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Toward the Synthesis of the Magellanine- and
Lycopladine-type *Lycopodium* Alkaloids

By

Rebecca Anne Murphy

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
Professor F. Dean Toste
Professor Wenjun Zhang

Fall 2013

Abstract

Toward the Synthesis of the Magellanine- and Lycopladiene-type *Lycopodium* alkaloids

By

Rebecca Anne Murphy

Doctor of Philosophy in Chemistry

University of California, Berkeley

Professor Richmond Sarpong, Chair

This dissertation describes our strategy toward the synthesis of a variety of fawcettimine-type *Lycopodium* alkaloids. The first section focuses on the classification, structure, and historical significance of these natural products. This section also includes a proposal for their biosynthesis and a survey of the biological activities of the members of this class.

The second section describes our work toward magellanine, magellanine, and paniculatin. Two existing syntheses of these molecules are discussed, along with the strategy that we chose to employ in our work. We first pursue the synthesis of these natural products using a C4 pyridine C-H functionalization strategy that is based on precedent by the Fagnou and Echavarren groups. We then describe a C3 pyridine C-H functionalization approach that has more diverse methodological inspiration, although the original synthetic disconnection strategy derives from work done by the Jin Quan Yu group. Both of these synthetic endeavors are detailed herein.

Finally, the third section covers our efforts toward the synthesis of lycopladienes B, C, and D. We describe our “Heathcock-inspired” cascade approach toward the divergent synthesis of these three natural products. In this work, we have pursued the synthesis of a number of different substrates. We conclude with a summary of how this approach has evolved into a number of other projects within our group.

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I want to thank Dr. Jessica Douglas and Tiffany Pham for being such wonderful friends and running partners throughout graduate school. Additionally, I would like to thank the rest of my friends and family who have supported me. I would particularly like to thank my grandfather, Mr. Henry H. Meyer, who has taken a particular interest in my studies.

Chapter 1: *Lycopodium* Alkaloid Background

1.1 Classification and Historical Significance

Since their discovery, the *Lycopodium* alkaloids have been of great interest to the scientific community as compounds that are both structurally interesting and biologically active. This large class of compounds includes nearly 300 natural products isolated from over 50 of the 500 extant species in the *Lycopodium* genus of club mosses.¹ These club mosses are found all over the world, with various species in Northern Ontario, Canada;² the Guizhou province of China;³ the Blue Mountain range of Jamaica;⁴ the Eastern Transvaal region of South Africa;⁵ and many other locations.

The *Lycopodium* alkaloids were first known in the context of traditional Chinese folk medicine. *Qian Ceng Ta*, the Chinese herbal medicine made from the club moss *Huperzia serrata*, is used to treat a variety of maladies including contusions, schizophrenia, fever, inflammation, and more. The name *Qian Ceng Ta* translates to “thousand-laid pagodas” and is in reference to the tall leafy appearance of the plant. It is also called *Jin Bu Huan*, which means “more valuable than gold” – this time referring to its medicinal properties.⁶ In the late 19th century the *Lycopodium* alkaloids became of interest to isolation chemists. Lycopodine (**1.1**, see Figure 1) was the first member of this large class of natural products to be isolated and was described in 1881 by Bödeker.⁷ In the modern era, the organic chemistry community has become enamored with these compounds as structurally complex targets for total synthesis.

1.2 Structure, Biosynthesis and Biological Activity

From their beginnings in Chinese folk medicine to now, the *Lycopodium* alkaloids have retained their allure as medicinally useful molecules. Over the past few decades, many of these alkaloids have been and continue to be investigated as treatments for the symptoms of cognitive deterioration that is characteristic of a number of diseases, such as Alzheimer’s and Parkinson’s disease. Of particular interest is huperzine A (**1.2**, Figure 1), which was isolated from *Huperzia Serrata*.⁸ It has been found to be a potent, reversible inhibitor of acetylcholinesterase (AChE).⁹

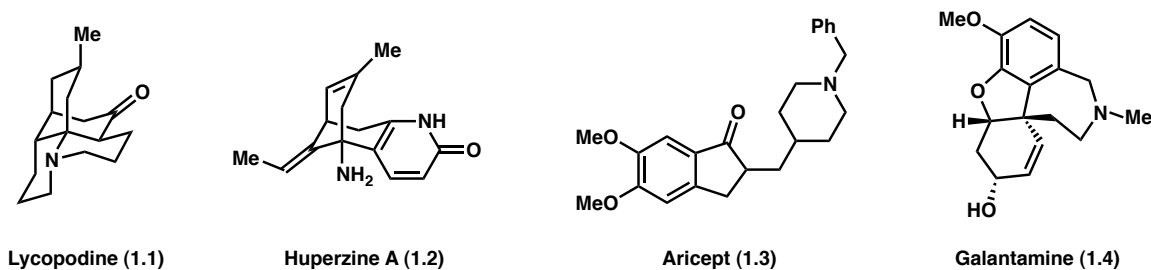
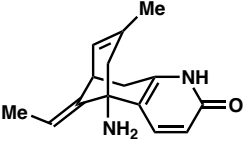
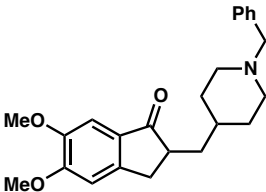
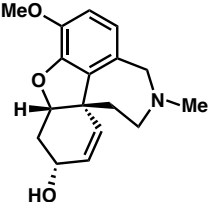


Figure 1. *Lycopodium* alkaloids and other AChE Inhibitors

This inhibition results in increased levels of the neurotransmitter acetylcholine and a corresponding improvement in cognitive ability. Notably, huperzine A has an IC₅₀ that compares favorably to other acetylcholinesterase inhibitors that are on the market as

treatments for Alzheimer's disease (Table 1).

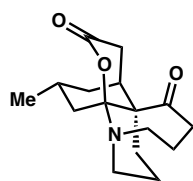
Table 1. Comparative Inhibition of AChE

		
Huperzine A (1.2)	Aricept (1.3)	Galantamine (1.4)

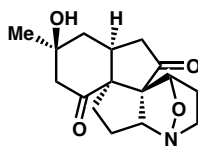
Compound	AChE IC ₅₀ (μM)
Huperzine A (1.2)	0.082
Aricept (1.3)	0.01
Galantamine (1.4)	1.99

Aricept (**1.3**), which is marketed by Pfizer, is the top-selling drug to combat Alzheimer's as of 2011 with an IC₅₀ of 0.01 μM. Another commercially available drug for the treatment of Alzheimer's disease is galantamine (**1.4**), which has an IC₅₀ of 1.99 μM. Comparatively, huperzine A has an IC₅₀ of 0.082 μM.⁶ Along with excellent biological activity, huperzine A has been shown to be devoid of unexpected toxicity and has a low rate of side effects.¹⁰

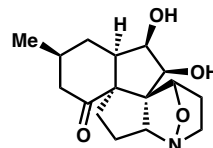
Despite these advantageous properties, the FDA has not approved huperzine A in the United States, although it is sold as a nonprescription dietary supplement. Likely, this is because the process for extracting huperzine A was published without patent, making it non-profitable for pharmaceutical companies to pursue clinical trials and obtain FDA approval. Huperzine A has been the subject of clinical trials and is used as a treatment for Alzheimer's disease in China, even though it has not been pursued with as much vigor elsewhere. In addition to patenting challenges, the lack of interest in commercializing huperzine A is also attributable to the fact that AChE inhibition likely only treats symptoms of cognitive decline, as opposed to eradicating the root cause of Alzheimer's disease. Much effort is now being devoted to developing treatments related to the other pathologies of Alzheimer's disease. Nonetheless, biological activity among various members of the *Lycopodium* alkaloids continues to attract attention to these molecules. For example, lycojapodine A (**1.5**, Figure 2) has anti-HIV-1 activity with an EC₅₀ value of 85 μg/mL (MTT method).^{3,11} Lycojaponicumins A-C (**1.6-1.8**) inhibit lipopolysaccharide (LSP)-induced pro-inflammatory factors in BV2 macrophages with IC₅₀ ranging from 43.61 to 64.97 μM,¹² and sieboldine A (**1.9**) is cytotoxic against murine lymphoma L1210 cells with an IC₅₀ of 5.1 μg/mL in vitro.¹³ Finally, complanadine A (**1.10**) has been shown to induce neurite extension through the secretion of neurotrophic growth factor from 1321N1 cells and promotion of neuronal differentiation of PC-12 cells.¹⁴



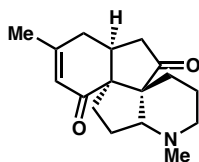
Lycojapodine A (1.5)
Anti-HIV-1 activity
 $EC_{50} = 85 \text{ mg/mL}$



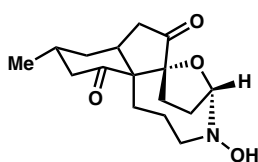
Lycojaponicumins A (1.6)
Inhibition of (LSP)-induced
pro-inflammatory factors
 $IC_{50} = 43.61 \text{ mM}$



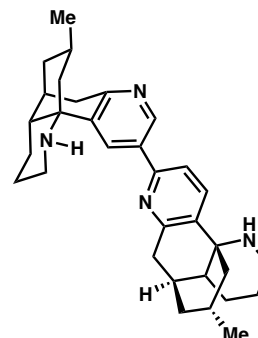
Lycojaponicumins B (1.7)
Inhibition of (LSP)-induced
pro-inflammatory factors
 $IC_{50} = 61.98 \text{ mM}$



Lycojaponicumins C (1.8)
Inhibition of (LSP)-induced
pro-inflammatory factors
 $IC_{50} = 64.97 \text{ mM}$



Sieboldine A (1.9)
Cytotoxic against murine
lymphoma L1210 cells
 $IC_{50} = 5.1 \text{ mg/mL}$



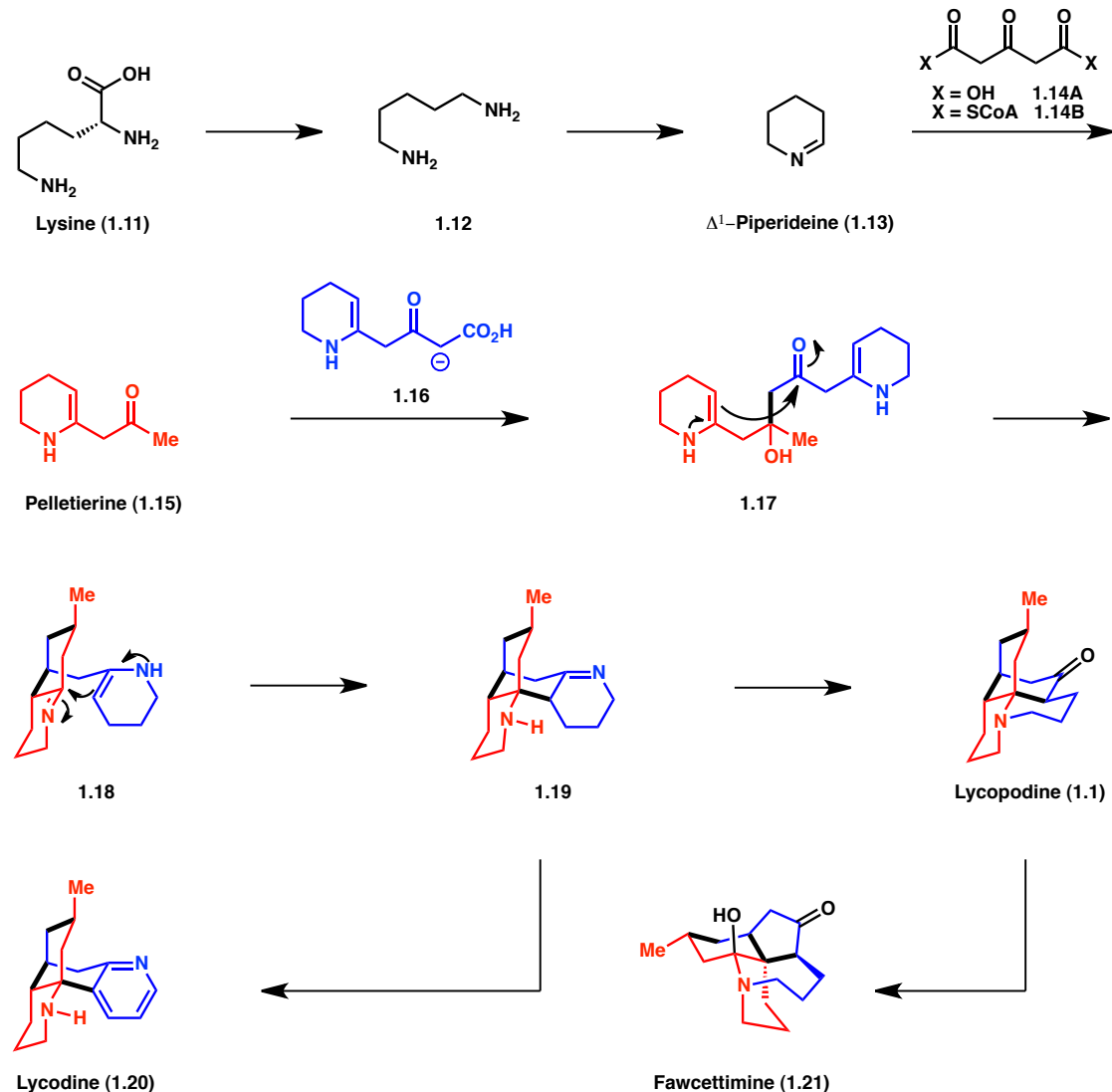
Complanadine A (1.10)
Induced secretion of neurotrophic
factors from 1321N1 cells

Figure 2. Varied biological activity of *Lycopodium* alkaloids

This fascinating array of biological activity as well as the complex and elegant structural features inherent in these molecules has continued to inspire many synthetic efforts for the preparation of *Lycopodium* alkaloid natural products.

As with many natural products, total synthesis is an important tool for the biological study of the *Lycopodium* alkaloids. This is especially important because the *Lycopodium* genus has a particularly low content of these alkaloids (0.1-0.3%).¹⁵ For example, to isolate 30 to 40 mg of lycojaponicumins A-C (**1.6-1.9**), 100 kg of the whole plant was required.¹² These club mosses are known to be very slow growing and difficult to cultivate. As a consequence, biosynthetic studies have been fairly limited. Initial feeding studies were conducted with radiolabeled lysine, within their natural environment in Ontario, Canada because of the aforementioned difficulty in cultivation.¹⁶ These studies provided support for the hypothesis that these alkaloids are derived from the amino acid lysine (**1.11**, Scheme 1).

Scheme 1. Proposed biosynthesis of the *Lycopodium* alkaloids



Lysine (**1.11**) can undergo a decarboxylation reaction to provide diamine **1.12**, which is oxidatively cyclized to provide Δ^1 -piperidine (**1.13**). Reaction with acetone dicarboxylic acid (**1.14A**) or its bis-coenzyme A ester (**1.14B**) and subsequent decarboxylation furnishes pelletierine (**1.15**). Pelletierine (**1.15**) can undergo an aldol reaction with **1.16** followed by decarboxylation to yield **1.17**. Addition of the enamine to the carbonyl group forges the six-membered ring of bicycle **1.18**. A second enamine addition provides **1.19**, which can be diversified into many *Lycopodium* alkaloids including lycodine (**1.20**), lycopodine (**1.1**) and fawcettimine (**1.21**).

While all *Lycopodium* alkaloids are thought to be biosynthetically derived from lysine, they have been divided into four classes in order to further characterize them based on structural features. These classes include the lycodine, lycopodine, fawcettimine, and miscellaneous classes (Figure 3). They are generally described by the

molecules they are named after: lycodine (**1.20**), lycopodine (**1.1**), and fawcettimine (**1.21**).

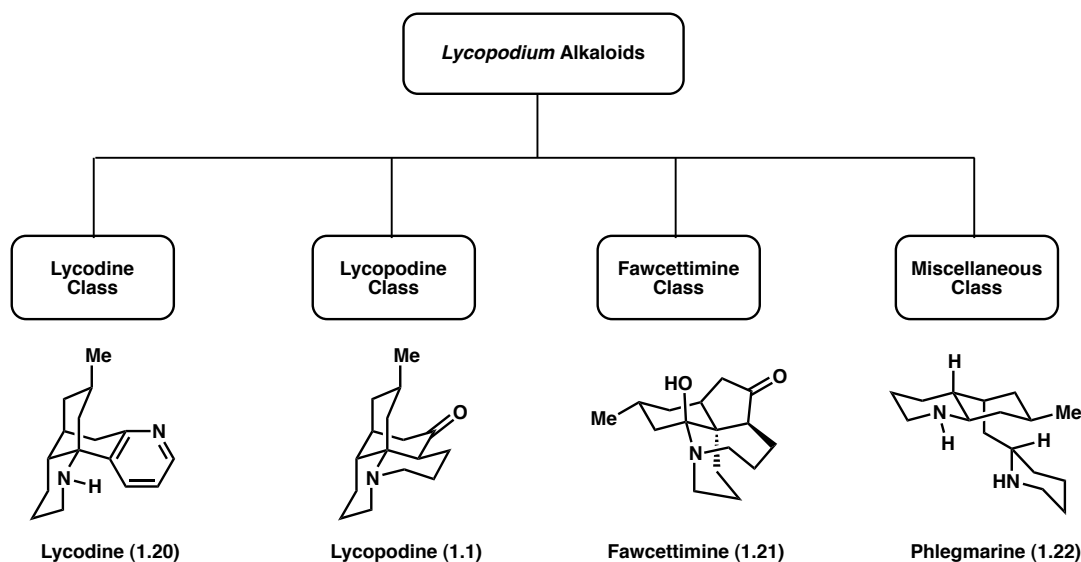


Figure 3. Classes of *Lycopodium* alkaloids

The miscellaneous class is commonly associated with phlegmarine (**1.22**), although it contains a wide range of structurally diverse alkaloids. The work described herein focuses on the fawcettimine class, which contains over 80 members. As exhibited by fawcettimine (**1.21**), this class contains a *cis*-fused 6–5 bicycle and an azonine ring with one quaternary center.

While there are fairly specific structural requirements for compounds to be classified as fawcettimine-type *Lycopodium* alkaloids, there is still quite a lot of variation across the class (Figure 4). Compounds such as 8-deoxyserratinine (**1.23**) and lycoflexine (**1.24**) possess an alternative C-N bond. Alopecuridine (**1.25**) has the same core as fawcettimine (**1.21**) with additional oxygenation, whereas lycoplamine D (**1.26**) and palhinine A (**1.27**) contain additional bridging rings. Magellaninone (**1.28**) contains a unique carbon-carbon bond splitting the nine-membered ring into a 6-5 system. In addition to this array of structural diversity, there is additional variability among the other members of the fawcettimine class.

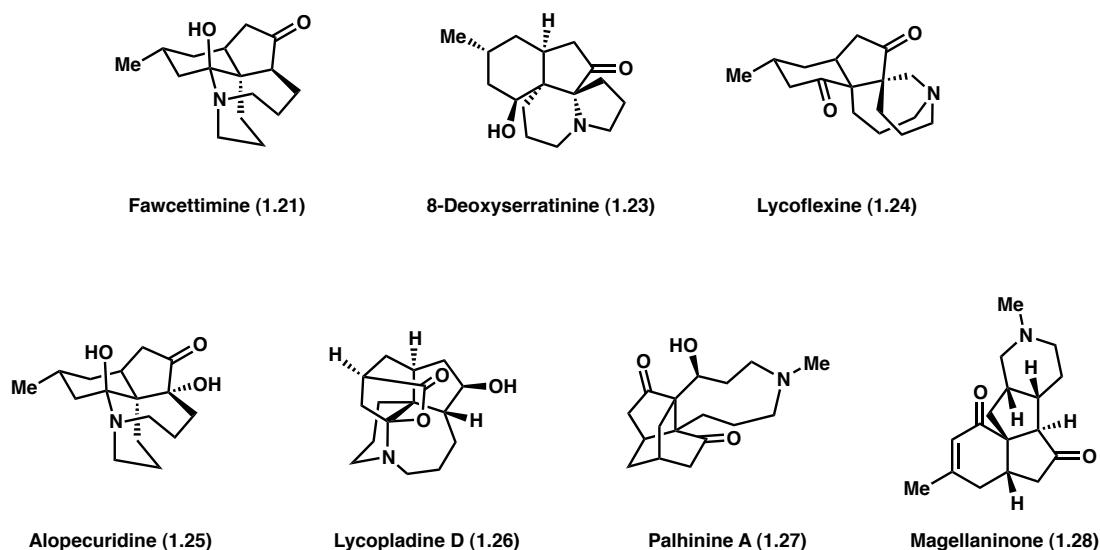


Figure 4. Various members of the fawcettimine class of *Lycopodium* alkaloids

The fawcettimine class of *Lycopodium* alkaloids boasts a number of compounds that our group has been drawn to as synthetic targets. Some of these molecules include magellaninone (**1.28**) and lycopladiene D (**1.26**). As described herein, we envisioned accessing these and other related natural products through the synthesis and elaboration of a number of 6-5 bicyclic systems.

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Chapter 2: Toward the Synthesis of the Magellaninone-type *Lycopodium* Alkaloids

2.1 Previous Approaches and Synthetic Design

The magellaninone-type *Lycopodium* alkaloids (**2.1-2.3**, Figure 1) have garnered significant attention from the synthetic organic chemistry community since their isolation in the late 1970's.¹ While they do not share the same biological activity as many other members of the *Lycopodium* alkaloids, they do possess a complex tetracyclic structure that has inspired many synthetic strategies and tactics toward their synthesis. Magellaninone (**2.1**), magellanine (**2.2**), and paniculatine (**2.3**) contain between five and seven stereocenters including one quaternary center as well as a basic tertiary amine. Additionally, they are quite unique when compared to other members of the fawcettimine sub-class of *Lycopodium* alkaloids by virtue of a very unusual carbon-carbon bond between C3 and C10 (see **2.1**). These natural products are the only three members of the *Lycopodium* alkaloids that contain this rare structural element.

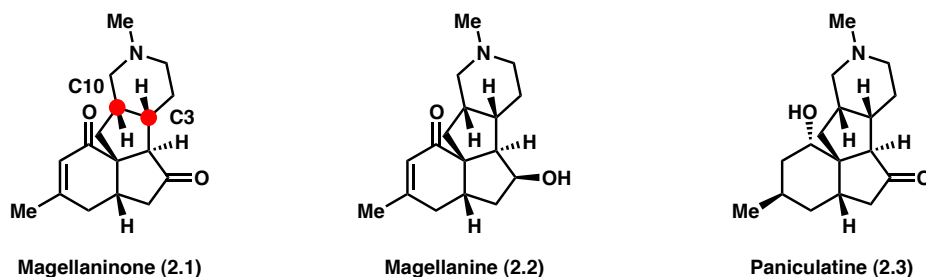
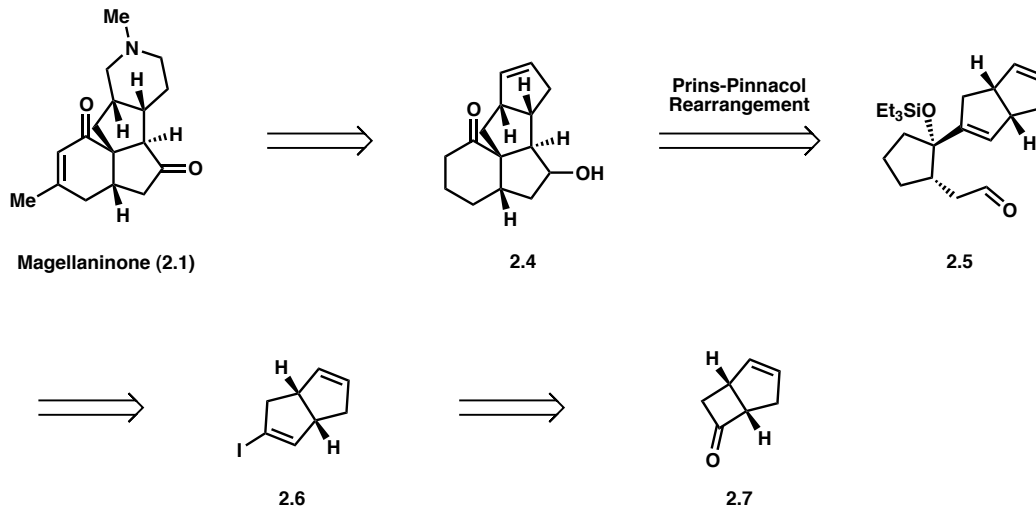


Figure 1. *Lycopodium* alkaloids magellaninone (**2.1**), magellanine (**2.2**) and paniculatine (**2.3**)

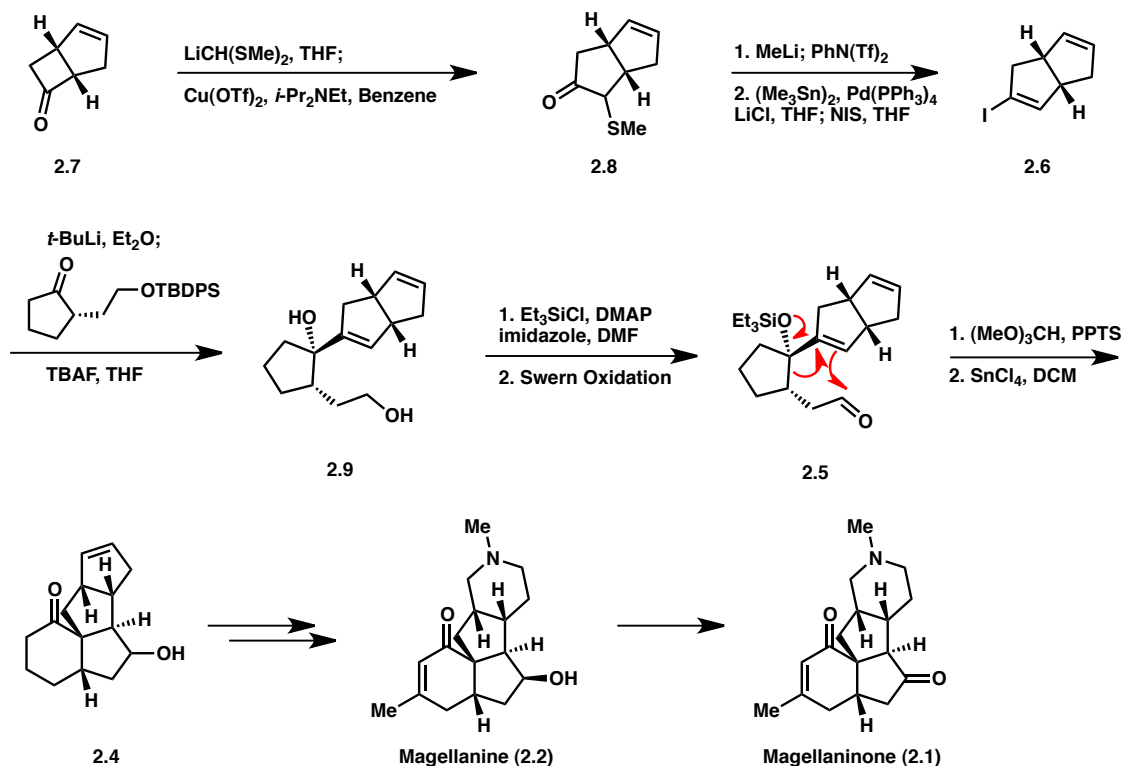
The first total synthesis of the magellaninone-type *Lycopodium* alkaloids was reported by the Overman group in 1993.² Their strategy to access magellanine was based on the use of a Prins-pinacol rearrangement to forge the polycyclic core of the natural product. Retrosynthetically, they envisioned that magellaninone (**2.1**) could be elaborated from tetracycle **2.4** (Scheme 1). This polycycle could arise from **2.5** using a Prins-pinacol rearrangement. Aldehyde **2.5** could form from the addition of lithiated **2.6** into an appropriate ketone and further functionalization. Finally, vinyl iodide **2.6** could be accessed from enantiopure ketone **2.7**.³

Scheme 1. Overman's retrosynthesis of magellanimone (**2.1**)



The Overman synthesis commenced with ketone **2.7** (Scheme 2), which was converted to a ring expanded α -sulfenyl ketone (**2.8**). Further functionalization of α -sulfenyl ketone **2.8** yielded vinyl triflate (not shown), which was then converted to vinyl iodide **2.6**. Vinyl iodide **2.6** was lithiated using *t*-BuLi and added into the requisite ketone, then treated with tetrabutylammonium fluoride to furnish **2.9**. The less tertiary hydroxyl group of diol **2.9** was selectively protected as the triethylsilyl ether, and the primary alcohol was oxidized to give aldehyde **2.5**. Aldehyde **2.5** was converted to the dimethyl acetal and then treated with tin tetrachloride to promote the key Prins-pinacol rearrangement to forge tetracycle **2.4**. This efficient transformation establishes five of the six stereocenters in a single step and proceeds in 57% yield. Tetracycle **2.4** was readily advanced to both magellanine (**2.2**) and magellanimone (**2.1**).

Scheme 2. Overman's forward synthesis to access magellanine (**2.2**) and magellaninone (**2.1**)

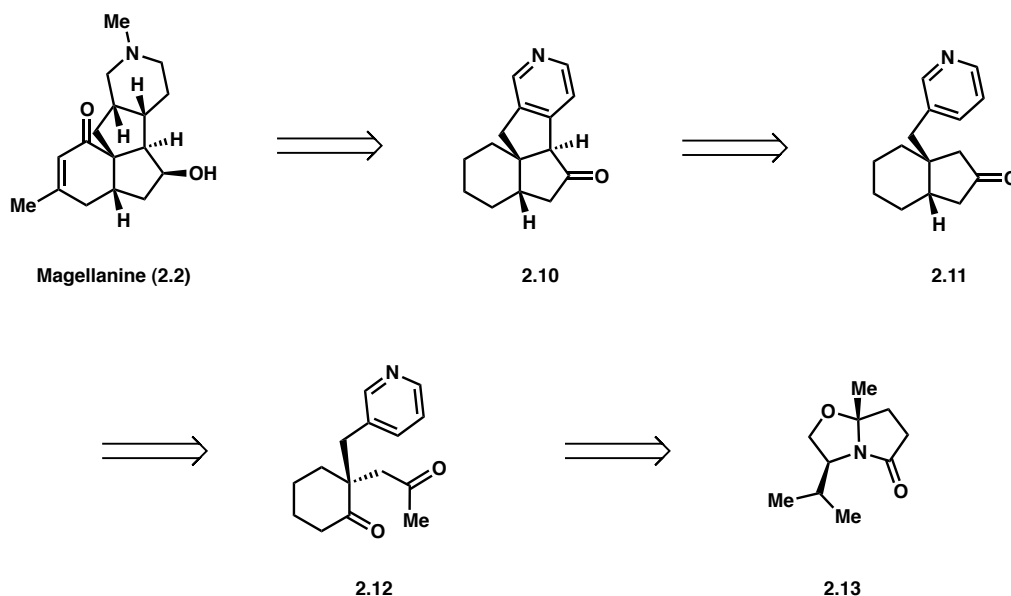


Overman's work, which constitutes the first total synthesis of the magellaninone-type *Lycopodium* alkaloids, proceeded in 25-26 steps from ketone **2.7**. The Overman group was able to make use of a particularly impressive Prins-pinacol rearrangement to form the carbon skeleton of the natural product. The basic tertiary amine and other functionality were then installed in the late stages of the synthesis.

Since Overman's initial publication, there have been a number of reports of varied syntheses of the magellaninone-type alkaloids.⁴ These works each display a unique key step to arrive at the core structure of these natural products. While they are quite diverse, they are similar in the fact that the basic tertiary amine is brought in during the late stages of the synthesis. Strategically, this might have been planned to avoid carrying through this challenging functional group from the outset of the synthesis. In 1995, the Meyers group reported the one approach that made use of an alternative disconnection strategy. They were able to introduce the amine in the early stages of the synthesis by masking the piperidine moiety present in the natural product as a pyridine.⁵

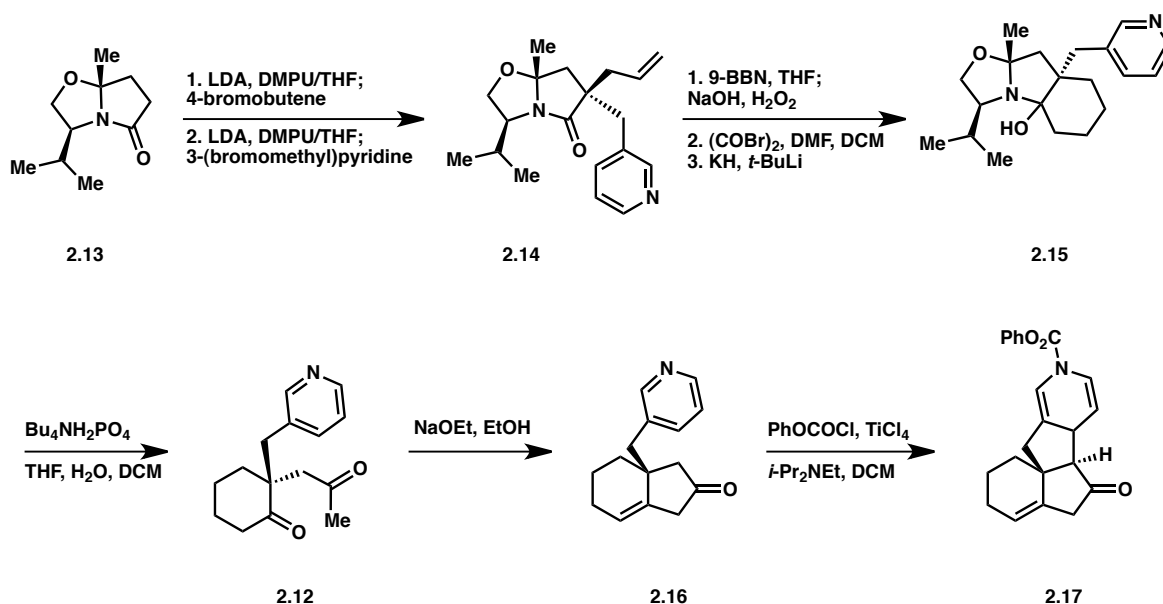
Meyers' strategy toward magellanine (**2.2**, Scheme 3) involved bringing the natural product back to pyridine containing tetracycle **2.10**. Masking of the piperidine moiety as a pyridine allows the tetracycle (**2.10**) to be forged using a nucleophilic addition into the 4-position of pyridine **2.11** in the forward sense. Bicycle **2.11** can be formed using an aldol condensation from diketone **2.12**, which can be derived from chiral bicyclic lactam **2.13**.

Scheme 3. Meyers' retrosynthesis of magellanine (**2.2**)



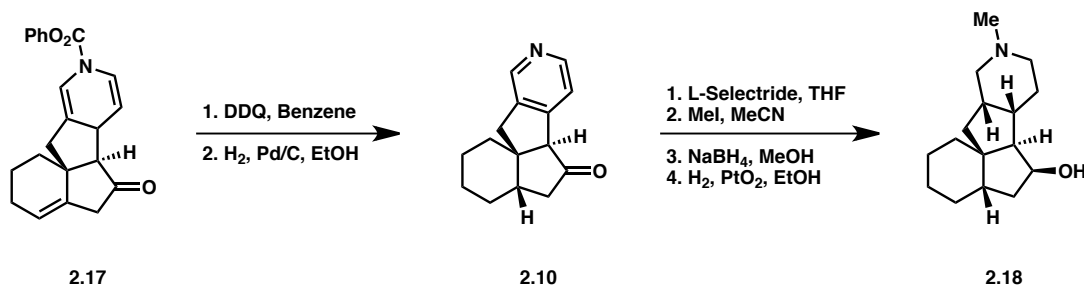
In the forward sense, chiral bicyclic lactam **2.13** (Scheme 4) was sequentially bis-alkylated to provide **2.14**. Alkene **2.14** was submitted to hydroboration using 9-BBN, converted to the corresponding bromide, and added into the carbonyl group after exposure to *tert*-butyl lithium, to provide **2.15**. Hydrolysis of tricycle **2.15** provides cyclohexanone **2.12**, which is used in an aldol reaction to furnish 6-5 bicycle **2.16**. Activation of the pyridine with phenyl chloroformate and formation of the titanium enolate promotes addition into the 4-position of the pyridine to forge the tetracyclic core of magellanine (**2.17**).

Scheme 4. Meyers' forward synthesis of the core of magellanine (**2.17**)



Exposure of tetracycle **2.17** to 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) regenerated the pyridine with *N*-deprotection and hydrogenation then reduced the carbon-carbon double bond in the six-membered ring to give **2.10**. Pyridine-containing tetracycle **2.10** was further manipulated by reduction of the carbonyl group, *N*-alkylation, and reduction of the resulting pyridinium. This furnished **2.18**, which only differs from magellanine in the functionality on the six-membered ring.

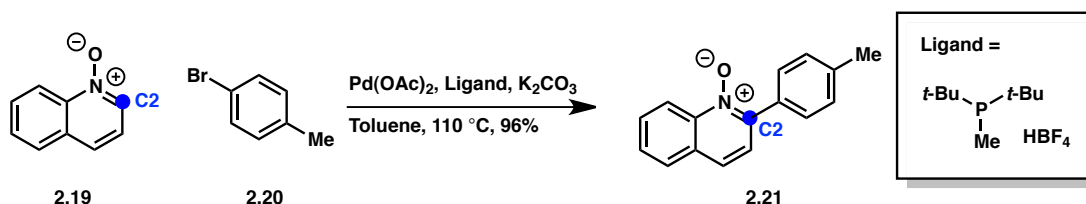
Scheme 5. Meyers' synthesis of piperidine **2.18**



The work by the Meyers' group described in Schemes 3–5 was highly influential in the way we thought about building these alkaloids. As a part of our approach, we also sought to mask the piperidine moiety in magellaninone as a pyridine, as we appreciated that this type of strategy allowed for unique synthetic disconnections. This strategy has also previously been made use of in our group by Kimberly Larson in her synthesis of G.B. 13.⁶ In our case, we believe that employing pyridine substrates in our synthetic design allows us to investigate a number of interesting key steps to form the tetracyclic core of the natural product. Along these lines, we were particularly inspired by the possibility of using C-H functionalization methodologies to form carbon-carbon bonds to the pyridine unit.

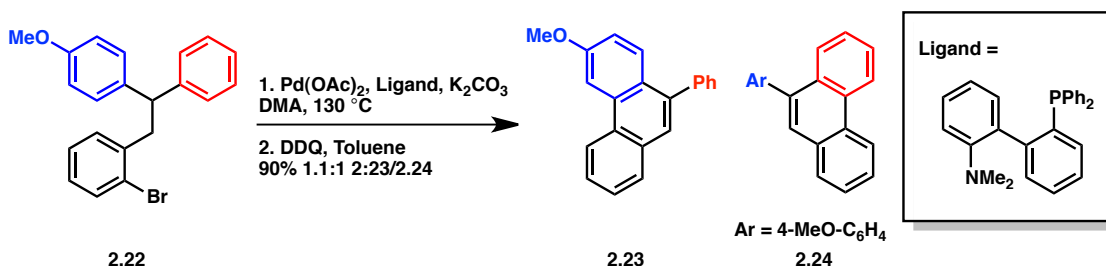
The C-H functionalization methodologies that we were most drawn to had been published by the Fagnou⁷ and Echavarren groups.⁸ In the early 2000's the Fagnou group developed a C-H functionalization method that allowed for arylation at the C2 position of heteroaromatic *N*-oxides under palladium catalyzed conditions (Scheme 6). The mechanism for this transformation is thought to proceed through a concerted-metalation-deprotonation (CMD) type transition state where the carbonate base, which may serve as a ligand on the palladium metal center, assists with the deprotonation. This mechanism explains the selectivity for the C2 position, as the proton which resides at this position is most acidic.

Scheme 6. Fagnou's C-H functionalization methodology



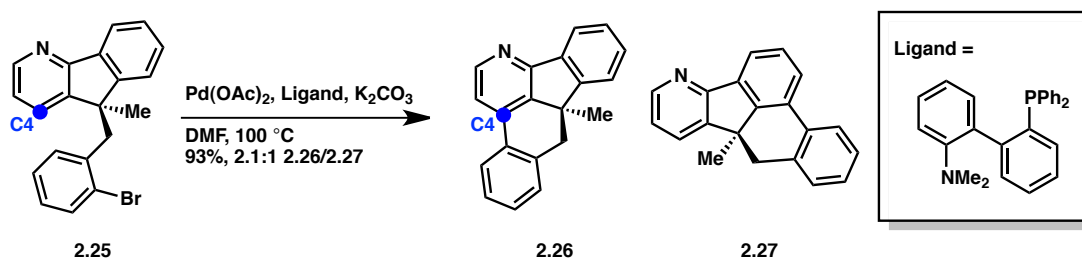
The Echavarren group developed a complimentary C-H functionalization methodology at the same time as the Fagnou group. They also performed a direct arylation reaction, but this time of aromatic and heteroaromatic systems as opposed to heteroaromatic *N*-oxides (Scheme 7). Exposure of **2.22** to similar palladium-catalyzed conditions to Fagnou's followed by oxidation furnishes a 1.1:1 mixture of **2.23**:**2.24** in a 90% yield. Similar to Fagnou's method, this transformation is thought to proceed through a CMD transition state.

Scheme 7. Echavarren's C-H functionalization methodology



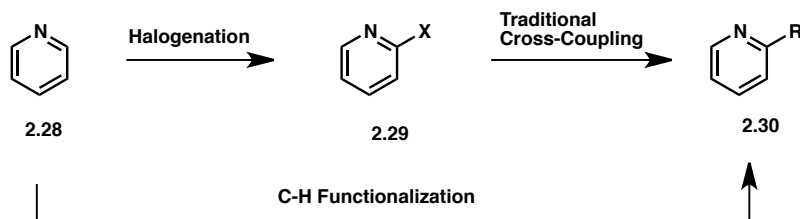
Also reported by Echavarren was a pyridine arylation at C4 (Scheme 8).⁸ This example showed that pyridine **2.25** was arylated to give a 2.1:1 ratio of **2.26**:**2.27**. This example is particularly interesting because, to our knowledge, this is the only example in the literature of direct arylation at the C4 position of pyridines.

Scheme 8. Echavarren's example of C4-arylation of pyridines



These methods by Fagnou and Echavarren are important advancements for the field of total synthesis. Direct C-H functionalization cuts out additional steps that would be required for carbon-carbon bond formation. More traditional methods for arylation of a pyridine system (**2.28**, Scheme 9) would require activation (e.g., halogenation) at the desired position on the heteroaromatic system to give **2.29**, followed by traditional cross-coupling methods to furnish the arylated product (**2.30**).

Scheme 9. C-H functionalization vs. traditional cross-coupling

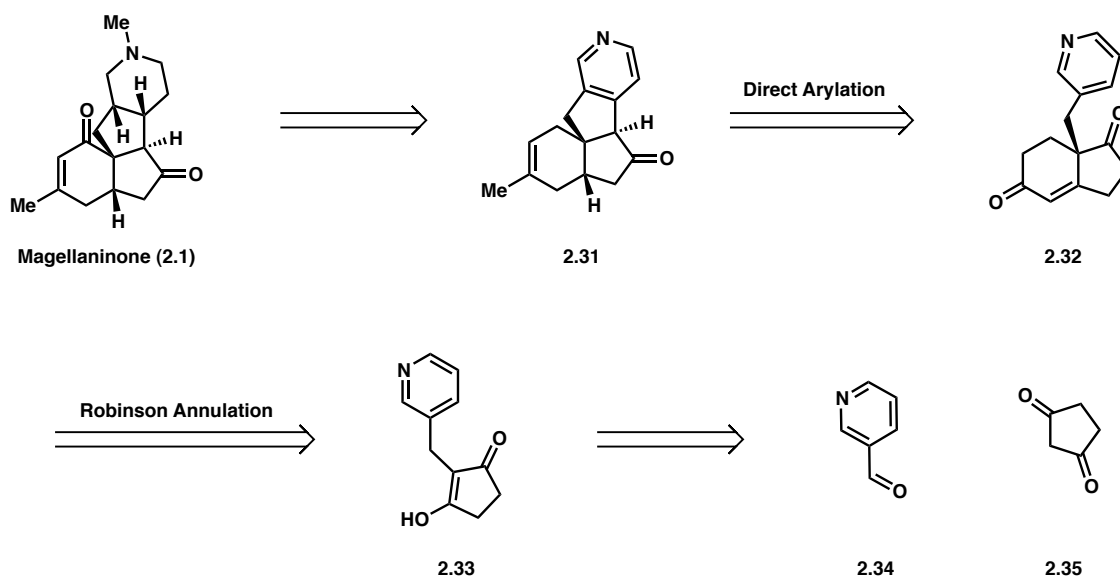


Because of the above-mentioned step-economy, C-H functionalization produces less chemical waste, making it very environmentally friendly. We recognized that the mild and direct nature of the Fagnou and Echavarren methods could potentially enable the type of retrosynthetic disconnections that we sought to utilize to make magellanicone.

2.2 C-4 Pyridine C-H Functionalization Approach

We envisioned being able to obtain magellanicone (2.1, Scheme 10) from pyridine containing tetracycle 2.31. Tetracycle 2.31 could be formed from a derivative of 6-5 bicycle 2.32 using a direct arylation reaction to form the carbon-carbon bond to the C4 position of the pyridine. This would make use of the above discussed methodologies published by the Fagnou and Echavarren groups.^{7,8} Bicycle 2.32 could be formed from pyridinedione 2.33 and methyl vinyl ketone using an asymmetric Robinson annulation. In turn, pyridine dione 2.33 could arise from 3-formyl pyridine (2.34) and 1,3-cyclopentanedione (2.35) via a Knoevenagel reaction. We particularly liked this sequence to arrive at bicycle 2.32 because a similar sequence has been previously used by Brittain and coworkers to make a number of Hajos-Parrish ketone derivatives, although none with a heteroaromatic moiety.⁹

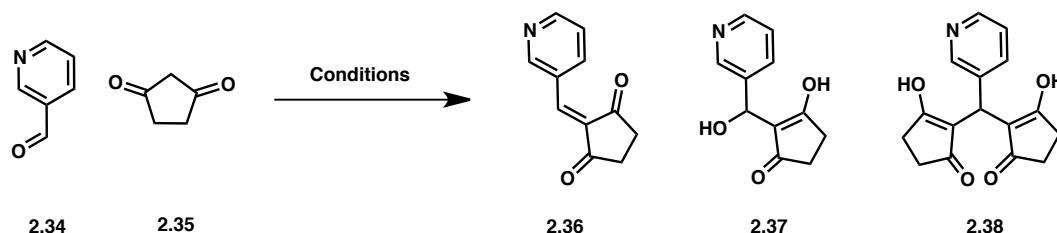
Scheme 10. Retrosynthetic analysis of magellanicone (2.1)



2.2.1 Synthesis of Unsubstituted Pyridine Substrates

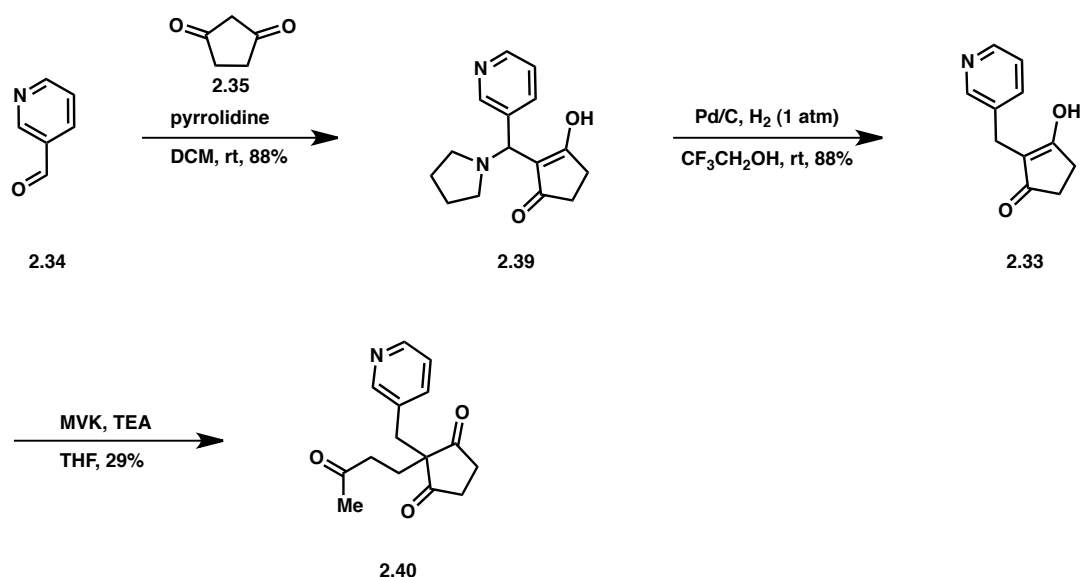
Our synthetic efforts began with an investigation into the synthesis of pyridine **2.36** (Scheme 11). We attempted to effect a Knoevenagel reaction between 3-formylpyridine (**2.34**) and 1,3-cyclopentanedione (**2.35**) to give benzylidene **2.36**. Under a variety of conditions, only a minimal amount of **2.36** was observed. Instead of the desired product (i.e., **2.36**) a variety of other products were observed where nucleophiles present in the reaction mixture add into the β -position of enone **2.36**. Some of the isolated products included alcohol **2.37** and pyridine **2.38**. On the basis of these results and previous literature examples of Knoevenagel couplings using 1,3-cyclopentanedione,¹⁰ it became apparent that benzylidene **2.36** would be too reactive as a Michael acceptor to be isolable.

Scheme 11. Knoevenagel reaction between pyridine **2.34** and diketone **2.35**



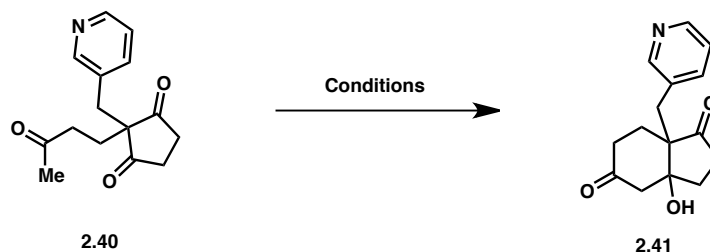
Knowing that 1,4 addition of external nucleophiles to the desired enone (**2.36**) was such a facile pathway led us to investigate a Mannich reaction as an alternative to the Knoevenagel reaction. We were pleased to see that Mannich reaction of 3-formylpyridine (**2.34**) with 1,3-cyclopentanedione (**2.35**) and pyrrolidine furnished **2.39** in good yield (Scheme 12). Hydrogenolysis of the pyrrolidine moiety then yields the desired pyridinedione (**2.33**) in 88% yield. While yields were good for this two-step sequence, the isolation of these intermediates (**2.39** and **2.33**) was quite challenging because both are very polar. Nonetheless, we were able to perform a Michael reaction from pyridinedione **2.33** to furnish triketone **2.40**, albeit in low yield (29%).

Scheme 12. Synthesis of triketone **2.40**



From triketone **2.40**, we then hoped to perform an asymmetric aldol reaction to provide 6-5 bicycle **2.41** (Table 1). Unfortunately, we still had issues with the polarity of triketone **2.40**. While triketone **2.40** is readily soluble in DCM, (*S*)-proline is not, as such reaction over 3 days at room temperature returned starting material (entry 1). Reaction with (*S*)-proline in other solvents only furnished decomposition (entries 2-3). Both basic (entry 4) and acidic (entry 5) conditions similarly lead to decomposition. Using pyrrolidine as a catalyst in chloroform over a period of 8 days gives trace amounts of desired bicycle **2.41**. We were excited to see that we could achieve the desired transformation even though it was now conducted to give racemic product.

Table 1. Aldol reaction to furnish bicycle **2.41**

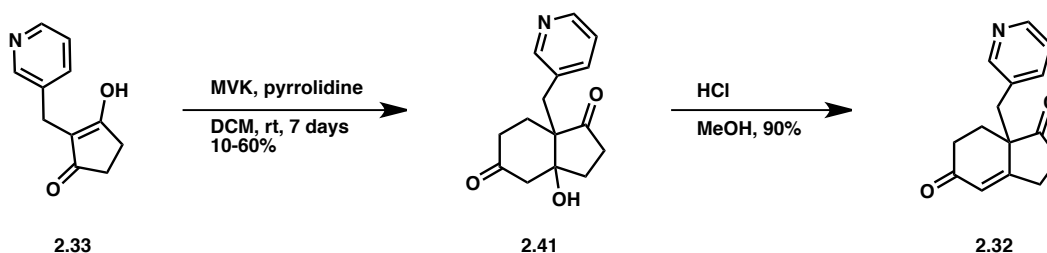


Entry	Additive	Solvent	Temperature (°C)	Time	Result
1	(<i>S</i>)-Proline	DCM	25	3 d	Starting Material
2	(<i>S</i>)-Proline, D-CSA	Acetonitrile	30	10 h	Decomposition
3	(<i>S</i>)-Proline	DMF	25	7 d	Decomposition
4	5% KOH	Methanol	65	10 h	Decomposition
5	TsOH, 4 Å MS	Toluene	110	10 h	Decomposition
6	Pyrrolidine	Chloroform	25	8 d	Trace 2.41

Upon further experimentation, we were very excited to see that the one-step Robinson annulation was more effective (Scheme 13). Thus, pyridinedione **2.33** could be

exposed to methylvinylketone and pyrrolidine in DCM for a period of 7 days to give bicycle **2.41**. The reaction was run in the dark over the course of 7 days after rigorous freeze-pump-thaw cycles. Even with these precautions, the yield of this reaction was highly variable and the product formation was accompanied by a large amount of decomposition. Tertiary alcohol **2.41** could be dehydrated under acidic conditions to provide enone **2.32** in 90% yield.

Scheme 13. Synthesis of 6-5 bicycle **2.32**

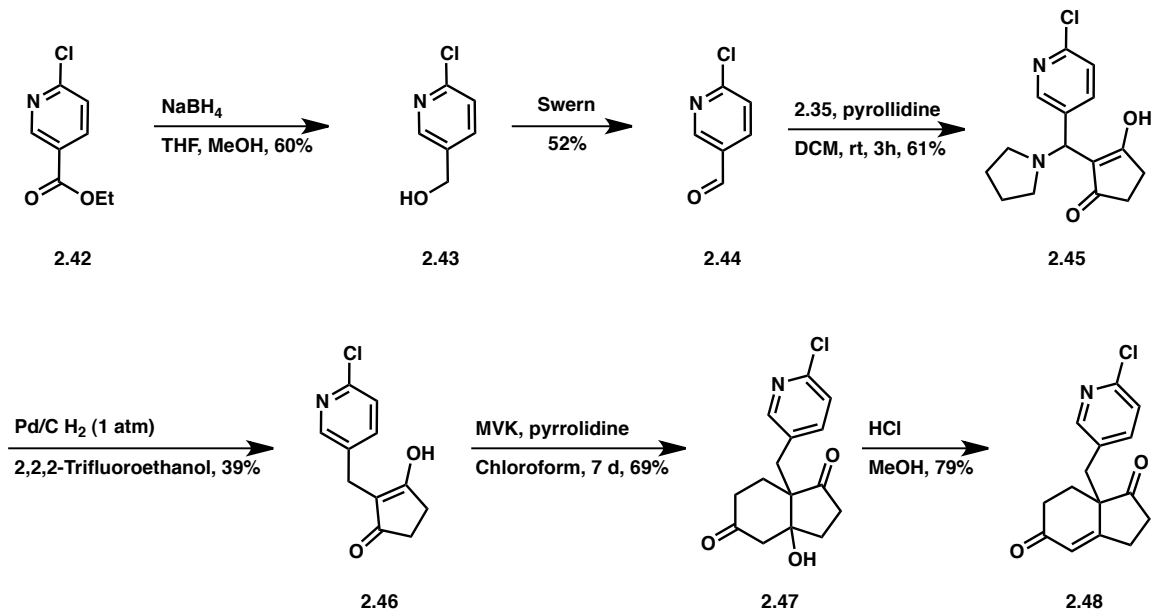


Ultimately, the low yield of the Robinson annulation combined with poor scalability led us to investigate alternative substrates that were less polar than pyridinedione **2.33**. We hoped that this would make the intermediates easier to isolate and more easily co-solubilized with (*S*)-proline in order to effect an asymmetric Robinson annulation, thus rendering our synthesis enantioselective. We sought to do this by mitigation of the basicity of the pyridine nitrogen by taking advantage of substitution on the pyridine.

2.2.2 Synthesis of Substituted Pyridine Derivatives

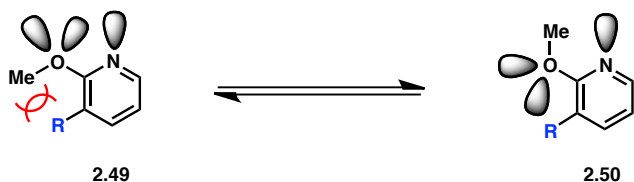
In order to mitigate the basicity of the pyridine nitrogen, we prepared a number of substrates with an electron withdrawing substituent alpha to the nitrogen. The first substituent that we chose to investigate is a 2-chloro group (Scheme 14). Commercially available ester **2.42** was reduced to alcohol **2.43** using sodium borohydride and then oxidized to the corresponding aldehyde (**2.44**). Mannich reaction furnishes **2.45**, which is then reduced to provide pyridinedione **2.46** in 24% yield over 2 steps. While these two steps are fairly low yielding, the Robinson annulation gratifyingly proceeds in an elevated 69% yield to furnish bicycle **2.47**, although it is still performed racemically with pyrrolidine. Dehydration then provides enone **2.48**. From aldehyde **2.43**, enone **2.48** is accessible in 13% yield over 4 steps. This is relative to 7-41% yield over 4 steps for the unsubstituted pyridine (see **2.32**, Scheme 13). While the chloropyridine derivatives were less polar and easier to isolate as compared to the unsubstituted derivatives, the sequence was still not scalable, so we chose to investigate other alternatives.

Scheme 14. Synthesis of 2-chloropyridine derivative **2.48**



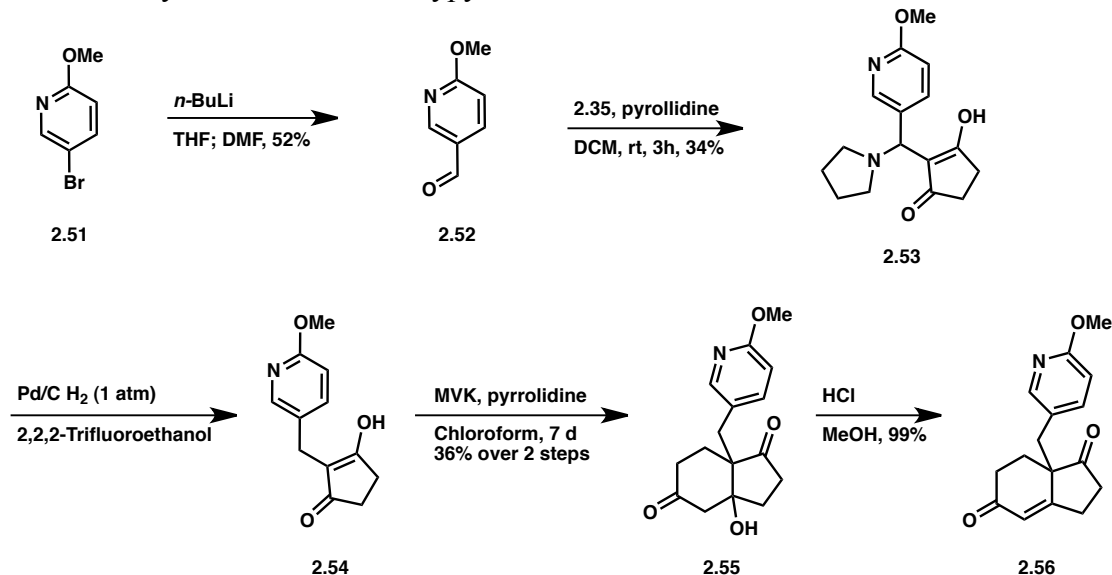
The next substrate that we investigated was a 2-methoxypyridine derivative. One might expect a methoxy-substituent to serve as an electron-releasing group by donation into the pyridine ring through resonance, but in fact, the methoxy group acts as an electron-withdrawing group. Methoxypyridines have an additional steric effect that further reduces the basicity of the nitrogen (Scheme 15). The methyl group can exist in one of two conformations, one where the methyl group is not sterically blocking the lone pair on the nitrogen (**2.49**) and one where it is (**2.50**). The conformer where the methyl group is blocking the lone pair (**2.50**) is favored. This is due to dipole minimization, as well as avoidance of pseudo- $A_{1,3}$ strain. When $R = H$, **2.50** is favored over **2.49** by 2.85 kcal/mol. When the bulk of the R-group is increased to $R = \text{Me}$, **2.50** is favored over **2.49** by 11.23 kcal/mol. This steric effect has been described by Corey and Chein in the context of other methoxy-substituted heteroaromatic systems.¹¹

Scheme 15. Conformational equilibrium of 2-methoxypyridines



Toward our goal of accessing methoxy-substituted pyridine derivatives, bromopyridine **2.51** can undergo formylation to give aldehyde **2.52** (Scheme 16). Mannich reaction of aldehyde **2.52** with 1,3-cyclopentanedione (**2.35**) and pyrrolidine proceeds in a low 34% yield. Reduction of **2.53** and subsequent Robinson annulation provide 6-5 bicycle **2.55** in 36% yield over 2 steps. Alcohol **2.55** is then dehydrated under acidic conditions to furnish racemic **2.56**.

Scheme 16. Synthesis of 2-methoxypyridine derivative **2.56**

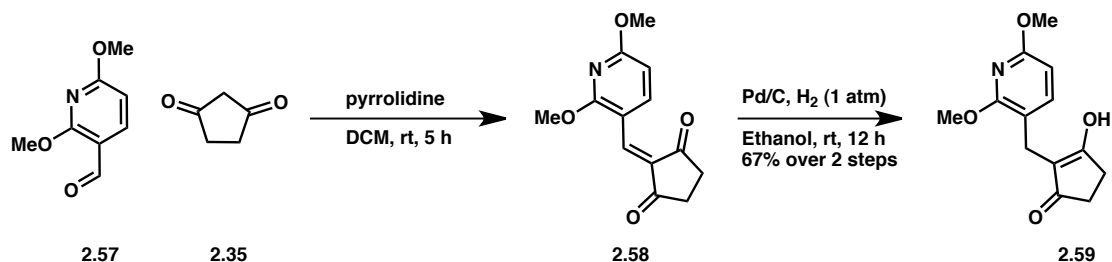


Once again, while these intermediates are easier to isolate than the unsubstituted pyridine variant (see Scheme 13), the yields are quite low – bicycle **2.56** is accessible in 12% over 4 steps from aldehyde **2.52**. Additionally, the sequence did not scale well and the Robinson annulation proceeded in racemic fashion. This led us to more drastically modify the electronics of the pyridine system through multiple substitutions on the ring.

2.2.3 Synthesis of Dimethoxypyridine Substrates

We were drawn to dimethoxypyridines because of the dual steric and electronic basicity-reducing effects described above for methoxy substituents. Additionally, 2,6-dimethoxypyridine substrates are commercially available. Interestingly, exposure of 2,6-dimethoxy-3-formyl pyridine (**2.57**) to Mannich reaction conditions that we had used previously did not provide the expected Mannich adduct, but instead provided enone **2.58** (Scheme 17). Enone **2.58** is formally a Knoevenagel product that is furnished upon loss of pyrrolidine. The isolation of **2.58** shows us that this system is electronically different from previous systems (see **2.39**, Scheme 12; **2.45**, Scheme 14; **2.53**, Scheme 16), as it is not as potent of a Michael acceptor. Reduction of the carbon-carbon double bond in **2.58** provides pyridinedione **2.59** in 67% yield over two steps.

Scheme 17. Synthesis of pyridinedione **2.59**



We were pleased to see that pyridinedione **2.59** was much less polar compared to previously synthesized substrates (see **2.33**, Scheme 13; **2.46**, Scheme 14; **2.54**, Scheme 16). This allowed us to optimize an asymmetric variant of the desired Robinson annulation, as pyridinedione **2.59** is now easily co-solublizes with (*S*)-proline (Table 2). Using (*S*)-proline as a catalyst in DMSO, bicycle **2.60** was isolated in 55% yield, along with 21% of enone **2.61** (entry 1). Reducing the catalyst loading to 30 mol% led to a yield of 22% of **2.60** (entry 2). Changing the solvent to dioxane reduces the formation of the product and provided 85% recovered starting material (entry 3). The use of dimethyl tetrahydrofuran as the solvent provided 88% of triketone **2.62** (entry 4). We were delighted to observe that using acetonitrile as the solvent, we were able to isolate the desired 6,5-bicycle **2.60** in 69% yield (entry 5). Further, the reaction could be run on multiple gram scale and afforded the desired 6-5 bicycle in 87% enantioexcess.

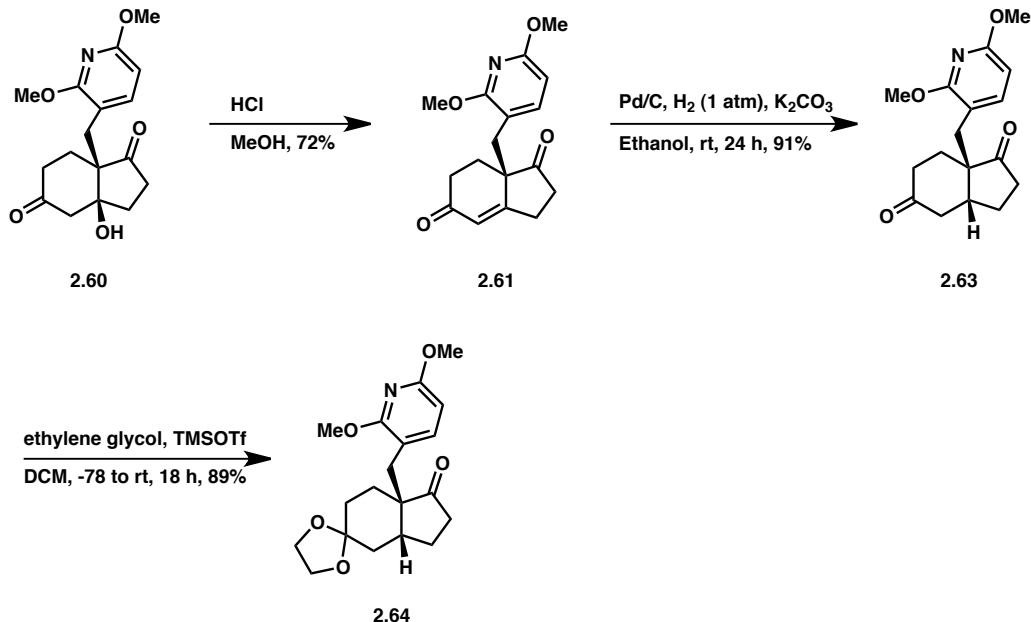
Table 2. Optimization of asymmetric Robinson annulation

Reaction scheme: **2.59** (a pyridine ring with a methoxy group at position 6 and a 2-hydroxy-2-methyl-1,3-dioxol-5-yl group at position 3) reacts with (*S*)-Proline and MVK (2 equiv) in various solvents at room temperature for 7 days to yield **2.60** (a bicyclic ketone with a hydroxyl group), **2.61** (an enone), and **2.62** (a triketone).

Entry	Equiv (<i>S</i>)-Proline	Solvent	Result
1	1	DMSO	55% 2.60 /21% 2.61
2	0.3	DMSO	22% 2.60
3	0.3	Dioxane	Starting Material
4	0.3	Dimethyl THF	88% 2.62
5	0.3	Acetonitrile	69% 2.60 (87% ee)

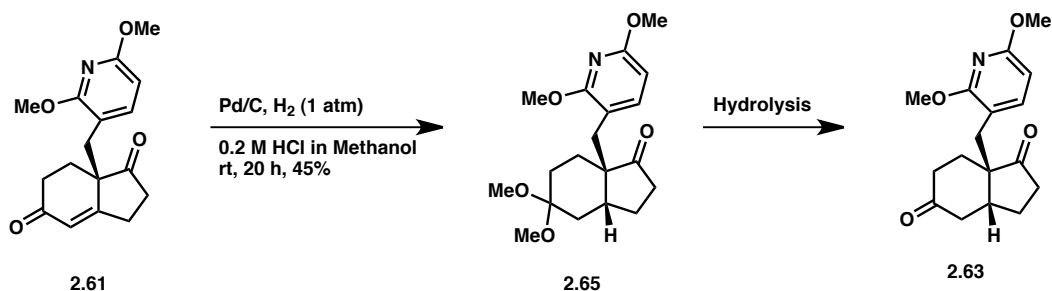
We were then able to dehydrate tertiary alcohol **2.60** to provide enone **2.61** in 72% yield (Scheme 18). Reduction of the carbon-carbon double bond in **2.61** then cleanly furnished bicycle **2.63**. Selective protection of the carbonyl group in the six-membered ring furnished ketal **2.64**.

Scheme 18. Synthesis of ketal 2.64



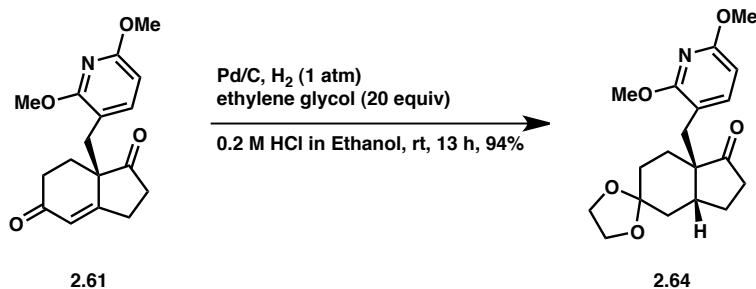
In the course of optimizing the reduction (i.e., **2.61** to **2.63**, Scheme 18) we observed an interesting result. Under reductive conditions in methanol, dimethyl ketal **2.65** was observed as the major product (Scheme 19). This type of ketal formation during the hydrogenation of cyclic α , β -unsaturated ketones has been previously documented.¹² We observed that dimethyl ketal **2.65** readily hydrolyzes to provide ketone **2.63** under a variety of conditions. Although dimethyl ketal **2.65** was not useful for our synthesis due to its instability, we recognized the opportunity to perform a one-pot reduction/ketal formation with an alternative, less hydrolyzable alcohol, such as ethylene glycol.

Scheme 19. Observed reactivity under reductive conditions



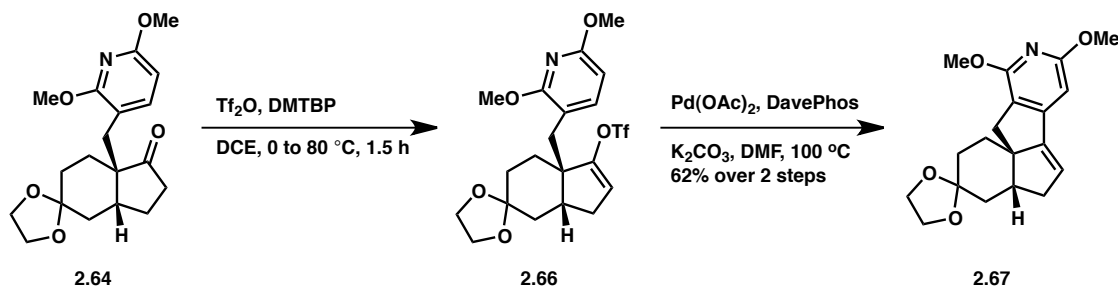
Toward this goal, we began to screen conditions to enable the formation of cyclic ketal **2.64** (Scheme 20). We hoped that by adding a large excess of ethylene glycol, we could promote the formation of **2.64** over **2.65**. When the reaction was run in methanol, we obtained an inseparable mixture of **2.64** and **2.65**. When we used ethanol instead, we were able to selectively obtain ketal **2.64** in 94% yield.

Scheme 20. Formation of ketal **2.64**



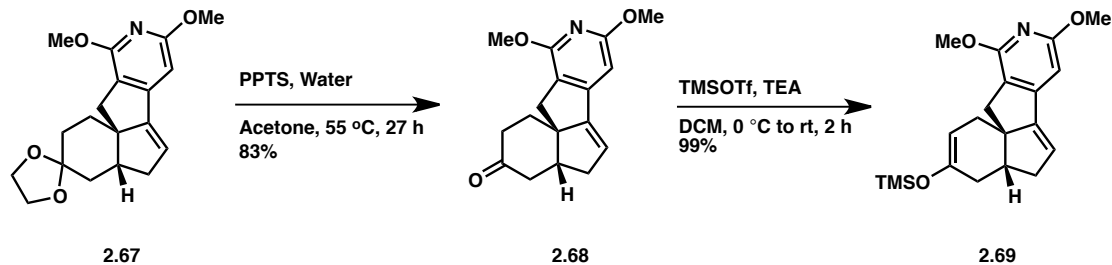
From ketone **2.64** (Scheme 21), we are able to effect vinyl triflate formation under soft enolization conditions, to furnish vinyl triflate **2.66**. This material is brought on crude and was subjected to Fagnou/Echavarren-type direct arylation conditions. We were delighted to observe that tetracycle **2.67** could be formed in 62% yield over two steps, with minimal optimization needed for the C-H functionalization step. This step is notable because it is, to our knowledge, the second example of selective C-H functionalization at the C4 position over the C2 position of pyridine substrates. The selectivity in this step is enabled by the use of the methoxy-group substitution on the pyridine. Without these blocking groups, we would expect to obtain a mixture of competing products that had been functionalized at the C2 position of the pyridine.

Scheme 21. Formation of tetracycle **2.67**



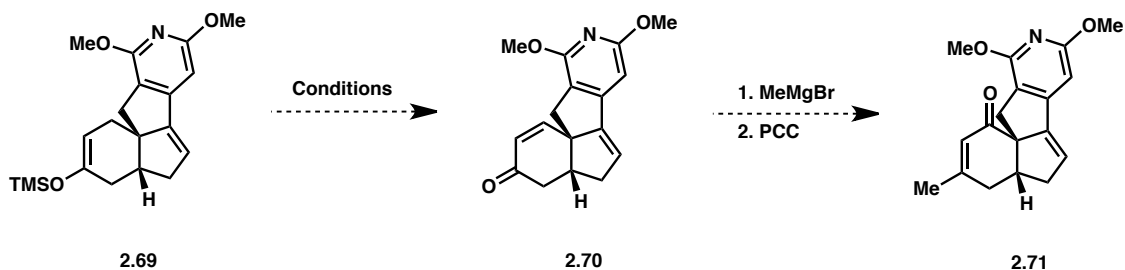
From tetracycle **2.67**, we sought to functionalize the southwestern portion of the molecule before cleaving the methyl groups and reducing the pyridine. We were able to cleave the ketal protecting group to provide ketone **2.68** in 83% yield (Scheme 22). Ketone **2.68** was readily advanced to silyl enol ether **2.69** under soft enolization conditions.

Scheme 22. Synthesis of silyl enol ether **2.69**



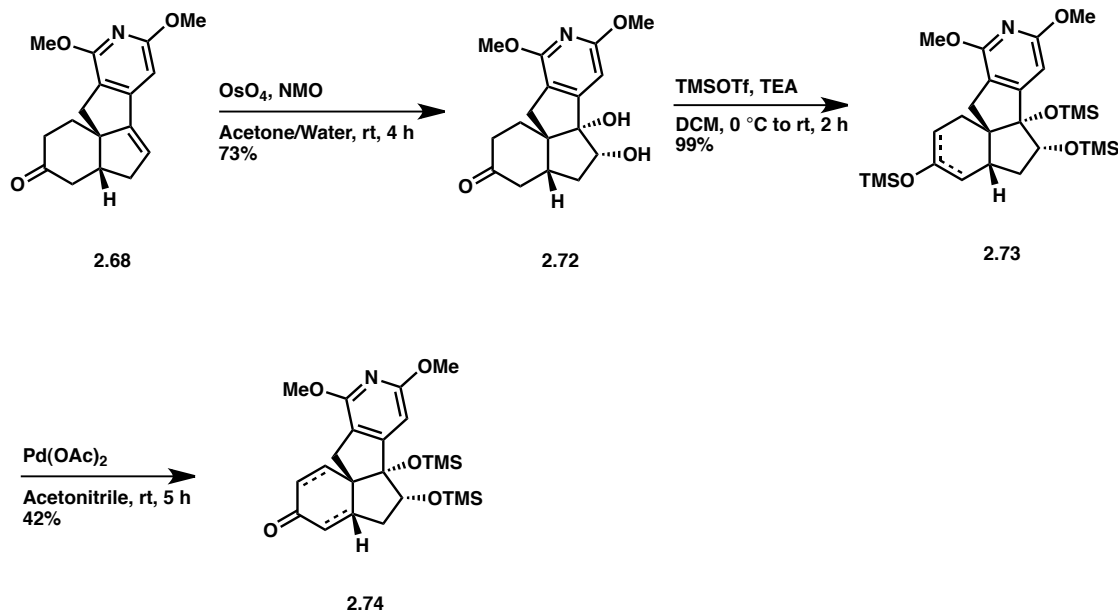
We envisioned using silyl enol ether **2.69** directly in a Saegusa-Ito oxidation to furnish enone **2.70** (Scheme 23). Enone **2.70** could then undergo methyl Grignard addition followed by Dauben transposition to provide enone **2.71**.¹³ Unfortunately, we were unable to effect the Saegusa-Ito oxidation under a variety of oxidative conditions, including the use of stoichiometric palladium acetate, 2-iodoxybenzoic acid or DDQ-mediated conditions. In all cases these conditions provoked the decomposition of the starting material. We believe that this is because the tetracycle with five sp^2 centers in the 6-5 bicycle (see **2.71**, Scheme 23) is too unstable due to ring strain.

Scheme 23. Synthetic plan to advance to enone **2.71**



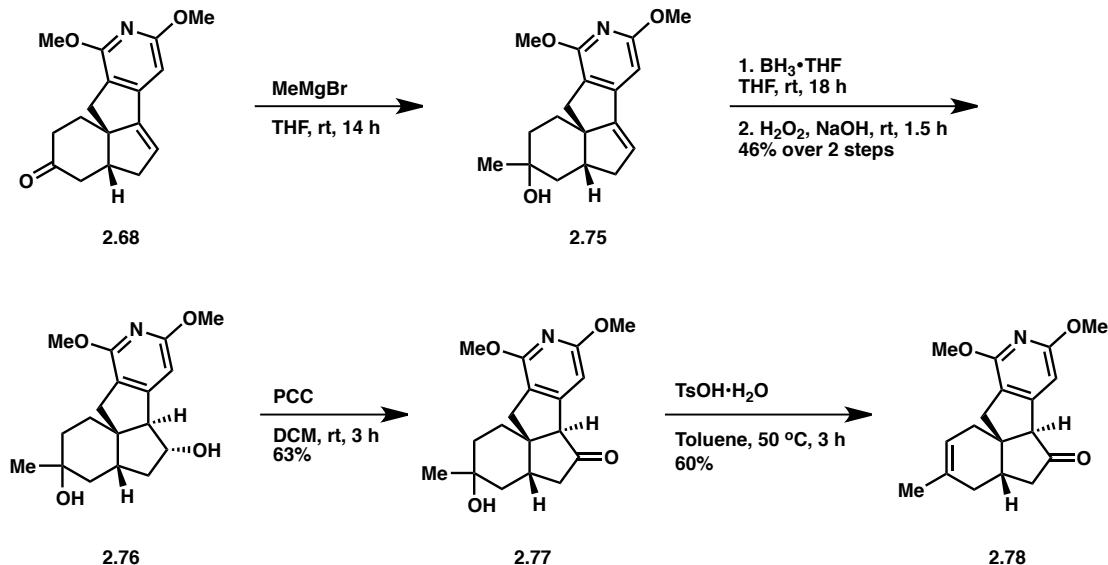
In light of this, we chose to investigate our hypothesis regarding the instability of **2.71** by removing the carbon-carbon double bond in the five-membered ring and pursuing the same sequence outlined in Scheme 23. From ketone **2.68**, dihydroxylation furnished a single diastereomer of diol **2.72** (Scheme 24) in 73% yield. Interestingly, silyl enol ether formation gave a 1:1 mixture of regioisomers of **2.73**. Saegusa-Ito oxidation of silyl enol ether **2.73** provided the expected 1:1 mixture of regioisomers of enone **2.74**. These results gave us insight to the reactivity and strain limits of our system.

Scheme 24. Access to enone **2.74**



On the basis of the results described above, we chose to pursue an alternative sequence that would avoid introducing too many sp^2 -centers into our tetracycle. From ketone **2.68**, methyl Grignard addition provided tertiary alcohol **2.75** (Scheme 25). Hydroboration/oxidation of alkene **2.75** then furnished diol **2.76**, which was oxidized with pyridinium chlorochromate to afford ketone **2.77**. Dehydration of the tertiary alcohol group gave a single regioisomer of alkene **2.78**. The oxidation of the secondary alcohol in **2.76** was deliberately performed before the dehydration in order to introduce another sp^2 -center into the ring system. We hoped that analogous to the regioselective silyl enol ether formation (see Scheme 22), this would promote the formation of a single regioisomer in the dehydration step.

Scheme 25. Synthesis of alkene **2.78**



From alkene **2.78**, we sought to perform the final oxidation to arrive at enone **2.79** before reducing the pyridine to obtain magellaninone (Table 3). A variety of oxidation conditions furnished either starting material (entry 1) or decomposition (entries 2-3). Chromium trioxide afforded what appears to be the benzylic oxidation product (**2.80**) over the desired allylic oxidation product (**2.79**). Because of this, we instead chose to reduce the pyridine before performing the final oxidation in order to preclude this side reaction.

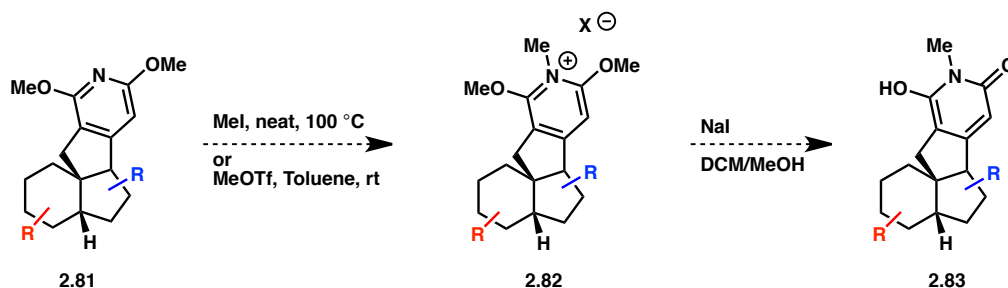
Table 3. Attempted allylic oxidation to furnish **2.79**

Entry	Conditions	Result
1	Mn(OAc) ₂ •2 H ₂ O, TBHP, O ₂ (1 atm), Ethyl acetate, 3 Å MS, rt, 17 h	Starting Material
2	Mg(OAc) ₂ •4 H ₂ O, TBHP, PhI(OAc) ₂ , Ethyl acetate, 0 °C, 1.5 h	Decomposition
3	Rh ₂ (cap) ₄ , K ₂ CO ₃ , TBHP, DCM, rt, 1 h	Decomposition
4	CrO ₃ , 3,5-dimethylpyrazole, DCM, rt, 24 h	2.80

In order to cleave the methyl groups and reduce the pyridine, we first exposed a variety of substituted tetracycles (general structure: **2.81**, Scheme 26) to methylating reagents in order to *N*-alkylate to provide pyridinium **2.82**. Heating **2.81** neat in methyl iodide for an extended period of time only returned starting material. We were

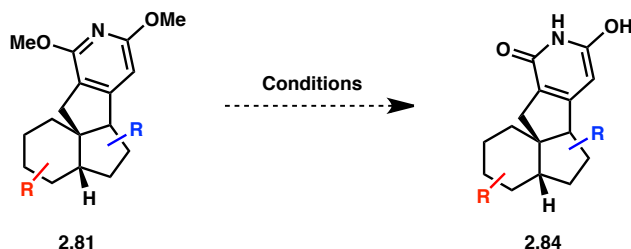
particularly disappointed to see that **2.81** was unreactive under these conditions because it is known that heating methoxypyridines in neat methyl iodide not only leads to *N*-alkylation, but also cleaves alpha-methyl groups to give *N*-methyl pyridones.¹⁴ Stronger alkylating reagents such as methyl triflate similarly returned starting material (**2.81**).

Scheme 26. Attempted *N*-alkylation and methyl group cleavage



A second alternative to the above-discussed sequence would be to use a traditional method for the cleavage of aryl methyl ethers and *N*-alkylate the resulting pyridone. From a variety of substituted tetracycles (general structure: **2.81**, Table 4) we were unable to cleave the methyl ether to arrive at pyridone **2.84**. Lewis acids such as boron tribromide and boron trichloride left both methyl groups intact (entries 1-2). Sodium ethanethiolate in DMF at high heat was able to cleave one of the methyl ethers in 17% yield, with the remaining material undergoing nonspecific decomposition (entry 3). In order to reduce the amount of decomposition we lowered the temperature to 65 °C for an extended period of time (entry 4). Unfortunately, this gave a complex mixture of products. Moreover, acidic conditions (entries 5-6) afforded only decomposition.

Table 4. Methyl group cleavage conditions

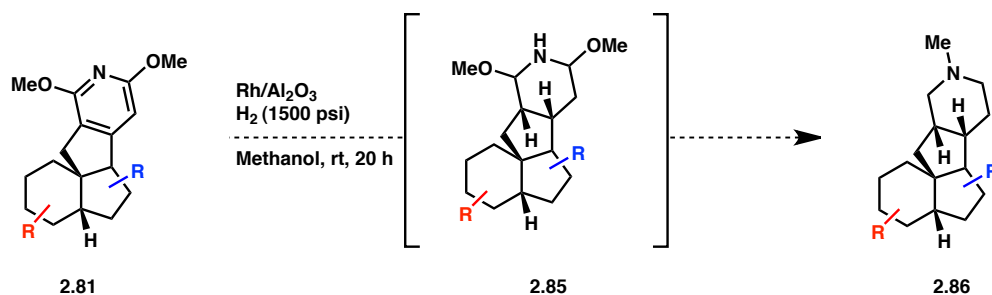


Entry	Reagent	Solvent	Temperature (°C)	Time (h)	Result
1	BBr ₃	DCM	0	1.5	Both Me Intact
2	BCl ₃	DCM	0	1.5	Both Me Intact
3	NaH, EtSH	DMF	130	2	One Me Cleaved (17%)
4	NaH, EtSH	DMF	65	42	Complex Mixture
5	HCl, AcOH	Acetic acid	140 (μW)	0.2	Decomposition
6	HBr	Acetic acid	70	23	Decomposition

We then began to investigate the direct reduction of the pyridine (general structure: **2.81**, Scheme 27) using heterogeneous catalysis conditions. We envisioned that

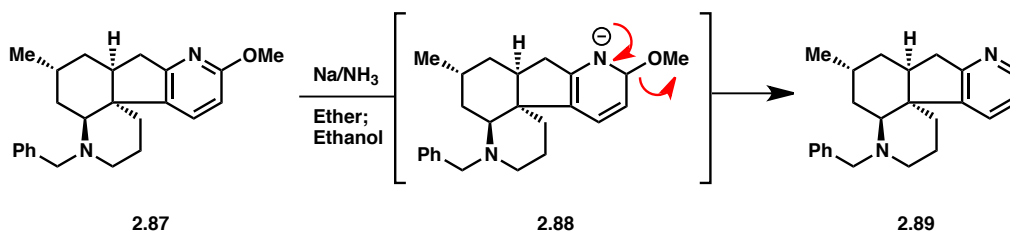
reduction of the heteroaromatic system would give dimethoxypiperidine **2.85**. Upon loss of methanol and reduction of the resulting imine intermediate, we would be able to arrive at piperidine **2.86**. We were drawn to the use of rhodium as the catalyst, as it is known to be a good heterogeneous catalyst for the reduction of pyridines, which can be conducted under atmospheric pressures of hydrogen.¹⁵ In our complex system, we were unable to effect this transformation even with up to 1500 psi of hydrogen.

Scheme 27. Attempted reduction under heterogeneous conditions



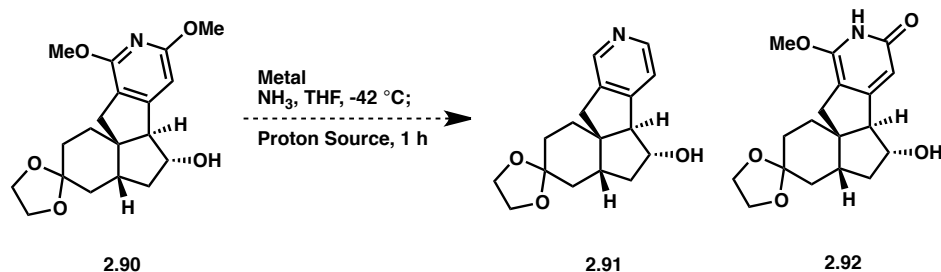
Since traditional methods to cleave the methyl groups failed, we began to investigate less common approaches. Previous results obtained in our group have shown that methoxypyridines such as **2.87** (Scheme 28) undergo the loss of methanol under single electron reduction conditions to give pyridine **2.89**.¹⁶ We believe that this reaction likely proceeds via the generation of anion **2.88**.

Scheme 28. Observed de-methoxylation under Birch reduction conditions



We sought to apply these reaction conditions to our system in order to transform dimethoxypyridine **2.90** to pyridine **2.91** (Table 5). We chose to work from tetracycle **2.90**, because it lacked other functionality that would be reactive under single electron reductive conditions. We found that standard conditions using sodium metal with ethanol as a proton source provided trace amounts of what appears to be pyridone **2.92** (entry 1) accompanied by a large amount of non-specific decomposition. Changing from sodium to either lithium or potassium afforded similar results (entries 2-3). The use of bis(2-methoxyethyl)amine (BMEA) as a proton source furnished a small amount of an unknown product along with a significant amount of decomposition of the starting material (entry 4).

Table 5. Birch reduction to remove methoxy groups

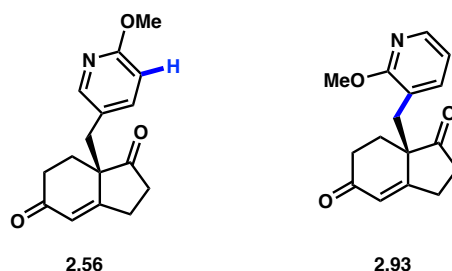


Entry	Metal	Proton Source	Result
1	Sodium	Ethanol	Trace 2.92
2	Lithium	Ethanol	Decomposition
3	Potassium	Ethanol	Decomposition
4	Sodium	Bis(2-methoxyethyl)amine (BMEA)	Unknown

While we were excited to test out these reaction conditions in our system, it is unsurprising that the bulk material decomposed. The effectiveness of Birch reductions are known to be very dependent on the substitution pattern of the aromatic ring. Tetrasubstituted aryl systems are documented to rarely work in these reductions.¹⁷

Having identified the cleavage of methyl ethers as a major challenge to this route, we began to consider yet another substrate class. From our earlier studies, we were cognizant of the need to reduce the basicity of the pyridine nitrogen. From our recent struggles we also recognized that these groups had to be readily removable in the late stages of the synthesis. We recalled that in the case of general methoxy-substitution, the bulk of the group alpha to the ether greatly influences the conformational preference of the methyl group (see Scheme 15). Appreciating this, we redesigned monomethoxypyridine substrates to be substituted on the other side of the pyridine nitrogen, so that they are now alpha to the alkyl substituent (see **2.56** vs. **2.93**, Scheme 29).

Scheme 29. New monomethoxypyridine substrate (**2.93**) compared to previously synthesized methoxypyridine substrate (**2.56**)



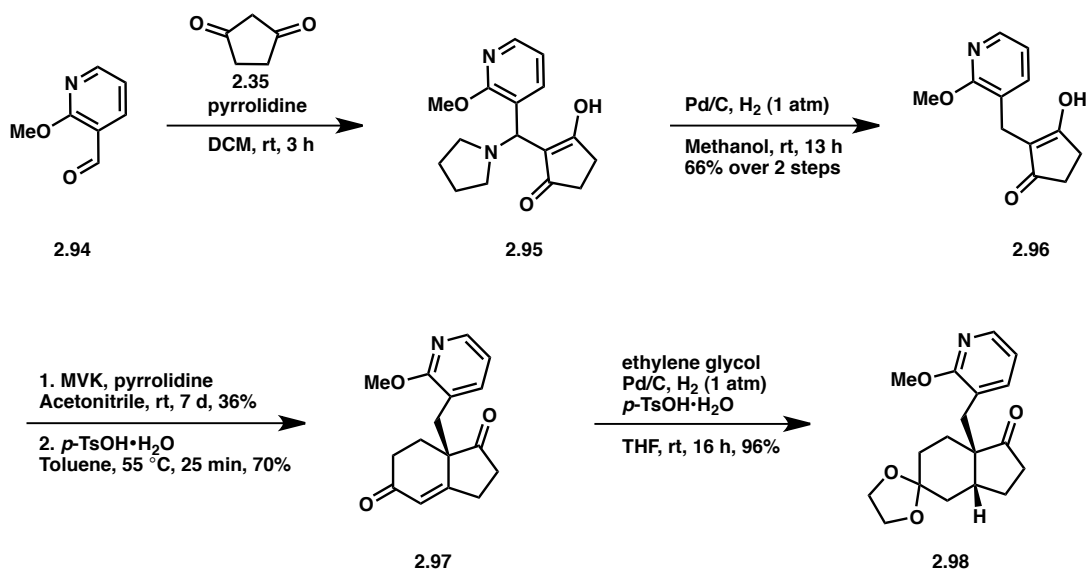
We hoped that this would increase the preference for the conformer where the methyl group is sterically blocking the lone pair on the nitrogen (see Scheme 15). This may

reduce the polarity of the initial substrates in order to achieve a scalable sequence in addition to being generally more cleavable at a late stage.

2.2.4 Synthesis of Monomethoxy Pyridine Substrates

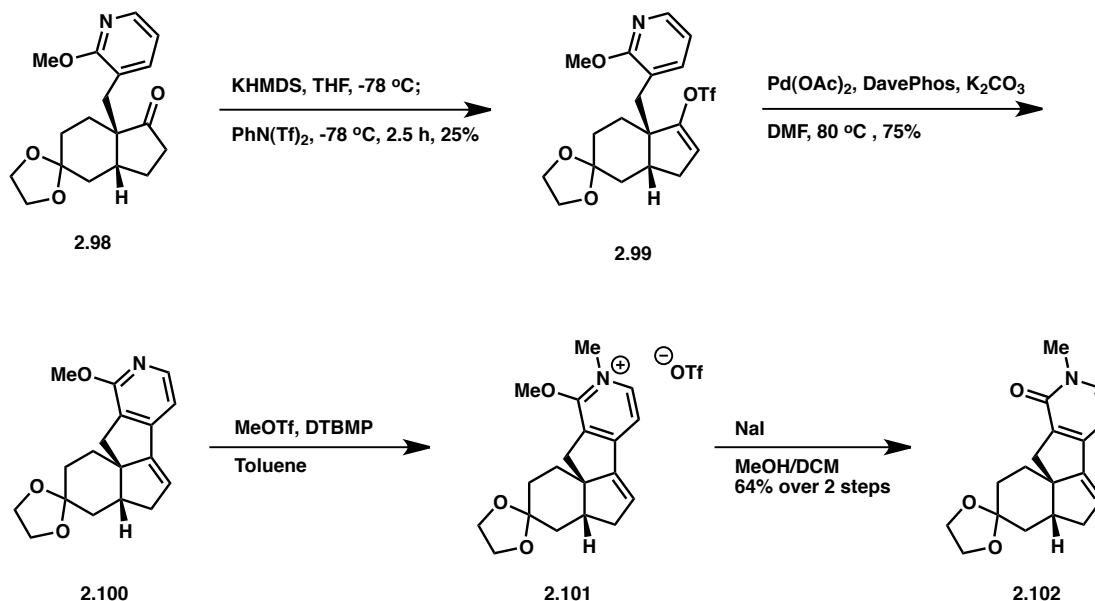
In order to synthesize the 2-methoxypyridine derivative, we began with 2-methoxy-3-formylpyridine (**2.94**) in a Mannich reaction to provide **2.95** (Scheme 30). Hydrogenolysis then furnishes pyridinedione **2.96**, which is used in an asymmetric Robinson annulation. Dehydration provides 6-5 bicycle **2.97** in 25% yield over 2 steps and 82% ee. The yield for the Robinson annulation was quite low and we were not able to optimize beyond the reported 36% yield. We were additionally unable to scale this step above 100 mg, as with previously reported substrates. Unlike previous substrates, the 2-methoxypyridine dione is reactive in an enantioselective Robinson annulation and the yield, while low, it is reproducible. We chose to continue to advance this intermediate along the route developed for the dimethoxypyridine substrate. We were pleased to see that bicycle **2.97** can be converted to ketal **2.98** in excellent yield.

Scheme 30. Synthesis of ketal **2.98**



From ketone **2.98** (Scheme 31) we are able to effect vinyl triflate formation using hard enolization conditions to provide **2.99** in an unoptimized 25% yield. With dimethoxy-substrate **2.64** (Scheme 21) we were able to use soft enolization conditions, but with **2.98** we only observed decomposition using those conditions. Vinyl triflate **2.99** undergoes Fagnou/Echavarren-type C-H functionalization to give tetracycle **2.100** in 75% yield. Since cleavage of the methyl groups had been such a challenge previously, we wanted to investigate this transformation on the initial tetracycle (**2.100**) before advancing further. We were unable to *N*-methylate pyridine **2.100** upon heating in methyl iodide, but we were very excited to see that pyridinium **2.101** could be readily formed upon stirring with methyl triflate. Exposure of *N*-methyl pyridinium **2.101** to sodium iodide then gave pyridone **2.102** in 64% yield over 2 steps.

Scheme 31. Synthesis of *N*-methyl pyridone **2.102**

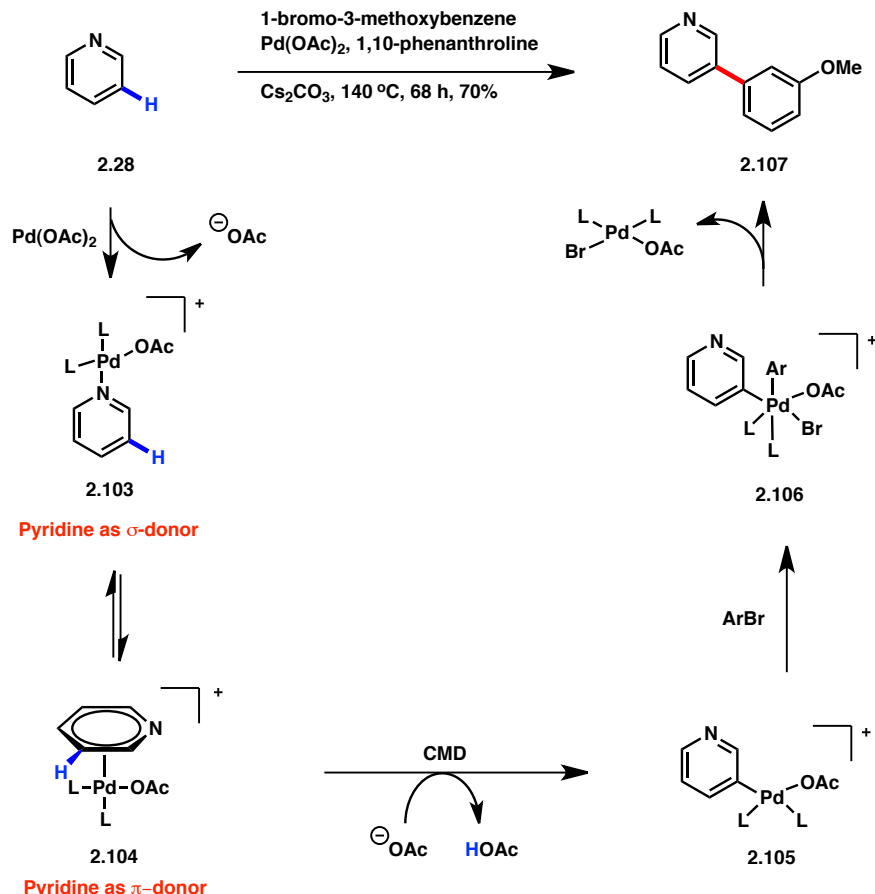


Unfortunately, low yields early on in the synthesis and problems with scalability precluded continued investigation of this route. At this stage, we chose to publish our route to the core of magellaninone¹⁸ and we began to pursue a more ambitious carbon-carbon bond disconnection strategy that would employ a C3 pyridine C-H functionalization key step.

2.3 C-3 Pyridine C-H Functionalization Approach

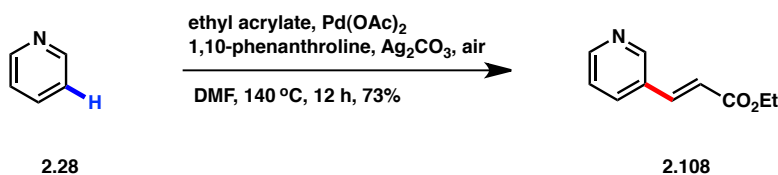
The C3 pyridine C-H functionalization methodology that we were most inspired by was published by the Jin-Quan Yu group in 2011.¹⁹ Under palladium-catalyzed conditions, Yu and coworkers showed that pyridine (**2.28**, Scheme 32) is selectively arylated at the C3 position to provide products such as **2.108** in good yield. Mechanistically, this reaction is thought to proceed through a palladium(II)/(IV) cycle where pyridine (**2.28**) first coordinates to the palladium complex as a σ -donor (**2.103**). From the σ -donor complex (**2.103**), the palladium is able to slip to interact with the pyridine as a π -donor (**2.104**). A concerted-metallation-deprotonation (CMD) event leads to palladation at the C3 position of the pyridine to give **2.105**. The regioselectivity of this step is rationalized by the increased electron density around the C3-positions of the pyridine derivatives, therefore directing the palladium center close to that position. Oxidative addition into the aryl halide, followed by reductive elimination provides the C3 arylated product (**2.107**) via **2.106**.

Scheme 32. Yu's C-H functionalization of pyridine



The Yu group also demonstrated selective olefination at the C3 position of pyridine **2.28** (Scheme 33) to provide products such as **2.108**. With these methods in mind, we designed our retrosynthesis around this type of C-H functionalization at the C3 position of pyridine.

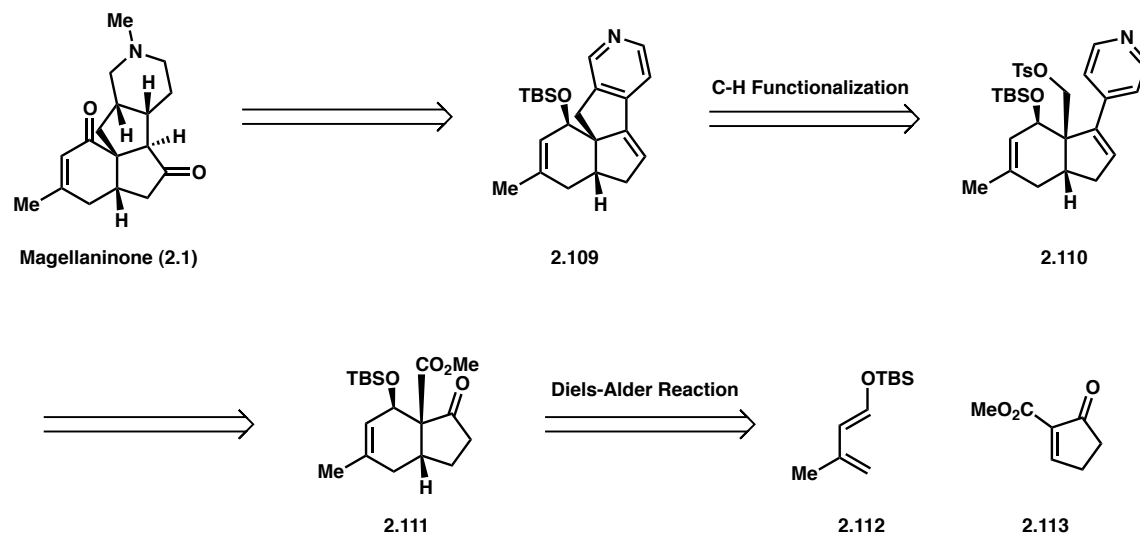
Scheme 33. Yu's olefination of pyridine



Our revised retrosynthesis brings magellaninone (**2.1**, Scheme 34) back to pyridine containing tetracycle **2.109**. We envisioned deriving tetracycle **2.109** from tosylate **2.110** using an ambitious C3 pyridine C-H functionalization in the forward sense. This is an extension on the Yu work as it requires a sp^3 - sp^2 cross coupling. We imagined that this may be an achievable goal by virtue of the fact that our planned transformation would be intramolecular as opposed to intermolecular like previous examples. We

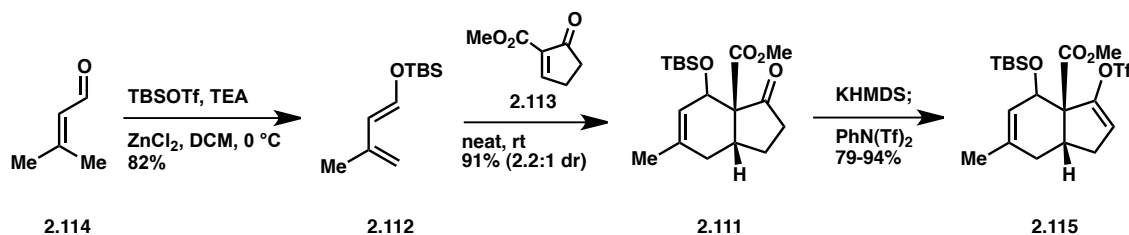
planned to work in collaboration with the Yu group to affect this challenging transformation. Pyridine **2.110** can arise from the functionalization of 6,5-bicycle **2.111**, which can be made from simple diene (**2.112**) and dieneophile (**2.113**) precursors using a Diels-Alder reaction.

Scheme 34. Revised retrosynthetic analysis of magellanimone (**2.1**)

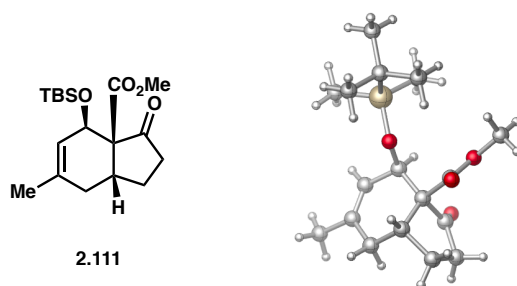


Starting from commercially available enal **2.114**, soft enolization conditions in the presence of *tert*-butyldimethylsilyl trifluoromethanesulfonate provide diene **2.112** (Scheme 35). This procedure was adapted from conditions that the Williams group used to make the trimethylsilyl variant.²⁰ We chose to use the *tert*-butyldimethylsilyl ether as opposed to the trimethylsilyl ether due to the labile nature of the trimethylsilyl protecting group. Diene **2.112** was then used in a Diels-Alder reaction (neat) at room temperature with readily available dieneophile **2.113** to furnish 6,5-bicycle **2.111** as a 2.2:1 mixture of diastereomers and in 91% yield. The identity of the major diastereomer was confirmed by X-ray crystallographic analysis (Scheme 36). Studies are currently underway to achieve an enantioselective Diels-Alder reaction, thereby rendering our synthesis enantioselective.²¹ Bicycle **2.111** was converted to vinyl triflate **2.115** under hard enolization conditions (Scheme 35). On small scale this reaction provides the desired product (**2.115**) in 94% yield, although yields decrease on scale-up due to a difficult purification to remove the *N*-phenylsulfonamide byproduct.

Scheme 35. Synthesis of vinyl triflate **2.115**

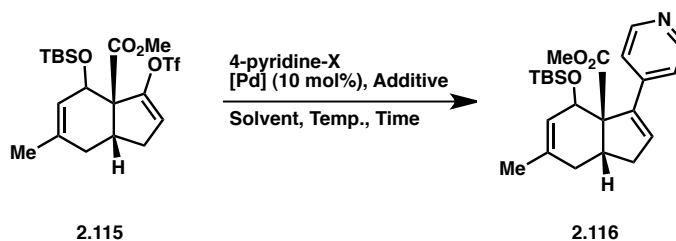


Scheme 36. Crystal structure of major diastereomer of **2.111**



In order to introduce the pyridine moiety, we began to investigate the conversion of vinyl triflate **2.115** to **2.116** (Table 6). Palladium-mediated Suzuki cross-coupling conditions in dioxane only furnished 18% of the desired pyridine (**2.116**, entry 1). Alternatively, palladium-mediated conditions using triphenylarsine as a ligand provided pyridine **2.116** in a variable 7-51% yield (entry 2). Increasing the loading of the ligand to increase the solubility of palladium (0) did not improve yield (entry 3). The use of the boronic acid or trifluoroborate cross coupling partners instead of 4-pyridine-boronic acid ester gave unsatisfactory results (entries 5-6). Switching from a Suzuki cross-coupling to a Stille cross-coupling gratifyingly provided the desired pyridine (**2.116**) in 93% yield. It is noteworthy that these conditions were specifically developed by Corey for sterically hindered vinyl triflate substrates.²²

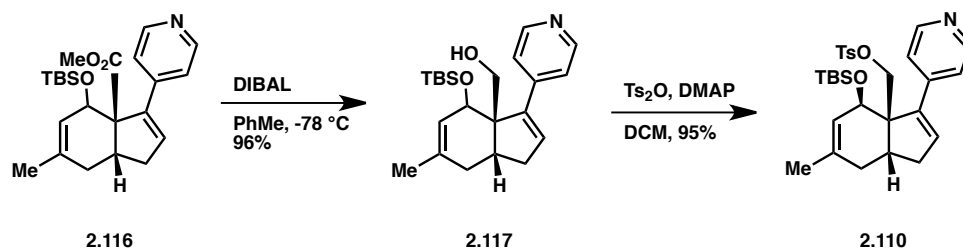
Table 6. Cross-coupling to provide pyridine **2.116**



Entry	X	[Pd]	Additive	Solvent	Temperature (°C)	Time (h)	Result
1	Bpin	PdCl ₂ (PPh ₃) ₄	K ₂ CO ₃	Dioxane	100	12	18% 2.116
2	Bpin	PdCl ₂ dppf	AsPh ₃ (10 mol%) Cs ₂ CO ₃ (1.9 equiv)	THF, DMF Water	60	15	7-51% 2.116
3	Bpin	PdCl ₂ dppf	AsPh ₃ (20 mol%) Cs ₂ CO ₃ (1.9 equiv)	THF, DMF Water	60	15	28% 2.116
4	Bpin	PdCl ₂ dppf	AsPh ₃ (10 mol%) Cs ₂ CO ₃ (1.9 equiv) LiCl (1 equiv)	THF, DMF Water	60	15	32% 2.116
5	B(OH) ₂	PdCl ₂ dppf	AsPh ₃ (10 mol%) Cs ₂ CO ₃ (1.9 equiv)	THF, DMF Water	60	15	25% 2.116
6	BF ₃ K	PdCl ₂ dppf	AsPh ₃ (10 mol%) Cs ₂ CO ₃ (1.9 equiv)	THF, DMF Water	70	15	Unknown
7	SnBu ₃	Pd(PPh ₃) ₄	CuCl (5 equiv) LiCl (6 equiv)	DMSO	70	18	93% 2.116

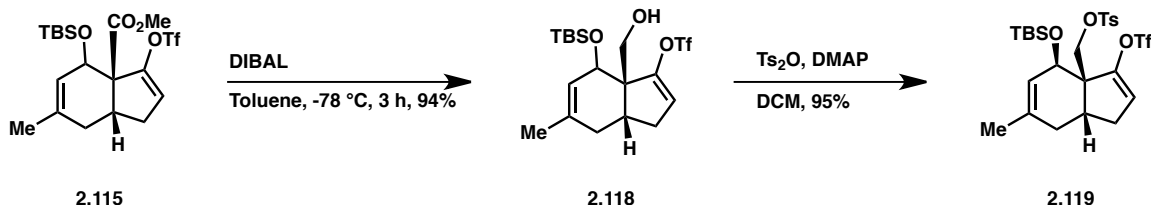
Pyridine **2.116** is reduced to the corresponding primary alcohol (**2.117**, Scheme 37) using diisobutylaluminum hydride (DIBAL). What is notable about this transformation is that DIBAL as a solution in hexane worked better than neat DIBAL. The workup uses acetic acid to quench the reaction, and is based on a report by the Stoltz group.²³ At this stage the two diastereomers were separable by column chromatography, and the major diastereomer was advanced by activation of the alcohol group as the tosylate (**2.110**). This was the substrate that we hoped to use in the intramolecular C-H functionalization.

Scheme 37. Synthesis of intramolecular C-H functionalization substrate (**2.110**)



We also sought to arrive at substrates that could be used to investigate an intermolecular C-H functionalization. Toward this goal, vinyl triflate **2.115** could also be reduced using DIBAL to provide alcohol **2.118** (Scheme 38). Diastereomers were separated at this stage, and the major diastereomer was brought forward. Sulfonation of the major diastereomer of alcohol **2.118** gave tosylate **2.119**, which was used for the investigation of the intermolecular Yu-type C-H functionalization.

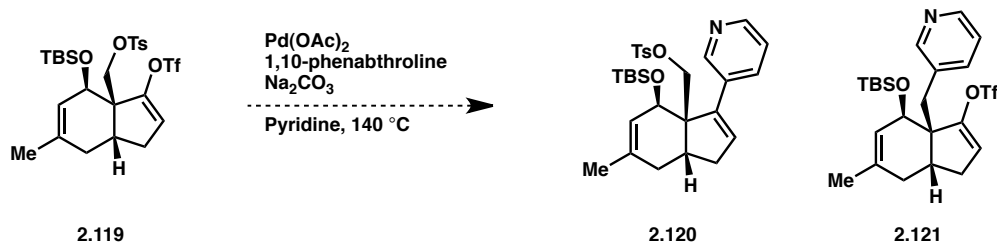
Scheme 38. Synthesis of intermolecular C-H functionalization substrate (**2.119**)



2.3.1 Investigation of Yu's C3 Pyridine C-H Functionalization

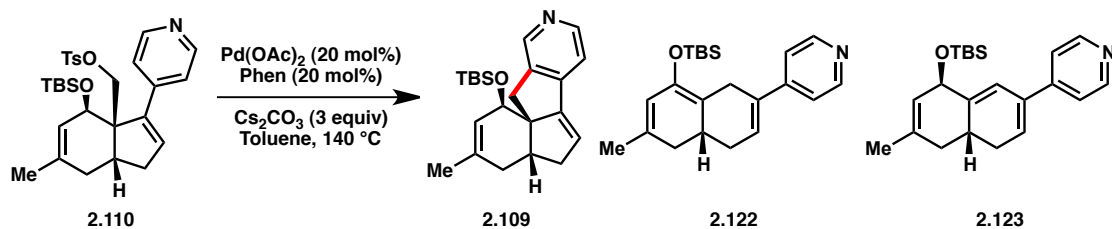
With substrates in hand for the intramolecular (see **2.110**, Scheme 37) and intermolecular (see **2.119**, Scheme 38) Yu-type C-H functionalization, we began to investigate the key step with the help of the Yu group.²⁴ With regards to the intermolecular reaction, vinyl triflate **2.119** was subjected to standard Yu C-H functionalization conditions (Scheme 39). We hoped to observe the generation of pyridine **2.121**, but also expected that pyridine **2.120** might be a significant byproduct. Unfortunately, we did not observe any reaction under these conditions.

Scheme 39. Intermolecular C-H functionalization



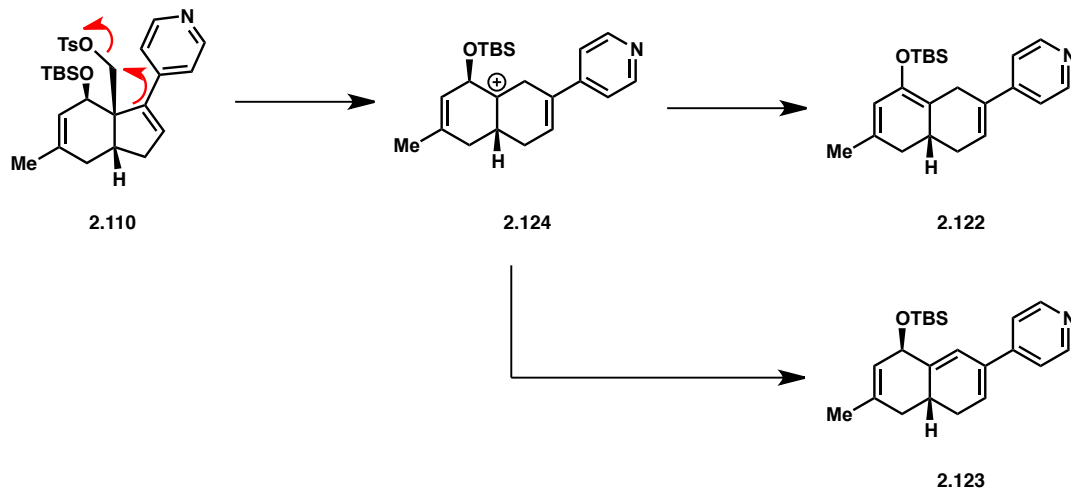
While the productive reactivity was not achieved with **2.119** under Yu's conditions, we hoped to be more successful with the intramolecular system. Upon subjection of tosylate **2.110** to palladium-catalyzed pyridine C-H functionalization conditions, we did not observe any of the desired tetracycle (**2.109**, Scheme 40). What was isolated instead was 6-6 bicycle **2.122** in 49% yield and isomeric product **2.123** in 11% yield. A control reaction, run in the absence of palladium also furnished similar amounts of bicycle **2.122** and **2.123** (48% and 18%, respectively).

Scheme 40. Intramolecular C-H functionalization



We were intrigued by this transformation, as it appeared to be a thermal rearrangement as opposed to a palladium-mediated transformation. A hypothesized mechanism may involve a 1,2 shift to give cation **2.124** (Scheme 41). Cation **2.124** could then be converted to either **2.122** or **2.123**. This is not the only explanation for this distribution of products, and we have not yet delved further into the investigation of the reaction mechanism.

Scheme 41. Mechanistic rational for the formation of **2.122** and **2.123**

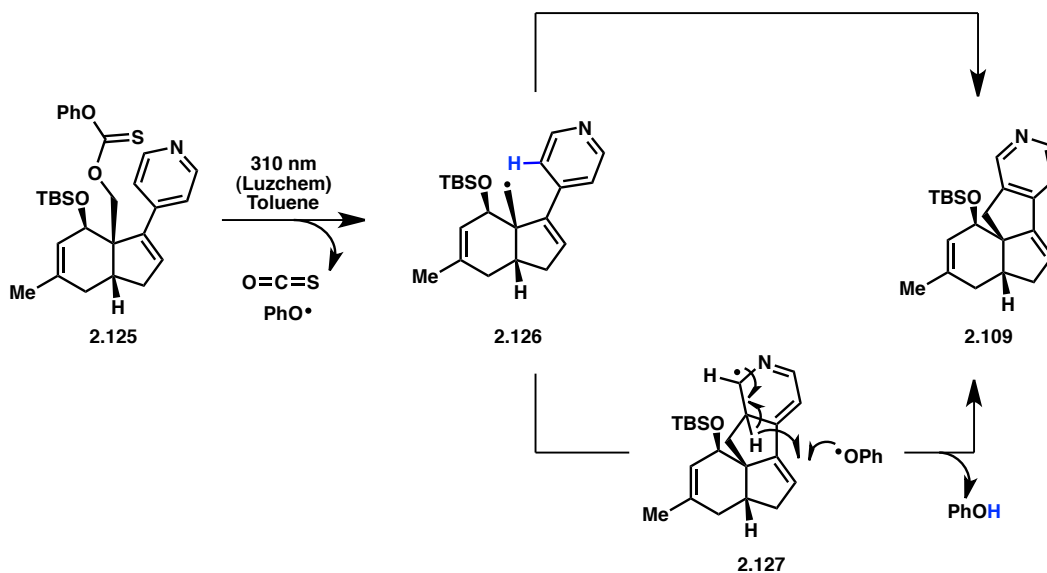


We plan to continue to work with the Yu group to further investigate this reaction. In the mean time, we began to look into alternative C-H functionalization reactions to form the desired carbon-carbon bond at the C3-position of the pyridine. In the long term, we envisioned being able to compare and contrast the scope of a number of different C-H functionalization reactions using our readily accessible substrate. The other approaches that we have investigated include radical, carbene, and iridium-catalyzed approaches.

2.3.2 Investigation of a Radical C-H Functionalization

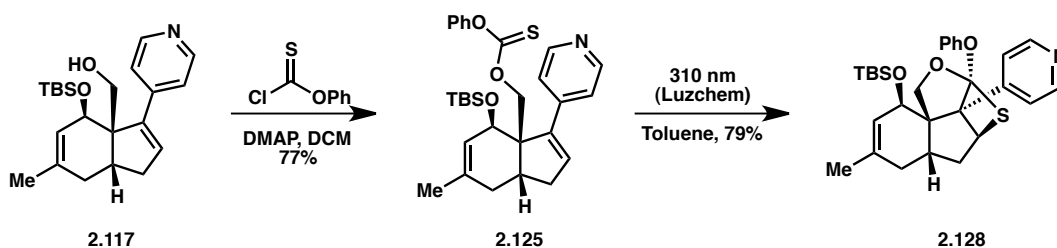
We were also inspired by the Minisci reaction as a means to formally perform a C-H functionalization of pyridine.²⁵ We were further inspired by a related radical cyclization onto the 3-position of pyridines that the Zard group published in 2012.²⁶ In the context of our system, we envisioned accessing thionocarbonate **2.125** as a radical precursor (Scheme 42). Upon irradiation with ultraviolet light the thionocarbonate (**2.125**) could break down to provide primary radical **2.126**, which would then be able to react with the pyridine moiety to furnish tetracycle **2.109**.

Scheme 42. Proposed radical C-H functionalization

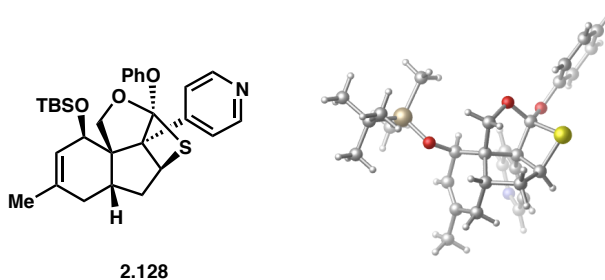


Alcohol **2.117** was easily converted to thionocarbonate **2.125** when exposed to *O*-phenyl thionochloroformate and 4-dimethylaminopyridine (Scheme 43). When thionocarbonate **2.125** was irradiated with 310 nm light, none of the desired tetracycle (see **2.109**, Scheme 42) was observed. Instead, tetracycle **2.128** was isolated in 79% yield. This interesting product results from a [2+2] cycloaddition between the thionocarbonate carbon-sulfur double bond and the carbon-carbon double bond in the 5-membered ring. We were able to unambiguously characterize this product by X-ray crystallography (Scheme 44). This type of [2+2] reaction has been documented in the literature previously.²⁷

Scheme 43. Observed reactivity under radical-generation conditions

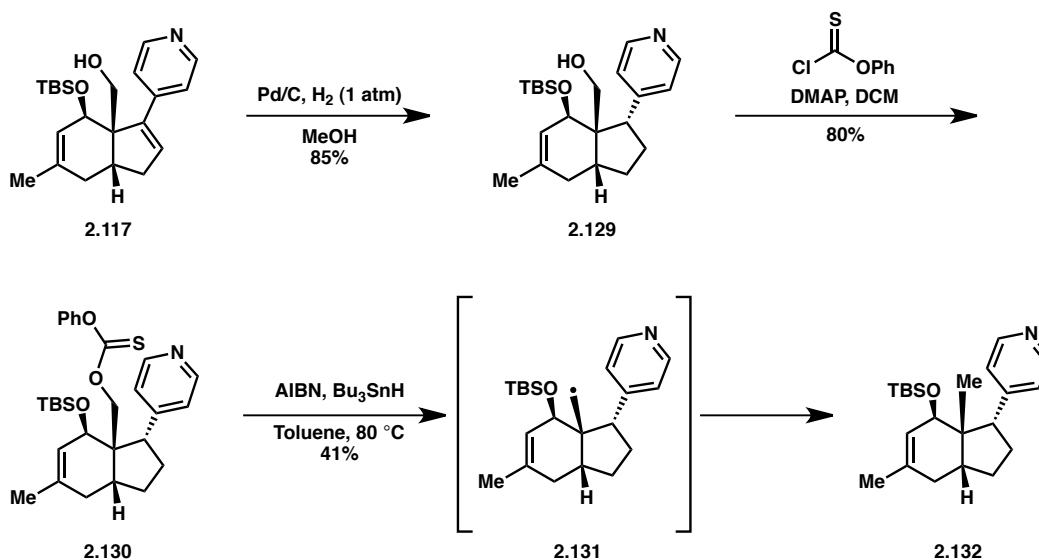


Scheme 44. X-ray analysis of unexpected tetracycle **2.128**



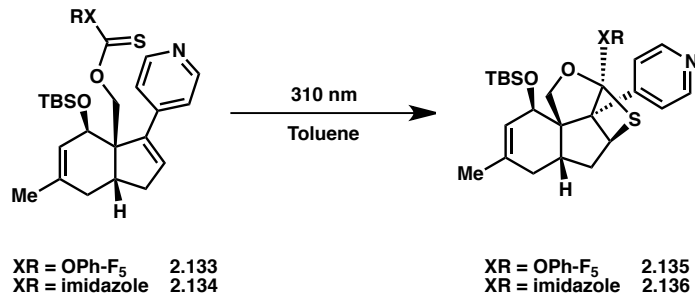
We suspected that this conversion (**2.125** to **2.109**, Scheme 42) was not successful due to the fact that the primary radical was too unstable to be generated under these reaction conditions. To verify this hypothesis, **2.117** was reduced to give a single diastereomer of **2.129** in 85% yield (Scheme 45). Primary alcohol **2.129** was converted to thionocarbonate **2.130**, which was exposed to radical reducing conditions. The reduced product (**2.132**) was isolated in approximately 41% yield, showing that it is possible to generate a primary radical at the desired primary position (see **2.131**). It is notable that this reaction is not easily reproducible.

Scheme 45. Control reaction to show feasibility of primary radical generation



Since we were now aware that it was possible to generate a radical at the desired position, we decided to tune the electronics of the thionocarbonate in order to facilitate the breakdown to the primary radical. If we were able to speed up the rate of breakdown to the primary radical, we envisioned that it might be possible to outcompete the [2+2] cycloaddition. With that in mind we synthesized pentafluorophenyl (**2.133**, Scheme 46) and imidazole (**2.134**) derivatives. Upon irradiation, none of the desired tetracycle (see **2.109**, Scheme 42) was formed; instead tetracycles **2.135** and **2.136** were isolated.

Scheme 46. Alternative thiocarbonate (**2.133**) and thiocarbamate (**2.134**) substrates



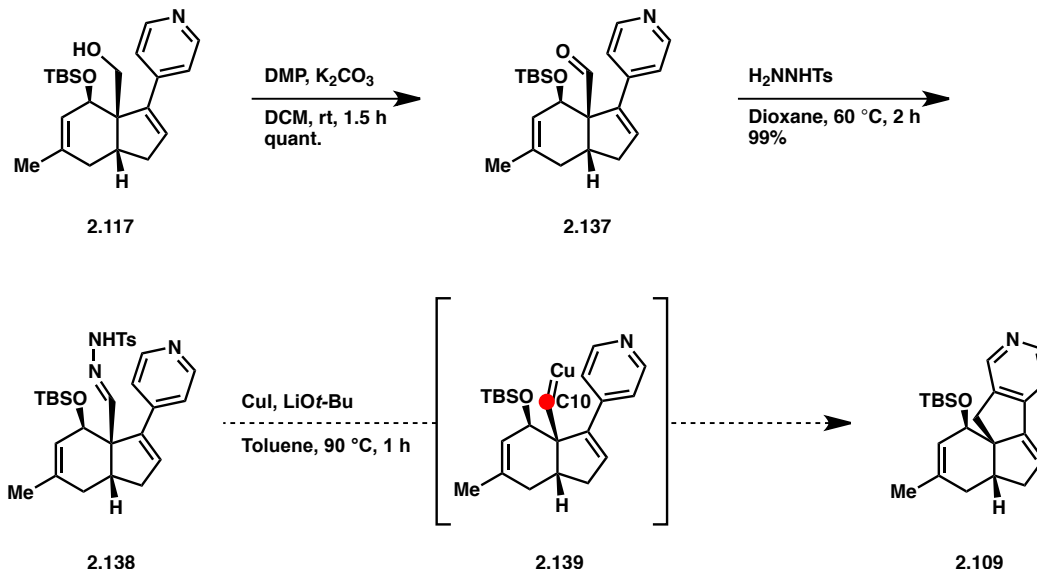
We noted at this point that it may be necessary to remove the carbon-carbon double bond in the five-membered ring before proceeding with a radical-type functionalization of the pyridine ring. The challenge associated with removing the double bond is that a *syn*-relationship is required between the pyridine relative to the alkyl group is required for the natural product (see magellaninone **2.1**, Scheme 34). We knew that this would be a challenge, as we have already shown that compounds such as **2.117** are reactive from the convex α -face (see **2.117** to **2.129**, Scheme 45). Before attempting to circumvent this issue, we chose to move forward with the investigation of other C-H functionalization methods.

2.3.3 Investigation of a Carbene C-H Functionalization

In early 2013, the Wang group published a method for the C-H functionalization of the 2-position of *N*-iminopyridinium ylides using an in-situ generated copper carbene.²⁸ While we hoped to functionalize the 3-position of our pyridine substrate, we thought that the structural limitations of our system would only allow a carbene generated at C10 (see **2.139**, Scheme 47) to interact at the pyridine C3-position.

Alcohol **2.117** (Scheme 47) could be oxidized to aldehyde **2.137**, which was condensed with tosyl hydrazine to provide hydrazone **2.138**. Upon exposure to Wang's conditions, this hydrazone (**2.138**) was expected to generate copper carbene **2.139** in-situ. Instead of observing the generation of tetracycle **2.109**, we obtained a complex mixture of products. We were unable to determine the identity of these products, but it appeared that many of them lacked the carbon-carbon double bond in the five-membered ring, also indicating its incompatibility in these reaction conditions.

Scheme 47. Observed reactivity under carbene-generation conditions

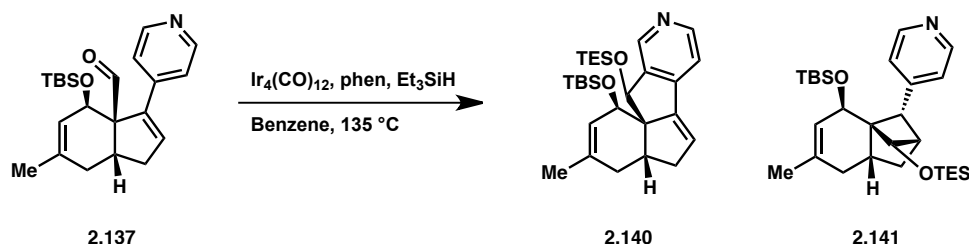


Although this reaction did not yield the desired product, we gained further insight into the reactivity of our system. It now appears to be a trend that reactivity occurs on the styrene-like moiety as opposed to the pyridine. This observation lends further support to the need to remove the double bond before proceeding with a C-H functionalization attempt.

2.3.4 Investigation of an Iridium-Catalyzed C-H Functionalization

In 2012 the Shi group published another pyridine C-H functionalization methodology that we thought might be useful for our purposes.³⁹ Their method forms a carbon-carbon bond between the C3-position of a pyridine substrate and an aldehyde to give a triethylsilyl-protected alcohol. We subjected aldehyde **2.137** (Scheme 48) to their conditions hoping to observe the generation of tetracycle **2.140**. Instead of this tetracycle, we believe that we observed **2.141** as the unexpected product in 47% yield. This product (**2.141**) could potentially arise from hydro-iridation across the styrenal carbon-carbon double bond, prior to interaction with the aldehyde.

Scheme 48. Application of Shi's C-H functionalization conditions

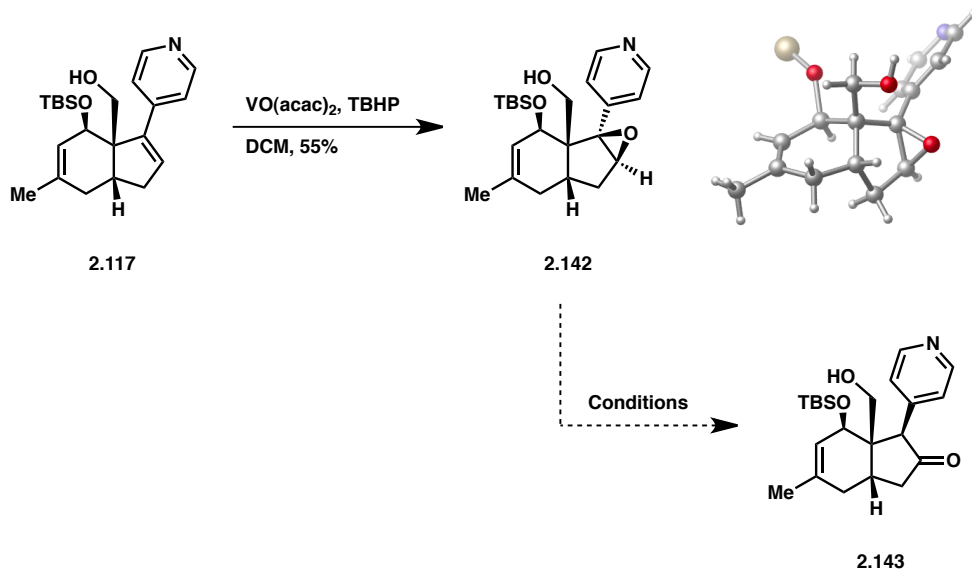


The above-observed reactivity once again reinforces the notion that the styrene-like moiety is more reactive than our pyridine. This drove us to pursue a creative solution to removing this interfering carbon-carbon double bond in the presence of the other trisubstituted carbon-carbon double bond and with the appropriate stereoselectivity that would place the pyridine on the α -face.

