Part A: Progress towards the Total Synthesis of (±)-Communesin F;

Part B: Aluminum as a Catalyst for the Diels-Alder Cycloaddition of Highly Hindered Dienophiles.

By

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A thesis submitted to the Faculty of Graduate Studies and Postdoctoral Studies in partial fulfillment of the requirements for the degree of Master of Science (M.Sc.) in chemistry

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For Sassy, Taku and Bear…

Table of Content

Table of Figures

Table of Schemes

Table of Tables

Abstract

This is a thesis in two parts. Part A examines two potential routes towards the synthesis of the communesin family of alkaloids, as well as an overview of some of the successful synthetic routes to date. Our first proposed route involves the gold catalyzed isomerization of an *o*-amino aryallene to a vinyl imine and subsequent (formal) cycloaddition with an indole. This would have allowed quick access to the pentacyclic core of the communesins; however, the unexpected 5-*endo-dig* product was exclusively obtained in good to excellent yields. The second route involves the use of a Meerwein- Eschenmoser Claisen rearrangement. This route was successful in affording the C, D, E and F rings of the communesin alkaloids, however future work is required for completion of the synthesis. Also discussed in these sections is an alternative endgame approach involving a novel Pictet-Spangler reaction to afford the G ring, and the possibility of an asymmetric variation to the proposed route.

Part B examines the use of alkyl aluminum sesquichlorides in the catalysis of Diels-Alder cycloadditions of sterically hindered systems, a current obstacle in organic chemistry. Previously developed methods are discussed and preliminary results are presented. Ethyl aluminum sesquichloride is compared to other alkyl aluminum catalyst, and the effects of temperature, catalysts loading, choice of solvent, the use of additives, and the use of chiral oxazolidinones are reported and what these result can tell us about the mechanism of catalysis are discussed.

Acknowledgements

First and foremost, I would like to thank Dr. Louis Barriault for taking me into his lab as a co-op student, as an honors student, and finally for my graduate studies. It has been an honor and privilege working under you for these past few years. You have been a source of encouragement; your door has always been open to me; and you`ve challenged me to be a better chemist and person. For this I wish to express my humblest of gratitude.

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A handful of professors have left an indelible mark on me throughout these past few years. Some of which I have had privilege of learning from in a formal manner, and many others I have not. All, however, have been open to questions and discussion, and eager to share their knowledge, opinions and stories. For this, I am grateful.

I would like to thank NSERC and the Telfer School of Management for allowing me to take part in the CREATE program (Collaborative Research and Training Experience Program). It has been an eye opening experience to be able to take part in something so fundamentally different than what I've been doing for so long.

Finally, I would like to thank my parents, my sister and my close friends. You`re the ones who are my constant, and no amount of thanks is enough for the support you`ve given me.

Is she weird?

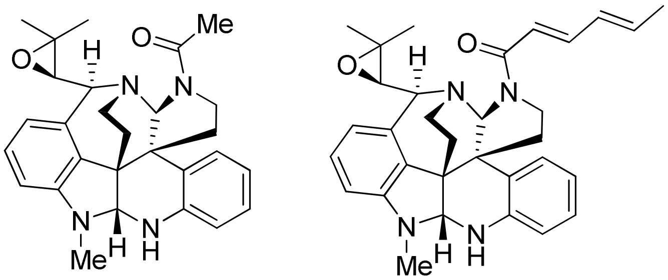
Part A: Progress towards the Total Synthesis of (±) Communesin F.

Chapter 1: An Introduction to Communesin Alkaloids

Introduction

The first of the communesin alkaloids, communesin A (**1.1**) and communesin B (**1.2**),[1] were isolated in 1993 by Numata and coworkers from a strain of *Penicillium* sp. found in a marine alga *Enteromorpha intestinalis*.[1] At the time, the structure was determined by spectroscopic analysis although the configuration about C21 and the absolute stereochemistry were still unknown. Early results showed that these alkaloids showed cytotoxicity towards the P-388 lymphocytic leukemia test systems with an ED_{50} of 3.5 and 0.45 ug mL^{-1}, respectively (Figure 1).[2]

Figure 1: ***Structure of communesin A and B***



1.1
communesin A

1.2
communesin B

In recent years, several other communesin alkaloids have been isolated. Communesin C (**1.3**) and communesin D (**1.4**) were isolated by Proksch and coworkers in 2004 from a fungus

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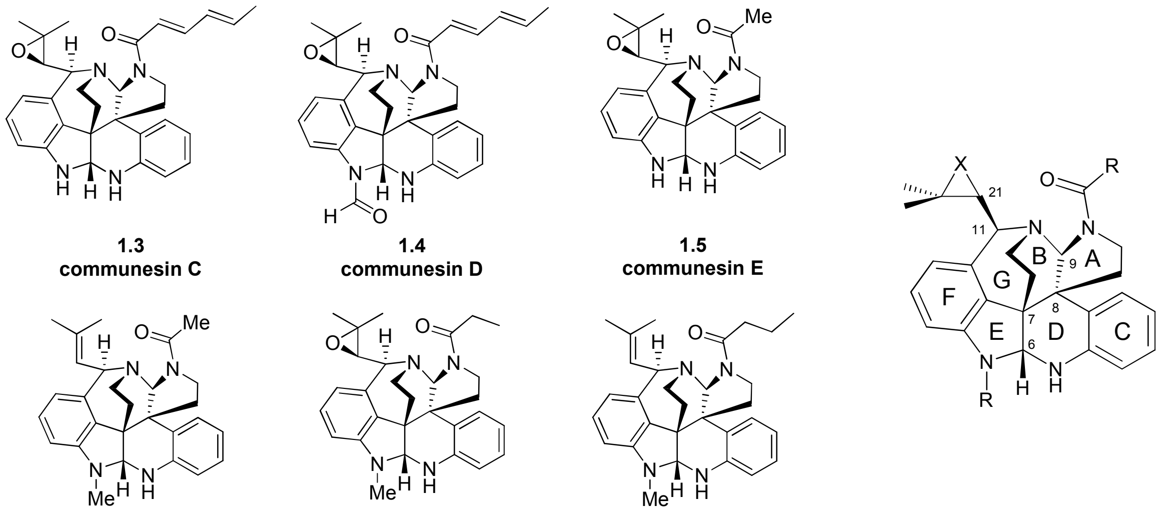
[1] Although this is the first report of communesins being reported in the literature, Mantel and coworkers would report in 2006 that both communesin A and B had been previously isolated under the names commindolines A and B by the Pfizer laboratories prior to Numata's publication. See Wigley, L. J.; Mantle, P. G.; Perry, D. A. *Phytochemistry* **2006**, *67*, 561-569.

Penicillium sp. derived from the Mediterranean sponge *Axinella verrucose*;[3] communesin E (**1.5**) and communesin F (**1.6**) were isolated by Hayashi and coworkers in 2004 from *Penicillium expansum* Link MK-57;[4] and communesin G (**1.7**) and communesin H (**1.8**) were isolated by Christophersen and coworkers in 2005 from the psychrotolerant *Penicillium rivulum* Frisvad.[5] All have the same polycyclic core containing two cyclic aminals and two vicinal quaternary centers at C7 and C8, and vary only by the substitution on aminal nitrogens or by the oxidation state about the alkene at C21-22 (Figure 2). Of their biological activity, the communesin alkaloids show moderate antiproliferative activity against several human leukemia cell lines[6] via microfilament disruption in mammalian cells,[7] activity against brine shrimp,[8] and some insecticidal activity against silk worms.[9] Despite their biological activity and structural complexity, they went relatively unnoticed by the synthetic community until the 'discovery' of nomofungin.

Figure 2: Structure of communesin C-H


1.3
communesin C

1.4
communesin D

1.5
communesin E

1.6
communesin F

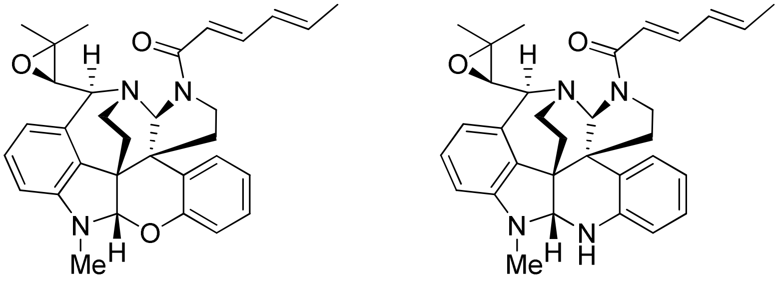
1.7
communesin G

1.8
communesin H

The Nomofungin Story

In 2001, eight years after the first discovery of communesins A and B, Hemscheidt and coworkers reported the isolation of a natural product from an unidentified fungus growing on the bark of *Ficus microcarpa* L.[10] Upon intensive spectroscopic studies, the structure was identified as compound **1.9** and all six stereocenters were assigned, including the absolute configuration. This new natural product, named nomofungin, contained the same chemical constitution as the previously discovered communesin B, with the exception of an N,O-acetal as opposed to the original aminal found in the communesin alkaloids (Figure 3). This natural product showed moderate cytotoxicity with MICs of 2 μg/mL and 4.5 μg/mL against LoVo and KB cells respectively.[11] Unfortunately, the fungus either died or was severely contaminated soon after isolation, and the natural product became unavailable for further study.

Figure 3: ***Proposed structure of nomofungin and structure of communesin B***



1.9
nomofungin

1.2
communesin B

The compound garnered considerable interest due to its uncommon N,O-acetal moiety and its constitutional similarity to communesin B. In fact, they had nearly identical ^{1}H and ^{13}C spectral data. It wouldn't be until the groups of Stoltz[12] and Funk[13] discovered independently, through comparing spectral data of synthesized analogues,[2] that nomofungin was in fact communesin B; and in 2003, Hemscheidt and coworkers would publish a retraction.[14] The circumstances surrounding the nomofungin story would be the cause for increased interest in the communesin alkaloids within the synthetic community and result in research towards the core and eventually several successful total syntheses.[15]

Biogenesis

Biogenic considerations often play an important role in the strategic design of total synthesis. In their early work towards the communesin alkaloids, Stoltz and coworkers proposed a biogenic pathway whereby the known alkaloid aurantioclavine (**1.10**) and diene **1.11**, derived from the oxidation of tryptamine, would undergo a hetero Diels-Alder reaction to afford adduct **1.12** which could then be carried forward to the communesin alkaloids (Scheme 1).[16] This was supported by experimental evidence that will be covered in the following section regarding model studies towards communesin alkaloids. This evidence was also proposed to support the idea that nomofungin and communesin B were identical structures.

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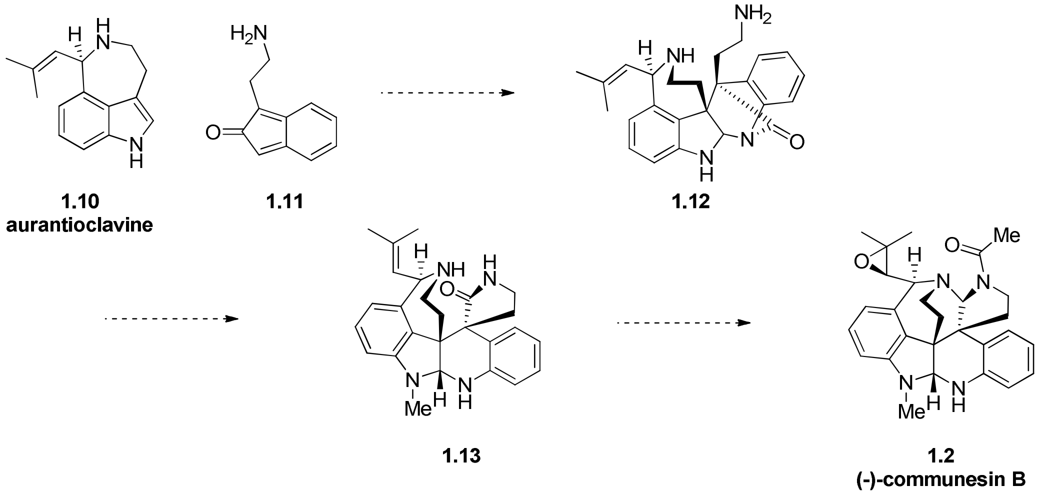
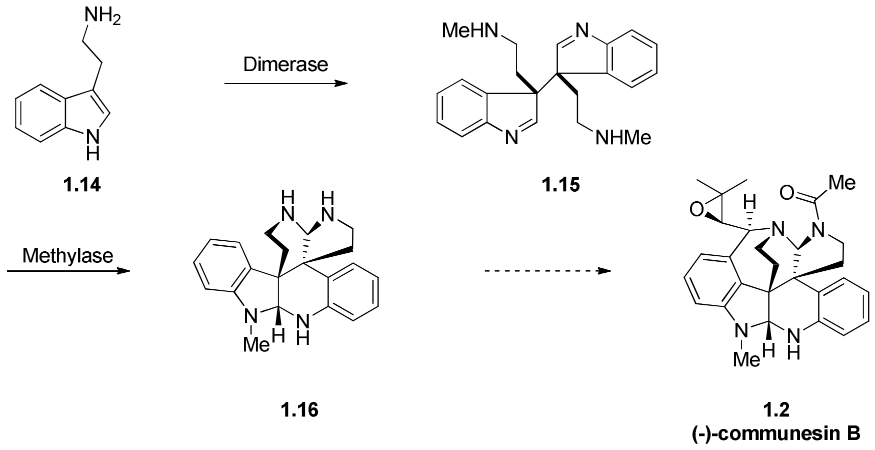
[2] Descriptions of the strategies used to synthesize these analogues are covered in the Model Study section of this thesis.

Scheme 1: *Biogenesis of communesin alkaloids as initially proposed by Stoltz*



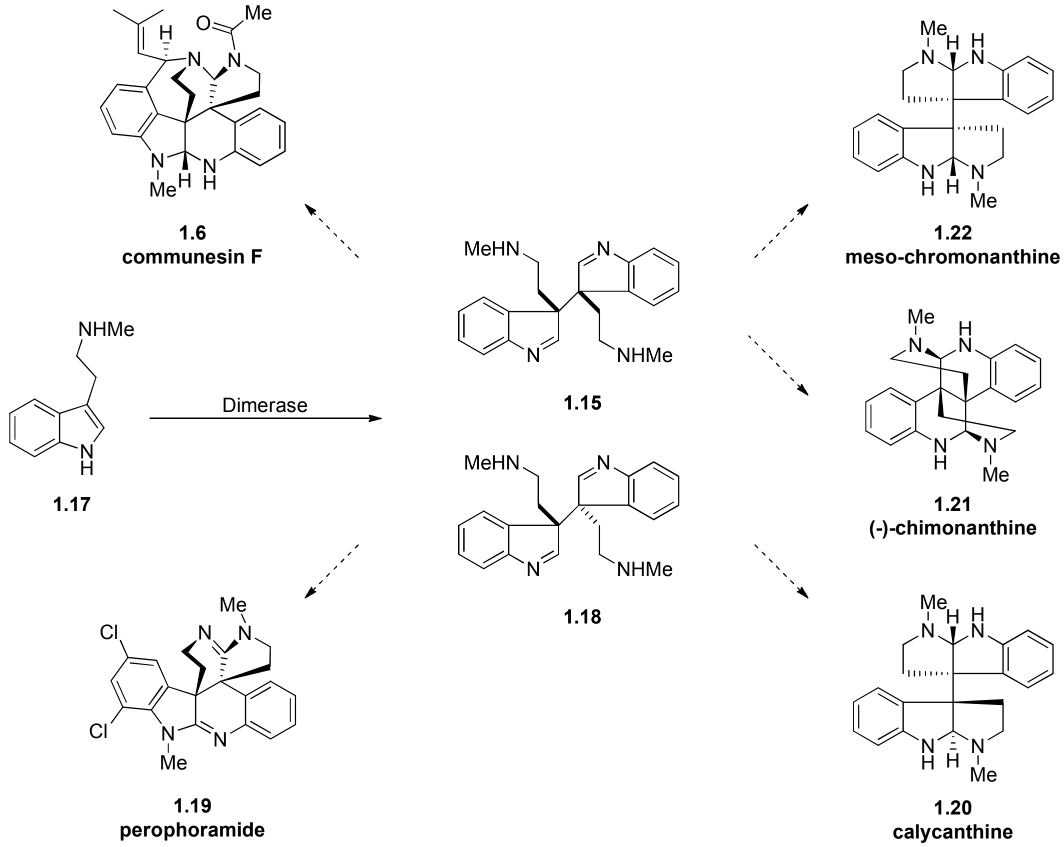
In 2006, Mantel would propose a new pathway based on labeling experiments.[17] This new pathway would lead to the communesin alkaloids via dimerization of tryptamine (**1.14**). The dimer would then undergo demethylation and a series of cyclizations to afford compound **1.16** (Scheme 2). However, it would remain unclear as to how compound **1.16** would lead to the communesin alkaloids.

Scheme 2: *Mantel's proposed biogenesis*



Later in 2006, Stoltz would propose a pathway similar to Mantle's in which dimerization of N-methyltryptamine **(1.17)** would give two isomers. From these two isomers the biogenesis of a number of natural products could be accounted for (Scheme 3).[18]

Scheme 3: *Stoltz's revised biogenesis can account for a variety of natural products*

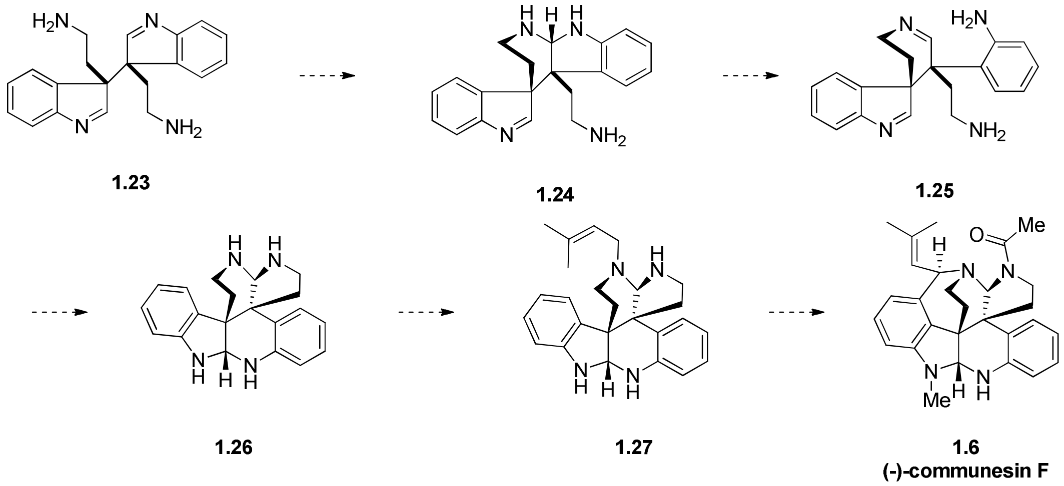


In this biogenesis, the dimers of tryptamine (**1.23**) undergo a series of cyclizations to afford intermediate **1.26**. N-prenylation yields intermediate **1.27** which could then undergo oxidative conversion and a series of minor transformation to yield compound **1.6**. Interestingly, Robinson and Teuber[19] and Woodward and coworkers[20] had proposed a similar biogenesis of calycanthaceous alkaloids from tryptamine roughly 50 years prior.

Previous Syntheses

Since their initial discovery as communesin alkaloids by Numata and coworkers in 1993, there have been two racemic syntheses of communesin F and one enantioselective synthesis whose strategy has been applied to the synthesis of communesins A, B, and F. The first of these being Qin's synthesis of (±)-communesin F in 2007. In this section, we will cover early strategies to access the communesin core, the three successful strategies used in the total synthesis of communesin, and more recent work towards the synthesis of the core.

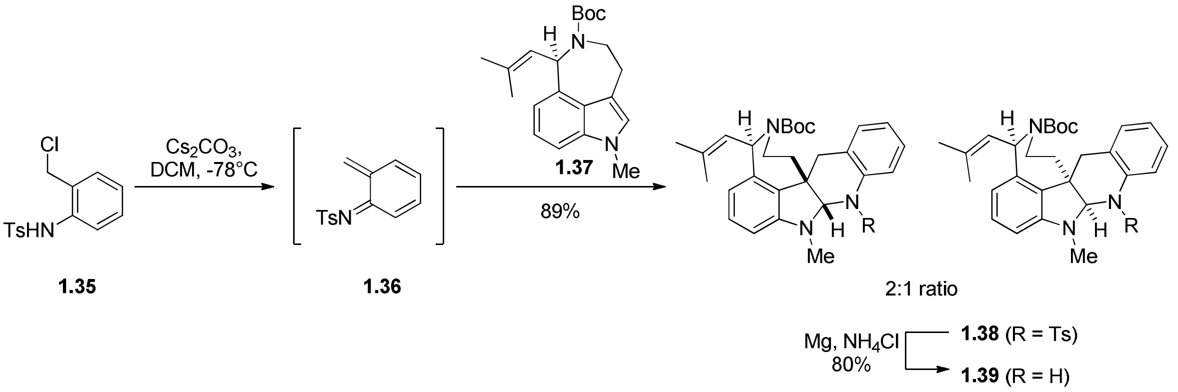
Scheme 4: *Stoltz's revised biogenesis of communesin alkaloids*



Model Studies

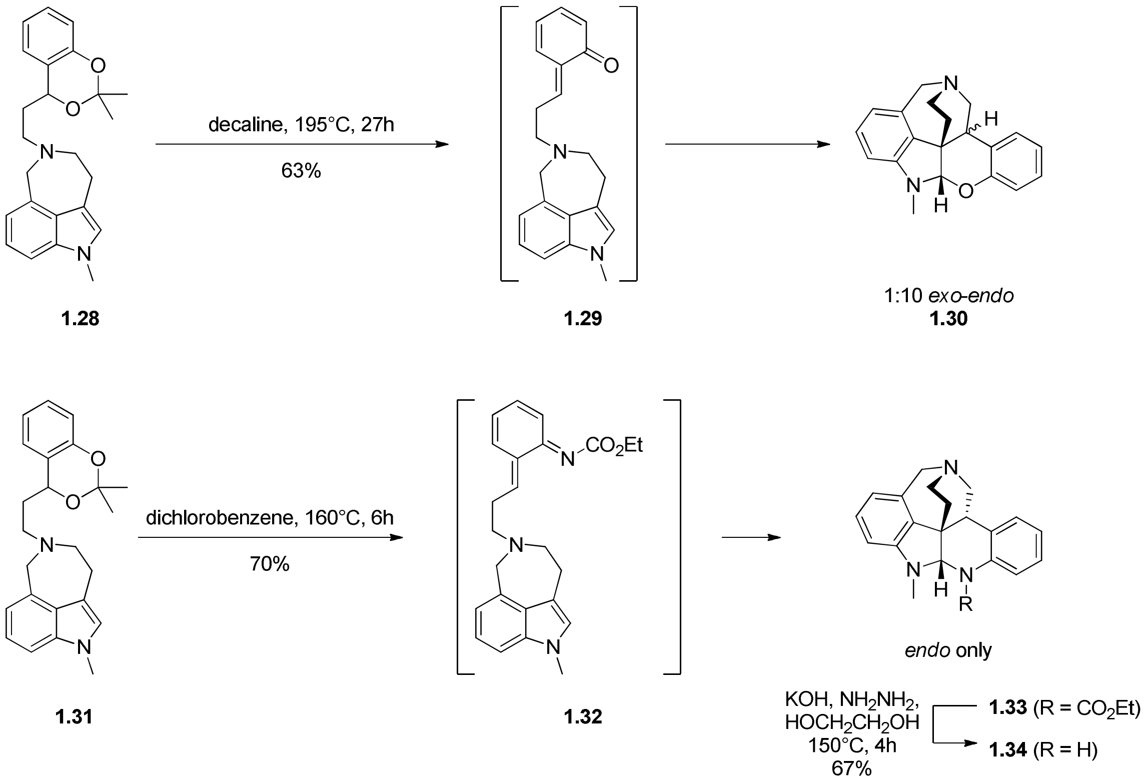
Much of the early work surrounding the synthesis of the core of the communesin alkaloids arose from the misidentification of nomofungin and efforts to clarify this error. Stoltz would be the first to report synthetic investigations towards the synthesis of the communesin alkaloids in 2003. In his first paper on the subject,[21] he describes a plausible biogenic route and a biomimetic strategy to access the C, D, E, and F rings of the communesin alkaloids. He showed that the methide imine (**1.36**), when generated in the lab, would undergo the hetero Diels-Alder reaction with Boc protected aurantioclavine (**1.37**) to afford the adduct (**1.38**) containing the partial core of the communesin alkaloids (Scheme 5); and that the shifts observed for C6 were in agreement with those found in the literature for communesin B. Despite accessing much of the core, further application of this strategy towards a total synthesis has not been reported.

Scheme 5: *Stoltz's biomimetic approach towards communesin alkaloids*



The next report to outline a strategy towards the construction of the communesin ring system (and also to reveal the structural misassignments of nomofungin) was that of Funk in 2003.[22] Therein, he reports a strategy for the construction of the hexacyclic ring systems of both the proposed structure of nomofungin and the communesin alkaloids via the intramolecular cycloaddition of an *in situ* generated ortho-quinone methides and *aza-ortho*-xylylene, respectively (Scheme 6).

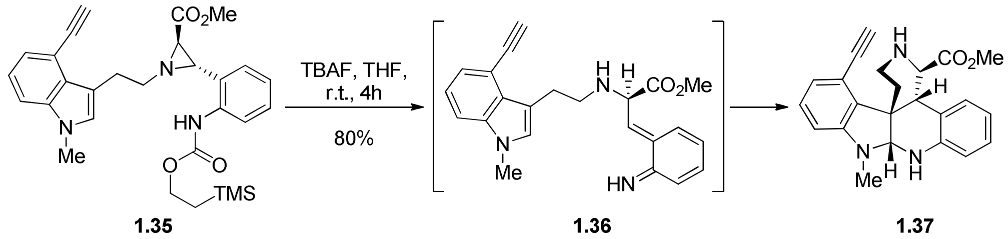
Scheme 6: ***Funk's approach towards communesin alkaloids***



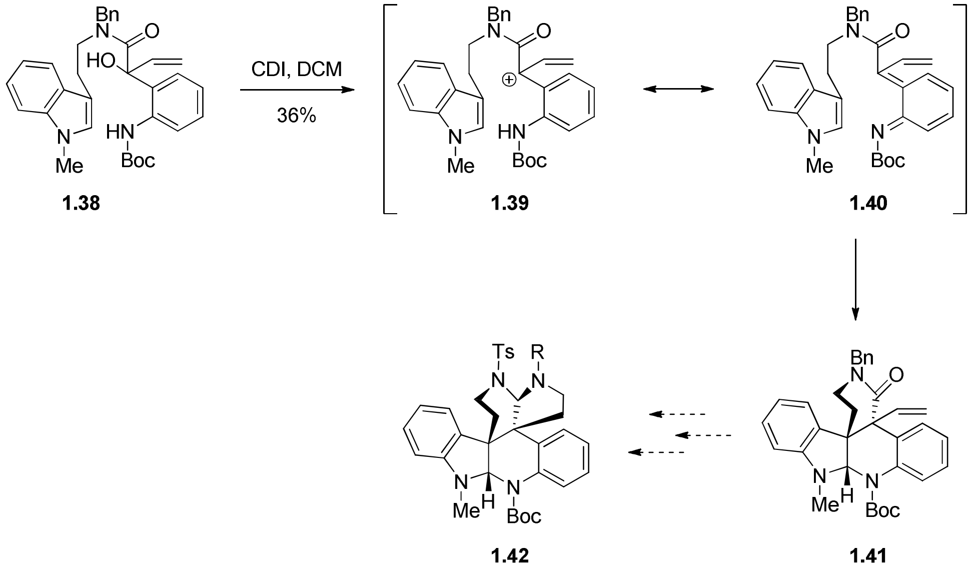
In a 2006 publication,[23] Funk would later report a new protocol in which he generates the *aza-ortho*-xylylene via either an acid-catalysed or fluoride-promoted ring opening of aziridine **1.35** (Scheme 7). The adduct of the subsequent cycloaddition was again then taken to give the B, C, D, E, F, and G rings of the communesin alkaloids.

The Adlington group would report a similar strategy in 2008,[24] generating a *aza-ortho*-xylylene from a tertiary alcohol to yield adduct **1.41** which the author claims has sufficient functionality to achieve the A, B, C, D, E, and F rings of the communesin alkaloids (Scheme 8).

Scheme 7: ***Funk's second approach towards communesin alkaloids***



Scheme 8: ***Adlington's approach towards communesin alkaloids***



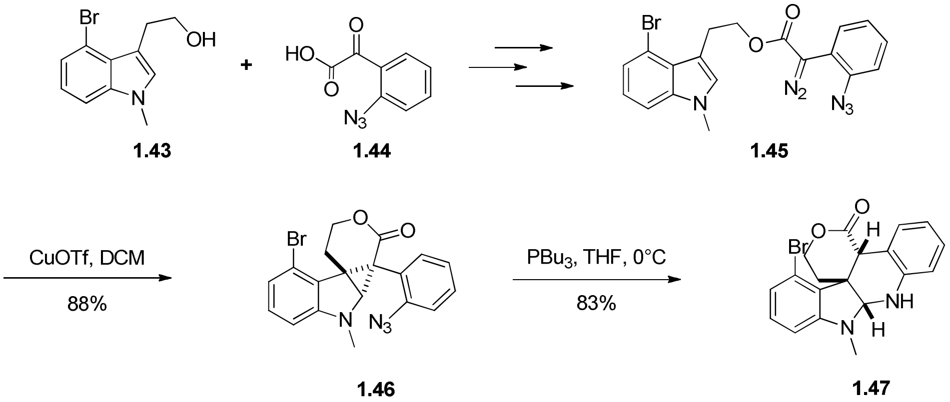
While each of these model studies has its own merits, they all follow the same general strategy of *in situ* generation of a methide imine followed by intramolecular hetero Diels-Alder reaction with the tryptamine side of the substrate. It is also interesting to note that, although this strategy has been the focus of many groups from the beginning of efforts towards a total synthesis, it has not yet yielded a complete total synthesis.

Total Syntheses

Qin's 2007 Total Synthesis of (±)-Communesin F

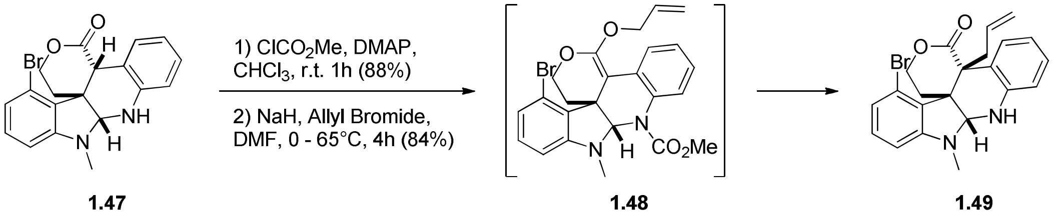
Following their 2006 publication whereby the B, C, D, E, and F rings of the communesin alkaloids were successfully synthesized via an intramolecular cyclopropanation reaction,[25] the Qin group published in 2007 the first racemic total synthesis of communesin F employing the same strategy.[26] The sequence took 23 steps and furnished (±)-communesin F as a mixture of amide rotamer about the acyl group in roughly 3% overall yield. The key step in this sequence involved the intramolecular cyclopropanation of diazo compound **1.44** using CuOTf to yield the stable cyclopropane **1.46** in 88%. Upon reduction of the azide group to the amine using *n*Bu$_3$P, spontaneous cyclization occurred to open the cyclopropane and give the a compound containing the pentacyclic substructure of the communesin alkaloids (**1.47**) (Scheme 9).

Scheme 9: ***Intramolecular cyclization in Qin's synthesis of (±)-communesin F***



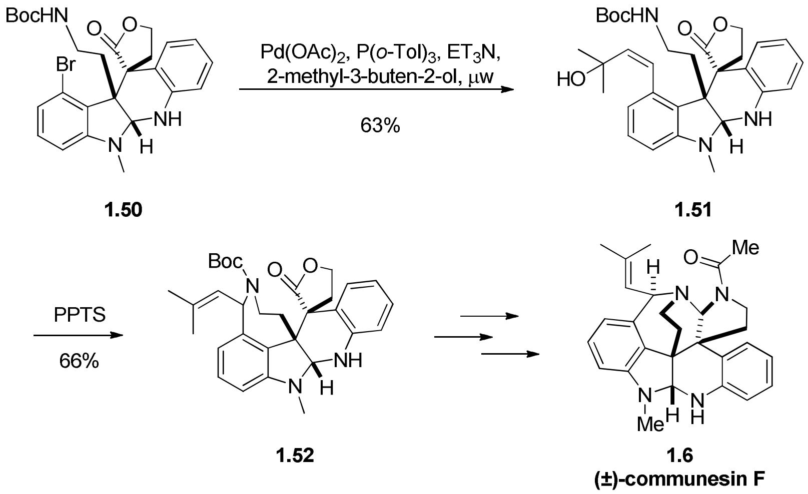
The configuration at C8 was established via O-allylation of compound **1.47** using NaH in DMF to give intermediate **1.48** which then proceeds through a 3,3-rearrangement, where one face is blocked by the bromophenyl group, to give exclusively the desired diastereomer **1.49** in 84% yield (Scheme 10). Weinreb had previously demonstrated this technique in his own work surrounding the communesin alkaloids.[27]

Scheme 10: ***Installation of the C8 allyl group in Qin's synthesis of (±)-communesin F***



Another interesting strategy employed was the acid catalyzed cyclization to form the G ring. Compound **1.50** was coupled to 2-methyl-3-buten-2-ol using a microwave-assisted Heck reaction to afford compound **1.51** in 63% yield. Upon treatment with PPTS, compound **1.51** cyclizes to form the G ring. Only a few short steps from here and Qin was able to reach (±)-communesin F (Scheme 11).

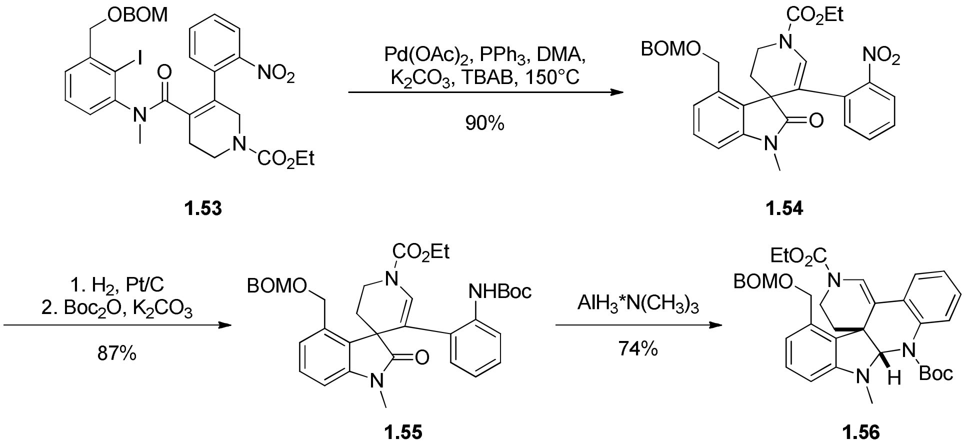
Scheme 11: ***Formation of the G ring in Qin's synthesis of (±)-communesin F***



Weinreb's 2010 Total Synthesis of (±)-Communesin F

The second group to publish a total synthesis of (±)-communesin F was that of Weinreb in 2010.[28] Based on their previous work,[29] their synthesis consisted of 31 steps and an overall yield of approximately 0.9%. The important key step in their synthesis was an intramolecular Heck reaction to furnish spiro-oxindole intermediate **1.54**.This spiro-oxindole intermediate upon reduction of the nitro using platinum, and subsequent Boc protection on the newly formed aniline, was submitted to reducing conditions which cyclized to produce aminal **1.56**. Similar end game strategies to those performed by Qin were used to complete the synthesis (Scheme 12).

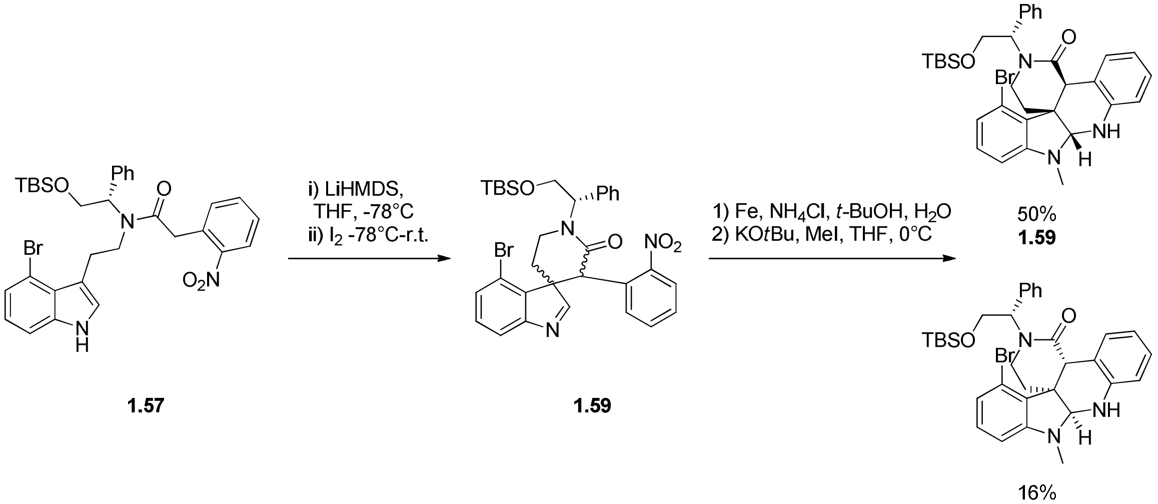
Scheme 12: ***Formation of the pentacyclic substructure in Weinreb's synthesis of (±)-communesin F***



Ma’s 2010 Total Synthesis of (-)-Communesin F and 2011 Total Synthesis of (-)-Communesin A and B

The three most recent syntheses were completed by Ma’s group in 2010 and 2011.[30] Using their strategy, they were able to synthesize communesin F, A, and B in an enantioselective manner. The longest linear sequence of steps for the total synthesis of (-)-communesin F was 19 steps with an overall yield of approximately 6%. The key step of this synthesis involves an intramolecular oxidative coupling reaction to give spiro-fused indoline **1.59** as a mixture of diastereomers. Reduction of the nitro group and selective methylation furnished the aminal **1.59** and **1.60** containing the pentacyclic substructure in 50% yield, along with its diastereomer (**1.59**) in 16% yield (Scheme 13).

