Title

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I. Pt-Catalyzed Tandem Epoxide Fragmentation/Pentannulation of Propargylic Esters
II. Progress Toward the *Kopsia* Family of Indole Alkaloids

by

Brian Gerard Pujanauski

A dissertation submitted in partial satisfaction of the

requirements for the degree of

Doctor of Philosophy

in

Chemistry

in the

Graduate Division

of the

University of California, Berkeley

Committee in charge:

Professor Richmond Sarpong, Chair
Professor K. Peter C. Vollhardt
Professor Danielle Tullman-Ercek

Spring 2010

Abstract

I. Pt-Catalyzed Tandem Epoxide Fragmentation/Pentannulation of Propargylic Esters
II. Progress Toward the *Kopsia* Family of Indole Alkaloids

by

Brian Gerard Pujanauski

Doctor of Philosophy in Chemistry

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Professor Richmond Sarpong, Chair

Chapter 1. The identification and development of novel reactivity of propargylic esters containing a pendant epoxide are described. This method allows for the synthesis of highly functionalized cyclopentenone products. A range of different functional groups are tolerated in this transformation. Isolation of intermediates and their ability to be carried on to products provides mechanistic evidence for a 4π-conrotatory ring closure to construct a carbon-carbon bond and stereospecifically set vicinal stereocenters.

Chapter 2. An overview of multiple drug resistance (MDR) and the possibility for the use of chemical tools to elucidate this phenomenon is outlined. The *Kopsia* alkaloids are introduced and previous synthetic work is described. Two different initial synthetic plans were investigated. To close the key eight-membered ring of these natural products the first route makes use of a Friedel-Crafts acylation. The second route utilizes a Dieckmann cyclization to close this ring.

Chapter 3. A route to lapidilectine B based on an Ugi four-component coupling is described. The Ugi reaction incorporates all the carbon atoms for lapidilectine B in a simple, high-yielding step. Elaboration of the Ugi-product is discussed and optimized, with special attention paid to the oxidative carbon-carbon bond cleavage necessary for the success of this strategy. A Friedel-Crafts hydroxyalkylation was utilized to form the eight-membered ring. Various methods for the formation of the final carbon-carbon bond of lapidilectine B are discussed.

I. Pt-Catalyzed Tandem Epoxide Fragmentation/Pentannulation of Propargylic Esters
II. Progress Toward the *Kopsia* Family of Indole Alkaloids

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Acknowledgements

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My eternal thanks also goes out to the entire first class of the Sarpong group. The leadership they demonstrated and the effort they expended setting up the lab did not go unnoticed. In particular, Eric Bunnelle is probably the person most responsible for my day to day development as a scientific thinker. Not a day went by that I didn't have some question about technique, theory, or tech. support. Eric Simmons had probably the best chemistry hands in the group, and his ability to do chemistry on sub-milligram scales was truly spectacular. Simmons was also my go-to synthesis guru, and improved many of my half-baked ideas to at least two-thirds baked. Andrew Marcus was housed in 837 for my first two years of grad school, and helped me tremendously when I was at my most inept. Having a Mets fan in the lab also provided endless entertainment during baseball season. Kimberley Larson's persistence was inspirational, and the knowledge that no matter what was going on that day, I could go over and get some sort of rise out of her was very comforting.

My classmates in the Sarpong group also deserve a round of thanks. Having such a great group of people going through the same ordeals at the same time is very beneficial, especially for someone like me who is always asking about the administrative stuff. I would like to thank Laura Miller for all her hard work with Chemistry in the Classroom, a fantastic experience for all involved. Even though I missed out on the first annual Sarpong Ski Trip, Scott West's efforts at organizing that year and each subsequent year was not forgotten. Sharing a desk with Cameron “The Dragon” Smith my first summer was definitely an experience, but unfortunately his cleanliness did not rub off on me.

The Sarpong group has been lucky to have a great group of post-docs as a part of the group. The initial duo of Maina Ndungu and B.A. Bhanu Prasad provided some much-needed experience to a fledgling group. Bhanu in particular worked at the hood next to me, and other than the time I blew up some chloramine-T following his suggestion, he was a fantastic mentor, as well as the co-author on my first publication. Alakesh Bisai shared his endless enthusiasm and energy with the whole lab. Vishnumaya's veggie cutlets are probably one of my all-time favorite snacks, and I never could get enough of them.

I would also like to share my thanks and give my encouragement to the current leaders of the Sarpong group. I have the utmost confidence in Alison Narayan, Jesse Cortez, and Jess Wood and their ability to carry the banner into the future. Alison and Jess both graciously agreed to edit chapters of this thesis, and for that I'm deeply grateful. New addition Steve Heller was a great deadline-deal acquisition, and I'm positive his expertise and experience will be of great help to the younger students in the group.

I'd like to thank all the various members of the Sarpong group who have shared the joy of 837 Latimer with me at some point. Steven Born, Jenna Jeffrey, and Erica Schultz have all put up with my music more than I could have hoped for. The *Kopsia* project is now in the capable hands of Erica, and I can leave with the knowledge that the project is in very good hands.

I was lucky to have the assistance of two wonderful and hardworking undergraduate students during my time. Kim Griffin had to deal with the difficulties of working with some really tough compounds on the ellipticine project. I'm sure she's having a much better time at Chicago in graduate school. Julius Reyes has been a great undergrad to mentor, and his questions were always welcomed, even the ones that I couldn't answer. I fully expect him to succeed at Chicago as well, but I'm wondering where my referral check from them is.

My family deserves thanks as well. My parents were instrumental in putting me on the path to success, and taught me all the lessons I needed to learn so that I could survive in this world, and most importantly, how to be a good person. I'd like to apologize to my sister for not warning her strenuously enough about graduate school, and hopefully our younger brother has heeded our experiences.

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Chapter 1: Pt-Catalyzed Tandem Epoxide Fragmentation/Pentannulation of Propargylic Esters

1.1. Introduction

1.1.1. Background

The last decade has seen an explosion in the use of transition metal Lewis acid catalysts for the activation of carbon-carbon π bonds.[1] Although Brønsted acids can be utilized for the activation of these functionalities, harsh conditions, which often produce multiple side-products, are typically required. In contrast, the use of metal salts of gold and platinum allows for lower temperatures, shorter reaction times, and alternative reaction pathways.[2] Due to their great versatility, these catalysts have received increasing attention in recent years.

Figure 1.1 illustrates the Dewar-Chatt-Duncanson model for the interaction of a transition metal with a carbon-carbon triple bond. The metal d-orbitals are shown on the left with the alkyne π-bonds of suitable symmetry on the right. The interaction that leads to the greatest net stabilization of a Pt metal complex occurs between the D_z^2 orbital of the metal with one of the filled π orbitals of the alkyne, which produces an interaction with σ-symmetry. Also important, but to a lesser degree, is the backbonding between the D_{xy} orbital of the metal with a π* orbital of the alkyne, which creates an interaction with π-symmetry. It can be useful to think of alkynes, and to a lesser extent alkenes, as having strong two-electron σ-donation with relatively weaker π-acceptor interactions.

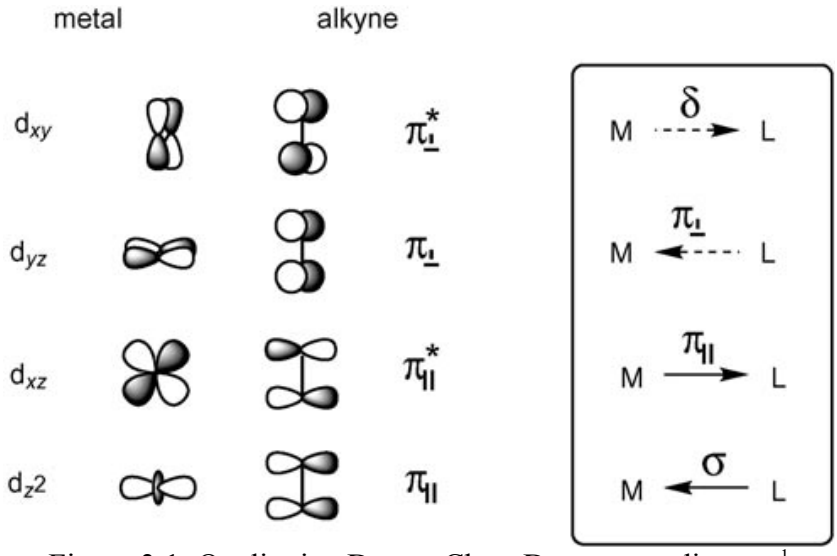


Figure 3.1: Qualitative Dewar-Chatt-Duncanson diagram[1]

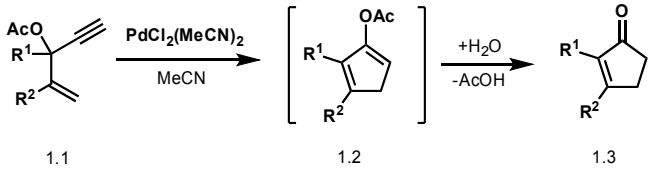
Whereas catalysis using palladium, nickel, rhodium, and copper typically relies on changes in oxidation state of these metals, gold and platinum catalysts generally do not undergo these redox changes. Recent advances in the understanding of these metals has taken advantage of this property, especially the robust nature of the simple metal salts $AuCl_3$ and $PtCl_2$. These metal catalysts have a number of advantages over other transition metals, such as their ability to convert a wide array of starting materials into products of higher chemical

complexity under safe, simple conditions that generally do not have to be rigorously inert, and are typically atom-economical.[3]

1.1.2. Pentannulation

Methods to synthesize five-membered rings continues to be an active area in organic synthesis due to their prevalence in fragrances, natural products, and pharmaceuticals.[4] Established procedures such as the Nazarov,[5] Karpf-Dreiding,[6] and Pauson-Khand[7] reactions allow access to pentannulated products; however, there remains a need for methods that generate highly functionalized five-membered rings.

Within the last two decades, the use of transition metals in the activation of alkynes to generate reactive metallocarbenoids has received increasing attention.[8] One of the first examples of this transformation was the synthesis of cyclopentenones from propargylic acetates using a palladium catalyst developed by Rautenstrauch (Scheme 1.1).[9]



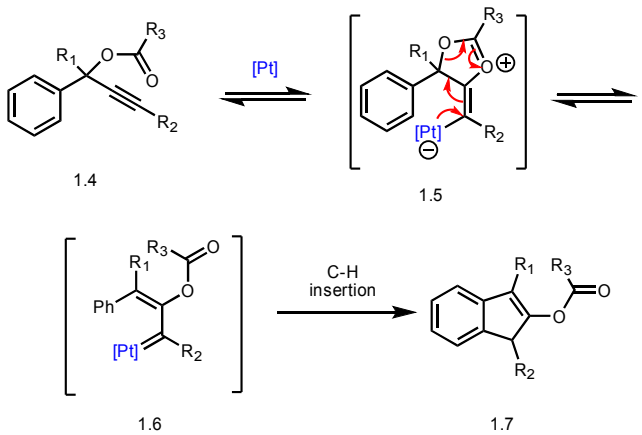
1.1 1.2 1.3

Scheme 1.1 Rautenstrauch pentannulation

This transformation (**1.1** → **1.3**) proceeds via initial alkyne activation and acetate shift, followed by formal C-H insertion to yield cyclopentadiene **1.2**. The diene **1.2** can be trapped with a dienophile such as N-phenylmaleimide to yield the Diels-Alder adduct or hydrolyzed to cyclopentanone **1.3**. Many other examples of the use of propargylic acetates for the formation of metallocarbenoids have since been reported in the literature.[10]

1.1.3. Inspiration from Previous Work

Initial studies by our group investigated the pentannulation of propargylic esters utilizing a Pt(II) catalyst system.[11] In this way, pentannulated products could be derived from easily obtained aromatic starting materials (Scheme 1.2). Treatment of substrate **1.4** with catalytic $PtCl_2(PPh_3)_2$ and PhIO as an additive presumably gave rise to metallocarbenoid **1.6** through a 1,2-acetate shift. Subsequent formal C-H insertion of the metallocarbenoid into the sp^2 C-H bond yielded pentannulated product **1.7** as a mixture of olefin isomers (major shown).



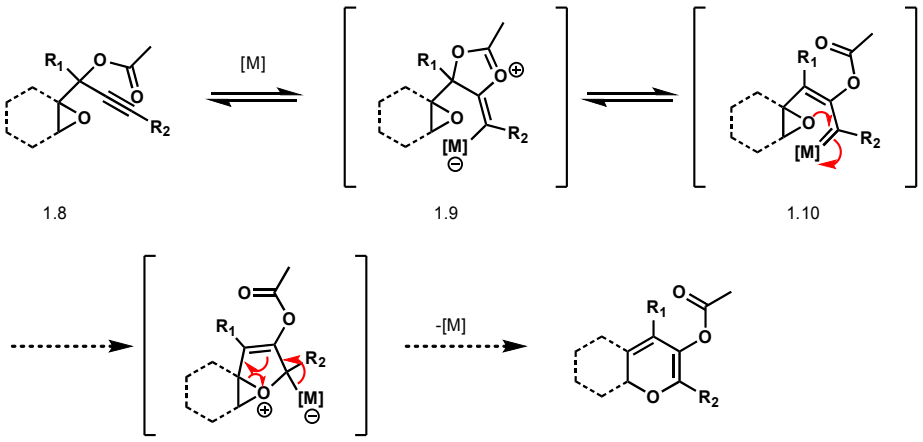
1.4 1.5 1.6 1.7

Scheme 1.2: Pentannulation of propargylic esters

1.2. Epoxide Fragmentation and Pentannulation of Propargylic Acetates

1.2.1. Proposed Reactivity

With the success of the initial pentannulation transformation depicted in Scheme 1.2, it was anticipated that other functionalities could be trapped by an intermediate metallocarbenoid. Specifically, we hypothesized that propargylic ester **1.8** (Scheme 1.3), in the presence of a transition metal catalyst, would form intermediate **1.10**. Formal insertion of the resulting metallocarbenoid into the C-O bond of the epoxide moiety would yield pyran intermediate **1.12**.



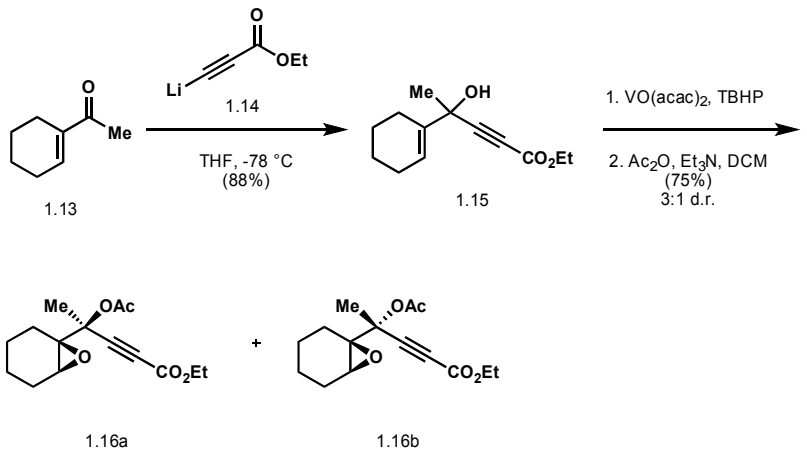
1.8 1.9 1.10 1.11 1.12

Scheme 1.3: Initial proposal for epoxide fragmentation/pentannulation

1.2.2 Substrate Synthesis

To test this hypothesis, substrate **1.16** was synthesized from commercially available enone **1.13** (Scheme 1.4). Addition of the lithium salt of ethyl propiolate (**1.14**) produced

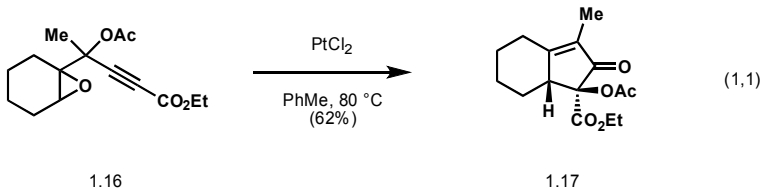
tertiary alcohol **1.15** in good yield. Directed epoxidation of **1.15** with $VO(acac)_2$ and *tert*-butyl hydrogen peroxide, followed by acetylation of the alcohol provided **1.16** in good overall yield as a 3:1 mixture of diastereomers.[12] A broad range of substrates could be synthesized using this strategy. The choice of the α-β unsaturated ketone, acetylide, and acylating reagent allows for three different points of diversity.

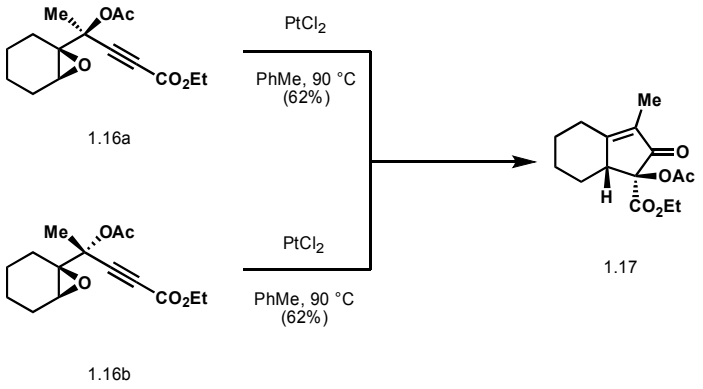


Scheme 1.4: Substrate synthesis

1.2.2. Initial Results

Subjecting **1.16** (as a mixture of diastereomers) to a variety of transition metal catalysts initially gave disappointing results. $PtCl_4$, $InCl_3$, and $Pt(PPh_3)_2Cl_2$/PhIO all consumed the starting material, but led to non-specific decomposition. However, treatment of **1.16** with a catalytic amount of $PtCl_2$ gave pentannulated cyclopentenone **1.17** in 62% yield as a single diastereomer (eq 1.1). This transformation led to products different from what was initially anticipated (see Scheme 1.3). Additionally, separating diastereomers **1.16a** and **1.16b** and subjecting each to the reaction conditions individually gave the same identical product (Scheme 1.5).





Scheme 1.5: Diastereoablative reaction confirmation

1.3. Reaction Scope

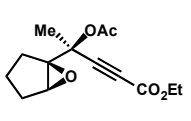
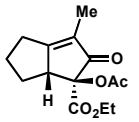
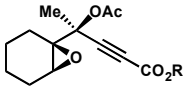
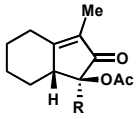
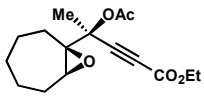
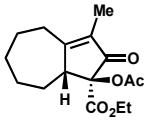
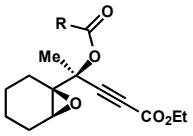
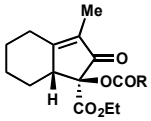
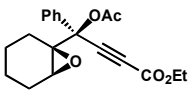
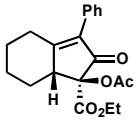
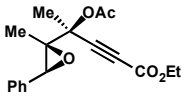
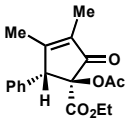
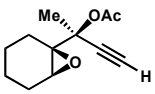
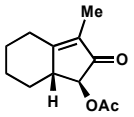
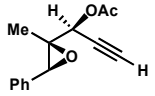
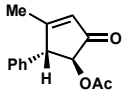
With the proof of concept demonstrated with **3.16a/b**, we sought to explore the substrate scope of this transformation using the optimized conditions of 0.1 equiv $PtCl_2$ in toluene (0.1M) at 100 °C (Table 1).[13] A range of bicycles, including [5,5]-, [6,5]- , and [7,5]-fused systems can be made successfully with this methodology (entries 1-3). Methyl, ethyl, and benzyl ester functions are tolerated at the terminus of the triple bond (entry 2). In addition to acetates, propargylic benzoates and pivalates are transformed to the pentannulated products (entry 4). Acyclic substrates also readily participate in the reaction to afford highly substituted cyclopentenones (entries 6 and 8).

In addition to ester groups at the terminus of the triple bond, it was found that terminal alkynes can be also tolerated (entry 7). This was surprising because it was found in the previous pentannulation study reported by our group that the electron-withdrawing character of an ester was needed for reactivity. Having a highly electron-withdrawing substituent on the triple-bond causes an increase in acidity for the hydrogen at the propargylic position and this increase in acidity leads to decomposition of the material during acylation. Propargylic alcohol **1.18** in Figure 1.2 decomposes under acylation conditions, whereas **1.19** does not. The ability to use terminal alkynes allows for substrates derived from enals to be constructed and used in this chemistry (entry 8).

1.18 1.19

Figure 1.2: Alkyne terminus comparison

Table 1.1.[14] Cycloisomerization of Epoxide Substrates

Entry	Substrate	Product	time (h)	yield (%)
1			3	70
2				
	a) R = Me		3	70
	b) R = Me		3	72
	c) R = Bn		3	56
3			3	60
4				
	a) R = Ph		10	67
	b) R = *t*-Bu		10	58
5			6	73
6			3	60
7			6	75
8			6	61

1.4. Reaction Mechanism

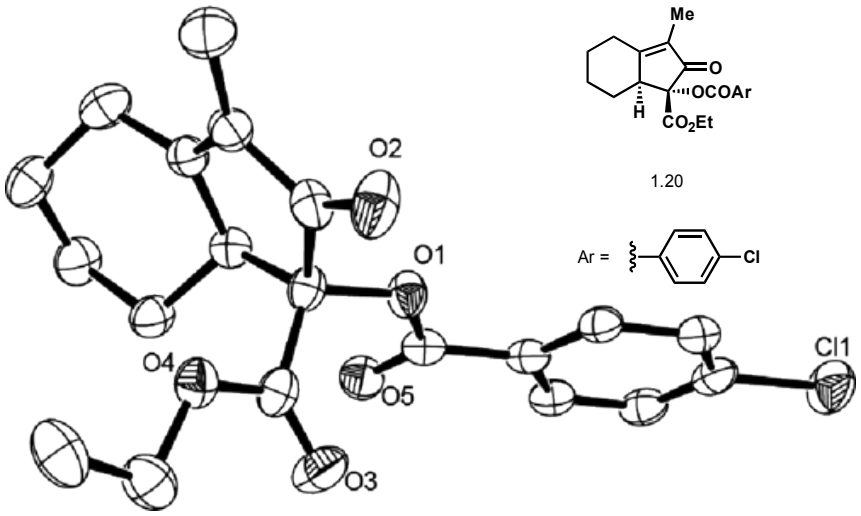
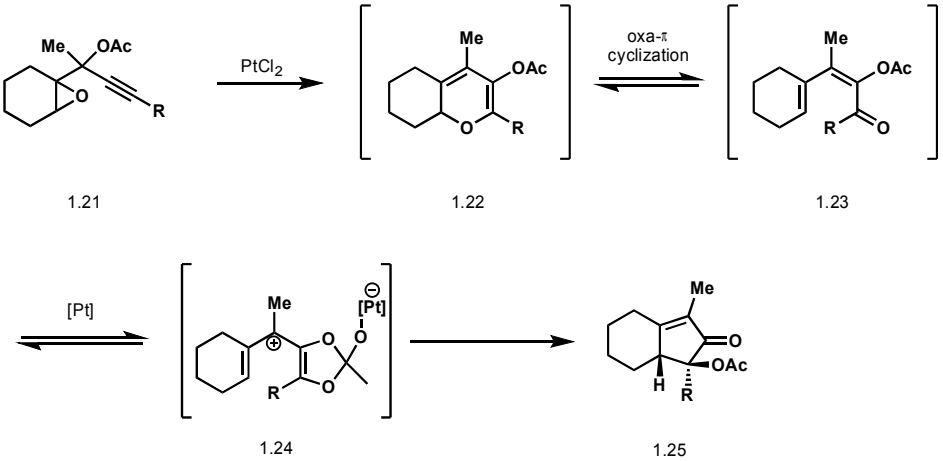


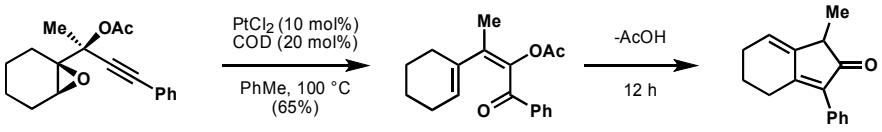
Figure 1.3: ORTEP illustration of 1.20 with hydrogens omitted

One interesting feature of this reaction is the stereospecificity, which leads to a single diastereomer of the product. As depicted in Figure 1.3, a crystal structure of **1.20** shows a *syn* stereochemical relationship between the bicyclic ring fusion hydrogen and the α-chlorobenzoate group.[15] This is consistent with the mechanism shown in Scheme 1.6. Formation of pyran **1.22** via the initially hypothesized mechanism (Scheme 1.3) could be followed by tautomerization to dienone **1.23** via an oxa-6π-electrocyclization. Intermediate **1.23** can then be activated by Pt(II) to yield pentadienyl cation **1.24**. At this stage, a pseudo-Nazarov 4π-conrotatory ring closure yields the product (**1.25**) as a single diastereomer.[16] A thermal pericyclic reaction with four electrons must involve an odd number of antarafacial interactions, which gives rise to the conrotatory cyclization, producing only a single diastereomer of product **1.25**.[17]



Scheme 1.6: Mechanism accounting for *syn* selectivity

Another substrate that was tested possessed a phenyl group at the terminus of the triple bond (**1.26**, Scheme 1.7). The initially isolated product was dienone **1.27** in 65% yield. Resubjecting dienone **1.27** to the reaction conditions induced pentannulation with concomitant loss of acetic acid to form cyclopentenone **1.28**. Subjecting substrate **1.26** to the reaction conditions overnight also led to final product **1.28** in comparable yield, whereas heating **1.27** without the $PtCl_2$ catalyst only returned **1.27**. The isolation of intermediate **1.27** as well as its competency in the pentannulation supports our proposed mechanism (Scheme 1.6).

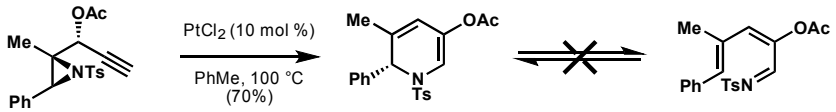


1.26 1.27 1.28

Scheme 1.7: Terminal phenyl substrate

1.5. Extensions of Reactivity

With the success of the epoxide methodology, our group began investigating other possibilities for intercepting the putative metallocarbenoid intermediates generated from 1,2-acetate shifts. One such example utilizes N-tosyl aziridines such as **1.29**, a logical extension from epoxides. This reaction stops at dihydropyridine **1.30**, as opposed to proceeding to the ring-opened product **1.31** or the pentannulated product obtained in the epoxide case. Running the reaction with enantiomerically enriched **1.29** shows that the product almost exclusively retains the chiral information of the starting material, indicating it does not equilibrate via a 6π-electrocyclization with the ring-opened, achiral imine **1.31**.[18]

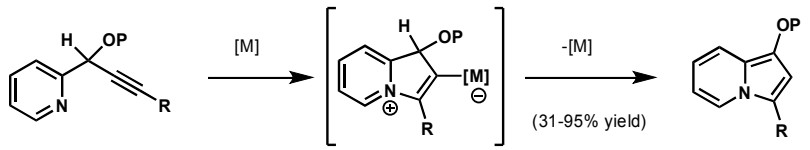


1.29 1.30 1.31

>99.9% ee *98% ee*

Scheme 1.8: Dihydropyridine synthesis

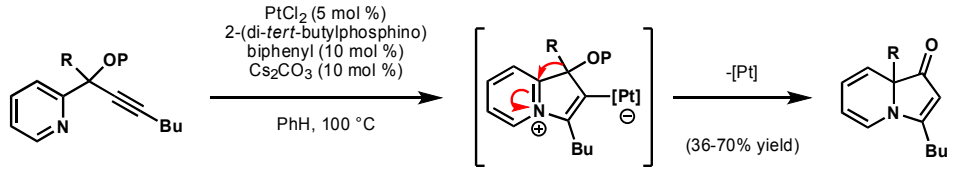
Our group has also investigated the interaction of pyridine nitrogens with metal-activated alkynes. Substrates such as **1.32** were treated with π-Lewis acid catalysts, leading to 5-*endo*-dig attack of the pyridine nitrogen onto the activated alkyne (**1.33**). Subsequent proton transfer and loss of the metal gives indolizine products such as **1.34** in yields ranging from moderate to excellent.[19]



1.32 1.33 1.34

Scheme 1.9: Indolizine synthesis

In contrast, substrates such as **1.35** (Scheme 1.10) do not have a proton to allow aromatization from an intermediate such as **1.36**. In this case, a carbon-carbon bond migration occurs, which is followed by protio-demetallation to give indolizinones such as **1.37**. Of note is the stereospecificity of this reaction, as enantioenriched substrates lead to products that show little loss of enantiomeric excess.



1.35 1.36 1.37

Scheme 1.10: Synthesis of indolizinones

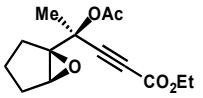
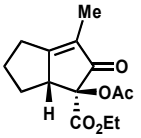
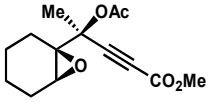
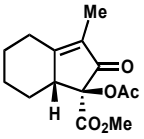
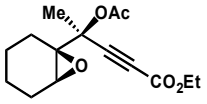
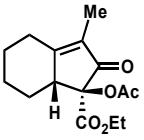
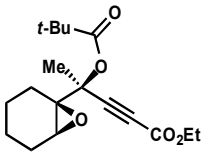
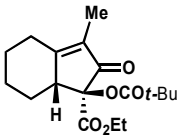
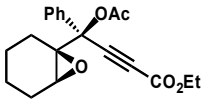
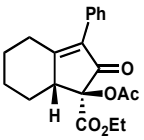
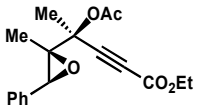
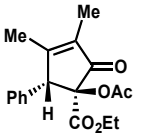
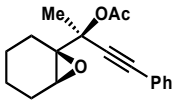
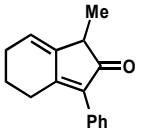
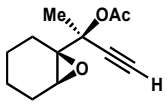
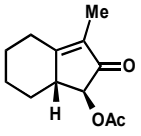
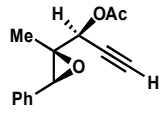
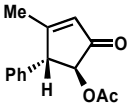
1.6. Conclusion

In conclusion, we have developed a method for the synthesis of highly functionalized cyclopentenone products from easily obtained epoxide substrates. The substrates can be synthesized from commercially available starting materials, which provides easy access to a highly diverse set of reaction substrates. A range of functional groups are tolerated in this transformation. Mechanistic evidence points to a 4π-conrotatory ring closure to construct a carbon-carbon bond and stereospecifically set vicinal stereocenters.

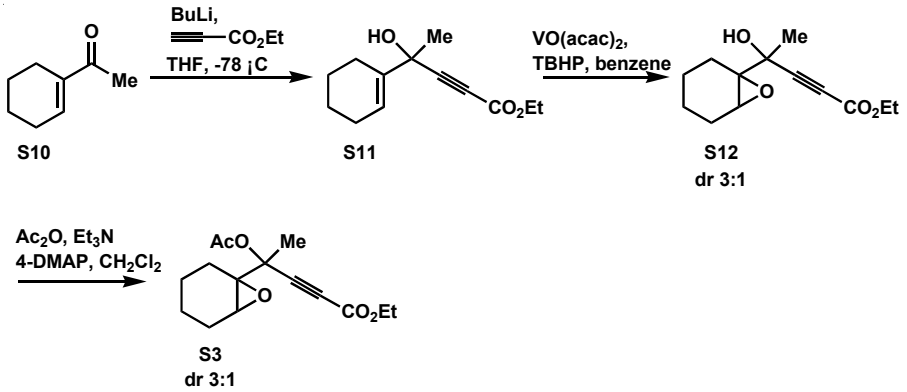
1.7. Experimental

General. All air or moisture sensitive reactions were conducted in flame-dried glassware under an atmosphere of nitrogen using dry, deoxygenated solvents. Toluene, methylene chloride, acetonitrile, and triethylamine were distilled under nitrogen from calcium hydride immediately prior to use and tetrahydrofuran (THF) was distilled under nitrogen from sodium benzophenone ketyl. All reagents were purchased from Aldrich, Acros, or Lancaster and used without further purification. $PtCl_2$ was purchased from Strem. Melting points were measured on a Büchi® melting point apparatus and are corrected using vanillin (mp 80-81 °C) as a standard. Reaction temperatures were controlled by an IKAmag temperature modulator. Thin-layer chromatography (TLC) was performed using Silicycle silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV and anisaldehyde stain. Sorbent silica gel 240-400 mesh (particle size 0.032-0.063) was used for flash chromatography. Pt-catalyzed reactions were performed in Schlenk flasks. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 500 (at 500 MHz and 125 MHz respectively) 400 (at 400 MHz and 100 MHz respectively) spectrometers in chloroform-*d* at 23 °C, unless otherwise stated. Chemical shifts were referenced to the residual chloroform-H peak, which was set at 7.26 ppm for ^{1}H and 77.0 ppm (center peak) for ^{13}C spectra. Data for ^{1}H NMR are reported as follows: chemical shifts (δ ppm). Multiplicity, (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublet, dt = doublet of triplet, m = multiplet, br = broad resonance), coupling constants (Hz) and integration. Data for ^{13}C NMR are reported in terms of chemical shift. IR spectra were recorded on a Nicolet MAGNA-IR 850 spectrometer and are reported in frequency of absorption (cm^{-1}). Low and high resolution mass spectral data were obtained from the University of California, Berkeley Mass Spectral Facility, on a VG 70-Se Micromass spectrometer for FAB, and a VG Prospec Micromass spectrometer for EI.

Table 1

Entry	Substrate		Product		Yield (%)
1		S1		P1	70
2		S2		P2	70
3		S3		P3	72
4		S4		P4	58
5		S5		P5	73
6		S6		P6	60
7		S7		P7	65
8		S8		P8	75
9		S9		P9	65

Scheme 1



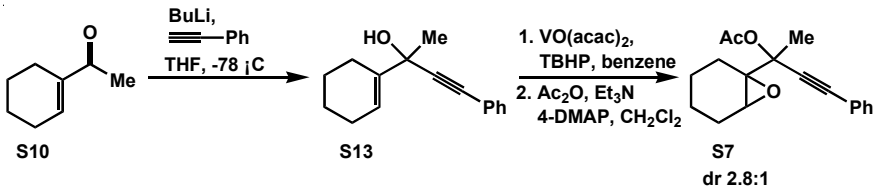
Representative Procedure for the Synthesis of Propargylic Esters (Table 1, entry 3):

A flame-dried, round-bottom flask was charged with anhydrous THF (120 mL) and ethyl propiolate (3.66 g, 37.5 mmol). The solution was cooled to -78 °C and BuLi (14.4 mL, 36.0 mmol, 2.5 M in hexanes) was added slowly over 20 min. The solution was stirred for 45 min at -78 °C, and then 1-acetyl-1-cyclohexene **S10** (SM Scheme 1) (3.72 g, 30.0 mmol) was added slowly over 20 min. The mixture was stirred for an additional 45 min at -78 °C, then the acetone bath was removed and the mixture was allowed to warm to 23 °C. After 30 min, sat. aqueous NH_4Cl solution (30 mL) was added slowly and stirring continued for 15 min. The mixture was diluted with ethyl acetate (100 mL) and washed with sat. aqueous NH_4Cl solution (60 mL). The aqueous layer was extracted with ethyl acetate (2 X 35 mL) and the combined organic layer was washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure and the concentrate mixture was purified by flash column chromatography (7:1 hexanes-ethyl acetate) to obtain the pure propargylic alcohol **S11** (5.06 g, 78% yield).

A solution of propargylic alcohol **S11** (2.28 g, 10 mmol) and $VO(acac)_2$ (450 mg, 1.70 mmol) in dry toluene or benzene (60 mL) was cooled to 0 °C. A solution of *t*-BuOOH (2.18 mL, 17.0 mmol, 70% w/v in water) was added under nitrogen and the mixture was stirred for 12 h at 23 °C. The reaction mixture was cooled to 0 °C and an aqueous solution of sat. $Na_2S_2O_3$ was added (4 mL). The mixture was stirred for 20 min at 23 °C and then extracted with ether (2 X 50 mL). The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure to yield the crude product, which was purified by flash column chromatography (7:1 hexanes-ethyl acetate) to obtain the pure epoxy alcohol **S12** as a 3:1 mixture of diastereomers in 72% yield (1.71 g).

To a 3:1 dr mixture of **S12** (230 mg, 1.00 mmol) in anhydrous methylene chloride (6 mL) was added triethylamine (420 µL, 3.00 mmol), acetic anhydride (120 µL, 1.25 mmol), and DMAP (12.2 mg, 0.1 mmol) under a nitrogen atmosphere at 23 °C. The resultant mixture was stirred for 18 h then washed with aqueous 1 N HCl solution (2 X 15 mL), brine (10 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure. The concentrate was purified by flash column chromatography (7:1 hexanes-ethyl acetate) to obtain the pure propargylic ester **S3** as a 3:1 mixture of diastereomers (0.23 g, 84% yield).

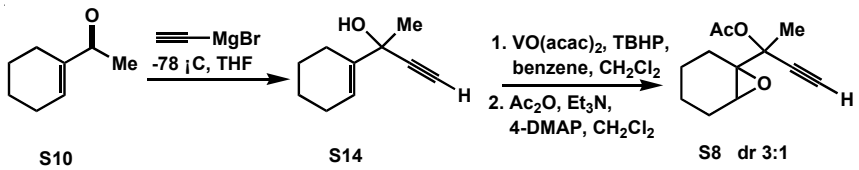
Scheme 4



Preparation of S14 (Table 1, entry 14): A flame-dried, round-bottom flask was charged with anhydrous THF (10 mL) and phenylacetylene (0.352 g, 3.45 mmol). The solution was cooled to -78 °C and BuLi (1.26 mL, 3.15 mmol, 2.5 M in hexanes) was added slowly over 10 min. The solution was stirred for 30 min at -78 °C, and then 1-acetyl-1-cyclohexene **S10** (372 mg, 3 mmol) (SM Scheme 4) was added slowly over 10 min. The mixture was stirred for an additional 2 h at -78 °C, then the acetone bath was removed and the mixture was allowed to warm to 23 °C. Sat. aqueous NH_4Cl solution (3 mL) was added slowly and stirring continued for 15 min. The mixture was diluted with ethyl acetate (15 mL) and washed with sat. aqueous NH_4Cl solution (7 mL). The aqueous layer was extracted with Ethyl acetate (2 X 15 mL) and the combined organic layer was washed with brine (15 mL) and dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the crude mixture was purified by flash column chromatography (7:1 hexanes-ethyl acetate) to obtain the pure propargylic alcohol **S13** (709 mg, 91% yield).

Epoxidation and acylation were performed as described in the representative procedure for **S3**.

Scheme 5



Preparation of S8 (Table 1, entry 8): A flame-dried, round-bottom flask was charged with anhydrous THF (15 mL) and the corresponding 1-acetyl-cyclohexene **S10** (0.59 ml, 5.0 mmol) (SM Scheme 5). The solution was cooled to -78 °C and a solution of ethynylmagnesium bromide (6.0 mmol, 0.5 M in THF) was added slowly over 10 min. The solution was stirred for 2 h at -78 °C, and then allowed to warm to room temperature. The mixture was diluted with ethyl ether (15 mL) and sat. aqueous NH_4Cl solution (15 mL) was added. The organic layer was separated and the aqueous layer was extracted twice with ethyl ether (2 X 20 mL). The combined organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The crude material was use without further purification.

Epoxidation and acylation were performed as described in the representative procedure for **S3**.

Spectral Data for the Substrates

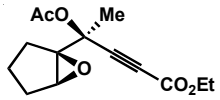


Table 1, (S1) (major isomer)**:** Dense liquid; R_F 0.22 (4:1 hexanes-ethyl acetate), diastereomeric ratio 3:1 (separable). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.17 (q, *J* = 7.5 Hz, 2H), 3.65 (brs, 1H), 2.04 (s, 3H), 1.96-1.90 (m, 2H), 1.70-1.59 (m, 3H), 1.67 (s, 3H), 1.48-139 (m, 1H), 1.25 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.6, 153.0, 83.8, 77.0, 73.1, 69.0, 63.6, 62.1, 26.6, 24.8, 23.1, 21.4, 19.3, 13.9; IR (film) 2962, 2237, 1751, 1715, 1271 cm^{-1}; LRMS (EI): *m/z* 266 (M); HRMS (EI) calcd for $[C_{14}H_{18}O_5]^+$: *m/z*, 266.1232 found 266.1230.

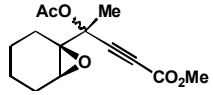


Table 1, (S2): Dense liquid; R_F 0.4 (4:1 hexanes-ethyl acetate), diastereomeric ratio 3:1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.63 (s, 6H, 3H from minor), 3.46 (br, 1H), 3.27 (br, 1H minor), 1.95 (s, 3H), 1.94 (s, 3H minor), 1.87-1.65 (m, 8H, 4H from minor), 1.58 (s, 3H minor), 1.53 (s, 3H), 1.39-1.03 (m, 8H, 4H from minor); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.3, 153.0, 83.9, 75.5, 60.1, 58.4, 55.3, 52.4, 23.9, 22.7, 21.5, 21.0, 20.0, 18.6; IR (film) 2942, 2240, 1750, 1720, 1266 cm^{-1}; LRMS (EI): *m/z* 266 (M+); HRMS (EI): calcd for $[C_{14}H_{18}O_5]^+$: *m/z*, 267.1232 found 267.1228.

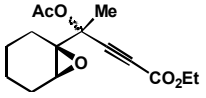


Table 1, (S3) (major isomer)**:** Dense liquid; R_F 0.31 (2:1 hexanes-ethyl acetate), diastereomeric ratio 3:1 (separable). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.20 (q, *J* = 7.0 Hz, 2H), 3.59 (br s, 1H), 2.07 (s, 3H), 1.99-1.79 (m, 4H), 1.66 (s, 3H), 1.48 (m, 1H), 1.39-1.17 (m, 3H), 1.29 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 153.0, 83.8, 77.6, 75.9, 62.1, 60.5, 58.8, 24.3, 23.0, 21.8, 21.3, 20.3, 18.9, 13.9; IR (film) 2940, 2234, 1750, 1714, 1245 cm^{-1}; LRMS (EI): *m/z* 280 (M+); HRMS (EI) calcd for $[C_{15}H_{19}O_5]^+$: *m/z*, 280.1317 found 280.1309.

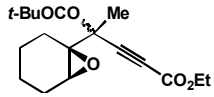


Table 1, (S4): Colorless oil; R_F 0.41 (4:1 hexanes-ethyl acetate), diastereomeric ratio 4:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.18 (q, *J* = 7.2 Hz, 2H), 4.19 (q, *J* = 7.2 Hz, 2H minor), 3.59 (br s, 1H), 3.37 (br s, 1H minor), 2.08-1.74 (m, 8H, 4H from minor), 1.67 (s, 3H minor), 1.64 (s, 3H), 1.51-1.43 (m, 2H, 1H from minor), 1.35-1.10 (m, 6H, 3H from minor), 1.27 (t, *J* = 7.2 Hz, 3H), 1.27 (t, *J* = 7.2 Hz, 3H minor), 1.19 (s, 9H), 1.17 (s, 9H minor); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.0, 153.0, 83.9, 75.6, 62.0, 60.5, 58.8, 55.6, 31.6, 26.9, 24.4, 23.1, 21.8, 20.5, 18.9, 14.0; IR (film) 2939, 2248, 1743, 1716, 1261 cm^{-1}; LRMS (EI): *m/z* 322 (M); HRMS (EI) calcd for $[C_{18}H_{26}O_5]^+$: *m/z*, 322.1858 found 322.1860.

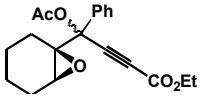


Table 1, (S5): Dense liquid; R_F 0.31 (2:1 hexanes-ethyl acetate), diastereomeric ratio 3.8:1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (m, 4H, 2H from minor), 7.38-7.33 (m, 6H, 3H from minor), 4.28 (m, 2H minor), 4.27 (q, *J* = 7.5 Hz, 2H), 3.55 (br s, 1H minor), 3.30 (br s, 1H), 2.12 (s, 3H), 2.09 (s, 3H minor), 1.95-1.90 (m, 4H, 2H from minor), 1.85-1.78 (m, 4H, 2H from minor), 1.46-1.30 (m, 2H, 1H from minor), 1.34 (m, 3H minor), 1.33 (t, *J* = 7.5 Hz, 3H), 1.26-1.12 (m, 6H, 3H from minor); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.0, 153.0, 136.0, 128.6, 128.0, 126.6, 82.5, 80.2, 79.3, 62.3, 62.2, 56.4, 24.4, 24.1, 21.4, 20.3, 19.0, 14.0; IR (film) 2937, 2239, 1745, 1715, 1233 cm^{-1}; LRMS (EI): *m/z* 342 (M+); HRMS (EI) calcd for $[C_{20}H_{22}O_5]^+$: *m/z*, 342.1467 found 342.1467.

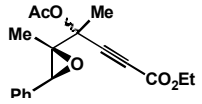


Table 1, (S6): Dense liquid; R_F 0.53 (2:1 hexanes-ethyl acetate), diastereomeric ratio 2.2:1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37-7.27 (m, 10H, 5H from minor), 4.65 (s, 1H), 4.35 (s, 1H minor), 4.23 (q, *J* = 7 Hz, 4H, 2H from minor), 2.11 (s, 3H minor), 2.09 (s, 3H), 1.84 (s, 3H), 1.79 (s, 3H), 1.29 (t, *J* = 7 Hz, 6H, 3H from minor), 1.18 (s, 3H minor), 1.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.7, 152.9, 135.1, 128.0, 127.8, 126.3, 83.4, 78.1, 75.7, 63.8, 63.3, 62.2, 23.0, 21.2, 13.9, 11.2; IR (film) 2984, 2238, 1750, 1715, 1226 cm^{-1}; LRMS (EI): *m/z* 316 (M); HRMS (EI) calcd for $[C_{18}H_{20}O_5]^+$: *m/z*, 316.1389 found 316.1381.

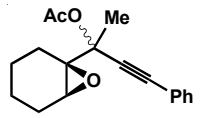


Table 1, (S7): Dense liquid; R_F 0.34 (4:1 hexanes-ethyl acetate), diastereomeric ratio 2.8:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46-7.41 (m, 4H, 2H from minor), 7.33-7.27 (m, 6H, 3H from minor), 3.74 (br s, 1H), 3.54 (br s, 1H minor), 2.12 (s, 3H), 2.11 (s, 3H minor), 2.12 (s, 3H), 2.11 (s, 3H minor), 2.11-1.87 (m, 8H, 4H from minor), 1.76 (s, 3H), 1.68-1.31 (m, 8H, 4H from minor), 1.64 (s, 3H minor); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.1, 132.0, 128.7, 128.3, 122.5, 86.8, 85.9, 61.3, 58.9, 56.1, 24.6, 23.5, 22.6, 21.9, 20.8, 19.2; IR (film) 2939, 2235, 1747, 1234 cm^{-1}; LRMS (EI): *m/z* 284 (M+); HRMS (EI) calcd for $[C_{18}H_{20}O_3]^+$: *m/z*, 284.1412 found 284.1411.

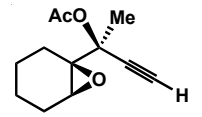


Table 1, (S8) (major isomer)**:** Dense liquid; R_F 0.51 (4:1 hexanes-ethyl acetate), diastereomeric ratio 3:1 (separable). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.59 (br s, 1H), 2.48 (s, 1H), 2.11 (s, 3H),

2.01-1.91 (m, 2H), 1.88-1.76 (m, 2H), 1.59 (s, 3H), 1.43 (m, 1H), 1.41-1.15 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 81.1, 76.6, 74.3, 60.6, 58.7, 24.4, 23.1, 22.4, 21.6, 20.5, 19.0; IR (film) 2940, 2116, 1749, 1238 cm^{-1}; LRMS (EI): *m/z* 208 (M); HRMS (EI) calcd for $[C_{12}H_{16}O_3]^+$: *m/z*, 208.1177 found 208.1174.

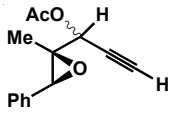


Table 1, (S9): Dense liquid; R_F 0.52 (4:1 hexane-ethyl acetate), diastereomeric ratio 5.6:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.28 (m, 10H, 5H from minor), 5.45 (d, *J* = 2 Hz, 1H), 5.27 (d, *J* = 2 Hz, 1H minor), 4.23 (s, 1H), 4.14 (s, 1H minor), 2.59 (d, *J* = 2.4 Hz, 1H), 2.57 (d, *J* = 2.4 Hz, 1H minor), 2.17 (s, 3H minor), 2.16 (s, 3H), 1.23 (s, 3H minor), 1.20 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 134.7, 128.1, 127.8, 126.4, 77.8, 75.4, 66.4, 62.3, 61.9, 20.7, 12.4; IR (film) 2980, 2126, 1747, 1225 cm^{-1}; LRMS (EI): *m/z* 230 (M); HRMS (EI) calcd for $[C_{14}H_{16}O_3]^+$: *m/z*, 230.1021 found 230.1023.

General Procedure for $PtCl_2$-Catalyzed Tandem Epoxide Cleavage/Pentannulation of Propargylic Esters: A flame-dried 25 mL Schlenk flask equipped with a Teflon screw-top cap was charged with propargylic ester (0.5 mmol) and $PtCl_2$ (0.05 mmol) in anhydrous toluene (0.2 M). The mixture was flushed with nitrogen by sparging over 1 min and capped tightly. The flask was placed in an oil bath which was heated to 100 °C (ca. 20 min) and held at this temperature for 3 h. At the completion of the reaction (determined by TLC analysis), the solvent was removed by evaporation under reduced pressure and the concentrate was purified by flash chromatography.

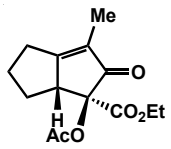


Table 1, P1: The reaction mixture was heated at 100 °C for 3 h, then cooled to room temperature and the solvent was removed by evaporation under reduced pressure. The concentrate was purified by flash chromatography (7:1 hexanes-ethyl acetate) to provide the desired product as a faint yellow oil in 70% yield as a single diastereomer. R_F 0.18 (4:1 hexanes-ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.16 (m, 2H), 3.12 (m, 1H), 2.55 (m, 2H), 2.17 (s, 3H), 2.13-1.91 (m, 4H), 1.79-1.71 (m, 1H), 1.77 (s, 3H), 1.20, (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.0, 181.0, 169.9, 165.3, 129.9, 86.7, 61.9, 54.9, 26.1, 25.8, 24.9, 21.0, 14.0, 9.0; IR (film) 2982, 1738, 1726, 1714, 1234 cm^{-1}; LRMS (EI): *m/z* 266 (M); HRMS (EI) calcd for $[C_{14}H_{18}O_5]$+: *m/z*, 266.1232 found 266.1228.

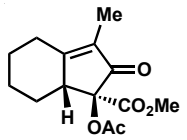


Table 1, P2: The reaction mixture was heated at 100 °C for 3 h, then cooled to room temperature and the solvent was removed by evaporation under reduced pressure. The concentrate was purified by flash chromatography (7:1 hexanes-ethyl acetate) to provide the desired product as a faint yellow liquid in 75% yield as a single diastereomer. R_F 0.23 (4:1 hexanes-ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.71 (s, 3H), 2.94-2.88 (m, 2H), 2.17-2.10 (m, 2H), 2.14 (s, 3H), 1.98-1.95 (m, 1H), 1.90-1.87 (m, 1H), 1.75 (t, *J* = 1.6 Hz, 3H), 1.44-1.21 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.6, 171.8, 169.6, 166.6, 131.6, 85.3, 52.4, 50.1, 28.1, 27.6, 25.3, 24.9, 21.0, 8.0; IR (film) 2941, 2862, 1745, 1716, 1242 cm^{-1}; LRMS (EI): *m/z* 266 (M); HRMS (EI) calcd for $[C_{14}H_{18}O_5]^+$: *m/z*, 266.1232 found 266.1229.

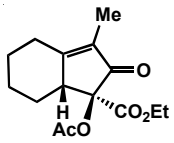


Table 1, P3: The reaction mixture was heated at 100 °C for 3 h, then cooled to room temperature and the solvent was removed by evaporation by evaporation under reduced pressure. The concentrate was purified by flash chromatography (7:1 hexanes:Ethyl acetate) to provide the desired product as a dense yellow liquid in 72% yield as a single diastereomer. R_F 0.28 (2:1 hexanes:Ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.13 (q, *J* = 7 Hz, 2H), 2.90-2.84 (m, 2H), 2.13-2.09 (m, 2H), 2.09 (s, 3H), 1.96-1.90 (m, 1H), 1.85-1.81 (m, 1H), 1.70 (t, *J* = 2 Hz, 3H), 1.43-1.31 (m, 3H), 1.18 (t, *J* = 7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.6, 171.7, 169.5, 165.9, 131.5, 85.1, 61.7, 50.0, 28.0, 27.5, 25.2, 24.8, 20.9, 13.9, 7.8; IR (film) 2940, 1747, 1716, 1650, 1245 cm^{-1}; LRMS *m/z* 280 (M); HRMS (EI) calcd for $[C_{15}H_{20}O_5]^+$: *m/z*, 280.1389 found 280.1387.

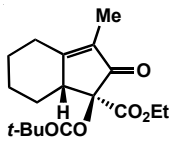


Table 1, P4: The reaction mixture was heated at 100 °C for 10 h, then cooled to room temperature and the solvent was removed by evaporation under reduced pressure. The concentrate was purified by flash chromatography (7:1 hexanes-ethyl acetate) to provide the desired product as a yellow oil in 58% yield as a single diastereomer. R_F 0.28 (4:1 hexanes-ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.19 (m, 2H), 2.92-2.85 (m, 2H), 2.19-2.11 (m, 2H), 1.98-1.89 (m, 2H), 1.76 (s, 3H), 1.50-1.38 (m, 3H), 1.25 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.7, 177.3, 171.7, 166.2, 131.6, 84.8, 61.7, 50.2, 39.0, 28.1, 27.6, 27.0, 25.4, 25.1, 14.1, 8.0; IR (film) 2939, 1760, 1740, 1650, 1243 cm^{-1}; LRMS (EI): *m/z* 322 (M+); HRMS (EI) calcd for $[C_{18}H_{26}O_5]^+$: *m/z*, 322.1780 found 322.1786.

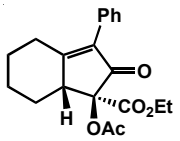


Table 1, P5: The reaction mixture was heated at 100 °C for 6 h, then cooled to room temperature and the solvent was removed by evaporation under reduced pressure. The concentrate was purified by flash chromatography (7:1 hexanes-ethyl acetate) to provide the desired product as a faint yellow liquid in 73% yield as a single diastereomer. R_F 0.51 (2:1 hexanes-ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42-7.38 (m, 2H), 7.35-7.30 (m, 3H), 4.30-4.12 (m, 2H), 3.18-3.15 (m, 1H), 3.09 (dt, *J* = 15, 2 Hz, 1H), 2.33-2.25 (m, 2H), 2.19 (s, 3H), 1.98-1.93 (m, 2H), 1.56-1.48 (m, 2H), 1.46-1.36 (m, 1H), 1.27 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.7, 172.4, 169.6, 166.0, 135.9, 130.6, 129.1, 128.3, 128.0, 85.8, 61.9, 49.6, 28.9, 27.8, 25.7, 24.9, 21.1, 14.1; IR (film) 2940, 1747, 1716, 1635, 1244 cm^{-1}; LRMS (EI): *m/z* 342 (M+); HRMS (EI) calcd for $[C_{20}H_{22}O_5]^+$: *m/z*, 342.1467 found 342.1464.

