ABSTRACT

PROGRESS TOWARD THE TOTAL SYNTHESIS OF THE WELWITINDOLINONE ALKALOIDS: EFFICIENT CONSTRUCTION OF THE CARBOCYCLIC SKELETON

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Recently, efforts to identify biologically important natural products from cyanobacteria resulted in the isolation of several welwitindolinone alkaloids, two of which have been identified as antagonists of the P-glycoprotein P-170 and hence as multiple drug resistance reversing agents. Herein are described efforts toward the total synthesis of these biologically and structurally intriguing natural products.

The C(3)-C(4)-bridged oxindole core of the welwitindolinones (i.e., **50**) has been constructed stereoselectively in seven steps from isatin, highlighted by a Rh(II)-catalyzed, Montmorillonite K10 clay-mediated aryl C-H insertion reaction. Ketone **50** can be advanced to α-diazo ketone **91**, a versatile intermediate from which the vicinal quaternary centers found in the welwitindolinones can be accessed in one remarkably mild step *via* Rh(II)-initiated Claisen rearrangement. Alternatively, **91** can be advanced by coupling to a secondary allylic alcohol in a novel Rh(II)-mediated ring-opening reaction. The complete carbon framework of the welwitindolinones including the requisite bridgehead nitrogen moiety can be efficiently accessed *via* transannular nitrone cycloaddition to furnish **199**. This product can conveniently be advanced to aldehyde **231** which contains a spiro-

ether ring at C(4) and a quaternary center at C(12), and hence is a suitable intermediate for advancement to *N*-methylwelwitindolinone D isonitrile.

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To My Family

ACKNOWLEDGEMENT

As I left for graduate school, my father, who completed his doctorate in Organic Chemistry under the direction of Professor Curtin, left me with some sound advise; "Do not work for an untenured professor". I would like to thank Professor Wood for first of all, taking a chance on a then not-so-sure-of-herself young graduate student and second, for helping me prove my father wrong. After sitting through one year of John's synthesis class and experiencing his intensity, I could not resist the Wood group. Over the years, his creativity, dedication, passion for synthesis and sense of humor which led me to my decision in the first place have made me very proud to be part of the Wood group. I am so grateful for the time he invested in me, not only with regard to technical work (i.e., "how does the TLC look?", and, "is this chromatographed?") and discussions about my project ("how does the material situation look?"), but also for the time he spent teaching me how to present my work, written and oral. I realize not every advisor takes the time to do that, and I want him to know how much I appreciated it. Most importantly, John has shown me that it is in fact possible to balance chemistry, fun and family in our lives.

I would like to acknowledge my committee, Prof. Fred Ziegler and Prof. Michael McBride, for their time and suggestions. I would like to thank Prof. McBride for his note on my application to Yale which convinced me to apply to Yale after I thought I had already applied to my last school, (i.e., something along the lines of "You'll like Organic Chemistry at Yale, there are a lot of people from Ohio here".

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support over the years, across the miles, for always being happy to see me, no matter how long it's been.

Next comes the difficult task of thanking the Wood group, or W6, in one paragraph. You were the reason it was so easy to get up every morning and come to work. I'd like to first thank the pre-W6 years members, Dr. Brian Stoltz, Dr. Derek Pflum, Dr. Dejah Petsch, Jon Njardarson, and Mauricio Navarro, for "begging me to join the group". I would especially like to thank Brian, who first taught me so much as my TA in synthesis, and put up with my and Erin's weekly list of questions. I also want to thank him for teaching me all those little lab tricks, for example, making spots small on the TLC plate so they actually separate, and for constantly reminding me that they call it "flash" chromatography for a reason. I thank him also for all of his help on the welwitindolinone (wit) project, in terms of actual lab work and ideas. I especially thank him teaching me dedication and efficiency, something that is hard to teach but he managed to. I thank Dejah, who I spent most of my time in the Wood labs working next to, for being such a fun and easy-to-work-next-to labmate, and for not only putting up with, but also joining, my illegal "horseplay". I owe so much gratitude to Matthew Weiss and George Moniz, for proofreading my thesis and catching all of those little and not-so-little mistakes, and Jon Njardarson and Matt for help with my presentation. I also thank Matt for all of his contributions to the wit project, for recognizing that a certain "side-product" really didn't have to be a "side-product" after all, and thus changing the course of our efforts dramatically. In addition, I thank him for thinking about the wit while he was on the project and while he was off, constantly suggesting brilliant ideas, many of which worked, and stopping whatever he was doing to interpret NMR's and discuss new strategies. I thank Derek and George for their thorough work on the Rh(II) project which has always benefited the wit project. As for George, I appreciate all of his chemical input, but especially I appreciate the constant entertainment. You know what I mean ("Oh yeah, Thompson..."). I would like to thank Dr. Julie Dixon, who joined the wit project during the detrimental [1,2]-shift problem days, and saved the project by applying her graduate work to this effort and convincing all of us that the cycloaddition was really going to work. I also thank her for many crystal structures, for teaching me to be more thorough as a chemist, and for being an excellent role model for me. I also thank Dr. Munenori Inoue and Dr. Brian Doan for their contributions to the wit project, the former for his ideas, persistence, and large-scale efficiency and the latter for throwing dirt into one of our reactions and

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LIST OF ABBREVIATIONS

Ac	Acetyl, acetate
AIBN	2,2'-Azobisisobutyronitrile
aq.	Aqueous
Bn	Benzyl
br	Broad
n-Bu	*n*-Butyl
t-Bu	*tert*-Butyl
BuLi	Butyl lithium
calcd	Calculated
cap	caprolactam
cat.	Catalytic amount
CI	Chemical ionization
d	doublet
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
dec.	Decomposition
DMAP	4-Dimethylaminopyridine
DME	1,2-Dimethoxyethane (glyme)
DMF	*N,N*-Dimethylformamide
DMSO	Dimethyl sulfoxide
DOSP	Dodecyl(arylsulfonyl)prolinate
ee	Enantiomeric excess
EI	Electron impact
equiv	Equivalent
Et	Ethyl
FAB	Fast atom bombardment
h	hour
HPLC	High performance liquid chromatography
hν	light
Hz	Hertz
IR	Infrared (spectrum)
m	Multiplet or medium
m	Mass
m-CPBA	*m*-Chloroperoxybenzoic acid
MDR	Multiple drug resistance

Me	Methyl
MEPY	Methyloxopyrrolidine
min	Minutes
mol	Mole
mp	Melting point
NMR	Nuclear magnetic resonance
[O]	Oxidation
OAc	Acetate
p-ABSA	*p*-Acetamidobenzenesulfonyl azide
p-BrBz	*p*-Bromobenzoyl
PCC	Pyridinium chlorochromate
pfb	perfluorobutyrate
pfm	perfluorobutyramide
ppm	Parts per million
p-TSA	*p*-Toluenesulfonic acid
Py	Pyridine
rt	Room temperature
s	Singlet or strong
t	Triplet
TBS	*tert*-Butyldimethylsilyl
TBSP	*t*-Butyl(arylsulfonyl)prolinate
TFA	Trifluoroacetic acid
tfa	Trifluoroacetate
tfm	trifluoroacetamide
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Trimethylsilyl
TsOH	*p*-Toluenesulfonic acid
w	Weak
Δ	Heat at reflux

CHAPTER ONE

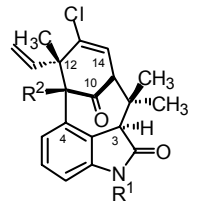
The Welwitindolinones: Structurally and Biologically Intriguing Natural Products from Cyanobacteria

1.1 Background and Introduction.

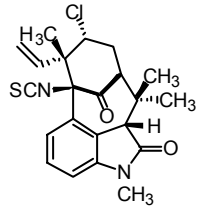
1.1.1 Isolation and Biological Activity.

In 1994, several welwitindolinone alkaloids (**1**-**7**, Figure 1.1.1) were isolated from the lipophilic extracts of two blue-green algae belonging to the Stigonemataceae, i.e., *Hapalosiphon welwitschii* W. & G.S. West (UH strain IC-52-3) and *Westiella intricata* Borzi (UH strain HT-29-1).[1] The former strain was found to exhibit antifungal and multiple-drug-resistance (MDR) reversing activity and the latter insecticidal activity, and these activities have been partly attributed to these welwitindolinone alkaloids. *N*-Methylwelwitindolinone C isothiocyanate (**1**), the major indole alkaloid isolated from these cyanobacteria, has been identified as an antagonist of the P-glycoprotein P-170 and hence as an MDR reversing agent, while the demethylated analog, welwitindolinone C isothiocyanate (**2**) has been found be an antimicrotubule agent which also reverses MDR.[2] The structures and absolute stereochemistries of these novel indole alkaloids were determined *via* X-ray crystallography.

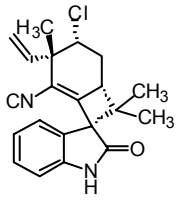
Figure 1.1.1



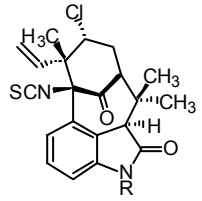
1 R^1 = Me, R^2 = NCS, *N*-Methyl-welwitindolinone C isothiocyanate
2 R^1 = H, R^2 = NCS, Welwitindolinone C isothiocyanate
3 R^1 = Me, R^2 = NC, *N*-Methyl-welwitindolinone C isonitrile



4 3-*epi* - N-Methylwelwit-indolinone B isothiocyanate



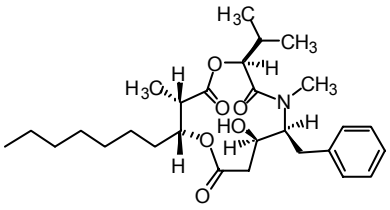
5 Welwitindolinone A isonitrile



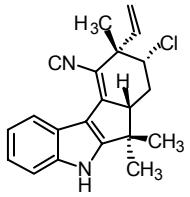
6 R = H, Welwitindolinone B isothiocyanate
7 R = Me, *N*-Methylwelwitindolinone B isothiocyanate

Several other natural products were co-isolated with the welwitindolinones, including hapalosin (**8**), a cyclic depsipeptide, which is responsible for the majority of the MDR reversing activity of *Hapalosiphon welwitschii* (see Figure 1.1.2)[3] as well as compounds thought to be biogenetically related to the welwitindolinones, namely fischerindoles **9**-**12**, and hapalindoles **13**-**16**. The isonitrile containing welwitindolinones, fischerindoles and hapalindoles (i.e., **3**, **5**, **9**, **10**, **11**, **13**, **14**) are collectively responsible for the antifungal activity associated with the blue-green algae.[1]

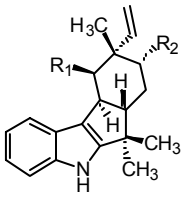
Figure 1.1.2



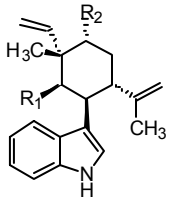
8 Hapalosin



9 12-*epi*-Fischerindole I isonitrile



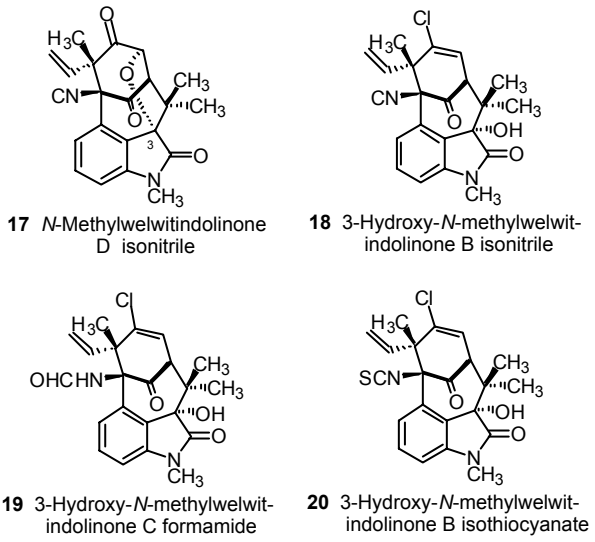
10 R_1 = NC, R_2 = Cl, 12-*epi*-Fischerindole G isonitrile
11 R_1 = NC, R_2 = H, 12-*epi*-Fischerindole U isonitrile
12 R_1 = NCS, R_2 = H, 12-*epi*-Fischerindole U isothiocyanate



13 R_1 = NC, R_2 = Cl, 12-*epi*-Hapalindole E isonitrile
14 R_1 = NC, R_2 = H, 12-*epi*-Hapalindole C isonitrile
15 R_1 = NCS, R_2 =Cl, 12-*epi*-Hapalindole F isothiocyanate
16 R_1 = NCS, R_2 =H, 12-*epi*-Hapalindole D isothiocyanate

Later, in 1999, Moore and coworkers isolated several welwitindolinones oxidized at the C(3) position, including two 3-hydroxywelwitindolinones (**18, 20**) and an interesting spiro-ether compound, *N*-methylwelwitindolinone D isonitrile (**17**) from terrestrial *Fischerella musciola* (Thuret) Gomont (HG-39-5) and *Fischerella* major Gomont (HX-7-4) (Figure 1.1.3). Along with these novel welwitindolinones were isolated formamide **19**, believed to be an artifact formed during the isolation of isonitrile **18**, and previously known compounds, *N*-methylwelwitindolinone C isonitrile (**3**), *N*-methylwelwitindolinone C isothiocyanate (**1**), welwitindolinone A isonitrile (**5**), and 12-*epi*-fischerindole I isonitrile (**9**). No biological activity associated with these new welwitindolinones has been reported to date.[4]

Figure 1.1.3



17 *N*-Methylwelwitindolinone D isonitrile

18 3-Hydroxy-*N*-methylwelwitindolinone B isonitrile

19 3-Hydroxy-*N*-methylwelwitindolinone C formamide

20 3-Hydroxy-*N*-methylwelwitindolinone B isothiocyanate

1.1.2 The Importance of Multiple Drug Resistance Reversing Agents.

1.1.2.1 Introduction: What is MDR?

More often than not, only brief clinical improvements are offered by chemotherapy before its ultimate failure. This is due to multiple drug resistance (MDR), which has evolved as a protective mechanism whereby tumor cells which survive initial cancer treatment develop resistance against several structurally unrelated classes of carcinostatic compounds. Particularly susceptible to this mode of protection are chemotherapeutic agents that can be classified as hydrophobic and relatively small in molecular weight (FW<1000).[5] This observation, coupled with the fact that MDR can protect carcinogenic cells against antitumor agents that operate *via* distinctly different modes of action, has suggested a mechanism whereby the drug is actively transported out of the cell, reducing its intracellular concentration and therefore its cytotoxicity. During the last decade, extensive research has revealed a correlation between the onset of MDR and the appearance of a specific P-glycoprotein, P-170.[6] Cloning and

sequencing of the human gene that encodes for P-170, (i.e., MDR1), has allowed researchers to clearly demonstrate, *via* transfection studies, that P-170, acting as an energy-dependent efflux pump, is sufficient for inducing resistance in previously sensitive cells.[7]

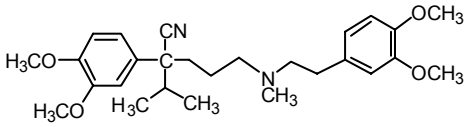
1.1.2.2 Screening for Potential MDR-Reversing Chemotherapeutics.

It is believed that MDR is responsible for restricting the success of many currently used anticancer drugs, including *Vinca* alkaloids, anthracyclines, and several antitumor antibiotics. Several chemical agents, including verapamil (**21**, Figure 1.1.4), the most extensively studied MDR reversing agent, have been found to attenuate MDR by competing with anticancer agents for binding to P-glycoprotein *in vitro*.[8] Unfortunately, cytotoxicity problems have limited their clinical use.[9] Therefore, a significant effort has been made to identify novel, less toxic MDR reversing agents.

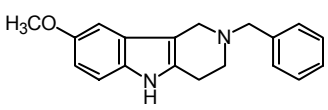
The identification of P-170 as a potential target for chemotherapeutic intervention has led to an extensive screening effort designed to identify small molecules capable of antagonizing the action of P-170 and hence acting as MDR-reversing agents. To date, screening has been effective in defining numerous compounds in several structural classes as P-glycoprotein antagonists. Included in the identified structural classes are naphtho-γ-pyrones,[10] cyclic peptides,[11] porphyrins,[12] and indole alkaloids.[1,13] In the class of indole alkaloids are included A-30312 and -39355 (**22** and **23**, respectively, Figure 1.1.4), reserpine (**24**), 5-*N*-acetylardeemin (**25**), staurosporine (**26**), and two welwitindolinones (**1** and **2**). In general, many MDR reversing agents which were found to interact with P-glycoprotein share several physical characteristics,

namely, they are hydrophobic, contain multiple rings, usually aromatic, and a substituted tertiary amino group.[8]

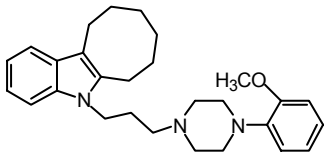
Figure 1.1.4



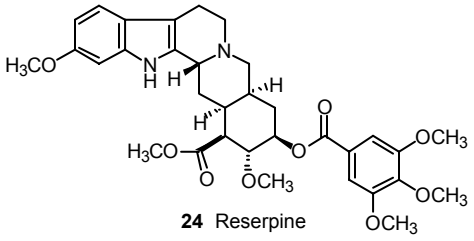
21 Verapamil



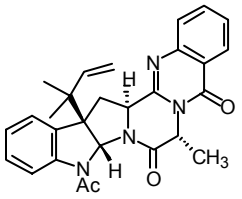
22 A - 30312



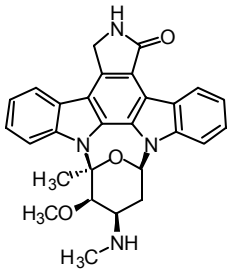
23 A - 39355



24 Reserpine



25 5 - N - Acetylardeemin



26 Staurosporine

1.1.2.3 Welwitindolinones as MDR Reversing Agents.

To measure MDR reversing activity, resistant cells are treated with combinations of the agent in question and several doses of anticancer drugs such as vinblastine and taxol and percentage of cells killed is determined. *N*-Methylwelwitindolinone C isothiocyanate (**1**) has been found to be a more potent MDR reversing agent than verapamil (**21**, Figure 1.1.5), chemosensitizing drug resistant MCF-7/ADR cells to vinblastine, taxol, colchinine and other anticancer drugs at doses as low as 0.1 μM. Also, [^{3}H]vinblastine accumulation in SK-VLB-

1 cells in the presence of the welwitindolinones was measured, and it was found that *N*-methylwelwitindolinone C isothiocyanate (**1**) and its demethylated analog, welwitindolinone C isothiocyanate (**2**, referred to as welwistatin by Smith and coworkers) reached 190 and 270% of the control, respectively, at 20 μM concentrations. Interestingly, *N*-methylwelwitindolinone C isonitrile (**3**) was almost inactive. In addition, photoaffinity labeling of P-glycoprotein with [^{3}H]azidopine in the same cells was reduced by compounds **1** and **2**, a result which infers binding of the MDR reversing agent to P-glycoprotein. In contrast, photoaffinity labeling was not reduced by isonitrile **3** suggesting that differences between the size and electronegativity of the isothiocyanate/isonitrile groups seem to be crucial for P-glycoprotein binding.[9]

1.1.3 Microtubule Effects.

1.1.3.1 Importance of Antimicrotubule Agents.

Microtubules are long, hollow cylinders found in the cellular cytoplasm which are responsible for many cellular functions, including organelle transport and formation of the mitotic spindle and cytoplasmic cytoskeleton. These processes are dependent on the addition and loss of tubulin dimers to microtubules. Certain compounds, such as colchinine, paclitaxel, and vinblastine, have been utilized as anticancer drugs due to their ability to arrest the cell cycle during mitosis by disturbing the equilibrium of microtubules.[14] Unfortunately, tumor cells become resistant to many natural products with antimicrotubule activity, *via* action of P-glycoprotein. One solution to this problem is to combine antimicrotubule and MDR reversing agents in cancer therapy.

1.1.3.2 Antimicrotubule Effects of the Welwitindolinones.

It was recently found that welwitindolinone C isothiocyanate (**2**) disrupts microtubule formation in SK-OV-3 human carcinoma cells and A-10 vascular smooth muscle cells. This natural product shows major promise as a future chemotherapeutic for several reasons. First, the effect on the microtubule equilibrium is reversible and specific (i.e., toward microtubules but not microfilaments). Second, in addition to **2** being an antimicrotubule agent itself, when previously resistant A-10 cells are pretreated with a 3.3 μM dose of **2**, they are chemosensitized to paclitaxel (0.1 μM), allowing it to prevent microtubule depolymerization. Finally, P-glycoprotein overexpressing cells have not developed a resistance to **2**.[14]

Interestingly, the antimicrotubule activity of *N*-methylwelwitindolinone C isothiocyanate (**1**) is less than that of welwitindolinone C isothiocyanate (**2**), while that of *N*-methylwelwitindolinone C isonitrile (**3**) is similar to **2**, however studies were not completed due to insufficient quantities of isonitrile **3**.[14]

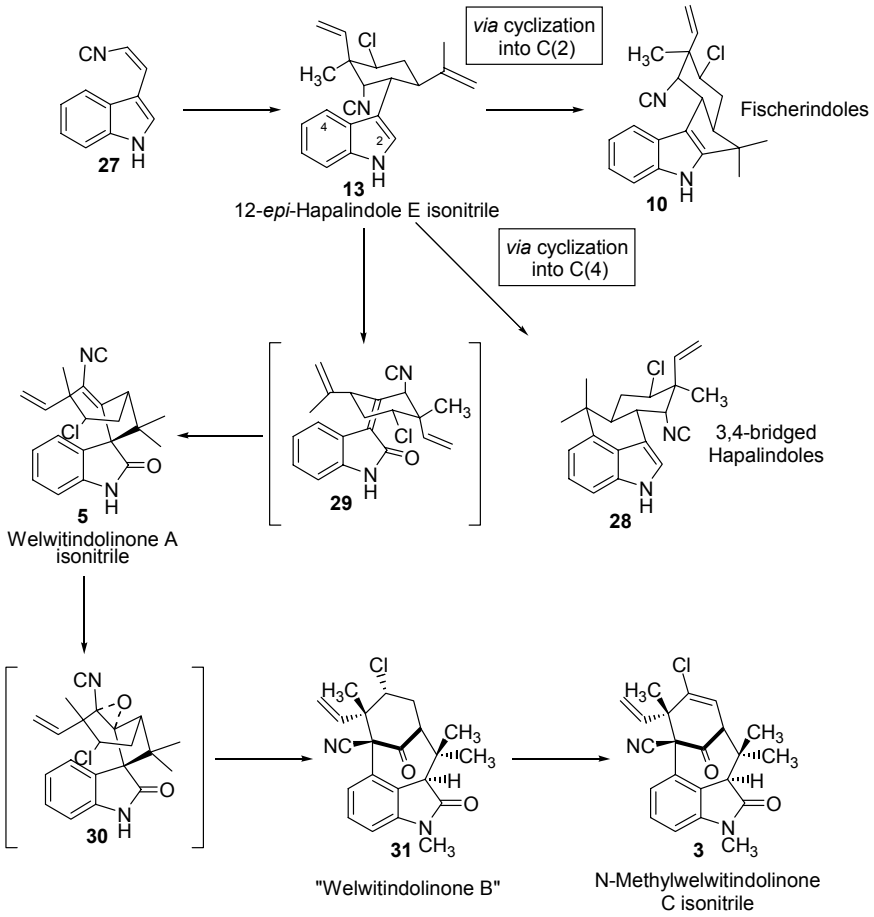
1.2 Biosynthesis.

1.2.1 Biogenetic Relationship of Welwitindolinones to Fischerindoles and Hapalindoles.

The common precursor to the chlorine and isonitrile containing welwitindolinones, hapalindoles and fischerindoles is proposed to be 12-*epi*-hapalindole E isonitrile (**13**), believed to arise from 3-((Z)-2'-isocyanoethenyl)indole (**27**) derived from tryptophan and geranyl pyrophosphate.[15] It is envisioned that the isonitrile group of these

alkaloid/terpenoid natural products may have its origins in glycine and cyanide, and the isothiocyanate group of these indole alkaloids may arise directly from an inorganic thiocyanate or indirectly by the insertion of a sulfur into an isonitrile. From intermediate **13**, 12-*epi*-Fischerindole G isonitrile (**10**) may arise *via* a condensation of the propenyl group into C(2) of the indole system with the assistance of an enzyme or acid catalysis.[16] However, if the isoprenyl group cyclizes into C(4), it may lead to formation of C(3)-C(4) bridged hapalindoles, such as 12-*epi*-hapalindole G isonitrile (**28**).[17]

Scheme 1.2.1



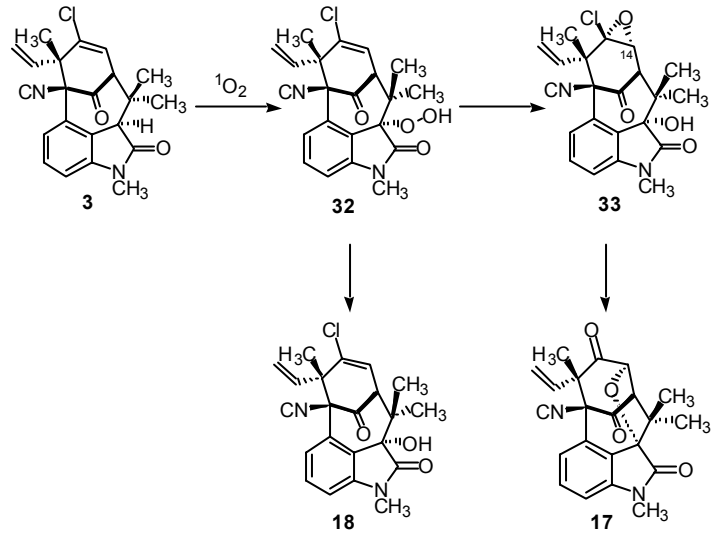
Since the relative stereochemistry of hapalindole **13** matches that of all of the welwitindolinones, it is assumed that **13** and its isothiocyanate analog **15** are precursors to all of the welwitindolinones. Although the exact pathway is not

clear, oxidation of the indole (i.e., in **13**) is believed to take place at an early stage in the biosynthesis, and an isocyano epoxide intermediate (i.e., **30**) may be involved in the pathway from welwitindolinone A isonitrile (**5**) to welwitindolinones B (e.g., **31**) and *N*-methylwelwitindolinone C isonitrile (**3**).

1.2.2 Origin of the Oxidized Welwitindolinones.

It was envisioned that the oxidized welwitindolinones **17**-**20** (Figure 1.1.3) may derive from *N*-methylwelwitindolinone C isonitrile (**3**) through a hydroperoxy intermediate (i.e., **32**, see Scheme 1.2.2) *via* photolytic oxidation of **3**. Subsequently, reduction of hydroperoxy derivative **32** would lead to the hydroxywelwitindolinones **18**-**20**. Alternatively, the authors vaguely propose that intramolecular epoxidation of **32** could give rise to epoxide **33**, which may then undergo cyclization of the 3-OH to C-14 and simultaneous opening of the epoxide to furnish *N*-methylwelwitindolinone D isonitrile (**17**). Jimenez and coworkers have shown that **17** can in fact be derived from **3** *via* treatment with oxygen while irradiating.[4]

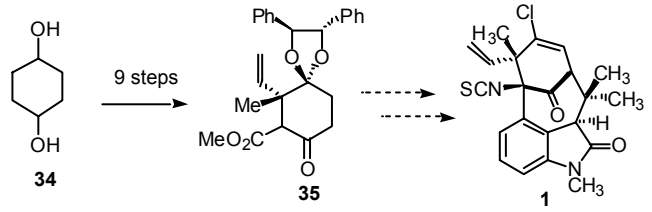
Scheme 1.2.2



1.3 Synthetic Studies Toward the Welwitindolinones.

Prior to our initiation of this project in 1996, there were no reports of synthetic efforts directed toward the welwitindolinones. In 1998, Konopelski reported the stereocontrolled synthesis of **35** from 1,4-cyclohexanediol (**34**) which is envisioned to be coupled to an indole system and advanced to **1** (Scheme 1.3.1).[18]

Scheme 1.3.1



1.4 Notes and References.

(1) *Hapalosiphon welwitschii* W. & G.S. West and *Westiella intricata* Borzi were isolated from Australian and Micronesian soil samples, respectively. Stratmann, K.; Moore, R. E.; Bonjouklian, R.; Deeter, J. B.; Patterson, G. M. L.; Shaffer, S.; Smith, C. D.; Smitka, T. A. *J. Am. Chem. Soc.* **1994**, *116*, 9935.

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([9]) For example, at the concentrations at which it reverses MDR, verapamil has been found to induce cardiovascular toxicity. Ford, J. M.; Haith, W. N. *Pharmacol. Rev.* **1990**, *42*, 155.

([10]) Ikeda, S.; Sugita, M.; Yoshimura, A.; Sumizawa, T.; Douzono, H.; Nagata, Y.; Akiyama, S. *Int. J. Cancer* **1990**, *45*, 508.

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([12]) Prinsep, M. R.; Caplan, F. R.; Moore, R. E.; Patterson, G. M. L.; Smith, C. D. *J. Am. Chem. Soc.* **1992**, *114*, 385.

([13]) A) Kadam, S.; Maus, M.; Poddig, J.; Schmidt, S.; Rasmussen, R.; Novosad, E.; Plattner, J.; McAlpine J. *Cancer Res.* **1992**, *52*, 4735. B) Hochlowski, J. E.; Mullally, M. M.; Spanton, S. G.; Whittern, D. N.; Hill, P.; McAlpine, J. B. *J. Antibiotic.* **1993**, *46*, 380. C) Wakusawa, S.; Inoko, K.; Miyamoto, K.-I.; Kajita, S.; Hasegawa, T.; Harimaya, K.; Koyama, M. *J. Antibiotic*. **1993**, *46*, 353.

([14]) Zhang, X.; Smith, C. D. *Molec. Pharmacology* **1996**, *49*, 288.

([15]) Park, A.; Moore, R. E.; Patterson, G. M. L. *Tetrahedron Lett.* **1992**, *33*, 3257.

([16]) Bonjouklian, R. *J. Org. Chem*. **1988**, *53*, 5866.

([17]) Hapalindole **28**, although proposed to arise from intermediate **13**, was not actually isolated from the extracts of *H*. *welwitschii*, see ref 1.

([18]) Konopelski, J. P.; Deng, H.; Schiemann, K.; Keane, J. M.; Olmstead, M. M. *Synlett* **1998**, 1105.

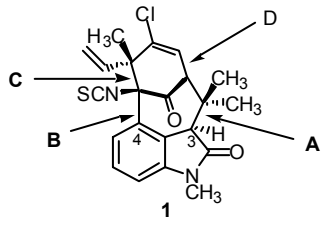
CHAPTER TWO

Construction of the Welwitindolinone Core

2.1 Initial Considerations.

In contemplating a synthesis of the welwitindolinones, attention was focused on methods for assembling four carbon-carbon bonds: A, B, C, and D (Figure 2.1.1). From a retrosynthetic perspective, disconnection of bonds A and B divides the molecule roughly in half while rupture of C strikes at the heart of the critical vicinal quaternary centers embedded in the cyclohexene core. In considering these synthetic challenges in the context of known chemistry, several limitations were recognized in available methods for constructing 3,4-bridged indoles and oxindoles (bonds A and B). Namely, most methods require initial preparation of a 4-substituted oxindole or indole (halogen, oxygen or alkyl substitution) and complete construction of the bridge by working from C(4) to C(3).[1] In the course of efforts in these laboratories, an approach wherein the 3,4-bridge would be assembled from C(3) to (C4) on a more readily accessible aryl-unfunctionalized oxindole core was considered.

Figure 2.1.1

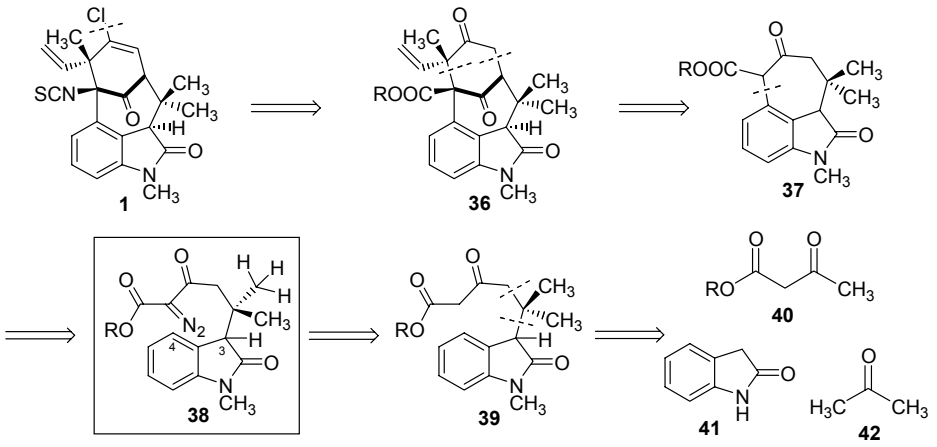


2.2 The First Generation Approach.

2.2.1 Retrosynthetic Analysis.

Initially, a method for skeleton construction was not planned in great detail (bonds C and D, Figure 2.1.1). Instead, efforts were focused on the construction of a flexible 3,4-bridged oxindole core (bonds A and B) from which the remaining cyclohexene portion of the carbon skeleton could be constructed. This led to the first, general retrosynthetic analysis as pictured in Scheme 2.2.1, which focuses on late introduction of the sensitive isothiocyanate and chloroolefin functionalities from the ester and ketone moieties in intermediate **36**, respectively.[2,3] Diketone **36** can be anticipated to arise from 3,4-bridged intermediate **37**, utilizing several possible strategies which take advantage of the β-keto ester functionality of **37** (discussed in Chapter 4). Ketone **37** may be accessible from β-keto ester **39** *via* diazo transfer followed by aryl C-H insertion of the derived α-diazo ketone. Ester **39**, in turn, was imagined to be conveniently constructed from three inexpensive, commercially available compounds, namely, an alkyl acetoacetate (i.e., **40**), oxindole (**41**), and acetone (**42**).

Scheme 2.2.1



Being aware of the literature concerning rhodium carbenoid chemistry, this initial approach, which calls for construction of the requisite seven membered ring directly *via* aryl C-H insertion (**38**→**37**), was quite speculative since the literature provides many examples of rhodium carbenoids preferentially forming five-membered rings when given the opportunity.[4] In the proposed system, (i.e., diazo ketone **38**), seven-membered ring formation was expected to prevail over 5-membered ring formation. Specifically, five-membered rings can arise *via* C-H insertion into the C(3) methine or either of the geminal methyl groups.[5] Also, in addition to the desired seven-membered ring, formation of a seven-membered ring *via* an intermediate carbonyl ylide is possible. Nevertheless, owing to the apparent ease of preparation of diazo ketone **38** from readily available starting materials, this audacious, initial approach was continued.

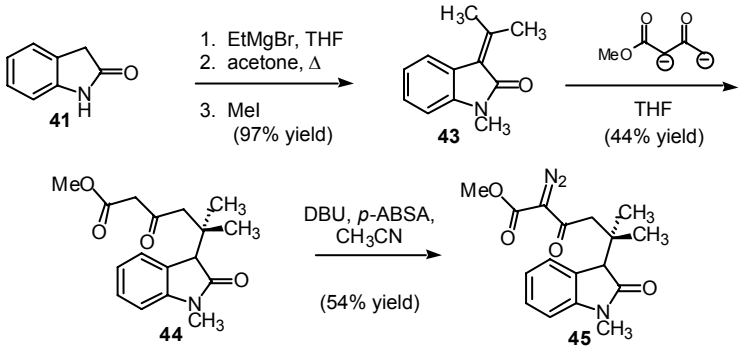
2.2.2 The Formation of C-H Insertion Substrate 45.

To this end, the condensation of oxindole (**41**) with acetone followed by methylation under phase transfer conditions furnishes a good Michael acceptor (i.e., **43**), which, when treated with the dianion derived from methyl acetoacetate

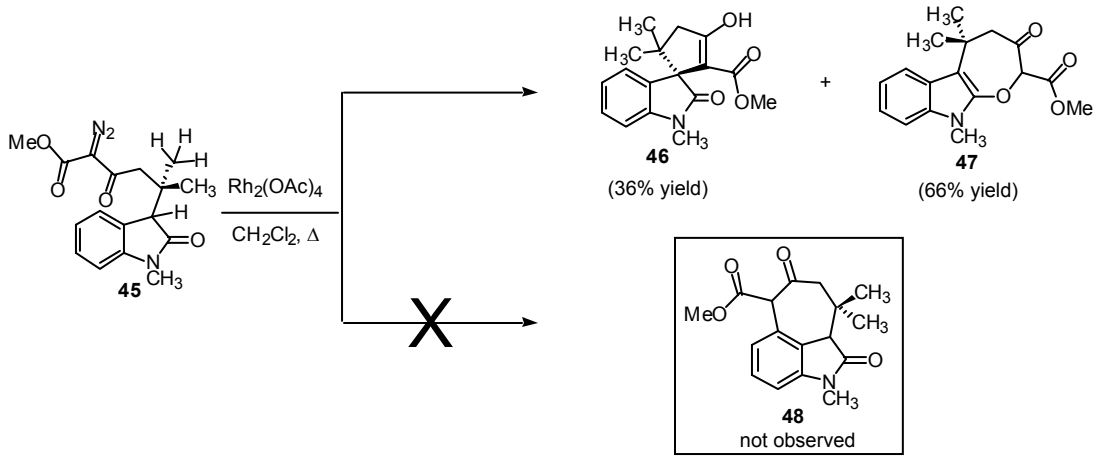
produces the desired Michael adduct **44** (see Scheme 2.2.2).[6] Subsequent diazotization of ketone **44** yields diazo ketone **45**, the desired substrate for aryl C-H insertion.[7]

Decomposition of α-diazo ketone **45** with $Rh_2(OAc)_4$ results in an extremely clean reaction (see Scheme 2.2.3). Unfortunately, the desired aryl C-H insertion product **48** was not observed. Instead, the new products generated were tentatively assigned as spirocycle **46**, the product of C-H insertion into the C(3) methine and oxepin **47**, arising from carbonyl ylide formation followed by proton transfer. The facile formation of **46** and **47** may be due to the acidity of the proton at C(3) and perhaps will prove useful in the context of other synthetic ventures. However, from these results it became clear that C(4) functionalization using the C-H insertion methodology would require alteration of the current substrate, which led to the second generation approach.

Scheme 2.2.2



Scheme 2.2.3

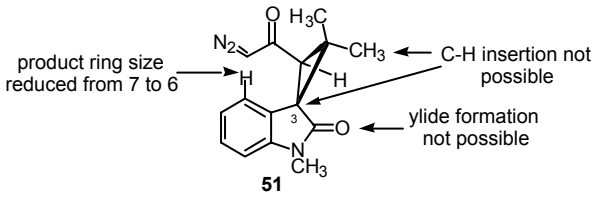


2.3 Second Generation Approach.

2.3.1 Retrosynthetic Analysis.

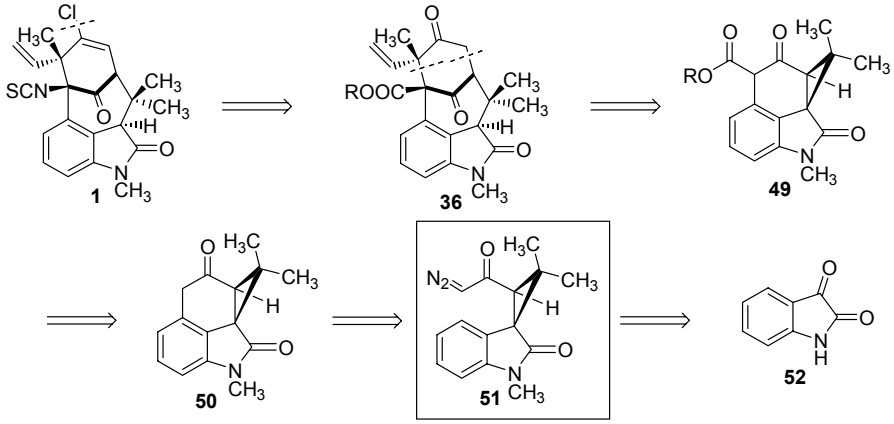
Having experienced problems advancing **45**, several other possible C-H insertion substrates were prepared and examined. After a few unsuccessful strategies, the reactivity of **51** was explored (Figure 2.3.1). Diazo ketone **51** is a carefully engineered substrate which contains a spiro-cyclopropyl ring at C(3), envisioned to serve several purposes. For example, quaternization of C(3) eliminates the C-H insertion problem in the previous substrate (diazo ketone **45**→**46**). Additionally, the cyclopropane ring eliminates the possibility of C-H insertion into one of the gem-dimethyl groups and, importantly, the deleterious carbonyl ylide formation that led to the production of oxepin **47**. Also, with this substrate, aryl C-H insertion would produce a six instead of a seven-membered ring, or if envisioned as proceeding *via* aryl cyclopropanation, a five- versus six-membered ring intermediate.[8]

Figure 2.3.1



The end game strategies of this approach were vague, as in the first generation approach (see Scheme 2.3.1). Similar to the initial plan, introduction of the vinyl chloride and isothiocyanate moieties would occur late in the synthesis, from intermediate **36**. The modified diazo ketone **51** would arise again from a commercially available, aryl-unfunctionalized oxindole, however, this time isatin (**52**) was chosen as the point of departure.

Scheme 2.3.1



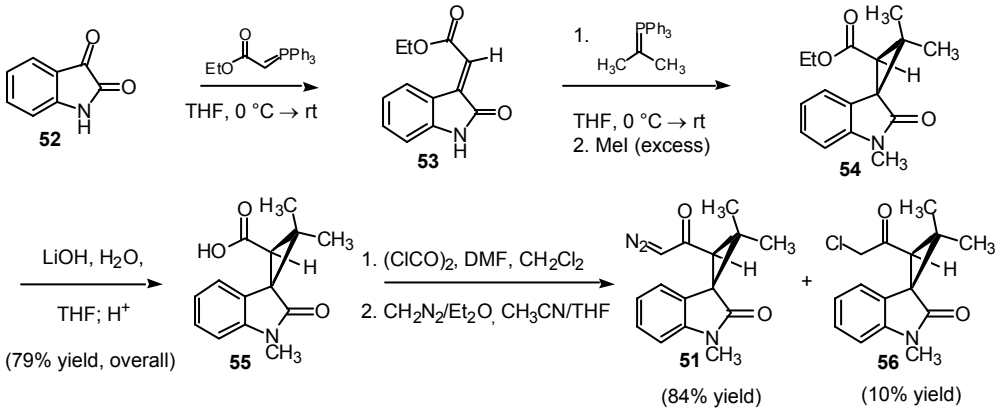
2.3.2 Formation of Modified C-H Insertion Substrate 51.

Thus, isatin (**52**) was found to be an excellent substrate for Wittig homologation with ethyl triphenylphosphoranylidene acetate (see Scheme 2.3.2).[9] The derived enoate **53** is produced in excellent yield and, within the limits of detection, complete selectivity for the (E)-isomer. Subsequent exposure

of **53** to isopropyl triphenylphosphorane under conditions developed by Grieco for activated olefins followed by methylation results in clean conversion to the corresponding gem-dimethyl cyclopropane ester **54**.[10,11] Rewardingly, the enoate stereochemistry is maintained throughout the cyclopropanation event, thus positioning the ester properly for future aryl C-H insertion chemistry. Saponification of the derived ester cleanly furnishes acid **55** which upon conversion to the corresponding acid chloride and reaction with diazomethane produces key intermediate **51** accompanied by a small amount of α-chloro ketone **56**.[12]

In the course of optimization, the conversion of isatin (**52**) to diazo ketone **51** was greatly improved upon scale-up to a six-step, two-pot procedure which requires no chromatographic purification. The first four steps can be performed on 30 grams of isatin to provide 39 grams of acid **55**. The next two steps can also be performed in one pot and are typically performed on 9 grams of acid **55** to furnish 8.4 grams of diazo ketone **51** which may be chromatographed or advanced crude.[13]

Scheme 2.3.2



2.4 The Aryl C-H Insertion.

2.4.1 Initial Results.

Having established access to multigram quantities of α-diazo ketone **51**, efforts to prepare **50** *via* aryl C-H insertion began.[14] Treatment of **51** with $Rh_2(OAc)_4$ in methylene chloride leads to the rapid evolution of nitrogen and results in a blood-red reaction mixture (Scheme 2.4.1). Crude NMR and TLC analysis shows a complex mixture of products, which after extensive and careful purification lead to the isolation of a red product, tentatively assigned *via* NMR analysis to be tricyclic heterocycle **57**. Further analysis of this complex mixture did not result in the isolation of the desired product **50**. After repeating the reaction with various catalysts, some of which are summarized in Table 2.4.1, rhodium catalysis with perfluorinated ligands provided the best means of inducing the desired C-H insertion and forming ketone **50**.[15] The most effective, albeit far from optimal, conditions for producing the desired product **50** requires using rhodium trifluoroacetate as the catalyst; these conditions furnish ketone **50** in 15% yield, again accompanied with a now equimolar amount of red by-product **57** and a trace of spirocycle **58**, the product of C-H insertion into the proximate cyclopropyl methyl group.

Scheme 2.4.1

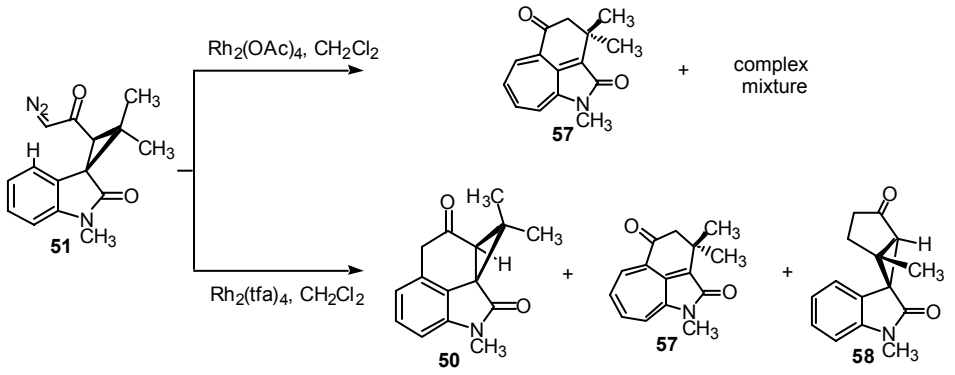


Table 2.4.1

Catalyst	% **50**	% **57**	% **58**
$Rh_2(OAc)_4$	0	42	trace
$Rh_2(pfm)_4$	5	50	trace
$Rh_2(tfm)_4$	0	50	trace
$Rh_2(cap)_4$	0	0	trace
$Rh_2(tfa)_4$	15	15	trace

Delighted with the ability to effect the C-H insertion reaction, the reaction was scaled from milligrams to grams (typically 9 g runs). Unfortunately, on these scales the yield of **50** decreased dramatically while production of the undesired by-product **57** remained unaffected. Moreover, this reaction proved quite capricious during small-scale (100 mg) optimization studies. Figure 2.4.1 compares two NMR spectra. The top spectrum is a representative NMR spectrum of the crude aryl C-H insertion reaction run on a 9 gram scale. The bottom spectrum is a purified sample of the desired product **50**. In comparing the two spectra, the aromatic protons of the desired product are buried in a complex multiplet of aromatic peaks in the top spectrum, and the diastereotopic methylene protons of ketone **50** at δ3.5 ppm are barely visible. Hopeful that this result could be improved, considerable time was invested on the optimization of this reaction.

Figure 2.4.1

^{1}H NMR (500 MHz, $CDCl_3$) comparison of

top: crude C-H insertion reaction, 9 g scale

bottom: analytical sample of desired product **50**

Before initiating optimization efforts, the structures of the new products were confirmed (i.e., **50**, **57**, **58**). To this end, the aryl C-H insertion product **50** undergoes $NaBH_4$ reduction to produce one diastereomer of alcohol **59**, a crystalline solid for which an X-ray structure was obtained (see Scheme 2.4.2). As is seen in the ORTEP, the bond to C(4) of the oxindole aryl ring was in fact formed, and the reduction occurred from the expected side of the molecule, the face away from the bulky gem-dimethyl cyclopropane ring. Similarly, heterocycle

57 was reduced with $NaBH_4$ and a crystal structure of the derived *p*-bromobenzoate **61** was obtained. The structure of spirocycle **58** was also confirmed *via* X-ray crystallography (see Figure 2.4.2 and Appendix 2 for X-ray reports).

Scheme 2.4.2

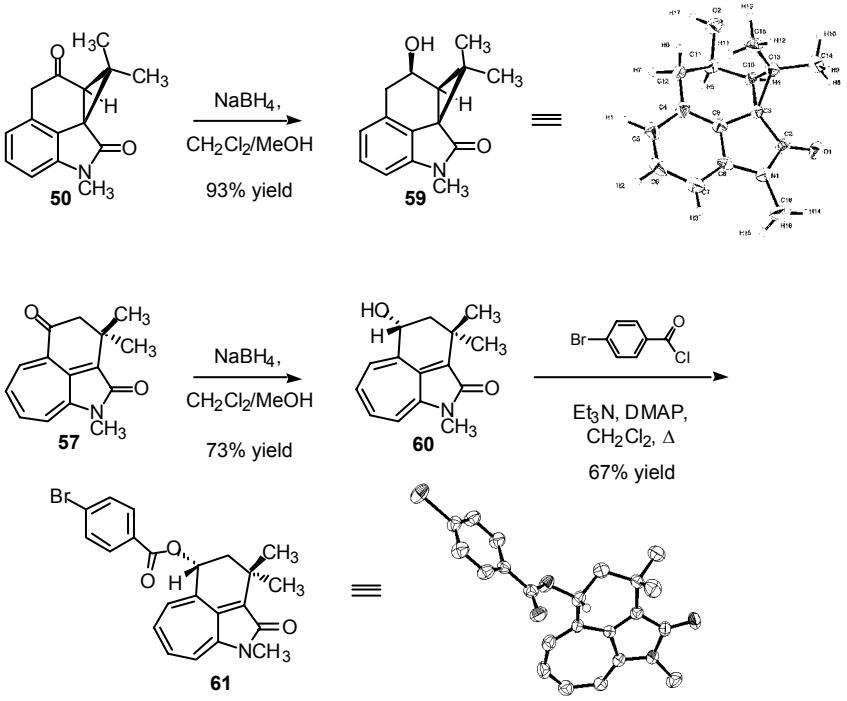
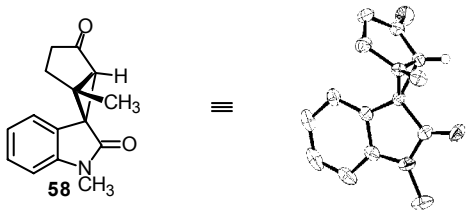


Figure 2.4.2



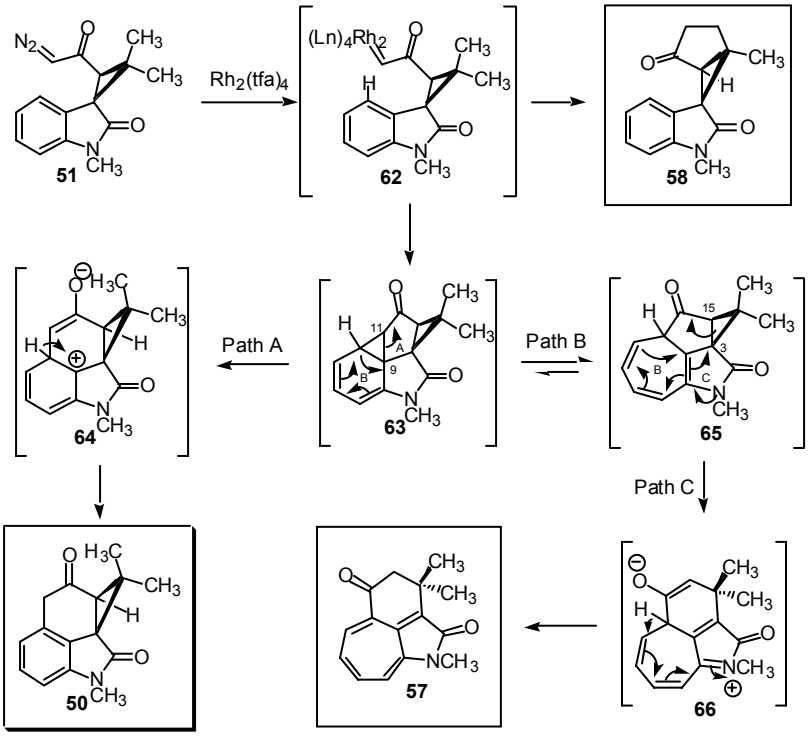
2.4.2 Proposed Mechanism.

Having confirmed the structures of the major products of the aryl C-H insertion reaction, initial optimization efforts were launched. These attempts

involved varying reaction parameters, including temperature, solvent, transition metal catalyst, catalyst ligands, and substituents at the oxindole nitrogen and aryl C(5) positions. Unfortunately, these initial efforts failed to improve the yield of the aryl C-H insertion. Hence, a mechanism for the formation of spirocycle **58**, ketone **50**, and heterocycle **57** was proposed with the hope that this insight would guide a few rationale changes designed to improve formation of the desired product **50**.

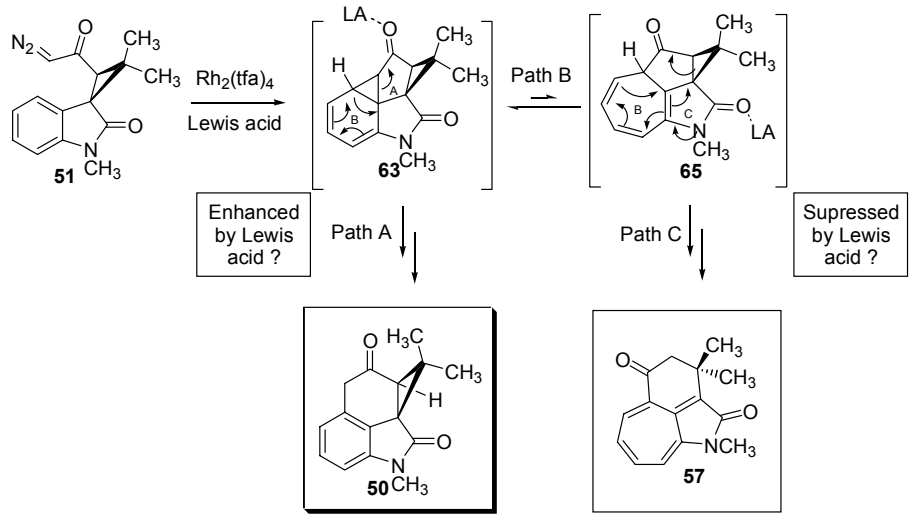
Of particular interest was the reaction's tendency to produce the undesired product **57**. In this regard, perhaps both the desired product, ketone **50**, and heterocycle **57** arise *via* a common intermediate, namely ketone **63**, produced by aryl cyclopropanation (Scheme 2.4.3). From intermediate **63**, cleavage of the internal bond of the newly formed cyclopropyl ring (C(9)-C(11)) would lead to the desired product, ketone **50** *via* **64** (Path A). Alternatively, norcaradiene **63** can undergo electrocyclic ring opening to the more stable cycloheptatriene **65** (Path B) which upon subsequent opening of the original cyclopropane ring (C(3)-C(15)), presumably with the assistance of the oxindole nitrogen lone pair (Path C, intermediate **66**), followed by tautomerization would give rise to heterocycle **57**.[16] Importantly, unlike other cycloheptatrienes, the proposed initial cycloheptatriene intermediate (**65**) cannot be isolated due to the facile cleavage of the second cyclopropane ring (i.e., **65**→**66**).

Scheme 2.4.3



Based on this mechanistic reasoning, possibilities were considered for diverting the reaction's course from Path B which provides **57** to Path A which furnishes **50**. To this end, it was speculated that the addition of a Lewis acid would improve the reaction by complexing to the ketone of intermediate **63** thereby enhancing Path A (Scheme 2.4.4).[17] Additionally, coordination of a Lewis acid to the amide carbonyl in intermediate **65** would minimize the influence of the nitrogen lone pair and hence suppress Path C and formation of by-product **57**.

Scheme 2.4.4

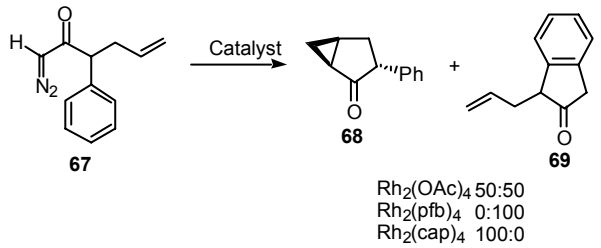


2.4.3 Optimization Efforts.

2.4.3.1 Ligand Effects.

It is common to find accounts in the literature involving the modulation of reactivity of rhodium carbenoids by changing the electronics of the ligands on rhodium. For example, Padwa and coworkers observed that when a rhodium catalyst with electron deficient ligands ($Rh_2(pfb)_4$) was used to decompose diazo ketone **67**, solely the product of aryl C-H insertion (**69**, Scheme 2.4.5) was isolated, and cyclopropanation (i.e., ketone **68**) was not observed. In contrast, the use of $Rh_2(cap)_4$, an electron rich catalyst, provided only the product of cyclopropanation of the olefin.[18] Since various rhodium catalysts were screened in the current system (i.e., **51**→**50**) without any success (Table 2.4.1), and given that efforts with the electron poor catalyst, $Rh_2(tfa)_4$, were meeting with limited success, this did not seem like a promising alternative.

Scheme 2.4.5

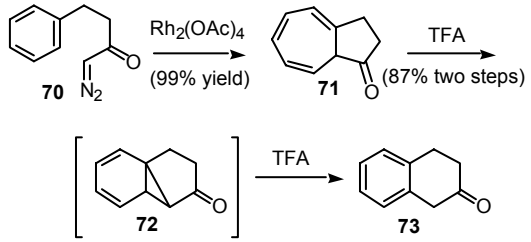


2.4.3.2 Lewis Acid Effects.

2.4.3.2.1 Introduction.

A potentially relevant report concerning the possibility of suppressing the norcaradiene/cycloheptatriene equilibrium between **63** and **65** (Scheme 2.4.3) by McKervey and coworkers describes conditions wherein cycloheptatriene **71**, derived from aryl cyclopropanation of diazo ketone **70** followed by ring opening, undergoes rearrangement to the formal C-H insertion product when treated with trifluoroacetic acid (Scheme 2.4.6). This occurs presumably through a norcaradiene intermediate (i.e., **72**).[19]

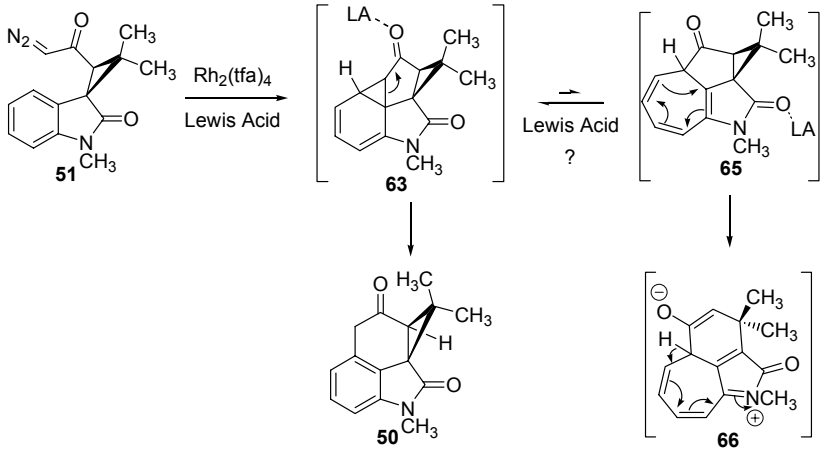
Scheme 2.4.6



Recognizing the similarity between diazo ketone **51** and diazo ketone **70**, a similar strategy could possibly be used to improve the aryl C-H insertion reaction. However, there was a crucial difference between the system of diazo

ketone **51** and McKervey's system. As was illustrated in Scheme 2.4.3, the initial cycloheptatriene intermediate **65** cannot be isolated due to the irreversible ring opening which eventually leads to product **57** (see also **65**→**66**, Scheme 2.4.7). In addition, direct addition of a protic acid to react with **65** as it is formed would destroy diazo ketone **51**. Therefore, an *in situ* variant to McKervey's strategy was required. Perhaps upon formation of the cycloheptatriene intermediate **65**, a Lewis acid in the reaction would effect rearrangement to the desired C-H insertion product **50** *via* norcaradiene intermediate **63** (see Scheme 2.4.7).

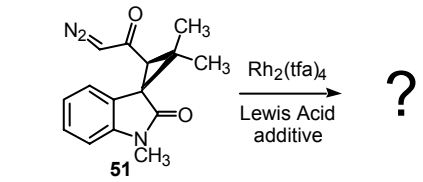
Scheme 2.4.7



2.4.3.2.2 Early Results.

In an effort to redirect the course of the reaction from **57** to **50** (Scheme 2.4.4) many different Lewis Acids were screened (see Scheme 2.4.8), by running small scale reactions and determining improvements qualitatively *via* TLC analysis.[20] After considerable experimentation, promising results were observed when $ZnCl_2$ or $MgBr_2 \bullet OEt_2$ were added to the reaction. Specifically, the reactions did not turn red as they did without an additive, and the TLC showed clean formation of the desired product and no sign of the red by-product **57**.

Scheme 2.4.8



Lewis acids screened:

$FeCl_3$	$Mg(OH)_2$	$SnCl_2$	$LaCl_3$
$CdCl_2$	MgF_2	$NiCl_2$	Cp_2HfCl_2
$CrCl_2$	$MgBr_2 \bullet OEt_2$	$Mg(OTf)_2$	CAN
Sb_2S_3	$ZnCl_2$	$Ti(OiPr)_4$	HgTFA
$Mg(OAc)_2$	$AgClO_4$	AgOTf	$EuCl_3$
$MgCl_2 \bullet 6H_2O$	MgO	AgO	$Pb(NO_3)_2$

Following the qualitative investigations, $MgBr_2 \bullet OEt_2$ and $ZnCl_2$ were explored on a larger scale. As was observed in the exploratory studies, pre-treatment of the α-diazo ketone **50** on a 9 gram scale with $ZnCl_2$ or $MgBr_2 \bullet OEt_2$ prior to addition of the rhodium catalyst completely eliminates the production of the undesired by-product **57** and considerably increases the yield of ketone **50** to ca. 50% (Scheme 2.4.9).

The dramatic effect of $ZnCl_2$ is clearly illustrated in Figure 2.4.3, which pictures two NMR spectra. The first spectrum is the same crude spectrum of the C-H insertion reaction run without the use of additives ($Rh_2(tfa)_4$ alone) as was

seen in Figure 2.4.1. The second is an NMR spectrum of the C-H insertion reaction run using $ZnCl_2$ as the Lewis acid additive. In the latter NMR, the aromatic peaks are defined and the diastereotopic methylene protons of the desired product are clearly seen at δ3.5 ppm. Unfortunately, while $ZnCl_2$ eliminates the formation by-product **57** and increases the yield of ketone **50**, the results using $ZnCl_2$ as an additive were irreproducible. Apparently, $ZnCl_2$ facilitates the clean but undesired formation of α-chloro ketone **56**, clearly seen in the bottom spectrum as the diastereotopic methylene protons at δ4.15 ppm, presumably formed *via* reaction of diazo ketone **51** with traces of HCl (from hydrolysis of the Lewis acid). In practice the extent to which $ZnCl_2$ hydrolyzes was found to be capricious and contributes greatly to the irreproducibility of the reaction, producing α-chloro ketone **56** (or α-bromo ketone **74** when using $MgBr_2$•OEt_2) in yields ranging from ca. 5% to 35% yield. Although a very important observation and some improvement had been made by adding a Lewis acid to this reaction, a new problem had arisen and further modifications needed to be made.

Scheme 2.4.9

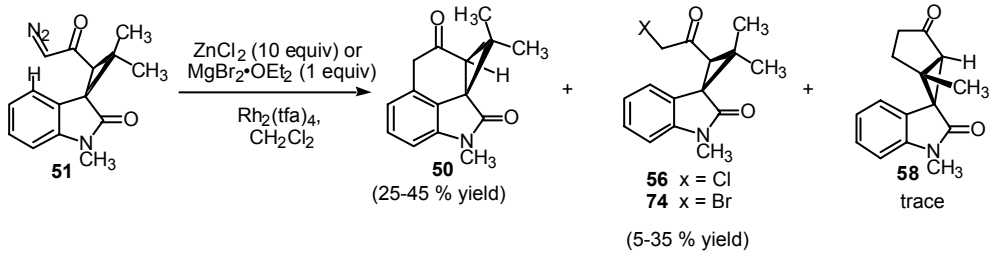


Figure 2.4.3

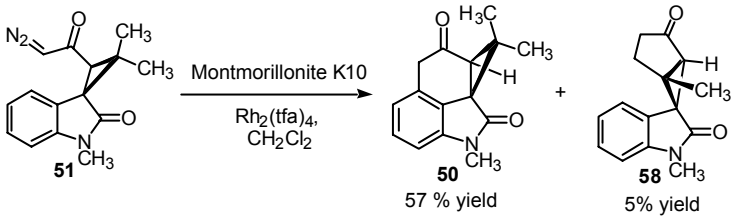
^{1}H NMR (500 MHz, $CDCl_3$) comparison of
top: crude C-H insertion reaction, no additive, $Rh_2(tfa)_4$ alone
bottom: crude C-H insertion reaction, $Rh_2(tfa)_4$ + $ZnCl_2$ additive

2.4.3.2.3 The Effect of Montmorillonite K10 Clay.

After obtaining only slight improvements from heroic attempts to dry the $ZnCl_2$, an interesting report was found in the literature wherein the reactivity of $ZnCl_2$ was improved greatly as a Friedel-Crafts catalyst by adsorbing it onto Montmorillonite K10, an aluminum silicate.[21] When the $ZnCl_2$/Montmorillonite

K10 combination was used as an additive in the system of **51**→**50**, the C-H insertion reaction gave similar, irreproducible results to those obtained with using $ZnCl_2$ alone. However, in the course of running several control experiments, the reaction was dramatically improved by the addition of Montmorillonite K10 clay alone (Scheme 2.4.10). Under these conditions, the yield of the ketone **50** was improved nearly four-fold (57% yield).

Scheme 2.4.10



The effect of Montmorillonite K10 is depicted in Figure 2.4.4, which again shows two crude NMR spectra. On the top is the same, additive-free aryl C-H insertion reaction, while the bottom illustrates the results of the reaction with the clay as an additive. The latter spectrum shows clean formation of the desired product, ketone **50**, with the only other resonances corresponding to traces of α-chloro ketone **56** (remaining from the previous reaction of the acid chloride derived from acid **55** and diazomethane) and spirocycle **58**. Thus, Montmorillonite K10 clay appears to be a sufficient Lewis acid to shift the norcaradiene/cycloheptatriene interconversion (i.e., **65**→**63**, Scheme 2.4.7) *in situ*, thereby eliminating the formation of by-product **57**, without causing detrimental side reactions as was observed with $ZnCl_2$.[22] Most importantly, the reactions using Montmorillonite K10 are very easy to run and consistent on large scale.[23]

Figure 2.4.4

^{1}H NMR (500 MHz, $CDCl_3$) comparison of

top: crude C-H insertion reaction, no additive, $Rh_2(tfa)_4$ alone

bottom: crude C-H insertion reaction, $Rh_2(tfa)_4$ + Montmorillonite K10 additive

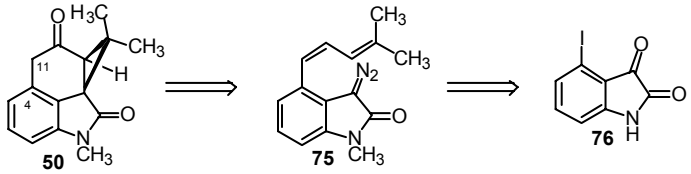
2.4.4 An Alternate Route to Ketone 50.