Scheme 13: ***Oxidative coupling and formation of the pentacyclic substructure in Ma’s synthesis of (-)-communesin F***



1.57

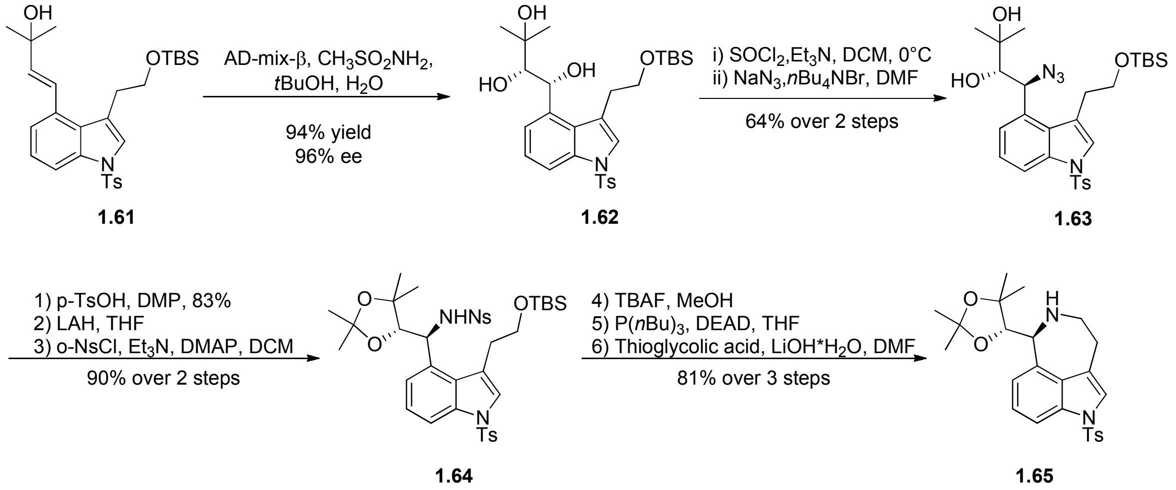
1.59

1.59

1.60

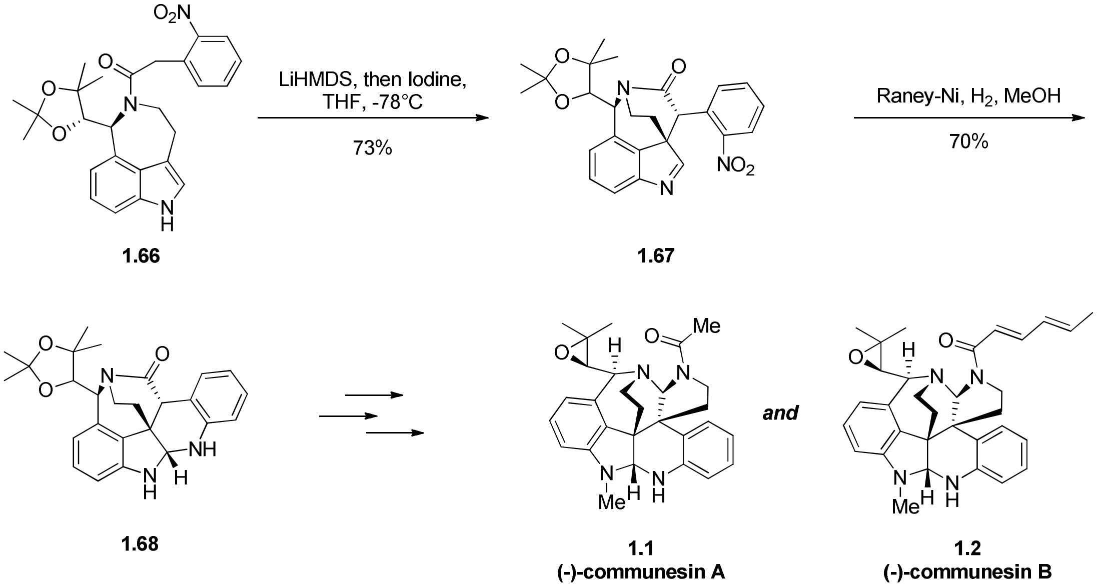
Ma used this same oxidative coupling strategy for the total synthesis of communesin A and B. This time, however, stereocontrol was achieved prior to the key step. Sharpless dihydroxylation using AD-mix-β of compound **1.61** gave triol **1.62** in 94% yield and 96% *ee*. Regioselective nucleophilic displacement of the *in situ* generated cyclic sulfite using sodium azide gave compound **1.63** in 64% yield. Protection of the diol, reduction of the azide, and nosyl protection of the newly-formed amine give compound **1.64**. Deprotection of the silyl group, Mitsunobu coupling, and deprotection of the nosyl group give the core structure (**1.65**) that will propagate stereo control through to the key step of the synthesis (Scheme 14).

Scheme 14: *Synthesis of left-hand side of molecule in Ma's synthesis of (-)-communesin A and B*



Ma found that, using this new substrate (**1.66**), his previous condition produced exclusively the iodination product. However, this was remedied by performing the addition of iodine at room temperature. This affords the coupling product **1.67** in 73% yield (based on recovered starting material). Reduction of the nitro group yields the spontaneously annulated product (**1.68**) in 70% yield. From this compound, the A ring was installed in a similar manner to the one described by Qin, and both communesin A and B were achieved (Scheme 15)

Scheme 15: *Oxidative coupling and annulation in Ma's synthesis of (-)-communesin A and B*

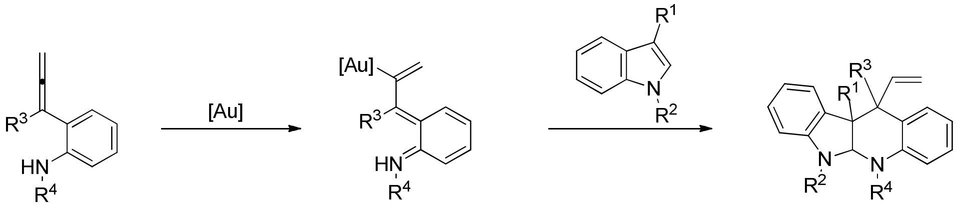


These routes all use different strategies to obtain the communesin core, while employing similar end game protocols. Aside from the shift from asymmetric to stereospecific, little progress has been made, particularly in reducing the linear sequence of steps or the overall yield of the synthesis. In the following chapter, we will discuss our strategy to obtain the communesin core through a [4+2] cycloaddition.

Chapter 2: The Gold-Induced Cycloaddition Route

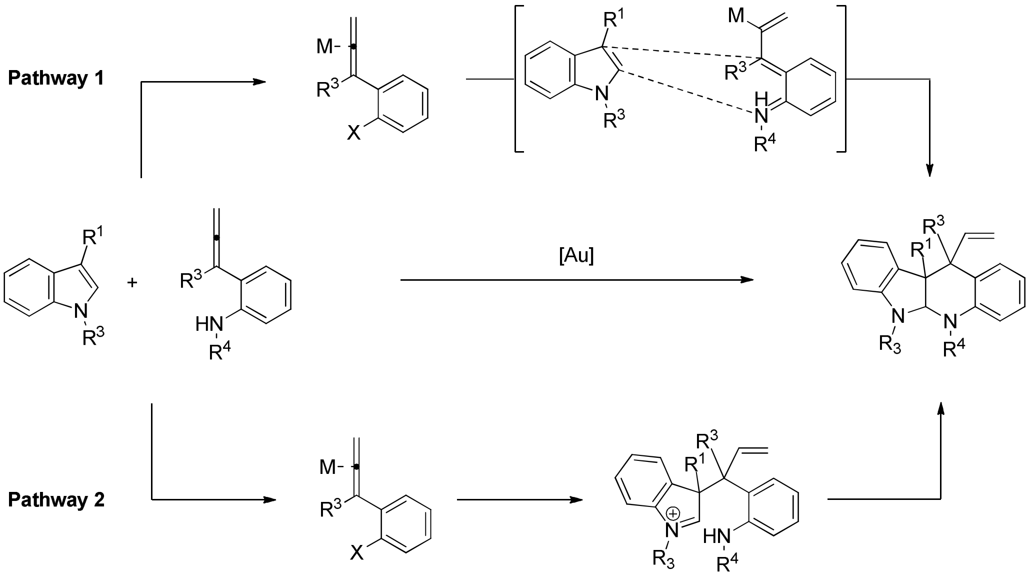
Looking back on earlier work conducted by Stoltz, Funk, and Adlington to generate the C, D, E, and F rings of the communesin alkaloids, we wished to pursue a similar strategy involving the [4+2] cycloaddition of a vinyl imine with an indole derivative. As gold catalyzed transformations have become more of a focus in our laboratory,[31] we envisioned the vinyl imine as the product of gold-induced isomerization of an *o*-amino aryallene (Scheme 16).

Scheme 16: Proposed gold-induced route to the core structure of the communesin alkaloids



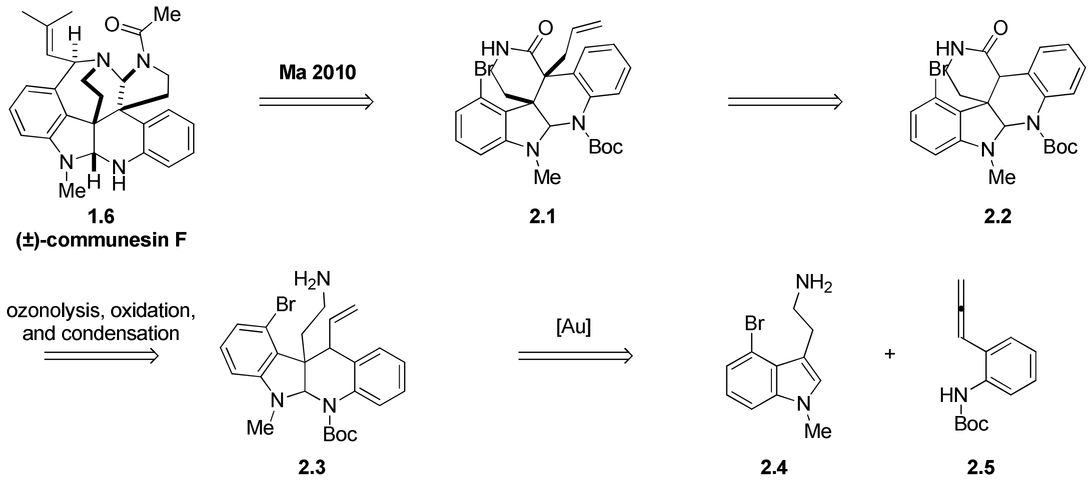
One can imagine the process proceeding through one of two plausible pathways, shown in Scheme 17. Both pathways begin with the gold's empty p-orbital accepting electron density from the accessible π-system of the allene. In pathway 1, electron density is then pushed from the amino group to generate the vinyl imine which can then undergo a [4+2] cycloaddition to generate the tetracyclic substructure of the communesin alkaloids. One could also imagine that this could occur through a more asynchronous, or even stepwise pathway, whereby activation of the allene by the coordination of gold allows for attack from the 3 position of the indole ring onto the allene, followed by a nucleophilic attack of the amino group onto the newly-formed imminium as seen in pathway 2. With the appropriate functionality, we can apply this methodology to the formation of the C, D, E, and F rings with the necessary structural building blocks to access the communesin alkaloids.

Scheme 17: Two potential pathways of the gold-induced route to the core structure of the communesin alkaloids



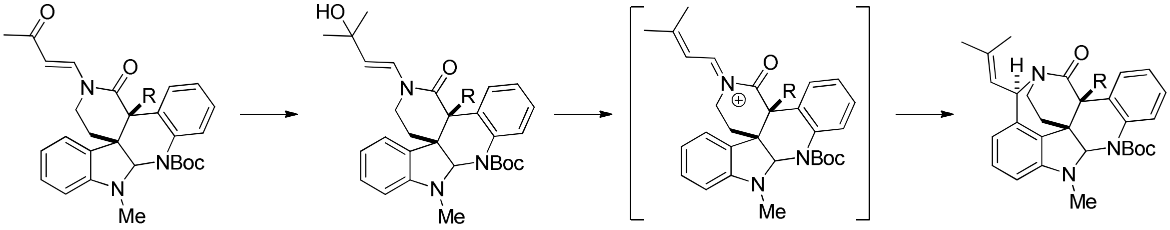
A general retrosynthesis for a formal synthesis is shown in Scheme 18 below. This synthesis would allow us to quickly intercept intermediate (**2.1**) from Ma's 2010 total synthesis of (-)-communesin F. Ma's advanced intermediate (**2.1**) can be accessed through allylation of intermediate **2.2**, which in turn is accessed through ozonolysis, oxidation, and condensation of intermediate (**2.3**). Access to intermediate (**2.3**) would be attained via our gold-induced (formal) Diels-Alder reaction of compounds **2.4** and **2.5**. Potential issues for this pathway include the possibly lengthy synthesis of the indole precursor (**2.4**) and the diastereoselectivity of the (formal) Diels-Alder reaction.

Scheme 18: *Proposed retrosynthesis leading to a formal synthesis of (±)-communesin F*



Although the previously proposed formal synthesis seemed reasonably attainable, we wished to pursue a different endgame from that of the syntheses that preceeded us. We propose a Pictet-Spengler-like ring closure for the formation of the G ring of the communesin alkaloids. This would be analogous to the base-promoted Pictet-Spengler reaction in the synthesis of (±)-aurantioclavine conducted by Ishimura in 2009.[32] In our case, aminobutenone **2.6**, upon alkylation of the ketone (and mild acid catalysis, if required), would generate the required synthetic intermediate **2.8** for the cyclization to occur (Scheme 19).

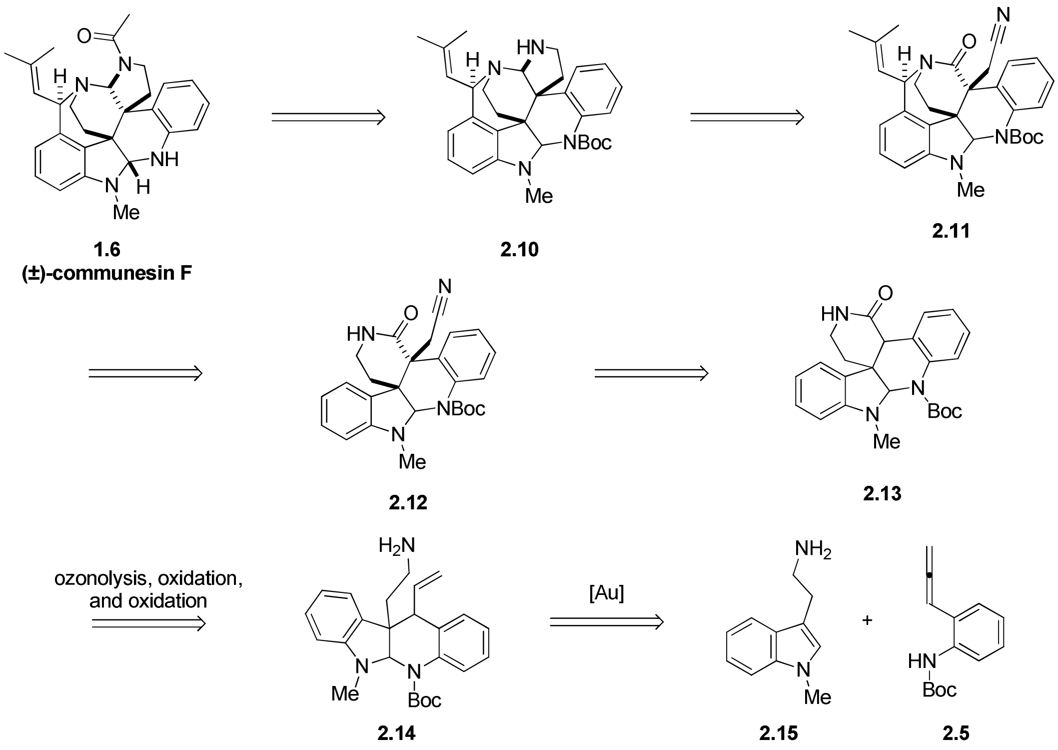
Scheme 19: ***Proposed formation of the G ring via a Pictet-Spengler-like ring closure***



2.6 **2.7** **2.8** **2.9**

Our revised retrosynthesis for the total synthesis of (±)-communesin F is show below (Scheme 20). (±)-Communesin F would be attained through acylation and deprotection of intermediate **2.10**. Formation of the A ring begins with intermediate **2.11**, which is subjected to a series of conditions first developed by Ma.[33] First, the nitrile is reduced using LAH to give the lactol which upon treatment using ammonium acetate and NaBH(OAc)$_3$ gives aminal **2.10**. Preceding this, the G ring is constructed as described in the previous paragraph using the Pictet-Spengler type cyclization. Intermediate **2.12** is treated with carbamic acid under refluxing conditions to give the aminobutenone, which is then alkylated to give the alcohol, and mild acid catalysis may be used to promote cyclization. Intermediate **2.12** is accessed via roughly the same route of a gold-induced (formal) Diels-Alder reaction of indole **2.15** and allene **2.5**. Following ozonolysis, oxidation, and condensation of intermediate **2.14**, pentacyclic structure **2.13** is then treated with 2-iodoacetonitrile and base to afford the alkylation product **2.12**. This pathway allows us to avoid the long and potentially difficult synthesis of the indole precursor **2.4**, and allows us to explore the possibility of a new route to construct the G ring.

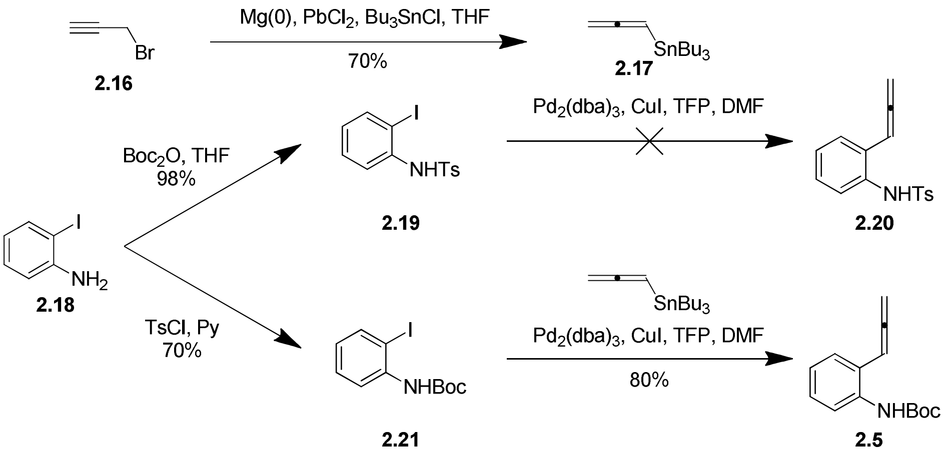
Scheme 20: *Proposed retrosynthesis of the total synthesis of (±)-communesin F*



Results and Discussion

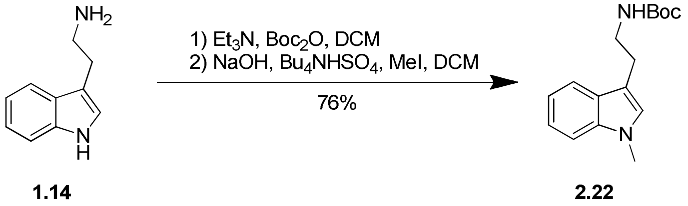
Commercially available starting material 2-iodoanaline (**2.18**) was both Boc and Tosyl protected, and Stille conditions were used to couple an alleneyl stannane prepared via a lead (II) chloride catalyzed reaction;[34] however, the Stille coupling only proved fruitful with the Boc protected 2-iodoanaline. (Scheme 21)

Scheme 21: *Synthesis of o-amino aryallene via Stille coupling*



Indole substrates **2.23** and **2.24** were obtained through commercially available sources, while indole **2.22** was prepared by Boc protection of tryptamine (**1.14**), followed by selective methylation of the nitrogen of the indole. These reactions conducted in sequence proceeded with a 76% yield over two steps (Scheme 22).

Scheme 22: ***Synthesis of the indole dienophile coupling partner***



With substrates in hand, we began our gold catalyzed reactions. Various indoles, gold catalysts and solvents were used (Figure 4). The summarized results are shown in Table 1 below. Our first attempt was with indole **2.23** and Echavarren's catalyst (**2.27**), which produced the product of the undesired 5-*endo-dig* cyclization (**2.28**) in 52% yield. Increasing the number of equivalents of indole **2.23** to 10 yielded a 1:10 mixture of the 5-*endo-dig* cyclization product (**2.27**). Changing from indole **2.23** to 1-methylindole (**2.24**) or a tryptamine derivative (**2.22**) still resulted in quantitative conversion to the 5-*endo-dig* cyclization product (**2.28**). Using various solvents (DCM, Acetone, DCE) continued to produce the undesired 5-*endo-dig* cyclization product in quantitative conversion. We turn our sights on different catalyst systems including $PtCl_2$, $Au(PPh_3)Cl/AgOTf$, a gold-NHC catalyst (**2.25**), and a gold-phosphine catalyst developed in our lab (**2.26**). Each of these systems resulted in quantitative conversion to the undesired 5-*endo-dig* product (**2.28**) and quantitative recovery of the starting indole.

Figure 4: ***Choice of indole substrates and catalysts for the test system***

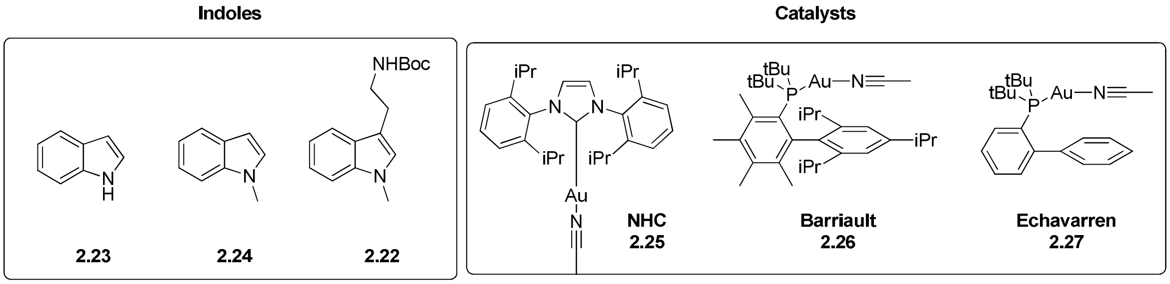
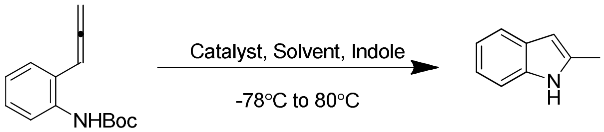


Table 1: *Results of gold catalyzed reactions under various conditions*



2.5 **2.28**

Entry	Indole (Equivalents)	Catalyst	Solvent	Cyclized Product (% Yield)	Recovered Indole
20	**2.23** (1 Eq)	Echavarren (**2.27**)	Toluene	52%	Obs.
22*	**2.23** (10 Eq)	Echavarren (**2.27**)	Toluene	1 to	10
23*	**2.24** (1 Eq)	Echavarren (**2.27**)	Toluene	1 to	1
35*	**2.22** (2 Eq)	Echavarren (**2.27**)	DCM	1 to	2.5
36*	**2.22** (2 Eq)	Echavarren (**2.27**)	Acetone	1 to	3.2
38	**2.22** (2 Eq)	Echavarren (**2.27**)	Toluene	Quant.	Quant.
39	**2.22** (2 Eq)	Echavarren (**2.27**)	DCE	Quant.	Quant.
44	**2.22** (2 Eq)	$PtCl_2$	Toluene	Quant.	Quant.
46	**2.22** (2 Eq)	$Au(PPh_3)Cl/AgOTf$	Toluene	Quant.	Quant.
47*	**2.22** (2 Eq)	NHC (**2.25**)	Toluene	1 to	2
48	**2.22** (2 Eq)	Barriault (**2.26**)	Toluene	Quant.	62%

*Ratio products in crude NMR

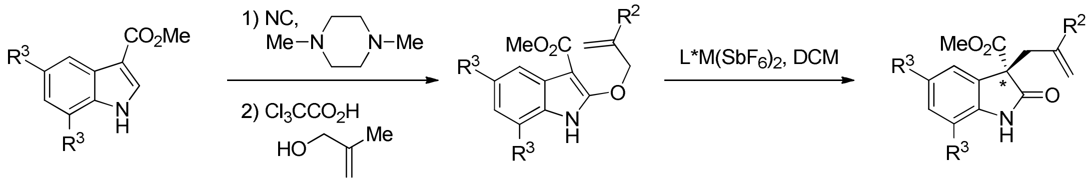
While this route would have provided quick and easy access to the communesin core, and potentially to the communesins themselves, the formation of the 5-*endo-dig* product (**2.28**) required us to seek alternative routes. Further analysis of the issues surrounding this strategy, and potential future work, is found in Chapter 4.

Chapter 3: The Meerwein-Eschenmoser Claisen Route

Precedent

Looking to pursue a new route towards the communesin alkaloids, we came across a paper published by the Kozlowski group. In this 2008 publication, they describe an enantioselective Meerwein-Eschenmoser Claisen rearrangement to access allyloxindoles in high yields and in good to excellent enantioselectivities[35] (Scheme 23). In their example, the N,O-acetal is synthesized via the nucleophilic addition of an alylic alcohol onto a NCS activated indole. Addition of chiral palladium complexes, which chelate the methylester found at the 3 position of the indole and the newly formed vinyl ether, catalyze the Claisen rearrangement and provide stereocontrol.

Scheme 23: ***Kozlowski's enantioselective Meerwein-Eschenmoser Claisen rearrangement***

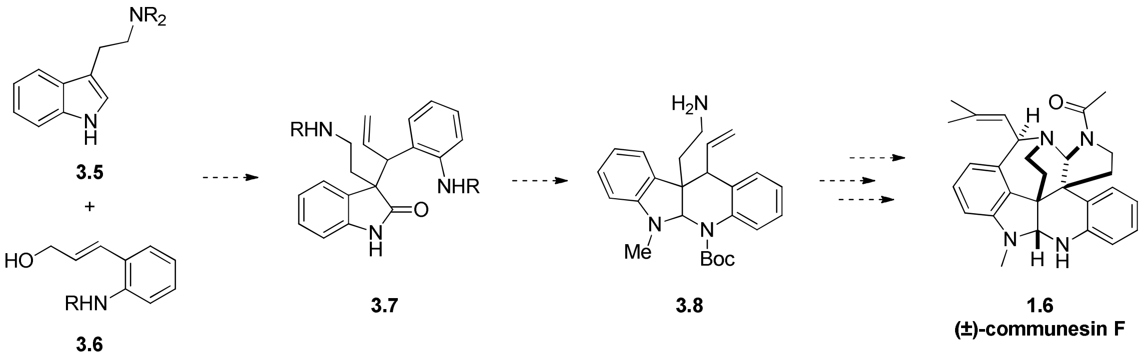


3.1 **3.2** **3.3** **3.4**

60-100% yield
85-92% *ee*

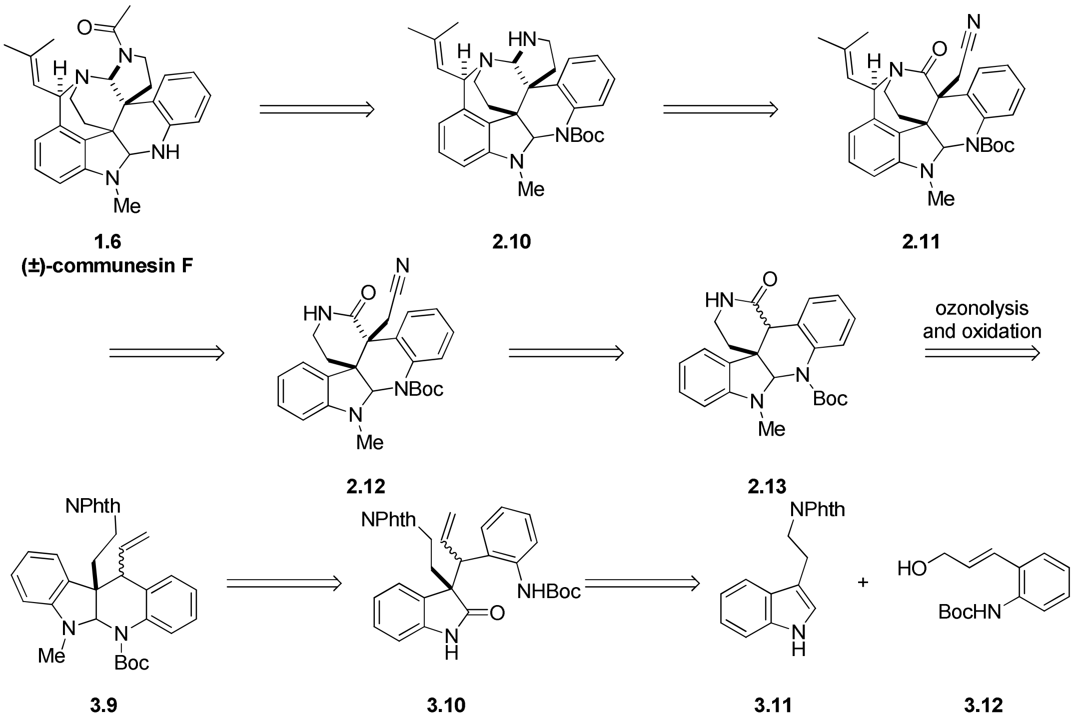
We thought that it may be possible, although not enantioselectively, to pursue a similar strategy to access compound **3.7**. Then, using chemistry developed by previous groups for the annulation of the aminal rings of other communesin alkaloids, access one of the intermediates in our previously proposed syntheses (Scheme 24).

Scheme 24: *Proposed route to access the pentacyclic substructure of communesin alkaloids*



The new proposed total synthesis would follow the retrosynthesis shown in Scheme 25 below. The endgame would remain the same. (±)-Communesin F would be attained through acylation and deprotection of intermediate **2.10**. Formation of the A ring begins with intermediate **2.11**, which is subjected to a series of conditions first developed by Ma.[36] First, the nitrile is reduced using LAH to give the lactol which upon treatment using ammonium acetate and NaBH(OAc)$_3$ gives aminal **2.10**. Preceding this, the G ring is constructed as described in the previous paragraph using the Pictet-Spengler type cyclization. Intermediate **2.12** is treated with carbamic acid under refluxing conditions to give the aminobutenone, which is then alkylated to give the alcohol, and mild acid or base catalysis may be used to promote cyclization. Intermediate **2.13** is accessed via ozonolysis, oxidation, and condensation of intermediate **3.9**. Pentacyclic structure **2.13** is then treated with 2-iodoacetonitrile and base to afford the alkylation product **2.12**. This intermediate is now accessed through a sequence of reactions involving the new Meerwein-Eschenmoser Claisen rearrangement, the product of which (**3.10**) is then annulated using conditions similar to those used in previous syntheses. The benefit of this new approach is that it allows us to proceed with our plan to establish a new endgame for the synthesis of the communesin alkaloids and only adds a few additional steps over our previously proposed synthesis.

Scheme 25: *Proposed retrosynthesis leading to a total synthesis of (±)-communesin F*



Results and Discussion

Using the conditions reported in the Kozlowski paper, we were unsuccessful in coupling indole **3.11** with a variety of *o*-amino cinnamaldehyde (**3.12, 3.15-3.18**) (Scheme 26). It wasn't until the amino group was substituted for a nitro group that the reaction began to afford a workable amount of product. Although there was high conversion directly into products when using the standard conditions of one equivalent of indole **3.11** and two equivalents of cinnamyl alcohol **3.13** (Entry 1), complications due to co-elution of product and the remaining equivalent of cinnamyl alcohol **3.13** forced us to invert the equivalents to put indole **3.11** in excess. This resulted in lower conversions but higher isolated yields (Table 2). However, this would add additional steps to the synthesis, as oxidation state adjustment would be required.

Scheme 26: *Meerwein-Eschenmoser Claisen reaction*

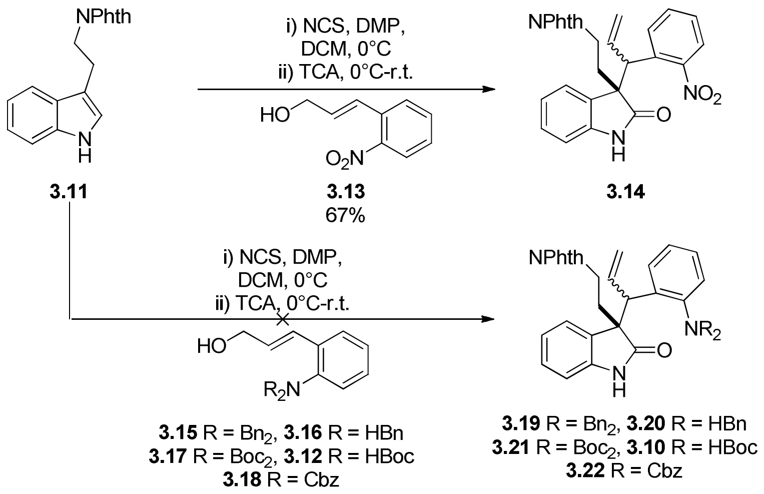
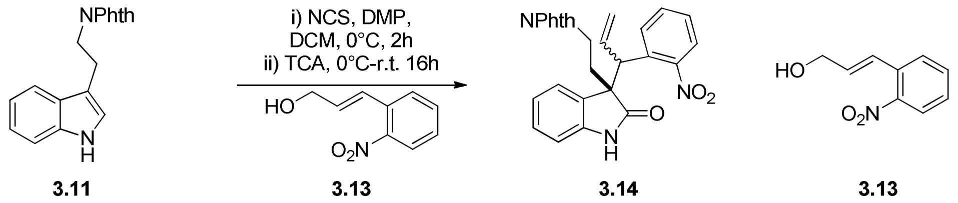


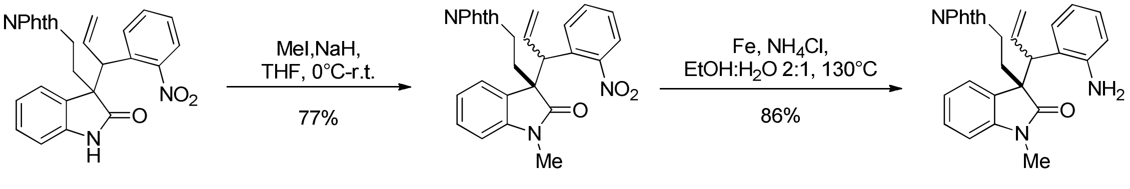
Table 2: *Optimization of Meerwein-Eschenmoser Claisen reaction*



Entry	Indole (Eq)	Alcohol (Eq)	NCS (Eq)	Ratio	
				3.14	3.13
1	1	2	1.1	1 :	0.9
2	1	1	1.1	1 :	1.2
3	1	1	1.5	1 :	0.5
4	1.2	1	1.5	1 :	0.2

Next, the indole nitrogen of compound **3.14** is methylated using iodomethane and sodium hydride in 77% yield; and the nitro group is reduced using elemental iron with ammonium chloride in 86% yield (Scheme 27). The conditions for the reduction were somewhat problematic (Table 3). Initial conditions using elemental iron with ammonium chloride led to the reduction of both the nitro and the alkene to give compound **3.25**; and using a variety of other conditions (Entry 2-4) gave no discernible product. Returning to the use of elemental iron with ammonium chloride conditions, we found that careful observation by TLC of the reaction every 10 minutes and immediate quenching upon complete consumption of starting material afforded an 86% yield of the desired product.

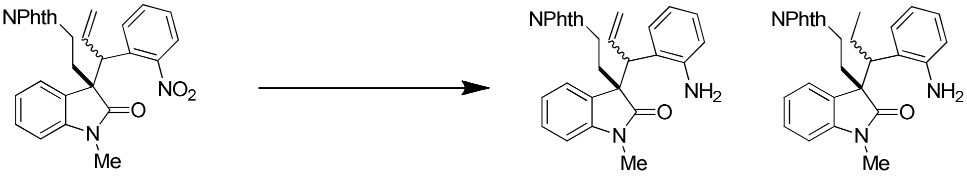
Scheme 27: *Methylation and subsequent reduction*



3.14 **3.23** **3.24**

Boc protecting of compound **3.24** gave mono-Boc compound **3.10** in 89% yield. Attempts were made to reduce the amide in the hope of forming the imminium and subsequent attack using AlH_3*Me_2NEt, LAH, sodium cyanoborohydride, and $LiEt_3BH$. Also, the $POCl_3$ was used in an attempt to form the Vilsmeier reagent analog; however, all attempts at formation of the aminal ring from both the Boc-protected compound (**3.10**) and the free aniline compound (**3.24**) proved unsuccessful (Scheme 28). We postulated that the reduction of the phthalamide protecting group was causing a variety of uncontrollable degradation pathways and so we set out to replace this protecting group with both a bis-Boc and bis-benzyl protection.

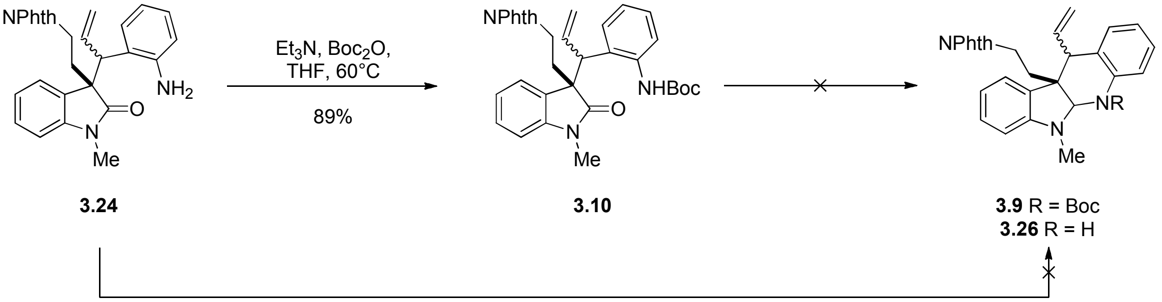
Table 3: *Screening of reduction conditions*



3.23 **3.24** **3.25**

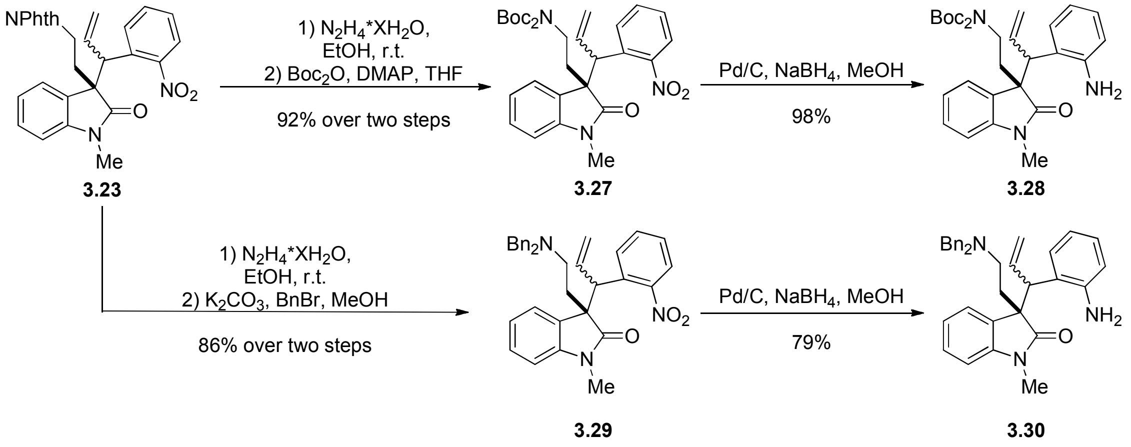
Entry	Conditions	Temperature	Time	Isolated Yield	
				3.24	3.25
1	Fe, NH_4Cl, EtOH:H_2O (2:1)	120°C	90 minutes	61%	29%
2	Pd/C, $NaBH_4$, MeOH	Room temperature	6 hours	-	-
3	$SnCl_2$, conc. HCl	Room temperature	3 hours	-	-
4	Zn, 30% AcOH in H_2O	Room temperature	3 hours	-	-
5	Fe, NH_4Cl, EtOH:H_2O (2:1)	120°C	1 hour	86%	-

Scheme 28: *Attempts at annulation*



A decision was made to not change the initial steps of the synthesis. This was to avoid the need to re-optimize the Meerwein-Eschenmoser Claisen reaction. Deprotection of the phthalamide from compound **2.23** was made complicated by the reduction of the alkene under standard conditions with hydrazine, and deprotection with methylamine was unsuccessful. Again, careful monitoring of the reaction time by TLC was able to furnish both the Boc and benzyl protected compounds, **3.27** and **3.29** respectively, in good yields over two steps. Reduction of the nitro was accomplished using a mixture of palladium on carbon and sodium borohydride to give the annulation substrates **2.28** and **3.30** in 98% and 79% yields respectively. (Scheme 29)

Scheme 29: *Substitution of phthalamide with Boc and benzyl protecting groups*



All annulation conditions subjected to the bis-Boc protected substrate (**2.28**) proved unsuccessful. Most conditions fared no better using the bis-benzyl protected substrate (**3.30**), with the exception of the use of the 'ate complex' of BuLi/DIBAL (0.4 M solution of DIBAL/BuLi in THF).[37] However, these conditions only worked using a single diastereomer in a yield of 41%

(Scheme 30). Attempts to yield a crystal for single crystal x-ray crystallography have been unsuccessful. NMR NOE spectra shows the two adjacent stereocenters at C6, C7, and C8 were found to be in a syn-anti configuration, the same relative configuration found in the natural product (Figure 5). Pushing forward with the synthesis, we attempted both ozonolysis and Lemieux-Johnson conditions on compound **3.31**; however, as of yet both have yielded nothing but unidentifiable mixtures of products.