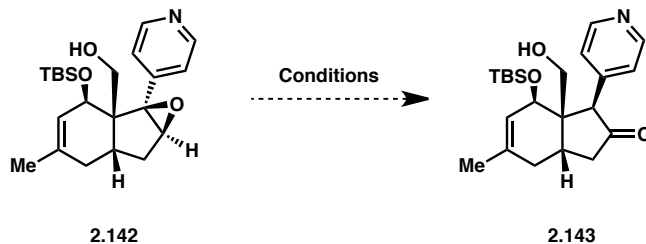
2.3.5 Epoxide Rearrangement

The solution that we came up with hinged on the use of a stereoselective epoxide rearrangement to efficiently install the required carbonyl group and place the pyridine in the required position (see **2.142** to **2.143**, Scheme 49). To differentiate between the two trisubstituted carbon-carbon double bonds (**2.117**) we used vanadium-mediated conditions that make use of the alcohol group to direct the epoxidation the alkene group in the five-membered ring to provide **2.142** as a single diastereomer. We were able to confirm the identity of this product through X-ray crystallography (substitution on silicon removed for clarity).

Scheme 49. Epoxide rearrangement to access **2.143**

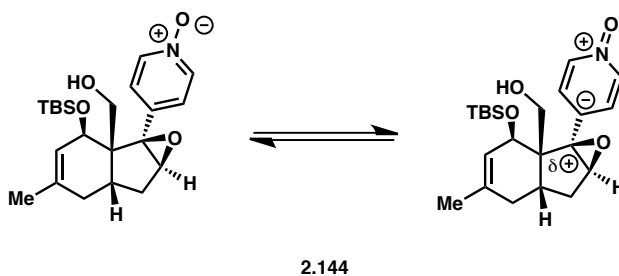


Using **2.142** as a substrate, we screened a wide range of conditions to effect the rearrangement to **2.143** (Table 7). Mild, palladium-mediated conditions returned starting material (entries 1-2).³⁰ Harsh acidic and Lewis acidic conditions gave either decomposition or starting material (entries 3-6).³¹ We suspected that our lack of success in mediating this transformation was due to the electron-withdrawing nature of the pyridine. The transition state for the rearrangement requires positive charge build-up on the carbon attached to the pyridine. Under typical acidic and Lewis acid conditions, the pyridine becomes even more electron-withdrawing through coordination to the reagent, thereby further deactivating the epoxide for this rearrangement.

Table 7. Epoxide rearrangement conditions

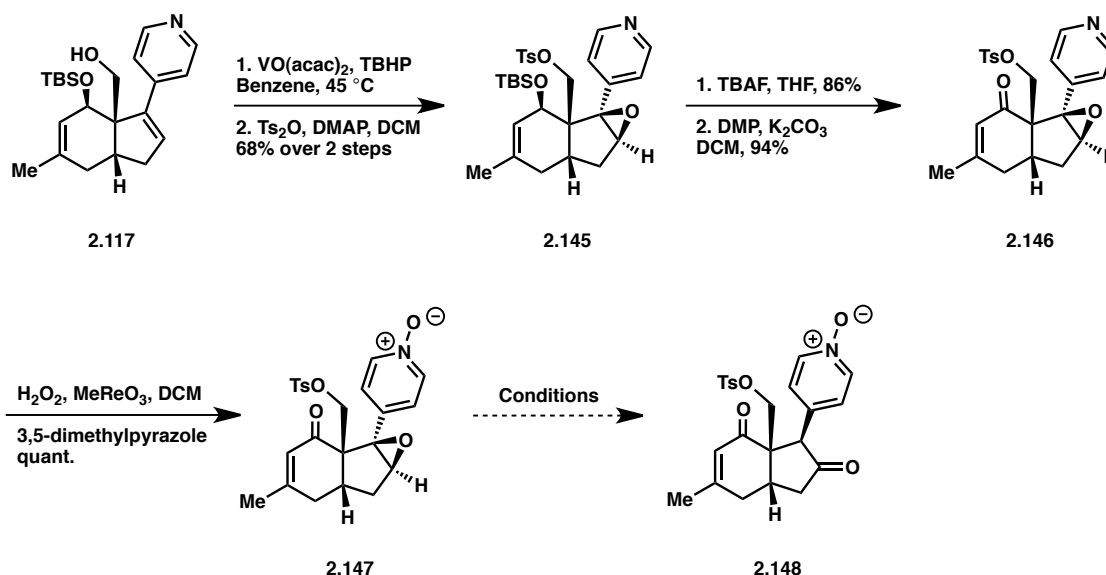
Entry	Conditions	Result
1	Pd(OAc) ₂ , PPh ₃ , Benzene, 80 0 °C, 16 h	Starting Material
2	Pd(OAc) ₂ , PBu ₃ , Benzene, 80 0 °C, 16 h	Starting Material
3	SnCl ₄ , CDCl ₃ , rt, 25 min	Decomposition
4	BF ₃ •Et ₂ O, CDCl ₃ , rt, 15 min	Decomposition
5	TfOH, CDCl ₃ , rt, 1.5 h	Decomposition
6	Acetic acid, Ethyl acetate, 60 °C, 3.5 h	Starting Material

To promote the desired rearrangement, we decided to exploit the pyridine *N*-oxide substrate as opposed to the pyridine substrate (see **2.142**, Table 7). Pyridine *N*-oxide is quite electronically different from pyridine. The *N*-oxide has both a LUMO-lowering and HOMO-raising effect that make pyridine *N*-oxides more susceptible to both nucleophilic and electrophilic aromatic substitution.³² We imagined that the *N*-oxide would stabilize positive charge build-up through resonance (Scheme 50).

Scheme 50. Relevant resonance structures of pyridine *N*-oxide **2.144**

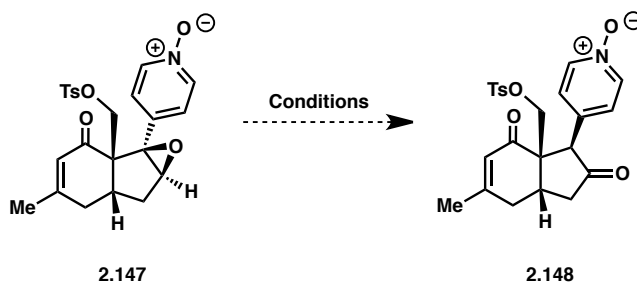
From alcohol **2.117** (Scheme 51), we performed a directed epoxidation followed by tosylate formation to furnish **2.145**. The conditions for the vanadium-mediated epoxidation are now optimized beyond the initial conditions shown in Scheme 47. The reaction requires the use of benzene as a solvent and portionwise addition of *tert*-butyl hydrogenperoxide for optimal yields. *Tert*-butyldimethylsilyl ether **2.145** can be deprotected to give the corresponding alcohol (not shown), which is then oxidized using Dess-Martin periodinane to provide enone **2.146**. Oxidation of pyridine **2.146** then gives the desired pyridine *N*-oxide substrate (**2.147**) for the epoxide rearrangement to **2.148**.

Scheme 51. Synthesis of pyridine *N*-oxide **2.147**



From *N*-oxide **2.147** (Table 8) we screened a number of conditions for the desired epoxide rearrangement to provide **2.148**. Indium trichloride returned starting material (entry 1) and gold trichloride gradually decomposed the starting material (entry 2). Samarium diiodide returned starting material when reacted with epoxide **2.147** at 0 °C (entry 3) and decomposed the material upon warming to room temperature (entry 4).³³ Heating with zinc chloride returned starting material, even after an extended period of time (entry 5).³⁴ Magnesium triflate gave a very interesting result (entry 6) and very cleanly furnished an unknown product that no longer had the tosylate by ¹H NMR and had two carbonyl groups by ¹³C NMR.

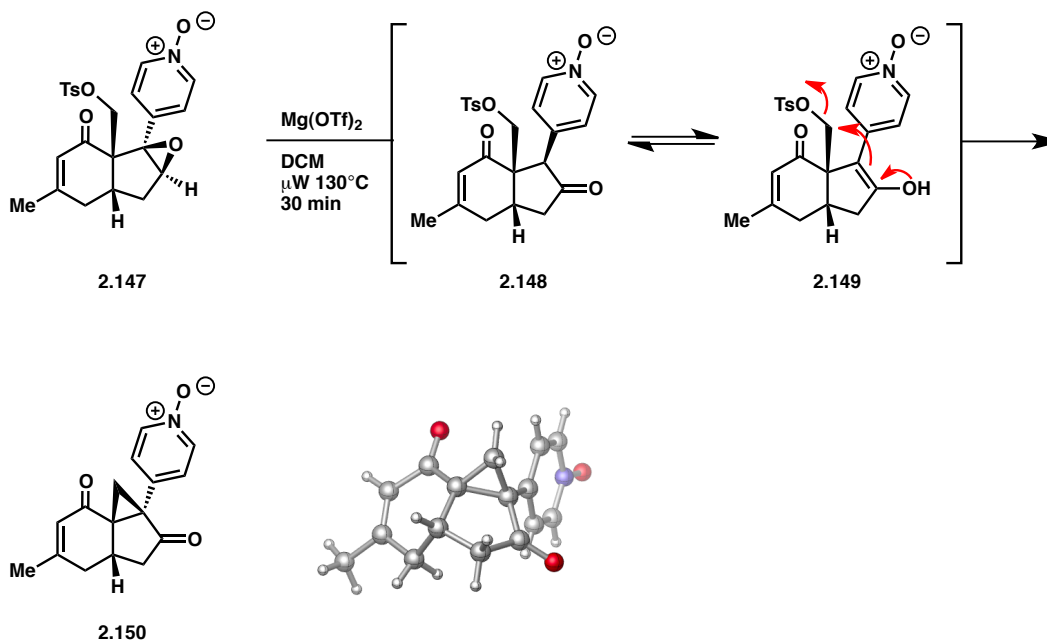
Table 8. Epoxide rearrangement conditions



Entry	Conditions	Result
1	InCl ₃ , THF-d ₈ , rt, 17h	Starting Material
2	AuCl ₃ , AgSbF ₆ , CDCl ₃ , rt to 50 °C, 17 h	Decomposition
3	Sml ₂ , HMPA, Methanol, THF, 0 °C, 1.5 h	Starting Material
4	Sml ₂ , HMPA, Methanol, THF, rt, 2 h	Decomposition
5	ZnCl ₂ , CDCl ₃ , rt to 50 °C, 21 h	Starting Material
6	Mg(OTf) ₂ , DCM, 130 °C, 30 min	Unknown

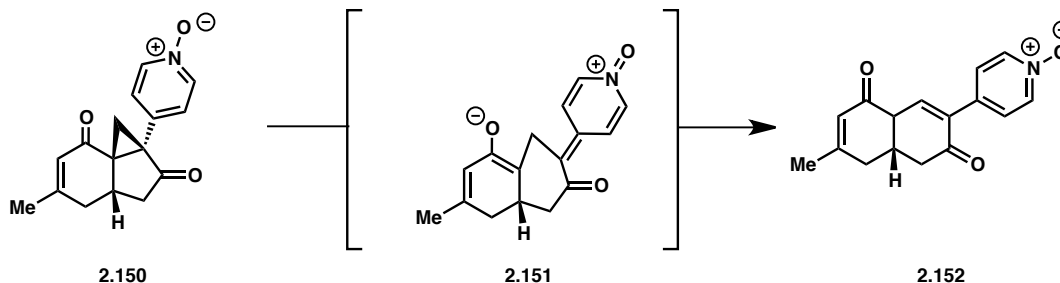
We were able to determine the identity of the unknown as tricycle **2.150** (Scheme 52) using X-ray crystallography. We believe that this interesting product arises from the desired product (**2.148**) which undergoes further rearrangement via displacement of the tosylate from enolate **2.149**. Tricycle **2.150** is furnished in 88% yield.

Scheme 52. Mechanistic rational for the generation of tricycle **2.150**



It is notable that when the reaction is heated for longer time periods, a second, unstable product is produced. We believe that this product is bicycle **2.152** and is generated via the intermediacy of **2.151** (Scheme 53). After 1 h of heating we observed a 1:1 ratio of **2.150**/**2.152**.

Scheme 53. Conversion of tricycle **2.150** to bicycle **2.152**

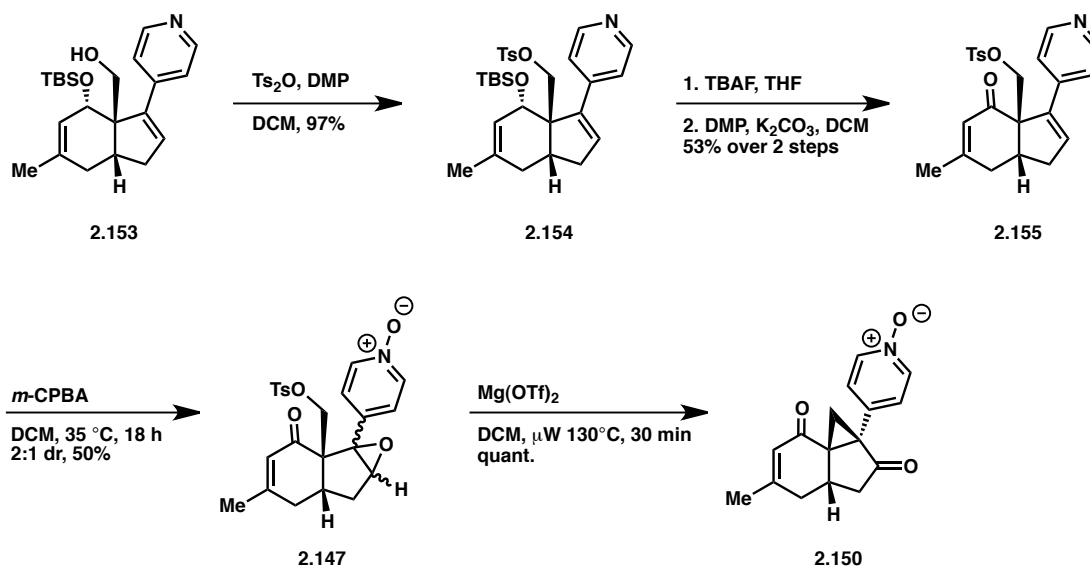


Although this was an unexpected product, we thought that we could make use of tricycle **2.150**. We envisioned being able to use it in either a C-H functionalization reaction or a vinylcyclopropane-cyclopentene rearrangement to arrive at the tetracyclic core of magellaninone. Since this required the synthesis of a large amount of tricycle

2.150, we began to investigate a method for converting the minor diastereomer of alcohol **2.153** to tricycle **2.150** (see Scheme 54). This new sequence was necessary because the minor diastereomer was not amenable to the reaction sequence developed for the major diastereomer (see Scheme 51).

From alcohol **2.153** (Scheme 54) we are able to form the corresponding tosylate (**2.154**). Cleavage of the *tert*-butyldimethylsilyl protecting group followed by oxidation provides enone **2.155** in an unoptimized 53% yield over two steps. Double oxidation using *meta*-chloroperoxybenzoic acid gives epoxide **2.147** as a 2:1 mixture of diastereomers. This ratio is inconsequential because epoxide rearrangement conditions convert both diastereomers to tricycle **2.150** in quantitative yield. The fact that both diastereomers of epoxide **2.147** are converted to tricycle **2.150** provides support that the reaction proceeds through an intermediate such as enol **2.149** (see Scheme 52), where the stereochemistry from the epoxide rearrangement is lost.

Scheme 54. Conversion of **2.153** to tricycle **2.150**

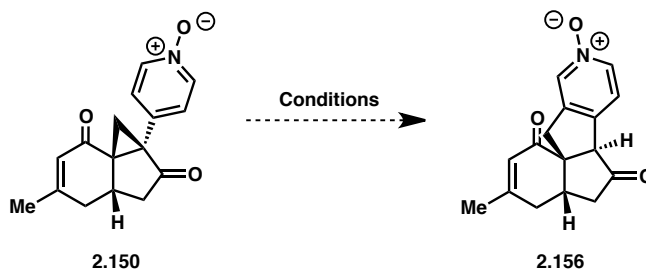


2.3.6 Investigation of a Vinylcyclopropane-Cyclopentene Rearrangement

To the best of our knowledge, there are no known examples of vinylcyclopropane-cyclopentene rearrangements that make use of a pyridine or pyridine *N*-oxide as the vinyl component,³⁵ despite the existence of examples with arenes.³⁶ Nonetheless, we were optimistic about the possibilities. Palladium on carbon in ethyl acetate returned starting material at room temperature (entry 1, Table 9) and upon heating, it afforded a complex mixture of products (entry 2). We irradiated cyclopropane **2.150** with ultraviolet light to potentially promote a radical mediated rearrangement (entry 3). Under these conditions we again observed a complex mixture of products. We also made use of nickel-mediated conditions based on a methodology published by Louie in 2004 (entry 4).³⁷ Unfortunately these conditions returned starting material (**2.150**). Rhodium-mediated conditions that were developed by Saigo³⁸ also returned starting material after extended heating at 75 °C (entry 5) and produced non-specific

decomposition after heating to 185 °C for 1 h (entry 6). Palladium-mediated conditions developed by the Oshima group³⁹ returned starting material (entry 7). Finally, tetrabutylammonium iodide-mediated conditions that proceed through a double S_N2 reaction also returned starting material after extended heating (entry 8).

Table 9. Vinylcyclopropane-cyclopentene rearrangement conditions

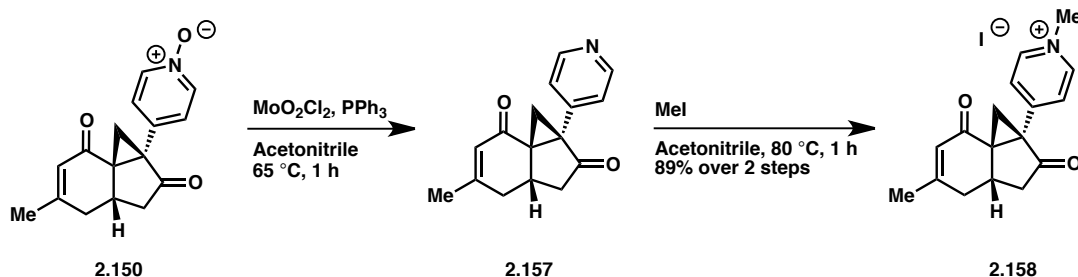


Entry	Conditions	Result
1	Pd/C, Ethyl acetate, rt, 24 h	Starting Material
2	Pd/C, Ethyl acetate, 70 °C, 15 h	Complex Mixture
3	310 nm, Toluene, 1.5 h	Complex Mixture
4	Ni(COD) ₂ , IPr, Benzene-d ₆ , 80 °C, 18 h	Starting Material
5	RhCl(PPh ₃) ₃ , Benzene-d ₆ , 75 °C, 24 h	Starting Material
6	RhCl(PPh ₃) ₃ , Benzene-d ₆ , 185 °C, 1 h	Decomposition
7	Pd(PPh ₃) ₄ , DMSO-d ₆ , 80 °C, 19 h	Starting Material
8	TBAI, DMF, 130 °C, 12 h	Starting Material

We hypothesized that this transformation was difficult to effect because the pyridine *N*-oxide would have to be dearomatized during the course of the reaction. This step may represent a very high energy barrier. Because of this, we chose to first reduce the pyridine to either the dihydropyridine or tetrahydropyridine prior to the vinylcyclopropane-cyclopentene rearrangement. This was expected to lower the activation energy required to mediate the desired transformation.

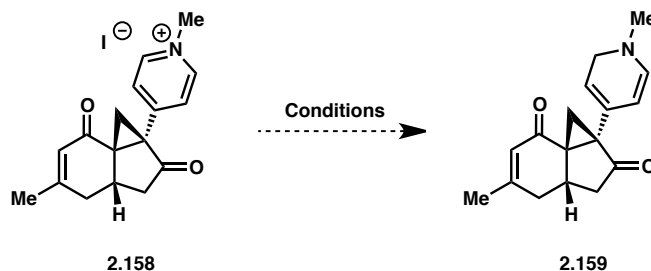
Pyridine *N*-oxide **2.150** (Scheme 55) was reduced to the corresponding pyridine (**2.157**) using triphenylphosphine and a molybdenum catalyst. Pyridine **2.157** was then methylated to provide *N*-methyl pyridinium **2.158** in 89% yield over two steps. While these steps are relatively straightforward, the reduction of pyridinium **2.158** to dihydropyridine **2.159** proved to be more problematic (Table 10).

Scheme 55. Conversion of *N*-oxide **2.150** to *N*-methyl pyridinium **2.158**



We first exposed pyridinium **2.158** to tetramethylammonium triacetoxyborohydride, hoping to arrive at dihydropyridine **2.159** (entry 1). Unfortunately, even after heating to 65 °C for an extended period of time the pyridine remained intact. Sodium cyanoborohydride gave a mixture of products at room temperature (entry 2). When acetic acid was added while heating with sodium cyanoborohydride the pyridine remained unreduced (entry 3).

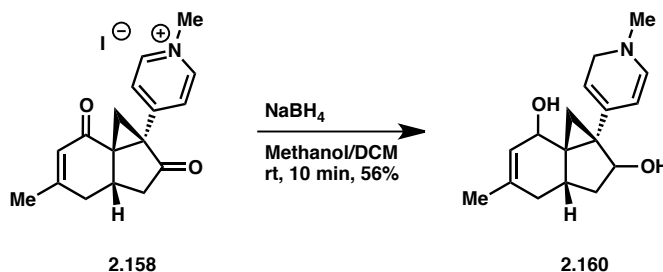
Table 10. Reduction of *N*-methyl pyridinium **2.158**



Entry	Conditions	Result
1	NMe ₄ NH(OAc) ₃ , Methanol, 65 °C, 21 h	Pyridine Intact
2	NaCNBH ₃ , Methanol-d ₄ , rt, 14 h	Mixture
3	NaCNBH ₃ , Acetic acid-d ₄ , Methanol-d ₄ , 65 °C, 24 h	Decomposition

Since the above described mild reducing conditions failed to effect the desired transformation we moved to a stronger reducing agent. We were pleased to see that sodium borohydride reduces pyridinium **2.158** (Scheme 56) to the dihydropyridine, although it also appears to have reduced both carbonyl groups to give diol **2.160** in 56% yield. Upon confirmation of this product, we hope to be able to use it as a substrate for the vinylcyclopropane-cyclopentene rearrangement.

Scheme 56. Reduction of *N*-methyl pyridinium **2.158** to dihydropyridine **2.160**

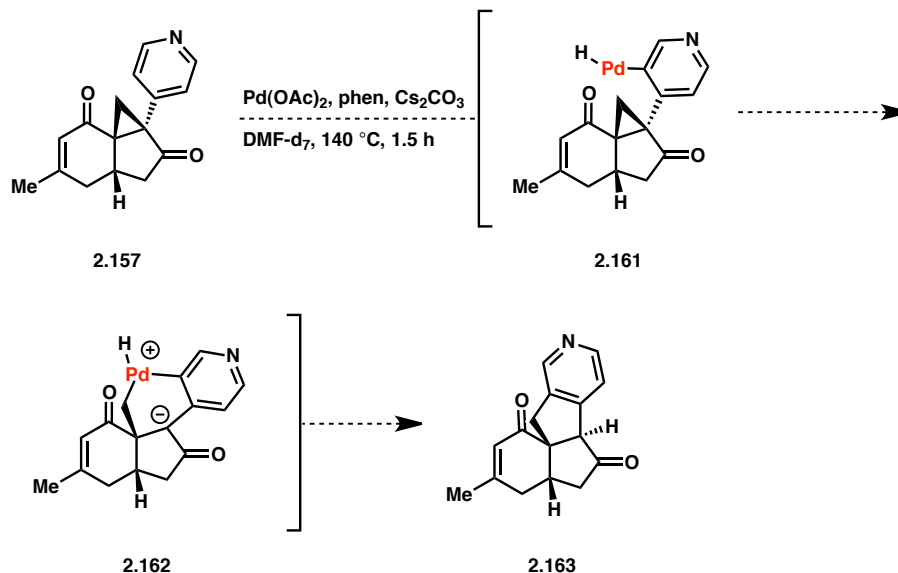


2.3.7 Investigation of the C-H Functionalization of Tricycle **2.157**

Tricycle **2.157** is an attractive substrate to use in a C-H functionalization reaction because a metal may easily interact with the strained cyclopropane. While oxidative addition into the sp³ carbon-oxygen bond of the originally proposed tosylate (see **2.110** to

2.109, Scheme 40) is a very ambitious step, oxidative addition into the cyclopropane may be lower energy due to the inherent ring strain. We envisioned that under the Yu conditions, pyridine **2.157** could be palladated at the C3-position to provide small amounts of **2.161** (Scheme 57). This C3-palladated pyridine (**2.161**) could interact with the cyclopropane to ultimately furnish the desired tetracycle (**2.163**). Unfortunately, upon subjection to the Yu conditions, pyridine **2.157** decomposed. This suggests that either pyridine **2.157** or **2.161** is unstable under these conditions.

Scheme 57. Yu's C-H functionalization conditions



2.4 Conclusion

We have completed the synthesis of the core of magellaninone through a C4 pyridine C-H functionalization approach that is based on chemistry developed in the Fagnou and Echavarren groups. We have also synthesized a number of advanced pyridine containing intermediates, which we have used toward the investigation of a number of C3 pyridine C-H functionalization approaches. These approaches include a Yu-type C-H functionalization that we have investigated in collaboration with their group, in addition to radical, carbene and iridium-mediated approaches. This work has ultimately led us to synthesize a novel cyclopropane-containing tricycle that we hope to employ in a vinylcyclopropane-cyclopentene rearrangement.

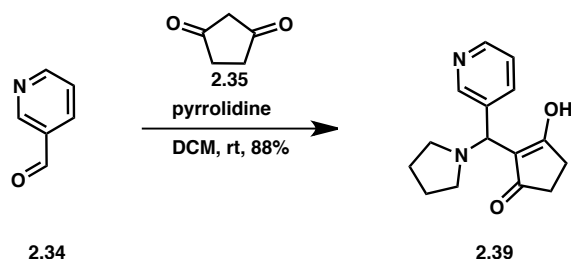
2.5 Experimental Contributors

Dr. Mengchun Ye (postdoc, Jin-Quan Yu group, The Scripps Research Institute) ran the C3 pyridine C-H functionalization reactions and determined the identity of the observed products (**2.119** to **2.121**, Scheme 39 and **2.110** to **2.109**, Scheme 40). Eugenia Pushkarskaya (undergraduate, Sarpong group) synthesized 20 g of 6,5-bicycle **2.111** (see Scheme 35). Dr. Vincent N. G. Lindsay (postdoc, Sarpong group) contributed equally to

section 2.4 – C3 Pyridine C-H Functionalization approach. The remainder of the work presented in this chapter was completed by Rebecca A. Murphy.

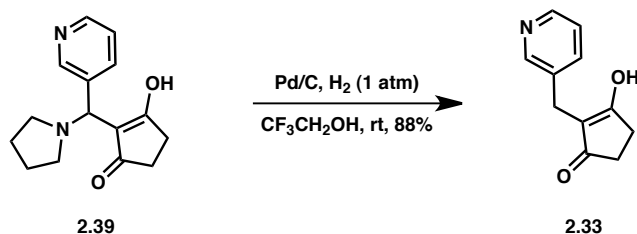
2.6 Experimental Methods

All reactions were run in flame-dried round-bottom flasks or vials under a nitrogen atmosphere. Reactions were monitored by thin layer chromatography (TLC) on Silicycle SiliaplateTM glass backed TLC plates (250 μm thickness, 60 $\text{\AA}$ porosity, F- 254 indicator) and visualized using UV irradiation and *para*-anisaldehyde stain. For heated reactions, the temperature was monitored using an IKA[®] temperature control. Dry acetonitrile, diethyl ether, tetrahydrofuran (THF), triethylamine (TEA), benzene, and methanol were obtained by passing these previously degassed solvents through activated alumina columns. Dichloromethane (DCM) was distilled over calcium hydride before use. Volatile solvents were removed under reduced pressure on a rotary evaporator. All flash chromatography was done using Sorbent Technologies 60 $\text{\AA}$, 230x400 mesh silica gel (40-63 μm). ¹H NMR and ¹³C NMR spectra were taken with Bruker 300, 400, 500, and 600 MHz (75, 100, 125, and 150 MHz for ¹³C NMR) spectrometers in CDCl₃. Chemical shifts were measured relative to the shift of the residual solvent (1H NMR - CDCl₃ δ = 7.26/MeOD δ = 3.31; ¹³C NMR CDCl₃ δ = 77.16/MeOD δ = 49.00). NMR data are reported as follows: chemical shift (multiplicity, coupling constant, integration). Splitting is reported with the following symbols: s = singlet, bs = broad singlet, d = doublet, t = triplet, q = quartet, m = multiplet. IR spectra were taken on a Nicolet 380 spectrometer as thin films on NaCl plates unless otherwise specified. Spectra are reported in frequency of absorption in cm⁻¹. Only selected resonances are reported. High-resolution mass spectra (HRMS) were performed by the mass spectral facility at the University of California, Berkeley. Enantiomeric excess (*ee*'s) was determined on Perkin Elmer Flexar Chiral HPLC.

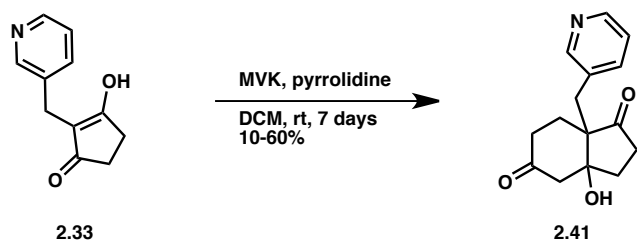


A round-bottom flask was charged with 3-formylpyridine (**2.34**, 0.80 mL, 8.0 mmol, 1.5 equiv), pyrrolidine (0.40 mL, 5.0 mmol, 1.0 equiv), and DCM (12 mL). In a separate flask, 1,3-cyclopentanone (**2.35**, 0.52 g, 5.3 mmol, 1.0 equiv) and pyrrolidine (0.20 mL, 3.0 mmol, 0.50 equiv) were dissolved in DCM (12 mL) and then added to the reaction mixture. The solution was stirred at room temperature for 2.5 h. Most of the solvent (15 mL) was removed under vacuum to give a brown solution. Ethyl acetate (4.0 mL) was added to precipitate a yellowish-white solid. The solid was filtered and washed with ethyl acetate to give 1.1 g (88%) of **2.39** as a tan powder. R_f = 0.23 (13% methanol in DCM); ¹H NMR (400 MHz, D₂O) δ 8.53 (d, J = 1.9 Hz, 1H), 8.32 (dd, J = 4.9, 1.3 Hz, 1H), 7.95 (dt, J = 8.1, 1.9 Hz, 1H), 7.29 (dd, J = 5.0, 3.0 Hz, 1H), 3.14-3.09 (m, 2H), 3.03-2.97 (m, 2H), 2.18 (s, 4H), 1.92-1.88 (m, 4H); ¹³C NMR (100 MHz, D₂O) δ 204.2,

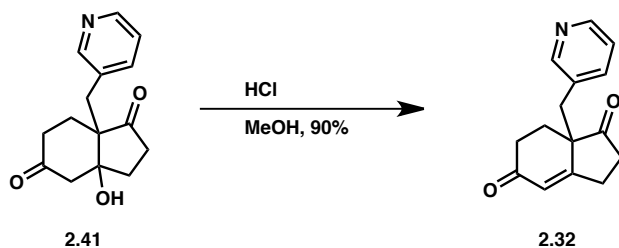
149.1, 147.8, 136.7, 133.4, 124.6, 109.2, 63.6, 53.9, 31.9, 23.4; IR (film) 2923, 1533, 1450 cm^{-1} ; HRMS (EI) calcd for $[\text{C}_{15}\text{H}_{18}\text{N}_2\text{O}_2]^+$ (M^+): m/z 259.3036, found 259.1446.



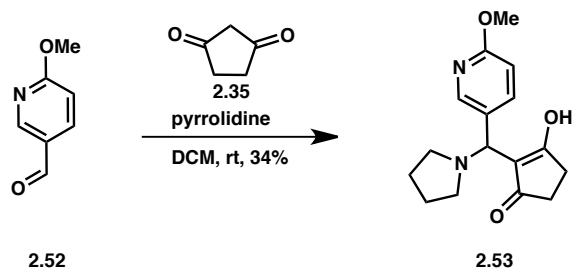
A round-bottom flask was charged with **2.39** (3.0 g, 13 mmol), 2,2,2-trifluoroethanol (130 mL), and palladium on carbon (10 wt%, 0.30 g). The flask was evacuated and backfilled with H_2 three times. The mixture was allowed to stir overnight at room temperature under a hydrogen atmosphere. The reaction mixture was filtered and then concentrated under vacuum to yield a mixture of **2.33** and pyrrolidine. This compound was used in the next step without purification. Note: this compound exists primarily in the enol form. $R_f = 0.13$ (13% methanol in DCM); ^1H NMR (400 MHz, D_2O) δ 8.51-8.48 (m, 2H), 8.30 (d, $J = 7.9$ Hz, 1H), 7.83 (t, $J = 7.8$ Hz, 1H), 3.56 (s, 2H), 3.15 (m, 4H), 2.56 (s, 4H), 1.85 (m, 4H); ^{13}C NMR (100 MHz; D_2O) δ 200.7, 146.7, 140.2, 138.8, 127.0, 113.5, 45.5, 30.3, 23.6; IR (film) 2918, 1627, 1505, 1429 cm^{-1} ; HRMS (EI) calcd for $[\text{C}_{11}\text{H}_{11}\text{NO}_2]^+$ (M^+): m/z 190.2009, found 190.0864.



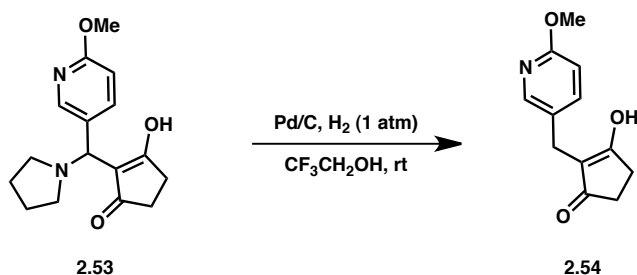
A 4 mL vial was charged with crude **2.33** (100 mg, 0.44 mmol, 1.0 equiv), chloroform (2.5 mL) and methyl vinyl ketone (86 μL , 1.1 mmol, 2.4 equiv). The solution was subjected to two freeze-pump-thaw cycles. Pyrrolidine (12 μL , 0.16 mmol, 0.35 equiv) was added. The solution was stirred for 7 days in the dark. The resulting translucent brown solution was concentrated under vacuum and purified by column chromatography (1% to 4% methanol in DCM). Alcohol **2.41** was obtained in a modest yield (41 mg; 37% over 2 steps) as a yellow solid. $R_f = 0.57$ (13% methanol in DCM); ^1H NMR (500 MHz, CDCl_3) δ 8.55 (s, 1H), 8.51 (d, $J = 4.1$ Hz, 1H), 7.69-7.67 (m, $J = 7.9$ Hz, 1H), 7.27 (dd, $J = 4.9, 2.9$ Hz, 1H), 3.10 (dd, $J = 37.6, 14.3$ Hz, 2H), 2.67-2.56 (m, 3H), 2.50-2.42 (m, 1H), 2.25-2.18 (m, 2H), 2.12-1.98 (m, 2H), 1.83 (t, $J = 6.9$ Hz, 2H); ^{13}C NMR (150 MHz, CDCl_3): δ 217.0, 208.7, 151.3, 147.7, 138.5, 123.2, 81.5, 56.0, 51.0, 36.8, 34.3, 33.8, 33.5, 27.2; IR (film) 3391, 2955, 1721, 1426 cm^{-1} ; HRMS (EI) calcd for $[\text{C}_{15}\text{H}_{17}\text{NO}_3]^+$ (M^+): m/z 260.2813, found 260.1288.



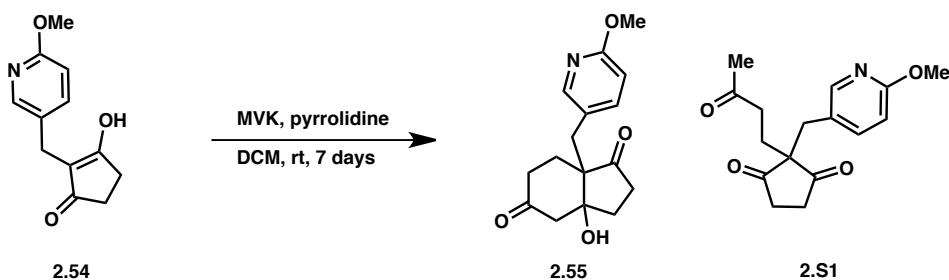
A 4 mL vial was charged with **2.41** (54 mg, 0.20 mmol) and 1.25 M HCl in methanol (2 mL). The solution was allowed to stir for 5 minutes and was then concentrated. The resulting solid was purified using column chromatography (1% to 3% methanol in DCM). Enone **2.32** (49 mg, 96%) was obtained as a yellow solid. $R_f = 0.42$ (13% methanol in DCM); ^1H NMR (600 MHz, CH_3OD) δ 8.45 (d, $J = 4.0$ Hz, 1H), 8.33 (s, 1H), 7.63 (dt, $J = 7.8, 1.9$ Hz, 1H), 7.39 (dd, $J = 4.9, 2.8$ Hz, 1H), 6.07 (s, 1H), 3.13 (dd, $J = 13.8, 4.3$ Hz, 2H), 2.83-2.77 (m, 1H), 2.69-2.57 (m, 3H), 2.50-2.43 (m, 1H), 2.40-2.35 (m, 1H), 2.16-2.09 (m, 1H), 1.87-1.81 (m, 1H); ^{13}C NMR (150 MHz, CH_3OD) δ 216.1, 199.0, 170.3, 149.8, 147.5, 138.3, 124.4, 123.6, 53.4, 36.7, 35.6, 32.1, 26.9; IR (film in CH_3OH) 2925, 1743, 1667, 1425 cm^{-1} ; HRMS (EI) calcd for $[\text{C}_{15}\text{H}_{15}\text{NO}_2]^+$ (M^+): m/z 242.2732, found 242.1177.



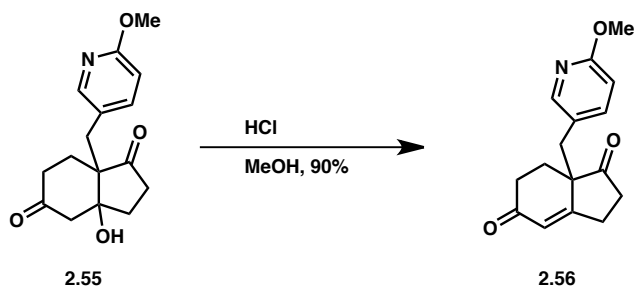
This compound was obtained according to the procedure for **2.39**, but 6-methoxynicotinaldehyde, was used in the place of 3-formylpyridine. The product (0.26 g, 34%) was obtained as a tan-pink solid. $R_f = 0.10$ (13% methanol in DCM); ^1H NMR (600 MHz, CDCl_3) δ 8.29 (d, $J = 1.9$ Hz, 1H), 7.92 (dd, $J = 6.7, 1.8$ Hz, 1H), 6.75 (d, $J = 8.7$ Hz, 1H), 4.79 (s, 1H), 3.90 (m, 3H), 3.14-3.10 (m, 4H), 2.37 (s, 4H), 2.09-2.05 (m, 4H); ^{13}C NMR (150 MHz, CDCl_3) δ 213.7, 200.0, 164.2, 147.0, 138.6, 126.4, 111.4, 66.0, 53.6, 32.4, 23.5; IR (film) 2924, 1572, 1533, 1495, 1450 cm^{-1} ; HRMS (EI) calcd for $[\text{C}_{16}\text{H}_{20}\text{N}_2\text{O}_3]^+$ (M^+): m/z 289.3150, found 289.1539.



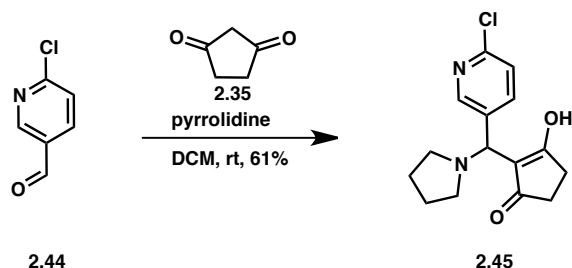
This compound was obtained according to the procedure for **2.33**, but **2.53** was used in the place of **2.39**. The material obtained was 0.26 g of a brown viscous liquid comprised of a mixture of **2.54** and pyrrolidine. The material was used in the next step without purification. $R_f = 0.05$ (13% methanol in DCM); ^1H NMR (600 MHz, CDCl_3) δ 7.92 (d, $J = 2.1$ Hz, 1H), 7.40 (dd, $J = 8.5, 2.4$ Hz, 1H), 6.50 (d, $J = 8.5$ Hz, 1H), 3.76 (s, 3H), 3.22 (s, 2H), 2.25 (s, 4H); ^{13}C NMR (150 MHz, CDCl_3) δ 201.5, 162.2, 145.6, 139.4, 130.2, 113.1, 109.4, 53.3, 50.9, 44.9, 32.2, 24.4, 23.6, 23.3, 18.9; IR (film) 2945, 1608, 1491, 1389 cm^{-1} ; HRMS (EI) calcd for $[\text{C}_{12}\text{H}_{13}\text{NO}_3]^+$ (M^+): m/z 220.2264, found 220.0973.



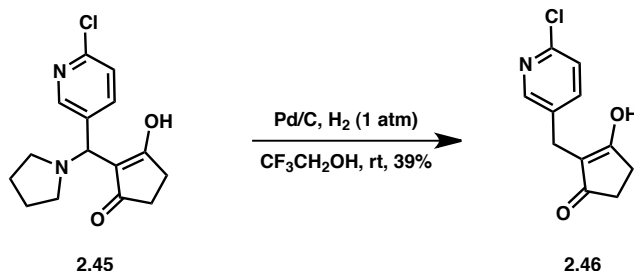
This compound was obtained according to the procedure for **2.41**, but **2.54** was used in the place of **2.33**. Triketone **2.S1** (14 mg, 47% over 2 steps from **2.53**) was recovered as a white solid. $R_f = 0.70$ (13% methanol in DCM); ^1H NMR (600 MHz, CDCl_3) δ 8.55 (d, $J = 2.4$ Hz, 1H), 7.82 (dd, $J = 8.5, 2.5$ Hz, 1H), 6.60 (d, $J = 8.5$ Hz, 1H), 3.88 (s, 3H), 2.84 (s, 2H), 2.67 (dd, $J = 12.8, 6.8$ Hz, 2H), 2.47 (t, $J = 7.2$ Hz, 2H), 2.14 (dd, $J = 10.8, 8.4$ Hz, 2H), 2.11 (s, 3H), 1.96 (t, $J = 7.2$ Hz, 2H); ^{13}C NMR (150 MHz, CDCl_3) δ 216.4, 207.4, 163.4, 147.7, 140.1, 123.4, 110.5, 60.7, 53.3, 37.6, 36.0, 29.9, 28.2; IR (film) 2923, 1720, 1680, 1493, 1394 cm^{-1} ; HRMS (EI) calcd for $[\text{C}_{16}\text{H}_{19}\text{NO}_4]^+$ (M^+): m/z 290.3128, found 290.1395. Alcohol **2.55** (30% over 2 steps from **2.53**) was recovered as a yellowish solid. $R_f = 0.60$ (13% Methanol in DCM); ^1H NMR (600 MHz, CDCl_3) δ 8.01 (d, $J = 2.4$ Hz, 1H), 7.52 (dd, $J = 8.5, 2.5$ Hz, 1H), 6.68 (d, $J = 8.5$ Hz, 1H), 3.91 (s, 3H), 182.98 (dd, $J = 45.8, 14.5$ Hz, 2H), 2.63-2.53 (m, 3H), 2.46-2.37 (m, 1H), 2.23-2.15 (m, 3H), 2.10-2.05 (m, 1H), 2.03-1.95 (m, 1H), 1.83-1.77 (m, 1H); ^{13}C NMR (150 MHz, CDCl_3) δ 216.6, 208.3, 163.3, 147.9, 141.0, 124.7, 110.4, 82.0, 56.0, 53.4, 51.3, 36.9, 34.2, 33.6, 32.8, 27.2; IR (film) 3400, 2919, 1724, 2608, 1494 cm^{-1} ; HRMS (EI) calcd for $[\text{C}_{16}\text{H}_{19}\text{NO}_4]^+$ (M^+): m/z 290.3128, found 290.1399.



This compound was obtained according to the procedure for **2.32**, but **2.55** was used in the place of **2.41**. The product was obtained as a yellow solid (quant). $R_f = 0.58$ (13% methanol in DCM); ^1H NMR (600 MHz, CH_3OD) δ 8.24-8.22 (m, 1H), 8.18 (dd, $J = 5.3, 0.4$ Hz, 1H), 7.41 (d, $J = 8.9$ Hz, 1H), 6.09 (s, 1H), 4.18 (s, 3H), 3.16 (dd, $J = 20.5, 14.4$ Hz, 2H), 3.00-2.79 (m, 4H), 2.49 (dt, $J = 19.4, 9.7$ Hz, 1H), 2.05-2.00 (m, 1H), 1.87-1.80 (m, 1H); ^{13}C NMR (150 MHz, CH_3OD) δ 215.9, 198.8, 170.0, 161.2, 148.1, 140.9, 126.6, 124.3, 110.0, 56.5, 52.8, 35.8, 34.2, 31.9, 26.7, 26.1; IR (film) 2924, 1741, 1666, 1608, 1493 cm^{-1} ; HRMS (EI) calcd for $[\text{C}_{16}\text{H}_{17}\text{NO}_3]^+$ (M^+): m/z 272.2890, found 272.1293.

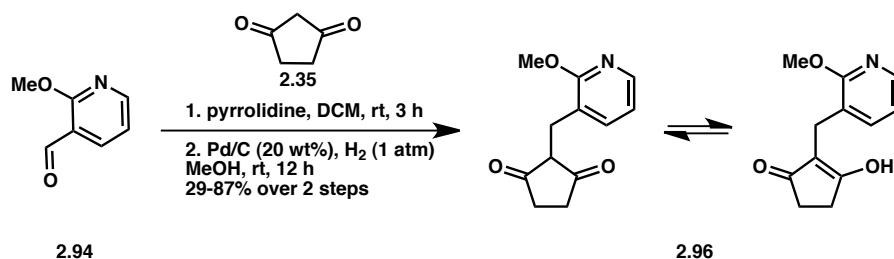


This compound was obtained according to the procedure for **2.39**, but 6-chloronicotinaldehyde was used in the place of 3-formylpyridine. The product (0.93 g, 61%) was recovered as a white solid. $R_f = 0.38$ (13% methanol in DCM); ^1H NMR (500 MHz, CDCl_3) δ 8.58 (d, $J = 0.5$ Hz, 1H), 7.95 (dd, $J = 7.1, 0.5$ Hz, 1H), 7.36 (d, $J = 8.4$ Hz, 1H), 4.83 (s, 1H), 3.15-3.02 (m, 3H), 2.39 (s, 4H), 2.13-2.02 (m, 4H); ^{13}C NMR (150 MHz, CDCl_3) δ 199.5, 148.7, 139.0, 124.2, 65.4, 31.9, 23.6; IR (film) 1535, 1107, 665 cm^{-1} ; HRMS (EI) calcd for $[\text{C}_{15}\text{H}_{17}\text{N}_2\text{O}_2\text{Cl}]^+$ (M^+): m/z 293.1051, found 293.1051.

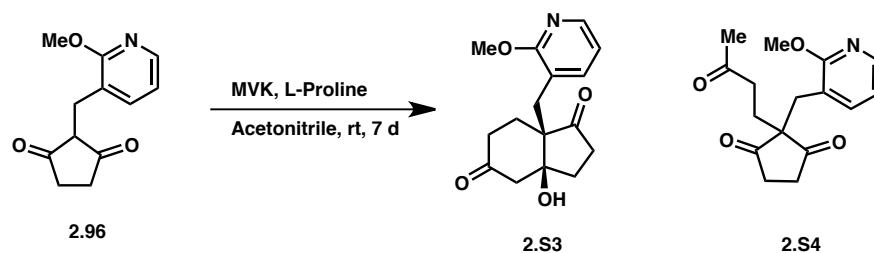


This compound was obtained according to the procedure for **2.33**, but **2.45** was used in the place of **2.39**. The product was purified using column chromatography (5% methanol in DCM). The product (0.27 g, 39%) was recovered as a white solid. $R_f = 0.26$ (13% methanol in DCM); ^1H NMR (600 MHz, CDCl_3) δ 8.24 (s, 1H), 7.64 (d, $J = 8.2$ Hz, 1H),

163.7, 147.0, 146.3, 136.3, 126.3, 122.1, 120.1, 49.6, 33.8, 32.5, 28.8, 24.6, 23.8; IR (film) 2922, 1742, 1667, 1461, 666 cm^{-1} ; HRMS (EI) calcd for $[\text{C}_{15}\text{H}_{14}\text{NO}_2\text{Cl}]^+$ (M^+): m/z 276.0786, found 276.0791.

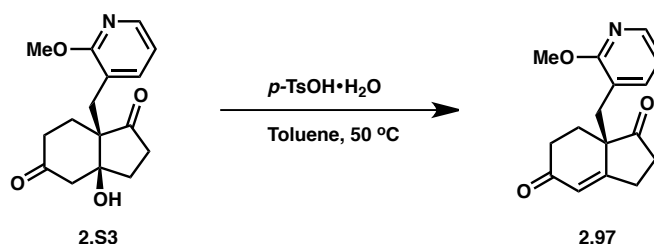


A 500 mL round-bottom flask equipped with a magnetic stir bar was charged with commercially available pyridine aldehyde **2.94** (2 g, 15 mmol, 1.5 equiv), pyrrolidine (0.8 mL, 9.7 mmol, 1.0 equiv), and DCM (25 mL). To the reaction mixture was added a solution of 1,3-cyclopentanedione (**2.35**, 0.95 g, 9.7 mmol, 1.0 equiv) and pyrrolidine (0.4 mL, 4.8 mmol, 0.50 equiv) in DCM (25 mL). The reaction mixture was allowed to stir for 3 h at 23 °C, at which point it was concentrated to give an orange-brown residue. This residue was dissolved in methanol (260 mL) and palladium on carbon was added (0.4 g, 20 wt% of pyridine aldehyde). The atmosphere was exchanged for hydrogen and the solution was stirred for 12 h, at which point it was filtered through a pad of Celite, washed with methanol (50 mL), and concentrated. The resulting yellow-orange viscous oil was purified by column chromatography (2% methanol in DCM) to yield 1.4 g (66%) of pyridinedione **2.96** as a yellow-white solid. This purification is particularly difficult because the desired product streaks through the column, and yields can be as low as 29% or as high as 87%. Yields are generally higher for smaller scale reactions. R_f = 0.55 (10% methanol in DCM); ^1H NMR (400 MHz, MeOD): δ 7.89 (t, J = 2.3 Hz, 1H), 7.30 (dt, J = 7.2, 0.9 Hz, 1H), 6.82-6.79 (m, 1H), 3.91 (s, 3H), 3.35 (s, 2H), 2.56 (s, 4H); ^{13}C NMR (100 MHz, MeOD): δ 162.2, 143.7, 137.3, 122.3, 116.6, 114.3, 52.0, 30.2, 20.5 [the carbonyl C's were not observed]; IR (film) 2922, 1592, 1464, 1409, 1382 cm^{-1} ; HRMS (EI) calcd for $[\text{C}_{12}\text{H}_{13}\text{NO}_3]^+$ (M^+): m/z 220.0895, found 220.0970.

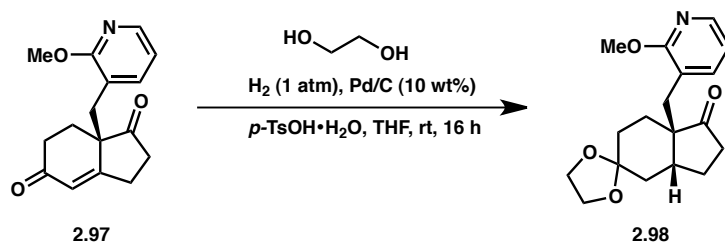


A 25 mL Schlenk flask was charged with pyridinedione **2.96** (87 mg, 0.40 mmol, 1.0 equiv), methyl vinyl ketone (66 μL , 1.2 mmol, 2.0 equiv), and acetonitrile (5 mL). Three 10-minute freeze pump thaw cycles were performed. After the third cycle, L-proline (14 mg, 0.18 mmol, 0.30 equiv) was added and the solution was allowed to warm under nitrogen atmosphere. The solution was allowed to stir in the dark for one week. It was important that the reaction mixture was not exposed to light. After 7 days, the solution was diluted with ethyl acetate (10 mL) and washed with water (3 x 5 mL). The organic

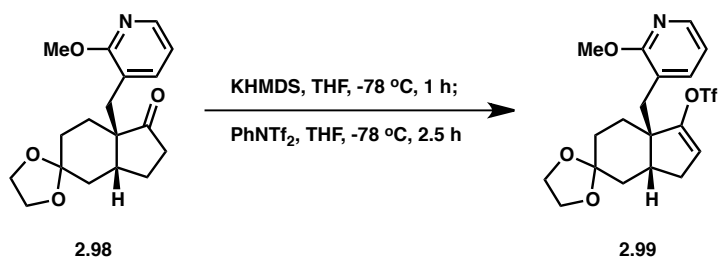
layer was dried over magnesium sulfate, filtered, and concentrated. The resulting material was purified by column chromatography (50% ethyl acetate in hexane) to yield 16 mg (14%) of the undesired triketone byproduct (**2.S4**). $R_f = 0.44$ (50% ethyl acetate in hexane); ^1H NMR (600 MHz, CDCl_3): δ 8.05 (dd, $J = 5.0, 1.8$ Hz, 1H), 7.31 (dd, $J = 7.2, 1.8$ Hz, 1H), 6.82 (dd, $J = 7.2, 5.0$ Hz, 1H), 2.86 (s, 2H), 2.67-2.50 (m, 3H), 2.36 (t, $J = 7.4$ Hz, 2H), 2.06 (s, 3H) 1.96 (t, $J = 7.4$ Hz, 2H); ^{13}C NMR (150 MHz, CDCl_3): δ 214.6, 161.8, 146.1, 140.2, 117.8, 116.8, 59.3, 52.9, 37.8, 36.3, 35.5, 29.9, 26.9; IR (film) 2951, 2926, 1721, 1588 cm^{-1} ; HRMS (EI) calcd for $[\text{C}_{16}\text{H}_{19}\text{NO}_4]^+$ (M^+): m/z 290.1314, found 290.1388. The remaining material (36 mg, 31%) was of alcohol **2.S3**. $R_f = 0.22$ (50% ethyl acetate in hexane); ^1H NMR (600 MHz, CDCl_3): δ 8.12 (dd, $J = 4.9, 1.9$ Hz, 1H), 7.57 (dd, $J = 7.3, 1.9$ Hz, 1H), 6.91 (dd, $J = 7.2, 4.9$ Hz, 1H), 3.98 (s, 3H), 3.66 (s, 1H), 3.04 (dd, $J = 107.9, 14.4$ Hz, 2H), 2.56-2.36 (m, 4H), 2.15-1.79 (m, 4H); ^{13}C NMR (150 MHz, CDCl_3): δ 217.1, 217.1, 161.7, 161.7, 147.1, 147.1, 141.4, 141.4, 120.9, 120.9, 117.8, 117.8, 82.1, 82.1, 56.9, 56.9, 53.9, 53.9, 51.5, 51.5, 37.8, 37.8, 34.8, 34.8, 33.1, 33.1, 31.5, 31.5, 28.4, 28.4 [Benzene present in spectrum $\delta = 128.4$ ppm]; IR (film) 3435, 2952, 1722, 1587, 1466, 1413 cm^{-1} ; HRMS (EI) calcd for $[\text{C}_{16}\text{H}_{19}\text{NO}_4]^+$ (M^+): m/z 290.1314, found 290.1390.



A 50 mL round-bottom flask equipped with a magnetic stir bar was charged with alcohol **2.S3** (0.14 g, 0.47 mmol, 1.0 equiv), toluenesulfonic acid monohydrate (0.36 g, 1.9 mmol, 4.0 equiv), and toluene (16 mL). The heterogeneous mixture was heated to 50 °C and carefully monitored by TLC. After 25 minutes, the starting material was consumed as determined by TLC, and the reaction mixture was cooled to room temperature, diluted with ethyl acetate (20 mL) and washed with saturated aqueous NaHCO_3 (4 x 10 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated to give 89 mg (70%) of enone **2.97**, which did not require purification. $R_f = 0.44$ (50% ethyl acetate in hexane); ^1H NMR (500 MHz, CDCl_3): δ 8.06 (dd, $J = 5.0, 1.8$ Hz, 1H), 7.27 (dd, $J = 7.3, 1.8$ Hz, 1H), 6.82 (dd, $J = 7.2, 5.0$ Hz, 1H), 6.00 (s, 1H), 2.99 (dd, $J = 131.8, 13.6$ Hz, 2H), 2.74-2.57 (m, 4H), 2.43-2.32 (m, 2H), 2.12 (ddd, $J = 17.4, 5.5, 1.7$ Hz, 1H), 1.71 (td, $J = 14.1, 5.3$ Hz, 1H); ^{13}C NMR (150 MHz, CDCl_3): δ 215.1, 198.0, 168.6, 162.2, 146.2, 139.7, 124.8, 118.1, 53.3, 53.1, 36.0, 33.9, 32.7, 27.3; IR (film) 2950, 2926, 1744, 1667, 1587, 1467 cm^{-1} ; HRMS (EI) calcd for $[\text{C}_{16}\text{H}_{17}\text{NO}_3]^+$ (M^+): m/z 272.1208, found 272.1278. 82% *ee* by HPLC using a Phenomenex Lux 5 micron cellulose-1 column (250 x 4.5 mm), 1 mL/min, 10% isopropanol in hexane, racemic $t_R = 23.314$ and 19.672 min; enantioenriched $t_R = 23.097$ (major) and 19.637 (minor) min, UV 220 nm.



A 50 mL round-bottom flask equipped with a magnetic stir bar was charged with enone **2.97** (0.43 mg, 1.6 mmol, 1.0 equiv), ethylene glycol (1.7 mL, 31 mmol, 20 equiv), toluenesulfonic acid monohydrate (1.2 g, 6.3 mmol, 4.0 equiv), palladium on carbon (43 mg, 10 wt%), and THF (20 mL) to give a light gray, heterogeneous solution. The atmosphere was exchanged for hydrogen and the reaction was allowed to stir for 16 h at 23 °C. The solution turned from light gray to black during this time. The mixture was filtered through a pad of Celite and washed with ethyl acetate (20 mL). The solution was transferred to a separatory funnel and washed with NaHCO₃ (3 x 50 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated to give 0.48 g (96%) of ketal **2.98**, which did not require further purification. *R*_f = 0.50 (50% ethyl acetate in hexane); ¹H NMR (600 MHz, CDCl₃): δ 7.97 (dd, *J* = 5.0, 1.8 Hz, 1H), 7.29 (dd, *J* = 7.2, 1.8 Hz, 1H), 6.73 (dd, *J* = 7.2, 5.0 Hz, 1H), 3.92-3.86 (m, 4H), 3.86 (s, 3H), 2.84 (dd, *J* = 267.2, 13.5 Hz, 2H), 2.26 (ddd, *J* = 18.9, 8.2, 5.1 Hz, 1H), 2.06 (dtd, *J* = 31.7, 15.5, 7.9 Hz, 3H), 1.97-1.89 (m, 3H), 1.78-1.63 (m, 2H), 1.47-1.40 (m, 3H); ¹³C NMR (150 MHz, CDCl₃) [The carbonyl C was not observed]: δ 162.5, 145.1, 140.3, 120.2, 116.7, 108.4, 64.3, 63.9, 53.0, 52.3, 39.2, 36.0, 35.2, 33.1, 30.6, 27.1, 23.7; IR (film) 2949, 2892, 1734, 1635, 1586, 1465 cm⁻¹; HRMS (EI) calcd for [C₁₈H₂₃NO₄]⁺ (*M*⁺): *m/z* 318.1627, found 318.1703.

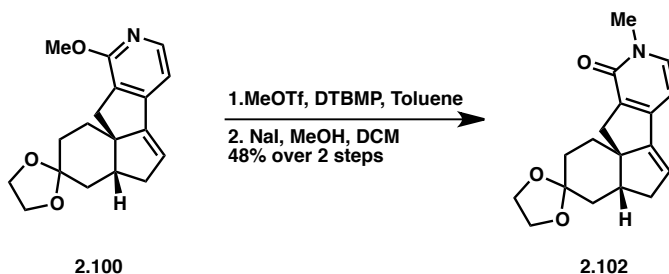


A 25 mL round-bottom flask equipped with a magnetic stir bar was charged with ketone **2.98** (0.11 g, 0.35 mmol, 1.0 equiv) and THF (1.5 mL) and cooled to -78 °C. A 0.5 M solution of KHMDS in THF (2.1 mL, 1.1 mmol, 3.0 equiv) was added and the reaction mixture was allowed to stir at -78 °C for 1 h, and *N*-phenyl triflimide (0.64 g, 1.8 mmol, 5.0 equiv) was added in one portion. After an additional 2.5 hours at -78 °C, the reaction mixture was quenched with saturated aqueous NaHCO₃ (5 mL). The biphasic solution was extracted with ethyl acetate (2 x 10 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated. The resulting product was purified by column chromatography (10% ethyl acetate in hexane with 1% triethylamine) to give 39 mg (23%) of vinyl triflate **2.99**. Starting material can also be recovered and re-subjected to the reaction conditions. *R*_f = 0.73 (50% ethyl acetate in hexane); ¹H NMR (400 MHz,

CDCl₃): δ 8.05 (dd, J = 4.8, 1.6 Hz, 1H), 7.39-7.37 (m, 1H), 6.83-6.80 (m, 1H), 5.54 (s, 1H), 3.95-3.89 (m, 7H), 3.02-2.60 (m, 2H), 2.26-2.04 (m, 3H), 1.91-1.82 (m, 2H), 1.79-1.61 (m, 2H); ¹³C NMR (150 MHz, CDCl₃): δ 162.8, 152.3, 145.2, 139.9, 120.1, 116.6, 113.7, 108.6, 64.2, 63.9, 53.1, 49.6, 38.0, 35.8, 34.6, 32.2, 30.6, 29.2; IR (film) 2951, 1733, 1646, 1587, 1466 cm⁻¹; HRMS (EI) calcd for [C₁₉H₂₂F₃NO₆S]⁺ (M⁺): m/z 450.1120, found 450.1191.



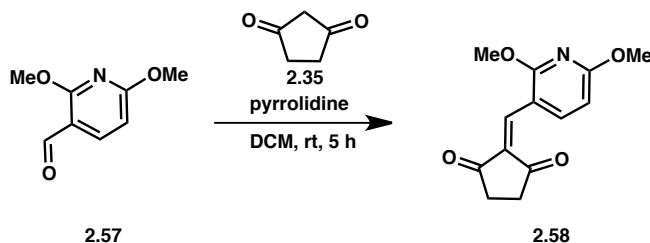
A 25 mL Schlenk flask was charged with vinyl triflate **2.99** (39 mg, 0.087 mmol, 1.0 equiv), palladium acetate (2 mg, 10 mol%), DavePhos (10 mg, 30 mol%), and potassium carbonate (46 mg, 0.33 mmol, 3.8 equiv). The Schlenk flask was evacuated and refilled with nitrogen gas three times. DMF (0.3 mL) was then added under a nitrogen atmosphere. The reaction mixture was heated to 80 °C and held at this temperature for 18 h. The solution was then filtered through Celite and washed with ethyl acetate (10 mL). The filtrate was washed with water (3 x 5 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated. The resulting product was purified by column chromatography (25% ethyl acetate in hexane) to yield 17 mg (66%) of tetracycle **2.100**. R_f = 0.66 (25% ethyl acetate in hexane); ¹H NMR (600 MHz, CDCl₃): δ 8.00 (d, J = 5.1 Hz, 1H), 6.90 (d, J = 5.2 Hz, 1H), 5.85 (bs, 1H), 4.01-3.90 (m, 7H), 3.15 (ddd, J = 16.4, 10.7, 1.6 Hz, 1H), 2.76 (d, J = 15.9 Hz, 1H), 2.54-2.50 (m, 1H), 2.45 (d, J = 15.9 Hz, 1H), 2.43-2.39 (m, 1H), 1.89-1.82 (m, 2H), 1.76-1.71 (m, 1H), 1.67-1.63 (m, 2H), 1.42 (dd, J = 13.5, 1.2 Hz, 1H); ¹³C NMR (150 MHz, CDCl₃): δ 162.0, 156.8, 145.9, 145.3, 129.0, 121.1, 110.9, 109.5, 64.4, 63.7, 54.9, 53.2, 47.8, 41.0, 37.2, 34.3, 30.9, 29.8; IR (film) 2926, 2853, 1596, 1561, 1465, 1403 cm⁻¹; HRMS (EI) calcd for [C₁₈H₂₁NO₃]⁺ (M⁺): m/z 300.1521, found 300.1587.



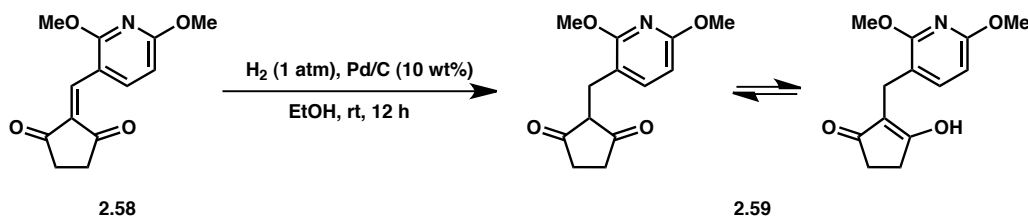
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A 4 mL vial was charged with pyridine **2.100** (2.7 mg, 0.009 mmol, 1.0 equiv), 2,6-di-*tert*-butyl-4-methyl pyridine (3.7 mg, 0.018 mmol, 2 equiv), and toluene (250 μ L) and cooled to 0 °C. Methyl triflate (20 μ L, 0.180 mmol, 20 equiv) was added and the solution was allowed to warm to room temperature and stir for 3 h. The reaction mixture was then

concentrated and re-dissolved in 1:1 methanol/DCM (300 μ L). Sodium iodide (16 mg, 0.108 mmol, 12 equiv) was added and the solution was allowed to stir at room temperature for 15 h. After this time period, the reaction was concentrated and purified by column chromatography (100% DCM) to provide *N*-methyl pyridone **2.102** (1.3 mg, 48%). R_f = 0.33 (100% DCM); ^1H NMR (500 MHz, CDCl_3): δ 7.57-7.55 (m, 1H), 6.51 (dd, J = 7.2, 0.7 Hz, 1H), 5.98-5.97 (m, 1H), 4.67-4.66 (m, 1H), 4.02-3.91 (m, 4H), 3.61-3.58 (m, 2H), 3.22-3.18 (m, 1H), 2.79-2.75 (m, 1H), 2.57-2.51 (m, 1H), 2.47-2.40 (m, 2H), 1.91-1.87 (m, 2H), 1.81-1.74 (m, 1H), 1.71-1.65 (m, 2H), 1.45-1.41 (m, 1H).

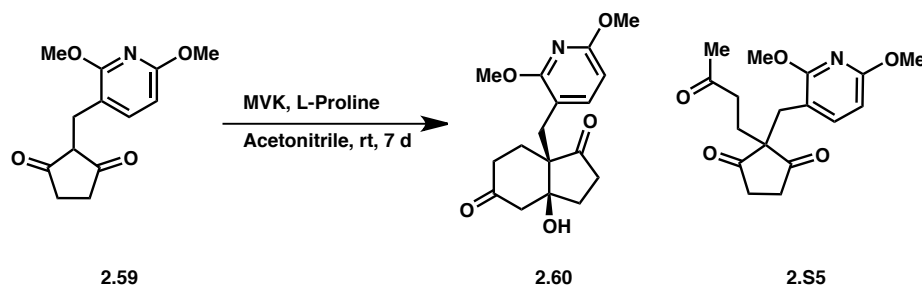


A 1 L round-bottom flask equipped with a magnetic stir bar was charged with 2,6-dimethoxy-3-formylpyridine **2.57** (19.6 g, 0.12 mol, 1.5 equiv), pyrrolidine (6.4 mL, 0.078 mol, 1.0 equiv), and DCM (200 mL). In a separate flask, 1,3-cyclopentanedione (7.7 g, 0.078 mol, 1.0 equiv) and pyrrolidine (3.2 mL, 0.039 mol, 0.50 equiv) were dissolved in DCM (200 mL) and then added to the reaction mixture. The solution was stirred at room temperature for 5 h. At that point, 400 mL of 1 M HCl (aq) was added. The solution was allowed to stir vigorously for 1 h, at that time the phases were allowed to separate and the aqueous layer was extracted with 200 mL DCM. The aqueous layer was then neutralized with NaOH (aq) and extracted with DCM (2 x 300 mL). The combined DCM layers were dried over magnesium sulfate, filtered, and concentrated. The resulting solid was purified by column chromatography (100% DCM) to yield 16.1 g (83%) of enone **2.58**. R_f = 0.75 (12% Methanol in DCM); ^1H NMR (600 MHz, CDCl_3): δ 9.56 (d, J = 8.9 Hz, 1H), 8.27 (s, 1H), 6.43 (d, J = 8.9 Hz, 1H), 4.04 (s, 3H), 4.01 (s, 3H), 2.78-2.68 (m, 4H); ^{13}C NMR (125 MHz, CDCl_3): δ 203.4, 202.6, 168.2, 165.7, 145.7, 143.8, 125.9, 109.4, 103.6, 54.4, 54.3, 34.7, 34.4; IR (film) 1620, 1550 cm^{-1} ; HRMS (EI) calcd for $[\text{C}_{13}\text{H}_{13}\text{NO}_4]^+$ (M^+): m/z 248.0854, found 248.0919.

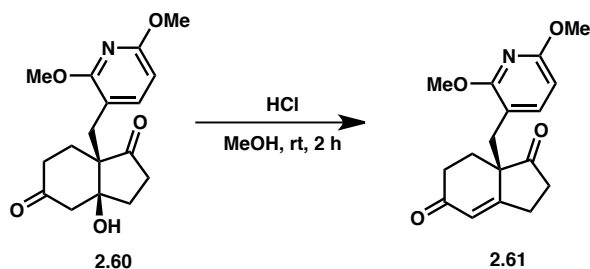


A 250 mL round-bottom flask equipped with a magnetic stir bar was charged with enone **2.58** (2.6 g, 0.01 mol), ethanol (90 mL), and palladium on carbon (0.26 g, 10 wt %). The atmosphere was exchanged for hydrogen gas and the solution was allowed to stir for 12 h. The reaction mixture was then filtered through Celite, which was washed with ethyl acetate (3 x 150 mL) then concentrated. The resulting solid was purified by column

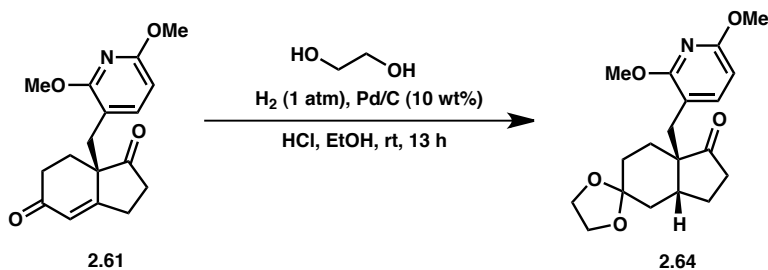
chromatography (8% methanol in DCM). This yielded 2.16 g (81%) of the desired pyridine dione (**2.59**). $R_f = 0.61$ (12% Methanol in DCM); ^1H NMR (600 MHz, CDCl_3): δ 7.47 (d, $J = 8.0$, 1H), 6.29 (d, $J = 8.0$ Hz, 1H), 4.07 (s, 3H), 3.86 (s, 3H), 3.33 (s, 2H), 2.46-2.42 (m, 4H); ^{13}C NMR (150 MHz, CDCl_3): δ 161.6, 158.3, 142.2, 117.3, 112.6, 102.4, 53.8, 53.6, 19.9 [The carbonyl C's were not observed]; IR (film) 3389, 2945, 1589 cm^{-1} ; HRMS (EI) calcd for $[\text{C}_{13}\text{H}_{15}\text{NO}_4]^+$ (M^+): m/z 250.1001, found 250.1076.



A 50 mL Schlenk flask was charged with pyridinedione **2.59** (0.48 g, 1.9 mmol, 1.0 equiv), methyl vinyl ketone (0.32 mL, 3.9 mmol, 2.0 equiv), and acetonitrile (22 mL). Three 10-minute freeze pump thaw cycles were performed. After the third cycle, L-proline (67 mg, 0.58 mmol, 0.30 equiv) was added in one portion to the frozen reaction and the Schlenk flask was evacuated and re-filled with nitrogen gas. The solution was allowed to warm under a nitrogen atmosphere and stirred in the dark for one week. It was important that the reaction mixture was not exposed to light. After 7 days, the solution was diluted with 100 mL of ethyl acetate and washed with water (3 x 50 mL). The organic layer was dried over magnesium sulfate and concentrated. The resulting solid was triturated with 3% ethyl acetate in hexane (3 x 15 mL). These washes were concentrated to yield 0.16 g (26%) of the undesired triketone byproduct (**2.S5**). $R_f = 0.56$ (50% ethyl acetate in hexane); ^1H NMR (400 MHz, CDCl_3): δ 7.22 (d, $J = 8.0$ Hz, 1H), 5.623 (d, $J = 8.0$ Hz, 1H), 3.87 (s, 3H), 3.84 (s, 3H), 2.79 (s, 2H), 2.66-2.48 (m, 4H), 2.34 (t, $J = 7.4$ Hz, 2H), 2.06 (s, 3H), 1.95 (t, $J = 7.4$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 215.6, 208.8, 163.0, 161.3, 142.9, 108.8, 101.4, 60.3, 53.9, 53.1, 38.2, 35.9, 35.6, 30.0, 26.4 [Benzene present in spectrum $\delta = 128.4$ ppm]; IR (film) 2947, 1720, 1604 cm^{-1} ; HRMS (EI) calcd for $[\text{C}_{17}\text{H}_{21}\text{NO}_5]^+$ (M^+): m/z 320.1420, found 320.1494. The remaining material (0.32 g, 60%) was of the desired product (**2.60**), which did not require any further purification. $R_f = 0.27$ (50% ethyl acetate in hexane); ^1H NMR (400 MHz, CDCl_3): δ 7.48 (d, $J = 8.0$ Hz, 1H), 6.34 (d, $J = 8.0$ Hz, 1H), 3.99 (s, 3H), 3.91 (s, 3H), 3.07-2.87 (dd, $J = 14.8, 44.8$ Hz, 2H), 2.55-2.33 (m, 4H), 2.16-2.04 (m, 2H), 1.99-1.76 (m, 4H); ^{13}C NMR (125 MHz, CDCl_3): δ 218.6, 209.5, 163.2, 159.9, 144.6, 109.7, 102.9, 82.2, 56.3, 53.7, 53.6, 51.0, 37.2, 34.3, 33.0, 30.5, 28.4; IR (film) 3388, 2949, 1721, 1604, 1586 cm^{-1} ; HRMS (EI) calcd for $[\text{C}_{17}\text{H}_{21}\text{NO}_5]^+$ (M^+): m/z 320.1420, found 320.1490.

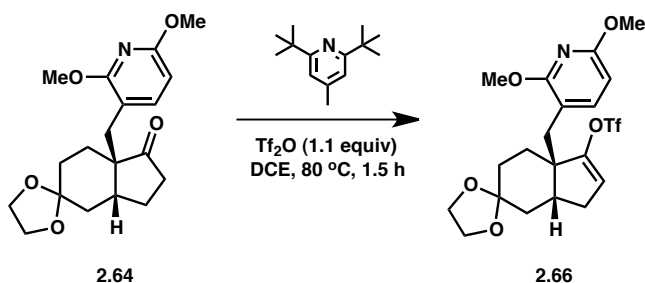


A 250 mL round-bottom flask equipped with a magnetic stir bar was charged with ketone **2.60** (0.32 g, 1.0 mmol) and 1 M anhydrous HCl in methanol (100 mL). The reaction progress was monitored by TLC. After 2 h, the starting material had been consumed. The solution was neutralized with 1 M NaOH, diluted with ethyl acetate (100 mL), and washed with water (3 x 50 mL). The combined organic layer was dried over magnesium sulfate, filtered, and concentrated, furnishing 0.29 g (83%) of enone **2.61**, which did not require any purification. R_f = 0.46 (50% ethyl acetate in hexane); ^1H NMR (400 MHz, CDCl_3): δ 7.24 (d, J = 8.0, 1H), 6.30 (d, J = 8.0, 1H), 6.06 (s, 1H), 3.93 (s, 3H), 3.89 (s, 3H), 3.13-2.84 (dd, J = 14.0, 82.4 Hz, 2H), 2.78 (m, 2H), 2.69 (m, 1H), 2.49 (m, 1H), 2.48 (m, 2H), 2.21 (m, 1H), 1.80 (dt, J = 5.6, 8.8 Hz, 1H) [Benzene present in spectrum δ = 7.3 ppm]; ^{13}C NMR (100 MHz, CDCl_3): δ 215.6, 6198.2, 169.4, 164.1, 161.0, 143.2, 124.6, 109.4, 100.9, 53.7, 53.5, 53.0, 35.9, 33.3, 32.8, 27.2, 27.1 [Benzene present in spectrum δ = 129.7 ppm]; IR (film) 2948, 1743, 1668, 1603, 1586 cm^{-1} ; HRMS (EI) calcd for $[\text{C}_{17}\text{H}_{19}\text{NO}_4]^+$ (M^+): m/z 302.1314, found 302.1389. 87% *ee* by HPLC using a Phenomenex Lux 5 micron cellulose-1 column (250 x 4.5 mm), 1 mL/min, 1% isopropanol in hexane; racemic t_R = 7.634 and 6.576 min; enantioenriched t_R = 7.521 (major) and 6.509 (minor) min, UV 254 nm.



A 100 mL round-bottom flask equipped with a magnetic stir bar was charged with enone **2.61** (0.58 g, 2.0 mmol, 1.0 equiv), palladium on carbon (58 mg, 10 wt%), ethylene glycol (2.3 mL, 0.038 mol, 20 equiv) and 0.2 M anhydrous HCl in ethanol (20 mL). The atmosphere was exchanged for hydrogen and the solution was allowed to stir for 13 h, filtered through Celite, and washed with ethyl acetate (3 x 50 mL). The filtrate was transferred to a separatory funnel and washed with saturated aqueous NaHCO_3 (4 x 100 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated to give 0.63 g (94%) of the desired ketal (**2.64**), which did not require further purification. R_f = 0.71 (50% ethyl acetate in hexane); ^1H NMR (400 MHz, CDCl_3): δ 7.28 (d, J = 8.0 Hz, 1H), 6.24 (d, J = 8.0 Hz, 1H), 4.00-3.94 (m, 4H), 3.91 (d, J = 2.5 Hz, 6H), 2.83 (dd, J = 177.3, 13.8 Hz, 2H), 2.33 (ddd, J = 18.6, 8.7, 4.6 Hz, 1H), 2.21-1.93 (m, 5H), 1.86-1.68 (m, 2H), 1.55-1.46 (m, 3H); ^{13}C NMR (125 MHz, CDCl_3): δ 221.2, 162.5, 161.6, 143.8,

110.5, 109.0, 101.0, 64.5, 64.1, 53.7, 53.2, 52.5, 39.3, 36.0, 35.5, 32.6, 30.8, 27.1, 23.7 [Benzene present in spectrum δ = 128.4 ppm]; IR (film) 2948, 1737, 1603, 1585, 1102 cm^{-1} ; HRMS (EI) calcd for $[\text{C}_{19}\text{H}_{25}\text{NO}_5]^+$ (M^+): m/z 348.1733, found 348.1805.

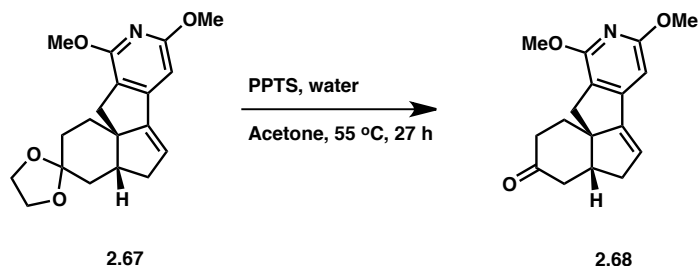


A 25 mL round-bottom flask equipped with a magnetic stir bar was charged with ketal **2.64** (0.475 g, 1.4 mmol, 1.0 equiv), 2,6-di-*t*-butyl-4-methyl-pyridine (0.42 g, 2.0 mmol, 1.5 equiv) and DCE (3.4 mL). The solution was cooled to 0 °C and triflic anhydride (0.25 mL, 1.5 mol, 1.1 equiv) was added slowly. After 5 min of stirring, the solution was warmed to room temperature and allowed to stir for 20 minutes. The reaction mixture was then heated to 80 °C and held at this temperature for 1.5 h. Upon cooling to room temperature, a white precipitate formed. This mixture was filtered by vacuum filtration and the filtrate was concentrated. The resulting brown residue (**2.66**) was taken on to the next step without purification. R_f = 0.59 (20% ethyl acetate in hexane); ^1H NMR (600 MHz, CDCl_3): δ 7.29 (d, J = 7.9 Hz, 1H), 6.23 (d, J = 7.9 Hz, 1H), 5.51 (t, J = 2.4 Hz, 1H), 3.94-3.90 (m, 4H), 3.90 (d, J = 2.5 Hz, 6H), 2.91-2.55 (dd, J = 127.2, 9.2 Hz, 4H), 2.25-2.07 (m, 4H), 1.87-1.82 (m, 1H), 1.75-1.69 (m, 2H), 1.65-1.56 (m, 2H); ^{13}C NMR (125 MHz, CDCl_3): δ 161.9, 161.3, 152.7, 142.7, 113.5, 110.4, 108.7, 108.7, 100.3, 64.2, 64.0, 53.5, 53.1, 49.6, 37.8, 35.7, 33.8, 32.3, 30.6, 29.2; IR (film) 2946, 1604, 1586, 1209, 1141 cm^{-1} ; HRMS (EI) calcd for $[\text{C}_{20}\text{H}_{24}\text{F}_3\text{NO}_7\text{S}]^+$ (M^+): m/z 480.1226, found 480.1299.

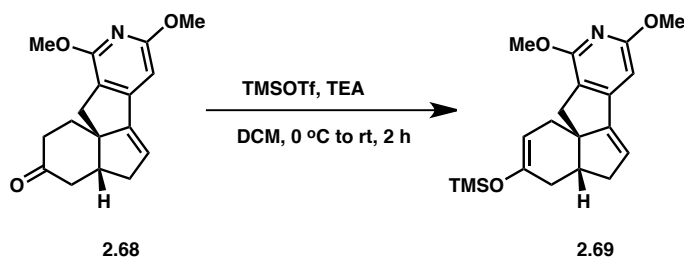


A 25 mL Schlenk flask was charged with crude vinyl triflate **2.66** (1.4 mmol, 1.0 equiv), palladium acetate (30 mg, 10 mol%), DavePhos (0.16 g, 30 mol%), potassium carbonate (700 mg, 0.005 mol, 3.8 equiv), and 2,6-di-*tert*-butyl-4-methylpyridine (0.29 g, 1.4 mmol, 1.0 equiv). The Schlenk flask was evacuated and refilled with nitrogen gas three times. DMF (4.4 mL) was then added under a nitrogen atmosphere. The reaction mixture was heated to 100 °C for 20 h. The solution was then filtered through Celite and washed with ethyl acetate (3 x 50 mL). The filtrate was washed with water (3 x 50 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated. The resulting

product was purified by column chromatography (5% ethyl acetate in hexane) to yield 0.28 g (62% over two steps) of the desired tetracycle (**2.67**). $R_f = 0.90$ (25% ethyl acetate in hexane); ^1H NMR (600 MHz, CDCl_3): δ 6.31 (s, 1H), 5.84 (broad s, 1H), 4.01-3.86 (m, 10H), 3.16-3.11 (m, 1H), 2.71 (d, $J = 12.1$ Hz, 1H), 2.51 (ddd, $J = 16.3, 7.3, 3.6$ Hz, 1H), 2.43-2.40 (m, 1H), 2.40-2.36 (d, $J = 12.1$ Hz, 1H), 1.88-1.81 (m, 2H), 1.75-1.70 (m, 1H), 1.68-1.60 (m, 2H), 1.45-1.42 (m, 1H); ^{13}C NMR (150 MHz, CDCl_3): δ 162.9, 159.6, 156.9, 148.9, 120.9, 120.3, 109.6, 93.8, 64.5, 63.9, 55.5, 53.9, 53.2, 48.1, 40.9, 36.6, 34.4, 31.2, 29.9; IR (film) 2928, 1615, 1086 cm^{-1} ; HRMS (EI) calcd for $[\text{C}_{19}\text{H}_{23}\text{NO}_4]^+$ (M^+): m/z 330.1627, found 330.1690.

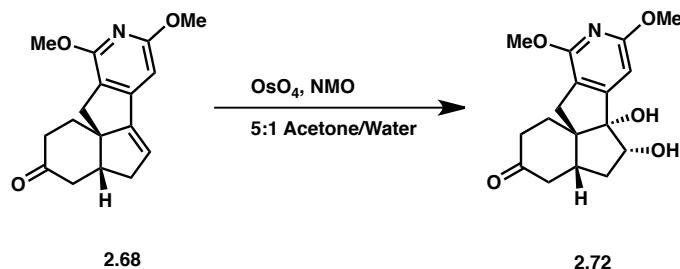


A 50 mL round-bottom flask equipped with a magnetic stir bar was charged with tetracycle **2.67** (0.28 g, 0.84 mmol, 1.0 equiv), pyridinium *p*-toluenesulfonate (0.43 g, 1.7 mmol, 2.0 equiv), acetone (18 mL) and water (8 mL). The solution was heated to 55 °C and held at this temperature for 27 h. The reaction mixture was diluted with ethyl acetate (100 mL) and washed with saturated aqueous NaHCO_3 (3 x 50 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated. This yielded 0.2 g (83%) of ketone **2.68**, without need for further purification. $R_f = 0.71$ (25% ethyl acetate in hexane); ^1H NMR (400 MHz, CDCl_3): δ 6.30 (s, 1H), 5.79 (bs, 1H), 3.94-3.86 (d, 6H), 2.83-2.38 (m, 9H), 2.21 (dddd, $J = 15.1, 5.8, 4.2, 1.4$ Hz, 1H), 1.84 (td, $J = 12.8, 3.5$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 212.9, 163.3, 159.6, 156.3, 148.6, 121.3, 119.9, 94.9, 57.0, 53.9, 53.3, 47.4, 43.5, 42.1, 37.7, 37.1, 32.1; IR (film) 2945, 2862, 1716, 1615, 1569 cm^{-1} ; HRMS (EI) calcd for $[\text{C}_{17}\text{H}_{19}\text{NO}_3]^+$ (M^+): m/z 286.1365, found 286.1440.

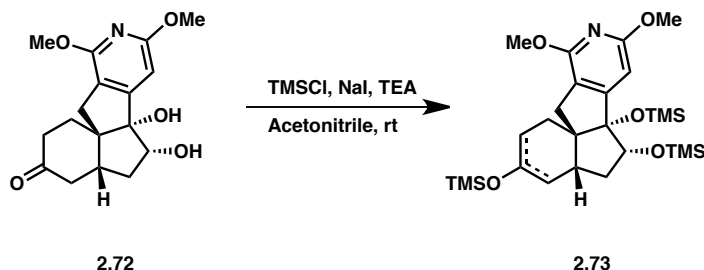


A 4 mL vial equipped with a magnetic stir bar was charged with ketone **2.68** (8 mg, 0.028 mmol, 1.0 equiv), triethylamine (32 μL , 0.23 mmol, 8.0 equiv), and DCM (0.57 mL). The solution was cooled to 0 °C and trimethylsilyl triflate (21 μL , 0.11 mmol, 4.0 equiv) was added and the reaction was warmed to room temperature. After 2.5 h, the reaction mixture was diluted with ethyl acetate (2 mL) and washed with saturated aqueous NaHCO_3 (3 x 1 mL). The organic layer was dried over magnesium sulfate, filtered, and

concentrated to yield 4 mg (99%) of trimethylsilyl enol ether **2.69** as a single regioisomer, which did not require further purification. $R_f = 0.98$ (20% ethyl acetate in hexane); ^1H NMR (400 MHz, CDCl_3): δ 6.32 (s, 1H), 5.83-5.82 (m, 1H), 5.00 (dd, $J = 5.0, 2.1$ Hz, 1H), 3.96 (s, 3H), 3.90 (s, 3H), 2.86-2.79 (m, 1H), 2.69-2.64 (m, 2H), 2.57-2.50 (m, 2H), 2.32-2.28 (m, 1H), 1.95-1.89 (m, 1H), 1.70-1.62 (m, 1H), 1.47-1.41 (m, 1H), 0.23 (s, 9H); ^{13}C NMR (150 MHz, CDCl_3): δ 162.6, 159.4, 156.0, 148.7, 120.5, 119.8, 106.0, 93.6, 55.3, 53.8, 53.1, 47.4, 44.3, 35.9, 28.0, 27.1, 0.3; IR (film) 2947, 1716, 1616, 1456 cm^{-1} ; HRMS (EI) calcd for $[\text{C}_{20}\text{H}_{27}\text{NO}_3\text{Si}]^+$ (M^+): m/z 358.1760, found 358.1833.

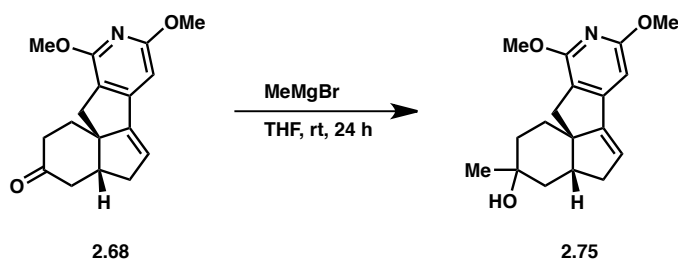


A 4 mL vial equipped with a magnetic stir bar was charged with ketone **2.68** (33 mg, 0.12 mmol, 1.0 equiv), NMO (67 mg, 0.57 mmol, 5.0 equiv), osmium tetroxide (2.5% solution of *tert*-butanol, 67 μL , 0.0057 mmol, 0.05 equiv), acetone (0.3 mL) and water (60 μL). The solution was allowed to stir for 4 h, at which point it was diluted with saturated aqueous Na_2SO_3 (1 mL) and ethyl acetate (1 mL). The biphasic mixture was washed with water (2 x 1 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated. This yielded 27 mg (73%) of diol **2.72** as a single diastereomer, which did not require further purification. $R_f = 0.22$ (20% ethyl acetate in hexane); ^1H NMR (600 MHz, CDCl_3): δ 6.26 (s, 1H), 4.24 (dd, $J = 7.5, 4.1$ Hz, 1H), 3.96-3.89 (d, $J = 26.4$ Hz, 6H), 2.87-2.81 (d, $J = 3.0$ Hz, 2H), 2.57-2.44 (m, 3H), 2.37-2.26 (m, 2H), 2.11-2.06 (m, 2H), 1.83 (dt, $J = 13.0, 3.7$ Hz, 1H), 1.63-1.58 (m, 1H), 1.27-1.25 (m, 1H); ^{13}C NMR (150 MHz, CDCl_3): δ 213.3, 164.2, 159.4, 158.9, 114.2, 95.3, 90.5, 53.9, 53.5, 53.3, 44.2, 42.3, 40.8, 39.2, 36.6, 30.3, 27.6; IR (film) 3413, 2948, 1712, 1615, 1588 cm^{-1} ; HRMS (EI) calcd for $[\text{C}_{17}\text{H}_{21}\text{NO}_5]^-$ (M^-): m/z 318.1420, found 318.1348.

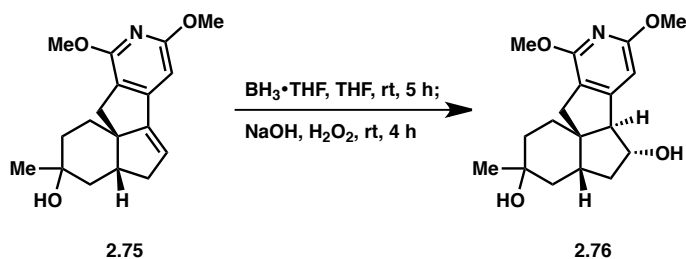


A 4 mL vial equipped with a magnetic stir bar was charged sequentially with diol **2.72** (7.5 mg, 0.023 mmol, 1.0 equiv), triethylamine (33 μL , 0.23 mmol, 10 equiv), trimethylsilyl chloride (30 μL , 0.23 mmol, 10 equiv), acetonitrile (0.25 mL) and sodium iodide (35 mg, 0.23 mmol, 10 equiv). Upon addition of the sodium iodide, the solution immediately became cloudy. After 35 min, the reaction mixture was diluted with ethyl

acetate (2 mL) and washed with saturated aqueous NaHCO₃ (3 x 1 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated. The crude oil was purified by column chromatography (10% ethyl acetate in hexane) to yield 7.9 mg (63%) of trimethylsilyl enol ether **2.73** as a 1:1 mixture of regioisomers. *R*_f = 0.95 (20% ethyl acetate in hexane); ¹H NMR (400 MHz, CDCl₃): δ 6.30 (s, 1H), 6.28 (s, 1H), 4.93-4.91 (m, 1H), 4.82-4.80 (m, 1H), 4.16-4.10 (m, 2H), 3.94 (s, 3H), 3.93 (s, 3H), 3.91 (s, 3H), 3.90 (s, 3H), 2.68-2.64 (m, 1H), 2.57-2.55 (m, 2H), 2.52-2.47 (m, 1H), 2.25-2.13 (m, 4H), 2.03-1.78 (m, 10H), 0.19 (s, 18H), 0.16-0.14 (s, 18H), 0.02-0.00 (s, 9H), -0.05 (s, 9H); ¹³C NMR (150 MHz, CDCl₃): δ 162.7, 161.7, 161.6, 158.9, 150.9, 115.6, 114.6, 105.0, 101.7, 96.6, 95.6, 92.2, 92.0, 78.4, 76.1, 53.8, 53.8, 53.2, 52.9, 41.4, 41.2, 40.6, 38.3, 31.2, 27.8, 27.5, 26.8, 2.6, 2.3, 0.6, 0.5, 0.3; IR (film) 3417, 2954, 1717, 1617, 1457 cm⁻¹; HRMS (EI) calcd for [C₂₆H₄₅NO₅Si₃]⁺ (M⁺): *m/z* 536.2606, found 536.2675.

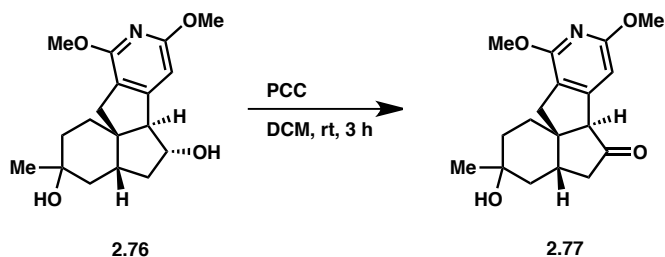


A 4 mL vial equipped with a magnetic stir bar was charged with ketone **2.68** (31 mg, 0.11 mmol, 1.0 equiv) and THF (1.3 mL) and cooled to 0 °C. A solution of 3 M methyl magnesium bromide in diethyl ether (0.18 mL, 0.54 mmol, 5.0 equiv) was added. After 5 minutes the reaction mixture was allowed to warm to room temperature. The reaction mixture was stirred for 24 h, and then quenched with saturated aqueous NaHCO₃ (1 mL) and extracted with ethyl acetate (3 x 2 mL). The combined organic layer was dried over magnesium sulfate, filtered, and concentrated to give alkene **2.75** as a yellow oil that was taken forward to the next step without purification. *R*_f = 0.58 (25% ethyl acetate in hexane); ¹H NMR (600 MHz, CDCl₃): δ 6.32 (s, 1H), 5.86 (s, 1H), 3.94 (s, 3H), 3.90 (s, 3H), 3.28-3.23 (m, 1H), 2.64 (d, *J* = 15.1 Hz, 1H), 2.55 (ddd, *J* = 16.2, 7.5, 3.5 Hz, 1H), 2.31 (d, *J* = 15.8 Hz, 1H), 2.27-2.23 (m, 1H), 1.85-1.77 (m, 2H), 1.66-1.59 (m, 2H), 1.56-1.52 (m, 2H), 1.27 (m, 3H); ¹³C NMR (150 MHz, CDCl₃): δ 162.9, 159.4, 157.2, 149.0, 121.6, 120.2, 93.6, 70.2, 55.5, 54.1, 53.3, 47.2, 41.9, 37.5, 36.6, 35.3, 33.2, 30.4, 27.8; IR (film) 3399, 2922, 2857, 1615, 1570 cm⁻¹; HRMS (EI) calcd for [C₁₈H₂₃NO₃]⁺ (M⁺): *m/z* 302.1678, found 302.1752.

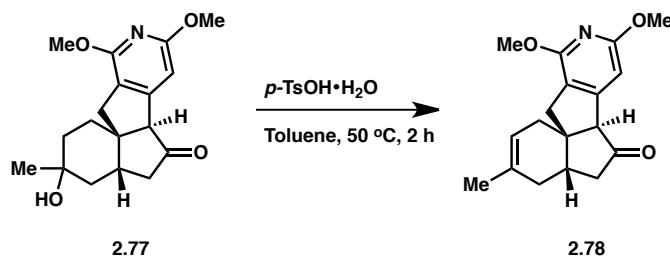


A 4 mL vial equipped with a magnetic stir bar was charged with the crude alkene (**2.75**)

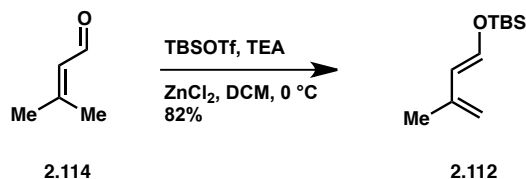
from the previous step (0.11 mmol, 1.0 equiv), THF (2.3 mL), and 1 M borane in THF (0.54 mL, 0.54 mmol, 5.0 equiv). The solution was allowed to stir for 5 hours, at which point 4 M sodium hydroxide (2.8 mL) and 30% aqueous hydrogen peroxide solution (2.8 mL) were added. The solution was stirred vigorously, open to the atmosphere for an additional 4 hours, at which point saturated aqueous NaHCO_3 (1 mL) and saturated aqueous Na_2SO_3 (1 mL) were added. This mixture was extracted with ethyl acetate (4 x 5 mL). The combined organic layer was dried over magnesium sulfate, filtered, and concentrated. The resulting material was purified by column chromatography (50% ethyl acetate in hexane) to yield 16 mg (46% over two steps) of alcohol **2.76**. $R_f = 0.27$ (50% ethyl acetate in hexane); ^1H NMR (600 MHz, CDCl_3): δ 6.30 (s, 1H), 4.15-4.10 (m, 1H), 3.93 (s, 3H), 3.88 (s, 3H), 3.07 (d, $J = 3.3$ Hz, 1H), 2.71 (d, $J = 15.8$ Hz, 1H), 2.45 (d, $J = 15.8$ Hz, 1H), 2.34-2.29 (m, 1H), 2.27-2.22 (m, 1H), 2.12-2.08 (m, 1H), 1.73-1.49 (m, 6H), 1.26 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3): δ 162.9, 160.4, 158.6, 114.7, 96.2, 79.5, 69.8, 66.3, 53.8, 53.2, 51.5, 42.0, 41.2, 38.9, 36.8, 36.3, 32.0, 30.7; IR (film) 3379, 2923, 1614, 1583 cm^{-1} ; HRMS (EI) calcd for $[\text{C}_{18}\text{H}_{25}\text{NO}_4]^+$ (M^+): m/z 320.1784, found 320.1853.



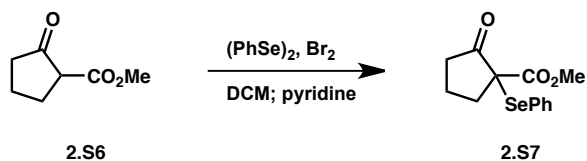
A 4 mL vial equipped with a magnetic stir bar was charged with pyridinium chlorochromate (19 mg, 0.090 mmol, 6.0 equiv) and DCM (0.1 mL). To this mixture was added alcohol **2.76** (5 mg, 0.015 mmol, 1.0 equiv) in DCM (0.1 mL). After stirring for 3 hours at 23 °C, the solution was diluted with diethyl ether (0.5 mL). The organic solvents were decanted from the dark solids, which were washed with ether (2 x 0.5 mL). The combined organic layers were then filtered through a plug of fluorosil and concentrated. The resulting material was purified by column chromatography (50% ethyl acetate in hexane) to yield 3 mg (63%) of keto alcohol **2.77**. $R_f = 0.70$ (50% ethyl acetate in hexane); ^1H NMR (600 MHz, CDCl_3): δ 6.38 (s, 1H), 3.94 (s, 3H), 3.87 (s, 3H), 3.44 (s, 1H), 3.00-2.97 (m, 1H), 2.97 (d, $J = 15.8$ Hz, 1H), 2.60 (d, $J = 15.8$ Hz, 1H), 2.33-2.29 (m, 1H), 2.20-2.16 (m, 1H), 2.09-2.06 (m, 1H), 1.77-1.74 (m, 1H), 1.67-1.62 (m, 4H), 1.32 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 215.6, 171.3, 163.2, 158.9, 153.4, 115.2, 96.9, 70.1, 60.5, 54.1, 53.3, 50.4, 44.7, 38.8, 38.0, 36.2, 29.0, 21.1, 14.2; IR (film) 3380, 2926, 2857, 1732, 1614, 1584 cm^{-1} ; HRMS (EI) calcd for $[\text{C}_{18}\text{H}_{23}\text{NO}_4]^+$ (M^+): m/z 318.1627, found 318.1701.



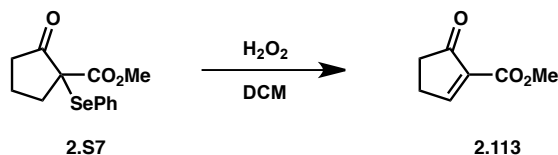
A 4 mL vial equipped with a magnetic stir bar was charged with keto alcohol **2.77** (24 mg, 0.074 mmol, 1.0 equiv), toluenesulfonic acid monohydrate (56 mg, 0.29 mmol, 4.0 equiv), and toluene (2.5 mL) and heated to $50\text{ }^\circ\text{C}$. When the reaction was complete by TLC analysis (2 h), the reaction mixture was diluted with ethyl acetate (2 mL) and washed with saturated aqueous NaHCO_3 (4 x 2 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated. The resulting material was purified by column chromatography (25% ethyl acetate in hexane) to yield 13 mg (60%) of alkene **2.78** as a single regioisomer. $R_f = 0.91$ (25% ethyl acetate in hexane); ^1H NMR (500 MHz, CDCl_3): δ 6.39 (s, 1H), 5.37 (s, 1H), 3.92 (s, 3H), 3.90 (s, 3H), 3.42 (s, 1H), 2.87 (d, $J = 15.9$ Hz, 1H), 2.67 (d, $J = 15.9$ Hz, 1H), 2.54-2.46 (m, 2H), 2.21-2.11 (m, 2H), 2.06-2.01 (m, 1H), 1.87 (ddd, $J = 13.5, 8.8, 5.0$ Hz, 1H), 1.78 (dd, $J = 9.1, 4.0$ Hz, 1H), 1.74 (d, $J = 9.7$ Hz, 3H); ^{13}C NMR (150 MHz, CDCl_3): δ 215.4, 163.0, 158.7, 153.2, 134.7, 122.2, 115.0, 96.6, 64.0, 53.2, 49.6, 45.0, 40.5, 39.3, 29.7, 27.5, 23.6; IR (film) 2919, 1740, 1621, 1582 cm^{-1} ; HRMS (EI) calcd for $[\text{C}_{18}\text{H}_{21}\text{NO}_3]^+$ (M^+): m/z 300.1521, found 300.1597.



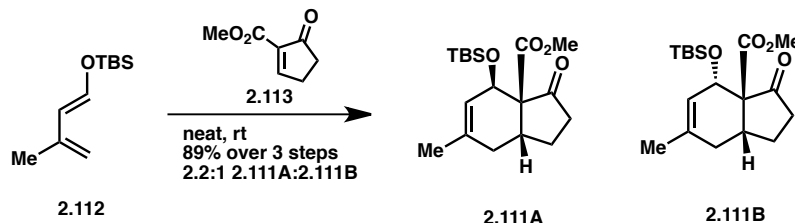
A dry 2 L round-bottom flask was charged with DCM (1.7 L) and 3-methyl-2-butenal (**2.114**, 10 mL, 136 mmol, 1.0 equiv). The solution was cooled to $0\text{ }^\circ\text{C}$ and zinc chloride (1.87 g, 13.6 mmol, 0.10 equiv), triethylamine (28.5 mL, 204 mmol, 1.5 equiv) and TBSOTf (28 mL, 122 mmol, 0.90 equiv) were added sequentially. The reaction was allowed to stir at $0\text{ }^\circ\text{C}$ for 3 h, at which point the reaction was washed with saturated aqueous NaHCO_3 (3 x 500 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated. The resulting oil was purified by column chromatography (3% diethyl ether in pentane) and left under vacuum with stirring overnight to remove any remaining traces of the enal starting material. This provided (E)-diene along with 5% of the (Z)-diene (**2.112**, 19.7 g, 82%). $R_f = 0.95$ (10% ethyl acetate in hexane); ^1H NMR (600 MHz, CDCl_3): δ 6.53 (d, $J = 12.1$ Hz, 1H), 5.83 (d, $J = 12.1$ Hz, 1H), 4.97 (dd, $J = 1.7, 0.8$ Hz, 0.05H), 4.93 (d, $J = 6.6$ Hz, 0.05H), 4.75 (dd, $J = 1.5, 0.7$ Hz, 1H), 4.73 (d, $J = 1.3$ Hz, 0.05H), 4.68 (s, 1H), 2.02 (d, $J = 0.6$ Hz, 0.15H), 1.80 (s, 3H), 0.93 (d, $J = 12.9$ Hz, 9H), 0.16 (d, $J = 0.8$ Hz, 6H); ^{13}C NMR (150 MHz, CDCl_3): δ 142.2, 139.7, 116.1, 112.7, 111.7, 25.5, 18.9, 18.2, -5.2; IR (film) 2930, 2856, 1644, 1472 cm^{-1} ; HRMS (EI) calcd for $[\text{C}_{11}\text{H}_{22}\text{OSi}]^+$ (M^+): m/z 199.1440, found 199.1467.



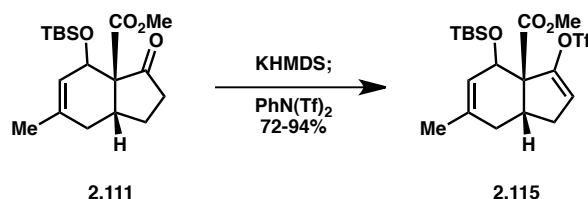
A dry 1 L round-bottom flask was charged with diphenyl diselenide (21.1 g, 67.7 mmol, 0.60 equiv) and DCM (450 mL). Bromine (3.4 mL, 66.5 mmol, 0.59 equiv) was added and the deep purple solution was allowed to stir for 25 min, at which point the solution was cooled to 0 °C. Commercially available β -keto ester **2.S6** (14 mL, 0.113 mol, 1 equiv) and pyridine (13.7 mL, 0.169 mol, 1.5 equiv) were added sequentially. After 10 min, the reaction mixture was allowed to warm to room temperature and stirred for an additional 2 h. The solution was then washed with a 1 N solution of HCl (3 x 300 mL), a saturated solution of sodium bicarbonate (3 x 300 mL) and brine (300 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated. The resulting oil (**2.S7**) was brought on to the next step without further purification.



A dry 250 mL round-bottom flask was charged with selenide **2.S7** (30.1 mmol, 1 equiv) and DCM (150 mL) and cooled to 0 °C. Hydrogen peroxide (9.0 mL) was added and the solution was stirred vigorously until complete by TLC (~30 min). The biphasic reaction mixture was then washed with water (3 x 100 mL), dried over magnesium sulfate, filtered and concentrated to give dienophile **2.113** as a pale-yellow oil, which was brought on without purification. R_f = 0.22 (25% ethyl acetate in hexane); ^1H NMR (600 MHz, CDCl_3): δ 8.39 (t, J = 2.7 Hz, 1H), 3.79 (s, 3H), 2.71 (td, J = 4.7, 2.7 Hz, 2H), 2.52-2.51 (m, 2H); ^{13}C NMR (150 MHz, CDCl_3): δ 202.9, 172.7, 162.3, 137.0, 51.9, 35.6, 26.6; IR (film) 3594, 2954, 1748, 1720, 1436 cm^{-1} ; HRMS (EI) calcd for $[\text{C}_7\text{H}_8\text{NaO}_3]^+$ (M^+): m/z 163.0371, found 163.0367.

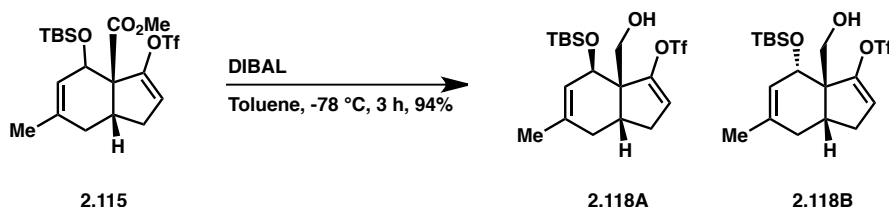


A dry 50 mL round-bottom flask was charged with diene **2.112** (4.0 g, 20.2 mmol, 1.0 equiv) and crude dieneophile **2.113** (30.2 mmol, 1.5 equiv). The reaction mixture was allowed to stir neat at room temperature for 22 h, or until complete as monitored by ^1H NMR. When complete, the reaction mixture was loaded onto silica gel and purified by column chromatography (10% ethyl acetate in hexane). This provided the product as a colorless oil as a 2.2:1 mixture of diastereomers (6.27 g, 89% over 3 steps). R_f (major diastereomer **2.111A**) = 0.29 (10% ethyl acetate in hexane); R_f (minor diastereomer **2.111B**) = 0.17 (10% ethyl acetate in hexane); ^1H NMR (500 MHz): δ 5.55-5.54 (m, 0.6H), 5.51 (dd, J = 2.9, 1.3 Hz, 1H), 4.86 (d, J = 5.1 Hz, 0.6H), 4.71 (d, J = 5.1 Hz, 1H), 3.70-3.70 (m, 3H), 3.70 (d, J = 0.5 Hz, 1.8H), 3.24-3.20 (m, 1H), 3.04-2.99 (m, 0.6H), 2.48-2.43 (m, 1H), 2.34 (d, J = 8.5 Hz, 0.6H), 2.31-2.25 (m, 2H), 2.19-1.95 (m, 4H), 1.72 (s, 1.8H), 1.67 (d, J = 4.8 Hz, 3H), 1.64-1.59 (m, 2H), 0.82 (s, 5H), 0.81 (s, 9H), 0.06-0.02 (m, 10H); ^{13}C NMR (125 MHz, CDCl_3): δ 212.8, 211.2, 171.1, 168.0, 137.4, 134.8, 122.4, 121.5, 66.9, 66.8, 66.2, 62.4, 52.6, 52.5, 39.2, 37.8, 35.0, 33.0, 32.7, 30.6, 27.2, 26.8, 25.8, 25.7, 23.8, 23.6, 17.8, -3.8, -4.4, -4.9, -5.2; IR (film) 2930, 2894, 1736, 1472, 1463, 1434 cm^{-1} ; HRMS (EI) calcd for $[\text{C}_{18}\text{H}_{30}\text{O}_4\text{NaSi}]^+$ (M^+): m/z 361.1811, found 361.1805.



A dry 500 mL round-bottom flask was charged with bicycle **2.111** (9.5 g, 28.1 mmol, 1.0 equiv) and THF (210 mL) and cooled to $-78\text{ }^\circ\text{C}$. A 0.5 M solution of KHMDS in THF (73 mL, 36.5 mmol, 1.3 equiv) was added slowly and the solution was allowed to stir at $-78\text{ }^\circ\text{C}$ for 2 h. After this period, *N*-Phenyl-bis(trifluoromethanesulfonimide) (14.1 g, 39.3 mmol, 1.4 equiv) was added and the reaction mixture was allowed to warm to room temperature. After 3 h at room temperature, the reaction was complete by TLC and was diluted with ethyl acetate (200 mL) and washed with saturated aqueous NaHCO_3 (3 x 150 mL) and brine (100 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated. The resulting oil was purified by column chromatography (2% to 5% diethyl ether in hexane). Any mixed fractions were dissolved in a minimal amount of hot hexane and cooled to $-20\text{ }^\circ\text{C}$ overnight in the refrigerator. Filtration to remove white solids and concentration then removed any remaining impurities. This provided the desired vinyl triflate (**2.115**, 9.5 g, 72%) as a yellow oil. R_f = 0.77 (10% ethyl acetate in

hexane); ^1H NMR (400 MHz, CDCl_3): δ 5.76 (t, $J = 2.6$ Hz, 1H), 5.68 (t, $J = 2.6$ Hz, 2H), 5.65-5.61 (m, 3H), 4.69 (d, $J = 4.3$ Hz, 1H), 4.52 (d, $J = 5.2$ Hz, 2H), 3.72 (s, 9H), 3.38-3.34 (m, 2H), 3.02-3.00 (m, 1H), 2.70 (ddd, $J = 16.8, 8.8, 2.4$ Hz, 2H), 2.64-2.56 (m, 3H), 2.21 (d, $J = 7.2$ Hz, 1H), 2.08 (t, $J = 7.7$ Hz, 1H), 1.99 (ddd, $J = 16.2, 5.9, 2.5$ Hz, 1H), 1.85-1.78 (m, 4H), 1.77 (d, $J = 5.4$ Hz, 6H), 1.74 (s, 3H), 0.84 (d, $J = 5.5$ Hz, 9H), 0.81-0.79 (m, 18H), 0.01 (d, $J = 7.1$ Hz, 12H), -0.00 (s, 6H); ^{13}C NMR (100 MHz, CDCl_3): δ 173.0, 171.1, 146.5, 146.2, 140.5, 138.0, 125.2, 123.2, 120.3, 120.1, 68.5, 67.1, 64.1, 63.8, 52.5, 52.1, 39.2, 35.7, 34.9, 34.6, 33.8, 25.7, 25.7, 24.3, 23.8, 18.1, 17.9, -3.9, -4.3, -5.2; IR (film) 2955, 2930, 2857, 1743, 1424 cm^{-1} ; HRMS (EI) calcd for $[\text{C}_{19}\text{H}_{29}\text{F}_3\text{O}_6\text{NaSSi}]^+$ (M^+): m/z 493.1304, found 493.1300.



A dry 50 mL round-bottom flask was charged with vinyl triflate **2.115** (202 mg, 0.430 mmol, 1 equiv) and toluene (8.6 mL). This solution was cooled to -78 $^{\circ}\text{C}$ and a 1 M solution of DIBAL in hexane was added slowly. The reaction mixture was allowed to stir for 3 h at which point sodium sulfate decahydrate and ethyl acetate (5 mL) was added and the solution was warmed to room temperature. After 2 h of vigorous stirring the solution was filtered and concentrated. The resulting material was purified by column chromatography (5% ethyl acetate in hexane). This provided alcohol **2.118A** (101 mg, 53%), alcohol **2.118B** (68 mg, 35%) in addition to a small amount of the two diastereomers as a mixture (11 mg, 6%) for a total yield of 94%. Characterization for major diastereomer (**2.118A**): $R_f = 0.30$ (10% ethyl acetate in hexane); ^1H NMR (500 MHz, CDCl_3): δ 5.70 (t, $J = 2.4$ Hz, 1H), 5.58-5.57 (m, 1H), 4.33 (d, $J = 4.0$ Hz, 1H), 3.85 (dd, $J = 11.3, 5.9$ Hz, 1H), 3.68 (dd, $J = 11.3, 7.2$ Hz, 1H), 2.74 (t, $J = 6.6$ Hz, 1H), 2.67-2.58 (m, 2H), 2.42-2.38 (m, 1H), 1.89-1.80 (m, 2H), 1.77 (s, 3H), 0.89 (s, 9H), 0.08 (d, $J = 18.5$ Hz, 6H); ^{13}C NMR (125 MHz, CDCl_3): δ 150.4, 138.9, 125.0, 119.7, 117.5, 117.2, 70.3, 66.0, 56.2, 36.6, 34.1, 33.8, 25.7, 24.0, 17.9, -4.1, -5.2; IR (film) 3455, 2931, 2858, 1666, 1423 cm^{-1} ; HRMS (EI) calcd for $[\text{C}_{18}\text{H}_{29}\text{F}_3\text{O}_5\text{NaSSi}]^+$ (M^+): m/z 465.1355, found 465.1352. Characterization of minor diastereomer (**2.118B**): $R_f = 0.25$ (10% ethyl acetate in hexane); ^1H NMR (500 MHz, CDCl_3): δ 5.70 (t, $J = 2.6$ Hz, 1H), 5.57-5.56 (m, 1H), 3.91 (d, $J = 4.9$ Hz, 1H), 3.65 (dd, $J = 11.5, 4.4$ Hz, 1H), 3.28 (dd, $J = 11.4, 8.7$ Hz, 1H), 2.63-2.50 (m, 2H), 2.09 (d, $J = 7.0$ Hz, 2H), 1.91 (ddd, $J = 15.9, 5.1, 2.6$ Hz, 1H), 1.75 (dd, $J = 8.7, 4.4$ Hz, 1H), 1.68 (s, 3H), 0.78 (d, $J = 5.7$ Hz, 9H), -0.05 (dd, $J = 15.6, 6.0$ Hz, 6H); ^{13}C NMR (150 MHz, CDCl_3): δ 148.3, 139.1, 124.7, 119.9, 119.5, 117.6, 67.2, 64.9, 59.2, 35.4, 34.8, 34.0, 25.8, 23.5, 18.1, -4.1, -5.3; IR (film) 3451, 2930, 2858, 1666, 1421 cm^{-1} ; HRMS (EI) calcd for $[\text{C}_{18}\text{H}_{29}\text{F}_3\text{O}_5\text{NaSSi}]^+$ (M^+): m/z 465.1355, found 465.1355.

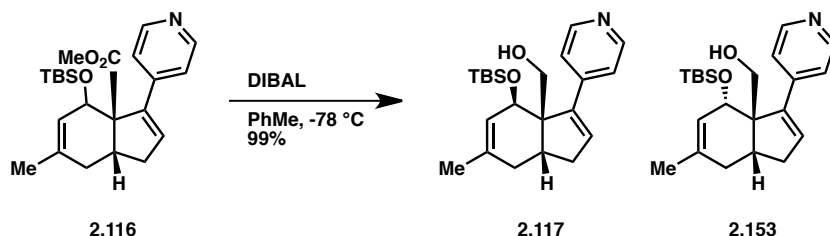


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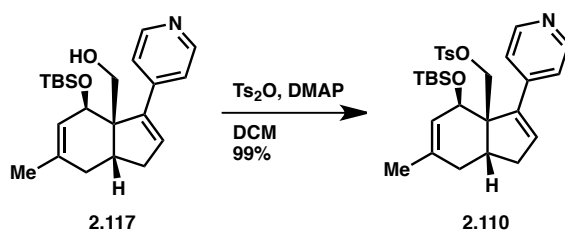


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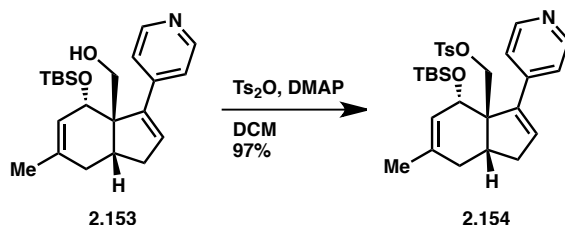
Hz, 1H), 1.76 (d, $J = 6.0$ Hz, 1.2H), 1.72 (s, 3H), 1.34 (dq, $J = 24.7, 8.0$ Hz, 0.8H), -0.02 (s, 3H), -0.09 (d, $J = 6.7$ Hz, 4H), -0.32 (d, $J = 3.0$ Hz, 1H); ^{13}C NMR (150 MHz, CDCl_3): δ 176.2, 173.2, 149.7, 149.3, 145.0, 144.1, 142.6, 141.2, 139.6, 136.9, 135.6, 135.4, 125.3, 123.1, 122.2, 120.5, 67.4, 66.6, 66.1, 64.8, 52.1, 51.4, 43.1, 40.4, 39.7, 38.1, 35.5, 33.3, 25.7, 25.5, 23.6, 23.4, 17.9, 17.8, -3.7, -3.9, -5.0, -5.5; IR (film) 2953, 2928, 2856, 1737 cm^{-1} ; HRMS (EI) calcd for $[\text{C}_{23}\text{H}_{33}\text{NO}_6\text{Si}]^+$ (M^+): m/z 400.2230, found 400.2301.



A 250 mL round-bottom flask was charged with ester **2.116** (2.44 g, 6.11 mmol, 1.0 equiv) and toluene (70 mL) and cooled to $-78\text{ }^{\circ}\text{C}$. A 1 M solution of DIBAL in hexane (30.6 mL, 30.6 mmol, 5.0 equiv) was added slowly and the reaction mixture was allowed to stir at $-78\text{ }^{\circ}\text{C}$ for 1.5 h. Glacial acetic acid (10 mL) was added over the period of 10 minutes and the solution was warmed to room temperature. The reaction mixture was transferred to a 1 L Erlenmeyer flask and diluted with ethyl acetate (400 mL), Rochelle's salt (400 mL) and a solution of saturated NaHCO_3 (250 mL). This biphasic solution was stirred vigorously for 12-20 h, at which point the layers were separated and the aqueous layer was extracted with ethyl acetate (2 x 400 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated. The resulting oil was purified by automated column chromatography (gradient of ethyl acetate in hexane) to provide alcohol **2.117** as a white solid (1.6 g, 70%) $R_f = 0.33$ (50% ethyl acetate in hexane); ^1H NMR (500 MHz, CDCl_3): δ 8.52 (dd, $J = 4.6, 1.6$ Hz, 2H), 7.28-7.26 (m, 2H), 6.07 (t, $J = 2.6$ Hz, 1H), 5.49 (t, $J = 1.6$ Hz, 1H), 4.33-4.32 (m, 1H), 4.11 (d, $J = 11.2$ Hz, 1H), 3.78 (d, $J = 11.2$ Hz, 1H), 2.90-2.85 (m, 1H), 2.72 (ddd, $J = 17.4, 8.2, 2.6$ Hz, 1H), 2.43 (dd, $J = 16.2, 6.7$ Hz, 1H), 2.04 (ddd, $J = 17.5, 5.3, 2.7$ Hz, 1H), 1.89 (dd, $J = 16.4, 4.1$ Hz, 1H), 1.77 (s, 3H), 0.89-0.85 (m, 9H), -0.05 (d, $J = 62.0$ Hz, 6H); ^{13}C NMR (100 MHz, CDCl_3): δ 149.6, 145.8, 145.3, 138.7, 134.5, 124.6, 122.7, 71.5, 66.7, 59.2, 39.1, 38.7, 33.7, 25.8, 24.0, 18.0, -3.7, -5.0; IR (film) 3319, 2928, 2856, 1599, 1471 cm^{-1} ; HRMS (EI) calcd for $[\text{C}_{22}\text{H}_{33}\text{NO}_2\text{Si}]^+$ (M^+): m/z 372.2281, found 372.2352. Alcohol **2.153** was also isolated as a colorless oil (0.67 g, 29%). $R_f = 0.17$ (50% ethyl acetate in hexane); ^1H NMR (400 MHz, CDCl_3): δ 8.43-8.42 (m, 2H), 7.23-7.21 (m, 2H), 6.16 (t, $J = 2.4$ Hz, 1H), 5.61 (dq, $J = 4.8, 1.5$ Hz, 1H), 4.24 (d, $J = 4.8$ Hz, 1H), 3.82 (d, $J = 10.9$ Hz, 1H), 3.52 (d, $J = 10.9$ Hz, 1H), 2.70-2.60 (m, 2H), 2.22 (d, $J = 7.5$ Hz, 1H), 2.18-2.12 (m, 2H), 1.76 (s, 3H), 0.63 (d, $J = 5.9$ Hz, 9H), -0.08--0.14 (m, 6H); ^{13}C NMR (100 MHz, CDCl_3): δ 149.3, 146.7, 142.7, 137.7, 136.4, 124.9, 122.2, 69.6, 66.1, 61.7, 39.9, 38.5, 33.5, 25.6, 23.6, 17.8, -3.7, -5.2; IR (film) 3254, 2927, 2855, 1600, 1471 cm^{-1} ; HRMS (EI) calcd for $[\text{C}_{22}\text{H}_{33}\text{NO}_2\text{Si}]^+$ (M^+): m/z 372.2281, found 372.2350.

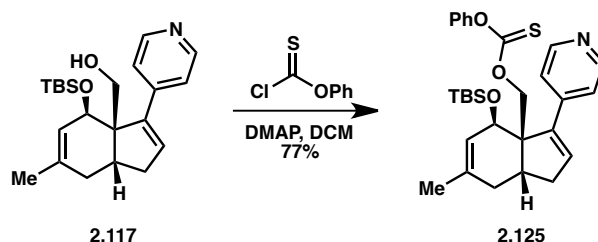


A dry 100 mL round-bottom flask was charged with *p*-toluenesulfonic anhydride (0.57 g, 1.78 mmol, 3.0 equiv), and DCM (10 mL). The solution was cooled to 0 °C and DMAP (0.43 g, 3.51 mmol, 6.0 equiv) was added and then warmed to room temperature. Alcohol **2.117** (218 mg, 0.586 mmol, 1.0 equiv) was then added in DCM (10 mL). The reaction mixture was allowed to stir at room temperature for 18 h at which point it was diluted with a solution of saturated NaHCO₃ (10 mL) and extracted with DCM (3 x 20 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated. The resulting product was purified by column chromatography (30% to 60% ethyl acetate in hexane) to provide tosylate **2.110** as a white solid (305 mg, 99%). *R*_f = 0.75 (50% ethyl acetate in hexane); ¹H NMR (600 MHz, CDCl₃): δ 8.30 (d, *J* = 4.1 Hz, 2H), 7.58 (d, *J* = 7.9 Hz, 2H), 7.24 (d, *J* = 7.9 Hz, 2H), 7.04 (d, *J* = 5.0 Hz, 2H), 6.08 (s, 1H), 5.37 (s, 1H), 4.31 (d, *J* = 10.1 Hz, 1H), 4.19 (s, 1H), 4.15 (d, *J* = 10.1 Hz, 1H), 2.71 (d, *J* = 7.5 Hz, 1H), 2.55 (ddd, *J* = 16.9, 8.3, 2.7 Hz, 1H), 2.44 (s, 3H), 2.25 (dd, *J* = 17.3, 6.9 Hz, 1H), 2.03 (dd, *J* = 16.9, 8.4 Hz, 1H), 1.86 (d, *J* = 17.3 Hz, 1H), 1.70 (s, 3H), -0.18 (d, *J* = 133.4 Hz, 6H); ¹³C NMR (150 MHz, CDCl₃): δ 149.4, 145.6, 144.8, 144.6, 137.1, 135.1, 132.3, 129.9, 127.9, 124.7, 122.3, 71.4, 70.6, 56.7, 40.0, 37.6, 31.6, 25.7, 23.6, 21.6, 17.9, -3.7, -5.1; IR (film) 2928, 2856, 1595, 1471 cm⁻¹; HRMS (EI) calcd for [C₂₉H₃₉NO₄SSi]⁺ (*M*⁺): *m/z* 526.2369, found 526.2444.

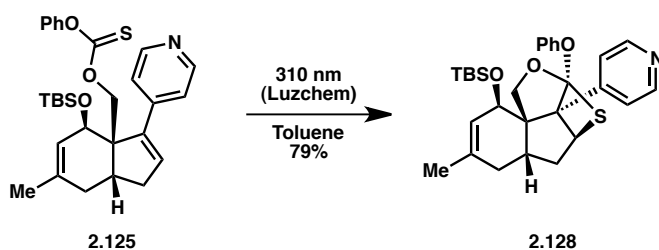


A dry 50 mL round-bottom flask was charged with *p*-toluenesulfonic anhydride (0.20 g, 0.606 mmol, 3.0 equiv), and DCM (3.5 mL). The solution was cooled to 0 °C and DMAP (0.15 g, 1.21 mmol, 6.0 equiv) was added and then warmed to room temperature. Alcohol **2.153** (75 mg, 0.202 mmol, 1.0 equiv) was then added in DCM (3.5 mL). The reaction mixture was allowed to stir at room temperature for 18 h at which point it was diluted with a solution of saturated NaHCO₃ (10 mL) and extracted with DCM (3 x 10 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated. The resulting product was purified by column chromatography (30% to 60% ethyl acetate in hexane) to provide tosylate **2.154** as a white solid (106 mg, 97%). *R*_f = 0.70 (50% ethyl acetate in hexane); ¹H NMR (600 MHz, CDCl₃): δ 8.31 (d, *J* = 5.5 Hz, 2H), 7.52 (d, *J* = 8.1 Hz, 2H), 7.20 (d, *J* = 8.0 Hz, 2H), 6.93 (d, *J* = 5.7 Hz, 2H), 6.04 (s, 1H), 5.52-5.51 (m, 1H), 4.16 (d, *J* = 4.7 Hz, 1H), 3.97 (s, 2H), 2.63-2.56 (m, 2H), 2.41 (s, 3H), 2.19-2.06 (m, 3H), 1.72 (s, 3H), -0.15 (d, *J* = 30.1 Hz, 6H); ¹³C NMR (150 MHz, CDCl₃): δ 149.0,

146.2, 144.8, 141.5, 137.7, 136.7, 132.2, 129.7, 127.7, 123.9, 122.1, 72.2, 68.9, 59.1, 39.7, 38.3, 33.1, 25.6, 23.5, 21.6, 17.7, -3.8, -5.2; IR (film) 2928, 1596, 1471 cm^{-1} ; HRMS (EI) calcd for $[\text{C}_{29}\text{H}_{39}\text{NO}_4\text{SSi}]^+$ (M^+): m/z 526.2369, found 526.2455.

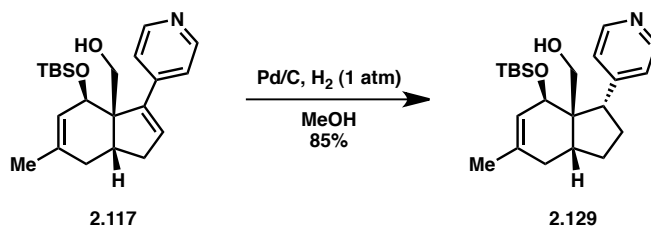


A 10 mL round-bottom flask was charged with alcohol **2.117** (115 mg, 0.309 mmol, 1.0 equiv), DCM (4.6 mL), DMAP (227 mg, 1.85 mmol, 6.0 equiv) and *O*-phenyl thionochloroformate (86 μL , 0.619 mmol, 2.0 equiv). The reaction mixture was allowed to stir at room temperature for 14 h, at which point the solution was loaded directly onto silica and purified by automated column chromatography (gradient of ethyl acetate in hexane). This provided thionocarbonate **2.125** (121 mg, 77%) as a yellow oil. A small amount of starting material was also isolated (11 mg, 10%). R_f = 0.77 (50% ethyl acetate in hexane); ^1H NMR (600 MHz, CDCl_3): δ 8.52 (t, J = 1.9 Hz, 2H), 7.37-7.34 (m, 2H), 7.28-7.23 (m, 3H), 6.98 (dd, J = 7.6, 0.5 Hz, 2H), 6.11 (s, 1H), 5.49 (s, 1H), 4.96 (d, J = 11.5 Hz, 1H), 4.70 (d, J = 11.5 Hz, 1H), 4.33 (s, 1H), 2.69 (t, J = 7.2 Hz, 1H), 2.63-2.59 (m, 1H), 2.47 (dd, J = 16.8, 6.9 Hz, 1H), 2.10-2.06 (m, 1H), 1.92 (d, J = 16.9 Hz, 1H), 1.76 (s, 3H), -0.09 (d, J = 96.9 Hz, 6H); ^{13}C NMR (150 MHz, CDCl_3): δ 194.9, 153.1, 149.4, 145.9, 145.1, 137.6, 134.8, 129.4, 126.4, 124.7, 122.6, 121.7, 75.7, 70.3, 60.3, 57.4, 40.3, 38.3, 32.6, 25.8, 23.7, 18.0, -3.8, -4.9; IR (film) 3041, 2928, 1593, 1492 cm^{-1} ; HRMS (EI) calcd for $[\text{C}_{29}\text{H}_{37}\text{NO}_3\text{SSi}]^+$ (M^+): m/z 508.2263, found 508.2328.

