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Oxabicyclo[3.2.1]octadienes as Building Blocks in the Synthesis of Natural Products

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Oxabicyclo[3.2.1]octadienes as Building Blocks in the Synthesis of Natural Products

Michael D. VanHeyst, Ph.D.

University of Connecticut, 2015

Abstract:

Since the initial report by Diels and Alder in 1928, the [4+2] cycloaddition remains one of the most powerful and most frequently employed methods for the construction of six membered ring systems, generating a high degree of structural complexity in a single synthetic transformation. This cycloaddition process not only generates two new σ -bonds, but also establishes up to four new contiguous stereocenters in the process, owing to the high regio- and stereoselectivities displayed by this pericyclic reaction. In the decades following its discovery, Tobey and Law would report on the intriguing reaction of furan, substituted furans, and cyclopentadiene with both tetrachloro- and tetrabromocyclopropene. The two unsaturated systems reacted smoothly to directly produce cycloheptanoid systems, the products of a formal [4+3] cycloaddition reaction. The authors proposed in their early manuscripts that the tetrahalocyclopropenes underwent an initial thermal Diels-Alder cycloaddition to produce the cyclopropyl norbornene derivatives. However, these workers were unable to isolate or characterize the primary cycloadducts and instead observed a product which had spontaneously rearranged by way of a halogen atom migration to yield the bicyclo[3.2.1]octadiene nucleus.

The majority of my research has been directed toward the application of this Diels-Alder reaction in the direct cycloaddition of furans and perhalocyclopropenes, for the synthesis of polycyclic natural products and their analogs. Of particular importance to our work was the early

finding that the oxabicyclo[3.2.1]octane adducts could be readily converted into a versatile dibromoenone building block through a high yielding, silver-mediated hydrolysis.

These building blocks serve as rigidified cycloheptenones with functional handles at each of the seven unique carbons of the ring that allows for excellent regio- and stereochemical control during subsequent synthetic elaboration of the core. The ability to effect cleavage, annulation, nucleophilic addition and rearrangement of has allowed the development of synthetic routes to a variety of natural products. Thusly, we have worked to make this reaction a central feature in the synthesis of a variety of natural product targets. Herein, we detail the asymmetric syntheses of terpenoid natural product frondosin A and the synthesis of novel platensimycin analogous compounds, where this formal cycloaddition process was employed to prepare an integral cycloheptane ring system embedded in the polycyclic frameworks.

**Oxabicyclo[3.2.1]octadienes as Building Blocks in the Synthesis of
Natural Products**

Michael D. VanHeyst

B.S., Allegheny College, 2009

A Dissertation

Submitted in Partial Fulfillment of the
Requirements for the Degree of Doctor of Philosophy
at the

University of Connecticut 2015

Doctor of Philosophy

**Oxabicyclo[3.2.1]octenes as Building Blocks in the Synthesis of
Natural Products**

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University of Connecticut
2015

To My Family

Acknowledgements:

The first person I would like to thank is my graduate advisor, Professor Dennis L. Wright for his continued support and desire that he has put into shaping me into the synthetic organic chemist that I am today. His enthusiasm and excitement in which he approaches each day has been an inspiration to me, and probably why I can spend hours in his office talking chemistry. Along with Dennis, my committee members, Professor Amy Anderson and Professor Mark Peczu, have been a wealth of support and knowledge over the past years and I can't thank them enough.

The next person that I would like to thank is the man whose passion and love for organic chemistry and guidance throughout my undergraduate studies fueled my own enthusiasm for chemistry, my undergraduate advisor, Professor Michael McGrath. Without his guidance and support I would never have made it to this point in my life and I am forever grateful.

Over the past half decade of my graduate career I have had the privilege of working with some very talented chemists and great friends, and I would like to thank them individually. In my early years at UCONN I had the privilege of working with one of the most brilliant organic chemists that I have ever met, Dr. E. Zachary Oblak. Zack was the man who picked me up at the airport on my first visit to UCONN, he was my mentor and trainer during my first two years, a groomsman at my wedding and has become like a brother to me. His unbridled enthusiasm for chemistry was present each and every day, and his dedication and hard work has inspired my own career. Narendran Gummudipundi Dayanan and Eric Scocchera were also at UCONN when I arrived, and they accepted me with open arms and we have grown to become great friends. Along with Dr. Santosh Keshipeddy, these guys have always taken the time to listen to some of my crazy ideas and have at most times in-turn inspired new ideas within me. They have provided a great lab space to work in; full of support and fun; and it doesn't get any better than going to work every day with your friends. I have had the good fortune of working with Eric Falcone and

Mohamed Ammar on the tropolone project, and I cannot express how much I appreciate all of the hard work and dedication that they put forth on making the project a success. For the newcomers in the lab, Haidong Feng (a.k.a. Aaron, Tito, Simba, Jackie Chan) and Alexavier Estrada, I wish you guys the best of luck and continued success.

Outside of the Wright lab, I would like to thank Dr. Amy Bataille for her friendship and guidance. I will miss certainly miss the coffee and lunch breaks that offered a welcome interruption to the day.

Last but not least, I would like to thank my family: my father Peter, my mother Kathy, my brothers Peter and Adam, my wonderful wife Stephanie and our dog Odie. My mother has been guiding light in my life with her relentless desire to shape me to become the very best that I can be. I can't thank her enough for the multiple times that she made me redo my homework or the nights she stayed up with me finishing school projects. It is not easy to be married to a graduate student, and my wife Stephanie has embraced my passion for organic chemistry, putting up with the long hours and me doodling chemistry schemes on napkins at the dinner table. Without her continued support I would not have been able to accomplish the achievements that I have. Mostly, this thesis is dedicated to *My Family*; my parents, brothers, wife, past grandparents, aunts, uncles, nephews, nieces, and my friends. All of you have somehow had an impact on my life and without you this thesis would not have been possible.

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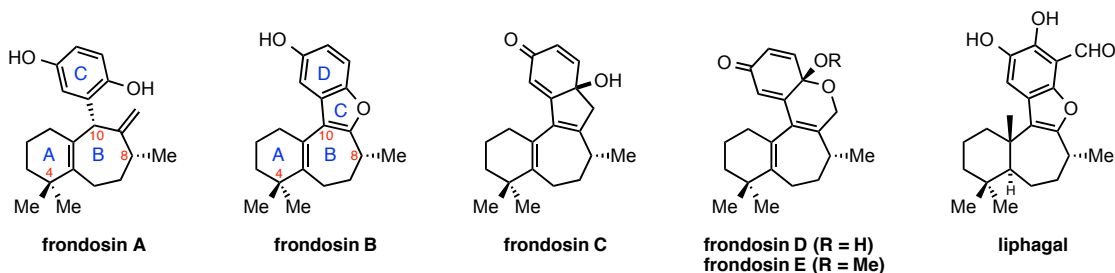
CHAPTER ONE

INTRODUCTION

The Frondosins: An Unusual Synthetic and Stereochemical Journey

The frondosin family¹ of marine-derived meroterpenoid natural products were first isolated from the marine sponge *Dysidea frondosa* in 1997 and were shown to exhibit significant inhibitory activity for the binding of the cytokine interleukin-8 (IL-8) to its receptor, CX-CLR1/2 (Figure 1.1). The frondosins represent an intriguing array of compounds possessing a bicyclo[5.4.0] undecene core with significant structural diversity introduced through an annulated (frondosins B–E) or tethered (frondosin A) hydroquinone derivative. The structure of frondosin B is also reminiscent of the marine natural product lipahal² as both incorporate an appended arene system in the form of a fused benzofuran motif.

Figure 1.1: Meroterpenoid natural products

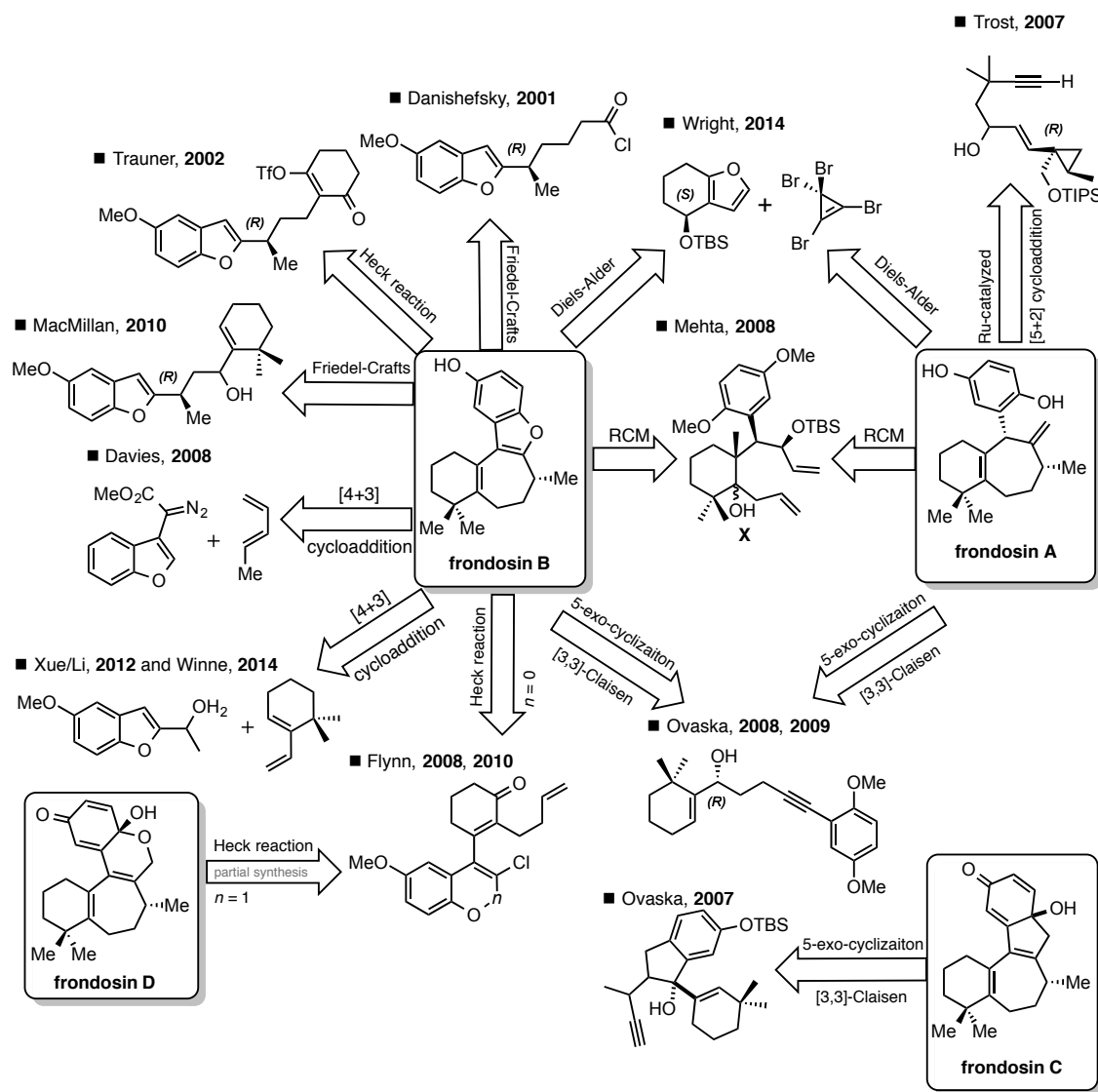


Several studies have associated IL-8 with various acute and chronic inflammatory conditions including sepsis syndrome, psoriasis, rheumatoid arthritis, gout, and asthma. Furthermore, various animal models of inflammation have established IL-8 as a principal leukocyte chemotactic factor directing neutrophil recruitment to and activation at the inflammatory focus.³ As such, the frondosins have gained interest as potential IL-8 receptor antagonists, a promising natural product target for the development of novel pharmacological agents against autoimmune hyperactivity. Moreover, neutrophil activation is known to be critical to malignant tumor progression and/or

metastasis in several human cancers, establishing the frondosin isolates as promising leads for oncology studies.⁴ Furthermore, preliminary anti-HIV assays have revealed that frondosins A and D exhibit HIV-inhibitory activity at the low micromolar level.⁵

With a host of biological implications surrounding IL-8, frondosin B became a popular target for total synthesis, which ultimately led to assignment of the absolute stereochemistry. The first two syntheses of (+)-frondosin B by Danishefsky⁶ in 2001 and (–)-frondosin B by Trauner⁷ in 2002 made a similar benzofuran (C10) disconnection yet produced conflicting assignments for

Figure 1.2: Syntheses of the frondosin natural products: Key cycloheptane disconnection



the single stereogenic center at C8 (Figure 1.2). These conflicting assignments of the C8 center prompted multiple subsequent asymmetric syntheses of frondosin B⁸⁻¹¹ and frondosin A that will be discussed herein. In addition there are also several racemic and formal syntheses of the frondosins over the years by Davies,¹² Ovaska,¹³ Flynn,¹⁴ Mehta,¹⁵ Xue/Li,¹⁶ and Winne.¹⁷

Succeeding asymmetric synthesis of (+)-frondosin A by the Trost group⁸ in 2007 and synthesis of (–)-frondosin B by the Ovaska⁹ group in 2009 gave evidence that C8 of (+)-frondosin A and B existed as the R-enantiomer. The Ovaska group was also able to convert one of their intermediates to (±)-frondosin A.¹⁸ It was not until 2010 that the MacMillan group¹⁰ sought to explain the discrepancy in the assignments, and proposed a scenario by which an unusual stereochemical relay mechanism during Trauner's key palladium-catalyzed cyclization caused a stereochemical inversion of the C8-center. Interestingly, during the Wright group's synthesis of (+) and (–)-frondosin B in 2014,¹¹ the same stereochemical inversion as noted as in the Trauner system was seen in their synthesis. The Wright group carried material, with a deuterium labeled C8 center, through to a late stage intermediate from the Trauner synthesis without inversion. This result had therefore narrowed down the transformation where the inversion was thought to take place. The Wright group proposed a mechanism surrounding a ringcontraction/expansion of a delocalized carbocation intermediate that ultimately led to inversion of the C8 center.