Scheme 30: ***Annulation of a single diastereomer***

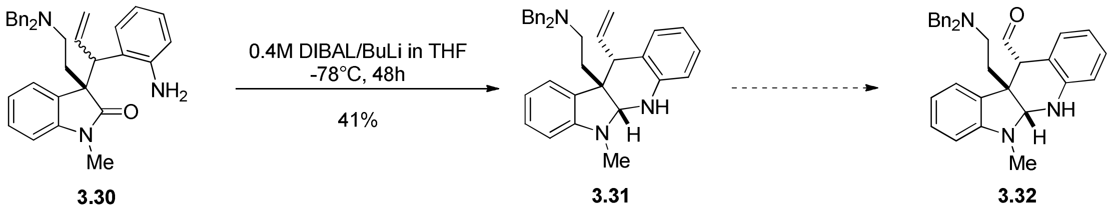
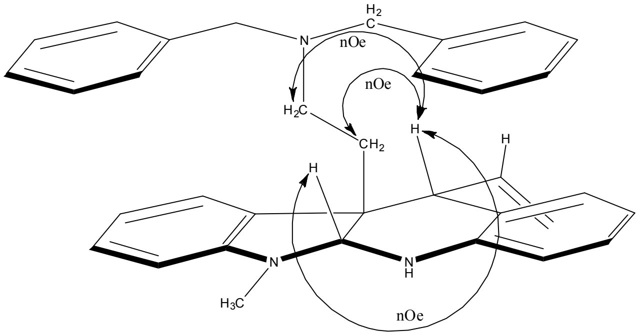
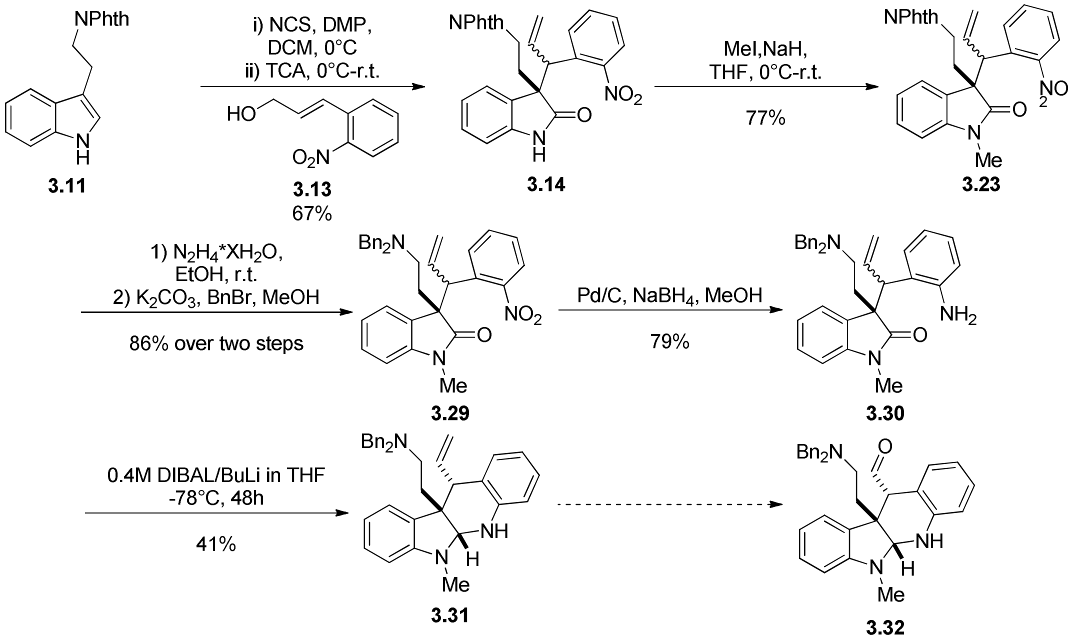


Figure 5: ***Select nOe correlations of compound*** *3.31*



Unfortunately, this is where my work leaves off. Below is a summary of the progress towards this synthesis to date (Scheme 31). Activation of indole **3.11** with NCS, followed by addition of cinnamyl alcohol **3.13**, gives the Meerwein-Eschenmoser Claisen product (**3.14**) in 67% yield. The indole nitrogen of compound **3.14** is then methylated using iodomethane and NaH to give methyl oxindole (**3.23**). The phthalamide protecting group is then removed (with careful monitoring by TLC) using hydrazine, and the free amine is benzylated in 86% yield over two steps to give compound **3.29**. Reduction of the nitro group is accomplished with palladium on carbon and sodium borohydride. Super hydride is then used to close the aminal ring to give our most advanced intermediate (**3.31**). Much more work is required to complete this synthesis. Our thoughts on next steps and future work, as well as an analysis of the condition of the synthesis, will be found in the following chapter.

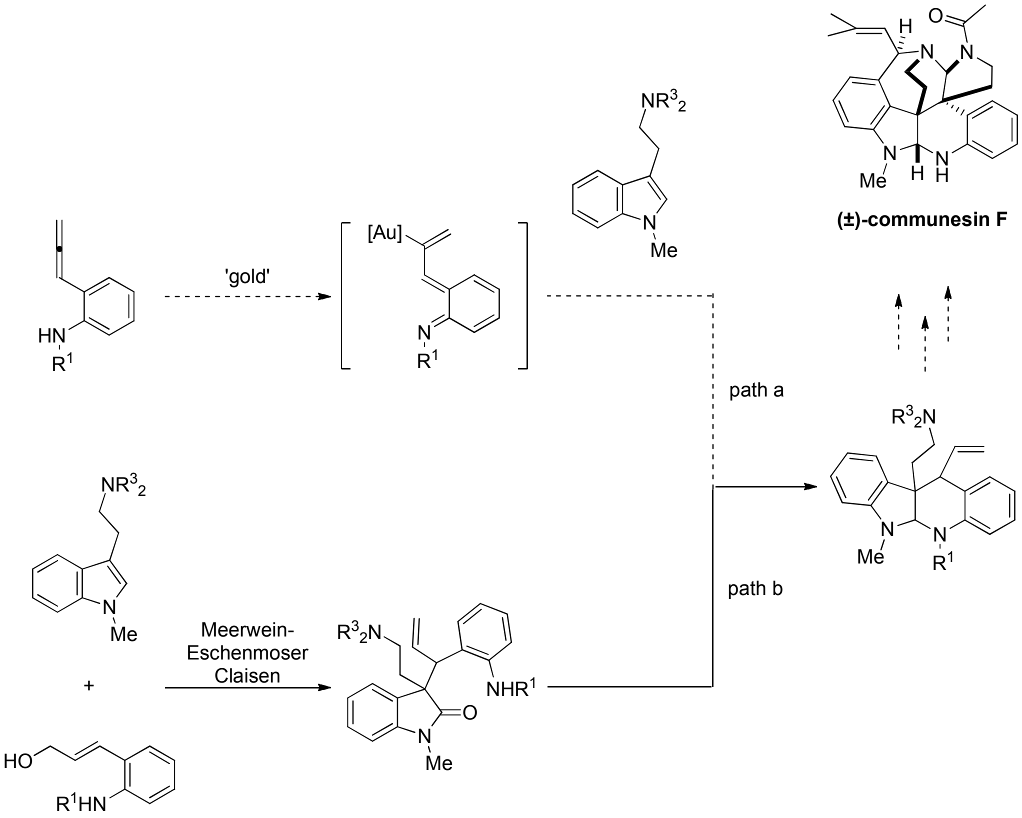
Scheme 31: *Summary of progress towards the total synthesis of (±)-communesin F*



Chapter 4: Conclusions and Future Work

We have presented two potential techniques for the construction of the core of the communesin alkaloids. The first, featuring a currently unsuccessful gold-induced (formal) Diels-Alder reaction of an *o*-amino arylallene; and the other featuring a Meerwein-Eschenmoser Claisen rearrangement (Scheme 32).

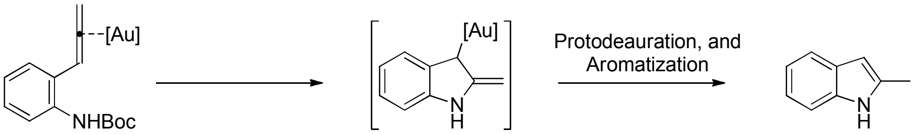
Scheme 32: ***Two proposed routes to communesin alkaloids***



Gold-Induced Cycloaddition Route

Although currently unsuccessful, the gold-induced (formal) Diels-Alder reaction between an *o*-amino arylallene and an indole would provide a substantially more effective route to the C, D, E, and F rings of the communesin alkaloids. The potential benefits of this route are the simplicity and accessibility of the substrates, and the significant amount of complexity that can be generated from the Diels-Alder reaction in a stereospecific manner. Unfortunately, under all our choices of conditions and substrates, the unforeseen 5-*endo-dig* cyclization giving 2-substituted indoles occurred (Scheme 33).

Scheme 33: ***Gold-induced 5-endo-dig cyclization giving 2-substituted indoles***



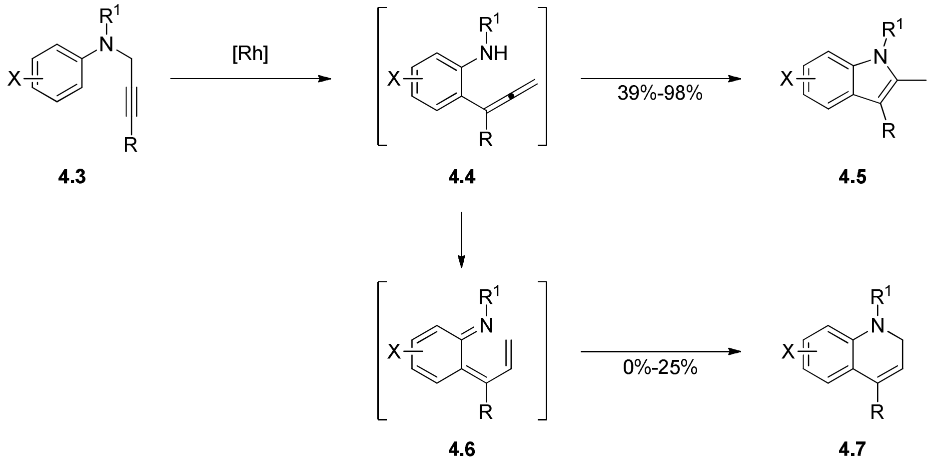
4.1 **4.2** **2.28**

It has come to our attention that a similar 5-*endo-dig* cyclization has been observed using a variety of rhodium catalysts (Scheme 34).[38] Although the output of this reaction is predominantly the indole product (**4.5**), under certain conditions low yields of quinoline **4.7** are also obtained. The author postulated that these could arise from a secondary pathway whereby a rearrangement occurs to give intermediate **4.6** which then undergoes an amino-Claisen rearrangement to give quinolone product **4.7**. This reactivity has also been observed with *o*-allenylaniline under thermal[39] and Cu-promoted[40] conditions. This intermediate is analogous to that which we wish to use for our Diels-Alder reaction, suggesting that the use of different metal catalysts and conditions should be explored.

The Meerwein-Eschenmoser Claisen Route

Although we had more success with this route, it does little to advance the efficiency of the synthesis of the early core of the molecule. We believe the Meerwein-Eschenmoser Claisen reaction provides much of the functionality to access the C, D, E, and F rings of the communesin alkaloids (and it does so using a significantly different way from any preceding syntheses); however, it does so racemically and in only moderate yields. Nevertheless, it should provide us access to intermediates later in the synthesis where we wish to experiment with the Pictet-Spengler reaction to furnish the G ring.

Scheme 34: *Rhodium catalysed synthesis of indoles via an amino-Claisen rearrangement of N-propargylanilines*

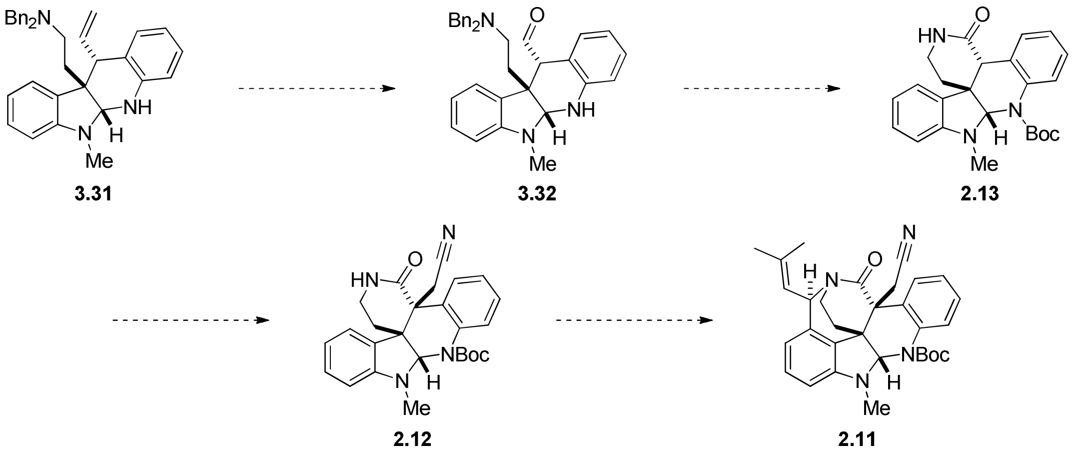


Earlier, issues with the Meerwein-Eschenmoser Claisen reaction when using a variety of protected (E)-3-(2-aminophenyl)prop-2-en-1-ols forced us to use the nitro equivalent resulting in additional oxidation state adjustments, increasing the overall length of the synthesis. Other issues involving the choice of protecting group and protecting group incompatibility with annulation reaction conditions forced us to switch protecting groups midway through the synthesis, further increasing the overall length of the synthesis. Although the annulation is only successful with a single diastereomer, the possibility of isomerization of the non-reactive diastereomer makes this a moot point.

Conversion of alkene **3.31** to aldehyde **3.32** remains the current obstacle in our synthesis (Scheme 35). Common methods such as ozonolysis and Lemieux-Johnson conditions have proven unsuccessful, possibly due to oxidation of the unprotected nitrogen or to the mono-substituted nature of the alkene. However, reaction conditions have not been exhausted and we are confident we will succeed in obtaining the desired product.

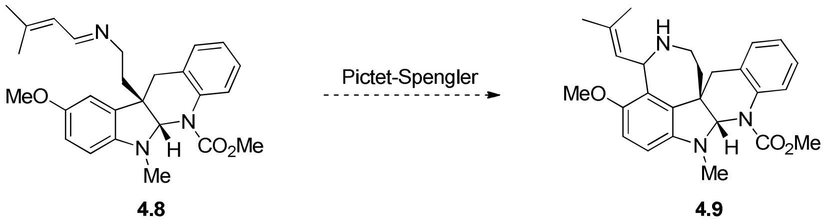
Upon synthesis of aldehyde **3.32**, many of the steps have already been performed as part of previous syntheses, albeit on slightly different substrates. Oxidation of **3.32** to acid and subsequent condensation give the pentacyclic substructure **2.13**. Intermediate **2.12** is then treated with carbamic acid to give the aminobutenone, which is then alkylated to give the alcohol, and mild acid/base catalysis may be used to promote cyclization to give compound **2.11**. (Scheme 35)

Scheme 35: *Proposed steps from intermediate 3.31 to intermediate 2.11*



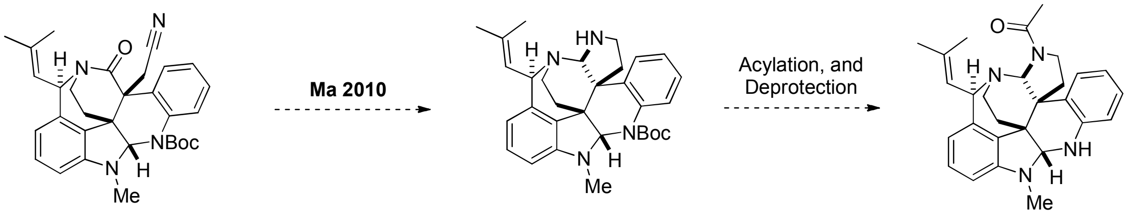
Unfortunately, a recent paper published by the Garg group[41] found, during their own synthetic approach to the communesin alkaloids, that "[their] efforts to arrive at pentacycle **4.9** through a Pictet-Spengler cyclization have been unsuccessful to date" (Scheme 36). They go on to say that attempts to form intermediate **4.9** via acid-promoted conditions led to hydrolysis of the imine, and base-promoted conditions led to recovery of the starting material. Although our two approaches are not exactly the same, this goes to show that this approach in not a trivial one. In Garg's case, they are using a much more electron rich aromatic relative to ours, favouring the attack on the imine. However, in our case, we have an iminium generated *in situ* directly adjacent to the aromatic. Either way, we believe that we can expect significant experimentation to accomplish this Pictet-Spengler.

Scheme 36: *Garg's unsuccessful synthesis of the G ring of the communesin alkaloids via a Pictet-Spengler cyclization*



Assuming we are successful in obtaining the Pictet-Spengler product, the next few steps of the synthesis involve a series of conditions first developed during Ma's synthesis.[42] First, the nitrile is reduced using LAH to give the amine, which upon treatment using ammonium acetate and $NaBH(OAc)_3$ gives aminal **2.10**. Finally, acylation and deprotection yield the final product, (±)-communesin F. (Scheme 37)

Scheme 37: *Proposed steps from intermediate 2.11 to (±)-communesin F*

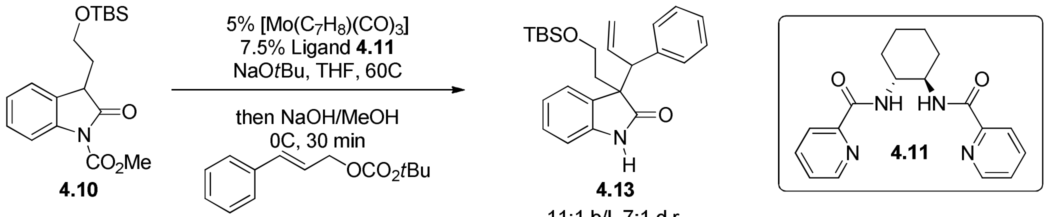


2.11 **2.10** **1.6** **(±)-communesin F**

Asymmetric Variation

As previously stated, a major drawback of our synthesis is that it is not asymmetric; however, a series of papers published by Trost and Zhang describes the molybdenum-catalyzed asymmetric allylic alkylation of 3-alkyloxindoles (Scheme 38).[43] Using these conditions, we could achieve an asymmetric variation of our proposed synthesis. Little would have to change from our initially proposed retrosynthesis, as the potential product of this reaction (**4.13**) would be the same as that of the Meerwein- Eschenmoser Claisen except as predominantly a single stereoisomer. Perhaps too, this would eliminate the need for a mid-synthesis change in protecting group, or an oxidation state adjustment that had previously added additional steps to our synthesis (Scheme 39). If successful, this would cause a significant increase in the impact of our synthesis.

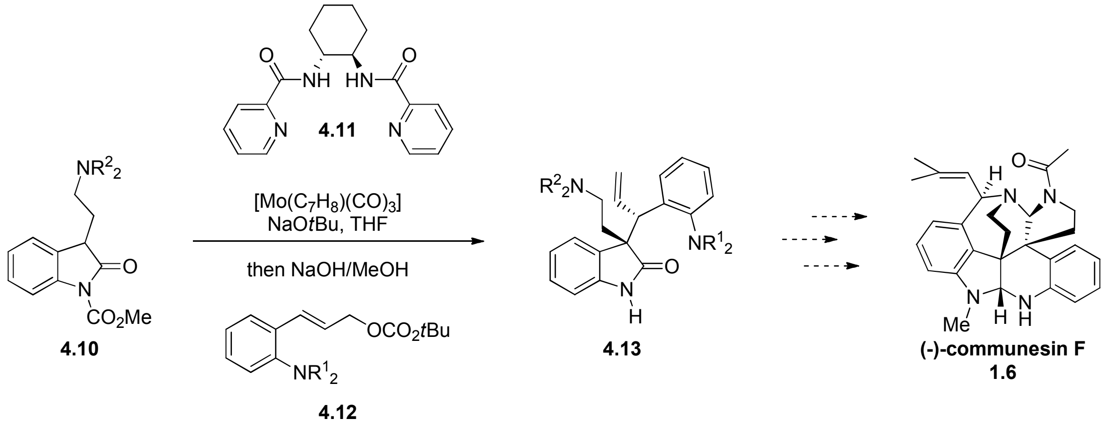
Scheme 38: *Mo catalyzed asymmetric allylic alkylation of oxindoles*



4.10 **4.12** **4.13**

11:1 b/l, 7:1 d.r.
83% yield, 97% *ee*

Scheme 39: *Proposed use of Mo catalyzed asymmetric allylic alkylation in the total synthesis of (-)-communesin F*



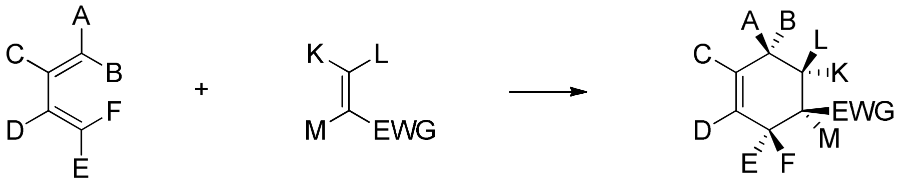
Part B: Aluminum as a Catalyst for the Diels-Alder Cycloaddition of Highly Hindered Dienophiles

Chapter 5: Diels-Alder Reaction

Introduction

The Diels-Alder reaction is a pericyclic reaction that involves the cycloaddition of a conjugated diene and a substituted alkene, alkyne, benzyne, or allene (often referred to as the dienophile) to form two new carbon-carbon sigma bonds, giving a cyclohexene ring as shown generally in Scheme 40. Early forms of this reaction involved mixing diene and dienophile in a non-polar solvent and heating to afford high yields of cycloadduct; however, a vast assortment of variations have been developed, including Lewis acid catalysed, high pressure, inverse-electron demand and *hetero*-variants. The synthetic value of the Diels-Alder reaction derives from a number of inherent features; most importantly, up to four stereo-centers can be established at once, and often with high regio- and stereo- selectivity.

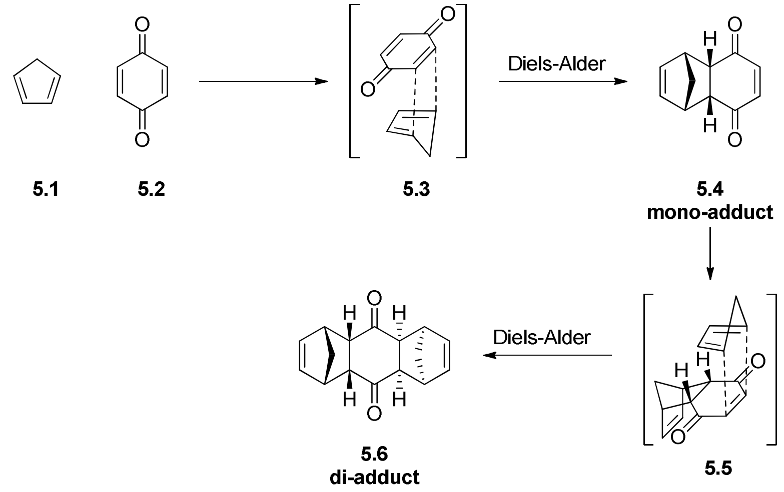
Scheme 40: *General Diels-Alder reaction*



Discovery

This novel reaction was first reported in 1928 by Otto Paul Hermann Diels and his student Kurt Alder.[44] Within their paper, they report the Diels-Alder reaction, or simply "diene synthesis" as it was known at the time of its discovery, of cyclopentadiene and quinone to yield both the mono-adduct (**5.4**) and the di-adduct (**5.6**). (Scheme 41) Prior to this, Zincke had discovered[45,46] and correctly identified[47] the structure of tetrachlorocyclopentadienone, and Lebedev[48,] had recognized vinylcyclohexene as the dimer of butadiene, but neither had realized the generality of the reaction. Diels and Alder would cite in their original paper a publication by Hans von Euler who, in 1920, had described the combination of isoprene and *p*-quinone in a 2:1 ratio and correctly identified the structure of the product.[49] However, von Euler felt that the structural proof was incomplete and that it would have to be an area of future study. He would never return to this work. For an interesting account of the early work and circumstantial events leading to the discovery of the Diels-Alder reaction, see Dr. Jerome A. Berson's article entitled "Discoveries Missed, Discoveries Made: Creativity, Influence, and Fame in Chemistry".[50]

Scheme 41: ***Formation of mono-adduct and di-adduct by Diels and Alder in their 1928 publication***



Since this initial discovery, the Diels-Alder reaction has grown to be one of the single most important reactions in the synthetic organic chemist's tool set. In 1950, both Otto Diels and Kurt Alder would be awarded the Nobel Prize in Chemistry "for their discovery and development of the diene synthesis".

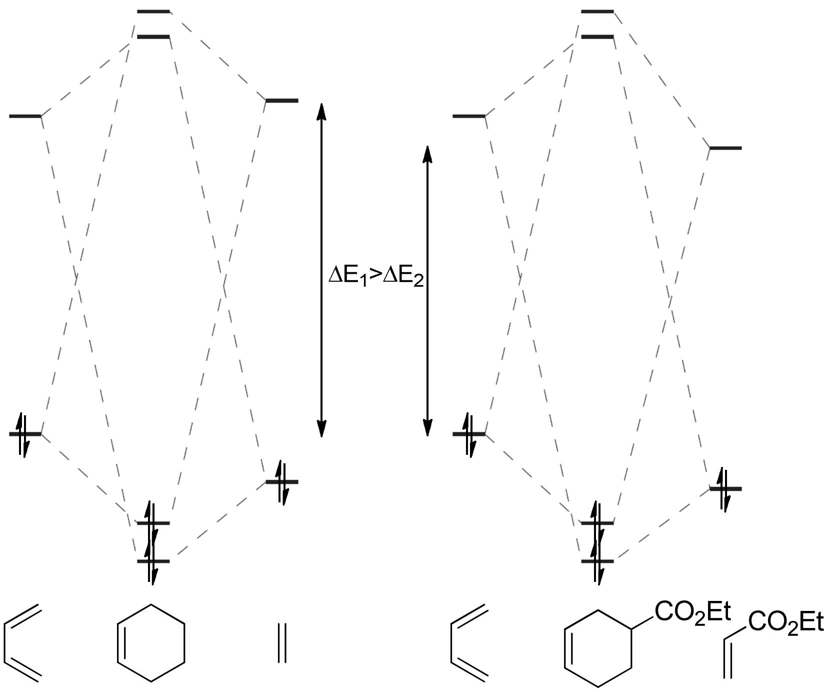
Stereo- and Regio- control of Diels-Alder Reactions

One of the major reasons the Diels-Alder reaction has proven so useful is the predictable nature of the reaction. The Woodward-Hoffmann rules outlined by Robert Burns Woodward and Roald Hoffmann are used to predict the stereochemical outcome of pericyclic reactions based on their molecular orbitals.[51]

The reaction is described by the Woodward-Hoffmann rules as a $[\pi 4_s + \pi 2_s]$ cycloaddition occurring in a concerted but not necessarily symmetrically synchronous fashion. This is said to be a *symmetry-allowed* process as the frontier molecular orbitals have matching wave function signs.

In a normal electron demand Diels-Alder reaction, the HOMO of the diene donates electrons into the LUMO of the dienophile. By adding electron withdrawing groups to the diene or electron donating groups to the dienophile, we can raise the energy of the diene's HOMO or lower the energy of the dienophile's LUMO, respectively. (Figure 6) By lowering the energy difference between these two frontier molecular orbitals, we can increase the rate of the reaction. This phenomena is correlated with the energy expression derived by Klopman[52] and Salem[53] from perturbation theory.

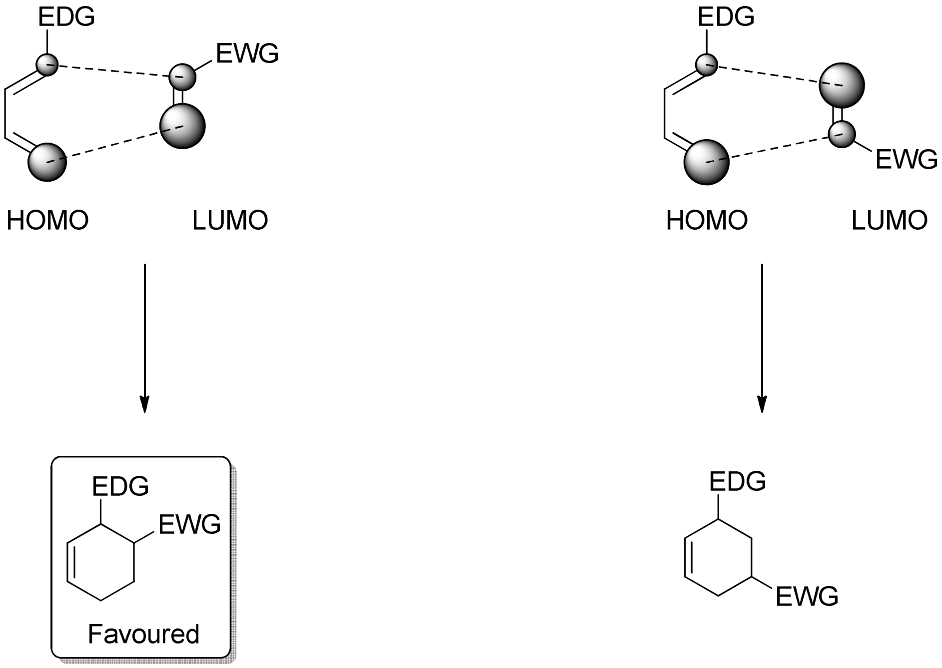
Figure 6: ***Generalized FMO diagram depicting a normal electron-demand Diels-Alder reaction***



These new bonds are formed in a stereospecific manner with respect to A) regiochemistry (*ortho* versus *para* orientation); and B) diastereoselectivity (*endo* versus *exo*). As a result, synthetic organic chemists are able to use these rules to effectively predict the major product expected from the combination of a diene and a dienophile.

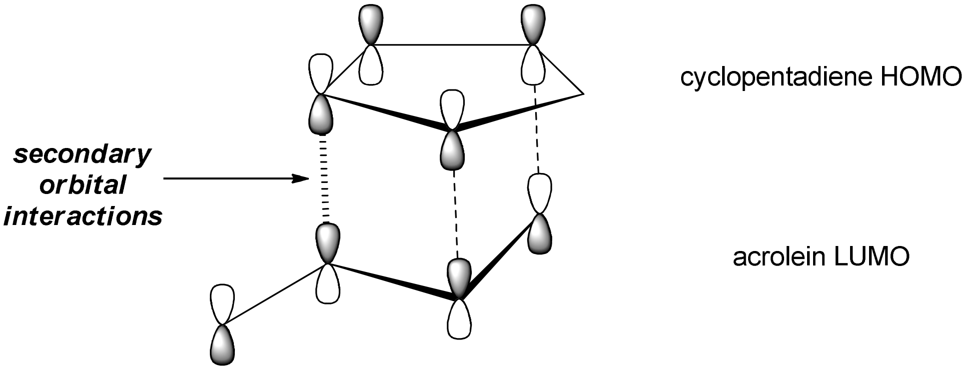
Generally, the regiochemistry depends on the substitution of both cycloaddition partners. It is possible to predict the regiochemical outcome by examining the atomic coefficients of the frontier molecular orbitals. (Figure 7)

Figure 7: *Use of atomic coefficients to determine regiochemical biases*



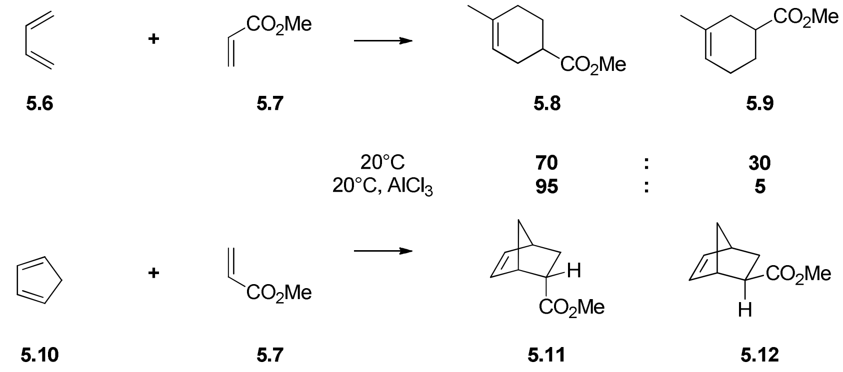
Since their proposal in 1965[54], secondary orbital interactions (SOI) have been used to describe how the *endo* product tends to be the major product in certain kinetic (irreversible) Diels-Alder reactions. This observation is called the *endo* rule.[55] The interactions between the non-bonding atomic orbitals of the diene and dienophile during the reorganization of the π system have been attributed with lowering the energy of the transition state leading to the kinetically favoured *endo* product. (Figure 8) It has been more recently suggested that a combination of common mechanisms such as steric interactions, solvent effects, hydrogen bonds, and electrostatic forces can be used to account for this observation without having to rely upon the presence of SOIs.[56]

Figure 8: endo *and* exo *transitions states of cyclopentadiene and acolein depicting secondary orbital interactions*



Use of Lewis acids can play a major role in enhancing diastereo- and regio- selectivity as well as increasing the rate. Typically, the Lewis acid complexes to a carbonyl conjugated to the π bond of the dienophile. This complexation lowers the energy of the LUMO and accentuates the coefficient of the frontier molecular orbital, thereby enhancing the rate as well as the regio- and diastereo-selectivities.[57] This is demonstrated in the examples shown in Scheme 42.[58]

Scheme 42: *Effects of Lewis acid on the regio- and diastereo- selectivity of the Diels-Alder reaction*

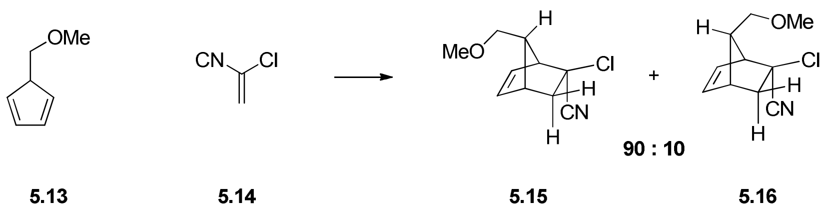


	5.8		5.9
20°C	**70**	:	**30**
20°C, $AlCl_3$	**95**	:	**5**

	5.11		5.12
CH_2Cl_2, 0°C	**80**	:	**20**
C_6H_6, $SnCl_4$, 25°C	**95**	:	**5**

Facial selectivity can arise from steric and electronic effects inherent in either of the substrates, or from the use of an asymmetric variant of the Diels-Alder reaction.[59] If the diene or dienophile does not have planar symmetry, there may be substantial facial selectivity as shown in an early intermediate of Corey's synthesis of prostaglandin F2α (Scheme 43).[60] Chiral auxiliaries and chiral catalysts have also been employed to enhance the facial selectivity of the Diels-Alder reaction. In the case of chiral auxiliaries, the chiral information can be imparted from either the diene or the dienophile. Common auxiliaries for the dienophile include N-acyloxazolidinones and camphor derived N-enoyl sultams amongst many others.

Scheme 43: *Diels-Alder reaction demonstrating inherent facial selectivity*

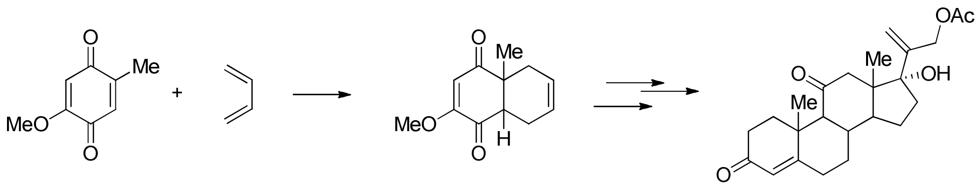


Diels-Alder in Total Synthesis

In their original publication[61] in 1928, Diels and Alder recognized the significance of their finding in the synthesis of complex natural products. They write the following in their report: “Thus it appears to us that the possibility of synthesis of complex natural compounds related to or identical with natural products such as terpenes, sesquiterpenes, perhaps also alkaloids, has been moved to the near prospect.” They were also quick to lay claim to this new methodology. “We explicitly reserve for ourselves the application of the reaction discovered by us to the solution of such problems.”

However, instead of focussing on synthetic applications of their new discovery, they would instead focus on its mechanistic and stereochemical aspects. As a result, this claim to ownership would eventually be ignored. Some of the first uses of the Diels-Alder reaction in natural product synthesis include Woodward[62,63] and Sarett’s[64] total synthesis of cortisone (Scheme 44) and Stork’s[65] stereospecific total synthesis of cantharidin.

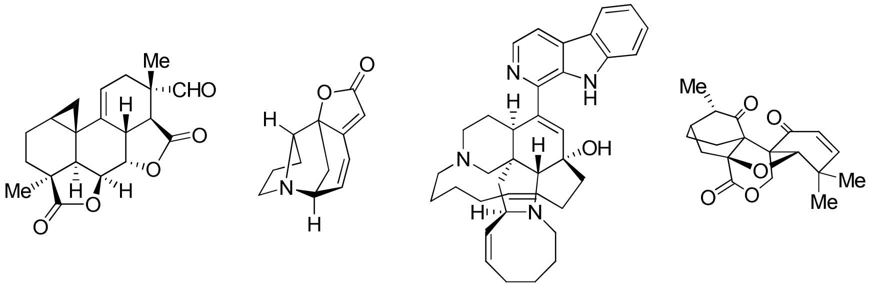
Scheme 44: ***Early total syntheses using the Diels-Alder reaction***



5.17 **5.6** **5.18** **5.19**

Since these early syntheses, much advancement to the selectivity and scope of the Diels-Alder reaction has been made. Looking over the years, we see that the Diels-Alder reaction continues to be used in attaining some very complex natural products (Figure 9).