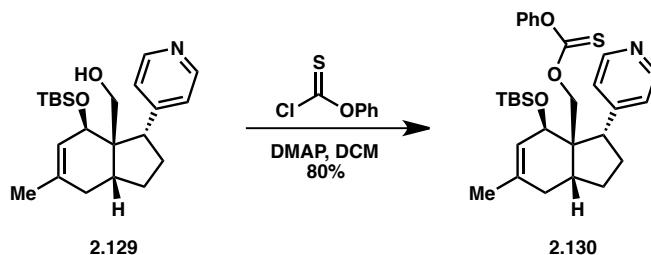


A 15 mL quartz test tube was charged with thionocarbonate **2.125** (41 mg, 0.081 mmol, 1.0 equiv) and toluene (8 mL). This solution was irradiated in a Luzchem photobox with 310 nm UV light for 2 h at which point the reaction mixture was concentrated. The resulting solid was purified by automated column chromatography (gradient of ethyl acetate in hexane). This provided tetracycle **2.128** (32 mg, 79%) as a white solid. R_f = 0.77 (50% ethyl acetate in hexane); ^1H NMR (600 MHz, CDCl_3): δ 8.56 (d, J = 3.8 Hz, 2H), 7.26 (t, J = 7.7 Hz, 2H), 7.17 (d, J = 3.2 Hz, 2H), 7.03 (t, J = 7.0 Hz, 1H), 6.91 (d, J = 7.9 Hz, 2H), 4.85 (dd, J = 1.9, 0.3 Hz, 1H), 4.79 (d, J = 9.8 Hz, 1H), 4.36 (d, J = 9.8 Hz, 1H), 4.06 (d, J = 5.9 Hz, 1H), 3.74-3.73 (m, 1H), 3.01 (dd, J = 7.5, 3.7 Hz, 1H), 2.54-

2.48 (m, 2H), 2.19-2.15 (m, 1H), 1.67-1.64 (m, 1H), 1.48 (s, 3H), 0.79 (dq, $J = 1.7, 0.6$ Hz, 10H), -0.09 (d, $J = 48.8$ Hz, 6H); ^{13}C NMR (150 MHz, CDCl_3): δ 153.1, 148.8, 145.9, 139.4, 129.3, 123.1, 117.7, 113.3, 78.9, 75.1, 66.8, 63.1, 43.7, 42.5, 39.8, 33.9, 25.8, 23.7, 18.1, -3.8, -4.9; IR (film) 2927, 2855, 1596, 1493 cm^{-1} ; HRMS (EI) calcd for $[\text{C}_{29}\text{H}_{37}\text{NO}_3\text{SSi}]^+$ (M^+): m/z 508.2263, found 508.2332.

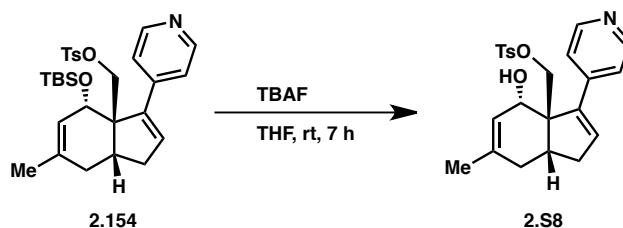


A 25 mL round-bottom flask was charged with alcohol **2.117** (94 mg, 0.253 mmol, 1.0 equiv), methanol (10 mL) and palladium on carbon (9 mg, 10 wt%). The atmosphere was exchanged for hydrogen (1 atm) and the reaction was allowed to stir for 14 h. The solution was then filtered through a pad of silica gel, washed with ethyl acetate, and concentrated. The resulting solid was purified by automated column chromatography (gradient of ethyl acetate in hexane) to provide **2.129** (80 mg, 85%) as a white solid. $R_f = 0.55$ (50% ethyl acetate in hexane); ^1H NMR (500 MHz, CDCl_3): δ 8.45-8.44 (m, 2H), 7.20 (d, $J = 5.7$ Hz, 2H), 5.27 (s, 1H), 4.35 (s, 1H), 3.72 (q, $J = 9.6$ Hz, 2H), 3.11 (t, $J = 9.2$ Hz, 1H), 2.35-2.30 (m, 1H), 2.22 (dt, $J = 5.7, 2.7$ Hz, 1H), 2.03-1.95 (m, 2H), 1.87 (dd, $J = 12.8, 6.7$ Hz, 1H), 1.78 (d, $J = 17.0$ Hz, 1H), 1.69 (s, 3H), 1.55-1.51 (m, 1H), -0.23 (d, $J = 161.1$ Hz, 6H); ^{13}C NMR (125 MHz, CDCl_3): δ 151.6, 149.3, 135.9, 125.0, 123.9, 69.7, 68.9, 52.6, 51.4, 43.1, 32.4, 30.0, 28.8, 25.8, 23.6, 18.0, -3.3, -5.0; IR (film) 3354, 2954, 2855, 1602, 1470 cm^{-1} ; HRMS (EI) calcd for $[\text{C}_{22}\text{H}_{35}\text{NO}_2\text{Si}]^+$ (M^+): m/z 374.2437, found 374.2507.

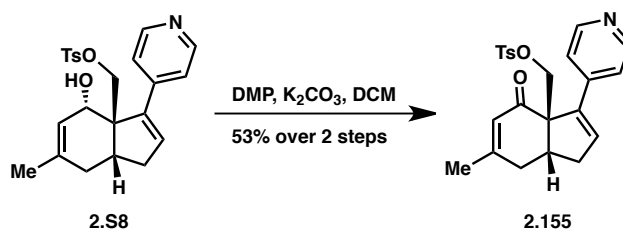


A dry 10 mL round-bottom flask was charged with alcohol **2.129** (80 mg, 0.214 mmol, 1 equiv), DCM (3.2 mL), 4-dimethylaminopyridine (157 mg, 1.28 mmol, 6.0 equiv) and O -phenyl thionochloroformate (60 μL , 0.428 mmol, 2.0 equiv). The yellow solution was allowed to stir for 12 h, at which point more 4-dimethylaminopyridine (157 mg, 1.28 mmol, 6.0 equiv) and O -phenyl thionochloroformate (60 μL , 0.428 mmol, 2.0 equiv) were added. After an additional 3 h of stirring the solution was concentrated and purified by automated column chromatography (gradient of ethyl acetate in hexane) to provide thionocarbonate **2.130** (86 mg, 80% – 90% pure). $R_f = 0.78$ (50% ethyl acetate in hexane); ^1H NMR (600 MHz, CDCl_3): δ 8.50 (t, $J = 9.1$ Hz, 2H), 7.45 (t, $J = 7.8$ Hz, 2H), 7.31 (t, $J = 7.5$ Hz, 1H), 7.20 (d, $J = 5.3$ Hz, 2H), 7.16 (d, $J = 7.9$ Hz, 2H), 5.23 (s, 1H),

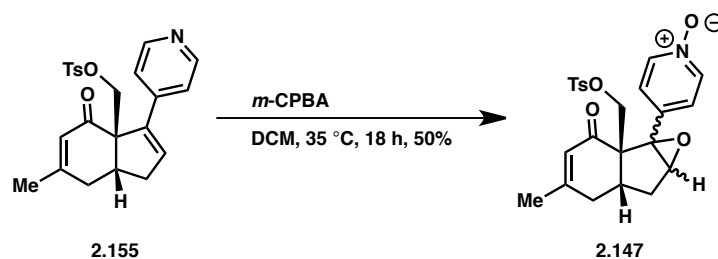
4.73 (d, $J = 11.5$ Hz, 1H), 4.49 (d, $J = 11.5$ Hz, 1H), 4.34 (s, 1H), 3.27 (t, $J = 9.6$ Hz, 1H), 2.42-2.35 (m, 2H), 2.15-2.12 (m, 1H), 1.98 (dt, $J = 8.7, 4.6$ Hz, 1H), 1.91-1.88 (m, 1H), 1.79 (d, $J = 17.2$ Hz, 1H), 1.71 (s, 3H), -0.07--0.26 (m, 6H); ^{13}C NMR (150 MHz, CDCl_3): δ 195.1, 153.3, 150.6, 149.2, 135.3, 129.5, 126.6, 124.5, 123.1, 121.9, 75.0, 66.7, 51.6, 49.1, 40.2, 31.4, 29.2, 26.9, 25.7, 23.5, 17.9, -3.1, -4.5; IR (film) 2954, 2928, 1596, 1491 cm^{-1} ; HRMS (EI) calcd for $[\text{C}_{29}\text{H}_{39}\text{NO}_3\text{SSi}]^+$ (M^+): m/z 510.2420, found 510.2497.



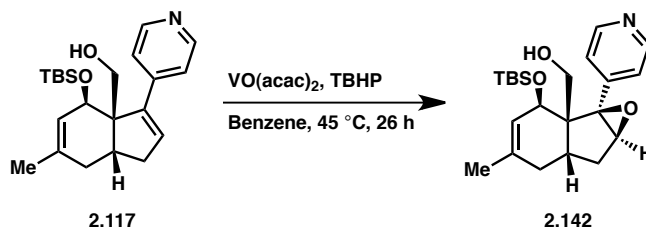
A dry 10 mL round-bottom flask was charged with *tert*-butyldimethylsilyl ether **2.154** (47 mg, 0.089 mmol, 1 equiv) and THF (3.5 mL) and cooled to 0 °C. A 1 M solution of TBAF in THF (0.40 mL, 0.039 mmol, 4.5 equiv) was added and the solution was allowed to warm to room temperature and stir for 7 h. The reaction mixture was concentrated, re-dissolved in 5% methanol in DCM, and filtered through a pad of silica gel eluting with 5% methanol in DCM (10 mL). The solution was concentrated to give crude **2.S8**, which was taken on in the next step without further purification.



A dry 4 mL vial was charged with alcohol **2.S8** (0.089 mmol, 1 equiv) and DCM (2.2 mL). Dess-martin periodinane (54 mg, 0.126 mmol, 1.4 equiv) and potassium carbonate (53 mg, 0.379 mmol, 4.2 equiv) were added and the reaction mixture was allowed to stir for 3.5 h. The solution was then diluted with DCM (5 mL) and washed with 1:1 saturated sodium bicarbonate/saturated sodium sulfite (3 x 5 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated. The resulting material was purified by automated column chromatography (gradient of methanol in DCM) to provide enone **2.155** (20 mg, 53% over 2 steps). $R_f = 0.45$ (5% methanol in DCM); ^1H NMR (600 MHz, CDCl_3): δ 8.41-8.40 (m, 2H), 7.54 (d, $J = 8.2$ Hz, 2H), 7.31 (d, $J = 5.7$ Hz, 2H), 7.25 (d, $J = 9.2$ Hz, 3H), 6.22 (t, $J = 2.4$ Hz, 1H), 6.05 (s, 1H), 4.37 (d, $J = 9.6$ Hz, 1H), 4.04 (d, $J = 9.6$ Hz, 1H), 3.13 (dd, $J = 5.9, 3.2$ Hz, 1H), 2.71-2.61 (m, 2H), 2.44 (s, 3H), 2.33-2.29 (m, 2H), 2.00 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3): δ 194.5, 161.5, 149.3, 145.0, 143.5, 142.1, 136.2, 131.9, 129.8, 128.1, 127.6, 122.6, 70.2, 60.9, 40.8, 36.8, 32.3, 24.8, 21.6; IR (film) 2982, 2852, 1655, 1594, 1538 cm^{-1} ; HRMS (EI) calcd for $[\text{C}_{23}\text{H}_{23}\text{NO}_4\text{S}]^+$ (M^+): m/z 410.1348, found 410.1425.



A dry 10 mL round-bottom flask was charged with pyridine **2.155** (48 mg, 0.117 mmol, 1 equiv), *m*-CPBA (55 mg, 0.246 mmol, 2.1 equiv), and DCM (3 mL) and heated to 35 °C for 18 h. The reaction mixture was diluted with DCM (10 mL) and washed with 1:1 saturated sodium bicarbonate/saturated sodium sulfite (3 x 5 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated. The resulting material was purified by automated column chromatography (gradient of methanol in DCM) to give the *N*-oxide **2.147** (26 mg, 50%) as a 2:1 mixture of diastereomers. R_f = 0.36 (5% methanol in DCM); Characterization for major diastereomer: ^1H NMR (500 MHz, CDCl_3): δ 8.06 (d, J = 6.5 Hz, 2H), 7.67 (d, J = 7.8 Hz, 2H), 7.32 (t, J = 6.4 Hz, 2H), 6.99 (d, J = 6.4 Hz, 2H), 5.93 (s, 1H), 4.29-4.29 (m, 2H), 3.50 (s, 1H), 2.80-2.75 (m, 1H), 2.67-2.63 (m, 1H), 2.43-2.43 (m, 3H), 2.37-2.32 (m, 1H), 2.23-2.18 (m, 1H), 2.02-1.97 (m, 3H), 1.88-1.83 (m, 1H); ^{13}C NMR (125 MHz, CDCl_3): δ 194.3, 162.4, 145.4, 138.3, 133.1, 132.1, 130.1, 127.8, 126.5, 126.3, 72.6, 67.5, 62.0, 56.4, 35.5, 33.1, 31.9, 25.1, 21.8; IR (film) 3387, 2927, 1655, 1492, 1441, 1360 cm^{-1} ; HRMS (EI) calcd for $[\text{C}_{23}\text{H}_{23}\text{NO}_6\text{S}]^+$ (M^+): m/z 442.1246, found 442.1323.

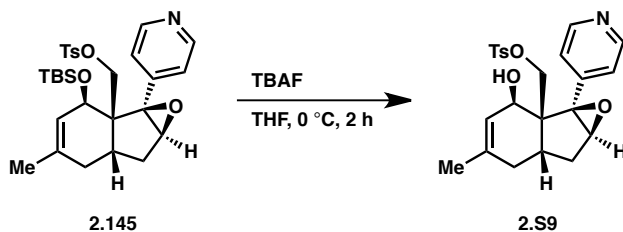


A dry 25 mL microwave vial was charged with alkene **2.117** (300 mg, 0.807 mmol, 1 equiv) and benzene (6 mL) and heated to 45 °C. A 0.014 M solution of vanadyl acetylacetonate in benzene (0.6 mL, 0.008 mmol, 0.01 equiv) was added followed by a 1.4 M solution of *tert*-Butyl hydroperoxide in 1:3 decane/benzene (0.3 mL, 0.420 mmol, 0.5 equiv). The solution was allowed to stir at 45 °C for 3 h, at which point a 1.4 M solution of *tert*-Butyl hydroperoxide in 1:3 decane/benzene (0.3 mL, 0.420 mmol, 0.5 equiv) was added. After an additional 3 h of heating, a third portion of a 1.4 M solution of *tert*-Butyl hydroperoxide in 1:3 decane/benzene (0.3 mL, 0.420 mmol, 0.5 equiv) was added. The reaction mixture was allowed to stir at 45 °C for 20 h, was cooled to room temperature and diluted with a saturated solution of sodium sulfite (0.6 mL) and stirred for 1.5 h. The biphasic solution was diluted with ethyl acetate (5 mL) and brine (5 mL) and extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated to give epoxide **2.142**. This material was taken on in the next step without purification. R_f = 0.29 (50% ethyl acetate in hexane); ^1H NMR (500 MHz, CDCl_3): δ 8.58 (d, J = 4.5 Hz, 2H), 7.36 (dd, J = 4.4, 1.5 Hz, 2H), 5.44 (dd, J

= 0.6, 0.3 Hz, 1H), 4.48 (t, J = 0.5 Hz, 1H), 4.11-4.07 (m, 1H), 3.97-3.93 (m, 1H), 3.53 (s, 1H), 2.63-2.60 (m, 1H), 2.47-2.37 (m, 2H), 2.16-2.11 (m, 1H), 1.81 (d, J = 17.3 Hz, 1H), 1.74 (s, 3H), 1.61-1.56 (m, 1H), 0.62 (dt, J = 1.6, 0.4 Hz, 10H), -0.17 (d, J = 156.9 Hz, 7H); ^{13}C NMR (125 MHz, CDCl_3): δ 149.6, 144.7, 136.8, 124.5, 122.5, 69.9, 65.7, 61.6, 50.3, 36.9, 32.9, 30.2, 25.6, 23.7, 17.9, -3.3, -5.2; IR (film) 3375, 2929, 2856, 1604, 1471, 1408 cm^{-1} ; HRMS (EI) calcd for $[\text{C}_{22}\text{H}_{33}\text{NO}_3\text{Si}]^+$ (M^+): m/z 388.2230, found 388.2303.

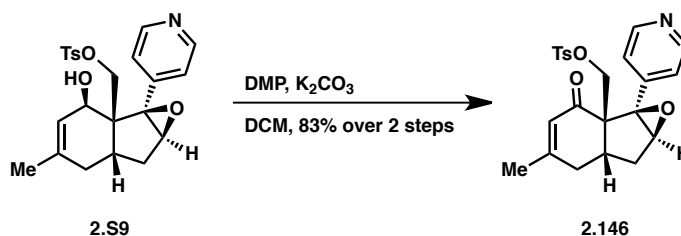


A 100 mL round-bottom flask was charged with *p*-toluenesulfonic anhydride (791 mg, 2.42 mmol, 3.0 equiv) and DCM (6 mL) and cooled to 0°C. A solution of 4-dimethylaminopyridine (592 g, 4.84 mmol, 6.0 equiv) in DCM (6 mL) was added and the reaction was allowed to warm to room temperature and stir for 30 min. Crude alcohol **2.142** (0.807 mmol, 1.0 equiv) was added in DCM (9 mL) and the reaction mixture was allowed to stir for 16 h at which point it was loaded onto silica gel and purified by column chromatography (30-70% ethyl acetate in hexane) to provide tosylate **2.145** as a white solid (341 mg, 68% over 2 steps). R_f = 0.50 (50% ethyl acetate in hexane); ^1H NMR (600 MHz, CDCl_3): δ 8.41 (d, J = 4.7 Hz, 2H), 7.85 (d, J = 7.9 Hz, 2H), 7.37 (d, J = 7.9 Hz, 2H), 7.04 (d, J = 4.8 Hz, 2H), 5.31 (s, 1H), 4.45 (s, 1H), 4.35 (d, J = 10.1 Hz, 1H), 4.22 (d, J = 10.2 Hz, 1H), 3.48 (s, 1H), 2.48 (d, J = 12.1 Hz, 4H), 2.22-2.18 (m, 1H), 2.09 (dd, J = 13.7, 7.4 Hz, 1H), 1.76 (d, J = 18.2 Hz, 1H), 1.68 (s, 3H), 1.54 (t, J = 12.5 Hz, 1H), -0.21 (d, J = 152.0 Hz, 6H); ^{13}C NMR (150 MHz, CDCl_3): δ 149.6, 144.8, 143.9, 134.8, 132.9, 129.8, 128.1, 124.0, 121.9, 69.8, 69.1, 68.2, 59.0, 48.9, 32.4, 31.7, 28.2, 25.6, 23.5, 21.6, 17.9, 14.2, -2.9, -4.7; IR 2955, 2928, 2856, 1601, 1366 (film) cm^{-1} ; HRMS (EI) calcd for $[\text{C}_{29}\text{H}_{39}\text{NO}_5\text{SSi}]^+$ (M^+): m/z 542.2318, found 542.2391.

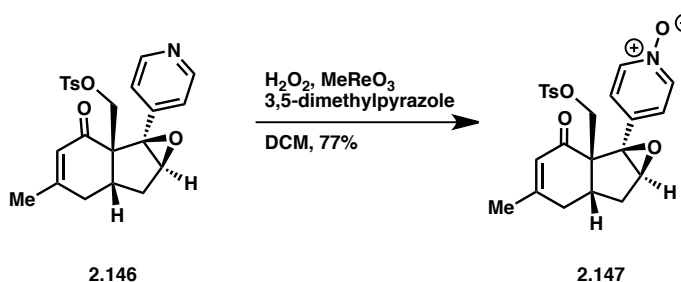


A 50 mL round-bottom flask was charged with **2.145** (0.43 g, 0.789 mmol, 1.0 equiv) and THF (30 mL) and cooled to 0 °C. A 1 M solution of TBAF in THF (0.83 mL, 0.828 mmol, 1.1 equiv) was added and the reaction mixture was allowed to stir at 0 °C for 2 h. At this point, the reaction mixture was loaded onto silica gel and purified by column chromatography (5% methanol in DCM) to provide alcohol **2.S9** as an oil, which contained <10% baseline impurities. It was taken on as is, without further purification. R_f = 0.14 (50% ethyl acetate in hexane); ^1H NMR (600 MHz, CDCl_3): δ 8.45 (d, J = 5.2 Hz,

2H), 7.76 (d, $J = 8.2$ Hz, 2H), 7.33 (d, $J = 8.0$ Hz, 2H), 7.26-7.24 (m, 2H), 5.24 (s, 1H), 4.44 (s, 1H), 4.28 (q, $J = 11.7$ Hz, 2H), 3.72 (s, 1H), 3.50 (s, 1H), 2.44 (s, 3H), 2.42-2.40 (m, 1H), 2.13 (dt, $J = 13.9, 7.1$ Hz, 2H), 2.06 (s, 1H), 1.85-1.83 (m, 1H), 1.77 (d, $J = 18.6$ Hz, 1H), 1.65 (s, 3H), 1.58 (t, $J = 12.8$ Hz, 1H); ^{13}C NMR (150 MHz, CDCl_3): δ 149.6, 145.0, 144.0, 135.0, 132.7, 129.9, 127.9, 123.4, 121.9, 69.6, 68.8, 67.9, 67.3, 59.7, 48.9, 32.6, 32.3, 28.9, 25.6, 23.0, 21.6; IR (film) 3236, 3033, 2962, 1604, 1409, 1360 cm^{-1} ; HRMS (EI) calcd for $[\text{C}_{23}\text{H}_{25}\text{NO}_5\text{S}]^+$ (M^+): m/z 428.1453, found 428.1526.

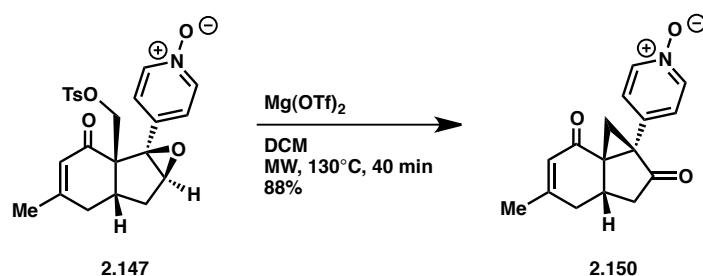


A 100 mL round-bottom flask was charged with crude alcohol **2.S9** (0.789 mmol, 1.0 equiv), Dess-Martin periodinane (0.59 g, 1.39 mmol, 1.8 equiv), potassium carbonate (0.58 g, 4.17 mmol, 5.3 equiv) and DCM (40 mL). The viscous white reaction mixture was allowed to stir for 2.5 h at room temperature, at which point it was diluted with DCM (50 mL) and washed with 1:1 $\text{NaHCO}_3/\text{Na}_2\text{SO}_3$ (3 x 50 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated. The resulting product was purified by automated column chromatography (gradient of methanol in DCM) to provide enone **2.146** as a white solid (0.29 g, 83% over 2 steps). $R_f = 0.23$ (5% methanol in DCM); ^1H NMR (600 MHz, CDCl_3): δ 8.49 (d, $J = 5.6$ Hz, 2H), 7.68 (d, $J = 8.2$ Hz, 2H), 7.31 (d, $J = 8.2$ Hz, 2H), 6.99-6.98 (m, 2H), 5.93 (s, 1H), 4.39 (q, $J = 11.9$ Hz, 2H), 3.50 (s, 1H), 2.79-2.76 (m, 1H), 2.66 (d, $J = 10.1$ Hz, 1H), 2.43 (s, 3H), 2.35 (dd, $J = 14.1, 7.7$ Hz, 1H), 2.19 (d, $J = 18.5$ Hz, 1H), 1.98 (s, 3H), 1.87 (dd, $J = 14.1, 10.4$ Hz, 1H); ^{13}C NMR (150 MHz, CDCl_3): δ 194.0, 161.7, 148.9, 145.1, 142.7, 132.2, 129.9, 127.7, 126.4, 123.7, 73.3, 68.5, 61.7, 56.6, 35.8, 33.3, 32.0, 25.0, 21.6; IR (film) 3033, 2928, 1659, 1601, 1436, 1408 cm^{-1} ; HRMS (EI) calcd for $[\text{C}_{23}\text{H}_{23}\text{NO}_5\text{S}]^+$ (M^+): m/z 426.1297, found 426.1371.

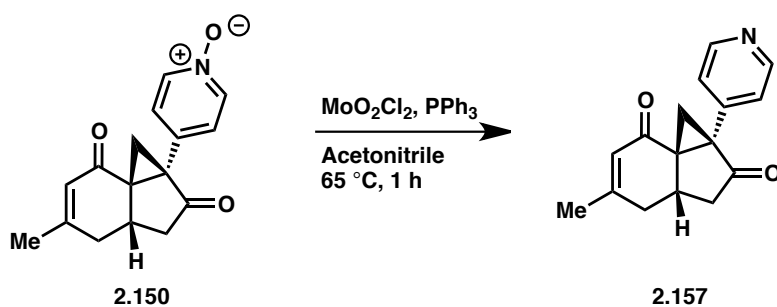


A 100 mL round-bottom flask was charged with pyridine **2.146** (0.29 g, 0.672 mmol, 1.0 equiv), methyltrioxorhenium (17 mg, 0.067 mmol, 0.10 equiv), hydrogen peroxide-urea complex (126 mg, 1.34 mmol, 2.0 equiv), 3,5-dimethylpyrazole (8.4 mg, 0.087 mmol,

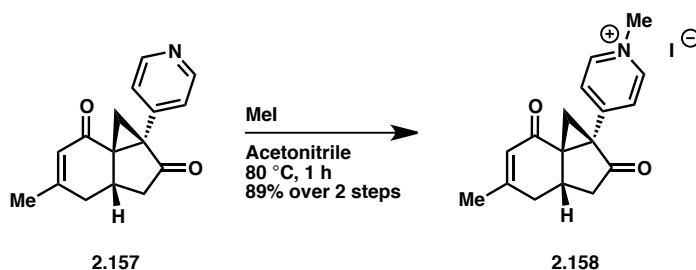
0.13 equiv) and DCM (25 mL). The reaction mixture was allowed to stir at room temperature for 16 h at which point it was diluted with DCM (25 mL) and washed with a solution of saturated Na₂SO₃ (3 x 50 mL) and brine (50 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated. The resulting solid was purified by automated column chromatography (gradient of methanol in DCM) to provide *N*-oxide **2.147** as a white solid (0.23 g, 77%). *R*_f = 0.36 (5% methanol in DCM); ¹H NMR (500 MHz, CDCl₃): δ 8.06 (d, *J* = 6.5 Hz, 2H), 7.67 (d, *J* = 7.8 Hz, 2H), 7.32 (t, *J* = 6.4 Hz, 2H), 6.99 (d, *J* = 6.4 Hz, 2H), 5.93 (s, 1H), 4.29-4.29 (m, 2H), 3.50 (s, 1H), 2.80-2.75 (m, 1H), 2.67-2.63 (m, 1H), 2.43-2.43 (m, 3H), 2.37-2.32 (m, 1H), 2.23-2.18 (m, 1H), 2.02-1.97 (m, 3H), 1.88-1.83 (m, 1H); ¹³C NMR (125 MHz, CDCl₃): δ 194.3, 162.4, 145.4, 138.3, 133.1, 132.1, 130.1, 127.8, 126.5, 126.3, 72.6, 67.5, 62.0, 56.4, 35.5, 33.1, 31.9, 25.1, 21.8; IR (film) 3387, 2927, 1655, 1492, 1441, 1360 cm⁻¹; HRMS (EI) calcd for [C₂₃H₂₃NO₆S]⁺ (M⁺): *m/z* 442.1246, found 442.1323.



A 20 mL microwave vial was charged with *N*-oxide **2.147** (36 mg, 0.081 mmol, 1.0 equiv), magnesium triflate (130 mg, 0.402 mmol, 5.0 equiv) and DCM (14 mL). This heterogeneous solution was heated in the microwave at 130 °C for 40 min at which point it was diluted with DCM (20 mL) and washed with a solution of saturated NaHCO₃ (3 x 10 mL) and brine (10 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated. The resulting product was purified by automated column chromatography (gradient of methanol in DCM) to provide tricycle **2.150** as a beige solid (19 mg, 88%). *R*_f = 0.30 (5% methanol in DCM); ¹H NMR (500 MHz, CDCl₃): δ 8.10-8.08 (m, 2H), 6.99 (t, *J* = 4.8 Hz, 2H), 6.01 (d, *J* = 0.8 Hz, 1H), 3.04 (dt, *J* = 12.2, 6.2 Hz, 1H), 2.77 (d, *J* = 5.2 Hz, 1H), 2.73-2.68 (m, 1H), 2.58 (dd, *J* = 17.9, 5.8 Hz, 1H), 2.24-2.20 (m, 1H), 2.17 (t, *J* = 14.6 Hz, 1H), 2.05 (s, 3H), 1.82 (d, *J* = 5.2 Hz, 1H); ¹³C NMR (150 MHz, CDCl₃): δ 207.7, 189.0, 160.9, 138.7, 130.5, 127.7, 127.5, 49.5, 48.1, 45.9, 40.0, 36.6, 32.8, 24.6, 21.3, 8.8, 1.0; IR (film) 3243, 2929, 2856, 1603, 1471 cm⁻¹; HRMS (EI) calcd for [C₁₆H₁₅NO₃]⁺ (M⁺): *m/z* 270.1052, not found.



A 25 mL round-bottom flask was charged with *N*-oxide **2.150** (47 mg, 0.175 mmol, 1.0 equiv), triphenylphosphine (50 mg, 0.193 mmol, 1.1 equiv), molybdenum chlorideoxide (7 mg, 0.035 mmol, 0.20 equiv), and acetonitrile (10 mL). The reaction mixture was heated to 65°C for 1 h at which point the solution was loaded onto silica gel neutralized with triethylamine and purified by column chromatography (5% diethyl ether in hexane + 1% triethylamine). This provided pyridine **2.157** along with triphenylphosphine oxide as a contaminant. This mixture was taken on without further purification.



A 20 mL vial was charged with pyridine **2.157** (0.175 mmol, 1.0 equiv), iodomethane (0.1 mL, 1.75 mmol, 10 equiv), and acetonitrile (3 mL) and heated to 80°C for 1 h. The reaction mixture was then concentrated and purified by column chromatography on neutralized alumina (5% to 10% methanol in DCM) to give *N*-methyl pyridinium **2.158** as a red-orange solid (61 mg, 89% over 2 steps). $R_f = 0.08$ (5% methanol in DCM); ^1H NMR (500 MHz, CDCl_3): δ 9.12-9.11 (m, 2H), 7.95-7.93 (m, 2H), 5.99-5.98 (m, 1H), 4.58-4.57 (m, 3H), 3.51-3.50 (m, 1H), 3.15-3.10 (m, 1H), 2.97-2.96 (m, 1H), 2.90-2.84 (m, 1H), 2.66-2.62 (m, 1H), 2.57-2.52 (m, 1H), 2.36-2.32 (m, 1H), 2.11-2.10 (m, 3H); ^{13}C NMR (150 MHz, CDCl_3): δ 207.4, 189.5, 164.3, 152.5, 145.5, 130.9, 127.7, 50.7, 49.3, 48.8, 41.0, 37.1, 33.1, 25.3; IR (film) 3427, 2927, 1727, 1651 cm^{-1} ; HRMS (EI) calcd for $[\text{C}_{17}\text{H}_{18}\text{NO}_2]^+$ (M^+): m/z 268.1332, found 268.1332.

2.8 References and Notes

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Appendix 1:
Spectra Relevant to Chapter 2

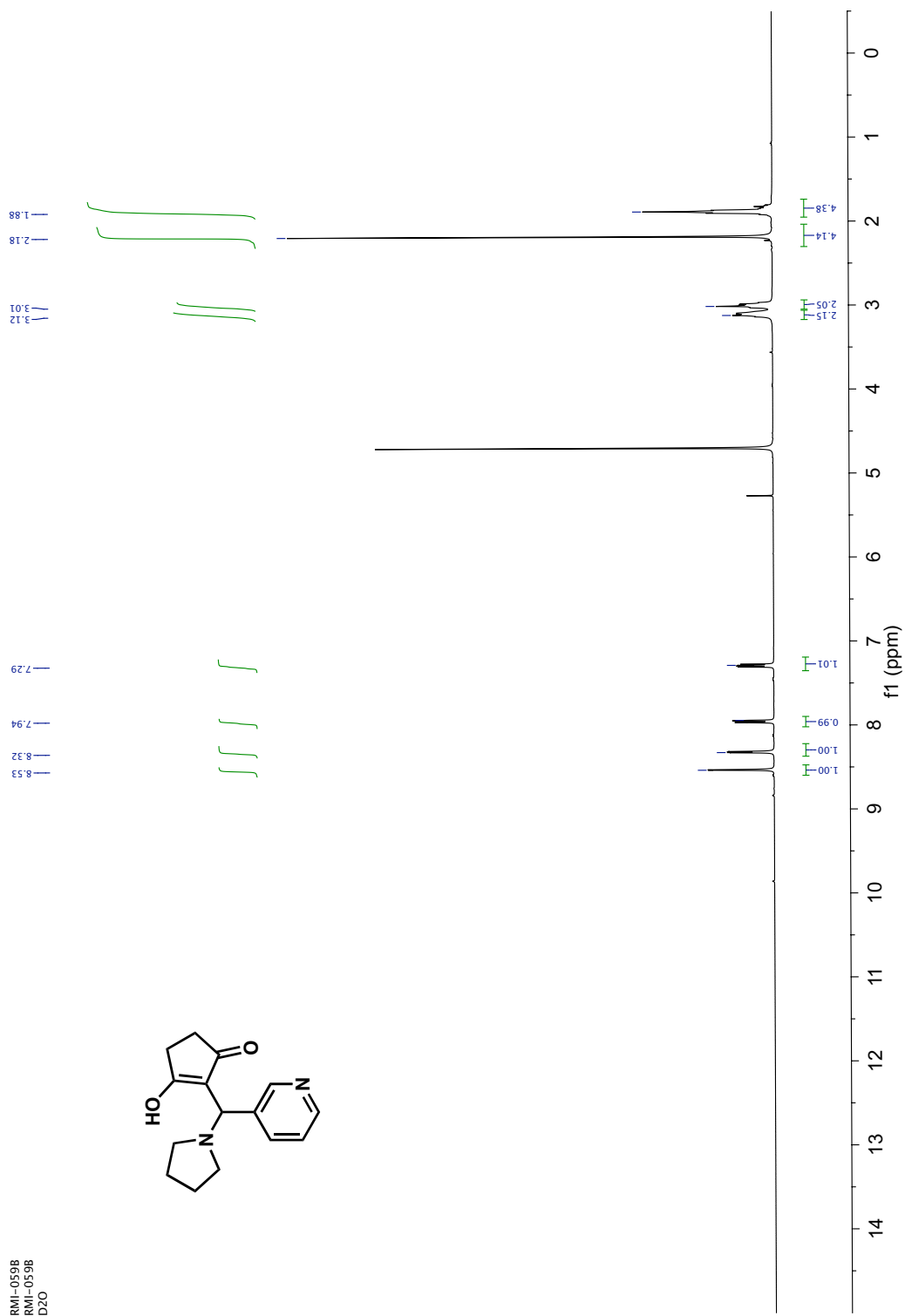


Figure A1.1 ¹H NMR of 2.39

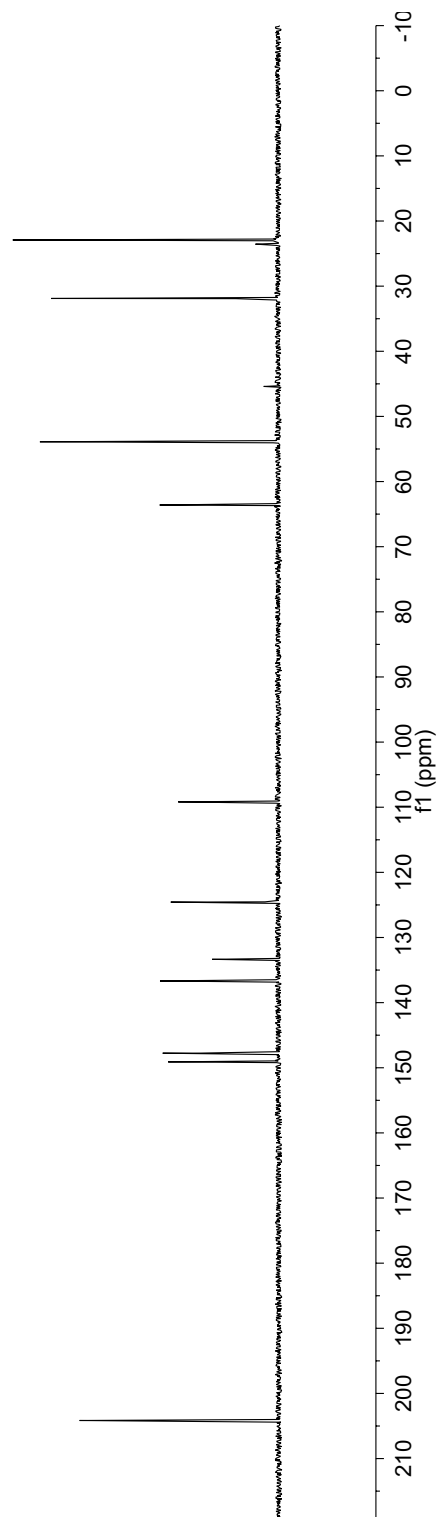
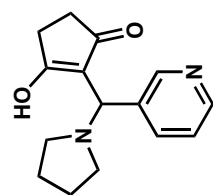


Figure A1.2 ^{13}C NMR of 2.39

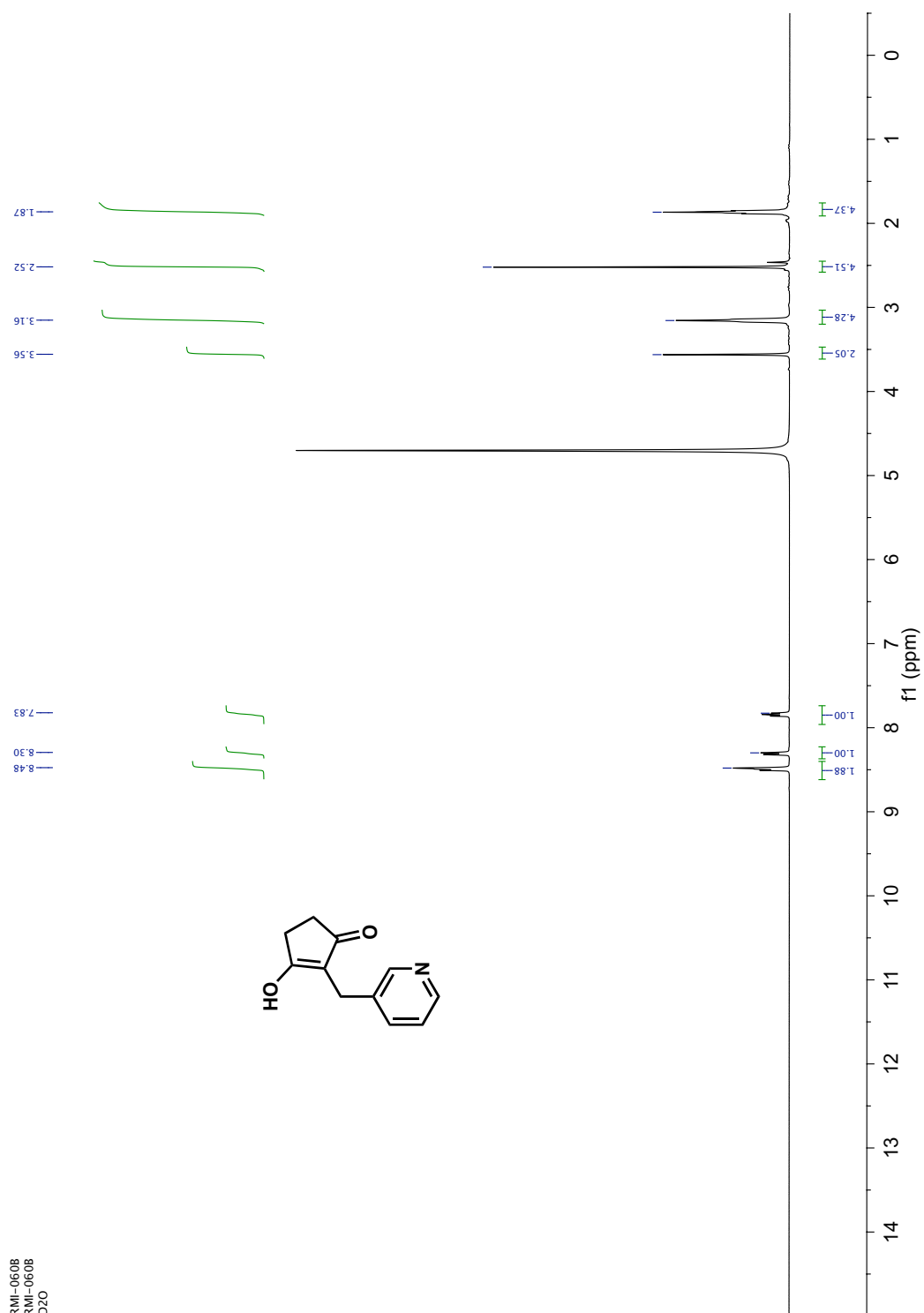


Figure A1.3 ¹H NMR of 2.33

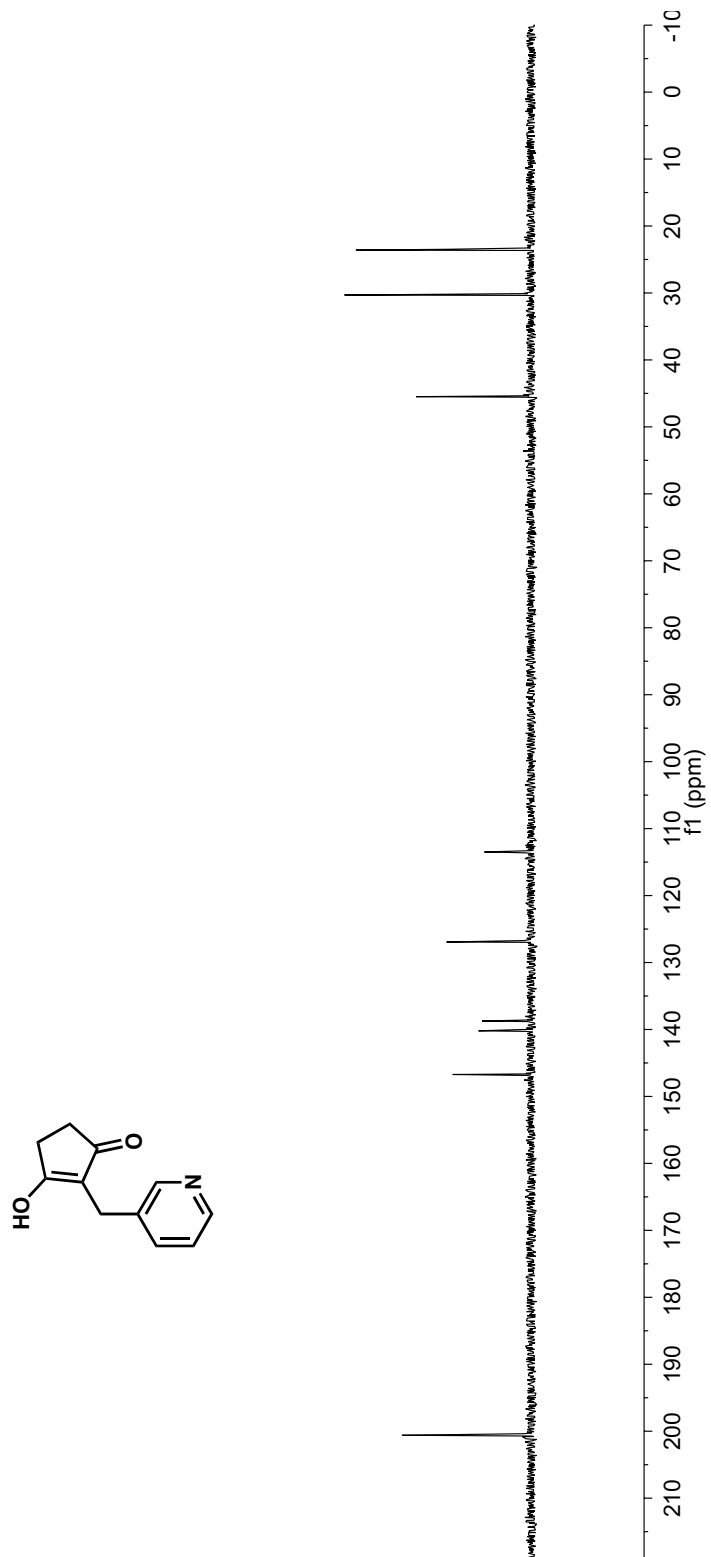


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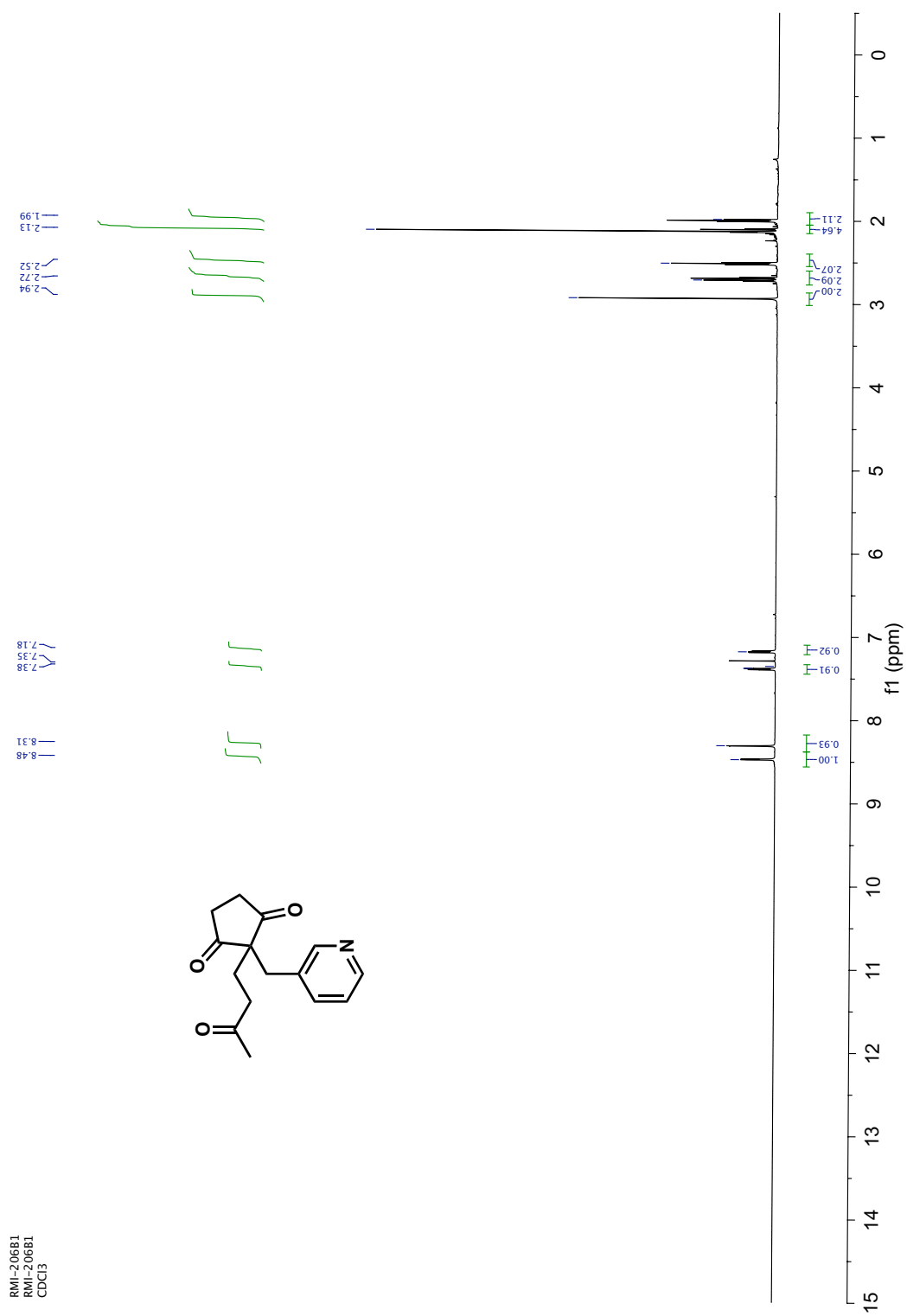


Figure A1.5 ^1H NMR of 2.40

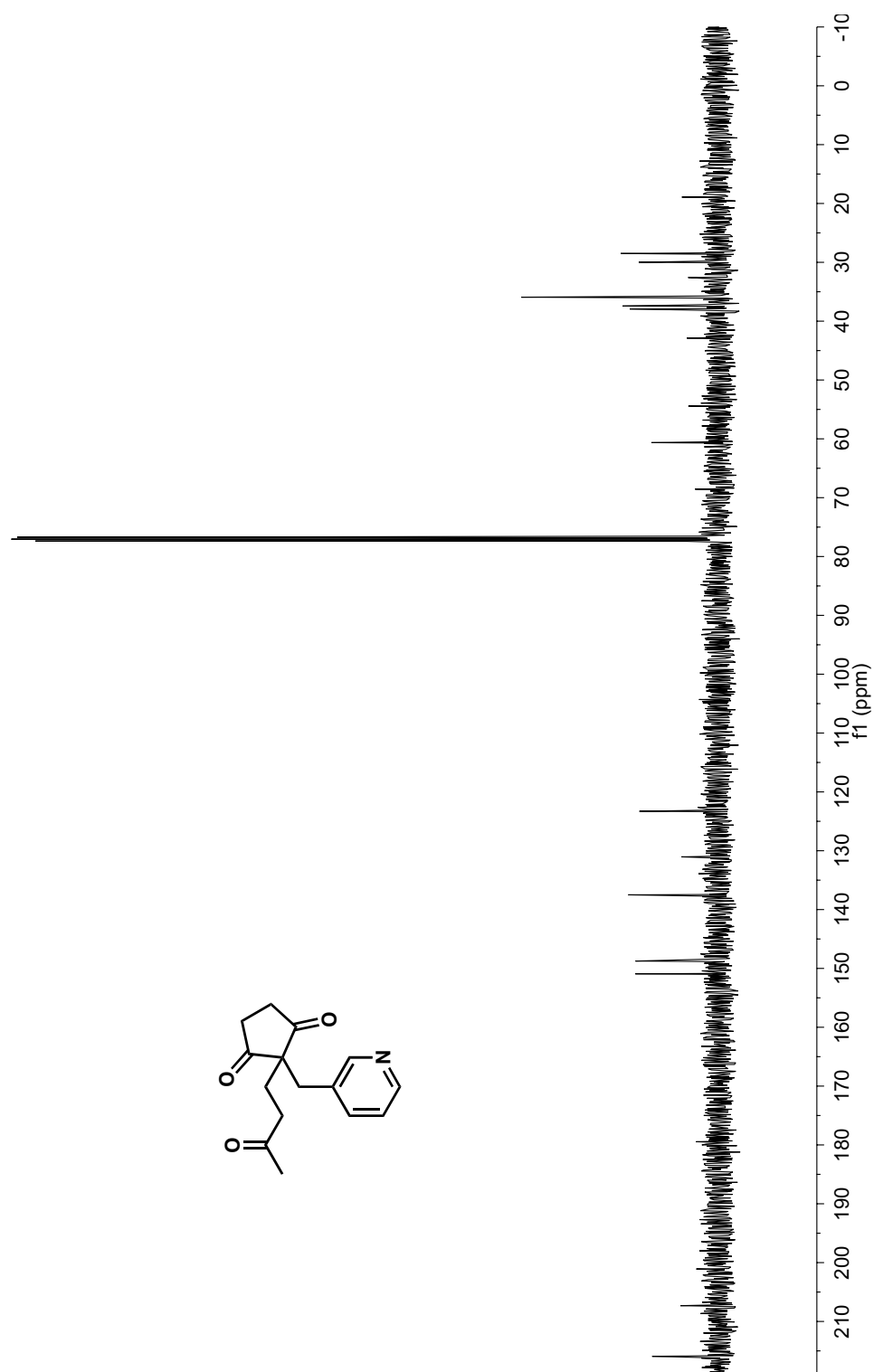


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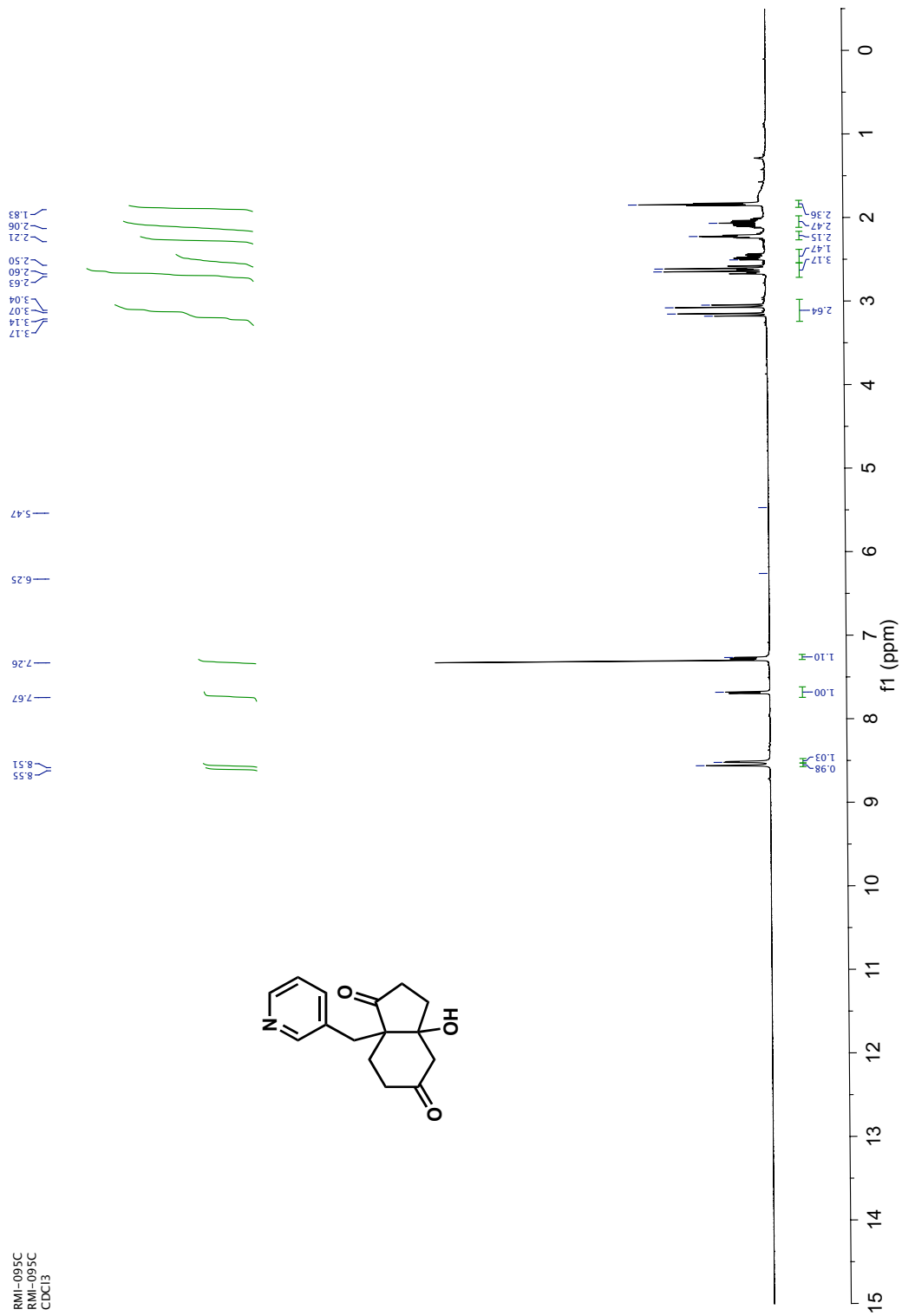


Figure A1.7 ¹H NMR of **2.41**

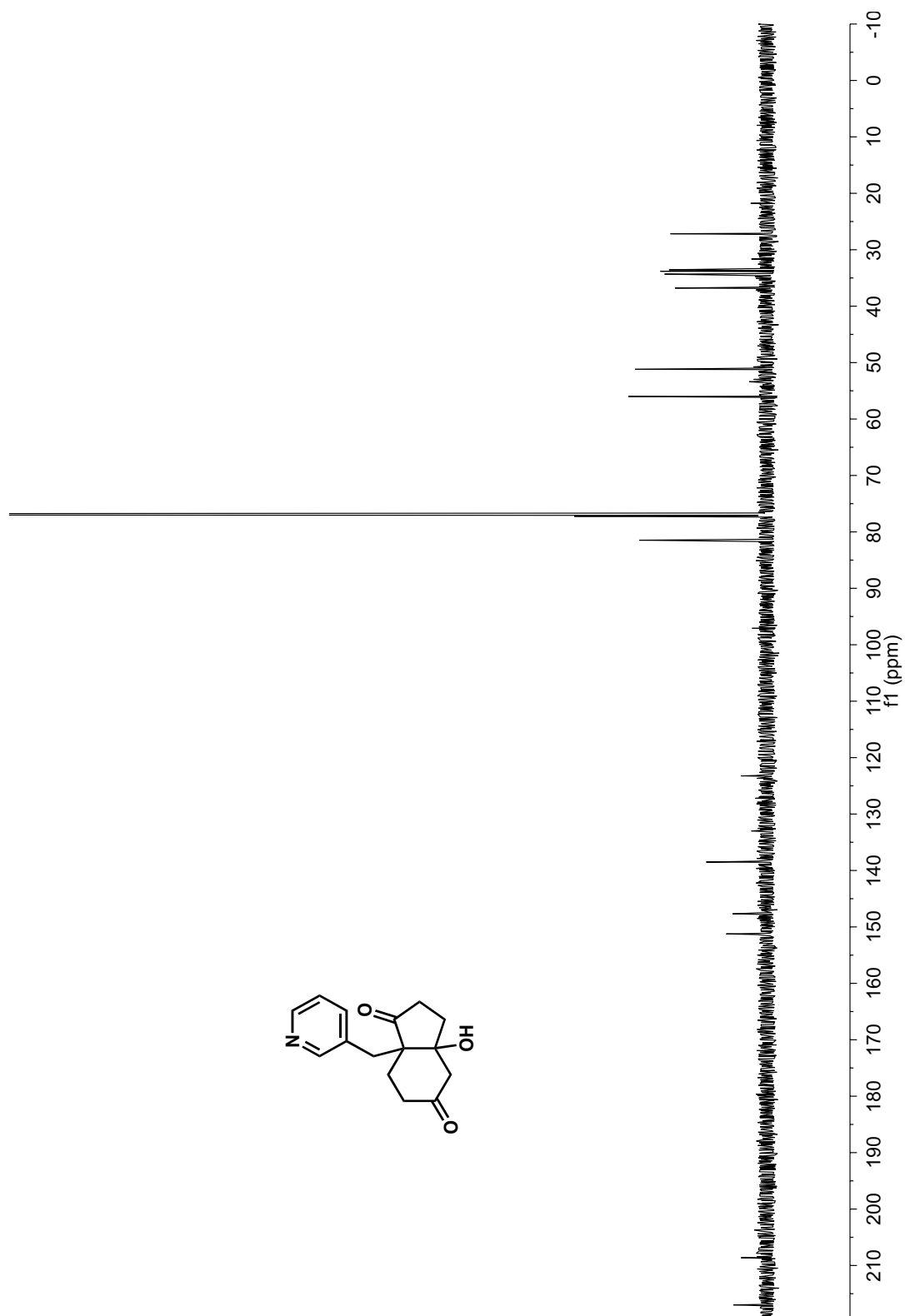


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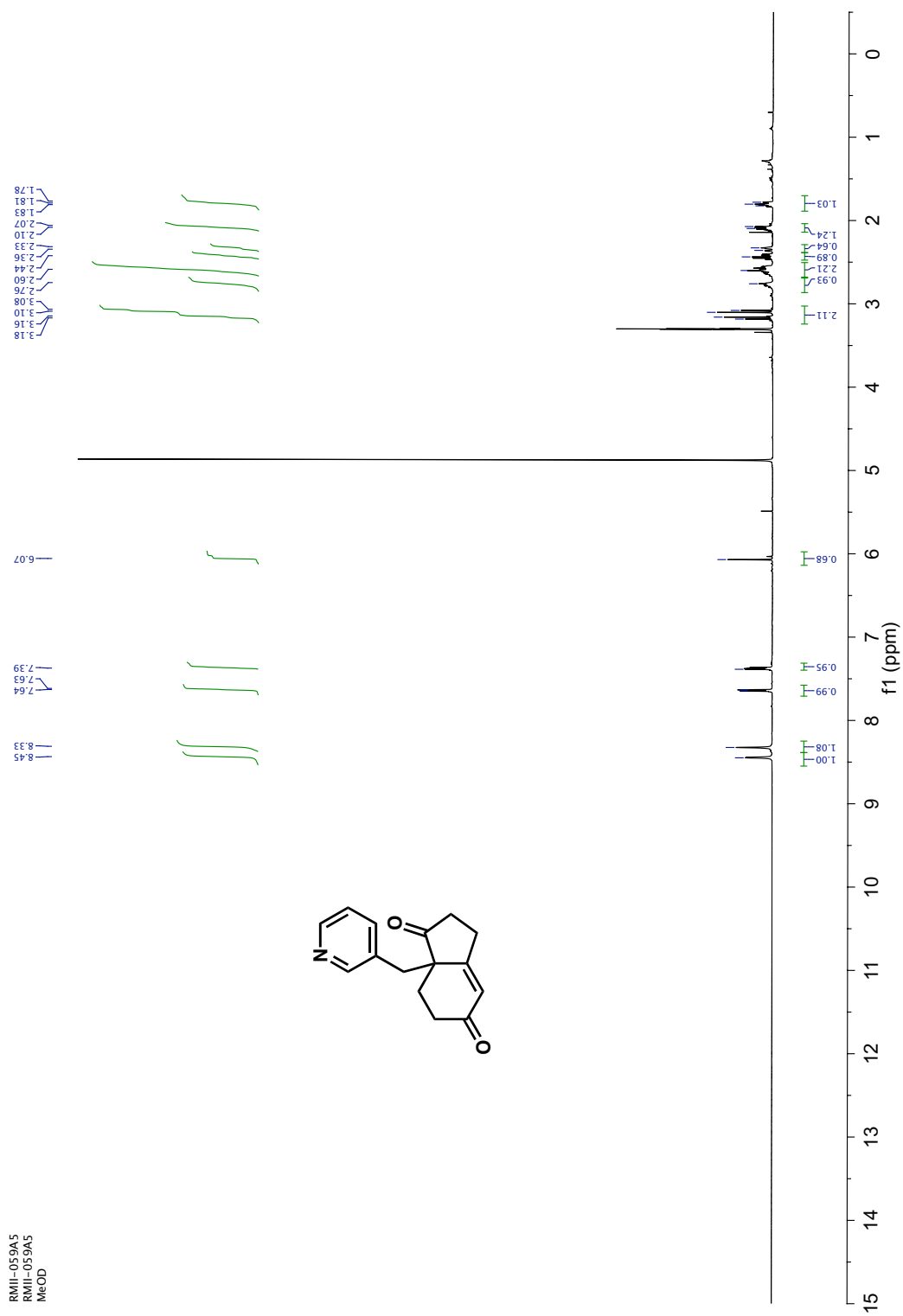


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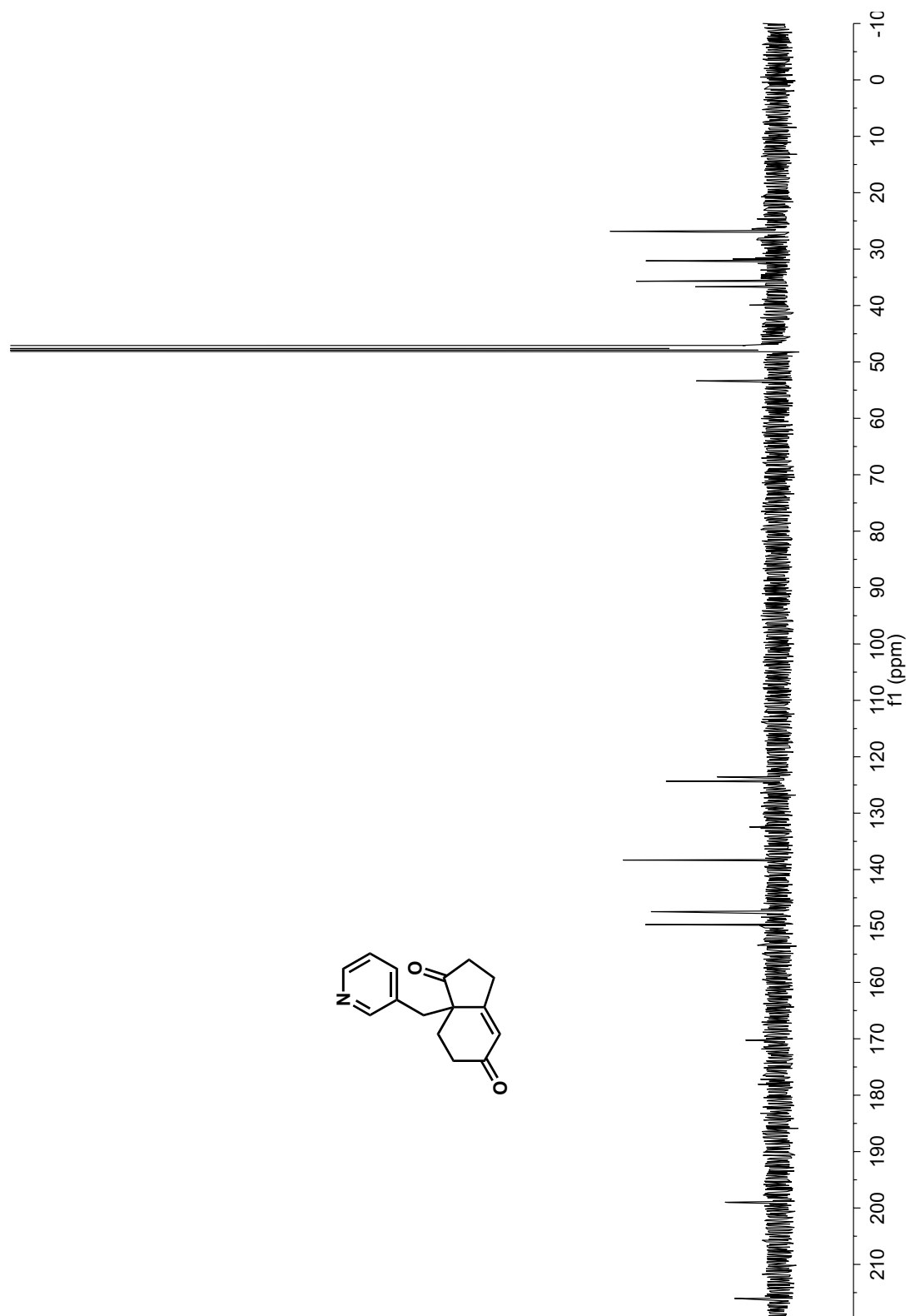