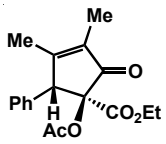


Table 1, P6: The reaction mixture was heated at 100 °C for 3 h, then cooled to room temperature and the solvent was removed by evaporation under reduced pressure. The concentrate was purified by flash chromatography (7:1 hexanes-ethyl acetate) to provide the desired product as a faint yellow liquid in 61% yield as a single diastereomer. R_F 0.18 (2:1 hexanes-ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30-7.26 (m, 3H), 7.10-7.08 (m, 2H), 4.34 (s, 1H), 3.72-3.66 (m, 1H), 3.62-3.56 (m, 1H), 2.18 (s, 3H), 1.95 (s, 3H), 1.89 (s, 3H), 0.86 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.4, 169.4, 165.7, 165.6, 137.6, 135.1, 129.8, 128.3, 127.9, 87.1, 61.6, 58.4, 21.1, 15.6, 13.4, 8.7; IR (film) 2983, 1746, 1716, 1648, 1232 cm^{-1}; LRMS (EI): *m/z* 316 (M); HRMS (EI) calcd for $[C_{18}H_{20}O_5]^+$: *m/z*, 316.1389 found 316.1380.

SM Scheme 8

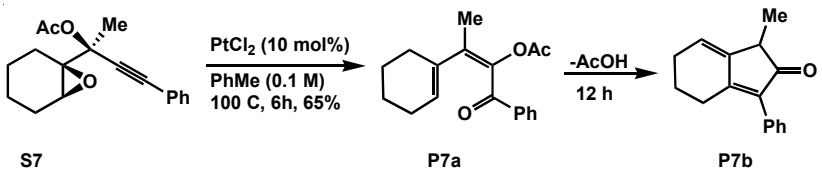


Table 1, P7a: Either compound **S7**/**P7a** was heated at 100 °C in the presence of 10 mol % $PtCl_2$ in dry toluene for 12 h, then cooled to room temperature and the solvent was removed by evaporation under reduced pressure. The concentrate was purified by flash chromatography (7:1 hexanes-ethyl acetate) to provide the desired product **P7b** as a faint yellow liquid in 65% yield. R_F 0.33 (4:1 hexanes-ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (m, 2H), 7.41-7.39 (m, 2H), 7.32-7.29 (m, 1H), 6.07 (t, *J* = 4 Hz, 1H), 2.88 (q, *J* = 7.5 Hz, 1H), 2.83 (m, 2H),

2.35 (m, 2H), 1.83 (m, 2H), 1.29 (d, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.4, 163.2, 141.5, 134.9, 131.5, 129.0, 128.1, 127.5, 125.6, 42.5, 25.7, 25.2, 22.3, 14.6; IR (film) 2930, 1696, 1491, 1297 cm^{-1}; LRMS (EI): *m/z* 224 (M+); HRMS (EI) calcd for $[C_{16}H_{16}O]$+: *m/z*, 224.1201 found 224.1203.

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Table 1, P7b: The compound **S7** was heated at 100 °C for 6 h, then cooled to room temperature and the solvent was removed by evaporation under reduced pressure. The concentrate was purified by flash chromatography (7:1 hexanes-ethyl acetate) to obtain the intermediate **S7a** as a faint yellow liquid in 72% yield as a single isomer. R_F 0.26 (4:1 hexanes-ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73-7.71 (m, 2H), 7.40-7.38 (m, 1H), 7.34-7.31 (m, 2H), 5.38 (m, 1H), 2.20 (s, 3H), 1.85 (s, 3H), 1.85-1.81 (m, 2H), 1.56-1.52 (m, 2H), 1.09-1.06 (m, 2H), 0.99 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.7, 169.4, 140.5, 139.9, 139.1, 135.9, 132.6, 131.6, 128.2, 128.1, 26.3, 25.6, 21.8, 21.1, 20.5, 15.1; IR (film) 2936, 1745, 1715, 1645, 1233 cm^{-1}; LRMS (EI): *m/z* 224 (M+); HRMS (EI) calcd for $[C_{16}H_{16}O]$+: *m/z*, 224.1212 found 224.1214.

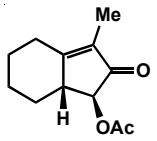

Table 1, P8: The reaction mixture was heated at 100 °C for 6 h with $PtCl_2$ (10 mol %), then cooled to room temperature and the solvent was removed by evaporation under reduced pressure. The concentrate was purified by flash chromatography (7:1 hexanes-ethyl acetate) to provide the desired product as a whie solid in 75% yield as a single diastereomer. mp 72 °C, R_F 0.23 (4:1 hexanes-ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.76 (br, 1H), 2.87 (dt, J = 14.4, 2 Hz, 1H), 2.49-2.46 (m, 1H), 2.40-2.35 (m, 1H), 2.16-2.06 (m, 1H), 2.12 (s, 3H), 2.03-1.95 (m, 1H), 1.91-1.83 (m, 1H), 1.70 (t, J = 1.6 Hz, 3H), 1.52-1.16 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.5, 172.6, 170.6, 131.9, 77.9, 47.0, 32.4, 28.2, 25.9, 25.0, 20.8, 7.7; IR (film) 2937, 1745, 1715, 1645, 1233 cm^{-1}; LRMS (EI): *m/z*, 208 (M+); HRMS (EI) calcd for $[C_{12}H_{16}O_3$+H]+: *m/z*, 209.1178 found 209.1175.

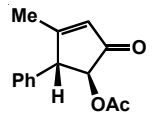

Table 1, P9: The reaction mixture was heated at 100 °C for 6 h, then cooled to room temperature and the solvent was removed by evaporation under reduced pressure. The concentrate was purified by flash chromatography (7:1 hexanes-ethyl acetate) to provide the desired product as an orange oil in 61% yield as a single diastereomer. R_F 0.15 (4:1 hexanes-ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38-7.29 (m, 3H), 7.14 (m, 2H), 6.18 (br, 1H), 5.15 (br, 1H), 3.87 (br, 1H), 2.12 (d, J = 2 Hz, 3H), 1.91 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.8, 176.9, 170.0, 138.2, 129.4, 129.1, 127.8, 127.7, 80.6, 56.3, 20.7, 18.1; IR (film) 2942, 1749, 1717, 1617, 1228 cm^{-1}; LRMS (EI): *m/z*, 170 (M-HOAc+); HRMS (EI) calcd for $[C_{14}H_{14}O_3$-HOAc]+: *m/z*, 170.0746 found 170.0732

[1] For a recent review see: Fürstner, A.; Davies, P. W. *Angew. Chem. Int. Ed.* **2007**, *46*, 3410-3449.
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[13] Entries 2c, 3, and 4b were synthesized and tested by Dr. B.A. Bhanu Prasaad.
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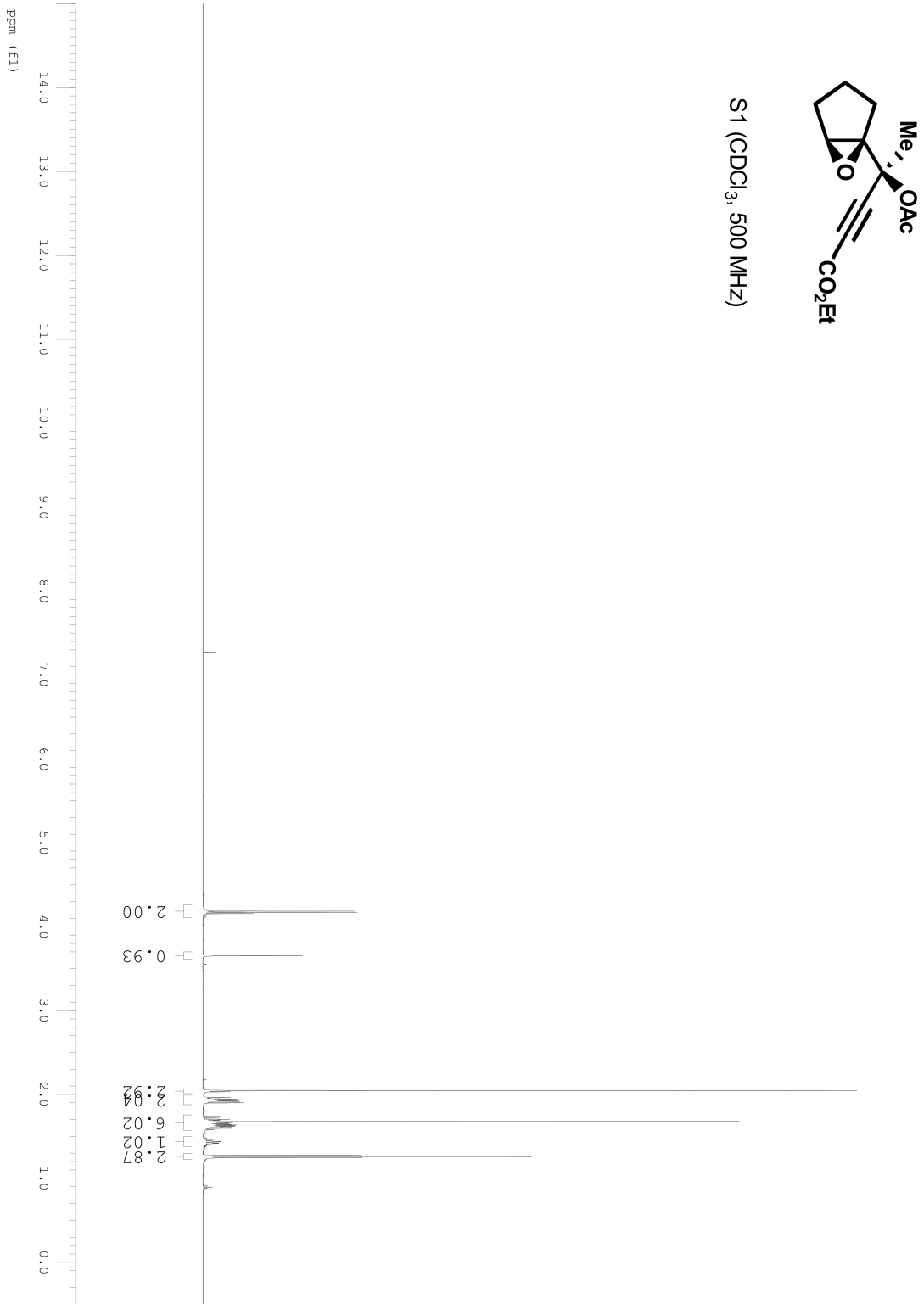
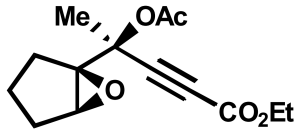
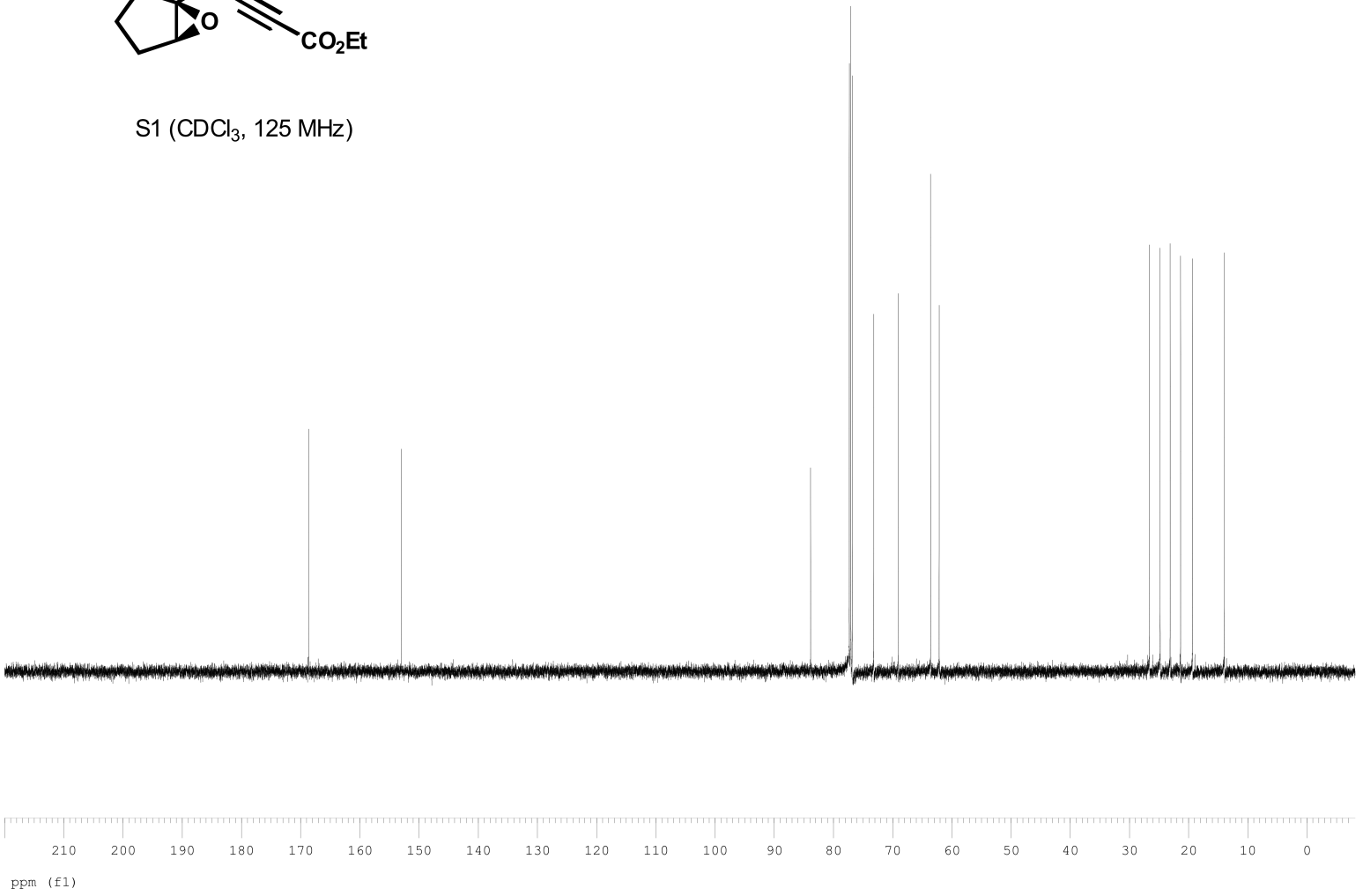
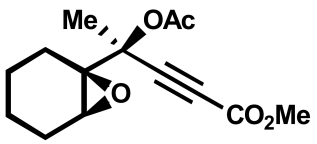
Appendix I: Selected Spectra



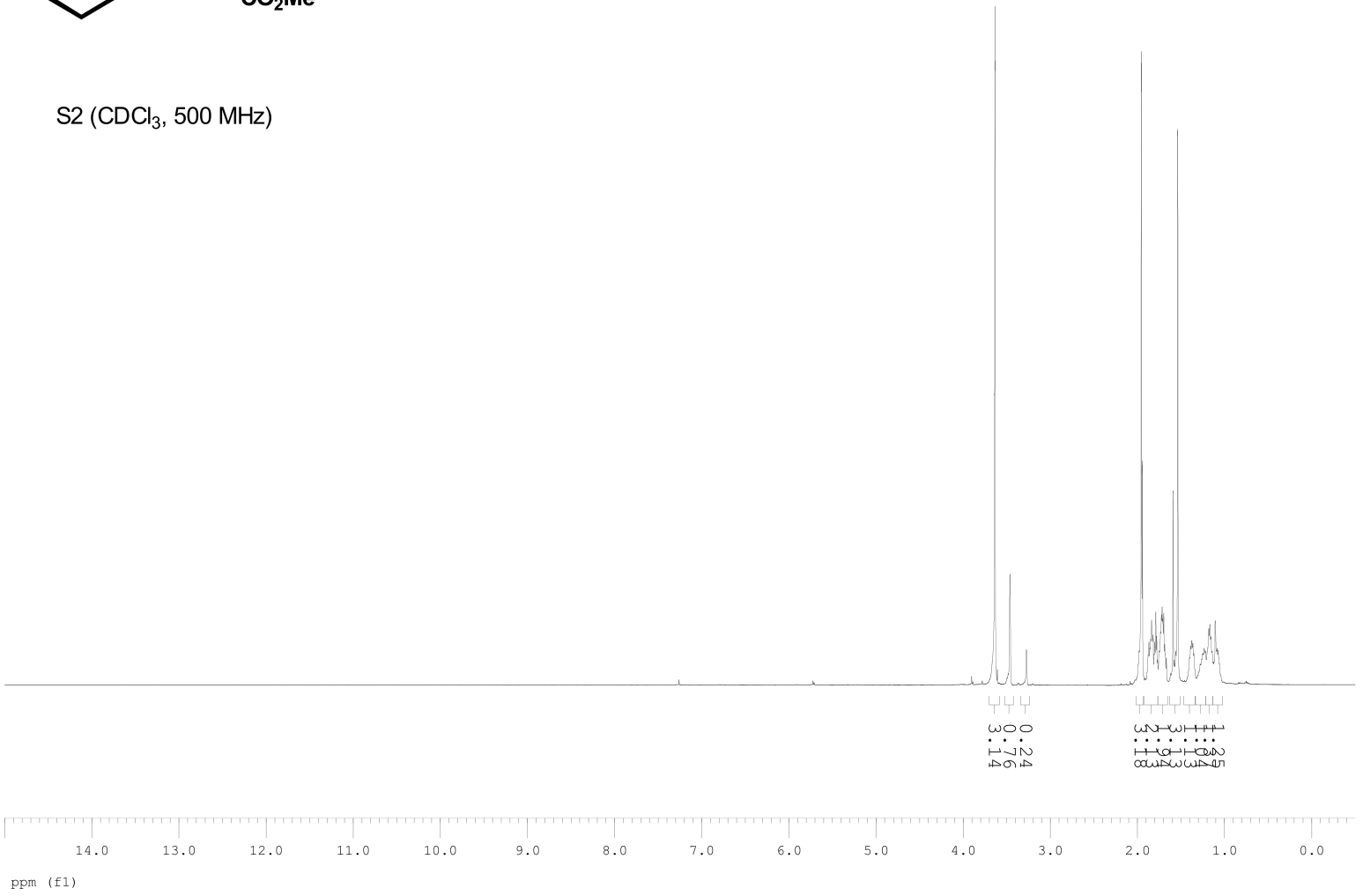


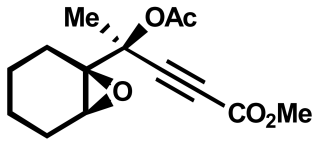
S1 ($CDCl_3$, 125 MHz)





S2 ($CDCl_3$, 500 MHz)





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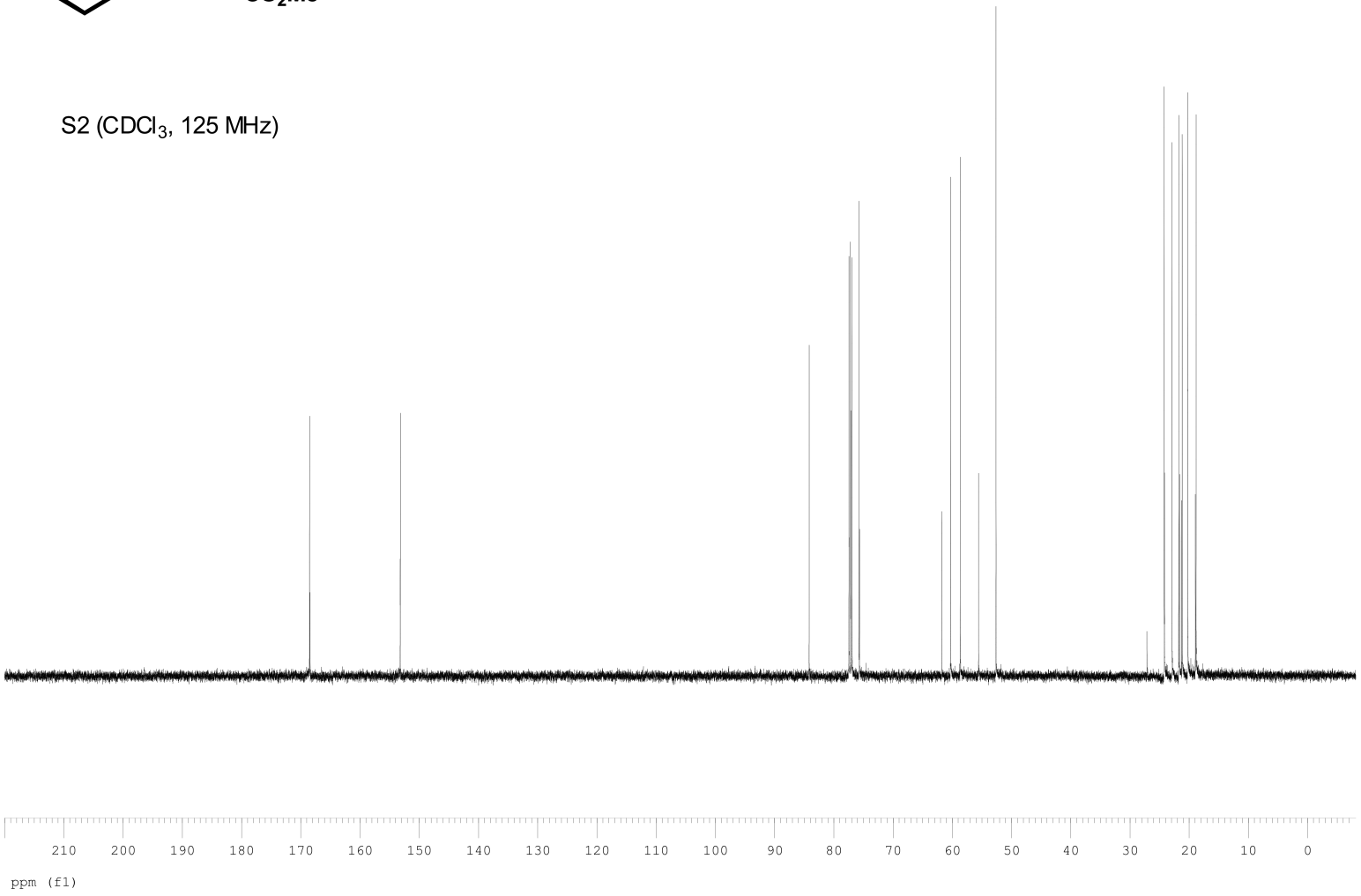
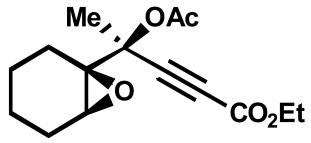
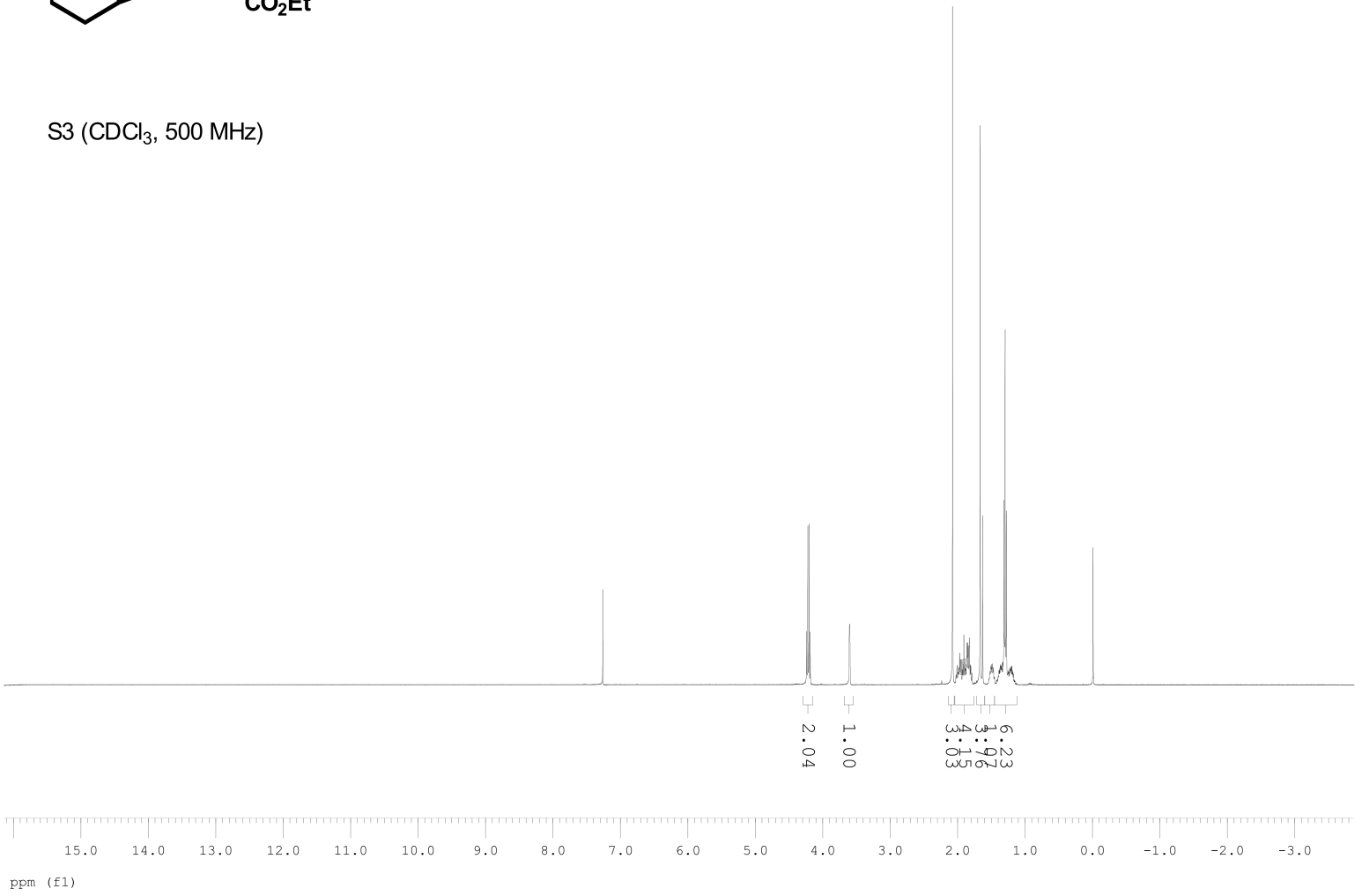
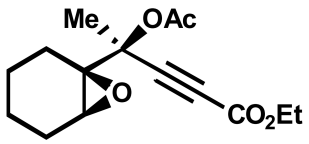


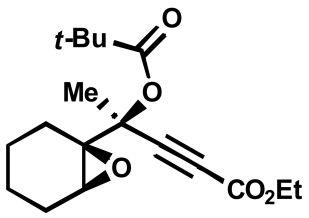


S3 ($CDCl_3$, 500 MHz)

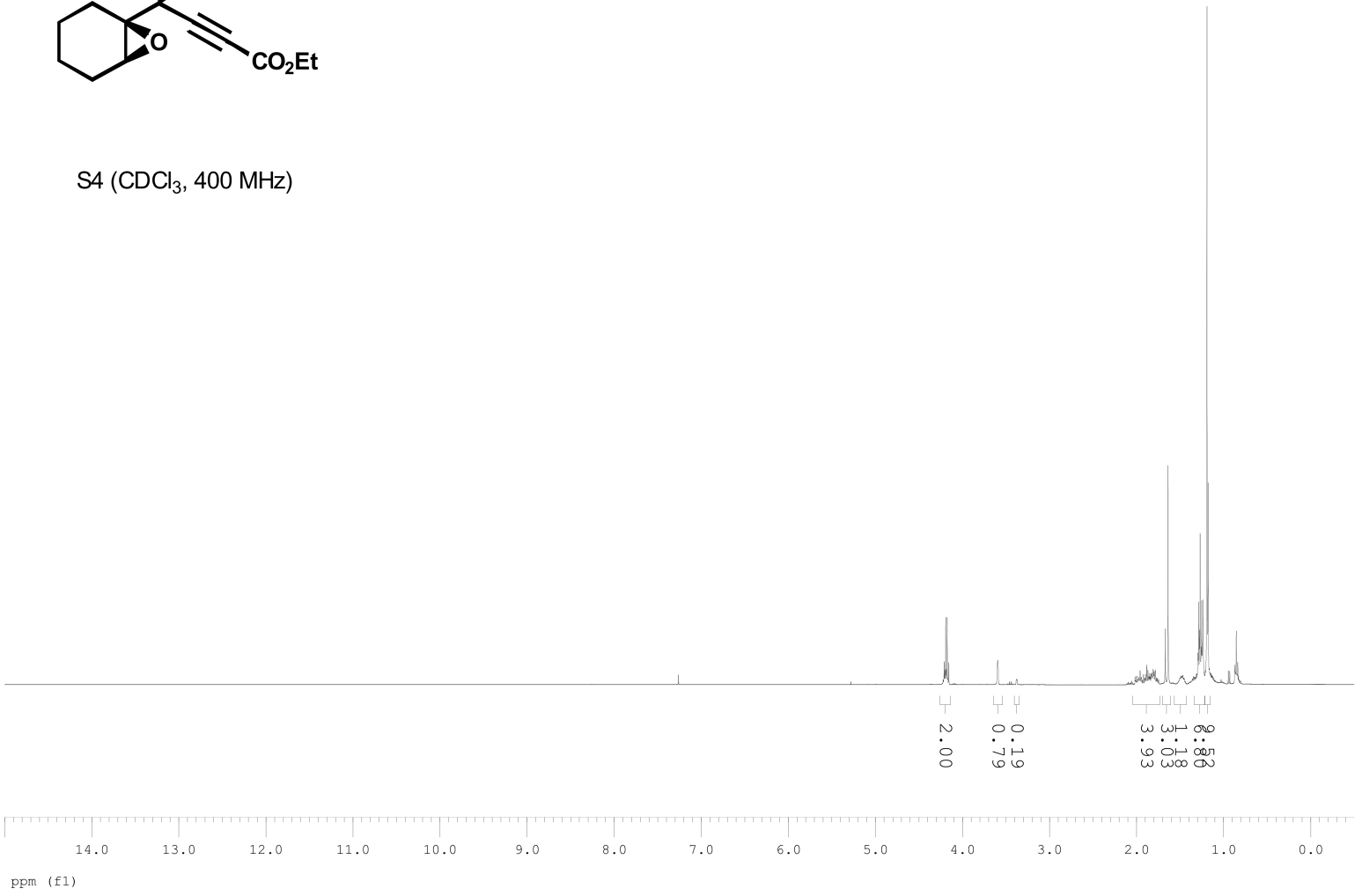


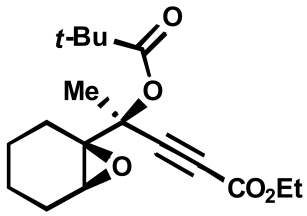


S3 ($CDCl_3$, 125 MHz)



S4 ($CDCl_3$, 400 MHz)





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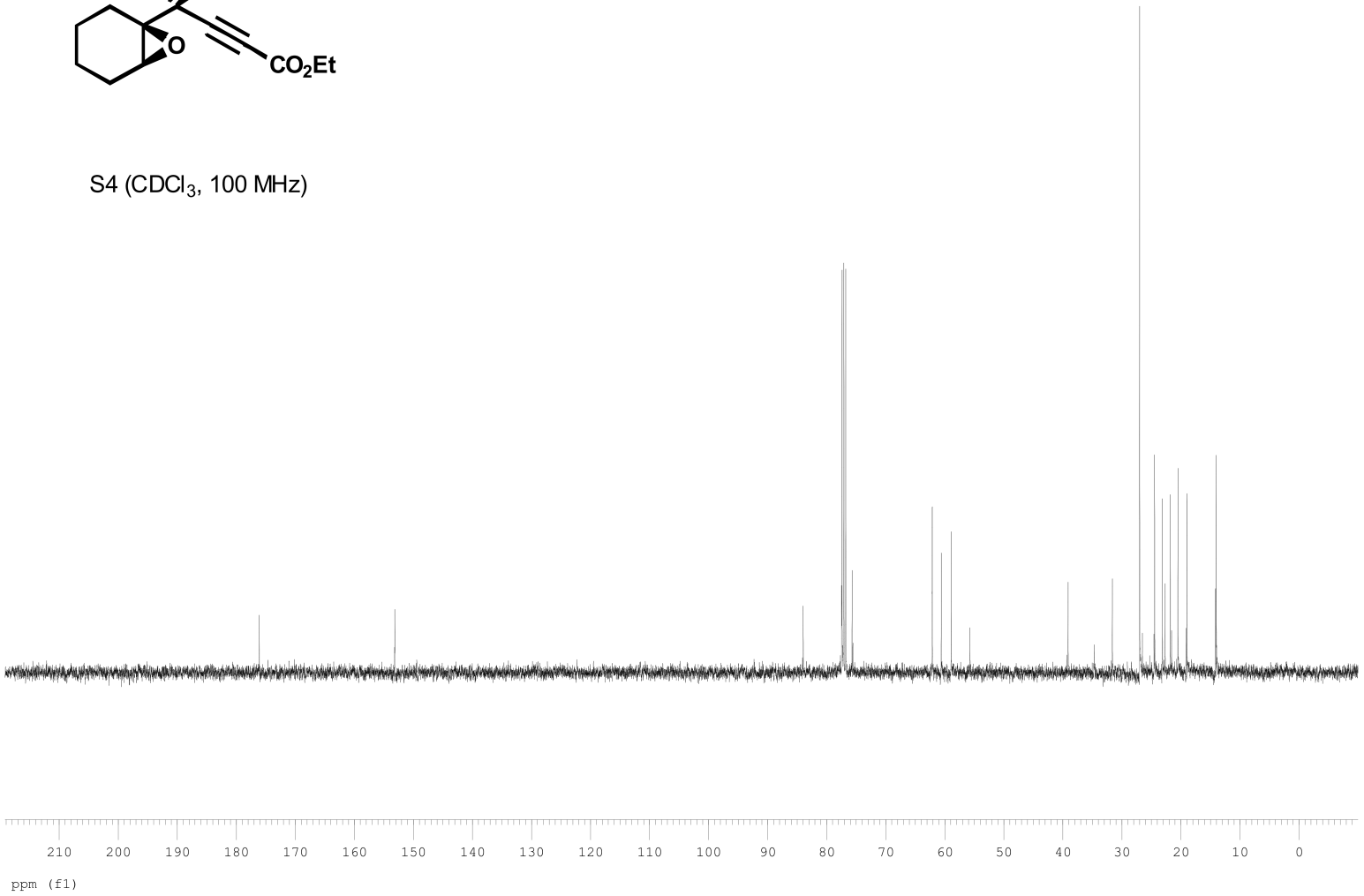
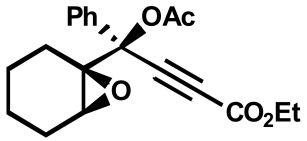
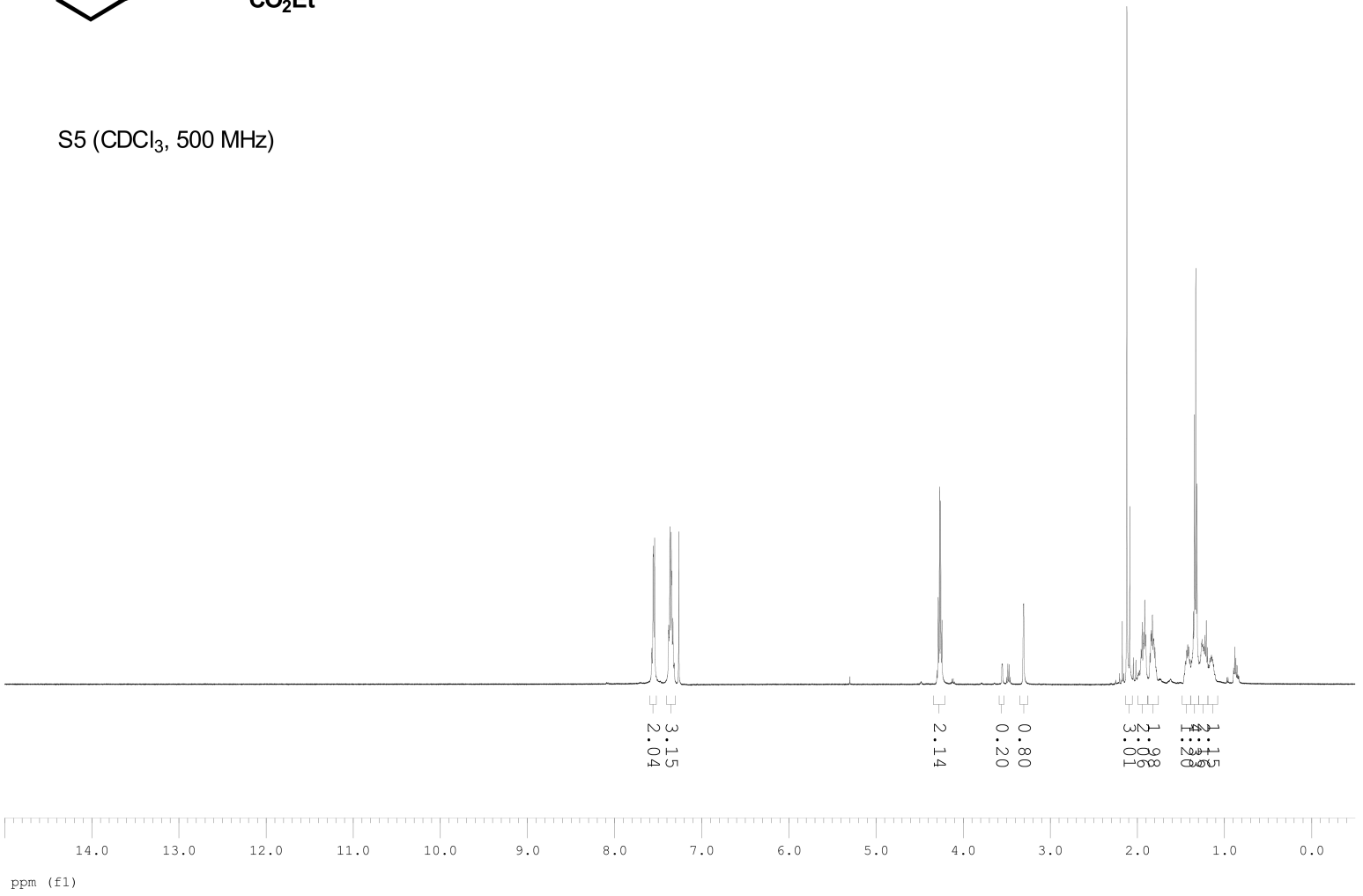
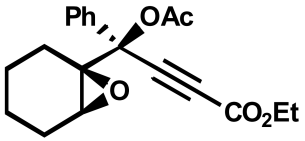


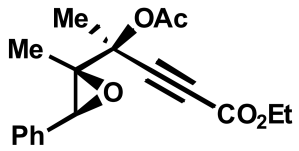


S5 ($CDCl_3$, 500 MHz)

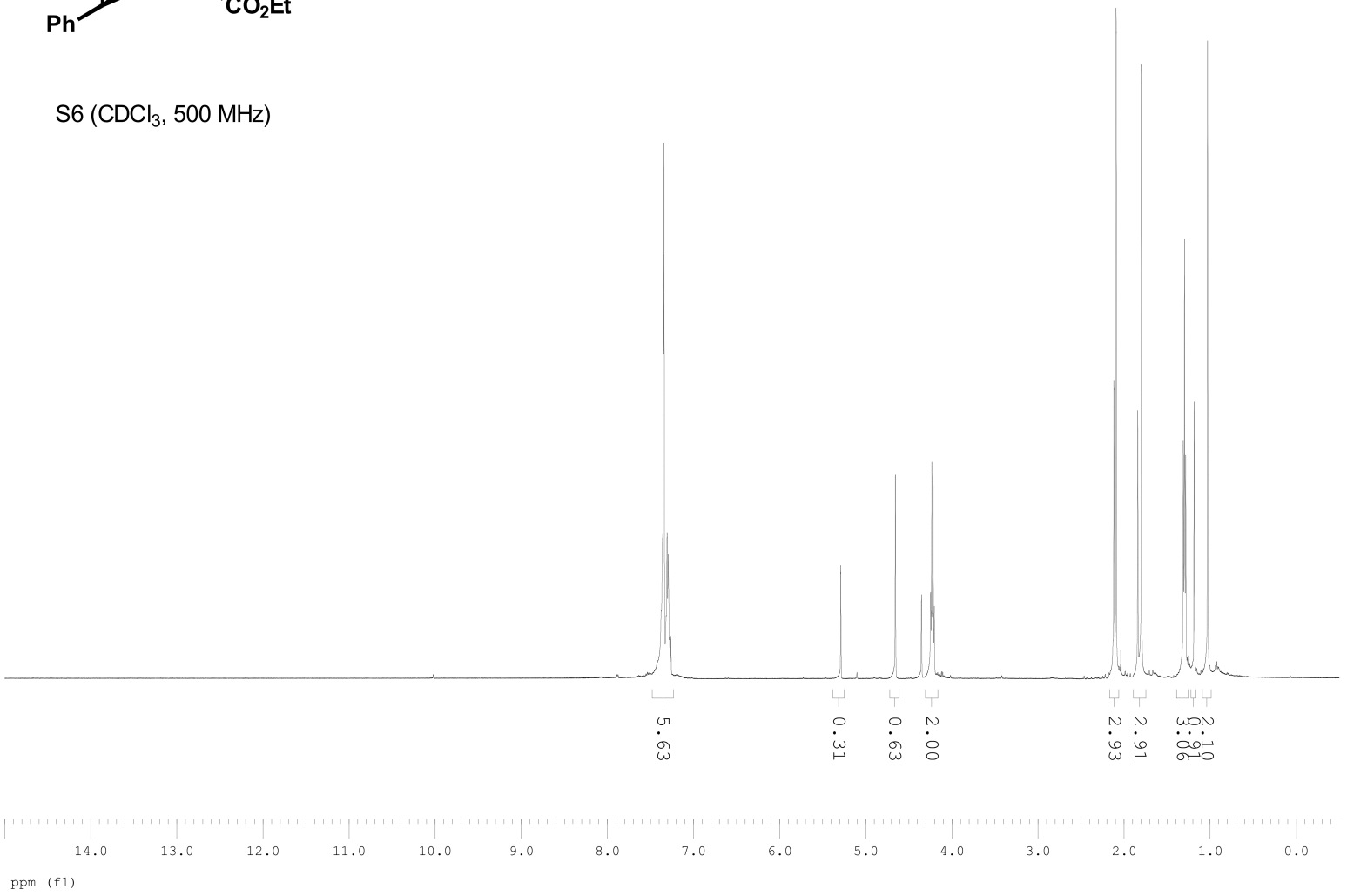


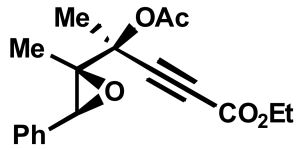


S5 ($CDCl_3$, 125 MHz)

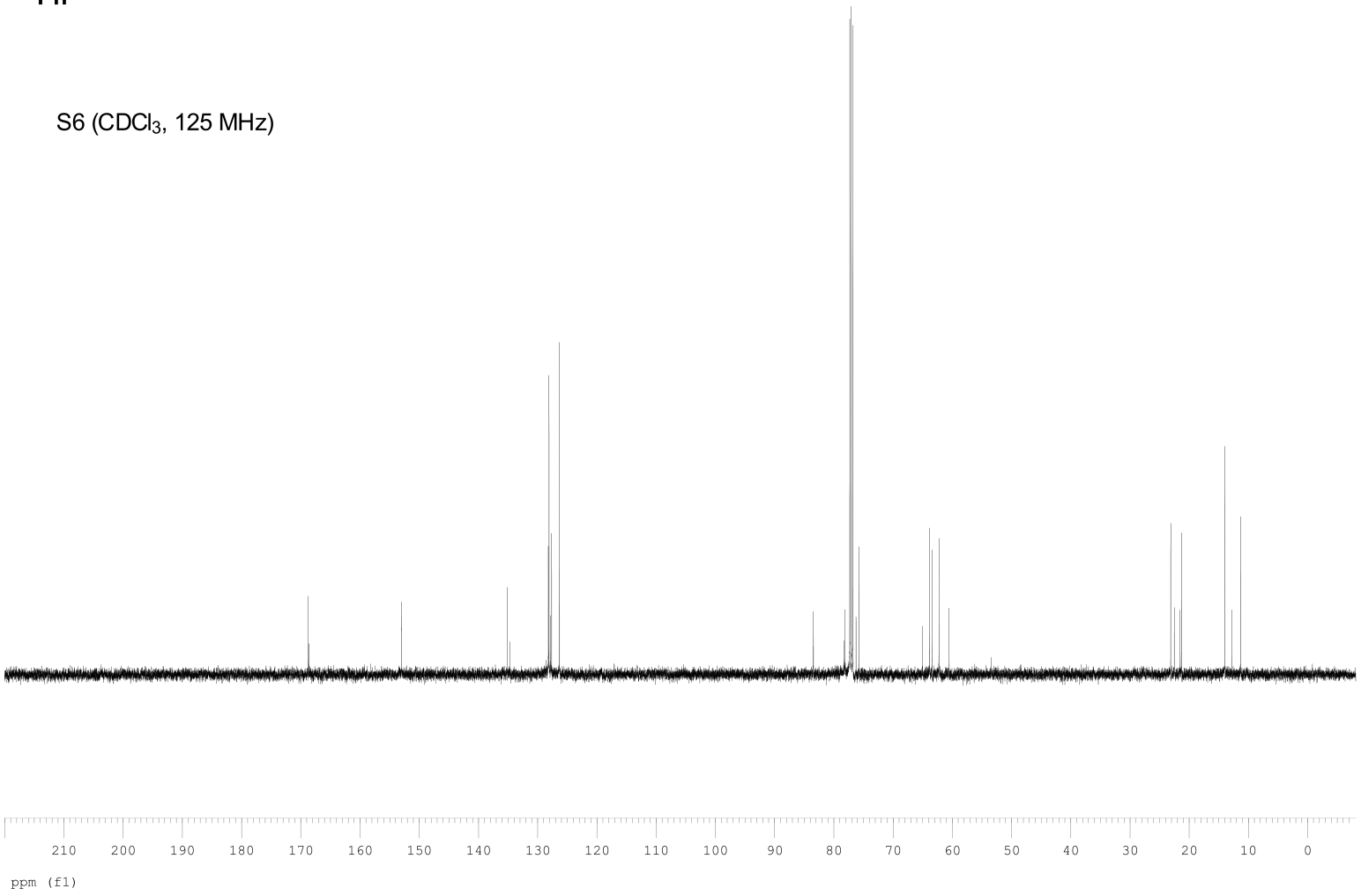


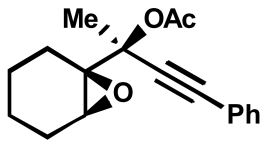
S6 ($CDCl_3$, 500 MHz)



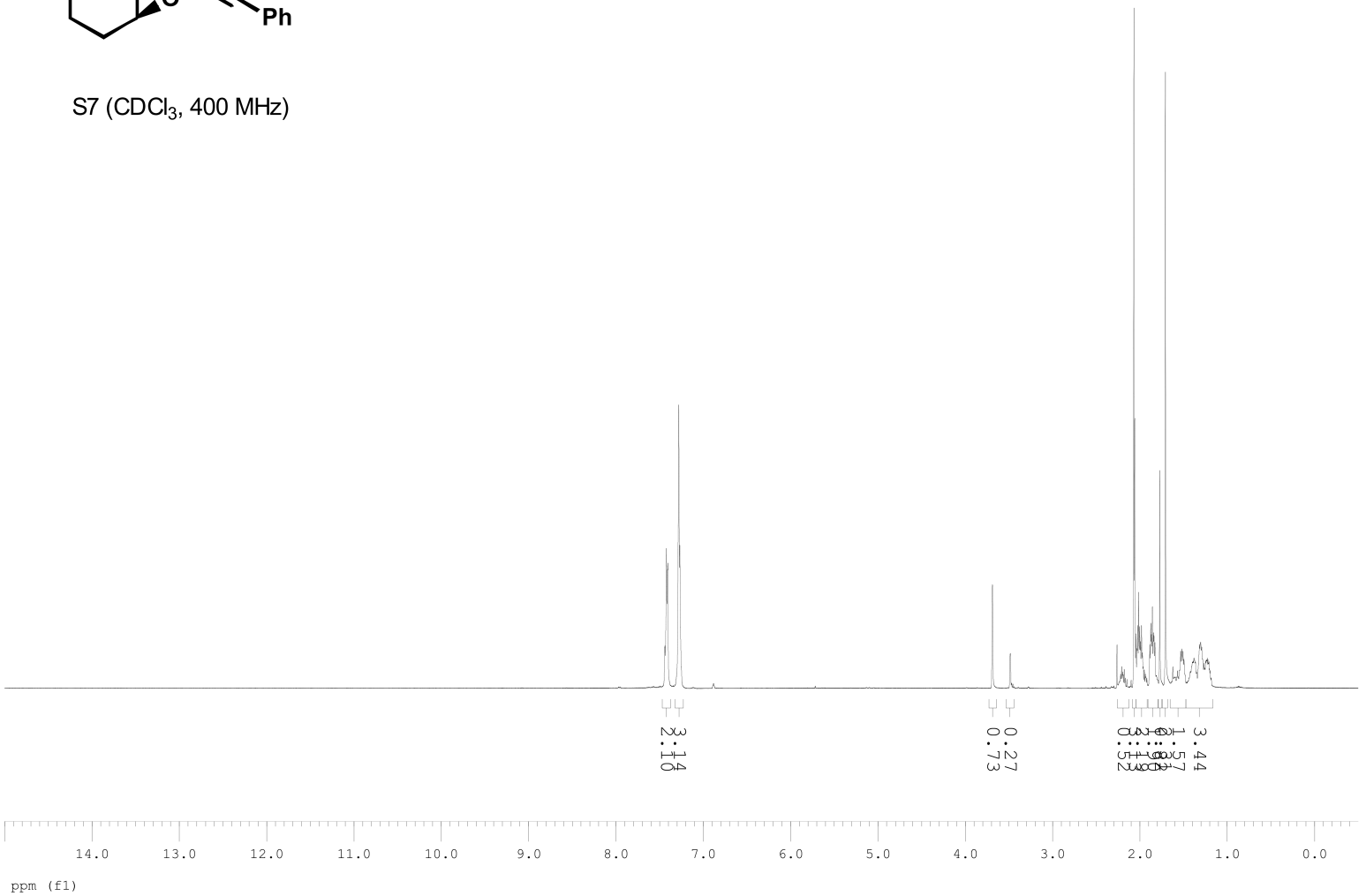


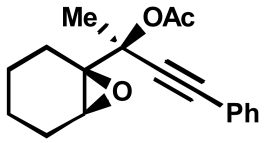
S6 ($CDCl_3$, 125 MHz)



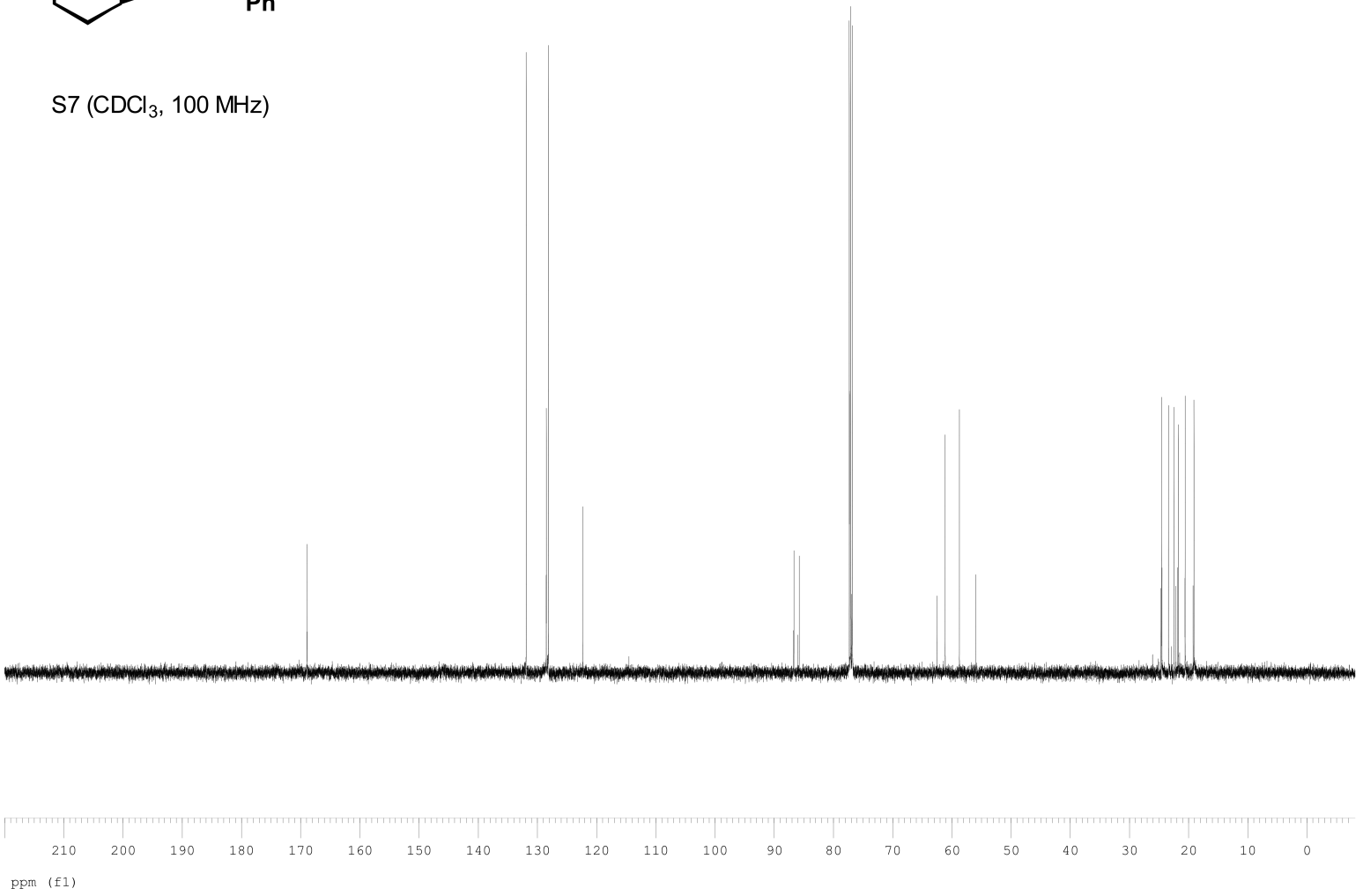


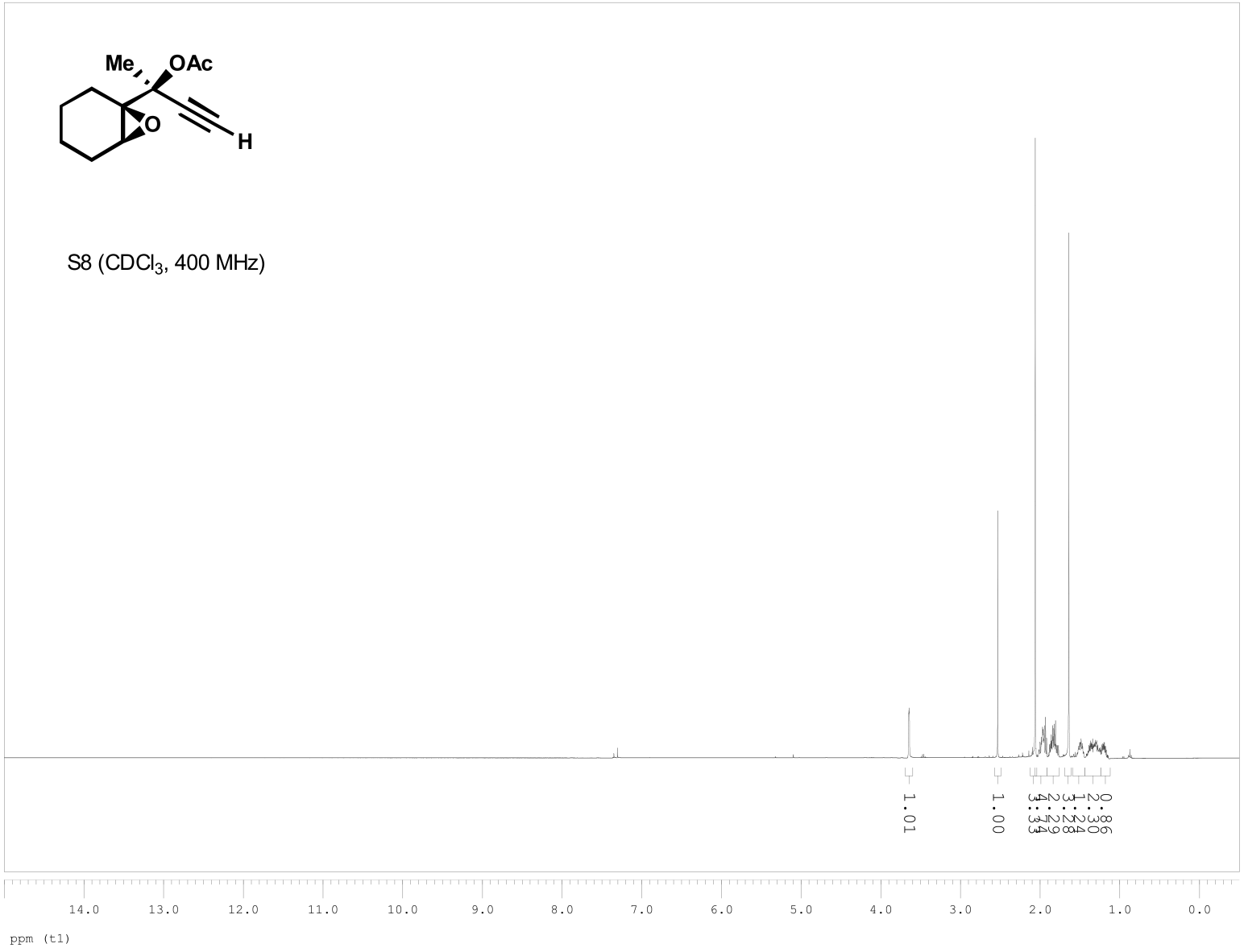
S7 ($CDCl_3$, 400 MHz)