Figure 9: ***Select total syntheses involving the Diels-Alder reactions***



5.20
myrocin C
1979

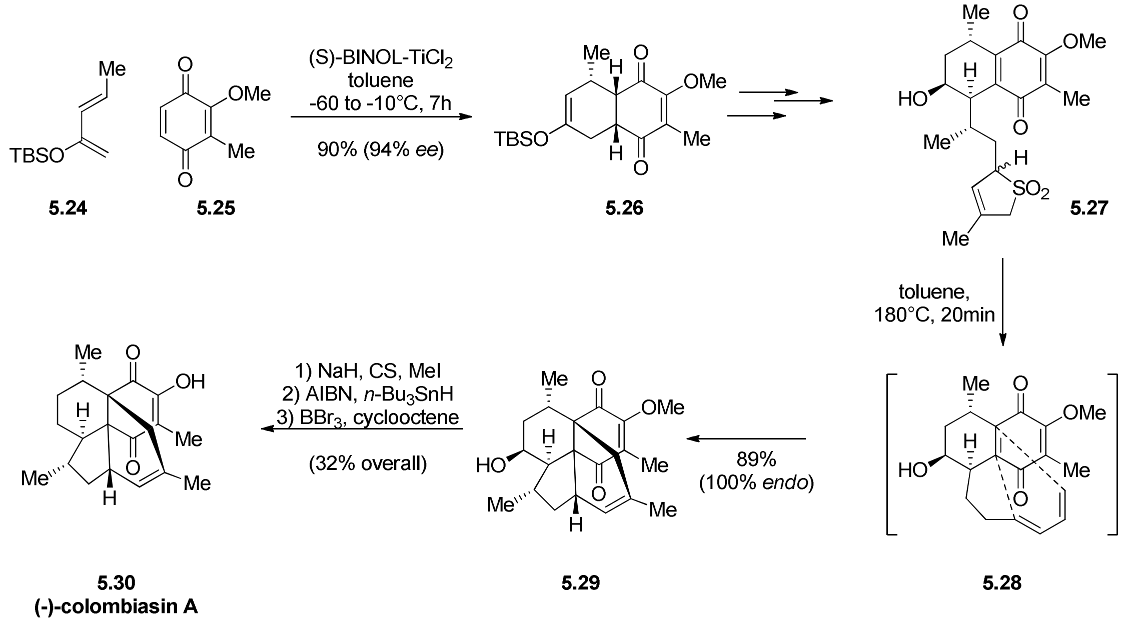
5.21
(-)-norsecurinine
1989

5.22
manzamine A
1999

5.23
maoecrystal V
2010

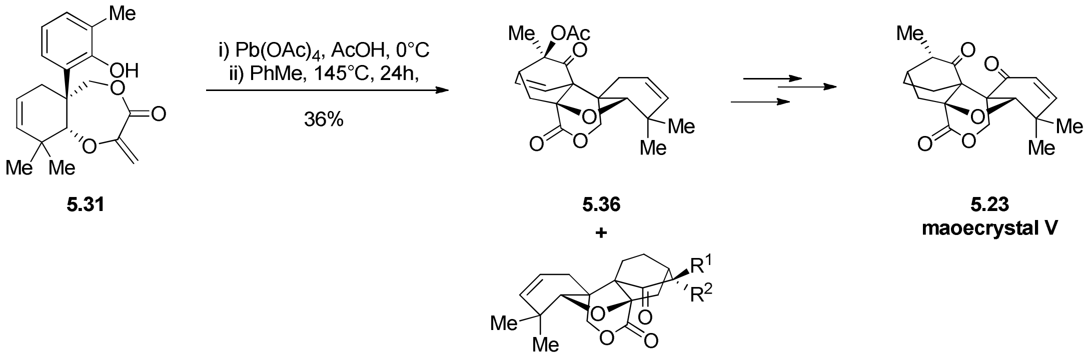
During Nicolaou's 2001 total synthesis of a unique terpenoid, (-)-colombiasin A,[66] he cleverly employs two Diels-Alder reactions (Scheme 45), the first of which is performed enantioselectively using Mikami's catalyst system to afford a single product in high yields and high enantiomer excess. This intermediate, containing a sulfone-masked diene, is then subjected to refluxing toluene to regenerate the diene (via thermal extrusion of SO_2) which is then in position to undergo an intramolecular Diels-Alder reaction. This intermediate is then converted to (-)-colombiasin A.

Scheme 45: *Nicolaou's total synthesis of (-)-colombiasin A*



Yang's total synthesis of the racemate of Maoecrystal V[67] is another excellent example of the total synthesis of a complex natural product using a Diels-Alder reaction. In this synthesis, the Wessely oxidative dearomatization of a phenol is used to generate a diene which then undergoes an intramolecular Diels-Alder reaction (IMDA) to afford the highly congested pentacyclic core of maoecrystal V (Scheme 46). Although the reaction produced an inseparable mixture of products, the desired compound was carried through to maoecrystal V in high yields.

Scheme 46: *Total Synthesis of (±)-Maoecrystal V by Yang and co-workers*



5.37 28% (R^1 = Me, R^2 = OAc)
5.38 12% (R^1 = OAc, R^2 = Me)

Right from the discovery of the Diels-Alder reaction in 1928, its importance in the synthesis of natural products was recognized. From early syntheses, such as cortisone, to more contemporary examples, such as maoecrystal V, the Diels-Alder reaction continues to play a prominent role in the synthesis of complex natural products.

Chapter 6: Current Methodology and Precedent

Despite great progress made in enhancing selectivity, widening scope, and employing increasingly tolerant reaction conditions, there remain certain challenges to be overcome in the Diels-Alder reaction. One such challenge is when highly hindered substrates, such as β,γ,γ -trisubstituted and γ,γ-disubstituted dienophiles, are used. Due to the additional steric encumbrance, substrates of this nature suffer from long reaction times and reduced selectivity, and often require forcing conditions.

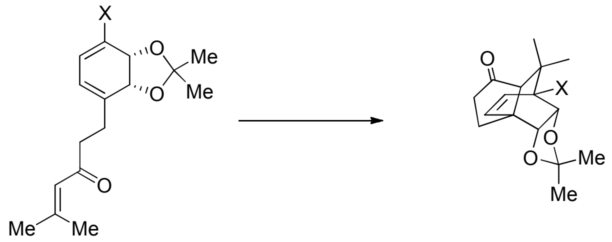
Current Methodology

A handful of methods have been developed, however all required some form of caveat and none have been shown to be generally applicable. Some of these methods include performing the Diels-Alder reaction intramolecularly, activating the dienophile by adding additional electron withdrawing groups, using dimethyl aluminum chloride as a catalyst, and using trimethyl aluminum as a desiccant. Herein we will describe these methods including their strengths and weaknesses.

The first method is to perform an intramolecular Diels-Alder reaction. By linking the diene and dienophile, not only does it impart additional regiochemical and stereochemical control imposed by conformational constraints, but it also lowers the entropic barrier to reaction causing an increase in rate. In Banwell's paper[68] describing the synthesis of bicyclo[2.2.2]octanes that incorporate 1,2-fused carbocycles, he found that substrate **6.1** would not proceed without using forcing conditions despite being intramolecular. In fact, no isolatable amount of product was formed when additional substituents were added to the diene **6.2** under the same conditions (Table 4).

The second method is to activate the dienophile by adding additional electron withdrawing groups thus reducing the HOMO-LUMO gap and increasing the rate of reaction. The problem with this is that it may add additional synthetic steps to remove the additional activating group or to transform it into a useable functionality. In the 2009 publication by Liu and Zhu[69], they showed that by using a variety of α-cyano α.β-alkenones they could gain access to a variety of highly substituted cyclohexene adducts, including those deriving from β,β-disubstituted dienophiles. They were then able to reductively alkylate certain adducts in good yields, however the methodology was far from general (Scheme 47).

Table 4: *Banwell's synthesis of bicyclo[2.2.2]octanes that incorporate 1,2-fused carbocycles using forcing conditions*

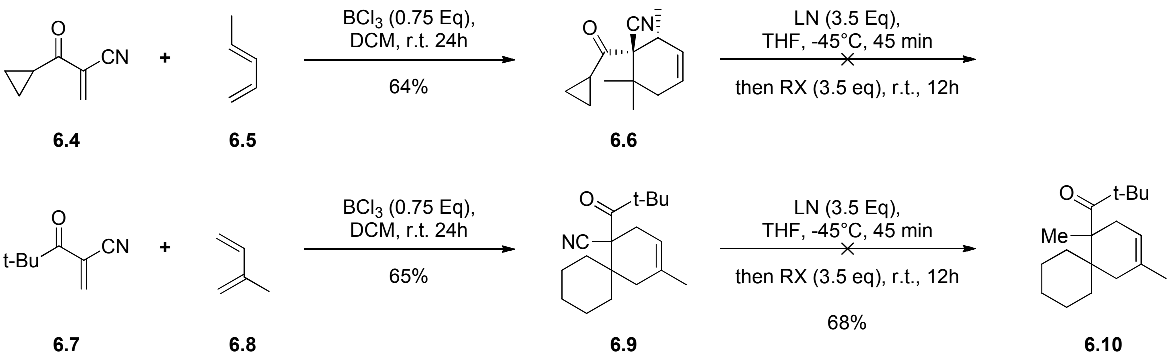


6.1 (X = H)
6.2 (X = Me)

6.3 (X = H)
6.4 (X = Me)

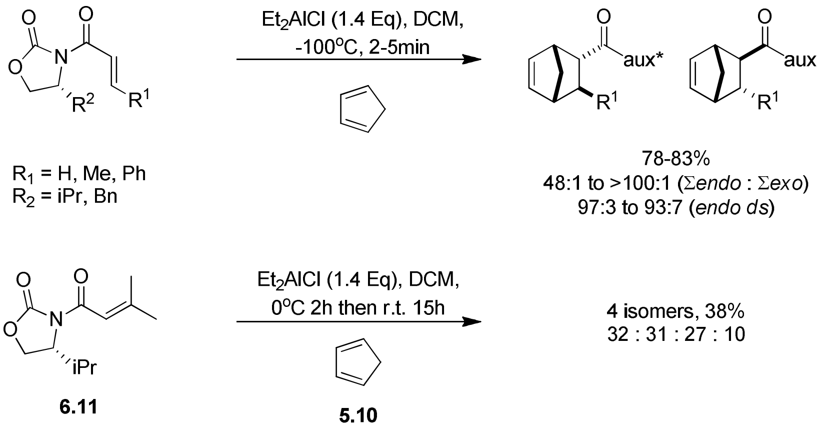
Substrate	Conditions	Adduct (% Yield)
6.1	Toluene, BHT, 112°C, 16h	No isolatable product
6.1	Mesitylene, BHT, 165°C, 96h	**6.3** (45%)
6.2	Mesitylene, BHT, 165°C, 96h	No isolatable product

Scheme 47: *Liu and Zhu demonstrate the use of α-cyano α.β-alkenones to gain access to highly substituted cyclohexene adducts*



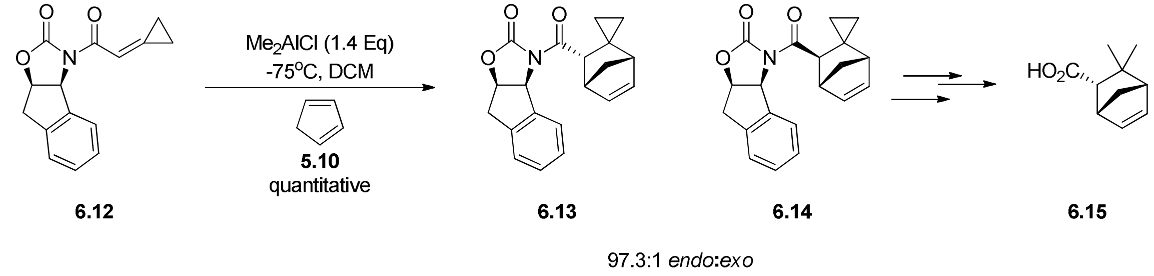
The third method is reported by the Kuethe group[70] in 2006. It uses a variation of the methodology first reported by the Evans group in 1988.[71] The Evans method involved the use of super-stoichiometric amounts of diethyl aluminum chloride to furnish the Diels-Alder adduct in high enantio- and diastereo- selectivity. The reaction fared poorly when using highly hindered dienophiles such as dienophile **6.11** (Scheme 48).

Scheme 48: *Evans demonstrates the use of super stoichiometric amounts of alkyl aluminum chloride to catalyze the Diels-Alder reaction*

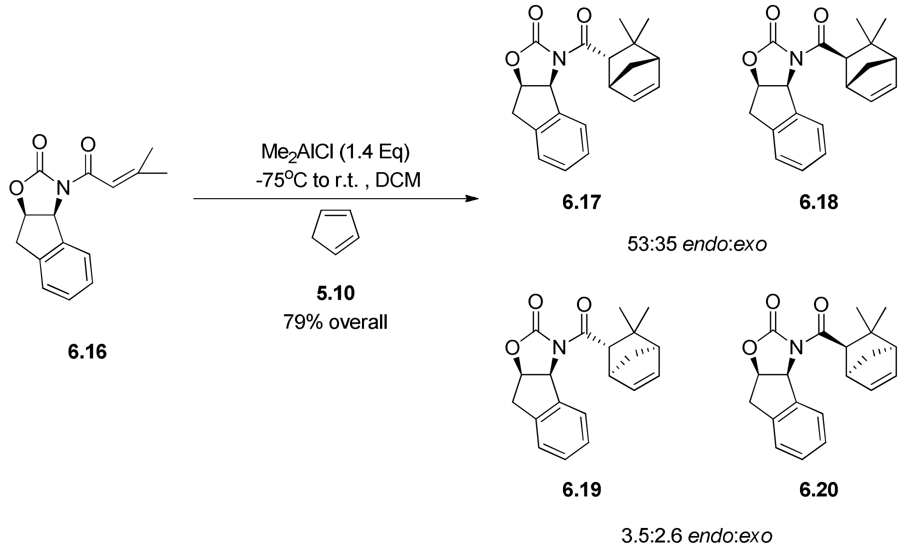


The Kuethe method was originally employed for the Diels-Alder reaction of chiral cyclopropylidene imide dienophiles to access gem-dimethyl- and spirocyclopropane norbornyl derivatives (Scheme 49). They take advantage of the increased Lewis acidity of dimethyl aluminum chloride to facilitate the reaction. This allows for an increase in selectivity and yield over the use of diethyl aluminum chloride. This increase in selectivity and yield can be seen when using dimethyl aluminum chloride to catalyse the Diels-Alder reaction between dienophile **6.12** and cyclopentadiene (**5.10**) (Scheme 50).

Scheme 49: *Kuethe demonstrates the use of super stoichiometric dimethyl aluminum chloride to access gem-dimethyl- and spirocyclopropane norbornyl derivatives asymmetrically*

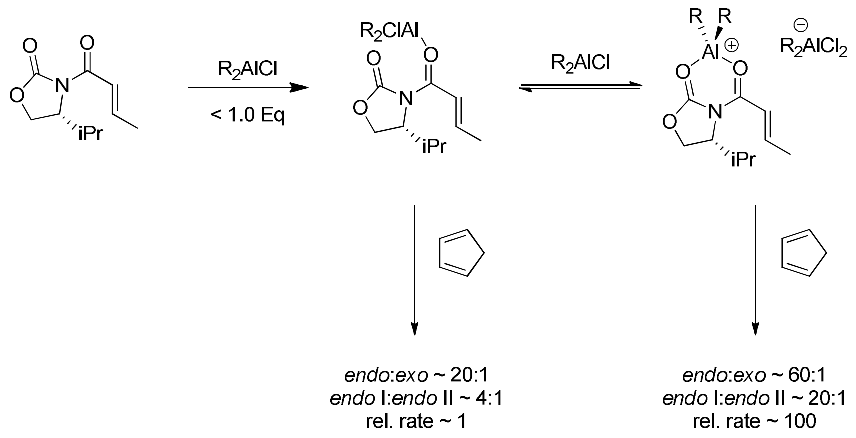


Scheme 50: *Example demonstrating the selectivity of Kuethe's method*



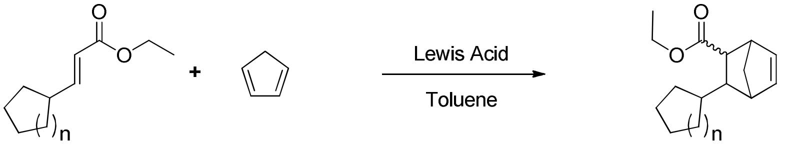
Evans proposes a cationic transition state as the reactive species. This was based on the observation that when using sub-stoichiometric amounts of diethyl aluminum chloride, the relative rate and facial selectivity are significantly reduced (Scheme 51). This was later supported spectroscopically by Castellino and Dwight who used ^{1}H and ^{13}C NMR to show the formation of a 1:1 complex upon addition of one equivalent of diethyl aluminum chloride and a 2:1 complex upon addition of two equivalents.[72] However, more recently, new evidence has been put forward to support the possibility of bi-complexes where each carbonyl is coordinated to different aluminum centers.[73]

Scheme 51: Evans' proposed cationic intermediate



The final method involves the use of trimethyl aluminum as a desiccant. During the Miller group's work on the Diels-Alder reaction between β,β-disubstituted dienophiles and cyclopentadiene,[74] they found that many of the common Lewis acid catalysts were ineffective at catalyzing the reaction. Concerned that residual water was interfering with the reaction, they pretreated the dienophile solution with a desiccant, trimethyl aluminum (0.05 eq), followed by aluminum trichloride (1.0 eq) and cyclopentadiene. This combination provided 50% conversion to the desired adduct after 48 hours. Reducing the ring size, and thus the steric influence, by one atom increased the yield to 89% with a 2:1 *endo*:*exo* ratio and, by lowering the temperature and catalyst loading, they were able to improve the yield and selectivity to 91% and 7:1 *endo*:*exo* respectively (Table 5).

Table 5: ***Example of mixed Lewis acid catalysis***



6.21 (n = 1)
6.22 (n = 2)

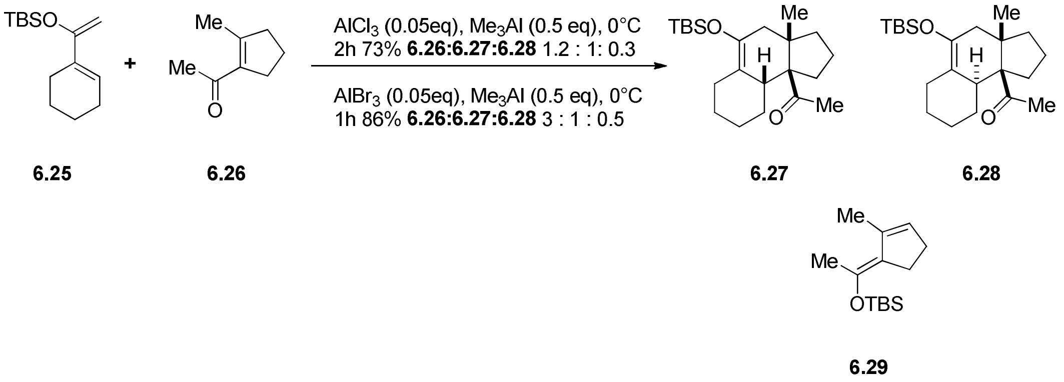
5.10

6.23 (n = 1)
6.24 (n = 2)

Entry	Substrate	Conditions	Adduct (% Yield)
1	**6.21**	$Al(CH_3)_3$ (0.05 eq), $AlCl_3$ (1.0 eq), r.t.	**6.23** (50% conversion after 48 h)
2	**6.22**	$Al(CH_3)_3$ (0.05 eq), $AlCl_3$ (1.0 eq), r.t.	**6.24** (89% yield, 2:1 *endo*:*exo*)
3	**6.22**	$Al(CH_3)_3$ (0.05 eq), $AlCl_3$ (0.5 eq), -20°C	**6.24** (91% yield, 7:1 *endo*:*exo*)

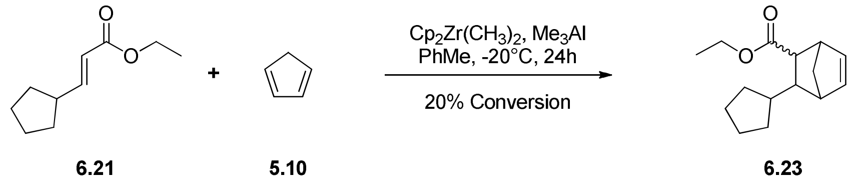
Another group to use this same mixed catalyst system is that of Jung and co-workers in their work towards an efficient synthesis of a tricyclic BCD analogue of ouabain.[75] Their initial attempts at thermal conditions returned only starting material, and the use of Lewis acid catalysts gave only the decomposition of the diene. Using the $AlCl_3$/$AlMe_3$ mixed catalyst system gave 73% conversion yielding a mixture of diastereomers and the TBS trapped enol **6.29**. By switching to the easier to handle aluminum tribromide rather than aluminum trichloride as desiccant, they were able to increase the yield to 86% and influence the selectivity to more heavily favour the *endo* product (Scheme 52).

Scheme 52: *Second example of mixed Lewis acid catalysis*



In both cases, the increase in reactivity was attributed to the drying effect of trimethyl aluminum. However, one interesting thing Miller noted was that when other known desiccants were used, such as $Cp_2Zr(CH_3)_2$, the reactivity was significantly reduced (Scheme 53). We found it surprising that changing desiccants would have such a drastic effect on the reactivity and we therefore began researching the possibility of other causes for the observed increase in reactivity when these two Lewis acids were used in combination.

Scheme 53: *Other known dessicants have been shown to be less effective in mixed Lewis acid catalysis*



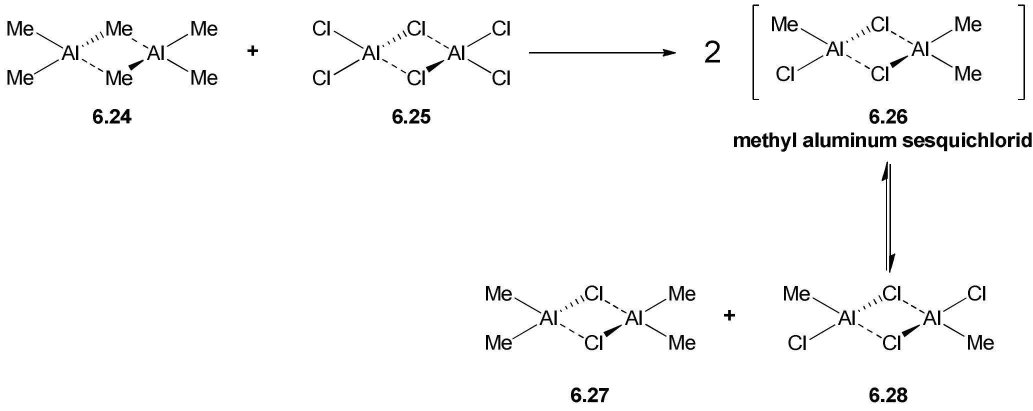
From our research, it came to our attention that this same combination of Lewis acids is known to form the sesquichloride dimers in equilibrium with the homodimers resulting from disproportionation (Scheme 54).[76] We wondered if it could be possible that this sesquichloride be the active catalyst that imparts the increase in reactivity.

Alkyl Aluminum Sesquichlorides

From this point, we turned the focus of our research towards common uses of alkyl aluminum sesquichloride. Generally, this aluminum catalyst is used in the copolymerization of conjugate dienes with acrylates[77] and as a co-catalyst for Ziegler-Natta polymerizations of α-olefins.[78] We were surprised when we were unable to find any examples where alkyl aluminum sesquichlorides were used intentionally for the catalysis of Diels-Alder reactions. Not surprisingly though, we were able to find examples where the Diels-Alder adduct was observed. In a report by

Gabbott and co-workers, during the co-polymerization of methyl methacrylate and isoprene using ethyl aluminum sesquichloride (EASC), the Diels-Alder adduct was observed although in trace amounts (Scheme 55).[79]

Scheme 54: *Methyl aluminum sesquichloride formed through disproportionation of homodimers of trimethyl aluminum chloride and aluminum trichloride*

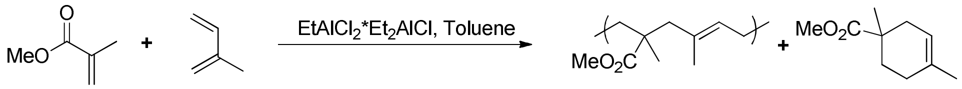


6.24 **6.25** **6.26**

methyl aluminum sesquichloride

6.27 **6.28**

Scheme 55: *Diels-Alder adduct observed during co-polymerizations when EASC is used as catalyst*

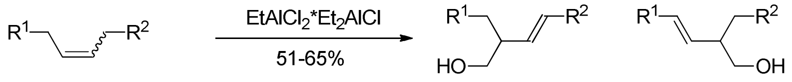


Observed

6.29 **6.8** **6.30** **6.31**

More interestingly, EASC has been reported to catalyse the intermolecular Ene reaction of fatty acids, ester, and alcohols with formaldehyde as reported by Metzger and co-workers (Scheme 56).[80]

Scheme 56: *EASC* catalysis of an Ene reaction



olic acid/methyl ester/alcohol
petroselinic acid/methyl ester/alcohol
10-undecenoic acid/methyl ester/alcohol

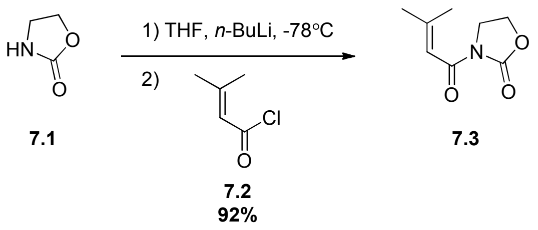
Returning our focus to the use of sesquichloride as a catalyst for Diels-Alder reactions, we established what the goals of our research would be; (1) to establish if alkyl aluminum sesquichlorides could be used to catalyse the Diels-Alder reaction of highly hindered dienophiles; (2) to establish the substrate scope of the reaction; (3) to determine if the reaction proceeds through a novel mode of reactivity other than the one seen in the Evans' superstoichiometric

Diels-Alder reaction; and (4) to apply this methodology to an asymmetric variant. Herein we will present and discuss the worked performed towards these goals.

Chapter 7: Results and Discussion

To begin our study, we selected dienophile **7.3** as our highly hindered dienophile due to its simple structure and the possibility of employing a chiral oxazolidinone moiety to facilitate an asymmetric variant. It would also allow for the chelation of aluminum catalysts, as proposed in the Evans cationic model shown earlier, to give the cationic intermediate. This starting material was obtained via coupling of the oxazolidinone (**7.1**) to pre-prepared acid chloride **7.2** as shown in Scheme 57.

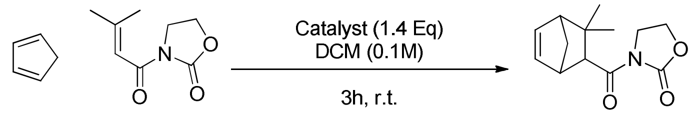
Scheme 57: *Preparation of highly hindered dienophile*



Lewis Acid Catalysts

With a dienophile prepared, we were able to probe the reactivity of a variety of aluminum derived Lewis acid catalysts in the Diels-Alder reaction of highly hindered dienophiles. (Table 6) We expected to see increased reactivity of the methyl derived catalysts over their ethyl derived counterparts as seen in the literature when Kuethe was able to increase reactivity over the Evans system by switching from ethyl aluminum chloride to methyl aluminum chloride. We were surprised when this wasn't the case. The ethyl derived catalyst preceded with an increased conversion over the same time period over its methyl counterparts albeit at a loss of diastereoselectivity. EASC at 70 mol% loading gave comparable conversions over 3 hours to the dialkyl aluminum chlorides but gave significantly higher corrected yields, again at a loss of diastereoselectivity. In the case of EASC at 1.4 equivalents, we see a drop in conversion over a 3 hour period, and a decrease in corrected yield compared to the use of 70 mol%. This is most likely the result of procedural complications due to polymerization of cyclopentadiene under these conditions. When using both homodimer constituents of EASC together, we found a comparable conversion over 3 hours and increased diastereoselectivity.

Table 6: ***Reactivity of a variety of aluminum catalysts on test system***



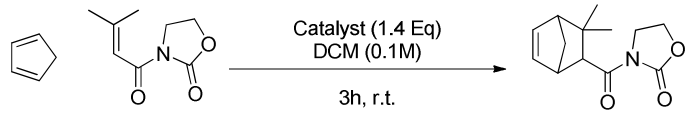
Entry	**Catalyst**	***Endo*:*Exo***	**Conversion (%)**	**Isolated yield (%)**	**Adjusted % Yield* (%)**
1	$MeAlCl_2$ (1.4 Eq)	0.8:1	82	77	94
2	$EtAlCl_2$ (1.4 Eq)	0.7:1	88	85	97
3	Me_2AlCl (1.4 Eq)	3.4:1	99	76	77
4	Et_2AlCl (1.4 Eq)	2.8:1	98	83	84
5	Et_2AlCl-Cl_2AlEt (1.4 Eq)	0.3:1	48	29	61
6	Et_2AlCl-Cl_2AlEt (0.7 Eq)	1.1:1	97	92	95
7	$EtAlCl_2$ (0.7 Eq) + Et_2AlCl (0.7 Eq)	2.1:1	93	86	93

*Based on recovered starting material

Temperature Effects

Next, we decided to explore the effects of temperature on the diastereoselectivity and conversion when using EASC as catalyst. Not surprisingly, we saw an increase in diastereoselectivity as the temperature was lowered and a subsequent drop in conversion (Table 7). At room temperature, the reaction was complete after 1.5 hours with high isolated yields, and with a diastereoselectivity of 1.6:1 *endo*:*exo*. When the temperature was lowered to 0°C, the reaction took 3 hours to reach completion and the isolated yield of product was slightly decreased; however, the diastereoselectivity had improved to 2.9:1 *endo*:*exo*. At -30°C, the reaction proceeded to roughly 60% conversion after 4.5 hours but the diastereoselectivity had increased to 3.4 *endo*:*exo*. Unfortunately, no product was observed at -78°C. In all cases, there is a degradation of diastereoselectivity over the course of the reaction. This was initially proposed to be due to epimerization under the reaction conditions; however, when a diastereo-enriched sample of product was resubmitted to reaction condition, no epimerization was observed. One thing to note is that, procedurally, all reactions are "started" at 0°C[3] to avoid polymerization of starting materials and this may account for the observed degradation in diastereoselectivity over time.

Table 7: *Effects of temperature on conversion and diastereoselectivity*



Entry	Temperature	Time (h)	*Endo*:*Exo*	Conversion (%)	Isolated yield (%)	Adjusted % Yield* (%)
1	0°C	0.5	3.3:1	51	44	86
2	r.t.	1.5	1.6:1	95	93	98
3	r.t.	3	1.1:1	97	92	95
4	0°C	1.5	3.2:1	92	87	95
5	0°C	3	2.9:1	96	89	92
6	-30°C	3	3.9:1	62	62	100
7	-30°C	4.5	3.4:1	60	50	84
8	-78°C	3	-	none	-	-

*Based on recovered starting material

Catalyst Loading

A quick screening of catalyst loading found that the reaction proceeds with practically complete conversion and high isolated yields at loadings as low as 50 mol% at 0°C (Table 8). As mentioned previously, loadings of 1.4 equivalents significantly reduce conversion and corrected yield due to procedural complications. When the loading was lowered to 40 mol% from 50 mol% at 0°C, the conversion was reduced from 93% to 72%; however, corrected yield remained high at around 90%. Lowering the loading further to 20 mol% at 0°C, we found that conversion was significantly reduced. Raising the temperature to room temperature, we were able to achieve complete conversion at 20 mol% over a 48h time period. This brings to light questions regarding

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[3] With the exception of reactions run at lower temperatures. These reaction temperatures are maintained constant.

the reactive intermediate. If this reaction was proceeding via the cationic intermediate Evans proposes, we would not expect the reaction to proceed at this conversion at loadings 50 mol% and below, since two aluminum species are required to form the cationic intermediate.

Table 8: ***Effects of catalyst loading on rate and diastereoselectivity***

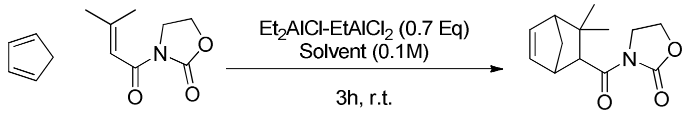
Entry	Loading (Eq)	Time (h)	Temperature	*endo*:*exo*	Conversion (%)	Isolated yield (%)	Adjusted % Yield* (%)
1	1.4	3	0°C	0.3:1	48	29	61
2	0.7	3	0°C	2.9:1	96	89	92
3	0.5	3	0°C	2.5:1	93	84	90
4	0.4	3	0°C	2.4:1	72	67	92
5	0.2	3	0°C	1.2:1	17	10	62
6	0.2	24	r.t.	1.6:1	77	74	95
7	0.2	48	r.t.	1.5:1	100	99	99

*Based on recovered starting material

Solvent Effects

We then compared the choice of solvent in the reaction (Table 9). We found that using dichloromethane or a 1:1 mixture of acetonitrile and toluene gave the corrected yields while maintaining a high conversion. A 1:1 mixture of acetonitrile and toluene gave improved diastereoselectivity over dichloromethane at room temperature, but still less than when using dichloromethane at lower temperatures. Another interesting thing to note is that both benzene and toluene gave high conversions and corrected yields with an inversion of diastereoselectivity.

Table 9: *Effects of solvent choice on rate and diastereoselectivity*



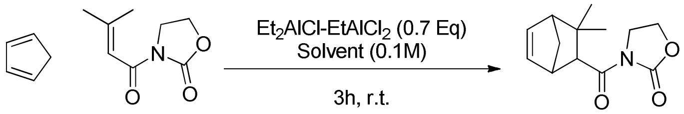
Entry	Solvent	*endo*:*exo*	Conversion (%)	Isolated yield (%)	Adjusted % Yield* (%)
1	DCM	1.1:1	97	92	95
2	Benzene	0.9:1	95	92	96
3	Toluene	0.9:1	95	88	93
4	$CHCl_3$	1.2:1	75	40	54
5	Hexanes	1.4:1	84	77	92
6	THF	-	28	0	0
7	MeCN	2.4:1	95	80	84
8	1:1 MeCN:DCM	2.3:1	91	88	96
9	1:1 MeCN:Toluene	2.4:1	96	95	99
10	1:1 MeCN:$CHCl_3$	2.2:1	98	86	88

*Based on recovered starting material

Exploration of an Alternative Reactive Intermediate

This brings us back to the possibility of a different reactive intermediate than the one by originally proposed by Evans. If we assume that our reaction proceeds through a different reactive intermediate, one potential intermediate could involve a bridged dimer coordination of EASC to both carbonyls of the substrate. In this case, there is a coordination site available for the coordination of Lewis basic groups, such as acetonitrile. This coordination of the nitrile could influence the electronics or geometry of the system and could perhaps account for the increased reactivity when using a 1:1 mixture of acetonitrile and toluene over dichloromethane. If this is the case, we could potentially improve our reaction by modifying the electronics and/or the sterics of the nitrile of choice. To explore this possibility, we then repeated the reaction using a variety of electron-poor and sterically hindered nitriles (Table 10). When using pivalonitrile and benzonitrile in a 1:1 mixture of toluene as solvent; we found little change in reactivity compared to when using a 1:1 acetonitrile:toluene mixture. However, when using the very electron-poor 2,2,2-trichloroacetonitrile, we saw a decreased isolated yield but still maintained the same diastereoselectivity. This partially supports the possibility of bridging aluminum reactive intermediate as the electron-poor 2,2,2-trichloroacetonitrile is less Lewis basic and therefore would be less able to coordinate. Unfortunately, these results are insufficient to make any concrete conclusions regarding the reactive intermediate and further investigation is required.

Table 10: ***Exploration of nitriles as additive***

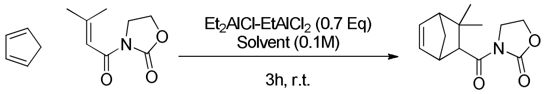


Entry	Solvent	*endo*:*exo*	Conversion (%)	Isolated yield (%)	Adjusted % Yield* (%)
1	1:1 ACN : Toluene	2.3:1	96	95	99
2	1:1 *t*BuCN : Toluene	2.2:1	92	94	100
3	1:1 PhCN : Toluene	1.9:1	98	97	99
4	1:1 CCl_3CN : Toluene	2.0:1	97	60	62

*Based on recovered starting material

Next, we observed the effect of nitrile concentration on reactivity. We varied the nitrile loading from 20 mol% in toluene to exclusively acetonitrile as solvent (Table 11). Conversions remained roughly the same regardless of acetonitrile loading; however, we noticed a general trend whereby increasing the acetonitrile content had the effect of increasing the diastereoselectivity while reducing the isolated yield. An optimal range where both diastereoselectivity and yield are maximized appears in the range of a 1:1 (v:v) of acetonitrile and toluene.

Table 11: *Effects of acetonitrile concentration on rate and diastereoselectivity*

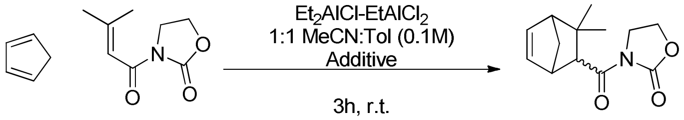


Entry	**Solvent**	***endo*:*exo***	**Conversion (%)**	**Isolated yield (%)**	**Adjusted % Yield* (%)**
1	Toluene	0.9:1	95	88	93
2	20 mol% MeCN in Toluene	1.4:1	98	92	94
3	70 mol% MeCN in Toluene	1.2:1	93	92	99
4	1:9 MeCN:Toluene	1.9:1	98	96	97
5	3:7 MeCN:Toluene	2.0:1	98	96	98
6	1:1 MeCN:Toluene	2.3:1	96	95	99
7	7:3 MeCN:Toluene	2.2:1	98	88	90
8	9:1 MeCN:Toluene	2.3.1	97	87	90
9	MeCN	2.4:1	95	80	84

*Based on recovered starting material

Next, we explored the use of additives that are capable of sequestering a chloride ion, theoretically facilitating either the formation of the cationic intermediate or freeing up a coordination site for the coordination of the nitrile (Table 12). When 20 mol% of either additive was used at 50 mol% loading of EASC, there was a slight improvement in rate and little effect on the corrected yield. This did not hold true when we lowered the loading of EASC to 20 mol% where the rate remained relatively unchanged and the corrected yield suffered. It is unclear as to why this was the case. In the end, these results remain inconclusive.

Table 12: *Exploration of other additives*



Entry	Additive	Loading (mol%)	*endo*:*exo*	Conversion (%)	Isolated yield (%)	Adjusted % Yield* (%)
1	none	50	1.8:1	70	69	99
2	20 mol% Al Powder	50	2.3:1	96	93	97
3	20 mol% $AgSbF_6$	50	2.1:1	93	98	94
4	none	20	1.6:1	31	9	29
5	20 mol% Al Powder	20	1.9.1	19	2	8
6	20 mol% $AgSbF_6$	20	1.3:1	30	8	26

*Based on recovered starting material

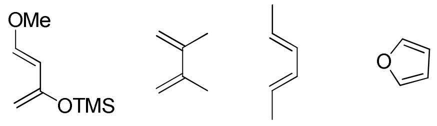
Attempts were made to obtain a crystal for x-ray crystallography of the reactive intermediate as this would provide the most conclusive evidence towards an alternative reaction intermediate; however, no attempt thus far has been successful.

It is unfortunate that the results that we have obtained thus far have been unable to give us deeper insight into the reactive intermediate when using EASC compared to the originally proposed model by Evans. More work is required to gain a deeper understanding of this intermediate so that proper optimization of the reaction conditions can be achieved.

Scope

Moving away from our model system, we looked towards exploring the scope of the reaction with regards to the diene. This is particularly important since the cyclical nature of cyclopentadiene can impart a major influence over the diastereoselectivity of the reaction. The dienes selected are shown below (Figure 10). These dienes were selected due to their availability and due to their common use in organic synthesis.

Figure 10: ***Dienes selected for exploration of scope***



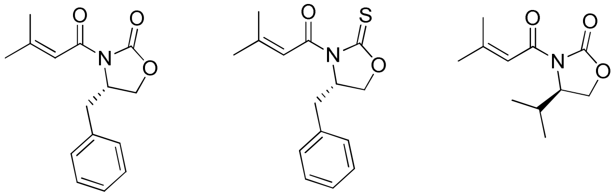
7.4 **7.5** **7.6** **7.7**

When subjected to our optimized conditions, we were unable to obtain more than trace amounts of product. In the case of dienes **7.4**, **7.5**, and **7.6**, we propose that this is the result of the unfavourable entropic effects of using acyclical dienes compared to the use of cyclopentadiene. This would result in an increase in the activation energy required, causing the reaction to favour the lower energy route of (co)polymerization. In the case of Danishefsky's dienes (**7.4**), it is suspected that hydrolysis of the silyl enol ether occurred in conjunction with the previous proposal. This is unfortunate, for if the conditions are not widely applicable, there is no real advantage to this method.

Asymmetric Variation

We then looked towards applying the use of EASC to an asymmetric variant despite our poor understanding of the reactive intermediate. Providing an asymmetric Diels-Alder reaction of highly hindered substrates would prove invaluable, particularly as this methodology would not require the forcing conditions or additional functionality seen in the examples shown in the previous chapters. Three substrates were prepared using standard methodology (Figure 11).

Figure 11: ***Dienophiles containing chiral auxiliaries selected for exploration of an asymmetric variant***



7.8 **7.9** **7.10**

When subjected to our optimized conditions, these reactions yielded only trace amounts of desired product. Most likely, the additional steric hindrance imposed by the appended chiral moiety shuts down the reaction. This is unfortunate, since a strength of this method is the possibility of it being applicable to an asymmetric variation. Without this, there is no advantage to our method.