Figure A1.10 ^{13}C NMR of 2.32

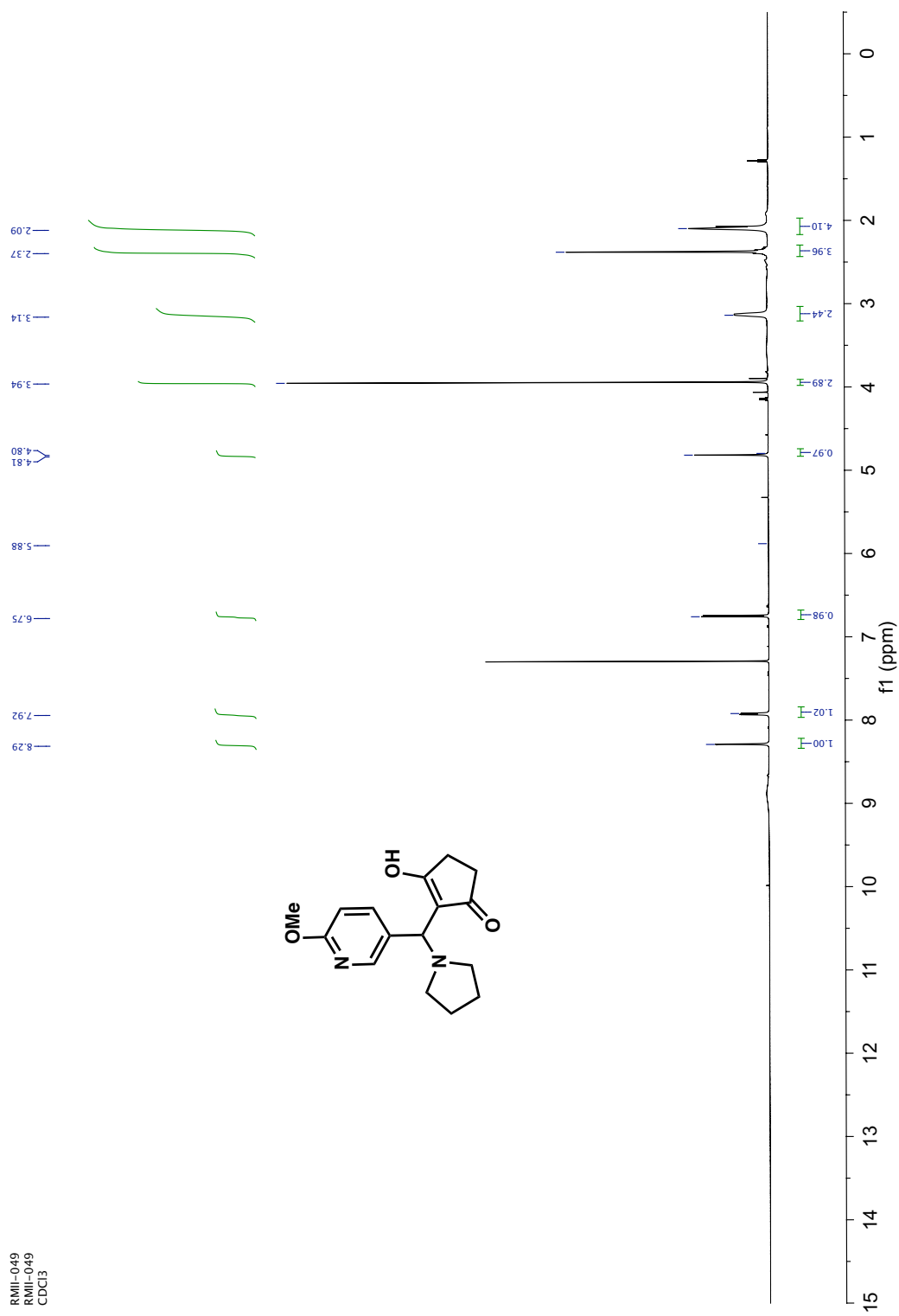


Figure A1.11 ¹H NMR of 2.53

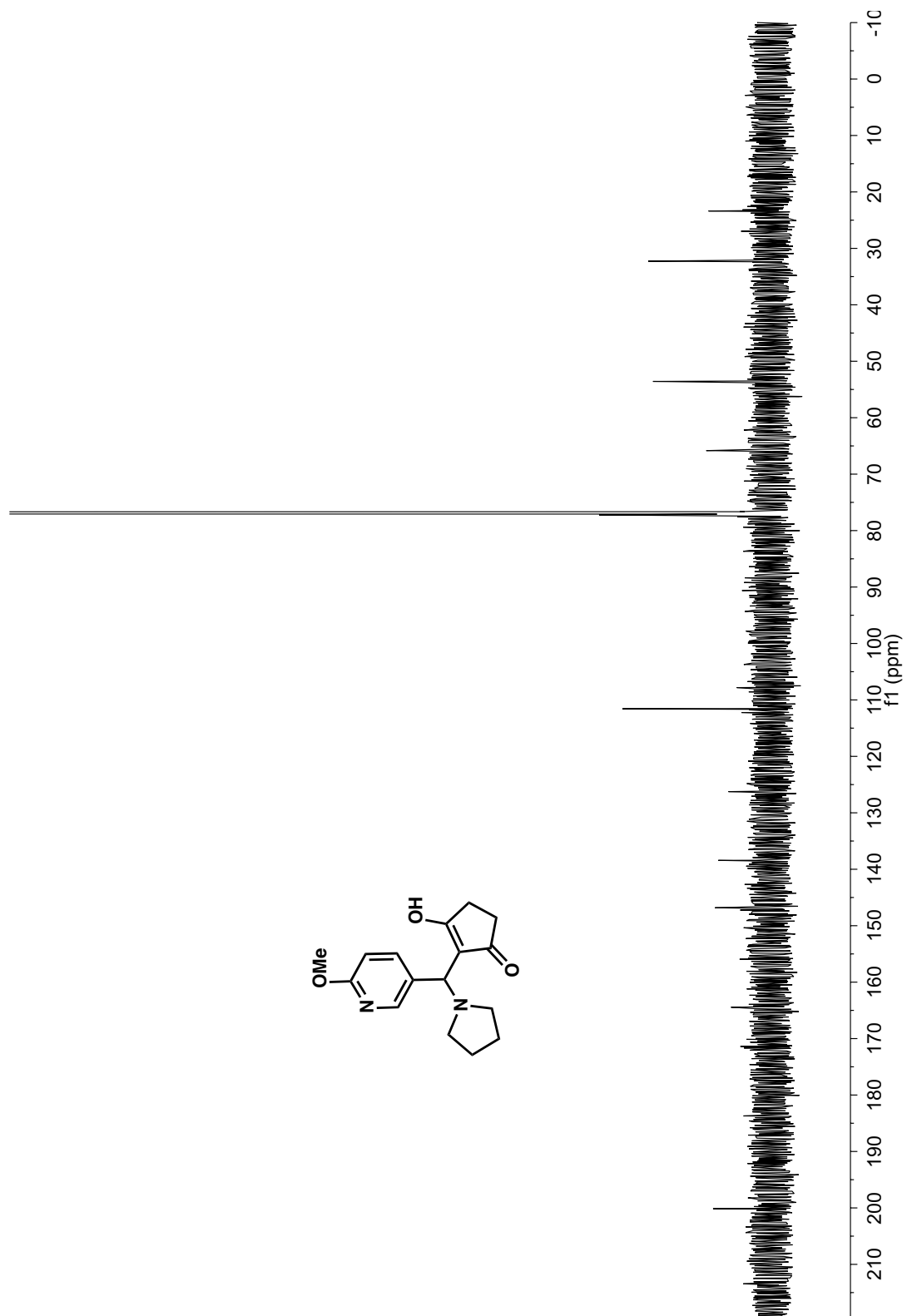


Figure A1.12 ^{13}C NMR of 2.53

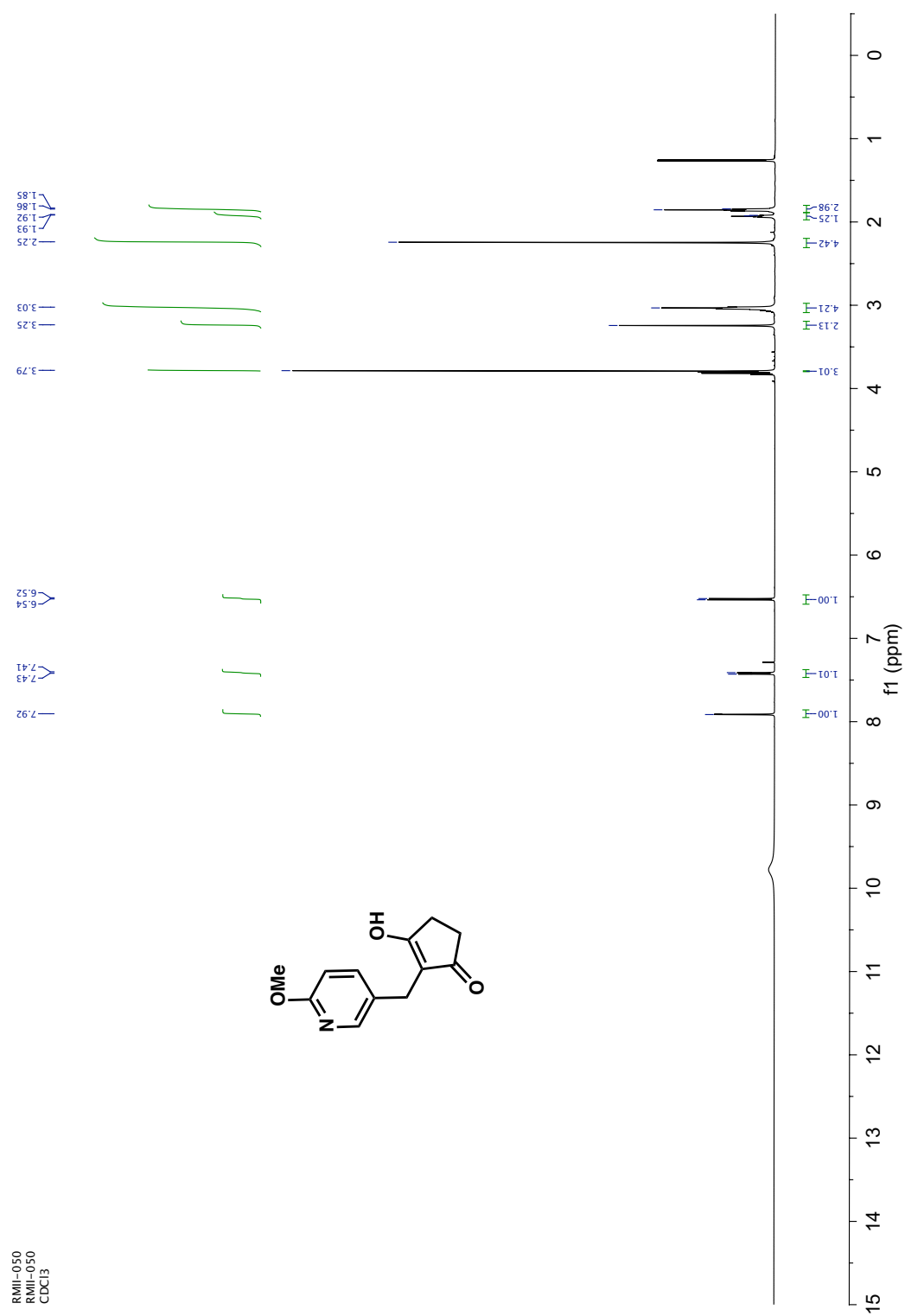


Figure A1.13 ¹H NMR of 2.54

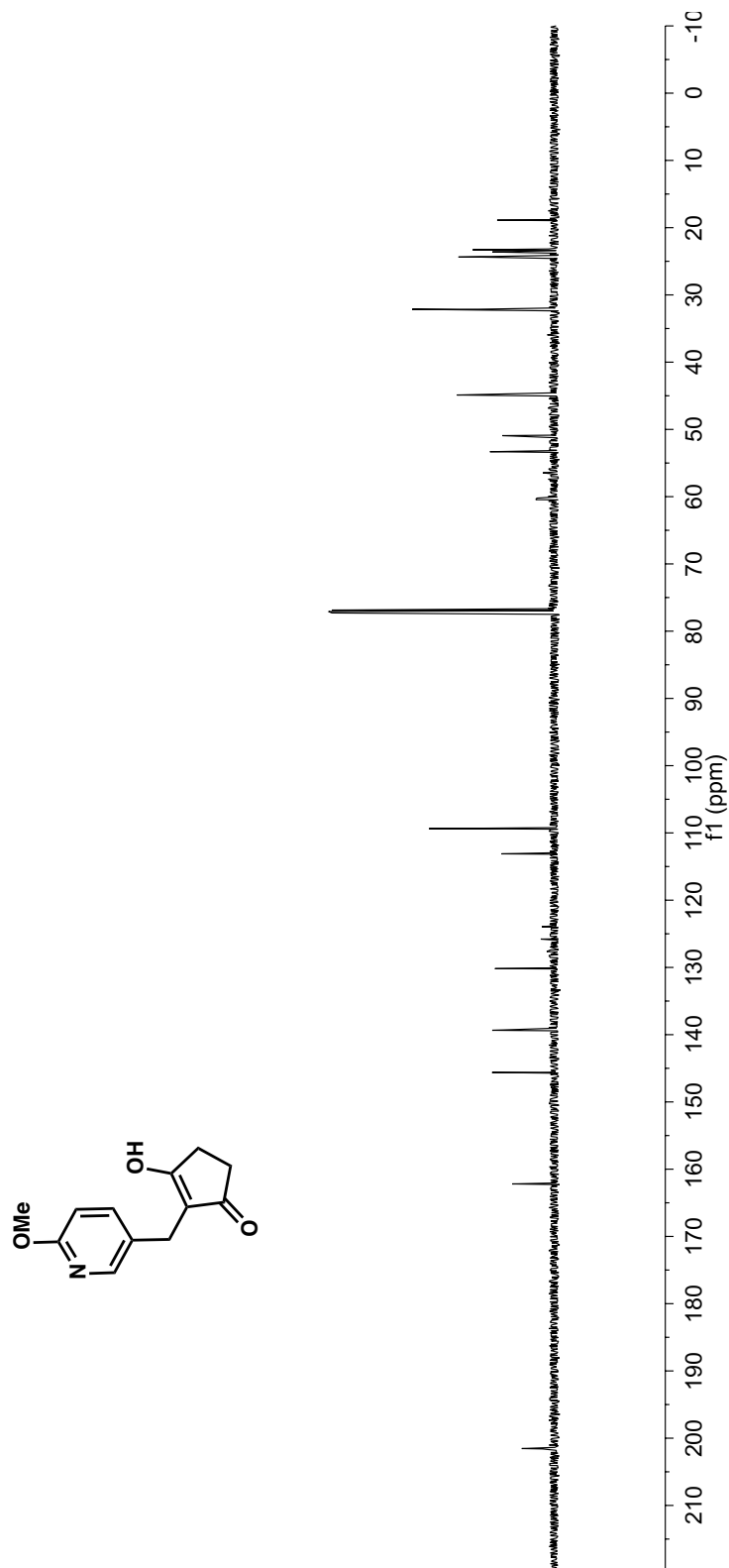


Figure A1.14 ^{13}C NMR of 2.54

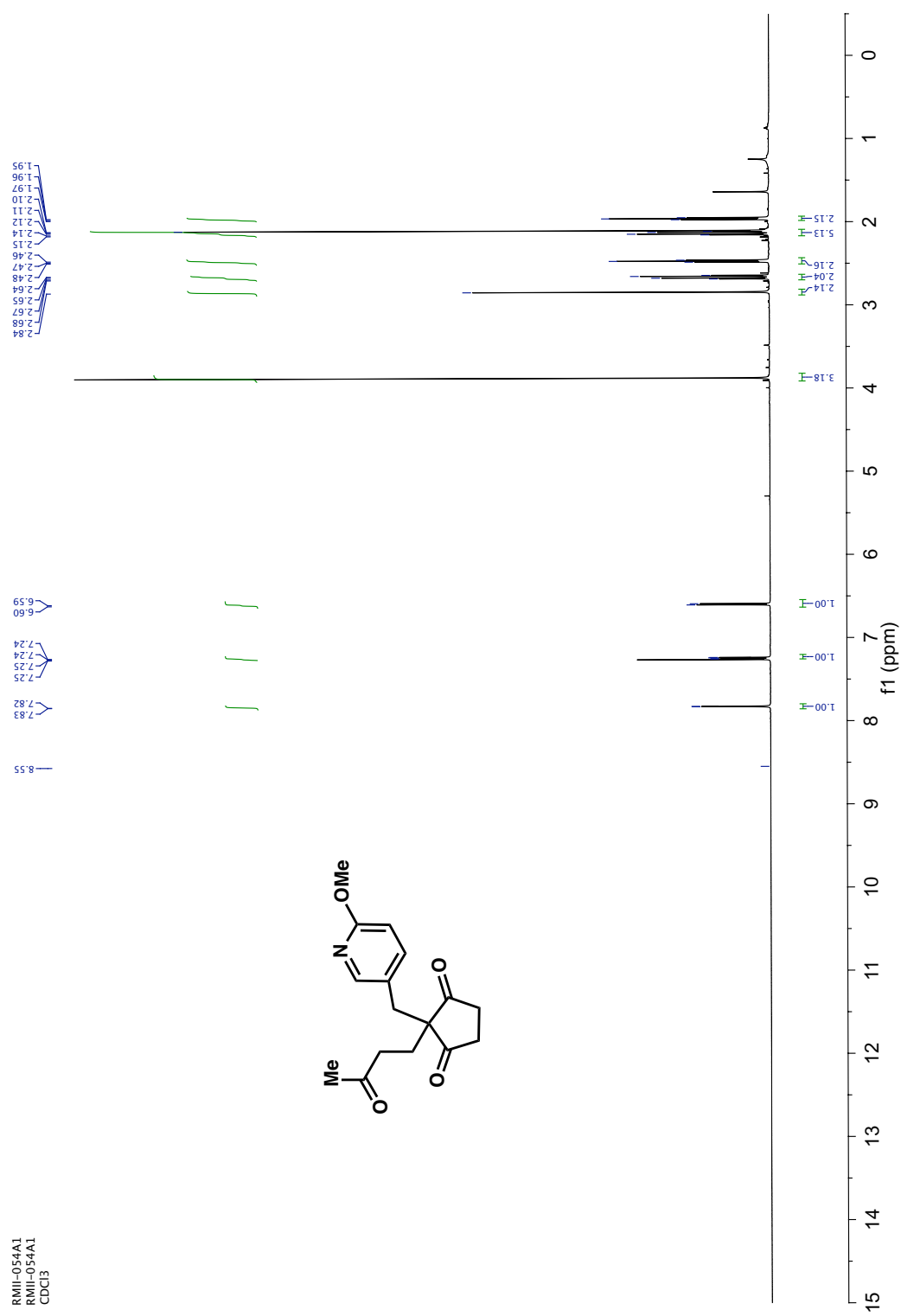


Figure A1.15 ¹H NMR of 2.S1

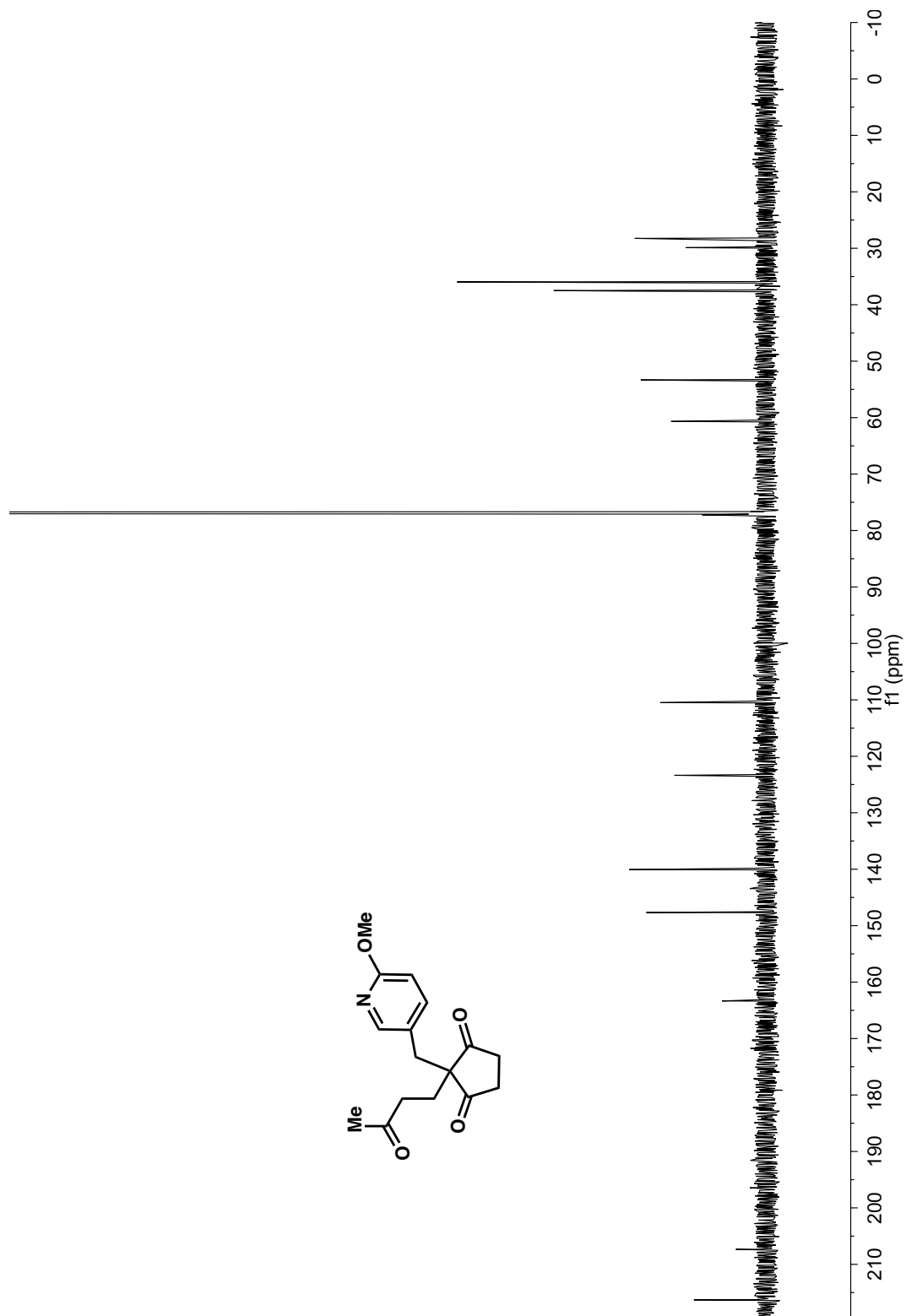


Figure A1.16 ^{13}C NMR of 2.S1

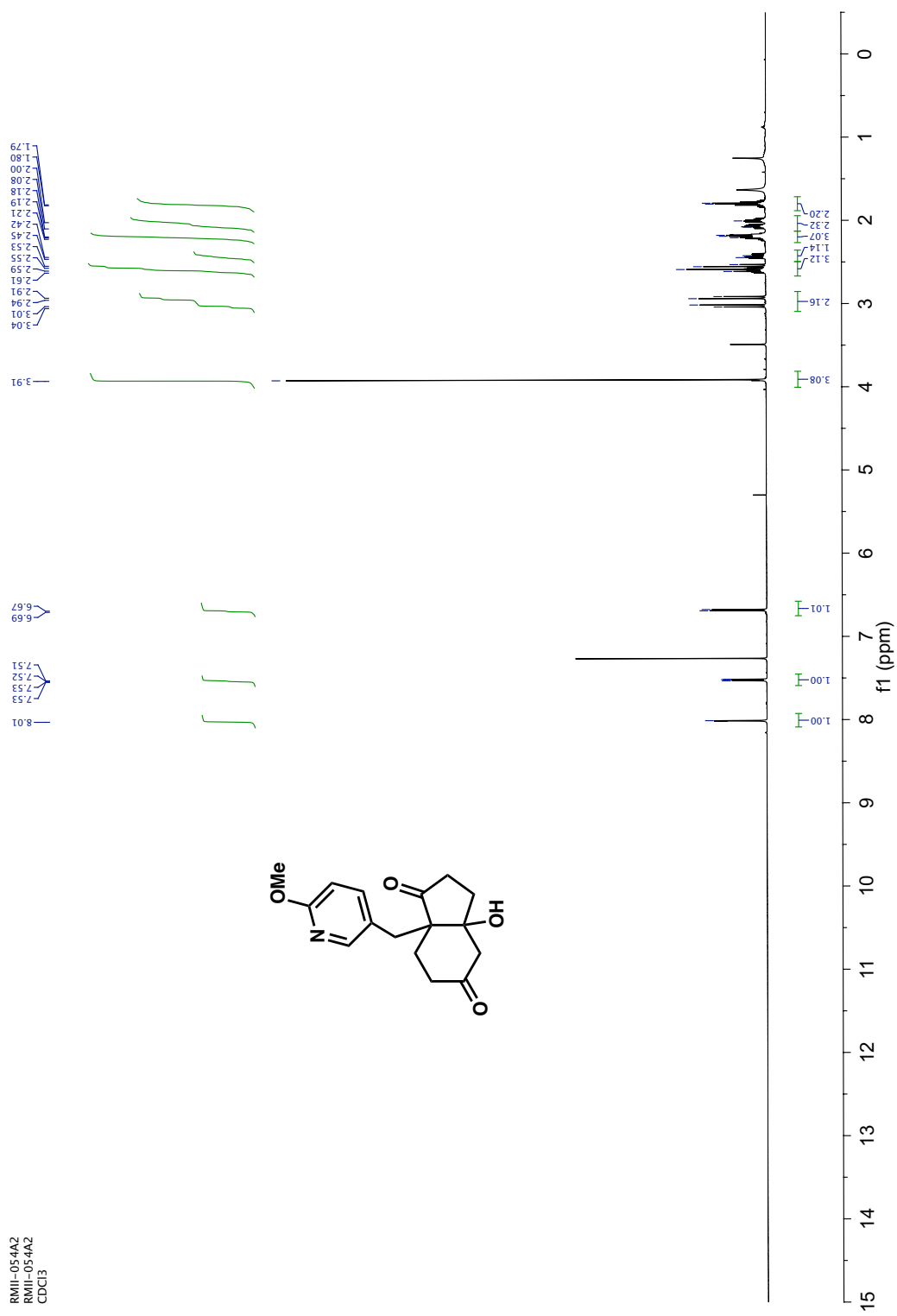


Figure A1.17 ¹H NMR of 2.55

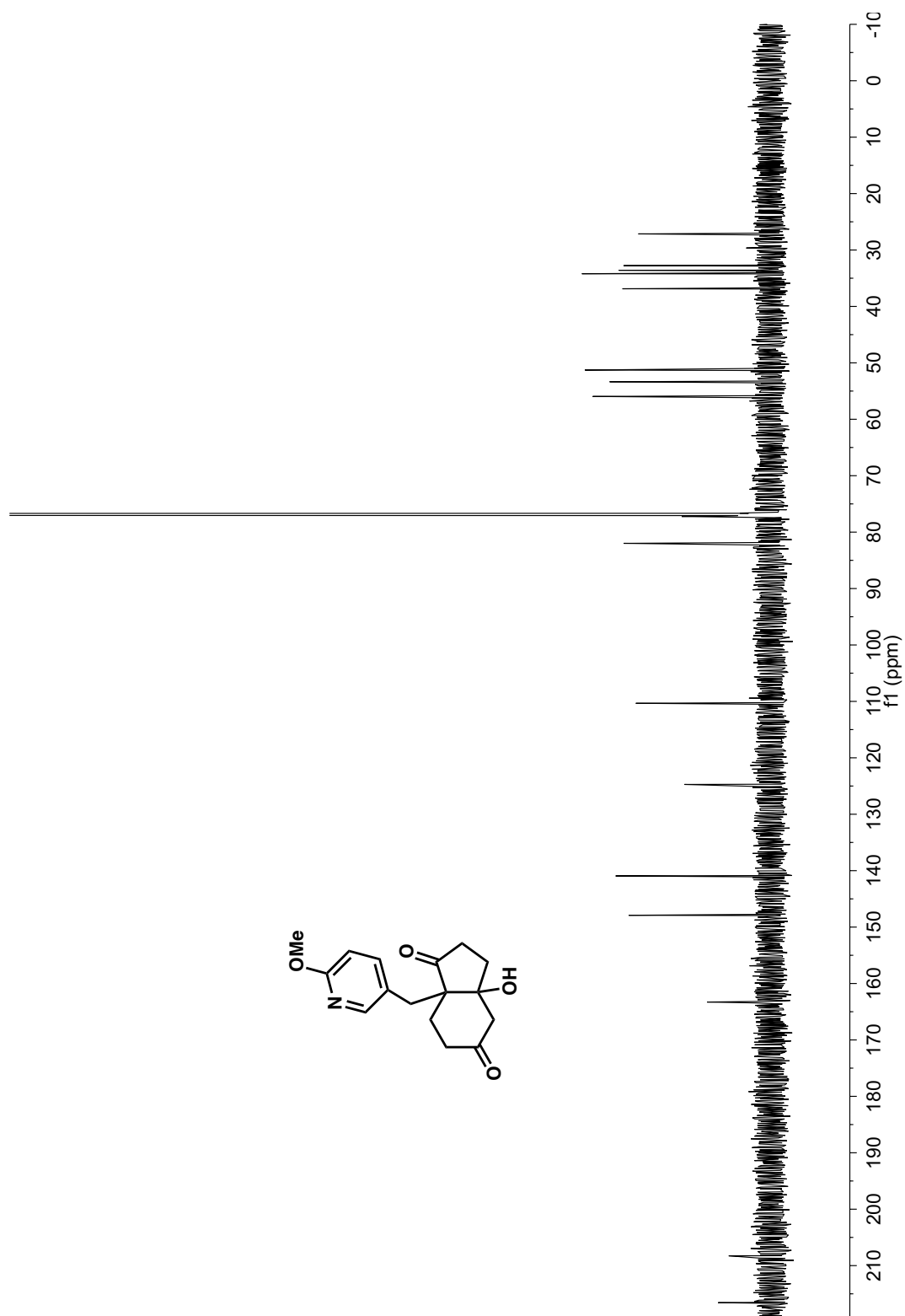


Figure A1.18 ^{13}C NMR of 2.55

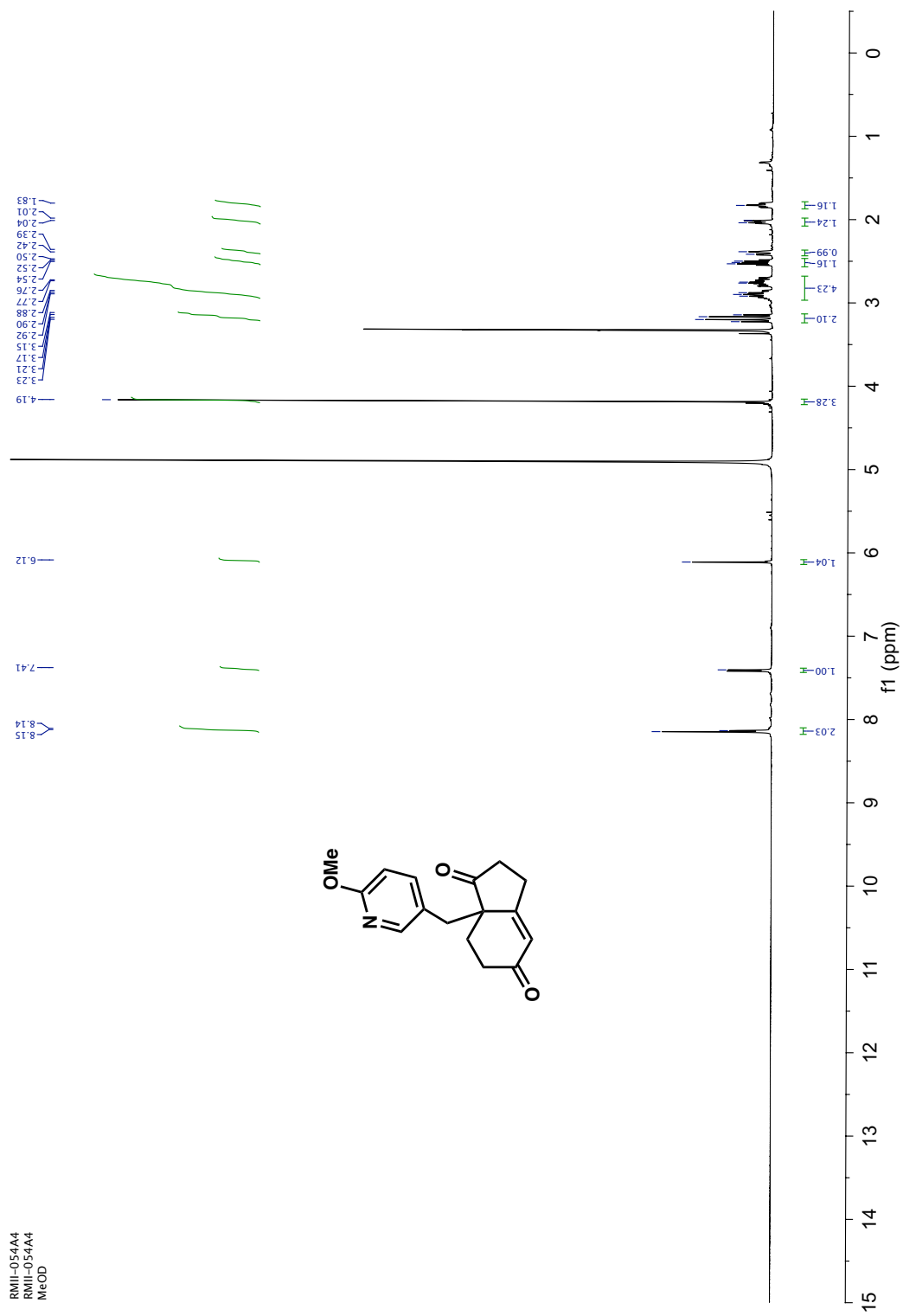


Figure A1.19 ¹H NMR of 2.56

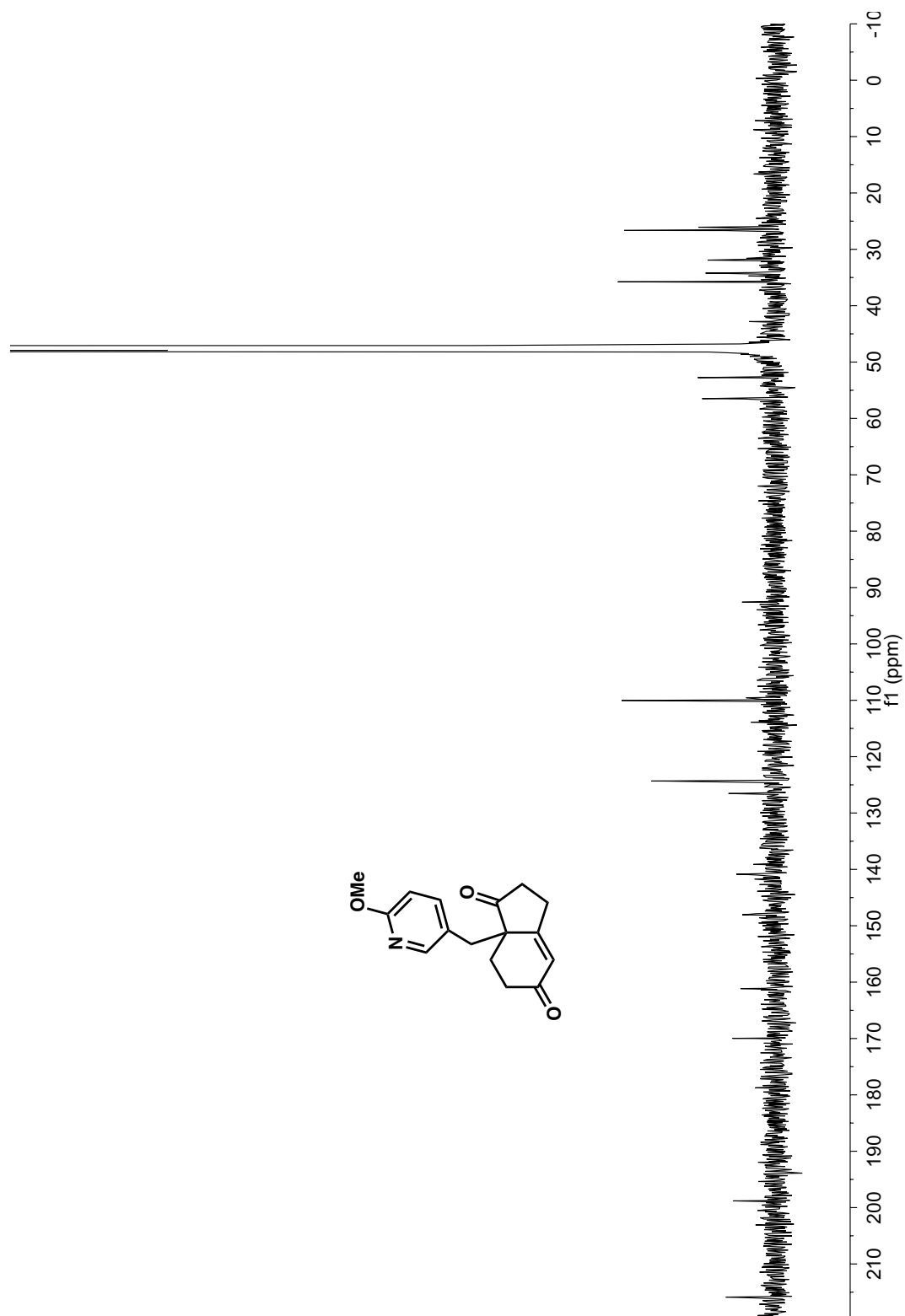


Figure A1.20 ^{13}C NMR of 2.56

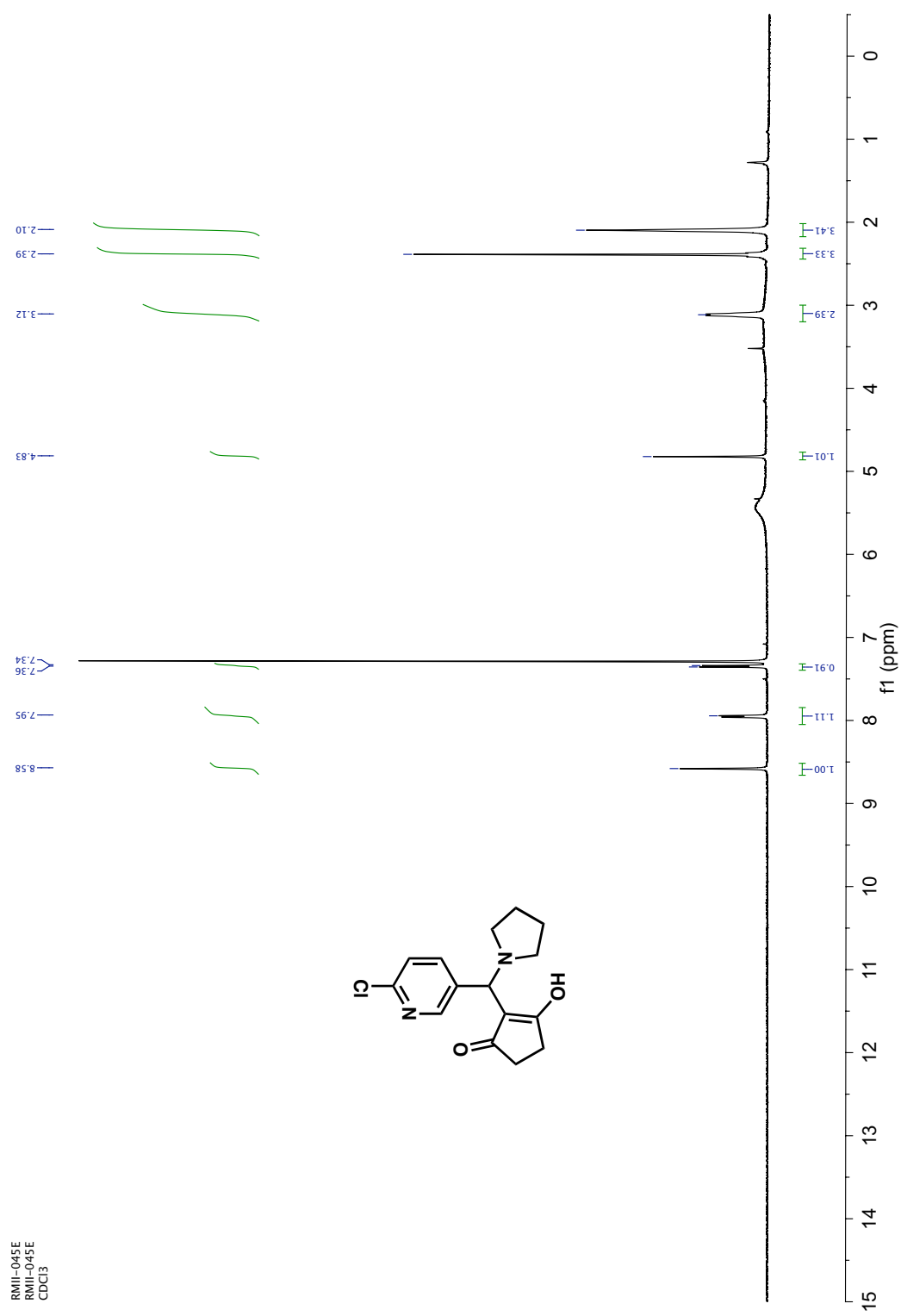


Figure A1.21 ^1H NMR of **2.45**

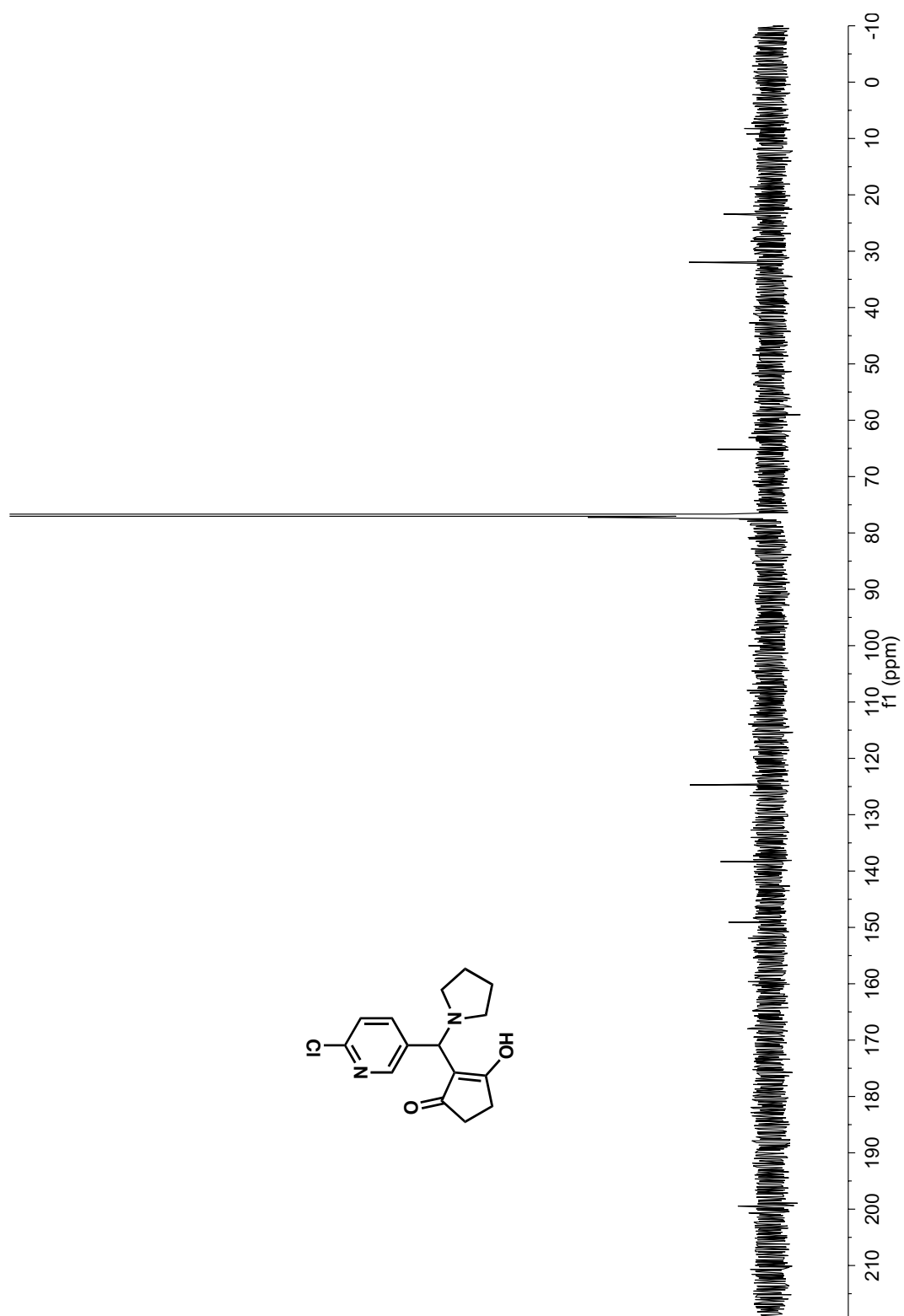


Figure A1.22 ^{13}C NMR of 2.45

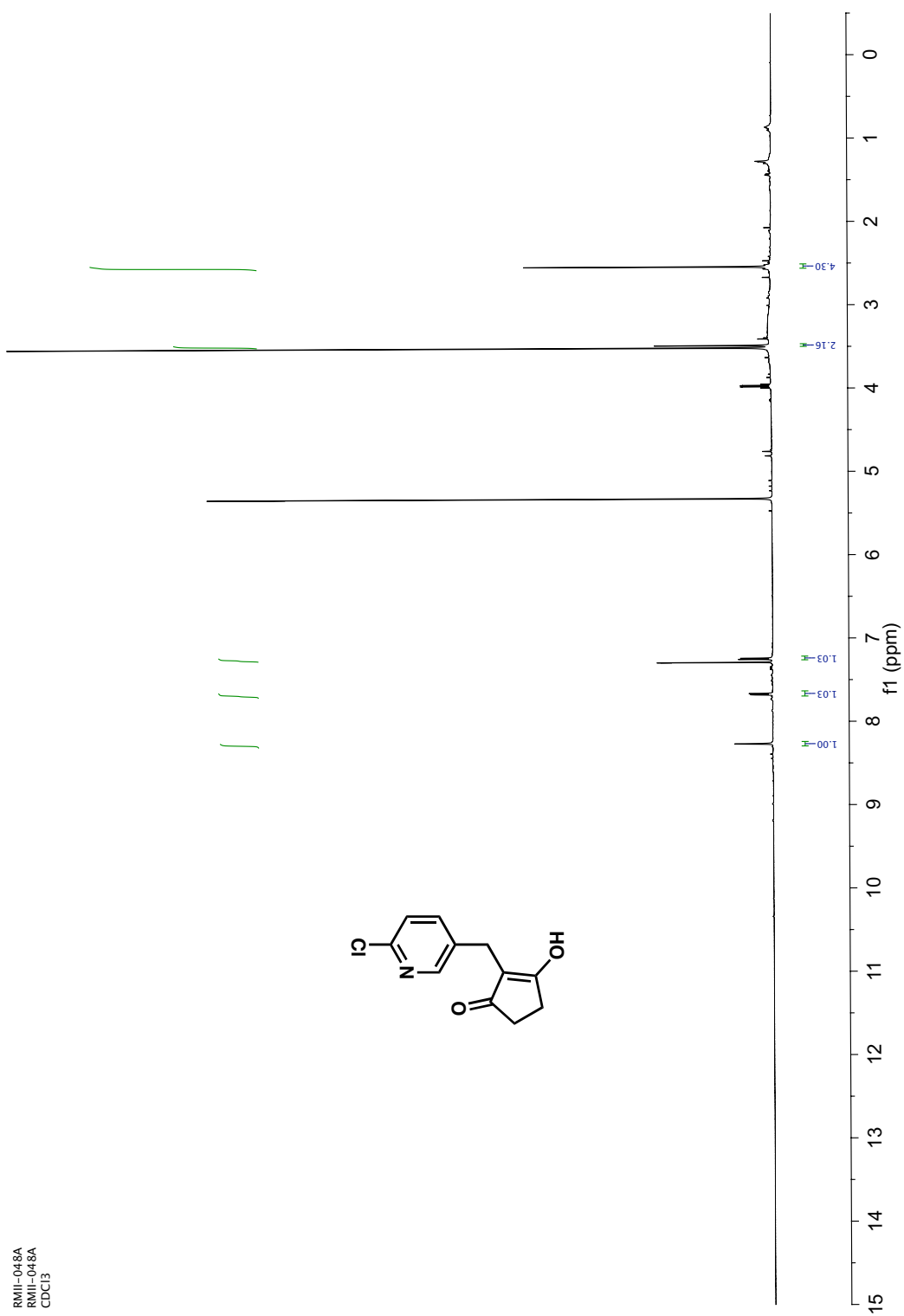


Figure A1.23 ¹H NMR of 2.46

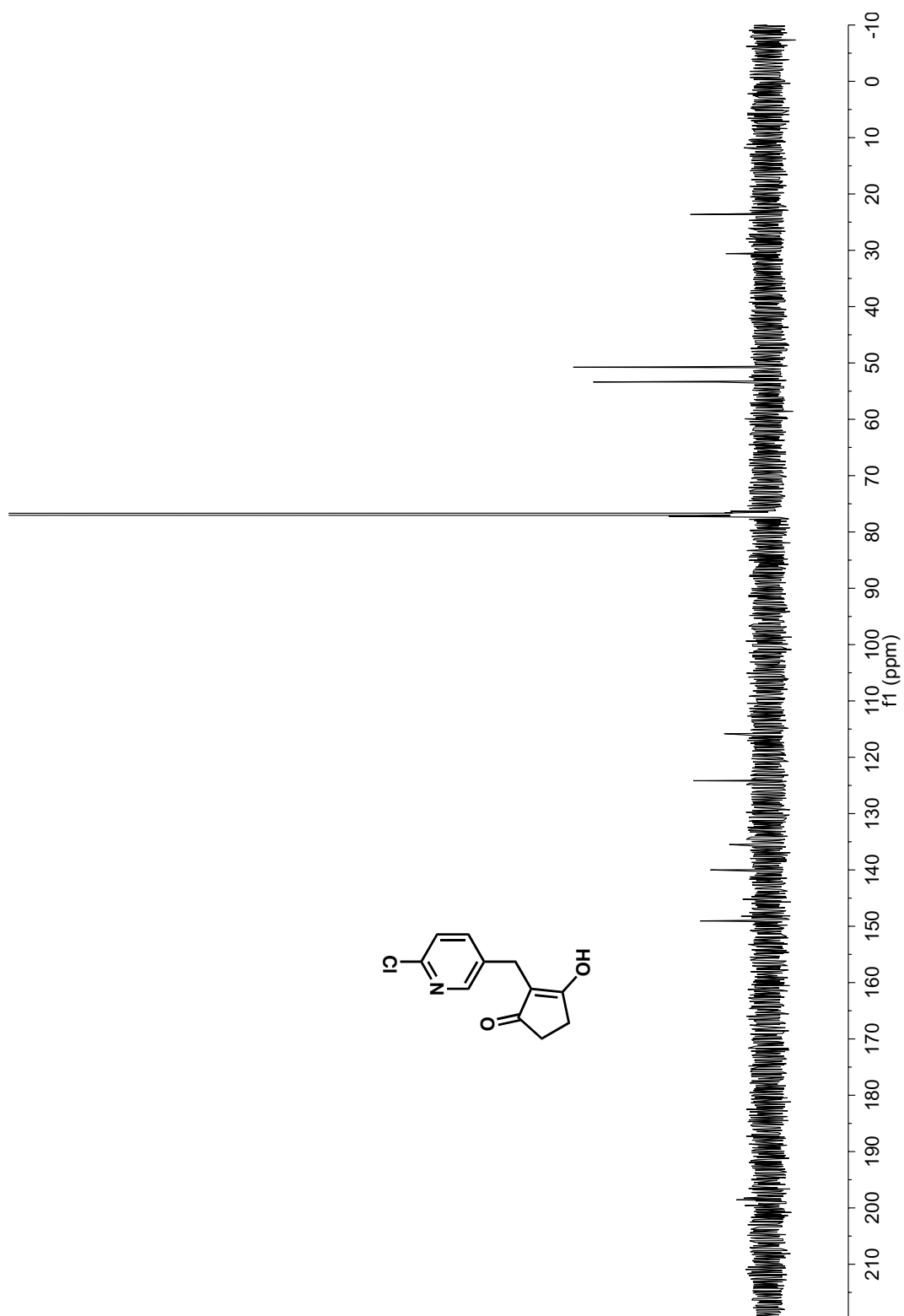


Figure A1.24 ^{13}C NMR of 2.46

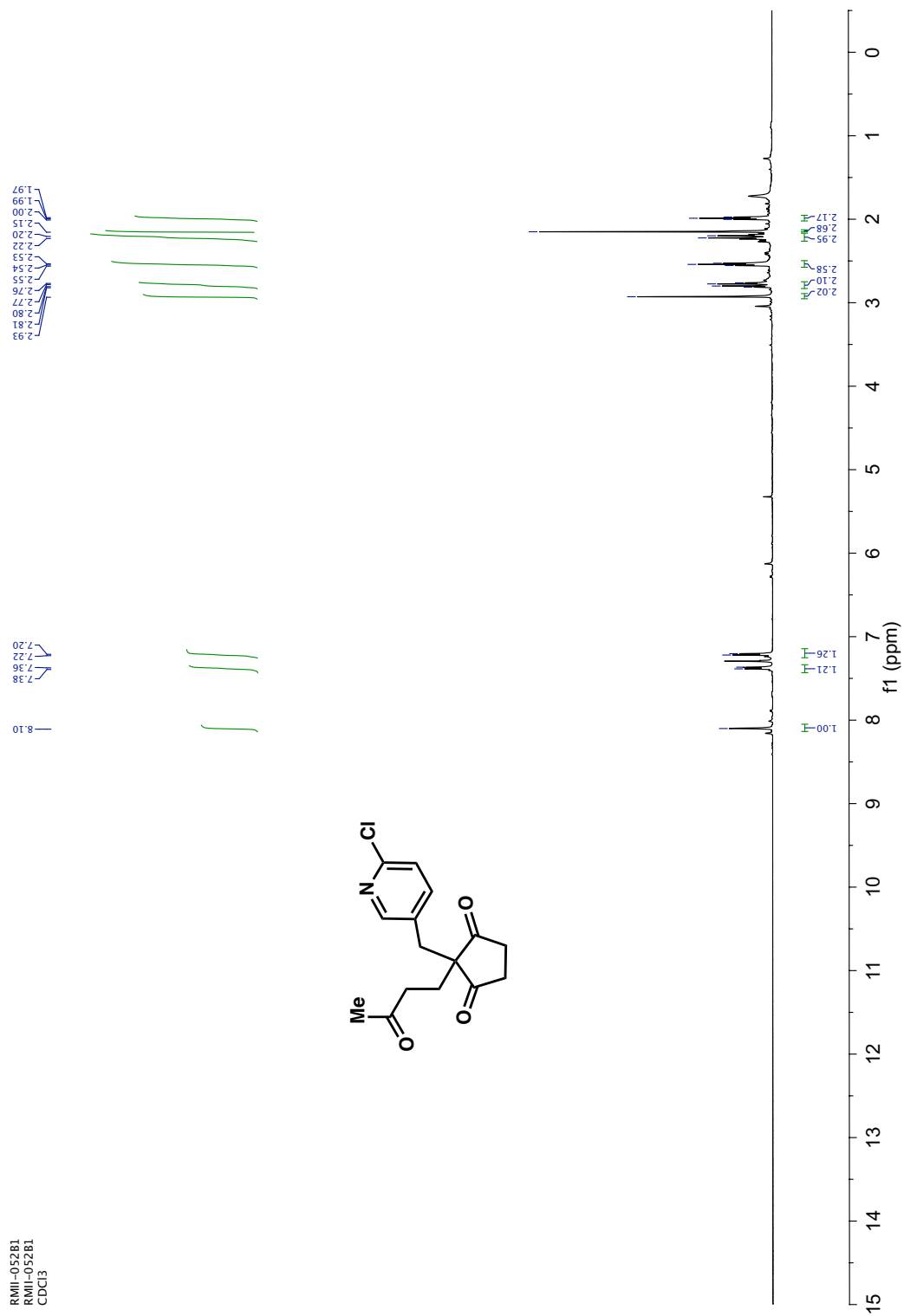


Figure A1.25 ¹H NMR of 2.S2

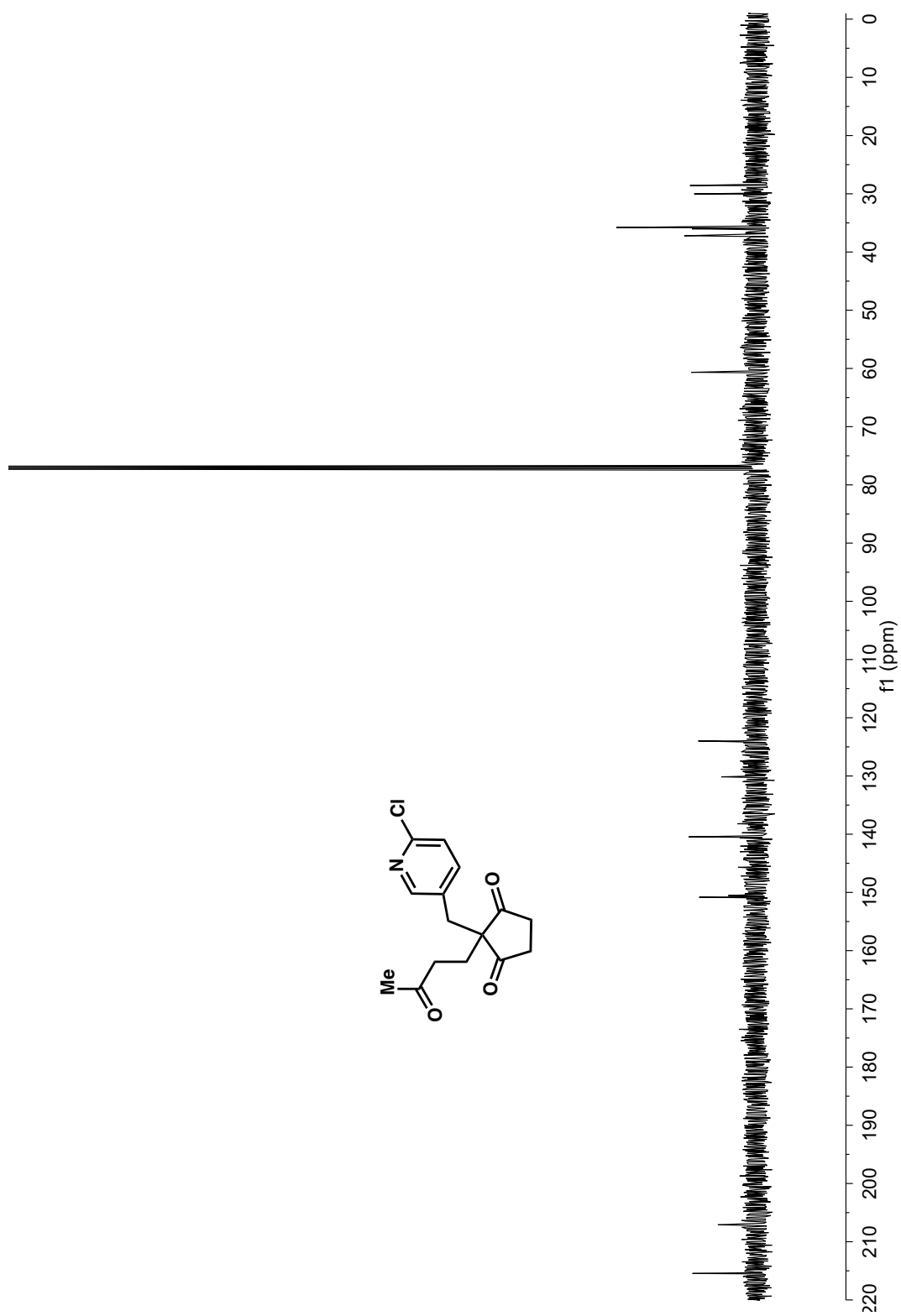


Figure A1.26 ^{13}C NMR of 2.S2

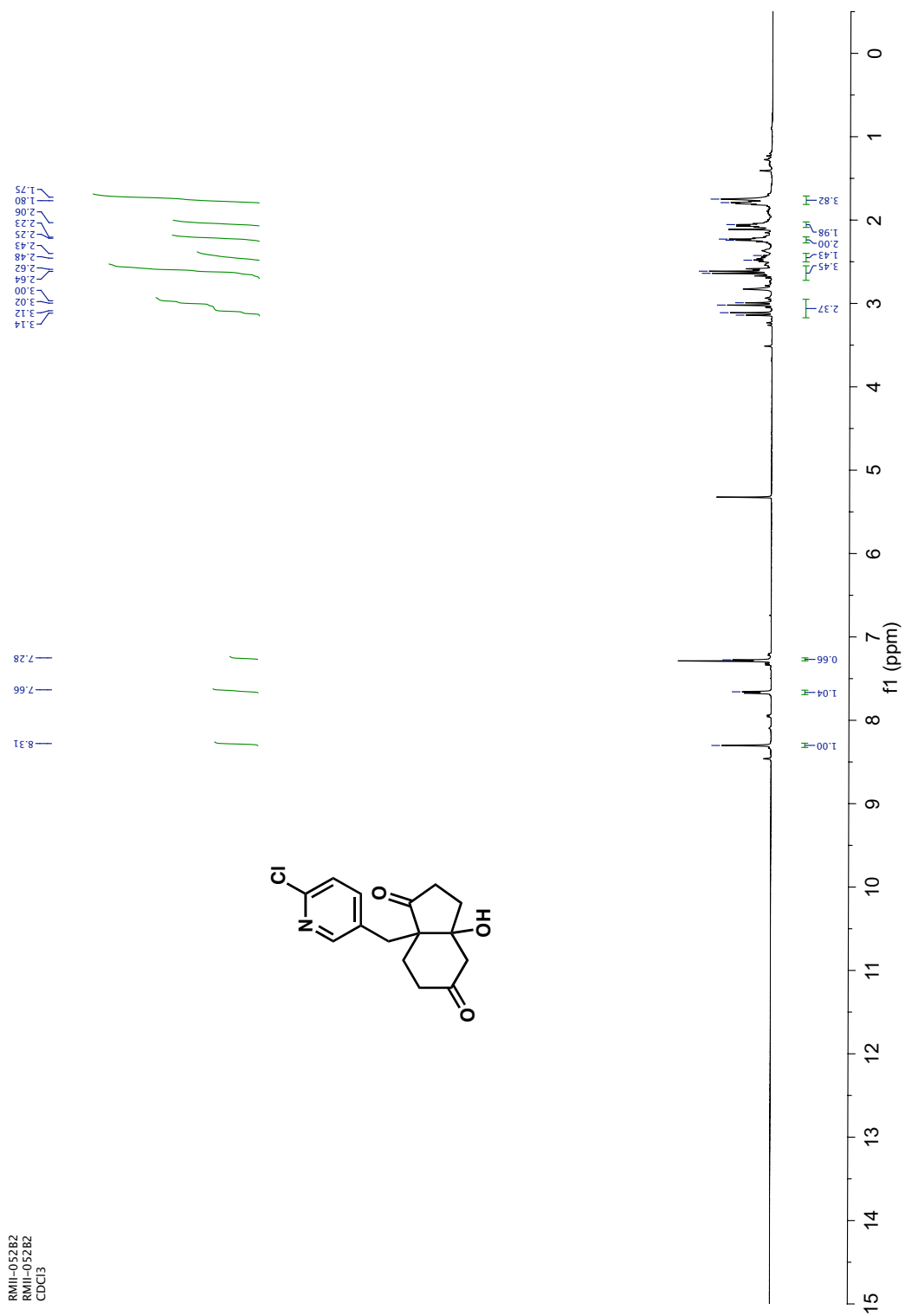


Figure A1.27 ¹H NMR of 2.47

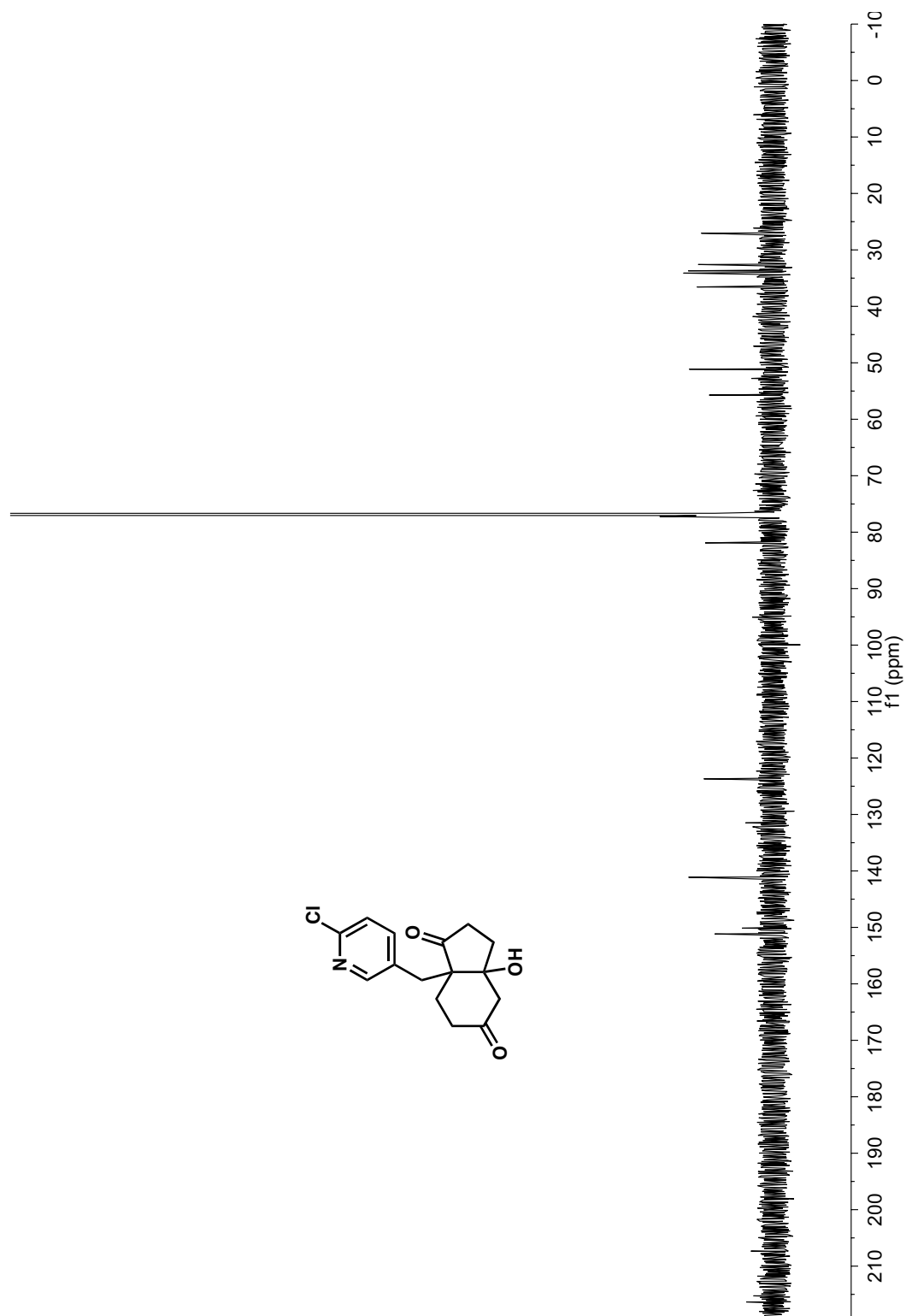


Figure A1.28 ^{13}C NMR of 2.47

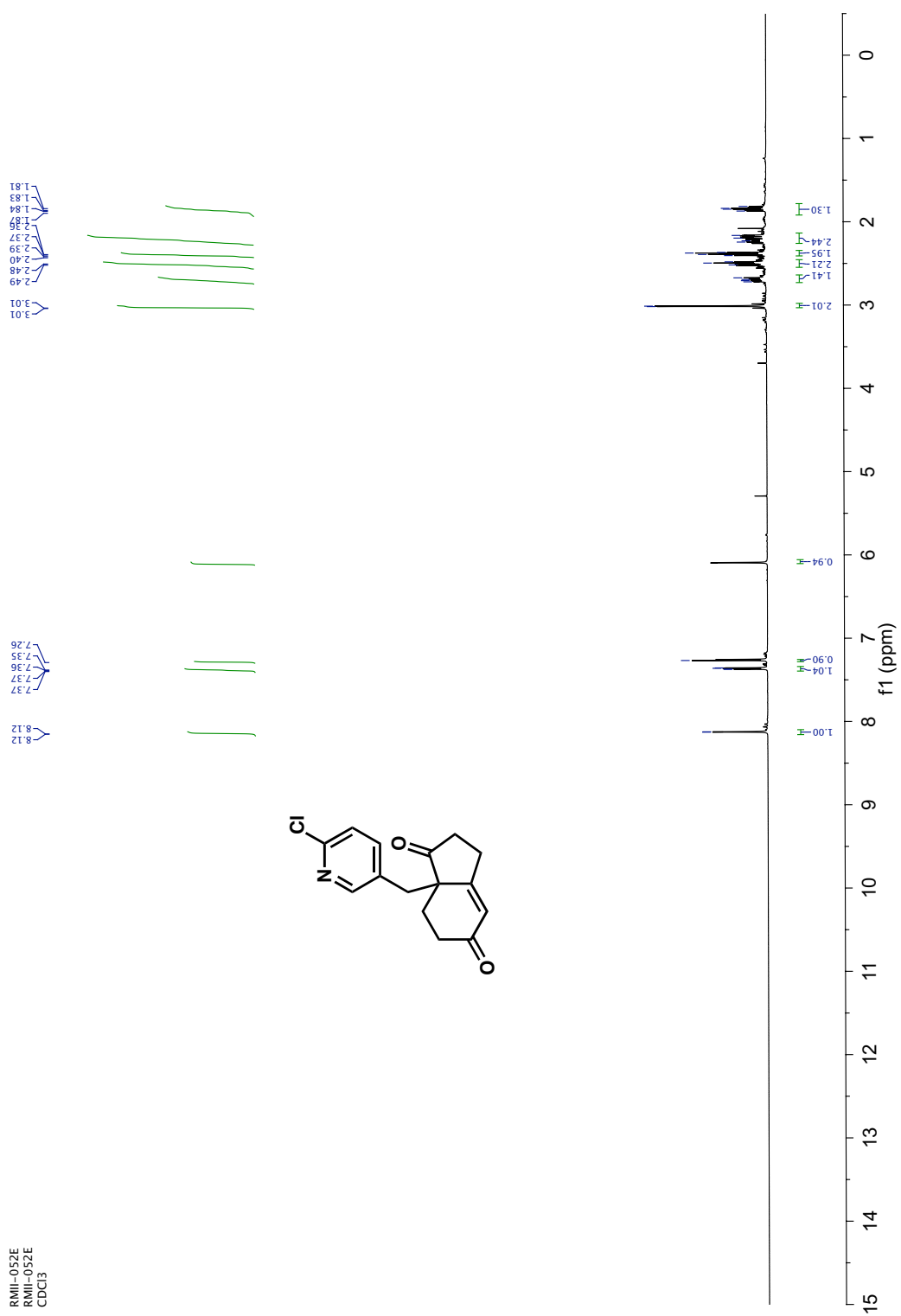


Figure A1.29 ¹H NMR of 2.48

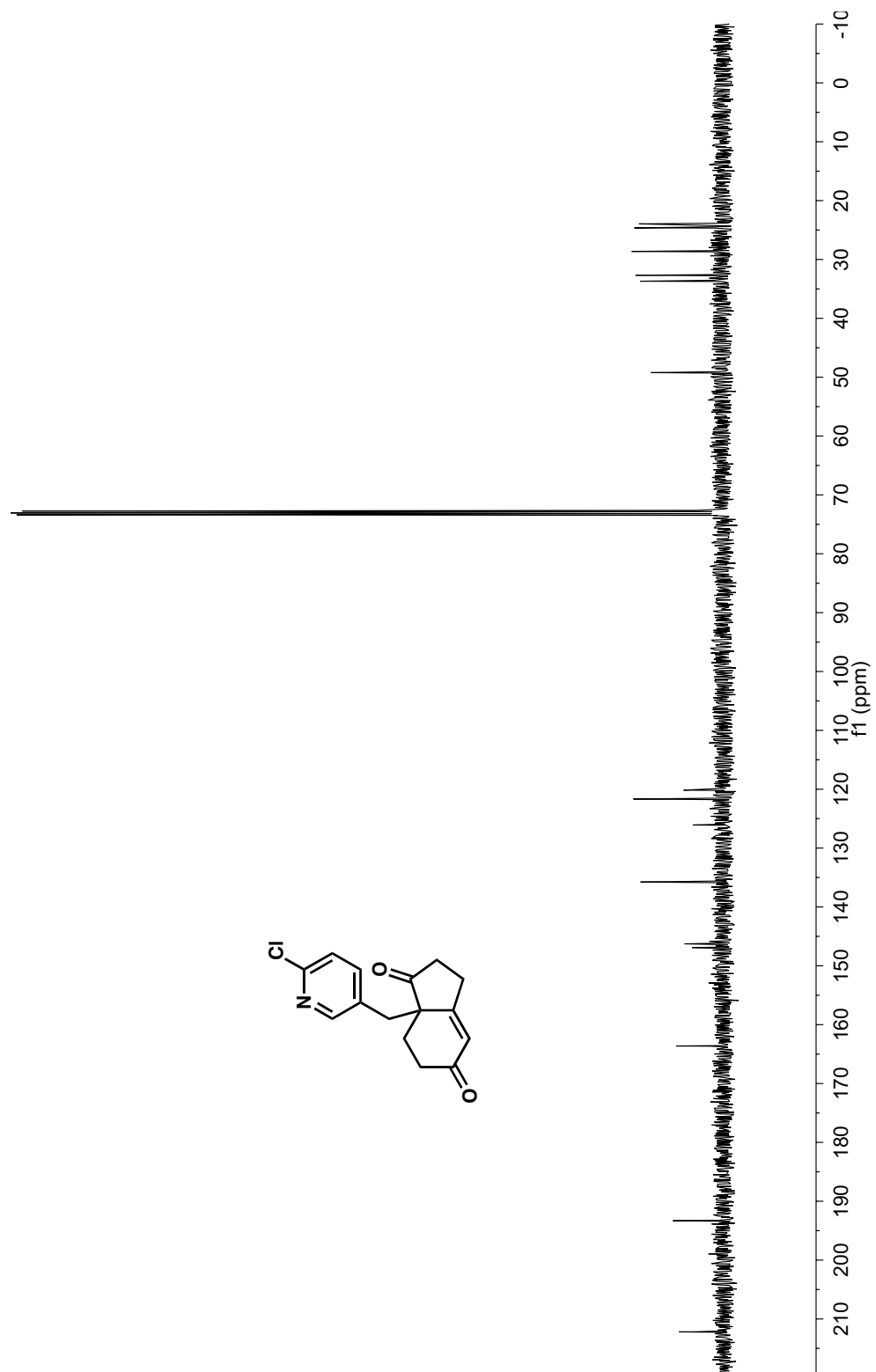


Figure A1.30 ^{13}C NMR of 2.48

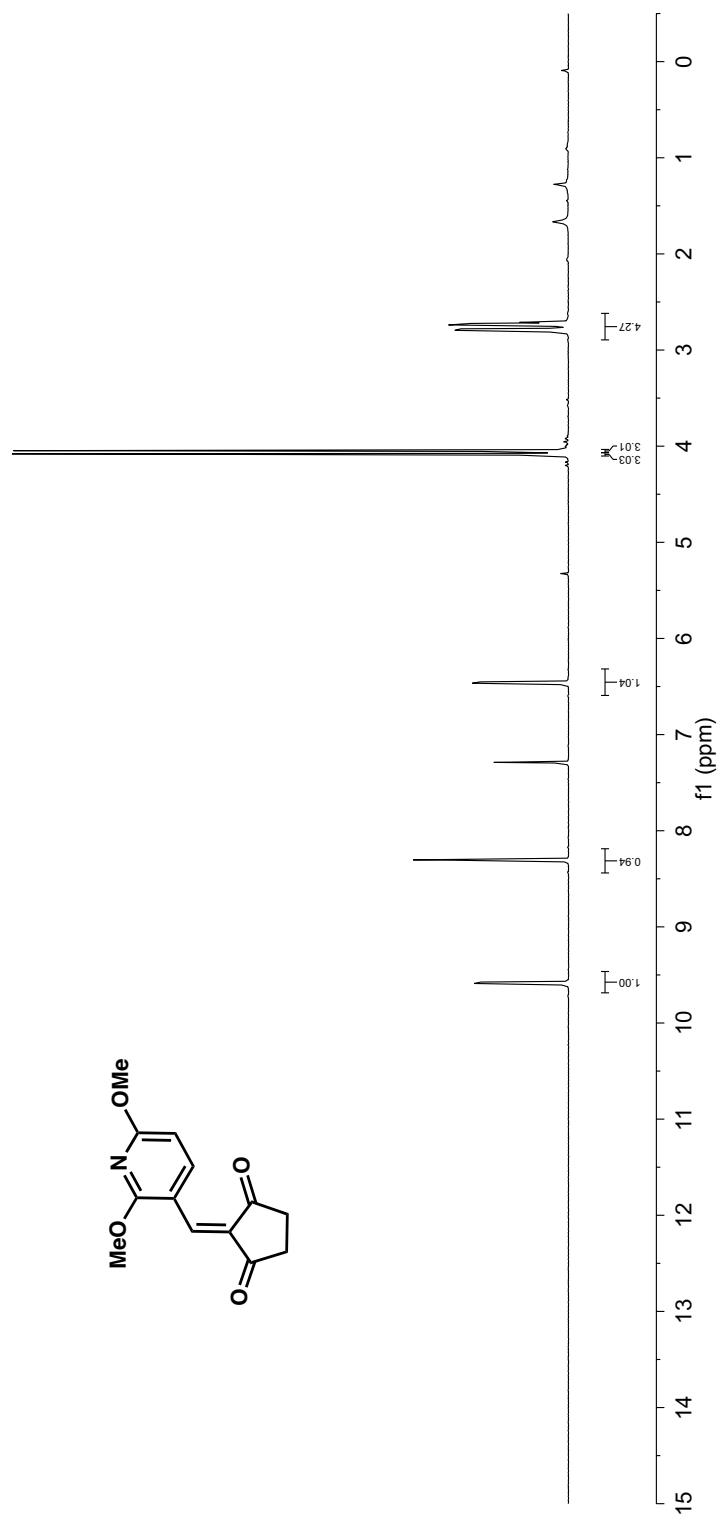


Figure A1.31 ^1H NMR of **2.58**

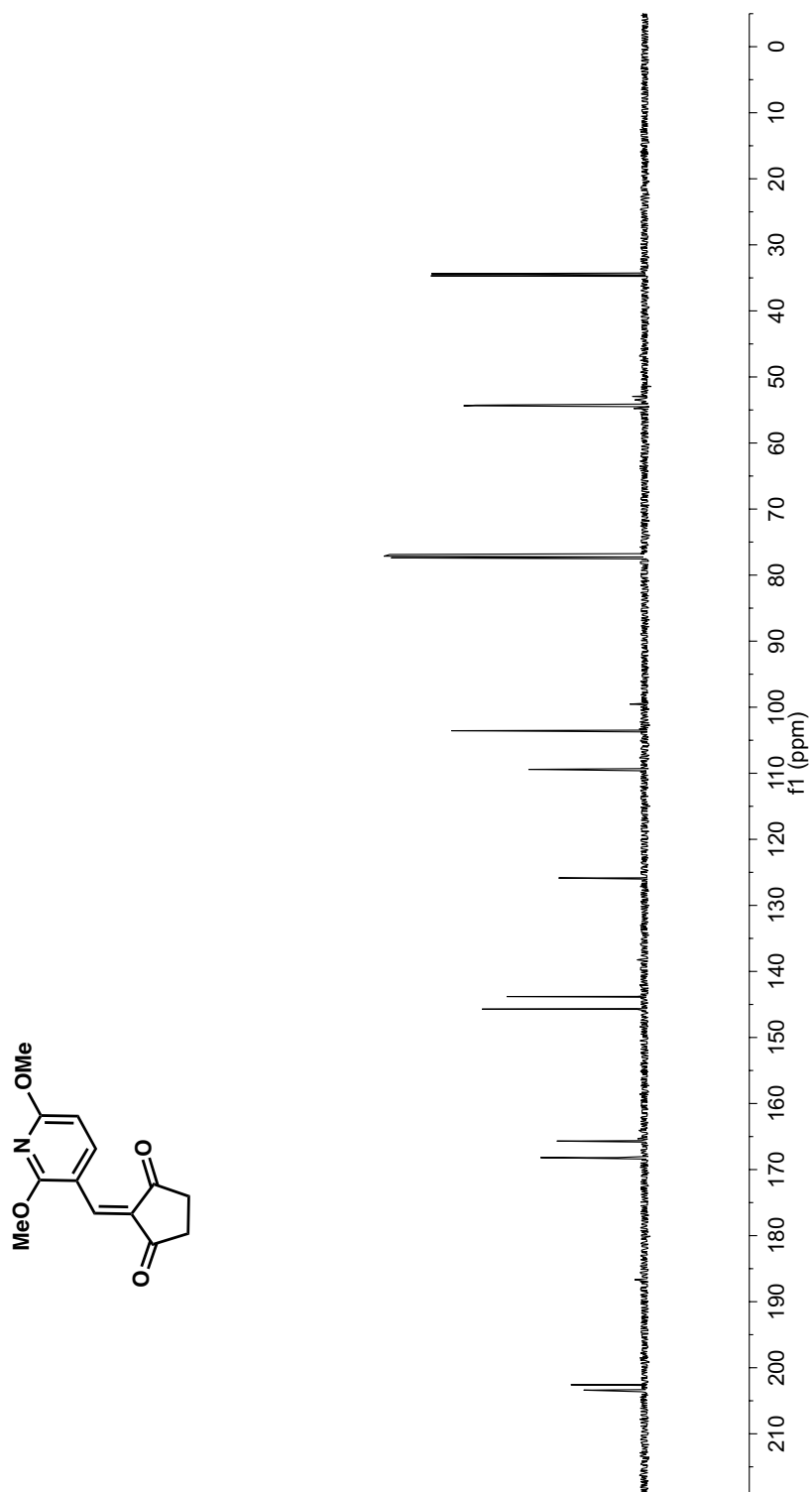


Figure A1.32 ^{13}C NMR of 2.58

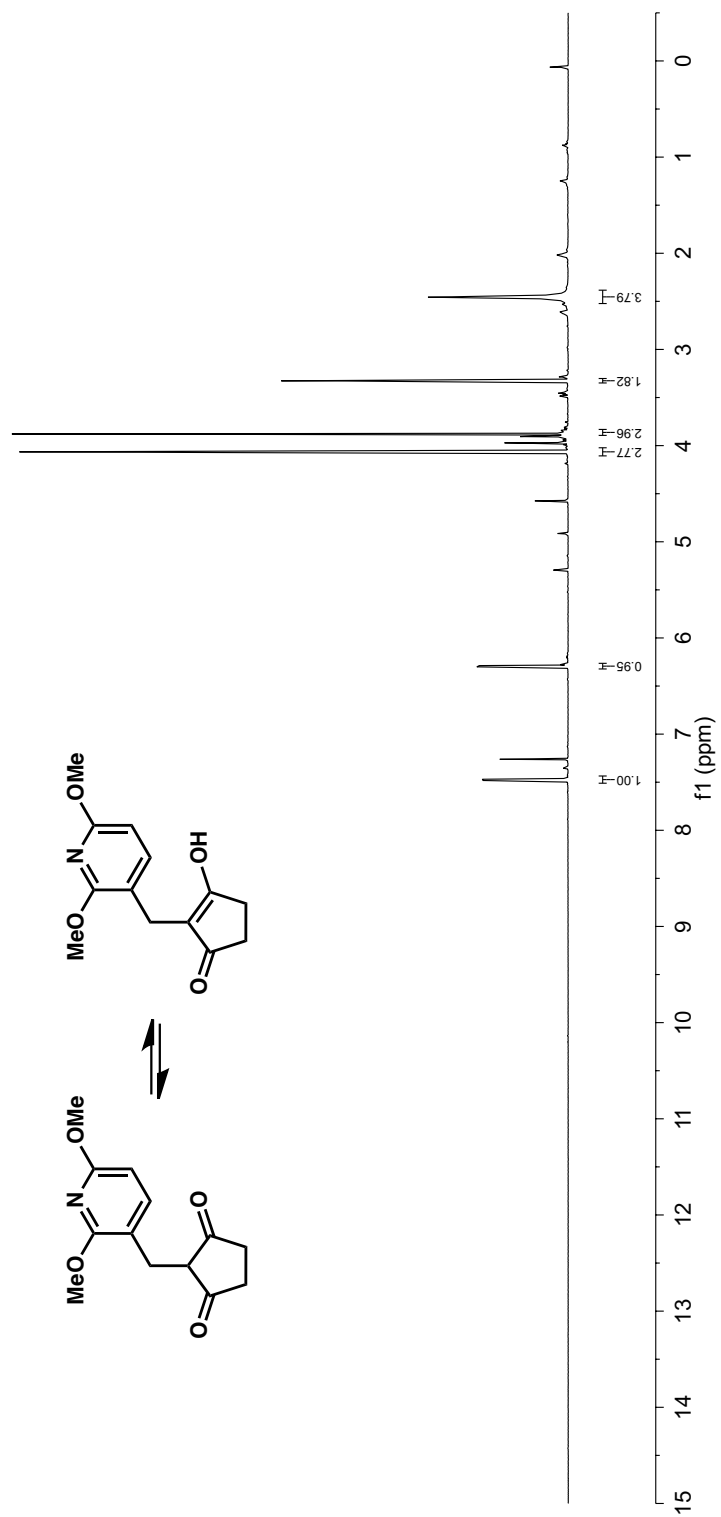


Figure A1.33 ^1H NMR of 2.59

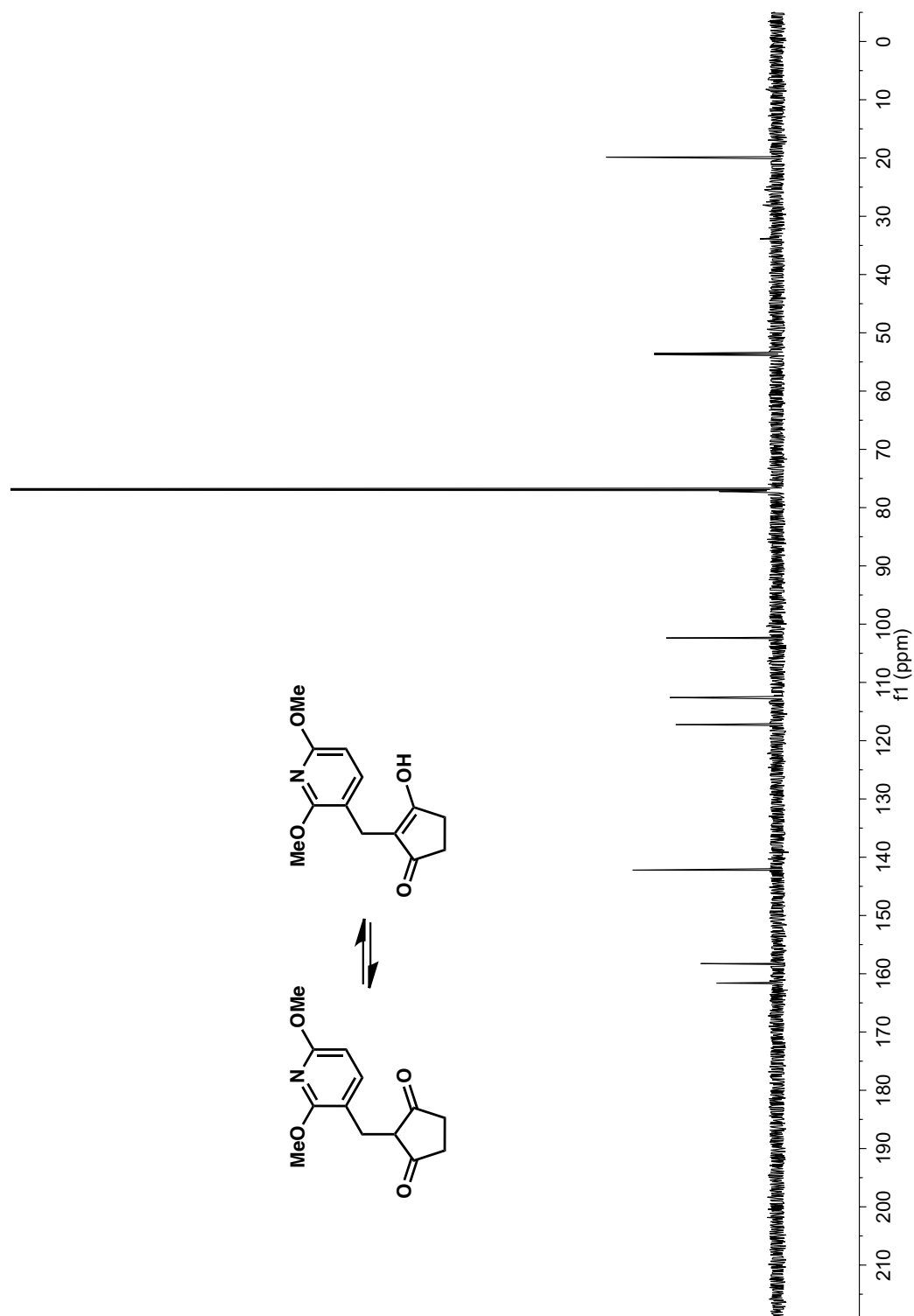


Figure A1.34 ^{13}C NMR of 2.59

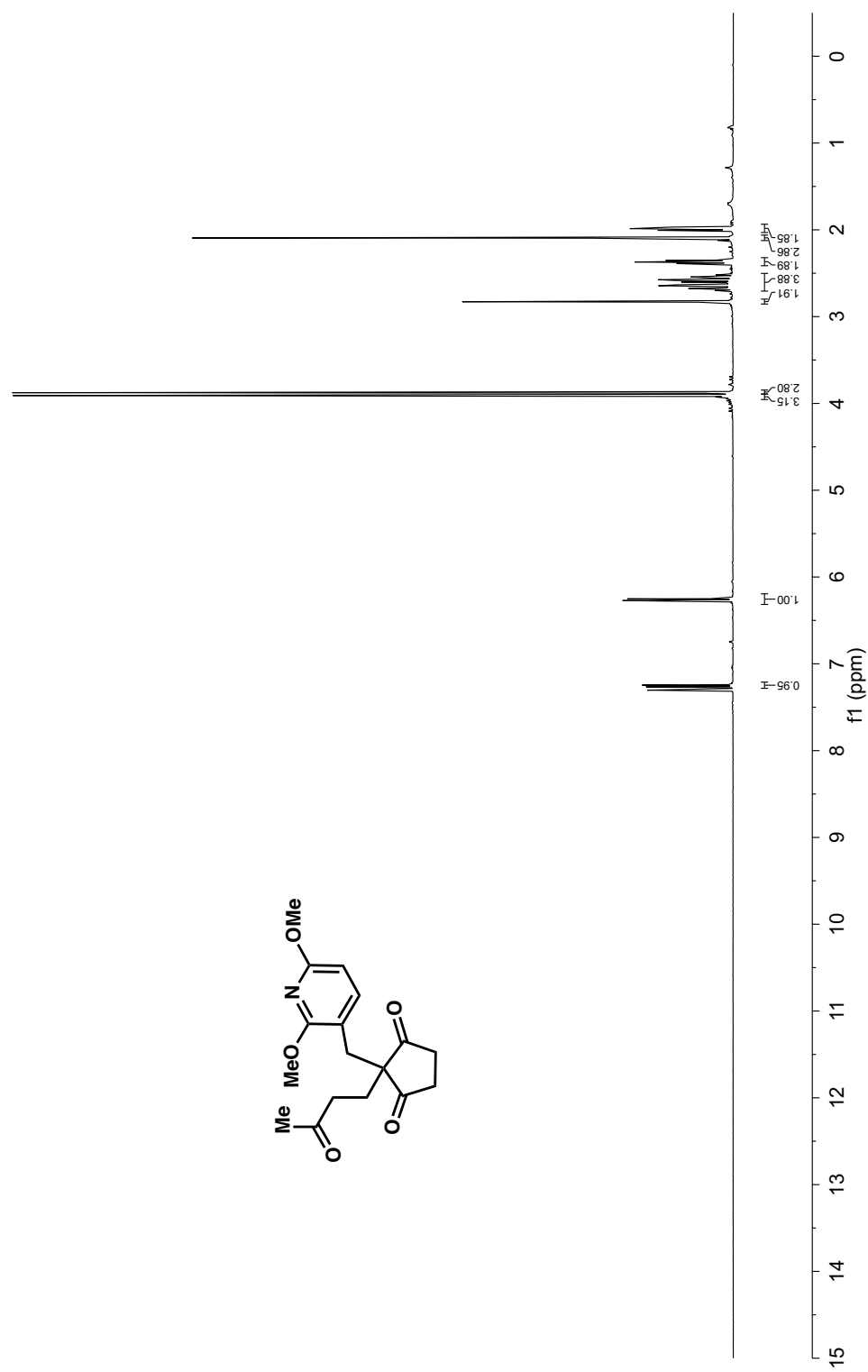


Figure A1.35 ^1H NMR of 2.62

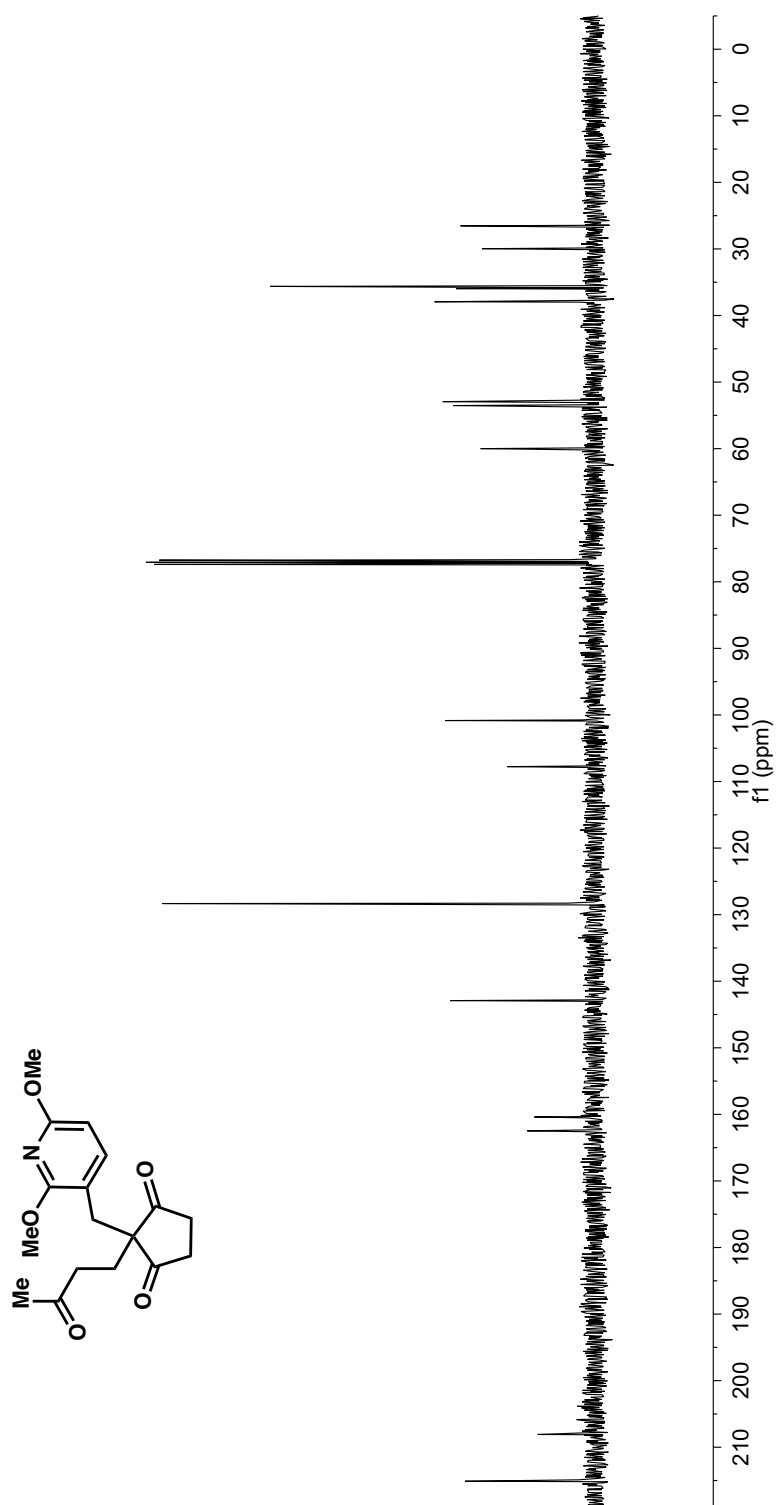


Figure A1.36 ^{13}C NMR of 2.62

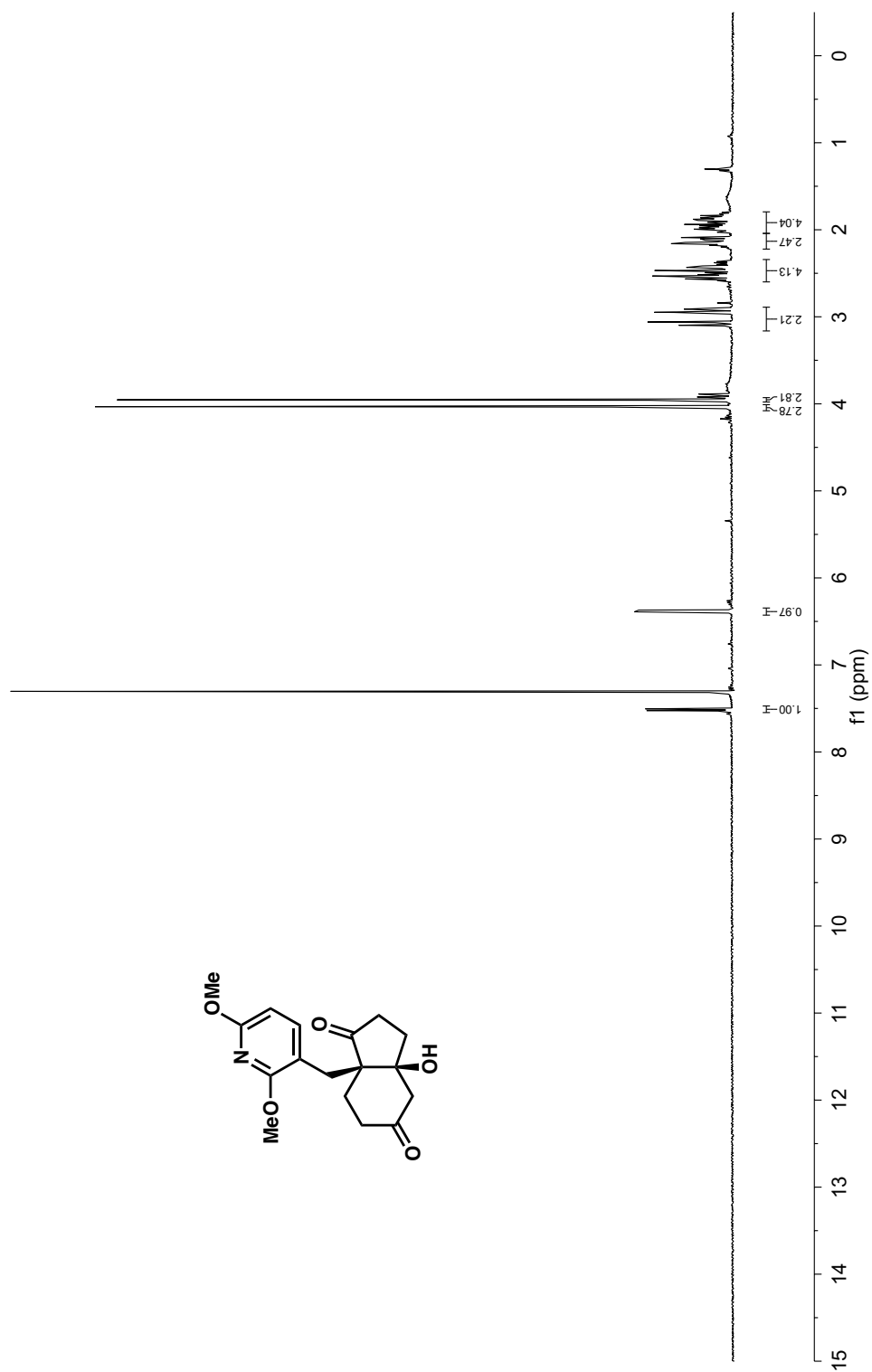


Figure A1.37 ^1H NMR of 2.60

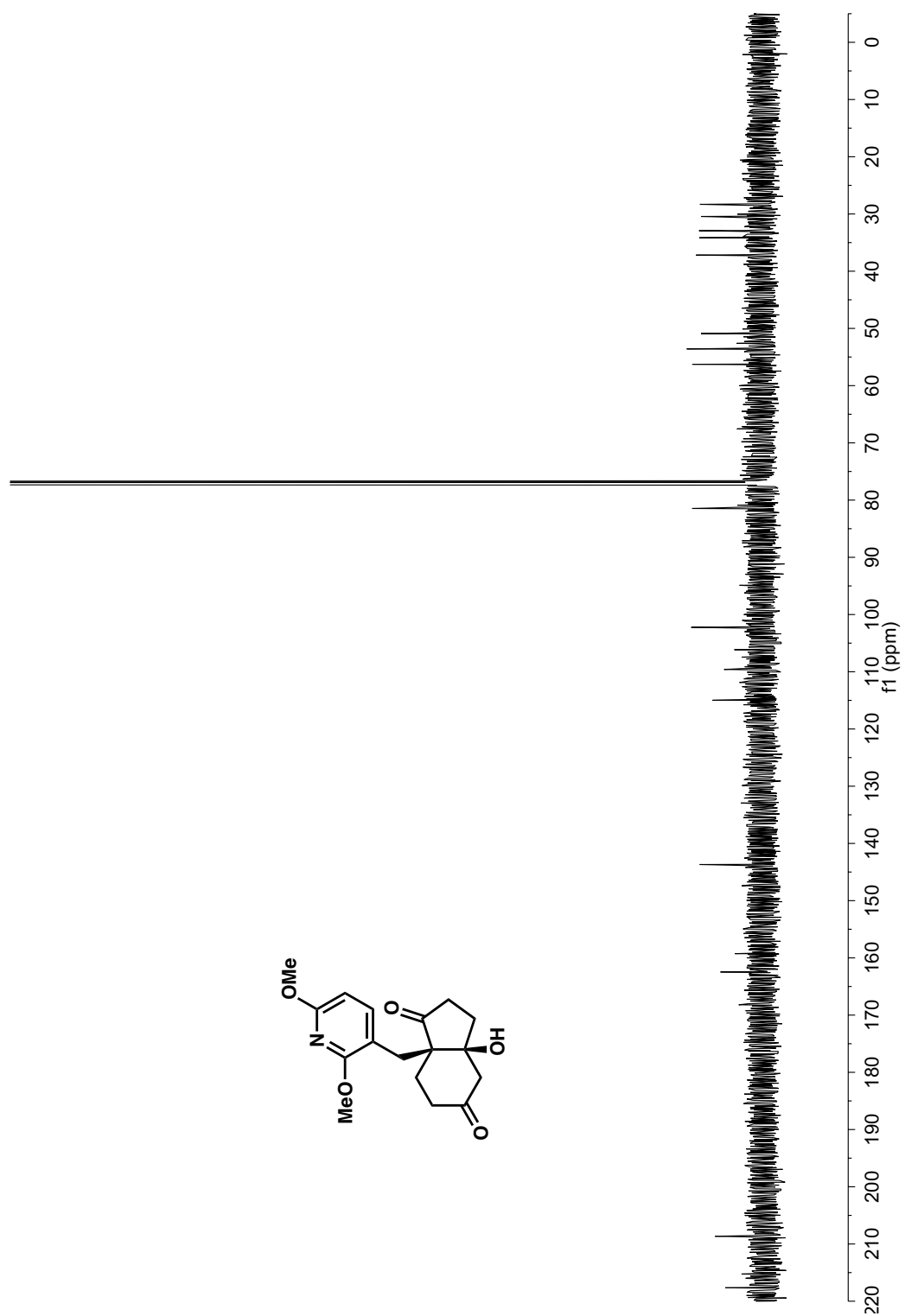


Figure A1.38 ^{13}C NMR of 2.60

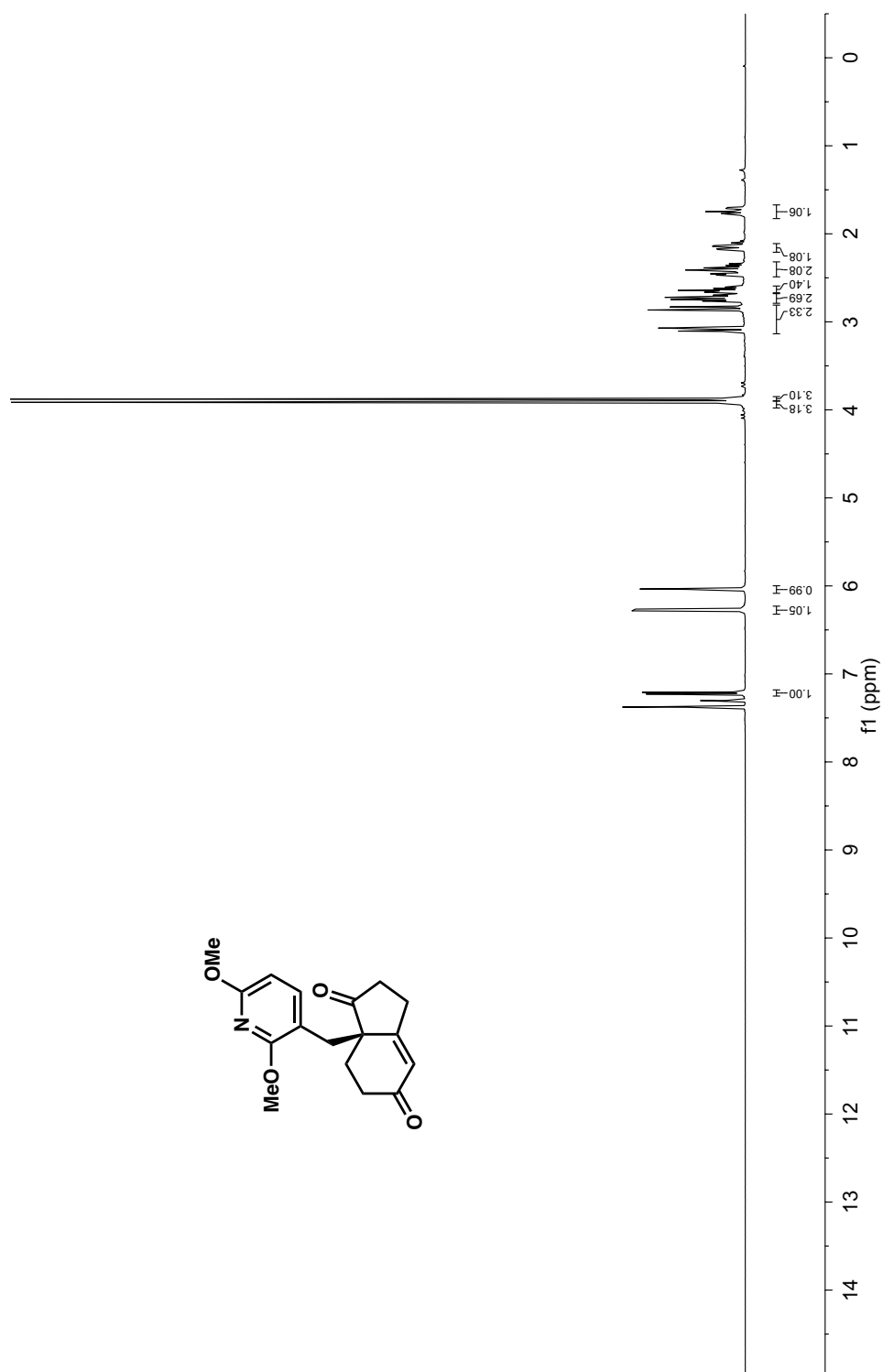


Figure A1.39 ^1H NMR of 2.61

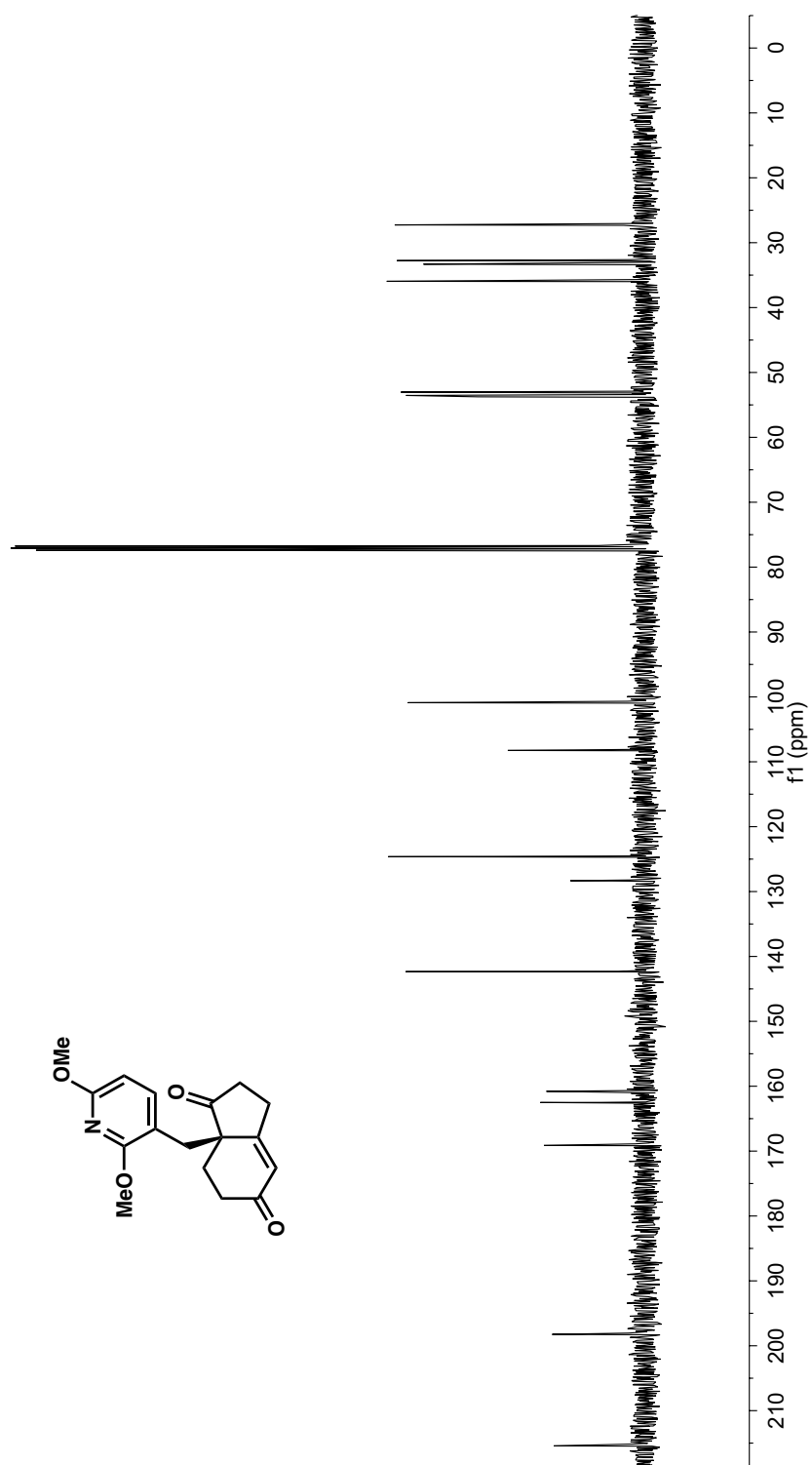


Figure A1.40 ^{13}C NMR of 2.61

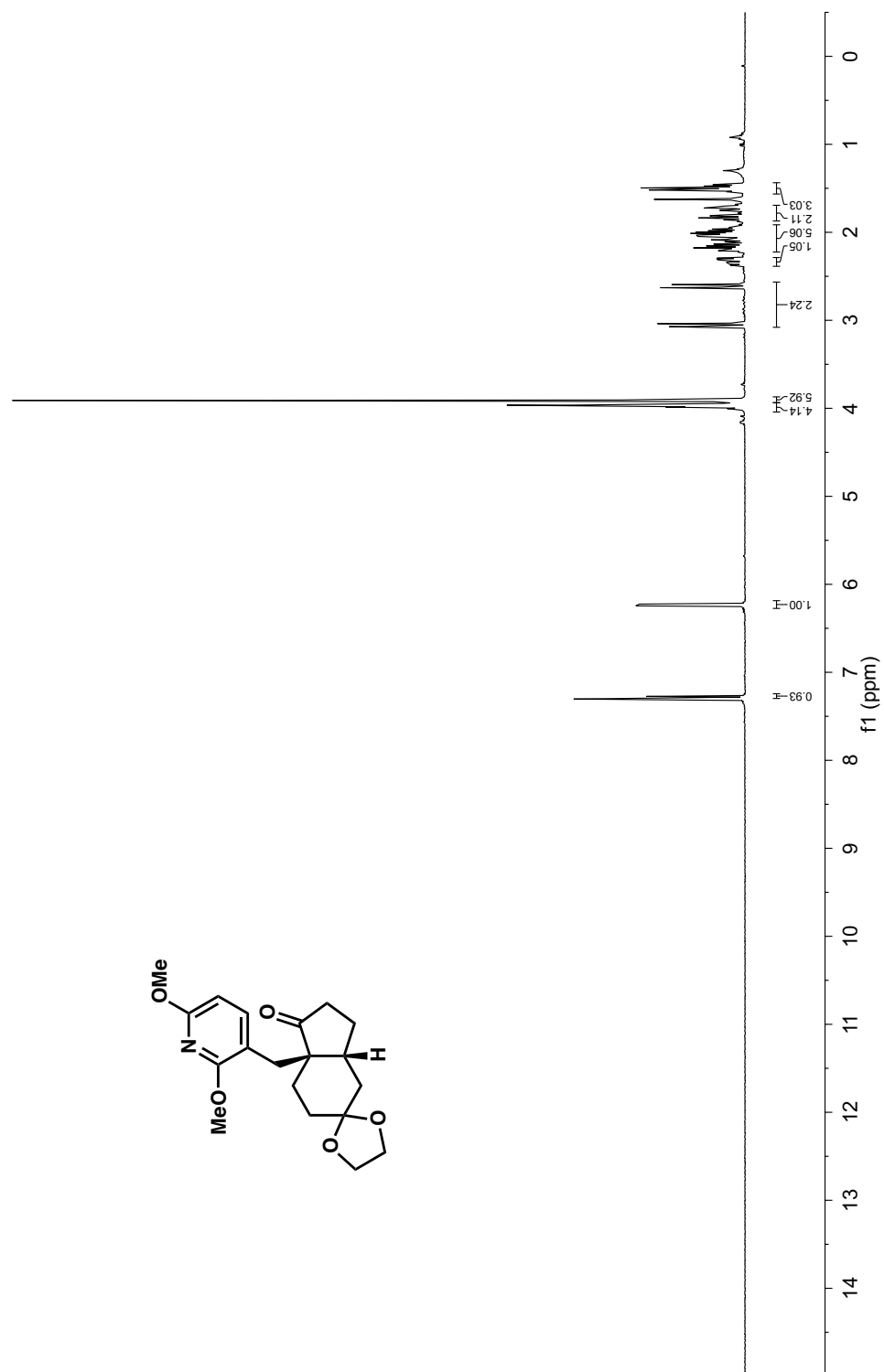


Figure A1.41 ^1H NMR of 2.64

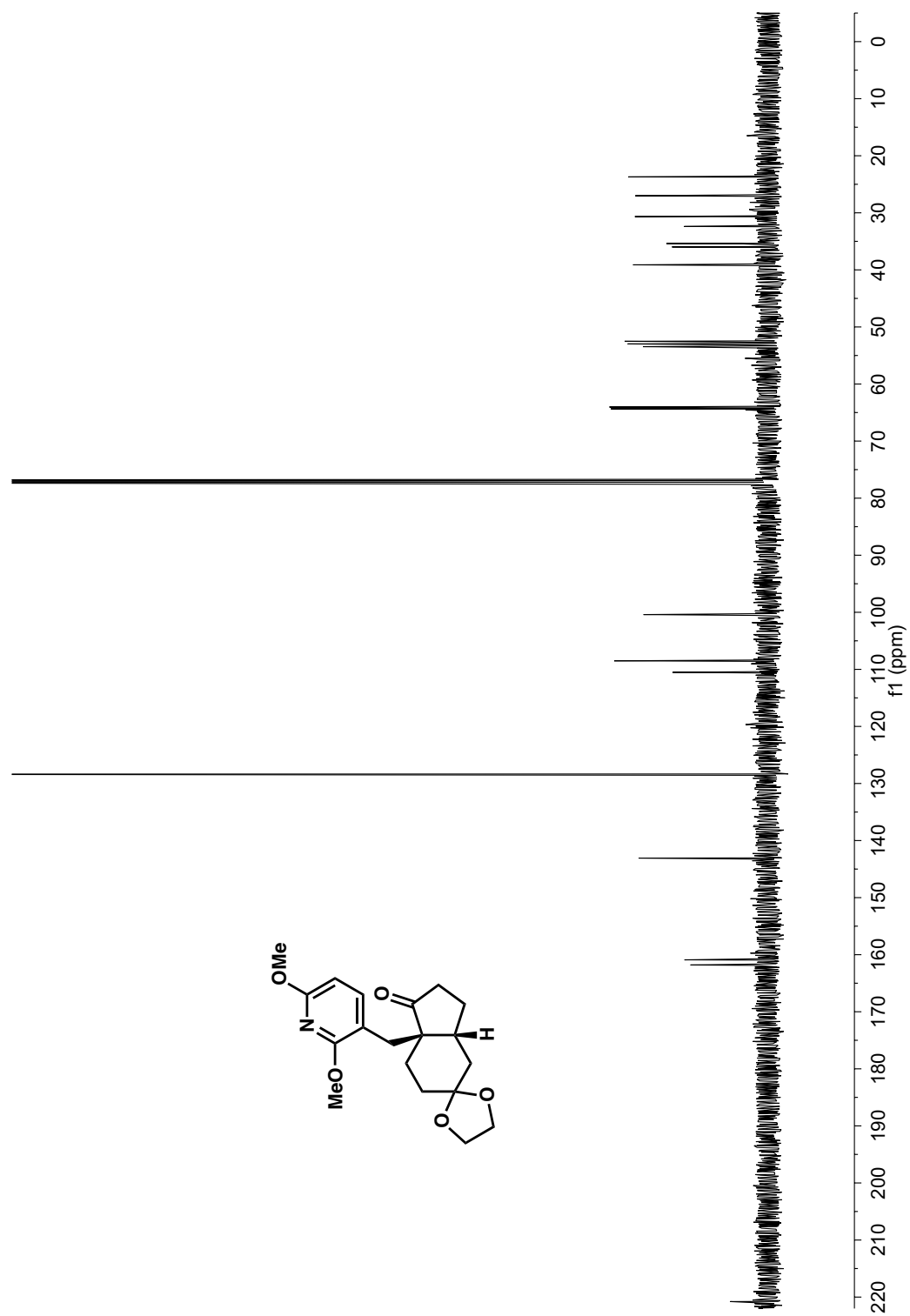


Figure A1.42 ^{13}C NMR of 2.64

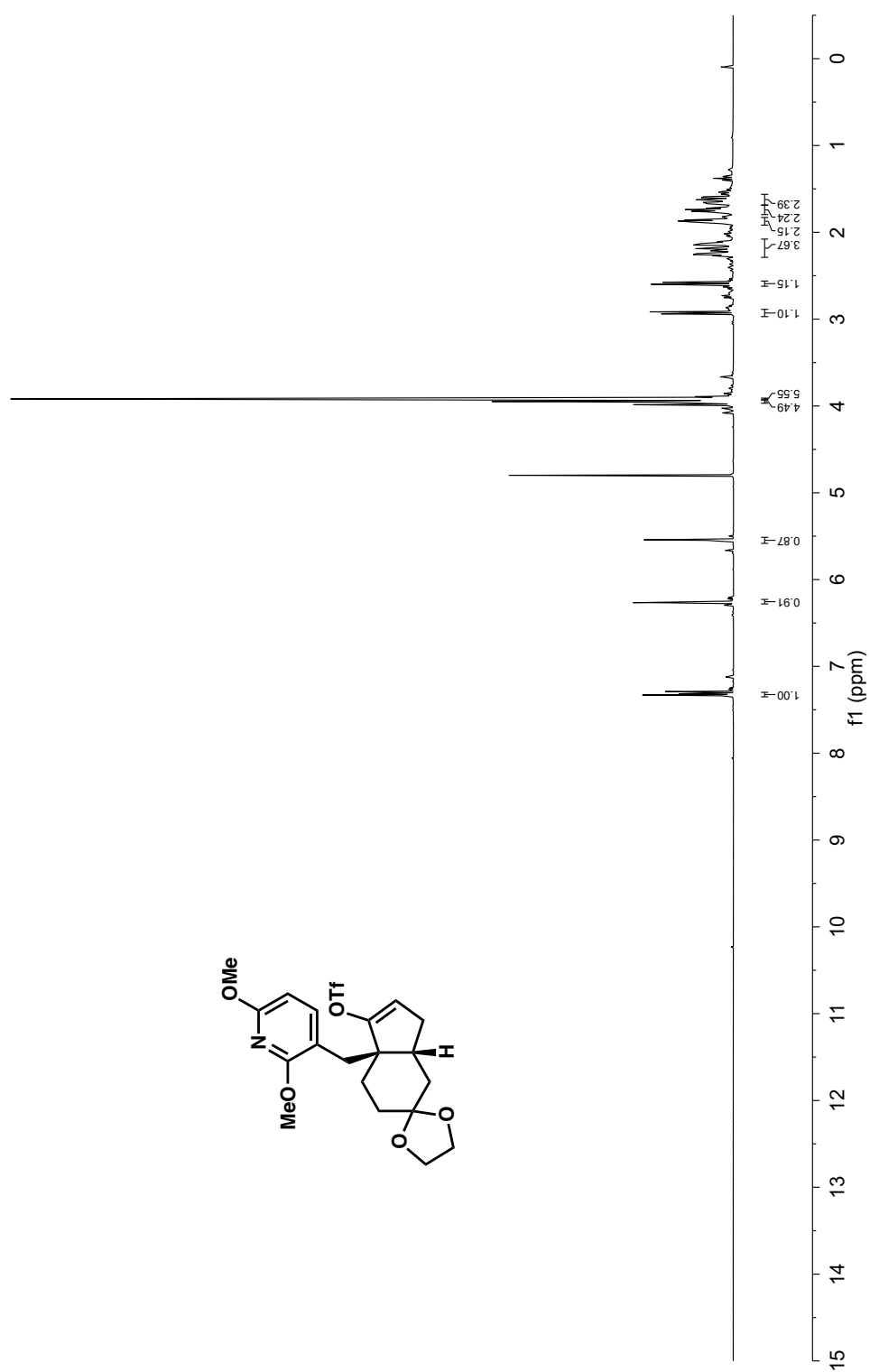


Figure A1.43 ^1H NMR of 2.66

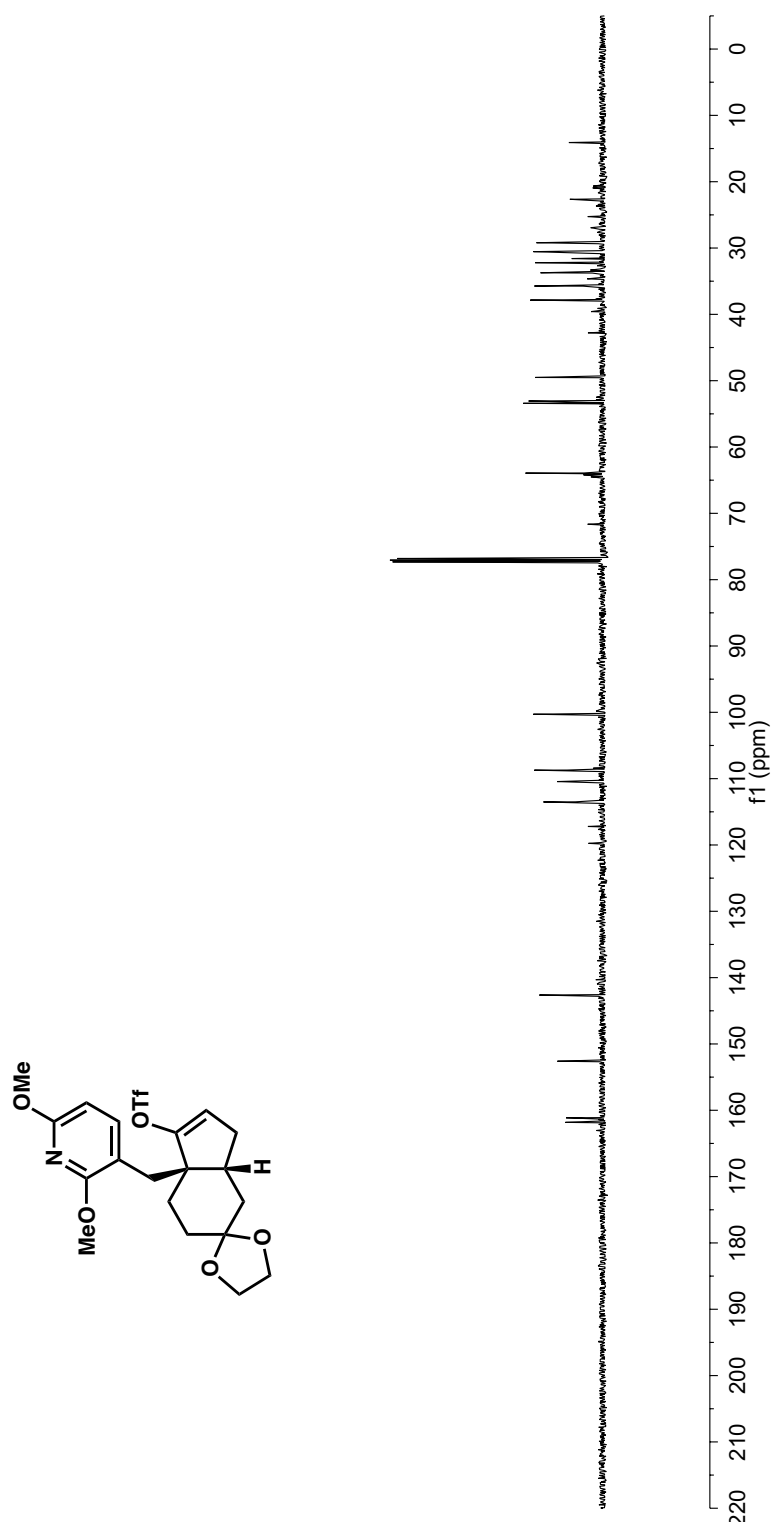


Figure A1.44 ^{13}C NMR of 2.66

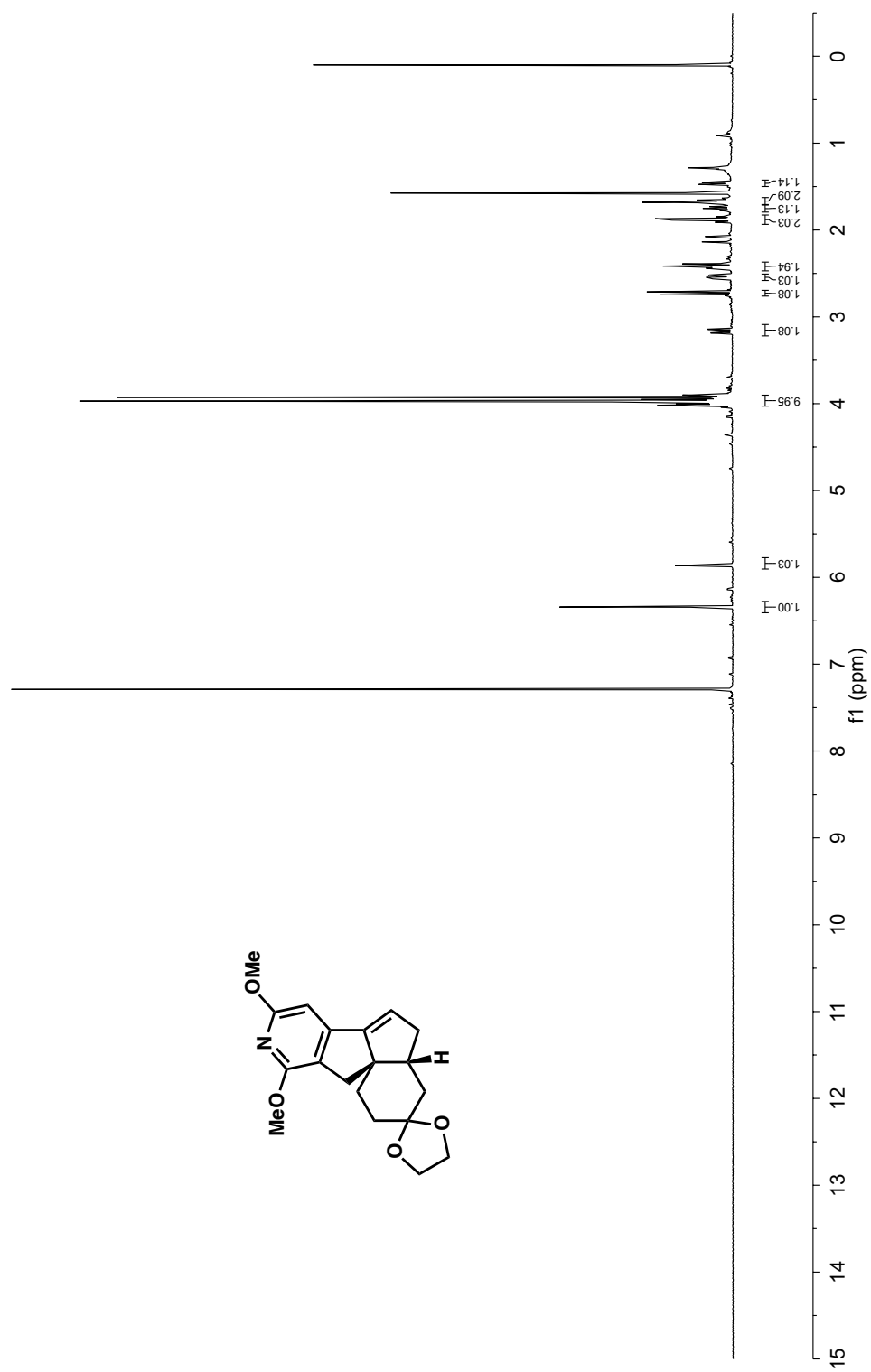


Figure A1.45 ¹H NMR of 2.67

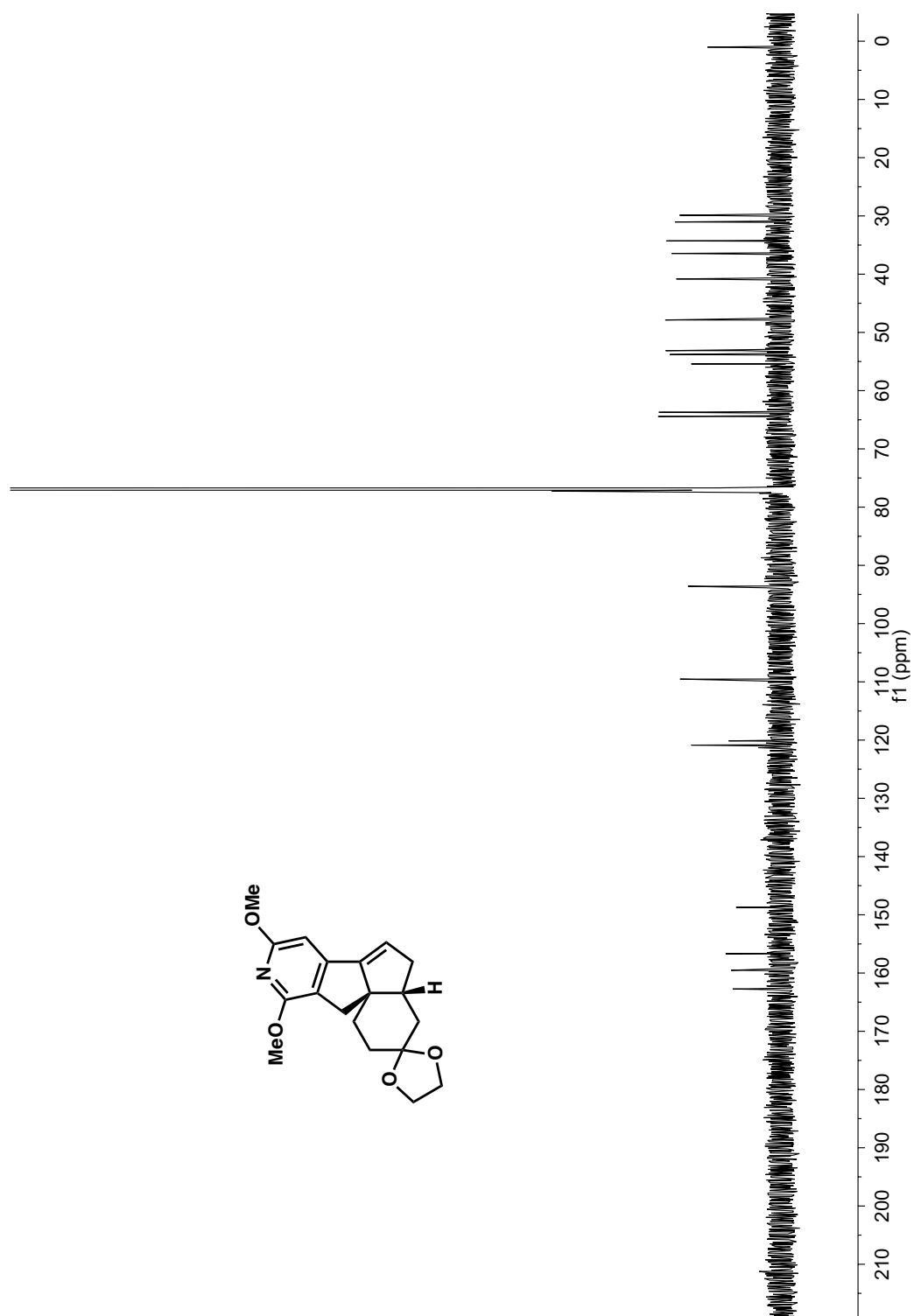


Figure A1.46 ^{13}C NMR of 2.67

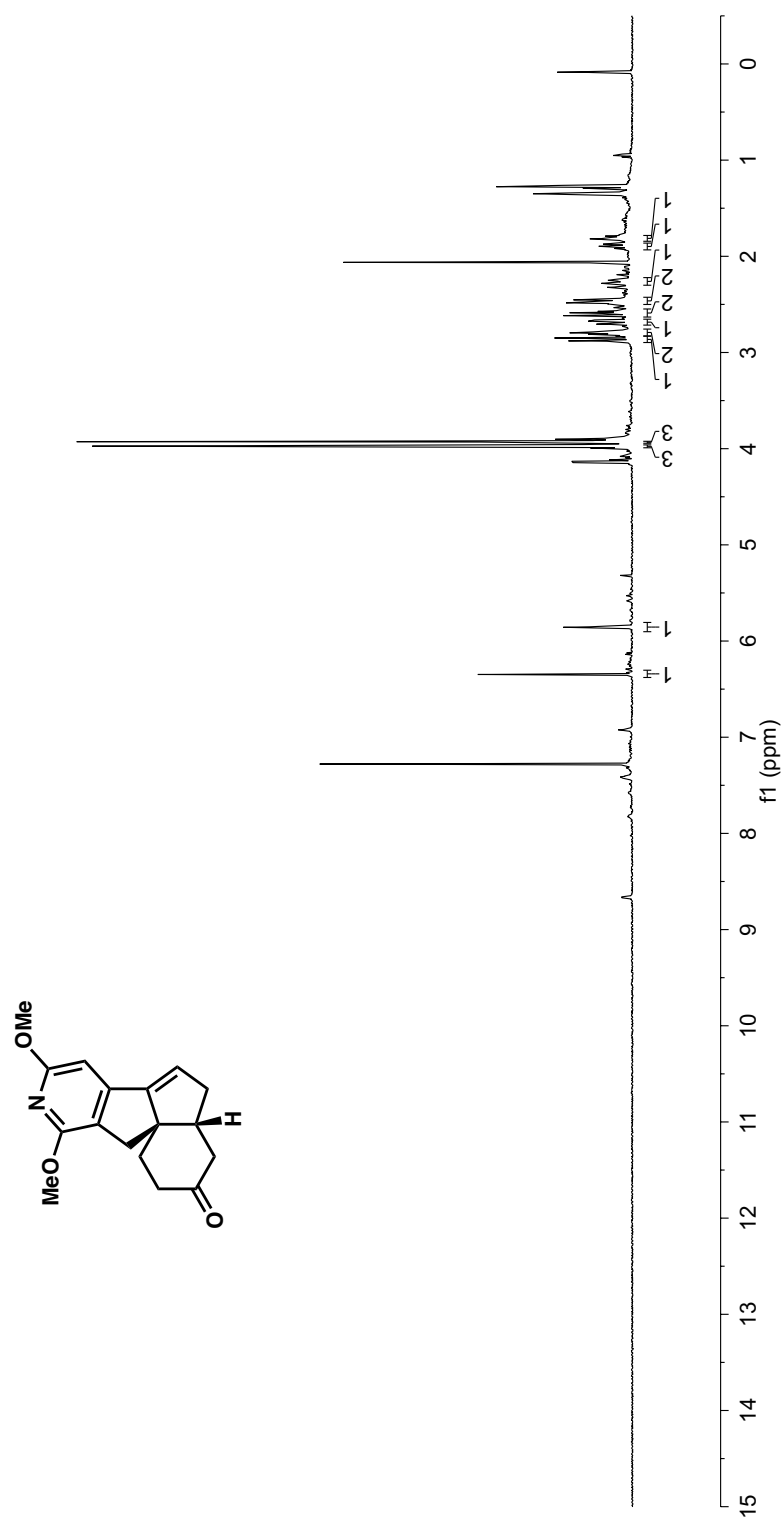


Figure A1.47 ^1H NMR of 2.68

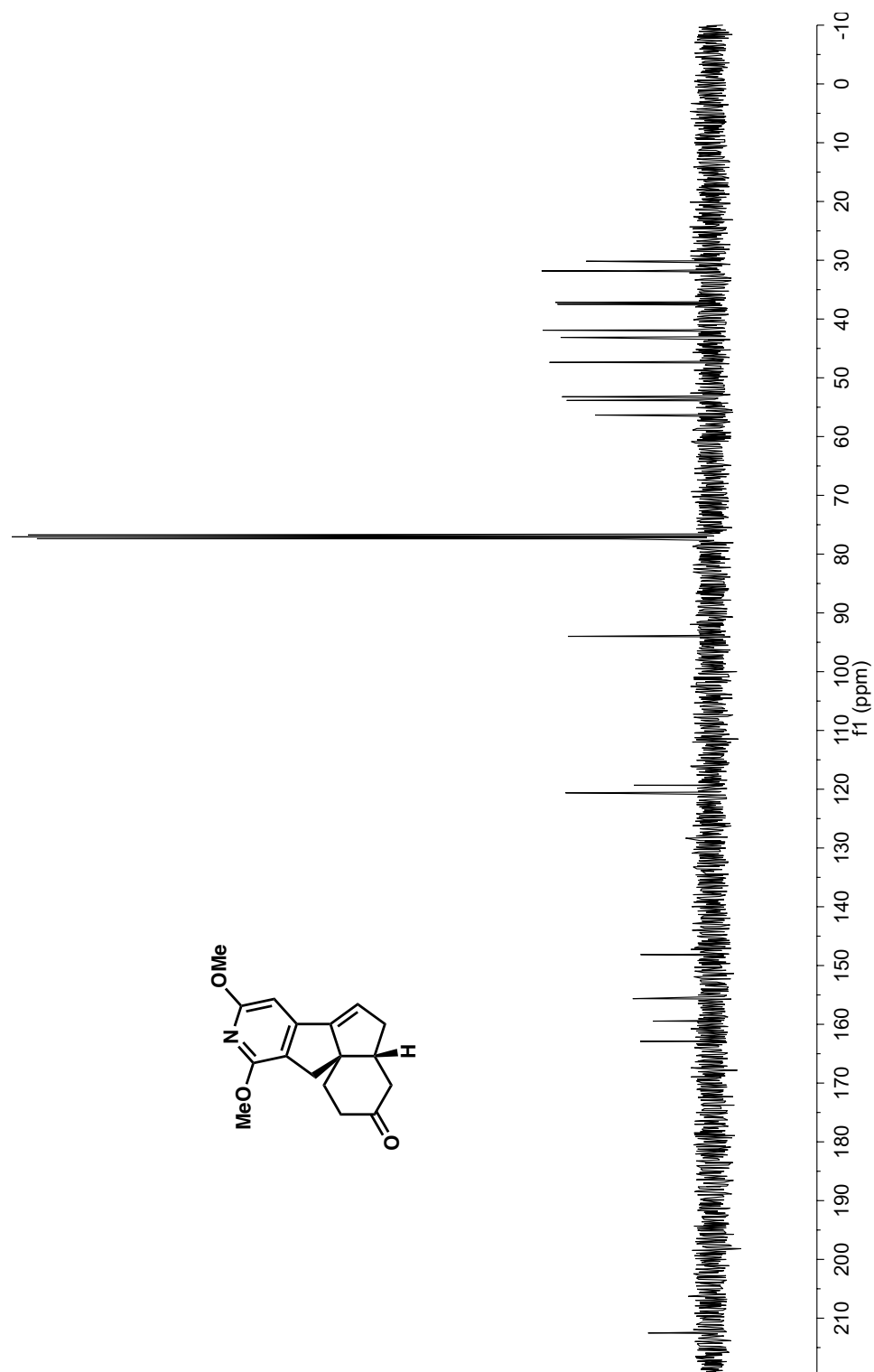


