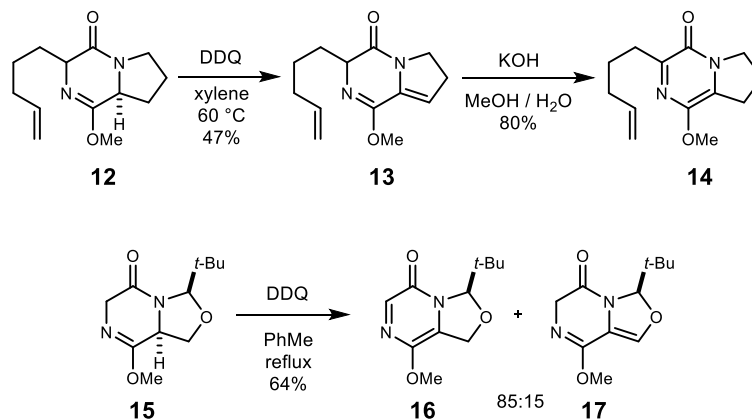
We started by synthesizing C2-carbomethoxy DKP **7** according to methods published by Trost and co-workers (Scheme 5).<sup>24</sup> The HCl salt of dimethylamino malonate was coupled with N-Cbz proline to form amide **8**. The Cbz group was removed by hydrogenation followed by heating in methanol to encourage intramolecular cyclization to C2-carbomethoxy DKP **7**. The methyl ester of **7** was then hydrolyzed to carboxylic acid **9** with LiOH, however **9** proved difficult to recover after aqueous work up and extraction resulting in detrimentally low yields. Instead, the methyl ester of **7** was transesterified to a benzyl ester in the presence of tributyltin oxide and BnOH. The benzyl group was then removed by hydrogenation to afford carboxylic acid **9** in good yield without need for an aqueous workup. The desired reverse prenylated ester **10** was formed through the coupling of **9** with 2-methyl-3-buten-2-ol in the presence of DCC. We also made allyl ester **11** by transesterification of **7** with allyl alcohol to serve as a model system for developing an oxidation-elimination method to form the desired pyrazinone.



**Scheme 5.** Synthesis of C2-reverse prenyl ester **10** and C2-allyl ester **11**.

### Oxidation-Elimination of DKP to Pyrazinone Azadiene

Initially, we explored known methods for the oxidation of a DKP to the pyrazinone tautomer with DDQ (Scheme 6). Williams and co-workers showed that DDQ could dehydrogenate an alkyl substituted lactim O-Me ether proline DKP **12** to give the exocyclic unsaturated product **13**.<sup>25</sup> The exocyclic product could then be easily isomerized in the presence of NaOH as a base to give pyrazinone **14**. Additionally, our lab has shown that oxidation of DKP **15** with DDQ gives a 85:15 mixture of both the pyrazinone **16** and the exocyclic unsaturated product **17** without need for a second isomerization step.<sup>25</sup> We were unsure whether oxidation of our model C2-allyl ester DKP with DDQ would directly yield the desired C2-allyl ester pyrazinone or a cycloadduct resulting from [4+2] cycloaddition with the pendent allyl group, but we were confident that the reaction would at least provide the exocyclic unsaturated product if it did not isomerize directly to the pyrazinone.

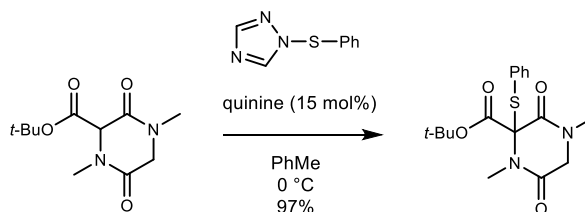


**Scheme 6.** Oxidation of various DKP rings with DDQ to provide pyrazinone azadienes.

The reaction of C2-allyl ester DKP **11** with DDQ in refluxing toluene yielded an intractable mixture that did not appear to contain any of the possible desired products by  $^1\text{H}$  NMR spectroscopic analysis. We surmised that the reaction did not work because DKP **11** lacks the lactim O-Me ether functionality present in both of the example DKP oxidations. The lactim O-Me ether likely stabilizes the initial exocyclic unsaturated product before isomerization to the desired pyrazinone. We then attempted the DDQ oxidation again with BSA added to the reaction as well. Again, the reaction yielded a complex mixture of products, however, the  $^1\text{H}$  NMR spectrum of the mixture contained peaks characteristic of the desired [2.2.2]-diazabicyclic cycloadduct. However, when the mixture was purified by column chromatography none of the isolated compounds contained these characteristic cycloadduct peaks. Further reaction attempts again yielded complex mixtures which appeared to contain the desired cycloadduct, but the supposed cycloadduct was never isolated upon attempted purification by column chromatography.

We then moved on to other oxidation-elimination methods to make the desired pyrazinone. First, we attempted to chlorinate the amide nitrogen of DKP **11** by reaction with *t*-BuOCl. However, the resulting N-chloro DKP product was not stable at room temperature or to column chromatography. Instead, we attempted to substitute a tosyl group onto the nitrogen by stirring with tosyl chloride in the presence of catalytic DMAP

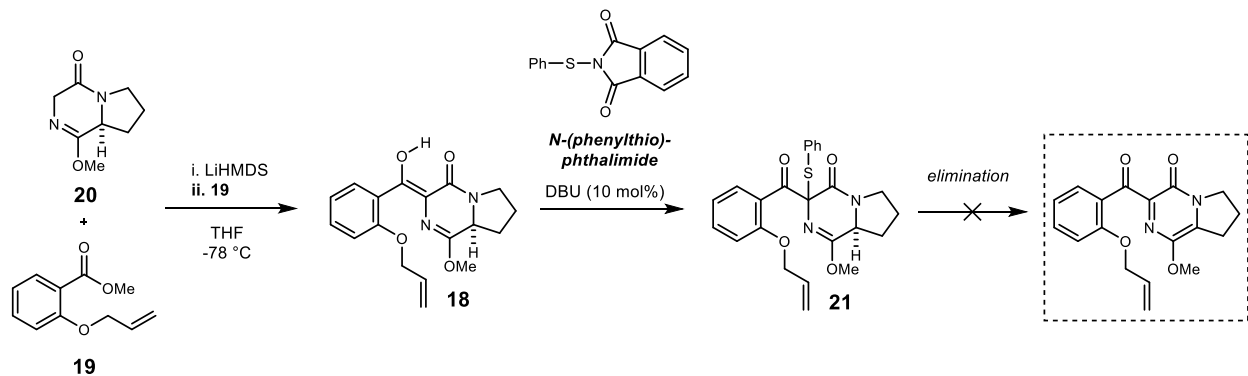
according to a procedure published by Olenyuk and co-workers for the N-tosylation of a similar C2-carboxy DKP.<sup>27</sup> After stirring for 3 days at room temperature no desired product was seen. In the same paper, Olenyuk and co-workers showed that it is possible to sulfenylate a C2-carboxy DKP at the C2 position using a number of triazole derived sulfenylation reagents (Scheme 7).<sup>26</sup> This type of chemistry could work for our system as well because it constitutes a formal oxidation of the DKP ring, so we decided to try a modified sulfenylation reaction on DKP **11** as well as a newly synthesized  $\beta$ -ketone DKP **18**.



**Scheme 7.** Example  $\alpha$ -sulfenylation of a C2-carboxy DKP by Olenyuk and co-workers.

### $\alpha$ -Sulfenylation of C2-carboxy DKPs

Before we began trying the sulfenylation, we wanted to synthesize a C2-carboxy DKP with a lactim O-Me ether present to aid in formation of the desired C2-carboxy pyrazinone during the elimination step. Our lab has previously developed a method for the synthesis of C2 substituted pyrazinones using aldol chemistry. We extended this chemistry slightly by doing a Claisen condensation to form the desired C2-carboxy lactim O-Me ether DKP **18** from the reaction of ester **19** with proline derived DKP **20** (Scheme 8). Interestingly, we found that **18** exists in the enol tautomer indicated by the presence of a singlet peak in the  $^1\text{H-NMR}$  far downfield at 13.4 ppm. This likely arises from the fact that **18** has a  $\beta$ -ketone functionality which is in contrast to the previous C2-carboxy DKP derivatives which have a  $\beta$ -ester functionality and do not display the downfield proton peak in their  $^1\text{H-NMR}$  spectra.



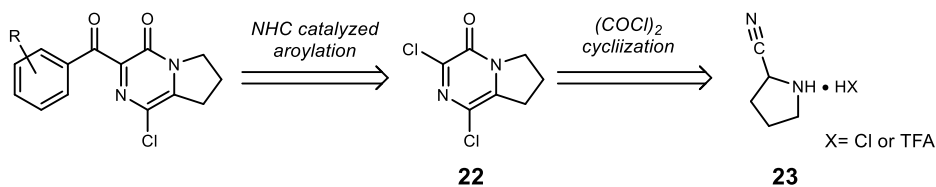
**Scheme 8.** Claisen condensation of ester **19** and DKP **20** to form C2-carboxy DKP **18** followed by  $\alpha$ -sulfenylation with *N*-(phenylthio)phthalimide.

Sulfenylation of **18** turned out to be quite easy to accomplish requiring a much less electrophilic sulfenylation reagent than what was used by Olenyuk and co-workers to sulfenylate their C2-carboxy ester DKP derivatives. Reaction of **18** with *N*-(phenylthio)phthalimide in the presence of catalytic DBU provided the desired  $\alpha$ -sulfenylation product **21** without issue. A number of methods to eliminate the sulfenyl group and produce the desired C2-carboxy pyrazinone substrate were tried including: heating in base, reaction with various silver(I) salts, and heating in the presence of 2-nitrophenol. None of the methods attempted provided the desired pyrazinone product or any cycloadducts which would result from an IMDA with the pyrazinone. Around the same time, we found a paper by Van der Eycken and co-workers on the NHC catalyzed arylation of 3,5-dichloropyrazinones which could provide the desired C2-carboxy pyrazinones directly without need for the oxidation-elimination of a C2-carboxy DKP.

### **NHC Catalyzed Arylation of 3,5-Dichloropyrazinones as a Method to Synthesize C2-carboxy Pyrazinones**

Diels-Alder and retro Diels-Alder reactions of 3,5-dichloropyrazinones have been explored previously as methods to access a number of biologically interesting natural product scaffolds.<sup>28</sup> Despite this, there are no examples where a Diels-Alder with 3,5-

dichloropyrazinone has been used in the synthesis of a [2.2.2]-diazabicyclic alkaloid natural product. A wide variety of methods have been published for functionalization of the C3 and C5 positions of 3,5-dihalopyrazinones.<sup>27</sup> In particular, Van der Eycken and co-workers developed an N-heterocyclic carbene catalyzed arylation of the C3 position of 3,5-dichloropyrazinones.<sup>28</sup> Their method relies on the umpolung nature of the C3 position of 3,5-dihalopyrazinones to add in an NHC activated aldehyde to the C3 carbon followed by elimination of chlorine to reform the pyrazinone aromaticity. We proposed a synthesis whereby this method could be used with a proline derived 3,5-dichloropyrazinone **22** to access the C2-carboxy pyrazinone scaffold (Scheme 9). This method would completely side step the problematic DKP oxidation and elimination steps of our previously proposed methods to provide the desired azadiene which could then be used in a subsequent Diels-Alder to form the [2.2.2]-diazabicyclic core.

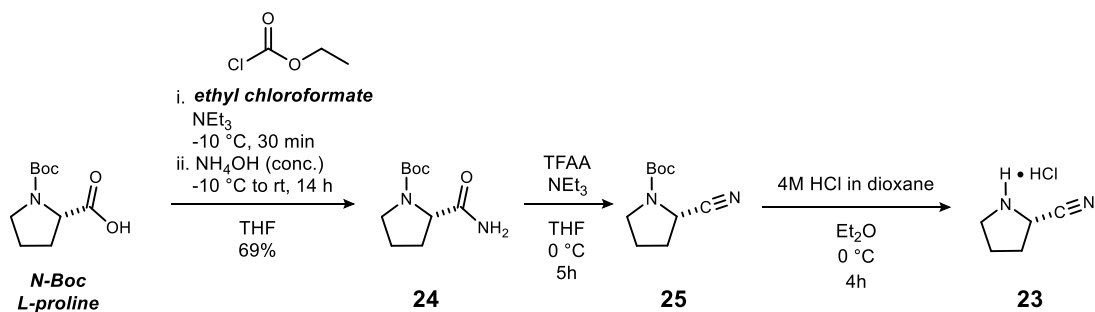


**Scheme 9.** Retrosynthetic plan for synthesis of C2-carboxy pyrazinones from 3,5-dichloropyrazinones.

### Synthesis of L-Proline Amino Nitrile

The synthesis of proline derived 3,5-dichloropyrazinone **22** was previously reported by De Borggraeve and co-workers from the reaction of L-prolinamide with oxalyl chloride and catalytic DMF.<sup>29</sup> Although their procedure involved all commercially available starting materials, it had a poor yield of only 27% and a long reaction time of heating for 3 days. More commonly, 3,5-dihalopyrazinones are synthesized through the reaction of substituted amino nitrile salts with oxalyl chloride. The majority of these methods have

higher reported yields ranging from 40-50%. Therefore, we decided to synthesize **22** from the corresponding L-proline amino nitrile salt **23** (Scheme 10).



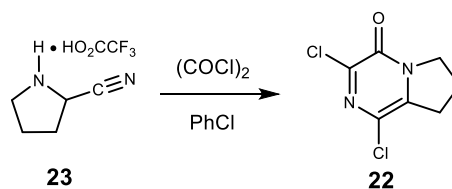
**Scheme 10.** Synthesis of the HCl salt of L-proline amino nitrile from N-Boc L-proline.

Following known methods, commercially available *N*-Boc L-proline was stirred with ethyl chloroformate and  $\text{NEt}_3$  followed by addition of concentrated ammonium hydroxide to afford *N*-Boc L-prolinamide **24** which was then dehydrated in the presence of TFAA and  $\text{NEt}_3$  to give *N*-Boc L-proline amino nitrile **25**. Boc deprotection of **25** with 4N HCl in dioxane yielded the HCl salt of L-proline amino nitrile **23**.<sup>30,31</sup>

### Synthesis of Proline Derived 3,5-Dichloropyrazinone

With the amino nitrile precursor in hand, we began synthesis of the desired 3,5-dichloropyrazinone **22**. The first reaction of L-proline amino nitrile HCl salt **23** with oxalyl chloride resulted in a poor isolated yield (22% after purification) of **22**. The HCl salt of **23** was quite gummy and wet making it difficult to properly measure and add to the reaction. Coupled with its poor solubility in the reaction solvent, chlorobenzene, we surmised that this was likely the cause of the poor yield. Instead of using the HCl salt of **23**, we made the TFA salt which could be recrystallized from ether to provide a much drier solid material that was easier to work with.<sup>32</sup> After a number of trials (Table 1), varying reaction temperature and adding a catalytic amount of DMF one hour into the reaction, we were able to raise the isolated yield of **22** to a reasonable 45% which was comparable with other reported literature yields for the synthesis of 3,5-dichloropyrazinones.

**Table 1.** Trials for the cyclization of the TFA salt of **23** to 3,5-dichloropyrazinone **22**.

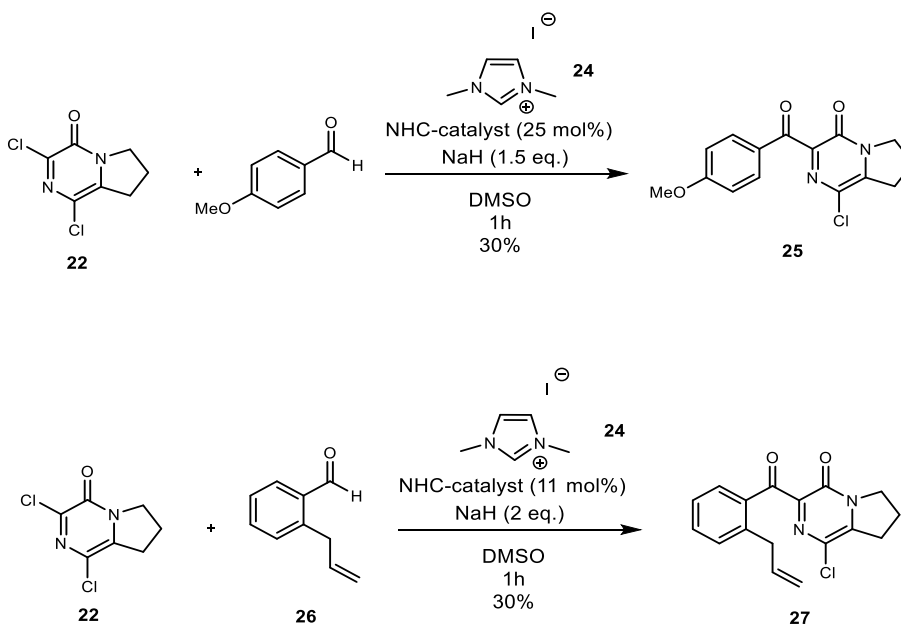


entry	scale	temp (°C)	time	yield of <b>22</b> (%)
1	366 mg	80	5 h	24
2	570 mg	80	18 h	22
3*	100 mg	100	18 h	40
4*	100 mg	rt	18 h	45
5*	500 mg	rt	60h	35

\* 3 drops of DMF added 1h into reaction

### NHC Catalyzed Aroylation

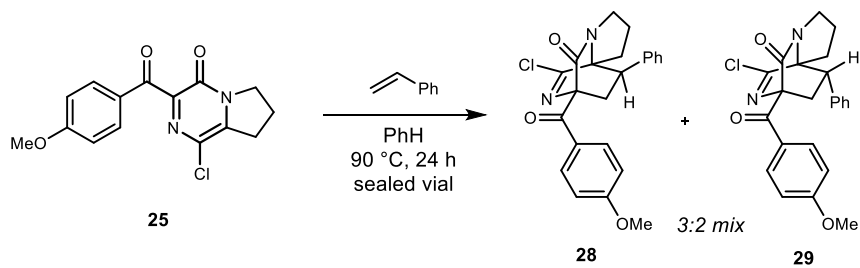
Following Van der Eycken and co-workers' procedure, 3,5 dichloropyrazinone **22** was reacted with *p*-anisaldehyde in the presence of NHC catalyst **24** and NaH to give C2-carboxy pyrazinone **25** for studying intermolecular Diels-Alder reactions. **22** was also reacted with aryl aldehyde **26** in the presence of NaH and **24** to give pyrazinone **27** for use in studying intramolecular Diels-Alder reactions (Scheme 11).



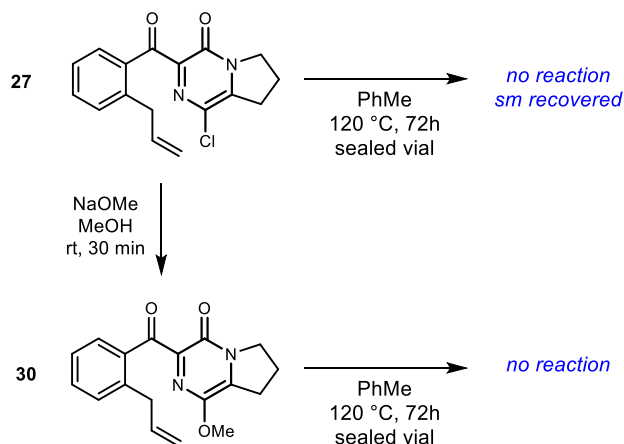
**Scheme 11.** NHC catalyzed aroylation of **22** to give C2-carboxy pyrazinones.