Danishefsky's and Trauner's syntheses: Synthetic debate surrounding the absolute stereochemistry of (+)-frondosin B

In 2001, the Danishefsky group reported the first total asymmetric synthesis of (+)-frondosin B in 17 total steps in approximately 1% overall yield.⁶ The synthesis introduces chirality by way of a Sharpless epoxidation of known materials. Friedel-Crafts cyclization with stannic chloride formed the central cycloheptenone B-ring followed by a Diels-Alder [4+2] cyclization to complete the tetracyclic core of frondosin B. Danishefsky's synthesis was the first asymmetric synthesis and established that (+)-frondosin B contains a *R*-stereocenter at C8 by matching the reported optical rotation.

In 2002, Trauner published a synthesis of (–)-frondosin B, making the same disconnection at the C10 center of the benzofuran, however, applying an intramolecular Heck reaction to close the central cycloheptenone ring.⁷ Their group introduced absolute chemistry in the same manner as Danishefsky, a Sharpless epoxidation followed by nucleophilic opening with AlMe₃

The group completed their synthesis with a 2 step transformation of an A-ring carbonyl to the required geminal dimethyl moiety of the natural product. Following aryl deprotection, in the same mode as Danishefsky, the group observed an optical rotation of similar magnitude but of opposite sign as to what was anticipated. Therefore, these investigations led to the conclusion that (+)-frondosin B existed as the *S*-enantiomer and proposed a plausible mechanistic rationale for a stereochemical inversion of an early intermediate of the Danishefsky synthesis.

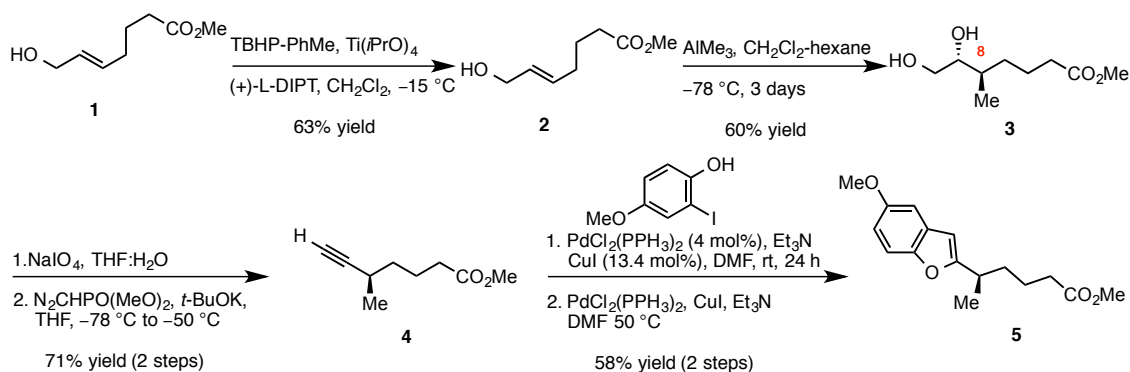
Danishefsky's synthesis: Evidence that (+)-frondosin B occurs as the *R*-enantiomer

The Danishefsky synthesis commenced with a stereoselective epoxidation of the known methyl heptanoate **1** under Sharpless conditions¹⁹ utilizing catalytic (+)-diisopropyl-L-tartrate to give (–)-methyl 5-(*S*), 6-(*S*)-epoxy-7-hydroxyheptanoate (84% ee) (Scheme 1.1). Ring opening of the resulting epoxy alcohol **2** with an application of excess AlMe₃ at low temperatures provided

(+)-methyl 6-(R), 7-dihydroxy-5-(R)-methyl heptanoate **3** (>95% ee). Cleavage of the resulting diol with periodate yielded an aldehyde that when subject to Gilbert's reagent²⁰ produced the terminal alkyne **4** required for a subsequent palladium coupling reaction.

Initial synthetic efforts were directed at a palladium-catalyzed heteroannulation of the terminal acetylenic region of **4**. However, with a multitude of attempts at this two-processes/one-pot transformation they were frustrated by poor conversion to the benzofuran product with the reaction halting at the Sonogashira product. Therefore, the group focused on optimizing the Sonogashira coupling and the cyclization separately and were able to produce benzofuran **5** in good yield over the two steps.²¹

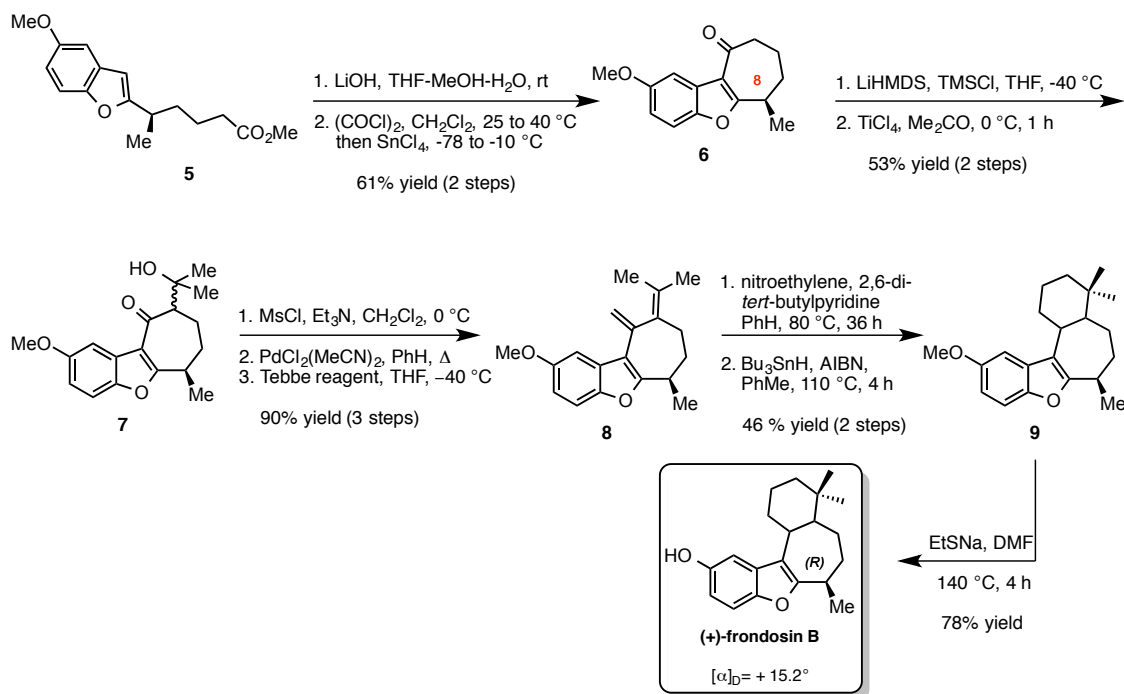
Scheme 1.1: Danishefsky group's synthesis of (+)-frondosin B: Incorporation of chirality



Saponification of ester **5** and subsequent conversion to the corresponding acyl chloride, the group was able to close the key cycloheptenone **6** with an intramolecular Friedel-Crafts acylation, promoted by tin(IV) chloride. En-route to a diene suitable for Diels-Alder cyclization, the Danishefsky group attempted to employ an aldol condensation to condense ketone **6** with acetone. Unfortunately, condensation with lithium enolates produced products with epimerization of the C8 center. To circumvent this problem, the group utilized Mukaiyama aldol reaction conditions to generate tertiary alcohol **7** without epimerization. Unfortunately, dehydration of **7** resulted in another setback. Conversion of **7** to mesylate ether, followed by elimination, provided a ~1:1 mixture of olefinic isomers. Initial attempts to form the thermodynamically stable tetrasubstituted

olefin with sodium methoxide resulted in racemization of the C8 center. However, the group saw that refluxing the olefinic mixture with $\text{PdCl}_2(\text{MeCN})_2$ in benzene effected isomerization without racemization of the C8 center.²² Generation of the desired diene partner **8** for the Diels-Alder cyclization, was brought about through methylenation of the B-ring ketone with Tebbe's reagent (Scheme 1.2).

Scheme 1.2: Danishefsky group's synthesis of (+)-frondosin B: Establishes (+)-frondosin B as the R-enantiomer



Initial Diels-Alder attempts were frustrated by low yields during reaction with maleic anhydride, while Lewis acid-promoted Diels-Alder reactions were problematic owing to olefin isomerization. Fortuitously, nitroethylene²³ could be used as a reactive ethylene equivalent under acid-free conditions as the nitro group could be easily removed through a subsequent free radical protocol to produce **9**.²⁴

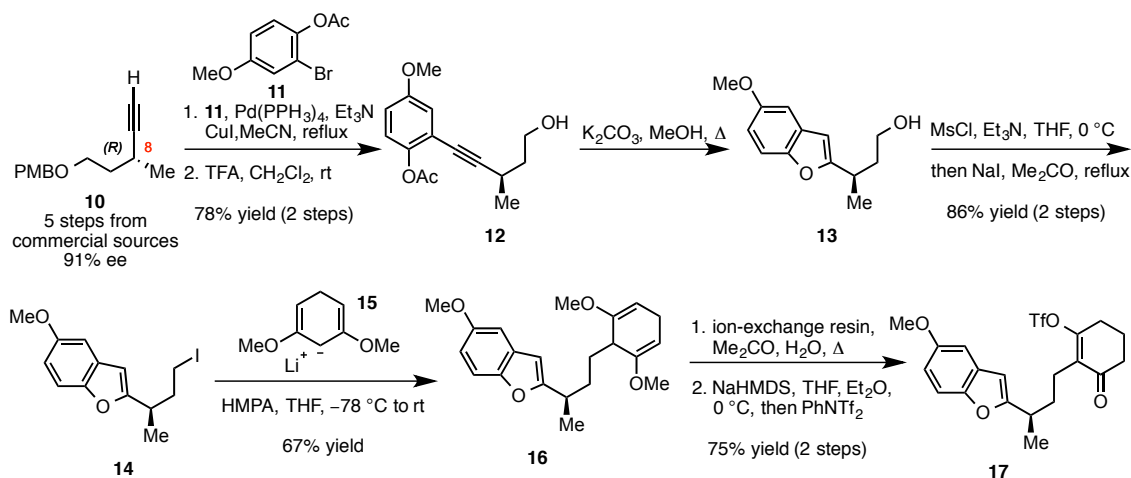
The group observed that deprotection of the aryl methyl ether with BBr_3 gave frondosin products isolated with a mixture of olefinic isomers. To circumvent this problem, they resorted to an alternative deprotection methodology applying sodium ethanethiolate²⁵ to produce (+)-

frondosin B in high yield and without olefin isomerization ($[\alpha]_D = +15.2^\circ$). The isolation literature reports that pure (+)-frondosin B has an optical rotation of $[\alpha]_D = +18.5^\circ$,^{1a} and thus the group concluded that (+)-frondosin B exists naturally as the *R*-enantiomer.

Trauner's synthesis of (–)-frondosin B: Evidence that (+)-frondosin B occurs as the *S*-enantiomer

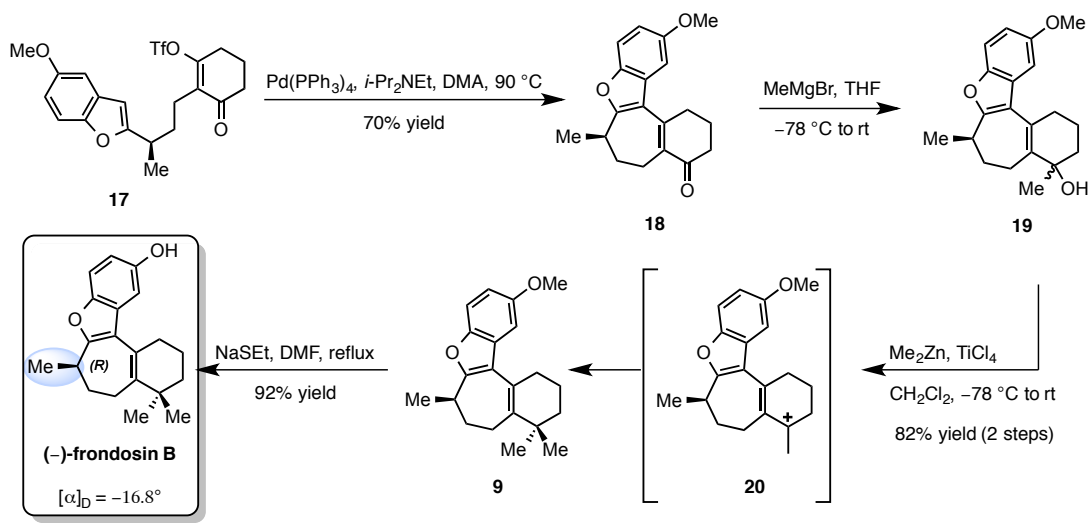
The Trauner synthesis commenced with *R*-configured alkyne **10**, produced based on Danishefsky's protocol for the production of alkyne **4** (Sharpless epoxidation conditions, 91% ee). The group elected to use aryl bromide **11** as the partner to **10** in a Sonogashira coupling to produce the desired arene, which following acidic deprotection of the primary *p*-methoxybenzyl group produced alcohol **12**. Treatment of **12** with K_2CO_3 in methanol effected saponification of the phenolic acetate and concomitant cyclization to afford benzofuran **13** directly (Scheme 1.3).²⁶