Figure A1.48 ¹³C NMR of 2.68

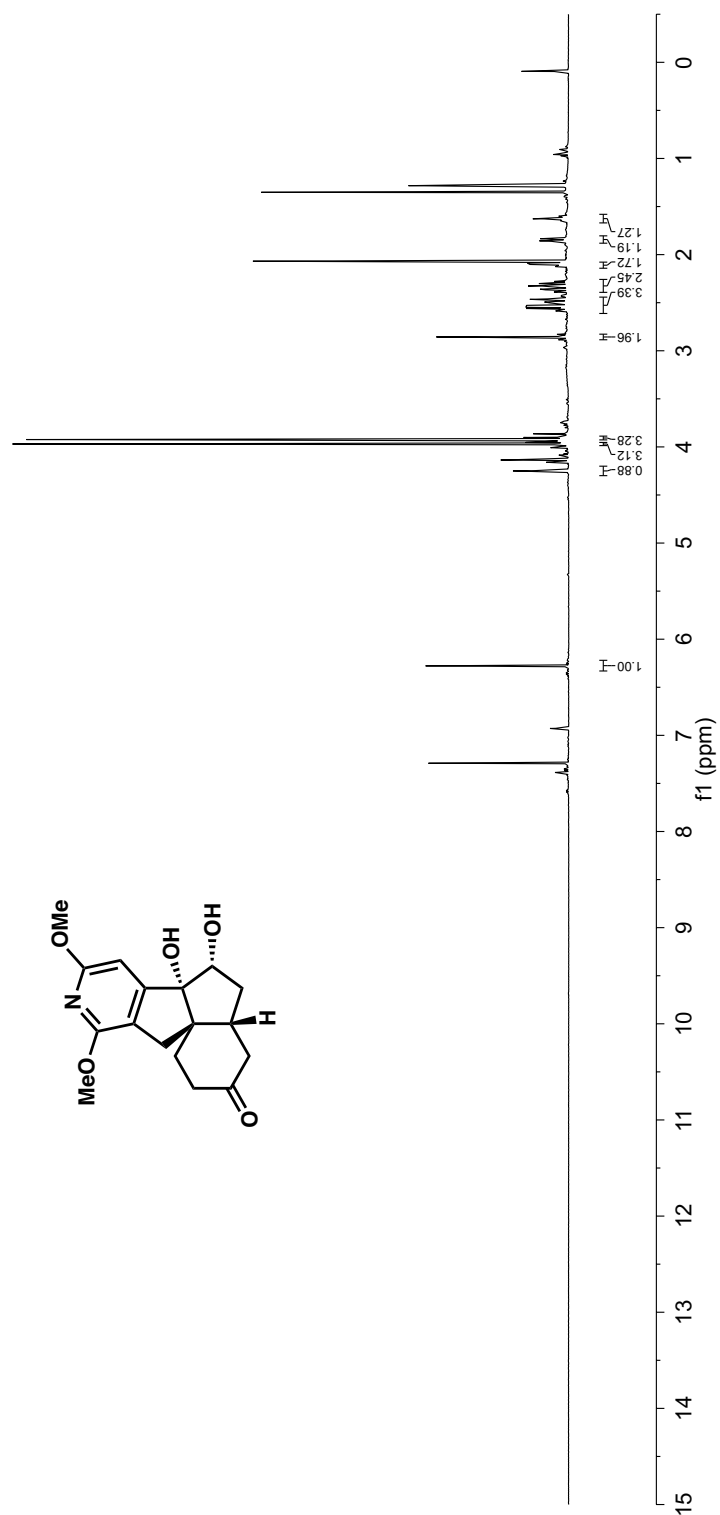


Figure A1.49 ^1H NMR of 2.72

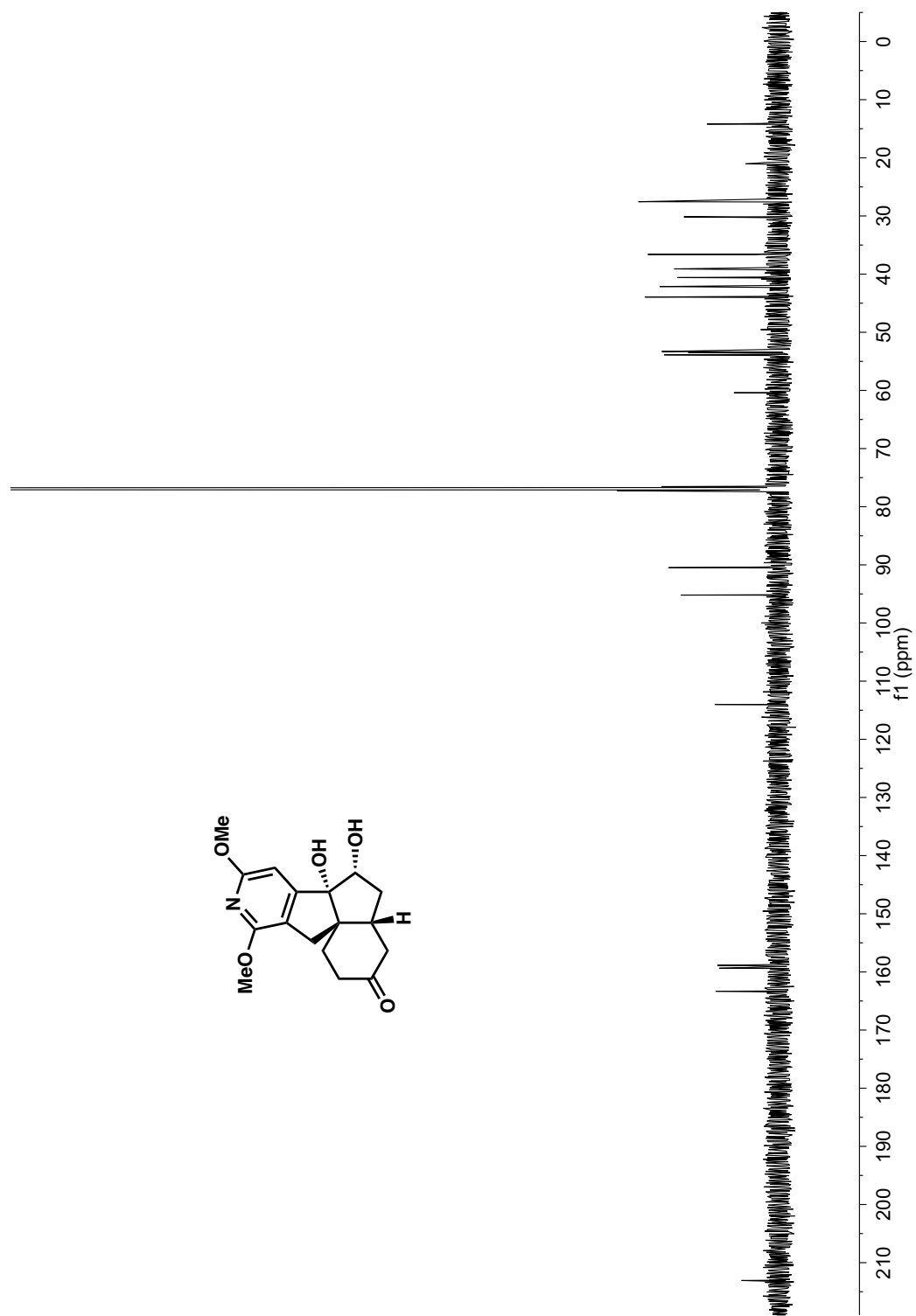


Figure A1.50 ^{13}C NMR of **2.72**

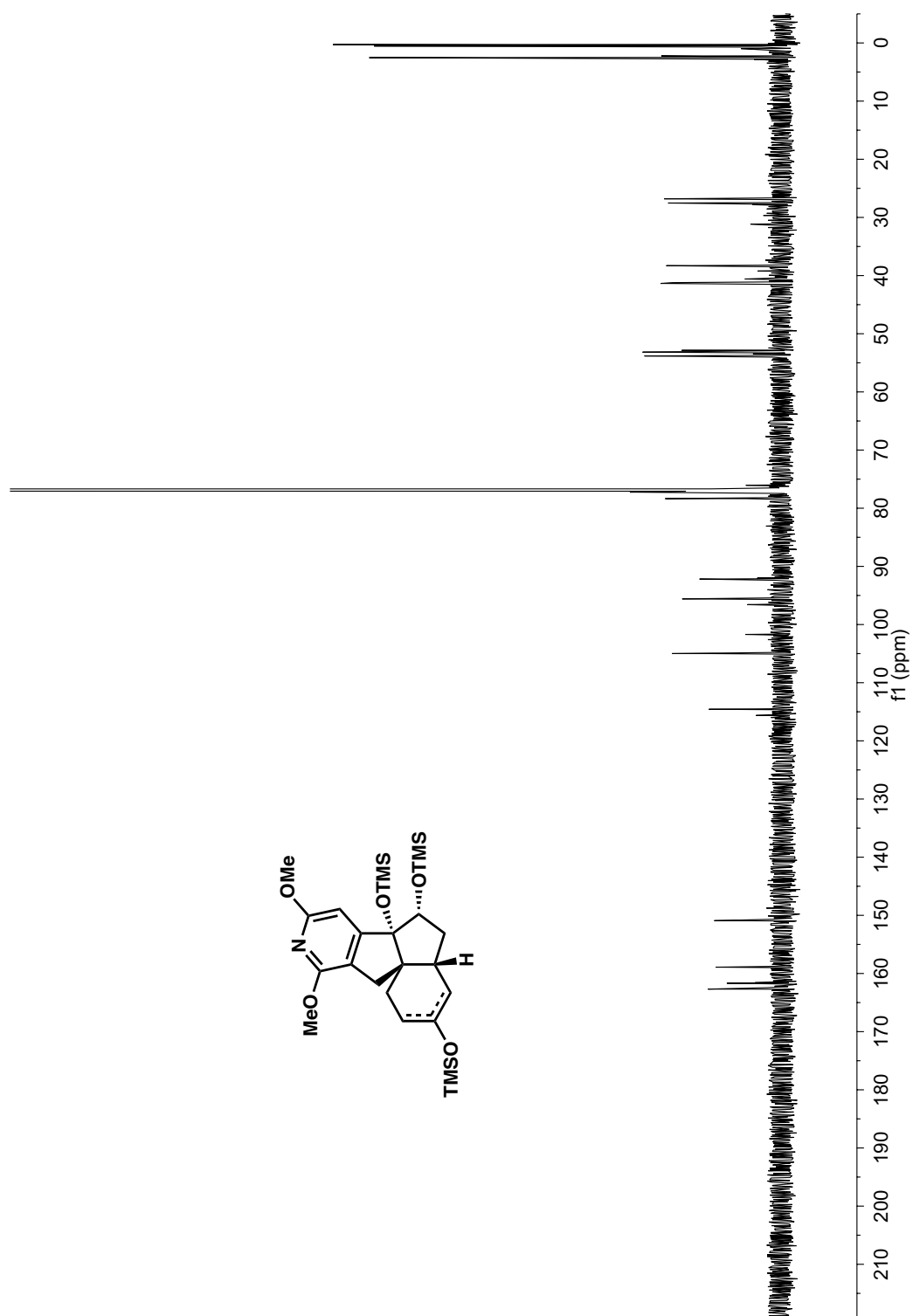


Figure A1.52 ^{13}C NMR of 2.73

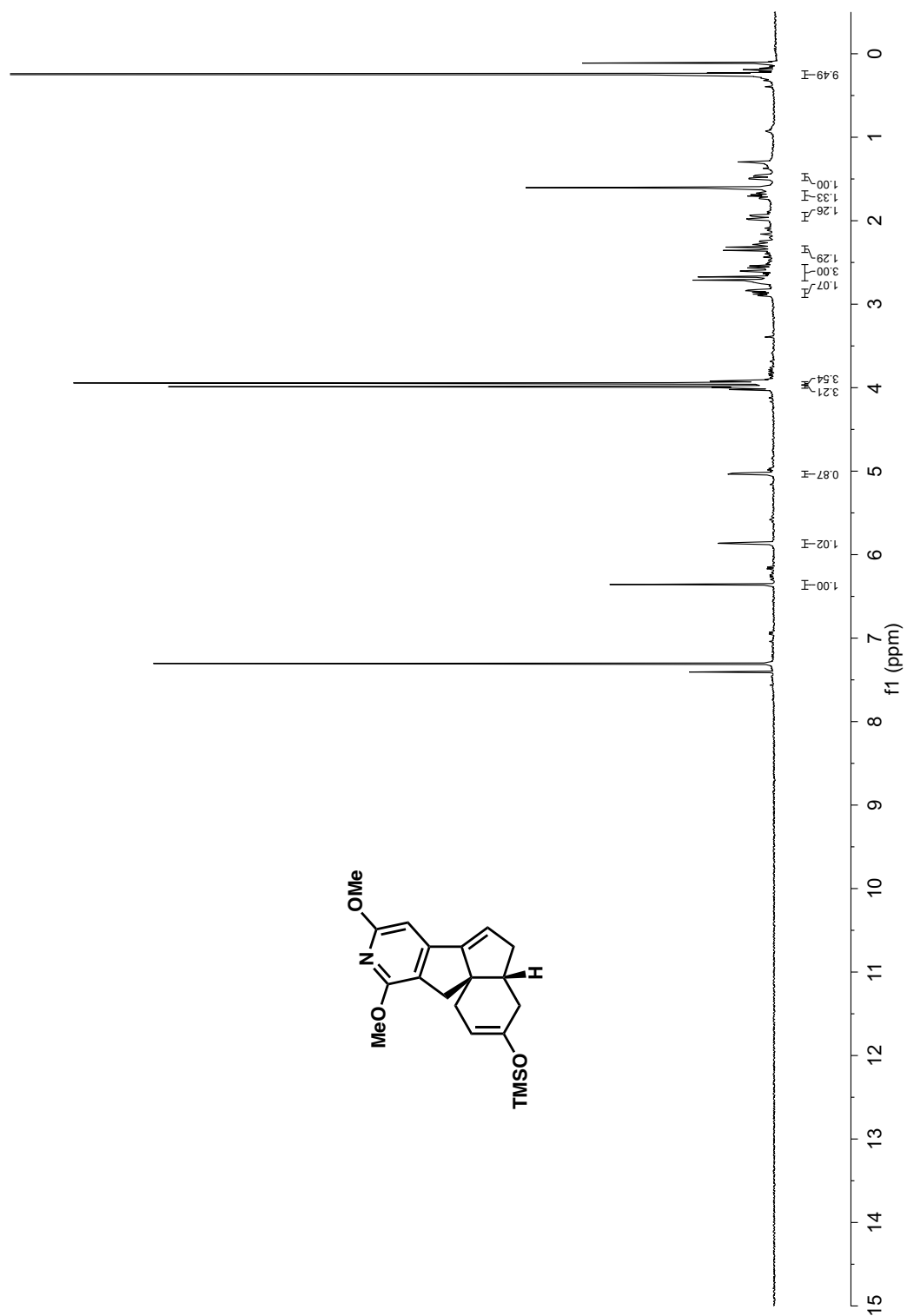


Figure A1.53 ^1H NMR of 2.69

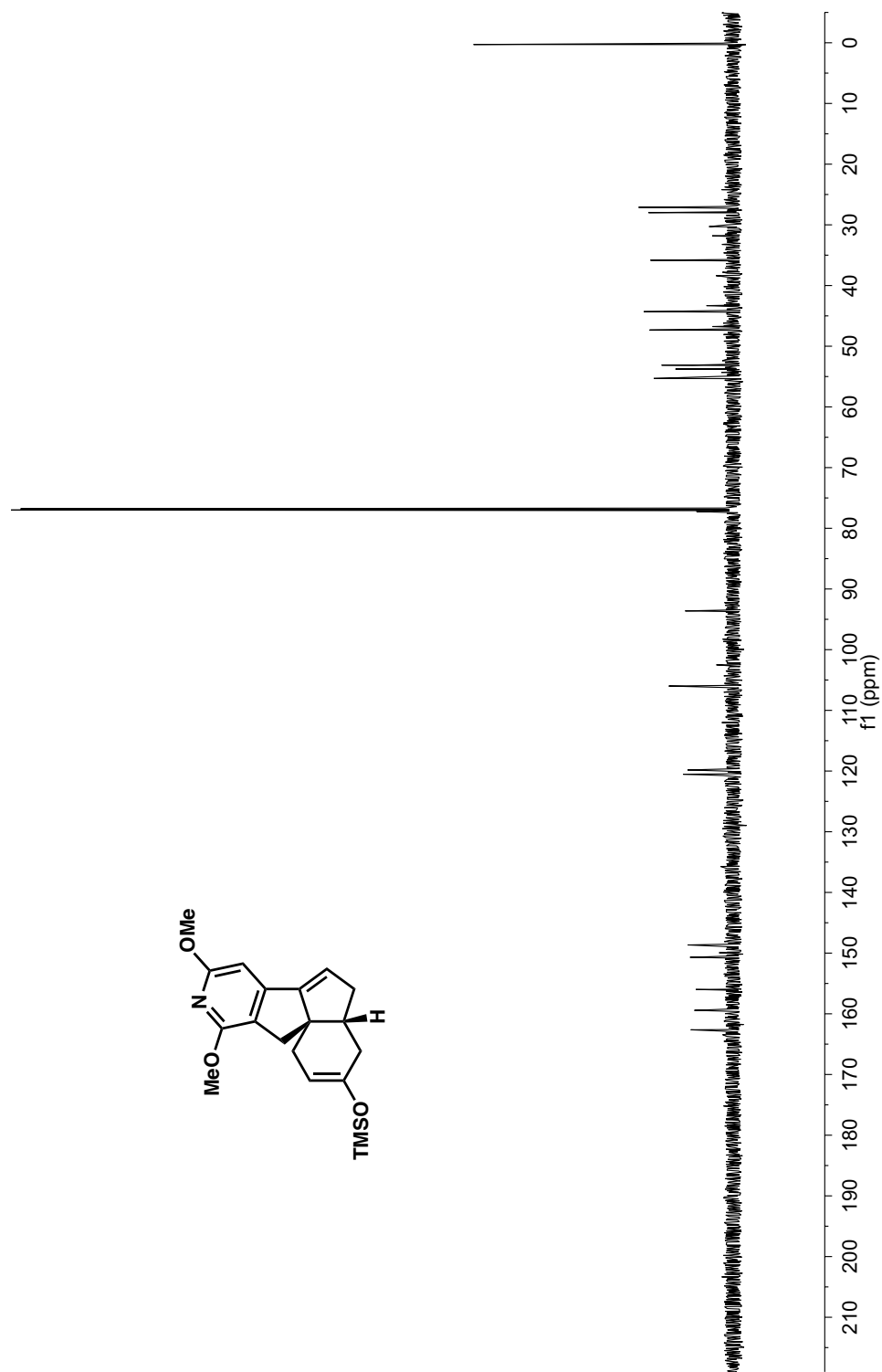


Figure A1.54 ^{13}C NMR of 2.69

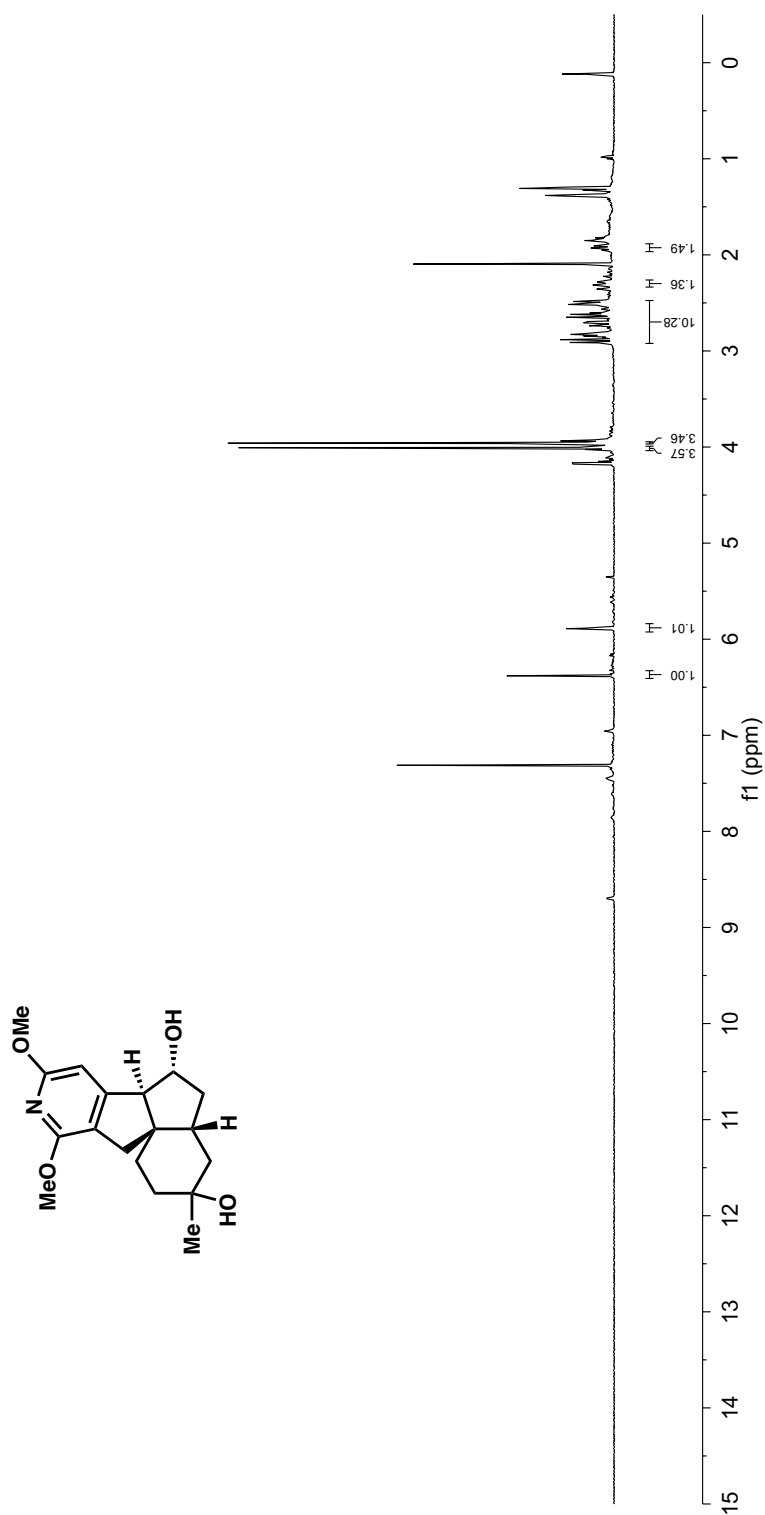


Figure A1.55 ^1H NMR of 2.76

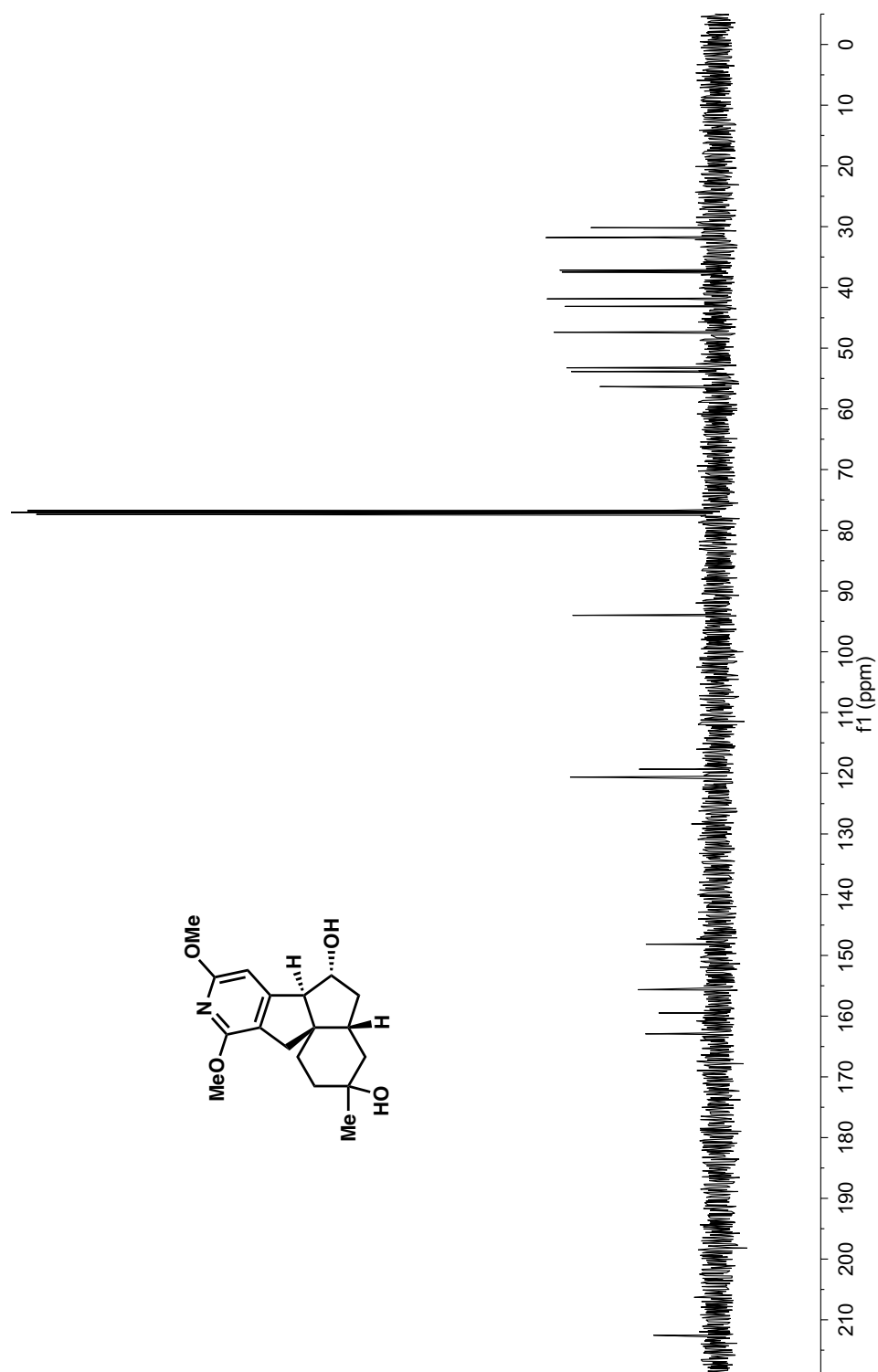


Figure A1.56 ^{13}C NMR of 2.76

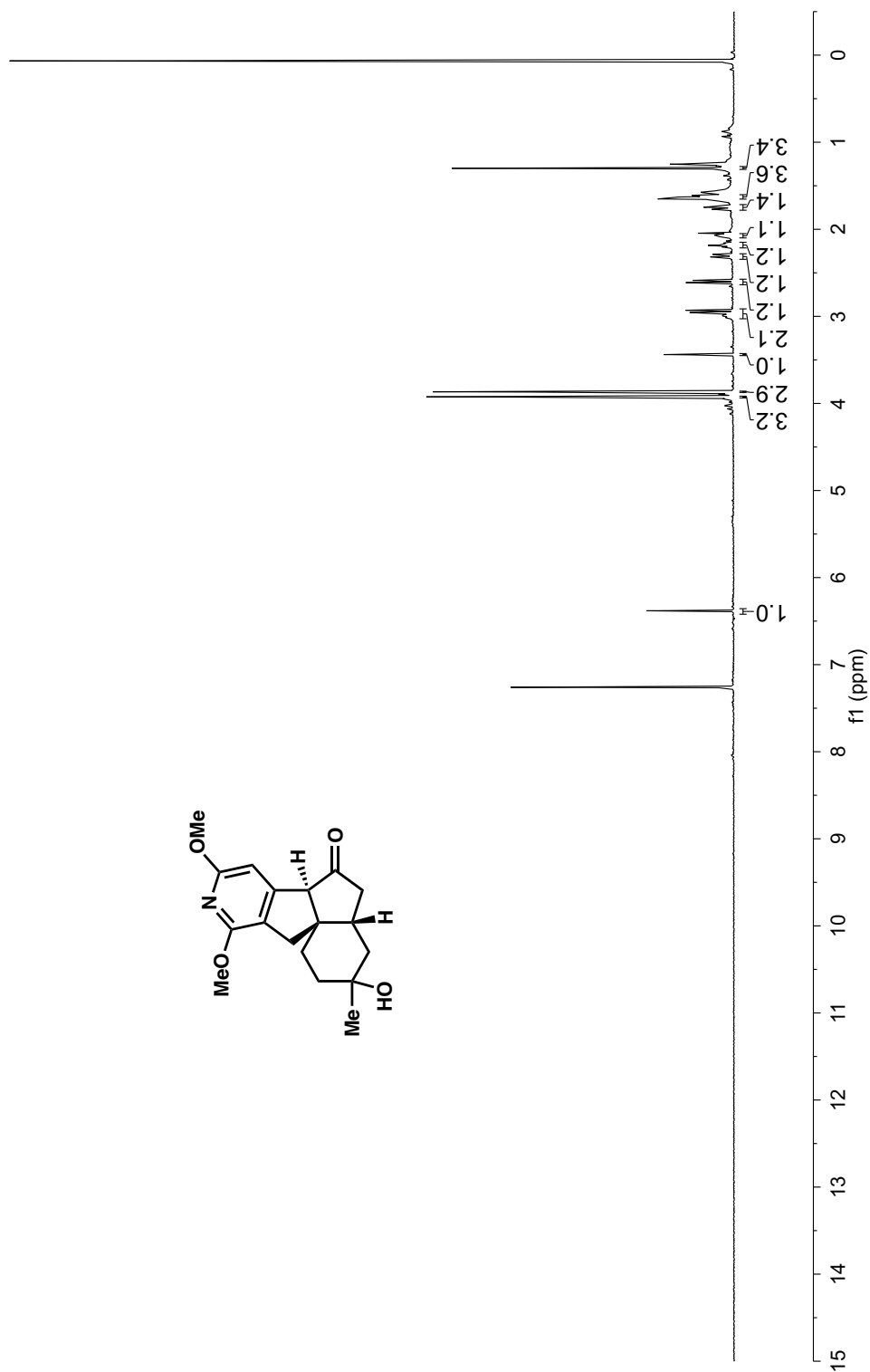


Figure A1.57 ^1H NMR of 2.77

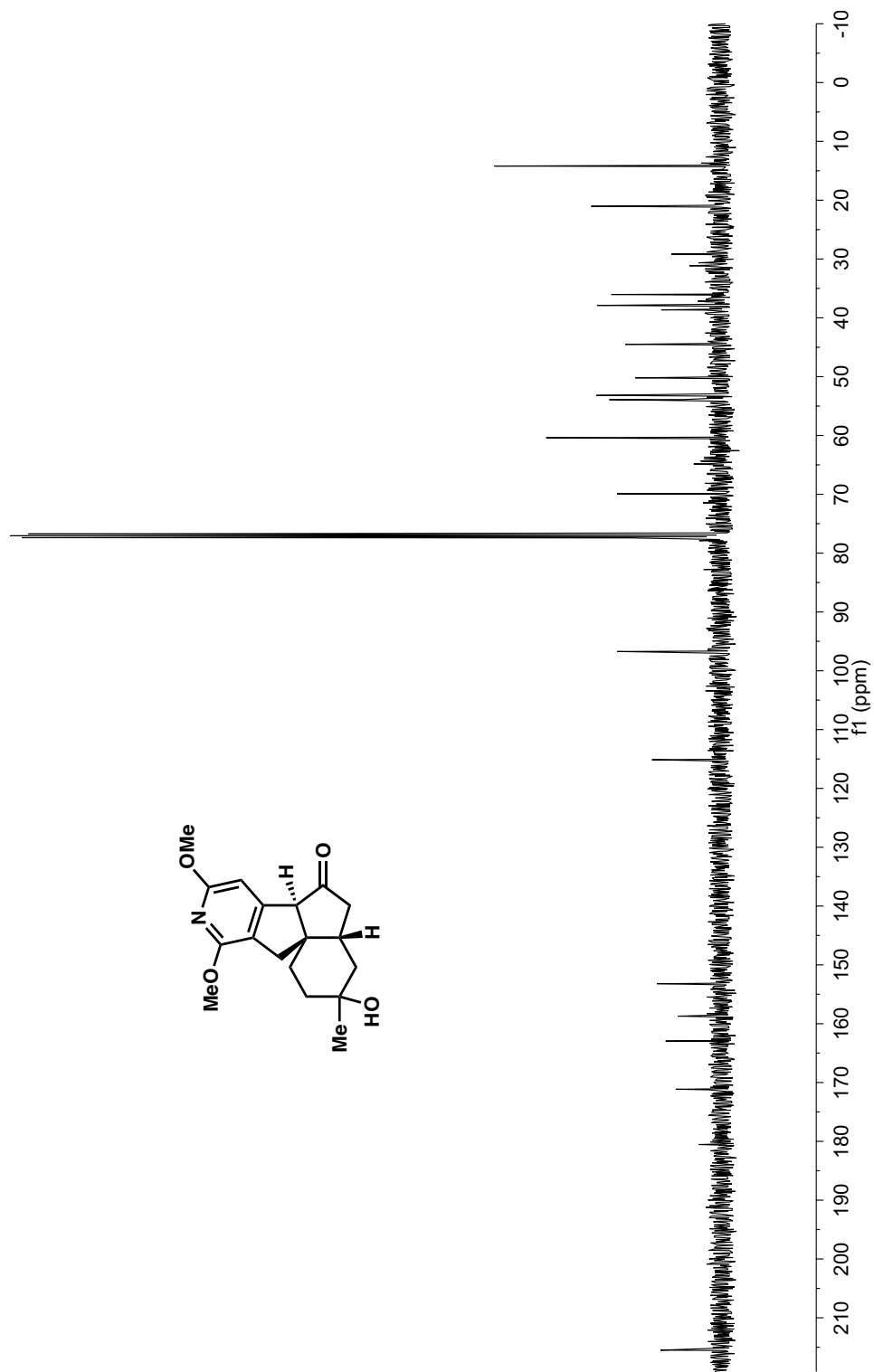


Figure A1.58 ^{13}C NMR of 2.77

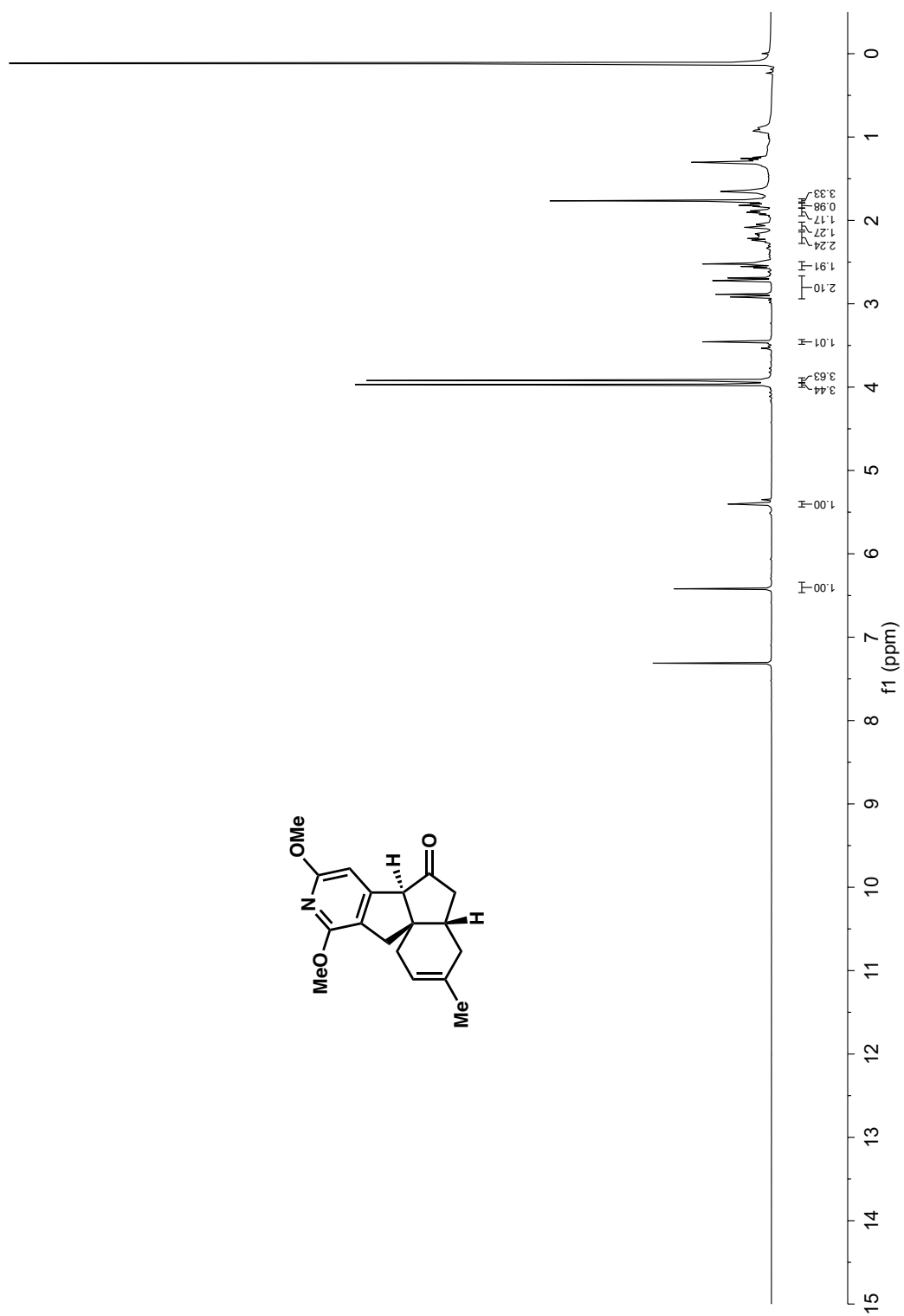


Figure A1.59 ¹H NMR of **2.78**

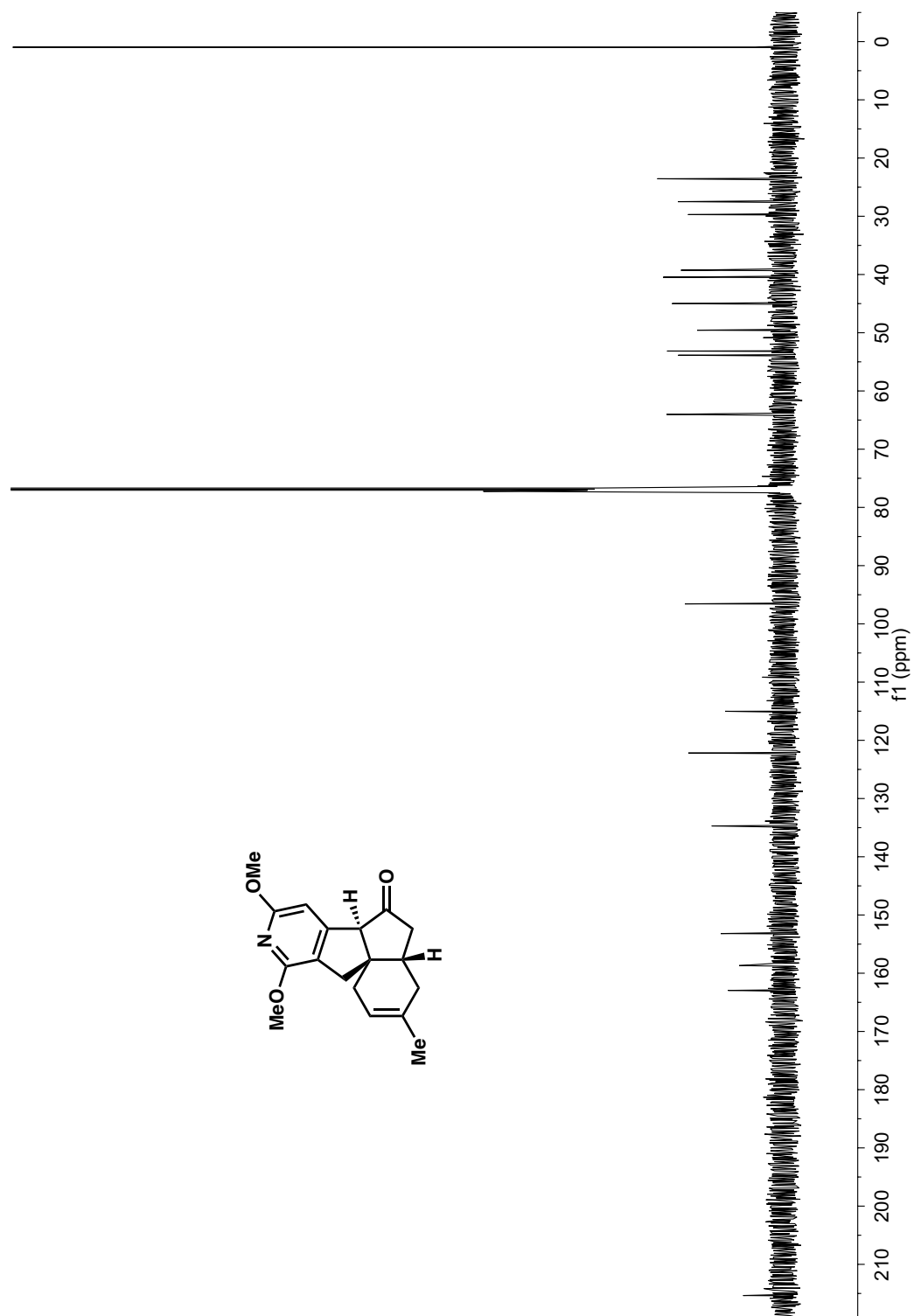


Figure A1.60 ^{13}C NMR of 2.78

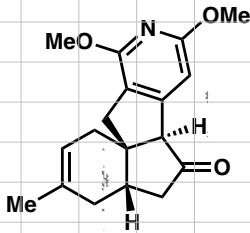


Figure A1.61 COSY NMR of **2.78**

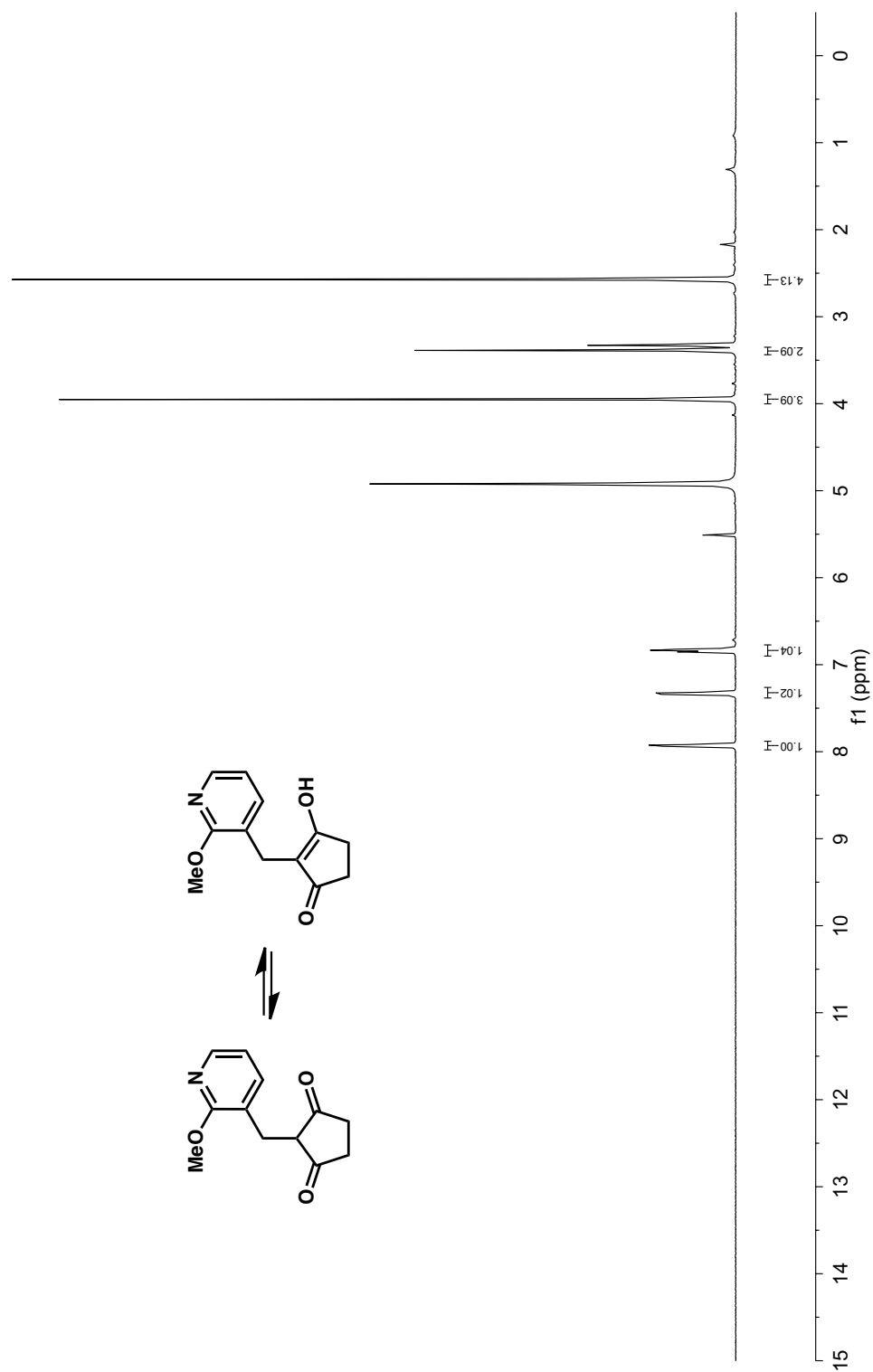


Figure A1.62 ^1H NMR of 2.96

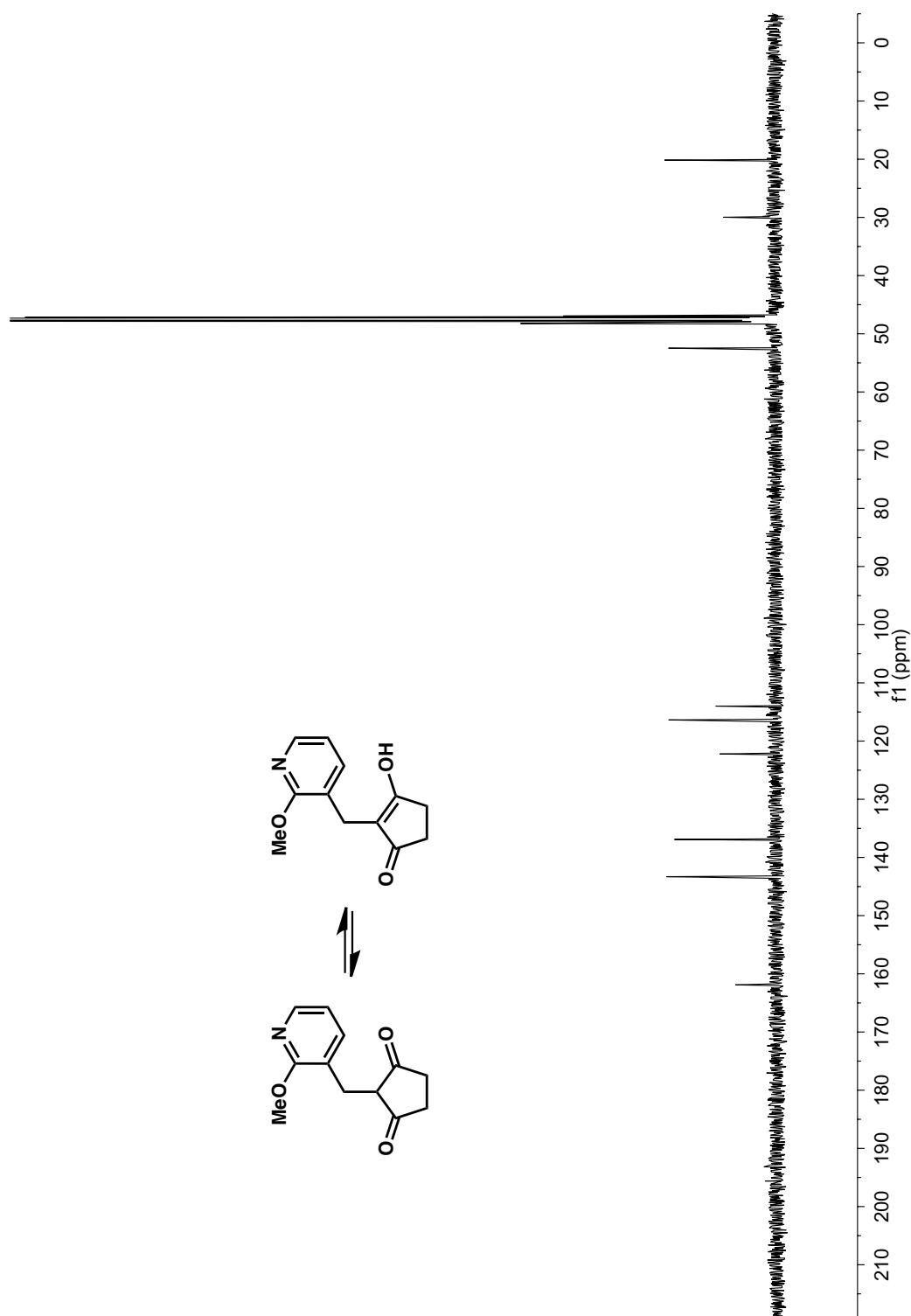


Figure A1.63 ^{13}C NMR of 2.96

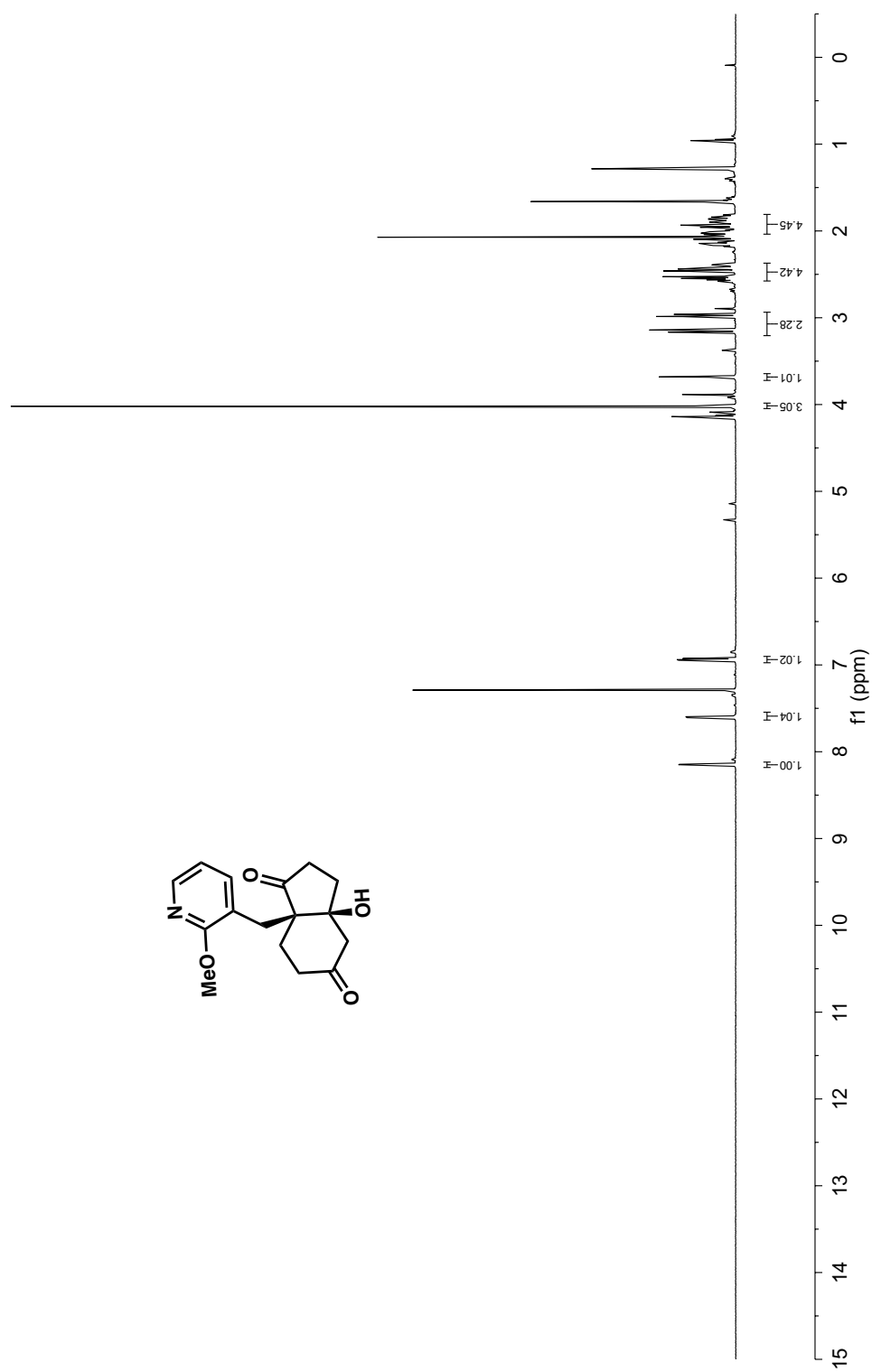


Figure A1.64 ^1H NMR of 2.S3

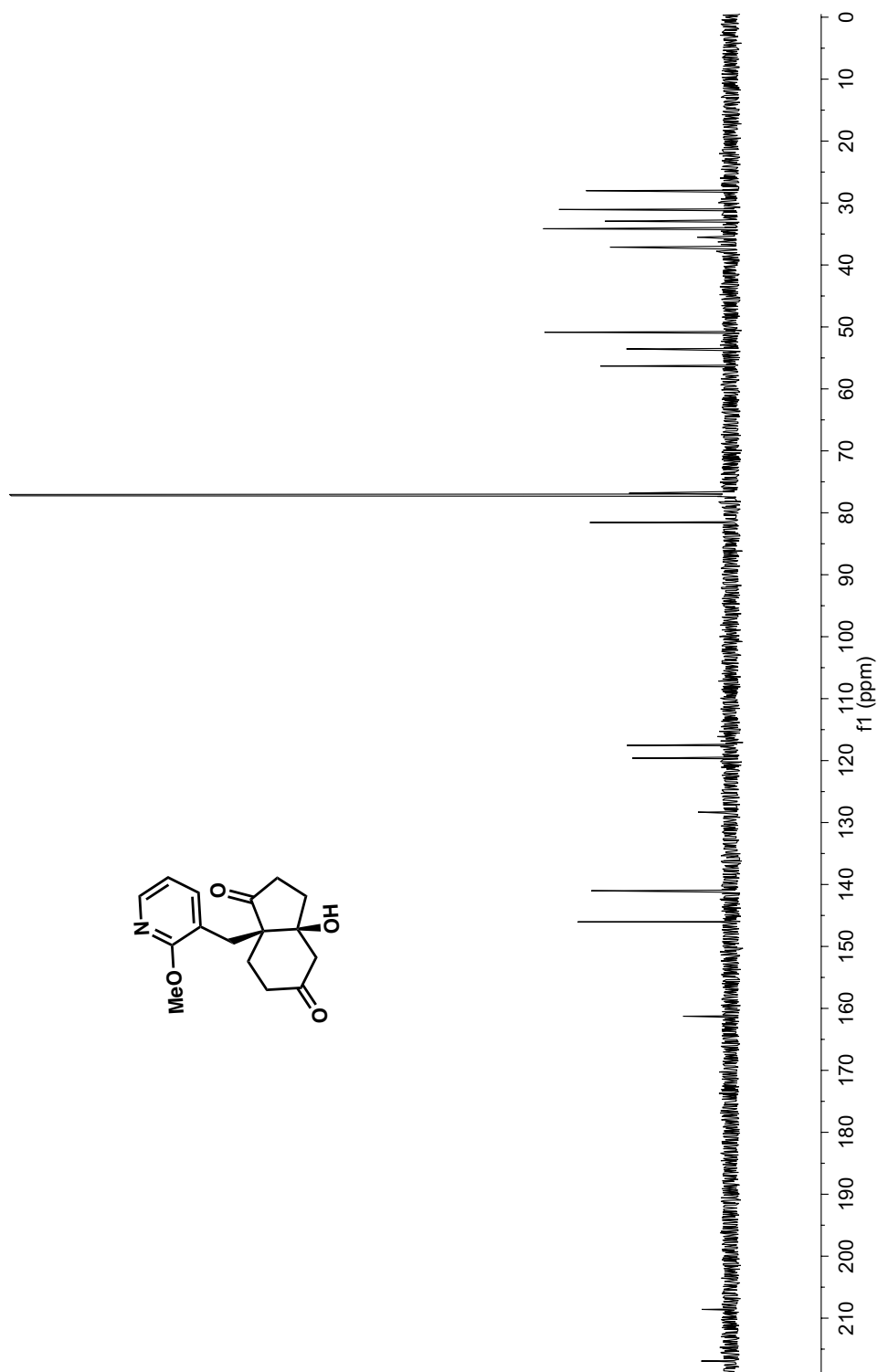


Figure A1.65 ^{13}C NMR of 2.S3

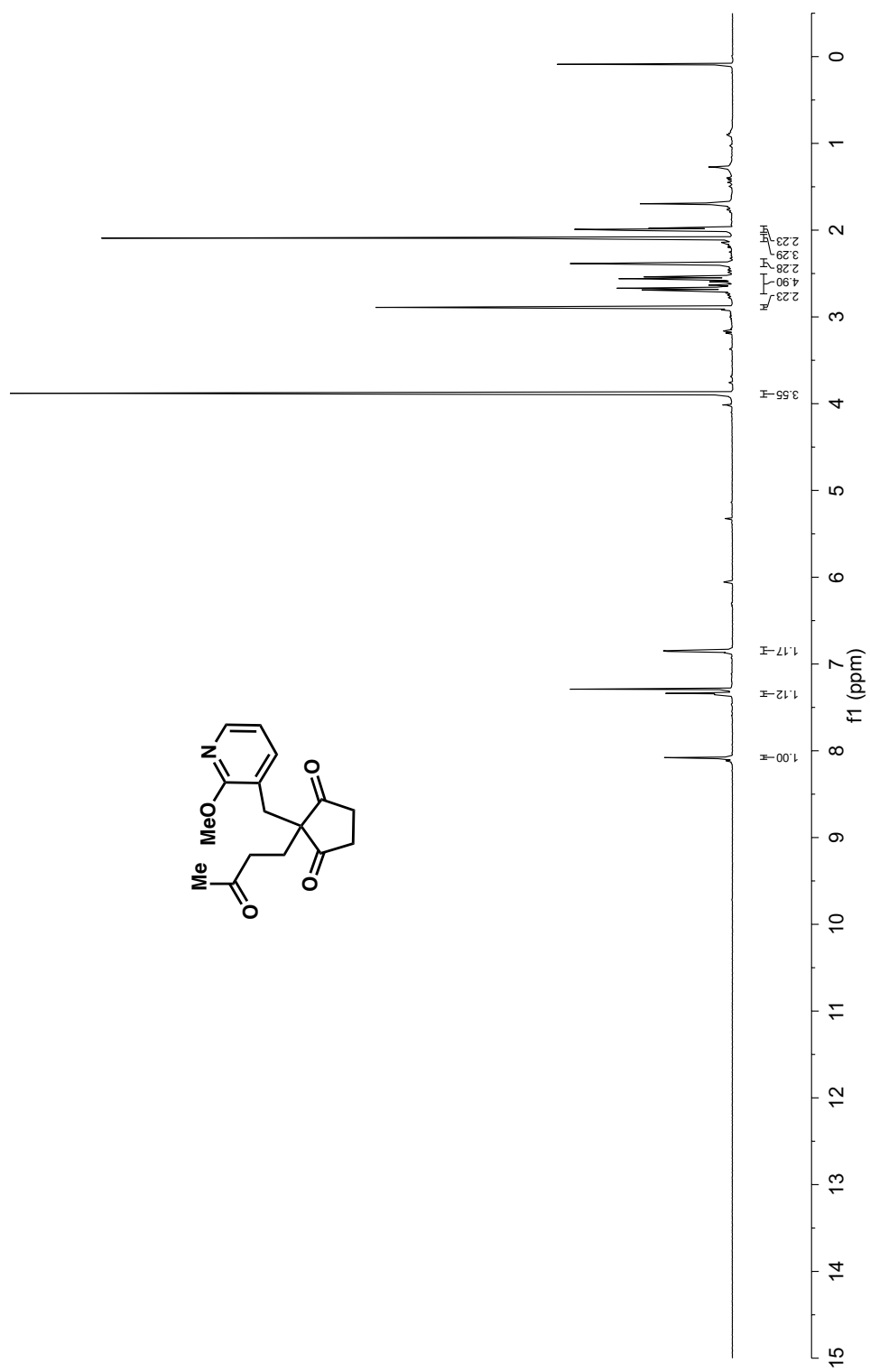


Figure A1.66 ¹H NMR of 2.S4

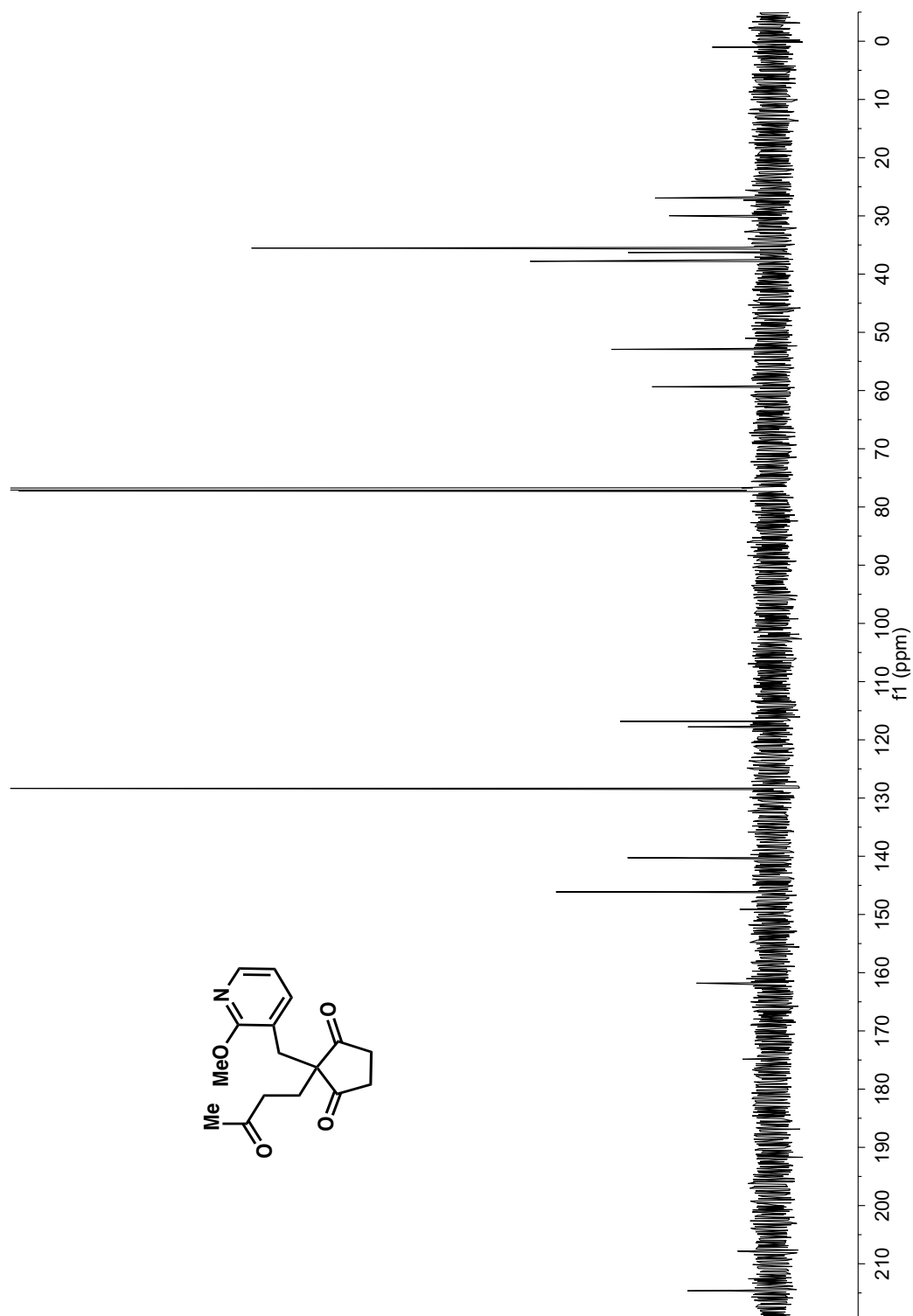


Figure A1.67 ¹³C NMR of 2.S4

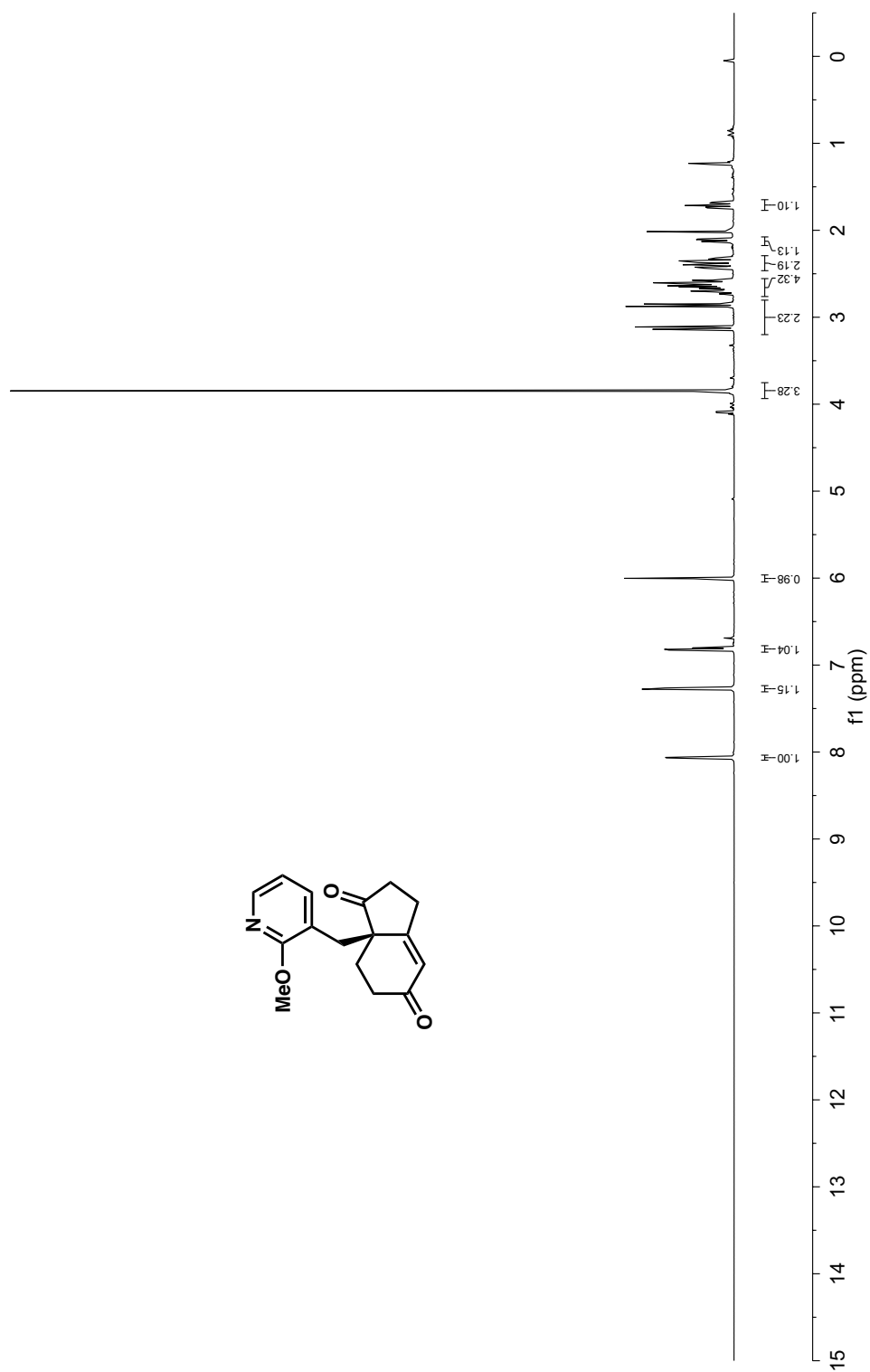


Figure A1.68 ¹H NMR of **2.97**

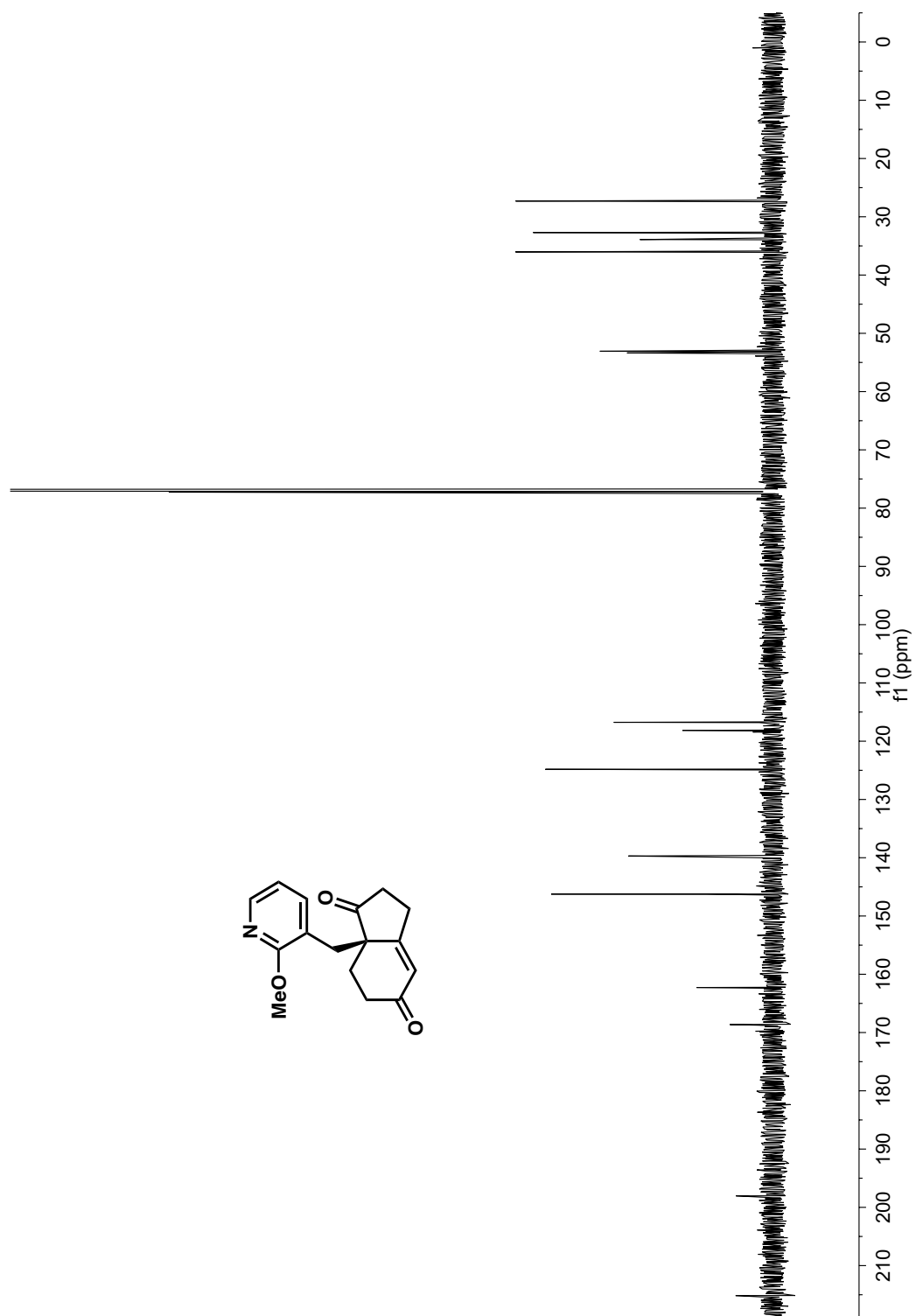


Figure A1.69 ^{13}C NMR of 2.97

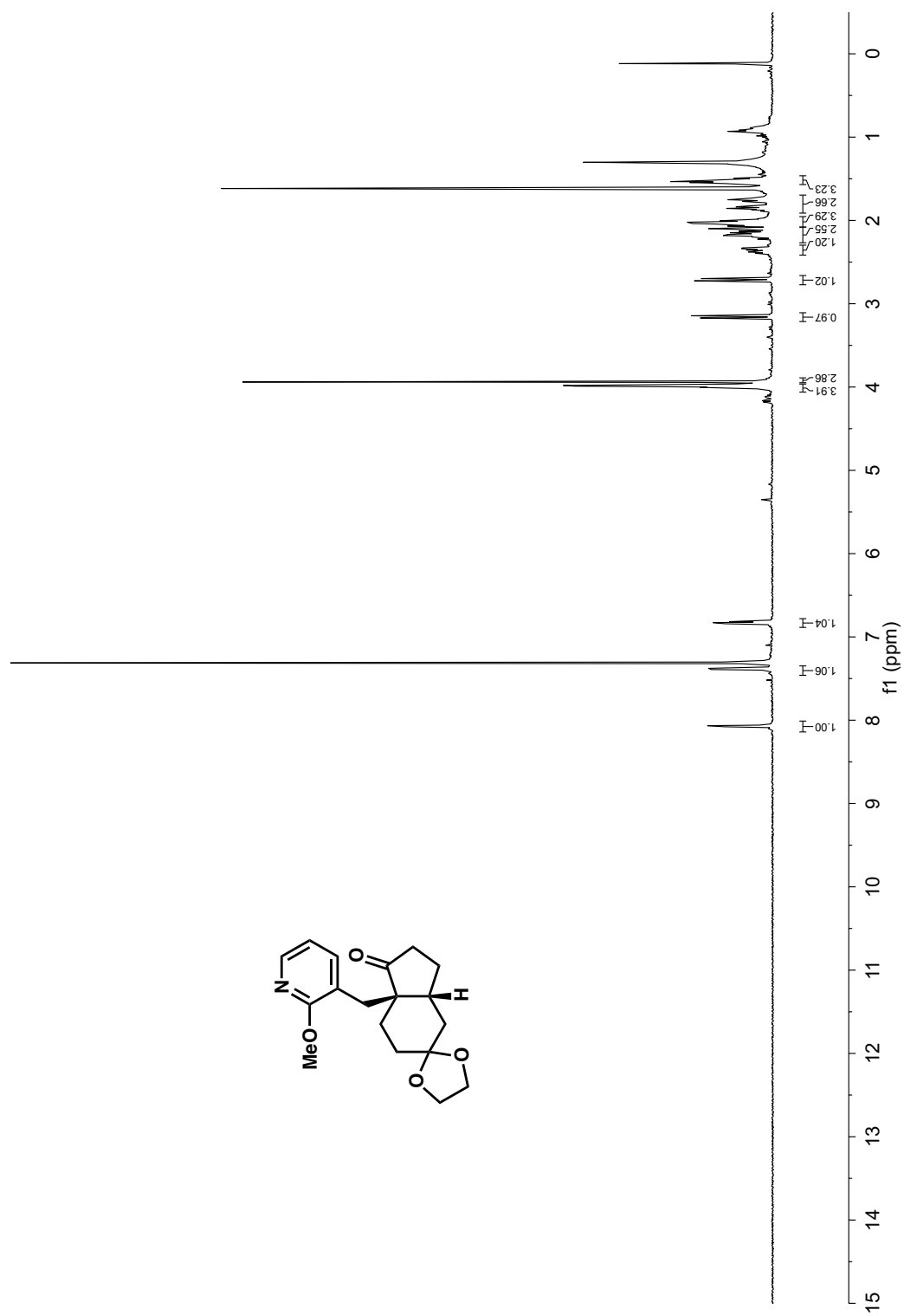


Figure A1.70 ^1H NMR of 2.98

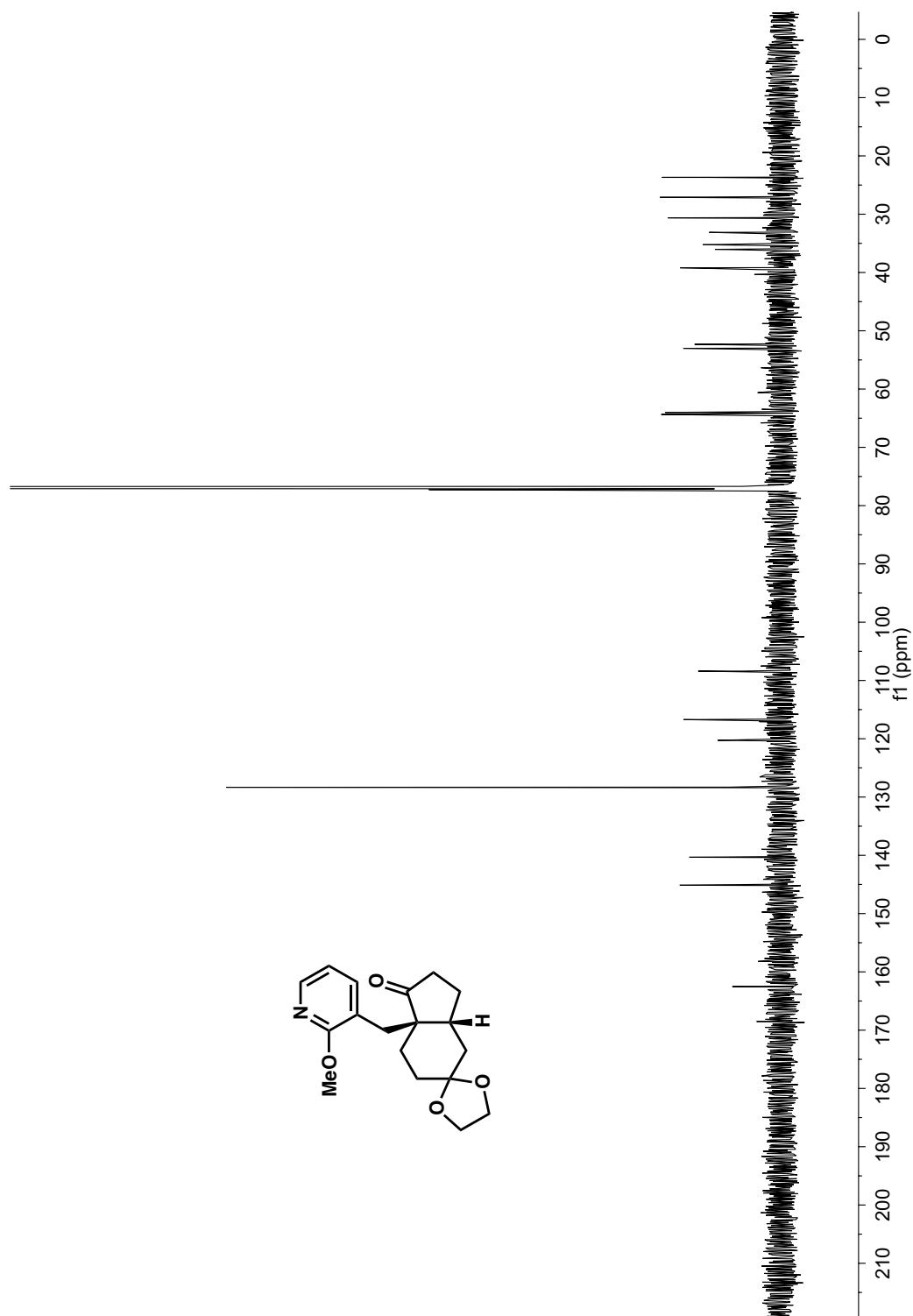


Figure A1.71 ^{13}C NMR of 2.98

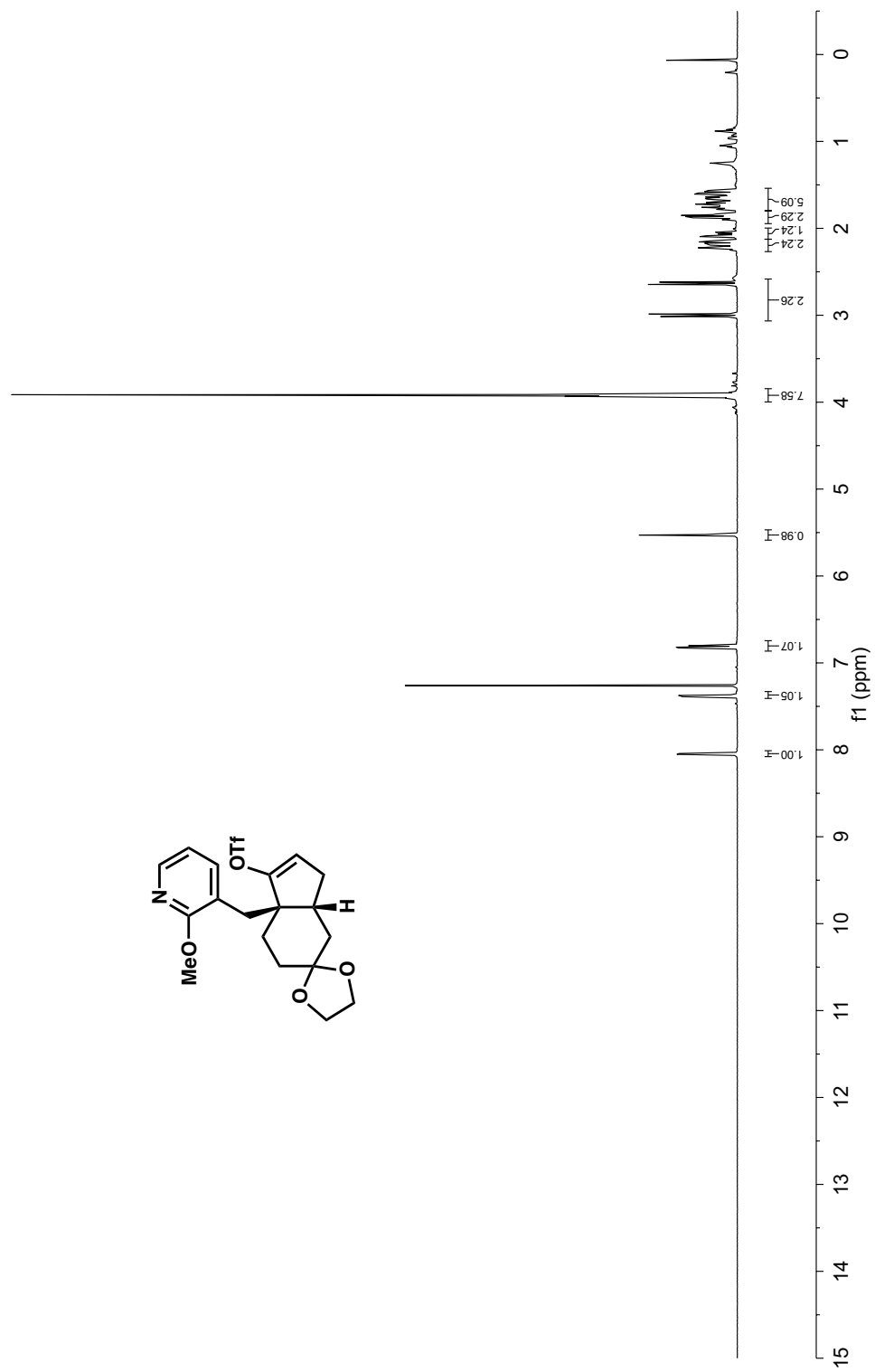


Figure A1.72 ^1H NMR of 2.99

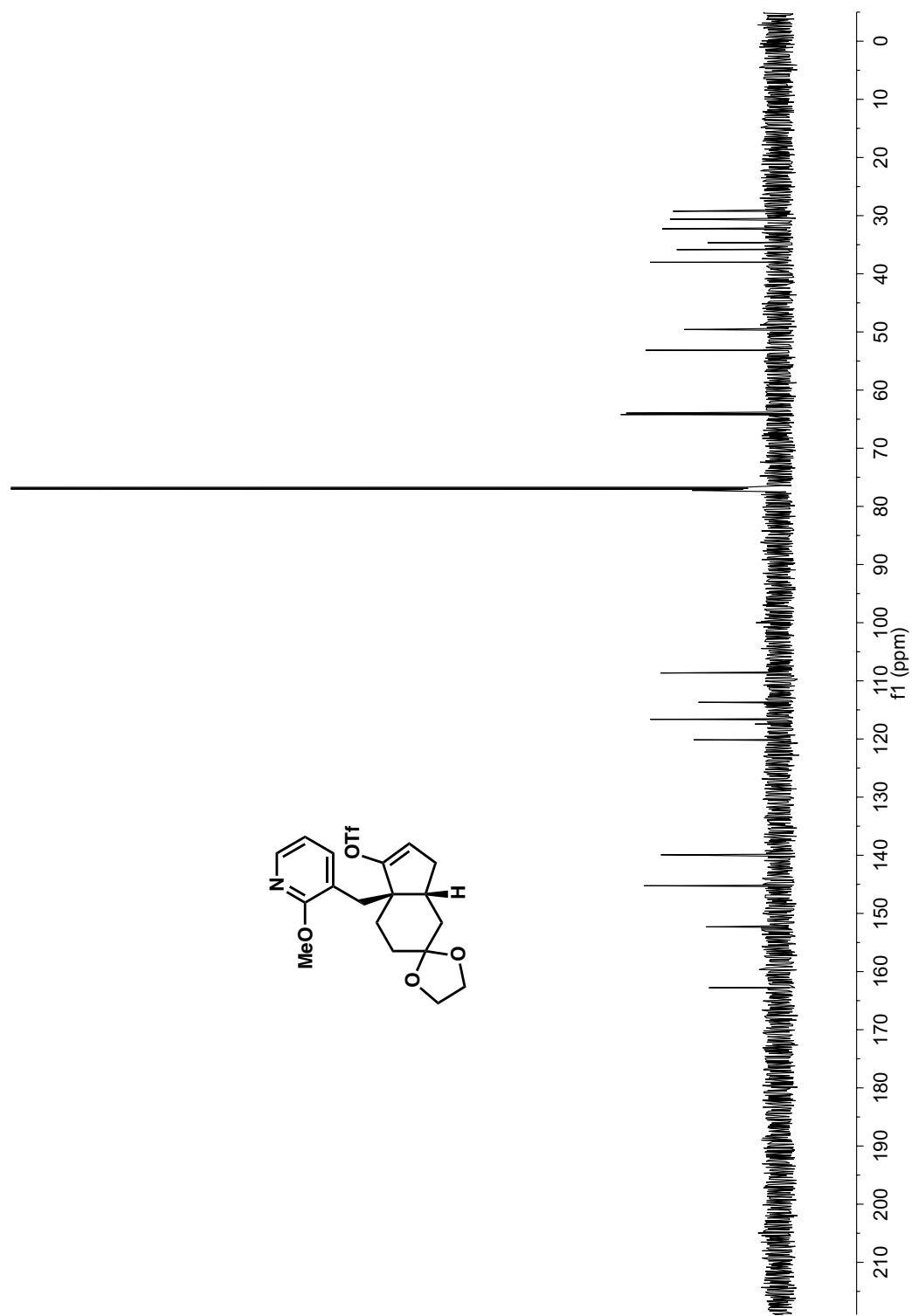
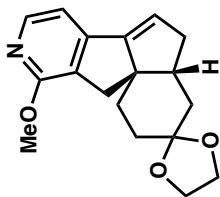


Figure A1.73 ^{13}C NMR of **2.99**



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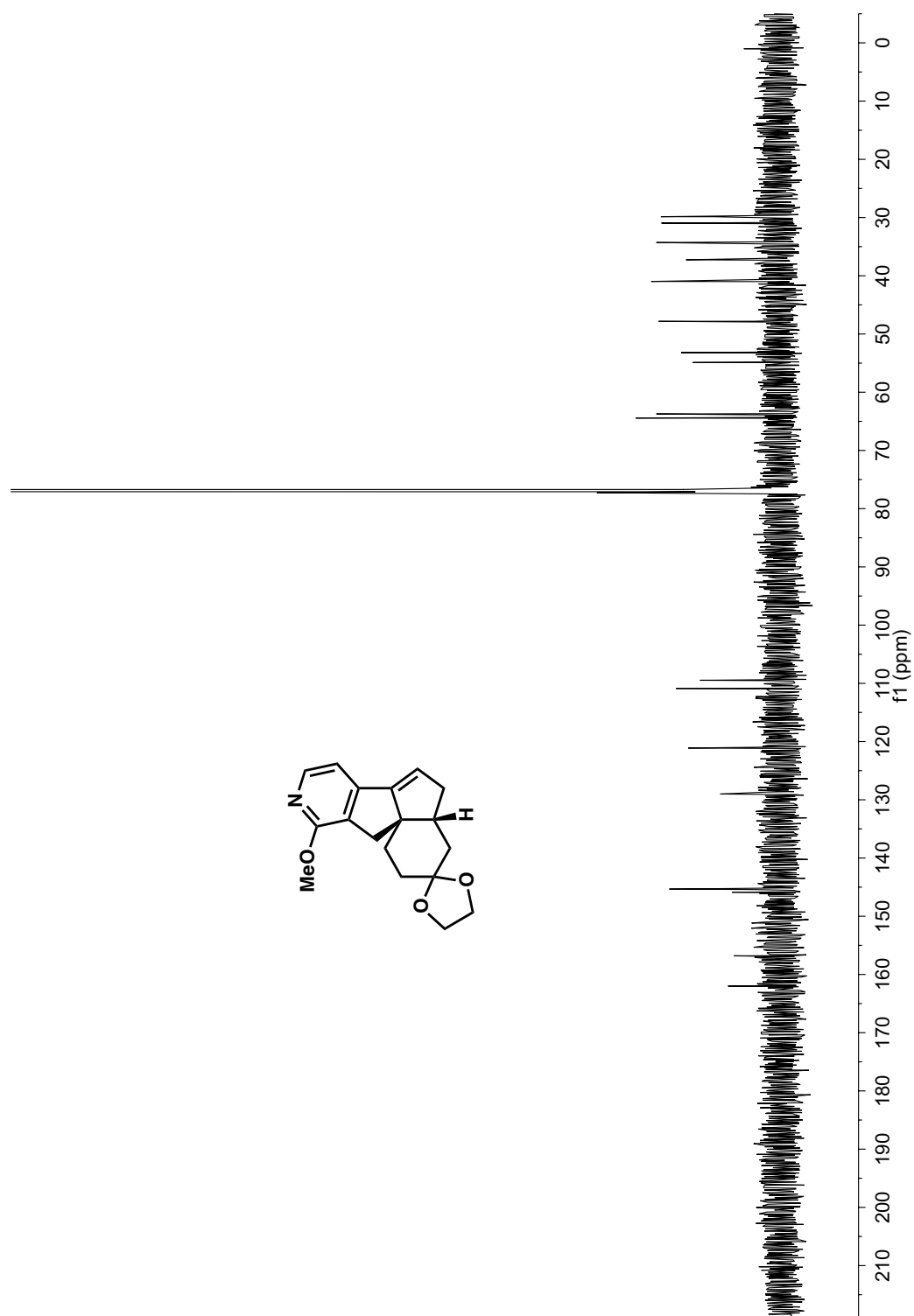


Figure A1.75 ^{13}C NMR of 2.100

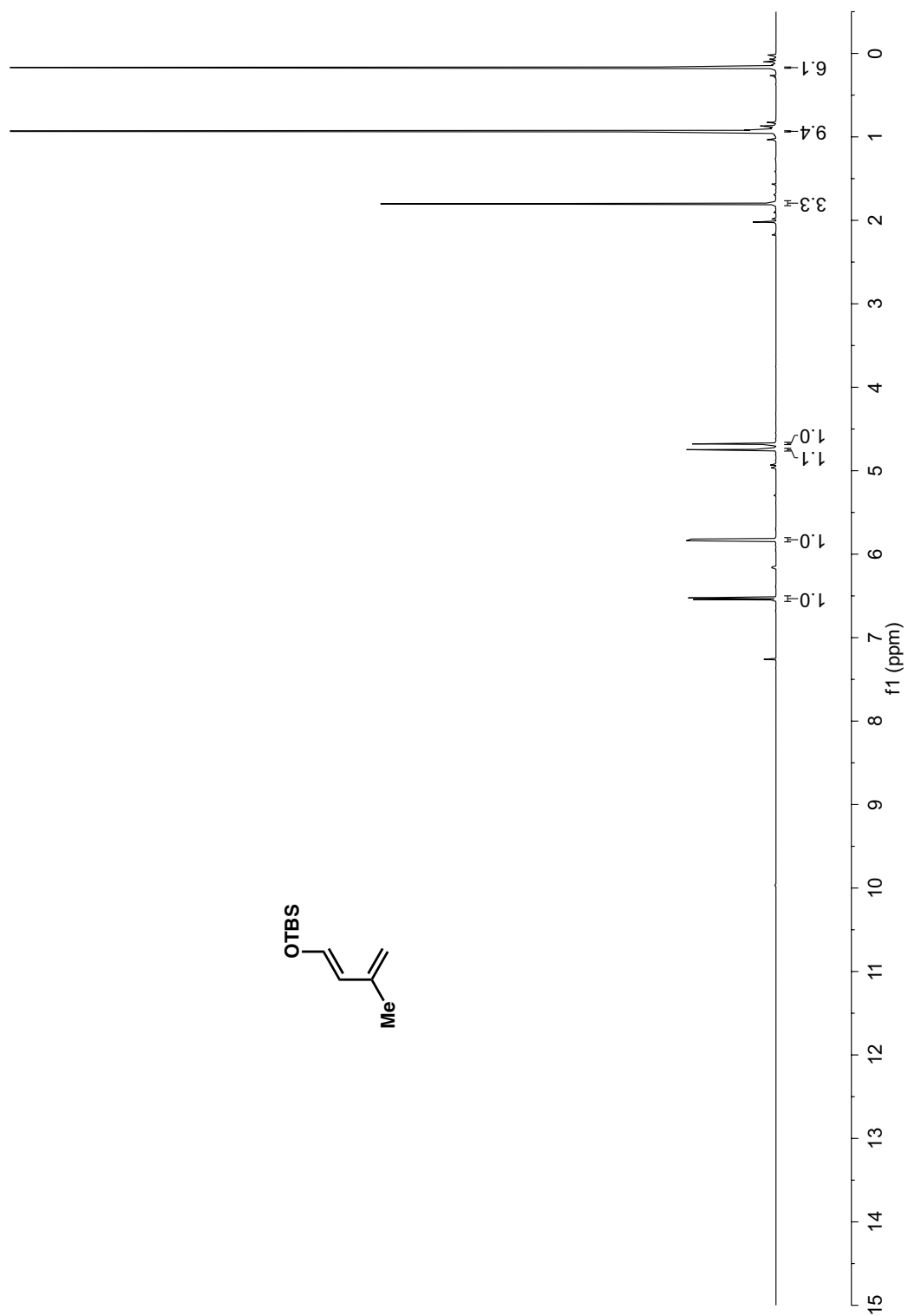


Figure A1.76 ^1H NMR of **2.112**

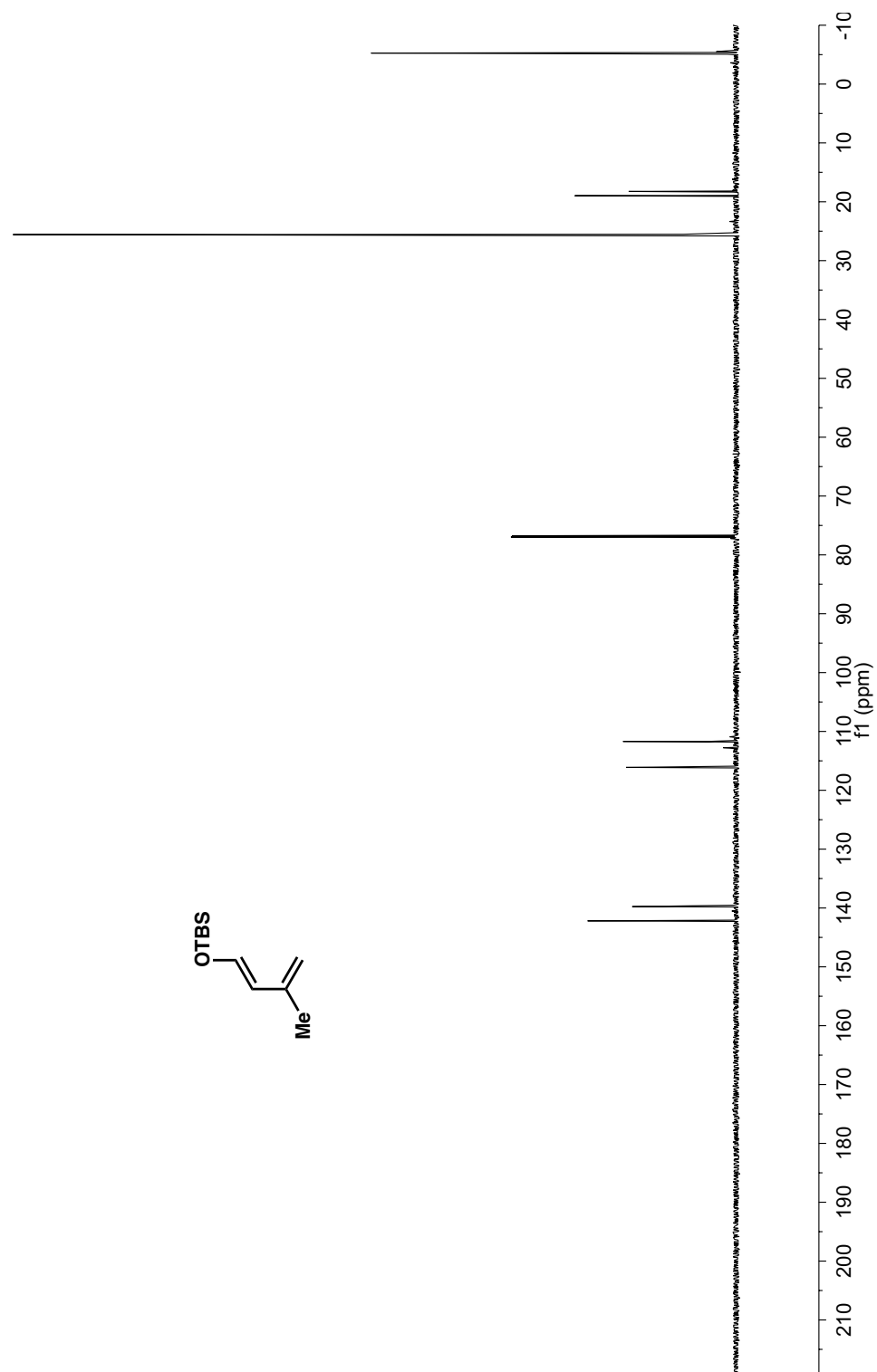


Figure A1.77 ^{13}C NMR of 2.112

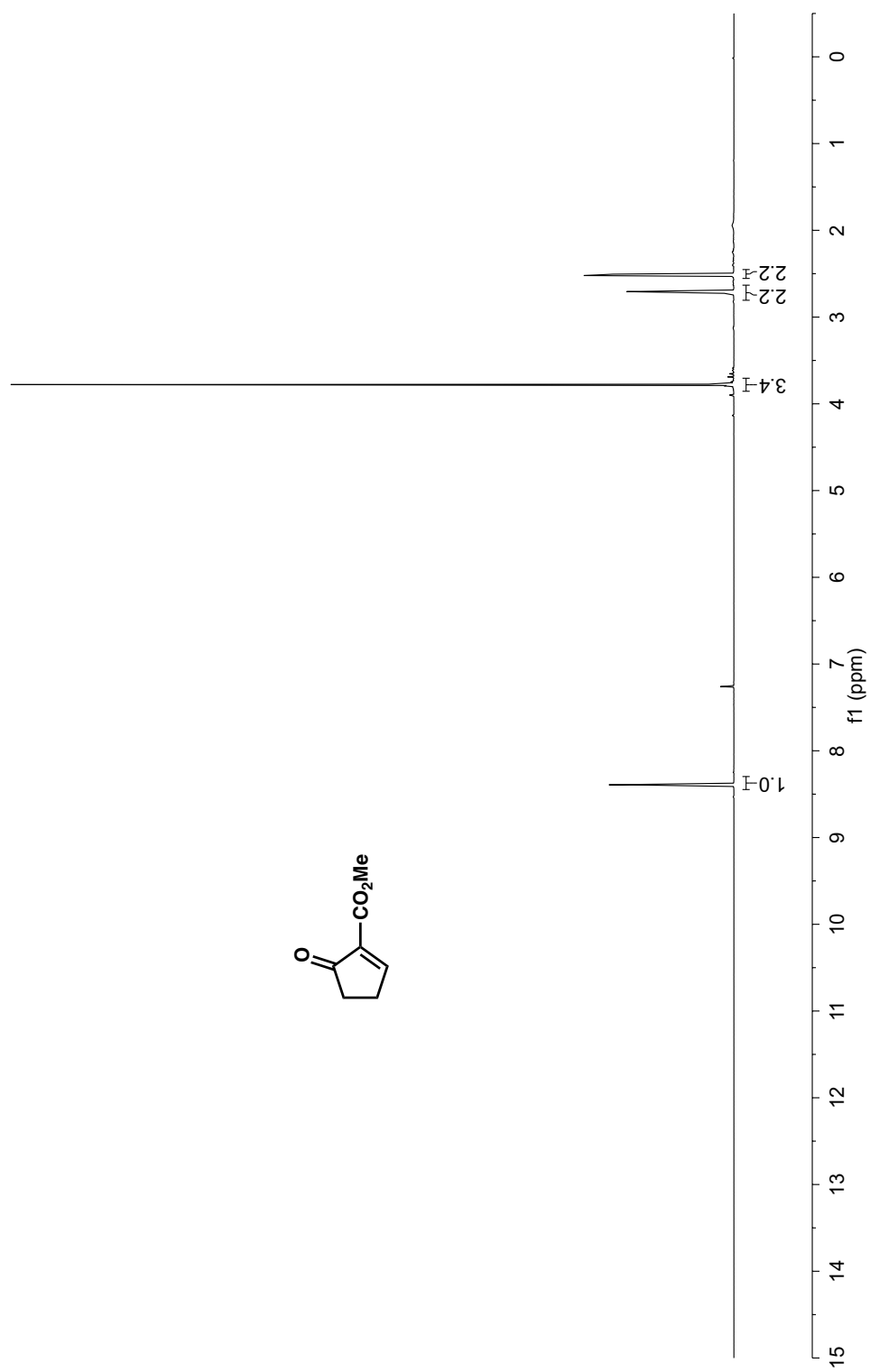


Figure A1.78 ^1H NMR of 2.113

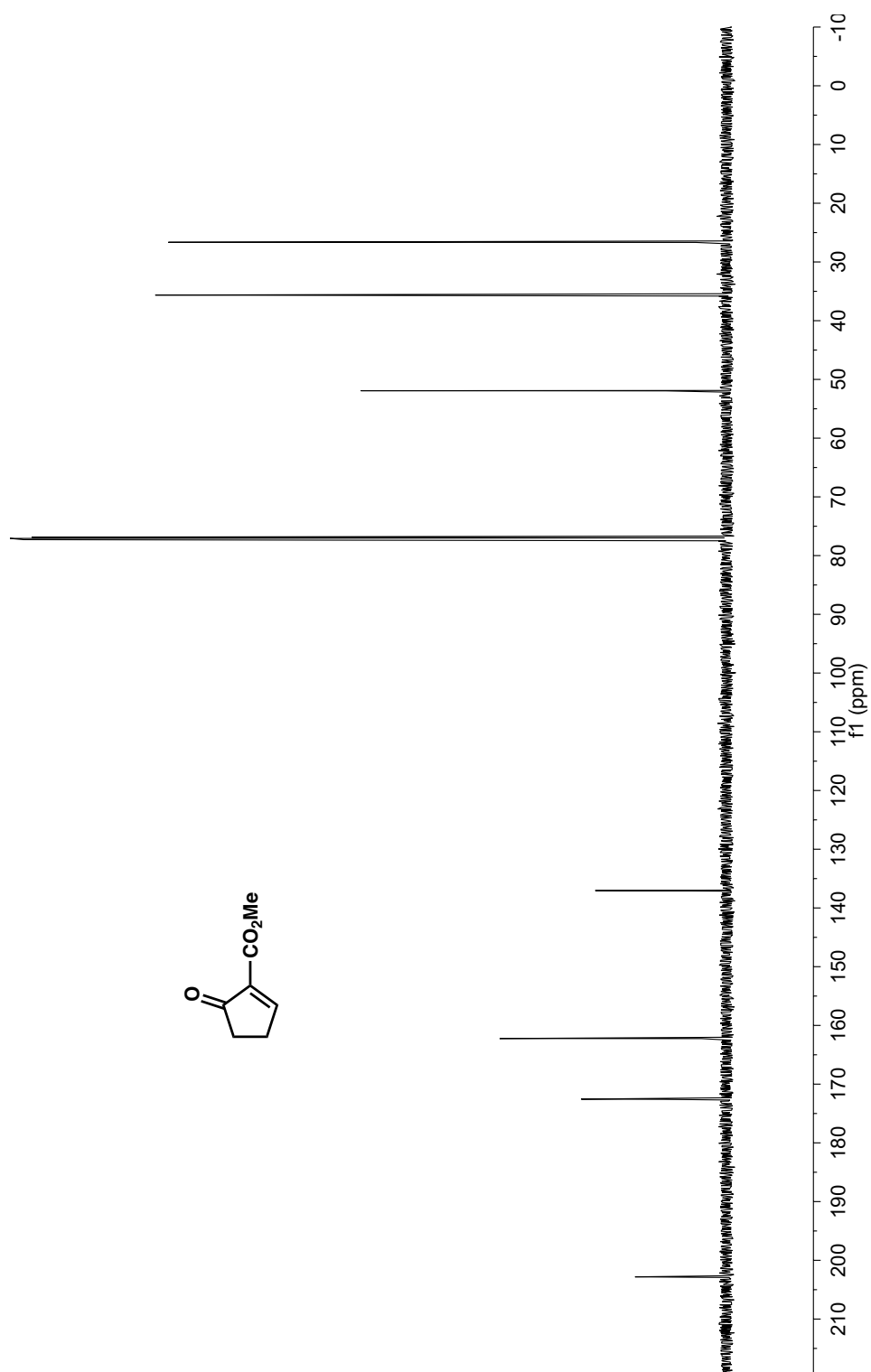


Figure A1.79 ^{13}C NMR of 2.113

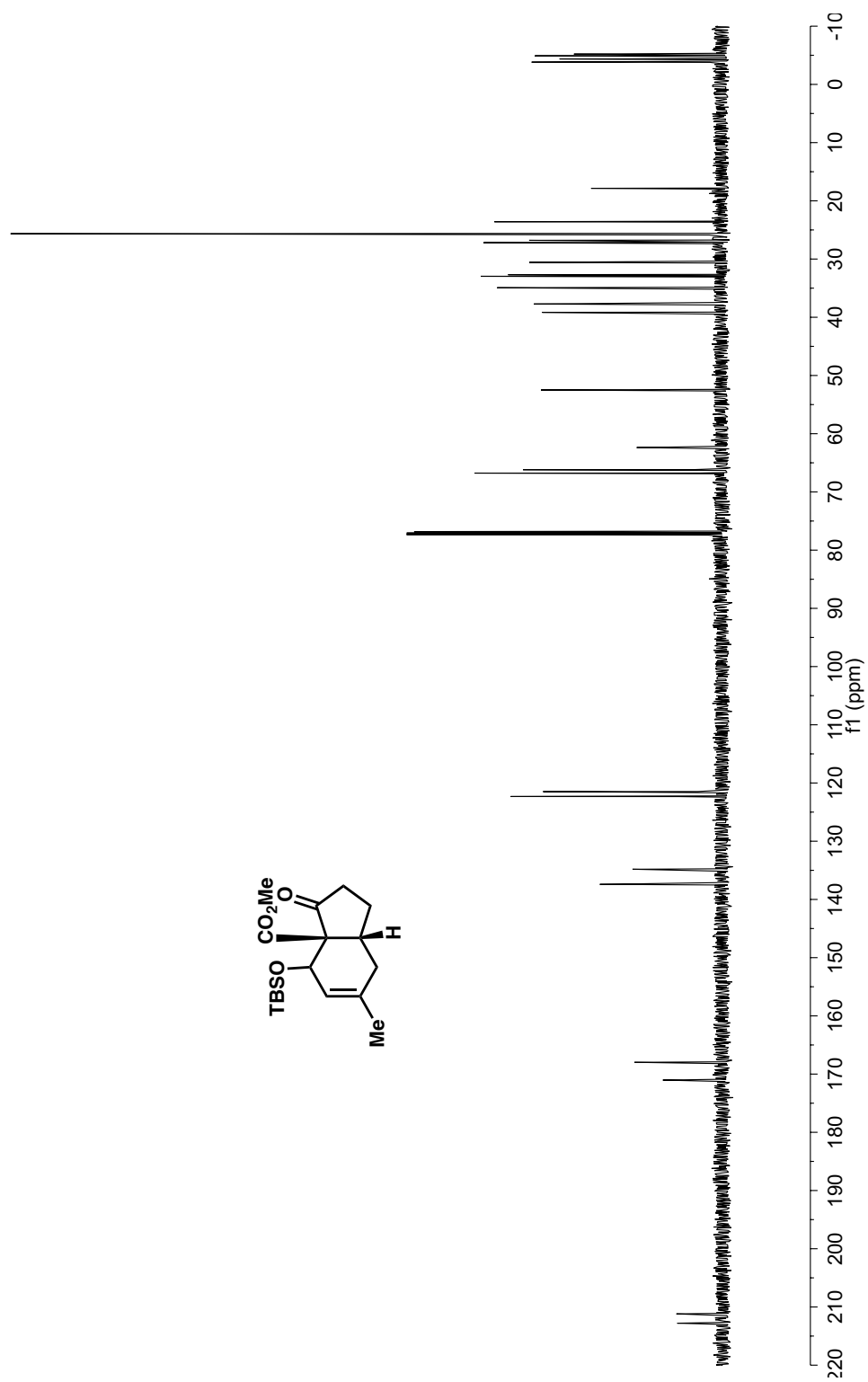


Figure A1.81 ¹³C NMR of 2.111

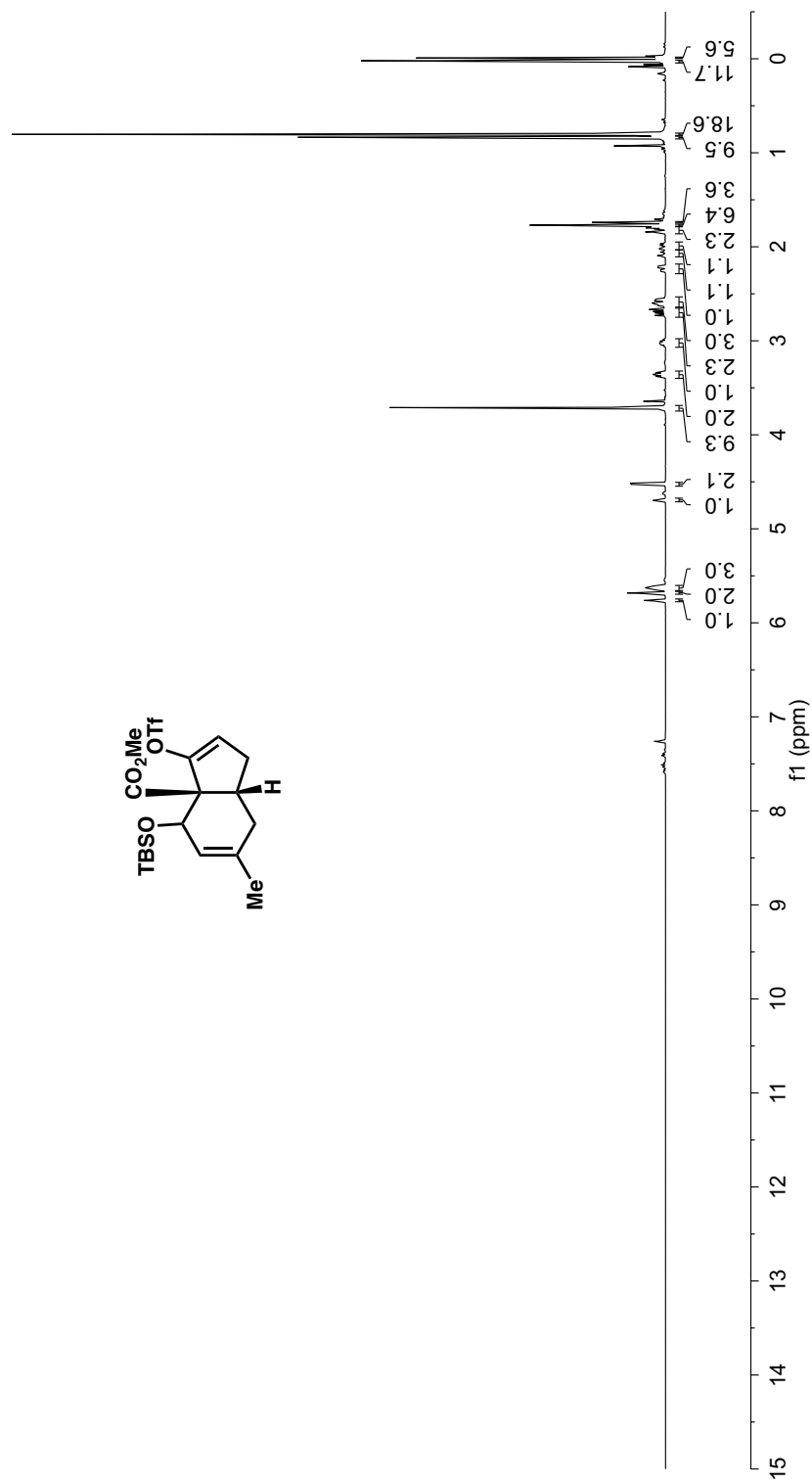


Figure A1.82 ¹H NMR of 2.115

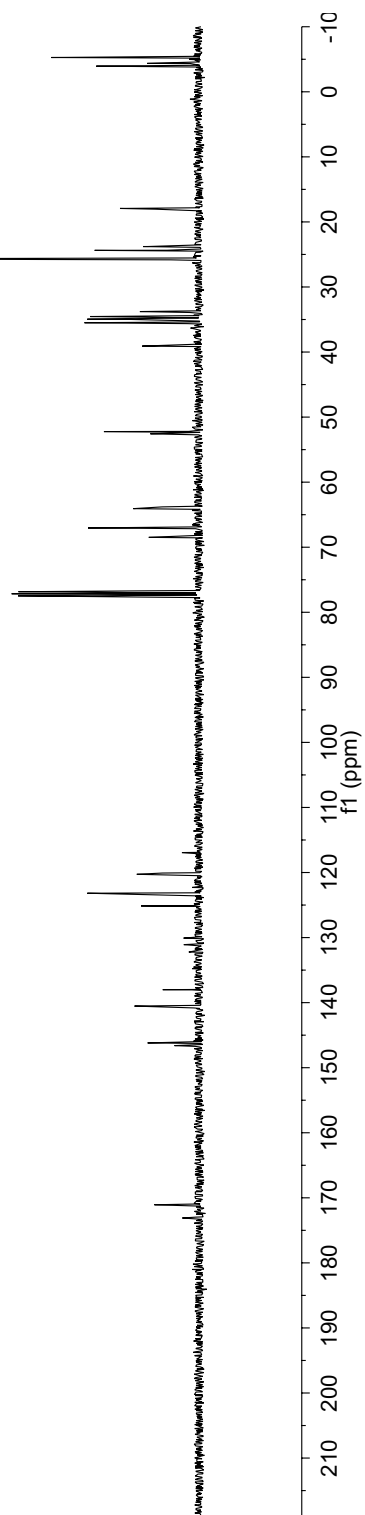
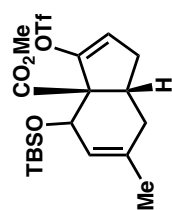


Figure A1.83 ¹³C NMR of 2.115

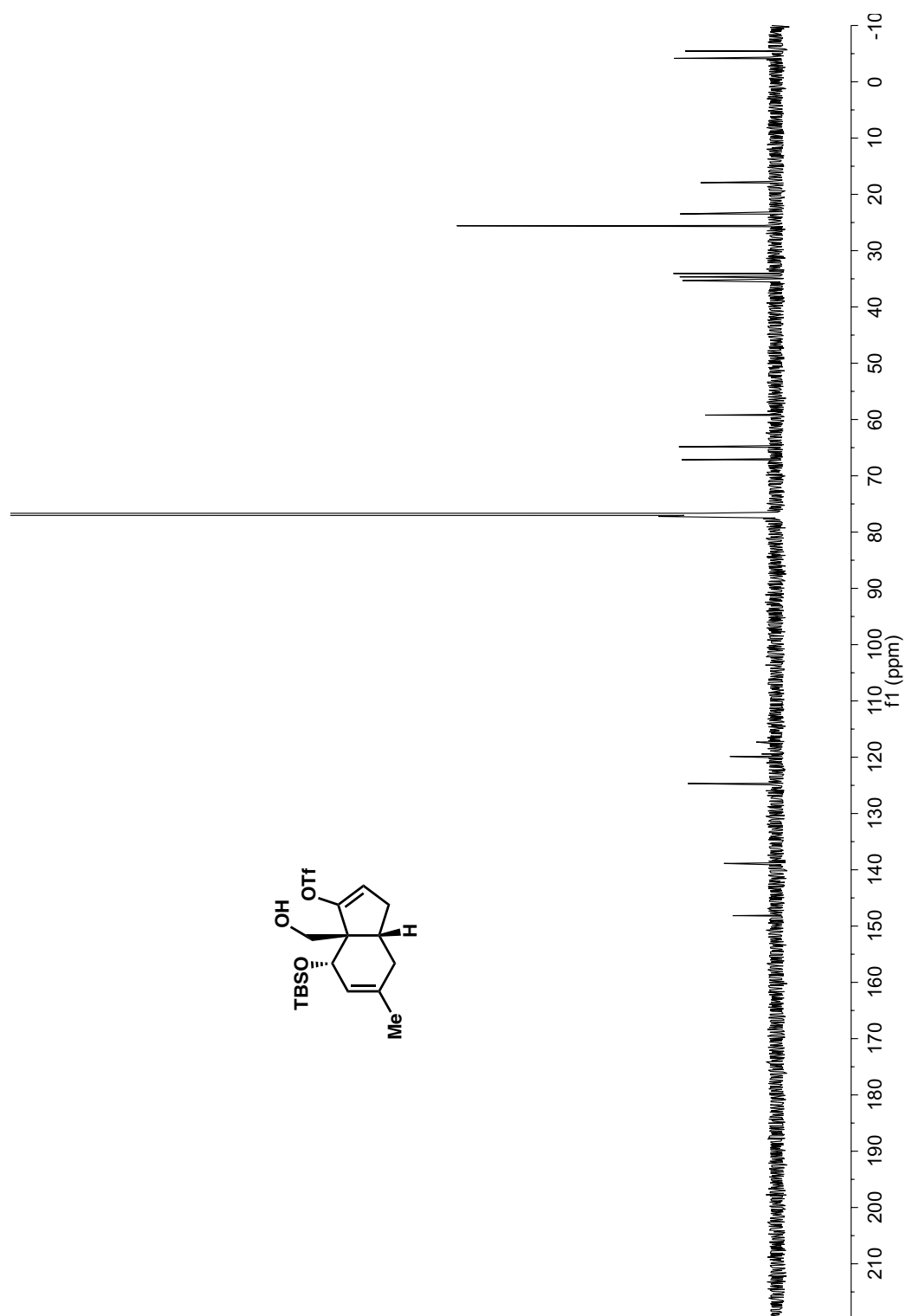
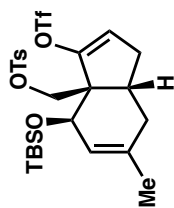
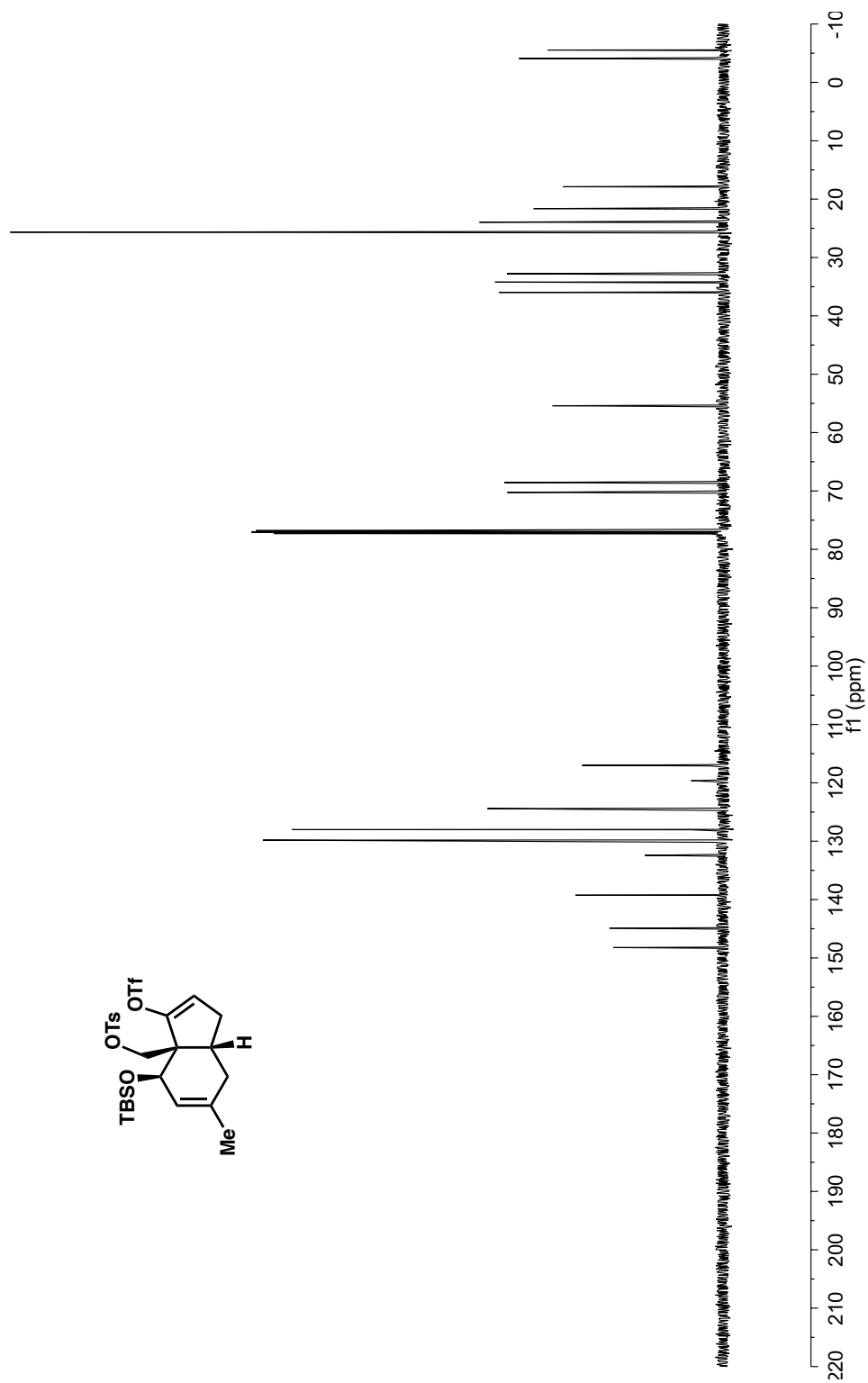


Figure A1.87 ^{13}C NMR of 2.118B



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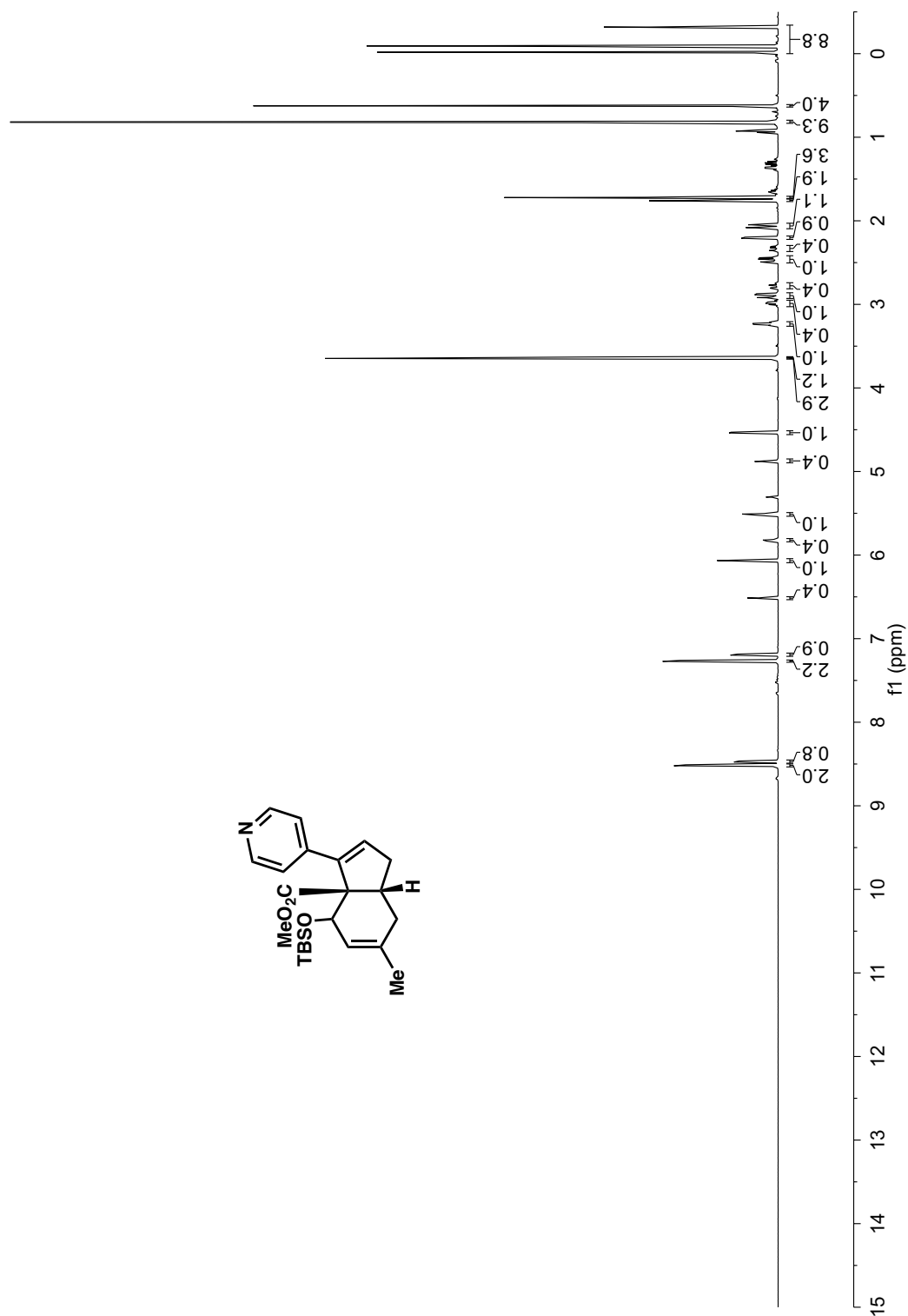


