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Progress Toward the *Kopsia* Family of Indole Alkaloids
and
The Synthesis of Fused Pyrroles and Dihydroazepines via Intramolecular
Cyclopropanation and Rearrangement
by

Erica Elizabeth Schultz

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 Robert G. Bergman
Professor Leonard F. Bjeldanes

Spring 2014

Abstract

Progress Toward the Kopsia Family of Indole Alkaloids and the Synthesis of Fused Pyrroles and Dihydroazepines via Intramolecular Cyclopropanation and Rearrangement

by

Erica Elizabeth Schultz

Doctor of Philosophy in Chemistry
University of California, Berkeley
Professor Richmond Sarpong, Chair

Chapter 1. An overview of multi-drug resistance (MDR) and the possibility of small molecule tools to elucidate the biological mechanism of MDR are outlined. The *Kopsia* family of natural products related to lapidilectine B is introduced, and previous synthetic efforts are discussed. Two synthetic strategies and the progress made toward the natural product are detailed. In the first route, the tetracyclic core of these molecules is accessed through a Friedel-Crafts type acylation. The second route employs an Ugi four-component coupling to introduce all the carbons found in the core of the natural product and accesses the tetracyclic core in three ways.

Chapter 2. Rh-bound trimethylenemethane (TMM) variants generated from the interaction of a Rh-carbenoid with an allene have been applied to the synthesis of substituted 3,4-fused pyrroles. An overview of the synthetic variants of TMM is given and access to rhodium carbenoid centers from 1,2,3-triazoles is discussed. A range of allenes bearing different substituents is tolerated in this reaction. The pyrrole products are useful starting points for the syntheses of various dipyrromethene ligands.

Chapter 3. A method for the direct formation of dihydroazepine derivatives from 1-sulfonyl-1,2,3-triazoles possessing a tethered diene is reported. Discussion of aza-Cope rearrangements and cyclopropanation from the decomposition of 1,2,3-triazoles into metallocarbenoids is given. The methodology involves an intramolecular cyclopropanation of an α -iminocarbene, leading to a transient 1-imino-2-vinylcyclopropane intermediate which rapidly undergoes a 1-aza-Cope rearrangement to generate fused dihydroazepine derivatives, mechanistic support is provided.

Chapter 4. The methodology described in Chapter 2 for the synthesis of substituted 3,4-fused pyrroles has been applied to a synthesis of the natural product cycloprodiginosin, which demonstrates antitumor and immunosuppressor activity. A history of the prodiginine family of natural products is given. The modes of action and the role of structure in regards to cycloprodiginosin's antitumor activity are also discussed.

Dedicated to all the women chemists that came before me,
especially Professor Rebecca C. Hoye for inspiring me to take this path.

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Chapter 1. Progress Toward the *Kopsia* Family of Indole Alkaloids

1.1. Introduction

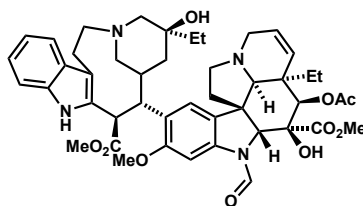
1.1.1. Multi-drug resistance

With the advancement of chemotherapies to treat a variety of cancers, the ability for cancer cells to become resistant to once effective drugs is a major challenge that needs to be addressed. This ability, known as multi-drug resistance (MDR), is found in a variety of cancer cells independent of the drug or mode of action. Because of this, there is assumed to be a general mechanism by which MDR arises. Early studies have shown that MDR cells have a decreased accumulation of the active drug agent in the cytoplasm as compared to drug-sensitive cells.¹ It has also been found that MDR cells overexpress two membrane bound proteins, P-glycoprotein and the multidrug resistance-associated protein (MRP), which act as efflux pumps that actively expel drugs from the inside of the cell before they can induce apoptosis or halt cell growth.²

In any given tumor, there are many malignant cells that are sensitive to drug treatment in addition to some which may have developed resistance. Once a cancer patient undergoes chemotherapy, effective drugs reduce the tumor size by targeting and killing cells that are susceptible to the drugs. However, the reduced tumor will consist of a higher proportion of resistant cancer cells, which can grow back and be untreatable using previously effective methods, resulting in a major failure for chemotherapy.

One class of chemotherapy agents, the *Vinca* alkaloids, a class of plant derived natural products, have been shown to be effective mitotic inhibitors.³ They have been shown to interact with tubulin and halt the formation of microtubules, arresting mitosis in metaphase, and eventually leading to apoptosis. One of the most widely used *Vinca* alkaloids in chemotherapy is vincristine (**1.1**, Figure 1.1), which is marketed as Oncovin®, Vincasar FPS®, and Vincrex®. Vincristine is used as a part of several chemotherapy regimens, including those for non-Hodgkin's lymphoma, Hodgkin's lymphoma, and acute lymphoblastic leukemia. Vincristine is also used in the treatment of neuroblastoma.⁴

Figure 1.1. *Vinca* alkaloid chemotherapy agent vincristine.

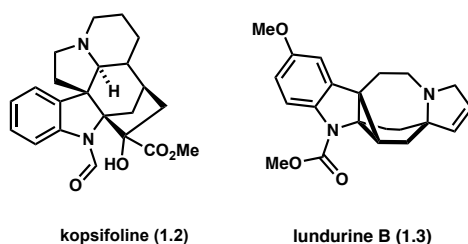


vincristine (1.1)

However, an issue with vincristine treatment is the tendency for the drug to trigger MDR. To increase the efficacy of the treatment of these cancers, a better understanding of MDR mechanisms in these cells and additional therapeutics to combat MDR are required. Therefore, there is an increased interest in MDR-reversing

compounds that could potentially be used in concert with vincristine to make the resistant cancer cells more susceptible to the anti-cancer agent. During a screen of natural products that exhibit MDR-reversing properties, Kam and co-workers discovered a number of indole alkaloids isolated from the *Kopsia* family of flowering plants that showed promising activity.⁵ Compounds such as kopsifoline (**1.2**) and lundurine B (**1.3**) showed MDR-reversing properties against vincristine resistant human KB cell lines.

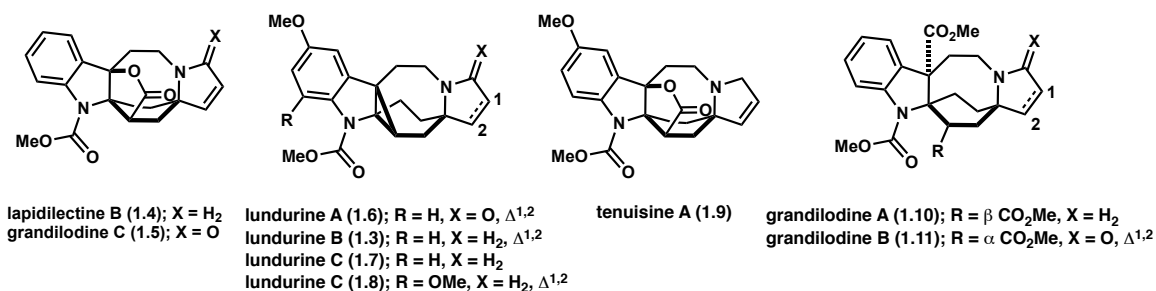
Figure 1.2. Bioactive *Kopsia* indole alkaloids with MDR-reversing properties.



1.1.2. *Kopsia* family of natural products

As part of a synthetic program aimed at synthesizing lundurine B,⁶ we became interested in a number of structurally related natural products, all isolated from the *Kopsia* family of flowering plants. In addition to their MDR-reversing properties, we were drawn to these molecules because they possess unique caged structures, which offer opportunities for new synthetic tactics, as well as their potential use as starting points for new pharmaceuticals. We envisioned a route that would provide access to lapidilectine B (**1.4**), which could be modified to allow access to related natural products such as grandilodine B (**1.11**). This route would also lay the groundwork for the synthesis of lundurine B (**1.3**) and tenuisine A (**1.9**), which possess an oxygenated electron-rich aryl ring. A unified synthetic route to these molecules would also provide access to strategic synthetic derivatives that could provide deeper understanding into the structure-activity relationships (SAR) that give rise to their MDR-reversing properties.

Figure 1.3. Select *Kopsia* alkaloids.

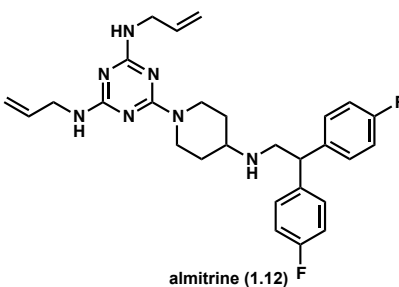


Lapidilectine B (**1.4**) was first isolated from the leaves of the Southeast Asian flowering plant *Kopsia lapidilecta*. Like many of the natural products isolated from the *Kopsia* plants, lapidilectine B is a structurally interesting alkaloid that bears an intricate, caged ring system (Figure 1.3). Although little pharmacological activity has been found

for lapidilectine B, extracts from other *Kopsia* species have been used to treat a variety of ailments such as rheumatoid arthritis, edema, tonsillitis, and hypertension.⁷

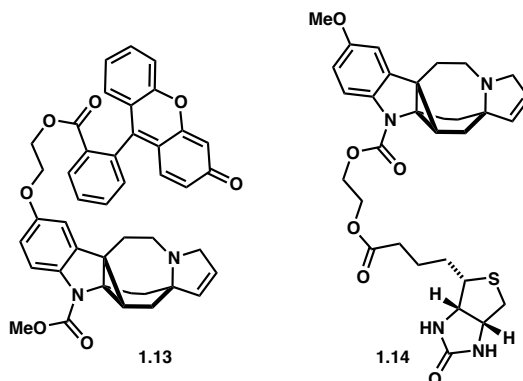
Adding to the intrigue of the *Kopsia* alkaloids, the other class of compounds that has been found to have MDR-reversing properties in vincristine-resistant cancer cells is characterized by a very different structural motif (**1.12**, Figure 1.4),⁸ and therefore, may operate through a different mechanism.

Figure 1.4. Triazine derivative with MDR-reversing properties.



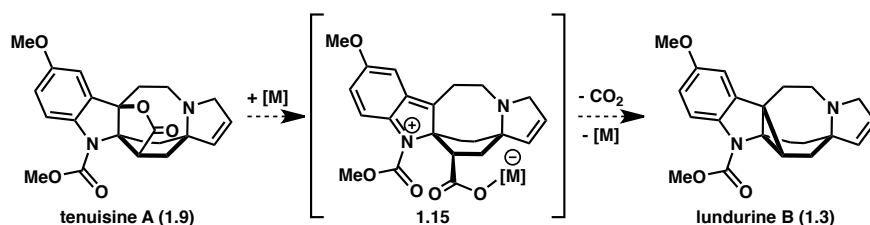
A synthetic route to the *Kopsia* alkaloids, as well as related analogs functionalized as biological probes, would be paramount in elucidating their mode of action. Understanding the biological mechanism of these compounds could lead to the design of a pharmacological agent that could be used as a co-drug in the treatment of tumors that exhibit multi-drug resistance. Therefore, in addition to SAR, we are interested in creating a synthetic route that would allow for the synthesis of molecular probes such as those illustrated in Figure 1.5, which can help elucidate the mode of action of lundurine B that leads to its MDR-reversing properties. Appending fluorescent probes, such as **1.13**, could help visualize intracellular interactions. Additionally, attaching biotin tags (see **1.14**) could help probe cellular ligands via affinity chromatography with streptavidin infused columns. The ability to access such biological probes is important because the efflux pumps are membrane bound proteins, which are often difficult to characterize using conventional methods like NMR and X-Ray crystallography.

Figure 1.5. Biologically relevant lundurine B analogues.



Another interest we have in developing a route to lundurine B is the structural relationship it has to tenuisine A, which has a lactone function in place of the cyclopropanyl ring (**1.9** and **1.3**, Scheme 1.1). Both molecules were isolated from the same plant source, which points to a possible biosynthetic link between these two structures. We are interested in studying this conversion via a possible decarboxylation reaction (Scheme 1.1). We envisioned that treatment of tenuisine A (**1.9**) with a Lewis acid would open the lactone ring to form a zwitterionic intermediate (**1.15**), which could then extrude carbon dioxide, in a manner similar to that which occurs in the Hunsdiecker reaction, and install the cyclopropane ring present in lundurine B (**1.3**).

Scheme 1.1. Lewis acid mediated cyclopropanation.



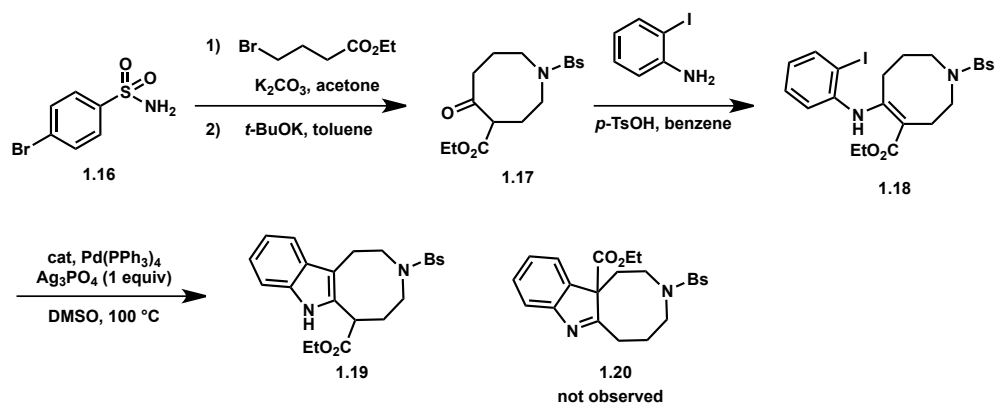
1.2 Previous Syntheses of Targeted *Kopsia* Alkaloids

To date, there has been one report of the synthesis of the indole-fused cyclooctylamine derivative⁹ **1.19** (Scheme 1.2) and a total synthesis of lapidilectine B, which was reported in 2001 by Pearson.¹⁰ As of 2014 Nishida has also reported two approaches to the total synthesis of lundurines A and B.¹¹

1.2.1. Nishida's synthesis of a model system

In 2004, Nishida and co-workers used a methodology they had developed to access the tricyclic core of lapidilectine B and related *Kopsia* alkaloids (Scheme 1.2). Starting from sulfonamide **1.16** they were able to access the 8-membered β -ketoester (**1.17**) in two steps by first alkylating with ethyl 3-bromobutylate and then subjecting the product to Dieckmann cyclization conditions. Condensation with 2-iodoaniline gave vinylogous carbamate **1.18** which served as the substrate for the methodology featured in their paper. Although they expected **1.20**, which would be useful to access grandilodine A and B (**1.10** and **1.11**, Figure 1.3), the only product they observed was fused indole **1.19**. While this product was not expected, the methodology does demonstrate the viability of constructing indole-fused cyclooctylamines that serve as the core of the lapidilectine family of natural products.

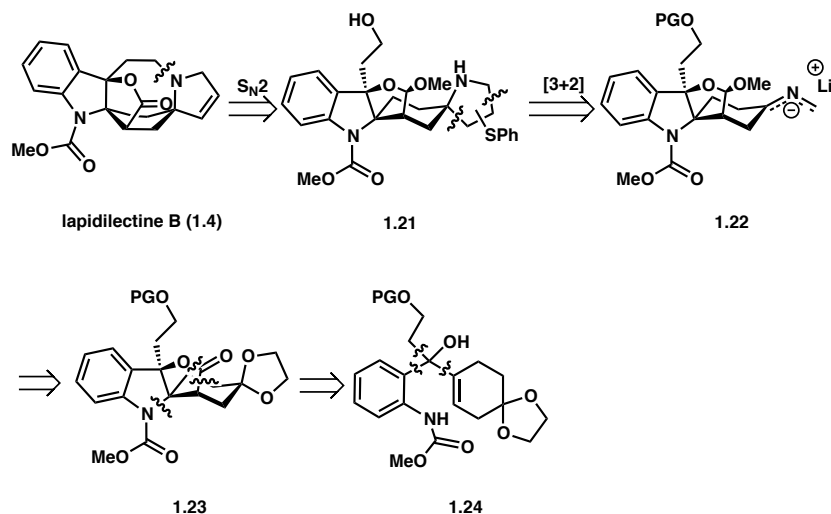
Scheme 1.2. Indole-fused cyclooctylamine derivative.



1.2.2. Pearson's synthesis of lapidilectine B

In their initial retrosynthetic plan, Pearson and co-workers envisioned forming the 8-membered ring in the last step of their synthesis to form **1.4** via alkylation of the pyrrolidine nitrogen in **1.21** (Scheme 1.3). They envisioned forming the pyrrolidine ring in **1.21** via a [3+2] cycloaddition of 2-aza-allyllithium **1.22** with phenyl vinyl sulfide. They anticipated being able to access **1.22** from lactone **1.23**, which could be achieved by employing a Smalley azido-enolate cyclization¹² of tertiary alcohol **1.24** to form the pseudo-indoxyl core of **1.23**.

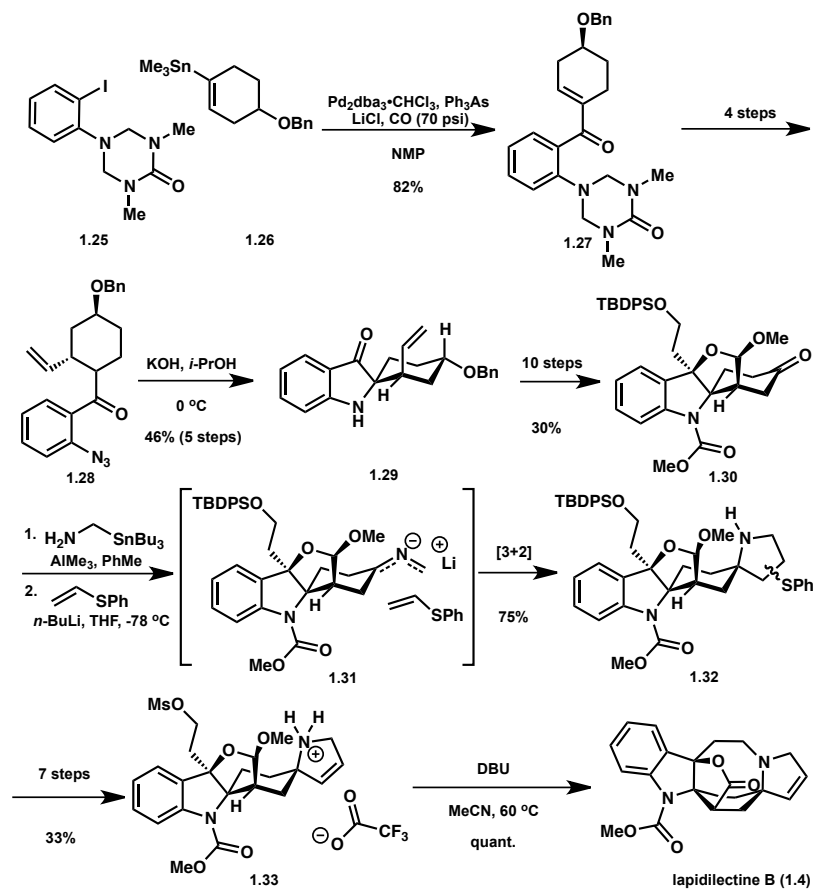
Scheme 1.3. Pearson's retrosynthesis.



In the forward direction, Pearson's synthesis commenced with a carbonylative Stille coupling of aryl iodide **1.25** and vinyl stannane **1.26** to form enone **1.27**. This was followed by a 1,4-addition of vinyl Grignard reagent, amine deprotection, and two-step conversion of the resulting amine into azide **1.28** (Scheme 1.4). In its first application in

complex molecule synthesis, a Smalley cyclization transformed azide **1.28** to indolyl **1.29** via an azido-enolate intermediate. Multiple functional group manipulations of indolyl **1.29** furnished methyl acetal **1.30**. Utilizing methodology developed in their lab,¹³ the Pearson group converted **1.30** to the non-stabilized aza-lithium intermediate **1.31**, which underwent a [3+2] cycloaddition with phenyl vinyl sulfide to form pyrrolidine **1.32** after aqueous work-up. Pyrrolidine **1.32** was advanced to the 2,5-dihydropyrrole salt (**1.33**) which, when treated with DBU, underwent an intramolecular S_N2 displacement of the mesylate to form (±)-lapidilectine B (**1.4**) in 23 linear steps and 0.10% overall yield.

Scheme 1.4. Pearson's forward synthesis.



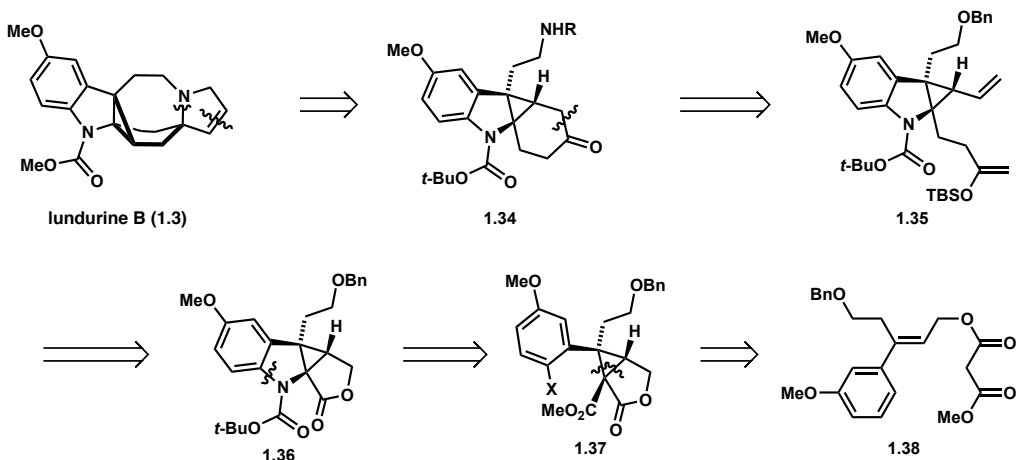
Although Pearson's synthesis highlighted the synthetic capabilities of the Smalley cycloaddition, as well as their aza-allyl lithium [3+2] cycloaddition, the synthesis of the key intermediates was lengthy, showed no obvious route to facile analogue synthesis, and proceeded in low overall yield. With that in mind, opportunities still exist to access the molecular framework of the *Kopsia* alkaloids in a more concise manner.

1.2.3. Nishida's synthesis of lundurine B

In their retrosynthetic plan, Nishida and co-workers envisioned arriving at lundurine B from a key tetracyclic intermediate (**1.34**, Scheme 1.5) by late-stage construction of the dihydropyrrole and azacycloheptane rings. They envisioned building

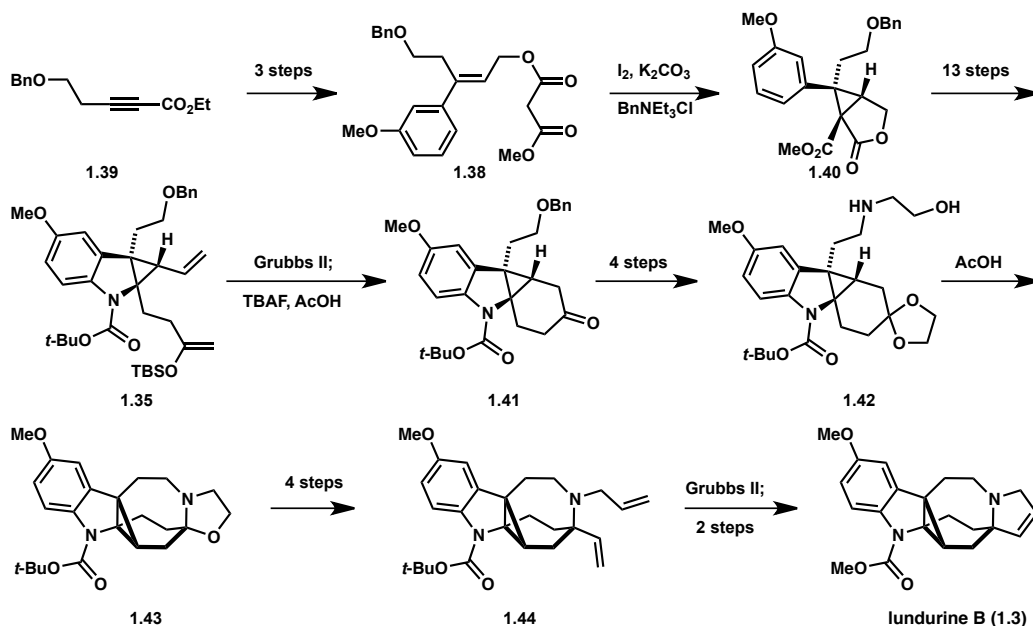
the cyclohexanone via a ring closing metathesis (RCM) reaction, bringing **1.34** back to siloxydiene **1.35**. In turn, they envisioned intermediate **1.35** arising from lactone **1.36** that contains the cyclopropane fused indoline skeleton. Intermediate **1.37** was envisioned to arise from cinnamyl malonate **1.38** via intramolecular cyclopropanation and aryl amination transforms.

Scheme 1.5. Nishida's retrosynthesis.



In the forward sense, Nishida and coworkers were able to arrive at lundurine B in 29 steps and 1.1 % overall yield from commercially available alkyne **1.39** (Scheme 1.6). Starting from alkyne **1.39**, they were able to access cinnamyl malonate **1.38** in three steps, which undergoes an iodine mediated cyclopropanation to afford **1.40**. After a series of functional group manipulations they formed cyclopropane fused indoline **1.35**, which underwent RCM using Grubb's second generation catalyst followed by hydrolysis of the resultant silyl enol ether to arrive at cyclohexanone **1.41**. After installation of a 2-hydroxyethylamino group, an acid-mediated intramolecular cyclization closed the azacycloheptane ring of **1.43**. From here, a series of functional group manipulations resulted in diene **1.44**, which was set up to undergo a RCM. This sequence furnished lundurine B (**1.3**) after replacing the *tert*-butyl carbamate protecting group on the indoline with the methyl carbamate found in the natural product.

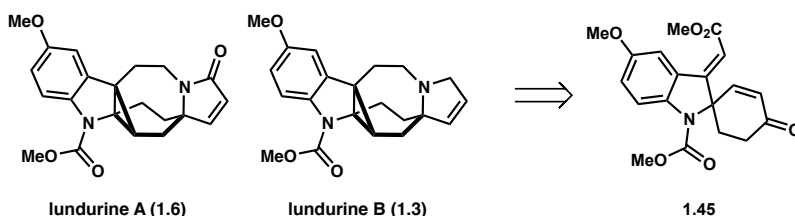
Scheme 1.6. Nishida's forward synthesis.



1.2.4. Nishida's synthesis of lundurines A and B

Arai, Nakajima, and Nishida recently described the first total synthesis of *Kopsia* alkaloid (\pm)-lundurine A and the second total synthesis of (\pm)-lundurine B, (the first synthesis of which was reported a month previously by the same group; see Section 1.2.3). The authors targeted the conserved spiroindoline core (**1.45**, Scheme 1.7) as a key synthetic intermediate that may allow access to a variety of related *Kopsia* alkaloids, such as the lipidilectines and grandilodines (Figure 1.3).

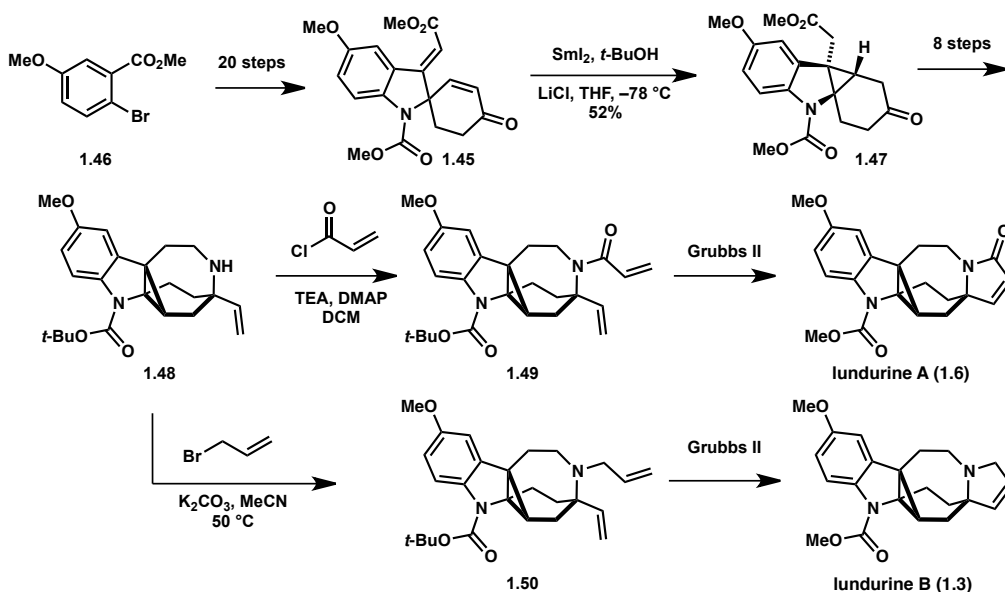
Scheme 1.7. Nishida's disconnection to spiroindoline core.



Nishida and co-workers successfully accessed the key spiroindoline intermediate (**1.45**, Scheme 1.8) in 20 steps from commercially available material with good yields on multi-gram scale with only four purifications by column chromatography. With the desired substrate in hand, the authors then investigated a key SmI_2 -mediated cyclopropanation. They found that LiCl was necessary as an additive to promote rapid conversion (<1 min) of the spiroenone (**1.45**) to the desired cyclopropane (**1.47**) in 52% yield. Of note, this transformation is stereoselective due to the structural rigidity of the spiroindoline precursor, and creates two vicinal stereogenic centers. The remaining rings

are constructed first by a palladium-catalyzed intramolecular amination to form the 7-membered ring in **1.48** (in 8 steps from **1.47**). Intermediate **1.48** is then elaborated into either **1.49** or **1.50** by acylation or alkylation, respectively, of the nitrogen of **1.48**. RCM afforded the final 5-membered dihydropyrrole ring.

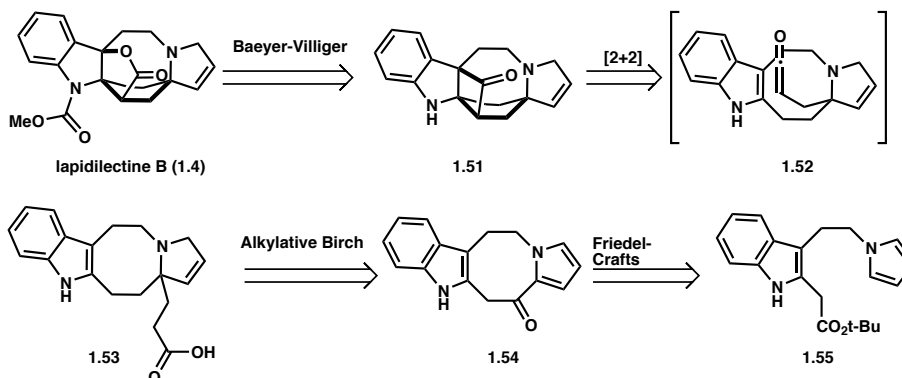
Scheme 1.8. Nishida's forward synthesis.



1.3. Our Initial Approach Toward Lapidilectine B

Our initial plan for the synthesis of lapidilectine B (**1.4**, Scheme 1.9) involved a late-stage Baeyer-Villiger oxidation of cyclobutanone **1.51** to install the lactone. It was anticipated that the desired regiochemistry of the natural product would be achieved due to the increased migratory aptitude of the benzylic carbon. Advanced intermediate **1.51** could arise from an intramolecular [2+2] cycloaddition of the ketene and the indole moieties of **1.52**.¹⁴ We presumed that the [2+2] cycloaddition would afford the desired regiochemistry due to the C-3 of the indole being more nucleophilic than the C-2 position. Tetracycle **1.53** could be derived from pyrrole **1.54** via an alkylative Birch reduction, and we envisioned **1.54** coming from an intramolecular Friedel-Crafts acylation of **1.55**.

Scheme 1.9. Initial retrosynthetic plan.

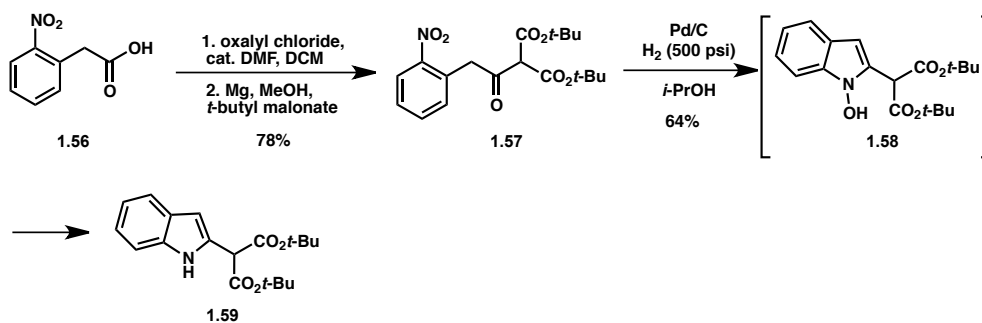


1.4. Forward Synthesis

1.4.1. Alkylation of indole 1.59

The reaction sequence to prepare Friedel-Crafts precursor **1.55** started by converting 2-nitrophenyl acetic acid (**1.56**, Scheme 1.10) into the corresponding acid chloride by treatment with oxalyl chloride and DMF, followed by the addition of the magnesium salt of *tert*-butyl malonate to afford **1.57** in 78% yield. The nitro group of **1.57** was then reduced with Pd/C under a hydrogen atmosphere for several days to give indole **1.59** in 64% yield. Under these reductive conditions, the cyclization to the indole core proceeded readily with the partially reduced nitro group, resulting in formation of an *N*-hydroxy indole (**1.58**) that was slow to fully reduce to **1.59**.

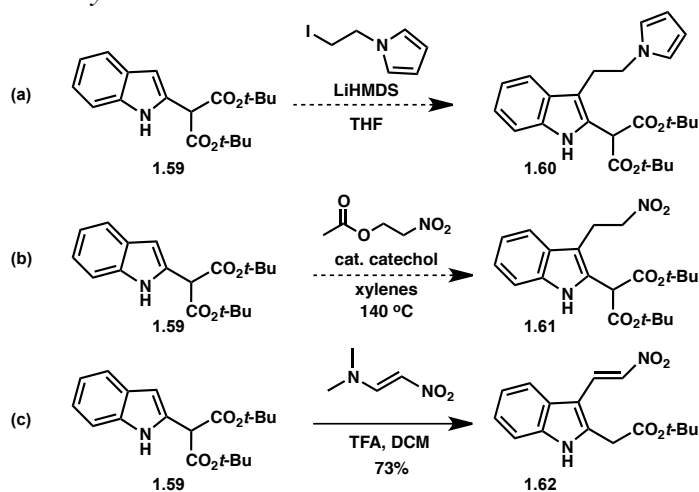
Scheme 1.10. Synthesis of indole 1.59.



Initial attempts to alkylate indole **1.59** at the 3-position using 1-(2-iodoethyl)-1H-pyrrole, which would install the desired pyrrole in a single step, proved unsuccessful (Scheme 1.11a). The indole proved too electron deficient to undergo this transformation and the pyrrole was consumed by polymerization and other non-specific decomposition under the reaction conditions. We attempted to alkylate the 3-position of the indole with nitroethyl acetate (Scheme 1.11b), envisioning a reduction of the nitro group to the primary amine, which in turn could be used to construct theazole ring through a Paal-

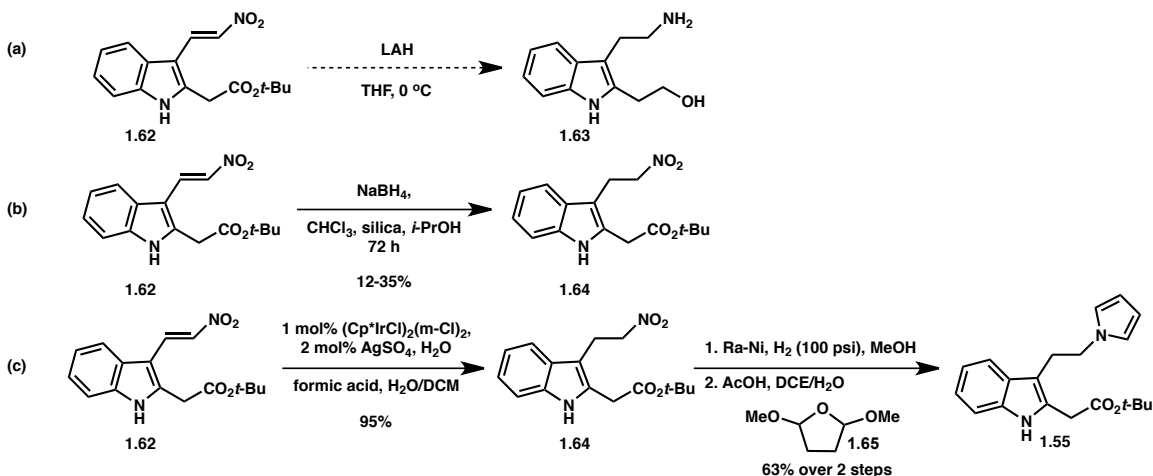
Knorr pyrrole synthesis. However, the indole again proved to not be a competent nucleophile for this transformation and the reaction returned only starting material. We then turned our attention to using a more powerful electrophile (for example, one created *in situ* from the treatment of dimethylaminonitroethylene and TFA), which afforded the functionalized indole (**1.62**). The acidic conditions for the alkylation also led to the cleavage and decarboxylation of one of the *tert*-butyl esters to provide **1.62**.

Scheme 1.11. Indole alkylation.



Initial attempts to reduce the nitroethylene moiety to amine **1.63** in a single step with lithium aluminum hydride (LAH) provided a complex mixture of products (Scheme 1.12a). Proceeding in a more stepwise fashion, employing a procedure developed by Bernauer (to reduce polymerization), yielded reduced product **1.64**;¹⁵ however, reduction of the double bond proved low yielding and unreliable (Scheme 1.12b). Reduction of the nitroethylene moiety mediated by an iridium catalyst¹⁶ in formic acid afforded the reduced nitro indole (**1.64**) in excellent yield. Reduction of the nitro group in **1.64** with Raney-nickel gave the corresponding amine, which was subjected to a Paal-Knorr pyrrole synthesis to provide pyrrole **1.55** in 45% yield over two steps (Scheme 1.12c).

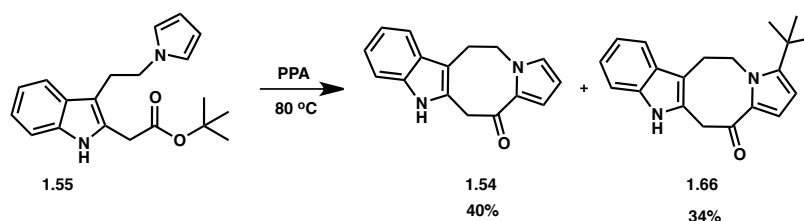
Scheme 1.12. Reduction of the nitroethylene **1.62** and pyrrole formation.



1.4.2. Tetracycle formation

With intermediate **1.55** in hand, we next performed a Friedel-Crafts cyclization between the pyrrole and *tert*-butyl ester groups of **1.55** in polyphosphoric acid (Scheme 1.13). Presumably, the acid creates an acylium ion, which is attacked by the pyrrole. The reaction gave the desired tetracycle (**1.54**) in 40% yield, but also gave undesired side product **1.66**, in which the pyrrole moiety has been alkylated with the putative *tert*-butyl cation that is formed during activation of the ester. For optimization purposes, product **1.66** could potentially be suppressed by the addition of *N*-methyl pyrrole to the reaction mixture as a *tert*-butyl cation scavenger.

Scheme 1.13. Tetracycle formation.

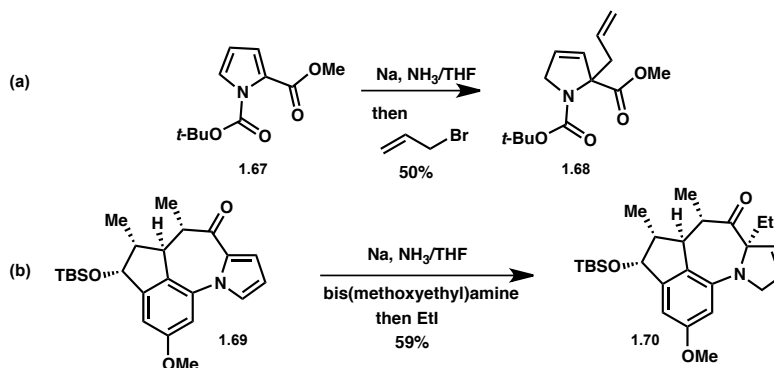


1.4.3. Reductive Birch alkylation

With the desired tetracycle (**1.54**) in hand, we set out to study a reductive Birch alkylation to ultimately provide **1.71** (Scheme 1.15). Work by Donohoe¹⁷ has shown that the reductive Birch alkylation of pyrroles only works if the pyrrole nitrogen has an electron-withdrawing substituent to confer some stability to the transient anion. Furthermore, a pyrrole with a carbonyl group at the 2-position is preferentially alkylated at that position to form a quaternary carbon center under the Birch conditions. Indeed, we observed this selectivity in the reductive Birch alkylation of model pyrrole **1.67**

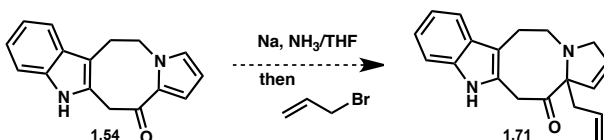
(Scheme 1.14a) to form **1.68**. Furthermore, work done by former group member Andrew Marcus has shown that selective Birch alkylations with a ketone instead of an ester at the 2-position are sufficiently electron deficient and follow a similar reactivity pattern (Scheme 1.14b).¹⁸

Scheme 1.14. Birch alkylation precedent.



We anticipated that the indole would not be reduced because it would be deprotonated under the Birch conditions. Thus it would likely be too electron rich to accept an electron from Na^0 , analogous to unprotected pyrroles.¹² Unfortunately, when the tetracycle (**1.54**) was subjected to alkylative Birch conditions, non-specific decomposition resulted (Scheme 1.15).

Scheme 1.15. Attempted reductive Birch alkylation.



At that stage, our efforts shifted to another route that addresses some other inherent pitfalls of the approach discussed above.

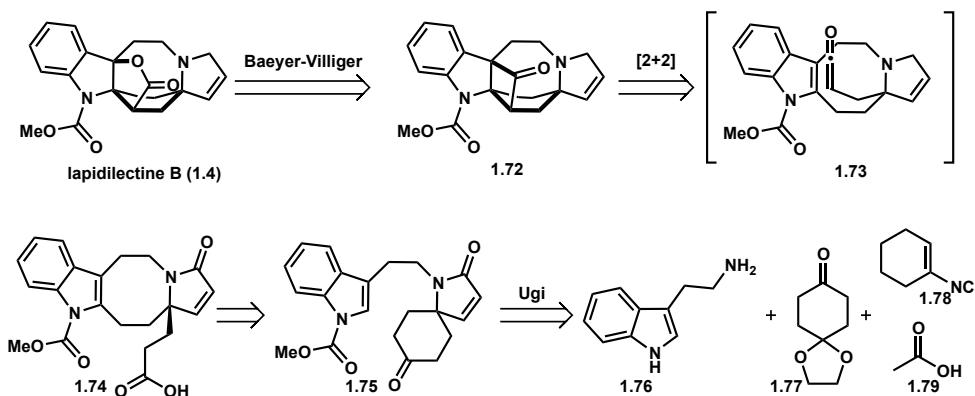
1.5. Revised Retrosynthesis

Recognizing that fused cyclobutanone **1.72** would be a versatile synthetic precursor that would give access to either the fused γ -lactone or cyclopropane framework, our revised retrosynthesis brings the target molecule back to **1.72** (Scheme 1.16) because it engendered exciting possibilities for its conversion to a γ -lactone of **1.4** using a Baeyer-Villiger type oxidation,¹⁹ or to a fused cyclopropane (as in **1.3**) using a C-C bond activation/decarbonylation sequence.²⁰ As such, **1.72** was selected as the penultimate target.

As in our initial retrosynthesis, we envisioned cyclobutanone **1.72** arising from a ketene [2+2] cycloaddition²¹ of the indole 2,3 double bond and a ketene moiety that would arise from carboxylic acid **1.74**. Tetracycle **1.74** could in turn arise from spiro-fused ene-lactam derivative **1.75** by cleavage of the cyclohexanone ring and

functionalization of the indole moiety's C-2 position. Enantiotopic cleavage of the C-C bond would render the synthesis enantioselective by a desymmetrization of ketone **1.75**. Tryptamine-derived lactam **1.75** could in turn be prepared from a four-component Ugi coupling²² of tryptamine **1.76**, mono-protected dione **1.77**, the Armstrong isocyanide (**1.78**),²³ and acetic acid (**1.79**).

Scheme 1.16. Revised retrosynthetic analysis.

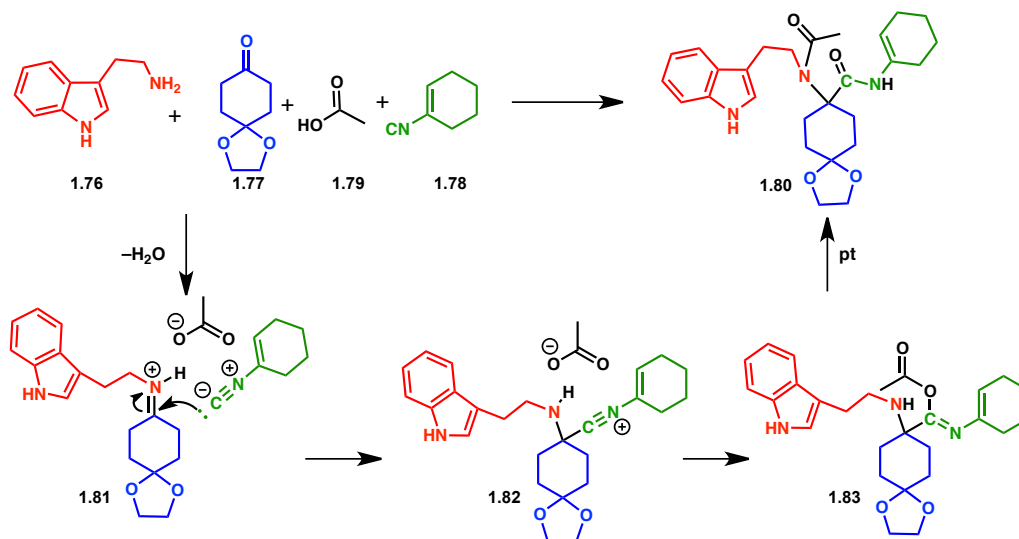


1.6. Forward Synthesis

1.6.1 Ugi four-component coupling

The Ugi four-component coupling is a powerful synthetic transformation that combines four reaction partners in one pot to give diamides, and in the case of lapidilectine B, installs all the carbons needed for the core of the molecule. The reaction proceeds first through a condensation between tryptamine (**1.76**) and the mono-protected dione (**1.77**, Scheme 1.17), the resulting imine is then protonated by acetic acid to form intermediate **1.81**. The iminium ion is then attacked by the isocyanide to form intermediate **1.82**. Acetate then adds into the nitrilium ion to quench the formal positive charge. The resulting intermediate (**1.83**) is then set up to undergo an intramolecular Mumm rearrangement,²⁴ which following a proton transfer, gives the Ugi adduct (**1.80**).

Scheme 1.17. Ugi four-component coupling mechanism.

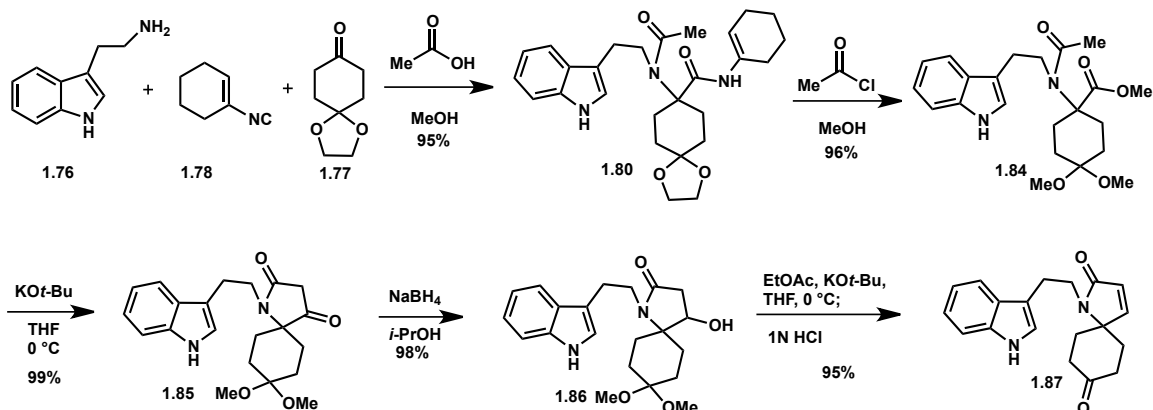


Our synthetic studies found that the Ugi four component coupling (Scheme 1.18), led to adduct **1.80** in 95% yield. The virtues of this coupling reaction are numerous. In addition to installing all the carbons of the lipidictine-type *Kopsia* alkaloid framework in this single step, the product precipitates out of the reaction mixture and only requires filtration to be obtained free of impurities. And finally, the reaction can be conducted on large scale (> 200 g) without compromising yield.²⁵

1.6.2. Construction of the lactam ring

The Armstrong isocyanide (**1.78**)²⁶ was selected for the Ugi coupling on the basis of the elegant synthetic studies of Sorensen and Seike on FR901483, which showed (as we found) that the Ugi product (**1.80**) could easily be converted to the corresponding methyl ester (see **1.84**).²⁷ Thus, treatment of **1.80** with methanolic HCl provided methyl ester **1.84**. The esterification conditions also resulted in a transketalization to the dimethylketal. Following the Sorensen protocol, we subjected acetamide ester **1.84** to potassium *tert*-butoxide in THF to effect a Dieckmann condensation. Selective reduction of the ketone group with sodium borohydride and elimination of the resulting hydroxy group in **1.86** (activated as the carbonate) provided spiro-fused lactam **1.87** in excellent yield over three steps (Scheme 1.18). Of note, the conversion of **1.80** to **1.87** can be consistently performed on >5g scale without appreciable degradation in yield.

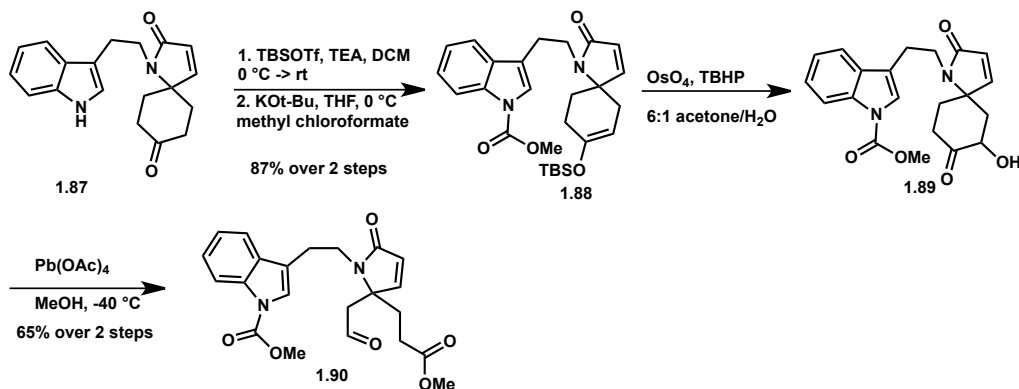
Scheme 1.18. Spiro-fused meso-lactam formation.



1.6.3. Lead-mediated oxidative cleavage

To effect an oxidative cleavage of spiro-fused cyclohexanone **1.87**, first ketone **1.87** was converted to the corresponding silyl enol ether and the indole moiety was protected with methyl chloroformate to give **1.88** (Scheme 1.19). In addition to serving as an electron-withdrawing group to protect the indole moiety from oxidative decomposition during the subsequent oxidative transformation, the methyl carbamate is an ideal protecting group as it is present in the natural product. Furthermore, it was found that a sulfonyl protecting group was too electron withdrawing and interfered with the indole's ability to act as a nucleophile. Silyl enol ether **1.88** was oxidized to α -hydroxy ketone **1.89** with osmium tetroxide in the presence of *tert*-butyl hydrogen peroxide (TBHP). The six-membered ring containing the α -hydroxy ketone group in **1.89** was opened via a $\text{Pb}(\text{OAc})_4$ -mediated cleavage in the presence of methanol, which afforded aldehyde ester **1.90**.

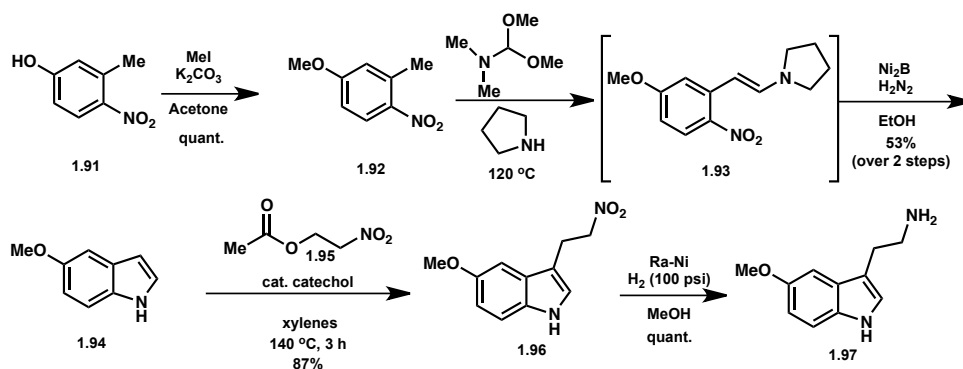
Scheme 1.19. Oxidative cleavage.



1.6.4. Expansion of the route toward lundurine B and related molecules

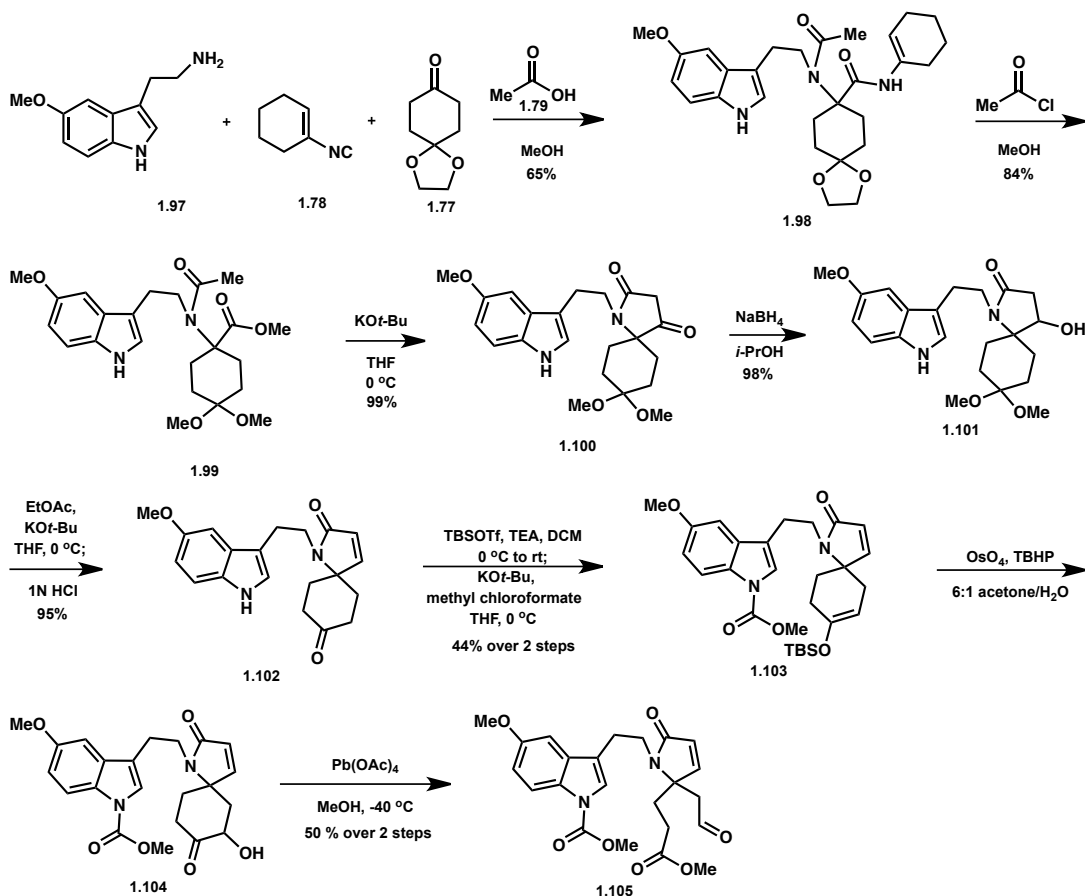
We also explored the use of serotonin in the Ugi four-component coupling to access lundurine B (**1.3**, Figure 1.3). Although serotonin is commercially available, as is 5-methoxytryptamine, the cost is prohibitive,²⁸ and its de novo synthesis could allow for further derivatization to install bio-tags or affinity probes for use in chemical biology studies. Our serotonin synthesis (Scheme 1.20) commenced with the Leimgruber-Batcho indole synthesis,²⁹ which was used to make 5-methoxyindole (**1.95**). Starting from commercially available 3-methyl-4-nitrophenol (**1.91**), treatment with methyl iodide and potassium carbonate in acetone furnished methyl ether **1.92**. The methyl group of **1.92** was then condensed with *N,N*-dimethylformamide dimethylacetal and pyrrolidine to yield imine **1.93**. This intermediate was carried on directly to the 5-methoxyindole (**1.94**) via a nickel boride³⁰ reduction using hydrazine as a stoichiometric reductant. Indole **1.94** is extremely sensitive to oxidation, but must be purified by flash chromatography before alkylating at the 3-position. In a procedure modified from the Repke synthesis of 5-methoxytryptamine,³¹ 5-methoxyindole (**1.94**) was first functionalized at the 3-position by immediately subjecting **1.94** to nitroethyl acetate (**1.95**). Once alkylated, indole **1.96** is significantly less sensitive to oxidation. Also, the more electron-rich 5-methoxyindole was required for this transformation and our previous synthetic route, using indole malonate **1.59** (Scheme 1.11b), returned only starting material when subjected to the same reaction conditions. Indole **1.96** was then converted to 5-methoxytryptamine by reduction of the nitro group to the free amine. The reduction was modified from the Repke procedure and proceeded quantitatively in the presence of Raney-nickel under a hydrogen atmosphere³² to yield the methyl ether of serotonin (**1.97**).

Scheme 1.20. Serotonin derivative synthesis.



With the serotonin derivative (**1.97**) in hand, we were able to carry out the Ugi four-component coupling to arrive at adduct **1.98**. Following a procedure similar to that used for **1.90** (Sections 1.6.2 and 1.6.3), we were able to arrive at the analogous aldehyde methyl ester (**1.105**), albeit in slightly diminished yield due mostly to the electron rich indole moiety's susceptibility to oxidative decomposition.

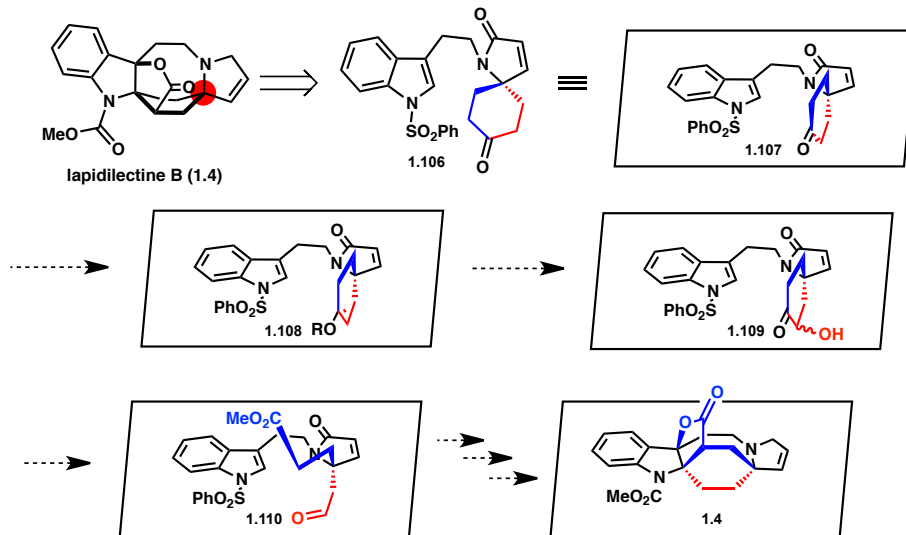
Scheme 1.21. Lactam formation, and oxidative cleavage for serotonin Ugi adduct.



1.6.5. Desymmetrization as an entry to an enantioselective synthesis

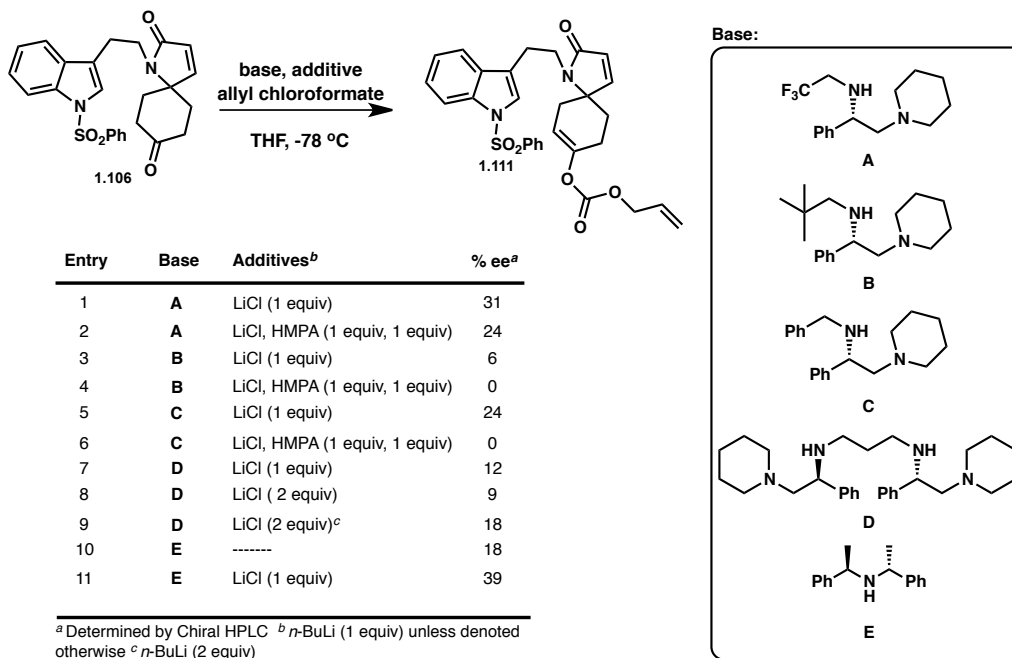
As noted above, one potential advantage of this route is the possibility of an enantioselective synthesis of the target molecules. We envisioned the route being rendered enantioselective by desymmetrization of ketone **1.106** using an enantioselective deprotonation. As illustrated in Scheme 1.22, we anticipated setting a single stereocenter (highlighted on **1.4**, Scheme 1.22), and then using this chiral information to direct all the other stereocenters formed en route to the natural product. Selectively deprotonating at the α -face of spiro lactam **1.106** (see **1.108**) sets the stereochemistry of the spiro-ring fusion, and directs the α -oxidation (see **1.109**) and subsequent oxidative cleavage to the aldehyde/methyl ester **1.110** and eventually to all the stereocenters present in the natural product.

Scheme 1.22. Concept for rendering the route enantioselective.



As illustrated in Table 1.1, a variety of chiral non-racemic lithium amides was screened to form the enolate enantioselectively. The resulting enolate was then trapped with allyl chloroformate to form **1.111**, which has enhanced stability over the silyl enol ethers and made analysis via chiral HPLC easier.³³ Previous reports by Koga³⁴ have suggested that use of lithium chloride or zinc chloride as an additive enhances enantioselectivity by creating a heterodimer with the chiral non-racemic bases. Without the additive, the chiral non-racemic base forms aggregates with itself, and this aggregation is thought to lead to a decrease in the enantioselectivity of the deprotonation. We found that addition of lithium chloride did increase the *ee* by 20% (entry 10 vs 11). While we have yet to test the effect of zinc chloride, other additives such as HMPA, which has also been shown to break up aggregates,³² were unsuccessful in our system (entries 4 and 6). Although further optimization is required to render the desymmetrization synthetically useful, as a proof of concept, we were able to achieve an *ee* of 39%.

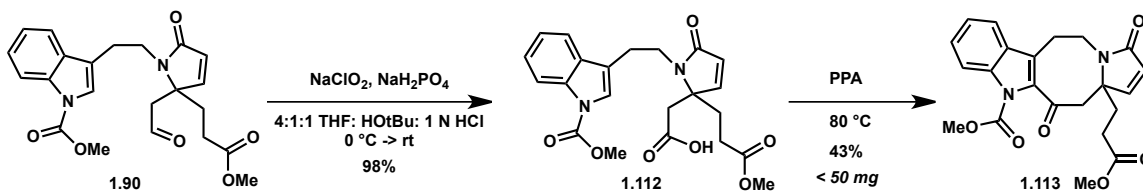
Table 1.1. Enantioselective desymmetrization of **1.106**.



1.6.6. Tetracycle formation via Friedel-Crafts acylation

Toward the goal of forming the tetracycle core through functionalization of the indole C-2 position, aldehyde **1.90** was converted to the corresponding carboxylic acid (**1.112**) via a Pinnick oxidation, in order to perform a Friedel-Crafts acylation between the indole moiety and acylium ion that is generated from the treatment of the carboxylic acid with polyphosphoric acid (PPA).³⁵ Despite the modest yield of this transformation, the usual ‘two-step’ Friedel-Crafts protocol, involving treatment of an acid chloride with a Lewis acid (e.g., AlCl₃) was less efficient and resulted in significant polymerization. However the PPA mediated Friedel-Crafts reaction proved difficult to scale because the yields dropped dramatically on scales greater than 50 mg. However, we were able to access enough material for subsequent explorations.

Scheme 1.23. PPA-mediated Friedel-Crafts acylation



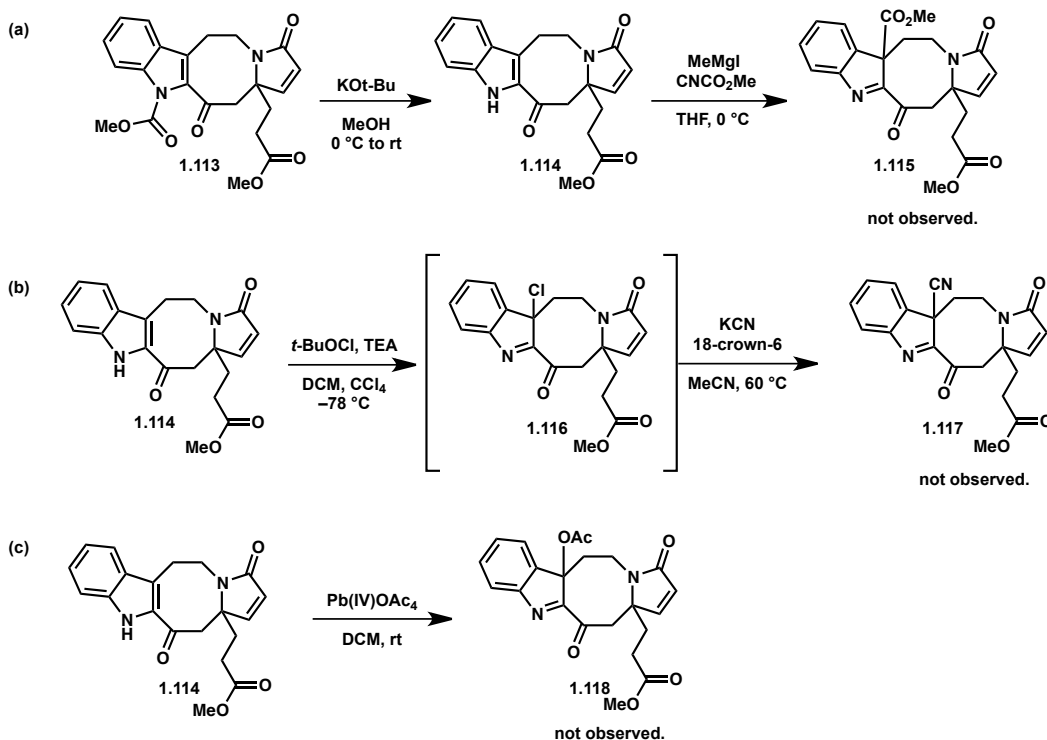
1.6.7. Functionalization of tetracycle 1.113 at the C-3 of indole moiety

Unfortunately, the instability of tetracycle **1.113** proved to be a major hindrance. Attempts to functionalize the methyl ester group in **1.113** into a ketene group were met with failure. Competition with other acidic protons, such as those *alpha* to the ketone group may have contributed to the decomposition observed under a variety of basic reaction conditions. In addition to this, the ketone group conjugated to the indole moiety hindered the indole moiety's ability to act as a nucleophile. For instance, attempts to functionalize the indole moiety at C-3 with Mander's reagent (which would give access to grandilodine A and B, see **1.10** and **1.11**, Figure 1.3) were also met with failure (Scheme 1.24a).

Efforts were also made to functionalize C-3 of the indole moiety with a cyano-group that could be later converted into an ester functional group.³⁶ Dmitrienko,³⁷ Gassman,³⁸ and Ban³⁹ all report forming unstable chloroindolenine intermediates (such as **1.116**) from treatment of 2,3-disubstituted indoles with methyl hypochlorite or *t*-butyl hypochlorite. These intermediates can then be treated with potassium cyanide to form 3-cyano indolenines.³⁹ However, the transformation shown in Scheme 1.24b led only to non-specific decomposition and a complex mixture of products.

We also visualized the functionalization of indole **1.114** with lead tetracetate as the electrophile,⁴⁰ which would place an acetate group at C-3 of the indole moiety (Scheme 1.24c). However, this reaction returned only starting material.

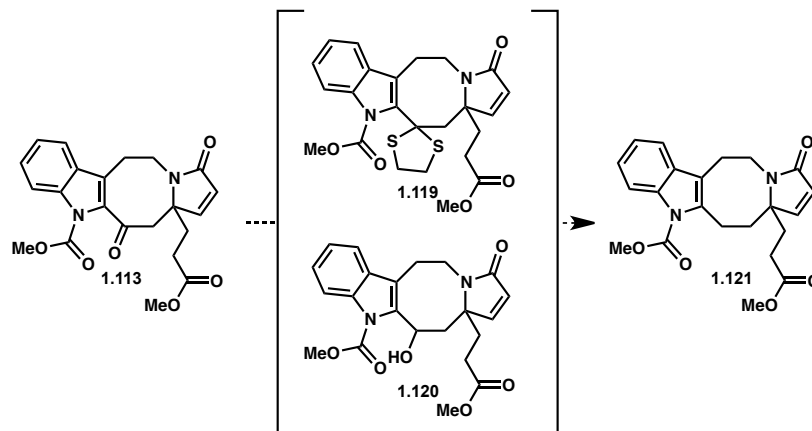
Scheme 1.24. Attempts to functionalize C-3 of the indole moiety of **1.114**.



1.6.8. Reduction of the ketone group

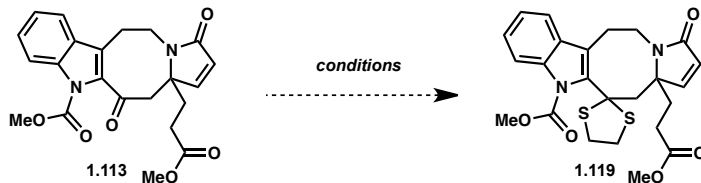
In an effort to increase the electron density of the indole moiety and therefore the nucleophilicity of C-3, we turned our attention to reducing the ketone group conjugated to the indole moiety through either conversion to a dithiane (**1.119**) and desulfuration upon treatment with Raney-Nickel or *selective* reduction to a hydroxyl group (**1.120**) and deoxygenation (Scheme 1.25).


Scheme 1.25. Ideas to reduce ketone group in 8-membered ring.



Initial attempts to convert **1.113** to **1.119** were made by screening a variety of Lewis acids with 1,2-ethanedithiol and 1,2-ethanedithiol derivatives (see Table 1.2). However all these attempts returned mostly starting material.

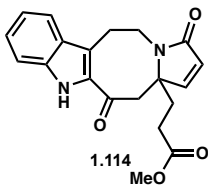
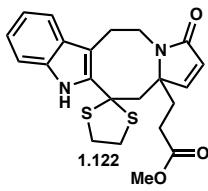

Table 1.2. Attempted conversion of ketone group in **1.113** to dithiane **1.119**.



| <u>Conditions</u> | <u>Result</u> | <u>Reference</u> |
|---|----------------------------|--|
| 1,2-ethane diol, amberlyst 15, CHCl ₃ | S. M. | |
| 1,2-ethane diol, ZnOTf ₂ (0.8 equiv), ZnCl ₂ (0.8 equiv), CHCl ₃ , 60 °C | S. M. | <i>J. Heterocyclic Chemistry</i> , 2007 , <i>44</i> , 1317. |
| 1,2-ethane diol, ZnOTf ₂ , CHCl ₃ , 60 °C | S. M. | <i>Tetrahedron Lett.</i> 1983 , <i>24</i> , 169. |
| 1,2-ethane diol, ZnOTf ₂ (0.8 equiv), ZnCl ₂ (1.6 equiv), CHCl ₃ , 60 °C | S. M. | |
| 1,2-ethane diol, ZnOTf ₂ (0.8 equiv), ZnCl ₂ (1.6 equiv), 4 Å MS, CHCl ₃ , 60 °C | S. M. | |
| 1,2-ethane diol, AlMe ₃ , DCE, 60 °C | deprotected indole | <i>J. Am. Chem. Soc.</i> , 2006 , <i>128</i> , 740. |
| 1,2-ethane diol, BF ₃ ·OEt ₂ , DCM, rt | S. M. | <i>J. Org. Chem.</i> 1979 , <i>44</i> , 656. |
|  CHCl ₃ , rt | S. M. | <i>J. Am. Chem. Soc.</i> , 1965 , <i>87</i> , 3045. |
| TMSS-CH ₂ -CH ₂ -STMS ZnI ₂ , CHCl ₃ | S. M. | <i>J. Org. Chem.</i> 1985 , <i>50</i> , 3615. |
| TMSS-CH ₂ -CH ₂ -STMS ZnCl ₂ , CHCl ₃ | S. M. | |
| TMSS-CH ₂ -CH ₂ -STMS TMSOTf | non-specific decomposition | |

We hypothesized that the indole methyl carbamate protecting group was sterically inhibiting the formation of the cyclic dithiane. After cleavage of the methyl carbamate, we again attempted the formation of the cyclic dithiane by screening similar Lewis acid mediated conditions (see Table 1.3), but again, a reaction was not observed.

Table 1.3. Attempted conversion of ketone **1.114** to dithiane **1.122**.

| | | |
|---|---|--|
|  <p>1.114</p> | <p>conditions</p> <p>-----></p> |  <p>1.122</p> |
| <p>Conditions</p> <p>1,2-ethane diol, ZnOTf₂ (0.8 equiv), ZnCl₂ (0.8 equiv), CHCl₃, 60 °C</p> <p>1,2-ethane diol, ZnOTf₂, CHCl₃, 60 °C</p> <p>1,2-ethane diol, ZnCl₂, CH₂Cl₂, 60 °C</p> <p>1,2-ethane diol, ZnOTf₂ (0.8 equiv), ZnCl₂ (1.6 equiv), CHCl₃, 60 °C</p> <p>1,2-ethane diol, ZnOTf₂ (2.0 equiv), ZnCl₂ (2.0 equiv), CHCl₃, 60 °C</p> <p>1,2-ethane diol, ZnOTf₂ (0.8 equiv), ZnCl₂ (1.6 equiv), 4 Å MS, CHCl₃, 60 °C</p> <p>1,2-ethane diol, AlMe₃, DCE, 60 °C</p> <p>1,2-ethane diol, BF₃•OEt₂, DCM, rt</p> <p> CHCl₃, rt</p> <p>TMSS-CH₂-CH₂-STMS ZnI₂, CHCl₃</p> <p>TMSS-CH₂-CH₂-STMS ZnCl₂, CHCl₃</p> | <p>Result</p> <p>S. M.</p> <p>S. M.</p> <p>S. M.</p> <p>S. M.</p> <p>S. M.</p> <p>S. M.</p> <p>S. M.</p> <p>S. M.</p> <p>S. M.</p> <p>S. M.</p> <p>S. M.</p> | <p>Reference</p> <p><i>J. Heterocyclic Chemistry</i>, 2007, <i>44</i>, 1317.</p> <p><i>Tetrahedron Lett.</i> 1983, <i>24</i>, 169.</p> <p><i>J. Heterocyclic Chemistry</i>, 2006, <i>43</i>, 585.</p> <p><i>J. Am. Chem. Soc.</i>, 2006, <i>128</i>, 740.</p> <p><i>J. Org. Chem.</i> 1979, <i>44</i>, 656.</p> <p><i>J. Am. Chem. Soc.</i>, 1965, <i>87</i>, 3045.</p> <p><i>J. Org. Chem.</i> 1985, <i>50</i>, 3615.</p> |

Concurrent with attempts to convert the ketone into a cyclic dithiane, we also attempted to reduce the ketone group to a hydroxyl group. Doing this selectively was a challenge due to the presence of the methyl ester functional group and the lactam, as can be seen from Table 1.4.

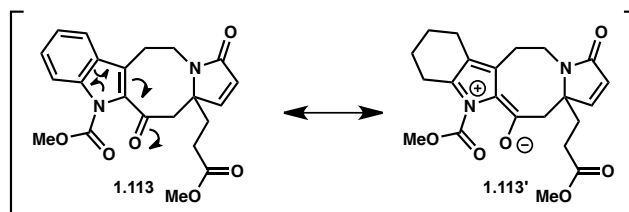
Table 1.4. Attempts to reduce ketone group in **1.113**.



| <u>Conditions</u> | <u>Result</u> | <u>Reference</u> |
|--|----------------------|---|
| NaBH ₄ , MeOH, 0 °C to rt | S.M. | |
| CeCl ₃ , NaBH ₄ , MeOH, 0 °C | S. M. | <i>J. Org. Chem.</i> 2002 , 67, 8726. |
| AlH(O <i>t</i> -Bu) ₃ , 3:1 ether:THF, 0 °C | S. M. | <i>Org. Lett.</i> 1999 , 1, 811. |
| AlH(O <i>t</i> -Bu) ₃ , THF, 0 °C | S. M. | <i>J. Am. Chem. Soc.</i> 2010 , 132, 3685. |
| AlH(O <i>t</i> -Bu) ₃ , THF, 40 °C | S. M. | |
| NaBH ₄ , 10:1 THF:MeOH, 0 °C to rt | methyl ester reduced | |
| NaBH ₄ , MeOH, 65 °C | methyl ester reduced | |
| BH ₃ , THF, 0 °C to rt, 2 h | complex mixture | |

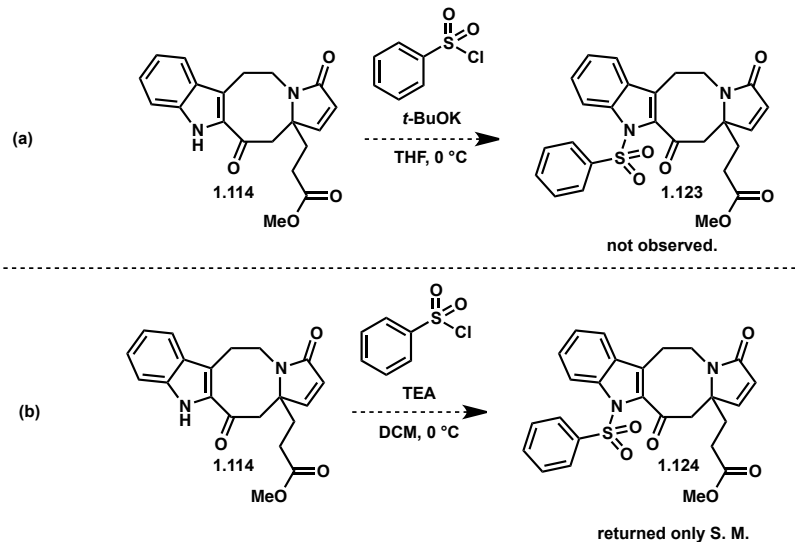
The reactivity observed in Tables 1.2, 1.3, and 1.4 is more aligned with that of an electron rich amide instead of a ketone group. Due to conjugation with the indole ring, the ketone group can be viewed as analogous to an amide,⁴¹ which appears to be more electron rich than we anticipated (see Scheme 1.26).

Scheme 1.26. Ketone group as an vinylogous amide.



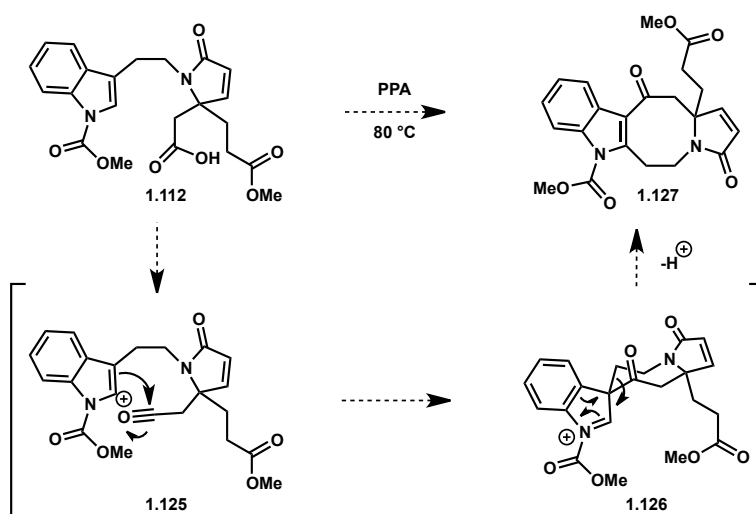
We anticipated a more electron-withdrawing group on the indole nitrogen, such as a sulfonyl instead of a carbamate, would attenuate the electron density of the carbonyl in the 8-membered ring resulting in the carbonyl reacting more like a ketone group than an amide functional group. However, attempts to switch the indole protecting group from a methyl carbamate to a benzyl sulfonyl were unsuccessful as the tetracycle with a deprotected indole moiety proved unstable to strongly basic conditions (Scheme 1.27a), and attempts to introduce the protecting group under mildly basic conditions returned only starting material (Scheme 1.27b).

Scheme 1.27. Attempts at placing strongly electron withdrawing group on indole moiety.



Though the regioselectivity was confirmed via independent synthesis of **1.113** (vide infra), the reactivity we were observing has precedent for ketone groups off the C-3 position of the indole moiety, which has a larger HOMO co-efficient than C-2.⁴² We became concerned that the Friedel-Crafts PPA-mediated reaction was going through a spirocyclic intermediate (**1.126**) followed by a 1,5-alkyl shift to give **1.127** (see Scheme 1.28) in a fashion analogous to that of the Pictet-Spengler reaction,⁴³ to place the ketone group at C-3, which could be a possible explanation the reactivity we were observing. This turned out not to be the case and our initially assigned structure was shown to be correct through an independent synthesis.

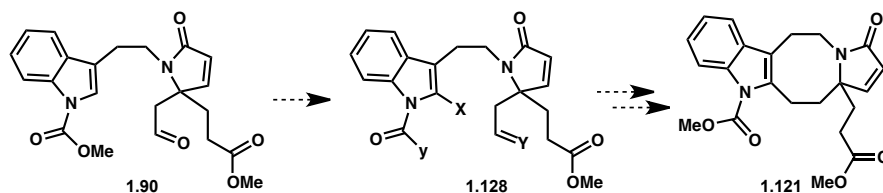
Scheme 1.28. Spirocyclic intermediate and 1,5-alkyl shift proposal.



1.6.9. Tetracycle via 2-bromoindole

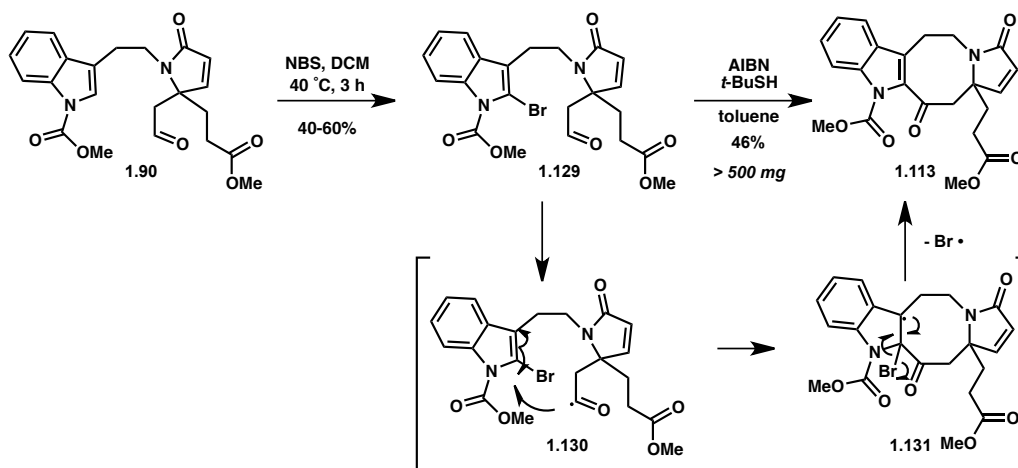
We became interested in exploring other ways to build a tetracycle through functionalization of the indole moiety at C-2 (**1.128**) instead of just relying on the indole moiety's innate nucleophilicity (see Scheme 1.29). We thought this could give access to a tetracyclic core that is more easily manipulated.

Scheme 1.29. Formation of tetracyclic intermediate through functionalization of indole moiety at C-2.



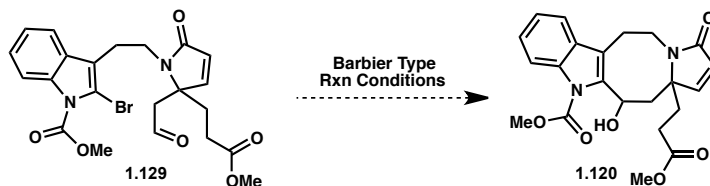
Initially we wanted to see if the product of the PPA-mediated Friedel-Crafts reaction leads to tetracycle **1.113** or **1.127**. Under radical conditions, the alkyl and acyl group migratory aptitudes are reversed, so even if this reaction was still going through a spirocyclic intermediate, it would display a different migration pattern. To test this we converted **1.90** into 2-bromoindole **1.129** with NBS.⁴⁴ Under radical conditions, aldehyde **1.129** was successfully converted to the same keto-tetracycle **1.113** in 46% yield upon treatment with AIBN and *t*-BuSH, presumably via an acyl radical intermediate (see Scheme 1.30).⁴⁵ We have found this particular protocol for the formation of **1.113** to be more effective (as compared to starting from acid **1.112**) because it generally leads to less byproduct formation. In addition, this outcome supports the course of the PPA-mediated Friedel-Crafts reaction (i.e., that it does lead ketotetracycle **1.113** and not the product of a 1,5-alkyl shift to form **1.127**).

Scheme 1.30. Tetracycle formation through acyl radical intermediate.



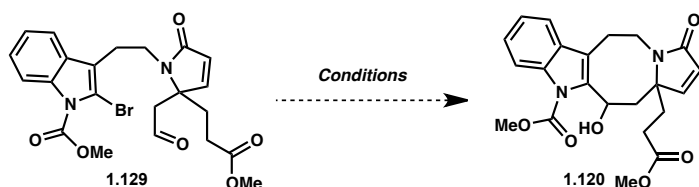
We therefore turned our attention to directly building a tetracyclic intermediate without a carbonyl in the 8-membered ring. We envisioned accomplishing this initially using a Barbier-type reaction,⁴⁶ which would form hydroxyl-tetracycle **1.120** (Scheme 1.31).

Scheme 1.31. Tetracycle formation through Barbier-type coupling reaction.



As illustrated in Table 1.5, Cr, Mg, and Sm based reagents were used to form the unstable organometallic intermediates, expecting them to add into the aldehyde carbonyl group in an intramolecular fashion, which would give a hydroxyl in the 8-membered ring. However, only nonspecific decomposition or over-reduction (loss of bromo group, in addition to reduction of the α,β unsaturated amide) was observed.

Table 1.5. Attempts at tetracycle formation through Barbier-type coupling reactions.



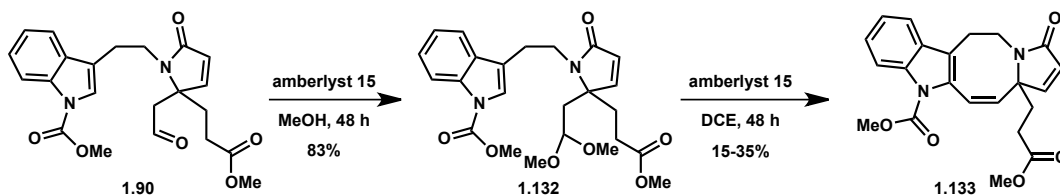
| <u>Conditions</u> | <u>Result</u> | <u>Reference</u> |
|---|--------------------------------|--|
| CrCl ₂ , NiCl ₂ , DMF, rt | nonspecific decomposition | <i>J. Org. Chem.</i> 2000 , 65, 5910. |
| Mg(0), THF, rt | S. M. | <i>Synthesis</i> 1977 , 18. |
| Mg(0), THF, 60 °C | nonspecific decomposition | |
| Mg(0), ZnCl ₂ , EtOAc, 50 °C | nonspecific decomposition | <i>Tetrahedron Lett.</i> 1989 , 30, 7373. |
| Mg(0), PbCl ₂ , TMSCl, THF, rt | nonspecific decomposition | <i>Tetrahedron Lett.</i> 1996 , 37, 7049. |
| SmI ₂ , THF, HMPA, rt | overreduction, des-bromoindole | <i>Tetrahedron</i> 2003 , 59, 10351. |
| SmI ₂ , NiI ₂ , THF, rt | nonspecific decomposition | <i>Tetrahedron</i> 2003 , 59, 10351. |

1.6.10. Intramolecular Friedel-Crafts-type reaction to form the 8-membered ring in **1.133**

We envisioned addition of the indole moiety into an oxocarbenium ion generated from the ionization of acetal **1.132** to form the key bond. We were able to form dimethylacetal **1.132** under standard acetalization conditions. From there, a Friedel-Crafts-type transformation could also be initiated from dimethyl acetal **1.132** using Amberlyst-15 as the source of acid (Scheme 1.32) to afford **1.133** in 54% yield (b.r.s.m.).⁴⁷ These conditions allow for the elimination of methanol to give a double bond

in the 8-membered ring. The mass balance of the material was accounted for by aldehyde **1.90**, which likely arises from a competing hydrolysis of the acetal group. Attempts to effect the conversion of **1.132**→**1.133** using Lewis acids or other protic acids resulted only in the hydrolysis of acetal **1.132** to revert back to aldehyde **1.90**.

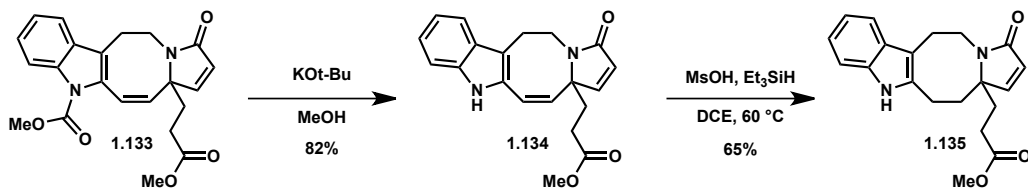
Scheme 1.32. Formation of tetracycle **1.133**.



1.6.11. Reduction of double bond in 8-membered ring of tetracycle 1.133

In preparation for the exploration of endgame scenarios, tetracycle **1.33** was converted to **1.135** (Scheme 1.33) by cleavage of the carbamate group and selective removal of the alkene group by ionic reduction using methanesulfonic acid and triethylsilane.⁴⁸ Efforts to selectively reduce the double bond in the 8-membered ring over the α,β -unsaturated amide using heterogeneous transition metals as catalysts were unsuccessful.

Scheme 1.33. Ionic reduction of double-bond in 8-membered ring of tetracycle **1.133**.



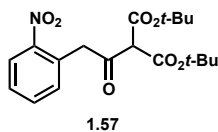
While tetracycle **1.135** is very sensitive to acidic and basic conditions, the ketene [2+2] cycloaddition remains to be tried, followed by subsequent chemistry toward the natural products from this tetracyclic intermediate.

1.7. Conclusion

In conclusion, while installation of the final lactone ring or functionalization of the indole moiety at the C-3 position has remained elusive, we were able to develop two routes to the tetracyclic core of lapidelectine B, one of which employs a highly scalable Ugi four-component coupling to install all the carbons found in these natural products. The reported strategy holds high potential for providing a unified approach to the subset of *Kopsia* alkaloids depicted in Figure 1.3. In addition, this route has been shown to be applicable toward the lundurine-type molecules that have a methoxy-substituent on the aryl ring. Furthermore, preliminary results on the enantioselective deprotonation of the spirocyclic ketone **1.106** provide a proof of concept for the possible enantioselective synthesis of these natural products.

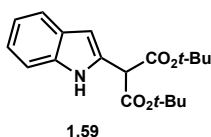
1.8 Experimental

Materials and Methods. All air or moisture sensitive reactions were conducted in flame-dried glassware, capped with a rubber septum and stirred with Teflon-coated magnetic stir bars under an atmosphere of nitrogen. All liquid reagents and solvents were transferred via syringe using standard Schlenk techniques. Tetrahydrofuran (THF), toluene, methanol, and triethylamine were degassed and dried by passage over a column of activated alumina; dichloromethane and 1,2-dichloroethane were distilled under nitrogen over calcium hydride. All other solvents and reagents were used as received unless otherwise noted. Melting points were measured on a Buchi melting point apparatus and were corrected using vanillin (mp 80-81 °C) as a standard. Reaction temperatures were controlled by an IKAmag temperature modulator. Thin-layer chromatography was performed using Silicycle Sorbent silica gel 60 F254 pre-coated plates (0.25 mm) and visualized under UV and by *p*-anisaldehyde stain. ¹H and ¹³C NMR spectra were recorded on Bruker AVQ-400, AVB-400, DRX-500, AV-500, and AV-600 MHz spectrometers with ¹³C operating frequencies of 100, 100, 125, 125 and 150 MHz, respectively. Chemical shifts (δ) are reported in ppm relative to the residual solvent signal (CDCl₃: δ = 7.26 for ¹H NMR spectra and δ = 77.2 ppm for ¹³C NMR spectra; DMSO-d₆: δ = 2.54 for ¹H NMR spectra and δ = 39.5 ppm for ¹³C NMR spectra). Data for ¹H spectra are reported as follows: chemical shifts (multiplicity, coupling, integration). Abbreviations are as follows: s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, dt = doublet of triplets, m = multiplet, br = broad resonance. Only select ¹³C spectra are reported. IR spectra were recorded on a Nicolet MAGNA-IR 850 spectrometer as thin films on NaCl plates and are reported in frequency of absorption (cm⁻¹). Only selected IR absorbencies are reported. 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. Enantiomeric excess was determined by integration ratios given by PerkinElmer Series 200 HPLC fitted with a 0.46 cm x 25 cm ChiralPak AS column.

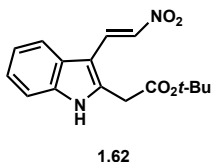


Malonate 1.57. A 50-mL round-bottom flask was charged with Mg turnings (443 mg, 18.2 mmol, 1.10 equiv) and MeOH (7.5 mL). The mixture was stirred until all the Mg went into solution, then di-*tert*-butyl malonate (4.08 mL, 18.2 mmol, 1.10 equiv) was added dropwise. After a white precipitate formed, the reaction mixture was concentrated via rotary evaporation, followed by azeotropic distillation with THF and dilution with THF (10 mL). A separate 250-mL round-bottom flask was charged with *o*-nitrophenyl acetic acid (3.00 g, 16.6 mmol, 1.00 equiv) and DCM (75 mL). Oxalyl chloride (1.85 mL, 21.6 mmol, 1.30 equiv) was added dropwise followed by one drop of DMF. The reaction mixture was stirred at RT for 2 h, then concentrated. The residue was subjected to azeotropic distillation with THF, then diluted with THF (10 mL) and added dropwise to

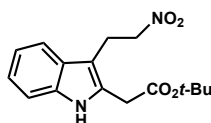
the 50-mL round-bottom flask containing the magnesium malonate solution in THF. The resulting reaction mixture was heated at 60 °C for 2 h, cooled to rt, and quenched with 1 N HCl (30 mL). The reaction mixture was extracted with EtOAc (3 x 20 mL), and the combined organic layers were washed with brine (20 mL), dried over Na₂SO₄, filtered and concentrated via rotary evaporation. The crude brown oil was purified via column chromatography (6:1 hexanes/ethyl acetate) to yield 4.92 g (78%) of **1.57** as a bright orange oil. Spectral data agreed with those reported for **1.57**.⁴⁹



Indole 1.59. A 300-mL Pyrex sleeve was charged with **1.57** (4.92 g, 13.0 mmol, 1.00 equiv), 10 wt % palladium on carbon (70.0 mg, 0.650 mmol, 0.0500 equiv), and *i*-PrOH (75 mL). The sleeve was placed into a Parr bomb, which was sealed, purged (2 x 100 psi) and pressurized with H₂ (500 psi). The reaction mixture was stirred at rt for 6 days. EtOAc (40 mL) was then added until the white ppt dissolved. The mixture was filtered through a pad of Celite, and the Celite pad was washed with EtOAc (40 mL). The combined filtrates were concentrated via rotary evaporation. The crude orange solid was purified via column chromatography (6:1 hexanes/ethyl acetate) to afford 2.75 g (64%) of **1.59** as a white crystalline solid, m. p. 146-147 °C (lit. 146-148 °C). Spectral data agreed with those reported for **1.59**.⁴⁹

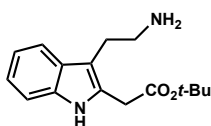


indole 1.62. A 10-mL pear-shaped flask was charged with **1.59** (130 mg, 1.1 mmol, 1.0 equiv) in DCM (0.6 mL). The reaction mixture was cooled to 0 °C, and a solution of trifluoroacetic acid (0.080 mL, 1.1 mmol, 1.4 equiv) in DCM (0.4 mL) was added, followed by dropwise addition of *N,N*-dimethyl-2-nitroethenamine⁵⁰ (250 mg, 0.75 mmol, 1.5 equiv) in DCM (1.0 mL). The flask was warmed to RT and the solution was stirred for 14 h, at which time it was concentrated via rotary evaporation. The crude brown oil was purified by column chromatography (4:1 hexanes/ethyl acetate) to afford 166 mg (73%) of **1.62** as a yellow crystalline solid, m. p. 261-262 °C. ¹H NMR (400 MHz, CDCl₃) δ 9.97 (s, 1H), 8.29 (d, *J* = 13.3 Hz, 1H), 7.80 (d, *J* = 13.3 Hz, 1H), 7.72 - 7.70 (m, 1H), 7.42 - 7.40 (m, 1H), 7.30 - 7.28 (m, 2H), 3.96 (s, 2H), 1.53 (s, 9H); ¹³C NMR (125 MHz, CDCl₃) δ 168.9, 139.9, 136.4, 132.3, 132.0, 125.3, 124.0, 122.8, 120.4, 112.3, 106.8, 83.7, 32.5, 28.2; IR (thin film) λ_{max} 3268, 2980, 2934, 1726, 1613, 1556, 1460, 1306, 1217, 733 cm⁻¹; HRMS (EI) *m/z*: calc for C₁₆H₁₈N₂O₄ 302.1267, found 302.1258.



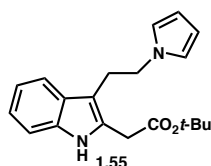
1.64

Nitroethyl indole 1.64. A 4-mL vial was charged with $(\text{Cp}^*\text{Ir}^{\text{III}}\text{Cl}_2)(\mu\text{-Cl})_2$ (0.8 mg, 1 μmol , 1 mol %), AgSO_4 (0.6 mg, 2 μmol , 2 mol %), and H_2O (0.4 mL). The reaction mixture was stirred for 12 h at rt, then the vial was charged with **1.62** (30 mg, 0.1 mmol, 1.0 equiv), formic acid (0.6 mL) and DCM (0.1 mL). The resulting reaction mixture was stirred for 24 h at RT, then diluted with H_2O (2 mL) and extracted with DCM (3 x 2 mL). The combined organic layers were dried over Na_2SO_4 , filtered and concentrated via rotary evaporation to afford 30 mg (95%) a crude yellow oil that was used without further purification. Crude $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.80 (s, 1H), 7.51 (d, $J = 7.8$ Hz, 2H), 7.34 (d, $J = 7.9$ Hz, 2H), 7.22 - 7.11 (m, 3H), 4.61 (t, $J = 7.4$ Hz, 3H), 3.73 (s, 3H), 3.45 (t, $J = 7.4$ Hz, 3H), 1.50 (s, 13H).



1.S1

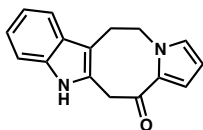
Amine 1.S1. A 4-mL vial was charged with crude **1.64** (1.0 equiv), Raney-nickel (1 drop, 50% slurry in H_2O) and MeOH (1 mL). The vial was placed in a Parr bomb, which was sealed, purged (2 x 50 psi) and pressurized with H_2 (100 psi). The reaction mixture was stirred for 6 h, after which time it was filtered through Celite (0.5 g). The Celite pad was washed with MeOH (2 mL). The combined filtrates were concentrated via rotary evaporation to afford 27 mg (99%) of **1.S1** as a crude orange solid was used without further purification.



1.55

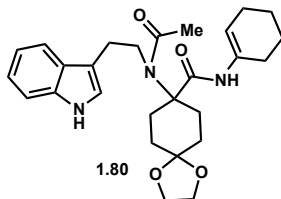
Pyrrole 1.55. A 4-mL vial was charged with crude **1.S1** (1.0 equiv), DCE (0.9 mL), H_2O (0.5 mL), 2,5-dimethoxy tetrahydrofuran (0.030 mL, 0.20 mmol, 1.2 equiv) and acetic acid (0.040 mL, 0.80 mmol, 4.0 equiv). The vial was capped and heated at 45 $^\circ\text{C}$ for 14 h. The reaction mixture was cooled to rt and quenched with saturated aq. NaHCO_3 (1 mL). The aqueous layer was extracted with DCM (2 x 1 mL), dried over Na_2SO_4 , filtered and concentrated via rotary evaporation. The crude yellow oil was purified via column chromatography (6:1 hexanes/ethyl acetate) to yield 20 mg (50% over three steps) of **1.55** as a colorless oil. $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.77 (s, 1H), 7.52 (d, $J = 7.7$ Hz, 1H), 7.35 (d, $J = 8.0$ Hz, 1H), 7.21 - 7.06 (m, 2H), 6.50 (t, $J = 2.1$ Hz, 2H), 6.10 (t, $J = 2.0$ Hz, 2H), 4.10 (q, $J = 6.6$ Hz, 2H), 3.26 (s, 2H), 3.10 (t, $J = 6.8$ Hz, 2H), 1.47 (s, 8H); ^{13}C

NMR (125 MHz, CDCl_3) δ 170.3, 135.8, 129.2, 127.7, 121.9, 120.8, 119.6, 118.0, 111.1, 109.5, 108.2, 82.0, 50.3, 31.9, 28.3, 27.4; **IR** (thin film) λ_{max} 3258, 2986, 2934, 1726, 1590, 1445, 1376, 1200, 768 cm^{-1} ; **HRMS** (EI) m/z calc: for $\text{C}_{20}\text{H}_{20}\text{N}_2\text{O}_2$ 324.1838, found 324.1842.



1.54

Tetracycle 1.54. A 4-mL vial was charged with **1.55** (90.0 mg, 0.280 mmol, 1.00 equiv) and polyphosphoric acid (30.0 mg). The vial was heated at 80 °C for 19 h, then cooled to rt and the reaction mixture was diluted with ice water. The aqueous layer was extracted with DCM (3 x 2 mL). The combined organic layers were washed with saturated aq. NaHCO_3 (2 mL), dried over Na_2SO_4 , filtered and concentrated via rotary evaporation. The crude yellow oil was purified via column chromatography (6:1 hexanes/ethyl acetate) to yield 24 mg (34%) of **1.54** as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 7.87 (s, 1H), 7.45 (d, $J = 6.7$ Hz, 1H), 7.19 (s, 1H), 7.04 - 6.98 (m, 1H), 6.68 (s, 1H), 6.43 (s, 1H), 6.23 - 6.12 (m, 1H), 4.07 - 4.03 (m, 2H), 3.25 - 3.14 (br, 2H), 3.10 - 2.89 (br, 2H); ^{13}C NMR (100 MHz, C_6D_6) δ 172.6, 170.0, 136.2, 132.7, 127.4, 127.2, 124.2, 123.9, 122.4, 122.3, 122.0, 109.2, 107.7, 65.9, 53.3, 29.0; **IR** (thin film) λ_{max} 3258, 2986, 2934, 1648, 1445, 1376, 1200, 768 cm^{-1} ; **HRMS** (EI) m/z calc: for $\text{C}_{16}\text{H}_{15}\text{N}_2\text{O}$ 250.2952, found 250.2960. NOTE: Due to the rapid decomposition of **1.54**, ^1H -NMR spectrum without alkyl impurities δ 0.75 - 1.75 has not been obtained.

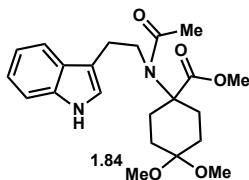


1.80

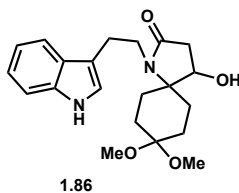
Ugi Adduct 1.80: A 25 mL round-bottom flask was charged with cyclohexeneformamide (125 mg, 1.00 mmol, 1.00 equiv), triethylamine (422 μL , 3.00 mmol, 3.00 equiv) and THF (3.3 mL) and the solution was cooled to 0 °C. Phosphorus oxychloride (121 μL , 1.30 mmol, 1.30 equiv) was added to the reaction mixture dropwise over 15 min. The reaction mixture was stirred at 0 °C for 30 min and then quenched with saturated aqueous ammonium chloride (5 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (2 x 10 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo*. The crude oil was loaded onto a 1-inch silica gel plug, which was flushed with 10:1 hexanes/ethyl acetate (2 x 30 mL portions) and the collected solvent was concentrated *in vacuo* to yield isonitrile **1.78**, which was used immediately without further purification.

A 50 mL recovery flask was charged with tryptamine (880 mg, 5.50 mmol, 1.00 equiv), ketone **1.77** (860 mg, 5.50 mmol, 1.00 equiv), and methanol (5.5 mL). Acetic acid (380 μL , 6.60 mmol, 1.20 equiv) was added. The reaction mixture was stirred for 15 min at

room temperature, isonitrile **1.78** (650 mg, 6.00 mmol, 1.10 equiv) was added dropwise as a solution in methanol (1.0 mL) and the resultant solution was stirred for 30 min, after which time the mixture had completely solidified. Water (10 mL) was added and the reaction mixture was stirred for an additional 15 min. The resultant slurry was filtered and the solids were dried under reduced pressure. This yielded adduct **1.80** (2.42 g, 95%) as an off-white solid, m. p. 108 - 111 °C. $^1\text{H NMR}$ (600 MHz, CDCl_3) δ 8.30 (s, 1H), 8.21 (s, 1H), 7.58 (t, $J = 7.9$ 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); $^{13}\text{C NMR}$ (150 MHz, CDCl_3) δ 174.1, 171.8, 136.3, 132.9, 127.0, 122.4, 122.2, 119.6, 118.3, 113.0, 112.1, 111.4, 107.7, 65.1, 64.4, 64.3, 31.5, 30.5, 28.1, 26.2, 24.3, 24.0, 22.5, 22.0; **IR** (thin film) ν_{max} 3324, 3053, 2931, 1662, 1634, 1510, 1405, 1231 cm^{-1} ; **HRMS** (EI^+) calc'd for $[\text{C}_{27}\text{H}_{35}\text{N}_3\text{O}_4]^+$: m/z , 465.5845 found 465.5836.