We set about studying the relative propensity of pyrazinones **25** and **27** to undergo both intermolecular and intramolecular [4+2] cyclizations. **25** was reacted with a large excess of styrene to give a 3:2 mixture of diastereomers **28** and **29**. This reactivity was not highly different than previously observed Diels-Alder reactions of pyrazinones in terms of selectivity. We attempted the reaction several more times with a number of Lewis acid additives, but none of the reactions provided any products resulting from cycloaddition (Table 2). Pyrazinone **27** was quite stable and did not readily undergo intramolecular cycloaddition at ambient temperatures. Heating **27** in refluxing toluene for 72 hours was also incapable of initiating cycloaddition. We hope to increase reactivity by converting the chlorine at C5 on the pyrazinone to a methoxy group with treatment of NaOMe to give pyrazinone **30**. However again, heating of **30** in refluxing toluene provided no desired cycloaddition products (Scheme 12).

**Table 2.** Intermolecular Diels-Alder reactions of pyrazinone **25** with styrene.



entry	additive	solvent	temp	yield (%)
1	HN(Tf) <sub>2</sub>	PhH	rt	no [4+2] polymerization
2	Cu(OTf) <sub>2</sub> , tBuBox	DCM	0 °C to rt	NR
3	Yb(OTf) <sub>3</sub>	DCM	0 °C to rt	NR



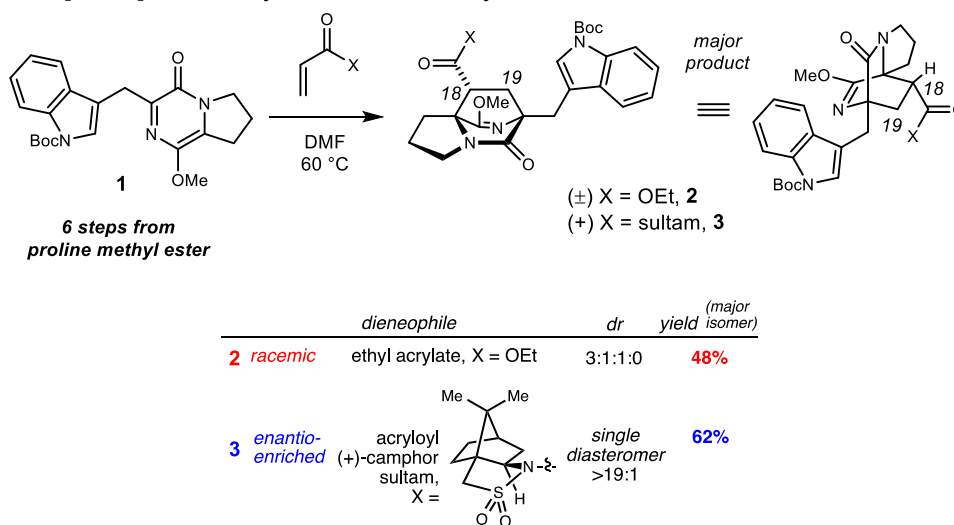
**Scheme 12.** Attempted IMDA reactions of C2-carboxy pyrazinones **27** and **30**.

## Conclusions

The intermolecular Diels-Alder with a C2-carboxy pyrazinone did not provide any increase to the selectivity of the Diels-Alder reaction when compared to reactions with substrates lacking oxidation at C2. Furthermore, attempts to increase selectivity with the addition of various Lewis acids was met without success. The intramolecular Diels-Alder reaction was also unsuccessful. Heating at high temperatures failed to induce cycloaddition of pyrazinones **27** and **30**, when similar compounds without the additional oxidation adjacent to the DKP ring are known to undergo cycloaddition at even ambient temperatures. These results coupled with the poor yields of reactions used to synthesize the C2-carboxy pyrazinone precursors led us to believe that further investigation would not provide meaningful results.

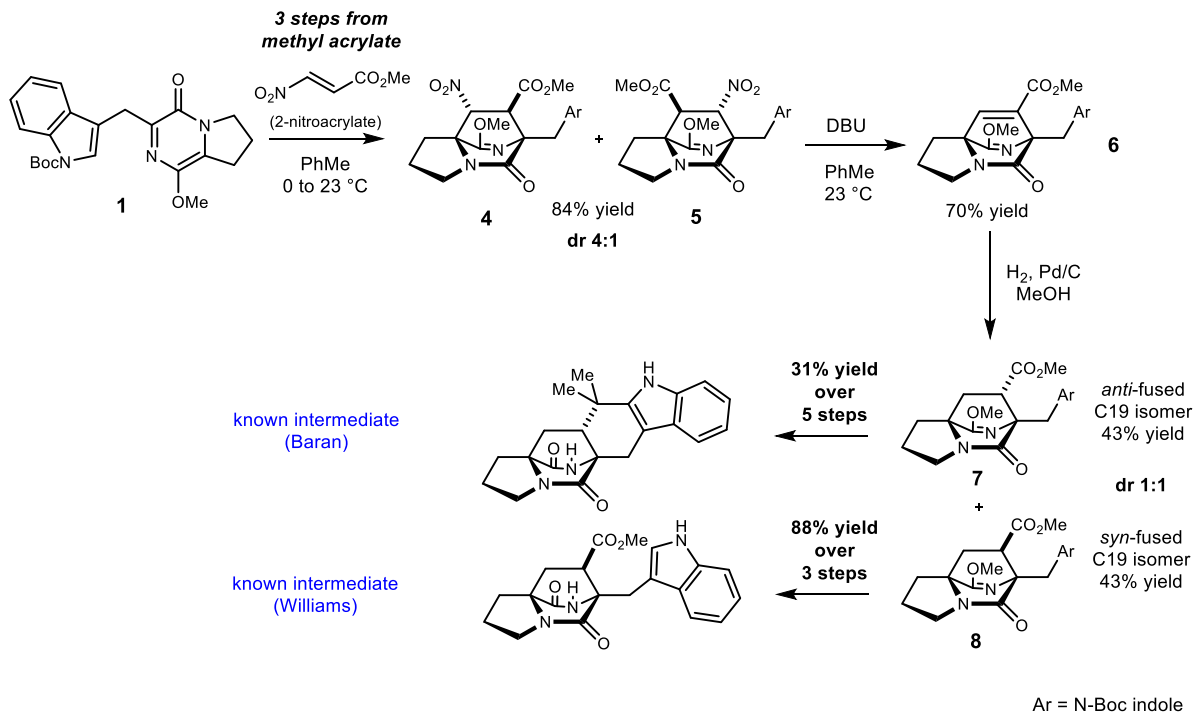
### Chapter 3: Intermolecular Diels-Alder of a Pyrazinone with Symmetric Dienophiles Introduction

The use of an intermolecular Diels-Alder cycloaddition to form the bicyclo[2.2.2]-diazaoctane core was explored previously by our lab.<sup>1</sup> The [4+2] cycloaddition of a proline derived pyrazinone (azadiene) **1** with both achiral and chiral acrylate dienophiles permits rapid assembly of the [2.2.2]-diazabicylic core in a stereoselective fashion (Scheme 1).<sup>33</sup> The thermal [4+2] cycloaddition of ethyl acrylate and **1** resulted in a 3:1:1 mixture of regio- and stereoisomers with the major product **2** corresponding to cycloaddition from the *endo* transition state with the ethyl ester positioned distal to the indole nucleus of the pyrazinone. Furthermore, the reaction of **1** with a chiral dienophile, (+)-acryloyl camphor sultam, proved capable of inducing asymmetry in the cycloaddition providing a single diastereomer **3** (dr > 19:1) corresponding to cycloaddition from the *endo* transition state with the amide positioned distal to the indole of the pyrazinone. Both cycloadditions provide products with regiochemistry that does not easily permit extrapolation to natural products in the [2.2.2]-diazabicylic alkaloid family.



**Scheme 1.** Racemic and enantio-enriched Diels-Alder cycloadditions of pyrazinone **1** with acrylate dienophiles.

In order to obtain the desired regioisomer with the carboxy group proximal to the indole nucleus, cycloaddition of **1** with methyl 2-nitroacrylate was performed. In the event, cycloaddition of **1** with the nitroacrylate dienophile provided the two regioisomeric products, **4** and **5**, in a 4:1 ratio with the desired product being the major isomer (Scheme 2). Both regioisomers were derived from cycloadditions where the nitro group is positioned *endo* in the cycloaddition transition state. However, the two regioisomers proved difficult to separate by column chromatography, and attempts to remove the nitro group resulted in elimination rather than direct reduction. Instead, it became more operationally simple to induce elimination of the nitro group with DBU and separate the two resulting unsaturated ester products by column chromatography. Attempted stereoselective hydrogenation of **5** with various catalysts such as Crabtree's catalyst and Striker's reagent under various reaction conditions gave limited success. Hydrogenation of unsaturated ester **6** with Pd/C resulted in a 1:1 mix of *anti*- and *syn*-fused C19 isomers, **7** and **8**. The two isomers were separated and carried forward in two separate routes to intercept known intermediates in the Williams synthesis of brevianamide B (*anti*-fused isomer **7**) and the Baran synthesis of premalbrancheamide (*syn*-fused isomer **8**).



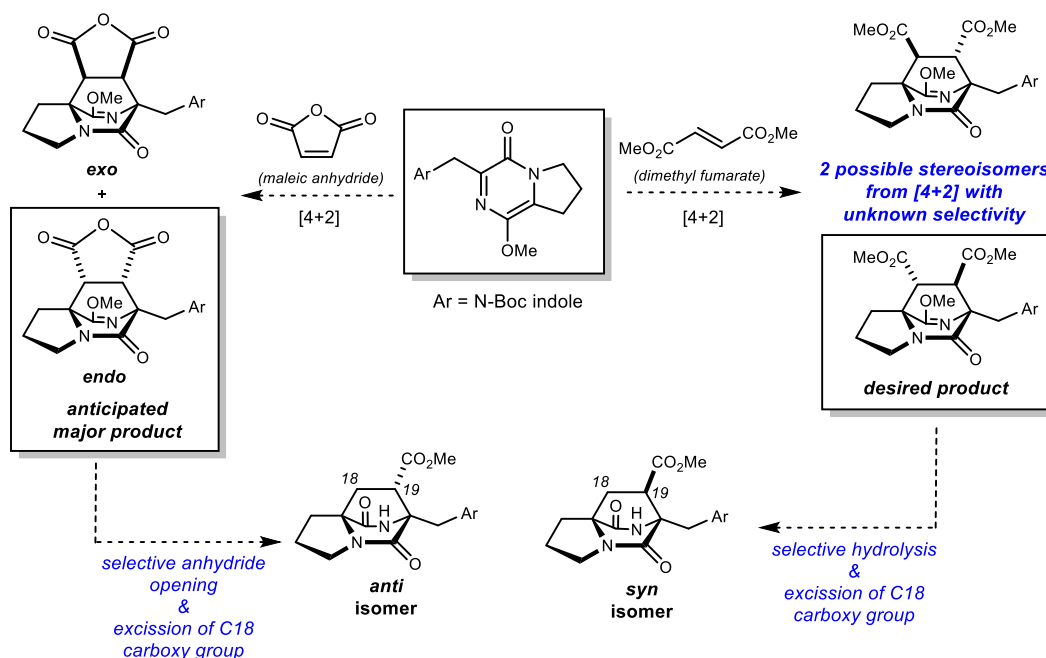
**Scheme 2.** Diels-Alder cycloaddition of pyrazinone **1** with 2-nitroacrylate to intercept known intermediates from two separate syntheses of bicyclo[2.2.2]diazaoctane alkaloids by Baran and Williams.

Overall, the route provided efficient entry to the bicyclo[2.2.2]diazaoctane core (four to five steps from proline methyl ester) and gave useful insight into the intermolecular Diels-Alder of pyrazinone **1** with a number of acrylate derived dienophiles. It demonstrated that the [4+2] cycloaddition is most favorable with electron deficient substrates. The more electron withdrawing substituent on the dienophile adds distal to the indole nucleus in an endo fashion. This was exploited in the cycloaddition with nitroacrylate to obtain the desired regiochemistry with the methyl ester positioned proximal to the indole nucleus. The route has a few limitations. Mainly, the Diels-Alder is not particularly selective providing a 4:1 mix of products, the nitroacrylate dienophile is not commercially available and must be synthesized in 3 steps from methyl acrylate, and the hydrogenation of the unsaturated methyl ester **6** is entirely unselective affording a 1:1 mix of *anti*- and *syn*-fused products. With these limitations in mind, we sought to explore the intermolecular Diels-Alder cycloadditions of commercially available symmetric dienophiles with pyrazinone **1**

with the goal of developing separate synthetic routes to the *anti*- and *syn*-fused methyl ester products, **7** and **8**.

### Developing Separate Routes to the *syn*- and *anti*-C19 Isomers

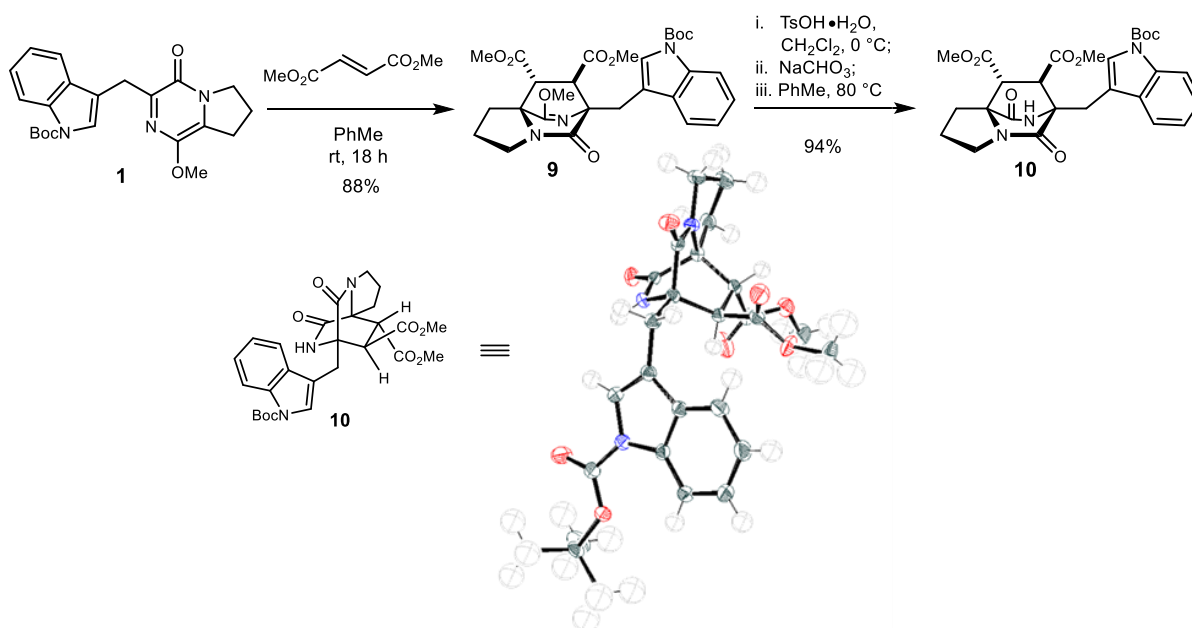
When thinking about developing separate synthetic routes to the *anti*- and *syn*-C19 isomer, we proposed that the use of symmetric electron deficient dienophiles would limit the number of possible regio- and stereoisomeric products of the Diels-Alder reactions when compared to the acrylate derived dienophiles. We envisioned that the *syn*-C19 isomer could be derived from the Diels-Alder reaction of pyrazinone **1** with dimethyl fumarate based on the selectivity of the nitroacrylate reactions. Selective hydrolysis of the methyl ester at C18 followed by excision of the resulting carboxy group using radical decarboxylation would give the *syn* methyl ester product **8**. Similarly, we proposed that the [4+2] cycloaddition of **1** with maleic anhydride would likely give the endo cycloadduct as the major product which would establish the desired *anti*-C19 stereochemistry. The desired *anti* methyl ester product **7** would then be achieved through selective anhydride opening and excision of the C18 carboxy group (Scheme 3).



**Scheme 3.** Proposed synthetic routes to *anti*- and *syn*-C19 isomers.

## Intermolecular Diels-Alder with Dimethyl Fumarate

The [4+2] cycloaddition of **1** with dimethyl fumarate proceeded readily at room temperature and yielded a single diastereomer **9** (dr > 20:1 as judged by <sup>1</sup>H NMR of the unpurified reaction) (Scheme 4). The unpurified reaction mixture was quite clean, containing only desired product and excess dimethyl fumarate. Using NOESY NMR spectroscopy, we initially determined that **9** possessed the *syn*-fused stereochemistry at C19. This result was in agreement with previous results wherein the group at C18 is oriented *endo* in the Diels-Alder transition state to push it as far from the pendant indole as possible. Surprisingly, the stereoselectivity for the major product with dimethyl fumarate was much higher than with either of the two acrylate derived dienophiles (i.e. dr > 20:1 with dimethyl fumarate vs dr = 4:1 with nitroacrylate). The absolute stereochemistry of **9** was confirmed from an X-ray crystal structure of the lactam product **10** obtained from hydrolysis of **9** with TsOH and H<sub>2</sub>O to give the open chain tautomer of the lactim O-methyl ether followed by recyclization to the lactam.

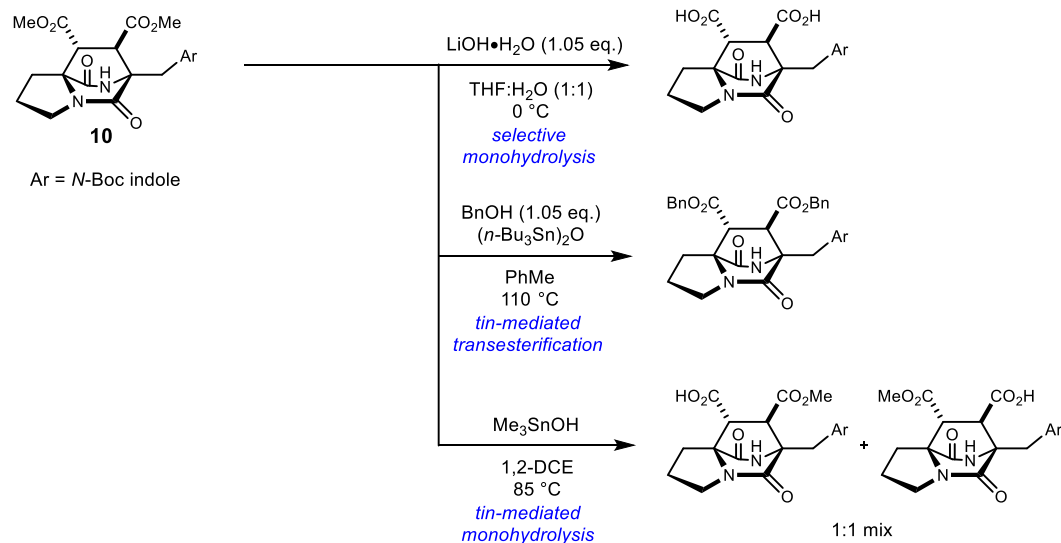


**Scheme 4.** [4+2] cycloaddition of pyrazinone **1** with dimethyl fumarate followed by hydrolysis of lactim O-methyl ether **9** to give lactam cycloadduct **10**.

## Selective Hydrolysis of the Dimethyl Fumarate Cycloadduct

With structure of the dimethyl fumarate cycloadduct determined by X-ray crystallography, we began work on the selective hydrolysis of the methyl ester at C18 to provide a carboxylic acid which could be removed by radical decarboxylation (Scheme 5). It was shown previously that monohydrolysis of bicyclo[2.2.1]heptane-2,3-dicarboxylate derivatives with LiOH or KOH is highly selective for the *exo* ester.<sup>34</sup> We found that hydrolysis of **10** with LiOH·H<sub>2</sub>O (1.05 equivalents) stirring at 0 °C for 18 hours gave only the bishydrolysis product and unreacted starting material. We then turned to tin mediated transesterification and hydrolysis methods with the hope that the bulkier tin reagents would be able to provide some selectivity.