2.4.4.1 Retrosynthetic Analysis.

During the course of optimizing the C-H insertion reaction, another route to ketone **50** was devised as an alternative plan. Retrosynthetically, the cyclopropyl ring could be introduced late, *via* Rh(II)-mediated intramolecular

cyclopropanation of diazo compound **75** (see Scheme 2.4.11). This route would thus allow for the possibility of introducing asymmetry into the synthesis *via* an asymmetric intramolecular cyclopropanation. Unlike the initial approach, this strategy calls for the use of an aryl C(4)-substituted (halo-) oxindole, and formation of the C(4)-C(11) bond early in the construction of the core.

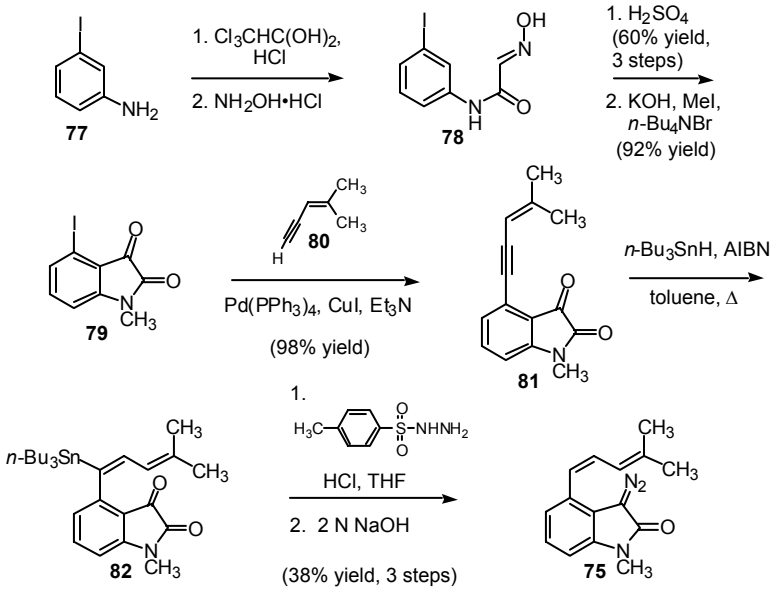
Scheme 2.4.11



2.4.4.2 Synthetic Scheme.

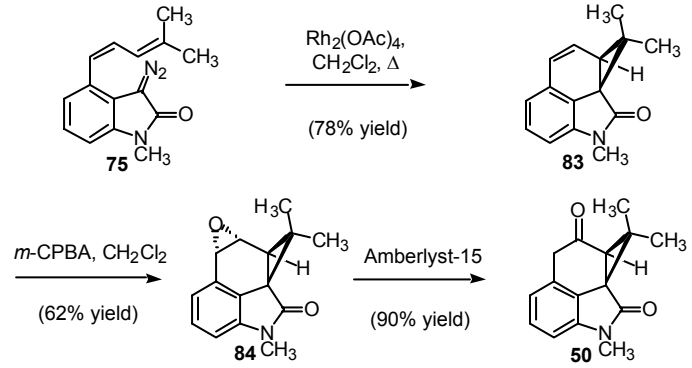
In the forward sense, 4-iodoisatin, prepared as described by Paquette,[24] was methylated under phase transfer conditions to furnish *N*-Me-4-iodoisatin (**79**, Scheme 2.4.12). Coupling of the aryl iodide to ene-yne **80** in a Sonigashira coupling reaction proceeds smoothly to form the C(4)-C(11) bond and produce ene-yne **81**.[25] After many attempts to selectively reduce the acetylene *via* hydrogenation, selective reduction was effected by treatment of ene-yne **81** with tributyltin hydride to furnish vinyl tin compound **82**, which after tosyl hydrazone formation along with concomitant protodestannylation and treatment with base, provides the desired diene **75** in good yield.[26]

Scheme 2.4.12



With diazo lactam **75** in hand, efforts to introduce the cyclopropyl ring were initiated. To this end, **75** was treated with $Rh_2(OAc)_4$ and heated in a sealed tube, which effects the desired cyclopropanation to provide olefin **83** in good yield (Scheme 2.4.13).[27,28] Epoxidation followed by acid-catalyzed rearrangement furnishes solely the desired homobenzylic ketone **50**.[29]

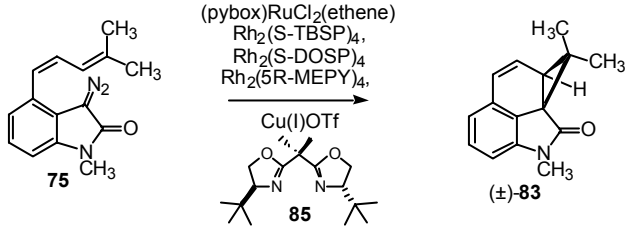
Scheme 2.4.13



2.4.4.3 Attempts to Introduce Asymmetry.

Owing to the success of the cyclopropanation reaction, an asymmetric variant was explored.[30] After much experimentation, the catalysts (pybox)$RuCl_2$(ethene),[31] $Rh_2(DOSP)_4$[32] and $Rh_2(TBSP)_4$,[33] Doyle dirhodium catalyst (Rh_2(5R-MEPY)$_4$)[34] and Cu(I)OTf with a bis-oxazoline ligand (**85**)[35] were all successful in installing the cyclopropyl ring to furnish olefin **83** (see Scheme 2.4.14). Unfortunately, no enantioselectivity was observed with any of these catalysts.[36]

Scheme 2.4.14

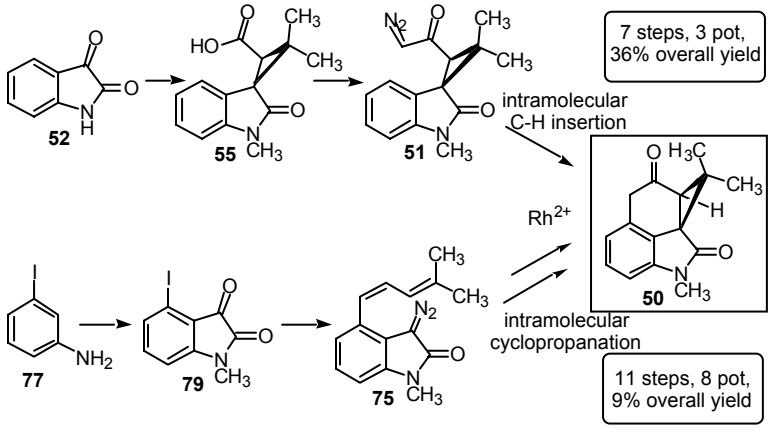


2.4.5 A Comparison of the Two Routes to Ketone 50.

In comparing the two pathways to ketone **50** (see Scheme 2.4.15), the first route utilizes a commercially available, inexpensive, aryl-unfunctionalized oxindole which is advanced to ketone **50** in seven steps. The route is conveniently performed on large scale in only three pots, and highlighted by a Rh(II)-catalyzed aryl C-H insertion. The second route requires the use of a C(4) aryl-functionalized oxindole (**79**) which is not commercially available, and the cyclopropyl ring is introduced *via* a Rh(II)-catalyzed intramolecular cyclopropanation in a longer sequence of eleven steps/eight pots. The first sequence is not only more amenable to large scale synthesis, but also gives

higher yields (36% vs. 9% yield). An advantage of the second route was the possibility of introducing asymmetry; however, considerable experimentation in this area failed to yield promising results. Given the significant improvements in the C-H insertion reaction (**51**→**50**) using Montmorillonite K10 as an additive, the first route was employed to make multigram quantities of ketone **50**, and other issues in the welwitindolinone synthesis were addressed.

Scheme 2.4.15



2.5 Conclusion.

The core of the welwitindolinone alkaloids (i.e., ketone **50**) was constructed *via* two separate routes. In the first pathway, **50** was efficiently and stereoselectively accessed in seven steps from commercially available isatin. The sequence is highlighted by a Rh(II)-catalyzed aryl C-H insertion, a reaction which was improved dramatically by the addition of a mild Lewis acid, Montmorillonite K10 clay. The second route, which is not as amenable to large scale synthesis, involves a Sonigashira coupling to form the bond to C(4) of the oxindole, followed by a Rh(II)-mediated intramolecular cyclopropanation and acid-catalyzed epoxide rearrangement.

2.6 Experimental Section.

2.6.1 Material and Methods.

Unless stated otherwise, reactions were performed in flame-dried glassware under a nitrogen atmosphere, using freshly distilled solvents. Diethyl ether (Et_2O) and tetrahydrofuran (THF) were distilled from sodium/benzophenone ketyl. Methylene chloride (CH_2Cl_2), benzene, and triethylamine (Et_3N) were distilled from calcium hydride. Methyl sulfoxide (DMSO), 1,2-dichloroethane, and BF_3•OEt_2 were purchased from the Aldrich Chemical Co. in Sure/Seal□ containers and used without further purification. All other commercially obtained reagents were used as received.

Unless stated otherwise all reactions were magnetically stirred and monitored by thin-layer chromatography (TLC) using E. Merck silica gel 60 F254

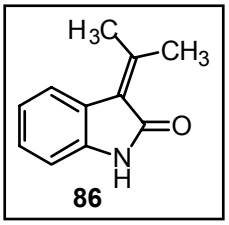
pre-coated plates (0.25-mm). Preparative TLC was also performed using E. Merck silica gel 60 F254 pre-coated plates (0.25-mm). Column or flash chromatography (silica) was performed with the indicated solvents using silica gel (particle size 0.032-0.063 mm) purchased from Fisher Scientific. In general, the chromatography guidelines reported by Still were followed.[37]

All melting points were obtained on a Gallenkamp variable temperature melting point apparatus (model: MPD350.BM2.1) and are uncorrected. Infrared spectra were recorded on a Midac M-1200 FTIR. ^{1}H and ^{13}C NMR spectra were recorded on Bruker AM-500 or Bruker Advance 400 spectrometers. Chemical shifts are reported relative to internal Me_4Si (^{1}H and ^{13}C, δ 0.00 ppm) or chloroform (^{1}H, δ 7.27 ppm, ^{13}C, δ 77.0 ppm). High resolution mass spectra were performed at The University of Illinois Mass Spectrometry Center. Single-crystal X-ray analyses were performed by Susan DeGala of Yale University. High performance liquid chromatography (HPLC) was performed on a Waters model 510 system using a Rainin Microsorb 80-199-C5 column, or a Rainin Dynamax SD-200 system with a Rainin Microsorb 80-120-C5 column. Optical rotations were measured on a Perkin-Elmer 241 polarimeter.

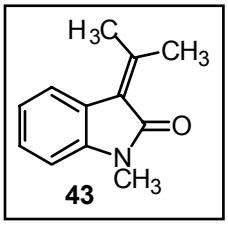
The determination of enantiomeric excess by Mosher ester derivatization involved esterification of the corresponding alcohols with *R*-(+)-MTPA (DCC, CH_2Cl_2) followed by purification and 500 MHz ^{1}H NMR analysis in benzene-d_6. Where possible an identical analysis was performed employing a racemic mixture of alcohols.

2.6.2 Preparative Procedures:

Preparation of Oxindole 43.



86



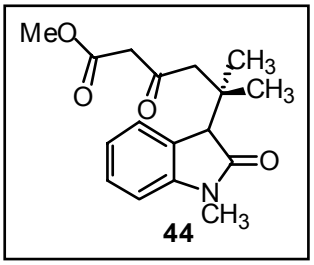
43

Oxindole 43. Oxindole (**41**) (1.00g, 7.50 mmol, 1.0 equiv) was stirred in THF (38 mL) at 10 °C in a 3-necked flask equipped with a dropping funnel and reflux condenser. Ethylmagnesium bromide (1 M in THF, 16.5 mL, 2.2 equiv) was introduced over 5 minutes and the solution was stirred for 30 minutes. Acetone (15 mL) was then added over 3 minutes *via* dropping funnel and the reaction was brought to reflux for 16 hours. After cooling to rt, 20 % aqueous citric acid (20 mL) was added and the THF was removed under reduced pressure. The aqueous layer was extracted with EtOAc (2 x 150 mL), and the organic layers were dried over $MgSO_4$. Evaporation of the solvent provided a residue that was used without further purification. All spectral data was in accordance with that reported in the literature for oxindole **86**.[38]

To a solution of the above product in THF (150 mL) was added iodomethane (1.40 mL, 22.5 mmol, 30 equiv), finely ground potassium hydroxide (1.50 g, 26.2 mmol, 3.5 equiv), and tetrabutylammonium bromide (500 mg, 1.50 mmol, 0.2 equiv). After stirring for 3 hours, the solvent was removed under reduced pressure, and the residue was dissolved in H_2O (75 mL) and extracted with EtOAc (3 x 100 mL). The organic layers were washed with brine (3 x 75

mL), dried over $MgSO_4$, and concentrated to provide oxindole **43** as a tan solid (1.36 g, 97% yield) which was used without further purification.

Preparation of β-Keto Ester 44.

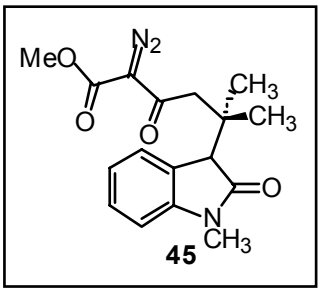


44

β-Keto Ester 44. To NaH (60% dispersion in mineral oil, 0.24 g, 5.88 mmol, 1.1 equiv) in THF (13 mL) at 0 °C was added methyl acetoacetate (0.58 mL, 5.35 mmol, 1.0 equiv) dropwise and the resulting mixture was stirred for 10 minutes at which point it became homogenous. Next, *n*-BuLi (2.5 M in hexanes, 2.25 mL, 1.05 equiv) was added dropwise and the reaction was stirred for 10 minutes resulting in an orange mixture. A solution of oxindole **43** (1.00 g, 5.35 mmol, 1.0 equiv) in THF (13 mL) was added dropwise *via* addition funnel over 2 minutes resulting in a deep red solution. After stirring for an additional 25 minutes (0 °C to rt), conc. HCl (1 mL) was added which resulted in the precipitation of a salt. H_2O (15 mL) and EtOAc (10 mL) were added, and the layers were separated. The organic layer was washed with H_2O (10 mL), dried over $MgSO_4$, and concentrated, resulting in a yellow oil which was purified *via* flash chromatography (25% EtOAc/hexanes eluent) to provide recovered oxindole **43** as a yellow solid (430 mg) and the desired Michael adduct **44** (which exists slightly in the enol form) as a yellow oil (405 mg, 25% yield, 44% yield based on recovered starting material): IR (thin film/NaCl) 3054 (w), 2958 (m),

2884 (w), 1748 (s), 1704 (s), 1611 (s), 1467 (s), 1348 (s), 1264 (s), 1175 (m), 1134 (m), 1090 (s), 1022 (m), 930 (m), 758 (s), 692 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, *J* = 7.7 Hz, 1H), 7.20 (t, *J* = 7.7 Hz, 1H), 6.94 (t, *J* = 7.6 Hz, 1H), 6.73 (d, *J* = 7.7 Hz, 1H), 3.81 (s, 1H), 3.68 (s, 3H), 3.52 (s, 2H), 3.31 (d, *J* = 18.1 Hz, 1H), 3.08 (s, 3H), 2.50 (d, *J* = 17.7 Hz, 1H), 1.33 (s, 3H), 0.65 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.8, 177.0, 168.2, 145.2, 128.3, 127.6, 126.2, 122.3, 108.2, 52.7, 51.7, 51.5, 50.8, 36.7, 27.1, 26.3, 24.4; HRMS (EI) *m/z* 303.1466 [calc'd for $C_{17}H_{21}NO_4$(M+) 303.1471].

Preparation of α-Diazo Ketone 45.

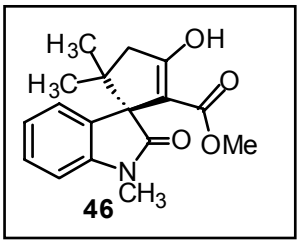


45

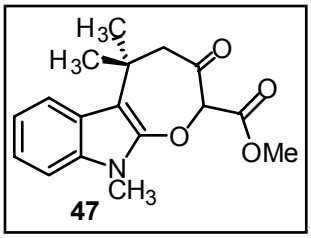
α-Diazo Ketone 45. To ester **44** (180 mg, 0.59 mmol, 1.0 equiv) and *p*-acetamidobenzenesulfonyl azide (170 mg, 0.71 mmol, 1.2 equiv)[39] in CH_3CN (4 mL) at 0 °C was added DBU (176 μL, 1.18 mmol, 2.0 equiv) dropwise. After stirring for 1 hour, Et_2O (15 mL) was added which resulted in the precipitation of a solid. The mixture was washed with NH_4Cl (3 x 10 mL), the organic layer dried over $MgSO_4$ and concentrated. The crude oil was subjected to flash chromatography (30% EtOAc/hexanes eluent) to provide α-diazo ketone **45** as a red oil (105 mg, 54% yield): IR (thin film/NaCl) 2958 (w), 2137 (s), 1708 (s), 1654 (m), 1611 (m), 1493 (m), 1469 (m), 1437 (m), 1370 (m), 1347 (m), 1310

(m), 1267 (w), 1210 (m), 1129 (m), 1090 (m), 1035 (m), 926 (w), 752 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, *J* = 7.4 Hz, 1H), 7.20 (t, *J* = 7.8 Hz, 1H), 6.94 (t, *J* = 7.6 Hz, 1H), 6.73 (d, *J* = 7.8 Hz, 1H), 3.95 (s, 1H), 3.76 (s, 3H), 3.58 (d, *J* = 17.8 Hz, 1H), 3.10 (s, 3H), 2.87 (d, *J* = 17.6 Hz, 1H), 1.25 (s, 3H), 0.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.3, 177.1, 162.2, 145.3, 128.3, 127.8, 126.3, 122.2, 108.1, 52.6, 52.2, 48.3, 37.5, 26.6, 26.3, 24.8; HRMS (EI) *m/z* 329.1384 [calc'd for $C_{17}H_{19}N_3O_4$(M+) 329.1376].

Preparation of Spirocycle 46 and Enol Ether 47.



46



47

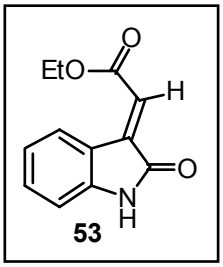
Spirocycle 46 and Enol Ether 47. To a solution of diazo ketone **45** (30 mg, 0.09 mmol, 1.0 equiv) in CH_2Cl_2 (3 mL) was added $Rh_2(OAc)_4$ (0.40 mg, 0.001 mmol, 0.01 equiv) and the mixture was heated to reflux for 0.5 hours. After cooling to rt the reaction was concentrated and purified using flash chromatography (30% EtOAc/hexanes eluent) to provide esters **46** (10 mg, 36% yield) and **47** (18 mg, 66% yield) as pale yellow oils.

46: The first compound to elute was ester **46** (keto and enol forms): IR (thin film/NaCl) 2961 (w), 1755 (s), 1725 (s), 1669 (w), 1619 (m), 1569 (m), 1447 (m), 1404 (m), 1364 (m), 1303 (w), 1268 (m), 1159 (m), 1095 (m), 1021 (w), 912 (w), 741 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.68 (s, 1H), 7.58-7.54 (m,

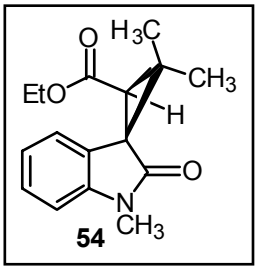
2H), 7.15-6.99 (comp m, 6H), 4.95 (s, 1H), 3.80 (s, 3H), 3.77 (s, 3H), 3.62 (s, 3H), 3.55 (s, 3H), 3.42 (d, *J* = 10.8 Hz, 1H), 2.79 (d, *J* = 11.2 Hz, 1H), 2.76 (s, 2H), 1.50-1.42 (comp m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.0, 168.2, 166.5, 163.5, 145.4, 144.0, 131.4, 130.2, 127.4, 123.9, 123.2, 120.0, 119.3, 119.1, 118.8, 118.4, 118.1, 108.1, 107.8, 101.4, 99.9, 87.3, 52.8, 52.2, 51.0, 44.3, 34.0, 33.3, 29.3, 28.2, 28.2, 26.8, 26.7; HRMS (EI) *m/z* 301.1317 [calc'd for $C_{17}H_{19}NO_4$(M+) 301.1314].

47: The second compound to elute was ester **47**: IR (thin film/NaCl) 3462 (br w), 2960 (s), 1749 (s), 1726 (s), 1469 (m), 1366 (s), 1256 (m), 1185 (m), 1077 (s), 1023 (s), 912 (s), 743 (m) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.0 Hz, 1H), 7.27-7.18 (comp m, 2H), 7.05 (t, *J* = 7.5 Hz, 1H), 4.55 (s, 1H), 3.73 (s, 3H), 3.65 (s, 3H), 3.09 (d, *J* = 12.7 Hz, 1H), 2.65 (d, *J* = 12.6 Hz, 1H), 1.61 (s, 3H), 1.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.9, 170.2, 139.4, 130.1, 124.2, 123.3, 121.8, 121.4, 119.8, 110.2, 78.4, 54.3, 52.1, 36.7, 30.9, 30.8, 30.4; HRMS (EI) *m/z* 301.1317 [calc'd for $C_{17}H_{19}NO_4$(M+) 301.1314].

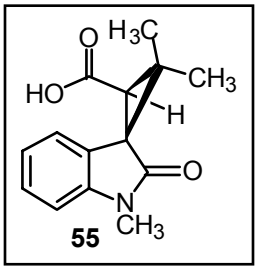
Preparation of Enoate 53, Ester 54 and Acid 55.



53



54



55

Enoate 53, Ester 54 and Acid 55. All solvents used in this procedure were used as received. To a solution of ethyl triphenylphosphoranylidene

acetate (74.6 g, 214 mmol, 1.05 equiv) in THF (244 mL) at 0 °C in a one-neck, 1L flask equipped with an addition funnel was added isatin (**52**, 30.0 g, 204 mmol, 1.0 equiv) in THF (232 mL) rapidly *via* addition funnel. The ice bath was removed and the solution was stirred until all starting material had been consumed and a new higher R_f spot appeared by TLC (ca. 30 minutes, visualized by UV). In a separate 3-neck flask equipped with a mechanical stirrer and addition funnel was introduced isopropyl triphenylphosphonium iodide (212 g, 490 mmol, 2.4 equiv) and THF (613 mL). This suspension was cooled to 0 °C and was treated slowly *via* syringe with *n*-BuLi (2.33 M in hexanes, 228 mL, 2.6 equiv). After stirring at 0 °C for 30 minutes the derived red mixture was treated with the entire crude reaction containing enoate **53** (dropwise *via* addition funnel). The resultant mixture was stirred for 2.5 hours (0 °C - rt) and then excess iodomethane (63.6 mL, 1.02 mol, 5.0 equiv) was added. After stirring for 1.5 hours at rt, the reaction was vacuum filtered to separate the methyl triphenylphosphonium iodide salt and the solid was washed with diethyl ether (1 x 1L). The filtrate was concentrated under reduced pressure to yield the cyclopropyl ester **54**. Crude ester **54** was dissolved in THF (577 mL) and placed into a 2L, one-necked flask equipped with a condenser. To this solution was added LiOH (4.6N, 577 mL, 13 equiv) and the two-phased reaction was heated to reflux overnight. After cooling, the THF was removed under reduced pressure and the aqueous layer was washed with CH_2Cl_2 (2 x 200 mL). After removing any remaining traces of CH_2Cl_2 *in vacuo*, the aqueous layer was acidified with conc. HCl at 0 °C to afford, after vacuum filtering and azeotropic drying with benzene, acid **55** as a tan solid (38.8 g, 79% yield, 4 steps).

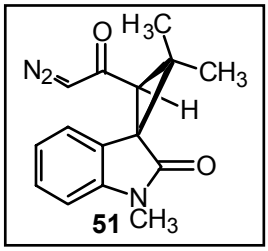
Although generally carried directly through to acid **55**, several intermediates were isolated and characterized. Thus, an analytical sample of

enoate **53** can be obtained by purification *via* silica gel flash chromatography (3:2 hexanes:EtOAc eluent) followed by recrystallization from EtOH. Enoate **53** was identical in all respects to data reported in the literature.[9]

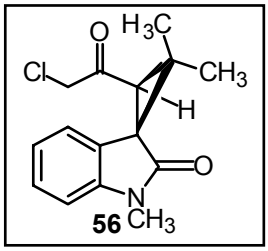
54: An analytically pure sample of ester **54** can be obtained *via* silica gel chromatography (25% EtOAc/hexanes eluent): m.p. 91-92 °C; IR (thin film/NaCl) 2945 (br w), 1731 (m), 1707 (s), 1611 (m), 1469 (m), 1346 (m), 1266 (w), 1168 (m), 1096 (m), 1022 (w), 752 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 (d, *J* = 7.7 Hz, 1H), 7.29 (td, *J* = 1.2, 7.7 Hz, 1H), 7.05 (td, *J* = 1.0, 7.7 Hz, 1H), 6.90 (d, *J* = 7.6 Hz, 1H), 4.13 (m, 2H), 3.27 (s, 3H), 2.77 (s, 1H), 1.60 (s, 3H), 1.59 (s, 3H), 1.24 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.8, 168.7, 144.2, 127.0, 125.6, 124.9, 121.4, 107.7, 60.5, 41.7, 40.9, 34.8, 26.4, 20.5, 16.9, 14.1; HRMS (CI) *m/z* 274.1443 [calc'd for $C_{16}H_{19}NO_3$ (M+H) 274.1443].

55: To obtain an analytical sample of acid **55**, the dry solid can be recrystallized from MeOH to yield white needles: m.p. 168-169 °C; IR (KBr pellet) 2934 (br m), 2675 (br w), 1752 (s), 1661 (s), 1608 (s), 1498 (m), 1378 (s), 1193 (s), 1103 (s), 1097 (s), 762 (s), 696 (m) cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.61 (s, 1H), 7.40 (d, *J* = 7.8 Hz, 1H), 7.28 (t, *J* = 7.9 Hz, 1H), 7.05 (d, *J* = 7.8 Hz, 1H), 7.00 (t, *J* = 7.9 Hz, 1H), 3.18 (s, 3H), 2.52 (s, 1H), 1.48 (s, 3H), 1.45 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 173.1, 169.2, 144.0, 127.0, 124.7, 124.6, 121.1, 108.3, 40.7, 40.6, 34.0, 26.4, 20.1, 16.8; HRMS (CI) *m/z* 246.1129 [calc'd for $C_{14}H_{15}NO_3$ (M+H) 246.1130].

Preparation of α-Diazo Ketone 51 and α-Chloro Ketone 56.



51



56

α-Diazo Ketone 51 and α-Chloro Ketone 56. To a 500 mL round bottom flask were added recrystallized acid **55** (9.00 g, 36.7 mmol, 1.0 equiv) and CH_2Cl_2 (200 mL). The resulting white slurry was cooled to 0 °C and stirred. Oxalyl chloride (4.66 g, 38.5 mmol, 1.05 equiv) was added neat *via* syringe followed by DMF (100 μL, 1.30 mmol, 0.04 equiv). The ice bath was removed after 1 hour and stirring continued for 90 minutes, at which time gas evolution had ceased and a clear, pale yellow solution remained. The solution was concentrated and azeotropically dried with benzene under reduced pressure to give the corresponding acid chloride as a yellow solid. The solid was then dried *in vacuo* for 45 minutes and used crude in the next step.

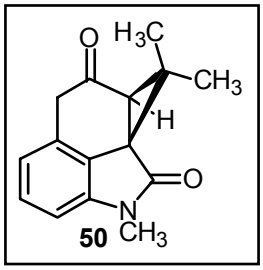
To a scratch-free 2L round bottom flask equipped with a 250 mL addition funnel was added triethylamine (4.36 g, 43.0 mmol, 1.2 equiv) and acetonitrile (25 mL) and the solution was cooled to 0 °C. Ethereal diazomethane (450 mL, prepared from 32.2 g Diazald□) was added to the flask through a plastic funnel. The dried acid chloride was dissolved in THF (200 mL), transferred to the addition funnel *via* cannula, and added dropwise over 30-40 minutes to the diazomethane solution with stirring. The funnel was rinsed with THF (10 mL) and the resulting heterogeneous mixture was stirred for 1 hour after which time 400 mL of 0.1N acetic acid was added slowly. After gas evolution ceased, the

biphasic mixture was transferred to a separatory funnel. The aqueous layer was removed and washed with ethyl ether (100 mL). The combined organic layers were concentrated under reduced pressure to give a yellow oil which solidified upon cooling. The solid was purified *via* silica gel flash chromatography, eluting with a gradient of hexanes:EtOAc (1:4-1:1) to afford α-chloro ketone **56** as a yellow solid (0.99 g, 10%) and α-diazo ketone **51** as a light yellow solid (8.36 g, 84% yield from acid **55**).

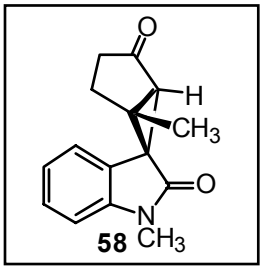
56: The first compound to elute was α-chloro ketone **56**: m.p. >135 °C (dec); IR (thin film/NaCl) 2932 (br w), 1702 (s), 1611 (m), 1469 (m), 1376 (m), 1349 (m), 1267 (w), 1141 (w), 1095 (m), 1024 (w), 753 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (d, *J* = 7.6 Hz, 1H), 7.30 (t, *J* = 7.7 Hz, 1H), 7.06 (t, *J* = 7.7 Hz, 1H), 6.89 (d, *J* = 7.8 Hz, 1H), 4.21 (d, *J* = 15.5 Hz, 1H), 4.09 (d, *J* = 15.5 Hz, 1H), 3.27 (s, 3H), 3.08 (s, 1H), 1.64 (s, 3H), 1.56 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.3, 173.4, 144.0, 127.4, 126.0, 124.2, 121.9, 107.9, 49.9, 45.0, 44.8, 37.6, 26.6, 20.6, 16.7; HRMS (EI) *m/z* 277.0867 [calc'd for $C_{15}H_{16}ClNO_2$ (M+) 277.0870].

51: The second compound to elute was α-diazo ketone **51**: m.p. >133 °C (dec); IR (thin film, NaCl) 3088 (br w), 2934 (br w), 2100 (s), 1703 (s), 1637 (m), 1469 (m), 1415 (w), 1349 (s), 1266 (m), 1146 (w), 1094 (m), 753 (m), 695 (w) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (br s, 1H), 7.29 (td, *J* = 1.57, 7.7 Hz, 1H), 7.06 (t, *J* = 6.7 Hz, 1H), 6.90 (dd, *J* = 1.3, 7.6 Hz, 1H), 5.37 (s, 1H), 3.27 (s, 3H), 2.67 (s, 1H), 1.63 (s, 3H), 1.59 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.2, 174.0, 144.0, 127.0, 126.0, 125.0, 121.7, 107.7, 57.1, 46.2, 36.9, 26.5, 20.8, 17.0; HRMS (EI) *m/z* 269.1167 [calc'd for $C_{15}H_{15}N_3O_2$ (M+) 269.1164].

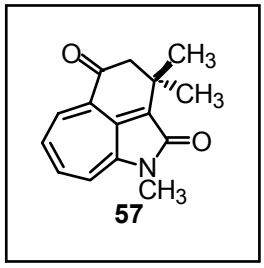
Preparation of Ketone 50, Spirocycle 58, and Heterocycle 57.



50



58



57

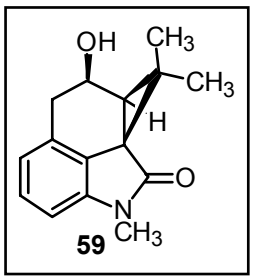
Ketone 50, Spirocycle 58, and Heterocycle 57. To a stirred solution of diazo ketone **50** (100 mg, 0.37 mmol, 1.0 equiv) in CH_2Cl_2 (4 mL) at rt was added rhodium(II)trifluoroacetate (1.0 mg, 0.002 mmol, 0.005 equiv). After 20 minutes, nitrogen evolution ceased and the reaction turned from yellow to bright yellow then red. The reaction mixture was adsorbed onto silica gel and purified *via* flash chromatography (4:1-2:1 hexanes:EtOAc eluent) to provide ketone **50** as a yellow solid (14 mg, 15% yield), spirocycle **58** as an off-white solid (1.0 mg, 1% yield), and heterocycle **57** as a red solid (14 mg, 15% yield).

50: The first compond to elute was ketone **50**: m.p. 139-140 °C; IR (thin film/NaCl) 2931 (br w), 1706 (s), 1611 (m), 1470 (m), 1377 (w), 1330 (w), 1280 (w), 1224 (w), 1104 (w), 1037 (m), 870 (w), 765 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.23 (t, *J* = 7.8 Hz, 1H), 6.77 (d, *J* = 7.7 Hz, 2H), 3.51 (d, *J* = 21.5 Hz, 1H), 3.42 (d, *J* = 21.7 Hz, 1H), 3.26 (s, 3H), 2.76 (s, 1H), 1.62 (s, 3H), 1.37 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.4, 173.7, 142.2, 129.6, 127.9, 124.1, 120.4, 106.0, 44.9, 43.2, 42.7, 36.5, 26.6, 21.4, 18.7; HRMS (EI) *m/z* 241.1102 [calc'd for $C_{15}H_{15}NO_2$ (M+) 241.1103].

58: The second compond to elute was spirocycle **58**. The solid was recrystallized from ethyl acetate/hexanes to provide white crystals suitable for X-ray analysis (see Appendix Two for X-ray structure report): m.p. 182-183 °C (EtOAc/hexanes); IR (thin film/NaCl) 2937 (w), 1709 (s), 1611 (w), 1493 (m), 1466 (w), 1379 (m), 1264 (w), 1138 (m), 1069 (m), 755 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (t, *J* = 7.7 Hz, 1H), 7.02 (t, *J* = 7.5 Hz, 1H), 6.93 (d, *J* = 7.8 Hz, 1H), 6.86 (d, *J* = 7.6 Hz, 1H), 3.27 (s, 3H), 2.84-2.30 (comp m, 4H), 2.82 (s, 1H), 1.70 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.3, 172.3, 144.9, 127.7, 125.0, 122.0, 121.3, 108.5, 48.9, 44.1, 41.0, 40.3, 27.8, 26.6, 15.6; HRMS (EI) *m/z* 241.1104 [calc'd for $C_{15}H_{15}NO_2$ (M+) 241.1103].

57: The final compound to elute was ketone **57**, of which an analytically pure sample was obtained *via* HPLC purification (5% MeOH/CH_2Cl_2): m.p. 193-198 °C; IR (thin film/NaCl) 2956 (w), 1665 (s), 1615 (m), 1590 (m), 1547 (m), 1473 (m), 1452 (w), 1414 (w), 1361 (w), 1269 (w), 1200 (m), 1088 (w), 830 (w), 757 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (d, *J* = 9.0 Hz, 1H), 7.15 (t, *J* = 10.0 Hz, 1H), 6.86 (t, *J* = 9.5 Hz, 1H), 6.78 (d, *J* = 9.2 Hz, 1H), 3.56 (s, 3H), 2.71 (s, 2H), 1.44 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.7, 166.3, 146.4, 139.0, 134.5, 129.7, 126.6, 119.0, 109.9, 53.6, 33.9, 27.4, 26.2; HRMS (EI) *m/z* 241.1107 [calc'd for $C_{15}H_{15}NO_2$ (M+) 241.1103].

Preparation of Alcohol 59.

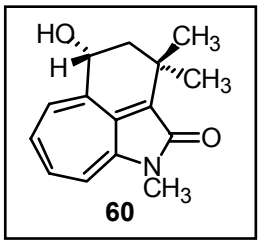


59

Alcohol 59. To a solution of ketone **50** (30 mg, 0.12 mmol, 1.0 equiv) in CH_2Cl_2/MeOH (8 mL, 1:1) was added $NaBH_4$ (15 mg, 0.40 mmol, 3.3 equiv). The reaction was stirred for 30 minutes in the open air, after which time the solvents were removed under reduced pressure. The flask was cooled to 0 °C, and the residue was treated with 1N HCl (5 mL). After stirring at 0 °C for 30 minutes, the reaction was extracted with CH_2Cl_2 (3 x 5 mL). The organic layers were combined, dried (Na_2SO_4), filtered, and concentrated. The product was purified *via* silica gel flash chromatography (1:1 hexanes:EtOAc eluent) to afford alcohol **59** as a white solid (28 mg, 93% yield). The solid was recrystallized from CH_2Cl_2/Et_2O/hexanes to provide white crystals suitable for X-ray analysis (see Appendix Two for X-ray structure report): m.p. 166-168 °C (CH_2Cl_2/Et_2O/hexanes); IR (thin film/NaCl) 3415 (br m), 3054 (w), 2999 (w), 2935 (br m), 2880 (w), 1686 (s), 1609 (s), 1471 (m), 1378 (m), 1339 (m), 1287 (m), 1175 (m), 1103 (m), 1037 (m), 961 (w), 914 (w), 761 (m), 732 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.19 (t, *J* = 7.7 Hz, 1H), 6.82 (d, *J* = 7.7 Hz, 1H), 6.73 (d, *J* = 7.7 Hz, 1H), 4.27 (m, 1H), 3.26 (s, 3H), 3.03 (dd, *J* = 7.3, 16.4 Hz, 1H), 2.80 (dd, *J* = 10.2, 16.4 Hz, 1H), 2.40 (d, *J* = 4.6 Hz, 1H), 1.59 (s, 4H), 1.31 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.1, 142.2, 130.1, 126.7, 125.8, 120.9,

105.6, 67.9, 40.2, 39.2, 38.0, 35.7, 26.6, 23.4, 19.1; HRMS (EI) *m/z* 243.1261 [calc'd for $C_{15}H_{17}N0_2$ (M+) 243.1259].

Preparation of Alcohol 60.

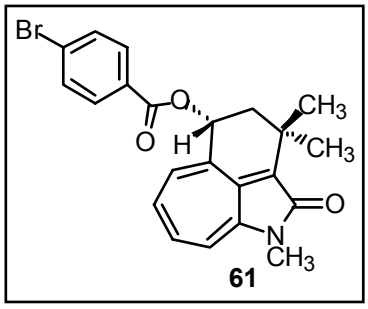


60

Alcohol 60. To a solution of **57** (100 mg, 0.41 mmol, 1.0 equiv) in CH_2Cl_2/MeOH (15 mL, 1:1) was added $NaBH_4$ (51.0 mg, 1.35 mmol, 3.3 equiv). After stirring for 45 minutes in the open air, the yellow reaction mixture was concentrated, cooled to 0 °C and treated with 1N HCl (5 mL). After stirring at 0 °C for 20 minutes, the reaction was extracted with CH_2Cl_2 (3 x 10 mL), the organic layers were combined, dried (Na_2SO_4), filtered, and concentrated. The product was purified *via* silica gel flash chromatography (3:2 hexanes:EtOAc eluent) to afford alcohol **60** as a yellow solid (73 mg, 73% yield): m.p. 187-192 °C; IR (thin film/NaCl) 3371 (br m), 2955 (w), 2862 (w), 1646 (s), 1590 (m), 1546 (m), 1514 (m), 1442 (m), 1408 (m), 1360 (w), 1275 (w), 1190 (w), 1092 (m), 1034 (w), 915 (w), 732 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34 (d, *J* = 8.5 Hz, 1H), 6.93 (t, *J* = 9.5 Hz, 1H), 6.84 (t, *J* = 9.9 Hz, 1H), 6.76 (d, *J* = 8.8 Hz, 1H), 4.84 (dd, *J* = 4.3, 11.2 Hz, 1H), 3.51 (s, 3H), 2.47 (d, *J* = 5.6 Hz, 1H), 2.08 (dd, *J* = 4.4, 8.0 Hz, 1H), 1.86 (t, *J* = 11.9 Hz, 1H), 1.52 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.6, 142.4, 141.5, 137.3, 128.4, 127.4, 125.0, 120.7,

110.3, 68.8, 47.2, 31.9, 27.8, 27.4, 26.0; HRMS (EI) *m/z* 243.1265 [calc'd for $C_{15}H_{17}NO_2$ (M+) 243.1259].

Preparation of Ester 61.

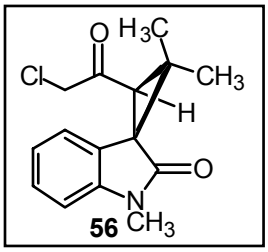


61

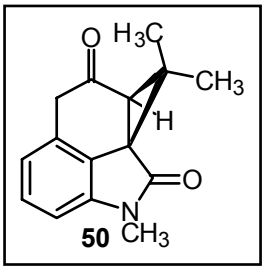
Ester 61. To alcohol **60** (52 mg, 0.21 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL) was added 4-bromobenzoyl chloride (52 mg, 0.24 mmol, 1.1 equiv), triethylamine (45μL, 0.32 mmol, 1.5 equiv), and finally DMAP (1.0 mg, 0.008 mmol, 0.04 equiv). The resulting solution was heated to reflux for 30 minutes. After cooling to rt, the reaction was adsorbed onto SiO_2 and chromatographed (4:1 hexanes:EtOAc eluent). The derived benzoate **61** (60 mg, 67% yield) was recrystallized from ethyl acetate to furnish yellow crystals suitable for X-ray analysis (see Appendix Two for X-ray structure report): m.p. 177-178 °C (EtOAc); IR (thin film/NaCl) 2955 (w), 2932 (w), 2865 (w), 2242 (w), 1719 (m), 1646 (s), 1590 (m), 1546 (w), 1514 (w), 1442 (w), 1414 (w), 1360 (w), 1275 (s), 1190 (w), 1092 (m), 917 (w), 886 (w), 750 (m), 732 (m) cm^{-1};^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.4 Hz, 2H), 7.61 (d, *J* = 8.5 Hz, 2H), 7.03 (d, *J* = 8.7 Hz, 1H), 6.96 (t, *J* = 10.0 Hz, 1H), 6.76 (m, 2H), 6.30 (t, *J* = 6.3 Hz, 1H), 3.55 (s, 3H), 2.12 (d, *J* = 6.7 Hz, 2H), 1.55 (s, 3H), 1.50 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.6, 165.3, 143.0, 137.2, 135.7, 131.9, 131.3, 129.5, 128.9, 128.5, 127.4,

126.9, 121.0, 110.0, 72.4, 42.8, 31.4, 27.9, 27.4, 26.1; HRMS (EI) *m/z* 425.0625 [calc'd for $C_{22}H_{20}NO_3Br$ (M+) 425.0627].

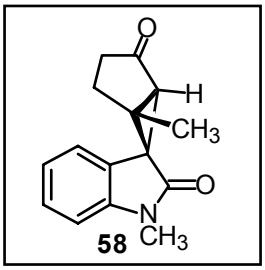
Preparation of α-Chloro Ketone 56, Ketone 50, and Spirocycle 58.



56



50

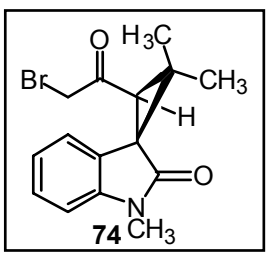


58

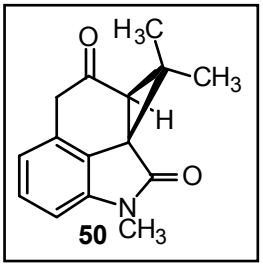
α-Chloro Ketone 56, Ketone 50, and Spirocycle 58. $ZnCl_2$ (20.3 g, 148.7 mmol, 10.0 equiv) was placed in a 4L Erlenmeyer flask and the solid was rinsed with CH_2Cl_2 (4 x 30 mL) to remove traces of HCl. CH_2Cl_2 (2L) was then added followed by diazo ketone **51** (4.00g, 14.9 mmol, 1.0 equiv). The mixture was stirred vigorously for 4 minutes when $Rh_2(tfa)_4$ (80.0 mg, 0.12 mmol, 0.008 equiv) was added. The reaction turned dark brown and bubbling continued for 15-20 minutes. The mixture was filtered though a sand/SiO_2/sand plug using CH_2Cl_2 and then ethyl acetate/hexanes (30%) as the eluent. After concentration, the reaction was purified *via* flash chromatography (20% ethyl acetate/hexanes eluent). The first compound to elute was α-chloro ketone **56**, isolated as a yellow solid (830 mg, 20% yield). The second compound to elute was ketone **50**, obtained after evaporation for the solvent *in vacuo* as a yellow solid (1.47 g, 41% yield). The final compound to elute was spirocycle **58** in trace amounts.

Data for these products may be found in previous procedures.

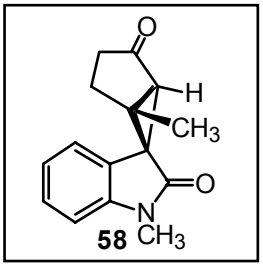
Preparation of α-Bromo Ketone 74, Ketone 50, and Spirocycle 58.



74



50



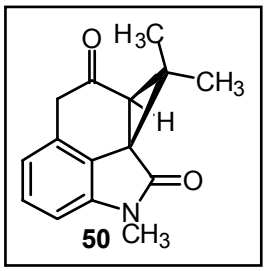
58

α-Bromo Ketone 74, Ketone 50, and Spirocycle 58. Diazoketone **51** (500 mg, 1.86 mmol, 1.0 equiv) and $MgBr_2$•OEt_2 (500 mg, 1.94 mmol, 1.0 equiv) were stirred in CH_2Cl_2 (250 mL) for 5 minutes at rt. $Rh_2(tfa)_4$ (25 mg, 0.04 mmol, 0.02 equiv) was added as a solution in CH_2Cl_2 (2.5 mL). After nitrogen evolution ceased (ca. 15 minutes), the reaction was filtered through celite, adsorbed onto SiO_2, and subjected to flash chromatography (20% EtOAc/hexanes eluent) to provide α-bromoketone **74** as a yellow solid (66.7 mg, 11.2% yield) and ketone **50** as a yellow solid (200 mg, 45% yield). Trace amounts of spirocycle **58** were observed in the fractions following ketone **50**.

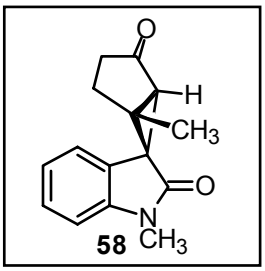
74: m.p. 139-140 °C; IR (thin film/NaCl) 3053 (w), 2933 (br w), 1701 (s), 1611 (m), 1492 (m), 1470 (m), 1420 (m), 1375 (m), 1349 (m), 1268 (m), 1180 (w), 1142 (m), 1096 (m), 1072 (m), 1027 (w), 913 (w), 834 (w), 789 (w), 753 (m), 734 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 7.6 Hz, 1H), 7.31 (t, *J* = 7.6 Hz, 1H), 7.08 (t, *J* = 7.5 Hz, 1H), 6.91 (d, *J* = 7.7 Hz, 1H), 4.03 (d, *J* = 12.6 Hz, 1H), 3.90 (d, *J* = 12.7 Hz, 1H), 3.28 (s, 3H), 3.16 (s, 1H), 1.65 (s, 3H), 1.56 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.5, 173.9, 144.5, 127.9, 126.6, 124.7, 122.3, 108.4, 45.8, 45.7, 38.4, 36.9, 27.0, 20.9, 17.1; HRMS (EI) *m/z* 321.0368 [calc'd for $C_{15}H_{16}NO_2Br$ (M+) 321.0364].

Data for ketone **50** and spirocycle **58** can be found in above procedures.

Preparation of Ketone 50 and Spirocycle 58: An Improved Aryl C-H Insertion Reaction.[40]



50

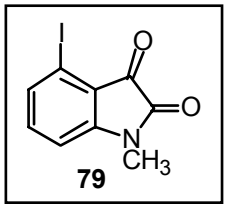


58

Ketone 50 and Spirocycle 58. Montmorillonite K10 (10 g) which had been previously microwaved until no traces of water were seen was flamed dried under vacuum for 10 minutes, cooled to rt and then suspended in CH_2Cl_2 (100 mL). The vigorously stirred suspension was treated with $Rh_2(tfa)_4$ (10 mg, 0.02 mmol, 0.005 equiv) followed by a solution of α-diazo ketone **51** (1.0 g, 3.72 mmol, 1.0 equiv) in CH_2Cl_2 (40 mL) (added over a 45 minute period *via* an addition funnel). Immediately after addition, the reaction mixture was filtered through a pad of celite topped with a thin layer of silica gel. The filter pad was washed with EtOAc (500 mL) and MeOH (50 mL). The filtrate was concentrated and the crude material purified by silica gel column chromatography (3:1 hexanes:EtOAc eluent) to afford cyclohexanone **50** as a yellow solid (512 mg, 57% yield) and spirocycle **58** as an off-white solid (45 mg, 5% yield).

Data for these products are listed under the initial procedures reported for the C-H insertion reaction.

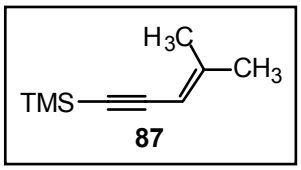
Preparation of *N*-Me-4-Iodoisatin (79).



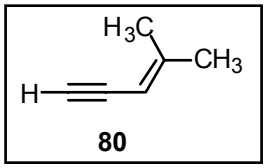
79

***N*-Me-4-Iodoisatin (79).** To a solution of 4-iodoisatin (**76**) (2.56 g, 9.40 mmol, 1.0 equiv, prepared as reported by Paquette, see ref. 23) in THF (190 mL) was added iodomethane (5.8 mL, 93.8 mmol, 10 equiv), finely ground potassium hydroxide (6.30 g, 113 mmol, 12 equiv), and tetrabutylammonium bromide (606 mg, 1.88 mmol, 0.2 equiv). After stirring for 3 hours, the solvent was removed under reduced pressure, and the residue was dissolved in H_2O (75 mL) and 1N NaOH (10 mL). After filtering the insoluble residue, the solution was cooled to 0 °C and was acidified with glacial acetic acid which resulted in the precipitation of *N*-Me-4-iodoisatin (**79**) as an orange solid (2.48 g, 92% yield), which in solution exists in the hydrate form: m.p. 176-179 °C; IR (thin film/NaCl) 1729 (s), 1591 (s), 1573 (s), 1448 (m), 1347 (w), 1310 (w), 1206 (w), 1163 (w), 1108 (w), 1038 (w), 863 (w), 783 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, J = 8.0 Hz, 1H), 7.25 (t, J = 8.4 Hz, 1H), 6.88 (d, J = 7.6 Hz, 1H), 3.26 (s, 3H), 1.60 (br s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 182.0, 157.8, 153.8, 138.4, 135.4, 119.5, 109.8, 93.2, 26.4; HRMS (EI) *m/z* 286.9438 [calc'd for $C_9H_6INO_2$(M+) 286.9443].

Preparation of TMS-Protected Ene-yne 87 and 2-Me-pent-2-ene-4-yne (80).



87

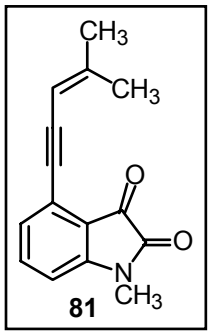


80

TMS-Protected Ene-yne 87. To a degassed solution of benzene (296 mL) and Et_2NH (30.7 mL, 296 mmol, 4.0 equiv) was added degassed 1-bromo-2-methylpropene (15.2 mL, 74 mmol, 1.0 equiv). After cooling to 10 °C and protecting from light with aluminum foil, the reaction was treated with $(Ph_3P)_2Pd(Cl)_2$ (2.30 g, 3.70 mmol, 0.05 equiv) and CuI (2.82 g, 14.8 mmol, 0.2 equiv) at which point the reaction turned red. A solution of (trimethylsilyl)acetylene (10.5 mL, 74 mmol, 1.0 equiv) in benzene (9.25 mL) was added *via* syringe and the resulting black reaction was stirred 1.5 hours while warming to rt. The reaction was poured into NH_4Cl (260 mL), diluted with hexanes (70 mL), and the organic layer washed with NH_4Cl (2 x 50 mL) and brine (50 mL). The organic layer was concentrated and purified *via* flash chromatography (100% hexanes eluent) to provide TMS-protected ene-yne **87** as a pale yellow oil (14.7 g, 72% yield).[41]

2-Me-pent-2-ene-4-yne (80). To a solution of ene-yne **87** (20.8 g, 136.8 mmol, 1.0 equiv) in DMSO (40 mL) was added potassium fluoride dihydrate (38.6 g, 410 mmol, 3.0 equiv). After stirring overnight, the reaction was distilled (63 - 68 °C, 720 mmHg) to provide the deprotected ene-yne **80** as a clear colorless oil (5.0 g, 46% yield), which correlated in all respects with NMR data provided in the literature.[42]

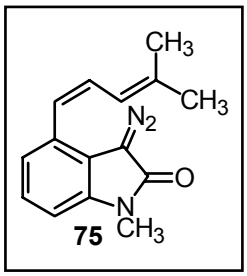
Preparation of Ene-yne 81.



81

Ene-yne 81. To a degassed solution of Et_3N (1.90 mL, 13.5 mmol, 3.0 equiv) in benzene (70 mL) was added *N*-Me-4-iodoisatin (1.30 g, 4.50 mmol, 1.0 equiv) and 4-Me-pent-3-ene-1-yne (**80**) (1.40 mL, 13.2 mmol, 2.9 equiv) and the resulting mixture was cooled to 10 °C. The solution was protected from light using aluminum foil, and was then treated with CuI (0.17 g, 0.90 mmol, 0.2 equiv) followed by $Pd(PPh_3)_4$ (0.26g, 0.22 mmol, 0.05 equiv). After stirring for 45 minutes (10 °C - rt), concentration and purification by flash chromatography (30 - 50% EtOAc/hexanes eluent) provided ene-yne **81** as an orange solid (1.05 g, 98% yield): m.p. 170-171 °C (MeOH); IR (thin film/NaCl) 3069 (w), 2939 (w), 2907 (w), 2194 (m), 1736 (s), 1594 (s), 1486 (w), 1451 (m), 1361 (m), 1337 (m), 1307 (m), 1202 (w), 1160 (m), 1057 (w), 878 (w), 795 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.46 (t, *J* = 7.9 Hz, 1H), 7.07 (d, *J* = 7.9 Hz, 1H), 6.75 (d, *J* = 7.8 Hz, 1H), 5.55 (s, 1H), 3.23 (s, 3H), 2.17 (s, 3H), 1.91 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 181.0, 158.1, 154.3, 151.1, 137.1, 127.3, 122.8, 116.5, 108.3, 104.9, 97.3, 88.0, 26.1, 25.3, 21.4; HRMS (EI) *m/z* 239.0952 [calc'd for $C_{15}H_{13}NO_2$(M+) 239.0946].

Preparation of Diene 75.



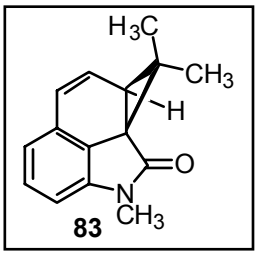
75

Diene 75. A solution of ene-yne **81** (5.00 g, 20.9 mmol, 1.0 equiv) in toluene (300 mL) was treated with tributyltin hydride (16.9 mL, 62.8 mmol, 3.0 equiv) followed by AIBN (69 mg, 0.42 mmol, 0.02 equiv) and the reaction was heated to reflux for 3.5 hours. After cooling to rt, most of the toluene was removed under reduced pressure, and the remaining solution (ca. 20 mL) was filtered through a plug of SiO_2. Removal of the solvent provided vinyltin intermediate **82** as a red oil (7.05g) which was used in the next step without further purification: HRMS (CI) *m/z* 532.2224 [calc'd for $C_{27}H_{42}NO_2Sn$(M+1) 532.2236].

The derived red oil was dissolved in THF (209 mL), and *p*-toluenesulfonhydrazide (3.90 g, 20.9 mmol, 1.0 equiv) followed by conc. HCl (5 drops) were added. The reaction was refluxed for 45 minutes, cooled to rt and concentrated. The resulting residue was dissolved in 2N NaOH (209 mL) and stirred at rt for 3 hours. EtOAc (75 mL) was added and the layers were separated. The aqueous layer was extracted with EtOAc (3 x 25 mL), and the combined organic layers were washed with brine (2 x 25 mL), dried over Na_2SO_4 and subjected to flash chromatography (30% EtOAc/hexanes eluent) to provide diazo ketone **75** as a yellow solid (2.00 g, 38% yield, 3 steps): m.p. >110 °C

(dec); IR (thin film/NaCl) 2934 (w), 2092 (s), 1681 (m), 1646 (w), 1588 (w), 1454 (w), 1391 (m), 1359 (w), 1286 (m), 1205 (w), 1049 (m), 790 (w), 756 (w), 739 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.18 (t, *J* = 7.8 Hz, 1H), 6.94 (d, *J* = 7.8 Hz, 1H), 6.80 (d, *J* = 7.8 Hz, 1H), 6.55 (t, *J* = 11.4 Hz, 1H), 6.29 (d, *J* = 11.3 Hz, 1H), 6.02 (dd, *J* = 1.2, 11.5 Hz, 1H), 3.33 (s, 3H), 1.83 (s, 3H), 1.77 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.6, 140.0, 134.4, 129.9, 129.1, 124.9, 122.9, 121.7, 120.8, 114.1, 106.9, 26.8, 26.3, 18.4; HRMS (EI) *m/z* 253.1217 [calc'd for $C_{15}H_{15}N_3O$ (M+) 253.1215].

Preparation of Olefin 83.

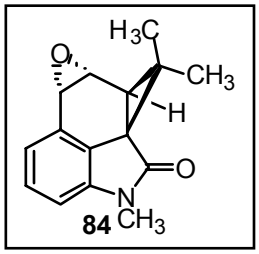


83

Olefin 83. Diazoketone **75** (22 mg, 0.09 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (2 mL) in a vial and $Rh_2(OAc)_4$ (1.0 mg, 0.002 mmol, 0.02 equiv) was added. The vial was sealed and placed in a sand bath (150 °C) and heated for 5 minutes. After cooling to rt and adsorbing the reaction onto silica gel, the reaction was purified *via* flash chromatography (20% EtOAc/hexanes eluent) which furnished olefin **83** as a yellow solid (16 mg, 78% yield). Recrystallization from MeOH provided an analytical sample: m.p. 164-165 °C (MeOH); IR (thin film/NaCl) 2946 (w), 2925 (w), 1698 (s), 1625 (w), 1607 (m), 1567 (w), 1469 (m), 1372 (w), 1339 (w), 1293 (m), 1019 (m), 819 (w), 783 (w), 771 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.25 (t, *J* = 7.7 Hz, 1H), 6.93 (d, *J* = 7.8 Hz, 1H), 6.82

(d, *J* = 7.6 Hz, 1H), 6.65 (d, *J* = 9.8 Hz, 1H), 6.07 (dd, *J* = 4.9, 9.7 Hz, 1H), 3.27 (s, 3H), 2.91 (d, *J* = 5.0 Hz, 1H), 1.23 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.6, 142.4, 129.2, 126.8, 125.1, 124.6, 122.9, 118.8, 106.5, 42.9, 42.0, 26.4, 20.9, 18.0 (br); HRMS (EI) *m/z* 225.1149 [calc'd for $C_{15}H_{15}NO$ (M+) 225.1154].

Preparation of Epoxide 84.

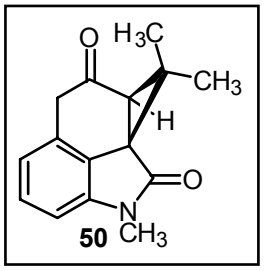


84

Epoxide 84. To a solution of olefin **83** (114 mg, 0.51 mmol, 1.0 equiv) in $CHCl_3$ (5 mL) at 0 °C was added at once 85% *m*-CPBA (206 mg, 1.01 mmol, 2.0 equiv). The reaction was stirred for 16 hours with warming to rt, at which time the $CHCl_3$ solution was washed with cold 5% NaOH (3 x 5 mL) and brine (2 x 5 mL). The combined aqueous layers were extracted with CH_2Cl_2 (3 x 5 mL), and the organic layers were dried (Na_2SO_4) and concentrated. Flash chromatography (30% EtOAc/hexanes eluent) provided recovered olefin **83** (28 mg) and epoxide **84** as a white solid (57 mg, 47% yield, 62% based on recovered starting material): m.p. 139-140 °C (dec); IR (thin film/NaCl) 2951 (w), 2926 (w), 2880 (w), 1704 (s), 1623 (w), 1606 (m), 1481 (m), 1424 (w), 1399 (m), 1370 (w), 1332 (m), 1289 (m), 1154 (w), 1105 (w), 1080 (w), 1024 (m), 1006 (m), 841 (m), 762 (m) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (t, *J* = 7.9 Hz, 1H), 7.08 (d, *J* = 7.8 Hz, 1H), 6.78 (d, *J* = 8.1 Hz, 1H), 3.81 (dd, *J* = 1.8, 4.0 Hz, 1H), 3.76 (d, *J* = 4.0 Hz, 1H), 3.20 (s, 3H), 2.75 (d, *J* = 1.6 Hz, 1H), 1.56 (s, 3H), 1.37 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.0, 143.6, 127.9, 127.4, 126.0, 121.8, 108.2, 56.8,

51.7, 37.3, 36.3, 35.2, 26.6, 20.8, 17.1; HRMS (EI) *m/z* 241.1107 [calc'd for $C_{15}H_{15}NO_2$ (M+) 241.1103].

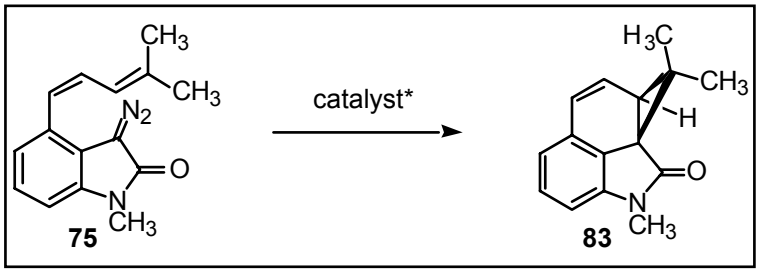
Preparation of Ketone 50.



50

Ketone 50. To epoxide **84** (10 mg, 0.04 mmol) in $CHCl_3$ (2 mL) were added acidic Amberlyst beads (ca. 10 beads, Amberlyst 15 ion exchange resin, strongly acidic) and the reaction was stirred for 1 hour, at which time crude NMR showed complete conversion of epoxide **84** to ketone **50**. After filtering through a plug of silica gel using 30% EtOAc/hexanes as eluent, ketone **50** was obtained as a yellow solid (9 mg, 90% yield). Data for ketone **50** can be found in a previous procedure.

Preparation of Olefin 83: Attempts at Asymmetric Catalysis.



75 **83**

Doyle dirhodium catalyst, Rh_2(5R-MEPY)$_4$: To diazo compond **75** (100 mg, 0.40 mmol, 1.0 equiv) in hexanes (40 mL) was added Rh_2(5R-MEPY)$_4$ (3 mg, 0.004 mmol, 0.01 equiv) and the reaction was heated to reflux for 24 hours. The mixture was cooled and the solvent was removed *in vacuo*. Flash chromatography (20% EtOAc/hexanes eluent) provided olefin **83** (58 mg, 64% yield) which did not rotate plane-polarized light.

Rh_2(S-DOSP)$_4$: Diazo compound **75** (50 mg, 0.20 mmol, 1.0 equiv) in CH_2Cl_2 was treated with Rh_2(S-DOSP)$_4$ (4 mg, 0.002 mmol, 0.01 equiv, commercially available from Aldrich) and the reaction was stirred for 15 minutes. After cooling, the reaction was subjected to flash chromatography (20% EtOAc/hexanes eluent) to provide olefin **83** (11.0 mg, 24% yield) which did not rotate plane-polarized light.

Rh_2(S-TBSP)$_4$: A solution of diazo ketone **75** (100 mg, 0.40 mmol, 1.0 equiv) in pentane (20 mL) was slowly added *via* syringe pump over 4 hours to a solution of Rh_2(S-TBSP)$_4$ (5 mg, 0.004 mmol, 0.01 equiv, commercially available from Aldrich) in pentane (20 mL). The reaction was then stirred for 16 hours when it was concentrated and purified by flash chromatography (20% EtOAc/hexanes eluent) to furnish a racemic mixture of olefin **83** (13 mg, 14% yield).

Cu(I)bis-oxazoline complex 84: Diazo compond **75** (100 mg, 0.40 mmol, 1.0 equiv) in CH_2Cl_2 (39.5 mL) was slowly added over 12 hours *via* syringe pump to a solution of Cu(I)bis-oxazoline complex **85** (0.72 mL, 0.004 mmol, 0.1 equiv, prepared as ref. 33) and the reaction was stirred for an additional 24 hours. At this time, the reaction was complete as visualized by TLC

analysis and concentration followed by purification *via* flash chromatography (20% EtOAc/hexanes eluent) provided olefin **83** (42 mg, 47% yield) which did not rotate plane-polarized light.

(Pybox)$RuCl_2$(ethene): A solution of (pybox)$RuCl_2$(ethene) (11.0 mg, 0.02 mmol, 0.05 equiv, prepared as ref. 29) in benzene (30 mL) containing molecular sieves was degassed for 1 hour by bubbling a stream of nitrogen through the reaction and then was brought to reflux. A solution of diazo lactam **75** (100 mg, 0.04 mmol, 1.0 equiv) in benzene (20 mL) was added dropwise over 5 hours *via* syringe pump and the reaction was allowed to reflux for an additional 3 hours. After cooling and removal of the solvent under reduced pressure, the reaction was purified by flash chromatography (20% EtOAc/hexanes eluent) to furnish olefin **83** as a yellow solid (30 mg, 33% yield) which did not rotate plane-polarized light.

2.7 Notes and References.

(1) a) Muratake, H.; Natsume, M. *Tetrahdron* **1990**, *46*, 6331. b) Harrington, P. J.; Hegedus, L. S.; McDaniel, K. F. *J. Am. Chem. Soc.* **1987**, *109*, 4335. c) Kozikowski, A. P.; Chen, Y. Y.; *J. Org. Chem.* **1981**, *46*, 5248.

(2) For an example of converting a similar bridgehead, benzylic acid (derived from an ester) to an amine *via* Curtius rearrangement, see Campiani, G.; Sun, L-.Q.; Kozikowski, A. P.; Aagaard, P.; McKinney, M. *J. Org. Chem.* **1993**, *58*, 7660.

([3]) The transformation of a ketone to a vinyl chloride is well precedented: a) Fleming, I.: Pearce, A. *J. Chem. Soc. Perkin Trans. 1* **1980**, 2485. b) Paukstelis, J. V.; Macharia, B. W. *J. Org. Chem.* **1973**, *38*, 646.