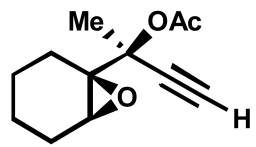




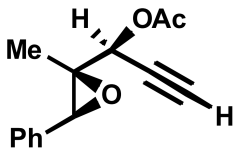
S7 ($CDCl_3$, 100 MHz)



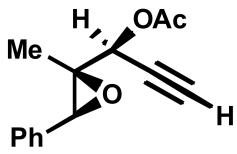

Me
OAc
O
H
S8 (CDCl3, 400 MHz)
1.01
1.00
3.43
2.26
3.24
2.00
0.89
14.0
13.0
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)



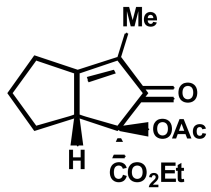
S8 ($CDCl_3$, 100 MHz)



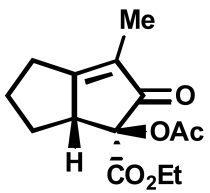
S9 ($CDCl_3$, 500 MHz)



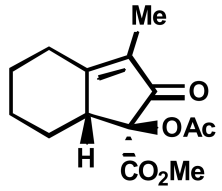
S9 ($CDCl_3$, 125 MHz)



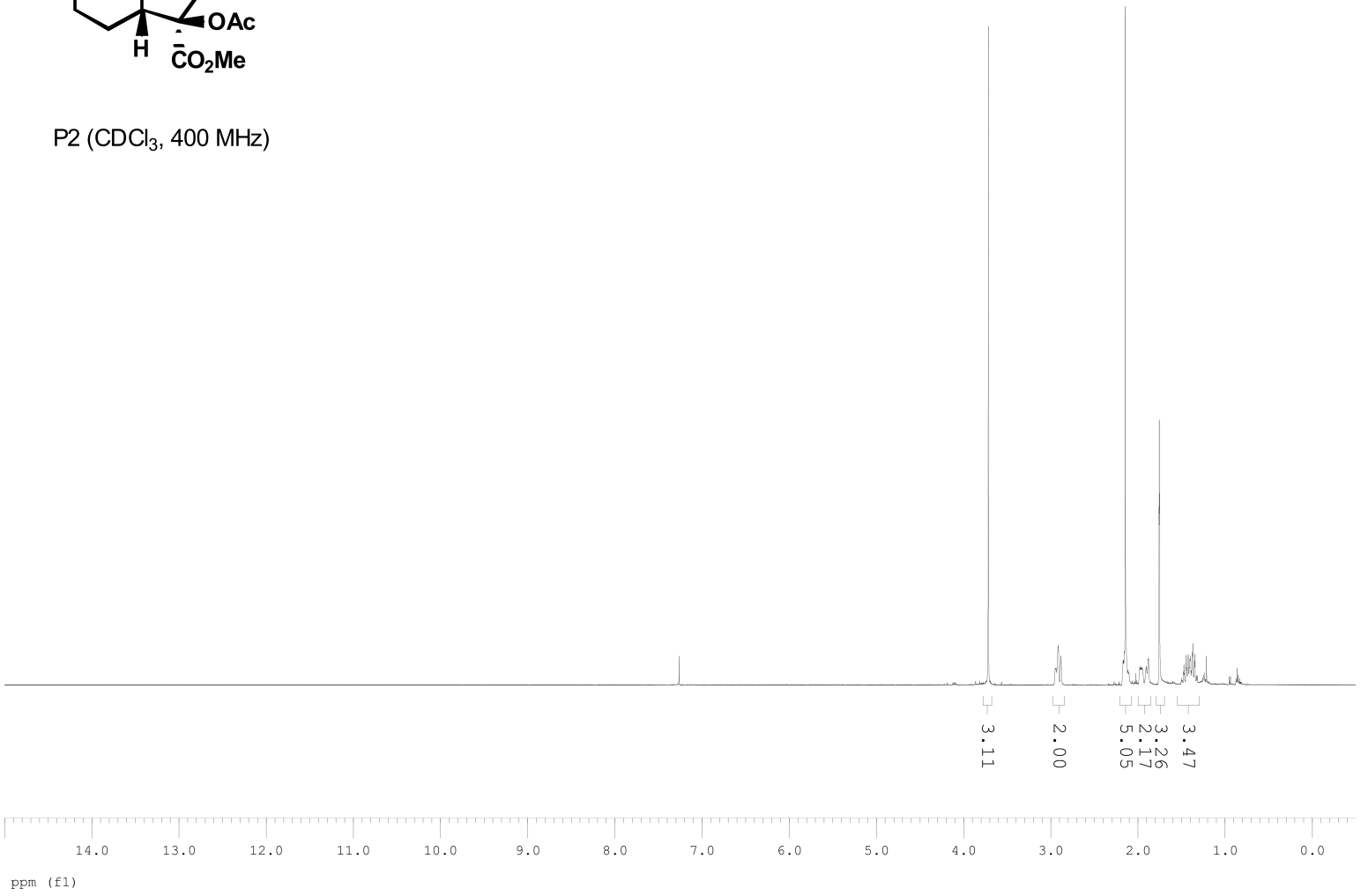
P1 ($CDCl_3$, 400 MHz)

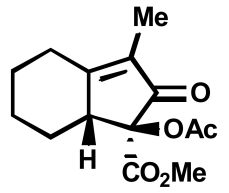


P1 ($CDCl_3$, 100 MHz)

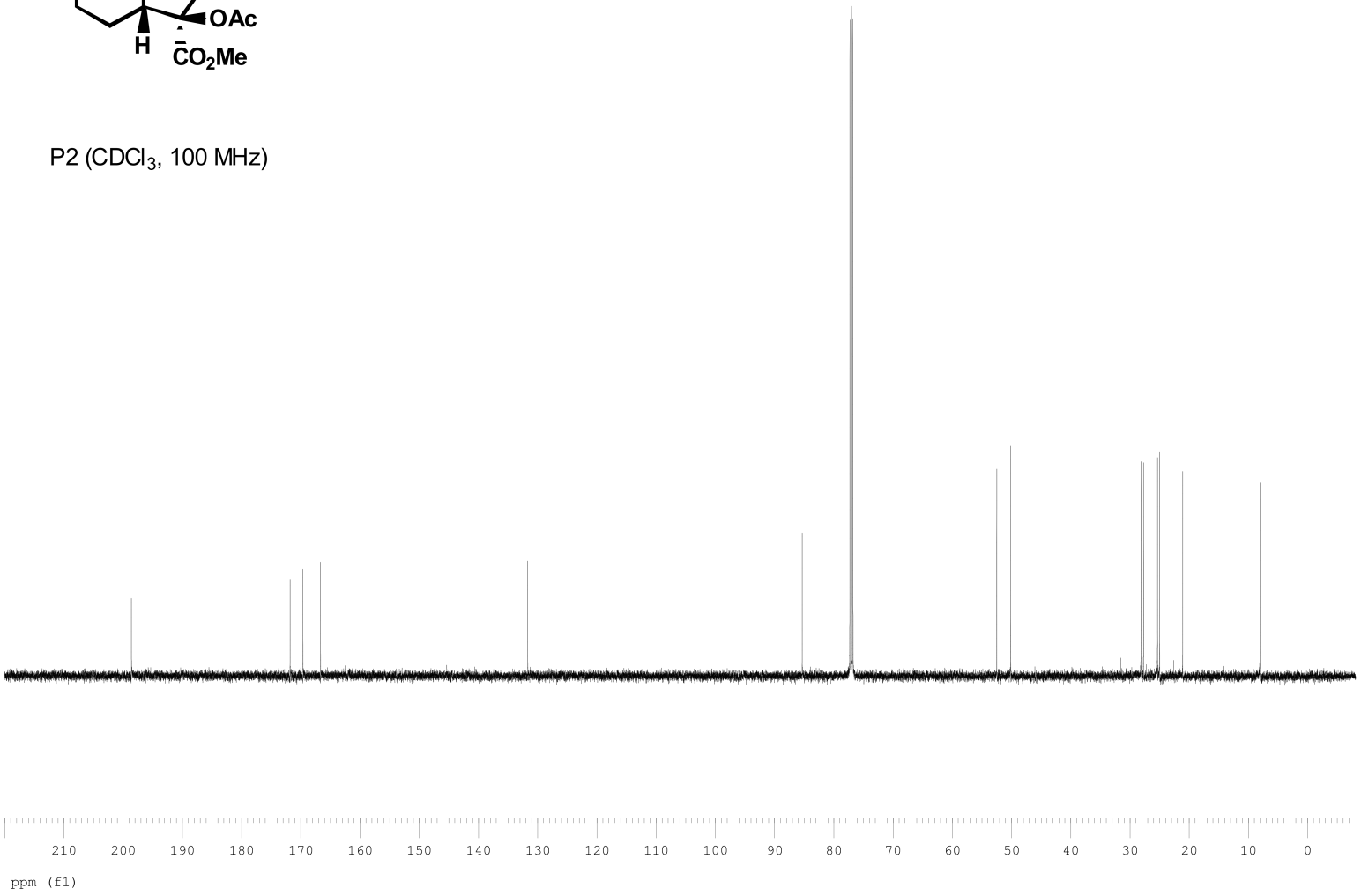


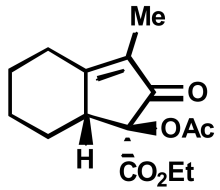
P2 ($CDCl_3$, 400 MHz)



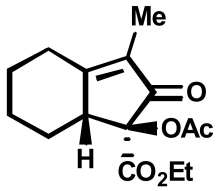


P2 ($CDCl_3$, 100 MHz)

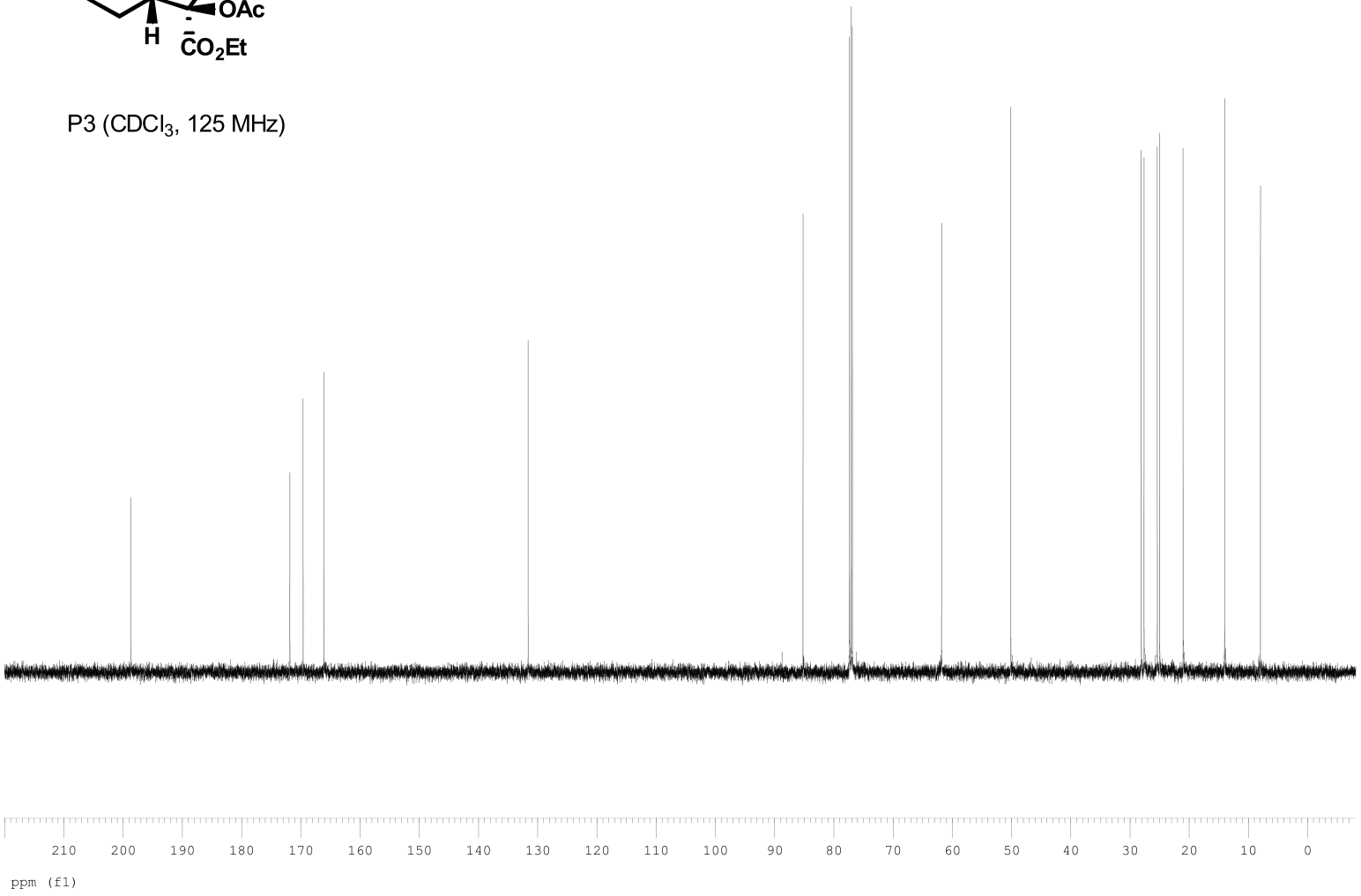


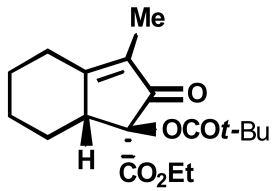


P3 ($CDCl_3$, 500 MHz)

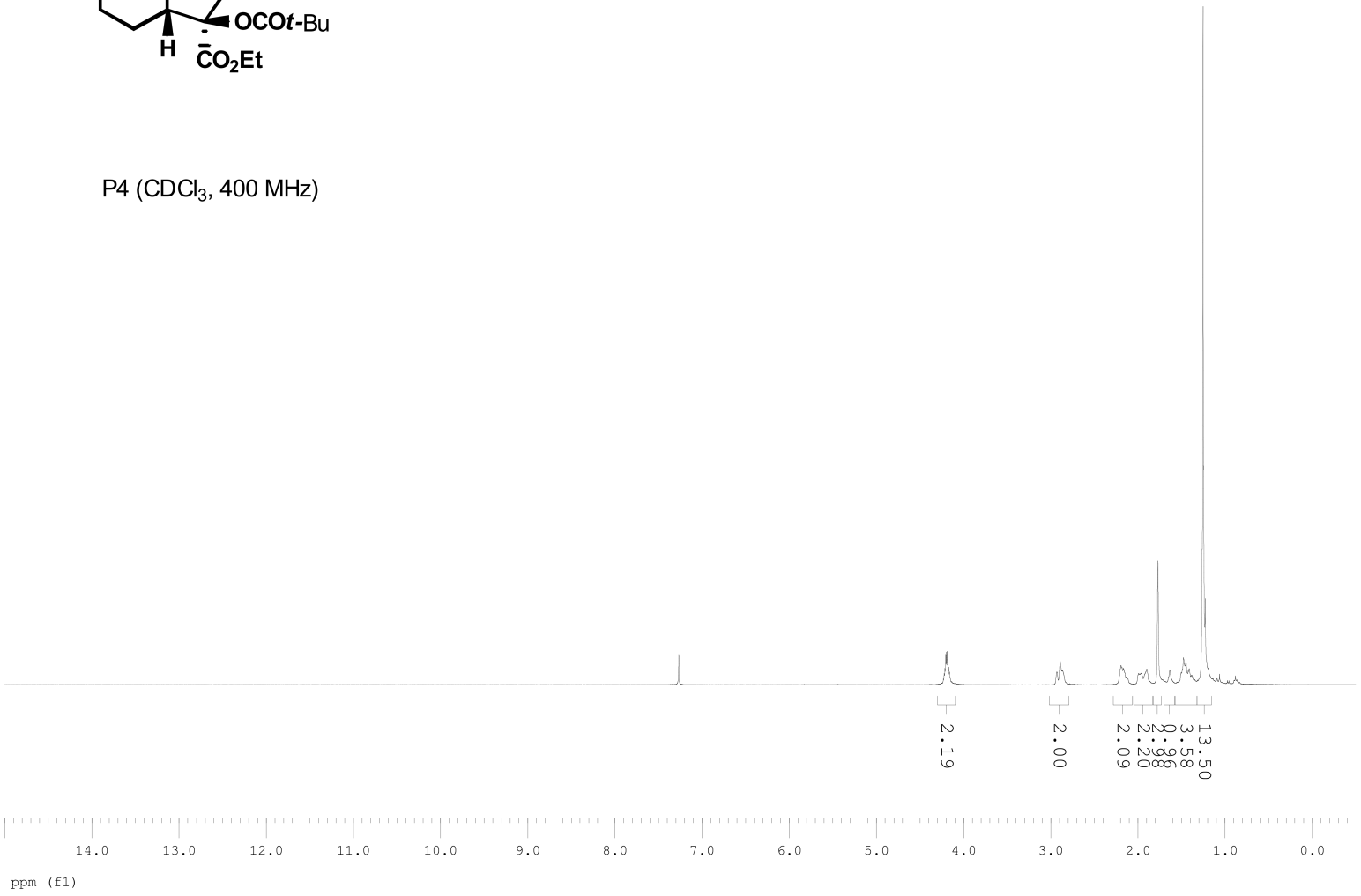


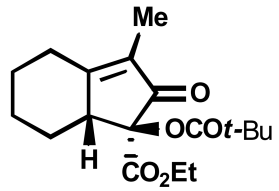
P3 ($CDCl_3$, 125 MHz)



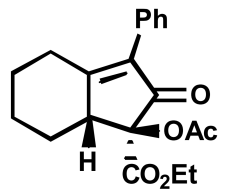


P4 ($CDCl_3$, 400 MHz)

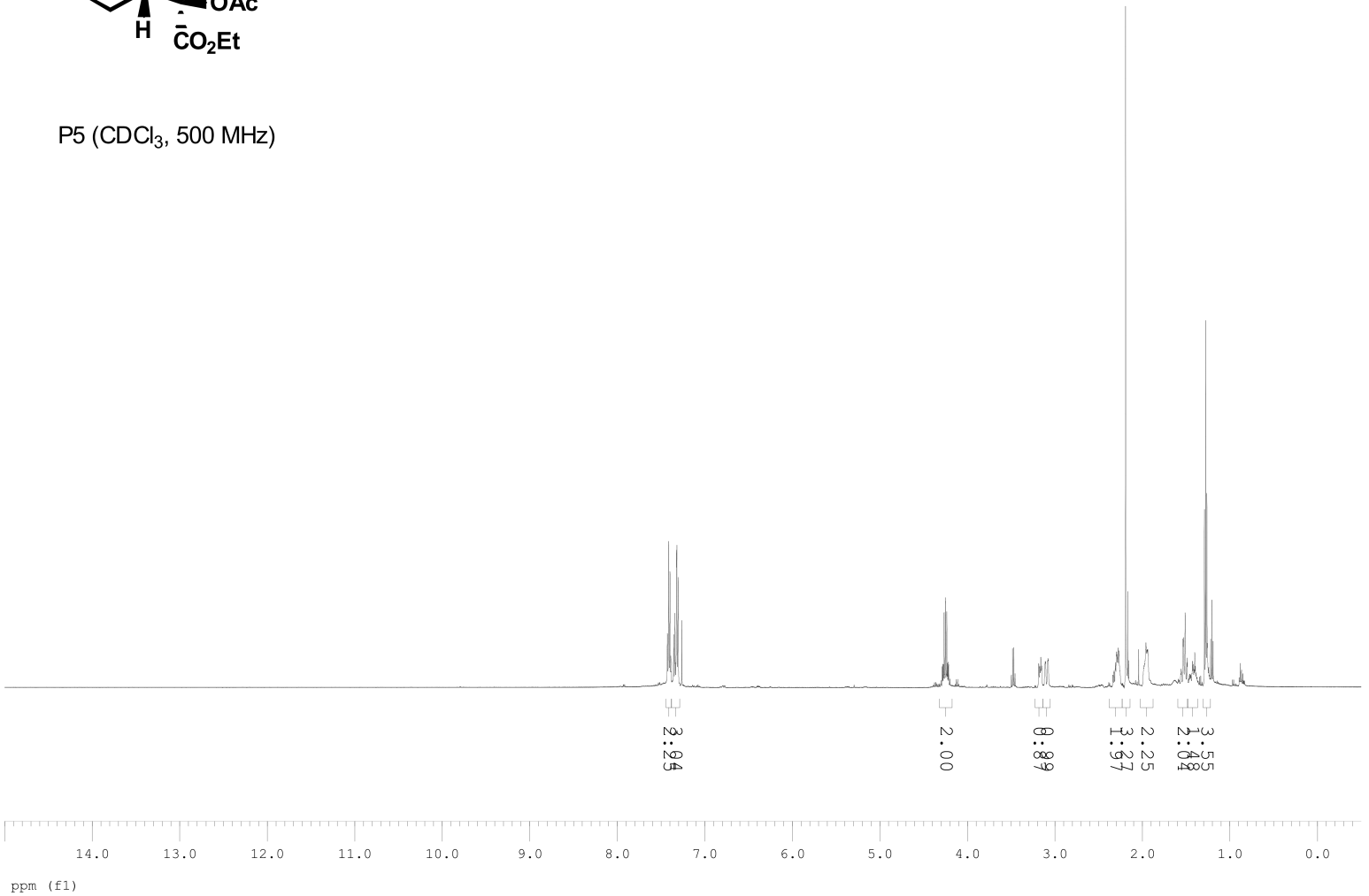


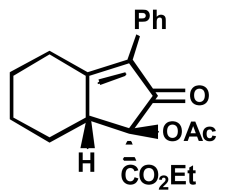


P4 ($CDCl_3$, 100 MHz)

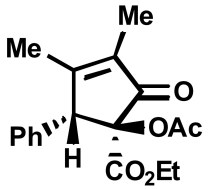


P5 ($CDCl_3$, 500 MHz)

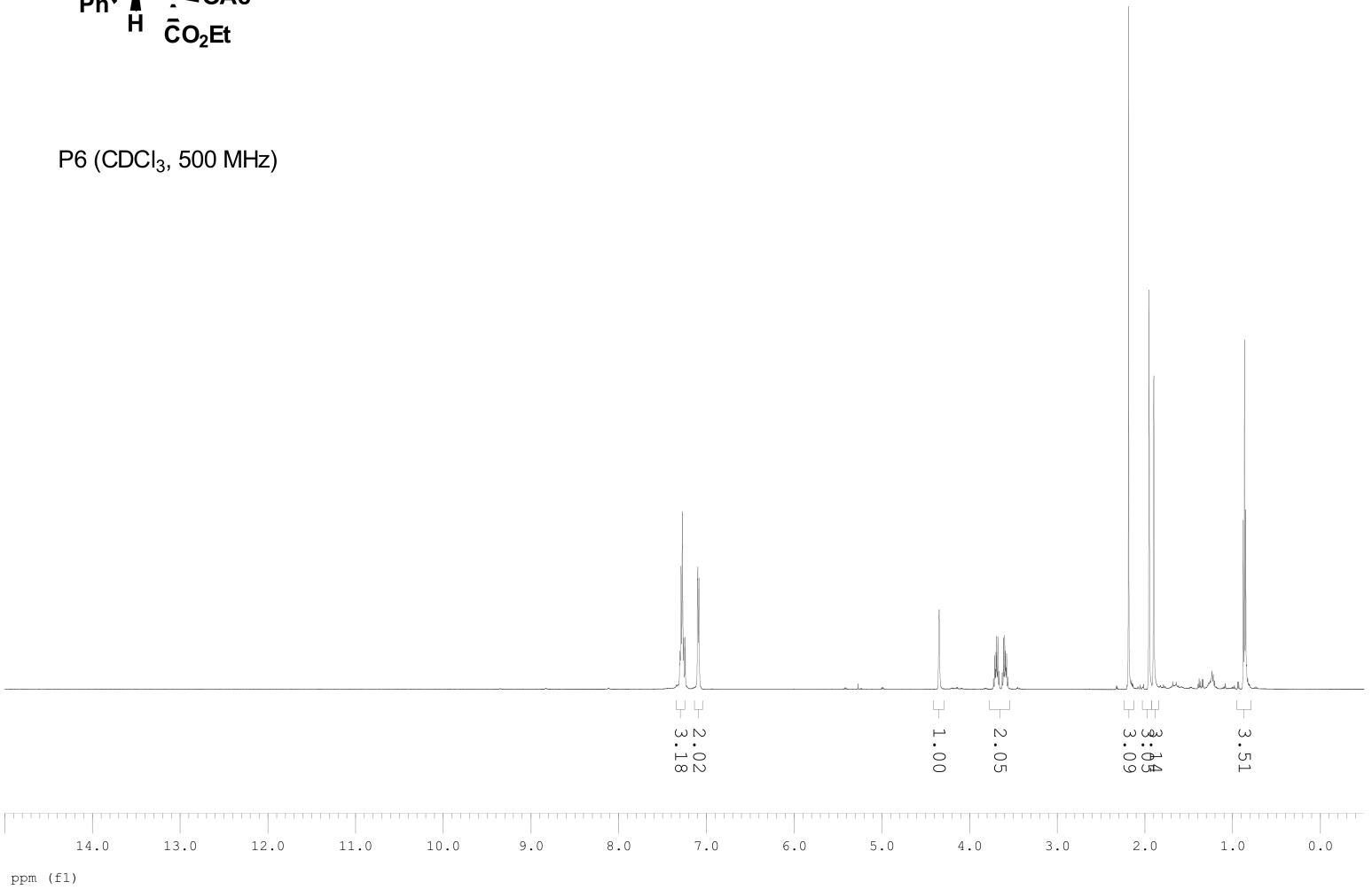


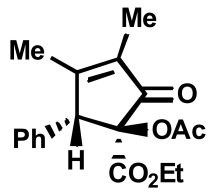


P5 ($CDCl_3$, 125 MHz)



P6 ($CDCl_3$, 500 MHz)





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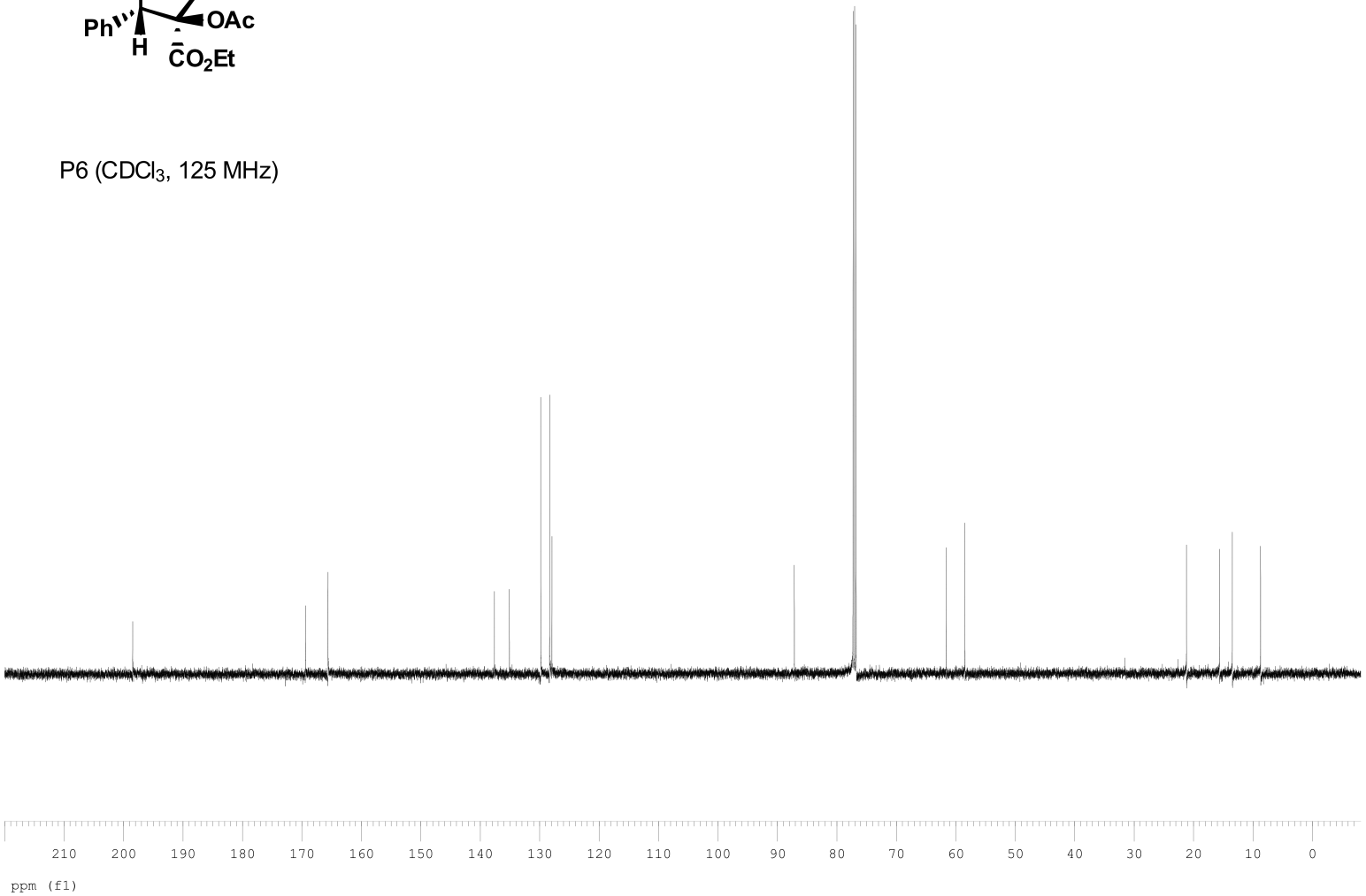

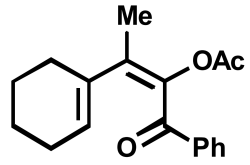

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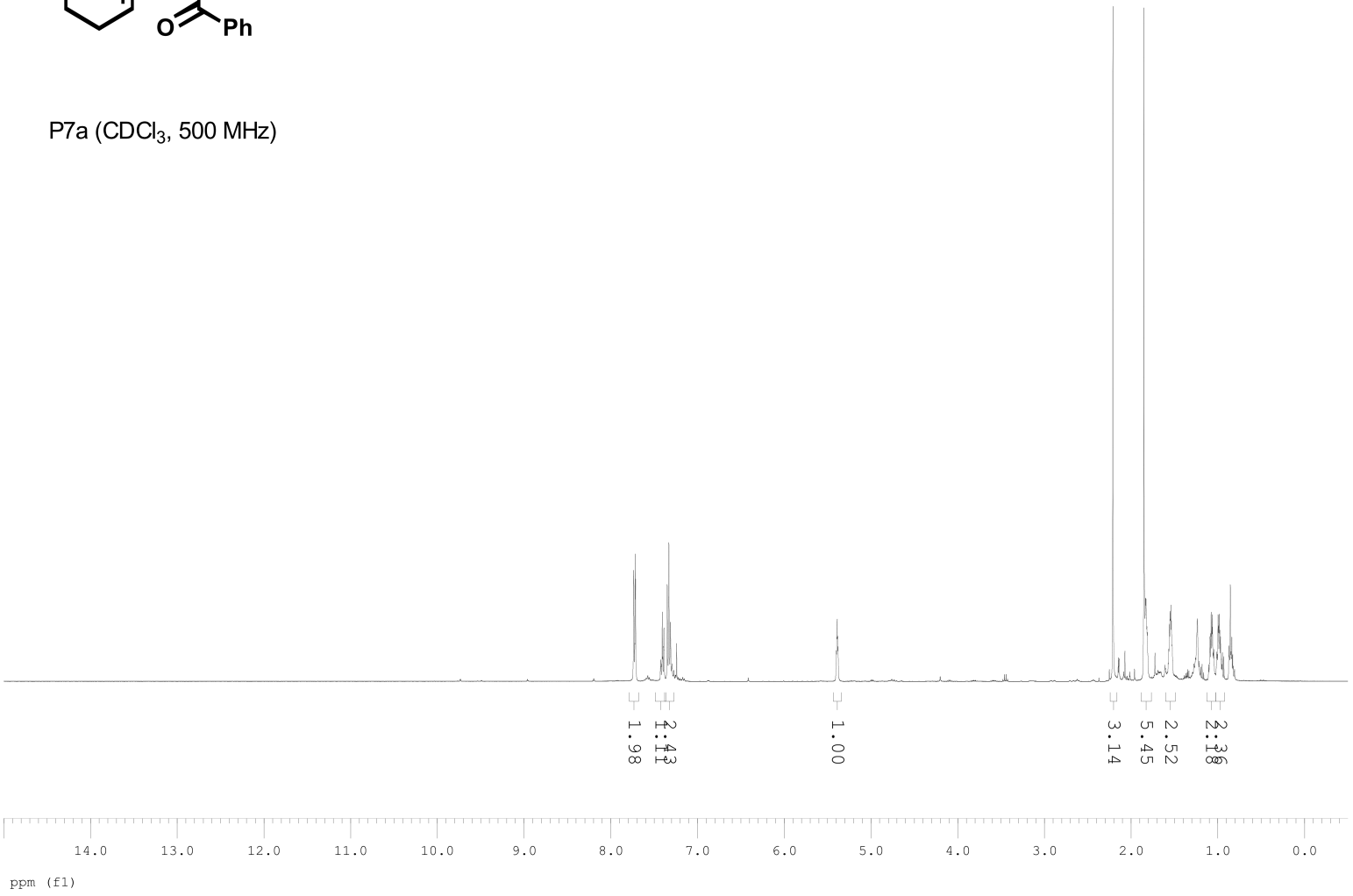

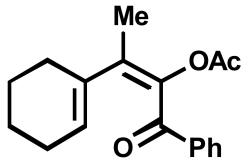

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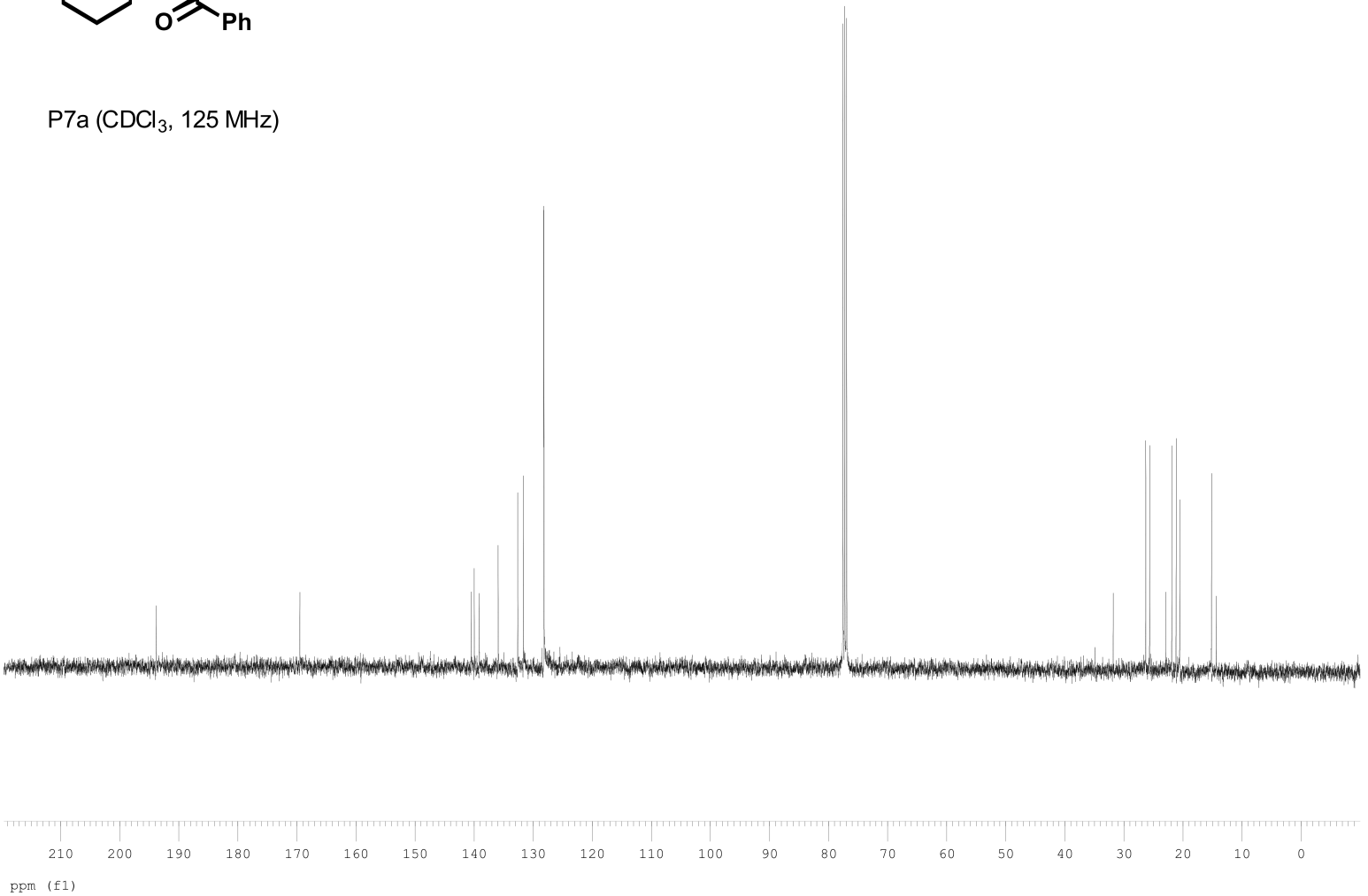

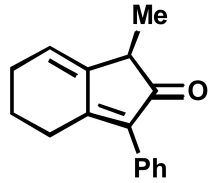

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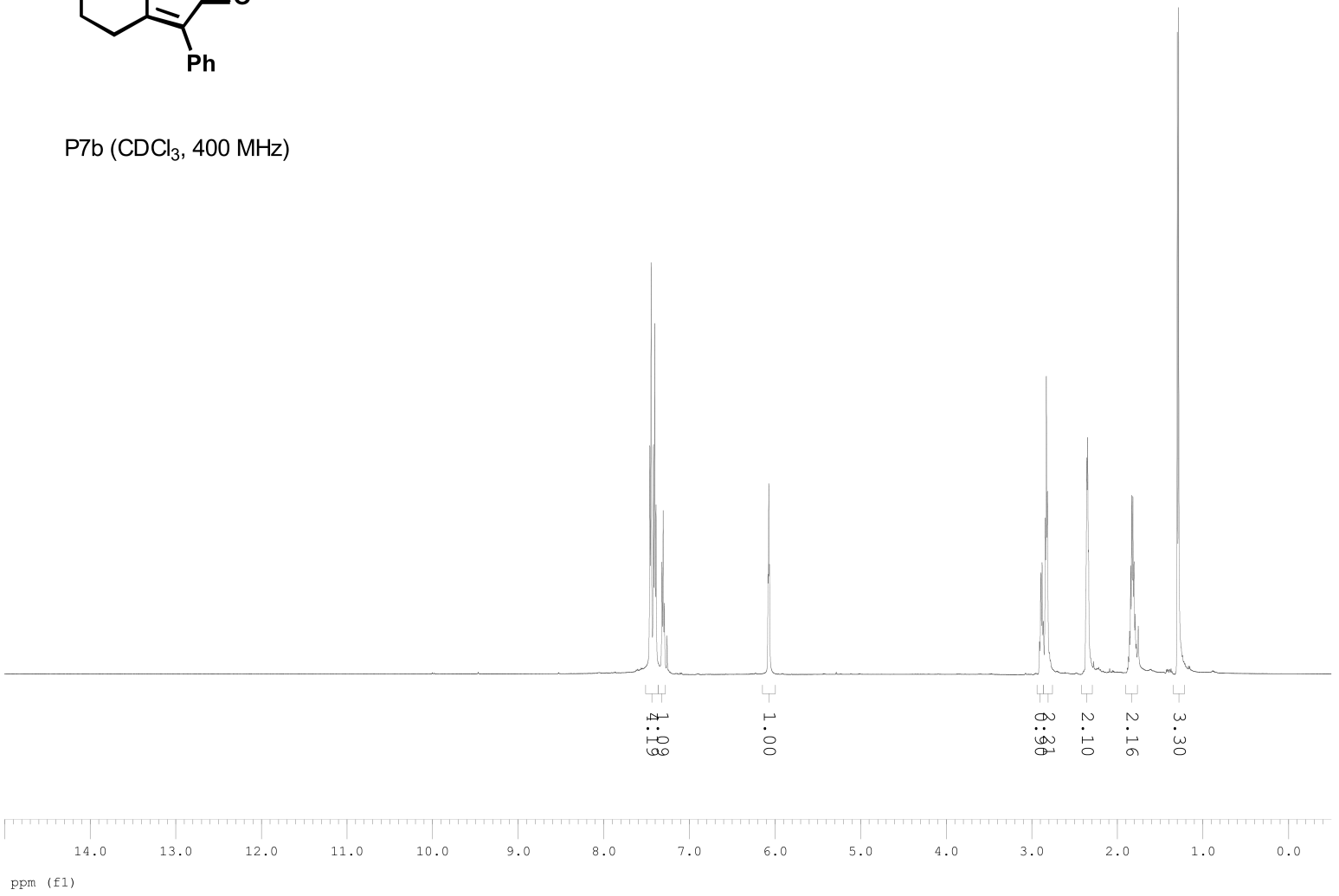

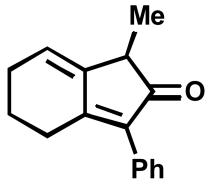

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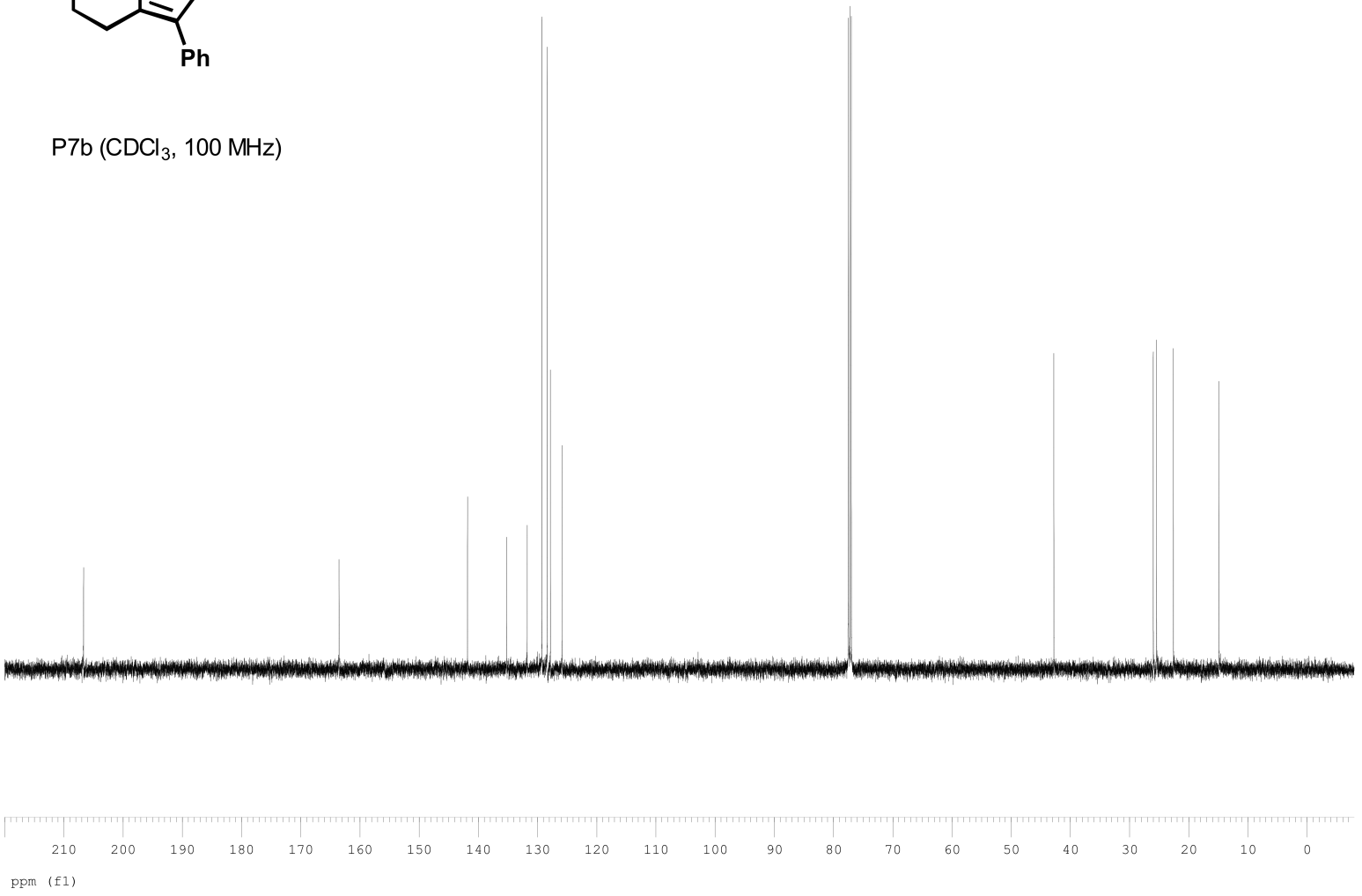
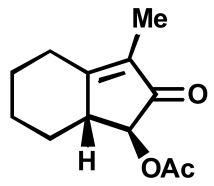
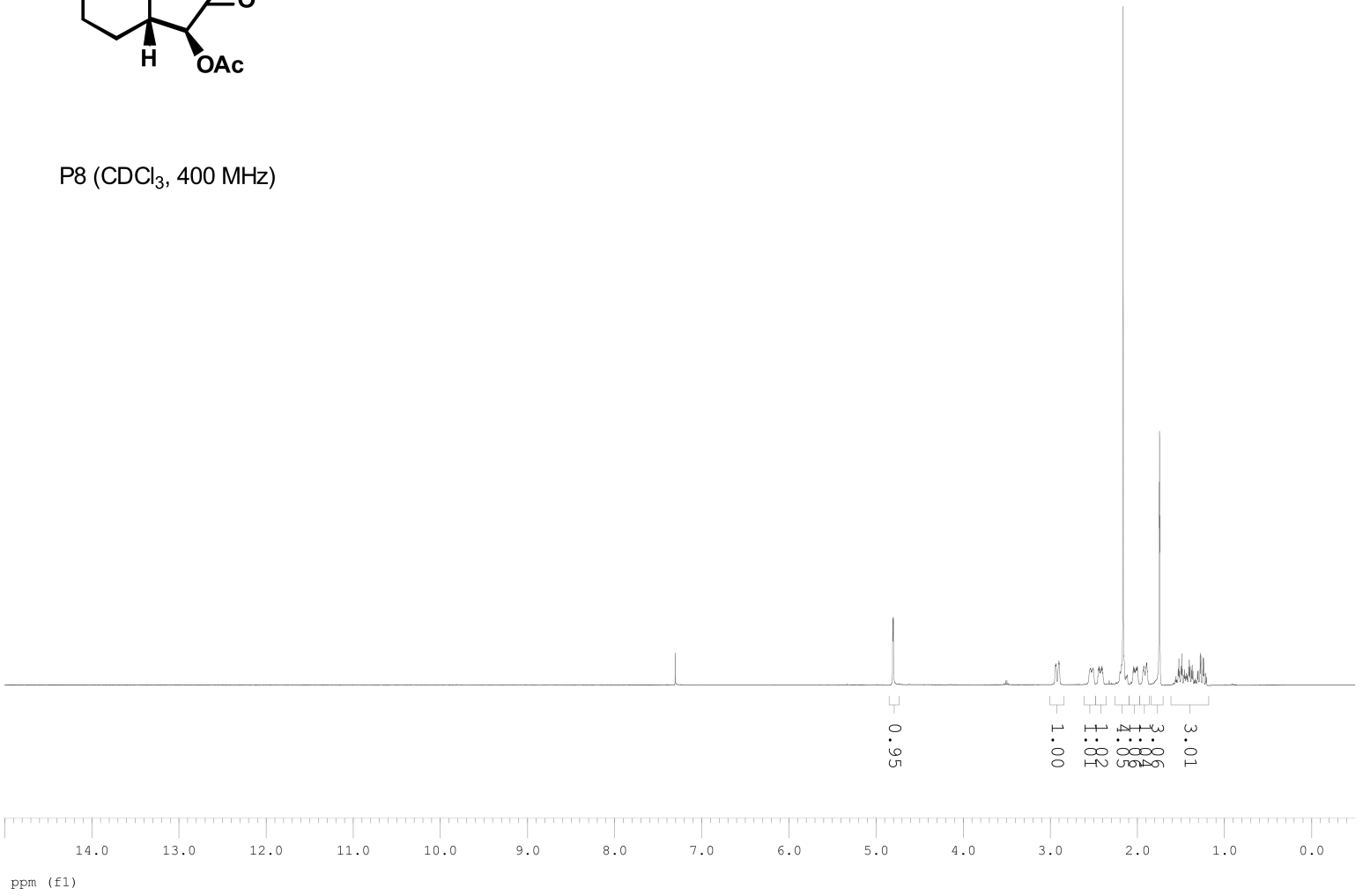
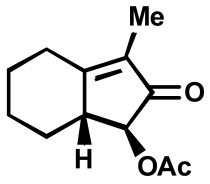


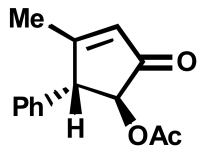


P8 ($CDCl_3$, 400 MHz)

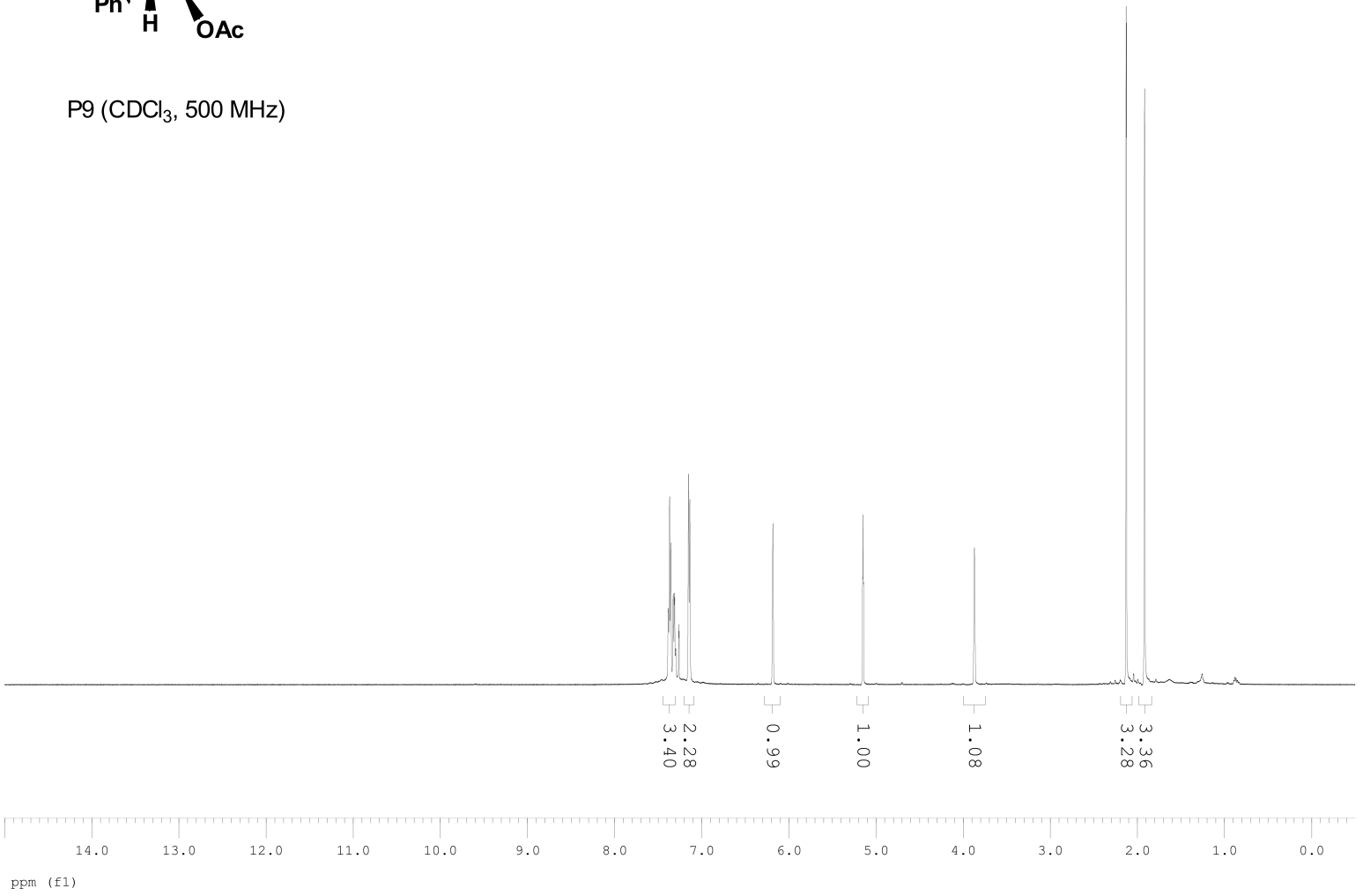


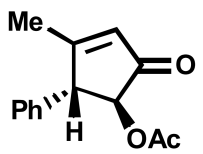


P8 ($CDCl_3$, 100 MHz)