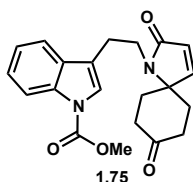


Methyl ester 1.84: A 100 mL round-bottom flask was charged with **1.80** (2.40 g, 5.10 mmol, 1.00 equiv) and methanol (25 mL). The solution was cooled to 0 °C, and acetyl chloride (730 μL , 10.2 mmol, 2.00 equiv) was added dropwise to the reaction slurry. The reaction mixture was stirred at 0 °C for 1 h, then at room temperature for 18 h, at which point it was concentrated *in vacuo*. Water (50 mL) was added to the resulting material, and the slurry was filtered to obtain **1.84** (1.97 g, 96%) as a white solid, m. p. 173 - 175 °C. $^1\text{H NMR}$ (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); $^{13}\text{C NMR}$ (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, 29.0, 28.9, 27.1, 22.8; **IR** (thin film) ν_{max} 3347, 1737, 1632, 1218, 1106 cm^{-1} ; **HRMS** (EI^+) calc'd for $[\text{C}_{22}\text{H}_{30}\text{N}_2\text{O}_5]^+$: m/z , 402.2155 found 402.2149.



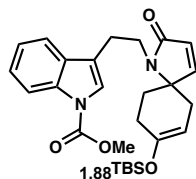
Alcohol 1.86: A 250 mL round-bottom flask was charged with **1.80** (2.00 g, 4.90 mmol, 1.00 equiv) and THF (50 mL). The flask was placed into a 0 °C ice bath and potassium *t*-

butoxide (1.10 g, 9.80 mmol, 2.00 equiv) was added in one portion. The reaction mixture was stirred for 2 h at 0 °C, at which point TLC showed consumption of **1.80**. Acetic acid (670 μ L, 11.8 mmol, 2.40 equiv) was added dropwise over 15 min, followed by *i*-propanol (25 mL), and sodium borohydride (280 mg, 7.40 mmol, 1.50 equiv) in one portion. The reaction mixture was stirred for an additional 2 h at 0 °C, and then 14 h at room temperature. The reaction was then quenched with saturated aqueous ammonium chloride (25 mL) and water (75 mL). The resultant biphasic solution was stirred at room temperature for 15 min, and filtered to give alcohol **1.86** (1.64 g, 90%) as an off-white solid, m. p. 222 - 223 °C. $^1\text{H NMR}$ (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); $^{13}\text{C NMR}$ (150 MHz, DMSO) δ 172.8, 136.8, 127.5, 123.2, 121.4, 118.7, 118.6, 112.0, 111.9, 98.9, 67.4, 66.7, 60.2, 47.6, 47.5, 29.6, 29.1, 28.9, 26.2, 25.4, 14.5; **IR** (thin film) ν_{max} 3399, 1658, 1441, 1104 cm^{-1} ; **HRMS** (EI^+) calc'd for $[\text{C}_{21}\text{H}_{28}\text{N}_2\text{O}_4]^+$: m/z , 372.2049 found 372.2038.

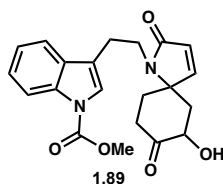


α,β -Unsaturated amide 1.75: A 250 mL round-bottom flask was charged with indole **1.86** (4.80 g, 12.9 mmol, 1.00 equiv) and THF (92 mL). The reaction mixture was cooled to 0 °C and potassium *t*-butoxide (2.89 g, 25.8 mmol, 2.00 equiv) was added in one portion. The reaction mixture was stirred at 0 °C for 10 min, at which point methyl chloroformate (1.25 mL, 16.1 mmol, 1.25 equiv) was added dropwise over a period of 15 min. The reaction mixture was stirred for 1 h at 0 °C, then additional potassium *t*-butoxide (2.89 g, 25.8 mmol, 2.00 equiv) was added in one portion. After 10 min of stirring additional methyl chloroformate (1.25 mL, 16.1 mmol, 1.25 equiv) was added dropwise over a period of 15 min. The reaction mixture was stirred while the cooling bath warmed to room temperature over 12 h, at which time TLC showed consumption of **1.86**. The reaction mixture was then cooled to 0 °C and 1N HCl (35 mL) was added in one portion, after which the reaction mixture was allowed to stir for 4 h at room temperature. The reaction was quenched with saturated aqueous sodium bicarbonate (50 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo* to give **1.75** (4.44 g, 94%) as a pale yellow solid, m.p. 175 - 178 °C, which was used without further purification. $^1\text{H NMR}$ (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); $^{13}\text{C NMR}$ (125 MHz, CDCl_3)

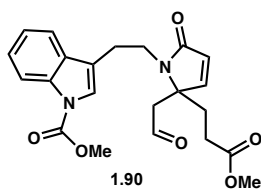
δ 207.7, 170.1, 151.4, 148.4, 135.5, 130.3, 128.1, 124.9, 123.1, 122.8, 119.1, 118.5, 115.3, 66.4, 53.8, 39.8, 38.7, 32.8, 24.5; **IR** (thin film) ν_{\max} 3069, 2955, 2934, 2863, 1732, 1683, 1456, 1094 cm^{-1} ; **HRMS** (EI^+) calc'd for $[\text{C}_{21}\text{H}_{22}\text{N}_2\text{O}_4]^+$: m/z , 366.1580 found 366.1577. Note: Compound **1.75** was isolated with 5-10% impurity.



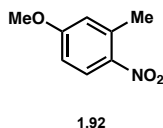
Silyl enol ether 1.88: A 100 mL round-bottom flask was charged with ketone **1.75** (2.00 g, 5.46 mmol, 1.00 equiv), triethylamine (1.53 mL, 10.9 mmol, 2.00 equiv) and dichloromethane (40 mL). The reaction flask was cooled to 0 °C, and *t*-butyldimethylsilyl triflate (1.50 mL, 6.55 mmol, 1.20 equiv) was added dropwise over 15 min. The flask was allowed to warm to room temperature and the reaction mixture was stirred at this temperature for 14 h. The reaction was quenched with saturated aqueous sodium bicarbonate (50 mL) and then extracted with dichloromethane (3 x 50 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo*. The crude oil was purified by column chromatography (gradient of 4:1 to 1:1 hexanes/ethyl acetate) to give silyl enol ether **1.88** (2.57 g, 98 %) as a white solid, m. p. 130 - 132 °C. **¹H 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); **¹³C 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, 66.3, 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 $[\text{C}_{27}\text{H}_{36}\text{N}_2\text{O}_4\text{Si}]^+$: m/z , 480.2444 found 480.2449.



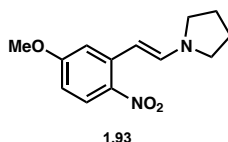
α -Hydroxy ketone 1.89: A 100 mL round-bottom flask was charged with silyl enol ether **1.88** (2.00 g, 4.16 mmol, 1.00 equiv), acetone (45 mL), and water (8 mL). Osmium tetroxide (2.5 wt % solution in *t*-butanol, 129 μL , 8.32 μmol , 0.2 mol %) was added, followed by *t*-butyl hydroperoxide (70% in water, 590 μL , 4.58 mmol, 1.10 equiv). The solution was stirred at room temperature for 36 h, at which time TLC showed consumption of **1.88**. The reaction was quenched with saturated aqueous sodium sulfite (10 mL) and the aqueous layer was extracted with dichloromethane (3 x 15 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford **1.89** as a light yellow oil that was brought forward without purification.



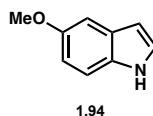
Aldehyde 1.90: A 25 mL round-bottom flask was charged with crude **1.89** (87.9 mg, 0.230 mmol, 1.00 equiv) and MeOH (5 mL). The reaction mixture was cooled to $-40\text{ }^{\circ}\text{C}$ and lead(IV) acetate (123 mg, 0.280 mmol, 1.20 equiv) was added in one portion. The reaction mixture was stirred at $-40\text{ }^{\circ}\text{C}$ for 15 min, then warmed to room temperature and quenched with H_2O (4 mL). The resulting biphasic solution was filtered through a pad of Celite (0.5 g). The filtrate was extracted with CHCl_3 (4 x 3 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo*. The resulting light yellow oil was purified by column chromatography (gradient of 2:1 hexanes/ethyl acetate to 1:2 hexanes/ethyl acetate) to yield aldehyde **1.90** (1.11 g, 65% over 2 steps) as a colorless oil. $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 9.42 (t, $J = 2.1$ Hz, 1H), 8.16 (s, 1H), 7.69 (d, $J = 7.6$ Hz, 1H), 7.49 (s, 1H), 7.38 – 7.33 (m, 1H), 7.32 – 7.28 (m, 1H), 7.10 (d, $J = 6.0$ Hz, 1H), 6.26 (d, $J = 6.0$ Hz, 1H), 4.03 (s, 3H), 3.62 (s, 3H), 3.62 – 3.56 (m, 1H), 3.44 (ddd, $J = 14.1, 10.2, 6.3$ Hz, 1H), 3.16 – 3.01 (m, 2H), 2.79 (dd, $J = 16.5, 1.9$ Hz, 1H), 2.57 (dd, $J = 16.5, 2.4$ Hz, 1H), 2.28 – 2.21 (m, 1H), 2.12 – 2.03 (m, 1H), 1.97 (dd, $J = 9.1, 2.7$ Hz, 1H); $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 197.8, 172.7, 172.7, 171.0, 149.0, 135.4, 130.1, 128.5, 124.9, 123.1, 122.9, 119.1, 118.3, 115.3, 67.6, 53.8, 52.0, 48.7, 39.8, 29.5, 27.4, 24.1; **IR** (thin film) ν_{max} 3054, 2954, 1731, 1682, 1608, 1585, 1260, 1095 cm^{-1} ; **HRMS** (EI^+) calc'd for $[\text{C}_{22}\text{H}_{24}\text{N}_2\text{O}_6]^+$: m/z , 412.1634 found 412.1633. Note: Compound **1.90** was isolated with 5-10% impurity.



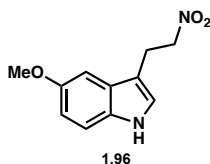
5-Methoxy-2-nitrotoluene 1.92. A 250-mL round-bottom flask was charged with 3-methyl-4-nitrophenol (10.0 g, 65.3 mmol, 1.00 equiv), K_2CO_3 (7.84 g, 78.3 mmol, 1.20 equiv) and acetone (200 mL). To the reaction mixture was added iodomethane (6.12 mL, 98.0 mmol, 1.50 equiv) dropwise. The reaction mixture was stirred at RT for 12 h, concentrated by rotary evaporation, then diluted with EtOAc (200 mL). The organic phase was washed sequentially with 10% aq. NaOH (75 mL) and brine (75 mL). The organic layer was dried over Na_2SO_4 , filtered and concentrated by rotary evaporation to yield 10.7 g (98%) of **1.92** as a yellow solid which was used without further purification.



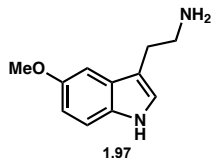
Pyrrolidine 1.93.²⁹ A 25-mL Schlenk flask was charged with **1.92** (1.70 g, 10.2 mmol 1.00 equiv), pyrrolidine (0.853 mL, 12.2 mmol, 1.20 equiv), and *N,N*-dimethylformamide-dimethylacetal (1.89 mL, 14.2 mmol, 1.40 equiv). The flask was sealed and heated at 120 °C for 14 h. The reaction mixture was cooled to rt, and excess pyrrolidine and *N,N*-dimethylformamide-dimethylacetal were removed under high vacuum. The crude dark red oil (2.37 g, 94%) was used without further purification.



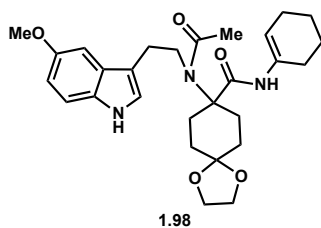
5-Methoxyindole 1.94.³⁰ A 250-mL round-bottom flask was charged with crude **1.93**, hydrazine hydrate (1.5 mL, 31 mmol, 3.0 equiv) and EtOH (100 mL). The flask was fitted with a reflux condenser, and heated at 80 °C for 30 min. The reaction mixture was then cooled to rt and a mixture of Ni₂B³⁰ (2.7 g, 21 mmol, 2.0 equiv) in EtOH (50 mL) was added. The flask was again fitted with a reflux condenser and heated to 50 °C. After stirring at 50 °C for 1 hour, an additional portion of hydrazine hydrate (0.77 mL, 16 mmol, 1.5 equiv) was added to the reaction mixture. The reaction mixture was stirred at 50 °C for an additional 2 h, and then cooled to rt. The reaction mixture was filtered through a plug of Celite (5 g) and the filtrate was concentrated by rotary evaporation. The crude brown oil was purified by column chromatography (8:1 hexanes/ethyl acetate) to yield 790 mg (51% over 2 steps) of **1.94** as a white crystalline solid, m. p. 54-55 °C (lit. 52-56 °C). agrees with those previously reported for **1.94**.⁵¹



Nitroethyl methoxyindole 1.96.³⁰ A 50-mL Schlenk flask was charged with **1.94** (782 mg, 5.30 mmol, 1.00 equiv), 2-nitroethyl acetate⁵² (775 mg, 5.83 mmol, 1.10 equiv), 4-methyl-catechol (66.0 mg, 0.530 mmol, 0.0500 equiv), and *p*-xylenes (12 mL). The reaction mixture was sparged with N₂ for 15 min, then the flask was sealed. The flask was placed into a 140 °C oil bath for 3 h, then cooled to rt. The resulting solution was loaded directly onto a column of silica gel and purified via column chromatography (8:1 hexanes/ethyl acetate) to recover 190 mg **1.94** (23%) and afford 888 mg (76%) of **1.96** as a yellow crystalline solid, m. p. 78-79 °C (no m.p. found in literature). Spectral data agree with that previously reported for **1.96**.⁵³

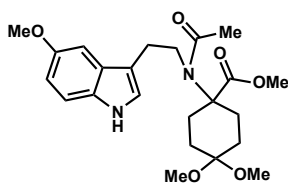


Serotonin 1.97.^{30,31} A 300-mL Pyrex sleeve was charged with **1.96** (3.17 g, 16.8 mmol, 1.0 equiv), Raney-nickel (1 drop of 50% slurry in H₂O), and MeOH (150 mL). The sleeve was placed in a Parr bomb, which was sealed, purged (2 x 50 psi) and pressurized with H₂ (100 psi). The reaction mixture was stirred for 18 h, then the mixture was filtered through a pad of Celite (5 g) and rinsed with MeOH (3 x 20 mL). The filtrate was concentrated until only 20 mL of methanol remained. The light brown solution was used immediately, without further purification. Spectral data agree with that previously reported for **1.97**.⁵⁴



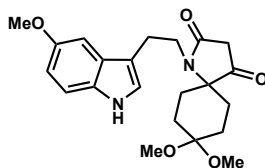
Enamide 1.98. A 250-mL round-bottom flask was charged with *N*-cyclohexenylformamide (3.50 g, 28.0 mmol, 1.00 equiv), Et₃N (11.8 mL, 84.0 mmol, 3.00 equiv) and THF (150 mL). The flask was cooled to 0 °C, and POCl₃ (3.84 mL, 42.0 mmol, 1.50 equiv) was added dropwise. The reaction mixture was stirred at 0 °C for 1 hour, then was quenched with ice (10 g). The aqueous layer was extracted with DCM (3 x 50 mL), dried over Na₂SO₄, filtered and concentrated via rotary evaporation. The crude brown oil was purified by column chromatography (8:1 hexanes/ethyl acetate) to yield 2.40 g (80%) of **1.78** as a light yellow oil that was used immediately.

To a 200-mL recovery-flask, containing **1.78** (3.20 g, 16.8 mmol, 1.00 equiv, crude from previous reaction) in 20 mL methanol, were added 1,4-dioxaspiro[4.5]decan-8-one (2.62 g, 16.8 mmol, 1.00 equiv) and acetic acid (1.15 mL, 20.2 mmol, 1.10 equiv). The reaction mixture was stirred at rt for 15 min, then **1.97** (1.93 g, 18.1 mmol, 1.20 equiv) was added dropwise. The reaction mixture was stirred for 12 h at rt, at which point H₂O (50 mL) was added. The reaction mixture was stirred for 30 min until it became a slurry, and then was filtered. The solids were dried under high-vacuum after which 5.31 g (65 %) of **1.98** were obtained as a white solid, m.p. 101-103 °C. ¹H NMR (500 MHz, CDCl₃) δ 8.29 (s, 1H), 8.10 (s, 1H), 7.30 - 7.23 (m, 1H), 7.00 (dd, *J* = 21.2, 2.2 Hz, 2H), 6.89 - 6.84 (m, 1H), 6.07 (s, 1H), 3.97 - 3.93 (m, 4H), 3.86 (s, 3H), 3.68 - 3.61 (m, 2H), 3.01 - 2.96 (m, 2H), 2.43 (s, 4H), 2.18 - 2.14 (m, 2H), 2.12 - 2.09 (m, 2H), 2.07 (s, 3H), 1.86 (dt, *J* = 12.3, 6.0 Hz, 2H), 1.70 - 1.52 (m, 6H); ¹³C NMR (125 MHz, CDCl₃) δ 221.3, 219.6, 218.7, 188.9, 174.3, 172.0, 156.1, 154.4, 133.1, 131.6, 127.6, 123.3, 113.3, 112.5, 112.3, 112.0, 107.9, 100.4, 65.3, 64.6, 56.1, 47.1, 31.7, 30.7, 28.3, 26.4, 24.5, 24.3, 22.8, 22.3; IR (thin film) λ_{max} 3326, 2933, 1739, 1683, 1585, 1520, 1218, 1103 cm⁻¹; HRMS (EI) calcd for [C₂₈H₃₈O₅N₂+Na]⁺: *m/z*, 518.2625 found 518.2627.



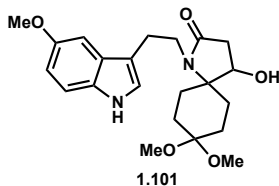
1.99

Methyl ester 1.99. A 100-mL round-bottom flask was charged with **1.98** (1.95 g, 3.90 mmol, 1.00 equiv) and MeOH (40 mL). The flask was placed into a 0 °C ice bath and acetyl chloride (0.280 mL, 3.90 mmol, 1.00 equiv) was added to the reaction mixture dropwise. The flask was allowed to warm to rt and the reaction mixture was stirred for 16 h. The reaction mixture was filtered to afford 1.41 g (84%) of **1.99** as a white powder, m.p. 148-149 °C. $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 8.40 (s, 1H), 7.29 (d, $J = 8.8$ Hz, 1H), 7.07 - 6.99 (m, 2H), 6.88 (dd, $J = 8.8, 2.1$ Hz, 1H), 3.87 (s, 3H), 3.72 (s, 3H), 3.67 - 3.60 (m, 2H), 3.20 (d, $J = 6.9$ Hz, 6H), 3.05 (dd, $J = 14.6, 6.4$ Hz, 2H), 2.43 (m, 2H), 2.04 (s, 3H), 1.95 (m, 2H), 1.92 - 1.65 (m, 4H); $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 174.1, 171.5, 154.2, 131.6, 127.6, 122.9, 112.4, 112.0, 100.5, 99.3, 63.6, 56.1, 52.3, 48.1, 47.7, 45.9, 29.2, 29.1, 27.2, 23.0; **IR** (thin film) λ_{max} 3345, 1734, 1634, 1217, 1106 cm^{-1} ; **HRMS** (EI) calcd for $[\text{C}_{22}\text{H}_{29}\text{O}_5\text{N}_2\text{-OMe}]^+$: m/z , 401.2071 found 401.2075.

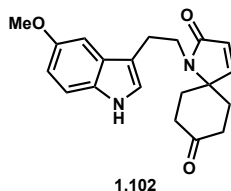


1.100

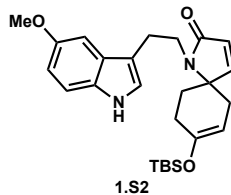
Pyrrolidine dione 1.100. A 100-mL round-bottom flask was charged with **1.99** (1.40 g, 3.24 mmol, 1.00 equiv) and THF (33 mL). The flask was placed into a 0 °C ice bath and potassium *tert*-butoxide (1.09 g, 9.71 mmol, 3.00 equiv) was added in one portion. The reaction mixture was stirred for 4 h at 0 °C, then quenched with saturated aq. NH_4Cl (30 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4 , filtered and concentrated via rotary evaporation to yield 1.29 g (99%) of **1.100** as a yellow solid, m.p. 149-151 °C. $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.96 (s, 1H), 7.25 (d, $J = 8.8$ Hz, 1H), 7.20 (d, $J = 2.3$ Hz, 1H), 7.04 (d, $J = 2.3$ Hz, 1H), 6.86 (dd, $J = 8.8, 2.4$ Hz, 1H), 3.90 (s, 3H), 3.57 - 3.47 (m, 2H), 3.20 (s, 3H), 3.12 (s, 1H), 3.13 - 3.09 (m, 4H), 3.09 (s, 3H), 2.00 - 1.88 (m, 4H), 1.80 (td, $J = 13.3, 5.2$ Hz, 2H), 1.51 (d, $J = 13.8$ Hz, 2H); $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 208.9, 168.6, 154.4, 131.6, 128.0, 123.0, 112.9, 112.6, 112.2, 100.9, 98.6, 68.6, 56.1, 48.2, 47.7, 40.7, 40.4, 28.3, 28.1, 25.4; Note: Compound **1.100** was characterized with trace ethyl acetate. **IR** (thin film) λ_{max} 3308, 1157, 1683, 1214, 1101 cm^{-1} ; **HRMS** (EI) calcd for $[\text{C}_{22}\text{H}_{28}\text{O}_5\text{N}_2]^+$: m/z , 400.1998 found 401.2001.



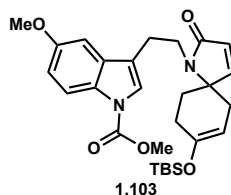
Alcohol 1.101. A 100-mL round-bottom flask was charged with **1.100** (1.29 g, 3.23 mmol, 1.00 equiv) and *i*-PrOH (30 mL). The flask was placed into a 0 °C ice bath and sodium borohydride (122 mg, 3.23 mmol, 1.00 equiv) was added in one portion. The flask was warmed to rt and the reaction mixture was stirred for 12 h, and then was concentrated via rotary evaporation. The crude oil was diluted in EtOAc (40 mL), and washed with saturated aq. NH₄Cl (30 mL) and brine (30 mL). The organic layer was dried over Na₂SO₄, filtered, and concentrated via rotary evaporation to yield 1.28 g (98%) of **1.101** as a yellow solid that was used without further purification.



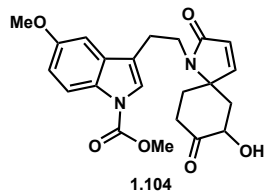
Lactam 1.102. A 100-mL round-bottom flask was charged with crude **1.101** (1.00 equiv) and THF (32 mL). The reaction mixture was cooled to 0 °C and potassium *tert*-butoxide (1.07 g, 9.56 mmol, 3.00 equiv) was added in one portion. The reaction mixture was stirred for 10 min at 0 °C, then EtOAc (1.87 mL, 19.1 mmol, 6.00 equiv) was added dropwise. The reaction mixture was stirred at 0 °C for 3 h. Following addition of 1 N HCl (10 mL), the reaction solution was warmed to rt over 14 h, then quenched with saturated aq. NaHCO₃ (30 mL). The aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (30 mL), dried over Na₂SO₄, filtered and concentrated via rotary evaporation. The crude yellow solid was purified via column chromatography (1:1 hexanes/ethyl acetate) to yield 1.20 g (95%) of **1.102** as a yellow crystalline solid, m.p. 203-204 °C. ¹H NMR (500 MHz, CDCl₃) δ 7.90 (s, 1H), 7.59 (d, *J* = 6.0 Hz, 1H), 7.24 (d, *J* = 8.8 Hz, 1H), 7.19 (s, 1H), 7.02 (s, 1H), 6.86 (d, *J* = 8.5 Hz, 1H), 6.34 (d, *J* = 6.0 Hz, 1H), 3.89 (s, 2H), 3.57 - 3.51 (m, 2H), 3.14 - 3.08 (m, 2H), 2.43 - 2.60 (m, 4H), 2.21 (t, *J* = 11.3 Hz, 2H), 1.63 (m, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 232.7, 208.1, 170.3, 154.3, 148.5, 131.5, 128.3, 128.1, 122.9, 113.2, 112.7, 112.1, 100.7, 66.6, 56.1, 40.8, 38.9, 32.9, 25.0; IR (thin film) λ_{max} 3273, 1721, 1677, 1215, 1118 cm⁻¹; HRMS (EI) calcd for [C₂₀H₂₃O₃N₂]⁺: *m/z*, 399.1703 found 399.1706. Note: Compound **1.102** was isolated with 5-10% impurity.



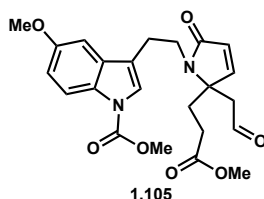
Silylenol ether 1.S2. A 100-mL round-bottom flask was charged with **1.102** (766 g, 1.90 mmol, 1.00 equiv) and DCM (40 mL). The flask was placed in a 0 °C ice bath. Triethylamine (0.540 mL, 3.86 mmol, 2.00 equiv) was added to the flask in one portion, followed by dropwise addition of *tert*-butyldimethylsilyl triflate (0.520 mL, 2.28 mmol, 1.20 equiv). The flask was allowed to warm to rt and the reaction mixture was stirred at this temperature for 12 h. The reaction mixture was then quenched with saturated aq. NH₄Cl (30 mL) and extracted with DCM (2 x 30 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated via rotary evaporation to yield 958 mg (111%) **1.S2** as a crude yellow solid, which was used without further purification.



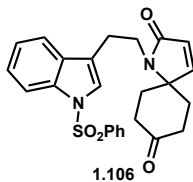
Carbamate 1.103. A 100-mL round-bottom flask was charged with crude **1.S2** (1.0 equiv) and THF (40 mL). The flask was placed into a 0 °C ice bath and potassium *tert*-butoxide (1.1 g, 9.6 mmol, 1.6 equiv) was added in one portion. The reaction mixture was stirred for 10 min at 0 °C, and the flask was then charged with methyl chloroformate (0.18 mL, 2.3 mmol, 1.2 equiv) via dropwise addition. The reaction mixture was allowed to stir at 0 °C for 5 h, then quenched with saturated aq. NH₄Cl (30 mL), and extracted with EtOAc (2 x 30 mL). The combined organic layers were washed with brine (30 mL), dried over Na₂SO₄, filtered and concentrated via rotary evaporation. The crude brown solid was purified via column chromatography (1:1 hexanes/ethyl acetate) to afford 230 mg (44%) of **1.103** as a yellow crystalline, m.p. 161-162 °C. ¹H NMR (500 MHz, CDCl₃) δ 7.99 (s, 1H), 7.38 (s, 1H), 7.25 (s, 1H), 7.20 (s, 1H), 6.92 (d, *J* = 13.8 Hz, 1H), 6.14 (d, *J* = 5.9 Hz, 1H), 4.80 (d, *J* = 4.8 Hz, 1H), 3.97 (s, 3H), 3.86 (s, 3H), 3.55 - 3.45 (m, 2H), 3.05 - 2.94 (m, 2H), 2.52 (d, *J* = 16.0 Hz, 1H), 2.25 - 2.19 (m, 2H), 2.15 - 2.05 (m, 1H), 1.68 (dd, *J* = 15.9, 4.8 Hz, 1H), 1.40 (d, *J* = 6.8 Hz, 1H), 0.90 (s, 9H), 0.13 (s, 6H); ¹³C NMR (125 MHz, CDCl₃) δ 170.7, 156.1, 151.2, 149.5, 131.3, 130.0, 126.2, 123.1, 118.8, 115.9, 113.5, 101.8, 101.0, 77.4 77.3, 77.1, 76.9, 66.1, 55.7, 53.6, 39.5, 30.6, 30.4, 29.1, 25.6, 24.7, 18.0, -4.3, -4.5; IR (thin film) λ_{max} 2954, 2930, 2856, 1734, 1685, 1268, 1089 cm⁻¹; HRMS (EI) calcd for [C₂₈H₃₈O₅N₂Si]⁺: *m/z*, 511.2623 found 511.2620.



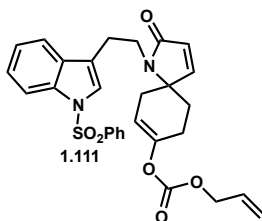
α -Hydroxy ketone 1.104. A 10-mL pear-shaped flask was charged with **1.103** (147 mg, 0.290 mmol, 1.00 equiv), acetone (4.5 mL) and H₂O (0.75 mL), followed by osmium tetroxide (6.00 mg of 2.5% wt/vol in 2-methyl-2-propanol, 0.2 mol %) and *tert*-butylhydroperoxide (0.0400 mL, 70% in H₂O, 0.320 mmol, 1.10 equiv). After stirring at rt for 24 h, the reaction mixture was quenched with saturated aq. Na₂SO₃ (3 mL). The aqueous layer was extracted with EtOAc (3 x 1 mL). The combined organic layers were washed with brine (1 mL), dried over Na₂SO₄, filtered and concentrated via rotary evaporation to afford 95 mg (80%) of **1.104** as a crude light yellow oil was used without further purification.



Aldehyde 1.105. A flame-dried 25-mL pear-shaped flask was charged with crude **1.104** (1.00 equiv) and MeOH (5.00 mL). The reaction mixture was cooled to -40 °C, and lead(IV) acetate (123 mg, 0.280 mmol, 1.20 equiv) was added to the reaction mixture. The reaction mixture was stirred at -40 °C for 15 min, then warmed to rt and quenched with H₂O (4 mL). The resulting mixture was filtered through a pad of Celite (0.5 g). The filtrate was extracted with CHCl₃ (4 x 3 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated via rotary evaporation. The crude light yellow oil was purified via column chromatography (gradient of 2:1 hexanes/ethyl acetate to 1:2 hexanes/ethyl acetate) to yield 50.0 mg (40% over 2 steps) of **1.105** as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 9.43 (s, 1H), 8.02 (s, 1H), 7.44 (s, *J* = 14.7 Hz, 1H), 7.23 (s, 1H), 7.10 (d, *J* = 6.0 Hz, 1H), 6.95 (dd, *J* = 9.0, 2.4 Hz, 1H), 6.26 (d, *J* = 6.0 Hz, 1H), 4.01 (s, 3H), 3.90 (s, 3H), 3.62 (s, 3H), 3.61 - 3.55 (m, 1H), 3.46 - 3.38 (m, 1H), 3.11 - 2.95 (m, 2H), 2.80 (dd, *J* = 16.5, 1.6 Hz, 1H), 2.58 (dd, *J* = 16.5, 2.3 Hz, 1H), 2.30 - 2.20 (m, 1H), 2.14 - 2.06 (m, 1H), 2.02 - 1.94 (m, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 198.0, 172.9, 171.2, 156.4, 151.6, 149.3, 131.1, 130.2, 128.5, 123.5, 118.3, 116.0, 113.8, 102.0, 67.8, 55.9, 53.9, 52.1, 48.8, 39.9, 29.6, 27.5, 24.3; IR (thin film) λ_{max} 3001, 2955, 1733, 1684, 1615, 1599, 1268, 1089 cm⁻¹; HRMS (EI) calcd for [C₂₃H₂₇O₇N₂]⁺: *m/z*, 443.1813 found 443.1821. Note: Compound **1.105** was isolated with 5-10% impurity.

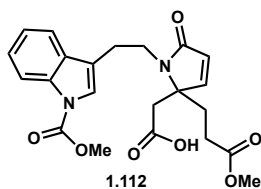


Sulfonamide 1.106. A 25 mL round-bottom flask was charged with **1.102** (200 mg, 0.530 mmol, 1.00 equiv) and THF (5.3 mL). The reaction mixture was cooled to 0 °C and potassium *t*-butoxide (214 mg, 1.91 mmol, 3.60 equiv) was added in one portion. After 10 min, benzenesulfonyl chloride (170 μ L, 1.33 mmol, 2.50 equiv) was added. The solution was allowed to stir, at which point the reaction mixture was quenched with 1 N HCl (5 mL), and warmed to room temperature and stirred for 24 h at this temperature, then quenched with saturated aqueous sodium bicarbonate (10 mL). The aqueous layer was extracted with ethyl acetate (2 x 5 mL). The combined organic layers were washed with brine (5 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. The resulting yellow solid was purified by column chromatography (1:1 hexanes/ethyl acetate) to afford **1.106** (123 mg, 52%) as a white crystalline solid, m. p. 200-201 °C. $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 8.00 (d, $J = 8.3$ Hz, 1H), 7.90 – 7.85 (m, 2H), 7.60 (d, $J = 7.6$ Hz, 1H), 7.57 (d, $J = 6.1$ Hz, 1H), 7.54 (t, $J = 7.5$ Hz, 1H), 7.46 – 7.42 (m, 2H), 7.38 (s, 1H), 7.33 (t, $J = 7.2$ Hz, 1H), 6.33 (d, $J = 6.1$ Hz, 1H), 3.53 – 3.50 (m, 2H), 3.10 – 3.04 (m, 2H), 2.56 – 2.47 (m, 2H), 2.47 – 2.43 (m, 2H), 2.16 – 2.06 (m, 2H), 1.55 – 1.51 (m, 2H); $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 207.7, 170.3, 148.6, 138.3, 135.3, 134.0, 130.8, 129.5, 128.1, 126.9, 125.2, 123.6, 123.6, 120.0, 119.7, 113.9, 66.5, 39.7, 38.8, 32.8, 24.4; **IR** (thin film) ν_{max} 3061, 2936, 2865, 1716, 1682, 1367, 1208, 1174, 1100 cm^{-1} ; **HRMS** (EI^+) calc'd for $[\text{C}_{25}\text{H}_{25}\text{O}_4\text{N}_2\text{S}]^+$: m/z , 449.1530 found 449.1527.

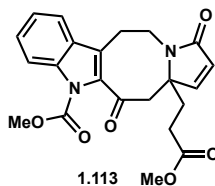


Representative procedure for enol carbonate 1.111. A 4 mL Schlenk tube was charged with LiCl (2 mg, 0.049 mmol, 1.1 equiv) and then flame-dried and cooled to room temperature under N_2 . THF (1 mL) and (+)-Bis[*(R)*-1-phenylethyl]amine (12 μ L, 0.054 mmol, 1.2 equiv) were then added to the Schlenk tube. The reaction mixture was cooled to -78 °C, and *n*-BuLi (2.4 M in hexanes, 20 μ L, 0.049 mmol, 1.1 equiv) was added dropwise over 5 min. After 30 min, a slurry of sulfonamide **1.106** (20 mg, 0.045 mmol, 1.0 equiv) in THF (1 mL) was added portionwise. After 2 h of stirring, the reaction mixture was transferred via cannula to a 10 mL round-bottom flask, also at -78 °C, containing allyl chloroformate (6 μ L, 0.054 mmol, 1.2 equiv) and THF (0.5 mL). The flask was allowed to warm to room temperature, and was stirred at this temperature for 12 h before the addition of dichloromethane (2 mL) and a 1:1 mixture of water/saturated aqueous ammonium chloride (3 mL). The aqueous layer was extracted with dichloromethane (2 x 2 mL). The combined organic layers were dried over sodium

sulfate, filtered, and concentrated *in vacuo*. The resultant yellow oil was purified using column chromatography (1:1 hexanes/ethyl acetate) to afford **1.111** (14 mg, 60%) as a clear oil. Enantiomeric excess was determined by HPLC analysis (Chiralpak AD-H column, 87.5:12.5 hexanes/ethanol, 1 mL/min) t_r 41.7 min (minor), 49.6 min (major): 38% *ee*. $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.99 (d, $J = 8.2$ Hz, 1H), 7.89 – 7.84 (m, 2H), 7.62 (d, $J = 7.6$ Hz, 1H), 7.52 – 7.50 (m, 1H), 7.47 – 7.41 (m, 2H), 7.38 (s, 1H), 7.31 – 7.29 (m, 2H), 6.17 (d, $J = 6.0$ Hz, 1H), 6.01 – 5.89 (m, 1H), 5.43 (d, $J = 5.8$ Hz, 1H), 5.42 – 5.35 (m, 1H), 5.33 – 5.28 (m, 1H), 4.66 (dt, $J = 5.8, 1.3$ Hz, 2H), 3.51 (t, $J = 7.8$ Hz, 2H), 3.15 – 3.00 (m, 2H), 2.51 – 2.43 (m, 2H), 2.40 – 2.32 (m, 1H), 2.10 (td, $J = 12.0, 6.6$ Hz, 1H), 1.68 – 1.66 (m, 1H), 1.45 – 1.37 (m, 1H), 1.27 – 1.25 (m, 1H); $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 170.9, 153.3, 150.9, 147.4, 138.4, 135.3, 133.9, 131.2, 130.9, 129.4, 126.9, 126.7, 125.1, 123.6, 123.5, 120.2, 119.8, 119.7, 113.9, 112.2, 69.2, 65.7, 39.8, 30.3, 30.2, 25.9, 24.5; **IR** (thin film) ν_{max} 3063, 2929, 2855, 1754, 1691, 1367, 1245, 1174, 1100 cm^{-1} ; **HRMS** (EI^+) calc'd for $[\text{C}_{29}\text{H}_{29}\text{O}_6\text{N}_2\text{S}]^+$: m/z , 533.1741 found 533.1739.

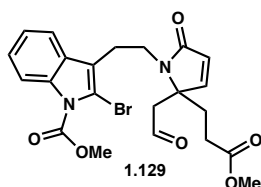


Carboxylic acid 1.112: A 10 mL flask was charged with aldehyde **1.90** (35 mg, 0.085 mmol, 1.0 equiv), THF (2.8 mL), 1N HCl (0.7 mL), *t*-BuOH (0.7 mL), and sodium phosphate (120 mg, 0.85 mmol, 10 equiv) and cooled to 0 °C. 2-Methyl-2-butene (40 μL , 0.85 mmol, 10 equiv) and sodium chlorite (15 mg, 0.17 mmol, 2.0 equiv) were added sequentially to the reaction mixture, and the resultant solution was then warmed to room temperature and stirred for 14 h. The reaction mixture was then quenched by addition of water (5 mL) and the aqueous layer was extracted with dichloromethane (3 x 10 mL). The combined organic layers were washed with brine, dried over sodium sulfate, filtered and concentrated *in vacuo*. The resultant carboxylic acid **1.112** (37 mg, 98%) was used without further purification.

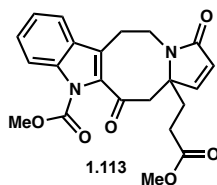


Tetracycle 1.113: A 20 mL vial was charged with crude carboxylic acid **1.112** (37 mg, 0.085 mmol, 1.0 equiv) and polyphosphoric acid (1.7 mL). The vial was then sealed, heated to 80 °C, and held at this temperature for 3 h. After this period, the reaction mixture was cooled to room temperature and quenched with ice (10 g). The aqueous layer was extracted with dichloromethane (3 x 10 mL), and the combined organic layers were washed sequentially with saturated aqueous sodium bicarbonate and brine, dried

over sodium sulfate, filtered, and concentrated *in vacuo*. The crude material was purified by column chromatography (1:1 hexanes/ethyl acetate) to afford tetracycle **1.113** (14 mg, 43% over 2 steps) as a colorless oil. $^1\text{H NMR}$ (600 MHz, CDCl_3) δ 7.90 (d, $J = 8.3$ Hz, 1H), 7.69 (d, $J = 8.0$ Hz, 1H), 7.49 (t, $J = 7.6$ Hz, 1H), 7.33 (t, $J = 7.7$ Hz, 1H), 7.00 (d, $J = 6.0$ Hz, 1H), 6.14 (d, $J = 5.9$ Hz, 1H), 4.31 – 4.24 (m, 1H), 3.95 (s, 3H), 3.70 (s, 3H), 3.64 (d, $J = 14.2$ Hz, 1H), 3.48 (dd, $J = 14.1, 4.3$ Hz, 1H), 3.44 – 3.37 (m, 1H), 3.31 (dd, $J = 14.3, 6.2$ Hz, 1H), 3.01 (d, $J = 13.7$ Hz, 1H), 2.46 – 2.39 (m, 1H), 2.35 – 2.29 (m, 1H), 2.10 (t, $J = 7.7$ Hz, 2H); $^{13}\text{C NMR}$ (150 MHz, CDCl_3) δ 186.1, 172.8, 170.7, 152.0, 149.8, 138.2, 135.5, 128.8, 127.6, 127.5, 126.3, 123.4, 120.5, 114.1, 67.0, 54.4, 52.0, 49.3, 35.8, 29.6, 27.8, 23.3; **IR** (thin film) ν_{max} 3056, 2953, 1738, 1690, 1659, 1604, 1247, 1108 cm^{-1} ; **HRMS** (EI^+) calc'd for $[\text{C}_{22}\text{H}_{22}\text{N}_2\text{O}_6+\text{Na}]^+$: m/z , 433.1374 found 433.1370. Note: Compound **1.113** was isolated with 10% impurity.

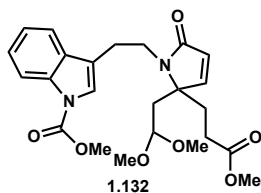


Bromoindole 1.129: To a 4 mL vial was charged with indole **1.90** (42 mg, 0.10 mmol, 1.0 equiv) and dichloromethane (1.0 mL). To this solution was added freshly recrystallized N-bromosuccinimide (18 mg, 0.10 mmol, 1.0 equiv) in one portion. The vial was sealed, heated to 40 °C, and held at this temperature for 3 h, at which point it was cooled to room temperature. The reaction was quenched with saturated aqueous sodium thiosulphate (3 mL), and the aqueous layer was extracted with dichloromethane (3 x 3 mL). The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. The resultant material was purified by column chromatography (1:1 hexanes/ethyl acetate) to give bromoindole **1.129** (30 mg, 60%) as a colorless oil. $^1\text{H NMR}$ (600 MHz, CDCl_3) δ 9.46 (s, 1H), 8.08 (d, $J = 7.7$ Hz, 1H), 7.79 (d, $J = 7.6$ Hz, 1H), 7.37 – 7.31 (m, 1H), 7.14 (d, $J = 5.8$ Hz, 1H), 6.29 (d, $J = 6.0$ Hz, 1H), 4.12 (s, 3H), 3.65 (s, 3H), 3.59 – 3.51 (m, 1H), 3.39 – 3.31 (m, 1H), 3.17 (t, $J = 8.6$ Hz, 1H), 2.86 (d, $J = 16.8$ Hz, 1H), 2.63 (d, $J = 16.7$ Hz, 1H), 2.34 – 2.27 (m, 1H), 2.17 – 2.10 (m, 1H), 2.01 (dd, $J = 14.9, 7.3$ Hz, 1H); $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 197.8, 172.7, 171.1, 151.2, 149.1, 136.2, 128.7, 128.4, 125.0, 123.7, 120.8, 118.6, 115.4, 109.3, 67.6, 53.9, 51.9, 48.6, 38.5, 29.4, 27.4, 24.2; **IR** (thin film) ν_{max} 3055, 2955, 1732, 1681, 1593, 1558, 1447, 1104 cm^{-1} ; **HRMS** (EI^+) calc'd for $[\text{C}_{22}\text{H}_{23}\text{N}_2\text{O}_6+\text{Na}]^+$: m/z , 513.0632 found 513.0635. Note: Compound **1.129** was isolated with 5% impurity.

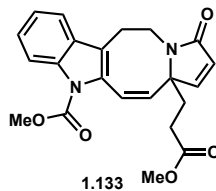


Tetracycle 1.113: A 4 mL Schlenk tube was charged with aldehyde **1.129** (43 mg, 0.088 mmol, 1.0 equiv), *t*-dodecylmercaptan (60 μL , 0.27 mmol, 3.0 equiv), and toluene (4.4

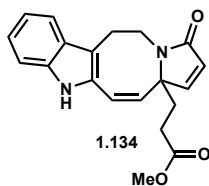
mL). To this was added 1,1'-azobis(cyclohexanecarbonitrile) (65 mg, 0.27 mmol, 3.0 equiv). The reaction mixture was degassed by three 4 min freeze-pump-thaw cycles and placed under a nitrogen atmosphere. The Schlenk tube was sealed, and the solution was heated to 110 °C and held at this temperature for 12 h. After this period, it was cooled to room temperature and concentrated *in vacuo*. The crude material was purified by column chromatography (1:1 hexanes/ethyl acetate) to give **1.113** (19 mg, 46%) as a colorless oil. ¹H NMR (600 MHz, CDCl₃) δ 7.90 (d, *J* = 8.3 Hz, 1H), 7.69 (d, *J* = 8.0 Hz, 1H), 7.49 (t, *J* = 7.6 Hz, 1H), 7.33 (t, *J* = 7.7 Hz, 1H), 7.00 (d, *J* = 6.0 Hz, 1H), 6.14 (d, *J* = 5.9 Hz, 1H), 4.31 – 4.24 (m, 1H), 3.95 (s, 3H), 3.70 (s, 3H), 3.64 (d, *J* = 14.2 Hz, 1H), 3.48 (dd, *J* = 14.1, 4.3 Hz, 1H), 3.44 – 3.37 (m, 1H), 3.31 (dd, *J* = 14.3, 6.2 Hz, 1H), 3.01 (d, *J* = 13.7 Hz, 1H), 2.46 – 2.39 (m, 1H), 2.35 – 2.29 (m, 1H), 2.10 (t, *J* = 7.7 Hz, 2H); ¹³C NMR (150 MHz, CDCl₃) δ 186.1, 172.8, 170.7, 152.0, 149.8, 138.2, 135.5, 128.8, 127.6, 127.5, 126.3, 123.4, 120.5, 114.1, 67.0, 54.4, 52.0, 49.3, 35.8, 29.6, 27.8, 23.3; IR (thin film) ν_{max} 3056, 2953, 1738, 1690, 1659, 1604, 1247, 1108 cm⁻¹; HRMS (EI⁺) calc'd for [C₂₂H₂₂N₂O₆+Na]⁺: *m/z*, 433.1374 found 433.1370. Note: Compound **1.113** was isolated with 10% impurity.



Acetal 1.132: A 100 mL round-bottom flask was charged with aldehyde **1.90** (2.27 g, 5.50 mmol, 1.00 equiv), methanol (55 mL), trimethyl orthoformate (1.82 mL, 16.5 mmol, 3.00 equiv), and Amberlyst[®]-15 resin (25 mg, 0.01 wt equiv). The reaction mixture was stirred for 48 h at room temperature, at which point TLC indicated the consumption of **1.90**. The reaction mixture was filtered through Celite and the residue was washed with ethyl acetate (15 mL). The filtrate was concentrated *in vacuo* and the resulting oil was purified by column chromatography (gradient of 2:1 to 1:3 hexanes/ethyl acetate) to give acetal **1.132** (2.09 g, 83%) as a colorless oil. ¹H NMR (600 MHz, CDCl₃) 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); ¹³C NMR (150 MHz, CDCl₃) δ 173.0, 171.6, 151.4, 151.0, 135.6, 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 (thin film) ν_{max} 3401, 2953, 1736, 1686, 1456, 1381, 1260, 1124, 1095, 814, 765 cm⁻¹; HRMS (EI⁺) calc'd for [C₂₄H₃₀N₂O₇]⁺: *m/z*, 458.2053 found 458.2060.

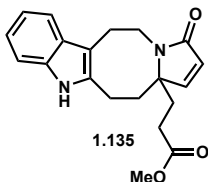


Tetracycline 1.133: An 25 mL Schlenk flask was charged with acetal **1.132** (85 mg, 0.19 mmol, 1.0 equiv), Amberlyst[®]-15 resin (43 mg, 0.5 wt equiv), and 1,2-dichloroethane (2.3 mL) and sealed. The Schlenk flask was heated to 65 °C and held at this temperature for 48 h, then cooled to room temperature. The reaction mixture was filtered through celite and concentrated *in vacuo*. The crude product was purified by column chromatography (gradient of 1:1 to 1:3 hexanes/ethyl acetate) to give tetracycline **1.133** (39 mg, 54%) as a colorless oil along with aldehyde **1.90** (18 mg, 23%) as a colorless solid, m. p. 133 - 134 °C. ¹H NMR (600 MHz, CDCl₃) 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); ¹³C NMR (150 MHz, CDCl₃) 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; IR (thin film) ν_{max} 3056, 2953, 1789, 1731, 1682, 1455, 1106 cm⁻¹; HRMS (EI⁺) calc'd for [C₂₂H₂₂N₂O₅]⁺: *m/z*, 394.1529 found 394.1534.



Tetracycline 1.134: A 10 mL round-bottom flask was charged with tetracycline **1.133** (60 mg, 0.15 mmol, 1.0 equiv) and methanol (3 mL). The reaction mixture was cooled to 0 °C, and potassium *t*-butoxide (34 mg, 0.30 mmol, 2.0 equiv) was added in one portion. The resultant solution was stirred at 0 °C for 2 h, at which time TLC showed consumption of **1.133**. The reaction mixture was quenched with saturated aqueous 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, filtered, and concentrated *in vacuo*. The resultant material was purified by column chromatography (1:1 hexanes/ethyl acetate) to give **1.134** (42 mg, 82%) as a colorless oil. ¹H NMR (600 MHz, CDCl₃) 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); ¹³C NMR (150 MHz, CDCl₃) δ 173.1, 172.1, 150.8, 136.3, 132.3, 128.3, 127.2, 125.5, 124.3, 119.0, 118.6, 117.6, 111.2, 110.0, 52.4,

51.4, 37.7, 30.3, 26.9, 22.5. **IR** (thin film) ν_{\max} 3291, 2950, 1737, 1678, 1439, 1375, 1176, 912, 813, 738 cm^{-1} ; **HRMS** (EI^+) calc'd for $[\text{C}_{20}\text{H}_{20}\text{N}_2\text{O}_3]^+$: m/z , 336.1474, found 336.1468.

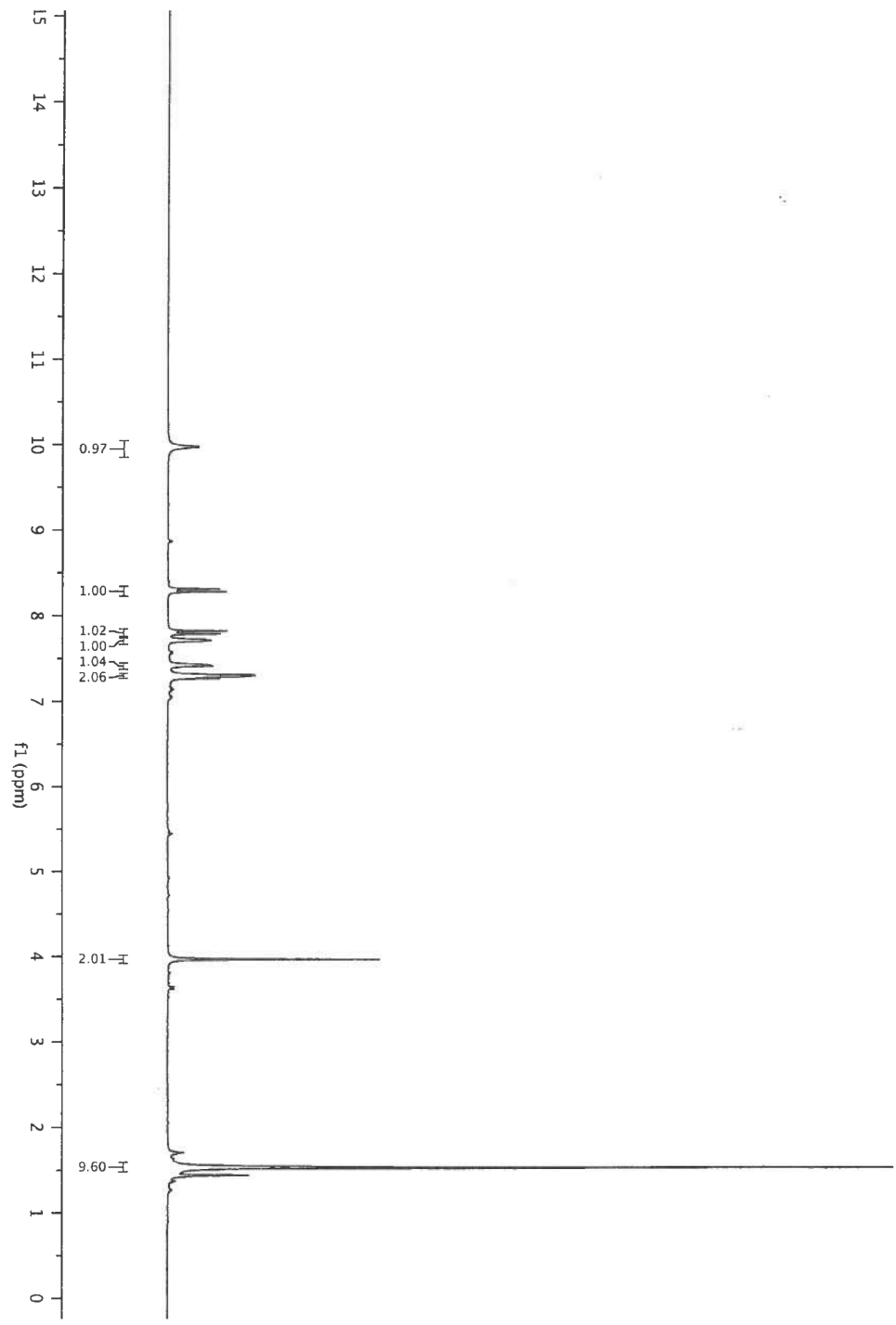
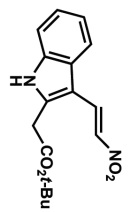


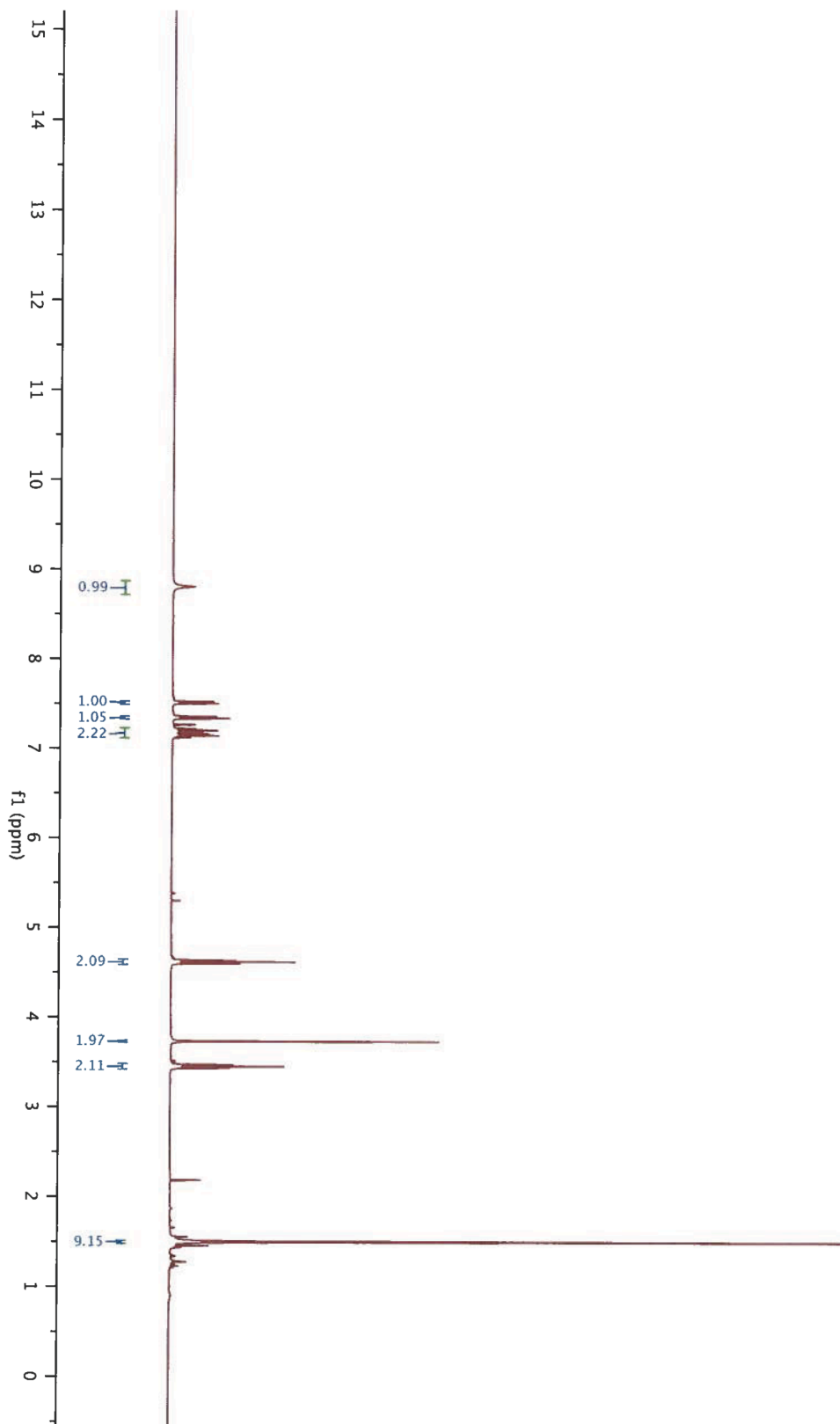
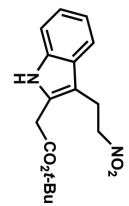
Tetracycle 1.135: An 24 mL Schlenk flask was charged with tetracycle **1.134** (10 mg, 0.0029 mmol, 1.0 equiv) and dichloroethane (3 mL). To this solution was added triethylsilane (45 μL , 0.29 mmol, 10 equiv) and methanesulfonic acid (10 μL , 0.15 mmol, 5.0 equiv). The Schlenk tube was sealed and heated to 60 $^{\circ}\text{C}$ and held at this temperature for 16 h, then cooled to room temperature. Triethylamine (50 μL) was added, and the reaction mixture was concentrated *in vacuo*. The resulting material was purified by silica gel chromatography (1:1 hexanes/ethyl acetate) to give **1.135** (7 mg, 65%) as a colorless oil. **¹H 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); **¹³C NMR** (150 MHz, CDCl_3) δ 172.8, 170.1, 149.8, 136.6, 132.2, 127.6, 123.9, 123.0, 119.2, 115.2, 112.2, 110.1, 67.8, 52.0, 41.7, 39.9, 29.1, 27.8, 27.7, 23.9; **HRMS** (EI^+) calc'd for $[\text{C}_{20}\text{H}_{22}\text{N}_2\text{O}_3]^+$: m/z , 338.1630 found 338.1625. Note: Compound **1.135** was isolated with 5% impurity.

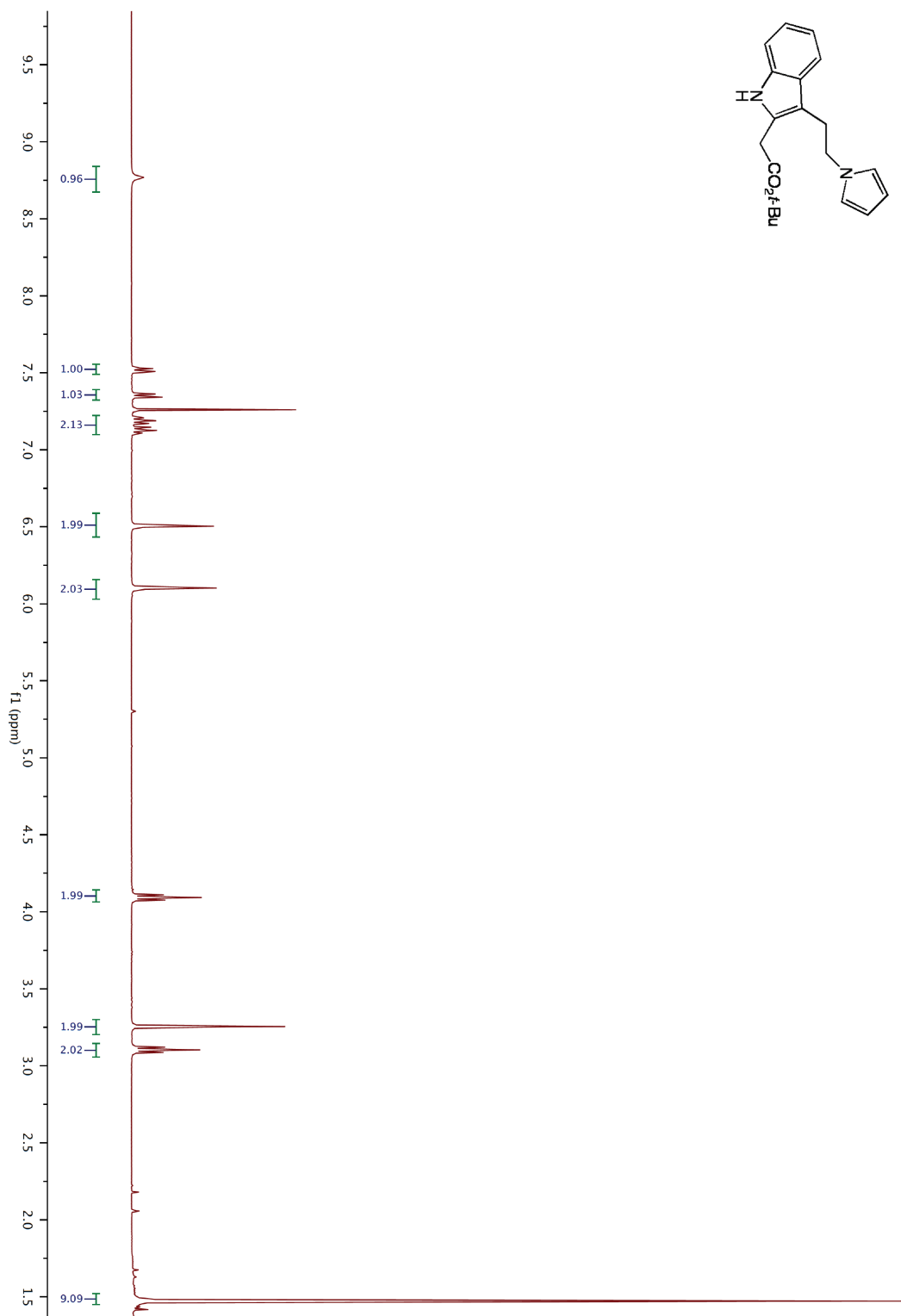
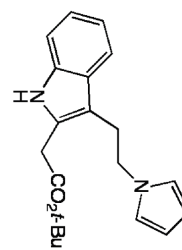
1.9 References and Notes

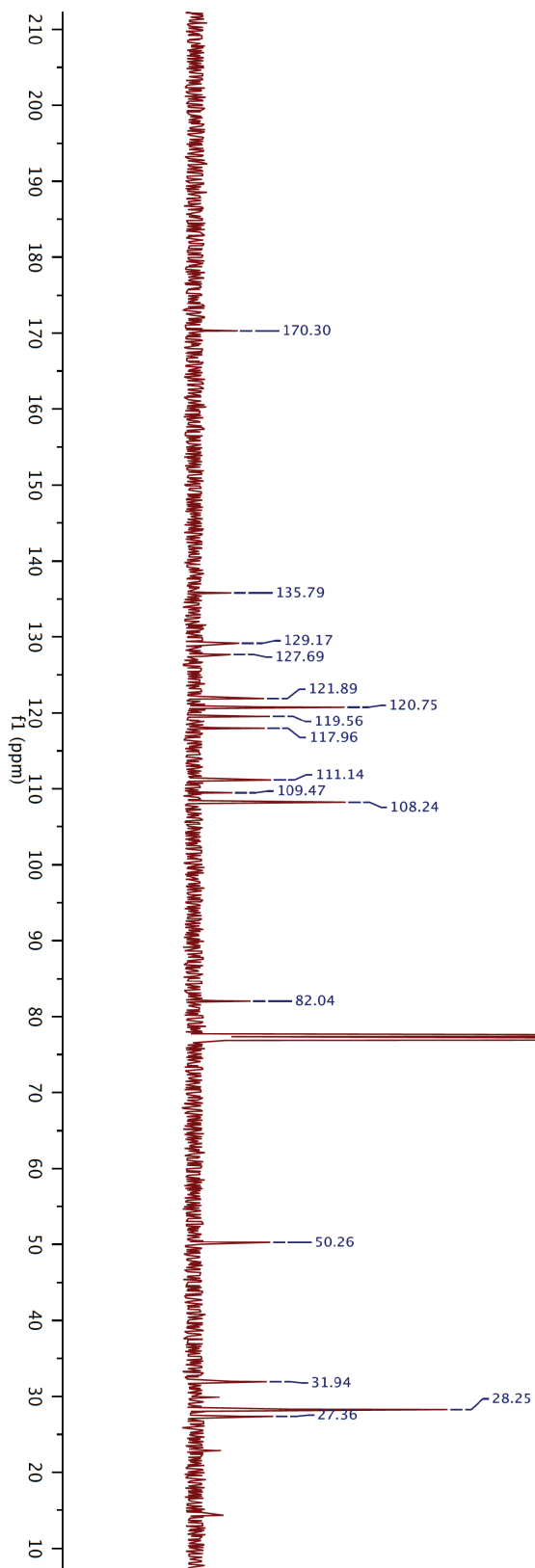
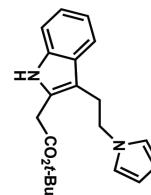
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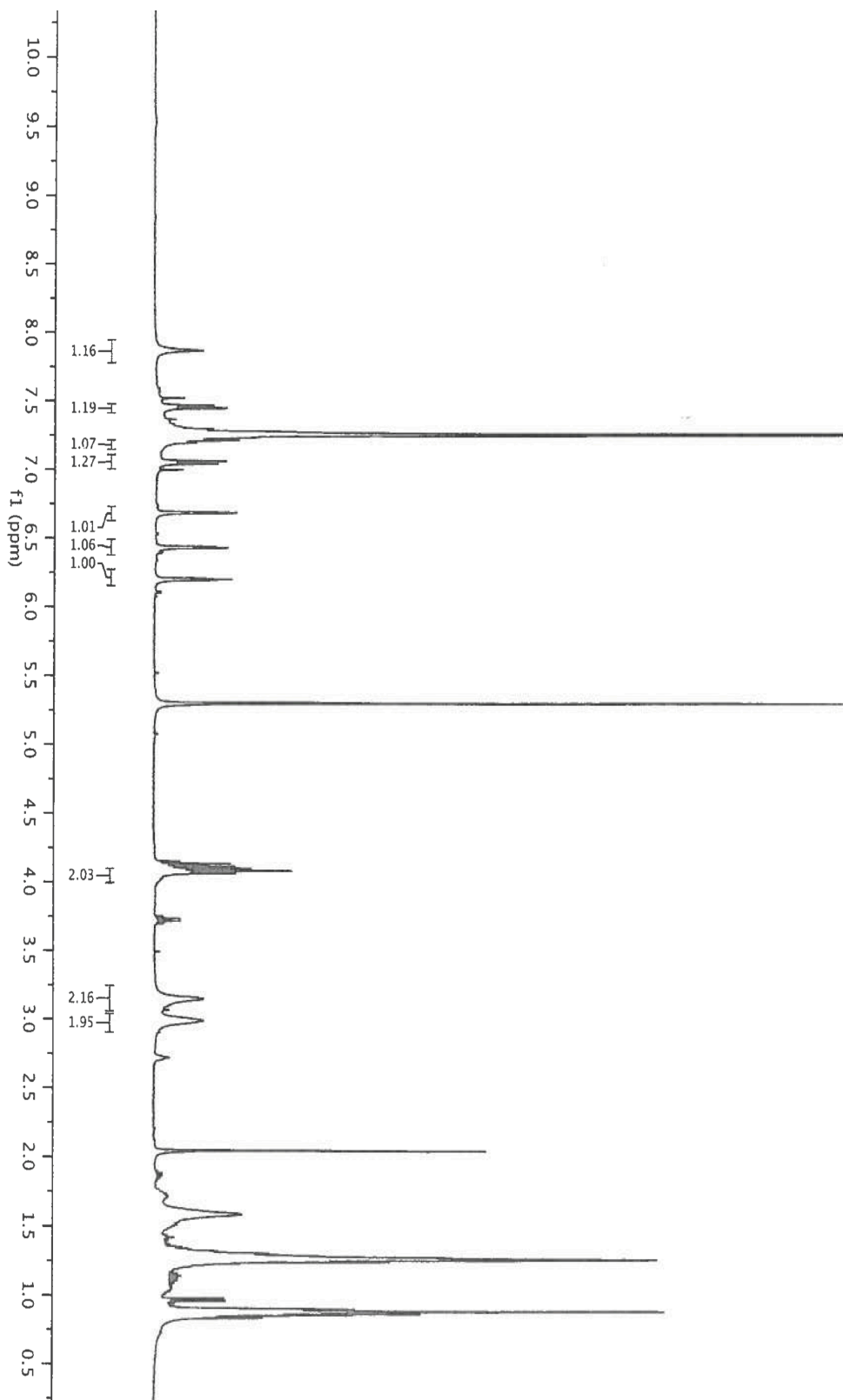
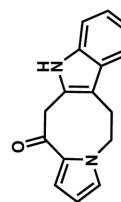
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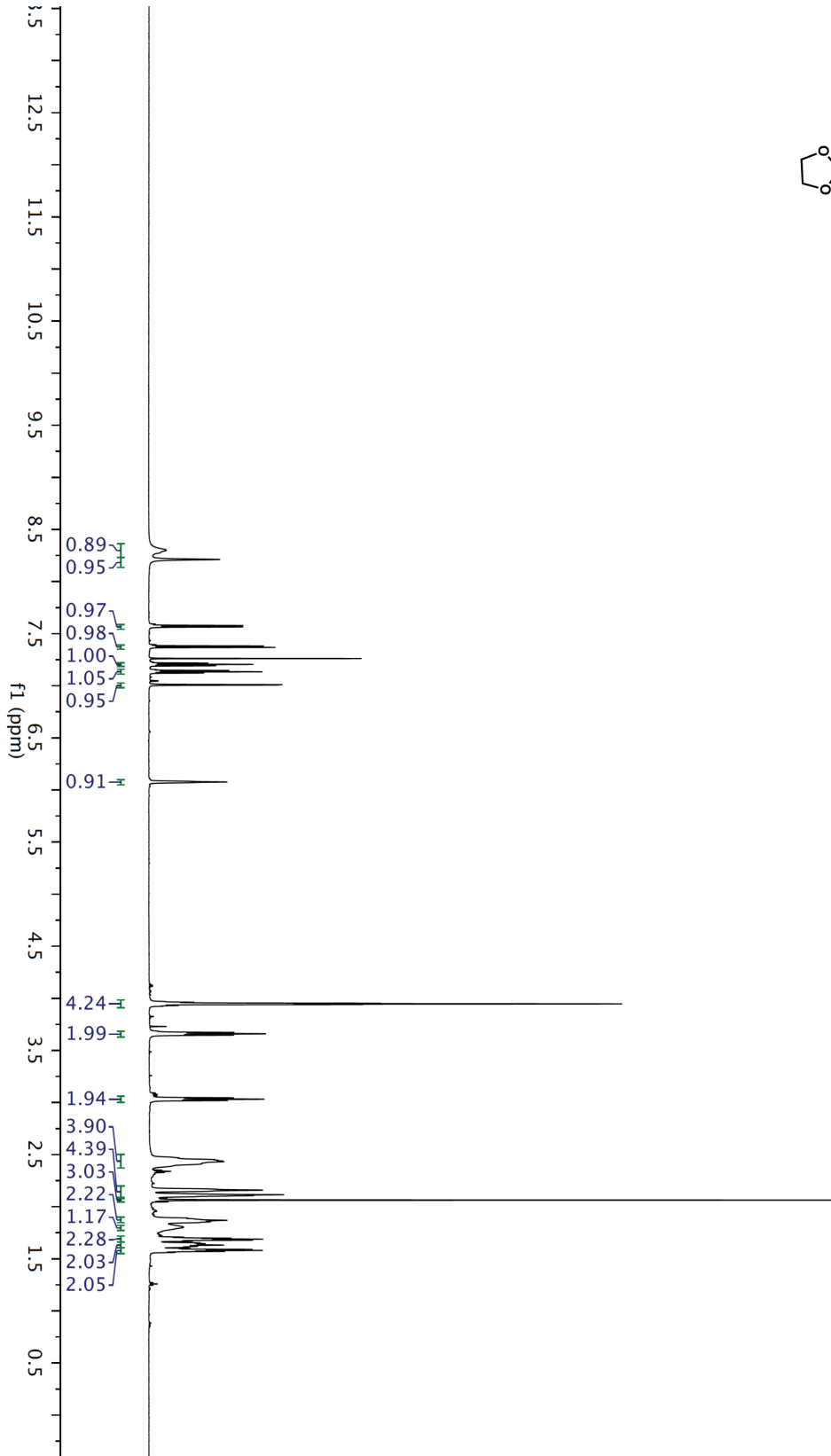
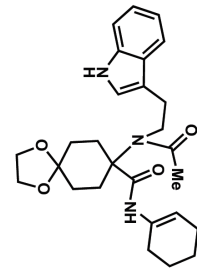


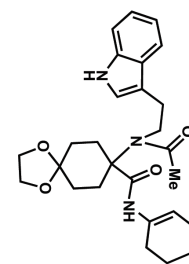
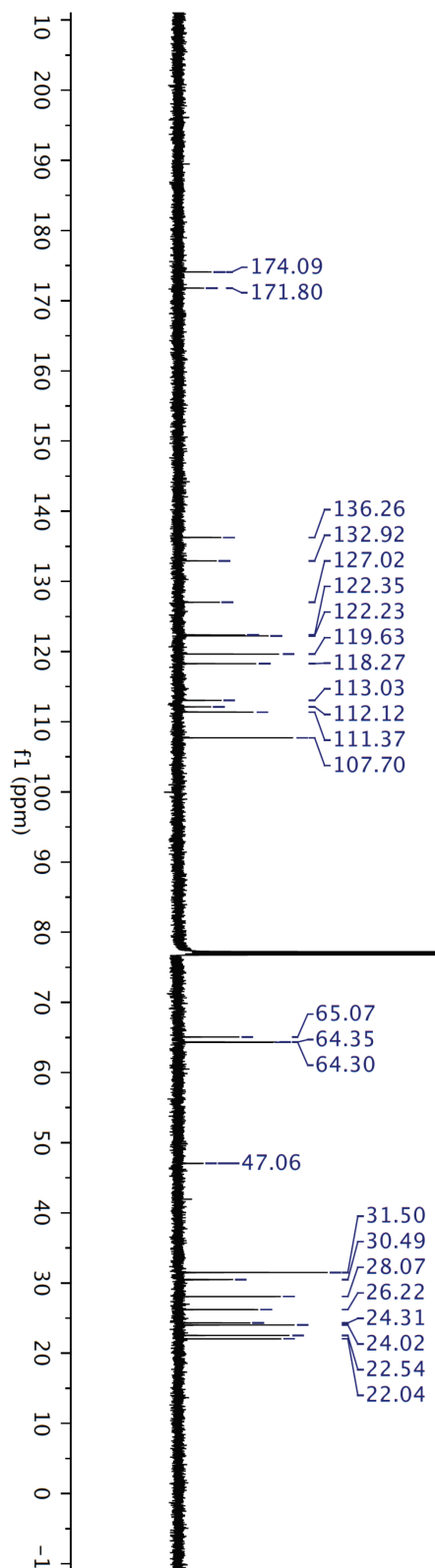


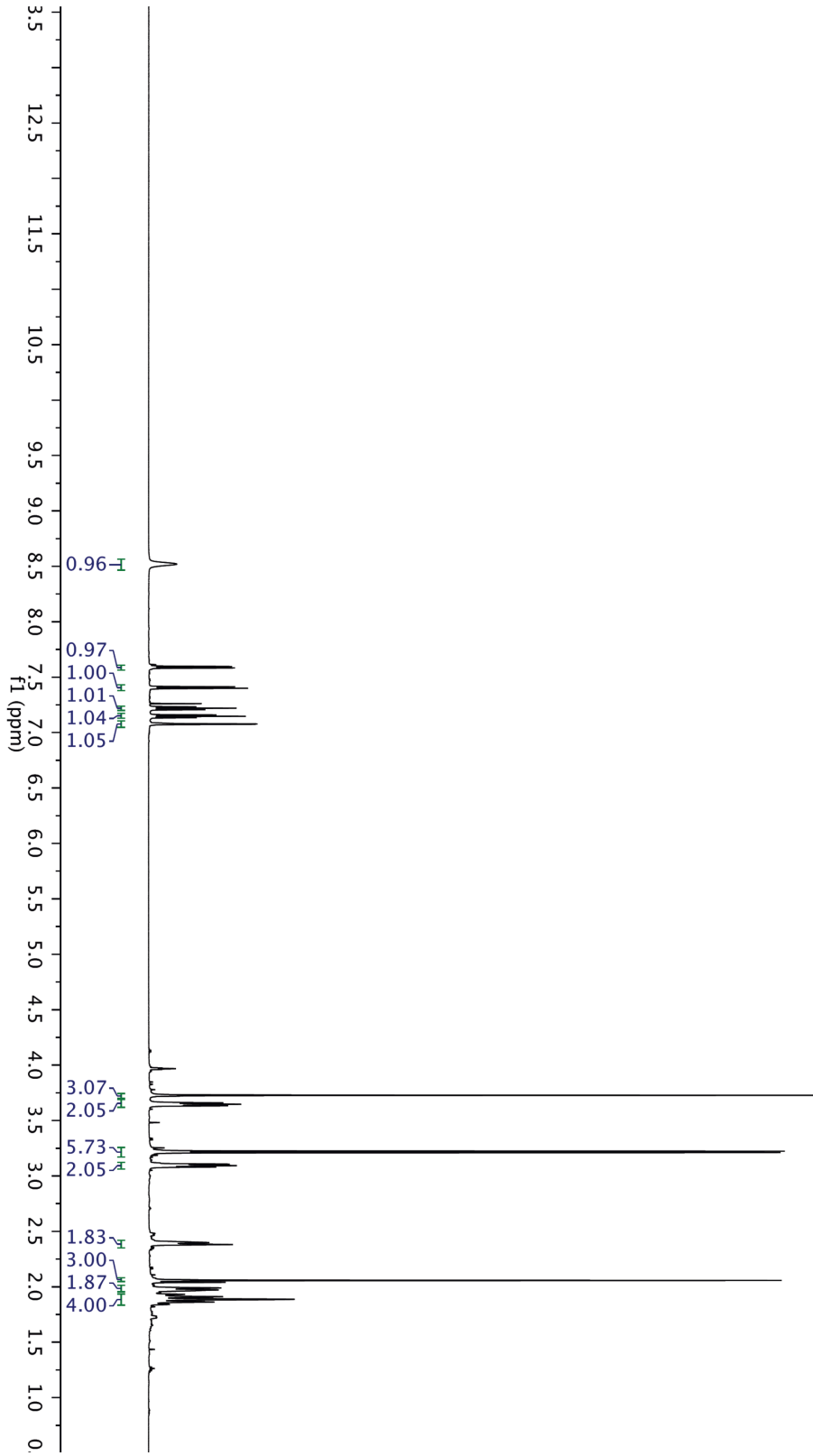
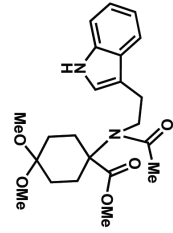


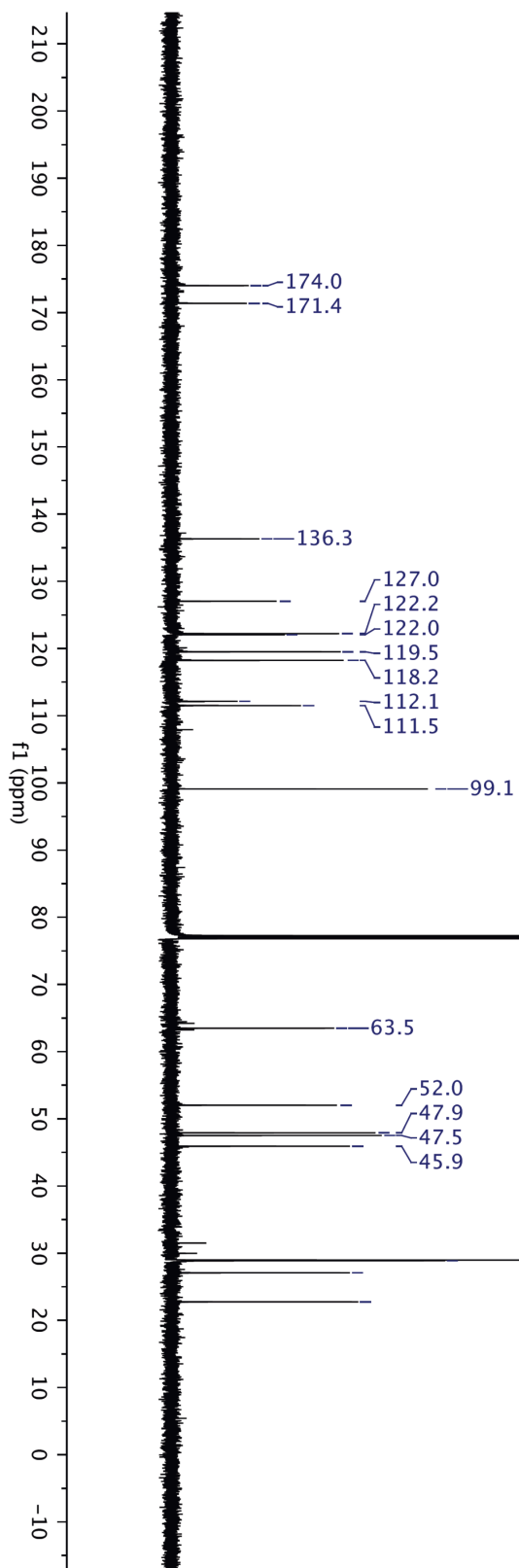
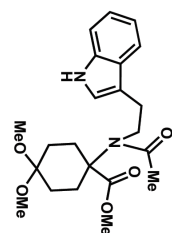


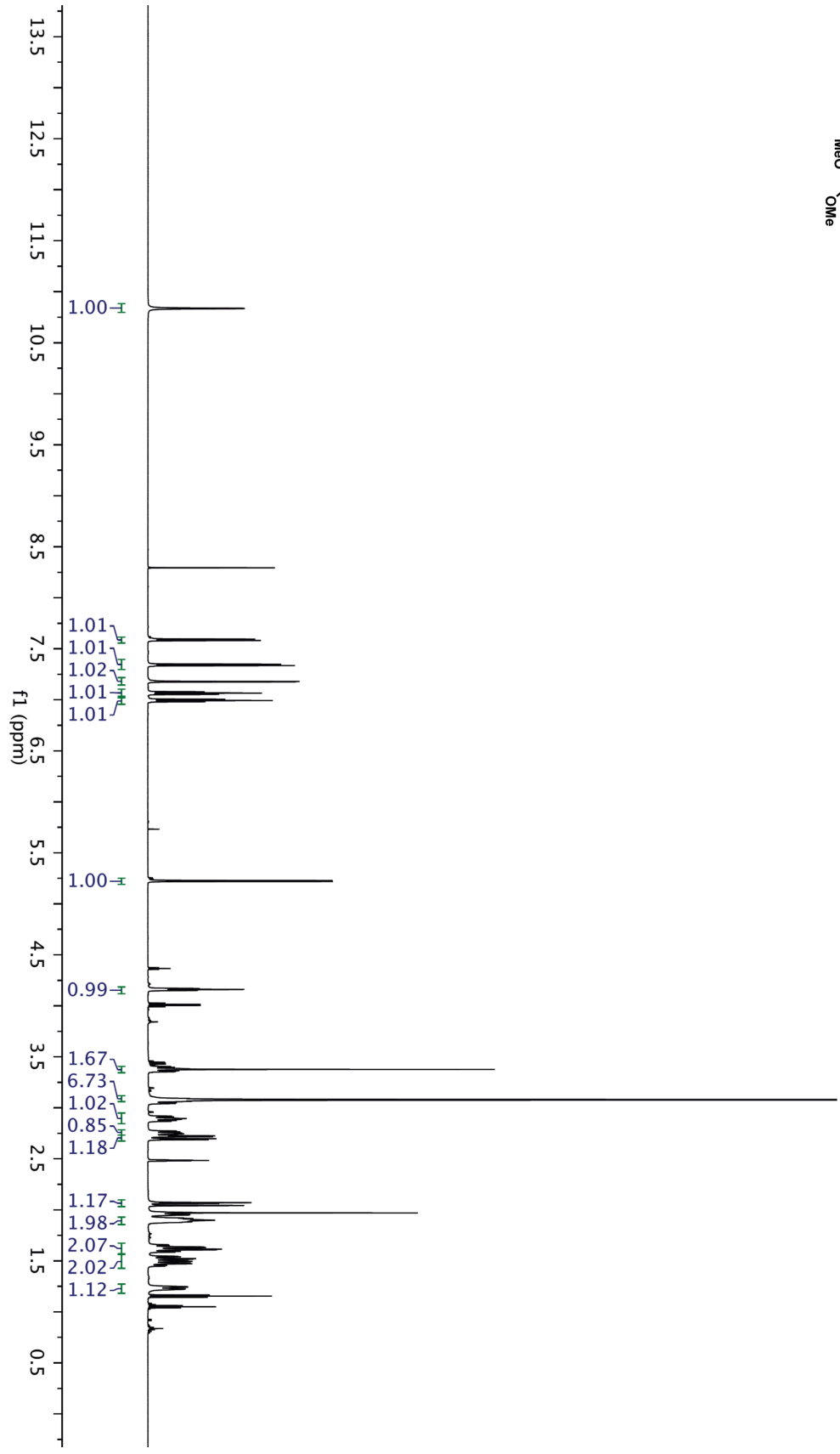
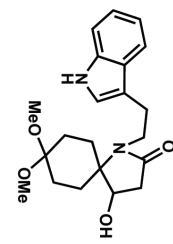


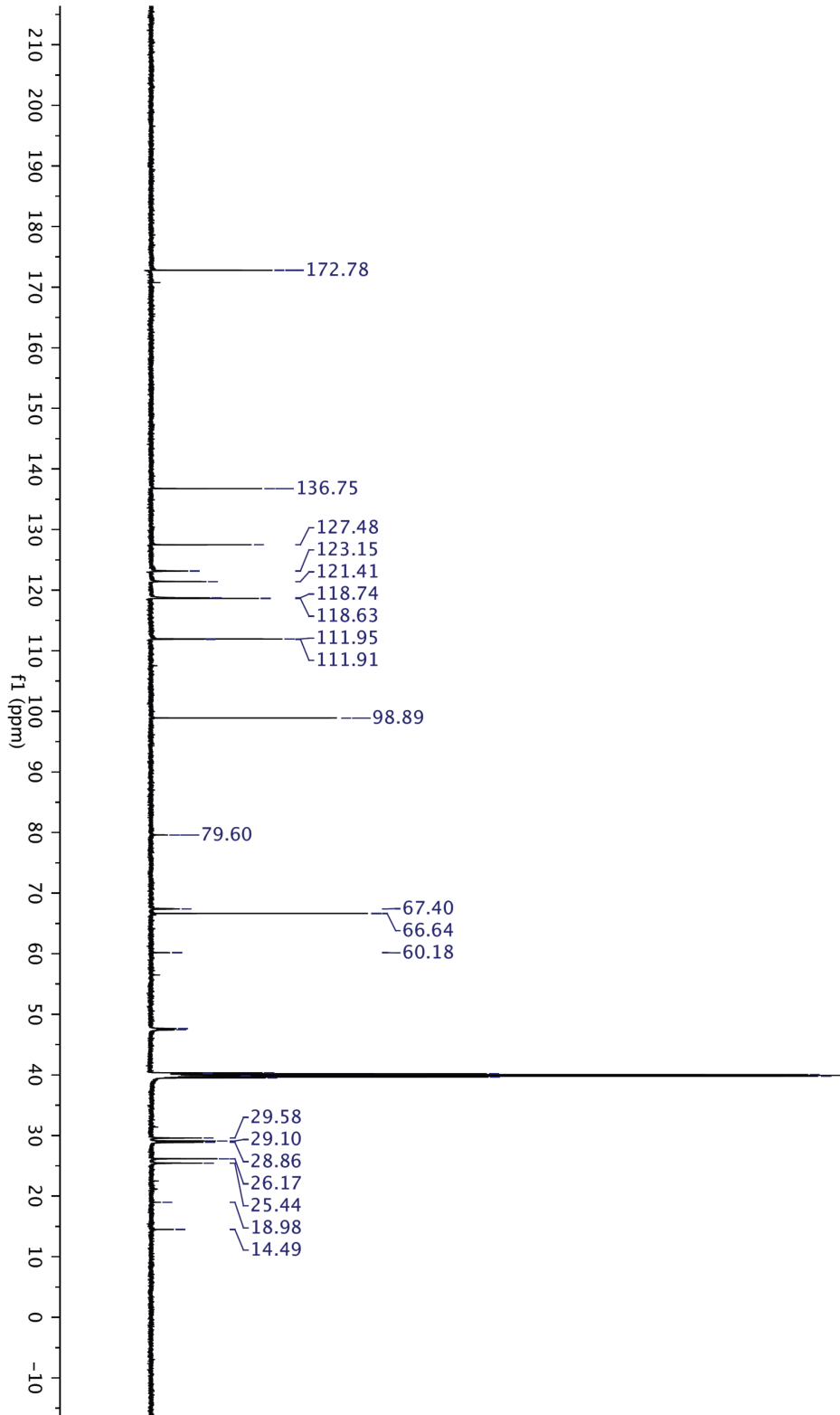
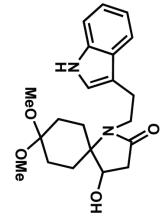


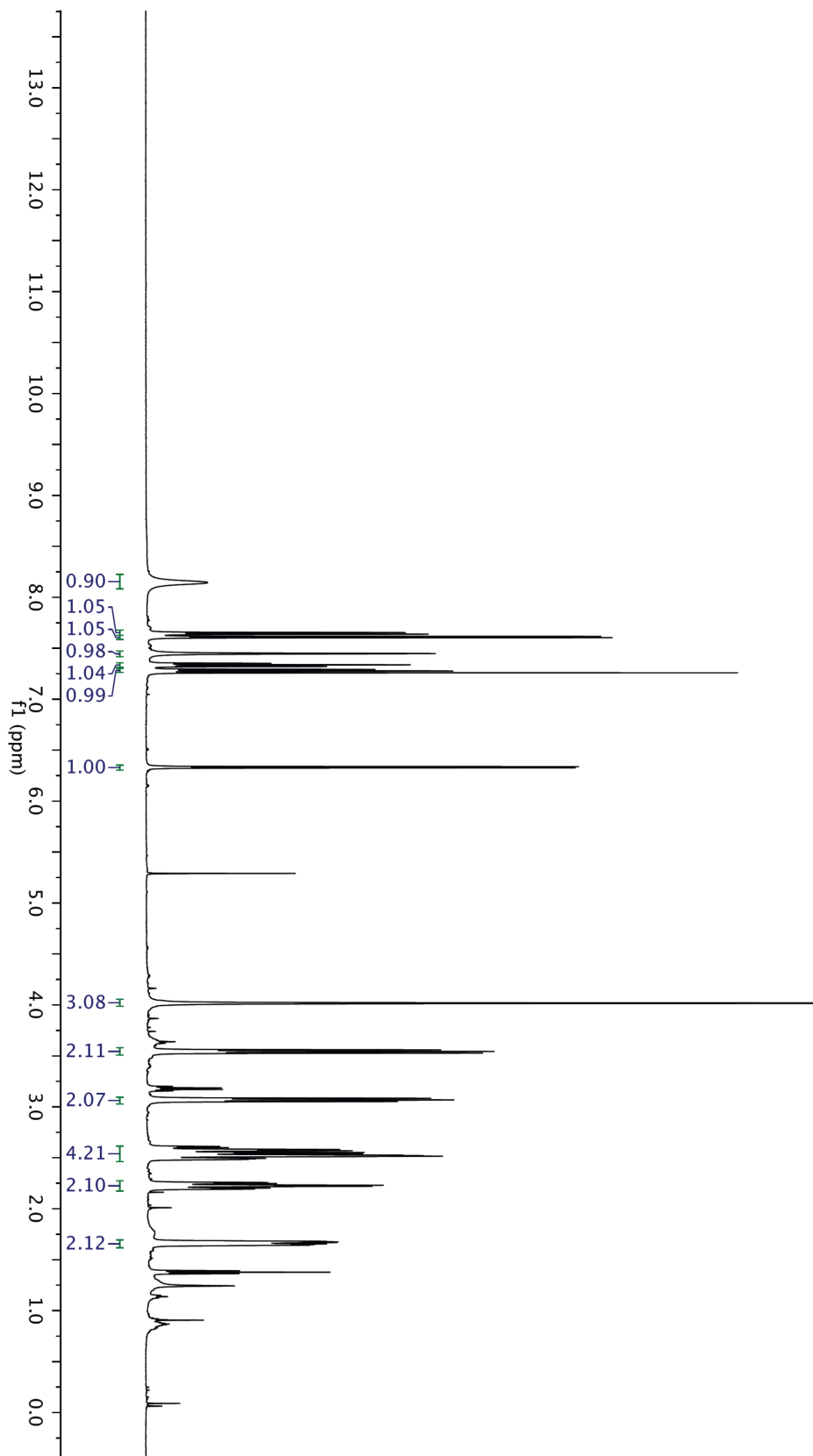
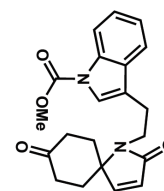


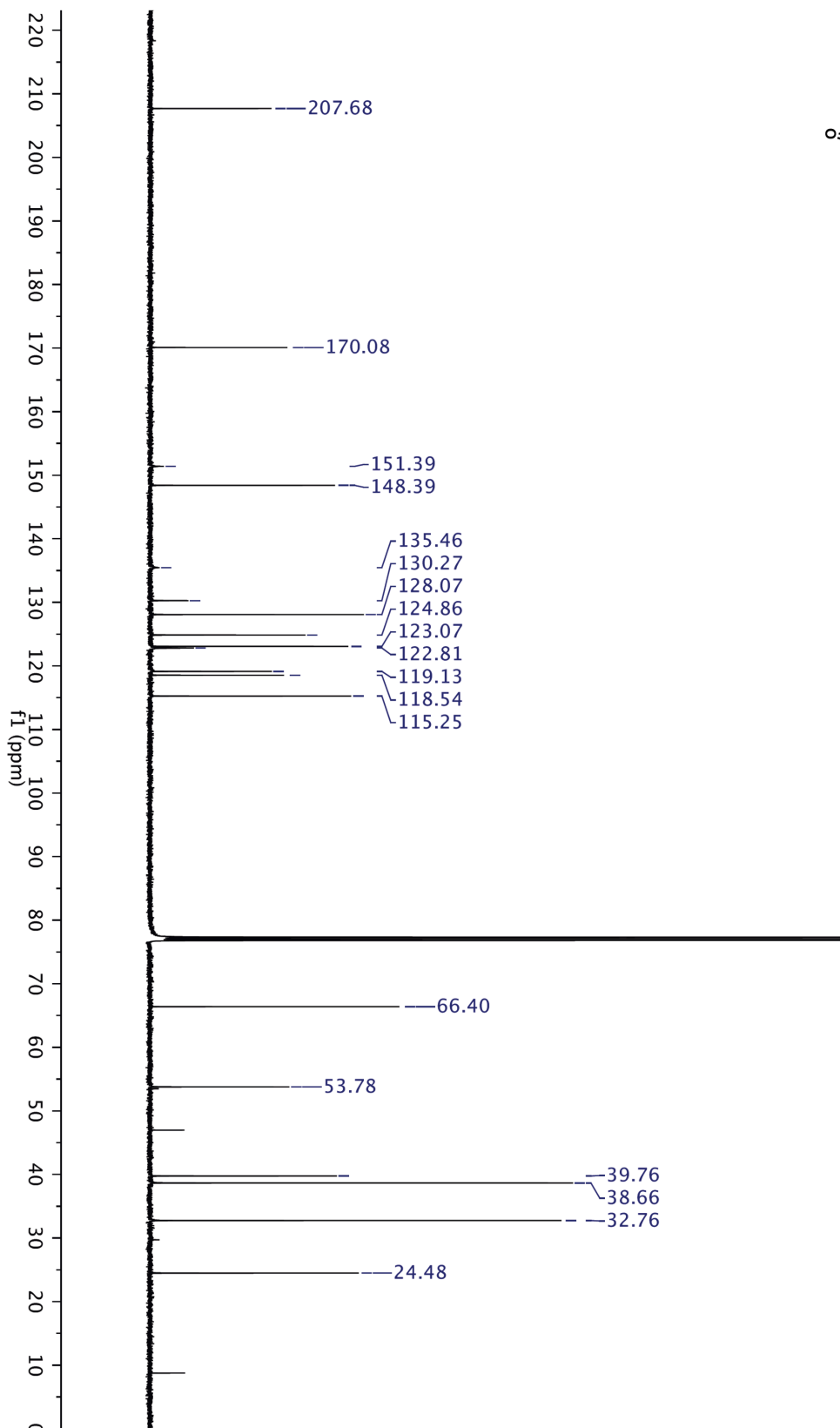
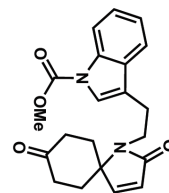


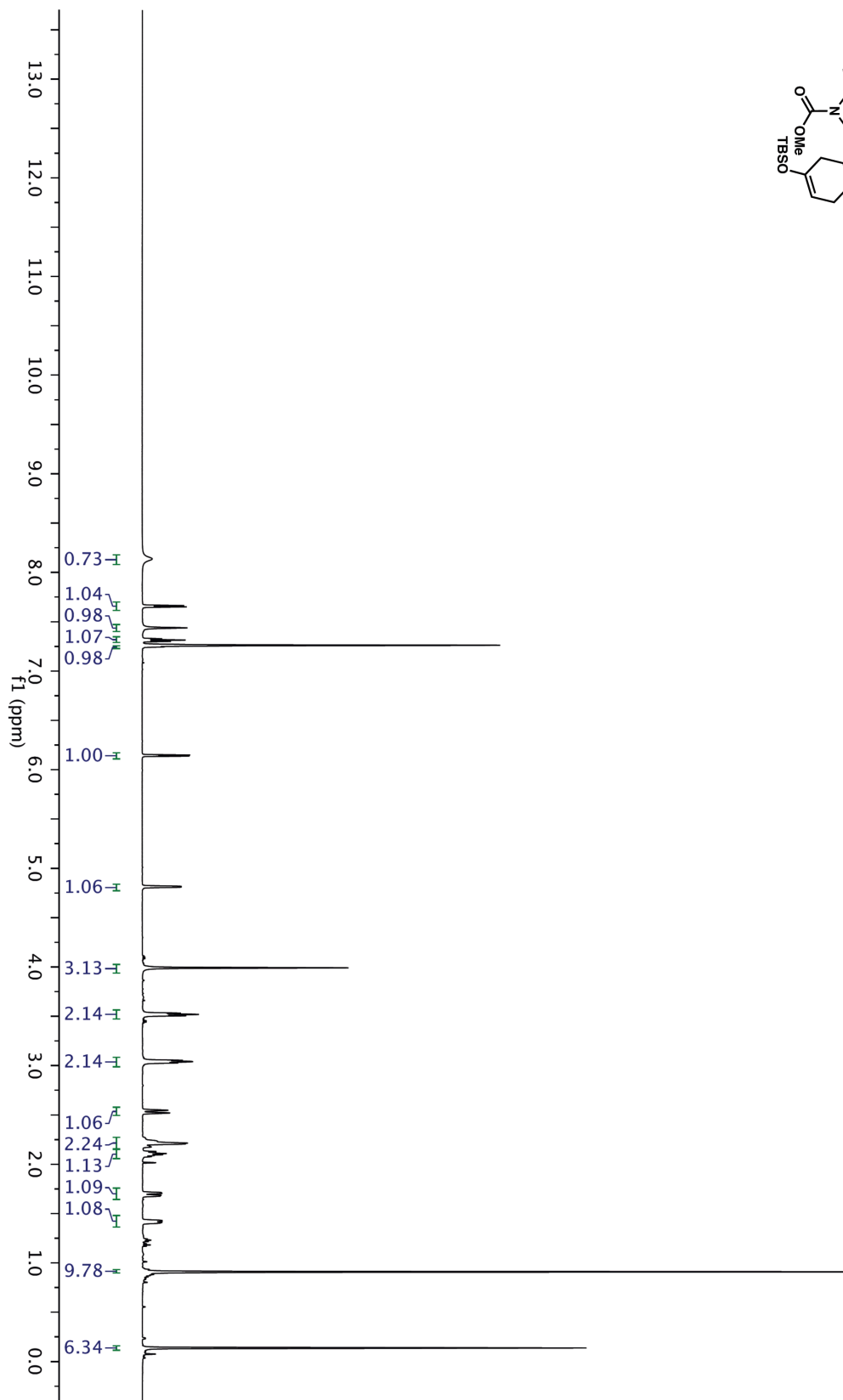
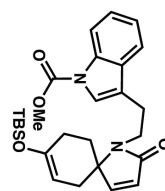


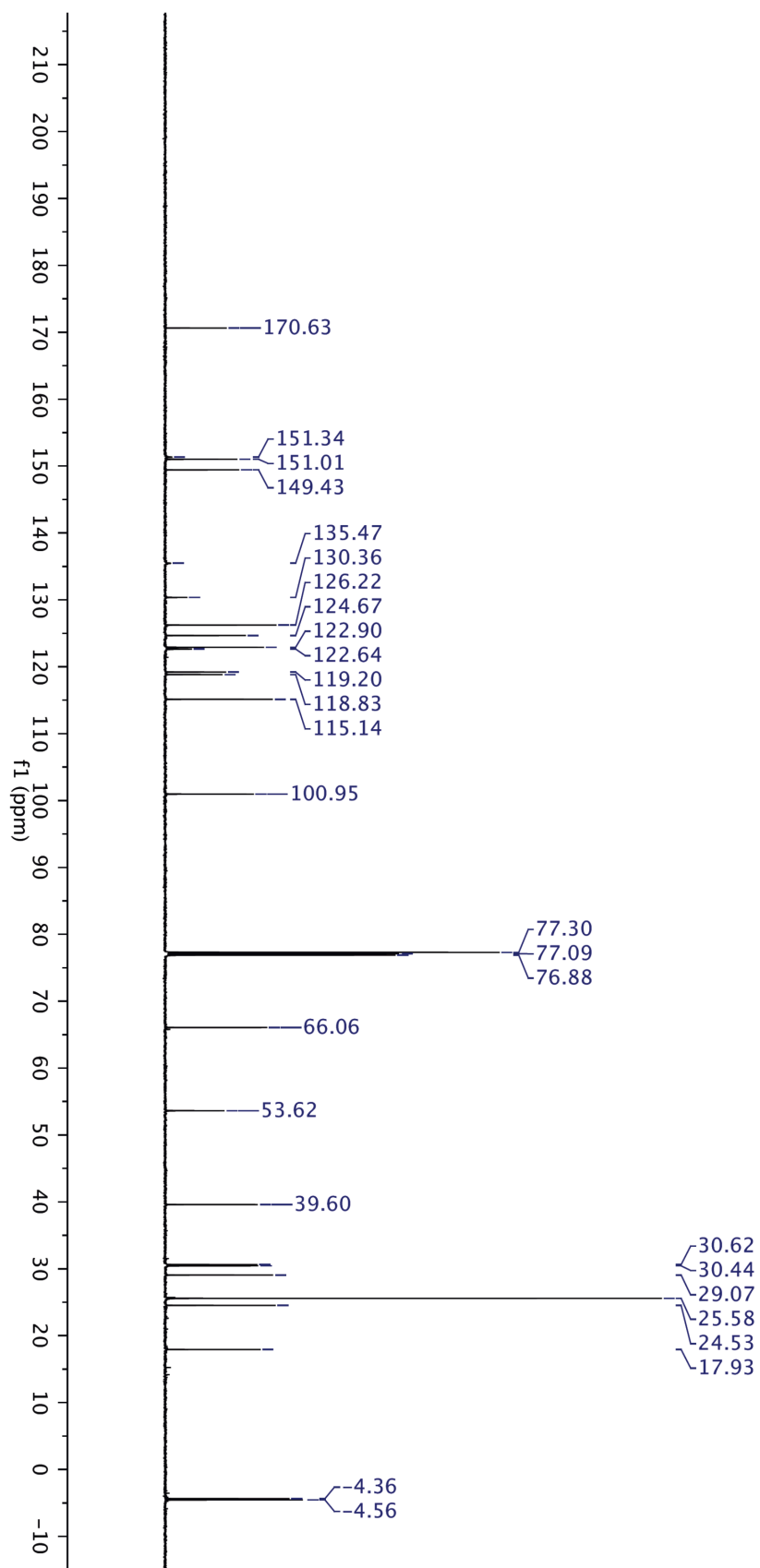
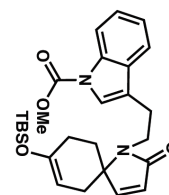