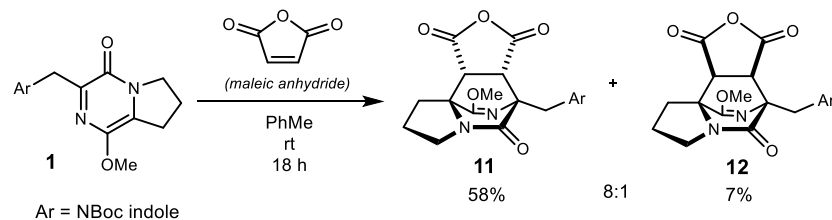
First, we attempted tin mediated transesterification, pioneered by Otera, by stirring **10** and BnOH in the presence of catalytic bis(tri-*n*-butyl tin) oxide in refluxing toluene for 24 hours.<sup>35</sup> The reaction afforded only the doubly transesterified product with no apparent selectivity. Nicolaou and co-workers showed that selective hydrolysis of a wide variety of methyl esters could be achieved using trimethyltin hydroxide.<sup>36</sup> Reaction of **10** with trimethyltin hydroxide in refluxing 1,2-dichloroethane provided a 1:1 mix of monohydrolysis products with no apparent selectivity. While the methods we attempted did not appear to provide selective hydrolysis, it is by no means exhaustive and there are certainly other methods that could provide selectivity, but we decided to focus more heavily on the reaction of **1** with maleic anhydride.



**Scheme 5.** Attempted methods for selective monohydrolysis and transesterification of dimethyl fumarate cycloadduct **10**.

### Intermolecular Diels-Alder with Maleic Anhydride

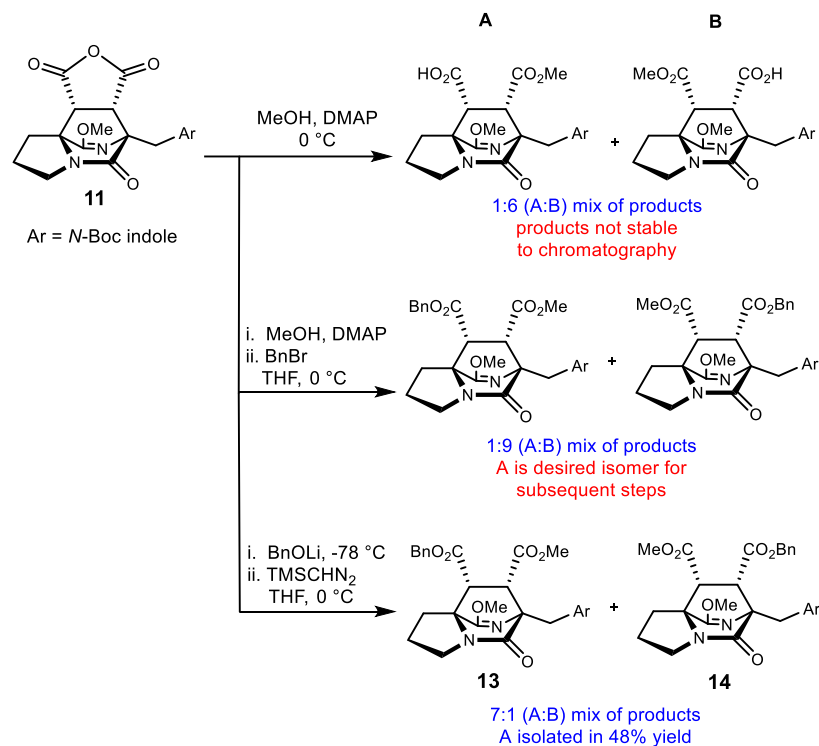
The intermolecular Diels-Alder of maleic anhydride with pyrazinone **1** could provide only two possible diastereomeric products. We surmised that the major product would likely be the product derived from the *endo* transition state providing the desired *anti*-fused stereochemistry at C19. When conducted, the [4+2] cycloaddition of maleic anhydride with pyrazinone **1** proceeded smoothly at room temperature yielding an 8:1 (*endo:exo*) mix of cycloadducts **11** and **12** as determined by <sup>1</sup>H-NMR analysis of the unpurified reaction mixture (Scheme 6). Cooling the reaction to -20 °C did not provide any change in selectivity, however heating the reaction at 50 °C decreased selectivity from 8:1 to 6:1 (*endo:exo*). The two isomers were easily separated by column chromatography providing the desired *endo* isomer **11**. To obtain the desired methyl ester product **7**, we needed to selectively open the anhydride cycloadduct with an appropriate nucleophile and selectively excise the carboxyl group at C18.



**Scheme 6.** Diels-Alder cycloaddition of pyrazinone **1** with maleic anhydride.

### Selective Opening of Malic Anhydride Cycloadduct

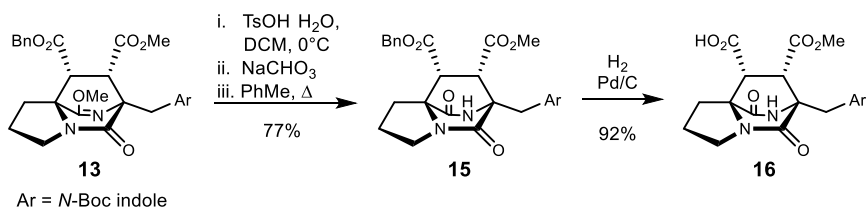
In order to determine if there was any inherent selectivity for opening the anhydride of the cycloadduct, we reacted cycloadduct **11** with methanol in the presence of DMAP. The reaction provided a 1:6 mix of mono-methyl ester products. Upon purification of the reaction mixture by flash column chromatography, both products degraded and were not recovered after being loaded onto the column. We suspected that the acid sensitive lactim O-methyl ether functionality was being hydrolyzed by the carboxylic acid formed during the anhydride opening. The lactim O-methyl ether hydrolysis product would be highly polar because of its Zwitter-ionic nature and not likely to come off the column with the conditions used. We overcame this problem by doing an *in situ* protection of the carboxylic acid with benzyl bromide after opening the anhydride cycloadduct **11** with methanol. The resulting products were then stable to column chromatography and were isolated in a 1:9 mix (Scheme 7).



**Scheme 7.** Selective nucleophilic opening of maleic anhydride cycloadduct **11** followed by *in situ* protection of the resulting carboxylic acid.

Using 2D-NMR we were able to determine that the major product had the methyl ester at C18 and the benzyl ester at C19 resulting from selective nucleophilic attack of the methanol at the anhydride carbonyl distal to the indole moiety. This provided the wrong regiochemistry for the resulting esters, as we wanted the methyl ester at C19 and the benzyl ester at C18. To obtain the desired regiochemistry, we instead opened the anhydride cycloadduct **11** with benzyl alcohol followed by *in situ* protection of the resulting carboxylic acid with methyl iodide affording a 6:1 mix of the desired and undesired regioisomers, **13** and **14**. Unfortunately, the sequence was plagued by a poor overall yield (< 30% over the two steps), so we sought to improve the yield by changing the electrophilic methylation reagent. Instead of methyl iodide we used TMS diazomethane as the methylation reagent. The reaction still provided the desired product, but the yield of 26% over two steps was still quite poor. Opening the anhydride at -78 °C with the more nucleophilic lithiated benzyl alcohol provided the desired product with an improved yield

of 49% and slightly improved selectivity of 7:1 for the desired regioisomer **13**. Hydrolysis of the lactim O-methyl ether functionality of **13** with TsOH·H<sub>2</sub>O and recyclization provided lactam **15** in high yield. Simple deprotection of the benzyl ester at C18 by hydrogenation provided the carboxylic acid precursor **16** necessary for radical decarboxylation (Scheme 8).



**Scheme 8.** Conversion of the lactim O-methyl ether **13** to lactam **15** by hydrolysis and recyclization followed by deprotection of the benzyl ester at C18 to give carboxylic acid **16**.

### Radical Decarboxylation to Obtain the *Anti*-fused Methyl Ester

Since Barton and co-workers published their seminal works on the eponymous Barton decarboxylation reaction in 1962 and 1980, methods for radical decarboxylation have been both widely used and improved upon to convert carboxylic acids into many other functional groups.<sup>37,38,39</sup> The original Barton decarboxylation protocol involved converting the carboxylic acid into an acid chloride followed by addition of 2-mercaptopyridine *N*-oxide to form a thiohydroxamate ester. The *N*-O bond of the thiohydroxamate ester is prone to homolytic bond cleavage. When heated in the presence of the radical initiator AIBN and a hydrogen donor such as tri-*n*-butyltin hydride, the ester undergoes radical bond cleavage, decarboxylation, and a radical hydride transfer to give the decarboxylated hydrocarbon product.

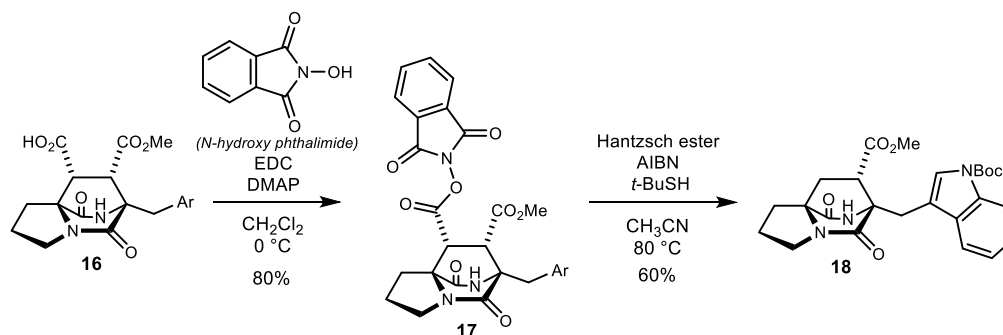
Modern methods have replaced the highly toxic tri-*n*-butyltin hydride with less toxic reductive hydride donors such as *t*-butyl thiol. In the early 1980s, Okada and co-workers published several articles demonstrating that *N*-hydroxy phthalimide derived esters were also capable of undergoing homolytic bond cleavage and decarboxylation to form alkyl radicals which they then reacted with hydride donors to form hydrocarbons or diphenyl

diselenide to form alkyl selenides.<sup>40,41</sup> They also demonstrated that homolytic N-O bond cleavage of the phthalimodoyl esters could be initiated using a variety of methods including: heating in the presence of AIBN (1) and photocatalytic initiation with both organic and inorganic photocatalysts (2). More recently, Nicewicz and co-workers have developed a catalytic hydrodecarboxylation method which uses an organic photocatalyst to directly convert carboxylic acids to hydrocarbons.<sup>42</sup>

While attempting the Barton decarboxylation method on a model system derived from the opening of 1,2-cyclohexane dicarboxylic anhydride, we found that the Barton ester could be formed in good yields by doing an EDC coupling of the carboxylic acid precursor with 2-mercaptopyridine N-oxide. We also discovered that the resulting Barton ester was light sensitive, and the use of column chromatography for purification resulted in diminished yield of pure product and isolation of an undesired by-product resulting from decarboxylation of the ester and recombination of the resulting alkyl radical with the thiopyridine radical produced from the initial N-O bond cleavage. Therefore, when working with our actual decarboxylation substrate **16**, we decided to attempt making both the thiohydroxamate and phthalimidoyl esters for decarboxylation. We surmised that the phthalimidoyl ester would be more stable to light and heat than the thiohydroxamate ester, and could therefore likely be purified and isolated by column chromatography without issue.

As predicted, the EDC coupling of carboxylic acid **16** with 2-mercaptopyridine N-oxide yielded a mix of products that was light sensitive and not stable to purification by column chromatography. On the other hand, the coupling of acid **16** with N-hydroxy phthalimide provided the desired ester **17** in good yield, and the product was easily purified to remove excess N-hydroxy phthalimide and EDC related compounds. Following the protocol from Okada and co-workers, we first attempted a photocatalyzed decarboxylation by stirring ester **17** under blue LEDs in the presence of a Hantzsch ester (diethyl-1,4-

dihydro-2,6-dimethyl-3,5-pyridine dicarboxylate), *t*-BuSH, 10 mol% of Ru(bpy)<sub>3</sub>Cl<sub>2</sub>·6H<sub>2</sub>O using a 7:3 mix of THF:H<sub>2</sub>O as the solvent. After stirring at room temperature for 24 hours, the reaction resulted in only recovered starting material and a by-product resulting from hydrolysis of the ester back to the carboxylic acid in the presence of water. The photocatalyzed decarboxylation was attempted once more using CH<sub>3</sub>CN as a solvent instead of a THF:H<sub>2</sub>O mixture, but it resulted in a mixture of products which did not appear to contain the desired methyl ester product. Clean decarboxylation of ester **17** to afford the desired *anti*-fused methyl ester **18** was finally achieved by heating in the presence of AIBN, Hantzsch ester, and *t*-BuSH using CH<sub>3</sub>CN as a solvent (Scheme 9).



**Scheme 9.** EDC coupling of carboxylic acid **16** with N-hydroxy phthalimide to form phthalimidoyl ester **17**, followed by radical decarboxylation to afford the desired *anti*-fused C19 methyl ester **18**.

## Conclusions

The structure of **18** was confirmed by making **18** using the methods described in the previous synthesis using nitroacrylate as the dienophile (*i.e.*, hydrogenation of the unsaturated methyl ester cycloadduct followed by lactam hydrolysis of the two isomer and separation by column chromatography).<sup>33</sup> Our overall route to the *anti*-C19 stereoisomer of methyl ester [2.2.2]-diazabicyclic alkaloid **18** takes 6 steps from proline derived DKP **1** with an overall yield of 12%. **18** is a known compound that is 3 steps from an intermediate in the Williams' synthesis of brevianamide B constituting a 15 step formal synthesis (longest linear route). The route improves upon the previous synthesis by our group, as it provides only a single stereoisomer at C19 instead of a 1:1 mix of *anti*:*syn* stereoisomers.

Additionally, the starting maleic anhydride dienophile is commercially available and does not have to be synthesized, unlike the nitroacrylate dienophile which requires 3 steps that are not particularly easy to accomplish. Although, the yields of the two routes are comparable the new route is an improvement in overall steps and the fact that it uses a commercially available dienophile.

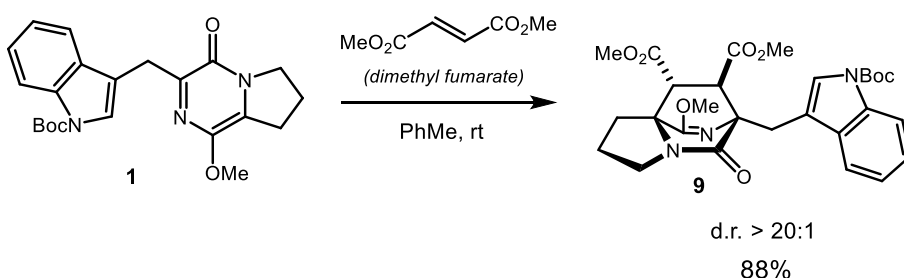
## **Experimental**

### **General Information**

Unless otherwise noted, all reactions were carried out in flame-dried or oven-dried glassware under an atmosphere of nitrogen with magnetic stirring. THF, toluene, and acetonitrile were degassed with argon and dried by passage through a column of molecular sieves and a bed of activated alumina. Dichloromethane was distilled from  $\text{CaH}_2$  prior to use. All reagents were used as received unless otherwise noted. Flash column chromatography was performed using SiliCycle siliaflash P60 silica gel (230-400 mesh). Analytical thin layer chromatography was performed on SiliCycle 60Å glass plates. Visualization was accomplished with UV light, ceric ammonium molybdate, potassium permanganate, or ninhydrin, followed by heating. Film infrared spectra were recorded using a Digilab FTS 7000 FTIR spectrophotometer.  $^1\text{H}$  NMR spectra were recorded on an A400b Agilent DD2 NMR (400 MHz) spectrometer and are reported in ppm using solvent as an internal standard ( $\text{CDCl}_3$  at 7.26 ppm) or TMS (0.00 ppm). Proton-decoupled  $^{13}\text{C}$  NMR spectra were recorded on an A400b Agilent DD2 NMR (100 MHz) spectrometer and are reported in ppm using solvent as an internal standard ( $\text{CDCl}_3$  at 77.00 ppm). All compounds were judged to be homogeneous (>95% purity) by  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectroscopy. Mass spectra data analysis was obtained through positive electrospray ionization (w/ NaCl) on a Bruker 12 Tesla APEX-Qe FTICR-MS with an Apollo II ion source.

\*All compounds listed were isolated as racemic mixtures.

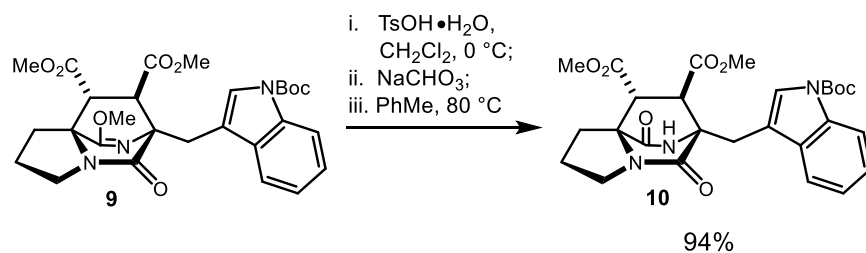
## Experimental Procedures



### Dimethyl (6R\*,7R\*,8R\*,8aR\*)-6-((1-(tert-butoxycarbonyl)-1H-indol-3-yl)methyl)-9-methoxy-5-oxo-2,3,5,6,7,8-hexahydro-1H-6,8a-(azeno-metheno)indolizine-7,8-dicarboxylate. (**9**)

A dry flask was charged with pyrazinone **1** (200 mg, 0.51 mmol) and dimethyl fumarate (146 mg, 1.01 mmol). The reaction flask was then flushed with N<sub>2</sub> gas for 10 min before toluene (5 mL) was added and the vessel evacuated to 40 torr for 5 min and backfilled with N<sub>2</sub> gas. The reaction flask was covered in foil to keep out ambient light, and the reaction stirred at rt for 16 h. The solution was concentrated *in vacuo* to afford a yellow oil, which contained a single cycloadduct **9** (dr > 20:1 as judged by <sup>1</sup>H NMR of the unpurified reaction mixture) and excess dimethyl fumarate. The resulting residue was purified by flash column chromatography on silica gel (gradient elution: 20% → 100% EtOAc in hexanes) to afford cycloadduct **9** as a yellow oil (240 mg, 88% yield): TLC (60% EtOAc in hexanes), R<sub>f</sub> 0.28 (UV, CAM); IR (film, cm<sup>-1</sup>) 2986, 2948, 1729, 1685, 1638, 1450, 1367, 1308, 1256, 1155, 1082, 1015, 745; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.10 (d, *J* = 8.3 Hz, 1H), 7.77 (dd, *J* = 7 Hz, 0.9 Hz, 1H), 7.74 (s, 1H), 7.27 (td, *J* = 7.5 Hz, 1.2 Hz, 1H), 7.19 (td, *J* = 7.8 Hz, 1.2 Hz, 1H), 3.72 (s, 3H), 3.71 (s, 3H), 3.64 (s, 3H), 3.56 (m, 1H), 3.51 (m, 1H), 3.49 (d, *J* = 15.2 Hz, 1H), 3.26 (d, *J* = 15.2 Hz, 1H), 3.16 (d, *J* = 5.5 Hz, 1H), 3.03 (d, *J* = 5.5 Hz, 1H), 2.62 (m, 1H), 2.05 (m, 2H), 1.95 (m, 1H), 1.66 (s, 9H); <sup>13</sup>C NMR (400 MHz, CDCl<sub>3</sub>) δ 171.5, 170.8, 170.6, 169.5, 149.9, 132.2, 125.6, 123.8, 121.8, 120.8, 116.0,

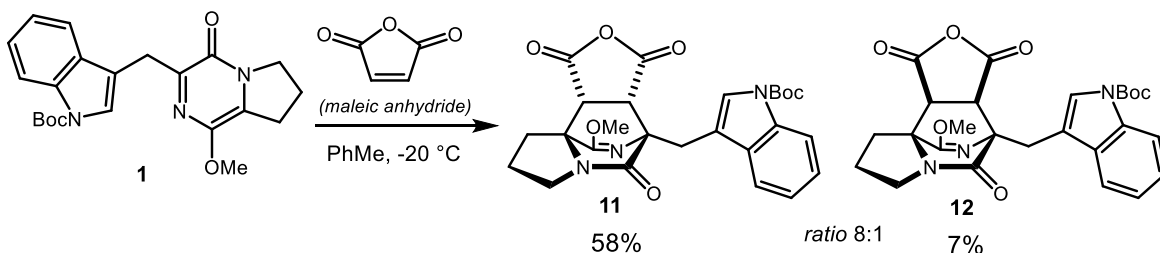
114.8, 83.1, 68.5, 64.8, 54.9, 52.9, 52.5, 50.0, 43.5, 28.2, 28.1, 28.1, 27.1, 24.5; MASS SPEC SAMPLE NEEDS TO BE SUBMITTED.