([4]) a) Taber, D. F.; Petty, E. H. *J. Org. Chem*. **1982**, *47*, 4808. b)Taber, D. F. Ruckle, R E. *Tetrahedron Lett.* **1985**, *26*, 3059. c) Wenkert, E.; Davis, L. L.; Mylari, B L.; Solomon, M F.; daSilva, R R.; Shulman, S.; Warnet, R. J.; Ceccherelli, P.; Curini, M; Pellicciari, R. *J. Org. Chem.*, **1982**, *47*, 3242.

([5]) However, C-H insertions into methyl groups are reported to be the least facile C-H insertion reactions. Taber, D. F. Ruckle, R E. *J. Am. Chem. Soc.* **1985**, *108*, 7686.

([6]) For the formation of the dianion of oxindole with EtMgBr, see: Brenner, M. Synthese von Arcyriacyanin A, N-Methylarcyroxocin A und weiterer Bisindolylmaleinimide, Ph.D. dissertation, Bonn, 1990, p 88.

([7]) Davies, H.M.L.; Matasi, J.J.; Ahmed, G. *J. Org. Chem.* **1996**, *61*, 2305.

([8]) See Scheme 2.4.3 for more details

([9]) Enoate **53** has previously been prepared by heating isatin and ethyl triphenylphosphoranylidene acetate in acetic acid for 4 hours, which produced the enoate in only 69% yield; see Brandman, H.A. *J. Heterocyclic Chem*. **1973**, *10*, 383.

([10]) a) Grieco, P.A.; Finkelhor, R.S. *Tetrahedron Lett*. **1972**, *36*, 3781. b) Krief, A.; Lecomte, P. *Tetrahedron Lett*. **1993**, *34*, 2695.

([11]) In this procedure an excess of iodomethane is used to react with triphenylphosphine produced during the cyclopropanation to form a salt which can conveniently be filtered.

([12]) a) Ye, T.; McKervey, M.A. *Chem Rev.* **1994**, *94*, 1091. b) Aoyama, T.; Shiori, T. *Tetrahedron Lett*. **1980**, *21,* 4461.

([13]) In the early stages of this project, the reaction was chromatographed to separate α-chloro ketone **56**. However, more recently, this mixture has been taken on crude into the next steps. See sections 2.6.2 and 3.4.2 for older and more recent procedures, respectvely.

([14]) For leading references relevant to the C-H insertion chemistry of **51**, see: a) Ye, T.; McKervey, M. A. *Chem. Rev.* **1994**, *94*, 1091. b) Wenkert, E.; Liu, S. *Synthesis* **1992**, 323. c) Taber, D. F.; Petty, E. H. *J. Org. Chem.* **1982**, *47*, 4808.

([15]) Typical procedure for screening Rh^{2+} catalysts: To a solution of α-diazo ketone **51** (50 mg, 0.19 mmol, 1.0 equiv) in CH_2Cl_2 (3 mL) was added the rhodium catalyst (0.01 equiv) and the reaction was stirred until nitrogen evolution ceased and starting material was not observed by TLC analysis. After concentration, the reaction was adsorbed onto silica gel and purified *via* flash chromatography (30 % EtOAc/hexanes eluent) to provide

mixtures of products as reported in Table 2.4.1. The analytical data for these products can be found in Section 2.6.2.

([16]) The ring-opening of norcaradiene intermediates to cycloheptatrienes is a well-documented event: a) Manitto, P.; Monti, D.; Speranza, G. *J. Org. Chem. Soc*. **1995**, *60*, 484. b) Kennedy, M.; McKervey, M. A.; Maguire, A. R.; Tuladhar, S. M.; Twohig, M. F. *J. Chem. Soc. Perkin Trans. 1* **1990**, 1047, and references therein.

([17]) For an example of a Lewis acid, namely $Sc(OTf)_3$, modulating the reactivity of a rhodium carbenoid, see: Prein, M.; Padwa, A. *Tetrahedron Lett*. **1996**, *37*, 6981.

([18]) Padwa, A.; Austin, D. J.; Hornbuckle, S F.; Semones, M. A.; Doyle, M. P.; Protopopova, M. N. *J. Am. Chem. Soc*. **1992**, *114*, 1874.

([19]) McKervey, M. A.; Tuladhar, S. M.; Twohig, M. F. *J. Chem. Soc. Chem. Commun*. **1984**, 129.

([20]) General procedure for screening Lewis acids in the aryl C-H insertion reaction: To α-diazo ketone **50** (ca. 3-5 mg) in CH_2Cl_2 (1 mL) in a vial was added the Lewis acid followed by $Rh_2(tfa)_4$. After bubbling ceased (ca. 1 minute), the reaction was analyzed *via* TLC analysis and compared to a TLC sample of the desired product **50**.

([21]) Cornelis, A.; Laszlo, P.; Wang, S. *Tetrahedron Lett.* **1993**, *34*, 3849.

(22) Montmorillonite K10 also suppresses the formation of cycloheptatrienes in the aryl C-H insertions of α-diazo esters. These results will be published elsewhere.

(23) Wood, J. L.; Holubec, A. A.; Stoltz, B. M.; Weiss, M. M.; Dixon, J. A.; Doan, B. D.; Shamji, M. F.; Chen, J. M.; Heffron, T. P. *J. Am. Chem. Soc.*, **1999**, *121*, 6326.

(24) For the preparation of 4-iodoisatin, see: Snow, R. A.; Denise, M. C.; Paquette, L. A. *J. Am. Chem. Soc.* **1977**, *99*, 3734.

(25) Ene-yne **80** was obtained *via* Sonigashira coupling of 1-bromo-2-methylpropene and trimethylsilyl acetylene followed by deprotection. For the Sonigashira procedure, see: Porco, J. A., Jr. Studies Toward the Synthesis of the Enediyne Antibiotics Ph.D. Dissertation, Harvard University, 1992.

(26) The diazotization procedure followed was similar to the Bamford-Stevens diazotization of isatin: Cava, M. P.; Litle, R. L.; Napier, D. R. *J. Am. Chem. Soc.*, **1958**, *80*, 2257.

(27) This reaction can be performed without the use of a sealed tube in CH_2Cl_2 at reflux, however, in slightly lower yields (ca. 60%).

([28]) Other catalysts that effected the desired cyclopropanation, although in lower yields, were $Rh_2(cap)_4$, $CuSO_4$, and Cu powder.

([29]) For the epoxidation and rearrangement of a similar benzylic olefin see Nichols, D. E.; Robinson, J. M.; Li, G. S.; Cassady, J. M.; Floss, H. G. *Org. Prep. and Procedures Int.* **1977**, *9*, 277.

([30]) For a comparison of several catalysts employed in asymmetric intramolecular cyclopropanation, see Doyle, M. P.; Peterson, C. S.; Zhou, Q. L.; Nishiyama, H. *J. Chem. Soc., Chem. Comm.* **1997**, 211. For a review on catalytic enantioselective cyclopropanation see Singh, V. K.; DattaGupta, A.; Sekar, G. *Synthesis* **1996**, 137.

([31]) For the preparation of this catalyst, see Bennett, M. A.; Smith, A. K. *J. Chem. Soc. Dalton* **1974**, 233. For experimental procedures for the use of this catalyst in cyclopropanation reactions, see Nishiyama, H.; Itoh, Y.; Sugawara, Y.; Matsumoto, H. *Bull. Chem. Soc. Jpn*. **1995**, *68*, 1247 and Nishiyama, H.; Itoh, Y.; Matsumoto, H.; Park, S. B.; Itoh, K. *J. Am. Chem. Soc.* **1994**, *116*, 2223.

([32]) Davies, H. M. L.; Bruzinski, P. R.; Lake, D. H.; Kong, N.; Fall, M. *J. Am. Chem. Soc.* **1996**, *118*, 6897.

([33]) Davies, H. M. L.; Kong, N. *Tetrahedron Lett*. **1997**, *38*, 4203.

([34]) Doyle, M. P.; Winchester, W. R.; Hoorn, A. A.; Lynch, V.; Simonsen, S. H.; Ghosh, R. *J. Am. Chem. Soc.* **1993**, *115*, 9968.

([35]) Evans, D. A.; Woerpel, K. A.; Hinman, M. M.; Faul, M. M. *J. Am. Chem. Soc.* **1991**, *113*, 726.

([36]) Optical rotations of olefin **83** were measured and showed no rotations or very minute rotions. In the cases of slight rotations, the olefin was epoxidized, rearranged, reduced and Mosher ester analysis was performed, to yield 1:1 mixtures of diastereomers (i.e., no enantiomeric excess was observed).

([37]) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

([38]) Ritchie, R.; Saxton, J. E. *J. Chem. Res. Miniprint* **1990**, *2*, 528.

([39]) For the preparation of *p*-ABSA, see ref. 7.

([40]) Later in the synthesis, ketone **50** was prepared from crude α-diazo ketone **51** and advanced without purification, see Section 3.4.2 for experimental procedures.

([41]) Rossi, R.; Bellina, F.; Biagetti, M. *Synth. Comm*. **1999**, *29*, 3415.

([42]) Hollingworth, G. J.; Richecoeur, A. M. E.; Sweeny, J. *J. Chem. Soc. Perkin Trans. 1* **1996** *23*, 2833.

APPENDIX ONE: SPECTRA RELEVANT TO CHAPTER TWO

Figure A.1.1

Figure A.1.2 Infrared Spectrum (thin film/NaCl) of compound **44**.

Figure A.1.3 ^{13}C NMR (100 MHz, $CDCl_3$) of compound **44**.

Figure A.1.4

Figure A.1.5 Infrared Spectrum (thin film/NaCl) of compound **45**.

Figure A.1.6 ^{13}C NMR (100 MHz, $CDCl_3$) of compound **45**.

Figure A.1.7

Figure A.1.8 Infrared Spectrum (thin film/NaCl) of compound **46**.

Figure A.1.9 ^{13}C NMR (100 MHz, $CDCl_3$) of compound **46**.

Figure A.1.10

Figure A.1.11 Infrared Spectrum (thin film/NaCl) of compound **47**.

Figure A.1.12 ^{13}C NMR (100 MHz, $CDCl_3$) of compound **47**.

Figure A.1.13

Figure A.1.14 Infrared Spectrum (thin film/NaCl) of compound **54**.

Figure A.1.15 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **54**.

Figure A.1.16

Figure A.1.17 Infrared Spectrum (KBr pellet) of compound **55**.

Figure A.1.18 ^{13}C NMR (125 MHz, DMSO-d_6) of compound **55**.

Figure A.1.19

Figure A.1.20 Infrared Spectrum (thin film/NaCl) of compound **51**.

Figure A.1.21 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **51**.

Figure A.1.22

Figure A.1.23 Infrared Spectrum (thin film/NaCl) of compound **56**.

Figure A.1.24 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **56**.

Figure A.1.25

Figure A.1.26 Infrared Spectrum (thin film/NaCl) of compound **50**.

Figure A.1.27 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **50**.

Figure A.1.28

Figure A.1.29 Infrared Spectrum (thin film/NaCl) of compound **57**.

Figure A.1.30 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **57**.

Figure A.1.31

Figure A.1.32 Infrared Spectrum (thin film/NaCl) of compound **58**.

Figure A.1.33 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **58**.

Figure A.1.34

Figure A.1.35 Infrared Spectrum (thin film/NaCl) of compound **59**.

Figure A.1.36 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **59**.

Figure A.1.37

Figure A.1.38 Infrared Spectrum (thin film/NaCl) of compound **60**.

Figure A.1.39 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **60**.

Figure A.1.40

Figure A.1.41 Infrared Spectrum (thin film/NaCl) of compound **61**.

Figure A.1.42 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **61**.

Figure A.1.43

Figure A.1.44 Infrared Spectrum (thin film/NaCl) of compound **74**.

Figure A.1.45 ^{13}C NMR (100 MHz, $CDCl_3$) of compound **74**.

Figure A.1.46

Figure A.1.47 Infrared Spectrum (thin film/NaCl) of compound **79**.

Figure A.1.48 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **79**.

Figure A.1.49

Figure A.1.50 Infrared Spectrum (thin film/NaCl) of compound **81**.

Figure A.1.51 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **81**.

Figure A.1.52

Figure A.1.53 Infrared Spectrum (thin film/NaCl) of compound **75**.

Figure A.1.54 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **75**.

Figure A.1.55

Figure A.1.56 Infrared Spectrum (thin film/NaCl) of compound **83**.

Figure A.1.57 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **83**.

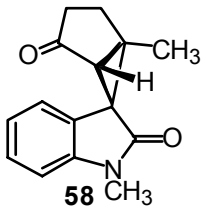
Figure A.1.58

Figure A.1.59 Infrared Spectrum (thin film/NaCl) of compound **84**.

Figure A.1.60 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **84**.

APPENDIX TWO: X-RAY CRYSTALLOGRAPHY REPORTS RELEVANT TO CHAPTER TWO

X-RAY CRYSTALLOGRAPHY REPORT FOR SPIROCYCLE 58



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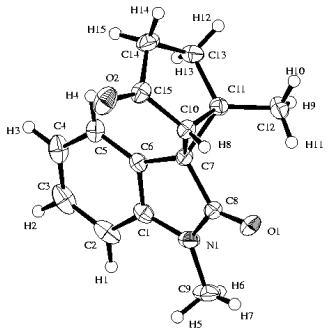


A. Crystal Data

Empirical Formula	$C_{15}H_{15}NO_2$
Formula Weight	241.29
Crystal Color, Habit	colorless, prism
Crystal Dimensions	0.21 X 0.38 X 0.40 mm
Crystal System	monoclinic
Lattice Parameters	a = 7.282(1)Å
	b = 16.256(1) Å
	c = 10.196(1) Å
	β = 91.46(1)o
	V = 1206.6(2) Å3
Space Group	$P2_1/c$ (#14)
Z value	4
Dcalc	1.328 g/cm^3
F000	512.00
μ(MoKα)	0.88 cm^{-1}

B. Intensity Measurements

Diffractometer	Nonius KappaCCD
Radiation	MoKα (λ = 0.71069 Å)
	graphite monochromated
Crystal to Detector Distance	35 mm
Temperature	23.0°C
Scan Type	ω
Scan Rate	60s/frame

Scan Width	1°/frame
2θmax	52.7°
No. of Reflections Measured	Total: 2439
Corrections	Lorentz-polarization

C. Structure Solution and Refinement

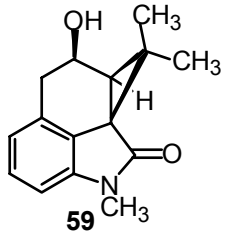
Structure Solution	Direct Methods (SIR92)
Refinement	Full-matrix least-squares
Function Minimized	Σ w (|Fo| - |Fc|)^2
Least Squares Weights	$1/\sigma^2(Fo) = 4Fo^2/\sigma^2(Fo^2)$
p-factor	0.0100
Anomalous Dispersion	All non-hydrogen atoms
No. Observations (I>3.00σ(I))	1988
No. Variables	163
Reflection/Parameter Ratio	12.20
Residuals: R; Rw	0.044 ; 0.068
Goodness of Fit Indicator	4.05
Max Shift/Error in Final Cycle	0.00
Maximum peak in Final Diff. Map	0.21 e-/Å3
Minimum peak in Final Diff. Map	-0.15 e-/Å3

Atomic coordinates and B_{iso}/B_{eq} for Spirocycle 58

atom	x	y	z	Beq
O(1)	0.2481(1)	-0.19964(6)	0.49693(8)	3.49(2)
O(2)	0.6122(1)	-0.11788(7)	0.0967(1)	4.23(3)
N(1)	0.2374(1)	-0.06022(7)	0.5318(1)	2.68(2)
C(1)	0.2605(2)	0.01112(8)	0.4567(1)	2.51(3)
C(2)	0.2722(2)	0.09138(9)	0.5008(2)	3.52(3)
C(3)	0.3000(2)	0.15271(9)	0.4083(2)	4.10(4)
C(4)	0.3146(2)	0.13388(8)	0.2770(2)	3.57(3)

C(5)	0.3038(2)	0.05275(7)	0.2339(1)	2.73(3)
C(6)	0.2774(1)	-0.00961(7)	0.3240(1)	2.19(2)
C(7)	0.2595(2)	-0.10055(7)	0.3155(1)	2.11(2)
C(8)	0.2476(2)	-0.12924(8)	0.4559(1)	2.45(3)
C(9)	0.2169(2)	-0.0622(1)	0.6727(1)	3.82(4)
C(10	0.3580(2)	-0.16107(7)	0.2261(1)	2.31(3)
C(11)	0.1545(2)	-0.15079(7)	0.2095(1)	2.32(3)
C(12)	0.0158(2)	-0.21498(8)	0.2453(1)	3.04(3)
C(13)	0.1165(2)	-0.10457(9)	0.0815(1)	3.04(3)
C(14)	0.3007(2)	-0.09830(9)	0.0117(1)	3.24(3)
C(15)	0.4482(2)	-0.12383(8)	0.1106(1)	2.76(3)
H(1)	0.2615	0.1042	0.5912	4.2264
H(2)	0.3091	0.2084	0.4360	4.9256
H(3)	0.3323	0.1768	0.2153	4.2832
H(4)	0.3144	0.0402	0.1434	3.2819
H(5)	0.3121	-0.0309	0.7139	4.5815
H(6)	0.1011	-0.0396	0.6941	4.5815
H(7)	0.2238	-0.1175	0.7026	4.5815
H(8)	0.4054	-0.2109	0.2621	2.7779
H(9)	-0.1010	-0.1898	0.2542	3.6446
H(1)	0.0084	-0.2556	0.1783	3.6446
H(11)	0.0522	-0.2401	0.3259	3.6446
H(12)	0.0297	-0.1339	0.0283	3.6492
H(13)	0.0704	-0.0512	0.0992	3.6492
H(14)	0.3009	-0.1340	-0.0621	3.8831
H(15)	0.3210	-0.0434	-0.0163	3.8831

X-RAY CRYSTALLOGRAPHY REPORT FOR ALCOHOL 59



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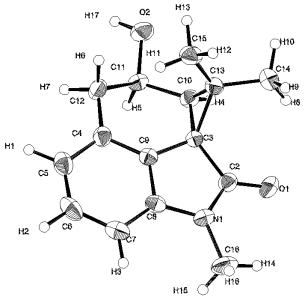


A. Crystal Data

Empirical Formula	$C_{15}H_{17}NO_2$
Formula Weight	243.30
Crystal Color/Habit	colorless prisms
Crystal Dimensions (mm)	0.21 X 0.39 X 0.48
Crystal System	monoclinic
No. Reflections Used for Unit Cell Determination (2θ range)	25(5.8 - 21.0°)
Omega Scan Peak Width at Half-height	0.19
Lattice Parameters:	a = 8.849 (3)Å b = 16.577 (3)Å c = 9.522 (2)Å β = 115.34 (2)° V = 1262 (1)Å^3
Space Group	$P2_1/c$ (#14)
Z value	4
Dcalc	1.280 g/cm^3
F000	520
μ(MoKα)	0.79 cm-1

B. Intensity Measurements

Diffractometer	Rigaku AFC5S
Radiation	MoKα(λ = 0.71069 Å)
Temperature	23° C

Attenuator	Zr foil (factors: 2.3, 5.2, 11.7)
Take-off Angle	6.0°
Detector Aperture	6.0 mm hor./6.0 mm vert.
Crystal to Detector Distance	285 mm
Scan Type	ω-2θ
Scan Rate	8.0° /min (in omega) (2 rescans)
Scan Width	(1.57 + 0.30 tanθ)°
2θmax	50.0°
No. of Reflections Measured	Total: 2478
Unique:	2323 (R_{int} = 0.031)
Corrections	Lorentz-polarizatin

C. Structure Solution and Refinement

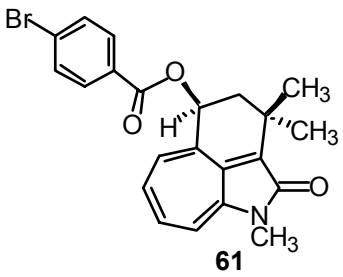
Structure Solution	Direct Methods
Refinement	Full-matrix least-squares
Function Minimized	Σ w (|Fo| - |Fc|)^2
Least-squares Weights	$4Fo^2/\sigma^2(Fo^2)$
p-factor	0.02
Anomalous Dispersion	All non-hydrogen atoms
No. Observations (I>3.00σ(I))	1023
No. Variables	231
Reflection/Parameter Ratio	4.43
Residuals:R; Rw	0.038; 0.040
Goodness of Fit Indicator	1.39
Max Shift/Error in Final Cycle	0.00
Maximum Peak in Final Diff. Map	0.15 e-/Å^3
Minimum Peak in Final Diff. Map	-0.14 e-/Å^3

Positional Parameters and $B_{(eq)}$ for Alcohol 59

atom	x	y	z	B(eq)
O(1)	0.6720(3)	0.2045(2)	0.3462(3)	4.8(1)
O(2)	-0.0150(3)	0.2267(2)	-0.0505(3)	4.7(1)
N(1)	0.5892(3)	0.1282(2)	0.5035(3)	3.5(1)
C(2)	0.5629(4)	0.1688(2)	0.3685(4)	3.4(2)
C(3)	0.3822(4)	0.1562(2)	0.2597(3)	2.8(1)
C(4)	0.1435(4)	0.1136(2)	0.3272(4)	3.4(2)
C(5)	0.1084(5)	0.0818(2)	0.4464(5)	4.4(2)
C(6)	0.2358(6)	0.0590(3)	0.5855(5)	4.9(2)
C(7)	0.4042(6)	0.0693(2)	0.6183(5)	4.3(2)
C(8)	0.4385(4)	0.1007(2)	0.5015(4)	3.2(2)
C(9)	0.3103(4)	0.1184(2)	0.3561(4)	2.8(1)
C(10)	0.2644(4)	0.2075(2)	0.1270(4)	3.0(1)
C(11)	0.0872(4)	0.2172(2)	0.1113(4)	3.4(2)
C(12)	0.0172(4)	0.1485(3)	0.1768(5)	4.0(2)
C(13)	0.3298(4)	0.1324(2)	0.0867(4)	3.1(1)
C(14)	0.4583(6)	0.1452(3)	0.0234(5)	4.8(2)
C(15)	0.2252(6)	0.0575(3)	0.0229(5)	4.2(2)
C(16)	0.7499(5)	0.1245(3)	0.6388(5)	5.2(2)
H(1)	-0.014(4)	0.080(2)	0.428(4)	5.4(9)
H(2)	0.210(4)	0.037(2)	0.666(4)	4.6(8)
H(3)	0.494(4)	0.056(2)	0.718(4)	4.7(8)
H(4)	0.306(4)	0.259(2)	0.104(3)	4.4(8)
H(5)	0.090(3)	0.271(2)	0.178(3)	2.9(7)

H(6)	-0.030(4)	0.108(2)	0.094(3)	3.8(8)
H(7)	-0.079(4)	0.170(2)	0.196(3)	4.1(7)
H(8)	0.533(4)	0.192(2)	0.066(4)	6(1)
H(9)	0.536(4)	0.099(2)	0.048(4)	6(1)
H(10)	0.396(4)	0.149(2)	-0.092(4)	5.6(9)
H(11)	0.176(4)	0.034(2)	0.086(4)	6(1)
H(12)	0.294(4)	0.015(2)	0.010(4)	6(1)
H(13)	0.136(5)	0.066(2)	-0.084(4)	7(1)
H(14)	0.830(6)	0.147(3)	0.611(5)	10(1)
H(15)	0.737(5)	0.144(2)	0.725(5)	7(1)
H(16)	0.792(6)	0.068(3)	0.664(5)	9(1
H(17)	-0.117(5)	0.245(3)	-0.067(4)	7(1)

X-RAY CRYSTALLOGRAPHY REPORT FOR BENZOATE 61



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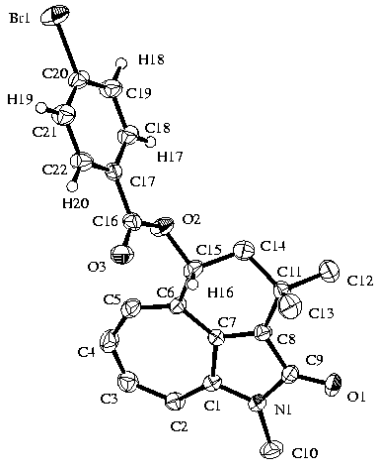


A. Crystal Data

Empirical Formula	$C_{22}H_{20}NO_3Br$
Formula Weight	426.31
Crystal Color, Habit	orange, prisms
Crystal Dimensions	0.15 X 0.23 X 0.29 mm
Crystal System	triclinic
Lattice Type	Primitive
Lattice Parameters	a = 8.1052(3)Å
	b = 9.4180(2) Å
	c = 13.4027(4) Å
	α = 101.220(2)°
	β = 107.306(2)°
	γ = 97.417(2)°
	V = 938.82(6) Å3
Space Group	P_{-1} (#2)
Z value	2
Dcalc	1.508 g/cm^3
F000	436.00
μ(MoKα)	22.18 cm^{-1}

B. Intensity Measurements

Diffractometer	Nonius KappaCCD

Radiation	MoKα (λ = 0.71069 Å) graphite monochromated
Take-off Angle	2.8°
Crystal to Detector Distance	21 mm
Temperature	23.0° C
Scan Type	ω
Scan Rate	20s/frame
Scan Width	1°/frame
2θmax	61.0°
No. of Reflections Measured Unique: 5071 (R_{int} = 0.035)	Total: 9204
Corrections Lorentz-polarization	Absorption: SORTAV

C. Structure Solution and Refinement

Structure Solution	Direct Methods (SIR92)
Refinement	Full-matrix least-squares
Function Minimized	Σ w (|Fo| - |Fc|)^2
Least Squares Weights	$1/\sigma^2(Fo) = 4Fo^2/\sigma^2(Fo^2)$
p-factor	0.0200
Anomalous Dispersion	All non-hydrogen atoms
No. Observations (I>3.00σ(I))	1978
No. Variables	244
Reflection/Parameter Ratio	8.11
Residuals: R; Rw	0.035 ; 0.031
Goodness of Fit Indicator	1.57
Max Shift/Error in Final Cycle	0.00
Maximum peak in Final Diff. Map	0.32 e-/Å3
Minimum peak in Final Diff. Map	-0.31 e-/Å3

Atomic coordinates and B_{iso}/B_{eq} for Benzoate 61

atom	x	y	z	Beq
Br(1)	-0.56783(7)	-0.87387(6)	0.39682(4)	5.52(1)
O(1)	0.4312(3)	0.4480(3)	0.8445(2)	3.93(7)
O(2)	0.0312(3)	-0.2495(3)	0.6888(2)	3.73(6)
O(3)	-0.0626(3)	-0.2972(3)	0.8229(2)	4.17(7)
N(1)	0.6028(4)	0.2827(3)	0.9063(2)	2.91(7)
C(1)	0.5844(4)	0.1328(4)	0.8963(3)	2.52(7)
C(2)	0.7151(4)	0.0664(4)	0.9398(3)	3.01(8)
C(3)	0.7062(5)	-0.0874(5)	0.9303(3)	3.74(10)
C(4)	0.5644(6)	-0.2010(4)	0.8803(3)	3.85(10)
C(5)	0.3861(5)	-0.1972(4)	0.8266(3)	3.33(8)
C(6)	0.3122(4)	-0.0806(4)	0.8018(3)	2.60(8)
C(7)	0.4003(4)	0.0700(4)	0.8273(3)	2.44(7)
C(8)	0.3208(4)	0.1815(4)	0.7975(3)	2.64(7)
C(9)	0.4469(5)	0.3199(4)	0.8484(3)	2.87(8)
C(10)	0.7581(5)	0.3958(4)	0.9720(3)	3.96(9)
C(11)	0.1336(4)	0.1630(4)	0.7259(3)	3.11(8)
C(12)	0.1211(6)	0.2477(5)	0.6378(3)	4.4(1)
C(13)	0.0214(6)	0.2168(5)	0.7925(4)	4.7(1)
C(14)	0.0703(4)	-0.0026(4)	0.6706(3)	3.68(9)
C(15)	0.1143(5)	-0.0979(4)	0.7500(3)	3.25(9)
C(16)	-0.0686(4)	-0.3297(4)	0.7298(3)	3.01(8)
C(17)	-0.1875(4)	-0.4618(4)	0.6478(3)	2.66(8)
C(18)	-0.1952(5)	-0.4901(4)	0.5417(3)	3.69(9)

C(19)	-0.3088(5)	-0.6120(4)	0.4671(3)	3.88(9)
C(20)	-0.4133(4)	-0.7048(4)	0.5004(3)	3.36(8)
C(21)	-0.4086(5)	-0.6797(4)	0.6049(3)	4.10(10)
C(22)	-0.2958(5)	-0.5554(4)	0.6797(3)	3.66(9)
H(1)	0.8256	0.1291	0.9817	3.6132
H(2)	0.8142	-0.1151	0.9633	4.4876
H(3)	0.5886	-0.2968	0.8816	4.6196
H(4)	0.3062	-0.2895	0.8045	3.9955
H(5)	0.8606	0.3641	0.9633	4.7471
H(6)	0.7487	0.4852	0.9498	4.7471
H(7)	0.7661	0.4119	1.0456	4.7471
H(8)	0.1622	0.1969	0.5843	5.2730
H(9)	0.1915	0.3442	0.6688	5.2730
H(10)	0.0018	0.2544	0.6056	5.2730
H(11)	0.0475	0.3217	0.8133	5.6640
H(12)	-0.0998	0.1833	0.7507	5.6640
H(13)	0.0464	0.1792	0.8550	5.6640
H(14)	-0.0540	-0.0221	0.6364	4.4218
H(15)	0.1255	-0.0270	0.6180	4.4218
H(16)	0.0639	-0.0706	0.8047	3.8988
H(17)	-0.1213	-0.4250	0.5196	4.4244
H(18)	-0.3145	-0.6311	0.3938	4.6508
H(19)	-0.4814	-0.7464	0.6264	4.9226
H(20)	-0.2935	-0.5350	0.7524	4.3979

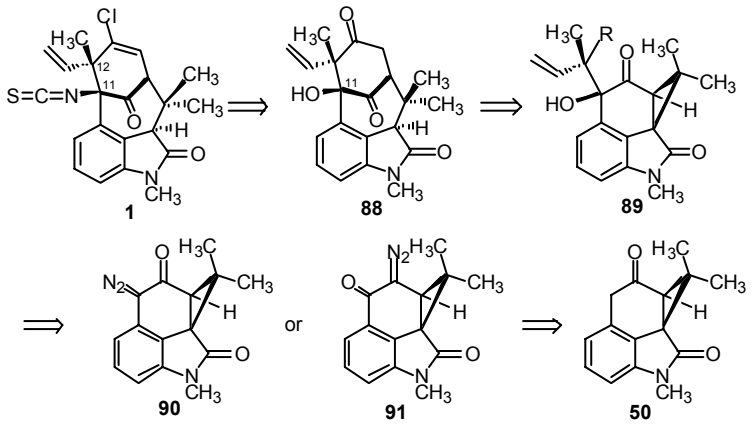
CHAPTER THREE

Addressing the Welwitindolinone Quaternary Centers

3.1 Retrosynthetic Analysis.

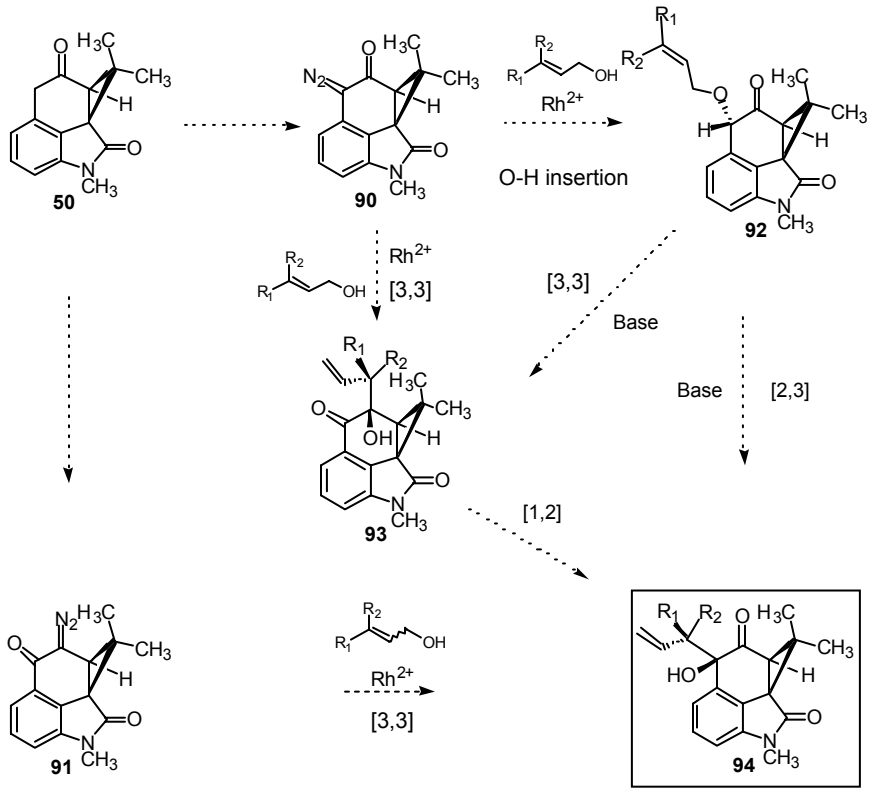
With a suitable welwitindolinone core in hand, explorations of strategies for introducing the vicinal quaternary centers of the welwitindolinones (see **1**, C(11) and C(12), Scheme 3.1.1) were initiated. Guided by interest in addressing this issue in a novel way, the retrosynthetic analysis illustrated in Scheme 3.1.1 evolved. As can be seen from the first disconnection (**1** $\Rightarrow$ **88**), as in the previous approaches, the isothiocyanate and vinyl chloride moieties would be introduced late in the synthesis. In contrast to the previous approach which called for the installation of the isothiocyanate from an ester *via* Curtius rearrangement, the isothiocyanate was now envisioned as arising from an amine which could be accessed from an alcohol (i.e., C(11) alcohol, diketone **88**).[1,2,3] Ring-contraction of the seven-membered ring and disconnection of the six-membered ring would lead to α-hydroxy ketone **89** and set the stage for the challenge of constructing the vicinal quaternary centers. Of particular interest with regard to the overall strategy was the prospect of employing a recently developed Rh(II)-initiated Claisen rearrangement developed in these laboratories to access **89** in a stereocontrolled manner from either **90** or **91**. Both α–diazo ketones **90** and **91** were envisioned as arising from ketone **50**, a compound accessed from isatin (see Chapter 2).

Scheme 3.1.1



As the previous routes, this strategy is also flexible, and allows access to **94** *via* diazo ketone **90**, or the regioisomeric α-diazo ketone **91**. As pictured in Scheme 3.1.2, versatility extends to diazo ketone **90** which can be envisioned as either being coupled to an allylic alcohol to afford O-H insertion product **92**,[4] or engaging in the rhodium(II)-initiated Claisen chemistry to furnish **93**. The former of these (**92**) could furnish α-hydroxy ketone **94** *via* either a [3,3]/[1,2]-sequence (through intermediate **93**) or alternatively, directly *via* [2,3]-rearrangement.[5,6] The latter, **93**, could be advanced to α-hydroxy ketone **94** *via* α-ketol rearrangement (see Section 3.2.1 for background). Alternatively, recognizing that by using regioisomeric diazo ketone **91**, the desired product **94** could be accessed directly by taking advantage of the mild and selective Rh(II)-initiated [3,3]-rearrangement. Although the latter route seemed more straightforward, the presumed accessibility and versatility of **90** led us to focus initial efforts on this substrate.

Scheme 3.1.2



3.2 The Rh(II)-Initiated Claisen Rearrangement.

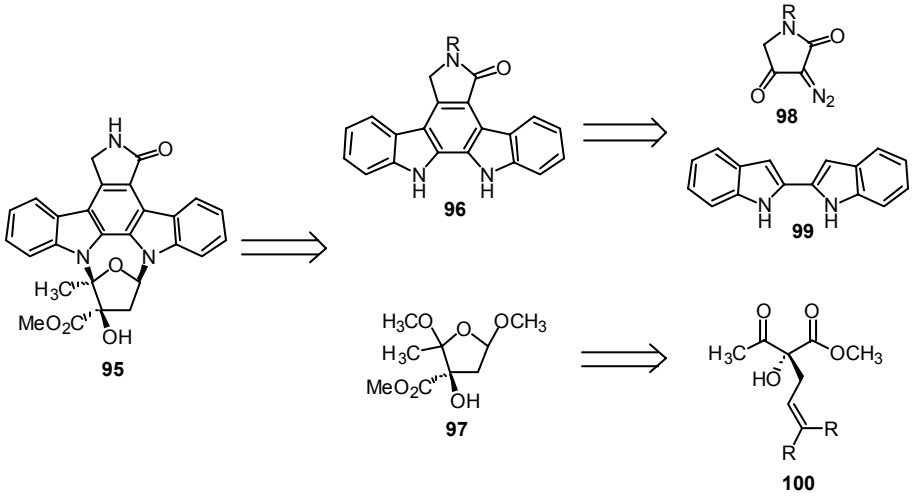
3.2.1 The Total Synthesis of K252a.[7]

3.2.1.1 K252a Retrosynthetic Analysis.

In 1993, studies were initiated in these laboratories directed toward a total synthesis of K252a (**95**, Scheme 3.2.1). From the outset, the synthetic effort toward K252a and the indolocarbazoles was directed along a convergent approach that called for the separate preparation of the aglycon (**96**) and carbohydrate moieties (**97**), followed by their coupling in a late-stage bis-glycosidation event. Aglycon **96** was prepared using a novel rhodium-catalyzed

coupling between 2,2'-biindole (**99**) and protected diazo lactam **98** while furanose **97** was derived from β-keto ester **100**.

Scheme 3.2.1

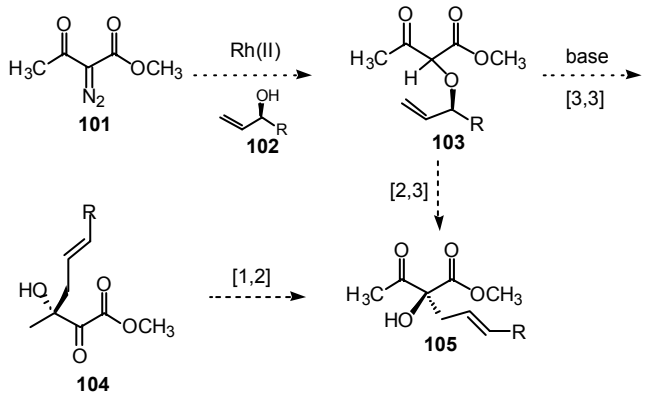


3.2.1.2 Synthesis of the K252a Furanose.

3.2.1.2.1 The Discovery of a Novel Reaction.

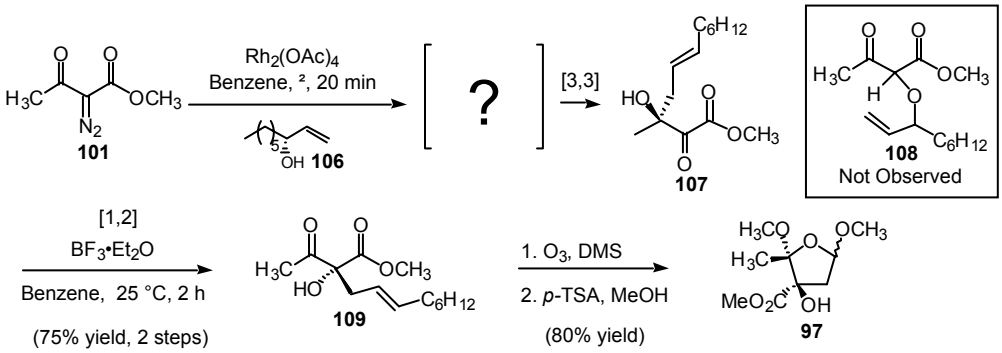
In scanning the rhodium carbenoid literature while planning the synthesis of the K252a furanose, many examples of carbenoids inserting into heteroatom-hydrogen bonds were found.[4] As pictured in Scheme 3.2.2, the plan therefore involved inserting the rhodium carbenoid derived from methyl diazo acetoacetate (**101**) into an allylic alcohol (e.g., **102**), to produce **103** thus setting the stage for a well-precedented [3,3]-sigmatropic rearrangement, which after subsequent α-ketol rearrangement would provide the desired tertiary alcohol **105**.[6] Alternatively, [2,3]-rearrangement of ether **103** would directly furnish alcohol **105**.[8]

Scheme 3.2.2



Surprisingly, Rh(II)-catalyzed dediazotization of **101** in the presence of allylic alcohol **106** at reflux for only 20 minutes produced **107**, the product of apparent O-H insertion followed by [3,3]-rearrangement (Scheme 3.2.3). Subsequent α-ketol rearrangement followed by reductive ozonolysis and acid work-up in the presence of methanol led to the carbohydrate unit **97**.

Scheme 3.2.3

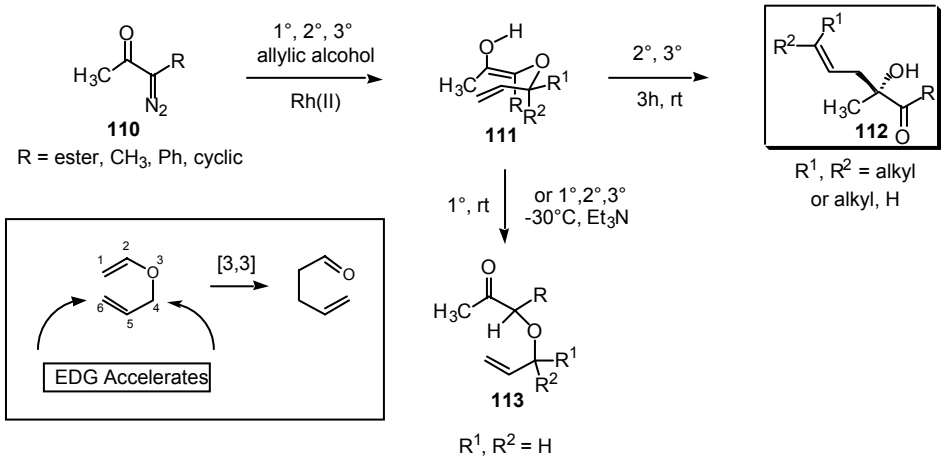

Rh2(OAc)4
Benzene, ², 20 min
101
106
?
[3,3]
107
108
Not Observed
[1,2]
BF3•Et2O
Benzene, 25 °C, 2 h
(75% yield, 2 steps)
109
1. O3, DMS
2. p-TSA, MeOH
(80% yield)
97

3.2.1.2.2 Mechanism and Results.

At this point, the mechanism of the reaction was uncertain. However, subsequent work performed in these laboratories has shown that this novel reaction is quite general with regard to the diazo ketone and allylic alcohol, and that the postulated O-H insertion product **108** is not an intermediate in the process.[9] In fact, the initial product arising from the coupling of an allylic alcohol and an α-diazo ketone is an enol (e.g., compound **111**, Scheme 3.2.4).[10] Furthermore, in the case of tertiary allylic alcohols, Claisen rearrangement of the resulting enols is fast and furnishes α-hydroxy ketone products (e.g., **112**) in good yields. On the other hand, when coupled to primary allylic alcohols, Claisen rearrangement of the resulting enols is slow and tautomerization to the O-H insertion products (e.g., **113**) becomes a competitive process. The results concerning the rate of the Claisen rearrangement are consistent with reports wherein electron-donating groups on the C(4) position of allylic enol ethers have been found to accelerate the rearrangement, and enol ethers which lack electron-donating substituents undergo rearrangement more slowly (see Scheme 3.2.4).[11]

Importantly, these efforts have demonstrated that the course of this reaction can be controlled. For example, if the O-H insertion product is desired, it can be obtained in excellent yields simply by coupling the diazo ketone with a primary, secondary or tertiary allylic alcohol at low temperatures and tautomerizing the resulting enol intermediate with an appropriate base.

Scheme 3.2.4



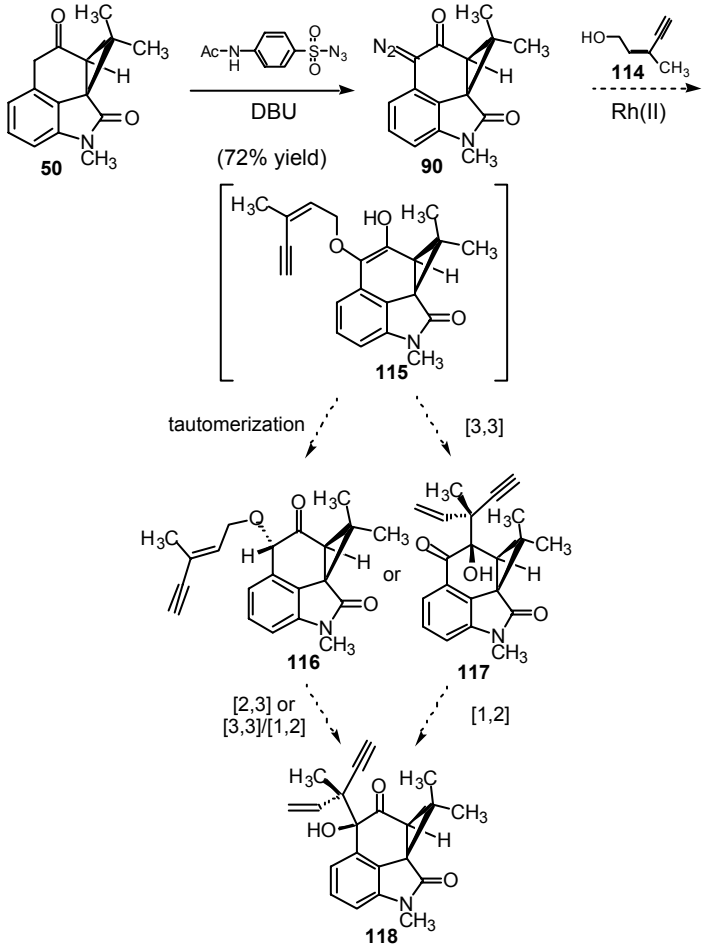
3.2.2 Application of Sigmatropic Rearrangements to the Welwitindolinones.

3.2.2.1 Exploration of α-Diazo Ketone 90.

Due to its flexibility and ease of preparation, initial studies explored the reactivity of diazo ketone **90**, a compound which could be prepared from the welwitindolinone core **50** by simply treating **50** with DBU and *p*-ABSA (Scheme 3.2.5).[12] In initial studies of the rearrangement chemistry of **90**, cis-3-methyl-2-penten-4-yn-1-ol (**114**), a commercially available primary allylic alcohol, was chosen as its coupling partner. After coupling to diazo ketone **90**, **114** was expected to eventually provide a suitable product for advancement (i.e., **118**). Thus, if α-diazo ketone **90** and ene-yne **114** behave as was previously observed with several other diazo ketones and allylic alcohols in the course of studying this reaction, their coupling would result in enol formation (i.e., **115**). If Claisen rearrangement of the resulting enol is slow, then the derived enol would tautomerize to the O-H insertion product (i.e., **116**). On the other hand, if Claisen rearrangement is fast, then α-hydroxy ketone **117** would arise. An extremely

attractive aspect of this strategy involving diazo ketone **90** is that either possible product can theoretically be advanced to alcohol **118**. For example, as illustrated in Scheme 3.2.5, ether **116** can be advanced *via* thermal or base-promoted [2,3]- or [3,3]/[1,2]-rearrangement, while α-hydroxy ketone **117** can be advanced by α-ketol rearrangement.

Scheme 3.2.5

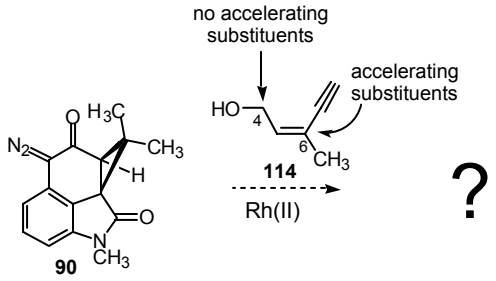


50 **90** **114** **115** **116** **117** **118**

Since the successful incorporation of **114** would produce a compound carrying the fully functionalized vicinal quaternary centers and an acetylene moiety for further elaboration to the complete welwitindolinone carbon skeleton, this appeared to be the ideal allylic alcohol substrate. However, previous

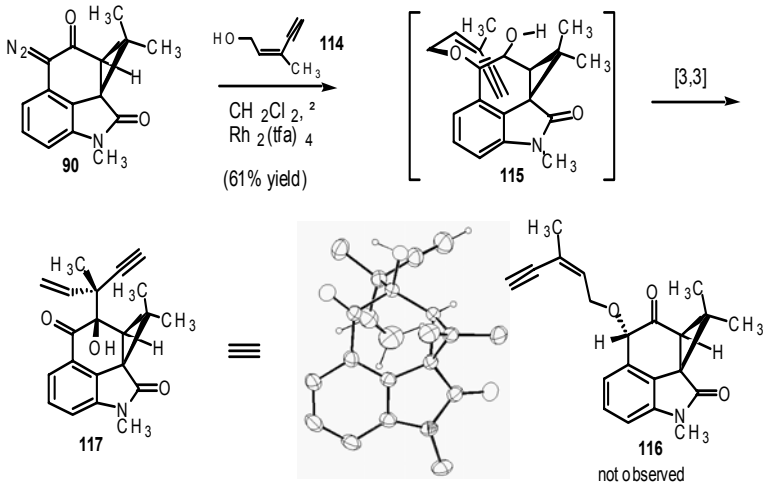
investigations with less functionalized primary allylic alcohols had demonstrated that these were usually poor substrates owing to the sluggish Claisen chemistry of the intermediate enols. Nevertheless, a primary allylic alcohol carrying accelerating substituents at C(6) (Scheme 3.2.6) had yet to be investigated.[11a] Thus, in any case, the results of this investigation would prove interesting.

Scheme 3.2.6



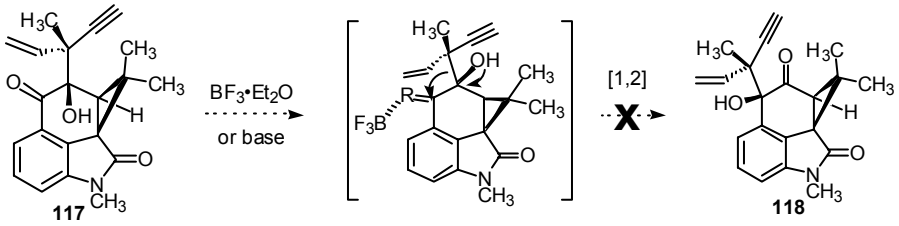
In the event, the $Rh_2(tfa)_4$-promoted coupling of ketone **90** with allylic alcohol **114** was found to produce one diastereomer of tertiary alcohol **117**, and not the O-H insertion product **116** (see Appendix 4 for X-ray crystal report confirming the structure of **117**). Thus, in this system, enol formation (i.e., **115**) was followed by a facile [3,3]-rearrangement. The stereochemical outcome is rationalized by envisioning the rearrangement taking place *via* a transition state (i.e., **115**, Scheme 3.2.7) wherein the more sterically demanding methyl group is in the equatorial position of a chair conformation poised to undergo C-C bond formation on the face opposite the bulky cyclopropane ring.

Scheme 3.2.7



Delighted by the ease with which the rearrangement was implemented,[13] the [1,2]-shift chemistry needed to place the vicinal quaternary centers in proper position was explored. Unfortunately, numerous conditions, including $BF_3 \bullet Et_2O$ and basic conditions (Scheme 3.2.8), were ineffective in converting **117** to **118**, a result which may be due to the thermodynamically unfavorable repositioning of the ketone out of conjugation with the aromatic ring.

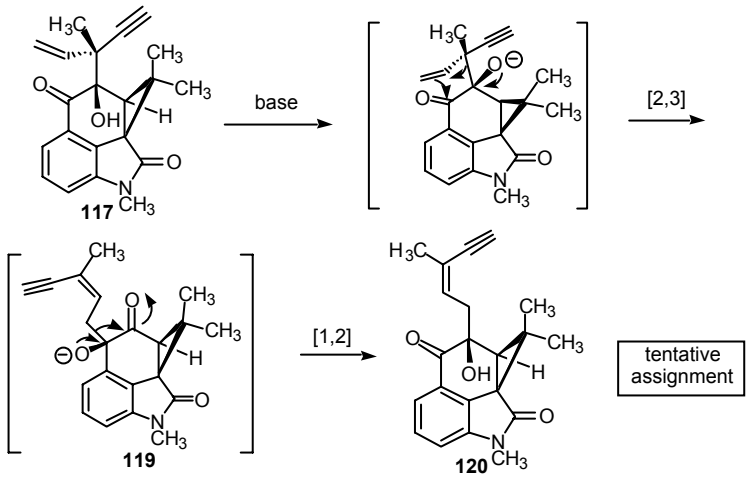
Scheme 3.2.8



Although the majority of these attempts provided complex mixtures of products which could not be purified, a major product was observed under basic conditions. This product was tentatively assigned *via* crude NMR analysis as alcohol **120**. The product is presumed to arise *via* an initial [2,3]-rearrangement which is driven by placing the olefin back into conjugation with the acetylene to

produce alcohol **119**, which, in turn, undergoes a [1,2]-shift to reconjugate the ketone with the aromatic ring (see Scheme 3.2.9).

Scheme 3.2.9

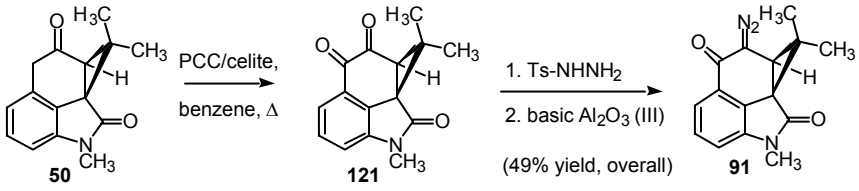


3.2.2.2 Exploration of α-Diazo Ketone 91: A Direct Alternative.

3.2.2.2.1 Formation of α-Diazo Ketone 91.

Although the entire [3,3]/[1,2] rearrangement protocol could not be implemented, the performance of the rhodium-initiated Claisen chemistry in the first stage was encouraging. Intrigued by the possibility of directly constructing the vicinal quaternary centers by applying this chemistry to **91**, (as was illustrated in Scheme 3.1.2), attention was turned toward the preparation of the requisite regioisomeric α-diazo ketone. To this end, PCC oxidation of ketone **50** produces diketone **121** which, when treated with tosylhydrazide and then base in a Bamford-Stevens protocol selectively furnishes diazo ketone **91** (Scheme 3.2.10).[14,15]

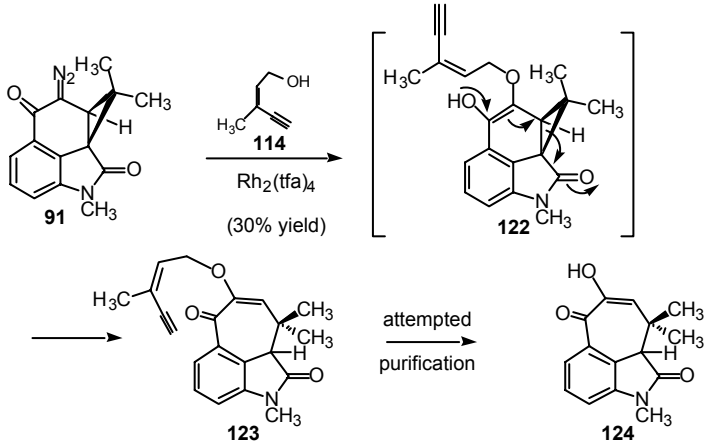
Scheme 3.2.10



3.2.2.2.2 Coupling with Ene-Yne 114, a Primary Allylic Alcohol.

As with diazo ketone **90**, initial studies with diazo ketone **91** involved coupling to ene-yne **114**. Thus, treatment of **91** with $Rh_2(tfa)_4$ in the presence of **114** (Scheme 3.2.11) results in the rapid formation of a new product which, based on analysis of the crude NMR, appears to be ring-opened allylic enol ether **123**, the product of enol formation (i.e., **122**) followed by cleavage of the cyclopropane. Efforts to isolate and characterize this product result in hydrolysis to enol **124**.[16,17] These findings suggest that in this system, the Claisen rearrangement of enol **122** is slow, which allows ring-opening of the cyclopropane ring to become a competitive process.

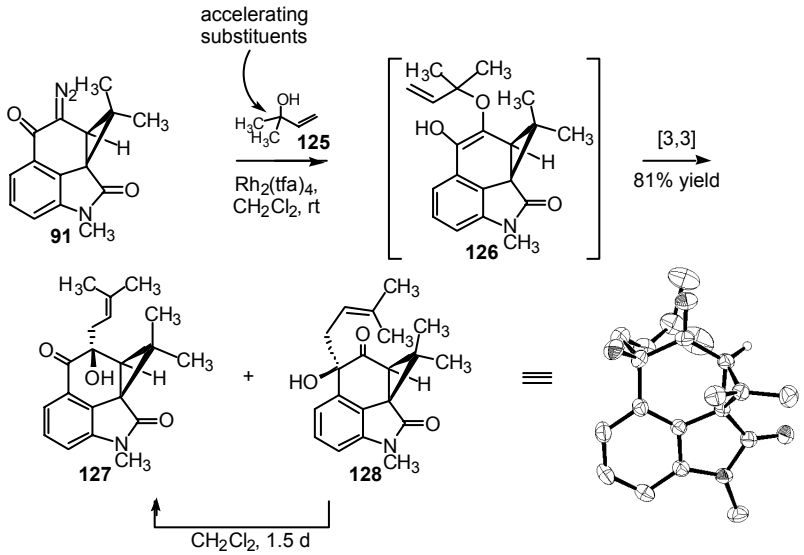
Scheme 3.2.11



3.2.2.2.3 Coupling with a Tertiary Allylic Alcohol: A Model Study.

Although intrigued by the ring-opening phenomenon which unveils the seven-membered ring found in the welwitindolinones, efforts to advance diazo ketone **91** *via* Claisen chemistry continued by coupling to other allylic alcohols. Relying on ongoing investigations in these laboratories which had shown that tertiary alcohols undergo facile [3,3]-rearrangement, the coupling of **91** with 2-methyl-3-buten-2-ol (**125**, Scheme 3.2.12) was explored. In the event, $Rh_2(tfa)_4$-promoted coupling furnishes exclusively the Claisen rearrangement product **128**. However, flash chromatography was found to partially convert α-hydroxy ketone **128** to the product of a [1,2]-shift reaction that places the ketone in the favored benzylic position (i.e., **127**). When the mixture is left undisturbed for 1.5 days, complete conversion to the α-ketol rearranged product **127** is observed. The structure of alcohol **128** was confirmed *via* X-ray crystallography (see Appendix 4 for X-ray crystal report). The crystal structure demonstrates that the rearrangement again occurrs on the face opposite the cyclopropane ring, as was observed in the rearrangement using the regioisomeric diazo ketone **90** (Scheme 3.2.7).

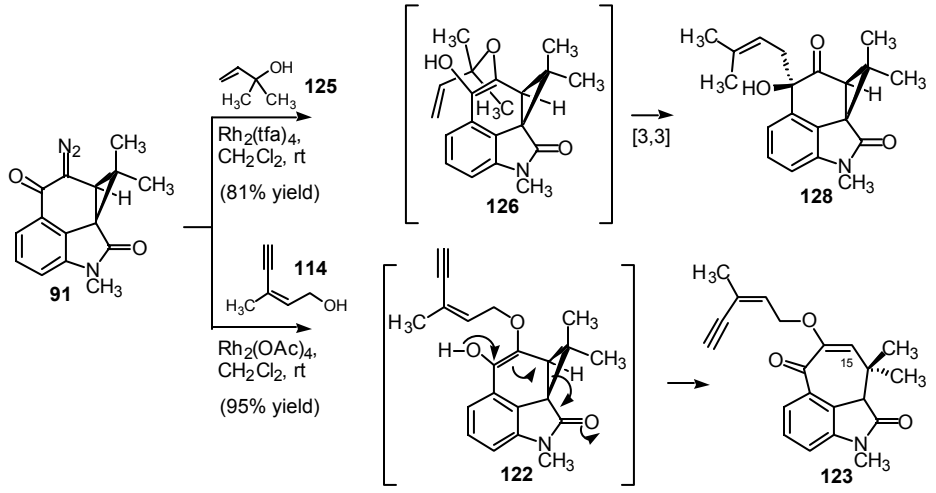
Scheme 3.2.12


accelerating
substituents
91
125
Rh2(tfa)4,
CH2Cl2, rt
126
[3,3]
81% yield
127
128
CH2Cl2, 1.5 d

3.2.2.2.4 Summary of Results and Mechanism.

The results of these studies have thus been in accord with previous explorations of the Rh(II)-initiated coupling of diazo ketones with allylic alcohols, wherein the rhodium carbenoid derived from **91** was found to couple rapidly with allylic alcohol substrates to furnish enol intermediates. In this case, depending upon the nature of the allylic alcohol, the derived enol either undergoes Claisen rearrangement or cyclopropane opening (cf., **91**→**128** and **91**→**123**). Thus, as summarized in Scheme 3.2.13, when the substrate alcohol contains electron-donating substituents at C(4), the incipient enol undergoes Claisen rearrangement to furnish an α-hydroxy ketone (e.g., **128**). In contrast, the enol derived from the coupling of **91** with primary alcohol **114** preferentially undergoes a competing ring-opening reaction and furnishes exclusively **123**.[18]

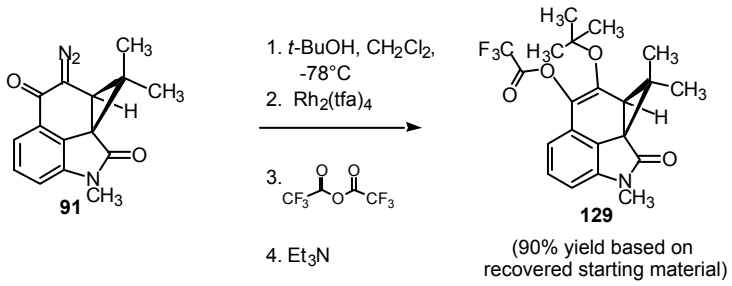
Scheme 3.2.13



In an effort to establish the intermediacy of an enol in the chemistry of diazo ketone **91**, attempts were made to trap the enol formed from coupling of diazo ketone **91** and an alcohol. Thus, decomposition of diazo ketone **91** in the

presence of *t*-BuOH followed by trapping with trifluoroacetic anhydride provides enol trifluoroacetate **129** which proved to be a stable characterizable compound (Scheme 3.2.14).[19]

Scheme 3.2.14

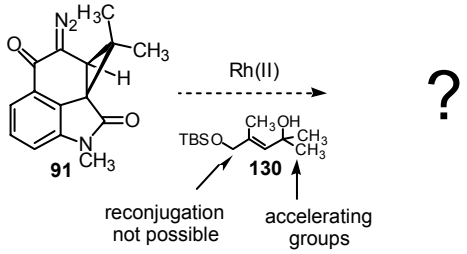


3.2.2.2.5 Coupling to An Advanced Tertiary Alcohol.

3.2.2.2.5.1 Selection of an Appropriate Alcohol.

Importantly, the routes producing **128** and **123** (Scheme 3.2.13) can both be viewed as eventually leading to the welwitindolinones. The former provides a stereocontrolled means of introducing the vicinal quaternary centers while the latter unveils the seven-membered ring and sets the stage for homologation of C(15) (enol **123**, Scheme 3.2.13). Focusing on the former, explorations of the coupling of **91** with allylic alcohol substrates that would directly furnish the vicinal quaternary centers embedded in the cyclohexene core of **1** were initiated. To this end, allylic alcohol **130** (Scheme 3.2.15) was chosen for two reasons. First, it does not contain groups that, after undergoing [3,3]-rearrangement, would be driven to reconjugate with each other (as was seen in Scheme 3.2.9). Second, the alcohol is tertiary, and tertiary alcohols have proven to be the best substrates for this novel [3,3]-rearrangement, as was illustrated by the model study using alcohol **125** (Scheme 3.2.12), where no ring-opening was observed.[20]

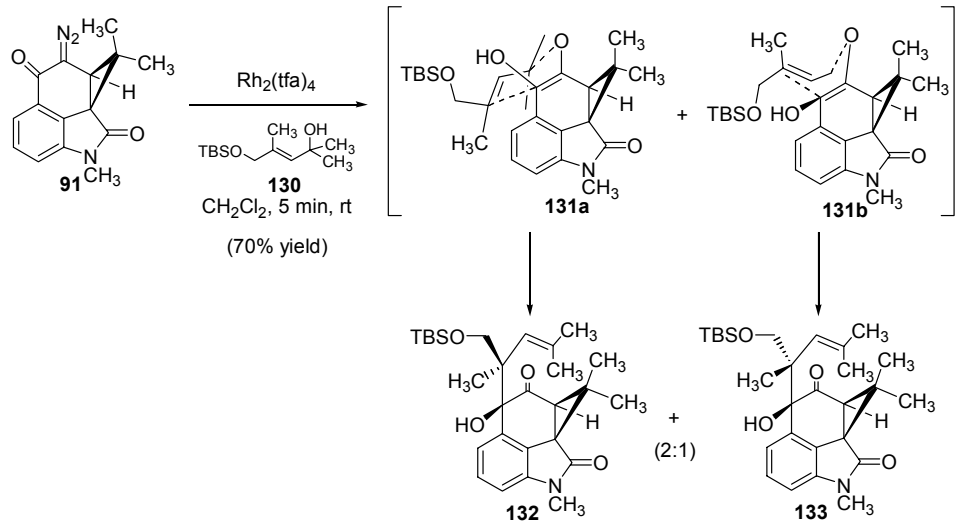
Scheme 3.2.15



3.2.2.2.5.2 A Facile Claisen Rearrangement.

Rewardingly, these investigations revealed that exposure of α-diazo ketone **91** to alcohol **130** under remarkably mild conditions (room temperature, catalytic $Rh_2(tfa)_4$) results in enol formation followed by Claisen rearrangement to furnish a 2:1 ratio of diastereomeric alcohols **132** and **133** (Scheme 3.2.16).[21] The rearrangement is again assumed to take place on the face away from the bulky cyclopropane ring, and the diastereomers are believed to arise due to chair-like and boat-like transition states (i.e., **131a** and **131b**, respectively) in the Claisen rearrangement.[22]

Scheme 3.2.16

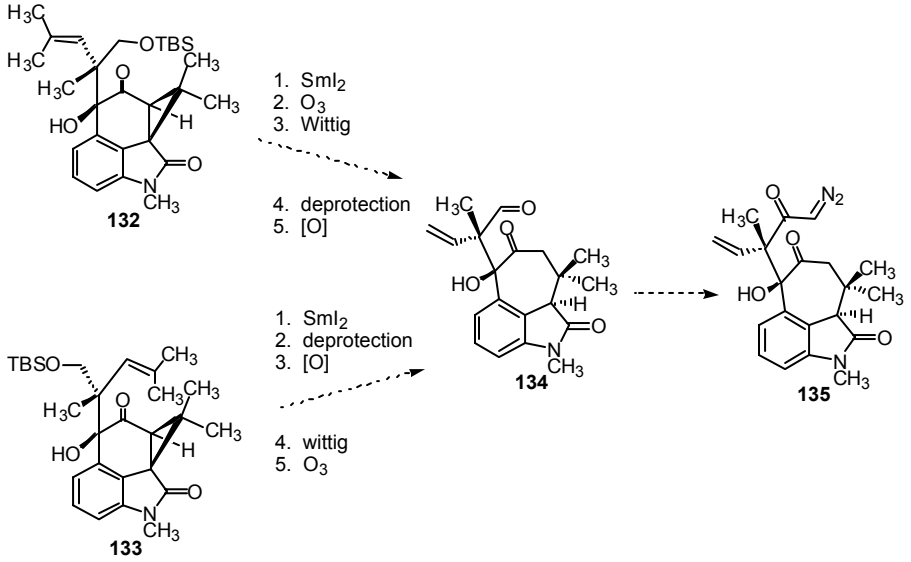


3.2.2.2.5.3 Attempts to Advance the Claisen Products.

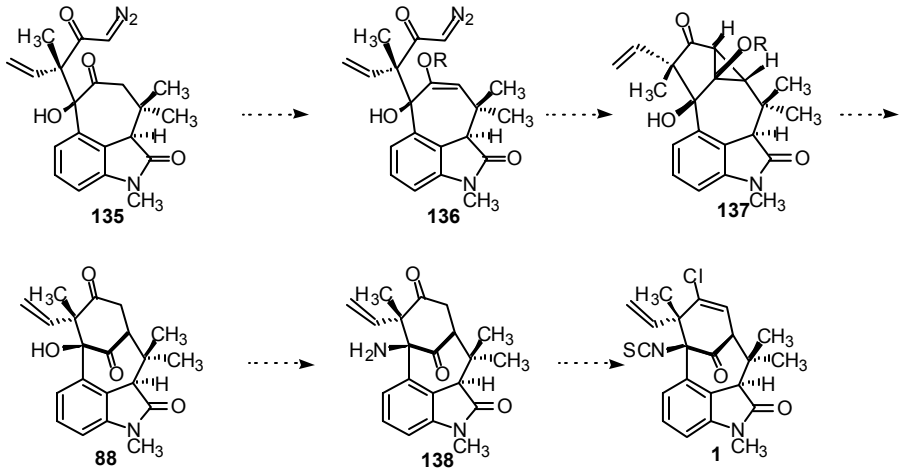
Excited by the ability to install the vicinal quaternary centers in a single step under unusually mild conditions, it was imagined that both diastereomers **132** and **133** could be advanced to the target by manipulating the protected alcohol and trisubstituted olefin in different ways. For example, as illustrated in

Scheme 3.2.17, samarium diiodide-induced ring opening of diastereomer **132**, followed by ozonolysis of the tri-substituted olefin and Wittig homologation would provide the corresponding terminal olefin. Deprotection of the alcohol and subsequent oxidation would furnish an aldehyde (**134**) that could be advanced to diazo ketone **135**. Similar transformations of diastereomer **133** could also lead to aldehyde **134** and diazo ketone **135**, which could be advanced to the target molecule *via* enol ether formation to furnish **136** followed by Rh(II)-catalyzed cyclopropanation/ring-opening (i.e., **136**→**88**) and conversion of the tertiary benzylic alcohol to tertiary amine **138** using Ritter chemistry (Scheme 3.2.18).[2]

Scheme 3.2.17

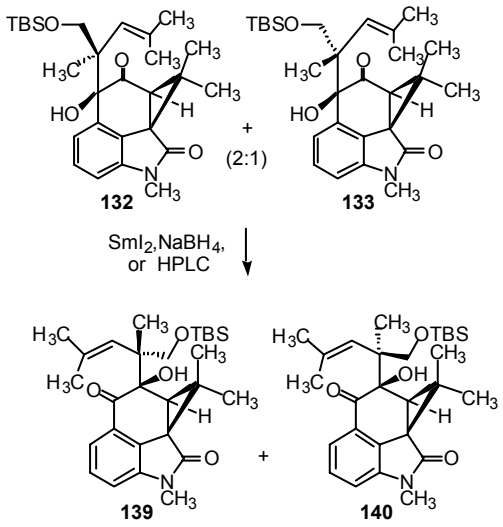


Scheme 3.2.18

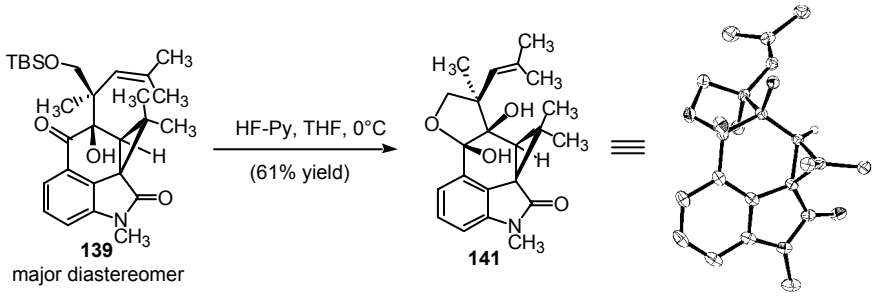


Unfortunately, **132** and **133** proved very difficult to handle and all attempts to isolate them or advance crude reaction mixtures induced facile α-ketol rearrangements that furnished **139** and **140** (Scheme 3.2.19). For example, attempts to cleave the cyclopropane ring with SmI_2 or simply attempting to separate the diastereomers *via* HPLC affected α-ketol rearrangement to provide the benzylic ketones **139** and **140**.[23] To confirm this event, the major diastereomer **139** was deprotected to furnish hemiacetal **141**, a crystalline solid for which an X-ray structure was obtained (Scheme 3.2.20, see Appendix 4 for X-ray crystal report).