Figure A1.90 ^1H NMR of 2.116

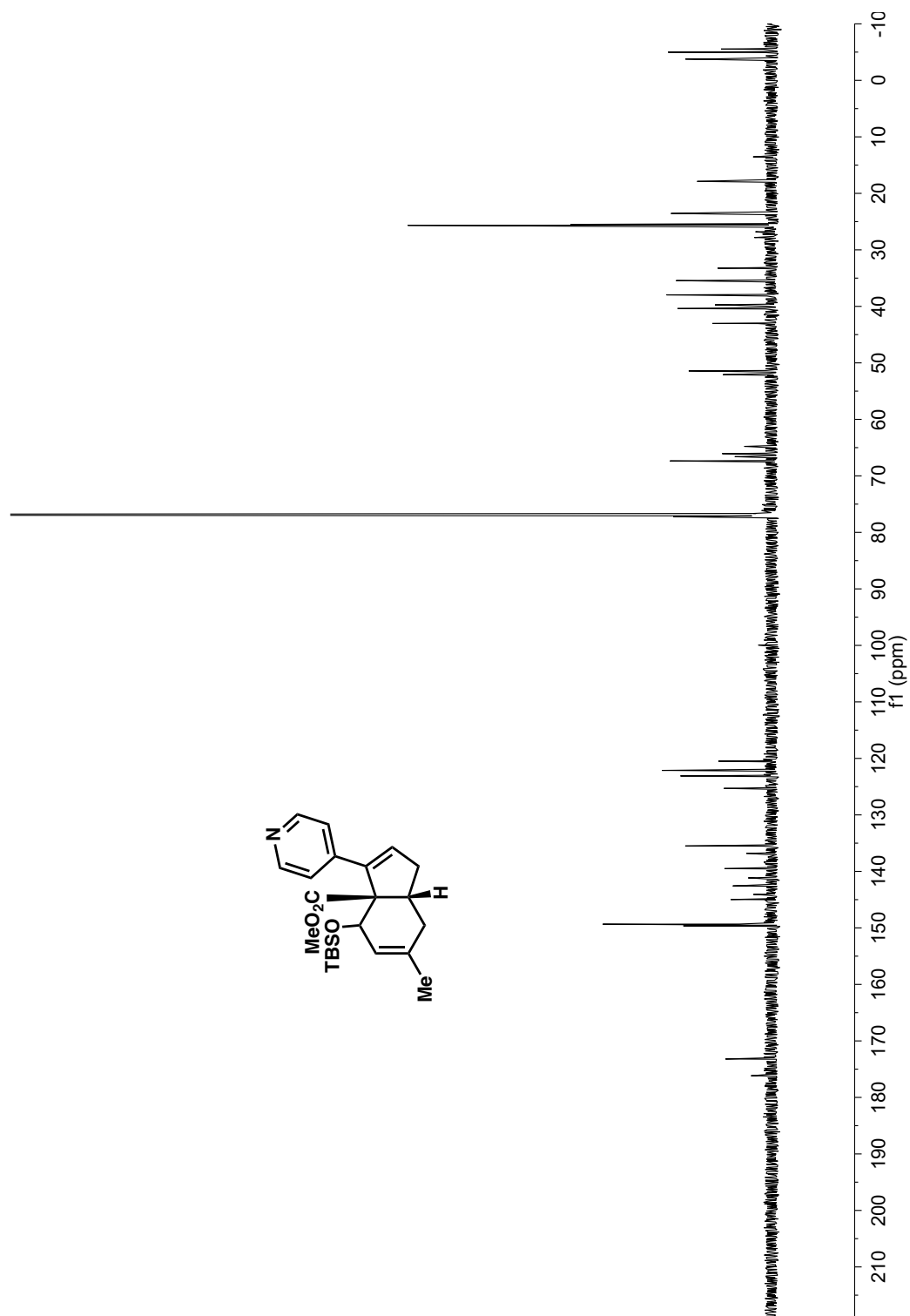


Figure A1.91 ¹³C NMR of 2.116

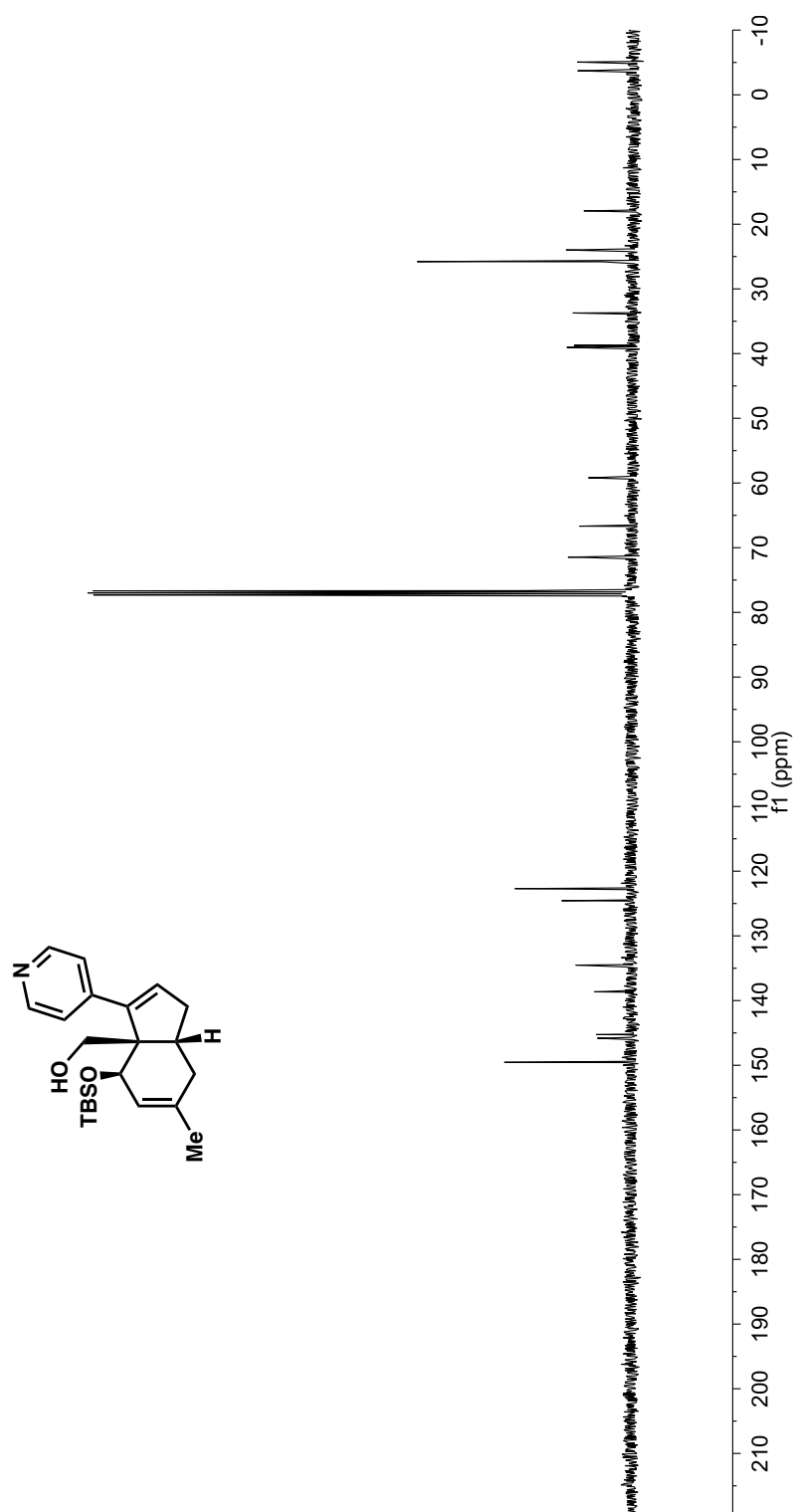


Figure A1.93 ^{13}C NMR of 2.117

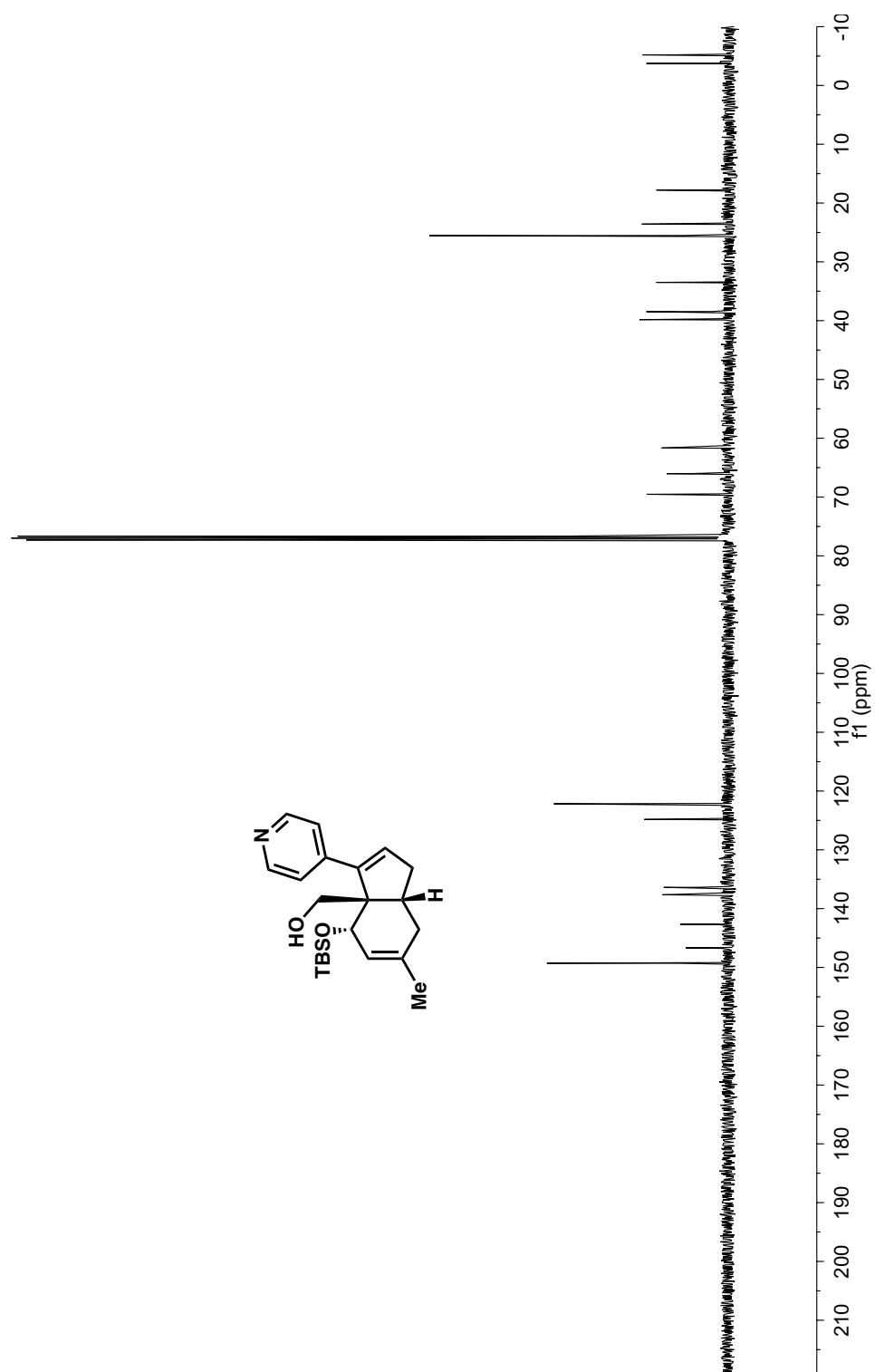


Figure A1.95 ^{13}C NMR of 2.153

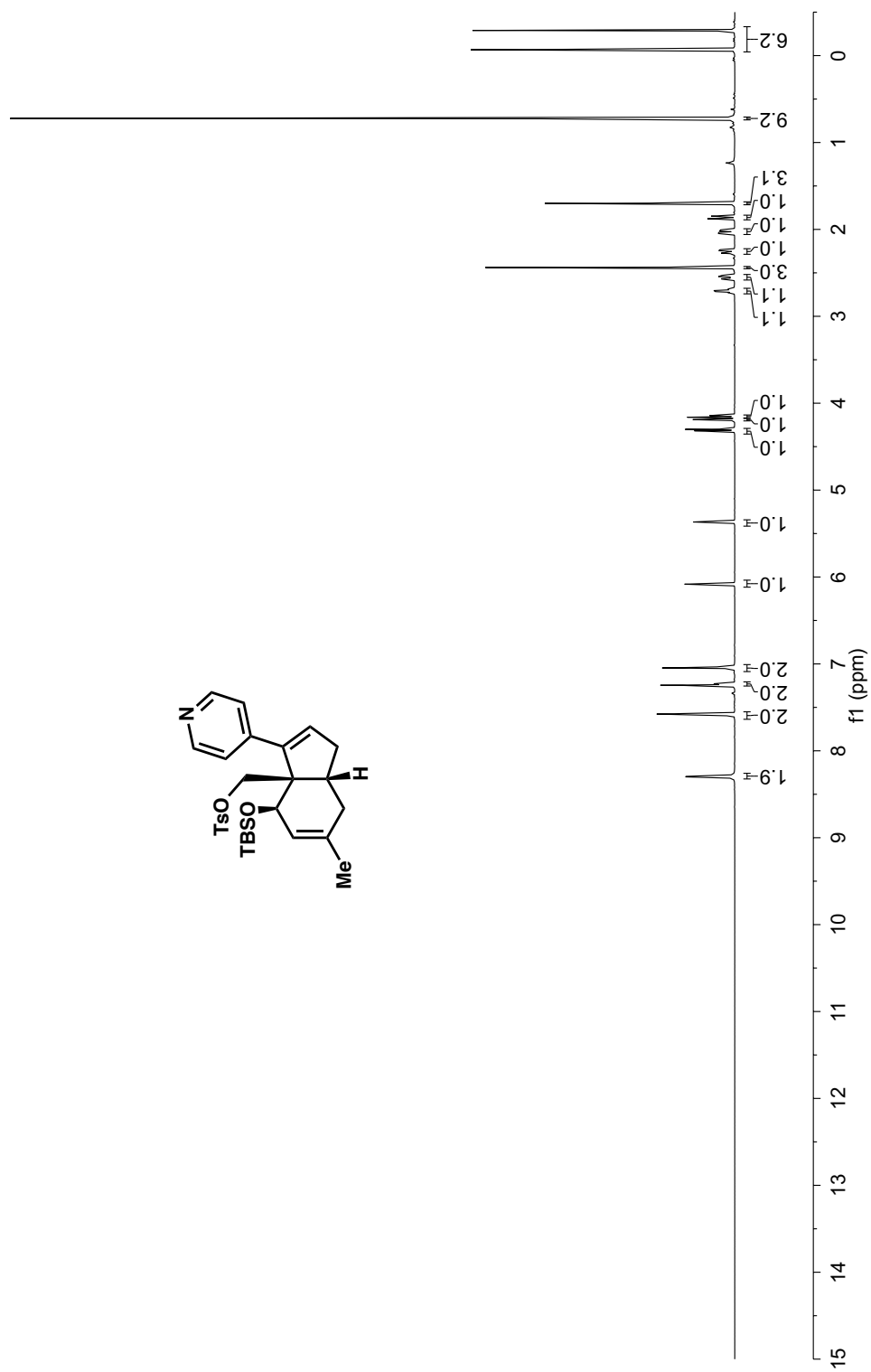


Figure A1.96 ¹H NMR of 2.110

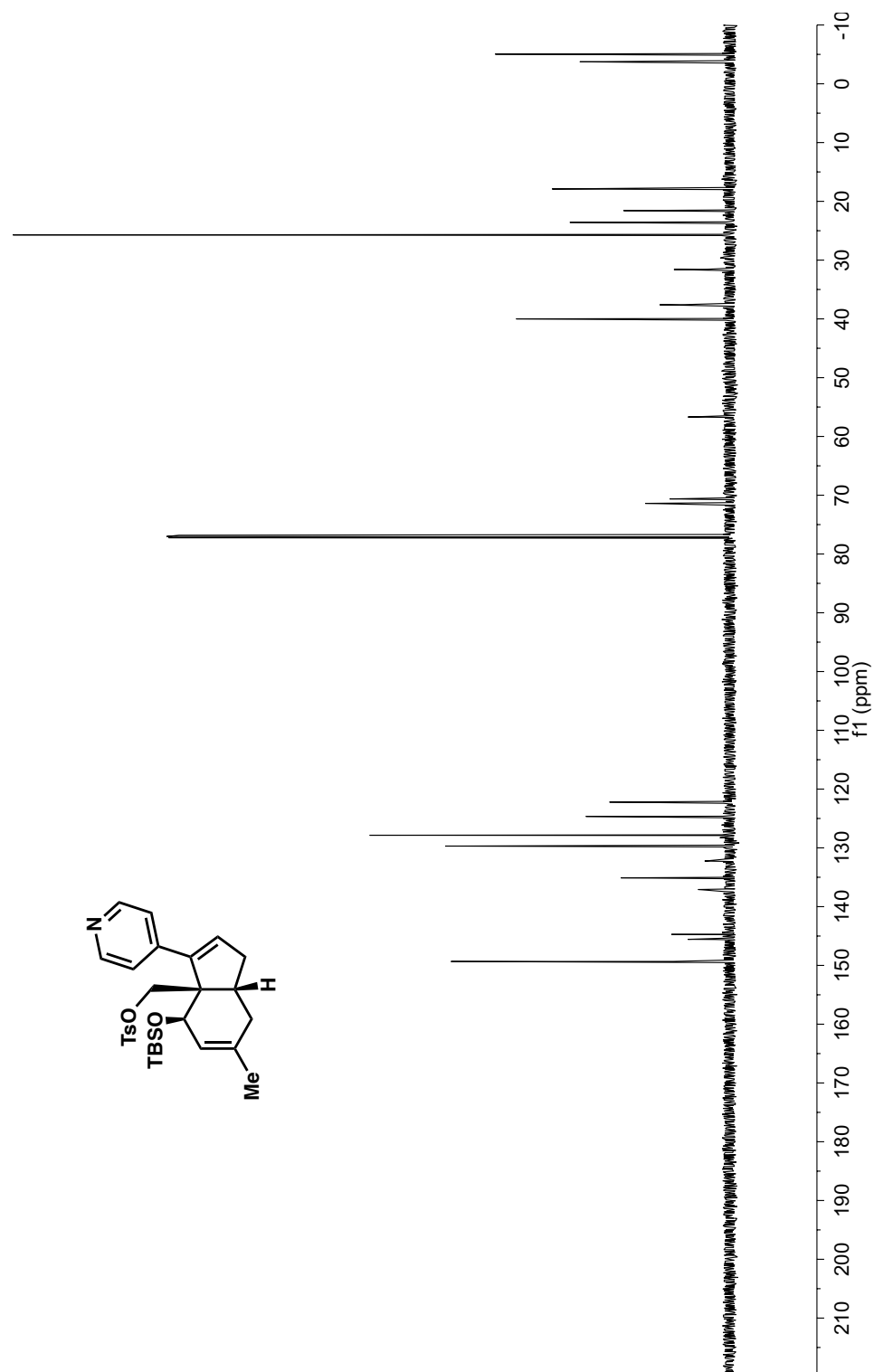


Figure A1.97 ^{13}C NMR of 2.110

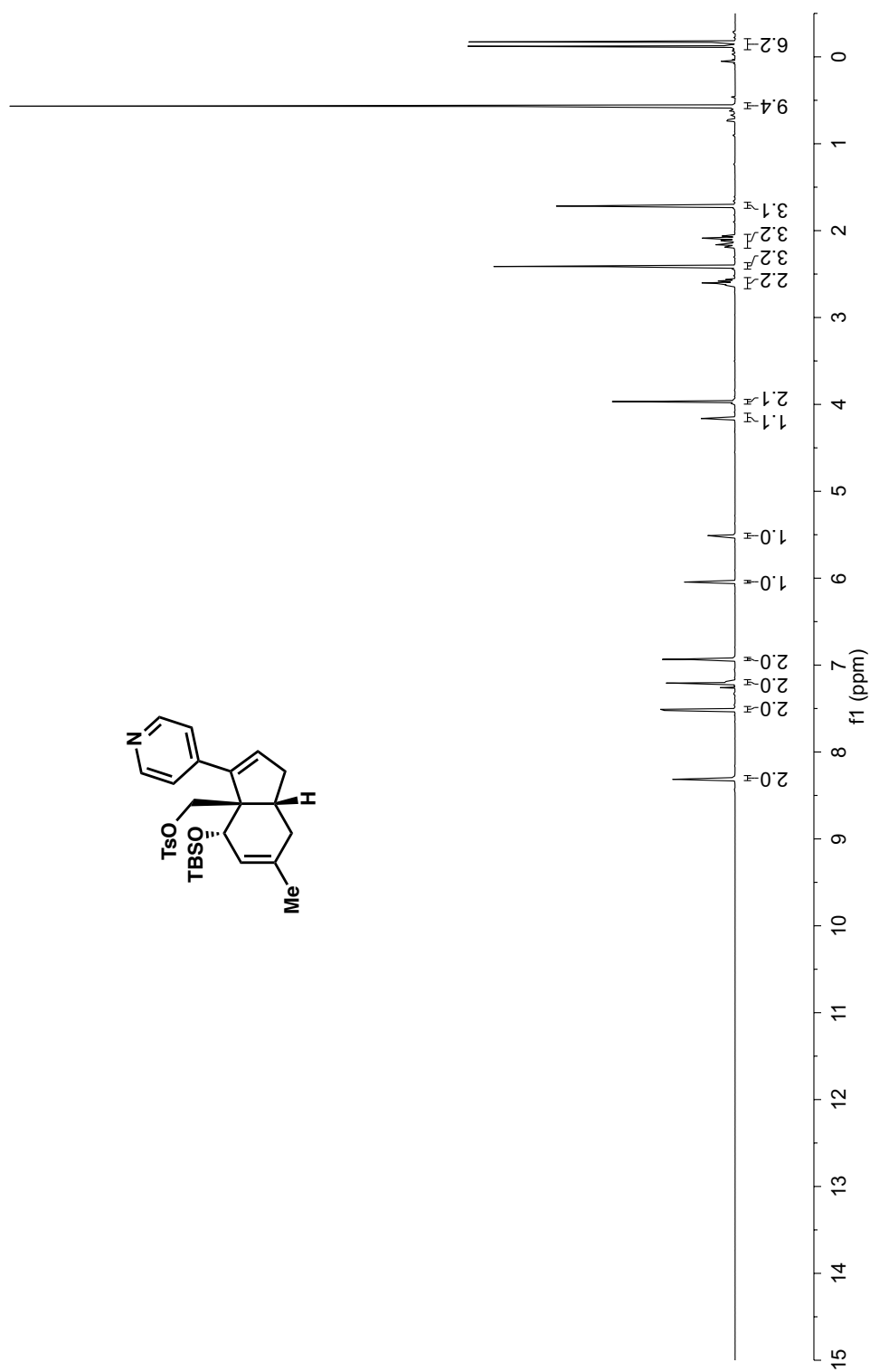


Figure A1.98 ^1H NMR of 2.154

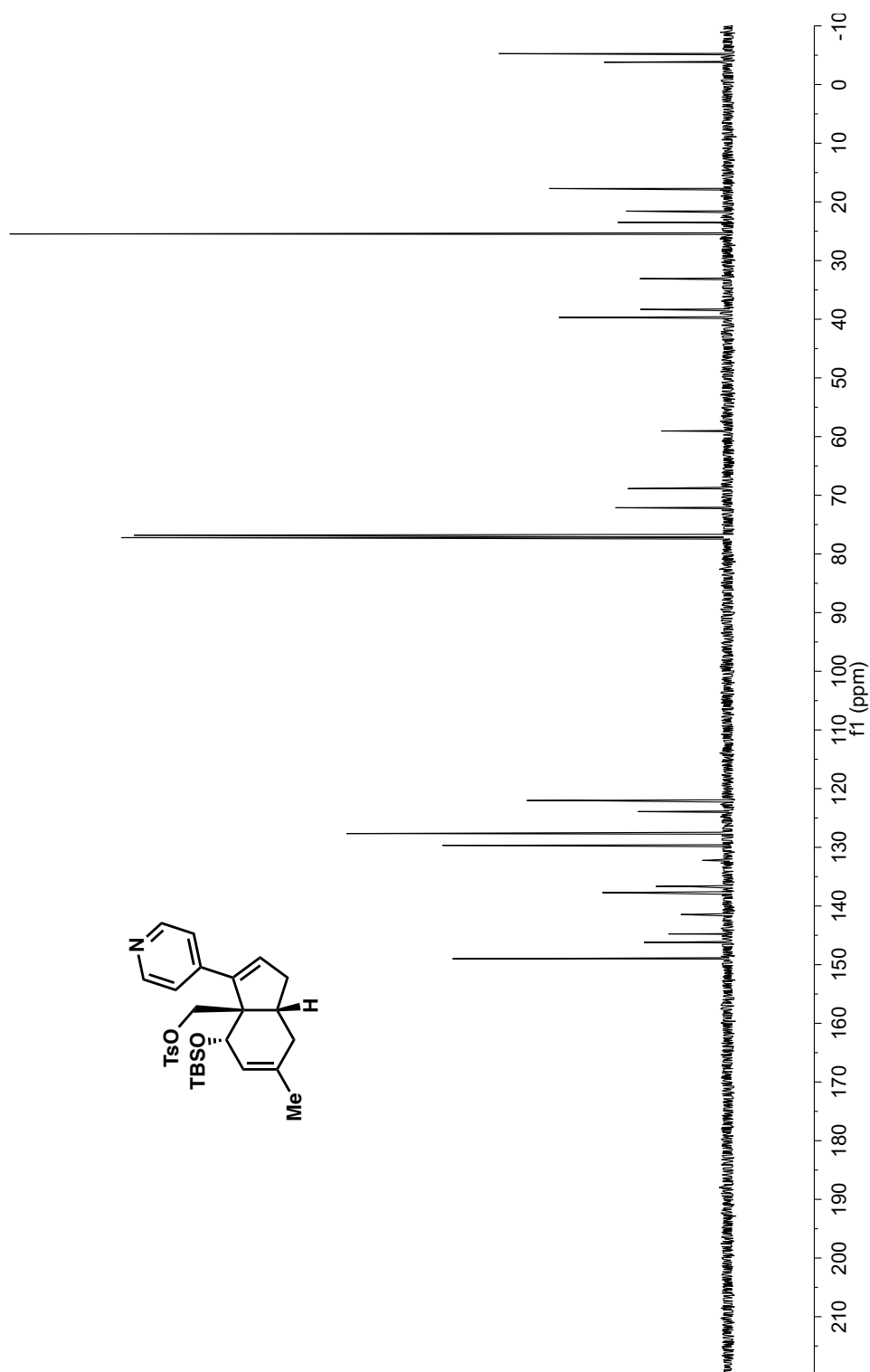


Figure A1.99 ^{13}C NMR of 2.154

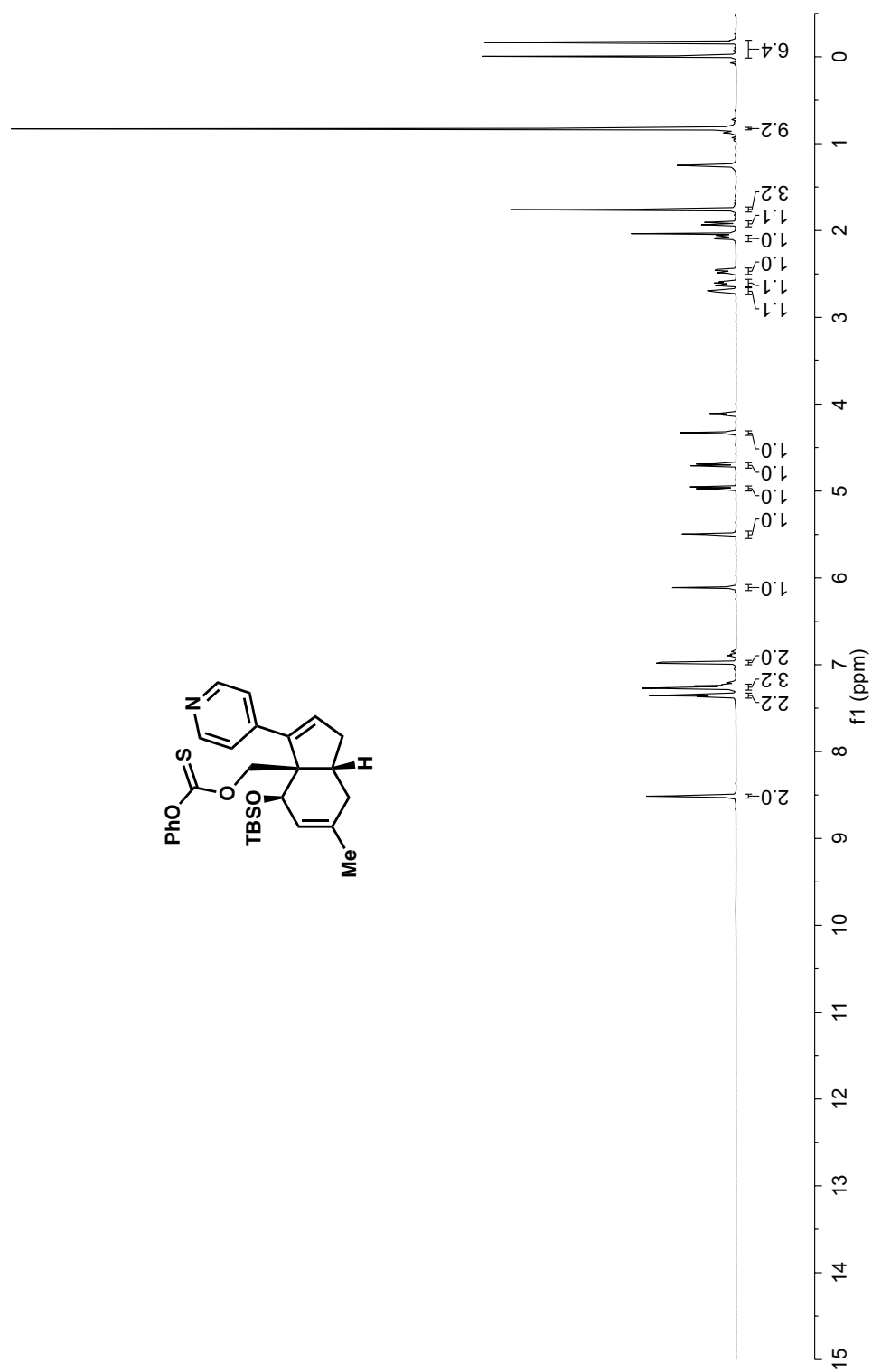


Figure A1.100 ^1H NMR of 2.125

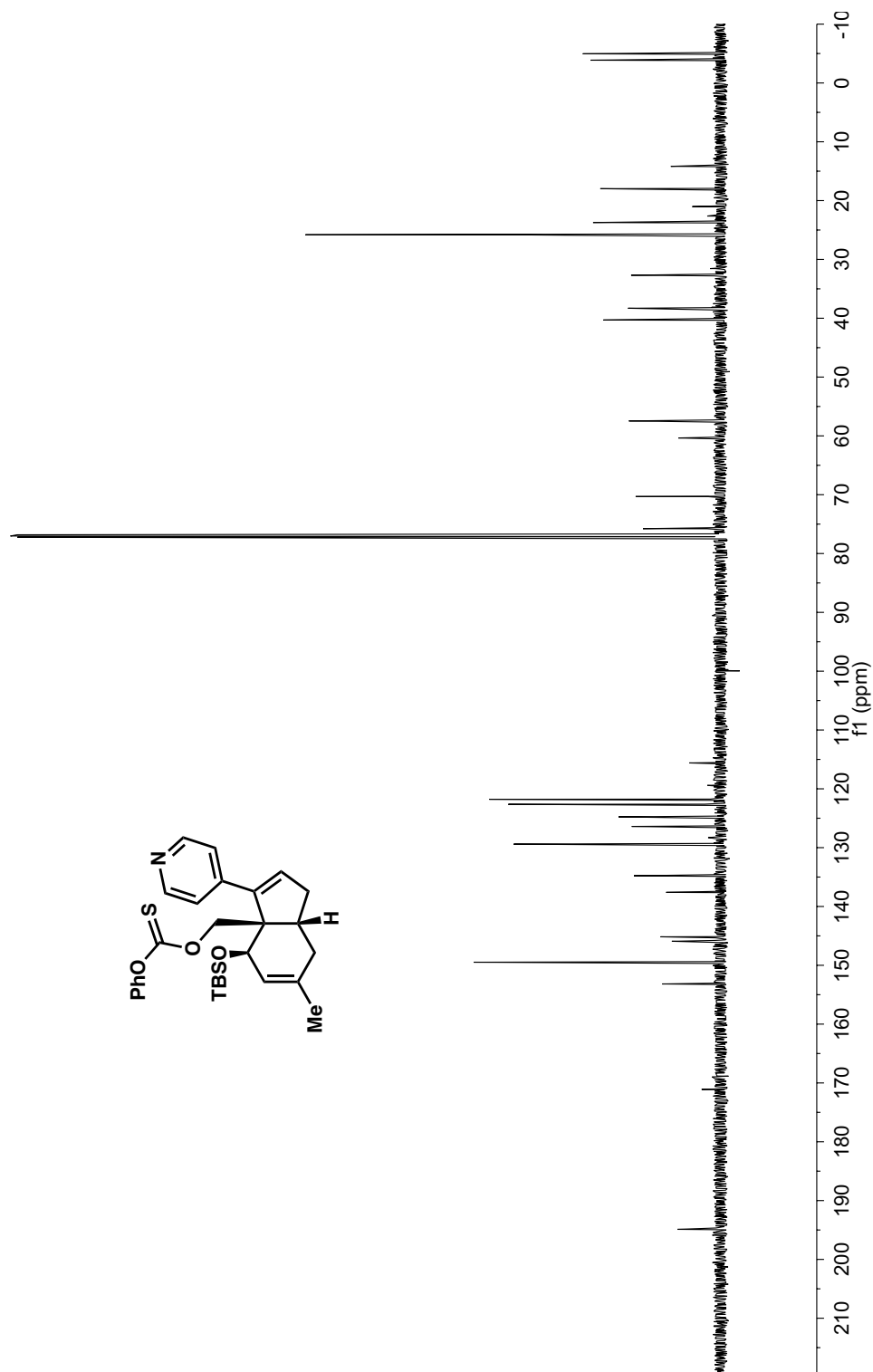


Figure A1.101 ^{13}C NMR of 2.125

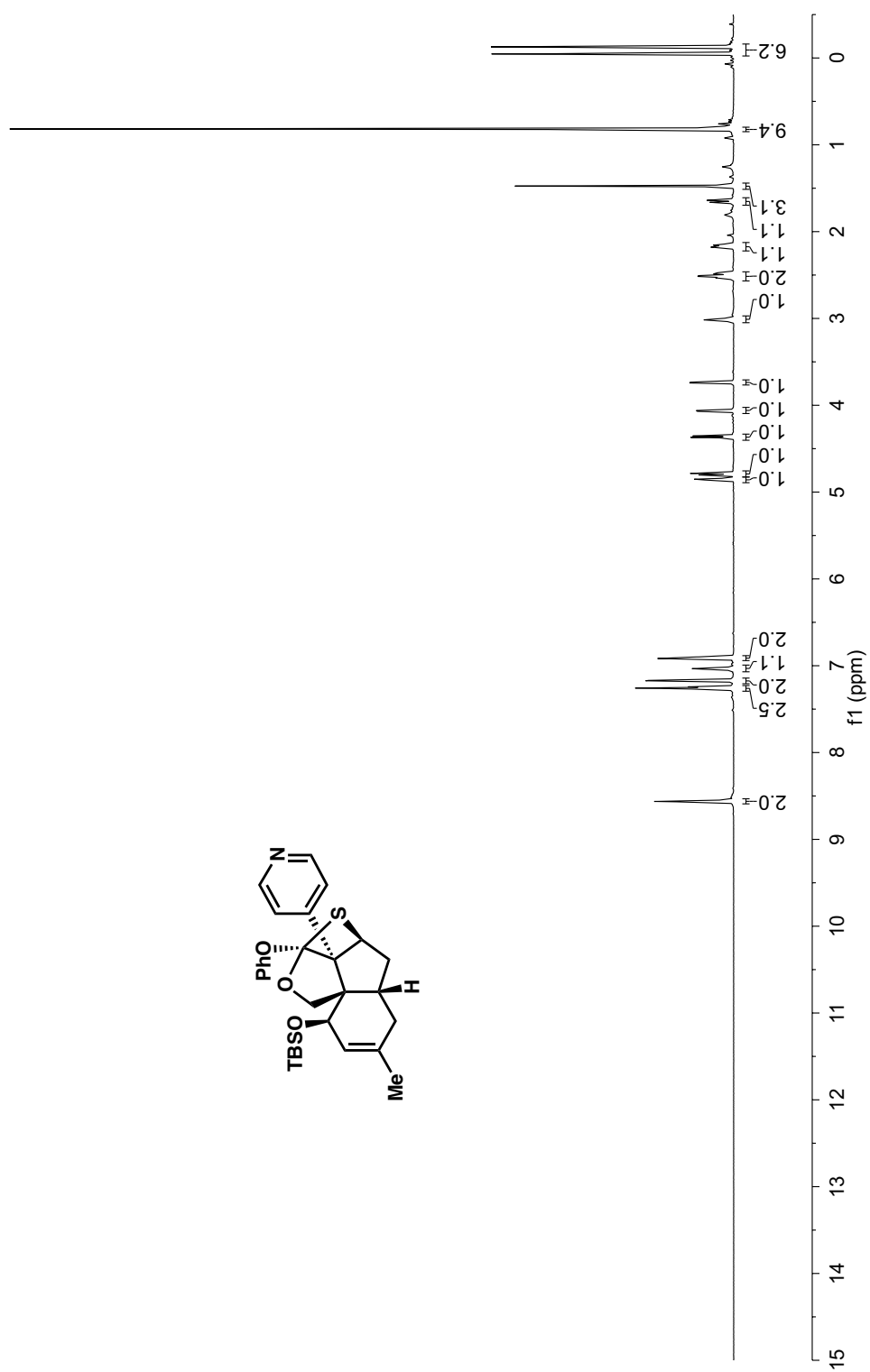


Figure A1.102 ¹H NMR of 2.128

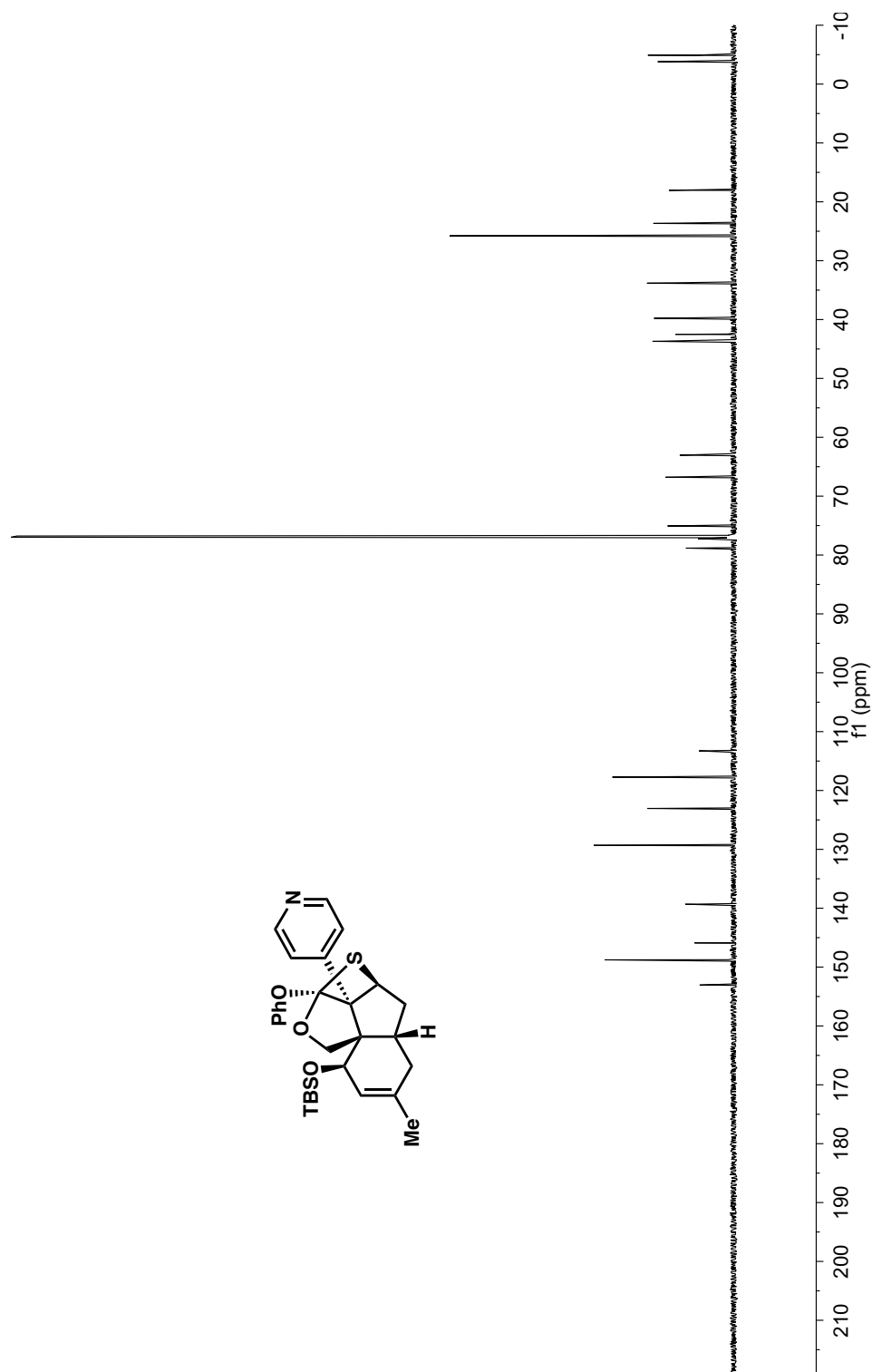


Figure A1.103 ^{13}C NMR of 2.128

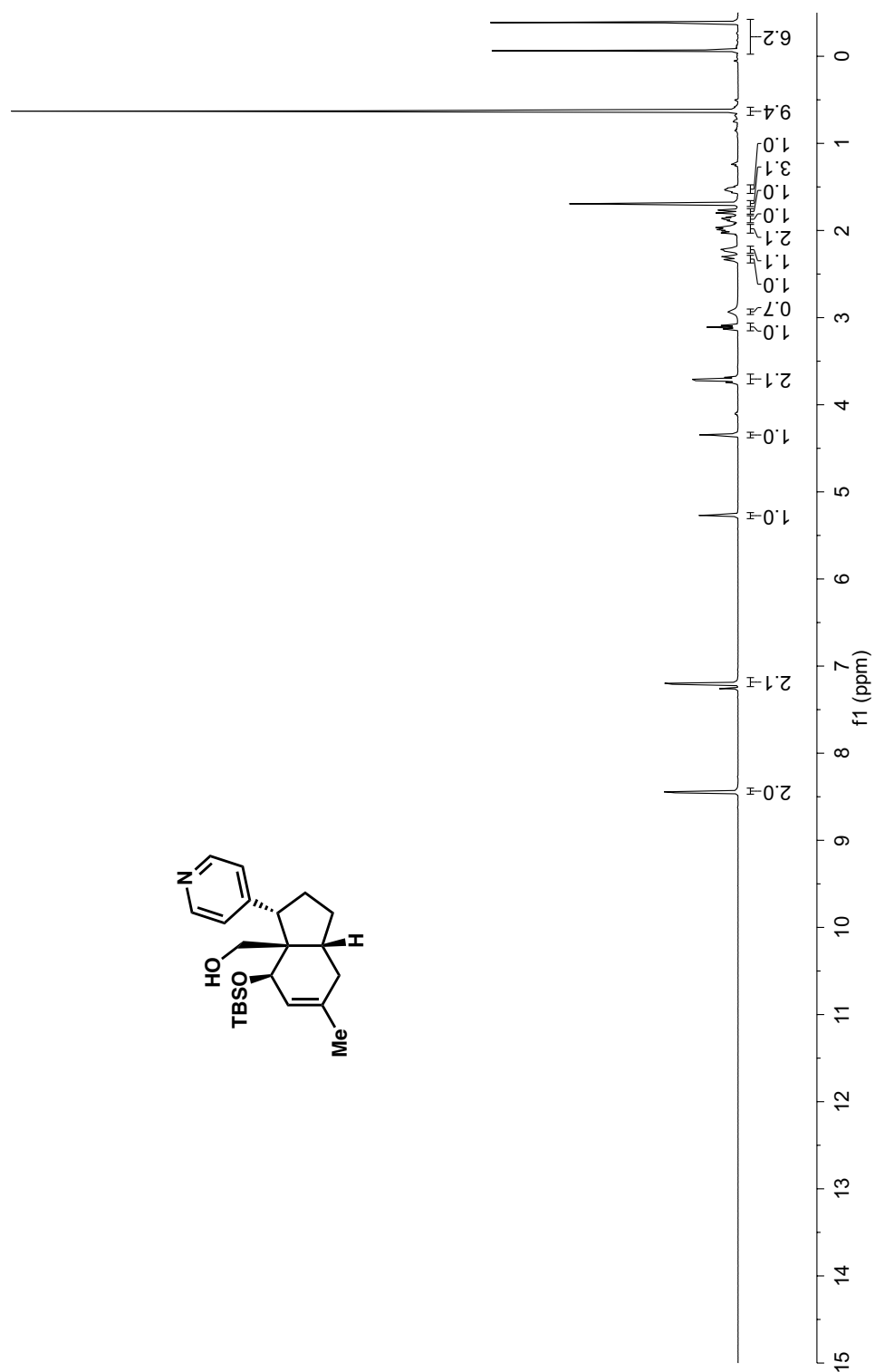


Figure A1.104 ¹H NMR of 2.129

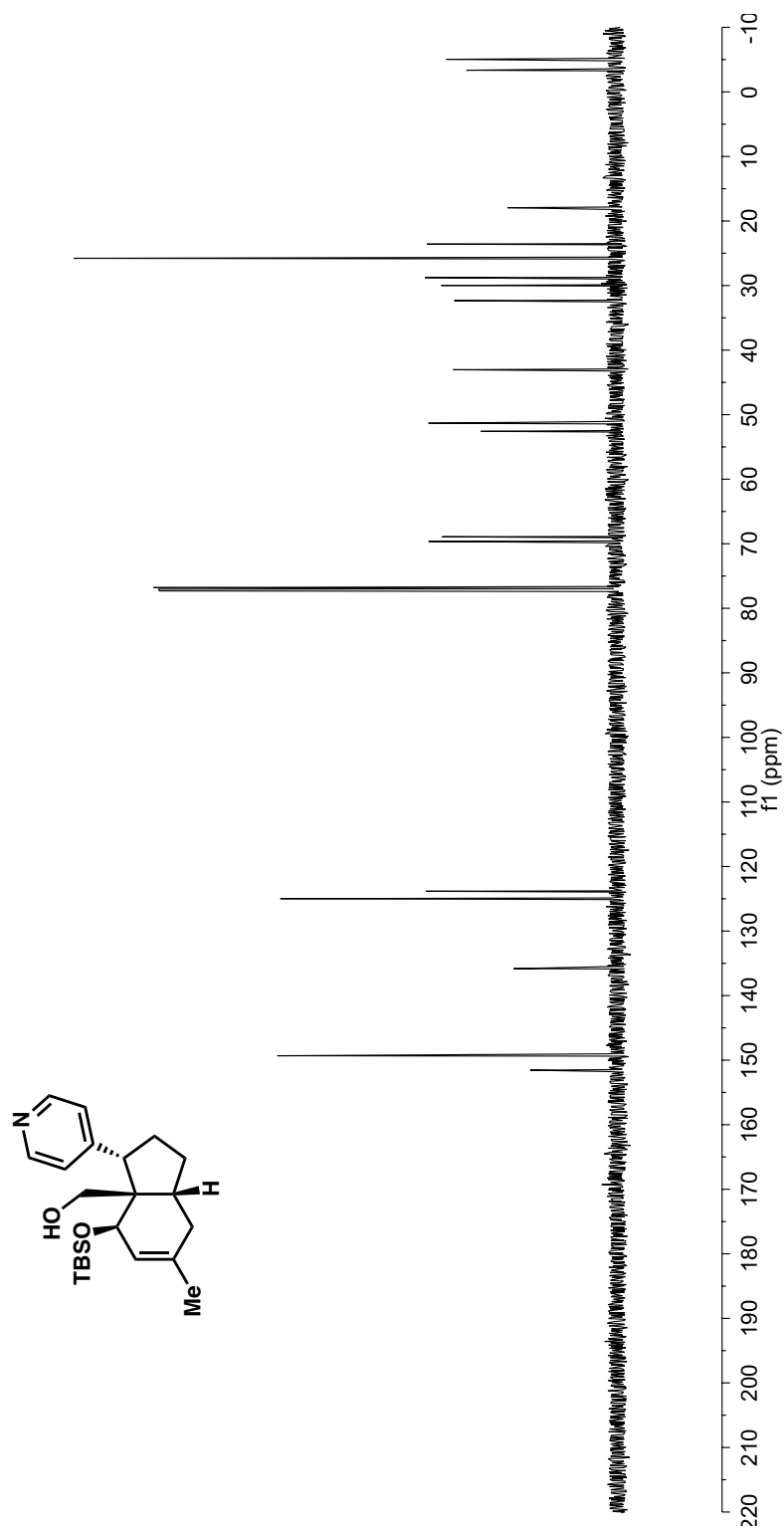


Figure A1.105 ^{13}C NMR of 2.129

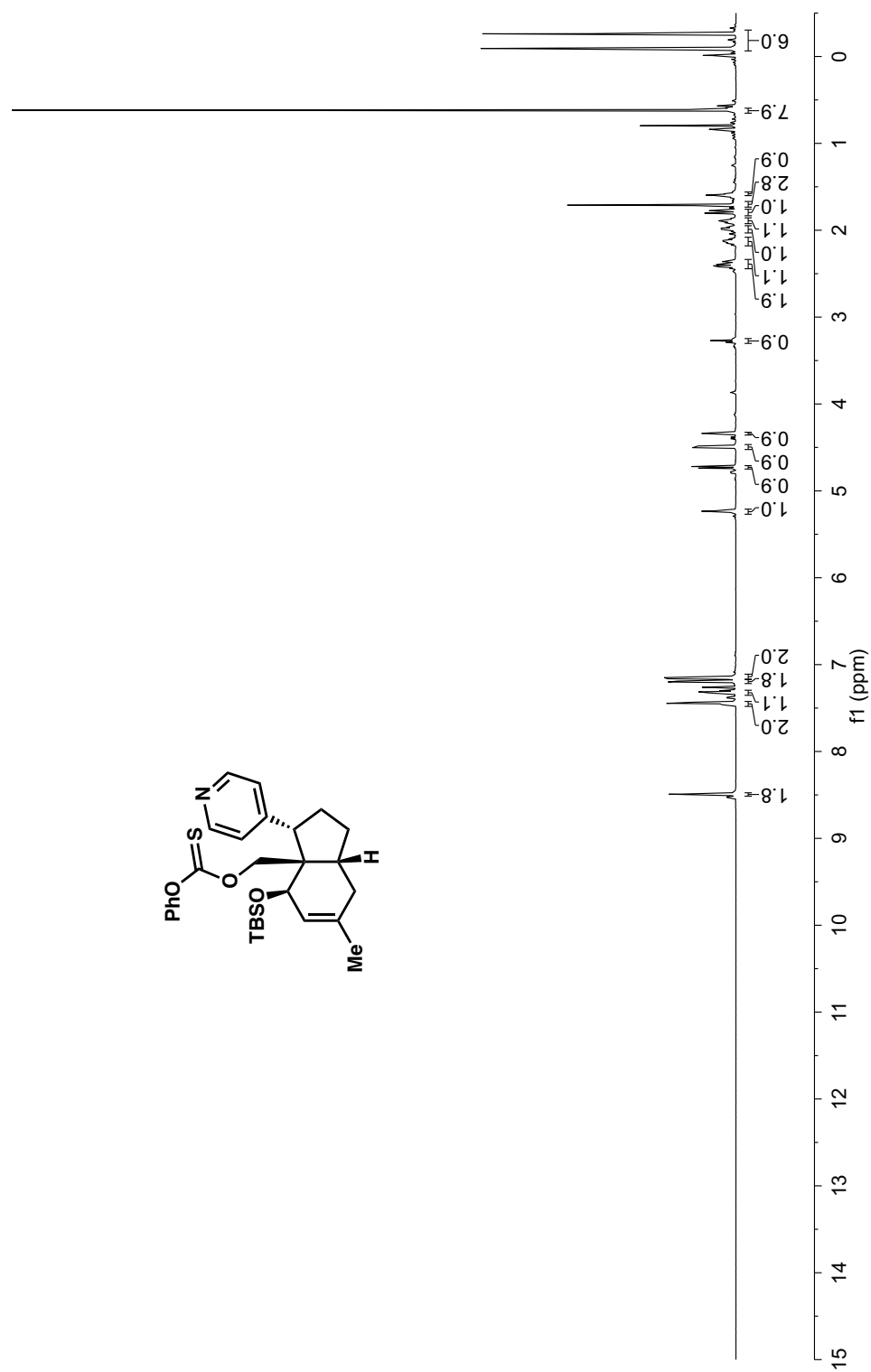


Figure A1.106 ^1H NMR of 2.130

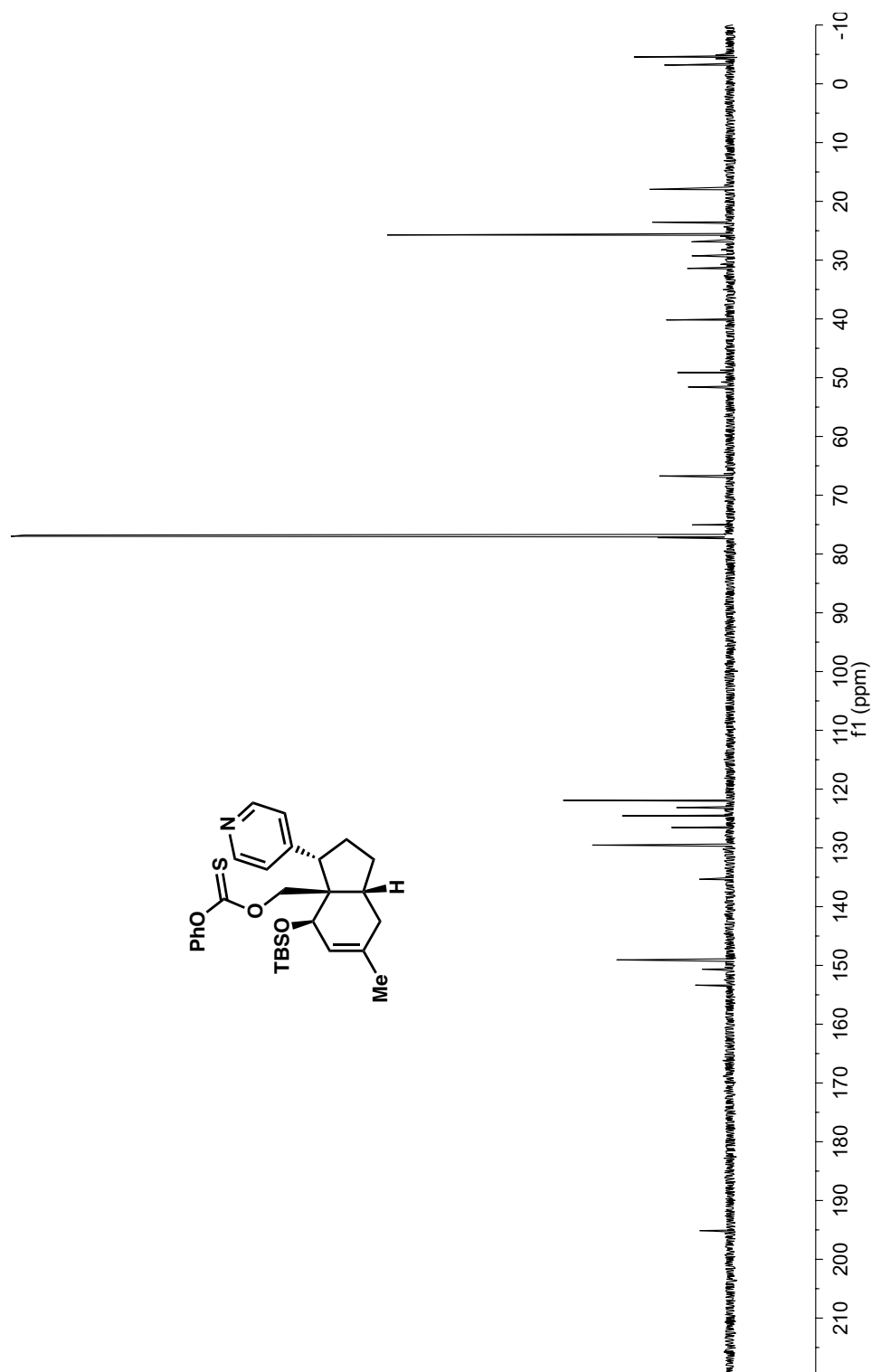


Figure A1.107 ^{13}C NMR of 2.130

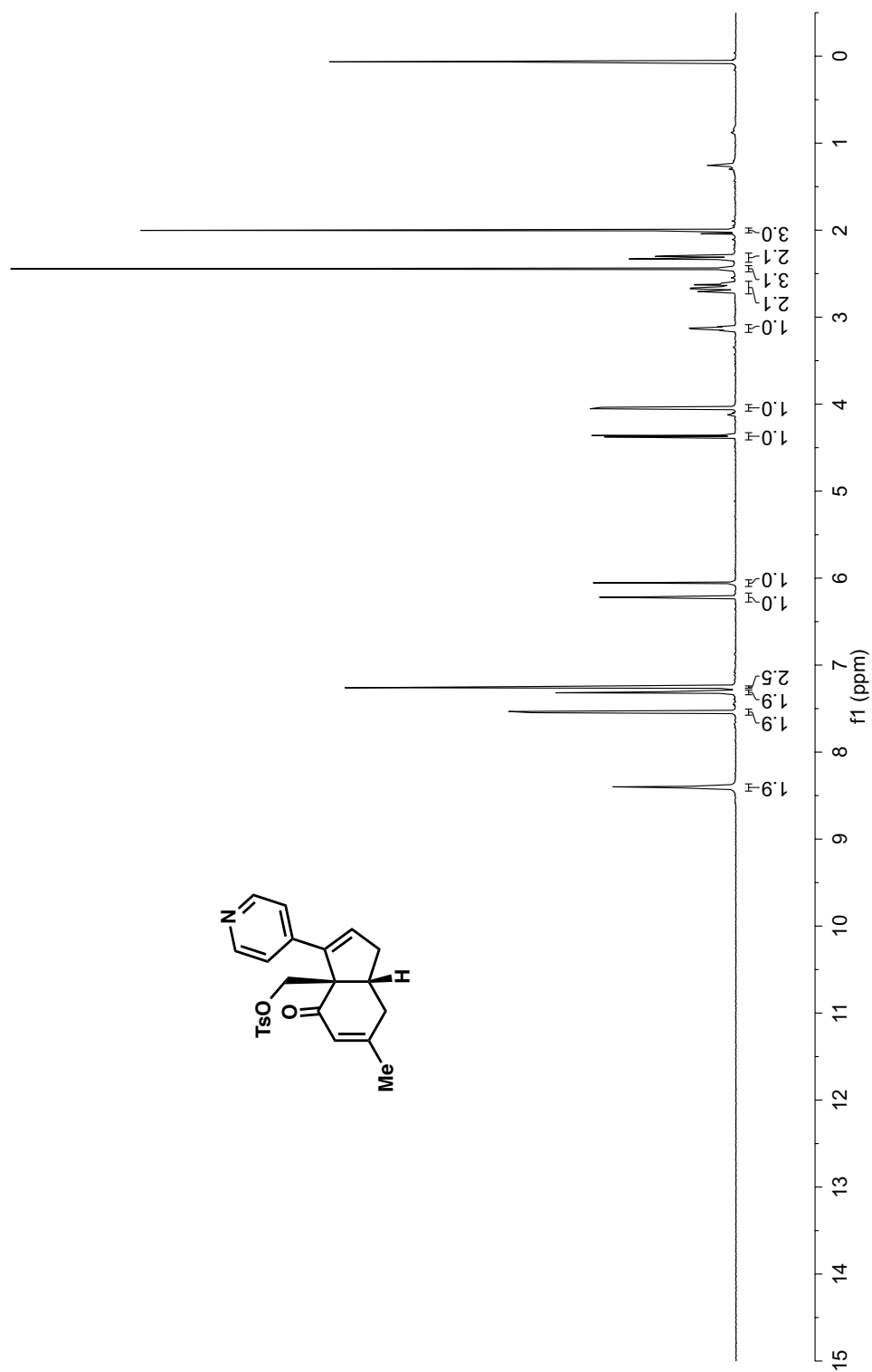


Figure A1.108 ^1H NMR of 2.155

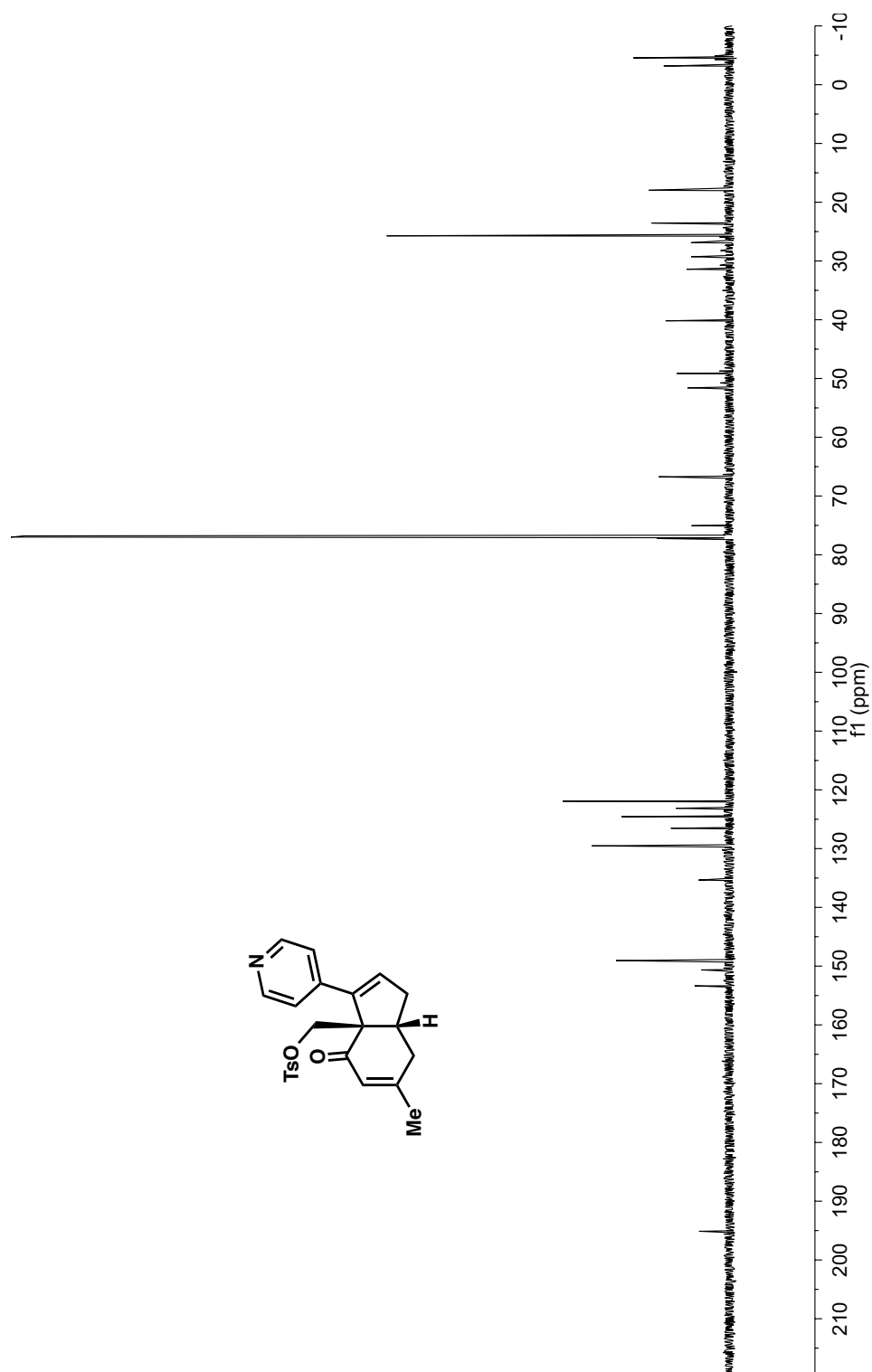


Figure A1.109 ^{13}C NMR of 2.155

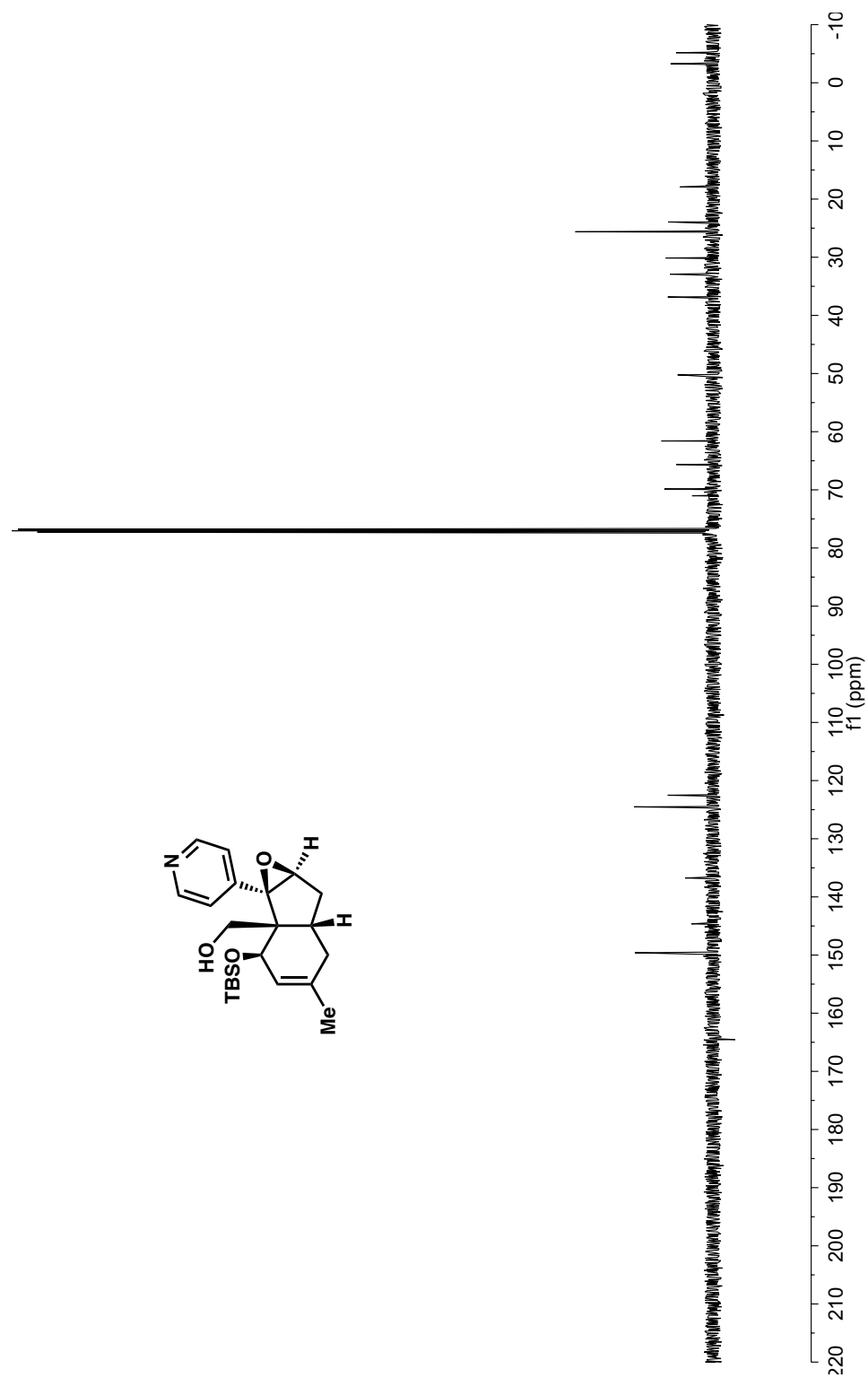


Figure A1.111 ^{13}C NMR of 2.142

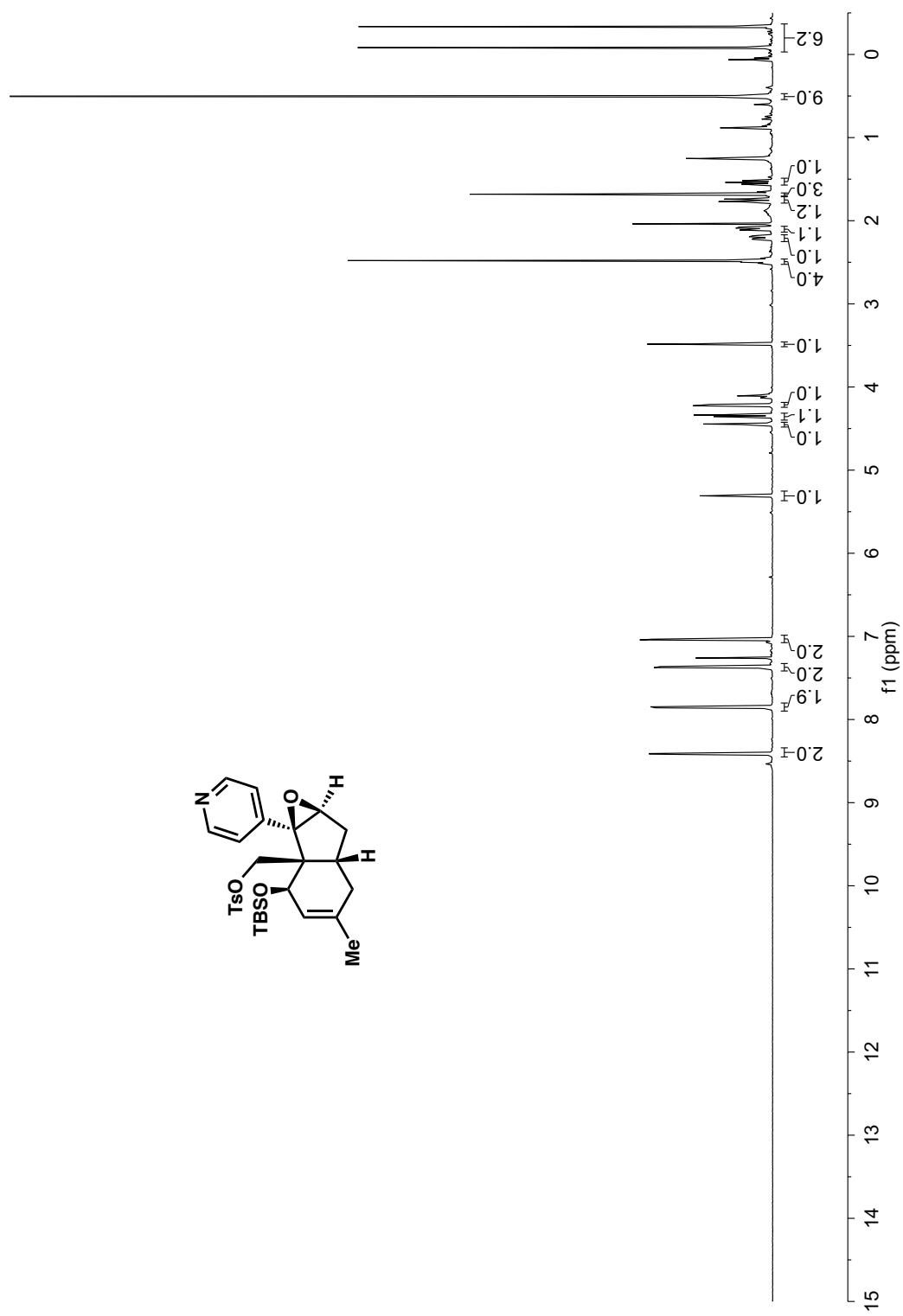


Figure A1.112 ^1H NMR of 2.145

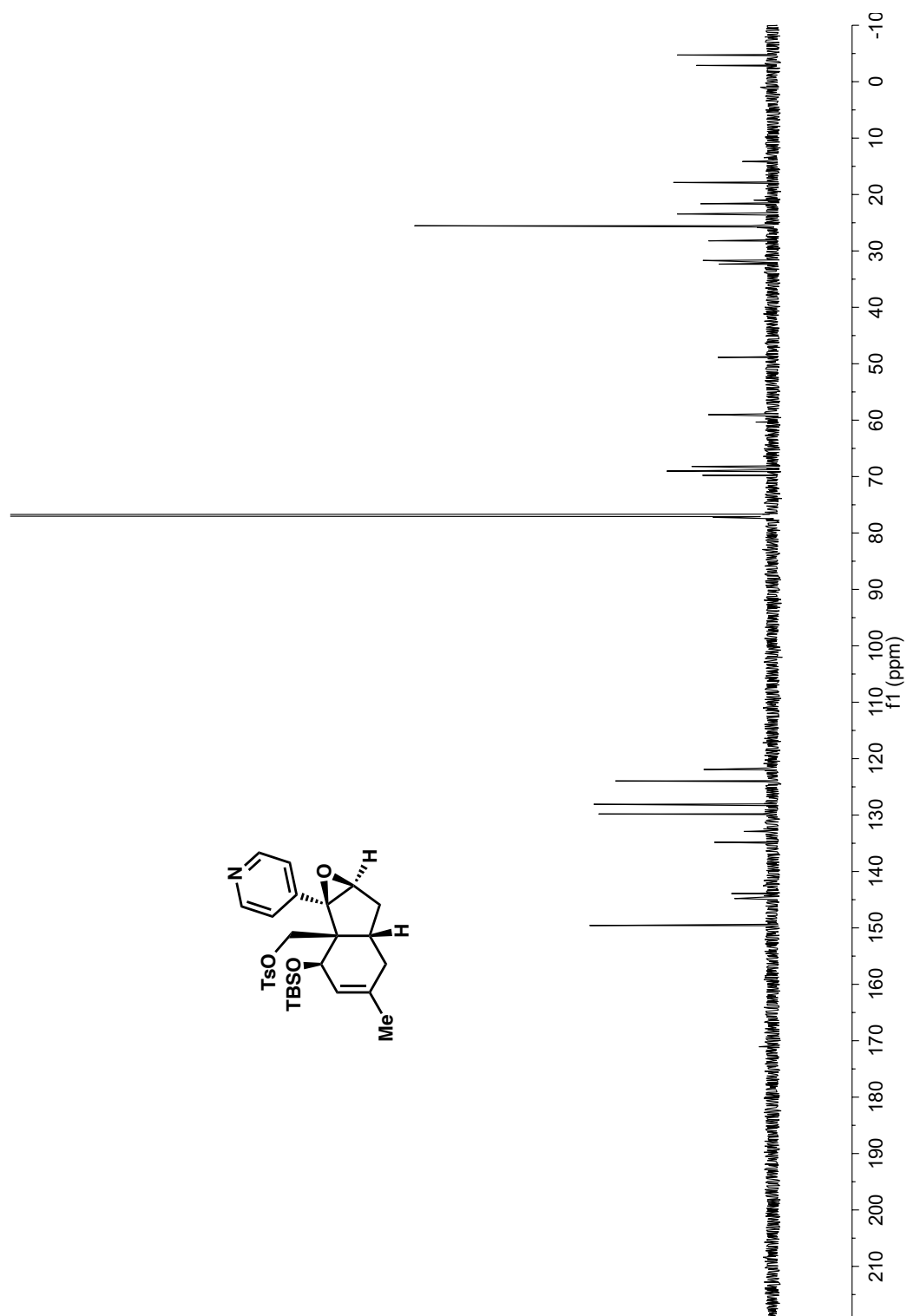


Figure A1.113 ^{13}C NMR of 2.145

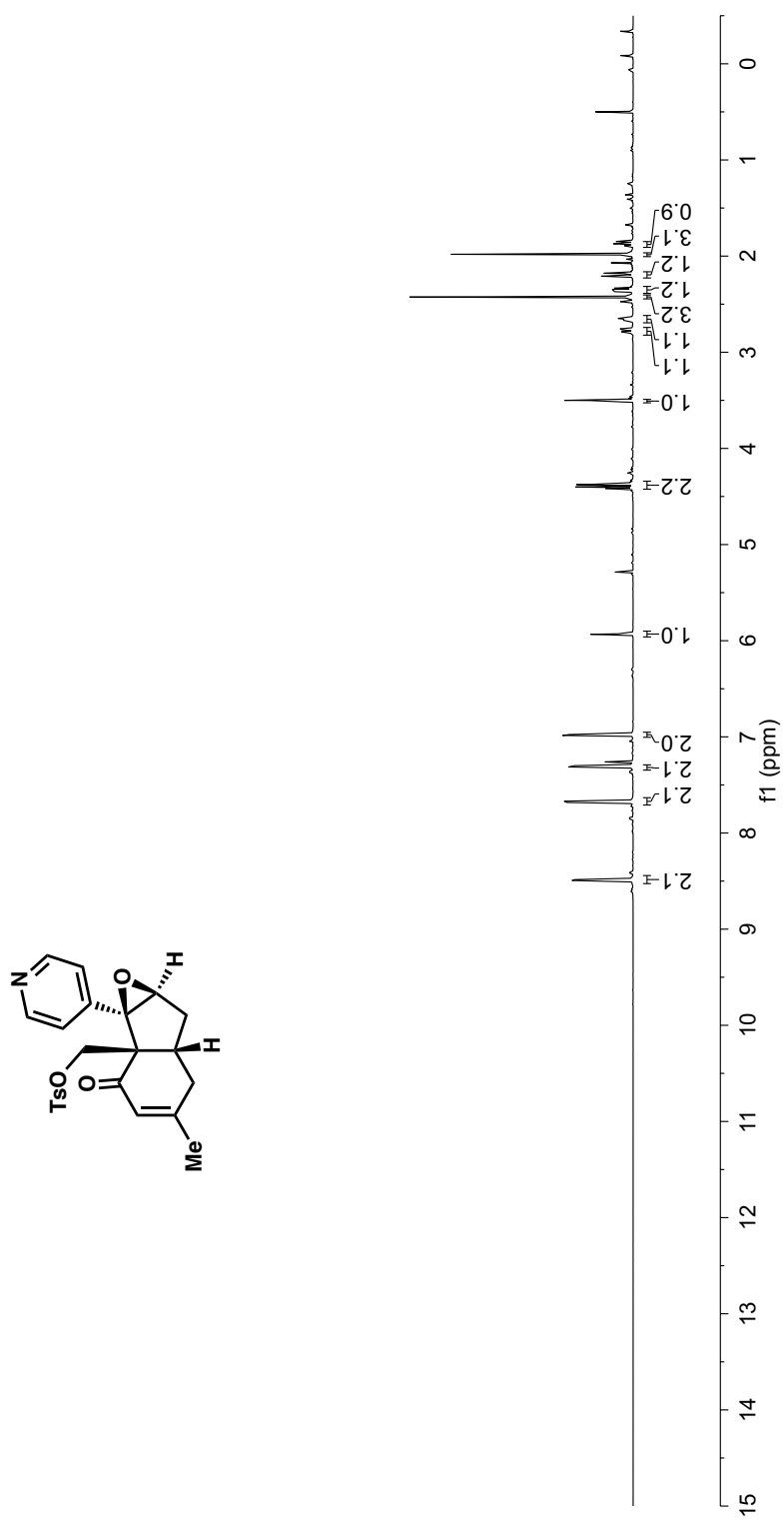


Figure A1.114 ^1H NMR of 2.146

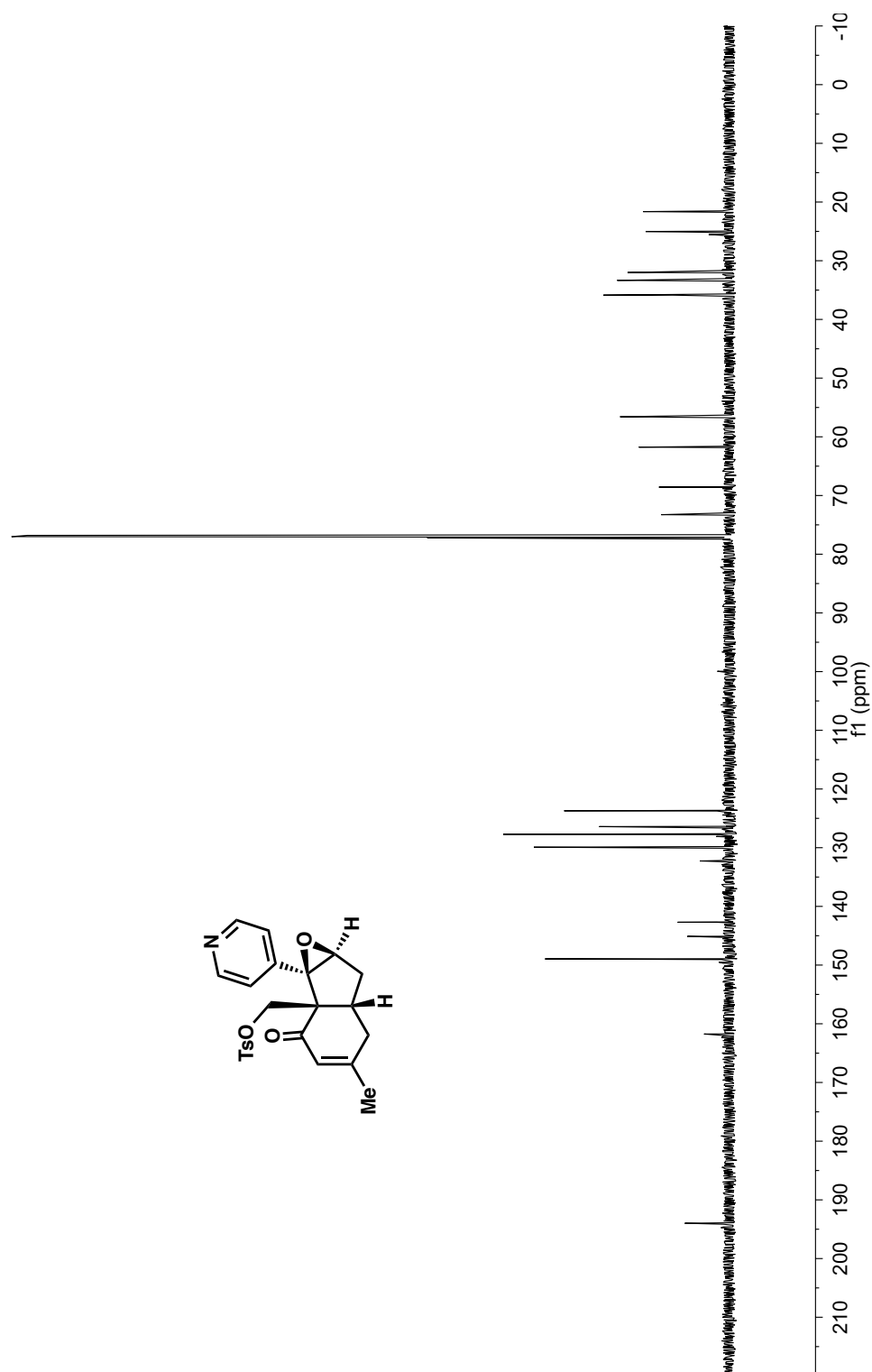


Figure A1.115 ^{13}C NMR of 2.146

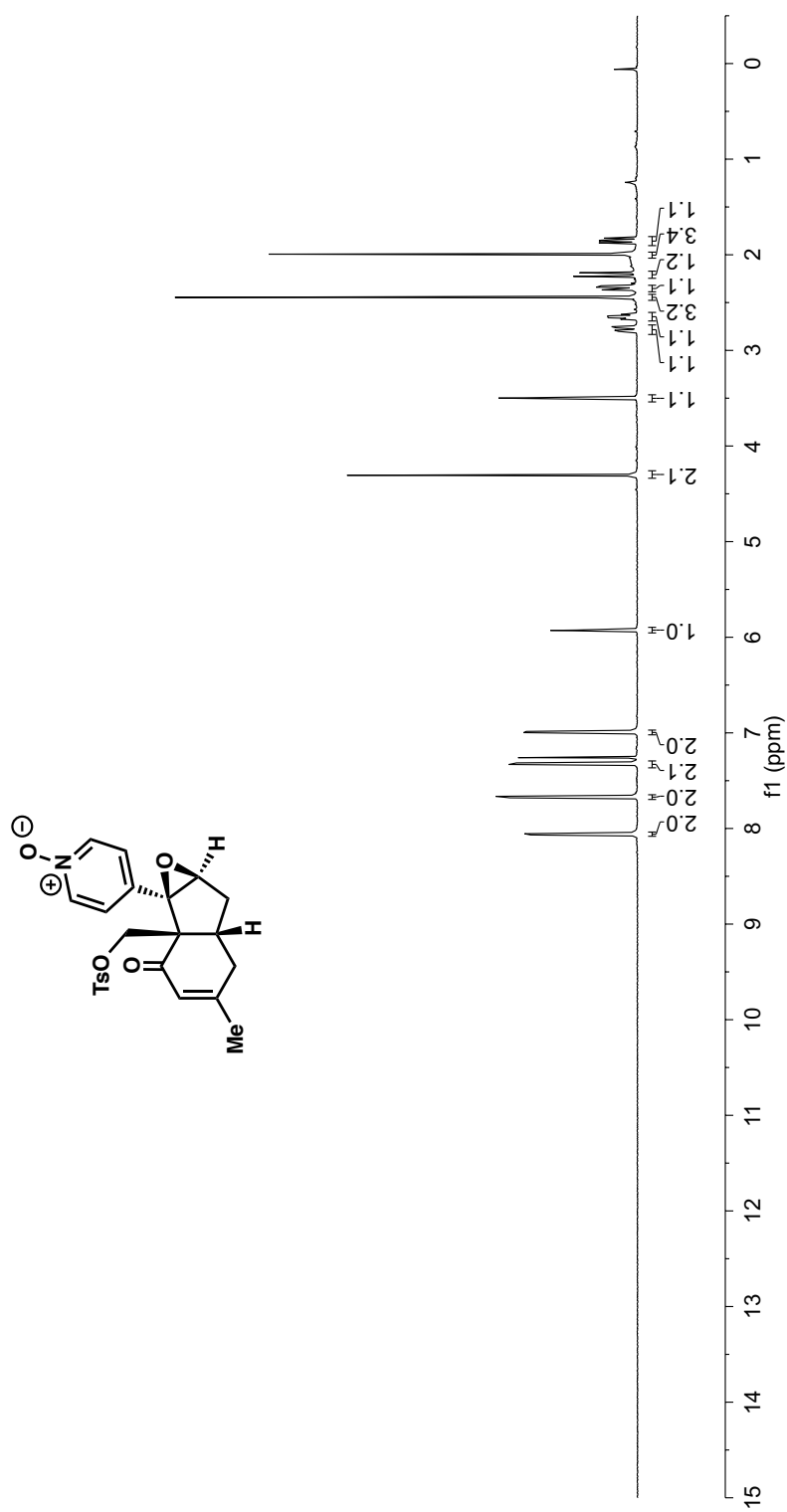


Figure A1.116 ^1H NMR of 2.147

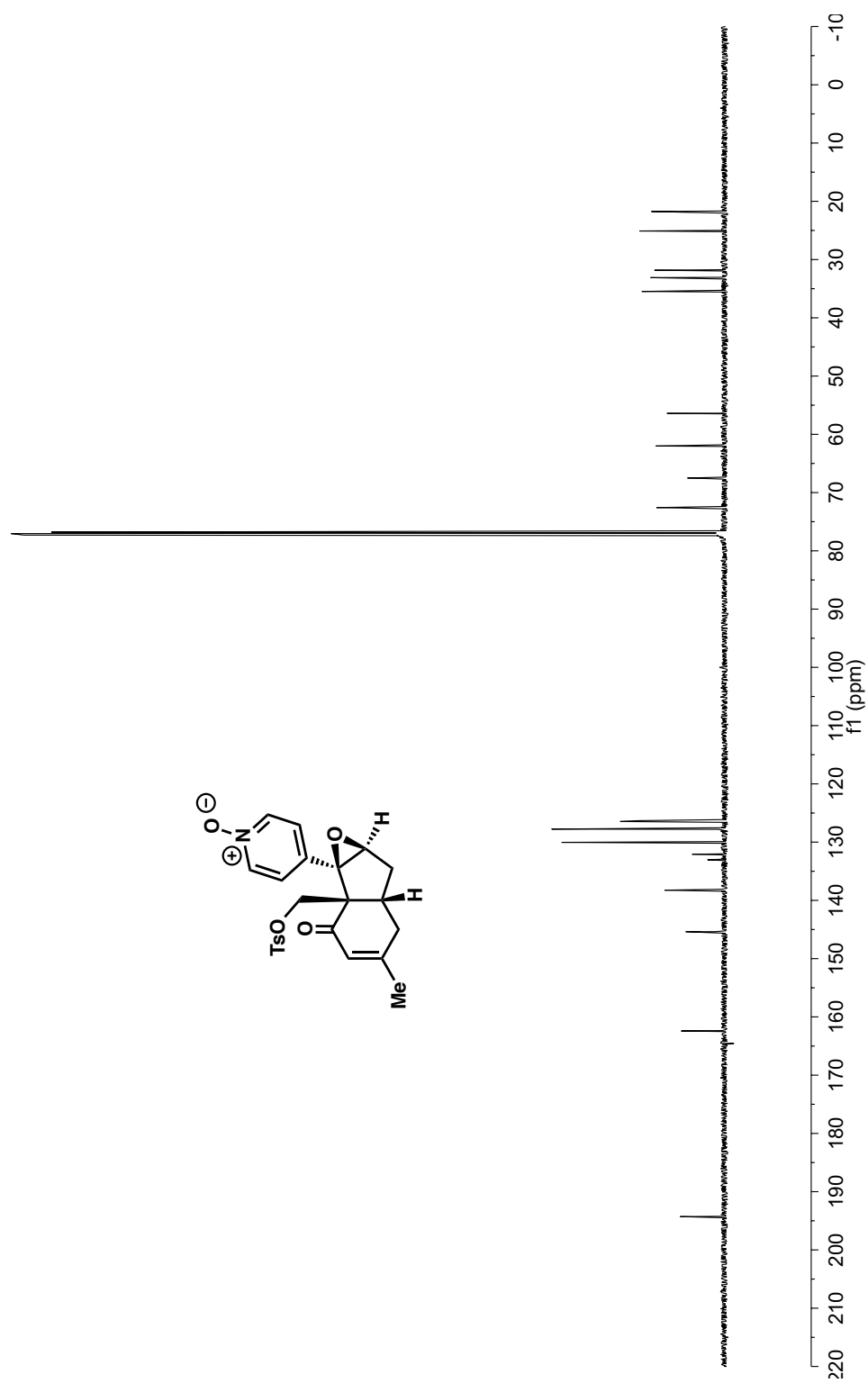


Figure A1.117 ^{13}C NMR of 2.147

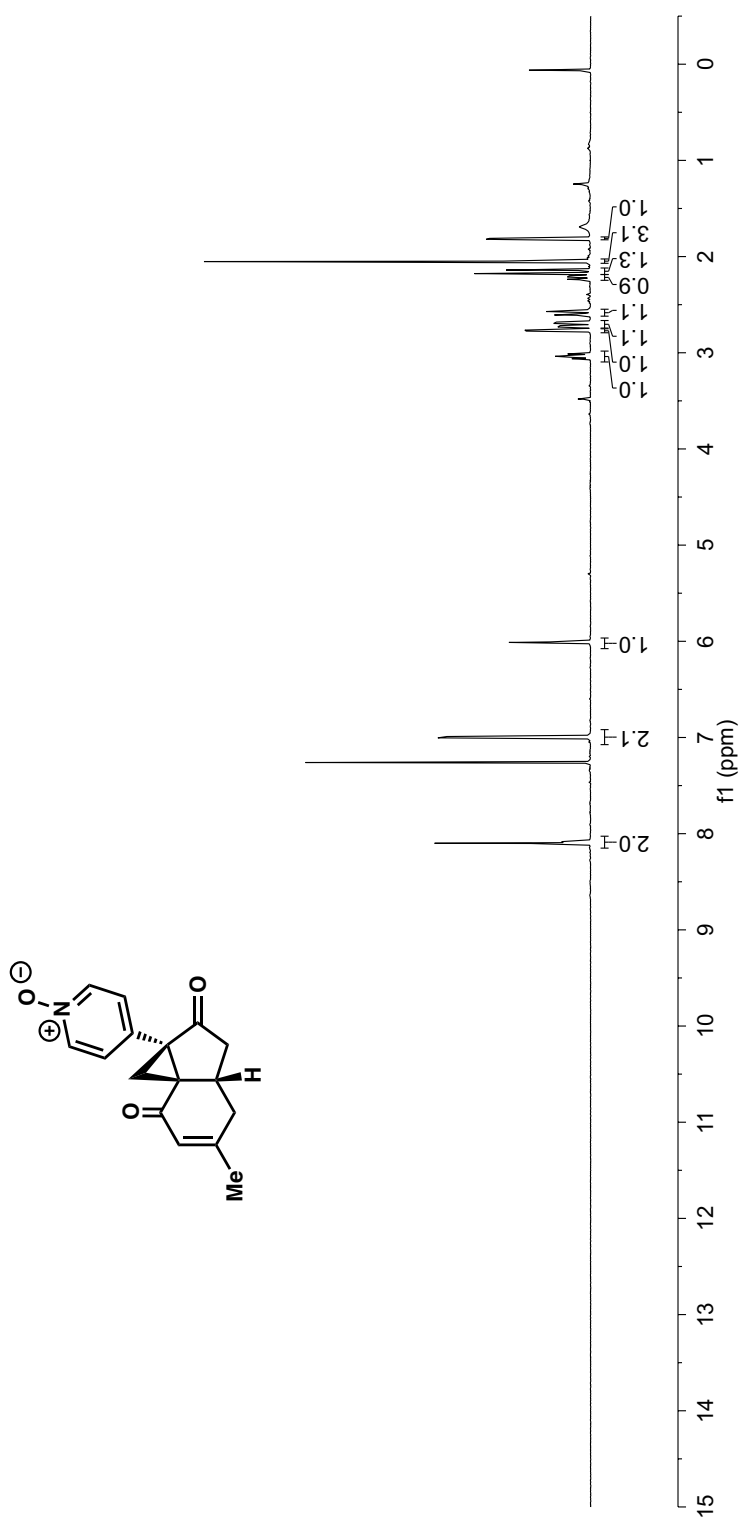


Figure A1.118 ^1H NMR of 2.150

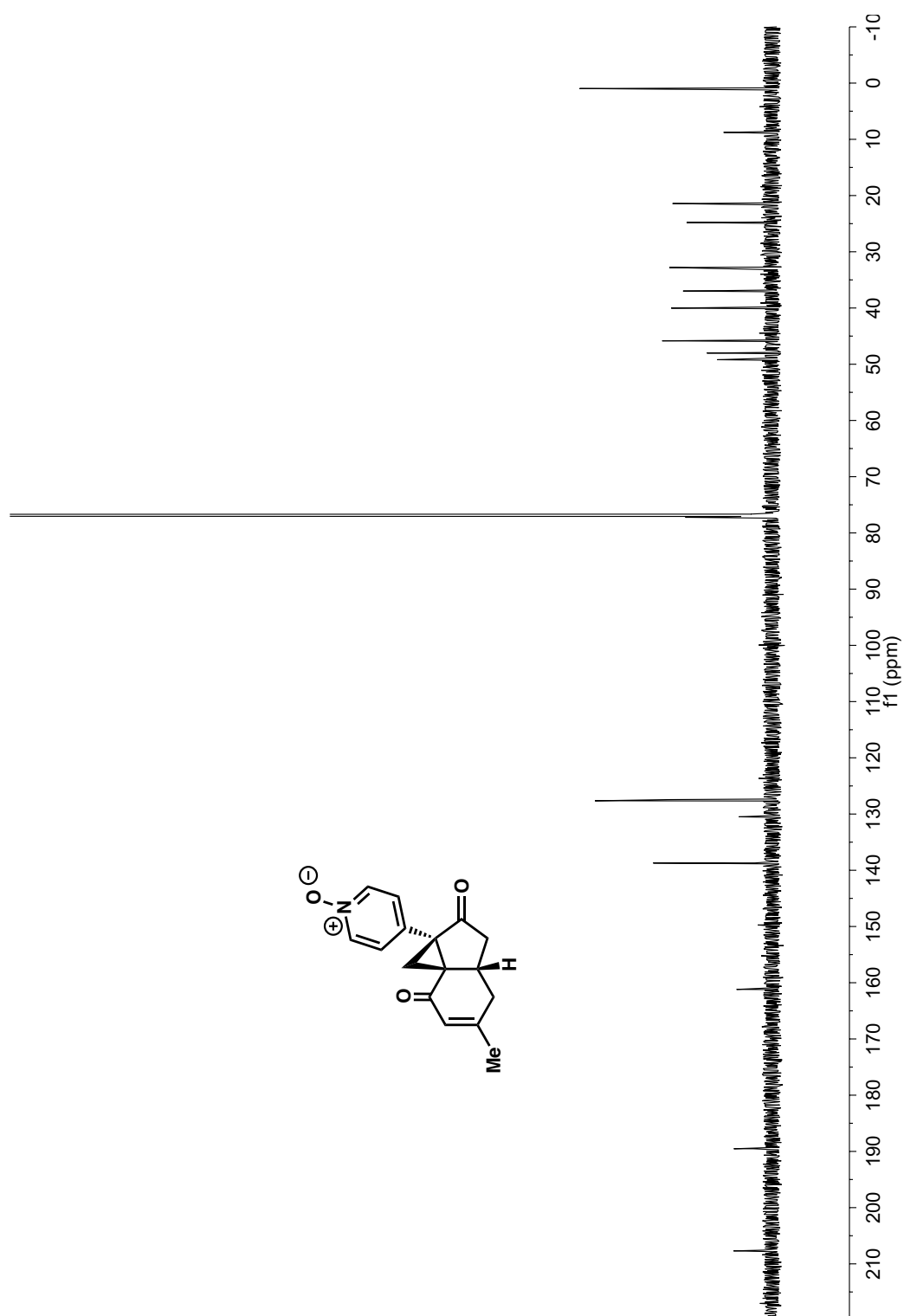


Figure A1.119 ¹³C NMR of 2.150

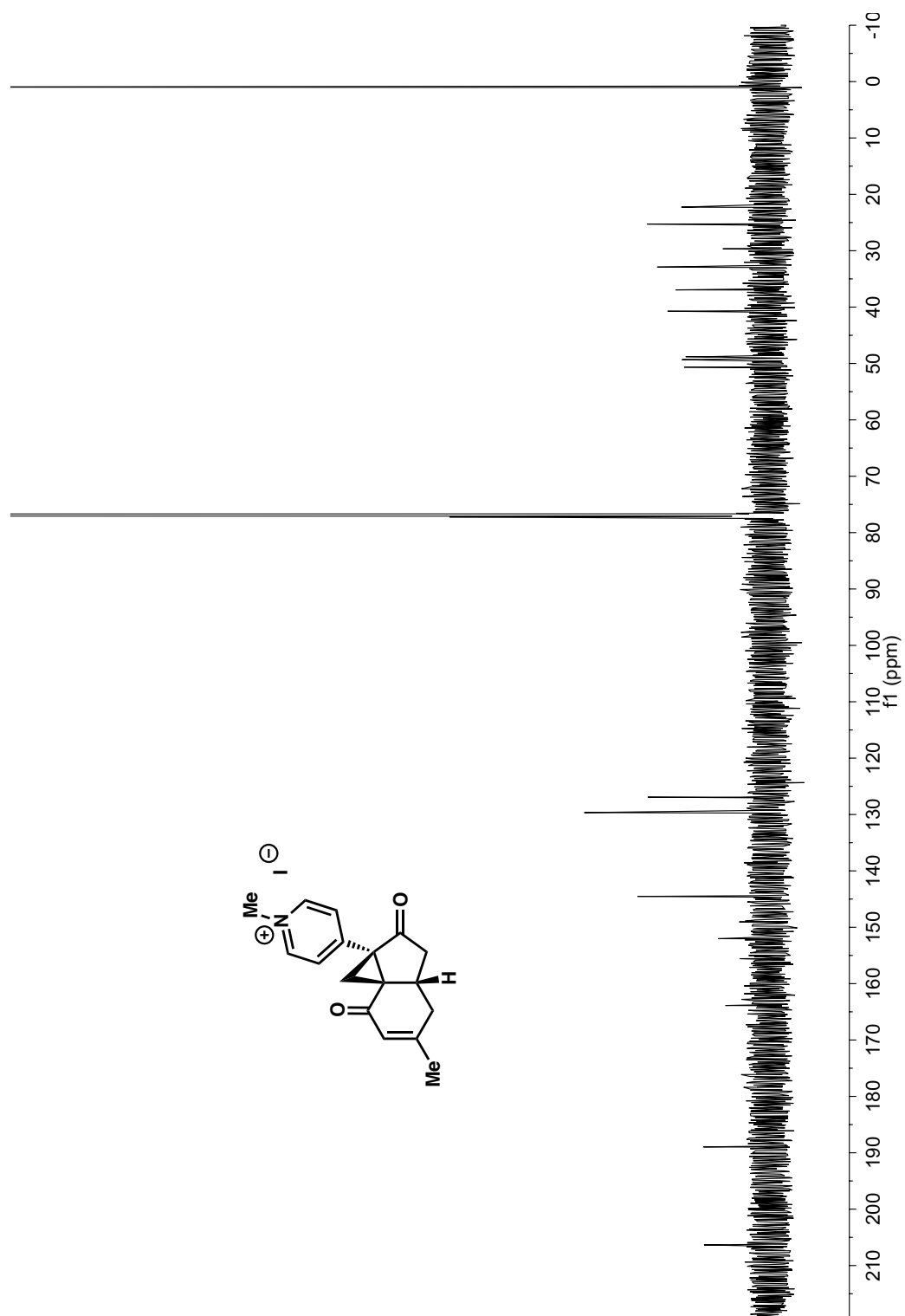
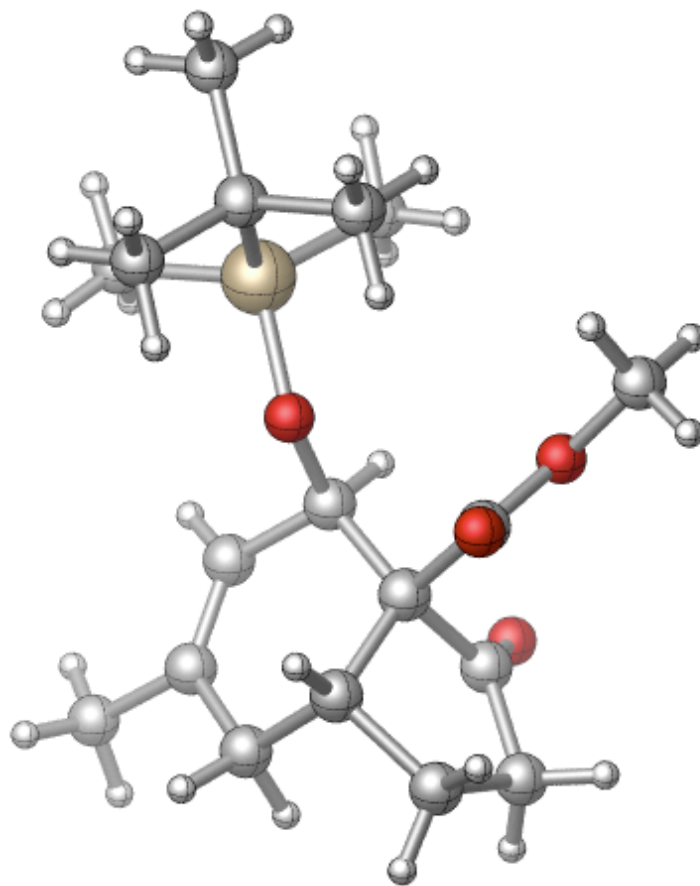


Figure A1.121 ^{13}C NMR of 2.158

X-ray Crystallography Data for Bicycle 2.111A (major diastereomer)



Crystal data and Structure Refinement for Bicycle 2.111A (major diastereomer)

A colorless prism 0.200 x 0.200 x 0.200 mm in size was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using phi and omega scans. Crystal-to-detector distance was 60 mm and exposure time was 10 seconds per frame using a scan width of 0.5°. Data collection was 99.9% complete to 25.000° in q . A total of 22218 reflections were collected covering the indices, $-8 \leq h \leq 8$, $-8 \leq k \leq 8$, $-24 \leq l \leq 24$. 3493 reflections were found to be symmetry independent, with an R_{int} of 0.0181. Indexing and unit cell refinement indicated a primitive, triclinic lattice. The space group was found to be $P -1$ (No. 2). The data were integrated using the Bruker SAINT software program and scaled using the SADABS software program. Solution by direct methods (SIR-2011) produced a complete heavy-atom phasing model consistent with the proposed structure. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2012). All hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2012.

Table 1. Crystal data and structure refinement for **2.111A**.

X-ray ID	sarpong43	
Sample/notebook ID	VLI-005B3	
Empirical formula	C18 H30 O4 Si	
Formula weight	338.51	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P -1	
Unit cell dimensions	a = 6.9205(7) Å	a = 81.6640(10)°.
	b = 7.0658(7) Å	b = 80.2810(10)°.
	c = 20.0779(19) Å	g = 80.8850(10)°.
Volume	948.40(16) Å ³	
Z	2	
Density (calculated)	1.185 Mg/m ³	
Absorption coefficient	0.140 mm ⁻¹	
F(000)	368	
Crystal size	0.200 x 0.200 x 0.200 mm ³	
Crystal color/habit	colorless prism	
Theta range for data collection	2.074 to 25.401°.	
Index ranges	-8 ≤ h ≤ 8, -8 ≤ k ≤ 8, -24 ≤ l ≤ 24	
Reflections collected	22218	
Independent reflections	3493 [R(int) = 0.0181]	
Completeness to theta = 25.000°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.862 and 0.788	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	3493 / 0 / 215	
Goodness-of-fit on F ²	1.026	
Final R indices [I > 2sigma(I)]	R1 = 0.0292, wR2 = 0.0751	
R indices (all data)	R1 = 0.0301, wR2 = 0.0760	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.334 and -0.241 e.Å ⁻³	

Table 2. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for **2.111A**. $U(\text{eq})$ is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	$U(\text{eq})$
C(1)	1994(2)	5695(2)	3388(1)	13(1)
C(2)	298(2)	6219(2)	2964(1)	14(1)
C(3)	-1279(2)	7715(2)	3253(1)	15(1)
C(4)	-1075(2)	8783(2)	3723(1)	16(1)
C(5)	803(2)	8596(2)	4026(1)	18(1)
C(6)	2620(2)	7367(2)	3674(1)	15(1)
C(7)	3921(2)	6322(2)	4210(1)	19(1)
C(8)	2930(2)	4525(2)	4523(1)	19(1)
C(9)	1496(2)	4349(2)	4048(1)	15(1)
C(10)	3757(2)	4637(2)	2953(1)	16(1)
C(11)	4799(2)	1833(2)	2405(1)	24(1)
C(12)	-292(2)	4236(2)	1582(1)	22(1)
C(13)	-2001(2)	8501(2)	1504(1)	21(1)
C(14)	2315(2)	7361(2)	866(1)	16(1)
C(15)	1669(2)	7265(2)	177(1)	24(1)
C(16)	4215(2)	5936(2)	930(1)	22(1)
C(17)	2738(2)	9414(2)	896(1)	23(1)
C(18)	-2744(2)	10212(2)	4013(1)	21(1)
O(1)	5317(1)	5206(1)	2744(1)	22(1)
O(2)	3301(1)	2946(1)	2840(1)	19(1)
O(3)	1158(1)	6890(1)	2282(1)	15(1)
O(4)	145(1)	3407(1)	4175(1)	21(1)
Si(1)	277(1)	6729(1)	1577(1)	13(1)

Table 3. Bond lengths [$\text{\AA}$] and angles [$^\circ$] for **2.111A**.

C(1)-C(2)	1.5319(15)	C(11)-H(11B)	0.9800
C(1)-C(10)	1.5324(15)	C(11)-H(11C)	0.9800
C(1)-C(6)	1.5350(15)	C(12)-Si(1)	1.8631(12)
C(1)-C(9)	1.5381(15)	C(12)-H(12A)	0.9800
C(2)-O(3)	1.4412(13)	C(12)-H(12B)	0.9800
C(2)-C(3)	1.4984(15)	C(12)-H(12C)	0.9800
C(2)-H(2)	1.0000	C(13)-Si(1)	1.8640(12)
C(3)-C(4)	1.3284(16)	C(13)-H(13A)	0.9800
C(3)-H(3)	0.9500	C(13)-H(13B)	0.9800
C(4)-C(18)	1.5052(16)	C(13)-H(13C)	0.9800
C(4)-C(5)	1.5061(16)	C(14)-C(17)	1.5355(17)
C(5)-C(6)	1.5385(16)	C(14)-C(16)	1.5357(16)
C(5)-H(5A)	0.9900	C(14)-C(15)	1.5394(15)
C(5)-H(5B)	0.9900	C(14)-Si(1)	1.8873(12)
C(6)-C(7)	1.5498(15)	C(15)-H(15A)	0.9800
C(6)-H(6)	1.0000	C(15)-H(15B)	0.9800
C(7)-C(8)	1.5417(17)	C(15)-H(15C)	0.9800
C(7)-H(7A)	0.9900	C(16)-H(16A)	0.9800
C(7)-H(7B)	0.9900	C(16)-H(16B)	0.9800
C(8)-C(9)	1.5172(16)	C(16)-H(16C)	0.9800
C(8)-H(8A)	0.9900	C(17)-H(17A)	0.9800
C(8)-H(8B)	0.9900	C(17)-H(17B)	0.9800
C(9)-O(4)	1.2040(14)	C(17)-H(17C)	0.9800
C(10)-O(1)	1.1996(14)	C(18)-H(18A)	0.9800
C(10)-O(2)	1.3427(14)	C(18)-H(18B)	0.9800
C(11)-O(2)	1.4459(14)	C(18)-H(18C)	0.9800
C(11)-H(11A)	0.9800	O(3)-Si(1)	1.6583(8)
C(2)-C(1)-C(10)	107.68(9)	O(3)-C(2)-C(3)	111.28(9)
C(2)-C(1)-C(6)	116.38(9)	O(3)-C(2)-C(1)	106.90(8)
C(10)-C(1)-C(6)	110.82(9)	C(3)-C(2)-C(1)	112.04(9)
C(2)-C(1)-C(9)	113.61(9)	O(3)-C(2)-H(2)	108.8
C(10)-C(1)-C(9)	107.51(9)	C(3)-C(2)-H(2)	108.8
C(6)-C(1)-C(9)	100.47(8)	C(1)-C(2)-H(2)	108.8

C(4)-C(3)-C(2)	124.66(10)	O(2)-C(11)-H(11A)	109.5
C(4)-C(3)-H(3)	117.7	O(2)-C(11)-H(11B)	109.5
C(2)-C(3)-H(3)	117.7	H(11A)-C(11)-H(11B)	109.5
C(3)-C(4)-C(18)	122.17(11)	O(2)-C(11)-H(11C)	109.5
C(3)-C(4)-C(5)	122.72(10)	H(11A)-C(11)-H(11C)	109.5
C(18)-C(4)-C(5)	115.06(10)	H(11B)-C(11)-H(11C)	109.5
C(4)-C(5)-C(6)	116.22(9)	Si(1)-C(12)-H(12A)	109.5
C(4)-C(5)-H(5A)	108.2	Si(1)-C(12)-H(12B)	109.5
C(6)-C(5)-H(5A)	108.2	H(12A)-C(12)-H(12B)	109.5
C(4)-C(5)-H(5B)	108.2	Si(1)-C(12)-H(12C)	109.5
C(6)-C(5)-H(5B)	108.2	H(12A)-C(12)-H(12C)	109.5
H(5A)-C(5)-H(5B)	107.4	H(12B)-C(12)-H(12C)	109.5
C(1)-C(6)-C(5)	110.72(9)	Si(1)-C(13)-H(13A)	109.5
C(1)-C(6)-C(7)	103.23(9)	Si(1)-C(13)-H(13B)	109.5
C(5)-C(6)-C(7)	109.63(9)	H(13A)-C(13)-H(13B)	109.5
C(1)-C(6)-H(6)	111.0	Si(1)-C(13)-H(13C)	109.5
C(5)-C(6)-H(6)	111.0	H(13A)-C(13)-H(13C)	109.5
C(7)-C(6)-H(6)	111.0	H(13B)-C(13)-H(13C)	109.5
C(8)-C(7)-C(6)	104.53(9)	C(17)-C(14)-C(16)	109.17(10)
C(8)-C(7)-H(7A)	110.8	C(17)-C(14)-C(15)	109.37(10)
C(6)-C(7)-H(7A)	110.8	C(16)-C(14)-C(15)	108.67(9)
C(8)-C(7)-H(7B)	110.8	C(17)-C(14)-Si(1)	109.49(8)
C(6)-C(7)-H(7B)	110.8	C(16)-C(14)-Si(1)	110.61(8)
H(7A)-C(7)-H(7B)	108.9	C(15)-C(14)-Si(1)	109.51(8)
C(9)-C(8)-C(7)	105.47(9)	C(14)-C(15)-H(15A)	109.5
C(9)-C(8)-H(8A)	110.6	C(14)-C(15)-H(15B)	109.5
C(7)-C(8)-H(8A)	110.6	H(15A)-C(15)-H(15B)	109.5
C(9)-C(8)-H(8B)	110.6	C(14)-C(15)-H(15C)	109.5
C(7)-C(8)-H(8B)	110.6	H(15A)-C(15)-H(15C)	109.5
H(8A)-C(8)-H(8B)	108.8	H(15B)-C(15)-H(15C)	109.5
O(4)-C(9)-C(8)	126.50(10)	C(14)-C(16)-H(16A)	109.5
O(4)-C(9)-C(1)	125.80(10)	C(14)-C(16)-H(16B)	109.5
C(8)-C(9)-C(1)	107.61(9)	H(16A)-C(16)-H(16B)	109.5
O(1)-C(10)-O(2)	124.37(10)	C(14)-C(16)-H(16C)	109.5
O(1)-C(10)-C(1)	126.06(10)	H(16A)-C(16)-H(16C)	109.5
O(2)-C(10)-C(1)	109.57(9)	H(16B)-C(16)-H(16C)	109.5

C(14)-C(17)-H(17A)	109.5
C(14)-C(17)-H(17B)	109.5
H(17A)-C(17)-H(17B)	109.5
C(14)-C(17)-H(17C)	109.5
H(17A)-C(17)-H(17C)	109.5
H(17B)-C(17)-H(17C)	109.5
C(4)-C(18)-H(18A)	109.5
C(4)-C(18)-H(18B)	109.5
H(18A)-C(18)-H(18B)	109.5
C(4)-C(18)-H(18C)	109.5
H(18A)-C(18)-H(18C)	109.5
H(18B)-C(18)-H(18C)	109.5
C(10)-O(2)-C(11)	115.59(9)
C(2)-O(3)-Si(1)	125.50(7)
O(3)-Si(1)-C(12)	110.01(5)
O(3)-Si(1)-C(13)	110.30(5)
C(12)-Si(1)-C(13)	109.82(6)
O(3)-Si(1)-C(14)	104.48(5)
C(12)-Si(1)-C(14)	111.99(5)
C(13)-Si(1)-C(14)	110.13(5)

Table 4. Anisotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for **2.111A**. The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2} U^{11} + \dots + 2 h k a^* b^* U^{12}]$

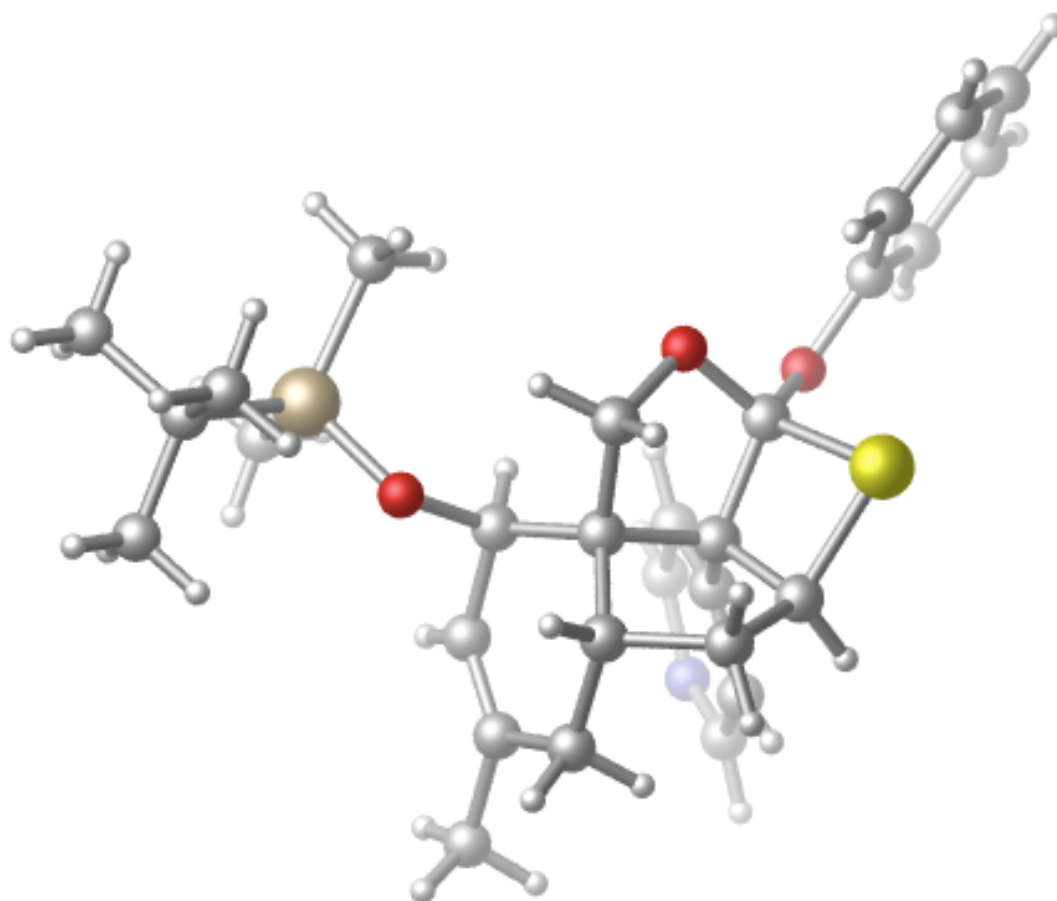
	U ¹¹	U ²²	U ³³	U ²³	U ¹³	U ¹²
C(1)	14(1)	14(1)	11(1)	-1(1)	-1(1)	-2(1)
C(2)	15(1)	16(1)	10(1)	-1(1)	-1(1)	-5(1)
C(3)	13(1)	18(1)	14(1)	0(1)	-1(1)	-2(1)
C(4)	17(1)	14(1)	15(1)	1(1)	0(1)	-3(1)
C(5)	22(1)	14(1)	18(1)	-4(1)	-6(1)	-2(1)
C(6)	16(1)	16(1)	14(1)	0(1)	-4(1)	-6(1)
C(7)	18(1)	23(1)	16(1)	-3(1)	-5(1)	-3(1)
C(8)	21(1)	21(1)	13(1)	0(1)	-3(1)	1(1)
C(9)	18(1)	11(1)	13(1)	-3(1)	1(1)	2(1)
C(10)	17(1)	18(1)	10(1)	1(1)	-4(1)	0(1)
C(11)	28(1)	21(1)	18(1)	-4(1)	2(1)	7(1)
C(12)	25(1)	22(1)	21(1)	-6(1)	-3(1)	-5(1)
C(13)	16(1)	26(1)	20(1)	-4(1)	-4(1)	3(1)
C(14)	17(1)	20(1)	11(1)	-2(1)	-2(1)	1(1)
C(15)	26(1)	32(1)	12(1)	-3(1)	-4(1)	2(1)
C(16)	17(1)	28(1)	17(1)	-3(1)	0(1)	2(1)
C(17)	24(1)	24(1)	19(1)	0(1)	0(1)	-5(1)
C(18)	21(1)	20(1)	22(1)	-6(1)	-1(1)	-1(1)
O(1)	15(1)	31(1)	19(1)	-4(1)	1(1)	-4(1)
O(2)	21(1)	17(1)	18(1)	-5(1)	2(1)	1(1)
O(3)	15(1)	20(1)	9(1)	-1(1)	-1(1)	-3(1)
O(4)	26(1)	16(1)	19(1)	-2(1)	2(1)	-9(1)
Si(1)	13(1)	16(1)	11(1)	-3(1)	-2(1)	0(1)

Table 5. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for **2.111A**.

	x	y	z	U(eq)
H(2)	-302	5029	2952	16
H(3)	-2514	7915	3088	18
H(5A)	539	8031	4508	21
H(5B)	1141	9908	4022	21
H(6)	3398	8179	3308	18
H(7A)	5296	5946	3993	22
H(7B)	3940	7162	4563	22
H(8A)	3931	3359	4550	22
H(8B)	2218	4691	4986	22
H(11A)	5067	2586	1957	36
H(11B)	4330	633	2352	36
H(11C)	6017	1525	2610	36
H(12A)	891	3306	1647	33
H(12B)	-705	4123	1148	33
H(12C)	-1362	3969	1955	33
H(13A)	-3082	8100	1851	32
H(13B)	-2373	8555	1051	32
H(13C)	-1747	9781	1571	32
H(15A)	438	8145	134	36
H(15B)	1451	5943	149	36
H(15C)	2705	7645	-193	36
H(16A)	5260	6295	561	32
H(16B)	3960	4627	902	32
H(16C)	4637	5978	1369	32
H(17A)	3127	9484	1338	34
H(17B)	1544	10334	837	34
H(17C)	3813	9733	532	34
H(18A)	-3957	10094	3840	32

H(18B)	-2410	11524	3877	32
H(18C)	-2950	9947	4511	32

X-ray Crystallography Data for Tetracycline 2.128



Crystal data and Structure Refinement for Tetracycle 2.128

A colorless plate 0.050 x 0.040 x 0.020 mm in size was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using phi and omega scans. Crystal-to-detector distance was 60 mm and exposure time was 5 seconds per frame using a scan width of 1.0°. Data collection was 99.8% complete to 67.000° in q . A total of 48163 reflections were collected covering the indices, $-15 \leq h \leq 17$, $-15 \leq k \leq 15$, $-19 \leq l \leq 16$. 4986 reflections were found to be symmetry independent, with an R_{int} of 0.0323. Indexing and unit cell refinement indicated a primitive, monoclinic lattice. The space group was found to be P 21/c (No. 14). The data were integrated using the Bruker SAINT software program and scaled using the SADABS software program. Solution by iterative methods (SHELXT) produced a complete heavy-atom phasing model consistent with the proposed structure. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2013). All hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2013.

Table 1. Crystal data and structure refinement for **2.128**.

X-ray ID	sarpong58	
Sample/notebook ID	RMXII-168	
Empirical formula	C ₂₉ H ₃₇ N O ₃ S Si	
Formula weight	507.74	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	P 21/c	
Unit cell dimensions	a = 14.6635(10) Å	a = 90°.
	b = 13.0080(9) Å	b = 117.089(2)°.
	c = 16.0726(11) Å	g = 90°.
Volume	2729.4(3) Å ³	
Z	4	
Density (calculated)	1.236 Mg/m ³	
Absorption coefficient	1.708 mm ⁻¹	
F(000)	1088	
Crystal size	0.050 x 0.040 x 0.020 mm ³	
Crystal color/habit	colorless plate	
Theta range for data collection	3.385 to 68.221°.	
Index ranges	-15 ≤ h ≤ 17, -15 ≤ k ≤ 15, -19 ≤ l ≤ 16	
Reflections collected	48163	
Independent reflections	4986 [R(int) = 0.0323]	
Completeness to theta = 67.000°	99.8 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.929 and 0.849	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	4986 / 0 / 322	
Goodness-of-fit on F ²	1.047	
Final R indices [I > 2sigma(I)]	R1 = 0.0453, wR2 = 0.1241	
R indices (all data)	R1 = 0.0479, wR2 = 0.1268	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.626 and -0.330 e.Å ⁻³	

Table 2. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for **2.128**. $U(\text{eq})$ is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	$U(\text{eq})$
C(1)	7794(1)	9370(1)	2126(1)	23(1)
C(2)	6993(1)	9803(2)	1223(1)	27(1)
C(3)	6632(1)	10749(2)	1149(1)	31(1)
C(4)	7044(2)	11502(2)	1940(2)	36(1)
C(5)	7856(2)	11115(2)	2891(1)	32(1)
C(6)	8673(2)	11945(2)	3390(1)	37(1)
C(7)	9482(2)	11787(2)	3045(1)	30(1)
C(8)	9294(1)	10713(1)	2557(1)	24(1)
C(9)	10322(1)	10210(1)	3270(1)	27(1)
C(10)	9161(1)	9720(2)	3762(1)	30(1)
C(11)	8471(1)	10202(1)	2800(1)	24(1)
C(12)	6675(1)	7121(2)	1287(1)	28(1)
C(13)	8426(2)	6972(2)	3251(1)	37(1)
C(14)	6181(2)	7302(2)	2958(1)	31(1)
C(15)	6564(2)	7725(2)	3945(2)	59(1)
C(16)	5168(2)	7822(2)	2307(2)	42(1)
C(17)	5991(2)	6139(2)	2966(2)	47(1)
C(18)	5817(2)	11168(2)	243(2)	44(1)
C(19)	9067(1)	10699(1)	1539(1)	25(1)
C(20)	9210(1)	9825(2)	1119(1)	33(1)
C(21)	8921(2)	9842(2)	167(2)	46(1)
C(22)	8360(2)	11472(2)	19(2)	45(1)
C(23)	8656(2)	11548(2)	969(1)	33(1)
C(24)	11956(2)	9594(2)	3511(2)	36(1)
C(25)	12353(2)	9547(2)	4470(2)	46(1)
C(26)	13386(2)	9302(2)	4998(2)	58(1)
C(27)	13994(2)	9107(2)	4572(3)	66(1)
C(28)	13584(2)	9153(2)	3613(3)	59(1)
C(29)	12558(2)	9398(2)	3067(2)	44(1)

N(1)	8485(2)	10640(2)	-393(1)	53(1)
O(1)	10097(1)	9429(1)	3740(1)	30(1)
O(2)	7278(1)	8830(1)	2575(1)	25(1)
O(3)	10946(1)	9836(1)	2908(1)	34(1)
Si(1)	7149(1)	7561(1)	2515(1)	24(1)
S(1)	10776(1)	11438(1)	3942(1)	33(1)

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Table 3. Bond lengths [$\text{\AA}$] and angles [$^\circ$] for **2.128**.

C(1)-O(2)	1.444(2)	C(13)-Si(1)	1.865(2)
C(1)-C(2)	1.500(2)	C(13)-H(13A)	0.9800
C(1)-C(11)	1.533(2)	C(13)-H(13B)	0.9800
C(1)-H(1)	1.0000	C(13)-H(13C)	0.9800
C(2)-C(3)	1.323(3)	C(14)-C(15)	1.525(3)
C(2)-H(2)	0.9500	C(14)-C(16)	1.531(3)
C(3)-C(4)	1.497(3)	C(14)-C(17)	1.540(3)
C(3)-C(18)	1.504(3)	C(14)-Si(1)	1.8844(19)
C(4)-C(5)	1.533(3)	C(15)-H(15A)	0.9800
C(4)-H(4A)	0.9900	C(15)-H(15B)	0.9800
C(4)-H(4B)	0.9900	C(15)-H(15C)	0.9800
C(5)-C(11)	1.539(3)	C(16)-H(16A)	0.9800
C(5)-C(6)	1.539(3)	C(16)-H(16B)	0.9800
C(5)-H(5)	1.0000	C(16)-H(16C)	0.9800
C(6)-C(7)	1.534(3)	C(17)-H(17A)	0.9800
C(6)-H(6A)	0.9900	C(17)-H(17B)	0.9800
C(6)-H(6B)	0.9900	C(17)-H(17C)	0.9800
C(7)-C(8)	1.565(2)	C(18)-H(18A)	0.9800
C(7)-S(1)	1.842(2)	C(18)-H(18B)	0.9800
C(7)-H(7)	1.0000	C(18)-H(18C)	0.9800
C(8)-C(19)	1.514(2)	C(19)-C(20)	1.385(3)
C(8)-C(9)	1.562(2)	C(19)-C(23)	1.385(3)
C(8)-C(11)	1.575(2)	C(20)-C(21)	1.390(3)
C(9)-O(3)	1.376(2)	C(20)-H(20)	0.9500
C(9)-O(1)	1.393(2)	C(21)-N(1)	1.331(4)
C(9)-S(1)	1.8722(19)	C(21)-H(21)	0.9500
C(10)-O(1)	1.439(2)	C(22)-N(1)	1.325(3)
C(10)-C(11)	1.543(2)	C(22)-C(23)	1.388(3)
C(10)-H(10A)	0.9900	C(22)-H(22)	0.9500
C(10)-H(10B)	0.9900	C(23)-H(23)	0.9500
C(12)-Si(1)	1.8588(18)	C(24)-C(25)	1.378(3)
C(12)-H(12A)	0.9800	C(24)-C(29)	1.387(3)
C(12)-H(12B)	0.9800	C(24)-O(3)	1.388(2)
C(12)-H(12C)	0.9800	C(25)-C(26)	1.395(3)

C(25)-H(25)	0.9500	C(28)-C(29)	1.391(3)
C(26)-C(27)	1.371(5)	C(28)-H(28)	0.9500
C(26)-H(26)	0.9500	C(29)-H(29)	0.9500
C(27)-C(28)	1.378(5)	O(2)-Si(1)	1.6602(14)
C(27)-H(27)	0.9500		
O(2)-C(1)-C(2)	107.98(14)	C(6)-C(7)-C(8)	108.22(15)
O(2)-C(1)-C(11)	107.91(13)	C(6)-C(7)-S(1)	116.19(14)
C(2)-C(1)-C(11)	112.90(15)	C(8)-C(7)-S(1)	93.19(12)
O(2)-C(1)-H(1)	109.3	C(6)-C(7)-H(7)	112.6
C(2)-C(1)-H(1)	109.3	C(8)-C(7)-H(7)	112.6
C(11)-C(1)-H(1)	109.3	S(1)-C(7)-H(7)	112.6
C(3)-C(2)-C(1)	122.72(17)	C(19)-C(8)-C(9)	116.88(15)
C(3)-C(2)-H(2)	118.6	C(19)-C(8)-C(7)	117.05(15)
C(1)-C(2)-H(2)	118.6	C(9)-C(8)-C(7)	96.60(13)
C(2)-C(3)-C(4)	122.84(17)	C(19)-C(8)-C(11)	116.57(14)
C(2)-C(3)-C(18)	122.24(19)	C(9)-C(8)-C(11)	103.50(13)
C(4)-C(3)-C(18)	114.82(18)	C(7)-C(8)-C(11)	103.38(14)
C(3)-C(4)-C(5)	117.50(17)	O(3)-C(9)-O(1)	109.79(15)
C(3)-C(4)-H(4A)	107.9	O(3)-C(9)-C(8)	116.24(14)
C(5)-C(4)-H(4A)	107.9	O(1)-C(9)-C(8)	108.38(14)
C(3)-C(4)-H(4B)	107.9	O(3)-C(9)-S(1)	114.51(12)
C(5)-C(4)-H(4B)	107.9	O(1)-C(9)-S(1)	114.83(13)
H(4A)-C(4)-H(4B)	107.2	C(8)-C(9)-S(1)	92.13(11)
C(4)-C(5)-C(11)	112.43(15)	O(1)-C(10)-C(11)	106.27(14)
C(4)-C(5)-C(6)	110.87(17)	O(1)-C(10)-H(10A)	110.5
C(11)-C(5)-C(6)	103.85(15)	C(11)-C(10)-H(10A)	110.5
C(4)-C(5)-H(5)	109.9	O(1)-C(10)-H(10B)	110.5
C(11)-C(5)-H(5)	109.9	C(11)-C(10)-H(10B)	110.5
C(6)-C(5)-H(5)	109.9	H(10A)-C(10)-H(10B)	108.7
C(7)-C(6)-C(5)	105.36(15)	C(1)-C(11)-C(5)	113.13(15)
C(7)-C(6)-H(6A)	110.7	C(1)-C(11)-C(10)	109.89(15)
C(5)-C(6)-H(6A)	110.7	C(5)-C(11)-C(10)	111.33(15)
C(7)-C(6)-H(6B)	110.7	C(1)-C(11)-C(8)	116.38(14)
C(5)-C(6)-H(6B)	110.7	C(5)-C(11)-C(8)	104.28(14)
H(6A)-C(6)-H(6B)	108.8	C(10)-C(11)-C(8)	101.14(13)

Si(1)-C(12)-H(12A)	109.5	C(3)-C(18)-H(18A)	109.5
Si(1)-C(12)-H(12B)	109.5	C(3)-C(18)-H(18B)	109.5
H(12A)-C(12)-H(12B)	109.5	H(18A)-C(18)-H(18B)	109.5
Si(1)-C(12)-H(12C)	109.5	C(3)-C(18)-H(18C)	109.5
H(12A)-C(12)-H(12C)	109.5	H(18A)-C(18)-H(18C)	109.5
H(12B)-C(12)-H(12C)	109.5	H(18B)-C(18)-H(18C)	109.5
Si(1)-C(13)-H(13A)	109.5	C(20)-C(19)-C(23)	116.68(17)
Si(1)-C(13)-H(13B)	109.5	C(20)-C(19)-C(8)	121.89(17)
H(13A)-C(13)-H(13B)	109.5	C(23)-C(19)-C(8)	121.36(17)
Si(1)-C(13)-H(13C)	109.5	C(19)-C(20)-C(21)	119.1(2)
H(13A)-C(13)-H(13C)	109.5	C(19)-C(20)-H(20)	120.5
H(13B)-C(13)-H(13C)	109.5	C(21)-C(20)-H(20)	120.5
C(15)-C(14)-C(16)	109.5(2)	N(1)-C(21)-C(20)	124.6(2)
C(15)-C(14)-C(17)	109.17(19)	N(1)-C(21)-H(21)	117.7
C(16)-C(14)-C(17)	108.46(18)	C(20)-C(21)-H(21)	117.7
C(15)-C(14)-Si(1)	110.16(14)	N(1)-C(22)-C(23)	124.2(2)
C(16)-C(14)-Si(1)	109.07(13)	N(1)-C(22)-H(22)	117.9
C(17)-C(14)-Si(1)	110.45(14)	C(23)-C(22)-H(22)	117.9
C(14)-C(15)-H(15A)	109.5	C(19)-C(23)-C(22)	119.7(2)
C(14)-C(15)-H(15B)	109.5	C(19)-C(23)-H(23)	120.2
H(15A)-C(15)-H(15B)	109.5	C(22)-C(23)-H(23)	120.2
C(14)-C(15)-H(15C)	109.5	C(25)-C(24)-C(29)	121.6(2)
H(15A)-C(15)-H(15C)	109.5	C(25)-C(24)-O(3)	124.3(2)
H(15B)-C(15)-H(15C)	109.5	C(29)-C(24)-O(3)	114.2(2)
C(14)-C(16)-H(16A)	109.5	C(24)-C(25)-C(26)	118.6(3)
C(14)-C(16)-H(16B)	109.5	C(24)-C(25)-H(25)	120.7
H(16A)-C(16)-H(16B)	109.5	C(26)-C(25)-H(25)	120.7
C(14)-C(16)-H(16C)	109.5	C(27)-C(26)-C(25)	120.7(3)
H(16A)-C(16)-H(16C)	109.5	C(27)-C(26)-H(26)	119.7
H(16B)-C(16)-H(16C)	109.5	C(25)-C(26)-H(26)	119.7
C(14)-C(17)-H(17A)	109.5	C(26)-C(27)-C(28)	120.0(2)
C(14)-C(17)-H(17B)	109.5	C(26)-C(27)-H(27)	120.0
H(17A)-C(17)-H(17B)	109.5	C(28)-C(27)-H(27)	120.0
C(14)-C(17)-H(17C)	109.5	C(27)-C(28)-C(29)	120.7(3)
H(17A)-C(17)-H(17C)	109.5	C(27)-C(28)-H(28)	119.7
H(17B)-C(17)-H(17C)	109.5	C(29)-C(28)-H(28)	119.7

C(24)-C(29)-C(28)	118.5(3)
C(24)-C(29)-H(29)	120.8
C(28)-C(29)-H(29)	120.8
C(22)-N(1)-C(21)	115.65(19)
C(9)-O(1)-C(10)	106.56(14)
C(1)-O(2)-Si(1)	121.82(11)
C(9)-O(3)-C(24)	119.25(15)
O(2)-Si(1)-C(12)	110.21(8)
O(2)-Si(1)-C(13)	108.44(8)
C(12)-Si(1)-C(13)	109.20(9)
O(2)-Si(1)-C(14)	103.98(8)
C(12)-Si(1)-C(14)	111.34(9)
C(13)-Si(1)-C(14)	113.52(9)
C(7)-S(1)-C(9)	77.88(8)

Table 4. Anisotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for **2.128**. The anisotropic displacement factor exponent takes the form: $-2p^2[h^2 a^{*2} U^{11} + \dots + 2 h k a^* b^* U^{12}]$

	U ¹¹	U ²²	U ³³	U ²³	U ¹³	U ¹²
C(1)	21(1)	29(1)	21(1)	5(1)	11(1)	0(1)
C(2)	22(1)	35(1)	20(1)	4(1)	7(1)	-5(1)
C(3)	20(1)	40(1)	30(1)	9(1)	8(1)	0(1)
C(4)	30(1)	40(1)	40(1)	2(1)	17(1)	9(1)
C(5)	32(1)	40(1)	29(1)	-2(1)	19(1)	3(1)
C(6)	44(1)	38(1)	30(1)	-7(1)	18(1)	4(1)
C(7)	34(1)	29(1)	23(1)	-4(1)	10(1)	-5(1)
C(8)	23(1)	27(1)	20(1)	0(1)	10(1)	-2(1)
C(9)	23(1)	31(1)	23(1)	-1(1)	8(1)	-4(1)
C(10)	27(1)	40(1)	20(1)	3(1)	8(1)	-5(1)
C(11)	24(1)	31(1)	18(1)	3(1)	10(1)	-1(1)
C(12)	29(1)	32(1)	23(1)	3(1)	11(1)	4(1)
C(13)	32(1)	40(1)	31(1)	12(1)	8(1)	4(1)
C(14)	33(1)	39(1)	25(1)	1(1)	17(1)	-7(1)
C(15)	65(2)	93(2)	34(1)	-16(1)	35(1)	-33(2)
C(16)	36(1)	51(1)	50(1)	6(1)	30(1)	2(1)
C(17)	47(1)	45(1)	57(1)	11(1)	32(1)	-7(1)
C(18)	31(1)	43(1)	42(1)	16(1)	2(1)	2(1)
C(19)	21(1)	35(1)	21(1)	-3(1)	10(1)	-9(1)
C(20)	28(1)	43(1)	30(1)	-8(1)	15(1)	-9(1)
C(21)	44(1)	65(2)	37(1)	-22(1)	25(1)	-16(1)
C(22)	46(1)	61(2)	27(1)	9(1)	16(1)	-13(1)
C(23)	33(1)	39(1)	27(1)	4(1)	14(1)	-9(1)
C(24)	21(1)	26(1)	52(1)	-1(1)	9(1)	-2(1)
C(25)	27(1)	44(1)	52(1)	7(1)	4(1)	-2(1)
C(26)	29(1)	42(1)	73(2)	14(1)	-4(1)	-2(1)
C(27)	24(1)	30(1)	115(3)	10(1)	7(1)	3(1)
C(28)	32(1)	27(1)	116(3)	-7(1)	32(2)	3(1)
C(29)	35(1)	23(1)	73(2)	-8(1)	25(1)	-1(1)
N(1)	53(1)	84(2)	25(1)	-4(1)	21(1)	-17(1)
O(1)	24(1)	34(1)	27(1)	7(1)	6(1)	-2(1)

O(2)	24(1)	32(1)	22(1)	4(1)	13(1)	-2(1)
O(3)	22(1)	43(1)	33(1)	-4(1)	10(1)	-1(1)
Si(1)	22(1)	30(1)	19(1)	5(1)	9(1)	0(1)
S(1)	32(1)	40(1)	24(1)	-6(1)	8(1)	-10(1)

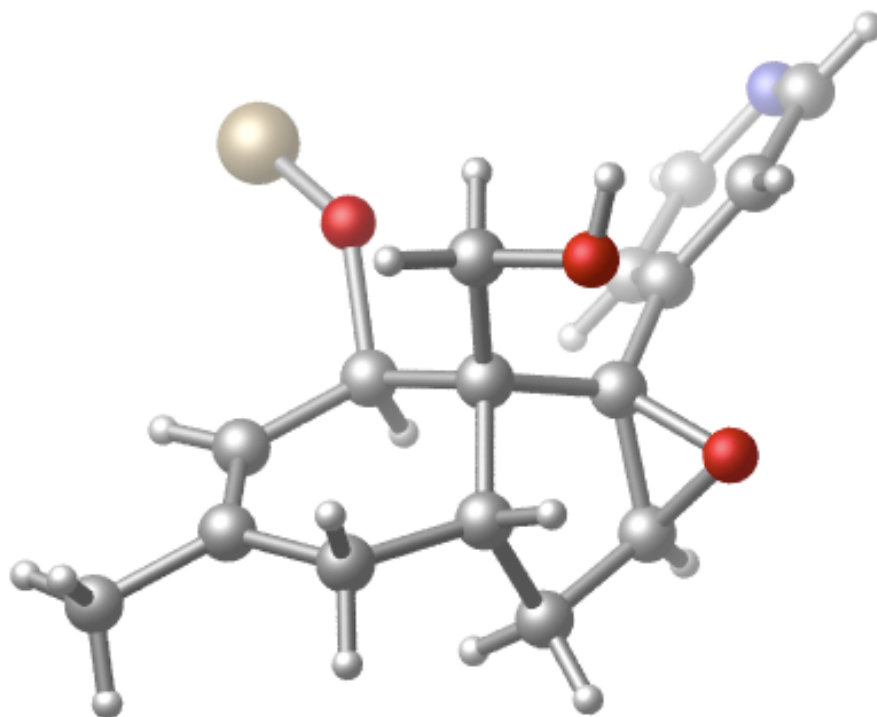
Table 5. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for **2.128**.

	x	y	z	U(eq)
H(1)	8234	8877	1993	28
H(2)	6735	9381	681	32
H(4A)	6460	11772	2024	43
H(4B)	7340	12088	1752	43
H(5)	7523	10916	3289	39
H(6A)	8370	12641	3225	44
H(6B)	8981	11859	4076	44
H(7)	9489	12359	2632	36
H(10A)	9302	10225	4267	36
H(10B)	8825	9111	3871	36
H(12A)	6038	7482	887	42
H(12B)	6546	6379	1252	42
H(12C)	7191	7270	1076	42
H(13A)	8900	7157	2998	55
H(13B)	8357	6223	3248	55
H(13C)	8694	7227	3893	55
H(15A)	6692	8465	3945	89
H(15B)	7201	7376	4365	89
H(15C)	6046	7608	4160	89
H(16A)	4668	7709	2545	62
H(16B)	4908	7529	1679	62
H(16C)	5280	8562	2282	62
H(17A)	6631	5795	3386	70
H(17B)	5745	5863	2332	70
H(17C)	5475	6018	3183	70
H(18A)	5617	10639	-242	66
H(18B)	6084	11770	57	66
H(18C)	5219	11370	325	66

H(20)	9500	9223	1477	39
H(21)	9044	9242	-103	56
H(22)	8048	12055	-361	54
H(23)	8577	12179	1227	40
H(25)	11931	9678	4765	55
H(26)	13672	9270	5660	70
H(27)	14696	8940	4939	79
H(28)	14008	9016	3321	71
H(29)	12275	9431	2406	52

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X-ray Crystallography Data for Epoxide 2.142



Crystal data and Structure Refinement for Epoxide 2.142

A colorless plate 0.050 x 0.030 x 0.030 mm in size was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using phi and omega scans. Crystal-to-detector distance was 60 mm and exposure time was 5 seconds per frame using a scan width of 1.0°. Data collection was 100.0% complete to 67.000° in q . A total of 32201 reflections were collected covering the indices, $-21 \leq h \leq 20$, $-11 \leq k \leq 13$, $-13 \leq l \leq 13$. 3982 reflections were found to be symmetry independent, with an R_{int} of 0.0255. Indexing and unit cell refinement indicated a primitive, monoclinic lattice. The space group was found to be P 21/c (No. 14). The data were integrated using the Bruker SAINT software program and scaled using the SADABS software program. Solution by iterative methods (SHELXT) produced a complete heavy-atom phasing model consistent with the proposed structure. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2013). All hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2013.

Table 1. Crystal data and structure refinement for **2.142**.

X-ray ID	sarpong59	
Sample/notebook ID	RMXII-193	
Empirical formula	C ₂₂ H ₃₃ N O ₃ Si	
Formula weight	387.58	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	P 21/c	
Unit cell dimensions	a = 17.6138(8) Å	a = 90°.
	b = 11.1045(5) Å	b = 93.906(2)°.
	c = 11.1829(5) Å	g = 90°.
Volume	2182.21(17) Å ³	
Z	4	
Density (calculated)	1.180 Mg/m ³	
Absorption coefficient	1.110 mm ⁻¹	
F(000)	840	
Crystal size	0.050 x 0.030 x 0.030 mm ³	
Crystal color/habit	colorless plate	
Theta range for data collection	2.514 to 68.247°.	
Index ranges	-21 ≤ h ≤ 20, -11 ≤ k ≤ 13, -13 ≤ l ≤ 13	
Reflections collected	32201	
Independent reflections	3982 [R(int) = 0.0255]	
Completeness to theta = 67.000°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.929 and 0.877	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	3982 / 0 / 259	
Goodness-of-fit on F ²	1.043	
Final R indices [I > 2σ(I)]	R1 = 0.0563, wR2 = 0.1435	
R indices (all data)	R1 = 0.0631, wR2 = 0.1498	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.429 and -0.404 e.Å ⁻³	

Table 2. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for **2.142**. $U(\text{eq})$ is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	$U(\text{eq})$
C(1)	3471(1)	3823(2)	2720(2)	22(1)
C(2)	4019(1)	4596(2)	3526(2)	22(1)
C(3)	4486(1)	3776(2)	4303(2)	25(1)
C(4)	4307(1)	2496(2)	3945(2)	25(1)
C(5)	3925(1)	2628(2)	2671(2)	22(1)
C(6)	3460(1)	1544(2)	2222(2)	28(1)
C(7)	2683(1)	1476(2)	2690(2)	34(1)
C(8)	2375(1)	2418(2)	3197(2)	37(1)
C(9)	2749(1)	3621(2)	3420(2)	27(1)
C(10)	3270(1)	4362(2)	1485(2)	30(1)
C(11)	3844(1)	5864(2)	3859(2)	22(1)
C(12)	3476(1)	6165(2)	4872(2)	27(1)
C(13)	3392(1)	7365(2)	5160(2)	30(1)
C(14)	4005(1)	7978(2)	3542(2)	30(1)
C(15)	4104(1)	6806(2)	3173(2)	26(1)
C(16)	2281(2)	282(2)	2547(3)	55(1)
C(17)	1065(3)	3902(5)	1443(5)	45(1)
C(18)	738(3)	3971(4)	4115(4)	47(1)
C(19)	1128(2)	6314(3)	2846(3)	36(1)
C(20)	332(3)	6543(5)	2248(5)	60(1)
C(21)	1724(2)	6935(4)	2125(4)	43(1)
C(22)	1174(3)	6865(5)	4104(4)	50(1)
C(17A)	1503(8)	6708(12)	3950(12)	86(4)
C(18A)	1002(5)	4121(8)	4523(8)	50(2)
C(19A)	768(5)	5088(8)	1905(7)	50(2)
C(20A)	-50(6)	5366(9)	2179(9)	66(3)
C(21A)	1041(7)	6114(11)	1090(11)	83(3)
C(22A)	844(8)	3953(14)	1305(14)	82(4)
N(1)	3655(1)	8275(2)	4523(2)	30(1)

O(1)	3950(1)	4593(1)	919(1)	38(1)
O(2)	4821(1)	4431(1)	3340(1)	26(1)
O(3)	2250(5)	4558(8)	3316(6)	24(1)
O(3A)	2220(11)	4700(17)	2971(12)	39(3)
Si(1)	1314(1)	4647(2)	2948(1)	26(1)
Si(1A)	1418(1)	5151(3)	3335(3)	43(1)

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Table 3. Bond lengths [$\text{\AA}$] and angles [$^\circ$] for **2.142**.

C(1)-C(10)	1.524(3)	C(14)-N(1)	1.336(3)
C(1)-C(2)	1.537(3)	C(14)-C(15)	1.379(3)
C(1)-C(5)	1.552(3)	C(14)-H(14)	0.9500
C(1)-C(9)	1.555(3)	C(15)-H(15)	0.9500
C(2)-O(2)	1.453(2)	C(16)-H(16A)	0.9800
C(2)-C(3)	1.471(3)	C(16)-H(16B)	0.9800
C(2)-C(11)	1.493(3)	C(16)-H(16C)	0.9800
C(3)-O(2)	1.457(2)	C(17)-Si(1)	1.899(6)
C(3)-C(4)	1.505(3)	C(17)-H(17A)	0.9800
C(3)-H(3)	1.0000	C(17)-H(17B)	0.9800
C(4)-C(5)	1.541(3)	C(17)-H(17C)	0.9800
C(4)-H(4A)	0.9900	C(18)-Si(1)	1.865(4)
C(4)-H(4B)	0.9900	C(18)-H(18A)	0.9800
C(5)-C(6)	1.523(3)	C(18)-H(18B)	0.9800
C(5)-H(5)	1.0000	C(18)-H(18C)	0.9800
C(6)-C(7)	1.499(3)	C(19)-C(21)	1.531(5)
C(6)-H(6A)	0.9900	C(19)-C(22)	1.532(6)
C(6)-H(6B)	0.9900	C(19)-C(20)	1.533(6)
C(7)-C(8)	1.324(3)	C(19)-Si(1)	1.882(4)
C(7)-C(16)	1.506(3)	C(20)-H(20A)	0.9800
C(8)-C(9)	1.503(3)	C(20)-H(20B)	0.9800
C(8)-H(8)	0.9500	C(20)-H(20C)	0.9800
C(9)-O(3)	1.361(9)	C(21)-H(21A)	0.9800
C(9)-O(3A)	1.579(16)	C(21)-H(21B)	0.9800
C(9)-H(9)	1.0000	C(21)-H(21C)	0.9800
C(10)-O(1)	1.415(3)	C(22)-H(22A)	0.9800
C(10)-H(10A)	0.9900	C(22)-H(22B)	0.9800
C(10)-H(10B)	0.9900	C(22)-H(22C)	0.9800
C(11)-C(12)	1.385(3)	C(17A)-Si(1A)	1.864(14)
C(11)-C(15)	1.393(3)	C(17A)-H(17D)	0.9800
C(12)-C(13)	1.381(3)	C(17A)-H(17E)	0.9800
C(12)-H(12)	0.9500	C(17A)-H(17F)	0.9800
C(13)-N(1)	1.337(3)	C(18A)-Si(1A)	1.935(9)
C(13)-H(13)	0.9500	C(18A)-H(18D)	0.9800

C(18A)-H(18E)	0.9800	C(21A)-H(21D)	0.9800
C(18A)-H(18F)	0.9800	C(21A)-H(21E)	0.9800
C(19A)-C(22A)	1.438(17)	C(21A)-H(21F)	0.9800
C(19A)-C(20A)	1.524(12)	C(22A)-H(22D)	0.9800
C(19A)-C(21A)	1.556(14)	C(22A)-H(22E)	0.9800
C(19A)-Si(1A)	1.904(9)	C(22A)-H(22F)	0.9800
C(20A)-H(20D)	0.9800	O(1)-H(1)	0.8400
C(20A)-H(20E)	0.9800	O(3)-Si(1)	1.675(8)
C(20A)-H(20F)	0.9800	O(3A)-Si(1A)	1.58(2)
C(10)-C(1)-C(2)	114.20(16)	C(4)-C(5)-C(1)	104.03(15)
C(10)-C(1)-C(5)	113.04(16)	C(6)-C(5)-H(5)	107.6
C(2)-C(1)-C(5)	101.15(15)	C(4)-C(5)-H(5)	107.6
C(10)-C(1)-C(9)	111.48(17)	C(1)-C(5)-H(5)	107.6
C(2)-C(1)-C(9)	106.72(15)	C(7)-C(6)-C(5)	114.12(17)
C(5)-C(1)-C(9)	109.61(15)	C(7)-C(6)-H(6A)	108.7
O(2)-C(2)-C(3)	59.77(12)	C(5)-C(6)-H(6A)	108.7
O(2)-C(2)-C(11)	111.92(15)	C(7)-C(6)-H(6B)	108.7
C(3)-C(2)-C(11)	123.57(17)	C(5)-C(6)-H(6B)	108.7
O(2)-C(2)-C(1)	115.05(15)	H(6A)-C(6)-H(6B)	107.6
C(3)-C(2)-C(1)	107.74(16)	C(8)-C(7)-C(6)	121.3(2)
C(11)-C(2)-C(1)	122.71(16)	C(8)-C(7)-C(16)	122.5(2)
O(2)-C(3)-C(2)	59.50(12)	C(6)-C(7)-C(16)	116.2(2)
O(2)-C(3)-C(4)	111.29(16)	C(7)-C(8)-C(9)	125.9(2)
C(2)-C(3)-C(4)	109.18(16)	C(7)-C(8)-H(8)	117.0
O(2)-C(3)-H(3)	120.6	C(9)-C(8)-H(8)	117.0
C(2)-C(3)-H(3)	120.6	O(3)-C(9)-C(8)	113.1(4)
C(4)-C(3)-H(3)	120.6	O(3)-C(9)-C(1)	113.1(4)
C(3)-C(4)-C(5)	103.09(15)	C(8)-C(9)-C(1)	114.11(17)
C(3)-C(4)-H(4A)	111.1	C(8)-C(9)-O(3A)	112.3(7)
C(5)-C(4)-H(4A)	111.1	C(1)-C(9)-O(3A)	102.4(7)
C(3)-C(4)-H(4B)	111.1	O(3)-C(9)-H(9)	105.1
C(5)-C(4)-H(4B)	111.1	C(8)-C(9)-H(9)	105.1
H(4A)-C(4)-H(4B)	109.1	C(1)-C(9)-H(9)	105.1
C(6)-C(5)-C(4)	114.84(16)	O(1)-C(10)-C(1)	109.01(17)
C(6)-C(5)-C(1)	114.88(16)	O(1)-C(10)-H(10A)	109.9

C(1)-C(10)-H(10A)	109.9	H(18B)-C(18)-H(18C)	109.5
O(1)-C(10)-H(10B)	109.9	C(21)-C(19)-C(22)	107.9(3)
C(1)-C(10)-H(10B)	109.9	C(21)-C(19)-C(20)	109.6(3)
H(10A)-C(10)-H(10B)	108.3	C(22)-C(19)-C(20)	108.9(4)
C(12)-C(11)-C(15)	117.26(18)	C(21)-C(19)-Si(1)	110.6(3)
C(12)-C(11)-C(2)	123.21(18)	C(22)-C(19)-Si(1)	109.8(3)
C(15)-C(11)-C(2)	119.39(17)	C(20)-C(19)-Si(1)	109.9(3)
C(13)-C(12)-C(11)	119.16(19)	C(19)-C(20)-H(20A)	109.5
C(13)-C(12)-H(12)	120.4	C(19)-C(20)-H(20B)	109.5
C(11)-C(12)-H(12)	120.4	H(20A)-C(20)-H(20B)	109.5
N(1)-C(13)-C(12)	123.98(19)	C(19)-C(20)-H(20C)	109.5
N(1)-C(13)-H(13)	118.0	H(20A)-C(20)-H(20C)	109.5
C(12)-C(13)-H(13)	118.0	H(20B)-C(20)-H(20C)	109.5
N(1)-C(14)-C(15)	123.6(2)	C(19)-C(21)-H(21A)	109.5
N(1)-C(14)-H(14)	118.2	C(19)-C(21)-H(21B)	109.5
C(15)-C(14)-H(14)	118.2	H(21A)-C(21)-H(21B)	109.5
C(14)-C(15)-C(11)	119.47(19)	C(19)-C(21)-H(21C)	109.5
C(14)-C(15)-H(15)	120.3	H(21A)-C(21)-H(21C)	109.5
C(11)-C(15)-H(15)	120.3	H(21B)-C(21)-H(21C)	109.5
C(7)-C(16)-H(16A)	109.5	C(19)-C(22)-H(22A)	109.5
C(7)-C(16)-H(16B)	109.5	C(19)-C(22)-H(22B)	109.5
H(16A)-C(16)-H(16B)	109.5	H(22A)-C(22)-H(22B)	109.5
C(7)-C(16)-H(16C)	109.5	C(19)-C(22)-H(22C)	109.5
H(16A)-C(16)-H(16C)	109.5	H(22A)-C(22)-H(22C)	109.5
H(16B)-C(16)-H(16C)	109.5	H(22B)-C(22)-H(22C)	109.5
Si(1)-C(17)-H(17A)	109.5	Si(1A)-C(17A)-H(17D)	109.5
Si(1)-C(17)-H(17B)	109.5	Si(1A)-C(17A)-H(17E)	109.5
H(17A)-C(17)-H(17B)	109.5	H(17D)-C(17A)-H(17E)	109.5
Si(1)-C(17)-H(17C)	109.5	Si(1A)-C(17A)-H(17F)	109.5
H(17A)-C(17)-H(17C)	109.5	H(17D)-C(17A)-H(17F)	109.5
H(17B)-C(17)-H(17C)	109.5	H(17E)-C(17A)-H(17F)	109.5
Si(1)-C(18)-H(18A)	109.5	Si(1A)-C(18A)-H(18D)	109.5
Si(1)-C(18)-H(18B)	109.5	Si(1A)-C(18A)-H(18E)	109.5
H(18A)-C(18)-H(18B)	109.5	H(18D)-C(18A)-H(18E)	109.5
Si(1)-C(18)-H(18C)	109.5	Si(1A)-C(18A)-H(18F)	109.5
H(18A)-C(18)-H(18C)	109.5	H(18D)-C(18A)-H(18F)	109.5

H(18E)-C(18A)-H(18F)	109.5	O(3A)-Si(1A)-C(17A)	109.8(8)
C(22A)-C(19A)-C(20A)	113.0(9)	O(3A)-Si(1A)-C(19A)	105.7(6)
C(22A)-C(19A)-C(21A)	109.0(9)	C(17A)-Si(1A)-C(19A)	111.9(5)
C(20A)-C(19A)-C(21A)	107.7(8)	O(3A)-Si(1A)-C(18A)	112.2(6)
C(22A)-C(19A)-Si(1A)	110.7(8)	C(17A)-Si(1A)-C(18A)	108.6(5)
C(20A)-C(19A)-Si(1A)	110.3(6)	C(19A)-Si(1A)-C(18A)	108.7(4)
C(21A)-C(19A)-Si(1A)	105.8(6)		
C(19A)-C(20A)-H(20D)	109.5		
C(19A)-C(20A)-H(20E)	109.5		
H(20D)-C(20A)-H(20E)	109.5		
C(19A)-C(20A)-H(20F)	109.5		
H(20D)-C(20A)-H(20F)	109.5		
H(20E)-C(20A)-H(20F)	109.5		
C(19A)-C(21A)-H(21D)	109.5		
C(19A)-C(21A)-H(21E)	109.5		
H(21D)-C(21A)-H(21E)	109.5		
C(19A)-C(21A)-H(21F)	109.5		
H(21D)-C(21A)-H(21F)	109.5		
H(21E)-C(21A)-H(21F)	109.5		
C(19A)-C(22A)-H(22D)	109.5		
C(19A)-C(22A)-H(22E)	109.5		
H(22D)-C(22A)-H(22E)	109.5		
C(19A)-C(22A)-H(22F)	109.5		
H(22D)-C(22A)-H(22F)	109.5		
H(22E)-C(22A)-H(22F)	109.5		
C(14)-N(1)-C(13)	116.53(18)		
C(10)-O(1)-H(1)	109.5		
C(2)-O(2)-C(3)	60.73(12)		
C(9)-O(3)-Si(1)	133.2(6)		
Si(1A)-O(3A)-C(9)	132.7(10)		
O(3)-Si(1)-C(18)	112.2(3)		
O(3)-Si(1)-C(19)	103.7(3)		
C(18)-Si(1)-C(19)	109.70(19)		
O(3)-Si(1)-C(17)	110.9(3)		
C(18)-Si(1)-C(17)	110.0(2)		
C(19)-Si(1)-C(17)	110.3(2)		

Table 4. Anisotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for **2.142**. The anisotropic displacement factor exponent takes the form: $-2p^2[h^2 a^{*2}U^{11} + \dots + 2 h k a^* b^* U^{12}]$

	U ¹¹	U ²²	U ³³	U ²³	U ¹³	U ¹²
C(1)	24(1)	18(1)	24(1)	-1(1)	2(1)	1(1)
C(2)	21(1)	22(1)	22(1)	0(1)	6(1)	0(1)
C(3)	23(1)	26(1)	26(1)	0(1)	2(1)	0(1)
C(4)	25(1)	23(1)	27(1)	2(1)	4(1)	3(1)
C(5)	23(1)	18(1)	26(1)	0(1)	5(1)	2(1)
C(6)	32(1)	20(1)	30(1)	-2(1)	3(1)	2(1)
C(7)	29(1)	24(1)	47(1)	-4(1)	2(1)	-3(1)
C(8)	23(1)	33(1)	54(1)	-6(1)	6(1)	-5(1)
C(9)	21(1)	26(1)	36(1)	-4(1)	3(1)	3(1)
C(10)	41(1)	22(1)	26(1)	-1(1)	-1(1)	6(1)
C(11)	20(1)	20(1)	24(1)	-2(1)	0(1)	-1(1)
C(12)	32(1)	23(1)	26(1)	0(1)	7(1)	-2(1)
C(13)	35(1)	28(1)	28(1)	-6(1)	8(1)	1(1)
C(14)	34(1)	22(1)	35(1)	2(1)	7(1)	-1(1)
C(15)	29(1)	24(1)	26(1)	-1(1)	7(1)	0(1)
C(16)	36(1)	35(1)	96(2)	-16(1)	13(1)	-9(1)
N(1)	34(1)	22(1)	34(1)	-5(1)	4(1)	0(1)
O(1)	62(1)	25(1)	29(1)	7(1)	14(1)	9(1)
O(2)	22(1)	24(1)	34(1)	0(1)	8(1)	0(1)
O(3)	19(2)	20(3)	32(3)	0(2)	-5(2)	4(2)
O(3A)	38(4)	23(4)	54(8)	3(5)	-13(6)	18(3)
Si(1)	20(1)	26(1)	32(1)	1(1)	2(1)	2(1)
Si(1A)	31(1)	44(2)	54(1)	-24(1)	-4(1)	7(1)

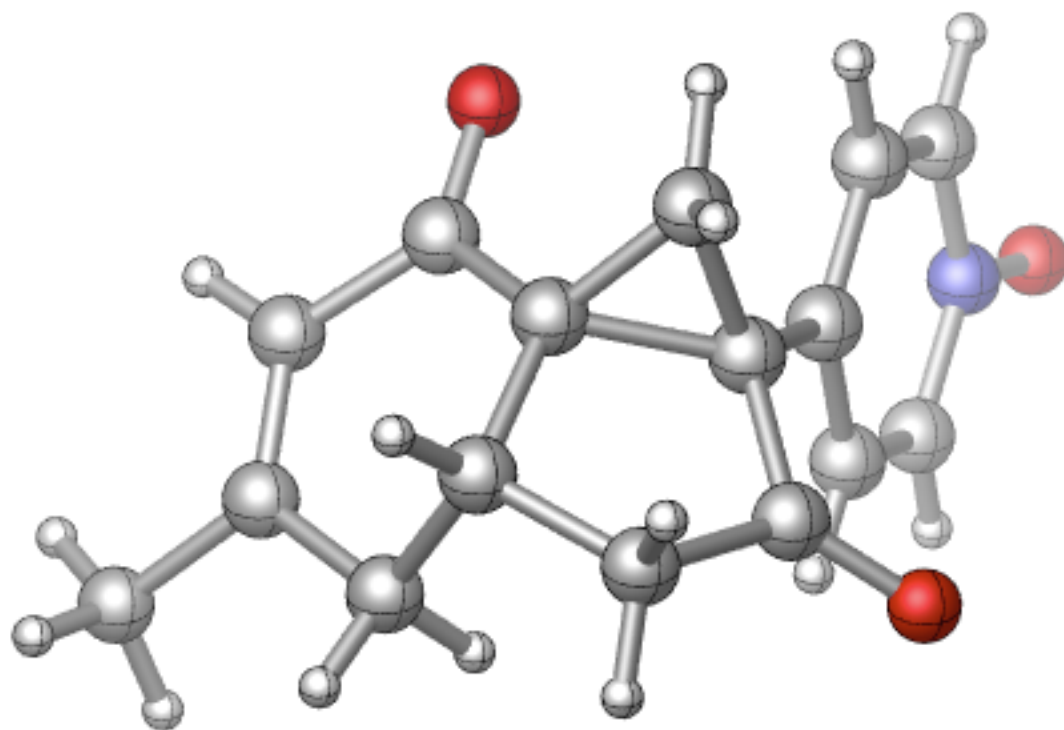
Table 5. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for **2.142**.

	x	y	z	U(eq)
H(3)	4622	3987	5161	30
H(4A)	3956	2121	4492	30
H(4B)	4776	2005	3941	30
H(5)	4337	2753	2112	27
H(6A)	3404	1569	1336	33
H(6B)	3743	801	2457	33
H(8)	1873	2325	3442	44
H(9)	2936	3610	4284	33
H(10A)	2947	3793	995	36
H(10B)	2983	5120	1565	36
H(12)	3282	5554	5363	33
H(13)	3132	7556	5853	36
H(14)	4196	8608	3072	36
H(15)	4346	6644	2458	31
H(16A)	1779	340	2871	83
H(16B)	2582	-340	2982	83
H(16C)	2220	71	1695	83
H(17A)	1338	4307	822	67
H(17B)	516	3963	1247	67
H(17C)	1214	3052	1484	67
H(18A)	792	3093	4103	70
H(18B)	201	4187	3950	70
H(18C)	918	4279	4906	70
H(20A)	242	7412	2185	90
H(20B)	-51	6178	2732	90
H(20C)	295	6185	1445	90
H(21A)	1740	6545	1342	64
H(21B)	2225	6873	2560	64

H(21C)	1590	7786	2013	64
H(22A)	1085	7734	4045	75
H(22B)	1680	6715	4496	75
H(22C)	787	6497	4577	75
H(17D)	1759	6683	4756	128
H(17E)	995	7057	3990	128
H(17F)	1801	7203	3428	128
H(18D)	797	3388	4136	75
H(18E)	594	4548	4901	75
H(18F)	1404	3906	5135	75
H(20D)	-364	5453	1426	99
H(20E)	-62	6118	2636	99
H(20F)	-248	4707	2650	99
H(21D)	1556	5934	860	125
H(21E)	1045	6878	1528	125
H(21F)	695	6175	368	125
H(22D)	535	3961	543	122
H(22E)	670	3302	1812	122
H(22F)	1379	3822	1152	122
H(1)	3877	5157	424	57

—

X-ray Crystallography Data for Cyclopropane 2.150



Crystal data and Structure Refinement for Cyclopropane 2.150

A colorless plate 0.060 x 0.040 x 0.020 mm in size was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using phi and omega scans. Crystal-to-detector distance was 60 mm and exposure time was 10 seconds per frame using a scan width of 1.0°. Data collection was 100.0% complete to 67.000° in q . A total of 15734 reflections were collected covering the indices, $-7 \leq h \leq 7$, $-13 \leq k \leq 10$, $-20 \leq l \leq 20$. 2352 reflections were found to be symmetry independent, with an R_{int} of 0.0153. Indexing and unit cell refinement indicated a primitive, orthorhombic lattice. The space group was found to be P 21 21 21 (No. 19). The data were integrated using the Bruker SAINT software program and scaled using the SADABS software program. Solution by iterative methods (SHELXT) produced a complete heavy-atom phasing model consistent with the proposed structure. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2013). All hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2013.

Table 1. Crystal data and structure refinement for **2.150**

X-ray ID	sarpong62	
Sample/notebook ID	RMXIII-128B1	
Empirical formula	C16 H15 N O3	
Formula weight	269.29	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Orthorhombic	
Space group	P 21 21 21	
Unit cell dimensions	a = 6.3718(4) Å	a = 90°.
	b = 11.6995(7) Å	b = 90°.
	c = 17.3017(10) Å	g = 90°.
Volume	1289.79(13) Å ³	
Z	4	
Density (calculated)	1.387 Mg/m ³	
Absorption coefficient	0.786 mm ⁻¹	
F(000)	568	
Crystal size	0.060 x 0.040 x 0.020 mm ³	
Crystal color/habit	colorless plate	
Theta range for data collection	4.562 to 68.230°.	
Index ranges	-7<=h<=7, -13<=k<=10, -20<=l<=20	
Reflections collected	15734	
Independent reflections	2352 [R(int) = 0.0153]	
Completeness to theta = 67.000°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.929 and 0.880	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	2352 / 0 / 183	
Goodness-of-fit on F ²	1.114	
Final R indices [I>2sigma(I)]	R1 = 0.0307, wR2 = 0.0820	
R indices (all data)	R1 = 0.0308, wR2 = 0.0821	
Absolute structure parameter	0.5(3)	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.210 and -0.132 e.Å ⁻³	

Table 2. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for **2.150**. $U(\text{eq})$ is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	$U(\text{eq})$
C(1)	9554(3)	1184(2)	2128(1)	22(1)
C(2)	11249(4)	1949(2)	2470(1)	25(1)
C(3)	10426(3)	1011(2)	2968(1)	23(1)
C(4)	11814(3)	3(2)	3112(1)	25(1)
C(5)	11113(4)	-797(2)	3711(1)	26(1)
C(6)	9161(4)	-771(2)	4000(1)	26(1)
C(7)	7626(4)	132(2)	3757(1)	26(1)
C(8)	8647(4)	1264(2)	3529(1)	24(1)
C(9)	7117(4)	2020(2)	3080(1)	26(1)
C(10)	7407(3)	1682(2)	2235(1)	22(1)
C(11)	9944(3)	373(2)	1485(1)	22(1)
C(12)	11837(3)	319(2)	1082(1)	26(1)
C(13)	12096(4)	-454(2)	492(1)	30(1)
C(14)	8687(4)	-1161(2)	673(1)	29(1)
C(15)	8381(4)	-404(2)	1273(1)	25(1)
C(16)	8353(4)	-1659(2)	4544(1)	35(1)
N(1)	10527(3)	-1171(2)	279(1)	31(1)
O(1)	13393(2)	-160(1)	2732(1)	29(1)
O(2)	6125(2)	1787(1)	1723(1)	26(1)
O(3)	10760(3)	-1864(2)	-308(1)	44(1)

Table 3. Bond lengths [$\text{\AA}$] and angles [$^\circ$] for **2.150**.

C(1)-C(11)	1.484(3)	C(8)-H(8)	1.0000
C(1)-C(10)	1.498(3)	C(9)-C(10)	1.527(3)
C(1)-C(2)	1.522(3)	C(9)-H(9A)	0.9900
C(1)-C(3)	1.568(3)	C(9)-H(9B)	0.9900
C(2)-C(3)	1.490(3)	C(10)-O(2)	1.211(3)
C(2)-H(2A)	0.9900	C(11)-C(12)	1.395(3)
C(2)-H(2B)	0.9900	C(11)-C(15)	1.397(3)
C(3)-C(4)	1.495(3)	C(12)-C(13)	1.374(3)
C(3)-C(8)	1.522(3)	C(12)-H(12)	0.9500
C(4)-O(1)	1.217(3)	C(13)-N(1)	1.356(3)
C(4)-C(5)	1.466(3)	C(13)-H(13)	0.9500
C(5)-C(6)	1.341(3)	C(14)-N(1)	1.356(3)
C(5)-H(5)	0.9500	C(14)-C(15)	1.378(3)
C(6)-C(16)	1.494(3)	C(14)-H(14)	0.9500
C(6)-C(7)	1.499(3)	C(15)-H(15)	0.9500
C(7)-C(8)	1.527(3)	C(16)-H(16A)	0.9800
C(7)-H(7A)	0.9900	C(16)-H(16B)	0.9800
C(7)-H(7B)	0.9900	C(16)-H(16C)	0.9800
C(8)-C(9)	1.529(3)	N(1)-O(3)	1.307(2)
C(11)-C(1)-C(10)	119.61(18)	C(4)-C(3)-C(8)	119.18(18)
C(11)-C(1)-C(2)	123.27(18)	C(2)-C(3)-C(1)	59.61(13)
C(10)-C(1)-C(2)	111.82(17)	C(4)-C(3)-C(1)	117.79(17)
C(11)-C(1)-C(3)	123.52(18)	C(8)-C(3)-C(1)	107.60(17)
C(10)-C(1)-C(3)	105.06(17)	O(1)-C(4)-C(5)	122.3(2)
C(2)-C(1)-C(3)	57.64(13)	O(1)-C(4)-C(3)	121.5(2)
C(3)-C(2)-C(1)	62.75(13)	C(5)-C(4)-C(3)	116.17(19)
C(3)-C(2)-H(2A)	117.5	C(6)-C(5)-C(4)	122.1(2)
C(1)-C(2)-H(2A)	117.5	C(6)-C(5)-H(5)	118.9
C(3)-C(2)-H(2B)	117.5	C(4)-C(5)-H(5)	118.9
C(1)-C(2)-H(2B)	117.5	C(5)-C(6)-C(16)	122.6(2)
H(2A)-C(2)-H(2B)	114.6	C(5)-C(6)-C(7)	121.1(2)
C(2)-C(3)-C(4)	117.99(19)	C(16)-C(6)-C(7)	116.2(2)
C(2)-C(3)-C(8)	119.15(18)	C(6)-C(7)-C(8)	113.92(19)

C(6)-C(7)-H(7A)	108.8	C(6)-C(16)-H(16B)	109.5
C(8)-C(7)-H(7A)	108.8	H(16A)-C(16)-H(16B)	109.5
C(6)-C(7)-H(7B)	108.8	C(6)-C(16)-H(16C)	109.5
C(8)-C(7)-H(7B)	108.8	H(16A)-C(16)-H(16C)	109.5
H(7A)-C(7)-H(7B)	107.7	H(16B)-C(16)-H(16C)	109.5
C(3)-C(8)-C(7)	108.23(17)	O(3)-N(1)-C(13)	120.7(2)
C(3)-C(8)-C(9)	105.24(17)	O(3)-N(1)-C(14)	119.6(2)
C(7)-C(8)-C(9)	111.17(18)	C(13)-N(1)-C(14)	119.73(18)
C(3)-C(8)-H(8)	110.7		
C(7)-C(8)-H(8)	110.7		
C(9)-C(8)-H(8)	110.7		
C(10)-C(9)-C(8)	105.06(17)		
C(10)-C(9)-H(9A)	110.7		
C(8)-C(9)-H(9A)	110.7		
C(10)-C(9)-H(9B)	110.7		
C(8)-C(9)-H(9B)	110.7		
H(9A)-C(9)-H(9B)	108.8		
O(2)-C(10)-C(1)	124.42(19)		
O(2)-C(10)-C(9)	126.34(19)		
C(1)-C(10)-C(9)	109.24(18)		
C(12)-C(11)-C(15)	117.10(19)		
C(12)-C(11)-C(1)	123.31(19)		
C(15)-C(11)-C(1)	119.57(19)		
C(13)-C(12)-C(11)	120.3(2)		
C(13)-C(12)-H(12)	119.8		
C(11)-C(12)-H(12)	119.8		
N(1)-C(13)-C(12)	121.3(2)		
N(1)-C(13)-H(13)	119.3		
C(12)-C(13)-H(13)	119.3		
N(1)-C(14)-C(15)	120.4(2)		
N(1)-C(14)-H(14)	119.8		
C(15)-C(14)-H(14)	119.8		
C(14)-C(15)-C(11)	121.0(2)		
C(14)-C(15)-H(15)	119.5		
C(11)-C(15)-H(15)	119.5		
C(6)-C(16)-H(16A)	109.5		

Table 4. Anisotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for **2.150**. The anisotropic displacement factor exponent takes the form: $-2p^2 [h^2 a^{*2} U^{11} + \dots + 2 h k a^* b^* U^{12}]$

	U ¹¹	U ²²	U ³³	U ²³	U ¹³	U ¹²
C(1)	25(1)	22(1)	19(1)	1(1)	-1(1)	-3(1)
C(2)	27(1)	23(1)	25(1)	-2(1)	-2(1)	-4(1)
C(3)	27(1)	22(1)	20(1)	-3(1)	-3(1)	-1(1)
C(4)	26(1)	24(1)	23(1)	-7(1)	-8(1)	-1(1)
C(5)	32(1)	24(1)	22(1)	-3(1)	-7(1)	4(1)
C(6)	38(1)	23(1)	19(1)	-5(1)	-4(1)	-2(1)
C(7)	30(1)	29(1)	21(1)	-2(1)	1(1)	1(1)
C(8)	30(1)	24(1)	20(1)	-4(1)	0(1)	2(1)
C(9)	31(1)	25(1)	24(1)	-2(1)	2(1)	3(1)
C(10)	27(1)	17(1)	24(1)	2(1)	0(1)	-2(1)
C(11)	27(1)	20(1)	18(1)	3(1)	-2(1)	2(1)
C(12)	29(1)	27(1)	22(1)	3(1)	0(1)	2(1)
C(13)	33(1)	33(1)	22(1)	2(1)	2(1)	9(1)
C(14)	38(1)	23(1)	27(1)	-1(1)	-10(1)	2(1)
C(15)	30(1)	22(1)	22(1)	1(1)	-4(1)	2(1)
C(16)	46(1)	29(1)	30(1)	3(1)	1(1)	1(1)
N(1)	44(1)	28(1)	19(1)	-2(1)	-5(1)	14(1)
O(1)	26(1)	31(1)	31(1)	-3(1)	-3(1)	4(1)
O(2)	25(1)	26(1)	26(1)	2(1)	-1(1)	-1(1)
O(3)	62(1)	42(1)	28(1)	-17(1)	-10(1)	23(1)

Table 5. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for **2.150**.

	x	y	z	U(eq)
H(2A)	12691	1866	2265	30
H(2B)	10851	2741	2607	30
H(5)	12073	-1351	3900	31
H(7A)	6636	272	4188	32
H(7B)	6803	-157	3313	32
H(8)	9187	1673	3996	29
H(9A)	5655	1880	3249	32
H(9B)	7450	2839	3157	32
H(12)	12954	820	1216	31
H(13)	13401	-488	227	35
H(14)	7602	-1679	535	35
H(15)	7089	-410	1547	30
H(16A)	9398	-2267	4601	52
H(16B)	7046	-1982	4340	52
H(16C)	8083	-1310	5050	52

Chapter 3: Toward the Synthesis of the Lycoplamine-type *Lycopodium* Alkaloids

3.1 Previous Approaches and Synthetic Design

Lycoplamines B, C, and D (**3.1-3.3**, Figure 1) are three unique fawcettimine-type *Lycopodium* alkaloids that were isolated from *Lycopodium complanatum* in 2006 by Kobayashi and coworkers.¹ At the outset of our work toward their total synthesis, they had not yet been synthesized. They are structurally quite similar to fawcettimine (**3.4**). For example, lycoplamine B-D and fawcettimine share the same fused 6-5 bicycle (highlighted in red) and nine-membered azonine ring system (highlighted in blue) with a carbon-nitrogen bond at C13. Lycoplamine B, C and D differ from fawcettimine in the additional functionality on the six-membered ring. While the lycoplamine are unique from fawcettimine in this way, we hoped to make use of some of the strategies that had been applied to the synthesis of fawcettimine in the past for the synthesis of **3.1-3.3**.

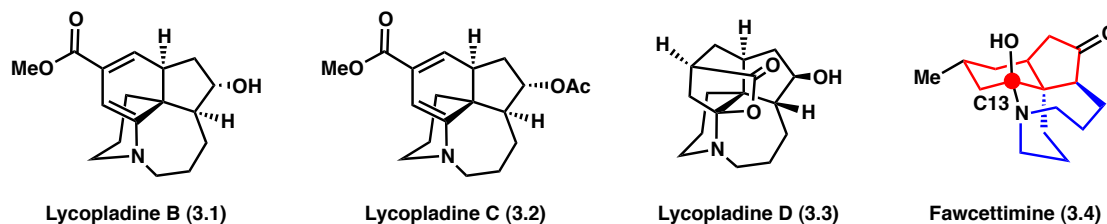


Figure 1. Lycoplamine B-D (**3.1-3.3**) and fawcettimine (**3.4**)

Fawcettimine (**3.4**, Figure 2), also referred to as Burnell's Base A, was first isolated as the perchlorate salt in 1959.² Its structure was originally assigned as tricycle **3.5** which isomerizes to hemiaminal **3.4** and **3.6**. In 1967, a collaboration between three research groups suggested that the correct structure of fawcettimine was the hemiaminal form (**3.4**), with minimal isomerism to **3.5** or **3.6**.³

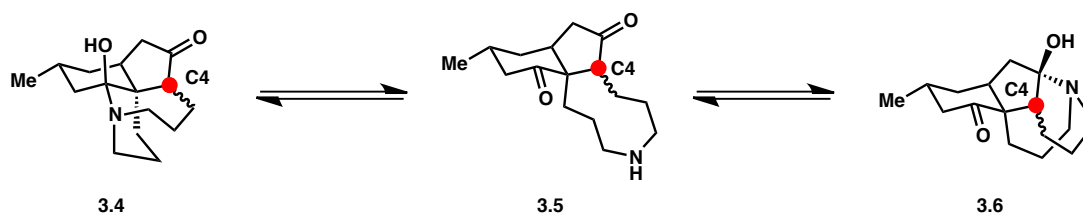
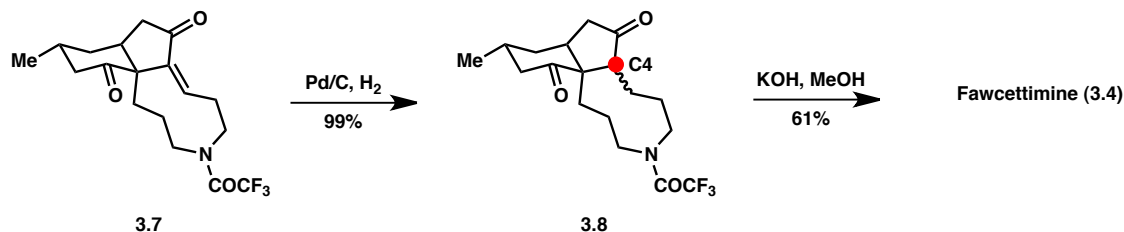


Figure 2. Isomerism of fawcettimine

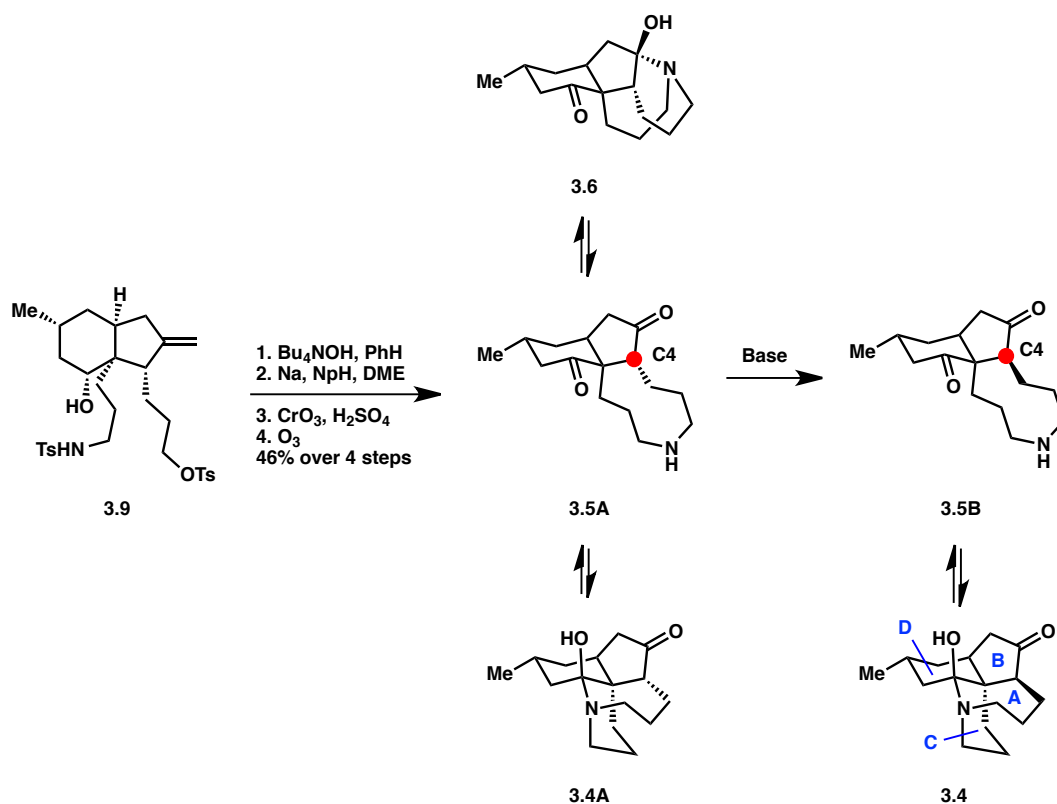
Twenty years after its initial discovery, Inubushi completed the first synthesis of fawcettimine in 1979 via 6-5-9 tricycle **3.7** (Scheme 1).⁴ Hydrogenation of **3.7** under standard conditions gave **3.8** as a mixture of diastereomers at C4 which, following hydrolysis of the trifluoroacetamide, gives fawcettimine. This 26-step synthesis yielded fawcettimine in 0.1% yield. Even after the publication of the Inubushi synthesis, there was still continued doubt about the stereochemistry at the C4 center. Since Inubushi had a mixture of diastereomers at the C4 center (resulting from the hydrogenation), it was still unknown which corresponded to the natural product.

Scheme 1. Inubushi's synthesis of fawcettimine (**3.4**)



Heathcock pioneered conformational studies on the fawcettimine framework when he applied a similar 6-5-9 tricycle to the synthesis of fawcettimine in 1986.⁵ In this landmark synthesis, Heathcock and coworkers were able to access 6-5-9 tricycle **3.5A** from bicycle **3.9** through intramolecular displacement of the tosylate to form the 9-membered ring, oxidation, and ozonolysis (Scheme 2).

Scheme 2. Heathcock's synthesis of fawcettimine (**3.4**)



This tricycle (**3.5A**) was available as a single diastereomer at the C4 center. NMR studies of **3.5A** showed minimal isomerism to **3.6**, and none at all to **3.4A**. Diastereomer **3.5B** was more relevant, as it was shown to correspond to the natural product. In this case, hemiaminal **3.4** was favored over the diketoamine form (**3.5B**). In fact, exposure of **3.5A** to basic conditions leads to formation of fawcettimine (**3.4**), which is formed in

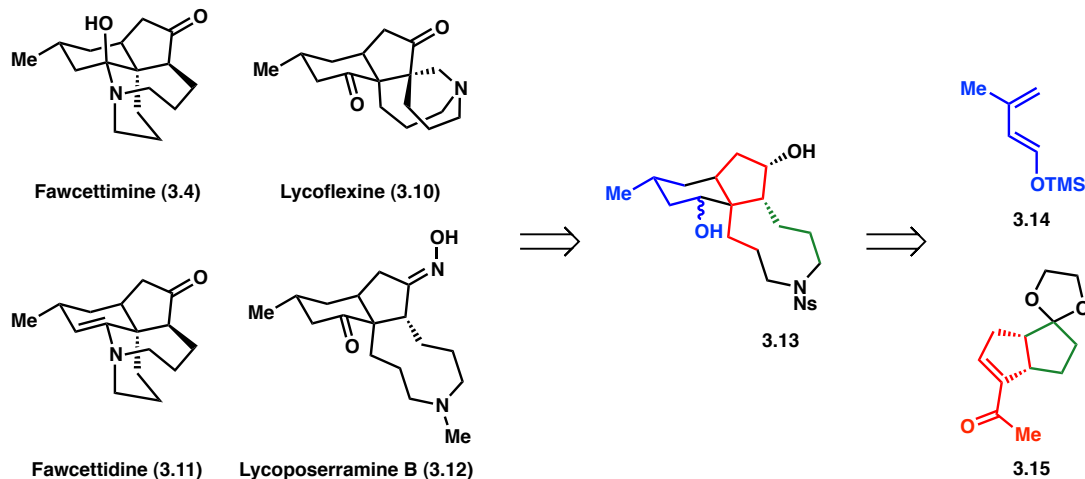
95% yield via isomerization to the thermodynamically favored β -diastereomer at the C4 position. Heathcock's 13-step synthesis arrives at fawcettimine in an impressive 16.6% overall yield. This efficient synthesis set the stage for the first X-ray analysis and complete structural assignment of fawcettimine.

Heathcock and Inubushi's early work has had a lasting influence on other strategies employed in the synthesis of these molecules. Even with the great advances in chemistry made since then, the 6-5-9 tricycles prepared by Heathcock and Inubushi, and derivatives thereof, have long been considered the best way to access fawcettimine and related molecules. Because of the elegance of this type of route, Heathcock's observations have been exploited to access many related fawcettimine-type *Lycopodium* alkaloids. Significant effort has been dedicated to creative ways to access the Heathcock tricycle (**3.5B**, Scheme 2), but there is limited diversity in methods to advance this intermediate. Much of the novelty in the syntheses of fawcettimine related molecules comes from the innovative construction of the initial *cis*-fused 6-5 bicycle. We recently published a review on this subject entitled: Heathcock-Inspired Strategies for the Synthesis of Fawcettimine-type *Lycopodium* Alkaloids.⁶

Our approach to lycopladienes B-D was also shaped by the Heathcock-strategy. As we considered methods to synthesize our 6-5 bicycle en route to the Heathcock tricycle, we were drawn to the Diels-Alder reaction. Diels-Alder reactions have long been attractive transformations in total synthesis. The stereospecific nature of this reaction represents an elegantly simple way to set relative stereochemistry and rapidly generate molecular complexity. Not surprisingly, the Diels-Alder reaction has been utilized previously for the synthesis of the 6-5 bicycle of the fawcettimine-type *Lycopodium* alkaloids. While advantageous in some senses, it is still a challenge to perform a Diels-Alder reaction enantioselectively.

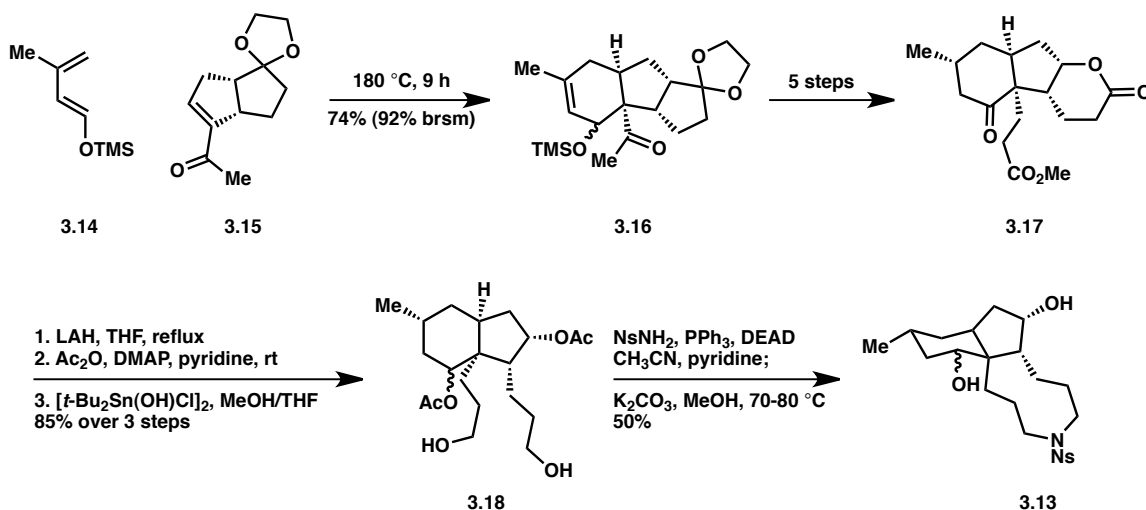
In 2013, after we had begun our studies to access a Heathcock-type tricycle using a Diels-Alder reaction, the Williams group was able to access fawcettimine (**3.4**), lycoflexine (**3.10**), fawcettidine (**3.11**), and lycoposerramine B (**3.12**) from the elaboration of a common 6-5-9 tricycle (**3.13**, Scheme 3).⁷ This key Heathcock-type tricycle was available from diene (**3.14**) and dienophile (**3.15**) as precursors using a Diels-Alder reaction in the forward sense.

Scheme 3. Williams' retrosynthetic strategy to access various *Lycopodium* alkaloids



Williams' Diels-Alder reaction was very challenging due to the fact that enones such as **3.15** are known to be poor dienophiles. This is because of the lack of a second activating group and the electronically and sterically deactivating β -substituent. Additionally, dienophile **3.15** is sensitive to Brønsted and Lewis acidic conditions because of the labile ketal group. The Williams group was able to surmount these challenges by reacting diene **3.14** and dienophile **3.15** at 180 °C (neat) for 9 h to give tricycle **3.16** in 74% yield (Scheme 4), which constitutes the first Diels-Alder reaction of this type. While this reaction is not enantioselective, the precursor to dienophile **3.15** was subjected to kinetic resolution to provide an enantioselective synthesis.