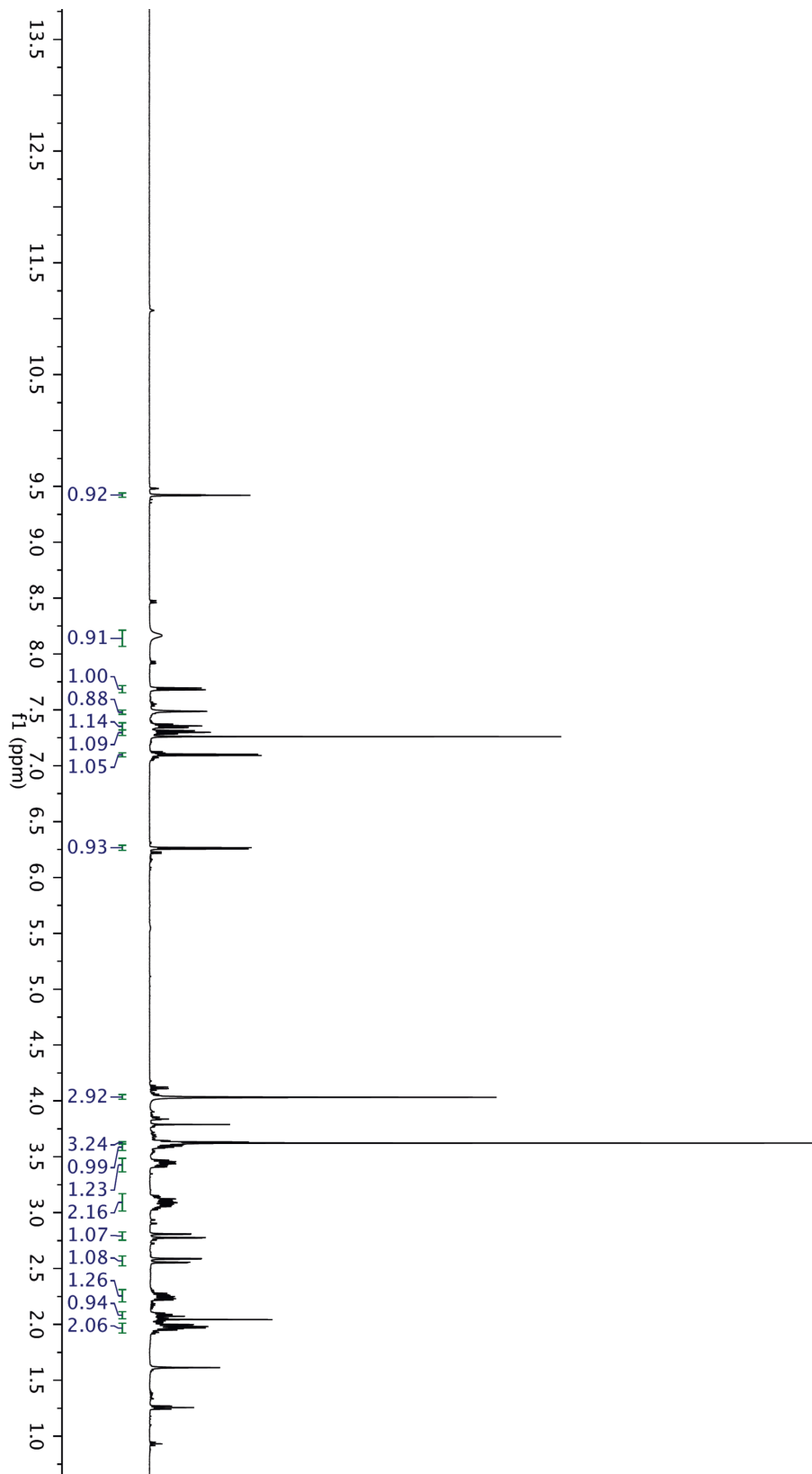
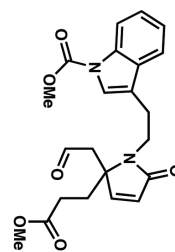


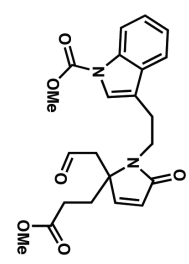
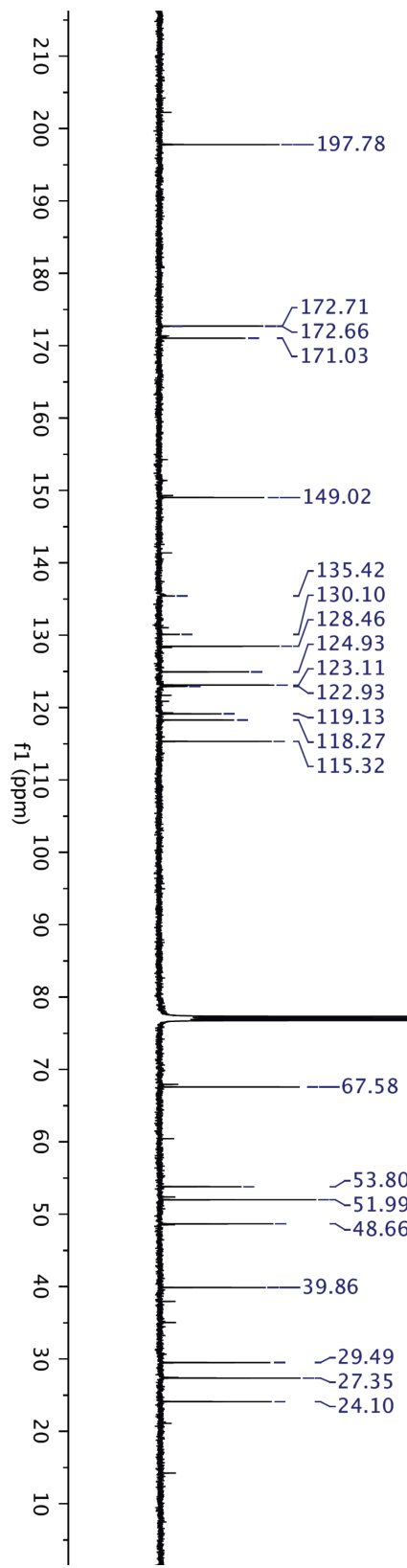


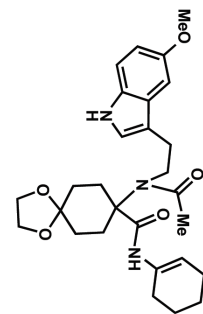
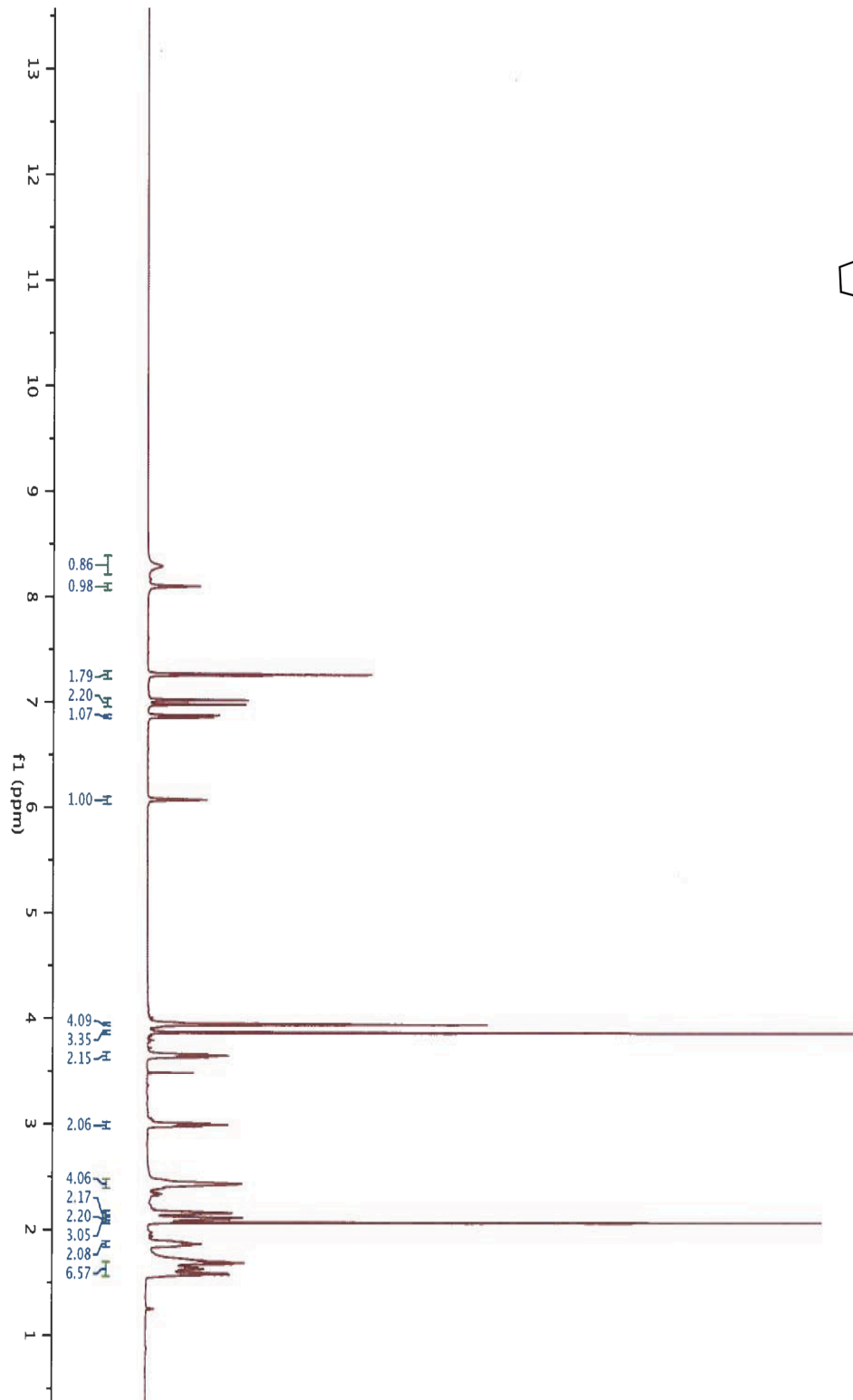


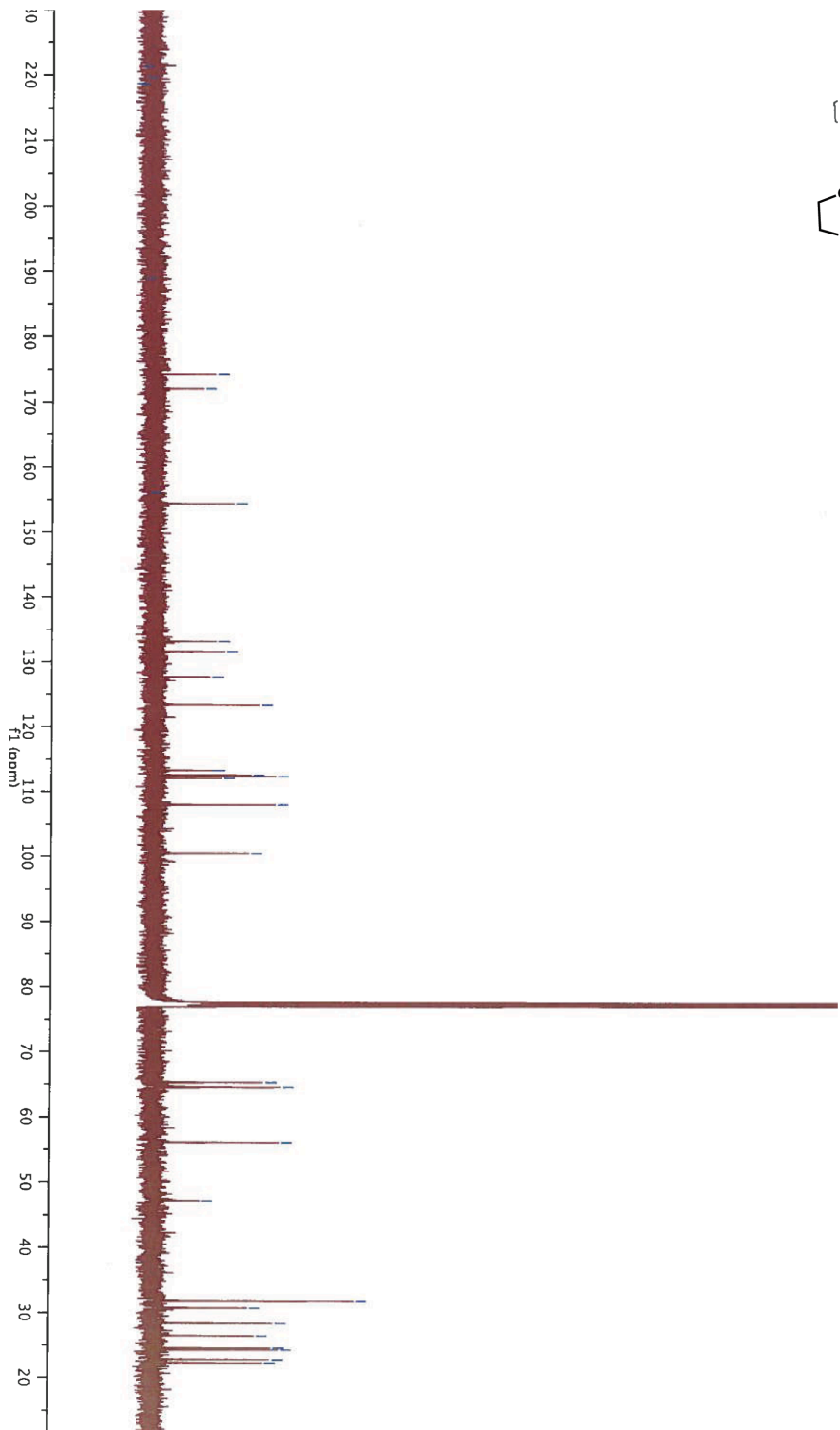
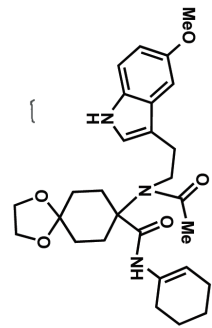


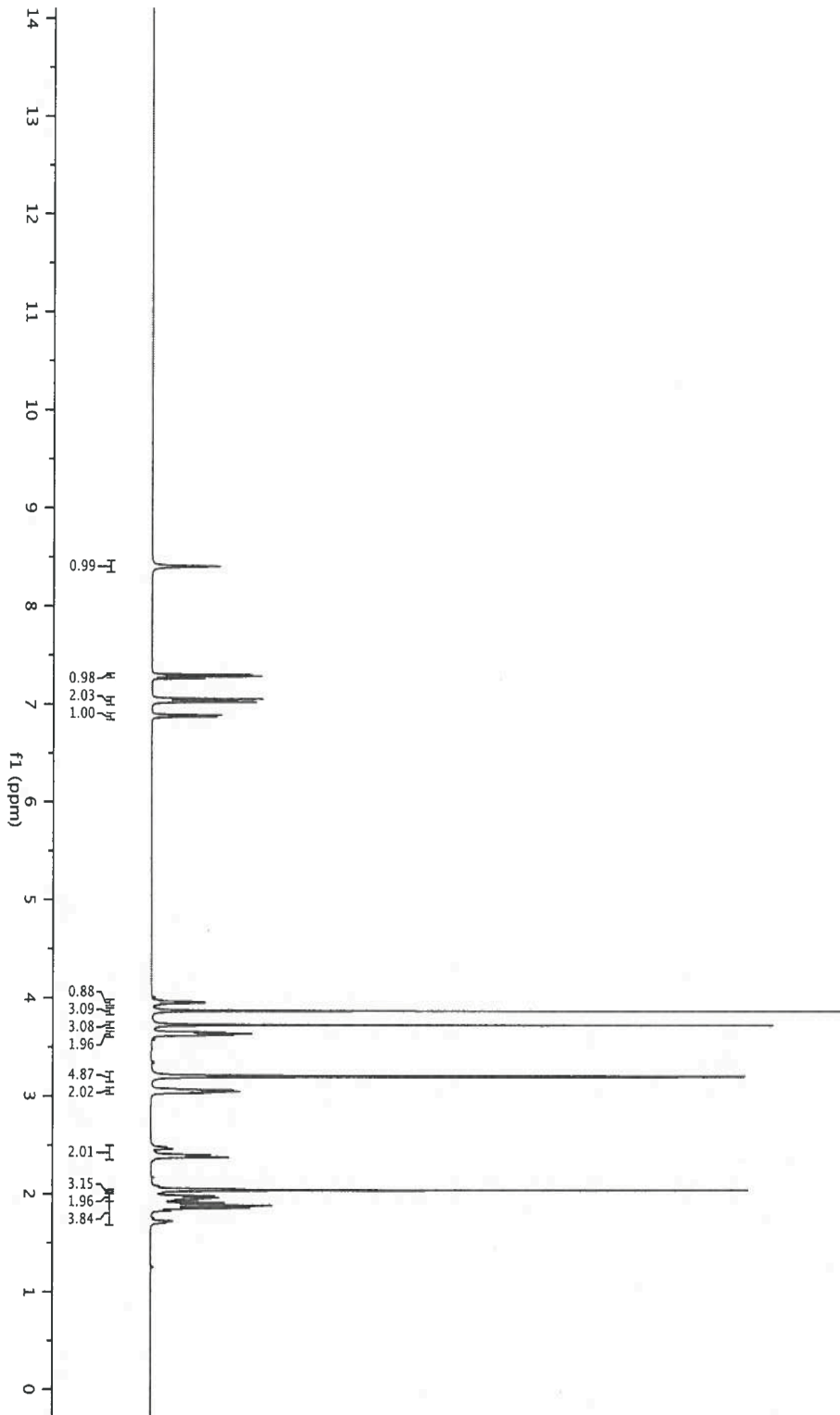
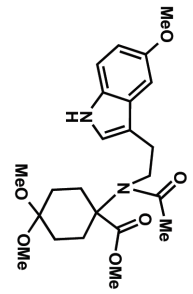


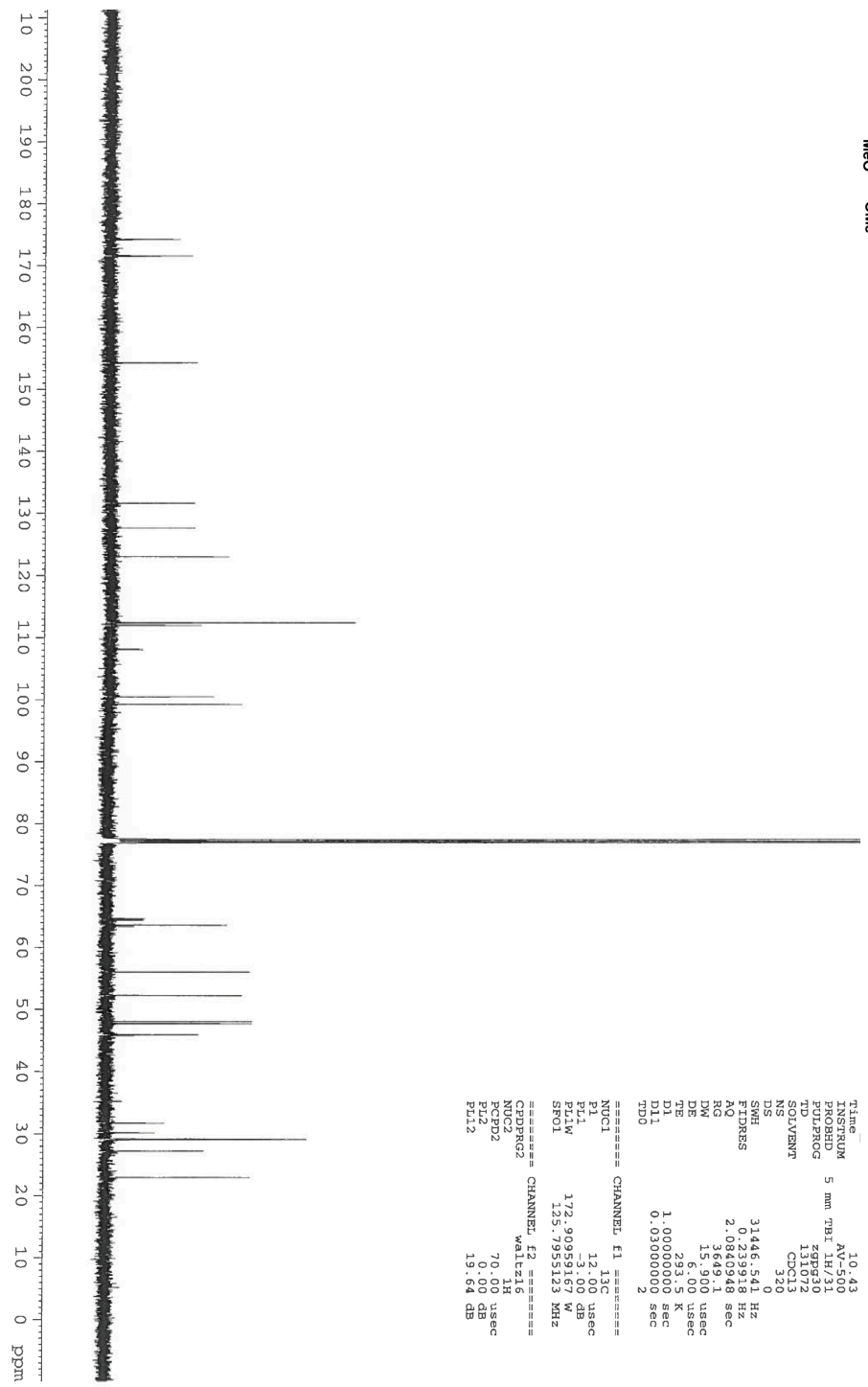
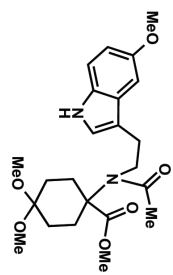










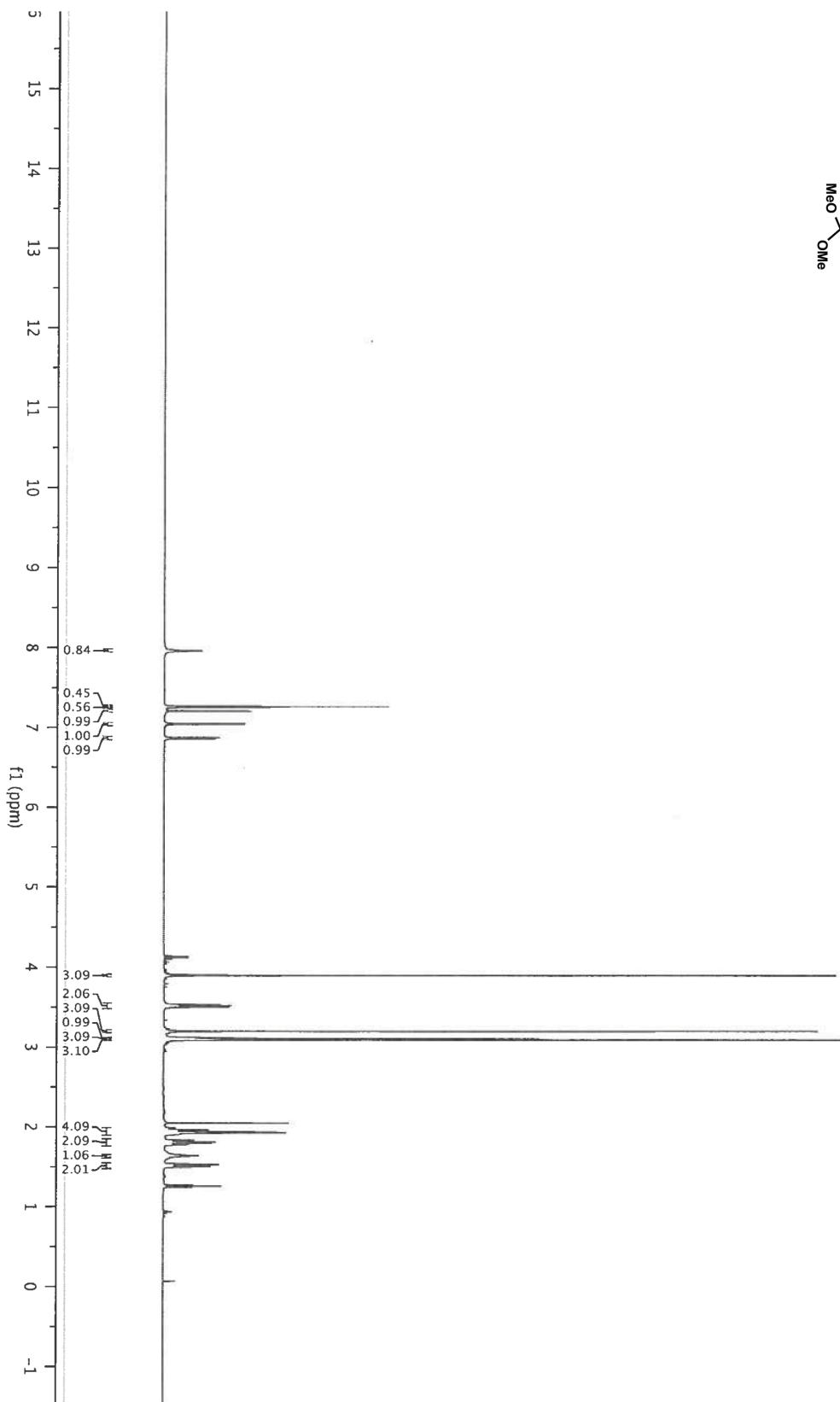
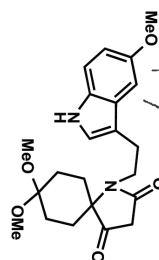


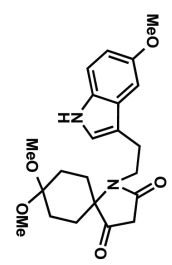
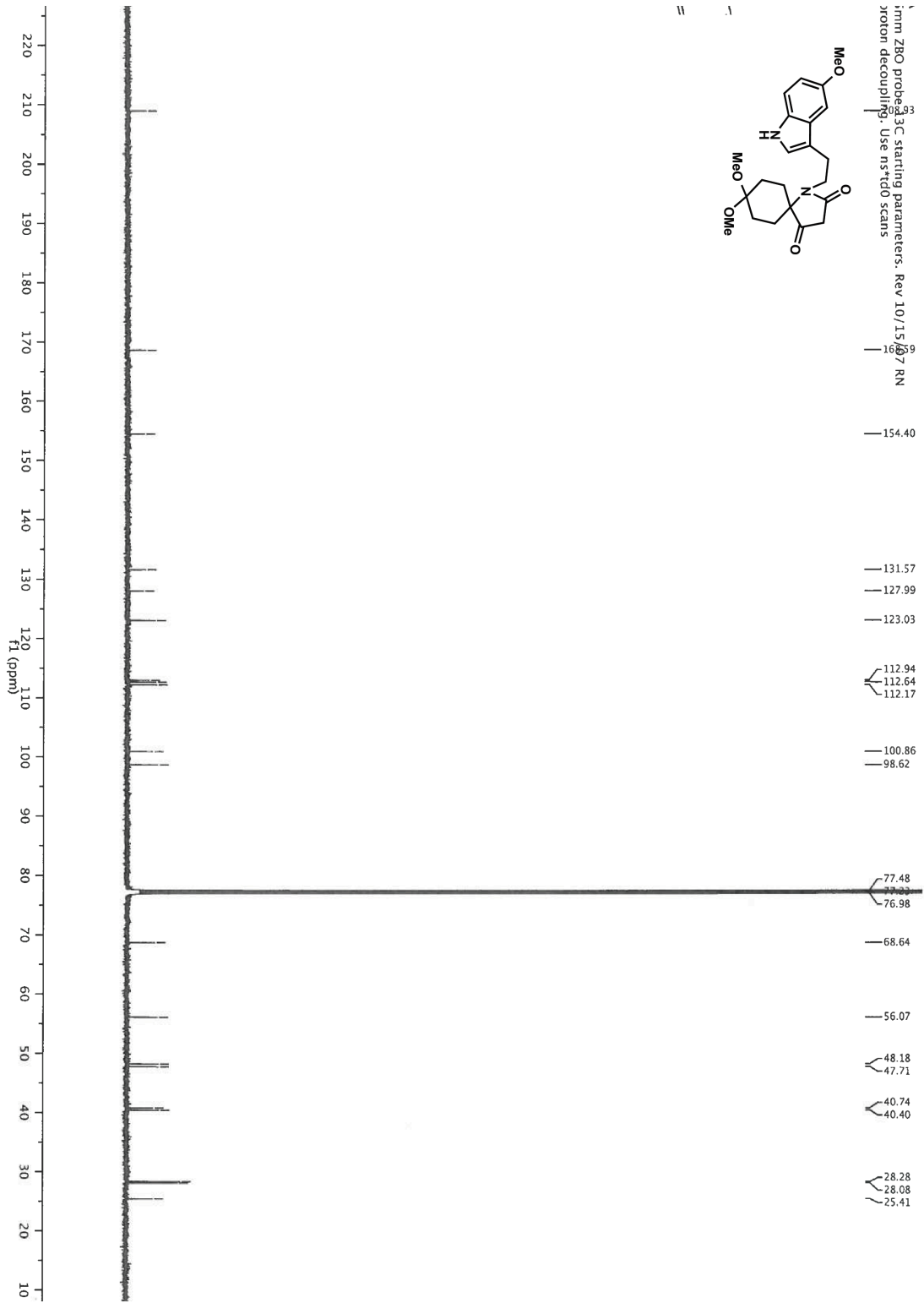
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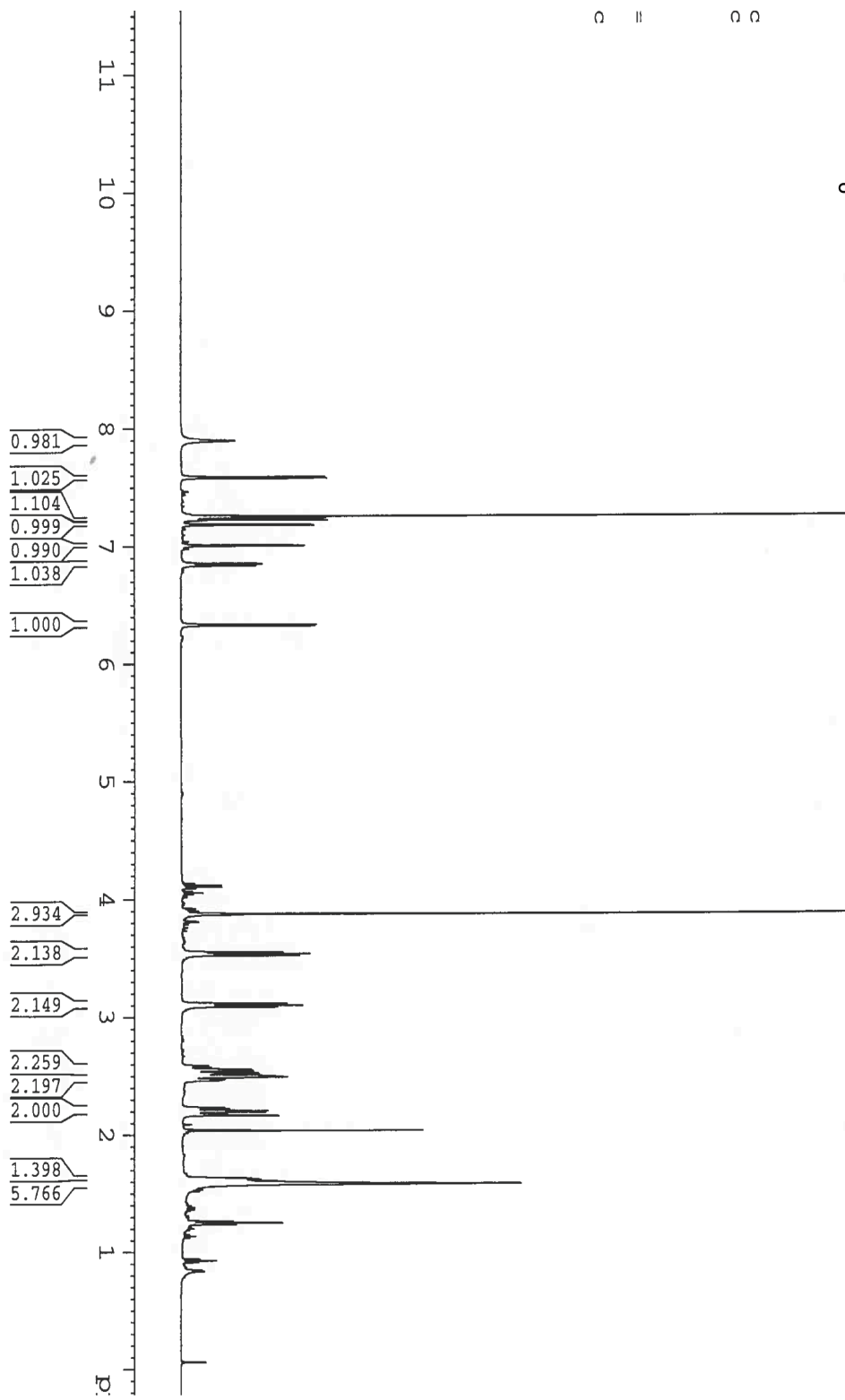
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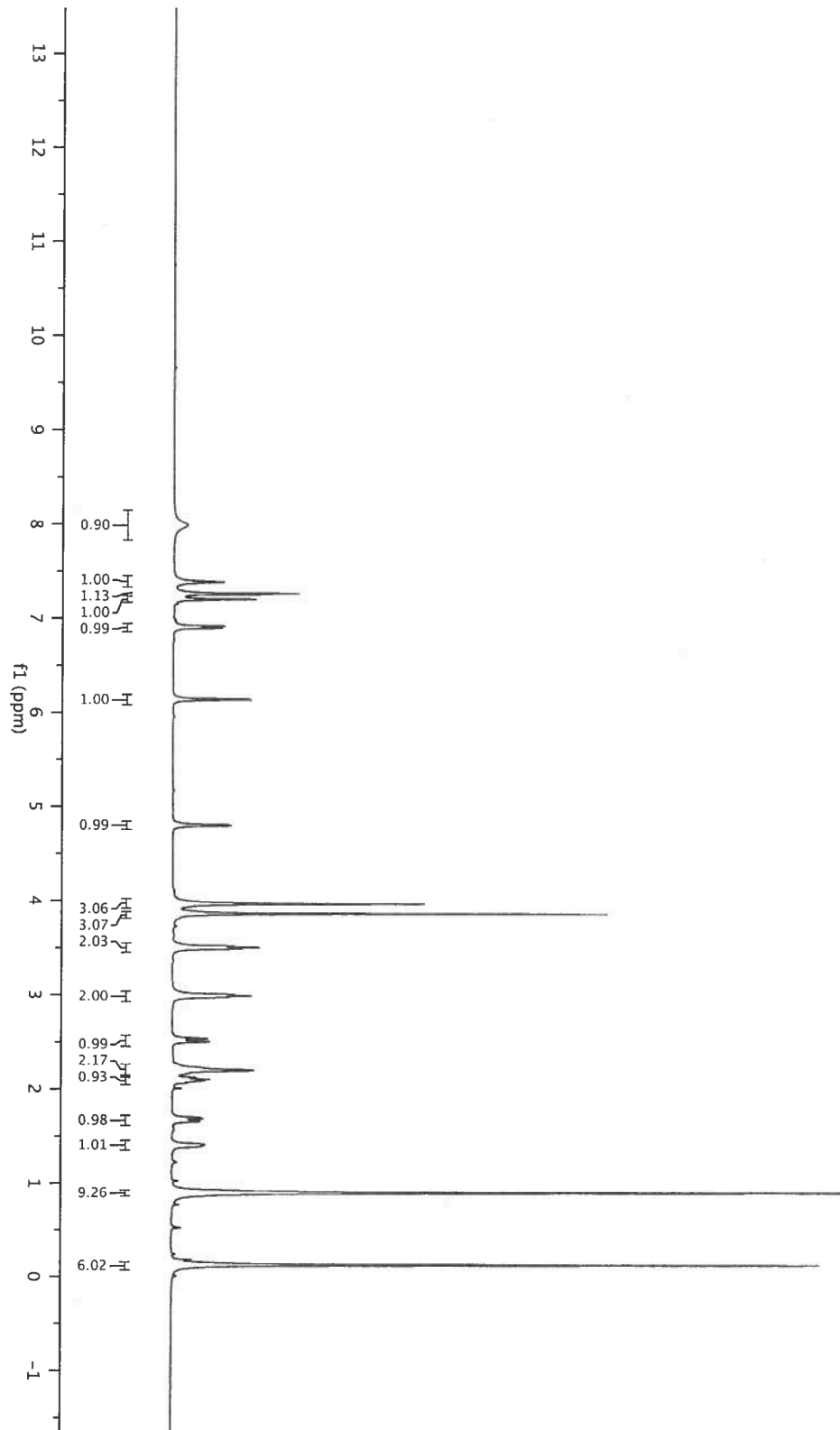
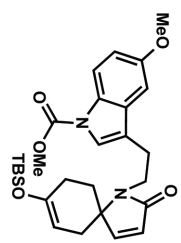
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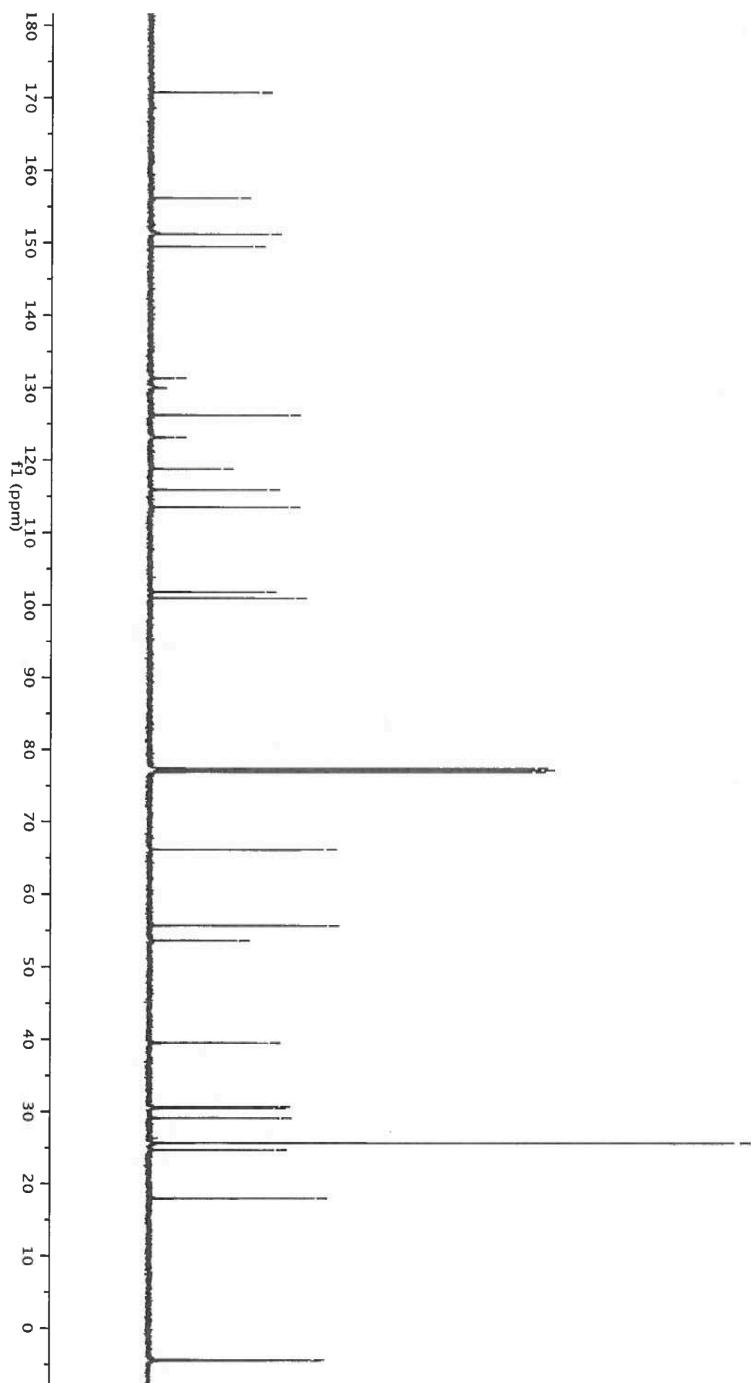
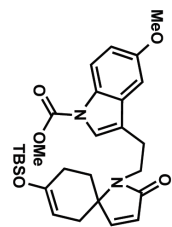



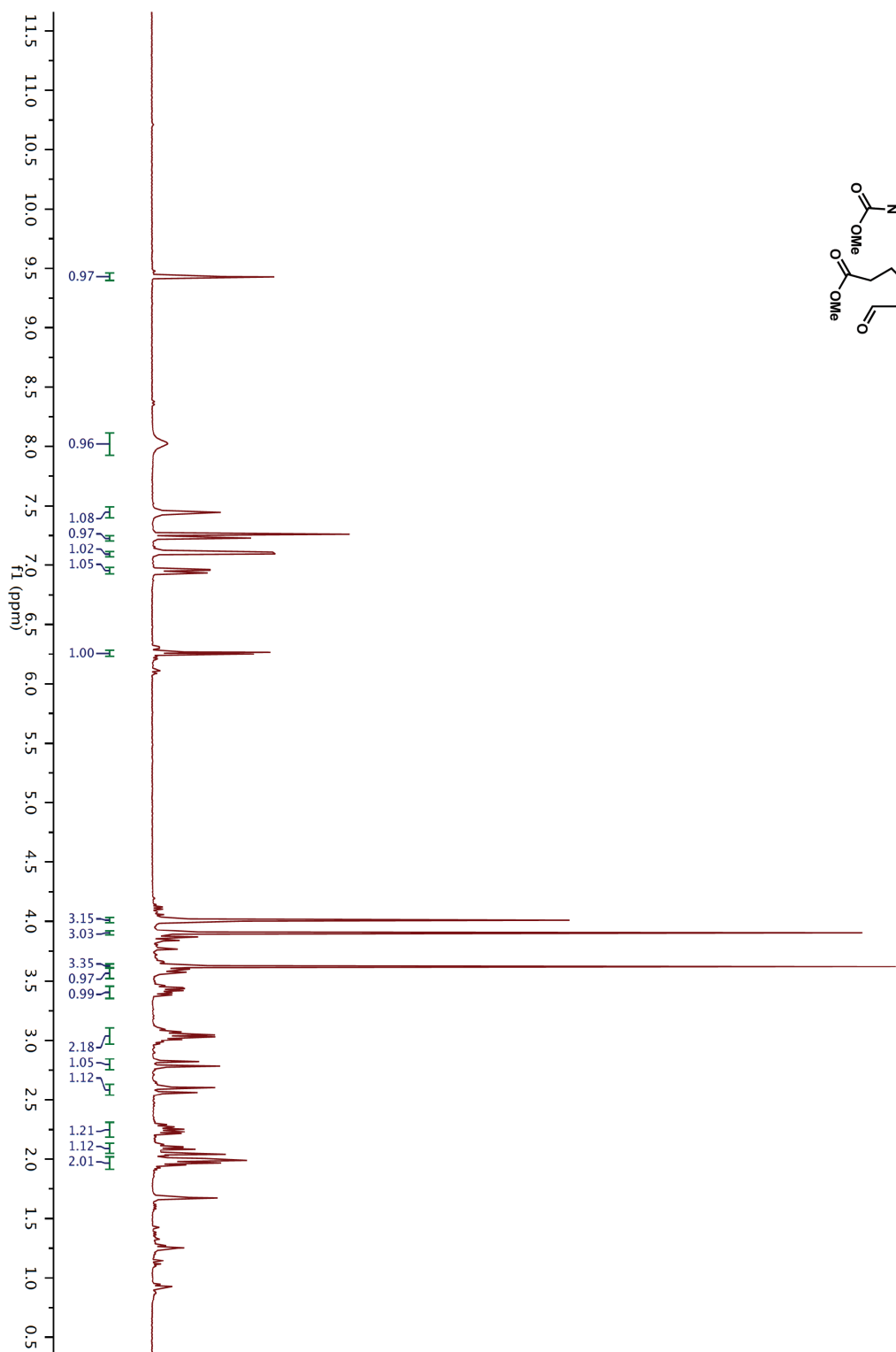
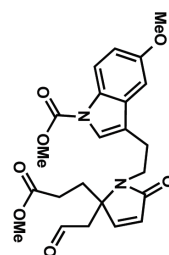


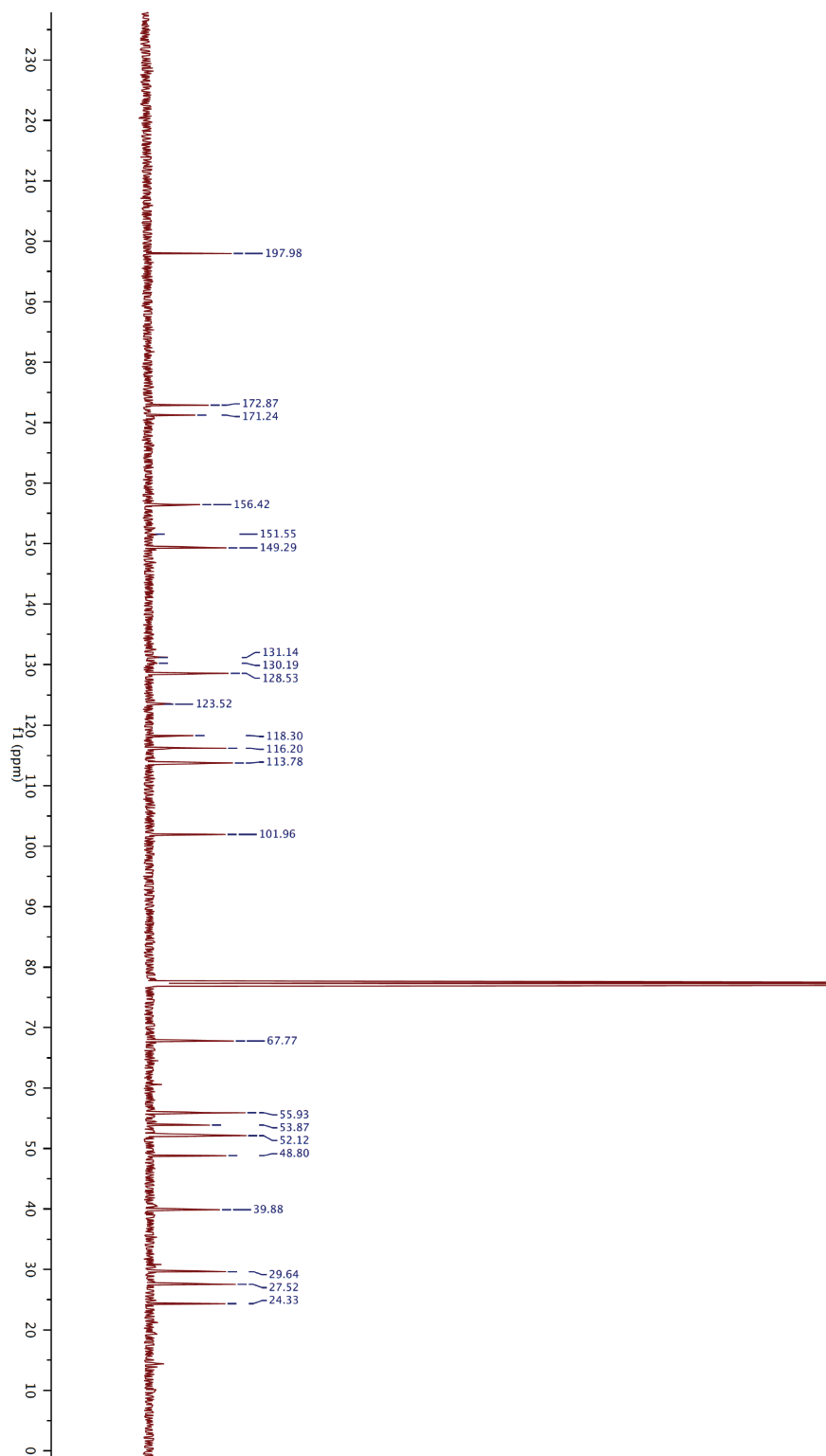
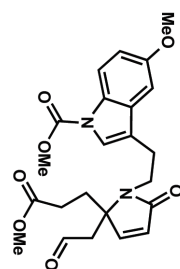
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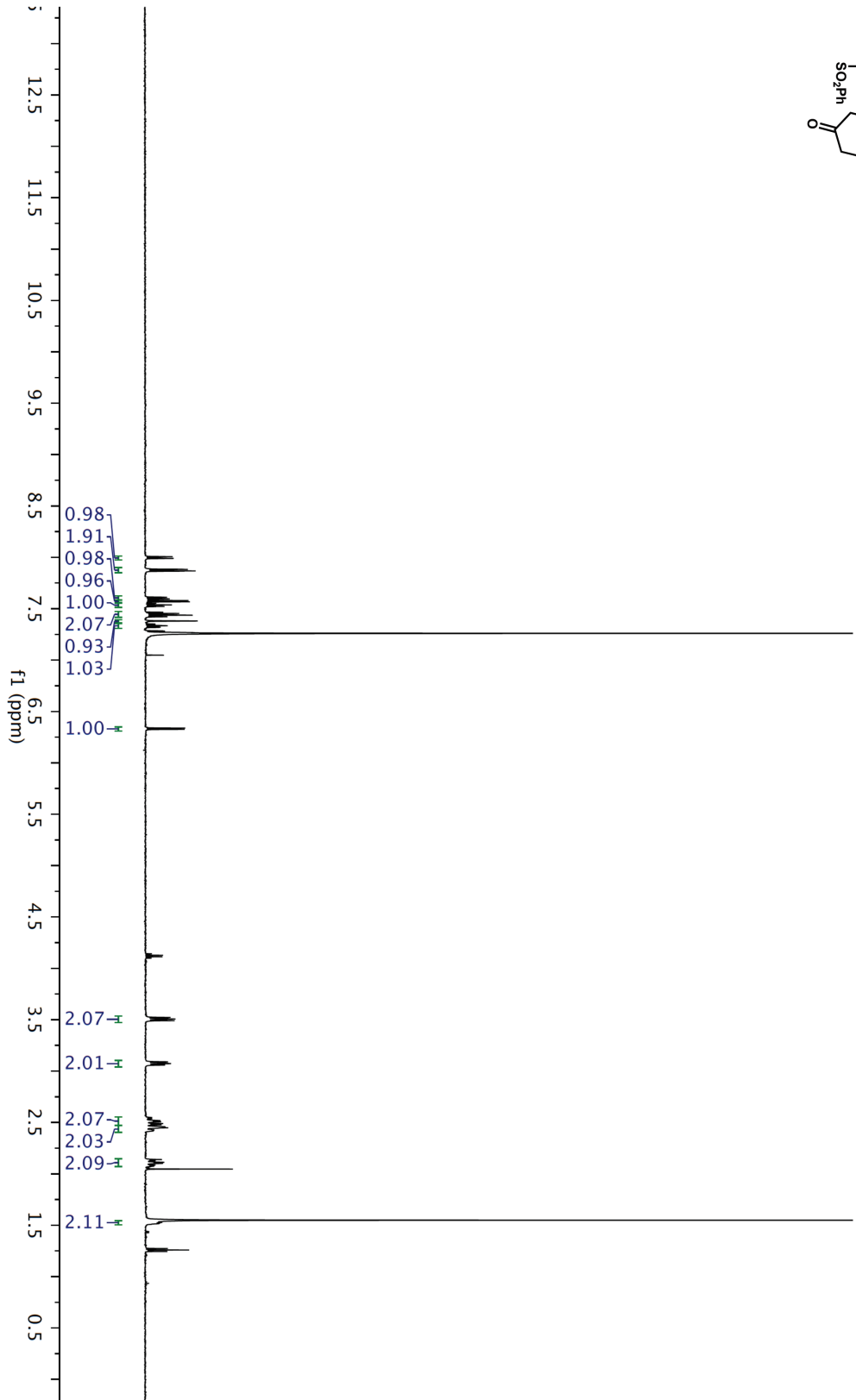
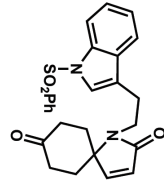


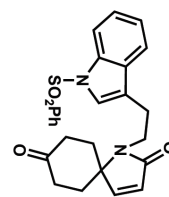
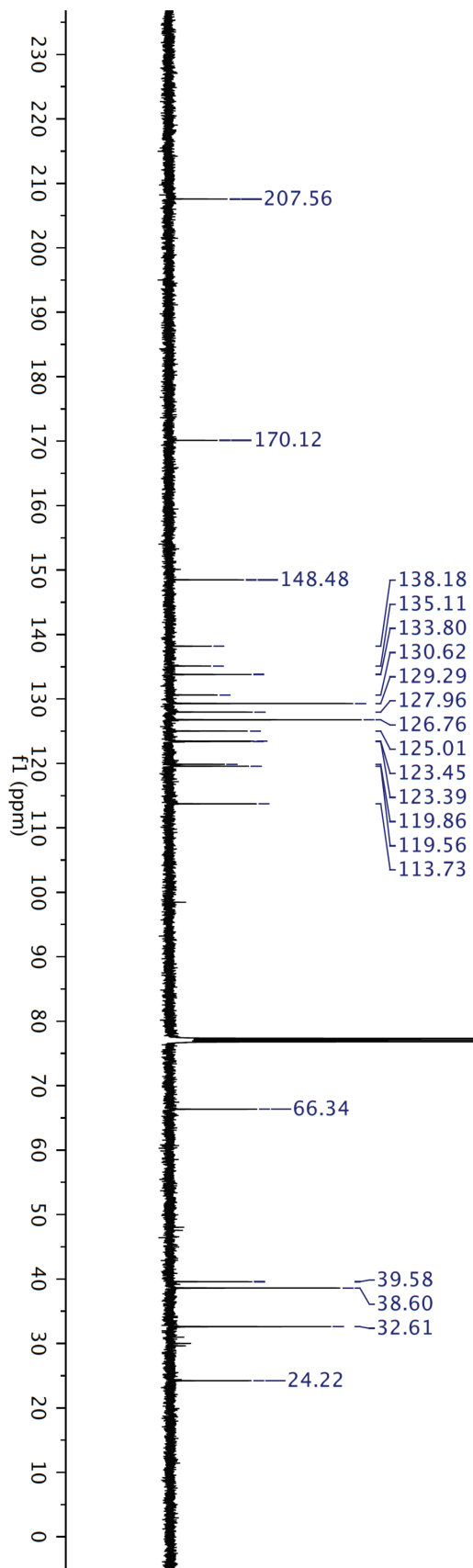


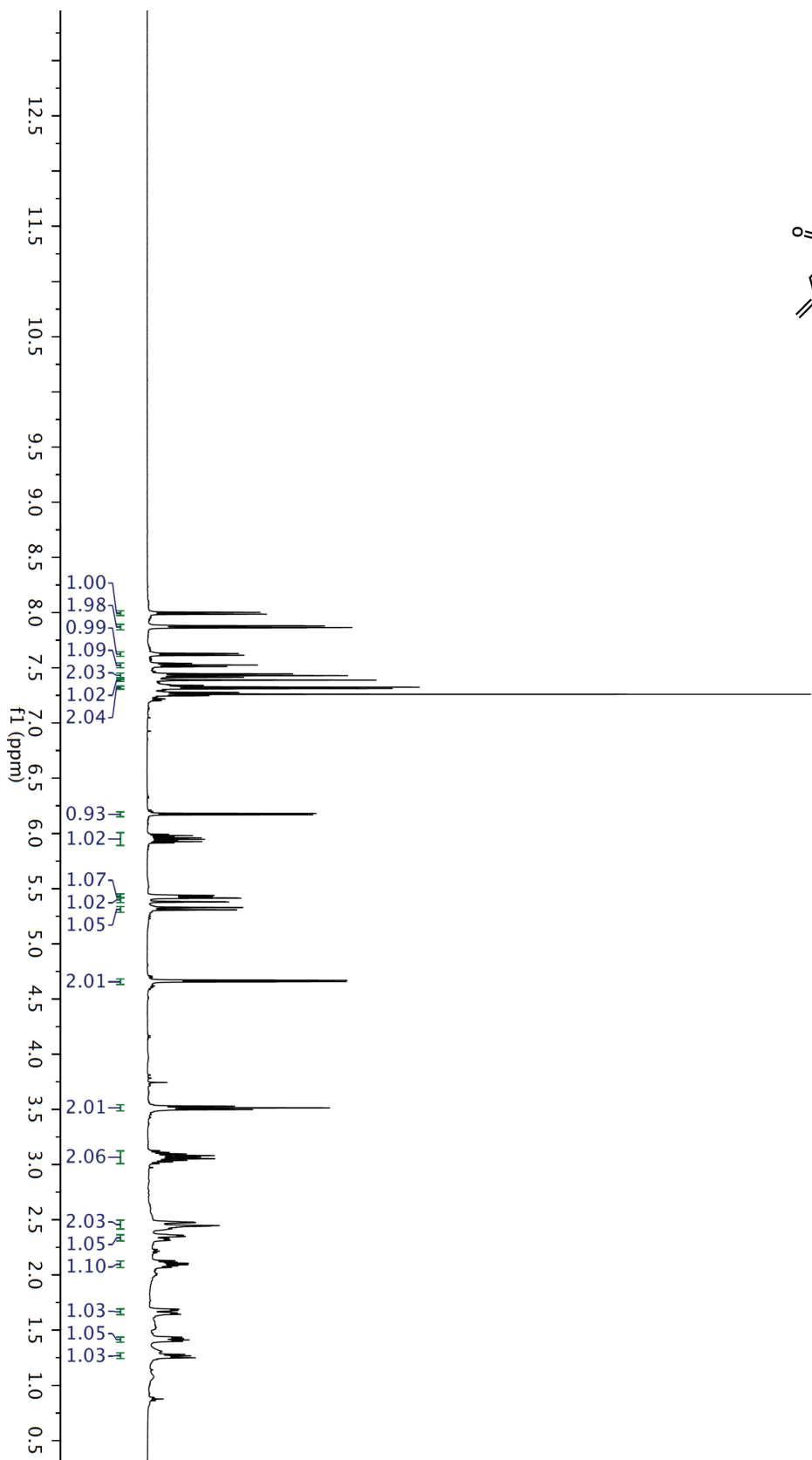


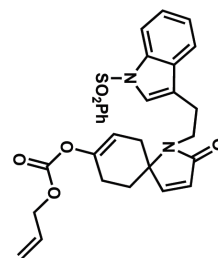
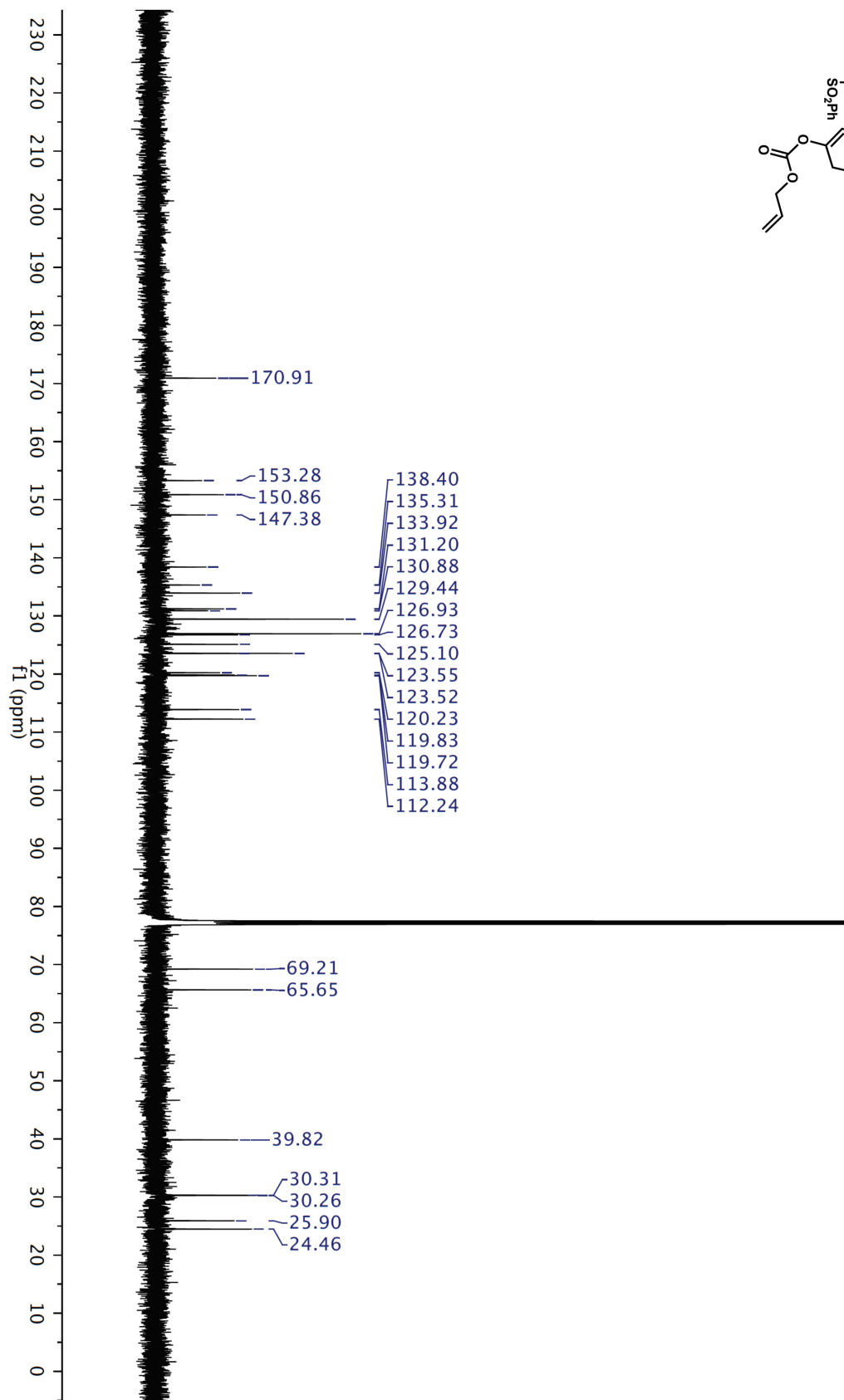


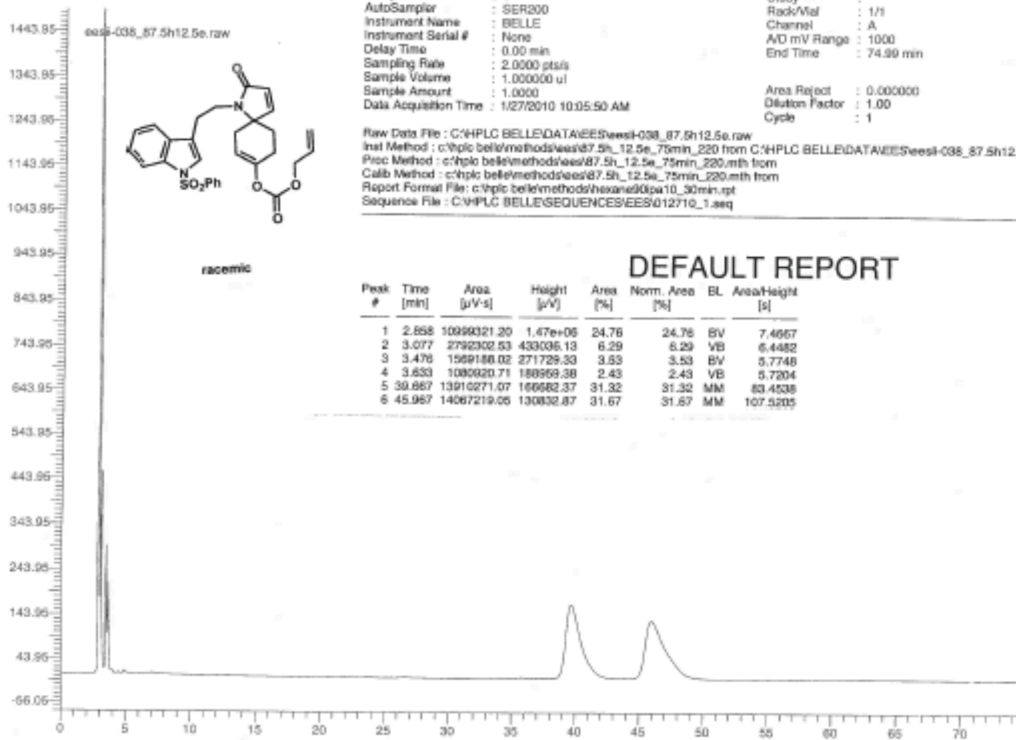












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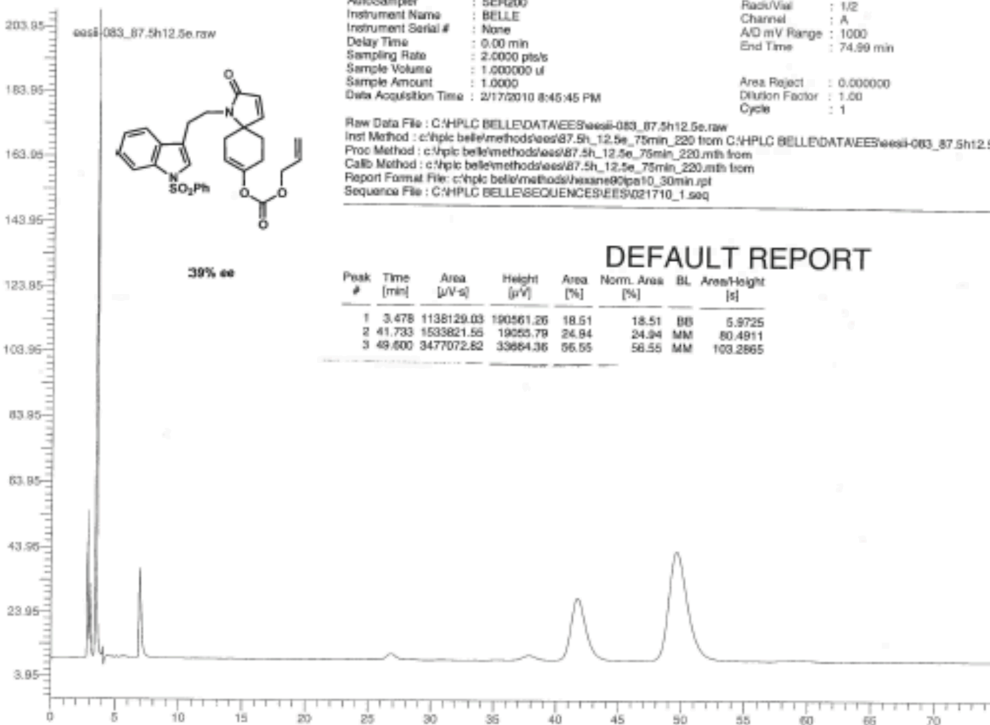
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 Dilution Factor : 1.00
 Cycle : 1

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 Proc Method : c:\hplc\bellemethods\eesi\87.5h_12.5e_75min_220.mth from
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 Sequence File : C:\HPLC BELLE\SEQUENCES\EESI\012710_1.seq

DEFAULT REPORT

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| 2 | 3.077 | 2792302.53 | 430036.13 | 6.29 | 6.29 | VB | 6.4482 |
| 3 | 3.476 | 1569186.02 | 271729.33 | 3.53 | 3.53 | BV | 5.7748 |
| 4 | 3.633 | 1065620.71 | 166969.38 | 2.43 | 2.43 | VB | 5.7204 |
| 5 | 39.667 | 13910271.07 | 166662.37 | 31.32 | 31.32 | MM | 63.4538 |
| 6 | 45.957 | 14567219.05 | 130832.87 | 31.67 | 31.67 | MM | 107.5205 |



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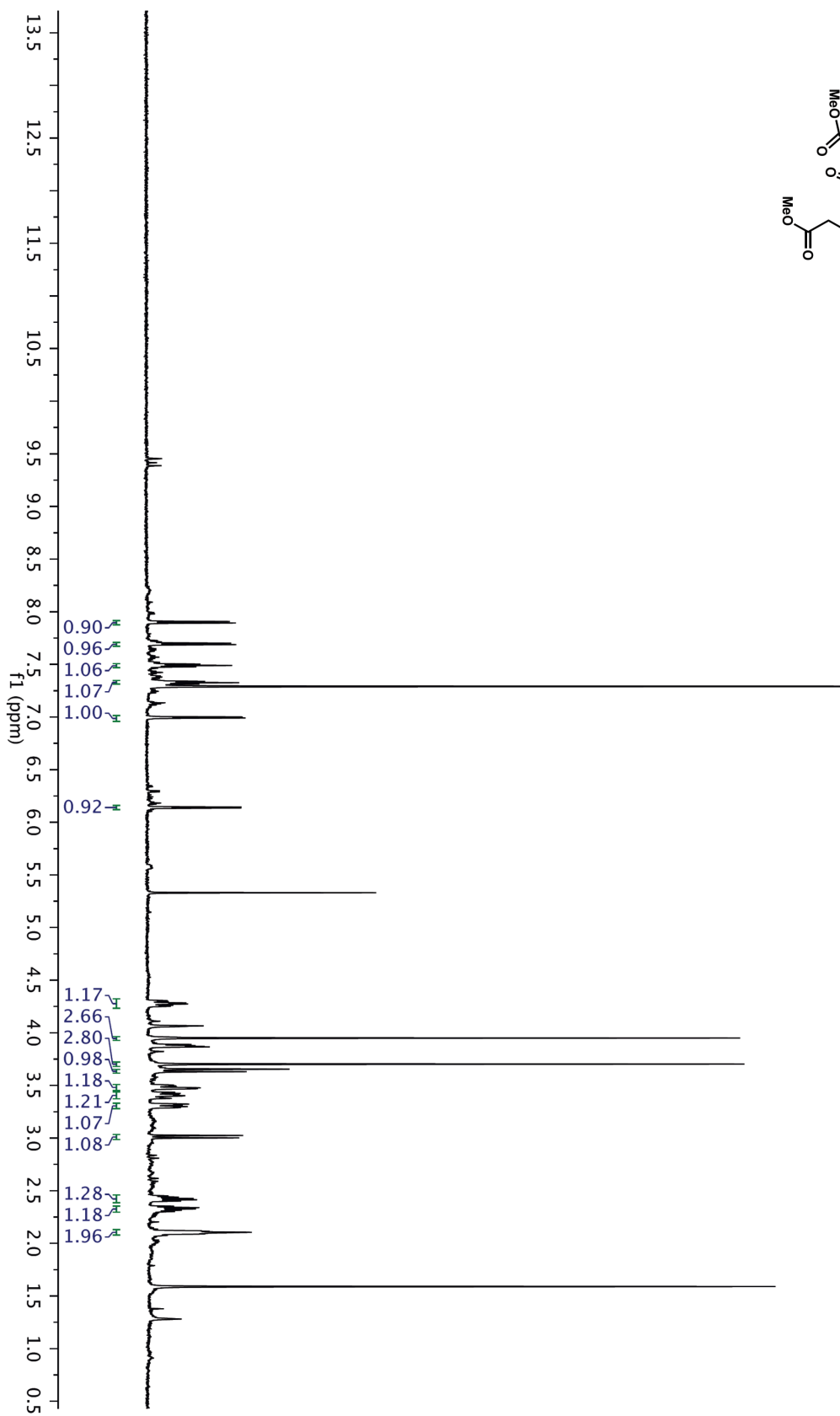
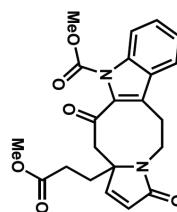
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 A/D mV Range : 1000
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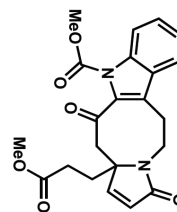
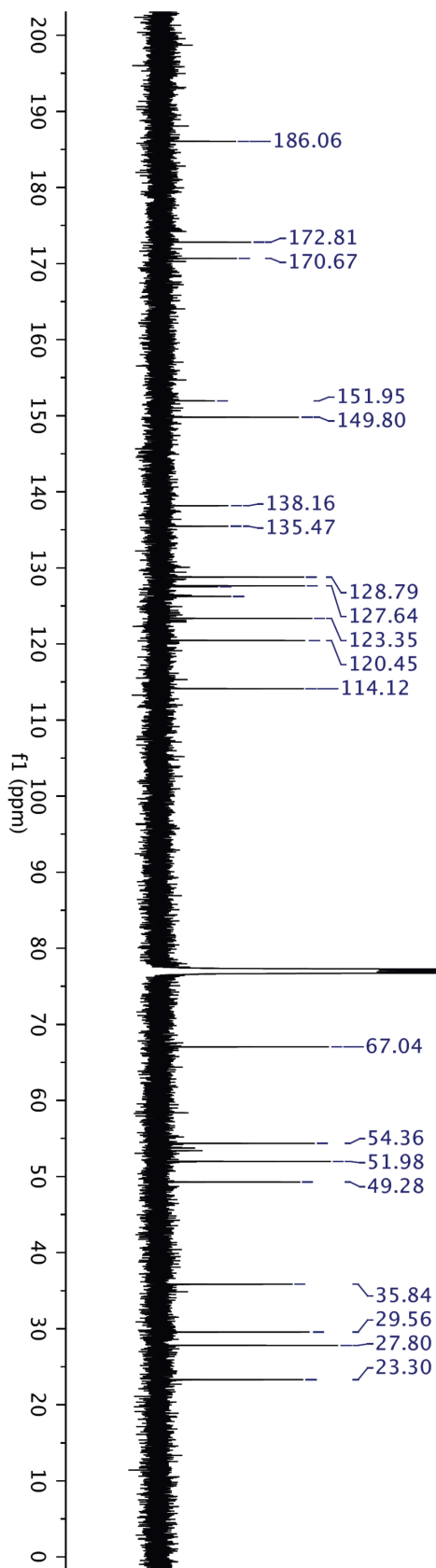
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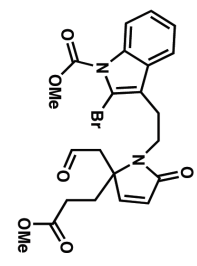
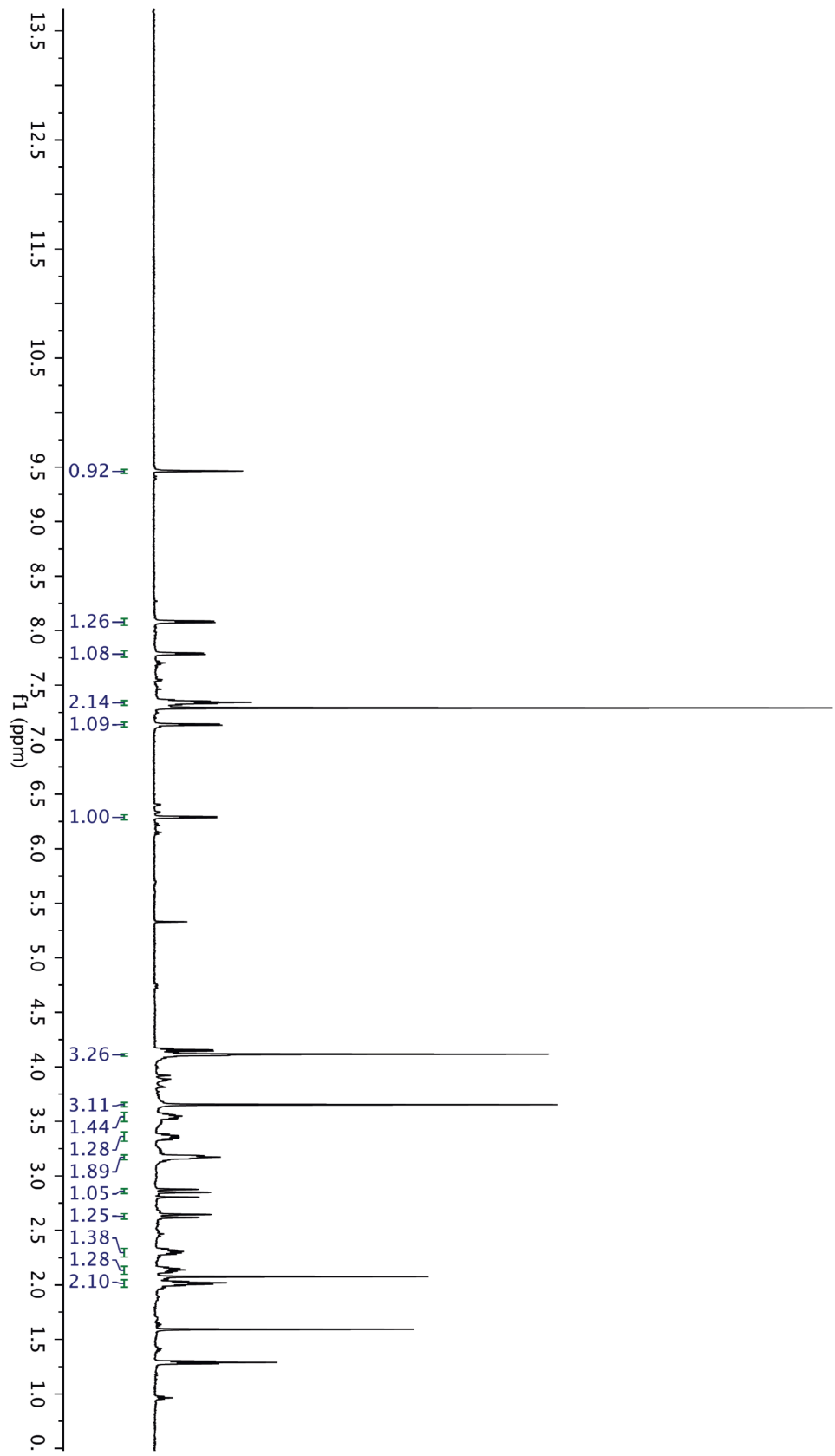
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 Calib Method : c:\hplc\bellemethods\eesi\87.5h_12.5e_75min_220.mth from
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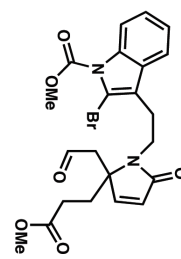
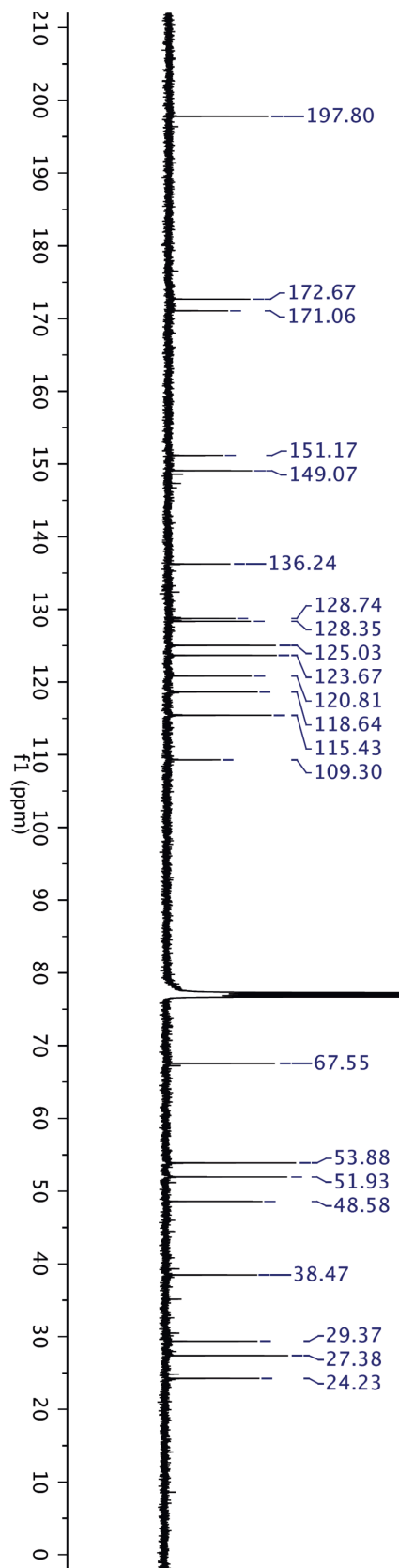
DEFAULT REPORT

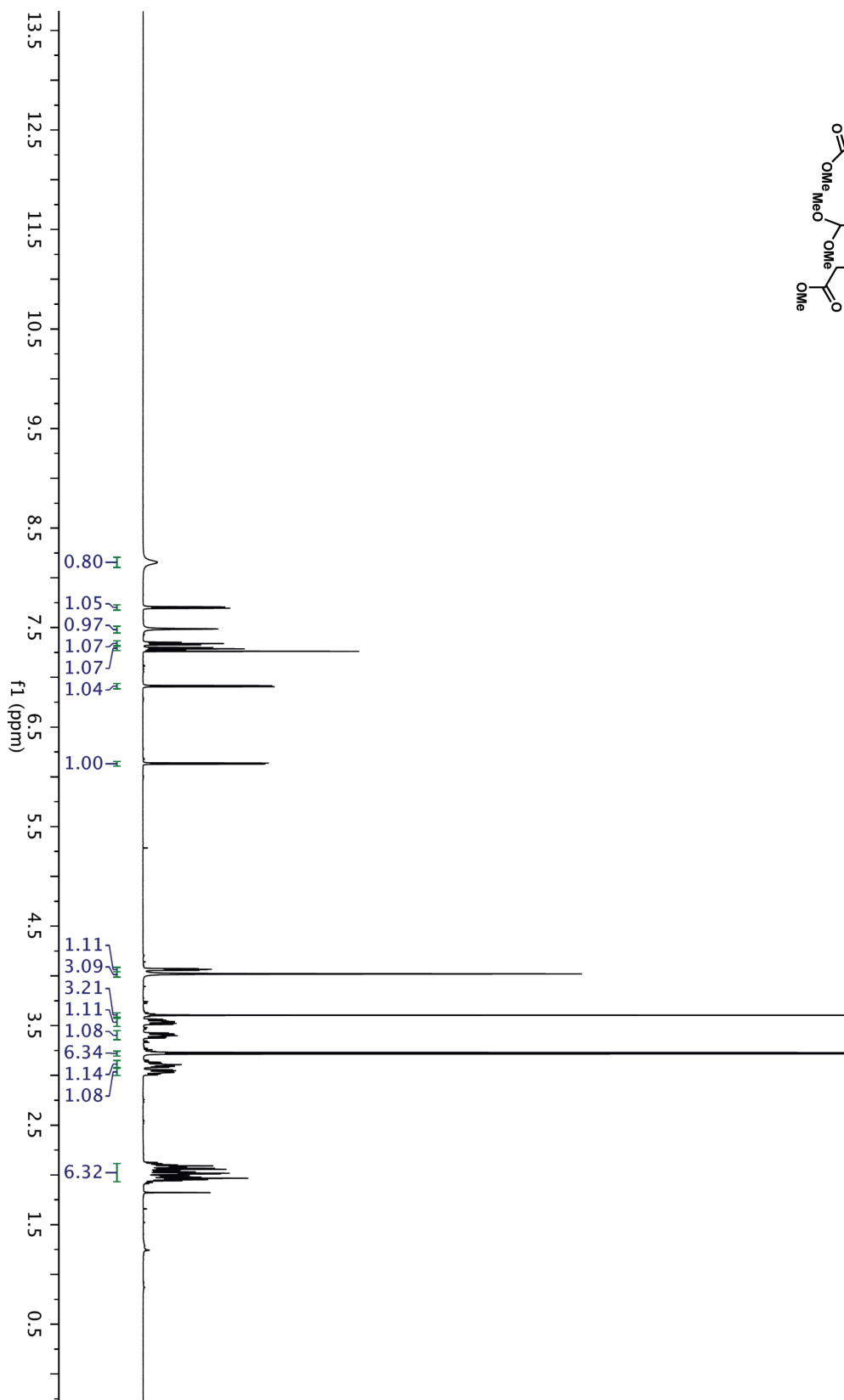
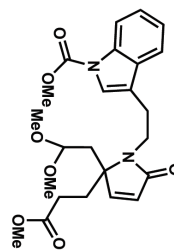
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| 2 | 41.733 | 1533821.55 | 19055.79 | 24.94 | 24.94 | MM | 80.4911 |
| 3 | 49.600 | 3477072.82 | 33664.36 | 56.55 | 56.55 | MM | 103.2865 |

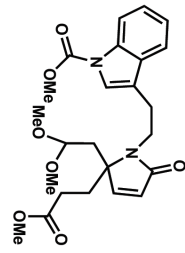
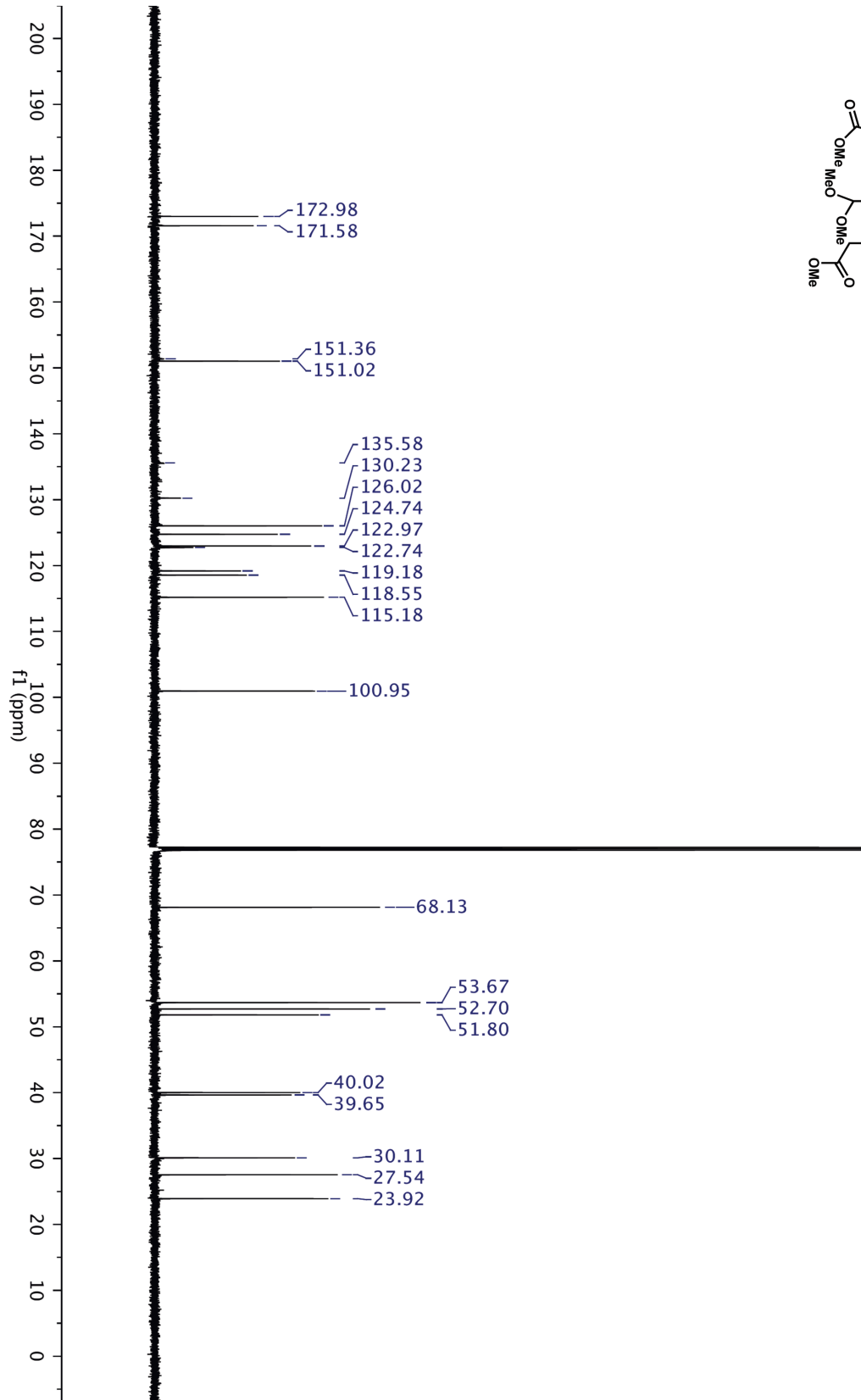


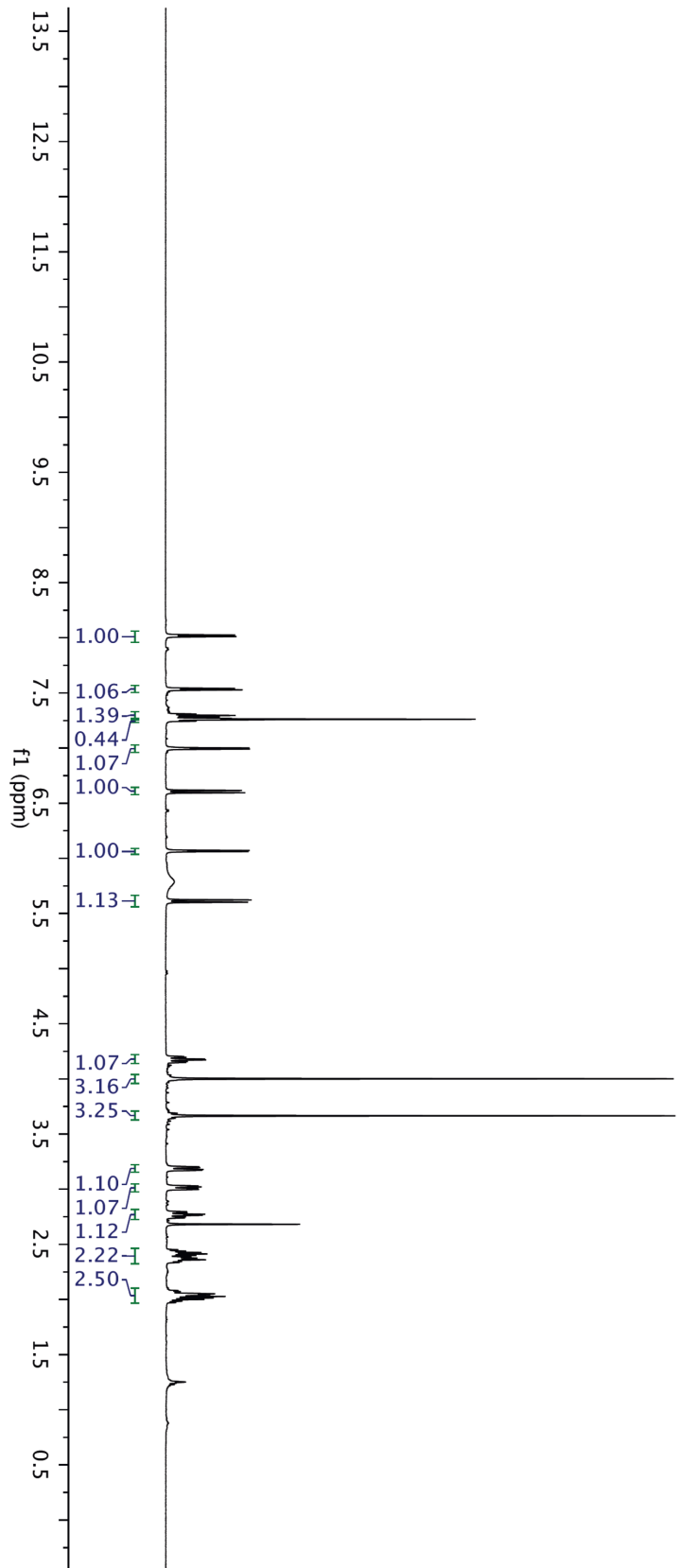
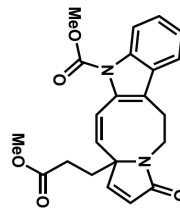


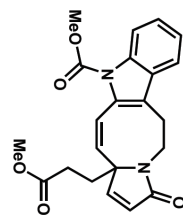
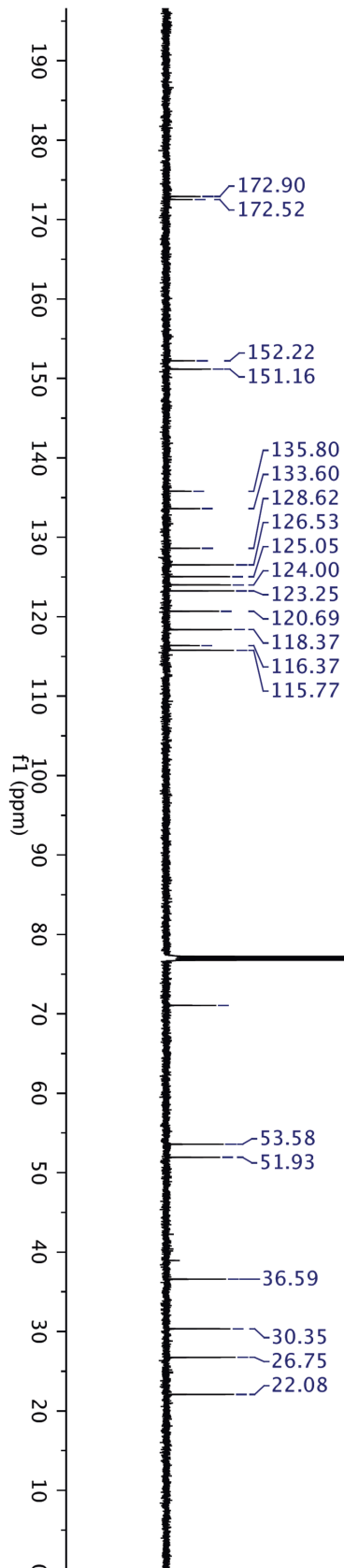


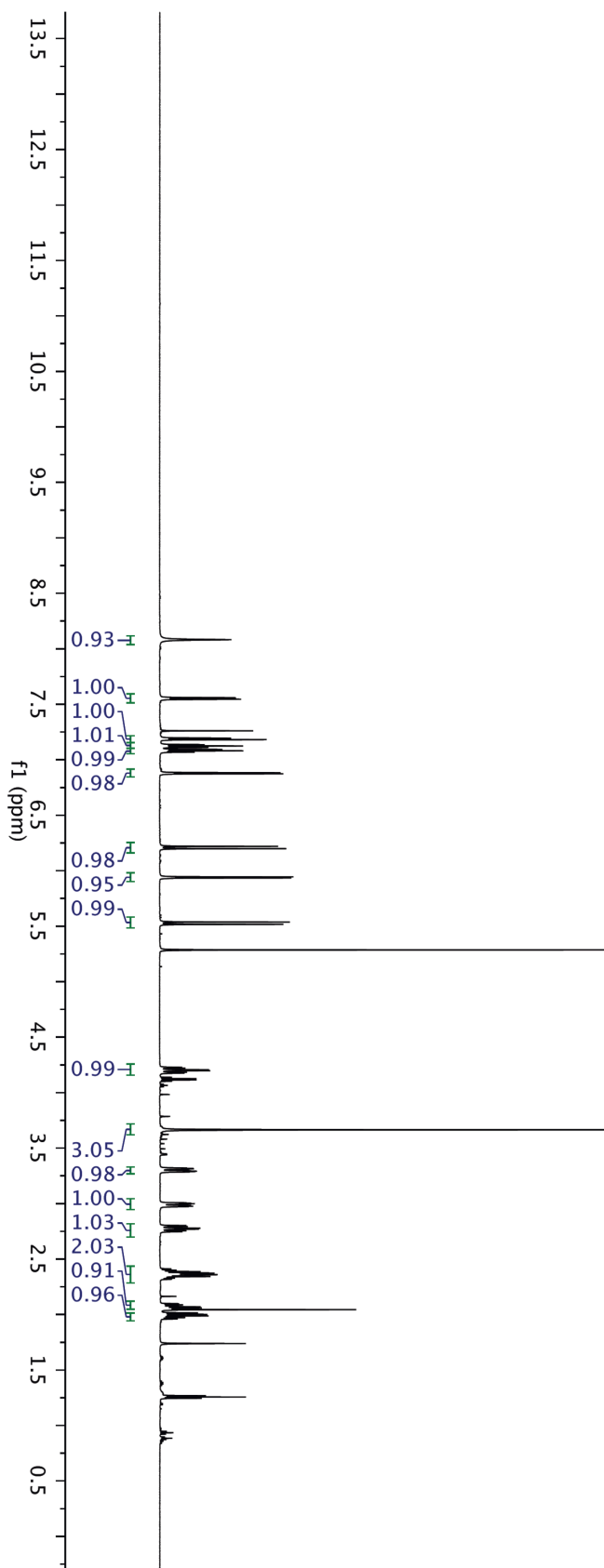
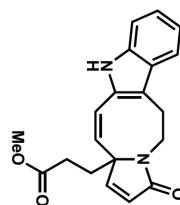


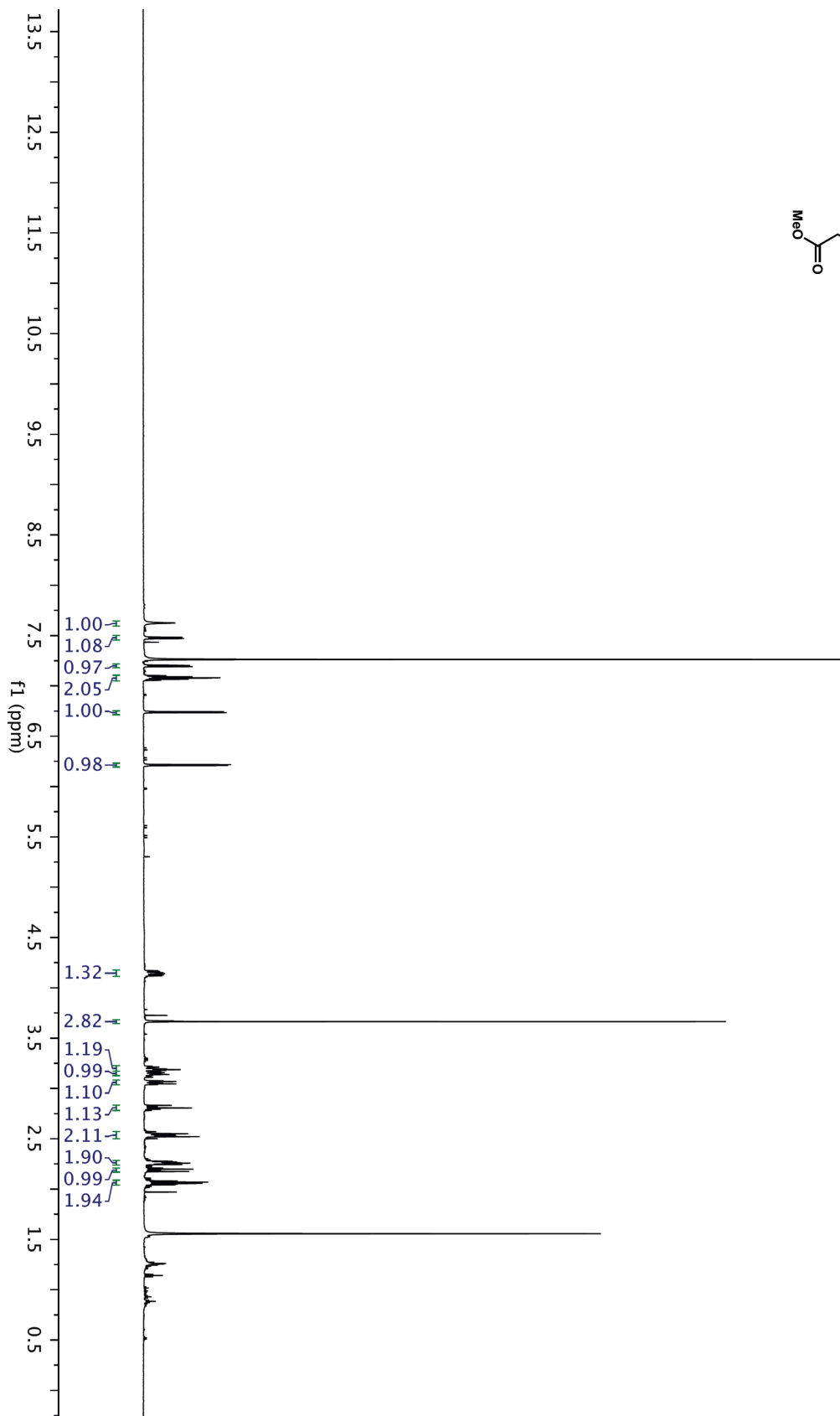
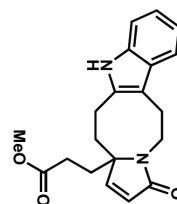












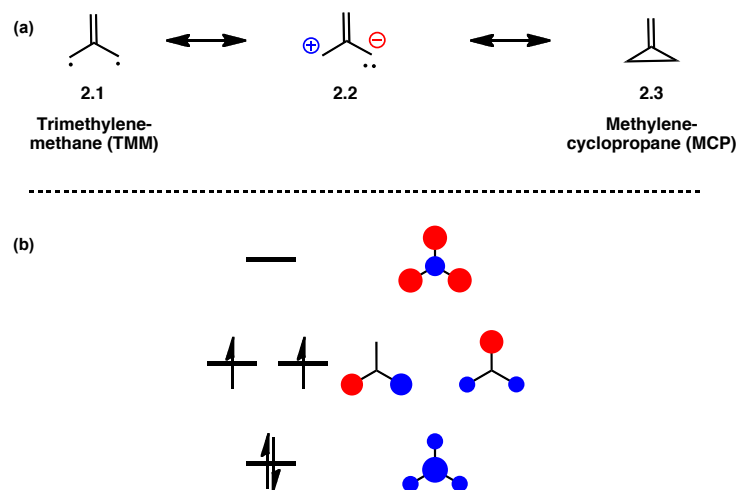
Chapter 2. Application of In Situ-Generated Rh-Bound Trimethylenemethane Variants to the Synthesis of 3,4-Fused Pyrroles

2.1 Introduction

2.1.1. Trimethylenemethane

Trimethylenemethane (TMM) was discovered in the 1940's and has been studied extensively for its bonding and reactivity (Figure 2.1a). Seminal work by Moffit¹ and pioneering studies by Dowd² have established TMM is a ground state triplet diradical. Even though the triplet state is 14 kcal/mol lower in energy than the singlet state, TMM has a low barrier of conversion between the triplet (**2.1**) and singlet state (**2.2**), and upon converting to the singlet state, will spontaneously close to methylenecyclopropane (MCP, **2.3**). TMM has substantial resonance stability with three equivalent resonance forms, and because both radicals are a part of the same π -system, they interact strongly (which accounts for the difference of 14 kcal/mol between the triplet and singlet states). This is easy to understand by looking at the molecular orbital diagram for the π -orbitals of TMM (Figure 2.1b). Because the non-bonding orbitals are orthogonal, there is no overlap integral, and therefore no energy is gained by pairing their spin. However, since both orbitals have electron density on the same atoms, the energy from the exchange integral (the basis of Hund's rule) favors the triplet state over the ground state.³

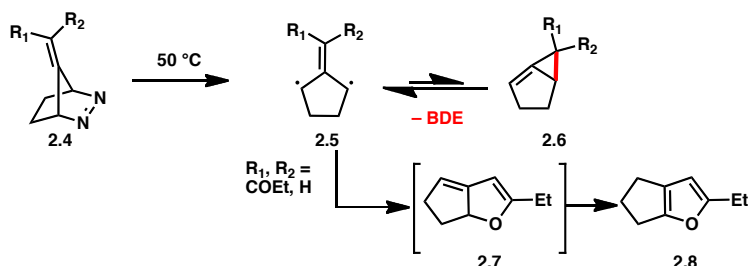
Figure 2.1. Trimethylenemethane.



As noted above, the barrier of conversion between the triplet and singlet states is low resulting in spontaneous closure of TMM to MCP at any temperature or conditions outside of an argon matrix. Therefore to be considered synthetically useful, TMM-moieties are often constrained into a ring system, such as is shown in Scheme 1.⁴ When the TMM-moiety is constrained into a 5-membered ring, the MCP analogue actually has a negative bond dissociation energy, and prefers to sit as the diradical, which can favor the singlet or triplet state depending on its substituents (R_1 and R_2 of **2.5**). Little and co-

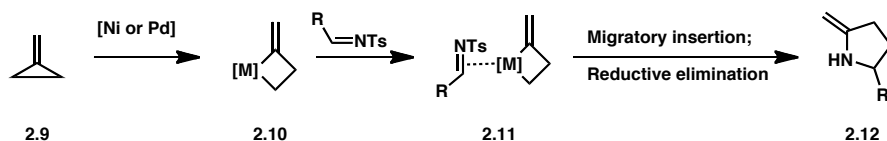
workers were able to generate TMM-moieties through loss of nitrogen gas from diaza-bicycles such as **2.4**, which have been shown to interact with ketone groups to form fused furans such as **2.8**.

Scheme 2.1. TMM constrained into ring for synthetic applications.



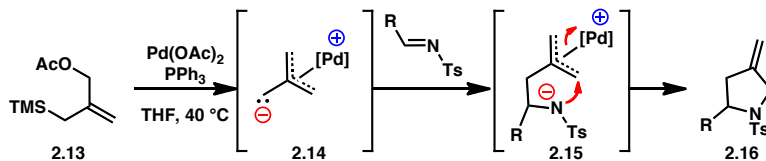
Another strategy for rendering TMM synthetically useful is to complex MCP or TMM to a metal center. As a result, many metal-mediated processes that convert MCPs to metal-complexed TMMs have been reported over the last two decades (see Scheme 2.2).⁵

Scheme 2.2 Metal-complexed MCP for synthetic applications.



By far, the most recognized and utilized metal-complexed TMM is **2.14** (Scheme 2.3) where the Pd is closely associated with the cationic terminus. The Pd–TMM complex **2.14** was introduced by Trost and has been featured as a “three-carbon partner” in numerous cycloaddition reactions, one example in which Trost and co-workers use a Pd-bound TMM-moiety to build a pyrrolidine ring (**2.16**) is shown in Scheme 3.⁶

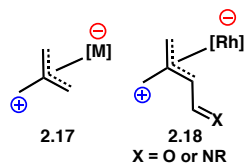
Scheme 2.3. Pd-bound TMM and use in synthetic applications.



2.1.2. Trimethylenemethane bound to an anionic metal center

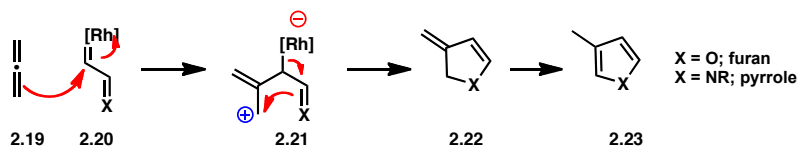
Despite the well-established utility of metal-complexed TMM variants, there have been comparatively few reported TMM equivalents where the metal is bound to the anionic portion of this reactive intermediate (**2.17**, Figure 2.2). As part of a general program to access such intermediates, we became interested in generating unique Rh-bound TMM derivatives (**2.18**).

Figure 2.2. Anionic terminus of TMM closely associated with metal center.



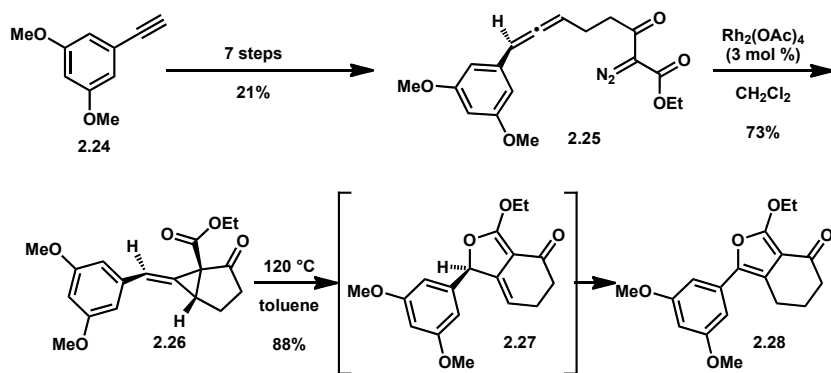
Rhodium was our metal of choice because we envisioned intermediates such as **2.18** arising from an interaction of a metal-carbenoid center (**2.20**) with an allene (**2.19**). Indeed, rhodium has a rich history of interacting with diazo compounds to rapidly and chemoselectively form Rh-carbenoids,⁷ which are electrophilic in nature. Rh-carbenoids are often generated alpha to carbonyls or imines, and therefore we envisioned such Rh-bound TMM variants would cyclize to give the corresponding furans or pyrroles (**2.23**), following initial cyclization to zwitterionic intermediate **2.21** and double bond isomerization (Scheme 2.4).

Scheme 2.4. Proposed generation of Rh-bound TMM and application toward aromatic heterocycles.



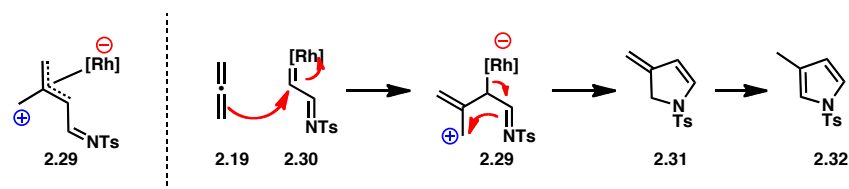
Previously, our group demonstrated the validity of this concept by isolating MCP derivative **2.26** from an intramolecular cyclopropanation of allene **2.25** by the tethered Rh-carbenoid formed from the treatment of diazo compound **2.25** with rhodium(II) acetate (see Scheme 5).⁸ Upon heating, the MCP derivative presumably fragments to form a TMM-moieity that interacts with the neighboring ester to yield hydrofuran **2.27**, which aromatizes to **2.28** following double bond migration.