P9 ($CDCl_3$, 500 MHz)





P9 ($CDCl_3$, 125 MHz)

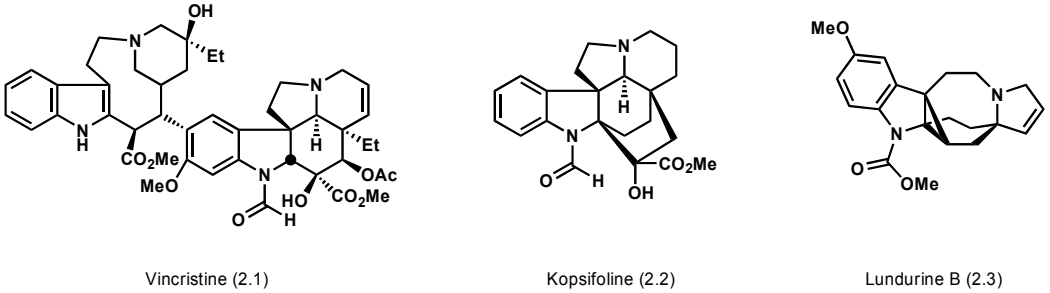
Chapter 2: Initial Endeavors into the Synthesis of the *Kopsia* Natural Products

2.1. Introduction

2.1.1. Multiple Drug Resistance

With the advancement of chemotherapy as a treatment for numerous types of cancers, one of the continuing challenges in the field is the ability of cancer cells to develop resistance to what had previously been effective chemotherapeutic drugs. This ability, known as multi-drug resistance (MDR), has been shown to be relatively independent of drug structure or mechanism of action, leading to the conclusion that a general mechanism is responsible for resistance.[1] Early studies demonstrated a lower level of cytotoxic drug accumulation in MDR cells compared to drug-sensitive cells.[2] It was found that MDR cells overexpress a cell surface membrane protein P-glycoprotein (P-gp), which is thought to be responsible for the decreased drug accumulation.[3] This lower drug accumulation is generally ascribed to efflux-pump activity, with an increase in outward transport, as opposed to a decrease in inward transport.[4] In accordance with this hypothesis of active transport, experiments with MDR cells which were deficient in ATP, showed an increase in sensitivity to cytotoxic drugs. This result was reversed with the addition of ATP.[5]

The *Vinca* alkaloids are a class of plant-derived indole alkaloids that have shown potent anti-cancer activity as mitotic inhibitors, presumably via binding to tubulin and eventual disruption of microtubule assembly. Vincristine (**2.1**, Figure 2.1), one of the most prominent members of this family, is currently marketed under the names Oncovin®, Vincasar PFS®, and Vincrex® and is used for the treatment of leukemia, Hodgkin's disease and other lymphomas, and neuroblastoma. One of the issues associated with vincristine treatment is the tendency for the drug to trigger MDR. Increasing the efficacy of these therapeutics necessitates further understanding of the details of MDR as well as identification of potent MDR-reversing compounds. These MDR-reversing compounds could be used in combination with the traditional chemotherapies to increase the overall effectiveness of the therapy. During the course of a screen of natural products for MDR-reversing properties, Kam and coworkers discovered a number of indole alkaloids from the *Kopsia* family of flowering trees that showed activity.[6] Compounds such as kopsifoline (**2.2**) and lundurine B (**2.3**) were found to exhibit MDR-reversing activity against vincristine resistant human KB cells.[7]

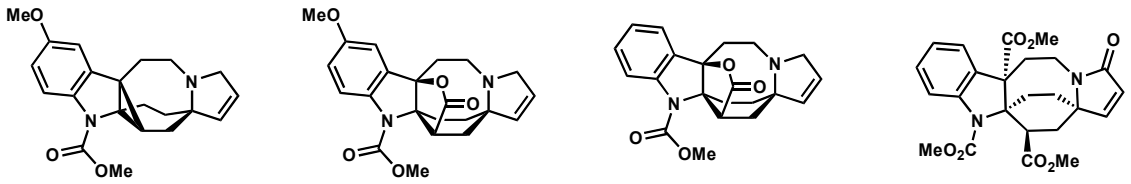


Vincristine (2.1) Kopsifoline (2.2) Lundurine B (2.3)

Figure 2.1: Bioactive indole alkaloid natural products

2.1.2. The *Kopsia* Family of Natural Products

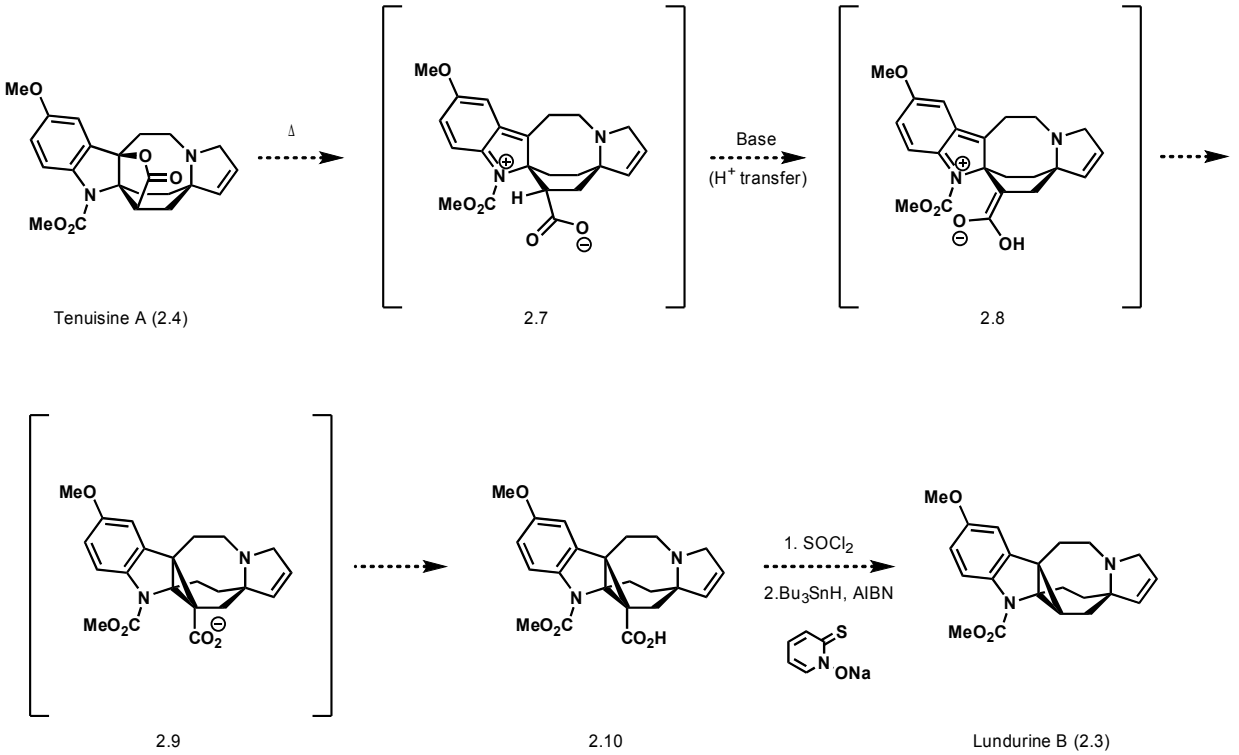
As a part of a synthetic program aimed at the synthesis of lundurine B, our group became interested in a number of structurally related natural products isolated from the *Kopsia* family of flowering plants (Figure 2.2). In addition to the MDR-reversing lundurine B (**2.3**), a number of structurally similar natural products have been isolated from the *Kopsia* family. We envisioned that a synthetic route that was able to provide access to lapidilectine B (**2.5**) would allow for the synthesis of other natural products such as tenuisine A (**2.4**) and lapidilectam (**2.6**), along with strategic derivatives that could be studied for their biological activity. Furthermore, a synthesis of **2.5** would lay the groundwork for syntheses of **2.4** and **2.3**. In this way we sought to provide a deeper understanding of the structure-activity relationships that are important for the MDR-reversing properties for this subset of *Kopsia* alkaloids.



Lundurine B (2.3) Tenuisine A (2.4) Lapidilectine B (2.5) Lapidilectam (2.6)

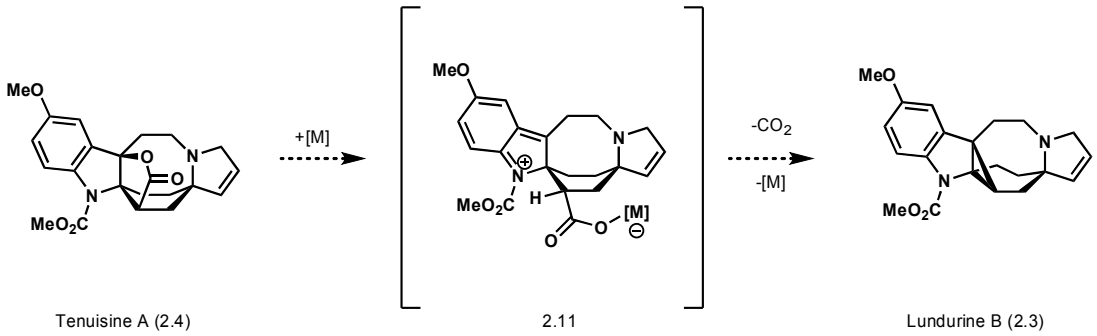
Figure2. 2: Representative *Kopsia* alkaloids

One of the synthetic goals for this project was to study the conversion of tenuisine A (**2.4**) into lundurine B (**2.3**) as outlined in Scheme 2.1. The fact that both natural products are isolated from the same source points towards a biosynthetic link between these two structures. This strategy would thus allow for an investigation of a key cyclopropanation transformation (see Scheme 2.1 **2.4** → **2.3**). One possibility for this step would be to heat tenuisine A (**2.4**), which could lead to fragmentation to open the lactone ring and arrive at zwitterion **2.7**. In the presence of an appropriate base, carboxylate **2.7** could undergo proton transfer to form ketene hemienolate **2.8**. Nucleophilic addition of the ketene hemienolate to the extended imminium ion moiety should yield cyclopropane **2.9**. These reversible steps can presumably be driven towards the carboxylate product by the addition of a base, which would provide an enthalpic balance to the increase in strain associated with the introduction of the cyclopropane. From here, **2.10** may be converted into lundurine B via a Barton decarboxylation under standard conditions.[8]



Scheme 1.1: Proposed synthetic conversion of tenuisine A to lundurine B

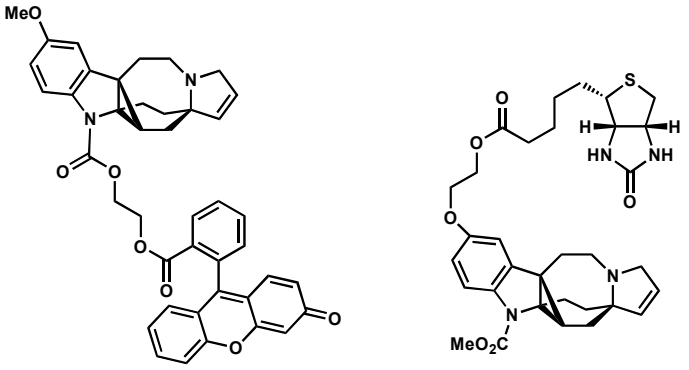
Another interesting possibility for the conversion of the γ-lactone in **2.4** into a cyclopropane is outlined in Scheme 2.2. Coordination of a Lewis acid to the carbonyl of the lactone in **2.4** should facilitate fragmentation to zwitterion **2.11**. From here, a process similar to a Hunsdiecker[9] transformation would extrude carbon dioxide to install the cyclopropane and furnish lundurine B directly.



Scheme 2.2: Lewis acid mediated cyclopropanation

In addition to structure-activity relationship studies, syntheses of these compounds can aid in the study of the mode of action of lundurine B that leads to its MDR-reversing bioactivities. Because the efflux pumps are most likely membrane-bound proteins, structural characterization via conventional methods (NMR, X-ray etc.) is quite difficult. The

development of a synthetic route towards lundurine B would enable the synthesis of molecular probes such as **2.12** to help illuminate the cellular interactions via well-precedented fluorescent imaging techniques.[10] Additionally, attachment of a biotin tag as in **2.13** could be used to probe cellular ligands via affinity chromatography with strepavidin impregnated columns.[11]



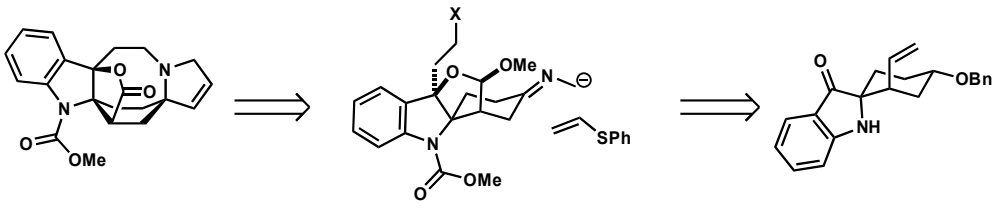
2.12 2.13

Figure 2.3: Biologically relevant lundurine B derivatives

2.2. Previous Synthetic Approaches

2.2.1. Pearson's Synthetic Work

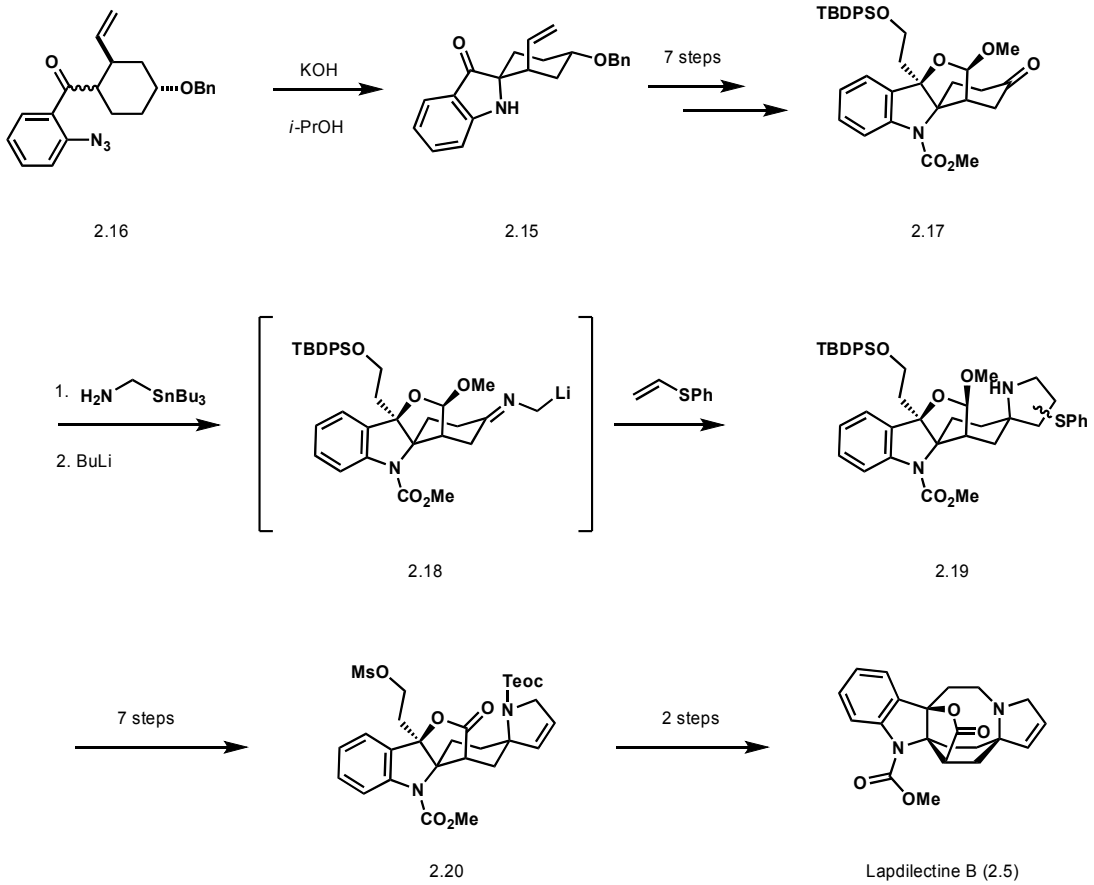
In 2001 Pearson disclosed the first and only synthesis to date of a member of the lapidilectine family of natural products.[12] Pearson's key disconnections include a [3+2] cycloaddition between an aza-allyl-lithium and a vinyl-sulfide to forge the five-membered dihydropyrrole followed by a late-stage alkylation to install the 8-membered ring (Scheme 2.3). Intermediate **2.14** was brought back to oxindole derivative **2.15**, which utilized a Smalley oxindolization to form the carbon-nitrogen spirocyclic bond.



Lapidilectine B (2.5) 2.14 2.15

Scheme 2.3: Pearson's general retrosynthesis

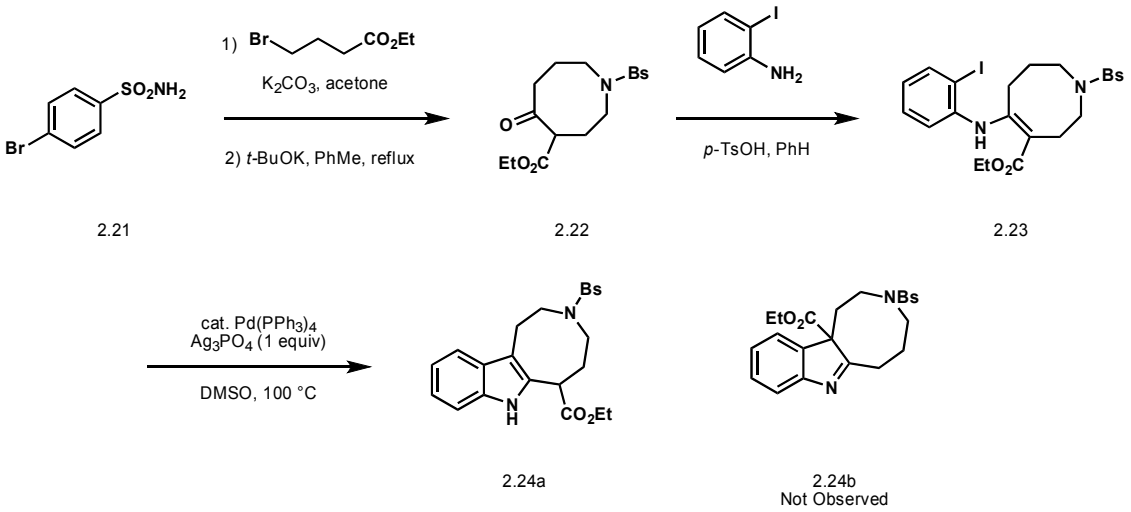
Pearson's forward synthesis (Scheme 2.4) began with the construction of aryl-azide **2.16** in a total of 6 steps from commercially available 4-hydroxycyclohexanone. This azide is set up to undergo a Smalley oxindolization[13] reaction to form spirocycle **2.15**. In 7 steps from **2.15** Pearson et al. were able to efficiently install the *tert*-butyldiphenylsilyl-protected hydroxyl side-chain, the lactol 5-membered ring, and the ketone in the cyclohexanone ring to arrive at **2.17**, which set the stage for the key transformation of the synthesis. Condensation of ketone **2.17** with tributylstannylmethyleneamine furnished an imine, which when treated with *n*-butyl lithum underwent a lithium-tin exchange to generate aza-allyl-lithium species **2.18** in situ. This aza-allyl-lithium underwent a formal [3+2] cycloaddition with vinyl-phenylsulfide to yield **2.19** as an inconsequential mixture of regio- and diastereomers. From here another sequence of functional group manipulations was required to protect the amine, eliminate the sulfide, oxidize the lactol to a lactone, and convert the protected hydroxyl-group into a mesylate to afford penultimate intermediate **2.20**. After that sequence, only two steps were required to furnish the natural product: amine deprotection and alkylative ring-closing finished the synthesis of lapidilectine B in a total of 25 steps from commercially available materials. This remains the only published synthesis of this natural product to date, and represents an impressive demonstration of synthetic strategy and the aza-allyl cycloaddition tactic to obtain this highly caged molecule.



Scheme 2.4: Pearson's synthesis of lapidilectine B

2.2.2. Nishida's Synthesis of a Model System

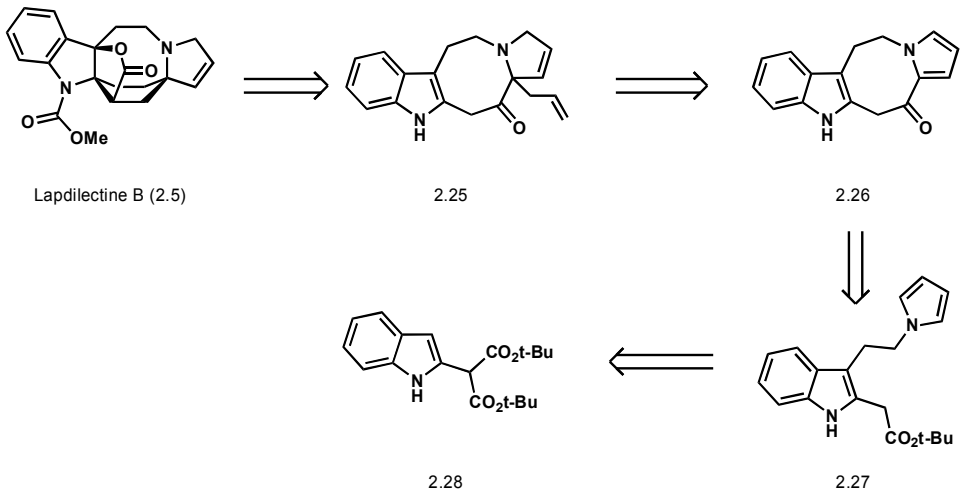
The only other approach to the lapidilectine family of natural products that has been disclosed was by Nishida in 2004.[14] This was a preliminary communication that described the synthesis of a moderately functionalized tricyclic precursor to these natural products. As shown in Scheme 2.5, sulfonamide **2.21** was bis-alkylated with ethyl 3-bromobutylate and then subjected to a Dieckmann cyclization to form eight-membered beta-keto-ester **2.22**. From here a condensation with 2-iodoaniline gave vinylogous carbamate **2.23** and set the stage for the featured methodology of the paper. Treatment of this substrate with a palladium(0) source effected a cyclization to give tricycle **2.24a** in good yield. The authors had initially hypothesized that these conditions would give rise to products such as **2.24b**, which would be useful for the synthesis of natural products such as lapidilectam (**2.6**, Figure 2.2). Even though the product formed was not what was initially envisioned, this methodology demonstrated the viability of constructing the indole ring of the lapidilectine family of natural products onto a system that already contained the requisite eight-membered ring.



Scheme 2.5: Nishida's synthesis of a tricycle

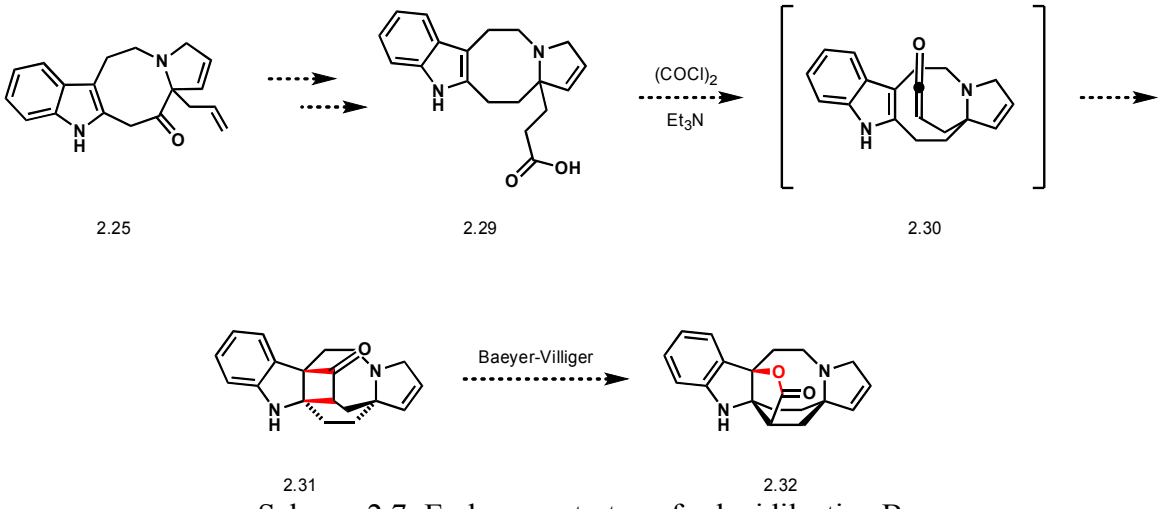
2.3. Our Initial Approach

Our initial retrosynthesis of lapidilectine B (Scheme 2.6) focused on the disconnection of the five-membered lactone ring in the natural product back to simplified tetracycle **2.25**. This tetracycle was envisioned to arise from an alkylative Birch reduction of acyl-pyrrole **2.26**. The eight-membered ring in **2.26** was envisioned to arise from an intramolecular Friedel-Crafts acylation of substrate **2.27**. We believed that this functionalized substrate could be brought back to known malonyl-indole **2.28**.



Scheme 2.6: Initial retrosynthesis of lapidilectine B

The end-game envisioned for the conversion of tetracycle **2.25** to the natural product is further detailed in Scheme 2.7. Tetracycle **2.25** can be converted to carboxylic acid **2.29** via a series of functional group manipulations. From here, treatment with oxalyl chloride and triethylamine should furnish ketene **2.30**, which is poised to undergo an intramolecular [2+2] cycloaddition to give cyclobutanone **2.31**. From here, a strain-release mediated Baeyer-Villiger oxidation should furnish lactone **2.32** which possesses the complete skeletal framework of the natural product. The Baeyer-Villiger oxidation was expected to proceed with the correct regioselectivity due to the greater migratory aptitude for the tertiary, benzylic carbon (see **2.31**) over the secondary one.[15]

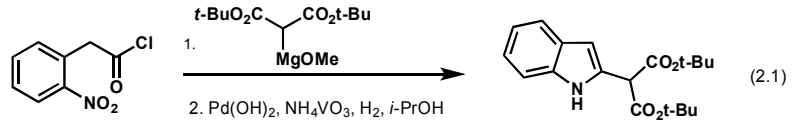


Scheme 2.7: End game strategy for lapidilectine B

2.4. Forward Synthesis

2.4.1. Alkylation of indole 2.28

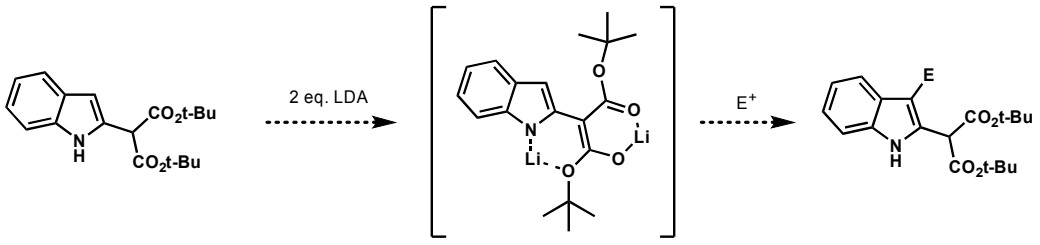
Synthesis of key intermediate **2.25** began with the synthesis of indole **2.28** following literature precedent.[16] Readily prepared acyl-chloride **2.33** was treated with the magnesium anion of *tert*-butyl malonate and the resultant product was subjected to reductive cyclization using palladium and hydrogen (eq 2.1). The use of ammonium vanadate as a co-catalyst prevents the reaction from stalling at the hydroxy-indole intermediate.[17] With coupling partner **2.28** in hand, the most direct access to pyrrole **2.27** would be an alkylation utilizing an alkyl halide such as **2.35**. The iodide was prepared as shown in eq 2.2. Ethanolamine (**2.34**, eq 2.2) was treated under Paal-Knorr conditions[18] to install the pyrrole, after which the hydroxyl group was activated using methanesulfonic chloride and then displaced utilizing sodium iodide in acetone.[19]



2.33 (74% over 2 steps) 2.28

2.34 (68% over 3 steps) 2.35

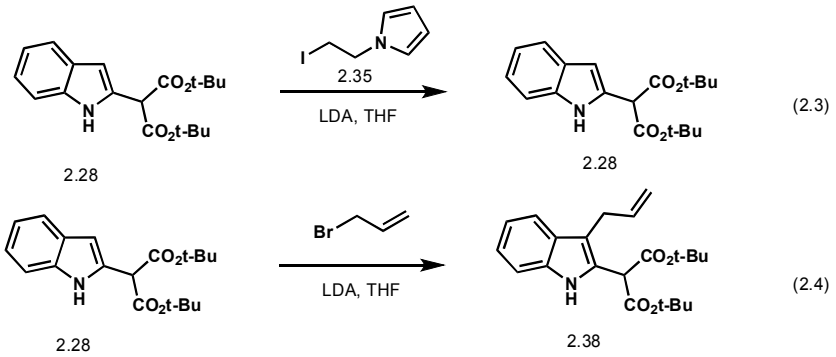
It has been shown that deprotonation of malonyl indoles such as **2.28** with excess strong base (e.g., LDA) forms dianions such as **2.36** (Scheme 2.9).[20] These dianions can then be treated with an electrophile and functionalized at the 3-position of the indole.



2.28 2.36 2.37

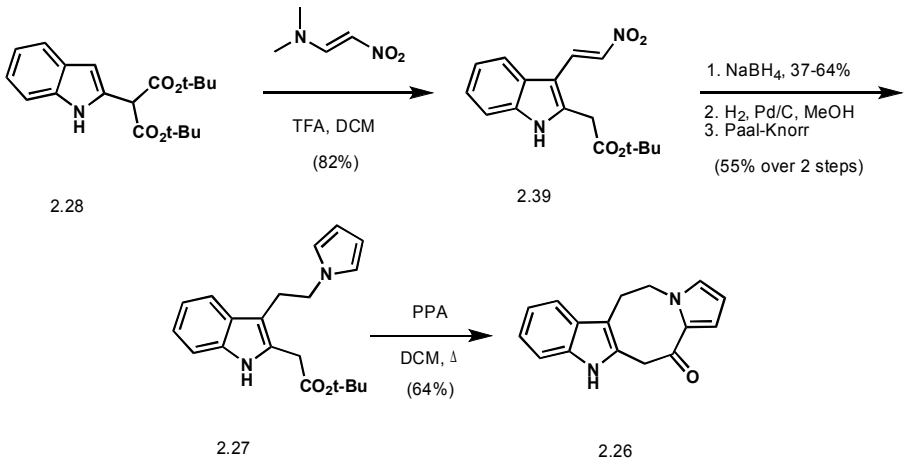
Scheme 2.8: Alkylation of **2.28**

Treatment of indole **2.28** with excess LDA and then iodo-ethyl pyrrole **2.35** only returned starting material (eq 2.3). This result was disappointing, as this would have produced the Friedel-Crafts substrate (**2.27**, Scheme 2.6) in a highly convergent manner in only a few very high yielding steps. To verify that alkyl iodide **2.35** was not a competent electrophile, the same alkylation procedure was performed with a more active electrophile, allyl bromide. Indeed, functionalization at the C-3 position was observed (eq 2.4).



2.4.2. Alternative Indole Functionalization

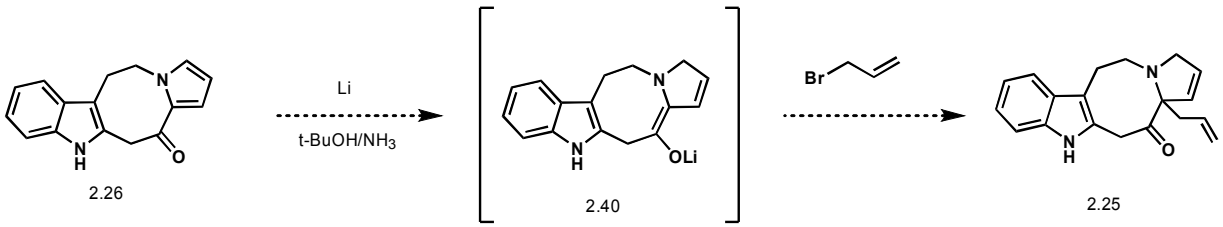
Although the direct alkylation of **2.28** to yield **2.27** was not successful, we desired a way of obtaining the key pyrrole **2.26** to test the Birch chemistry. Thus, a more methodical approach was devised to access substrate **2.27** (Scheme 2.9). Indole **2.28** was treated with N,N-dimethylamino nitroethylene[21] and trifluoroacetic acid to afford C-3 functionalized indole **2.39**. Interestingly, we observed cleavage and decarboxylation of one of the *t*-butyl esters. The resulting nitro-olefin was subjected to sequential reduction of the carbon-carbon double bond utilizing sodium borohydride followed by reduction of the nitro group to yield a primary amine using heterogeneous transition metal reduction conditions. Both these reductions suffered from difficulties with reproducibility and scalability. Following these reductions, the primary amine was subjected to Paal-Knorr conditions to install the pyrrole to yield **2.27**. This pyrrole was then treated with polyphosphoric acid and heated to arrive at tetracycle **2.26**.



Scheme 2.9: Synthesis of tetracycle **2.26**

2.4.3. Birch Reduction and Alkylation

With key substrate **2.26** in hand, we could now test the Birch/alkylation reaction.[22] The proposed reaction scheme is shown below. Treatment of acylpyrrole **2.26** with lithium metal in an ammonia/*t*-butanol solution was expected to yield enolate **2.40** via sequential single electron transfer and protonation events. This enolate could then be trapped with an electophile such as allyl-bromide to deliver ketone **2.25**. Unfortunately, numerous attempts to effect conversion of **2.26** to **2.25** at this reaction failed to yield a discernible product. In addition to being unable to effect this key alkylation, this strategy suffered from an inability to be rendered asymmetric, so we began to pursue other strategies.



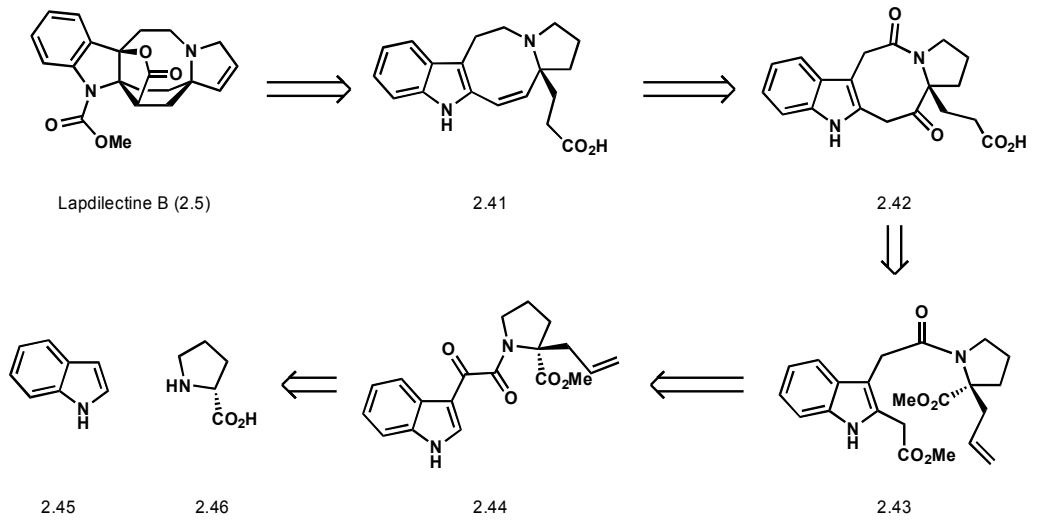
Scheme 2.10: Attempts at the Birch reduction/alklyation of **2.26**

2.5. Dieckmann Based Approach to Lapidilectine B

2.5.1. Retrosynthesis

With the difficulties encountered with the Birch strategy (see Section 2.4.3), other routes were investigated in an attempt to synthesize the *Kopsia* alkaloids. An alternative retrosynthesis is shown in Scheme 2.12. The same end game approach brings lapidilectine B

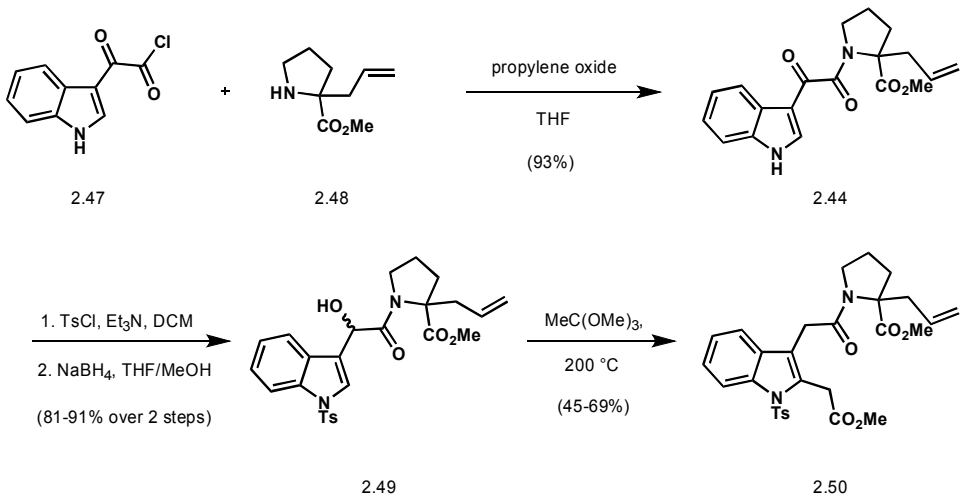
back to carboxylic acid **2.41**. This substrate could be derived via functional group manipulations of ketone **2.42**. The key disconnection in this strategy is the Claisen-rearrangment/Dieckmann-cyclization that brings **2.42** back to **2.44**, which can be synthesized from indole and proline. This route provides an opportunity to introduce an enantioenriched fragment via "memory of chirality" from proline.[23]



Scheme 2.11: Dieckmann based retrosynthesis

2.5.2. Forward Synthesis

The forward synthesis commenced with the coupling of acid chloride **2.47**[24] with proline derivative **2.48**[25] utilizing propylene oxide as a hydrochloric acid scavenger, which produced amide **2.44** in excellent yield (see Scheme 2.12). Initial trials utilizing other more traditional bases afforded the desired product in much more modest yields of 35-45%. Protection of the indole nitrogen with tosylchloride was facilitated by the electron-withdrawing nature of the acyl group on the 3-position. This protected indole was then reduced using sodium borohydride to yield **2.49**. This alcohol was heated with trimethylorthoacetate to give rise to the Claisen-rearrangement product **2.50** in acceptable yields.[26] This reaction proceeds only at a temperature significantly higher than the boiling point of trimethylorthoacetate, so the choice of reaction flask was of vital importance. It was discovered that a flask much larger than the final reaction volume was necessary. All reaction mixtures that occupied over one third the volume of the flask would lead to significant amounts of over-boiling, resulting in significant residence time for the reaction mixture in the reflux condenser (which is much colder than the required temperature for the reaction).

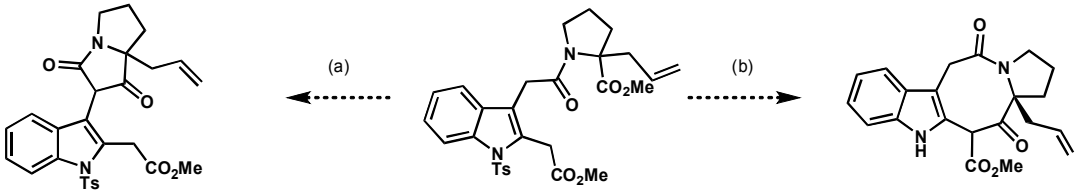


2.47 2.48 2.44

2.49 2.50

Scheme 2.12: Synthesis of **2.53**

With diester **2.50** in hand, the key Dieckmann cyclization[27] was investigated. One of the potential issues that was considered was the relative acidities of the α positions of both the amide and the ester. We hoped that the 2-3 pKa advantage the ester has in acidity over the amide would overcome the entropic advantage of cyclizing from the amide (five- vs. eight-membered ring formation, **2.51** vs **2.52** in Scheme 2.15).



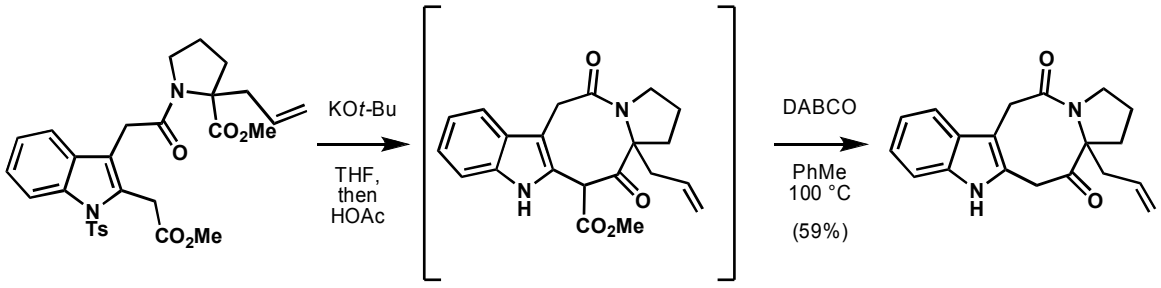
2.52 2.50 2.51

Scheme 2.13: Alternative cyclization possibilities

Initial attempts at the Dieckmann cyclization using potassium *tert*-butoxide gave TLC's that indicated clean product formation, but all attmpts at isolation led to decomposition. Further TLC investigations indicated that the product was stable to the reaction and workup conditions, but decomposed upon concentration, no matter how brief.

We hypothesized that a one-pot Dieckmann/Krapcho decarboxylation might afford a more stable product (see Scheme 2.16). We pursued this by treating diester **2.50** with potassium *tert*-butoxide in tetrahydrofuran until TLC analysis indicated full consumption of starting material. This was followed by neutralization of all anionic species using acetic acid. The issue of instability was solved by using a solvent switch to toluene for the required Krapcho demethylation.[28] Using DABCO under refluxing conditions, a new product, tetracycle

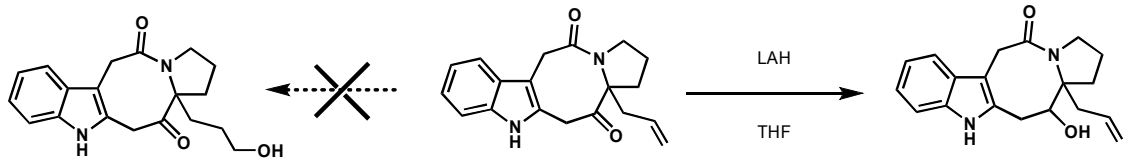
2.53, was produced and found to be exceptionally stable.



2.50 2.51 2.53

Scheme 2.14: Dieckmann cyclization of **2.53**

Unfortunately, the stability of tetracycle **2.53** proved to be a major hindrance. Attempts to functionalize the allyl sidechain via hydroboration/oxidation were met with failure. Additionally, efforts to reduce the ketone-group using sodium borohydride were unsuccessful. The only reagent that proved capable of reacting with **2.53** was lithium aluminum hydride, and even then, only the ketone functional group was reduced, not the amide. Because of the difficulties encountered with ketone **2.53**, as well as the necessity of functionalizing the pyrrolidine ring, an alternative synthetic strategy was developed.



2.54 2.53 2.55

Scheme2.15: Attempted functionalization of **2.56**

2.6. Conclusion

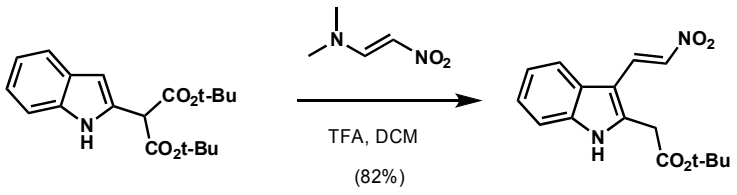
Combating multiple drug resistance is an important area of research in the field of oncology. The ability of cancer cells to develop resistance to a wide array of chemotherapies necessitates the study and development of compounds that are able to counteract this defensive mechanism. Lundurine B shows promise as a molecule with MDR-reversing properties for vincristine-resistant cancer cells. Lapidilectine B was chosen as the initial target for this synthetic program, in anticipation that a route to this molecule could be modified for the synthesis of a number of other related natural products, as well as unnatural analogs of lundurine B for the study of its bioactivity.

Two preliminary routes towards lapidilectine B were investigated. Both routes arrived at the tetracyclic core of the natural product. The key medium-sized ring constructing steps were a Friedel-Crafts acylation and a one-pot Dieckmann/Krapcho sequence. Unfortunately,

neither of these approaches was amenable to further progress towards this class of molecules. Because of this, we sought to develop an alternative synthetic strategy to these very important natural products (see Chapter 3).

2.7. Experimental

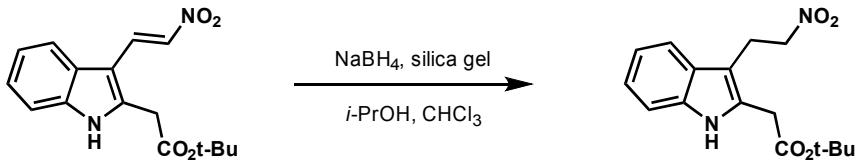
General. All air or moisture sensitive reactions were conducted in flame-dried glassware under an atmosphere of nitrogen using dry, deoxygenated solvents. Toluene, methylene chloride (DCM), acetonitrile, tetrahydrofuran (THF), diethyl ether, and triethylamine were dried via passage through columns of deactivated alumina using argon. All reagents were purchased from Aldrich, Acros, or Lancaster and used without further purification. Melting points were measured on a Büchi® melting point apparatus and are corrected using vanillin (mp 80-81 °C) as a standard. Reaction temperatures were controlled by an IKAmag temperature modulator. Thin-layer chromatography (TLC) was performed using Silicycle silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV (254 nm) and anisaldehyde stain. Sorbent silica gel 240-400 mesh (particle size 0.032-0.063) was used for flash chromatography. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AV-500 (at 500 MHz and 125 MHz respectively) and on a Bruker AV-600 (at 600 MHz and 150 MHz respectively) in chloroform-*d* at 23 °C, unless otherwise stated. Chemical shifts were referenced to the residual chloroform-H peak, which was set at 7.26 ppm for ^{1}H and 77.0 ppm (center peak) for ^{13}C spectra. Data for ^{1}H NMR are reported as follows: chemical shifts (δ ppm). Multiplicity, (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublet, dt = doublet of triplet, m = multiplet, br = broad resonance), coupling constants (Hz) and integration. Data for ^{13}C NMR are reported in terms of chemical shift. IR spectra were recorded on a Nicolet MAGNA-IR 850 spectrometer and are reported in frequency of absorption (cm^{-1}). Low and high resolution mass spectral data were obtained from the University of California, Berkeley Mass Spectral Facility, on a VG 70-Se Micromass spectrometer for FAB, and a VG Prospec Micromass spectrometer for EI. Abbreviations used can be found on the Internet at http://pubs.acs.org/paragonplus/submission/joceah/joceah_abbreviations.pdf.



2.28 2.39

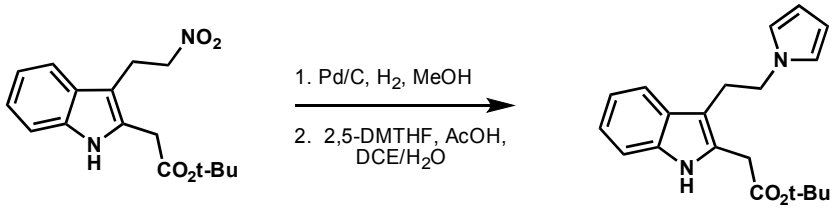
A flame-dried roundbottom flask was charged with N,N-dimethylaminonitroethylene (0.074 g, 0.63 mmol) and 300 µL of DCM and cooled to 0 ºC. To this solution was added TFA (0.067 g, 0.59 mmol) in 200 µL of DCM was added . **2.28** (0.140 g, 0.422 mmol) in 500 µL of DCM was then added dropwise and the resultant yellowish solution was stirred at 0 ºC for 3

hours. Warmed to rt and stirred overnight. The brownish mixture was concentrated under reduced pressure, and loaded directly onto silica gel column and purified by flash column chromatography (4:1 hexanes/ethyl acetate) afforded **2.39** (112 mg, 88% yield) as a bright yellow solid: mp 104 ºC; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.96 (s, 1H), 8.32 (d, J = 13.3 Hz, 1H), 7.84 (d, J = 13.3 Hz, 1H), 7.75 (dd, J = 8.5, 4.5 Hz, 1H), 7.51 – 7.43 (m, 1H), 7.38 – 7.27 (m, 3H), 4.01 (s, 2H), 1.51 (d, J = 57.3 Hz, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.6, 139.9, 136.2, 132.0, 131.9, 125.1, 123.8, 122.5, 120.1, 112.1, 106.6, 83.4, 77.2, 77.0, 76.8, 32.5, 27.9; IR (thin film) λ_{max} 3268, 2980, 2934, 1726, 1613, 1556, 1460, 1306, 1217, 733 cm^{-1}; HRMS (EI) *m/z:* calc for $C_{16}H_{18}N_2O_4$ 302.1267, found 302.1258.



2.39 S1

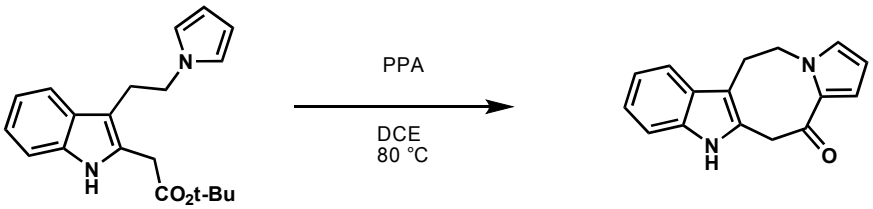
A flame-dried roundbottom flask was charged with **2.39** (0.165 g, 0.546 mmol), chloroform (4.9 mL) and isopropanol (0.6 mL). To this mixture was added silica gel (0.824 g) and then sodium borohydride (77.0 mg, 2.18 mmol) and the reaction mixture was stirred at rt for 3 hours at which time the reaction was judged complete by TLC. The solvent was removed via rotary evaporation to give a free-flowing powder of the crude mixture loaded onto silica gel, which was loaded onto 1 inch pad of silica gel and flushed with 1:1 hexanes/ethyl acetate. The combined eluent was concentrated via rotary evaporation, and the crude **S1** was used in the next step as-is. Crude ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.76 (s, 1H), 7.50 (d, J = 7.8 Hz, 1H), 7.36 (t, J = 11.3 Hz, 1H), 7.22 – 7.16 (m, 1H), 7.16 – 7.10 (m, 1H), 4.61 (t, J = 7.4 Hz, 2H), 3.72 (s, 2H), 3.45 (t, J = 7.4 Hz, 2H), 1.49 (s, 9H); crude ^{13}C NMR (151 MHz, $CDCl_3$) δ 169.5, 135.6, 129.0, 127.1, 122.1, 119.8, 117.5, 111.1, 106.7, 82.2, 75.0, 32.7, 28.0, 27.8.



S1 2.27

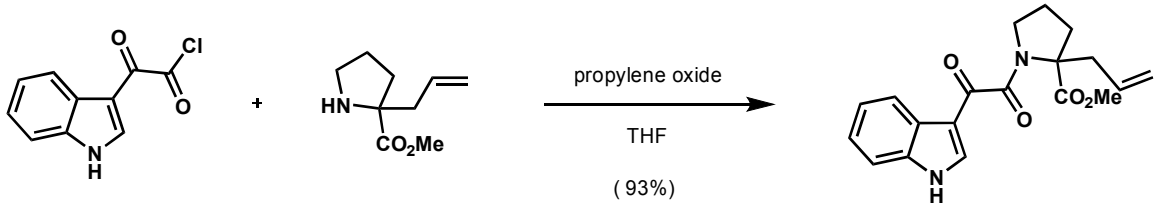
A roundbottom flask was charged with indole **S1** (135 mg, 0.447 mmol), methanol (5 mL), and Pd/C (15 mg). The reaction mixture was stirred under a balloon of hydrogen for 3 hours until the reaction was judged complete by TLC. The reaction mixture was filtered through celite, and concentrated via rotary evaporation. A flame-dried roundbottom flask was charged with the crude amine in DCE (1.5 mL) and water (1.0 mL). To this biphasic mixture

was added 2,5-dimethoxytetrahydrofuran (0.087 mL, 0.671 mmol) and acetic acid (0.067 mL, 1.166 mmol). The vial was capped and heated to 45 ºC for 10 hours and then cooled to room temperature. The reaction was quenched with saturated sodium bicarbonate (5 mL) and the aqueous layer was extracted with DCM (2 x 5 mL). The combined organic layer was dried over sodium sulfate and concentrated via rotary evaporation. The crude oil was purified via silica gel chromatography (6:1 hexanes/ethyl acetate) to obtain 2.27 (45 mg, 42% yield over 3 steps) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.79 (s, 1H), 7.55 (t, *J* = 10.8 Hz, 1H), 7.38 (d, *J* = 8.0 Hz, 1H), 7.21 (dd, *J* = 11.1, 4.0 Hz, 1H), 7.15 (t, *J* = 7.4 Hz, 1H), 6.52 (t, *J* = 2.1 Hz, 2H), 6.12 (t, *J* = 2.1 Hz, 2H), 4.15 – 4.08 (m, 2H), 3.27 (s, 2H), 3.12 (t, *J* = 6.9 Hz, 2H), 1.49 (s, 9H); IR (thin film) λ_{max} 3258, 2986, 2934, 1726, 1590, 1445, 1376, 1200, 768 cm^{-1}; HRMS (EI) *m/z* calc: for $C_{20}H_{20}N_2O_2$ 324.1838, found 324.1842.



2.27 2.26

An oven-dried vial was charged with pyrole **2.27** (8.0 mg , .058 mmol), dichloroethane (1 mL) and polyphosphoric acid (1 g). The vial was capped and heated to 80 °C for 4 hours and then cooled to rt. The reaction mixture was diluted with dichloromethane (5 mL) and the organic layer was washed with saturated sodium bicarbonate (3 X 5 mL) and dried over magnesium sulfate. The organic layer was concentrated via rotary evaporation and the crude mixture was purified by flash column chromatography (2:1 hexanes/ethyl acetate) to obtain **2.26** (4.0 mg, 64% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.62 (s, 1H), 7.49 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.34 – 7.30 (m, 1H), 7.27 – 7.23 (m, 1H), 7.06 (dd, *J* = 7.9, 1.0 Hz, 1H), 6.74 – 6.69 (m, 1H), 6.46 (dd, *J* = 3.7, 1.4 Hz, 1H), 6.25 – 6.20 (m, 1H), 4.12 (dd, *J* = 13.6, 6.6 Hz, 2H), 1.90 (dd, *J* = 14.6, 7.5 Hz, 1H), 1.75 (d, *J* = 7.2 Hz, 1H), 1.70 – 1.62 (m, 1H), 1.55 (dd, *J* = 7.4, 3.4 Hz, 1H); IR (thin film) λ_{max} 3258, 2986, 2934, 1648, 1445, 1376, 1200, 768 cm^{-1}; HRMS (EI) *m/z* calc: for $C_{16}H_{15}N_2O$ 250.2952, found 250.2960.