Scheme 4. Williams' synthesis of tricycle **3.13**

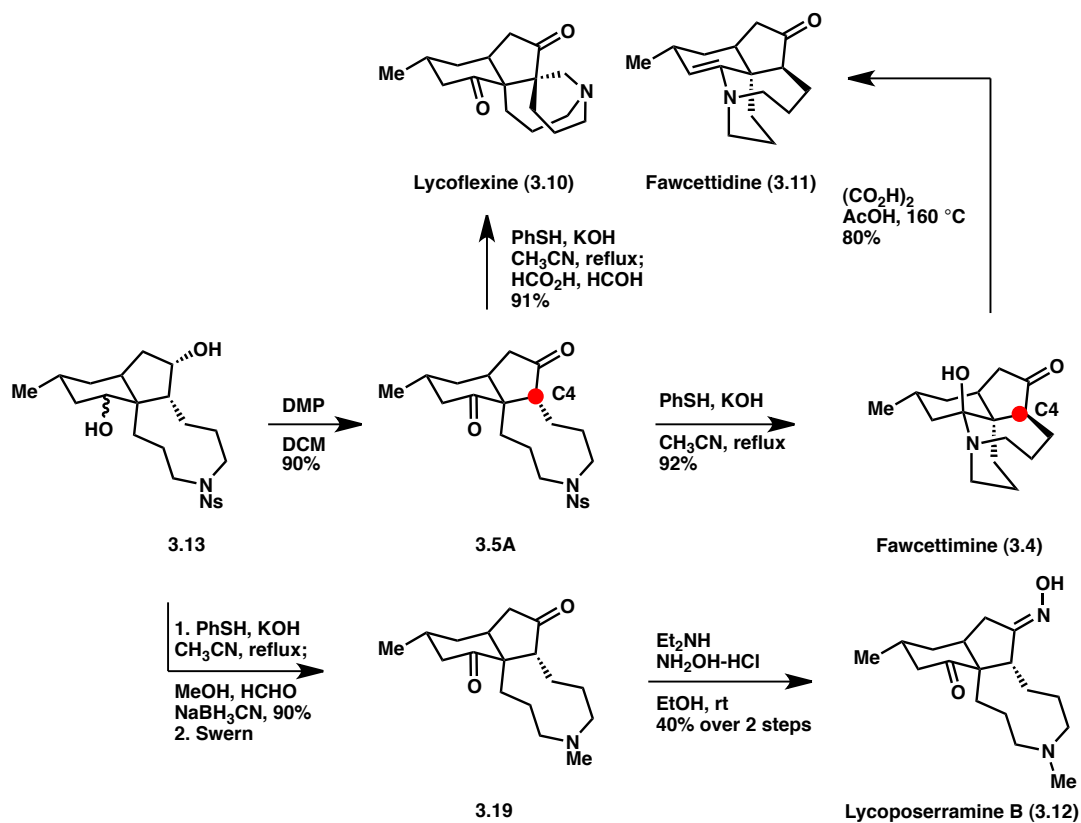


The product of the Diels-Alder reaction, tricycle **3.16**, was further elaborated in 5 steps to give γ -lactone **3.17**. Opening of this lactone and further manipulation to give diol **3.18** constitutes a creative way to access the precursor to the key Heathcock-type 6-5-9 tricycle. This diol (**3.18**) was converted to the azonine ring via a challenging double

Fukuyama-Mitsunobu reaction to provide tricycle **3.13**.

Tricycle **3.13** served as a common intermediate that was differentially functionalized to provide *Lycopodium* alkaloids fawcettimine (**3.4**), lycoflexine (**3.10**), fawcettidine (**3.11**), and lycoposerramine B (**3.12**). Oxidation of **3.13** affords the *N*-nosyl protected version of the Heathcock tricycle (**3.5A**, Scheme 5). Consistent with Heathcock's observations, unveiling the amine group in **3.5A** proceeds with equilibration of the C4 stereocenter to furnish the β -diastereomer, which adds into the cyclohexanone carbonyl group to give fawcettimine (**3.4**). Fawcettimine (**3.4**) can then be dehydrated to give fawcettidine (**3.11**).

Scheme 5. Williams' endgame to various *Lycopodium* alkaloids

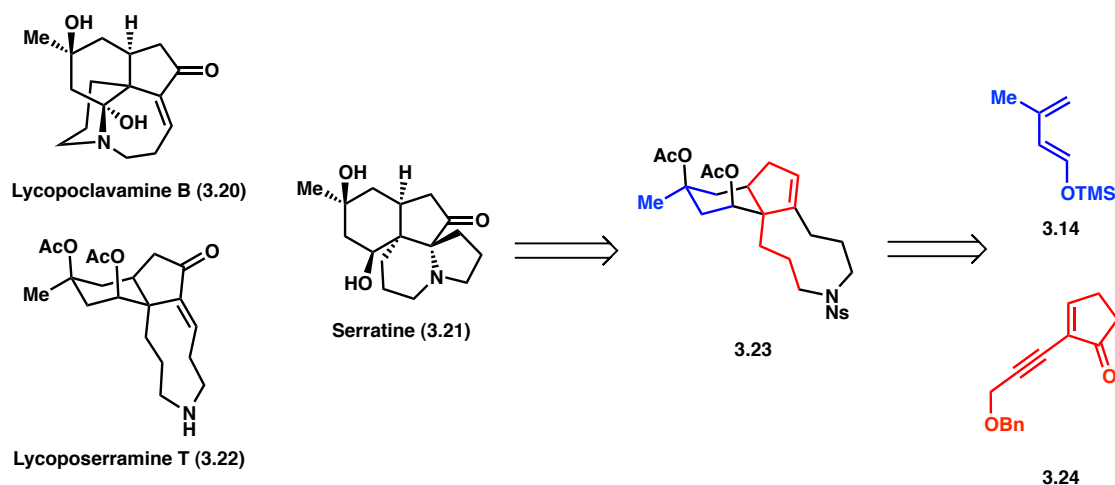


Alternatively, Williams' tricycle **3.5A** was converted to lycoflexine (**3.10**) by deprotection of the secondary amine and subsequent Mannich reaction. This transformation is based on the biosynthetic proposal made by Ayer in 1973 when lycoflexine was first isolated.⁸ In 2010 Ramharter and Mulzer also exploited this biosynthetic transformation to access lycoflexine.⁹ Tricycle **3.13** was applied to the synthesis of lycoposerramine B (**3.19**) by exchange of the nosyl protecting group for a methyl group and selective oxime formation.

The Williams work constitutes a very effective approach to the Heathcock-type tricycles that can be applied to the synthesis of a range of *Lycopodium* alkaloids. This use of the Diels-Alder reaction provides an efficient way to access the initial 6-5 bicycle that is easily resolved using a kinetic resolution of the dienophile precursor.

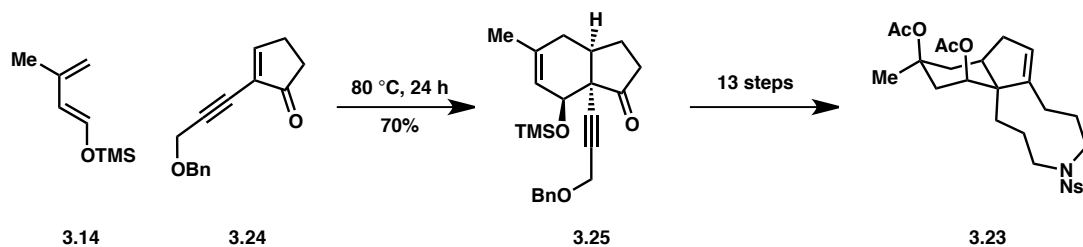
The Taniguchi group subsequently published a second example of the Diels-Alder reaction being applied to great effect in the synthesis of a number of *Lycopodium* alkaloids in 2013.¹⁰ They were able to access lycopoclavamine B (**3.20**), lycoposerramine T (**3.22**) and serratine (**3.21**) from a common Heathcock-like tricycle (**3.23**, Scheme 6). This tricycle was elaborated from the Diels-Alder adduct forged from diene **3.14**, identical to that used in the Williams work, and dienophile **3.24**.

Scheme 6. Taniguchi's retrosynthetic strategy to access various *Lycopodium* alkaloids



In line with the Williams group's observations, this Diels-Alder reaction was also very difficult to effect. Ultimately, heating diene **3.14** and dienophile **3.24** neat at 80 °C yielded 70% of the endo product (**3.25**, Scheme 7) in addition to 7% of the exo product (not shown). This hydrindinone derivative could be further elaborated into the key 6-5-9 tricycle (**3.23**) in 13 steps. The nine-membered ring was formed using two sequential Mitsunobu reactions.

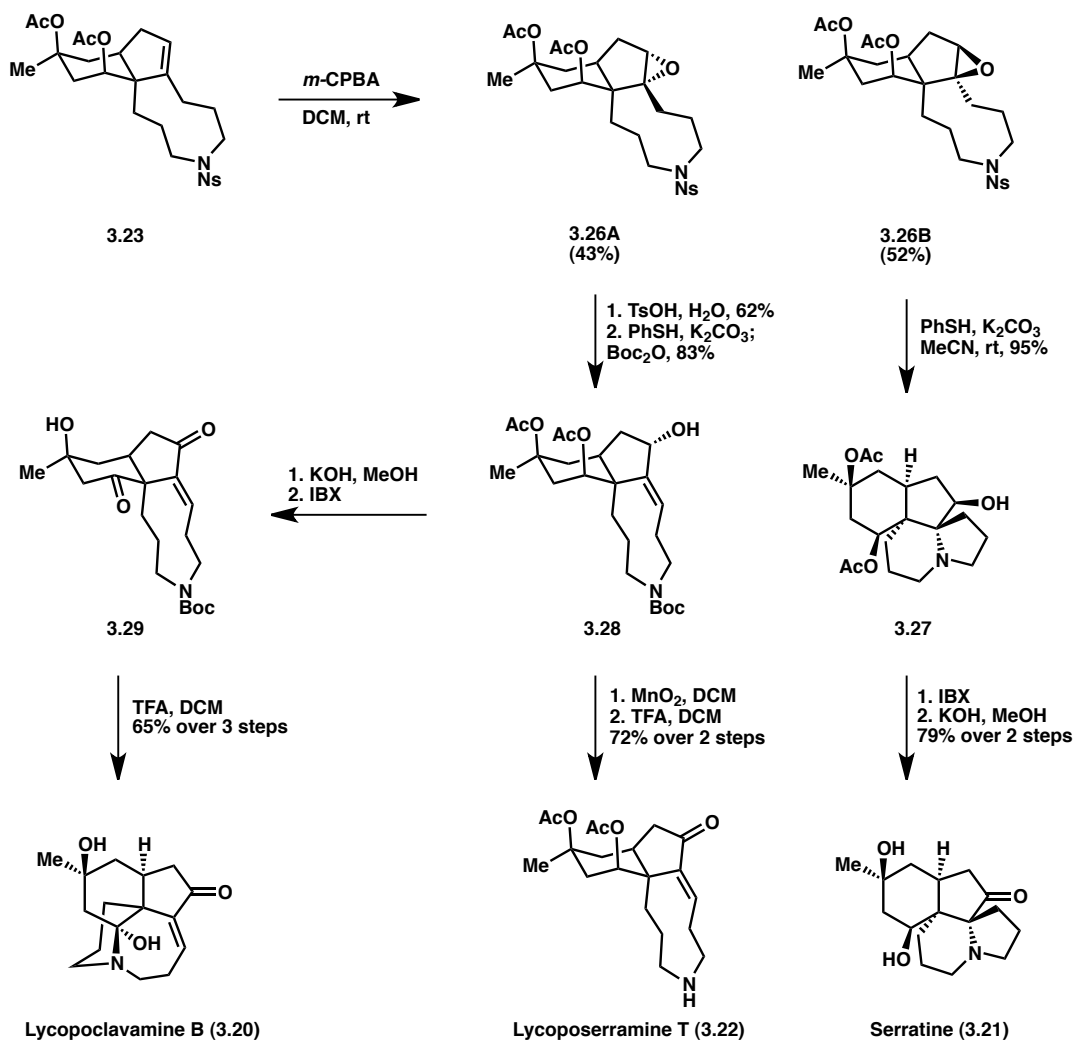
Scheme 7. Taniguchi's synthesis of tricycle **3.23**



Tricycle **3.23** was applied to the synthesis of lycopoclavamine B (**3.20**), lycoposerramine T (**3.22**) and serratine (**3.21**) via the intermediacy of epoxides **3.26A** and **3.26B** respectively (Scheme 8). The two epoxide diastereomers (**3.26A** and **3.26B**) were separated and used in a divergent synthesis of the aforementioned natural products. The major diastereomer of the epoxide (**3.26B**) cyclizes to form the core structure of serratine (**3.27**) upon deprotection of the amine. Oxidation and protecting group cleavage then furnishes the natural product (**3.21**). The minor diastereomer of the epoxide (**3.26A**) was

opened via elimination to give **3.28**, which is further manipulated through oxidation and Boc-cleavage to give lycoposerramine T (**3.22**). Alternatively, **3.28** was exposed to potassium hydroxide in methanol to unveil the hydroxyl groups. Subsequent oxidation furnishes enone **3.29**. Interestingly, upon cleavage of the Boc protecting group, the amine adds into the adjacent carbonyl on the 6-membered ring to give lycopoclavamine B (**3.20**).

Scheme 8. Taniguchi's endgame to various *Lycopodium* alkaloids



The formation of **3.20** is a fascinating sequence because it mimics the reactivity that Heathcock observed in his 1989 synthesis of fawcettimine. His work showed that only the β -diastereomer at C4 would add into the carbonyl on the 6-membered ring (see Scheme 2). Taniguchi's work sheds further light on the equilibrium of the ketoamines and shows that the corresponding unsaturated system is capable of forming a similar hemiaminal, albeit with different stereochemistry.

While the Taniguchi synthesis was achieved in a racemic fashion, it is a valuable demonstration of the use of a Diels-Alder reaction to create the initial 6–5 *cis*-fused

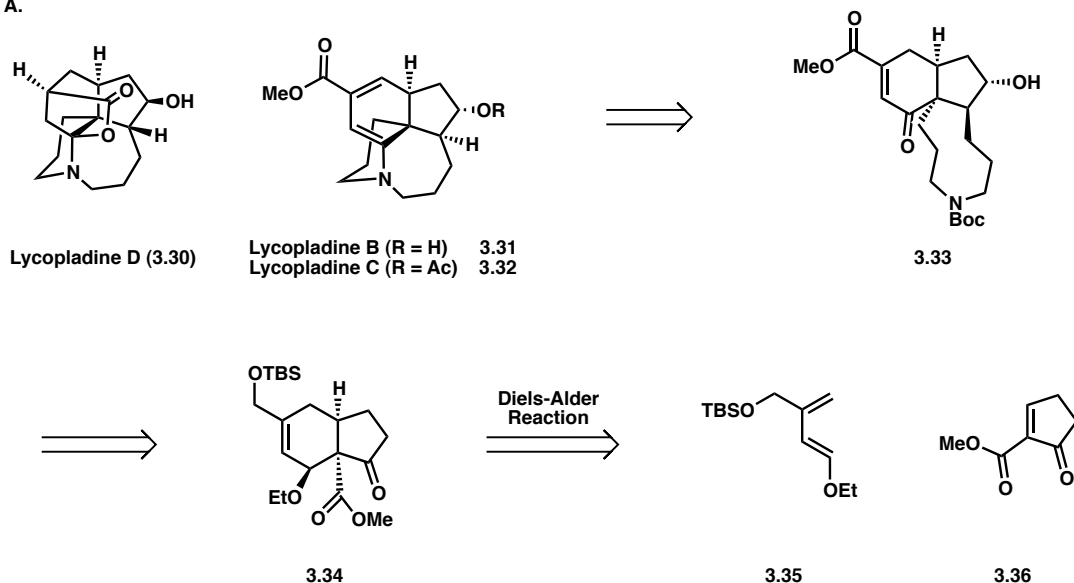
bicycle. The use of a Diels-Alder reaction in this context is appropriate, because the dienophile (**3.25**) already has the required three-carbon chain installed, which increases convergency.

As we considered lycopladienes B, C, and D (**3.1-3.3**, Scheme 9A) we envisioned pursuing a divergent route that would retrosynthetically bring all three natural products back to Heathcock-tricycle **3.33**. This tricycle (**3.33**) could arise from the functionalization of 6-5 bicycle **3.34**, which could be derived from diene (**3.35**) and dieneophile (**3.36**) precursors. Like the Williams and Taniguchi syntheses that were published after we began our work toward lycopladienes B-D, we appreciated the stereoselective nature of the Diels-Alder reaction to set the *syn*-ring fusion of the 6-5 bicycle.

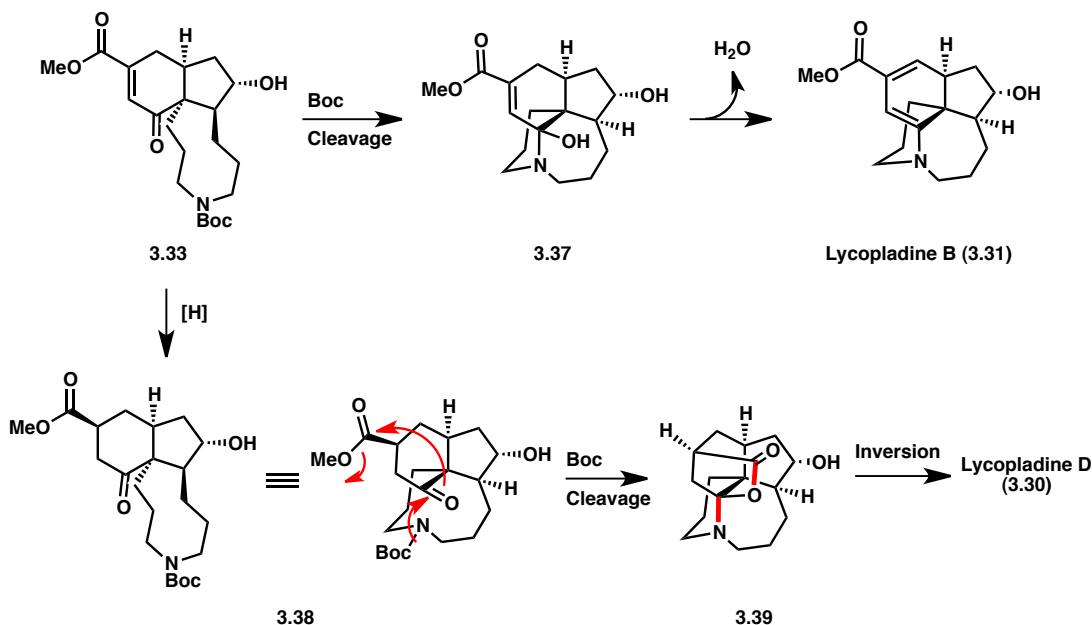
Our disconnection strategy is an extension of the Heathcock work because we hope to use the Heathcock tricycle (**3.33**, Scheme 9B) in an extended cascade reaction as a part of the key step. After the amine addition into the adjacent carbonyl group of the six-membered ring (**3.33** to **3.37**) the alcohol group could further undergo dehydration to give lycopladiene B (**3.31**). If we reduce the carbon-carbon double bond of **3.33** to give **3.38** prior to cleaving the Boc-group, we envision that the alcohol of the resulting hemiaminal could interact with the methyl ester to form the caged carbon skeleton of lycopladiene D (**3.39**). We would then invert the stereocenters on the five-membered ring to give the natural product (**3.30**).

Scheme 9. Retrosynthetic analysis of lycopladines B-D (3.30-3.32)

A.



B.

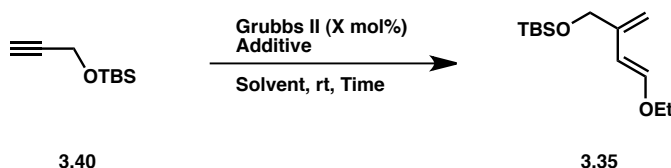


3.2 Synthesis of Heathcock-type 6-5-9 Tricycle

Our initial goal en route to lycopladines B, C and D was to build a simple 6-5-9 tricycle. Toward this goal, we began to evaluate methods to access diene **3.35** (Table 1). We were drawn to using enyne metathesis because it is known as a very efficient and clean method for making a variety of substituted dienes.¹¹ We decided to make use of ethyl vinyl ether as the alkene component because it has a low boiling point and is easy to

remove the large amount of excess reagent that is often required. It is also commercially available and inexpensive. We were happy to see that standard conditions using 5 mol% of Grubbs 2nd generation catalyst (Grubbs II) in benzene cleanly provided 76% of the desired diene (entry 1, Table 1). Running the reaction in the presence of ethylene (1 atm) did not appreciably improve the yield (entry 2) and increasing the pressure of ethylene to 40 psi actually provided a decreased yield of the desired diene (entry 3). Although we were able to access multiple gram quantities of diene **3.35** using the conditions in entry 1, it was still less than ideal because Grubbs II is quite expensive. To synthesize 4.5 g of diene **3.35**, 1.1 g of Grubbs II (\$284) is required. Because of this, we wanted to lower the catalyst loading. Lipshutz and coworkers recently published a paper on the addition of copper iodide to metathesis reactions as a method for increasing turnover number and decreasing catalyst loading.¹² This is proposed to be an effect of the copper cation sequestering the phosphine ligand and iodide acting to stabilize the ruthenium catalyst through a ligand effect. The increased stability of the catalyst reduces decomposition and allows for a lower catalyst loading. For our reaction, we were pleased to see that the addition of 3 mol% of copper iodide allowed us to use 2 mol% of Grubbs II, and obtain a 49% yield of the desired diene (**3.35**, entry 4). We were further excited to see that by switching the solvent from benzene to diethyl ether, the yield was increased to 80% (entry 5). Now for the same \$284 of Grubbs II, we can now access 12.5 g of diene **3.35**.

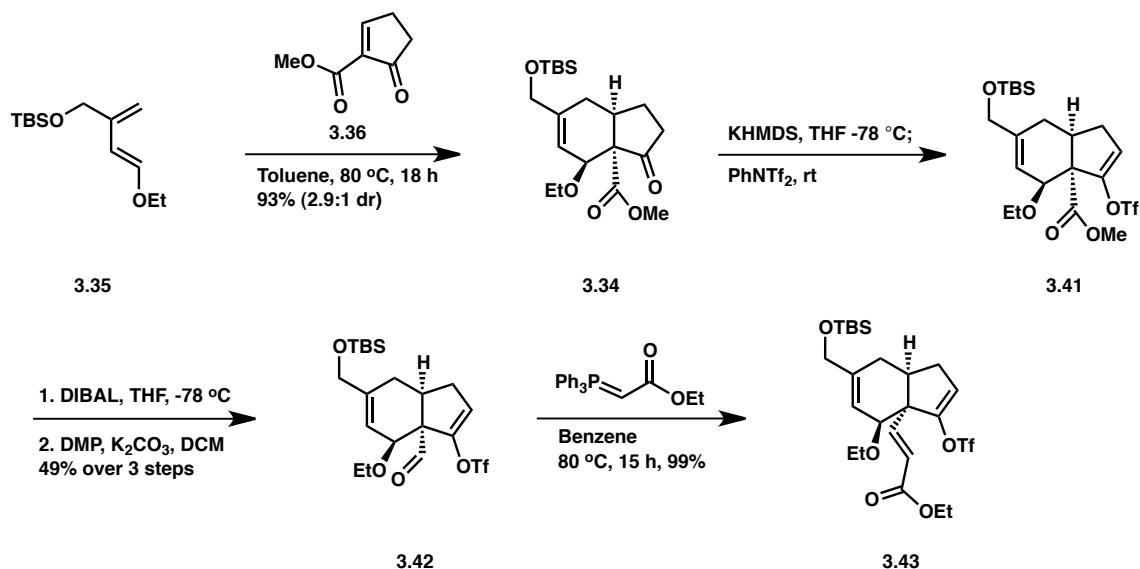
Table 1. Grubbs enyne metathesis to access diene **3.35**



Entry	Amount Grubbs II	Additive	Solvent	Time (h)	E/Z	Yield 3.35
1	5 mol%	-	Benzene	20	2.6:1	76%
2	5 mol%	ethylene (1 atm)	Benzene	20	3.1:1	79%
3	5 mol%	ethylene (40 psi)	Benzene	20	3.4:1	67%
4	2 mol%	3 mol% CuI	Benzene	18	2.6:1	49%
5	2 mol%	3 mol% CuI	Diethyl Ether	18	2.9:1	80%

With diene **3.35** in hand, we were able to effect a Diels-Alder reaction with dieneophile **3.36** (Scheme 10). The Diels-Alder reaction proceeded readily when heated in toluene at 80 °C to provide the desired 6-5 bicycle (**3.34**) in 93% yield. Bicycle **3.34** was isolated in a 2.9:1 mixture of diastereomers at the ethyl ether position (major diastereomer illustrated). For simplicity, we separated the diastereomers at this stage and chose to bring forward only the major diastereomer. From bicycle **3.34**, we were able to effect vinyl triflate formation to furnish **3.41**. Ester **3.41** was then reduced to the corresponding alcohol (not shown), which was oxidized to provide aldehyde **3.42** in 49% yield over 3 steps. Aldehyde **3.42** was then used in a Wittig reaction with (ethoxycarbonylmethylene) triphenylphosphorane to provide α , β -unsaturated ester **3.43** in 99% yield.

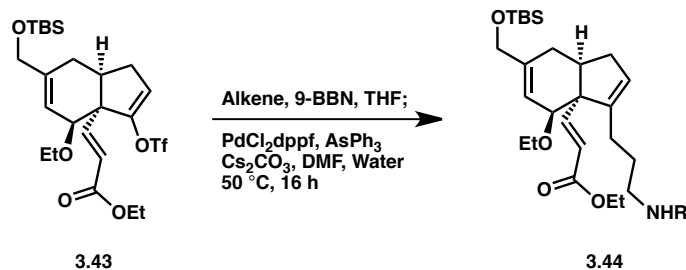
Scheme 10. Synthesis of ester **3.43**



From vinyl triflate **3.43** we began to look into methods for installing the final three-carbon chain required for the natural product (Table 2). We were drawn to conditions that were used by the Toste group in their synthesis of fawcettimine, given the similarity of our substrate to theirs.¹³ These conditions are unique, because they enable cross coupling to an in-situ generated sp³ borane species. This type of cross coupling partner was also used by the Trost group in 1998 in their synthesis of sphingofungin F.¹⁴ The Toste group proposes that β -hydride elimination in the organo-palladium intermediate is avoided due to intramolecular coordination of the palladium center to the alkene in the substrate (**3.43**). This coordination reduces the amount of β -hydride elimination through the occupation of the vacant site on the palladium center, which is required for this undesired pathway. These conditions are also unique because triphenylarsine is used as a ligand. This is known as a Johnson-Braun modification and it is proposed that triphenylarsine promotes a cleaner reaction with a higher turnover rate for the palladium catalyst than the traditional reaction with triphenylphosphine. This is thought to be through ligand effects. Triphenylarsine is a less strong σ -donor as compared to triphenylphosphine, so it is more readily dissociating and can aid in accelerating the transmetallation step.¹⁵

Using the Trost/Toste conditions with the borane generated from allylamine and 9-BBN gave a mixture of products with low mass recovery (entry 1, Table 2). The *N*-nosyl-allylamine similarly provided a mixture of products with low mass recovery (entry 2). When we made use of the *N*-Boc-allylamine, we were pleased to see that we could obtain 79% of the desired amine (**2.44**).

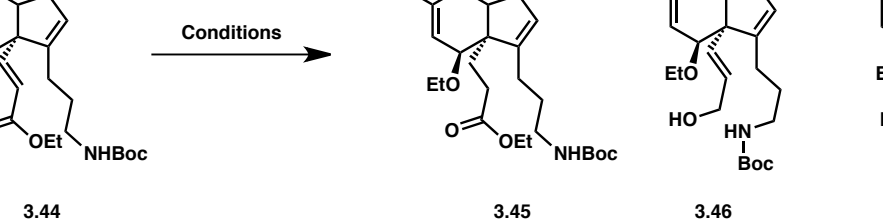
Table 2. Suzuki cross-coupling to furnish amine **2.44**



Entry	Alkene	R	Result
1	allyl amine	H	Mixture/Low Mass Recovery
2	<i>N</i> -Ns-allylamine	Ns	Mixture/Low Mass Recovery
3	<i>N</i> -Boc-allylamine	Boc	79% 3.44

We then looked to reduce the di-substituted carbon-carbon double bond of ester **3.44** (Table 3). A major challenge in performing this reduction was differentiating between three carbon-carbon double bonds. We hoped to exploit the fact that the di-substituted carbon-carbon double bond is in conjugation with the ester, and would allow us to arrive at **3.47** through sequential 1,4- and 1,2-reductions. Lithium triethylborohydride is known to mediate this transformation.¹⁶ With our substrate we obtained a 2:1 mixture of the starting material (**3.44**) and allyl alcohol **3.46** (entry 1, Table 3). Allowing the reaction to stir for a longer period of time at -78°C before warming to room temperature provided 53% of allyl alcohol **3.46** (entry 2). We also investigated conditions using sodium borohydride and copper chloride that were used in Forsyth's synthesis of (-)-cacospongionolide F.¹⁷ Unfortunately, these conditions returned starting material (entry 3). Both Stryker's reagent (entry 4) and magnesium turnings in methanol (entry 5)¹⁸ also returned starting material. We also attempted to use heterogeneous reduction conditions with Pd/C and hydrogen to test if we could selectively reduce the di-substituted carbon-carbon bond over the tri-substituted carbon-carbon bonds. We chose tetrahydrofuran as a solvent, as these reductions are slower in less polar solvents and we hoped that this would impart the desired selectivity. Under these conditions we only obtained starting material (entry 6). Upon switching to ethanol as a more polar solvent (entry 7) we isolated a mixture of products. Heterogeneous reduction conditions with barium sulfate and quinoline to poison the catalyst and slow down the reaction to impart selectivity returned starting material even under 750 psi of hydrogen (entries 8-9).

Table 3. Reduction of α , β -unsaturated ester **3.44**

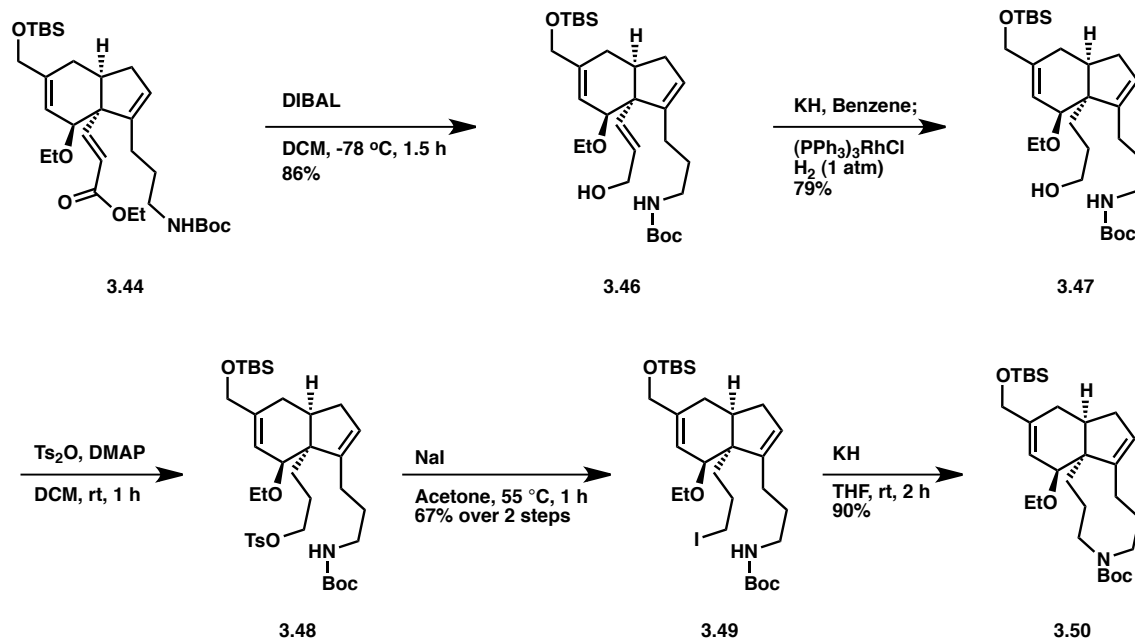


Chemical reaction scheme showing the reduction of compound **3.44** to compounds **3.45**, **3.46**, and **3.47** under various conditions.

Entry	Conditions	Result
1	LiEt ₃ BH, THF, -78 °C, 30 min; rt, 1 h	2:1 3.44/3.46
2	LiEt ₃ BH, THF, -78 °C, 2.5 h; rt, 1 h	53% 3.46
3	NaBH ₄ , CuCl ₂ , Methanol, 0 °C, 2 h	Starting Material
4	[Ph ₃ PCuH] ₆ , Benzene, rt, 7 h	Starting Material
5	Mg turnings, Methanol, rt, 23 h	Starting Material
6	Pd/C, H ₂ (1 atm), THF, 22 h	Starting Material
7	Pd/C, H ₂ (1 atm), Ethanol, 24 h	Complex Mixture
8	Pd/C, H ₂ (1 atm), BaSO ₄ , quinoline, Methanol, 22 h	Starting Material
9	Pd/C, H ₂ (750 psi), BaSO ₄ , quinoline, Methanol, 22 h	Starting Material

Because we were unable to effect a 1,4-reduction, we instead aimed to reduce the carbonyl group of the ester and then use the resulting allylic alcohol to direct a reduction of the proximal carbon-carbon double bond (see **3.44** to **3.47**, Scheme 11). We were able to reduce ester **3.44** with DIBAL to furnish alcohol **3.46** in 86% yield. As we envisioned, we were able to use this allylic alcohol (**3.46**) in a directed reduction of the proximal carbon-carbon double bond to give **3.47**, although yields for this transformation could not be consistently reproduced. The conditions for this step are unusual for a directed reduction. Through screening conditions, we discovered that potassium hydride was the most effective base for this reaction. Additionally, we found that it was optimal to use near-stoichiometric amounts of Wilkinson's catalyst. This is presumably due to the fact that the catalyst does not readily dissociate from the product. Normally, reactions such as these would be run with methanol or ethanol as a co-solvent,¹⁹ but in our case this shut down the reaction and returned the starting material unreacted. While our optimal reaction conditions are not consistently high yielding, we were grateful that we could obtain primary alcohol **3.47**. From **3.47**, we can activate the alcohol as the tosylate (**3.48**) and perform a displacement with iodide to furnish alkyl iodide **3.49** in 67% yield over two steps. Alternatively, we can convert alcohol **3.47** to iodide **3.49** in one step using an Appel reaction, but this was lower yielding on scale up so we prefer the two-step sequence. When exposed to potassium hydride, Boc-amine **3.49** is deprotonated and displaces the primary iodide to provide 6-5-9 tricycle **3.50** in 90% yield. Through this sequence we are able to arrive at upwards of 300 mg of Heathcock-like tricycle **3.50**.

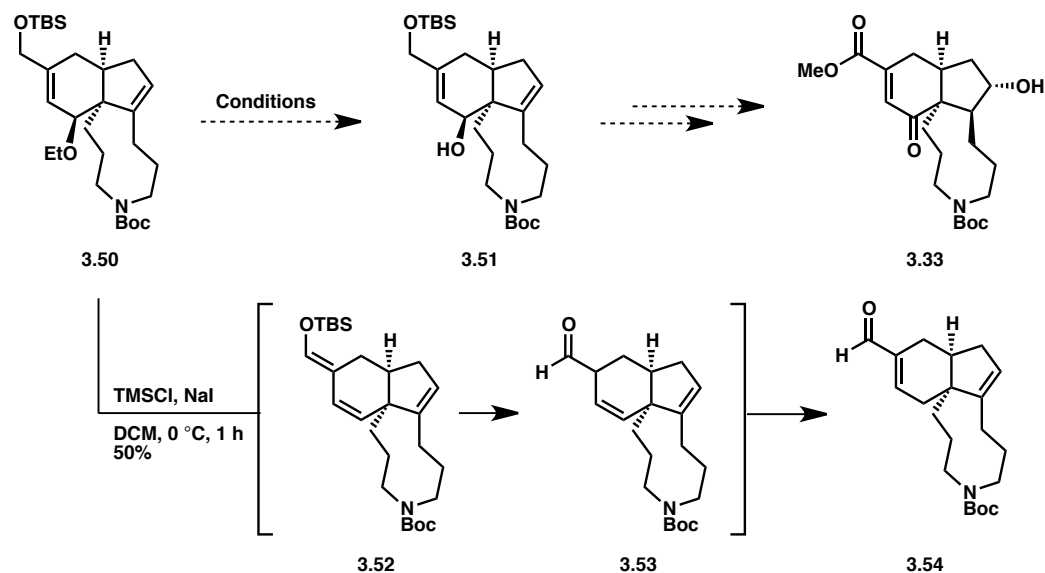
Scheme 11. Functionalization to provide tricycle **3.50**



3.3 Elaboration of the 6-5-9 Tricycle

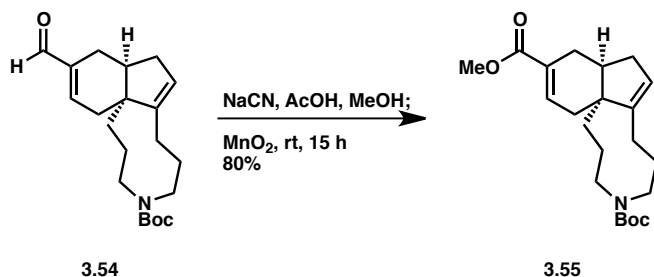
With tricycle **3.50** (Scheme 12) in hand, we next sought to perform appropriate functionalization to arrive at the desired common intermediate (**3.33**) from which we could diverge to access lycopladienes B, C, and D. Initially, we hoped to cleave the ethyl ether of tricycle **3.50** to furnish the corresponding secondary alcohol (**3.51**). The challenge that we faced with this sequence is that most conditions to cleave alkyl-protecting groups on an alcohol are Brønsted or Lewis acidic, and our substrate (**3.50**) is very acid sensitive. Because of this we chose to employ in-situ generated trimethylsilyl iodide as a non-acid generating method to cleave the ethyl ether. Under these conditions we observed generation of an unexpected product that we believe is enal **3.54**. This unexpected product could arise via trimethylsilyl-assisted loss of ethanol to give diene **3.52**. Diene **3.52** can be hydrolyzed to provide aldehyde **3.53**, which isomerizes to produce enal **3.53**. Interestingly, the addition of triethylamine shuts down the reaction, which could indicate that trace amounts of hydrogen iodide are mediating this transformation. This was not the substrate that we hoped to obtain in this transformation, but we nonetheless attempted to make use of this unique intermediate.

Scheme 12. Conversion of tricycle **3.50** to enal **3.54**



Toward our goal of advancing this intermediate, we were able to oxidize enal **3.54** to α , β -unsaturated methyl ester **3.55** in a single step using conditions developed by the Corey group (Scheme 13).²⁰

Scheme 13. Oxidation of enal **3.54** to provide enoate **3.55**



From enoate **3.55**, our first plan was to oxidize at the γ -position of the α , β -unsaturated methyl ester to furnish **3.57** (Table 4). We envisioned utilizing the conditions published by the Doyle group. Their methodology performs rhodium-mediated allylic oxidation of cyclic olefins and their substrate scope contains various olefins bearing esters and other electron withdrawing groups that are similar to our substrate.²¹ We were disappointed to see that under the Doyle conditions our substrate decomposed (**3.55**, entry 1 and **3.54**, entry 3). We also investigated chromium-mediated oxidations that Mehta and coworkers made use of in their synthesis of (+)-coronafacic acid.²² Once again, these conditions decomposed our tricyclic substrates (**3.55**, entry 2 and **3.54**, entry 4).

Table 4. Oxidation of γ -position to furnish **3.56** or **3.57**

Entry	R	Conditions	Result
1	OMe	Rh ₂ (cap) ₄ , K ₂ CO ₃ , <i>t</i> -BuOOH, O ₂ (1 atm) DCM, rt, 4 h	Decomposition
2	OMe	PDC, <i>t</i> -BuOOH, Benzene, 0 °C to rt, 5 h	Decomposition
3	H	Rh ₂ (cap) ₄ , K ₂ CO ₃ , <i>t</i> -BuOOH, O ₂ (1 atm) DCM, rt, 4 h	Decomposition
4	H	PDC, <i>t</i> -BuOOH, Benzene, 0 °C to rt, 5 h	Decomposition

Our inability to effect the transformation of **3.55** to **3.57** (Table 4) led us instead to a hydroboration/oxidation to convert alkene **3.55** to alcohol **3.58** (Table 5). We anticipated that this would be a challenging transformation because we needed to avoid the hydroboration of the carbon-carbon double bond on the six-membered ring. We anticipated that this selectivity might arise because the electron-withdrawing nature of the ester should deactivate the alkene group toward hydroboration. We further needed to avoid the reduction of the carbonyl group of the ester. We were hopeful that the required selectivity might be achievable due to encouraging examples in the literature.²³ Unfortunately we found that our substrate gave a mixture of products under hydroboration conditions (entries 1-2, Table 5).

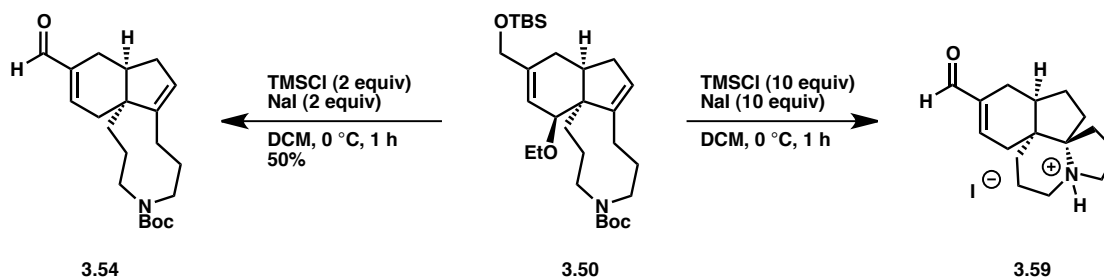
Table 5. Hydroboration of alkene **3.55** to provide alcohol **3.58**

Entry	Conditions	Result
1	BH ₃ •THF (5 equiv), THF, rt, 2 h; NaOH, H ₂ O ₂ , rt, 20 min	Mixture
2	BH ₃ •THF (5 equiv), THF, rt, 2 h; NaBO ₃ •4 H ₂ O, rt, 12 h	Mixture

We were disappointed that the above-discussed attempts to advance 6-5-9 tricycle **3.50** to the desired common intermediate (**3.33**, Scheme 12) were unsuccessful. In the course of scaling up material to access enal **3.54** (see Scheme 12), we made an interesting

observation. Conditions for the conversion of tricycle **3.50** to enal **3.54** require 2 equivalents of in-situ generated trimethylsilyliodide in DCM at 0 °C for 1 h (Scheme 14), but when the amount of trimethylsilyliodide was increased to 10 equivalents an alternative product was formed. We were able to use X-ray crystallography to determine the identity of this unknown as **3.59**. In addition to the generation of the enal functionality (see Scheme 12), the Boc-protecting group is cleaved and the carbon-carbon double bond in the five-membered ring is hydroaminated to furnish tetracycle **3.59**. This transformation is likely mediated by trace hydrogen iodide that is generated in-situ. Studies are currently underway to further investigate this surprising reaction.²⁴

Scheme 14. Reactivity of tricycle **3.50** when exposed to trimethylsilyliodide



We are particularly excited to continue studies on the above system (**3.59**) because this carbon scaffold maps onto other members of the fawcettimine-type *Lycopodium* alkaloids (Figure 3). Serratine (**3.60**) and 8-deoxyserratine (**3.61**) share the same carbon skeleton as our tetracycle (**3.59**). The hydroamination approach that we take to arrive at this core is unique from methods that other groups have used to access these natural product, which form the carbon-nitrogen bond via displacement of oxygenation at the C4 position.²⁵

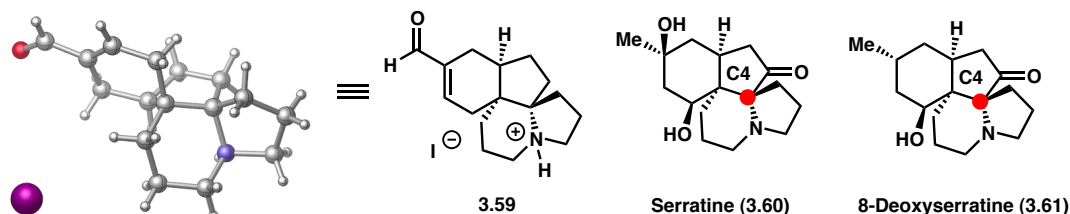
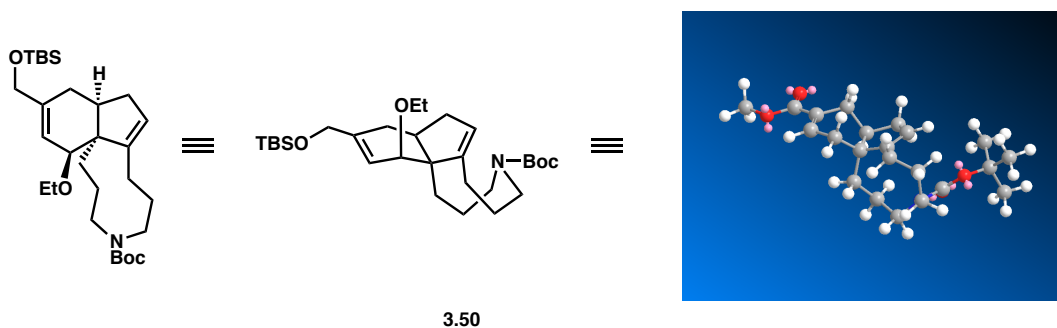


Figure 3. Tetracycle **3.59** and related natural products serratine (**3.60**) and 8-deoxyserratine (**3.61**)

Not only does this fortuitously observed reactivity (**3.50** to **3.59**, Scheme 14) provide us with potential access to serratine (**3.60**) and 8-deoxyserratine (**3.61**), but it also gives us insight to the three-dimensional structure of our 6-5-9 tricycle (**3.50**). For the hydroamination to take place, we hypothesize that the nine-membered ring is tucked under the bicycle, as shown in Figure 4. Chem3D generates a similar energy-minimized structure where the nine-membered ring is cupped under the 6-5 bicycle. This

conformation may help explain why the hydroboration reaction (see **3.55** to **3.58**, Table 5) was so difficult to effect.

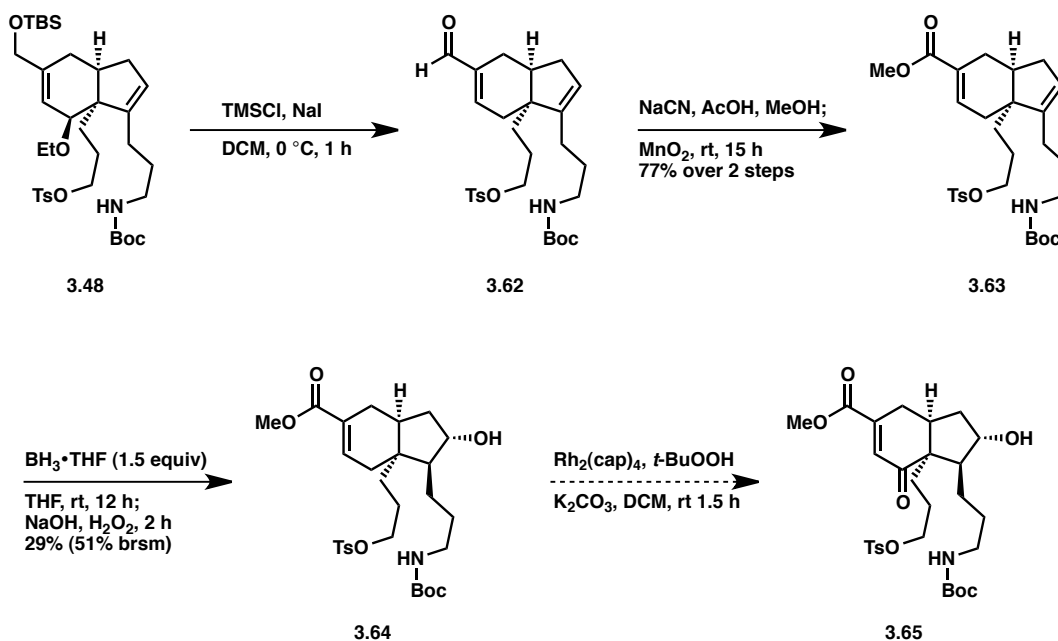


3.50

Figure 4. Proposed 3D structure of tricyclic **3.50**

We were curious to see if part of the problem with the above system (**3.55** to **3.58**, Table 5) was the fact that the carbon-carbon double bond in the five-membered ring was inaccessible. To determine if hindrance from the cyclononane ring was deleterious, we focused on accessing a ring-open form of **3.55**. Toward this goal, we subjected **3.48** to the same in-situ generated trimethylsilyliodide conditions that we had used previously to provide enal **3.62** (Scheme 15). Enal **3.62** was then converted to methyl ester **3.63**, which was subjected to hydroboration conditions. Interestingly, the desired alcohol (**3.64**) was isolated in 29% yield (51% based on recovered starting material). Unfortunately, this substrate decomposed upon attempted oxidation to furnish **3.65**.

Scheme 15. Conversion of 6-5 bicycle **3.48** to alcohol **3.64**

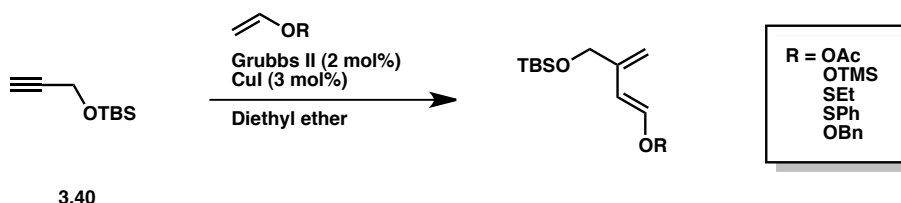


At this point, we decided that it would be best to redesign our original substrate in order to make use of the oxygenation that we have in the form of the ethyl ether. With a more readily cleavable protecting group, the opportunity existed to more easily access the desired late-stage common intermediate.

3.4 Synthesis of an Alternative 6-5 Bicycle

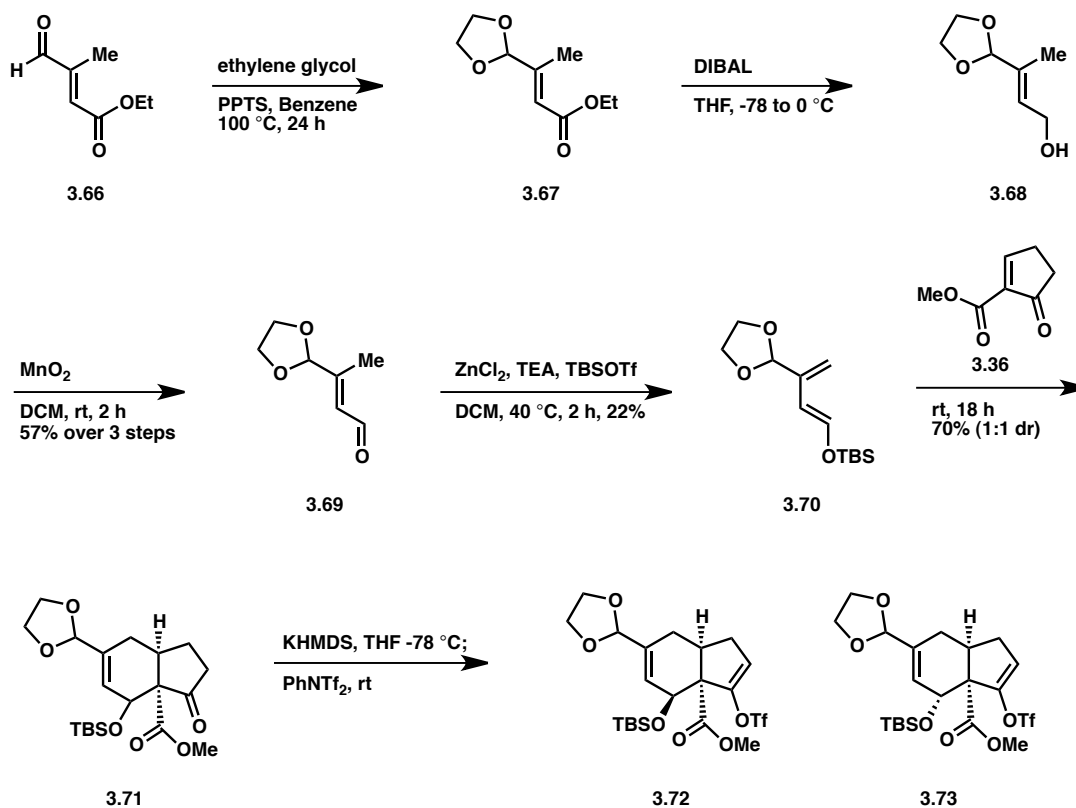
In order to continue to make use of the same enyne metathesis reaction that had been used previously (Scheme 16), a number of other commercially available vinyl ethers were evaluated. Some of the options include: vinyl acetate, vinyloxy-trimethylsilane, ethyl vinyl sulfide, phenyl vinyl sulfide, benzyl vinyl ether and *tert*-butyl vinyl ether. Unfortunately decomposition in the metathesis reaction (vinyloxy-trimethylsilane), difficult purification of the product (ethyl vinyl sulfide, phenyl vinyl sulfide and benzyl vinyl ether), and high prices of the starting material (*tert*-butyl vinyl ether) precluded our ability to use these enyne metathesis partners.

Scheme 16. Alternative substrates in the enyne metathesis reaction



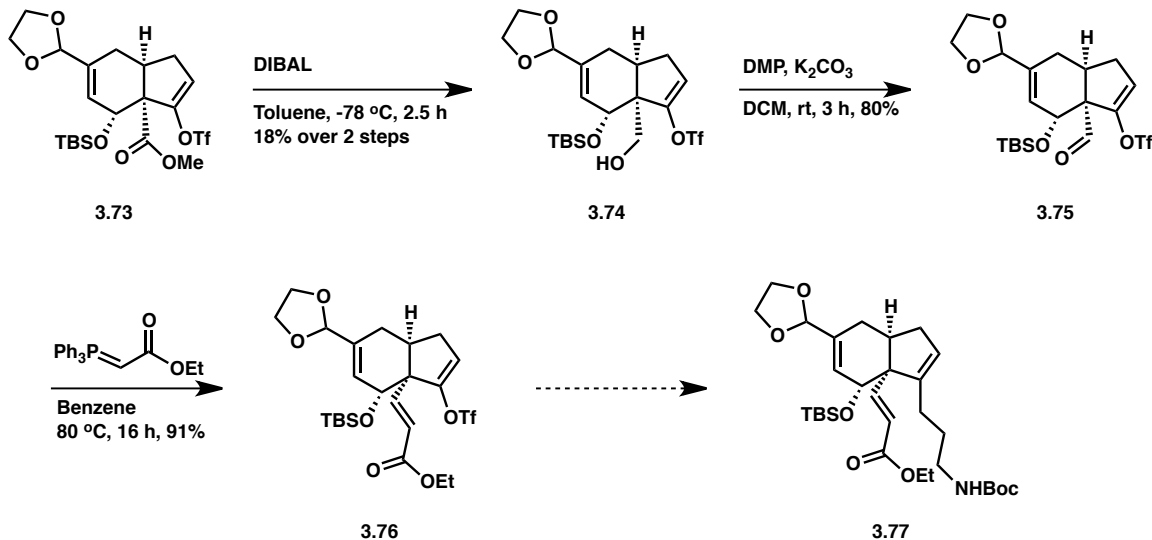
Instead, we chose to pursue another approach to the diene through the enolization of an enal. From commercially available aldehyde **3.66** (Scheme 17), protection of the aldehyde group as the acetal (**3.67**) and reduction of the ester group to give primary alcohol **3.68** proceeds according to literature precedent (Scheme 17).²⁶ Alcohol **3.68** was then oxidized with manganese dioxide to provide enal **3.69** in 57% yield over the three steps. Enal **3.69** was then converted to diene **3.70** under soft enolization conditions that are based on an approach to related dienes.²⁷ This step is notably low yielding (22%) and could not be further optimized. Diels-Alder reaction with dieneophile **3.36** to arrive at 6-5 bicycle **3.71** in 70% yield and as a 1:1 mixture of diastereomers. Ketone **3.71** could then be converted to the corresponding vinyl triflate (**3.72** and **3.73**). The diastereomers were separated at this stage and taken on separately.

Scheme 17. Access to alternative 6-5 bicycles (**3.72** and **3.73**)



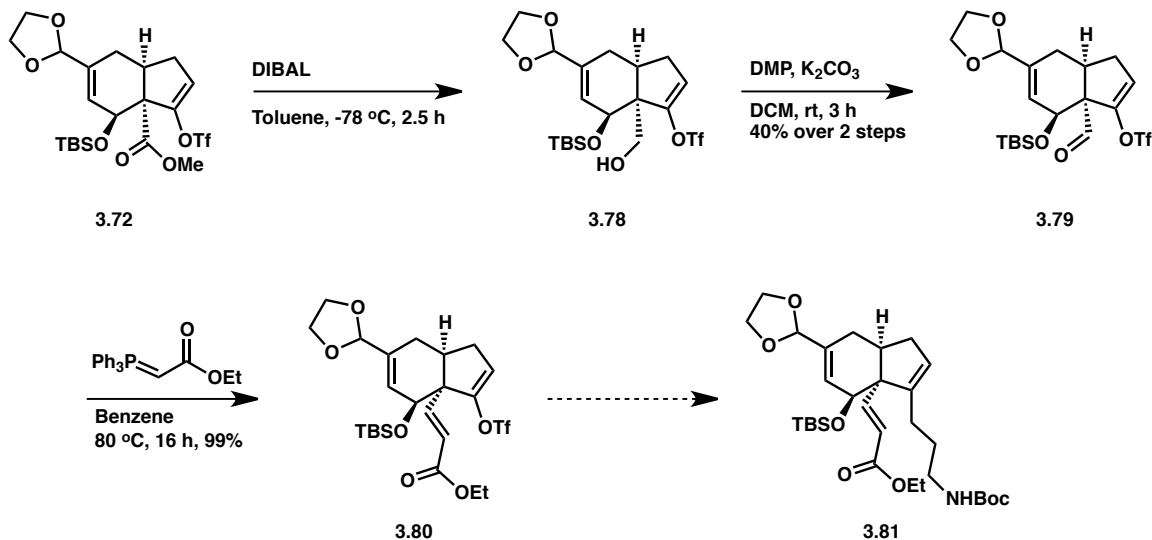
The first eluting diastereomer (**3.73**) was reduced to the primary alcohol (**3.74**, Scheme 18) in an unoptimized 18% yield over two steps. Alcohol **3.74** was then oxidized with Dess-Martin periodinane and used in a Wittig reaction to cleanly furnish α , β -unsaturated ester **3.76**. Unfortunately, this substrate was not amenable to the previously optimized Suzuki cross-coupling conditions to arrive at *N*-Boc amine **3.77**. The failure of this reaction to provide the desired product (**3.77**) might have to do with the bulky *tert*-butyldimethylsilyl protecting group in proximity to the vinyl triflate.

Scheme 18. Functionalization of bicycle **3.73**



To investigate this hypothesis, the other diastereomer was advanced along the same route. Ester **3.72** was reduced to the corresponding alcohol (**3.78**) and oxidized to furnish aldehyde **3.79** in an unoptimized 40% yield over 2 steps (Scheme 19). This aldehyde was taken on in a Wittig reaction to provide α , β -unsaturated ester **3.80** in 99% yield. Once again, we were unable to effect the Suzuki reaction to install the remaining carbons required to access the natural product.

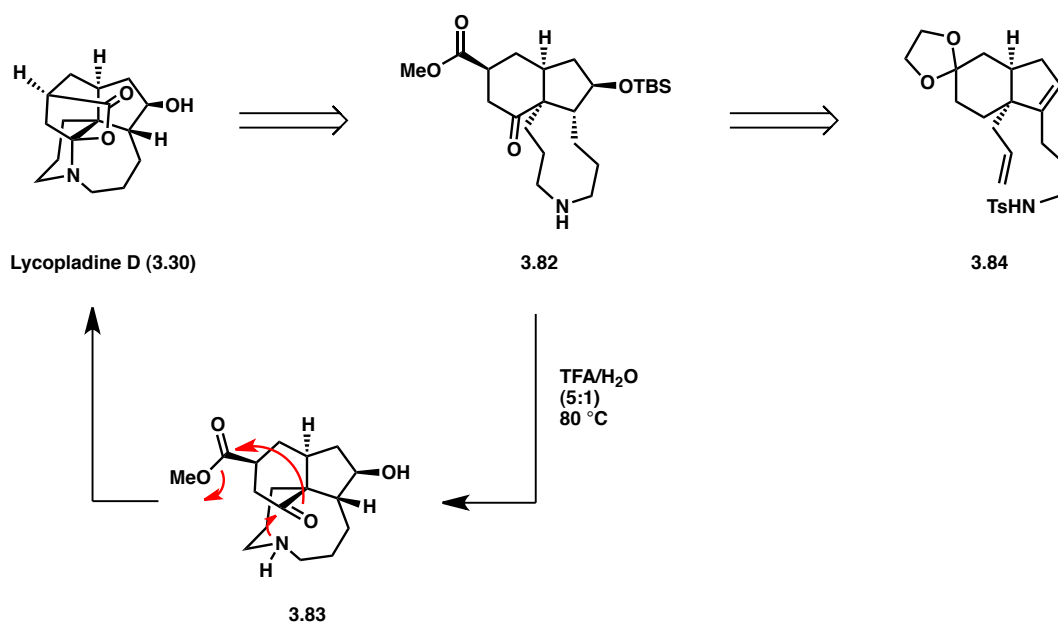
Scheme 19. Functionalization of bicycle **3.72**



It may be possible to advance to highly functionalized systems such as **3.58** (Table 5) if we are able to synthesize other 6-5 bicycles with alternative protecting groups. The optimal system would have a small, unreactive protecting group that could be easily accessed and advanced to the late stages of the synthesis where it can be cleaved

to unveil a hydroxyl group. As we were evaluating potential systems, the Zhao group published a synthesis of lycopladiene D that makes use of a similar strategy to the one we had envisioned.²⁸ They were able to construct the highly functionalized tricycle (**3.82**) that we hoped to access (Scheme 20). Upon exposure of **3.82** to trifluoroacetic acid, the *tert*-butyldimethyl silyl protecting group was cleaved and the secondary amine added into the adjacent carbonyl group, similar to what was shown by Heathcock in 1986.⁵ The resulting hemiaminal proceeded to interact with the proximal ester to create the caged carbon skeleton of lycopladiene D and efficiently furnish the natural product. This reaction is surprising, because they are able to perform the amine addition into the adjacent carbonyl group using the opposite diastereomer at the C4 position (see Scheme 2).

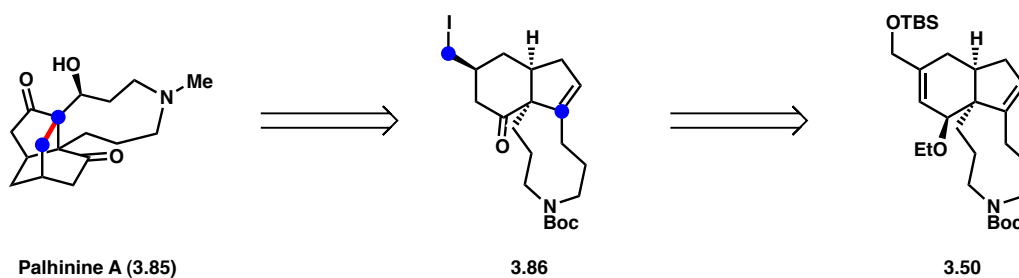
Scheme 20. Zhao's retrosynthetic strategy to access lycopladiene D (**3.30**)



3.5 Related Projects

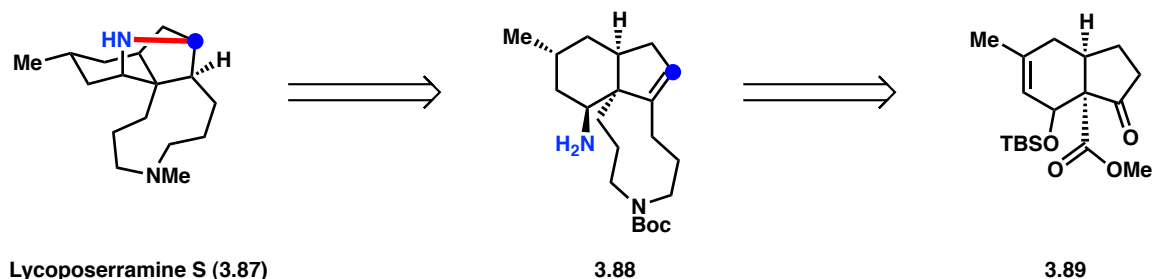
Our access to interesting 6-5-9 tricycles has inspired synthetic efforts to other related *Lycopodium* alkaloids. Paul Leger in our laboratory has been working to synthesize palhinine A (**3.85**, Scheme 21) using a radical cyclization from alkyl iodide **3.86**. This substrate (**3.86**) may be accessed from 6-5-9 tricycle **3.50** that we have prepared previously (see Scheme 11).

Scheme 21. Retrosynthetic strategy for palhinine A (3.85)



We have also envisioned a plan to access lycoposerramine S (3.87, Scheme 22). Lycoposerramine S could potentially arise from related tricycle 3.88 using a hydroamination reaction. Tricycle 3.88 could be derived from bicycle 3.89, which has previously been synthesized in the context of our work toward magellanimine (see 2.111, Scheme 35, Section 2.3, Chapter 2).

Scheme 22. Retrosynthetic strategy for lycoposerramine S (3.87)



3.6 Conclusion

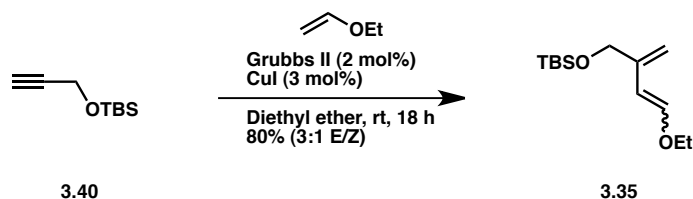
We have been able to construct an advanced 6-5-9 tricycle and investigate its functionalization toward a common precursor to access lycoplamine B, C, and D via a Heathcock-inspired cascade approach. Additionally, we have been able to synthesize other 6-5 bicycles with more readily cleavable protecting groups that could be amenable to accessing similar 6-5-9 tricycles. The endgame for this planned synthesis has since been published by the Zhao group.

3.7 Experimental Contributors

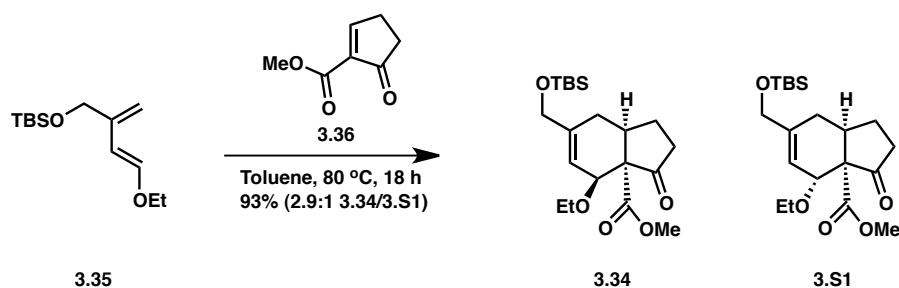
Eugenia Pushkarskaya (undergraduate, Sarpong group) synthesized 10 g of 6-5 bicycle 3.71 (see Scheme 17). She also investigated the addition of copper iodide in the optimization of the Grubbs enyne metathesis reactions to make diene (see entries 4-5, Table 1). Paul Leger provided the IR spectra for 3.46, 3.47, and 3.49. The remainder of the work presented in this chapter was completed by Rebecca A. Murphy.

3.8 Experimental Methods

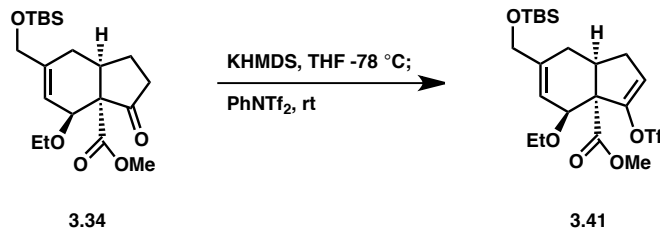
All reactions were run in flame-dried round-bottom flasks or vials under a nitrogen atmosphere. Reactions were monitored by thin layer chromatography (TLC) on Silicycle SiliaplateTM glass backed TLC plates (250 μm thickness, 60 $\text{\AA}$ porosity, F- 254 indicator) and visualized using UV irradiation and *para*-anisaldehyde stain. For heated reactions, the temperature was monitored using an IKA[®] temperature control. Dry acetonitrile, diethyl ether, tetrahydrofuran (THF), triethylamine (TEA), benzene, and methanol were obtained by passing these previously degassed solvents through activated alumina columns. Dichloromethane (DCM) was distilled over calcium hydride before use. Volatile solvents were removed under reduced pressure on a rotary evaporator. All flash chromatography was done using Sorbent Technologies 60 $\text{\AA}$, 230x400 mesh silica gel (40-63 μm). ^1H NMR and ^{13}C NMR spectra were taken with Bruker 300, 400, 500, and 600 MHz (75, 100, 125, and 150 MHz for ^{13}C NMR) spectrometers in CDCl_3 . Chemical shifts were measured relative to the shift of the residual solvent (^1H NMR - CDCl_3 δ = 7.26/MeOD δ = 3.31; ^{13}C NMR CDCl_3 δ = 77.16/MeOD δ = 49.00). NMR data are reported as follows: chemical shift (multiplicity, coupling constant, integration). Splitting is reported with the following symbols: s = singlet, bs = broad singlet, d = doublet, t = triplet, q = quartet, m = multiplet. IR spectra were taken on a Nicolet 380 spectrometer as thin films on NaCl plates unless otherwise specified. Spectra are reported in frequency of absorption in cm^{-1} . Only selected resonances are reported. High-resolution mass spectra (HRMS) were performed by the mass spectral facility at the University of California, Berkeley. Enantiomeric excess (*ee*'s) was determined on Perkin Elmer Flexar Chiral HPLC.



A dry 2 L round-bottom flask was charged with *tert*-butyldimethylsilyl protected propargyl alcohol **3.40** (6.45 g, 37.9 mmol, 1 equiv), Grubbs II (0.64 g, 0.758 mmol, 2 mol%), copper (I) iodide (0.22 g, 1.14 mmol, 3 mol%) and diethyl ether (380 mL). Ethyl vinyl ether (68 mL, 0.948 mol, 25 equiv) was added immediately and the reaction mixture was allowed to stir at room temperature. After 18 h the reaction was concentrated and purified by column chromatography (3% to 10% ethyl acetate in hexane) to give diene **3.35** (7.3 g, 80%) as a 3:1 mixture of E/Z isomers. R_f = 0.71 (10% ethyl acetate in hexane); ^1H NMR (600 MHz, CDCl_3): δ 6.64 (d, J = 13.1 Hz, 1H), 5.99 (d, J = 6.9 Hz, 0.3H), 5.54 (d, J = 13.1 Hz, 1H), 5.22-5.20 (m, 0.6H), 4.97 (s, 1H), 4.86 (s, 1H), 4.82 (d, J = 7.0 Hz, 0.3H), 4.34 (s, 0.6H), 4.24 (s, 2H), 3.85 (d, J = 7.0 Hz, 0.6H), 3.80 (q, J = 7.0 Hz, 2H), 1.30-1.26 (m, 4H), 0.92 (d, J = 13.5 Hz, 12H), 0.07 (s, 9H); ^{13}C NMR (150 MHz, CDCl_3): δ 147.4, 146.1, 143.2, 142.9, 110.1, 109.5, 105.8, 104.1, 68.6, 65.6, 65.2, 63.9, 25.9, 18.4, 15.3, 14.8, -5.3; IR 2956, 2930, 2857, 1651, 1472, 1389 (film) cm^{-1} ; HRMS (EI) calcd for $[\text{C}_{13}\text{H}_{26}\text{O}_2\text{Si}]^+$ (M^+): m/z 243.1702, not found.

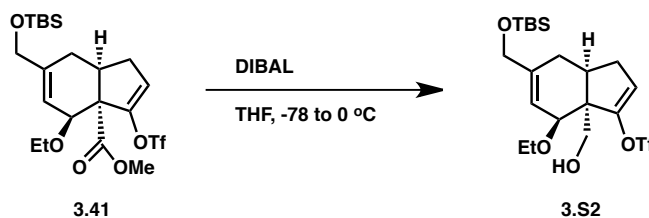


A 50 mL round-bottom flask was charged with diene **3.35** (8.14 g, 33.6 mmol, 1.5 equiv), dieneophile **3.36** (7.8 g, 26.2 mmol, 1 equiv), and toluene (18 mL) and heated to 80 °C for 18 h. The solution was concentrated and purified by sequential column chromatography to separate the two diastereomers (2-10% ethyl acetate). Major diastereomer **3.34** (5.96 g, 69%); $R_f = 0.52$ (25% ethyl acetate in hexane); ^1H NMR (600 MHz, CDCl_3): δ 5.91 (d, $J = 0.6$ Hz, 1H), 4.50 (d, $J = 3.7$ Hz, 1H), 4.05 (s, 2H), 3.69 (s, 3H), 3.56 (t, $J = 7.7$ Hz, 1H), 3.41 (t, $J = 7.8$ Hz, 1H), 3.01 (dd, $J = 13.0, 6.7$ Hz, 1H), 2.38 (dd, $J = 18.6, 8.6$ Hz, 1H), 2.25 (td, $J = 18.2, 8.6$ Hz, 2H), 2.07-2.02 (m, 2H), 1.96-1.93 (m, 1H), 1.06 (t, $J = 7.0$ Hz, 3H), 0.89 (d, $J = 24.1$ Hz, 9H), 0.05 (d, $J = 16.3$ Hz, 6H); ^{13}C NMR (150 MHz, CDCl_3): δ 212.6, 171.1, 138.1, 118.2, 72.1, 66.4, 66.0, 62.9, 52.6, 38.9, 37.1, 26.2, 25.8, 18.3, 15.2, -5.3, -5.3; IR (film) 2954, 2929, 2857, 1756, 1729 cm^{-1} ; HRMS (EI) calcd for $[\text{C}_{20}\text{H}_{34}\text{NaO}_5\text{Si}]^+ (\text{M}^+)$: m/z 405.2073, found 405.2073. Minor diastereomer **3.51** (2.06 g, 24%); $R_f = 0.48$ (25% ethyl acetate in hexane); ^1H NMR (600 MHz, CDCl_3): δ 5.86 (d, $J = 1.5$ Hz, 1H), 4.36 (d, $J = 3.7$ Hz, 1H), 3.99 (s, 2H), 3.73 (s, 3H), 3.61 (t, $J = 8.0$ Hz, 1H), 3.45 (t, $J = 8.0$ Hz, 1H), 3.17-3.15 (m, 1H), 2.37 (dd, $J = 17.9, 8.0$ Hz, 1H), 2.31 (t, $J = 8.6$ Hz, 1H), 2.20-2.15 (m, 2H), 1.68 (d, $J = 8.5$ Hz, 1H), 1.59 (dd, $J = 17.8, 8.2$ Hz, 1H), 1.11 (t, $J = 7.0$ Hz, 3H), 0.91 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (150 MHz, CDCl_3): δ 210.5, 167.8, 140.5, 118.4, 72.0, 66.6, 66.1, 64.9, 52.6, 34.1, 32.8, 27.5, 26.4, 25.9, 18.3, 15.5, -5.4; IR (film) 2954, 2929, 2857, 1736, 1463, 1435 cm^{-1} ; HRMS (EI) calcd for $[\text{C}_{20}\text{H}_{34}\text{NaO}_5\text{Si}]^+ (\text{M}^+)$: m/z 405.2073, found 405.2075.

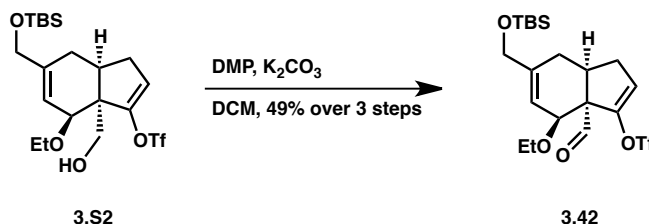


A 250 mL round-bottom flask was charged with ketone **3.34** (7.3 g, 19.1 mmol, 1 equiv) and THF (42 mL) and cooled to -78 °C in an acetone/dry ice bath. A 0.5 M solution of KHMDS in THF (42 mL, 21.0 mmol, 1.1 equiv) was added slowly and the brown-orange solution was allowed to stir at -78 °C for 1 h, at which point *N*-Phenyl-bis(trifluoromethanesulfonimide) (8.1 g, 22.9 mmol, 1.2 equiv) was added and the reaction was warmed to room temperature. After an additional 1.5 h of stirring at room temperature the reaction was diluted with ethyl acetate (200 mL) and washed with a saturated solution of NaHCO_3 (3 x 100 mL) and brine (100 mL). The organic layer was

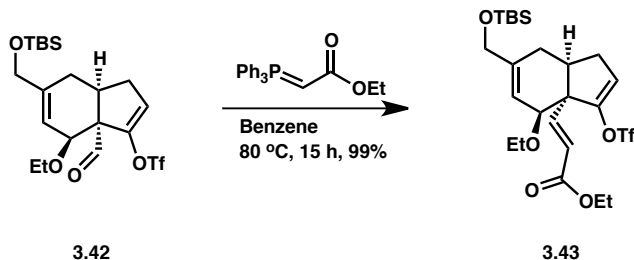
concentrated and dried over magnesium sulfate, filtered, and concentrated. The resulting material (**3.41**) was brought on in the next step without further purification.



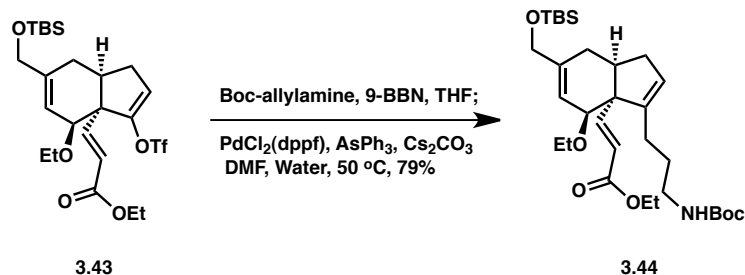
A dry 1 L round-bottom flask was charged with crude vinyl triflate **3.41** (19.1 mmol, 1 equiv) and THF (210 mL) and cooled to -78 °C. Neat DIBAL (17 mL, 95.5 mmol, 5 equiv) was added and the reaction was allowed to stir at -78 °C for 1 h before warming to 0 °C and stirring an additional 1 h. After this time ethyl acetate (200 mL) and a saturated solution of Rochelle's salt (200 mL) were added and the biphasic mixture was allowed to stir vigorously. After stirring for an extended period of time, the layers were separated and the aqueous layer was extracted with ethyl acetate (2 x 200 mL). The combined organic layer was dried over magnesium sulfate, filtered, and concentrated. The resulting alcohol (**3.S2**) was taken on in the next step without further purification.



A 500 mL round-bottom flask was charged with alcohol **3.S2** (19.1 mmol, 1 equiv), Dess-martin periodinane (9.7 g, 22.9 mmol, 1.2 equiv), potassium carbonate (9.5 g, 68.7 mmol, 3.6 equiv) and DCM (280 mL). The solution was allowed to stir for 30 minutes and was diluted with dichloromethane (200 mL) and washed with a 1:1 solution of saturated sodium bicarbonate and saturated sodium sulfite (3 x 200 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated. The crude product was purified by column chromatography (10% ethyl acetate in hexane) to give aldehyde **3.42** (4.5 g, 49% over 3 steps). *R_f* = 0.61 (10% ethyl acetate in hexane); ¹H NMR (500 MHz, CDCl₃): δ 9.63 (s, 1H), 6.00 (dd, *J* = 2.0, 0.7 Hz, 1H), 5.89-5.88 (m, 1H), 4.41 (d, *J* = 3.9 Hz, 1H), 4.08 (s, 2H), 3.64-3.44 (m, 2H), 2.90-2.87 (m, 1H), 2.68-2.62 (m, 1H), 2.18-2.13 (m, 3H), 1.18 (t, *J* = 7.0 Hz, 3H), 0.93-0.90 (m, 10H); ¹³C NMR (100 MHz, CDCl₃): δ 199.1, 145.3, 141.9, 122.7, 121.4, 72.5, 68.5, 65.9, 65.5, 36.6, 34.6, 29.2, 25.9, 18.4, 15.3, -5.4.; IR (film) 2956, 2930, 2857, 1731, 1661, 1424 cm⁻¹; HRMS (EI) calcd for [C₂₀H₃₁F₃O₆SSi]⁺ (M⁺): *m/z* 485.1563, not found.

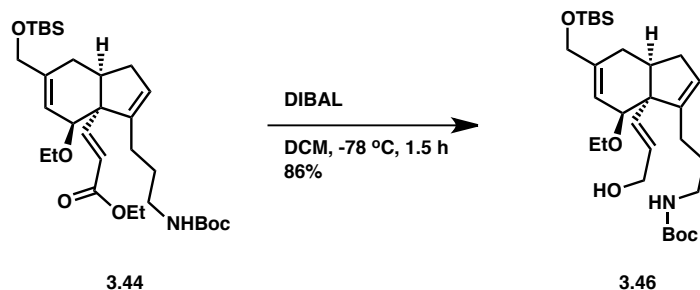


A 50 mL round-bottom flask was charged with aldehyde **3.42** (1.05 g, 2.17 mmol, 1 equiv), (Ethoxycarbonylmethylene)triphenylphosphorane (1.7 g, 4.34 mmol, 2 equiv), and benzene (16 mL) and heated to 80 °C for 15 h. The reaction mixture was loaded onto silica gel and purified by column chromatography (5% ethyl acetate in hexane) to give α , β -unsaturated ester **3.43** (1.2 g, 99%). R_f = 0.24 (10% ethyl acetate in hexane); ^1H NMR (500 MHz, CDCl_3): δ 6.93-6.89 (m, 1H), 6.04-6.02 (m, 1H), 5.86-5.82 (m, 1H), 5.76-5.74 (m, 1H), 4.24-4.19 (m, 2H), 4.13-4.10 (m, 2H), 3.95 (dd, J = 4.7, 0.5 Hz, 1H), 3.60-3.55 (m, 1H), 3.42-3.36 (m, 1H), 2.64-2.59 (m, 1H), 2.53-2.49 (m, 1H), 2.23-2.08 (m, 3H), 1.34-1.30 (m, 3H), 1.18-1.14 (m, 3H), 0.93 (t, J = 6.4 Hz, 9H), 0.08 (s, 9H); ^{13}C NMR (150 MHz, CDCl_3): δ 166.4, 150.5, 147.6, 143.4, 121.6, 121.2, 117.4, 74.8, 65.9, 65.1, 60.6, 58.9, 41.9, 34.2, 29.8, 26.3, 18.4, 15.4, 14.3, 1.0, -5.2; IR (film) 2957, 2930, 2857, 1724, 1649, 1425 cm^{-1} ; HRMS (EI) calcd for $[\text{C}_{24}\text{H}_{37}\text{F}_3\text{NaO}_7\text{SSi}]^+$ (M^+): m/z 577.1879, 577.1891.

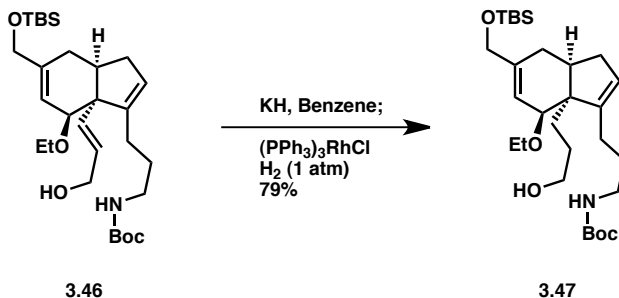


A dry 250 mL round-bottom flask was charged with Boc-allylamine (1.9 g, 12.2 mmol, 1.5 equiv) and THF (65 mL). A 0.5 M solution of 9-BBN in THF (32.5 mL, 12.2 mmol, 2 equiv) was added and the reaction mixture was allowed to stir at room temperature. After 4 h, water (3.2 mL) was added and the mixture was added to a solution of vinyl triflate **3.43** (4.5 g, 8.12 mmol, 1 equiv), [1,1'-Bis(diphenylphosphino)ferrocene]-dichloropalladium(II), complex with dichloromethane (0.6 g, 0.812 mmol, 10 mol%), triphenylarsine (0.25 g, 0.812 mmol, 10 mol%), cesium carbonate (5.0 g, 15.4 mmol, 1.9 equiv), and DMF (33 mL) in a dry 250 mL round-bottom flask. This solution was heated to 50 °C for 16 h, at which point it was diluted with ethyl acetate (200 mL) and washed with 1 M sodium hydroxide (3 x 100 mL) and brine (100 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated. The resulting oil was purified by column chromatography (5-10% ethyl acetate in hexane) to provide Boc-amine **3.44** (3.6 g, 79%). R_f = 0.58 (25% ethyl acetate in hexane); ^1H NMR (600 MHz, CDCl_3): δ 6.98 (d, J = 16.0 Hz, 1H), 5.92-5.91 (m, 1H), 5.67 (d, J = 16.0 Hz, 1H), 5.50-5.49 (m,

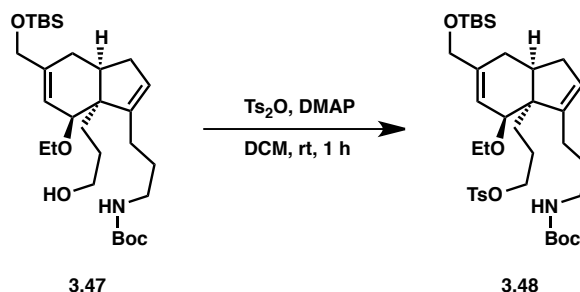
1H), 4.68-4.65 (bs, 1H), 4.18 (q, $J = 7.1$ Hz, 2H), 4.08-4.06 (m, 2H), 3.96-3.95 (m, 1H), 3.60-3.57 (m, 1H), 3.36-3.33 (m, 1H), 3.15-3.11 (m, 2H), 2.55-2.50 (m, 1H), 2.42-2.39 (m, 1H), 2.10-2.00 (m, 3H), 1.97-1.93 (m, 2H), 1.88-1.82 (m, 2H), 1.47-1.41 (m, 9H), 1.31-1.27 (m, 3H), 1.15-1.12 (m, 3H), 0.92-0.89 (m, 9H), 0.06-0.04 (m, 6H); ^{13}C NMR (100 MHz, CDCl_3): δ 167.4, 156.2, 155.6, 144.0, 142.7, 126.8, 122.3, 119.6, 66.2, 64.9, 62.7, 60.5, 44.0, 40.7, 39.1, 30.5, 28.7, 28.2, 25.9, 25.8, 22.2, 18.7, 15.6, 14.4, 1.2, -5.1; IR (film) 3368, 2979, 2929, 2856, 1717, 1644, 1518, 1451 cm^{-1} ; HRMS (EI) calcd for $[\text{C}_{31}\text{H}_{53}\text{NO}_6\text{Si}]^+$ (M^+): m/z 564.3642, found 564.5579.



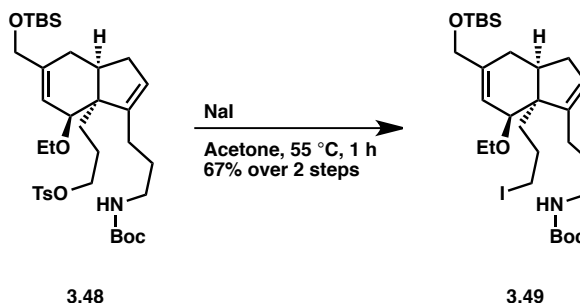
A dry 250 mL round-bottom flask was charged with ester **3.44** (1.5 g, 2.66 mmol, 1 equiv) and DCM (30 mL) and cooled to $-78\text{ }^\circ\text{C}$. A 1 M solution of DIBAL in toluene (13 mL, 13.3 mmol, 5 equiv) was added and the reaction mixture was allowed to stir at $-78\text{ }^\circ\text{C}$ for 1.5 h, at which point the solution was diluted with ethyl acetate (50 mL) and a saturated solution of Rochelle's salt (50 mL). The biphasic mixture was stirred vigorously for an extended time period. The layers were separated and the aqueous layer was extracted with ethyl acetate (2 x 100 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated. The resulting oil was purified by column chromatography (25-50% ethyl acetate in hexane) to provide alcohol **3.46** (1.2 g, 86%). $R_f = 0.43$ (25% ethyl acetate in hexane); ^1H NMR (500 MHz, CDCl_3): δ 5.92-5.91 (m, 1H), 5.73 (d, $J = 15.9$ Hz, 1H), 5.54 (dt, $J = 15.8, 5.7$ Hz, 1H), 5.44 (s, 1H), 4.73-4.72 (bs, 1H), 4.14-4.11 (m, 2H), 4.08 (s, 2H), 3.90 (d, $J = 4.0$ Hz, 1H), 3.61-3.56 (m, 1H), 3.37-3.33 (m, 1H), 3.15-3.12 (m, 2H), 2.53-2.49 (m, 1H), 2.42-2.40 (m, 1H), 1.96-1.93 (m, 1H), 1.49-1.40 (m, 5H), 1.35 (s, 9H), 1.29-1.26 (m, 1H), 1.14 (t, $J = 7.0$ Hz, 3H), 0.90 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (150 MHz, CDCl_3): δ 156.6, 150.8, 140.0, 136.0, 124.1, 123.0, 80.9, 66.3, 65.3, 64.4, 58.4, 43.9, 37.8, 28.9, 28.5, 28.3, 26.0, 18.5, 15.6, 8.2, 1.4, -4.9; IR (film) 3359, 2954, 2929, 2856, 1692, 1518 cm^{-1} ; HRMS (EI) calcd for $[\text{C}_{29}\text{H}_{51}\text{NNaO}_5\text{Si}]^+$ (M^+): m/z 544.3434, found 544.3451.



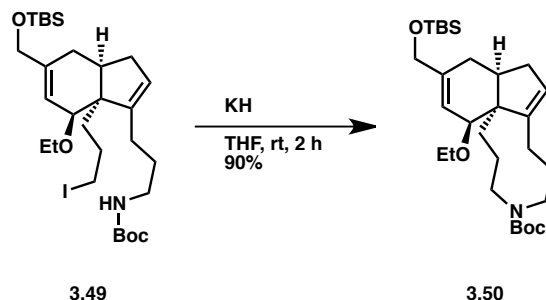
A dry 100 mL round-bottom flask was charged with alcohol **3.46** (1.1 g, 2.11 mmol, 1 equiv) and benzene (45 mL). Potassium hydride (0.17 g, 4.22 mmol, 2 equiv) was added followed by Wilkinson's catalyst (1.6 g, 1.73 mmol, 0.8 equiv). The atmosphere was exchanged for hydrogen gas (1 atm) and the solution was allowed to stir. The reaction was monitored by ^1H NMR. After 30 min the starting material was consumed and methanol (20 mL) was added. The reaction was loaded onto silica gel and purified by column chromatography (25% ethyl acetate in hexane) to provide alcohol **3.47** (0.87 g, 79%). R_f = 0.43 (25% ethyl acetate in hexane); ^1H NMR (500 MHz, CDCl_3): δ 5.89-5.88 (m, 1H), 5.34 (s, 1H), 4.84 (s, 1H), 4.08 (s, 2H), 3.66 (d, J = 3.6 Hz, 1H), 3.63-3.55 (m, 3H), 3.32 (dq, J = 9.5, 7.0 Hz, 1H), 3.17-3.13 (m, 2H), 2.46-2.41 (m, 1H), 2.24 (dd, J = 9.5, 4.3 Hz, 1H), 2.13-1.97 (m, 3H), 1.90-1.83 (m, 3H), 1.75-1.63 (m, 3H), 1.45 (s, 9H), 1.33 (t, J = 10.5 Hz, 2H), 1.15 (t, J = 7.0 Hz, 3H), 0.90 (s, 9H), 0.09 (s, 6H); ^{13}C NMR (125 MHz, CDCl_3): δ 156.5, 145.1, 142.0, 125.1, 124.0, 80.5, 66.6, 65.2, 63.8, 60.2, 40.3, 40.2, 39.1, 33.5, 30.9, 28.5, 27.6, 25.9, 24.9, 18.4, 15.5; IR (film) 3351, 2953, 2929, 2855, 1694, 1520 cm^{-1} ; HRMS (EI) calcd for $[\text{C}_{29}\text{H}_{53}\text{NNaO}_5\text{Si}]^+$ (M^+): m/z 546.3591, found 546.3600.



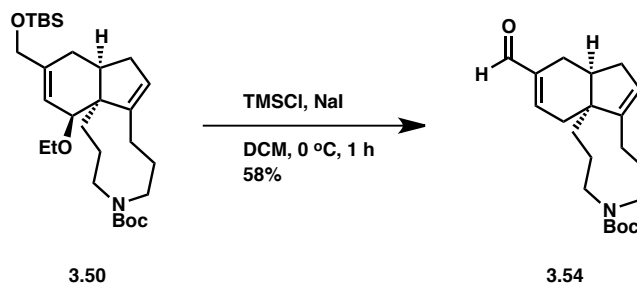
A 50 mL round-bottom flask was charged with alcohol **3.47** (0.59 g, 1.13 mmol, 1 equiv), *p*-toluenesulfonic anhydride (0.92 g, 2.83 mmol, 2.5 equiv), 4-dimethylaminopyridine (0.69 g, 5.66 mmol, 5 equiv) and DCM (28 mL). The solution was allowed to stir at room temperature for 1 h, at which point the solution was loaded onto silica gel and purified by column chromatography (10% ethyl acetate in hexane) to give tosylate **3.48** with 4-dimethylaminopyridine. This mixture was taken on in the next step without further purification.



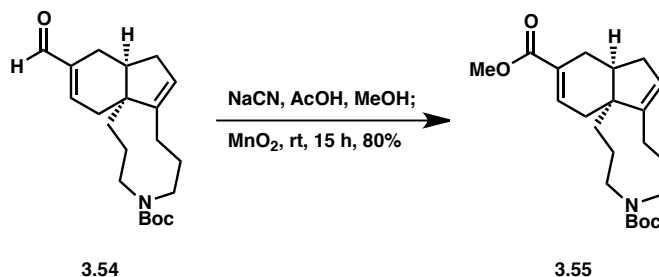
A dry 100 mL round-bottom flask was charged with crude tosylate **3.48** (1.13 mmol, 1 equiv), sodium iodide (0.85 g, 5.66 mmol, 5 equiv) and acetone (38 mL). The reaction mixture was heated to 55 °C for 1 h, at which point the solution was diluted with water (10 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic layer was dried over magnesium sulfate, filtered, and concentrated. The resulting oil was purified by column chromatography (10-25% ethyl acetate in hexane) to provide alkyl iodide **3.49** (0.48 g, 67% over 2 steps). R_f = 0.91 (25% ethyl acetate in hexane); ^1H NMR (600 MHz, CDCl_3): δ 5.87 (d, J = 0.3 Hz, 1H), 5.33 (s, 1H), 4.07 (s, 2H), 3.65 (s, 1H), 3.30 (s, 1H), 3.15 (s, 4H), 2.03-1.99 (m, 4H), 1.85 (s, 2H), 1.71 (d, J = 9.0 Hz, 4H), 1.43 (s, 9H), 1.14 (t, J = 6.9 Hz, 3H), 0.90 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (150 MHz, CDCl_3): δ 156.2, 145.0, 141.9, 125.0, 123.5, 79.8, 78.8, 66.3, 64.7, 59.9, 40.4, 39.5, 38.4, 30.8, 28.6, 28.5, 28.0, 25.9, 25.0, 18.4, 15.5, 8.0; IR (film) 3361, 2928, 2855, 1716, 1510 cm^{-1} ; HRMS (EI) calcd for $[\text{C}_{29}\text{H}_{52}\text{INNaO}_4\text{Si}]^+$ (M^+): m/z 656.2608, found 656.2619.



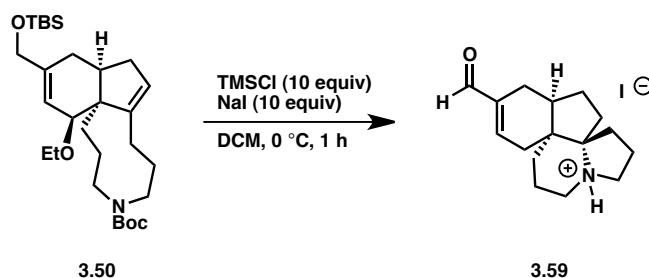
A dry 100 mL round-bottom flask was charged with alkyl iodide **3.49** (0.48 g, 0.758 mmol, 1 equiv) and THF (32 mL). Potassium hydride (0.12 g, 3.03 mmol, 4 equiv) was added and the solution was allowed to stir for 2 h at room temperature. Methanol (10 mL) was then added and the reaction was concentrated and purified by column chromatography (10% ethyl acetate in hexane) to provide tricycle **3.50** (345 mg, 90%) as a mixture of Boc-rotomers. R_f = 0.30 (10% ethyl acetate in hexane); ^1H NMR (500 MHz, CDCl_3): δ 5.92-5.89 (m, 1H), 5.53-5.45 (m, 1H), 4.10-4.09 (m, 2H), 3.61-3.54 (m, 3H), 3.35-3.30 (m, 1H), 3.18-2.96 (m, 3H), 2.51-2.48 (m, 1H), 2.19-2.00 (m, 6H), 1.90-1.83 (m, 1H), 1.72-1.67 (m, 2H), 1.56-1.54 (m, 2H), 1.50-1.48 (m, 9H), 1.16-1.12 (m, 3H), 0.91 (d, J = 0.5 Hz, 9H), 0.09-0.07 (m, 6H); ^{13}C NMR (100 MHz, CDCl_3): δ 157.2, 145.2, 141.9, 126.3, 124.1, 80.4, 79.1, 66.3, 64.8, 61.6, 48.8, 41.3, 40.4, 39.8, 30.8, 28.7, 28.6, 27.3, 26.5, 26.1, 23.1, 21.0, 18.6, 15.6, -5.1; IR (film) 2928, 2856, 1696 cm^{-1} ; HRMS (EI) calcd for $[\text{C}_{29}\text{H}_{51}\text{NNaO}_4\text{Si}]^+$ (M^+): m/z 528.3485, found 528.3499.



A dry 4 mL vial was charged with tricycle **3.50** (34 mg, 0.067 mmol, 1 equiv) and DCM (0.7 mL) and cooled to 0 °C. Chlorotrimethylsilane (17 μ L, 0.134 mmol, 2 equiv) and sodium iodide (20 mg, 0.134 mmol, 2 equiv) were added and the translucent yellow solution was stirred for 1 h at 0 °C. A solution of saturated sodium bicarbonate was then added and the biphasic mixture was extracted with DCM (3 x 2 mL). The combined organic layer was dried over magnesium sulfate, filtered, and concentrated. The resulting oil was purified by column chromatography (10-25% ethyl acetate in hexane) to give enal **3.54** (14 mg, 58%). R_f = 0.39 (25% ethyl acetate in hexane).

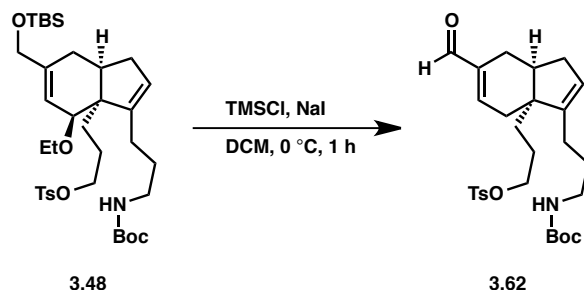


A dry 4 mL vial was charged with enal **3.54** (4.7 mg, 0.014 mmol, 1 equiv) and methanol (0.2 mL). Sodium cyanide (13 mg, 0.272 mmol, 20 equiv) and glacial acetic acid (8 μ L, 0.136 mmol, 10 equiv) were added and the solution was allowed to stir at room temperature for 30 min before manganese dioxide (12 mg, 0.136 mmol, 10 equiv) was added. This black, heterogeneous solution was allowed to stir for 15 h before filtration through a plug of silica gel. The resulting material was purified by column chromatography (25% ethyl acetate in hexane) to give α , β -unsaturated ester **3.55** (4.1 mg, 80%). R_f = 0.48 (25% ethyl acetate in hexane).

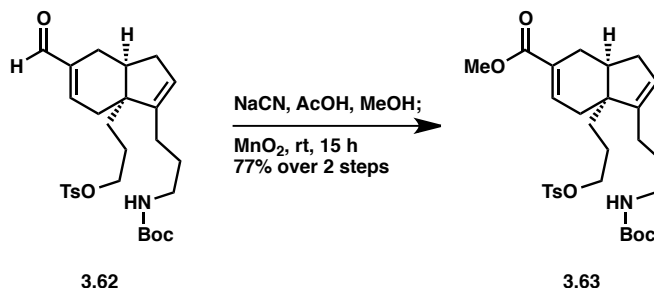


A dry 20 mL vial was charged with tricycle **2.50** and DCM (3 mL) and cooled to 0 °C. Trimethylsilylchloride and sodium iodide were added and the solution was allowed to stir at 0 °C for 1 h, at which point it was diluted with DCM (10 mL) and washed with a saturated solution of sodium bicarbonate (3 x 3 mL) and brine (3 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated to cleanly provide tetracycle **3.59**. ^1H NMR (600 MHz, CDCl_3): δ 10.52-10.47 (bs, 1H), 9.47-9.45 (m, 1H), 6.69 (dt, J = 1.5, 0.7 Hz, 1H), 3.91-3.85 (m, 1H), 3.47-3.40 (m, 1H), 3.09-2.99 (m, 2H), 2.71-2.64 (m, 1H), 2.45-2.39 (m, 2H), 2.34-2.27 (m, 2H), 2.20-2.17 (m, 4H), 2.08-1.88 (m, 4H), 1.80-1.76 (m, 1H), 1.71-1.67 (m, 1H); ^{13}C NMR (150 MHz, CDCl_3): δ 193.7, 145.1, 138.4, 80.4, 53.0, 51.7, 43.7, 35.8, 33.8, 33.0, 29.0, 28.6, 26.8, 26.0, 20.5, 18.3, 18.1; IR

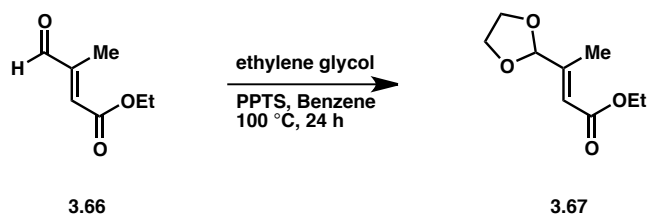
(film) 2961, 2926, 1681, 1462, 1413 cm^{-1} ; HRMS (EI) calcd for $[\text{C}_{16}\text{H}_{24}\text{NO}]^+$ (M^+): m/z 246.1852, found 246.1855.



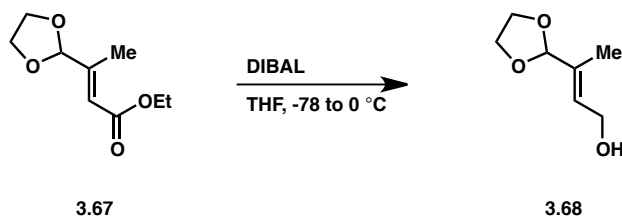
A dry 4 mL vial was charged with **3.48** (50 mg, 0.074 mmol, 1 equiv) and DCM (1.1 mL) and cooled to 0 $^\circ\text{C}$. Trimethylsilylchloride (19 μL , 0.148 mmol, 2 equiv) and sodium iodide (22 mg, 0.148 mmol, 2 equiv) were added and the reaction was allowed to stir at 0 $^\circ\text{C}$ for 35 min. The reaction was diluted with DCM (5 mL) and washed with a saturated solution of sodium bicarbonate (3 x 5 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated. The resulting material was taken on in the next step without further purification.



A dry 10 mL round-bottom flask was charged with enal **3.62** (0.074 mmol, 1 equiv), sodium cyanide (72 mg, 1.47 mmol, 20 equiv), glacial acetic acid (42 μL , 0.738 mmol, 10 equiv) and methanol (3.2 mL). The solution was allowed to stir at room temperature for 30 min, at which point manganese dioxide (64 mg, 0.738 mmol, 10 equiv) was added. The reaction mixture was allowed to stir for 15 h, at which point it was filtered through a plug of silica gel and washed with ethyl acetate (10 mL). The resulting solution was washed with a saturated solution of sodium bicarbonate (3 x 5 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated. The resulting material was purified by column chromatography (25% ethyl acetate in hexane) to provide enoate **3.63** (31 mg, 77% over 2 steps). ^1H NMR (500 MHz, CDCl_3): δ 7.80-7.78 (m, 2H), 7.37-7.35 (m, 2H), 7.06-7.04 (m, 1H), 5.30-5.28 (m, 1H), 4.62-4.59 (m, 1H), 4.01-3.97 (m, 2H), 3.76-3.74 (m, 3H), 3.17-3.13 (m, 2H), 2.47 (s, 3H), 2.44-2.37 (m, 2H), 2.23-2.17 (m, 1H), 2.14-2.09 (m, 1H), 2.09-1.99 (m, 2H), 1.90-1.79 (m, 4H), 1.69-1.61 (m, 4H), 1.46 (s, 9H); ^{13}C NMR (150 MHz, CDCl_3): δ 167.34, 156.4, 147.4, 145.1, 140.8, 133.5, 131.9, 130.1, 128.3, 124.3, 71.3, 53.6, 51.7, 41.0, 38.3, 35.1, 28.8, 24.6, 23.9, 21.6; IR (film) 3399, 2829, 1711, 1518, 1437 cm^{-1} ; HRMS (EI) calcd for $[\text{C}_{29}\text{H}_{41}\text{NNaO}_7\text{S}]^+$ (M^+): m/z 570.2501, found 570.2504.



This procedure was based on a similar preparation of this compound.²⁶ A dry 1 L round-bottom flask was charged with aldehyde **3.66** (30 mL, 0.220 mol, 1 equiv), ethylene glycol (120 mL, 2.20 mol, 10 equiv), pyridinium *p*-toluenesulfonate (61 g, 0.242 mol, 1.1 equiv) and benzene (400 mL). The solution was heated to 100 °C for 24 h, after which time it was cooled to room temperature and diluted with ethyl acetate (200 mL) and washed with a saturated solution of sodium bicarbonate (3 x 200 mL) and brine (200 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated to give a 13:1 mixture of acetal **2.67**/starting material (**2.66**). This material was taken on in the next step without further purification.

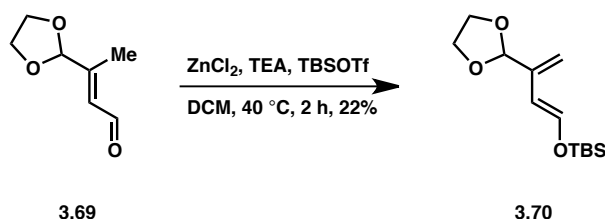


This procedure was based on a similar preparation of this compound.²⁶ A dry 2 L round-bottom flask was charged with ester **3.67** (0.220 mol, 1 equiv) and THF (1 L) and cooled to -78 °C. Neat DIBAL (98 mL, 0.551 mol, 2.5 equiv) was slowly added and the reaction mixture was allowed to warm to 0 °C. After 1 h, the solution was cooled to -78 °C and ethyl acetate (300 mL) was added. After stirring for 10 min the reaction was warmed to room temperature and diluted with a saturated solution of Rochelle's salt (500 mL). The biphasic solution was allowed to stir vigorously for 12 h, at which point the layers were separated and the aqueous phase was extracted with ethyl acetate (2 x 300 mL). The combined organic layer was dried over magnesium sulfate, filtered and concentrated to give alcohol **3.68**, which was brought on in the next step without further purification.

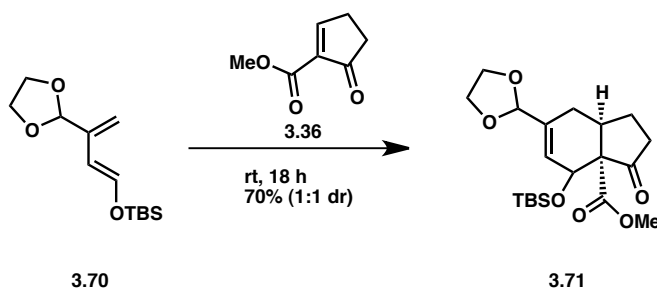


A dry 2 L round-bottom flask was charged with alcohol **3.68** (0.220 mol, 1 equiv), DCM (1.2 L), and activated manganese dioxide (172 g, 1.98 mol, 9 equiv). The black, heterogeneous solution was allowed to stir at room temperature for 2 h. The reaction mixture was then filtered through a pad of silica gel and rinsed with DCM (2 x 200 mL). Between the rinses with DCM, the top of the silica gel pad was stirred with a spatula. The

DCM was then concentrated to provide enal **3.69** (17.7 g, 57% over 3 steps). R_f = 0.24 (10% ethyl acetate in hexane); ^1H NMR (400 MHz, CDCl_3): δ 10.08 (d, J = 7.9 Hz, 1H), 6.16-6.13 (m, 1H), 5.27 (s, 1H), 4.03-3.95 (m, 4H), 2.14 (d, J = 1.4 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 191.3, 155.9, 127.6, 104.6, 65.5, 12.0; IR (film) 2889, 1680, 2443, 1371 cm^{-1} ; HRMS (EI) calcd for $[\text{C}_7\text{H}_{10}\text{NaO}_3]^+$ (M^+): m/z 165.0528, found 165.0520.

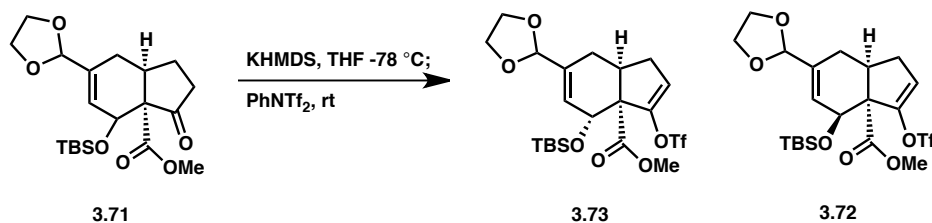


A dry 1 L round bottom flask was charged with enal **3.69** (7 g, 49.2 mmol, 1 equiv) and DCM (490 mL). Zinc chloride (0.68 g, 4.92 mmol, 0.1 equiv) was added followed by triethylamine (10.3 mL, 73.9 mmol, 1.5 equiv) and trimethylsilyl trifluoromethanesulfonate (10.7 mL, 46.7 mmol, 0.95 equiv) and the reaction mixture was warmed to 40 °C. After 2.5 h, the solution was cooled to room temperature and washed with a saturated solution of sodium bicarbonate (2 x 75 mL), dried over magnesium sulfate, filtered and concentrated. The resulting oil was purified by column chromatography (3% ethyl acetate in hexane) to give diene **3.70** as a 9:1 mixture of E/Z isomers (2.8 g, 22%). R_f = 0.24 (10% ethyl acetate in hexane); ^1H NMR (400 MHz, CDCl_3): δ 6.82 (dd, J = 12.3, 0.3 Hz, 1H), 6.44-6.43 (m, 0.1H), 5.90 (d, J = 2.1 Hz, 0.1H), 5.67 (dd, J = 12.3, 0.7 Hz, 1H), 5.43 (dd, J = 1.9, 0.9 Hz, 0.1H), 5.36 (s, 1H), 5.25 (s, 0.1H), 5.13-5.02 (m, 2H), 4.90-4.88 (m, 0.1H), 4.04-3.90 (m, 4H), 0.94 (s, 1H), 0.92 (d, J = 6.1 Hz, 9H), 0.17 (s, 0.6H), 0.16 (s, 6H); ^{13}C NMR (100 MHz, CDCl_3): δ 143.5, 140.5, 111.9, 110.1, 103.3, 65.2, 64.9, 25.7, 25.6, 18.3, -2.9, -5.1; IR (film) 2956, 2930, 2886, 2859, 1647, 1472 cm^{-1} ; HRMS (EI) calcd for $[\text{C}_{13}\text{H}_{24}\text{O}_3\text{Si}]^+$ (M^+): m/z 257.1495, found 257.1565.

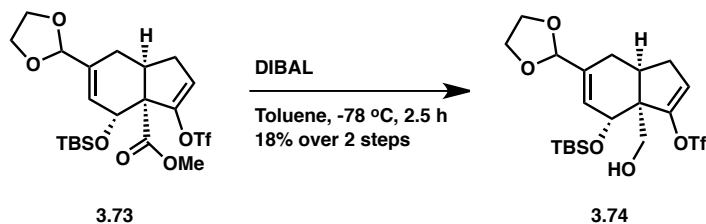


A dry 50 mL round-bottom flask was charged with diene **3.70** (8.6 g, 33.5 mmol, 1 equiv) and dieneophile **3.36** (7.0 g, 50.3 mmol, 1.5 equiv). The reaction was allowed to stir at room temperature for 18 h, at which point it was purified by column chromatography (10-25% ethyl acetate in hexane) to provide bicycle **3.71** (9.4 g, 70%) as a 1:1 mixture of diastereomers. R_f = 0.68 (25% ethyl acetate in hexane); ^1H NMR (500 MHz, CDCl_3): δ 5.96-5.95 (m, 1H), 5.92 (d, J = 4.4 Hz, 1H), 5.15 (s, 1H), 5.07 (s, 1H), 4.91 (d, J = 4.7 Hz, 1H), 4.74 (d, J = 4.9 Hz, 1H), 3.94-3.85 (m, 8H), 3.67 (s, 3H), 3.66 (a, 3H), 3.20-3.19 (m, 1H), 3.03-3.01 (m, 1H), 2.51 (ddd, J = 17.5, 8.4, 1.8 Hz, 1H), 2.33-

1.93 (m, 9H), 1.74 (dd, $J = 17.6, 6.2$ Hz, 1H), 1.68-1.67 (m, 1H), 0.78-0.79 (m, 18H), 0.03 (d, $J = 18.9$ Hz, 12H); ^{13}C NMR (125 MHz, CDCl_3): δ 212.2, 210.9, 170.7, 167.8, 138.0, 135.0, 127.2, 126.0, 105.0, 104.5, 67.6, 66.2, 65.2, 63.1, 52.6, 52.5, 39.0, 37.2, 35.2, 33.1, 27.2, 26.2, 25.7, 25.6, 25.2, 22.9, 17.8, 17.7, -3.9, -4.4, -5.2; IR (film) 2954, 2887, 1756, 1735 cm^{-1} ; HRMS (EI) calcd for $[\text{C}_{20}\text{H}_{32}\text{NaO}_6\text{Si}]^+$ (M^+): m/z 419.1866, found 419.1859.

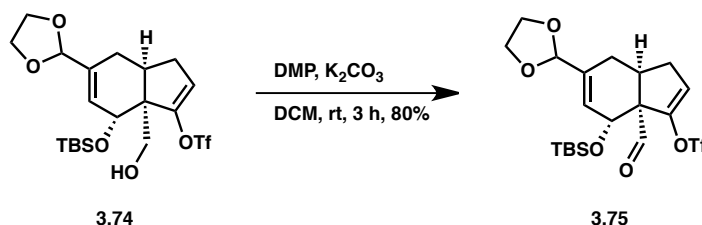


A 250 mL round-bottom flask was charged with ketone **3.71** (9.7 g, 24.5 mmol, 1 equiv) and THF (190 mL) and cooled to $-78\text{ }^\circ\text{C}$ in an acetone/dry ice bath. A 0.5 M solution of KHMDS in THF (64 mL, 31.9 mmol, 1.3 equiv) was added slowly and the brown-orange solution was allowed to stir at $-78\text{ }^\circ\text{C}$ for 2 h, at which point *N*-Phenyl-bis(trifluoromethanesulfonimide) (12.3 g, 34.3 mmol, 1.4 equiv) was added and the reaction was warmed to room temperature. After an additional 2 h of stirring at room temperature the reaction was diluted with ethyl acetate (200 mL) and washed with a saturated solution of NaHCO_3 (3 x 100 mL) and brine (100 mL). The organic layer was concentrated and dried over magnesium sulfate, filtered, and concentrated. The resulting material was purified by column chromatography (5-25% ethyl acetate in hexane) to separate the diastereomers. This provided one diastereomer (**3.73**) contaminated with an unknown product (3.8 g, est. 29%) separated from the other diastereomer (**3.72**, 5.1 g, 39%). Vinyl triflate **3.73** was brought on in the next step without further purification. Vinyl triflate **3.72**: ^1H NMR (500 MHz, CDCl_3): δ 6.08 (d, $J = 3.3$ Hz, 1H), 5.77 (s, 1H), 5.18 (s, 1H), 4.84 (d, $J = 3.4$ Hz, 1H), 3.96 (dd, $J = 36.0, 3.4$ Hz, 4H), 3.75 (s, 3H), 2.97-2.94 (m, 1H), 2.62-2.57 (m, 1H), 2.20 (d, $J = 4.9$ Hz, 2H), 2.14-2.10 (m, 1H), 0.86 (s, 9H), 0.06 (t, $J = 11.4$ Hz, 7H); IR (film) 2955, 2931, 2889, 2858, 1745, 1423.

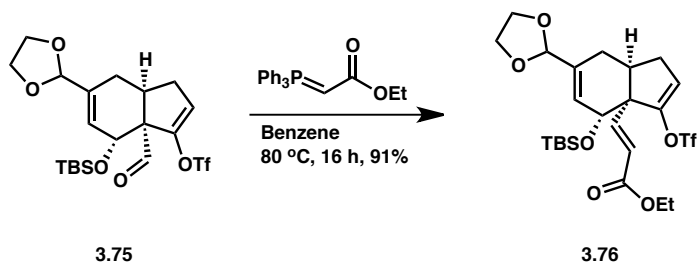


A 500 mL round-bottom flask was charged with crude ester **3.73** (~7.19 mmol, 1 equiv) and toluene (150 mL) and cooled to $-78\text{ }^\circ\text{C}$. A 1 M solution of DIBAL in toluene (29 mL, 28.8 mmol, 4 equiv) was added and the reaction was allowed to stir at $-78\text{ }^\circ\text{C}$ for 2.5 h. Ethyl acetate (50 mL) was added and the solution was warmed to room temperature. A saturated solution of Rochelle's salt (100 mL) was added and the biphasic solution was stirred vigorously for 12 h. The layers were separated and the aqueous phase was

extracted with ethyl acetate (2 x 100 mL). The combined organic layer was dried over magnesium sulfate, filtered and concentrated. The resulting material was purified by column chromatography (10-25% ethyl acetate in hexane) to give alcohol **3.74** as a pale yellow solid (2.2 g, 18% over 2 steps). R_f = 0.51 (25% ethyl acetate in hexane); ^1H NMR (600 MHz, CDCl_3): δ 6.03 (d, J = 3.9 Hz, 1H), 5.71 (s, 1H), 5.17 (s, 1H), 4.38 (d, J = 4.1 Hz, 1H), 4.00-3.90 (m, 4H), 3.81 (dd, J = 11.4, 6.5 Hz, 1H), 3.71 (dd, J = 11.3, 6.6 Hz, 1H), 2.64-2.63 (m, 1H), 2.60-2.57 (m, 2H), 2.44 (dd, J = 15.3, 5.3 Hz, 1H), 2.00 (dd, J = 12.4, 2.5 Hz, 1H), 1.92 (dd, J = 15.2, 4.6 Hz, 1H), 0.89 (s, 9H), 0.09 (d, J = 18.4 Hz, 6H); ^{13}C NMR (150 MHz, CDCl_3): δ 149.6, 138.8, 131.1, 118.1, 104.1, 69.6, 65.5, 65.3, 57.4, 36.4, 33.7, 26.6, 25.6, 17.8, -4.2, -5.3; HRMS (EI) calcd for $[\text{C}_{30}\text{H}_{31}\text{F}_3\text{NaO}_7\text{SSi}]^+$ (M^+): m/z 523.1410, found 523.1410.

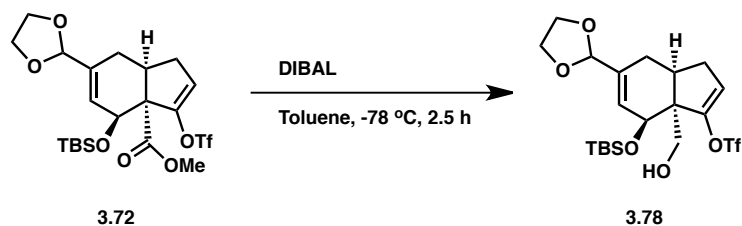


A 250 mL round-bottom flask was charged with alcohol **3.74** (2.2 g, 4.36 mmol, 1 equiv) and DCM (100 mL). Dess-martin periodinane (6.3 g, 14.9 mmol, 3.4 equiv) and potassium carbonate (6.2 g, 44.9 mmol, 10.3 equiv) were added and the solution was stirred at room temperature for 3 h. The reaction mixture was diluted with dichloromethane (100 mL) and washed with a 1:1 solution of saturated sodium bicarbonate and saturated sodium sulfite (3 x 100 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated. The crude product was purified by column chromatography (10% ethyl acetate in hexane) to give aldehyde **3.75** (1.7 g, 80%). R_f = 0.82 (25% ethyl acetate in hexane); ^1H NMR (500 MHz, CDCl_3): δ 9.58 (s, 1H), 6.14-6.13 (m, 1H), 5.81-5.80 (m, 1H), 5.21-5.20 (m, 1H), 4.64 (dd, J = 4.2, 1.6 Hz, 1H), 4.03-3.93 (m, 4H), 2.87-2.85 (m, 1H), 2.64-2.58 (m, 1H), 2.51-2.46 (m, 1H), 2.08-2.03 (m, 1H), 1.93-1.89 (m, 1H), 0.83-0.82 (m, 9H), 0.09-0.06 (m, 6H); IR (film) 2931, 2954, 2888, 2859, 1732, 1689, 1423 cm^{-1} ; HRMS (EI) calcd for $[\text{C}_{20}\text{H}_{29}\text{F}_3\text{NaO}_7\text{SSi}]^+$ (M^+): m/z 521.1253, found 521.1256.



A 100 mL round-bottom flask was charged with aldehyde **3.75** (1.7 g, 3.35 mmol, 1 equiv), (Ethoxycarbonylmethylene)triphenylphosphorane (3.9 g, 10.1 mmol, 3 equiv), and benzene (35 mL) and heated to 80 $^\circ\text{C}$ for 16 h. The reaction mixture was loaded onto silica gel and purified by column chromatography (10-25% ethyl acetate in hexane) to

give α , β -unsaturated ester **3.76** (1.2 g, 99%). R_f = 0.73 (25% ethyl acetate in hexane); ^1H NMR (400 MHz, CDCl_3): δ 7.21 (d, J = 16.3 Hz, 1H), 6.04-6.03 (m, 1H), 5.84-5.78 (m, 2H), 5.19 (s, 1H), 4.33-4.32 (m, 1H), 4.23-4.09 (m, 2H), 4.01-3.92 (m, 4H), 2.66-2.46 (m, 3H), 2.10-2.05 (m, 1H), 1.96-1.91 (m, 1H), 1.30-1.25 (m, 3H), 0.90-0.86 (m, 9H), 0.08-0.04 (m, 6H); ^{13}C NMR (150 MHz, CDCl_3): δ 166.2, 149.4, 148.1, 138.3, 131.1, 121.1, 116.8, 104.1, 69.0, 65.2, 60.3, 58.5, 41.1, 33.7, 26.4, 25.6, 17.9, 14.2, -4.1, -5.4; IR (film) 2955, 2931, 2889, 2858, 1721, 1651, 1473, 1424 cm^{-1} ; HRMS (EI) calcd for $[\text{C}_{24}\text{H}_{35}\text{F}_3\text{NaO}_8\text{SSi}]^+ (\text{M}^+)$: m/z 591.1672, found 591.1657.

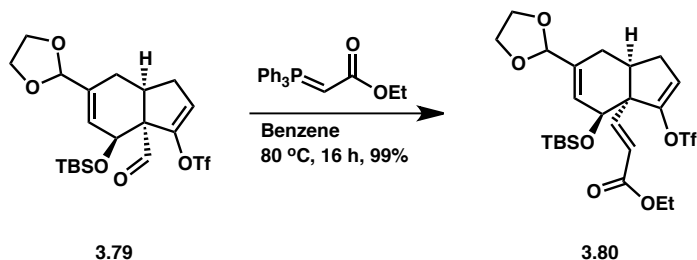


A 500 mL round-bottom flask was charged with ester **3.72** (5 g, 9.47 mmol, 1 equiv) and toluene (200 mL) and cooled to -78 °C. A 1 M solution of DIBAL in toluene (29 mL, 28.4 mmol, 3 equiv) was added and the reaction was allowed to stir at -78 °C for 2.5 h. Ethyl acetate (50 mL) was added and the solution was warmed to room temperature. A saturated solution of Rochelle's salt (100 mL) was added and the biphasic solution was stirred vigorously for 12 h. The layers were separated and the aqueous phase was extracted with ethyl acetate (2 x 100 mL). The combined organic layer was dried over magnesium sulfate, filtered and concentrated. The resulting material was purified by column chromatography (10-25% ethyl acetate in hexane) to give an inseparable mixture of aldehyde **3.79** and alcohol **3.78** (3.6 g). This mixture was brought on in the next step without further purification. R_f = 0.47 (25% ethyl acetate in hexane).



A 500 mL round-bottom flask was charged with crude alcohol **3.78** (3.6 g, 1 equiv) and DCM (170 mL). Dess-martin periodinane (9.2 g, 21.7 mmol, 3.0 equiv) and potassium carbonate (9.1 g, 65.8 mmol, 9.0 equiv) were added and the solution was stirred at room temperature for 3 h. The reaction mixture was diluted with dichloromethane (100 mL) and washed with a 1:1 solution of saturated sodium bicarbonate and saturated sodium sulfite (3 x 100 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated. The crude product was purified by column chromatography (10% ethyl acetate in hexane) to give aldehyde **3.79** (1.9 g, 40% over 2 steps). R_f = 0.78 (25% ethyl acetate in hexane); ^1H NMR (500 MHz, CDCl_3): δ 9.62 (s, 1H), 6.13 (d, J = 4.0 Hz, 1H), 5.93 (t, J = 2.6 Hz, 1H), 5.17 (s, 1H), 4.78 (d, J = 4.0 Hz, 1H), 4.01-3.89 (m, 4H), 2.93-2.90 (m, 1H), 2.66 (ddd, J = 16.8, 9.4, 2.8 Hz, 1H), 2.23-2.18 (m, 3H), 0.87-0.84 (m, 9H),

0.09-0.04 (m, 6H); ^{13}C NMR (150 MHz, CDCl_3): δ 199.1, 145.0, 137.5, 131.9, 121.9, 103.7, 69.3, 66.8, 65.3, 65.2, 36.5, 34.6, 26.3, 25.7, 17.9, -4.4, -5.3; HRMS (EI) calcd for $[\text{C}_{20}\text{H}_{29}\text{F}_3\text{NaO}_7\text{SSi}]^+ (\text{M}^+)$: m/z 521.1253, found 521.1253.



A 100 mL round-bottom flask was charged with aldehyde **3.79** (2.3 g, 4.52 mmol, 1 equiv), (Ethoxycarbonylmethylene)triphenylphosphorane (5.2 g, 13.6 mmol, 3 equiv), and benzene (50 mL) and heated to 80 °C for 16 h. The reaction mixture was loaded onto silica gel and purified by column chromatography (10-25% ethyl acetate in hexane) to give α , β -unsaturated ester **3.80** as a white solid (2.6 g, 99%). R_f = 0.65 (25% ethyl acetate in hexane); ^1H NMR (300 MHz, CDCl_3): δ 6.96 (d, J = 16.1 Hz, 1H), 6.11 (dd, J = 4.1, 0.3 Hz, 1H), 5.86 (d, J = 16.1 Hz, 1H), 5.79-5.77 (m, 1H), 5.20 (s, 1H), 4.30-4.29 (m, 1H), 4.24-4.16 (m, 2H), 4.02-3.92 (m, 4H), 2.65-2.59 (m, 2H), 2.26-2.22 (m, 2H), 2.16-2.11 (m, 1H), 1.29 (dd, J = 8.3, 6.0 Hz, 3H), 0.87-0.85 (m, 9H), 0.07-0.04 (m, 6H); ^{13}C NMR (150 MHz, CDCl_3): δ 166.0, 150.1, 147.7, 138.1, 130.9, 122.0, 118.2, 104.3, 70.4, 65.4, 65.2, 60.5, 59.3, 40.8, 34.6, 26.9, 25.7, 18.0, 14.1, -4.3, -5.2; IR 2955, 2931, 2888, 2858, 1721, 1651, 1473, 1249 (film) cm^{-1} ; HRMS (EI) calcd for $[\text{C}_{24}\text{H}_{35}\text{F}_3\text{NaO}_8\text{SSi}]^+ (\text{M}^+)$: m/z 591.1672, found 591.1669.