Scheme 2.5. Formation of methylenecyclopropane intermediates and its application to the synthesis of substituted furans.



We were also interested in accessing pyrrole compounds (**2.32**, Scheme 2.6) for reasons discussed in Section 2.3.1. To achieve this goal, we envisioned that access to a rhodium carbenoid *alpha* to an imine group (**2.29**), instead of an ester functional group would be necessary. A tosyl imine moiety tethered to the Rh-bound TMM derivative should interact with the allyl cation of **2.29** to give dihydropyrrole **2.31** which could then aromatize to the pyrrole following double bond migration.

Scheme 2.6. Proposed application of Rh-bound TMM to pyrrole formation.



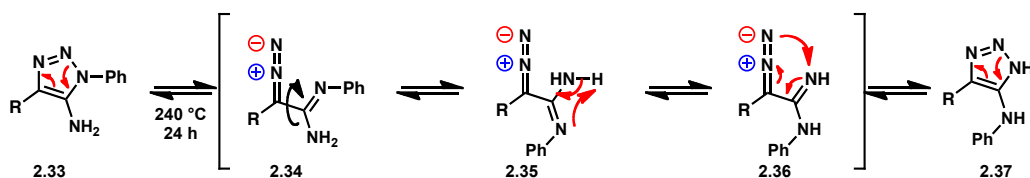
The success of the transformation shown in Scheme 2.6 hinges upon the effective generation of Rh-carbenoids related to **2.30**. This is historically difficult, because usually diazo transfer with reagents such as 4-acetamidobenzenesulfonyl azide (*p*-ABSA) usually require a lot of enolic character (e.g., in β -ketoesters), which leads to furans (Scheme 2.5). However, recently Rh-carbenoids related to **2.30** have been shown to arise from the decomposition of *N*-tosyl-1,2,3-triazoles.

2.2. Decomposition of *N*-tosyl-1,2,3-triazoles to *N*-sulfonylimino Rh-carbenoids.

2.2.1. Historical background

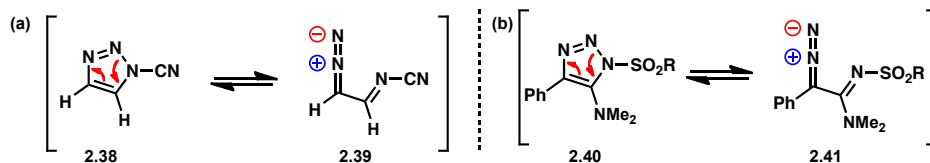
It has been known since the early 1900s that 1,2,3-triazoles are in equilibrium with an open imino-diazo form (see Scheme 2.7) owing to the work of Dimroth, which demonstrated that 1,2,3-triazoles bearing exocyclic amine groups (**2.33**) isomerize through ring-opened diazo-intermediates.⁹

Scheme 2.7. Dimroth rearrangement.



Sixty years later, Hermes and Marsh found that the open form of a 1,2,3-triazole is more prevalent if an electron-withdrawing group is attached to *N*-1. For instance, *N*-cyano-1,2,3-triazoles¹⁰ and *N*-sulfonyl-5-amino-1,2,3-triazoles¹¹ are found to exist in a 1:1 isomeric ratio between the open and closed forms (see Scheme 2.8).

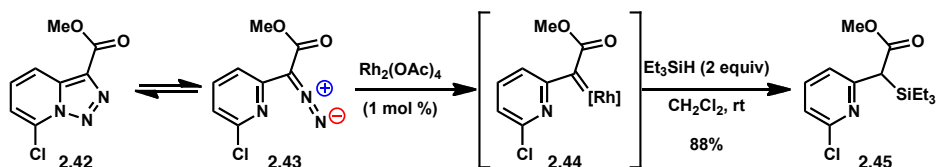
Scheme 2.8. Early observations of 1,2,3-triazole as closed and open form isomers.



2.2.2. 1,2,3-Triazoles as precursors to transient metallocarbenes

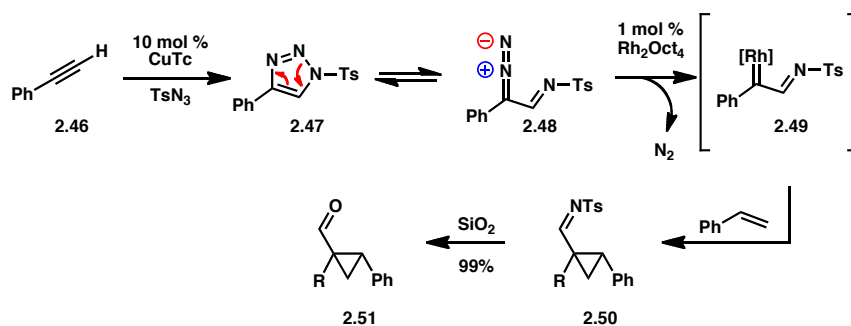
In 2007, Gevorgyan and co-workers exploited the closed/open triazole equilibrium present in pyridotriazoles (**2.42** to **2.43**) to decompose the triazole ring in the presence of a catalytic amount of rhodium(II) acetate to form transient Rh-carbenoids (**2.44**, Scheme 2.9). These imino metallocarbenoids were efficient in performing known Rh-carbenoid chemistry, such as insertion into a silicon-hydrogen bond.

Scheme 2.9. Rhodium carbenoid insertion into a Si-H bond.



Gevorgyan, in collaboration with Fokin, went on to show that *N*-sulfonyl-1,2,3-triazoles are also competent precursors to imino metallocarbenes (Scheme 2.10). The advent of the copper-catalyzed Huisgen reaction,¹² which provides access to *N*-sulfonyl-1,2,3-triazoles in a single step from alkynes (**2.46** to **2.47**), has made access to imino metallocarbenoids extremely convenient. Therefore, the decomposition of 1,2,3-triazoles bearing an electron-withdrawing group has had a major impact on the field of synthetic organic chemistry with many synthetic groups taking advantage of this chemistry to convert *N*-sulfonyl-1,2,3-triazoles to a variety of other heterocycles and structural motifs.^{13,14}

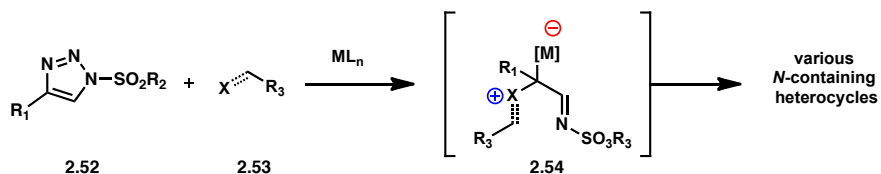
Scheme 2.10. Generation of Rh(II)-stabilized imino carbenoids from 1,2,3-triazoles.



2.2.3. Applications of 1,2,3-Triazoles as precursors to transient metallocarbenes

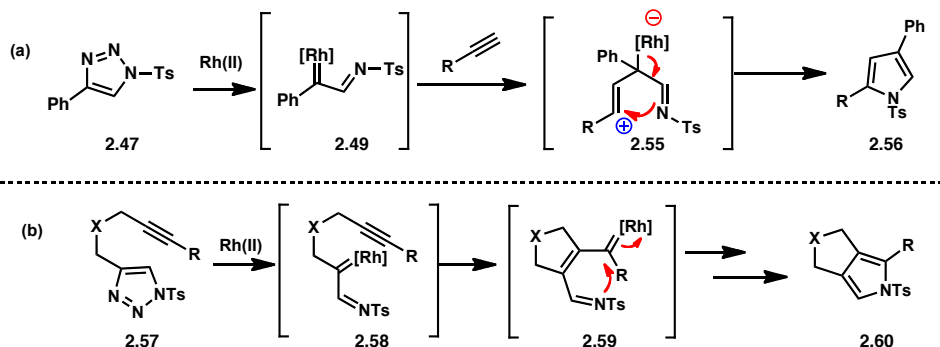
Since the initial reports by Gevorgyan and Fokin (Scheme 2.10), there have been many reports utilizing the pendant sulfonyl imine group to form *N*-containing heterocycles from a zwitterionic intermediate (**2.54**, Scheme 2.11) that results from initial nucleophilic attack on the electrophilic Rh-carbenoid. In many of these cases, the nucleophile (**2.53**) contains a heteroatom that helps to stabilize the resultant zwitterion. For instance if **2.53** is an aldehyde, intermediate **2.54** cyclizes to form 4-oxazolines.¹⁵ When **2.53** is a furan, the new heterocycle formed is a pyrrole with a pendant ketone group.¹⁶ When **2.53** is a nitrile, imidazoles are formed.¹⁷ Trans-2,3-disubstituted dihydropyrroles are formed when **2.53** is an α,β -unsaturated aldehyde.¹⁸ Reactions with imines, isocyanides, and isothiocyanates give imidazole,¹⁹ imidazolone, and thiazole²⁰ products, respectively.

Scheme 2.11. Formation of zwitterionic intermediate.



Gevorgyan and co-workers have also reported the formation of pyrroles by intermolecular reactions of the triazoles with terminal alkynes,²¹ that presumably proceeds via zwitterionic intermediate **2.55** bearing a vinyl cation (Scheme 2.12a). In addition, Gevorgyan has reported the intramolecular²² interaction of the Rh-carbenoids with alkynes that proceed through a carbene-alkyne metathesis mechanism (Scheme 2.12b).

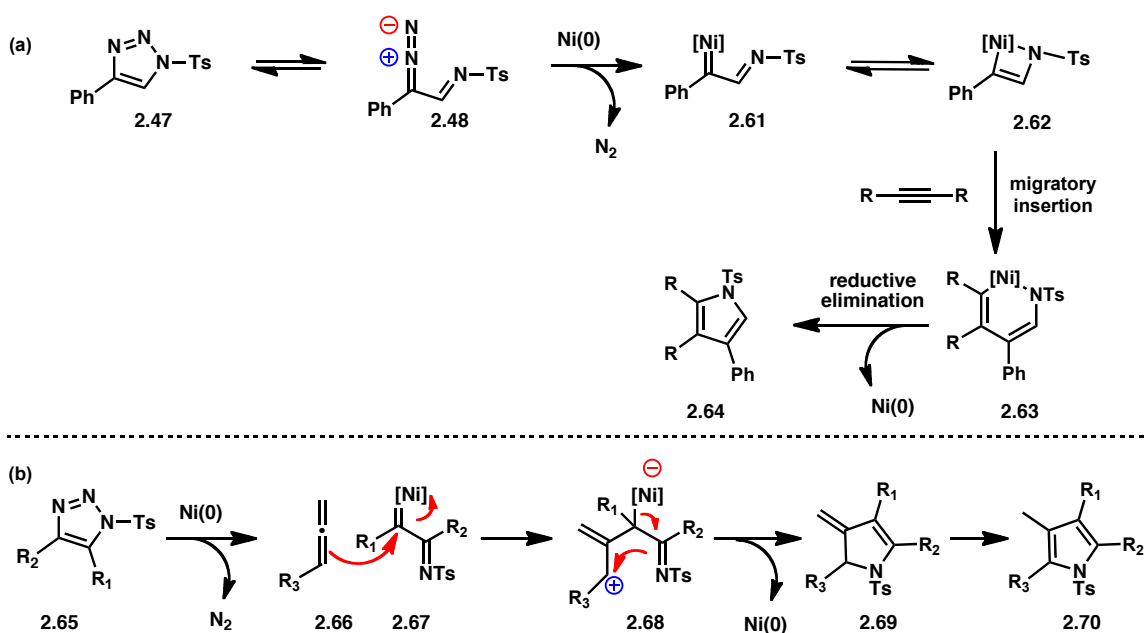
Scheme 2.12. Gevorgyan's pyrrole inter- and intramolecular pyrrole synthesis.



Murakami and co-workers have also reported the intermolecular interaction of these carbenes with carbon nucleophiles to form pyrroles. For instance, they found that internal alkynes²³ insert into an azanickelacycle (**2.62**) formed from the Ni-carbenoid tethered to an imine group (**2.61**). The intermediates form pyrroles after reductive

elimination (Scheme 2.13a). Furthermore, Murakami has found that addition of allenes to Ni-carbenoids,²⁴ (which they propose also goes through Ni-bound TMM variant **2.68**) will also form substituted pyrrole compounds (Scheme 2.13b).

Scheme 2.13. Murakami's Ni-catalyzed pyrrole formation from triazoles and alkynes or allenes.



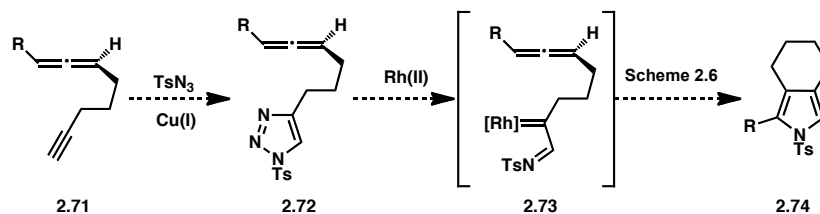
2.3. Synthesis of 3,4-fused pyrroles from N-tosyl-1,2,3-triazoles

This section incorporates previously published work.²⁵

2.3.1. Proposed reactivity and application

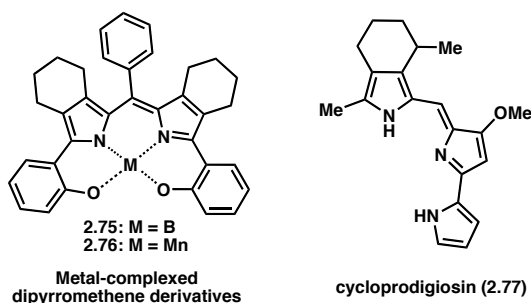
We were drawn to the intramolecular variant of the transformation outlined in Scheme 2.6 wherein allenylalkynes (**2.71**, Scheme 2.14) could be subjected to the Cu-catalyzed Huisgen cycloaddition to yield triazole **2.72**. On the basis of the observations of Fokin and co-workers, we anticipated that exposure of **2.72** to a catalytic amount of rhodium(II) acetate would lead to decomposition of the triazole to α -imino Rh-carbenoid intermediate **2.73**, which, following the sequence outlined in Scheme 2.6, should yield 3,4-fused-N-tosylpyrrole **2.74**.

Scheme 2.14. Intramolecular pyrrole annulation reaction for the formation of 3,4-fused pyrroles.



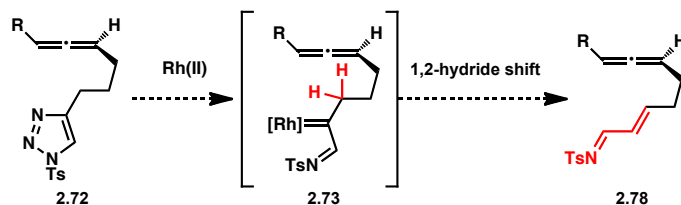
Pyrrole derivatives related to **2.74** are valuable starting points for the preparation of dipyrromethene ligands, which are used as dyes²⁶ (eg., **2.75**, Figure 2.3) and scavengers of reactive oxygen species²⁷ (eg., **2.76**). In addition, 3,4-fused pyrroles are found in natural products such as cycloprodigiosin (**2.77**), and we anticipated that a methodology allowing for facile access to such structural motifs could inform an efficient synthesis (see Chapter 4).

Figure 2.3. Metal-complexed dipyrromethene derivatives and cycloprodigiosin.



One significant potential pitfall of our planned transformation of **2.72** to **2.74** was the possibility that Rh-carbenoid intermediates related to **2.73**, consistent with well-documented precedent,²⁸ would undergo a competing 1,2-hydride shift to yield α,β -unsaturated *N*-tosylimines (**2.78**) instead of engaging the allene group (Scheme 2.15). Although 1,2-hydride shifts of α -keto Rh-carbenoids have been shown to be minimal at lower temperature,²⁹ Murakami showed that this pathway is facile for some α -*N*-sulfonylimino Rh-carbenoids,³⁰ especially at the high temperatures that are required for the decomposition of *N*-tosyl-1,2,3-triazoles to the corresponding Rh-carbenoids (>100 °C). As a result, the successful transformation of **2.72** to **2.74** would require that the 1,2-hydride shift from the Rh-carbenoid intermediates does not compete with the desired pathway (Scheme 2.14).

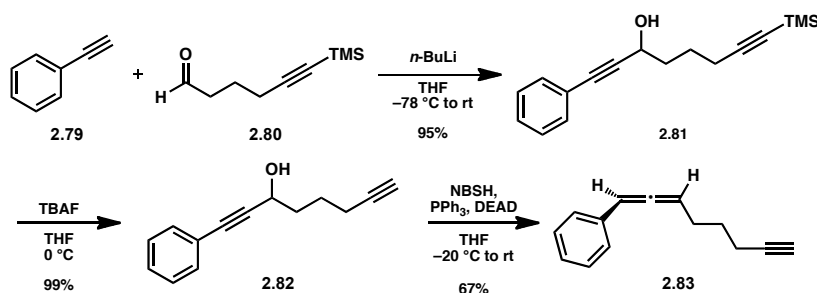
Scheme 2.15. Potential undesired 1,2-hydride shift to form **2.78**.



2.3.2. Substrate synthesis

We initiated our studies with allenylalkyne **2.83** (Scheme 2.16), which was readily prepared in three steps from phenylacetylene (**2.79**) and trimethylsilyl (TMS)-protected hex-5-ynal (**2.80**). Addition of phenylacetylene into aldehyde **2.80**, followed by removal of the TMS group formed **2.82** in excellent yield over two steps. Propargyl alcohol **2.82** was then subjected to the Myers' allene synthesis,³¹ which consists of a Mitsunobu reaction with *o*-nitrobenzylsulfonylhydrazine (NBSH) followed by an elimination and an allylic diazene rearrangement to release N₂ and form allene **2.83**.

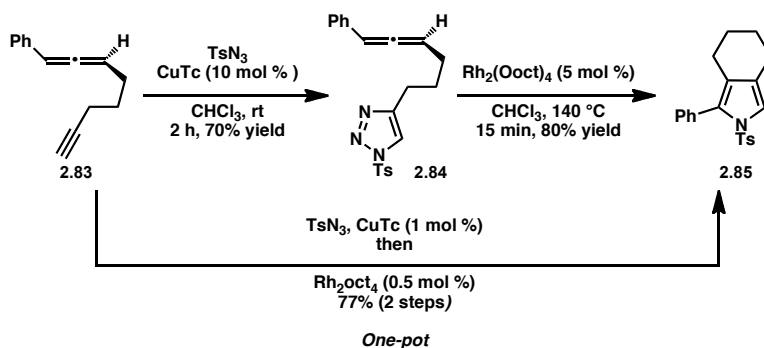
Scheme 2.16. Substrate synthesis.



2.3.3. Initial results

The copper(I) thiophene-2-carboxylate (CuTc)-catalyzed Huisgen cycloaddition of **2.83** with TsN₃ proceeded without event to give *N*-tosyl-1,2,3-triazole **2.84** in 70% yield following purification by column chromatography (Scheme 2.17). Gratifyingly, exposure of **2.84** to Rh₂(Ooct)₄ (5 mol %) in CHCl₃ at 140 °C (microwave), following the conditions of Fokin and Murakami,³² gave 2,3,4-substituted pyrrole **2.85** in 80% yield. Since both the Cu-catalyzed Huisgen azide–alkyne cycloaddition and the Rh-catalyzed triazole decomposition/pyrrole formation were conducted in chloroform, the development of a one-pot sequence to convert **2.83** to **2.85** was straightforward. Importantly, the catalyst loadings of both CuTc and Rh₂(Ooct)₄ could be reduced significantly (to 1 and 0.5 mol %, respectively), and **2.85** was obtained in higher overall yield (77% yield over two steps) than in the sequence where the triazole intermediate was isolated and purified.³³

Scheme 2.17. Initial results.



2.4. Substrate scope

Under the optimized one-pot conditions, a range of allenylalkyne substrates are efficiently transformed to the corresponding fused pyrroles (Table 2.1). For example, a variety of aryl substituents, including a naphthyl group (entry 1a) as well as arenes bearing electron-withdrawing (entries 1b and 1c) and electron-donating (entry 1d) groups on the allenylalkyne substrates are tolerated. In addition, cycloalkyl- and alkylbearing substrates are transformed to the corresponding pyrrole products in good yields (entries 1e and 1f). A bicyclo[3.3.0]-pyrrole, which is inherently more strained than the corresponding bicyclo[4.3.0] systems,³⁴ could also be accessed (entry 2), albeit in a slightly diminished overall yield (55%). Of note, only in the cases where moderate yields of the pyrrole products were obtained (<75% yield over the two steps), were small amounts of α,β -unsaturated imine byproducts also detected.

Table 2.1. Scope of 3,4-fused pyrrole formation.

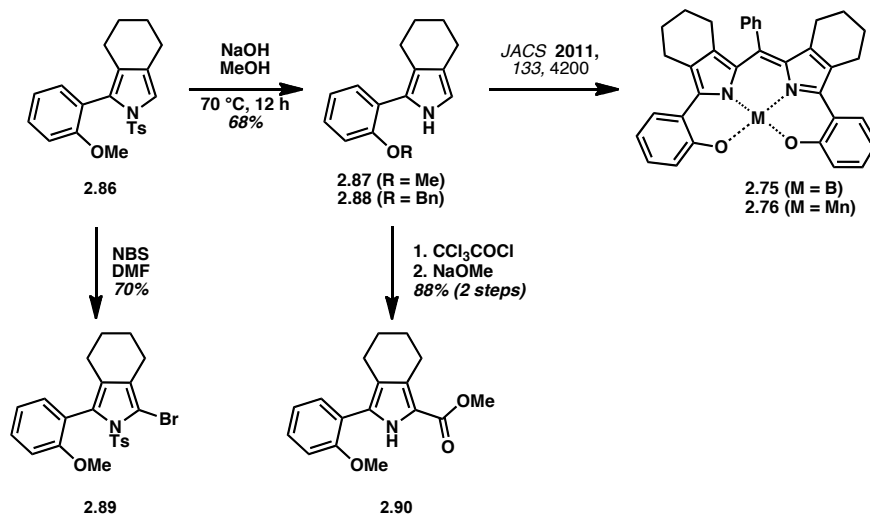
| entry | substrate | product | yield (%) |
|-------|--------------|---------|-----------|
| 1 | | | |
| (a) | | | 66 |
| (b) | | | 78 |
| (c) | | | 79 |
| (d) | | | 75 |
| (e) | | | 92 |
| (f) | <i>n</i> -Bu | | 74 |
| 2 | | | 55 |

2.5. Synthetic utility of 3,4-fused pyrrole products

The utility of the 3,4-fused pyrrole products is evident in the conversions involving **2.86** (Scheme 2.18). For example, after cleavage of the tosyl group, a related benzyl derivative of pyrrole **2.88** has been readily transformed to dipyrromethene

derivative **2.75**, a peroxyxynitrite scavenger, by Neumann and co-workers.³⁵ Furthermore, **2.87** and **2.86** can be transformed to ester-substituted pyrrole **2.90** and bromo derivative **2.89**, respectively, in good yields in preparation for subsequent pyrrole functionalization reactions.

Scheme 2.18. Synthetic utility of 3,4-fused pyrroles.



In addition to the applications detailed in Scheme 2.18, we applied our method for 3,4-fused pyrrole synthesis to the total synthesis of the natural product cycloprodigosin (**2.77**, Figure 2.3), see Chapter 4 for discussion.

2.6. Conclusion

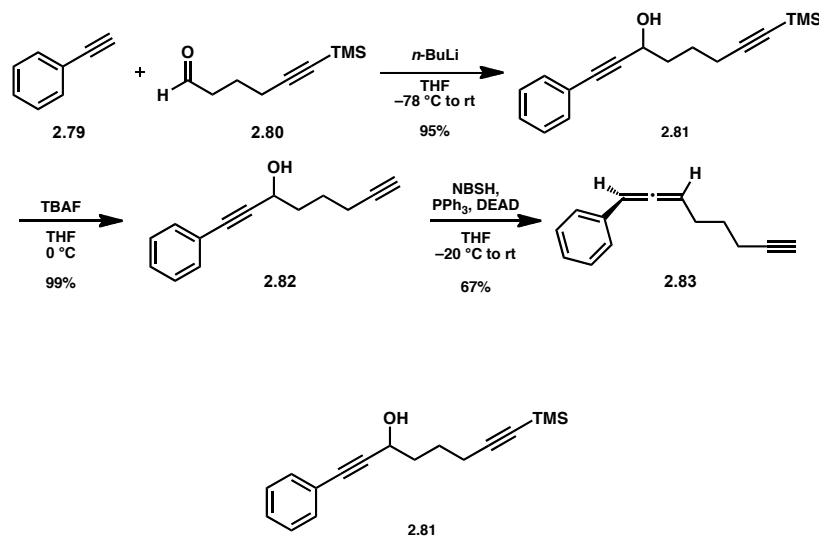
In conclusion, we have developed a synthesis of 2-substituted 3,4-fused pyrroles from allenylalkyne substrates. The one-pot transformation has its basis in a hypothesis for accessing unique Rh-bound trimethylenemethane intermediates. A range of functional groups are tolerated in this transformation. The pyrrole products should prove to be versatile starting points for a range of applications, as illustrated by the conversion of **2.88** to a dipyrromethene derivative as well as the conversion of **2.86** and **2.87** to other multiply-substituted pyrroles (Scheme 2.18).

2.7. Experimental

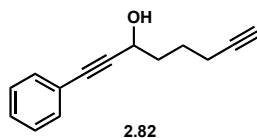
Materials and Methods.

Unless stated otherwise, reactions were performed in oven-dried glassware sealed with rubber septa under a nitrogen atmosphere and were stirred with Teflon-coated magnetic stir bars. Liquid reagents and solvents were transferred via syringe using standard Schlenk techniques. Tetrahydrofuran (THF), toluene, acetonitrile (MeCN), and methanol (MeOH) were dried by passage over a column of activated alumina; dichloromethane was distilled over calcium hydride. Anhydrous chloroform was obtained in a Sure/Seal bottle from Aldrich. All other solvents and reagents were used as received unless otherwise noted. Thin layer chromatography was performed using SiliCycle silica gel 60 F-254 precoated plates (0.25 mm) and visualized by UV irradiation and anisaldehyde, CAM, potassium permanganate, or iodine stain. Sorbent silica gel (particle size 40-63 μm) was used for flash chromatography. NMR experiments were performed on Bruker spectrometers operating at 300, 400, 500 or 600 MHz for ^1H and 75, 101, 126, or 151 MHz for ^{13}C experiments. ^1H and ^{13}C chemical shifts (δ) are reported relative to the residual solvent signal. Data are reported as follows: chemical shift (multiplicity, coupling constants where applicable, number of hydrogens). Abbreviations are as follows: s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublet), dt (doublet of triplet), p (pentet), hept (heptet), m (multiplet), bs (broad singlet). IR spectra were recorded on a Nicolet MAGNA-IR 850 spectrometer as thin films on NaCl plates and are reported in frequency of absorption (cm^{-1}). Only selected IR absorbencies are reported. 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. The microwave-assisted reactions were conducted using a Biotage Initiator 2.5 reactor.

Representative procedure for allene substrate synthesis.

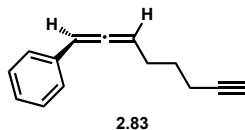


Propargylic alcohol (2.81). To a solution of phenyl acetylene (0.30 mL, 2.7 mmol, 1.0 equiv) in THF (9 mL, 0.3 M) at -78 °C was added *n*-BuLi (1.1 mL of a 2.5 M solution in hexanes, 2.9 mmol, 1.1 equiv) dropwise over 20 minutes. After holding at this temperature for 15 min, the dry ice/acetone bath was replaced with a 0 °C ice bath and the reaction mixture was held at 0 °C for 20 min before being cooled to -78 °C. The reaction flask was charged with TMS-protected hex-5-ynal,³⁶ which was added dropwise via syringe over 20 minutes. The reaction mixture was stirred for 15 min at -78 °C, then 1 h at ambient temperature, at which time TLC indicated complete consumption of the starting material, and the reaction mixture was quenched by the slow addition of saturated aqueous ammonium chloride (10 mL). The biphasic mixture was stirred for 15 min, then diluted with ethyl acetate (10 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo* to give **2.81** (690 mg, 95%) as a colorless oil, which was used without further purification.

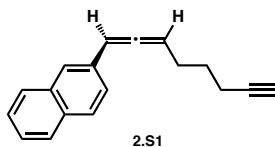


Terminal alkyne (2.82). A solution of TBAF (3.1 mL of a 1.0 M solution in THF, 3.1 mmol, 1.2 equiv) was added dropwise to a solution of propargylic alcohol **2.81** (690 mg, 2.6 mmol, 1.0 equiv) in THF (13 mL, 0.2 M) at 0 °C. The reaction mixture was allowed to stir at 0 °C for 30 min at which time TLC analysis indicated complete consumption of the starting material. The reaction mixture was quenched by the addition of saturated aqueous ammonium chloride (15 mL) and diluted with diethyl ether (10 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over sodium sulfate,

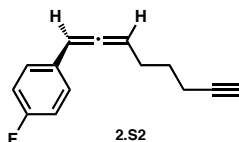
filtered, and concentrated *in vacuo* to give **2.82** (510 mg, 99%) as a colorless oil, which was used without further purification.



Octa-1,2-dien-7-yn-1-yl benzene (2.83).³⁷ To a solution of triphenylphosphine (1.0 g, 3.9 mmol, 1.5 equiv) in THF (5.2 mL, 0.75 M) at -20 °C (dry ice/brine bath) was added diethyl azodicarboxylate (0.61 mL, 1.5 equiv) dropwise over 1 min. The reaction mixture was stirred at -20 °C for an additional 10 min, then charged with **2.82** (510 mg, 2.6 mmol, 1.0 equiv) as a solution in THF (4.3 mL, 0.5 M) added dropwise over 10 min. After 30 minutes, 2-nitrobenzylsulfonylhydrazine (NBSH)³⁸ (850 mg, 3.9 mmol, 1.5 equiv) as a solution in THF (5.2 mL, 0.75 M) was added dropwise over 10 min. The reaction mixture was held at -20 °C for an additional 2 h then allowed to warm to ambient temperature and stirred for 10 h. After this time, the reaction mixture was diluted with dichloromethane (10 mL), the stirbar was removed and silica gel (2 g) was added to the reaction flask and the mixture was concentrated *in vacuo* and filtered through a short silica plug eluting with pentanes to give **2.83** (320 mg, 67%) as a colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 7.29 - 7.25 (m, 4H), 7.16 (tt, *J* = 5.8, 2.9 Hz, 1H), 6.13 (dt, *J* = 6.4, 3.1 Hz, 1H), 5.56 (q, *J* = 6.6 Hz, 1H), 2.28 - 2.21 (m, 1H), 1.93 (t, *J* = 2.6 Hz, 1H), 1.75-1.85 (m, 2H). Spectra were consistent with those reported previously.³⁹

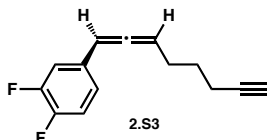


2-(octa-1,2-dien-7-yn-1-yl)naphthalene (2.S1). Prepared from 2-ethynynaphthalene using the representative procedure. IR (film): 3230, 3055, 2920, 2849, 1947, 1598, 1510, 1433, 1128, 895, 857, 820, 749. ¹H NMR (600 MHz, CDCl₃) δ 7.83 - 7.72 (m, 3H), 7.65 (s, 1H), 7.49 (d, *J* = 8.5 Hz, 1H), 7.45 (t, *J* = 7.4 Hz, 1H), 7.42 (t, *J* = 7.3 Hz, 1H), 6.34 (dt, *J* = 6.3, 3.1 Hz, 1H), 5.66 (q, *J* = 6.6 Hz, 1H), 2.33 - 2.27 (m, 4H), 1.97 (t, *J* = 2.7 Hz, 1H), 1.80 - 1.72 (m, 2H). ¹³C NMR (150 MHz, CDCl₃) δ 205.8, 133.7, 132.5, 132.3, 128.2, 127.7, 127.6, 126.1, 125.5, 125.3, 124.6, 95.4, 94.3, 84.0, 68.6, 27.7, 27.6, 17.9. HRMS (*m/z*): M⁺ calcd for C₁₈H₁₆, 232.1252; found, 232.1253.

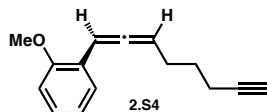


1-fluoro-4-(octa-1,2-dien-7-yn-1-yl)benzene (2.S2). Prepared from 1-ethynyl-4-fluorobenzene using the representative procedure. ¹H NMR (600 MHz, CDCl₃) δ 7.25 (dd, *J* = 8.5, 5.4 Hz, 2H), 7.00 (t, *J* = 8.5 Hz, 2H), 6.13 (dt, *J* = 6.4, 3.1 Hz, 1H), 5.58 (q,

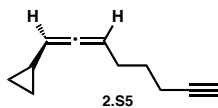
$J = 6.6$ Hz, 1H), 2.32 - 2.21 (m, 4H), 1.97 (t, $J = 2.8$ Hz, 1H), 1.78 - 1.67 (m, 2H). ^{13}C NMR (150 MHz, CDCl_3) δ 205.0, 162.6, 161.0, 130.7, 130.7, 128.0, 127.9, 115.5, 115.4, 94.3, 94.0, 84.0, 68.6, 27.7, 27.6, 17.9. HRMS (m/z): M^+ calcd for $\text{C}_{18}\text{H}_{16}$, 232.1252; found, 232.1253. HRMS (m/z): M^+ calcd for $\text{C}_{14}\text{H}_{13}\text{F}$, 200.1001; found, 200.1003.



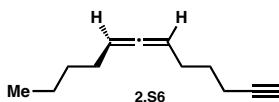
1,2-Difluoro-4-(octa-1,2-dien-7-yn-1-yl)benzene (2.S3). Prepared from 1-ethynyl-3,4-difluorobenzene using the representative procedure. IR (film): 3309, 2927, 2855, 2119, 1951, 1606, 1516, 1455, 1410, 1228, 1206, 1150, 1116, 960, 882, 785, 741, 631. ^1H NMR (600 MHz, CDCl_3) δ 7.15 - 7.03 (m, 2H), 7.00 - 6.93 (m, 1H), 6.07 (dt, $J = 6.4$, 3.1 Hz, 1H), 5.61 (q, $J = 6.6$ Hz, 1H), 2.31 - 2.24 (m, 4H), 1.97 (t, $J = 2.9$ Hz, 1H), 1.78 - 1.65 (m, 2H). ^{13}C NMR (150 MHz, CDCl_3) δ 205.3, 205.3, 151.4, 151.3, 150.1, 150.0, 149.7, 149.7, 148.4, 148.4, 132.1, 132.1, 132.1, 132.0, 122.4, 122.4, 122.4, 122.4, 117.3, 117.2, 115.0, 114.9, 94.9, 93.7, 93.7, 93.6, 83.8, 68.7, 27.6, 27.4, 17.9. HRMS (m/z): M^+ calcd for $\text{C}_{14}\text{H}_{12}\text{F}_2$, 218.0907; found, 218.0905.



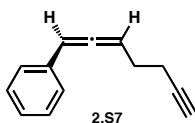
1-Methoxy-2-(octa-1,2-dien-7-yn-1-yl)benzene (2.S4). Prepared from 1-ethynyl-4-methoxybenzene using the representative procedure. IR (film): 3230, 2938, 2836, 2117, 1948, 1727, 1596, 1493, 1464, 1288, 1246, 1099, 1049, 1029, 885, 752, 629. ^1H NMR (600 MHz, CDCl_3) δ 7.37 (d, $J = 7.5$ Hz, 1H), 7.17 (t, $J = 7.8$ Hz, 1H), 6.92 (t, $J = 7.5$ Hz, 1H), 6.86 (d, $J = 8.2$ Hz, 1H), 6.56 (dt, $J = 6.3$, 3.1 Hz, 1H), 5.54 (q, $J = 6.6$ Hz, 1H), 3.85 (s, 3H), 2.32 - 2.20 (m, 4H), 1.96 (t, $J = 2.6$ Hz, 1H), 1.77 - 1.68 (m, 2H). ^{13}C NMR (150 MHz, CDCl_3) δ 205.6, 155.9, 127.8, 127.5, 123.2, 120.7, 110.9, 93.2, 88.8, 84.1, 68.5, 55.5, 27.8, 27.7, 17.9. HRMS (m/z): M^+ calcd for $\text{C}_{15}\text{H}_{16}\text{O}$, 212.1201; found, 212.1219.



Octa-1,2-dien-7-yn-1-ylcyclopropane (2.S5). Prepared from ethynylcyclopropane using the representative procedure. ^1H NMR (600 MHz, CDCl_3) δ 5.16 (qd, $J = 6.5$, 1.3 Hz, 1H), 4.98 (tt, $J = 6.2$, 2.9 Hz, 1H), 2.23 (td, $J = 7.2$, 2.7 Hz, 2H), 2.12 - 2.05 (m, 2H), 1.94 (t, $J = 2.6$ Hz, 1H), 1.63 (p, $J = 7.3$ Hz, 2H), 1.26 - 1.16 (m, 1H), 0.70 - 0.64 (m, 2H), 0.37 - 0.29 (m, 2H). ^{13}C NMR (150 MHz, CDCl_3) δ 203.3, 95.6, 91.7, 84.2, 68.3, 28.0, 27.8, 17.8, 9.5, 6.7, 6.5. HRMS (m/z): M^+ calcd for $\text{C}_{11}\text{H}_{14}$, 146.1096; found, 146.1095.

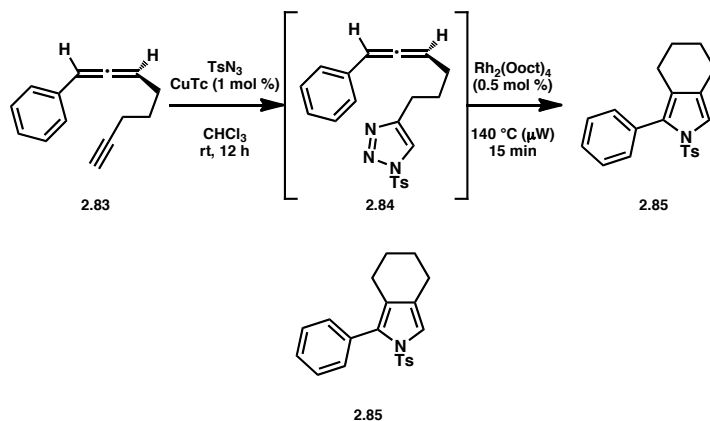


Dodeca-6,7-dien-1-yne (2.S6). Prepared from 1-hexyne using the representative procedure. $^1\text{H NMR}$ (600 MHz, CDCl_3) δ 5.13 - 5.02 (m, 2H), 2.23 (td, $J = 7.2, 2.7$ Hz, 2H), 2.09 (qd, $J = 7.0, 3.1$ Hz, 2H), 2.02 - 1.95 (m, 2H), 1.94 (t, $J = 2.7$ Hz, 1H), 1.64 (p, $J = 7.3$ Hz, 2H), 1.42 - 1.30 (m, 4H), 0.90 (t, $J = 7.0$ Hz, 3H). $^{13}\text{C NMR}$ (150 MHz, CDCl_3) δ 204.0, 91.4, 89.7, 84.3, 68.2, 31.3, 28.6, 27.9, 27.8, 22.1, 17.8, 13.9. **HRMS** (m/z): M^+ calcd for $\text{C}_{12}\text{H}_{18}$, 162.1409; found, 162.1410.



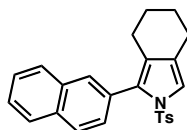
Hepta-1,2-dien-6-yn-1-ylbenzene (2.S7). Prepared from phenyl acetylene and TMS-protected pent-4-ynal⁴⁰ using the representative procedure. $^1\text{H NMR}$ (600 MHz, Chloroform-*d*) δ 7.34 - 7.28 (m, 4H), 7.22 - 7.17 (m, 1H), 6.22 - 6.17 (m, 1H), 5.68 - 5.62 (m, 1H), 2.41 - 2.33 (m, 4H), 1.99 (t, $J = 2.3$ Hz, 1H). $^{13}\text{C NMR}$ (150 MHz, CDCl_3) δ 205.2, 134.5, 128.5, 126.8, 126.7, 95.6, 93.4, 83.7, 68.9, 28.0, 18.3. **HRMS** (m/z): M^+ calcd for $\text{C}_{13}\text{H}_{12}$, 168.0939; found, 168.0942.

Representative procedure for pyrrole synthesis.



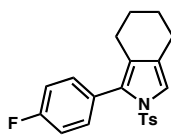
1-Phenyl-2-tosyl-4,5,6,7-tetrahydro-2H-isoindole (2.85). To a flame-dried microwave vial was added copper (I) thiophene carboxylate (CuTc , 1.0 mg, 5 mol %). The vial was sealed, and evacuated and backfilled with N_2 (3x), then allene **2.83** (100 mg, 0.54 mmol, 1.0 equiv) in chloroform (2.7 mL, 0.2 M) was added, followed by tosyl azide (84 mL, 0.54 mmol, 1.0 equiv). The reaction mixture was allowed to stir at ambient temperature for 12 h at which time TLC analysis indicated complete consumption of the starting material, and formation of triazole **2.84**. The reaction flask was then charged with $\text{Rh}_2(\text{Ooct})_4$ (2.1 mg, 0.5 mol %) dissolved in chloroform (0.2 mL, 0.015 M) via syringe. The resulting mixture was heated to 140 °C under microwave irradiation for 15 min. After cooling to ambient temperature, silica gel was added to the reaction mixture and the

solvent was removed *in vacuo*. The resulting residue was purified by column chromatography eluting with 6:1 hexanes:ethyl acetate to give **2.85** (146 mg, 77%) as a colorless oil. $^1\text{H NMR}$ (500 MHz, Chloroform-*d*) δ 7.34 - 7.29 (m, 3H), 7.26 - 7.22 (m, 2H), 7.18 - 7.13 (m, 2H), 7.13 - 7.08 (m, 3H), 2.56 (t, $J = 6.6$ Hz, 2H), 2.36 (s, 3H), 2.26 (t, $J = 6.3$ Hz, 2H), 1.70 - 1.63 (m, 2H), 1.63 - 1.55 (m, 2H). **HRMS** (m/z): M^+ calcd for $\text{C}_{21}\text{H}_{21}\text{NO}_2\text{S}$, 351.1293; found, 351.1294.



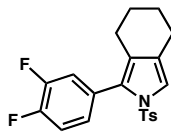
2.88

1-(naphthalen-2-yl)-2-tosyl-4,5,6,7-tetrahydro-isoindole (2.88). Prepared from **2.S1** using the representative procedure. **IR** (film): 2928, 2856, 1726, 1596, 1369, 1248, 1166, 1056, 817, 742, 672. $^1\text{H NMR}$ (600 MHz, Chloroform-*d*) δ 7.87 (dd, $J = 7.4, 1.9$ Hz, 1H), 7.81 (d, $J = 8.4$ Hz, 1H), 7.75 (dd, $J = 7.5, 1.8$ Hz, 1H), 7.53 - 7.48 (m, 3H), 7.38 (dd, $J = 8.4, 1.7$ Hz, 1H), 7.25 - 7.23 (m, 2H), 7.15 (s, 1H), 7.05 (d, $J = 8.0$ Hz, 2H), 2.59 (t, $J = 6.5$, 2H), 2.35 (s, 3H), 2.31 (t, $J = 6.3$ Hz, 2H), 1.73 - 1.65 (m, 2H), 1.64 - 1.55 (m, 2H). $^{13}\text{C NMR}$ (150 MHz, CDCl_3) δ 144.1, 136.0, 132.7, 132.6, 130.1, 129.5, 129.3, 129.2, 128.8, 128.0, 127.7, 127.1, 127.0, 126.6, 126.2, 126.2, 125.9, 124.3, 118.4, 23.2, 23.2, 22.2, 22.0, 21.5. **HRMS** (m/z): M^+ calcd for $\text{C}_{25}\text{H}_{23}\text{NO}_2\text{S}$, 401.1449; found, 401.1454.



2.89

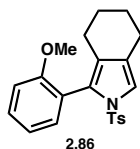
1-(4-fluorophenyl)-2-tosyl-4,5,6,7-tetrahydro-2H-isoindole (2.89). Prepared from **2.S2** using the representative procedure. **IR** (film): 2930, 2857, 1596, 1495, 1369, 1222, 1173, 1101, 671. $^1\text{H NMR}$ (400 MHz, Chloroform-*d*) δ 7.26 - 7.22 (m, 2H), 7.15 - 7.07 (m, 5H), 7.04 - 6.96 (m, 2H), 2.55 (td, $J = 6.4, 1.4$ Hz, 2H), 2.37 (s, 3H), 2.22 (t, $J = 6.2$ Hz, 2H), 1.70 - 1.56 (m, 4H). $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 163.6, 161.2, 144.3, 135.9, 133.1, 133.0, 129.3, 128.3, 127.0, 127.0, 126.9, 125.8, 124.0, 118.2, 114.4, 114.2, 23.1, 22.1, 21.8, 21.6. **HRMS** (m/z): M^+ calcd for $\text{C}_{21}\text{H}_{20}\text{FNO}_2\text{S}$, 369.1199; found, 369.1195.



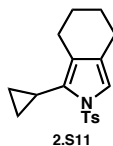
2.810

1-(3,4-difluorophenyl)-2-tosyl-4,5,6,7-tetrahydro-2H-isoindole (2.810). Prepared from **2.S3** using the representative procedure. $^1\text{H NMR}$ (600 MHz, Chloroform-*d*) δ 7.28 (d, $J = 8.1$ Hz, 2H), 7.15 (d, $J = 8.0$ Hz, 2H), 7.14 - 7.07 (m, 2H), 6.94 - 6.87 (m, 2H), 2.55 (t, $J = 6.3$ Hz, 2H), 2.38 (s, 3H), 2.23 (t, $J = 6.2$ Hz, 2H), 1.71 - 1.57 (m, 4H). $^{13}\text{C NMR}$

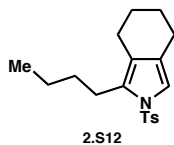
(151 MHz, CDCl₃) δ 149.2, 149.2, 148.5, 148.4, 144.0, 135.9, 129.4, 127.7, 127.7, 127.6, 127.2, 127.0, 126.4, 124.1, 120.2, 120.1, 118.6, 116.2, 116.1, 23.1, 22.0, 21.8, 21.5. **HRMS** (m/z): M⁺ calcd for C₂₁H₁₉F₂NO₂S, 387.1105; found, 387.1104.



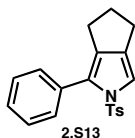
1-(2-methoxyphenyl)-2-tosyl-4,5,6,7-tetrahydro-2H-isoindole (2.86). Prepared from **2.S4** using the representative procedure. **IR** (film): 2931, 2856, 1737, 1596, 1434, 1367, 1246, 1171, 1098, 670. **¹H NMR** (400 MHz, Chloroform-*d*) δ 7.52 - 7.28 (m, 3H), 7.26 - 7.11 (m, 3H), 7.09 - 6.99 (m, 1H), 6.99 - 6.93 (m, 1H), 6.91 - 6.81 (m, 1H), 3.62 (s, 3H), 2.71 - 2.56 (m, 2H), 2.40 (s, 3H), 2.31 - 2.17 (m, 2H), 1.80 - 1.56 (m, 4H). **¹³C NMR** (101 MHz, CDCl₃) δ 158.5, 143.8, 136.5, 133.4, 129.9, 129.1, 127.3, 125.8, 125.5, 123.8, 120.0, 119.4, 117.6, 110.3, 55.2, 23.3, 23.1, 22.0, 21.8, 21.6. **HRMS** (m/z): M⁺ calcd for C₂₂H₂₃NO₃S, 381.1399; found, 381.1403.



1-cyclopropyl-2-tosyl-4,5,6,7-tetrahydro-2H-isoindole (2.S11). Prepared from **2.S5** using the representative procedure. **¹H NMR** (500 MHz, Chloroform-*d*) δ 7.70 (d, J = 8.0 Hz, 2H), 7.29 (d, J = 8.0 Hz, 2H), 7.04 (s, 1H), 2.52 (t, J = 5.1 Hz, 2H), 2.45 (t, J = 6.2 Hz, 1H), 2.42 (s, 3H), 1.78 - 1.69 (m, 1H), 1.68 - 1.59 (m, 4H), 0.72 - 0.70 (m, J = 4.2 Hz, 2H), 0.46 - 0.39 (m, 2H). **¹³C NMR** (126 MHz, CDCl₃) δ 144.0, 137.0, 129.5, 129.0, 127.0, 123.3, 122.5, 117.0, 23.4, 23.0, 22.8, 21.9, 21.5, 6.9, 6.4. **HRMS** (m/z): M⁺ calcd for C₁₈H₂₁NO₂S, 315.1293; found, 315.1293.

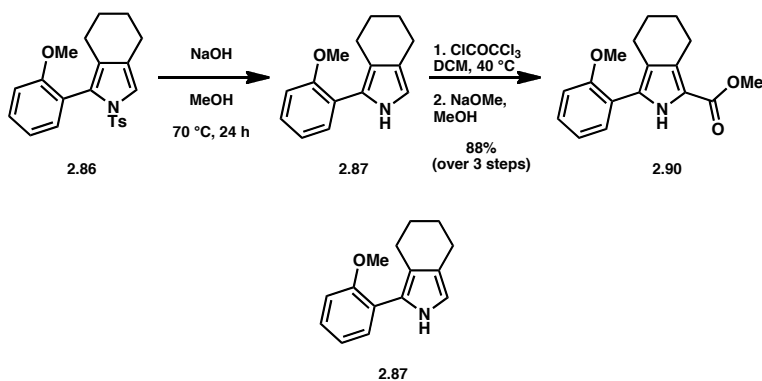


1-butyl-2-tosyl-4,5,6,7-tetrahydro-2H-isoindole (2.S12). Prepared from **2.S6** using the representative procedure. **IR** (film): 2930, 2858, 1597, 1440, 1365, 1249, 1187, 1174, 1100, 1066, 668, 587. **¹H NMR** (400 MHz, Chloroform-*d*) δ 7.62 (d, J = 8.3 Hz, 2H), 7.26 (d, J = 8.1 Hz, 2H), 6.92 (s, 1H), 2.61 - 2.52 (m, 2H), 2.49 (td, J = 5.7, 4.9, 1.9 Hz, 2H), 2.39 (s, 3H), 2.38 - 2.32 (m, 2H), 1.70 - 1.59 (m, 4H), 1.45 - 1.34 (m, 2H), 1.33 - 1.21 (m, 2H), 0.85 (t, J = 7.2 Hz, 3H). **¹³C NMR** (101 MHz, CDCl₃) δ 144.1, 137.2, 129.9, 129.8, 126.6, 123.6, 123.0, 116.5, 32.1, 25.2, 23.4, 23.3, 22.7, 21.9, 21.7, 21.6, 13.9. **HRMS** (m/z): M⁺ calcd for C₁₉H₂₅NO₂S, 331.1606; found, 331.1602.

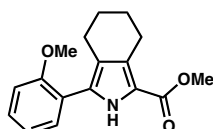


1-phenyl-2-tosyl-2,4,5,6-tetrahydrocyclopenta[*c*]pyrrole (2.S13). Prepared from **2.S7** using the representative procedure. $^1\text{H NMR}$ (500 MHz, Chloroform-*d*) δ 7.36 - 7.30 (m, 3H), 7.29 - 7.23 (m, 4H), 7.10 (d, $J = 7.9$ Hz, 2H), 7.01 (s, 1H), 2.59 (t, $J = 7.2$ Hz, 2H), 2.44 (t, $J = 7.2$ Hz, 2H), 2.35 (s, 3H), 2.21 (p, $J = 7.2$ Hz, 2H). $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 144.5, 138.7, 136.2, 135.5, 132.1, 130.9, 129.6, 128.0, 127.8, 127.6, 127.4, 115.5, 31.2, 25.3, 25.2, 22.0. **HRMS** (m/z): M^+ calcd for $\text{C}_{20}\text{H}_{19}\text{NO}_2\text{S}$, 337.1136; found, 337.1137.

Further functionalization of pyrrole **2.86**.

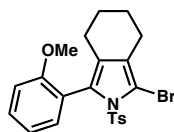
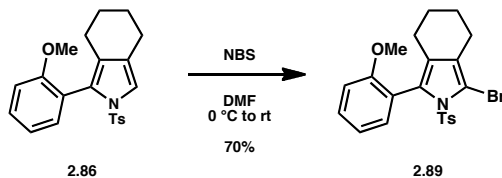


Deprotected pyrrole (2.87). To a degassed solution of **2.86** (38 mg, 0.10 mmol, 1.0 equiv) in methanol (1 mL, 0.1 M), was added finely powdered NaOH (60 mg, 1.5 mmol, 15 equiv) under a stream of N_2 . The reaction mixture was heated to 70 °C and held at this temperature for an additional 24 h. After this time, the reaction mixture was cooled to ambient temperature and quenched by the addition of saturated ammonium chloride (2 mL) and diluted with dichloromethane (2 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (2 x 2 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo* to give **2.87** as a purple film, which was used immediately without further purification. **IR** (film): 3315, 2934, 2857, 2360, 1693, 1489, 1463, 1437, 1245, 1047, 1023, 754, 679. $^1\text{H NMR}$ (600 MHz, Chloroform-*d*) δ 7.35 - 7.30 (m, 1H), 7.18 (dd, $J = 7.8, 1.8$ Hz, 1H), 7.02 - 6.94 (m, 2H), 6.43 (s, 1H), 3.93 (s, 3H), 2.48 - 2.38 (m, 2H), 2.18 - 2.11 (m, 2H), 1.74 - 1.62 (m, 4H). $^{13}\text{C NMR}$ (150 MHz, CDCl_3) δ 172.8, 157.0, 156.8, 132.1, 129.8, 127.4, 126.5, 121.4, 111.4, 88.6, 55.7, 22.0, 22.0, 21.7, 19.8.



2.90

Pyrrole methyl ester (2.90). Dichloromethane (0.5 mL, 0.2 M) was added to a vial containing pyrrole **2.87** (0.10 mmol, 1.0 equiv) and imidazole (11 mg, 0.16 mmol, 1.6 equiv). To this solution was added 2,2,2-trichloroacetyl chloride (17 mL, 0.15 mmol, 1.5 equiv). The resulting solution was heated to 40 °C and held at this temperature for 2 h. Upon cooling to ambient temperature, the reaction mixture was quenched by the addition of saturated aqueous sodium bicarbonate (1 mL). The layers were separated the aqueous layer was extracted with dichloromethane (2 x 2 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo*. To this residue was added a stirbar and NaOMe (2 mL as a freshly prepared 0.05 M solution in methanol, 0.10 mmol, 1.0 equiv). After stirring at ambient temperature for 2 h, the reaction mixture was quenched by the addition of saturated ammonium chloride (1 mL). The methanol was then removed *in vacuo* and the resulting residue was diluted with water (2 mL) and ethyl acetate (2 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (3 x 2 mL). The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo* to give **2.90** (24.5 mg, 88% over 3 steps) as a colorless film. $^1\text{H NMR}$ (500 MHz, Chloroform-*d*) δ 9.82 (bs, 1H), 7.53 (dd, $J = 7.7, 1.7$ Hz, 1H), 7.30 - 7.24 (m, 1H), 7.06 - 6.98 (m, 2H), 3.93 (s, 3H), 3.86 (s, 3H), 2.87 (t, $J = 6.1$ Hz, 2H), 2.71 (t, $J = 5.9$ Hz, 2H), 1.84 - 1.72 (m, 4H). $^{13}\text{C NMR}$ (125 MHz, CDCl₃) δ 162.2, 156.1, 129.2, 129.0, 128.6, 128.3, 121.0, 120.7, 120.6, 116.7, 111.4, 55.8, 51.2, 24.5, 23.9, 23.5, 23.1.



2.89

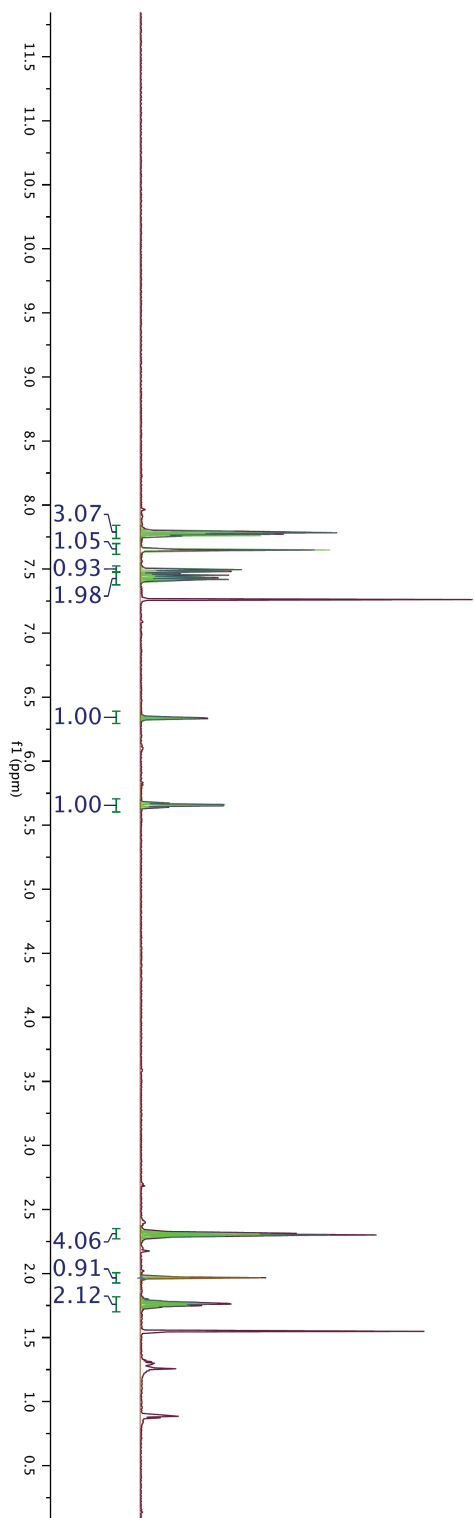
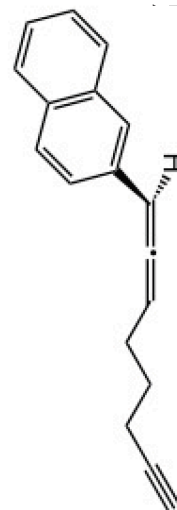
Bromopyrrole (2.89). To a degassed solution of **2.86** (27 mg, 0.071 mmol, 1.0 equiv) in DMF (0.7 mL, 0.1 M) cooled to 0 °C, was added NBS (14 mg, 0.078 mmol, 1.1 equiv) portionwise under a stream of N₂. The reaction mixture was allowed to warm to ambient temperature over 1 h, then quenched by the addition of saturated aqueous sodium thiosulfate (1 mL), and diluted with dichloromethane (2 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (2 x 2 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo* to give

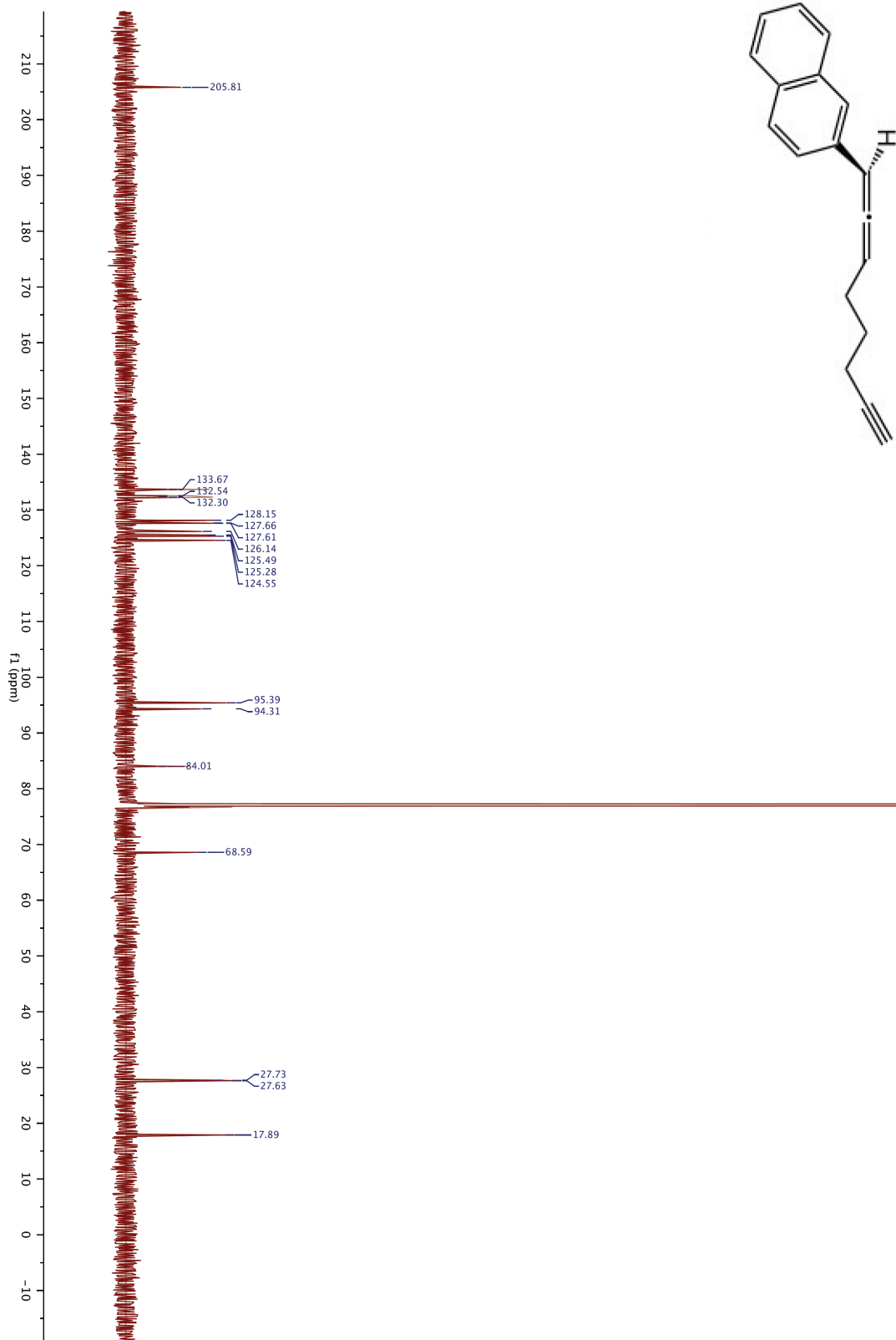
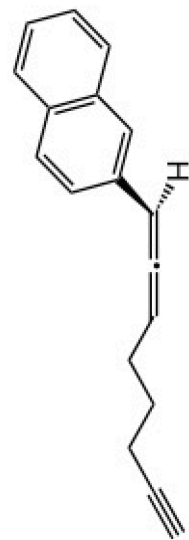
2.89 (22 mg, 70%) as a colorless oil. **IR** (film): 2932, 2857, 1595, 1486, 1378, 1180, 1028, 667. **¹H NMR** (500 MHz, Chloroform-*d*) δ 7.59 (d, J = 8.1 Hz, 2H), 7.36 (td, J = 7.7, 1.7 Hz, 1H), 7.21 (d, J = 8.0 Hz, 2H), 7.16 - 7.11 (m, 1H), 6.97 (t, J = 7.4 Hz, 1H), 6.93 (d, J = 8.3 Hz, 1H), 3.80 (s, 3H), 2.39 (s, 3H), 2.34 (t, J = 6.5 Hz, 2H), 2.26 - 2.12 (m, 2H), 1.74 - 1.57 (m, 4H). **¹³C NMR** (125 MHz, CDCl₃) δ 158.2, 144.3, 136.3, 132.2, 129.9, 129.7, 129.3, 127.6, 127.5, 125.9, 121.7, 119.7, 110.6, 99.3, 55.4, 23.1, 22.8, 22.7, 22.1, 21.7, 14.2. **HRMS** (m/z): M⁺ calcd for C₂₂H₂₂BrNO₃S, 459.0504; found, 459.0504.

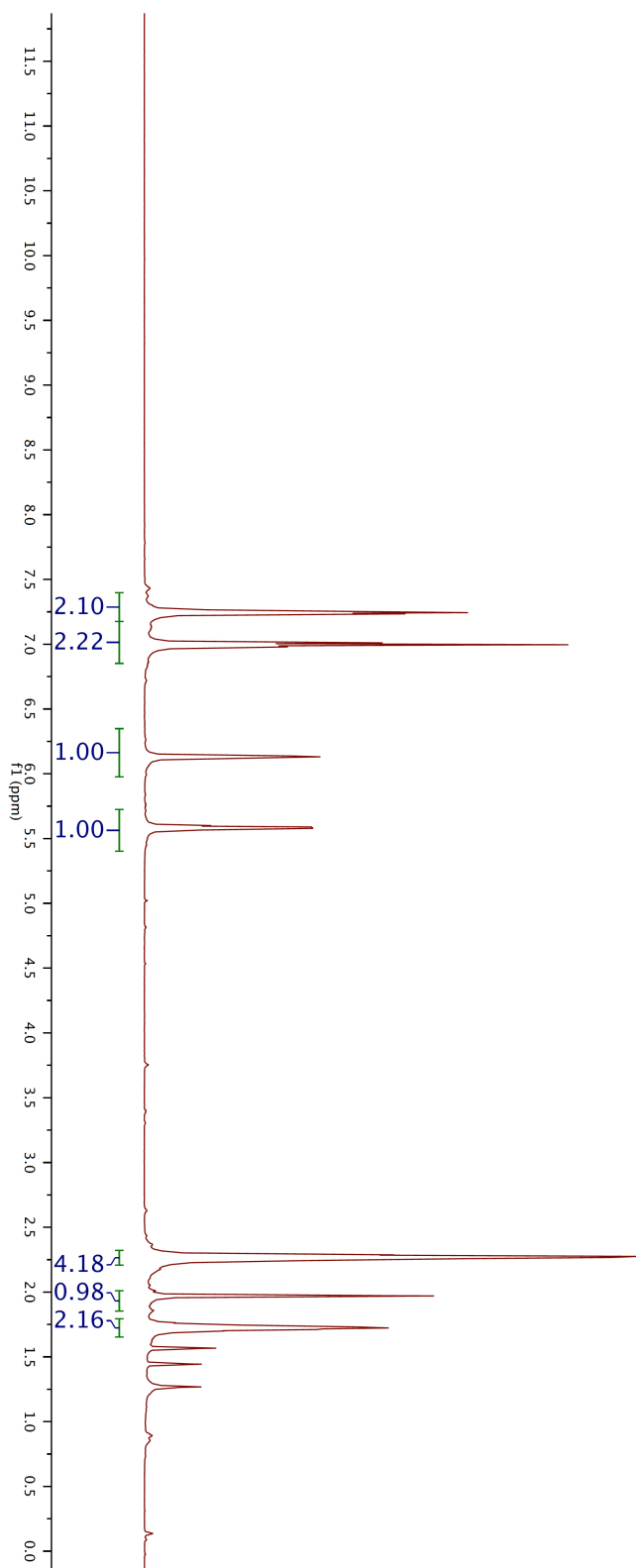
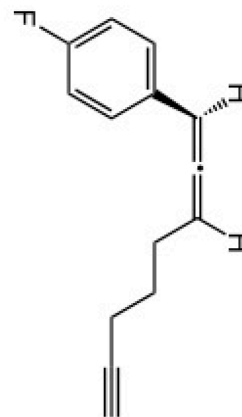
2.8 References and Notes

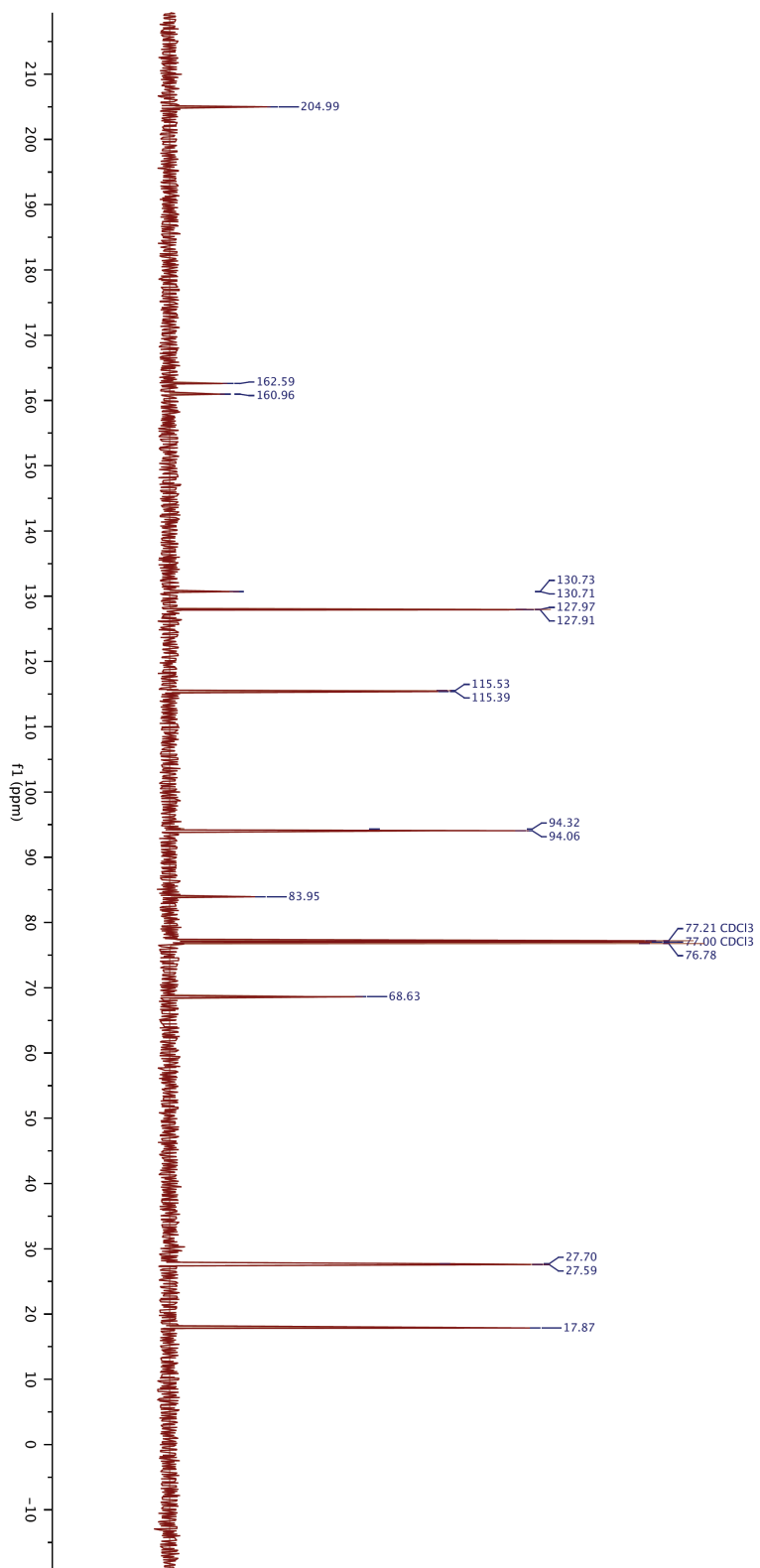
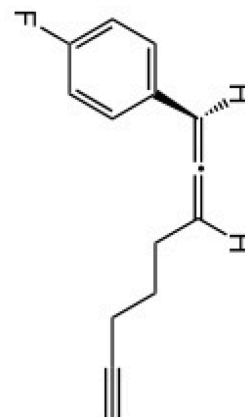
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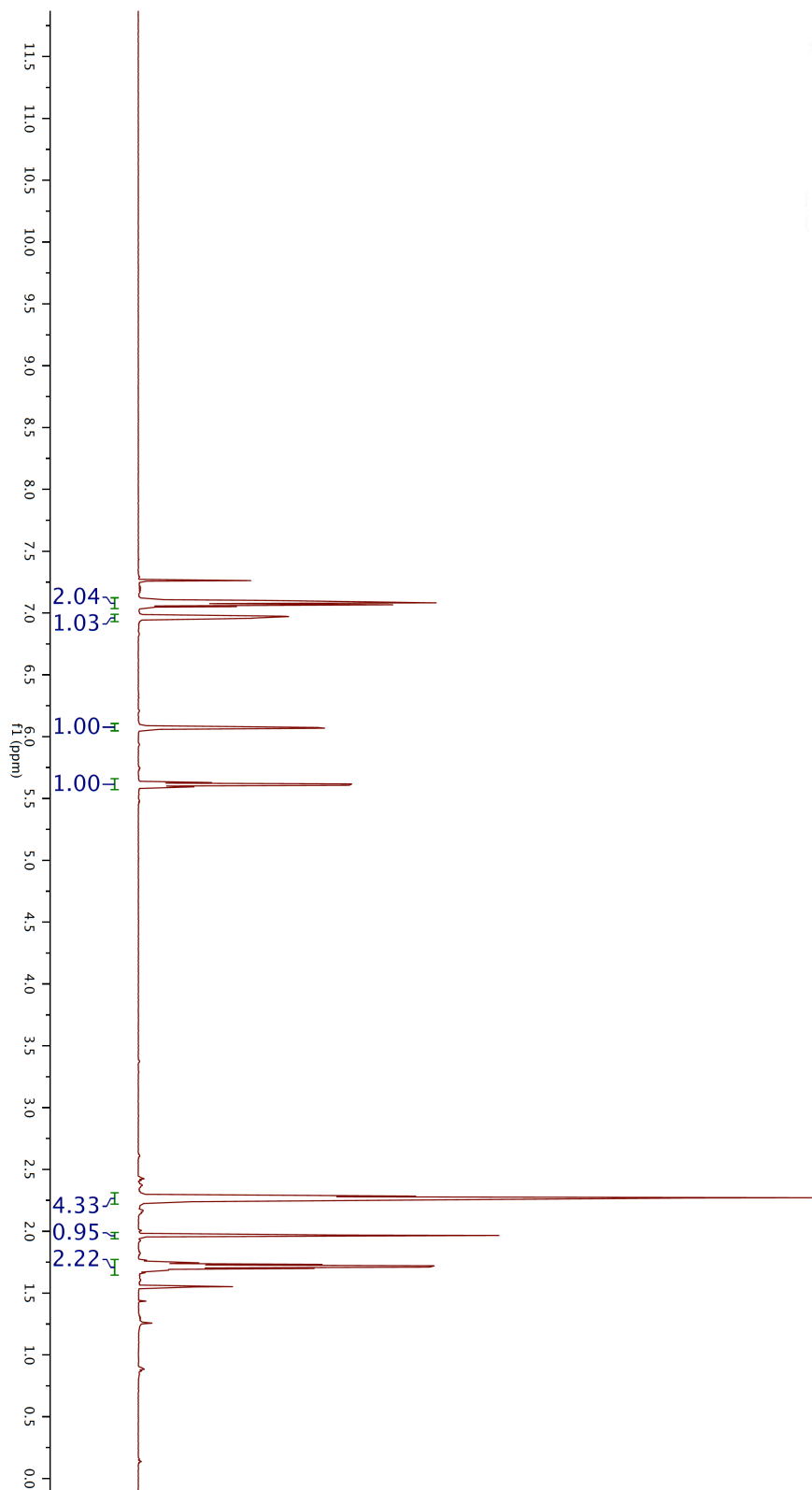
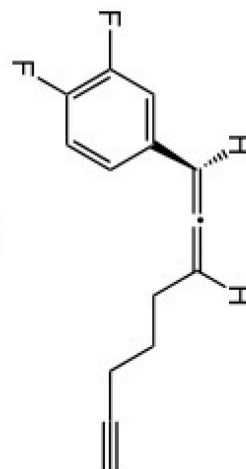
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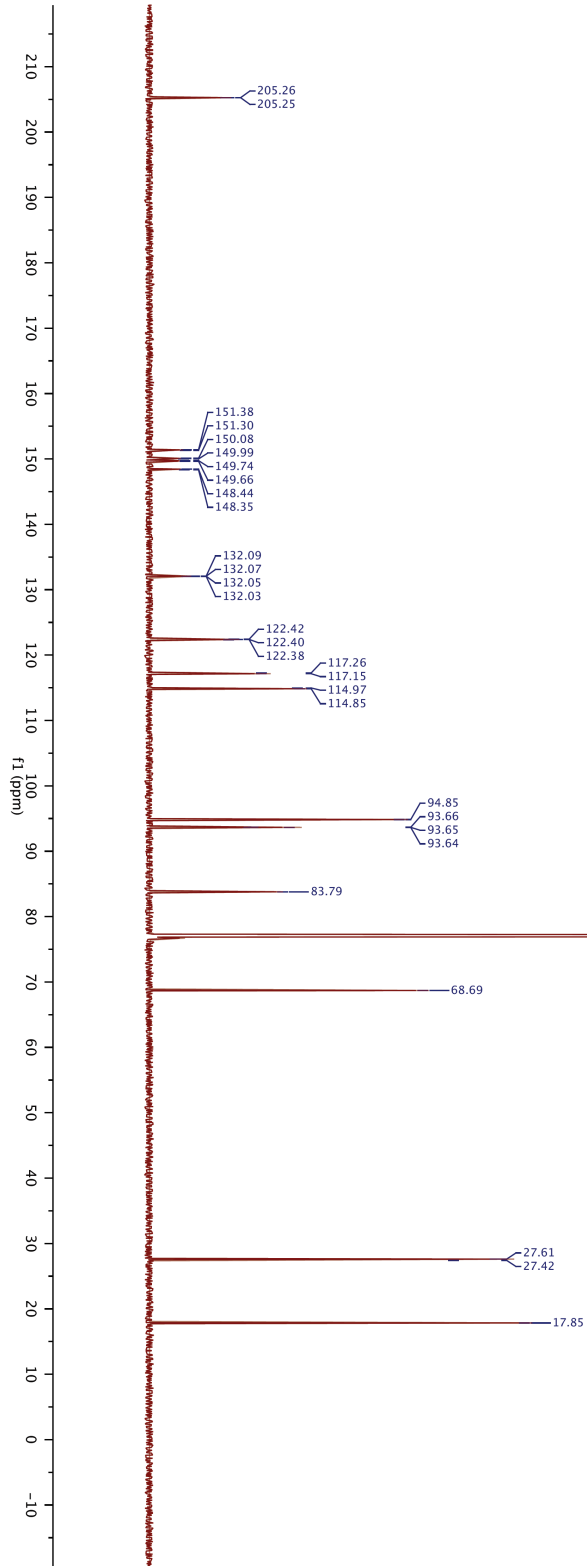
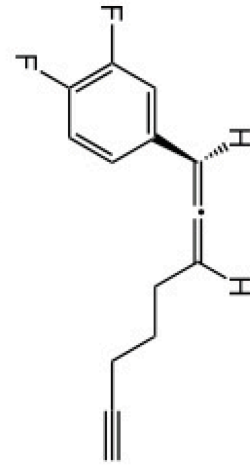


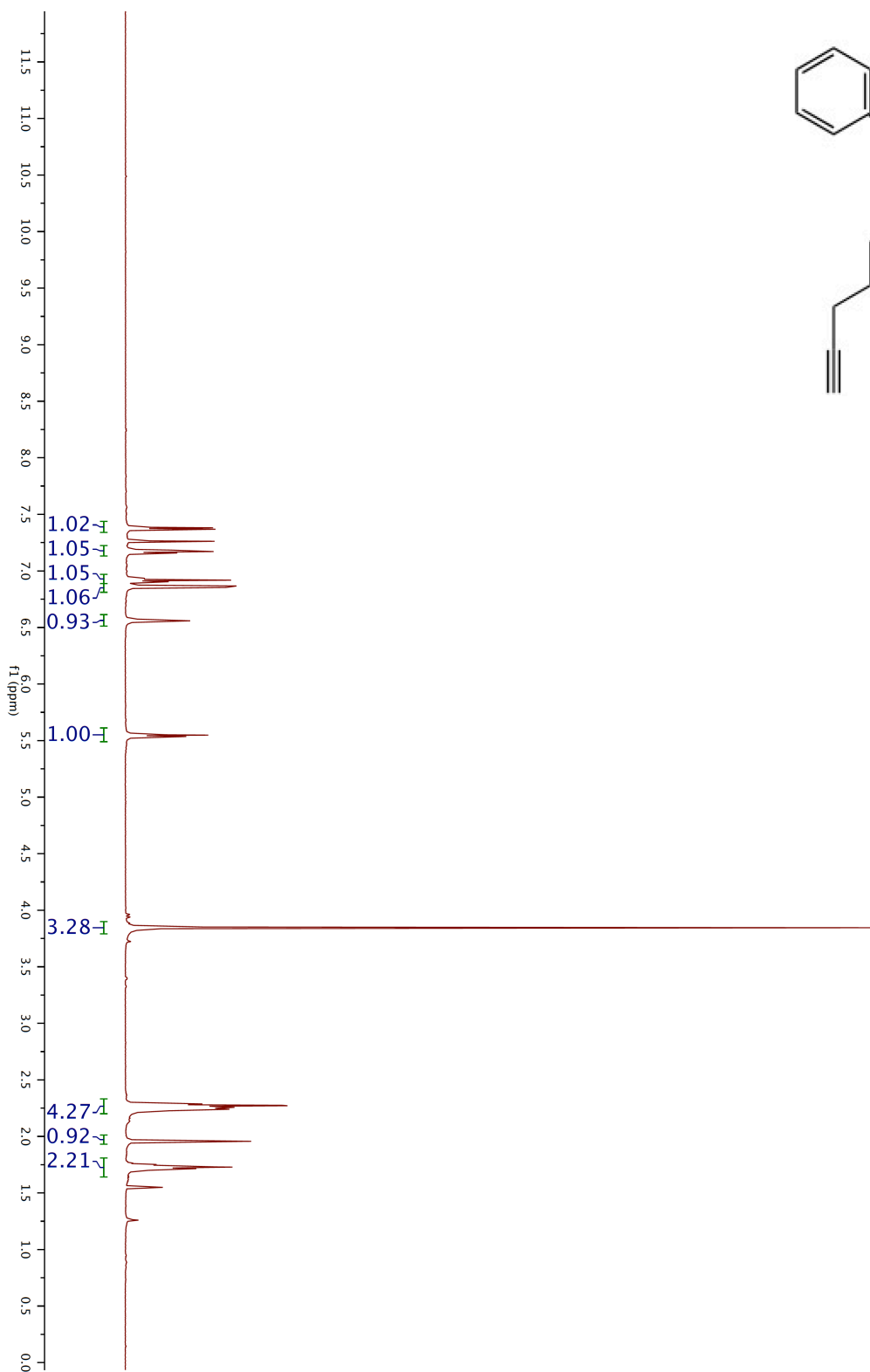
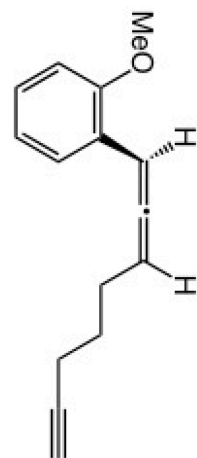


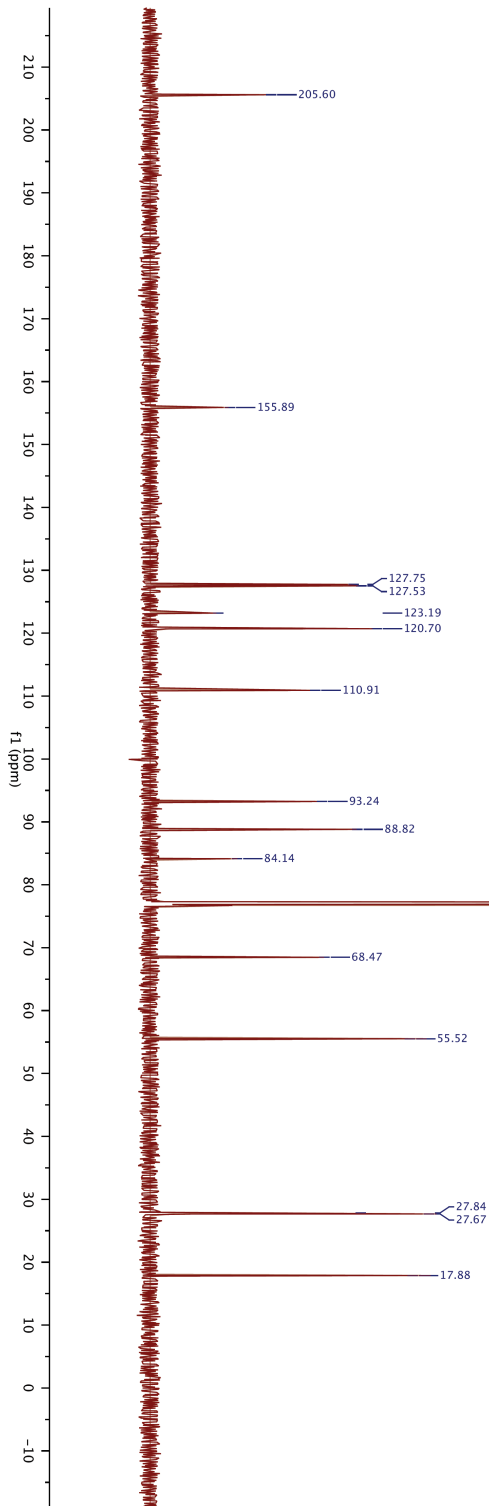
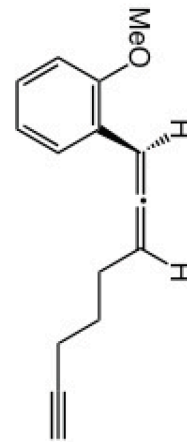


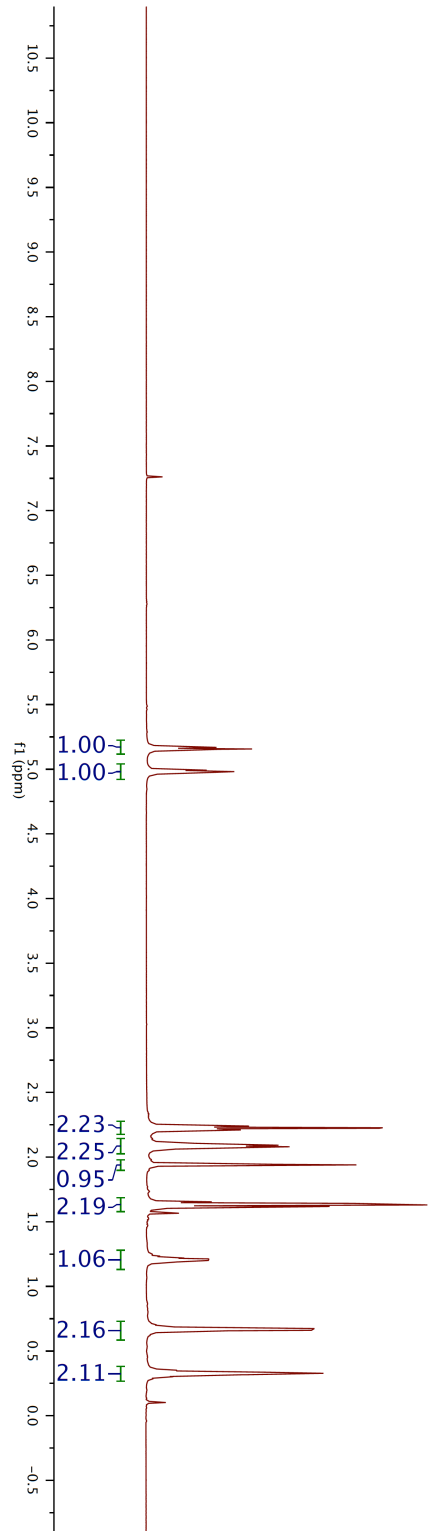
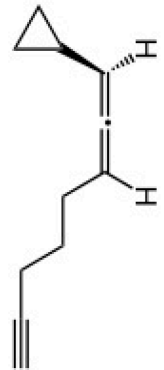


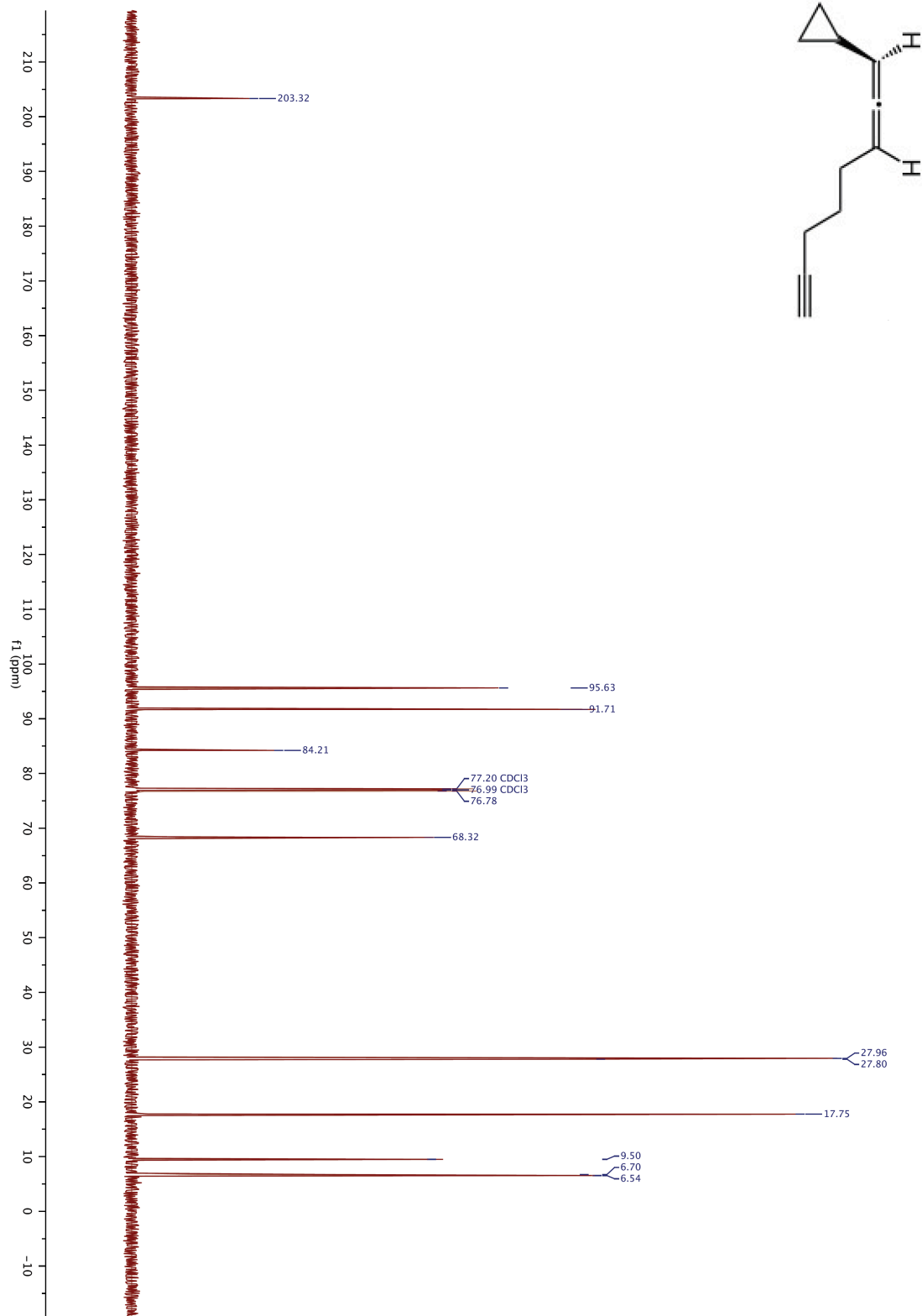


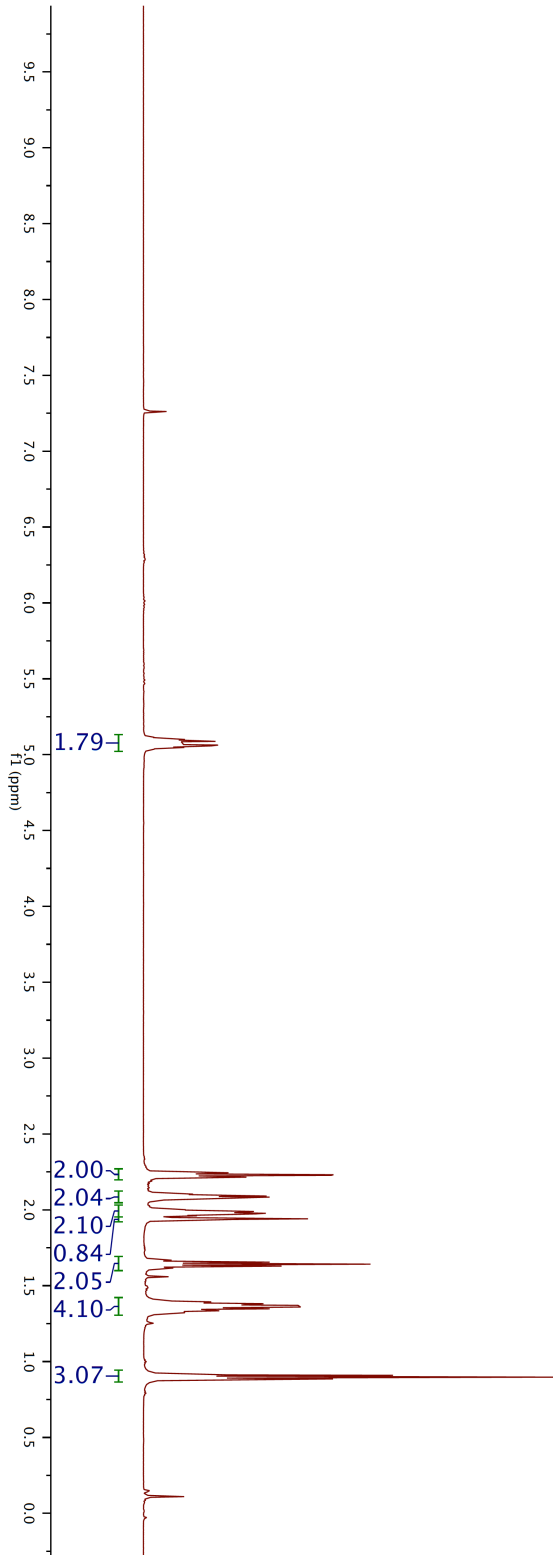
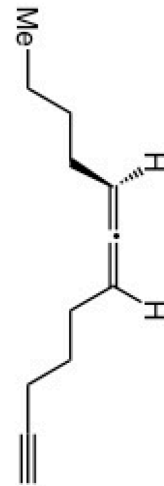


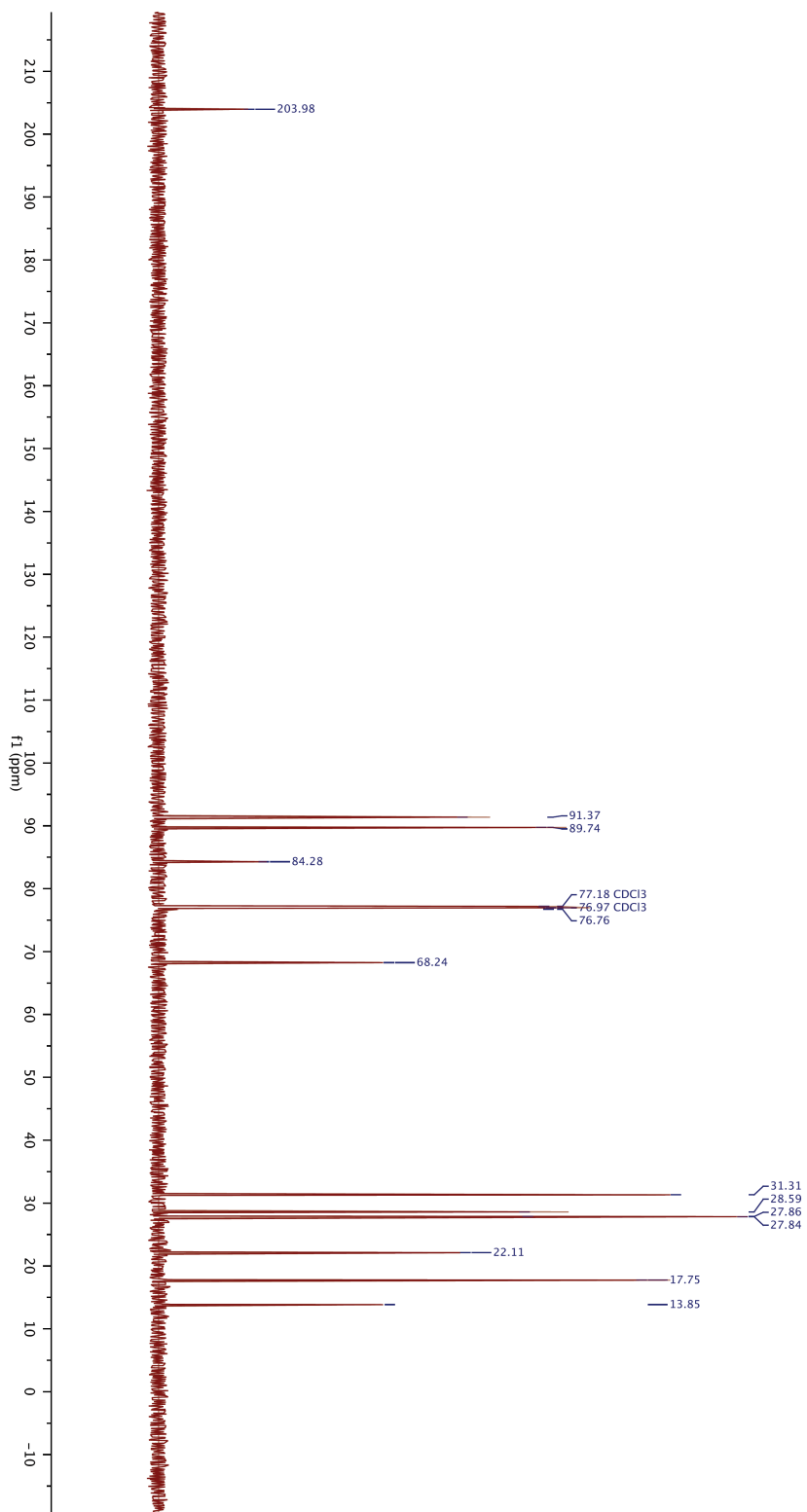
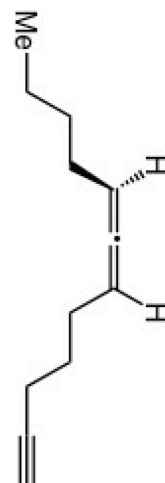


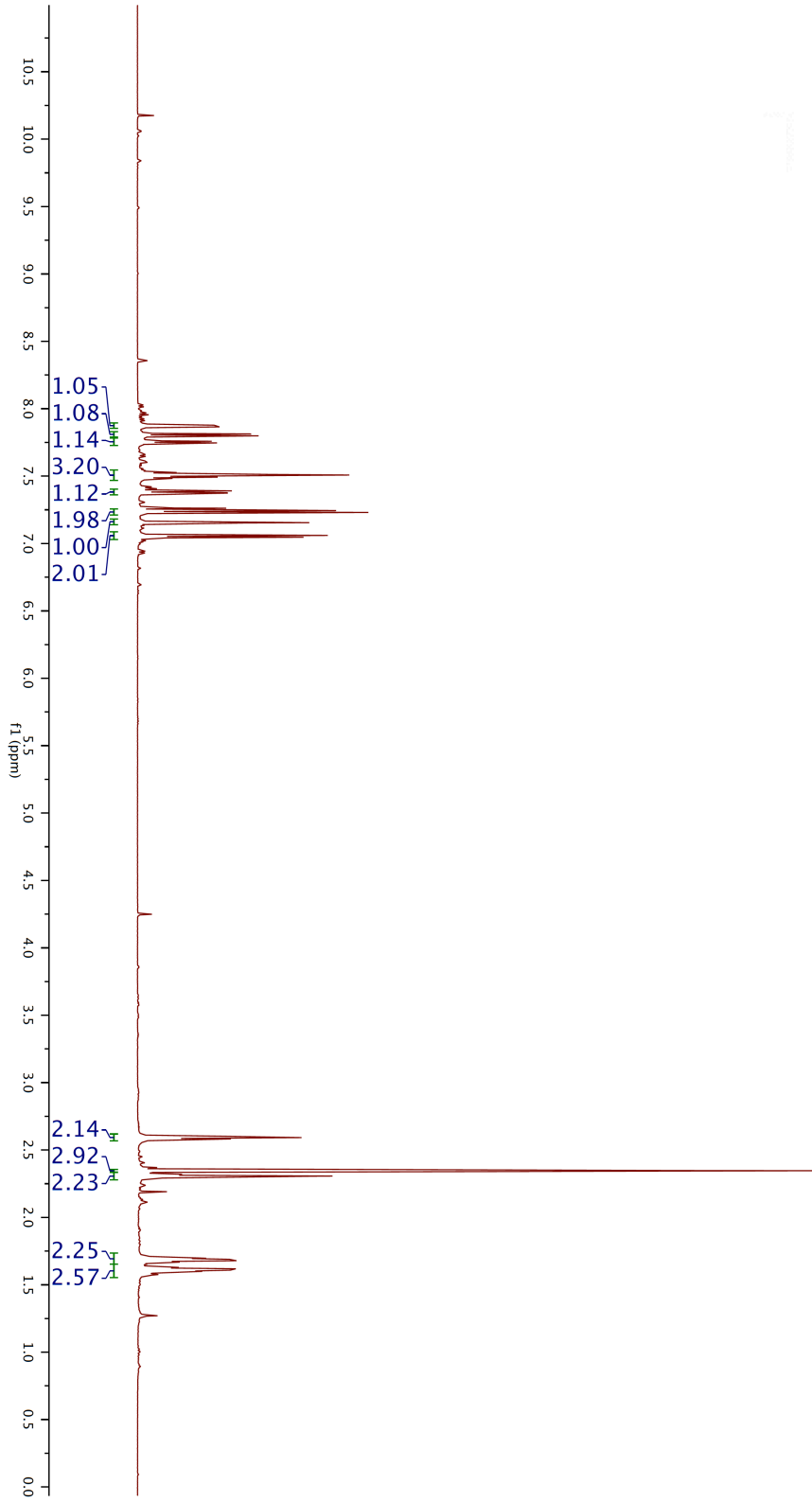
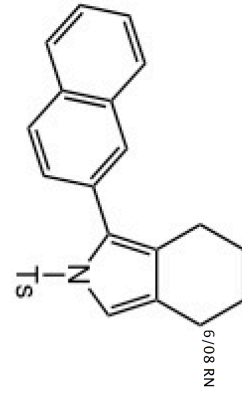


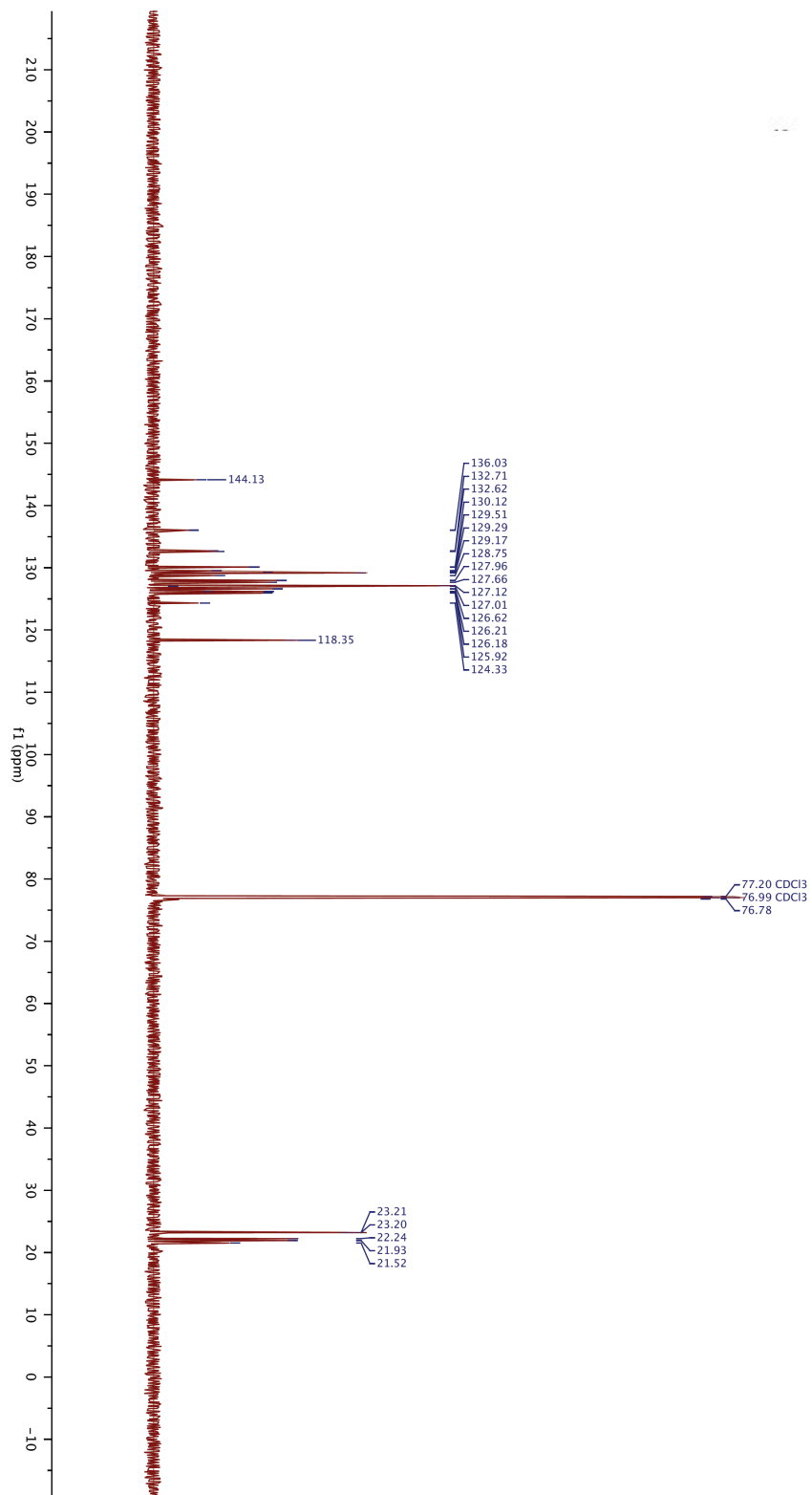
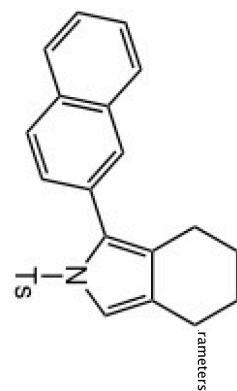