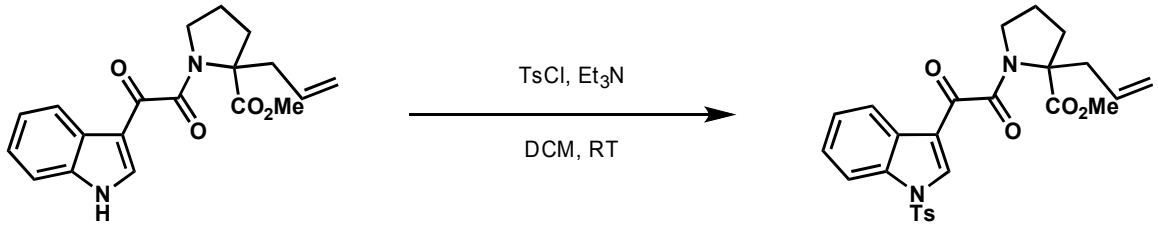


2.47 2.48 2.44

A flame-dried roundbottom flask was charged with amine **2.48** (1.18 g, 6.97 mmol),

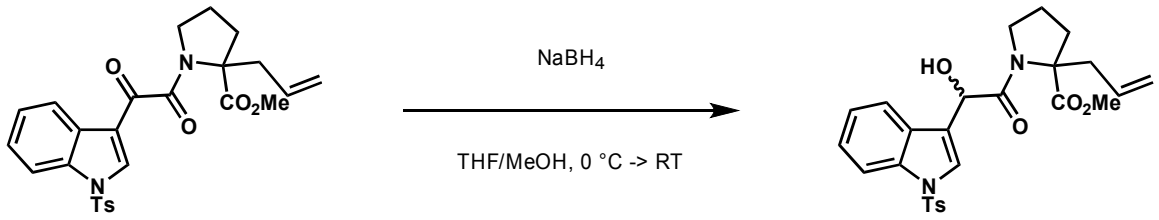
propylene oxide (0.864 mL, 12.2 mmol) and THF (15 mL) and cooled to 0 ºC. To this was added acid chloride **2.47** (1.45 g, 6.97 mmol) in THF (15 mL) dropwise over 10 minutes. The resultant slurry was stirred at 0 ºC for 45 minutes, then warmed to rt and quenched with water (30 mL). The aqueous layer was extracted with ether (2 x 30 mL). The combined organic layer was washed with saturated sodium bicarbonate, then brine and dried over sodium sulfate and concentrated via rotary evaporation to give indole **2.44** (2.23 g, 6.48 mmol, 93% yield) as yellowish solid which was utilized in the next step with no further purification. ^{1}H NMR (600 MHz, CDCl3) δ 10.35 (bs, 1H), 8.32 (d, *J* = 7.7 Hz, 1H), 7.97 (d, *J* = 3.3 Hz, 1H), 7.44 – 7.33 (m, 1H), 7.27 (dd, *J* = 10.5, 4.5 Hz, 1H), 7.26 – 7.21 (m, 1H), 5.81 (ddd, *J* = 24.8, 12.5, 7.3 Hz, 1H), 5.24 – 5.11 (m, 2H), 4.04 – 3.97 (m, 1H), 3.71 (dd, *J* = 11.1, 5.8 Hz, 1H), 3.63 (dd, *J* = 3.4, 2.4 Hz, 3H), 3.62 – 3.56 (m, 2H), 3.47 – 3.43 (m, 1H), 3.28 (dd, *J* = 14.1, 6.5 Hz, 1H), 2.74 (dd, *J* = 14.2, 8.3 Hz, 1H), 2.17 (dt, *J* = 13.3, 8.3 Hz, 1H), 2.10 – 2.04 (m, 2H), 1.94 – 1.87 (m, 2H), 1.28 – 1.25 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 185.1, 173.8, 166.0, 136.7, 132.4, 125.4, 124.1, 123.1, 121.9, 119.9, 113.8, 112.1, 68.5, 67.9, 67.6, 52.5, 49.6, 37.5, 35.0, 25.5, 23.9, 20.1; HRMS (EI) *m/z:* calc for $C_{19}H_{20}N_2O_4$ $(M)^+$ 340.1423, found 340.1418.

CAUTION: Product will go into 1N NaOH solution, the indole N-H is quite acidic.



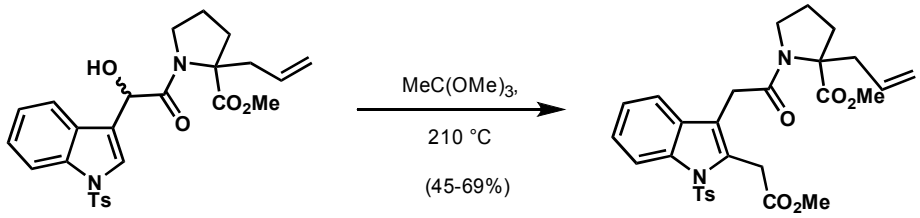
2.44 S2

A flame-dried roundbottom flask was charged with indole **2.41** (2.40 g, 7.05 mmol) and DCM (35 mL). To this solution was added triethylamine (2.00 mL, 14.0 mmol) and then p-toluenesulfonyl chloride (1.48 g, 7.76 mmol) and the resultant mixture was stirred at rt overnight at which point it was judged complete via TLC. The crude reaction mixture was filtered through a 2 inch pad of silica gel, which was flushed with 2:1 hexanes/ethyl acetate and the combined organic fractions were concentrated via rotary evaporation to give indole **S2** (3.15 g, 6.37 mmol, 90% yield) as colorless, viscous oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.52 (s, 1H), 8.35 – 8.27 (m, 1H), 7.94 (dd, *J* = 12.6, 6.3 Hz, 1H), 7.86 (d, *J* = 8.4 Hz, 1H), 7.43 – 7.33 (m, 1H), 7.29 (t, *J* = 9.0 Hz, 1H), 5.88 – 5.77 (m, 1H), 5.24 (s, 1H), 5.21 (d, *J* = 3.4 Hz, 1H), 3.91 (s, 1H), 3.74 – 3.67 (m, 1H), 3.59 (dt, *J* = 15.4, 8.2 Hz, 1H), 3.31 (dd, *J* = 14.2, 6.7 Hz, 1H), 2.82 – 2.74 (m, 1H), 2.37 (s, 2H), 2.24 – 2.16 (m, 1H), 2.16 – 2.09 (m, 1H), 2.01 – 1.89 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 185.6, 173.4, 164.2, 146.1, 136.9, 134.8, 134.3, 132.5, 130.2, 127.3, 127.2, 126.0, 125.0, 122.7, 119.9, 117.3, 113.2, 68.6, 52.7, 49.4, 37.6, 35.0, 23.9, 21.6.



S2 2.49

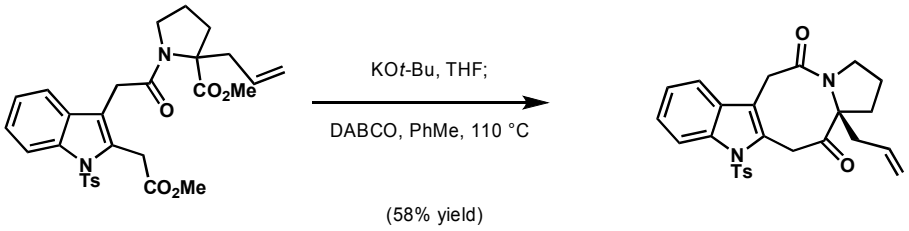
A flame-dried roundbottom flask was charged with indole **S2** (3.10 g, 6.27 mmol), MeOH (30 mL) and THF (30 mL) and was cooled to 0 ºC. To this solution was added sodium borohydride (0.355 mg, 10.0 mmol) and the resultant mixture was stirred for 45 minutes at 0 ºC at which point the reaction was judged complete via TLC. The reaction was quenched with saturated ammonium chloride (30 mL). The aqueous phase was extracted with dichloromethane (3 x 50 mL) and the combined organic layer was dried over sodium sulfate and concentrated via rotary evaporation to give alcohol **2.49** (2.85 g, 5.74 mmol, 92 % yield) as a pale yellow oil which was used without further purification.



2.49 2.50

A flame-dried 100 mL roundbottom flask was charged with crude alcohol **2.49** (0.900 g, 1.81 mmol), 2,6 dimethylbenzoic acid (0.054 g, 0.36 mmol), and trimethylorthoacetate (17 mL) and was equipped with a distillation head. The flask was heated to 130 ºC for 20 minutes while the methanol and trimethylorthoacetate distilled over. The flask was cooled and the distillation head was replaced with a reflux condenser and an additional aliquot of trimethylorthoacetate (10 mL) was added. The flask was heated to 210 ºC for 3 hours and then cooled to room temperature and the reaction solution was concentrated via rotary evaporation. The crude material was purified via silica gel chromatography (2:1 to 1:1 hexanes/ethyl acetate) to give **2.50** (0.570 g, 0.103 mmol, 56.9 % yield) as colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.3 Hz, 1H), 7.67 (d, *J* = 8.3 Hz, 2H), 7.48 (d, *J* = 7.8 Hz, 1H), 7.21 (t, *J* = 7.5 Hz, 1H), 7.17 (d, *J* = 8.2 Hz, 2H), 5.54 (td, *J* = 17.2, 7.5 Hz, 1H), 4.98 (dd, *J* = 18.8, 13.7 Hz, 2H), 4.15 (d, *J* = 1.8 Hz, 2H), 3.74 (d, *J* = 6.4 Hz, 1H), 3.70 (s, 2H), 3.68 (s, 1H), 3.67 – 3.61 (m, 6H), 3.41 (dd, *J* = 9.5, 6.9 Hz, 1H), 3.04 (dd, *J* = 14.1, 6.8 Hz, 1H), 2.60 (dd, *J* = 14.0, 8.0 Hz, 1H), 2.32 (s, 3H), 2.03 – 1.81 (m, 4H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.9, 171.0, 170.1, 167.7, 144.7, 136.1, 136.0, 133.2, 130.8, 129.7, 129.6, 126.6, 124.7, 123.4, 119.2, 118.9, 116.6, 114.5, 77.2, 76.9, 76.7, 68.6, 60.3, 52.2, 52.2, 49.0, 37.7, 35.0, 32.2, 31.6, 31.5, 23.8, 22.6, 21.4, 20.9, 14.1, 14.0; HRMS (ESI) *m/z* calc for $C_{29}H_{32}N_2NaO_7S$ $(M+Na)^+$ 575.6283,

found 521.1761.



2.50 2.51

A flame-dried roundbottom was charged with indole **2.50** (650 mg, 1.176 mmol) and THF (19.6 mL) and cooled to 0 ºC. To this solution was added potassium t-butoxide (277 mg, 2.470 mmol). The resultant solution was stirred at 0 ºC for 1 hour, at which piont TLC indicated complete consumption of starting material. Acetic acid (0.148 mL, 2.59 mmol) was added followed by toluene (19.60 mL) and the THF was removed via rotary evaporation to give the crude product in toluene. To this crude mixture was added DABCO (1,4-Diazabicyclo(2.2.2)octane) (0.388 mL, 3.53 mmol) and this was heated to 110 ºC for 2 hours, then cooled and quenched with 1 N HCl (10 mL). The aqeuos phase was extracted with ethyl acetate (2 x 10 mL). The combined organic layer was washed with brine and dried over sodium sulfate then concentrated via rotary evaporation. The crude material was purified via silica gel chromatography (1:1 hexanes/ethyl acetate to 2:3 hexanes/ethyl acetate) to give tetracycle **2.51** (320 mg, 0.692 mmol, 58.8 % yield) as a colorless oil. ^{1}H NMR (600 MHz, CDCl3) δ 8.80 (s, 1H), 8.08 – 7.99 (bs, 1H), 8.04 (t, J = 7.8 Hz, 1H), 7.72 (d, *J* = 8.3 Hz, 2H), 7.42 (d, *J* = 7.8 Hz, 1H), 7.35 – 7.28 (m, 1H), 7.23 (d, *J* = 8.3 Hz, 2H), 5.89 – 5.71 (m, 1H), 5.13 (d, *J* = 17.1 Hz, 1H), 5.09 (d, *J* = 10.1 Hz, 1H), 4.11 (dt, *J* = 29.7, 14.7 Hz, 1H), 3.89 (d, *J* = 8.8 Hz, 1H), 3.87 (s, 2H), 3.86 – 3.82 (m, 1H), 3.77 – 3.69 (m, 1H), 3.66 – 3.57 (m, 1H), 3.28 – 3.17 (m, 1H), 2.60 – 2.45 (m, 2H), 2.35 (s, 3H), 2.29 – 2.13 (m, 2H), 1.97 – 1.85 (m, 2H), 1.85 – 1.76 (m, 1H), ^{13}C NMR (151 MHz, CDCl3) δ 176.74, 176.29, 175.77, 174.49, 174.25, 171.13, 145.23, 136.15, 135.80, 133.54, 131.98, 130.55, 130.02, 129.73, 129.25, 128.88, 126.67, 125.24, 124.71, 123.68, 123.57, 121.23, 120.99, 119.00, 118.14, 114.57, 113.96, 99.54, 99.31, 72.46, 65.80, 60.36, 53.36, 53.22, 43.20, 42.57, 39.15, 38.71, 34.08, 33.70, 32.70, 31.54, 27.56, 27.37, 22.61, 22.29, 21.52, 20.99, 15.22, 14.16, 14.08, 14.02; HRMS (ESI) *m/z* calc for $C_{26}H_{30}N_2NaO_6S$ $(M+2H_2O+Na)^+$ 521.1722, found 521.1761.

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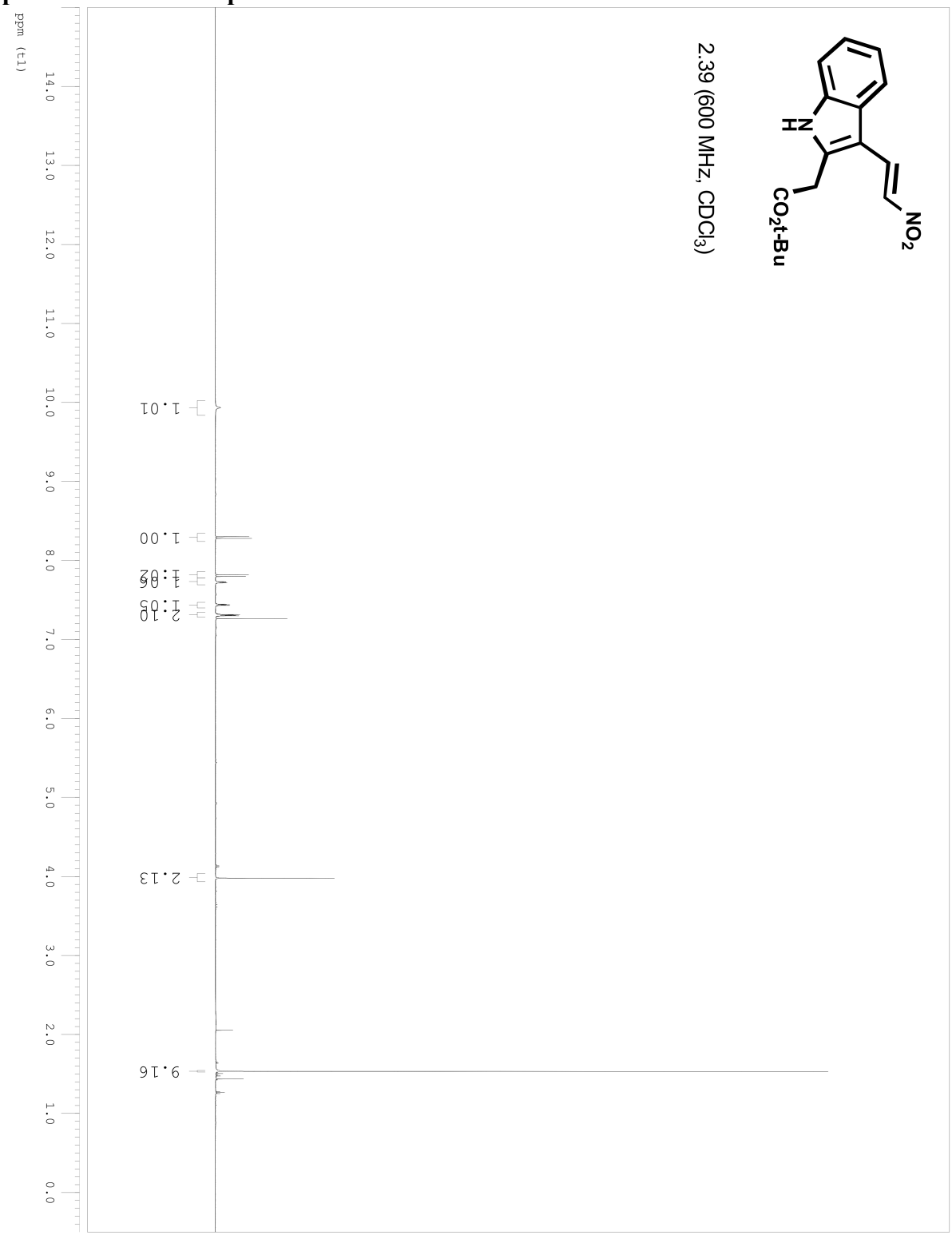
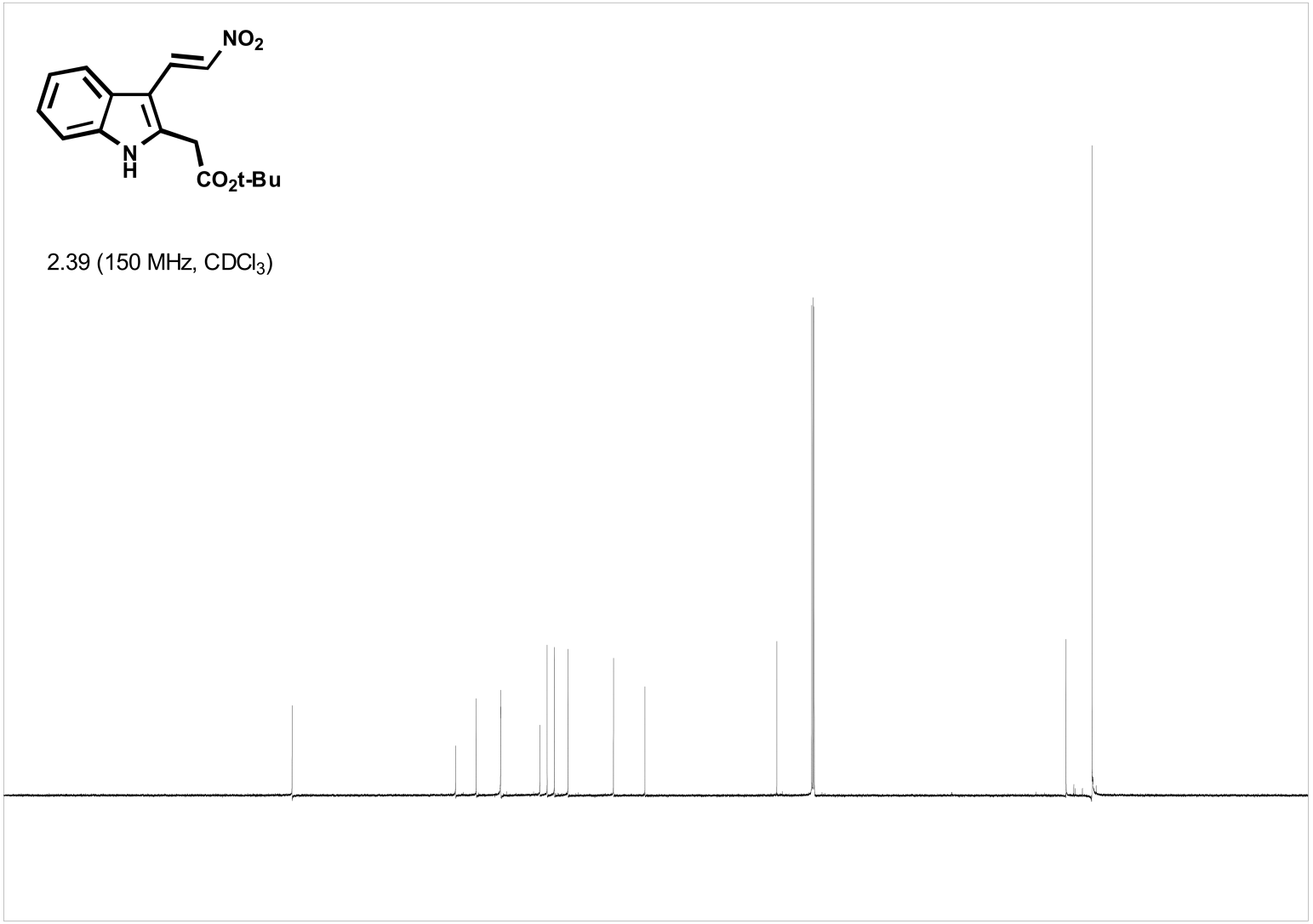
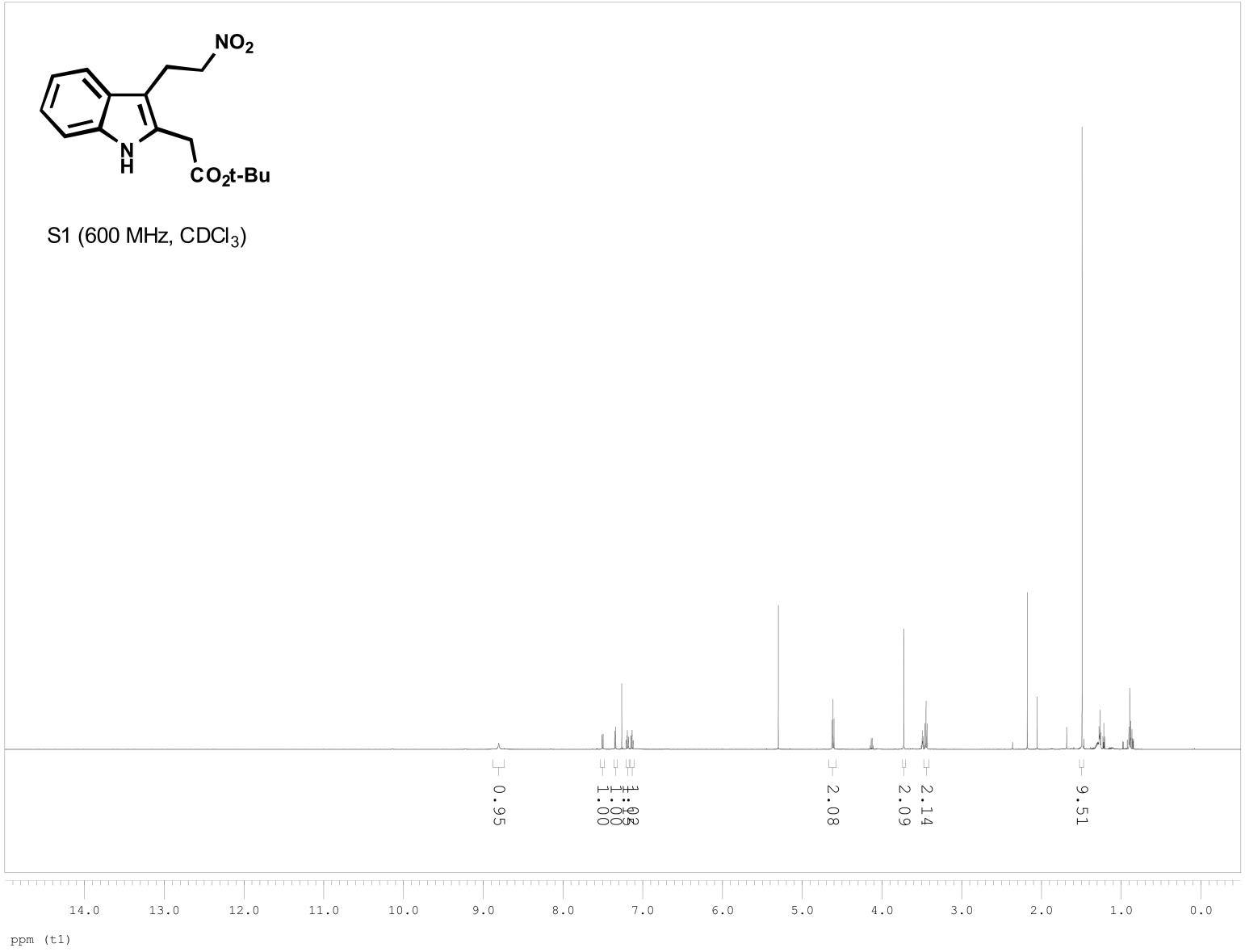
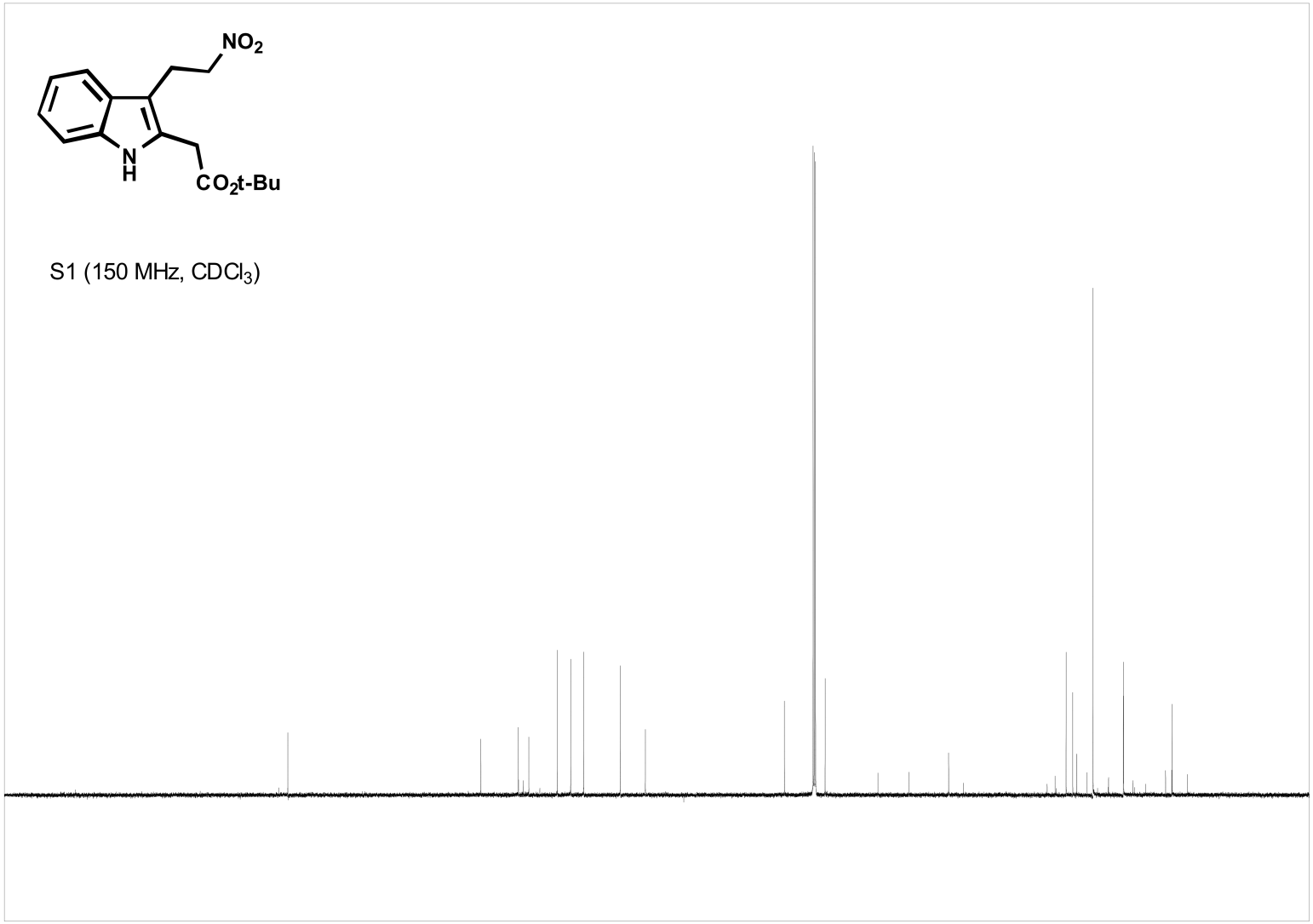
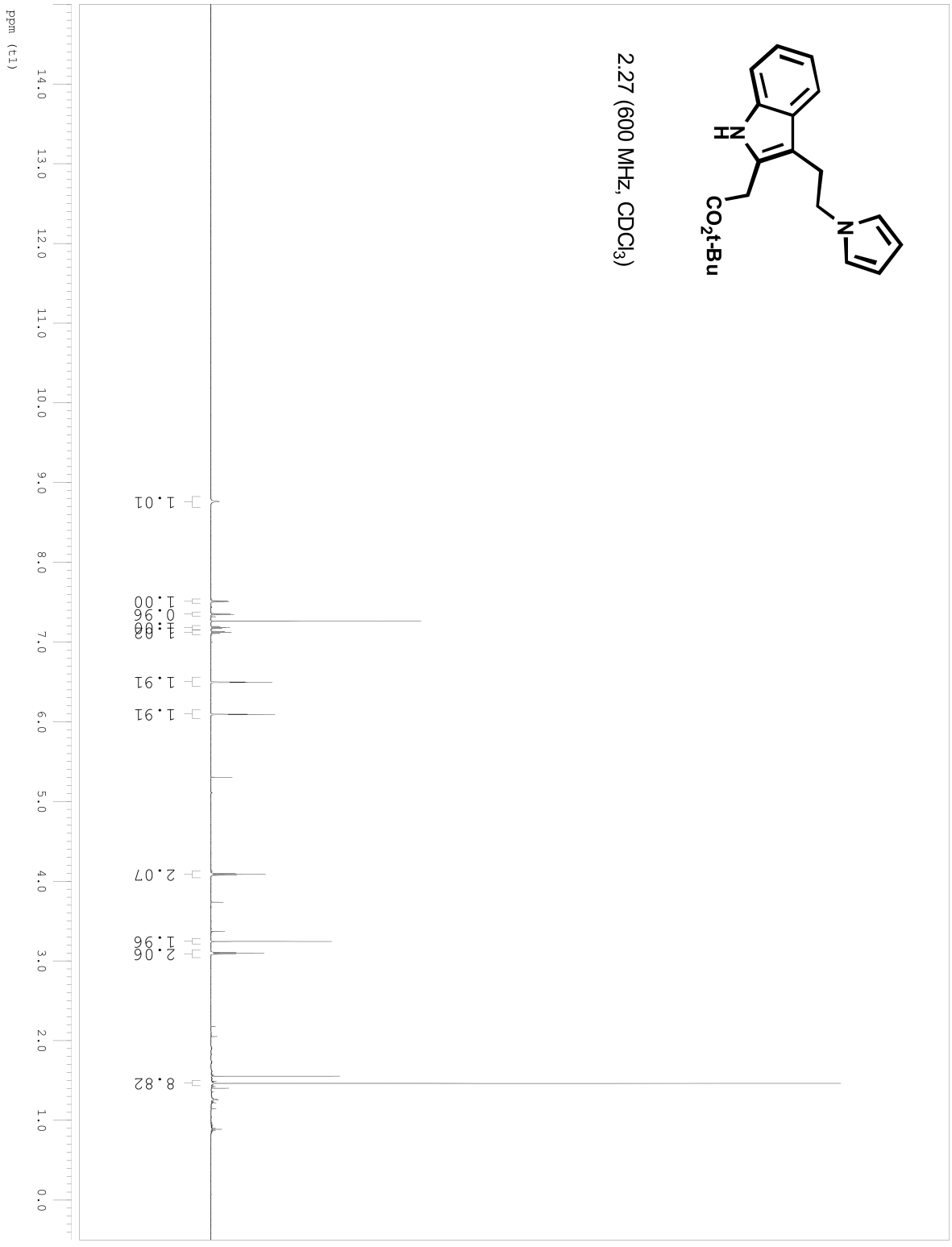
Appendix II: Selected Spectra

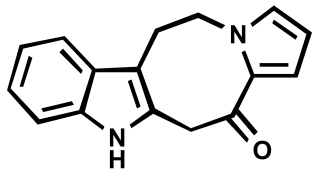



NO2
N
H
CO2t-Bu
2.39 (150 MHz, CDCl3)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm (t1)

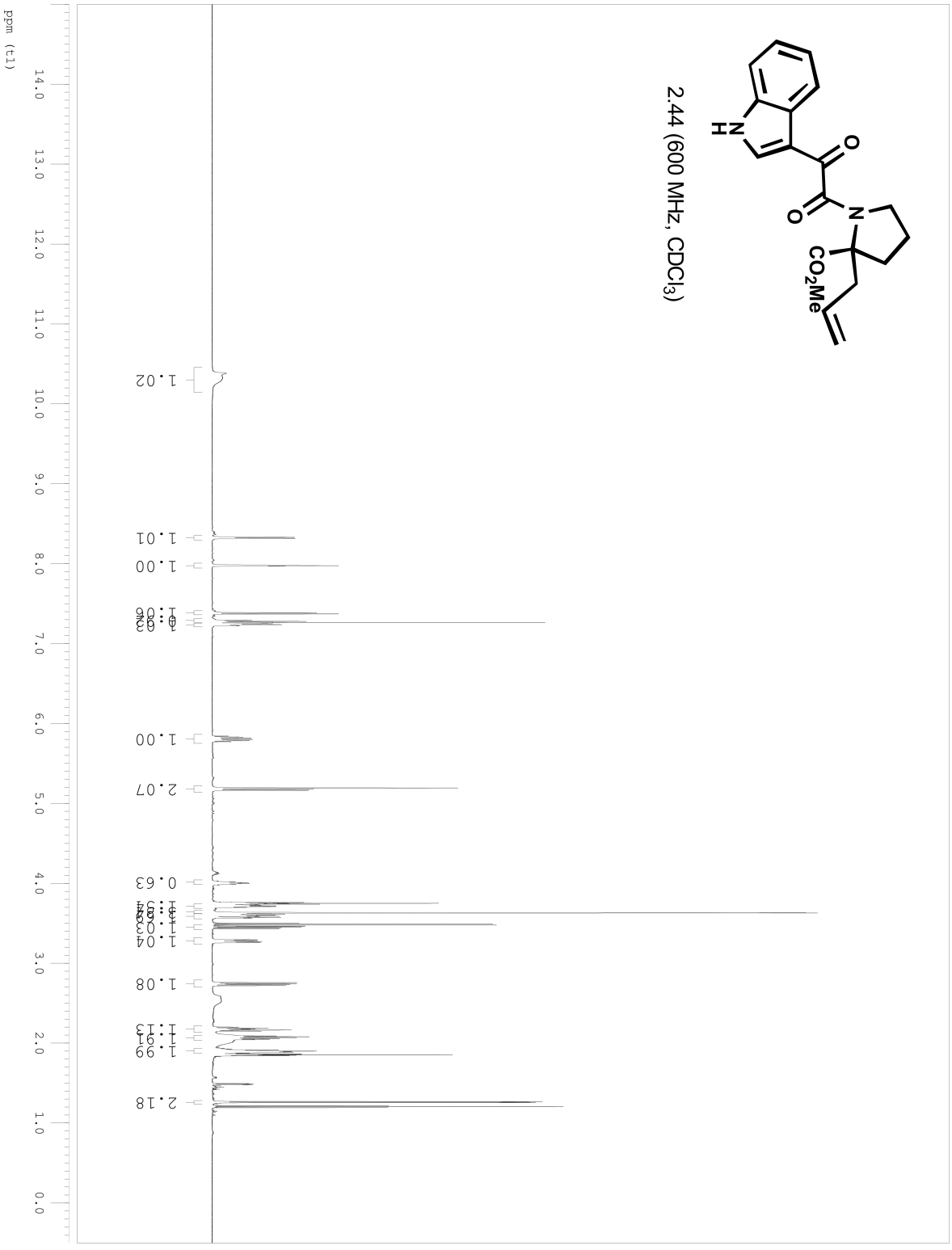

NO2
N
H
CO2t-Bu
S1 (600 MHz, CDCl3)
0.95
1.00
1.00
1.03
1.03
2.08
2.09
2.14
9.51
14.0
13.0
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

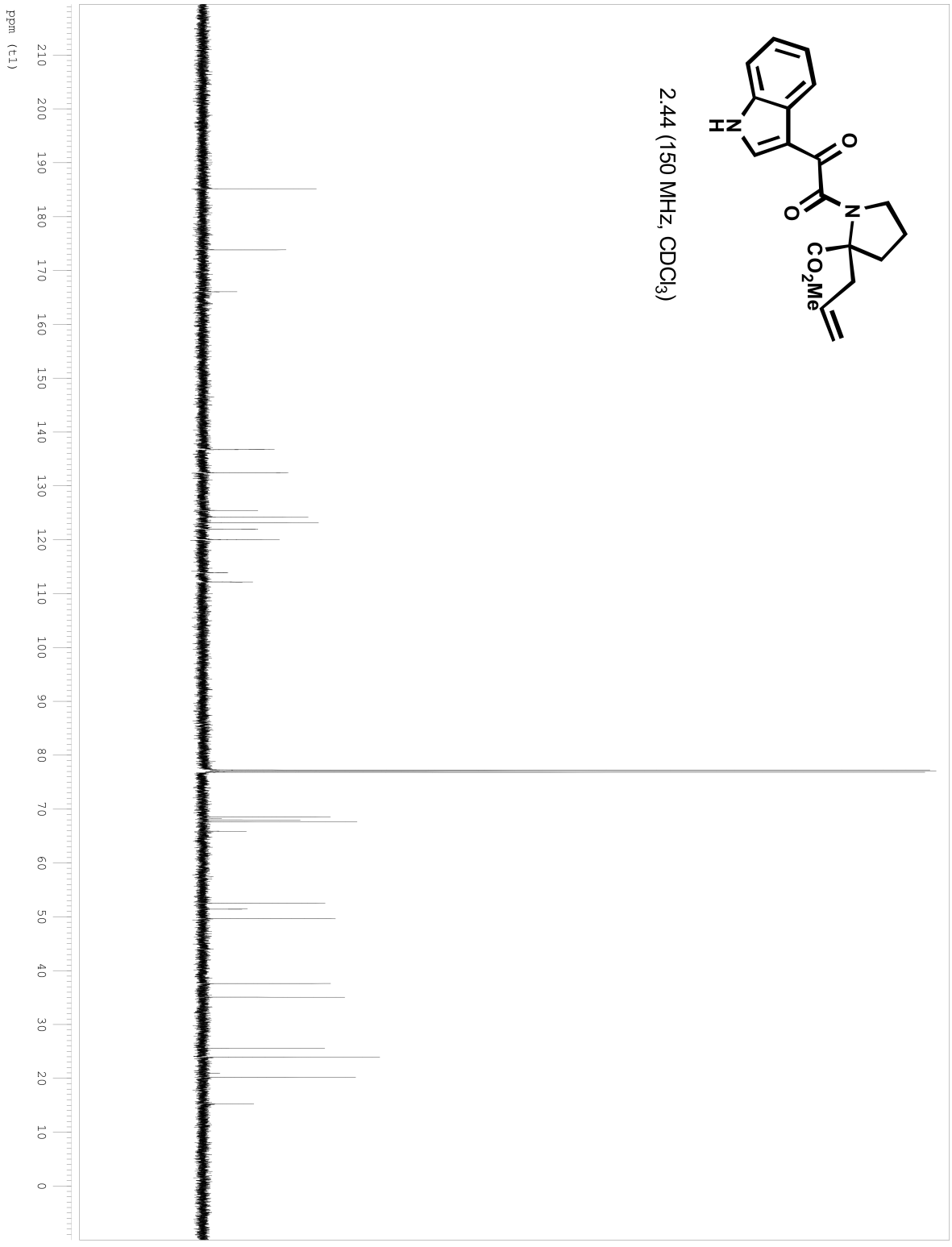

NO2
N
H
CO2t-Bu
S1 (150 MHz, CDCl3)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm (t1)

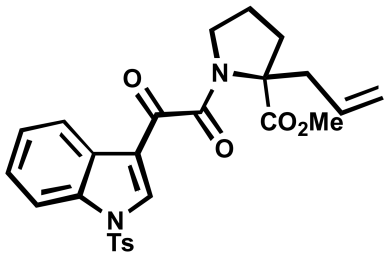

2.27 (600 MHz, CDCl3)
CO2t-Bu
N
H
N
ppm (t1)
14.0
13.0
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
1.01
1.00
0.96
0.96
1.91
1.91
2.07
1.96
2.06
8.82



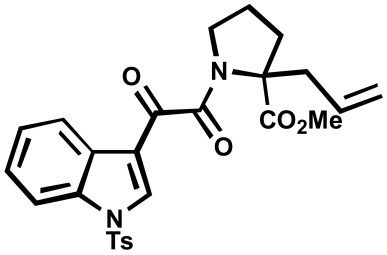
2.26 ($CDCl_3$, 500 MHz)


2.44 (600 MHz, CDCl3)
CO2Me
1.02
1.01
1.00
1.00
2.07
0.63
1.08
2.18
ppm (t1)

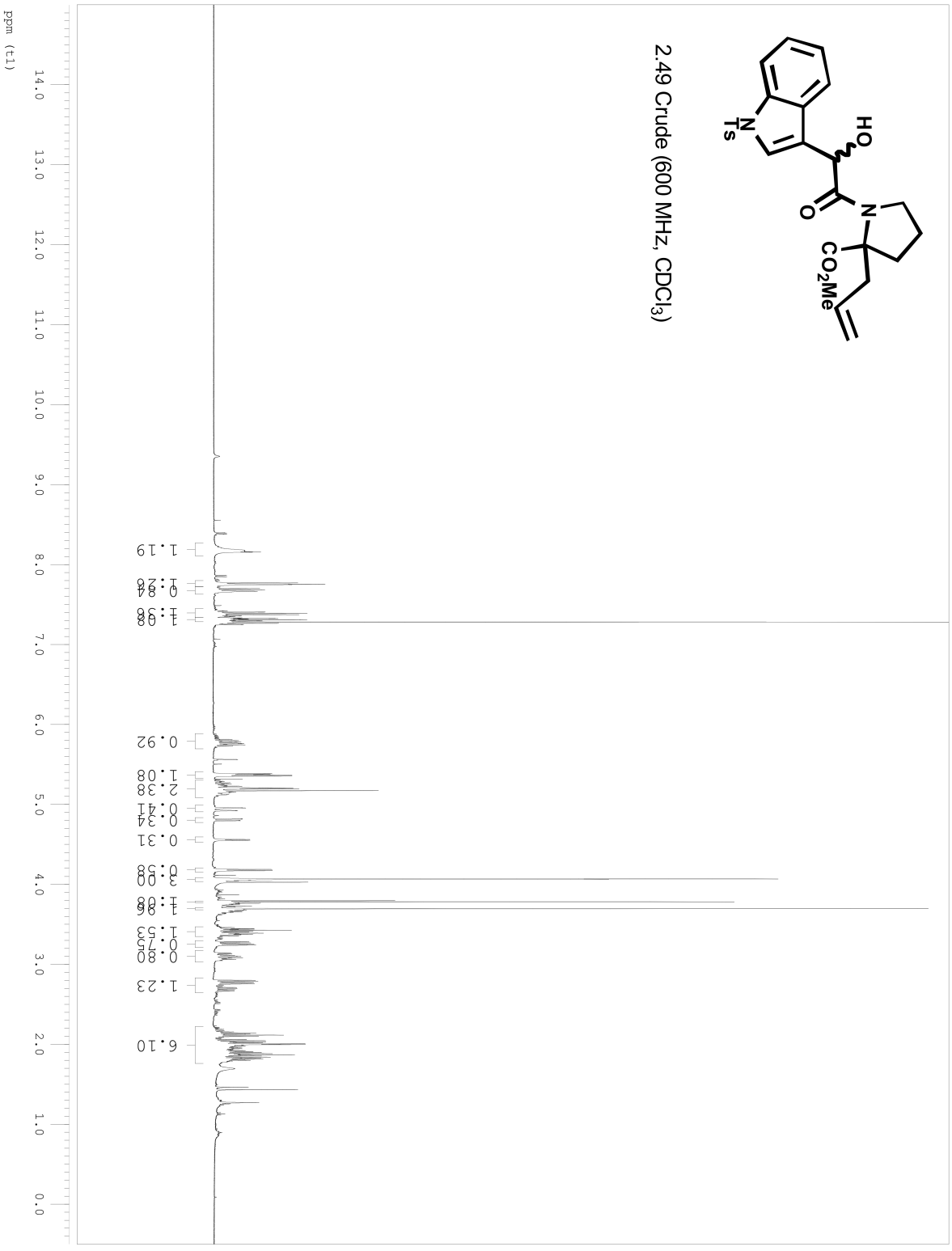

2.44 (150 MHz, CDCl3)
CO2Me
ppm (t1)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

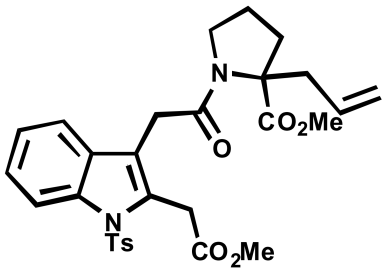


S2 (600 MHz, $CDCl_3$)

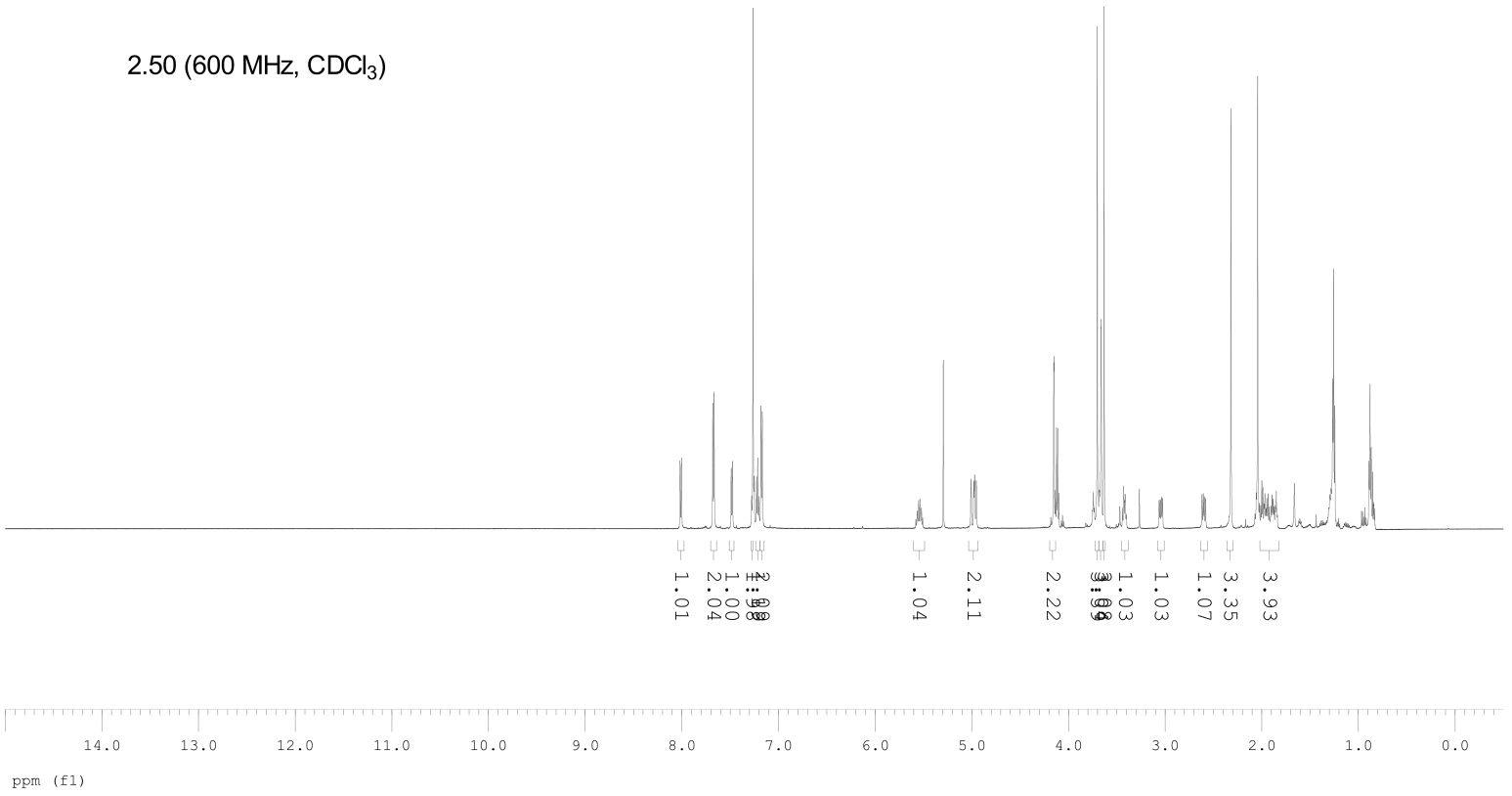


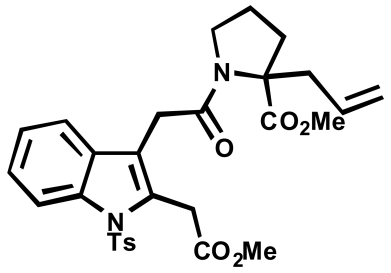
S2 (150 MHz, $CDCl_3$)


HO
N
Ts
O
N
CO2Me
2.49 Crude (600 MHz, CDCl3)
1.19
0.84
1.26
1.36
0.92
1.08
2.38
0.41
0.34
0.31
0.58
3.00
1.08
1.00
0.80
0.75
1.53
1.23
6.10
ppm (t1)
14.0
13.0
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0

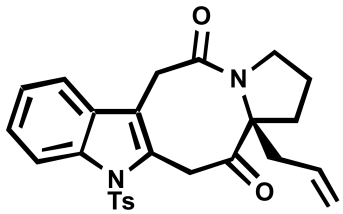


2.50 (600 MHz, $CDCl_3$)

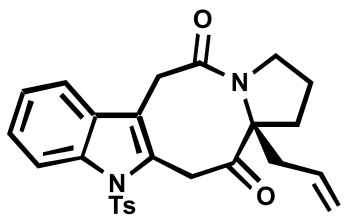




2.50 (150 MHz, $CDCl_3$)



2.51 ($CDCl_3$, 600 MHz)



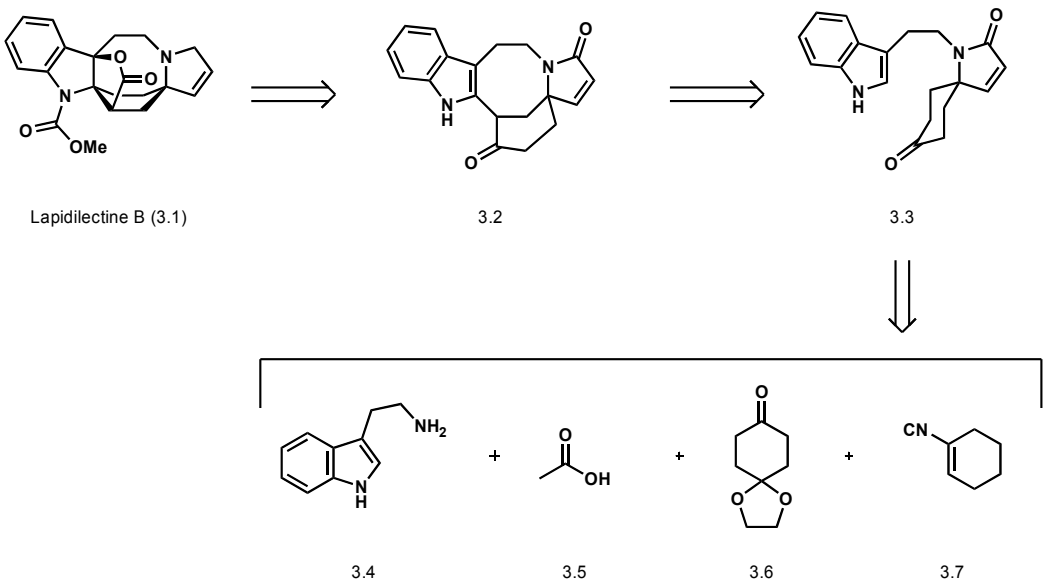
2.51 ($CDCl_3$, 150 MHz)

Chapter 3: An Ugi Four-Component Coupling Approach to the *Kopsia* Alkaloids

3.1. A New Synthetic Approach

3.1.1. Initial Retrosynthesis

Although the ability to construct the tetracycle of the *Kopsia* alkaloids was an encouraging development (see Chapter 2), the previously described synthetic efforts suffered from significant roadblocks, thus a new strategy was devised. As shown in Scheme 3.1, the natural product could arise from ketone **3.2** via an oxidation/rearrangement. This ketone could be derived from an intramolecular oxidative coupling of the meso-symmetric ketone **3.3** with the 2-position of the indole. Ketone **3.3** could be made via a series of functional group manipulations from the product of an Ugi four-component coupling of readily available starting materials (**3.4-3.7**), which contain all the necessary carbons for lapidilectine B.

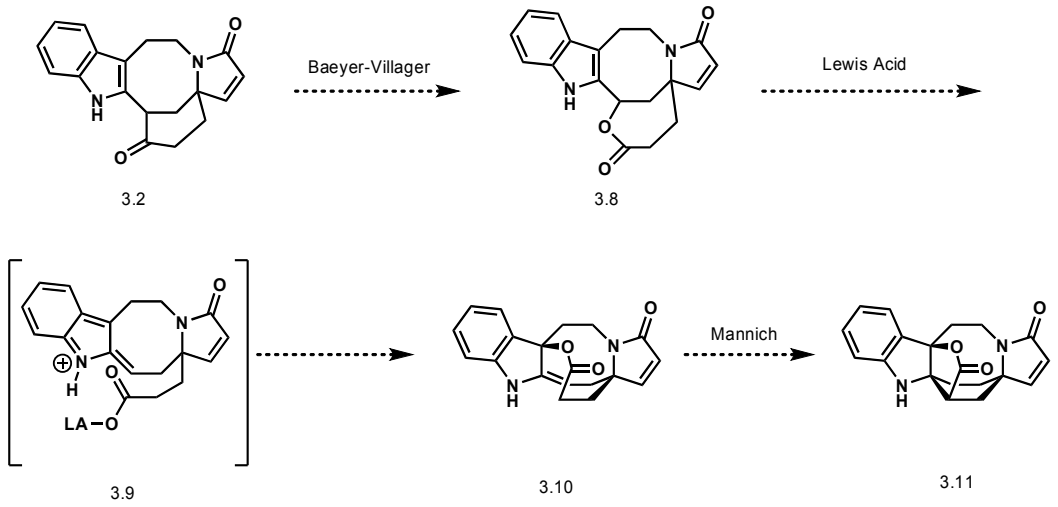


Scheme 3.1: Ugi four-component coupling-based retrosynthesis

3.1.2 An Alternative End-Game

Our initial vision for the late-stage sequence to transform pentacycle **3.2** into the natural product is depicted in Scheme 3.2. A Baeyer-Villager oxidation of the the ketone would furnish lactone **3.8** with preferential migration of the tertiary carbon over the methylene carbon. Lewis-acid activation of the ester carbonyl could allow ionization with assistance from the indole-ring to form intermediate **3.9**. This intermediate could revert back to the lactone **3.8**. Alternatively, addition of the Lewis-acid bound carboxylate to the 3-position of the indole could form enamine **3.10**. It was anticipated that the close proximity would facilitate an intramolecular Mannich reaction to close the five-membered lactone ring and furnish the

natural product skeleton (**3.11**).