Chapter 8: Conclusions and Future Work

Generally, we found that the use of EASC provides slight increases in reactivity over previously reported methods. This holds true even at loading as low as 20 mol % where we would expect the rate to be prohibitively slow. The choice of solvent appears to play an important role on conversion and diastereoselectivity. Mixtures of acetonitrile and non-polar solvents, such as DCM and toluene, seem to provide the best diastereoselectivity in the highest yields.

Despite early positive results using EASC, gaining insight into the reactivity of this reaction has been very difficult. Probes into the possibility of a free coordination site available for binding of Lewis basic solvents, such as nitriles, have proven inconclusive. So too has been the use of other additives such as aluminum powder and silver hexafluoroantimonate.

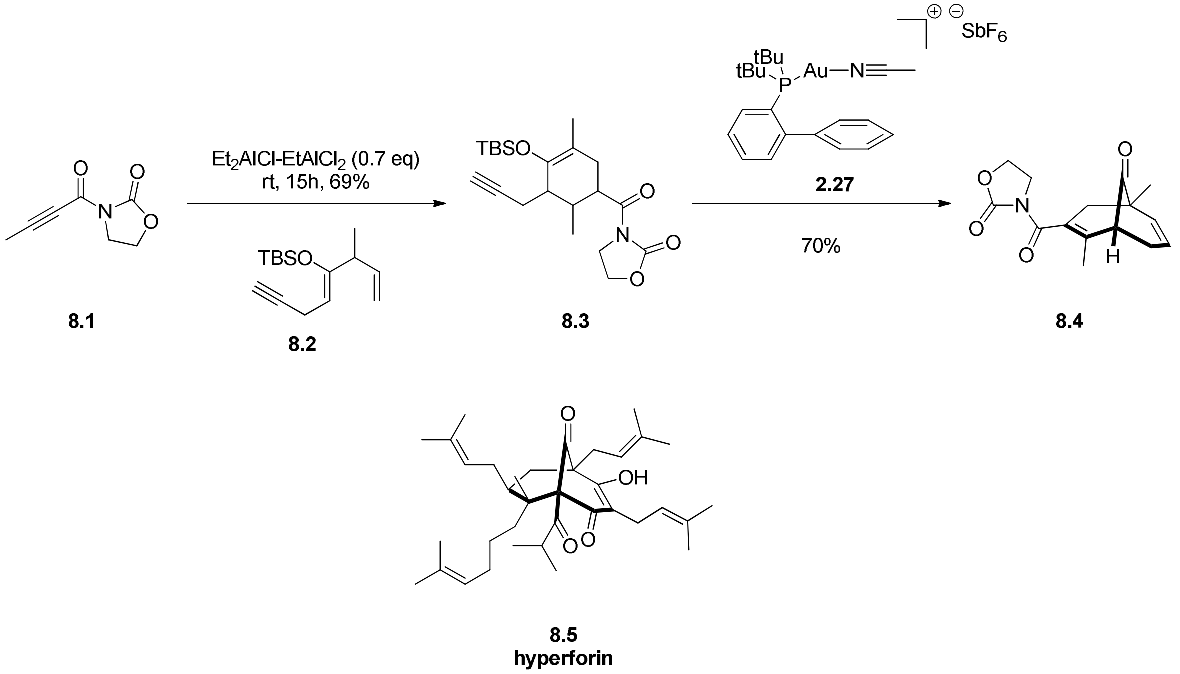
When exploring the reaction scope outside of our test system, we observed only trace amounts of products. This could be the result of a variety of reasons including the entropic effects of using acyclical dienes and the hydrolysis of the silyl enol ethers under the reaction conditions. Similar low reactivity was observed when employing chiral oxazolidinones, most likely due to the additional steric encumbrance.

Our efforts so far have shown that this reaction is extremely limited in scope and provides no advantage over other alternatives. It could, however, be part of a larger set of tools for catalyzing the Diels-Alder reaction of hindered dienophiles racemically, whereby it would be used alongside other techniques, the best of which would then be selected.

Metal catalyzed Diels-Alder reactions rely on a combination of factors aligning in an particular manner for the reaction to proceed. Choice of catalyst, including metal center and ligands, as well as the nature of the Lewis basic site and the overall electronics and sterics of the substrates are all important for the overlap of the HOMO and LUMO to be correct and for the reaction to proceed. By selecting other chiral auxiliaries with reduced sterics, we may be able to shift the entropic and electronic factors in our favour. The exploration of new catalysts such as methyl aluminum sesquichloride might prove interesting, as a significant increase in reactivity was observed between diethyl aluminum chloride and dimethyl aluminum chloride.

For this methodology to become widely accepted, significant work must be done to gain a better understanding of the reactive intermediate. This could be accomplished through NMR experiments, such as those conducted by Castellino and Dwight as evidence to support Evans' proposed cationic intermediate, or by single crystal x-ray crystallography of the given intermediate. Unfortunately, the limited attempts at this in our lab have proven unsuccessful. Despite these difficulties, this methodology is currently being explored in our laboratory in the total synthesis of hyperforin (Scheme 58).

Scheme 58: ***Use of ethyl aluminum sesquichloride in the synthesis of the core of hyperforin***



Claims to Original Research

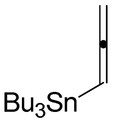
1. Investigation into the synthesis of (±) Communesin F using a gold induced [4+2] cycloaddition between an o-amino aryallene and an indole.
2. Investigation into the synthesis of (±) Communesin F using a Meerwein-Eschenmoser Claisen reaction.
3. Proposal for the transformation of the functionalized core of (±) Communesin F into the natural product.
4. Investigation into the use of alkyl aluminum sesquichlorides to catalyze Diels-Alder cycloaddition.
5. Investigations into the effects of temperature, catalyst loading, and choice of solvent on the Diels-Alder reaction using alkyl aluminum sesquichlorides.
6. Investigations into the mode of reactivity of Diels-Alder reactions using alkyl aluminum sesquichlorides.

Experimental

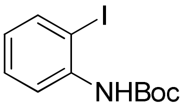
General Experimental

All reactions were carried out under argon atmosphere with glassware flame dried under vacuum unless otherwise indicated. Solvents for reactions were distilled prior to use unless otherwise indicated; DCM, toluene, and DMF were distilled over calcium hydride, and THF and diethyl ether were distilled over sodium in the presence of benzophenone. Solvents which were not distilled (benzene, DMSO, acetonitrile, methanol, ethanol, and acetone) were used as supplied and were of ACS grade unless otherwise indicated. Reactions were monitored by thin layer chromatography (TLC) using glass or aluminum backed 250 µm ultrapure silica gel TLC plates and visualized using a short wave-length UV lamp and *p*-anisaldehyde or $KMnO_4$ stain. Column chromatography was performed with 60 silica gel (230-400 mesh, Merck). Fridge temperature was 4 °C. All ^1H and ^{13}C spectra were recorded on either a *Bruker Avance 400MHz spectrometer* or a *Bruker Avance 300MHz spectrometer.* Chemical shifts (δ) were reported in ppm relative to solvent residual peak. Spectral features for characterization are reported in the following order for ^1H spectra: chemical shifts (δ, ppm); multiplicity (s-singlet, d-doublet, t-triplet, q-quartet, m-multiplet); coupling constant (J in Hertz); number of protons. For ^{13}C spectra: chemical shifts (δ, ppm); multiplicity (C, CH, CH_2, CH_3). Infrared (IR) spectra were recorded with a *Bomen Michaelson 100 Fournier* instrument. IR spectra were obtained as a thin film of pure compound on sodium chloride plates. HRMS (EI) spectra were obtained on a *Kratos Analytical Concept* instrument.

Experimental Chapter 2



allenyl-(tributyl)stannane (2.17): To a flask containing magnesium (61.3 mg, 2.52 mmol), lead dichloride (35.1 mg, 0.13 mmol), THF (5 mL), and chloro(tributyl)stannane (0.68 mL, 2.52 mmol) was added propargyl bromide (0.23 mL, 2.52 mmol) over 5 min and the mixture was heated carefully. The mixture was stirred for 1 hour at room temperature, quenched with saturated aqueous NH_4Cl, filtered through a pad of Celite®, and the residue was washed with EtOAc. Products were extracted with EtOAc and the combined organic layers were dried over anhydrous $MgSO_4$. The solvents were removed under reduced pressure, and purification by flash chromatography (100% Hexane) gave the desired product (**2.17**) as a yellow oil (0.4896 g, 59%). ^{1}H NMR was compared to spectral data found in the literature.[81]



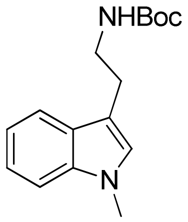
tert-butyl 2-iodophenylcarbamate (2.21): To a solution of the iodoaniline (1.00 g, 4.57 mmol) in THF (46 mL) was added di-tert-butyl dicarbonate (2.99 g, 13.70 mmol) followed by DMAP (56.0 mg, 0.46 mmol). The solution was stirred at reflux for 2 hours then concentrated to dryness and partitioned between 0.5 N HCl and EtOAc. The aqueous layer was extracted with EtOAc twice and the combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered through cotton, and concentrated to afford the crude material.

The crude material was dissolved in methanol (46 mL), treated with potassium carbonate (1.89 g, 13.70 mmol) and stirred at reflux for 2 hours. The mixture was concentrated to dryness and partitioned between 0.5 N HCl and EtOAc. The aqueous phase was extracted with EtOAc twice and the combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered through cotton, and concentrated to afford the crude product. This was purified by flash chromatography (10% hexane/EtOAc) to afford the desired product (**2.21**) as a colourless oil (1.260 g, 87%). ^{1}H NMR was compared to spectral data found in the literature.[82]

tert-butyl 2-(propa-1,2-dienyl)phenylcarbamate (2.5): To a solution of tert-butyl 2-iodophenylcarbamate (**2.21**) (200.0 mg, 0.63 mmol) and allenyl-(tributyl)stannane (**2.17**) (226.9

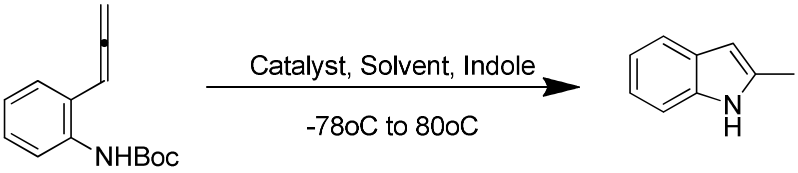
mg, 0.069 mmol) in DMF (5 mL) was added CuI (11.9 mg, 0.063 mmol), TFP (29.1 mg, 0.13 mmol) and $Pd_2(dba)_3$ (17.2 mg, 0.019 mmol). The reaction was stirred under argon at room temperature until complete conversion of starting material by TLC. The reaction was then quenched by the addition of a saturated solution of NH_4Cl, extracted with Et_2O, dried over anhydrous Na_2SO_4, filtered through cotton, and concentrated under reduced pressure. The desired product was isolated by flash chromatography (5% EtOAc/hexanes) to afford the desired product (**2.5**) as a colourless oil (116.0 mg, 80%)

IR (neat, cm^{-1}): 3405 (m), 3344 (m), 2964 (s), 1933 (s), 1876 (m), 1854 (m), 1941 (m), 1732 (s); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.83 (d, J = 7.6 Hz, 1H), 7.23-7.20 (m, 2H), 7.04 (dd, J = 7.5, 1.2 Hz, 1H), 6.28 (t, J = 7.0 Hz, 1H), 5.19 (d, J = 7.0 Hz, 2H), 1.51 (s, 3H); ^{13}C NMR ($CDCl_3$, 400.0 MHz) δ 210.2 (C), 153.2 (C), 135.8 (C), 128.9 (CH), 128.1 (CH), 123.9 (CH), 123.1 (C), 122.0 (CH), 90.8 (CH), 80.5 (CH), 78.7 (CH2), 28.5 (CH3); HRMS (EI) m/z calcd for C_9H_8N [M-BOC]$^+$ 130.0657, found 130.0662.



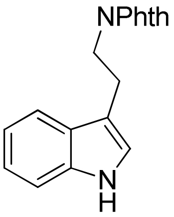
tert-butyl 2-(1-methyl-1H-indol-3-yl)ethylcarbamate (2.22): A solution of tryptamine (250.0 mg, 1.56 mmol) and Et_3N (310.0 mg, 3.0 mmol) was stirred in DCM (10 mL) at room temperature for 10 min, then the solution of di-tert-butyl dicarbonate (374.6 mg, 1.72 mmol) in DCM (6 mL) was added dropwise at 0 °C for 10 min. The mixture was stirred at room temperature for 2 hours and was extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure. A mixture of the residue, crushed NaOH (187.2 mg, 4.68 mmol) and Bu_4NHSO_4 (26.5 mg, 0.078 mmol) was stirred in DCM (8 mL) at room temperature for 10 min, MeI (0.11 mL, 1.72 mmol) was added into the solution at room temperature. After the mixture was stirred for 6 h, the reaction mixture was extracted with DCM. The combined organic layers were dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (10-20% EtOAc/hexanes) to give the desired product (**2.22**) as a white solid (0.324 g, 76%). ^{1}H NMR was compared to spectral data found in the literature.[83]

General Metal Catalyzed Procedure:

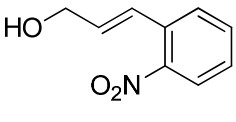


The **catalyst** was added to a solution of tert-butyl 2-(propa-1,2-dienyl)phenylcarbamate (**2.5**) and the **indole** dissolved in **solvent** at -78°C. The reaction was allowed to warm to room temperature and was monitored by TLC. Reaction was left overnight at room temperature periodically monitoring by TLC. If the reaction had not reached 100% conversion, the reaction was heated at 50°C overnight. The reaction mixture was cooled to room temperature concentrated under reduced pressure and the components were isolated by flash chromatography.

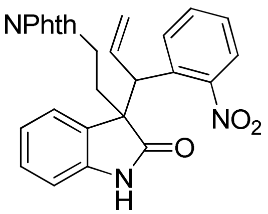
Experimental Chapter 3



2-(2-(1H-indol-3-yl)ethyl)isoindoline-1,3-dione (3.11): Tryptamine (3.00 g, 18.72 mmol) and phthalic anhydride (2.91 g, 19.66 mmol) were suspended in toluene (297 mL) and heated at reflux overnight. The mixture was concentrated under reduced pressure to give a residual solid which was recrystallized from DCM and hexanes to afford the desired product (**3.11**) as yellow crystals (4.59 g, 84%). ^{1}H NMR was compared to spectral data found in the literature.[84]

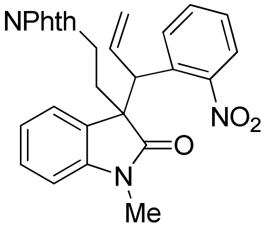


(E)-3-(2-nitrophenyl)prop-2-en-1-ol (3.13): $NaBH_4$ (0.235 g, 6.21 mmol) was added to a solution of 2-nitrocinnamaldehyde (1.00 mL, 5.64 mmol) in methanol (14 mL) at 0°C. After 10 minutes, the reaction was quenched by the addition of water and the mixture was extracted with DCM three times dried over anhydrous $MgSO_4$. The crude material was concentrated under reduced pressure and filtered through a short plug of silica eluting with 30% EtOAC/hexanes and concentrated once again to afford the desired product (**3.13**) product as a white solid (0.998 g, quantitative). ^{1}H NMR was compared to spectral data found in the literature.[85]



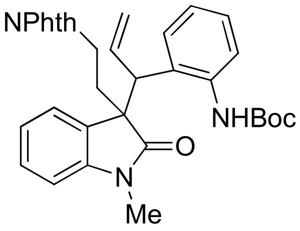
Compound 3.14: To a suspension of indole **3.11** (5.35 g, 18.4 mmol) dissolved in DCM (33.5 mL) and cooled to 0°C, was added freshly distilled dimethylpipirizine (1.2 mL, 9.21 mmol) followed by recrystallized NCS (2.68 g, 20.1 mmol). The reaction was stirred at 0°C until complete consumption of the starting material (ca. 1 hour). From a separate flame dried round-bottomed flask containing distilled trichloroacetic acid (0.684 g, 4.19 mmol) and allylic alcohol **3.13** (3.00 g, 16.7 mmol) dissolved in DCM (33.5 mL) was cannulated into the reaction mixture at 0°C and the reaction was allowed to stir and warm to room temperature overnight. The reaction was concentrated under reduced pressure and filtered through a short plug of silica eluting with 30% EtOAC/DCM. The filtrate was concentrated and the residue was purified by flash chromatography (10-20% EtOAc/hexanes) to give the desired product (**3.14**) as an off-white powder (5.24 g, 67%).

IR (neat, cm^{-1}): 3473 (m), 3409 (w), 3082 (s), 3059 (s), 2937 (s), 2884 (m), 2257 (s), 1767 (m); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.46 (s, 1H), 7.71-7.60 (m, 4H), 7.42 (dd, J = 8.2, 1.1 Hz, 1H), 7.35 (d, J = 7.5 Hz, 1H), 7.23-7.01 (m, 3H), 6.93 (td, J = 11.3, 0.9 Hz, 1H), 6.79 (d, J = 7.7 Hz, 1H), 6.65-6.57 (m, 1H), 6.16 (dt, J = 16.8, 9.7 Hz, 1H), 5.36 (d, J = 11.0 Hz, 1H), 5.33-5.30 (m, 1H), 4.55 (d, J = 9.3 Hz, 1H), 3.50-3.38 (m, 2H), 2.65 (dt, 14.0, 7.6 Hz, 1H), 2.24 (ddd, J = 13.8, 7.5, 5.5 Hz, 1H); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.21 (s, 0.8H), 7.71-7.60 (m, 4H), 7.56 (dd, J = 8.0, 1.2, 0.8H), 7.38 (dd, J = 7.5, 1.3 Hz, 0.8H), 7.23-7.01 (m, 0.8H), 6.98 (d, J = 7.4 Hz, 0.8H), 6.83 (td, J = 11.6, 1.2 Hz, 0.8H), 6.68 (td, J = 7.5, 1.0 Hz, 0.8H), 6.65-6.57 (m, 0.8H), 6.54 (d, J = 7.7 Hz, 0.8H), 5.43 (dd, J = 16.9, 0.8 Hz, 0.8H), 5.33-5.30 (m, 0.8H), 4.69 (d, J = 9.7 Hz, 0.8 H), 3.50-3.38 (m, 1.6H), 2.57 (ddd, J = 13.9, 6.6, 5.6 Hz, 0.8H), 2.37 (dt, J = 15.4, 7.1 Hz, 0.8H); ^{13}C NMR ($CDCl_3$, 400.0 MHz) δ: 179.7 (C), 179.7 (C), 167.9 (C), 167.9 (C), 150.7 (C), 149.9 (C), 141.9 (C), 140.3 (C), 134.2 (CH), 134.0 (CH), 133.9 (CH), 133.8 (CH), 133.8 (C), 132.6 (C), 132.3 (CH), 132.0 (C), 131.9 (C), 131.4 (CH), 129.5 (CH), 129.5 (C), 129.3 (CH), 129.0 (C), 128.9 (CH), 128.3 (CH), 127.8 (CH), 127.5 (CH), 124.4 (CH), 124.3 (CH), 124.2 (CH), 123.1 (CH), 123.1 (CH), 122.6 (CH), 120.9 (CH_2), 120.2 (CH_2), 110.7 (CH), 109.9 (CH), 55.6 (C), 55.3 (C), 50.5 (CH), 50.0 (CH), 34.3 (CH_2), 34.2 (CH_2), 33.6 (CH_2), 33.5 (CH_2); HRMS (EI) m/z calcd for $C_9H_6NO_2$ $[M- C_{18}H_{15}N_2O_3]^+$ 160.0399, found 160.0413; Off-white powder MP = 170.9 - 172.5°C



Compound 3.23: To a suspension of NaH (0.045 g, 60% dispersion in mineral oil, 1.18 mmol) in THF (4.0 mL) was added a solution of oxindole **3.14** (0.500 g, 1.07 mmol) in THF (3.4 mL) at 0°C. The mixture was stirred at 0°C for 15 minutes and freshly distilled iodomethane (0.10 mL, 1.60 mmol) was added at this temperature. The reaction mixture was warmed to room temperature and stirred overnight. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ and extracted with EtOAC three times. The combined organic layers were dried over anhydrous $MgSO_4$, filtered through cotton, and concentrated under reduced pressure. The residue was purified by flash chromatography (10% EtOAC/Hexanes then 40-50% EtOAc/Hexanes) to afford the desired product (**3.23**) as an off-white powder (0.398 g, 77%).

IR (neat, cm^{-1}): 3059 (w), 2934 (w), 2858 (w), 2253 (w), 1771 (w), 1721 (s), 1607 (m); ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.64-7.58 (m, 4H), 7.37-7.27 (m, 2H), 7.18 (td, J = 7.7, 1.2 Hz, 1H), 7.09-7.01 (m, 2H), 6.82 (t, J = 7.2 Hz, 1H), 6.68-6.58 (m, 1H), 6.53 (d, J = 7.7 Hz, 1H), 6.10 (dt, J = 17.1, 9.4 Hz, 1H), 5.27-5.32 (m, 2H), 4.51 (d, J = 9.2 Hz, 1H), 3.49-3.33 (m, 2H), 2.95 (t, 3H), 2.69-2.58 (m, 1H), 2.25 (dt, J = 14.1, 5.9 Hz, 1H); ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.64-7.58 (m, 4.5H), 7.37-7.27 (m, 0.75H), 7.09-7.01 (m, 0.75H), 6.94 (d, J = 7.5 Hz, 0.75H), 6.77 (td, J = 11.6, 1.1 Hz, 0.75H), 6.68-6.58 (m, 1.5H), 6.31 (d, J = 7.7 Hz, 0.75H), 5.40 (dd, J = 16.9, 0.79 Hz, 0.75H), 5.30 (dd, J = 10.0, 1.4 Hz, 0.75H), 4.63 (d, J = 9.7 Hz, 0.75H), 3.49-3.33 (m, 1.5H), 2.76 (t, 2.25H), 2.69-2.58 (m, 0.75H), 2.39 (ddd, J = 14.3, 8.8, 6.1 Hz, 0.75H); ^{13}C NMR ($CDCl_3$, 400.0 MHz) δ: 177.2 (C), 177.0 (C), 167.7 (C), 167.7 (C), 150.5 (C), 149.8 (C), 144.4 (C), 142.9 (C), 134.1 (CH), 134.0 (CH), 133.8 (CH), 133.7 (CH), 133.7 (CH), 132.7 (C), 131.9 (C), 131.8 (C), 131.5 (CH), 131.1 (CH), 129.4 (CH), 129.1 (CH), 128.9 (C), 128.7 (C), 128.6 (CH), 128.0 (CH), 127.5 (CH), 127.3 (CH), 124.2 (CH), 124.0 (CH), 123.7 (CH), 123.0 (CH), 122.9 (CH), 122.8 (CH), 122.4 (CH), 122.3 (CH), 120.6 (CH_2), 120.1 (CH_2), 108.4 (CH), 107.9 (CH), 55.0 (CH), 54.8 (CH), 50.7 (CH), 50.3 (CH), 34.4 (CH_2), 34.3 (CH_2), 32.7 (CH_2), 32.5 (CH_2), 26.0 (CH_3), 25.8 (CH_3); HRMS (EI) m/z calcd for $C_9H_6NO_2$ $[M- C_{19}H_{17}N_2O_3]^+$ 160.0399, found 160.0422; Off-white powder MP = 172.3 - 174.2°C



Compound 3.10: A suspension of oxindole **3.23** (1.00 g, 2.08 mmol), iron powder (0.649 g, 11.6 mmol) and ammonium chloride (0.067 g, 1.25 mmol) in 2:1 EtOH:H_2O (20.8 mL) was heated to reflux (ca. 90°C)

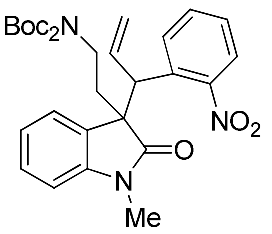
until complete consumption of starting material (ca. 1 hour). The hot mixture was filtered through a short plug of Celite® rinsing with 2:1 EtOH:H_2O. The organic solvents were removed under reduced pressure and the remaining aqueous phase extracted with EtOAc three times. The combined organic layers were dried over anhydrous $MgSO_4$, filtered through cotton, and concentrated under reduced pressure to afford the crude material.

To a solution of crude material from the previous step and triethylamine (0.58 mL, 4.15 mmol) dissolved in THF (10.4 mL) was added di-tert-butyl-dicarbonate (0.907 g, 4.15 mmol). The reaction was heated to reflux with stirring overnight (ca. 16 hours). The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ and extracted with EtOAC three times. The combined organic layers were dried over anhydrous $MgSO_4$, filtered through cotton, and concentrated under reduced pressure. The residue was purified by flash chromatography (10% EtOAC/Hexanes) to afford the desired product (**3.10**) as a colourless oil (0.991 g, 86%).

IR (neat, cm^{-1}): 3340 (w), 3013 (w), 2979 (w), 2936 (w), 1772 (w), 1714 (s), 1690 (m); ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.67 (m, 4H), 7.41-7.39 (m, 2H), 7.31 (dd, J = 7.4, 0.68 Hz, 1H), 7.04 (td, J = 11.6, 1.2 Hz, 1H), 6.99 (td, J = 13.9, 1.5 Hz, 1H), 6.86 (td, J = 7.6, 0.96 Hz, 1H), 6.53 (td, J = 15.3, 1.3 Hz, 1H), 6.50 (d, J = 7.7 Hz, 1H), 6.13 (dt, J = 16.5, 10.0 Hz, 1H), 5.99 (dd, J = 7.9, 1.3 Hz, 1H), 5.29-5.25 (m, 2H), 4.06 (d, J = 9.7 Hz, 1H), 3.54-3.44 (m, 2H), 2.80-2.73 (m, 1H), 2.71 (s, 3H), 2.45 (dt, J = 14.2, 6.0 Hz, 1H), 1.54 (s, 9H); ^{13}C NMR ($CDCl_3$, 400.0 MHz) δ: 179.5 (C), 167.9 (C), 154.4 (C), 144.3 (C), 135.3 (C), 135.2 (CH), 133.8 (CH), 132.0 (C), 131.6 (CH), 128.5 (C), 128.4 (CH), 127.2 (CH), 127.1 (CH), 126.2 (CH), 124.1 (CH), 123.9 (CH), 123.0 (CH), 122.6 (CH), 119.9 (CH_2), 108.7 (C), 80.0 (C), 55.7 (C), 50.1 (CH), 34.5 (CH_2), 33.2 (CH_2), 28.6 (CH_3), 25.9 (CH_3); HRMS (EI) m/z calcd for $C_{29}H_{24}N_3O_4$ $[M- tBuO]^+$ 478.1767, found 478.1866.

IR (neat, cm^{-1}): 3067 (w), 2983 (w), 2937 (w), 2888 (w), 2257 (w), 1774 (w), 1713 (s), 1611 (w); ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.65-7.59 (m, 4H), 7.23-7.2 (m, 1H), 7.11-7.10 (m, 2H), 7.04 (td, J = 11.3, 1.5 Hz, 1H), 6.96 (td, J = 15.2, 1.2 Hz, 1H), 6.92 (td, J = 11.6, 1.1 Hz, 1H), 6.74-6.70 (m, 1H), 6.47 (d, J = 7.8 Hz, 1H), 6.30 (dt, J = 16.9, 9.9 Hz, 1H), 5.99 (br, 1H), 5.18-5.11 (m, 2H), 3.90 (d, J = 9.69 Hz, 1H), 3.49-3.38 (m, 2H), 2.98 (s, 3H), 2.62 (dt, J = 14.1, 6.0 Hz, 1H), 2.38-2.31 (m, 1H), 1.50 (s, 9H); ^{13}C NMR ($CDCl_3$, 400.0 MHz) δ: 177.8 (C), 167.9 (C), 153.7 (C), 144.0 (C), 135.3 (CH), 135.0 (C), 133.7 (CH), 132.0 (C), 131.6 (C), 129.3 (C), 128.7 (CH), 128.3 (CH), 127.4 (CH), 125.5 (CH), 124.8 (CH), 123.0 (CH), 123.0 (CH), 122.0 (CH), 118.6 (CH_2), 108.3 (CH), 80.4 (C), 55.3 (C), 51.8 (CH), 34.5

(CH_2), 32.2 (CH_2), 28.5 (CH_3), 26.0 (CH_3); HRMS (EI) m/z calcd for $C_{29}H_{24}N_3O_4$ [M- tBuO]$^+$ 478.1767, found 478.1661;

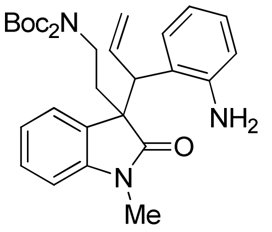


Compound 3.27: To a solution of oxindole **3.23** (0.500 g, 1.04 mmol) dissolved in ethanol (10.4 mL) was added hydrazine (0.49 mL, 13.5 mmol). The reaction was allowed to stir at room temperature until the complete conversion of starting material (ca. 30 minutes). It is important to observe the reaction every 15 minutes and quench the reaction immediately upon completion to avoid reduction of alkene. The reaction is quenched by the addition of conc. HCl (3 mL/mmol) and filtered through a Celite® plug. The pH of the filtrate was raised to > 10 with 1.0 N NaOH and extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered through cotton, and concentrated under reduced pressure to afford the crude material.

To a solution of the crude material and DMAP (0.127 g, 1.04 mmol) dissolved in THF (10.4 mL) was added di-tert-butyl-dicarbonate (1.133 mg, 5.19 mmol) at 0°C. The reaction was allowed to warm to room temperature and stir overnight (ca. 16 hours). The reaction was quenched by the addition of saturated aqueous NH_4Cl and the THF was removed under reduced pressure. The remaining aqueous phase was then extracted with EtOAC three times. The combined organic layers were dried over anhydrous $MgSO_4$, filtered through cotton, and concentrated under reduced pressure. The residue was purified by flash chromatography (40-50% EtOAC/Hexanes) to afford the desired product (**3.27**) as a yellow oil (0.528 mg, 92%).

IR (neat, cm^{-1}): 3086 (w), 2987 (m), 2937 (m), 2257 (w), 1786 (s), 1748 (s), 1713 (s), 1614 (m); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.67-7.65 (m, 1H), 7.41-7.21 (m, 7H), 7.14-7.03 (m, 5H), 6.97 (td, J = 7.5, 0.9 Hz, 1H), 6.72-6.62 (m, 2H), 6.46 (d, J = 7.2 Hz, 1H), 6.01 (m, 1H), 5.40 (dd, J = 16.9, 0.9 Hz, 1H), 5.31 (dd, J = 10.0, 1.5 Hz, 1H), 5.18-5.16 (m, 1H), 6.11-5.07 (m, 1H), 4.67 (d, J = 9.6 Hz, 1H), 4.46 (d, J = 8.9 Hz, 1H), 3.13-2.9 (m, 7H), 2.87 (s, 3H), 2.50-2.42 (m, 1H), 2.32-2.26 (m, 1H), 2.07-1.96 (m, 2H), 1.45 (s, 18H), 1.42 (s, 18H); ^{13}C NMR ($CDCl_3$, 400.0 MHz) δ: 177.2 (C), 176.9 (C), 151.8 (C), 151.7 (C), 150.7 (C), 149.8 (C), 144.1 (C), 142.8 (C), 134.4 (CH), 134.1 (CH), 134.0 (C), 133.0 (C), 131.4 (CH), 131.2 (CH), 130.0 (CH), 129.3 (C), 129.2 (CH), 128.9 (C), 128.8 (CH), 128.4 (CH), 127.5 (CH), 127.3 (CH), 124.1 (CH), 124.0 (CH), 124.0 (CH), 123.2 (CH), 122.9 (CH), 122.7 (CH), 120.0

(CH_2), 119.8 (CH_2), 108.0 (CH), 107.6 (CH), 82.4 (C), 82.3 (C), 54.5 (C), 54.5 (C), 50.4 (CH), 49.9 (CH), 42.4 (CH_2), 42.3 (CH_2), 34.4 (CH_2), 34.1 (CH_2), 28.0 (CH_3), 28.0 (CH_3), 25.8 (CH_3), 25.8 (CH_3); HRMS (EI) m/z calcd for $C_{29}H_{24}N_3O_4$ [M- tBuO]$^+$ 478.1978, found 478.1969.

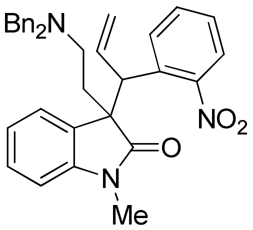


Compound 3.28: To a solution of Pd/C (0.017 g, 0.016 mmol) in methanol (2.7 mL) was added oxindole **3.27** (0.150 mg, 0.272 mmol) through the neck of the flask. $NaBH_4$ (0.144 g, 3.81 mmol) was added portion-wise at 0°C and the reaction was allowed to warm to room temperature and stir until complete consumption of starting material (ca. 30 minutes). The reaction was quenched by the addition of water and filtered through Celite® rinsing with EtOAc. The filtrate was then extracted with EtOAc three times. The combined organic layers were dried over anhydrous $MgSO_4$, filtered through cotton, and concentrated under reduced pressure. The residue was purified by flash chromatography (10-20% EtOAC/Hexanes) to afford the desired product (**3.28**) as a yellow oil (0.139 mg, 98%).

IR (neat, cm^{-1}): 3586 (w), 2987 (w), 2937 (w), 1710 (s) 1611 (m); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.40 (d, J = 6.7 Hz, 1H), 7.29 (td, J = 7.8, 1.4 Hz, 1H), 7.12 (td, J = 7.6, 0.7 Hz, 1H), 6.80, (td, J = 7.9, 1.5 Hz, 1H), 6.62 (d, J = 7.7 Hz, 1H), 6.56 (dd, J = 7.9, 1.1 Hz, 1H), 6.24 (t, J = 7.6 Hz, 1H), 6.17 (dt, J = 16.8, 9.8 Hz, 1H), 5.96 (dd, J = 7.8, 1.4 Hz, 1H), 5.30-5.23 (m, 2H), 4.01 (d, J = 9.61 Hz, 1H), 3.92 (br. s, 2H), 3.23-3.15 (m, 2H), 3.06 (ddd, J = 13.5, 11.5, 0.7 Hz, 1H), 2.77 (s, 3H), 2.42 (td, J = 12.3, 5.0 Hz, 1H), 2.27 (td, J = 17.9, 4.7 Hz, 1H), 1.47 (s, 18H); ^{13}C NMR ($CDCl_3$, 400.0 MHz) δ: 179.1 (C), 151.9 (C), 144.3 (C), 144.3 (C), 136.1 (CH), 128.7 (C), 128.5 (CH), 127.6 (CH), 127.2 (CH), 125.0 (C), 124.4 (CH), 122.4 (CH), 118.7 (CH_2), 118.3 (CH), 117.6 (CH), 108.2 (CH), 82.3 (C), 55.0 (C), 49.2 (CH), 42.4 (CH_2), 34.4 (CH_2), 28.1(CH_3), 25.8 (CH_3); HRMS (EI) m/z calcd for $C_9H_{10}N$ [M- $C_{21}H_{29}N_2O_5$]$^+$ 132.0813, found 132.0803.

IR (neat, cm^{-1}): 3578 (w), 2983 (m), 2937 (w), 2253 (w), 1789 (m), 1744 (m), 1709 (s), 1615 (s); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.24 (td, J = 11.5, 1.2 Hz, 1H); 7.17 (dd, J = 7.4, 0.85 Hz, 1H), 7.04-6.93 (m, 3H), 6.73-6.55 (m, 3H), 5.93 (dt, J = 16.9, 9.8 Hz, 1H), 5.12 (dd, J = 16.8, 1.2 Hz, 1H), 4.98 (dd, J = 10.1, 1.6 Hz, 1H), 3.85 (d, J = 9.5 Hz, 1H), 3.12 (s, 3H), 3.10-2.83 (m, 2H), 2.43-2.34 (m, 1H), 2.10-2.02 (m, 1H), 1.42 (s, 18H); ^{13}C NMR ($CDCl_3$, 400.0 MHz) δ: 178.5 (C), 151.9 (C), 144.4 (C), 144.2 (C), 135.7 (CH), 129.2 (CH), 128.9 (C), 128.5 (CH), 127.7 (CH), 124.6 (CH), 124.4 (C), 122.0 (CH), 118.4

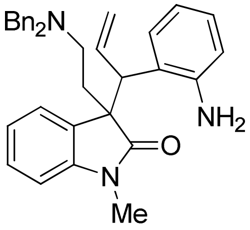
(CH), 117.6 (CH_2), 116.9 (CH), 107.9 (CH), 82.4 (C), 55.9 (C), 50.6 (CH), 42.6 (CH_2), 33.4 (CH_2), 28.1 (CH_3), 26.1 (CH_3); HRMS (EI) m/z calcd for $C_9H_{10}N$ [M- $C_{21}H_{29}N_2O_5$]$^+$ 132.0813, found 132.0803.



Compound 3.29: To a solution of oxindole **3.23** (3.00 g, 6.23 mmol) dissolved in ethanol (62.3 mL) was added hydrazine (3.0 mL, 81.0 mmol). The reaction was allowed to stir at room temperature until the complete conversion of starting material (ca. 30 minutes). (It is important to observe the reaction every 15 minutes and quench the reaction immediately upon completion to avoid reduction of alkene.) The reaction is quenched by the addition of conc. HCl (3 mL/mmol) and filtered through a Celite® plug. The pH of the filtrate was raised to > 10 with 1.0 N NaOH and extracted with EtOAc. The combined organic layers were dried over anhydrous $MgSO_4$, filtered through cotton, and concentrated under reduced pressure to afford the crude material.

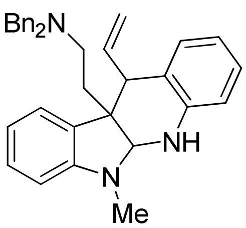
To a solution of the crude material in methanol (62 mL) was added K_2CO_3 (2.33 g, 16.8 mmol) and benzyl bromide (1.6 mL, 2.34 mmol). The reaction was allowed to stir at room temperature overnight. The reaction was quenched by the addition of saturated aqueous NH_4Cl and then extracted with DCM three times. The combined organic layers were dried over anhydrous $MgSO_4$, filtered through cotton, and concentrated under reduced pressure. The residue was purified by flash chromatography (20% EtOAC/Hexanes) to afford the desired product (**3.29**) as a yellow oil (2.85 g, 86%).

IR (neat, cm^{-1}): 3067 (s), 3032 (s), 2937 (s), 2888 (m), 2804 (s), 2706 (m), 1952 (w), 1873 (w), 1812 (w), 1713 (s), 1611 (s); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.66 (dd, J = 8.1, 1.4 Hz, 1H), 7.41-7.09 (m, 28H), 7.06-6.98 (m, 2H), 6.86-6.80 (m, 2H), 6.71-6.63 (m, 2H), 6.56 (d, J = 7.7 Hz, 1H), 6.38 (d, J = 7.8 Hz, 1H), 6.06 (ddd, J = 16.8, 10.1, 9.2 Hz, 1H), 5.40-5.35 (m, 1H), 5.30 (dd, J = 9.9, 1.6 Hz, 1H), 5.27-5.21 (m, 2H), 4.66 (d, J = 9.5 Hz, 1H), 4.52 (d, J = 9.0 Hz, 1H), 3.44 (s, 2H), 3.42 (s, 2H), 3.39 (s, 4H), 2.91 (s, 3H), 2.73 (s, 3H), 2.51-2.45 (m, 1H), 2.23-1.89 (m, 7H); ^{13}C NMR ($CDCl_3$, 400.0 MHz) δ: 177.9 (C), 177.7 (C), 150.7 (C), 149.9 (C), 144.4 (C), 142.9 (C), 139.4 (C), 139.3 (C), 134.6 (CH), 134.4 (CH), 133.2 (C), 131.5 (CH), 131.1 (CH), 129.5 (CH), 129.5 (CH), 129.4 (CH), 129.3 (C), 128.9 (CH), 128.9 (CH), 128.5 (CH), 128.2 (CH), 128.1 (CH), 128.1 (CH), 127.4 (CH), 127.2 (CH), 126.8 (CH), 126.7 (CH), 124.2 (CH), 124.1 (CH), 124.0 (CH), 123.1 (CH), 122.8 (CH), 122.5 (CH), 120.2 (CH_2), 119.7 (CH_2), 108.0 (CH), 107.5 (CH), 65.5 (CH), 58.0 (CH_2), 58.0 (CH_2), 55.3 (C), 55.0 (C), 50.3 (CH), 50.0 (CH), 48.8 (CH_2), 48.6 (CH_2), 32.7 (CH_2), 32.5 (CH_2), 25.9 (CH_3), 25.7 (CH_3); HRMS (EI) m/z calcd for C_7H_7 $[M-C_{27}H_{28}N_3]^+$ 91.0548**,** found 91.0577.