Scheme 1.3: The Trauner group's total synthesis of (–)-frondosin B: Initiation of synthesis



Conversion of alcohol **13** to its corresponding iodide species **14** allowed for alkylation to dimethoxylithiocyclohexadiene **15**. However, subsequent hydrolysis of **16** produced a cyclohexa-1,3-dione product in low yields. Thus, the group concluded that the diketone product, following hydrolysis of the methyl ethers, decomposed on standing. Thus, a very mild hydrolysis employing

Scheme 1.4: The Trauner group's total synthesis of (-)-frondosin B: Evidence that (+)-frondosin B occurs as the S-enantiomer



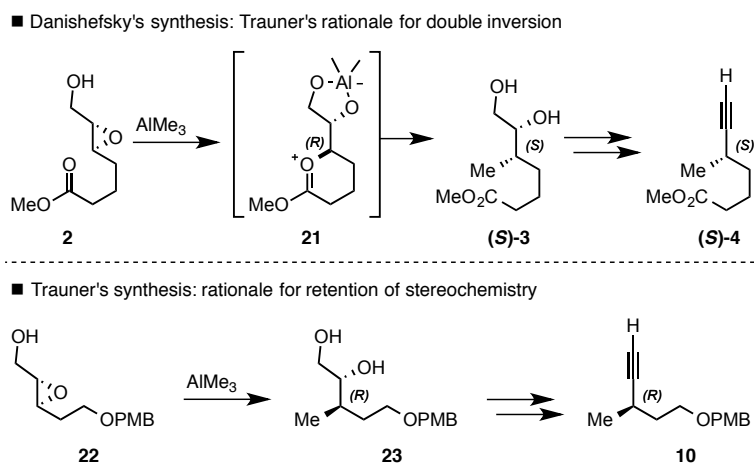
an ion-exchange resin was used to deprotect the methyl ethers and the resulting diketone was immediately converted into enol triflate **17**; setting the stage for the key cyclization step.

Treatment of **17** with a catalytic amount of $\text{Pd}(\text{PPh}_3)_4$ and Hünig's base at 90 °C resulted in the formation of the key cycloheptenone **18**, with no detectable epimerization of the C8 stereocenter. The conversion of the carbonyl group into a geminal dimethyl moiety was achieved using a protocol developed by Reetz et al.²⁷ The Trauner group modified this reaction into a two step sequence whereby ketone **18** was initially reacted with MeMgBr to give the corresponding, highly acid-sensitive tertiary alcohol **19**, which was subsequently subjected to the action of Me_2TiCl_2 . Interestingly, the Trauner group points out that upon addition of the substrate an intense dark violet color was observed, they presumed that this color originates from the stabilized carbocation **20** formed as an intermediate. Interestingly, the Wright group would later suggest that this intermediate carbocation is highly delocalized, leading to an inversion process of this common intermediate. None-the-less, this modified Reetz procedure afforded *O*-methyl frondosin B **9**. Deprotection of the aryl methyl ether, following Danishefsky's previously reported procedure, gave frondosin B in high optical purity. However the observed optical rotation was the antipode of the natural product, $[\alpha]_D = -16.8^\circ$ (Scheme 1.4)

Trauner's proposed inversion of the Danishefsky synthesis

The Trauner group had initiated their syntheses with an *R*-configured C8 center and was accordingly surprised to see that the optical rotation of their synthetic product was opposite that of the natural product. The Danishefsky group had assigned the natural product to the *R*-configuration; yet, according to the work of the Trauner group they proposed that the structure of (+)-frondosin B should be reassigned as the *S*-configuration.

Figure 1.3: Trauner's rationale of a double stereochemical inversion of intermediate 2 in Danishefsky's synthesis



With the discrepancy surrounding the absolute configuration at the C8 stereocenter, the Trauner group proposed that the Danishefsky's material must have undergone an inversion of configuration at an early stage of the synthesis. The group postulated that a likely candidate for such an inversion could have occurred during the nucleophilic opening of an epoxy alcohol **2** with AlMe_3 . The group suggested that there was an unanticipated retention of configuration; whereby, participation of the ester carbonyl group generated an intermediate oxonium ion such as **21** that ultimately produced the *S*-diol (S)-3. This diol would be elaborated to *S*-configured alkyne (S)-4 and ultimately to the *S*-configured natural product (Figure 1.3). rationale

The Trauner group presumed that this double inversion of configuration could not occur in their synthesis. Suggesting, that epoxy alcohol **22** similarly treated with AlMe_3 would not

participate in a transition state such as **21**, possibly because of the disfavored 4-membered ring transition state required given their intermediate. This discrepancy in the absolute configuration of (+)-frondosin B sparked a series of syntheses of the frondosin family of marine terpenes. The following syntheses would provide support for Danishefsky's original assignment, and in 2010 MacMillan would match early synthetic intermediates of both syntheses and suggest that an inversion had occurred in the Trauner synthesis rather than that of Danishefsky's. In 2014, the Wright group would add confirmation to Danishefsky's assignment and pinpoint that the inversion process in Trauner's synthesis was occurring during the installation of the geminal dimethyl group.

Trost's synthesis of (+)-frondosin A, Ovaska's synthesis of (–)-frondosin B, and MacMillan's syntheses of (+)-frondosin B: evidence that (+)-frondosin B occurs as the *R*-enantiomer

Following the dispute over the absolute stereochemistry of the C8 center of (+)-frondosin B there were many ensuing syntheses within the frondosin family. In 2007, the Trost⁸ group published the first asymmetric synthesis of (+)-frondosin A. Absolute stereochemistry was established with a Simmons-Smith cyclopropanation. The group utilized this cyclopropane in a novel Ru-catalyzed [5+2] cycloaddition of enynes to close the A and B-rings in a single step with high diastereoselectivity. However, the group was not able to effect the desired [5+2] of a 1,7-enyne and thus had to employ a ring expansion of the A-ring to correctly establish the bicyclic core of frondosin A. The group finished its total synthesis with a Claisen rearrangement to correctly introduce the aryl C-ring. Starting with materials that would reflect a *R*-enantiomeric C8 center in their synthesis, and since the group's synthetic sample of frondosin A had an optical rotation reflective to that of (+)-frondosin A they were able to assign (+)-frondosin A to exist (*R*)-C10, (*R*)-C8. Although (+)-frondosin A and (+)-frondosin B may not have the same

configuration at the C8 position, their results suggested that Danishefsky's original assignment was correct.

Trost's work was followed by an asymmetric synthesis of (–)-frondosin B by the Ovaska group.⁹ The Ovaska group had been working some time on the synthesis of seven-membered carbocyclic rings via a 5-exo-dig cyclization/Claisen rearrangement process and was able to apply this transformation in the synthesis of frondosin B. The group established absolute stereochemistry by way of a Corey-Bakshi-Shibata (CBS) protocol and utilized this stereocenter to convey a high degree of stereocontrol during their novel cyclization/Claisen process. With their synthesis, further confirmation was added to the original assignment of (+)-frondosin B by the Danishefsky group.

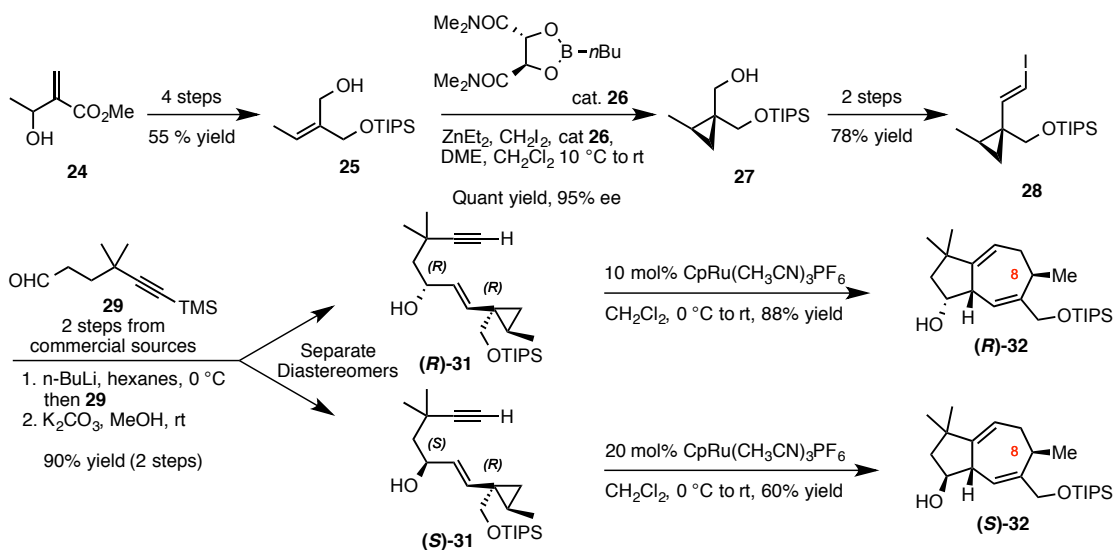
In 2010, the MacMillan¹⁰ group published their synthesis of (+)-frondosin B, and provided evidence that there was an inversion in the course of the Trauner synthesis. The MacMillan group was able to match a common intermediate (**49**) of their synthesis to one of the Trauner (**13**) and Danishefsky (**5**) syntheses, showing that a stereochemical inversion had occurred in the Trauner synthesis and not Danishefsky's. Not only did they prove that an inversion had occurred in the Trauner synthesis but they were also able to provide the shortest and most effective synthesis of (+)-frondosin B in only 3 steps and with 50% overall yield. The group utilized an enantioselective conjugate addition of a benzofuran-derived boronic acid to crotonaldehyde in the presence of an imidazolidinone organocatalyst to establish the stereogenic center of frondosin B. The A-ring was introduced by way of a Shapiro reaction and subsequently closed onto the benzofuran with a BBr₃ promoted Friedel-Crafts cyclization/deprotection step to complete (+)-frondosin B.

Trost's synthesis of (+)-frondosin A

The Trost synthesis centered around a Ru-catalyzed [5+2] cycloaddition of a 1,7-enyne to construct a central cycloheptadiene B-ring. However, initial model studies would show that 1,7-enynes were not be amenable to the Ru-catalyzed [5+2] cycloaddition and had to make recourse

to the more established 1,6-ene-yne cycloaddition. Thus, synthetic efforts towards materials for this key cycloaddition were initiated with alcohol **24** being progressed to allylic alcohol **25** in a series of 4 steps. Enantioselective cyclopropanation²⁸ of allylic alcohol **25** was effected using the chiraloxaborolane ligand **26** to establish the stereogenic centers, which were assigned as the *R,R*-configuration of alcohol **27** (Scheme 1.5).

Scheme 1.5: Trost group's total synthesis of (+)-frondosin A: 1,7-ene-yne cyclization

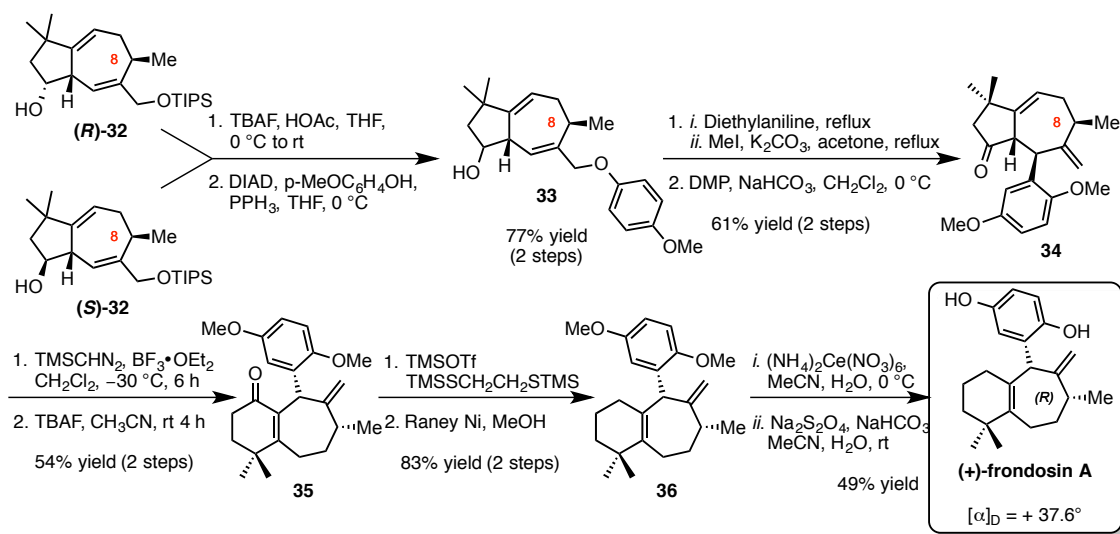


The group progressed alcohol **27** to a vinyl iodide intermediate **28** by way of a Swern oxidation followed by reaction with Takai conditions.²⁹ Employing *n*-butyllithium in a lithium-halogen exchange/addition reaction the vinyl iodide **28** was coupled to aldehyde **29** (prepared in two steps from commercial sources), The resulting alkyne was subsequently deprotected to afford cyclopropyl enyne **31** as the precursor for the key [5+2] cycloaddition. It is important to note that compound **31** was formed as approximately a 1:1 mixture of two diastereomers with respect to the newly formed stereogenic center.