**Dimethyl (6S\*,7R\*,8R\*,8aS\*)-6-((1-(tert-butoxycarbonyl)-1H-indol-3-yl)methyl)-5,9-dioxohexahydro-1H-6,8a-(epiminomethano)indolizine-7,8-dicarboxylate. (10)**

A dry flask was charged with cycloadduct **9** (275 mg, 0.51 mmol) and flushed with N<sub>2</sub> gas for 10 min, dissolved in CH<sub>2</sub>Cl<sub>2</sub> (5 mL), and cooled to 0 °C. To the reaction flask was added *p*TsOH·H<sub>2</sub>O (115 mg, 0.61 mmol), and the reaction was stirred for 2 h at 0 °C. The reaction mixture was diluted with sat'd aq NaHCO<sub>3</sub> (10 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (4 X 10 mL). The combined organic layers were washed with sat'd aq NaCl (50 mL), dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. The resulting product was dissolved in toluene (5 mL) and stirred at 80 °C for 18 h. The solution was concentrated *in vacuo* to afford lactam **10** as a white solid. The unpurified reaction mixture was purified by flash column chromatography on silica gel (gradient elution: 40% → 100% EtOAc in hexanes) to afford lactam **10** as a pale yellow solid (250 mg, 94% yield): TLC (60% EtOAc in hexanes) *R*<sub>f</sub>: 0.28 (UV, CAM); m.p. 96.8-97.9 °C; IR (film, cm<sup>-1</sup>) 3218, 3116, 2953, 2252, 1723, 1695, 1450, 1387, 1361, 1310, 1255, 1205, 1158, 1095, 1003, 911, 852, 724, 645; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.15 (d, *J* = 8.2 Hz, 1H), 7.73 (s, 1H), 7.60 (d, *J* = 8.2 Hz, 1H), 7.36 (td, *J* = 8.2 Hz, 1.2 Hz, 1H), 7.28 (td, *J* = 7.4 Hz, 1.2 Hz, 1H), 5.85 (s, 1H), 3.83 (s, 3H), 3.71 (s, 3H), 3.69 (d, *J* = 5.3 Hz, 1H), 3.61 (d, *J* = 15.6 Hz, 1H), 3.61 (m, 1H), 3.58 (m, 1H), 3.44 (d, *J* = 4.7 Hz, 1H), 3.20 (d, *J* = 15.7 Hz, 1H), 2.75 (m, 1H), 2.09 (m, 2H), 1.98 (m, 1H), 1.69 (s, 9H); <sup>13</sup>C NMR (400 MHz, CDCl<sub>3</sub>) δ 170.4, 169.8, 169.5, 166.3, 149.4, 135.3, 130.7,

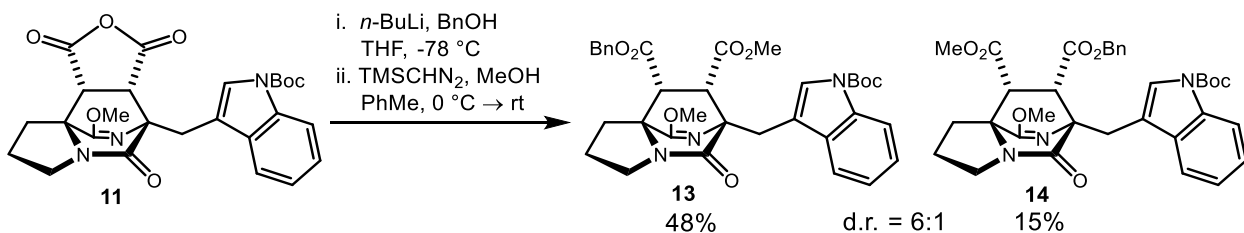
126.3, 125.0, 123.2, 118.2, 115.6, 112.0, 84.0, 68.0, 62.9, 53.0, 52.9, 52.4, 51.7, 44.3, 28.5, 28.1, 24.3, 24.1; exact mass calc'd for C<sub>27</sub>H<sub>31</sub>N<sub>3</sub>O<sub>8</sub>Na [M + Na]<sup>+</sup> 548.2003, found 548.2006. A single crystal of **10** was obtained by evaporation from Et<sub>2</sub>O and its structure was determined by X-Ray crystallographic analysis.



**tert-Butyl 3-(((3aS\*,4R\*,9aR\*,9bR\*)-10-methoxy-1,3,5-trioxo-1,3,3a,8,9,9b-hexahydro-7H-4,9a-(azenometheno)furo[3,4-g]indolizin-4(5H)-yl)methyl)-1H-indole-1-carboxylate (11) and Tert-butyl 3-(((3aR\*,4R\*,9aR\*,9bS\*)-10-methoxy-1,3,5-trioxo-1,3,3a,8,9,9b-hexahydro-7H-4,9a-(azenometheno)furo[3,4-g]indolizin-4(5H)-yl)methyl)-1H-indole-1-carboxylate. (12)**

A dry flask was charged with pyrazinone **1** (200 mg, 0.51 mmol) and maleic anhydride (98 mg, 1.01 mmol) and flushed with N<sub>2</sub> gas for 10 min, cooled to -20 °C, dissolved in toluene (10 mL), evacuated to 40 torr for 5 min, and backfilled with N<sub>2</sub> gas. The reaction flask was covered in foil to keep out ambient light, and the reaction stirred and allowed to warm to ambient temperature over 16 h. The solution was concentrated *in vacuo* to give a pale yellow solid containing the two diastereomeric cycloadducts **11** and **12** in an 8:1 ratio (as judged by <sup>1</sup>H NMR of the unpurified reaction mixture). The mixture was purified by flash column chromatography on silica gel (gradient elution: 20% → 100% EtOAc in hexanes) to afford pure **11** (144 mg, 58% yield) and **12** (18 mg, 7% yield) as pale yellow solids: **11**: TLC (60% EtOAc in hexanes) R<sub>f</sub>: 0.23 (UV, CAM); m.p. 126.4-128.2 °C; IR(film, cm<sup>-1</sup>) 2981, 1865, 1781, 1688, 1631, 1450, 1368, 1252, 1216, 1155, 1076, 917, 727; <sup>1</sup>H NMR

(400 MHz, CDCl<sub>3</sub>) δ 8.06 (d, *J* = 7 Hz, 1H), 7.83 (dd, *J* = 7 Hz, 1.6 Hz, 1H), 7.74 (s, 1H), 7.26 (td, *J* = 7.1 Hz, 1.6 Hz, 1H), 7.23 (td, *J* = 7.4 Hz, 1.6 Hz, 1H), 3.88 (dd, *J* = 14.5 Hz, 0.8 Hz, 1H), 3.70 (s, 3H), 3.62 (d, *J* = 14.5 Hz, 1H), 3.60 (d, *J* = 8.6 Hz, 1H), 3.45 (m, 1H), 3.38 (d, *J* = 8.2 Hz, 1H), 3.35 (m, 1H), 2.68 (dt, *J* = 14.1 Hz, 7.4 Hz, 1H), 2.48 (dt, *J* = 14.1 Hz, 7.1 Hz, 1H), 2.03 (m, 2H), 1.67 (s, 9H); <sup>13</sup>C NMR (400 MHz, CDCl<sub>3</sub>) δ 169.5, 168.3, 167.6, 167.2, 149.9, 134.8, 132.0, 126.2, 123.8, 122.0, 120.7, 116.0, 114.8, 83.2, 69.2, 65.4, 55.4, 51.2, 47.6, 43.9, 28.2, 27.2, 25.7, 23.9; exact mass calc'd for C<sub>26</sub>H<sub>24</sub>N<sub>3</sub>O<sub>7</sub>Na [M + Na]<sup>+</sup> 516.1741, found 516.1740. **12**: TLC (60% EtOAc in hexanes) R<sub>f</sub>: 0.33UV, CAM); m.p. 114.3-115.5 °C; IR (film, cm<sup>-1</sup>) 2977, 1870, 1780, 1683, 1631, 1451, 1368, 1254, 1217, 1154, 1076, 920, 728; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.12 (d, *J* = 7.8 Hz, 1H), 7.96 (d, *J* = 7.5 Hz, 1H), 7.79 (s, 1H), 7.29 (td, *J* = 7.8 Hz, 1.2 Hz, 1H), 7.21 (td, *J* = 7.5 Hz, 0.9 Hz, 1H), 3.76 (d, *J* = 14.8 Hz, 1H), 3.76 (s, 3H), 3.59 (m, 1H), 3.57 (d, *J* = 15.3 Hz, 1H), 3.45 (d, *J* = 9.4 Hz, 1H), 3.29 (m, 1H), 3.12 (d, *J* = 9.4 Hz, 1H), 2.69 (m, 2H), 2.11 (m, 1H), 1.89 (m, 1H), 1.65 (s, 9H); <sup>13</sup>C NMR (400 MHz, CDCl<sub>3</sub>) δ 171.8, 169.2, 167.8, 167.0, 149.7, 136.4, 131.7, 131.7, 126.1, 124.1, 122.0, 121.2, 115.3, 114.8, 83.5, 68.3, 65.8, 55.6, 48.0, 47.6, 44.4, 28.1, 26.0, 25.1, 24.6; exact mass calc'd for C<sub>26</sub>H<sub>24</sub>N<sub>3</sub>O<sub>7</sub>Na [M + Na]<sup>+</sup> 516.1741, found 516.1738.



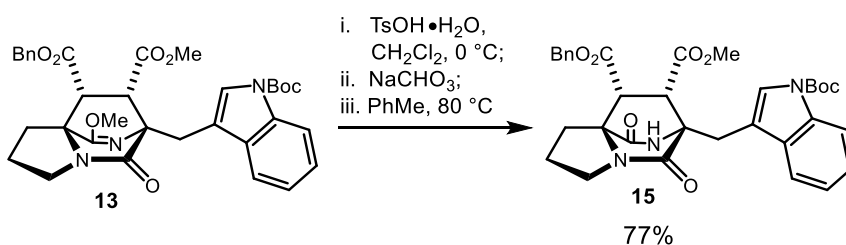
**8-Benzyl 7-methyl (6R\*,7R\*,8S\*,8aR\*)-6-((1-(tert-butoxycarbonyl)-1H-indol-3-yl)methyl)-9-methoxy-5-oxo-2,3,5,6,7,8-hexahydro-1H-6,8a-(azenometheno)indolizine-7,8-dicarboxylate (13) and 7-Benzyl 8-methyl**

**(6R\*,7R\*,8S\*,8aR\*)-6-((1-(tert-butoxycarbonyl)-1H-indol-3-yl)methyl)-9-methoxy-5-oxo-2,3,5,6,7,8-hexahydro-1H-6,8a-(azenometheno)indolizine-7,8-dicarboxylate.**

**(14)**

To a flame-dried reaction flask under N<sub>2</sub> was added BnOH (232 μL, 2.23 mmol) and THF (2 mL). The reaction vessel was then cooled to -78 °C, and a solution of *n*-BuLi (2.2 M in hexanes, 932 μL, 2.03 mmol) was added. The LiOBn solution was added dropwise *via* syringe to a second flask containing cycloadduct **11** (1.00 g, 2.03 mmol) in THF (17 mL) at -78 °C. The reaction was stirred at -78 °C for 30 min, diluted with 20 mL of sat'd NH<sub>4</sub>Cl, and extracted with CH<sub>2</sub>Cl<sub>2</sub> (4 X 25 mL). The combined organic layers were washed with sat'd aq NaHCO<sub>3</sub>, sat'd aq NaCl (100 mL), dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. The resulting solid was dissolved in PhMe (20 mL) and cooled to 0 °C and a solution of TMS-diazomethane (2M in hexanes, 1.22 mL, 2.44 mmol) and MeOH (2 mL), were added. The reaction was stirred at 0 °C for 30 min before another portion of TMS-diazomethane (2M in hexanes, 0.61 mL, 1.22 mmol) was added, and the reaction stirred at 0 °C for an additional 30 min. The reaction was concentrated *in vacuo* to afford a mix of compounds **13** and **14** in a 6:1 ratio (as judged by the unpurified <sup>1</sup>H-NMR). The reaction mixture was purified by flash column chromatography on silica gel (gradient elution: 20% → 100% EtOAc in hexanes) to afford pure **13** (599 mg, 48% yield) and **14** (186 mg, 15% yield) as amorphous solids. The structure of products **13** and **14** were validated using HSQC and HMBC NMR correlations: **13** TLC (60% EtOAc in hexanes) R<sub>f</sub>: 0.49 (UV, CAM); IR (film, cm<sup>-1</sup>) 2972, 1779, 1726, 1680, 1636, 1451, 1369, 1310, 1256, 1155, 1082, 949, 733; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.06 (d, *J* = 7.4 Hz, 1H), 7.76 (s, 1H), 7.74 (d, 1H), 7.34 (m, 5H), 7.21 (m, 2H), 5.06 (d, *J* = 12.1 Hz, 1H), 4.99 (d, *J* = 12.1 Hz, 1H), 3.75 (s, 3H), 3.53 (d, *J* = 14.4 Hz, 1H), 3.49 (d, *J* = 11.0 Hz, 1H), 3.45 (m, 1H), 3.29 (d, 1H), 3.28 (m, 1H), 3.27 (s, 3H), 3.21 (d, *J* = 11 Hz, 1H), 2.82 (m, 1H), 1.92 (m, 3H), 1.63 (s, 9H); <sup>13</sup>C NMR (400 MHz, CDCl<sub>3</sub>) δ 170.0, 169.4, 169.2, 132.1, 132.0,

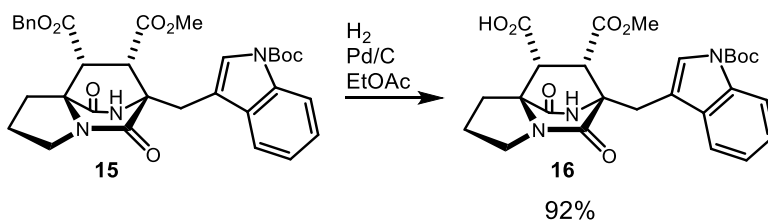
131.9, 128.6, 128.4, 126.0, 123.6, 121.9, 120.4, 116.2, 114.7, 68.5, 67.1, 64.9, 54.8, 53.9, 51.6, 49.6, 43.5, 28.9, 28.2, 27.4, 24; exact mass calc'd for C<sub>34</sub>H<sub>38</sub>N<sub>3</sub>O<sub>8</sub> [M + H]<sup>+</sup> 616.2653, found 616.2646. **14**: TLC (80% EtOAc in hexanes) R<sub>f</sub>: 0.59 (UV, CAM); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.07 (d, *J* = 6.9 Hz, 1H), 7.74 (s, 1H), 7.69 (d, *J* = 7.9 Hz, 1H), 7.25 (m, 7H), 5.01 (d, *J* = 12.1 Hz, 1H), 4.72 (d, *J* = 12.5 Hz, 1H), 3.76 (s, 3H), 3.56 (d, *J* = 14.8 Hz, 1H), 3.54 (d, *J* = 11.1 Hz, 1H), 3.45 (m, 1H), 3.38 (s, 3H), 3.29 (m, 1H), 3.25 (d, *J* = 14.8 Hz, 1H), 3.17 (d, *J* = 11.1 Hz, 1H), 2.83 (m, 1H), 1.92 (m, 3H), 1.63 (s, 9H); <sup>13</sup>C NMR (400 MHz, CDCl<sub>3</sub>) δ 170.2, 170.0, 169.7, 169.1, 149.9, 135.1, 132.2, 128.5, 128.4, 126.0, 123.6, 121.9, 120.6, 116.2, 114.7, 83.0, 68.5, 66.9, 64.9, 54.9, 53.6, 51.8, 49.9, 43.5, 28.8, 28.2, 27.4, 24.5.



**8-Benzyl 7-methyl (6S\*,7R\*,8S\*,8aS\*)-6-((1-(tert-butoxycarbonyl)-1H-indol-3-yl)methyl)-5,9-dioxohexahydro-1H-6,8a-(epiminomethano)indolizine-7,8-dicarboxylate. (15)**

A dry reaction flask was charged with lactim ether **13** (261 mg, 0.424 mmol) and flushed with N<sub>2</sub> gas for 10 min, dissolved in CH<sub>2</sub>Cl<sub>2</sub> (2.1 mL), and cooled to 0 °C. To the reaction flask was added *p*TsOH·H<sub>2</sub>O (85 mg, 0.446 mmol), and the reaction was stirred for 7 h at 0 °C. The reaction mixture was diluted with sat'd aq NaHCO<sub>3</sub> (10 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (4 X 10 mL). The combined organic layers were washed with sat'd aq NaCl (40 mL), dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. The resulting product was dissolved in toluene (2.1 mL) and stirred at 80 °C for 18 h. The solution was concentrated *in vacuo* to afford lactam **15** as a white solid. The unpurified product was

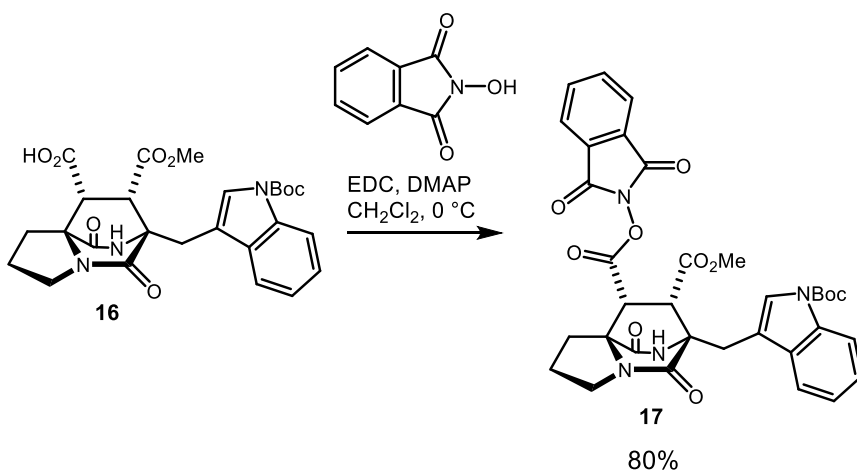
purified by flash column chromatography on silica gel (gradient elution: 40% → 100% EtOAc in hexanes) to afford pure lactam **15** as a yellow oil (195 mg, 77% yield): TLC (60% EtOAc in hexanes) R<sub>f</sub>: 0.47 (UV, CAM); IR (film, cm<sup>-1</sup>) 2986, 2244, 1695, 1458, 1368, 1257, 1153, 1079, 907, 726; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.11 (d, *J* = 7.9 Hz, 1H), 7.68 (s, 1H), 7.66 (d, *J* = 3.6 Hz, 1H), 7.31 (m, 8H), 5.98 (s, 1H), 5.12 (d, *J* = 12.1 Hz, 1H), 5.08 (d, *J* = 12.1 Hz, 1H), 3.67 (d, *J* = 14.5 Hz, 1H), 3.56 (m, 1H), 3.44 (m, 1H), 3.40 (s, 3H), 3.35 (d, *J* = 8.2 Hz, 1H), 3.33 (d, *J* = 14.5 Hz, 1H), 2.79 (m, 1H), 1.97 (m, 1H), 1.85 (m, 1H), 1.67 (s, 9H); <sup>13</sup>C NMR (400 MHz, CDCl<sub>3</sub>) δ 169.1, 169.0, 168.4, 167.2, 149.5, 135.1, 134.8, 131.0, 128.7, 128.6, 126.9, 124.6, 122.9, 118.7, 115.3, 112.8, 83.7, 68.0, 67.5, 63.2, 52.4, 51.9, 48.6, 44.4, 28.4, 28.2, 24.3, 23.4; MASS SPEC SAMPLE NEEDS TO BE SUBMITTED.