3.9 References and Notes

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Appendix 2:
Spectra Relevant to Chapter 3

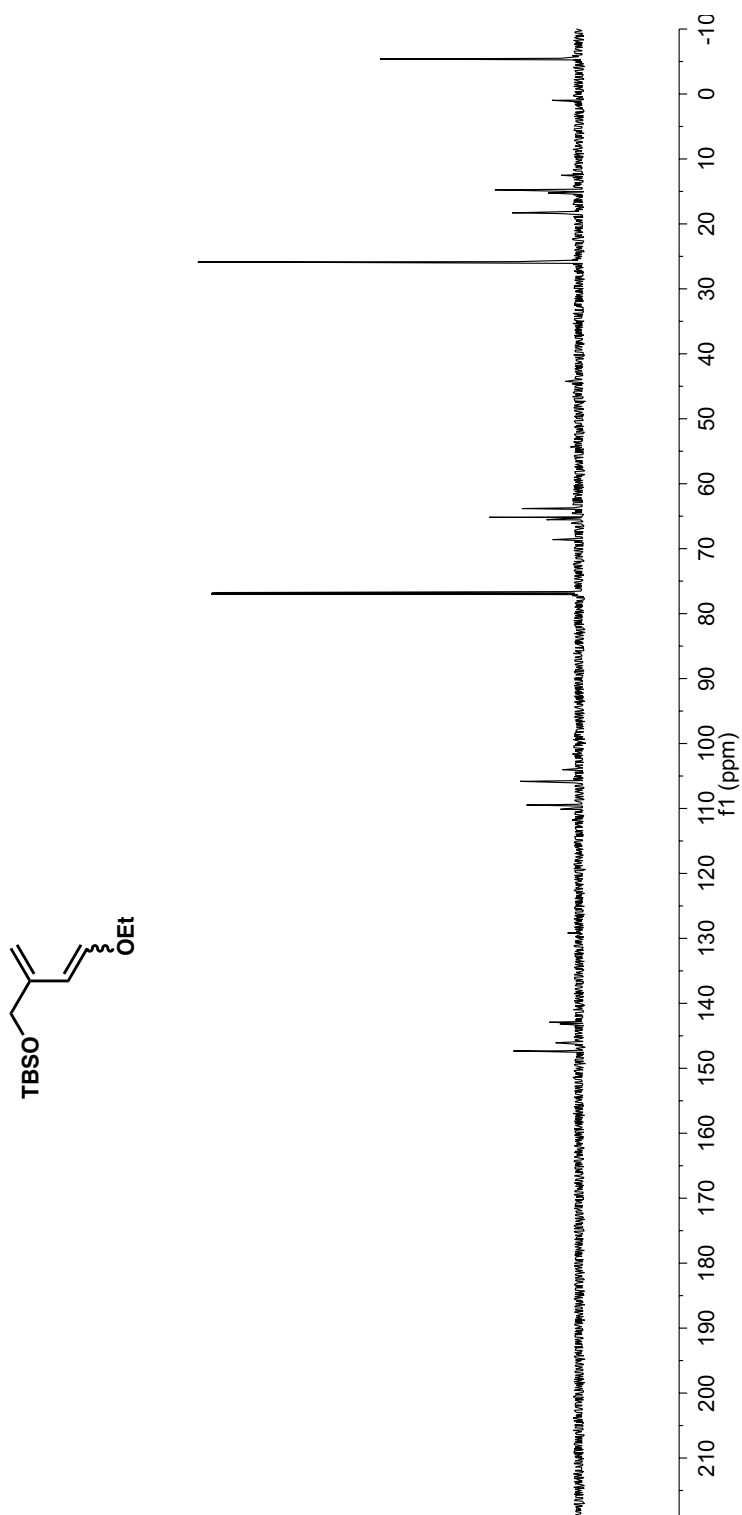


Figure A2.2 ^{13}C NMR of 2.40

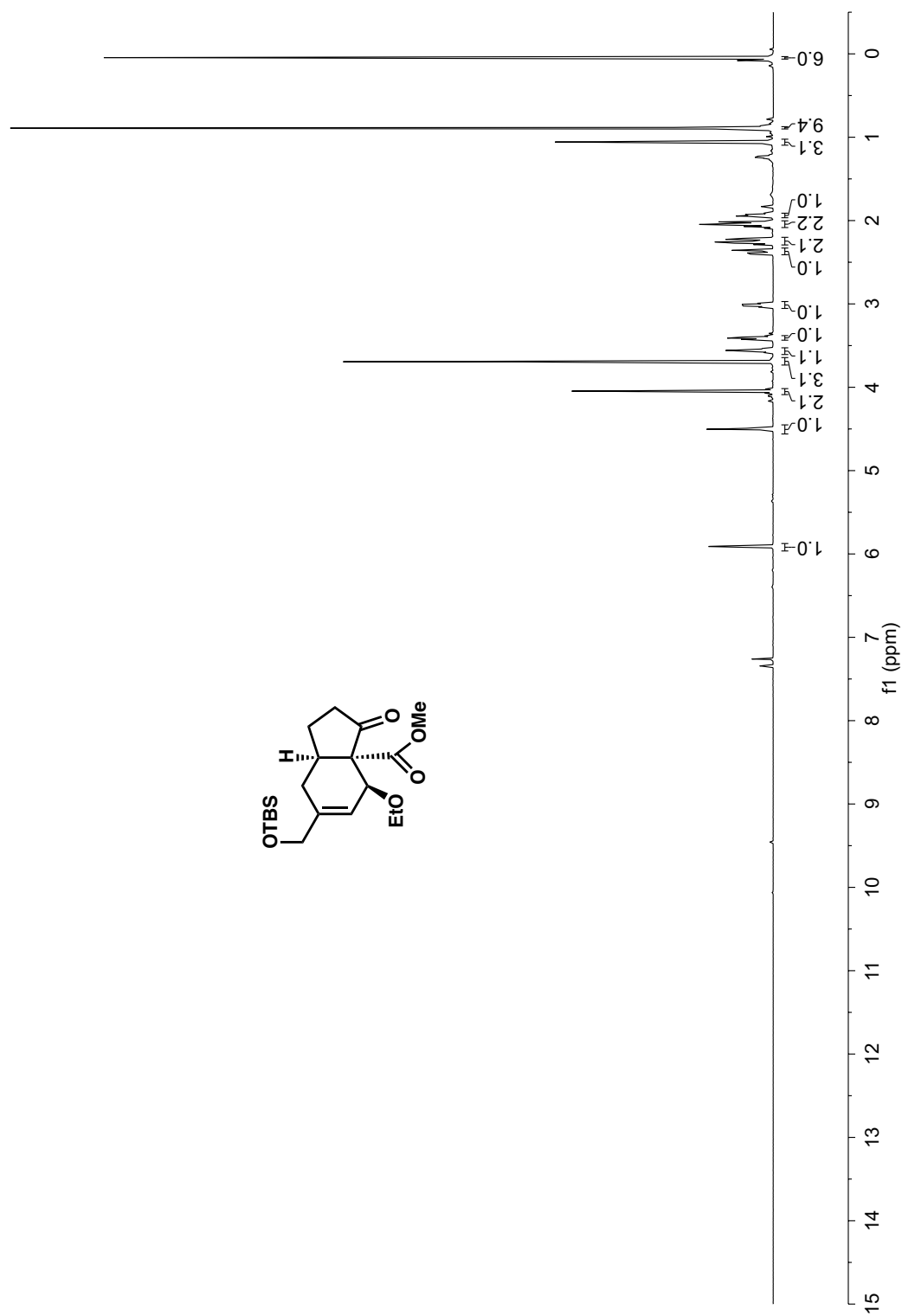


Figure A2.3 ¹H NMR of 2.34

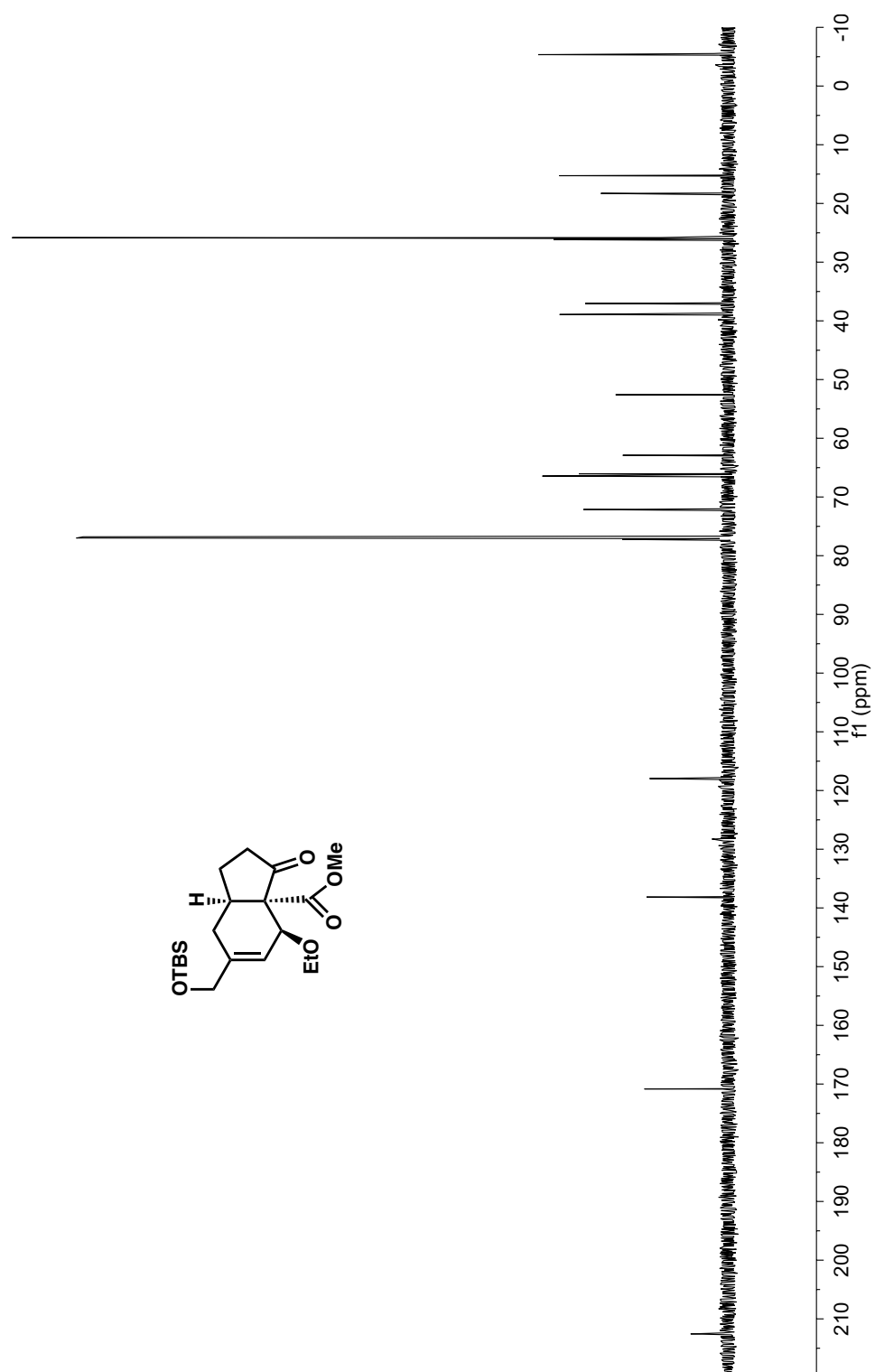


Figure A2.4 ^{13}C NMR of 2.34

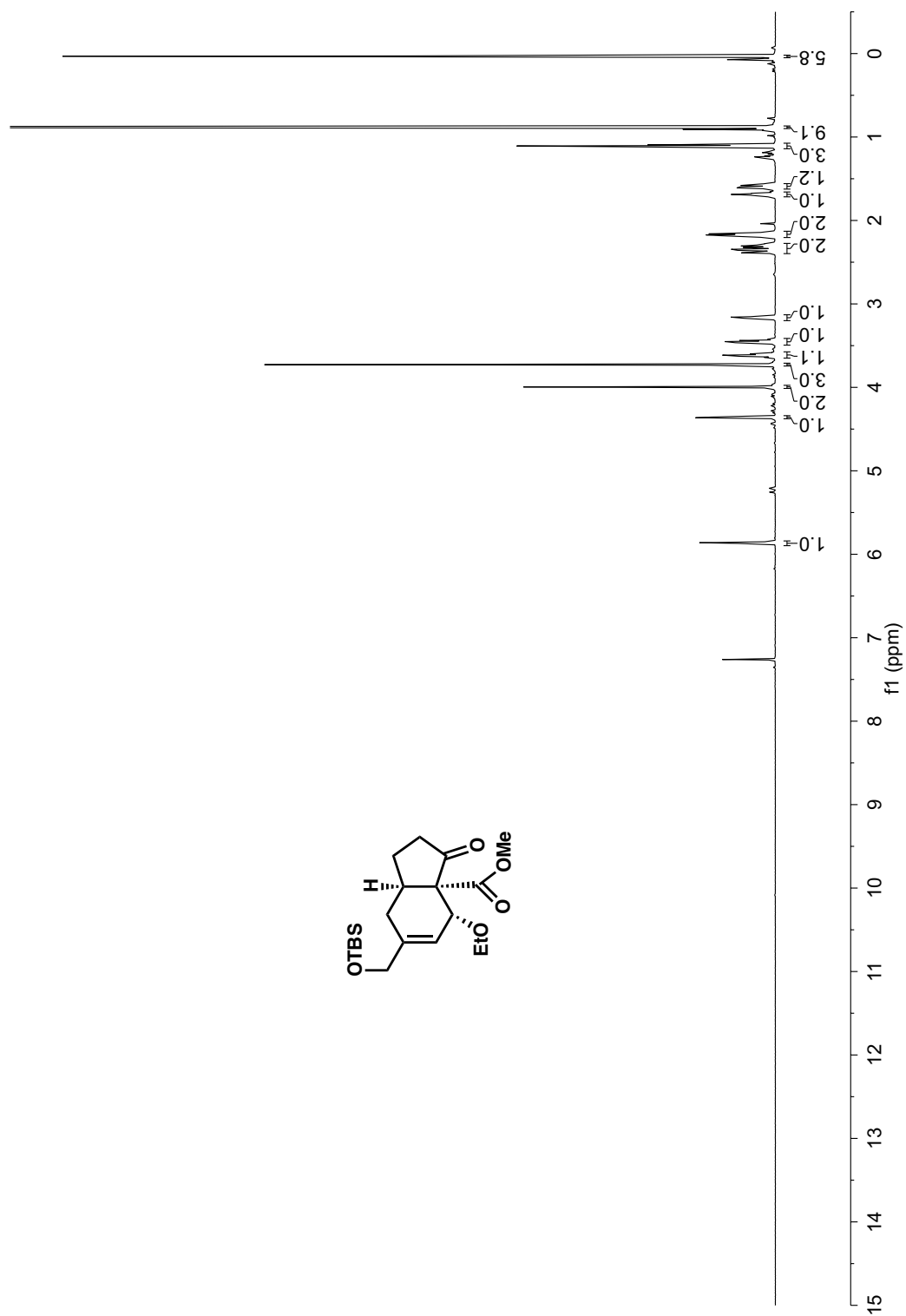


Figure A2.5 ^1H NMR of 2.S1

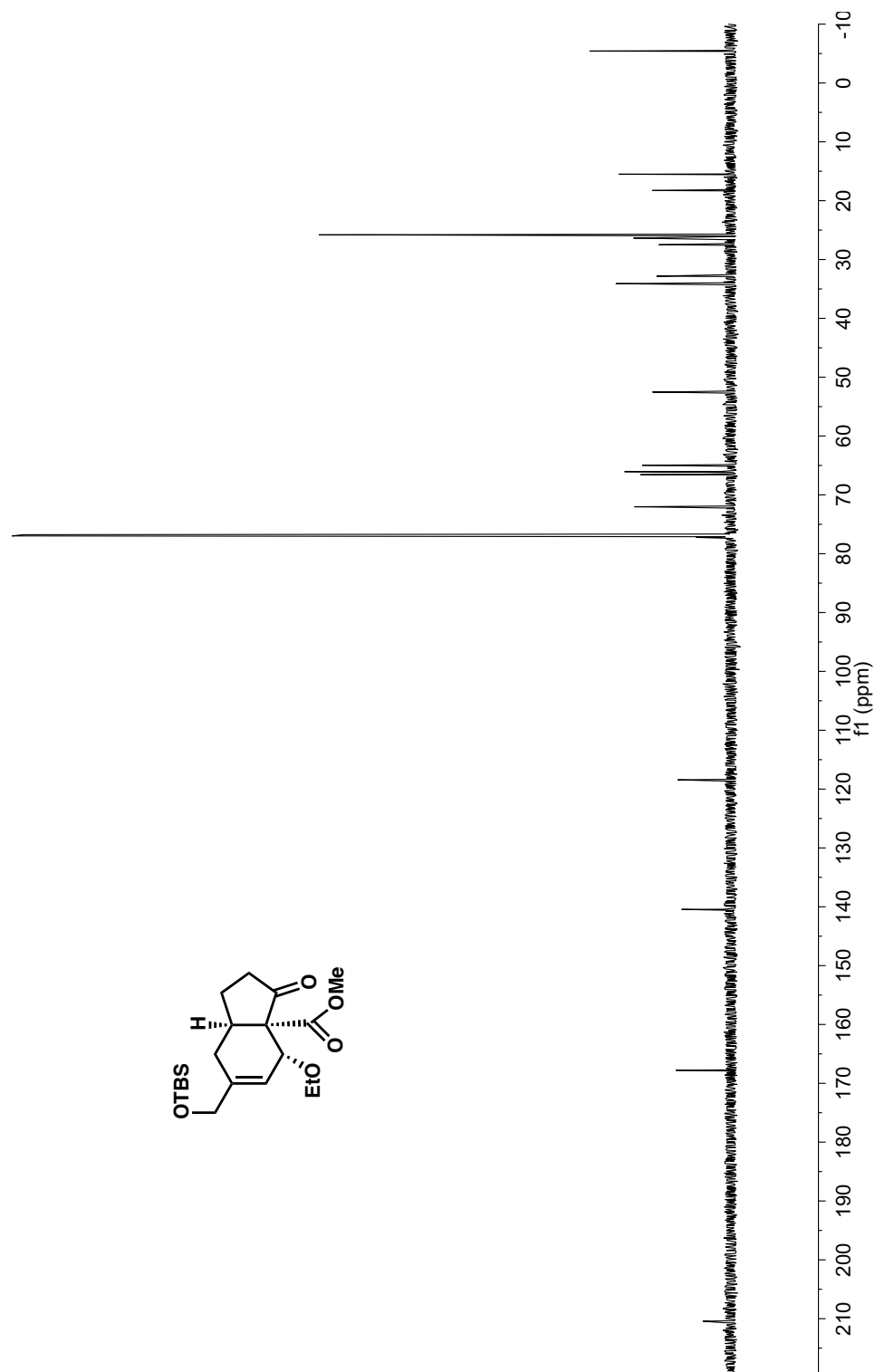


Figure A2.6 ^{13}C NMR of 2.S1

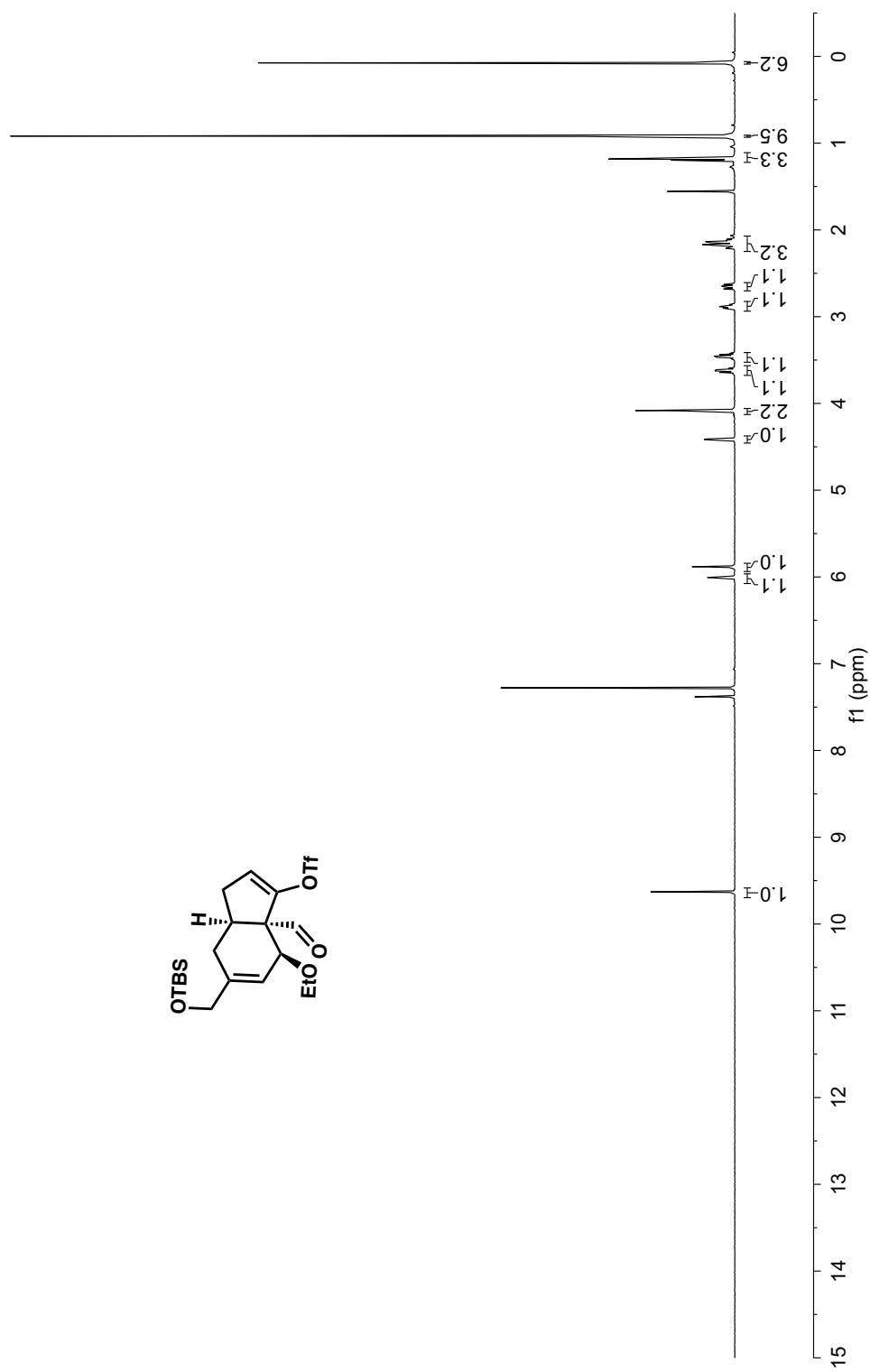


Figure A2.7 ^1H NMR of 2.42

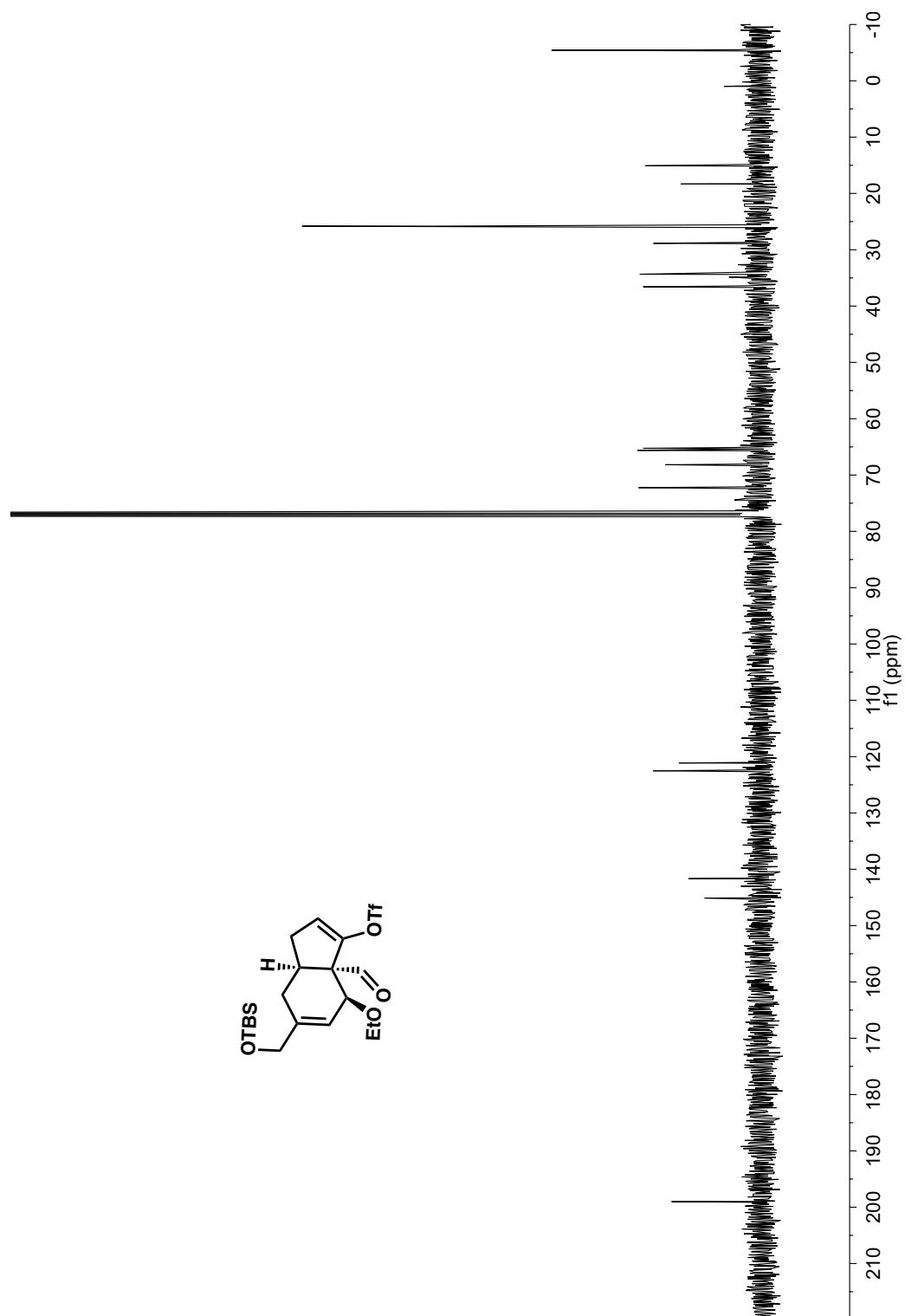


Figure A2.8 ^{13}C NMR of 2.42

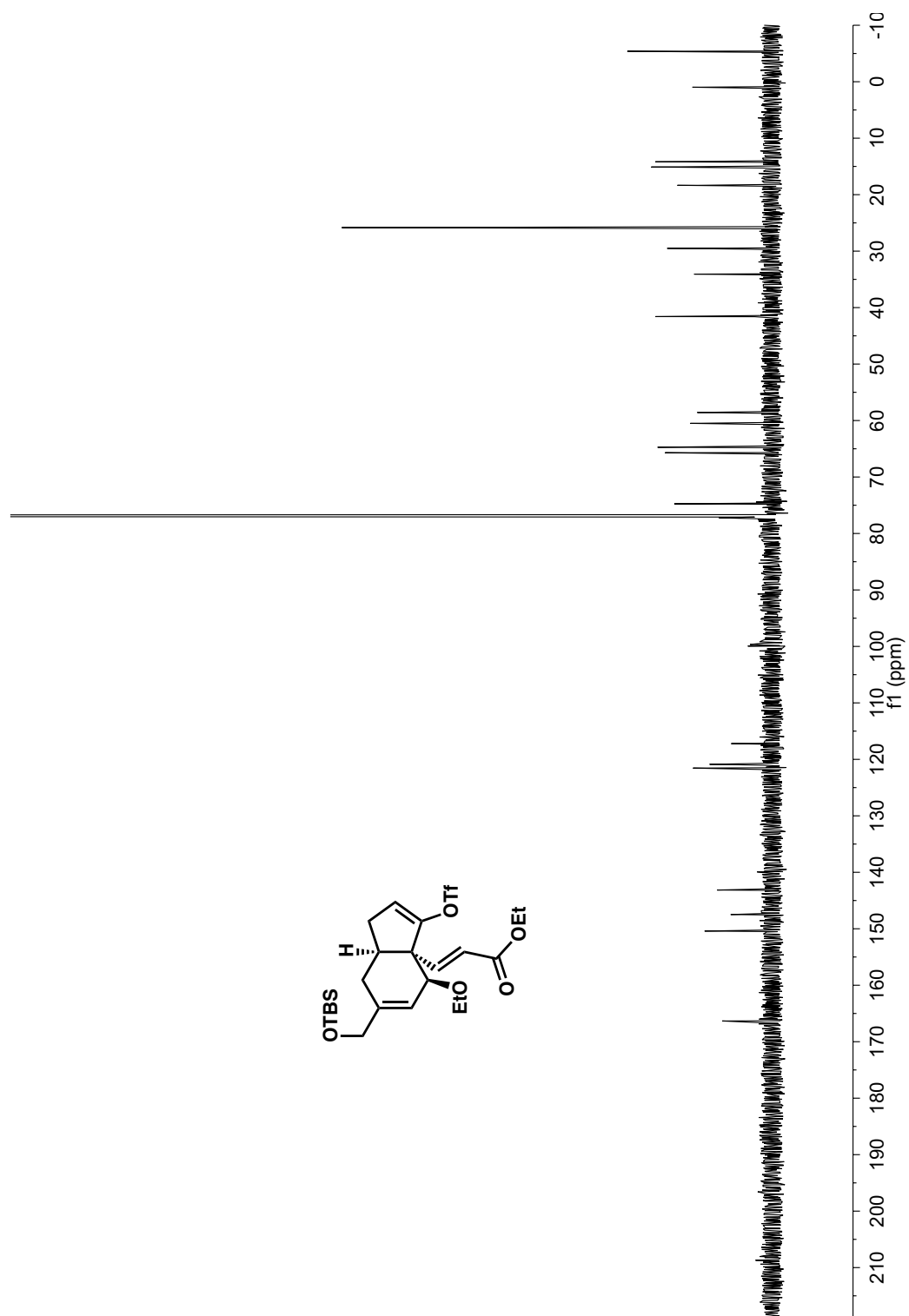


Figure A2.10 ^{13}C NMR of 2.43

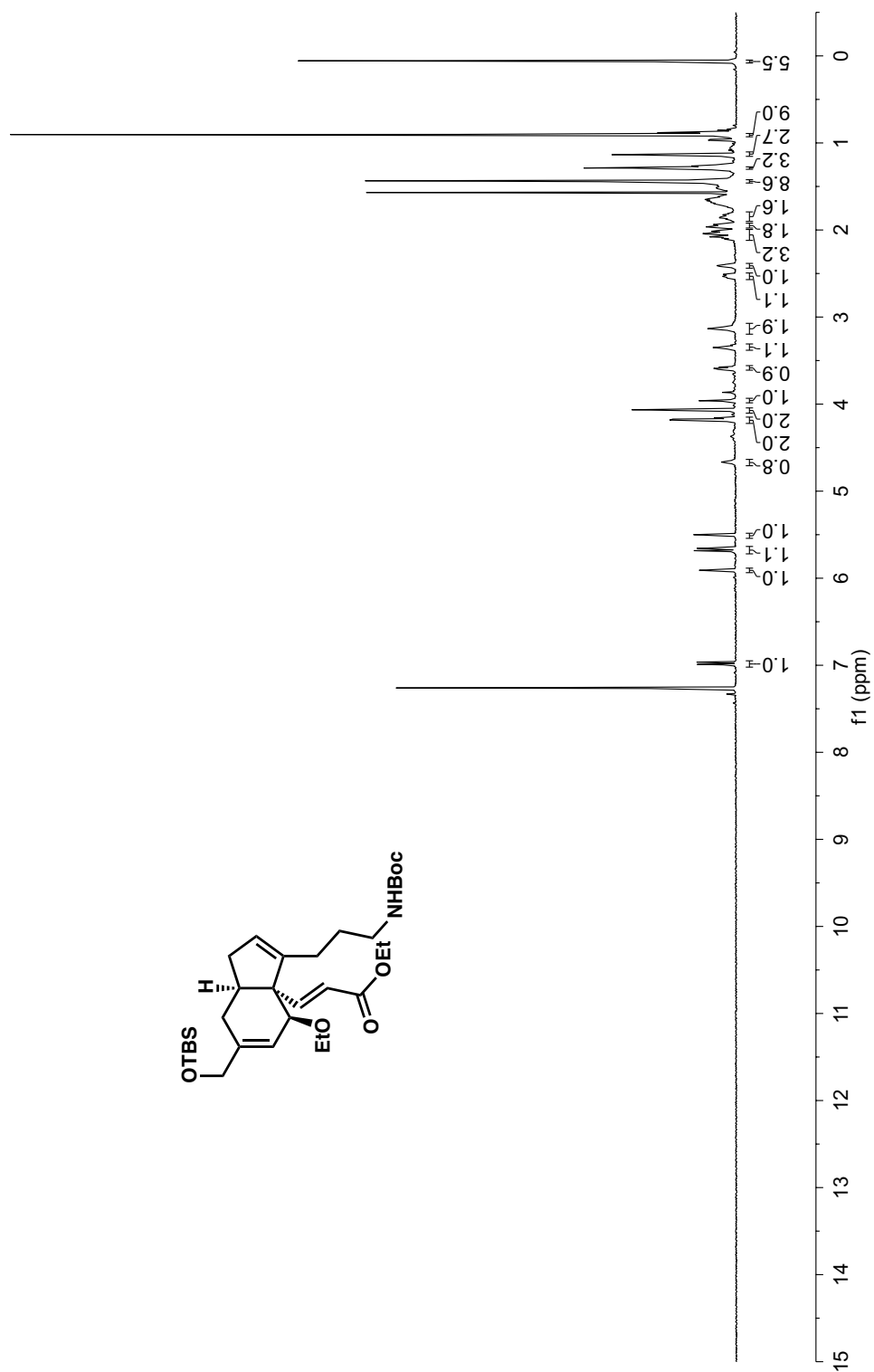


Figure A2.11 ^1H NMR of 2.44

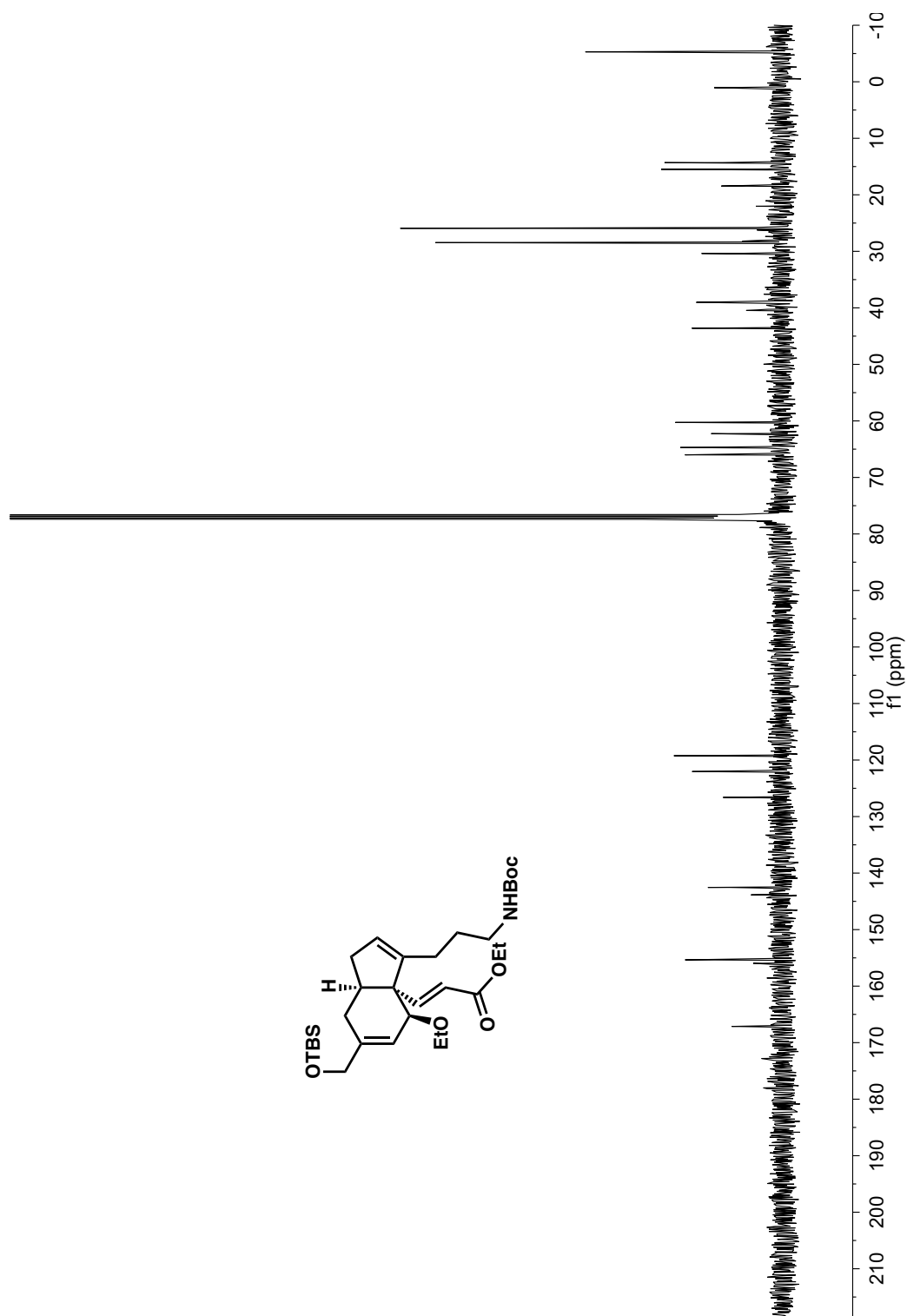


Figure A2.12 ^{13}C NMR of 2.44

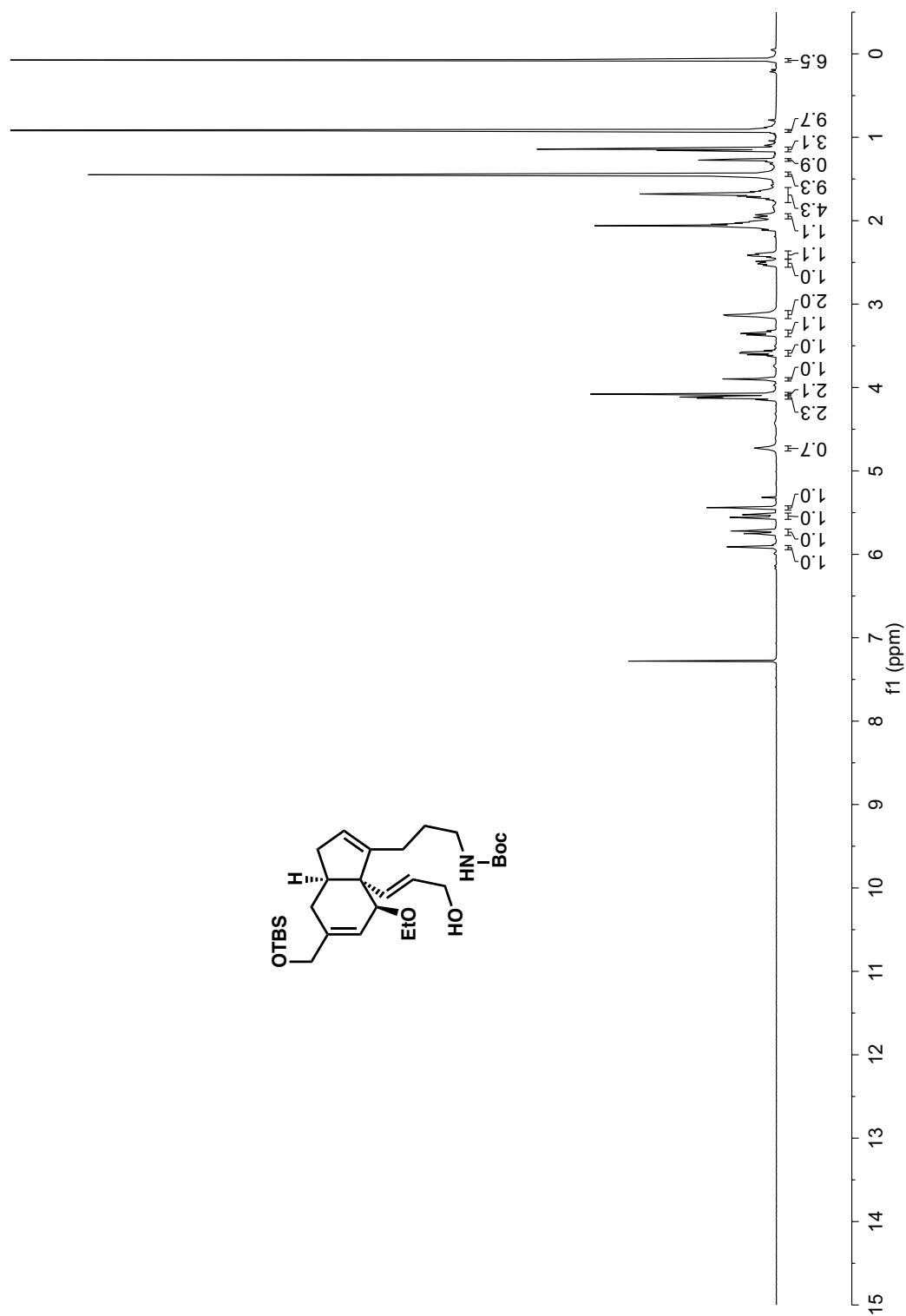


Figure A2.13 ^1H NMR of **2.46**

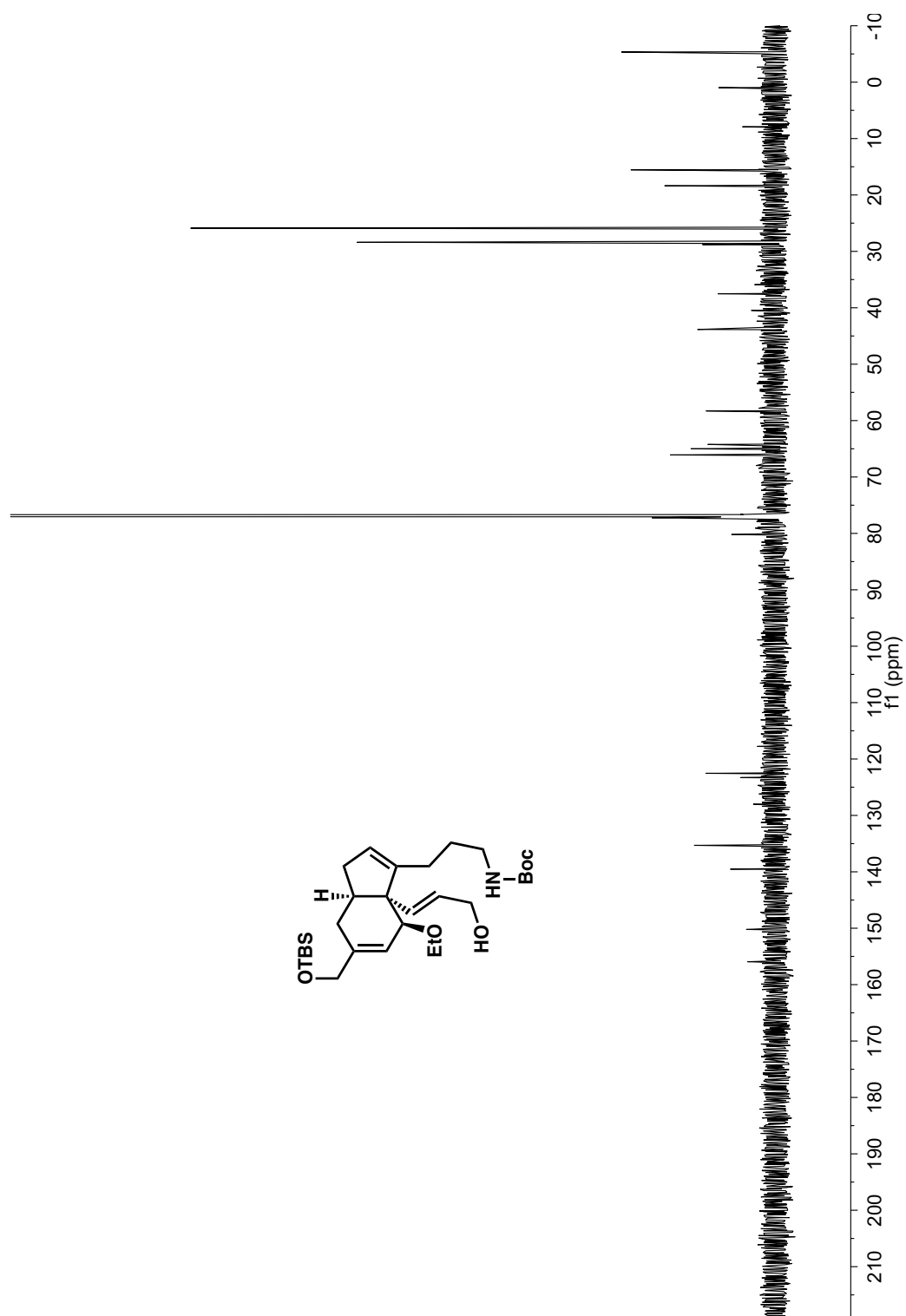


Figure A2.14 ^{13}C NMR of 2.46

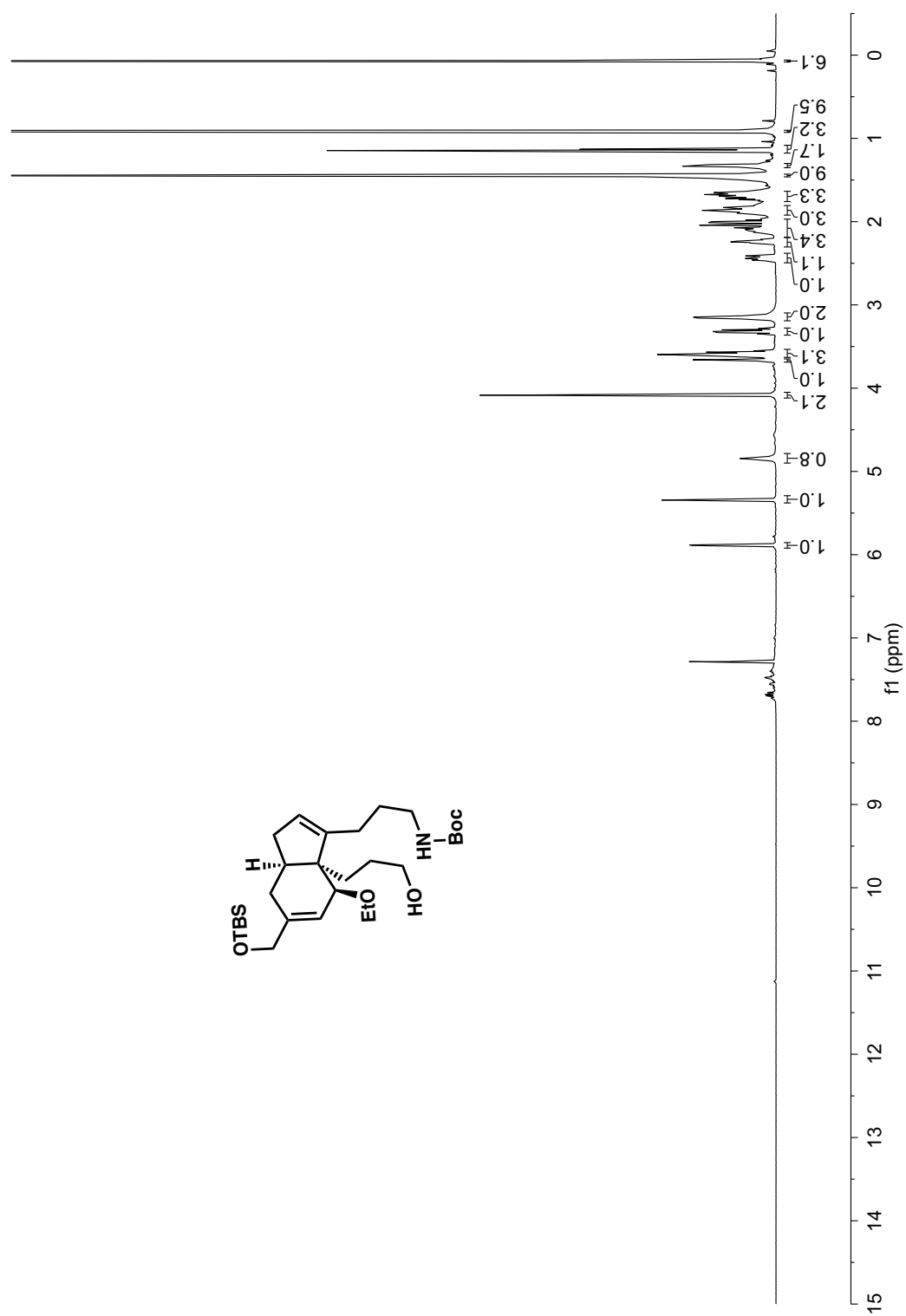


Figure A2.15 ^1H NMR of 2.47

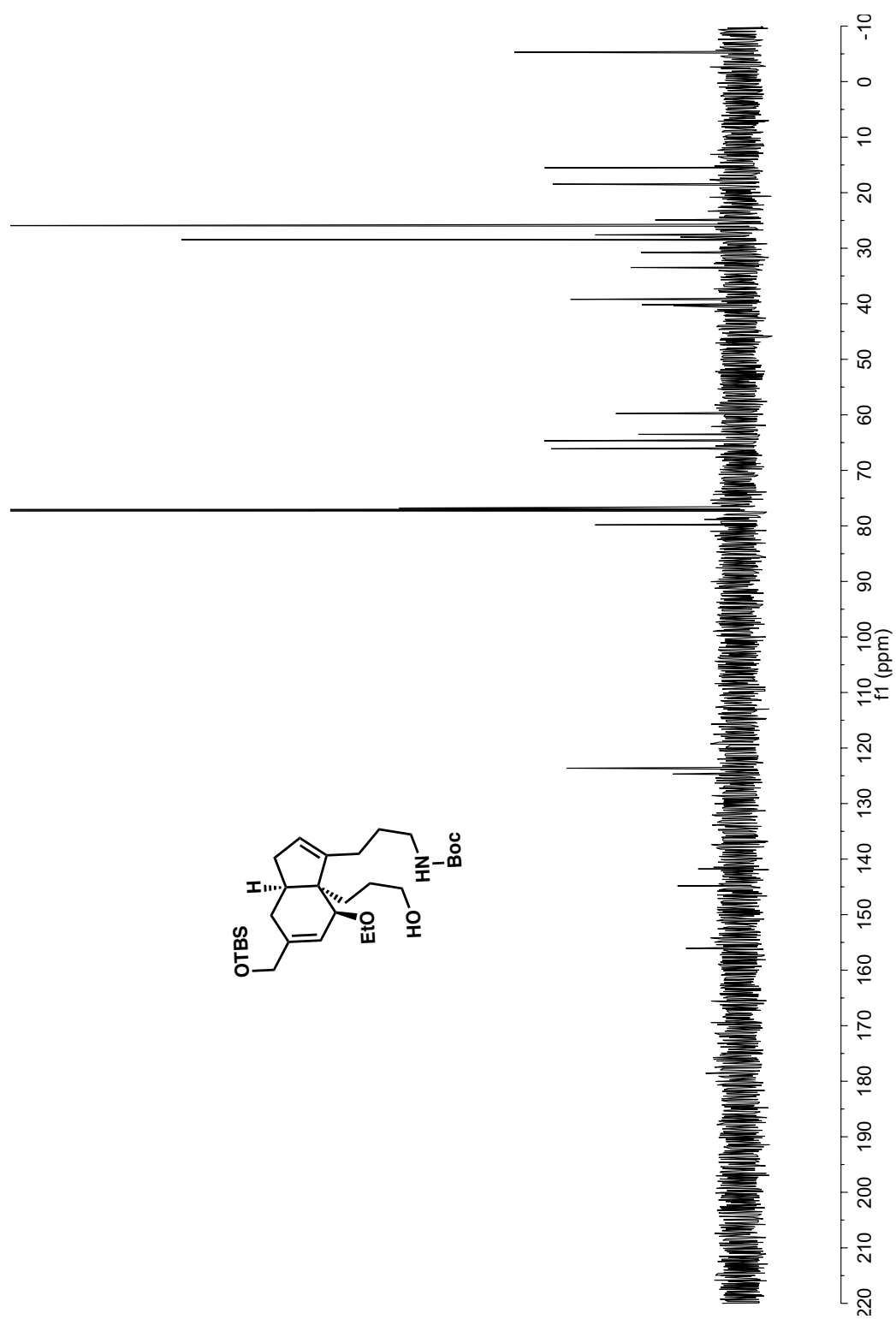


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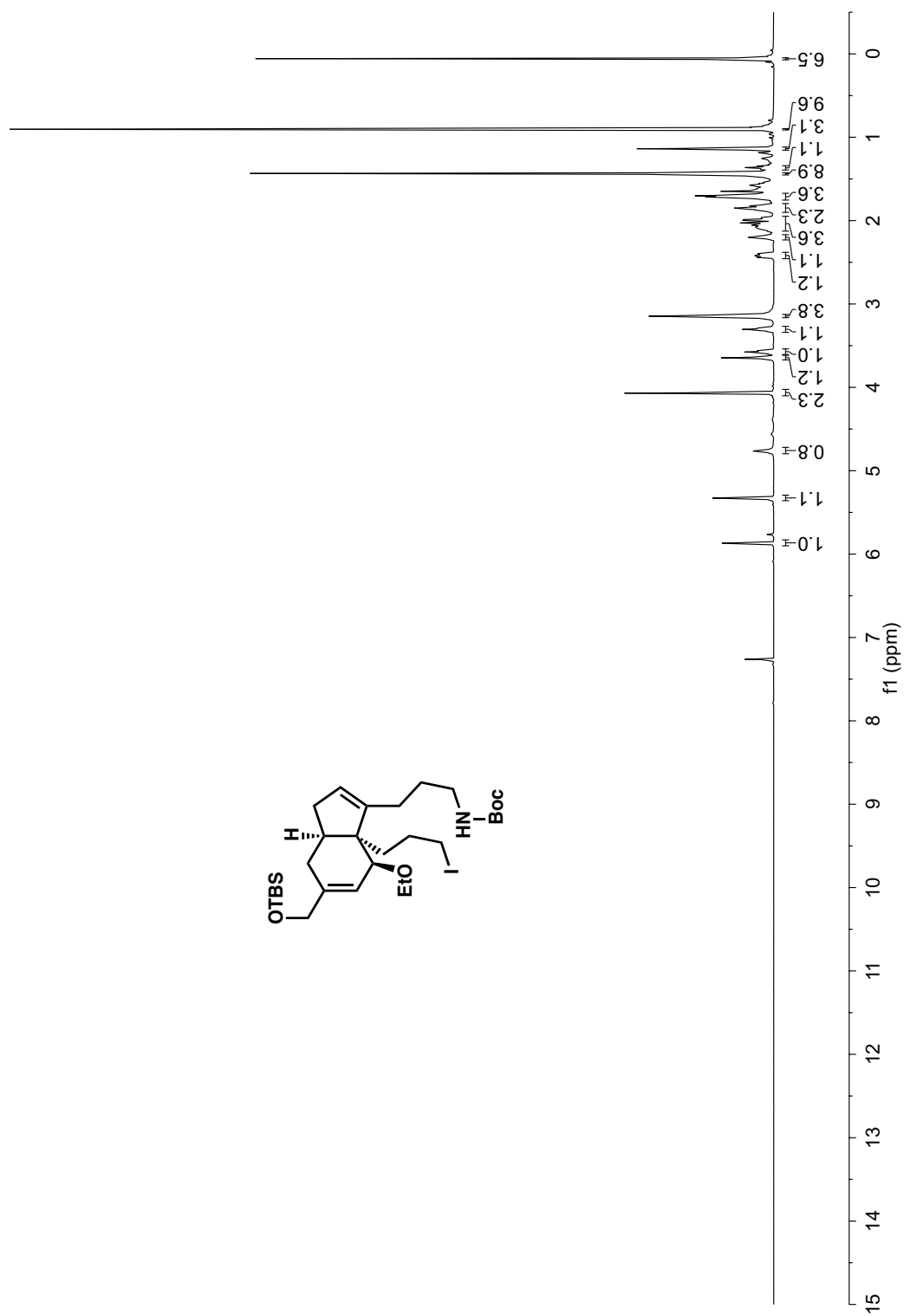


Figure A2.17 ^1H NMR of 2.49

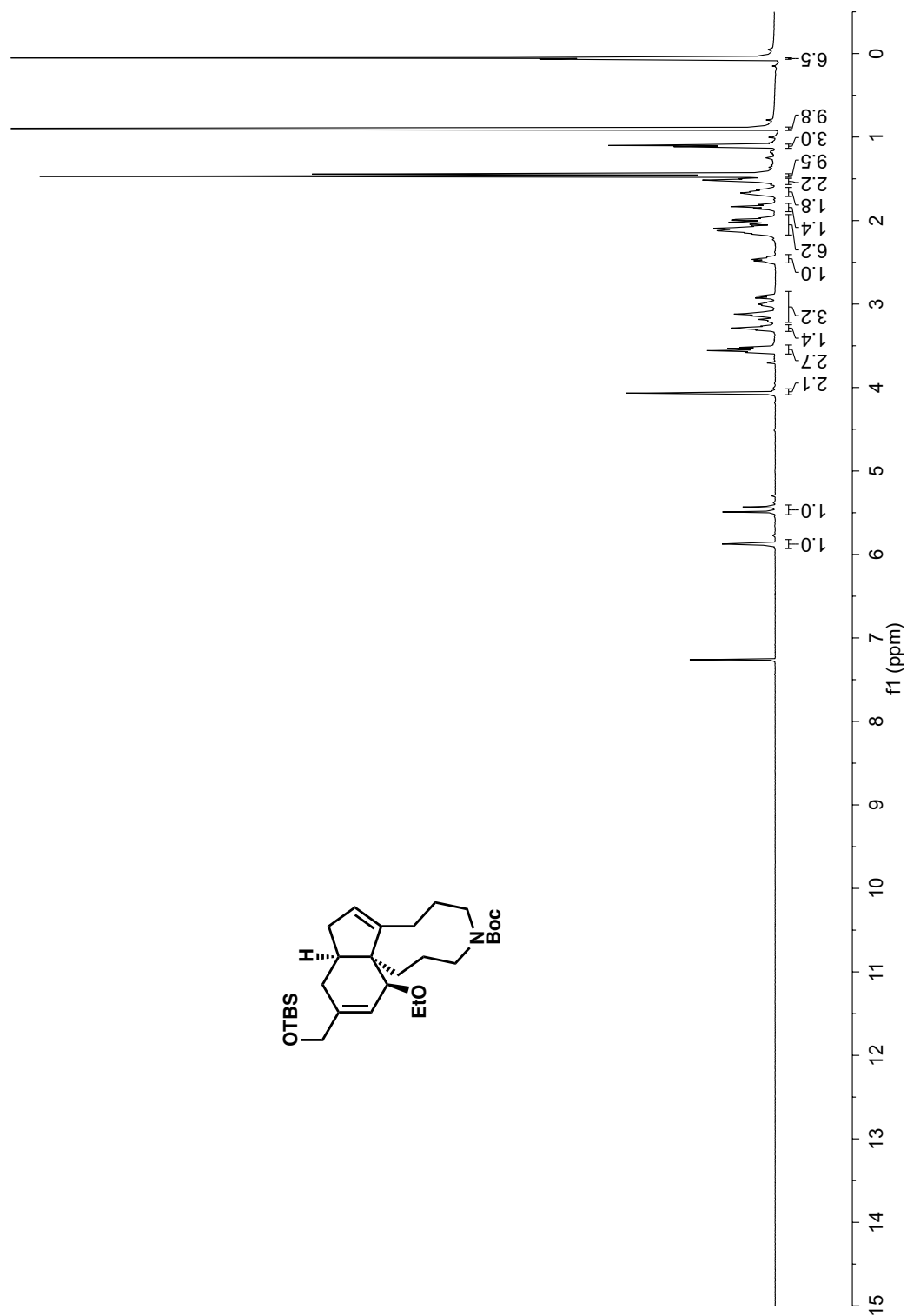


Figure A2.19 ^1H NMR of 2.50

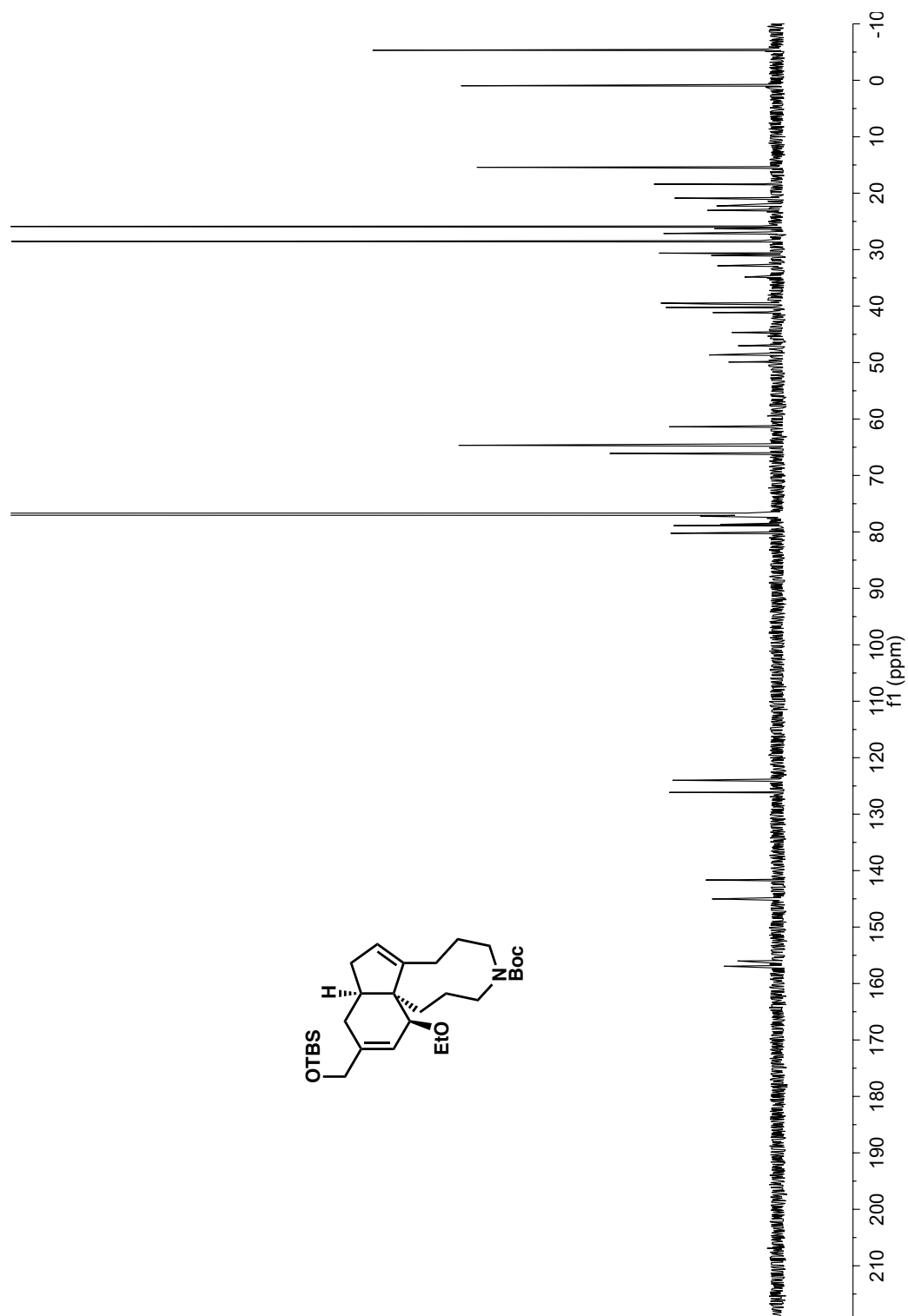


Figure A2.20 ^{13}C NMR of 2.50

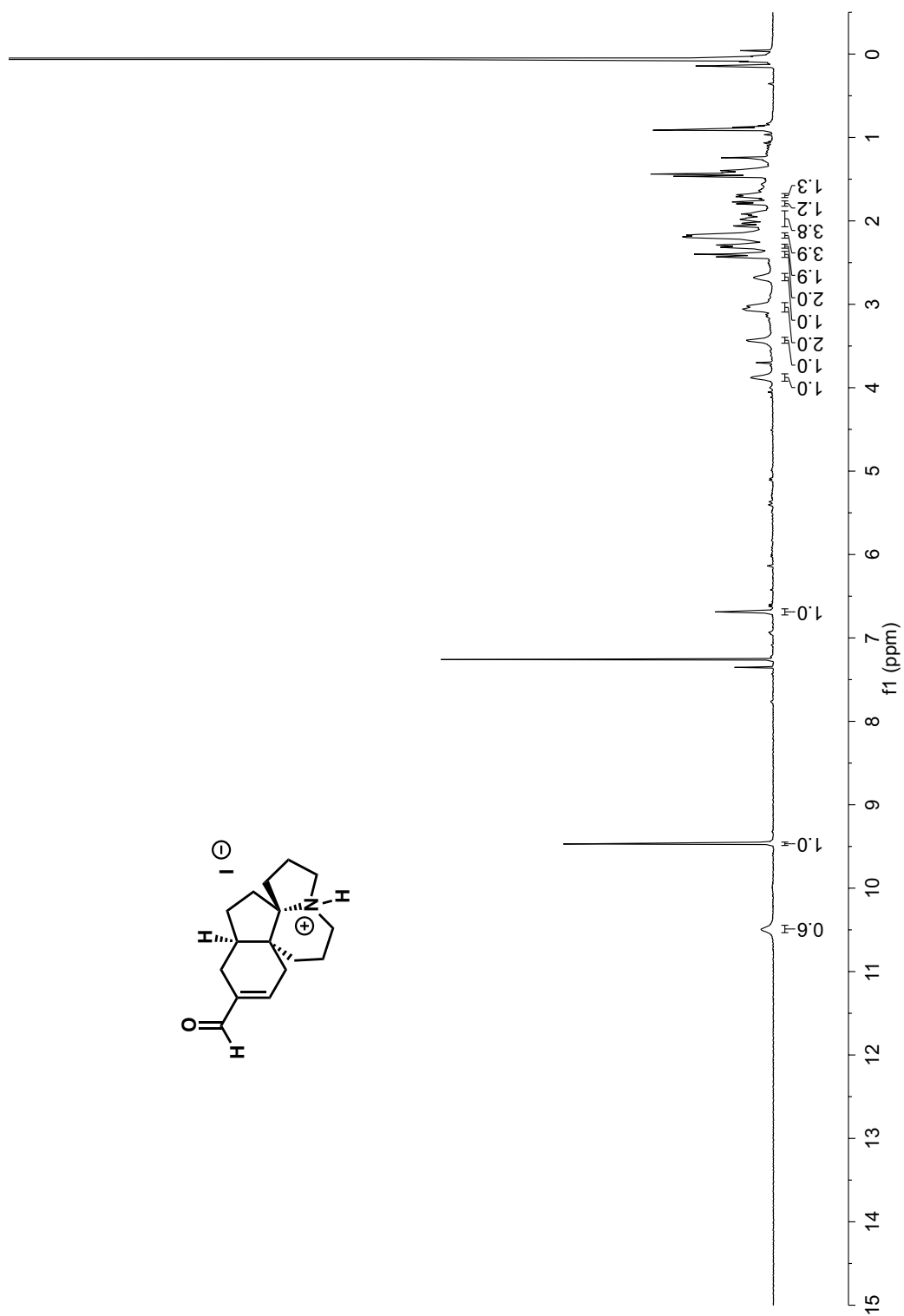


Figure A2.21 ^1H NMR of **2.59**

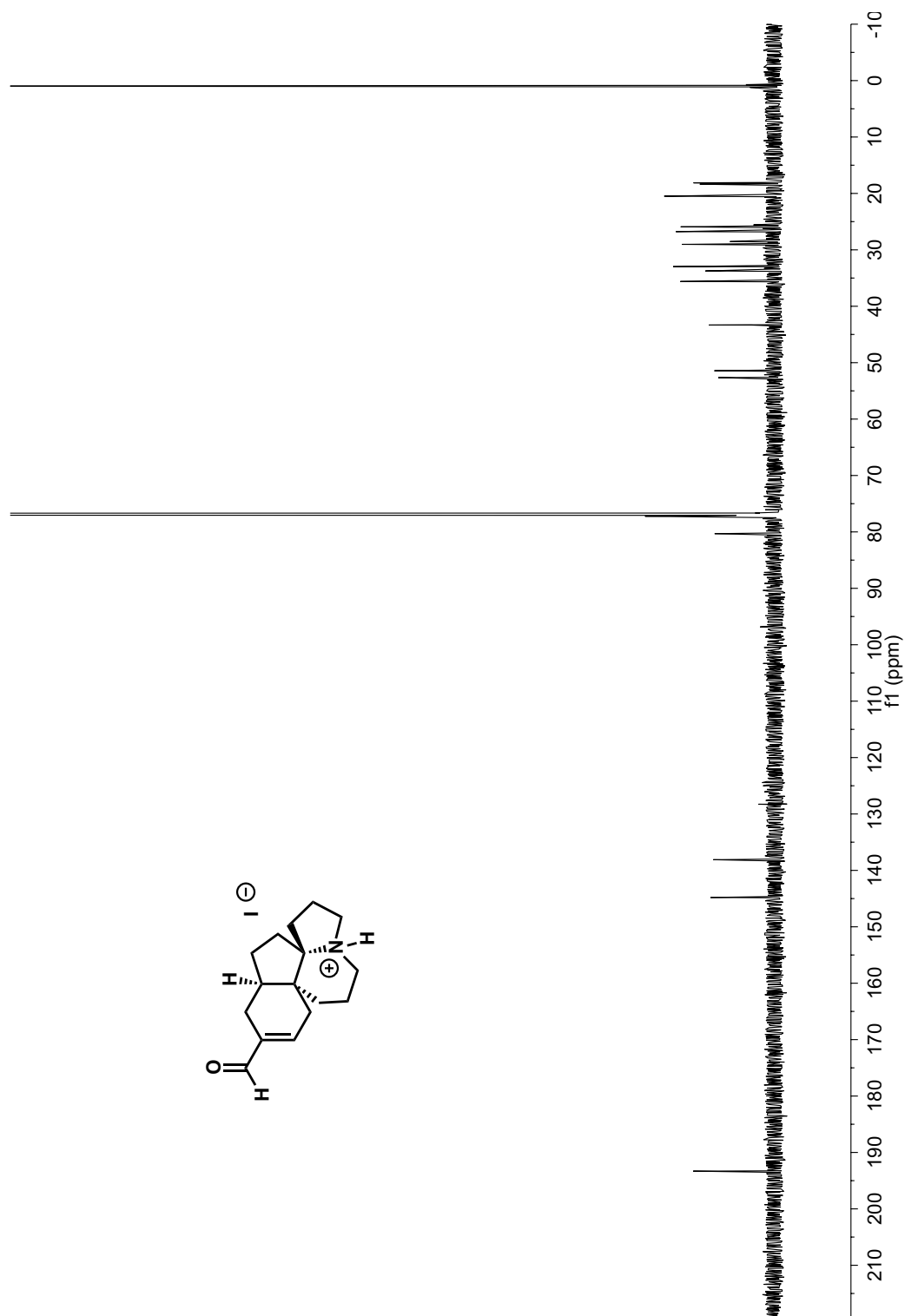


Figure A2.22 ^{13}C NMR of 2.59

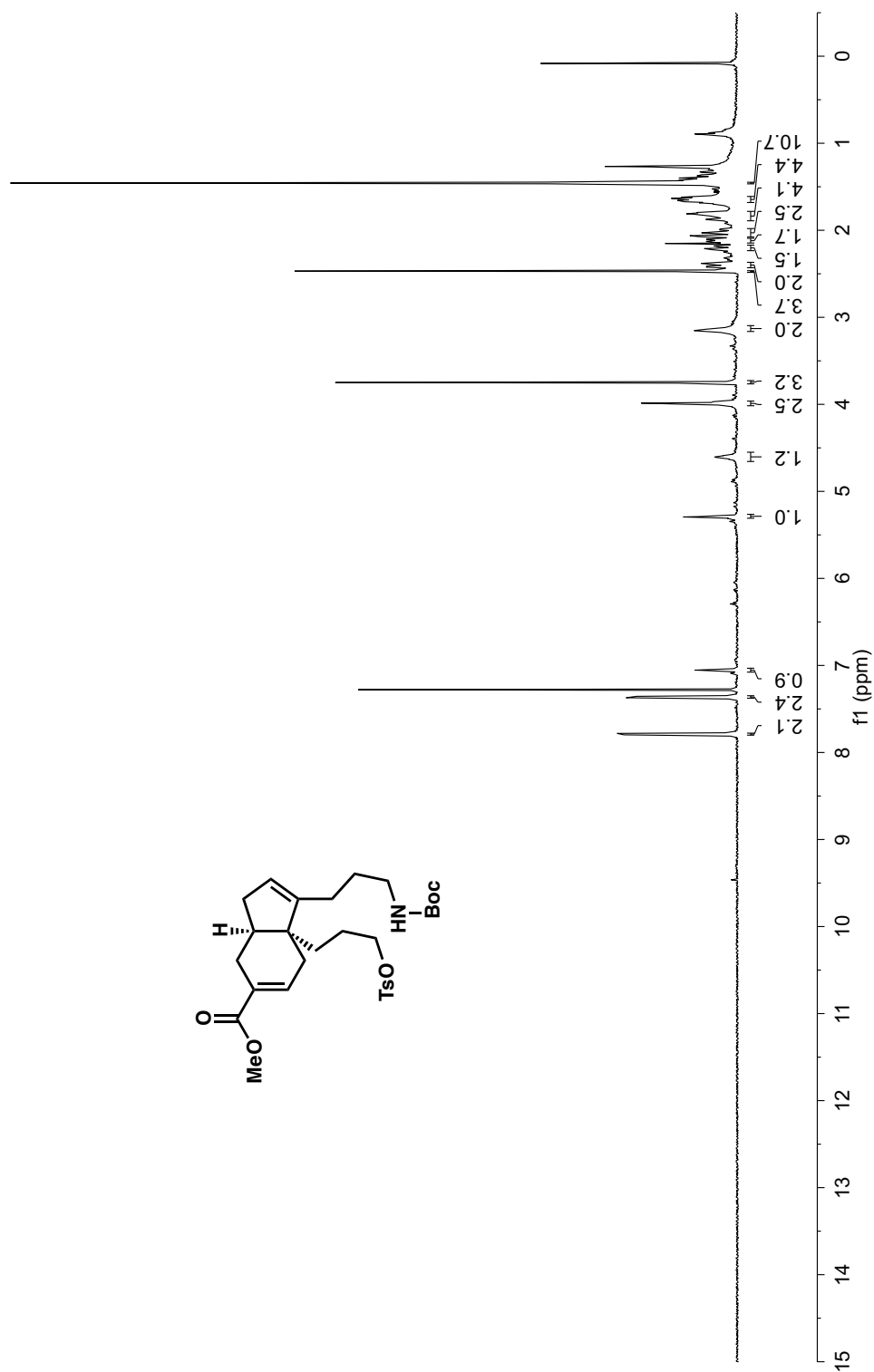


Figure A2.23 ^1H NMR of 2.63

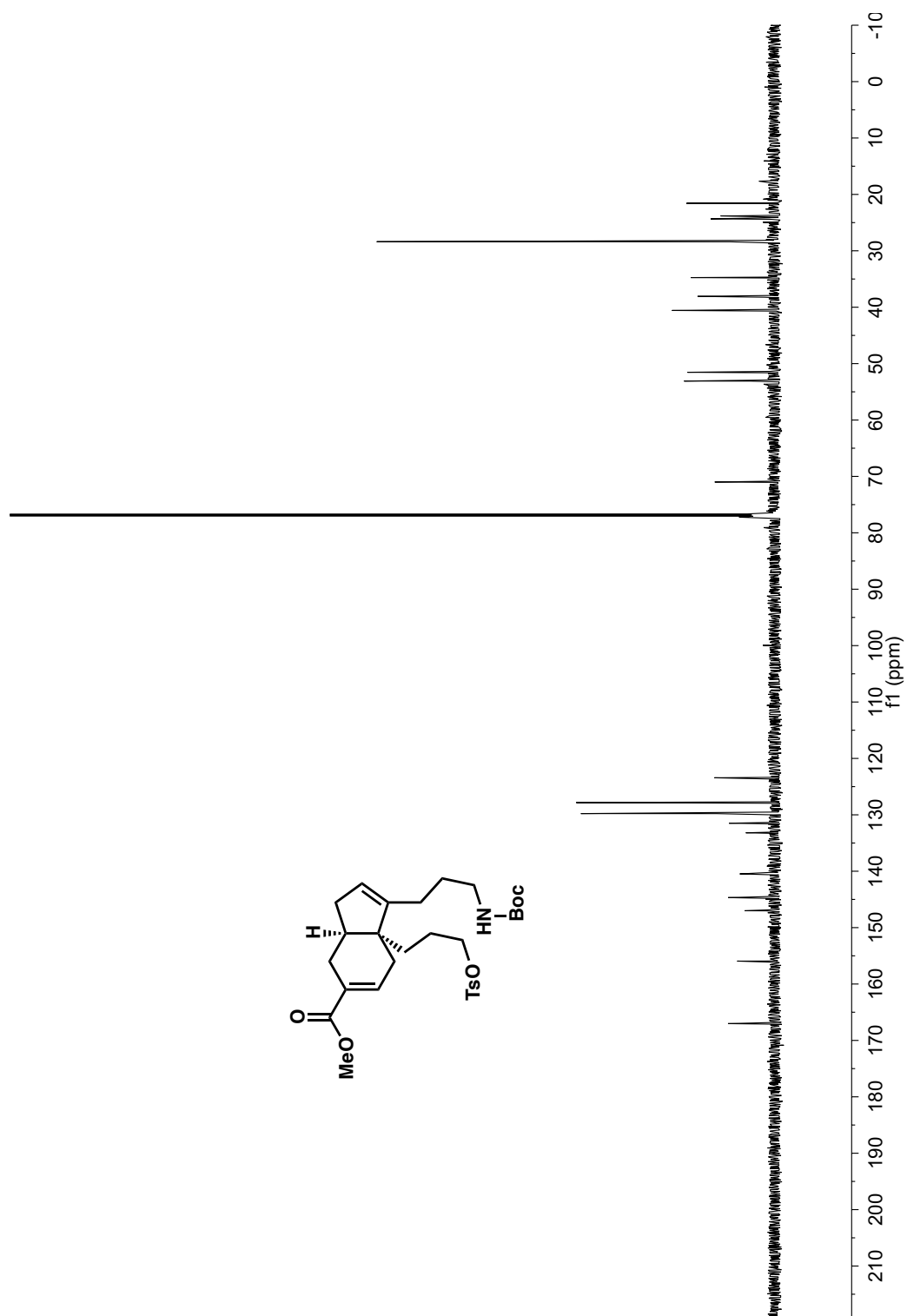


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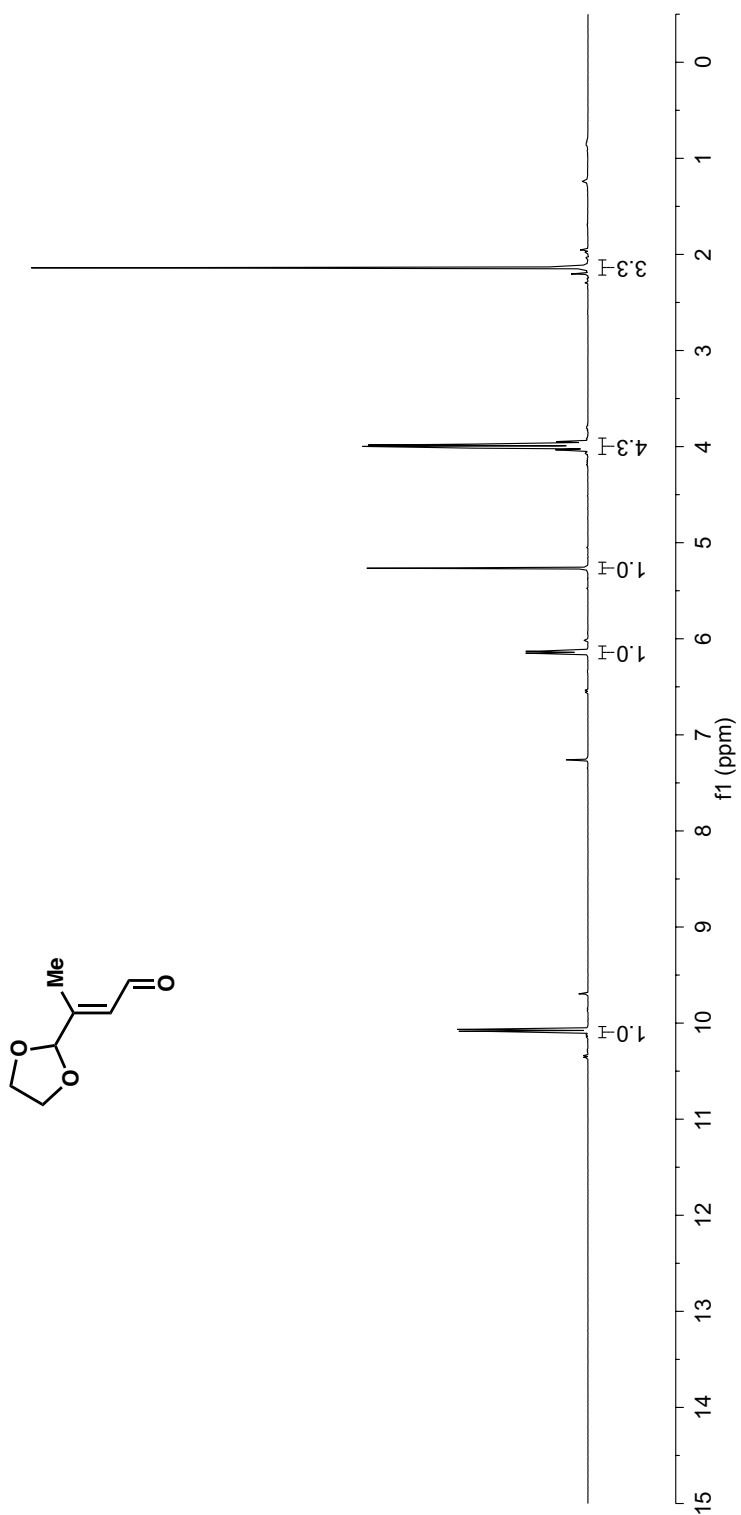


Figure A2.25 ^1H NMR of **2.69**

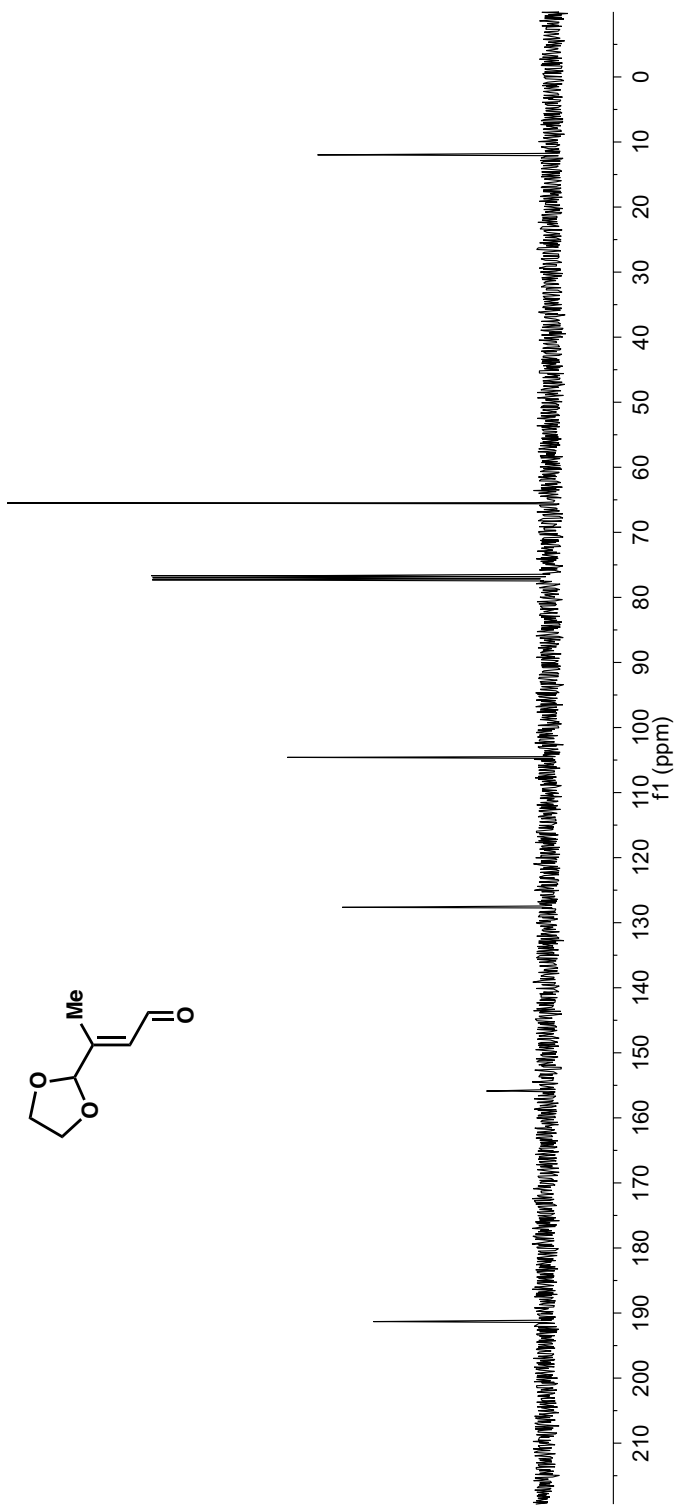


Figure A2.26 ^{13}C NMR of 2.69

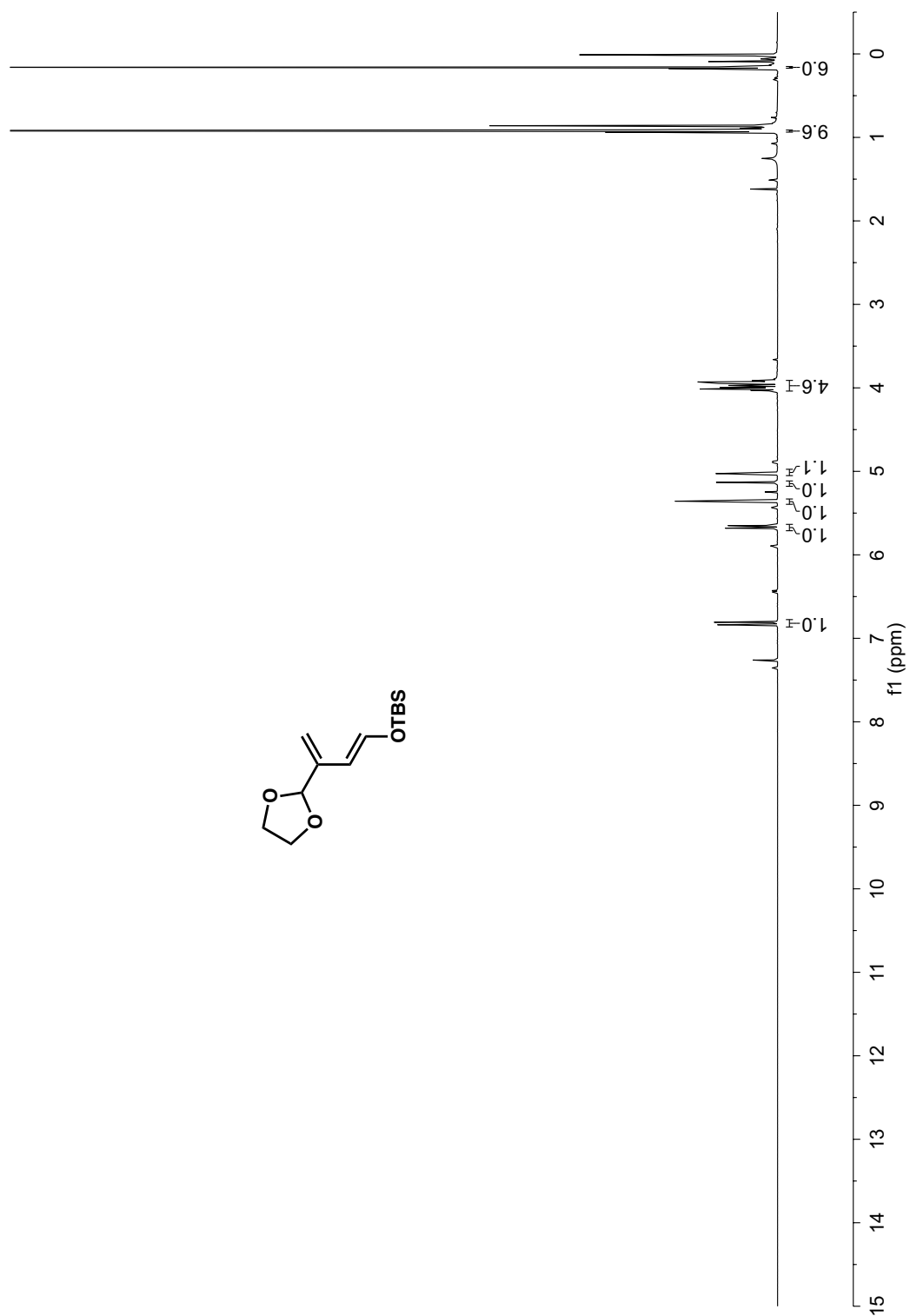


Figure A2.27 ¹H NMR of 2.70

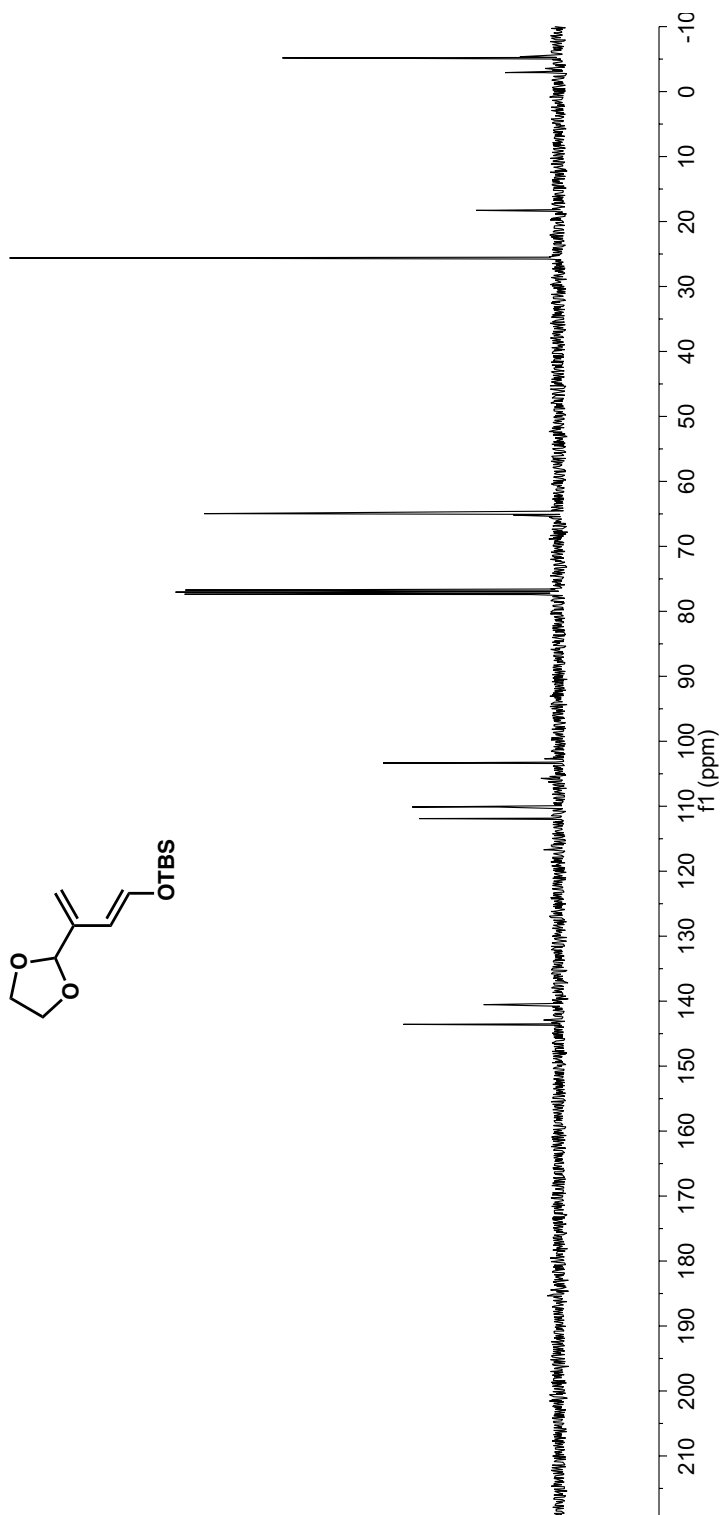


Figure A2.28 ^{13}C NMR of 2.70

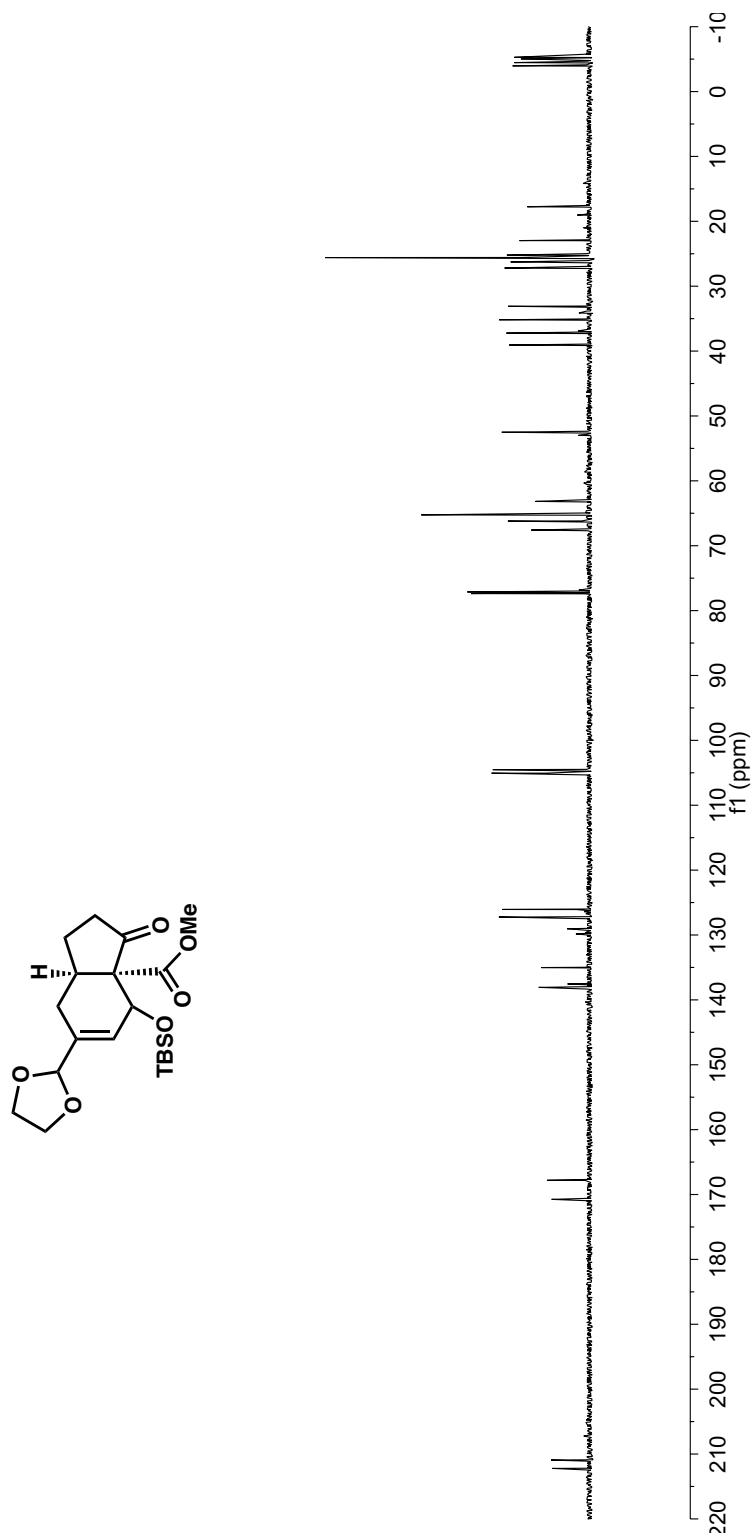


Figure A2.30 ^{13}C NMR of 2.71

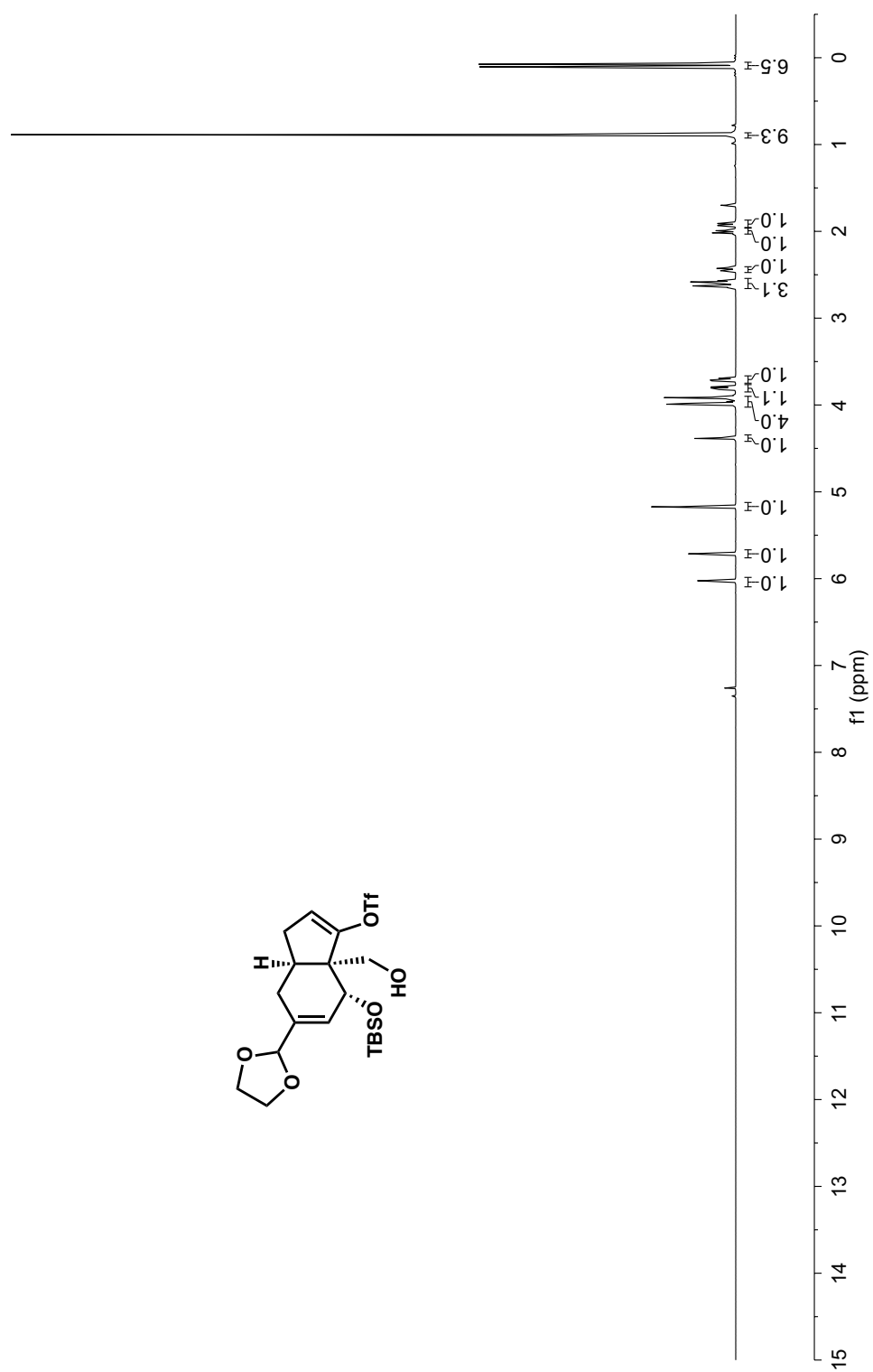


Figure A2.31 ^1H NMR of 2.74

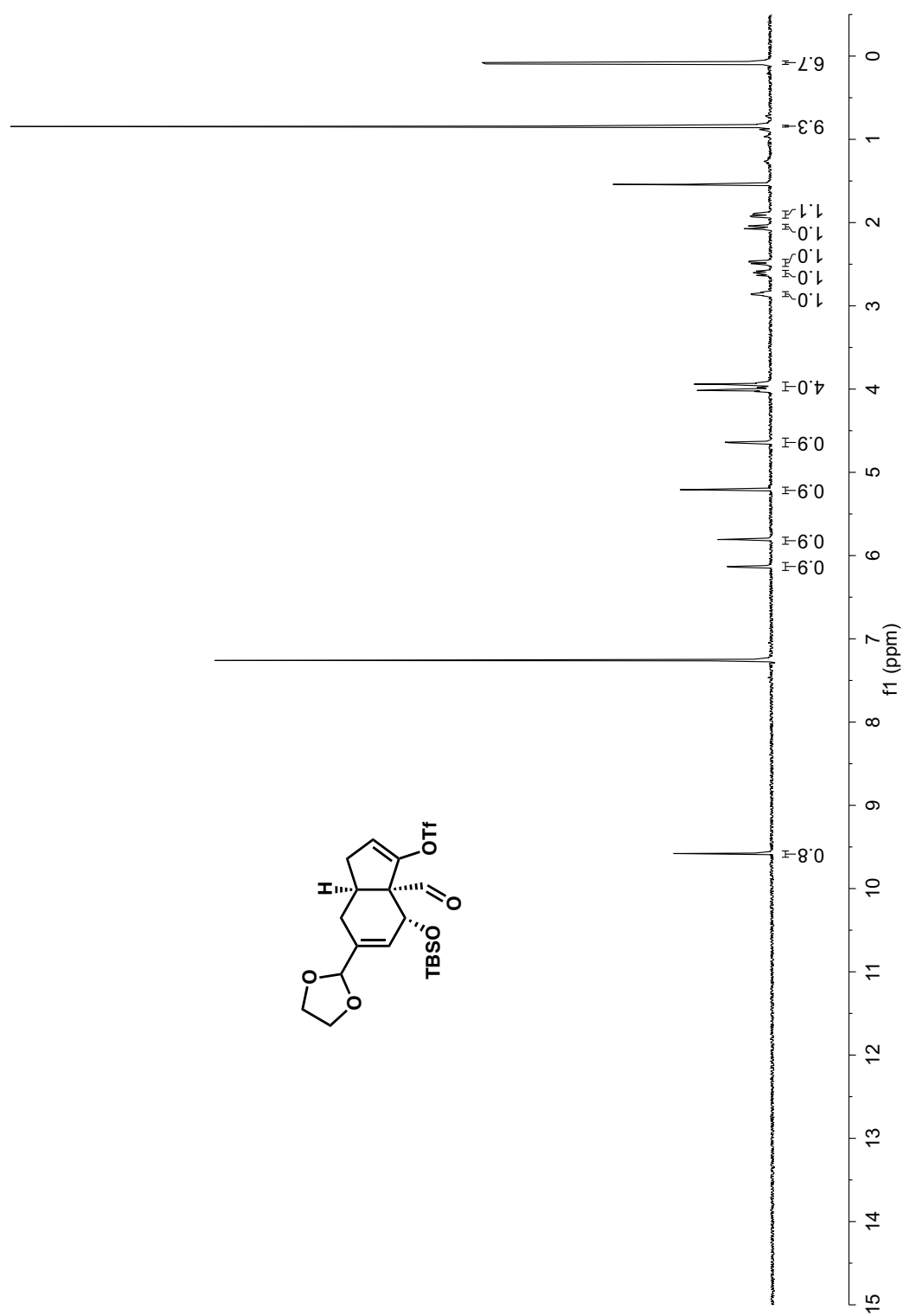


Figure A2.33 ^1H NMR of **2.75**

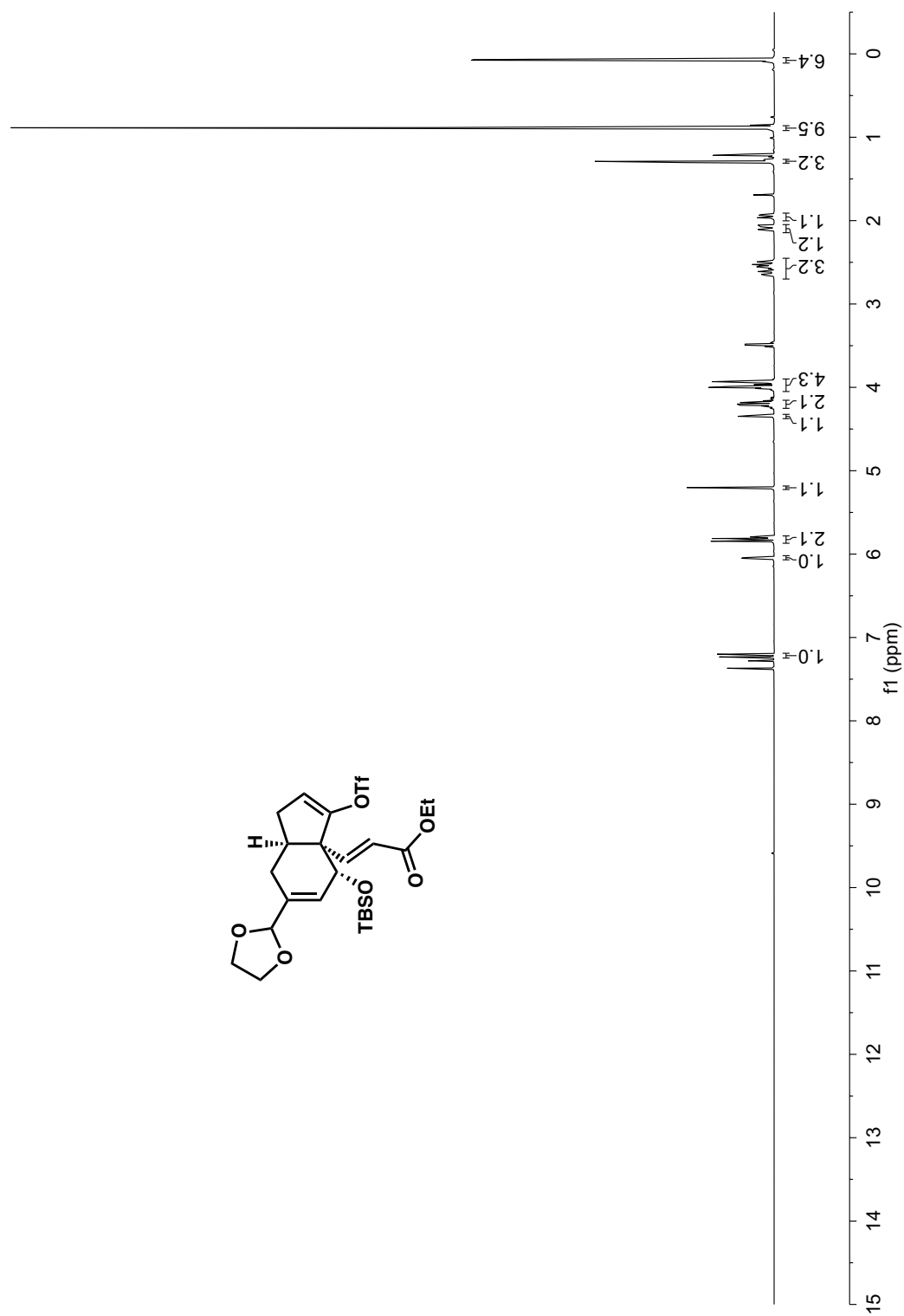


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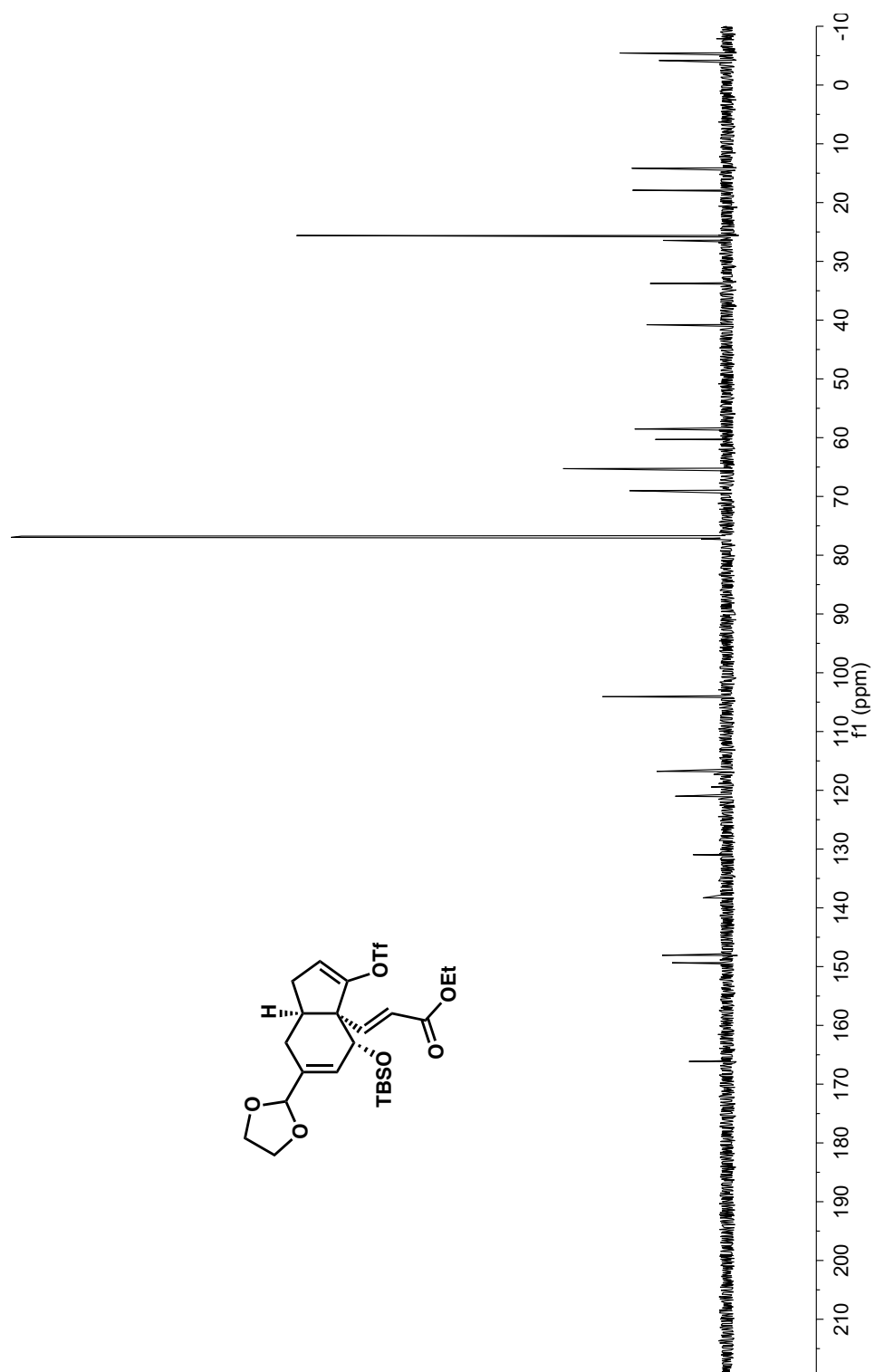


Figure A2.35 ^{13}C NMR of 2.76



Figure A2.36 ^1H NMR of **2.72**

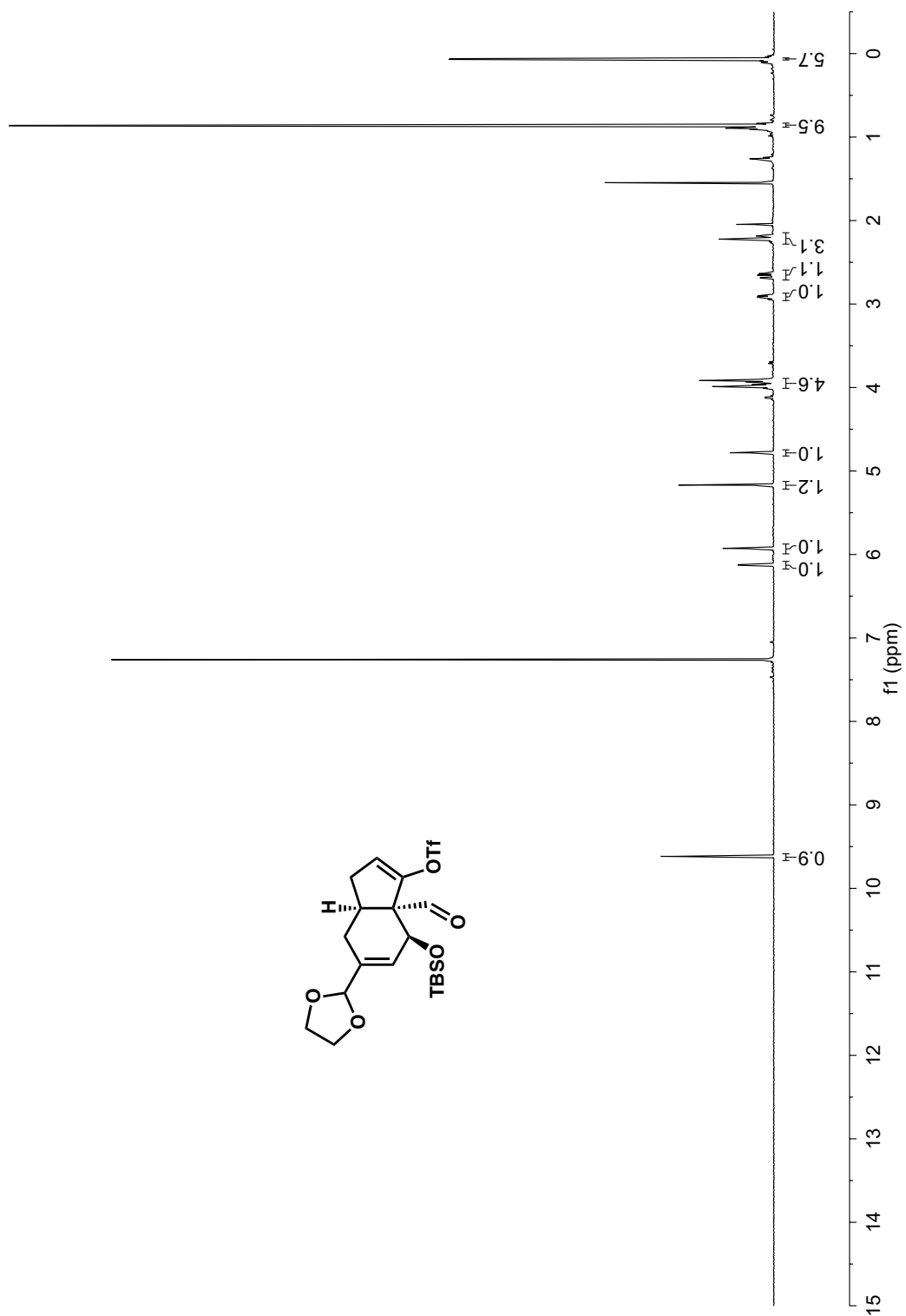


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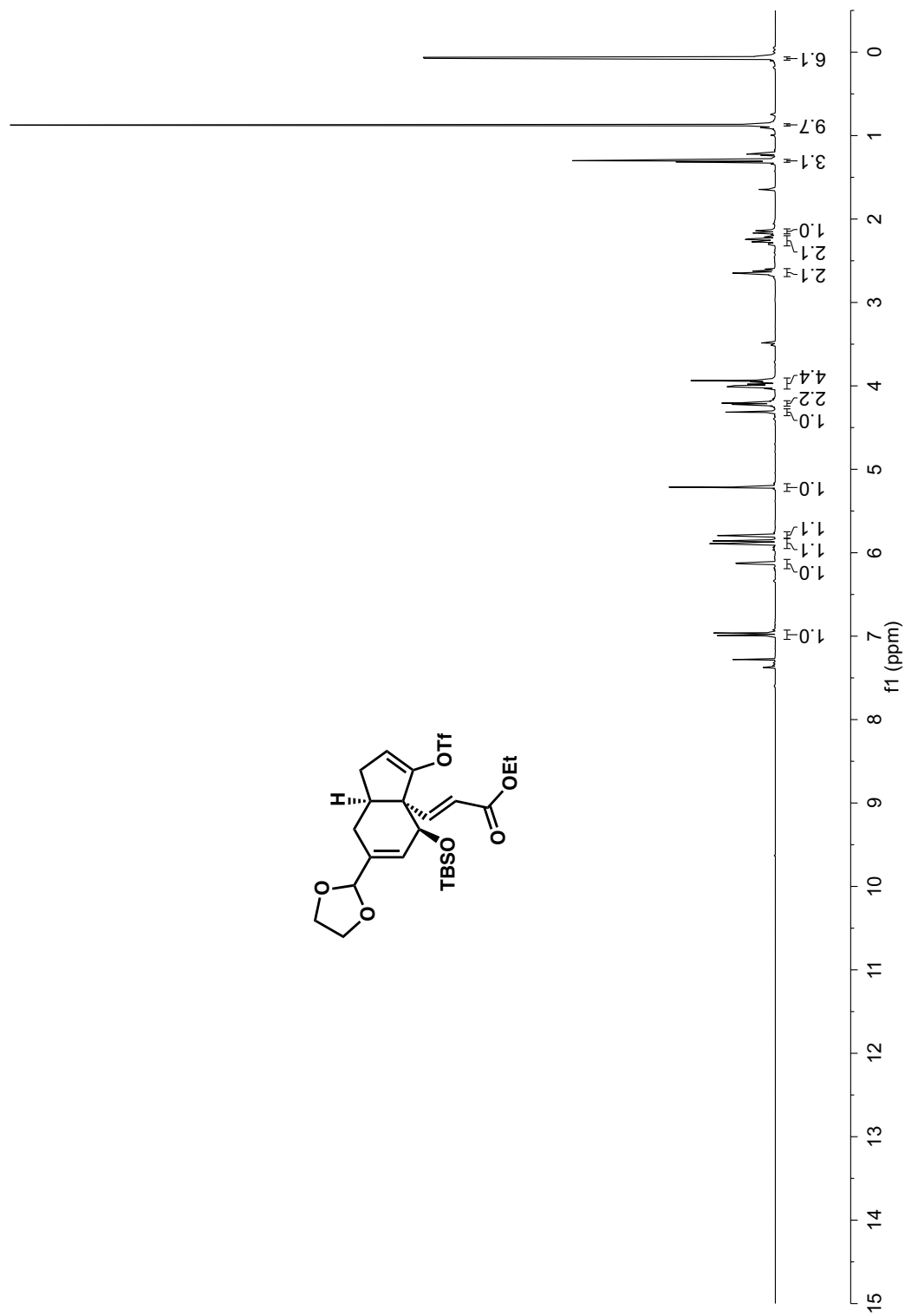


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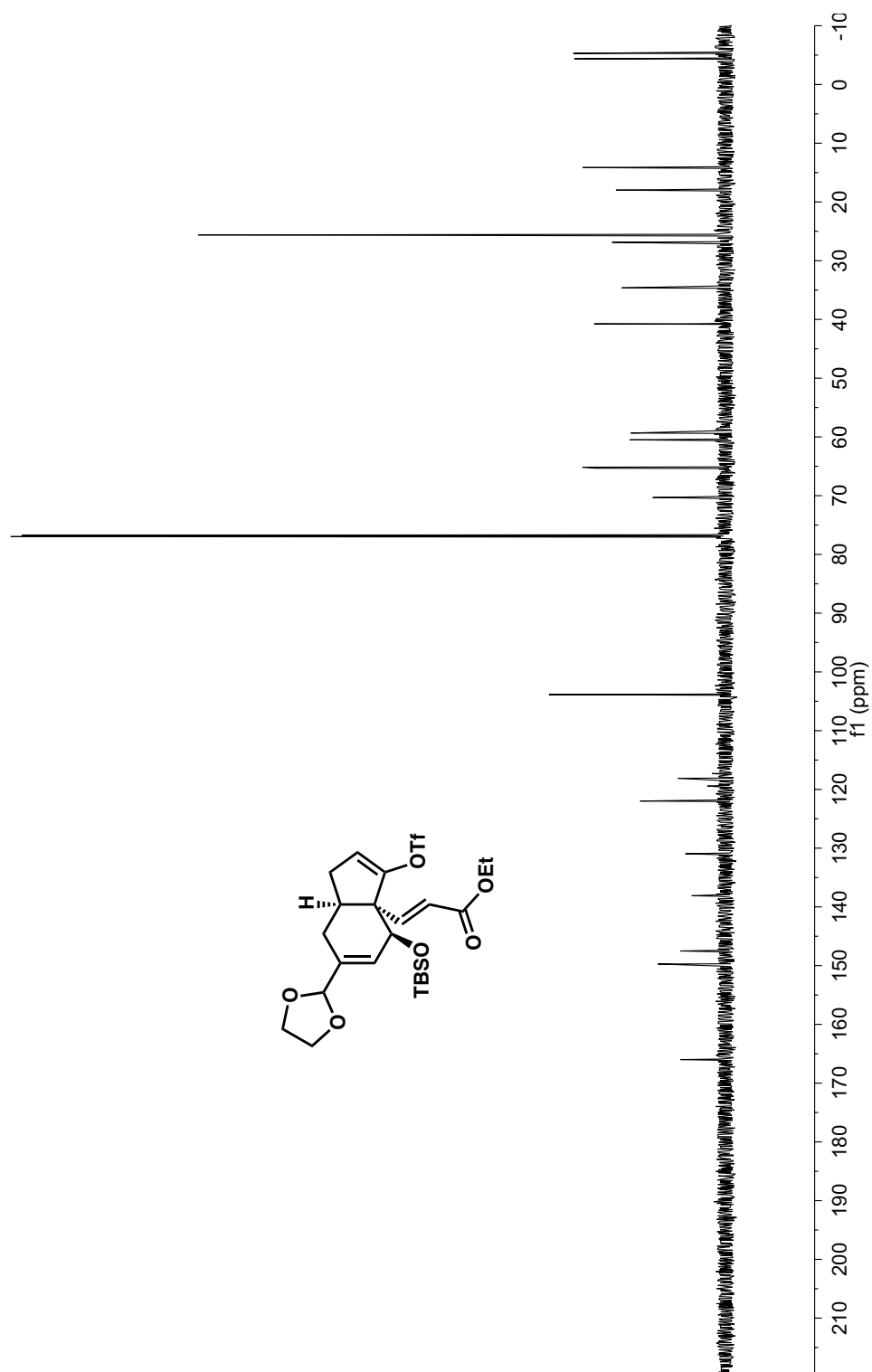
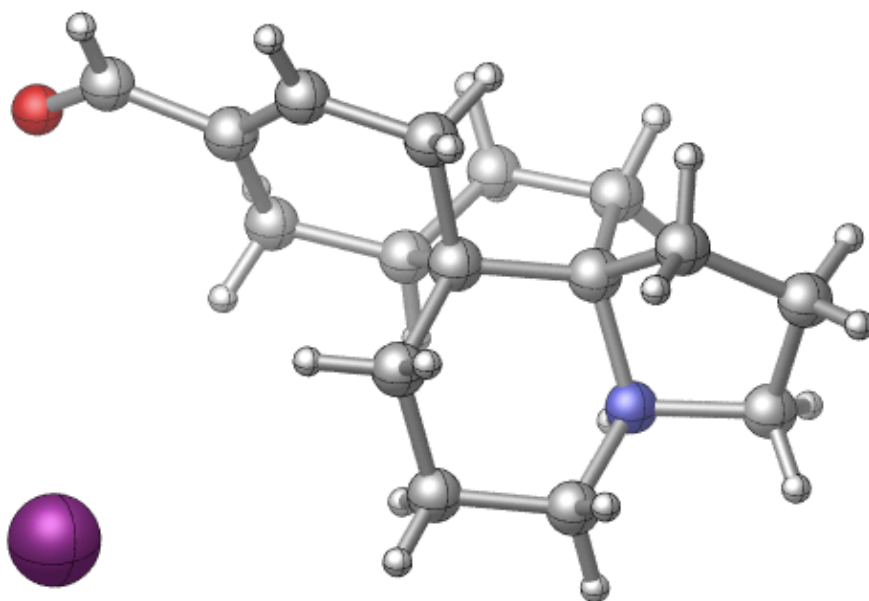


Figure A2.39 ^{13}C NMR of 2.80

X-ray Crystallography Data for tetracycline 3.59



Crystal data and Structure Refinement for tetracycle 3.59

A colorless prism 0.030 x 0.020 x 0.020 mm in size was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using phi and omega scans. Crystal-to-detector distance was 40 mm and exposure time was 10 seconds per frame using a scan width of 0.5°. Data collection was 99.9% complete to 25.000° in θ . A total of 12675 reflections were collected covering the indices, $-8 \leq h \leq 8$, $-16 \leq k \leq 16$, $-9 \leq l \leq 9$. 2796 reflections were found to be symmetry independent, with an R_{int} of 0.0229. Indexing and unit cell refinement indicated a primitive, monoclinic lattice. The space group was found to be P 21 (No. 4). The data were integrated using the Bruker SAINT software program and scaled using the SADABS software program. Solution by iterative methods (DIRDIF-2008) produced a complete heavy-atom phasing model consistent with the proposed structure. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2013). All hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2013. Absolute stereochemistry was unambiguously determined to be *R* at N1, C8, and C11, and *S* at C1, respectively.

Table 1. Crystal data and structure refinement for **3.59**.

X-ray ID	sarpong72	
Sample/notebook ID	RMXIV-009	
Empirical formula	C ₁₆ H ₂₄ I N O	
Formula weight	373.26	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 21	
Unit cell dimensions	a = 7.4235(4) Å	$\alpha = 90^\circ$.
	b = 13.9192(8) Å	$\beta = 97.699(2)^\circ$.
	c = 7.6105(5) Å	$\gamma = 90^\circ$.
Volume	779.30(8) Å ³	
Z	2	
Density (calculated)	1.591 Mg/m ³	
Absorption coefficient	2.048 mm ⁻¹	
F(000)	376	
Crystal size	0.030 x 0.020 x 0.020 mm ³	
Crystal color/habit	colorless prism	
Theta range for data collection	2.701 to 25.371°.	
Index ranges	-8 ≤ h ≤ 8, -16 ≤ k ≤ 16, -9 ≤ l ≤ 9	
Reflections collected	12675	
Independent reflections	2796 [R(int) = 0.0229]	
Completeness to theta = 25.000°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.929 and 0.873	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	2796 / 1 / 172	
Goodness-of-fit on F ²	1.119	
Final R indices [I > 2σ(I)]	R1 = 0.0179, wR2 = 0.0443	
R indices (all data)	R1 = 0.0183, wR2 = 0.0445	
Absolute structure parameter	-0.021(10)	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.663 and -0.444 e.Å ⁻³	

Table 2. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for **3.59**. $U(\text{eq})$ is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	$U(\text{eq})$
C(1)	2233(6)	5124(3)	2245(6)	8(1)
C(2)	3818(6)	4644(3)	3405(6)	11(1)
C(3)	3423(6)	4490(3)	5305(6)	14(1)
C(4)	1730(6)	3882(3)	5293(6)	14(1)
C(5)	-1482(6)	3641(3)	3978(7)	15(1)
C(6)	-1684(6)	3303(4)	2043(7)	19(1)
C(7)	-8(6)	3691(3)	1314(6)	14(1)
C(8)	375(6)	4635(3)	2298(5)	10(1)
C(9)	-1024(6)	5435(3)	1696(6)	11(1)
C(10)	12(7)	6392(3)	1808(6)	12(1)
C(11)	1873(5)	6166(6)	2833(5)	9(1)
C(12)	3414(7)	6867(3)	2598(6)	12(1)
C(13)	4315(6)	6657(3)	973(6)	10(1)
C(14)	3954(5)	5877(3)	-38(6)	9(1)
C(15)	2600(6)	5133(3)	294(5)	10(1)
C(16)	5667(6)	7337(3)	488(6)	13(1)
N(1)	118(5)	4334(2)	4199(5)	10(1)
O(1)	6107(4)	8068(2)	1291(4)	18(1)
I(1)	8199(1)	6079(1)	6534(1)	18(1)

Table 3. Bond lengths [Å] and angles [°] for **3.59**.

C(1)-C(2)	1.527(6)	C(8)-N(1)	1.542(5)
C(1)-C(8)	1.544(6)	C(8)-C(9)	1.550(6)
C(1)-C(15)	1.545(6)	C(9)-C(10)	1.536(6)
C(1)-C(11)	1.552(9)	C(9)-H(9A)	0.9900
C(2)-C(3)	1.528(6)	C(9)-H(9B)	0.9900
C(2)-H(2A)	0.9900	C(10)-C(11)	1.525(6)
C(2)-H(2B)	0.9900	C(10)-H(10A)	0.9900
C(3)-C(4)	1.515(6)	C(10)-H(10B)	0.9900
C(3)-H(3A)	0.9900	C(11)-C(12)	1.532(8)
C(3)-H(3B)	0.9900	C(11)-H(11)	1.0000
C(4)-N(1)	1.502(5)	C(12)-C(13)	1.511(6)
C(4)-H(4A)	0.9900	C(12)-H(12A)	0.9900
C(4)-H(4B)	0.9900	C(12)-H(12B)	0.9900
C(5)-N(1)	1.522(6)	C(13)-C(14)	1.337(6)
C(5)-C(6)	1.534(7)	C(13)-C(16)	1.462(6)
C(5)-H(5A)	0.9900	C(14)-C(15)	1.489(6)
C(5)-H(5B)	0.9900	C(14)-H(14)	0.9500
C(6)-C(7)	1.528(6)	C(15)-H(15A)	0.9900
C(6)-H(6A)	0.9900	C(15)-H(15B)	0.9900
C(6)-H(6B)	0.9900	C(16)-O(1)	1.210(5)
C(7)-C(8)	1.519(6)	C(16)-H(16)	0.9500
C(7)-H(7A)	0.9900	N(1)-H(1)	1.0000
C(7)-H(7B)	0.9900		
C(2)-C(1)-C(8)	114.4(3)	C(3)-C(2)-H(2B)	109.2
C(2)-C(1)-C(15)	109.7(3)	H(2A)-C(2)-H(2B)	107.9
C(8)-C(1)-C(15)	107.6(3)	C(4)-C(3)-C(2)	109.7(4)
C(2)-C(1)-C(11)	113.1(4)	C(4)-C(3)-H(3A)	109.7
C(8)-C(1)-C(11)	102.5(3)	C(2)-C(3)-H(3A)	109.7
C(15)-C(1)-C(11)	109.2(3)	C(4)-C(3)-H(3B)	109.7
C(1)-C(2)-C(3)	112.2(3)	C(2)-C(3)-H(3B)	109.7
C(1)-C(2)-H(2A)	109.2	H(3A)-C(3)-H(3B)	108.2
C(3)-C(2)-H(2A)	109.2	N(1)-C(4)-C(3)	111.6(4)
C(1)-C(2)-H(2B)	109.2	N(1)-C(4)-H(4A)	109.3

C(3)-C(4)-H(4A)	109.3	C(9)-C(10)-H(10A)	110.7
N(1)-C(4)-H(4B)	109.3	C(11)-C(10)-H(10B)	110.7
C(3)-C(4)-H(4B)	109.3	C(9)-C(10)-H(10B)	110.7
H(4A)-C(4)-H(4B)	108.0	H(10A)-C(10)-H(10B)	108.8
N(1)-C(5)-C(6)	106.0(4)	C(10)-C(11)-C(12)	116.6(5)
N(1)-C(5)-H(5A)	110.5	C(10)-C(11)-C(1)	103.0(4)
C(6)-C(5)-H(5A)	110.5	C(12)-C(11)-C(1)	113.6(4)
N(1)-C(5)-H(5B)	110.5	C(10)-C(11)-H(11)	107.7
C(6)-C(5)-H(5B)	110.5	C(12)-C(11)-H(11)	107.7
H(5A)-C(5)-H(5B)	108.7	C(1)-C(11)-H(11)	107.7
C(7)-C(6)-C(5)	105.1(4)	C(13)-C(12)-C(11)	113.1(4)
C(7)-C(6)-H(6A)	110.7	C(13)-C(12)-H(12A)	109.0
C(5)-C(6)-H(6A)	110.7	C(11)-C(12)-H(12A)	109.0
C(7)-C(6)-H(6B)	110.7	C(13)-C(12)-H(12B)	109.0
C(5)-C(6)-H(6B)	110.7	C(11)-C(12)-H(12B)	109.0
H(6A)-C(6)-H(6B)	108.8	H(12A)-C(12)-H(12B)	107.8
C(8)-C(7)-C(6)	103.6(4)	C(14)-C(13)-C(16)	118.1(4)
C(8)-C(7)-H(7A)	111.0	C(14)-C(13)-C(12)	123.4(4)
C(6)-C(7)-H(7A)	111.0	C(16)-C(13)-C(12)	118.4(4)
C(8)-C(7)-H(7B)	111.0	C(13)-C(14)-C(15)	123.7(4)
C(6)-C(7)-H(7B)	111.0	C(13)-C(14)-H(14)	118.1
H(7A)-C(7)-H(7B)	109.0	C(15)-C(14)-H(14)	118.1
C(7)-C(8)-N(1)	100.9(3)	C(14)-C(15)-C(1)	112.3(3)
C(7)-C(8)-C(1)	118.5(4)	C(14)-C(15)-H(15A)	109.2
N(1)-C(8)-C(1)	111.6(3)	C(1)-C(15)-H(15A)	109.2
C(7)-C(8)-C(9)	113.7(4)	C(14)-C(15)-H(15B)	109.2
N(1)-C(8)-C(9)	108.0(3)	C(1)-C(15)-H(15B)	109.2
C(1)-C(8)-C(9)	103.9(3)	H(15A)-C(15)-H(15B)	107.9
C(10)-C(9)-C(8)	107.2(3)	O(1)-C(16)-C(13)	124.4(4)
C(10)-C(9)-H(9A)	110.3	O(1)-C(16)-H(16)	117.8
C(8)-C(9)-H(9A)	110.3	C(13)-C(16)-H(16)	117.8
C(10)-C(9)-H(9B)	110.3	C(4)-N(1)-C(5)	110.3(3)
C(8)-C(9)-H(9B)	110.3	C(4)-N(1)-C(8)	116.4(3)
H(9A)-C(9)-H(9B)	108.5	C(5)-N(1)-C(8)	105.1(3)
C(11)-C(10)-C(9)	105.2(4)	C(4)-N(1)-H(1)	108.2
C(11)-C(10)-H(10A)	110.7	C(5)-N(1)-H(1)	108.2

C(8)-N(1)-H(1)	108.2
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Table 4. Anisotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for **3.59**. The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2}U^{11} + \dots + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	4(2)	9(2)	10(2)	0(2)	-2(2)	1(2)
C(2)	5(2)	13(2)	16(2)	3(2)	0(2)	1(2)
C(3)	8(2)	18(2)	14(2)	7(2)	-6(2)	1(2)
C(4)	11(2)	13(2)	15(3)	7(2)	-4(2)	1(2)
C(5)	8(2)	13(2)	23(3)	5(2)	-4(2)	-4(2)
C(6)	12(2)	17(2)	27(3)	-1(2)	-1(2)	-8(2)
C(7)	12(2)	15(2)	16(2)	-3(2)	0(2)	-3(2)
C(8)	8(2)	12(2)	7(2)	1(2)	0(2)	0(2)
C(9)	9(2)	15(2)	10(2)	2(2)	1(2)	2(2)
C(10)	13(2)	11(2)	12(2)	0(2)	4(2)	3(2)
C(11)	12(2)	7(3)	7(2)	-3(2)	1(1)	4(2)
C(12)	15(2)	12(2)	10(2)	-2(2)	3(2)	-4(2)
C(13)	5(2)	12(2)	12(2)	4(2)	-1(2)	1(2)
C(14)	6(2)	10(4)	10(2)	1(2)	0(2)	6(2)
C(15)	13(2)	9(2)	10(2)	-3(2)	1(2)	2(2)
C(16)	9(2)	17(2)	11(2)	5(2)	0(2)	2(2)
N(1)	6(2)	10(2)	13(2)	3(1)	-1(1)	-2(1)
O(1)	20(2)	15(2)	19(2)	0(1)	2(1)	-7(1)
I(1)	22(1)	18(1)	14(1)	-4(1)	5(1)	0(1)

Table 5. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($\text{\AA}^2 \times 10^{-3}$) for **3.59**.

	x	y	z	U(eq)
H(2A)	4917	5048	3423	13
H(2B)	4072	4015	2882	13
H(3A)	4468	4166	6006	17
H(3B)	3244	5119	5865	17
H(4A)	1948	3238	4808	16
H(4B)	1465	3797	6525	16
H(5A)	-2603	3968	4230	18
H(5B)	-1242	3089	4795	18
H(6A)	-1723	2593	1977	23
H(6B)	-2811	3563	1367	23
H(7A)	1031	3244	1565	17
H(7B)	-262	3798	19	17
H(9A)	-1599	5316	465	14
H(9B)	-1988	5449	2478	14
H(10A)	135	6636	608	14
H(10B)	-628	6881	2441	14
H(11)	1738	6149	4123	11
H(12A)	2921	7529	2511	14
H(12B)	4340	6836	3661	14
H(14)	4599	5793	-1024	11
H(15A)	3051	4494	-12	13
H(15B)	1445	5256	-486	13
H(16)	6239	7194	-526	15
H(1)	-240	4916	4840	12