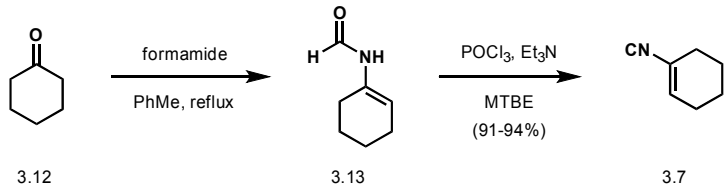


Scheme 3.2: Alternative end-game

3.2. Forward Synthesis

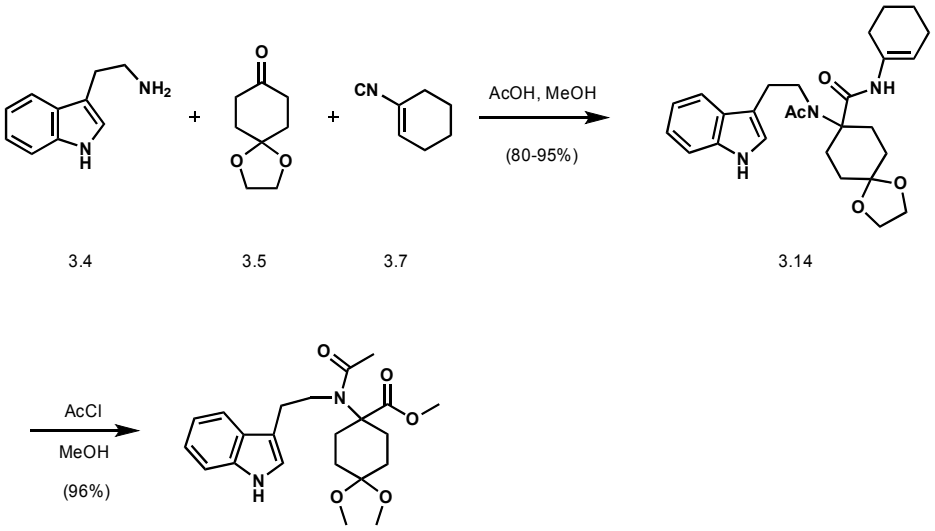
3.2.1. Ugi Four-Component Coupling

Isocyanide **3.7** is a well-known reagent developed by Armstrong that is popular for use in Ugi four-component coupling reactions.[1] There are several reports of the synthesis of this reagent; however, each has significant drawbacks. The most straightforward route involves the condensation of formamide with cyclohexanone followed by dehydration of ene-formamide **3.13** to yield the isocyanide (see Scheme 3.3). In the initial reports, phosgene is utilized as the dehydrating agent and dichloromethane (DCM) is used as the solvent. Although these conditions gave the desired product, silica gel chromatography was necessary for purification and yields were typically around 70%. It was found that by switching to phosphorous oxychloride, a cheap and tempered desiccant, and utilizing methyl *t*-butyl ether (MTBE), a much more environmentally friendly solvent compared to DCM,[2] the reaction proceeded with a considerable decrease in impurities, allowing the use of a short silica-gel plug in place of a column, and increasing yields to greater than 90%.



Scheme 3.3: Optimized synthesis of the Armstrong isocyanide

With the Armstrong isocyanide (**3.7**) in hand, the Ugi four-component coupling proceeded smoothly to furnish amide **3.14** (Scheme 3.4). To accomplish this transformation, tryptamine (**3.4**) and ketone **3.5** were premixed with an equivalent of acetic acid in methanol, and then the Armstrong isocyanide (**3.7**) was added in one portion. This reaction was run on scales up to 200 grams without loss of performance. The reaction proceeded remarkably quickly, with complete conversion occurring in under 15 minutes even on larger scale. Notably, the reaction solution solidifies completely upon completion. This feature initially hindered product isolation, but addition of water at the completion of the reaction allowed for the isolation of extremely pure material. Treatment of **3.14** with HCl in methanol converted the cyclohexene amide into methyl ester **3.15**, demonstrating the utility of the Armstrong isocyanide.[3]

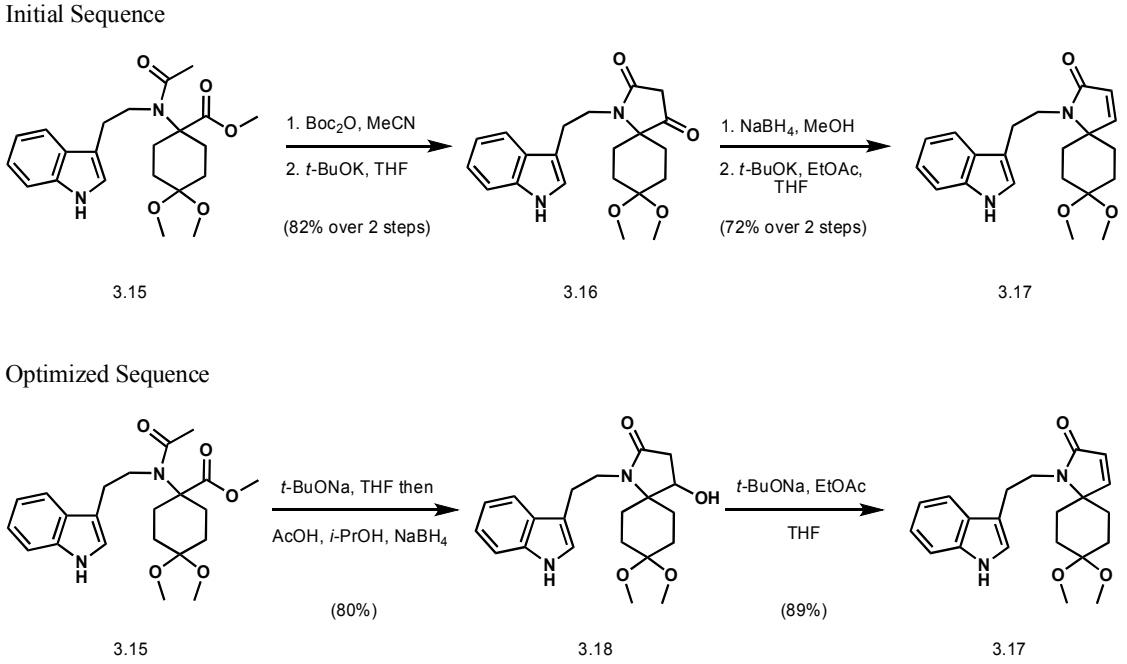


Scheme 3.4: Ugi four-component coupling

3.2.2. Construction of the Lactam Ring

With **3.15** in hand we investigated the installation of the five-membered lactam ring as depicted in Scheme 3.5. On the basis of literature precedent,[4] we attempted a Dieckmann condensation to close the ring and give **3.16**, but this only worked after protection of the indole as the BOC-carbamate, which was cleaved during the Dieckmann reaction. From here, reduction of β-keto amide **3.16** using sodium borohydride, followed by dehydration of the resultant β-hydroxy amide by activation of the hydroxyl group as an acetate, gave α,β-unsaturated lactam **3.17**. Although this procedure delivered product, we sought to minimize the number of isolations of synthetic intermediates. These intermediates were all only sparingly soluble in organic solvents, necessitating isolation via filtration, which always involves transfer losses. In that regard, it was found that switching the *t*-butoxide counterion from potassium to sodium accomplished the Dieckmann without need to protect the indole. The Dieckmann step was then telescoped with the borohydride reduction to give **3.18** directly. The resulting product

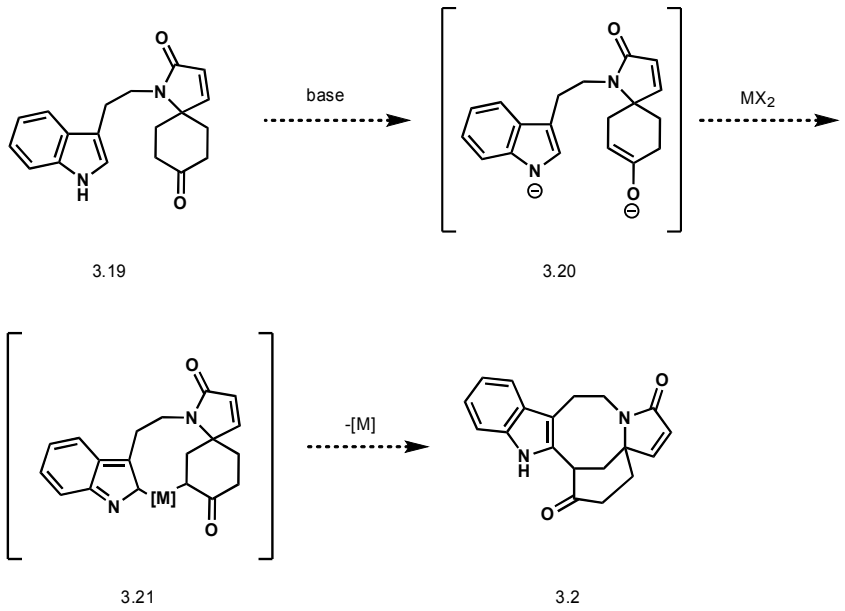
could then be treated with similar dehydrating conditions to give lactam **3.17** in improved yield (71% overall vs. 59% previously) and reduced the number of chemical manipulations.



Scheme 3.5: Lactam formation

3.2.3. Attempts at Oxidative C-C Bond Formation

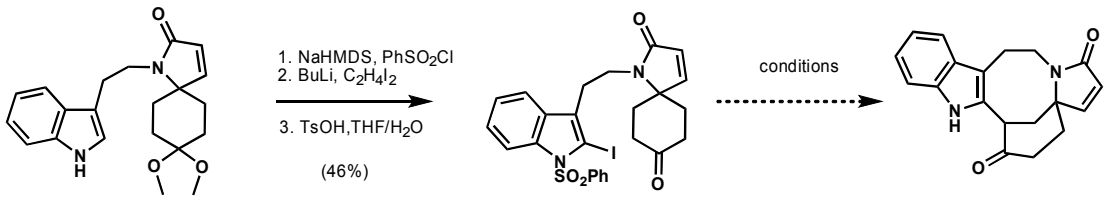
At this stage we began investigating an intramolecular carbon-carbon bond formation to install the eight-membered ring of the natural products (**3.3** → **3.2**, Scheme 3.1). Scheme 3.6 details the general method that was explored. After initial deprotonation of **3.19** using strong base, dianion **3.20** could be treated with an oxidant to effect bond formation.[5] Unfortunately, attempts with a number of different bases (LDA, LiHMDS, KHMDS, and LiTMP) and a number of different oxidants (iodine, potassium ferricyanide, copper chloride) failed to yield the desired product.



3.19 3.20 3.21 3.2

Scheme 3.6: Proposed oxidative coupling

We then explored a more step-wise approach to the carbon-carbon bond formation. It was hypothesized that a pre-oxidation to install functionality on the indole ring followed by a traditional transition metal-based cross-coupling could accomplish the crucial bond formation.[6] As depicted in Scheme 3.7, protection of the indole in **3.17** with benzene sulfonyl chloride provided the opportunity to accomplish a directed deprotonation at the C-2 position of the indole using *n*-butyl lithium. This carbanion was quenched with an electrophilic iodine source, which was followed by ketal hydrolysis to give functionalized indole **3.22**. From here, a variety of enolate cross-coupling conditions were attempted, but none produced the desired product (**3.2**).[7]



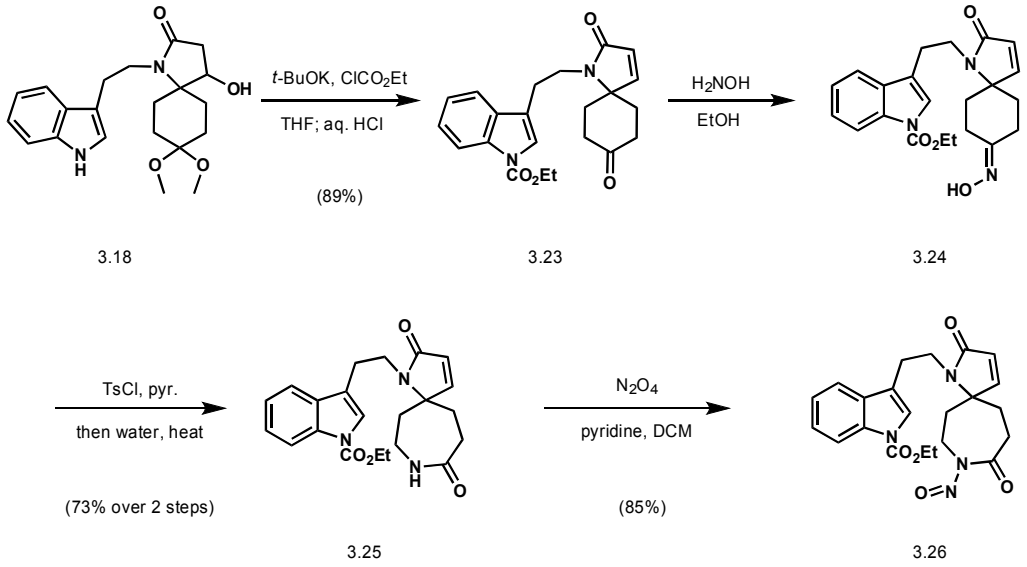
3.17 3.22 3.2

Scheme 3.7: Prefunctionalization of the indole ring

3.2.4. Beckmann Rearrangement Approaches

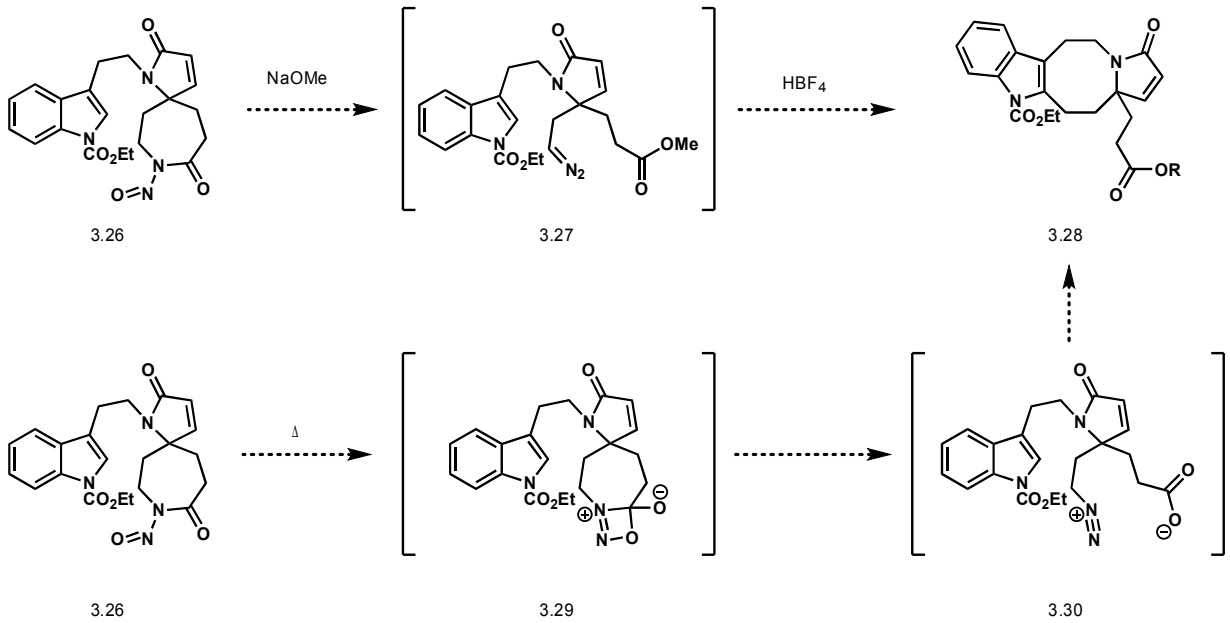
Because of the difficulties associated with formation of caged structure **3.2**, we next explored carbon-carbon bond cleavage prior to eight-membered ring formation. We postulated that relieving some of the ring-strain inherent in **3.22** might allow for construction of the eight-

membered ring, which could subsequently be functionalized to produce the natural product. As depicted in Scheme 3.8, we explored the Beckmann rearrangement as a way to accomplish this carbon-carbon bond cleavage.[8] A three-step, one-pot procedure allowed for the conversion of **3.18** into **3.23** via elimination of an activated carbonate and protection of the indole, followed by hydrolysis of the ketal to yield **3.23**. Formation of oxime **3.24** proceeded upon treatment of the ketone with hydroxylamine in ethanol. The Beckmann rearrangement was accomplished in a one-pot operation by subjecting oxime **3.24** to tosyl chloride and pyridine followed by addition of water and heating the resulting mixture to give ε-lactam **3.25**. This lactam could then be functionalized using nitrogen dioxide and base to give the brightly colored nitroso-amide **3.26**.[9]



Scheme 3.8: Beckmannm rearrangement

The highly functionalized substrate **3.26** presented several interesting opportunities for eight-membered ring formation (Scheme 3.9). On the basis of literature precedent, nitrosoamides can be treated with methoxide to give a methyl ester and a diazo group.[10] It was postulated that treating diazo-compound **3.27** with a non-coordinating acid such as tetrafluoroboric acid could lead to protonation of the diazo group and displacement of the subsequent diazonium moiety by the indole C-2 position to form the eight-membered ring. Alternatively, heating these compounds has been demonstrated to induce a rearrangement to form a carboxylate and a diazonium ion, as in **3.30**. This could then be engaged by the indole ring to form the eight-membered ring. Unfortunately, both sets of conditions failed to produce the desired tetracycle and only led to decomposition.

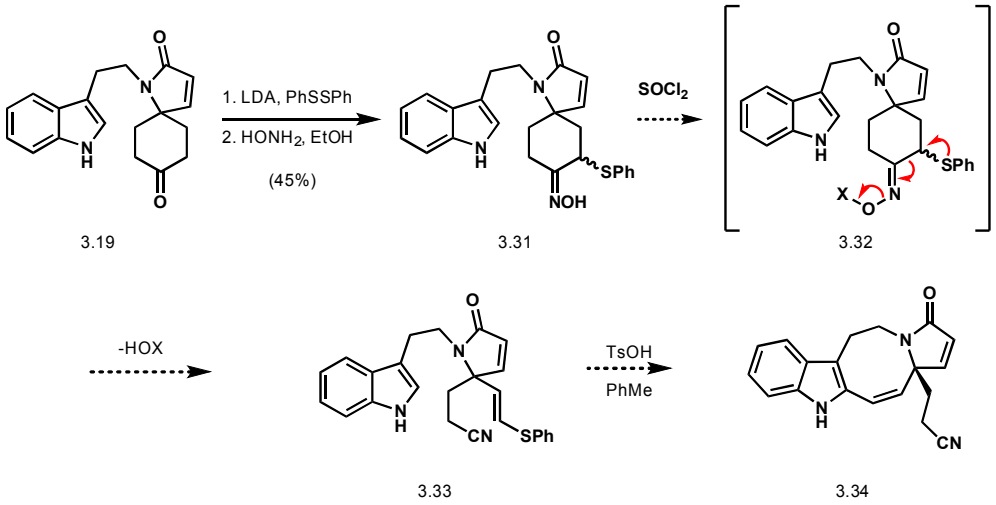


Scheme 3.9: Nitrosoamide chemistry

3.2.5. Beckmann Fragmentation

While exploring the literature of the Beckmann rearrangement, we came upon a lesser-known variant called the Beckmann fragmentation.[11] When the oxime in question contains an electron donating substituent at the α-position, activation of the oxime with a dehydrating agent such as thionyl chloride (see **3.31** to **3.32** in Scheme 3.10) can be followed by a Grob-type fragmentation,[12] which gives rise to a nitrile and a functional group at the aldehyde oxidation level. This sets the stage for a Friedel-Crafts alkylation to form the eight-membered ring.

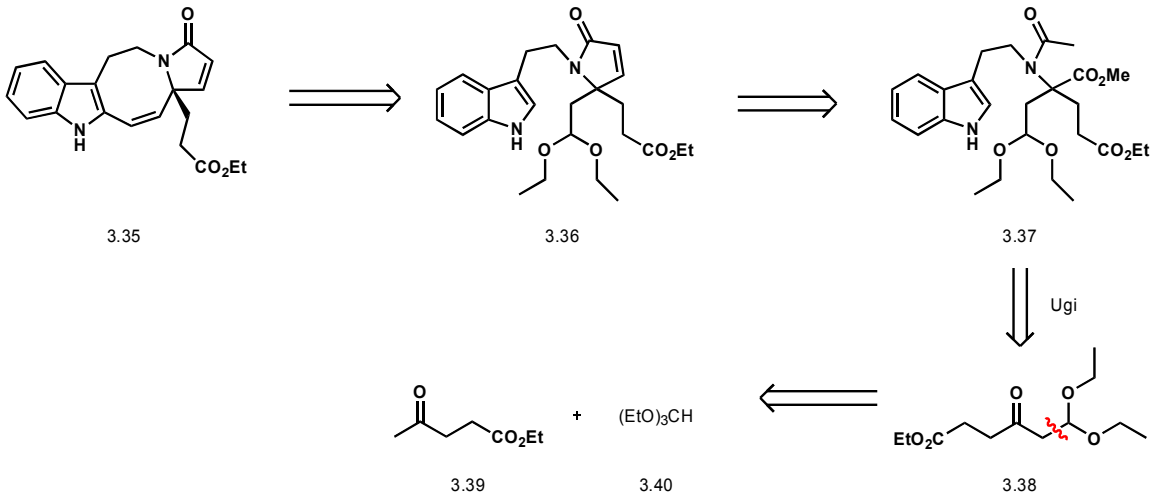
Treatment of ketone **3.19** with LDA and then diphenyl-disulfide was followed by oxime formation using hydroxylamine to produce **3.31** in modest yield. Unfortunately, several attempts at the Beckmann cleavage using thionyl chloride as well as other desiccants (tosyl chloride, mesyl chloride, sulfuric acid) all gave rise to non-specific decomposition.



Scheme 3.10: Beckmann fragmentation

3.2.6. A Pre-Functionalized Substrate

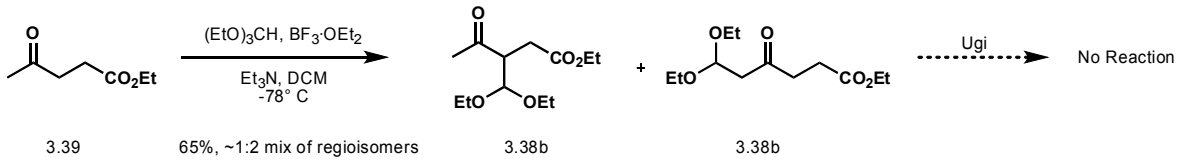
Because of the difficulties associated with cleaving the carbon-carbon bond in the six-membered ring of **3.19**, we decided to explore the Ugi four-component coupling on a substrate that was already pre-functionalized and at the correct oxidation level for future chemistry (Scheme 3.11). We began with ketone **3.38**, which can be synthesized from commercially available ethyl levulinate and triethyl orthoformate.



Scheme 3.11: Acyclic Ugi retrosynthesis

As depicted in Scheme 3.12, ethyl levulinate was treated with triethyl orthoformate and boron trifluoride followed by triethylamine to yield **3.39** as a 2:1 mixture of regioisomers. This tri-functionalized C6 unit was then subjected to Ugi conditions analogous to those mentioned previously (*vide supra*). No reaction was observed, even upon heating. We attempted to preform the imine required for this reaction, but this was also found not to be suitable for the

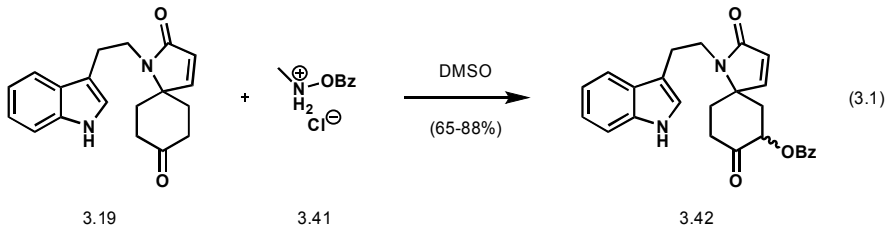
Ugi reaction.



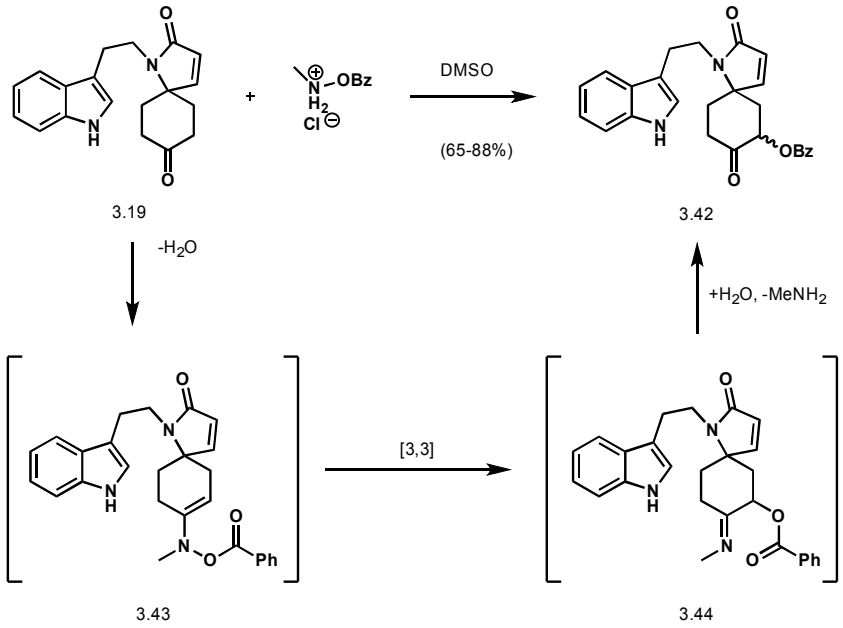
Scheme 3.12: Unsuccessful Ugi reaction

3.2.7. Lead-mediated Oxidative Cleavage

Alternative oxidative cleavage conditions of the cyclohexanone derivative were next examined. Because of the sensitive nature of the indole ring, especially toward oxidizing reagents, careful consideration was required. Amino-benzoate **3.41** has been utilized as a mild and selective reagent for the α-oxygenation of ketone and aldehyde substrates.[13] Treatment of **3.19** with **3.41** in DMSO smoothly produced **3.42** (eq 3.1).

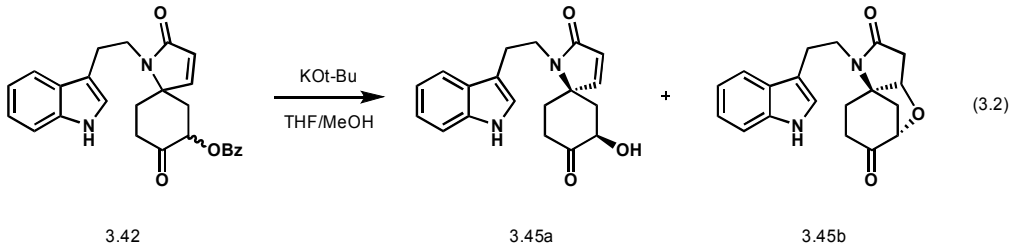


This aminobenzoate reagent (**3.41**) is able to accomplish the selective oxidation of carbonyl compounds in the presence of other sensitive functionalities such as sulfides or indoles. As shown in Scheme 3.13, the amine first condenses with the carbonyl to form enamine **3.43**. This enamine then undergoes a [3,3] sigmatropic rearrangement to break the weak N-O sigma bond and create a C-O σ-bond. From here, hydrolysis of imine **3.44** gives oxidized product **3.42** in good yield. This reaction is selective for aldehydes in the presence of ketones due to the differing rates of initial condensation and can also be selective on the basis of steric hindrance for the carbonyl in question.

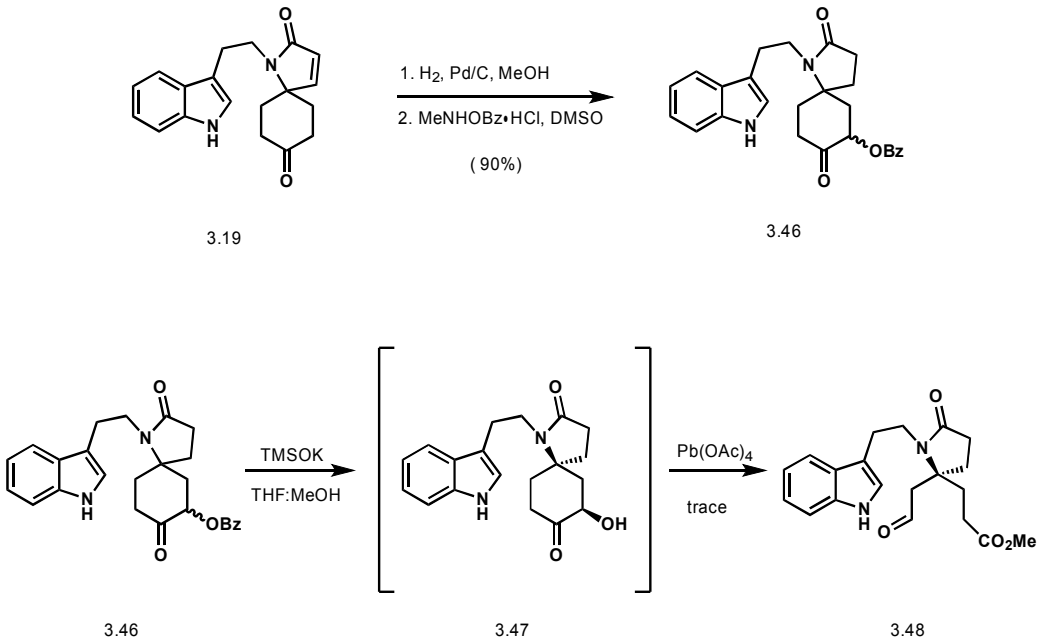


Scheme 3.13: α-Oxidation mechanism

Benzoate **3.42** could be hydrolyzed utilizing potassium methoxide; however, one of the diastereomers underwent an unanticipated intramolecular conjugate addition with the α,β-unsaturated lactam to produce **3.45b** in addition to the desired **3.45a** (eq 3.2).



To avoid this by-product while testing further chemistry, it was decided to remove the double bond in the α,β-unsaturated amide via hydrogenation, which was accomplished using heterogeneous conditions. The α-oxidation was unaffected by the change of substrate (Scheme 3.14). After oxidation, the benzoate group in **3.46** was then hydrolyzed utilizing potassium trimethylsilenoate (TMSOK) in THF/methanol to yield α-hydroxy ketone **3.47**, which was then treated with lead tetraacetate to effect the oxidative carbon-carbon bond cleavage. Trace amounts of an aldehyde (presumed to be **3.48**) were detected in the crude NMR, but a thorough screen of reaction conditions failed to identify a usable procedure.



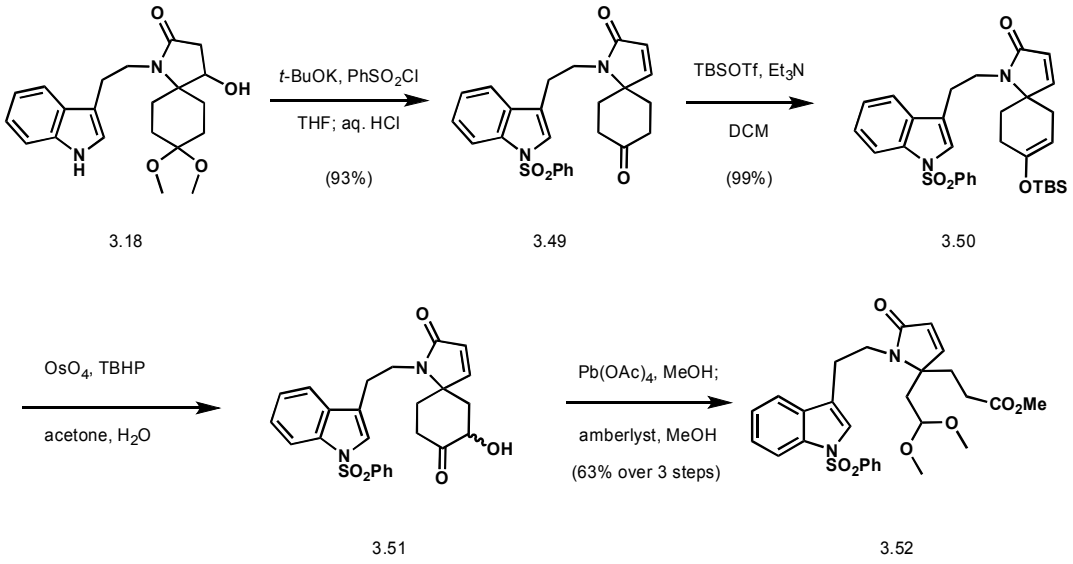
3.19 3.46

3.46 3.47 3.48

Scheme 3.14: Attempted lead oxidation

3.2.8. Protection of the Indole

Operating under the assumption that the indole moiety was susceptible to oxidation, we decided to explore options to reduce the electron density of the indole ring in hopes of making it more stable to oxidative conditions. A benzene sulfonamide group was chosen initially because of the robust nature of this protecting group.[14] The three-step, one-pot procedure developed previously for protection with ethyl chloroformate (see Scheme 3.8) was also amenable to the use of benzenesulfonyl chloride for the desired protection, which transformed **3.18** into **3.49** in high yield (Scheme 3.15). With the indole protected, we could now explore numerous other oxidation procedures. This opened up a number of possibilities for α-oxygenation of the ketone. The popular Rubottom oxidation[15] or one-step oxidation using the enolate and an oxaziridine[16] both suffered from low conversions with substrate **3.49.** Much better results were obtained by formation of silyl-enol ether **3.50** using TBSOTf and triethyl amine followed by selective dihydroxylation using osmium tetroxide and *tert*-butyl hydroperoxide as the stoichiometric oxidant.[17] *N*-methylmorpholine was initially used as the stoichiometric oxidant, but it was found that on scales larger than 250 mg, this led to intractable emulsions during workup. TBHP did not suffer from this drawback and had the added benefit of being a much cheaper and environmentally benign reagent. Oxidation of **3.51** using lead tetraacetate in methanol and immediate protection of the aldehyde as the dimethyl acetal led to substrate **3.52** in good yield. This route to acetal **3.52** marked an important milestone in our synthesis of lapidilectine B.



3.18 3.49 3.50

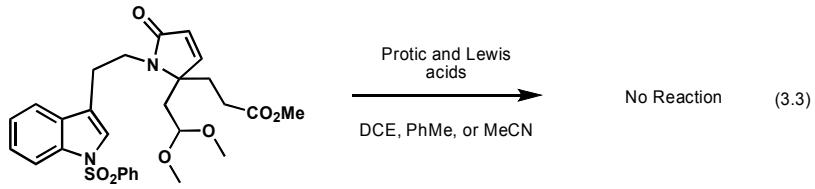
3.51 3.52

Scheme 3.15: Successful oxidative cleavage

3.3. Tetracycle Formation and Elaboration

3.3.1. Friedel-Crafts Alkoxyalkylation

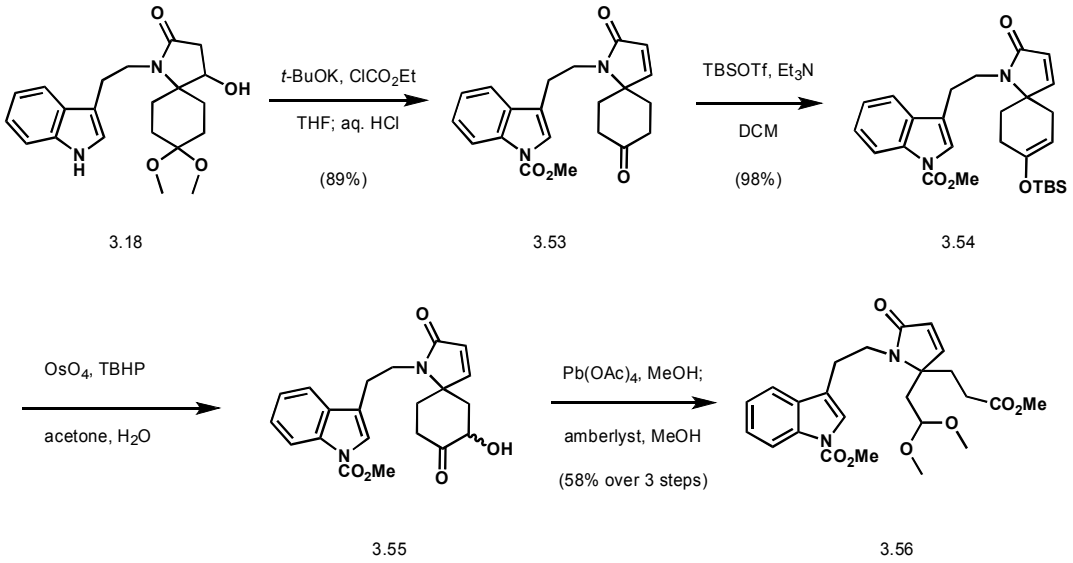
After solving the crucial problem of carbon-carbon bond cleavage to arrive at acetal **3.52**, we next turned our attention to the key cyclization to forge the eight-membered ring.[18] We envisioned addition of the indole into an oxocarbenium ion generated from the ionization of the acetal to form the key bond. Unfortunately, a number of different protic and Lewis acids either returned starting material or led to hydrolysis of the acetal (eq 3.3). The electron-withdrawing nature of the benzenesulfonamide group, which was beneficial for the oxidative steps, lowers the nucleophilicity of the indole ring to a point where it could not participate competently in the ring-forming reaction. Attempts to cleave the protective group to return the indole's inherent nucleophilicity were unsuccessful, as conditions that are typically used to cleave the sulfonamide group[19] decomposed the substrate.



3.52

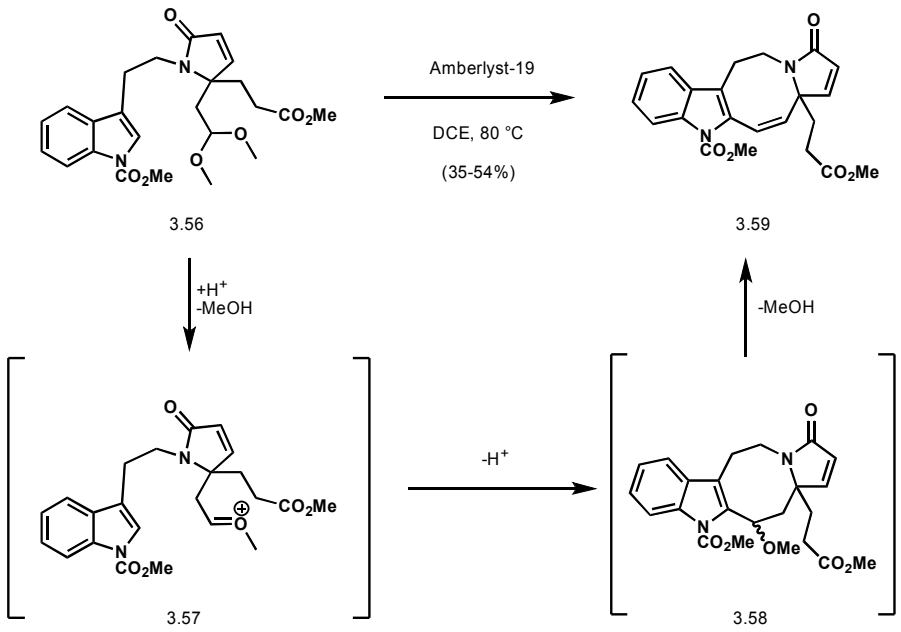
To overcome this roadblock, the methylcarbamate protecting group was investigated as a potential alternative protective group. Like the benzene sulfonamide, a carbamate group is electron-withdrawing, but not to the same extent. It was hoped that this group would provide a "Goldilocks" solution by both protecting the indole during the oxidative steps, but not preclude

cyclization. Carbamate groups are also very simple to cleave from indoles, which is a feature that has been utilized in the development of combinatorial chemistry platforms.[20] However, it also means that the utility of the carbamate as a protective group for the indole ring can be limited. The sequence in Scheme 3.16 is analogous to the one described for the synthesis of substrate **3.52** (Scheme 3.15), with all steps proceeding as predicted. Since the methylcarbamate is more labile than the sulfonamide, care had to be taken to avoid any small nucleophiles such as hydroxide or methoxide, which readily cleave this protecting group from indoles.



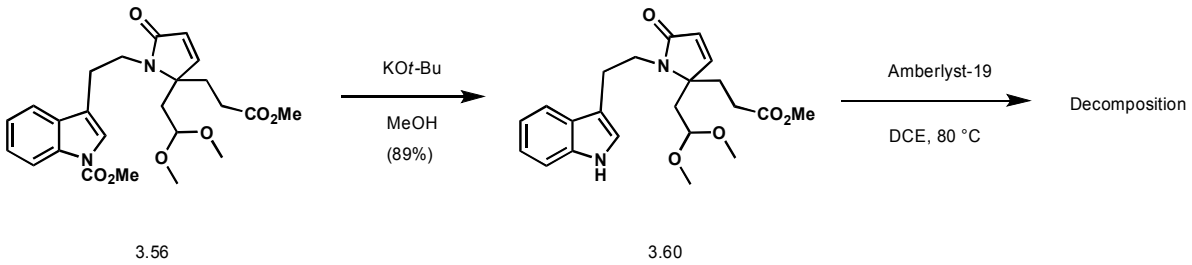
Scheme 3.16: Carbamate protected substrate synthesis

With acetal **3.56** in hand, we then attempted the key cyclization to form the eight-membered ring. Heating acetal **3.56** with Amberlyst®-15 acidic resin in dichloroethane did in fact achieve the cyclization (Scheme 3.17), presumably via initial engagement of oxocarbenium **3.57** by the indole ring to form a carbon-carbon bond, followed by subsequent elimination of methanol. This reaction was somewhat problematic, however, as extended reaction times lead to product decomposition, while shorter reaction times lead to incomplete conversion.



Scheme 3.17: Successful eight-membered ring formation

One option for improving the yield of this cyclization that was explored was the removal of the carbamate, which would increase the nucleophilicity of the indole ring. It was found that treating compound **3.56** with anyhydrous potassium methoxide readily cleaved the carbamate from the indole without saponification of the methyl ester (Scheme 3.18). Unfortunately, indole **3.60** was more prone to decomposition under the reaction conditions, and no suitable conditions for cyclization were found. Because of this outcome the carbamate-proteced indole **3.56** was the substrate chosen to move forward with the synthesis.

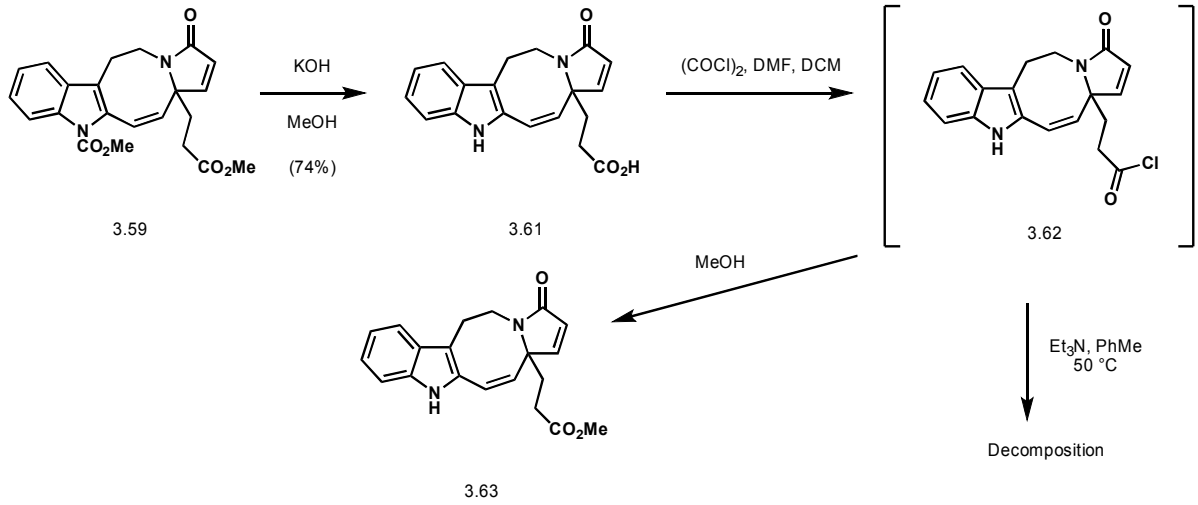


Scheme 3.18: Attempted cyclization of the free indole

3.3.2. Chemistry on the Tetracycle

With the construction of a tetracycle that may be applied to the synthesis of various *Kopsia* alkaloids developed, we turned our attention to the final stages of the synthesis of these natural products. We first investigated the ketene cycloaddition strategy outlined in Chapter 2 (Scheme 2.7). Subjecting tetracycle **3.59** to potassium hydroxide in methanol cleaved the carbamate from the indole and saponified the methyl ester to yield carboxylic acid **3.61** (Scheme 3.19). Ketene formation was attempted by treating the carboxylic acid with oxalyl

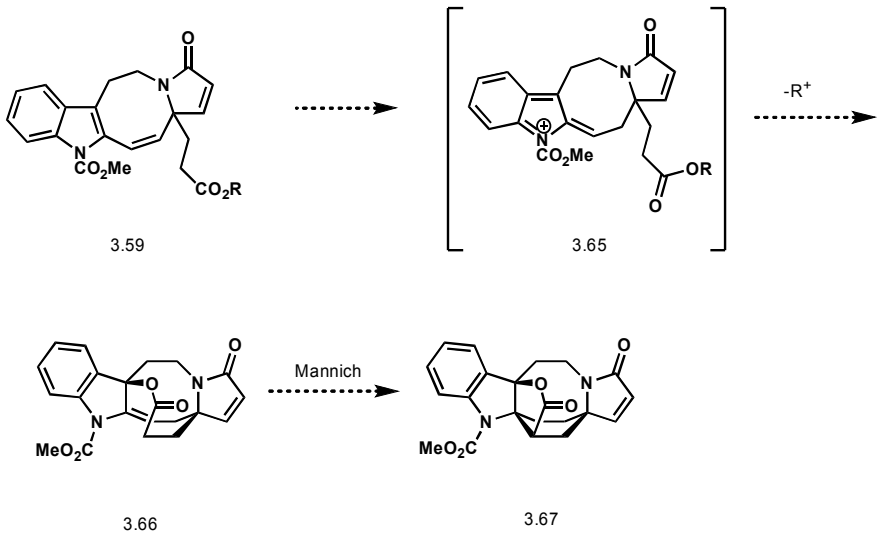
chloride and catalytic DMF to form acid chloride **3.62** in situ. Heating this acid chloride with triethylamine, which are standard ketene forming conditions,[21] lead only to decomposition products. Quenching the acid chloride cleanly returned methyl ester **3.63**, indicating that the decomposition occurs during attempted ketene formation.



3.59 3.61 3.62 3.63

Scheme 3.19: Attempted ketene formation

Although this ketene approach was conceptually attractive, other ideas were also explored. We noted that tetracycle **3.59** has the correct oxidation level for the lapidilectine B core (Scheme 3.20), which opens the possibility that an acid-catalyzed cascade could be used to construct the remaining bonds of the lapidilectine B skeleton. Intermediate **3.65** is presumably formed in the course of the cyclization of **3.56** to **3.59** (see Scheme 3.17), during the elimination of methanol, which produces tetracycle **3.59**. Nucleophilic addition of the carbonyl oxygen and hydrolysis of the resultant oxocarbenium ion would give macrolactone **3.66.** This lactone is then poised to undergo a Mannich reaction to close the final five-membered ring and give **3.67** which possesses all the appropriate carbon-carbon bonds in place for lapidilectine B. However, formation of this macrolactone is most likely entropically unfavorable; and attempts to effect this cascade utilizing protic acids were fruitless. Substrate **3.61** (Scheme 3.19) was also subjected to acidic conditions, but only starting material was recovered.

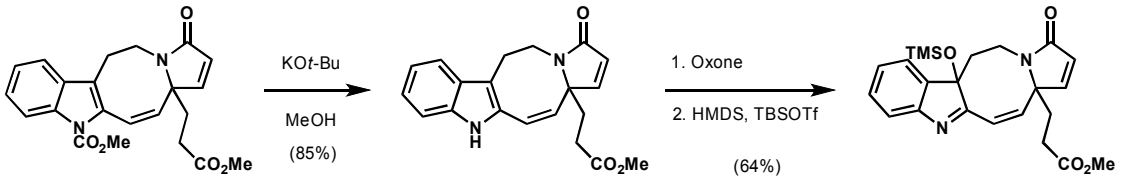


3.59 3.65 3.66 3.67

Scheme 3.20: Redox-neutral end game

3.3.3. Oxidation of the Indole Ring

Since the redox-neutral end-game cascade was unsuccessful, a more-stepwise approach was explored to complete the synthesis. In order to functionalize the indole moiety of **3.59**, the carbamate was cleaved using in situ generated potassium methoxide to avoid saponification of the methyl ester. Free indole **3.63** was treated with Oxone® to achieve selective oxidation of the 3-position, with the resultant hydroxyl functionality protected as the trimethylsilyl ether using HMDS and TBSOTf. This protection was thought to be necessary because of the ample precedent for similarly oxidized indole compounds undergoing carbon-carbon bond migration to form a spiro-oxindole under basic conditions.[22] Compound **3.68** is one carbon-carbon and one carbon-oxygen bond away from the skeleton of lapidilectine B.

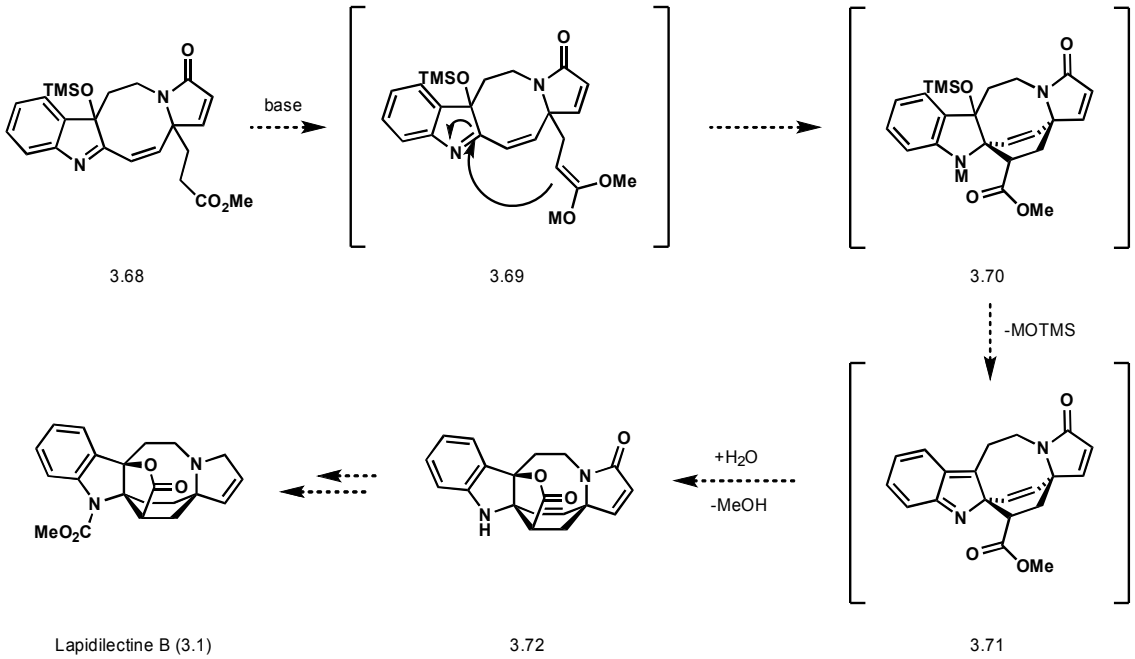


3.59 3.63 3.68

Scheme 3.21: Oxidation of the indole ring

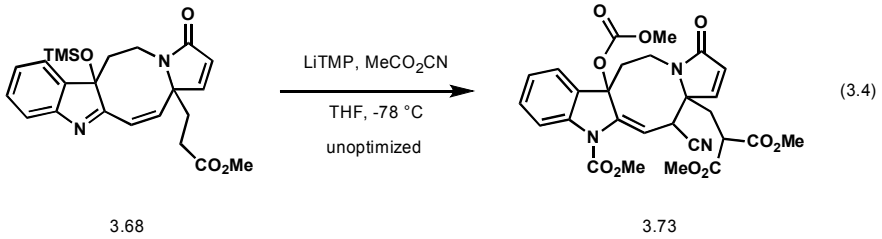
With compound **3.68** in hand, we envisioned formation of the final carbon-carbon bond for lapidilectine via initial deprotonation to form ester enolate **3.69** (Scheme 3.22). Although there are multiple electrophilic positions in **3.69** for the ester enolate to react with, the productive pathway produces a 6-membered ring whereas the two unproductive pathways would form highly strained four-membered rings. Upon enolate addition to form anilate **3.70** the TMS-ether could be ejected to give highly electophilic aza-quinone-methide **3.71**. Addition

of the ester carbonyl oxygen to form the γ-lactone ring would re-establish aromaticity, followed by hydrolysis to furnish the fully elaborated core of lapidilectine B.



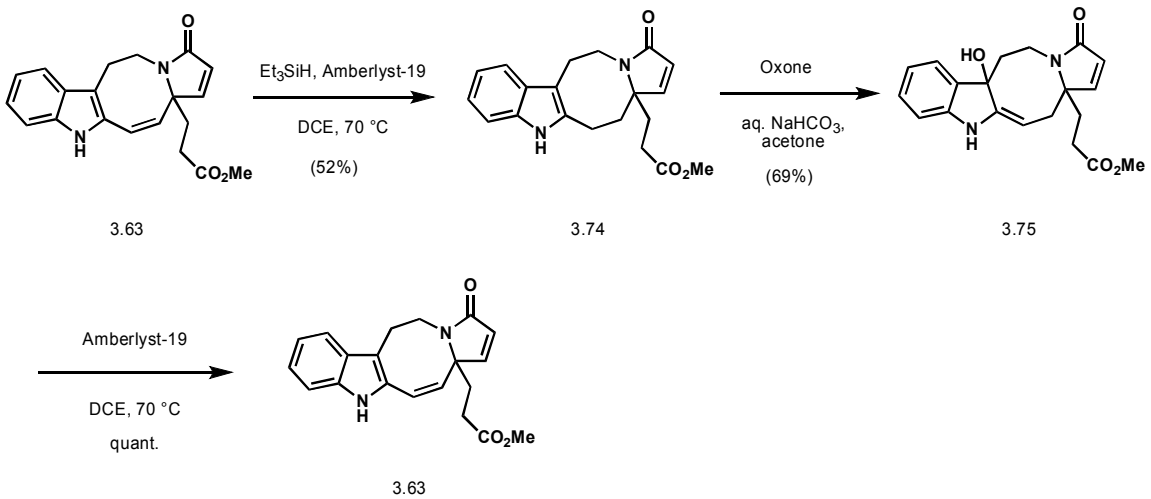
Scheme 3.22: Intramolecular hemi-enolate addition

Treatment of **3.68** with bases such as LDA, NaHMDS, and lithium tetramethylpiperidine (LiTMP) only returned starting material upon workup. One hypothesis is that the carbon-carbon bond formation is reversible, so we attempted to trap anilate **3.70** as the methyl carbamate using Mander's reagent.[23] Treatment of **3.68** with excess LiTMP at -78 °C, followed by addition of Mander's reagent gave a product that was identified as **3.73** (eq 3.4). Instead of adding into the imine, the enolate underwent C-acylation to give a dimethylmalonate derivative. In addition, cyanide that was liberated as a byproduct of this Claisen reaction, underwent a conjugate addition into the α,β-unsaturated imine, which was then trapped by Mander's reagent to give an acyl-enamine.