**(6S\*,7R\*,8S\*,8aS\*)-6-((1-(tert-butoxycarbonyl)-1H-indol-3-yl)methyl)-7-(methoxycarbonyl)-5,9-dioxohexahydro-1H-6,8a-(epiminomethano)indolizine-8-carboxylic acid. (16)**

Lactam **15** (364 mg, 0.607 mmol) was dissolved in EtOAc (6 mL) at rt, and 10% Pd/C (65 mg) was added. One balloon of H<sub>2</sub> gas was used to sparge the reaction mixture for 10 min, and another balloon of H<sub>2</sub> gas was left above the reaction to maintain an atmosphere of H<sub>2</sub>. The reaction mixture was stirred at rt for 1 h before the reaction mixture was filtered through Celite, and the filter pad was washed with EtOAc (3 X 10 mL). The filtered solution was then concentrated *in vacuo* to afford carboxylic acid **16** (285 mg, 92% yield) as a white solid that was used without further purification: TLC (5% MeOH in CHCl<sub>3</sub> with 1% AcOH) R<sub>f</sub>: 0.22 (UV, CAM); IR (film, cm<sup>-1</sup>) 3366, 2970, 2891, 1736, 1680, 1453, 1368,

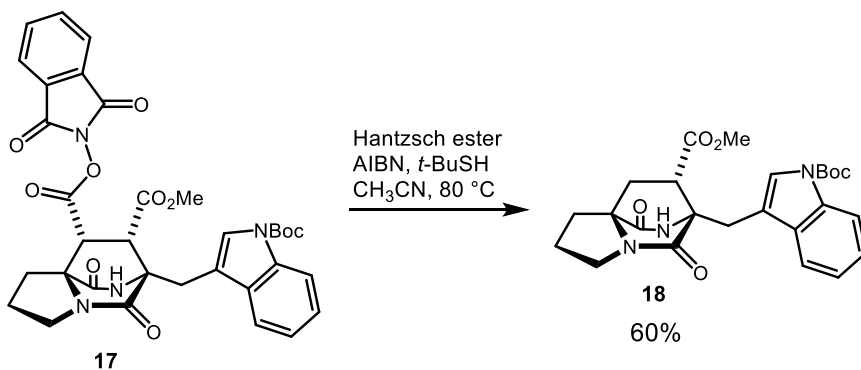
1309, 1257, 1158, 1128, 1081, 949, 816, 747;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.10 (d,  $J=7.8$  Hz, 1H), 7.69 (d,  $J=7.4$  Hz, 1H), 7.67 (s, 1H), 7.29 (m, 2H), 6.57 (s, 1H), 6.57 (s-broad, 1H), 3.68 (d,  $J=14.8$  Hz, 1H), 3.65 (s, 3H), 3.51 (m, 2H), 3.45 (d,  $J=14.5$  Hz, 1H), 3.40 (d,  $J=11.3$  Hz, 1H), 3.36 (d,  $J=11.4$  Hz, 1H), 2.77 (m, 1H), 2.00 (m, 3H), 1.67 (s, 9H);  $^{13}\text{C}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  169.6, 167.3, 149.6, 135.1, 131.1, 126.9, 124.5, 122.8, 119.0, 115.3, 113.0, 83.8, 68.2, 63.4, 52.6, 52.3, 48.4, 44.5, 28.3, 28.2, 24.3, 23.6; exact mass calc'd for  $\text{C}_{26}\text{H}_{30}\text{N}_3\text{O}_8$   $[\text{M} + \text{H}]^+$  512.2027, found 512.2030.



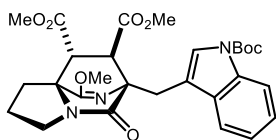
**8-(1,3-dioxoisindolin-2-yl) 7-methyl (6S\*,7R\*,8S\*,8aS\*)-6-((1-(tert-butoxycarbonyl)-1H-indol-3-yl)methyl)-5,9-dioxohexahydro-1H-6,8a-(epiminomethano)indolizine-7,8-dicarboxylate. (17)**

A dry flask was charged with carboxylic acid **16** (100 mg, 0.196 mmol), flushed with  $\text{N}_2$  gas for 10 min, dissolved in  $\text{CH}_2\text{Cl}_2$  (4 mL), and cooled to  $0^\circ\text{C}$ . EDC (56 mg, 0.294 mmol), DMAP (5 mg, 0.039 mmol), and N-hydroxyphthalimide (48 mg, 0.294 mmol) were added to the flask as solids, and the reaction was stirred and allowed to warm to rt over 6 h. The reaction mixture was diluted with 0.1 M HCl (20 mL) and extracted with  $\text{CH}_2\text{Cl}_2$  (3 X 15 mL). The combined organic layers were washed with sat'd aq  $\text{NaHCO}_3$  (25 mL), sat'd aq NaCl (25 mL), dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated *in vacuo* to afford phthalimidoyl ester **17** as a mixture containing excess N-hydroxyl phthalimide and EDC

by-products. The unpurified product was purified by flash column chromatography on silica gel (gradient elution: 10% → 80% EtOAc in hexanes) to afford pure **17** (104 mg, 80% yield) as a white solid: TLC (60% EtOAc in hexanes) *R<sub>f</sub>*: 0.64 (UV, CAM); m.p. 162.4-164.3 °C; IR (film, cm<sup>-1</sup>) 2971, 1814, 1784, 1743, 1700, 1452, 1369, 1257, 1155, 1080, 1017, 977, 911, 877, 729, 695; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.14 (d, *J*= 7.8 Hz, 1H), 7.90 (m, 2H), 7.83 (m, 2H), 7.69 (s, 1H), 7.59 (dd, *J*= 6.7 Hz, 1.2 Hz, 1H), 7.33 (td, *J*= 7.4 Hz, 1.5 Hz, 1H), 7.29 (td, *J*= 7 Hz, 1.2 Hz, 1H), 5.96 (s, 1H), 3.88 (s, 3H), 3.78 (d, *J*= 14.8 Hz, 1H), 3.60 (m, 1H), 3.56 (d, *J*= 5.9 Hz, 1H), 3.48 (m, 1H), 3.47 (d, *J*= 5.8 Hz, 1H), 3.29 (d, *J*= 14.8 Hz, 1H), 2.90 (ddd, *J*= 13.3 Hz, 7.9 Hz, 4.7 Hz, 1H), 2.42 (td, *J*= 14.1 Hz, 8.2 Hz, 1H), 2.15 (m, 1H), 1.96 (m, 1H), 1.67 (s, 9H); <sup>13</sup>C NMR (400 MHz, CDCl<sub>3</sub>) δ 170.0, 169.3, 167.4, 166.3, 149.5, 135.2, 135.1, 134.2, 130.9, 128.7, 127.1, 124.7, 124.2, 123.4, 123.1, 118.3, 115.5, 112.3, 83.9, 68.5, 63.6, 52.9, 50.7, 47.8, 45.1, 28.2, 26.6, 24.1, 23.2; exact mass calc'd for C<sub>34</sub>H<sub>33</sub>N<sub>4</sub>O<sub>10</sub> [M + H]<sup>+</sup> 657.2191, found 657.1828.



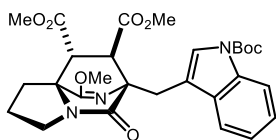
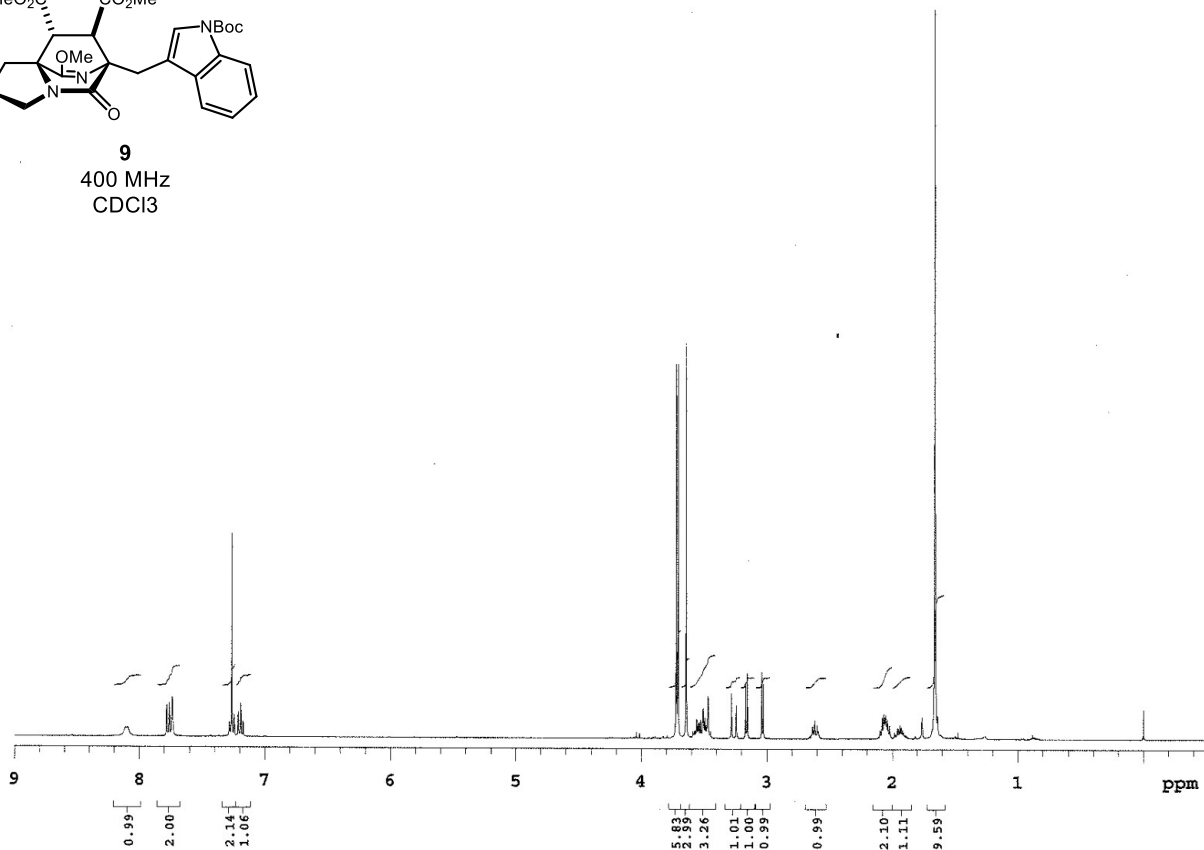
(10 mL) and extracted with  $\text{CH}_2\text{Cl}_2$  (3 X 10 mL). The combined organic layers were washed with sat'd aq NaCl (20 mL), dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated *in vacuo* to give decarboxylated product **18**. The product was purified by flash column chromatography on silica gel (gradient elution: 20% → 100% EtOAc in hexanes) to afford pure **18** (15 mg, 60% yield) as a colorless oil. The structure of **18** was validated by comparison to known material: TLC (80% EtOAc in hexanes) R<sub>f</sub>: 0.46 (UV, CAM); IR (film,  $\text{cm}^{-1}$ ) 2978, 1786, 1745, 1733, 1452, 1370, 1256, 1159, 1084;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.13 (d,  $J$ = 7.9 Hz, 1H), 7.64 (s, 1H), 7.57 (dd,  $J$ = 7.1 Hz, 1.2 Hz, 1H), 7.32 (td,  $J$ = 7.1 Hz, 1.2 Hz, 1H), 7.27 (td,  $J$ = 7.4 Hz, 1.2 Hz, 1H), 5.83 (s, 1H), 3.76 (s, 3H), 3.70 (d,  $J$ = 14.9 Hz, 1H), 3.51 (d,  $J$ = 15.2 Hz, 1H), 3.51 (m, 1H), 3.15 (d,  $J$ = 14.9 Hz, 1H), 3.05 (dd,  $J$ = 10.4 Hz, 4.9 Hz, 1H), 2.73 (dt,  $J$ = 13.3 Hz, 6.7 Hz, 1H), 2.28 (dd,  $J$ = 13.5 Hz, 10.3 Hz, 1H), 2.18 (dd,  $J$ = 13.7 Hz, 5.1 Hz, 1H), 2.00 (m,  $J$ = 7.0 Hz, 2H), 1.80 (dt,  $J$ = 13.3 Hz, 7.0 Hz, 1H), 1.67 (s, 9H);  $^{13}\text{C}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  171.9, 171.6, 167.2, 131.0, 126.8, 124.7, 123.0, 118.3, 115.5, 112.9, 83.8, 66.7, 63.9, 53.4, 52.3, 46.0, 44.3, 36.1, 28.9, 28.2, 24.3, 23.5; exact mass calc'd for  $\text{C}_{25}\text{H}_{30}\text{N}_3\text{O}_6$   $[\text{M} + \text{H}]^+$  468.2129, found 468.2127.



**9**

400 MHz

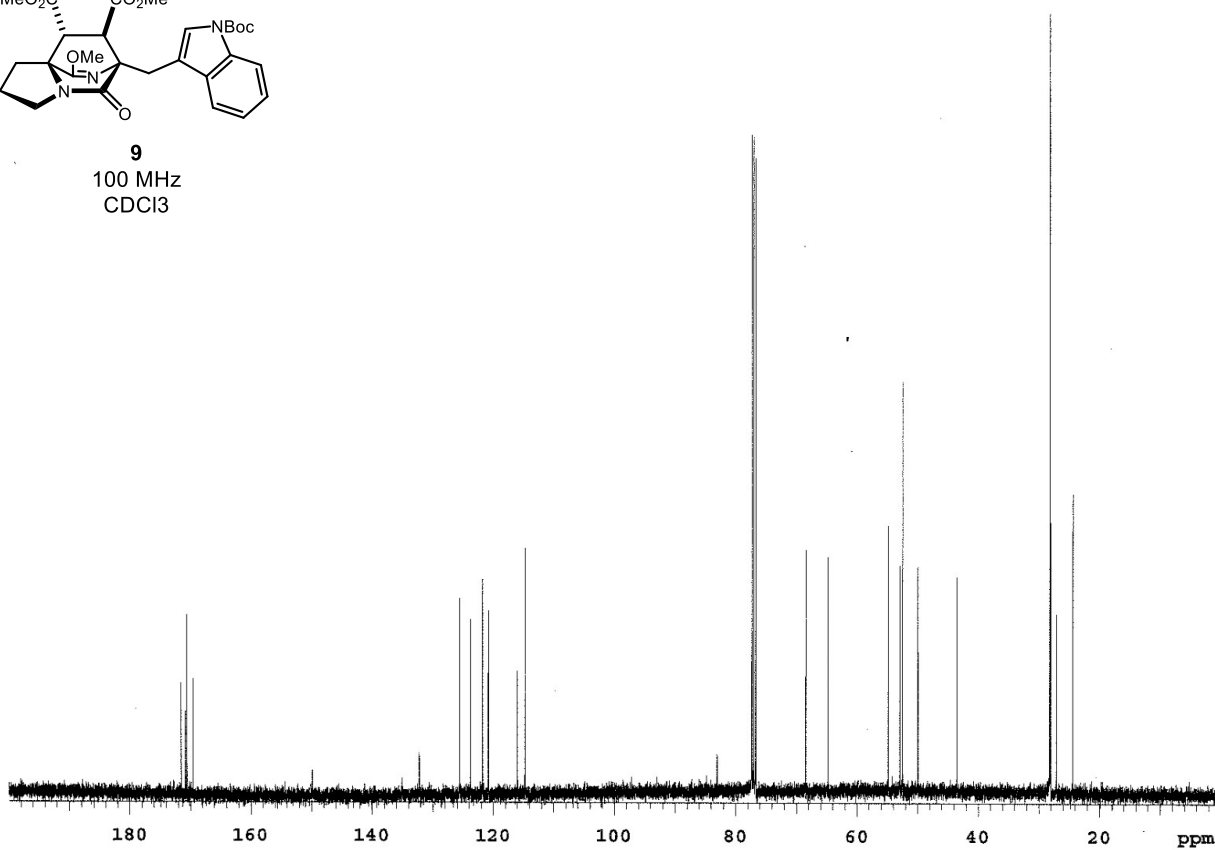
CDCl<sub>3</sub>

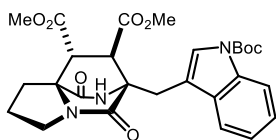


**9**

100 MHz

CDCl<sub>3</sub>

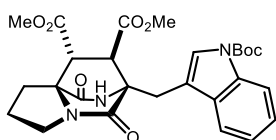
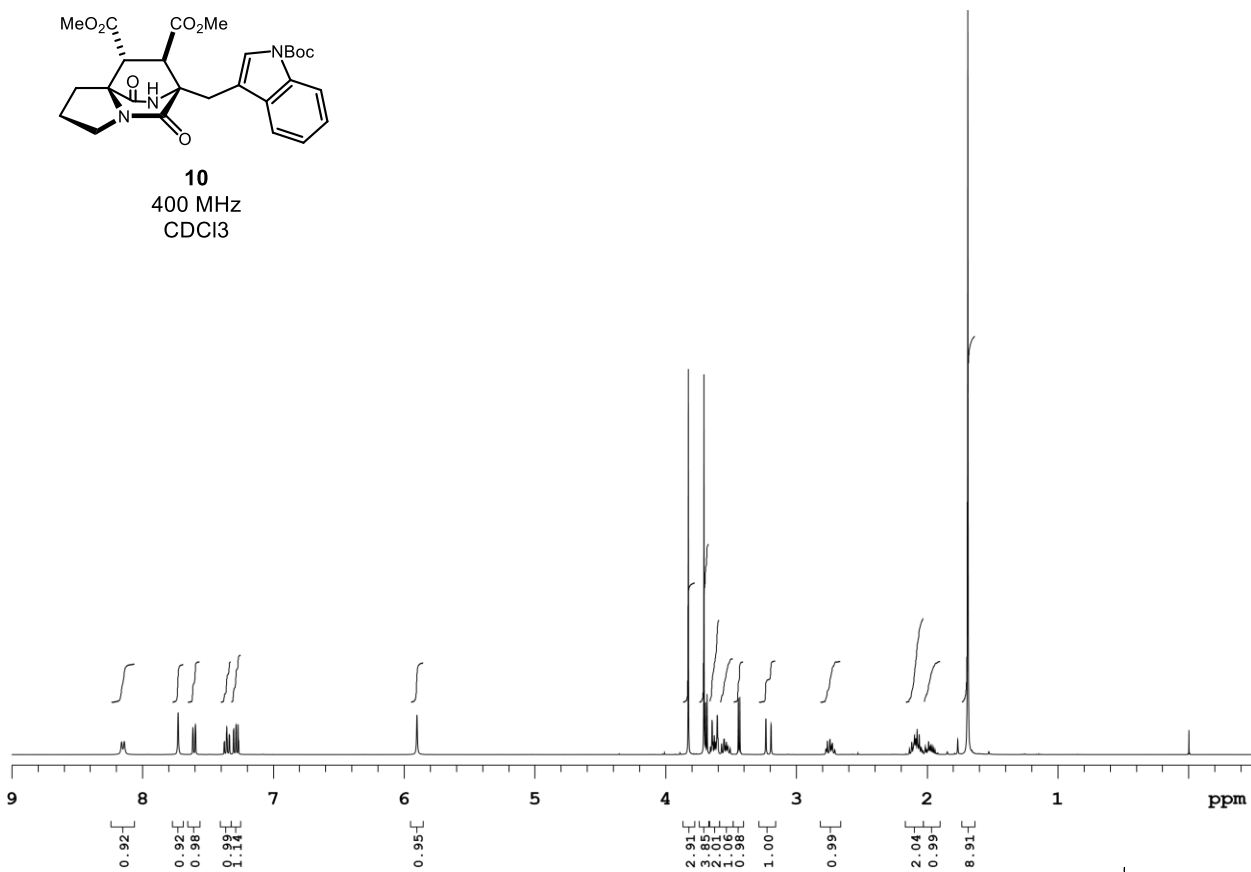