The stage was now set to attempt the [5+2] cycloaddition reaction. Under initial conditions, no desired products were observed, only adducts whereby the vinylcyclopropane group was opened by the addition of water. However, it was interesting to note that the starting material was recovered as a single diastereomer, suggesting that one diastereomer of the mixture was

consumed faster than the other one in the reaction. Optimization of this [5+2] cycloaddition was met with (1) dry solvent and (2) separation of the diastereomers and independent reaction of the separate diastereomers ((*R*)-**31** and (*S*)-**31**) to effectively produce cycloheptadiene **32**.³⁰

Scheme 1.6: Trost group's total synthesis of (+)-frondosin A: First asymmetric total synthesis establishes the C8 center as the R-enantiomer



Following the removal of the triisopropylsilyl protecting group with TBAF, the *p*-methoxyphenyl group was selectively installed on the more reactive allylic/primary hydroxyl group under Mitsunobu conditions to yield compound **33**. Claisen rearrangement under thermal conditions (diethylaniline, 215°) had to be immediately followed by Dess-Martin oxidation as the intermediate ether was very sensitive to acid, base and an oxidative atmosphere. A key ring expansion at the A-ring of **34** was required to complete the bicyclo[5.4.0] core structure of frondosin A. Expansion with (TMS)CHN₂ and catalytic BF₃·OEt₂, followed by desilylation with TBAF, produced the desired ring-expanded ketone **35** (Scheme 1.6).

The Trost group experienced difficulties in deoxygenation (Wolff-Kishner, Myers's modification) of the A-ring ketone with a multitude of decomposition and isomerization products resulting. However, bis[(trimethylsilyl)thio]ethane and catalytic trimethylsilyl triflate were used

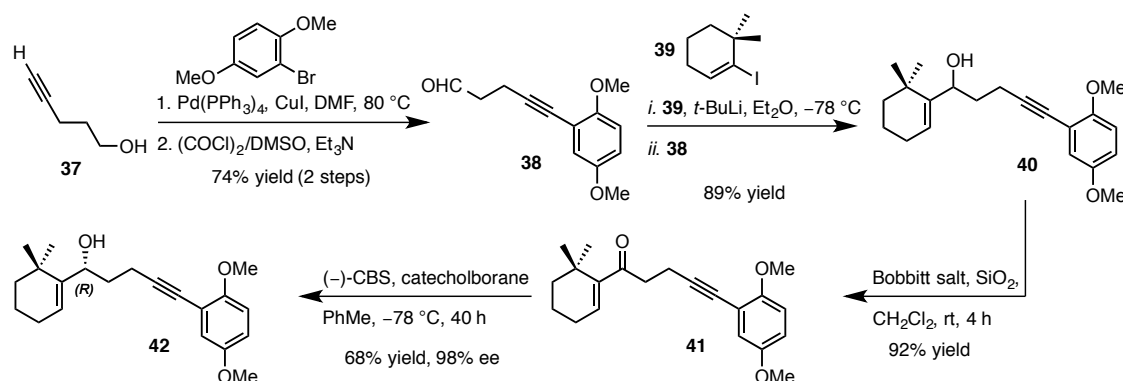
as mild conditions for thioketal formation.³¹ Upon treatment of the crude thioketal with Raney Ni, the desired deoxygenated product **36** was isolated.

Initial attempts for the final aryl deprotection were frustrated; whereby, treatment of **36** with BBr₃ resulted in decomposition and reaction with sodium ethanethiolate only afforded monodeprotection products. The most effective method for the deprotection proved to be an oxidation/reduction sequence using ceric ammonium nitrate (CAN) followed by sodium dithionite. However, the reaction was only performed to partial conversion because of the sensitivity of the system toward oxidation, and resulted in a 49% yield of this operation. This resulted in the first asymmetric total synthesis of (+)-frondosin A ([α]_D = +37.6°), and with a optical rotation reflective of the natural product ([α]_D = +31.5°) the Trost group concluded that the C8-center of (+)-frondosin A naturally occurs as the *R*-configuration.

Ovaska's synthesis of (–)-frondosin B

The Ovaska synthesis of (–)-frondosin B was centered around a 5-exo-dig cyclization/Claisen rearrangement of an optically active homopropargylic allyl alcohol. In an effort towards this intermediate, the group initiated their synthesis with coupling of the requisite aryl functionality to alkyne **37** under Sonogashira coupling conditions (Scheme 1.7). Following Swern oxidation, the resulting aldehyde (**38**) was reacted with geminal dimethyl cyclohexyl lithium, prepared in situ from the corresponding vinyl iodide **39** by lithium-halogen exchange/addition reaction. However,

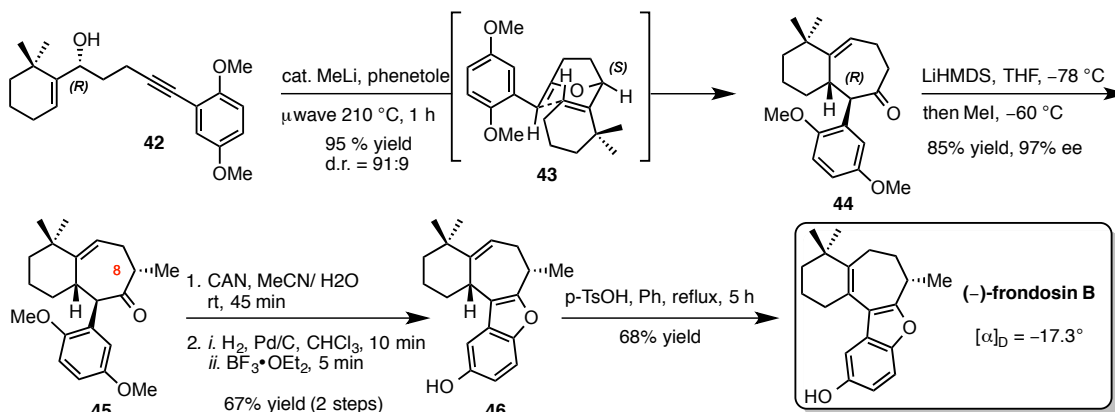
Scheme 1.7: Ovaska group's synthesis of (–)-frondosin B



given this synthetic design the resulting allylic alcohol **40** had to be oxidized to prochiral ketone **41** before being asymmetrically reduced back, with CBS, to an optically active (98% ee) homopropargylic allyl alcohol **42** suitable for a diastereoselective cyclization/Claisen reaction.

The optically active allylic alcohol **42** was subjected to catalytic MeLi and heated under microwave irradiation producing the expected 6-7 fused bicyclic with a high level of stereoselectivity (95% ee). The Ovaska group has proposed a mechanism for this reaction whereby the initial 5-exo-dig cyclization forms an intermediate such as **43** with high diastereoselectivity whereby the chair transformation state sets the aryl group in the equatorial position. This favored transformation state can then undergo the thermal [3,3] Claisen rearrangement to provided ketone **44** (Scheme 1.8).³²

Scheme 1.8: Ovaska group's synthesis of (–)-frondosin B: Support that (+)-frondosin B occurs as the R-enantiomer



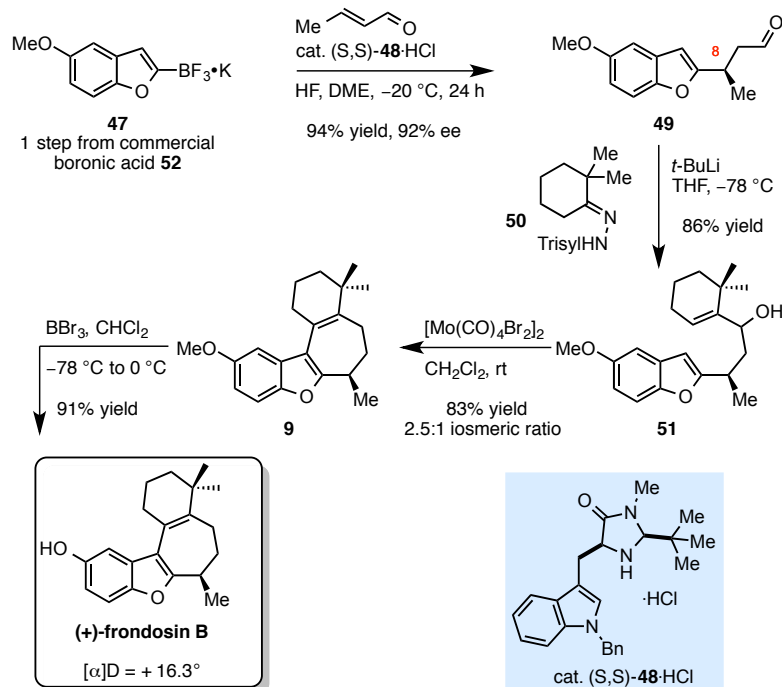
Following the key ring-forming reaction, completion of the natural product was initiated with introduction of the C8 methyl group via stereospecific enolate addition to MeI producing a C8 center of **45** in high optical purity (97% ee). The group was then poised with the challenge of closing the benzofuran C-ring. They chose an oxidation-reduction methodology, similar to that of Trost, to transform the dimethyl aryl group to the hydroquinone moiety that could be directly exposed to BF₃•OEt₂ to close the benzofuran to a close structural isomer **46** of frondosin B. Treatment of isomer **46** with catalytic *p*-TsOH in refluxing benzene afforded the conversion to

(-)-frondosin B, $[\alpha]_D = -17.3^\circ$. The Ovaska synthesis was the first subsequent synthesis of frondosin B that added support for Danishefsky's initial assignment of (+)-frondosin B naturally occurs as the *R*-enantiomer.

MacMillan's synthesis of (+)-frondosin B

Central to the MacMillan synthesis was the enantioselective conjugate addition of extended aldehydes to activated aryl systems. With this in mind, the group targeted heteroaryl trifluoroborate salt **47**, which could be accessed in one step from commercially available boronic acid **52**, by preparation using Molander's procedure.³³ The underlying activation mechanism for this enantioselective conjugate addition is the reversible formation of α,β -unsaturated iminium ion with chiral secondary amine catalyst **48**. The resulting iminium ion is appropriately electron-deficient to undergo coupling with the electron-rich aryl trifluoroborate to provide optically pure aldehyde **49** (92% ee, Scheme 1.9).³⁴

Scheme 1.9: First generation, total synthesis of (+)-frondosin B

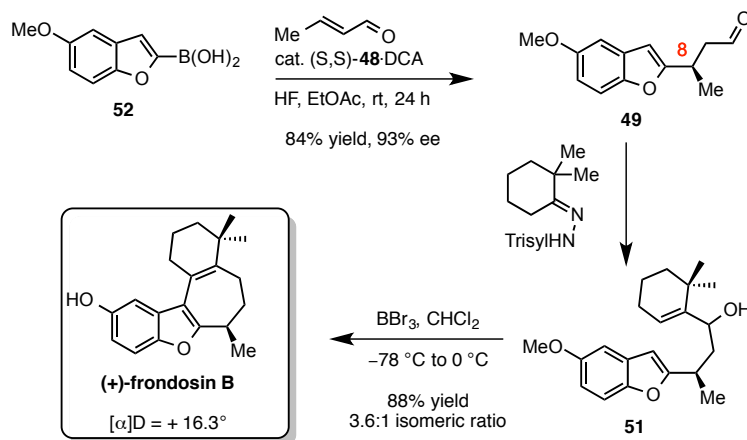


Shapiro reaction of known hydrazone **50** to aldehyde **49** proceeded to give allylic alcohol **51** as an inconsequential mixture of diastereomers.³⁵ Hydrazone **50** can be prepared in one step from commercially available starting materials, by condensation of 2,2-dimethylcyclohexanone and trisylhydrazide. The group discovered that catalytic amounts of molybdenum(II) dimer $[\text{Mo}(\text{CO})_4\text{Br}_2]_2$ readily facilitated the desired formation of tetracycle **52** with a 2.5:1 preference for the desired conjugated olefin isomer.³⁶ Having established a straightforward route to O-methyl frondosin B (**9**), the completion of the total synthesis was accomplished via deprotection of the methyl ether. Specifically, exposure of **9** to BBr_3 cleanly mediated demethylation to furnish (+)-frondosin B ($[\alpha]_{\text{D}} = +16.3^\circ$), obtained in a five-step synthetic sequence.

Although the MacMillan group had established a rapid synthetic route to (+)-frondosin B they observed that this first generation sequence had potential for synthetic improvements. They questioned if the aryl trifluoroborate salt **47** could be replaced by its precursor (boronic acid **52**) in the enantioselective conjugate addition step. Secondly they recognized the last three steps in this synthesis all occurred under acidic conditions and it was thought that an appropriate acidic reagent might be able to perform all three transformations in a single operation.

In efforts towards effecting enantioselective conjugate addition with boronic acid **52** the group discovered that specific choice of solvent (ethyl acetate), as well as the precise choice of

Scheme 1.10: Second generation, total synthesis of (+)-frondosin B



acid co-catalyst (dichloroacetic acid, DCA) led to the desired conjugate addition (**49**) with high yield while maintaining the desired stereoselectivity (93% ee). Following a productive enantioselective conjugate addition to group proceeded with the Shapiro reaction to generate allylic alcohol **51**.