Scheme 3.2.19



Scheme 3.2.20

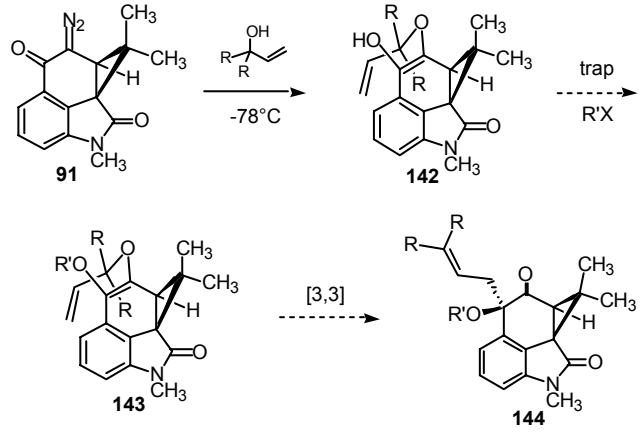


3.2.2.2.5.4 Attempts to Block the α-Ketol Rearrangement.

Still determined to advance alcohols **132** and **133**, considerable effort was focused on blocking the α-ketol rearrangement leading to **139** and **140**. For example, an attempt was made to reduce the homobenzylic ketones of **132** and **133** thereby making [1,2]-shift impossible.[24] Unfortunately, brief exposure of **132** and **133** to $NaBH_4$ again led to the formation of alcohols **139** and **140** (Scheme 3.2.19). In addition, many attempts were made to protect the benzylic tertiary alcohol which would subsequently block the detrimental [1,2]-shift, however all experiments led to no reaction or α-ketol rearrangement.[25]

In further attempts to circumvent the [1,2]-shift problem, the mechanism of the Rh(II)-initiated process was considered. Recognizing that the reaction proceeds *via* an enol intermediate, perhaps this enol (e.g., **142**, Scheme 3.2.21) could be trapped prior to Claisen rearrangement, thereby providing an indirect means of accessing the protected tertiary benzylic alcohol **144**.

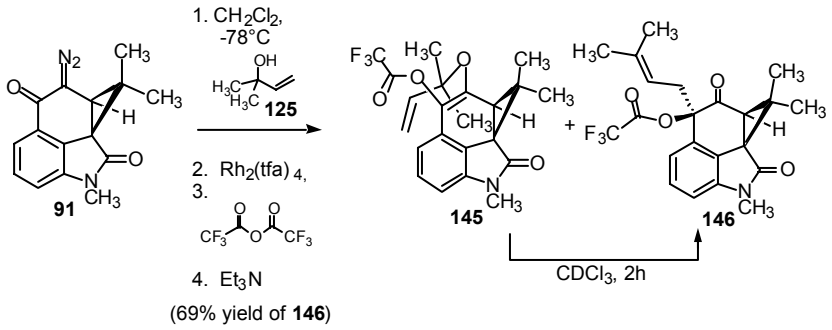
Scheme 3.2.21



Starting once again with a model system, the enol derived from coupling α-diazo ketone **91** and 2-methyl-3-buten-2-ol (**125**) can be trapped as the

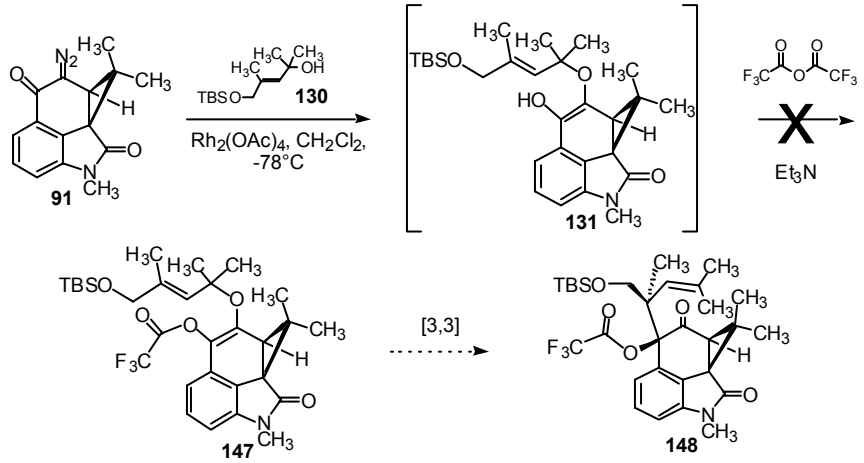
corresponding enol trifluoroacetate **145** (Scheme 3.2.22). Furthermore, after trapping, the resultant enol trifluoroacetate, upon standing, undergoes complete conversion to the desired protected alcohol **146**.[26,27]

Scheme 3.2.22



Based on the results of the model system, attempts were made to apply this chemistry to the fully elaborated system by exploring the coupling of diazo ketone **91** with tertiary alcohol **130** at low temperatures (Scheme 3.2.23). After considerable effort, neither enol trifluoroacetate **147** nor rearranged product **148** were observed, and only intractable mixtures of products were obtained .

Scheme 3.2.23



3.3 Conclusion

In summary, two regioisomeric α-diazo ketones (**90** and **91**) were prepared from the welwitindolinone core **50**, and both were explored as substrates for the stereoselective introduction of the welwitindolinone vicinal quaternary centers. To this end, coupling of **90** with primary allylic alcohol **114** leads to the rhodium(II)-initiated Claisen product **117**. Unfortunately, α-ketol rearrangement could not be effected to transpose the quaternary centers to the desired benzylic position. The quaternary centers were finally successfully introduced in one step *via* coupling of the regioisomeric α-diazo ketone **91** with tertiary allylic alcohol **130** in the presence of $Rh_2(tfa)_4$. This reaction provides alcohols **132** and **133**, two products which are suitable for advancement to the welwitindolinones but undergo an unavoidable and detrimental α-ketol rearrangement. In addition, decomposition of diazo ketone **91** with primary alcohol **114** leads only to ring-opened ether **123**, a product containing the seven-membered ring found in the welwitindolinones.

3.4 Experimental Section.

3.4.1 Material and Methods.

Unless stated otherwise, reactions were performed in flame-dried glassware under a nitrogen atmosphere, using freshly distilled solvents. Diethyl ether (Et_2O) and tetrahydrofuran (THF) were distilled from sodium/benzophenone ketyl. Methylene chloride (CH_2Cl_2), benzene, and triethylamine (Et_3N) were distilled from calcium hydride. Methyl sulfoxide

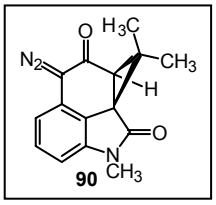
(DMSO), 1,2-dichloroethane, and BF_3•OEt_2 were purchased from the Aldrich Chemical Co. in Sure/Seal□ containers and used without further purification. All other commercially obtained reagents were used as received.

Unless stated otherwise all reactions were magnetically stirred and monitored by thin-layer chromatography (TLC) using E. Merck silica gel 60 F254 pre-coated plates (0.25-mm). Preparative TLC was also performed using E. Merck silica gel 60 F254 pre-coated plates (0.25-mm). Column or flash chromatography (silica) was performed with the indicated solvents using silica gel (particle size 0.032-0.063 mm) purchased from Fisher Scientific. In general, the chromatography guidelines reported by Still were followed.[28]

All melting points were obtained on a Gallenkamp variable temperature melting point apparatus (model: MPD350.BM2.1) and are uncorrected. Infrared spectra were recorded on a Midac M-1200 FTIR. ^1H and ^{13}C NMR spectra were recorded on Bruker AM-500 or Bruker Advance 400 spectrometers. Chemical shifts are reported relative to internal Me_4Si (^1H and ^{13}C, δ 0.00 ppm) or chloroform (^1H, δ 7.27 ppm, ^{13}C, δ 77.0 ppm). High resolution mass spectra were performed at The University of Illinois Mass Spectrometry Center. Single-crystal X-ray analyses were performed by Susan DeGala of Yale University. High performance liquid chromatography (HPLC) was performed on a Waters model 510 system using a Rainin Microsorb 80-199-C5 column, or a Rainin Dynamax SD-200 system with a Rainin Microsorb 80-120-C5 column.

3.4.2 Preparative Procedures:

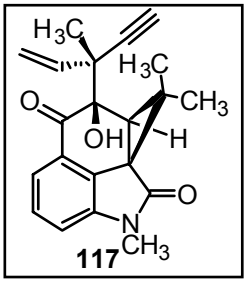
Preparation of Diazo Ketone 90.



90

Diazo Ketone 90. DBU (0.67 mL, 4.48 mmol, 1.2 equiv) was added dropwise to a solution of ketone **50** (0.90 g, 3.73 mmol, 1.0 equiv) and *p*-acetamidobenzenesulfonyl azide (1.08 g, 4.48 mmol, 1.2 equiv) in CH_3CN (37 mL) at 0 °C resulting in a brown solution. After stirring for 15 minutes (0 °C - rt), Et_2O (25 mL) was added which caused the precipitation of a solid. The mixture was washed with saturated NH_4Cl (3 x 10 mL) and dried over $MgSO_4$. The solvent was removed and the reaction was adsorbed onto SiO_2 and purified *via* flash chromatography (30% EtOAc/hexanes eluent) to furnish diazo ketone **90** as a yellow solid (720 mg, 72% yield): m.p. 136-140 °C (dec); IR (thin film/NaCl) 2926 (br w), 2091 (s), 1713 (s), 1630 (m), 1604 (m), 1475 (m), 1376 (w), 1320 (w), 1264 (s), 1127 (w), 1099 (w), 1033 (w), 861 (w), 774 (m), 733 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.31 (t, *J* = 7.9 Hz, 1H), 6.70 (d, *J* = 7.8 Hz, 1H), 6.65 (d, *J* = 8.0 Hz, 1H), 3.27 (s, 3H), 2.95 (s, 1H), 1.62 (s, 3H), 1.24 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 187.8, 173.9, 142.9, 128.7, 121.5, 118.0, 111.9, 104.6, 71.7, 44.2, 41.6, 32.0, 26.7, 20.7, 17.3; HRMS (EI) *m/z* 267.1008 [calc'd for $C_{15}H_{13}N_3O_2$ (M+) 267.1008].

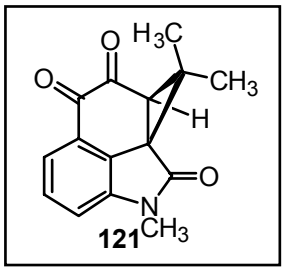
Preparation of α-Hydroxy Ketone 117.



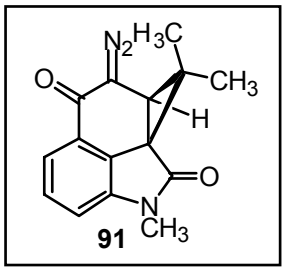
117

α-Hydroxy Ketone 117. To a solution of diazo ketone **90** (0.715 g, 2.680 mmol, 1.0 equiv) in CH_2Cl_2 (26.8 mL) and cis-3-methyl-2-penten-4-yn-1-ol **114** (0.307 mL, 2.95 mmol, 1.1 equiv) was added $Rh_2(tfa)_4$ (18 mg, 0.027 mmol, 0.01 equiv) and the whole was refluxed for 1.5 hours. The reaction was cooled, adsorbed onto SiO_2 and subjected to flash chromatography (10% acetone/hexanes eluent) to provide α-hydroxy ketone **117** as a yellow wax (0.55 g, 61% yield). A crystal suitable for X-ray analysis was obtained *via* recrystallization from MeOH (See Appendix 3 for X-ray structure report): m.p. 133-138 °C (dec/MeOH); IR (thin film/NaCl) 3459 (br w), 3289 (br w), 2936 (w), 1701 (s), 1614 (m), 1480 (m), 1399 (m), 1374 (w), 1337 (m), 1289 (m), 1116 (m), 1032 (m), 1006 (m), 921 (w), 861 (w), 815 (w), 775 (w), 732 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37-7.31 (m, 2H), 7.03 (dd, *J* = 1.0, 7.3 Hz, 1H), 5.20-5.09 (m, 2H), 4.83 (dd, *J* = 1.8, 9.6 Hz, 1H), 4.23 (br s, 1H), 3.32 (s, 3H), 2.94 (s, 1H), 2.05 (s, 1H), 1.64 (s, 3H), 1.23 (s, 3H), 1.08 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.5, 174.4, 142.6, 137.1, 134.8, 127.4, 126.9, 116.7, 115.6, 111.5, 83.7, 79.9, 73.5, 47.8, 38.5, 37.7, 36.2, 26.8, 22.3, 21.6, 16.9; HRMS (EI) *m/z* 335.1525 [calc'd for $C_{21}H_{21}NO_3$ (M+) 335.1521].

Preparation of Diketone 121 and α-Diazo Ketone 91.



121



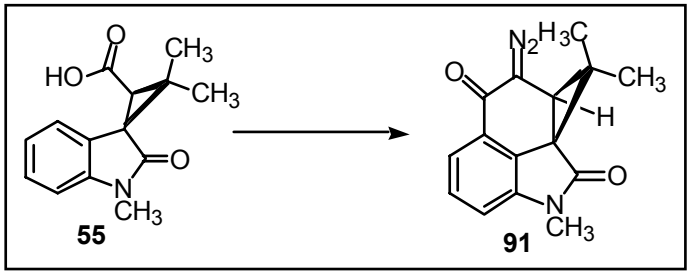
91

Diketone 121 and α-Diazo Ketone 91. To a solution of ketone **50** (1.5 g, 6.2 mmol, 1.0 equiv) in benzene (100 mL) was added celite (15 g) and pyridinium chlorochromate (PCC) (6.7 g, 31 mmol, 5 equiv). The reaction mixture was heated to reflux for 1 hour. After this time, isopropyl alcohol (approx. 50 mL) was added and heating was continued for an additional 0.5 hour. After cooling to rt, the mixture was filtered through a pad of celite (ca. 5 mm) topped with a thin layer of silica gel and $MgSO_4$ (ca. 2.5 mm each). The filter pad was washed with Et_2O and EtOAc (500 mL each). The filtrate was concentrated *in vacuo* and the resulting brown residue **121** was then dissolved in THF (60 mL). This solution was treated with *p*-toluenesulfonhydrazide (1.0 g, 5.6 mmol, 0.9 equiv) followed by a catalytic amount of conc. HCl (4 drops). The reaction was heated to reflux for 1 hour and concentrated under reduced pressure. To a stirring solution of the crude mixture in $CHCl_3$ (150 mL) was added basic alumina (III) (200 mg). The reaction mixture was then directly placed onto a flash column containing basic alumina (III) (450 g) and eluted with $CHCl_3$ to furnish a brown solid. Trituration of the brown solid with cold Et_2O afforded α-diazo ketone **91** (978 mg, 59% yield, 2 steps) as a yellow solid.

121: Although used crude in this reaction, diketone **121** can be purified *via* silica gel flash chromatography to obtain an analytically pure sample. m.p. >150 °C(dec); IR (thin film/NaCl) 3023 (w), 2955 (w), 1705 (s), 1609 (m), 1481 (m), 1416 (m), 1377 (m), 1330 (m), 1285 (m), 1125 (w), 1098 (m), 1058 (w), 1038 (m), 1015 (m), 948 (w), 862 (w), 774 (m), 765 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.0 Hz, 1H), 7.43 (t, *J* = 7.9 Hz, 1H), 7.12 (d, *J* = 7.7 Hz, 1H), 3.35 (s, 3H), 3.25 (s, 1H), 1.69 (s, 3H), 1.39 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.2, 178.6, 171.9, 142.9, 132.9, 129.0, 128.6, 119.3, 112.6, 43.6, 42.9, 40.4, 27.1, 21.2, 17.0; HRMS (EI) *m/z* 255.0895 [calc'd for $C_{15}H_{15}NO_3$ (M+) 255.0895].

91: m.p. >134 °C(dec); IR (thin film/NaCl) 2928 (w), 2247 (w), 2088 (s), 1712 (s), 1632 (m), 1601 (s), 1478 (m), 1419 (m), 1374 (m), 1337 (m), 1302 (m), 1244 (m), 1225 (w), 1192 (w), 1137 (m), 1104 (w), 1032 (m), 996 (m), 914 (w), 858 (w), 789 (m), 732 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (d, *J* = 7.7 Hz, 1H), 7.37 (t, *J* = 7.8 Hz, 1H), 7.00 (d, *J* = 7.6 Hz, 1H), 3.29 (s, 3H), 3.20 (s, 1H), 1.65 (s, 3H), 1.07 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 181.4, 174.6, 143.1, 129.2, 128.3, 127.6, 117.5, 111.0, 36.4, 32.7, 31.9, 26.8, 19.4, 16.7; HRMS (EI) *m/z* 267.1009 [calc'd for $C_{15}H_{13}N_3O_2$ (M+) 267.1008].

Large Scale Preparation of α-Diazo Ketone 91 from Acid 55.



α-Diazo Ketone 91. To a 1 L round bottom flask was added recrystallized acid **55** (10.0 g, 40.8 mmol, 1.0 equiv) and undistilled CH_2Cl_2 (408 mL) and the resulting white slurry was stirred. Oxalyl chloride (5.34 mL, 61.2 mmol, 1.5 equiv) was added neat *via* syringe followed by DMF (77 μL, 0.99 mmol, 0.024 equiv). Stirring continued for ca. 2 hours, at which time gas evolution had ceased and a clear, pale yellow solution remained. The solution was concentrated and azeotroped (3 x 25 mL) with benzene under reduced pressure to give the corresponding acid chloride as a yellow solid. The solid was then dried *in vacuo* for at least 45 minutes and used crude in the next step.

To a scratch-free 2L, 3-necked round bottom flask equipped with a 250 mL addition funnel was added ethereal diazomethane (450 mL, prepared from 32.2 g Diazald□) through a plastic funnel and triethylamine (6.60 mL, 89.8 mmol, 2.2 equiv) and the solution was cooled to 0 °C. The above dried acid chloride was dissolved in 1:1 THF/CH_3CN (170 mL) and transferred to the addition funnel and added dropwise over 1 hour to the diazomethane solution. The funnel was rinsed with THF (10 mL) and the resulting heterogeneous mixture was stirred for 1 hour or until TLC analysis showed complete consumption of starting material. At this time ca. 200 mL of 1N acetic acid was added dropwise *via* addition funnel.

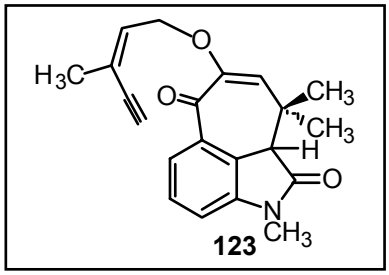
After gas evolution ceased, the biphasic mixture was transferred to a separatory funnel. The aqueous layer was removed and washed with ethyl ether (100 mL). The combined organic layers were washed with saturated $NaHCO_3$ (until acid was neutralized, ca. 3 x 100 mL), dried over $MgSO_4$ and concentrated under reduced pressure to give a 8.4:1 mixture of α-diazo ketone **51** and α-chloro ketone **56** as yellow oil which solidified upon cooling (10.2 g). The solid was taken onto the next step without further purification.

Montmorillonite clay was dried by microwaving (Hotpoint microwave) for 10 minutes on high, and then cooling under reduced pressure. This procedure was repeated at least three times, or until moisture was not observed after microwaving. Dry Montmorillonite K10 clay (75 g) was added to a 3-necked, 2 L flask and the flask with its contents were heated with a heating mantle (ca. 200 °C) *in vacuo* with vigorous stirring (using a mechanical stirrer) for 1 hour. After cooling, distilled CH_2Cl_2 (800 mL) and $Rh_2(tfa)_4$ (150 mg) were added and the mixture was stirred vigorously with a mechanical stirrer. A mixture of α-diazo ketone **51** and α-chloro ketone **56** (15 g) was dissolved in distilled CH_2Cl_2 (200 mL) and placed into an addition funnel. The solution was added to the clay mixture dropwise over 30 minutes at rt. When TLC showed the reaction was complete, PCC (75 g) was added and the reaction was heated to reflux for 18 hours. At this point isopropanol (20 mL) was added and the whole was refluxed for 30 minutes. After cooling, the mixture was filtered through a short layer of SiO_2 (30 mm) in a column. The column was washed with copious amounts (ca. 1 L) of EtOAc, until TLC analysis of the eluent showed no product remained. After concentration, the derived residue was chromatographed (30 - 75% EtOAc/hexanes eluent). Some fractions containing the desired product also contained traces of a dark orange product, identified as being *N*-Me-isatin

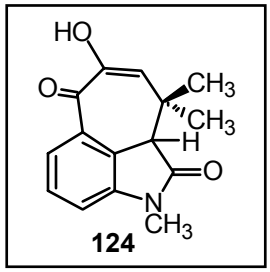
(formed from the oxidation of spirocycle **58**). The mixed and pure fractions were combined and concentrated. To the resulting solid was added a 1:1 mixture of cold EtOAc/Et_2O (ca. 50 mL). The solvent was decanted and a yellow solid, diketone **121**, remained. The red washings were concentrated and the procedure was repeated until no yellow solid was observed, to provide a combined 3.8 g of diketone **121**.

To a solution of diketone **121** (15.0 g, 58.8 mmol, 1.0 equiv) in undistilled THF (700 mL) was added *p*-toluenesulfonhydrazide (12.0 g, 64.4 mmol, 1.1 equiv) followed by a catalytic amount of conc. HCl (15 drops). The reaction was heated to reflux for 1 hour and then cooled and concentrated *in vacuo*. To a stirring solution of the crude mixture in undistilled $CHCl_3$ (600 mL) was added basic alumina (III) (1.50 g). The reaction mixture was then directly placed onto a flash column containing basic alumina (III) (1.5 kg) and eluted with $CHCl_3$ to furnish a brown solid. Trituration of the brown solid with cold Et_2O afforded α-diazo ketone **91** as a yellow solid (14.5 g, 92% yield, 2 steps).

Preparation of Enol Ether 123 and Enol 124.



123

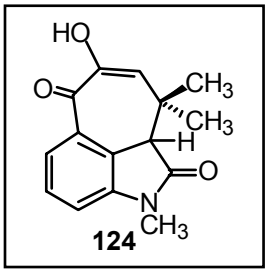


124

Enol Ether 123 and Enol 124. To a solution of diazo ketone **91** (48 mg, 0.18 mmol, 1.0 equiv) and cis-3-methyl-2-penten-4-yn-1-ol **114** (20.6 μL, 0.20 mmol, 1.1 equiv) in CH_2Cl_2 (2 mL) was added rhodium trifluoroacetate (1.0 mg, 0.002 mmol, 0.008 equiv) and the mixture was stirred until nitrogen evolution ceased (ca. 1 minute). Crude NMR analysis showed the presence of enol ether **123** along with a trace of enol **124**. In an attempt to isolate **123**, the reaction was subjected to flash chromatography (50% EtOAc/hexanes eluent) which provided a complex mixture of products which contained enol **124** as a pale yellow solid (14 mg, 30% yield). Enol ether **123** could therefore not be purified due to hydrolysis to **124**.

124: m.p. 151-153 °C; IR (thin film/NaCl) 3401 (br m), 2963 (w), 2930 (w), 2874 (w), 1710 (s), 1640 (m), 1599 (s), 1467 (m), 1408 (w), 1375 (m), 1342 (m), 1299 (m), 1258 (w), 1214 (w), 1025 (m), 968 (w), 761 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 7.8 Hz, 1H), 7.44 (t, *J* = 8.0 Hz, 1H), 7.04 (d, *J* = 7.7 Hz, 1H), 6.80 (s, 1H), 6.06 (s, 1H), 3.80 (s, 1H), 3.26 (s, 3H), 1.73 (s, 3H), 0.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.9, 173.9, 145.4, 144.2, 130.6, 128.8, 128.7, 128.1, 122.3, 112.2, 53.3, 37.5, 28.4, 26.4, 21.8; HRMS (EI) *m/z* 257.1048 [calc'd for $C_{15}H_{15}NO_3$(M+) 257.1052].

Preparation of Enol 124.

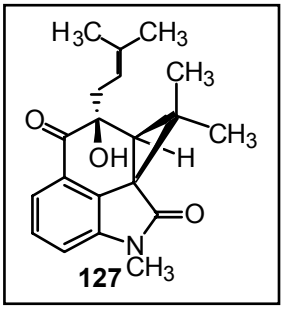


124

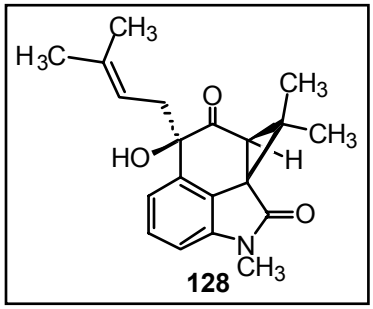
Enol 124. Diazo ketone **91** (60 mg, 0.22 mmol, 1.0 equiv) in wet CH_2Cl_2 (5 mL, containing one drop H_2O) was treated with $Rh_2(OAc)_4$ (1.0 mg, 0.002 mmol, 0.01 equiv). After nitrogen evolution ceased, the resulting brown reaction was concentrated and exposed to flash chromatography (50% EtOAc/hexanes eluent) which provided enol **124** as a yellow solid (52 mg, 94% yield).

The data for enol **124** can be found in the previous procedure.

Preparation of α-Hydroxy Ketones 127 and 128.



127



128

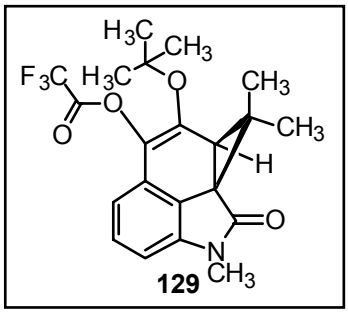
α-Hydroxy Ketones 127 and 128. To α-diazo ketone **91** (100 mg, 0.37 mmol, 1.0 equiv) and 2-methyl-3-buten-2-ol (**125**) (43 μL, 0.41 mmol, 1.1 equiv) in CH_2Cl_2 (4 mL) at rt was added $Rh_2(tfa)_4$ (2.4 mg, 0.004 mmol, 0.01 equiv). Gas evolution was noted and appeared to cease at which time the reaction was concentrated. NMR analysis of crude material indicated the presence of one compound, alcohol **128**. The reaction was chromatographed on silica gel (5:1 hexanes:EtOAc) to yield alcohol **128** (99 mg, 81% yield) as a yellow residue, which now contained a trace of regioisomer **127**. Upon stirring in CH_2Cl_2 for 1.5 d or standing in $CDCl_3$, alcohol **128** was completely converted to regioisomer **127** (98 mg, 99% yield), a clear, pale yellow oil.

127: IR (thin film, NaCl) 3442 (br w), 2961 (w), 2924 (w), 2885 (w), 1702 (s), 1605 (m), 1478 (m), 1377 (w), 1341 (m), 1285 (m), 1106 (w), 1027 (w), 789 (w), 743 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37 (d, *J* = 7.4 Hz, 1H), 7.33 (t, *J* = 7.6 Hz, 1H), 7.03 (d, *J* = 7.3 Hz, 1H), 4.76 (m, 1H), 3.85 (br s, 1H), 3.30 (s, 3H), 2.60 (s, 1H), 2.11 (dd, *J* = 8.3, 14.2 Hz, 1H), 1.98 (dd, *J* = 7.4, 14.2 Hz, 1H), 1.58 (s, 3H), 1.49 (s, 3H), 1.30 (s, 3H), 1.04 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$)

δ 199.1, 174.4, 142.5, 136.5, 133.2, 127.1, 125.4, 117.1, 116.1, 111.5, 77.6, 40.7, 39.0, 38.8, 36.5, 26.7, 25.7, 21.2, 17.7, 16.4; HRMS (EI) *m/z* 325.1680 [calc'd for $C_{20}H_{23}NO_3$(M+) 325.1678].

128: Before rearrangement to alcohol **127**, alcohol **128** was triturated from Et_2O to furnish white crystals suitable for X-ray analysis (see Appendix 4 for X-ray structure report). m.p. 120-123 °C; IR (thin film, NaCl) 2923 (br w), 1705 (s), 1616 (m), 1464 (w), 1377 (w), 1332 (w), 1285 (m), 1106 (w), 1031 (w), 782 (w), 735 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.32 (t, *J* = 7.9 Hz, 1H), 7.17 (d, *J* = 7.8 Hz, 1H), 6.81 (d, *J* = 7.6 Hz, 1H), 4.37 (m, 1H), 3.45 (s, 1H), 3.30 (s, 3H), 3.02 (s, 1H), 2.51 (dd, *J* = 9.0, 13.3 Hz, 1H), 2.30 (dd, *J* = 6.7, 13.3 Hz, 1H), 1.53 (s, 3H), 1.50 (s, 3H), 1.32 (s, 3H), 1.11 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.6, 173.7, 141.6, 137.2, 133.9, 128.2, 123.5, 119.1, 115.3, 106.3, 77.7, 45.5, 45.1, 38.7, 37.9, 26.8, 22.6, 20.8, 18.3, 14.1; HRMS (EI) *m/z* 325.1674 [calc'd for $C_{20}H_{23}NO_3$(M+) 325.1678].

Preparation of Trifluoroacetate 129.

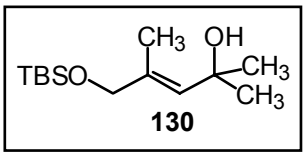


129

Trifluoroacetate 129. A solution of α-diazo ketone **91** (50 mg, 0.19 mmol, 1.0 equiv) and *t*-butanol (54 μL, 0.56 mmol, 3.0 equiv) in CH_2Cl_2 (10 mL)

was cooled to -78 °C and treated with $Rh_2(tfa)_4$ (1.2 mg, 0.002 mmol, 0.01 equiv). The cold bath was removed and the reaction was allowed to warm slightly (approx. 3 minutes) until nitrogen evolution commenced and the reaction turned brown. Immediately after gas evolution ceased (ca. 1 min), trifluoroacetic anhydride (134 μL, 0.95 mmol, 5.0 equiv) and Et_3N (132 μL, 0.95 mmol, 5.0 equiv) were added sequentially. The resulting yellow reaction was allowed to warm to rt at which time it was concentrated under reduced pressure. The resulting residue was chromatographed on silica gel (3:1 hexanes:EtOAc eluent) to provide enol trifluoroacetate **129** (20 mg, 27% yield) as a white solid, and diazo ketone **91** (30 mg). The yield of the desired trapped product was 90% based on recovered starting material. Data for trifluoroacetate **129**: m.p. 156-159 °C; IR (thin film, NaCl) 2697 (m), 2929 (m), 1800 (w), 1712 (s), 1656 (m), 1606 (m), 1466 (m), 1367 (m), 1341 (m), 1298 (m), 1172 (m), 1148 (m), 1021 (m), 770 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.28 (t, *J* = 7.8 Hz, 1H), 6.82 (d, *J* = 7.7 Hz, 1H), 6.79 (d, *J* = 8.0 Hz, 1H), 3.27 (s, 3H), 3.06 (s, 1H), 1.71 (br s, 3H), 1.42 (s, 9H), 0.97 (br s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.4, 154.9 (q, J_{CF} = 42.6 Hz), 142.7, 141.6, 132.2, 127.7, 126.0, 120.0, 114.7 (q, J_{CF} = 285.6 Hz), 112.8, 106.7, 82.2, 43.4, 42.7, 29.4, 26.6 (3), 20.9, 19.7 (br), 16.2 (br); HRMS (EI) *m/z* 409.1496 [calc'd for $C_{21}H_{22}F_3NO_4$(M+) 409.1501].

Preparation of Allylic Alcohol 130.



130

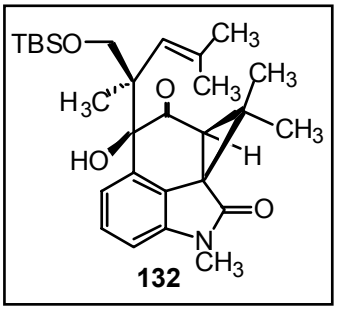
Allylic Alcohol 130. To ethyl-3-methyl-4-oxocrotonate (1.0 g, 7.0 mmol, 1.0 equiv) in CH_2Cl_2 and MeOH (70 mL, 1:1) was added $NaBH_4$ (530 mg, 14.0 mmol, 2.0 equiv). After stirring for 5 minutes, the solvents were removed *in vacuo* and the derived residue was cooled to 0 °C and treated with 1N HCl (50 mL). The reaction was stirred for 15 minutes and then extracted with CH_2Cl_2 (3 x 100 mL). The combined organic layers were dried ($MgSO_4$), filtered, then concentrated to yield an oil which was used in the next step without further purification.

A solution of the derived alcohol in CH_2Cl_2 (70 mL) was treated with TBSCl (1.1 g, 7.4 mmol, 1.1 equiv) and imidazole (572 mg, 8.4 mmol, 1.2 equiv). A white precipitate rapidly formed and the reaction was stirred for 20 min. After this time, 1N HCl (50 mL) was added and the layers were separated. The organic layer was washed with 1N HCl (3 x 50 mL) then brine (3 x 50 mL). Drying (K_2CO_3), filtering, and concentrating afforded an oil which was used crude in the next step.

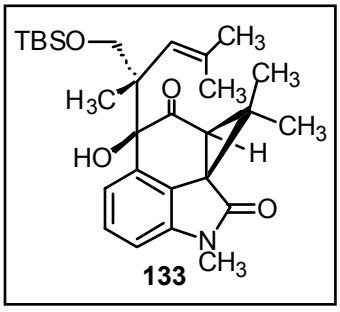
To a 1.4 M solution of methylmagnesium bromide in toluene/THF (25 mL, 35 mmol, 5.0 equiv) was added ether (35 mL) and a solution of the crude TBS-protected alcohol in ether (35 mL). After 5 minutes, the reaction was quenched with ice (750 mg). Extracting with ether (3 x 100 mL), drying (Na_2SO_4) and concentrating provided an oil which was subjected to silica gel chromatography

(5:1 pentane:Et_2O eluent) to yield tertiary alcohol **130** (1.1 g, 64% overall yield) as a clear, colorless oil: IR (thin film, NaCl) 3432 (br w), 2959 (s), 2934 (s), 2864 (s), 1693 (w), 1476 (m), 1463 (m), 1377 (m), 1358 (m), 1254 (s), 1144 (m), 1093 (s), 1008 (w), 843 (s), 774 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.51 (m, 1H), 3.89 (s, 2H), 2.00 (br s, 1H), 1.75 (s, 3H), 1.30 (m, 6H), 0.85 (s, 9H), .005 (s, 3H), 0.002 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.5, 131.1, 70.7, 68.7, 30.9, 25.8, 18.2, 13.9, -4.75; HRMS (EI) *m/z* 243.1774 [calc'd for $C_{13}H_{27}SiO_2$(M-H) 243.1780].

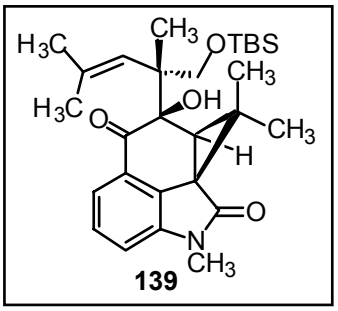
Preparation of α-Hydroxy Ketones 132, 133, 139, and 140.



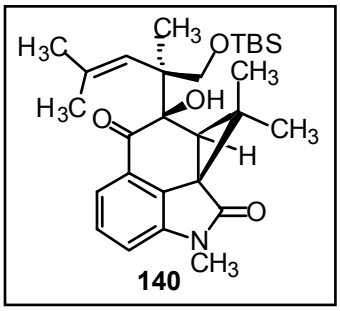
132



133



139



140

a-Hydroxy Ketones 132, 133, 139, and 140. To a solution of α-diazo ketone **91** (50 mg, 0.19 mmol, 1.0 equiv) and alcohol **130** (46 mg, 0.19 mmol, 1.0 equiv) in CH_2Cl_2 (5 mL) at rt was added $Rh_2(tfa)_4$ (1.2 mg, 0.002 mmol, 0.01

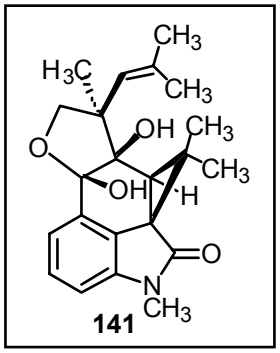
equiv). After 5 minutes, the reaction was concentrated under reduced pressure and chromatographed (10:1 hexanes:EtOAc eluent) to yield a residue (75 mg) which contained a mixture of diastereomeric alcohols **132** and **133** (2:1, **132**:**133**, 70% yield based on NMR integrations). Efforts to obtain analytically pure samples of **132** and **133** using HPLC (3:1 hexanes:EtOAc eluent) resulted in the isolation of diastereomeric alcohols **139** and **140** (2:1 ratio, **139**:**140**), which arise *via* α-ketol rearrangement of alcohols **132** and **133**, respectively.

139: The first compound to elute was alcohol **139**, the α-ketol rearrangement product of **132**. IR (thin film, NaCl) 3467 (br w), 2954 (m), 2858 (m), 2248 (w), 1714 (s), 1694 (s), 1607 (m), 1472 (m), 1387 (w), 1337 (m), 1284 (m), 1074 (m), 1022 (m), 913 (w), 839 (m), 778 (m), 732 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37 (d, *J* = 7.9 Hz, 1H), 7.31 (t, *J* = 7.7 Hz, 1H), 6.99 (d, *J* = 7.6 Hz, 1H), 5.20 (s, 1H), 4.95 (s, 1H), 3.50 (d, *J* = 10.1 Hz, 1H), 3.46 (d, *J* = 9.9 Hz, 1H), 3.31 (s, 3H), 2.91 (s, 1H), 1.61 (s, 3H), 1.52 (s, 3H), 1.51 (s, 3H), 1.09 (s, 3H), 0.91 (s, 9H), 0.62 (s, 3H), 0.07 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.8, 174.6, 142.4, 134.0, 133.8, 128.5, 127.0, 124.8, 116.7, 110.8, 81.7, 69.2, 48.6, 38.8, 37.6, 37.5, 29.1, 26.8, 25.8, 21.9, 19.3, 18.3, 17.0, -4.3, -4.4; HRMS (EI) *m/z* 483.2797 [calc'd for $C_{28}H_{41}NO_4Si$(M+) 483.2805].

140: The second compound to elute was alcohol **140**, the α-ketol rearrangement product of **133**. IR (thin film, NaCl) 3472 (br m), 2936 (m), 2857 (m), 1715 (s), 1693 (s), 1606 (m), 1472 (m), 1336 (m), 1283 (m), 1254 (m), 1075 (m), 1010 (m), 838 (m), 777 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37 (d, *J* = 7.5 Hz, 1H), 7.32 (t, *J* = 7.7 Hz, 1H), 6.97 (d, *J* = 7.2 Hz, 1H), 4.86 (s, 1H), 3.74 (s, 1H), 3.41 (d, *J* = 10.0 Hz, 1H), 3.28 (s, 3H), 3.13 (d, *J* = 10.0 Hz, 1H), 2.78 (s, 1H), 1.62 (s, 3H), 1.54 (s, 3H), 1.39 (s, 3H), 1.11 (s, 3H), 1.05 (s, 3H), 0.94 (s,

9H), 0.11 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.2, 174.7, 142.4, 133.9, 133.7, 128.6, 126.9, 124.5, 116.4, 110.7, 82.4, 69.8, 48.6, 38.2, 37.6, 37.2, 28.7, 26.7, 25.8, 21.8, 19.3, 18.3, 18.2, 17.0, -4.2, -4.4; HRMS (EI) *m/z* 483.2808 [calc'd for $C_{28}H_{41}NO_4Si$(M+) 483.2805].

Preparation of Hemi-Acetal 141.

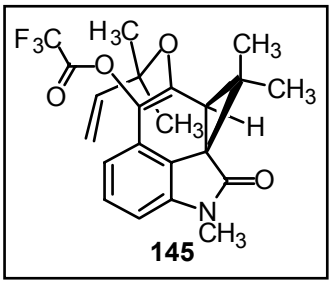


141

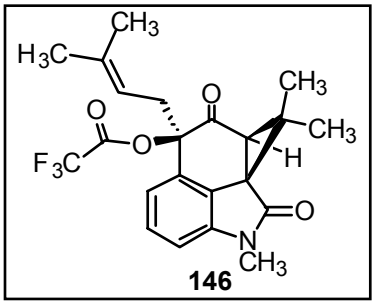
Hemi-Acetal 141. To a solution of TBS-alcohol **139** (246 mg, 0.51 mmol, 1.0 equiv) in THF (5 mL) at 0 °C was slowly added excess HF/Py (~5 mL of a 23% HF/Py solution). After stirring for 3 h and warming from 0 °C to rt, a saturated aqueous solution of $NaHCO_3$ was added until CO_2 evolution ceased (~250 mL). The reaction was extracted with EtOAc (10 x 50 mL) and the combined organic layers were washed with saturated $CuSO_4$ solution (3 x 20 mL), dried (Na_2SO_4), filtered and concentrated. The derived oil was purified *via* silica gel chromatography (3:1 hexanes:EtOAc eluent) to yield a white solid (114 mg, 61% yield) which was recrystallized from methanol to provide white crystals suitable for X-ray analysis (see Appendix 3 for X-ray structure report). Although recrystallization provided hemiacetal **141** for X-ray analysis, both the ketone and hemiacetal forms of **141** were observed in the ^1H and ^{13}C NMR spectra in a 1:1.5 ratio. m.p. 151-153 °C(dec); IR (thin film, NaCl) 3399 (br w), 2928 (br w),

2248 (w), 1693 (s), 1616 (m), 1465 (m), 1408 (m), 1347 (m), 1290 (m), 1047 (m), 1039 (m), 976 (w), 921 (m), 780 (m), 732 (m) cm^{-1};^{1}H NMR (500 MHz, CDCl3) d 7.39-7.25 (comp m, 4H), 7.02 (d, *J* = 7.3 Hz, 1H), 6.77 (d, *J* = 7.3 Hz, 1H), 5.42 (s, 1H), 4.95 (br s, 1H), 4.56 (s, 1H), 4.40 (br s, 1H), 4.25 (d, *J* = 8.1 Hz, 1H), 3.95 (d, *J* = 8.1 Hz, 1H), 3.88 (d, *J* = 11.4 Hz, 1H), 3.45 (d, *J* = 11.4 Hz, 1H), 3.30 (s, 3H), 3.25 (s, 3H), 2.95 (br s, 1H), 2.87 (s, 1H), 2.43 (s, 1H), 1.81 (s, 3H), 1.63 (s, 3H), 1.61 (s, 3H), 1.56 (s, 3H), 1.42 (s, 3H), 1.37 (s, 3H), 1.32 (s, 3), 1.26 (s, 1H), 1.06 (s, 3H), 0.87 (s, 3H), 0.67 (s, 3H); ^{13}C NMR (125 MHz, CDCl3) d 198.8, 175.1, 174.4, 142.5, 141.6, 139.7, 135.2, 134.3, 134.2, 127.7, 127.5, 127.2, 124.3, 124.0, 123.5, 117.7, 116.7, 111.3, 106.6, 102.5, 83.8, 82.3, 75.2, 68.2, 53.8, 49.4, 38.9, 38.6, 37.8, 37.6, 36.5, 36.4, 29.0, 27.9, 26.8, 26.6, 22.8, 21.9, 21.1, 19.5, 19.1, 18.6, 18.4, 16.8; HRMS (EI) *m/z* 369.1945 [calc'd for $C_{22}H_{27}NO_4$(M+) 369.1940].

Preparation of Enol Trifluoroacetate 145 and Trifluoroacetate 146.



145



146

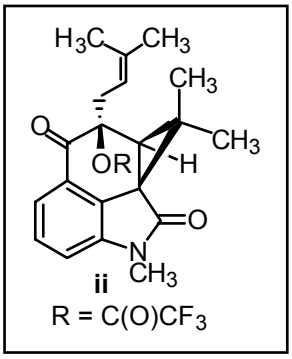
Enol Trifluoroacetate 145 and Trifluoroacetate 146; Method A: A solution of α-diazo ketone **91** (50 mg, 0.19 mmol, 1.0 equiv) and 2-methyl-3-buten-2-ol (**125**) (22 μL, 0.21 mmol, 1.1 equiv) in CH_2Cl_2 (5 mL) was cooled to -78 °C and treated with $Rh_2(tfa)_4$ (1.2 mg, 0.002 mmol, 0.01 equiv). The cold bath was removed and the reaction was allowed to warm slightly (approx. 3

minutes) until nitrogen evolution ceased and the reaction turned brown. Immediately after gas evolution ceased, trifluoroacetic anhydride (134 μL, 0.95 mmol, 5.0 equiv) and Et_3N (132 μL, 0.95 mmol, 5.0 equiv) were added sequentially. The resulting yellow reaction was allowed to warm to rt at which time it was concentrated and chromatographed on silica gel (3:1 hexanes:EtOAc eluent) to yield an inseparable mixture of enol trifluoroacetate **145** (assigned *via* NMR analysis) and ketone **146**. Upon standing for 2 h in $CDCl_3$, the mixture of compounds undergoes complete conversion to ketone **146** (55 mg, 69% yield) which can be isolated as a white solid.

Method B: A solution of α-diazo ketone **91** (50 mg, 0.19 mmol, 1.0 equiv and 2-methyl-3-buten-2-ol (**125**) (22 μL, 0.21 mmol, 1.1 equiv) in CH_2Cl_2 (5 mL) at rt was treated with $Rh_2(tfa)_4$ (1.2 mg, 0.002 mmol, 0.01 equiv). After N_2 evolution ceased, the reaction was cooled to 0 °C and trifluoroacetic anhydride (134 μL, 0.95 mmol, 5.0 equiv) was added followed by the addition of triethylamine (132 μL, 0.95 mmol, 5.0 equiv). The reaction was stirred for 0.5 h (0 °C to rt) then concentrated *in vacuo* and subjected to silica gel chromatography (3:1 hexanes:EtOAc eluent) to provide the protected alcohol **146** (60 mg, 75% yield) as a white solid: m.p. 89-94 °C; IR (thin film, NaCl) 2919 (w), 1797 (m), 1719 (s), 1610 (w), 1470 (w), 1369 (w), 1283 (w), 1223 (m), 1155 (m), 1055 (w), 980 (w), 775 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.28 (t, *J* = 7.9 Hz, 1H), 6.83 (d, *J* = 7.7 Hz, 1H), 6.82 (d, *J* = 8.0 Hz, 1H), 4.59 (tt, *J* = 1.3, 7.9 Hz, 1H), 3.28 (s, 3H), 3.12 (s, 1H), 2.57 (dd, *J* = 7.8, 13.9 Hz, 1H), 2.50 (dd, *J* = 8.0, 13.9 Hz, 1H), 1.56 (s, 3H), 1.53 (s, 3H), 1.29 (s, 3H), 1.21 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.3, 173.8, 154.9 (q, J_{CF} = 43.0), 142.9, 138.9, 131.4, 128.6, 124.6, 117.0, 116.6 (q, J_{CF} = 285.6), 113.9, 107.1, 87.7, 46.9, 41.4, 40.9,

38.7, 26.8, 25.8, 21.9, 18.8, 17.4; HRMS (EI) *m/z* 421.1505 [calc'd for $C_{22}H_{22}F_3NO_4$(M+) 421.1501].

Preparation of Trifluoroacetate ii.



ii

R = $C(O)CF_3$

Trifluoroacetate ii. A solution of alcohol **127** (30 mg, 0.09 mmol, 1.0 equiv) in CH_2Cl_2 (5 mL) at 0 °C was treated with trifluoroacetic anhydride (65 μL, 0.46 mmol, 5.0 equiv) and triethylamine (64 μL, 0.46 mmol, 5.0 equiv). The reaction was stirred for 0.5 h (0 °C to rt) and then concentrated *in vacuo* and chromatographed (3:1 hexanes:EtOAc eluent) to provide ketone **ii** (35 mg, 92% yield) as a clear colorless oil which solidified upon cooling. m.p. 64-68 °C; IR (thin film, NaCl) 2933 (br w), 1787 (m), 1713 (s), 1603 (m), 1358 (w), 1337 (m), 1286 (m), 1159 (s), 1038 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.42 (d, *J* = 7.8 Hz, 1H), 7.37 (m, *J* = 7.8 Hz, 1H), 7.05 (d, *J* = 7.5 Hz, 1H), 4.61 (t, *J* = 7.7 Hz, 1H), 3.32 (s, 3H), 3.14 (s, 1H), 2.70 (d, *J* = 7.8 Hz, 2H), 1.57 (s, 3H), 1.40 (s, 3H), 1.35 (s, 3H), 1.12 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.5, 173.6, 155.9 (q, J_{CF} = 42.2 Hz), 142.5, 138.0, 131.7, 127.7, 126.1, 117.9, 114.4 (q, J_{CF} = 286.6 Hz), 114.2, 111.7, 89.2, 38.1, 37.5, 36.9, 36.4, 26.9, 25.5, 20.7, 17.7, 16.9; HRMS (EI) *m/z* 421.1503 [calc'd for $C_{22}H_{22}F_3NO_4$(M+) 421.1501].

(1) For an example of obtaining an isothiocyanate from amine, see: Sakagami, M.; Muratake, H.; Natsume, M. *Chem. Pharm. Bull.* **1994**, *42*, 1393.

(2) a) For the conversion of an alcohol to an amine *via* the Ritter reaction, see: Ritter, J. J.; Kalish, J. *Org. Synth. Col*. Vol. V, **1973**, 471. b) For a modification of the Ritter reaction using TMS-cyanide, see: Chen, H. G.; Goel, O. P.; Knobelsdorf, J. *Tetrahedron Lett*. **1996**, *37*, 8129.

(3) Alcohols may be directly converted to isothiocyanates, see Kniezo, L.; Bernat, J. *Synth. Commun.* **1990**, *20*, 509.

(4) For examples, see: a) Padwa, A.; Hornbuckle, S. F. *Chem. Rev.* **1991**, *91*, 263. b) Ye, T.; McKervey, M. A. *Chem. Rev.* **1994**, *94*, 1091.

(5) Examples of both [2,3]- and [3,3]-rearrangement of α-allyloxy ketones have been reported, see: Ziegler, F. E. *Chem. Rev.* **1988**, *88*, 1423 and references therein.

(6) For a leading reference to the Lewis acid-catalyzed α-ketol rearrangement, see: Crout, D. H. G.; Rathbone, D. L. *J. Chem. Soc., Chem. Commun.* **1987**, 290.

(7) For a complete description of this work, see a) Stoltz, B. M. The Total Synthesis of Indolocarbazole Natural Products K252c, (+)-K252a, (+)-RK-286c, (+)-MLR-52, (-)-TAN-1030a, and (+)-Staurosporine, Ph.D.

dissertation, Yale University, 1997. See also b) Wood, J. L.; Stoltz, B. M.; Dietrich, H.-J. *J. Am. Chem. Soc.* **1995**, *117*, 10413; and c) Wood, J. L.; Stoltz, B. M.; Dietrich, H.-J.; Pflum, D. A.; Petsch, D. T. *J. Am. Chem. Soc.* **1997**, *119*, 9641.

([8]) Koreeda, M.; Luengo, J. *J. Am. Chem. Soc.* **1985**, *107*, 5572.

([9]) Wood, J. L.; Moniz, G. A.; Pflum, D. A.; Stoltz, B. M.; Holubec, A. A.; Dietrich, H.-J. *J. Am. Chem. Soc*. **1999**, *121*, 1748.

([10]) Wood, J. L.; Moniz, G. A. *Organic Lett.* **1999**, *1*, 371.

([11]) a) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868 (alkyl). b) Coates, R. M.; Rogers, B. D.; Hobbs, S. J.; Curran, D. P.; Peck, D. R. *J. Am. Chem. Soc.* **1987**, *109*, 1160 (OMe).

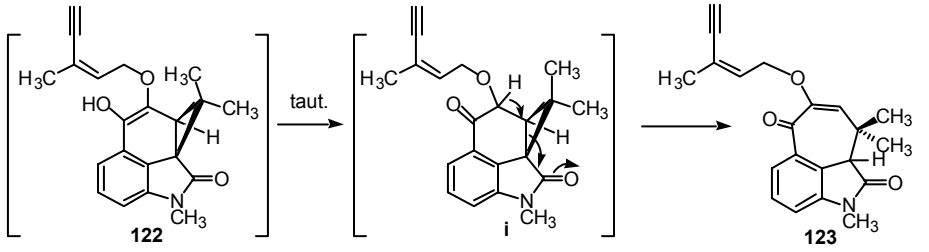
([12]) See ref. 7, Chapter 2.

([13]) Due to this exciting result, investigations of α-diazo-β-tetralone and β-diazo-α-tetralone as substrates in the Rh(II)-initiated Claisen rearrangement were initiated, see: Pflum, D. A. The Discovery and Development of a Rhodium Carbenoid-Initiated Claisen Rearrangement: The Stereoselective Synthesis of Tertiary Alcohols Ph.D. Dissertation, Yale University, 1999.

([14]) Muchowski, J. M. *Tetrahedron Lett.* **1966**, 1773.

([15]) For a modified procedure involving large scale production of diazo ketone **50** from acid **55** (Chapter 2), see Section 3.4.2.

([16]) Alternatively, this may occur *via* tautomerization to the O-H insertion product (**i**) followed by β-elimination:



([17]) For comparison, enol **124** was also prepared by decomposition of diazo ketone **91** with $Rh_2(tfa)_4$ in the presence of water. See Section 3.4.2 for experimental procedures.

([18]) The effect of electron-donating substitution on the rate of Claisen rearrangement at C(6) is not as great as C(4) substitution, see: Barluenga, J.; Aznar, F.; Liz, R.; Bayod, M. *J. Chem. Commun.* **1984**, 1427. See also ref. 11a.

([19]) A tertiary, non-allylic alcohol (i.e. *t*-BuOH) was required in these trapping studies. Similar trapping attempts using 2-methyl-3-buten-2-ol (**125**) were successful, although the resulting enol was unstable due to facile Claisen rearrangement, a result which would prove useful in another context (see Section 3.2.2.2.5.4). Therefore, when using *t*-BuOH which lacks an allylic

portion, the resulting enol is stable (i.e., Claisen rearrangement does not follow trapping). Further, the use of a primary alcohol (i.e., MeOH and 3-methyl-2-buten-1-ol) led only to ring-opened products.

([20]) Additionally, alcohol **130** contains two electron donating groups at C(6).

([21]) Alcohol **130** was prepared in three steps from ethyl-3-methyl-4-oxocrotonate, see Section 3.4 for details.

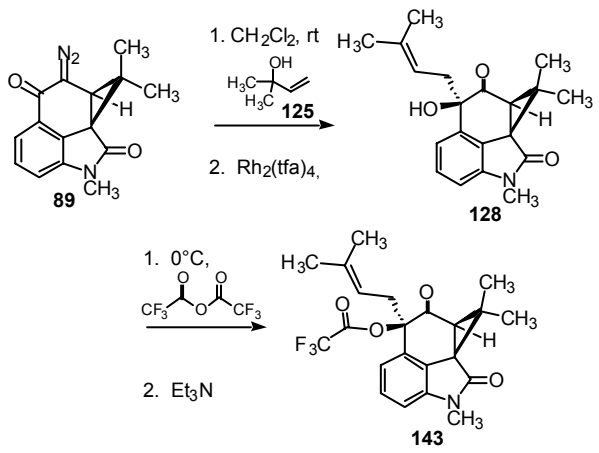
([22]) These results concerning reactivity of diazo ketone **91** with allylic alcohols were recently published, see ref. 23, Chapter 2.

([23]) For a typical procedure for samarium diiodide-promoted cleavage of cyclopropane rings see: Batey, R. A.; Motherwell, W. B. *Tetrahedron Lett*. **1991**, *32*, 6649. Procedure for treatment of alcohols **132** and **133** with SmI_2: To an excess of SmI_2 (prepared from diiodoethane and Sm) was added a solution of ketones **132** and **133** (5 mg, 0.01 mmol) in THF (1 mL) and DMPU (100 μL). After 15 minutes, the reaction was quenched with saturated $NaHCO_3$ and the product extracted with ether. Washing with H_2O (1 mL) and brine (1 mL) followed by drying over $MgSO_4$ furnished a mixture of ketones **139** and **140** which was purified *via* flash chromatography (25% EtOAc/hexanes eluent) to provide a yellow oil whose ^1H NMR spectrum corresponded to the spectrum of a mixture of ketones **139** and **140** obtained after HPLC purification of regioisomeric ketones **132** and **133** (see Section 3.4.2 for experimental data).

([24]) This reaction was run simply by treating a solution of the alcohols **132** and **133** in 1:1 CH_2Cl_2/MeOH with an excess of $NaBH_4$ for 10 minutes. After aqueous workup, crude NMR analysis showed complete conversion to regioisomeric alcohols **139** and **140**.

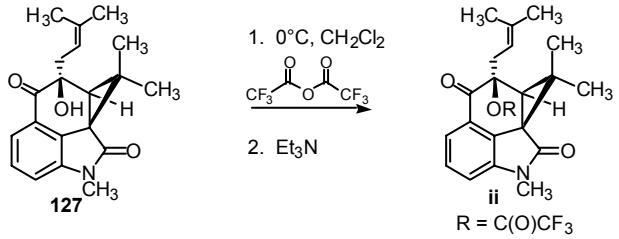
([25]) Some protecting groups attempted for the protection of alcohols **132** and **133** were phenyl carbamate (phenyl isocyanate, DMAP, CH_2Cl_2 or phenyl isocyanate, pyridine, CH_2Cl_2), methyl thiomethyl ether (MTM) (DMSO, acetic anhydride), benzoate (benzoic anhydride, DMAP, CH_2Cl_2, triethylamine), and trichloroacetate (trichloroacetic anhydride, DMAP, triethylamine, CH_2Cl_2).

([26]) Another way to access trifluoroacetate **143** is by trapping alcohol **128** after Claisen rearrangement but prior to α-ketol rearrangement:



([27]) Given the possibility that **128** could undergo isomerization to **127** prior to acylation (to furnish **ii** instead of the desired **143**), an authentic sample of the potential end product **ii** was prepared. Comparison of the data

obtained for **143** and **ii** clearly indicate they are different (see Section 3.4.2).



127 **ii**

([28]) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

APPENDIX THREE: SPECTRA RELEVANT TO CHAPTER THREE

Figure A.3.1

Figure A.3.2 Infrared Spectrum (thin film/NaCl) of compound **90**.

Figure A.3.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **90**.

Figure A.3.4

Figure A.3.5 Infrared Spectrum (thin film/NaCl) of compound **117**.

Figure A.3.6 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **117**.

Figure A.3.7

Figure A.3.8 Infrared Spectrum (thin film/NaCl) of compound **121**.

Figure A.3.9 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **121**.

Figure A.3.10

Figure A.3.11 Infrared Spectrum (thin film/NaCl) of compound **91**.

Figure A.3.12 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **91**.

Figure A.3.13

Figure A.3.14 Infrared Spectrum (thin film/NaCl) of compound **124**.

Figure A.3.15 ^{13}C NMR (100 MHz, $CDCl_3$) of compound **124**.

Figure A.3.16

Figure A.3.17 Infrared Spectrum (thin film/NaCl) of compound **127**.

Figure A.3.18 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **127**.

Figure A.3.19

Figure A.3.20 Infrared Spectrum (thin film/NaCl) of compound **128**.

Figure A.3.21 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **128**.

Figure A.3.22

Figure A.3.23 Infrared Spectrum (thin film/NaCl) of compound **129**.

Figure A.3.24 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **129**.

Figure A.3.25

Figure A.3.26 Infrared Spectrum (thin film/NaCl) of compound **130**.

Figure A.3.27 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **130**.

Figure A.3.28

Figure A.3.29 Infrared Spectrum (thin film/NaCl) of compound **139**.

Figure A.3.30 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **139**.

Figure A.3.31

Figure A.3.32 Infrared Spectrum (thin film/NaCl) of compound **140**.

Figure A.3.33 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **140**.

Figure A.3.34

Figure A.3.35 Infrared Spectrum (thin film/NaCl) of compound **141**.

Figure A.3.36 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **141**.

Figure A.3.37

Figure A.3.38 Infrared Spectrum (thin film/NaCl) of compound **146**.

Figure A.3.39 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **146**.

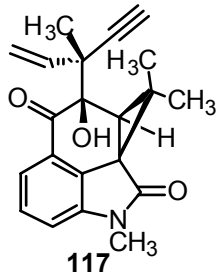
Figure A.3.40

Figure A.3.41 Infrared Spectrum (thin film/NaCl) of compound **ii**.

Figure A.3.42 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **ii**.

APPENDIX FOUR: X-RAY CRYSTALLOGRAPHY REPORTS RELEVANT TO CHAPTER THREE

X-RAY CRYSTALLOGRAPHY REPORT FOR α-ALCOHOL 117



117

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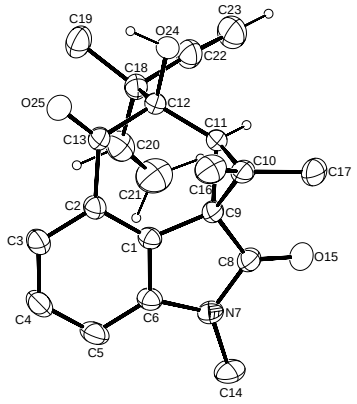


Formula:	$C_{21}H_{21}NO_3$
Formula weight:	335.39
Crystal class:	monoclinic
Space group:	$P2_1/n$ (#2)
Z	4
Cell constants:	
a	8.3143(1)Å
b	14.1132(3)Å
c	15.6528(3)Å
β	90.314(1)°
V	1836.69(6)Å^3
μ	0.81 cm^{-1}
crystal size, mm	0.40 x 0.25 x 0.20
D_{calc}	1.213 g/cm^3
F(000)	712
Radiation:	Mo-K_α (λ=0.71069Å)
2θ range	6.24–50.70°
hkl collected:	-9≤ h ≤9; -16≤ k ≤16; -18≤ l ≤18
No. reflections measured:	12035
No. unique reflections:	3125 (R_{int}=0.0217)
No. observed reflections	2842 (F>4σ)
No. reflections used in refinement	3125

No. parameters	243
R indices (F>4σ)	R_1=0.0560
	wR_2=0.1422
R indices (all data)	R1=0.0633
	wR2=0.1524
GOF:	1.189
Final Difference Peaks, e/Å^3	+0.152, -0.188

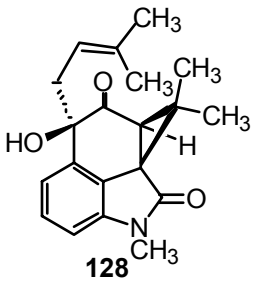
Refined Positional Parameters for Alcohol 117.