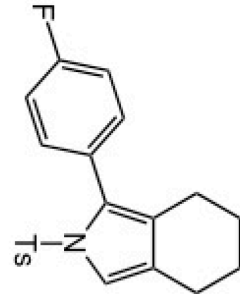




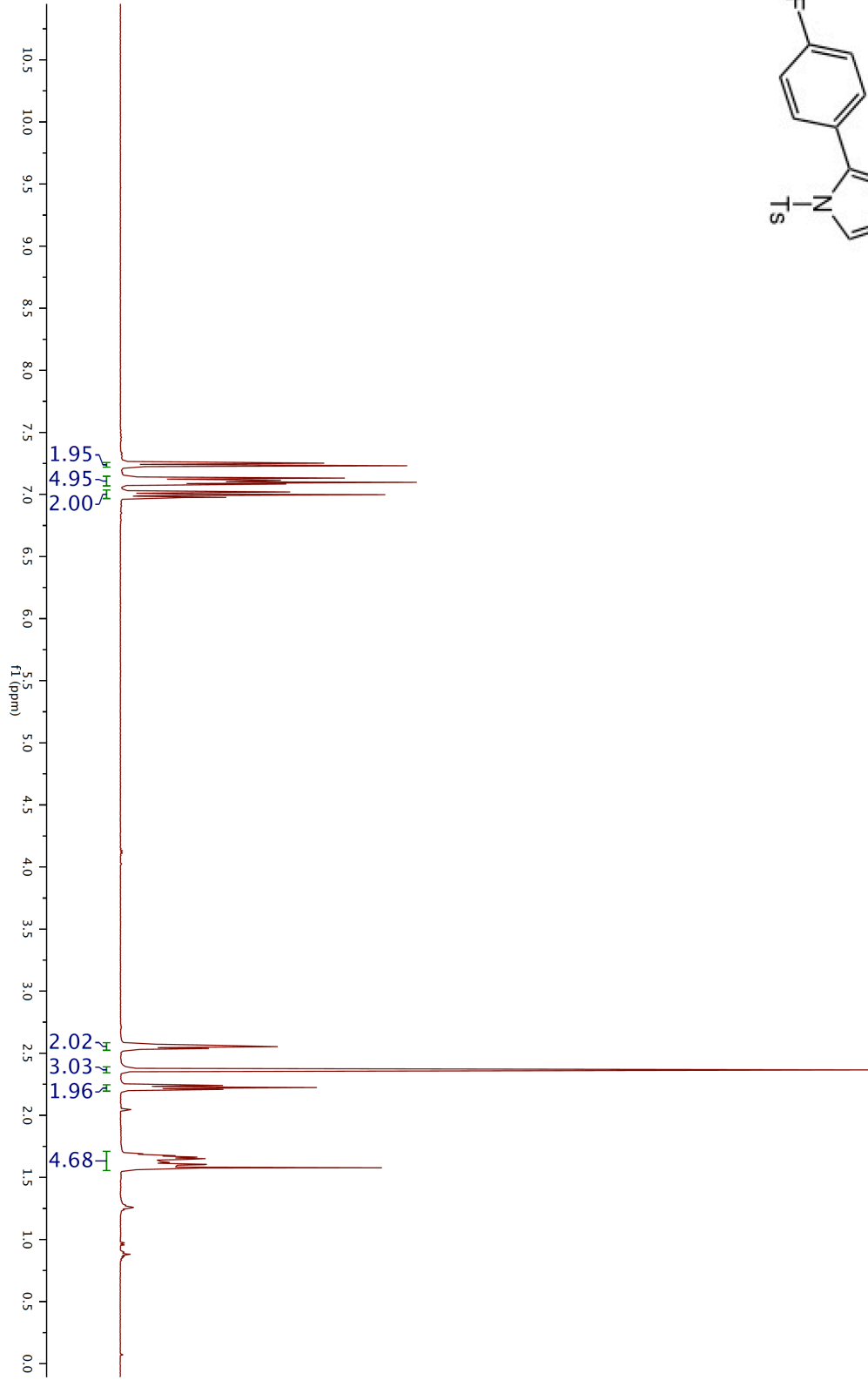


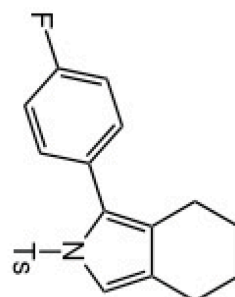




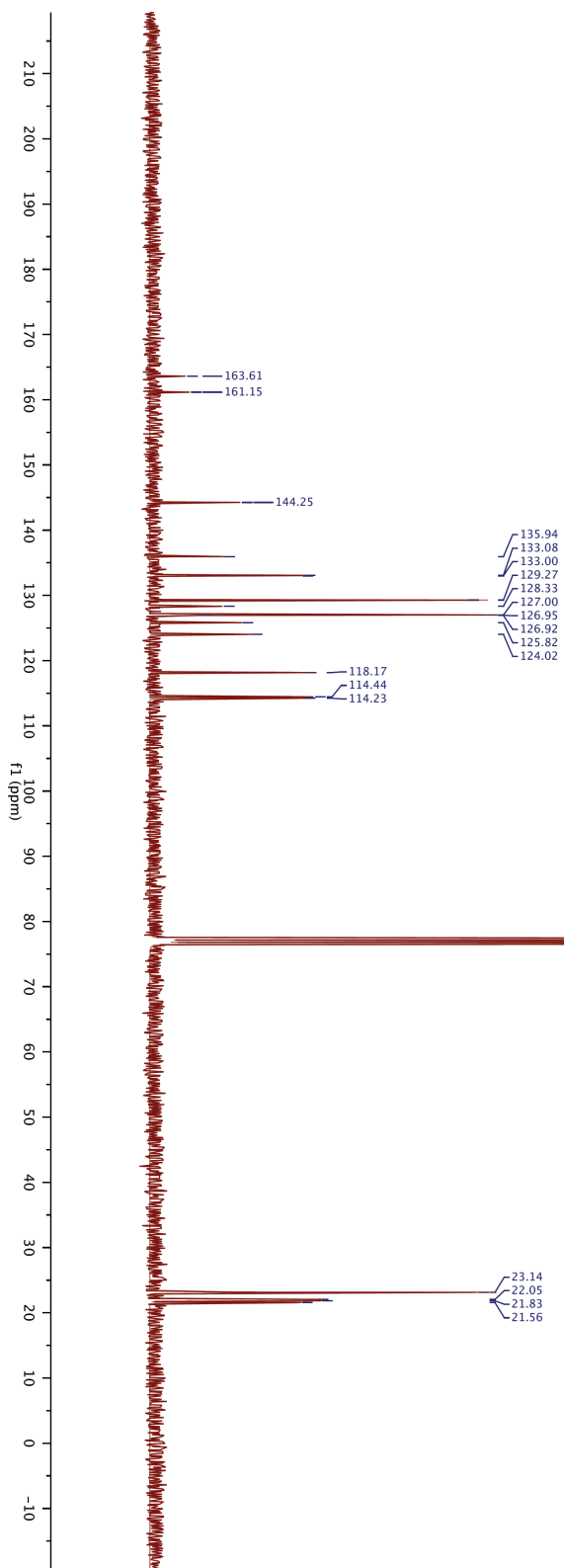


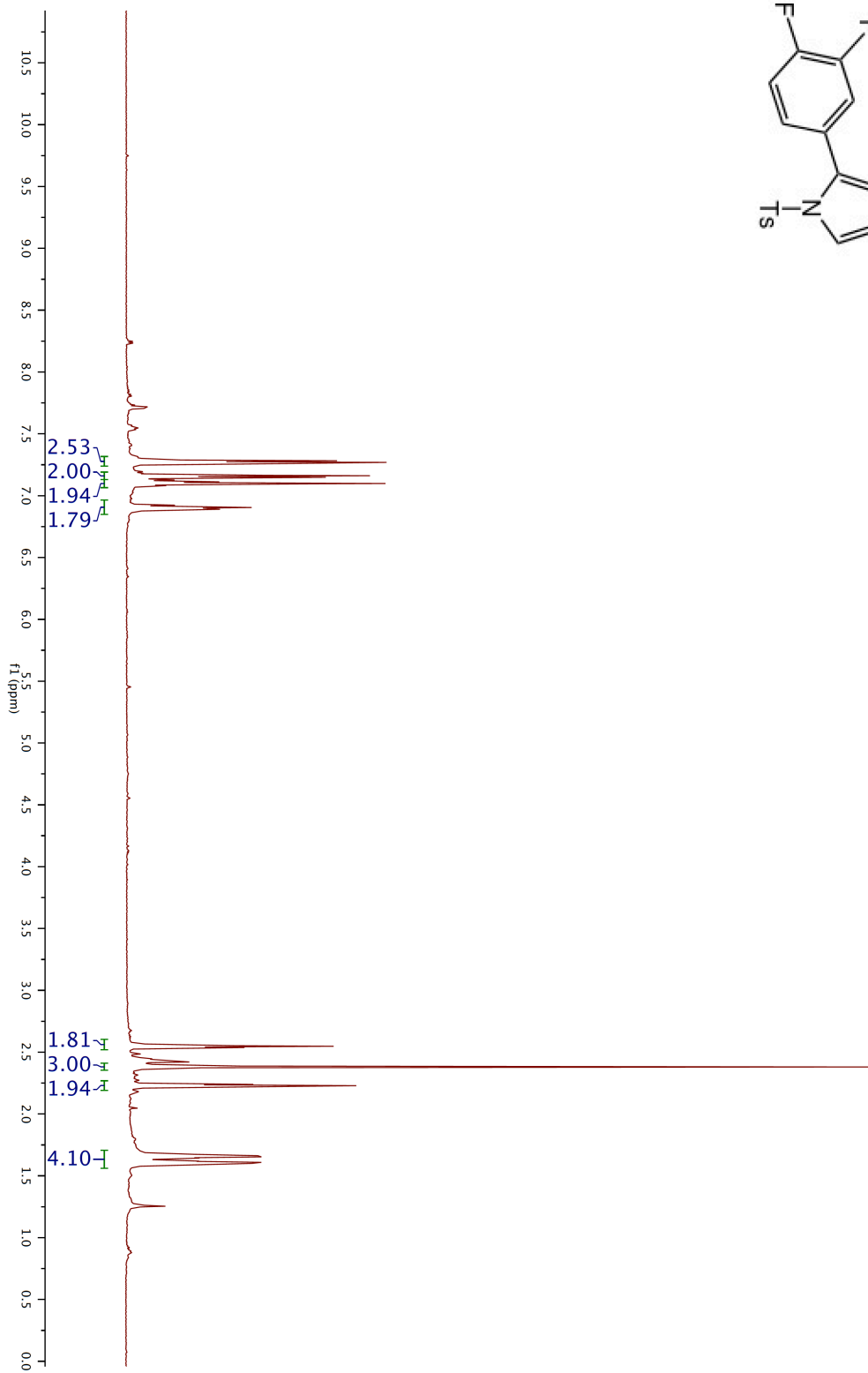
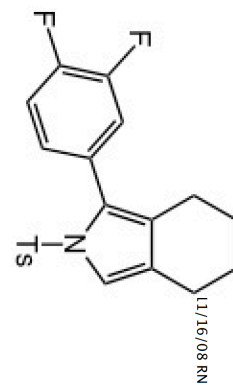
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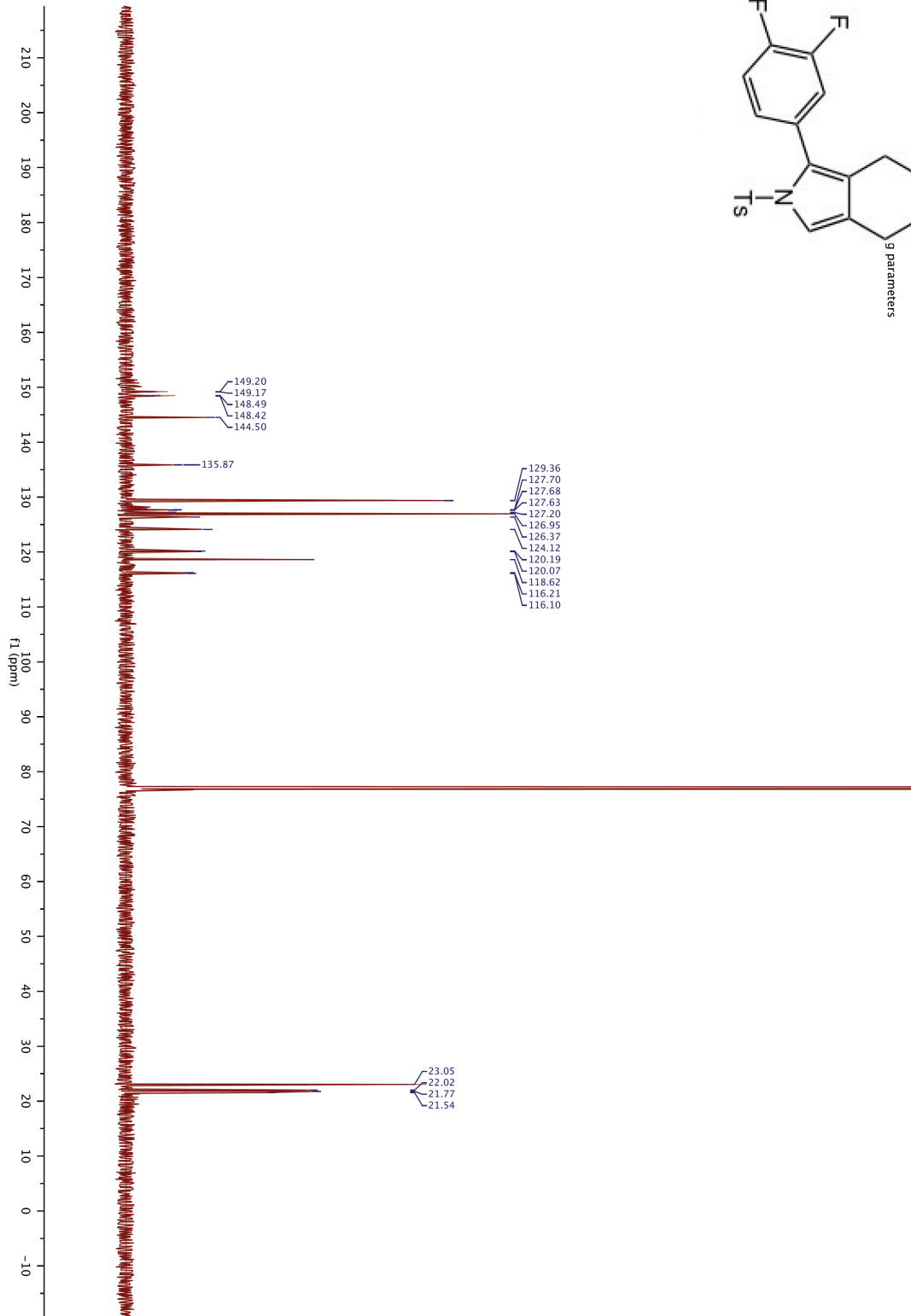
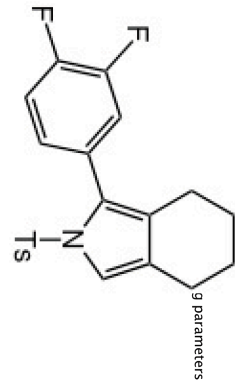


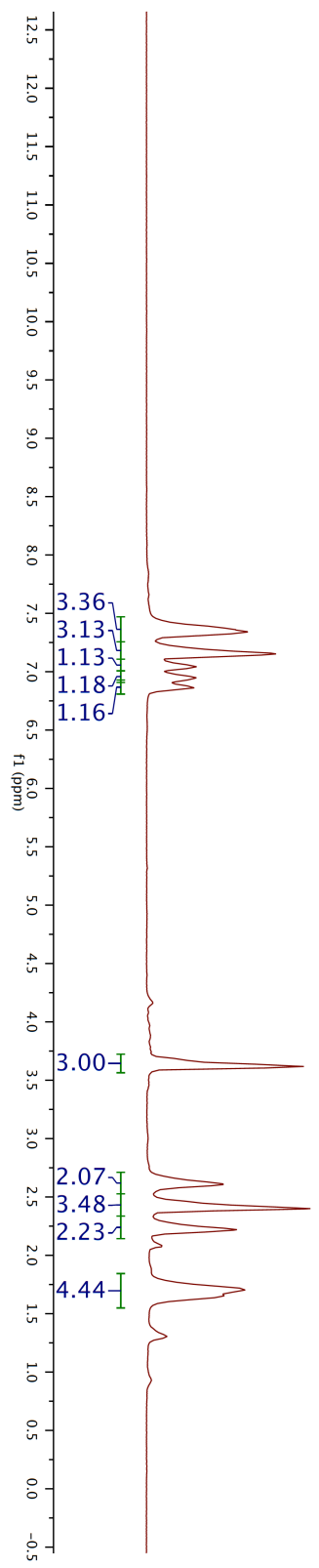
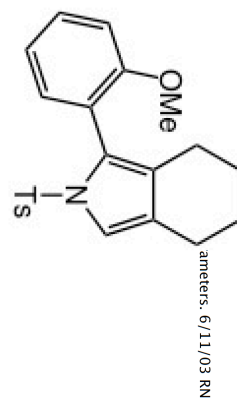


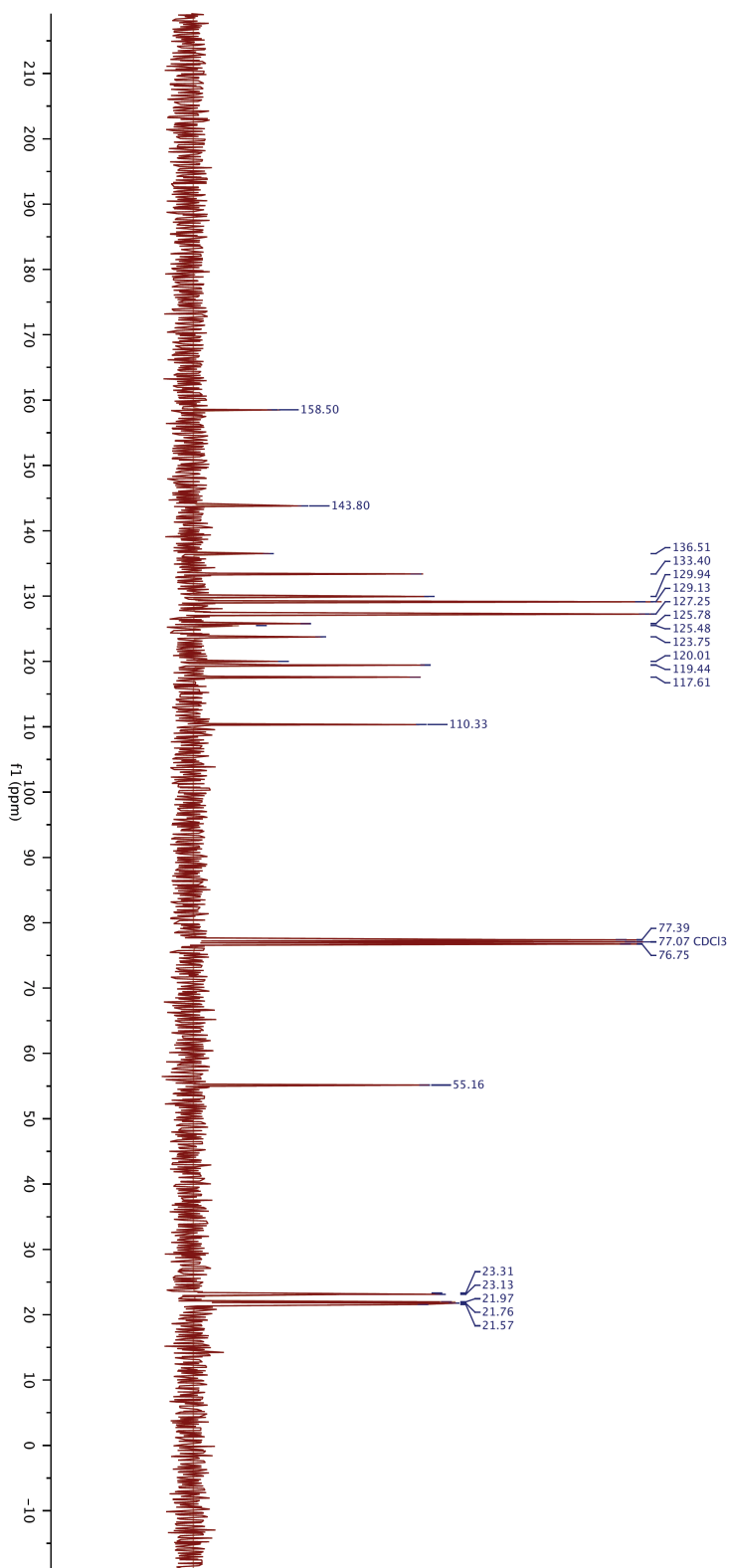
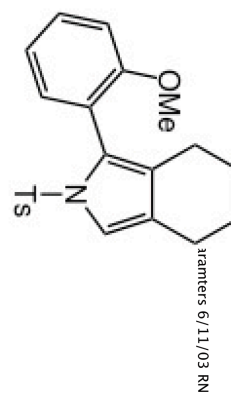
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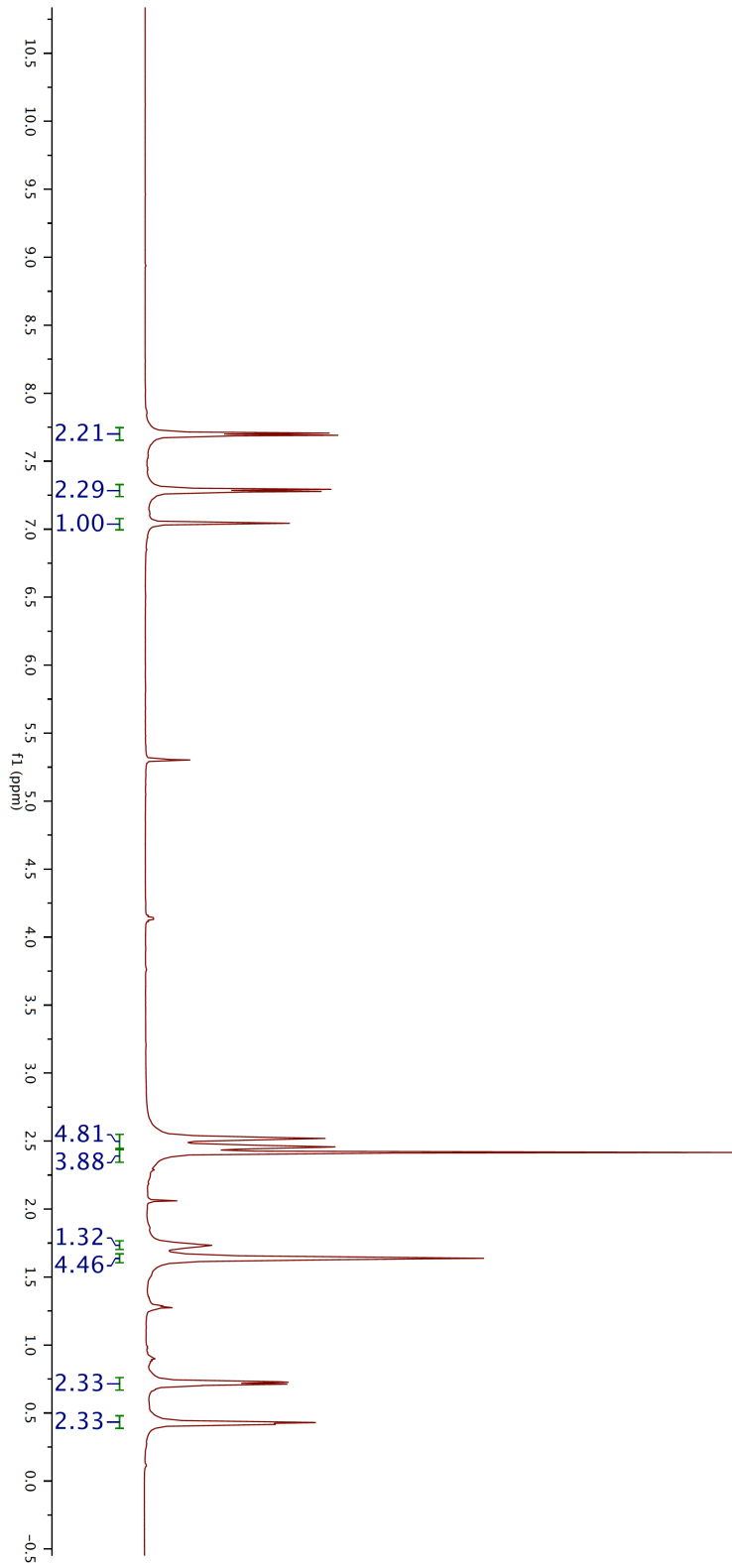
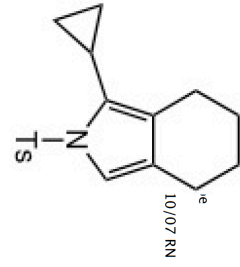


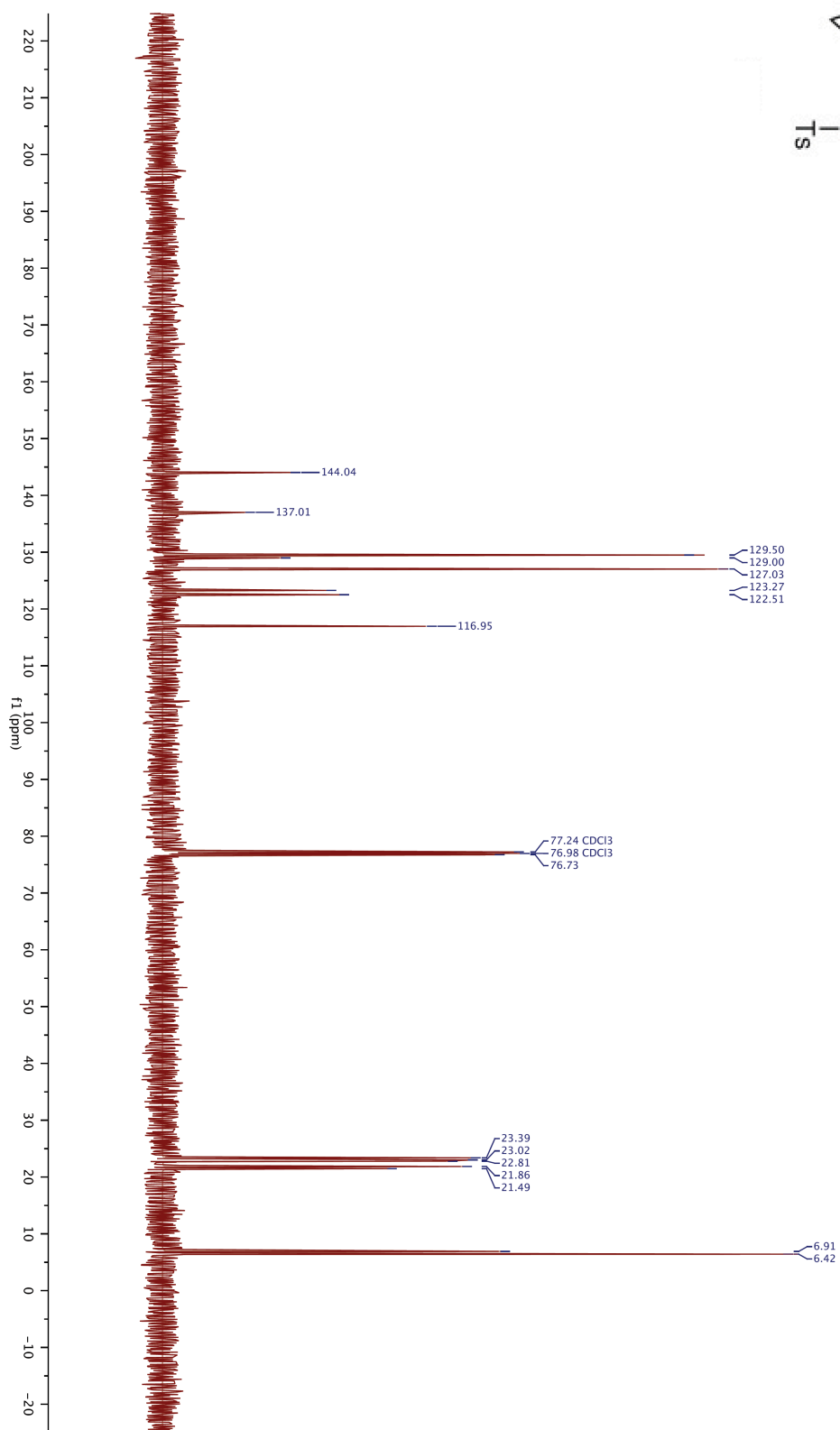


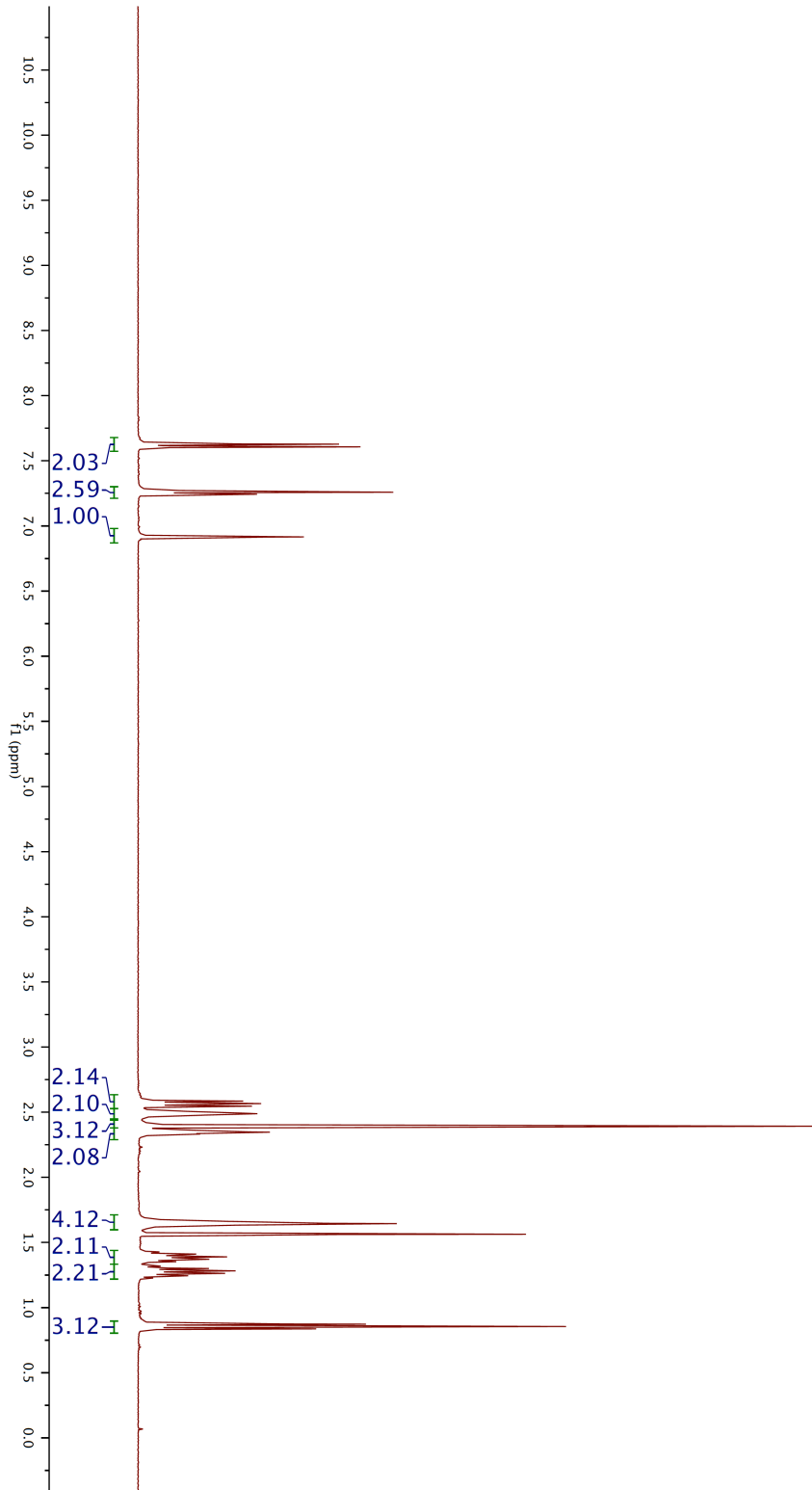
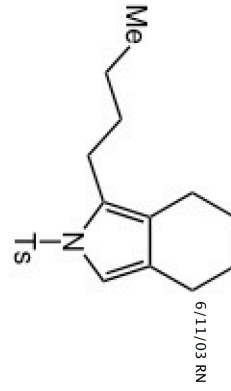


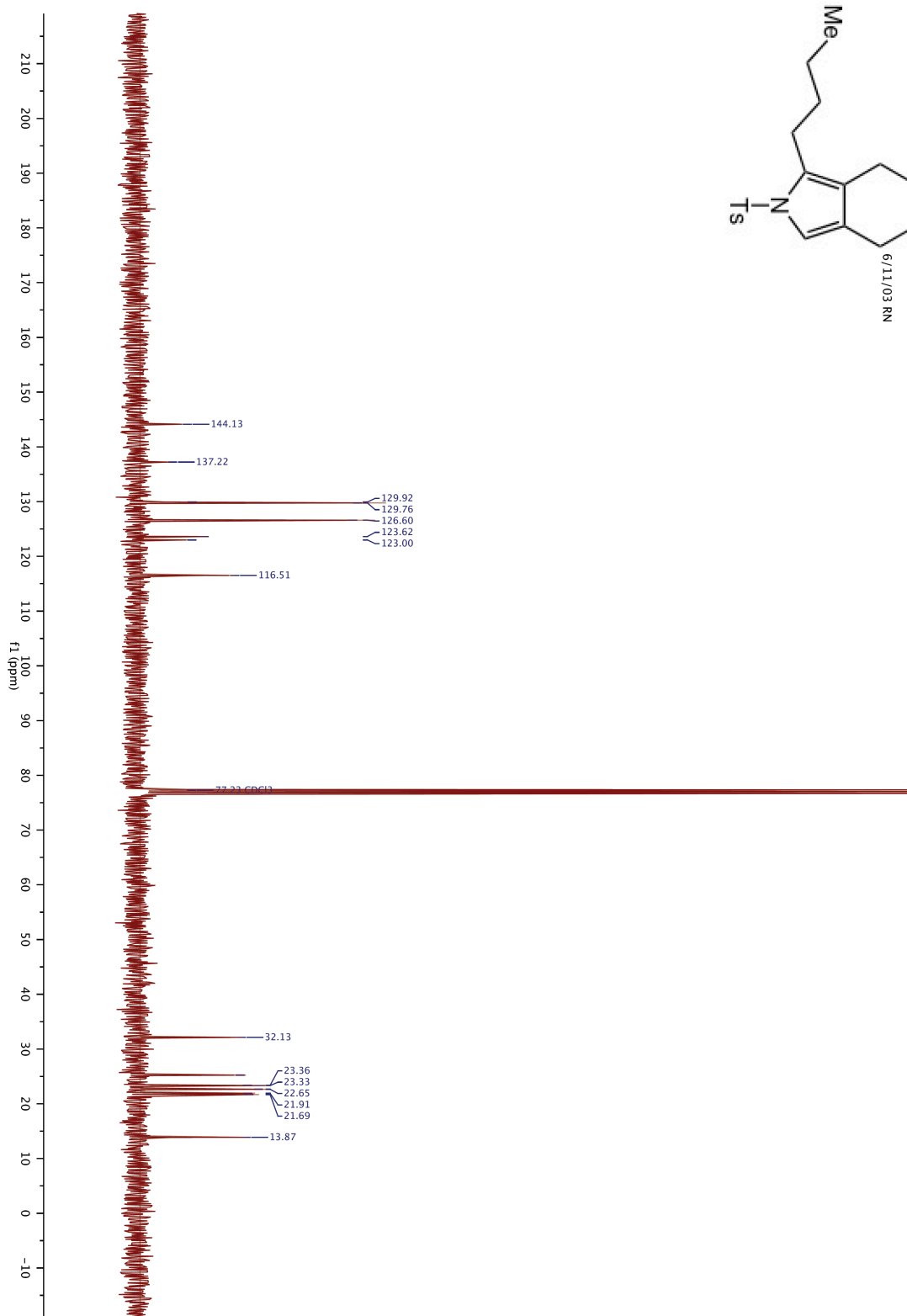
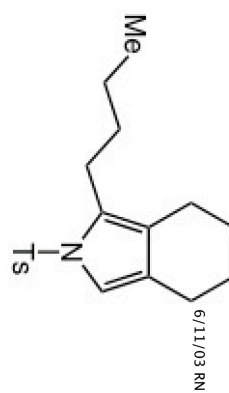


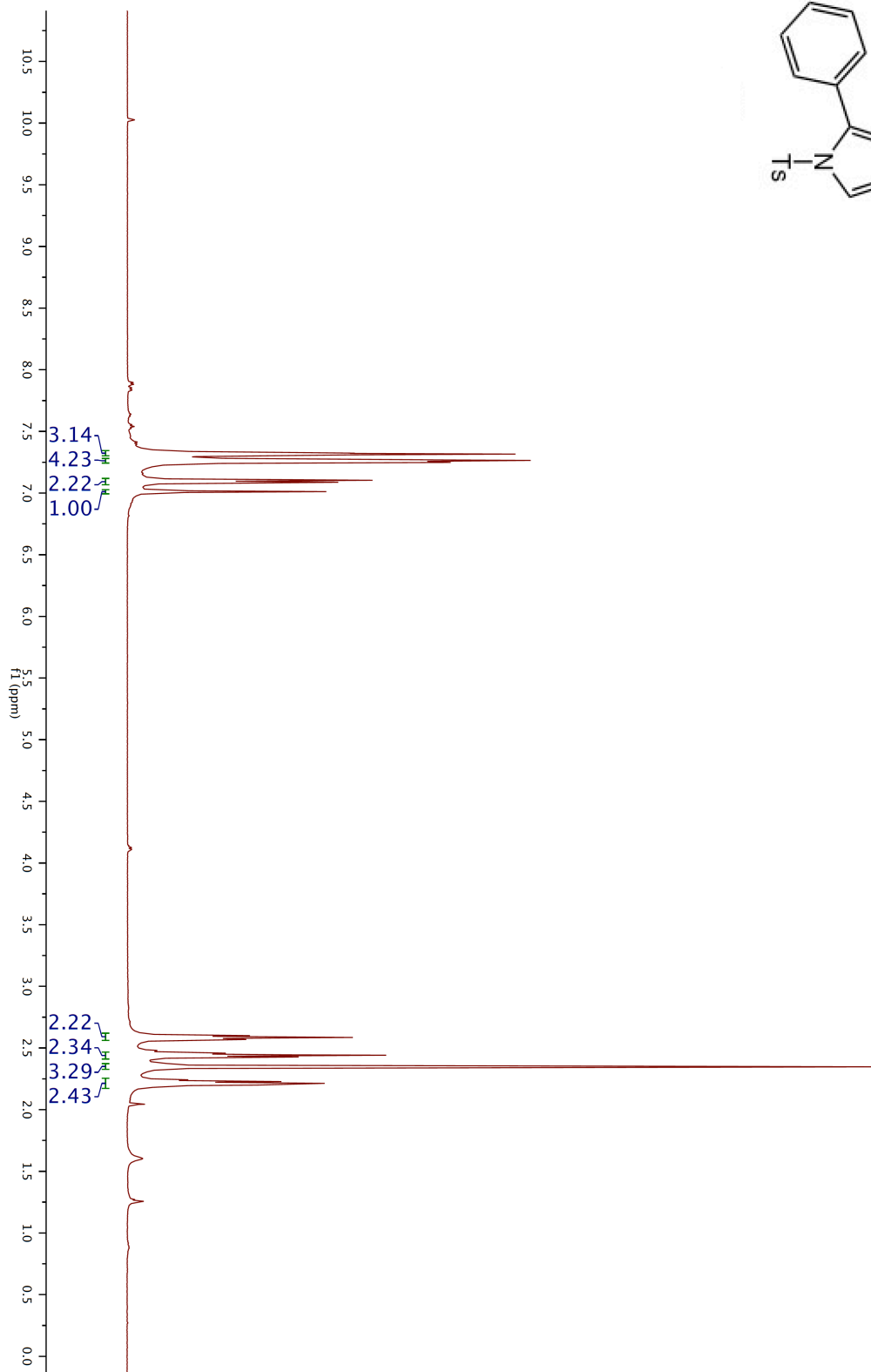
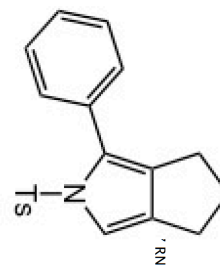


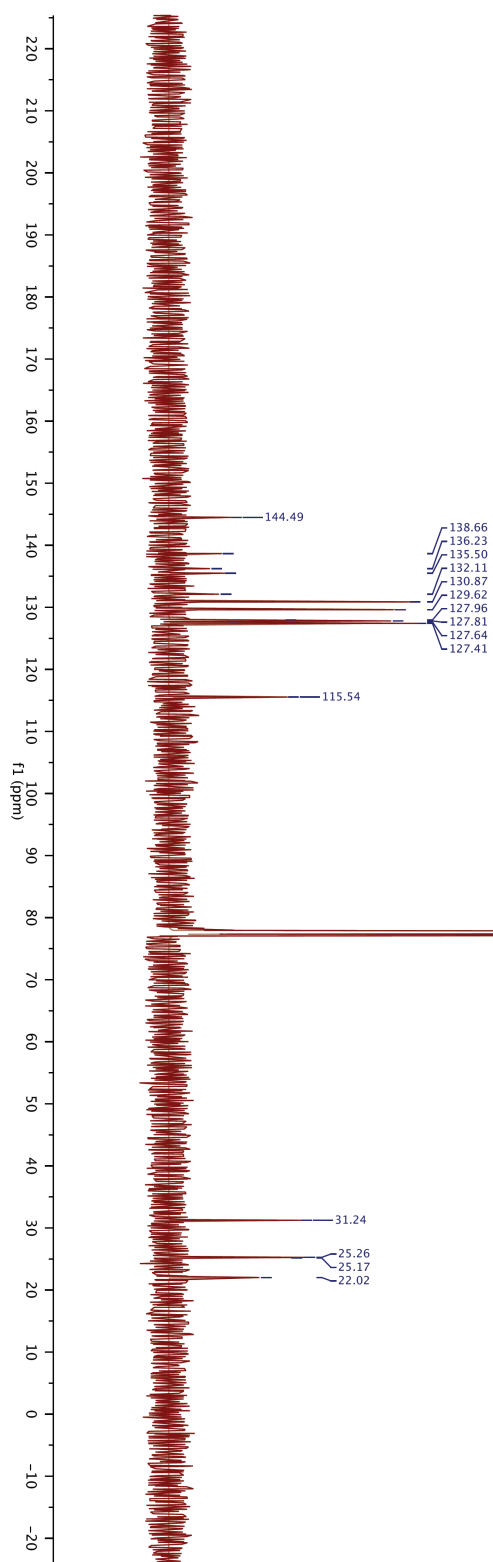
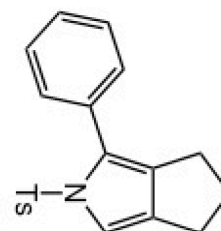


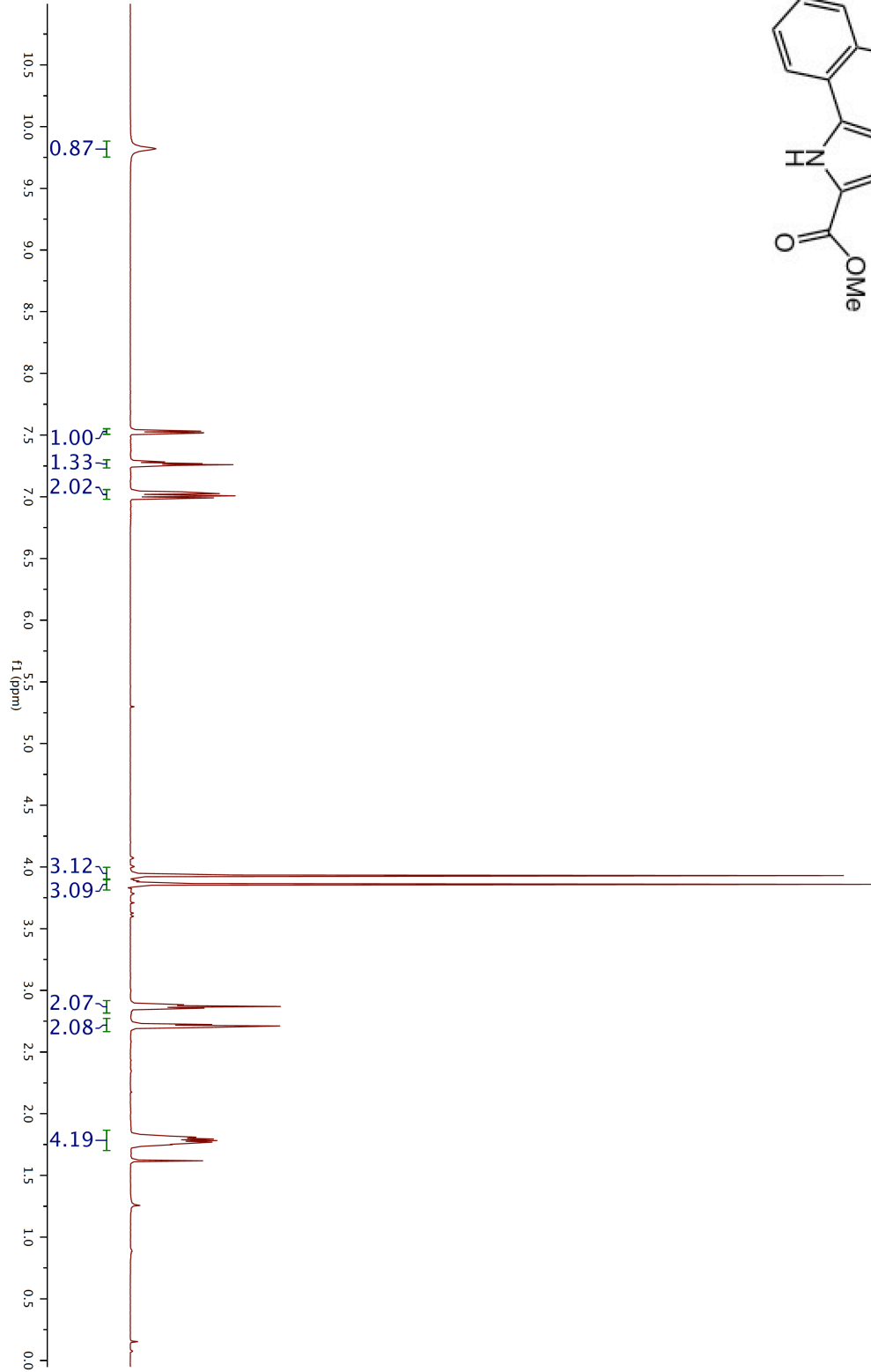
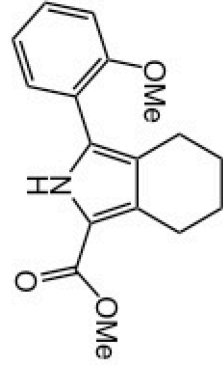


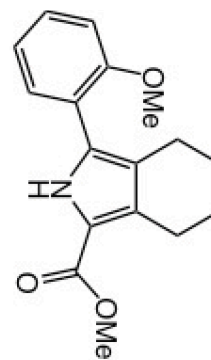




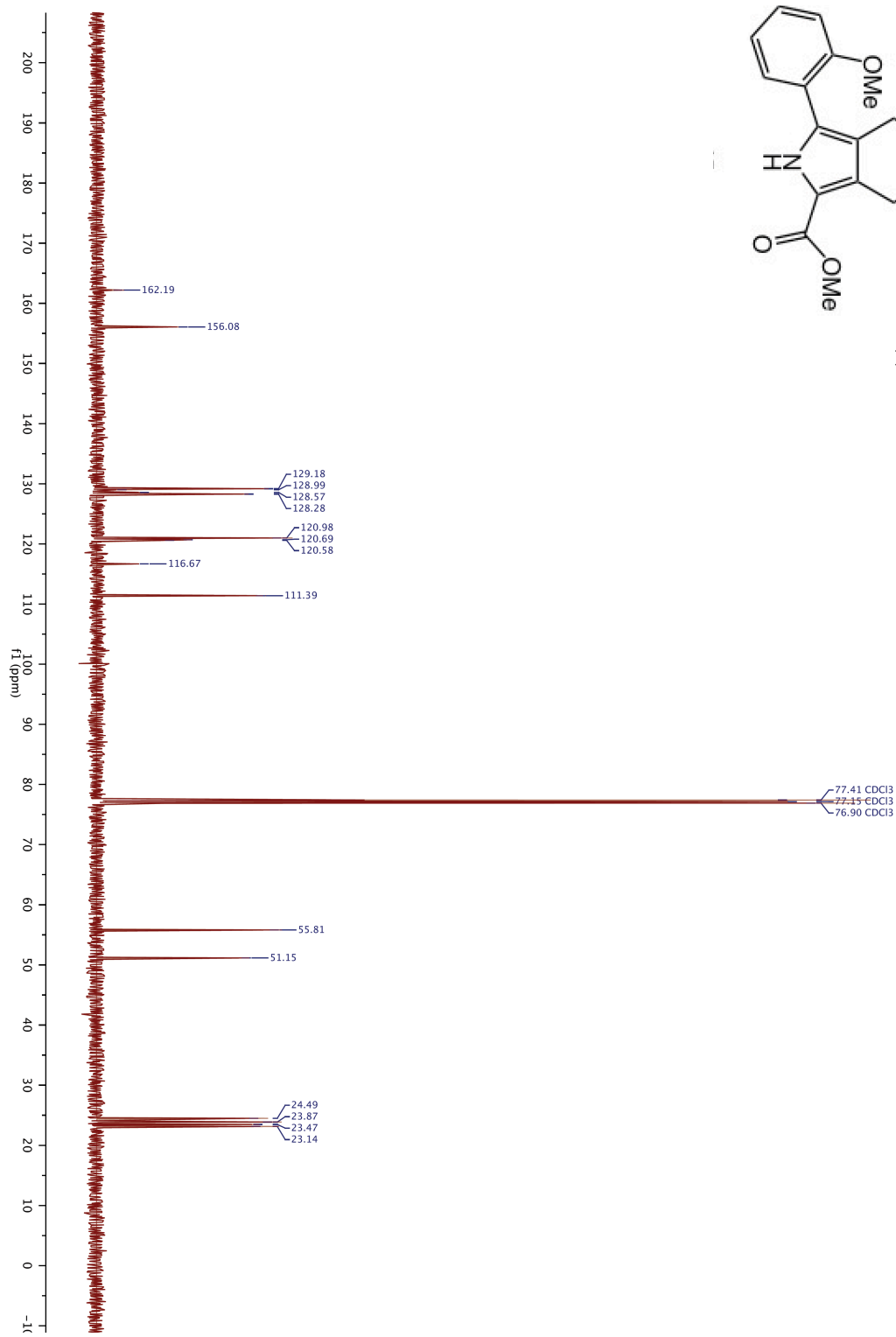








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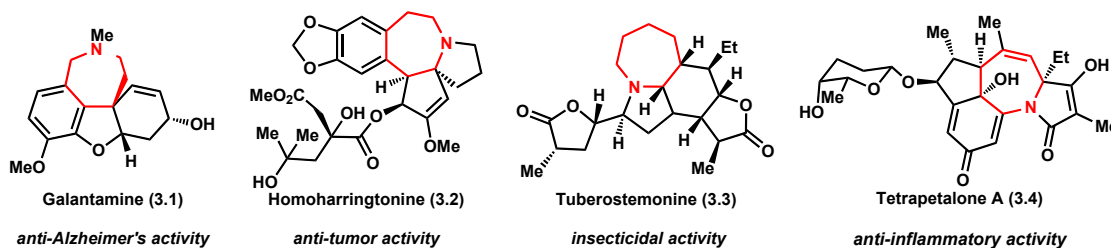
Chapter 3. Expedient Synthesis of Fused Dihydroazepines using a Sequential Rh(II)-Catalyzed Cyclopropanation / 1-Aza-Cope Rearrangement of Dienyltriazoles

3.1. Introduction

3.1.1. Azepane and azepine derivatives in natural products

Fused dihydroazepine derivatives are found in a variety of natural products with interesting biological activity and of pharmaceutical interest (Figure 3.1).^{1,2} As a part of a program to rapidly build ring systems from acyclic precursors, we saw a need for new methods to access fused azepine derivatives in a stereoselective manner. While there are a variety of methods to build azepine derivatives, relatively few methods exist to rapidly build fused-ring analogues.

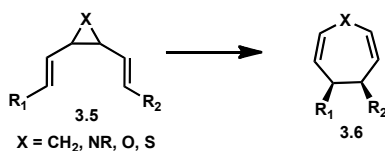
Figure 3.1. Fused dihydroazepine derivatives in biologically active natural products.



3.1.2. Divinylcyclopropane rearrangement

The thermal rearrangement of *cis*-divinylcyclopropanes was first studied in the 1960s by Vogel, while he was studying the mechanism of the Cope rearrangement of 1,5-hexadienes that were annulated to a series of carbocyclic rings. Over the past fifty years, the mechanism of the divinylcyclopropane rearrangement has been studied extensively and its synthetic scope and utility have proven to be quite broad, encompassing a variety of substituents about the double bonds in addition to the incorporation of heteroatoms to form heterocycles (Scheme 3.1).³

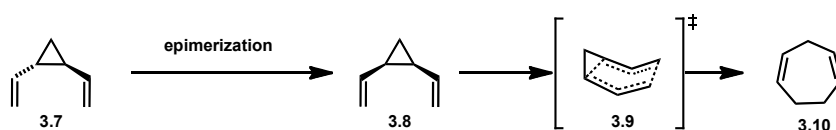
Scheme 3.1. Divinylcyclopropane rearrangement.



The mechanism of the divinylcyclopropane rearrangement has been contested in the literature for many years, as to whether the rearrangement proceeds through a concerted sigmatropic rearrangement or a diradical (stepwise) mechanism. Most likely, there is a spectrum of mechanisms that is possible depending on the substituents present on the 3-membered ring and the double bonds. It is agreed that the rearrangement goes

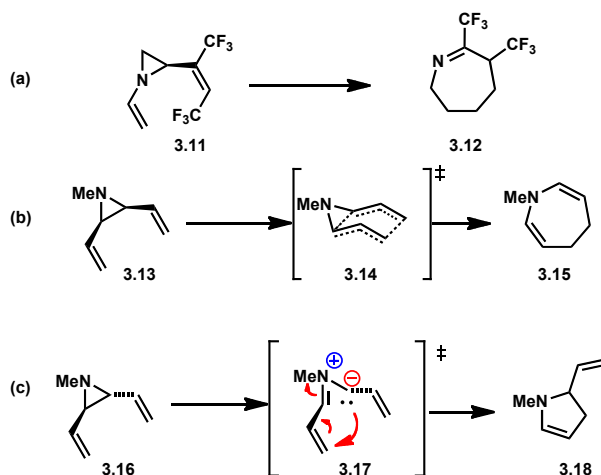
through a boat-like transition state (see **3.9**, Scheme 3.2). This inherent conformational preference accounts for the high stereoselectivity obtained with this rearrangement. Cyclopropanes typically rearrange to afford a single diastereomer of the corresponding cycloheptadiene product in cases where a new chiral center is formed. It is noteworthy that orbital overlap requires that the divinyl groups are *cis* to one another. *Trans*-divinyl cyclopropane derivatives (**3.7**, Scheme 3.2) have been shown to undergo the rearrangement to form 7-membered rings, but only after a one- or two-centered radical intermediate undergoes epimerization to form the *cis* epimer (**3.8**), and therefore the *trans*-divinylcyclopropanes require elevated temperatures whereas the *cis* version is able to undergo the rearrangement at or below room temperature.

Scheme 3.2. Mechanism of divinylcyclopropane rearrangement.



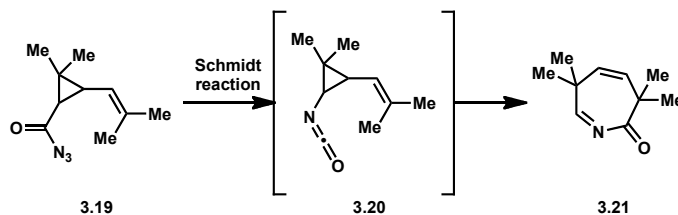
The divinylcyclopropane rearrangement has also been used to build 7-membered rings containing a nitrogen atom by using an aziridine ring instead of a cyclopropane³ (Scheme 3.3). Of note, due to the trivalent nature of the nitrogen atom, a variety of different substitution patterns about the azepine derivatives can be obtained (Scheme 3.3a vs 3.3b). It has been found that while *cis*-divinylaziridines afford dihydroazepines, most likely through a mechanism similar to the Cope rearrangement (Scheme 3.3b), *trans*-divinylaziridines have been shown to give dihydropyrrole products such as **3.18** (presumably via zwitterionic intermediate **3.17**; Scheme 3.3c).

Scheme 3.3. Azepine derivatives from rearrangement of divinyl aziridines.



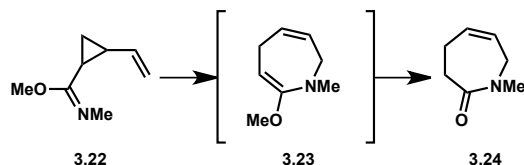
When one of the vinyl groups is replaced with an imine group (C=NR), a variety of additional azepine derivatives can be obtained. For instance, 2-aza-Cope rearrangements of this type are quite common, where the C=N bond often consists of a *in situ* generated isocyanate (**3.20**) to form 2-azepinones (**3.21**, Scheme 3.4).

Scheme 3.4. Azepine derivatives from the 2-aza-Cope rearrangement of *N*-vinylcyclopropyl isocyanates.



There is a single report of a 1-aza-Cope rearrangement with vinylcyclopropyl imidates to give lactams (**3.24**, Scheme 3.5).⁴ Examples of the corresponding 1-aza-Cope, directly leading to 2,5-dihydro[1*H*]azepines, are also scarce.⁵ The *cis*-1-imino-2-vinylcyclopropanes (IVC) required for such rearrangements to occur are obtained by a multi-step synthesis,⁶ which discourages the use of this approach for the preparation of azepine derivatives.

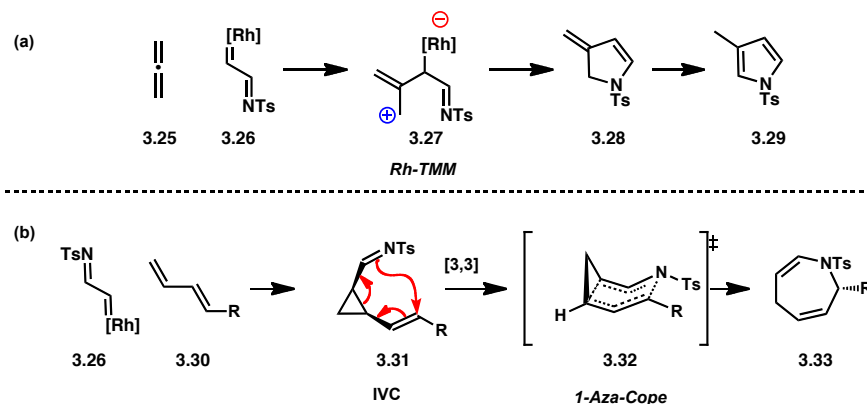
Scheme 3.5. Azepine derivatives from 1-aza-Cope rearrangement of vinylcyclopropyl imidates.



3.1.3. Inspiration from previous work

We anticipated expanding the chemistry described in Chapter 2 for the synthesis of 5-membered nitrogen containing rings (Scheme 3.6a) to 7-membered rings by interaction of an imino Rh-carbenoid (**3.26**), obtained from the decomposition of an *N*-tosyl-1,2,3-triazole, with a 1,3-diene (**3.30**) instead of an allene (Scheme 3.6b). In doing so, we envisioned accessing intermediate **3.31**, a *cis*-1-imino-2-vinylcyclopropane (IVC), from an intramolecular cyclopropanation reaction. This *cis*-cyclopropane would possess the appropriate substitution pattern to undergo a 1-aza-Cope rearrangement to form fused dihydroazepines related to **3.33**.

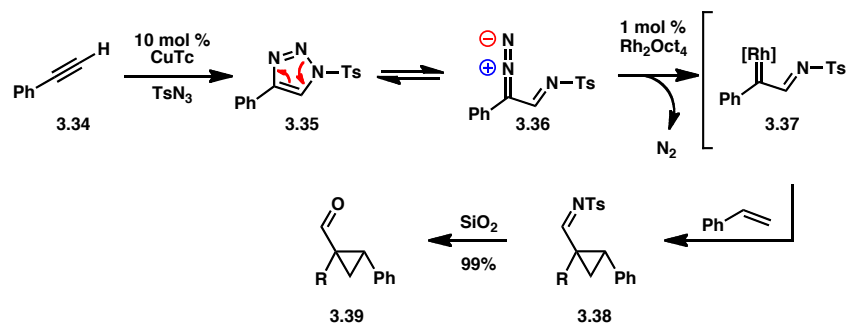
Scheme 3.6. Proposed generation of dihydroazepines from a 1-Aza-Cope rearrangement.



3.1.4. Cyclopropanation from α -imino metallocarbenes and rearrangements to form larger ring systems

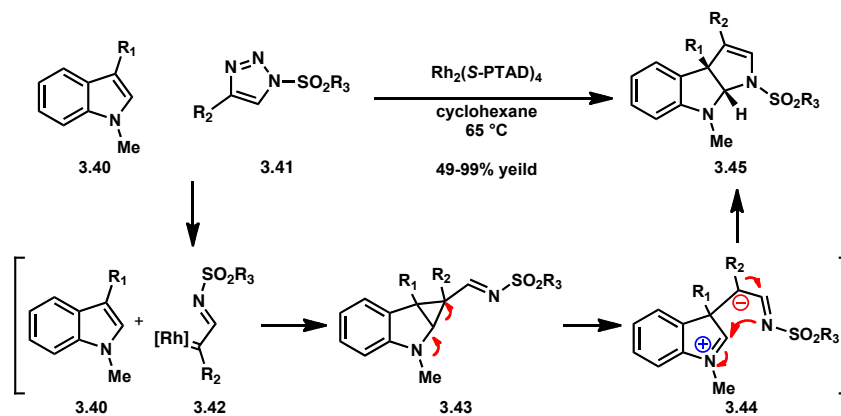
As discussed in Chapter 2.2, *N*-tosyl-1,2,3-triazoles decompose in the presence of suitable metal catalysts, such as Rh(II)-tetracarboxylates, to form α -imino Rh-carbenoids that have been shown to be electrophilic and undergo a variety of transformations,⁷ such as cyclopropanation (Scheme 3.7) of styrene.

Scheme 3.7. Cyclopropanation of styrene by α -imino Rh-carbenoids derived from 1,2,3-triazoles.



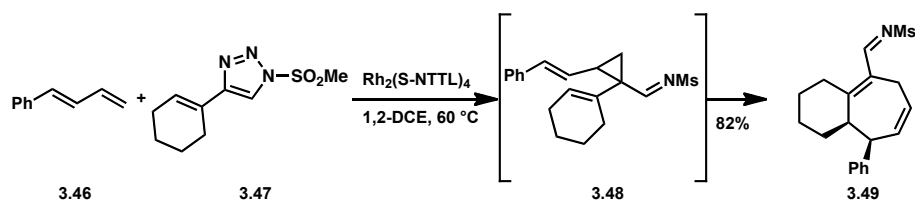
The inherent nucleophilicity of the attached imine nitrogen has been utilized to form a variety of *N*-containing heterocycles from iminocyclopropane intermediates. For instance, Davies and co-workers reported a synthesis of pyrroloindolines via initial cyclopropanation of indole **3.40** (Scheme 3.8), followed by a subsequent ring opening of the strained cyclopropylindoline **3.43** and recombination to form **3.45**.⁸

Scheme 3.8. Davies' pyrroloindoline synthesis via a cyclopropylindoline intermediate.



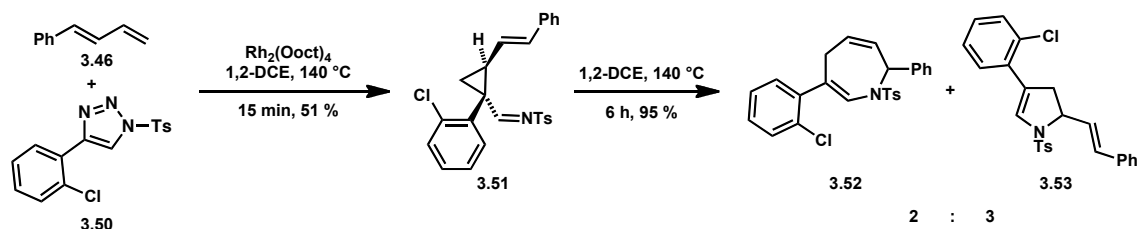
Davies and co-workers constructed a 7-membered ring via a tandem cyclopropanation/Cope rearrangement by decomposing alkenyl *N*-sulfonyl triazoles (such as **3.47**, Scheme 3.9) in the presence of catalytic $\text{Rh}_2(\text{S-NTTL})_4$ and a diene (**3.46**). The reaction proceeds by initial formation of *cis*-divinylcyclopropane intermediate **3.48**, which rapidly undergoes a [3,3]-sigmatropic rearrangement to yield **3.49**. It is noteworthy that the imino group does not participate in an analogous 1-aza-Cope rearrangement in this case (which would lead to an azepine derivative) most likely due to the *trans* relationship with the vinyl group.

Scheme 3.9. Davies' tandem α -aminocyclopropanation Cope rearrangement.



Tang and co-workers, concurrent with our work, reported an elegant divergent synthesis of nitrogen heterocycles by intermolecular reaction of triazoles with 1,3-dienes.⁹ The studies by Tang et al. provide access to a mixture of dihydroazepine and dihydropyrrole compounds through an iminovinylcyclopropane intermediate **3.51**. Intermediate **3.51** presumably rearranges upon heating to either dihydropyrrole **3.53** via a zwitterionic cyclopropane ring opening, or dihydroazepine **3.52**, presumably through isomerization of the *trans*-iminovinylcyclopropane to the *cis*-iminovinylcyclopropane followed by a 1-aza-Cope rearrangement (see Scheme 3.10).

Scheme 3.10. Tang's divergent dihydroazepine and dihydropyrrole synthesis.

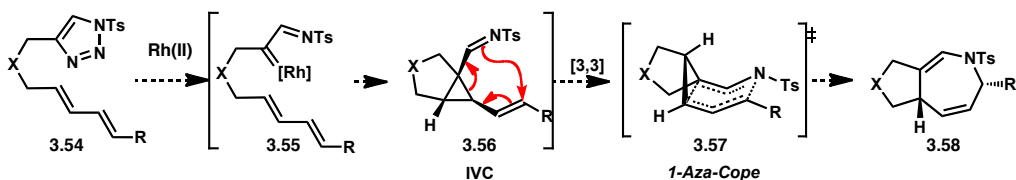


3.2. Synthesis of fused dihydroazepines using a sequential Rh(II)-catalyzed cyclopropanation / 1-aza-Cope rearrangement of dienyltriazaoles

3.2.1. Proposed reactivity

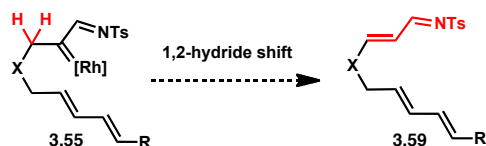
We envisioned that an intramolecular variant of this reaction would permit the synthesis of fused dihydroazepines via the direct formation of a *cis*-IVC intermediate, without the need for its isomerization at high temperatures (Scheme 3.11). Because the Rh-catalyzed cyclopropanation of an *E*-double bond is intramolecular and stereospecific, the vinyl group will be *cis* to the tethered imine group (**3.56**). This is opposite to the intermolecular case (Scheme 3.10, intermediate **3.51**), which due to sterics and electronic considerations places the vinyl group *trans* to the imine group.¹⁰ The stereospecific nature of both consecutive steps in this transformation should allow for a highly diastereoselective process, leading to stereodefined fused 2,5-dihydro[1*H*]azepines (**3.58**).

Scheme 3.11. Proposed reactivity.



As alluded to in our pyrrole synthesis,¹¹ one significant potential pitfall of our planned transformation of **3.54** to **3.58** was the possibility that Rh-carbenoid intermediates related to **3.55**, consistent with well-documented precedent,¹² would undergo a competing 1,2-hydride shift to yield α,β -unsaturated *N*-tosylimines (**3.59**, Scheme 3.12) instead of engaging a double bond of the dienyl group to form a cyclopropane (**3.56**). As a result, the successful transformation of **3.54** to **3.58** would require that the dienyl group be nucleophilic enough to engage the Rh-carbenoid center and out compete the 1,2-hydride shift.

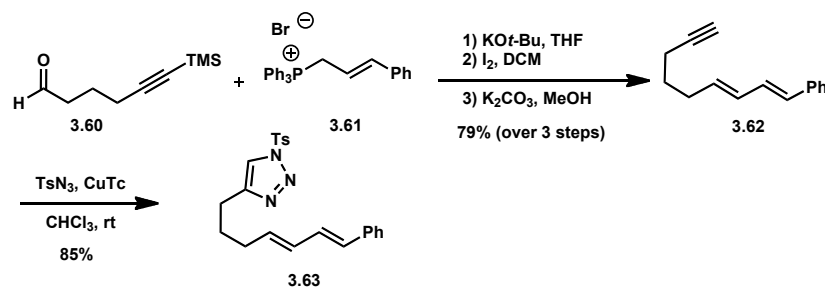
Scheme 3.12. Possible undesired 1,2-hydride shift.



3.2.2. Substrate synthesis

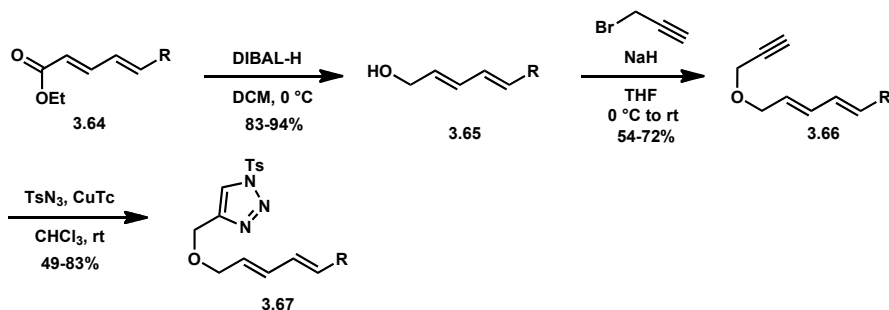
We initiated our studies with dienyltriazole **3.63** (Scheme 3.13) which was readily prepared in four steps from TMS-protected hex-5-ynal¹³ and cinnamyltriphenylphosphonium bromide using a Wittig reaction, isomerization of the diene to the *E,E*-isomer, and deprotection of the terminal alkyne to give **3.62**. From here, the alkyne was subjected to Cu-catalyzed Huisgen reaction conditions with tosyl azide to afford triazole product **3.63**.

Scheme 3.13. Initial substrate synthesis.



To access dienyltriazoles with various substituents on the diene portion, it was useful to incorporate an ether tether. These substrates could be accessed in three steps from the corresponding dienylester (**3.64**, Scheme 3.14). Upon reduction of the ester to the corresponding alcohol, propargylation with propargyl bromide provided the alkyne (**3.66**). Alkyne **3.66** was transformed into the *N*-tosyl-1,2,3-triazole (**3.67**) after being subjected to the Cu-catalyzed Huisgen reaction with tosyl azide.¹⁴

Scheme 3.14. Synthesis of substrates bearing an ether tether.

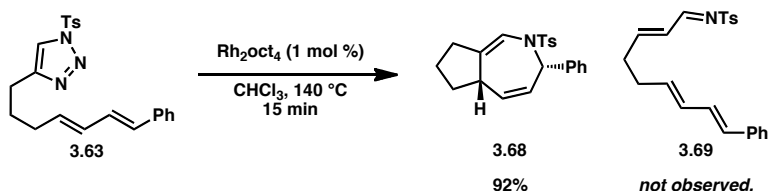


3.2.3. Initial Results

Gratifyingly, exposure of triazole **3.63** to Rh₂(oct)₄ (1 mol %) in CHCl₃ at 140 °C

(microwave), following the conditions we previously developed for the formation of 3,4-fused pyrroles from allenyltriazaoles to dienylnitrogen **3.63** (see Chapter 2),¹⁵ gave fused dihydroazepine **3.68** in 92% yield, where no 1,2-hydride shift byproduct **3.69** was observed. We were interested in this product because it maps on to the core structure of tetrapetalone A (**3.4**, Figure 3.1).

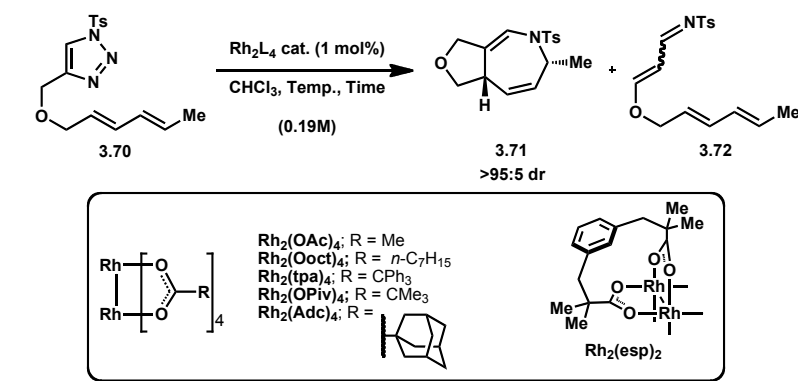
Scheme 3.15. *Initial results.*



Our attempts to expand the substrate scope were met with several notable challenges. Triazole **3.70**, with an ether bridge and methyl substituent on the dienylnitrogen portion, when exposed to the same reaction conditions as above, formed dihydroazepine **3.71** in 54% yield (Table 3.1, entry 1) with the major byproduct accounted for by α,β -unsaturated *N*-tosylimine **3.72** (34% yield) resulting from a competing 1,2-hydride shift following formation of the Rh-carbenoid center (see Scheme 3.12). This is unsurprising seeing as such a 1,2-hydride shift has been shown to be a significant side-reaction for other α -alkyl azavinyl-substituted Rh-carbenoids.¹⁶ In this particular case, this undesired pathway occurs to a high degree, likely due to the presence of the ether bridge in substrate **3.70**, which enhances the hydridic character of the β -hydrogen atoms (compared to the all carbon analogue, **3.63**). Also, with a methyl substituent on the dienylnitrogen portion of the molecule instead of the phenyl group, the dienylnitrogen group is less nucleophilic and thus less reactive toward the electrophilic Rh-carbenoid center.

Viewing **3.70** as an ideal substrate to optimize the reaction, we screened a variety of more sterically encumbered rhodium(II) catalysts (entries 3-6),¹⁷ as steric interactions between the Rh-complex and the metal-carbenoid substituents have been hypothesized to favor cyclopropanation over 1,2-hydride migration for intermolecular reactions. Gratifyingly, we found that $\text{Rh}_2(\text{Adc})_4$ afforded the desired dihydroazepine in increased yield (entry 6).¹⁸ Varying the nature of the solvent and the concentration of the reactants did not significantly improve the yield.¹⁹ Decreasing the temperature to 60°C and increasing the reaction time to 16 h afforded dihydroazepine **3.71** in 74% isolated yield (entry 7), with a minimal amount of the undesired α,β -unsaturated *N*-tosylimine **3.72** observed (<15%).

Table 3.1. Catalyst optimization.



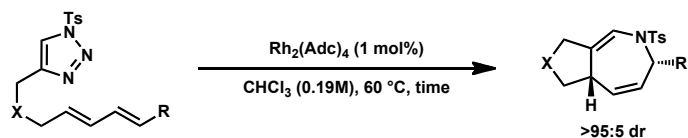
| entry | Rh ₂ L ₄ | temp (°C) | time | yield (%) ^a |
|-------|-------------------------------------|------------------|--------|------------------------|
| 1 | Rh ₂ (Ooct) ₄ | 140 ^b | 15 min | 54 |
| 2 | Rh ₂ (OAc) ₄ | 140 ^b | 15 min | 47 |
| 3 | Rh ₂ (tpa) ₄ | 140 ^b | 15 min | 18 |
| 4 | Rh ₂ (OPiv) ₄ | 140 ^b | 15 min | 58 |
| 5 | Rh ₂ (esp) ₂ | 140 ^b | 15 min | 66 |
| 6 | Rh ₂ (Adc) ₂ | 140 ^b | 15 min | 68 |
| 7 | Rh ₂ (Adc) ₂ | 60 | 16 h | 74 |

^aIsolated yield. ^bReaction was performed in a microwave apparatus.

3.3. Reaction scope

Using the optimized conditions (Table 3.1, entry 7), a range of dienylnitriazole substrates was transformed into the corresponding 3,4-fused dihydroazepines (Table 3.2). A variety of aryl-substituted substrates, including phenyl, electron rich and electron poor diene groups were tolerated (entries 2-4). In addition, internal substitution of the diene component was compatible in the transformation, albeit with slightly lower yield (entry 2 vs. 5). Furthermore, dienylnitriazole substrates with *N*-tosylamine or malonate tethers instead of the ether linker furnished the corresponding 3,4-fused dihydroazepines in moderate to good yields (entries 6-8). Importantly, when the standard conditions were applied to a substrate possessing an all-carbon tether, the same excellent yield was obtained (entry 9 vs. Scheme 3.15). In all cases, only one diastereomer of the dihydroazepine product was observed. It is noteworthy that the 1-aza-Cope rearrangement was found to be significantly slower for the substrates described in entries 5 and 6, and the reaction had to be run for 16 h in order to achieve complete conversion. In these cases, a significant amount of the IVC intermediate was clearly observed by NMR after 0.5 h.

Table 3.2. Substrate scope.



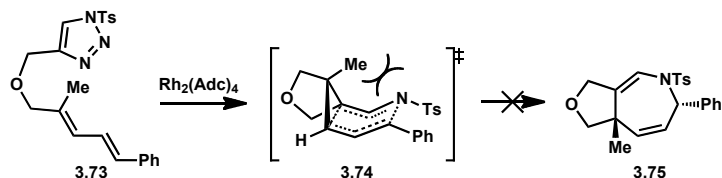
| entry | substrate | product | time | yield (%) ^a |
|-------|-----------|---------|--------|------------------------|
| 1 | | | 16 h | 74 |
| 2 | | | 30 min | 92 |
| 3 | | | 30 min | 61 |
| 4 | | | 16 h | 69 |
| 5 | | | 16 h | 63 |
| 6 | | | 30 min | 72 |
| 7 | | | 30 min | 72 |
| 8 | | | 30 min | 45 (60) ^b |
| 9 | | | 30 min | 92 |

^aIsolated yield. ^bReaction was performed in a microwave apparatus.

One limitation is the use of substrates such as **3.73**, which would generate a

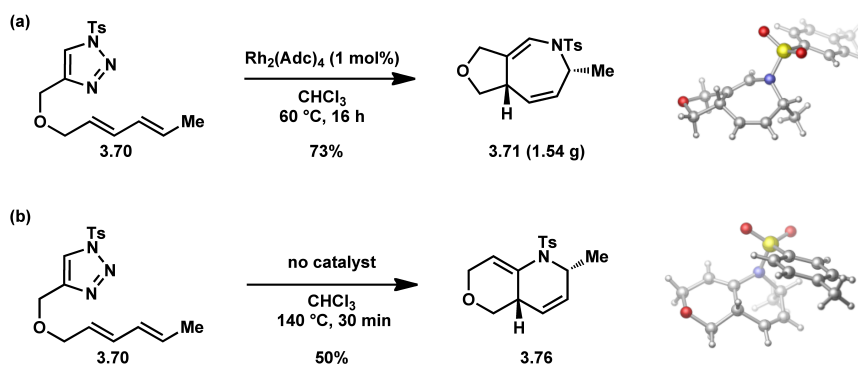
quaternary center at the ring fusion. In this case none of the desired dihydroazepine was obtained, likely due to a destabilizing steric interaction in the 1-aza-Cope transition state, following the intramolecular cyclopropanation reaction (see **3.74**, Scheme 3.16). This was unsurprising given that similar substitution effects have recently been demonstrated to significantly retard the rate of the divinylcyclopropane rearrangement with various derivatives by impeding the adoption of the requisite boat conformation needed for the 3,3-sigmatropic rearrangement.²⁰

Scheme 3.16. Limitation of substrate scope.



The synthesis of fused azepine derivatives using our method was also shown to be amenable to a gram-scale synthesis, as exemplified with **3.71** (Scheme 3.17a). Interestingly, we also found that in the absence of Rh(II) catalyst, under more forcing conditions, a distinct heterocyclic product (**3.76**) was formed in 50% yield, presumably issued from an iminoketene intermediate (Scheme 3.17b). In both cases, X-Ray analysis provided unambiguous structure and relative configuration confirmation of the product.

Scheme 3.17. Gram-scale synthesis of dihydroazepine **3.71** and metal-free access to [4.4.0] bicyclic **3.76**.

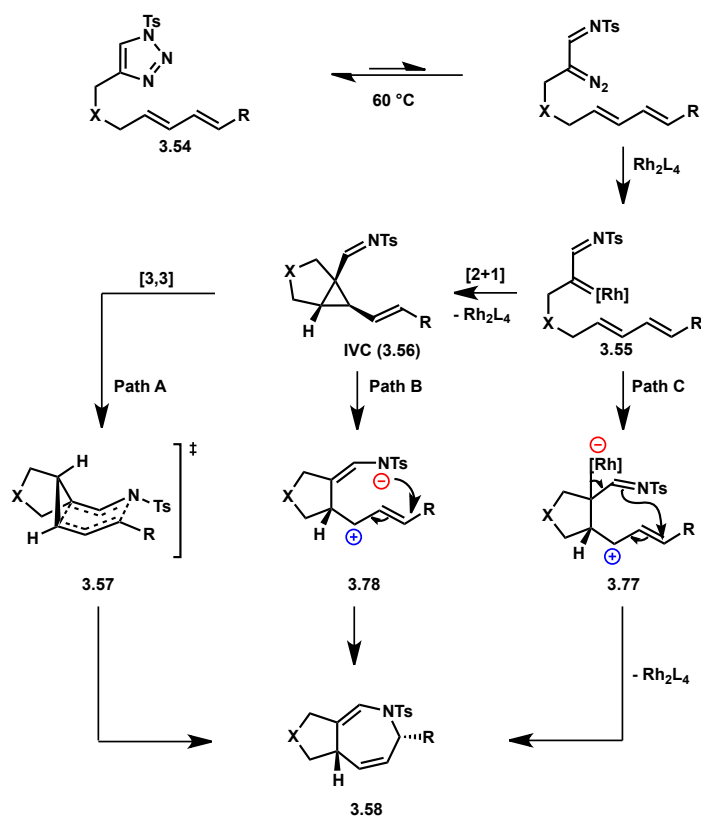


3.4 Reaction Mechanism

The Rh(II)-catalyzed dihydroazepine formation can in principle occur through three distinct mechanistic pathways (Scheme 3.18). First, the azavinyl-substituted Rh-carbenoid species formed by reaction of the dienyltriazole with the Rh catalyst could undergo a [2+1] cycloaddition with the proximal alkenyl group to generate a *cis*-1-imino-2-vinylcyclopropane (IVC, **3.56**), which could engage in a [3,3] sigmatropic rearrangement to directly lead to the dihydroazepine product (Path A). Alternatively, the IVC formed could undergo ring-opening to a zwitterionic intermediate, generating an

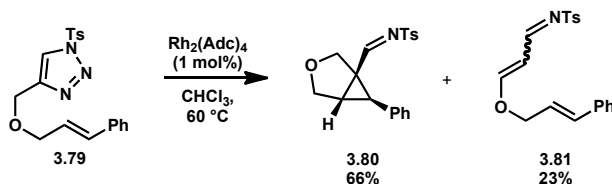
allyl cation capable of ring-closure via an intramolecular *N*-attack of the enamine anion thus formed on the distal alkenyl moiety (Path B). Similarly, the Rh-carbenoid center initially generated could be attacked by the dienyl moiety to generate a Rh-bound zwitterion able to cyclize via an analogous mechanism (Path C). While the stereospecificity of Path A should lead to a single diastereomer of the product with the predicted stereochemistry shown, Path B or C would likely give rise to a mixture of both isomers. Notably, the X-Ray structure of the single diastereomer detected in the reaction of Scheme 3.17a is consistent with the [2+1]/[3,3] sequence depicted in Path A.

Scheme 3.18. Mechanistic possibilities for dihydroazepine formation.



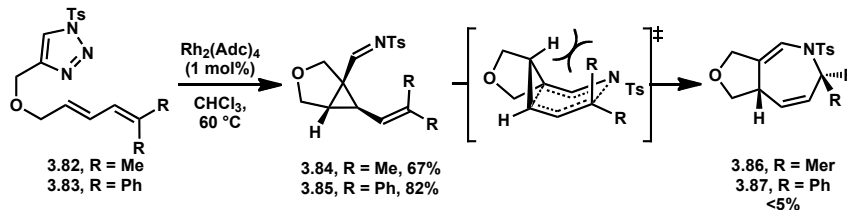
To gain further insight into the mechanism of this process, several other selected triazoles were synthesized and evaluated under the optimal reaction conditions (Scheme 3.19). To evaluate the viability of the iminocyclopropane intermediates that are postulated in our system, alkenyltriazole **3.79**, which lacks the distal alkenyl group required for the subsequent 1-aza-Cope to occur, was submitted to the standard reaction conditions, and iminocyclopropane **3.80** was obtained as a single diastereomer in 66% NMR yield (Scheme 3.19). Although 1-sulfonyl-1,2,3-triazoles have previously been shown to lead to iminocyclopropanes by intermolecular reaction with alkenes,²¹ to our knowledge, the analogous intramolecular cyclopropanation has never been reported.

Scheme 3.19. Intramolecular cyclopropanation.



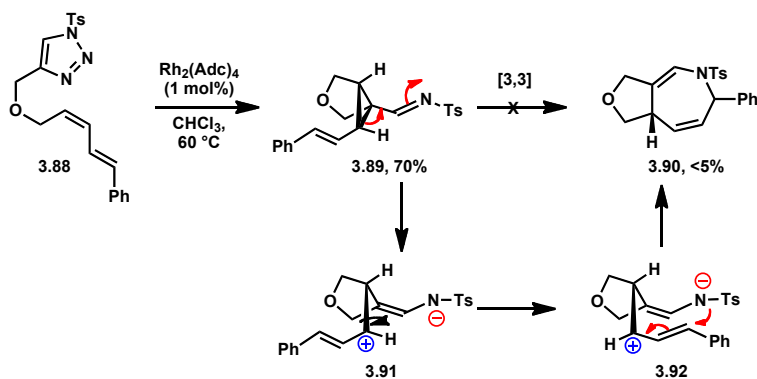
Sterically encumbered dienylnitrosotriazoles **3.82** and **3.83** led to the formation of IVC intermediates (**3.84** and **3.85**, respectively), which did not undergo the subsequent 1-aza-Cope rearrangement (Scheme 3.20). This is likely due to a disfavorable interaction with the *cis*-R groups in the transition state of the [3,3] rearrangement, significantly slowing this pathway.²² The fact that none of the dihydroazepine was observed in this particular case strongly suggests that a concerted mechanism is operational, as the increased flexibility of a ring-opened zwitterionic intermediate, as shown in Path B or C, should still allow for the cyclization to occur. Notably, the formation of such zwitterionic intermediates (**3.77**, **3.78**) should not be hampered by the steric hindrance of the distal alkenyl moiety in **3.82** or **3.83**.

Scheme 3.20. Sterically encumbered dienylnitrosotriazoles fail to undergo 1-aza-Cope rearrangement, stop at IVC.



Finally, *Z,E*-dienylnitrosotriazole **3.88**, leading to a *trans*-IVC (**3.89**), was also found to be unreactive for the dihydroazepine formation, due to the improbability for such an intermediate engaging in a concerted 1-aza-Cope rearrangement (Scheme 3.21). The corresponding zwitterionic intermediate formed from **3.88** (**3.91** or **3.92** after bond rotation) should be identical to the case of *E,E*-dienylnitrosotriazole (**3.78**), which in contrast to **3.88**, led to dihydroazepine formation in excellent yield in only 30 min (see Table 3.2, entry 2).

Scheme 3.21. *Z,E*-dienyltriazole fails to give dihydroazepine.



These results strongly support a sequential intramolecular Rh(II)-catalyzed cyclopropanation / 1-aza-Cope rearrangement as the operational pathway for the dihydroazepine formation (see Scheme 3.18, Path A). Moreover, if a zwitterionic intermediate was involved in the process, the formation of the corresponding 5-membered heterocycle (pyrroline) would be expected to be favored over the dihydroazepine, as the generation of 5-membered ring compounds from this type of zwitterionic intermediate is typically a fast process.²³ Five-membered ring products were not observed in any case throughout this study, again lending support to path A.

3.5. Conclusion

In summary, a general approach for the synthesis of fused dihydroazepines as single diastereomers from dienyltriazoles is reported. A range of substrates were found to participate in the transformation, and several mechanistic investigations support a sequential intramolecular Rh(II)-catalyzed cyclopropanation / 1-aza-Cope rearrangement as the operative mechanistic pathway. The transformation could be conducted on gram-scale with similar efficiency, and the use of catalyst-free conditions provided access to a [4.4.0] bicyclic heterocycle. Given the ubiquity of fused azepine derivatives in biologically relevant compounds, this work contributes to new methods to access a variety of fused azepine-based building blocks for the synthesis of complex molecules.

3.6 Experimental Contributions

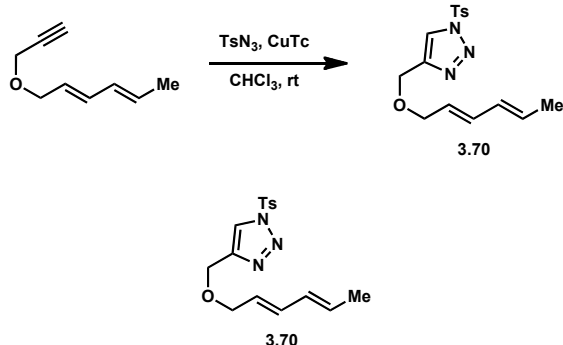
Dr. Vincent G. N. Lindsay contributed characterization and spectral data for the following compounds 3.S4, 3.S5, 3.S6, 3.S10, 3.79, 3.82, 3.88, 3.S13, 3.S14, 3.S15, 3.S17, 3.76, 3.80', 3.84', and 3.89'.

3.7. Experimental

Materials and Methods.

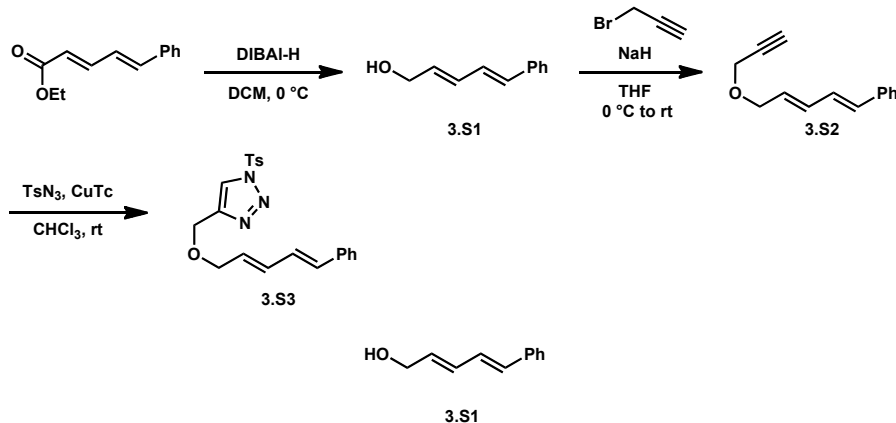
Unless stated otherwise, reactions were performed in oven-dried glassware sealed with rubber septa under a nitrogen atmosphere and were stirred with Teflon-coated magnetic stir bars. Liquid reagents and solvents were transferred via syringe using standard Schlenk techniques. Tetrahydrofuran (THF), toluene, and methanol (MeOH) were dried by passage over a column of activated alumina; dichloromethane was distilled over calcium hydride. Anhydrous chloroform was obtained in a Sure/Seal bottle from Aldrich. All other solvents and reagents were used as received unless otherwise noted. Thin layer chromatography was performed using SiliCycle silica gel 60 F-254 precoated plates (0.25 mm) and visualized by UV irradiation and anisaldehyde, CAM, potassium permanganate, or iodine stain. Sorbent silica gel (particle size 40-63 μm) was used for flash chromatography. NMR experiments were performed on Bruker spectrometers operating at 300, 400, 500 or 600 MHz for ^1H and 75, 100, 125, or 150 MHz for ^{13}C experiments. ^1H and ^{13}C chemical shifts (δ) are reported relative to the residual solvent signal. Data are reported as follows: chemical shift (multiplicity, coupling constants where applicable, number of hydrogens). Abbreviations are as follows: s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublet), dt (doublet of triplet), p (pentet), hept (heptet), m (multiplet), bs (broad singlet). Only select ^1H and ^{13}C spectra are reported. IR spectra were recorded on a Nicolet MAGNA-IR 850 spectrometer as thin films on NaCl plates and are reported in frequency of absorption (cm^{-1}). Only selected IR absorbencies are reported. 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. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. The microwave-assisted reactions were conducted using a Biotage Initiator 2.5 reactor. $\text{Rh}_2(\text{OAc})_4$, $\text{Rh}_2(\text{tpa})_4$, $\text{Rh}_2(\text{Ooct})_4$, $\text{Rh}_2(\text{OPiv})_4$, and $\text{Rh}_2(\text{esp})_2$ were purchased from commercial sources and used without further purification. $\text{Rh}_2(\text{Adc})_4$ was synthesized from $\text{Rh}_2(\text{OAc})_4$ and the corresponding carboxylic acid according to literature procedures.²⁴

Representative Procedure A for the Preparation of *N*-sulfonyltriazoles.

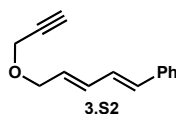


4-[[*(2E,4E)*-hexa-2,4-dien-1-yloxy] methyl]- 1-tosyl- 1*H*- 1,2,3-triazole (3.70). To a flame-dried flask under N₂ was added (*2E,4E*)-hexa-2,4-dien-1-yl prop-2-yn-1-yl ether²⁵ (160 mg, 1.2 mmol, 1.0 equiv) in chloroform (6 mL, 0.2 M). The solution was then sparged with N₂ for 15 min. The flask was then charged with copper (I) thiophene carboxylate (CuTc, 46 mg, 20 mol %) in a single portion, and the solution was again sparged with N₂ for an additional 5 min. Tosyl azide (0.22 mL, 1.3 mmol, 1.1 equiv) was then added to the reaction flask dropwise via syringe over 5 min. The reaction mixture was stirred at ambient temperature for 2 h at which time TLC analysis indicated complete consumption of the starting material. The reaction mixture was quenched by the addition of saturated aqueous ammonium chloride (10 mL). The biphasic mixture was stirred vigorously for 15 min, and then diluted with dichloromethane (5 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (3 x 5 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo*. The resulting residue was purified by column chromatography eluting with 4:1 hexanes:ethyl acetate to yield *N*-tosyltriazole **3.70** (330 mg, 83%) as a white solid, m.p. 64-65 °C. ¹H NMR (600 MHz, CDCl₃) δ 8.10 (s, 1H), 7.97 (d, *J* = 8.1 Hz, 2H), 7.37 (d, *J* = 8.1 Hz, 2H), 6.21 (dd, *J* = 15.3, 10.5 Hz, 1H), 6.07 - 6.01 (m, 1H), 5.76 - 5.67 (m, 1H), 5.59 (dt, *J* = 15.3, 6.4 Hz, 1H), 4.59 (s, 2H), 4.06 (d, *J* = 6.4 Hz, 2H), 2.43 (s, 3H), 1.74 (d, *J* = 6.7 Hz, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 147.3, 145.2, 134.3, 132.9, 130.7, 130.5, 130.4, 128.7, 125.5, 122.2, 71.3, 62.8, 21.8, 18.1; IR (thin film) ν_{max} 3150, 3020, 2915, 2855, 1660, 1594, 1448, 1393, 1215, 1196, 1178, 1091 cm⁻¹; HRMS (ESI⁺) cal'd for [C₁₆H₁₉N₃O₃S+Na]⁺: *m/z*, 356.1039 found 356.1045.

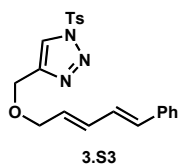
Representative Procedure B for the Preparation of *N*-sulfonyltriazoles.



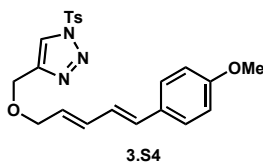
(2*E*,4*E*)-5-phenylpenta-2,4-dien-1-ol (3.S1). To a solution of ethyl-(2*E*,4*E*)-5-phenylpenta-2,4-dienoate²⁶ (1.1 g, 5.4 mmol, 1.0 equiv) in dichloromethane (17 mL, 0.33 M) at 0 °C was added DIBAL-H (7.1 mL of a 1.7 M solution in toluene, 12 mmol, 2.2 equiv) dropwise via syringe over 20 min. After holding at this temperature for 45 min, the reaction mixture was quenched by the slow addition of saturated aqueous sodium potassium tartrate (Rochelle's salt, 20 mL). The biphasic mixture was stirred at ambient temperature for 2 h, then diluted with diethyl ether (20 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (2 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. The resulting residue was purified by column chromatography eluting with 4:1 petroleum ether:ethyl acetate to give **3.S1** (810 mg, 93%) as a white solid, m.p. 66 - 68 °C. Spectra are consistent with those reported previously for **3.S1**.²⁷



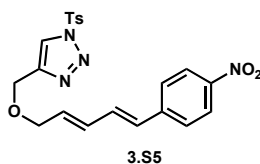
(2*E*,4*E*)-5-phenylpenta-2,4-dien-1-yl prop-2-yn-1-yl ether (3.S2). To a solution of NaH (310 mg, 60% dispersion in mineral oil, 7.6 mmol, 1.5 equiv) in THF (10 mL, 0.5 M) at 0 °C was added alcohol **3.S1** (800 mg, 5.0 mmol, 1.0 equiv). After holding at this temperature for 30 min, propargyl bromide (0.84 mL, 80% (w/w) solution in toluene, 7.6 mmol, 1.5 equiv) was added dropwise via syringe over 5 min. The reaction mixture was warmed to ambient temperature and stirred for 14 h. After this time, the reaction mixture was quenched by the addition of saturated aqueous ammonium chloride (10 mL) and diluted with diethyl ether (10 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over sodium sulfate, filtered and concentrated *in vacuo*. The resulting residue was purified by column chromatography eluting with 8:1 hexanes:ethyl acetate to give dienylalkyne **3.S2** (670 mg, 68%) as a colorless oil. Spectra were consistent with those reported previously for **3.S2**.²⁸



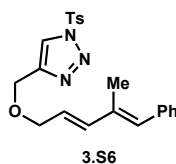
1-Tosyl-4-((2E,4E)-5-phenylpenta-2,4-dien-1-yl)oxy)methyl-1H-1,2,3-triazole (3.S3). To a flame-dried flask under N₂ was added alkyne **3.S2** (570 mg, 2.9 mmol, 1.0 equiv) in chloroform (14 mL, 0.2 M). The solution was then sparged with N₂ for 15 min. The flask was then charged with copper (I) thiophene carboxylate (CuTc, 110 mg, 20 mol %) in a single portion, and the solution was again sparged with N₂ for an additional 5 min. Tosyl azide (0.49 mL, 3.2 mmol, 1.1 equiv) was then added to the reaction flask dropwise via syringe over 5 min. The reaction mixture was stirred at ambient temperature for 2 h at which time TLC analysis indicated complete consumption of the starting material. The reaction mixture was quenched by the addition of saturated aqueous ammonium chloride (20 mL). The biphasic mixture was stirred vigorously for 15 min, and then diluted with dichloromethane (10 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (3 x 10 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo*. The resulting residue was purified by column chromatography eluting with 4:1 hexanes:ethyl acetate to yield triazole **3.S3** (770 mg, 68%). ¹H NMR (600 MHz, CDCl₃) δ 8.14 (s, 1H), 7.99 (d, *J* = 8.5 Hz, 2H), 7.39 (d, *J* = 7.7 Hz, 2H), 7.36 (d, *J* = 8.2 Hz, 2H), 7.31 (t, *J* = 7.7 Hz, 2H), 7.23 (t, *J* = 7.4 Hz, 1H), 6.77 (dd, *J* = 15.7, 10.5 Hz, 1H), 6.56 (d, *J* = 15.7 Hz, 1H), 6.43 (dd, *J* = 15.3, 10.6 Hz, 1H), 5.87 (dt, *J* = 15.4, 6.3 Hz, 1H), 4.64 (s, 2H), 4.16 (d, *J* = 6.2 Hz, 2H), 2.42 (s, 3H). ¹³C NMR (150 MHz, CDCl₃) δ 147.4, 145.1, 137.0, 133.8, 133.3, 133.0, 130.4, 128.9, 128.7, 128.6, 127.9, 127.7, 126.4, 122.3, 71.2, 63.0, 21.8, 14.2; **IR** (thin film) ν_{max} 3379, 3033, 2923, 2870, 1674, 1595, 1450, 1393, 1195, 1177, 1090 cm⁻¹; **HRMS** (ESI⁺) cal'd for [C₂₁H₂₁N₃O₃S+Na]⁺: *m/z*, 418.1201 found 418.1199.



1-Tosyl-4-((2E,4E)-5-(4-methoxyphenyl)penta-2,4-dien-1-yl)oxy)methyl-1H-1,2,3-triazole (3.S4). Prepared from ethyl (2E,4E)-5-(4-methoxyphenyl)penta-2,4-dienoate²⁹ using Representative Procedure B. ¹H NMR (600 MHz, CDCl₃) δ 8.13 (s, 1H), 7.98 (d, *J* = 8.3 Hz, 2H), 7.36 (d, *J* = 8.4 Hz, 2H), 7.32 (d, *J* = 8.8 Hz, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 6.64 (dd, *J* = 15.6, 10.4 Hz, 1H), 6.51 (d, *J* = 15.6 Hz, 1H), 6.40 (dd, *J* = 15.3, 10.4 Hz, 1H), 5.81 (dt, *J* = 15.1, 6.4 Hz, 1H), 4.63 (s, 2H), 4.14 (d, *J* = 6.4 Hz, 2H), 3.79 (s, 3H), 2.42 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 159.5, 147.4, 145.3, 134.3, 133.1, 133.0, 130.5, 129.9, 128.8, 127.8, 126.0, 122.3, 114.2, 71.4, 63.0, 55.4, 21.9; **IR** (thin film) ν_{max} 1603, 1510, 1391, 1251, 1195, 1176, 989 cm⁻¹; **HRMS** (ESI⁺) cal'd for [C₂₂H₂₃N₃O₄S+Na]⁺: *m/z*, 448.1301 found 448.1302.

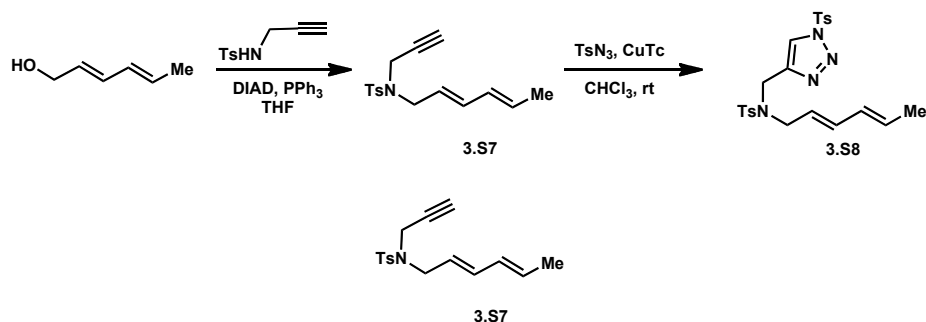


1-tosyl- 4-(((2E,4E)-5-(4-nitrophenyl) penta-2,4-dien-1-yl)oxy)methyl-1H-1,2,3-triazole (3.S5). Prepared from ethyl (2E,4E)-5-(4-nitrophenyl)penta-2,4-dienoate³⁰ using Representative Procedure B. ¹H NMR (400 MHz, CDCl₃) δ d 8.16 (d, *J* = 8.6 Hz, 2H), 8.13 (s, 1H), 7.99 (d, *J* = 8.1 Hz, 2H), 7.50 (d, *J* = 8.6 Hz, 2H), 7.38 (d, *J* = 8.1 Hz, 2H), 6.91 (dd, *J* = 15.6, 10.6 Hz, 1H), 6.59 (d, *J* = 15.7 Hz, 1H), 6.46 (dd, *J* = 15.3, 10.5 Hz, 1H), 6.00 (dt, *J* = 15.3, 5.9 Hz, 1H), 4.66 (s, 2H), 4.19 (d, *J* = 6.0 Hz, 2H), 2.44 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 147.5, 146.9, 145.0, 143.7, 133.0, 132.5, 132.5, 132.5, 130.7, 130.6, 128.9, 126.9, 124.2, 122.4, 70.9, 63.3, 22.0; IR (thin film) ν_{max} 1592, 1511, 1391, 1340, 1195, 1179, 670, 585 cm⁻¹; HRMS (ESI⁺) cal'd for [C₂₁H₂₀N₄O₅S+Na]⁺: *m/z*, 463.1047 found 463.1042.

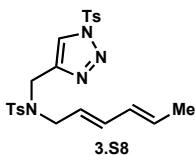


1-tosyl-4- (((2E,4E)-4-methyl-5-phenylpenta-2,4-dien-1-yl) oxy} methyl-1H-1,2,3-triazole (3.S6). Prepared from (2E,4E)-ethyl 4-methyl-5-phenylpenta-2,4-dienoate³¹ using Representative Procedure B. ¹H NMR (600 MHz, CDCl₃) δ 8.15 (s, 1H), 7.99 (d, *J* = 8.4 Hz, 2H), 7.39-7.20 (m, 7H), 6.53 (s, 1H), 6.47 (d, *J* = 15.7 Hz, 1H), 5.84 (dt, *J* = 15.6, 6.4 Hz, 1H), 4.66 (s, 2H), 4.20 (d, *J* = 6.4 Hz, 2H), 2.43 (s, 3H), 1.99 (d, *J* = 1.3 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 147.4, 145.2, 138.9, 137.6, 134.9, 133.0, 132.2, 130.5, 129.2, 128.7, 128.2, 126.8, 124.2, 122.3, 71.7, 63.1, 21.9, 13.9; IR (thin film) ν_{max} 1594, 1391, 1195, 1178, 967, 672, 584 cm⁻¹; HRMS (ESI⁺) cal'd for [C₂₂H₂₃N₃O₃S+Na]⁺: *m/z*, 432.1352 found 432.1347.

Representative Procedure C for the Preparation of *N*-sulfonyltriazoles.