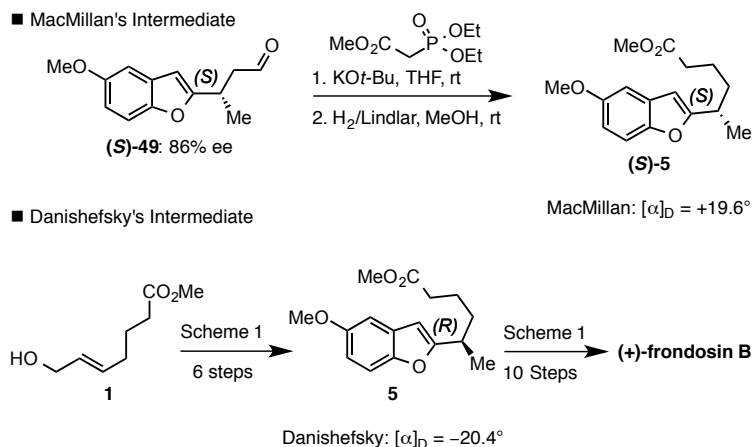
After production of the requisite allylic alcohol **51**, the group reasoned that a suitable Lewis acid might be utilized to initiate the allylic Friedel–Crafts alkylation and the final demethylation step. The group chose the Lewis acid BBr₃ to effect the desired transformation as they assumed that an equivalent of the Brønsted acid HBr would be generated in the course of the Lewis acid-mediated cyclization, which would participate in olefin isomerization to the desired product. It was found that this one-pot strategy with 3.5 equivalents of BBr₃ at low temperature provided (+)-frondosin B along with its olefin isomer in a 3.6:1 ratio in favor of the natural product, which could be separated from its olefin isomer. Thus, this second generation synthesis of (+)-frondosin B ($[\alpha]_D = +16.3^\circ$) required only three chemical steps and was produced in a 50% overall yield.

MacMillan’s proposal for stereochemical relay inversion process in Trauner’s synthesis

The MacMillan group had observed an optical rotation for frondosin B that was identical to that of the natural product and that obtained from Danishefsky’s synthesis, but opposite in sign to that published by Trauner. Yet all of these syntheses were based on production of intermediates that would lead to an *R*-configuration at the methyl (C8) stereogenic center of frondosin B. Since the MacMillan synthesis made the same key benzofuran (C10) disconnection as the Danishefsky’s and Trauner’s syntheses, it afforded them an opportunity to match the early stage intermediates of both syntheses and confirm that Trauner’s synthesis had undergone inversion.

MacMillan initiated his studies into this debate with his synthesis of (*S*)-**49**, prepared in a catalyst-controlled conjugate addition, and absolute configuration of (*S*)-**49** was unambiguously determined by X-ray crystallographic analysis. In this way, had the Danishefsky synthesis undergone the early stage inversion proposed by Trauner they would be able to match the optical

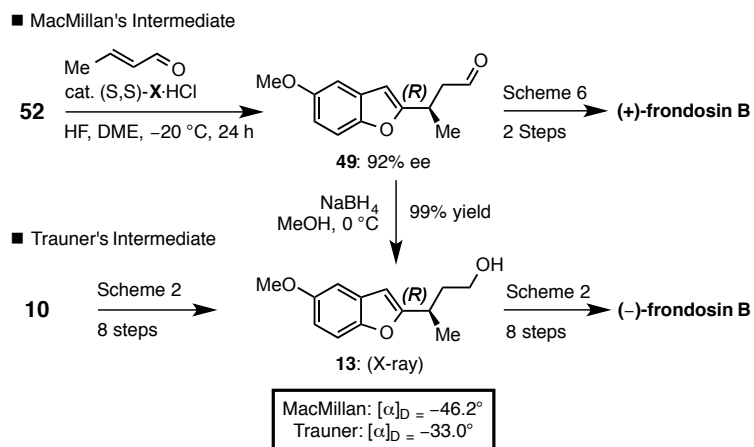
Figure 1.4: MacMillan attempts to match Trauner's proposed "double inversion" intermediate in Danishefsky's synthesis: Support for Danishefsky's initial stereochemical assignment



rotation of this common intermediate. Intermediate (S)-49 was progressed through a series of Horner-Wadsworth-Emmons olefination and subsequent reduction to match the early intermediate **5** of the Danishefsky synthesis. Interestingly, Trauner had proposed that at this point in Danishefsky's synthesis this early intermediate had already undergone inversion, however, MacMillan opposed both sign and magnitude of this common intermediate.

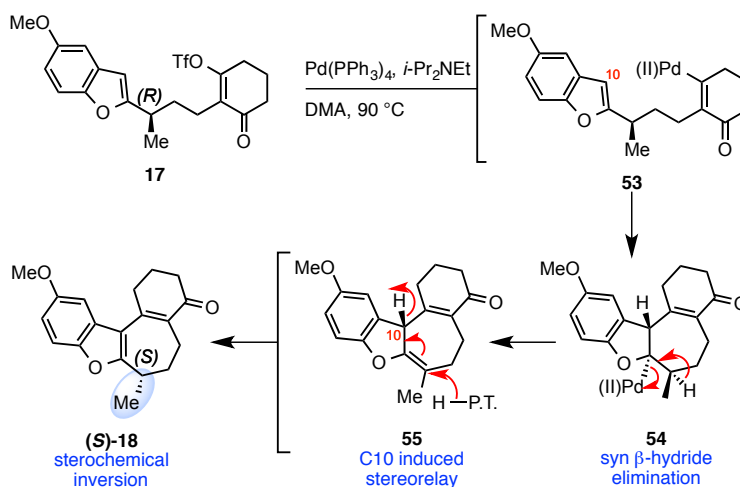
With MacMillan having disproved Trauner's proposed inversion of Danishefsky's synthesis, he turned towards determining at which point in the Trauner synthesis inversion transpired. Initiation of studies with MacMillan's intermediate **49**, reduction with NaBH₄ produced an early

Figure 1.5: MacMillan matches Trauner's intermediate 13: Evidence for a late stage inversion event in Trauner's synthesis



intermediate of the Trauner synthesis (**13**) with optical rotation reflective of both sign and magnitude. The absolute stereochemistry of this similar intermediate was then further confirmed with X-ray crystallographic analysis by conversion to the corresponding 4-bromobenzoate. This initial result confirmed that Trauner had produced an enantiomerically pure early intermediate and that a later stage stereochemical inversion must have occurred.

Figure 1.6: MacMillan's proposed stereorelay mechanism leading to stereochemical inversion at C8



Considering the MacMillan group had matched intermediate **13** of the Trauner synthesis with identical optical rotation and with unambiguous assignment of stereochemistry, it was likely that inversion of the Trauner synthesis must have occurred during the succeeding eight chemical steps to (–)-frondosin B. The MacMillan group was under the assumption that the key intramolecular aryl Heck reaction in the Trauner synthesis was a possible culprit for stereochemical inversion. They proposed a mechanism whereby intermediate production of a stereogenic C10 center of the benzofuran (**54**) with concomitant production of an exocyclic enol ether (which would destroy the C-8 stereocenter). Furthermore, they presumed that protonation of enol ether **55**, during re-aromatization, would selectively install an S-configuration at C8 based upon a stereorelay mechanism, influenced by an intermediate benzofuran C10 stereocenter, and would eventually lead to an S-configuration at C8 of frondosin B.

In conclusion, they provided an expedited route to (+)-frondosin B with only three chemical steps and a 50% overall yield. More-so, they were able to match, early intermediates of both Danishefsky's and Trauner's syntheses and showed that although both had initially set the *R*-configuration at C8 that a late stage stereochemical inversion could have occurred in the Trauner synthesis and proposed a possible mechanism for the inversion. However, subsequent work by the Wright group would match a later stage Trauner intermediate **18** (with a deuterium labelled C8 center), without stereochemical inversion, leading to an alternative mechanism for the stereorelay inversion.

Wright group's synthesis of (+) and (–)-frondosin B: Confirmation that (+)-frondosin B occurs as the *R*-enantiomer

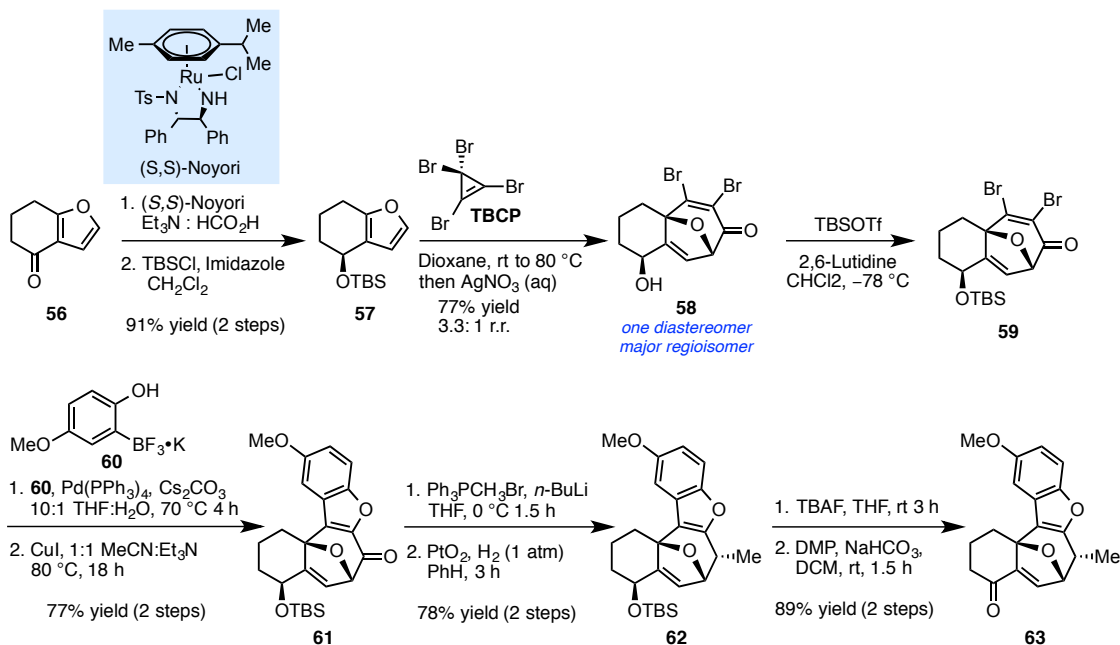
The Wright group's¹¹ planned enantioselective synthesis of frondosin B unexpectedly led to the opposite epimer of the natural product, as seen in the Trauner synthesis, suggesting a late stage stereoinversion at C8 in both syntheses. To investigate this phenomenon Wright carried material through to late stage intermediate **18** from the Trauner synthesis, with a deuterium labelled C8 center, without inversion. With this deuterium labelling study, the group had determined during which synthetic transformation inversion was thought to take place, and proposed a mechanism surrounding a ring contraction/expansion of a delocalized carbocation intermediate that ultimately led to the epimer of the C8 center.

Wright's synthesis of (+)- and (–)-frondosin B was centered on a diastereoselective cycloaddition between tetrabromocyclopropene and an annulated furan to provide a highly functionalized common building block. The resulting bridged bicyclic intermediate was stereo- and chemoselectively manipulated to produce the structurally distinct member of the frondosin family of natural products. The syntheses feature regioselective palladium-coupling reactions and an unprecedented phosphine-mediated ether bridge cleavage.

Wright's synthesis of (+) and (-)-frondosin B

The Wright synthesis was centered around a formal [4+3] Diels-Alder cycloaddition strategy bringing together an annulated furan diene with a perhalogenated cyclopropene dienophile.³⁷ The group prepared the *S*-furyl-alcohol with excellent selectivity through reduction of ketone **56** with the (*S,S*)-Noyori transfer hydrogenation catalyst (Scheme 1.11).³⁸ Following conversion to the corresponding silyl alcohol, **57** could be condensed with tetrabromocyclopropene (TBCP) to give a mixture of regioisomeric tetrabromides that when directly treated with aqueous silver nitrate produced regioisomeric enones **58** and **58b** (**58b** not shown) in a 3.3:1 ratio. The C4-silyloxy exerted a strong directing effect on the initial Diels-Alder reaction leading to a syn-relationship between the protected alcohol and the oxabridge, resulting in extremely diastereoselective cycloaddition.

Scheme 1.11: The Wright group's total synthesis of (-)-frondosin B: Formal [4+3] cycloaddition

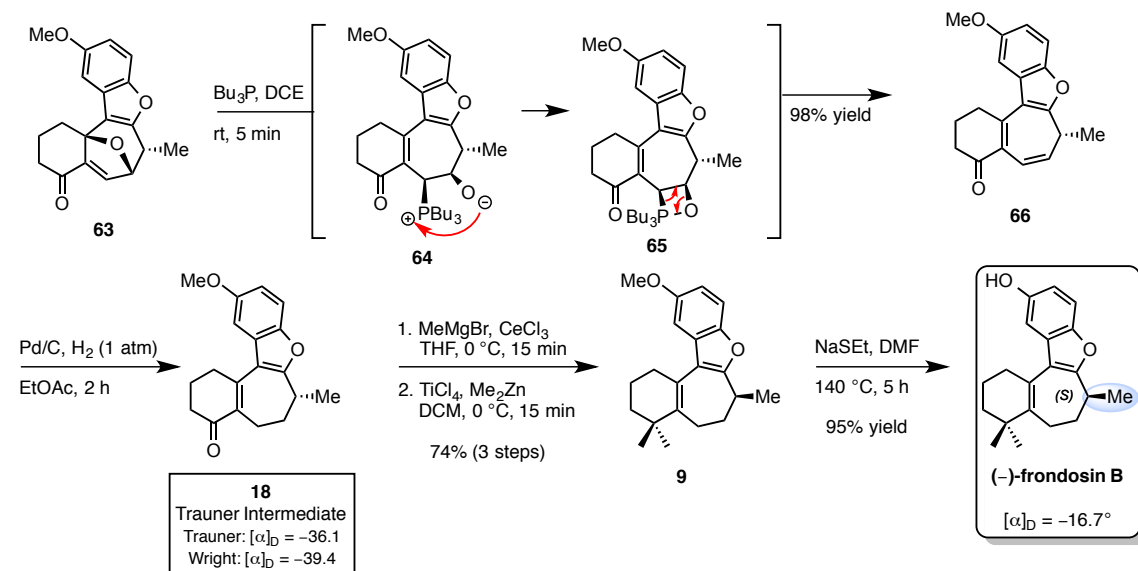


The two vinylic bromides displayed considerably different levels of reactivity that allowed for the regiocontrolled, stepwise introduction of functionality. Suzuki cross-coupling of **59** with

aryl trifluoroborate salt **60** occurred exclusively at the β -bromide to deliver a phenol that when the crude material was subjected to stoichiometric copper(I)iodide led to a smooth coupling of the phenolic hydroxyl group to the α -bromide, thus giving the annulated benzofuran **61**.³⁹

The group saw that the temporary ether bridge induces rigidity into the otherwise flexible cycloheptyl ring and effectively differentiates the two faces of the carbocycle. Exploitation of this rigidity by Wittig condensation gave an *exo*-methylene derivative that could be stereoselectively hydrogenated from the *exo*-face, producing **62** as a single diastereomer (confirmed though X-ray crystallography). Deprotection of the silyl ether preceded oxidation of the resulting allylic alcohol to give enone **63**.