Atom	**x**	**y**	**z**	**U_{eq}, Å^2**
O(15)	0.3713(2)	0.53718(10)	0.08267(10)	0.0633(5)
O(24)	0.0261(2)	0.85066(11)	-0.03909(9)	0.0532(4)
H(24)	-0.002(3)	0.913(2)	-0.0329(5)	0.080
O(25)	0.1340(2)	0.97725(10)	0.07603(10)	0.0574(4)
N(7)	0.4688(2)	0.63901(12)	0.18524(10)	0.0487(4)
C(1)	0.3610(2)	0.77779(13)	0.14190(11)	0.0407(4)
C(2)	0.2964(3)	0.86719(13)	0.15126(12)	0.0445(5)
C(3)	0.3366(3)	0.9188(2)	0.22506(14)	0.0577(6)
H(3)	0.2996(11)	0.982(2)	0.2319(2)	0.077
C(4)	0.4302(4)	0.8768(2)	0.2876(2)	0.0668(7)
H(4)	0.4602(10)	0.9141(12)	0.338(2)	0.089
C(5)	0.4838(3)	0.7831(2)	0.2813(2)	0.0595(6)
H(5)	0.544(2)	0.7534(9)	0.3275(14)	0.079
C(6)	0.4476(3)	0.73463(14)	0.20716(12)	0.0453(5)
C(8)	0.3874(3)	0.61683(14)	0.11036(13)	0.0470(5)
C(9)	0.3295(2)	0.70934(13)	0.07433(12)	0.0416(5)
C(10)	0.3442(3)	0.7356(2)	-0.02222(12)	0.0489(5)
C(11)	0.1834(3)	0.72882(14)	0.01859(11)	0.0424(5)

H(11)	0.125(2)	0.6758(14)	0.0038(4)	0.056
C(12)	0.0818(2)	0.81507(13)	0.03981(12)	0.0416(5)
C(13)	0.1733(2)	0.89509(13)	0.08832(12)	0.0432(5)
C(14)	0.5532(3)	0.5698(2)	0.2369(2)	0.0637(6)
H(14a)	0.506(2)	0.5672(10)	0.2922(10)	0.095
H(14b)	0.663(2)	0.5874(8)	0.2420(10)	0.095
H(14c)	0.545(2)	0.5091(10)	0.2105(7)	0.095
C(16)	0.4198(3)	0.8290(2)	-0.0465(2)	0.0663(7)
H(16a)	0.367(2)	0.8537(8)	-0.0989(11)	0.099
H(16b)	0.536(2)	0.8196(4)	-0.0572(12)	0.099
H(16c)	0.406(2)	0.8750(9)	0.0006(9)	0.099
C(17)	0.3849(3)	0.6555(2)	-0.08324(14)	0.0696(7)
H(17a)	0.502(2)	0.6503(9)	-0.0886(10)	0.104
H(17b)	0.337(2)	0.6687(7)	-0.1397(10)	0.104
H(17c)	0.341(2)	0.5955(11)	-0.0610(7)	0.104
C(18)	-0.0675(3)	0.7828(2)	0.09703(14)	0.0496(5)
C(19)	-0.1855(3)	0.8664(2)	0.1097(2)	0.0708(7)
H(19a)	-0.1310(12)	0.9177(10)	0.1435(12)	0.106
H(19b)	-0.283(2)	0.8438(5)	0.1413(12)	0.106
H(19c)	-0.219(2)	0.8920(10)	0.0525(10)	0.106
C(20)	-0.0108(3)	0.7476(2)	0.1837(2)	0.0641(6)
H(20)	0.0203(10)	0.799(2)	0.2269(13)	0.085
C(21)	0.0033(4)	0.6615(3)	0.2102(2)	0.0923(10)
H(21a)	-0.0273(8)	0.603(2)	0.1682(10)	0.123
H(21b)	0.0457(11)	0.6474(5)	0.274(2)	0.123
C(22)	-0.1535(3)	0.7068(2)	0.0515(2)	0.0624(6)

C(23)	-0.2177(4)	0.6415(2)	0.0208(2)	0.0832(9)
H(23)	-0.273(2)	0.586(2)	-0.0055(10)	0.111

X-RAY CRYSTALLOGRAPHY REPORT FOR ALCOHOL 128



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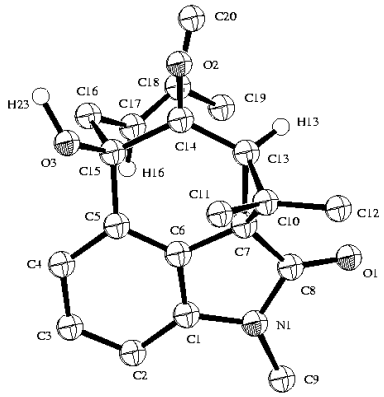


A. Crystal Data

Empirical Formula	$C_{20}H_{23}NO_3$
Formula Weight	325.41
Crystal Color, Habit	colorless, irregular plate
Crystal Dimensions (mm)	0.08 X 0.15 X 0.18
Crystal System	monoclinic
Lattice Type	Primitive
Lattice Parameters	a = 8.1900(4)Å b = 13.932(1) Å c = 16.002(1) Å β = 99.271(3)° V = 1802.0(2) Å3
Space Group	P_21/n (#14)
Z value	4
Dcalc	1.199 g/cm^3
F000	696.00
μ(MoKα)	0.80 cm^{-1}

B. Intensity Measurements

Diffractometer	Nonius KappaCCD
Radiation	MoKα (λ = 0.71069 Å) graphite monochromated
Take-off Angle	2.8°
Crystal to Detector Distance	35 mm
Temperature	23.0°C
Scan Rate	60sec/frame
Scan Width	1°/frame
2θmax	60.9°
No. of Reflections Measured	Total: 5116
Corrections	Lorentz-polarization
Secondary Extinction (coefficient: 4.75234e-06)	

C. Structure Solution and Refinement

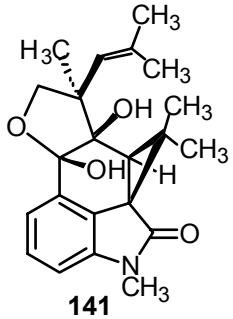
Structure Solution	Direct Methods (SAPI91)
Refinement	Full-matrix least-squares
Function Minimized	Σ w (|Fo| - |Fc|)^2
Least Squares Weights	1/σ^2(Fo)
p-factor	0.0100
Anomalous Dispersion	All non-hydrogen atoms
No. Observations (I>3.00σ(I))	1963
No. Variables	217
Reflection/Parameter Ratio	9.05
Residuals: R; Rw	0.061 ; 0.059
Goodness of Fit Indicator	2.56
Max Shift/Error in Final Cycle	0.00
Maximum peak in Final Diff. Map	0.23 e-/Å3
Minimum peak in Final Diff. Map	-0.26 e-/Å3

Atomic coordinates and B_{iso}/B_{eq} for Alcohol 128.

atom	x	y	z	Beq
O(1)	-0.2777(3)	-0.4808(1)	-0.9316(1)	5.00(5)
O(2)	-0.3439(3)	-0.2325(1)	-0.6632(1)	6.50(6)
O(3)	-0.2391(3)	-0.0666(1)	-0.7332(1)	5.63(5)
N(1)	-0.1630(3)	-0.3496(1)	-0.9882(1)	3.95(5)
C(1)	-0.1170(3)	-0.2559(2)	-0.9616(2)	3.72(7)
C(2)	-0.0140(4)	-0.1918(2)	-0.9920(2)	4.66(8)
C(3)	0.0224(4)	-0.1081(2)	-0.9456(2)	5.30(8)
C(4)	-0.0343(4)	-0.0918(2)	-0.8700(2)	4.98(8)
C(5)	-0.1365(3)	-0.1582(2)	-0.8388(2)	3.84(7)
C(6)	-0.1847(3)	-0.2361(2)	-0.8889(2)	3.43(6)
C(7)	-0.2868(3)	-0.3177(2)	-0.8720(1)	3.54(6)
C(8)	-0.2448(3)	-0.3952(2)	-0.9304(2)	3.87(7)
C(9)	-0.1060(4)	-0.3978(2)	-1.0587(2)	4.94(7)
C(10)	-0.4695(4)	-0.3029(2)	-0.8600(2)	4.16(7)
C(11)	-0.5462(4)	-0.2043(2)	-0.8710(2)	5.41(8)
C(12)	-0.5890(4)	-0.3826(2)	-0.8895(2)	6.24(9)
C(13)	-0.3368(4)	-0.3223(2)	-0.7858(2)	4.05(7)
C(14)	-0.2895(4)	-0.2384(2)	-0.7288(2)	4.31(7)
C(15)	-0.1723(4)	-0.1572(2)	-0.7491(2)	4.18(7)
C(16)	-0.0085(4)	-0.1749(2)	-0.6882(2)	5.79(9)
C(17)	0.0733(4)	-0.2675(2)	-0.7048(2)	5.66(9)
C(18)	0.0749(4)	-0.3492(3)	-0.6632(2)	6.34(10)
C(19)	0.1522(6)	-0.4376(3)	-0.6922(3)	10.8(2)

C(20)	0.0009(6)	-0.3647(3)	-0.5856(2)	9.6(1)
H(1)	0.0302	-0.2041	-1.0424	5.5891
H(2)	0.0883	-0.0604	-0.9665	6.3590
H(3)	-0.0030	-0.0348	-0.8389	5.9734
H(4)	0.0114	-0.3998	-1.0493	5.9281
H(5)	-0.1439	-0.3638	-1.1096	5.9281
H(6)	-0.1484	-0.4614	-1.0634	5.9281
H(7)	-0.5914	-0.1946	-0.9289	6.4873
H(8)	-0.4640	-0.1572	-0.8536	6.4873
H(9)	-0.6316	-0.1992	-0.8375	6.4873
H(10)	-0.6400	-0.3706	-0.9461	7.4903
H(11)	-0.6713	-0.3855	-0.8539	7.4903
H(12)	-0.5311	-0.4419	-0.8869	7.4903
H(13)	-0.3366	-0.3837	-0.7600	4.8637
H(14)	0.0653	-0.1237	-0.6942	6.9536
H(15)	-0.0313	-0.1759	-0.6318	6.9536
H(16)	0.1319	-0.2673	-0.7514	6.7976
H(17)	0.0843	-0.4622	-0.7413	12.9648

X-RAY CRYSTALLOGRAPHY REPORT FOR HEMIACETAL 141



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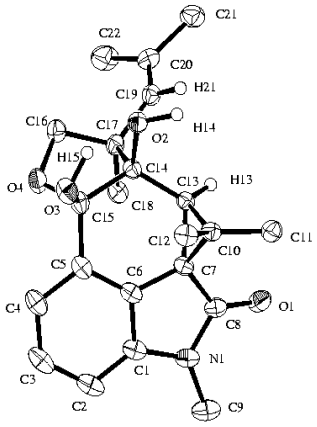


A. Crystal Data

Empirical Formula	$C_{22}H_{27}NO_4$
Formula Weight	369.46
Crystal Color, Habit	colorless, cut-block
Crystal Dimensions	0.20 X 0.33 X 0.45 mm
Crystal System	monoclinic
Lattice Type	Primitive
Lattice Parameters	a = 10.1123(3)Å b = 12.437(1) Å c = 15.961(1) Å β = 104.98(1)° V = 1939.2(2) Å3
Space Group	$P2_1/a$ (#14)
Z value	4
Dcalc	1.265 g/cm^3
F000	792.00
μ(MoKα)	0.86 cm^{-1}

B. Intensity Measurements

Diffractometer	Nonius KappaCCD

Radiation	MoKα (λ = 0.71069 Å) graphite monochromated
Take-off Angle	2.8°
Crystal to Detector Distance	35 mm
Temperature	-90.0° C
Scan Type	ω
2θmax	52.8°
No. of Reflections Measured	Total: 4067
Corrections	Lorentz-polarization
Secondary Extinction (coefficient: 1.54856e 06)	

C. Structure Solution and Refinement

Structure Solution	Direct Method(SIR92)
Refinement	Full-matrix least squares
Function Minimized	Σ w (|Fo| - |Fc|)^2
Least Squares Weights	$1/\sigma^2(Fo)$ = $4Fo^2/\sigma^2(Fo^2)$
p-factor	0.0200
Anomalous Dispersion	All non-hydrogen atoms
No. Observations (I>3.00σ(I))	3010
No. Variables	244
Reflection/Parameter Ratio	12.34
Residuals: R; Rw	0.047; 0.065
Goodness of Fit Indicator	2.56
Max Shift/Error in Final Cycle	0.00
Maximum peak in Final Diff. Map	0.22 e-/Å3
Minimum peak in Final Diff. Map	-0.22 e-/Å3

Atomic coordinates and B_{iso}/B_{eq} for Hemiacetal 141.

atom	x	y	z	Beq
O(1)	-0.1615(1)	-0.1489(1)	-0.37814(7)	3.23(3)
O(2)	-0.64204(10)	-0.18756(10)	-0.25923(7)	2.48(3)
O(3)	-0.6784(1)	0.0137(1)	-0.25830(8)	3.31(3)
O(4)	-0.5171(1)	-0.0071(1)	-0.12718(7)	3.19(3)
N(1)	-0.1828(1)	0.0317(1)	-0.35412(9)	2.90(3)
C(1)	-0.2656(2)	0.0977(2)	-0.3157(1)	2.82(4)
C(2)	-0.2464(2)	0.2016(2)	-0.2858(1)	3.54(4)
C(3)	-0.3311(2)	0.2379(2)	-0.2354(1)	3.69(5)
C(4)	-0.4278(2)	0.1720(2)	-0.2142(1)	3.15(4)
C(5)	-0.4489(2)	0.0673(1)	-0.2470(1)	2.65(4)
C(6)	-0.3713(2)	0.0342(1)	-0.30180(10)	2.52(4)
C(7)	-0.3614(2)	-0.0723(1)	-0.3377(1)	2.34(4)
C(8)	-0.2257(2)	-0.0727(2)	-0.3585(1)	2.61(4)
C(9)	-0.0560(2)	0.0655(2)	-0.3731(1)	4.11(5)
C(10)	-0.4878(2)	-0.1296(1)	-0.39996(10)	2.43(4)
C(11)	-0.4588(2)	-0.2069(2)	-0.4660(1)	3.07(4)
C(12)	-0.6170(2)	-0.0651(2)	-0.4348(1)	3.04(4)
C(13)	-0.4375(2)	-0.1624(1)	-0.30720(10)	2.17(4)
C(14)	-0.5107(1)	-0.1361(1)	-0.23735(10)	2.21(3)
C(15)	-0.5412(2)	-0.0142(1)	-0.2195(1)	2.59(4)
C(16)	-0.5023(2)	-0.1135(2)	-0.0906(1)	2.86(4)
C(17)	-0.4271(2)	-0.1759(1)	-0.14655(10)	2.34(4)
C(18)	-0.2776(2)	-0.1369(2)	-0.1274(1)	2.72(4)

C(19)	-0.4318(2)	-0.2972(2)	-0.1425(1)	2.51(4)
C(20)	-0.3843(2)	-0.3638(2)	-0.0762(1)	2.87(4)
C(21)	-0.3884(2)	-0.4828(2)	-0.0904(1)	3.68(5)
C(22)	-0.3207(2)	-0.3304(2)	0.0150(1)	4.32(5)
H(1)	-0.1785	0.2467	-0.2988	4.2524
H(2)	-0.3223	0.3100	-0.2151	4.4309
H(3)	-0.4803	0.1981	-0.1770	3.7784
H(4)	0.0133	0.0733	-0.3204	4.9327
H(5)	-0.0285	0.0129	-0.4083	4.9327
H(6)	-0.0699	0.1323	-0.4030	4.9327
H(7)	-0.3729	-0.2407	-0.4428	3.6899
H(8)	-0.5288	-0.2599	-0.4795	3.6899
H(9)	-0.4566	-0.1687	-0.5171	3.6899
H(10)	-0.6317	-0.0190	-0.3906	3.6488
H(11)	-0.6080	-0.0231	-0.4827	3.6488
H(12)	-0.6927	-0.1125	-0.4529	3.6488
H(13)	-0.3897	-0.2289	-0.2988	2.6026
H(14)	-0.6491	-0.2437	-0.3065	3.5348
H(15)	-0.7263	-0.0605	-0.2666	3.5348
H(16)	-0.4501	-0.1119	-0.0318	3.4372
H(17)	-0.5893	-0.1446	-0.0939	3.4372
H(18)	-0.2760	-0.0607	-0.1312	3.2599
H(19)	-0.2295	-0.1588	-0.0707	3.2599
H(20)	-0.2352	-0.1672	-0.1686	3.2599
H(21)	-0.4755	-0.3313	-0.1957	3.0060
H(22)	-0.4348	-0.4981	-0.1490	4.4209

H(23)	-0.4354	-0.5161	-0.0529	4.4209
H(24)	-0.2976	-0.5100	-0.0784	4.4209
H(25)	-0.3240	-0.2544	0.0193	5.1827
H(26)	-0.3695	-0.3621	0.0522	5.1827
H(27)	-0.2281	-0.3537	0.0316	5.1827

CHAPTER FOUR

Construction of the Welwitindolinone Skeleton

4.1 Initial Attempts at Assembling the Welwitindolinone Skeleton.

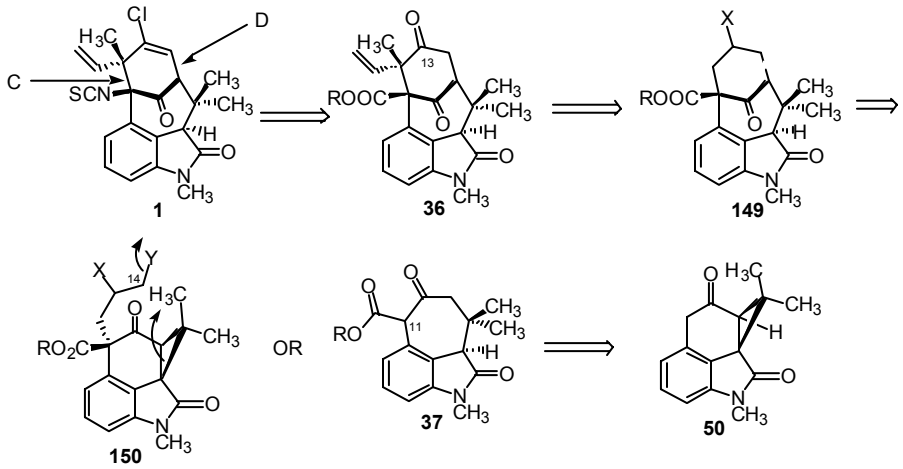
4.1.1 Retrosynthetic Analysis.

After encountering problems advancing alcohols **132** and **133** (Chapter 3), the strategy was modified by considering alternatives for advancing ketone **50** (Scheme 4.1.1). In advancing this substrate, several issues needed consideration, including unveiling of the seven-membered ring found in the natural products and construction of the final six-membered ring. Focusing efforts on installing the final cyclohexene ring and thus completing the skeleton of the welwitindolinone alkaloids, a new retrosynthetic analysis was devised, one which entails a more detailed, yet still flexible plan for the construction of bonds C and D.

As previously described, an approach was envisioned which would call for the late introduction of the sensitive isothiocyanate and chloroolefin moieties. However, in this approach, the isothiocyanate would be introduced from an ester, as found in diketone **36**, a compound which can be simplified to **149** by removing the quaternary centers, which will be addressed at a later stage, and generalizing the functionality at C(13). Intermediate **149** was imagined as arising from the

oxindole core **50**, either through **150** or **37**. Using intermediate **150**, which may be accessed from **50** *via* benzylic acylation and alkylation, unveiling the seven-membered ring and concomitantly forming bond D was envisioned to furnish **149**. Alternatively, **37**, which may be accessed from **50** by benzylic acylation and cleavage of the cyclopropane ring, would provide a flexible means of building the skeleton *via* alkylation chemistry, possibly in one step, taking advantage of the β-keto ester functionality. Both approaches (i.e., **149**⇒**150** or **37**) focus on the reactivity of a β-keto ester, and involve construction of bond C prior to bond D.

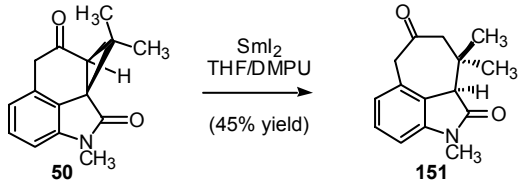
Scheme 4.1.1



4.1.2 First Attempt at Constructing the Skeleton: Alkylation With Acrolein.

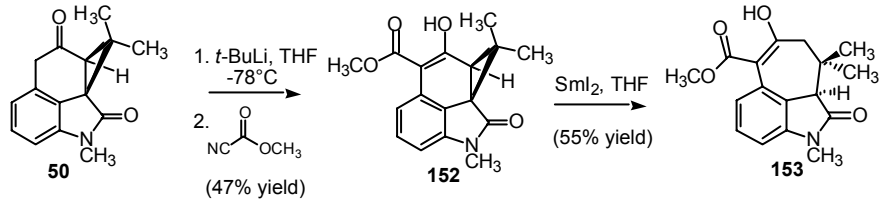
Focusing on the approach involving **37**, the issue of ring-opening was first addressed. Thus, exposure of ketone **50** to samarium diiodide leads to rapid cleavage of the desired, internal bond of the cyclopropane ring to provide cycloheptane **151** (Scheme 4.1.2).[1] Although this furnishes a rather under-functionalized system, this experiment established the feasibility of reductive cyclopropane opening and hence the possibility of carrying a more elaborate system into a tandem sequence like that illustrated in 4.1.1 (**149**⇒**150**).

Scheme 4.1.2



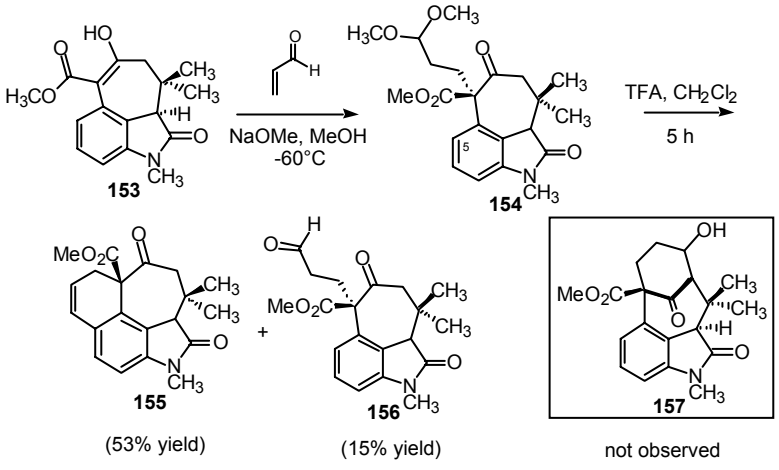
Having established conditions for unveiling the seven-membered ring, efforts toward construction of a more advanced oxindole core were initiated by functionalizing at the benzylic position. To this end, **153** can be accessed quite easily *via* initial alkylation of **50** with methylcyanoformate in a modified Mander reaction (Scheme 4.1.3).[2] Treatment of the derived ester **152** with SmI_2 for several days was found to rupture the cyclopropane ring and furnish the requisite ring-expanded product **153**.[3]

Scheme 4.1.3



With access to **153**, studies on its reactivity with different electrophiles were initiated. In the event, **153** was found to be quite amenable to alkylation, reacting with base and acrolein to produce **154**, the dimethylacetal of the corresponding Michael adduct (Scheme 4.1.4). In an effort to complete the welwitindolinone carbon skeleton, the latter product was employed in numerous intramolecular aldol reactions. Unfortunately, the tendency of this substrate to undergo Friedel-Crafts-type chemistry was prohibitive to this effort (see **154**→**155**, **156**).[4]

Scheme 4.1.4

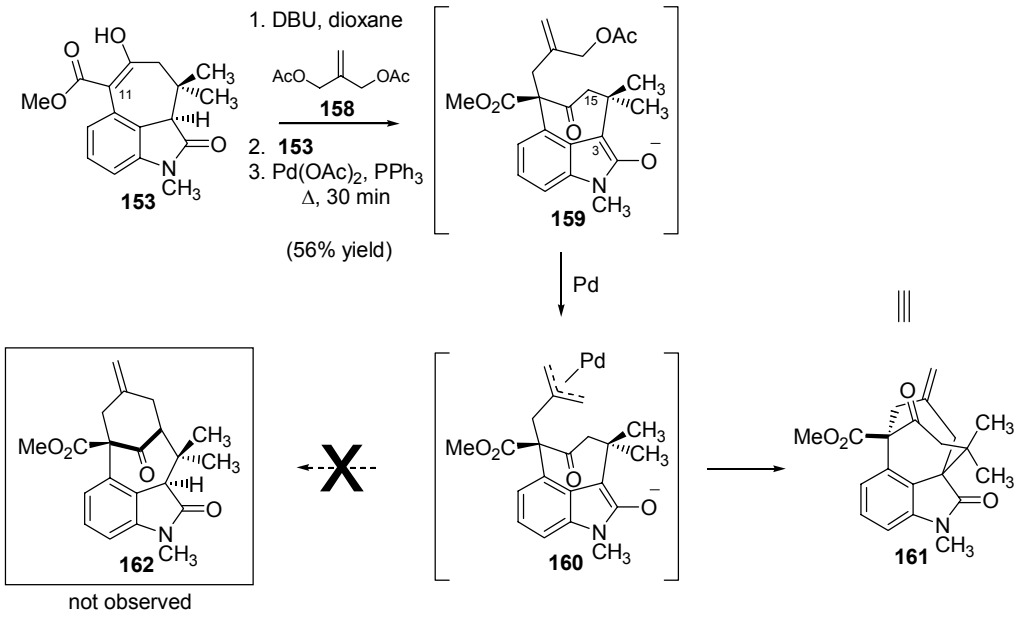


4.1.3 Second Attempt at the Skeleton: A Palladium Approach.

Given the undesired propensity for aryl substitution, a new approach for skeleton construction was devised. Thus, it was envisioned that both bonds C

and D of the skeleton (Scheme 4.1.1) could be installed in one step, using palladium chemistry. For example, treatment of **153** with diacetate **158** in the presence of a catalytic amount of $Pd(OAc)_2$ may lead to olefin **162** (Scheme 4.1.5).[5,6] Unfortunately, the sole product formed in this reaction was not olefin **162**, but rather **161**, a product which derives from intermediate acetate **159** *via* intramolecular alkylation of a C(3) enolate with the π-allyl system. This experiment highlights potential problems associated with the acidic proton at C(3) and is reminiscent of observations made in Chapter 2 (i.e., **45**→**46** and **47**). All attempts to protect C(3) or alter the reaction by using excess base were unsuccessful, thus yet another new approach was devised.

Scheme 4.1.5



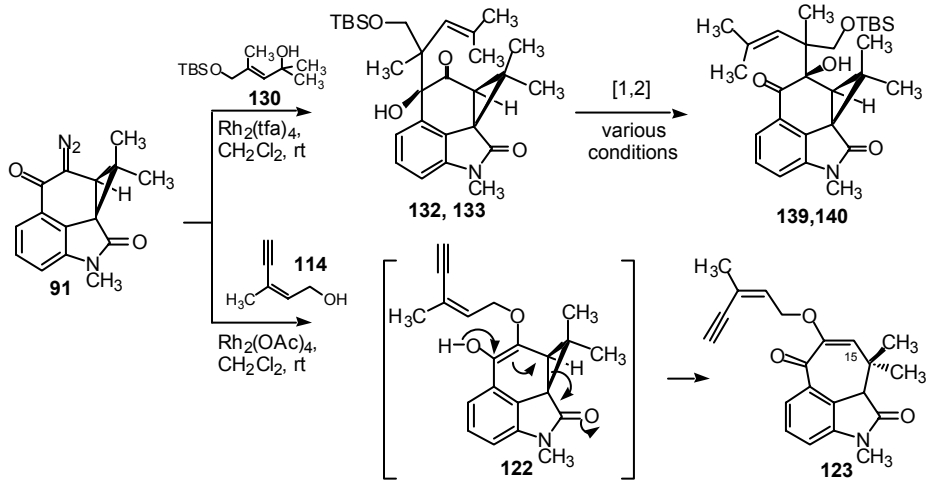
4.2 Construction of the Welwitindolinone Skeleton.

4.2.1 Background: A Ring-Closing Metathesis Approach to the Welwitindolinone Skeleton.[7]

4.2.1.1 Retrosynthetic Analysis.

After these unsuccessful attempts, the strategy was dramatically modifed. First, realizing that diazo ketone **91** (Scheme 4.2.1) is an easily prepared and versatile intermediate, its advancement was reconsidered. Unable to circumvent the deleterious rearrangements of **132** and **133** to **139** and **140**, attention was turned to advancing **91** by taking advantage of the ring-opening phenomenon (i.e., **91**→**123**).

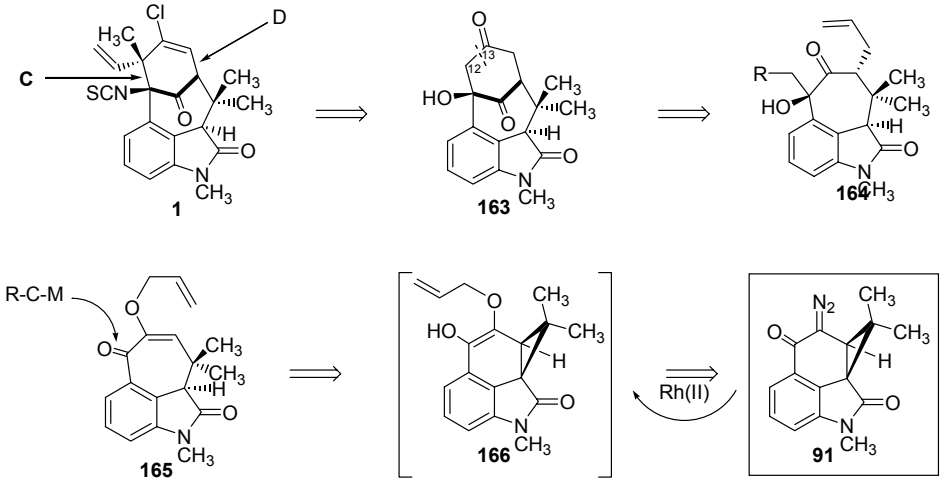
Scheme 4.2.1



In returning to diazo ketone **91**, the notion of introducing the isothiocyanate from an alcohol, instead of an ester (see **1**→**63**, Scheme 4.2.2), was also reconsidered. Cleavage of the C(12)-C(13) bond of **163** provides

alcohol **164**. The cyclopropane ring was again envisioned as a handle in forming bond D, this time indirectly, from **91**. Thus, **164** could be accessed from enol ether **165** by nucleophillic addition into the benzylic ketone and thermal Claisen rearrangement to construct bonds C and D of the skeleton, respectively. The allylic enol ether **165** was expected to arise from diazo ketone **91** through an enol intermediate (i.e., **166**) as was discussed in Chapter 3.

Scheme 4.2.2

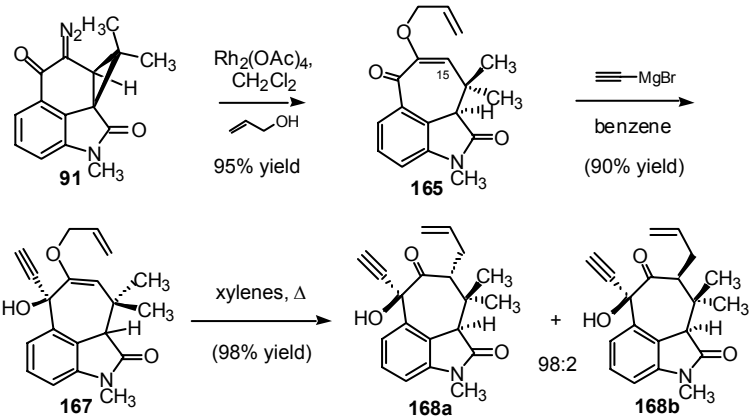


4.2.1.2 Completion of the Skeleton.

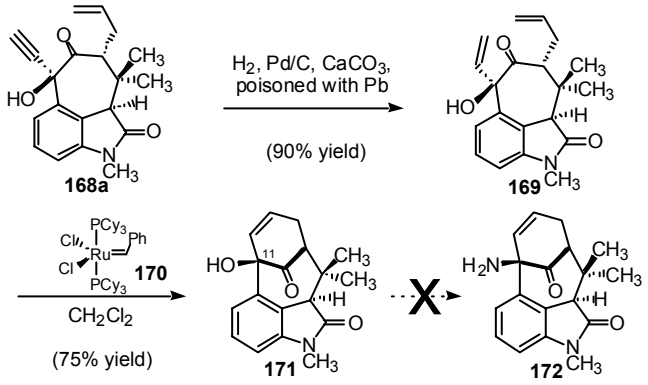
In accord with previous studies (Chapter 3), the Rh(II)-catalyzed coupling of diazo ketone **91** with allyl alcohol results in enol formation followed by ring-opening to furnish enol ether **165** (Scheme 4.2.3). Delightfully, **165** can be advanced to **167** by exposure to ethynyl Grignard and, in turn, **167** rearranges to a 98:2 mixture of ketones **168a** and **168b** upon heating.[8] Having finally constructed the fastidious bond D, the major isomer (**168a**, confirmed *via* X-ray crystallography) was exposed to H_2 in the presence of Lindlar's catalyst and the derived diene **169** was treated with Grubbs's catalyst (**170**) to provide olefin **171**,

a compound possessing the complete welwitindolinone carbon skeleton (Scheme 4.2.4).[9,10] Unfortunately, all attempts to convert the C(11) alcohol of **171** to an amine (i.e., **172**) *via* Ritter chemistry were unsuccessful which led to the following, final approach.

Scheme 4.2.3



Scheme 4.2.4

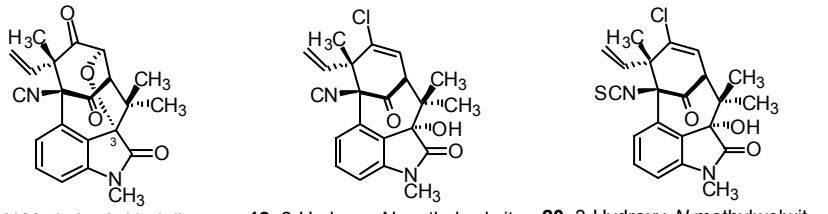


4.2.2 Completion of the Welwitindolinone Skeleton *via* a Nitrone-Olefin Cycloaddition.

4.2.2.1 Isolation of Oxidized Welwitindolinones 17, 18, and 20.

As discussed in Chapter 1, several novel welwitindolinones were recently isolated, all of which are oxidized at C(3) (i.e., **17**, **18** and **20**, Figure 4.2.1).[11] Given that the compounds were isolated about the time modifications of the synthesis were being made, efforts focused on approaches which could access not only the original welwitindolinones, but also the oxidized welwitindolinones from a common intermediate.

Figure 4.2.1



17 *N*-Methylwelwitindolinone D isonitrile

18 3-Hydroxy-*N*-methylwelwitindolinone B isonitrile

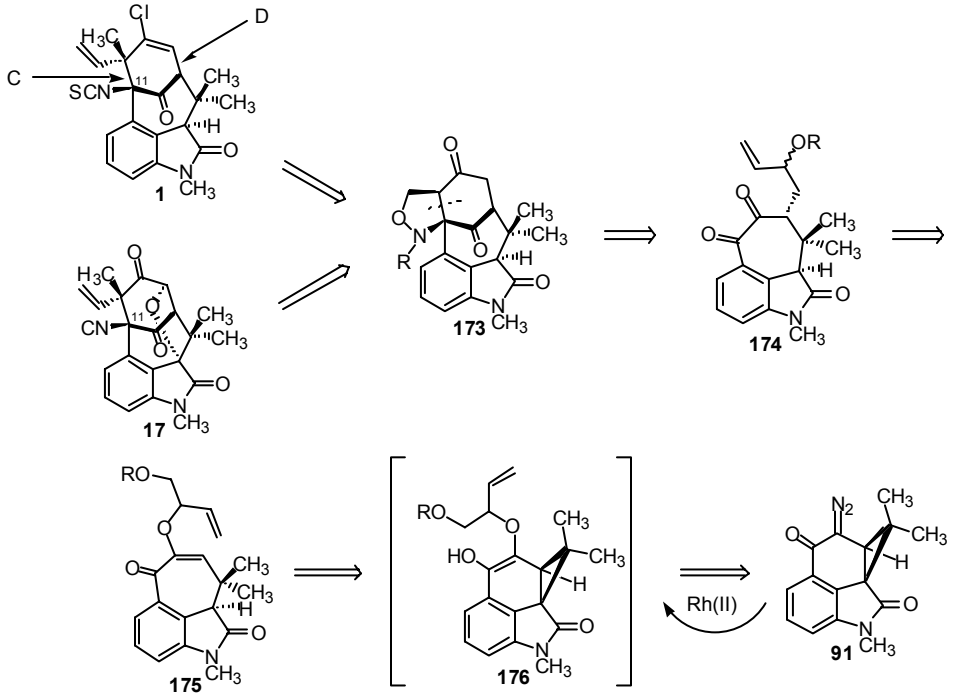
20 3-Hydroxy-*N*-methylwelwitindolinone B isothiocyanate

4.2.2.2 Retrosynthetic Analysis.

In addition to accounting for the recently isolated welwitindolinone congeners, a strategy was considered that would benefit, as much as possible, from previous efforts. To this end, several welwitindolinones could be accessed from diketone **173**, obtaining both the isonitrile and isothiocyanate moieties from the corresponding amine (Scheme 4.2.5).[12] In contrast to previous routes, which focused on late construction of bond D, this new strategy calls for the formation of bond C at a late stage, from diketone **174**. Bond D and the requisite

bridgehead amine are now envisioned as arising *via* nitrone formation at the benzylic ketone of olefin **174** followed by transannular cycloaddition.[13] In accord with previous efforts, construction of bond D to furnish olefin **174** was envisioned to take place *via* thermal Claisen rearrangement of enol ether **175**, which, in turn, derives from diazo ketone **91** *via* enol intermediate **176**.

Scheme 4.2.5

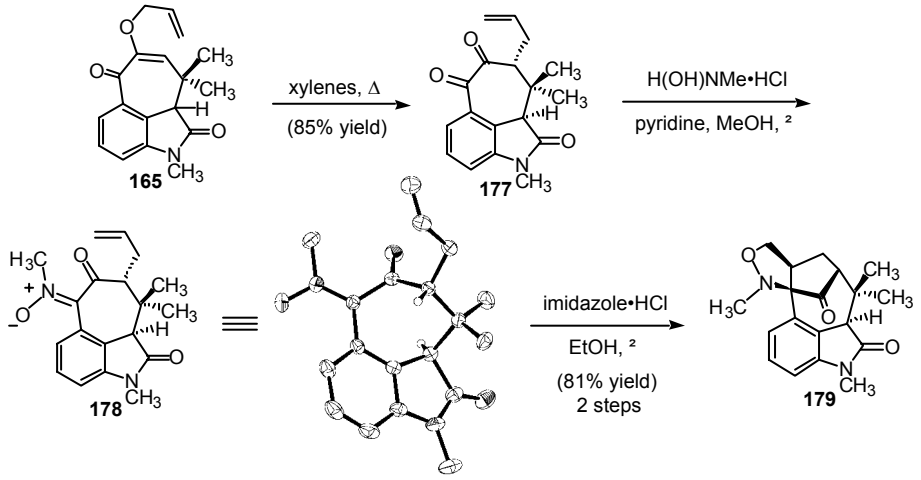


4.2.2.3 Nitrone Cycloaddition: A Model Study.

Recognizing the potential utility of intermediates like diketone **174**, feasibility studies into the requisite regioselective nitrone formation and transannular cycloaddition were initiated (Scheme 4.2.6). To set the stage for these studies, enol ether **165** was converted to the corresponding diketone **177** by simply warming in xylenes at reflux. Surprisingly, this reaction provides a single diastereomer of diketone **177**, which undergoes selective nitrone formation

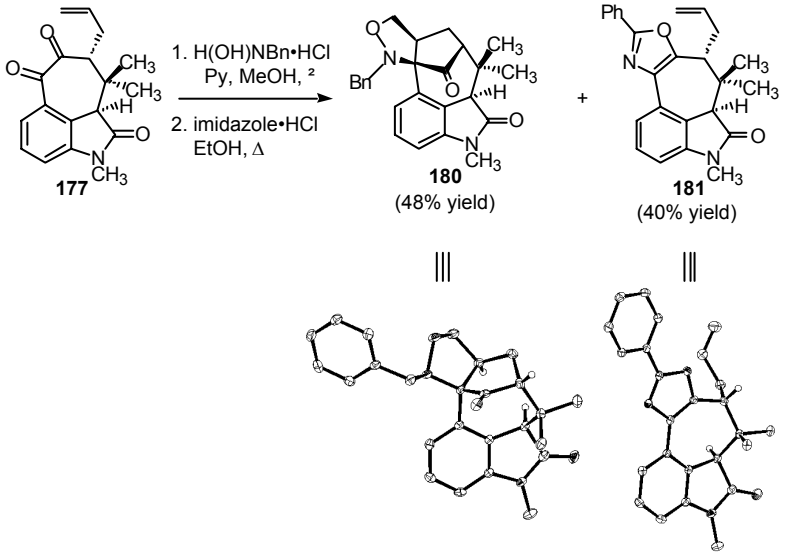
at the benzylic position upon treatment with *N*-methylhydroxylamine to furnish **178**, a result which was confirmed by X-ray crystallography (see Appendix 6 for X-ray report). Moreover, upon further heating, **178** undergoes a clean [3+2] nitrone cycloaddition to furnish **179**, a compound possessing the requisite bridgehead nitrogen.

Scheme 4.2.6

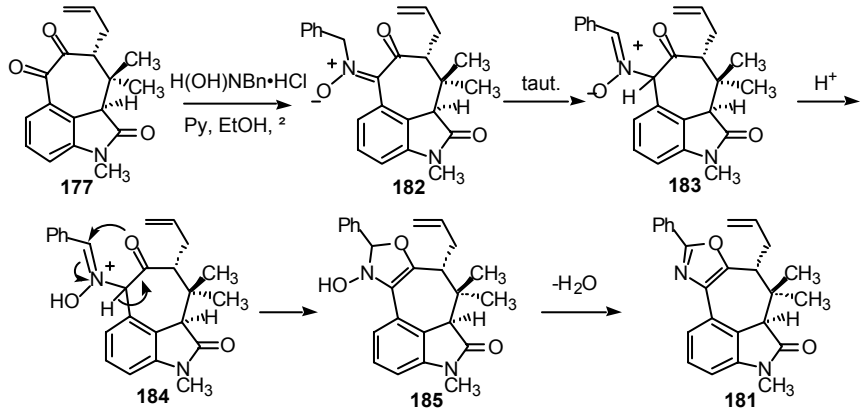


Concerned about future difficulty in demethylating the isoxazolidine nitrogen, similar studies were performed utilizing *N*-benzylhydroxylamine (see Scheme 4.2.7). Although the desired product **180** was obtained by heating diketone **177** in the presence of *N*-benzylhydroxylamine, it was accompanied by a nearly equimolar amount of oxazole **181**. As illustrated in Scheme 4.2.8, this product is believed to arise from benzylic nitrone **182** *via* tautomerization and protonation which affords cyclization substrate **184**. Dehydration of the cyclized product **185** would then furnish oxazole **181**.[14] Based on this mechanistic hypothesis, the acidic methylene protons of the benzyl group were believed to be promoting the deleterious side reaction, hence *N*-methylhydroxylamine was used in subsequent studies.[15]

Scheme 4.2.7



Scheme 4.2.8



4.2.2.4 Nitrone Cycloaddition: Introduction of the Quaternary Centers.

Further investigation using *N*-methylhydroxylamine revealed that similar regioselectivity in the nitrone formation could be achieved with more heavily functionalized dipolarophiles, namely one which could provide access to the desired six-membered ring. Thus, as depicted in Scheme 4.2.9, exposure of diazo ketone **91** to alcohol **186** produces enol ether **187** which upon heating

undergoes smooth conversion to **188**.[16] Subsequent exposure of **188** to *N*-methylhydroxylamine did indeed furnish a transannular nitrone cycloadduct. However, the nitrone preferentially reacts with the olefin to again provide a five-membered ring (i.e., cyclopentane **189**) instead of the desired [4.3.1] bicycle **190**. Confirmation of structure followed from single crystal X-ray analysis (see Figure 4.2.2 and Appendix 6 for X-ray structure report). Of particular note is that although the proper ring size was not installed directly, this transformation delivers the complete vicinal quaternary system in a single stereoselective step. Thus, as one might imagine, the possibility of effecting a ring expansion of **189** to a compound containing the welwitindolinone skeleton was considered. These efforts, which would in any case ultimately destroy the newly formed quaternary center, were of no avail.[17,18] Therefore, an alternative allylic alcohol substrate was explored.

Scheme 4.2.9

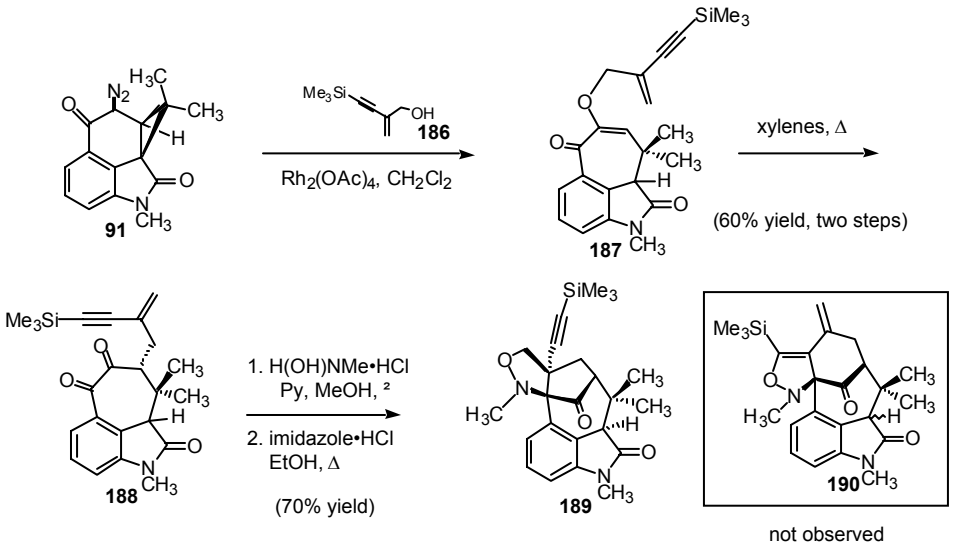
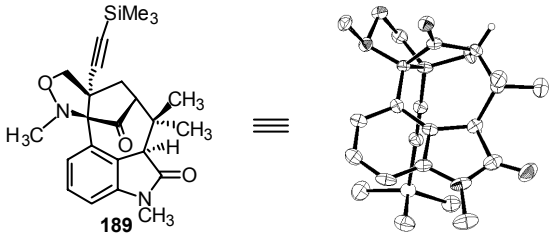


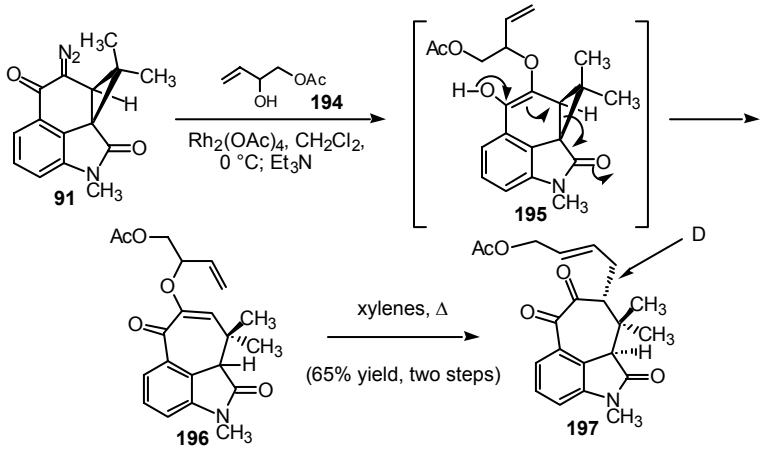
Figure 4.2.2



4.2.2.5 Construction of a 4.3.1 System.

In considering alternative allylic alcohols, approaches were envisioned incorporating substrates that, in addition to furnishing the appropriate ring size would be suitable for constructing the vicinal quaternary centers. To this end, coupling α-diazo ketone **91** with allylic alcohol **194** in the presence of $Rh_2(OAc)_4$ followed by tautomerization of the resulting enol **195** with triethylamine furnishes enol ether **196** (Scheme 4.2.10).[19,20] Subsequent thermal Claisen rearrangement of crude vinyl ether **196** stereoselectively provides the vicinal diketone **197**.

Scheme 4.2.10



With bond D formed (**197**, Scheme 4.2.10), the required allylic transposition was explored . After much experimentation, it was found that a

palladium-mediated allylic migration provides two diastereomers of the desired, contrathermodynamic acetate **198** in a 1:1.4 ratio with recovered starting acetate **197** (Scheme 4.2.11).[21] Fortunately, **197** and **198** can be separated *via* flash chromatography and the former recycled. The structure of the minor diastereomer **198a** was confirmed *via* X-ray crystallography (see Figure 4.2.3 and Appendix 6 for X-ray structure report).

Scheme 4.2.11

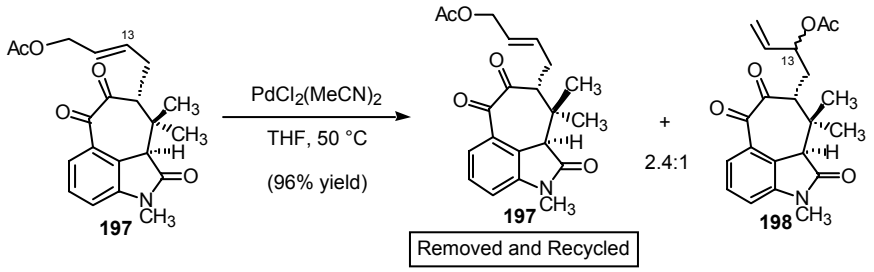
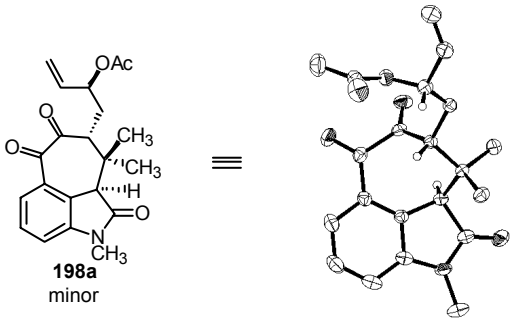


Figure 4.2.3



Having finally accessed a substrate with the potential for providing the entire welwitindolinone carbon framework and the requisite C(11) nitrogen, the nitrone cycloaddition was explored. After considerable experimentation,[22] it was found that exposure of diketones **198** to *N*-methylhydroxylamine in refluxing ethanol produces a complex mixture of products comprised of three diastereomeric transannular nitrone cycloadducts **199** (65% yield) and oxazole **200** (3% yield) (Scheme 4.2.12).[23] To establish the structure, one of the

diastereomeric cycloadducts (**199a**) was separated, recrystallized, and subjected to single crystal X-ray analysis (see ORTEP, Figure 4.2.4, and Appendix 6 for X-ray structure report).

Scheme 4.2.12

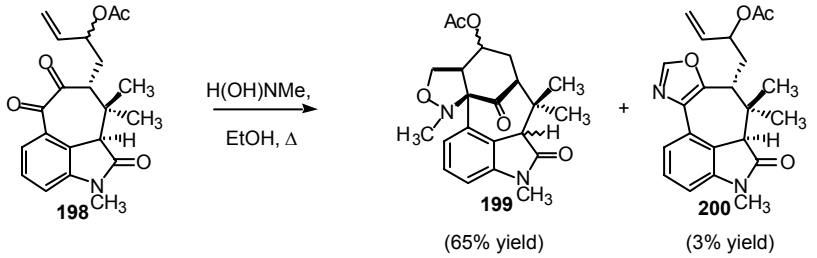
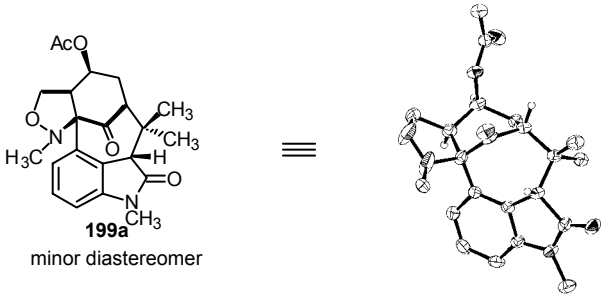
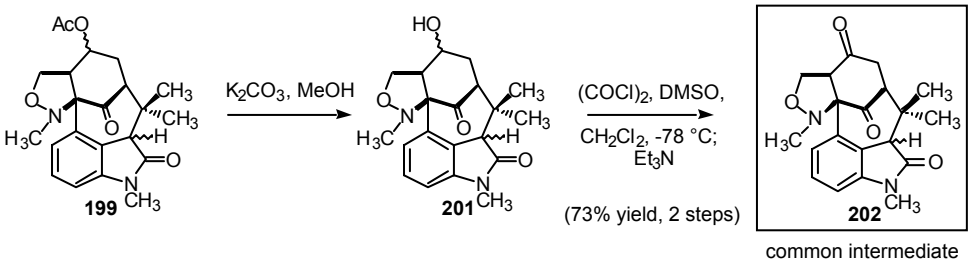


Figure 4.2.4



Moving beyond the complete carbon framework, efforts were focused on advancing the [4.3.1] system to an intermediate that would provide flexible access to several of the welwitindolinones. Thus, the mixture of diastereomers **199** were, without separation, deprotected to provide four diastereomeric alcohols **201** (Scheme 4.2.13), again reaffirming the epimerizability of C(3).[24] Oxidation of **201** using the Swern protocol furnishes ketones **202**, the common intermediates which may provide access to several welwitindolinones. To this end, issues remaining to be addressed in this synthesis are introduction of the quaternary center, N-O bond cleavage, *N*-demethylation, and introduction of the vinyl chloride and isonitrile/isothiocyanate moieties.

Scheme 4.2.13

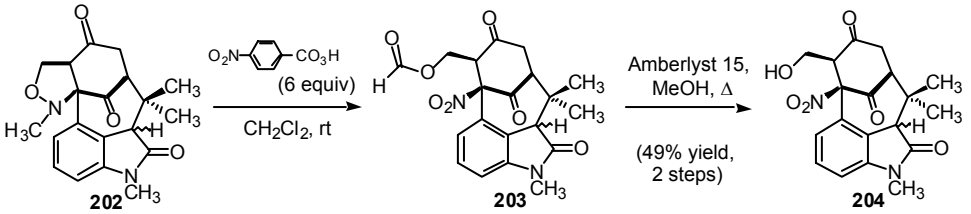


4.2.2.6 Advancement of Ketones 202.

In advancing ketones **202** to *N*-methylwelwitindolinone C isothiocyanate (**1**), the first issues addressed were cleavage of the isoxazolidine and *N*-demethylation.[25] The most common method reported for N-O bond cleavage of isoxazolidines involves reductive cleavage of the isoxazolidine bond,[26] which in the current system leads to mixtures of products due to epimerization at C(3) and reduction of the ketones to provide diastereomeric alcohols. Therefore, an oxidative approach to N-O bond cleavage was envisioned, *via* formation of the *N*-oxide followed by manipulation to cleave the N-O bond.

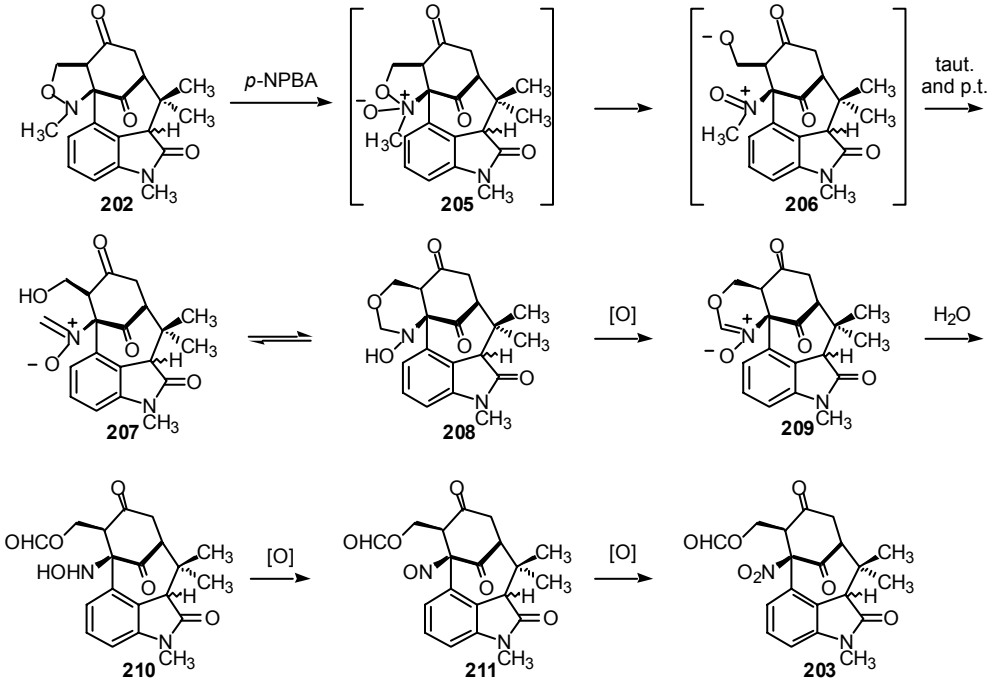
To this end, treating isoxazolidine **202** with an excess of *p*-nitroperoxybenzoic acid exhaustively oxidizes the isoxazolidine moiety to furnish nitro-formate **203** (Scheme 4.2.14),[27] a seemingly useful reaction given that it not only cleaves the N-O bond but also *N*-demethylates and simultaneously protects the reactive amine as a nitro group. Removal of the formate under acidic conditions gives rise to alcohol **204**.

Scheme 4.2.14

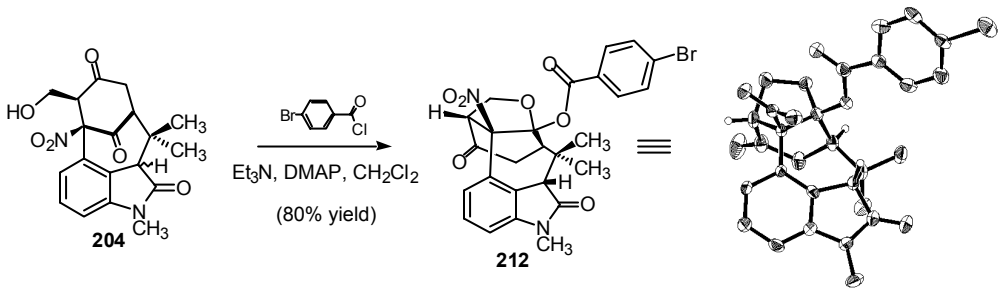


As illustrated in Scheme 4.2.15, **203** is believed to arise *via* initial *N*-oxide formation of **202** (i.e., **205**), followed by fragmentation to **206**, tautomerization and proton transfer to nitrone **207** which can close to yield oxazine **208**. Further oxidation of **208** leads to nitroso formate **211** (*via* **210**) which upon additional oxidation leads to nitro formate **203**. Confirmation of this oxidation event (**202**→**203**) was secured *via* X-ray crystallography of the *p*-bromobenzoyl derivative of **204** (**212,** Scheme 4.2.16, see Appendix 6 for X-ray structure report).[26]

Scheme 4.2.15



Scheme 4.2.16



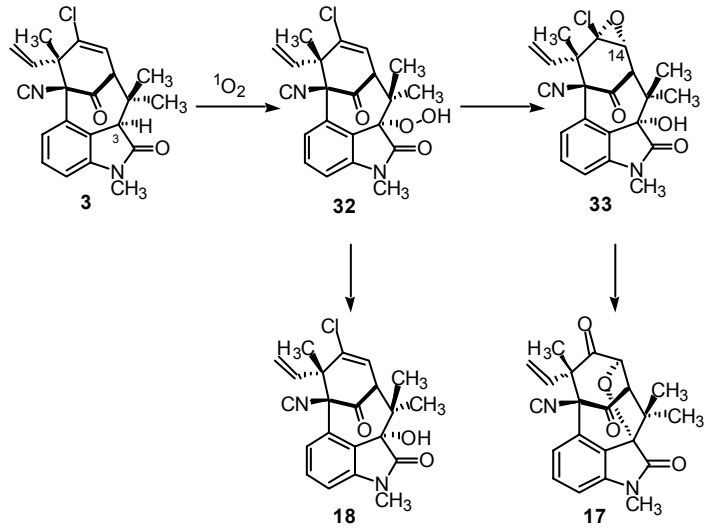
After attempting to advance alcohol **204**, this approach became discouraging when extensive attempts to reduce the tertiary nitro moiety to an amine were unsuccessful.[28] Thus, efforts were focused on other means of N-O bond cleavage[29] and the feasibility of advancing ketone **202** to the C(3)-oxidized welwitindolinones (Figure 4.2.1).

4.2.2.7 Progress Towards the C(3)-Oxidized Welwitindolinones.

4.2.2.7.1 Background.

As was discussed in Chapter 1 (Section 1.2.2) *N*-methylwelwitindolinone D isonitrile (**17**, Scheme 4.2.17) is believed to arise *via* photooxidation of *N*-methylwelwitindolinone C isonitrile (**3**). Jimenez and coworkers have shown that **17** can in fact be derived from **3** *via* treatment with oxygen while irradiating.[30] Although this result was significant biosynthetically, the yields were extremely low and reaction times were long.[31] Nevertheless, based on these previous results, it was reasoned that if ketone **202** or its corresponding enolate or enol ether could be oxidized at C(3), the products might undergo similar chemistry as observed by Jimenez.

Scheme 4.2.17

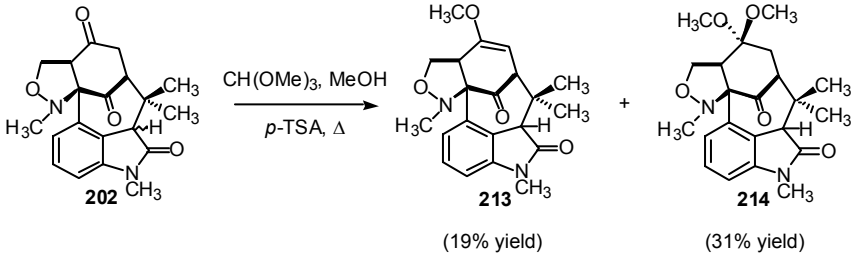


4.2.2.7.2 Oxidation at C(3).

To explore this hypothesis, efforts to oxidize at C(3) were initiated. Several examples were found in the literature involving oxidation at a benzylic position *via* treatment with base and oxygen.[32] The first substrate to be explored was enol ether **213**, a substrate imagined to be easiest to study due to the fact that it contains only one acidic proton (i.e., at C(3)). Thus, **213** was prepared from diketone **202** by treatment with trimethylorthoformate in acidic MeOH (Scheme 4.2.18, this reaction also provides dimethylacetal **214**).[33] Delightfully, subsequent exposure of **213** to oxygen under basic conditions cleanly results in a mixture of peroxide **215** and a small amount of alcohol **216** (Scheme 4.2.19), which, after treatment with thioanisole, leads to the complete conversion to alcohol **216**. Single crystal X-ray analysis of **216** demonstrated that oxidation of **213** takes place solely on the desired α-face (Figure 4.2.5, see Appendix 6 for X-ray report). Interestingly, when the mixture of **215** and **216** is left undisturbed in $CDCl_3$ for one day, NMR analysis shows the presence of several products (Scheme 4.2.20). Purification by flash chromatography provides a mixture of

unreacted alcohol **216** in addition to a new compound, which was tentatively assigned *via* NMR analysis and mass spectrometry as ether **217**.[34]

Scheme 4.2.18



Scheme 4.2.19

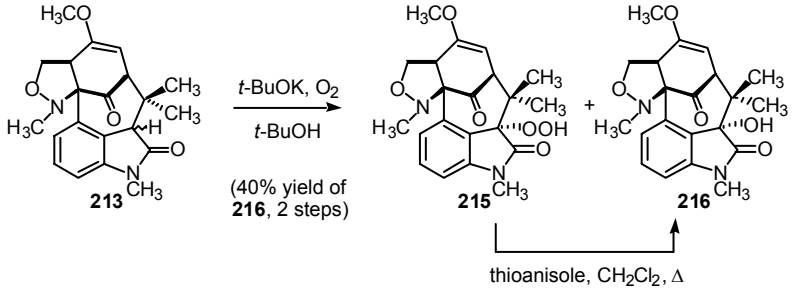
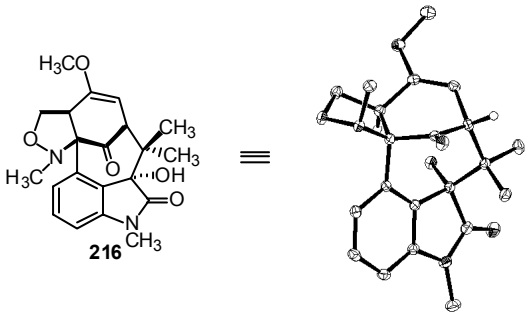
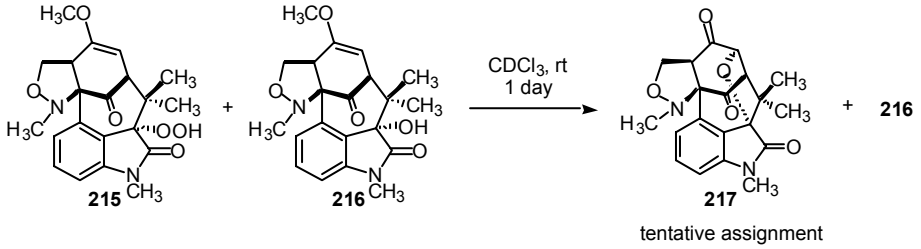


Figure 4.2.5

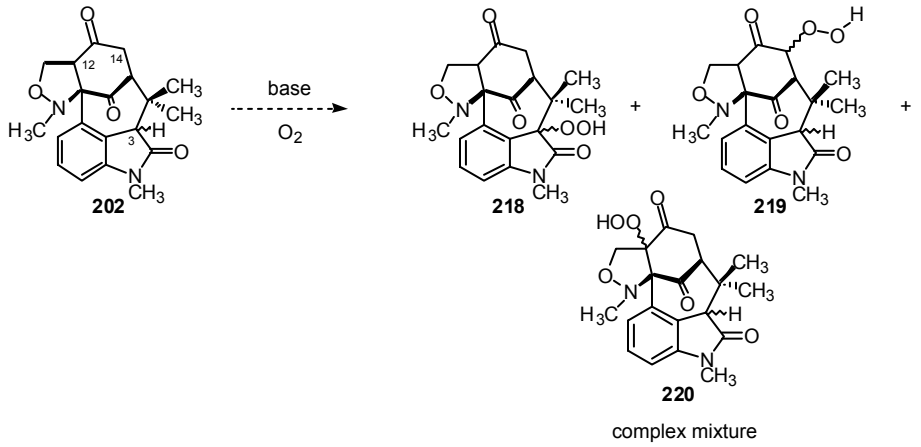


Scheme 4.2.20



Owing to the poor yield in preparing the methyl enol ether **213** and the uncertainty of the structure assigned to **217**, the ability of the parent ketone **202** to engage in similar reactions was explored. This approach was bold and not promising due to the presence of three acidic protons (at C(12), C(14), and C(3)), all of which were imagined to form enolates under basic conditions and subsequently react with oxygen, which could give rise to a complex mixture of diastereomeric peroxides (Scheme 4.2.21).