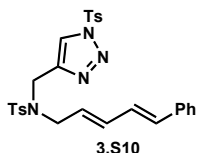


***N*-((2*E*,4*E*)-hexa-2,4-dien-1-yl)-4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (**3.S7**).** *N*-Tosylpropargylamine (200 mg, 0.94 mmol) and triphenylphosphine (150 mg, 0.94 mmol) were dissolved in THF (9.4 mL, 0.1 M). (2*E*,4*E*)-hexa-2,4-dien-1-ol (92 mg, 0.94 mmol) was added, followed by DIAD (0.19 mL, 0.94 mmol). The reaction mixture was stirred for 5 h at ambient temperature, then concentrated *in vacuo*. The resulting residue was purified by column chromatography eluting with a gradient of 7% to 16% ethyl acetate in hexanes to give dienylalkyne **3.S7** (670 mg, 68%) as a white solid. Spectra were consistent with those reported previously for **3.S7**.³²

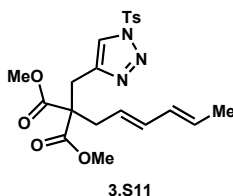


4-(((2*E*,4*E*)-hexa-2,4-dien-1-yloxy)methyl)-1-tosyl-1*H*-1,2,3-triazole (3.S8**).** To a flame-dried flask under N₂ was added alkyne **3.S7** (350 mg, 1.2 mmol, 1.0 equiv) in chloroform (6 mL, 0.2 M). The solution was then sparged with N₂ for 15 min. The flask was then charged with copper (I) thiophene carboxylate (CuTc, 46 mg, 20 mol %) in a single portion, and the solution was again sparged with N₂ for an additional 5 min. Tosyl azide (0.22 mL, 1.3 mmol, 1.1 equiv) was then added to the reaction flask dropwise via syringe over 5 min. The reaction mixture was stirred at ambient temperature for 2 h at which time TLC analysis indicated complete consumption of the starting material, and the reaction mixture was quenched by the addition of saturated aqueous ammonium chloride (10 mL). The biphasic mixture was stirred vigorously for 15 min, and then diluted with dichloromethane (5 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (3 x 5 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo*. The resulting residue was purified twice by column chromatography eluting first with 4:1 hexanes:ethyl acetate then 1% methanol in dichloromethane to yield triazole **3.S8** (180 mg, 32%). ¹H NMR (600 MHz, CDCl₃) δ 7.95 (d, *J* = 8.1 Hz, 2H), 7.94 (s, 1H), 7.62 (d, *J* = 8.0 Hz, 2H), 7.38 (d, *J* = 8.1 Hz, 2H), 7.25 (d, *J* = 7.9 Hz, 2H), 6.04 (dd, *J* = 15.2, 10.4 Hz, 1H), 5.88 (dd, *J* = 14.4, 11.1 Hz, 1H), 5.62 (dq, *J* = 13.9, 6.7 Hz, 1H), 5.23 (dt, *J* = 14.6, 7.0 Hz, 1H), 4.41

(s, 2H), 3.83 (d, $J = 6.8$ Hz, 2H), 2.44 (s, 3H), 2.41 (s, 3H), 1.70 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 147.4, 143.9, 143.7, 136.8, 135.7, 132.9, 131.1, 130.5, 130.1, 129.7, 128.7, 127.1, 123.1, 122.8, 49.7, 41.1, 21.8, 21.5, 18.1; IR (thin film) ν_{max} 3090, 3024, 2920, 2855, 2361, 2342, 1660, 1596, 1446, 1341, 1184, 1159, 1121 cm^{-1} ; HRMS (ESI^+) cal'd for $[\text{C}_{23}\text{H}_{26}\text{N}_4\text{O}_4\text{S}_2+\text{Na}]^+$: m/z , 509.1290 found 509.1288. Note: Compound **3.S8** was isolated with 5% impurity.

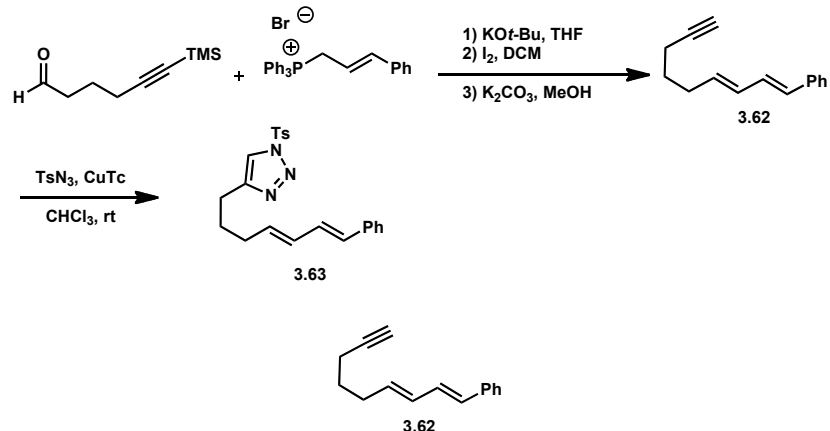


4-methyl-*N*-((2*E*,4*E*)-5-phenylpenta-2,4-dien-1-yl)-*N*-((1-tosyl-1*H*-1,2,3-triazol-4-yl)methyl)benzenesulfonamide (3.S10). Prepared from (2*E*,4*E*)-5-phenylpenta-2,4-dien-1-ol (**3.S1**) using Representative Procedure C. ^1H NMR (400 MHz, CDCl_3) δ 7.97 (d, $J = 8.1$ Hz, 2H), 7.96 (s, 1H), 7.65 (d, $J = 8.1$ Hz, 2H), 7.39 – 7.19 (m, 9H), 6.62 (dd, $J = 15.7, 10.3$ Hz, 1H), 6.48 (d, $J = 15.7$ Hz, 1H), 6.27 (dd, $J = 15.2, 10.3$ Hz, 1H), 5.53 (dt, $J = 14.4, 6.9$ Hz, 1H), 4.46 (s, 2H), 3.94 (d, $J = 6.9$ Hz, 2H), 2.44 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 147.5, 144.0, 143.8, 137.0, 135.6, 133.8, 133.0, 130.6, 129.9, 128.9, 128.7, 128.0, 127.5, 127.3, 126.7, 126.6, 123.0, 49.8, 41.4, 22.0, 21.7; IR (thin film) ν_{max} 3026, 2923, 2854, 1596, 1392, 1343, 1195, 1180, 1159, 1091, 1038, 672, 585 cm^{-1} ; HRMS (ESI^+) cal'd for $[\text{C}_{28}\text{H}_{28}\text{N}_4\text{O}_4\text{S}_2+\text{Na}]^+$: m/z , 571.1444 found 571.1438.



Dimethyl [(2*E*,4*E*)-5-phenylpenta-2,4-dien-1-yl][(N-tosyl-1,2,3-triazol-4-yl)methyl]propanedioate (3.S11). Prepared from dimethyl [(2*E*,4*E*)-5-methylpenta-2,4-dien-1-yl][(prop-2-yn-1-yl)propanedioate³³ using Representative Procedure A. ^1H NMR (600 MHz, CDCl_3) δ 7.95 (d, $J = 8.4$ Hz, 2H), 7.87 (s, 1H), 7.37 (d, $J = 8.2$ Hz, 2H), 6.06 – 5.96 (m, 2H), 5.62 (dq, $J = 13.4, 6.6$ Hz, 1H), 5.35 (dt, $J = 14.5, 7.6$ Hz, 1H), 3.69 (s, 6H), 3.29 (s, 2H), 2.58 (d, $J = 7.6$ Hz, 2H), 2.44 (s, 3H), 1.73 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 170.6, 147.2, 142.7, 135.3, 133.1, 130.9, 130.4, 129.2, 128.6, 123.4, 122.4, 58.0, 52.6, 36.0, 28.7, 21.8, 18.0; IR (thin film) ν_{max} 3147, 3019, 2954, 2854, 1735, 1437, 1394, 1295, 1195, 1179 cm^{-1} ; HRMS (ESI^+) cal'd for $[\text{C}_{21}\text{H}_{25}\text{N}_3\text{O}_6\text{S}+\text{Na}]^+$: m/z , 470.1356 found 470.1368.

Procedure for *N*-sulfonyltriazaole 1i bearing a hydrocarbon tether.

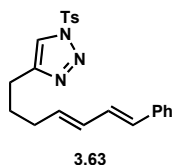


(1*E*,3*E*)-nona-1,3-dien-8-yn-1-ylbenzene (3.62). To a flask containing potassium *t*-butoxide (150 mg, 1.3 mmol, 1.1 equiv) in diethyl ether (6 mL, 0.2 M) at ambient temperature, cinnamyltriphenylphosphonium bromide (500 mg, 1.3 mmol, 1.1 equiv) was added portionwise. After holding at this temperature for 30 min, the reaction mixture was cooled to 0 °C, and TMS-protected hex-5-ynal³⁴ (200 mg, 1.2 mmol, 1.0 equiv) dissolved in ether (1.0 mL) was added dropwise over 10 min. The reaction mixture was then allowed to warm to ambient temperature and stirred for 5 h. After this time, the reaction mixture was quenched by the addition of water (10 mL) and diluted with diethyl ether (10 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. The resulting residue was filtered through a short silica plug eluting with pentanes to give crude trimethyl(9-phenylnona-6,8-dien-1-yn-1-yl) silane (320 mg, quant.) as a yellow oil that was used without further purification.

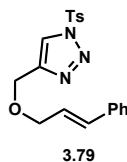
The crude diene (320 mg, 1.2 mmol, 1.0 equiv) was dissolved in dichloromethane (2.7 mL, 0.5 M), and to this solution was added iodine (15 mg, 0.065 mmol, 5.0 mol %). The reaction mixture was stirred at ambient temperature for 30 min, then was quenched by the addition of sodium thiosulfate (5 mL). The biphasic mixture was vigorously stirred for 15 min, then the layers were separated and the aqueous layer was extracted with dichloromethane (3 x 5 mL). The combined organic layers were dried over sodium sulfate, filtered, concentrated *in vacuo* to give the crude trimethyl((6*E*,8*E*)-9-phenylnona-6,8-dien-1-yn-1-yl)silane (320 mg, quant.) as a yellow oil.

The TMS-protected alkyne (320 mg, 1.2 mmol) was dissolved in methanol (6 mL, 2.0 M) and potassium carbonate (330 mg, 2.4 mmol, 2.0 equiv) was added. The resulting mixture was stirred at ambient temperature for 14 h at which time the reaction mixture was quenched by the addition of saturated aqueous ammonium chloride (5 mL) and diluted with diethyl ether (5 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (3 x 5 mL). The combined organic layers were washed with brine (5 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo* and passed

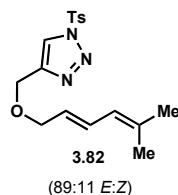
through a short silica plug eluting with pentanes to give **3.62** (185 mg, 79% over 3 steps) as a yellow oil. **¹H NMR** (600 MHz, CDCl₃) δ 7.38 (d, *J* = 7.2 Hz, 2H), 7.30 (t, *J* = 7.7 Hz, 2H), 7.20 (t, *J* = 7.3 Hz, 1H), 6.75 (dd, *J* = 15.7, 10.4 Hz, 1H), 6.46 (d, *J* = 15.7 Hz, 1H), 6.24 (dd, *J* = 15.1, 10.4 Hz, 1H), 5.80 (dt, *J* = 14.7, 7.1 Hz, 1H), 2.27 (q, *J* = 7.5 Hz, 2H), 2.23 (td, *J* = 7.1, 2.6 Hz, 2H), 1.97 (t, *J* = 2.6 Hz, 1H), 1.67 (p, *J* = 7.2 Hz, 2H); **IR** (thin film) ν_{\max} 3297, 3023, 2934, 2863, 2117, 1595, 1448, 1433, 1133, 989 cm⁻¹; **HRMS** (EI⁺) cal'd for [C₁₅H₁₆]⁺: *m/z*, 196.1252 found 196.1252.



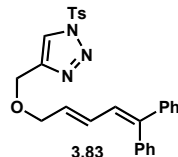
4-((4*E*,6*E*)-7-phenylhepta-4,6-dien-1-yl)-1-tosyl-1*H*-1,2,3-triazole (3.63). Prepared from alkyne **3.62** using Representative Procedure A. (90:10 *E:Z* mixture of diastereomers). **¹H NMR** (600 MHz, CDCl₃, *E* isomer) δ 7.98 (d, *J* = 8.0 Hz, 2H), 7.88 (s, 1H), 7.44 - 7.34 (m, 4H), 7.30 (t, *J* = 7.1 Hz, 2H), 7.20 (t, *J* = 7.5 Hz, 1H), 6.83 - 6.69 (m, 1H), 6.45 (d, *J* = 15.7 Hz, 1H), 6.30 - 6.13 (m, 1H), 5.79 (dt, *J* = 14.6, 7.0 Hz, 1H), 2.74 (t, *J* = 7.3 Hz, 2H), 2.42 (s, 3H), 2.20 (q, *J* = 7.4 Hz, 2H), 1.87 - 1.73 (m, 2H); **¹³C NMR** (150 MHz, CDCl₃) δ 147.8, 147.1, 137.5, 134.2, 133.2, 131.4, 130.5, 130.4, 129.0, 128.5, 128.5, 127.2, 126.2, 120.4, 32.1, 28.4, 24.8, 21.8; **IR** (thin film) ν_{\max} 3147, 3061, 2924, 2859, 1595, 1391, 1009 cm⁻¹; **HRMS** (ESI⁺) cal'd for [C₂₂H₂₃N₃O₂S+Na]⁺: *m/z*, 416.1403 found 416.1412.



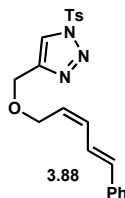
(*E*)-4-((cinnamyloxy)methyl)-1-tosyl-1*H*-1,2,3-triazole (3.79). Prepared from (*E*)-3-phenylprop-2-en-1-ol³⁵ using Representative Procedure A. **¹H NMR** (600 MHz, CDCl₃) δ 8.14 (s, 1H), 7.99 (d, *J* = 8.4 Hz, 2H), 7.40-7.34 (m, 4H), 7.34-7.29 (m, 2H), 7.29-7.21 (m, 1H), 6.63 (d, *J* = 16.0 Hz, 1H), 6.28 (dt, *J* = 16.0, 6.2 Hz, 1H), 4.67 (s, 2H), 4.24 (dd, *J* = 6.2, 1.5 Hz, 2H), 2.43 (s, 3H); **¹³C NMR** (150 MHz, CDCl₃) δ 147.4, 145.2, 136.5, 133.5, 133.1, 130.5, 128.8, 128.7, 128.0, 126.6, 125.1, 122.3, 71.6, 63.1, 21.9; **IR** (thin film) ν_{\max} 3146, 3029, 2922, 2857, 1595, 1393, 1306, 1196, 1179, 1091, 1010, 969, 670, 585 cm⁻¹; **HRMS** (ESI⁺) cal'd for [C₁₉H₁₉N₃O₃S+Na]⁺: *m/z*, 392.1039 found 392.1038.



(*E*)-4-(((5-methylhexa-2,4-dien-1-yl)oxy)methyl)-1-tosyl-1*H*-1,2,3-triazole (3.82). Prepared from (*E*)-ethyl 5-methylhexa-2,4-dienoate³⁶ using Representative Procedure B. (89:11 *E:Z* mixture of diastereomers). ¹H NMR (600 MHz, CDCl₃, *E* isomer) δ 8.10 (s, 1H), 7.97 (d, *J* = 8.4 Hz, 2H), 7.36 (d, *J* = 8.2 Hz, 2H), 6.45 (dd, *J* = 15.0, 11.0 Hz, 1H), 5.81 (d, *J* = 10.9 Hz, 1H), 5.59 (dt, *J* = 15.0, 6.6 Hz, 1H), 4.60 (s, 2H), 4.09 (d, *J* = 6.5 Hz, 2H), 2.43 (s, 3H), 1.76 (s, 3H), 1.74 (s, 3H); ¹³C NMR (150 MHz, CDCl₃, *E* isomer) δ 147.4, 145.4, 137.0, 133.1, 130.8, 130.5, 128.8, 125.4, 124.2, 122.3, 71.8, 62.9, 26.1, 21.9, 18.4; IR (thin film) ν_{max} 2914, 2859, 1595, 1394, 1196, 1178, 1091, 1011, 963, 671, 587 cm⁻¹; HRMS (ESI⁺) cal'd for [C₁₇H₂₁N₃O₃S+Na]⁺: *m/z*, 370.1196 found 370.1194.



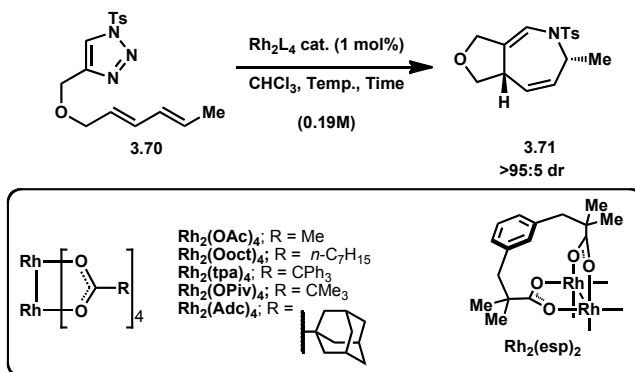
(*E*)-4-(((5,5-diphenylpenta-2,4-dien-1-yl)oxy)methyl)-1-tosyl-1*H*-1,2,3-triazole (3.83). Prepared from (*E*)-ethyl 5,5-diphenylpenta-2,4-dienoate³⁷ using Representative Procedure B. ¹H NMR (600 MHz, CDCl₃) δ 8.06 (s, 1H), 7.96 (d, *J* = 8.4 Hz, 2H), 7.47 - 7.34 (m, 6H), 7.33 (d, *J* = 8.1 Hz, 2H), 7.29 - 7.22 (m, 4H), 7.23 - 7.17 (m, 2H), 6.70 (d, *J* = 11.0 Hz, 1H), 6.35 (dd, *J* = 15.3, 11.0 Hz, 1H), 5.93 (dt, *J* = 15.2, 6.3 Hz, 1H), 4.57 (s, 2H), 4.06 (d, *J* = 6.1 Hz, 2H), 2.40 (s, 1H). ¹³C NMR (150 MHz, CDCl₃) δ 147.8, 145.6, 144.1, 142.4, 139.9, 133.4, 132.1, 130.9, 130.8, 130.6, 129.1, 128.7, 128.7, 128.1, 128.0, 128.0, 127.3, 122.7, 71.8, 63.5, 22.3; IR (thin film) ν_{max} 3378, 3151, 3057, 3029, 2923, 2867, 2248, 1705, 1666, 1595, 1395, 1195, 1179, 1091 cm⁻¹; HRMS (ESI⁺) cal'd for [C₂₇H₂₅N₃O₃S+Na]⁺: *m/z*, 494.1514 found 494.1510. Note: Compound **3.83** was isolated with 5% impurity.



4-(((2*Z*,4*E*)-5-phenylpenta-2,4-dien-1-yl)oxy)methyl)-1-tosyl-1*H*-1,2,3-triazole (3.88). Prepared from (2*Z*,4*E*)-ethyl 5-phenylpenta-2,4-dienoate³⁸ using Representative Procedure B. ¹H NMR (400 MHz, CDCl₃) δ 8.13 (s, 1H), 7.98 (d, *J* = 8.8 Hz, 2H), 7.45 - 7.38 (m, 2H), 7.38 - 7.29 (m, 4H), 7.28 - 7.21 (m, 1H), 7.02 (dd, *J* = 15.4, 11.2, 1H), 6.60 (d, *J* = 15.5 Hz, 1H), 6.34 (t, *J* = 11.0 Hz, 1H), 5.62 (dt, *J* = 10.9, 6.8 Hz, 1H), 4.67 (s, 2H), 4.35 (dd, *J* = 6.9, 1.4 Hz, 2H), 2.43 (s, 3H); ¹³C NMR (150 MHz, CDCl₃)

δ 147.4, 145.2, 137.0, 134.8, 133.1, 132.5, 130.5, 128.7, 128.0, 126.7, 123.4, 122.4, 66.8, 63.2, 21.8; **IR** (thin film) ν_{\max} 3147, 3031, 2864, 1594, 1393, 1196, 1179, 1091, 1010, 979, 670, 586 cm^{-1} ; **HRMS** (ESI⁺) cal'd for $[\text{C}_{21}\text{H}_{21}\text{N}_3\text{O}_3\text{S}+\text{Na}]^+$: m/z , 418.1196 found 418.1191.

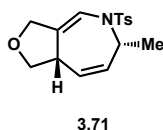
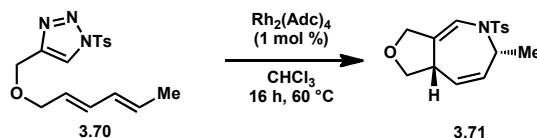
Optimization of the reaction conditions for the dihydroazepine formation



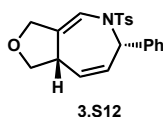
| Entry | Rh_2L_4 | Solvent | Temp. (°C) | time | yield % ^a |
|-----------|---|-----------------------------------|------------------|-------------|----------------------|
| 1 | $\text{Rh}_2(\text{Ooct})_4$ (1) | CHCl_3 | 140 ^b | 0.25 h | 54 |
| 2 | $\text{Rh}_2(\text{OAc})_4$ (1) | CHCl_3 | 140 ^b | 0.25 h | 47 |
| 3 | $\text{Rh}_2(\text{tpa})_4$ (1) | CHCl_3 | 140 ^b | 0.25 h | 18 |
| 4 | $\text{Rh}_2(\text{OPiv})_4$ (1) | CHCl_3 | 140 ^b | 0.25 h | 58 |
| 5 | $\text{Rh}_2(\text{esp})_2$ (1) | CHCl_3 | 140 ^b | 0.25 h | 66 |
| 6 | $\text{Rh}_2(\text{Adc})_4$ (1) | CHCl_3 | 140 ^b | 0.25 h | 68 |
| 7 | $\text{Rh}_2(\text{Ooct})_4$ (1) | MeCN | 140 ^b | 0.25 h | 47 |
| 8 | $\text{Rh}_2(\text{Ooct})_4$ (1) | DME | 140 ^b | 0.25 h | 50 |
| 9 | $\text{Rh}_2(\text{Ooct})_4$ (1) | Heptane | 140 ^b | 0.25 h | 13 |
| 10 | $\text{Rh}_2(\text{Adc})_4$ (1) | CHCl_3 | 60 | 16 h | 74 |
| 11 | $\text{Rh}_2(\text{Ooct})_4$ (1) | CHCl_3 | 60 | 16 h | 57 |
| 12 | $\text{Rh}_2(\text{Ooct})_4$ (1) | TBME | 60 | 16 h | 59 |
| 13 | $\text{Rh}_2(\text{Ooct})_4$ (1) | PhH | 60 | 16 h | 56 |
| 14 | $\text{Rh}_2(\text{OPiv})_4$ (1) | CHCl_3 | 60 | 16 h | 62 |
| 15 | $\text{Rh}_2(\text{OPiv})_4$ (1) | CHCl_3 | 23 | 16 h | 66 |
| 16 | $\text{Rh}_2(\text{OPiv})_4$ (1) | TBME | 60 | 16 h | 63 |
| 17 | $\text{Rh}_2(\text{OPiv})_4$ (1) | 1,2-DCE | 60 | 16 h | 55 |
| 18 | $\text{Rh}_2(\text{esp})_2$ (1) | CHCl_3 | 23 | 16 h | 39 |

^aIsolated yield. ^bReaction was performed in a microwave apparatus.

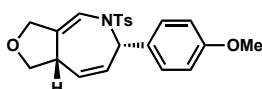
Representative Procedure D for the Rh(II)-Catalyzed Cyclopropanation / 1-Aza-Cope Rearrangement of Dienyltriazaoles



6-methyl-5-tosyl-3,5,6,8a-tetrahydro-1H-furo[3,4-c]azepine (3.71). A flame-dried microwave vial was charged with $\text{Rh}_2(\text{Adc})_4$ (1.4 mg, 1.0 mol %) and *N*-tosyltriazaole **3.70** (50 mg, 0.15 mmol) in chloroform (0.75 mL, 0.20 M) via syringe. The resulting mixture was heated to 60 °C and held at this temperature for 16 h. After cooling to ambient temperature, silica gel was added to the reaction mixture and the solvent was removed *in vacuo*. The resulting residue was purified by column chromatography eluting with 6:1 hexanes:ethyl acetate to give **3.71** (34 mg, 74% isolated yield, >95:5 dr). The diastereomeric ratio was determined by ^1H NMR analysis of the crude mixture. ^1H NMR (600 MHz, CDCl_3) δ 7.71 (d, $J = 8.3$ Hz, 2H), 7.27 (d, $J = 8.0$ Hz, 2H), 6.15 (d, $J = 2.5$ Hz, 1H), 5.51 (ddd, $J = 11.5, 5.2, 2.8$ Hz, 1H), 5.18 (dt, $J = 11.6, 1.8$ Hz, 1H), 4.93 - 4.75 (m, 1H), 4.50 (d, $J = 13.4$ Hz, 1H), 4.28 (dt, $J = 13.5, 2.3$ Hz, 1H), 4.11 (t, $J = 8.4$ Hz, 1H), 3.32 (dd, $J = 10.2, 8.4$ Hz, 1H), 3.08 - 2.95 (m, 1H), 2.42 (s, 3H), 1.25 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 143.4, 143.3, 137.9, 132.0, 129.5, 126.9, 122.2, 115.8, 74.2, 70.1, 53.2, 42.4, 21.5, 21.2; IR (thin film) ν_{max} 2960, 2930, 2856, 1724, 1692, 1343, 1159, 1106 cm^{-1} ; HRMS (ESI $^+$) cal'd for $[\text{C}_{16}\text{H}_{19}\text{NO}_3\text{S}+\text{Na}]^+$: m/z , 328.0983 found 328.0981.



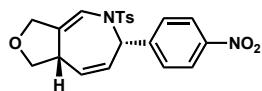
(6-phenyl-5-tosyl-3,5,6,8a-tetrahydro-1H-furo[3,4-c]azepine (3.S12). Prepared from *N*-sulfonyltriazaole **3.S3** following Representative Procedure D, but the reaction was run for 0.5 h instead of 16 h. (92% isolated yield, >95:5 dr). ^1H NMR (600 MHz, CDCl_3) δ 7.74 (d, $J = 7.8$ Hz, 2H), 7.38 (d, $J = 7.4$ Hz, 2H), 7.35 - 7.28 (m, 3H), 7.26 (d, $J = 6.3$ Hz, 2H), 6.01 (t, $J = 4.5$ Hz, 1H), 5.80 (s, 1H), 5.71 (ddd, $J = 11.0, 5.3, 2.6$ Hz, 1H), 5.48 (d, $J = 11.5$ Hz, 1H), 4.41 (d, $J = 13.7$ Hz, 1H), 4.31 - 4.02 (m, 2H), 3.39 (t, $J = 9.4$ Hz, 1H), 2.87 (t, $J = 9.4$ Hz, 1H), 2.43 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 144.6, 143.3, 139.0, 138.1, 129.5, 128.6, 128.3, 128.3, 127.9, 126.9, 124.3, 116.5, 74.1, 70.1, 60.0, 42.6, 21.5; IR (thin film) ν_{max} 2904, 2850, 1674, 1586, 1451, 1407, 1335, 1162, 1034 cm^{-1} ; HRMS (ESI $^+$) cal'd for $[\text{C}_{21}\text{H}_{21}\text{NO}_3\text{S}+\text{Na}]^+$: m/z , 390.1140 found 390.1138. Note: Compound **3.S12** was isolated with 5-10% impurity.



3.S13

6-(4-methoxyphenyl)-5-tosyl-3,5,6,8a-tetrahydro-1H-furo[3,4-c]azepine (3.S13).

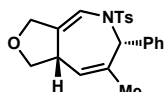
Prepared from *N*-sulfonyltriazole **3.S4** following Representative Procedure D, but the reaction was run for 0.5 h instead of 16 h. (61% isolated yield, >95:5 dr). $^1\text{H NMR}$ (600 MHz, CDCl_3) δ 7.73 (d, $J = 8.3$ Hz, 2H), 7.29 (d, $J = 8.3$ Hz, 2H), 7.26 (d, $J = 8.4$ Hz, 2H), 6.84 (d, $J = 8.7$ Hz, 2H), 5.98-5.94 (m, 1H), 5.80-5.76 (m, 1H), 5.68 (ddd, $J = 11.5$, 5.4, 2.8 Hz, 1H), 5.46 (dt, $J = 11.5$, 1.9 Hz, 1H), 4.41 (d, $J = 13.5$ Hz, 1H), 4.20-4.10 (m, 2H), 3.80 (s, 3H), 3.38 (dd, $J = 10.3$, 8.5 Hz, 1H), 2.88 (s (br), 1H), 2.42 (s, 3H); $^{13}\text{C NMR}$ (150 MHz, CDCl_3) δ 159.5, 144.6, 143.4, 138.4, 131.2, 130.0, 129.7, 129.1, 127.1, 124.2, 116.7, 113.8, 74.3, 70.3, 59.7, 55.4, 42.8, 21.7; **IR** (thin film) ν_{max} 2919, 2838, 1608, 1510, 1341, 1249, 1159, 1094, 1069, 1026, 828, 692, 580 cm^{-1} ; **HRMS** (ESI^+) cal'd for $[\text{C}_{22}\text{H}_{23}\text{NO}_4\text{S}+\text{Na}]^+$: m/z , 420.1240 found 420.1239.



3.S14

6-(4-nitrophenyl)-5-tosyl-3,5,6,8a-tetrahydro-1H-furo [3,4-c]azepine (3.S14).

Prepared from *N*-sulfonyltriazole **3.S5** following Representative Procedure D. (69% isolated yield, >95:5 dr). $^1\text{H NMR}$ (600 MHz, CDCl_3) δ 8.17 (d, $J = 8.6$ Hz, 2H), 7.73 (d, $J = 8.0$ Hz, 2H), 7.57 (d, $J = 8.6$ Hz, 2H), 7.28 (d, $J = 8.0$ Hz, 2H), 6.11-6.05 (m, 1H), 5.81 (s(br), 1H), 5.71 (ddd, $J = 11.5$, 5.4, 2.8 Hz, 1H), 5.57 (d, $J = 11.5$ Hz, 1H), 4.40 (d, $J = 13.8$ Hz, 1H), 4.17-4.10 (m, 2H), 3.38 (dd, $J = 10.2$, 8.5 Hz, 1H), 2.86 (s(br), 1H), 2.43 (s, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 147.7, 146.5, 145.3, 143.9, 137.8, 129.8, 129.5, 127.4, 127.0, 125.9, 123.7, 116.2, 74.1, 70.1, 59.2, 42.6, 21.7; **IR** (thin film) ν_{max} 3035, 2925, 2852, 1597, 1521, 1346, 1160, 1093, 1069, 689, 586 cm^{-1} ; **HRMS** (ESI^+) cal'd for $[\text{C}_{21}\text{H}_{20}\text{N}_2\text{O}_5\text{S}+\text{Na}]^+$: m/z , 435.0985 found 435.0987.

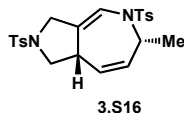


3.S15

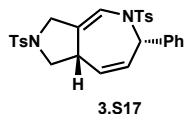
7-methyl-6-phenyl-5-tosyl-3,5,6,8a-tetrahydro-1H-furo[3,4-c]azepine (3.S15).

Prepared from *N*-sulfonyltriazole **3.S6** following Representative Procedure D. (63% isolated yield, >95:5 dr). $^1\text{H NMR}$ (600 MHz, CDCl_3) δ 7.71 (d, $J = 8.2$ Hz, 2H), 7.35 – 7.23 (m, 7H), 5.74 (d, $J = 3.1$ Hz, 1H), 5.70 – 5.65 (m, 1H), 5.26 – 5.22 (m, 1H), 4.41 (d, $J = 13.4$ Hz, 1H), 4.15 – 4.09 (m, 2H), 3.37 (dd, $J = 10.7$, 8.4 Hz, 1H), 2.86 – 2.77 (m, 1H), 2.42 (s, 3H), 1.63 (s, 3H); $^{13}\text{C NMR}$ (150 MHz, CDCl_3) δ 144.0, 143.4, 138.4, 138.3, 135.0, 129.6, 129.0, 128.5, 128.1, 127.0, 120.1, 116.3, 74.5, 70.2, 63.8, 42.9, 24.4, 21.7; **IR** (thin film) ν_{max} 3028, 2922, 2848, 1598, 1493, 1453, 1342, 1162, 1102, 1089,

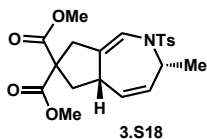
1068, 1043, 814, 754, 701 cm^{-1} ; **HRMS** (ESI^+) cal'd for $[\text{C}_{22}\text{H}_{23}\text{NO}_3\text{S}+\text{Na}]^+$: m/z , 404.1291 found 404.1289.



6-methyl-2,5-ditosyl-1,2,3,5,6,8a-hexahydropyrrolo [3,4-c] azepine (3.S16). Prepared from *N*-sulfonyltriazaole **3.S8** following Representative Procedure D, but the reaction was run for 0.5 h instead of 16 h. (72% isolated yield, >95:5 dr). $^1\text{H NMR}$ (600 MHz, CDCl_3) δ 7.68 (d, $J = 8.3$ Hz, 2H), 7.66 (d, $J = 8.0$ Hz, 2H), 7.35 (d, $J = 7.8$ Hz, 2H), 7.25 (d, $J = 7.8$ Hz, 2H), 6.13 (s, 1H), 5.43 (ddd, $J = 11.6, 5.3, 2.8$ Hz, 1H), 5.11 (d, $J = 11.9$ Hz, 1H), 4.77 - 4.70 (bs, 1H), 4.07 (d, $J = 14.0$ Hz, 1H), 3.64 (t, $J = 8.9$ Hz, 1H), 3.58 (d, $J = 14.1$ Hz, 1H), 3.23 - 3.07 (bs, 1H), 2.57 (t, $J = 9.7$ Hz, 1H), 2.45 (s, 3H), 2.43 (s, 3H), 1.12 (d, $J = 6.8$ Hz, 3H); $^{13}\text{C NMR}$ (150 MHz, CDCl_3) δ 144.1, 143.6, 139.1, 137.5, 132.0, 131.8, 129.8, 129.7, 128.0, 126.8, 123.0, 118.6, 54.0, 53.0, 50.8, 40.9, 21.6, 21.5, 20.8; **IR** (thin film) ν_{max} 3463, 2978, 2928, 2872, 2251, 1669, 1597, 1344, 1162, 1092 cm^{-1} ; **HRMS** (ESI^+) cal'd for $[\text{C}_{23}\text{H}_{26}\text{N}_2\text{O}_4\text{S}_2+\text{Na}]^+$: m/z , 481.1226 found 481.1236.

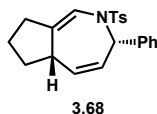


6-phenyl-2,5-ditosyl-1,2,3,5,6,8a-hexahydropyrrolo[3,4-c]azepine (3.S17). Prepared from *N*-sulfonyltriazaole **3.S10** following Representative Procedure D, but the reaction was run for 0.5 h instead of 16 h. (72% isolated yield, >95:5 dr). $^1\text{H NMR}$ (600 MHz, CDCl_3) δ 7.70-7.64 (m, 4H), 7.36 (d, $J = 8.0$ Hz, 2H), 7.27-7.20 (m, 7H), 5.95-5.90 (m, 1H), 5.80 (d, $J = 2.5$ Hz, 1H), 5.65 (ddd, $J = 11.6, 5.5, 2.8$ Hz, 1H), 5.41 (dt, $J = 11.5, 1.9$ Hz, 1H), 3.98 (d, $J = 14.2$ Hz, 1H), 3.66 (t, $J = 8.9$ Hz, 1H), 3.47 (dt, $J = 14.3, 2.4$ Hz, 1H), 3.05 - 2.99 (m, 1H), 2.63 (t, $J = 9.7$ Hz, 1H), 2.47 (s, 3H), 2.44 (s, 3H); $^{13}\text{C NMR}$ (150 MHz, CDCl_3) δ 144.2, 143.7, 140.6, 138.8, 137.9, 132.0, 129.9, 129.8, 128.9, 128.5, 128.4, 128.1, 128.1, 127.0, 125.2, 119.4, 59.9, 54.1, 50.9, 41.3, 21.7; **IR** (thin film) ν_{max} 3089, 3034, 2923, 2856, 1598, 1494, 1479, 1453, 1346, 1162, 1093, 1039, 815, 706, 672 cm^{-1} ; **HRMS** (EI^+) cal'd for $[\text{C}_{28}\text{H}_{28}\text{N}_2\text{O}_4\text{S}_2+\text{Na}]^+$: m/z , 543.1383 found 543.1373.



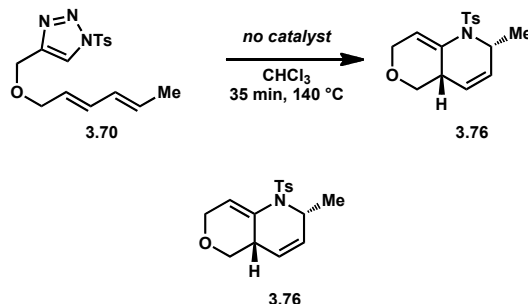
Dimethyl 3-methyl-2-tosyl-2,3,5a,6-tetrahydrocyclopenta[c] azepine-7,7(8H)-dicarboxylate (3.S18). Prepared from *N*-sulfonyltriazaole **3.S11** following Representative Procedure D, but the reaction was run for 0.5 h instead of 16 h. (45% isolated yield, >95:5 dr). $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.70 (d, $J = 8.2$ Hz, 2H), 7.25 (d, $J = 8.2$ Hz, 2H), 6.14 (s, 1H), 5.40 (ddd, $J = 11.5, 5.1, 2.9$ Hz, 1H), 5.25 - 5.17 (m, 1H), 4.83 - 4.75 (m, 1H), 3.74 (s, 3H), 3.72 (s, 3H), 3.15 - 3.02 (m, 1H), 3.02 - 2.94 (m, 1H), 2.86 - 2.77

(m, 1H), 2.60 - 2.50 (m, 1H), 2.43 (s, 3H), 1.86 (dd, $J = 12.7, 11.2$ Hz, 1H), 1.24 (d, $J = 6.9$ Hz, 3H). ^{13}C NMR (150 MHz, CDCl_3) δ 171.1, 170.9, 144.0, 143.0, 130.6, 129.4, 126.8, 126.0, 118.3, 100.0, 58.3, 52.8, 52.8, 52.8, 40.9, 40.1, 38.7, 21.5, 21.2; IR (thin film) ν_{max} 2954, 2926, 2852, 232, 1735, 1598, 1434, 1340, 1252, 1164 cm^{-1} ; HRMS (ESI^+) cal'd for $[\text{C}_{21}\text{H}_{25}\text{NO}_6\text{S}+\text{Na}]^+$: m/z , 442.1295 found 442.1304.



3-phenyl-2-tosyl-2,3,5a,6,7,8-hexahydrocyclopenta[c]azepine (3.68). Prepared from *N*-sulfonyltriazone **3.63** following Representative Procedure D, but the reaction was run for 0.5 h instead of 16 h. (92% isolated yield, >95:5 dr). ^1H NMR (600 MHz, CDCl_3) δ 7.73 (d, $J = 7.7$ Hz, 2H), 7.36 (d, $J = 7.4$ Hz, 2H), 7.33 - 7.20 (m, 5H), 5.94 (s, 1H), 5.70 (s, 1H), 5.63 - 5.47 (m, 1H), 2.62 - 2.57 (m, 1H), 2.42 (s, 3H), 2.38 - 2.31 (m, 1H), 2.25 - 2.15 (m, 1H), 1.94 (t, $J = 8.4$ Hz, 1H), 1.76 - 1.66 (m, 1H), 1.66 - 1.54 (bs, 1H), 1.44 - 1.31 (m, 2H); ^{13}C NMR (150 MHz, CDCl_3) δ 149.5, 142.9, 139.5, 138.5, 129.9, 129.2, 128.7, 128.1, 127.6, 127.0, 126.5, 117.0, 59.8, 42.0, 34.8, 31.6, 24.8, 21.5; IR (thin film) ν_{max} 3029, 2955, 2867, 1665, 1598, 1451, 1337, 1161, 1094 cm^{-1} ; HRMS (ESI^+) cal'd for $[\text{C}_{22}\text{H}_{23}\text{NO}_2\text{S}+\text{Na}]^+$: m/z , 388.1347 found 388.1343.

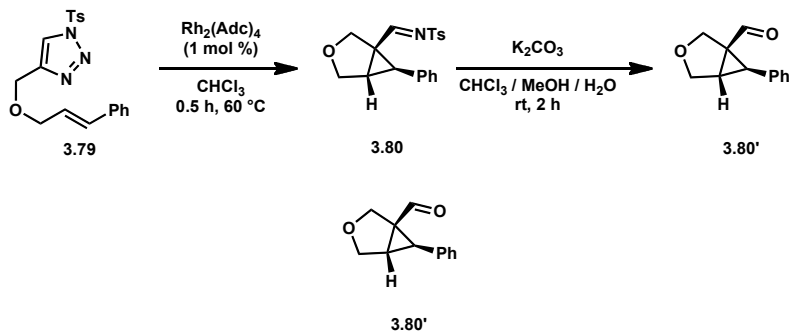
Procedure for the Synthesis of **4** via a thermal non-catalyzed process.



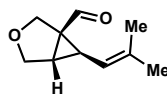
2-methyl- 1- [(4-methylphenyl) sulfonyl]- 1,4a,5,7- tetrahydro- 2H-pyrano[4,3-*b*]pyridine (3.76). A flame-dried 2 mL microwave vial was charged with **3.70** (50 mg, 0.15 mmol, 1.0 equiv), the vial was sealed and backfilled with N_2 . Chloroform (0.8 mL, 0.2 M) was added, and the vial was heated at 140 $^\circ\text{C}$ in the microwave for 35 min. The mixture was allowed to cool to room temperature and concentrated to dryness, and the product was purified by silica-gel chromatography using 1% diethyl ether in dichloromethane as eluent, to afford pure bicyclic compound **3.76** (23 mg, 50% yield) as a white crystalline solid, m.p. 128-129 $^\circ\text{C}$. It is noteworthy that none of the dihydroazepine **3.71** was observed in the crude mixture under these conditions. ^1H NMR (600 MHz, CDCl_3) δ 7.68 (d, $J = 8.0$ Hz, 2H), 7.25 (d, $J = 16.7$ Hz, 2H), 6.03 (s (br), 1H), 5.62 (ddd, $J = 10.3, 4.1, 2.6$ Hz, 1H), 5.17 (d, $J = 10.3$ Hz, 1H), 4.69-4.62 (m, 1H), 4.35 (dt, $J = 16.9, 3.1$ Hz, 1H), 4.25 (ddd, $J = 16.9, 4.1, 1.9$ Hz, 1H), 3.90 (dd, $J = 10.8,$

5.5 Hz, 1H), 3.05 (t, $J = 10.7$ Hz, 1H), 2.51 (s (br, 1H), 2.40 (s, 3H), 1.32 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 143.4, 137.7, 130.2, 129.7, 129.7, 127.3, 125.6, 121.8, 68.9, 66.1, 52.7, 33.5, 22.9, 21.7; IR (thin film) ν_{max} 3031, 2970, 2926, 2851, 1675, 1599, 1458, 1342, 1165, 1136, 1101, 1036, 976, 763, 675, 568, 548 cm^{-1} ; HRMS (ESI^+) cal'd for $[\text{C}_{16}\text{H}_{19}\text{NO}_3\text{S}+\text{Na}]^+$: m/z , 328.0978 found 328.0979.

Representative Procedure E for the Synthesis and Hydrolysis of Cyclopropanecarboximines from *N*-sulfonyltriazaoles



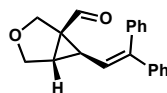
6-phenyl-3-oxabicyclo[3.1.0]hexane-1-carbaldehyde (3.80'). A flame-dried microwave vial was charged with $\text{Rh}_2(\text{Adc})_4$ (1.4 mg, 1.0 mol %) and *N*-tosyltriazaole **3.79** (55 mg, 0.15 mmol, 1.0 equiv) in chloroform (0.75 mL, 0.20 M) via syringe. The resulting mixture was heated to 60 °C for 0.5 h. After cooling to ambient temperature, an equal volume of methanol (0.75 mL), water (a few drops), and anhydrous potassium carbonate (41 mg, 0.30 mmol, 2.0 equiv) were added to the reaction mixture, and the resulting suspension was stirred vigorously for 2 h at which time TLC analysis indicated complete hydrolysis of imine **3.80**. Solvents were removed *in vacuo*. The residue was re-suspended in dichloromethane (5 mL) and dried over sodium sulfate, filtered and concentrated *in vacuo*. The resulting residue was purified by column chromatography eluting with 6:1 hexanes:ethyl acetate to give **3.80'** (51% isolated yield, >95:5 dr, 66% NMR yield, >95:5 dr for imine **3.80**) as a colorless oil. Diastereomeric ratio was determined by ^1H NMR analysis of the crude mixture. ^1H NMR (600 MHz, CDCl_3) δ 8.95 (s, 1H), 7.37 - 7.29 (m, 4H), 7.30 - 7.24 (m, 1H), 4.21 (d, $J = 9.1$ Hz, 1H), 4.08 (d, $J = 8.7$ Hz, 1H), 4.03 (d, $J = 9.1$ Hz, 1H), 3.90 (dd, $J = 8.8, 3.1$ Hz, 1H), 2.99 (dd, $J = 5.6, 3.0$ Hz, 1H), 2.93 (d, $J = 5.6$ Hz, 1H); ^{13}C NMR (150 MHz, CDCl_3) δ 198.3, 134.0, 129.0, 128.9, 127.6, 68.9, 68.2, 46.9, 33.5, 32.0; IR (thin film) ν_{max} 2930, 2863, 1692, 1371, 1239, 1199, 1072, 1058, 1027, 909, 795, 733, 698 cm^{-1} ; HRMS (EI^+) cal'd for $[\text{C}_{12}\text{H}_{12}\text{O}_2]^+$: m/z , 188.0837 found 188.0837.



3.84'

6-(2-methylprop-1-en-1-yl)-3-oxabicyclo[3.1.0]hexane-1-carbaldehyde (3.84').

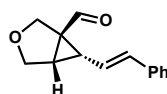
Prepared from *N*-sulfonyltriazole **3.82** (*E:Z* = 89:11) following Representative Procedure E. (49% isolated yield, >95:5 dr, 67% NMR yield, 88:12 dr for imine **3.84**). $^1\text{H NMR}$ (600 MHz, CDCl_3) δ 9.35 (s, 1H), 5.21 (d, $J = 8.0$ Hz, 1H), 4.13 (d, $J = 9.0$ Hz, 1H), 3.93 (d, $J = 8.8$ Hz, 1H), 3.89 (d, $J = 9.0$ Hz, 1H), 3.76 (d, $J = 8.9$, 1H), 2.47-2.41 (m, 1H), 2.32-2.25 (m, 1H), 1.73 (s, 3H), 1.70 (s, 3H); $^{13}\text{C NMR}$ (150 MHz, CDCl_3) δ 198.7, 137.5, 118.1, 68.8, 68.0, 46.9, 35.8, 29.4, 25.6, 18.7; **IR** (thin film) ν_{max} 2931, 2873, 1693, 1381, 1238, 1200, 1075, 1015, 903, 704, 626 cm^{-1} ; **HRMS** (EI^+) cal'd for $[\text{C}_{10}\text{H}_{14}\text{O}_2]^+$: m/z , 166.0994 found 166.0992.



3.85'

6-(2,2-diphenylvinyl)-3-oxabicyclo[3.1.0]hexane-1-carbaldehyde (3.85').

Prepared from *N*-sulfonyltriazole **3.83** following Representative Procedure E. (64% isolated yield, >95:5 dr, 82% NMR yield, >95:5 dr for imine **3.85**). $^1\text{H NMR}$ (600 MHz, CDCl_3) δ 9.56 (s, 1H), 7.38 (t, $J = 7.4$ Hz, 2H), 7.34 (d, $J = 7.3$ Hz, 1H), 7.31 - 7.25 (m, 3H), 7.21 (t, $J = 6.3$ Hz, 4H), 6.09 (d, $J = 9.1$ Hz, 1H), 4.15 (d, $J = 9.1$ Hz, 1H), 3.88 (d, $J = 8.8$ Hz, 1H), 3.83 (d, $J = 9.1$ Hz, 1H), 3.77 (dd, $J = 8.9, 2.9$ Hz, 1H), 2.63 (dd, $J = 5.4, 2.9$ Hz, 1H), 2.33 (dd, $J = 9.2, 5.3$ Hz, 1H); $^{13}\text{C NMR}$ (150 MHz, CDCl_3) δ 197.7, 145.4, 141.8, 139.1, 129.9, 128.4, 128.2, 127.7, 127.6, 127.5, 122.4, 68.6, 67.7, 48.5, 37.1, 31.7; **IR** (thin film) ν_{max} 3053, 3030, 2960, 2928, 2863, 2745, 1693, 1494, 1444, 1374, 1205, 1068, 1018 cm^{-1} ; **HRMS** (EI^+) cal'd for $[\text{C}_{20}\text{H}_{18}\text{O}_2]^+$: m/z , 290.1307 found 290.1303.

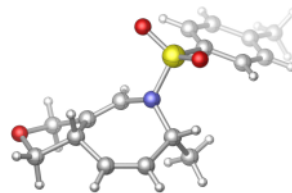
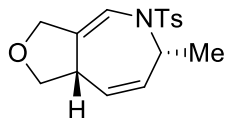


3.89'

6-((*E*)-styryl)-3-oxabicyclo[3.1.0]hexane-1-carbaldehyde (3.89').

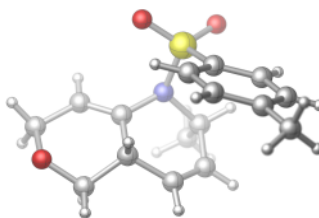
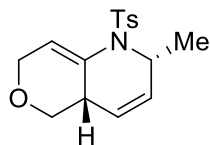
Prepared from *N*-sulfonyltriazole **3.88** following Representative Procedure E. (61% isolated yield, >95:5 dr, 70% NMR yield, >95:5 dr for imine **3.89**). $^1\text{H NMR}$ (600 MHz, CDCl_3) δ 9.24 (s, 1H), 7.41-7.34 (m, 2H), 7.35-7.27 (m, 2H), 7.26-7.20 (m, 1H), 6.73 (d, $J = 15.9$ Hz, 1H), 6.23 (dd, $J = 15.9, 9.2$ Hz, 1H), 4.43 (d, $J = 9.6$ Hz, 1H), 4.12-4.03 (m, 3H), 2.74 (t, $J = 8.8$ Hz, 1H), 2.55 (ddd, $J = 8.5, 3.1, 1.2$ Hz, 1H); $^{13}\text{C NMR}$ (150 MHz, CDCl_3) δ 196.8, 137.0, 135.3, 128.7, 127.7, 126.3, 120.9, 67.8, 66.4, 48.3, 33.8, 32.4; **IR** (thin film) ν_{max} 2924, 2874, 1703, 1693, 1493, 1451, 1203, 1114, 1075, 1041, 1023, 966, 910, 755, 696 cm^{-1} ; **HRMS** (EI^+) cal'd for $[\text{C}_{13}\text{H}_{14}\text{O}_2]^+$: m/z , 214.0994 found 214.0992.

X-Ray Data of compound **3.71**:



| | | |
|-----------------------------------|--|----------|
| X-ray ID | sarpong55 | |
| Empirical formula | C ₁₆ H ₁₉ N O ₃ S | |
| Formula weight | 305.38 | |
| Temperature | 100(2) K | |
| Wavelength | 1.54178 Å | |
| Crystal system | Orthorhombic | |
| Space group | P b c a | |
| Unit cell dimensions | a = 14.1109(14) Å | α = 90°. |
| | b = 8.0225(8) Å | β = 90°. |
| | c = 27.064(3) Å | γ = 90°. |
| Volume | 3063.8(5) Å ³ | |
| Z | 8 | |
| Density (calculated) | 1.324 Mg/m ³ | |
| Absorption coefficient | 1.960 mm ⁻¹ | |
| F(000) | 1296 | |
| Crystal size | 0.120 x 0.050 x 0.050 mm ³ | |
| Crystal color/habit | colorless rod | |
| Theta range for data collection | 3.266 to 68.391°. | |
| Index ranges | -14 ≤ h ≤ 16, -8 ≤ k ≤ 9, -32 ≤ l ≤ 32 | |
| Reflections collected | 50557 | |
| Independent reflections | 2806 [R(int) = 0.0294] | |
| Completeness to theta = 67.000° | 100.0 % | |
| Absorption correction | Semi-empirical from equivalents | |
| Max. and min. transmission | 0.864 and 0.774 | |
| Refinement method | Full-matrix least-squares on F ² | |
| Data / restraints / parameters | 2806 / 0 / 192 | |
| Goodness-of-fit on F ² | 1.059 | |
| Final R indices [I > 2σ(I)] | R1 = 0.0364, wR2 = 0.0960 | |
| R indices (all data) | R1 = 0.0368, wR2 = 0.0963 | |
| Extinction coefficient | n/a | |
| Largest diff. peak and hole | 0.406 and -0.441 e.Å ⁻³ | |

X-Ray Data of compound **3.76**:



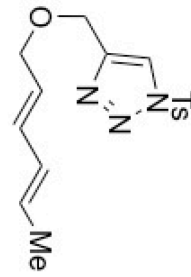
| | | |
|-----------------------------------|--|-----------------|
| X-ray ID | sarpong57 | |
| Empirical formula | C ₁₆ H ₁₉ N O ₃ S | |
| Formula weight | 305.38 | |
| Temperature | 100(2) K | |
| Wavelength | 1.54178 Å | |
| Crystal system | Monoclinic | |
| Space group | P 21/c | |
| Unit cell dimensions | a = 7.3521(5) Å | α = 90°. |
| | b = 8.0929(5) Å | β = 94.599(3)°. |
| | c = 25.1517(17) Å | γ = 90°. |
| Volume | 1491.70(17) Å ³ | |
| Z | 4 | |
| Density (calculated) | 1.360 Mg/m ³ | |
| Absorption coefficient | 2.013 mm ⁻¹ | |
| F(000) | 648 | |
| Crystal size | 0.100 x 0.100 x 0.020 mm ³ | |
| Crystal color/habit | colorless blade | |
| Theta range for data collection | 3.526 to 68.323°. | |
| Index ranges | -8 ≤ h ≤ 8, -9 ≤ k ≤ 7, -30 ≤ l ≤ 30 | |
| Reflections collected | 26265 | |
| Independent reflections | 2724 [R(int) = 0.0263] | |
| Completeness to theta = 67.000° | 99.7 % | |
| Absorption correction | Semi-empirical from equivalents | |
| Max. and min. transmission | 0.929 and 0.847 | |
| Refinement method | Full-matrix least-squares on F ² | |
| Data / restraints / parameters | 2724 / 0 / 192 | |
| Goodness-of-fit on F ² | 1.041 | |
| Final R indices [I > 2σ(I)] | R1 = 0.0352, wR2 = 0.0938 | |
| R indices (all data) | R1 = 0.0366, wR2 = 0.0950 | |
| Extinction coefficient | n/a | |
| Largest diff. peak and hole | 0.441 and -0.375 e.Å ⁻³ | |

3.8 References and Notes

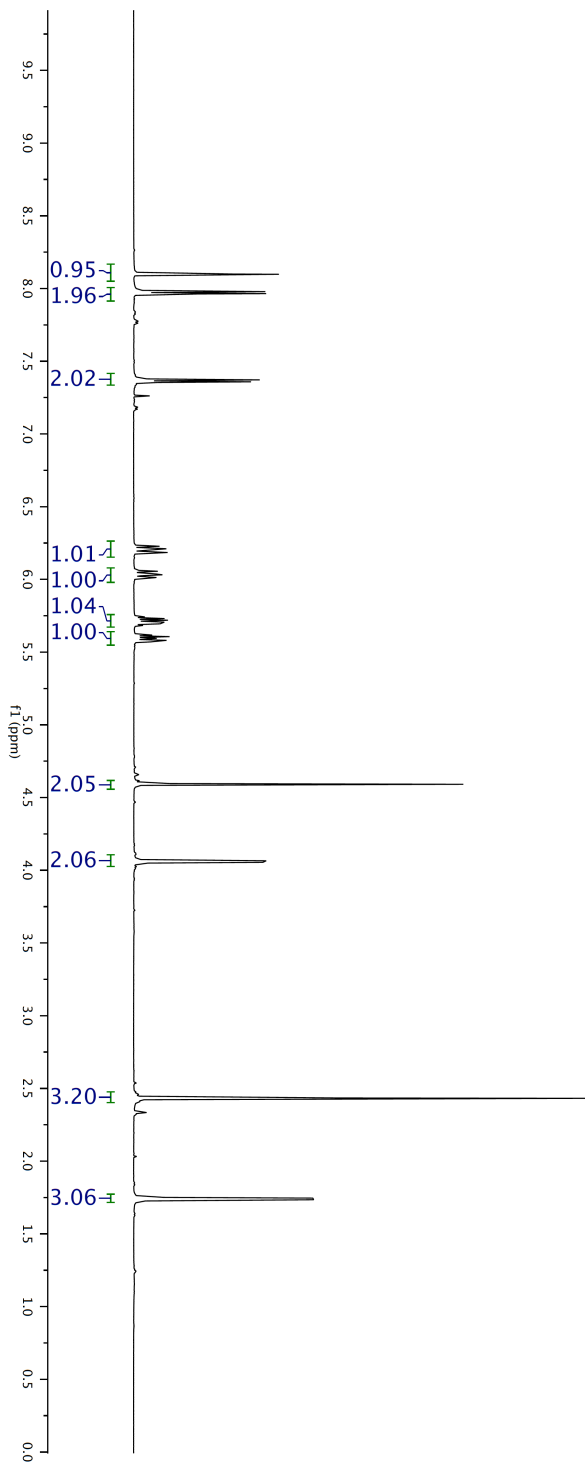
1. For reviews on the synthesis, properties and natural occurrences of azepine derivatives, see: (a) Vaquero, J. J.; Cuadro, A. M.; Herradón, B. In *Modern Heterocyclic Chemistry*; Wiley-VCH Verlag GmbH & Co. KGaA: 2011, p 1865-1988. (b) Smalley, R. K. In *Comprehensive Heterocyclic Chemistry*, vol. 7; Katritzky, A. R., Rees, C. W. (Eds.); Pergamon: Oxford, 1984, p 491-546. (c) Le Count, D. J. In *Comprehensive Heterocyclic Chemistry II*, vol. 9; Katritzky, A. R., Rees, C. W., Scriven, E. F. V. (Eds.); Pergamon: Oxford, 1996, p 1-43. (d) Bremner, J. B.; Samosorn, S. In *Comprehensive Heterocyclic Chemistry III*, vol. 13; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Taylor, R. (Eds.). Elsevier: Oxford, 2008, p 1-43. (e) Proctor, G.R. and Redpath, J. In *The Chemistry of Heterocyclic Compounds*, vol. 56 (ed. E.C. Taylor), Wiley-Interscience Publication, Chichester, 1996. (f) Sammes, P. G. In *Comprehensive Organic Chemistry, Heterocyclic Chemistry*, Vol. 4, Part 17.6; Barton, D.; Ollis, W. D. (Eds.); Pergamon: Oxford, 1979, 582.
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4. Paquette, L. A.; Ewing, G. D. *J. Am. Chem. Soc.* **1978**, *100*, 2908.
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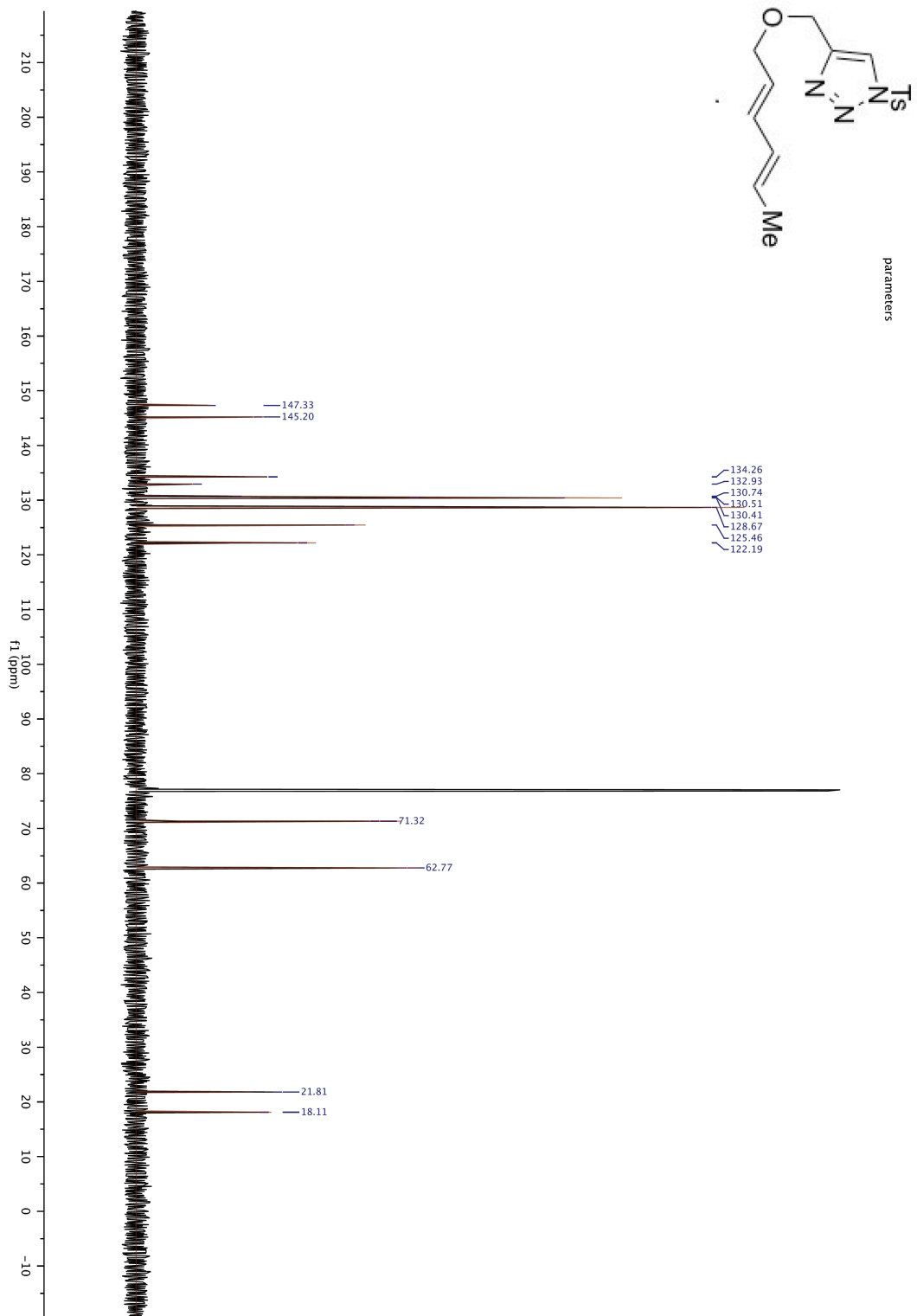
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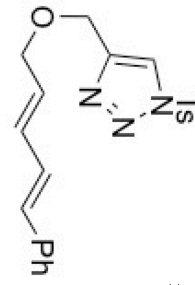
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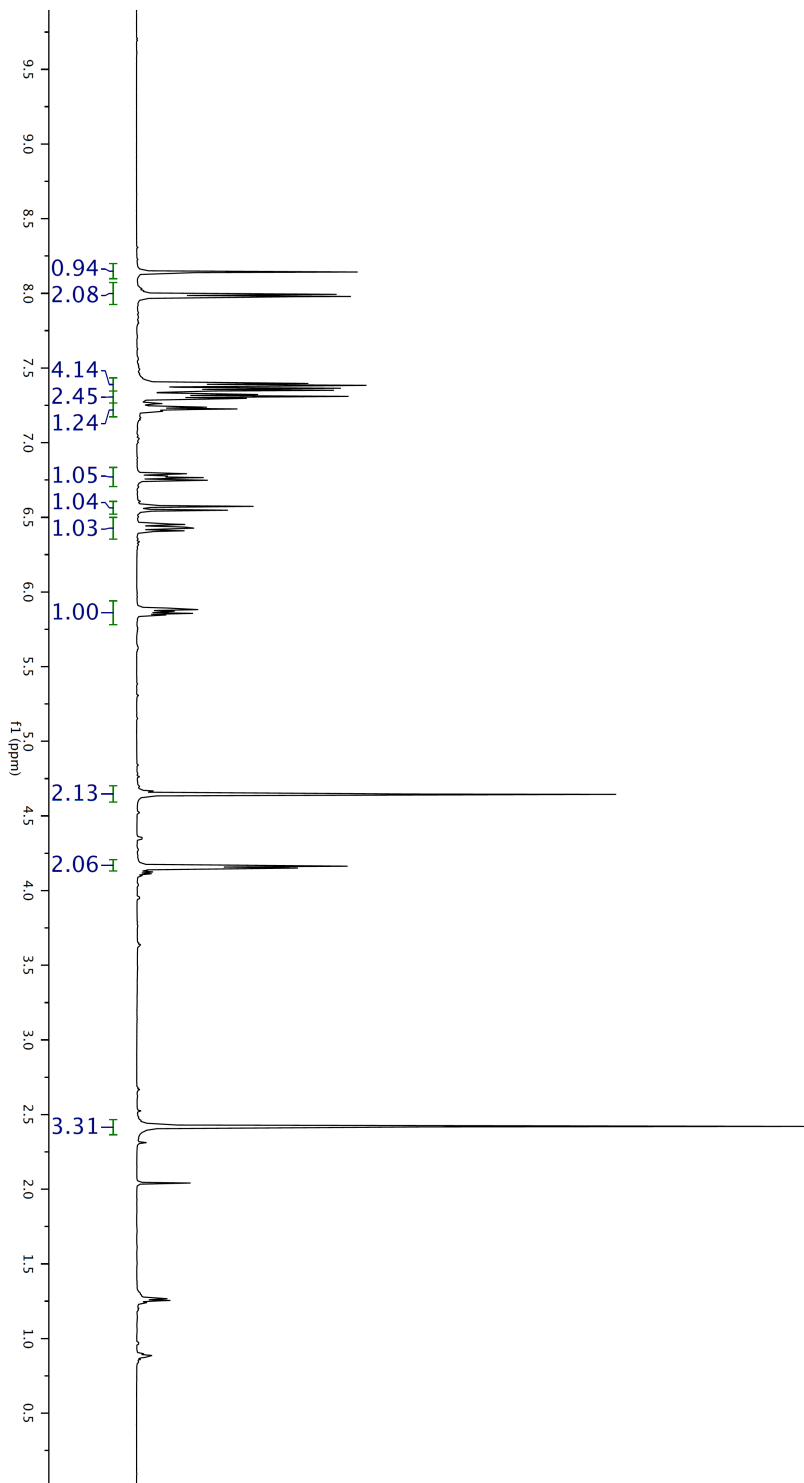
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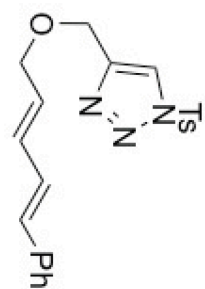




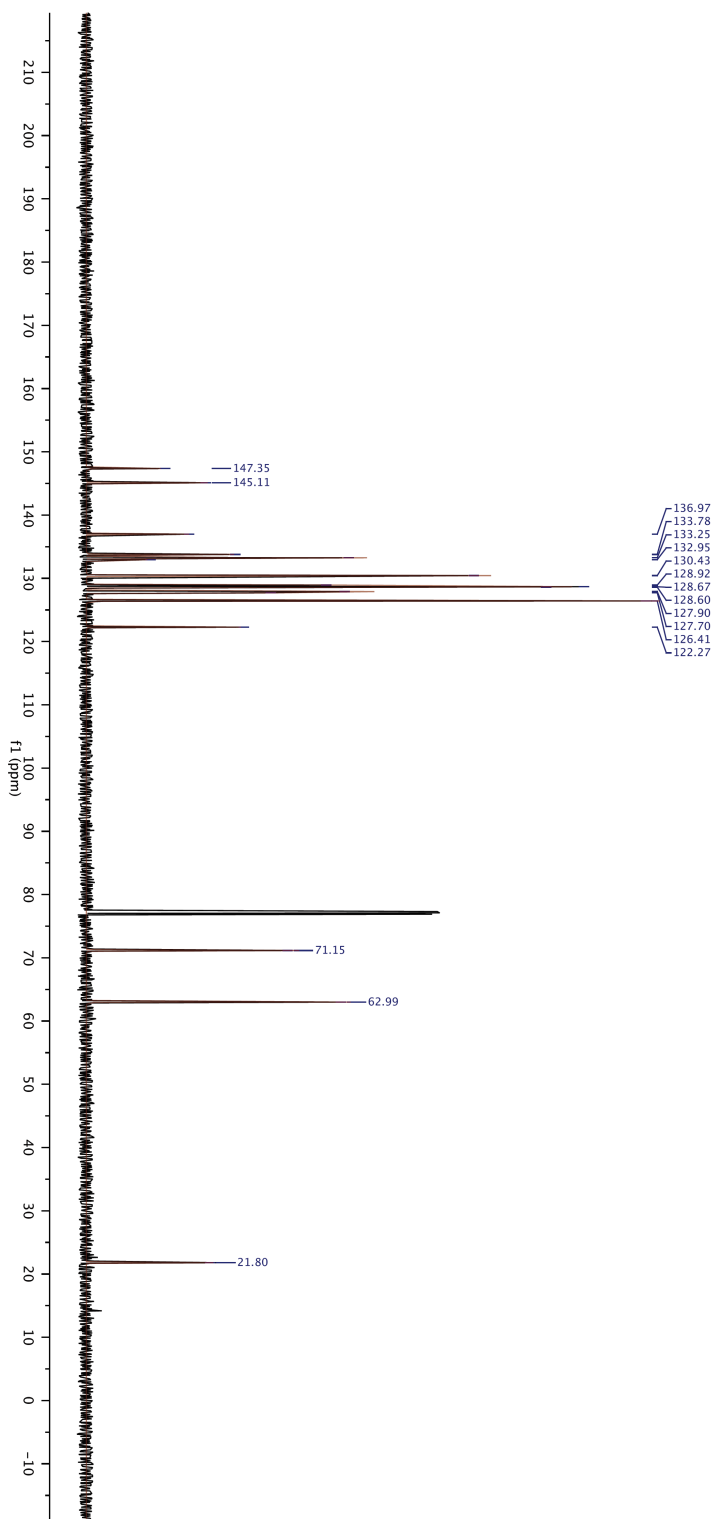


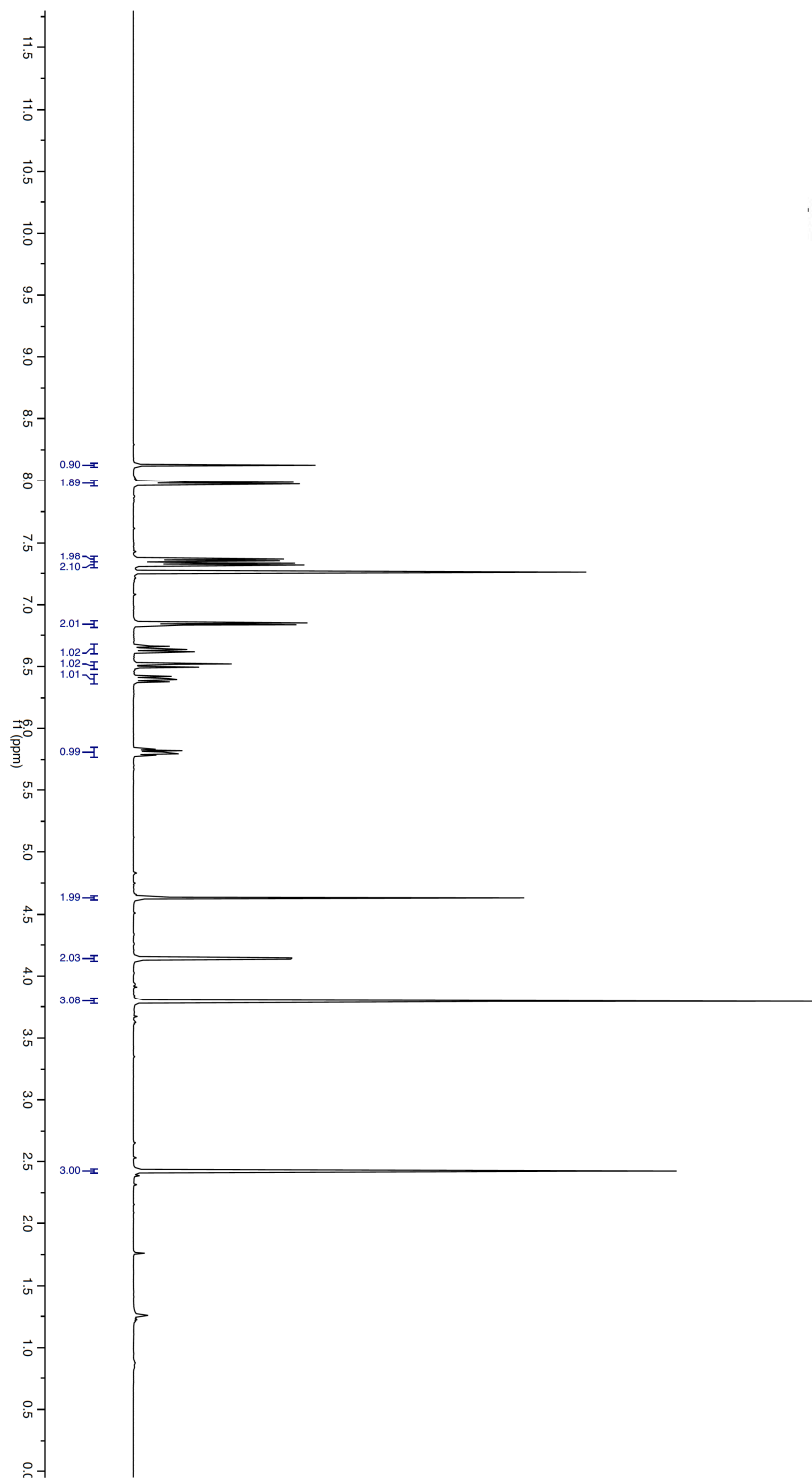
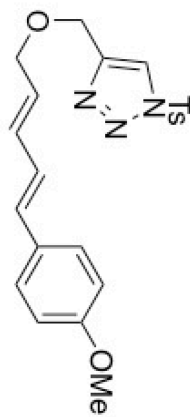
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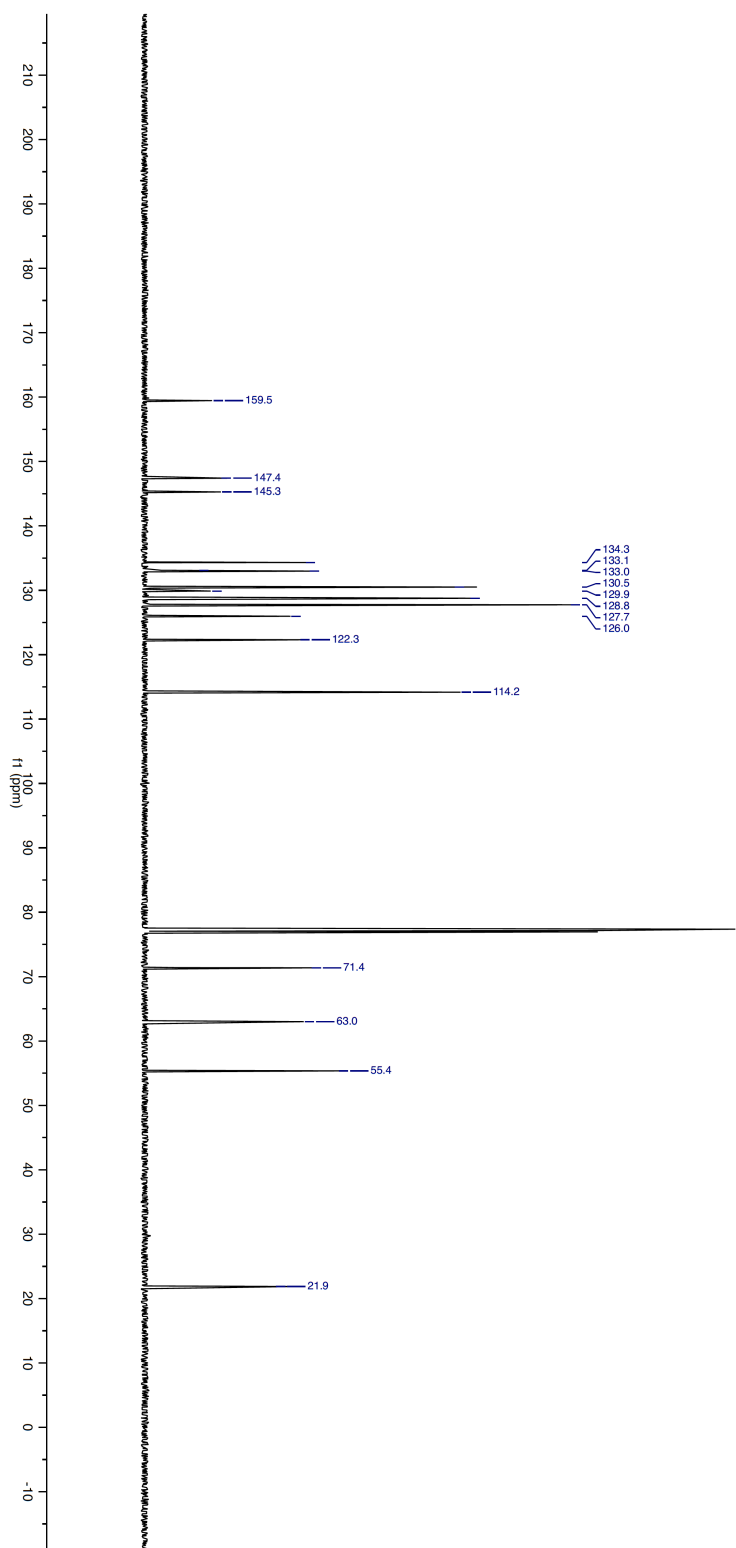
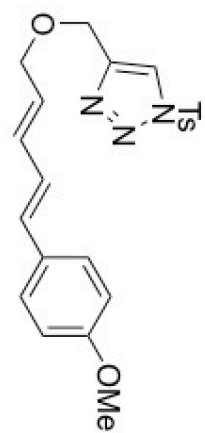


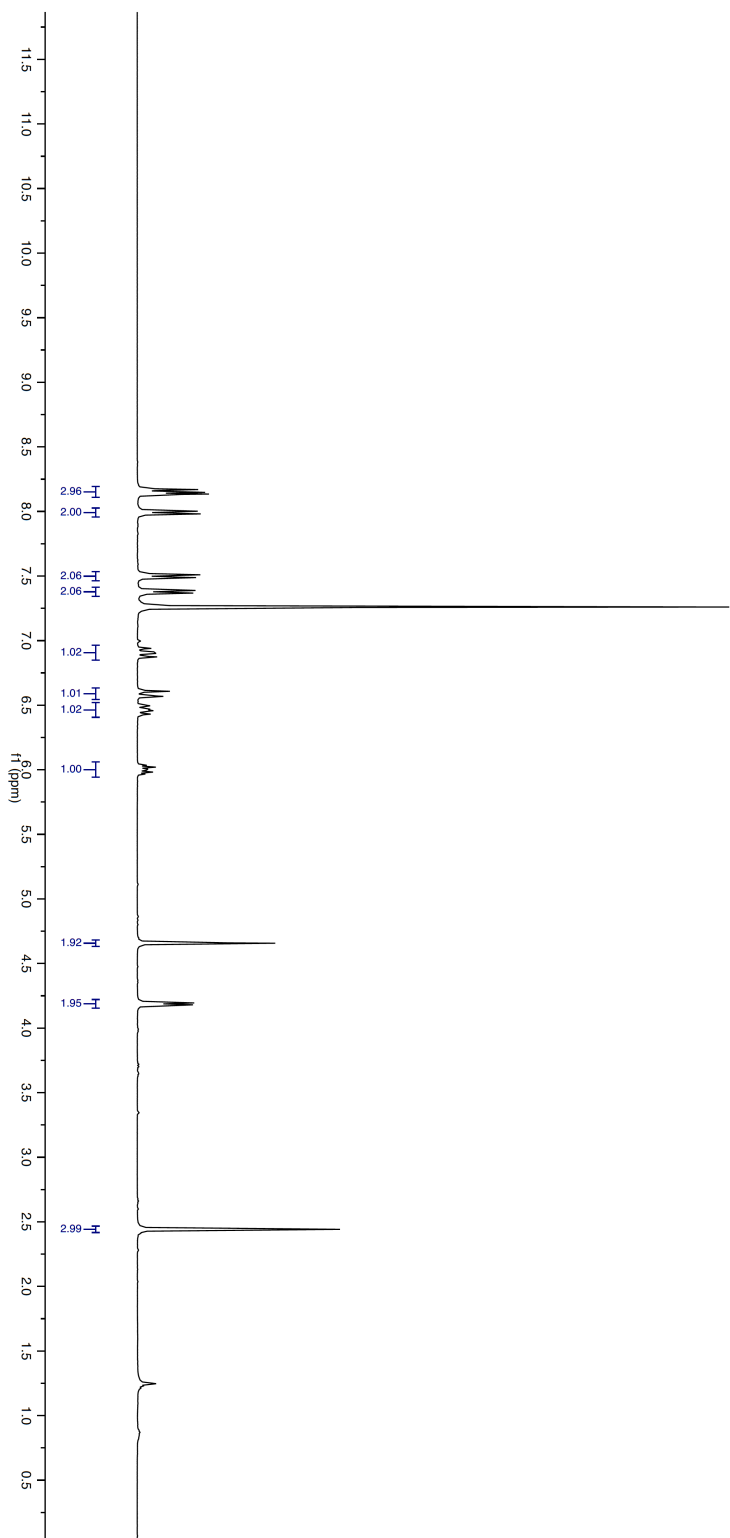
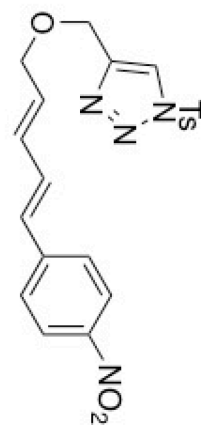


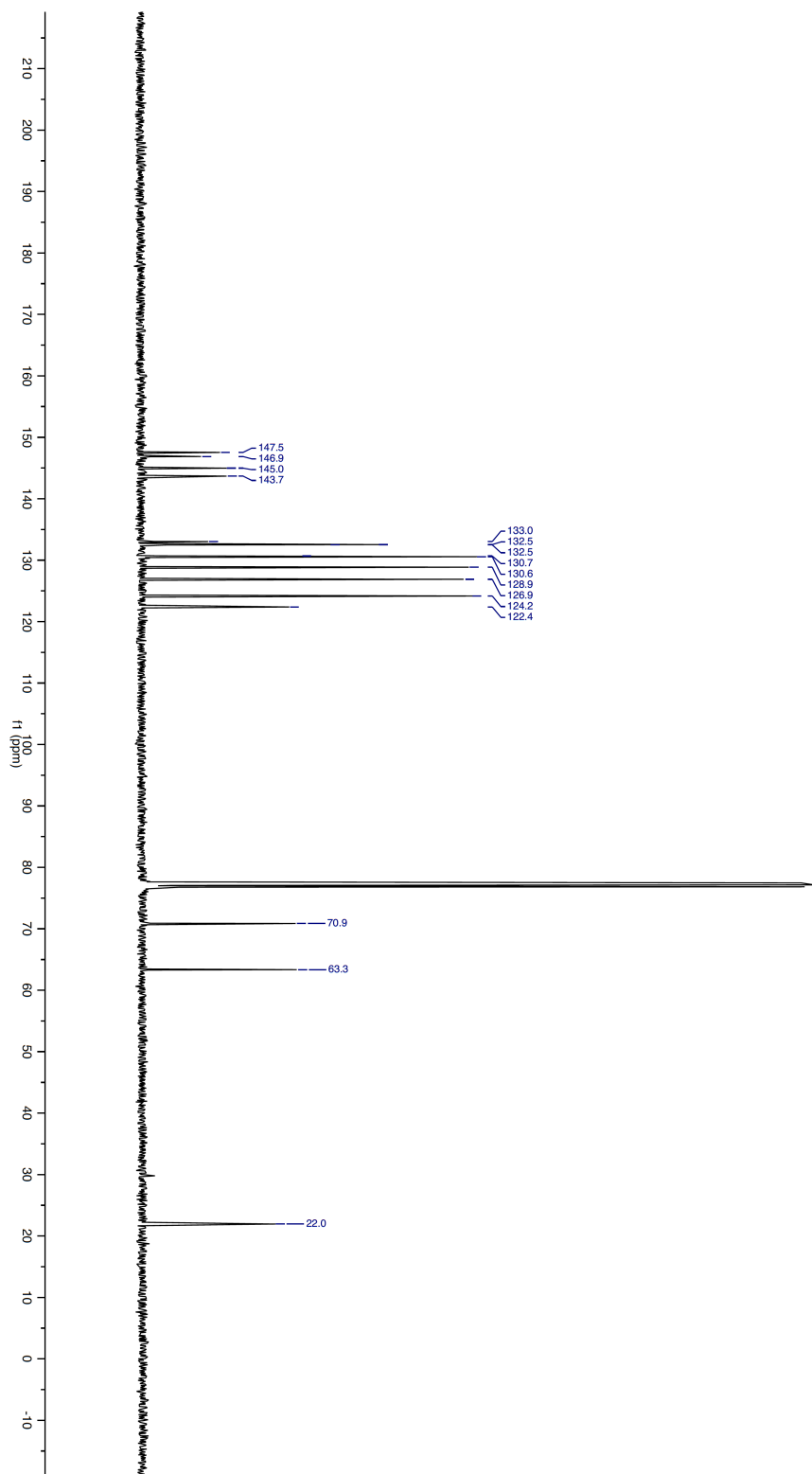
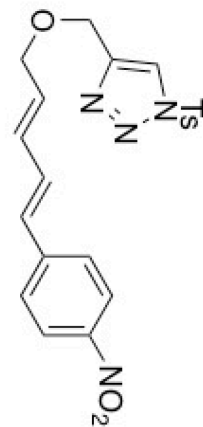
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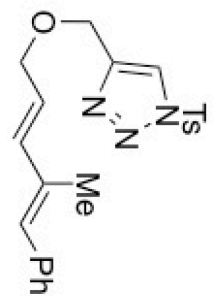




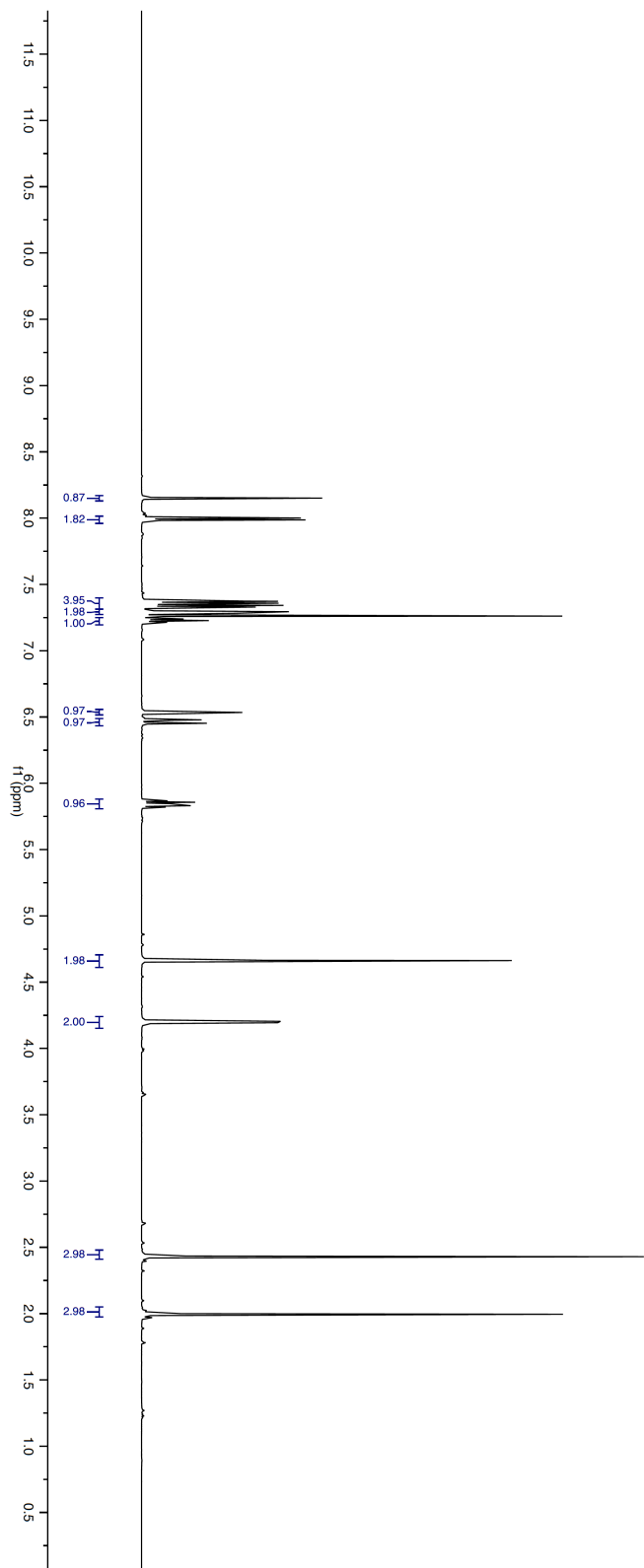


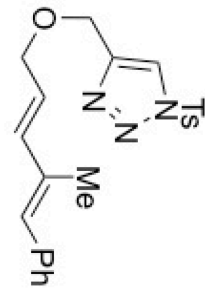




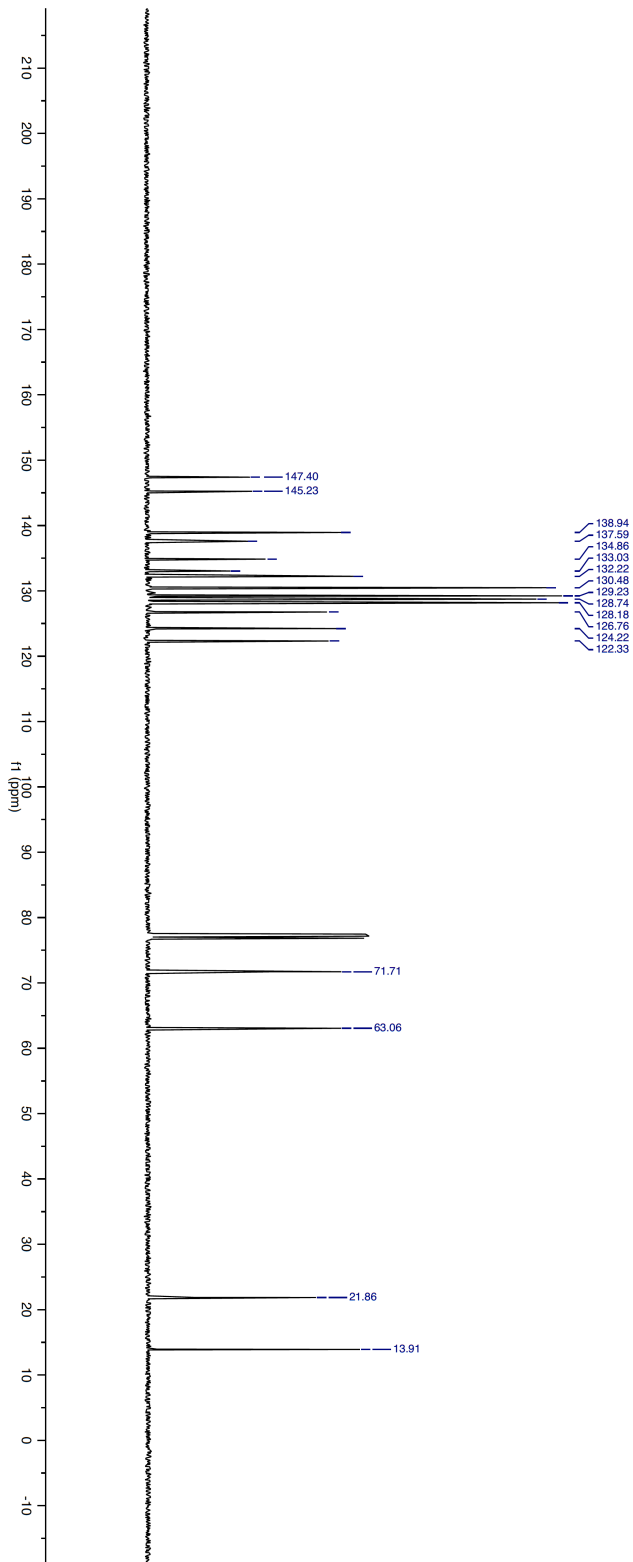


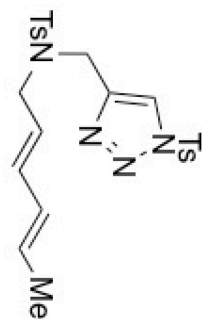
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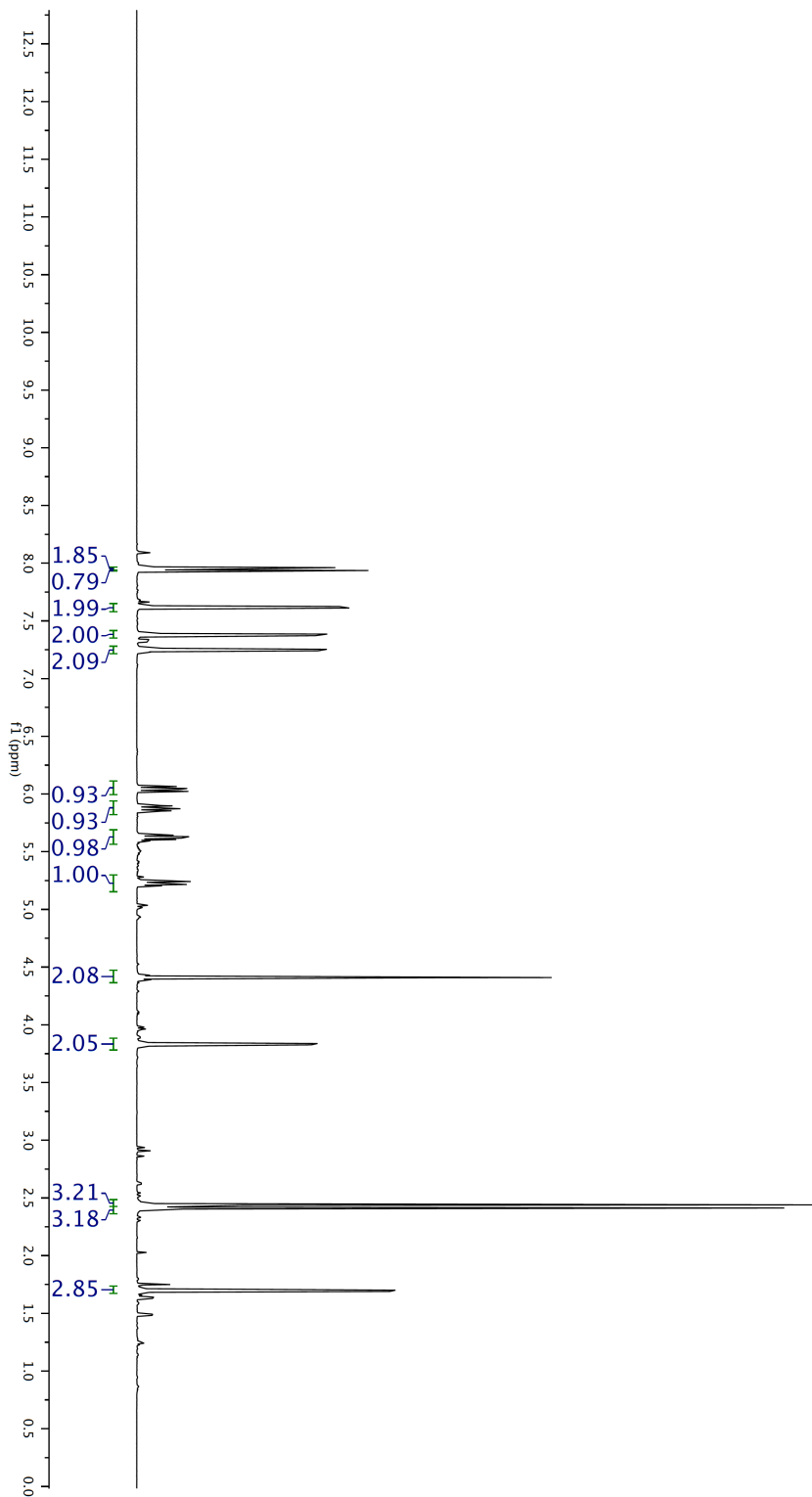


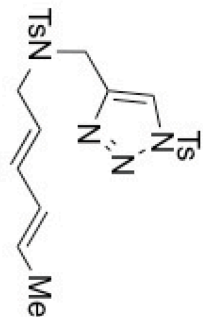
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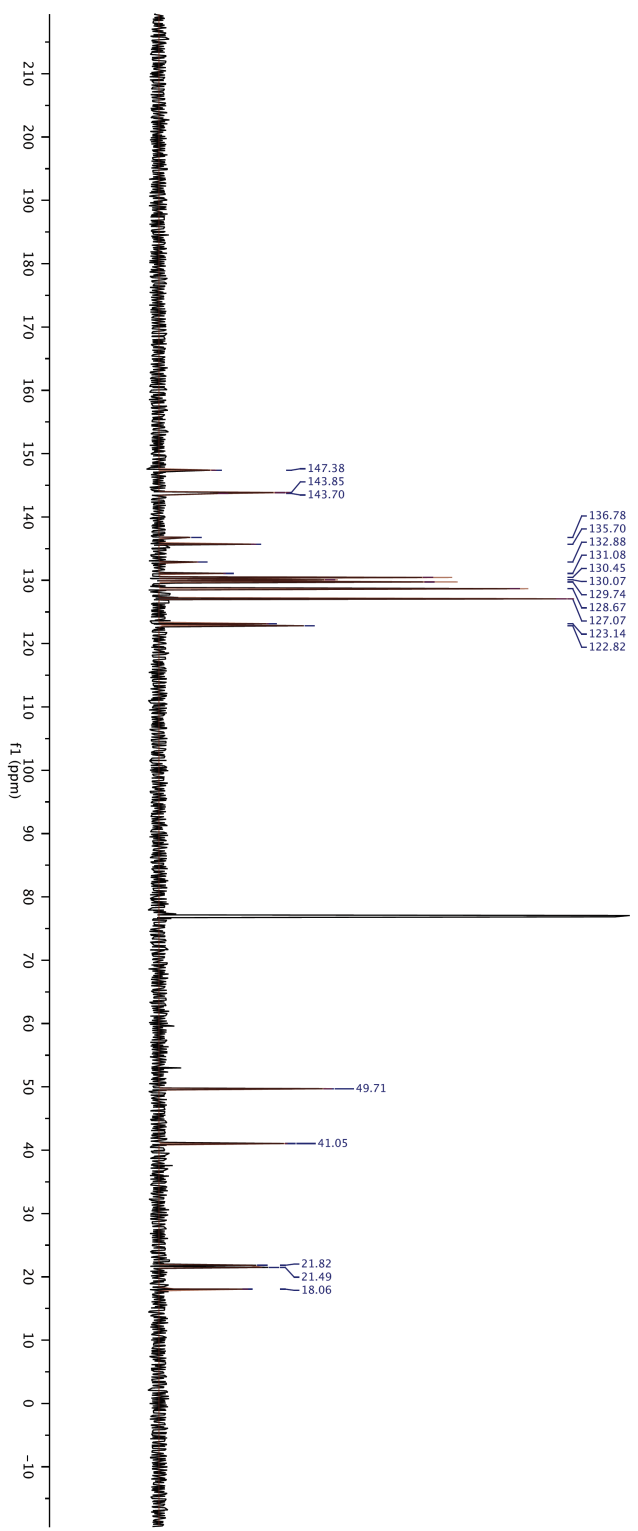


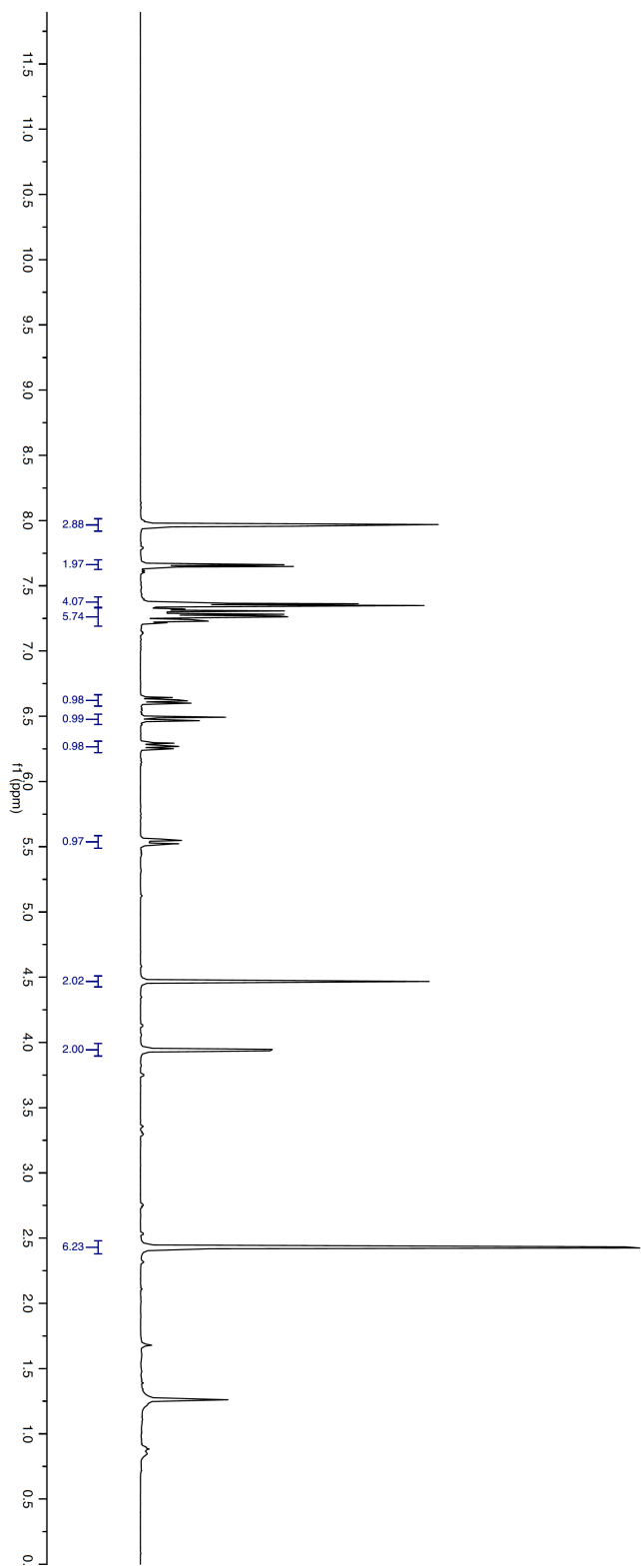
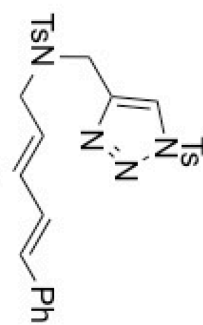
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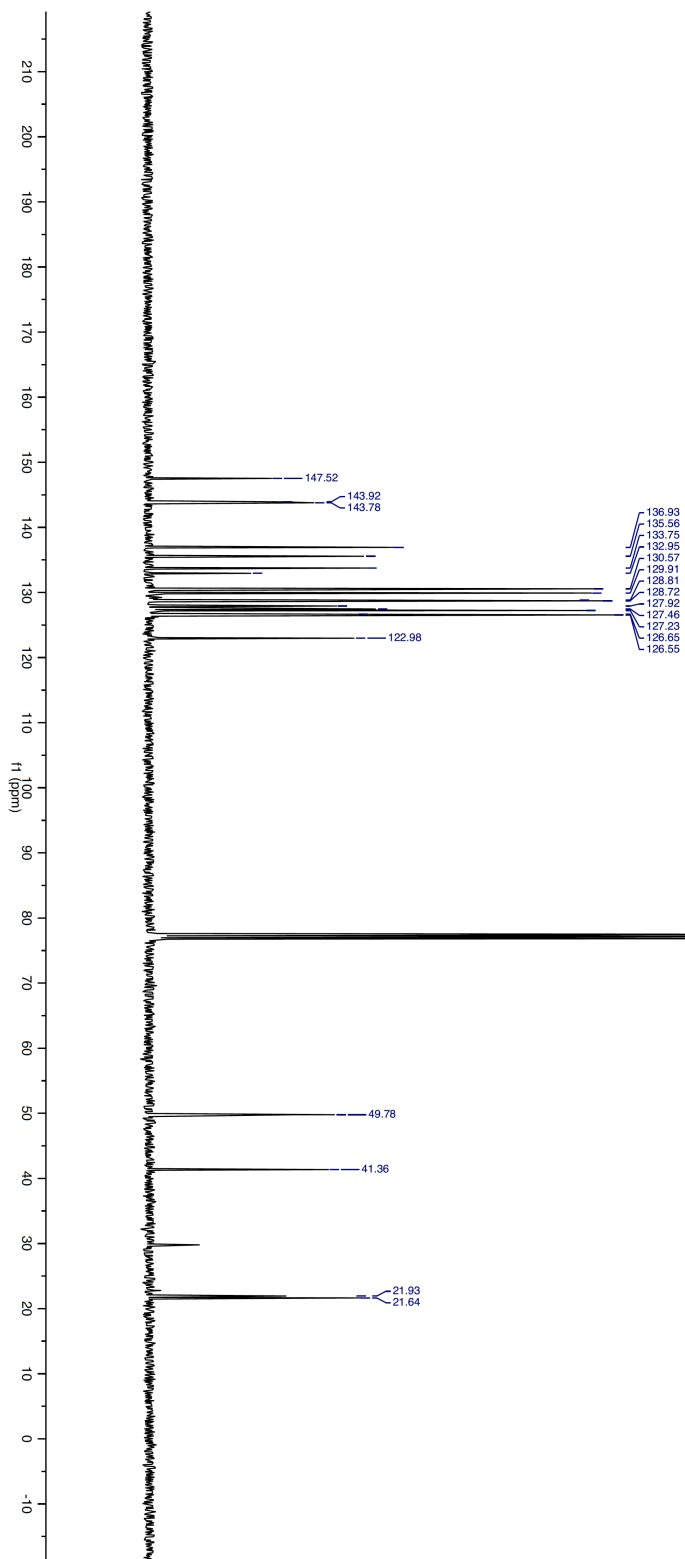
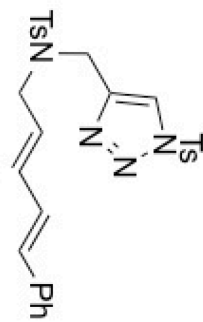