(3.4)

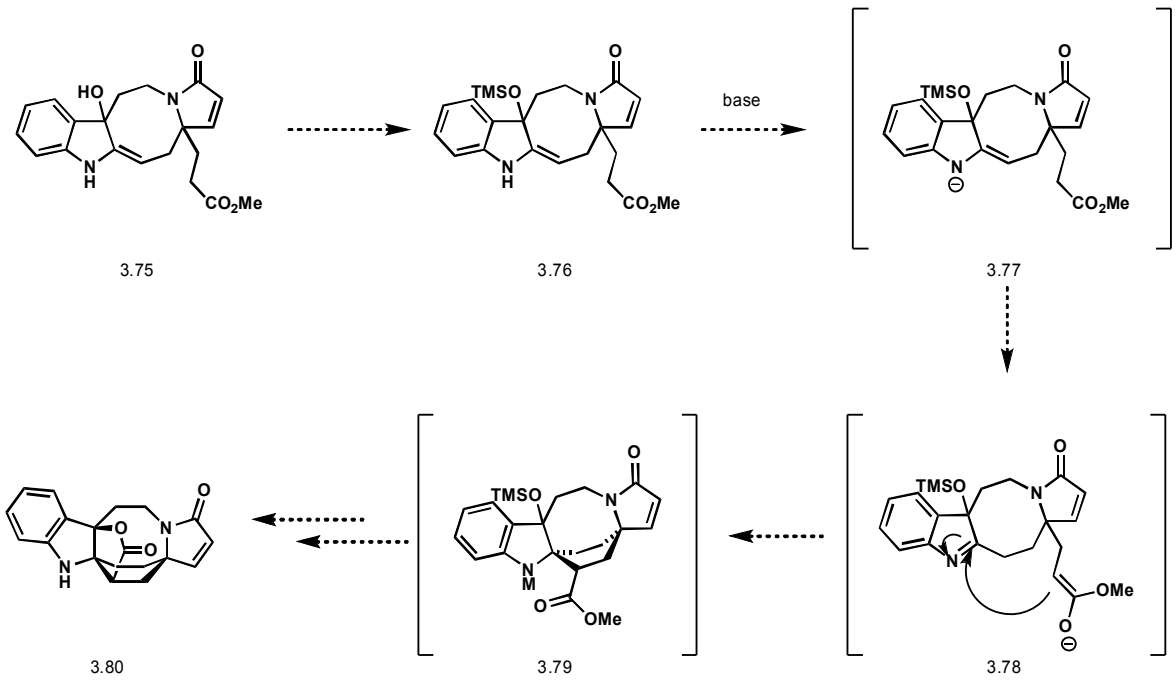
One reason for the failure of this cyclization may be the rigidity enforced by the eight-membered ring containing extra sp^2 carbons. Efforts to selectively reduce the double bond in the eight-membered ring over the α,β-unsaturated amide using heterogeneous transition metals as catalysts were unsuccessful; however, an ionic reduction utilizing triethylsilane and methanesulfonic acid was able to selectively reduce the desired alkene to give tetracycle **3.74** (Scheme 3.23). This could then be oxidized utilizing identical conditions to those described in Scheme 3.21 to give enamine **3.75**. We hoped that **3.75** could be lactonized utilizing acidic conditions. Unfortunately, treatment with Amberlyst®-15 returned tetracycle **3.63.**



Scheme 3.23: Ionic reduction of the tetracycle

3.3.4. Other Options for Lactone Formation

Our current strategy to form the key carbon-carbon bond is to attempt to utilize basic conditions, this time with substrate **3.76** (Scheme 2.24). We are cognizant of the possibility that the introduction of a new acidic proton on the enamine could cause problems (compared with **3.68**, Scheme 3.22). As shown in Scheme 3.24, protection of the hydroxyl group of **3.75** as TMS-ether **3.76** would be followed by treatment with base. We anticipate the enamine N-H to be the most acidic proton in the system, which would lead to metallo-enamine **3.77**. This metallo-enamine has the possibility to become acylated by the methyl ester, however molecular modeling indicates this would lead to a highly strained intermediate.[24] The metallo-enamine could also act as an internal base to deprotonate the pendant ester and form imine **3.78**. The ester enolate could then add into the imine, and proceed to the natural product framework as described in Scheme 3.22.

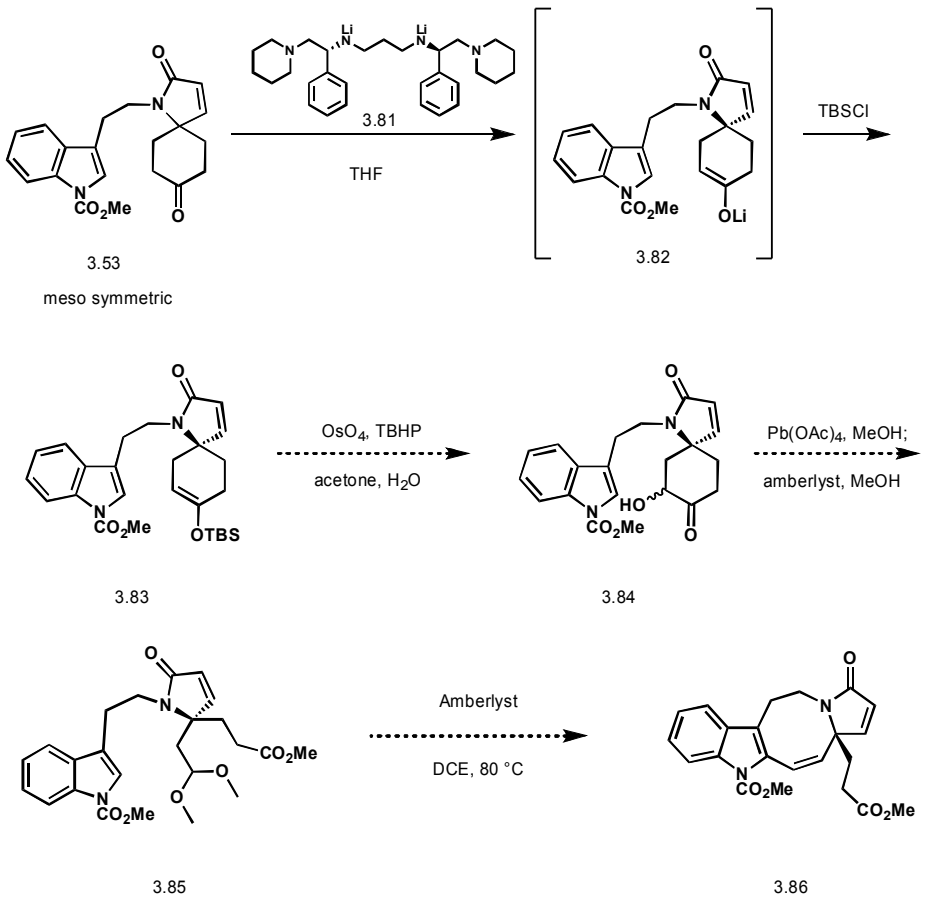


Scheme 3.24: Current end game strategy

3.4. Future Directions

3.4.1. Desymmetrization as an Entry to an Enantioselective Synthesis

One appealing feature of this synthetic strategy was the opportunity to desymmetrize a meso-symmetric compound to render the synthesis asymmetric. The enantio-determining event in the sequence is the formation of the silyl enol ether **(3.83**, Scheme 3.25). One possibility that is currently being explored in our lab is the use of chiral Koga bases[25] for the enantioselective deprotonation of the prochiral ketone **3.53** to give an enantiomerically enriched enolate (**3.82**), which can then be trapped with electrophiles such as TBSCl to furnish **3.83** in optically active form. From here, the sequence would be the same, with dihydroxylation and oxidative cleavage followed by cyclization to give **3.86**. Initial work by Erica Schultz in our group has shown that deprotonation using the R,R Koga base (**3.81**) followed by trapping the resultant enolate with allyl chloroformate is able to give enantiomeric excesses (ee) of around 40%. We hope to build from this encouraging result to achieve synthetically useful ee's.

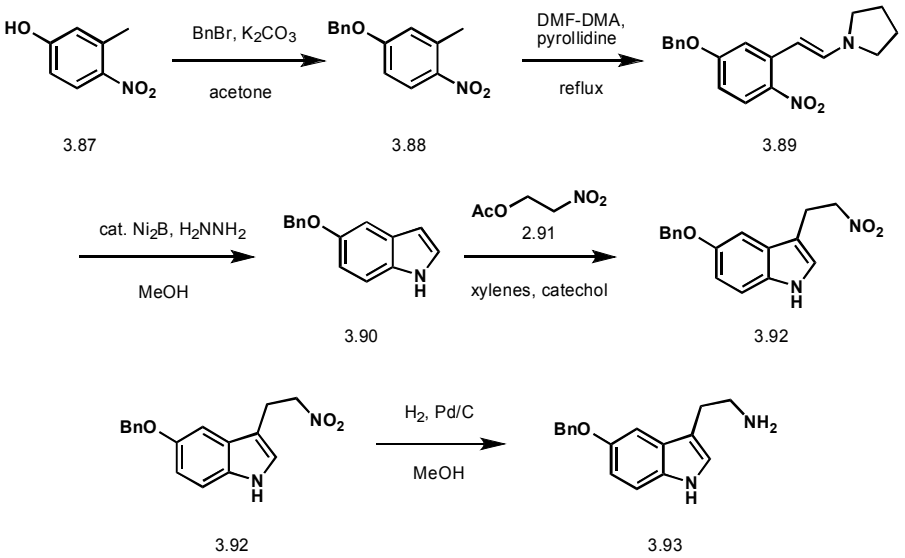


Scheme 3.25: Desymmetrization of a meso ketone

3.4.2. Synthesis of a Serotonin Derivative

In addition to these desymmetrization studies, we have also explored the synthesis of seratonin derivatives for use in the synthesis of a number of natural products that possess a methoxy-group at C5 of the indole ring (see Figure 1.1). Although serotonin is commercially available, the cost is prohibitive, and the ability to synthesize it allows for further derivatization to install bio-tags or affinity probes for use in chemical biology studies. The synthesis of our protected serotonin derivative is depicted in Scheme 3.26 and opens with commercially available four-nitro-3-methylphenol (**3.87**), which is protected utilizing benzylbromide. A Leimgruber-Batcho indolization sequence using dimethylformamide-dimethylacetal and pyrrolidine then installs the necessary one-carbon unit to yield **3.89**.[26] Reductive cyclization was initially carried out using hydrazine and Raney nickel. However, it was found that nickel boride as the catalyst gave significantly higher yields and purities of 5-benzyloxyindole (**3.90**).[27] This indole was extremely air sensitive, and was used immediately with nitroethylacetate to functionalize the 3-position to give **3.92**. Reduction of the nitro group gave protected serotonin **3.93**, which could then be used in the Ugi four-component coupling. This sequence has been carried out by Erica Schultz in our group utilizing a methyl-protecting group

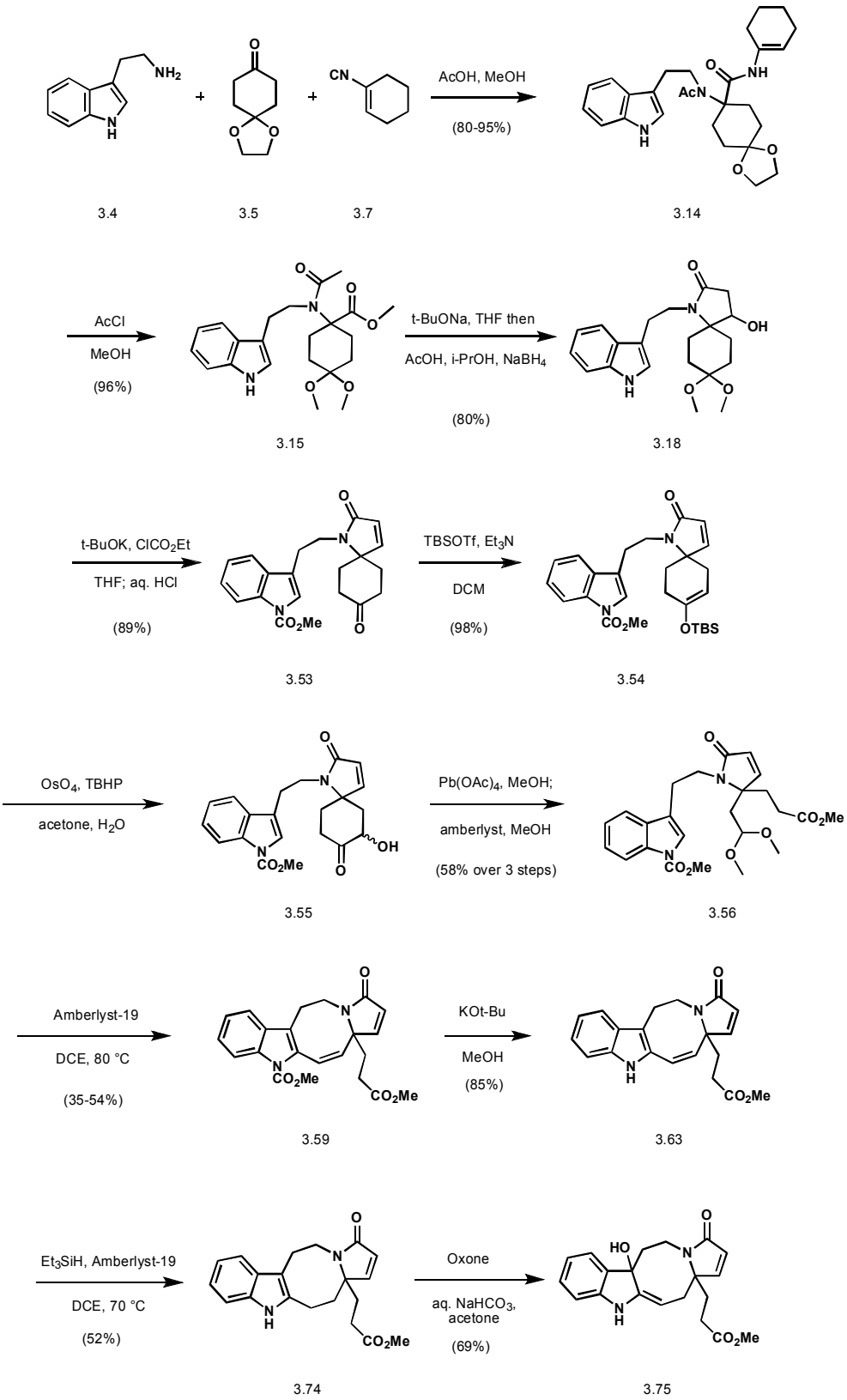
as well, and has been advanced through the Ugi, lactam formation, and oxidative cleavage sequence.



Scheme 3.26: Serotonin derivative synthesis

3.5. Conclusion

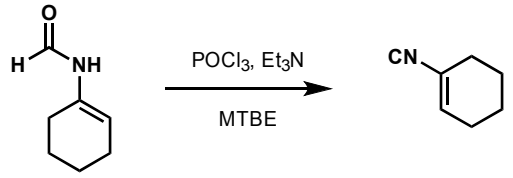
We have successfully developed a synthetic route to the skeleton of members of the *Kopsia* family of natural products (see Scheme 3.27 for a summary). The sequence utilizes an Ugi four-component coupling which brings together all the carbons for the natural product (**3.14**). Formation of the D-ring was accomplished in an optimized 3-step telescoped sequence (**3.15** → **3.53**). Key to the success of this strategy was an oxidative carbon-carbon bond cleavage as described in Section 3.2.8. A Friedel-Crafts hydroxyalkylation was utilized to form the eight-membered ring (**3.56** → **3.59**). Installation of the final lactone ring is currently under investigation.



Scheme 3.1: Overall synthetic scheme

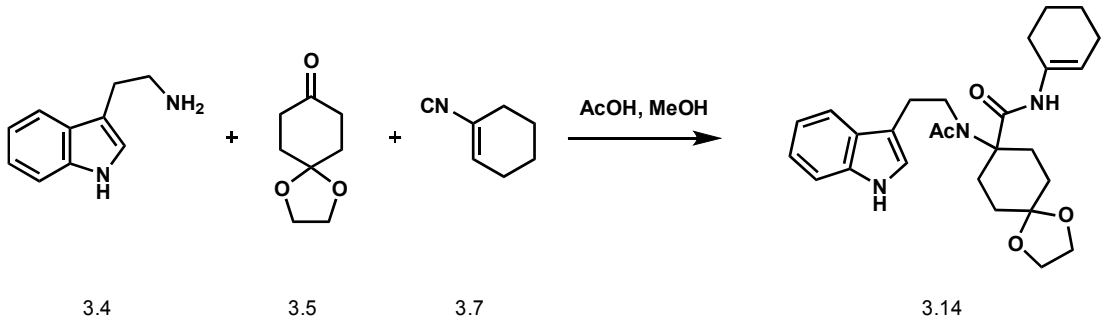
3.6. Experimental

General. All air or moisture sensitive reactions were conducted in flame-dried glassware under an atmosphere of nitrogen using dry, deoxygenated solvents. Toluene, methylene chloride, acetonitrile, triethylamine, and tetrahydrofuran (THF) were passed through a column of deactivated alumina. All reagents were purchased from Aldrich, Acros, or Lancaster and used without further purification. Melting points were measured on a Büchi® melting point apparatus and are corrected using vanillin (mp 80-81 °C) as a standard. Reaction temperatures were controlled by an IKAmag temperature modulator. Thin-layer chromatography (TLC) was performed using Silicycle silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV and anisaldehyde stain. Sorbent silica gel 240-400 mesh (particle size 0.032-0.063) was used for flash chromatography. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AV-600 (at 600 MHz and 150 MHz respectively), on a Bruker AV-500 (at 500 MHz and 125 MHz respectively) and on a Bruker AVB-400 (at 400 MHz and 100 MHz respectively) in chloroform-*d* at 23 °C, unless otherwise stated. Chemical shifts were referenced to the residual chloroform-H peak, which was set at 7.26 ppm for ^{1}H and 77.0 ppm (center peak) for ^{13}C spectra. Data for ^{1}H NMR are reported as follows: chemical shifts (δ ppm). Multiplicity, (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublet, dt = doublet of triplet, m = multiplet, br = broad resonance), coupling constants (Hz) and integration. Data for ^{13}C NMR are reported in terms of chemical shift. IR spectra were recorded on a Nicolet MAGNA-IR 850 spectrometer and are reported in frequency of absorption (cm^{-1}). Low and high resolution mass spectral data were obtained from the University of California, Berkeley Mass Spectral Facility, on a VG 70-Se Micromass spectrometer for FAB, and a VG Prospec Micromass spectrometer for EI.



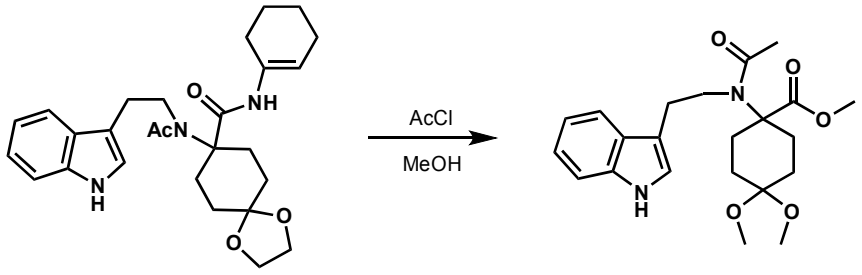
3.13 3.7

1-Isocyanocyclohex-1-ene (3.7): A flame-dried round-bottom flask was charged with cyclohexeneformamide **3.13** (0.125 g, 1.00 mmol), triethylamine (0.422 ml, 3.00 mmol) and MTBE (3.33 mL) and cooled to 0 ºC. To the resultant solution was added phosphorus oxychloride (0.121 ml, 1.300 mmol) dropwise over several minutes. The reaction mixture was stirred at 0 ºC for 30 minutes and then quenched with saturated ammonium chloride (5 mL). The layers were separated and the aqueous layer was extracted with DCM (2 x 10 mL). The combined organic layer was dried over sodium sulfate and concentrated via rotary evaporation. The crude oil was loaded onto a 1 inch silica gel plug which was flushed with 4:1 hexanes/ethyl acetate (2 x 30 mL portions) and the collected solvent was concentrated via rotary evaporation to yield the purified Armstrong isonitrile (100.5 mg, 94%) which was used without further purification.



3.4 3.5 3.7 3.14

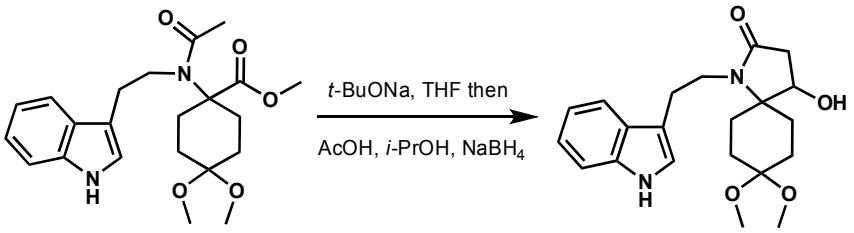
Ugi product 3.14: A round-bottom flask was charged with tryptamine **3.4** (882 mg, 5.50 mmol), ketone **3.5** (860 mg, 5.50 mmol), and methanol (6 mL, 1.0M). Acetic acid (380 uL, 6.60 mmol) was added and the mixture was stirred for 0.25 h and then isonitrile **3.7** (650 mg, 6.10 mmol) was added as a solution in methanol (1 mL) and the resultant solution was stirred for 0.5 h, at which time the mixture completely solidified. 10 mL of water was added to the solid and the resultant slurry was stirred for an additional 0.25 h, and then filtered to collect **3.14** (2.37 g, 93% yield) as a beige solid, m.p. 87 ºC. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.30 (s, 1H), 8.21 (s, 1H), 7.58 (t, *J* = 8.0 Hz, 1H), 7.37 (d, *J* = 8.0 Hz, 1H), 7.21 (dd, *J* = 14.1, 6.8 Hz, 1H), 7.16 – 7.11 (m, 1H), 7.01 (d, *J* = 1.9 Hz, 1H), 6.08 (s, 1H), 3.99 – 3.90 (m, 5H), 3.69 – 3.62 (m, 2H), 3.06 – 3.01 (m, 2H), 2.53 – 2.37 (m, 4H), 2.16 (s, 2H), 2.11 (d, *J* = 5.3 Hz, 2H), 2.08 – 2.04 (m, 3H), 1.87 (t, *J* = 10.6 Hz, 3H), 1.81 (s, 2H), 1.71 – 1.67 (m, 2H), 1.67 – 1.60 (m, 2H), 1.60 – 1.56 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.0, 171.8, 136.2, 132.9, 127.0, 122.3, 122.2, 119.6, 118.2, 113.0, 112.1, 111.3, 107.7, 65.0, 64.3, 64.3, 31.5, 30.4, 28.0, 26.2, 24.3, 24.0, 22.5, 22.0; IR (film) ν_{max} 3323, 2932, 2359, 1661, 1508, 1406, 1231, 1105, 1035, 931, 739 cm^{-1}; HRMS (EI^{+}) calc'd for $[C_{27}H_{35}N_3O_4]^{+}$: *m/z*, 465.5845 found 465.5836.



3.14 3.15

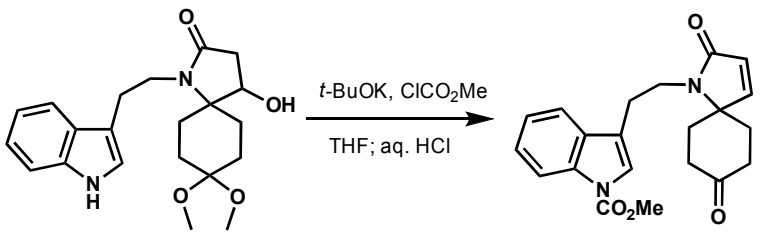
Methyl ester 3.15: A flame-dried round-bottom flask was charged with **3.14** (2.37 g, 5.10 mmol) and methanol (25 ml, 0.2M) and cooled to 0 °C. Acetyl chloride (725 uL, 10.2 mmol) was added dropwise to this slurry, which was stirred at 0 °C for 1 h, then at rt for 18 h . The slurry was concentrated via rotary evaporation and water (50 mL) was added. The resultant solid was collected via filtration to obtain **3.15** (1.97 g, 96% yield) as a brown solid m.p. 68 ºC. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.52 (s, 1H), 7.59 (d, *J* = 7.9 Hz, 1H), 7.41 (d, *J* = 8.1 Hz, 1H), 7.22 (t, *J* = 7.6 Hz, 1H), 7.15 (t, *J* = 7.5 Hz, 1H), 7.08 (d, *J* = 1.8 Hz, 1H), 3.72 (d, *J* = 4.3 Hz, 3H), 3.68 – 3.61 (m, 2H), 3.22 (s, 3H), 3.21 (s, 3H), 3.10 (dd, *J* = 15.1, 6.7 Hz, 2H), 2.39 (d, *J*

= 10.6 Hz, 2H), 2.06 (s, 3H), 1.98 (d, *J* = 10.8 Hz, 2H), 1.94 – 1.83 (m, 4H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.0, 171.4, 136.3, 127.0, 122.2, 122.0, 119.5, 118.2, 112.1, 111.5, 99.1, 63.5, 52.0, 47.9, 47.5, 45.9, 28.9, 28.9, 27.1, 22.7; IR (film) ν_{max} 3354, 2948, 1737, 1633, 1418, 1219, 1107, 740 cm^{-1}; HRMS (EI$^+$) calc'd for $[C_{22}H_{30}N_2O_5]^+$: *m/z*, 402.2155 found 402.2149.



3.15 3.18

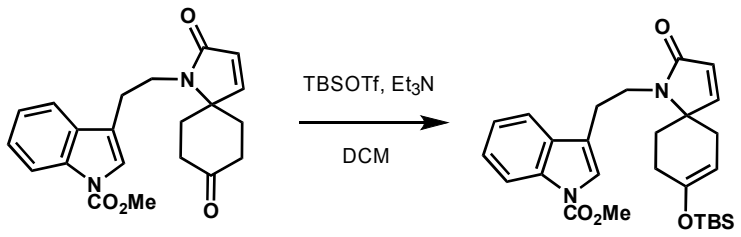
β-Hydroxy amide 3.18: A flame-dried round-bottom flask was charged with **3.15** (1.97 g, 4.9 mmol) and THF (50 mL, 0.1M) and cooled to 0 °C. Sodium *t*-butoxide (940 mg, 9.8 mmol) was added and the reaction mixture was stirred for 2 hours at 0 ºC, at which point the reaction was judged complete by TLC. Acetic acid (672 uL, 11.8 mmol) was added dropwise, followed by *i*-PrOH (25 mL) and then sodium borohydride (280 mg, 7.4 mmol) was added and the reaction mixture was stirred for 2 hours at 0 ºC and then 14 h at rt. The reaction was quenched with saturated ammonium chloride (25 mL) and then water (75 mL) and stirred at room temperature for 0.25 h . The solid was collected via filtration to give **3.18** (1.46 g, 80% yield) as an off-white solid, m.p. 106 ºC. ^{1}H NMR (600 MHz, DMSO) δ 10.84 (d, *J* = 1.4 Hz, 1H), 7.60 (t, *J* = 10.8 Hz, 1H), 7.34 (d, *J* = 8.1 Hz, 1H), 7.18 (d, *J* = 2.2 Hz, 1H), 7.11 – 7.03 (m, 1H), 7.03 – 6.96 (m, 1H), 5.24 (dd, *J* = 16.1, 5.5 Hz, 1H), 5.23 (t, *J* = 8.0 Hz, 1H), 4.16 (t, *J* = 5.5 Hz, 1H), 4.16 (t, *J* = 5.5 Hz, 1H), 3.42 – 3.33 (m, 2H), 3.12 – 3.04 (m, 7H), 2.93 – 2.85 (m, 1H), 2.80 – 2.66 (m, 2H), 2.12 – 2.01 (m, 1H), 1.93 – 1.85 (m, 2H), 1.62 (qd, *J* = 13.5, 3.6 Hz, 2H), 1.55 – 1.43 (m, 2H), 1.23 (d, *J* = 11.2 Hz, 1H); ^{13}C NMR (150 MHz, DMSO) δ 172.8, 136.7, 127.5, 123.1, 121.4, 118.7, 118.6, 111.9, 111.9, 98.9, 67.4, 66.6, 60.2, 47.6, 47.5, 29.6, 29.1, 28.8, 26.2, 25.4, 14.5; IR (film) ν_{max} 3401, 2924, 1650, 1455, 1226, 1107, 1062, 734, 655 cm^{-1}; HRMS (EI$^+$) calc'd for $[C_{21}H_{28}N_2O_4]^+$: *m/z*, 372.2049 found 372.2038.



3.18 3.53

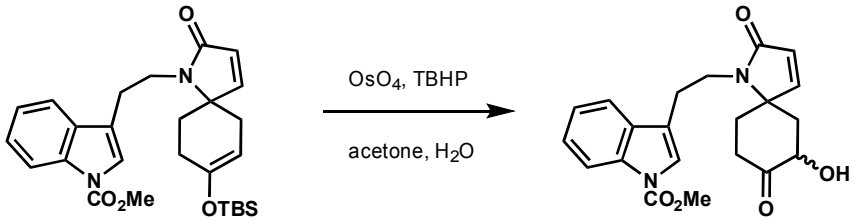
α,β-Unsaturated amide 3.53: A flamed-dried round-bottom flask was charged with indole

3.18 (4.8 g, 12.89 mmol) and THF (92 mL) and was cooled to 0 ºC. Potassium *t*-butoxide (2.89 g, 25.8 mmol) was added in one portion and the slurry was stirred at 0 ºC for 10 minutes, then methyl chloroformate (1.248 ml, 16.11 mmol) was added dropwise and the slurry was stirred at 0 ºC for 1 h. Potassium *t*-butoxide (2.89 g, 25.8 mmol) was added in one portion and the slurry was stirred for 10 minutes, then methyl chloroformate (1.248 ml, 16.11 mmol) was added dropwise and the slurry was stirred while bath warmed to RT overnight, at which time the reaction was judged complete by TLC. The reaction mixture was cooled to 0 ºC and 1N HCl (35 mL) was added in one portion, The reaction mixture was stirred for 4 h at rt. Saturated sodium bicarbonate (50 mL) was added and the aqueous layer was extracted with dichloromethane (3 x 50 mL). The combined organic layers were dried over sodium sulfate and concentrated via rotary evaporation to give **3.53** (4.20 g, 89 % yield) as a pale-yellow solid which was used without further purification. Crude ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.14 (s, 1H), 7.65 (t, *J* = 7.7 Hz, 1H), 7.61 (d, *J* = 5.8 Hz, 1H), 7.46 (d, *J* = 21.1 Hz, 1H), 7.33 (t, *J* = 7.7 Hz, 1H), 7.30 – 7.26 (m, 1H), 6.33 (d, *J* = 5.8 Hz, 1H), 4.02 (d, *J* = 13.1 Hz, 3H), 3.58 – 3.51 (m, 2H), 3.10 – 3.03 (m, 2H), 2.57 (td, *J* = 14.8, 5.4 Hz, 2H), 2.54 – 2.47 (m, 2H), 2.22 (td, *J* = 13.4, 4.1 Hz, 2H), 1.66 (dd, *J* = 13.0, 3.1 Hz, 2H).



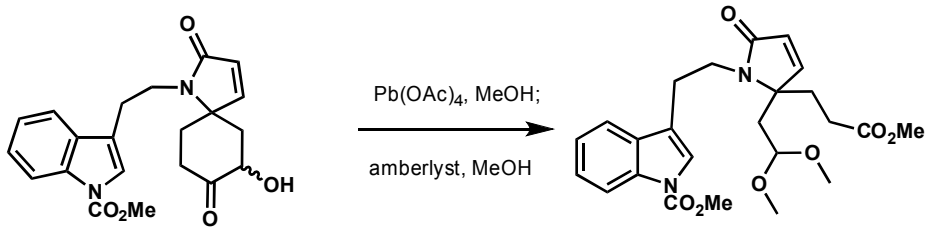
3.53 3.54

Silyl enol ether 3.54: A flame-dried round-bottom flask was charged with ketone **3.53** (2.00 g, 5.46 mmol) triethylamine (1.53 ml, 10.9 mmol) and DCM (40 mL) and cooled to 0 ºC. TBSOTf (1.50 ml, 6.55 mmol) was added dropwise over 15 minutes and the resultant solution was stirred overnight at rt. The reaction was quenched with saturated sodium bicarbonate (50 mL) and then extracted with dichloromethane (2 x 50 mL). The combined organics were dried over sodium sulfate and concentrated via rotary evaporation. The crude oil was purified via silica gel chromatography (4:1 to 1:1 hexanes/ethyl acetate) to give silylenol ether **3.54** (2.59 g, 99 % yield) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.14 (s, 1H), 7.66 (d, *J* = 7.7 Hz, 1H), 7.44 (s, 1H), 7.35 – 7.28 (m, 1H), 6.14 (d, *J* = 5 Hz, 1H), 4.81 (d, *J* = 5.0 Hz, 1H), 3.99 (s, 3H), 3.53 (dd, *J* = 19.0, 11.2 Hz, 2H), 3.09 – 2.99 (m, 2H), 2.53 (d, *J* = 16.3 Hz, 1H), 2.29 – 2.15 (m, 2H), 2.10 (td, *J* = 11.8, 7.0 Hz, 1H), 1.70 (dd, *J* = 16.3, 5.0 Hz, 1H), 1.42 (dd, *J* = 12.0, 3.1 Hz, 1H), 0.91 (d, *J* = 0.7 Hz, 9H), 0.14 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.6, 151.0, 149.4, 130.3, 126.2, 124.7, 122.9, 122.6, 119.2, 118.8, 115.1, 100.9, 77.3, 53.6, 39.6, 30.6, 30.4, 29.0, 25.5, 24.5, 17.9, -4.3, -4.5; IR (film) ν_{max} 3434, 2953, 1545, 1230, 1100, 1062, 722 cm^{-1} HRMS (EI$^+$) calc'd for $[C_{27}H_{36}N_2O_4Si]^+$: *m/z*, 480.2444 found 480.2449.



3.54 3.55

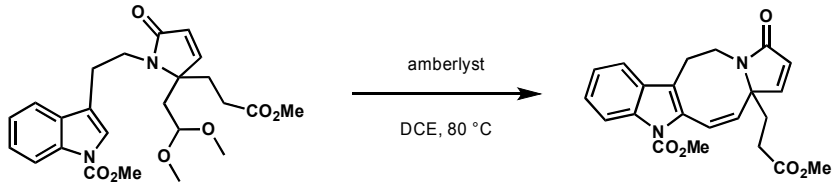
α-Hydroxy ketone 3.55: A round-bottom flask was charged with silyl enol ether **3.54** (2.00 g, 4.16 mmol), acetone (44.6 mL), and water (7.43 mL). Osmium tetroxide (8.46 mg, 0.832 µmol) was added followed by *t*-butyl hydroperoxide (0.59 ml, 4.58 mmol, as a 70% solution in water). The solution was stirred at rt for 36 hours at which time the reaction was judged complete by TLC. The reaction was quenched with sat. sodium sulfite (10 mL) and the aqueous layer was extracted with dichloromethane (3x15 mL). The combined organic layer was dried over sodium sulfate and concentrated via rotary evaporation. The crude **3.55** was used in the next step without purification. Crude ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 (s, 1H), 7.66 (d, *J* = 7.5 Hz, 1H), 7.57 (d, *J* = 6.1 Hz, 1H), 7.47 (d, *J* = 11.9 Hz, 1H), 7.39 – 7.33 (m, 1H), 7.32 – 7.29 (m, 1H), 6.38 (d, *J* = 6.1 Hz, 1H), 4.44 – 4.36 (m, 1H), 4.02 (s, 3H), 3.64 (t, *J* = 6.2 Hz, 1H), 3.58 – 3.50 (m, 2H), 3.16 – 2.98 (m, 2H), 2.73 – 2.61 (m, 2H), 2.25 – 2.13 (m, 2H), 1.76 (s, 1H), 1.73 – 1.65 (m, 2H).



3.55 3.56

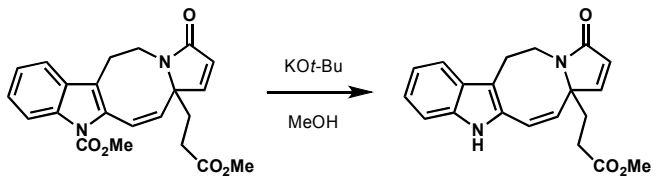
Acetal 3.56: A flame-dried round-bottom flask was charged with crude **3.55** (2.10 g, 5.49 mmol) in MeOH (55 ml, 0.1M) and cooled to -40 °C with an acetonitrile/dry ice bath. Lead tetraacetate (2.92 g, 6.59 mmol) was added portionwise over 10 minutes and the resultant mixture was stirred for 15 minutes at -40 ºC and then warmed to rt over 30 minutes. The reaction was quenched with water (20 mL), diluted with chloroform (50 mL) and then the mixture was stirred for 10 minutes. The slurry was filtered through a pad of celite and the retentate was washed thoroughly with chloroform. The filtrate was phase-separated and the aqueous layer was extracted with chloroform (3 x 40 mL). The combined organic layer was dried over sodium sulfate and concentrated via rotary evaporation to give the crude aldehyde. To the crude material was added methanol (55 mL), trimethyl orthoformate (1.82 ml, 16.5 mmol) and 25 mg of Amberlyst®-15 resin. The reaction mixture was stirred for 48 h at rt, at which point the reaction was judged complete by TLC. The mixture was filtered through celite

and the retentate was washed with ethyl acetate (15 mL). The combined filterate was concentrated via rotary evaporation and the resulting oil was purified via silica gel chromatography (2:1 to 1:3 hexanes/ethyl acetate) to give acetal **3.56** (1.46 g, 58% yield) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.16 (s, 1H), 7.70 (d, *J* = 7.7 Hz, 1H), 7.49 (s, 1H), 7.34 (t, *J* = 7.7 Hz, 1H), 7.29 (t, *J* = 7.5 Hz, 1H), 6.91 (d, *J* = 6.0 Hz, 1H), 6.13 (d, *J* = 6.0 Hz, 1H), 4.06 (dd, *J* = 5.9, 3.8 Hz, 1H), 4.02 (s, 4H), 3.60 (s, 3H), 3.54 (ddd, *J* = 14.1, 11.2, 5.5 Hz, 1H), 3.40 (ddd, *J* = 14.1, 11.0, 5.5 Hz, 1H), 3.23 (s, 3H), 3.22 (s, 4H), 3.14 – 3.07 (m, 1H), 3.07 – 2.99 (m, 1H), 2.14 – 1.93 (m, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.0, 171.6, 151.0, 130.2, 126.0, 124.7, 123.0, 122.7, 119.2, 118.5, 115.2, 100.9, 68.1, 53.7, 52.7, 51.8, 40.0, 39.6, 30.1, 27.5, 23.9; IR (film) ν_{max} 3401, 2953, 1736, 1686, 1456, 1381, 1260, 1124, 1095, 814, 765 cm^{-1}; HRMS (EI$^+$) calc'd for $[C_{24}H_{30}N_2O_7]^+$: *m/z*, 458.2053 found 458.2060.



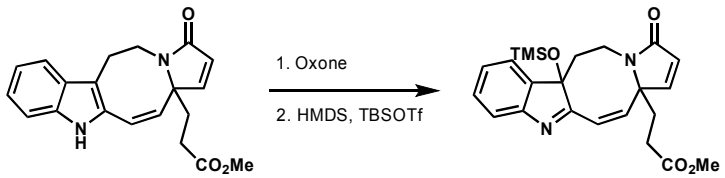
3.56 3.59

Tetracycle 3.59: An oven-dried vial was charged with acetal **3.56** (85.0 mg, 0.185 mmol), Amberlyst®-15 resin (42.5 mg, 0.5 weight equivalents), and dichloroethane (2.3 mL) and capped. The vial was heated to 65 ºC for 48 h and cooled. The reaction mixture was filtered through celite and concentrated via rotary evaporation. The crude product was purified via silica gel chromatography (1:1 to 1:3 hexanes/ethyl acetate) to give tetracycle **3.59** (34.2 mg, 46.8% yield) along with starting material **3.56** (17.8 mg). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.02 (d, *J* = 8.2 Hz, 1H), 7.53 (d, *J* = 7.7 Hz, 1H), 7.30 (t, *J* = 7.7 Hz, 1H), 7.25 (d, *J* = 10.2 Hz, 2H), 7.00 (d, *J* = 5.8 Hz, 1H), 6.61 (d, *J* = 12.3 Hz, 1H), 6.07 (d, *J* = 5.8 Hz, 1H), 5.61 (d, *J* = 12.3 Hz, 1H), 4.18 (td, *J* = 13.7, 4.5 Hz, 1H), 4.02 (d, *J* = 19.6 Hz, 3H), 3.67 (s, 3H), 3.19 (dd, *J* = 14.2, 4.2 Hz, 1H), 3.01 (dd, *J* = 13.7, 5.3 Hz, 1H), 2.77 (td, *J* = 14.0, 5.5 Hz, 1H), 2.68 (s, 1H), 2.39 (tdd, *J* = 14.5, 12.1, 6.6 Hz, 2H), 2.11 – 1.95 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.9, 172.5, 152.2, 151.1, 135.8, 133.6, 128.6, 126.5, 125.0, 124.0, 123.2, 120.7, 118.4, 116.4, 115.8, 71.0, 53.6, 51.9, 36.6, 30.3, 26.7, 22.1. HRMS (EI$^+$) calc'd for $[C_{22}H_{22}N_2O_5]^+$: *m/z*, 394.1529 found 394.1534.



3.59 3.61

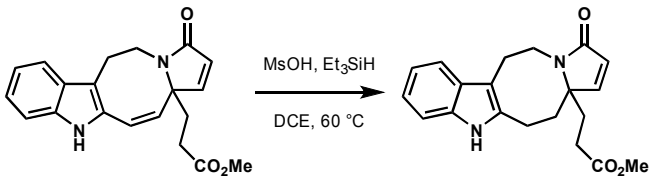
Indole 3.61: A round-bottom flask was charged with tetracycle **3.59** (60.0 mg, 0.152 mmol) and methanol (3.0 mL). To this solution was added potassium *t*-butoxide (34.1 mg, 0.304 mmol) and the resultant solution was stirred at RT for 2 hours, at which time the reaction was judged complete by TLC. The reaction was quenched with saturated ammonium chloride (5 mL), and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layer was washed with brine, dried over sodium sulfate, and concentrated via rotary evaporation. The crude material was purified via silica gel chromatography (1:1 hexanes/ethyl acetate) to give **3.61** (42.3 mg, 82%) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.08 (s, 1H), 7.55 (d, J = 7.8 Hz, 1H), 7.19 (d, J = 7.9 Hz, 1H), 7.16 – 7.10 (m, 1H), 7.10 – 7.06 (m, 1H), 6.88 (d, J = 5.9 Hz, 1H), 6.21 (d, J = 12.3 Hz, 1H), 5.94 (d, J = 5.8 Hz, 1H), 5.53 (d, J = 12.3 Hz, 1H), 4.20 (td, J = 13.6, 4.6 Hz, 1H), 3.67 (s, 3H), 3.30 (ddd, J = 14.6, 4.5, 2.3 Hz, 1H), 2.99 (ddd, J = 13.6, 5.1, 2.3 Hz, 1H), 2.77 (td, J = 14.1, 5.2 Hz, 1H), 2.45 – 2.29 (m, 2H), 2.07 (ddd, J = 15.9, 8.7, 5.3 Hz, 1H), 1.99 (ddd, J = 16.5, 9.0, 7.2 Hz, 1H); ^{13}C NMR (150 MHz, CDCl3) δ 173.1, 172.0, 150.1, 136.3, 132.2, 128.9, 127.3, 125.0, 122.5, 119.6, 118.5, 118.1, 110.6, 110.2, 51.9, 37.6, 30.4, 26.9, 22.5; IR (film) ν_{max} 3291, 2950, 1737, 1678, 1439, 1375, 1176, 912, 813, 738 cm^{-1}; HRMS (EI^+) calc'd for $[C_{20}H_{20}N_2O_3]^+$: *m/z*, 336.1474 found 336.1468.



3.63 3.68

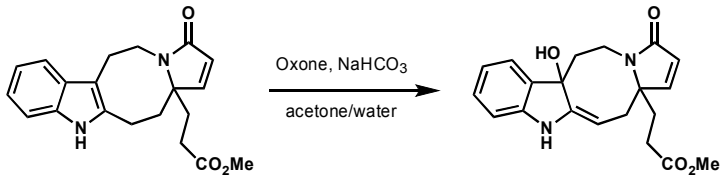
3-Siloxy indole 3.68: A round-bottom flask was charged with **3.63** (15 mg, 0.045 mmol), acetone (1.8 mL), and saturated sodium bicarbonate (1.2 mL). The round-bottom was cooled to 0 ºC and a solution of Oxone® (30. mg, 0.049 mmol) in water (0.6 mL) was added dropwise over 15 minutes and the resultant mixture was stirred at 0 ºC for an additional 15 minutes, at which point the reaction was judged complete by TLC. The reaction was quenched with saturated sodium sulfite (3 mL) and the aqueous layer was extracted with DCM (3 x 5 mL). The combined organic layer was dried over sodium sulfate and concentrated via rotary evaporation. This crude material was dissolved in DCM (1.5 mL) and hexamethyldisilazane (18 μL, 0.085 mmol) and TBSOTf (3 μL, 0.0085 mmol) were added. The resultant solution was stirred at rt for 2 h, at which point the reaction was judged complete via TLC. The reaction solution was loaded directly onto a pipette silica gel column, and flushed with DCM (4 mL), and then fractions were collected while eluting with ethyl acetate. Recovered **3.68** (12.4 mg, 64.8%) as a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (d, *J* = 7.6 Hz, 1H), 7.15 – 7.08 (m, 2H), 7.00 (t, *J* = 7.1 Hz, 1H), 6.22 (d, *J* = 12.6 Hz, 1H), 6.07 (d, *J* = 5.9 Hz, 1H), 5.75 (d, *J* = 5.9 Hz, 1H), 5.34 (d, *J* = 12.6 Hz, 1H), 3.85 (ddd, *J* = 14.2, 8.2, 2.9 Hz, 1H), 3.34 (s, 3H), 2.99 (ddd, *J* = 14.1, 8.2, 2.4 Hz, 1H), 2.34 (ddd, *J* = 14.6, 8.2, 2.5 Hz, 1H), 2.20 (ddd, *J* = 14.6, 8.2, 2.9 Hz, 1H), 2.09 (dt, *J* = 14.8, 7.5 Hz, 1H), 1.86 (dt, *J* = 8.6, 7.7 Hz, 2H), 1.09 – 0.89 (m, 3H), -0.04 (s, 9H); IR (film) ν_{max} 3400, 2954, 1737, 1693, 1252, 1438, 1226, 1199,

1118, 878, 638 cm^{-1} HRMS (EI^+) calc'd for $[C_{23}H_{28}N_2O_4Si]^+$: *m/z*, 424.1818 found 424.1829.



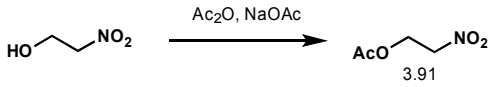
3.63 3.74

Indole 3.74: An oven-dried vial was charged with indole **3.63** (10.0 mg, .0029 mmol) and dichloroethane (3 mL). To this solution was added triethyl silane (45 µL, .29 mmol) and methane sulfonic acid (10 µL, .14 mmol) and the vial was sealed and heated to 60 ºC for 16 h and then cooled to rt. Triethyl amine (50 uL) was added to quench the acid and the reaction mixture was concentrated via rotary evaporation and the crude material was purified via silica gel chromatography (1:1 hexanes/ethyl acetate) to give **3.74** (6.5 mg, 65%) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.62 (s, 1H), 7.50 – 7.46 (m, 1H), 7.20 (dd, *J* = 6.8, 1.5 Hz, 1H), 7.12 – 7.03 (m, 2H), 6.74 (d, *J* = 5.9 Hz, 1H), 6.21 (d, *J* = 5.9 Hz, 1H), 4.19 – 4.10 (m, 1H), 3.67 (d, *J* = 4.3 Hz, 3H), 3.24 – 3.10 (m, 2H), 3.06 (dt, *J* = 13.8, 4.2 Hz, 1H), 2.86 – 2.77 (m, 1H), 2.60 – 2.47 (m, 2H), 2.32 – 2.22 (m, 2H), 2.20 (t, *J* = 6.6 Hz, 1H), 2.12 – 2.00 (m, 2H). HRMS (EI^+) calc'd for $[C_{20}H_{22}N_2O_3]^+$: *m/z*, 338.1630 found 338.1625.



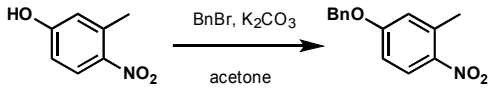
3.74 3.75

Enamine 3.75: A round-bottom flask was charged with **3.74** (15 mg, 0.045 mmol), acetone (1.8 mL), and saturated sodium bicarbonate (1.2 mL). The round-bottom was cooled to 0 ºC and a solution of Oxone® (30. mg, 0.049 mmol) in water (0.6 mL) was added dropwise over 15 minutes and the resultant mixture was stirred at 0 ºC for an additional 15 minutes, at which point the reaction was judged complete by TLC. The reaction was quenched with saturated sodium sulfite (3 mL) and the aqueous layer was extracted with DCM (3 x 5 mL). The combined organic layer was dried over sodium sulfate and concentrated via rotary evaporation. ^{1}H NMR (500 MHz, C_6D_6) δ 7.48 (t, *J* = 9.2 Hz, 1H), 7.23 – 7.14 (m, 6H), 6.93 (d, *J* = 7.5 Hz, 1H), 6.77 – 6.66 (m, 1H), 6.13 (t, *J* = 10.5 Hz, 1H), 5.69 (d, *J* = 3.9 Hz, 1H), 5.67 (d, *J* = 2.5 Hz, 1H), 4.93 (d, *J* = 12.3 Hz, 1H), 4.31 (td, *J* = 13.5, 4.7 Hz, 1H), 3.32 – 3.28 (m, 3H), 3.01 – 2.92 (m, 2H), 2.58 (ddd, *J* = 13.6, 5.3, 2.3 Hz, 1H), 2.44 (td, *J* = 14.0, 5.3 Hz, 1H), 1.98 – 1.92 (m, 2H), 1.79 – 1.63 (m, 4H). HRMS (EI^+) calc'd for $[C_{20}H_{22}N_2O_4]^+$: *m/z*, 354.1580 found 354.1592.



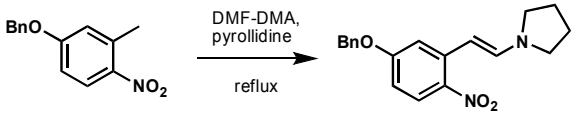
3.91

2-Nitroethyl acetate (3.91): A flame-dried round-bottom was charged with Ac_2O (12.3 mL, 130.2 mmol), NaOAc (2.75 g, 34.0 mmol). The flask was cooled to 5 °C and nitroethanol **45** (10.2 g, 113.2 mmol) was added dropwise over 40 minutes. The reaction was allowed to warm to RT and stirred for 14 hours. The reaction mixture was poured into 75 mL of cold H_2O and extracted with DCM (3x15 mL). The combined organics were washed with brine (15 mL), dried with $MgSO_4$ and concentrated by rotary evaporation to yield 13.2 g (88%) of a golden oil. ^{1}H NMR (400 MHz, $CDCl_3$) - δ 4.56 (s, 4H) , 2.06 (s, 3H). ^{1}H spectral data agree with previously reported values.[28]



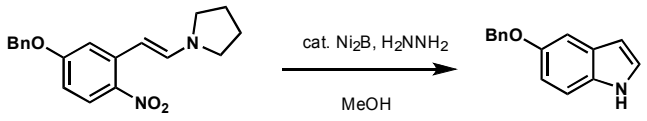
3.87 3.88

5-Benzyloxy-2-nitrotoluene (3.88): A flame-dried 100 mL Schlenk flask was charged with 4-nitro-*m*-cresol (7.66 g, 50.0 mmol),[29] K_2CO_3 (6.91 g, 50.0 mmol), and acetone (50 mL). To this was added benzyl bromide (6.53 mL, 55.0 mmol) dropwise. The flask was sealed and placed in an oil bath, which was heated to 60 °C for 4 h. The reaction mixture was cooled, filtered through celite, and the filtrate was concentrated via rotary evaporation. The crude orange oil was dissolved in Et_2O (100 mL) and the organic layer was washed with 1 N NaOH (50 mL) and brine (50 mL), dried over $MgSO_4$, and concentrated by rotary evaporation. The crude oil was crystallized from MeOH to afford 9.10 g of off-white needles, m.p. 70-71 °C. ^{1}H NMR (500 MHz, $CDCl_3$) - δ 8.08 (m, 1H), 7.32-7.43 (m, 5H), 6.83-6.89 (m, 2H), 5.13 (s, 2H), 2.63 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) – δ 162.3, 142.5, 137.3, 135.9, 129.0, 128.6, 127.8, 127.7, 118.557, 112.8, 70.7, 21.9. ^{1}H NMR spectral data and m.p. agree with previously reported values.[30]



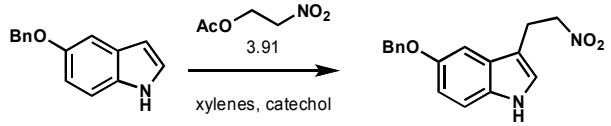
3.88 3.89

1-(5-(Benzyloxy)-2-nitrostyryl)pyrrolidine (3.89): A flame-dried 250 mL round-bottom flask was charged with **3.88** (8.44 g, 34.7 mmol), pyrrolidine (3.5 mL, 41.7 mmol), and dimethylformamide-dimethylacetal (6.5 mL, 48.6 mmol). The flask was fitted with a reflux condenser, and heated to 120 °C for 16 h. The flask was cooled, and excess pyrrolidine and dimethylformamide-dimethylacetal were removed under high-vacuum. The crude dark red oil was utilized without further purification.