Scheme 4.2.21

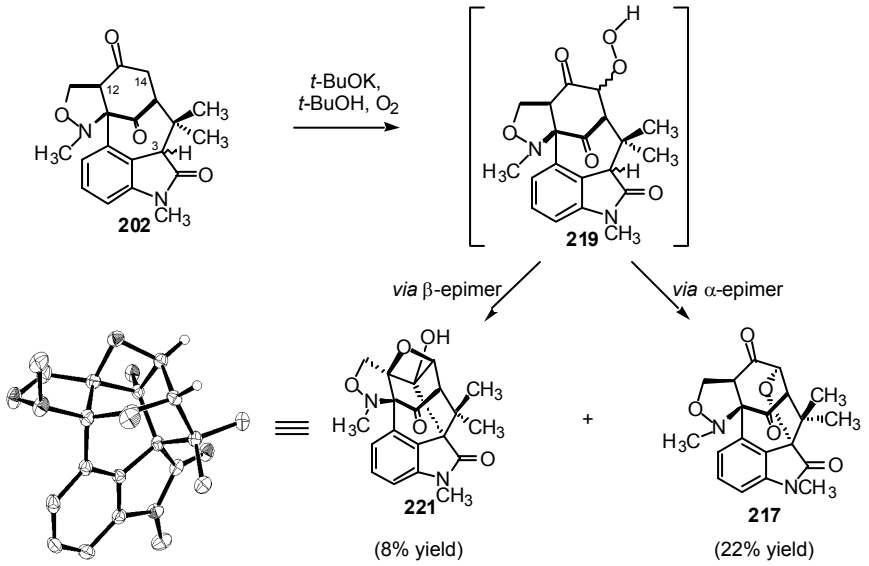


Nevertheless, in the event, treatment of diketone **202** with one equivalent of base followed by oxygen leads only to epimerization at C(3). Surprisingly, when **202** is treated with excess base (4 equiv) and oxygen, the clean formation of only two products is observed *via* crude NMR analysis, rather than the

expected complex mixture (Scheme 4.2.22). After isolation and characterization, these products were determined to be oxetane **221** and the desired ether **217**. Interestingly, the NMR spectrum for the latter product was identical in all respects to the product obtained from peroxide **215** (**217**, Scheme 4.2.20), thus supporting the tentative structure assignment.

The results of these investigations suggest that upon treatment of **202** with excess base, enolates are initially formed at C(3) and C(14) (Scheme 4.2.22). Subsequent reaction of the more reactive enolate at C(14) with oxygen from both the α- and β-face would lead to formation of diastereomeric α-hydroperoxy ketones **219**, from which both **221** and **217** may arise. In the case of the β-face α-hydroperoxy ketone **219**, an enolate subsequently formed at C(12) can displace a hydroxyl group to form an oxetane. Ensuing attack of the C(3) enolate into the ketone furnishes tertiary alcohol **221**, a product confirmed *via* X-ray crystallography (see Appendix 6). Alternatively, if the peroxide is formed from the α-face, then displacement of a hydroxyl by the C(3) enolate would provide the ether-bridged ketone **217**.

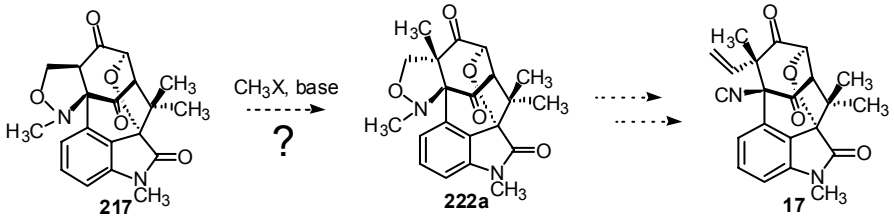
Scheme 4.2.22



4.2.2.7.3 Introduction of the Final Quaternary Center.

After completing the assembly of the entire cyclic skeleton of *N*-methylwelwitindolinone D isonitrile, efforts were focused on the quaternary center at C(12). To this end, only one additional C-C bond needed to be formed, and given the nature of the substrate, the newly introduced atom could be either a methyl or a precursor to the requisite vinyl moiety. The most direct route was explored first, i.e., β-face methylation of ketone **217**, even though this would lead to a strained, trans-fused product (**222a**, Scheme 4.2.23).

Scheme 4.2.23



To this end, treatment of ketone **217** with base and methyl iodide leads to the clean formation of two products, identified as the O-alkylation product **223** and C-alkylation product **222b** (Scheme 4.2.24). X-ray analysis of ketone **222b** (Figure 4.2.6) illustrates two important points. First, the ether bridge from C(3) to C(14) was in fact formed with the treatment of **202** with base and oxygen (Scheme 4.2.22). Second, the ORTEP unambiguously shows that, as suspected, the alkylation occurs from the α-face providing the incorrect relative stereochemistry at C(12) (see Appendix 6 for X-ray report).

Scheme 4.2.24

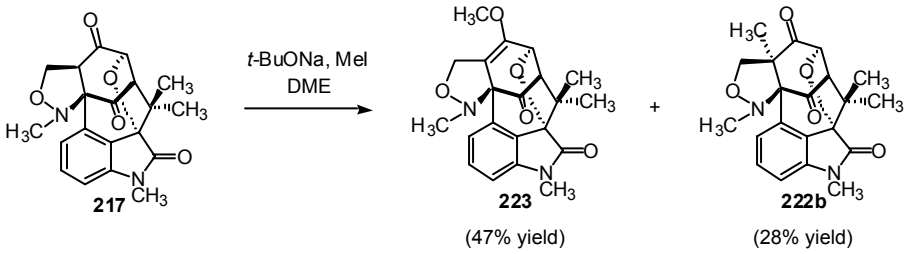
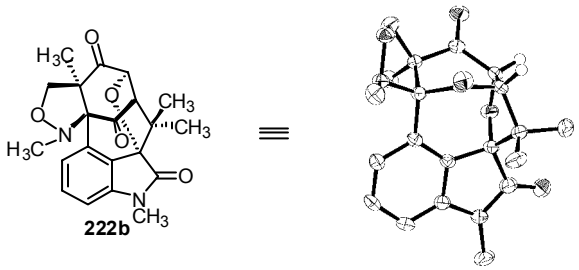


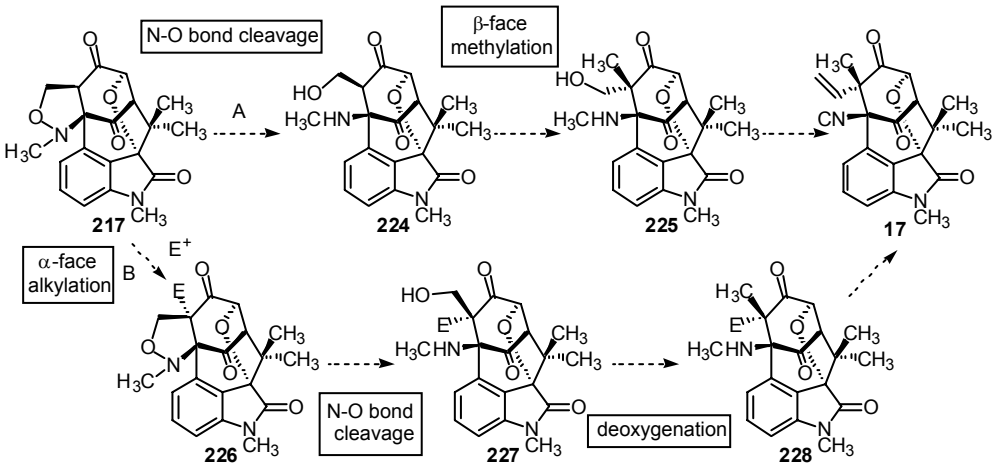
Figure 4.2.6



Since alkylation of **217** is preferred from the α-face, there remained two options for proper introduction of the quaternary centers. As illustrated in Scheme 4.2.25, initial cleavage of the N-O bond of **217** (Path A) to furnish **224** would eliminate the issue of strain and thus may allow for β-face methylation (i.e., **224**$\rightarrow$**225**). Alternatively, as shown in Path B, an electrophile capable of conversion to the vinyl moiety could be used to alkylate the α-face (**217**$\rightarrow$**226**).

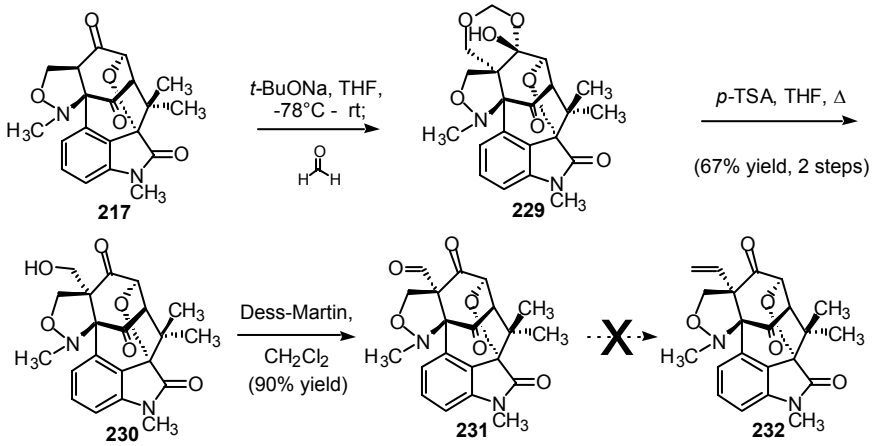
The primary alcohol functionality remaining after N-O bond cleavage to **227** could then be converted into the requisite methyl group *via* deoxygenation (i.e., **227**→**228**). Both of these strategies were explored, however the latter, Path B, proved to be more successful.

Scheme 4.2.25



Thus, treatment of ketone **217** with base and formaldehyde quickly furnishes a new product identified by crude NMR as acetal **229** (Scheme 4.2.26). Hydrolysis of **229** provides alcohol **230**, the desired aldol product. Dess-Martin oxidation of **230** gives rise to aldehyde **231**, a product well-suited for advancement to *N*-methylwelwitindolinone D isonitrile. Unfortunately, attempts to advance **231** to **232** have to date been unsuccessful,[35] and new strategies towards the welwitindolinone synthesis from cycloadduct **199** are currently being explored.[36]

Scheme 4.2.26



4.3 Conclusion.

After several unsuccessful attempts in constructing the welwitindolinone skeleton, the goal was finally realized, first *via* an olefin metathesis approach as part of another study in these laboratories. Although the metathesis product (**171**) could not be advanced, in the course of these studies was discovered a means of using the already beneficial cyclopropane ring as a handle in forming bond D of the welwitindolinone skeleton. These studies opened doors to a new and successful approach in building the framework that involves a nitrone [3+2] cycloaddition of diketone **198**. This transannular reaction not only constructs the entire carbon framework of the welwitindolinones, but also simultaneously installs the requisite C(11) nitrogen functionality. The cycloadduct (**199**) is easily advanced to ketone **202**, a versatile intermediate which may provide access to several welwitindolinones. In one step from **202**, the five-membered ether ring bridging C(3) and C(14) was installed, with subsequent introduction of the final quaternary center *via* Aldol reaction to ultimately furnish **231**, a compound

containing quaternary centers suitable for advancement to *N*-methylwelwitindolinone D isonitrile (**17**).

4.4 Experimental Section.

4.4.1 Material and Methods.

Unless stated otherwise, reactions were performed in flame-dried glassware under a nitrogen atmosphere, using freshly distilled solvents. Diethyl ether (Et_2O) and tetrahydrofuran (THF) were distilled from sodium/benzophenone ketyl. Methylene chloride (CH_2Cl_2), benzene, and triethylamine (Et_3N) were distilled from calcium hydride. Methyl sulfoxide (DMSO), 1,2-dichloroethane, and BF_3•OEt_2 were purchased from the Aldrich Chemical Co. in Sure/Seal□ containers and used without further purification. All other commercially obtained reagents were used as received.

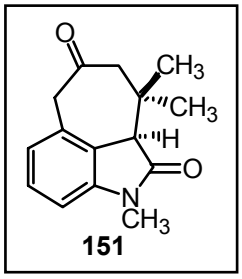
Unless stated otherwise all reactions were magnetically stirred and monitored by thin-layer chromatography (TLC) using E. Merck silica gel 60 F254 pre-coated plates (0.25-mm). Preparative TLC was also performed using E. Merck silica gel 60 F254 pre-coated plates (0.25-mm). Column or flash chromatography (silica) was performed with the indicated solvents using silica gel (particle size 0.032-0.063 mm) purchased from Fisher Scientific. In general, the chromatography guidelines reported by Still were followed.[37]

All melting points were obtained on a Gallenkamp variable temperature melting point apparatus (model: MPD350.BM2.1) and are uncorrected. Infrared spectra were recorded on a Midac M-1200 FTIR. ^1H and ^{13}C NMR spectra were recorded on Bruker AM-500 or Bruker Advance 400 spectrometers. Chemical

shifts are reported relative to internal Me_4Si (^1H and ^{13}C, δ 0.00 ppm) or chloroform (^1H, δ 7.27 ppm, ^{13}C, δ 77.0 ppm). High resolution mass spectra were performed at The University of Illinois Mass Spectrometry Center. Single-crystal X-ray analyses were performed by Susan DeGala of Yale University. High performance liquid chromatography (HPLC) was performed on a Waters model 510 system using a Rainin Microsorb 80-199-C5 column, or a Rainin Dynamax SD-200 system with a Rainin Microsorb 80-120-C5 column.

4.4.2 Preparative Procedures:

Preparation of Ketone 151.



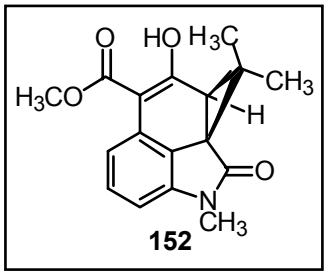
151

Ketone 151. To a solution of ketone **50** (200 mg, 0.83 mmol, 1.0 equiv) in 9:1 THF/DMPU (14 mL) was added a 0.1M solution of SmI_2 in THF (purchased from Aldrich as solution) until the purple color persisted (ca. 32 mL). After stirring for 10 minutes, the reaction was quenched with saturated aqueous $NaHCO_3$ (30 mL). The aqueous layer was extracted with Et_2O (3 x 20 mL) and the combined organic layers washed with H_2O (20 mL), brine (20 mL), dried over $MgSO_4$ and concentrated. Flash chromatography (20% EtOAc/hexanes eluent) furnished

ketone **151** as a yellow solid (90 mg, 45% yield) and recovered ketone **50** (30 mg).

151: m.p. 135-137 °C; IR (thin film/NaCl) 2960 (w), 2929 (w), 2873 (w), 1706 (s), 1606 (m), 1470 (m), 1370 (w), 1340 (w), 1299 (w), 1279 (w), 1090 (w), 998 (w), 779 (w), 730 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.25 (t, *J* = 7.8 Hz, 1H), 6.86 (d, *J* = 7.8 Hz, 1H), 6.73 (d, *J* = 7.8 Hz, 1H), 4.00 (d, *J* = 14.3 Hz, 1H), 3.51 (dd, *J* = 1.8, 14.4 Hz, 1H), 3.42 (s, 1H), 3.20 (s, 3H), 2.74 (d, *J* = 11.4 Hz, 1H), 2.57 (dd, *J* = 1.6, 11.4 Hz, 1H), 1.56 (s, 3H), 0.68 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.2, 175.1, 144.4, 130.0, 128.9, 125.4, 122.8, 106.5, 59.9, 53.6, 50.1, 39.7, 28.2, 26.2, 21.9; HRMS (EI) *m/z* 243.1258 [calc'd for $C_{15}H_{17}NO_2$(M+) 243.1259].

Preparation of Ester 152.

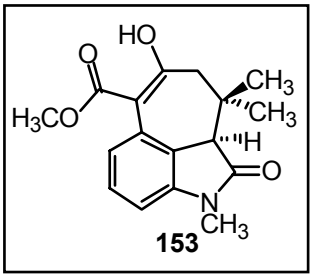


152

Ester 152. To a THF solution (18 mL) of ketone **50** (450 mg, 1.87 mmol, 1.0 equiv) at -78 °C was added 1.4M *t*-BuLi (1.6 mL, 1.2 equiv) in benzene in a dropwise fashion *via* syringe. After stirring for 10 minutes the reaction was treated with methyl cyanoformate (740 μL, 9.35 mmol, 5.0 equiv) and the cold bath was removed. The reaction proceeded rapidly to a single product as viewed

by TLC analysis. After stirring for an additional 10 minutes, 1N NaOH (10 mL) was added at 0 °C to quench the reaction. The reaction was transferred to a separatory funnel, 20 mL Et_2O was added, and the layers were separated. The organic layer was extracted with 1N NaOH (3 x 15 mL). Traces of organic solvents were removed from the combined aqueous layers under reduced pressure, followed by acidification of the aqueous layer at 0 °C using conc. HCl. Extraction with CH_2Cl_2 (3 x 75 mL), drying over Na_2SO_4 and concentration followed by flash chromatography (25% EtOAc/hexanes eluent) provided ester **152** as a yellow solid (260 mg, 47% yield): m.p. 171-173 °C; IR (thin film/NaCl) 2953 (br w), 1711 (s), 1639 (m), 1606 (s), 1552 (m), 1466 (m), 1442 (m), 1378 (m), 1358 (m), 1334 (m), 1287 (m), 1233 (s), 1082 (m), 1032 (m), 1006 (w), 863 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 13.76 (s, 1H), 7.64 (d, *J* = 8.2 Hz, 1H), 7.26 (t, *J* = 8.0 Hz, 1H), 6.74 (d, *J* = 7.5 Hz, 1H), 4.01 (s, 3H), 3.26 (s, 3H), 2.98 (s, 1H), 1.70 (s, 3H), 0.95 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.1, 173.9, 173.3, 142.6, 128.0, 127.9, 118.9, 118.7, 105.4, 98.8, 52.6, 43.0, 40.3, 26.9, 24.0, 20.3, 16.8; HRMS (EI) *m/z* 299.1150 [calc'd for $C_{17}H_{17}NO_4$ (M+) 299.1158].

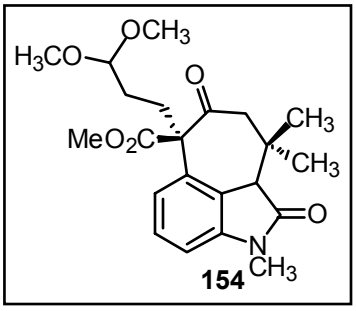
Preparation of Ester 153.



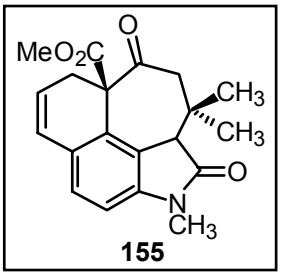
153

Ester 153. To a mixture of freshly ground Sm (1.20 g, 7.98 mmol, 11.9 equiv) in THF (11 mL) was added diiodoethane (2.08 g, 7.36 mmol, 11.0 equiv, purified by washing an Et_2O solution with $Na_2S_2O_3$) and the reaction was stirred until it turned blue (at least 2 hours). Ester **152** (200 mg, 0.67 mmol, 1.0 equiv) in THF (1 mL) was added and the reaction was stirred for 24 hours, when it was quenched with saturated ammonium chloride (20 mL), extracted with Et_2O (3 x 15 mL) and dried over Na_2SO_4. Flash chromatography (25% EtOAc/hexanes eluent) yielded ester **153** as a yellow solid (110 mg, 55% yield). An analytically pure sample was obtained *via* recrystallization from hexanes: m.p. 139-140 °C (hexanes); IR (thin film, /NaCl) 2955 (br w), 1707 (s), 1642 (m), 1605 (m), 1465 (m), 1443 (m), 1368 (m), 1329 (m), 1295 (m), 1233 (m), 1094 (w), 1065 (w), 1030 (m), 980 (w), 932 (w), 868 (br w), 793 (w), 732 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 13.12 (s, 1H), 7.30 (t, *J* = 7.8 Hz, 1H), 7.15 (d, *J* = 7.9 Hz, 1H), 6.70 (d, *J* = 7.6 Hz, 1H), 3.82 (s, 3H), 3.19 (s, 3H), 3.01 (s, 1H), 2.23 (d, *J* = 12.5 Hz, 1H), 2.09 (d, *J* = 12.7 Hz, 1H), 1.54 (s, 3H), 0.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.9, 176.6, 172.1, 144.0, 131.7, 128.0, 127.2, 123.9, 106.0, 101.7, 52.9, 52.3, 48.7, 48.6, 29.0, 26.5, 25.2; HRMS (EI) *m/z* 301.1308 [calc'd for $C_{17}H_{19}NO_4$ (M+) 301.1314].

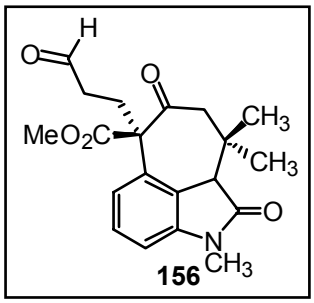
Preparation of Ester 155 and Aldehyde 156.



154



155



156

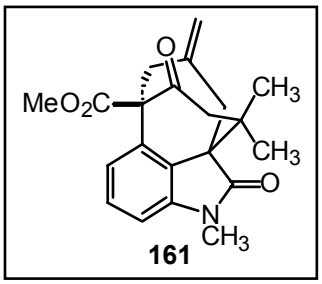
Ester 155 and Aldehyde 156. To a solution of acrolein (125 μL, 1.87 mmol, 5.0 equiv) and ester **153** (113 mg, 0.38 mmol, 1.0 equiv) in MeOH (4 mL) at -60 °C was added a solution of NaOMe (22 mg, 0.41 mmol, 1.1 equiv) in MeOH (1 mL). The reaction was stirred for 2 hours (-60 °C to rt) when 2 drops of conc. HCl were added. The reaction was concentrated and filtered through SiO_2 to provide intermediate dimethylacetal **154** as a yellow oil that was used in the next reaction without further purification. The derived residue was dissolved in CH_2Cl_2 (1 mL) and trifluoroacetic acid (1 mL) and stirred for 5 hours. The reaction was quenched with H_2O (2 mL), and the layers were separated. The organic layer was washed with H_2O (1 x 2 mL) then $NaHCO_3$ (2 x 2 mL), dried over Na_2SO_4, and concentrated. Flash chromatography (25% EtOAc/hexanes eluent) provided ester **155** (68 mg, 53% yield, 2 steps) and aldehyde **156** (20 mg, 15% yield) as pale yellow oils.

155: The first compound to elute was ester **155**: m.p. 162-163 °C; IR (thin film/NaCl) 2959 (br w), 2876 (w), 1742 (m), 1708 (s), 1612 (w), 1593 (m), 1479 (m), 1362 (w), 1340 (w), 1279 (m), 1212 (m), 1090 (w), 1017 (w), 820 (w), 732 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.03 (d, J = 7.9 Hz, 1H), 6.75 (d, J =

7.8 Hz, 1H), 6.42 (dd, *J* = 3.2, 9.6 Hz, 1H), 5.96 (ddd, *J* = 2.2, 6.4, 9.5 Hz, 1H), 3.62 (s, 3H), 3.49 (s, 1H), 3.21 (s, 3H), 3.12 (d, *J* = 10.7 Hz, 1H), 2.97 (dd, *J* = 6.2, 16.8 Hz, 1H), 2.56 (ddd, *J* = 2.6, 2.6, 16.7 Hz, 1H), 2.13 (d, *J* = 10.7 Hz, 1H), 1.56 (s, 3H), 0.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.6, 175.9, 170.0, 144.3, 127.9, 127.9, 127.1, 127.0, 126.8, 124.4, 108.1, 65.3, 53.4, 52.3, 51.7, 41.1, 29.5, 27.2, 26.5, 24.8; HRMS (EI) *m/z* 339.1478 [calc'd for $C_{20}H_{21}NO_4$(M+) 339.1471].

156: The second compound to elute was aldehyde **156**: m.p. 140-142 °C; IR (thin film/NaCl) 2960 (w), 1741 (m), 1711 (s), 1601 (m), 1465 (m), 1368 (w), 1336 (w), 1237 (m), 1170 (w), 1143 (w), 732 (w) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.52 (s, 1H), 7.35 (t, *J* = 7.9 Hz, 1H), 6.98 (d, *J* = 8.1 Hz, 1H), 6.81 (d, *J* = 7.6 Hz, 1H), 3.79 (s, 3H), 3.20 (s, 3H), 3.18 (d, *J* = 11.1 Hz, 1H), 3.13 (s, 1H), 2.46-2.24 (comp m, 4H), 2.25 (d, *J* = 11.2 Hz, 1H), 1.55 (s, 3H), 0.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.5, 201.1, 175.1, 170.2, 145.0, 134.3, 129.4, 125.0, 121.8, 107.7, 68.5, 54.0, 53.5, 51.8, 39.7, 39.6, 28.3, 27.0, 26.3, 24.6; HRMS (EI) *m/z* 357.1567 [calc'd for $C_{20}H_{23}NO_5$(M+) 357.1576].

Preparation of Ester 161.

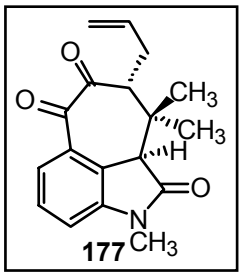


161

Ester 161. A mixture of $Pd(OAc)_2$ (0.74 mg, 0.003 mmol, 0.05 equiv) and triphenylphosphine (3.46 mg, 0.013 mmol, 0.2 equiv) in dioxane (1 mL) was stirred for 30 minutes. In a separate flask, DBU (19.9 μL, 0.13 mmol, 2.0 equiv), ester **153** (20 mg, 0.07 mmol, 1.0 equiv), diacetate **158** (11.4 mg, 0.07 mmol, 1.0 equiv)[38] and dioxane (1 mL) were combined and the solution was added to the palladium mixture. The reaction was brought to reflux for 30 minutes, cooled to rt, concentrated and subjected to flash chromatography (20% EtOAc/hexanes eluent) to provide olefin **161** as a yellow solid (13 mg, 56% yield). Recrystallization from Et_2O/hexanes provided crystals suitable for X-ray crystallography (see Appendix 6 for data): m.p. 174-175 °C (Et_2O, hexanes); IR (thin film/NaCl) 2954 (w), 2923 (w), 2850 (w), 1746 (m), 1709 (s), 1607 (m), 1470 (m), 1435 (w), 1340 (w), 1298 (w), 1244 (m), 1204 (m), 911 (m), 734 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.32 (t, *J* = 7.9 Hz, 1H), 6.84 (d, *J* = 7.8 Hz, 1H), 6.58 (d, *J* = 8.0 Hz, 1H), 4.92 (s, 1H), 4.87 (s, 1H), 3.84 (s, 3H), 3.32 (d, *J* = 13.8 Hz, 1H), 3.23 (s, 3H), 2.93 (d, *J* = 14.8 Hz, 1H), 2.66 (d, *J* = 12.0 Hz, 1H), 2.54 (d, *J* = 13.8 Hz, 1H), 2.17 (d, *J* = 11.9 Hz, 1H), 2.14 (d, *J* = 13.2 Hz, 1H), 1.45 (s, 3H), 0.79 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.0, 178.6, 171.1, 143.2, 141.7, 137.3, 129.2, 129.0, 119.9, 118.9, 107.3, 67.2, 56.9, 54.4, 52.7, 45.1,

41.6, 38.8, 28.3, 26.1, 22.9; HRMS (EI) *m/z* 353.1636 [calc'd for $C_{21}H_{23}NO_4$(M+) 353.1627].

Preparation of Diketone 177.

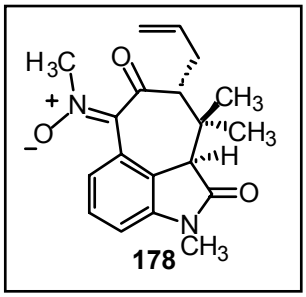


177

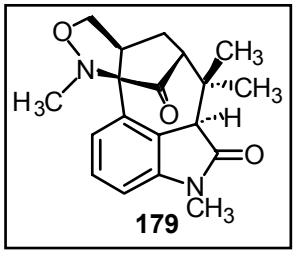
Diketone 177. To a solution of diazo ketone **91** (630 mg, 2.36 mmol, 1.0 equiv) and allyl alcohol (161 μL, 2.36 mmol, 1.0 equiv) in CH_2Cl_2 (24 mL) was added Rh_2OAc_4 (10.4 mg, 0.024 mmol, 0.01 equiv). Gas evolution was observed and the reaction turned dark brown. After stirring at rt for 20 minutes, the mixture was concentrated to afford a dark brown oil which was subsequently dissolved in xylenes (35 mL) and heated to reflux for 1 hour. After cooling to rt, the reaction was concentrated and purified by silica gel column chromatography (30% hexane/EtOAc eluent) to afford diketone **177** as yellow crystals (596 mg, 85% yield). An analytical sample of **177** was obtained by recrystallization (hexane/EtOAc): m.p. 196-197 °C; IR (thin film/NaCl) 3079 (w), 2895 (br w), 1706 (s), 1597 (m), 1467 (m), 1408 (w), 1368 (w), 1337 (m), 1295 (m), 1269 (m), 1187 (w), 1161 (w), 1140 (w), 1019 (m), 986 (m), 798 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, *J* = 7.6 Hz, 1H), 7.50 (t, *J* = 8.0 Hz, 1H), 7.12 (d, *J* = 7.6 Hz, 1H), 5.59 (dddd, *J* = 6.7, 6.7, 10.3, 17.0 Hz, 1H), 5.02-4.98 (m, 2H), 3.36 (s, 1H), 3.25 (s, 3H), 2.93 (dd, *J* = 2.4, 11.6 Hz, 1H), 2.74 (ddd, *J* = 6.9, 12.2, 13.2

Hz, 1H), 2.18 (ddd, *J* = 1.0, 6.4, 14.0 Hz, 1H), 1.50 (s, 3H), 0.93 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.7, 192.5, 174.3, 145.1, 134.8, 129.6, 129.1, 128.6, 120.7, 117.6, 113.3, 57.2, 53.0, 38.4, 29.9, 26.4, 22.7, 20.9; HRMS (EI) *m/z* 297.1364 [calc'd for $C_{18}H_{19}NO_3$ (M+) 297.1365].

Preparation of Nitrone 178 and Isoxazolidine 179.



178



179

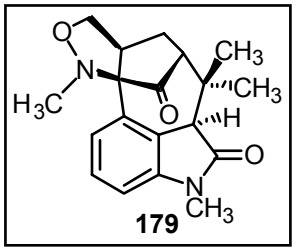
Nitrone 178 and Isoxazolidine 179. To a solution of diketone **177** (213 mg, 0.72 mmol, 1.0 equiv) in MeOH (20 mL) was added *N* -methylhydroxylamine hydrochloride (600 mg, 7.16 mmol, 10.0 equiv) followed by pyridine (700 μL, 8.59 mmol, 12.0 equiv). The reaction mixture was heated to 55 °C for 18 hours and was concentrated after cooling to rt. The crude organic concentrate was purified by silica gel column chromatography (30% hexane/EtOAc eluent) to provide nitrone **178** (127 mg, 54% yield) and cycloadduct **179** (64 mg, 27% yield) as yellow solids.

178: Crystals suitable for X-ray analysis and an analytical sample of nitrone **178** were obtained by recrystallization from hexanes/EtOAc. See Appendix 6 for X-ray report. m.p. 173-174 °C (dec); IR (thin film/NaCl) 2965 (m), 2874 (w), 1712 (s), 1677 (m), 1640 (w), 1600 (m), 1508 (m), 1468 (m), 1431 (m),

1368 (m), 1327 (m), 1210 (m), 1146 (m), 1100 (m), 1077 (m), 913 (m), 794 (m), 735 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.34 (d, *J* = 8.7 Hz, 1H), 7.42 (t, *J* = 7.8 Hz, 1H), 6.88 (d, *J* = 7.7 Hz, 1H), 5.63 (m, 1H), 5.02-4.98 (m, 2H), 4.06 (s, 3H), 3.20 (s, 3H), 3.12 (s, 1H), 2.82 (dd, *J* = 2.0, 11.8 Hz, 1H), 2.73 (ddd, *J* = 7.8, 12.7, 12.7 Hz, 1H), 2.09 (ddd, *J* = 1.6, 3.7, 13.8 Hz, 1H), 1.40 (s, 3H), 0.80 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.3, 174.9, 144.2, 143.8, 136.2, 128.3, 127.4, 125.8, 122.3, 116.9, 109.3, 58.5, 55.1, 52.8, 43.5, 30.5, 26.0, 21.4, 20.5; HRMS (EI) *m/z* 326.1625 [calc'd for $C_{19}H_{22}N_2O_3$ (M+) 326.1630].

179: An analytical sample of **179** was obtained by recrystallization (hexane/EtOAc): m.p. 206-207 °C; IR (thin film/NaCl) 2964 (m), 2928 (m), 2872 (m), 1709 (s), 1593 (m), 1588 (m), 1468 (m), 1368 (m), 1334 (m), 1300 (m), 1210 (m), 1169 (m), 1146 (m), 1115 (w), 1077 (m), 1008 (m), 967 (m), 938 (w), 913 (m), 867 (w), 794 (m), 735 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.33 (t, *J* = 8.2 Hz, 1H), 7.02 (d, *J* = 8.0 Hz, 1H), 6.72 (d, *J* = 8.1 Hz, 1H), 3.99 (dd, *J* = 6.5, 8.7 Hz, 1H), 3.77 (d, *J* = 8.8 Hz, 1H), 3.49 (s, 1H), 3.28 (m, 1H), 3.23 (s, 3H), 3.19 (s, 3H), 2.61 (dd, *J* = 9.7, 14.1 Hz, 1H), 2.38 (d, *J* = 8.3 Hz, 1H), 1.97 (ddd, *J* = 8.7, 8.7, 14.1 Hz, 1H), 1.58 (s, 3H), 0.77 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.8, 175.0, 144.5, 135.1, 128.9, 123.6, 117.3, 106.8, 76.4, 73.1, 65.3, 52.4, 51.7, 42.2, 39.7, 28.8, 26.3, 25.1, 21.4; HRMS (EI) *m/z* 326.1627 [calc'd for $C_{19}H_{22}N_20_3$ (M+) 326.1630].

Alternative Preparation of Isoxazolidine 179.

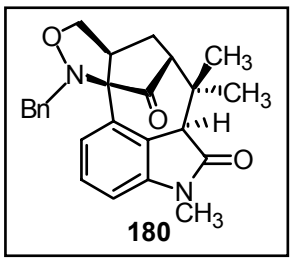


179

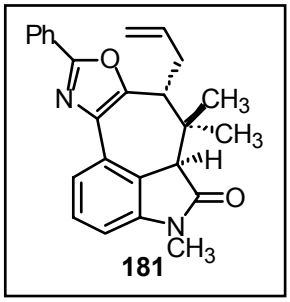
Isoxazolidine 179. To a solution of diketone **177** (386 mg, 1.30 mmol, 1.0 equiv) in MeOH (15 mL) was added *N*-methylhydroxylamine hydrochloride (543 mg, 6.50 mmol, 5.0 equiv) followed by pyridine (736 μ L, 9.10 mmol, 7.0 equiv). The reaction mixture was heated to reflux for 15 hours and was concentrated after cooling to rt. The residual pyridine was removed *in vacuo* and the crude white solid was redissolved in EtOH (18 mL) and imidazole hydrochloride was added (272 mg, 2.60 mmol, 2.0 equiv). The mixture was heated to reflux for an additional 14 hours. After cooling to rt, the reaction was concentrated and purified by silica gel column chromatography (30% hexane/EtOAc) to furnish cycloadduct **179** as white crystals (342 mg, 81% yield).

Data for isoxazolidine **179** can be found in the previous procedure.

Preparation of Isoxazolidine 180 and Oxazole 181.



180



181

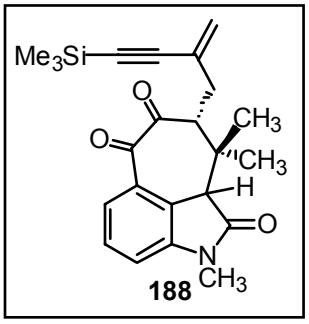
Isoxazolidine 180 and Oxazole 181. To a solution of diketone **177** (96 mg, 0.32 mmol, 1.0 equiv) in MeOH (5 mL) was added *N*-benzylhydroxylamine hydrochloride (258 mg, 1.62 mmol, 5.0 equiv) followed by pyridine (131 μ L, 1.62 mmol, 5.0 equiv). The reaction mixture was heated to reflux for 15 hours and was concentrated after cooling to rt. The residual pyridine was removed *in vacuo* and the crude white solid was redissolved in EtOH (8 mL) and imidazole hydrochloride was added (34 mg, 0.32 mmol, 1.0 equiv). The mixture was heated to reflux for an additional 18 hours. After cooling to rt, the reaction was concentrated and purified by silica gel column chromatography (30% hexane/EtOAc) to afford oxazole **181** as a white solid (50 mg, 40% yield) and cycloadduct **180** as a white solid (62 mg 48% yield). Analytical samples of oxazole **181** and [3+2] cycloadduct **180** and crystals suitable for X-ray analysis were obtained by recrystallization (hexane/CH_2Cl_2). See Appendix 6 for X-ray data reports.

180: m.p. >243 °C (dec/hexanes, CH_2Cl_2); IR (thin film/NaCl) 2969 (w), 2924 (w), 2873 (w), 1739 (m), 1697 (s), 1608 (m), 1592 (m), 1470 (m), 1368 (w), 1341 (m), 1304 (w), 1149 (w), 1080 (w), 1012 (m), 986 (w), 910 (w), 774 (w), 728 (m), 699 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.56 (d, *J* = 7.7 Hz, 2H), 7.40 (t,

J = 7.6 Hz, 2H), 7.30 (t, m, 2H), 7.06 (d, *J* = 7.9 Hz, 1H), 6.74 (d, *J* = 7.6 Hz, 1H), 4.89 (d, *J* = 16.4 Hz, 1H), 4.52 (d, *J* = 16.5 Hz, 1H), 4.02 (dd, *J* = 6.8, 8.6 Hz, 1H), 3.78 (d, *J* = 8.6 Hz, 1H), 3.55 (s, 1H), 3.32 (dd, *J* = 9.0, 15.6 Hz, 1H), 3.21 (s, 3H), 2.66 (dd, *J* = 10.0, 14.4 Hz, 1H), 2.45 (d, *J* = 8.5 Hz, 1H), 2.03 (ddd, *J* = 8.6, 8.6, 14.4 Hz, 1H), 1.62 (s, 3H), 0.82 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.4, 175.1, 144.6, 139.4, 135.0, 129.1, 128.4, 127.5, 126.9, 123.7, 117.4, 106.9, 76.6, 73.6, 65.1, 55.3, 51.9, 51.7, 42.2, 28.9, 26.3, 25.1, 21.5; HRMS (FAB) *m/z* 403.2022 [calc'd for $C_{25}H_{27}N_2O_3$ (M+1) 403.2022].

181: m.p. 156-157 °C (CH_2Cl_2/hexanes); IR (thin film/NaCl) 2930 (br w), 1707 (s), 1618 (w), 1600 (w), 1464 (m), 1372 (w), 1337 (w), 1299 (w), 1083 (w), 915 (w), 784 (w) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (m, *J* = 1.7, 8.0 Hz, 2H), 7.91 (d, *J* = 7.5 Hz, 1H), 7.51-7.47 (comp m, 3H), 7.41 (t, *J* = 7.9 Hz, 1H), 6.78 (d, *J* = 7.5 Hz, 1H), 5.91 (dddd, *J* = 6.3, 8.4, 10.3, 16.8 Hz, 1H), 5.10-5.03 (comp m, 2H), 3.74 (s, 1H), 3.25 (s, 3H), 3.00 (dd, *J* = 4.2, 7.4 Hz, 1H), 2.90 (m, 1H), 2.49 (ddd, *J* = 7.4, 7.6, 14.7 Hz, 1H), 1.68 (s, 3H), 0.77 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.2, 160.0, 150.6, 143.8, 136.3, 133.5, 130.2, 128.8, 128.2, 128.1, 127.5, 126.3, 122.7, 119.1, 116.9, 106.6, 50.4, 50.1, 38.2, 34.2, 26.4, 25.9, 24.9; HRMS (EI) *m/z* 384.1839 [calc'd for $C_{25}H_{24}N_2O_2$ (M+) 384.1838].

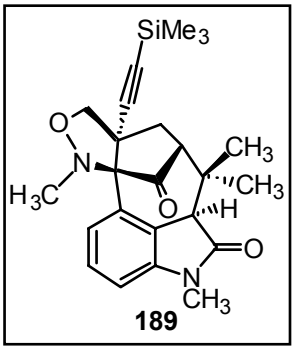
Preparation of Diketone 188.



188

Diketone 188. To a solution of diazo ketone **91** (115 mg, 0.43 mmol, 1.0 equiv) and allylic alcohol **186** (66 mg, 0.43 mmol, 1.0 equiv) in CH_2Cl_2 (5 mL) was added $Rh_2(OAc)_4$ (1.9 mg, 0.004 mmol, 0.01 equiv).[39] Gas evolution was observed and the reaction turned dark brown. After stirring at rt for 30 minutes, the mixture was concentrated to afford a dark brown oil which was subsequently dissolved in xylenes (8 mL) and heated to reflux for 20 minutes. After cooling to rt, the reaction was concentrated and purified by silica gel column chromatography (30% hexane/EtOAc eluent) to afford diketone **188** as yellow crystals (103 mg, 60% yield). An analytical sample of **188** was obtained by recrystallization (hexane/EtOAc): m.p. 137-139 °C (dec); IR (thin film/NaCl) 2966 (w), 2900 (w), 1705 (s), 1599 (m), 1469 (m), 1411 (w), 1370 (w), 1338 (m), 1295 (m), 1268 (m), 1251 (m), 1082 (w), 1022 (m), 986 (m), 913 (w), 875 (m), 842 (m), 802 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, *J* = 7.8 Hz, 1H), 7.52 (t, *J* = 7.8 Hz, 1H), 7.13 (d, *J* = 7.7 Hz, 1H), 5.36 (s, 1H), 5.28 (s, 1H), 3.39 (s, 1H), 3.32 (dd, *J* = 2.2, 11.0 Hz, 1H), 3.27 (s, 3H), 2.87 (dd, *J* = 11.2, 13.8 Hz, 1H), 2.27 (d, *J* = 14.1 Hz, 1H), 1.50 (s, 3H), 0.95 (s, 3H), 0.07 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.7, 191.7, 174.4, 145.0, 129.6, 129.4, 128.3, 128.2, 124.4, 120.8, 113.1, 104.1, 96.4, 56.0, 53.0, 38.4, 33.2, 26.4, 22.4, 20.9, -0.32; HRMS (EI) *m/z* 393.1756 [calc'd for $C_{23}H_{27}NO_3Si$ (M+) 393.1760].

Preparation of Isoxazolidine 189.

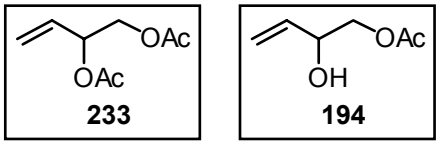


189

Isoxazolidine 189. To a solution of diketone **188** (118 mg, 0.30 mmol, 1.0 equiv) in MeOH (6 mL) was added *N* -methylhydroxylamine hydrochloride (126 mg, 1.50 mmol, 5.0 equiv) followed by pyridine (171 μL, 2.10 mmol, 7.0 equiv). The reaction mixture was heated to reflux for 15 hours and was concentrated after cooling to rt. The residual pyridine was removed *in vacuo* and the crude white solid was redissolved in EtOH (12 mL) and imidazole hydrochloride was added (63 mg, 0.60 mmol, 2.0 equiv). The mixture was heated to reflux for an additional 14 hours. After cooling to rt, the reaction was concentrated and purified by silica gel column chromatography (25% EtOAc/hexane eluent) to furnish cycloadduct **189** as white crystals (89 mg, 70% yield). Crystals suitable for X-ray analysis and an analytical sample of **189** were obtained by recrystallization (Et_2O/hexanes). See Appendix x for X-ray data: m.p. 210-211 °C (dec/Et_2O, hexanes); IR (thin film/NaCl) 2967 (m), 2928 (m), 2873 (w), 2172 (w), 1736 (m), 1708 (s), 1606 (m), 1589 (m), 1467 (m), 1386 (w), 1338 (m), 1299 (w), 1250 (m), 1214 (w), 1172 (w), 1106 (w), 1084 (w), 960 (w), 915 (m), 844 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.30 (t, J = 7.8 Hz, 1H),

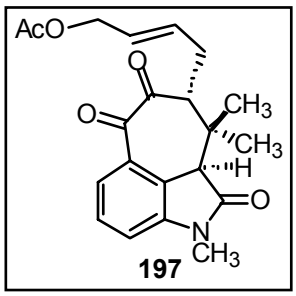
6.95 (d, *J* = 8.0 Hz, 1H), 6.72 (d, *J* = 7.6 Hz, 1H), 4.09 (d, *J* = 8.3 Hz, 1H), 4.00 (d, *J* = 8.2 Hz, 1H), 3.96 (s, 1H), 3.28 (s, 3H), 3.16 (s, 3H), 2.71 (d, *J* = 14.4 Hz, 1H), 2.46-2.38 (m, 2H), 1.56 (s, 3H), 0.81 (s, 3H), -0.25 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.1, 175.0, 144.2, 132.1, 128.6, 125.0, 118.6, 107.2, 107.1, 90.7, 81.8, 64.4, 54.2, 52.8, 41.0, 39.3, 37.4, 26.1, 25.1, 21.8, -0.75, -0.98; HRMS (EI) *m/z* 422.2018 [calc'd for $C_{24}H_{30}N_2O_3Si$ (M+) 422.2026].

Preparation of Diacetate 233 and Alcohol 194.



Diacetate 233 and Alcohol 194. To a solution of 3-butene-1,2-diol (3.00 g, 34.1 mmol, 1.0 equiv, prepared from 2-butene-1,4-diol),[40] in CH_2Cl_2 (340 mL) at -78 °C was added 2,4,6-collidine (8.99 mL, 68.0 mmol, 2.0 equiv) and acetyl chloride (2.91 mL, 40.9 mmol, 1.2 equiv). The cold bath was removed and the reaction was stirred for 30 minutes, at which time it was poured into a separatory funnel containing saturated aqueous $CuSO_4$ solution (500 mL). The layers were separated and the organic layer was washed with $CuSO_4$ until no more collidine remained as visualized by TLC analysis (ca. 1.5 L $CuSO_4$). The aqueous layers were extracted with EtOAc (5 x 250 mL), and the combined organic layers were dried over Na_2SO_4, concentrated and purified *via* flash chromatography (30-40% EtOAc/hexanes eluent) to furnish diacetate **233** as a clear colorless oil (0.76 g, 13%) and acetate **194** as a pale yellow oil (3.13 g, 71% yield).[41]

Preparation of Acetate 197.

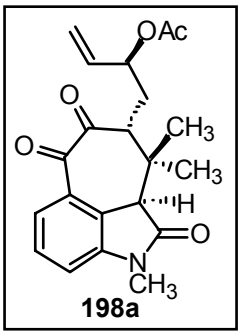


197

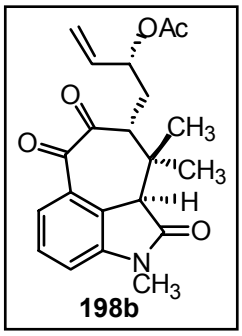
Acetate 197. To a solution of diazo ketone **91** (6.00g, 22.4 mmol, 1.0 equiv) and allylic alcohol **194** (3.50 g, 26.9 mmol, 1.2 equiv) in CH_2Cl_2 (224 mL) at rt was added $Rh_2(OAc)_4$ (250 mg, 0.56 mmol, 0.02 equiv). As soon as gas evolution ceased (ca. 1 minute), Et_3N (15.6 mL, 112 mmol, 5.0 equiv) was quickly added at once *via* syringe. The mixture was concentrated to afford a dark purple oil which was subsequently dissolved in xylenes (224 mL) and heated to reflux for 45 minutes. After cooling to rt, the reaction was concentrated and purified by silica gel column chromatography (20% acetone/hexanes eluent) to afford diketone **197** as a yellow solid (5.36 g, 65% yield). An analytical sample was obtained by recrystallization from acetone/hexanes: m.p. 170-172 °C (acetone/hexanes); IR (thin film/NaCl) 2971 (w), 2939 (w), 2885 (w), 1716 (s), 1603 (s), 1472 (m), 1372 (m), 1339 (m), 1300 (m), 1268 (m), 1233 (s), 1025 (m), 980 (s), 915 (s) cm^{-1}; ^1H NMR (500 MHz, d_6-acetone) δ 7.63 (d, J = 7.9 Hz, 1H), 7.48 (t, J = 7.9 Hz, 1H), 7.10 (d, J = 7.7 Hz, 1H), 5.55-5.46 (m, 2H), 4.40 (dd, J = 3.6, 27.0 Hz, 1H), 4.37 (dd, J = 4.7, 27.0 Hz, 1H), 3.30 (s, 1H), 3.22 (s, 3H), 2.89 (dd, J = 2.3, 11.5 Hz, 1H), 2.72 (m, 1H), 2.17-2.13 (comp m, 1H), 2.00 (s, 3H), 1.45 (s, 3H), 0.89 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.2, 193.3, 174.9, 170.6, 146.5, 132.6, 130.4, 130.0, 129.8, 127.9, 120.6, 114.4, 64.7, 57.9, 53.6,

38.9, 29.1, 26.5, 22.9, 21.1, 20.7; HRMS (EI) *m/z* 369.1571 [calc'd for $C_{21}H_{23}NO_5$ (M+) 369.1576].

Preparation of Acetates 198a and 198b.



198a



198b

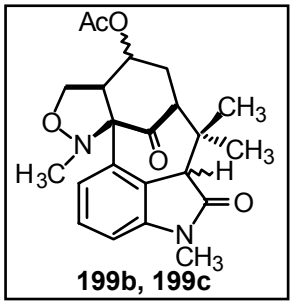
Acetates 198a and 198b. To a solution of a acetate **197** (4.25 g, 11.5 mmol, 1.0 equiv) in THF (115 mL) was added $PdCl_2(MeCN)_2$ (119 mg, 0.46 mmol, 0.04 equiv) and the reaction was warmed to 50 °C. After stirring for 2 hours, the reaction was cooled to rt, concentrated, adsorbed onto SiO_2 and subjected to flash chromatography (30% EtOAc/hexanes eluent) to provide a 1:1.4 ratio of diastereomers of olefins **198a** and **198b** (1.20 g, 28% yield, 96% yield based on recovered starting material) and recovered acetate **197** (3.00 g, 71% yield).

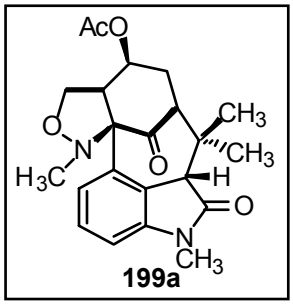
198a: Although the mixture will be carried on in the next step, separation of the minor diastereomer (**198a**) can be affected *via* recrystallization from EtOAc/hexanes. See Appendix 6 for X-ray data of acetate **198a** m.p. 194-195 °C; IR (thin film/NaCl) 2974 (w), 2938 (br w), 1716 (s), 1603 (m), 1473 (m), 1372 (m), 1339 (m), 1299 (m), 1271 (m), 1234 (m), 1018 (m), 994 (m), 922 (w), 790 (w), 731 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.65 (d, J = 8.0 Hz, 1H), 7.51 (t,

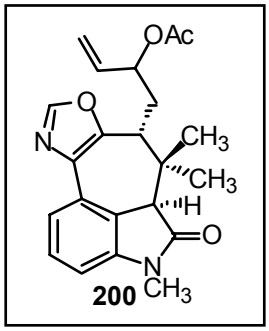
J = 7.9 Hz, 1H), 7.13 (d, *J* = 7.8 Hz, 1H), 5.66 (ddd, *J* = 6.3, 10.6, 17.1 Hz, 1H), 5.19-5.14 (m, 2H), 5.04 (ddd, *J* = 4.8, 4.8, 9.4 Hz, 1H), 3.34 (s, 1H), 3.25 (s, 3H), 2.83 (d, *J* = 10.6 Hz, 1H), 2.46 (ddd, *J* = 10.0, 10.0, 14.2 Hz, 1H), 2.06 (s, 3H), 1.76 (dd, *J* = 4.1, 14.2 Hz, 1H), 1.47 (s, 3H), 0.89 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.0, 192.4, 174.3, 170.5, 145.0, 135.4, 129.7, 129.1, 128.3, 120.6, 117.6, 113.3, 74.1, 53.9, 52.7, 38.5, 30.9, 26.4, 22.5, 21.2, 20.5; HRMS (EI) *m/z* 369.1586 [calc'd for $C_{21}H_{23}NO_5$ (M+) 369.1576].

198b: m.p. 97-99 °C (wax); IR (thin film/NaCl) 2972 (w), 2939 (br w), 1717 (s), 1603 (m), 1472 (m), 1373 (m), 1339 (m), 1299 (m), 1271 (m), 1233 (m), 1022 (m), 992 (m), 920 (m), 791 (w), 733 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.0 Hz, 1H), 7.52 (t, *J* = 7.9 Hz, 1H), 7.12 (d, *J* = 7.8 Hz, 1H), 5.58 (m, 1H), 5.29 (m, 1H), 5.12-5.09 (comp m, 2H), 3.35 (s, 1H), 3.25 (s, 3H), 2.93 (d, *J* = 11.1 Hz, 1H), 2.55 (ddd, *J* = 5.7, 11.2, 14.1 Hz, 1H), 2.07 (s, 3H), 1.67 (dd, *J* = 4.0, 14.1 Hz, 1H), 1.45 (s, 3H), 0.86 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.2, 192.0, 174.4, 170.0, 144.9, 134.9, 129.6, 129.3, 128.2, 120.5, 117.3, 113.2, 71.9, 52.7, 51.6, 38.2, 30.0, 26.4, 22.4, 20.8, 20.5; HRMS (EI) *m/z* 369.1575 [calc'd for $C_{21}H_{23}NO_5$ (M+) 369.1576].

Preparation of Isoxazolidines 199 and Oxazole 200.







Isoxazolidines 199 and Oxazole 200. *N*-Methylhydroxylamine hydrochloride (3.35 g, 40.1 mmol, 10.0 equiv) was dissolved in EtOH (200 mmol) *via* gentle heating with a heat gun. NaOMe (3.38 g, 40.5 mmol, 10.1 equiv) was added, which resulted in immediate salt formation. The mixture was stirred for 2 hours, and was then filtered into a round bottom flask containing acetates **198** (1.48 g, 4.01 mmol, 1.0 equiv). The reaction was heated to reflux for 18.5 hours which resulted in a complex mixture of products as visualized by NMR. After cooling to rt, the reaction was concentrated *in vacuo* , adsorbed onto SiO_2, and subjected to flash chromatography (30 - 75% EtOAc/hexanes eluent).

200: The first compound to elute was oxazole **200**, obtained after concentration of the solvent as a yellow oil (51 mg, 3% yield). An analytical sample of oxazole **200** can be obtained *via* flash chromatography (30% EtOAc/hexanes eluent) followed by preparative TLC (30% EtOAc/hexanes eluent): IR (thin film/NaCl) 2972 (w), 2932 (w), 1735 (s), 1708 (s), 1601 (m), 1526 (w), 1464 (m), 1372 (m), 1338 (m), 1297 (m), 1239 (m), 1104 (m), 1022 (m), 983 (w), 925 (w), 789 (w), 732 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.88 (s, 1H), 7.78 (d, *J* = 8.0 Hz, 1H), 7.39 (t, *J* = 7.9 Hz, 1H), 6.78 (d, *J* = 7.8 Hz, 1H), 5.85 (ddd, *J* = 7.0, 10.4, 17.2 Hz, 1H), 5.48-5.44 (m, 2H), 5.35 (d, *J* = 10.3 Hz,

1H), 3.51 (s, 1H), 3.24 (s, 3H), 2.82 (dd, *J* = 3.0, 8.9 Hz, 1H), 2.22 (ddd, *J* = 3.2, 7.8, 13.4 Hz, 1H), 2.01 (s, 3H), 1.87 (ddd, *J* = 6.4, 8.8, 13.6 Hz, 1H), 1.61 (s, 3H), 0.71 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.3, 170.3, 151.3, 150.0, 144.2, 136.1, 131.8, 128.7, 128.1, 123.0, 119.4, 119.1, 107.2, 74.3, 50.3, 46.9, 39.4, 34.1, 26.7, 26.0, 24.6, 21.5; HRMS (EI) *m/z* 380.1727 [calc'd for $C_{22}H_{24}N_2O_4$ (M+) 380.1736].

199b and **199c:** The second fractions contained two diastereomers of cycloadduct **199** (865 mg, 54% yield). An analytical sample of this mixture was obtained *via* HPLC (50% EtOAc/hexanes eluent): m.p. 137-139 °C; IR (thin film/NaCl) 2968 (m), 2933 (m), 2878 (m), 1744 (s), 1708 (s), 1603 (m), 1592 (m), 1464 (m), 1368 (m), 1339 (m), 1300 (m), 1235 (s), 1143 (w), 1118 (w), 1037 (m), 975 (w), 916 (m), 732 (s) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.0 Hz, 1H), 7.41 (t, *J* = 8.0 Hz, 1H), 7.35-7.26 (m, 2H), 6.79 (d, *J* = 8.0 Hz, 1H), 6.75 (d, *J* = 7.6 Hz, 1H), 5.15 (m, 1H), 4.67 (ddd, *J* = 2.4, 10.0, 12.2 Hz, 1H), 4.27-4.09 (comp m, 3H), 3.83 (s, 1H), 3.74 (t, *J* = 8.4 Hz, 1H), 3.43 (dd, *J* = 8.2, 17.8 Hz, 1H), 3.28 (s, 1H), 3.24-3.17 (m, 4H), 3.21 (s, 3H), 3.20 (s, 3H), 3.02 (s, 3H), 2.73 (dd, *J* = 8.8, 12.4 Hz, 1H), 2.64-2.58 (comp m, 3H), 2.24-2.16 (m, 1H), 2.11 (s, 3H), 2.02 (s, 3H), 1.86 (dd, *J* = 12.6, 25.0 Hz, 1H), 1.70 (s, 3H), 1.49 (s, 3H), 0.82 (s, 3H), 0.64 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.0, 202.7, 174.8, 174.4, 170.3, 170.0, 144.5, 144.4, 136.4, 135.0, 129.1, 128.9, 124.1, 122.8, 122.2, 120.3, 107.4, 107.3, 80.3, 72.1, 71.6, 70.7, 69.6, 63.5, 61.5, 56.9, 54.9, 52.1, 49.0, 43.9, 40.0, 38.2, 38.1, 31.0, 30.2, 29.9, 26.4, 26.2, 24.6, 21.3, 21.0, 21.0, 19.4; HRMS (EI) *m/z* 398.1840 [calc'd for $C_{22}H_{26}N_2O_5$ (M+) 398.1842].

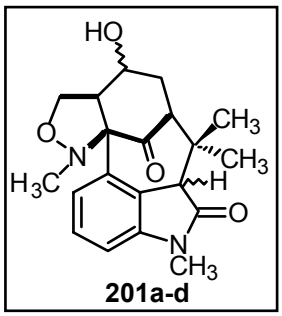
199b: One of the above diastereomers could be separated by recrystallizing from MeOH: m.p. 144-146 °C (MeOH); IR (thin film/NaCl) 2968

(w), 2932 (w), 2876 (w), 1743 (m), 1706 (s), 1607 (m), 1588 (w), 1465 (m), 1368 (w), 1338 (w), 1299 (w), 1233 (m), 1037 (m), 917 (w), 731 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.0 Hz, 1H), 7.33 (t, *J* = 8.0 Hz, 1H), 6.75 (d, *J* = 8.0 Hz, 1H), 5.15 (m, 1H), 4.21-4.09 (m, 2H), 3.83 (s, 1H), 3.23-3.17 (comp m, 4H), 3.02 (s, 3H), 2.66-2.61 (comp m, 2H), 2.21-2.11 (comp m, 4H), 1.49 (s, 3H), 0.65 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.7, 174.8, 170.3, 144.5, 136.5, 129.2, 122.8, 120.3, 107.4, 80.3, 72.2, 69.7, 61.6, 55.0, 49.1, 44.0, 40.1, 30.3, 26.4, 24.7, 21.3, 21.1; HRMS (EI) *m/z* 398.1851 [calc'd for $C_{22}H_{26}N_2O_5$ (M+) 398.1842].

199a: The third compound to elute was acetate **199a** (171 mg, 11% yield), the third diastereomer of the cycloaddition. Recrystallization from MeOH provided an analytical sample as well as X-ray quality crystals. See Appendix 6 for X-ray data: m.p. 189-190 °C (MeOH); IR (thin film/NaCl) 2967 (w), 2882 (w), 1738 (s), 1713 (s), 1603 (m), 1462 (m), 1370 (m), 1340 (m), 1308 (w), 1233 (s), 1054 (m), 917 (m), 787 (m), 732 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36 (t, *J* = 8.0 Hz, 1H), 7.21 (d, *J* = 8.1 Hz, 1H), 6.76 (d, *J* = 7.6 Hz, 1H), 5.23 (t, *J* = 4.7 Hz, 1H), 4.10 (t, *J* = 8.1 Hz, 1H), 3.69 (t, *J* = 9.1 Hz, 1H), 3.52 (ddd, *J* = 5.1, 8.0, 9.3 Hz, 1H), 3.34 (s, 1H), 3.18 (s, 3H), 2.71 (dd, *J* = 8.0, 12.1 Hz, 1H), 2.58 (s, 3H), 2.31 (ddd, *J* = 5.3, 8.2, 13.8 Hz, 1H), 2.07 (s, 3H), 1.81 (t, *J* = 13.2 Hz, 1H), 1.72 (s, 3H), 0.80 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.6, 174.5, 170.2, 144.5, 135.8, 128.7, 123.9, 122.0, 107.1, 74.6, 66.5, 66.4, 63.8, 53.7, 52.5, 39.1, 36.9, 30.4, 29.7, 26.1, 20.8, 19.3; HRMS (EI) *m/z* 398.1851 [calc'd for $C_{22}H_{26}N_2O_5$ (M+) 398.1842].

A trace amount of the fourth diastereomer was observed only *via* crude NMR analysis. The overall yield of the cycloaddition for the 3 diastereomers of **199** was 65%.

Preparation of Alcohols 201:



201a-d

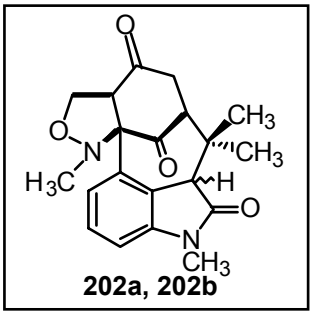
Alcohols 201: To a mixture of acetates **199** (1.4 g, 3.52 mmol, 1.0 equiv) in MeOH (35 mL) was added K_2CO_3 (729 mg, 5.28 mmol, 1.5 equiv) which resulted in a deep purple color. After 45 minutes, saturated aqueous NH_4Cl was added until the purple color disappeared and the reaction turned yellow (ca. 5 mL). Evaporation of the solvent, adsorption onto SiO_2 and flash chromatography (30 - 50% EtOAc/hexanes eluent) provided a mixture of four diastereomeric alcohols **201** (1.10 g, 88% yield) as a white foam, which could be further purified *via* preparative TLC (75% EtOAc/hexanes eluent).

201a and **201b**: The first band contained two diastereomers of alcohol **201** as a white solid: m.p. 141-143 °C; IR (thin film/NaCl) 3443 (br w), 2964 (w), 2936 (w), 2882 (w), 1699 (s), 1601 (m), 1592 (w), 1461 (m), 1368 (w), 1341 (w), 1296 (w), 913 (w), 731 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.62-7.58 (m, 2H), 7.32 (t, *J* = 8.1 Hz, 2H), 6.74 (d, *J* = 7.8 Hz, 2H), 4.32-4.23 (comp m, 4H),

4.12-4.03 (comp m, 2H), 3.84 (s, 1H), 3.71 (s, 1H), 3.22-3.17 (comp m, 9H), 3.04-2.97 (comp m, 5H), 2.63-2.46 (comp m, 6H), 1.95 (br s, 1H), 1.58 (br s, 1H), 1.51 (s, 3H), 1.49 (s, 3H), 0.69 (s, 3H), 0.65 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.9, 203.4, 175.1, 175.1, 144.6, 144.4, 137.2, 136.7, 129.1, 128.9, 123.0, 122.9, 120.7, 120.3, 107.4, 79.9, 74.1, 70.6, 70.0, 68.9, 66.9, 61.8, 58.4, 57.7, 56.4, 49.5, 49.1, 43.7, 43.3, 40.0, 39.7, 34.4, 33.7, 26.4, 26.4, 25.0, 24.8, 21.5, 21.4; HRMS (EI) *m/z* 356.1728 [calc'd for $C_{20}H_{24}N_2O_4$ (M+) 356.1736].

201c and **201d**: The second band to elute contained the remaining two diastereomers of alcohol **201**: m.p. 175-176 °C (dec); IR (thin film/NaCl) 3439 (br w), 2963 (br w), 2880 (br w), 1710 (s), 1605 (m), 1462 (m), 1341 (w), 1299 (w), 1095 (w), 915 (w), 786 (w), 731 (m) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.33 (m, 2H), 7.28-7.23 (m, 2H), 6.78-6.74 (m, 2H), 4.39 (m, 1H), 4.26 (m, 1H), 4.14 (m, 1H), 4.01 (t, *J* = 9 Hz, 1H), 3.75-3.67 (comp m, 2H), 3.43-3.18 (comp m, 2H), 3.37 (s, 1H), 3.27 (s, 1H), 3.19 (s, 3H), 3.18 (s, 3H), 2.92 (dd, *J* = 8.4, 12.0 Hz, 1H), 2.68-2.62 (m, 1H), 2.64 (s, 3H), 2.61 (s, 3H), 2.23 (ddd, *J* = 5.3, 8.4, 13.8 Hz, 1H), 2.09 (br s, 1H), 2.02 (br s, 1H), 1.92-1.67 (comp m, 3H), 1.73 (s, 3H), 1.69 (s, 3H), 0.82 (s, 3H), 0.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.1, 210.8, 174.8, 174.6, 144.3, 136.2, 135.2, 128.8, 128.5, 124.0, 124.0, 122.6, 122.4, 107.2, 106.9, 75.9, 74.4, 71.0, 70.1, 66.5, 66.4, 65.8, 63.8, 57.5, 53.2, 52.8, 52.2, 39.1, 38.4, 38.1, 36.7, 35.0, 32.6, 30.6, 30.1, 26.2, 26.1, 19.6, 19.5; HRMS (EI) *m/z* 356.1739 [calc'd for $C_{20}H_{24}N_2O_4$ (M+) 356.1736].