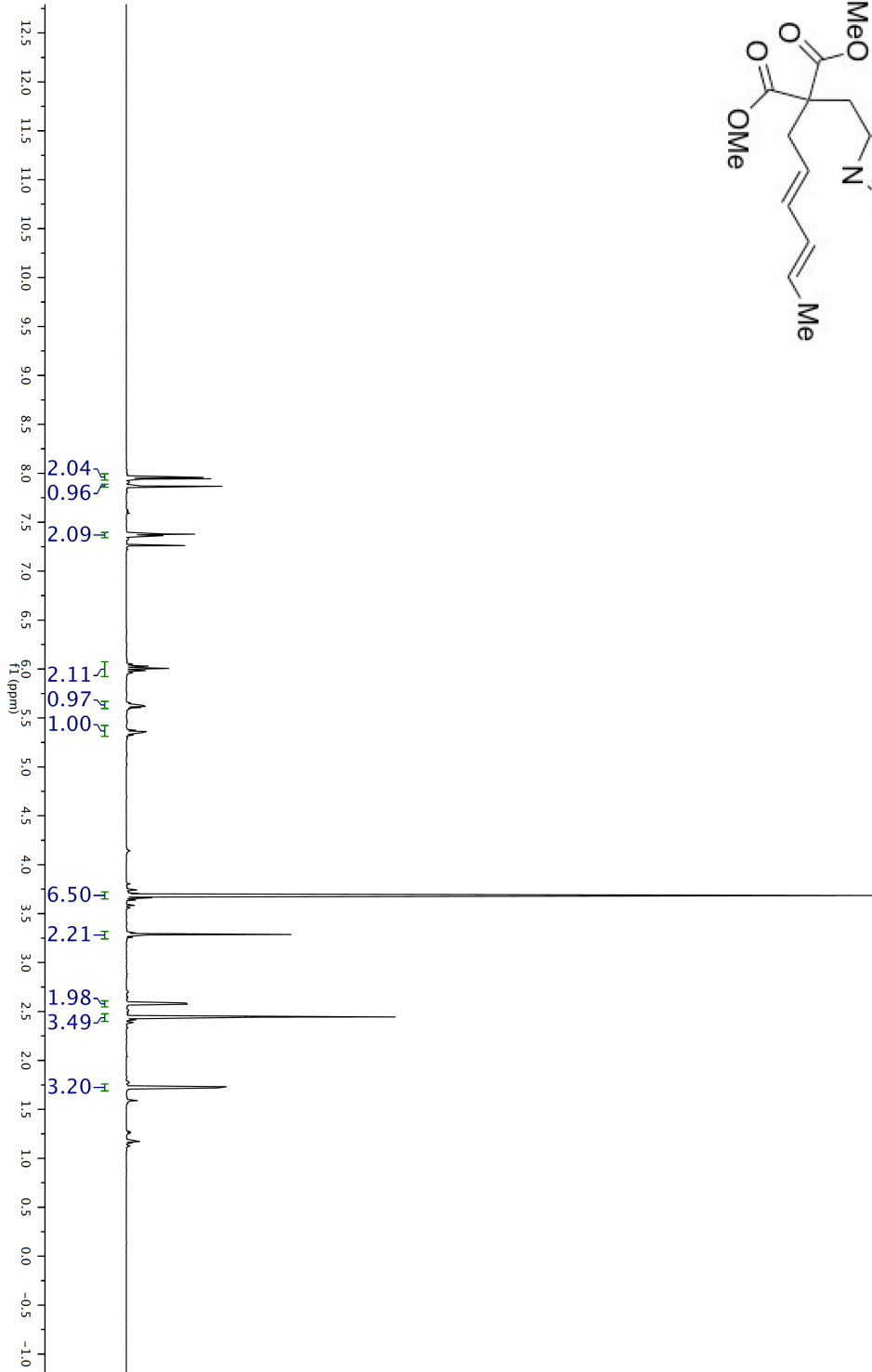
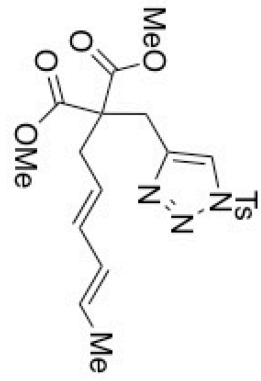


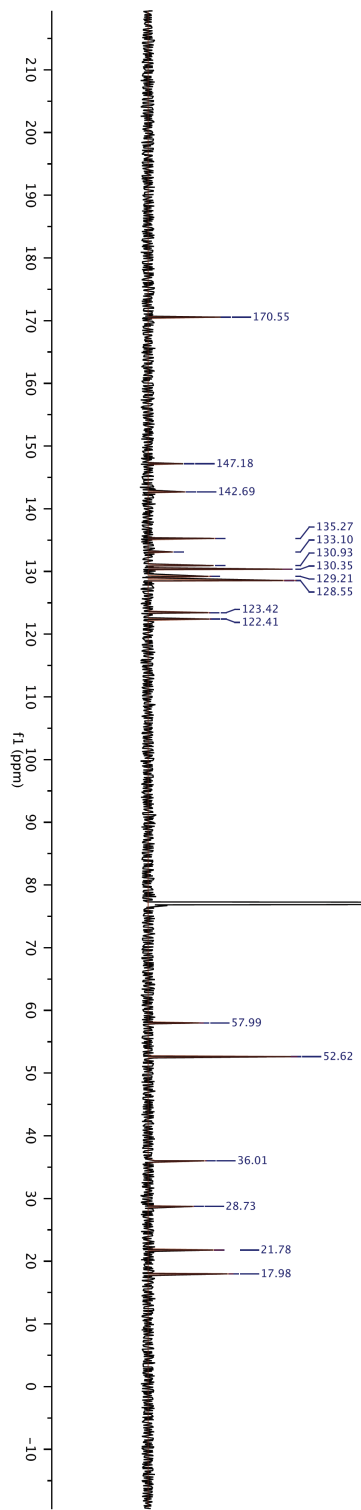
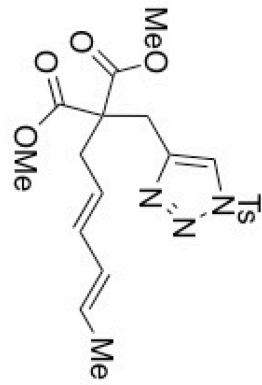
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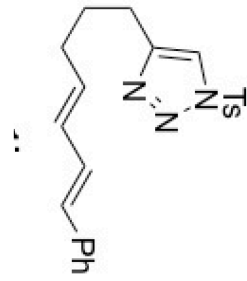




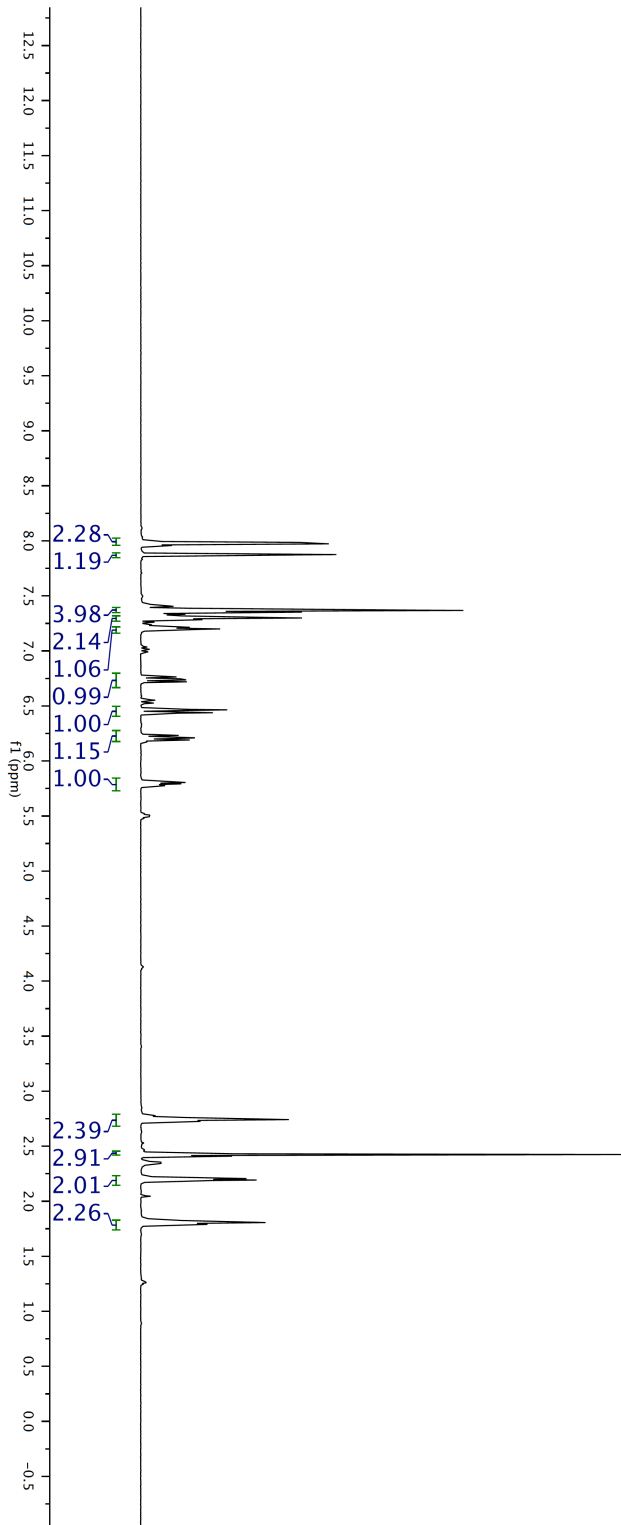


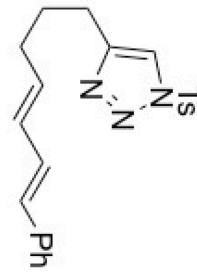




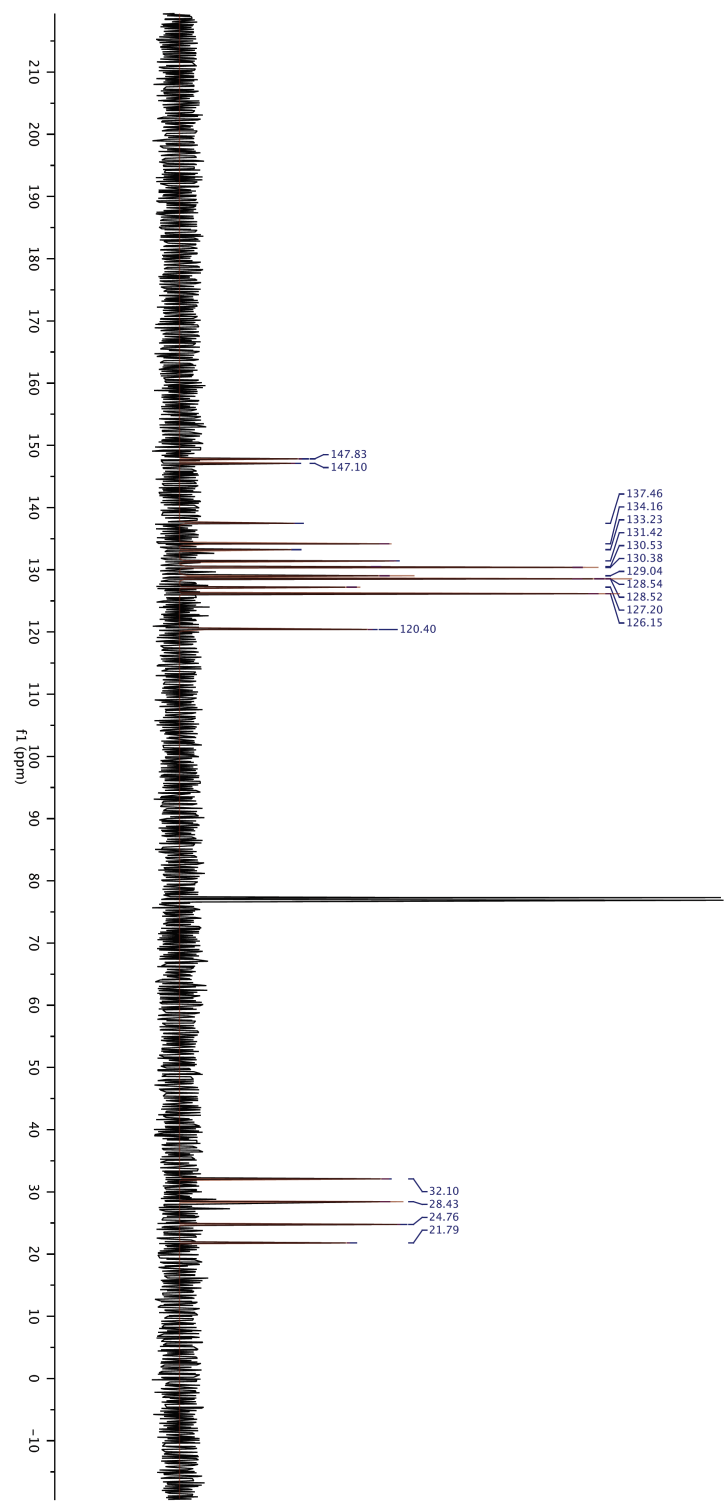


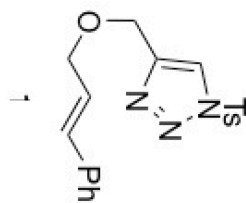
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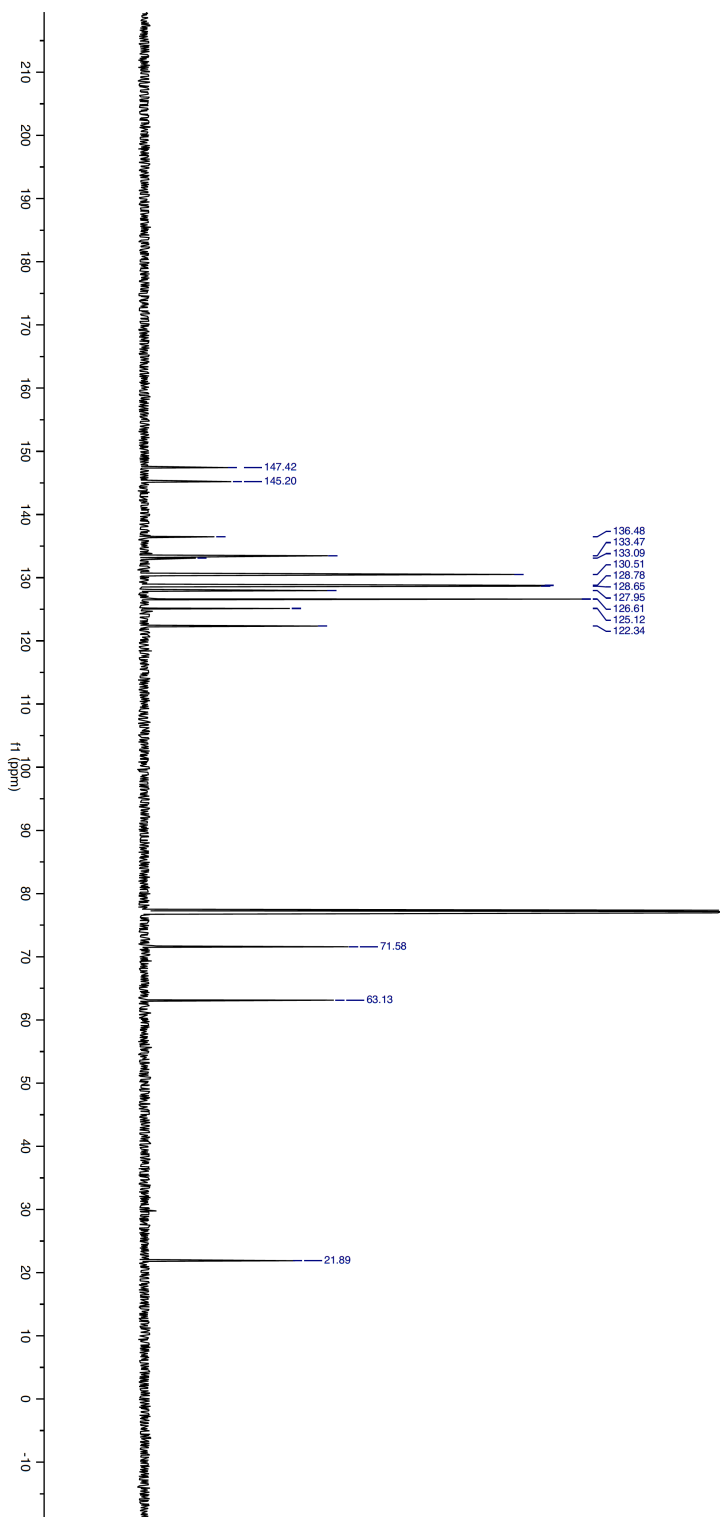


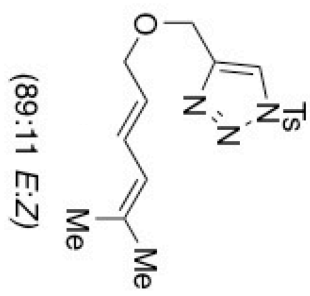
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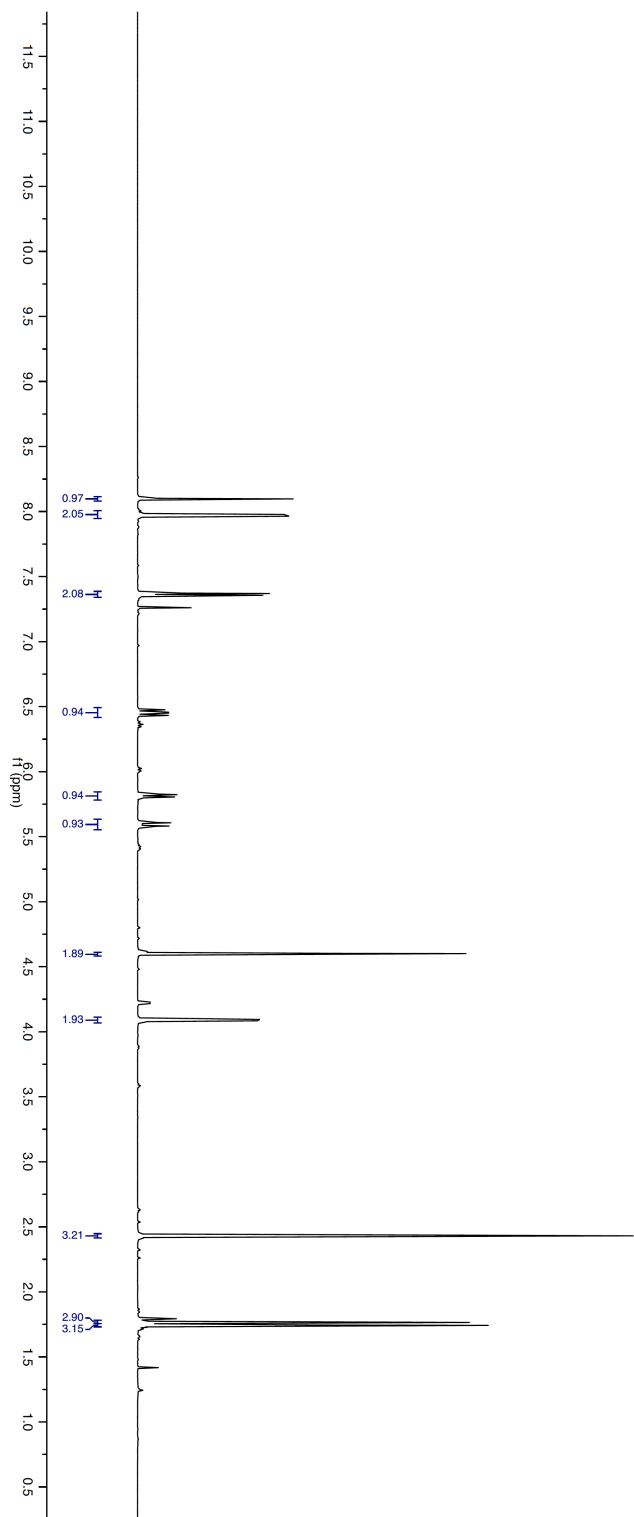


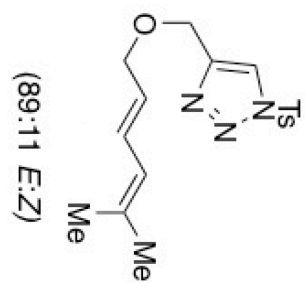
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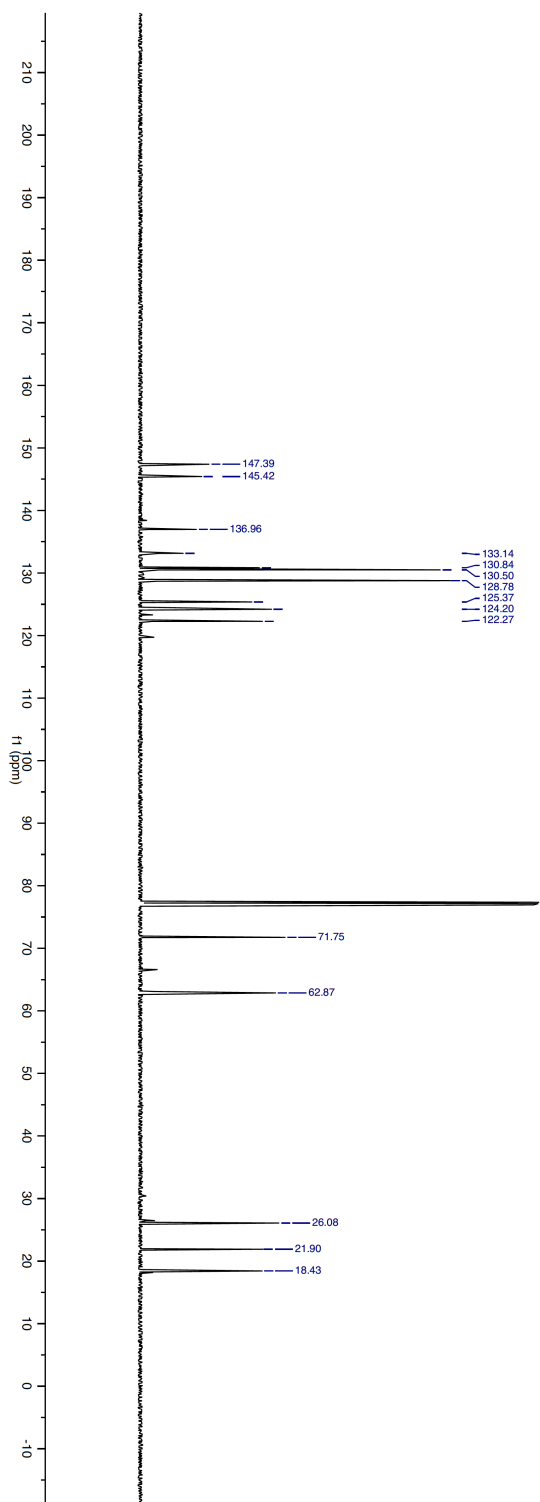


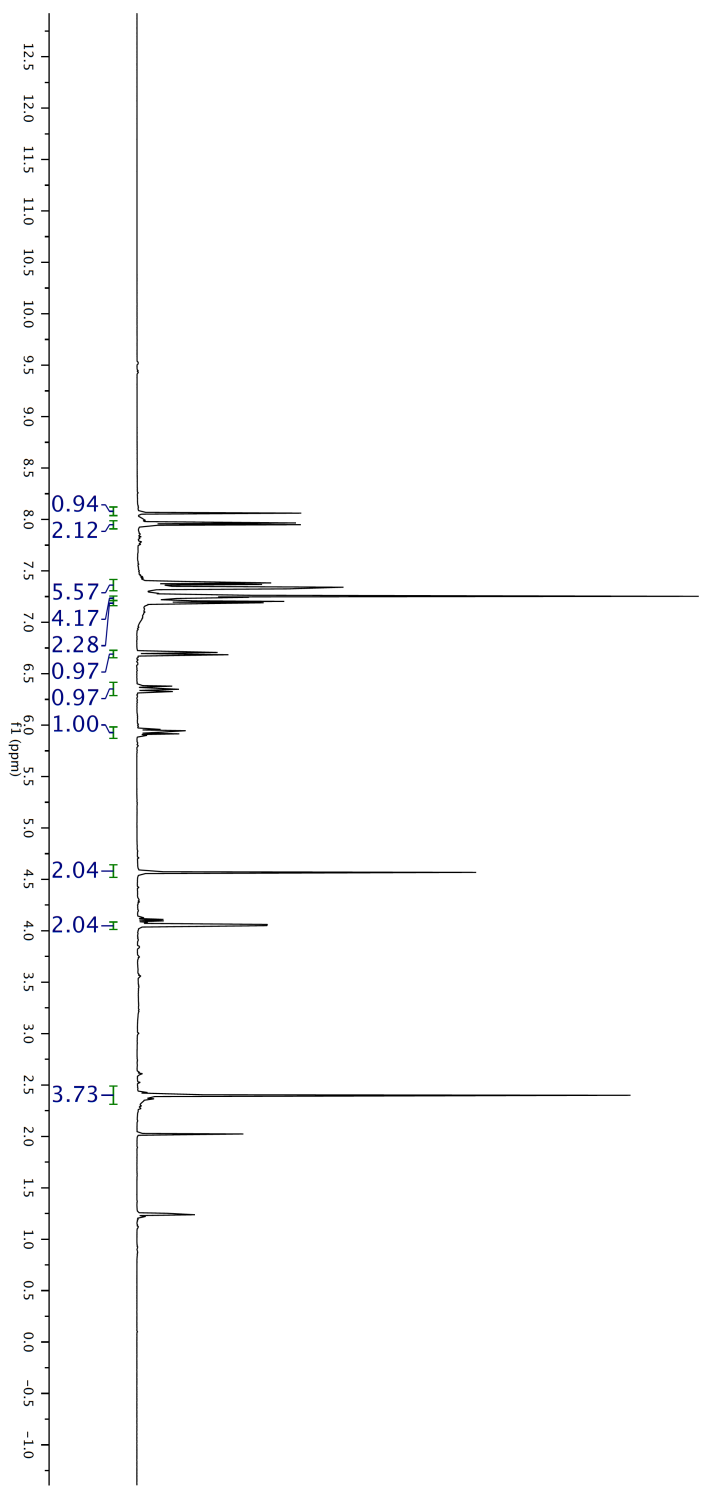
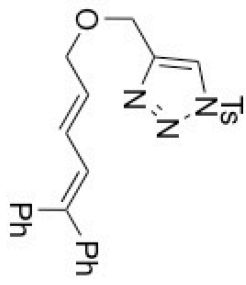
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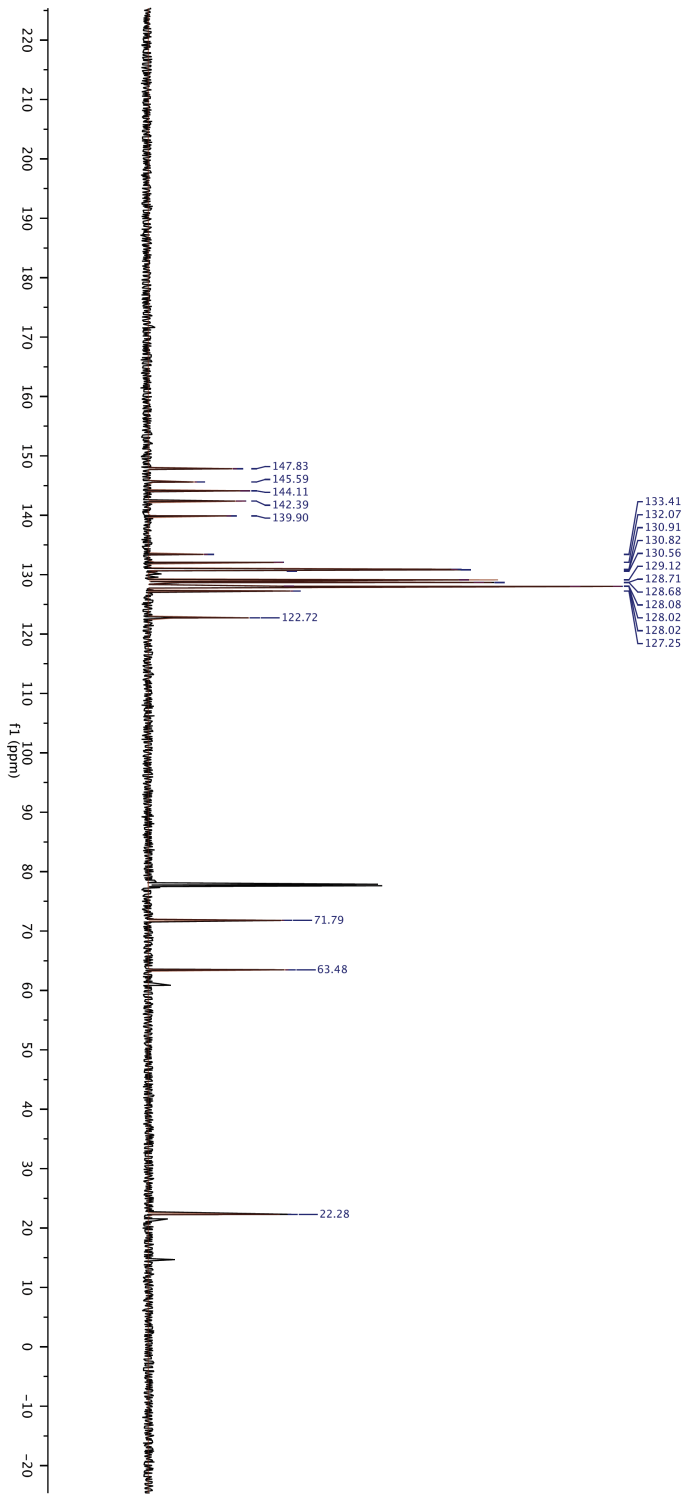
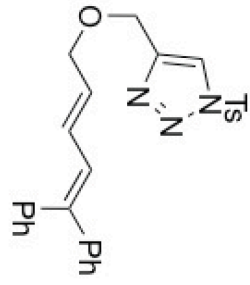


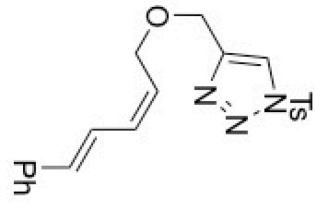


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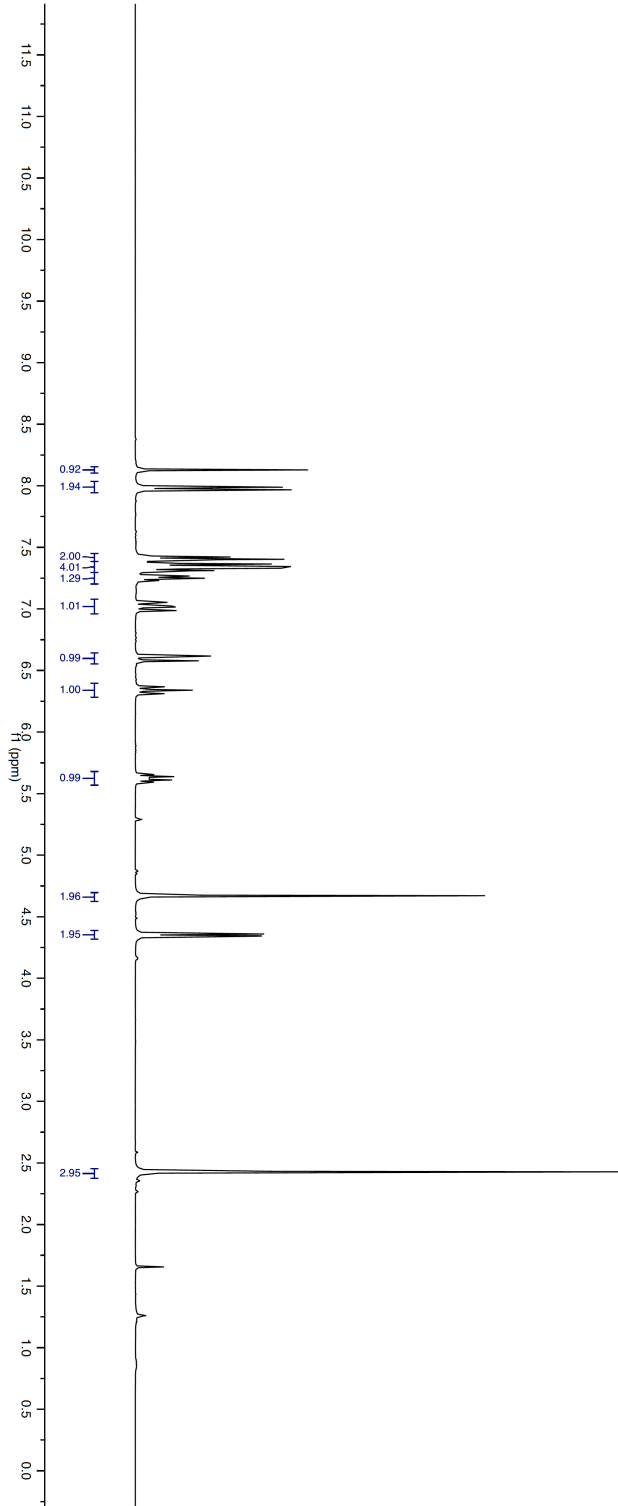


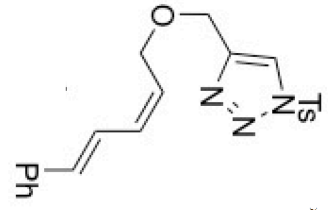




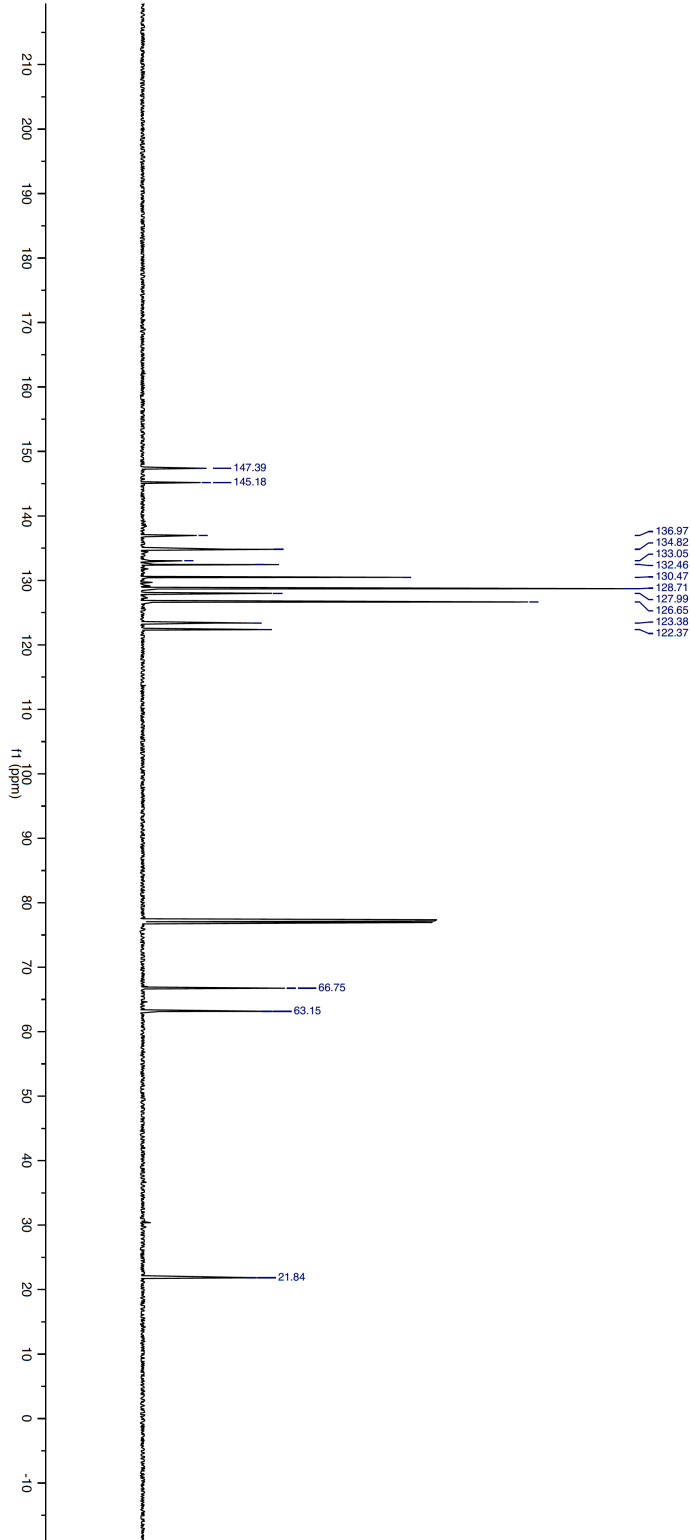


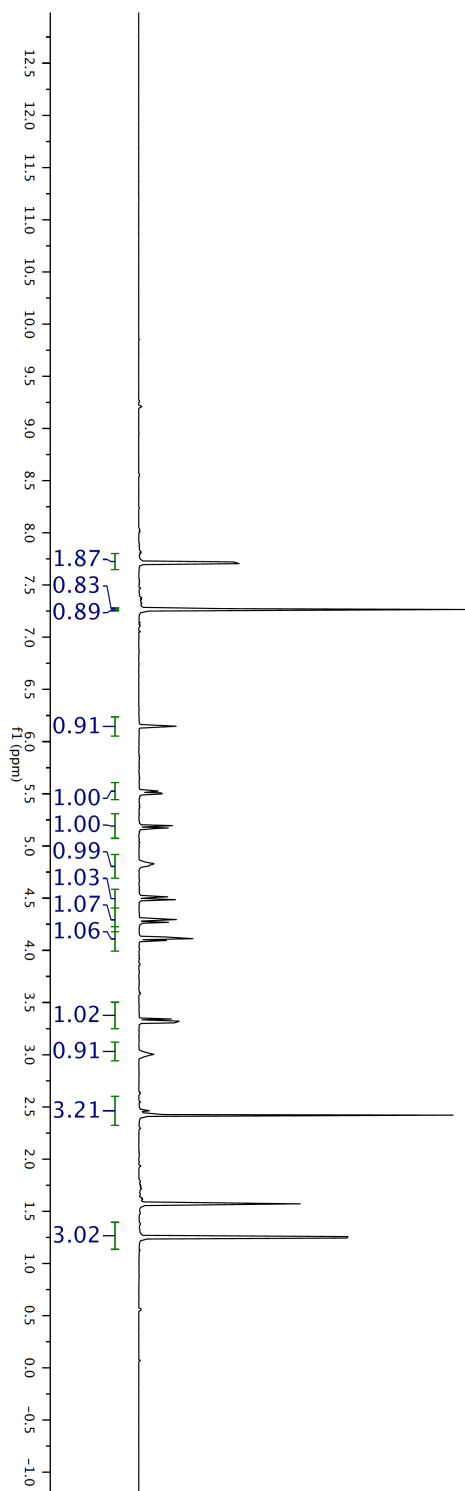
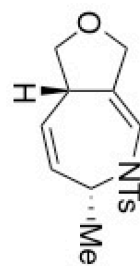
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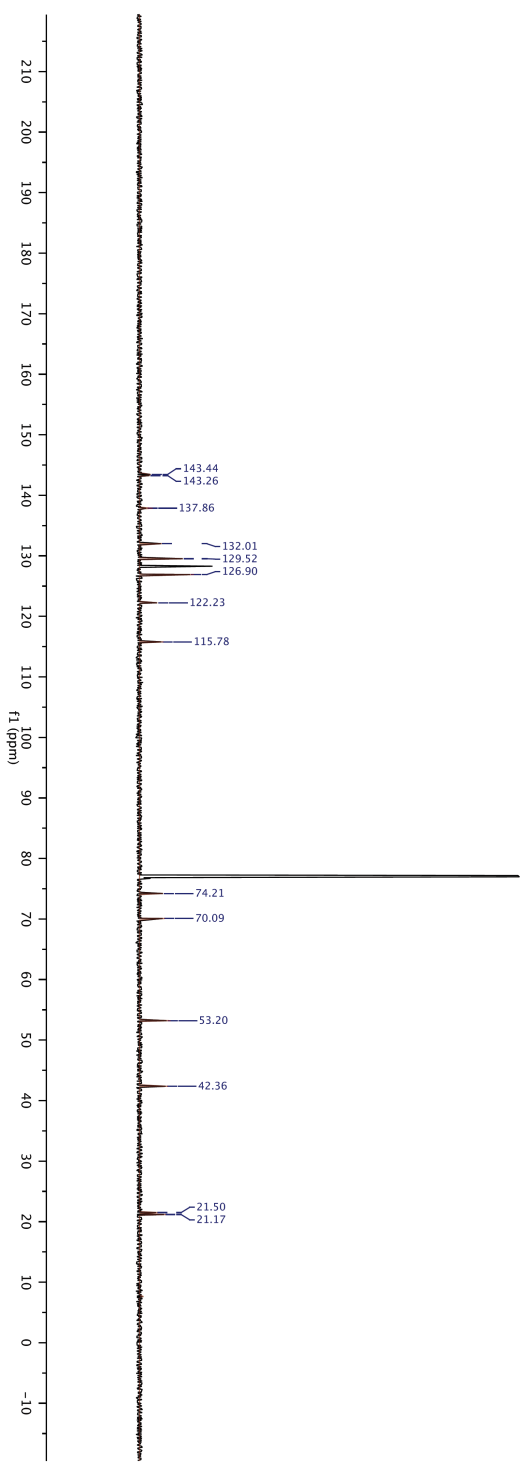
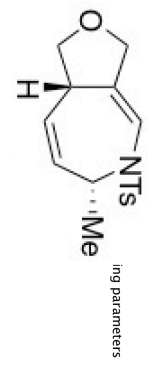


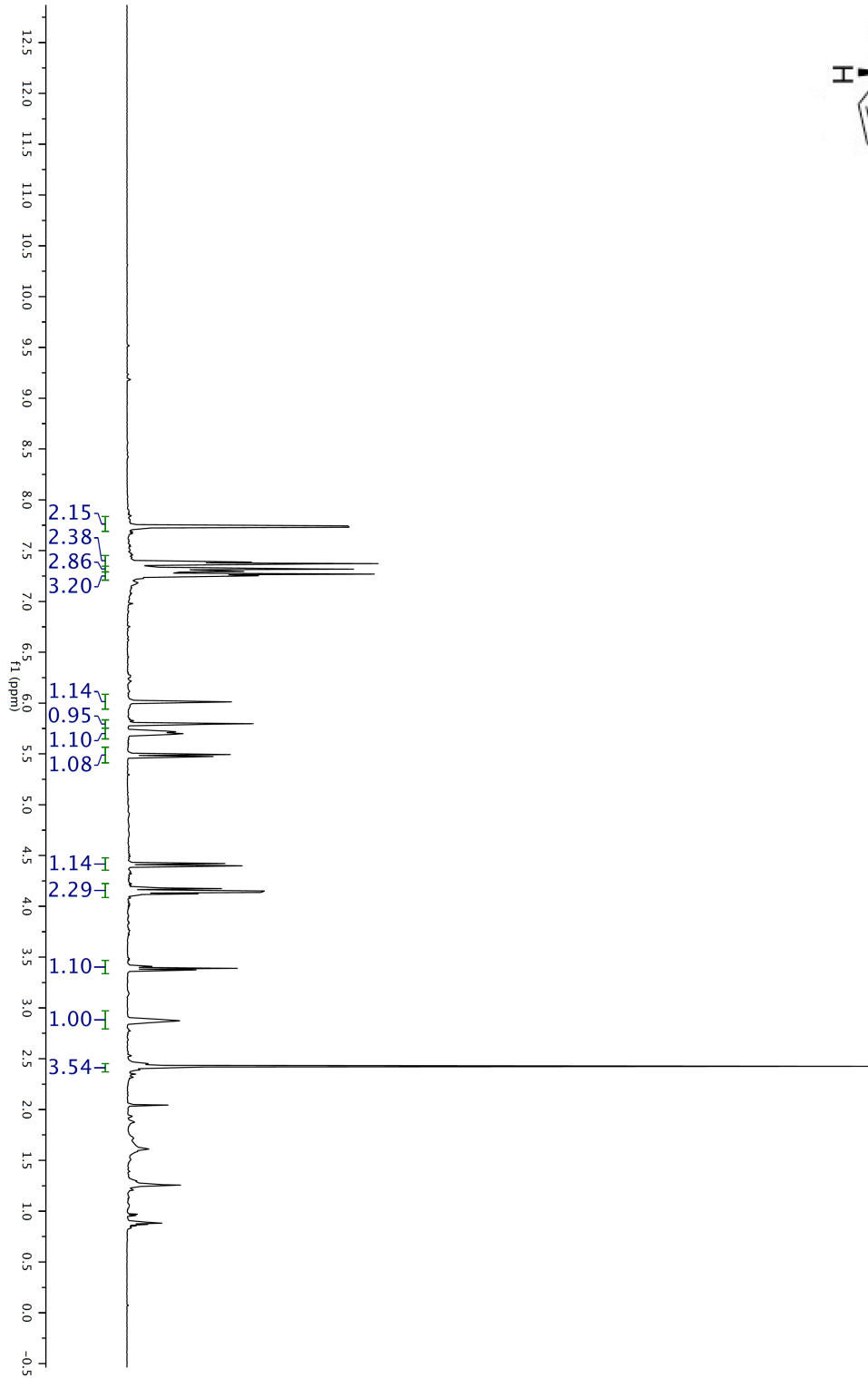
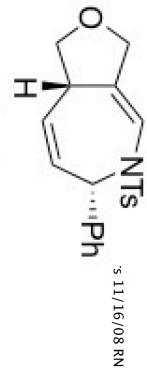


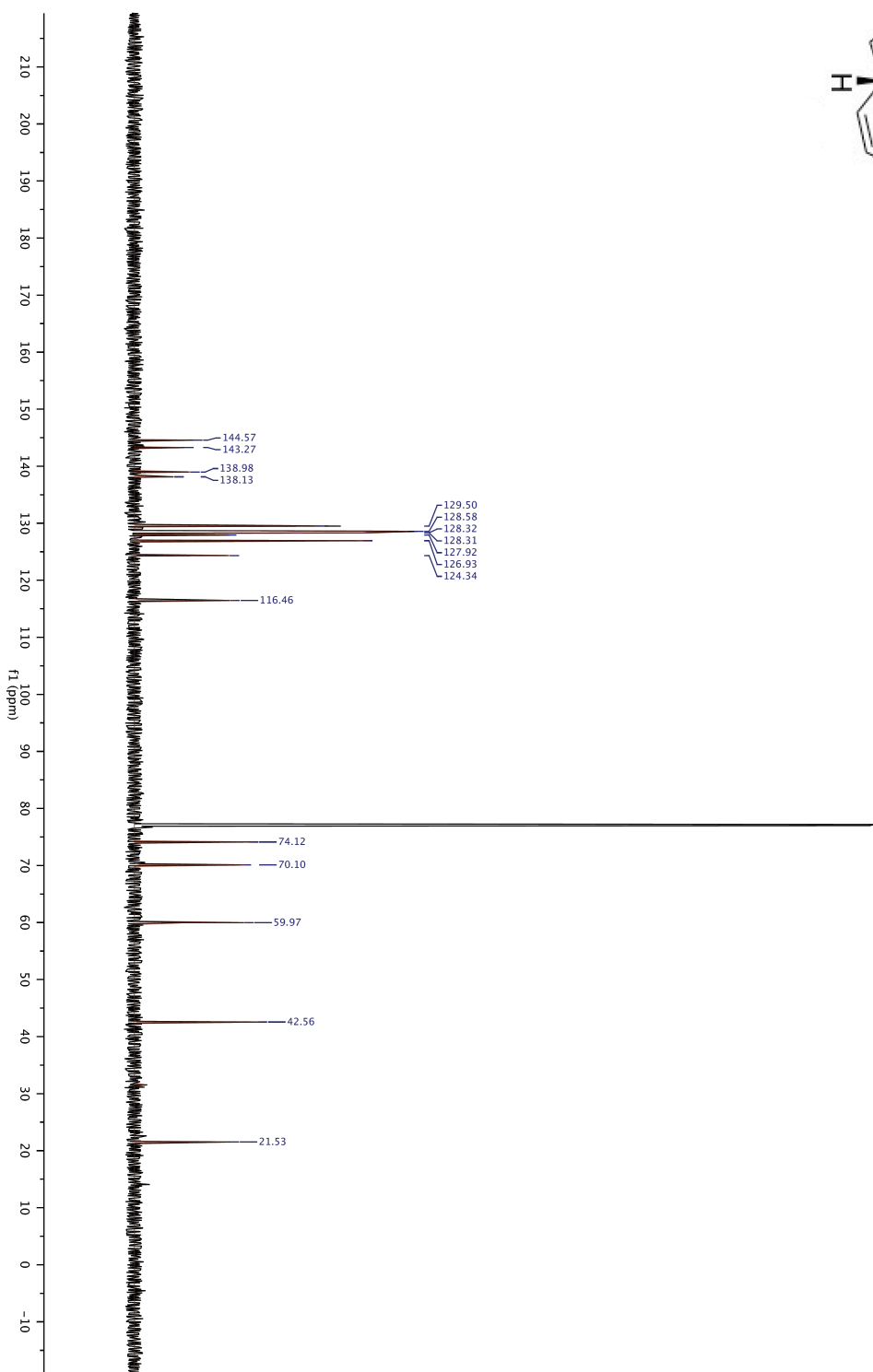
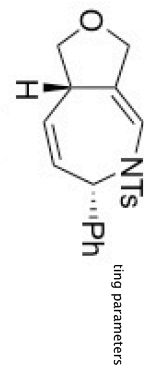
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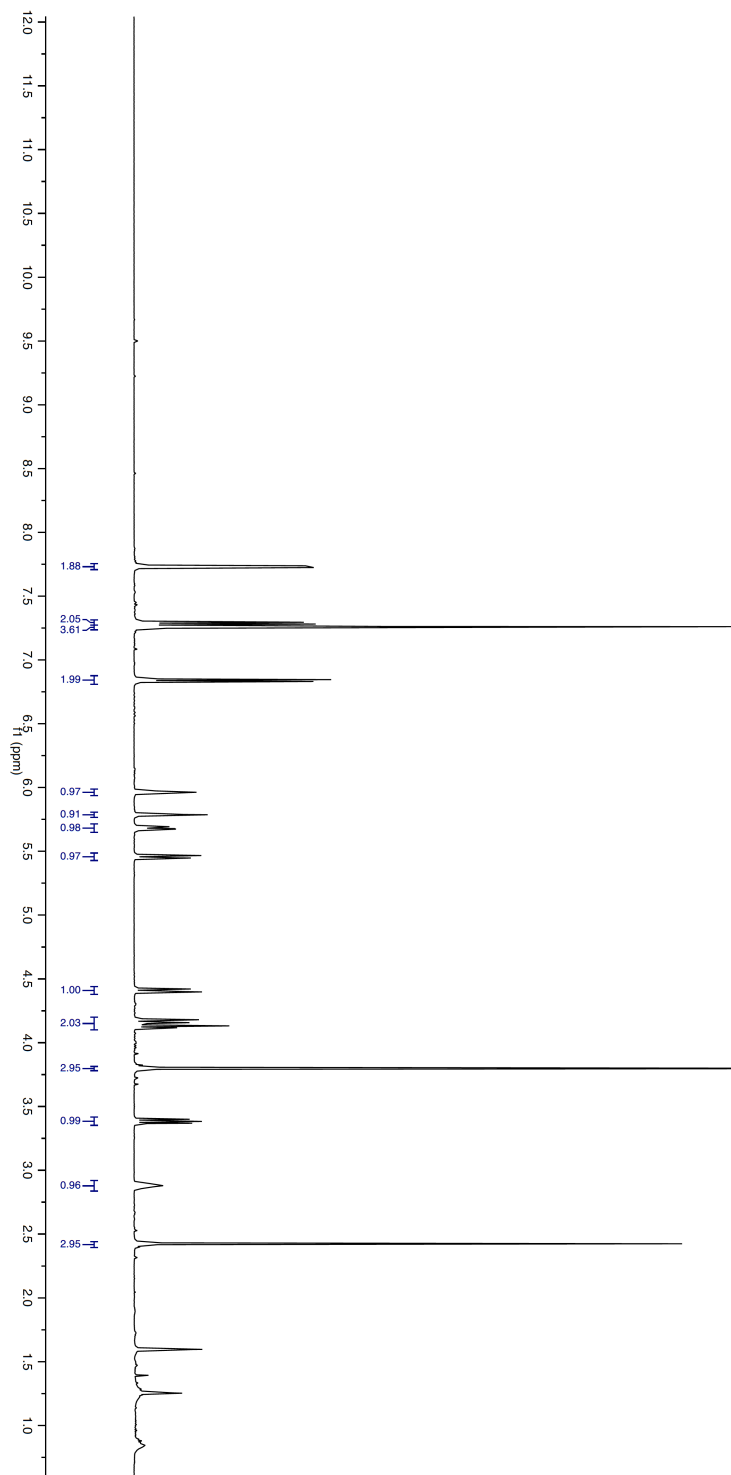
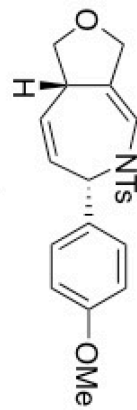


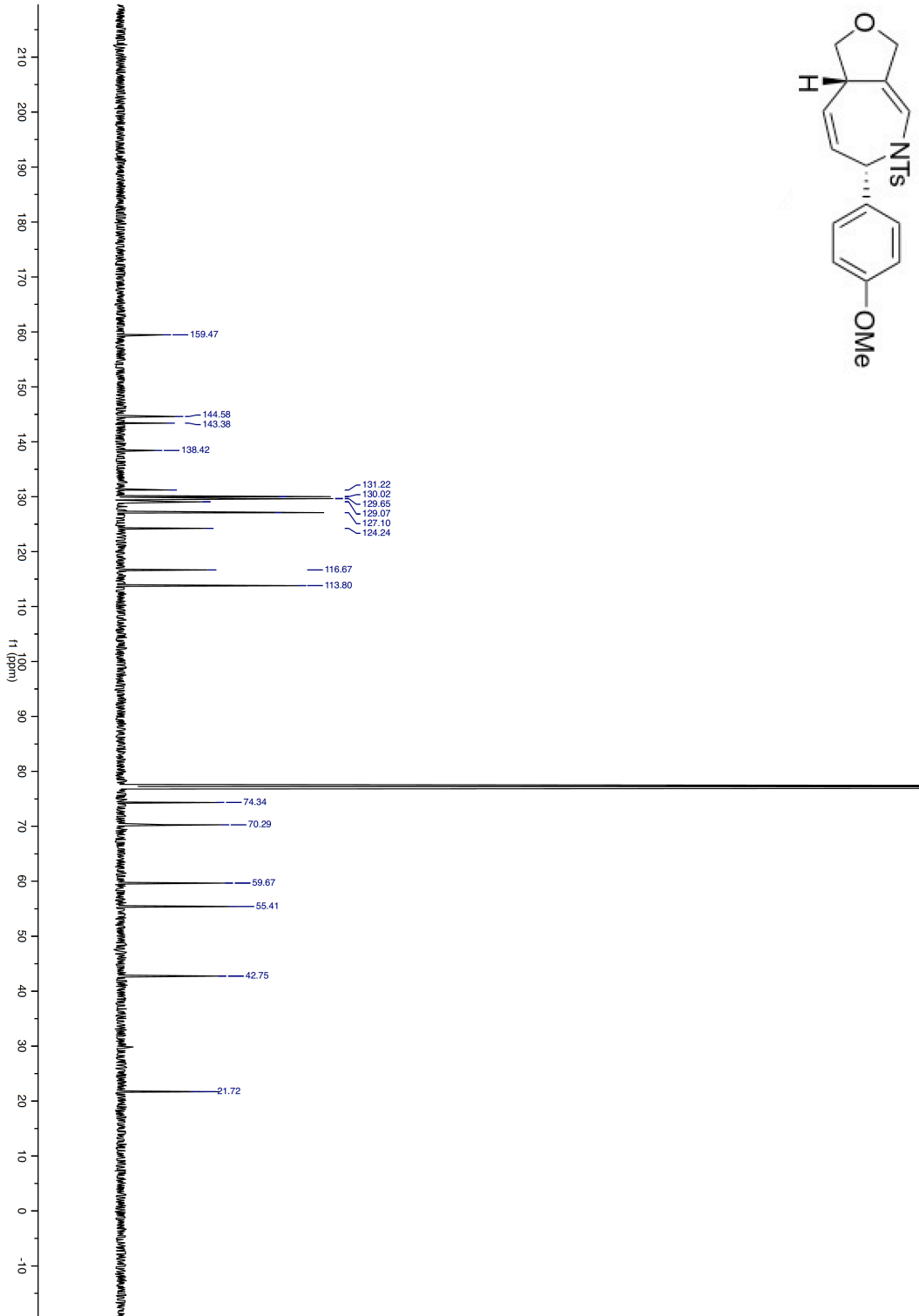
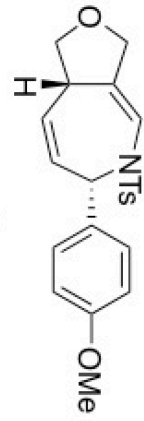


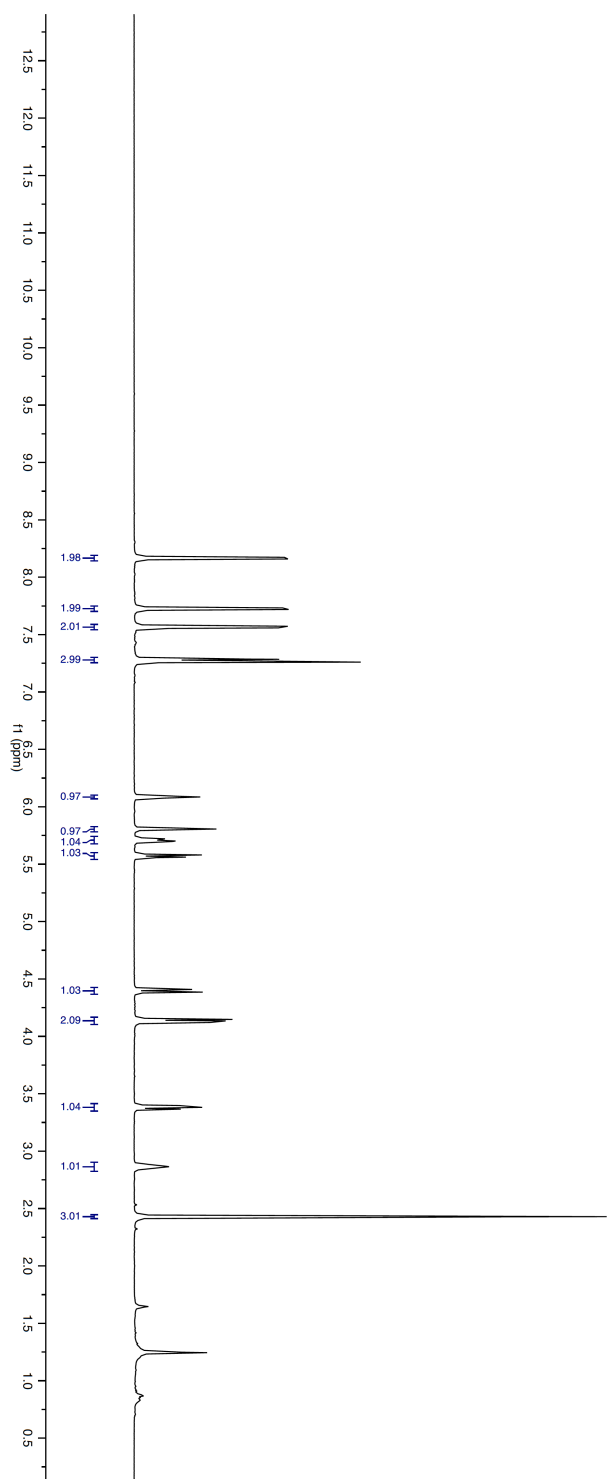
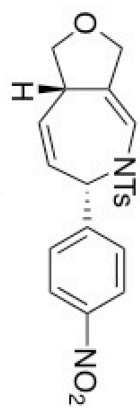


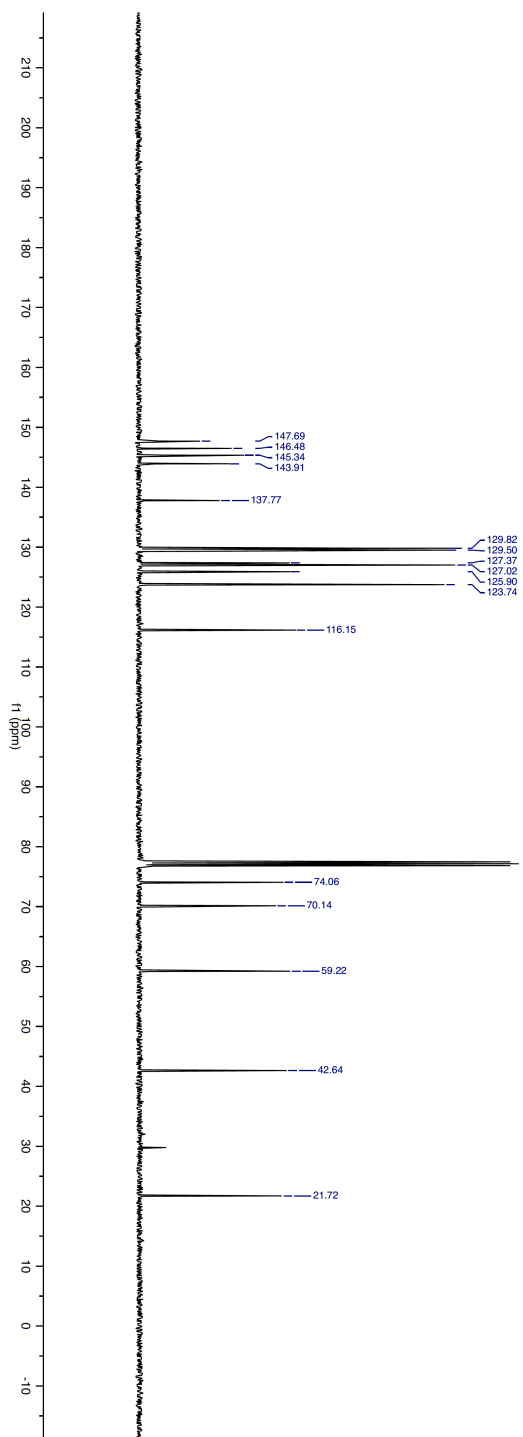
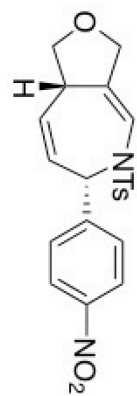


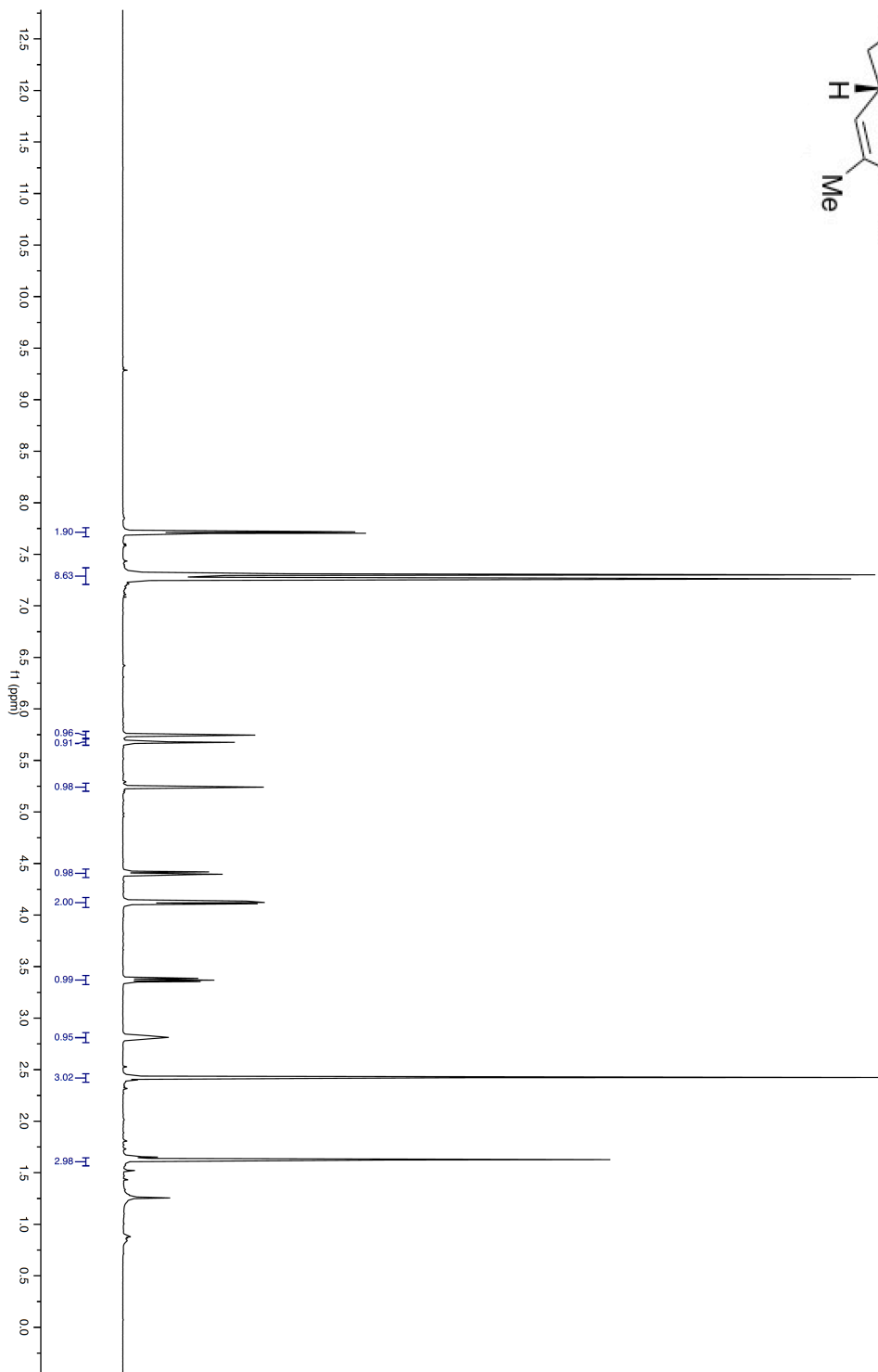
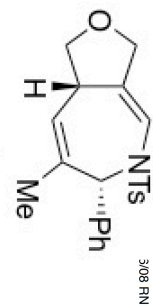


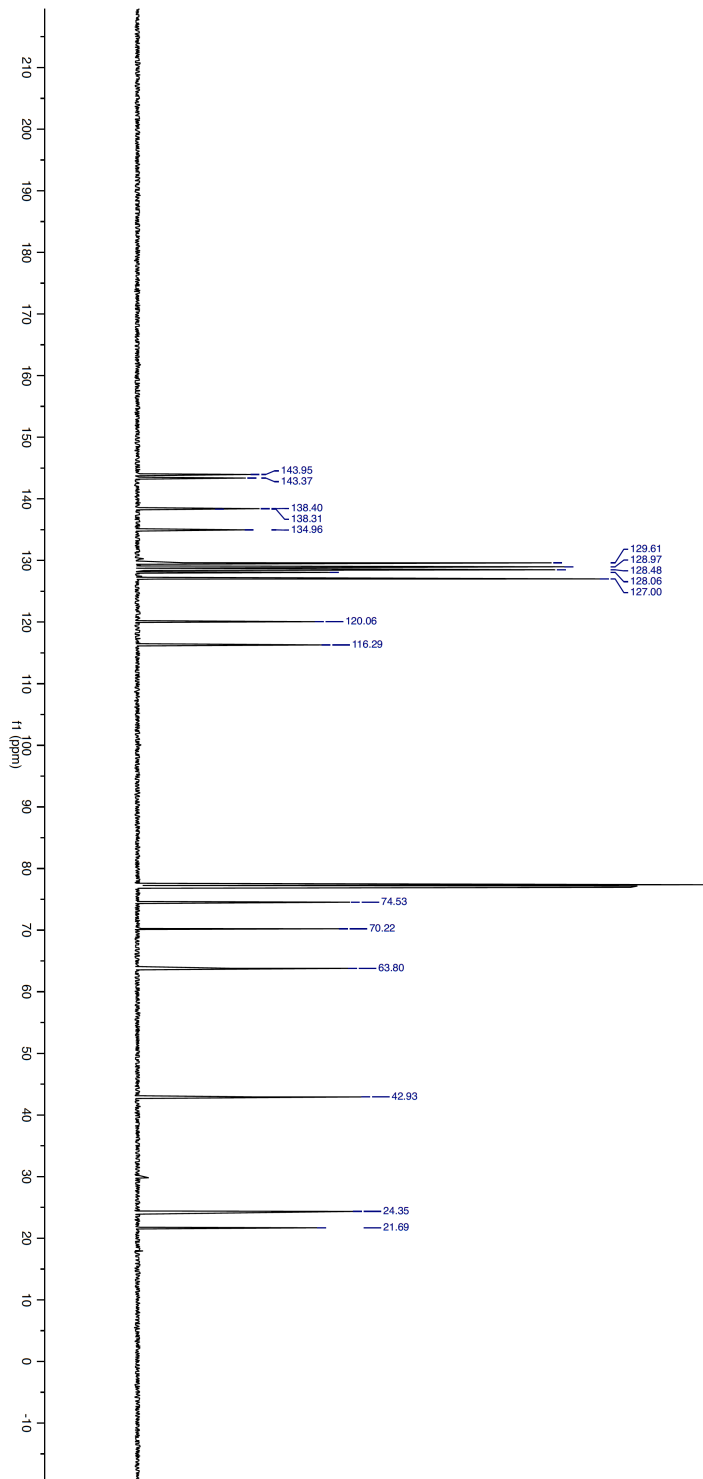
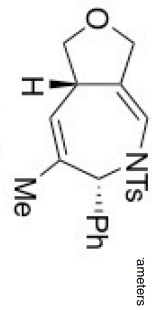


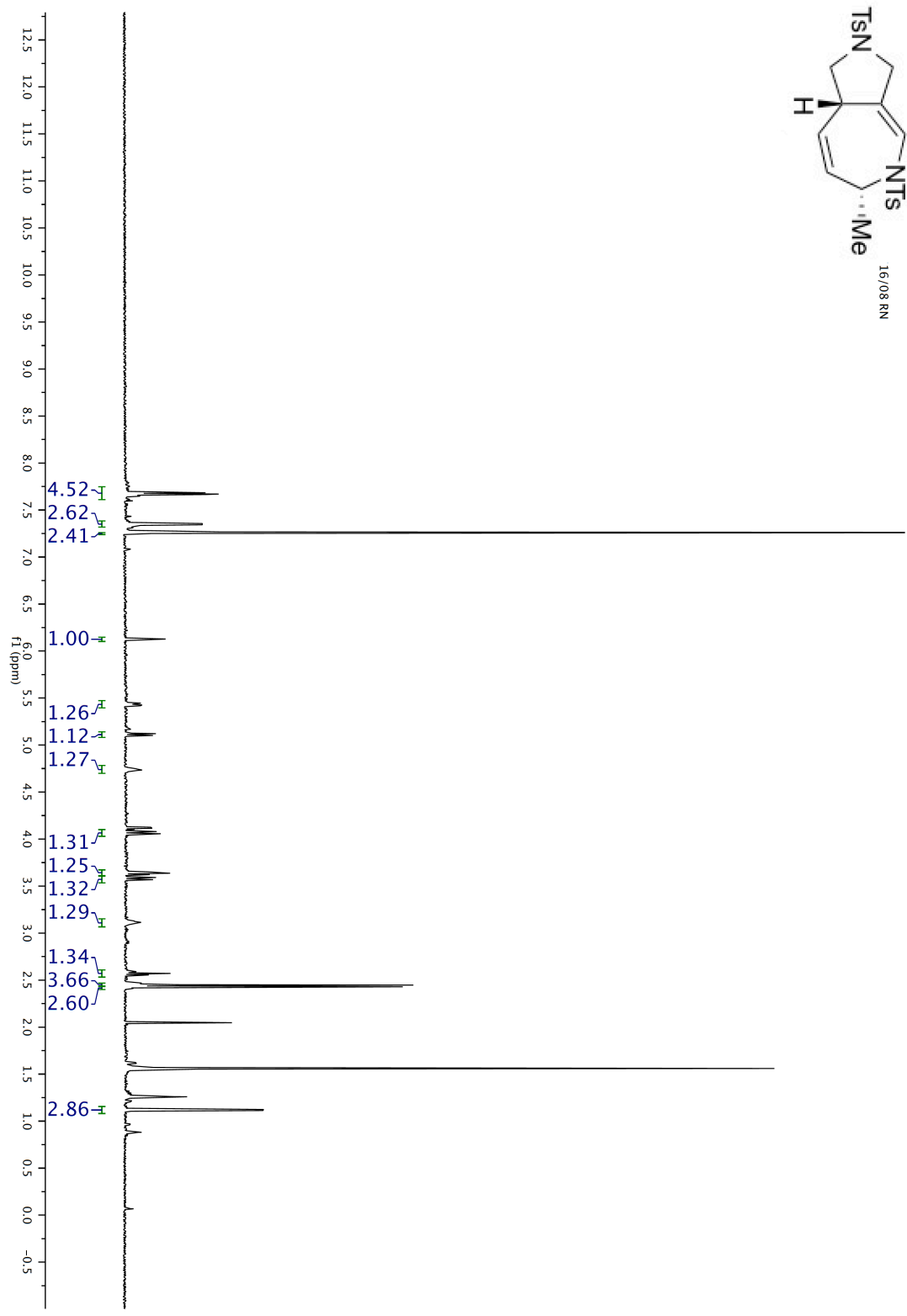
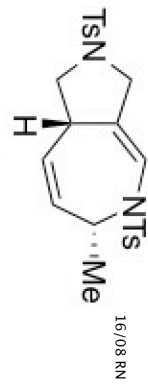


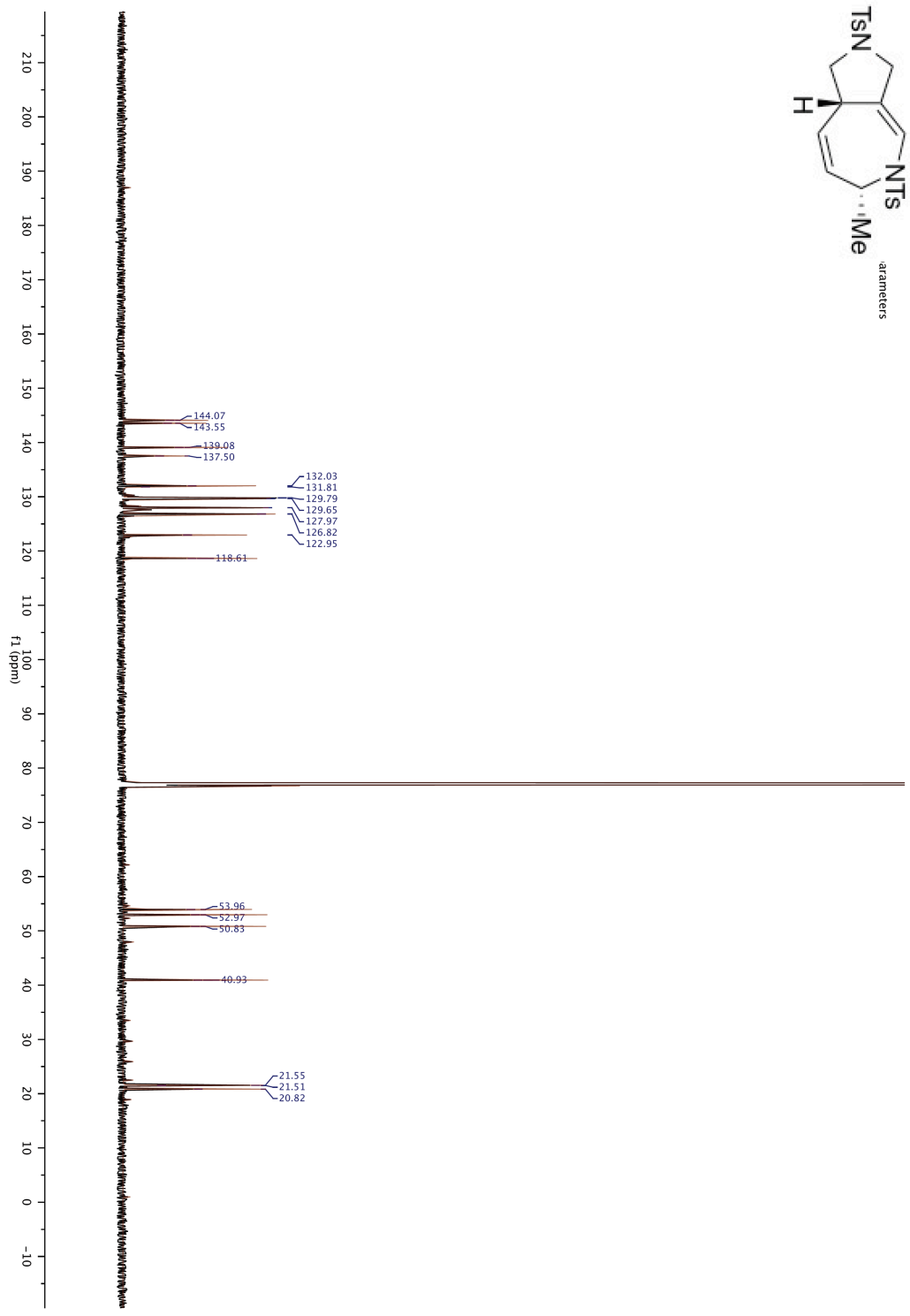
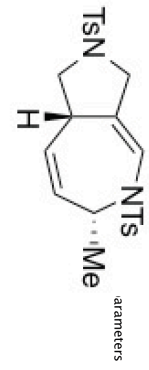


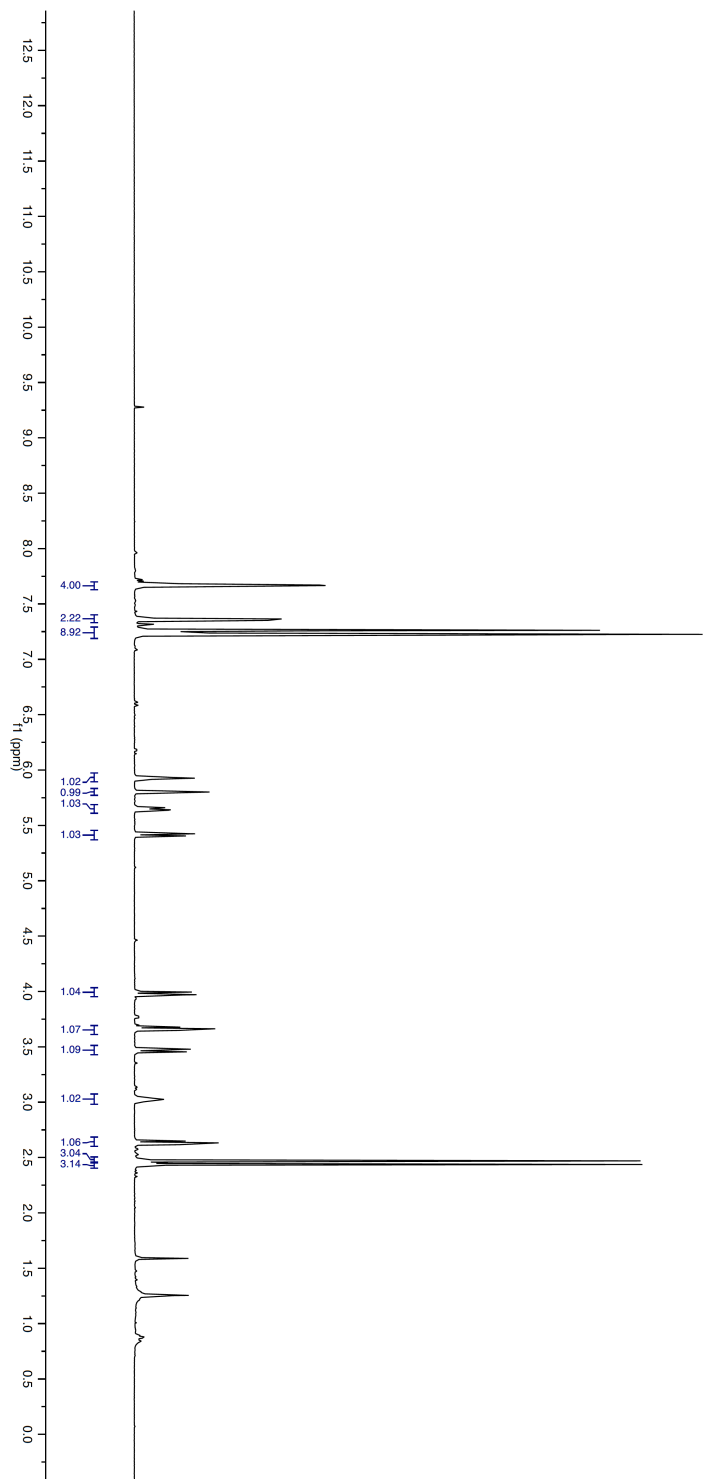
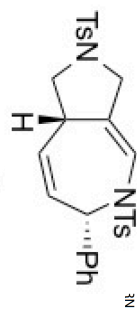


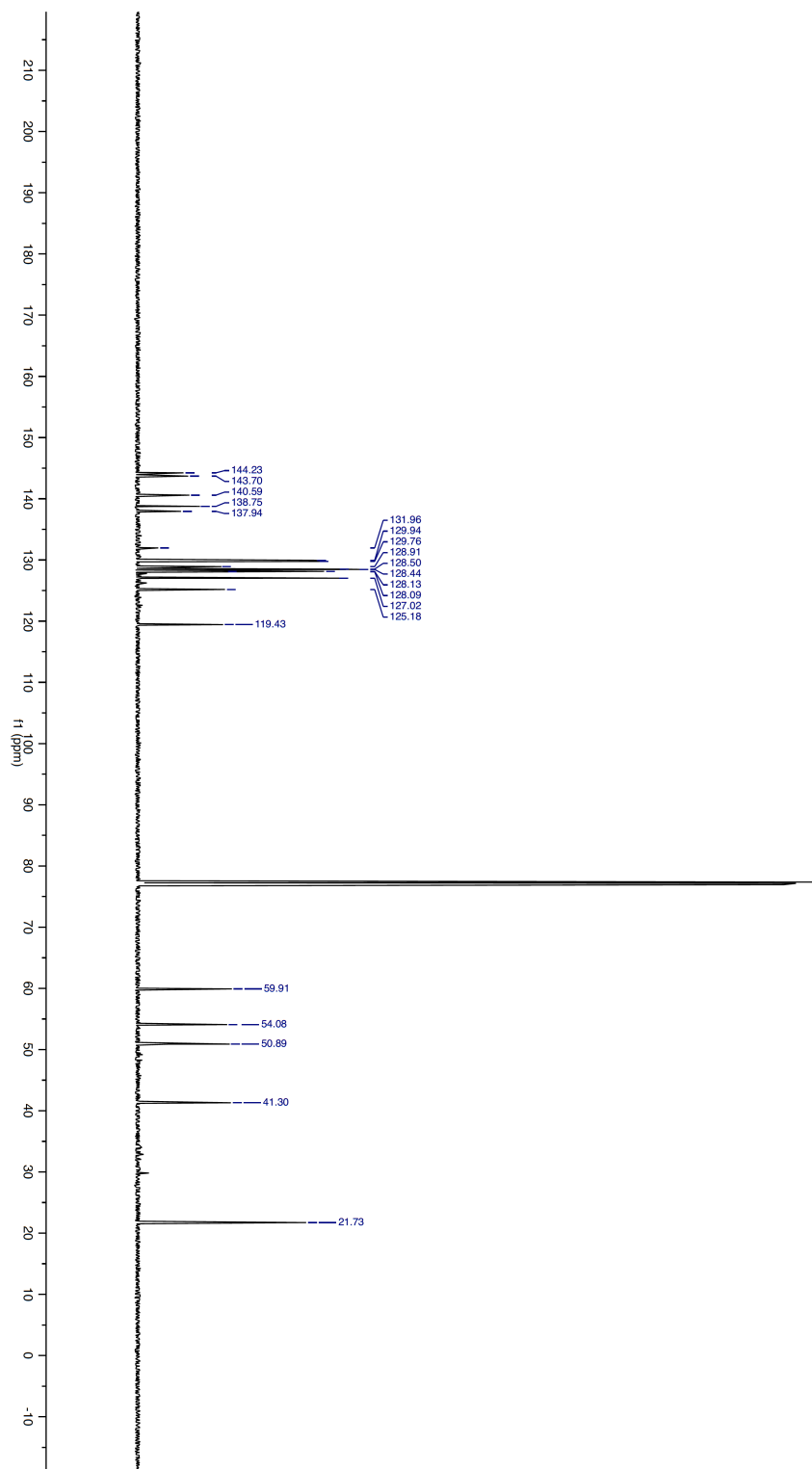
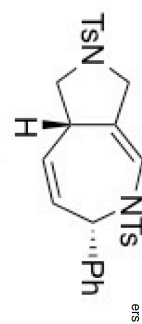


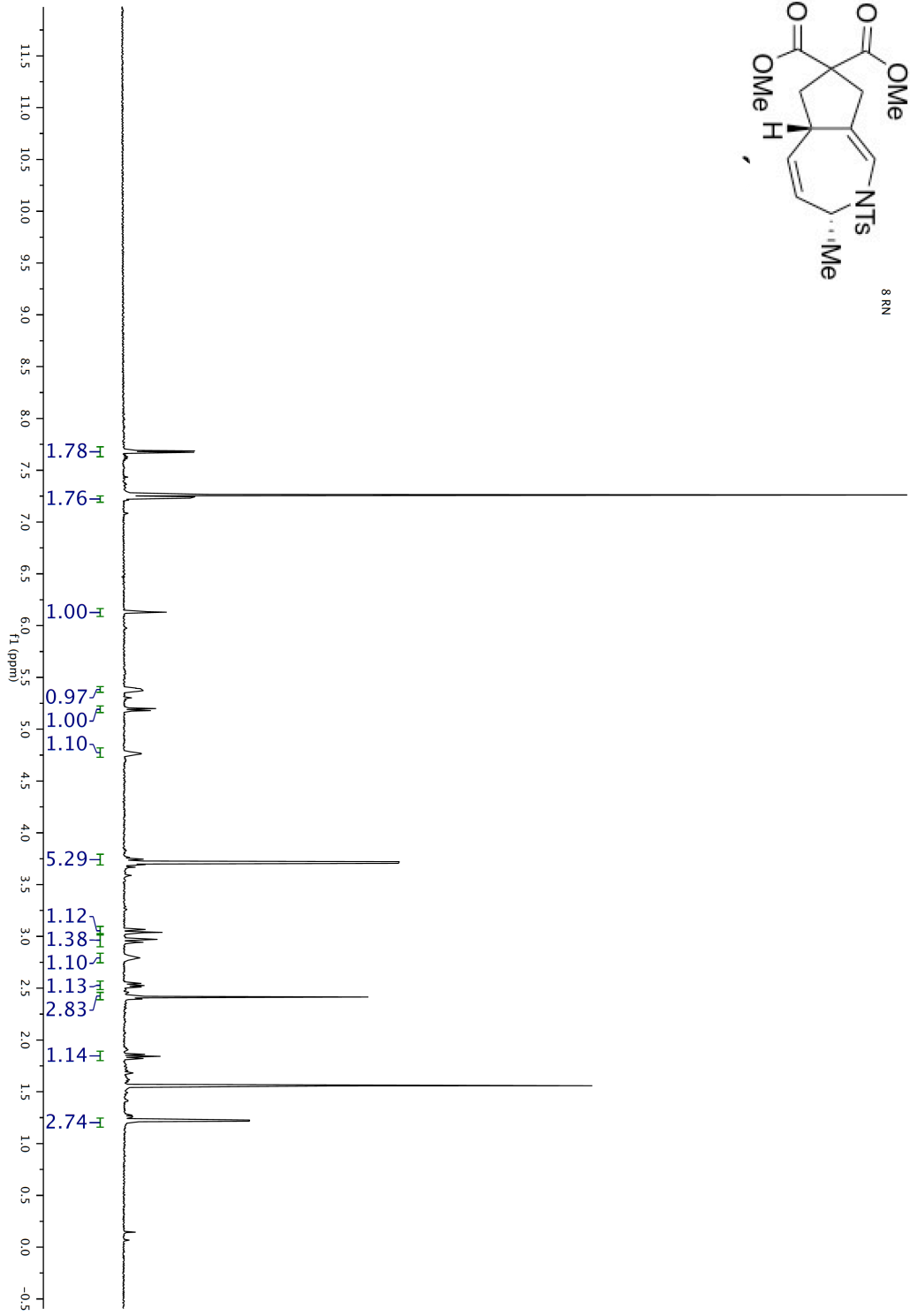
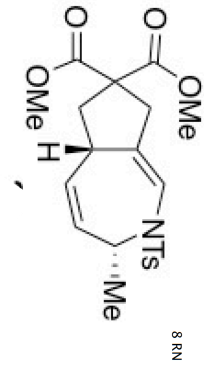


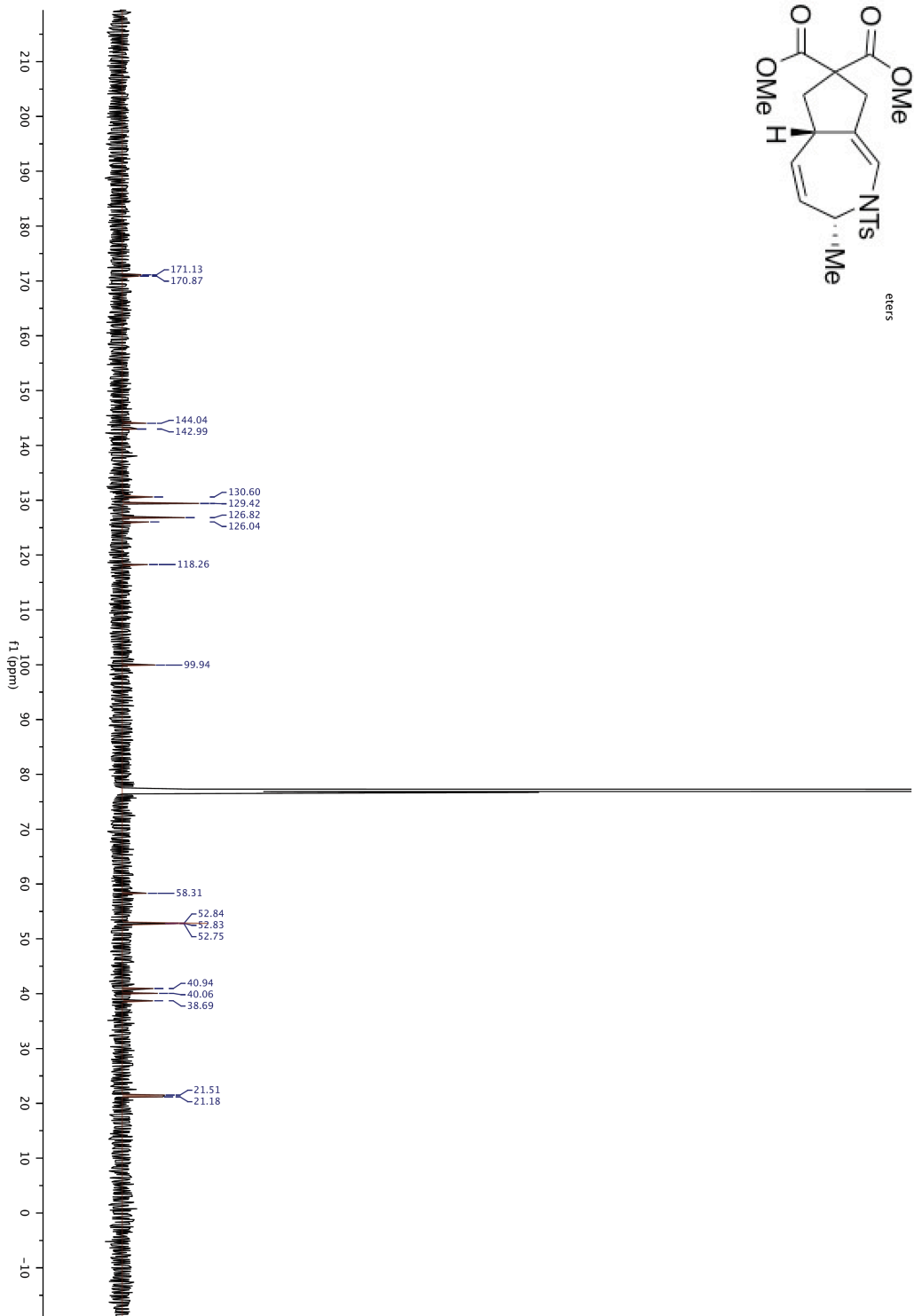
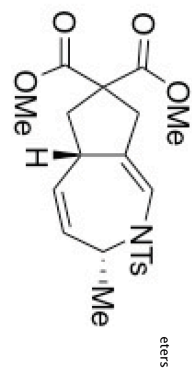


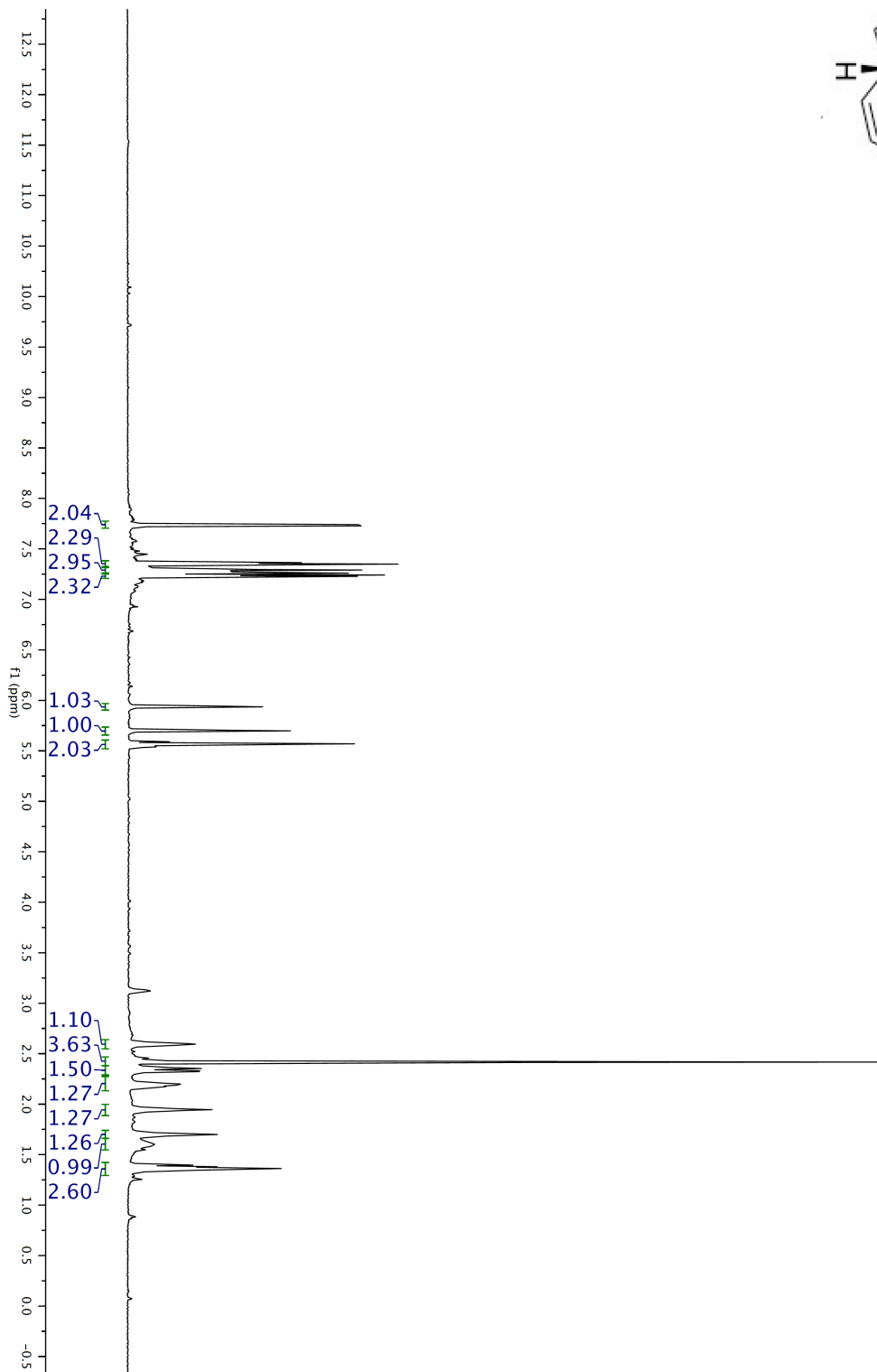
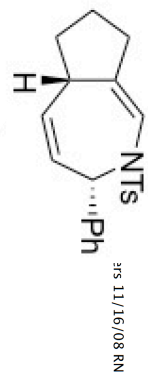


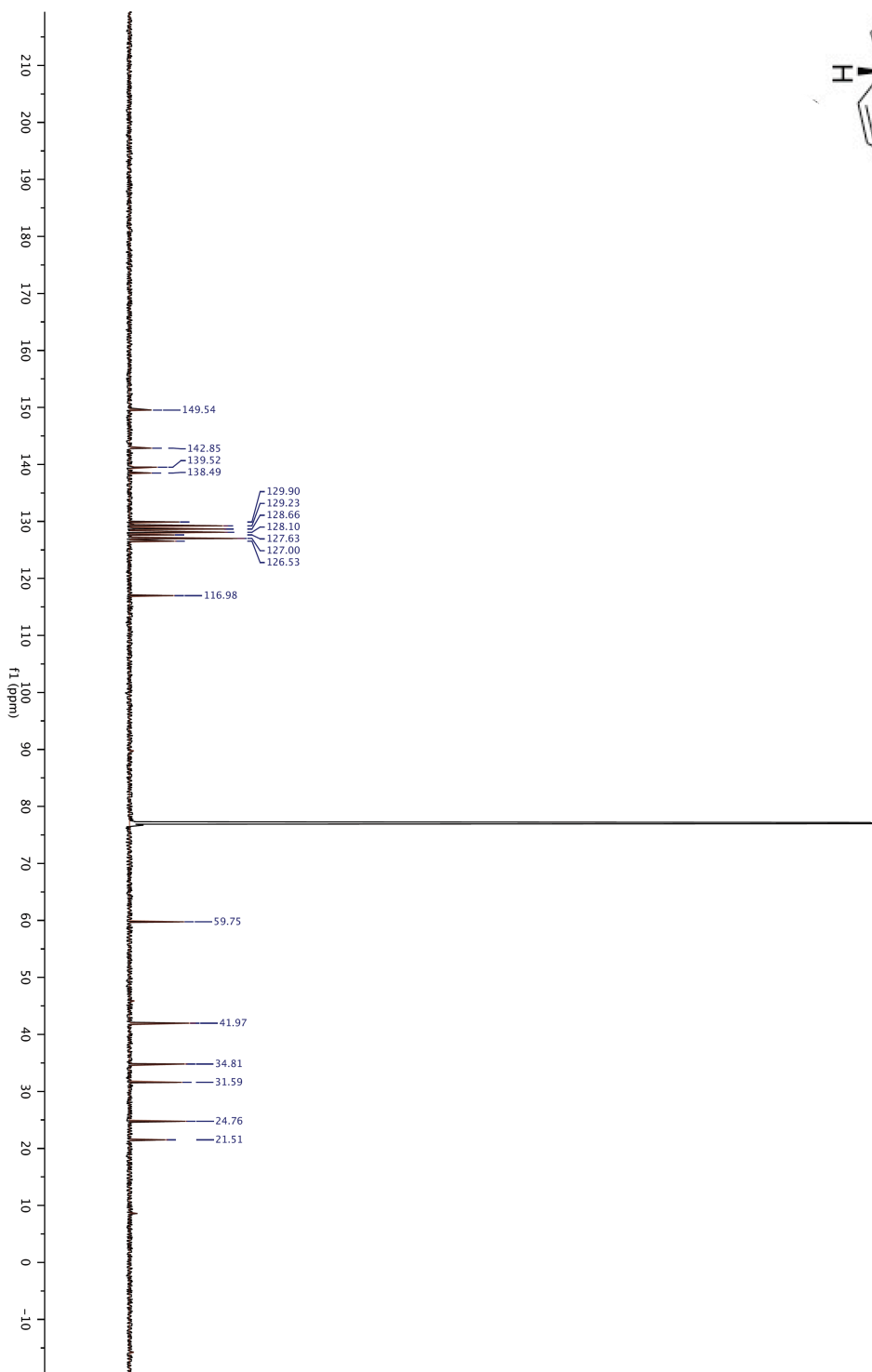


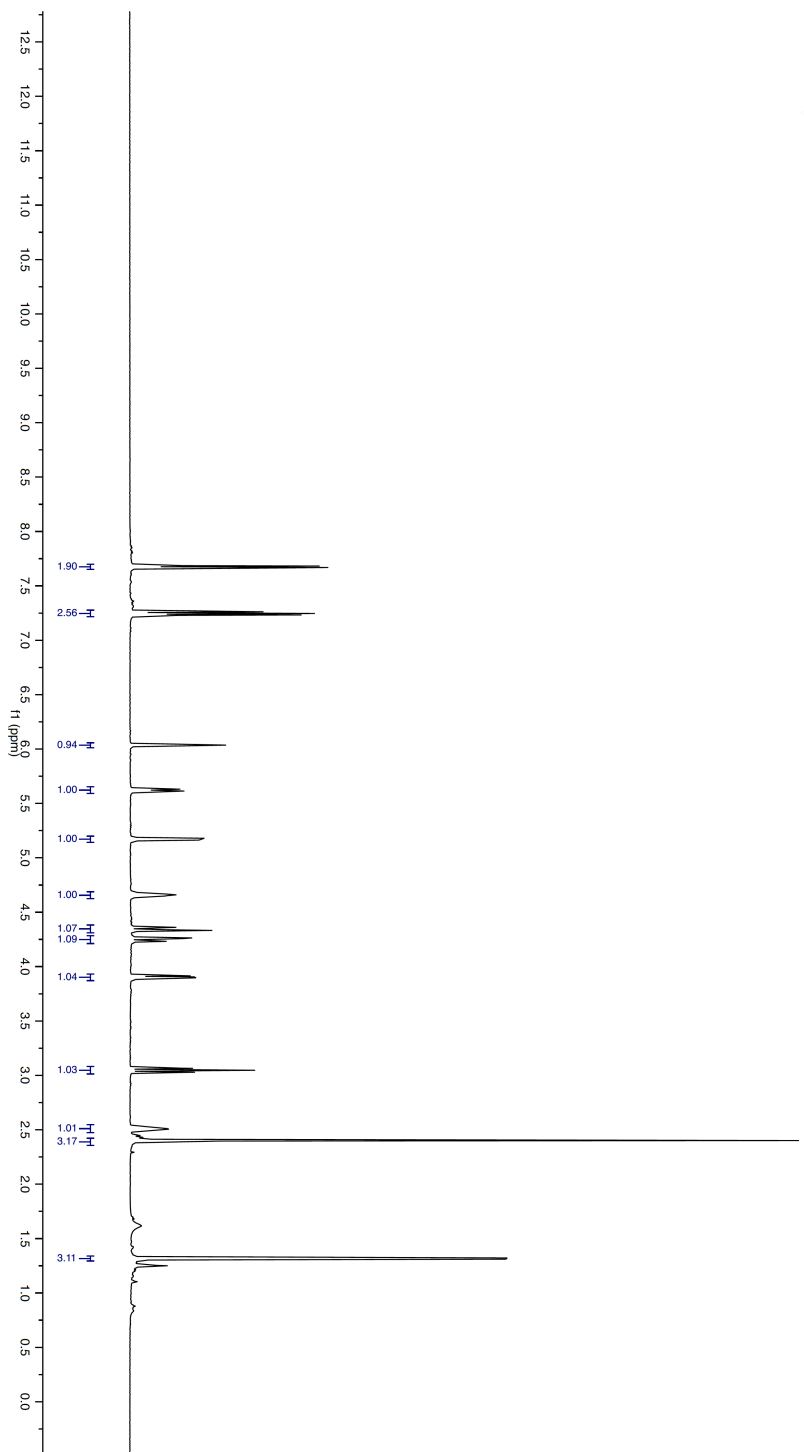
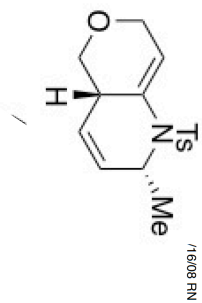


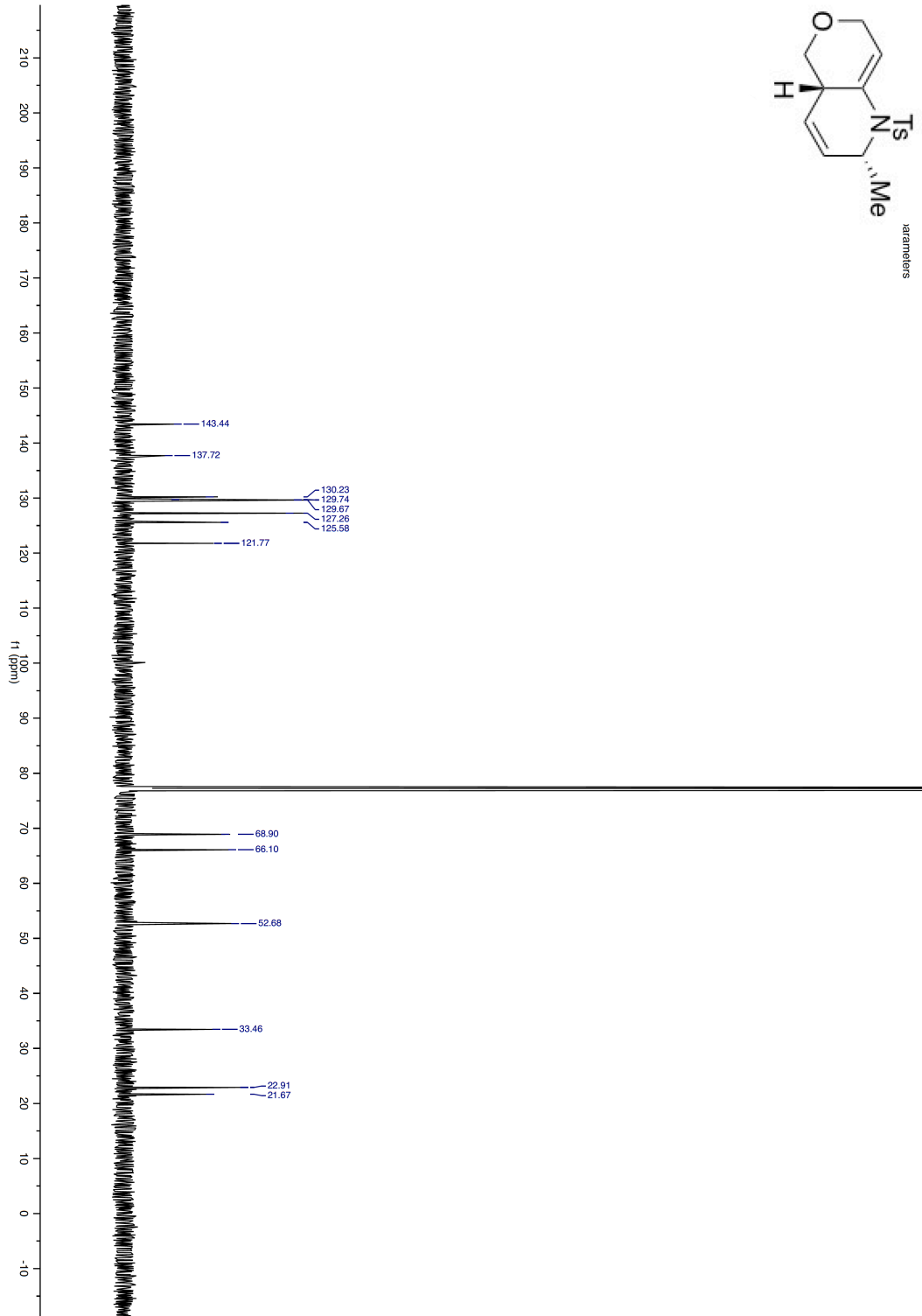
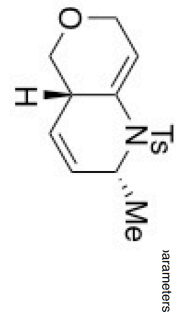