Compound 3.30: To a solution of Pd/C (0.025 mg, 0.023 mmol) in methanol (3.9 mL) was added oxindole **3.29** (0.200 g, 0.386 mmol) through the neck of the flask. $NaBH_4$ (0.205 g, 5.42 mmol) was added portion-wise at 0°C and the reaction was stirred at 0°C (ca. 30 minutes). The reaction was quenched by the addition of water and filtered through Celite® rinsing with EtOAc. The filtrate was then extracted with EtOAc three times. The combined organic layers were dried over anhydrous $MgSO_4$, filtered through cotton, and concentrated under reduced pressure. The residue was purified by flash chromatography (20% EtOAC/hexanes) to afford the desired product (**3.30**) as a white powder (0.149 g, 79%).

IR (neat, cm^{-1}): 3424 (m), 3359 (m), 3070 (m), 3025 (m), 2937 (m), 2804 (m), 2253 (w), 1702 (s), 1615 (s); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.24-7.15 (m, 12H), 7.01 (t, J = 7.4 Hz, 1H), 6.82-6.78 (m, 1H), 6.56 (dd, J = 7.8, 1.2 Hz, 1H), 6.55 (d, J = 7.7 Hz, 1H), 6.24 (td, J = 7.5, 1.2 Hz, 1H), 6.13, (dt, J = 16.8, 9.8 Hz, 1H), 5.91 (d, J = 7.7 Hz, 1H), 5.25 (d, J = 16.8 Hz, 1H), 5.23 (d, J = 5.5 Hz, 1H), 4.00 (d, J = 9.6 Hz, 1H), 3.94 (br. s, 2H), 3.49-3.42 (m, 4H), 2.71 (s, 3H), 2.39-3.32 (m, 2H), 2.18-1.96 (m, 2H); ^{13}C NMR ($CDCl_3$, 400.0 MHz) δ: 178.0 (C), 144.6 (C), 144.5 (C), 139.6 (C), 136.5 (C), 129.0 (C), 128.4 (CH), 128.2 (CH), 127.8 (CH), 127.2 (CH), 126.9 (CH), 125.4 (CH), 124.4 (CH), 122.4 (CH), 118.7 (CH_2), 118.4 (CH), 117.7 (CH), 108.3 (CH), 58.2 (CH_2), 55.7 (C), 49.7 (CH), 49.0 (CH_2), 32.9 (CH_2), 25.9 (CH_3); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.24-7.10 (m, 11H), 6.99 (m, 4H), 6.68-6.54 (m, 3H), 5.92 (td, J = 16.8, 9.8 Hz, 1H), 5.08 (d, J = 16.8 Hz, 1H), 4.96 (dd, J = 10.1, 1.6 Hz, 1H), 3.80 (d, J = 9.5 Hz, 1H), 3.54 (br. s, 2H), 3.40 (s, 4H), 3.04 (s, 3H), 2.49-2.42 (m, 1H), 2.01-1.85 (m, 3H);^{13}C NMR ($CDCl_3$, 400.0 MHz) δ: 179.2 (C), 144.6 (C), 144.3 (C), 139.6 (C), 136.1 (C), 129.5 (C), 129.0 (CH), 128.2 (CH), 128.2 (CH), 127.7 (CH), 126.8 (CH), 124.8 (CH), 124.4 (CH), 121.9 (CH), 118.5 (CH), 117.4 (CH_2), 117.0 (CH), 107.8 (CH), 58.4 (CH_2), 56.3 (C), 50.9 (CH), 49.4 (CH_2), 31.9 (CH_2), 26.1 (CH_3); HRMS (EI) m/z calcd for $C_{34}H_{35}N_3O$ $[M]^+$ 501.2780, found 501.2785; MP=55.8-57.1°C.

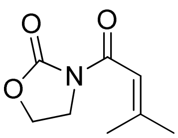


Compound 3.31: To a solution of oxindole **3.30** (0.200 g, 0.399 mmol) dissolved in THF (4.0 mL) was added a 0.4M solution of DIBAL/BuLi (5.98 mL, 2.39 mmol) at -78°C. The reaction was allowed to stir at this temperature for 15 minutes then warmed to room temperature for 72 hours. The reaction was quenched by the addition of an L-tartrate solution at 0°C and allowed to stir for ca. 4 hours. The quenched reaction mixture is then extracted with EtOAc three times. The combined organic layers were dried over anhydrous $MgSO_4$, filtered through cotton, and concentrated under reduced pressure. The residue was purified by flash chromatography (10-20% EtOAC/Hexanes) to afford the desired product (**3.31**) as a yellow oil (0.165 mg, 41%).

Preparation of 0.4M solution of DIBAL/BuLi solution: to a solution of THF (11.04 mL) cooled to -78°C was added 1.0 M DIBAL in Toluene (6.4 mL) followed by 2.5 M n-BuLi in THF (2.56 mL). The solution was allowed to stir at -78°C for 5 minutes then warmed to room temperature with stirring for 15 minutes. The solution is then used in the reaction.

IR (neat, cm^{-1}): 3029 (m), 2937 (m), 2804 (m), 1656 (w), 1607 (s); ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.28-7.24 (m, 10H), 7.04 (t, J = 7.5 Hz, 1H), 6.98 (t, J = 7.6 Hz, 1H), 6.90 (d, J = 7.3 Hz, 1H), 6.82 (d, J = 6.8 Hz, 1H), 6.70 (t, J = 7.3 Hz, 1H), 6.59 (d, J = 7.8 Hz, 1H), 6.54 (t, J = 7.4 Hz, 1H), 6.25 (d, J = 7.7 Hz, 1H), 5.90 (dt, J = 17.0, 9.7 Hz, 1H), 4.88 (d, J = 10.0, 1H), 4.82 (d, J = 16.6 Hz, 1H), 4.32 (s, 1H), 3.57-3.46 (m, 4H), 3.17 (d, J = 9.5 Hz, 1H), 2.58 (s, 3H), 2.47-2.41 (m, 2H), 2.05-1.91 (m, 2H); ^{13}C NMR ($CDCl_3$, 400.0 MHz) δ: 151.1 (C), 141.7 (C), 139.8 (C), 137.5 (CH), 131.3 (C), 128.9 (CH), 128.3 (CH), 128.2 (CH), 127.8 (CH), 127.2 (CH), 126.9 (CH), 126.5 (C), 124.0 (CH), 119.3 (CH), 117.5 (CH), 116.6 (CH_2), 114.7 (CH), 106.2 (CH), 81.3 (CH), 58.5 (CH_2), 51.8 (CH), 50.2 (C), 48.8 (CH_2), 34.7 (CH_2), 32.0 (CH_3); HRMS (EI) m/z calcd for C_7H_7 $[M-C_{27}H_{28}N_3]^+$ 91.0548, found 91.0557.

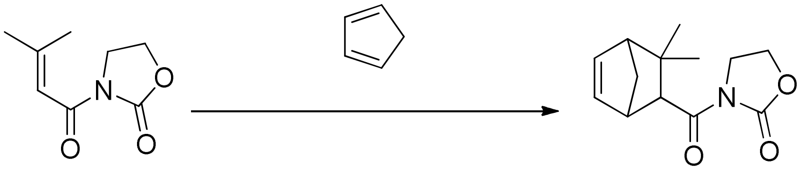
Experimental Chapter 7



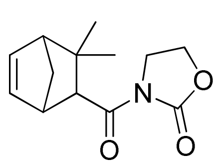
3-(3-methylbut-2-enoyl)oxazolidin-2-one (7.3): To a solution of oxazolidinone (2.8 g, 32.2 mmol) in THF (106 mL) at -78°C is added n-butyllithium (2.5 M, 12.9 mL, 32.2 mmol) dropwise. The solution was stirred for an additional 5 minutes and then freshly distilled acid chloride **7.2** (4.2 g, 35.4 mmol) is added dropwise and allowed to stir for 1 hour at -78°C. The reaction is then warmed to room temperature and quenched by the addition of a saturated solution of saturated aqueous NH_4Cl and the organic solvents removed under reduced pressure. The mixture is then extracted with DCM three times and the combined organic phases was rinsed with brine. The combined organic layers were dried over anhydrous $MgSO_4$, filtered through cotton, and concentrated under reduced pressure. The product was isolated by flash chromatography 10%-20% EtOAC/hexanes to afford the desired product (**7.3**) as a white solid (5.01 g, 92%).

IR (neat, cm^{-1}): 2987 (m), 2914 (m), 1793 (m), 1675 (m), 1620 (m); ^1H NMR ($CDCl_3$, 400 MHz) δ: 6.94-6.93 (m, 1H), 4.39 (t, J = 8.0 Hz, 2H), 4.04 (t, J = 8.0 Hz, 2H), 2.18 (s, 3H), 2.18 (s, 3H); ^{13}C NMR ($CDCl_3$, 400.0 MHz) δ: 165.3 (C), 159.5 (C), 153.6 (C), 115.4 (CH_2), 61.9 (CH_3), 42.8 (CH_3), 28.2 (CH_2), 21.5 (CH_2); HRMS (EI) m/z calcd for $C_8H_{11}NO_3$ $[M]^+$269.0739, found 169.07337.

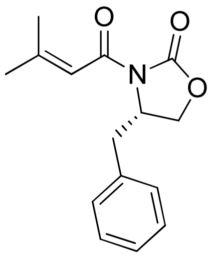
General Diels-Alder Procedure



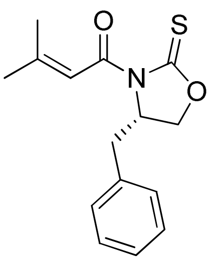
To a solution of 3-(3-methylbut-2-enoyl)oxazolidin-2-one (**7.3**) (1.0 Eq) and freshly distilled cyclopentadiene (**5.10**) (20 Eq) in **Solvent** (0.1 M) at 0°C was added **Catalyst** (0.7 Eq). The reaction mixture was allowed to stir at 0°C for 30 minutes. The reaction was then allowed to warm to room temperature and continued to stir for another 2.5 hours. The reaction was then quenched by the addition of a saturated solution of ammonium chloride. The organic solvents were then removed under reduced pressure and the aqueous residue was filtered through a pad of Celite® rinsing with DCM. The organic layer was separated and the aqueous layer was extracted with DCM three times. The combined organic phase was then washed with brine, dried over anhydrous $MgSO_4$, and fltered through cotton. To the filtrate was added silica, and the solvent was removed under reduced pressure. The crude/silica mixture was placed on the high vacuum until a free flowing consistency was achieved. The product was then isolated by flash chromatography to afford a solid white powder.



3-(3,3-dimethylbicyclo[2.2.1]hept-5-enecarbonyl)oxazolidin-2-one: IR (neat, cm^{-1}) 3067 (w), 2960 (s), 2922.1 (m), 2873 (m), 1782 (s), 1691 (s), 1474 (m), 1387 (m), 1364 (m), 1330 (m); ^{1}H NMR (CDCl$_3$, 400 MHz) δ 6.30 (dd, J=5.6,2.9 Hz, 1H^{endo}), 6.24 (dd, J=2.4 Hz, 1H^{exo}), 6.12 (dd, J=5.8, 3.2 Hz, 1H^{exo}), 6.10 (dd, J=5.6, 3.2 Hz, 1H^{endo}), 4.37-4.27 (m, 2H^{endo,}2H^{exo}), 4.12 (d, J = 3.0 Hz, 1H^{endo}), 4.07-3.83 (m, 2H^{endo},2H^{exo}), 3.33 (d, J=1.8 Hz, 1H^{exo}), 2.92-2.90 (m, 1H^{endo}), 2.83.2.80 (m, 1H^{exo}), 2.33-2.29 (m, 1H^{endo}, 1H^{exo}), 2.11 (d, J=8.8 Hz, 1H^{exo}), 1.70 (d, J=8.6 Hz, 1H^{endo}), 1.43-1.36 (m, 1H^{exo}, 4H^{endo}), 1.05 (s, 3H^{exo}), 1.01 (s, 3H^{exo}), 0.74 (s, 3H^{endo}) ^{13}C NMR (CDCl$_3$, 400 MHz) δ 176.0 (C), 174.3 (C), 153.5 (C), 153.4 (C), 138.9 (CH), 136.0 (CH), 135.9 (CH), 134.5 (CH), 61.66 (CH2), 61.63 (CH2), 55.3 (CH), 54.2 (CH), 52.9 (CH), 51.1 (CH), 47.88 (CH), 47.85 (CH), 47.7 (CH2), 46.9 (CH2), 46.1 (C), 44.7 (C), 43.11 (CH), 43.04 (CH), 31.3 (CH3), 29.0 (CH3), 26.4 (CH3), 24.2 (CH3); HRMS (EI) m/z calcd for $C_{13}H_{17}NO_3$ $[M-C_8H_{11}NO_3]^+$ 66.0470, found 66.0584.

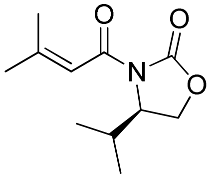


4-benzyl-3-(3-methylbut-2-enoyl)oxazolidin-2-one (7.8): To a solution of (S)-4-benzyloxazolidin-2-one (0.250 g, 1.41 mmol) in THF (14.1 mL) at -78°C is added n-butyllithium (1.55 M, 1.00 mL, 1.55 mmol) dropwise. The solution was stirred for an additional 5 minutes and then acid chloride **7.2** (0.17 mL, 1.56 mmol) is added dropwise and allowed to stir for 1 hour at -78°C. The reaction is then warmed to room temperature and quenched by the addition of a saturated solution of saturated aqueous NH$_4$Cl and the organic solvents removed under reduced pressure. The mixture is then extracted with DCM three times and the combined organic phase was rinsed with brine. The combined organic layers were dried over MgSO$_4$, concentrated under reduced pressure, and the product was isolated by flash chromatography (10%-20% EtOAC/hexanes) to afford the desired product (**7.8**) as a white solid (0.278 g, 76 %). ^{1}H NMR was compared to spectral data found in the literature.[86]



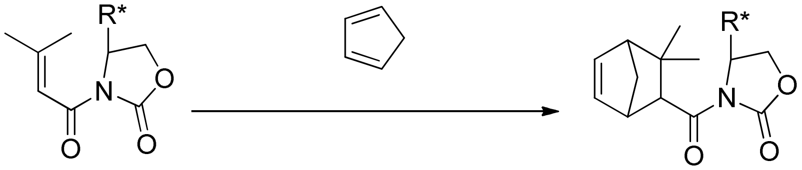
1-(4-benzyl-2-thioxooxazolidin-3-yl)-3-methylbut-2-en-1-one (7.9): A solution of (S)-4-benzyloxazolidine-2-thione (1.27 g, 6.56 mmol) in THF (6.4 mL) was added dropwise to a suspension of NaH (60% dispersion in mineral oil, 0.377 g, 9.84 mmol) in THF (12.9 mL) cooled to 0°C. The resulting mixture was stirred at 0°C for 45 minutes at which point a solution of acid chloride **7.2** (0.877 g, 7.87 mmol) in THF (2.6 mL) was added slowly and the reaction was allowed to stir at 0°C for 8 hours. The reaction was quenched by the addition of a saturated solution of saturated aqueous NH_4Cl at 0^oC and the organic solvents removed under reduced pressure. The mixture is then extracted with DCM three times and the combined organic phase was rinsed with brine. The combined organic layers were dried over $MgSO_4$, concentrated under reduced pressure, and the product was isolated by flash chromatography (10%-20% EtOAC/hexanes) to afford the desired product (7.9) as a white powder (1.22 g, 67%).

IR (neat, cm^{-1}): 3093 (m), 1067 (m), 3032 (m), 2979 (m), 2918 (m), 2865 (w), 1778 (s), 1698 (m), 1620 (m); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.29-7.22 (m, 6H), 4.94-4.88 (m, 1H), 4.32-4.26 (m, 2H), 3.37 (dd, J = 13.3, 3.4 Hz, 1H), 2.79 (dd, J = 13.3, 10.1 Hz, 1H), 2.20 (d, J = 1.1 Hz, 3H), 2.02 (d, J = 1.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 400.0 MHz) δ: 185.6 (C), 165.9 (C), 158.7 (C), 135.5 (C), 129.5 (CH), 129.0 (CH), 127.4 (CH), 117.8 (CH), 70.3 (CH_2), 60.0 (CH), 37.7 (CH_2), 27.8 (CH_3), 21.5 (CH_3); HRMS (EI) m/z calcd for $C_{15}H_{17}NO_2S$ $[M]^+$ 275.0980, found 275.10005.



4-benzyl-3-(3-methylbut-2-enoyl)oxazolidin-2-one (7.10): To a solution of (R)-4-isopropyloxazolidin-2-one (0.500 g, 3.87 mmol) in THF (12.9 mL) at -78°C is added n-butyllithium (1.60 M, 2.66 mL, 4.26 mmol) dropwise. The solution was stirred for an additional 5 minutes and then acid chloride **7.2** (0.47 mL, 4.26 mmol) is added dropwise and allowed to stir for 1 hour at -78°C. The reaction is then warmed to room temperature and quenched by the addition of a saturated solution of saturated aqueous NH_4Cl and the organic solvents removed under reduced pressure. The mixture is then extracted with DCM three times and the combined organic phase was rinsed with brine. The combined organic layers were dried over $MgSO_4$, concentrated under reduced pressure, and the product was isolated by flash chromatography (10%-20% EtOAC/hexanes) to afford the desired product **7.10** (0.680 g, 83 %) as a white solid. ^{1}H NMR was compared to spectral data found in the literature.[87]

General Asymmetric Diels-Alder Procedure



To a solution of the **chiral dienophile** (1.0 Eq) in **Solvent** (0.1M) at 0°C was added **Catalyst** (0.7 Eq). The reaction was allowed to stir for 20 minutes at 0°C then freshly distilled cyclopentadiene (20 Eq) was added dropwise. The reaction mixture was allowed to stir at 0°C for 30 minutes. The reaction was then allowed to warm to room temperature and continued to stir for another 2.5 hours. The reaction was then quenched by the addition of a saturated solution of NH_4Cl. The organic solvents were then removed under reduced pressure and the aqueous residue was filtered through a pad of Celite® rinsing with DCM. The organic layer was separated and the aqueous layer was extracted with DCM three times. The combined organic phase was then washed with brine, dried over anhydrous $MgSO_4$, and filtered through cotton. To the filtrate was added silica, and the solvent was removed under reduced pressure. The crude/silica mixture was placed on the high vacuum until a free flowing consistency was achieved. The product was then isolated by flash chromatography.

Glossary of Abbreviations

Ac – acetyl

ACS – American Chemical Society

ACN - acetonitrile

aux - auxilary

AIBN - azobisisobutyronitrile

BHT - butylated hydroxytoluene

BINOL - 1,1'-Bi-2-naphthol

Bn - benzyl

Boc - di-tert-butyl dicarbonate

BOM – benzyloxymethyl

BOP - benzotriazole-1-yl-oxy-tris-(dimethylamino)-phosphonium hexafluorophosphate

Bu - butyl

Cbz - carbobenzyloxy

CDI - 1,1’-carbonyldiimidazole

Cp - cyclopentadienyl

dba – dibenzylideneacetone

DCE - dichloroethane

DCM – dichloromethane

DEAD - diethyl azodicarboxylate

DIBAL - diisobutylaluminium hydride

DMA – N,N-dimethylaceta- mide

DMAP - 4-Dimethylaminopyridine

DMF - dimethylformamide

EASC – ethylaluminum sesquichloride

EDG – electron donating group

ee – enantiomeric excess

Et - ethyl

EWG – electron withdrawing group

Eq - equivalent

HOMO – highest occupied molecular orbital

LAH – lithium aluminum hydride

LiHMDS – lithium hexamethyldisilazide

LN – lithium napthalenide

LUMO – lowest unoccupied molecular orbital

Me - methyl

NCS - N-chlorosuccinimide

NMR - nuclear magnetic resonance

Ns - nitrobenzenesulfonyl

Ph - phenyl

Phth - phthalamide

PPTS - pyridinium *p*-toluenesulfonate

Py - pyridine

SOI – secondary orbital interactions

TBAB - tetrabutylammonium bromide

TBAF - tetrabutylammonium floride

TBS - *t*-Butyldimethylsilyl

TCA – trichloroacetic acid

Tf – trifluoromethanesulfonyl

TFP - tri(2-furyl)phosphine

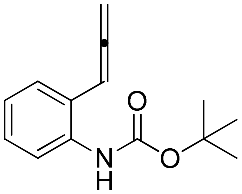
THF - tetrahydrofuran

TLC – thin layer chromatography

TMS - trimethylsilyl

Ts- tosyl

Supporting Information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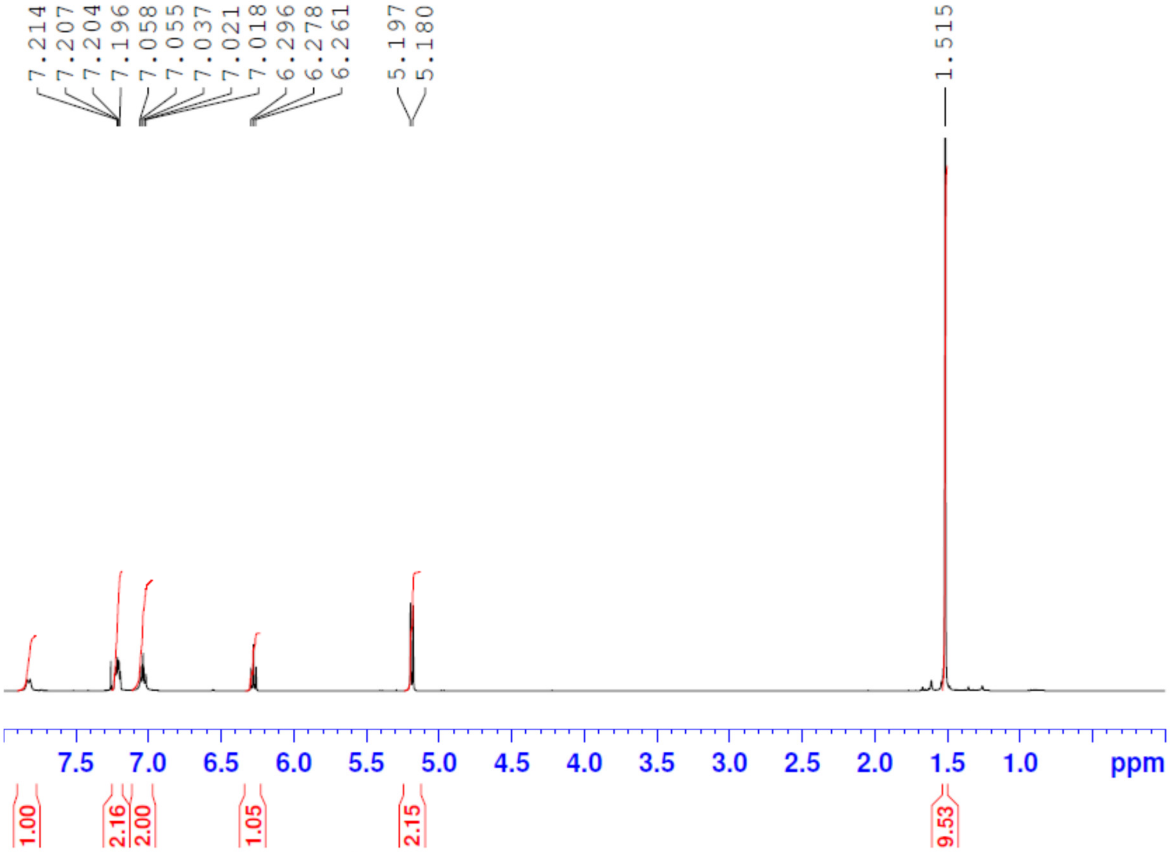
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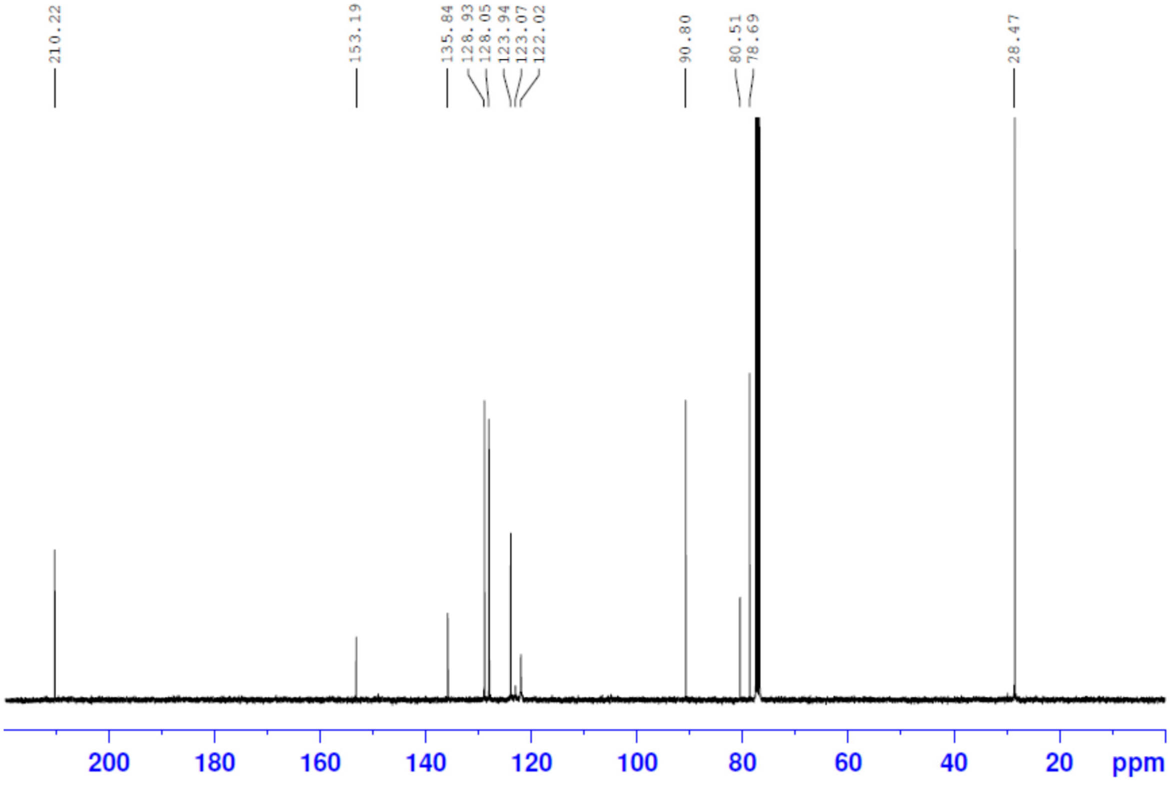
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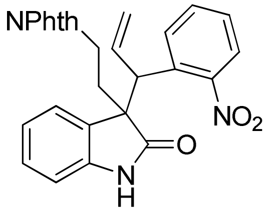
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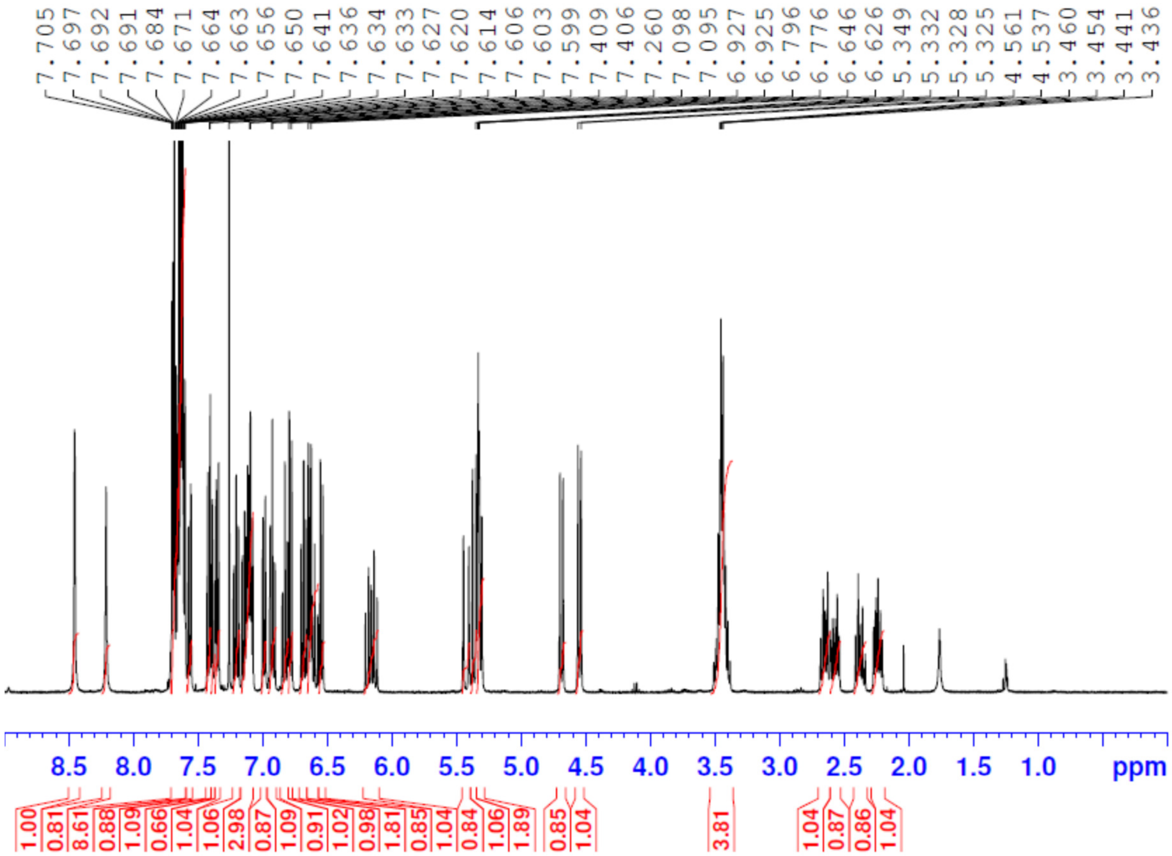
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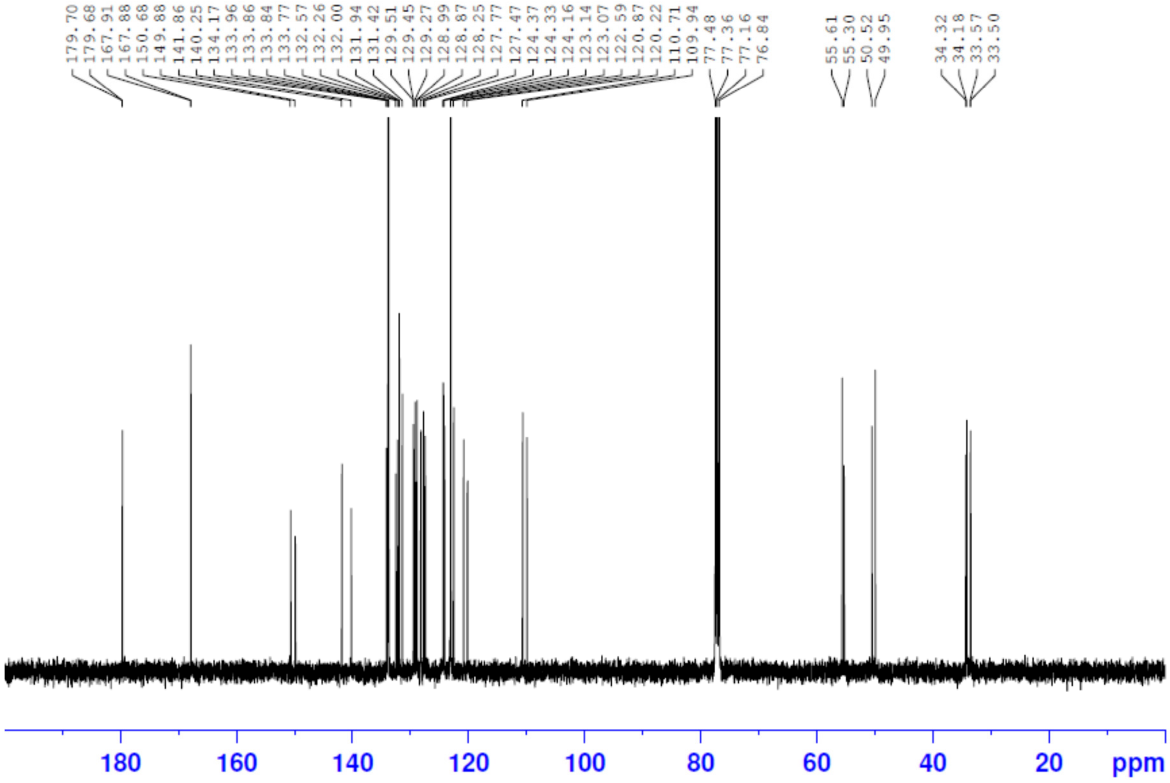
1.04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124.33
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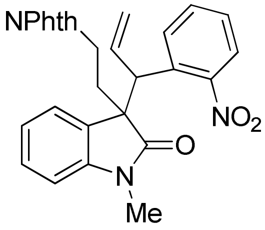
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NO2
O
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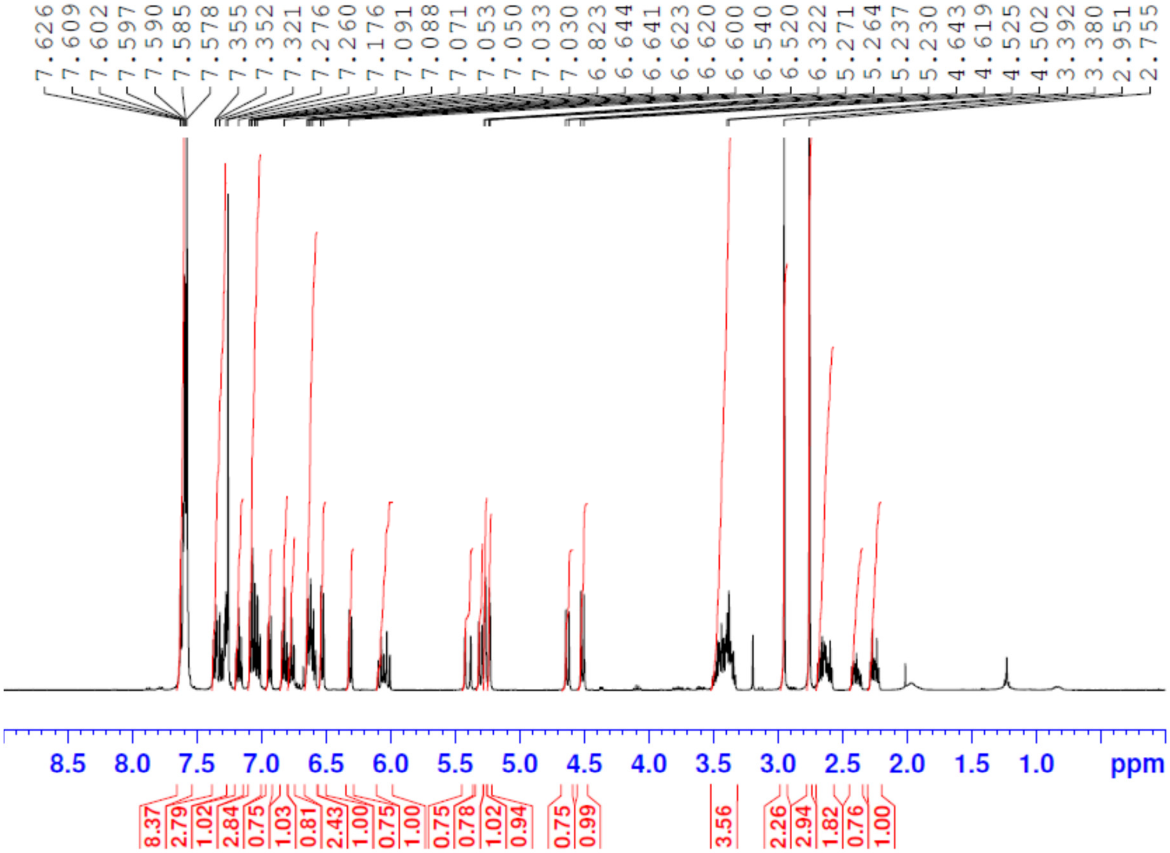
Me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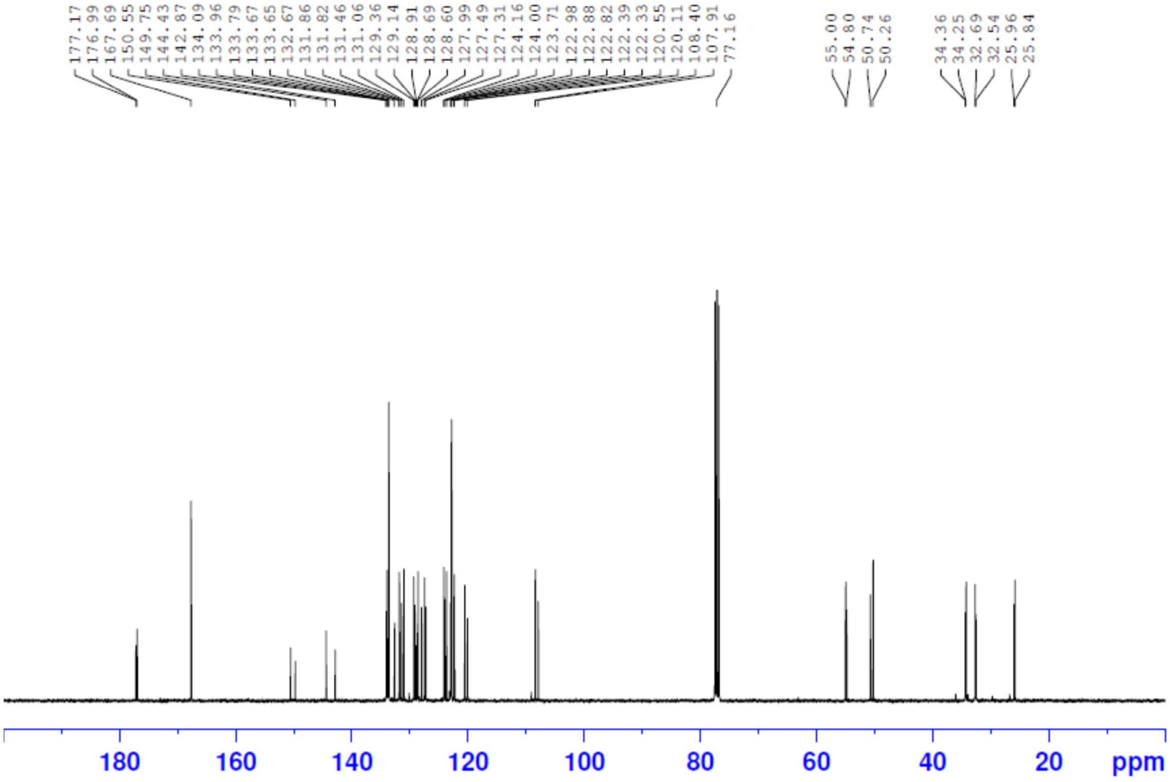
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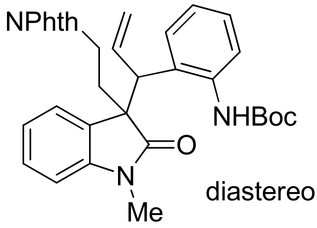
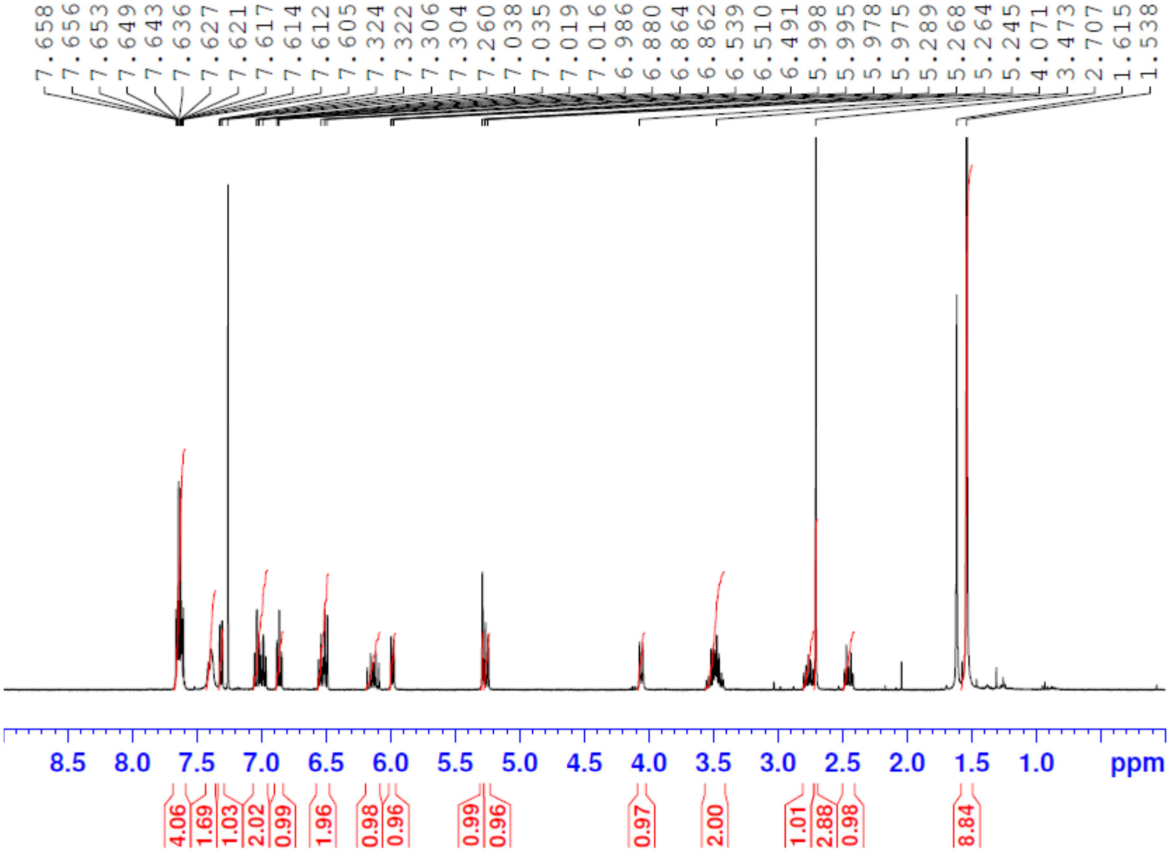
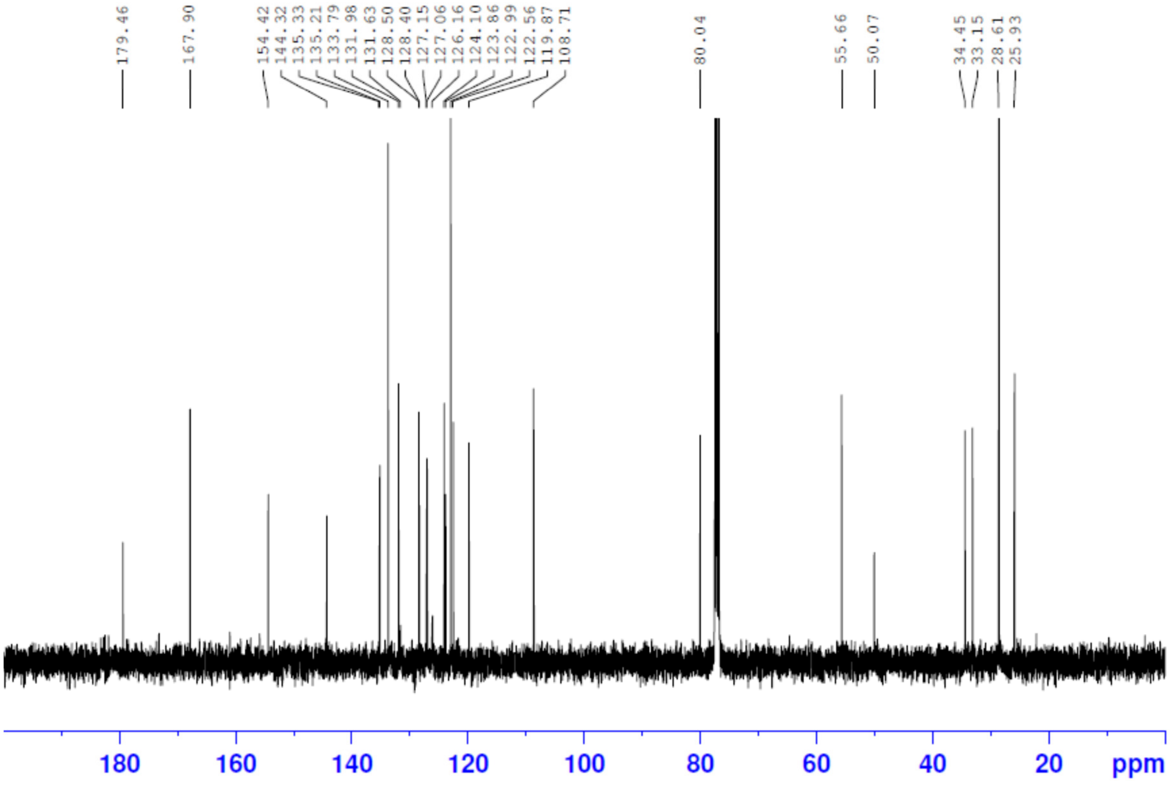
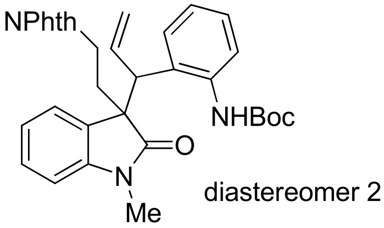