Preparation of Ketones 202.



202a, 202b

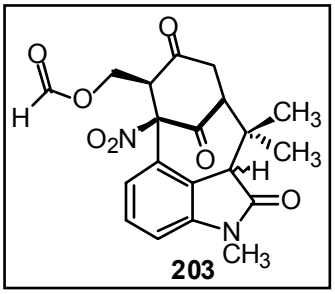
Ketones 202. A solution of oxalyl chloride (170 μL, 1.99 mmol, 1.2 equiv) in CH_2Cl_2 (14 mL) at -78 °C was treated with DMSO (259 μL, 3.64 mmol, 2.2 equiv) and the solution was stirred for 20 minutes at -78 °C. A solution of alcohols **201** (589 mg, 1.65 mmol, 1 equiv) in CH_2Cl_2 (2.5 mL) was added, and stirring continued for another 20 minutes. Et_3N was added and the reaction was allowed to warm to rt over one hour. Flash chromatography furnished ketones **202** (400 mg, 68% yield) and recovered alcohol **201** (103 mg, 17% yield). The yield of ketones **202** was 83% based on recovered starting material.

202a: An analytical sample of the more polar diastereomer (ketone **202a**) was obtained *via* recrystallization of the mixture from Et_2O: m.p. 193-194 °C (dec); IR (thin film/NaCl) 2974 (w), 2934 (w), 2893 (w), 1714 (s), 1605 (m), 1465 (m), 1339 (m), 1095 (m), 915 (w), 783 (m), 731 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.46 (t, *J* = 7.9 Hz, 1H), 7.34 (d, *J* = 8.2 Hz, 1H), 6.86 (d, *J* = 7.7 Hz, 1H), 4.29 (t, *J* = 9.1 Hz, 1H), 4.14 (dd, *J* = 6.1, 9.1 Hz, 1H), 3.93 (dd, *J* = 6.0, 9.8 Hz, 1H), 3.40 (s, 1H), 3.23 (s, 3H), 2.90 (s, 3H), 2.79 (t, *J* = 12.3 Hz, 1H), 2.67 (dd, *J* = 7.7, 12.0 Hz, 1H), 2.47 (dd, *J* = 7.6, 12.4 Hz, 1H), 1.70 (s, 3H), 0.85 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.4, 204.2, 174.1, 144.7, 133.4, 129.6,

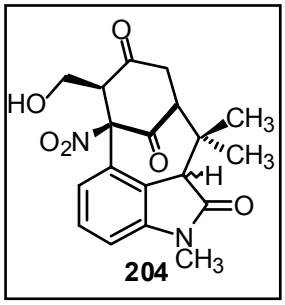
125.1, 121.1, 108.1, 77.1, 68.3, 65.7, 57.0, 51.9, 41.9, 39.0, 36.8, 29.2, 26.3, 19.7; HRMS (EI) *m/z* 354.1579 [calc'd for $C_{20}H_{22}N_2O_4$ (M+) 354.1580].

202a and **202b**: The mother liquor contained a mixture of two diastereomers of ketone **202**: m.p. 113-116 °C (dec); IR (thin film/NaCl) 2972 (w), 2936 (w), 1710 (s), 1605 (m), 1465 (m), 1366 (w), 1340 (m), 1300 (w), 1096 (w), 914 (m), 782 (w), 732 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.44-7.40 (m, 2H), 7.34 (t, *J* = 7.4 Hz, 2H), 6.86 (d, *J* = 7.6 Hz, 1H), 6.77 (d, *J* = 7.6 Hz, 1H), 4.47 (dd, *J* = 5.6, 8.8 Hz, 1H), 4.29 (t, *J* = 9.1 Hz, 1H), 4.16-4.11 (m, 2H), 3.93 (dd, *J* = 6.2, 9.8 Hz, 1H), 3.82 (ddd, *J* = 1.4, 5.8, 9.6 Hz, 1H), 3.72 (s, 1H), 3.39 (s, 1H), 3.23 (s, 3H), 3.21 (s, 3H), 3.06-2.99 (m, 2H), 2.89 (s, 3H), 2.85 (s, 3H), 2.82-2.76 (m, 2H), 2.66 (dd, *J* = 7.4, 11.8 Hz, 1H), 2.46 (dd, *J* = 7.4, 12.2 Hz, 1H), 1.70 (s, 3H), 1.56 (s, 3H), 0.84 (s, 3H), 0.72 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.9, 205.7, 204.7, 202.2, 174.6, 174.5, 145.2, 145.1, 136.9, 133.7, 130.0, 130.0, 125.5, 123.4, 121.5, 119.6, 108.6, 108.2, 81.5, 77.7, 68.7, 66.5, 66.1, 64.1, 61.7, 57.4, 52.3, 50.9, 43.6, 42.3, 40.7, 39.6, 39.4, 37.3, 29.6, 26.9, 26.8, 25.2, 22.6, 20.1; HRMS (EI) *m/z* 354.1579 [calc'd for $C_{20}H_{22}N_2O_4$ (M+) 354.1580].

Preparation of Formate 203 and Alcohol 204.



203



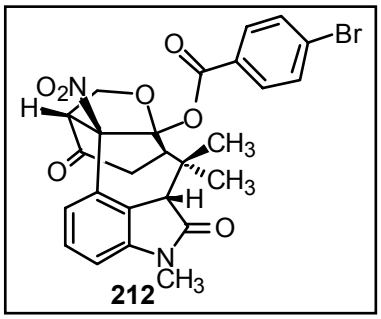
204

Formate 203 and Alcohol 204. To a mixture of ketone **202** (90 mg, 0.25 mmol, 1.0 equiv) and solid $NaHCO_3$ (256 mg, 3.05 mmol, 12 equiv) in CH_2Cl_2 (5 mL) was added at once 85% *p*-nitroperoxybenzoic acid (279 mg, 1.30 mmol, 5.1 equiv). The reaction immediately turned blue-green and eventually yellow while stirring for 10.5 hours. A saturated aqueous solution of $NaHCO_3$ was added (5 mL) and the layers were separated. The organic layer was washed with $NaHCO_3$ (5 mL) and dried over Na_2SO_4 to provide formate **203** as a yellow solid (69 mg, 68% crude yield) after evaporation of the solvent. An analytical sample was not obtained due to decomposition of the product upon further purification.

The derived residue was dissolved in MeOH (5 mL) and Amberlyst 15 beads (wet) were added (ca. 10 beads, Amberlyst 15 ion exchange resin, strongly acidic). After refluxing for 5 hours, the reaction was cooled and the product purified *via* flash chromatography (50% EtOAc/hexanes eluent) to provide alcohol **204** as a white solid (46 mg, 49% yield, two steps). An analytical sample (in solution existing as a mixture of the hemiacetal and free alcohol) was obtained *via* preparative TLC (50% EtOAc/hexanes eluent) followed by recrystallization from Et_2O: m.p. >178 °C (dec/Et_2O); IR (thin film/NaCl) 3429 (br w), 2976 (w), 2897 (w), 1709 (s), 1603 (m), 1551 (s), 1468 (m), 1339 (m), 1133

(w), 1063 (w), 918 (w), 729 (m) cm^{-1}; ^1H NMR (400 MHz, CD_2Cl_2) δ 7.34 (t, *J* = 7.8 Hz, 1H), 7.27 (t, *J* = 7.9 Hz, 1H), 6.95 (d, *J* = 8.0 Hz, 1H), 6.90 (d, *J* = 7.9 Hz, 1H), 6.89 (d, *J* = 7.9 Hz, 1H), 6.81 (d, *J* = 7.6 Hz, 1H), 5.03 (s, 1H), 4.36-3.90 (comp m, 7H), 3.47 (s, 1H), 3.11 (s, 3H), 3.08 (s, 3H), 2.89 (t, *J* = 9 Hz, 1H), 2.66-2.15 (comp m, 5H), 1.86 (m, 1H), 1.65 (s, 3H), 1.62 (s, 3H), 0.78 (s, 3H), 0.61 (s, 3H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 204.6, 204.2, 200.4, 175.6, 174.0, 146.0, 145.7, 130.9, 130.8, 129.8, 127.1, 127.0, 126.2, 122.1, 119.3, 110.7, 109.9, 109.0, 96.7, 95.7, 67.4, 62.2, 61.3, 60.4, 51.2, 50.9, 42.3, 42.0, 40.2, 38.3, 31.5, 30.0, 28.7, 26.5, 26.3, 22.8, 20.7; HRMS (EI) *m/z* 372.1326 [calc'd for $C_{19}H_{20}N_2O_6$ (M+) 372.1321].

Preparation of Benzoate 212.

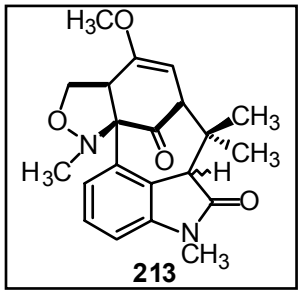


212

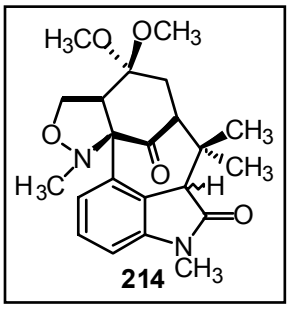
Benzoate 212. A solution of alcohol **204** (10 mg, 0.03 mmol, 1.0 equiv) in CH_2Cl_2 was treated with 4-bromobenzoyl chloride (6.5 mg, 0.03 mmol, 1.1 equiv), Et_3N (5.6 μL, 0.04 mmol, 1.5 equiv) and 4-dimethylaminopyridine (1 mg, 0.008 mmol, 0.3 equiv) and the reaction was stirred for 0.5 hour. Concentration of the solvent *in vacuo*, adsorption onto SiO_2 and flash chromatography (30%

EtOAc/hexanes eluent) provided **212** as a white solid (12 mg, 80% yield). Recrystallization from Et_2O furnished X-ray quality crystals, see Appendix 6 for the X-ray report: m.p. >199 °C (dec/Et_2O); IR (thin film/NaCl) 2976 (br w), 2932 (br w), 1741 (s), 1712 (s), 1611 (m), 1590 (m), 1555 (s), 1468 (m), 1340 (m), 1254 (m), 1123 (m), 1062 (s), 912 (m), 731 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.91 (d, *J* = 7.8 Hz, 2H), 7.75 (d, *J* = 8.4 Hz, 2H), 7.40 (t, *J* = 8.0 Hz, 1H), 6.95 (d, *J* = 8.1 Hz, 1H), 6.91 (d, *J* = 7.8 Hz, 1H), 5.05 (dd, *J* = 4.4, 8.7 Hz, 1H), 4.30 (d, *J* = 8.6 Hz, 1H), 4.19 (d, *J* = 4.3 Hz, 1H), 4.04 (s, 1H), 3.65 (dd, *J* = 2.3, 11.6 Hz, 1H), 3.22 (s, 3H), 2.86 (dd, *J* = 11.5, 19.4 Hz, 1H), 2.43 (dd, *J* = 1.7, 20.2 Hz, 1H), 1.51 (s, 3H), 0.75 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.5, 174.9, 162.7, 145.0, 132.2, 131.7, 130.1, 129.7, 128.1, 127.2, 126.4, 122.0, 111.2, 109.6, 96.9, 70.2, 60.5, 50.7, 50.5, 39.5, 38.0, 31.0, 26.3, 23.1; HRMS (EI) *m/z* 555.0760 [calc'd for $C_{26}H_{23}N_2O_7Br$ (M+) 555.0767].

Preparation of Enol Ether 213 and Acetal 214.



213



214

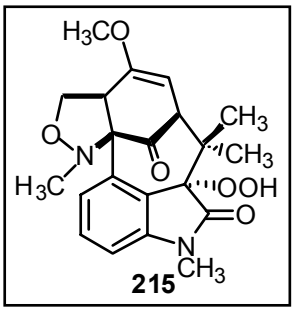
Enol Ether 213 and Acetal 214. Ketone **202** (200 mg, 0.56 mmol, 1.0 equiv) was dissolved in MeOH (5.6 mL) and to the solution was added trimethylorthoformate (155 μL, 1.40 mmol, 2.5 equiv) and *p*-toluenesulfonic acid monohydrate (10.6 mg, 0.06 mmol, 0.1 equiv). The reaction was heated to reflux

for 17 hours, when it was cooled to rt and concentrated. Flash chromatography (50% EtOAc/hexanes eluent) provided enol ether **213** (40 mg, 19% yield) and acetal **214** (70 mg, 31% yield) as yellow solids.

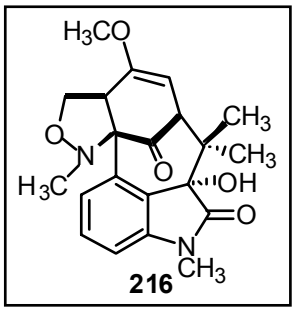
213: The first compound to elute was enol ether **213**: m.p. 252-254 °C (dec); IR (thin film/NaCl) 2966 (w), 2928 (w), 2902 (w), 1707 (s), 1658 (m), 1607 (m), 1598 (m), 1468 (m), 1370 (m), 1335 (m), 1295 (w), 1219 (m), 1166 (w), 1119 (w), 1081 (w), 732 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (d, *J* = 8.0 Hz, 1H), 7.30 (t, *J* = 7.9 Hz, 1H), 6.71 (d, *J* = 7.8 Hz, 1H), 4.88 (dd, *J* = 1.7, 6.5 Hz, 1H), 4.26-4.18 (m, 2H), 3.81-3.78 (comp m, 2H), 3.67 (s, 3H), 3.18 (s, 3H), 3.00 (s, 3H), 2.90 (d, *J* = 6.4 Hz, 1H), 1.51 (s, 3H), 0.72 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.6, 176.1, 158.0, 145.0, 138.3, 129.6, 124.5, 118.7, 107.6, 91.5, 79.7, 69.0, 64.0, 55.7, 55.5, 50.9, 46.1, 40.8, 26.8, 25.0, 22.0; HRMS (EI) *m/z* 368.1737 [calc'd for $C_{21}H_{24}N_2O_4$ (M+) 368.1736].

The second compound to elute was dimethyl acetal **214** of which an analytical sample could not be obtained due to decomposition upon purification.

Preparation of Peroxide 215 and Alcohol 216.



215

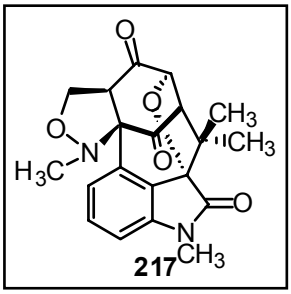


216

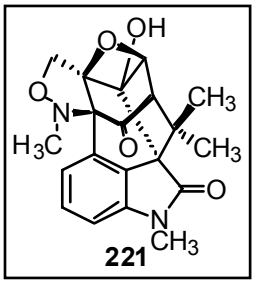
Peroxide 215 and Alcohol 216. A solution of enol ether **213** (50 mg, 0.14 mmol, 1.0 equiv) in *t*-BuOH (3 mL) was treated with 95% KO*t*-Bu (32 mg, 0.27 mmol, 2.0 equiv). Oxygen was then bubbled through the solution for 10 minutes, at which point saturated NH_4Cl (5 mL) was added and *t*-BuOH was subsequently removed *in vacuo*. Extraction with EtOAc (3 x 5 mL) followed by drying over $MgSO_4$ and concentration provided a mixture of peroxide **215** and alcohol **216**. The residue was dissolved in CH_2Cl_2 (3 mL) and was treated with thioanisol (32 μL, 0.27 mmol, 2.0 equiv). After refluxing for one hour, flash chromatography (40% EtOAc/hexanes eluent) furnished alcohol **216** as a white solid (21 mg, 40% yield). X-ray quality crystals were obtained *via* recrystallization from MeOH. See Appendix 6 for X-ray data pertaining to alcohol **216**: m.p. 230-232 °C (MeOH); IR (thin film/NaCl) 3422 (br w), 2969 (w), 2933 (w), 2907 (w), 1706 (s), 1663 (w), 1607 (m), 1590 (m), 1461 (m), 1367 (m), 1292 (w), 1173 (w), 1145 (w), 959 (w), 732 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.65 (d, *J* = 8.2 Hz, 1H), 7.38 (t, *J* = 8.0 Hz, 1H), 6.75 (d, *J* = 7.6 Hz, 1H), 4.90 (dd, *J* = 2.2, 6.7 Hz, 1H), 4.47 (dt, *J* = 2.1, 8.8 Hz, 1H), 4.39 (t, *J* = 8.4 Hz, 1H), 4.23 (t, *J* = 9.1 Hz, 1H), 3.66 (s, 3H), 3.17 (s, 3H), 2.95 (s, 3H), 2.88-2.87 (m, 2H), 1.57 (s, 3H), 0.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.2, 176.1, 158.4, 145.0, 140.4, 131.4, 125.2, 120.1, 108.3, 91.0, 82.2, 80.8, 68.5, 63.1,

55.6, 54.1, 44.5, 40.8, 26.8, 23.6, 19.9; HRMS (EI) *m/z* 384.1682 [calc'd for $C_{21}H_{24}N_2O_5$ (M+) 384.1685].

Preparation of Ether 217 and Oxetane 221.



217



221

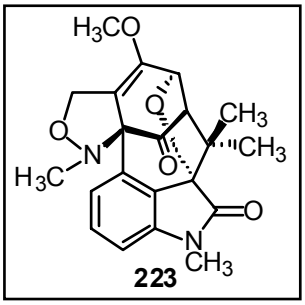
Ether 217 and Oxetane 221. To ketone **202** (200 mg, 0.56 mmol, 1.0 equiv) in *t*-BuOH (6 mL) was added KO*t*-Bu (254 mg, 2.26 mmol, 4.0 equiv) and oxygen gas was bubbled through the resulting dark brown mixture for 15 minutes. The reaction was quenched with saturated NH_4Cl (5 mL), and *t*-BuOH was removed *in vacuo*. H_2O (5 mL) was added and the reaction was extracted with EtOAc (3 x 5 mL). Drying over $MgSO_4$ and concentration of the solvent provided a dark yellow solid (120 mg) which contained two products. Analytical samples of the products were obtained *via* preparative TLC (75% EtOAc/hexanes eluent) which provided oxetane **221** (17 mg, 8% yield) and ketone **217** (46 mg, 22%) as a white solids.

221: Recrystallization from Et_2O/hexanes of the less polar product, oxetane **221**, furnished X-ray quality crystals. See Appendix 6 for X-ray data.: m.p. >192 °C (dec/Et_2O, hexanes); IR (thin film/NaCl) 3389 (br w), 2974 (w), 2934 (w), 2876 (w), 1700 (s), 1690 (s), 1613 (m), 1472 (m), 1336 (w), 1287 (w),

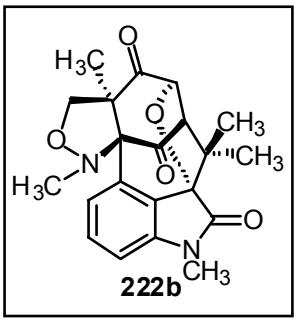
1179 (w), 1059 (w), 915 (w), 780 (w), 734 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.2 Hz, 1H), 7.36 (t, *J* = 7.8 Hz, 1H), 6.78 (d, *J* = 7.8 Hz, 1H), 5.20 (d, *J* = 5.8 Hz, 1H), 4.28 (d, *J* = 11.1 Hz, 1H), 4.11 (s, 1H), 3.70 (d, *J* = 11.1 Hz, 1H), 3.23 (s, 3H), 3.02-3.01 (m, 4H), 1.30 (s, 3H), 0.61 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.2, 175.6, 141.0, 129.9, 129.7, 129.5, 119.2, 107.7, 105.4, 93.9, 87.3, 84.7, 69.1, 67.0, 58.2, 57.4, 40.8, 26.9, 26.1, 21.0; HRMS (EI) *m/z* 368.1367 [calc'd for $C_{20}H_{20}N_2O_5$ (M+) 368.1372].

217: The second compound to elute was ether **217**: m.p. 239-241 °C; IR (thin film/NaCl) 2963 (w), 2932 (w), 1725 (s), 1599 (m), 1463 (m), 1364 (w), 1341 (m), 1297 (w), 1232 (w), 1169 (w), 1127 (w), 1065 (w), 1036 (m), 966 (w), 953 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.40 (t, *J* = 7.9 Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 1H), 6.85 (d, *J* = 8.0 Hz, 1H), 5.00 (d, *J* = 5.7 Hz, 1H), 4.47 (dd, *J* = 3.1, 8.1 Hz, 1H), 4.02 (dd, *J* = 3.3, 8.4 Hz, 1H), 3.94 (t, *J* = 8.3 Hz, 1H), 3.28 (s, 3H), 3.25 (s, 3H), 3.19 (d, *J* = 5.7 Hz, 1H), 1.47 (s, 3H), 0.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.3, 202.6, 171.9, 143.3, 134.0, 131.0, 126.3, 120.0, 108.5, 89.0, 83.6, 78.1, 69.5, 64.6, 63.2, 53.7, 39.7, 26.9, 24.4, 19.3; HRMS (EI) *m/z* 368.1375 [calc'd for $C_{20}H_{20}N_2O_5$ (M+) 368.1372].

Preparation of Enol Ether 223 and Ketone 222b.



223



222b

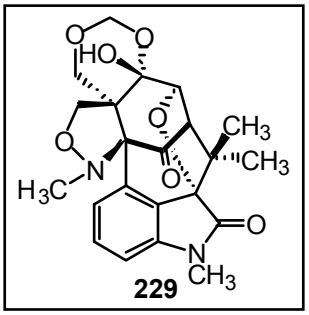
Enol Ether 223 and Ketone 222b. Ketone **217** (31 mg, 0.08 mmol, 1.0 equiv) in DME (3 mL) at -78 °C was treated with 95% NaO*t*-Bu (10 mg, 0.10 mmol, 1.2 equiv) and the mixture was stirred for 30 minutes. At this point iodomethane (26 μL, 0.42 mmol, 5.0 equiv) was added and the reaction was stirred for 11 hours while slowly warming to rt. After quenching with saturated NH_4Cl, the product was extracted with EtOAc (3 x 5 mL) which after drying over $MgSO_4$ and concentrating provided a mixture of C-alkylation product **222b** and O-alkylation product **223** (29 mg, 91% crude yield). Analytical samples were obtained preparative TLC (30% EtOAc/hexanes eluent).

222b: The first product to elute was the C-alkylation product **222b** obtained as a white solid (15 mg, 47% yield). X-ray quality crystals were obtained by recrystallizing from MeOH. See Appendix 6 for X-ray data pertaining to ketone **222b**. m.p. 252-254 °C (dec/MeOH); IR (thin film/NaCl) 2976 (w), 2934 (w), 2870 (w), 1727 (s), 1720 (s), 1601 (m), 1461 (m), 1366 (w), 1339 (w), 1063 (w), 1040 (m), 954 (w), 795 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42 (t, *J* = 7.9 Hz, 1H), 7.16 (d, *J* = 7.8 Hz, 1H), 6.87 (d, *J* = 7.7 Hz, 1H), 4.95 (d, *J* = 6.0 Hz, 1H), 4.54 (d, *J* = 8.2 Hz, 1H), 3.59 (d, *J* = 7.9 Hz, 1H), 3.35 (s, 3H), 3.25 (s, 3H), 3.16 (d, *J* = 6.1 Hz, 1H), 1.47 (s, 3H), 1.09 (s, 3H), 0.82 (s, 3H); ^{13}C NMR (100

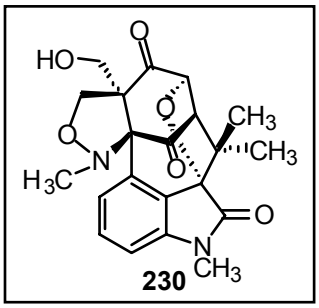
MHz, $CDCl_3$) δ 206.4, 204.3, 171.9, 143.1, 130.7, 129.2, 127.0, 122.8, 108.5, 88.4, 84.5, 79.7, 75.9, 67.8, 65.8, 52.9, 39.3, 26.9, 24.3, 24.3, 19.3; HRMS (EI) *m/z* 382.1520 [calc'd for $C_{21}H_{22}N_2O_5$ (M+) 382.1529].

223: The second product to elute was O-alkylation product **223** isolated as a white solid (9 mg, 28% yield): m.p. 114-116 °C; IR (thin film/NaCl) 2979 (w), 2938 (w), 2866 (w), 1722 (s), 1607 (m), 1586 (m), 1458 (m), 1362 (m), 1341 (m), 1293 (w), 1234 (m), 1156 (w), 1137 (w), 1040 (m), 731 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.3 Hz, 1H), 7.33 (t, *J* = 8.0 Hz, 1H), 6.76 (d, *J* = 7.8 Hz, 1H), 5.18 (d, *J* = 7.2 Hz, 1H), 4.92 (d, *J* = 12.2 Hz, 1H), 4.64 (d, *J* = 12.8 Hz, 1H), 3.79 (s, 3H), 3.19 (s, 3H), 3.10 (d, *J* = 6.7 Hz, 1H), 2.90 (s, 3H), 1.52 (s, 3H), 0.70 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.4, 171.2, 149.7, 143.5, 138.1, 130.5, 126.5, 122.6, 119.5, 108.5, 89.0, 79.8, 78.3, 65.9, 64.0, 57.2, 56.7, 40.9, 27.0, 25.0, 19.1; HRMS (EI) *m/z* 382.1538 [calc'd for $C_{21}H_{22}N_2O_5$ (M+) 382.1529].

Preparation of Hemiacetal 229 and Alcohol 230.



229

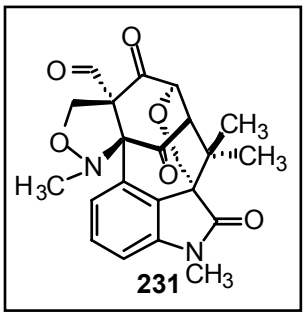


230

Hemiacetal 229 and Alcohol 230. Ketone **217** (62 mg, 0.17 mmol, 1.0 equiv) was dissolved in THF (5 mL) by gently heating with a heat gun. The

solution was brought to -78 °C and was treated with 95% NaO*t*-Bu (26 mg, 0.25 mmol, 1.5 equiv). After stirring for 30 minutes, paraformaldehyde was added (50 mg, 1.68 mmol, 10 equiv), the cold bath was removed and the reaction was stirred for 15 minutes. Quenching with saturated NH_4Cl (5 mL), extracting with EtOAc (3 x 5 mL) and drying over Na_2SO_4 provided a white solid which by NMR was identified as a mixture of alcohol **230** and acetal **229**. The mixture was dissolved in THF (5 mL), *p*-toluenesulfonic acid monohydrate (3 mg, 0.02 mmol, 0.1 equiv) was added and the reaction was heated to reflux for 1 hour. Cooling to rt, removal of the solvent *in vacuo*, adsorption of the reaction onto SiO_2 followed by flash chromatography (75% EtOAc/hexanes eluent) furnished alcohol **230** as a white solid (45 mg, 67% overall yield): m.p. 230-232 °C; IR (thin film/NaCl) 3501 (br w), 2980 (w), 2939 (w), 2890 (w), 1723 (s), 1601 (m), 1462 (m), 1341 (w), 1125 (w), 1038 (m), 913 (w), 793 (w), 732 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.43 (t, *J* = 8.0 Hz, 1H), 7.19 (d, *J* = 8.2 Hz, 1H), 6.89 (d, *J* = 8.1 Hz, 1H), 4.98 (d, *J* = 6.0 Hz, 1H), 4.40 (d, *J* = 8.8 Hz, 1H), 4.12 (d, *J* = 8.8 Hz, 1H), 3.60-3.52 (m, 2H), 3.28 (s, 3H), 3.18 (s, 3H), 3.13 (d, *J* = 4.7 Hz, 1H), 1.57 (m, 1H), 1.48 (s, 3H), 0.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.1, 202.7, 171.7, 143.2, 131.0, 127.5, 127.1, 122.3, 108.9, 88.4, 84.5, 78.4, 72.0, 69.9, 67.5, 67.0, 52.9, 39.2, 26.9, 24.3, 19.3; HRMS (EI) *m/z* 398.1479 [calc'd for $C_{21}H_{22}N_2O_6$ (M+) 398.1478].

Preparation of Aldehyde 231.



231

Aldehyde 231. A solution of alcohol **230** (50 mg, 0.13 mmol, 1.0 equiv) in undistilled CH_2Cl_2 (5 mL) was treated with Dess-Martin periodinate (110 mg, 0.26 mmol, 2.0 equiv) and the reaction was stirred 1 hour. At this time, saturated aqueous $NaHCO_3$ (2 mL) and $Na_2S_2O_3$ (2 mL) were added and the whole was stirred for an additional hour. Separation of the layers followed by extraction of the aqueous layer with CH_2Cl_2 (3 x 5 mL) provided aldehyde **231** as a white solid (45 mg, 90% yield). An analytical sample was obtained *via* recrystallization from Et_2O: m.p. >205 °C (dec/Et_2O); IR (thin film/NaCl) 2982 (w), 2940 (w), 1728 (s), 1601 (m), 1463 (m), 1364 (w), 1338 (w), 1123 (w), 1038 (w), 911 (w), 793 (w), 732 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.01 (s, 1H), 7.46 (t, *J* = 8.1 Hz, 1H), 7.26 (d, *J* = 7.6 Hz, 1H), 6.91 (d, *J* = 8.0 Hz, 1H), 5.05 (d, *J* = 5.5 Hz, 1H), 4.63 (d, *J* = 8.8 Hz, 1H), 4.03 (d, *J* = 8.4 Hz, 1H), 3.40 (s, 3H), 3.25 (s, 3H), 3.23 (d, *J* = 5.5 Hz, 1H), 1.49 (s, 3H), 0.83 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.5, 197.5, 191.7, 171.9, 144.1, 131.8, 127.8, 127.2, 122.4, 109.7, 89.1, 83.9, 79.3, 79.0, 69.2, 69.0, 53.1, 39.6, 27.2, 24.6, 19.7; HRMS (EI) *m/z* 396.1327 [calc'd for $C_{21}H_{20}N_2O_6$ (M+) 396.1321].

4.5 Notes and References.

(1) For examples of SmI_2-induced cyclopropyl ketone ring-openings, see: Batey, R. A.; Motherwell, W. B. *Tetrahedron Lett*. **1991**, *32*, 6649.

(2) For the original report on alkylation with methylcyanoformate, see: Mander, L. N.; Sethi, S. P. *Tetrahedron Lett.* **1983**, 5425. The procedure used was modified from the reported procedure, mainly in the base used (*t*-BuLi instead of LDA), see Experimental Section 4.4.2 for details.

(3) This reaction presumably takes several days because the starting material exists mostly in the enol form in solution.

(4) Attempts to form bond C *via* intramolecular Aldol reaction of aldehyde **156** also lead to formation of **155**.

(5) For data corresponding to diacetate **158**, see: Chalova, O. B.; Chistoedova, G. B.; Kiladze, T. K.; Germash, E. V.; Kantor, E. A.; Rakhmankulov, D. L. *J. Appl. Chem. USSR* **1988**, *61*, 853.

(6) For an example of building a similar bridged system using this method, see: Campiani, G.; Sun, L. Q.; Kozikowski, A. P.; Aagaard, P.; McKinney, M. *J. Org. Chem.* **1993**, *58*, 7660.

(7) All of the data corresponding to this section will be published in the thesis of Matthew Weiss. See also ref. 23, Chapter 2 for more information

including experimental procedures and data in the corresponding Supplementary Materials.

([8]) In addition, these studies showed that **165** can also be advanced *via* Claisen rearrangement before addition of a nucleophile (see Section 4.2.2.3).

([9]) See Supplementary Materials of Wood, J. L.; Holubec, A. A.; Stoltz, B. M.; Weiss, M. M.; Dixon, J. A.; Doan, B. D.; Shamji, M. F.; Chen, J. M.; Heffron, T. P. *J. Am. Chem. Soc.*, **1999**, *121*, 6326 for X-ray structure reports of **168a** and the diol resulting from $NaBH_4$ reduction of **171**.

([10]) Although ring-closing metathesis has been widely used in synthesis, its application in constructing medium-sized bridged carbocycles is less common. For a recent discussion, see: Morehead Jr., A.; Grubbs, R. H. *J. Chem. Soc. Chem. Commun.* **1998**, 275.

([11]) See ref. 4, Chapter 1.

([12]) For examples of accessing isonitriles from amines *via* formamides, see: Ichikawsi, Y. *J. Chem. Soc. Perkin Trans.1* **1992**, *16*, 2135, and Nakamura, H.; Ye, B.; Murai, A. *Tetrahedron Lett.* **1992**, *33*, 8113.

([13]) For examples of building bridged bicycloalkanes *via* nitrone-olefin cycloaddition, see: Funk, R. L.; Horcher, H. M.; Daggett, J. U.; Hansen, M. M. *J. Org. Chem.* **1983**, *48*, 2632.

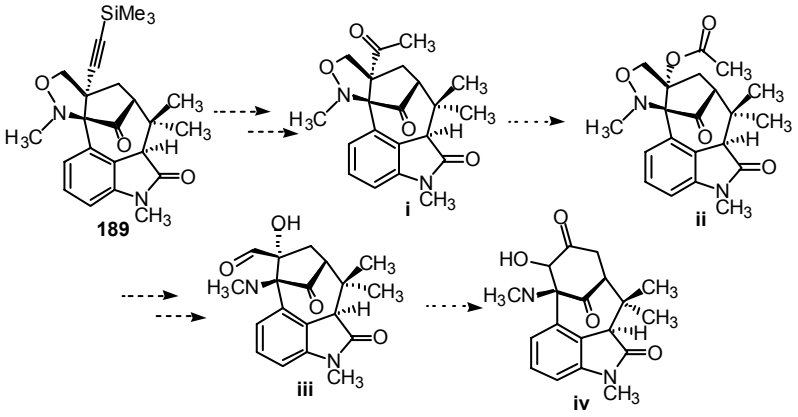
([14]) a) Sevast'yanova, T. K.; Volodarskii, L. B. *J. Org. Chem., USSR* **1971**, *7*, 2046. b) Ooi, N. S.; Wilson, D. A. J. *Chem. Res.* **1980**, *11*, 4501 (MTM-nitrone).

([15]) Attempts to effect cycloaddition with commercially available *t*-butylhydroxylamine were also unsuccessful.

([16]) For the preparation of alcohol 186, see: Nicolaou, K. C.; Koide, K.; *Tetrahedron Lett*. **1997**, *38*, 3667.

([17]) In addition, attempts to make the acetylene moiety more prone to cycloaddition relative to the olefin, (e.g., removal of the olefin *via* epoxide or diol formation, deprotection of the trimethylsilyl group on the acetylene) were unsuccessful.

([18]) One route that was investigated for possible ring expansion was the following:



([19]) For data corresponding to alcohol **194**, see: Uemura, et al. *Nippon Kagaku Zasshi* **1966**, *87*, 986.

([20]) Since acetate **194** is a secondary alcohol, if Et_3N is not added rapidly after nitrogen evolution ceases, the product of enol formation/Claisen rearrangement is observed. Also, since the resulting enol ether **196** hydrolyzes upon purification, it is used crude in the next step.

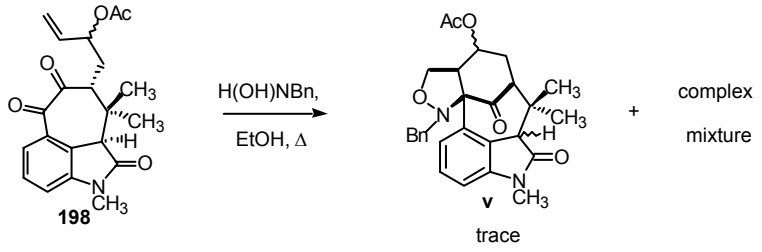
([21]) a) Overman, L. E.; Campbell, C. B.; Knoll, F. M. *J. Am. Chem. Soc.* **1978**, *100*, 4822. b) Overman, L. E. *Agnew. Chem. Int. Ed*. **1984**, *23*, 579.

([22]) Conditions used for the previous cycloadditions (i.e., diketones **177** and **188**) were unsuccessful in this system due to basic conditions interfering with the acetate moiety. Therefore, in this system, *N*-methylhydroxylamine hydrochloride was pretreated with less than 1 equiv of NaOMe in EtOH to free the hydroxylamine, and the EtOH solution of *N*-methylhydroxylamine was filtered into a flask containing diketone **198**. Thus, the cycloaddition was performed under "base-free" and "salt-free" conditions. See Section 4.4.2 for complete experimental details.

([23]) A trace amount of the fourth diastereomer was seen by crude NMR analysis however was not observed after extensive purifications.

([24]) From this point forward, epimerization at C(3) is often observed to provide mixtures of C(3) epimers.

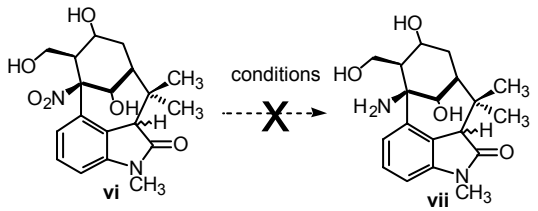
([25]) Attempts to effect nitrone formation and cycloaddition using *N*-benzyl hydroxylamine led to a complex mixture of products including only trace amounts of desired product (**v**):



([26]) a) Falb, E.; Bechor, Y.; Nudelman, A.; Hassner, A.; Albeck, A.; Gottlieb, H. E. *J. Org. Chem*. **1999**, *64*, 498. b) Palmisano, G.; Danieli, B.; Lesma, G.; Trupiano, F.; Pilati, T. *J. Org. Chem*. **1988**, *53*, 1056. c) Katagiri, N.; Okada, M.; Morishita, Y.; Kaneko, C. *Tetrahedron* **1997**, *53*, 5725.

([27]) For an example, see LeBel, N. A.; Post, M. E.; Hwang, D. *J. Org. Chem*. **1979**, *44*, 1819. In this report, the authors treat isoxazolidines with 1 equiv of *m*-CPBA at low temperatures and isolate the corresponding oxazines. They found that upon further treatment of the derived oxazines with *m*-CPBA, nitro-formates are obtained.

([28]) Triol **vi** (prepared by reduction of alcohol **204**) was explored in the reduction of the nitro moiety to an amine (i.e., **vii**) without any success. Several of the reducing agents investigated were: zinc, Raney nickel, SmI_2, NiB_2•$NaBH_4$, $SnCl_2$•H_2O, H_2NNH_2•H_2O, $Cu(OAc)_2/NaBH_4$, $LiAlH_4$, $HgCl_2/Mg/TiCl_4$.



([29]) This issue was explored by Matthew Weiss and will be discussed in his thesis.

([30]) See ref. 4, Chapter 1.

([31]) The authors treat 25 mg of **3** with oxygen while irradiating for 4 days and recover 12.5 mg of **3**, along with trace amounts of **18** and **17**.

([32]) a) Sawaki, Y.; Ogata, Y. *J. Am. Chem. Soc.* **1975**, *97*, 6983. b) Magnus, P.; Booth, J.; Magnus, N.; Tarrant, J.; Thom, S.; Ujjainwalla, F. *Tetrahedron Lett.* **1995**, *36*, 5331. c) Mailey, E. J.; Barton, D. H.; Elks, J.; Templeton, J. F. *J. Chem. Soc*. **1975**, *97*, 6983. d) Chu-Moyer, M.; Danishefsky, S. *J. J. Am. Chem. Soc*. **1992**, *114*, 8333. e) Johnson, W. S.; Dumas, D. J.; Berner, D. *J. Am. Chem. Soc.* **1982**, *104*, 3510.

([33]) Dimethylacetal **214** is tentatively assigned because purification led to decomposition.

([34]) This study was performed on ca. 3 mg of sample, and results were qualitative. See following sections for confirmation of structure of ether **217**, and Section 4.4.2 for experimental data.

([35]) Attempts to homologate aldehyde **231** under either Wittig or Nozaki-Hiyama conditions ($CrCl_2$, CH_2I_2, DMF, THF) led to deformylation to provide diketone **217**. Treatment of **231** with Tebbe reagent led to decomposition.

([36]) Wood, J. L.; Weiss, M. M., unpublished results.

([37]) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

([38]) Diacetate **157** was prepared in 92% yield from 2-methylene-1,3-propanediol, see ref. 5 for corresponding data.

([39]) For the preparation of alcohol **185**, see ref. 17.

([40]) For the preparation of 3-butene-1,2-diol, see Rao, A. V. R.; Bose, D. S.; Gurjar, M. K.; Ravindranathan, T. *Tetrahedron* **1989**, 7031.

([41]) For data corresponding to diacetate **233**, see: Baltes, H. *Chem. Ber.* **1979**, *112*, 807, and for alcohol **194**, see ref. 20.

APPENDIX FIVE: SPECTRA RELEVANT TO CHAPTER FOUR

Figure A.5.1

Figure A.5.2 Infrared Spectrum (thin film/NaCl) of compound **151**.

Figure A.5.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **151**.

Figure A.5.4

Figure A.5.5 Infrared Spectrum (thin film/NaCl) of compound **152**.

Figure A.5.6 ^{13}C NMR (100 MHz, $CDCl_3$) of compound **152**.

Figure A.5.7

Figure A.5.8 Infrared Spectrum (thin film/NaCl) of compound **153**.

Figure A.5.9 ^{13}C NMR (100 MHz, $CDCl_3$) of compound **153**.

Figure A.5.10

Figure A.5.11 Infrared Spectrum (thin film/NaCl) of compound **155**.

Figure A.5.12 ^{13}C NMR (100 MHz, $CDCl_3$) of compound **155**.

Figure A.5.13

Figure A.5.14 Infrared Spectrum (thin film/NaCl) of compound **156**.

Figure A.5.15 ^{13}C NMR (100 MHz, $CDCl_3$) of compound **156**.

Figure A.5.16

Figure A.5.17 Infrared Spectrum (thin film/NaCl) of compound **161**.

Figure A.5.18 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **161**.

Figure A.5.19

Figure A.5.20 Infrared Spectrum (thin film/NaCl) of compound **177**.

Figure A.5.21 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **177**.

Figure A.5.22

Figure A.5.23 Infrared Spectrum (thin film/NaCl) of compound **178**.

Figure A.5.24 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **178**.

Figure A.5.25

Figure A.5.26 Infrared Spectrum (thin film/NaCl) of compound **179**.

Figure A.5.27 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **179**.

Figure A.5.28

Figure A.5.29 Infrared Spectrum (thin film/NaCl) of compound **180**.

Figure A.5.30 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **180**.

Figure A.5.31

Figure A.5.32 Infrared Spectrum (thin film/NaCl) of compound **181**.

Figure A.5.33 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **181**.

Figure A.5.34

Figure A.5.35 Infrared Spectrum (thin film/NaCl) of compound **188**.

Figure A.5.36 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **188**.

Figure A.5.37

Figure A.5.38 Infrared Spectrum (thin film/NaCl) of compound **189**.

Figure A.5.39 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **189**.

Figure A.5.40

Figure A.5.41 Infrared Spectrum (thin film/NaCl) of compound **197**.

Figure A.5.42 ^{13}C NMR (125 MHz, d_6-acetone) of compound **197**.

Figure A.5.43

Figure A.5.44 Infrared Spectrum (thin film/NaCl) of compound **198a**.

Figure A.5.45 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **198a**.

Figure A.5.46

Figure A.5.47 Infrared Spectrum (thin film/NaCl) of compound **198b**.

Figure A.5.48 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **198b**.

Figure A.5.49

Figure A.5.50 Infrared Spectrum (thin film/NaCl) of compound **200**.

Figure A.5.51 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **200**.

Figure A.5.52

Figure A.5.53 Infrared Spectrum (thin film/NaCl) of compounds **199b** and **199c**.

Figure A.5.54 ^{13}C NMR (100 MHz, $CDCl_3$) of compounds **199b** and **199c**.

Figure A.5.55

Figure A.5.56 Infrared Spectrum (thin film/NaCl) of compound **199b**.

Figure A.5.57 ^{13}C NMR (100 MHz, $CDCl_3$) of compound **199b**.

Figure A.5.58

Figure A.5.59 Infrared Spectrum (thin film/NaCl) of compound **199a**.

Figure A.5.60 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **199a**.

Figure A.5.61

Figure A.5.62 Infrared Spectrum (thin film/NaCl) of compounds **201a** and **201b**.

Figure A.5.63 ^{13}C NMR (100 MHz, $CDCl_3$) of compounds **201a** and **201b**.

Figure A.5.64

Figure A.5.65 Infrared Spectrum (thin film/NaCl) of compound **201c** and **201d**.

Figure A.5.66 ^{13}C NMR (100 MHz, $CDCl_3$) of compound **201c** and **201d**.

Figure A.5.67

Figure A.5.68 Infrared Spectrum (thin film/NaCl) of compound **202a**.

Figure A.5.69 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **202a**.

Figure A.5.70

Figure A.5.71 Infrared Spectrum (thin film/NaCl) of compound **202a** and **202b**.

Figure A.5.72 ^{13}C NMR (100 MHz, $CDCl_3$) of compound **202a** and **202b**.

Figure A.5.73

Figure A.5.74 Infrared Spectrum (thin film/NaCl) of compound **204**.

Figure A.5.75 ^{13}C NMR (125 MHz, CD_2Cl_2) of compound **204**.

Figure A.5.76

Figure A.5.77 Infrared Spectrum (thin film/NaCl) of compound **212**.

Figure A.5.78 ^{13}C NMR (100 MHz, $CDCl_3$) of compound **212**.

Figure A.5.79

Figure A.5.80 Infrared Spectrum (thin film/NaCl) of compound **213**.

Figure A.5.81 ^{13}C NMR (100 MHz, $CDCl_3$) of compound **213**.

Figure A.5.82

Figure A.5.83 Infrared Spectrum (thin film/NaCl) of compound **216**.

Figure A.5.84 ^{13}C NMR (100 MHz, $CDCl_3$) of compound **216**.

Figure A.5.85

Figure A.5.86 Infrared Spectrum (thin film/NaCl) of compound **221**.

Figure A.5.87 ^{13}C NMR (100 MHz, $CDCl_3$) of compound **221**.

Figure A.5.88

Figure A.5.89 Infrared Spectrum (thin film/NaCl) of compound **217**.

Figure A.5.90 ^{13}C NMR (100 MHz, $CDCl_3$) of compound **217**.

Figure A.5.91

Figure A.5.92 Infrared Spectrum (thin film/NaCl) of compound **222b**.

Figure A.5.93 ^{13}C NMR (100 MHz, $CDCl_3$) of compound **222b**.

Figure A.5.94

Figure A.5.95 Infrared Spectrum (thin film/NaCl) of compound **223**.

Figure A.5.96 ^{13}C NMR (100 MHz, $CDCl_3$) of compound **223**.

Figure A.5.97

Figure A.5.98 Infrared Spectrum (thin film/NaCl) of compound **230**.

Figure A.5.99 ^{13}C NMR (100 MHz, $CDCl_3$) of compound **230**.

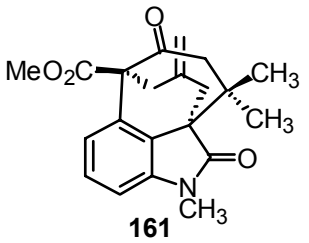
Figure A.5.100

Figure A.5.101 Infrared Spectrum (thin film/NaCl) of compound **231**.

Figure A.5.102 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **231**.

APPENDIX SIX: X-RAY CRYSTALLOGRAPHY REPORTS RELEVANT TO CHAPTER FOUR

X-RAY CRYSTALLOGRAPHY REPORT FOR OLEFIN 161



161

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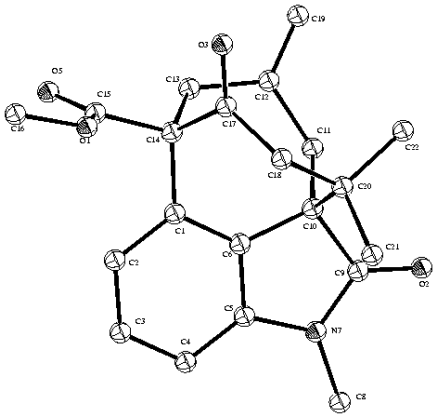


Crystal Data and Structure Refinement

Empirical Formula	$C_{21}H_{23}NO_4$
Formula Weight	353.40
Crystal Color, Habit	colorless, needle
Crystal size	0.06 x 0.15 x 0.50 mm
Crystal system	monoclinic
Temperature	293(2) K
Wavelength	0.71073 Å
Unit cell dimensions	a = 9.1375 (10) Å
	alpha = 90°
	b = 20.858 (2) Å
	beta = 105.179(2)°
	c = 9.4853 (10)
	gamma = 90°
Space group	P2(1)/ n
Z value	4
Density (calculated)	1.345 Mg/m^3
F(000)	752
Volume, Z	1744.7 (3) $Å^3$, 4
Absorption coefficient	0.093 mm^{-1}
θ range for data collected	1.95 to 28.33°
Limiting indices	-11 < h < 11, -22 < k < 27,
	-10 < 1 < 12

Reflections collected	11532
Independent reflections	4223 (R_{int} = 0.0374)
Completeness to θ = 28.33°	97.1%
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	4223 / 0 / 263
Goodness-of-fit on F^2	1.063
Final R indices [I>2σ(I)]	R1 = 0.0378, wR2 = 0.0731
R indices (all data)	R1 = 0.0678, wR2 = 0.0781
Extinction coefficient	0.047 (7)
Largest diff. peak and hole	0.275 and -0.173 eÅ^{-3}
Diffractometer	Bruker SMART 1000 CCD
Crystal to Detector Distance	4.895 cm
$2\theta_{max}$	56.5°

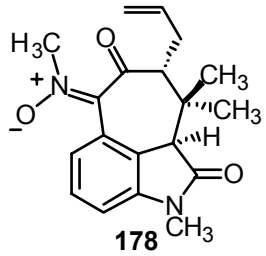
Atomic coordinates and $B_{iso}/_{eq}$ for Olefin 161.

atom	x	y	z	eq
C(1)	5810 (1)	1053 (1)	6082 (1)	20 (1)
C(2)	7168 (1)	1086 (1)	5658 (2)	23 (1)
C(3)	7204 (1)	1329 (1)	4305 (2)	25 (1)
C(4)	5891 (1)	1544 (1)	3305 (2)	24 (1)
C(5)	4567 (1)	1523 (1)	3745 (1)	21 (1)
C(6)	4516 (1)	1290 (1)	5102 (1)	19 (1)
N(7)	3094 (1)	1706 (1)	2957 (1)	22 (1)
C(8)	2732 (2)	1976 (1)	1496 (2)	32 (1)
C(9)	2066 (1)	1590 (1)	3750 (1)	21 (1)
C(10)	2925(1)	1331 (1)	5263 (1)19	(1)

C(11)	2251 (1)	657 (1)	5390 (1)	22 (1)
C(12)	2937 (1)	275 (1)	6757 (1)	23 (1)
C(13)	4620 (1)	138 (1)	7163 (2)	23 (1)
C(14)	5650 (1)	744 (1)	7496 (1)	21 (1)
C(15)	7225 (2)	541 (1)	8392 (1)	24 (1)
C(16)	9508 (2)	915 (1)	9988 (2)	33 (1)
C(17)	4930 (1)	1188 (1)	8430 (2)	22 (1)
C(18)	4275 (1)	1822 (1)	7802 (1)	22 (1)
C(19)	2076 (2)	29 (1)	7545 (2)	32 (1)
C(20)	2841 (1)	1838 (1)	6484 (1)	21 (1)
C(21)	2821 (2)	2522 (1)	5857 (2)	25 (1)
C(22)	1413 (1)	1745 (1)	7017 (2)	27 (1)
O(1)	7968 (1)	1037 (1)	9144 (1)	29 (1)
O(2)	694 (1)	1677 (1)	3310 (1)	27 (1)
O(3)	4924 (1)	1019 (1)	9656 (1)	31 (1)
O(5)	7757 (1)	14 (1)	8371 (1)	34 (1)
H(2)	8062	943	6296	27 (4)
H(3)	8124	1348	4059	27 (4)
H(4)	5907	1695	2386	27 (4)
H(8A)	1676	2086	1199	37 (4)
H(8B)	2950	1666	830	55 (5)
H(8C)	3332	2354	1493	47 (5)
H(11A)	1177	708	5310	21 (3)
H(11B)	2341	405	4557	20 (3)
H(13A)	4859	-97	6368	24 (4)
H(13B)	4861	-138	8016	22 (3)

H(16A)	9554	508	10471	53 (5)
H(16B)	9825	-1248	10703	71 (6)
H(16C)	10168	909	9349	81 (7)
H(18A)	5071	2053	7512	24 (4)
H(18B)	4042	2065	8588	27 (4)
H(19A)	1032	89	7260	37 (4)
H(19B)	2516	-205	8384	36 (4)
H(21A)	1850	2604	5191	21 (3)
H(21B)	3599	2560	5351	35 (4)
H(21C)	3001	-2828	6640	31 (4)
H(22A)	1336	2086	7674	25 (4)
H(22B)	1470	1342	7517	35 (4)
H(22C)	536	1748	6196	29 (4)

X-RAY CRYSTALLOGRAPHY REPORT FOR NITRONE 178



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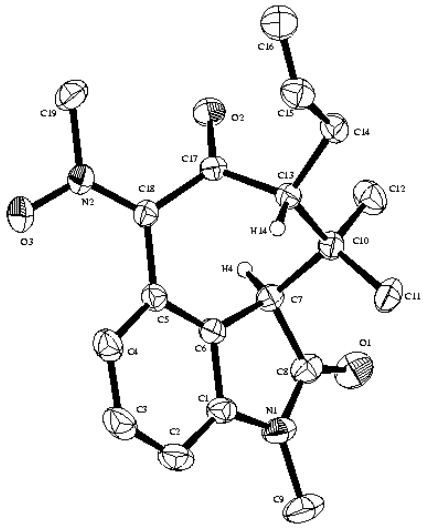


A. Crystal Data

Empirical Formula	$C_{19}H_{22}N_2O_3$
Formula Weight	326.39
Crystal Color, Habit	colorless, plate
Crystal Dimensions	0.17 X 0.35 X 0.40 mm
Crystal System	triclinic
Lattice Type	Primitive
Lattice Parameters	a = 9.3960(3)Å
	b = 9.968(1) Å
	c = 10.734(1) Å
	α = 111.159(2)o
	β = 112.427(3)o
	γ = 95.384(3)o
	V = 834.7(1) Å3
Space Group	P_{-1} (#2)
Z value	2
D_{calc}	1.298 g/cm3
F_{000}	348.00
μ(MoKα)	0.88 cm^{-1}

B. Intensity Measurements

Diffractometer	Nonius KappaCCD
Radiation	MoKα (λ = 0.71069 Å) graphite monochromated
Take-off Angle	2.8°
Crystal to Detector Distance	33 mm
Temperature	23.0°C
Scan Width	1°
$2\theta_{max}$	52.7°
No. of Reflections Measured	Total: 3314
Corrections	Lorentz-polarization

C. Structure Solution and Refinement

Structure Solution	Direct Methods (SIR92)
Refinement	Full-matrix least-squares
Function Minimized	Σ w (|Fo| - |Fc|)^2
Least Squares Weights	$1/\sigma^{2(Fo)}$ = 4Fo2/σ^2(Fo^2)
p-factor	0.0100
Anomalous Dispersion	All non-hydrogen atoms
No. Observations (I>3.00σ(I))	2794
No. Variables	217
Reflection/Parameter Ratio	12.88
Residuals: R; Rw	0.046 ; 0.069
Goodness of Fit Indicator	3.20
Max Shift/Error in Final Cycle	0.00
Maximum peak in Final Diff. Map	0.18 e-/Å3
Minimum peak in Final Diff. Map	-0.15 e-/Å3

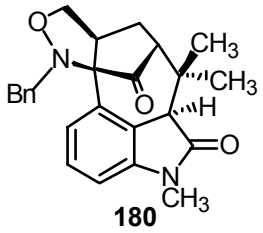
Atomic coordinates and $B_{iso}/_{eq}$ for Nitrone 178.

atom	x	y	z	eq
O(1)	-0.7143(1)	-0.3418(2)	0.0485(1)	5.44(3)
O(2)	-1.1731(1)	-0.0796(1)	-0.2021(1)	4.39(3)
O(3)	-0.9018(1)	0.1946(2)	-0.2878(2)	6.71(4)

N(1)	-0.5950(1)	-0.2668(2)	-0.0754(1)	4.11(3)
N(2)	-0.9998(1)	0.1005(1)	-0.2840(1)	3.98(3)
C(1)	-0.6223(1)	-0.1842(2)	-0.1596(2)	3.60(3)
C(2)	-0.5243(2)	-0.1342(2)	-0.2107(2)	4.80(4)
C(3)	-0.5747(2)	-0.0470(2)	-0.2839(2)	5.10(4)
C(4)	-0.7161(2)	-0.0074(2)	-0.3049(2)	4.33(4)
C(5)	-0.8164(1)	-0.0580(2)	-0.2527(2)	3.19(3)
C(6)	-0.7681(1)	-0.1492(2)	-0.1807(1)	3.02(3)
C(7)	-0.8427(1)	-0.2185(2)	-0.1101(1)	3.06(3)
C(8)	-0.7126(2)	-0.2831(2)	-0.0331(2)	3.89(3)
C(9)	-0.4540(2)	-0.3215(2)	-0.0312(2)	5.86(4)
C(10)	-1.0040(1)	-0.3440(2)	-0.2225(2)	3.19(3)
C(11)	-0.9689(2)	-0.4869(2)	-0.3068(2)	4.41(3)
C(12)	-1.0905(2)	-0.3708(2)	-0.1360(2)	4.82(4)
C(13)	-1.1027(1)	-0.2882(2)	-0.3392(1)	2.93(3)
C(14)	-1.2798(2)	-0.3768(2)	-0.4357(2)	3.90(3)
C(15)	-1.3577(2)	-0.3406(2)	-0.5659(2)	4.44(4)
C(16)	-1.4855(2)	-0.2952(2)	-0.5978(2)	5.41(4)
C(17)	-1.0896(1)	-0.1238(2)	-0.2634(1)	3.00(3)
C(18)	-0.9688(1)	-0.0206(2)	-0.2672(1)	3.04(3)
C(19)	-1.1540(2)	0.1382(2)	-0.3045(2)	4.65(4)
H(1)	-0.4258	-0.1590	-0.1959	5.7653
H(2)	-0.5097	-0.0125	-0.3215	6.1241
H(3)	-0.7458	0.0543	-0.3550	5.1923
H(4)	-0.8596	-0.1428	-0.0369	3.6712
H(5)	-0.4619	-0.4049	-0.1150	7.0294

H(6)	-0.4469	-0.3508	0.0454	7.0294
H(7)	-0.3611	-0.2445	0.0047	7.0294
H(8)	-0.9029	-0.4645	-0.3492	5.2890
H(9)	-1.0665	-0.5578	-0.3841	5.2890
H(10)	-0.9156	-0.5270	-0.2396	5.2890
H(11)	-1.1824	-0.4533	-0.2014	5.7794
H(12)	-1.1221	-0.2843	-0.0944	5.7794
H(13)	-1.0210	-0.3916	-0.0581	5.7794
H(14)	-1.0555	-0.2993	-0.4052	3.5102
H(15)	-1.2867	-0.4805	-0.4721	4.6794
H(16)	-1.3346	-0.3528	-0.3756	4.6794
H(17)	-1.3085	-0.3521	-0.6304	5.3269
H(18)	-1.5386	-0.2822	-0.5363	6.4919
H(19)	-1.5266	-0.2749	-0.6828	6.4919
H(20)	-1.1436	0.2078	-0.2113	5.5848
H(21)	-1.1818	0.1808	-0.3738	5.5848
H(22)	-1.2351	0.0500	-0.3414	5.5848

X-RAY CRYSTALLOGRAPHY REPORT FOR ISOXAZOLIDINE 180



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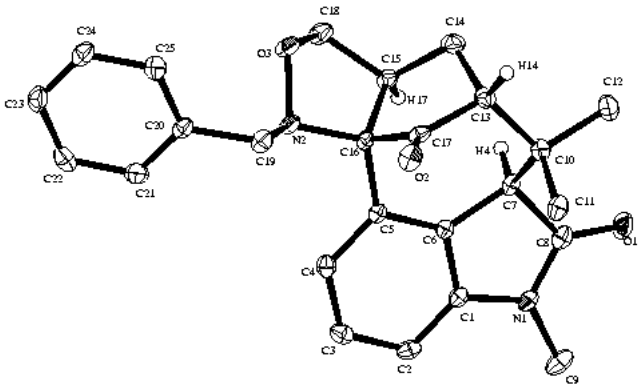


A. Crystal Data

Empirical Formula	$C_{25}H_{26}N_2O_3$
Formula Weight	402.49
Crystal Color, Habit	colorless plate
Crystal Dimensions	0.03 X 0.12 X 0.15 mm
Crystal System	monoclinic
Lattice Type	Primitive
Lattice Parameters	a = 10.1614(5)Å
	b = 17.393(1) Å
	c = 11.2787(3) Å
	β = 92.944(3)o
	V = 1990.7(1) Å3
Space Group	P21/c (#14)
Z value	4
D_{calc}	1.343 g/cm3
F_{000}	856.00
μ(MoKα)	0.88 cm^{-1}

B. Intensity Measurements

Diffractometer	Nonius KappaCCD
Radiation	MoKα (λ = 0.71069 Å)
	graphite monochromated
Take-off Angle	2.8°
Crystal to Detector Distance	33 mm

Temperature	-90.0°C
Scan Rate	90sec/frame
Scan Width	1°/frame
$2\theta_{max}$	61.0°
No. of Reflections Measured	Total: 5688
Corrections	Lorentz-polarization
Secondary Extinction (coefficient: 1.70022e-06)	

C. Structure Solution and Refinement

Structure Solution	Direct Methods (SIR92)
Refinement	Full-matrix least-squares
Function Minimized	Σ w (|Fo| - |Fc|)^2
Least Squares Weights	$1/\sigma^{2(Fo)}$
p-factor	0.0200
Anomalous Dispersion	All non-hydrogen atoms
No. Observations (I>5.00σ(I))	2044
No. Variables	271
Reflection/Parameter Ratio	7.54
Residuals: R; Rw	0.042 ; 0.049
Goodness of Fit Indicator	1.91
Max Shift/Error in Final Cycle	0.00
Maximum peak in Final Diff. Map	0.28 e-/Å3
Minimum peak in Final Diff. Map	-0.28 e-/Å3

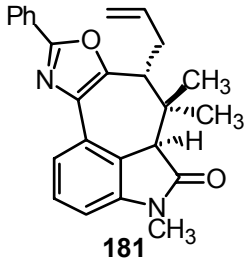
Atomic coordinates and $B_{iso}/_{eq}$ for Isoxazolidine 180.

atom	x	y	z	eq
O(1)	0.9483(2)	0.0569(1)	1.1521(1)	3.07(5)
O(2)	0.6700(2)	0.2565(1)	0.7561(1)	2.65(5)
O(3)	0.5863(2)	0.0957(1)	0.5477(1)	2.50(4)
N(1)	0.7251(2)	0.0733(1)	1.1601(2)	2.07(5)

N(2)	0.5143(2)	0.1180(1)	0.6523(2)	1.96(5)
C(1)	0.6173(3)	0.0876(1)	1.0805(2)	1.78(6)
C(2)	0.4873(3)	0.0931(1)	1.1056(2)	2.24(7)
C(3)	0.3962(3)	0.1050(2)	1.0113(2)	2.35(7)
C(4)	0.4359(3)	0.1120(2)	0.8953(2)	2.06(7)
C(5)	0.5690(3)	0.1072(1)	0.8711(2)	1.61(6)
C(6)	0.6606(2)	0.0947(1)	0.9658(2)	1.60(6)
C(7)	0.8091(3)	0.0857(1)	0.9707(2)	1.89(6)
C(8)	0.8401(3)	0.0707(1)	1.1035(2)	2.23(7)
C(9)	0.7159(3)	0.0598(2)	1.2863(2)	3.01(7)
C(10)	0.8875(3)	0.1538(2)	0.9190(2)	2.15(6)
C(11)	0.8569(3)	0.2277(2)	0.9863(2)	2.74(7)
C(12)	1.0365(3)	0.1384(2)	0.9309(2)	3.04(7)
C(13)	0.8493(3)	0.1646(2)	0.7841(2)	2.13(6)
C(14)	0.8524(3)	0.0913(2)	0.7075(2)	2.55(7)
C(15)	0.7151(3)	0.0540(1)	0.7110(2)	1.96(6)
C(16)	0.6199(2)	0.1187(1)	0.7483(2)	1.66(6)
C(17)	0.7089(3)	0.1904(2)	0.7611(2)	1.93(6)
C(18)	0.6538(3)	0.0288(2)	0.5910(2)	2.57(7)
C(19)	0.4516(3)	0.1910(2)	0.6160(2)	2.32(6)
C(20)	0.3393(3)	0.1749(1)	0.5269(2)	2.00(6)
C(21)	0.2222(3)	0.1429(2)	0.5615(2)	2.65(7)
C(22)	0.1231(3)	0.1237(2)	0.4791(3)	3.12(8)
C(23)	0.1375(3)	0.1377(2)	0.3595(2)	2.93(8)
C(24)	0.2519(3)	0.1705(2)	0.3241(2)	2.77(7)
C(25)	0.3528(3)	0.1887(2)	0.4068(2)	2.40(7)

H(1)	0.4603	0.0890	1.1848	2.6863
H(2)	0.3052	0.1084	1.0262	2.8206
H(3)	0.3719	0.1200	0.8321	2.4682
H(4)	0.8296	0.0404	0.9282	2.2684
H(5)	0.6813	0.1042	1.3224	3.6089
H(6)	0.6592	0.0173	1.2980	3.6089
H(7)	0.8010	0.0489	1.3210	3.6089
H(8)	0.8743	0.2199	1.0690	3.2848
H(9)	0.9106	0.2683	0.9598	3.2848
H(10)	0.7667	0.2408	0.9717	3.2848
H(11)	1.0595	0.1018	0.8731	3.6539
H(12)	1.0591	0.1191	1.0080	3.6539
H(13)	1.0828	0.1850	0.9190	3.6539
H(14)	0.9063	0.2018	0.7525	2.5607
H(15)	0.8706	0.1042	0.6281	3.0559
H(16)	0.9180	0.0570	0.7389	3.0559
H(17)	0.7161	0.0127	0.7662	2.3460
H(18)	0.5941	-0.0126	0.6001	3.0847
H(19)	0.7199	0.0137	0.5391	3.0847
H(20)	0.4189	0.2159	0.6834	2.7791
H(21)	0.5143	0.2233	0.5810	2.7791
H(22)	0.2103	0.1342	0.6433	3.1828
H(23)	0.0445	0.1007	0.5043	3.7386
H(24)	0.0689	0.1247	0.3026	3.5131
H(25)	0.2621	0.1807	0.2423	3.3203
H(26)	0.4319	0.2109	0.3811	2.8784