**10**

400 MHz

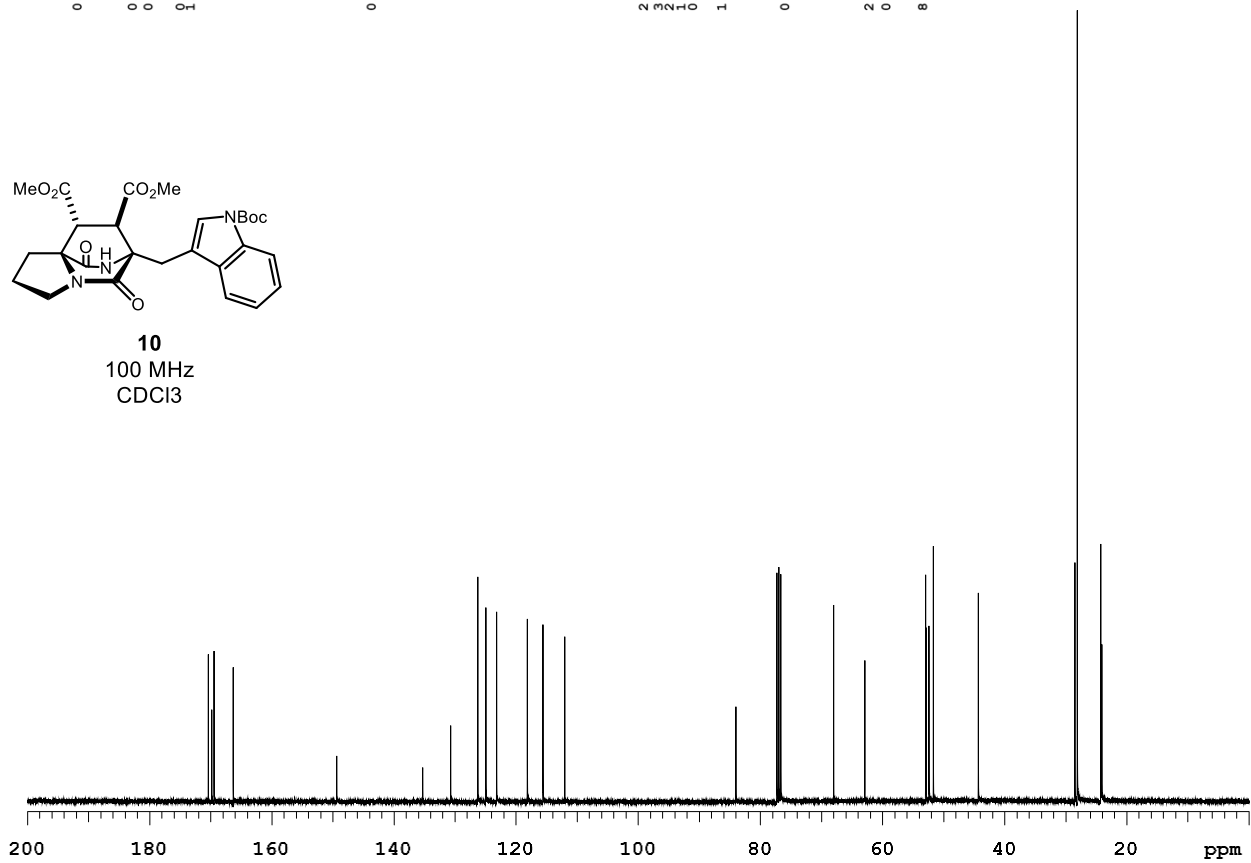
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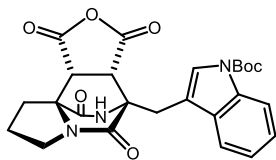


**10**

100 MHz

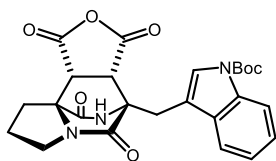
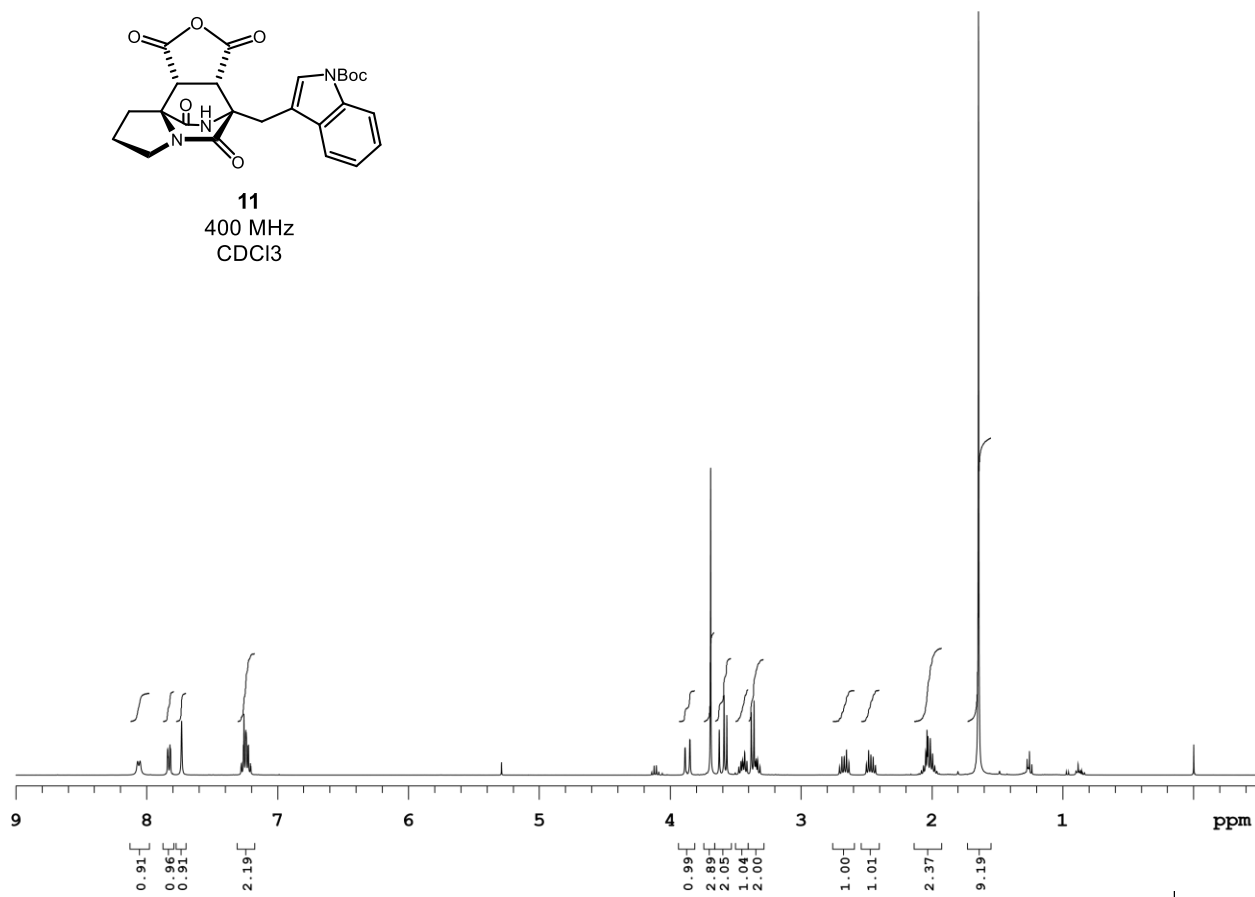
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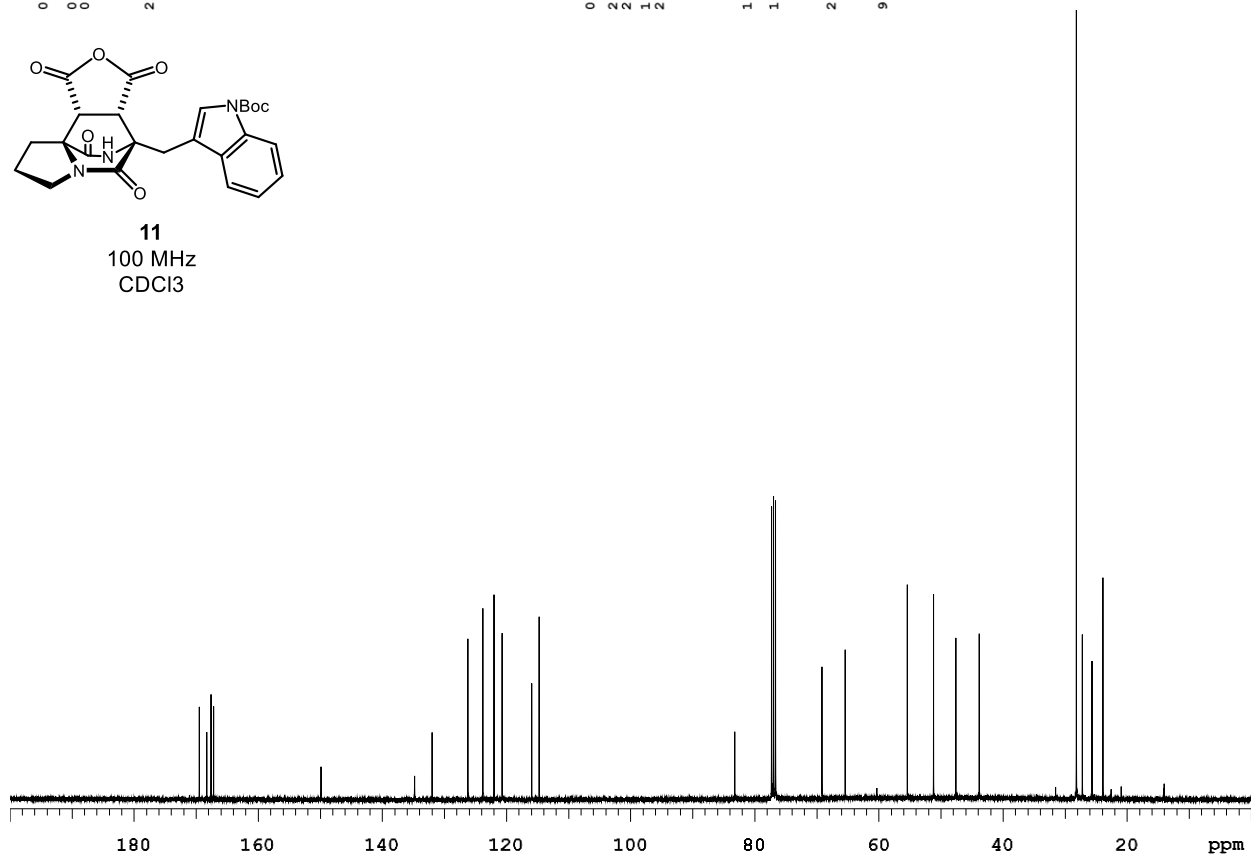
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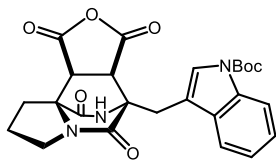
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CDCl<sub>3</sub>



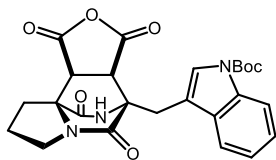
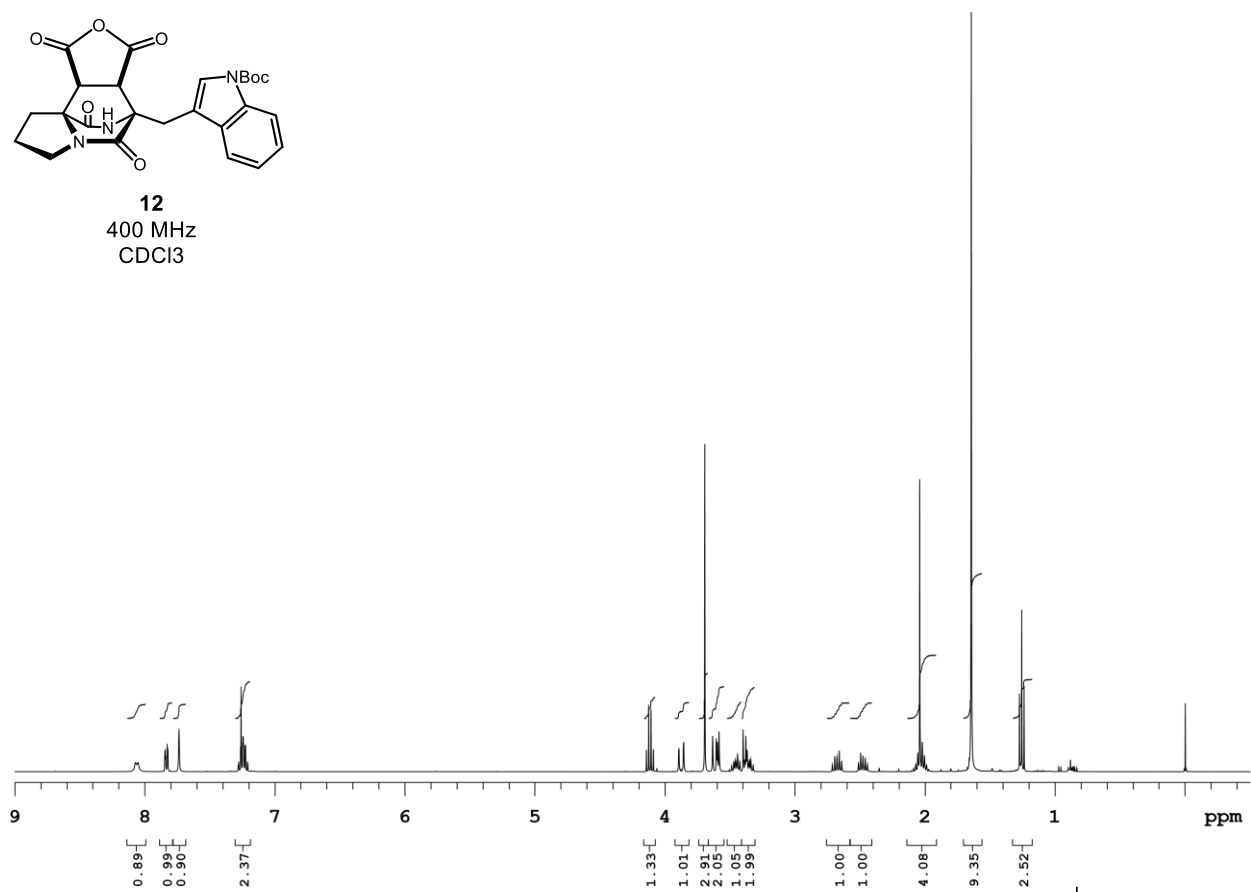
11

100 MHz  
CDCl<sub>3</sub>

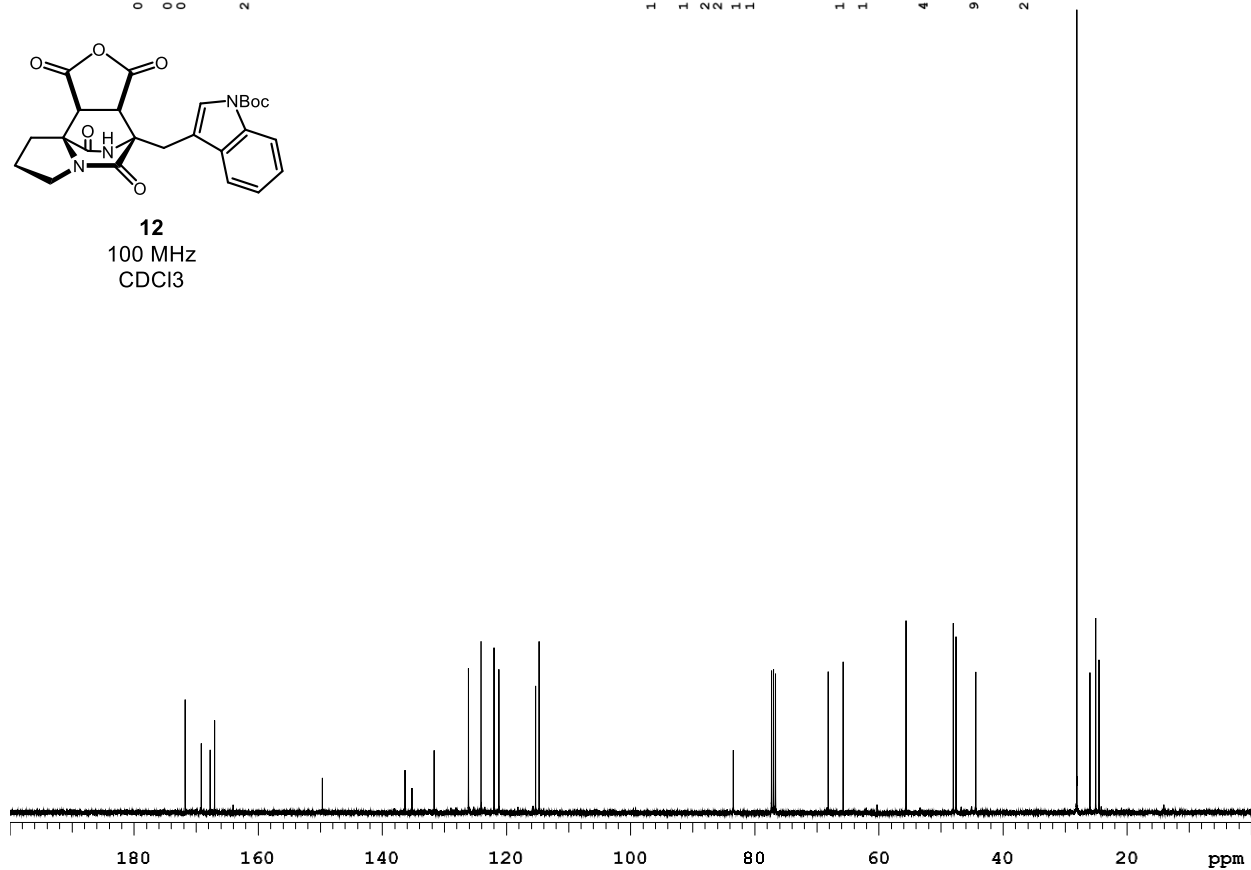


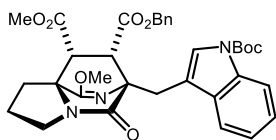


**12**  
400 MHz  
CDCl<sub>3</sub>



**12**  
100 MHz  
CDCl<sub>3</sub>

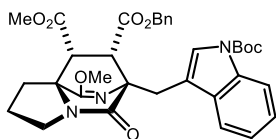
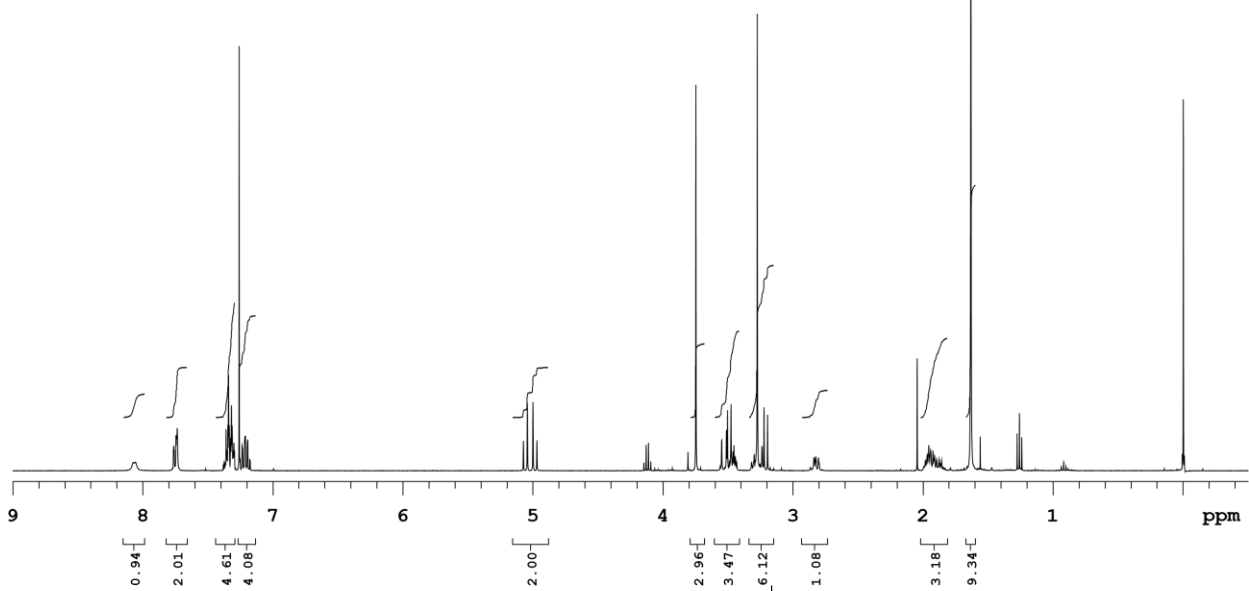