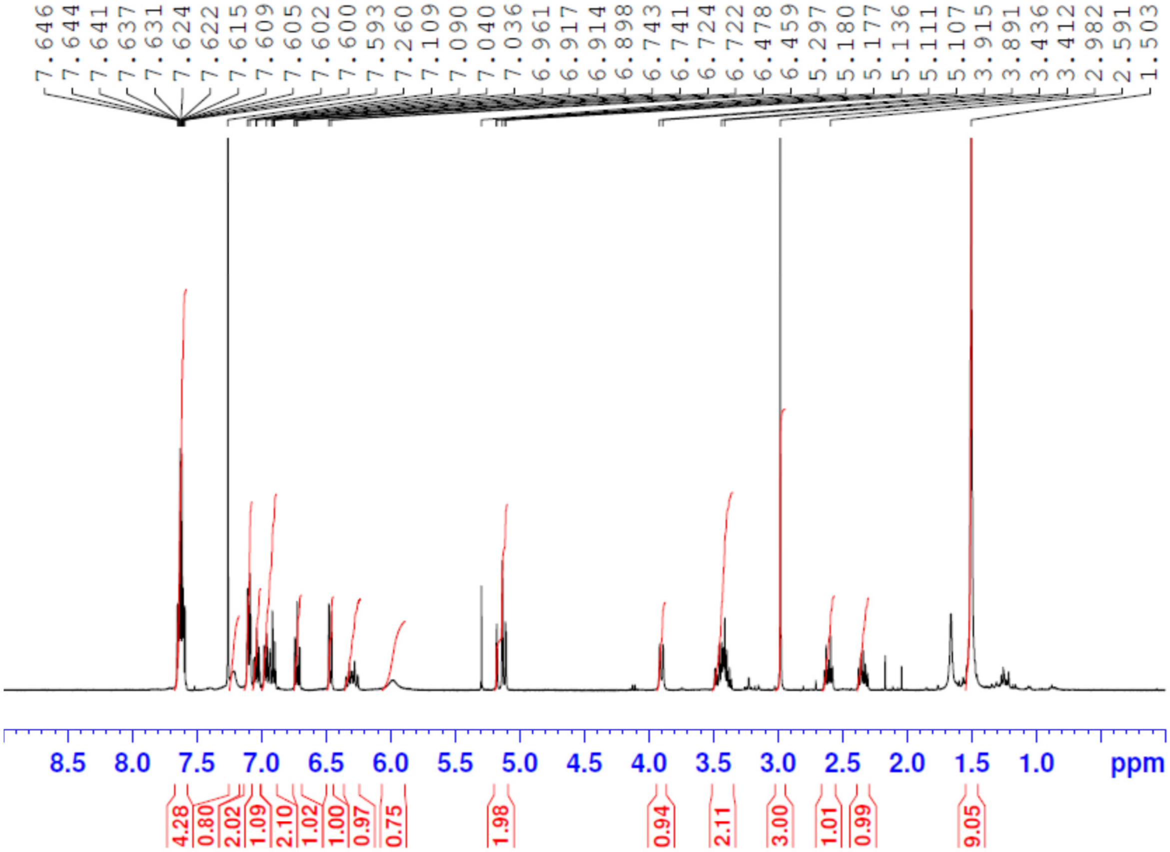
diastereomer 1

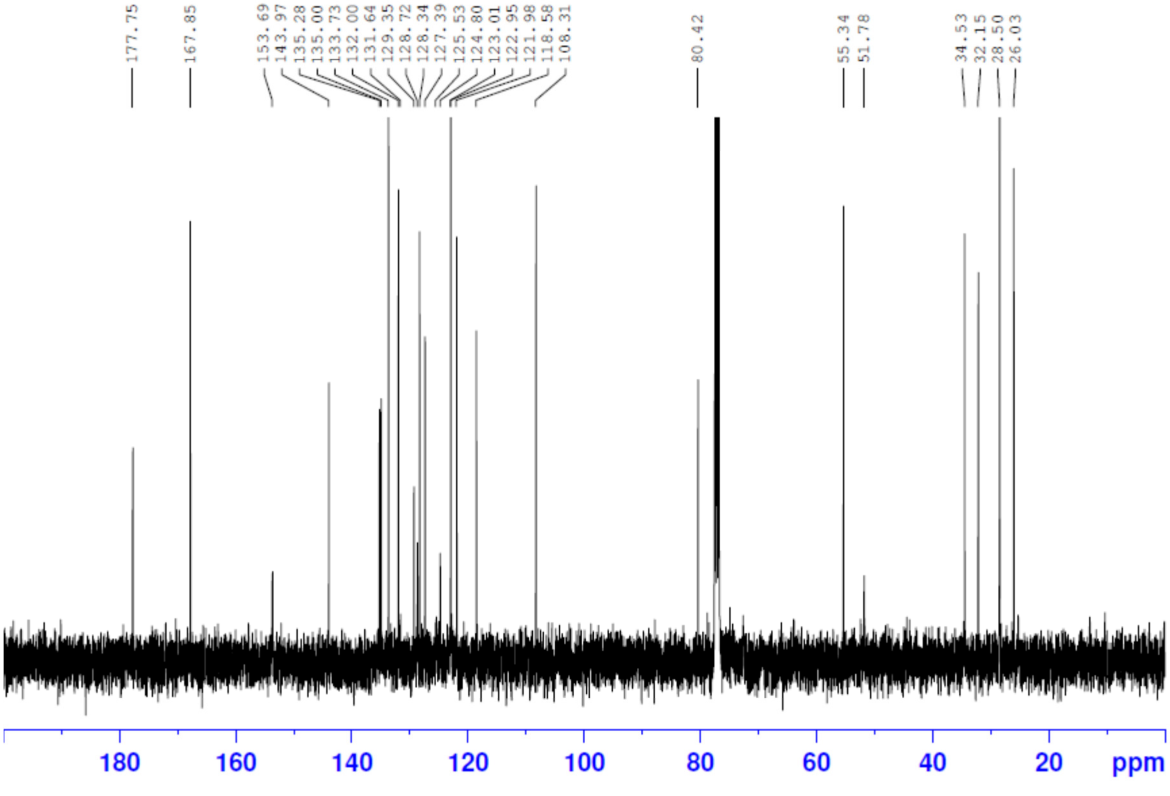


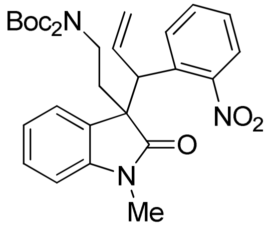




diastereomer 2



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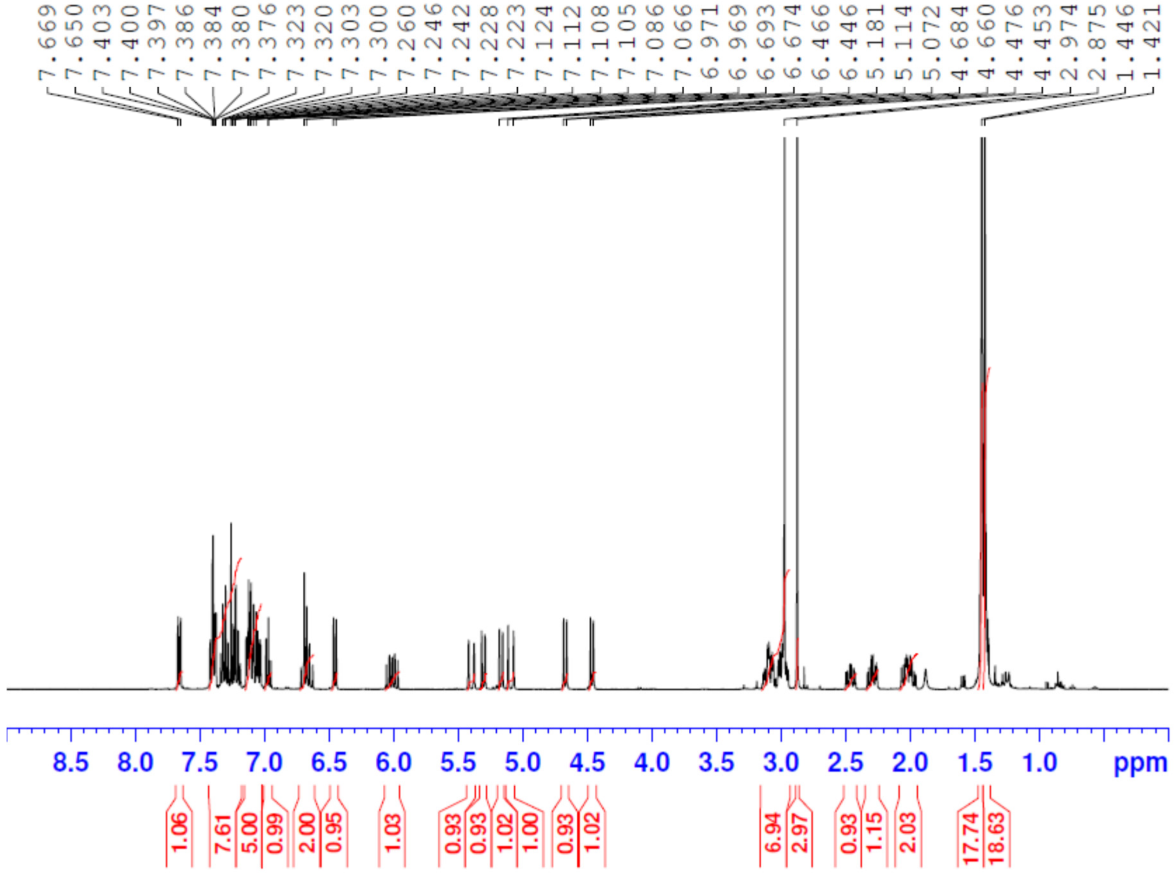
O
N
Me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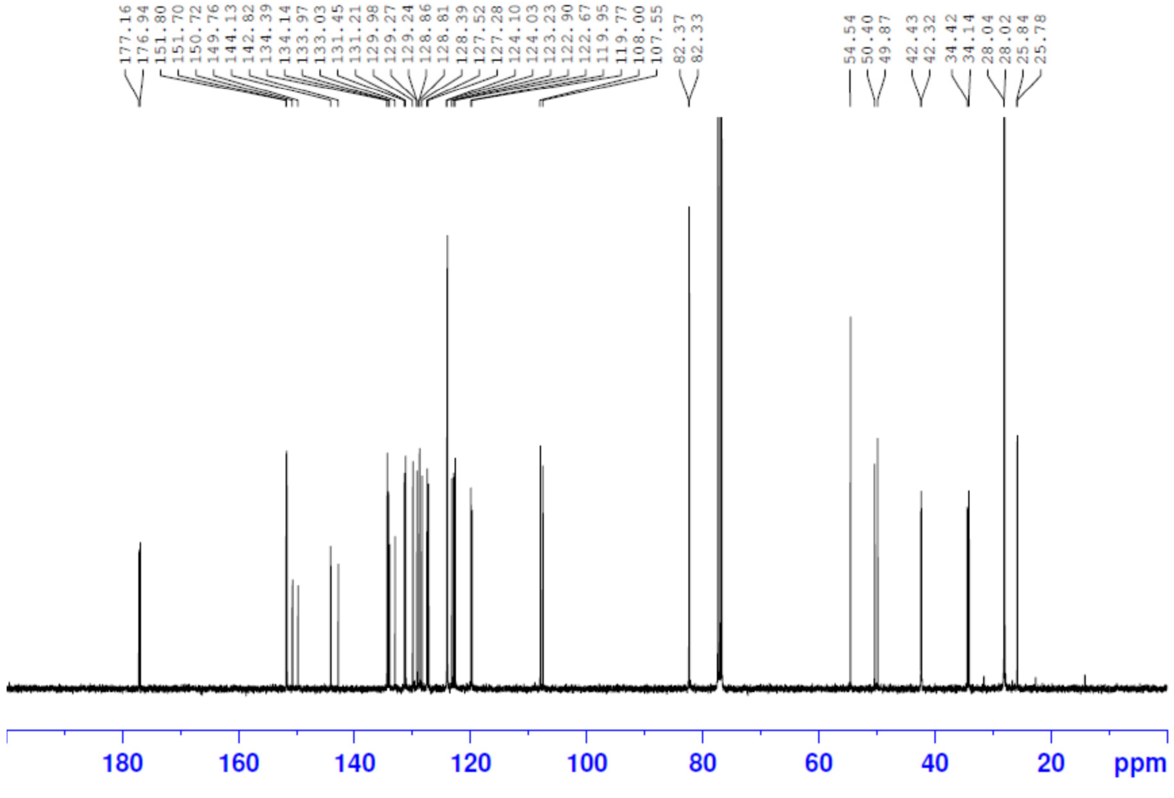
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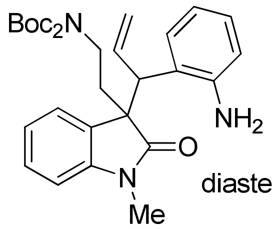

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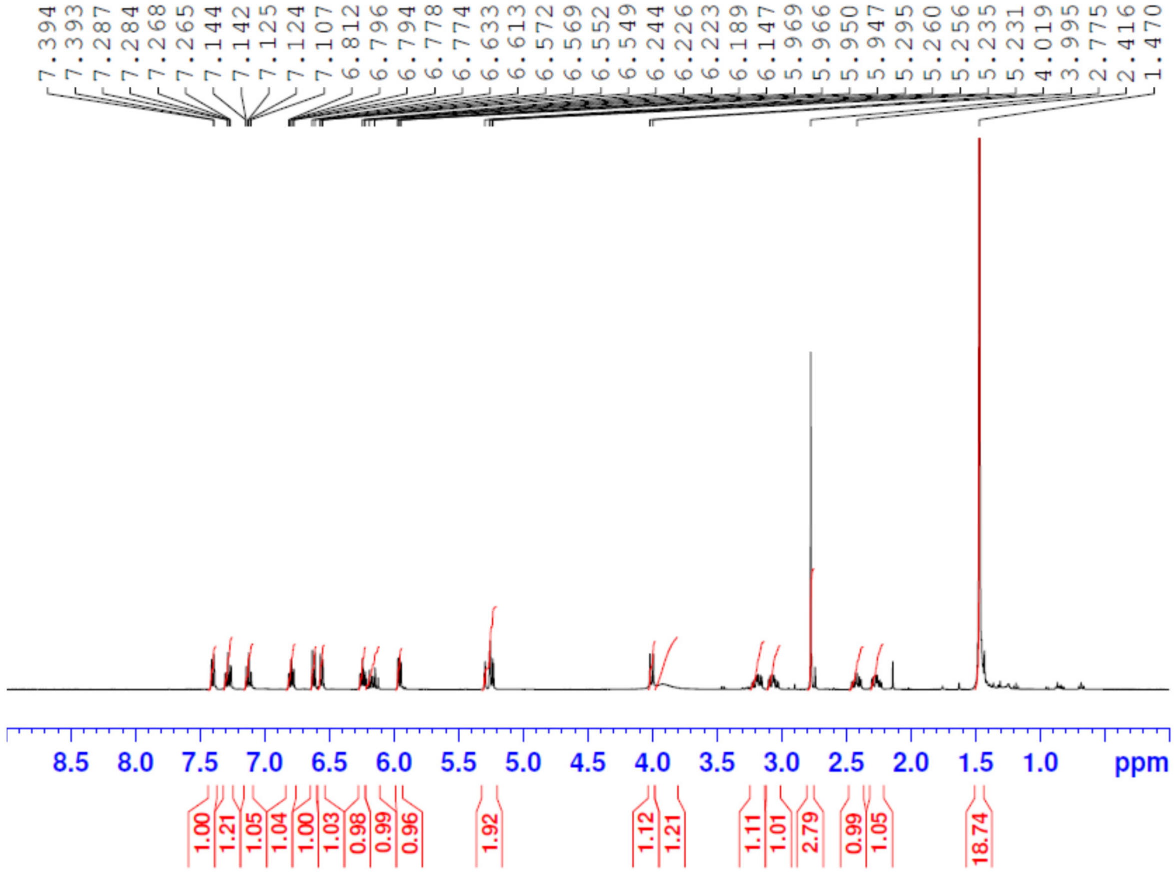
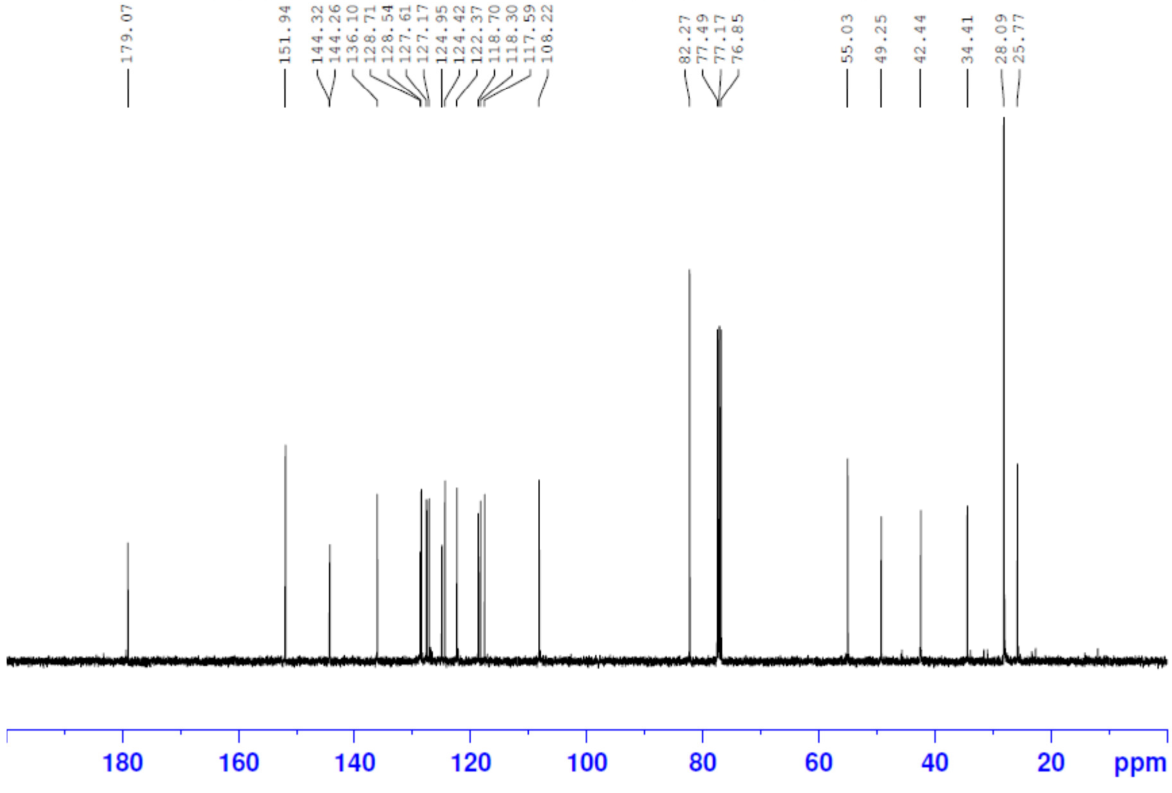
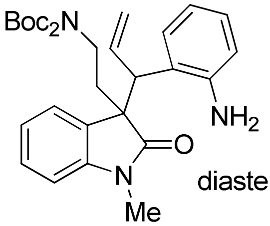
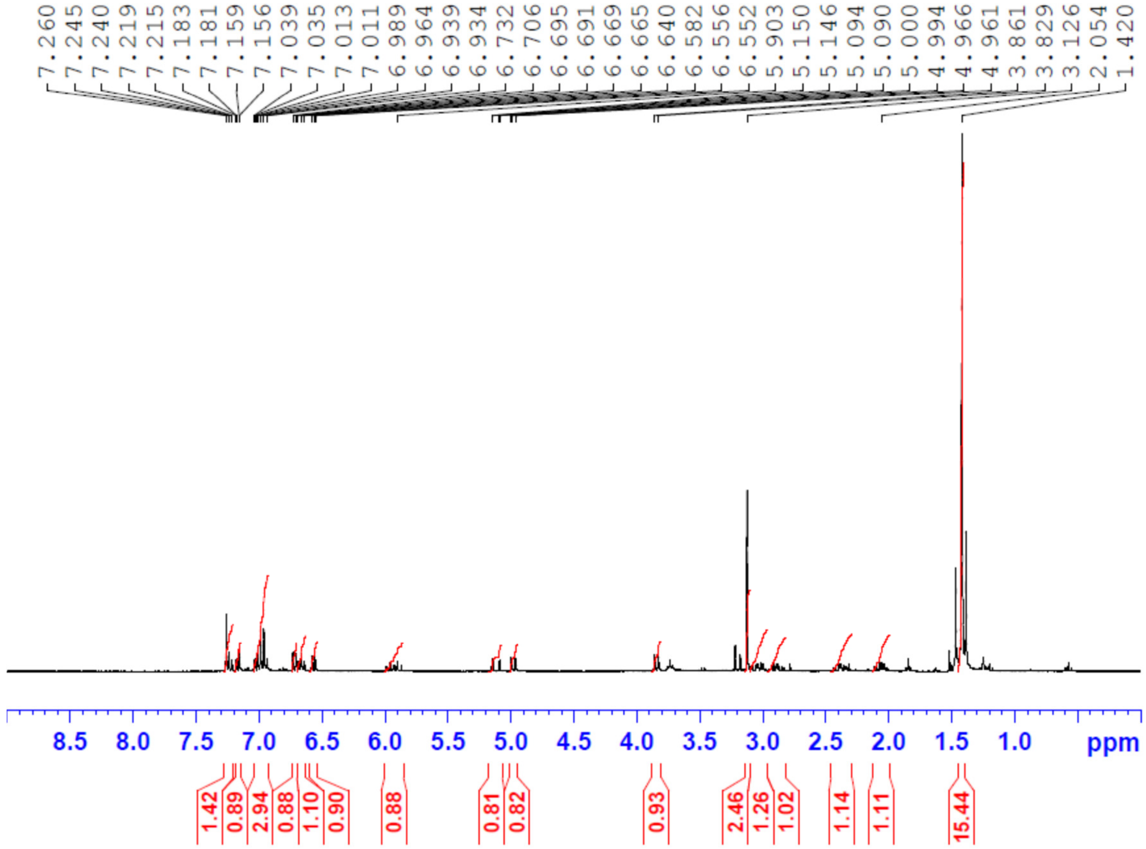
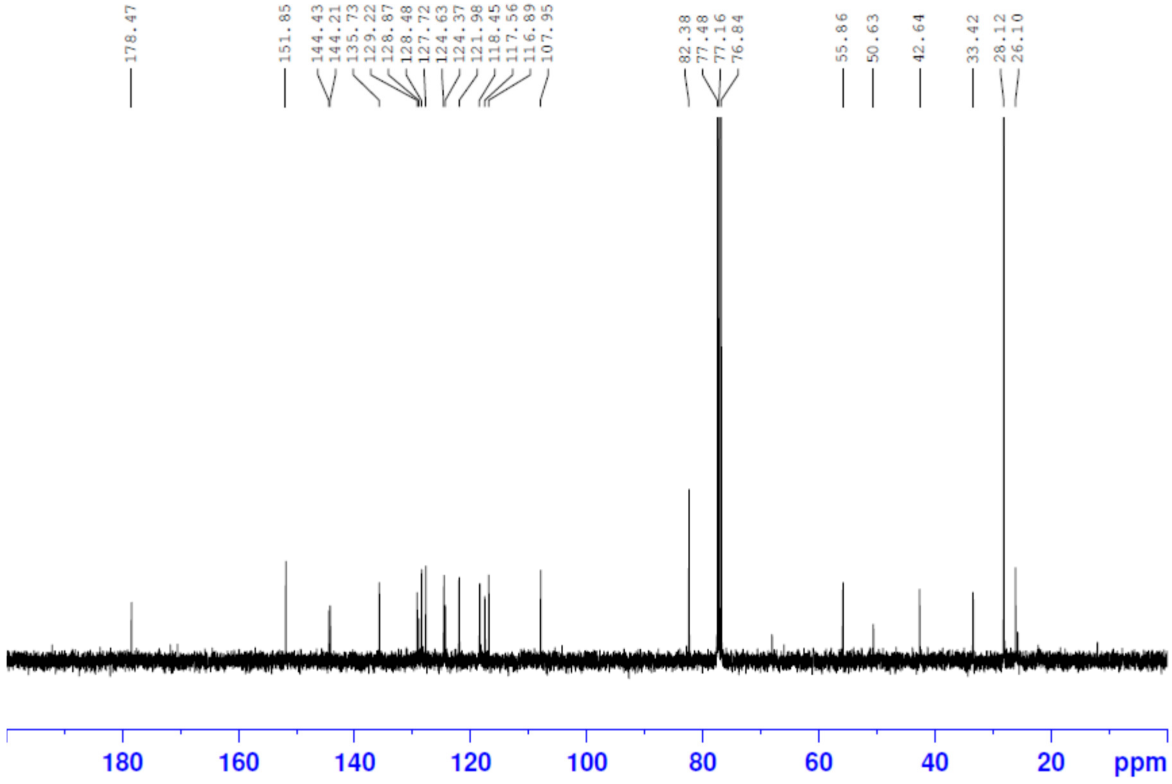


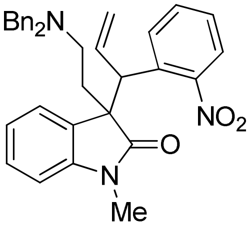


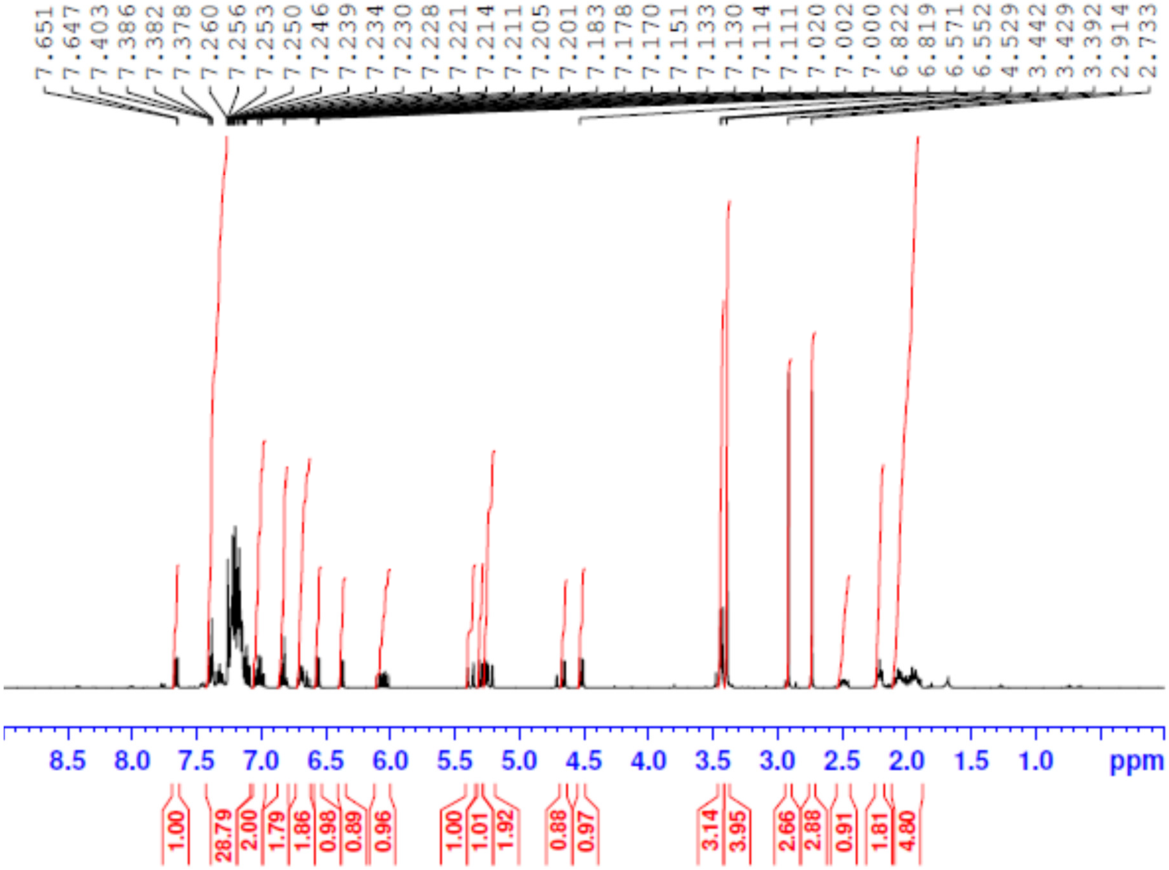


diastereomer 2






Bn$_2$N
NO$_2$
O
N
Me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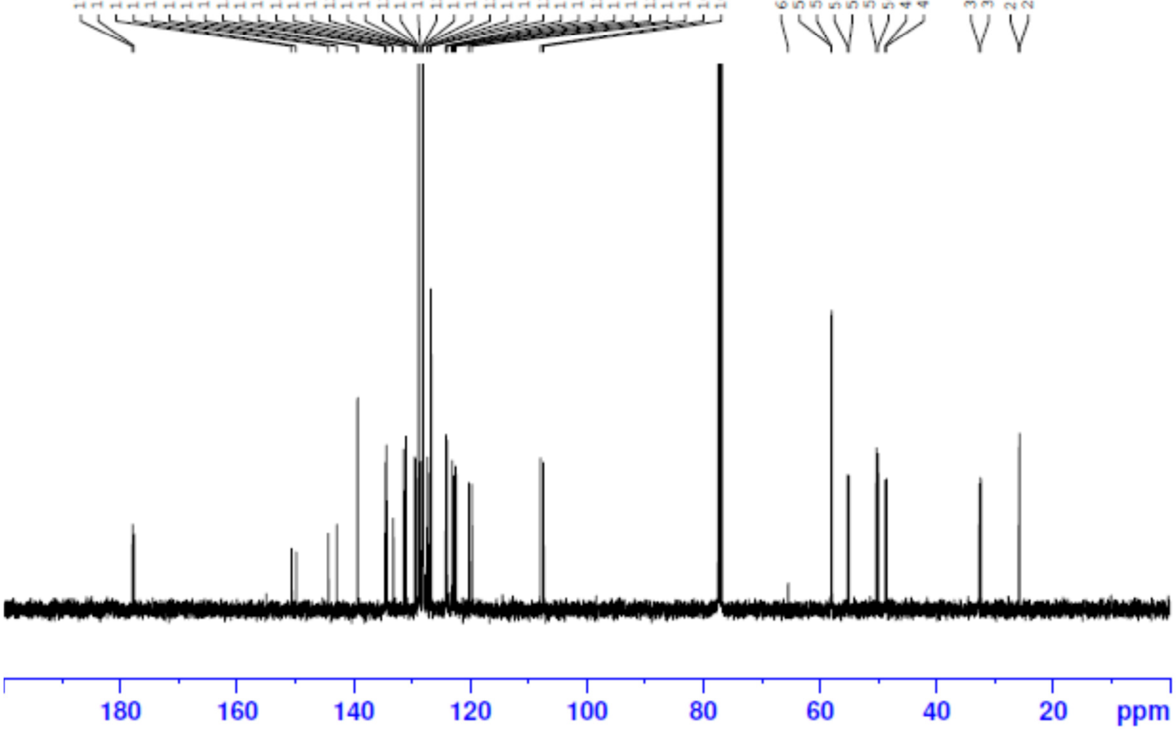
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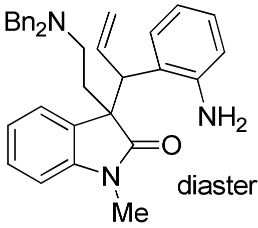