Scheme 1.12: The Wright group's total synthesis of (–)-frondosin B: Identification of a late stage stereochemical inversion as seen in the Trauner synthesis.



The group was frustrated by various attempts (radical, SmI_2 , Lewis-acid) at cleavage of the oxa-bridge but eventually developed an interesting phosphine-mediated deoxygenation protocol. Addition of Bu_3P to the enone **63** led to direct conversion to the triene **66** with complete regiocontrol of the final elimination reaction. They proposed a mechanism, whereby initial conjugate addition of phosphine to the more accessible *exo*-face produced a short-lived enolate

followed by ejection of the β -disposed ether yielding a transient betaine **64**. This betaine then collapses through the intermediacy of the oxaphosphatane **65** to deliver the desired olefin.

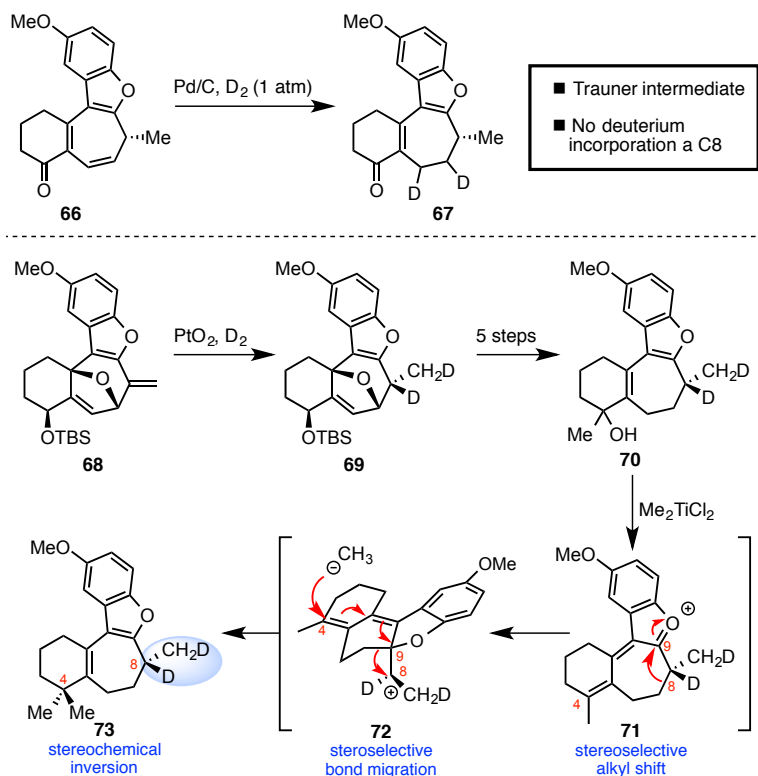
Regioselective hydrogenation of the C6-C7 alkene produced enone **18**, a late stage intermediate in the Trauner synthesis. At this point the group was pleased that **18** matched the reported spectral data, yet, their intermediate also matched Trauner's reported optical rotation. This result was disconcerting, as compound was later shown to possess the incorrect *S*-configuration at C8, ultimately leading to the antipode of the natural product. The Wright group advanced compound **18** to frondosin B according to Trauner's protocol and, as reported, possessed the opposite rotation as that reported for (+)-frondosin B, $[\alpha]_D = -16.7^\circ$. It was straightforward for the group to prepare the natural configuration using the antipode of silyoxy **57**. Utilizing the (R,R)-Noyori catalyst for the reduction of ketone **56** produced the enantiomeric compound (+)-**57** (after protection as its silyl ether) which could be taken through the same sequence to deliver (+)-frondosin B, $[\alpha]_D = +16.4^\circ$.

Wright group's proposal for stereochemical inversion during transformation of 18 to 9

With single crystal structure determination of dibromoenone **59** and silyoxy **62**, the group had unambiguously established that the C8 center possessed the correct *R*-configuration at intermediate **63** and was somehow inverted to the incorrect *S*-configuration during the final steps of the synthesis. The group thought that possibly the configuration at C8 had somehow been inverted in the processing of **63** to the Trauner intermediate **18**. However, strong NOE enhancements between the C8 methyl group and the C6-vinyl protons of intermediate **18** showed no such inversion. To further probe the configuration of this center during the final stages of the synthesis, reduction of the dieneone **66** under a deuterium atmosphere only showed incorporation at C6-C7 and no incorporation at the C8 position of **67**. Likewise, reduction of the exomethylene derived **68** with deuterium gas gave labeled intermediate **69** that was converted to

the Trauner-like intermediate **70** without exchange of the methine deuterium for hydrogen. As inversion of configuration occurred in both the Wright and Trauner syntheses, it seems most likely that it is related to a common process, namely the conversion of the C4 ketone **18** to O-methyl frondosin B **9** through an intermediate carbonium ion (Figure 1.7)

Figure 1.7: Isotopic labelling studies: Working model for stereochemical inversion in the Wright and Trauner syntheses



Wright proposed a working hypothesis centered on the initial highly delocalized carbocation **71** that may undergo a stereoselective, reversible alkyl shift producing an intermediate ring contracted cation **72**. Suggesting that this migration generates a new stereogenic center at C9 and acts to preserve the stereochemical information embedded in the molecule. Furthermore they theorized that in intermediate **72**, the planarized C8 carbon should adopt a conformation that orients the methyl group outside the ring system such that when the final nucleophilic attack at C4 triggers reformation of the C7-C8 bond, in that the migration is stereoselective. In summation, the initial C8 configuration controls the stereochemistry produced at C9 of **72**, which in turn

dictates the configuration when the C8 center is re-established. The intermediacy of a C8 cation allows for the process to occur with overall stereochemical inversion producing **73**.

Racemic/Formal/Partial syntheses of the frondosins: Davies, Ovaska, Flynn, Mehta, Xue/Li, and Winne

Along the same time that there were a series of asymmetric total syntheses of the frondosins there were also several of racemic and formal syntheses of the frondosins. In 2008, the Davies' group¹² published a formal synthesis of (+)-frondosin B that intersected Danishefsky's intermediate ketone **6**. The main focus of this formal synthesis was the design of a benzofuranyldiazoacetate that could asymmetrically cyclized with 1-methyl-1,3-butadiene to form the key cycloheptane ring and stereogenic C8 center in a single step.

The Ovaska group^{13,18} completed the total synthesis of (±)-frondosin C in 2007 and in 2008 the formal synthesis of (±)-frondosin A. Both syntheses focused on the rapid assembly of the requisite bicyclo[5.4.0]undecane scaffold utilizing their anionic tandem cyclization–Claisen rearrangement sequence. Ovaska's synthesis of (±)-frondosin C was their first synthesis a frondosin natural product, and they would use this standard blueprint for the synthesis of frondosin A and B.

In 2008 and 2010, the Flynn group¹⁴ reported on syntheses of (±)-frondosin B and the carbocyclic framework of frondosins D and E. In both syntheses, the group focused on a the synthesis of a benzofuryl(frondosin B)/pyranyl(frondosin D and E) scaffold with a bis-vinyl triflate/chloride to introduce the key cycloheptane ring via tandem Stille-Heck couplings. The group initially tried to produce this key transformation in a one-pot sequence; however, they found that a two-step process produced optimal yields. From this stage, both syntheses were completed with introduction of the geminal dimethyl group, utilizing Reetz protocol, in both the

traditional one-pot process (frondosin B) and Trauner's modified two-step sequence (frondosin D and E).

Around the same time (2008) the Mehta group¹⁵ published the formal synthesis of (±)-frondosin A and a total synthesis of (±)-frondosin B. Mehta's strategy was fixated on the rapid construction of the bicyclo[5.4.0]undecane core of the frondosins with an appropriate tethered aryl functionality based on readily available cyclohexanone and dimethyl-gentisic aldehyde. The key cycloheptane ring was closed in a Grubbs catalyzed RCM to generate a late stage intermediate that could be progressed to an intermediate of the Ovaska synthesis, that was shown to be elaborated to both (±)-frondosin A and B.

In 2012, Xue's and Li's group¹⁶ developed a novel approach to the 6,7,5-tricyclic skeleton of frondosin B based on an acid-catalyzed intermolecular [4+3]-cycloaddition. The group developed a divergent synthetic plan based around the production of a benzofuran-carbinol as a dienophile equivalent and an advanced cyclohexyl fragment as the diene equivalent. The group then focused on screening Lewis and Brønsted acid conditions for properly forming the benzofuran cation necessary for cycloaddition, finally settling on CSA (camphorsulfonic acid) as the ideal acid catalyst. In 2014, the Winne group¹⁷ would attempt to improve upon these conditions by screening a different set of acids. However, the group would show diminished yields as to what was previously reported on.

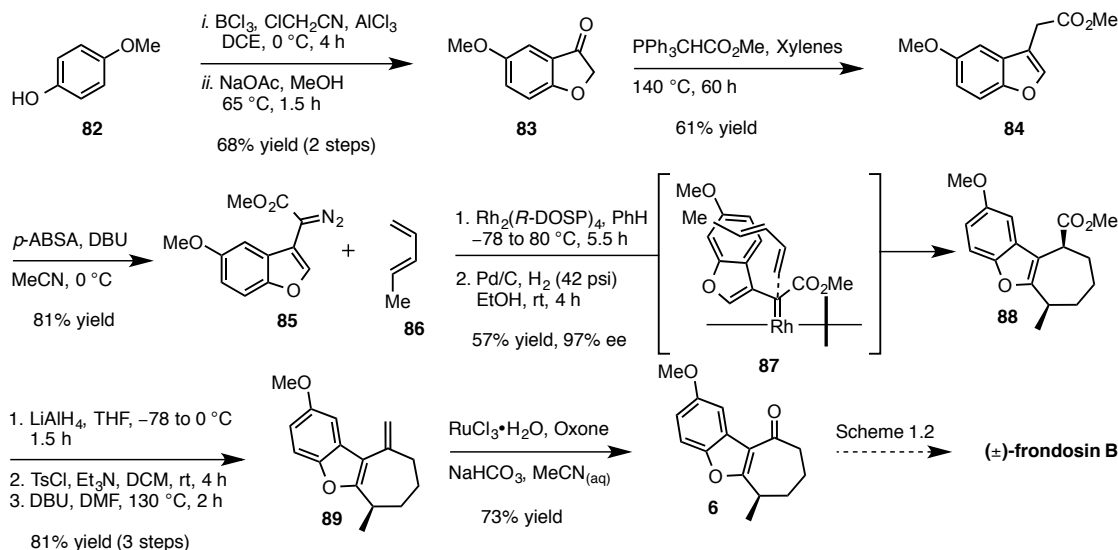
Davies' formal total synthesis of (+)-frondosin B

Central to the Davies' synthesis of intermediate **6** was the asymmetric cyclopropanation/Cope rearrangement between benzofuranyldiazoacetate and 1-methyl-1,3-butadiene to form the key cycloheptane ring and stereogenic C8 center in a single step.⁴⁰ Synthesis was initiated with commercially available 4-methoxyphenol **82** being cyclized with chloroacetonitrile to generate the benzofuranone **83**. Benzofuranone **83** was then homologated out to ester **84** by refluxing with methyl (triphenylphosphoranylidene)acetate in xylenes. Successive reaction of ester **84** with *p*-

acetamidobenzenesulfonyl azide (*p*-ABSA) allowed for a diazo transfer reaction resulting in benzofuranyldiazoacetate **85** (Scheme 1.15).

When **85** was reacted with 1-methyl-1,3-butadiene **86** in the presence of $\text{Rh}_2(R\text{-DOSP})_4$,⁴¹ it proceeded through an intermediate such as **87**, upon heating to 80 °C, the mixture was completely converted to the desired [4+3] cycloadduct. The group noted that the cycloadduct intermediate rapidly decomposed, thus, it was immediately subjected to hydrogenation to produce compound **88**. This product was then reduced with lithium aluminum hydride, and the resulting alcohol was subsequently eliminated using toluenesulfonyl chloride and triethylamine, followed by heating in the presence of DBU to produce **89**. Exocyclic olefin **89** could then be cleaved by the action of a ruthenium-catalyzed oxidative cleavage⁴² to produce Danishefsky's intermediate **6** (Scheme 1.13).