X-RAY CRYSTALLOGRAPHY REPORT FOR OXAZOLE 181



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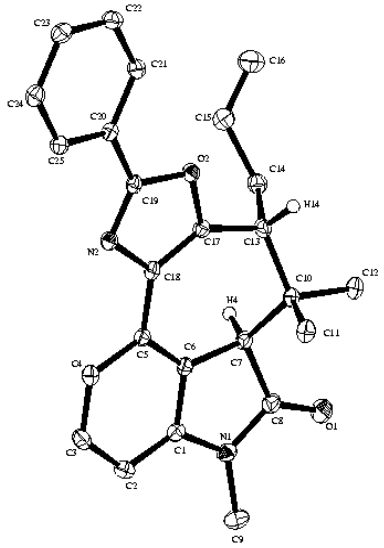


A. Crystal Data

Empirical Formula	$C_{25}H_{24}N_2O_2$
Formula Weight	384.48
Crystal Color, Habit	colorless, prism
Crystal Dimensions	0.24 X 0.30 X 0.35 mm
Crystal System	monoclinic
Lattice Type	C-centered
Lattice Parameters	a = 25.430(1)Å
	b = 9.9996(3) Å
	c = 15.445(1) Å
	β = 96.248(2)o
	V = 3904.1(3) Å3
Space Group	C2/c (#15)
Z value	8
D_{calc}	1.308 g/cm^3
F_{000}	1632.00
μ(MoKα)	0.83 cm^{-1}

B. Intensity Measurements

Diffractometer	Nonius KappaCCD

Radiation	MoKα (λ = 0.71069 Å) graphite monochromated
Take-off Angle	2.8°
Crystal to Detector Distance	35 mm
Temperature	-90.0°C
Scan Rate	90sec/frame
Scan Width	1°/frame
$2\theta_{max}$	61.1°
No. of Reflections Measured	Total: 6081
Corrections	Lorentz-polarization

C. Structure Solution and Refinement

Structure Solution	Direct Methods
Refinement	Full-matrix least-squares
Function Minimized	Σ w (|Fo| - |Fc|)^2
Least Squares Weights	$1/\sigma^2$(Fo)
p-factor	0.0100
Anomalous Dispersion	All non-hydrogen atoms
No. Observations (I>5.00σ(I))	3801
No. Variables	262
Reflection/Parameter Ratio	14.51
Residuals: R; Rw	0.046 ; 0.057
Goodness of Fit Indicator	2.66
Max Shift/Error in Final Cycle	0.00
Maximum peak in Final Diff. Map	0.32 e-/Å3
Minimum peak in Final Diff. Map	-0.23 e-/Å3

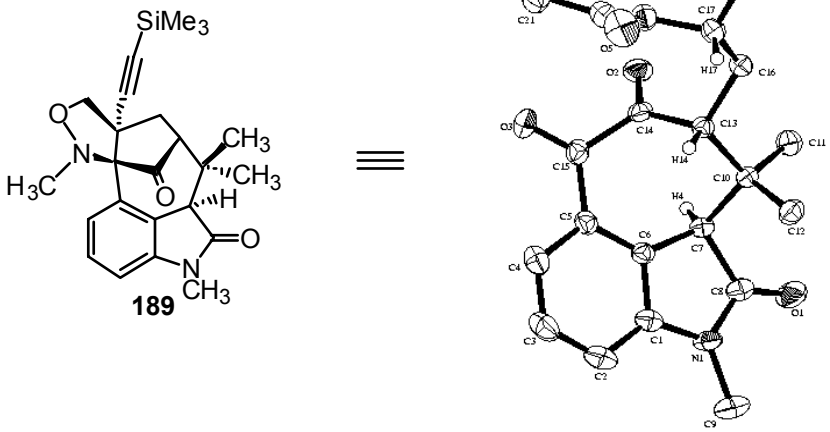
Atomic coordinates and $B_{iso}/_{eq}$ for Oxazole 181.

atom	x	y	z	eq
O(1)	0.74411(4)	-0.24783(10)	0.11050(8)	3.48(3)
O(2)	1.00595(4)	-0.23361(8)	0.06883(6)	1.97(2)

N(1)	0.77217(5)	-0.0377(1)	0.15038(8)	2.25(3)
N(2)	1.00610(4)	-0.0225(1)	0.11436(7)	1.90(2)
C(1)	0.81942(5)	0.0351(1)	0.15806(9)	1.93(3)
C(2)	0.82825(6)	0.1622(1)	0.19243(9)	2.29(3)
C(3)	0.87951(6)	0.2107(1)	0.19771(9)	2.30(3)
C(4)	0.92024(5)	0.1356(1)	0.17063(9)	2.12(3)
C(5)	0.91079(5)	0.0078(1)	0.13397(8)	1.74(3)
C(6)	0.85921(5)	-0.0412(1)	0.12667(8)	1.77(3)
C(7)	0.83521(5)	-0.1709(1)	0.09026(8)	1.87(3)
C(8)	0.77908(6)	-0.1633(1)	0.11784(9)	2.26(3)
C(9)	0.72379(6)	0.0048(2)	0.1834(1)	2.91(4)
C(10)	0.86631(5)	-0.3028(1)	0.11174(9)	1.92(3)
C(11)	0.88445(6)	-0.3093(1)	0.20978(10)	2.57(3)
C(12)	0.83153(6)	-0.4253(1)	0.08717(10)	2.56(3)
C(13)	0.91529(5)	-0.3114(1)	0.06009(9)	1.96(3)
C(14)	0.90185(6)	-0.3312(1)	-0.03947(10)	2.40(3)
C(15)	0.94804(6)	-0.3255(1)	-0.09201(10)	2.64(3)
C(16)	0.96787(7)	-0.4272(2)	-0.1294(1)	3.66(4)
C(17)	0.95446(5)	-0.2007(1)	0.07994(9)	1.83(3)
C(18)	0.95442(5)	-0.0722(1)	0.10809(8)	1.79(3)
C(19)	1.03432(5)	-0.1204(1)	0.09059(8)	1.78(3)
C(20)	1.09102(5)	-0.1262(1)	0.08382(8)	1.72(3)
C(21)	1.11311(6)	-0.2310(1)	0.04065(9)	2.16(3)
C(22)	1.16684(6)	-0.2327(1)	0.03425(10)	2.56(3)
C(23)	1.19898(6)	-0.1313(2)	0.07043(10)	2.56(3)
C(24)	1.17720(6)	-0.0273(1)	0.11383(10)	2.37(3)

C(25)	1.12353(5)	-0.0249(1)	0.12058(9)	2.05(3)
H(1)	0.8003	0.2138	0.2115	2.7480
H(2)	0.8868	0.2978	0.2205	2.7647
H(3)	0.9552	0.1707	0.1768	2.5422
H(4)	0.8316	-0.1621	0.0287	2.2477
H(5)	0.7139	0.0903	0.1602	3.4951
H(6)	0.6965	-0.0578	0.1665	3.4951
H(7)	0.7292	0.0100	0.2451	3.4951
H(8)	0.9001	-0.3940	0.2236	3.0832
H(9)	0.9097	-0.2408	0.2248	3.0832
H(10)	0.8548	-0.2971	0.2415	3.0832
H(11)	0.8142	-0.4142	0.0300	3.0677
H(12)	0.8059	-0.4343	0.1271	3.0677
H(13)	0.8530	-0.5032	0.0892	3.0677
H(14)	0.9333	-0.3907	0.0802	2.3573
H(15)	0.8855	-0.4162	-0.0487	2.8801
H(16)	0.8776	-0.2631	-0.0602	2.8801
H(17)	0.9641	-0.2408	-0.0985	3.1691
H(18)	0.9530	-0.5137	-0.1244	4.3876
H(19)	0.9973	-0.4153	-0.1616	4.3876
H(20)	1.0913	-0.3012	0.0157	2.5922
H(21)	1.1818	-0.3042	0.0047	3.0670
H(22)	1.2359	-0.1330	0.0656	3.0685
H(23)	1.1992	0.0424	0.1390	2.8400
H(24)	1.1087	0.0465	0.1505	2.4588

X-RAY CRYSTALLOGRAPHY REPORT FOR ISOXAZOLIDINE 189



A. Crystal Data

Empirical Formula	$C_{24}H_{28}N_2O_3Si$
Formula Weight	420.58
Crystal Color, Habit	colorless, block
Crystal Dimensions	0.23 X 0.30 X 0.37 mm
Crystal System/Lattice Type	monoclinic C-centered
No. of Reflections Used for Unit Cell Determination (2θ range)	25 (8.6 - 18.1°)
Omega Scan Peak Width at Half-height	0.18°
Lattice Parameters	a = 17.168(4)Å b = 13.213(3) Å c = 21.147(4) Å β = 105.30(2)o V = 4627(1) Å3
Space Group	C2/c (#15)
Z value	8
D_{calc}	1.207 g/cm^3
F_{000}	1792.00
μ(MoKα)	1.28 cm^{-1}

B. Intensity Measurements

Diffractometer	Rigaku AFC5S
Radiation	MoKα (λ = 0.71069 Å) graphite monochromated
Attenuator	Zr foil (1.00, 2.28, 5.28, 11.73)
Take-off Angle	6.0°
Detector Aperture	6.0 mm hor./6.0 mm vert.
Crystal to Detector Distance	285 mm
Temperature	23.0°C
Scan Type	ω-2θ
Scan Rate	4.0°/min (in ω) (up to 3 scans)
Scan Width	(1.42 + 0.30 tan θ)o
$2\theta_{max}$	50.0°
No. of Reflections Measured	Total: 4424 Unique: 4267 (R_{int} = 0.038)
Corrections	Lorentz-polarization
Secondary Extinction (1.70840e-07)	

C. Structure Solution and Refinement

Structure Solution	Direct Methods (SIR92)
Refinement	Full-matrix least-squares
Function Minimized	Σ w (|Fo| - |Fc|)^2
Least Squares Weights	1/σ ^{2}(Fo) = 4Fo2/σ2(Fo2)
p-factor	0.0200
Anomalous Dispersion	All non-hydrogen atoms
No. Observations (I>3.00σ(I))	1373
No. Variables	271
Reflection/Parameter Ratio	5.07
Residuals: R; Rw	0.056 ; 0.055
Goodness of Fit Indicator	1.91
Max Shift/Error in Final Cycle	0.00
Maximum peak in Final Diff. Map	0.39 e-/Å3

Minimum peak in Final Diff. Map -0.21 e-/Å3

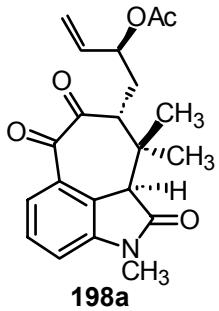
Atomic coordinates and $B_{iso}/_{eq}$ for Isoxazolidine 189.

atom	x	y	z	eq
Si	-0.7933(1)	-0.3177(2)	-0.7629(1)	4.84(6)
O(1)	-0.4181(4)	-0.3644(5)	-0.6918(3)	8.6(2)
O(2)	-0.4799(3)	-0.1544(4)	-0.4580(2)	5.2(1)
O(3)	-0.6718(3)	-0.0546(4)	-0.5061(2)	4.6(1)
N(1)	-0.4931(5)	-0.4566(6)	-0.6375(4)	6.1(2)
N(2)	-0.6621(3)	-0.1644(5)	-0.4969(3)	4.2(2)
C(1)	-0.5454(5)	-0.4394(6)	-0.5970(4)	4.6(2)
C(2)	-0.5863(6)	-0.5099(6)	-0.5711(4)	5.8(3)
C(3)	-0.6374(5)	-0.4741(7)	-0.5357(4)	5.8(3)
C(4)	-0.6464(4)	-0.3718(6)	-0.5258(4)	4.8(2)
C(5)	-0.6030(4)	-0.3002(6)	-0.5511(3)	3.8(2)
C(6)	-0.5534(4)	-0.3356(6)	-0.5893(3)	3.9(2)
C(7)	-0.5062(4)	-0.2810(6)	-0.6309(3)	4.5(2)
C(8)	-0.4656(5)	-0.3677(9)	-0.6580(4)	6.1(3)
C(9)	-0.4697(6)	-0.5560(8)	-0.6548(5)	8.8(3)
C(10)	-0.4479(4)	-0.1930(6)	-0.6010(3)	4.6(2)
C(11)	-0.4160(5)	-0.1413(7)	-0.6542(4)	6.7(3)
C(12)	-0.3760(4)	-0.2345(6)	-0.5476(4)	5.9(2)
C(13)	-0.4945(4)	-0.1096(6)	-0.5725(3)	4.5(2)
C(14)	-0.5205(4)	-0.1508(5)	-0.5144(4)	4.0(2)
C(15)	-0.6082(4)	-0.1885(5)	-0.5387(3)	3.4(2)

C(16)	-0.6334(4)	-0.1772(6)	-0.4257(3)	5.3(2)
C(17)	-0.6992(4)	-0.0492(5)	-0.5759(4)	4.7(2)
C(18)	-0.6440(4)	-0.1218(5)	-0.6019(3)	3.9(2)
C(19)	-0.5723(4)	-0.0666(5)	-0.6200(3)	4.2(2)
C(20)	-0.6938(4)	-0.1818(5)	-0.6567(3)	3.9(2)
C(21)	-0.7342(4)	-0.2324(6)	-0.6999(4)	4.4(2)
C(22)	-0.7914(5)	-0.2697(6)	-0.8449(3)	6.6(2)
C(23)	-0.8989(5)	-0.3206(8)	-0.7560(4)	8.6(3)
C(24)	-0.7446(6)	-0.4435(6)	-0.7452(5)	7.6(3)
H(1)	-0.5798	-0.5803	-0.5771	6.9102
H(2)	-0.6674	-0.5211	-0.5175	6.9875
H(3)	-0.6827	-0.3500	-0.5015	5.7157
H(4)	-0.5452	-0.2532	-0.6673	5.3573
H(5)	-0.4336	-0.5492	-0.6817	10.5917
H(6)	-0.5164	-0.5921	-0.6780	10.5917
H(7)	-0.4438	-0.5919	-0.6160	10.5917
H(8)	-0.3893	-0.1898	-0.6742	8.0504
H(9)	-0.3792	-0.0893	-0.6349	8.0504
H(10)	-0.4599	-0.1128	-0.6864	8.0504
H(11)	-0.3925	-0.2926	-0.5281	7.0747
H(12)	-0.3574	-0.1841	-0.5151	7.0747
H(13)	-0.3336	-0.2524	-0.5667	7.0747
H(14)	-0.4585	-0.0548	-0.5576	5.3450
H(15)	-0.6139	-0.2442	-0.4160	6.3257
H(16)	-0.6767	-0.1654	-0.4064	6.3257
H(17)	-0.5911	-0.1304	-0.4085	6.3257

H(18)	-0.6944	0.0179	-0.5905	5.6336
H(19)	-0.7539	-0.0704	-0.5904	5.6336
H(20)	-0.8108	-0.2020	-0.8498	7.8971
H(21)	-0.7377	-0.2714	-0.8489	7.8971
H(22)	-0.8249	-0.3110	-0.8779	7.8971
H(23)	-0.9218	-0.2549	-0.7642	10.3296
H(24)	-0.8993	-0.3415	-0.7131	10.3296
H(25)	-0.9296	-0.3668	-0.7872	10.3296
H(26)	-0.7531	-0.4694	-0.7057	9.0910
H(27)	-0.7673	-0.4886	-0.7802	9.0910
H(28)	-0.6882	-0.4371	-0.7407	9.0910

X-RAY CRYSTALLOGRAPHY REPORT FOR ACETATE 198a



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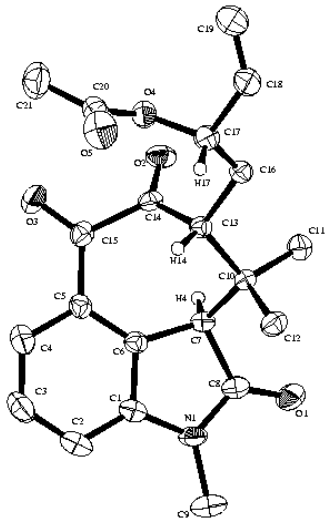


A. Crystal Data

Empirical Formula	$C_{21}H_{23}NO_5$
Formula Weight	369.42
Crystal Color, Habit	pale yellow, prism
Crystal Dimensions	0.17 X 0.22 X 0.24 mm
Crystal System	monoclinic
Lattice Type	Primitive
Lattice Parameters	a = 10.0430(4)Å
	b = 16.3247(4) Å
	c = 11.558(1) Å
	β = 91.744(2)o
	V = 1894.0(1) Å3
Space Group	P21/c (#14)
Z value	4
D_{calc}	1.295 g/cm^3
F_{000}	784.00
μ(MoKα)	0.92 cm^{-1}

B. Intensity Measurements

Diffractometer	Nonius KappaCCD
Radiation	MoKα (λ = 0.71069 Å)

	graphite monochromated
Take-off Angle	2.8°
Crystal to Detector Distance	35 mm
Temperature	23.0°C
Scan Rate	30sec/frame
Scan Width	1°/frame
$2\theta_{max}$	61.0°
No. of Reflections Measured	Total: 5691
Corrections	Lorentz-polarization

C. Structure Solution and Refinement

Structure Solution	Direct Methods (SIR92)
Refinement	Full-matrix least-squares
Function Minimized	Σ w (|Fo| - |Fc|)^2
Least Squares Weights	$1/2\sigma$(Fo) = 4Fo2/σ2(Fo2)
p-factor	0.0100
Anomalous Dispersion	All non-hydrogen atoms
No. Observations (I>5.00σ(I))	2276
No. Variables	244
Reflection/Parameter Ratio	9.33
Residuals: R; Rw	0.046 ; 0.055
Goodness of Fit Indicator	2.76
Max Shift/Error in Final Cycle	0.00
Maximum peak in Final Diff. Map	0.29 e-/Å3
Minimum peak in Final Diff. Map	-0.20 e-/Å3

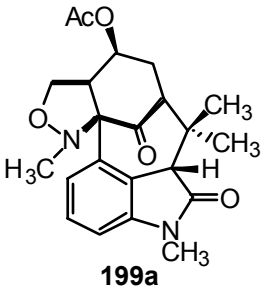
Atomic coordinates and $B_{iso}/_{eq}$ for Acetate 198a.

atom	x	y	z	eq
O(1)	0.1323(2)	0.2075(1)	1.0060(2)	5.19(5)
O(2)	0.6027(2)	0.03968(9)	0.9056(2)	4.26(4)
O(3)	0.4990(2)	-0.10464(9)	0.8020(2)	5.16(5)

O(4)	0.6801(2)	0.04984(9)	0.6380(1)	3.82(4)
O(5)	0.6396(2)	0.0197(1)	0.4501(2)	6.46(6)
N(1)	0.0390(2)	0.0998(1)	0.9068(2)	3.88(5)
C(1)	0.0824(2)	0.0290(1)	0.8507(2)	3.64(6)
C(2)	0.0082(2)	-0.0344(2)	0.8040(3)	5.04(7)
C(3)	0.0747(3)	-0.1007(2)	0.7583(3)	5.29(8)
C(4)	0.2121(3)	-0.1038(1)	0.7607(2)	4.45(7)
C(5)	0.2875(2)	-0.0390(1)	0.8076(2)	3.20(5)
C(6)	0.2216(2)	0.0279(1)	0.8514(2)	2.91(5)
C(7)	0.2725(2)	0.1033(1)	0.9129(2)	2.89(5)
C(8)	0.1437(2)	0.1447(1)	0.9497(2)	3.67(6)
C(9)	-0.1000(2)	0.1230(2)	0.9184(3)	5.46(7)
C(10)	0.3609(2)	0.1631(1)	0.8419(2)	2.75(5)
C(11)	0.4350(2)	0.2186(1)	0.9288(2)	3.90(6)
C(12)	0.2733(2)	0.2133(1)	0.7576(2)	3.92(6)
C(13)	0.4610(2)	0.1127(1)	0.7690(2)	2.74(5)
C(14)	0.5101(2)	0.0383(1)	0.8364(2)	3.03(5)
C(15)	0.4344(2)	-0.0428(1)	0.8140(2)	3.36(6)
C(16)	0.5774(2)	0.1648(1)	0.7277(2)	3.24(5)
C(17)	0.6396(2)	0.1331(1)	0.6180(2)	3.74(6)
C(18)	0.7570(3)	0.1843(1)	0.5858(2)	4.69(7)
C(19)	0.8795(3)	0.1617(2)	0.5816(3)	6.58(9)
C(20)	0.6802(3)	-0.0004(2)	0.5451(3)	4.28(7)
C(21)	0.7353(3)	-0.0810(2)	0.5761(3)	6.54(9)
H(1)	-0.0864	-0.0328	0.8032	6.0528
H(2)	0.0251	-0.1447	0.7247	6.3539

H(3)	0.2559	-0.1503	0.7303	5.3430
H(4)	0.3216	0.0868	0.9805	3.4639
H(5)	-0.1540	0.0752	0.9162	6.5470
H(6)	-0.1103	0.1505	0.9899	6.5470
H(7)	-0.1263	0.1583	0.8565	6.5470
H(8)	0.4688	0.2650	0.8896	4.6819
H(9)	0.5066	0.1892	0.9647	4.6819
H(10)	0.3754	0.2362	0.9861	4.6819
H(11)	0.2192	0.1775	0.7116	4.7020
H(12)	0.2180	0.2490	0.8000	4.7020
H(13)	0.3282	0.2448	0.7089	4.7020
H(14)	0.4136	0.0934	0.7020	3.2848
H(15)	0.5458	0.2188	0.7135	3.8872
H(16)	0.6443	0.1660	0.7876	3.8872
H(17)	0.5748	0.1345	0.5564	4.4898
H(18)	0.7387	0.2398	0.5663	5.6267
H(19)	0.9037	0.1069	0.6002	7.8996
H(20)	0.9457	0.1999	0.5599	7.8996
H(21)	0.8298	-0.0777	0.5811	7.8527
H(22)	0.7027	-0.0975	0.6488	7.8527
H(23)	0.7092	-0.1198	0.5186	7.8527

X-RAY CRYSTALLOGRAPHY REPORT FOR ISOXAZOLIDINE 199a



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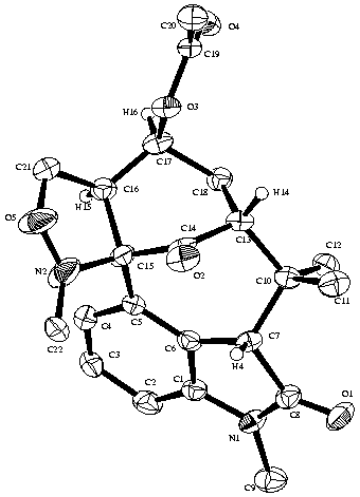


A. Crystal Data

Empirical Formula	$C_{22}H_{26}N_2O_5$
Formula Weight	398.46
Crystal Color, Habit	colorless, plate
Crystal Dimensions	0.07 X 0.15 X 0.23 mm
Crystal System	orthorhombic
Lattice Type	Primitive
Lattice Parameters	a = 10.076(1)Å
	b = 12.037(1) Å
	c = 16.221(1) Å
	V = 1967.4(2) Å3
Space Group	Pna21 (#33)
Z value	4
D_{calc}	1.345 g/cm3
F_{000}	848.00
μ(MoKα)	0.96 cm^{-1}

B. Intensity Measurements

Diffractometer	Nonius KappaCCD
Radiation	MoKα (λ = 0.71069 Å)
	graphite monochromated

Take-off Angle	2.8°
Crystal to Detector Distance	35 mm
Temperature	23.0°C
Scan Rate	60sec/frame
Scan Width	1°/frame
$2\theta_{max}$	61.0°
No. of Reflections Measured	Total: 5371 Unique: 3097 (R_{int} = 0.092)
Corrections	Lorentz-polarization

C. Structure Solution and Refinement

Structure Solution	Direct Methods (SIR92)
Refinement	Full-matrix least-squares
Function Minimized	Σ w (|Fo| - |Fc|)^2
Least Squares Weights	$1/\sigma^2$(Fo)
p-factor	0.0000
Anomalous Dispersion	All non-hydrogen atoms
No. Observations (I>3.00σ(I))	1142
No. Variables	261
Reflection/Parameter Ratio	4.38
Residuals: R; Rw	0.058 ; 0.057
Goodness of Fit Indicator	2.15
Max Shift/Error in Final Cycle	0.00
Maximum peak in Final Diff. Map	0.30 e-/Å3
Minimum peak in Final Diff. Map	-0.31 e-/Å3

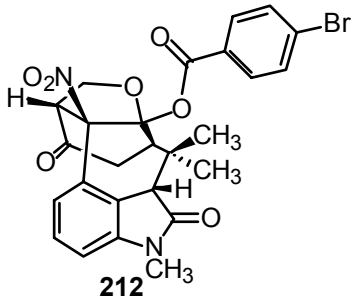
Atomic coordinates and $B_{iso}/_{eq}$ for Isoxazolidine 199a.

atom	x	y	z	eq
O(1)	-0.2628(5)	-0.8444(4)	-0.4839	5.3(1)
O(2)	-0.2139(5)	-0.4114(3)	-0.4152(5)	4.8(1)
O(3)	-0.4685(5)	-0.2464(3)	-0.5019(5)	4.1(1)

O(4)	-0.6103(6)	-0.2009(4)	-0.6028(5)	5.6(2)
O(5)	-0.3868(10)	-0.2714(4)	-0.2831(6)	10.4(2)
N(1)	-0.4243(6)	-0.8270(4)	-0.3867(6)	3.8(2)
N(2)	-0.3830(9)	-0.3805(5)	-0.2776(6)	8.0(3)
C(1)	-0.4908(8)	-0.7432(5)	-0.3449(6)	3.4(2)
C(2)	-0.5867(9)	-0.7532(6)	-0.2862(6)	4.6(2)
C(3)	-0.6385(9)	-0.6548(7)	-0.2512(6)	4.9(2)
C(4)	-0.5853(8)	-0.5528(5)	-0.2747(6)	4.2(2)
C(5)	-0.4873(8)	-0.5415(5)	-0.3344(6)	3.4(2)
C(6)	-0.4405(7)	-0.6391(5)	-0.3713(6)	3.3(2)
C(7)	-0.3349(7)	-0.6590(5)	-0.4346(6)	3.3(2)
C(8)	-0.3316(8)	-0.7879(5)	-0.4410(6)	3.7(2)
C(9)	-0.4369(8)	-0.9450(5)	-0.3683(7)	4.9(2)
C(10)	-0.3493(7)	-0.5994(5)	-0.5199(6)	3.3(2)
C(11)	-0.2166(8)	-0.6054(5)	-0.5647(6)	4.9(2)
C(12)	-0.4542(8)	-0.6581(5)	-0.5724(6)	4.3(2)
C(13)	-0.3861(6)	-0.4737(4)	-0.5060(6)	3.4(2)
C(14)	-0.3306(8)	-0.4359(4)	-0.4243(6)	3.5(2)
C(15)	-0.4312(8)	-0.4298(5)	-0.3536(6)	3.7(2)
C(16)	-0.5383(7)	-0.3432(5)	-0.3788(7)	3.9(2)
C(17)	-0.5595(7)	-0.3308(5)	-0.4701(6)	3.9(2)
C(18)	-0.5348(7)	-0.4423(5)	-0.5137(6)	3.5(2)
C(19)	-0.5067(9)	-0.1873(5)	-0.5678(6)	3.9(2)
C(20)	-0.4069(9)	-0.1030(5)	-0.5895(7)	5.4(2)
C(21)	-0.4983(10)	-0.2383(5)	-0.3290(7)	5.4(2)
C(22)	-0.2834(8)	-0.4269(5)	-0.2298(6)	4.2(2)

H(1)	-0.6179	-0.8241	-0.2693	5.4851
H(2)	-0.7086	-0.6581	-0.2121	5.8358
H(3)	-0.6177	-0.4876	-0.2486	5.0148
H(4)	-0.2529	-0.6360	-0.4113	3.9904
H(5)	-0.5064	-0.9557	-0.3295	5.9286
H(6)	-0.4566	-0.9844	-0.4175	5.9286
H(7)	-0.3558	-0.9716	-0.3458	5.9286
H(8)	-0.1945	-0.6809	-0.5748	5.8381
H(9)	-0.2227	-0.5667	-0.6156	5.8381
H(10)	-0.1497	-0.5723	-0.5315	5.8381
H(11)	-0.5376	-0.6548	-0.5452	5.1218
H(12)	-0.4606	-0.6225	-0.6245	5.1218
H(13)	-0.4295	-0.7336	-0.5801	5.1218
H(14)	-0.3406	-0.4327	-0.5474	4.0337
H(15)	-0.6200	-0.3685	-0.3564	4.6439
H(16)	-0.6483	-0.3079	-0.4800	4.6498
H(17)	-0.5578	-0.4360	-0.5703	4.2515
H(18)	-0.5875	-0.4984	-0.4887	4.2515
H(19)	-0.3250	-0.1384	-0.6017	6.5119
H(20)	-0.4361	-0.0626	-0.6365	6.5119
H(21)	-0.3952	-0.0534	-0.5445	6.5119
H(22)	-0.5683	-0.2159	-0.2934	6.4219
H(23)	-0.4763	-0.1788	-0.3650	6.4219
H(24)	-0.2956	-0.5050	-0.2268	5.0878
H(25)	-0.1996	-0.4112	-0.2539	5.0878
H(26)	-0.2867	-0.3962	-0.1758	5.0878

X-RAY CRYSTALLOGRAPHY REPORT FOR BENZOATE 212



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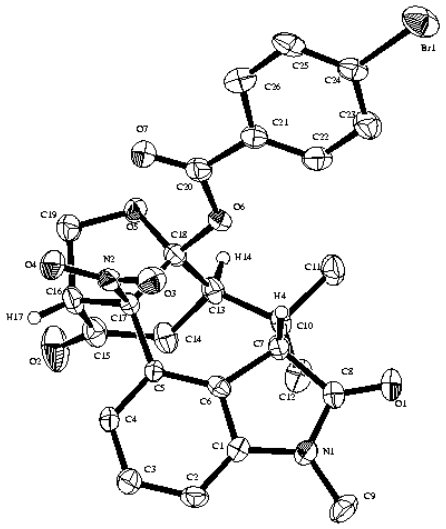


A. Crystal Data

Empirical Formula	$C_{26}H_{23}N_2O_7Br$
Formula Weight	555.38
Crystal Color, Habit	colorless, plate
Crystal Dimensions	0.10 X 0.15 X 0.28 mm
Crystal System	monoclinic
Lattice Type	Primitive
Lattice Parameters	a = 9.0813(3)Å
	b = 19.187(1) Å
	c = 13.6009(4) Å
	β = 96.056(2)o
	V = 2356.6(1) Å3
Space Group	P21/c (#14)
Z value	4
D_{calc}	1.565 g/cm3
F_{000}	1136.00
μ(MoKα)	18.01 cm^{-1}

B. Intensity Measurements

Diffractometer	Nonius KappaCCD
Radiation	MoKα (λ = 0.71069 Å)

	graphite monochromated
Take-off Angle	2.8°
Crystal to Detector Distance	35 mm
Temperature	23.0°C
Scan Rate	90s/frame
Scan Width	1°/frame
$2\theta_{max}$	61.0°
No. of Reflections Measured	Total: 20985
	Unique: 7081 (R_{int} = 0.087)
Corrections	Lorentz-polarization
Absorption (SORTAV)	

C. Structure Solution and Refinement

Structure Solution	Patterson Methods (DIRDIF92 PATTY)
Refinement	Full-matrix least-squares
Function Minimized	Σ w (|Fo| - |Fc|)^2
Least Squares Weights	$1/\sigma^2$(Fo)
p-factor	0.0100
Anomalous Dispersion	All non-hydrogen atoms
No. Observations (I>5.00σ(I))	2007
No. Variables	417
Reflection/Parameter Ratio	4.81
Residuals: R; Rw	0.058 ; 0.066
Goodness of Fit Indicator	2.95
Max Shift/Error in Final Cycle	0.00
Maximum peak in Final Diff. Map	0.80 e-/Å3
Minimum peak in Final Diff. Map	-0.41 e-/Å3

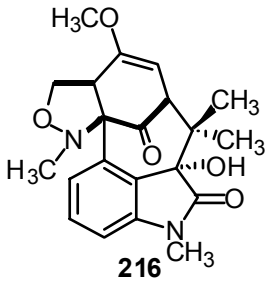
Atomic coordinates and $B_{iso}/_{eq}$ for Benzoate 212.

atom	x	y	z	eq
Br(1)	0.0468(1)	0.22765(5)	0.28180(7)	6.73(3)
O(1)	0.0115(6)	0.0983(3)	0.8571(4)	5.5(2)
O(2)	-0.7880(7)	-0.0475(4)	0.8050(5)	7.7(2)
O(3)	-0.5344(6)	0.2132(3)	0.6682(3)	4.4(1)
O(4)	-0.7675(6)	0.1864(3)	0.6430(3)	5.0(1)
O(5)	-0.6148(5)	0.0170(2)	0.5869(3)	3.9(1)
O(6)	-0.4073(5)	0.0878(2)	0.5969(3)	3.4(1)
O(7)	-0.5847(6)	0.1331(3)	0.4850(4)	4.8(1)
N(1)	-0.1677(7)	0.1338(3)	0.9522(4)	3.9(2)
N(2)	-0.6381(8)	0.1730(3)	0.6708(4)	3.8(2)
C(1)	-0.3228(8)	0.1396(3)	0.9426(5)	3.0(2)
C(2)	-0.4126(9)	0.1646(4)	1.0100(6)	4.1(2)
C(3)	-0.5613(10)	0.1668(5)	0.9821(6)	4.2(2)
C(4)	-0.6212(9)	0.1445(4)	0.8903(6)	3.6(2)
C(5)	-0.5304(7)	0.1196(3)	0.8208(4)	2.7(2)
C(6)	-0.3795(8)	0.1166(3)	0.8490(5)	3.0(2)
C(7)	-0.2526(8)	0.0911(4)	0.7963(6)	3.4(2)
C(8)	-0.1173(9)	0.1064(4)	0.8684(6)	3.7(2)
C(9)	-0.071(1)	0.1546(6)	1.0382(7)	5.1(3)
C(10)	-0.2656(7)	0.0134(4)	0.7654(5)	3.6(2)
C(11)	-0.157(1)	-0.0051(5)	0.6909(8)	4.6(2)
C(12)	-0.226(1)	-0.0330(5)	0.8572(8)	5.2(3)
C(13)	-0.4275(8)	-0.0034(4)	0.7175(6)	3.5(2)

C(14)	-0.5343(9)	-0.0323(5)	0.7910(7)	4.3(2)
C(15)	-0.6942(9)	-0.0116(4)	0.7757(6)	4.4(2)
C(16)	-0.7366(9)	0.0545(4)	0.7162(6)	4.1(2)
C(17)	-0.6003(7)	0.1005(4)	0.7188(5)	3.0(2)
C(18)	-0.5105(8)	0.0533(4)	0.6524(5)	3.1(2)
C(19)	-0.7616(9)	0.0338(6)	0.6093(7)	4.8(3)
C(20)	-0.458(1)	0.1237(4)	0.5125(6)	4.1(2)
C(21)	-0.3308(9)	0.1499(4)	0.4617(5)	3.6(2)
C(22)	-0.1836(10)	0.1435(4)	0.4989(6)	4.5(2)
C(23)	-0.070(1)	0.1669(5)	0.4458(6)	4.9(2)
C(24)	-0.1062(10)	0.1966(4)	0.3567(6)	4.1(2)
C(25)	-0.251(1)	0.2068(5)	0.3157(7)	4.6(3)
C(26)	-0.363(1)	0.1834(4)	0.3689(6)	4.5(2)
H(1)	-0.376(8)	0.181(4)	1.068(5)	4(1)
H(2)	-0.619(6)	0.182(3)	1.021(4)	0(1)
H(3)	-0.716(7)	0.142(3)	0.875(4)	3(1)
H(4)	-0.250(5)	0.116(2)	0.746(3)	0(1)
H(5)	-0.11(1)	0.131(7)	1.111(10)	15(3)
H(6)	0.01(1)	0.160(5)	1.015(6)	7(2)
H(7)	-0.09(1)	0.196(5)	1.053(7)	6(2)
H(8)	-0.154(8)	-0.055(4)	0.676(5)	5(1)
H(9)	-0.173(10)	0.027(5)	0.628(6)	7(2)
H(10)	-0.056(9)	0.006(3)	0.711(5)	3(1)
H(11)	-0.264(8)	-0.016(4)	0.922(6)	5(1)
H(12)	-0.255(7)	-0.085(4)	0.841(4)	4(1)
H(13)	-0.127(9)	-0.026(4)	0.871(5)	5(1)

H(14)	-0.414(5)	-0.037(3)	0.678(3)	0(1)
H(15)	-0.516(8)	-0.093(5)	0.797(5)	7(1)
H(16)	-0.497(7)	-0.026(3)	0.855(5)	3(1)
H(17)	-0.809(8)	0.078(4)	0.740(5)	3(1)
H(18)	-0.801(9)	0.064(4)	0.562(6)	5(2)
H(19)	-0.814(9)	-0.003(4)	0.588(5)	4(1)
H(20)	-0.162(6)	0.121(3)	0.563(5)	3(1)
H(21)	0.026(7)	0.161(3)	0.470(4)	3(1)
H(22)	-0.278(4)	0.229(2)	0.272(3)	-2.1(9)
H(23)	-0.462(6)	0.186(3)	0.352(4)	1(1)

X-RAY CRYSTALLOGRAPHY REPORT FOR ALCOHOL 216



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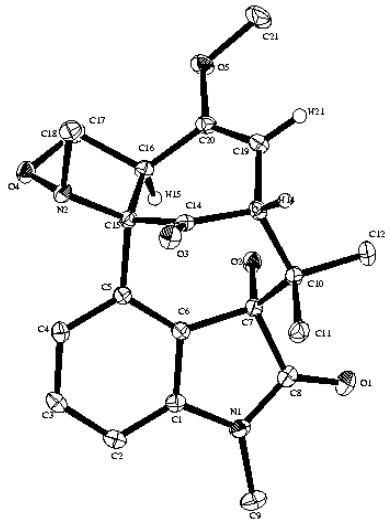


A. Crystal Data

Empirical Formula	$C_{22}H_{28}N_2O_6$
Formula Weight	416.47
Crystal Color, Habit	colorless, prism
Crystal Dimensions	0.17 X 0.21 X 0.25 mm
Crystal System	monoclinic
Lattice Type	Primitive
Lattice Parameters	a = 7.7616(2)Å
	b = 17.990(1) Å
	c = 14.771(1) Å
	β = 103.463(2)o
	V = 2005.7(2) Å3
Space Group	P21/c (#14)
Z value	4
D_{calc}	1.379 g/cm^3
F_{000}	888.00
μ(MoKα)	1.00 cm^{-1}

B. Intensity Measurements

Diffractometer	Nonius KappaCCD

Radiation	MoKα (λ = 0.71069 Å) graphite monochromated
Take-off Angle	2.8°
Temperature	-90.0°C
Scan Rate	40s/frame
Scan Width	1°/frame
$2\theta_{max}$	60.1°
No. of Reflections Measured	Total: 5833
Corrections	Lorentz-polarization

C. Structure Solution and Refinement

Structure Solution	Direct Methods (SIR92)
Refinement	Full-matrix least-squares
Function Minimized	Σ w (|Fo| - |Fc|)^2
Least Squares Weights	$1/\sigma^2$(Fo)
p-factor	0.0100
Anomalous Dispersion	All non-hydrogen atoms
No. Observations (I>5.00σ(I))	3702
No. Variables	383
Reflection/Parameter Ratio	9.67
Residuals: R; Rw	0.038 ; 0.045
Goodness of Fit Indicator	2.23
Max Shift/Error in Final Cycle	0.00
Maximum peak in Final Diff. Map	0.29 e-/Å3
Minimum peak in Final Diff. Map	-0.23 e-/Å3

Atomic coordinates and $B_{iso}/_{eq}$ for Alcohol 216.

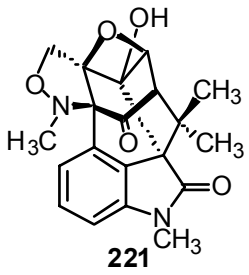
atom	x	y	z	eq
O(1)	0.2592(1)	-0.21600(6)	0.53638(7)	3.07(2)
O(2)	0.5637(1)	-0.14660(6)	0.66564(6)	1.95(2)
O(3)	0.2787(1)	0.01750(6)	0.84695(7)	2.35(2)

O(4)	0.7690(1)	0.09640(5)	0.81843(6)	2.08(2)
O(5)	0.8832(1)	-0.11755(6)	0.91474(7)	2.62(2)
O(6)	0.6511(1)	-0.29183(6)	0.66239(8)	2.86(2)
N(1)	0.2285(1)	-0.09246(7)	0.49822(8)	2.16(3)
N(2)	0.5953(1)	0.08594(6)	0.83653(7)	1.78(2)
C(1)	0.2940(2)	-0.02470(8)	0.53951(9)	1.85(3)
C(2)	0.2777(2)	0.04423(9)	0.4981(1)	2.17(3)
C(3)	0.3565(2)	0.10386(9)	0.5519(1)	2.24(3)
C(4)	0.4427(2)	0.09435(8)	0.64419(10)	1.91(3)
C(5)	0.4588(1)	0.02408(8)	0.68602(9)	1.58(3)
C(6)	0.3864(2)	-0.03671(8)	0.63206(9)	1.64(3)
C(7)	0.3874(2)	-0.11973(8)	0.65217(9)	1.76(3)
C(8)	0.2824(2)	-0.15070(8)	0.55695(10)	2.15(3)
C(9)	0.1277(2)	-0.1008(1)	0.4030(1)	2.79(4)
C(10)	0.2962(2)	-0.14162(8)	0.73206(9)	1.83(3)
C(11)	0.1021(2)	-0.11633(9)	0.7049(1)	2.30(3)
C(12)	0.3025(2)	-0.22554(9)	0.7480(1)	2.42(3)
C(13)	0.3850(2)	-0.10470(8)	0.82803(9)	1.78(3)
C(14)	0.3905(2)	-0.02126(8)	0.82510(9)	1.70(3)
C(15)	0.5419(1)	0.01390(8)	0.78996(9)	1.56(3)
C(16)	0.7167(2)	-0.03284(8)	0.80705(9)	1.72(3)
C(17)	0.8596(2)	0.02603(8)	0.8407(1)	2.19(3)
C(18)	0.6184(2)	0.08412(9)	0.9385(1)	2.31(3)
C(19)	0.5669(2)	-0.13205(9)	0.87764(9)	1.97(3)
C(20)	0.7144(2)	-0.09727(8)	0.87078(9)	1.88(3)
C(21)	0.8983(2)	-0.1785(1)	0.9782(1)	3.75(4)

C(22)	0.8187(2)	-0.3002(1)	0.7250(2)	3.60(4)
H(1)	0.216(2)	0.0499(9)	0.432(1)	2.8(3)
H(2)	0.348(2)	0.1529(10)	0.524(1)	3.1(3)
H(3)	0.497(2)	0.1361(9)	0.6810(9)	2.3(3)
H(4)	0.015(2)	-0.0725(10)	0.393(1)	3.3(3)
H(5)	0.191(2)	-0.085(1)	0.360(1)	4.8(4)
H(6)	0.103(2)	-0.153(1)	0.393(1)	5.0(5)
H(7)	0.567(2)	-0.197(1)	0.661(1)	4.7(4)
H(8)	0.090(2)	-0.060(1)	0.690(1)	3.1(3)
H(9)	0.040(2)	-0.1429(9)	0.6499(10)	2.5(3)
H(10)	0.042(2)	-0.1259(9)	0.757(1)	3.0(3)
H(11)	0.429(2)	-0.2431(9)	0.7640(10)	2.7(3)
H(12)	0.246(2)	-0.238(1)	0.800(1)	3.8(4)
H(13)	0.238(2)	-0.254(1)	0.693(1)	3.4(4)
H(14)	0.301(2)	-0.1170(8)	0.8697(9)	1.8(3)
H(15)	0.728(2)	-0.0535(8)	0.7478(9)	1.7(3)
H(16)	0.952(2)	0.0256(9)	0.805(1)	3.0(3)
H(17)	0.914(2)	0.0214(9)	0.908(1)	2.7(3)
H(18)	0.686(2)	0.1299(10)	0.963(1)	3.1(3)
H(19)	0.497(2)	0.0852(8)	0.9524(9)	2.4(3)
H(20)	0.686(2)	0.0409(9)	0.9671(10)	2.6(3)
H(21)	0.568(2)	-0.1755(9)	0.9150(10)	2.4(3)
H(22)	1.021(2)	-0.1862(10)	1.003(1)	4.0(4)
H(23)	0.849(2)	-0.223(1)	0.944(1)	4.7(5)
H(24)	0.819(2)	-0.168(1)	1.027(1)	5.4(5)
H(25)	0.588(2)	-0.328(1)	0.673(1)	5.3(5)

H(26)	0.812(3)	-0.295(1)	0.789(2)	7.5(6)
H(27)	0.879(4)	-0.344(2)	0.714(2)	9.5(8)
H(28)	0.891(3)	-0.265(2)	0.711(2)	8.6(7)

X-RAY CRYSTALLOGRAPHY REPORT FOR OXETANE 221



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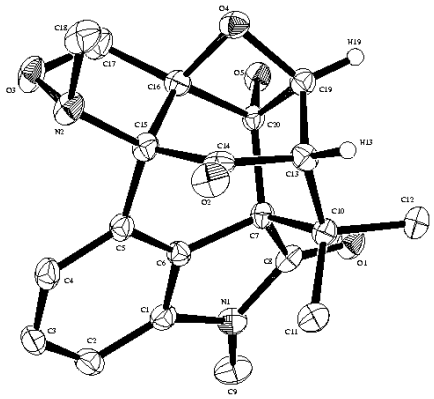


A. Crystal Data

Empirical Formula	$C_{20}H_{20}N_2O_5$
Formula Weight	368.39
Crystal Color, Habit	colorless, cubic
Crystal Dimensions	0.19 X 0.20 X 0.20 mm
Crystal System	monoclinic
Lattice Parameters	a = 10.280(1)Å
	b = 14.311(1) Å
	c = 11.4453(5) Å
	β = 101.916(4)o
	V = 1647.5(2) Å3
Space Group	P21/n (#14)
Z value	4
D_{calc}	1.485 g/cm3
F_{000}	776.00
μ(MoKα)	1.08 cm^{-1}

B. Intensity Measurements

Diffractometer	Nonius KappaCCD
Radiation	MoKα (λ = 0.71069 Å)
	graphite monochromated
Take-off Angle	2.8°
Crystal to Detector Distance	33 mm
Temperature	-90.0°C

Scan Type	ω
Scan Rate	180s/frame
Scan Width	2°/frame
$2\theta_{max}$	50.1°
No. of Reflections Measured	Total: 3033
Corrections	Lorentz-polarization

C. Structure Solution and Refinement

Structure Solution	Direct Methods (SIR92)
Refinement	Full-matrix least-squares
Function Minimized	Σ w (|Fo| - |Fc|)^2
Least Squares Weights	$1/\sigma^2$(Fo)
p-factor	0.0100
Anomalous Dispersion	All non-hydrogen atoms
No. Observations (I>3.00σ(I))	1923
No. Variables	244
Reflection/Parameter Ratio	7.88
Residuals: R; Rw	0.048 ; 0.055
Goodness of Fit Indicator	2.08
Max Shift/Error in Final Cycle	0.00
Maximum peak in Final Diff. Map	0.23 e-/Å3
Minimum peak in Final Diff. Map	-0.26 e-/Å3

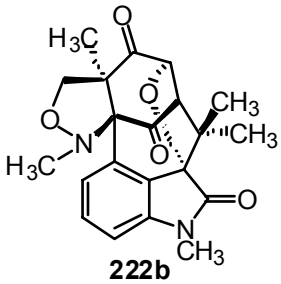
Atomic coordinates and $B_{iso}/_{eq}$ for Oxetane 221.

atom	x	y	z	eq
O(1)	0.8088(2)	0.3958(1)	1.0885(1)	2.98(5)
O(2)	1.3577(2)	0.2009(2)	1.3547(2)	3.80(5)
O(3)	1.4571(2)	0.4615(1)	1.2021(2)	3.66(5)
O(4)	1.2880(2)	0.2816(1)	1.0572(1)	2.88(4)
O(5)	1.0655(2)	0.4066(1)	0.9820(1)	2.49(4)
N(1)	0.9099(2)	0.4791(2)	1.2544(2)	2.59(5)

N(2)	1.4665(2)	0.3772(2)	1.2758(2)	3.29(6)
C(1)	1.0397(3)	0.4882(2)	1.3239(2)	2.45(6)
C(2)	1.0939(3)	0.5490(2)	1.4143(2)	3.15(7)
C(3)	1.2291(3)	0.5390(2)	1.4637(2)	3.28(7)
C(4)	1.3094(3)	0.4760(2)	1.4205(2)	3.10(7)
C(5)	1.2540(3)	0.4168(2)	1.3259(2)	2.46(6)
C(6)	1.1191(2)	0.4222(2)	1.2849(2)	2.13(6)
C(7)	1.0411(2)	0.3624(2)	1.1898(2)	2.13(6)
C(8)	0.9059(3)	0.4125(2)	1.1669(2)	2.48(6)
C(9)	0.8040(3)	0.5458(2)	1.2539(2)	3.60(7)
C(10)	1.0343(2)	0.2569(2)	1.2312(2)	2.41(6)
C(11)	1.0288(3)	0.2455(2)	1.3628(2)	3.25(7)
C(12)	0.9150(3)	0.2057(2)	1.1550(2)	3.07(7)
C(13)	1.1618(3)	0.2151(2)	1.1993(2)	2.51(6)
C(14)	1.2899(3)	0.2493(2)	1.2791(2)	2.72(7)
C(15)	1.3247(2)	0.3508(2)	1.2560(2)	2.54(6)
C(16)	1.2706(2)	0.3676(2)	1.1213(2)	2.38(6)
C(17)	1.3536(3)	0.4482(2)	1.0950(2)	3.20(7)
C(18)	1.5540(3)	0.3102(3)	1.2303(3)	4.06(8)
C(19)	1.1564(2)	0.2533(2)	1.0723(2)	2.46(6)
C(20)	1.1160(2)	0.3548(2)	1.0850(2)	2.08(6)
H(1)	1.0416	0.5955	1.4418	3.7776
H(2)	1.2675	0.5771	1.5298	3.9384
H(3)	1.4018	0.4729	1.4547	3.7217
H(4)	0.8106	0.5704	1.3320	4.3164
H(5)	0.8113	0.5952	1.2002	4.3164

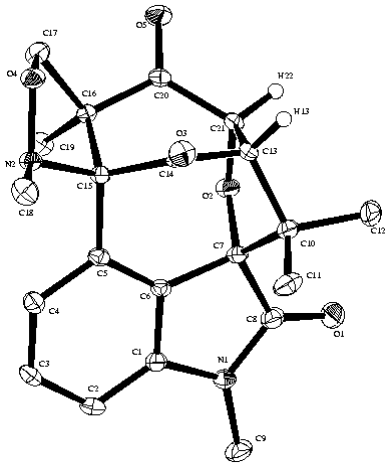
H(6)	0.7206	0.5156	1.2292	4.3164
H(7)	0.9494	0.2729	1.3771	3.9038
H(8)	1.0302	0.1809	1.3822	3.9038
H(9)	1.1035	0.2755	1.4109	3.9038
H(10)	0.9151	0.2147	1.0728	3.6883
H(11)	0.8349	0.2298	1.1721	3.6883
H(12)	0.9212	0.1408	1.1730	3.6883
H(13)	1.1582	0.1488	1.1987	3.0128
H(14)	1.3008	0.5029	1.0785	3.8383
H(15)	1.3924	0.4341	1.0285	3.8383
H(16)	1.5109	0.2888	1.1534	4.8757
H(17)	1.5722	0.2586	1.2833	4.8757
H(18)	1.6349	0.3402	1.2249	4.8757
H(19)	1.1041	0.2189	1.0085	2.9498
H(20)	0.9724	0.3858	0.9497	4.5396

X-RAY CRYSTALLOGRAPHY REPORT FOR KETONE 222b



222b

≡



A. Crystal Data

Empirical Formula	$C_{21}H_{22}N_2O_5$
Formula Weight	382.42
Crystal Color, Habit	colorless, prism
Crystal Dimensions	0.08 X 0.12 X 0.15 mm
Crystal System	monoclinic
Lattice Type	Primitive
Lattice Parameters	a = 9.9584(4)Å
	b = 15.879(1) Å
	c = 11.705(1) Å
	β = 101.628(3)o
V = 1813.0(2) Å3	
Space Group	P21/c (#14)
Z value	4
D_{calc}	1.401 g/cm^3
F_{000}	808.00
μ(MoKα)	1.01 cm^{-1}

B. Intensity Measurements

Diffractometer	Nonius KappaCCD
Radiation	MoKα (λ = 0.71069 Å)
	graphite monochromated

Take-off Angle	2.8°
Crystal to Detector Distance	35 mm
Temperature	-90.0°C
Scan Type	ω
Scan Rate	120s/frame
Scan Width	2°/frame
$2\theta_{max}$	55.5°
No. of Reflections Measured	Total: 4032
Corrections	Lorentz-polarization

C. Structure Solution and Refinement

Structure Solution	Direct Methods (SIR92)
Refinement	Full-matrix least-squares
Function Minimized	Σ w (|Fo| - |Fc|)^2
Least Squares Weights	$1/\sigma^2$(Fo)
p-factor	0.0100
Anomalous Dispersion	All non-hydrogen atoms
No. Observations (I>3.00σ(I))	2130
No. Variables	253
Reflection/Parameter Ratio	8.42
Residuals: R; Rw	0.047 ; 0.046
Goodness of Fit Indicator	1.75
Max Shift/Error in Final Cycle	0.00
Maximum peak in Final Diff. Map	0.28 e-/Å3
Minimum peak in Final Diff. Map	-0.27 e-/Å3

Atomic coordinates and $B_{iso}/_{eq}$ for Ketone 222b.

atom	x	y	z	eq
O(1)	-0.0312(2)	0.2580(1)	1.2752(2)	3.17(5)
O(2)	0.2700(1)	0.28942(9)	1.3173(2)	2.04(4)
O(3)	0.4027(2)	0.5533(1)	1.3975(2)	2.59(5)

O(4)	0.6580(2)	0.50304(10)	1.3038(2)	2.20(4)
O(5)	0.5966(2)	0.27636(10)	1.4337(2)	2.62(5)
N(1)	-0.0102(2)	0.3303(1)	1.1098(2)	2.20(5)
N(2)	0.5363(2)	0.5119(1)	1.2101(2)	1.90(5)
C(1)	0.0909(2)	0.3803(1)	1.0723(3)	1.87(6)
C(2)	0.0906(2)	0.4077(2)	0.9616(3)	2.47(7)
C(3)	0.2050(3)	0.4526(2)	0.9449(3)	2.48(7)
C(4)	0.3136(2)	0.4685(1)	1.0370(3)	2.13(6)
C(5)	0.3141(2)	0.4398(1)	1.1499(2)	1.66(6)
C(6)	0.1992(2)	0.3952(1)	1.1665(2)	1.61(6)
C(7)	0.1679(2)	0.3512(1)	1.2726(2)	1.84(6)
C(8)	0.0309(2)	0.3056(2)	1.2231(3)	2.27(7)
C(9)	-0.1360(2)	0.3017(2)	1.0338(3)	2.87(7)
C(10)	0.1635(2)	0.4098(2)	1.3767(3)	2.14(6)
C(11)	0.0920(2)	0.4939(2)	1.3429(3)	2.98(7)
C(12)	0.0995(3)	0.3668(2)	1.4706(3)	3.07(7)
C(13)	0.3211(2)	0.4169(1)	1.4251(2)	1.86(6)
C(14)	0.3889(2)	0.4814(2)	1.3603(2)	1.82(6)
C(15)	0.4385(2)	0.4539(1)	1.2500(2)	1.64(6)
C(16)	0.5337(2)	0.3740(1)	1.2773(2)	1.61(6)
C(17)	0.6785(2)	0.4145(2)	1.3066(3)	2.41(7)
C(18)	0.5084(3)	0.6024(2)	1.2004(3)	2.86(7)
C(19)	0.5249(2)	0.3143(1)	1.1728(3)	2.26(6)
C(20)	0.5083(2)	0.3223(1)	1.3803(2)	1.77(6)
C(21)	0.3681(2)	0.3267(1)	1.4117(2)	1.96(6)
H(1)	0.0158	0.3966	0.8991	2.9624

H(2)	0.2089	0.4727	0.8692	2.9766
H(3)	0.3898	0.4998	1.0229	2.5612
H(4)	-0.1800	0.2616	1.0739	3.4488
H(5)	-0.1147	0.2765	0.9660	3.4488
H(6)	-0.1953	0.3484	1.0117	3.4488
H(7)	0.1368	0.5227	1.2901	3.5758
H(8)	-0.0010	0.4841	1.3068	3.5758
H(9)	0.0956	0.5273	1.4109	3.5758
H(10)	0.1176	0.3081	1.4708	3.6794
H(11)	0.1381	0.3899	1.5448	3.6794
H(12)	0.0033	0.3759	1.4540	3.6794
H(13)	0.3371	0.4312	1.5055	2.2331
H(14)	0.7304	0.3984	1.2503	2.8972
H(15)	0.7253	0.3974	1.3819	2.8972
H(16)	0.4158	0.6113	1.1624	3.4274
H(17)	0.5235	0.6266	1.2762	3.4274
H(18)	0.5677	0.6280	1.1564	3.4274
H(19)	0.4393	0.2857	1.1592	2.7161
H(20)	0.5328	0.3458	1.1056	2.7161
H(21)	0.5973	0.2743	1.1892	2.7161
H(22)	0.3688	0.2963	1.4817	2.3530

APPENDIX SEVEN: NOTEBOOK CROSS-REFERENCE

NOTEBOOK CROSS-REFERENCE

The following notebook cross-reference has been included to facilitate access to the original spectroscopic data obtained for the compounds presented in this thesis. For each compound a folder name is given (i.e., AAHXIV-189) which corresponds to an archived characterization folder hard copy and a notebook number (for example, AAHXIV-189 corresponds to notebook AAHXIV, page 189). The filenames corresponding to each compound are listed under the appropriate type of spectrum (i.e., ^{1}H NMR, ^{13}C NMR, IR), and these files are stored on ZIP disks and a CD. All notebooks, spectral data, and diskettes are stored in the Wood Group archives.

Compounds Appearing in Chapter Two

Compound	Folder	^{1}H NMR	^{13}C NMR	IR
44	AAHXIV-189	Feb28-2000-hol-50	Feb-29-2000-hol-10	AAH14a189
45	AAHXIV-191	Feb-29-2000-hol-70	Feb-29-2000-hol-61	AAH14191
46	AAHXIV-195	hol-carbylide-70	hol-carbylide-71	AAH14c195
47	AAHXIV-195	hol-carbylide-10	hol-carbylide-40	AAH14195
54	BMSVIII-265	BMS8b.265	BMS8c.265	BMS8r265
55	AAHII-111	AAH2b.111	AAH2c.111	theacid
51	BMSVIII-297	BMS8b.297	BMS8c.297	BMS8r297
56	JADII-180	AAH.ACH	AAH2.ACH	AAHrACH

Compound	Folder	^{1}H NMR	^{13}C NMR	IR
50	AAHIII-275	AAH3a.275	AAH3b.275	AAH3r275
58	JADIV-122	JAD.111	JADc.111	JADr111
57	AAHIX-261	AAHp.red	AAHc.red	AAHrred
59	BMSIX-049	BMS9a-049	BMS9b-049	JAD3r211
60	AAHIX-265	AAH9d.265	AAH9c.265	AAH9r265
61	AAHIX-287	AAH9a.287	AAH9b.287	AAH9r287
74	BMSIX-301	hol-bromo-40	hol-bromo-50	AAHbro
79	AAHI-145	jun01-2000-hol.10	jun02-2000-hol-10	isatin2
81	AAHVI-73	AAHV6d.73	AAH6c.73	AAHHAGI2
75	AAHV-277	AAH5b.277	AAH5d.277	AAH5f277
83	AAHVI-029	AAH6f.029	AAH6g.029	AAH6h029
84	AAHXIV-161	Feb15-2000-hol.10	AAH14a.161	AAH14161a

Compounds Appearing in Chapter Three

Compound	Folder	^{1}H NMR	^{13}C NMR	IR
90	AAHIX-147	AAH9a.147	AAH9b.147	AAH9r147
117	AAHVIII-115	AAH8e.115	AAH8f.115	AAH8r115
121	AAHIX-131	AAH.dik	AAHc.dik	AAHrdik
91	MMWV-153	MMW5b.153	MMW5c.153	MMW5r.153
124	AAHXIV-183	Feb25-2000-hol-10	Feb25-2000-hol-11	AAHOHins
128	AAHXI-183	AAH11a.183	AAH11b.183	AAH11183
127	AAHXI-199	AAH11a.199	AAH11b.199	AAH11199
129	AAHXI-179	AAH11a.179	AAH11b.179	AAH11179
130	AAHIX-131	AAH9a.131	AAH9c.131	AAH9130
139	AAHIX-137	AAH9a.137	AAH9c.137	AAH9r1137
140	AAHIX-137	AAH9b.137	AAH9d.137	AAH9r2137
141	AAHIX-155	AAH9a.155	AAH9b.155	AAH9r155
146	AAHXI-195	AAH11b.195	AAH11c.195	AAH11195
146	AAHVIII.037	AAH08AP.037	AAH08AC.037	AAH08A037
ii	AAH11.201	AAH11a.201	AAH11e.201	AAH11201

Compounds Appearing in Chapter Four

Compound	Folder	^{1}H NMR	^{13}C NMR	IR
151	AAHXI-129	AAH11a.129	AAH11b.129	AAH11129
152	BMSX-287	Feb17-2000-hol-50	Feb18-2000-hol-10	BMS10287
153	AAHVII-153	Feb21-2000-hol-80	Feb21-2000-hol-71	AAH7a153
155	AAHXIV-197	Mar7-2000-hol-70	Mar7-2000-hol-61	AAH14197
156	AAHXIV-197	Hol-ald-20	Hol-ald-21	AAH14ald
161	AAHVII-085	AAH7a.85	AAH7b.85	AAHpd2
177	JADIV-047	JAD04.047	JAD04.47c	jadallyl
178	JADIV-049	JAD04.049	JAD4.49ac	nitrone
179	JADIV-049	JAD04.049b	JAD4.49bc	jad5me
180	JADIV-299	JAD04.299	JAD04.93bc	jad5bn
181	JADII-285	JAD02.285	JAD04.93c	jadoxa
188	JADV-057	JAD05b.57h	JAD05b.57c	jadtms
189	JADV-069	JAD05h.069	JAD05.069	jadtms2b
197	AAHXII.077	AAH12a.077	AAH12d.077	AAH12077
198a	JADIV-119	diast1.jad	diast1c.jad	diast1jad
198b	JADIV-119	diast2h.jad	diast2c.jad	diast2jad
199b,c	AAHXIV-141	AAH14z.141	jan30-2000-inoue-40	aah14z141
199b	AAHXIV-141	AAH14y.141	jan30-2000-inoue-50	aah14y141

Compound	Folder	^{1}H NMR	^{13}C NMR	IR
199a	AAHXIV-141	AAH14e.141	AAH14ec2.141	aah14e1141
200	AAHXIV-221	mar15-2000-hol-10	mar16-2000-hol-20	aah14b221
201a,b	AAHXIV-145	hol-alc12-10	hol-alc12-82	aah14ac145
201c,d	AAHXIV-145	hol-alc34-30	hol-alc34-20	aah14b145
202a	AAHXIV-147	AAH14b.147	AAH14c.147	aah14b147
202a,b	AAHXIV-147	hol-ket-50	feb23-2000-hol-50	aahket
204	AAHXIV-157	AAH14c.157	feb19-2000-hol-11	aah14157
212	AAHXIV-153	AAH14a.153	feb08-2000-hol-40	aah14153
213	AAHXIV-199	AAH.OMe	feb07-2000-hol-10	aahome
216	AAHXIV-155	AAH14b.155	feb10-2000-hol-11	aah14b155
217	AAHXIV-159	AAH14a.159	AAH14b.159	aah14159
221	AAHXIII-215	aah.009	aah.008	aah13215a
223	AAHXIV-205	mar12-2000-hol-20	mar13-2000-hol-11	aah14b205
222b	AAHXIV-163	feb16-2000-hol-50	feb16-2000-hol-51	aah14a163
230	AAHXIV-179	feb21-2000-hol-110	feb23-2000-hol-41	aah14179

Compound	Folder	^{1}H NMR	^{13}C NMR	IR
231	AAHXIV-215	mar16-2000-hol-30	mar16-2000-hol-31	aah14215

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ABOUT THE AUTHOR

The author, Alexandra A. Holubec, was born on May 31, 1973 in Parma, Ohio to Zenowie and Myroslawa Holubec. Her parents, born in Ukraine, immigrated to the United States as children, and since then have accomplished a great deal, and set a very high standard for their children. Her mother, Myroslawa, earned a Master's of Library Science degree at the University of Illinois at Champagne, Urbana, and her father, Zenowie, merited a Doctorate of Organic Chemistry at the same institution working under the direction of Professor Curtin, and more recently became a CPA. In addition, they raised Alexandra, the baby of the family, and two sons, Lev and Orest. Lev, born in 1967, earned an MBA at Columbia University and lives in Cleveland with his wife Halyna. Orest, born 15 months before Alexandra, currently is the Director of Boards and Commissions, Office of Ohio Governor Bob Taft in Columbus, Ohio.

Alexandra's parents taught their children the Ukrainian language at a very early age, before they even spoke English, and have managed to maintain the language in the household still to this day. Alexandra, or Lesia, her Ukrainian nickname, experienced a typical Ukrainian-American childhood, attending Ukrainian school on Saturday mornings for eleven years, where she studied Ukrainian culture, language, history, and geography. She attended St. Josaphat Ukrainian-Catholic grade school, where her mother currently teaches the third grade, and was voted to be President of the school in the eighth grade. Some of her extracurricular activities throughout grade school and high school included Ukrainian dancing, which she studied for eleven years, soccer, and activities associated with PLAST, a Ukrainian youth organization, involving weekly meetings and scout camps including specialty camps such as sports and ski camps. After completing high school at Holy Name High School in Parma Heights, OH, she attended John Carroll University, also in Ohio, where she had the pleasure of studying organic chemistry with Dr. Weaver, a professor who had taught her father years before as part of his Master's Degree in Chemistry. Following in her father's footsteps, she majored in Chemistry, and performed undergraduate research under the direction of Dr. James Walsh, studying redox reactions of organo-sulfur compounds. Between years throughout college, she spent two summers at the Lubrizol Corporation, where her father worked for 33 years, and one summer at Columbia University as an NSF-REU fellow, working

under the guidance of Prof. Koji Nakanishi on the synthesis of a glutamate receptor inhibitor.

In 1995, after graduating from JCU Summa Cum Laude, she finally left the Heartland and came to Yale University where she had the opportunity and pleasure of joining the laboratories of Professor John Wood, and initiated a project directed toward the total synthesis of the welwitindolinone alkaloids. In 1996 she earned her Master's Degree in chemistry, and in 2000 her doctorate. She accepted a position as Research Investigator II at Bristol-Myers Squibb where she will work in the Medicinal Chemistry Department.