3.89 3.90

5-Benzyloxyindole (3.90): A 250 mL round-bottom was charged with **3.89** (34.7 mmol from previous reaction), THF (70 ml), MeOH (70 mL), and Ni_2B[12] (1.5 mL of slurry in MeOH). The vessel was sealed and purged with N_2. After heating to 30 °C, hydrazine hydrate (2.5 mL, 52 mmol) was added and the oil-bath temperature was brought to 45 °C. Additional portions of hydrazine hydrate (2.5 mL, 52 mmol) were added after stirring at 45 °C for half an hour and one hour, respectively. After stirring at 45 °C for two hours following the final addition, the reaction mixture was cooled to room temperature. The reaction mixture was filtered through Celite and the filtrate was concentrated by rotary evaporation. The crude brown oil was purified by column chromatography (2:1 hexanes/ethyl acetate) to yield 5.3 g (68%) of off-white crystals, m.p. 108-110 °C. ^{1}H NMR (400 MHz, $CDCl_3$) - δ 8.22 (br s, 1H), 7.56 (d, *J* = 7.5 Hz, 2H), 7.47 (t, *J* = 7.3 Hz, 2H), 7.41 (d, *J* = 7.2 Hz, 1H), 7.33 (d, *J* = 8.8 Hz, 1H), 7.27 (s, 1H), 7.21 (br s, 1H), 7.03 (d, *J* = 8.7 Hz, 1H), 6.54 (br s, 1H), 5.18 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) - δ 153.4, 137.8, 131.2, 128.6, 128.3, 127.8, 127.7, 125.1, 113.1, 111.8, 104.1, 102.4, 71.0. ^{1}H NMR data are consistent with previously reported values.[31]



3.90 3.92

3-(2-Nitroethyl)-5-benzyloxyindole (3.92): A flame-dried 250 ml Schlenk flask was charged with **3.90** (5.3 g, 23.7 mmol), **3.91** (3.48 g, 26.1 mmol, 1.1 equiv.), and 3-methyl-catechol (250 mg, 2.3 mmol, 0.1 equiv.), and toluene (100 mL). The reaction solution was sparged with N_2 for 15 minutes while stirring, and the flask was sealed. The flask was placed in an oil bath which was heated to 120 °C for 14 hours, then cooled to room temperature. The reaction solution was concentrated by rotary evaporation, and purified by passing through a plug of silica gel (2:1 hexanes-ethyl acetate eluent), and crystallized with dichloromethane/pentane to afford 5.3 g (76%) of brown crystals, m.p. 96-97 °C. ^{1}H NMR (400 MHz, $CDCl_3$) – δ 7.98 (br s, 1H), 7.49 (m, 2H), 7.40 (m, 2H), 7.32 (m, 1H), 7.28 (d, *J* = 8.8 Hz, 1H), 7.08 (d, 2.4 Hz, 1H), 7.04 (d, 2.3 Hz, 1H), 6.97 (dd, *J* = 8.7, 2.3 Hz, 1H), 5.12 (s, 2H), 4.63 (t, *J* = 7.3 Hz, 2H), 3.45 (t, *J* = 7.3 Hz, 2H) ^{13}C NMR (125 MHz, $CDCl_3$) – δ 153.5, 137.5, 131.6, 128.6, 127.9, 127.7, 127.1, 123.4, 113.4, 112.2, 109.8, 101.9, 75.6, 71.1, 23.7. Melting point agrees with previously reported value.[31]

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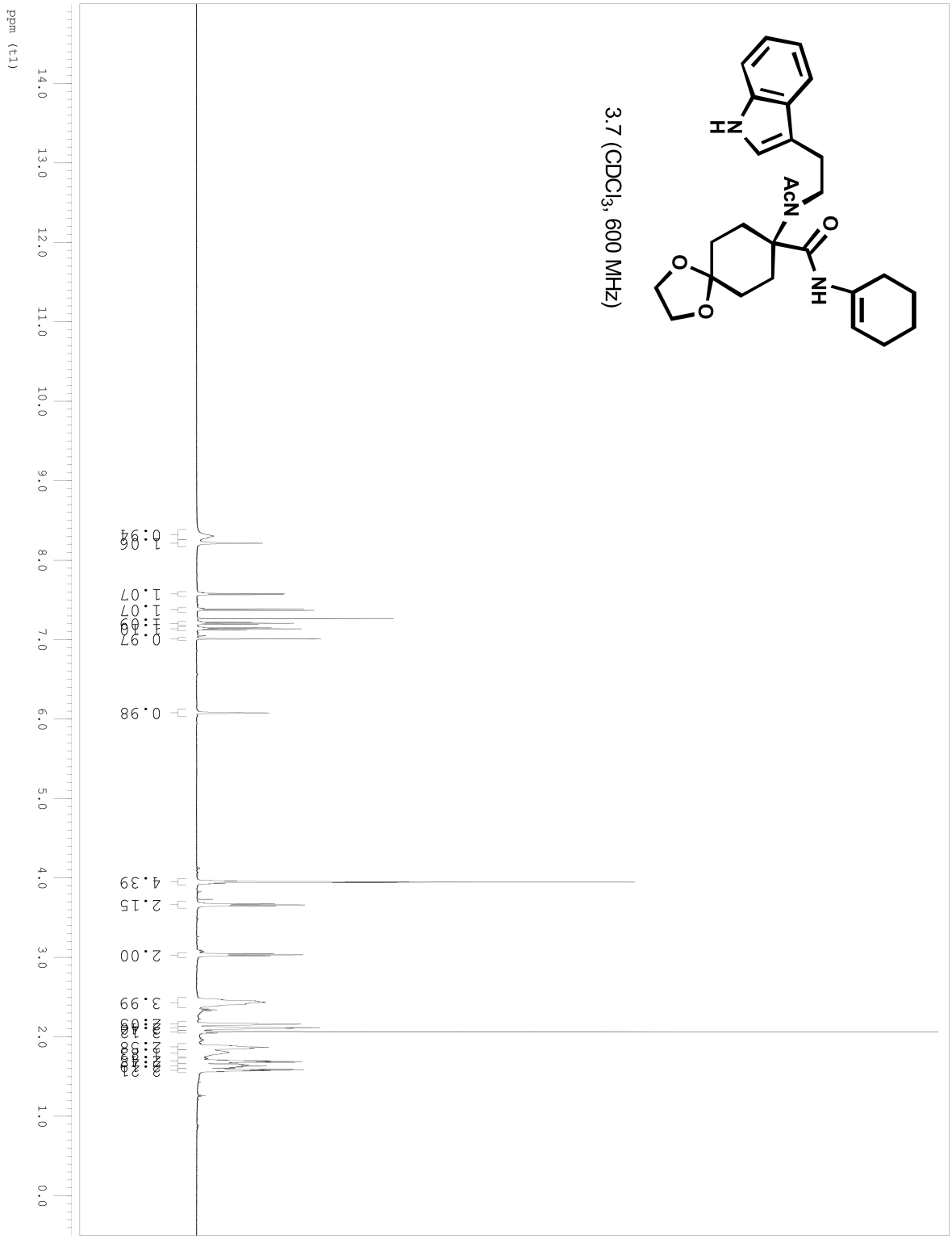
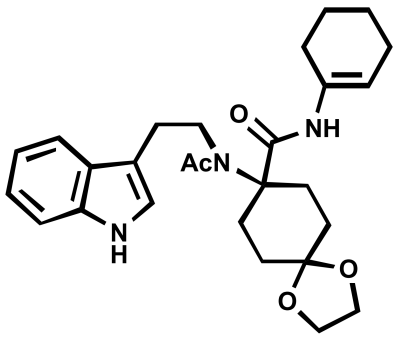
Appendix III: Selected Spectra





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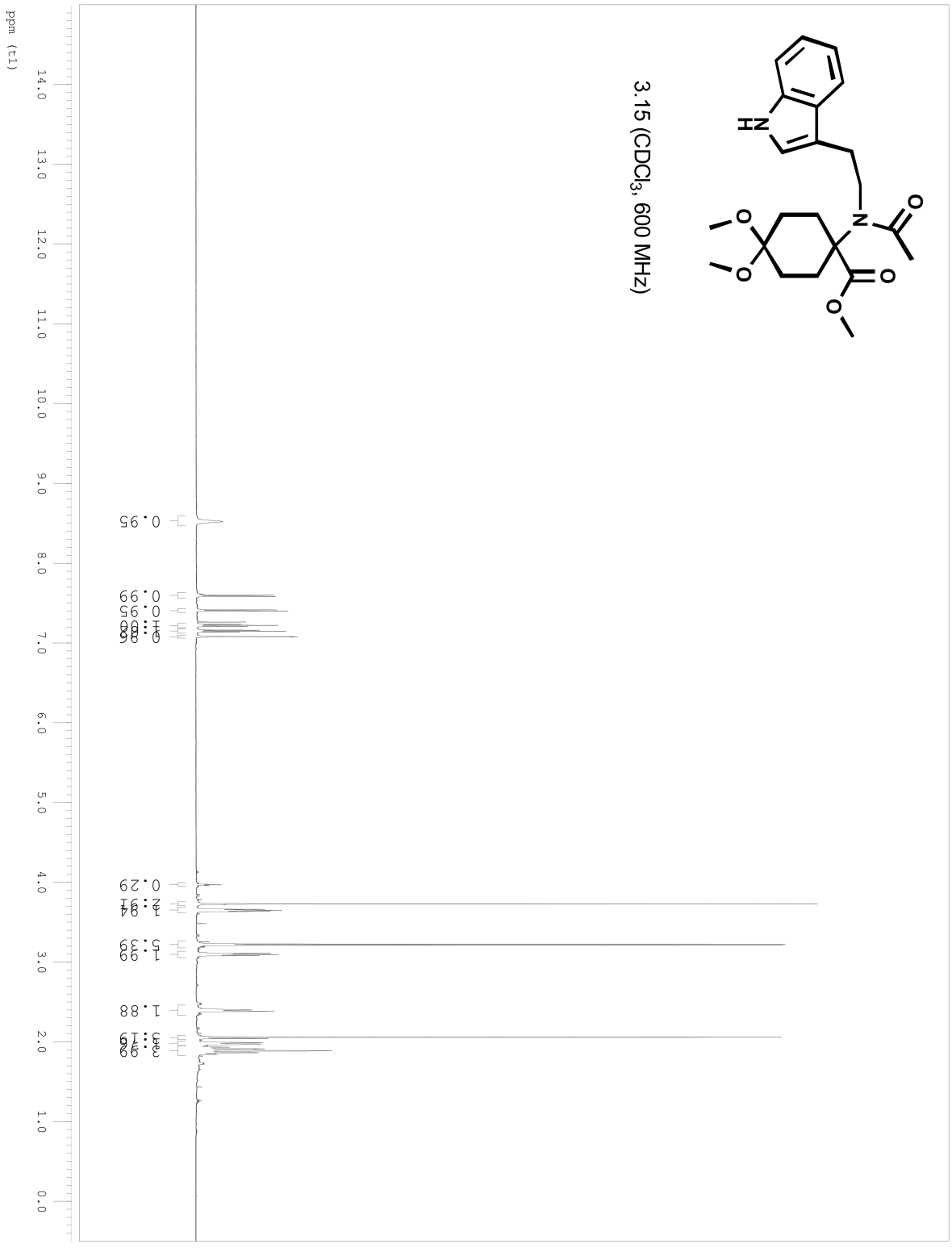
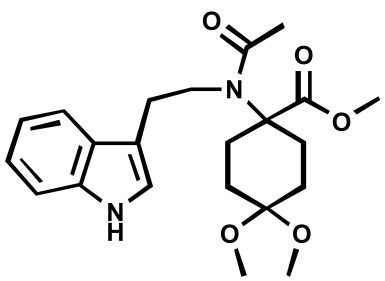
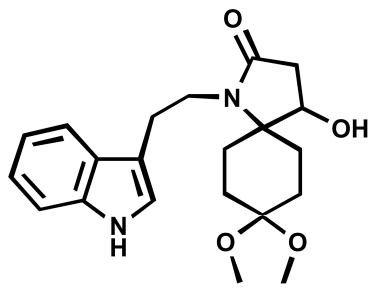
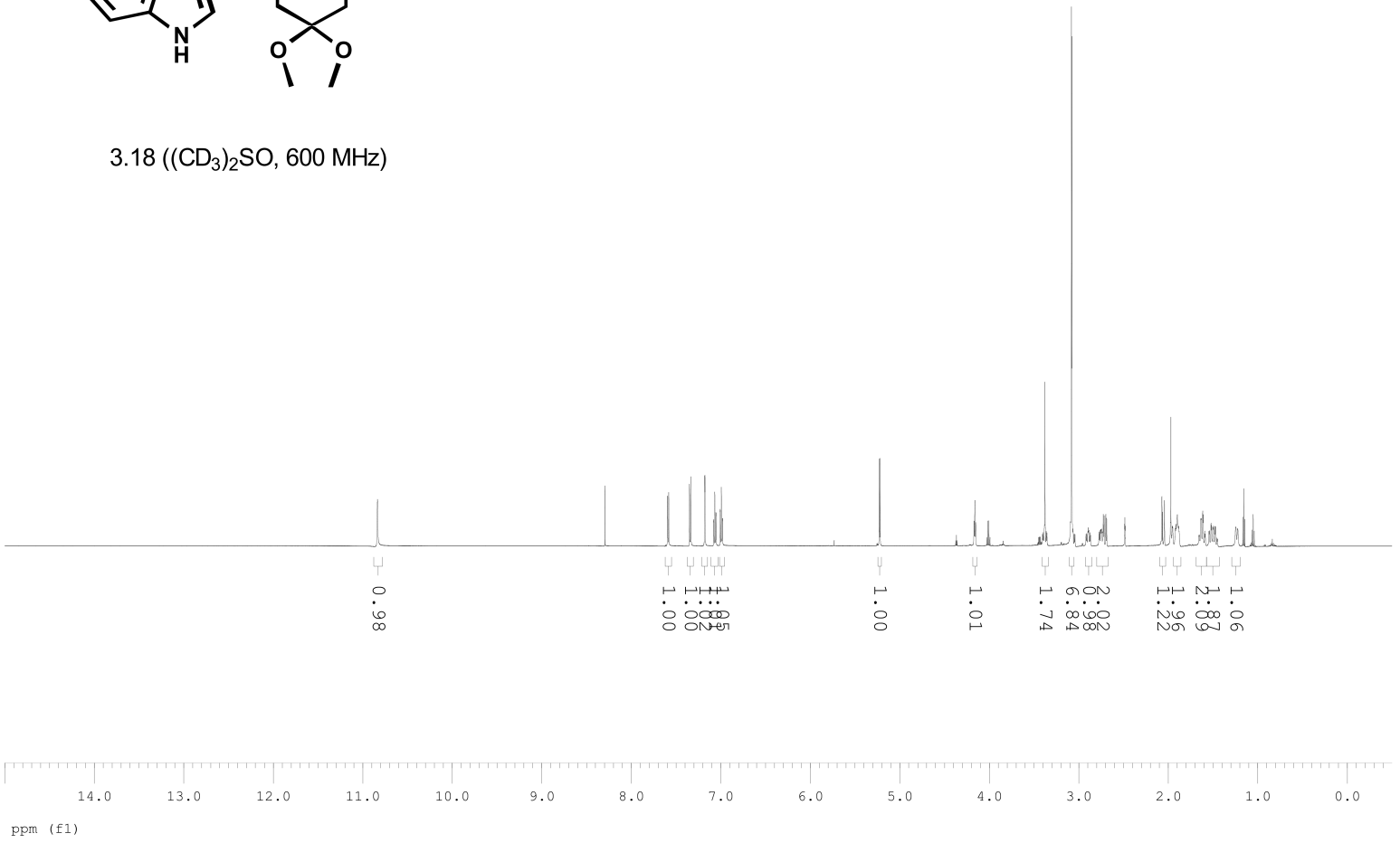

3.15 (CDCl3, 600 MHz)
ppm (t1)

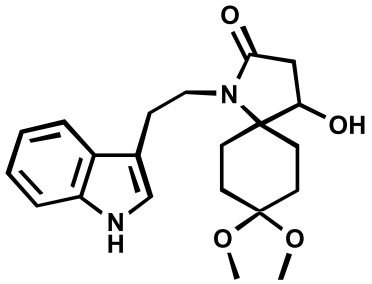


3.15 ($CDCl_3$, 150 MHz)

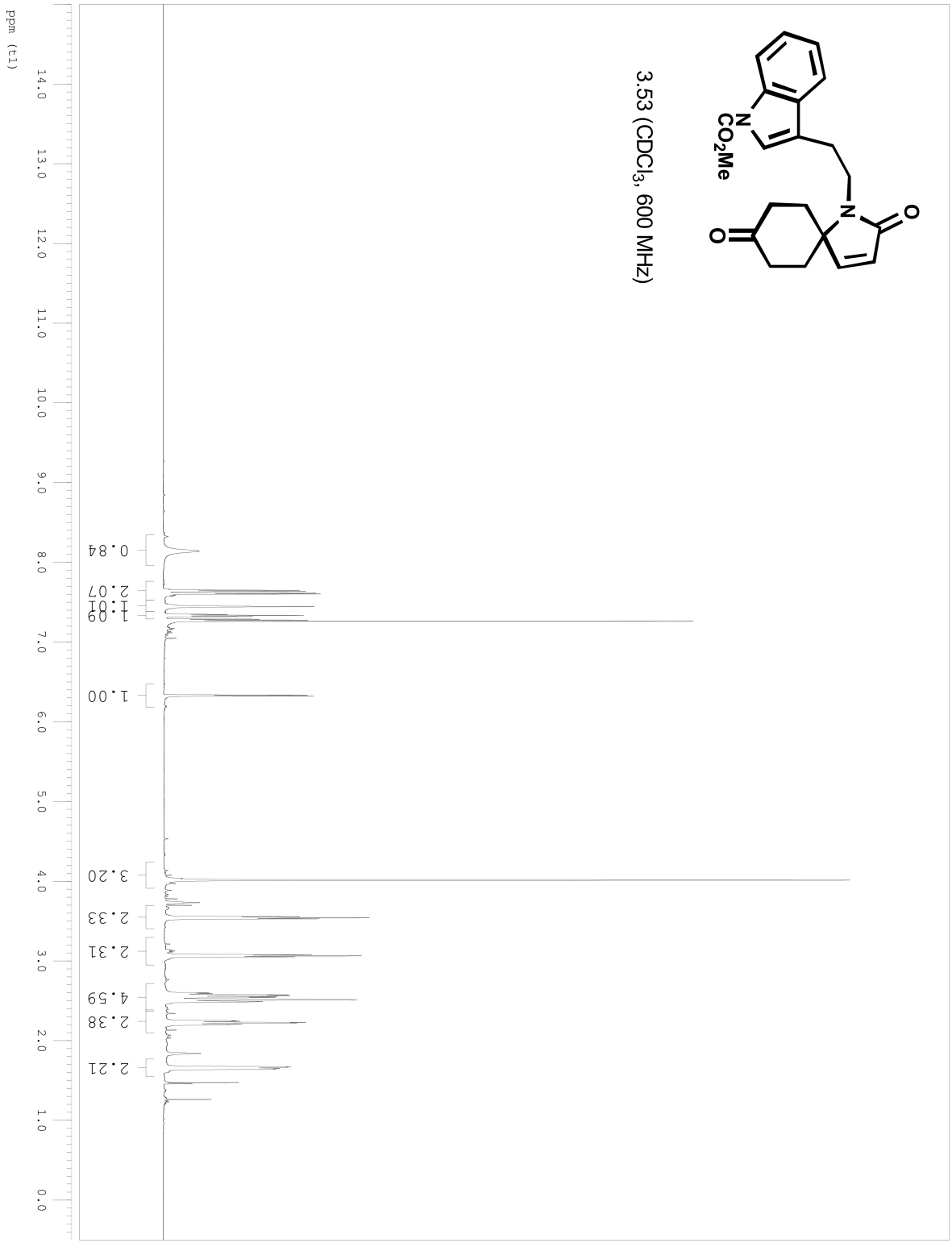


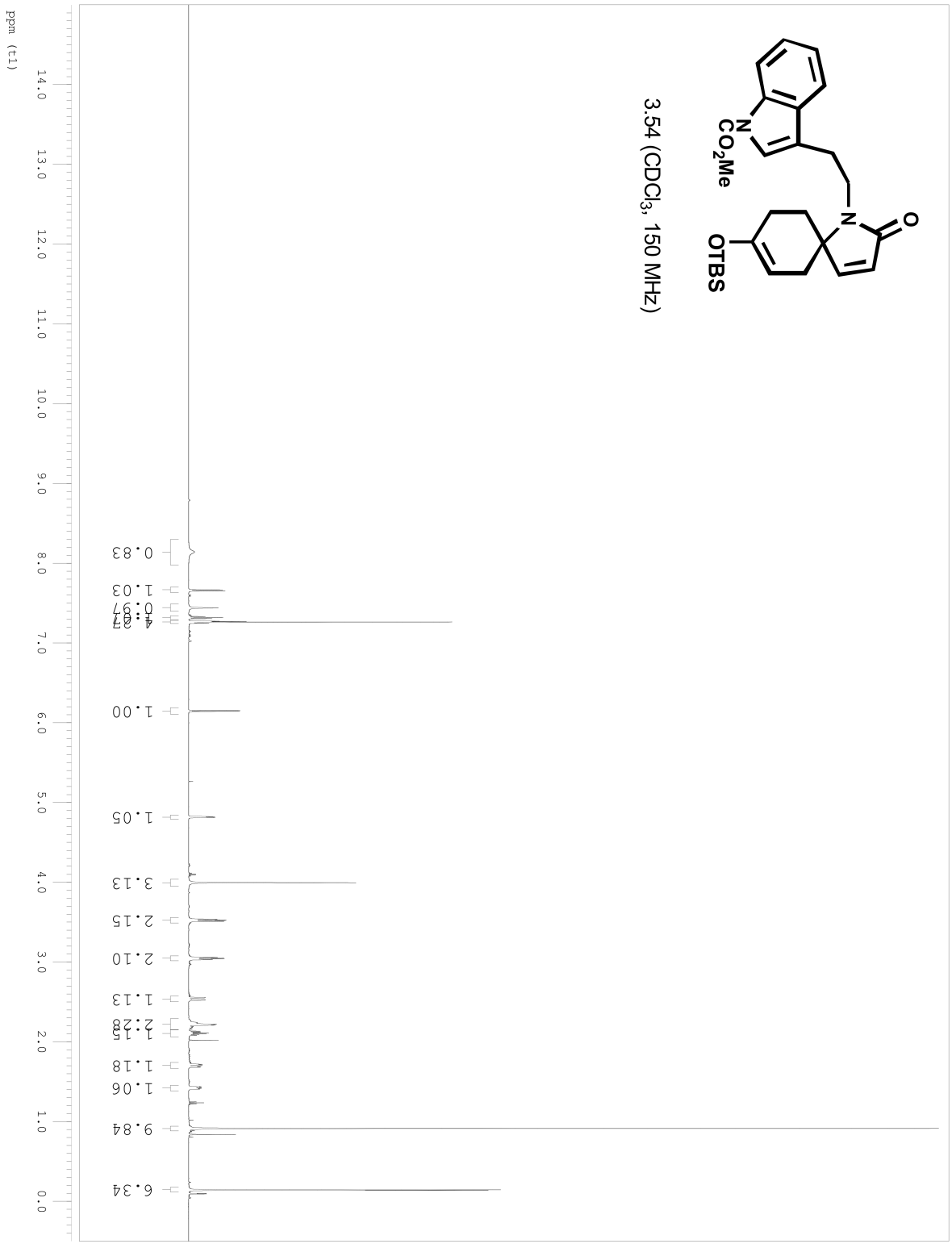
3.18 ($(CD_3)_2SO$, 600 MHz)

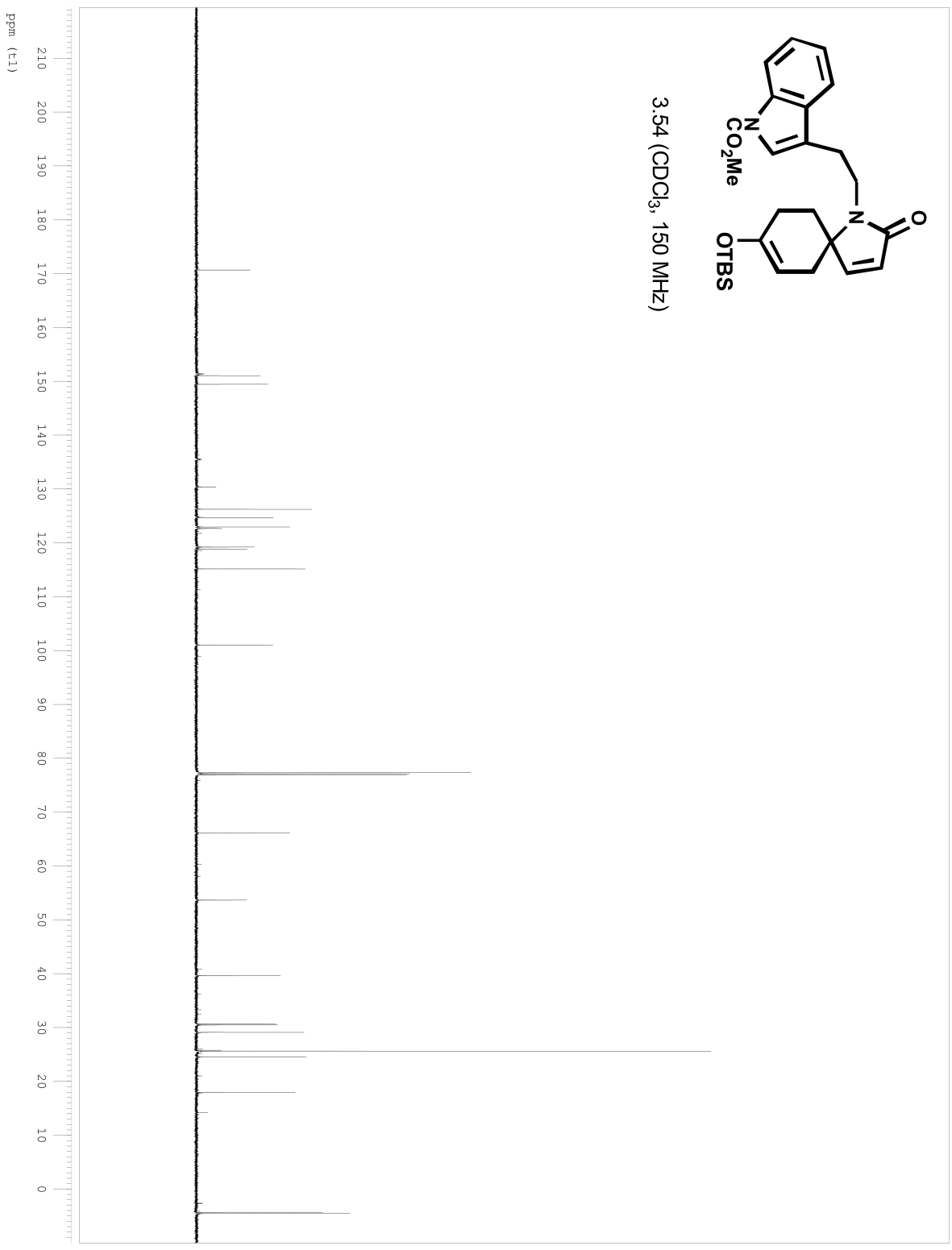


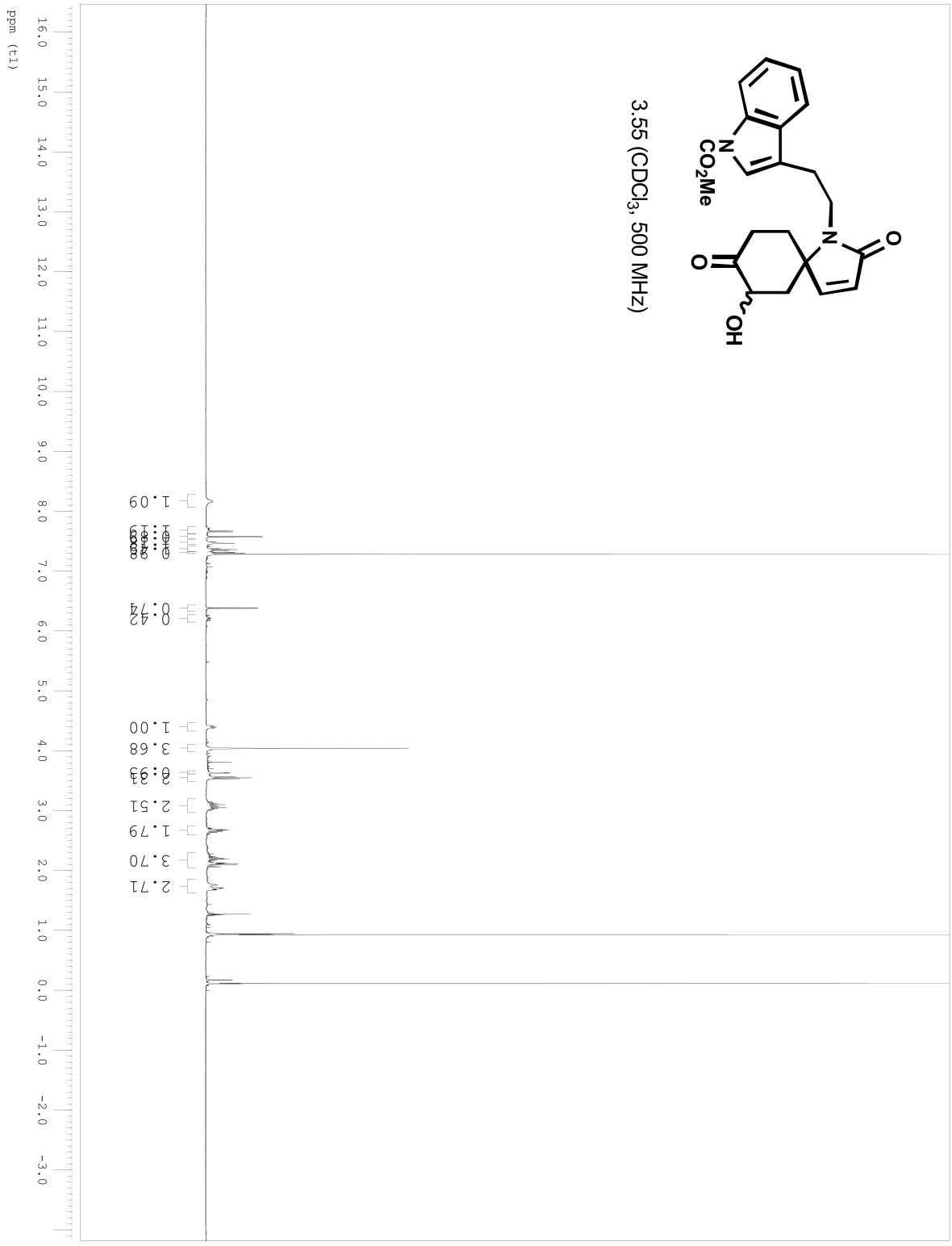


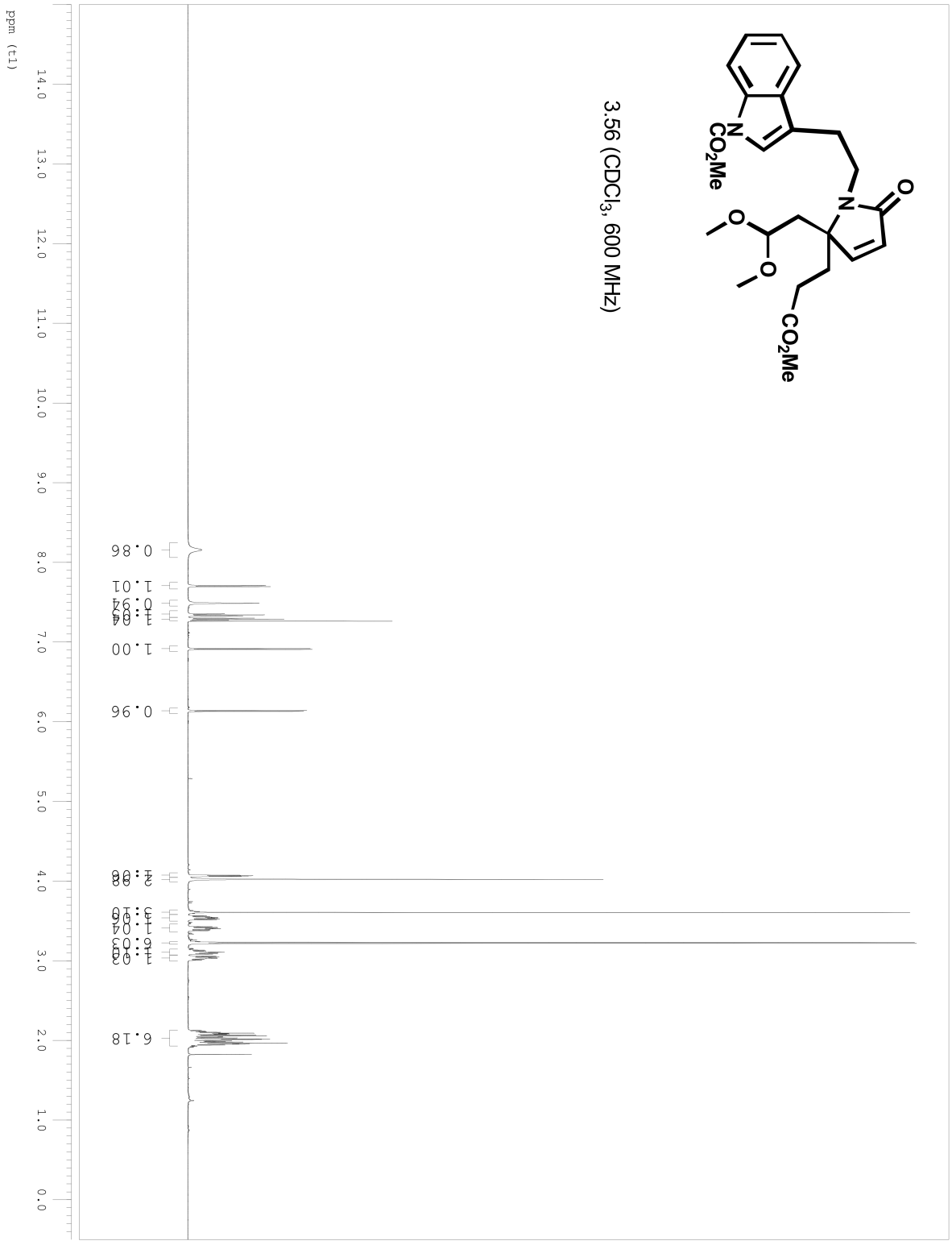
3.18 ($(CD_3)_2SO$, 150 MHz)

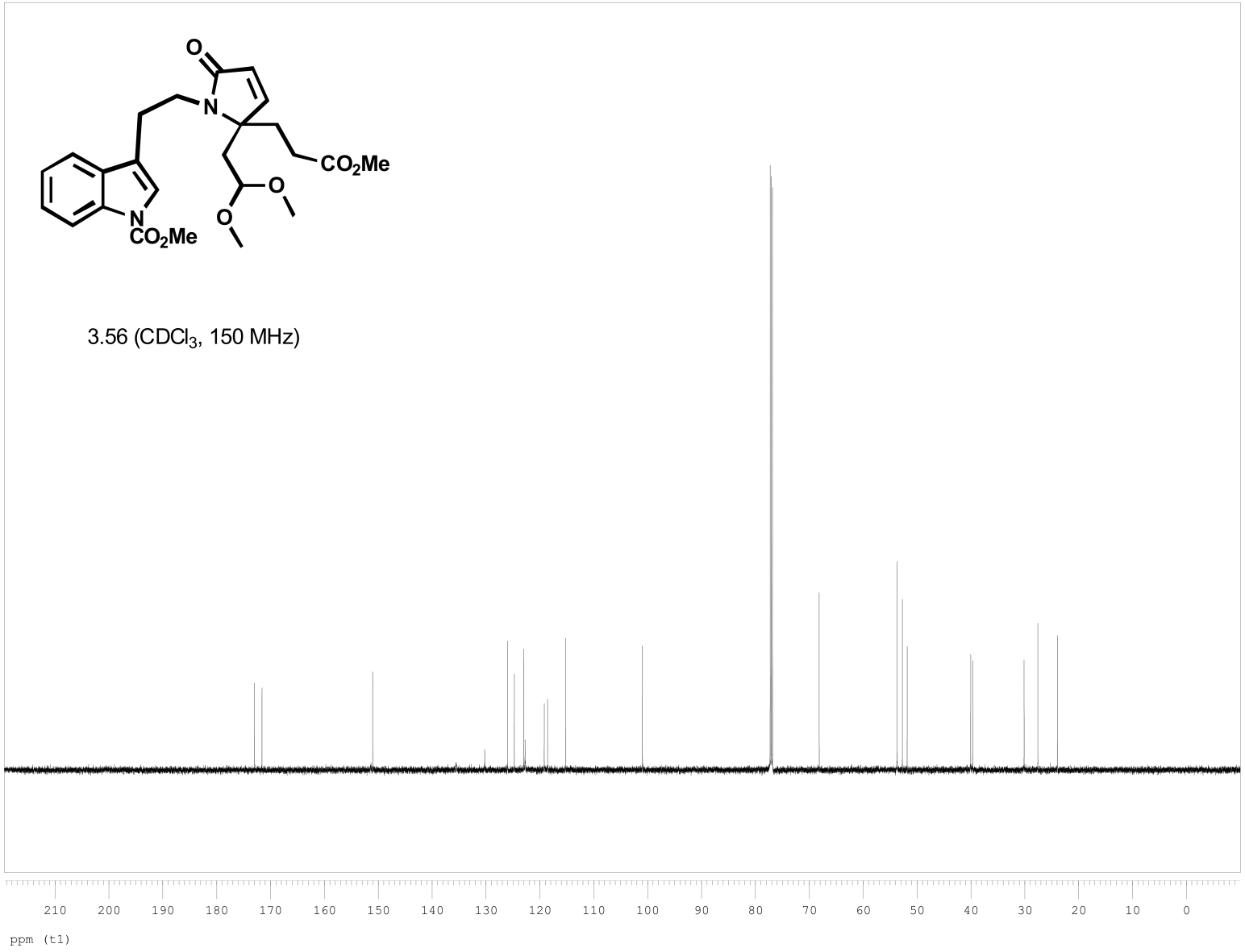

3.53 (CDCl3, 600 MHz)
N
CO2Me
N
O
O
0.84
2.07
1.01
1.09
1.00
3.20
2.33
2.31
4.59
2.38
2.21
ppm (t1)
14.0
13.0
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0

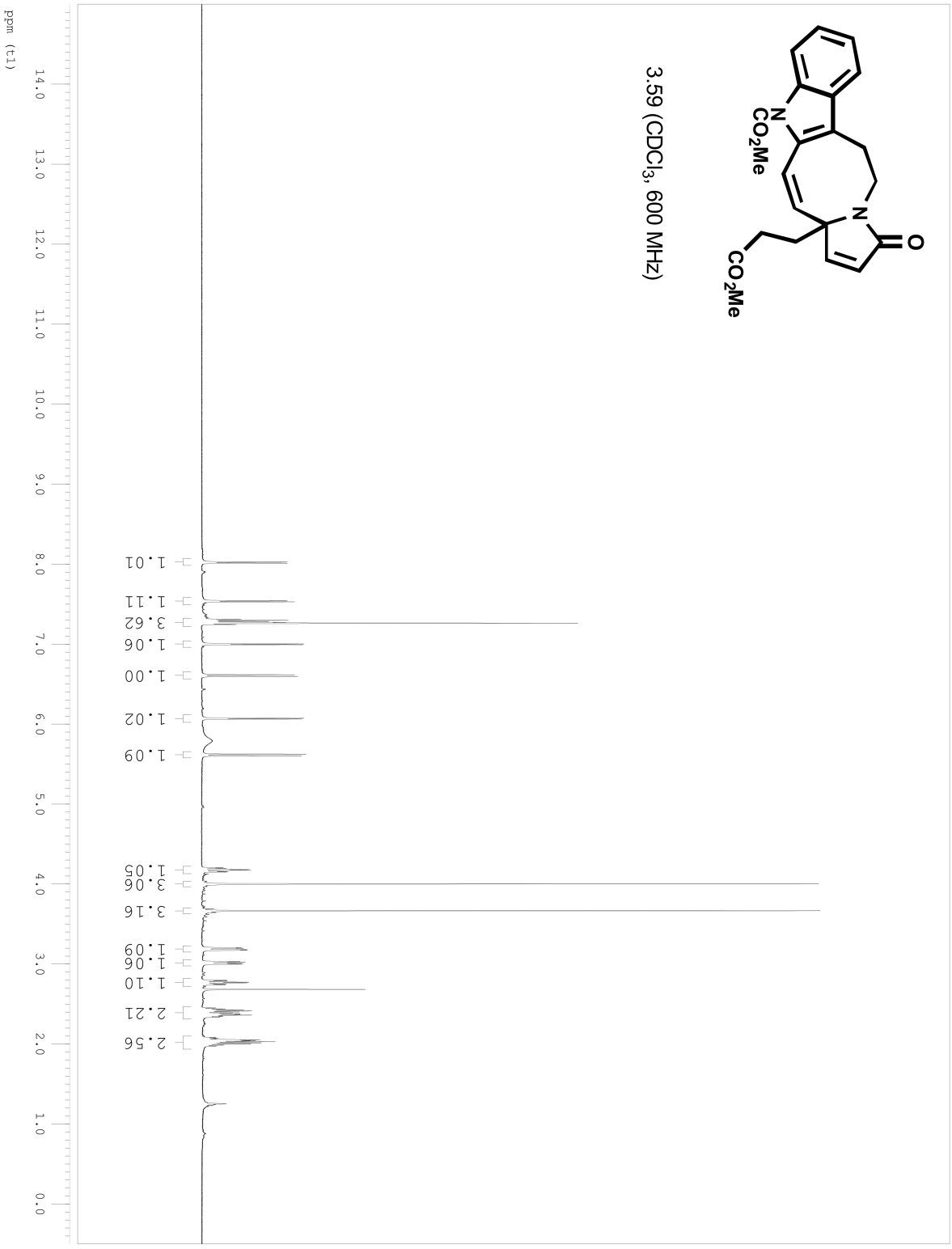

3.54 ($CDCl_3$, 150 MHz)
N
CO_2Me
N
O
OTBS
0.83
1.03
0.97
4.27
1.00
1.05
3.13
2.15
2.10
1.13
1.15
2.28
1.18
1.06
9.84
6.34
ppm (t1)
14.0
13.0
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0

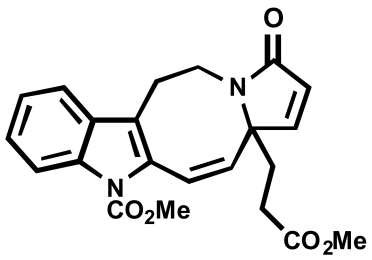

3.54 ($CDCl_3$, 150 MHz)
N
CO_2Me
N
O
OTBS
ppm (t1)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


3.55 (CDCl3, 500 MHz)
CO2Me
N
N
O
O
OH
ppm (t1)
16.0
15.0
14.0
13.0
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
-1.0
-2.0
-3.0
1.09
0.74
1.00
3.68
0.93
2.13
2.51
1.79
3.70
2.71

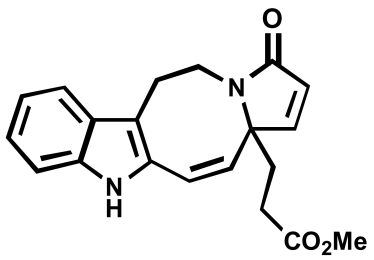

3.56 ($CDCl_3$, 600 MHz)
CO_2Me
CO_2Me
O
N
O
O
N
O
ppm (t1)
14.0
13.0
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
0.86
1.01
0.97
1.00
0.96
6.18


O
N
CO2Me
O
O
N
CO2Me
3.56 (CDCl3, 150 MHz)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm (t1)

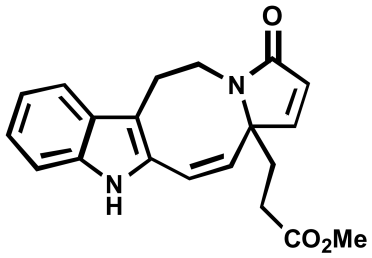

3.59 (CDCl3, 600 MHz)
CO2Me
CO2Me
N
N
O
1.01
1.11
3.62
1.06
1.00
1.02
1.09
1.05
3.06
3.16
1.09
1.06
1.10
2.21
2.56
ppm (t1)



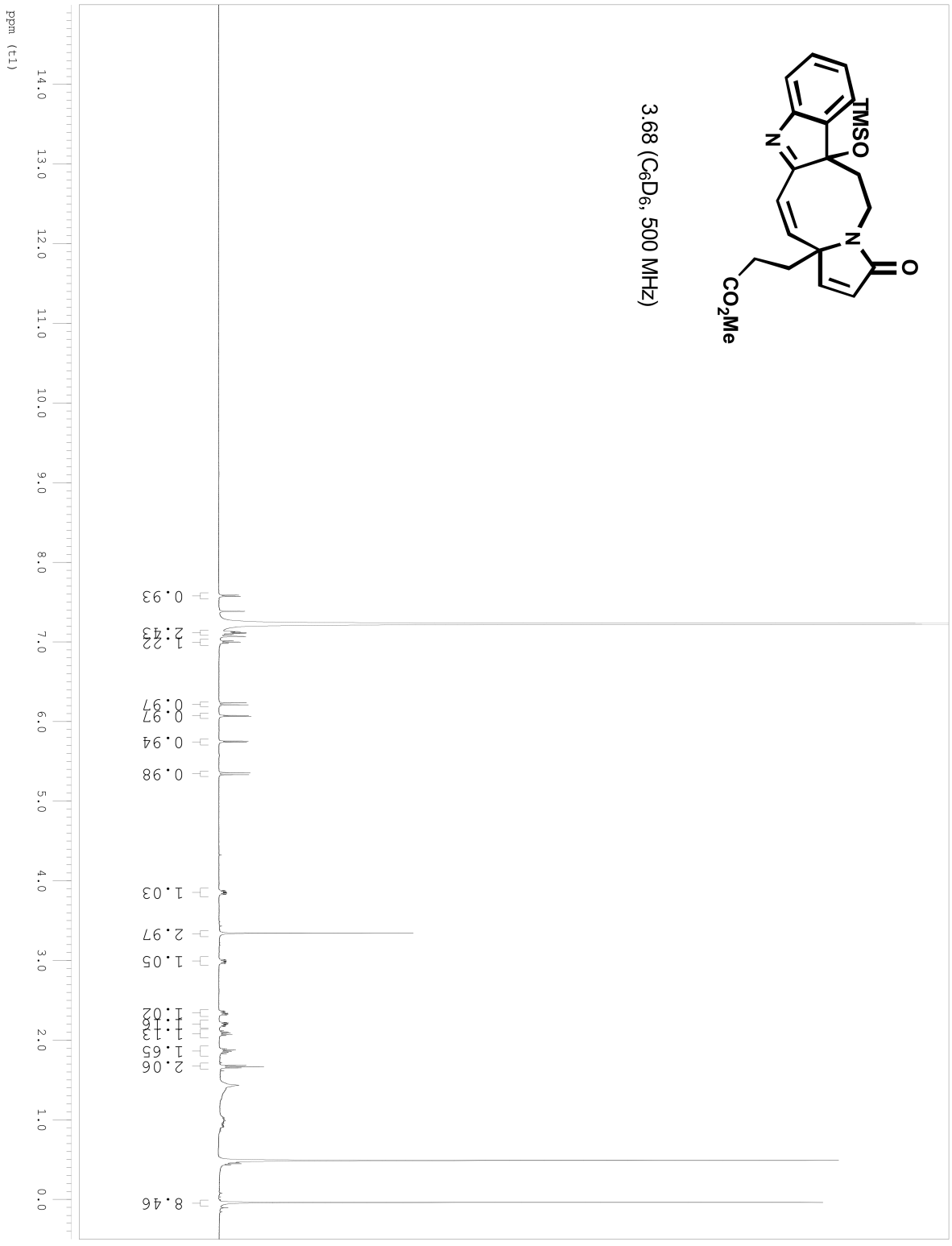
3.59 ($CDCl_3$, 150 MHz)

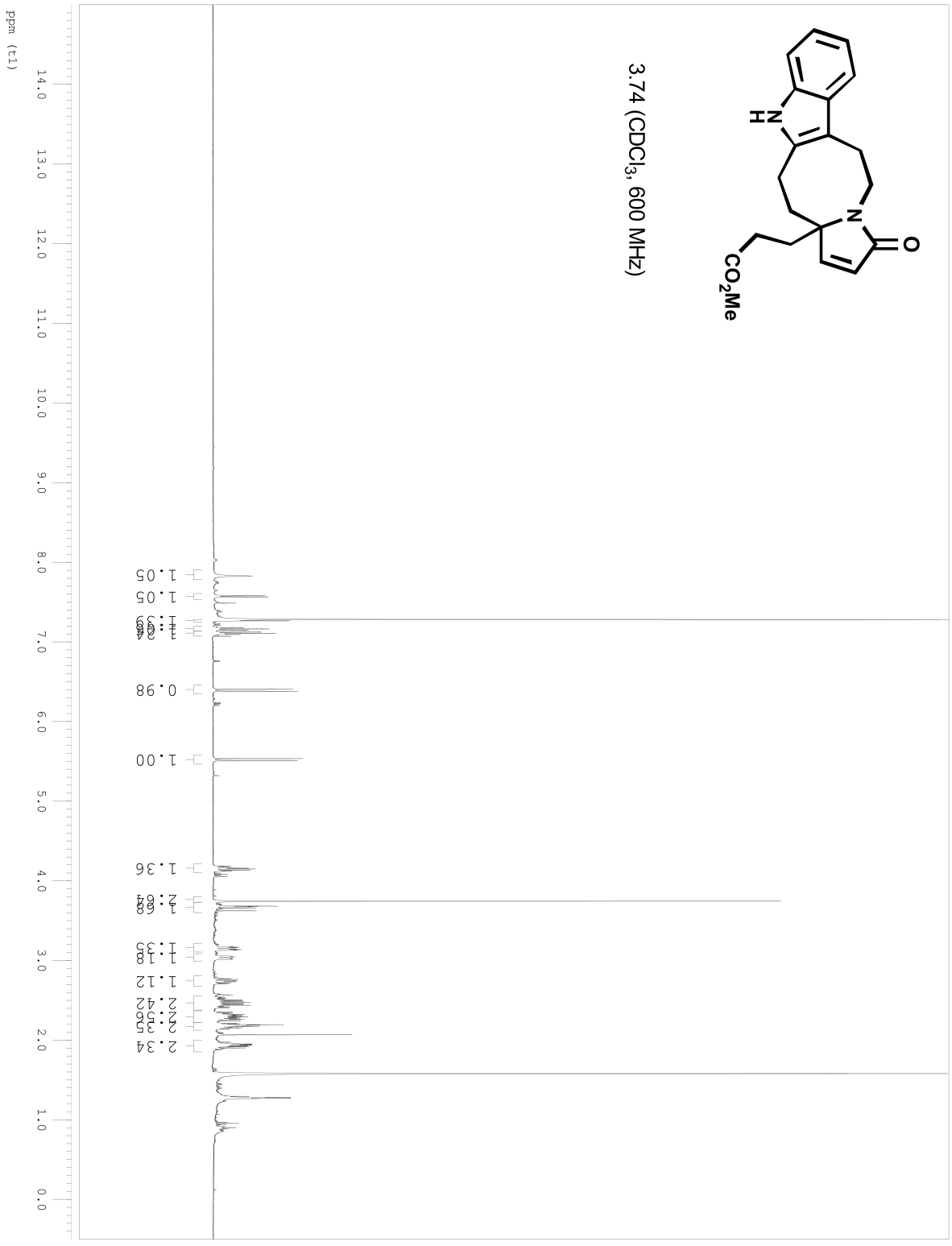


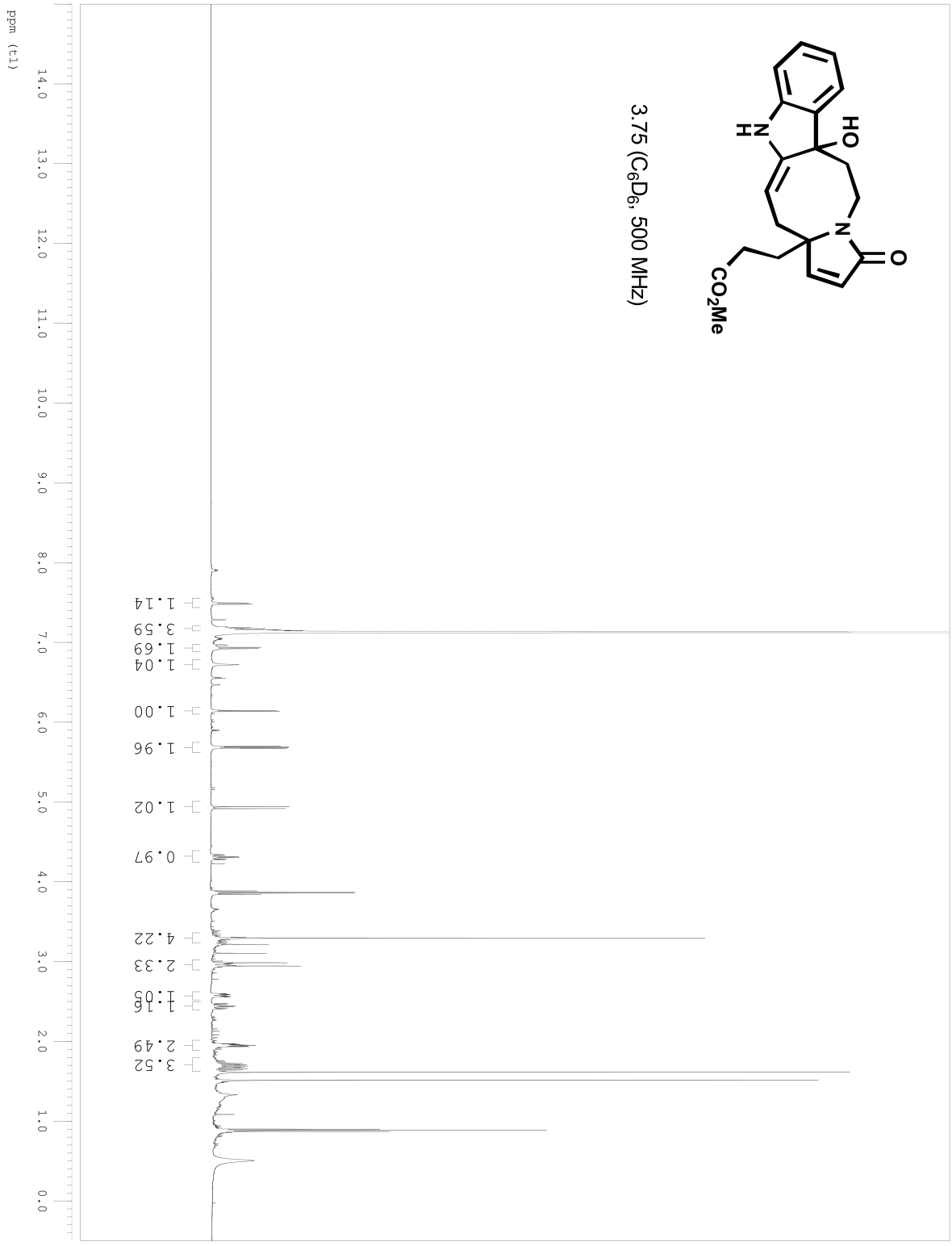
3.63 ($CDCl_3$, 600 MHz)



3.63 ($CDCl_3$, 150 MHz)


TMSO
N
N
O
CO2Me
3.68 (C6D6, 500 MHz)
0.93
2.43
1.22
0.97
0.97
0.94
0.98
1.03
2.97
1.05
1.02
1.00
1.00
1.00
2.06
1.65
1.00
8.46
ppm (t1)


3.74 (CDCl3, 600 MHz)
CO2Me
N
H
N
O
ppm (t1)
14.0
13.0
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
1.05
1.05
0.98
1.00
1.36
2.34
1.12
1.35


3.75 (C_6D_6, 500 MHz)
HO
N
H
N
O
CO_2Me
1.14
3.59
1.69
1.04
1.00
1.96
1.02
0.97
4.22
2.33
1.05
1.16
3.52
2.49
ppm (t1)