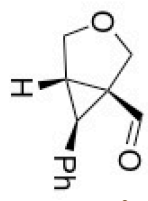




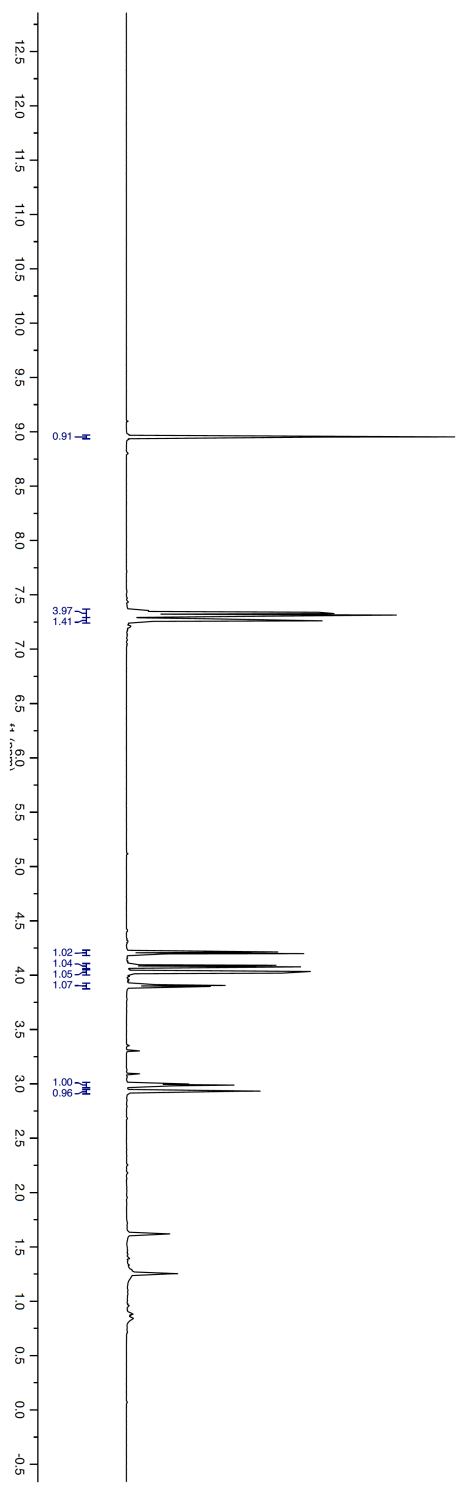


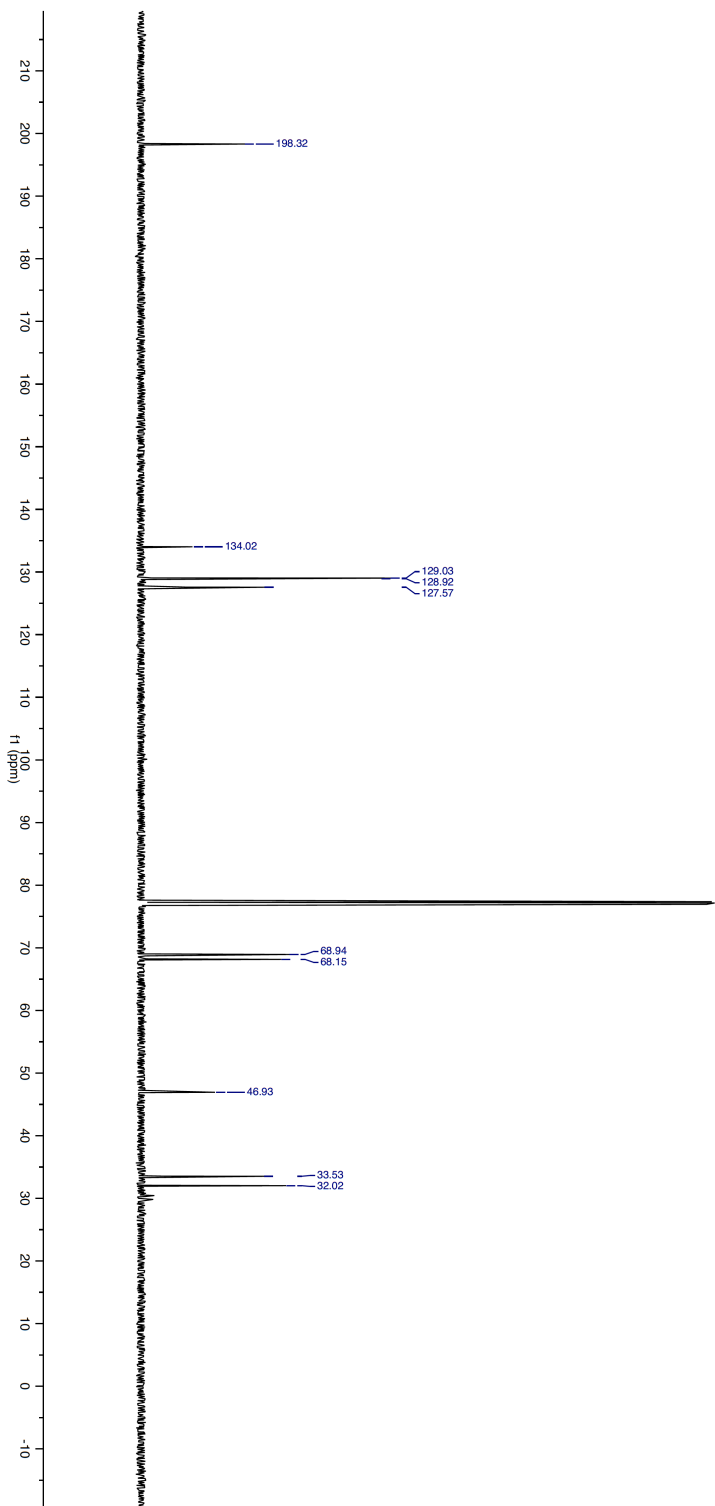
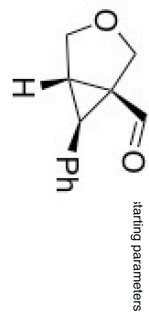


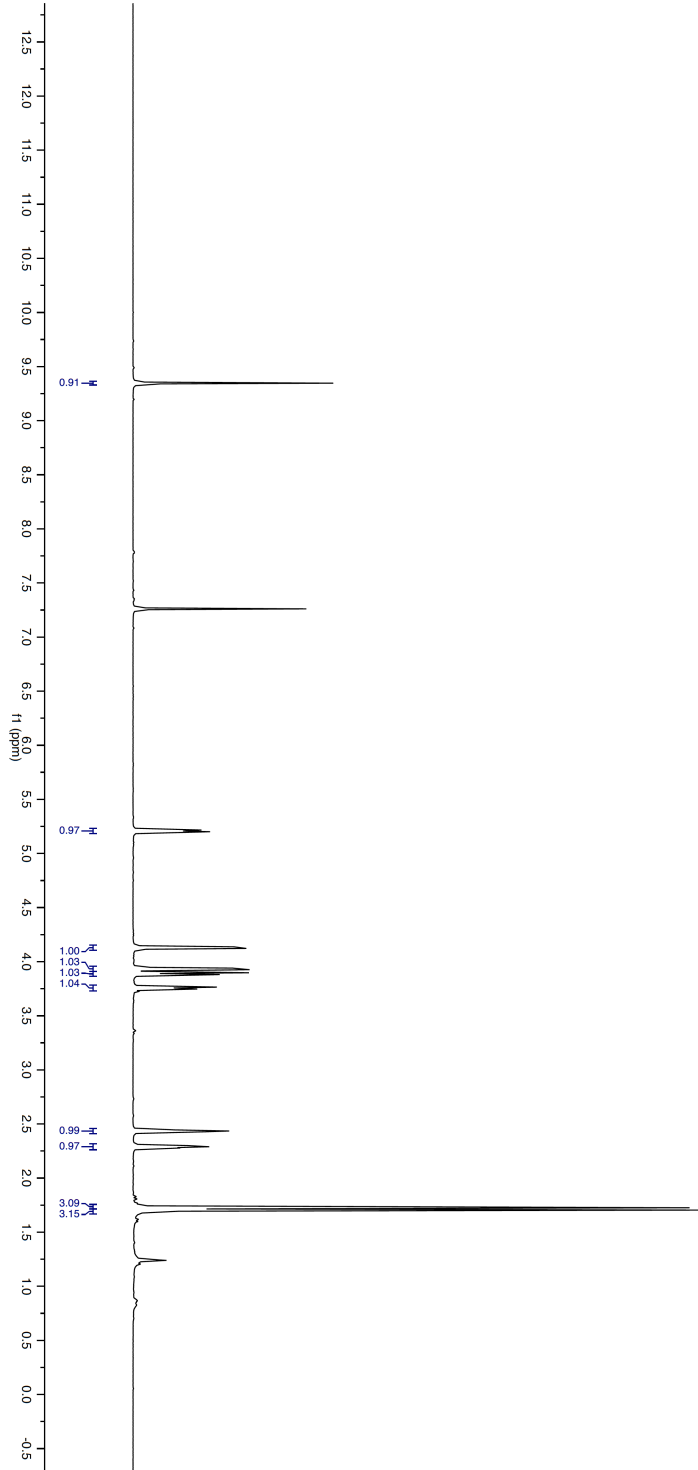
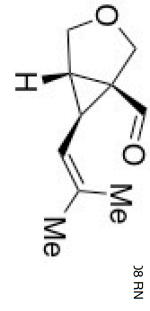


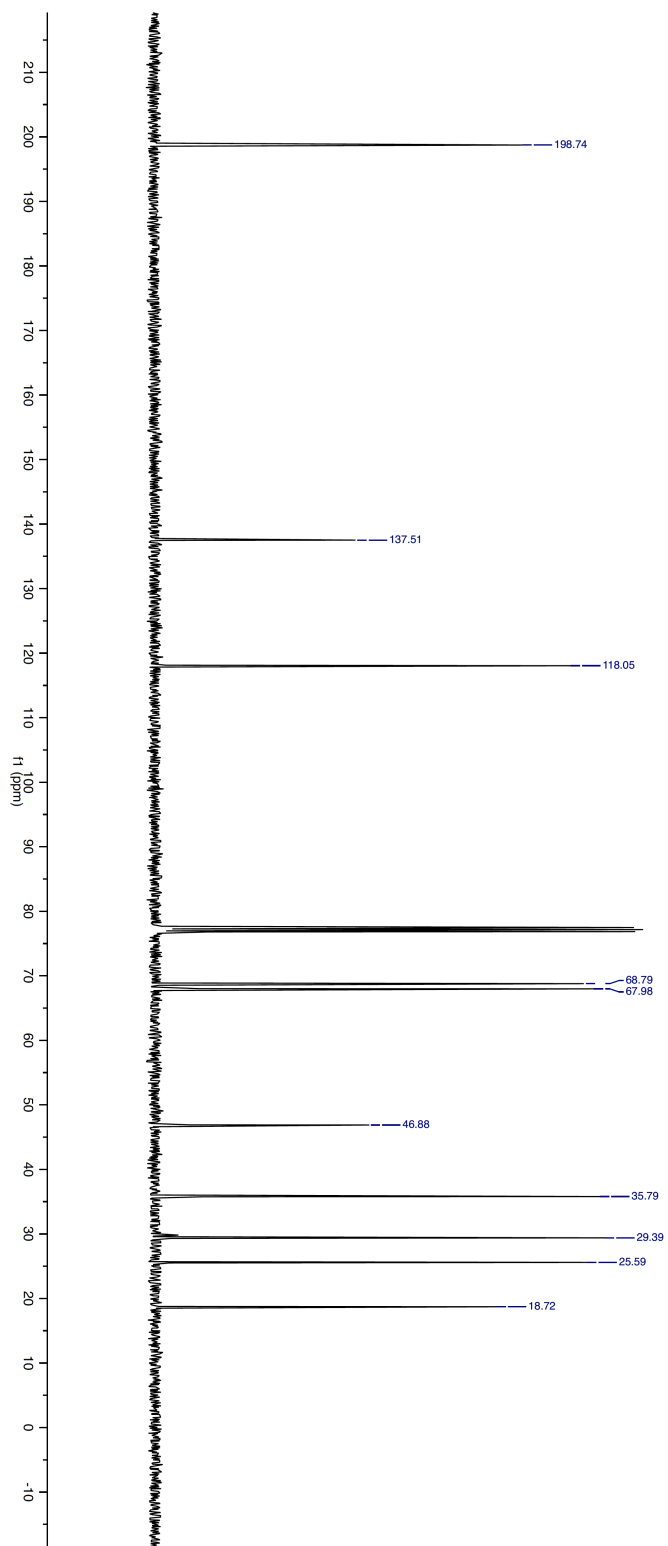
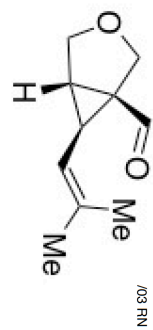


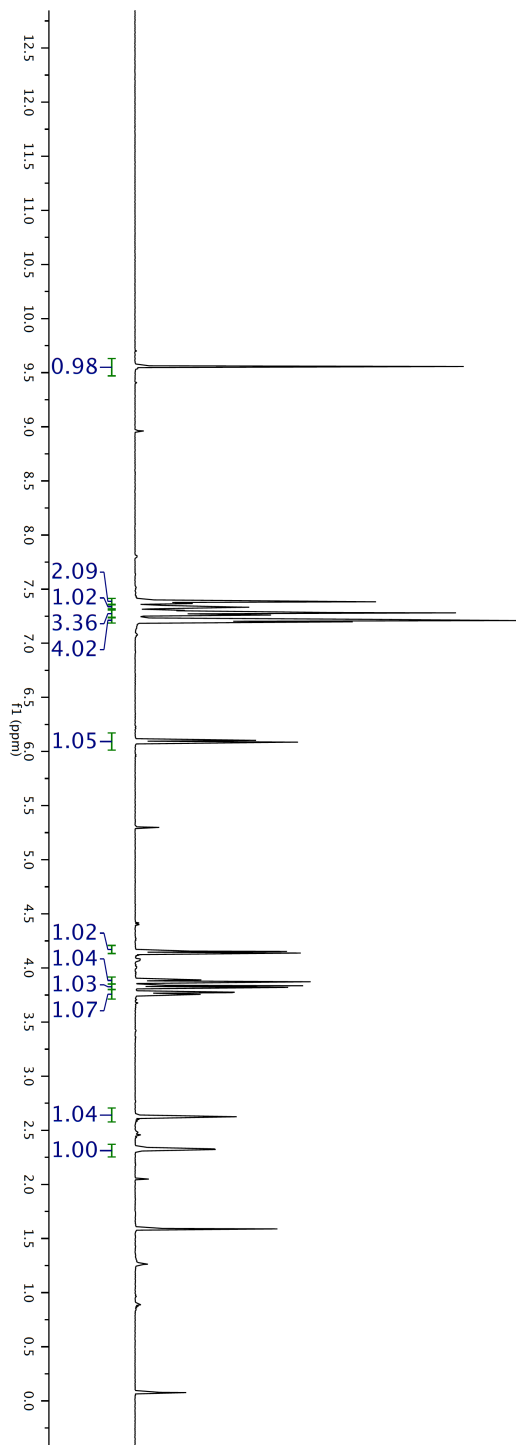
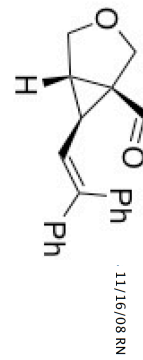
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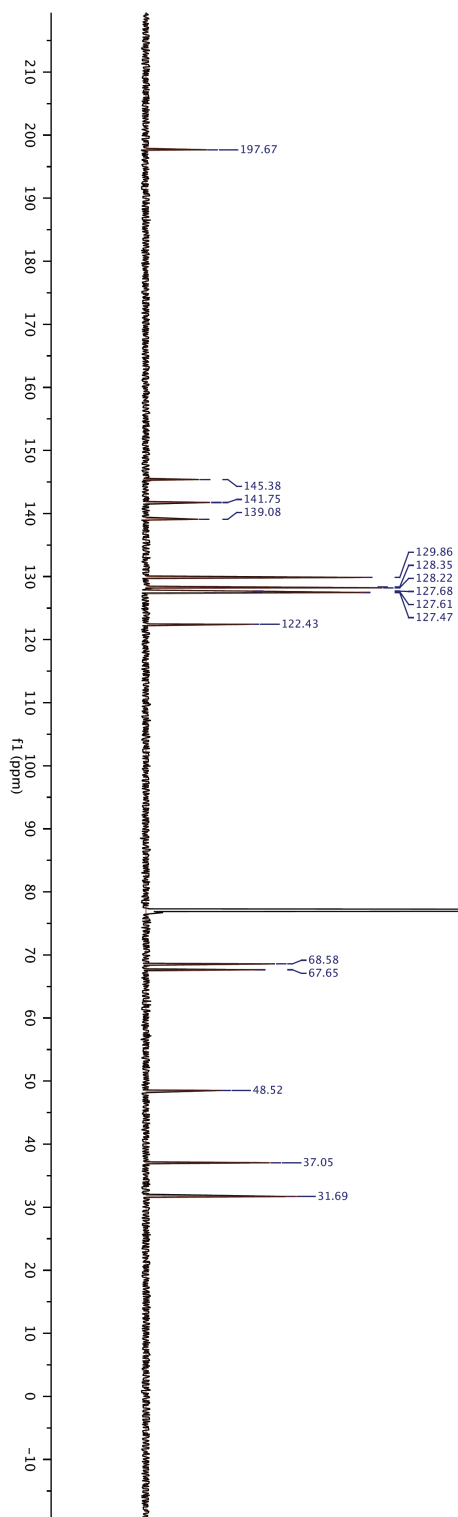
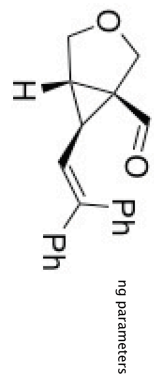


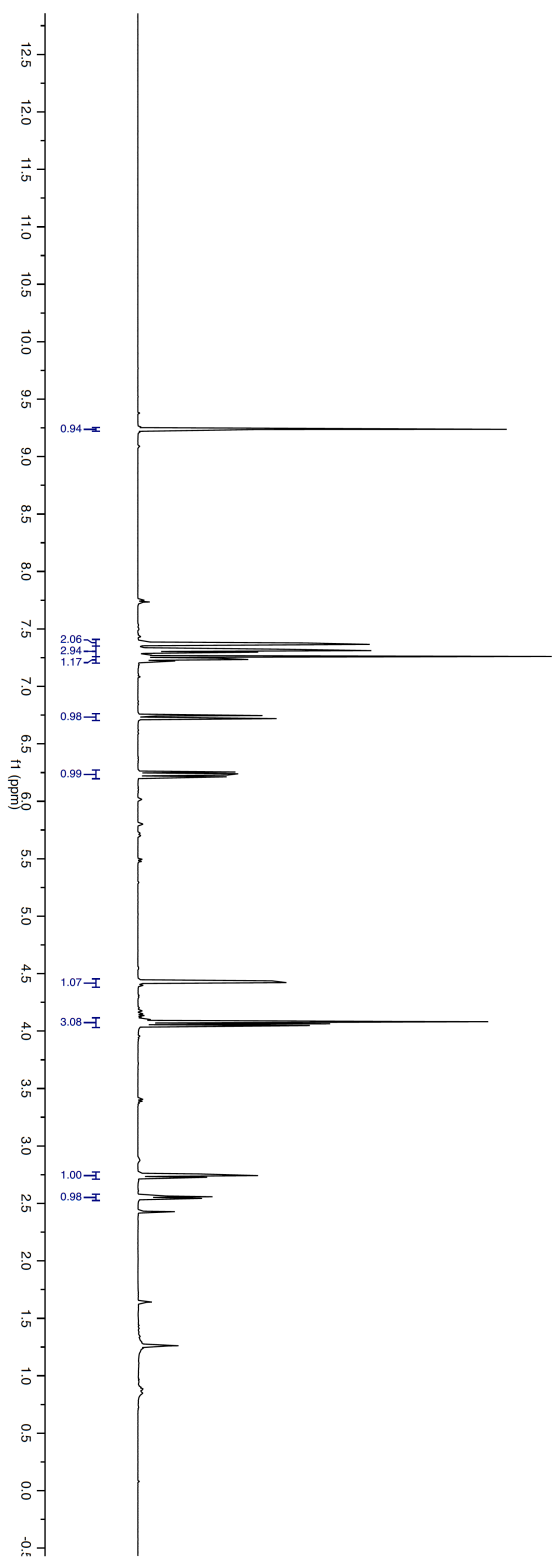
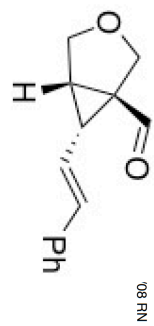


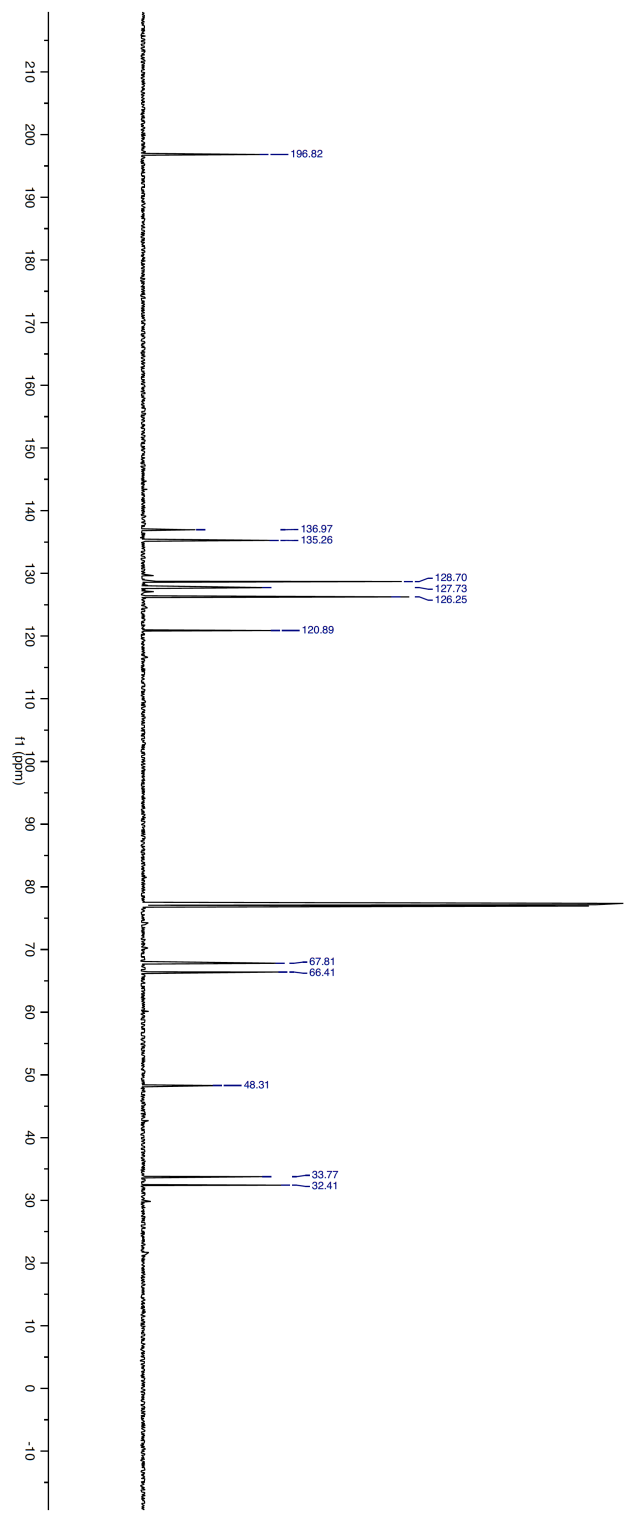
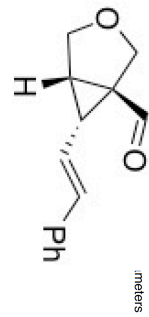












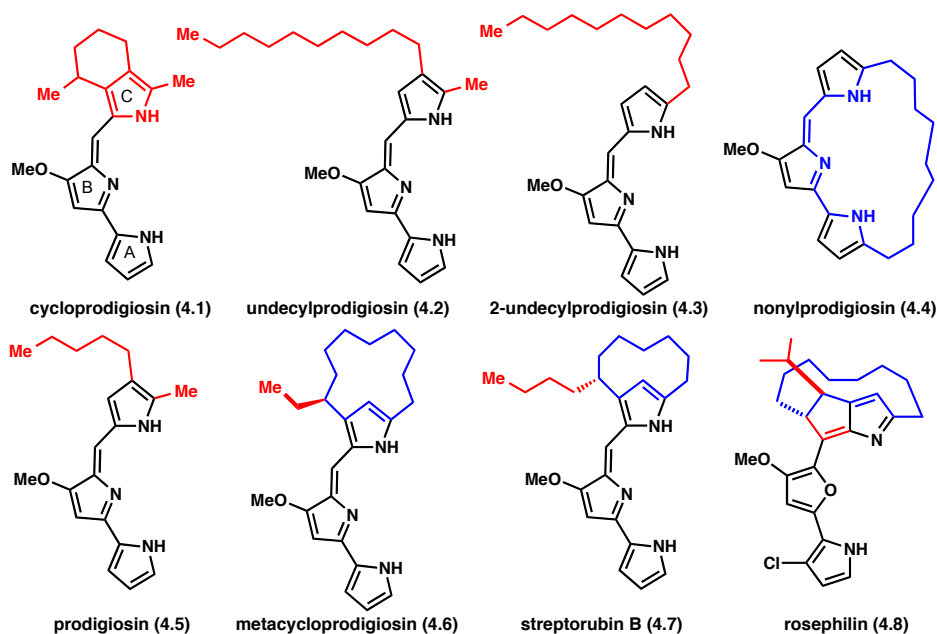
Chapter 4. Enantioselective Total Synthesis of Cycloprodigiosin.

4.1. Introduction

4.1.1. Prodiginines

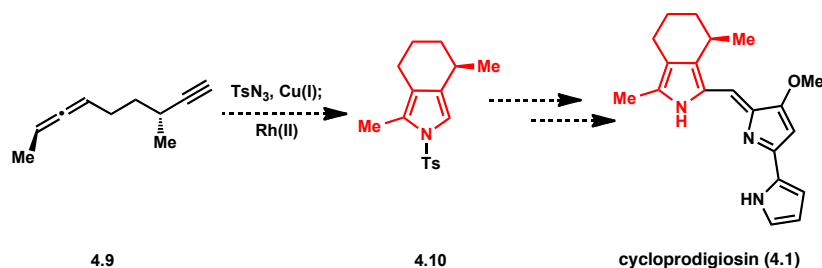
The prodiginines are a family of natural products produced by gram-negative bacteria within the *Streptomyces* and *Serratia* strains and possess a defining tripyrrolic core (see Figure 4.1). The tripyrrolic core is mostly conserved throughout the family, the exception being rosephilin (**4.8**) which contains a furan in place of the central pyrrole ring. While the A and B rings are conserved throughout the family, the tripyrrolic core differs by alkyl substitution on the C ring.¹ It is hypothesized that the cyclic forms (e.g., **4.1**, **4.6/4.7**) arise biosynthetically from the linear analogues (**4.5** and **4.3** respectively).²

Figure 4.1. Prodiginine family of natural products.



We envisioned using the methodology that we developed to synthesize 3,4-fused pyrroles (Chapter 2) to access the C-ring of cycloprodigiosin to facilitate an efficient total synthesis of cycloprodigiosin (**4.1**) from allenylalkyne **4.9** (Scheme 4.1).

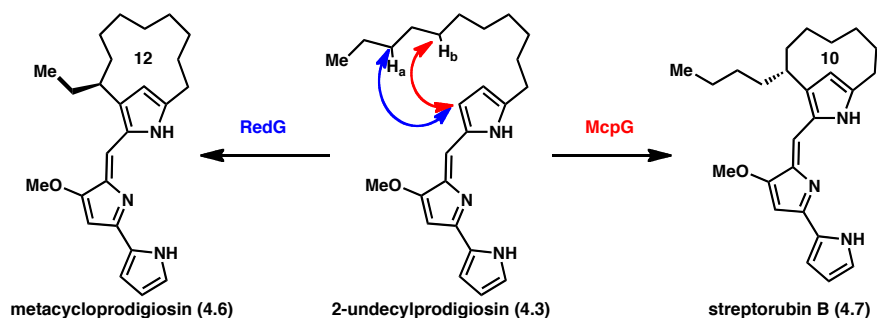
Scheme 4.1. Application of 3,4-fused pyrrole synthesis to cycloprodigiosin.



4.1.2. Biosynthesis

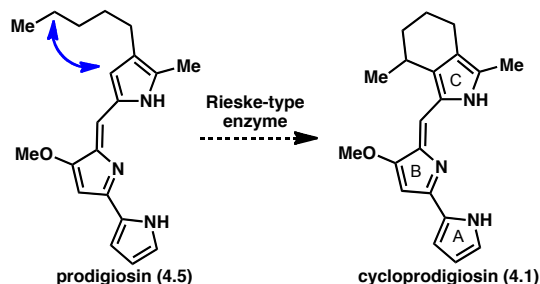
It has been found that the cyclic prodiginines streptorubin B (**4.7**) and metacycloprodigiosin (**4.6**) arise from the linear precursor undecylprodigiosin (**4.3**) through a Rieske oxygenase (RedG or McpG) mediated radical cyclization.² It is of note, that these enzymes can turn the same precursor into natural products bearing different strained ring sizes and stereochemical configuration at the stereogenic centers (See Scheme 4.2).

Scheme 4.2. Biosynthesis of cyclic prodiginines from linear precursor.



While the biosynthesis of cycloprodigiosin (**4.1**) has not been studied, presumably the six-membered ring is formed through a similar Rieske oxygenase-mediated radical process from a linear precursor (**4.5**, Scheme 4.3). No information has been reported with regard to the stereochemical information of the methyl bearing stereocenter, and seeing as Rieske oxygenases have been shown to selectively form both *R* and *S*-stereocenters (see Scheme 4.2), we hypothesize that this center is likely formed with stereochemical preference to yield an enantioenriched product.

Scheme 4.3. Proposed biosynthesis of cycloprodigiosin.

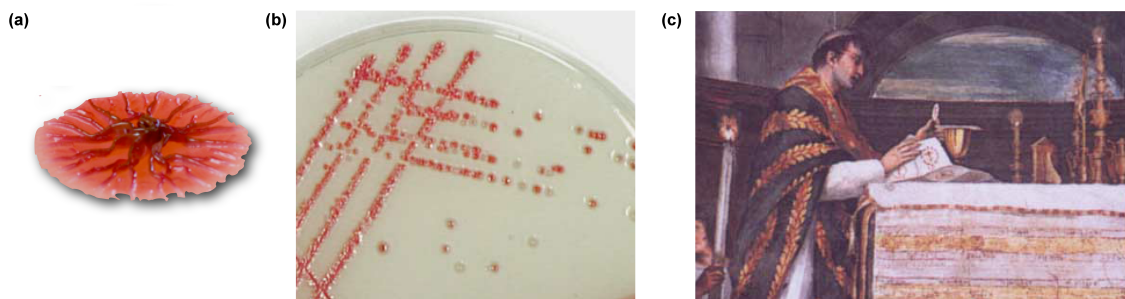


Due to the strain incorporated into the molecules after ring synthesis, the substitution on the C-ring likely plays an important role in the bioactivity of these molecules (see Section 4.2.2 for a discussion).

4.1.3. History

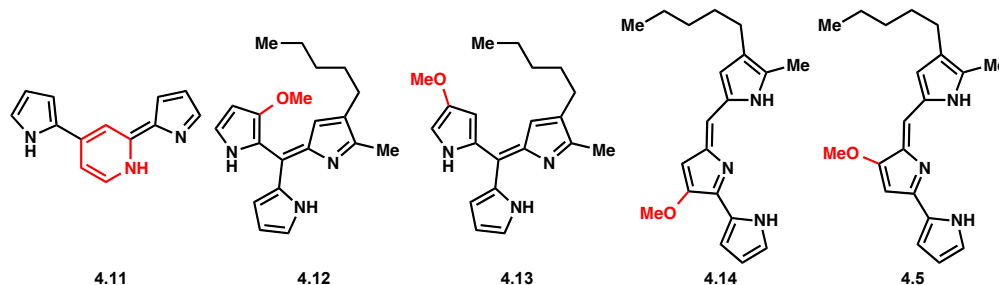
The prodiginines are red pigments produced by a limited group of ubiquitous eubacteria and actinomycetes of the *Serratia* and *Streptomyces* family of microorganisms.¹ Once mature, these colonies become fluid and suspiciously resemble droplets of blood in their color, consistency, and shape (see Figure 4.2a and 4.2b). Historical literature is full of reports of prodigious “bleeding” breads and other foods, which is how this family of natural products procured its name. For instance, in 322 B.C.E., during Alexander the Great's siege of Tyre, Macedonian soldiers noticed the appearance of blood inside a piece of bread. The royal seers interpreted this as a good omen that blood would be spilt throughout the besieged town, and used this to justify the attack. In the middle ages, the Catholic Church documented the miraculous “bleeding” of communion hosts, one such instance being the miracle of Corpus Christi (1263 C.E., shown in Figure 4.2c). The Catholic Church used these “miracles” for centuries to justify violent persecutions and pogroms against Jewish people. Finally, in the mid-1800s, public frenzy in Italy as a result of the “bleeding” of various foods, contributed to a major advance in microbiology, as scientists were able to prove that the “blood” was due to microorganisms and not witchcraft.¹

Figure 4.2. Mature colonies of bacteria producing prodiginines.¹



Though the prodiginines were isolated beginning in the mid-1800s, their structure was not determined until the 1960s.³ There was a debate in the literature by the isolation chemists as to which of five proposed structures for prodigiosin, shown in Figure 4.3, was correct. Rapoport and coworkers, through their efforts of total synthesis, finally determined the structure to be **4.5**.⁴

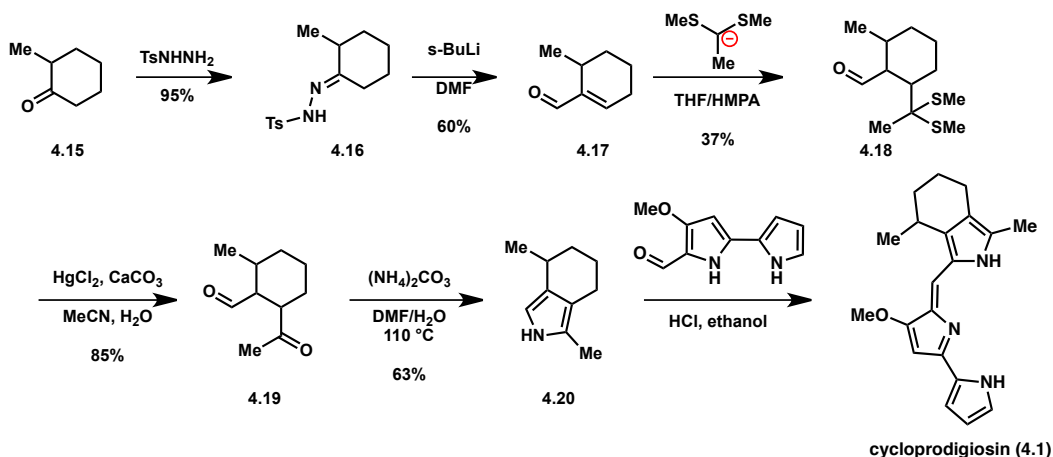
Figure 4.3. Possible structures of prodigiosin.



4.1.4. Previous synthesis

Cycloprodigiosin is produced by several bacterial strains including *Pseudoalteromonas (Alteromonas) rubra*, *Pseudoalteromonas denitrificans*, and *Vibrio gazogenes*, and has been known for a long time.⁵ However, its structure was only determined in 1983. While there has been sustained synthetic interest in the prodiginine family for over two decades,⁶ there is only one synthesis of cycloprodigiosin.⁷ Wasserman and co-workers reported their synthesis (detailed in Scheme 4.4) in 1984, a year after the structure was assigned.

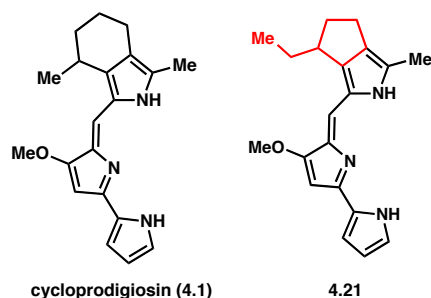
Scheme 4.4. Wasserman's racemic synthesis of cycloprodigiosin.



Wasserman's synthesis aided to the confirmation of cycloprodigiosin's structure. Early structural work on cycloprodigiosin was complicated by the presence of an aliphatic impurity with a long alkyl chain. Thus, the initial assignment of structure **4.21** (with the C-ring annulated to a 5-membered ring bearing an ethyl group; Figure 4.4) was

made for cycloprodigiosin instead of the 6-membered ring bearing a methyl group. This misassignment is attributed to the presence of a spurious triplet in the $^1\text{H-NMR}$ spectrum.⁸

Figure 4.4. Structures assigned to cycloprodigiosin.

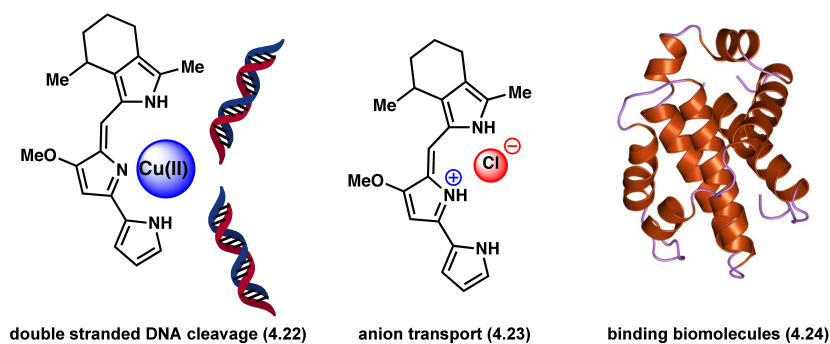


4.2. Biological activity of cycloprodigiosin

4.2.1. Modes of action

Since cycloprodigiosin's isolation, it has emerged as a potent proapoptotic anti-cancer compound⁹ and immunosuppressant.¹⁰ It is a particularly potent anti-cancer compound because it acts via several modes of action to stop cell growth and induce apoptosis (Figure 4.5). For instance, the tripyrrolic core can act as a ligand for Cu(II), which mediates the double stranded cleavage of DNA (**4.22**), a break that is much more damaging to the cell than single strand cleavage, which is easily repaired by cellular enzymes. Cycloprodigiosin can also bind anions such as chloride and transport them across the lipid bilayer (**4.23**).¹¹ This chloride transport has implications for cancer treatment because the acidification of the cytoplasm is an early event in apoptosis, and it has been suggested that molecules that can change the internal pH regulation through anion transport can offer a possible approach to anti-cancer therapy.¹² Finally, molecules related to cycloprodigiosin have been shown to bind to and inhibit enzymes in the Bcl-2 family (**4.24**), which are pro-survival proteins overexpressed in many tumors. The presence of these proteins is attributed to the tumors maintenance, progression and chemoresistance.¹³

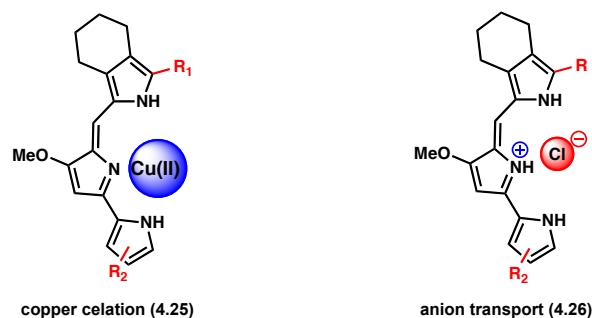
Figure 4.5. Proapoptotic modes of action for cycloprodigiosin.



4.2.2. Role of structure

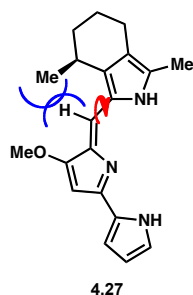
We hypothesize that the acidity of the tripyrrolic core could affect the ability of the molecule to bind both anions and metals (Figure 4.6). We are interested in accessing analogues of cycloprodigiosin with various substituents on the C-ring that could change the pyrrole moieties' N-H acidity. We are able to readily access 3,4-fused pyrrole from linear precursors (Chapter 2), which is an opportunity to use this methodology to access analogues of cycloprodigiosin. These analogues could allow us to probe the importance of the tripyrrolic core's acidity on biological activity with the ultimate goal of identifying a small molecule variant that is well suited to be administered as an anti-cancer agent.

Figure 4.6. Acidity of tripyrrolic core may have effect on binding affinity.



We also hypothesize that the stereogenic center may lead to helical chirality, seeing as the molecule may torque to avoid a steric clash between the methyl group and the vinyl hydrogen (Figure 4.7). The loss of planarity could affect the acidity or the ability of the molecule to bind to biomolecules. Either way, there is likely an evolutionary advantage for the incorporation of the methyl group into the C-ring.¹⁴

Figure 4.7. Stereogenic center may lead to helical chirality.

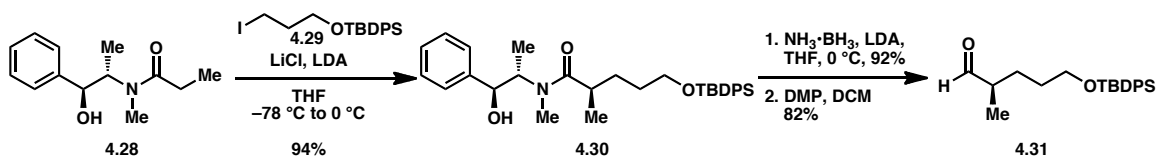


4.3 Cycloprodigiosin synthesis

This section incorporates previously published work.¹⁵

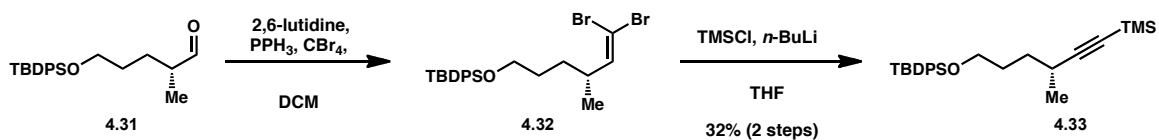
Our synthesis of cycloprodigiosin (**4.1**) began with Myers' asymmetric alkylation¹⁶ between amide **4.28** and alkyl iodide **4.29**, which utilized pseudoephedrine as a chiral auxiliary. This procedure was reproducible on large scale (94%, >10 gram scale). The aldehyde (**4.31**) was obtained using a two step procedure reported by Paterson that utilizes lithium amidotrihydroborate¹⁶ (LiH_2NBH_3 , LAB), a reagent developed by Myers for the reduction of amides like **4.30** to the primary alcohol (instead of the tertiary amine produced by metal hydrides like lithium aluminum hydride (LAH) and diborane) without loss of enantioenrichment.¹⁶ The resultant primary alcohol (not shown) was oxidized with Dess–Martin periodinane to the required aldehyde **4.31** (82%) and used directly in the next step to avoid significant racemization. Of note, although the use of LAH in ethyl acetate, which forms a lithium triethoxyaluminum hydride reagent *in situ*, is reported to yield the aldehyde in a single step from the pseudoephedrine amide, we found this transformation to be difficult to reproduce on large scale.

Scheme 4.5. Aldehyde synthesis.



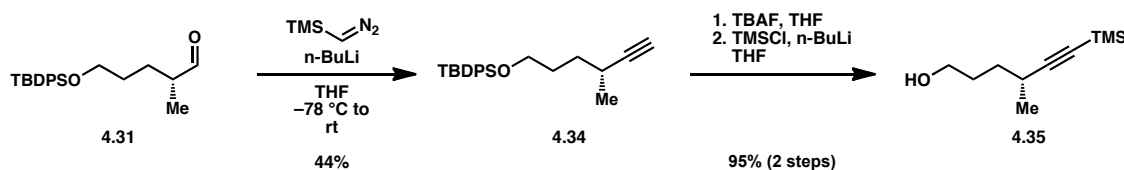
Following precedent from Panek¹⁷ and Zhao¹⁸ for the homologations of aldehydes α to an easily epimerized stereocenter, we were able to convert aldehyde **4.31** to TMS-protected alkyne **4.33** employing a two-step Corey-Fuchs reaction. However, due to low yields (32% over two steps), we explored other options for the homologation.

Scheme 4.6. Corey-Fuchs homologation.



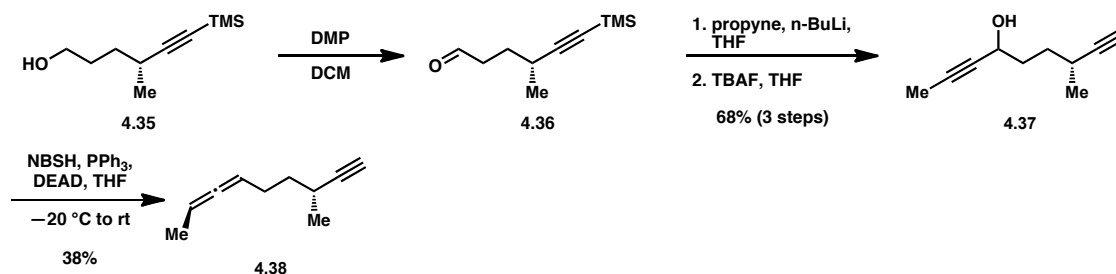
While the Ohira-Bestmann modification of the Seyferth-Gilbert homologation led to racemization of **4.31**, Miwa's protocol,¹⁹ which employs lithiated TMS-diazomethane as a nucleophile at low temperatures, afforded the desired alkyne in modest yield. Homologation proceeded without loss of *ee*. Protecting group manipulation then led to TMS-alkyne **4.35** bearing a free hydroxyl group.

Scheme 4.7. Seyferth-Gilbert homologation.



Primary alcohol **4.35** was oxidized to the corresponding aldehyde (**4.36**) by treatment with Dess–Martin periodinane. Aldehyde **4.36** was then converted into propargyl alcohol **4.37** by addition of lithium propyne, and subsequent cleavage of the TMS-protecting group. Following the same protocol for substrate synthesis as shown in Chapter 2 (see Scheme 4.8), propargyl alcohol **4.37** was then subjected to Myers' allene synthesis conditions²⁰ which consists of a Mitsunobu reaction with *o*-nitrobenzylsulfonylhydrazine (NBSH) followed by an elimination and an allylic diazene rearrangement to form allene **4.38**.

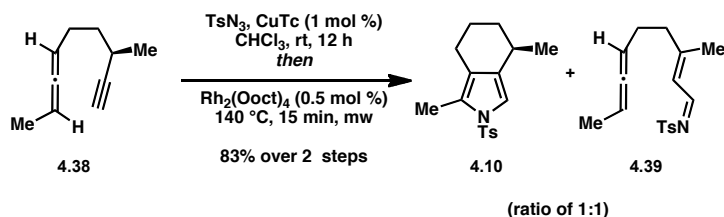
Scheme 4.8. Synthesis of allenylalkyne.



Under the conditions for pyrrole annulation outlined in Chapter 2, **4.38** was transformed in 83% yield to a 1:1 mixture of α,β -unsaturated imine **4.39** and desired pyrrole **4.10**.²¹ Presumably, the higher propensity of the methine hydrogen atom in **4.38** toward migration (compared with the methylene hydrogens as described for the substrates in Table 2.1, Chapter 2) results in the competing formation of a significant amount of **4.39**. Efforts to minimize the formation of **4.39** using other metal salts or complexes known to modulate the reactivity of carbenes,²² including Rh₂(TFA)₄,

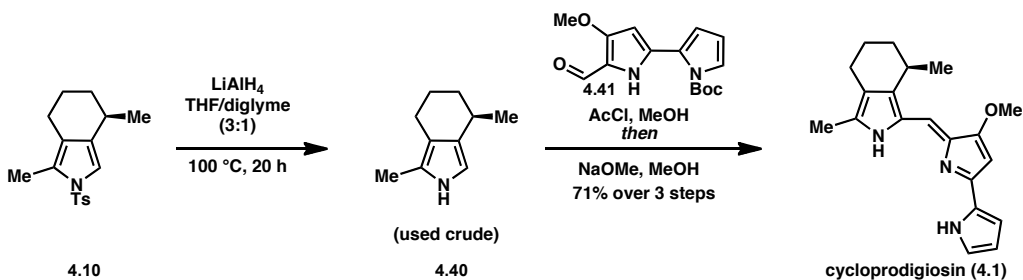
$\text{Rh}_2(\text{cap})_4$, $\text{Rh}(\text{OAc})_2(\text{PC})_2$ (PC = ortho-metalated phosphine),²³ $\text{RuCl}_2(\text{PPh}_3)_3$, AgOBz , and $\text{Cu}(\text{tert-butylsalicylimine})_2$,²⁴ resulted either in low conversion [with $\text{Cu}(\text{tert-butylsalicylimine})_2$ and $\text{Rh}_2(\text{cap})_4$], the exclusive formation of **4.39** [with $\text{Rh}_2(\text{TFA})_4$], or nonspecific decomposition.²⁵

Scheme 4.9. *Synthesis of C-ring of cycloprodigosin.*



With access to reasonable quantities of **4.10**, we proceeded with the synthesis by attempting to remove the tosyl group to give pyrrole **4.40**. Among the many conditions for tosyl group removal that we surveyed,²⁶ only the use of lithium aluminum hydride (LAH) successfully accomplished the conversion of **4.10** to **4.40**,²⁷ which was carried on without purification to the next step. Condensation of **4.40** with **4.41** using the conditions of Lindsley in their work toward marineosins A and B²⁸ of afforded cycloprodigosin (**4.1**) in 71% yield over the three steps from **4.10**. The ^1H and ^{13}C NMR spectral data for synthetic **4.1** were in close agreement with those reported by the isolation chemists, Laatsch and Thomson.⁸

Scheme 4.10. *Tosyl cleavage, coupling of 4.40 and 4.41 to give cycloprodigosin.*



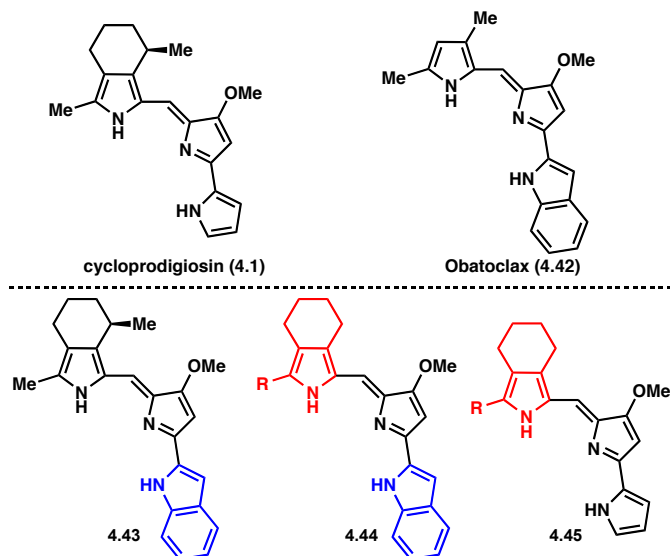
Our synthesis of **4.1** is the first enantioselective synthesis of cycloprodigosin and should enable a full evaluation of the influence of the methyl bearing stereocenter on the biological properties of the natural product.²⁹ This is especially important since the reports on the isolation and subsequent work with cycloprodigosin do not comment on whether it was obtained as a scalemic or racemic mixture.

4.4 Future directions

Studies on the bioactivity of the prodigosins led to the development of a clinical candidate known as Obatoclax® (**4.42**),³⁰ which is currently being pursued at various stages of clinical development to treat different types of cancer.³¹ We are interested in building a variety of cycloprodigosin analogues that incorporate aspects of obatoclax

(4.43, 4.44) and have various substitutions on the C ring (4.44, 4.45) that would modulate both the acidity of the pyrrole core and the dihedral angle between the B and C rings. Such analogues would allow us to gain an indepth understanding of the structural properties of these molecules to provide a better understanding of the mode of action of these compounds in inhibiting the growth of cancer cells. The results of these studies could lead to the identification of a better-suited small molecule variant of 4.1 as an administered anti-cancer agent.

Figure 4.8. Obatoclax, cycloprodigiosin, and possible analogues.



4.5. Conclusion

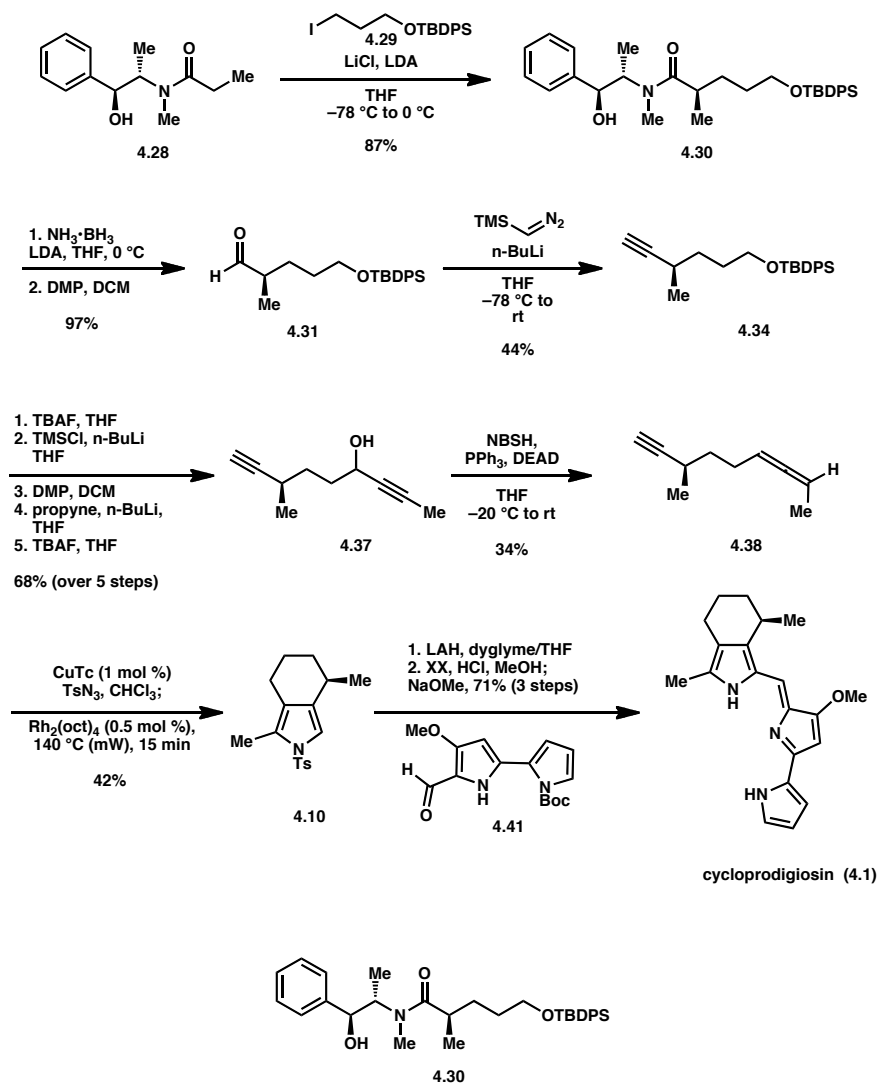
Cycloprodigiosin, as well as other members of the prodiginine family of natural products, is a brightly colored dye produced by bacteria with an interesting and “bloody” history, but has been shown in recent years to have potent anti-cancer activity. This anti-cancer activity likely arises from three modes of action, including ion transport, Cu-mediated double-stranded DNA cleavage, and inhibition of pro-survival enzymes. We applied the 3,4-fused pyrrole synthesis methodology (Chapter 2) to the first enantioselective synthesis of the natural product cycloprodigiosin. Our current efforts are centered on exploring the utility of this reaction in the synthesis of natural-product-like structures to understand the structure-reactivity function in these molecules in regards to their anti-cancer activity.

4.6. Experimental

Materials and Methods.

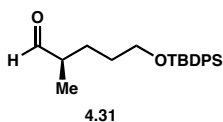
Unless stated otherwise, reactions were performed in oven-dried glassware sealed with rubber septa under a nitrogen atmosphere and were stirred with Teflon-coated magnetic stir bars. Liquid reagents and solvents were transferred via syringe using standard Schlenk techniques. Tetrahydrofuran (THF), toluene, acetonitrile (MeCN), and methanol (MeOH) were dried by passage over a column of activated alumina; dichloromethane was distilled over calcium hydride. Anhydrous chloroform was obtained in a Sure/Seal bottle from Aldrich. All other solvents and reagents were used as received unless otherwise noted. Thin layer chromatography was performed using SiliCycle silica gel 60 F-254 precoated plates (0.25 mm) and visualized by UV irradiation and anisaldehyde, CAM, potassium permanganate, or iodine stain. Sorbent silica gel (particle size 40-63 μm) was used for flash chromatography. NMR experiments were performed on Bruker spectrometers operating at 300, 400, 500 or 600 MHz for ^1H and 75, 100, 125, or 150 MHz for ^{13}C experiments. ^1H and ^{13}C chemical shifts (δ) are reported relative to the residual solvent signal. Data are reported as follows: chemical shift (multiplicity, coupling constants where applicable, number of hydrogens). Abbreviations are as follows: s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublet), dt (doublet of triplet), p (pentet), hept (heptet), m (multiplet), bs (broad singlet). ^1H and ^{13}C spectra of intermediates leading to known compound **4.31** not shown. IR spectra were recorded on a Nicolet MAGNA-IR 850 spectrometer as thin films on NaCl plates and are reported in frequency of absorption (cm^{-1}). Only selected IR absorbencies are reported. 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. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. The microwave-assisted reactions were conducted using a Biotage Initiator 2.5 EXP microwave reactor.

Synthesis of cycloprodigiosin.



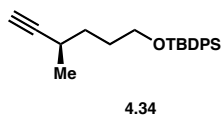
Pseudophedrine alkylation product (4.30). Flame-dried LiCl (8.43 g, 221 mmol, 6.0 equiv) was placed in a 250 mL round-bottom flask. The reaction flask was charged with THF (34 mL, 6.0M), and diisopropyl amine (10.8 mL, 77.0 mmol, 2.3 equiv). The reaction mixture was cooled to -78 °C, then *n*-BuLi (28.1 mL of a 2.5 M solution in hexanes, 70.3 mmol, 2.1 equiv) was added. The solution was stirred at -78 °C for 15 min, then warmed to 0 °C. After 15 min, the reaction mixture was re-cooled to -78 °C, and **4.28** (7.40 g, 33.5 mmol, 1.0 equiv) was added via cannula as a solution in THF (67 mL, 0.5 M). The reaction mixture was stirred for an additional hour at -78 °C, then warmed to 0 °C for 15 min, then to ambient temperature for 5 min. The reaction mixture was then re-cooled to 0 °C and **4.29** (28.4 g, 67.0 mmol, 2.0 equiv) as a solution in THF (17 mL, 4.0 M) was added via cannula. The reaction mixture was held at 0 °C for 12 h then quenched by slow addition of saturated aqueous ammonium chloride. The layers were separated and the aqueous layer was extracted with ethyl acetate (2 x 200 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in*

vacuo and purified by column chromatography (1:1 hexanes:ethyl acetate) to give **4.30** (15.0 g, 87%) as a colorless viscous oil. **IR** (film): 3385, 3070, 2932, 2858, 2739, 1960, 1890, 1824, 1739, 1620, 1472, 1428, 1110, 939, 912, 823, 741, 701, 613. **¹H NMR** (600 MHz, Chloroform-*d*) δ 7.70 - 7.62 (m, 4H), 7.45 - 7.28 (m, 10H), 7.23 (t, $J = 7.3$ Hz, 1H), 4.60 (d, $J = 6.7$ Hz, 1H), 4.39 (bs, 1H), 3.61 (tt, $J = 10.5, 5.3$ Hz, 2H), 2.79 (s, 3H), 2.58 (q, $J = 6.7$ Hz, 1H), 1.77 - 1.62 (m, 2H), 1.53 - 1.40 (m, 3H), 1.12 (d, $J = 7.0$ Hz, 3H), 1.08 (d, $J = 6.7$ Hz, 3H), 1.05 (s, 9H). **¹³C NMR** (150 MHz, CDCl₃) δ 178.9, 142.6, 135.5, 135.5, 133.9, 129.5, 128.3, 127.6, 127.5, 126.2, 76.5, 67.9, 63.6, 36.2, 30.2, 30.1, 26.8, 25.6, 19.2, 17.2, 14.4. **HRMS** (*m/z*): [M-*t*Bu]⁺ calcd for C₂₈H₃₄O₃SiN, 460.2308, found 460.2287.



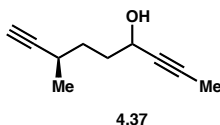
Aldehyde (4.31). To a cooled a solution of diisopropyl amine (11.5 mL, 81.6 mmol, 4.2 equiv) in THF (72 mL) at -78 °C was added *n*-BuLi (36.2 mL of a 2.2 M solution in hexanes, 79.7 mmol, 4.1 equiv) dropwise over 20 min, and the reaction mixture was warmed to 0 °C. After 15 min, ammonia borane (2.40 g, 77.7 mmol, 4.0 equiv) was added portionwise. After an additional 15 min at 0 °C, the reaction mixture was warmed to ambient temperature for 15 min, then re-cooled to 0 °C and **4.30** (10.0 g, 19.4 mmol, 1.0 equiv) was added. The reaction mixture was stirred for an additional 2 h at 0 °C, then was quenched by its addition via cannula into a pre-cooled solution of saturated aqueous ammonium chloride (70 mL), methanol (35 mL), and diethyl ether (35 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (2 x 200 mL). The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo* and purified by column chromatography (10:1 hexanes:ethyl acetate) to give the resulting primary alcohol (6.7 g, 97%) as a colorless oil. Spectra were consistent with those reported previously.³²

The alcohol (18.8 mmol, 1.0 equiv) was dissolved in dichloromethane (70 mL, 0.25 M), and charged with Dess-Martin periodinane (10.3 g, 24.4 mmol, 1.3 equiv). The reaction mixture was allowed to stir at ambient temperature for 90 min, then was quenched by the addition of saturated sodium bicarbonate (100 mL) and sodium thiosulfate (100 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (100 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo* and purified by column chromatography (4:1 hexanes:ethyl acetate) to give **4.31** as a colorless oil which was used immediately in the next reaction. Spectra were consistent with those reported previously.³²



Terminal alkyne (4.34).³³ A solution of TMS-diazomethane (9.34 mL of a 2.0 M solution in diethyl ether, 20.6 mmol, 1.2 equiv) in THF (60 mL, 0.3 M) was cooled to -

78 °C under a N₂ atmosphere. The reaction flask was charged with *n*-BuLi (9.34 mL of a 2.2 M solution in hexanes, 20.5 mmol, 1.2 equiv). After 45 min, **4.31** (18.8 mmol, 1.0 equiv) in THF (18 mL, 1.0 M) was added dropwise over 20 min. After the reaction mixture was stirred at -78 °C for an hour, it was warmed to 0 °C for 30 min, and finally ambient temperature for 1 h. The reaction mixture was quenched by the addition of saturated aqueous ammonium chloride (200 mL) and diluted with diethyl ether (200 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (2 x 200 mL). The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo* and purified by column chromatography (50:1 hexanes:ethyl acetate) to give **4.34** (2.8 g, 43% over 3 steps) as a colorless oil. IR (film): 308, 3071, 3050, 2932, 2858, 2113, 1959, 1889, 1824, 1589, 1473, 1390, 1112, 999, 938, 823, 741, 702, 614. ¹H NMR (500 MHz, Chloroform-*d*) δ 7.75 (dt, *J* = 6.5, 1.7 Hz, 4H), 7.50 - 7.41 (m, 6H), 3.76 (t, *J* = 6.3 Hz, 2H), 2.56 - 2.42 (m, 1H), 2.07 (d, *J* = 2.4 Hz, 1H), 1.90 - 1.79 (m, 1H), 1.79 - 1.68 (m, 1H), 1.68 - 1.54 (m, 2H), 1.24 (d, *J* = 6.9 Hz, 3H), 1.13 (s, 9H). ¹³C NMR (126 MHz, CDCl₃) δ 135.7, 134.1, 134.1, 129.6, 127.7, 89.0, 68.4, 63.7, 33.1, 30.3, 27.0, 25.5, 21.1, 19.3. HRMS (*m/z*): [M-*t*Bu]⁺ calcd for C₁₉H₂₁OSi, 293.1362; found, 293.1366. [α]_D²³ - 13.2 (c 1.1, CH₂Cl₂) lit. for (*S*)-**4.34** [α]_D²⁰ + 12.3 (c 1.1, CH₂Cl₂).



Propargylic alcohol (4.37). A solution of TBAF (10.7 mL of a 1.0 M solution in THF, 10.7 mmol, 2.0 equiv) was added dropwise to a solution of **4.34** (1.87 g, 5.44 mmol, 1.0 equiv) in THF (10 mL, 0.5 M) at 0 °C. The reaction mixture was warmed to ambient temperature and stirred for 5 h at which time TLC analysis indicated complete consumption of the starting material. The reaction mixture was quenched by the addition of saturated aqueous ammonium chloride (20 mL) and diluted with diethyl ether (20 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (3 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over sodium sulfate, filtered, concentrated *in vacuo* and passed through a short silica plug eluting with hexanes then 6:1 (hexanes:ethyl acetate) to give the deprotected primary alcohol (590 mg, quant.) after concentrating as a colorless oil, which was used without further purification.

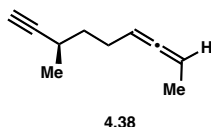
The alcohol (590 mg, 5.44 mmol, 1.0 equiv) was dissolved in THF (16 mL, 0.33 M) and the resulting solution was cooled to -78 °C. The flask was charged with *n*-BuLi (7.28 mL of a 2.2 M solution in hexanes, 16.0 mmol, 3.0 equiv). After the reaction mixture was stirred at -78 °C for 1 h, trimethylsilyl chloride (2.36 mL, 18.7 mmol, 3.5 equiv) was added dropwise. The reaction mixture was then warmed to ambient temperature and stirred for 1 h before being quenched by the addition of water (20 mL) and 1N HCl (5 mL). The resulting biphasic mixture was stirred vigorously for 30 min, then diluted with ether (30 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (3 x 30 mL). The combined organic layers were washed with brine (20 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo* and passed through a short silica plug eluting with hexanes then 6:1 hexanes:ethyl acetate to give the TMS-protected

alkyne as a colorless oil (980 mg, quant.), which was used without further purification.

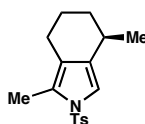
The TMS-protected alkyne (980 mg, 5.44 mmol, 1.0 equiv) was dissolved in dichloromethane (27 mL, 0.2 M), and to this solution was added Dess-Martin periodinane (2.94 g, 6.94 mmol, 1.3 equiv). The reaction mixture was stirred at ambient temperature for 90 min, and then was quenched by the addition of saturated sodium bicarbonate (50 mL) and sodium thiosulfate (50 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (3 x 50 mL). The combined organic layers were dried over sodium sulfate, filtered, concentrated *in vacuo* and purified by column chromatography (8:1 hexanes:ethyl acetate) to give the resulting unstable aldehyde (691 mg, 71%) as a colorless oil which was used immediately in the next reaction.

Condensed propyne (> 1.3 mL, > 6.0 equiv) at -78 °C, was diluted with THF (20 mL, 0.25 M). The flask was charged with *n*-BuLi (5.0 mL of a 2.2 M solution in hexanes, 11.4 mmol, 3.0 equiv). After the reaction mixture was stirred at -78 °C for 2 h, the aldehyde (690 mg, 3.79 mmol, 1.0 equiv) in THF (10 mL, 0.4 M) was added dropwise via syringe. The reaction mixture was stirred at -78 °C for an additional 4 h then warmed to ambient temperature and stirred for 8 h. The reaction mixture was quenched by the addition of saturated aqueous ammonium chloride (20 mL) and diluted with diethyl ether (20 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (3 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo* and passed through a short silica plug eluting with 4:1 hexanes:ethyl acetate to give the propargylic alcohol (807 mg, 96%) which was used immediately in the next step.

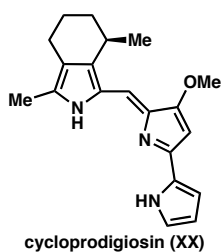
A solution of TBAF (7.58 mL of a 1.0 M solution in THF, 7.58 mmol, 2.0 equiv) was added dropwise to a solution of the propargylic alcohol (840 mg, 3.79 mmol, 1.0 equiv) in THF (20 mL, 0.2 M) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min at which time TLC analysis indicated complete consumption of the starting material. The reaction mixture was quenched by the addition of saturated aqueous ammonium chloride (15 mL) and diluted with diethyl ether (10 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over sodium sulfate, filtered, concentrated *in vacuo* and purified by column chromatography (10:1 hexanes:ethyl acetate) to yield **4.37** (387 mg, 68% over 5 steps, 1:1 dr) as a colorless oil. **IR** (film): 3298, 2951, 2922, 2873, 1455, 1377, 1331, 1018, 630. **¹H NMR** (500 MHz, Chloroform-*d*) δ 4.38 - 4.32 (m, 1H), 2.53 - 2.39 (m, 1H), 2.04 (dd, *J* = 2.4, 1.3 Hz, 1H), 2.00 - 1.93 (bs, 1H), 1.89 - 1.84 (m, 1H), 1.83 (d, *J* = 2.2 Hz, 3H), 1.80 - 1.70 (m, 1H), 1.65 - 1.51 (m, 2H), 1.19 (dd, *J* = 7.1, 1.0 Hz, 3H). **¹³C NMR** (125 MHz, CDCl₃) δ 88.6, 88.6, 81.2, 81.2, 80.2, 80.2, 68.7, 68.7, 62.5, 62.3, 35.8, 35.7, 32.2, 32.1, 25.5, 25.4, 21.0, 21.0, 3.6, 3.6. **HRMS** (*m/z*): [M+H]⁺ calcd for C₁₀H₁₅O, 151.1123; found, 151.1117.



(3R)-3-methylnona-6,7-dien-1-yne (4.38). To a solution of triphenylphosphine (1.0 g, 3.9 mmol, 1.5 equiv) in THF (5.2 mL, 0.75 M) at -20 °C (dry ice/brine bath) was added diethyl azodicarboxylate (0.61 mL, 1.5 equiv) dropwise over 1 min. The reaction mixture was stirred at -20 °C for an additional 10 min, then charged with **4.37** (390 mg, 2.6 mmol, 1.0 equiv) as a solution in THF (4.3 mL, 0.5 M) dropwise over 10 min. After 30 minutes, 2-nitrobenzylsulfonylhydrazine (NBSH)³⁴ (850 mg, 3.9 mmol, 1.5 equiv) as a solution in THF (5.2 mL, 0.75 M) was added dropwise over 10 min. The reaction mixture was held at -20 °C for an additional 2 h then warmed to ambient temperature and stirred for 10 h. After this time, the reaction mixture was diluted with dichloromethane (10 mL), the stirbar was removed and silica gel (2 g) was added to the reaction flask and the mixture was concentrated *in vacuo* and filtered through a short silica plug eluting with pentanes to give **4.38** (121 mg, 34%, 1:1 dr) as a very volatile colorless liquid. **IR** (film): 3067, 2999, 2918, 2349, 1964, 1475, 1306, 1202, 1179, 1087, 1026, 742, 694. **¹H NMR** (600 MHz, Chloroform-*d*) δ 5.11 - 5.00 (m, 2H), 2.53 - 2.46 (m, 1H), 2.22 - 2.12 (m, 1H), 2.12 - 2.05 (m, 1H), 2.05 - 2.03 (m, 1H), 1.64 (dt, *J* = 6.6, 3.3 Hz, 3H), 1.61 - 1.48 (m, 2H), 1.19 (d, *J* = 6.9 Hz, 3H). **¹³C NMR** (150 MHz, CDCl₃) δ 204.7, 204.7, 89.6, 89.6, 88.8, 88.8, 85.9, 85.8, 68.3, 35.9, 35.9, 26.5, 26.4, 25.0, 25.0, 20.8, 20.8, 14.5, 14.5.



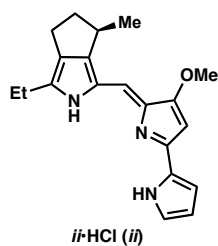
(R)-1,4-dimethyl-2-tosyl-4,5,6,7-tetrahydro-2H-isoindole (4.10). To a flame-dried microwave vial, was added copper (II) thiophene carboxylate (CuTc, 1.7 mg, 5 mol %). The vial was sealed and evacuated and backfilled with N₂ (3x), then allene **4.38** (121 mg, 0.91 mmol, 1.0 equiv) in chloroform (4.6 mL, 0.2 M) was added, followed by tosyl azide (140 mL, 0.91 mmol, 1.0 equiv). The reaction mixture was allowed to stir at ambient temperature for 12 h at which time TLC analysis indicated complete consumption of the starting material. The reaction flask was then charged with Rh₂(oct)₄ (3.5 mg, 0.5 mol %) dissolved in chloroform (0.2 mL, 0.023 M) via syringe. The resulting mixture was heated to 140 °C under microwave irradiation for 15 min. After cooling to ambient temperature, silica gel was added to the reaction mixture and the solvent was removed *in vacuo*. The resulting residue was purified by column chromatography eluting with 6:1 hexanes:ethyl acetate to give **4.10** (114 mg, 42%) as a colorless oil. **IR** (film): 2954, 2925, 2855, 1365, 1262, 1187, 1104, 671. **¹H NMR** (500 MHz, Chloroform-*d*) δ 7.66 (d, *J* = 8.3 Hz, 2H), 7.28 (d, *J* = 8.2 Hz, 2H), 7.01 (d, *J* = 1.6 Hz, 1H), 2.63 - 2.54 (m, 1H), 2.40 (s, 3H), 2.39 - 2.36 (m, 1H), 2.26 - 2.18 (m, 2H), 2.15 (s, 3H), 1.90 - 1.77 (m, 2H), 1.54 - 1.46 (m, 1H), 1.18 (d, *J* = 6.7 Hz, 3H). **¹³C NMR** (150 MHz, CDCl₃) δ 144.2, 136.9, 129.8, 129.8, 126.8, 124.3, 122.5, 115.9, 32.5, 28.5, 22.7, 21.6, 21.5, 21.3, 11.0. **HRMS** (*m/z*): [M+H]⁺ calcd for C₁₇H₂₂NO₂S, 304.1371; found, 304.1368. [α]_D²³ - 36.4 (c 0.3, CDCl₃).



Cycloprodigosin (4.1). To a degassed solution of **4.10** (55 mg, 0.18 mmol, 1.0 equiv) in THF (1.0 mL, 0.18 M) and diglyme (0.4 mL, 0.45 M) in a Schlenk tube was added lithium aluminum hydride (138 mg, 3.62 mmol, 20.0 equiv). After sealing the Schlenk tube, the reaction mixture was heated to 100 °C. After stirring at 100 °C for 20 h, the reaction mixture was cooled to 0 °C and quenched by the sequential addition of water (0.14 mL), 15% aqueous sodium hydroxide (0.14 mL), and again water (0.43 mL). After 1 h at 0 °C, the resulting slurry was diluted with diethyl ether (4 mL) and filtered through celite and washed with diethyl ether (10 x 2 mL). The filtrate was then transferred to a separatory funnel and the layers were separated. The organic layer was washed with water (10 x 5 mL), brine (5 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. The deprotected pyrrole (**4.40**) was used immediately without purification.

To a flask containing pyrrole **4.40** (0.18 mmol, 1.0 equiv) and aldehyde **4.41**³⁵ (62 mg, 0.22 mmol, 1.2 equiv) was added methanol (3 mL, 0.06 M). The flask was placed into an ambient temperature water bath, and then charged with anhydrous HCl (0.18 mL of a freshly prepared 1.0 M solution of acetyl chloride in methanol, 0.18 mmol, 1.0 equiv). The reaction mixture was allowed to stir at ambient temperature for 75 min at which time TLC analysis indicated complete consumption of the starting material. The reaction flask was then charged with sodium methoxide (47 mg, 1.8 mmol, 10 equiv). After an additional 45 min, the reaction mixture was diluted with diethyl ether (5 mL) and water (5 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (3 x 5 mL). The combined organic layers were washed with brine (5 mL), dried over sodium sulfate, filtered, concentrated *in vacuo* and purified by column chromatography (eluting with 99:1 to 98:2 chloroform:methanol) to afford cycloprodigosin (**4.1**) (46mg, 71% over 3 steps) as the HCl salt, which is a purple-black microcrystalline solid (m.p. > 220 °C, decomposes at > 220 °C). ¹H NMR (500 MHz, Chloroform-*d*) δ 12.61 (s, 2H), 12.48 (s, 1H), 7.19 (s, 1H), 7.01 (s, 1H), 6.87 (s, 1H), 6.36 - 6.31 (m, 1H), 6.08 (s, 1H), 4.00 (s, 3H), 3.19 - 3.07 (m, 1H), 2.50 (s, 3H), 2.48 - 2.42 (m, 1H), 2.30 (dt, *J* = 15.8, 7.8 Hz, 1H), 1.84 - 1.57 (m, 4H), 1.29 (d, *J* = 7.1 Hz, 3H). ¹³C NMR (125 MHz, CDCl₃) δ 166.0, 147.3, 146.3, 145.8, 126.2, 123.9, 123.1, 122.6, 119.2, 115.9, 113.1, 111.5, 92.6, 58.7, 30.5, 26.3, 24.0, 20.9, 18.4, 12.4. HRMS (*m/z*): [M+H]⁺ calcd for C₂₀H₂₄N₃O, 322.1919; found, 322.1923. Spectra were consistent with those reported previously.³⁶

Minor isomer:

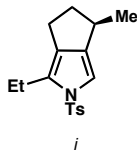


¹H NMR (500 MHz, Chloroform-*d*) δ 12.70 (s, 1H), 12.28 (s, 1H), 7.20 (s, 1H), 6.96 (s, 1H), 6.89 (s, 1H), 6.32 (s, 1H), 6.08 (s, 1H), 4.00 (s, 3H), 2.95 (q, $J = 7.7$ Hz, 1H), 2.74 - 2.54 (m, 3H), 1.70 - 1.68 (m, 1H), 1.36 - 1.31 (m, 6H). **¹³C NMR** (125 MHz, CDCl₃) δ 165.4, 156.5, 147.1, 133.2, 126.6, 122.5, 119.8, 119.6, 116.5, 114.4, 111.6, 92.8, 58.8, 39.8, 34.4, 24.1, 21.6, 12.8.

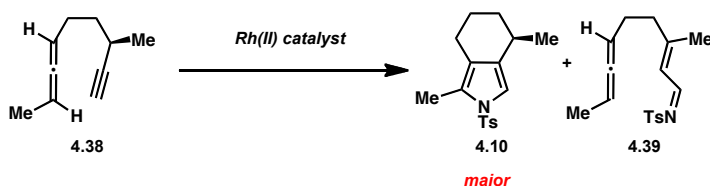
4.7 References and Notes

1. For a review of prodiginine's history and biological activity see: Fuerstner, A. *Angew. Chem. Int. Ed.* **2003**, *42*, 3582.
2. (a) Sydor, P. K.; Barry, S. M.; Odulate, O. M.; Barona-Gomez, F.; Haynes, S. W.; Corre, C.; Song, L.; Challis, G. L. *Nat. Chem.* **2011**, *3*, 388.
3. See Reference 1.
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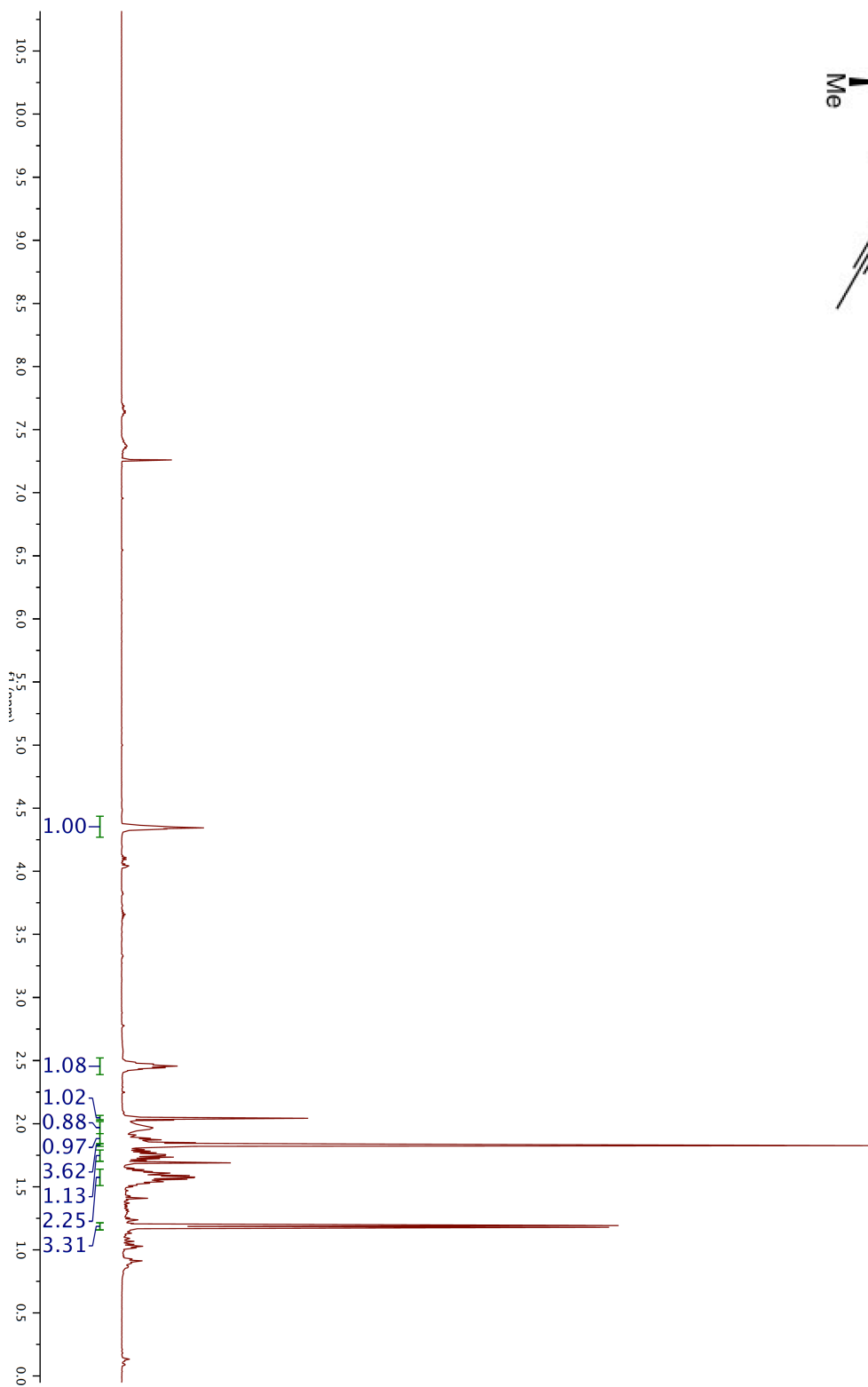
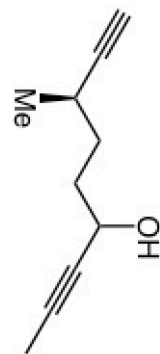


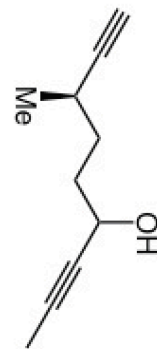
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 25. This work was done before that of Chapter 3, and having optimized the cyclopropanation over the 1,2-hydride shift (Chapter 3, Table 3.1), we would like to apply that knowledge to the synthesis of the C-ring of cycloprodigiosin. Using a more sterically encumbered rhodium(II)-catalyst may allow for pyrrole formation to be the favored pathway over the 1,2-hydride shift for substrates containing methine hydrogen atoms such as **4.38** (compared with the methylene hydrogen atoms as described for the substrates in Table 2.1, Chapter 2).



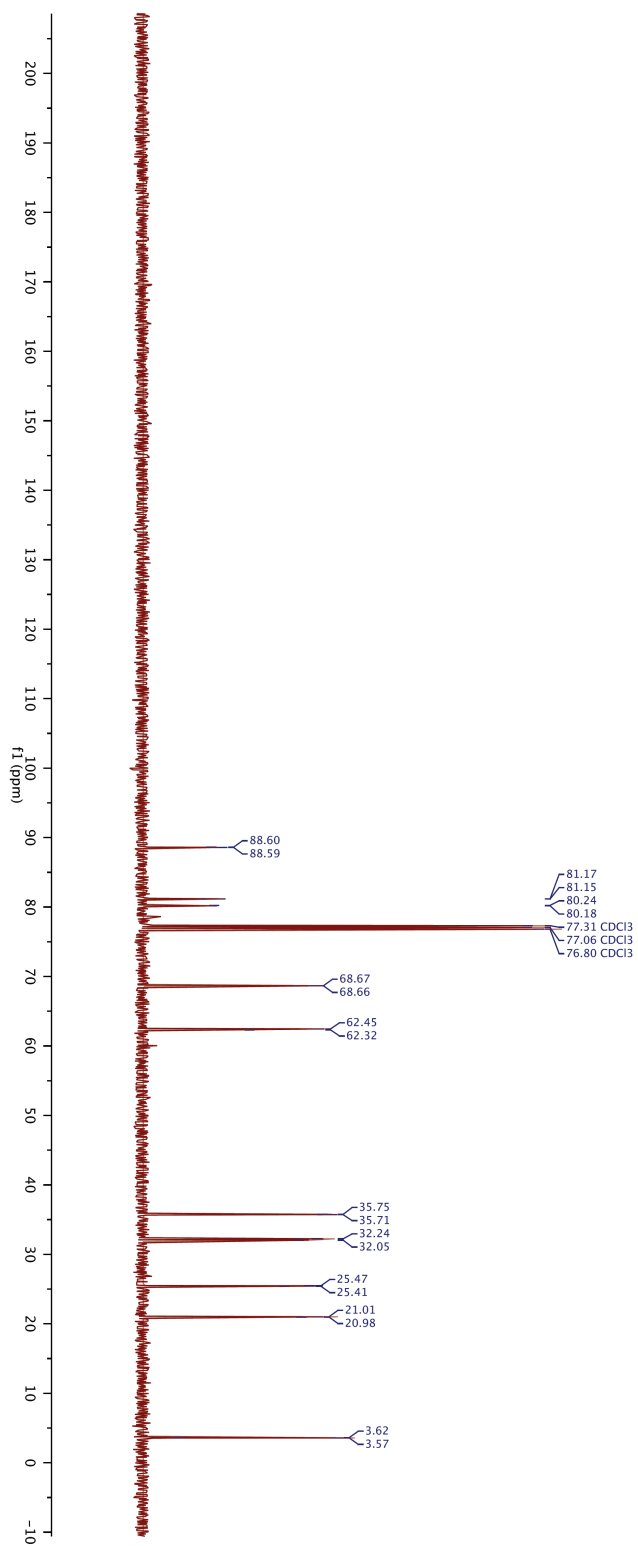
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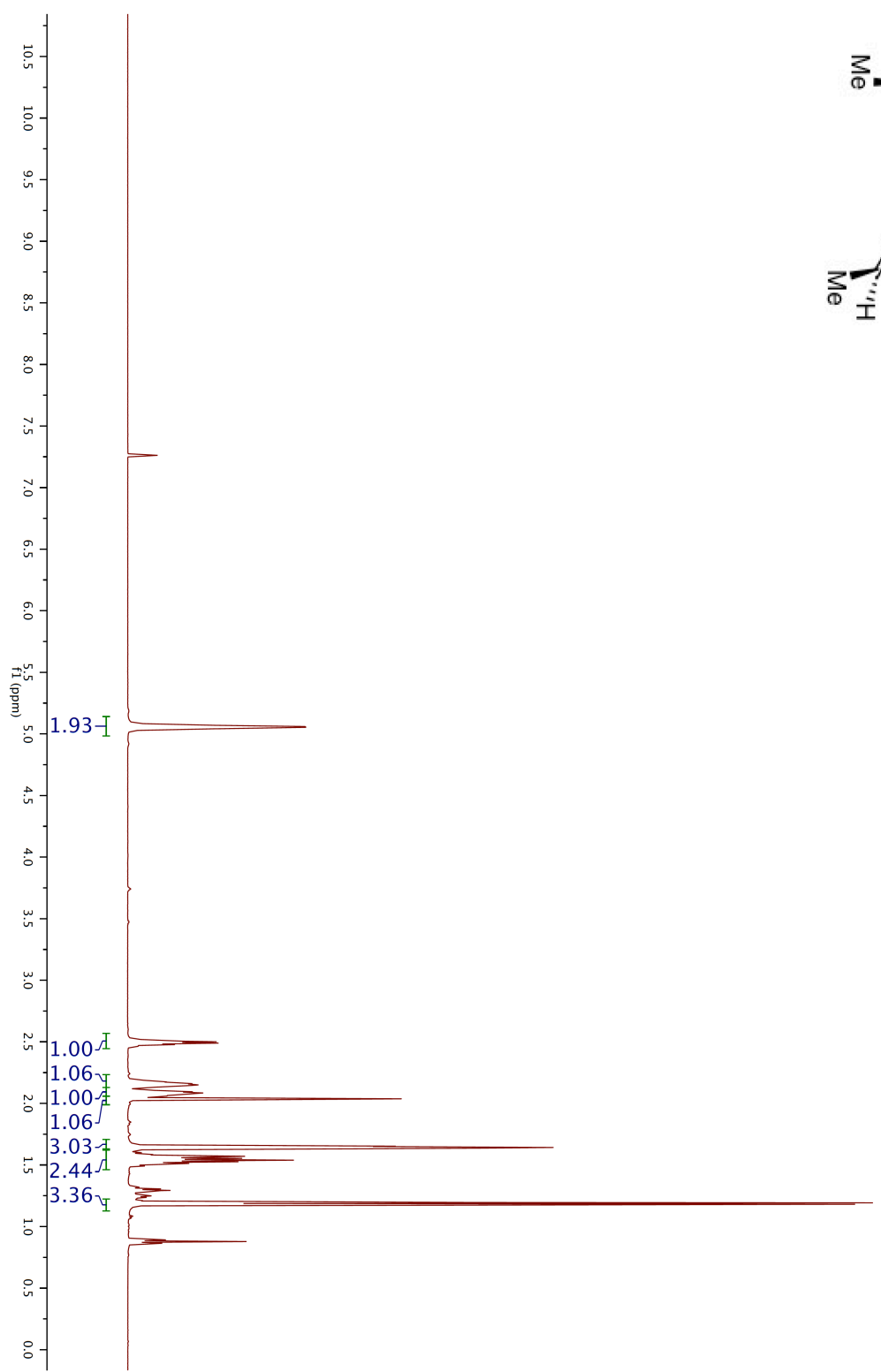
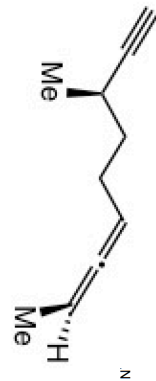
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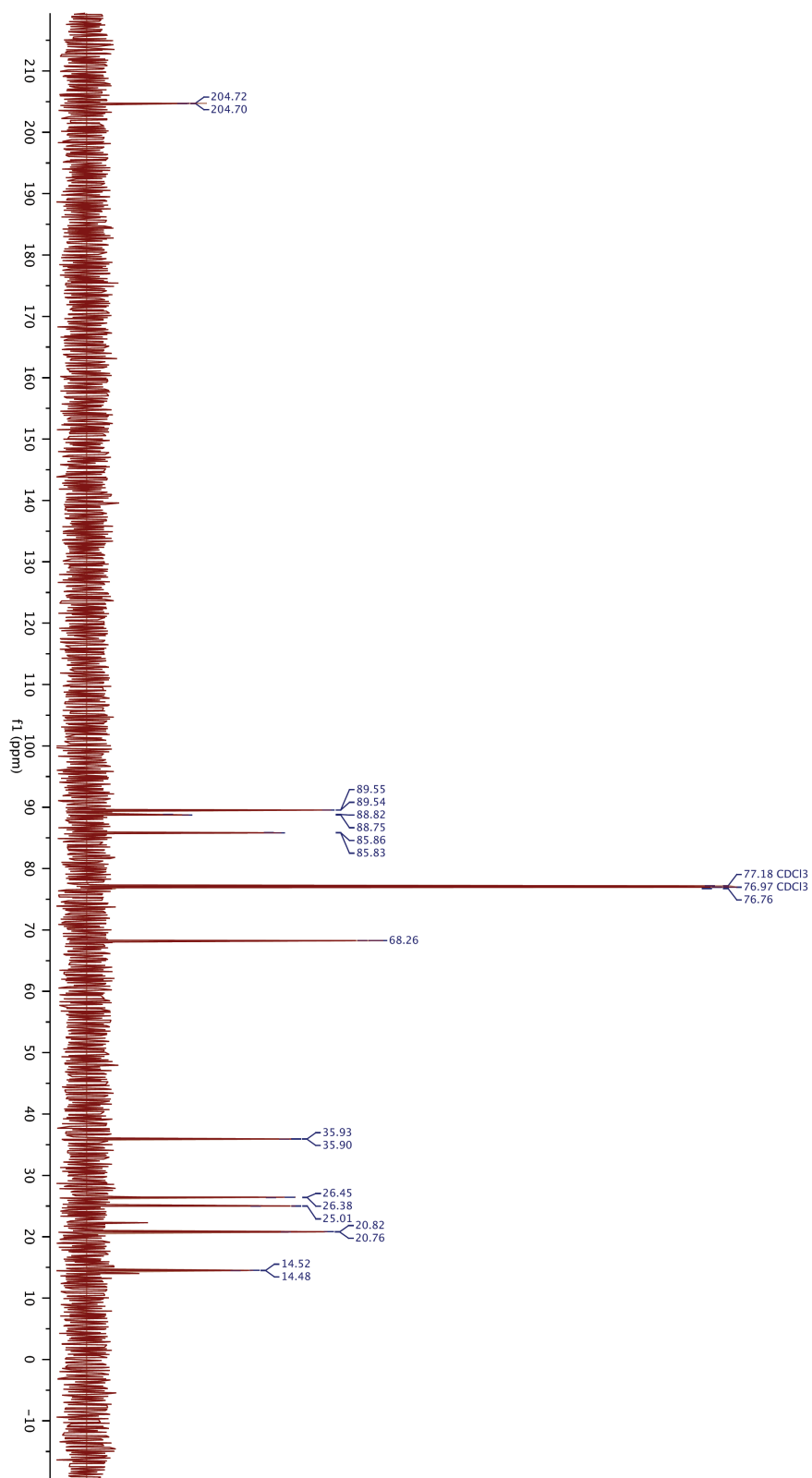


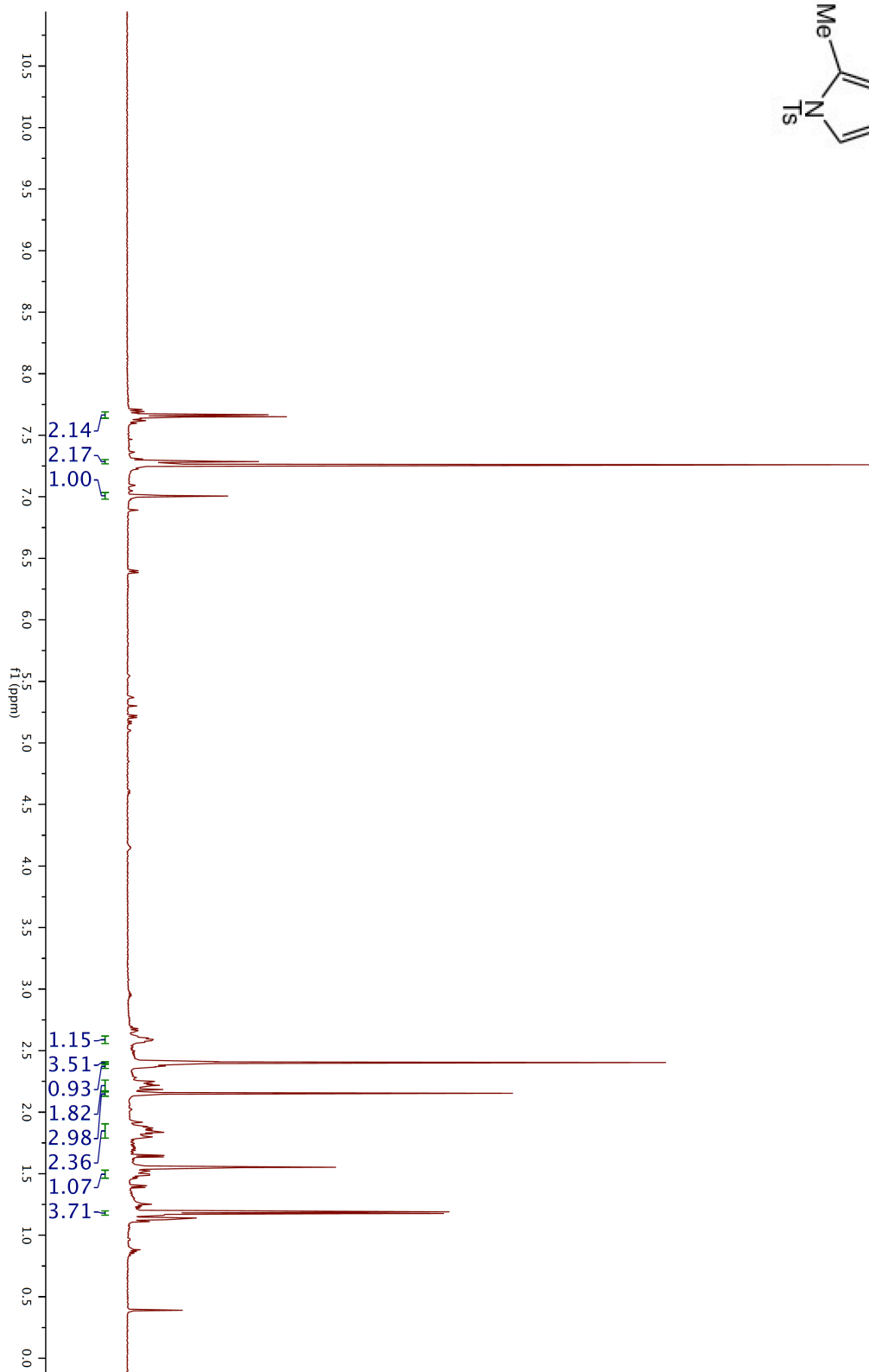
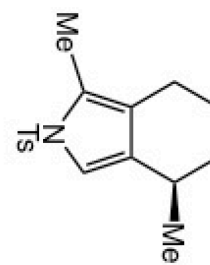


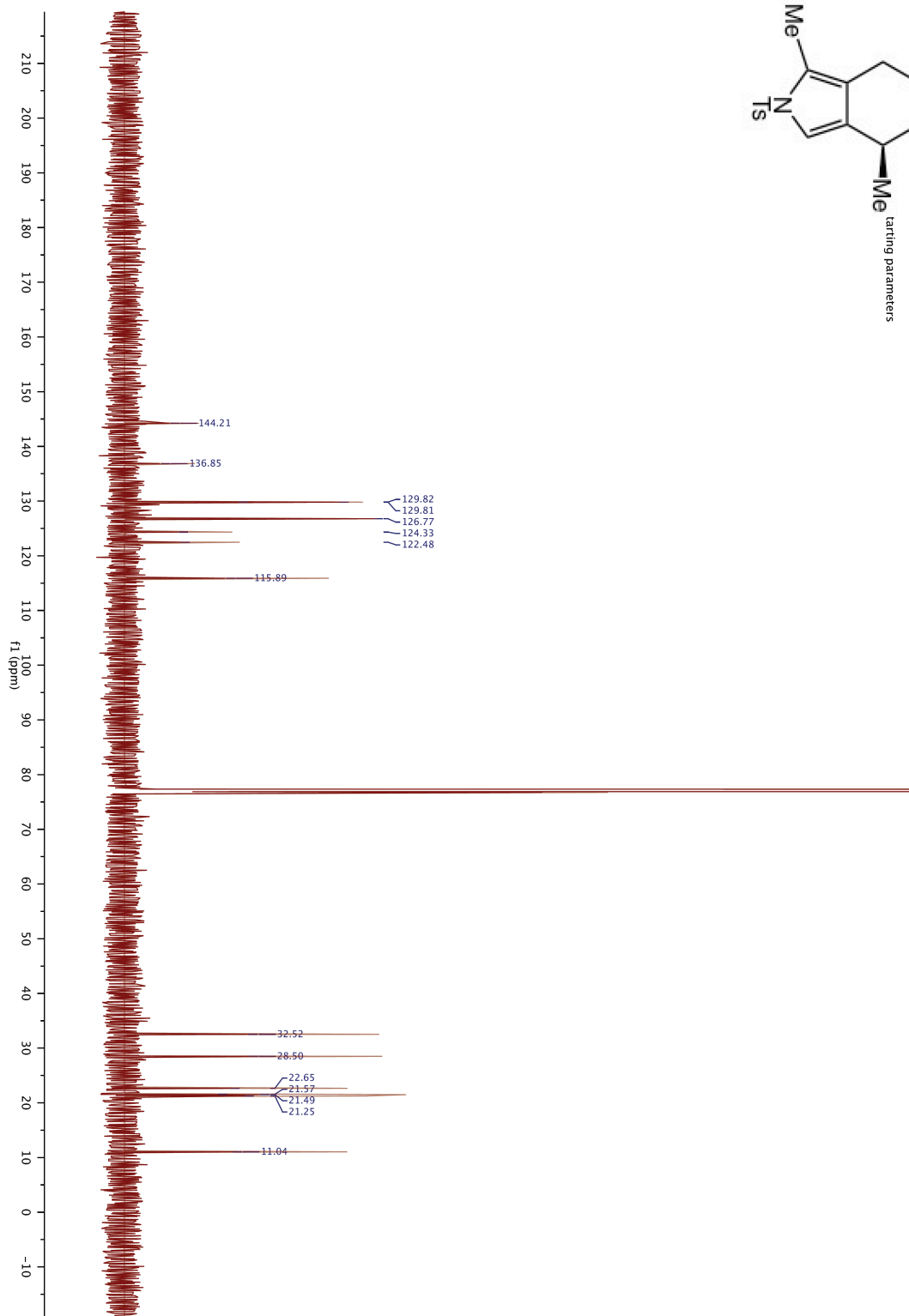
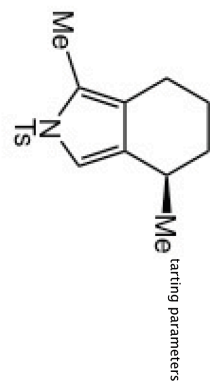
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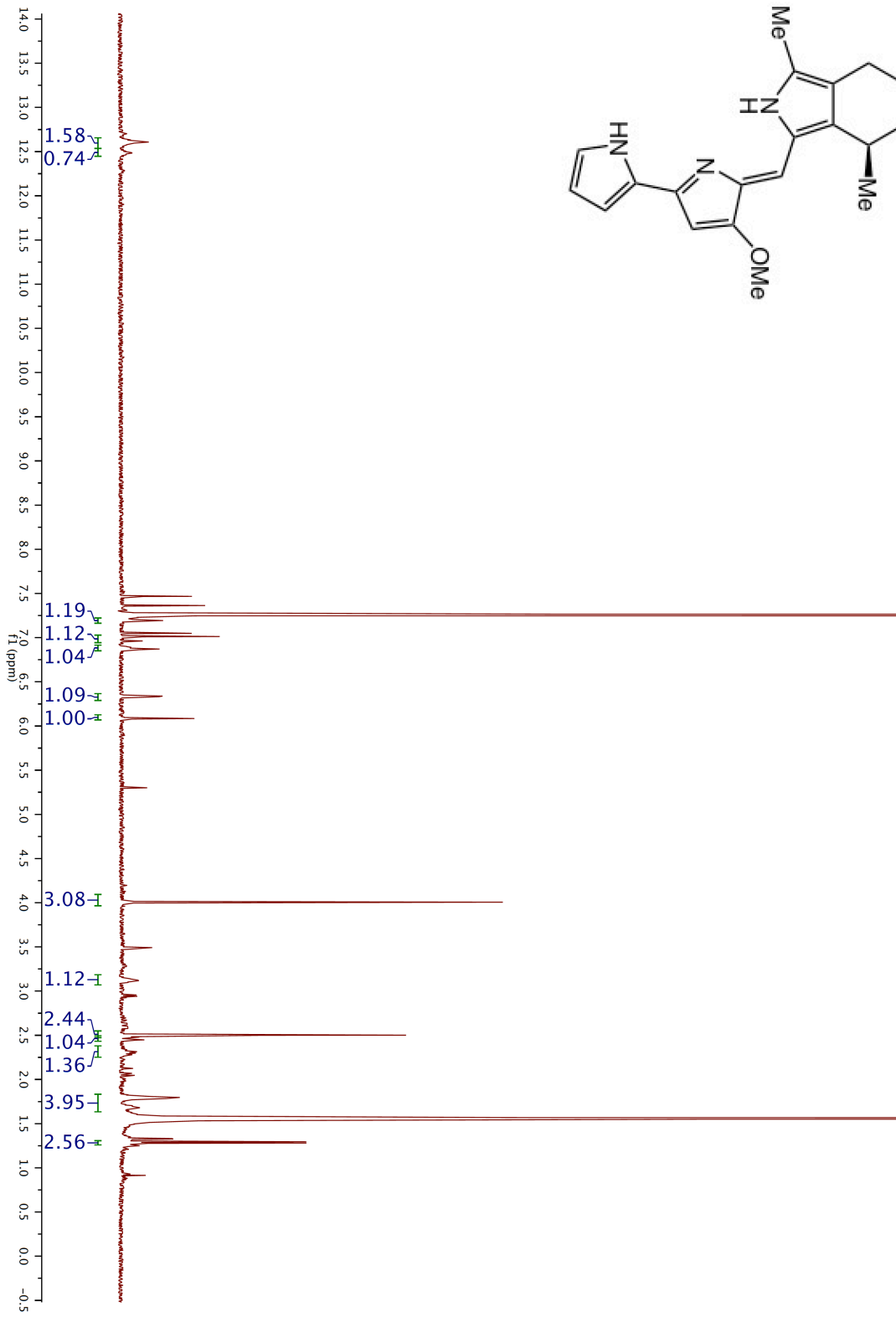
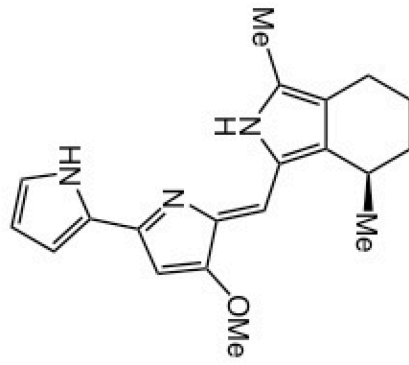


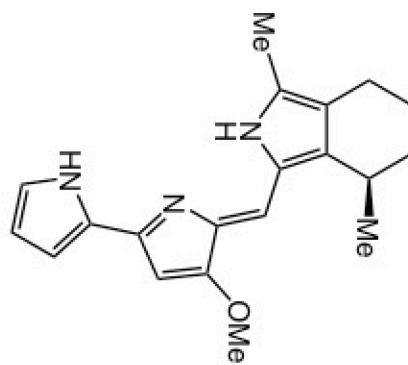












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