Scheme 1.13: Davies synthesis of Danishefsky's intermediate 6: Asymmetric [4+3] cyclopropanation/Cope rearrangement between benzofuranyldiazoacetates and 1-methyl-1,3-butadiene



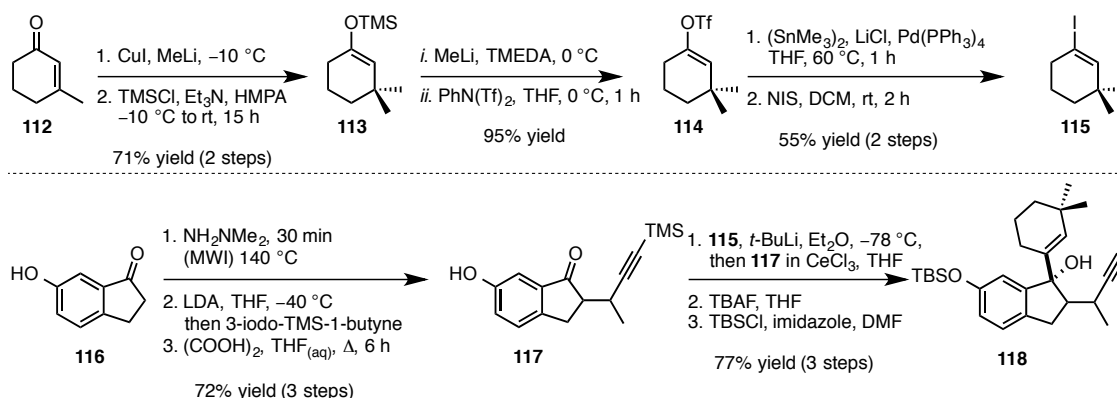
In summation of the Davies work, they broadened the scope of the tandem asymmetric cyclopropanation/Cope rearrangement sequence by using benzofuranyldiazoacetates and 1-methyl-1,3-butadiene as substrates. In the process of developing these new chemical methods, the Davies' group utilized these conditions in formal [4 + 3] cycloadducts, demonstrating its

application toward the formal enantioselective synthesis of (+)-frondosin B. In doing so the intersected intermediate **6** of the Danishefsky synthesis in 10 synthetic steps and were able to confirm an asymmetric synthesis based on optical rotation and chiral HPLC analysis.

Ovaska's synthesis of (±)-frondosin C

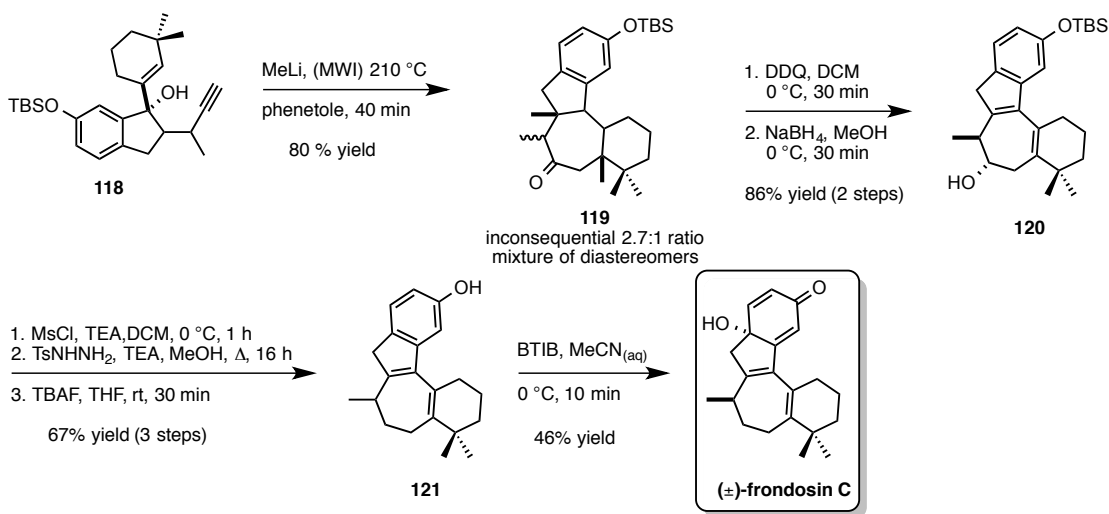
The Ovaska group has shown synthetic access to three of the frondosins with their first synthesis being (±)-frondosin C in 2007. The group was again focused on the generation of the tetracyclic core of the frondosins utilizing their standard microwave-assisted tandem 5-*exo*-dig cyclization/Claisen rearrangement protocol.⁴³ Initiation of synthetic studies began with the group preparing vinyl-iodo A-ring (**115**) from 3-methylcyclohexen-1-one **112**. Cyclohexenone **112** was converted to the corresponding TMS silyl enol ether **113** by a series of 1,4-addition of a methyl moiety via cuprate addition with successive generation of the TMS silyl enol ether in the presence of Et₃N and TMSCl. Conversion to the requisite triflate **114** was accomplished with lithiation of silyl enol ether **113** with methyl lithium being quenched with PhN(Tf)₂. Vinyl iodo building block **115** was achieved through a sequence of stannylation of enol triflate **114** via palladium coupling conditions followed by a radical halogenation in the presence of NIS to deliver vinyl iodo species **115** (Scheme 1.14).

Scheme 1.14: Ovaska's synthesis of (±)-frondosin C: Preparation of intermediate **118**



Preparation of the benzofuran portion was initiated with conversion of 6-hydroxy-1-indanone (**116**) to the corresponding hydrazone with microwave-assisted conditions. The intermediate hydrazone could be alkylated with 3-iodo-1-trimethylsilyl-1-butyne in the presence of LDA to introduce the C8 methyl moiety, to be followed by conversion of the hydrazone to the ketone **117** with oxalic acid. Preparation of key acetylenic alcohol **118** was accomplished by metalation of **115** and reaction of the resulting organocerium species with ketone **117**. Global deprotection of this intermediate, followed by a selective silylation of the resulting phenol resulted in the key acetylenic alcohol **118** required for the key cyclization/Claisen rearrangement step.

*Scheme 1.15: Ovaska synthesis of (±)-frondosin C: 5-*exo*-dig-cyclization/Claisen rearrangement*



The Ovaska group proceeded with standard conditions for the 5-*exo*-dig cyclization/Claisen rearrangement sequence to deliver ketone **119**, as an inconsequential 2.7:1 mixture of diastereomers. The requisite B ring diene functionality was introduced by the action of DDQ and the ketone of the resulting material could be reduced with sodium borohydride to deliver alcohol **120**. Alcohol **120** could be mesylated, in the presence of TEA and MsCl, and the resulting triene could be selectively reduced with diimide. Deprotection of the corresponding TBS analogue with TBAF proceeded cleanly to provide the desired indenol **121**. Treatment of indenol **121** with

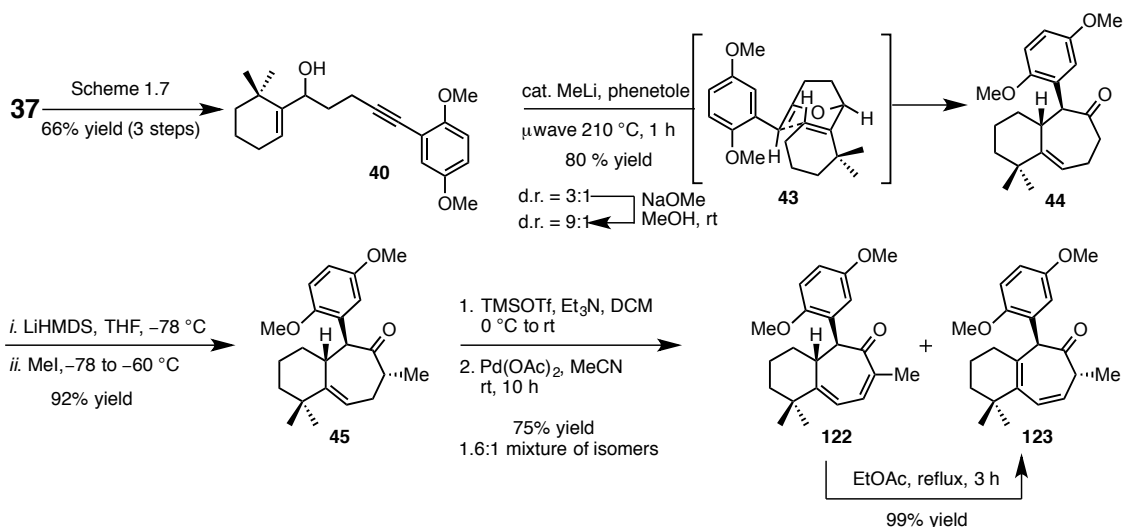
BTIB⁴⁴ resulted in rapid formation of (±)-frondosin C (47% yield) and the corresponding (±)-8-*epi*-frondosin C (37% yield, Scheme 1.15).

The Ovaska group completed the total synthesis of (±)-frondosin C in 14 steps and in 20.8% overall yield. The anionic tandem cyclization–Claisen rearrangement sequence was successfully applied to the construction of the requisite tetracyclic core of frondosin C in eight steps, and subsequent manipulation of the core to the natural product was completed in six steps. This was Ovaska’s first synthesis a frondosin natural product, and they would use this standard blueprint for the synthesis of frondosin A and B.

Ovaska’s synthesis of (±)-frondosin A

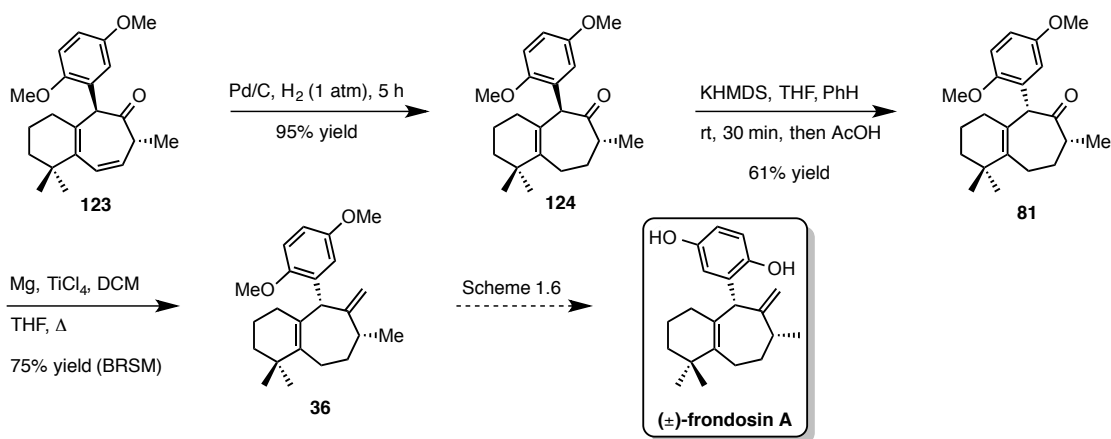
Prior to the synthesis of (+)-frondosin B by the Ovaska group they focused their efforts on the rapid synthesis of the bicyclo[5.4.0]undecane core of the frondosins via a 5-*exo*-dig cyclization/Claisen rearrangement strategy similar to that of their synthesis of (±)-frondosin C. As described earlier in the publication (Schemes 1.7 and 1.8) the Ovaska group progressed alcohol **37** to homopropargylic alcohol **40** over a series of 3 steps. This alcohol could be subject to their standard anionic tandem cyclization/Claisen rearrangement sequence to construct the

*Scheme 1.16: Ovaska’s formal synthesis of (±)-frondosin A: 5-*exo*-dig cyclization/Claisen rearrangement*



bicyclic[5.4.0]undecane core of frondosin A (**44**). Following the key ring-forming reaction, the C8 methyl group was installed via enolate addition to MeI producing a C8 center of **45**. Compound **45** was shown earlier (Scheme 1.8) to be synthetically extrapolated by the Ovaska group to complete the total synthesis of (+)-frondosin B. Saegusa oxidation of ketone **45** led to smooth conversion to a mixture of isomeric dienones **122** and **123**. However, heating **122** in refluxing EtOAc lead to complete conversion to the less conjugated isomer **123** (Scheme 1.16).

*Scheme 1.17: Ovaska's formal synthesis of (±)-frondosin A: Completion to intermediate **36***



Brief exposure of diene **123** to catalytic hydrogenation conditions provided ketone **124**. Subsequent treatment of **124** with KHMDS at room temperature for 30 min, led to epimerization in a 1.6:1 ration favoring the desired *syn*-epimer **81**. The synthesis of (±)-frondosin A dimethyl ether **36** was achieved from **81** by employing the TiCl₄-Mg promoted olefination protocol. At this point the Ovaska group had matched the Trost synthesis of frondosin A and had thus completed their formal synthesis. What is interesting, is that in this publication Ovaska group showed that a novel two-step oxidation(CAN)/reduction(H₂) protocol could be used to deprotect the dimethylether of the C8-C10 epimer of frondosin A, however, they were not able to extrapolate these condition to the correct epimer to complete a novel total synthesis (Scheme 1.17).