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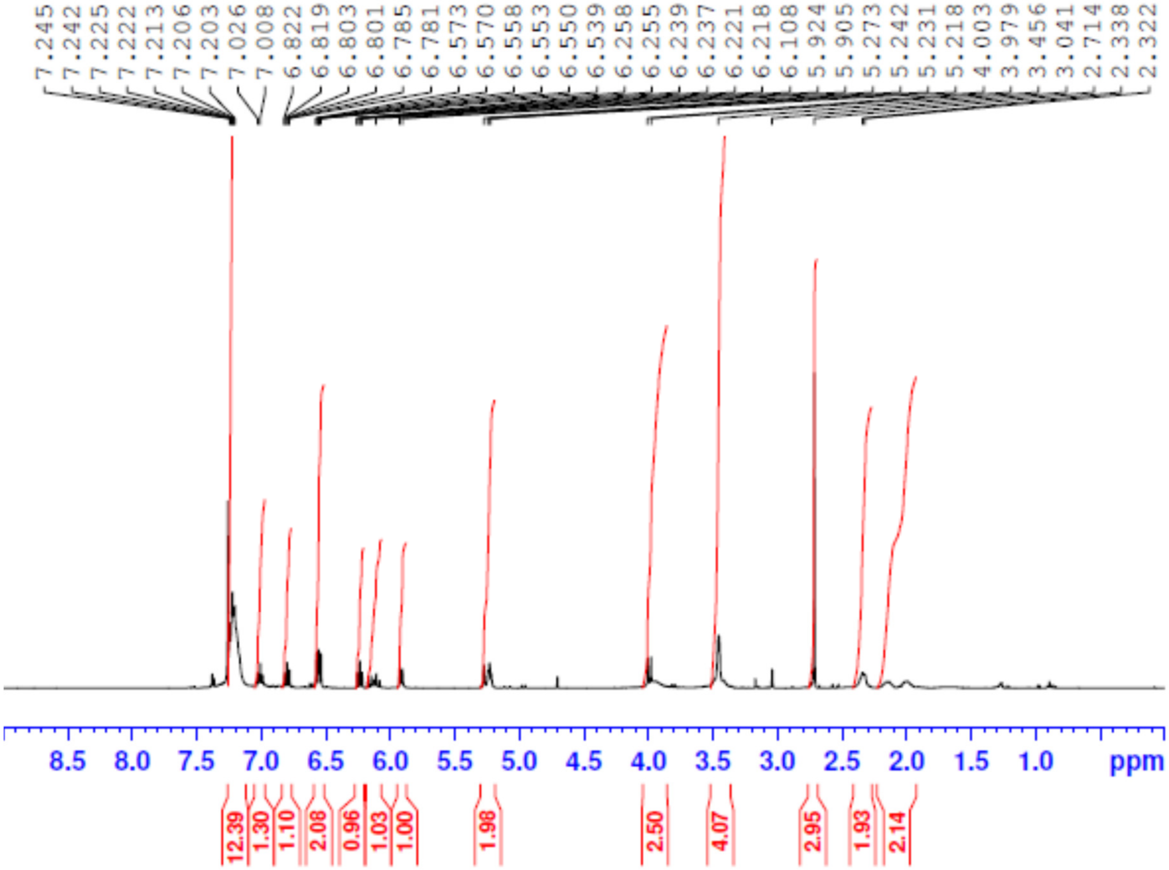
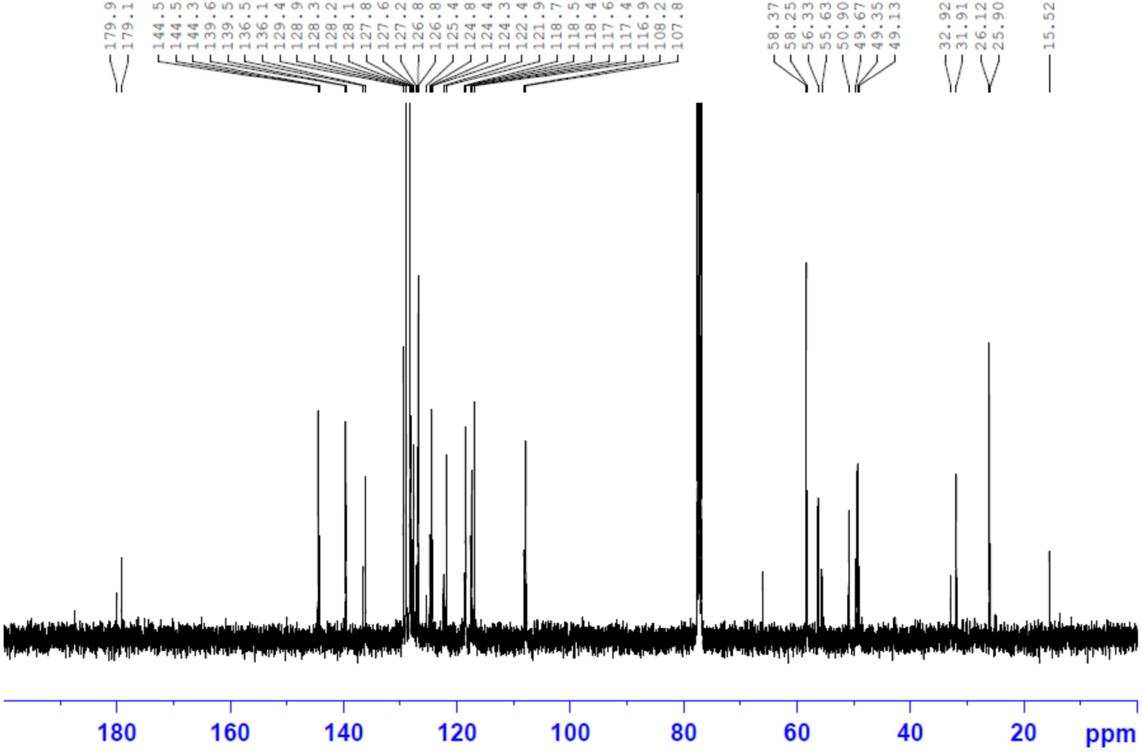
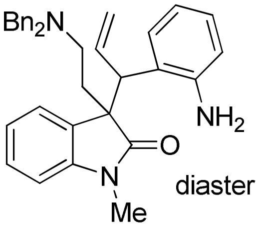
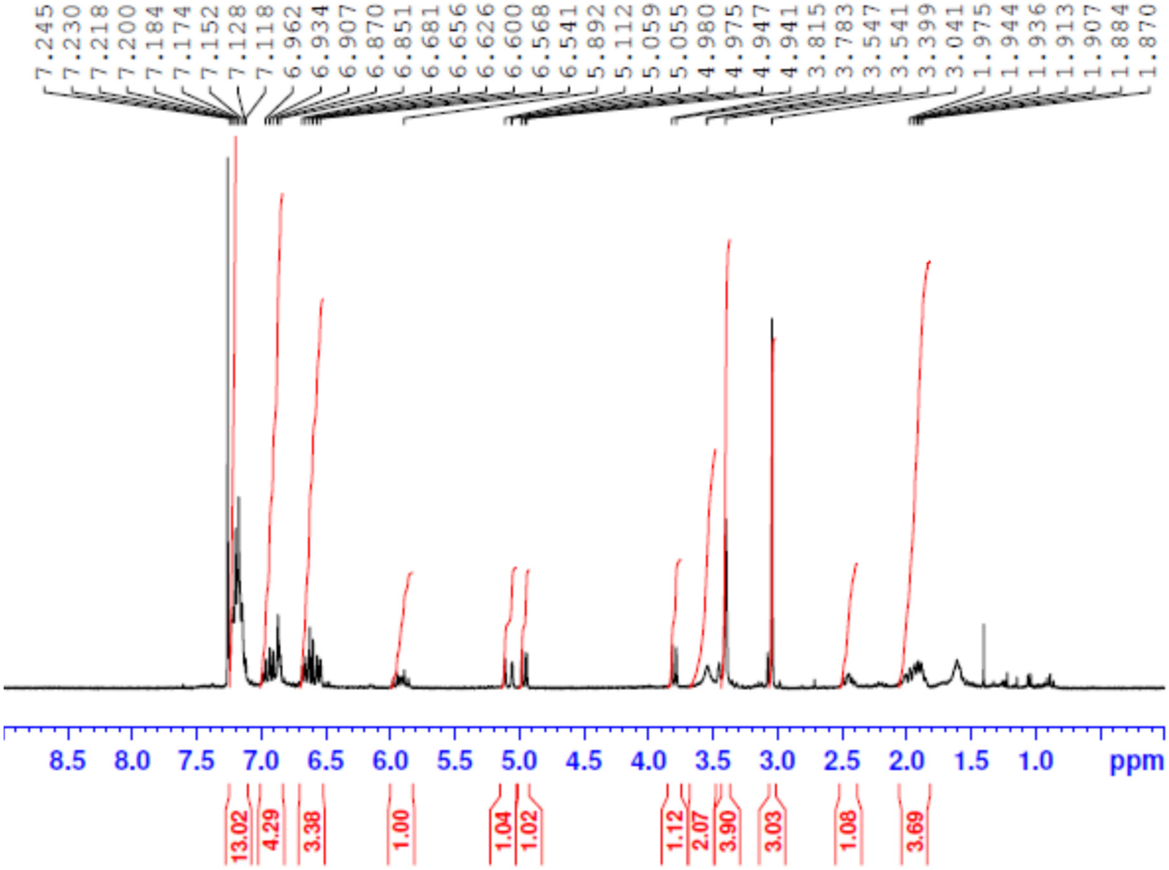
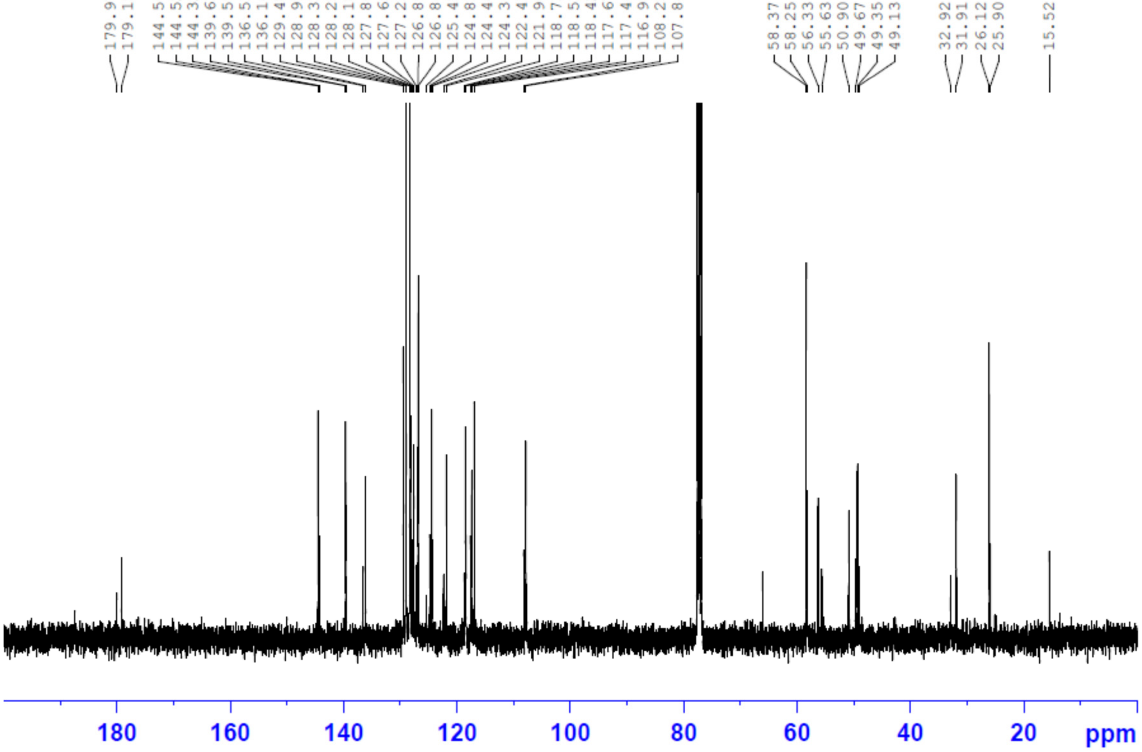


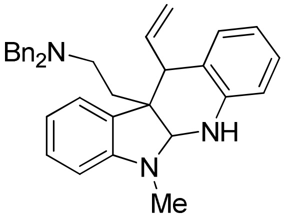




diastereomer 2






Bn2N
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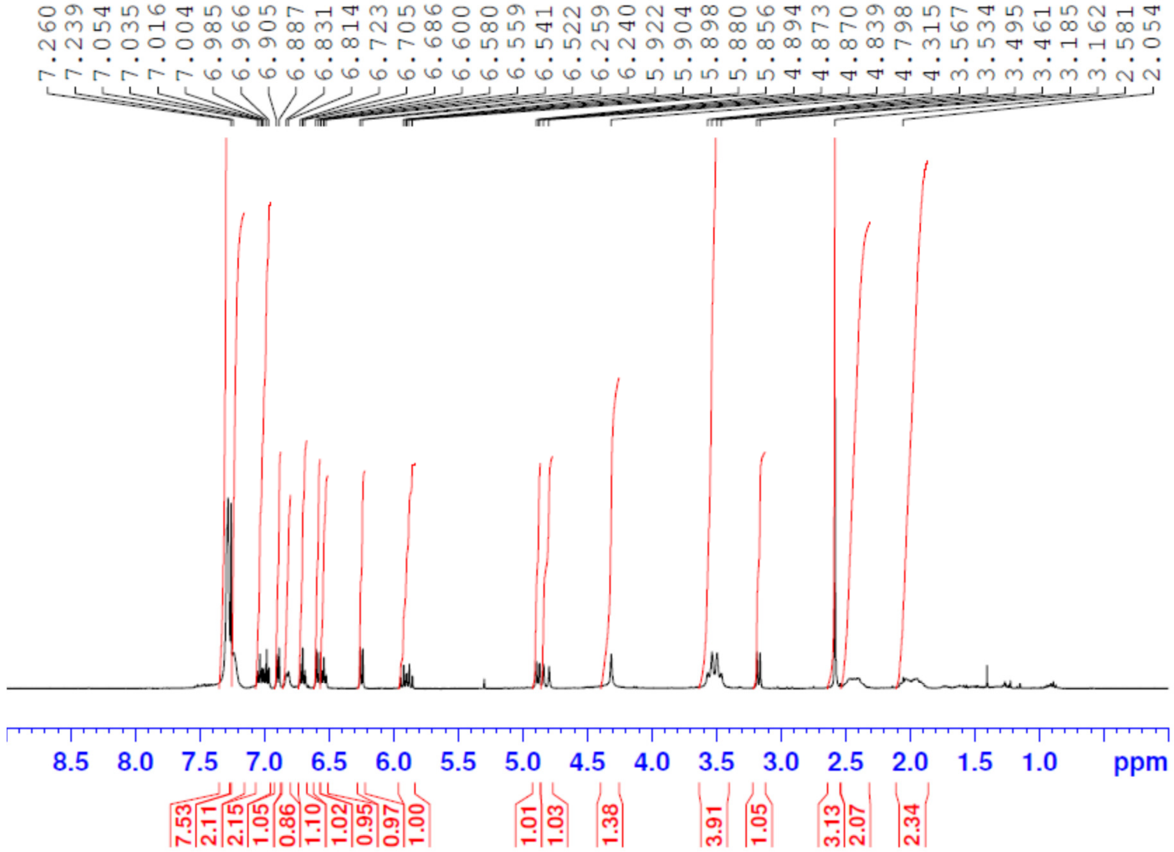
N
Me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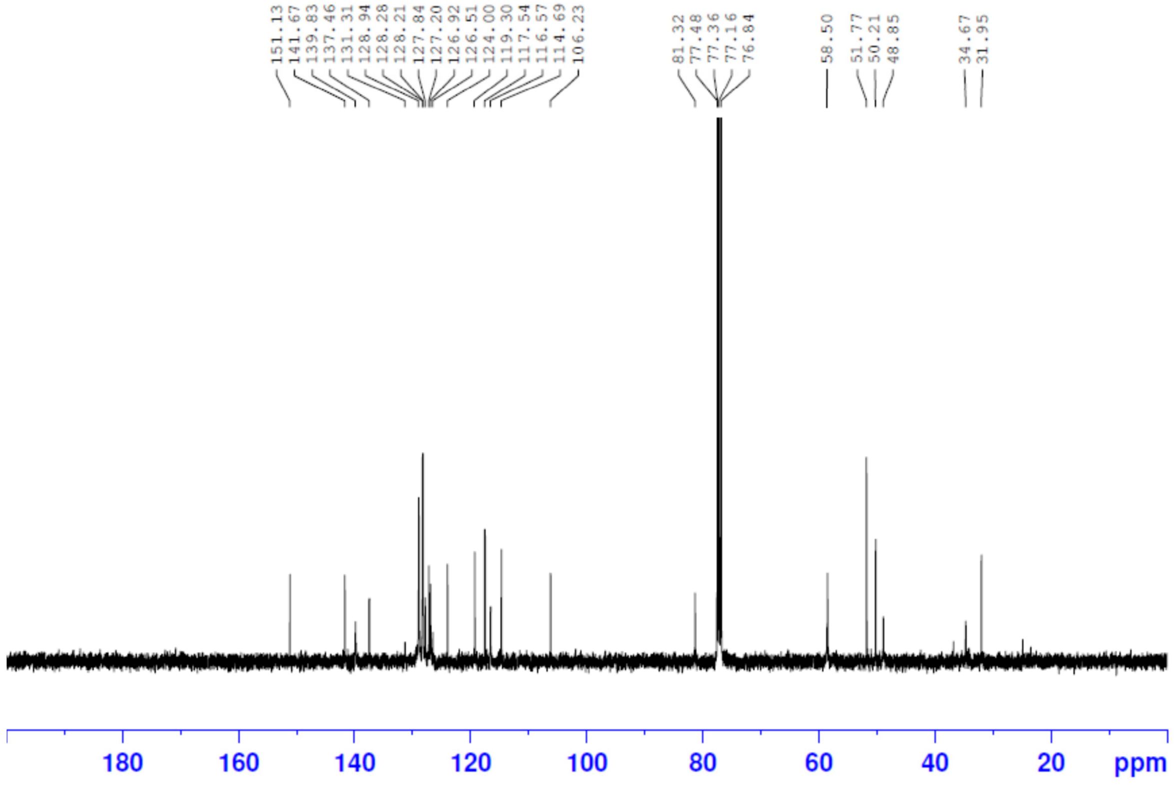
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80
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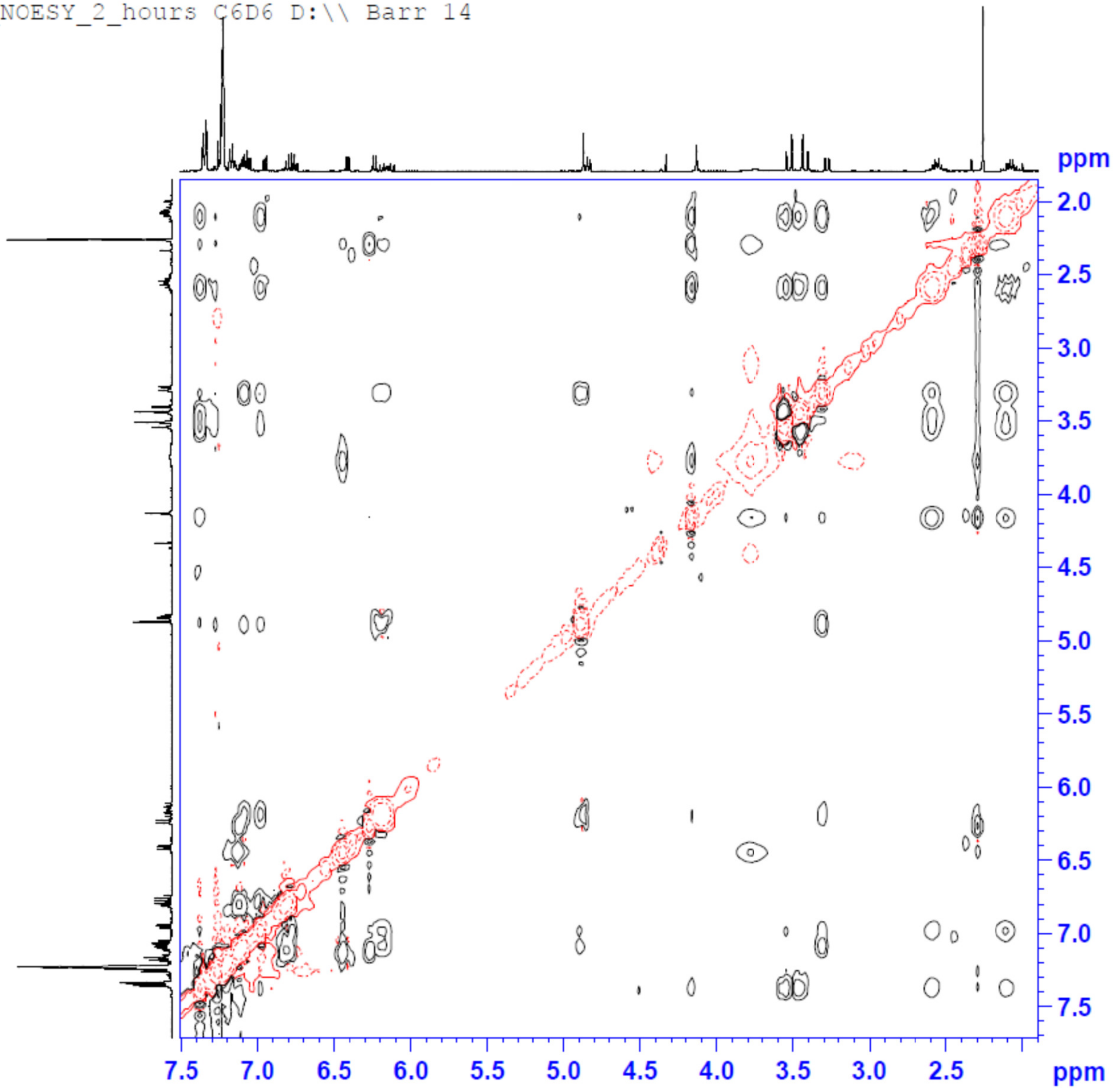
ppm

2d_NOESY_2_hours C6D6 D:\\ Barr 14



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EXPNO                      5
PROCNO                     1

F2 - Acquisition Parameters
Date_               20120920
Time                   20.08
INSTRUM                spect
PROBHD   5 mm PABBO BB-
PULPROG            noesygpph
TD                      1024
SOLVENT                 C6D6
NS                        16
DS                         0
SWH                 4201.681 Hz
FIDRES              4.103204 Hz
AQ                 0.1219060 sec
RG                       256
DW                   119.000 usec
DE                      6.00 usec
TE                     296.5 K
d0                0.00010405 sec
D1                1.00000000 sec
D8                1.00000000 sec
D16               0.00020000 sec
IN0               0.00023790 sec
TAU               0.49880001 sec

======== CHANNEL f1 ========
NUC1                      1H
P1                     11.70 usec
P2                     23.40 usec
PL1                    -4.00 dB
SFO1             400.3217014 MHz

====== GRADIENT CHANNEL =====
GPNAM1              sine.100
GPNAM2              sine.100
GPZ1                   40.00 %
GPZ2                  -40.00 %
P16                  1000.00 usec

F1 - Acquisition parameters
TD                       256
SFO1                400.3217 MHz
FIDRES             16.419714 Hz
SW                    10.500 ppm
FnMODE                  TPPI

F2 - Processing parameters
SI                       512
SF               400.3200000 MHz
WDW                    QSINE
SSB                        2
LB           0 Hz
GB           0
PC                      1.00

F1 - Processing parameters
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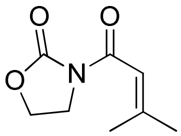
MC2                     TPPI
SF               400.3200000 MHz
WDW                      PPI
SSB                        2
LB           0 Hz
GB           0
```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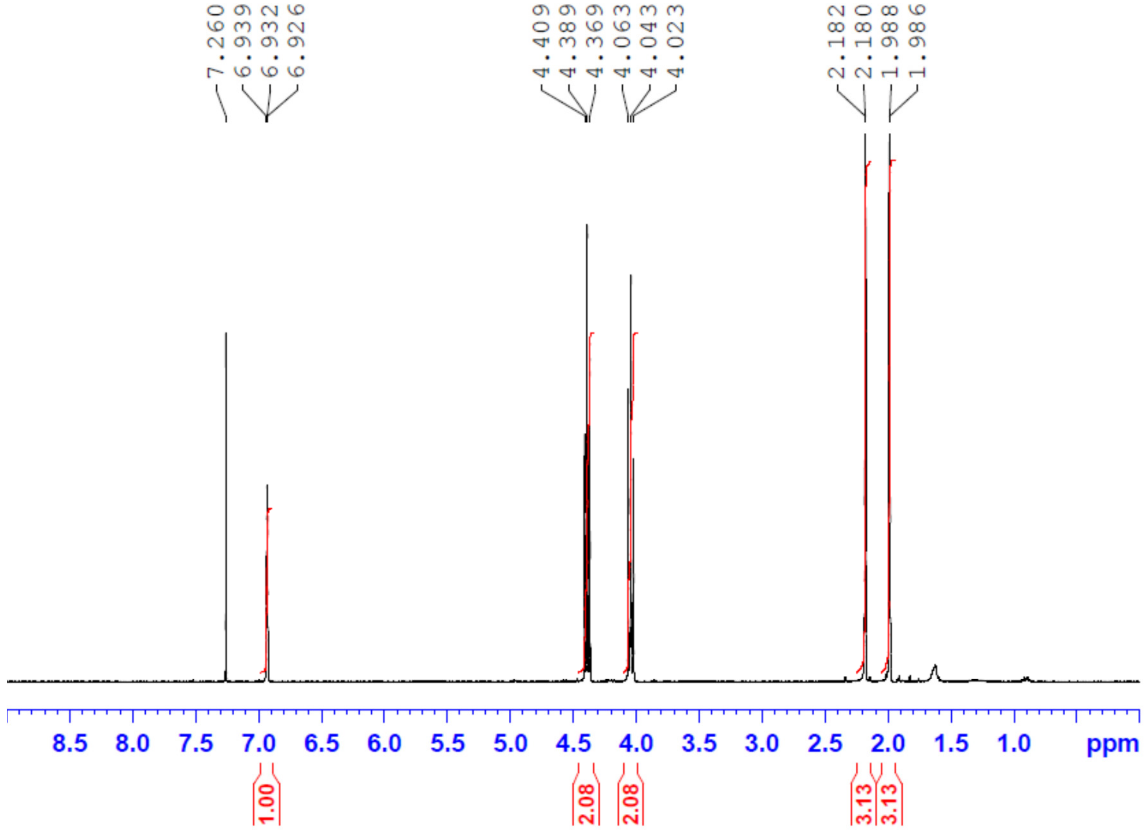
O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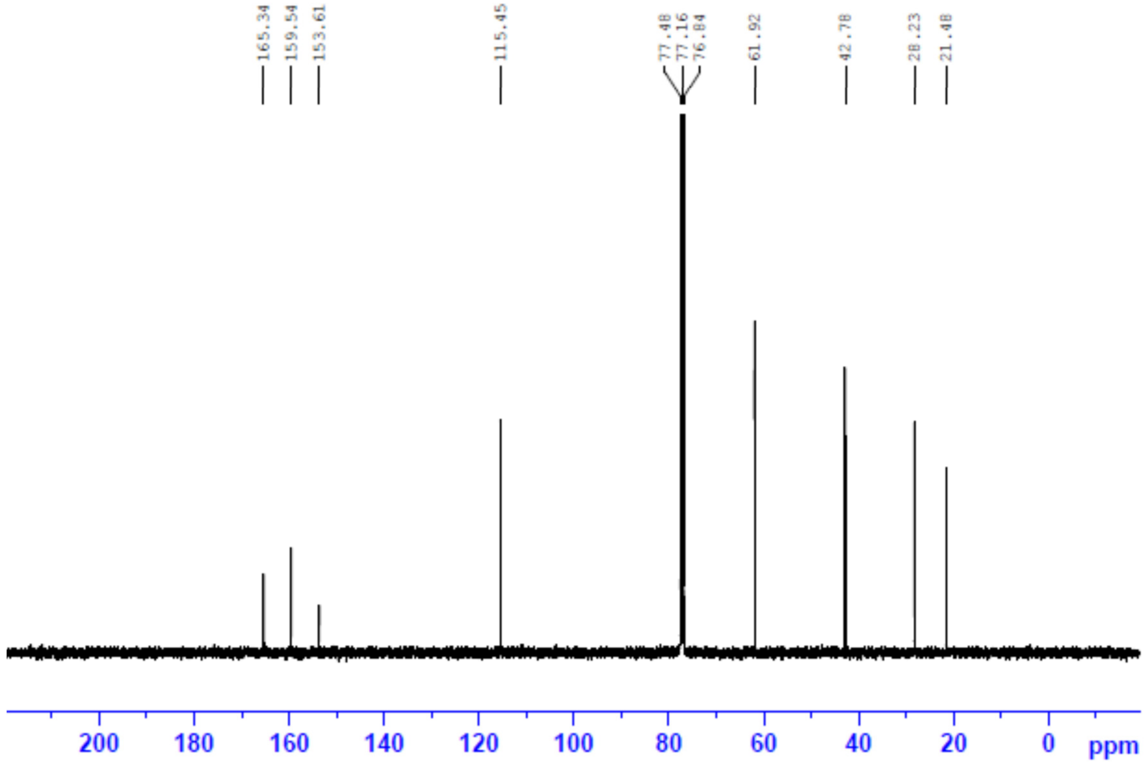
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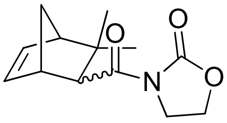
O
O
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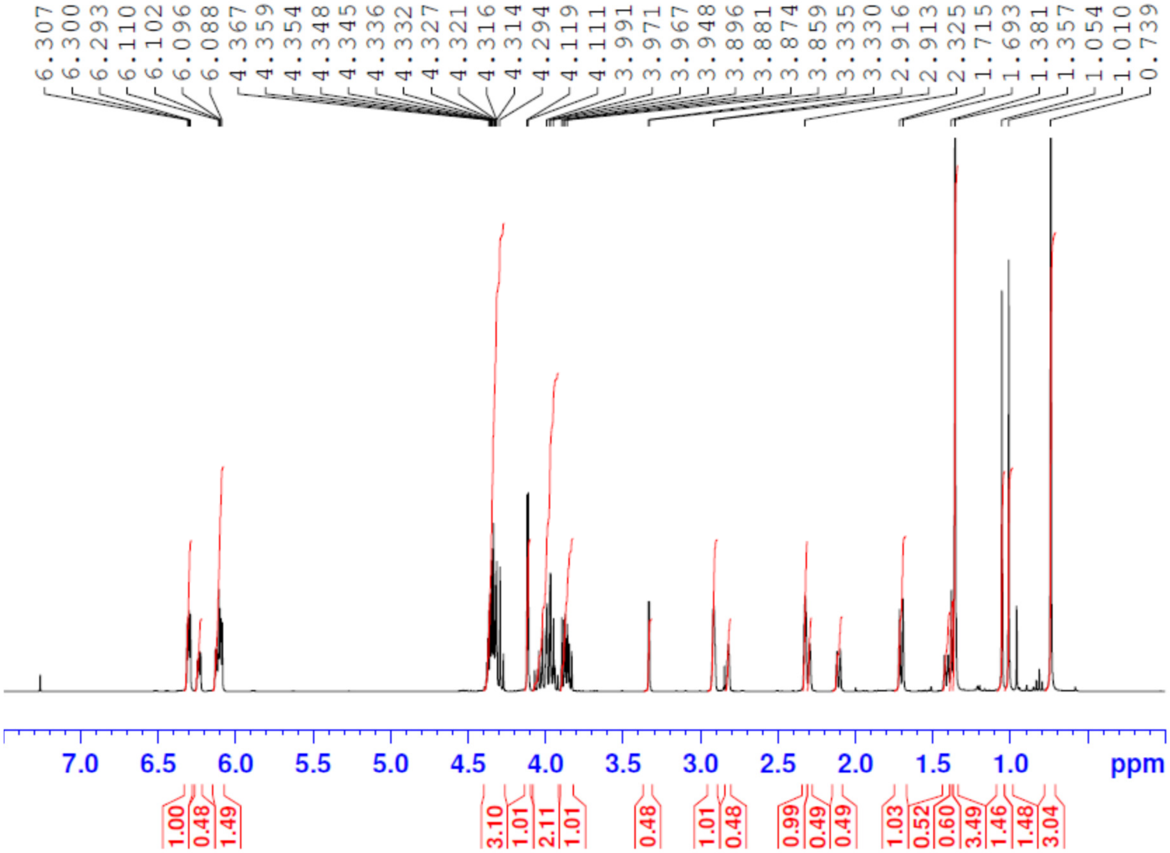
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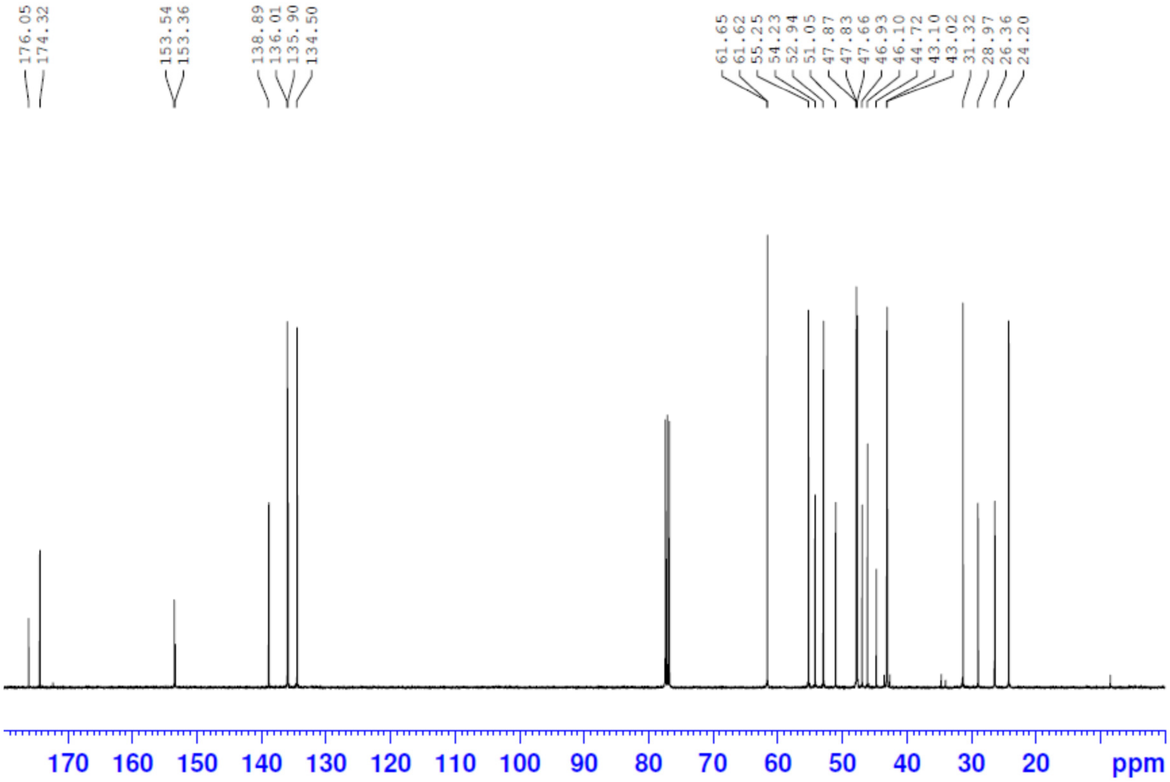
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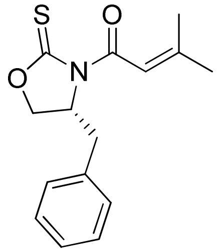
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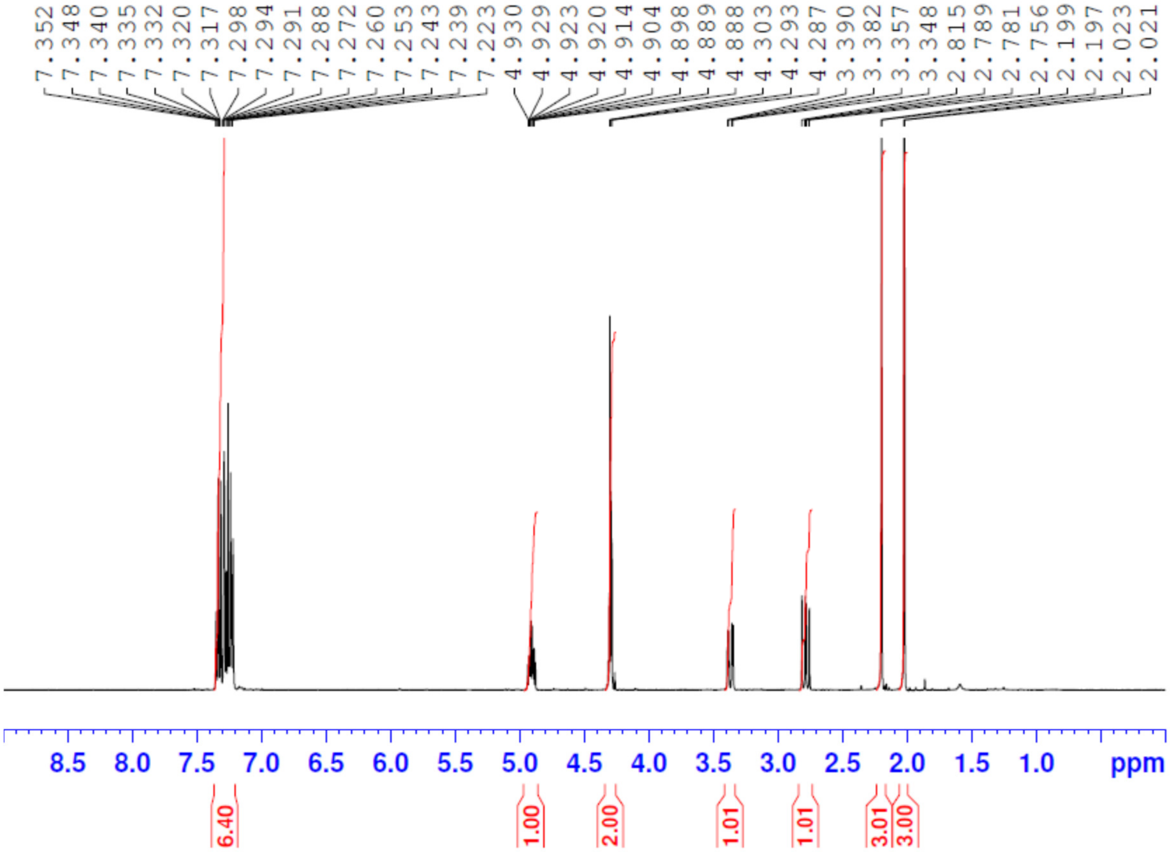
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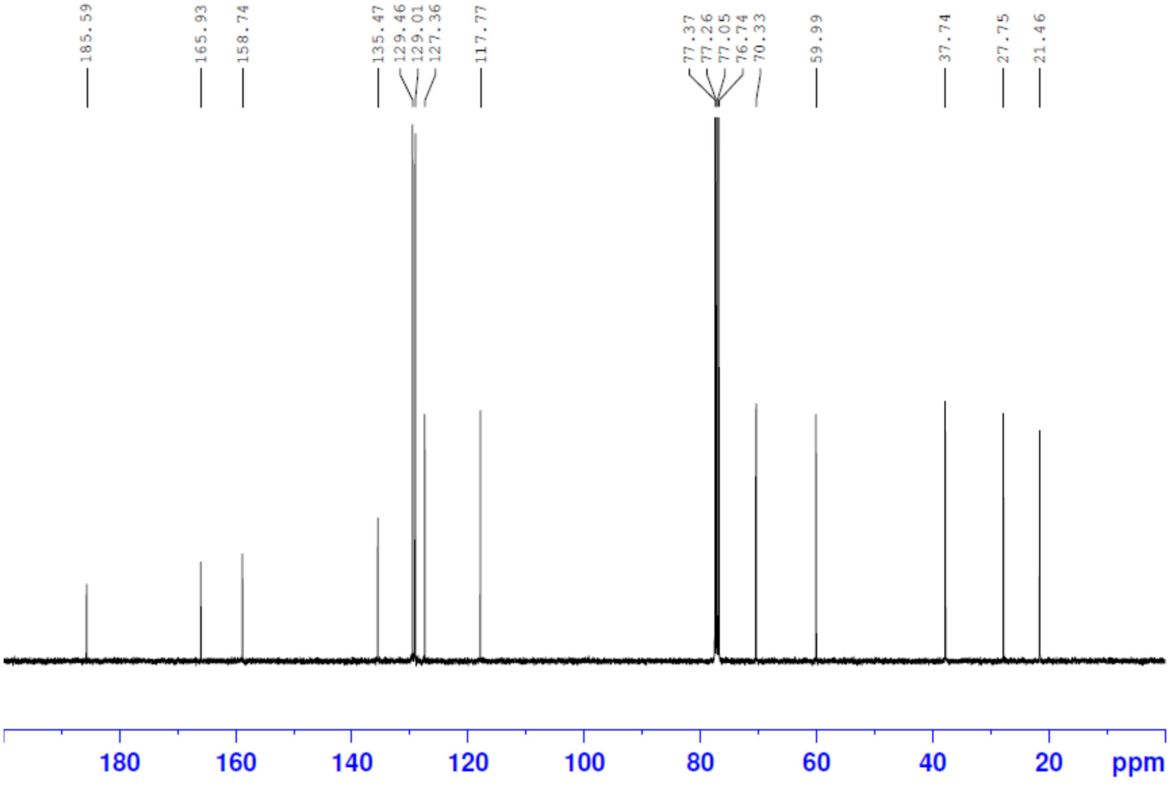
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ppm

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