**13**

400 MHz

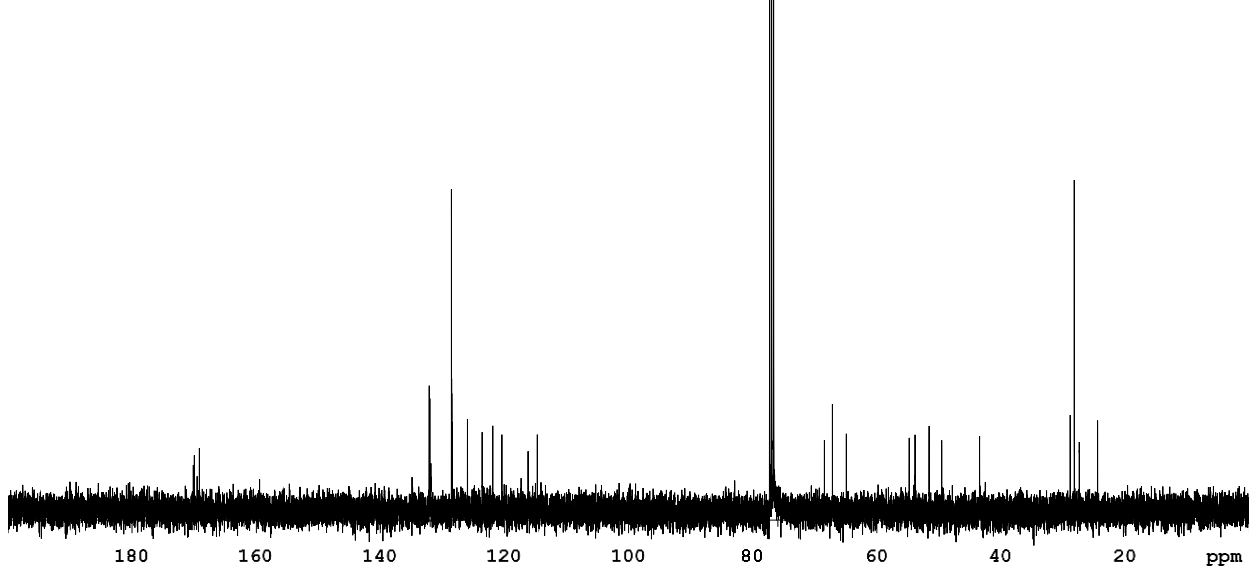
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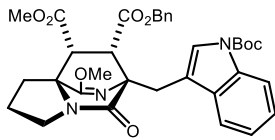


**13**

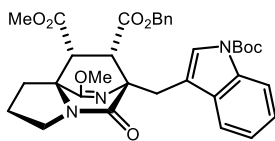
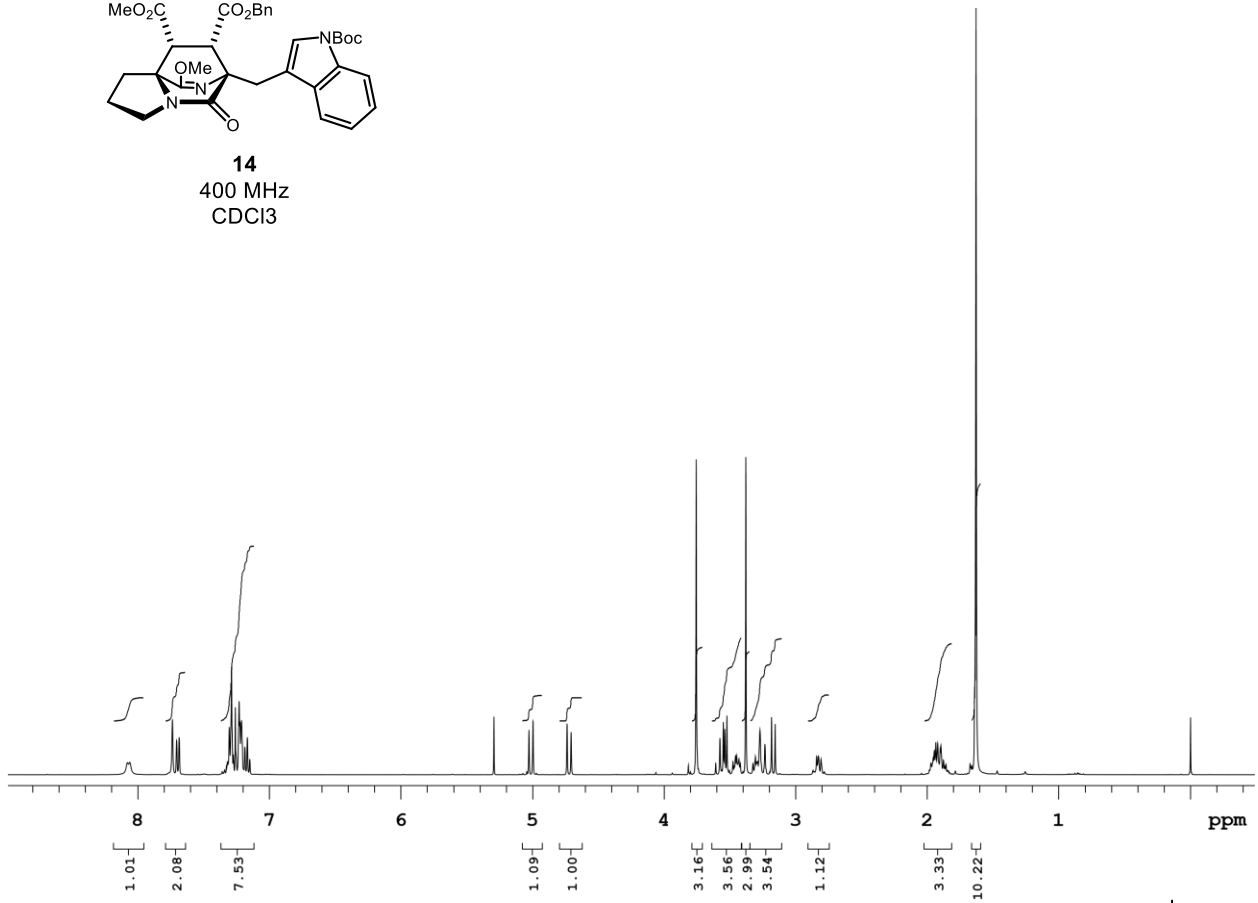
100 MHz

CDCl<sub>3</sub>

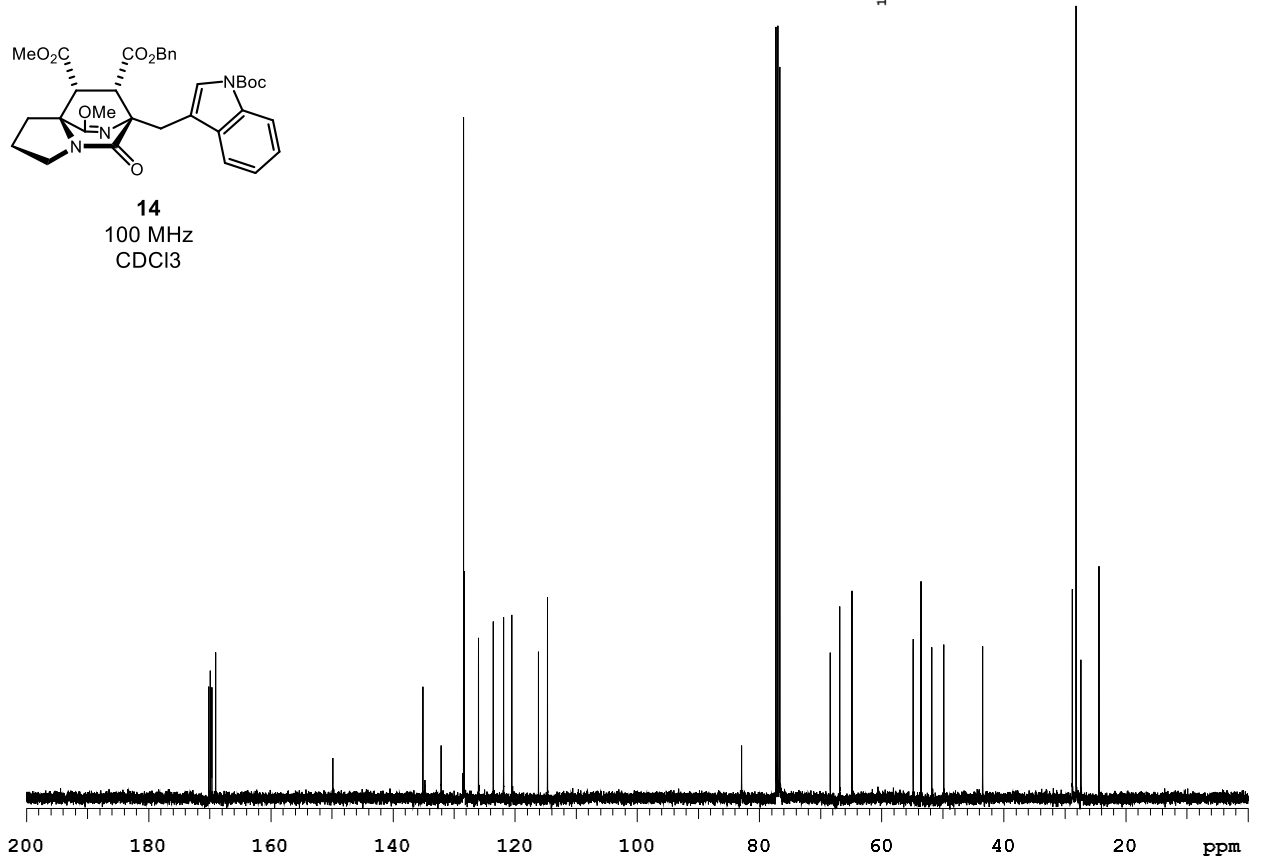


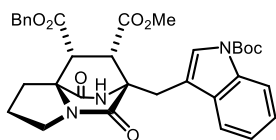


**14**  
400 MHz  
CDCl<sub>3</sub>

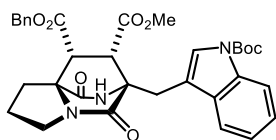
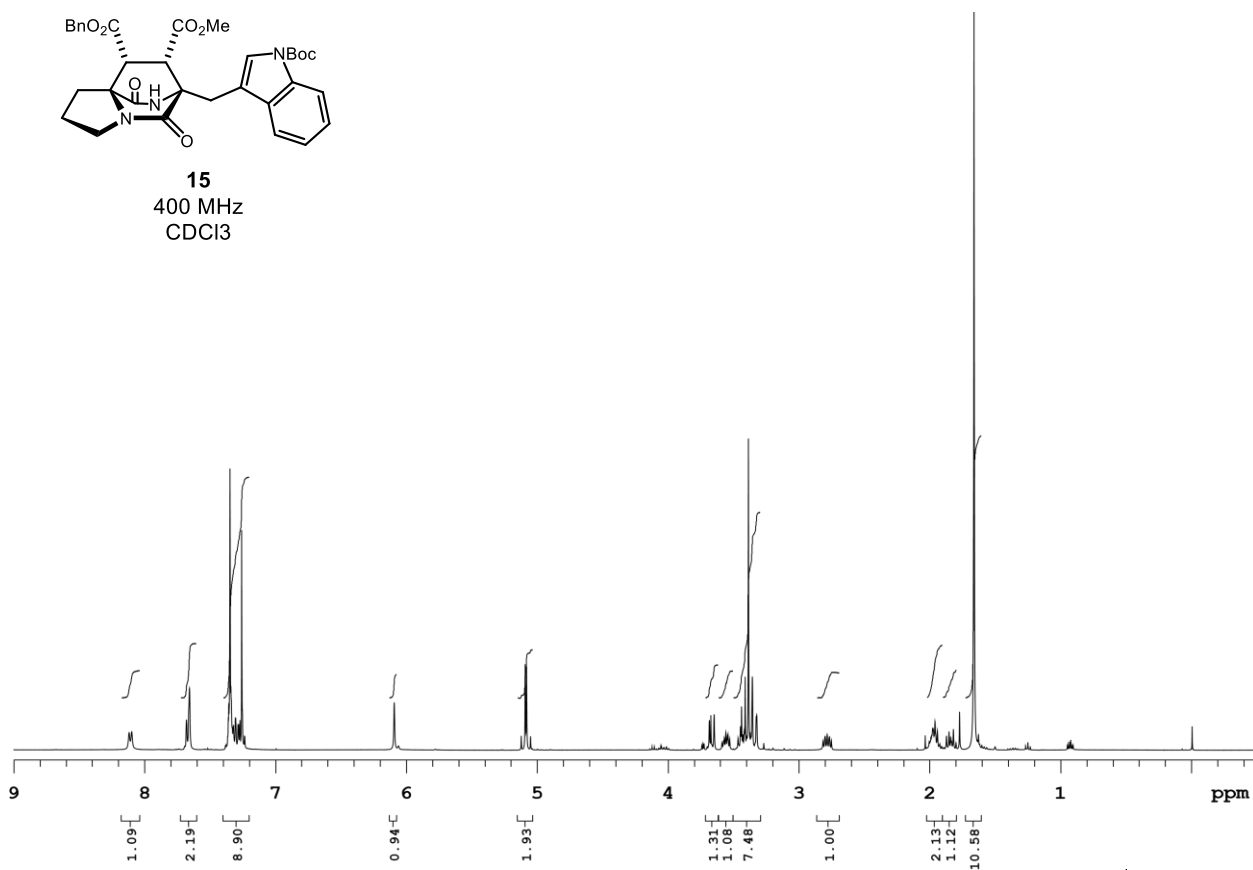


**14**  
100 MHz  
CDCl<sub>3</sub>

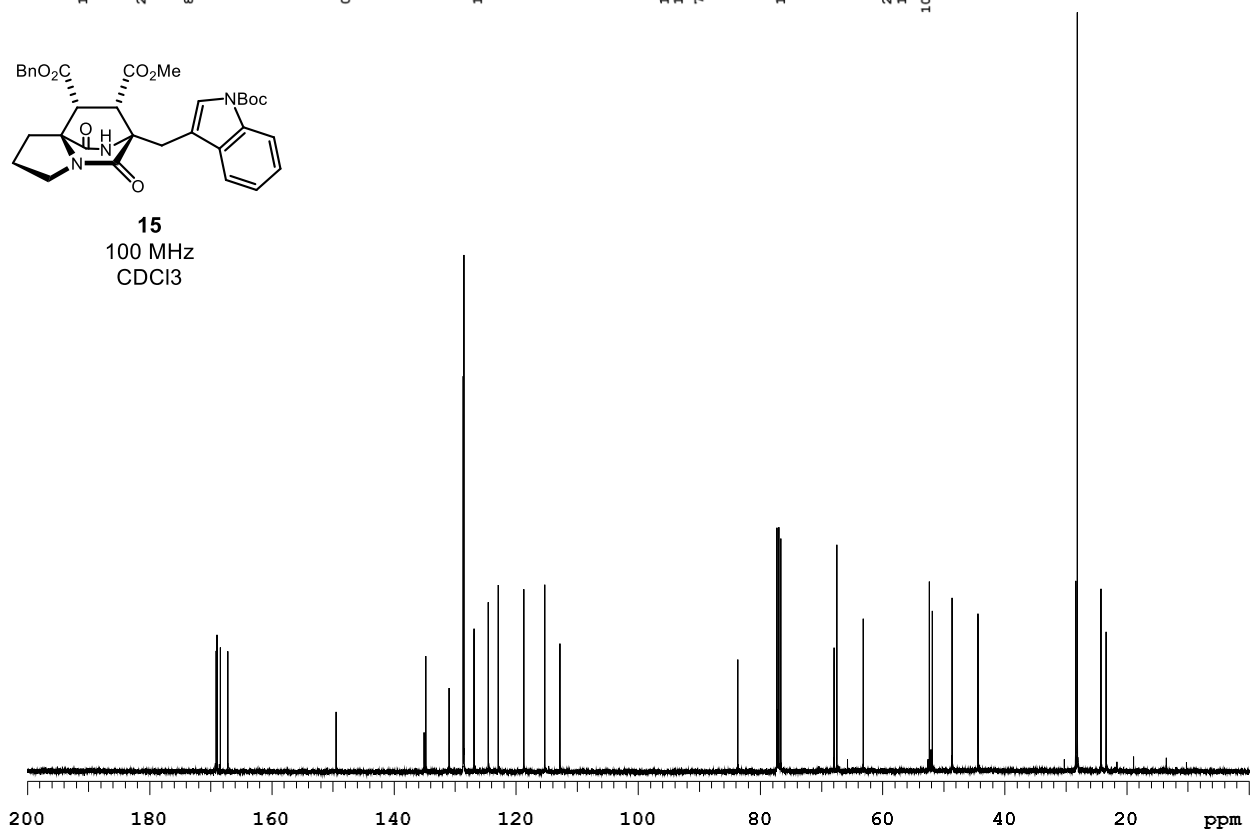


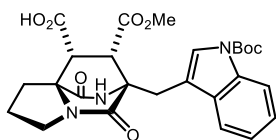


**15**  
400 MHz  
CDCl<sub>3</sub>

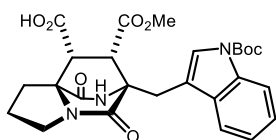
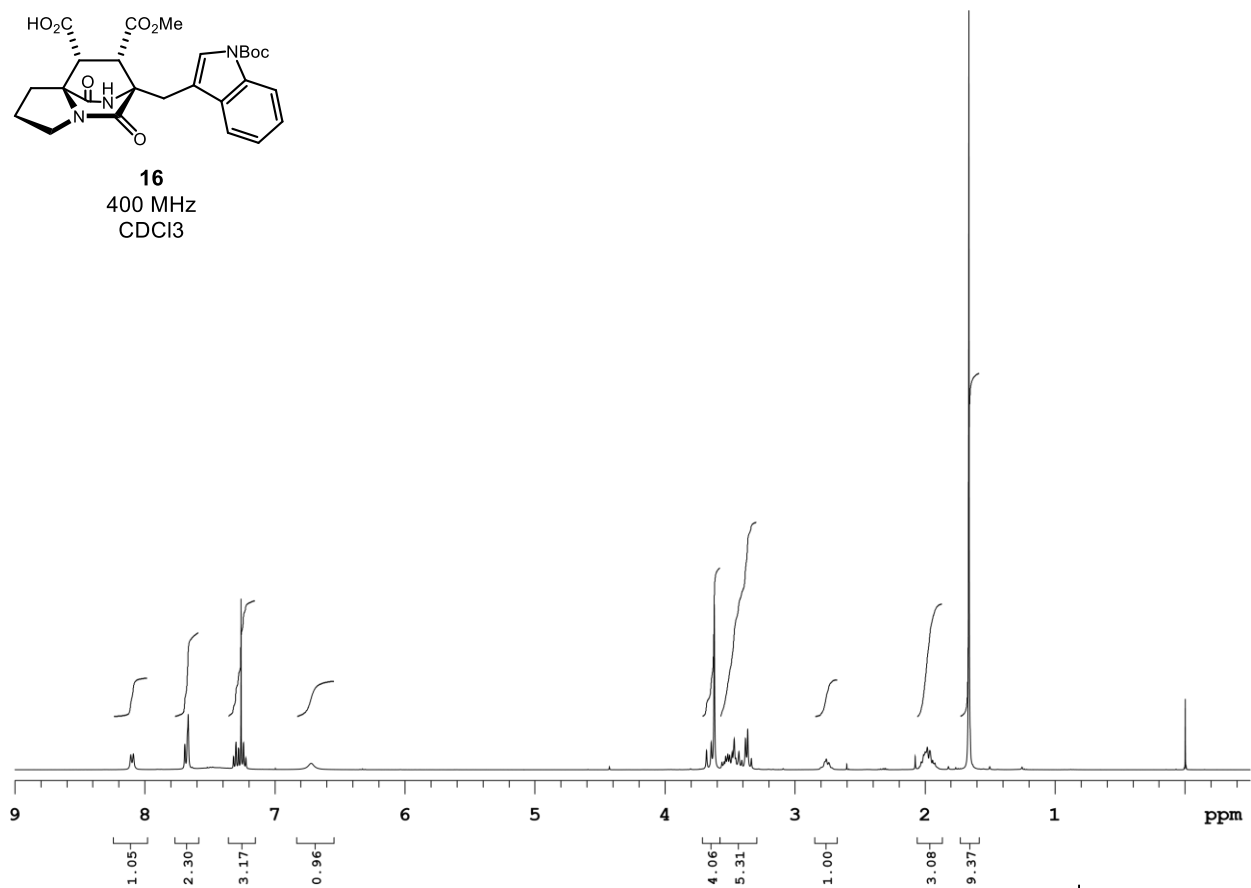


**15**  
100 MHz  
CDCl<sub>3</sub>

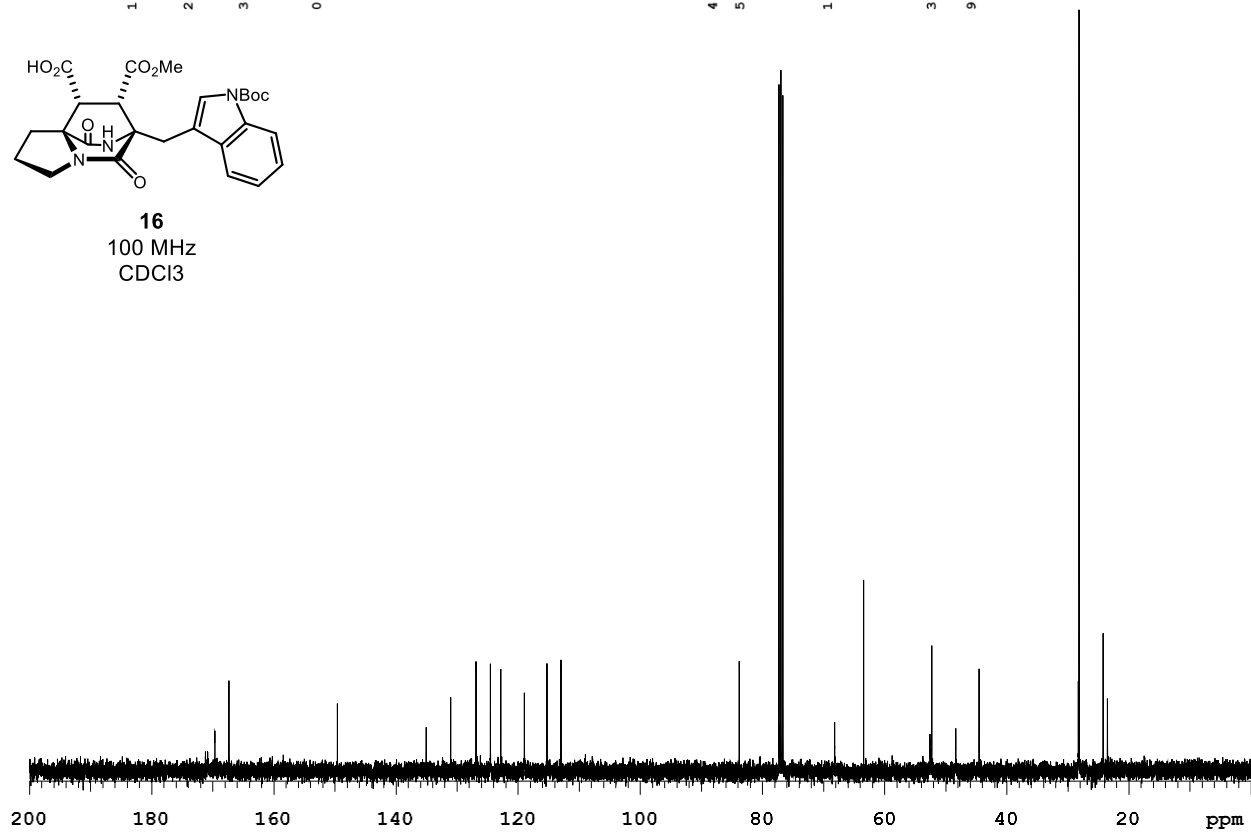


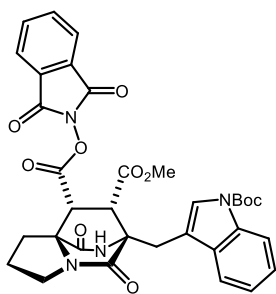


**16**  
400 MHz  
CDCl<sub>3</sub>

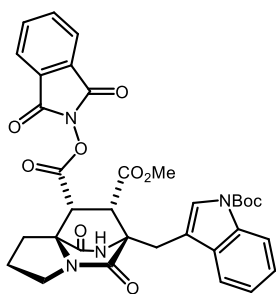
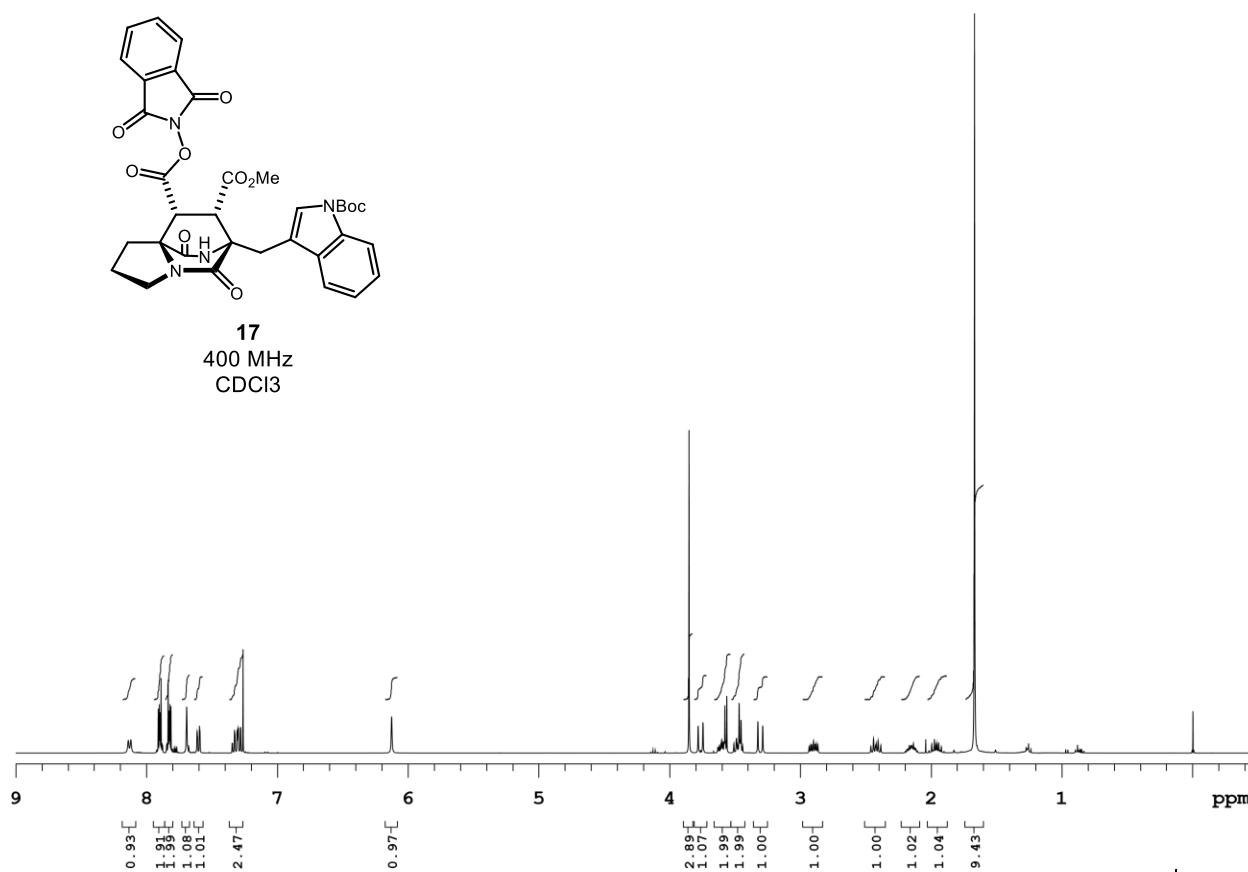


**16**  
100 MHz  
CDCl<sub>3</sub>

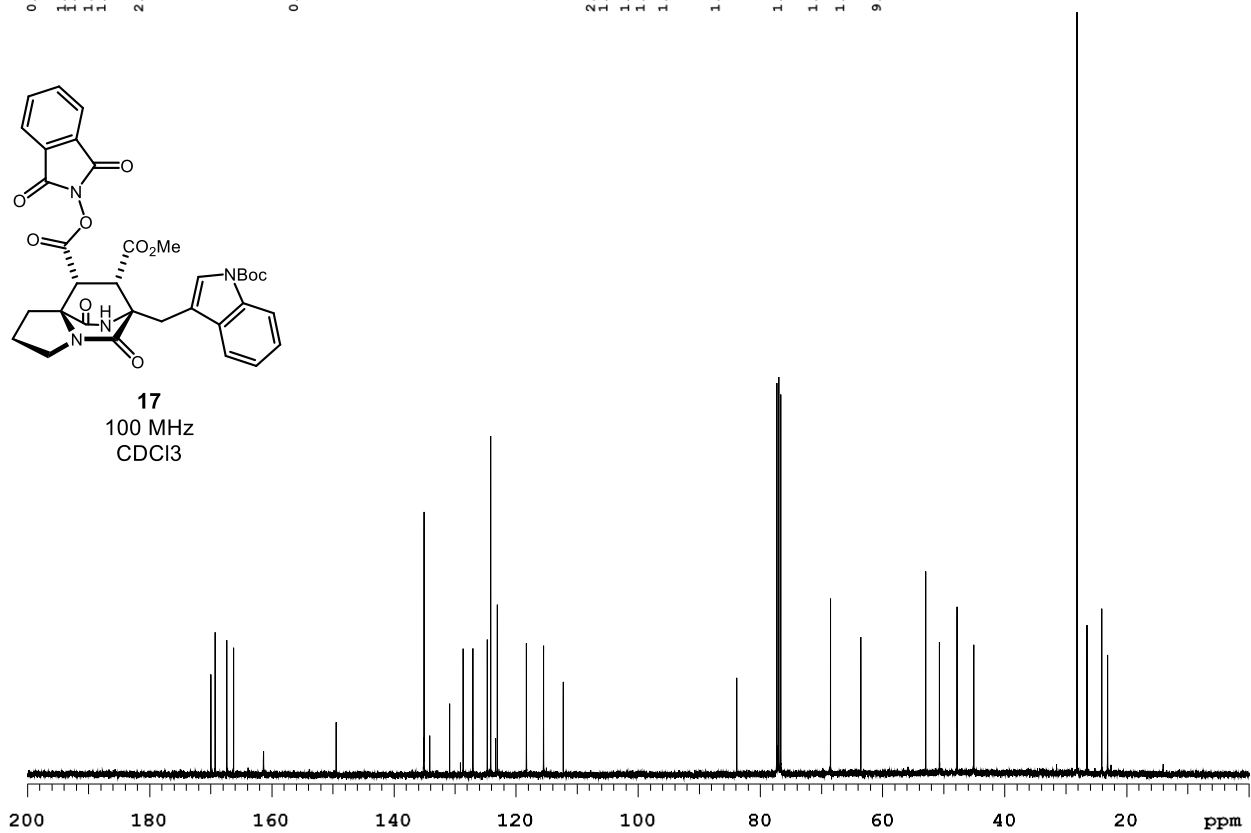


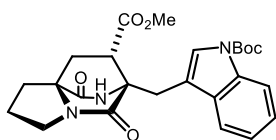


**17**  
400 MHz  
CDCl<sub>3</sub>

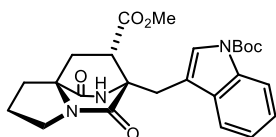
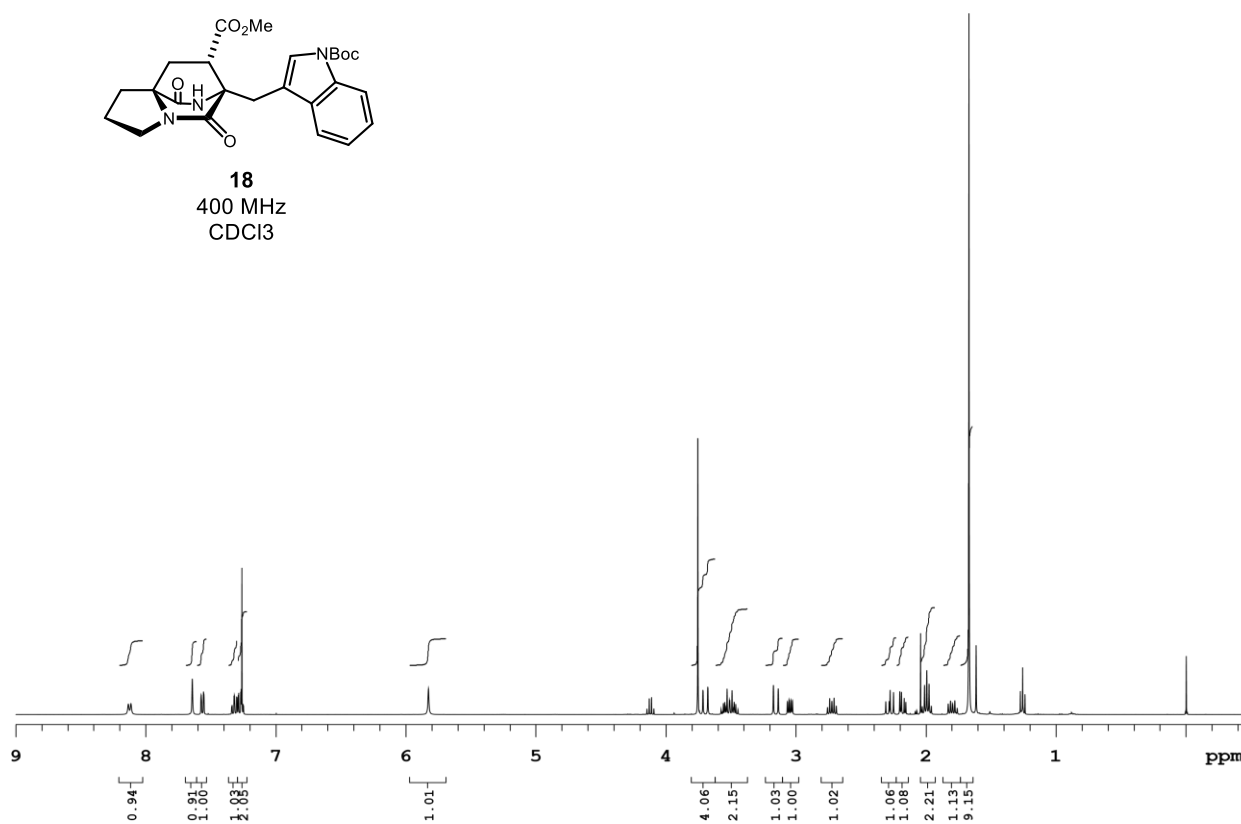


**17**  
100 MHz  
CDCl<sub>3</sub>

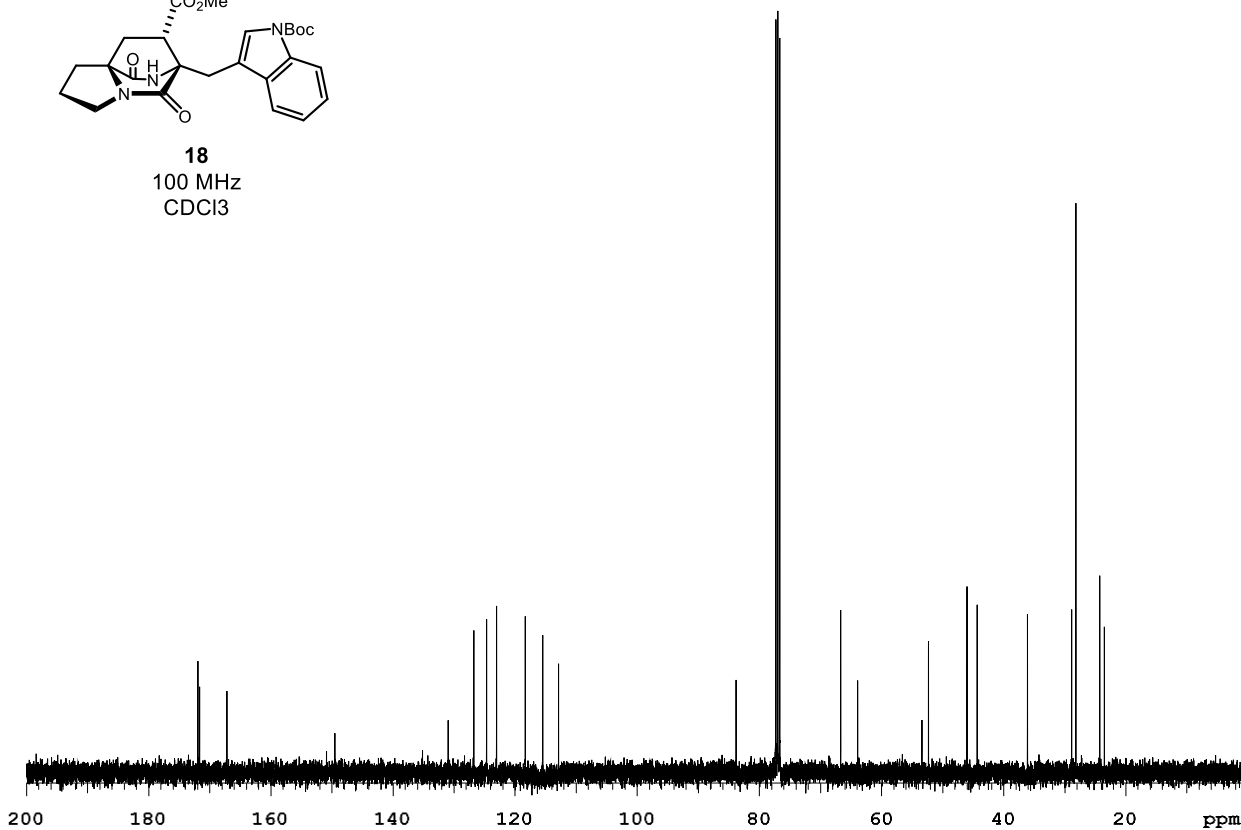




**18**  
400 MHz  
 $\text{CDCl}_3$



**18**  
100 MHz  
 $\text{CDCl}_3$



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