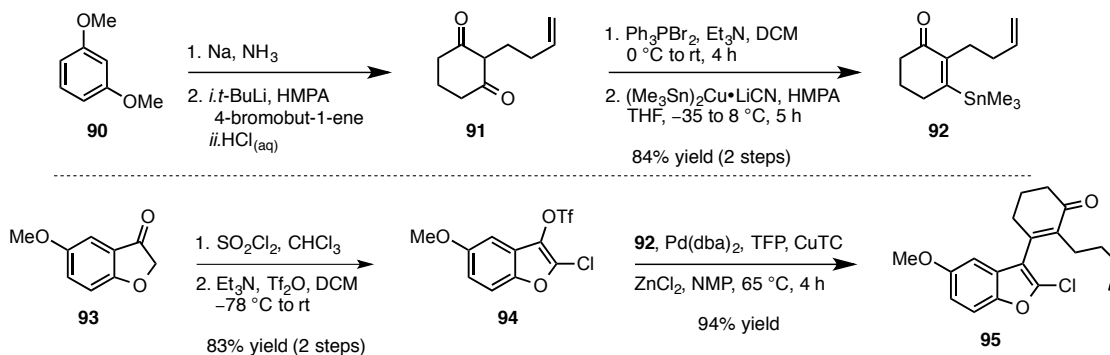
In conclusion, the formal total synthesis of (±)-frondosin A was achieved, focusing on the rapid assembly of the requisite bicyclo[5.4.0]undecane scaffold through the tandem 5-*exo*-dig

cyclization/Claisen rearrangement process.

Flynn's synthesis of (±)-frondosin B

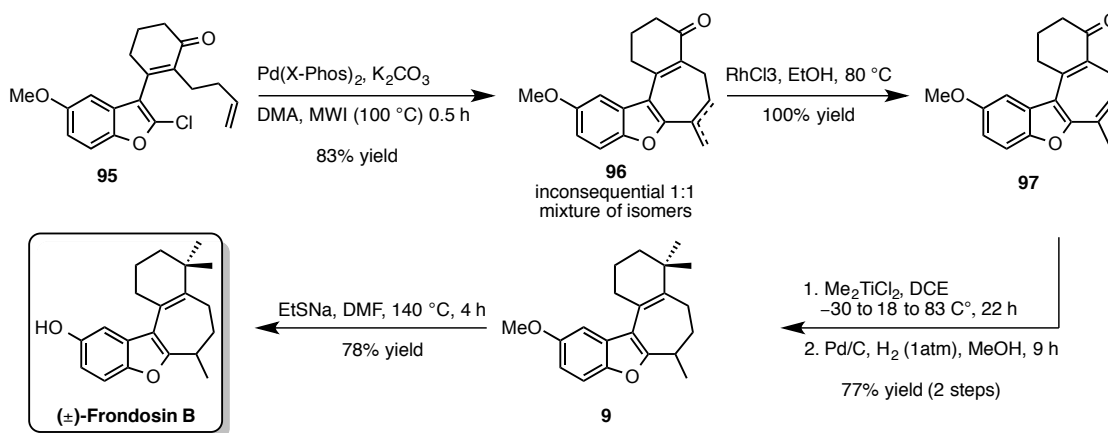
The Flynn synthesis of (±)-frondosin B was centered around tandem Stille/Heck couplings to introduce the central cycloheptane. Efforts towards stanane **93** were initiated with commercially available 3-methoxyanisole **90** being reduced by the action of sodium followed by enolate alkylation with 4-bromobut-1-ene to produce diketone **91**.⁴⁵ Cyclohexanedione **91** could be converted to the corresponding stannane **92** by way of Wittig bromination conditions preceding lithium halogen exchange to introduce the requisite stannyl group. To construct the requisite coupling partner to **92** the group α -chlorinated commercially available 5-methoxybenzo[*b*]furan-3-one **93** with subsequent enol-triflation, utilizing triethylamine and triflic anhydride at low temperature, to give bis-vinyl chloro/triflate **94** (Scheme 1.18).

Scheme 1.18: Flynn synthesis of (±)-frondosin B: Preparation of 95 via Stille coupling



When the group initiated their synthesis, they envisioned preforming a tandem Stille-Heck coupling to intermediates such as **92** and **94** whereas they were able to perform these two reactions in a one-pot setting. However, in performing this operation the group saw a multitude of products, and ultimately decided to focus on optimizing each procedure individually. Toward this end, the Flynn developed a set of conditions, utilizing Pd(dba)₂, TFP, CuTC, ZnCl₂ and NMP, to optimize the Stille coupling to produce vinyl chloride **95** in excellent yield.

Scheme 1.19: Flynn's synthesis of (±)-frondosin B: Completion of synthesis via Heck coupling



With vinyl chloride **95** in hand, the group initiated studies toward the intramolecular Heck coupling to close the cycloheptane ring. A catalyst screen would show that the palladium pre-catalyst $\text{Pd}(\text{X-Phos})_2$ was ideal to produce the desired couple product.⁴⁶ Through a base and solvent screen the group also found potassium carbonate and the aprotic polar solvent dimethylacetamide to be superior for this transformation to produce **96** in an ideal yield, as an inconsequential 1:1 mixture of isomers. This mixture of double-bond isomers **96** could be quantitatively converted to the thermodynamically more stable internal double-bond isomer **97**, upon reaction with RhCl_3 in refluxing ethanol. Enone **97** was then converted into (±)-frondosin B through a sequence of gem-dimethylation of the ketone, following the previously described Reetz protocol, with succeeding chemoselective hydrogenation of the C7-C8 double-bond to produce *O*-methyl frondosin B **9**, that could be converted to frondosin B using known procedures (Scheme 1.19).

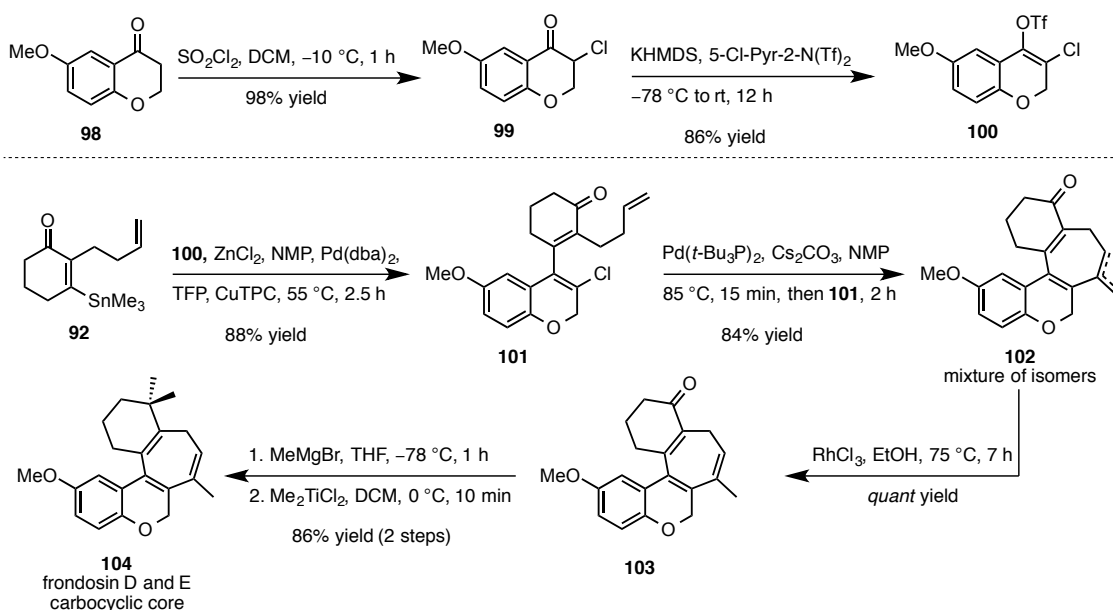
Flynn's partial synthesis of (±)-frondosin D and E

In the same way as the Flynn group initiated studies toward the synthesis of frondosin B they targeted a vinyl triflate/chloride **100** as a suitable coupling partner. Thusly, commercially available methoxy-chromanone **98** was chlorinated with SOCl_2 to provide α -chlorite **99** which

could be converted to the corresponding enol-triflate **100** by action with KHMDS and 5-Cl-Pyr-2-N(tf)₂ (Scheme 1.20).

Having devised optimal conditions for a two-step Stille-Heck coupling sequence for the coupling of vinyl triflate/chloride **94** to stannane **92**, the coupling of vinyl triflate/chloride **100** was straightforward. Therefore, the Stille coupled product **101** was obtained in optimal yields which could be then subject to the devised intramolecular Heck coupling conditions to produce **102** as an inconsequential mixture of double-bond isomers. This mixture of double-bond isomers **102** could be quantitatively converted to the thermodynamically more stable internal double-bond isomer, **103**, upon reaction with RhCl₃ in refluxing ethanol. The geminal dimethyl group was introduced in a two-step manner with the usual methods, utilizing Reetz conditions, to complete the structural framework of frondosins D and E.

Scheme 1.20: Flynn's synthetic efforts towards (±)-frondosin D and E: Featuring Stille-Heck couplings



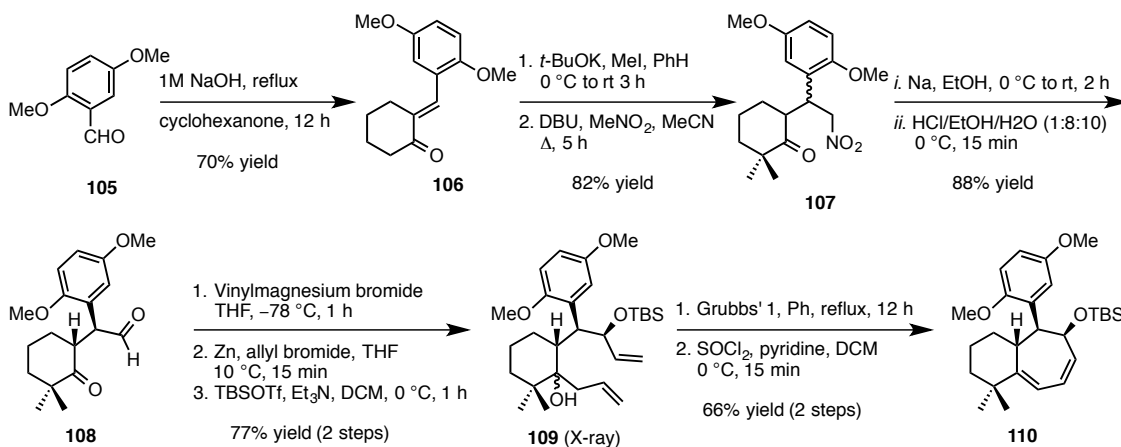
In conclusion of Flynn's work, they reported syntheses of (±)-frondosin B and the carbocyclic framework of frondosins D and E. The group focused on a the synthesis of a benzofuryl(frondosin B)/pyranyl(frondosin D and E) structure with a bis- vinyl triflate/chloride to

introduce the key cycloheptane ring via tandem Stille-Heck couplings. The group initially tried to produce this key transformation in a one-pot sequence; however, they found that a two-step process produced optimal yields.

Mehta's synthesis of (±)-frondosin A and B

The Mehta strategy toward the frondosins was focused on the rapid construction of the bicyclo[5.4.0]undecane core of the frondosins with an appropriate tethered aryl functionality. Toward this end, cyclohexanone was condensed with dimethyl-gentisic aldehyde **105** to furnish arylidene **106**. Exhaustive methylation of ketone **106** introduced the gem-dimethyl moiety; that could be followed by Michael addition of the anion derived from nitromethane, to lead to a diastereomeric mixture (1:1) of **107**. Although the two diastereomers of **107** could be separated, the group noted that the mixture could be used without separation for the next step. Mehta utilized the Nef reaction on **107** as a productive method that led to aldehyde **108** as a single diastereomer, through equilibration under the reaction conditions. (Scheme 1.21).⁴⁷

Scheme 1.21: Mehta's synthesis of (±)-frondosin A and B: Grubbs RCM

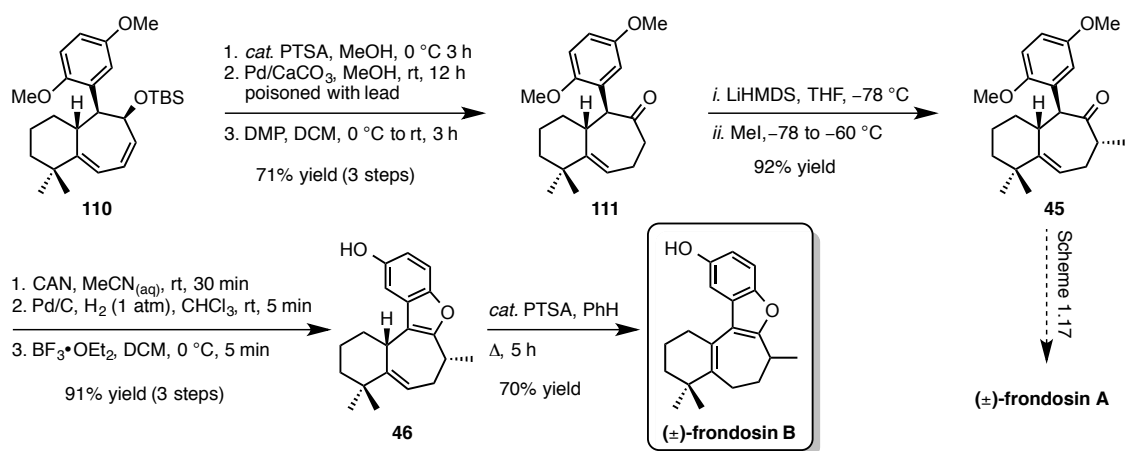


The stage was now set to introduce the two alkenyl arms onto the ketone and aldehyde groups of **108** to set up the RCM precursor for construction of the cycloheptane ring. Addition of vinylmagnesium bromide to **108** was chemoselective with respect to the aldehyde and furnished

diastereomeric vinyl alcohols, in which the *syn*-hydroxy isomer predominated (2:1). The major *syn*-hydroxy isomer was subsequently subjected to Barbier-type reaction in the presence of zinc to furnish a diastereomeric mixture of diols; whereby the secondary alcohols were successively protected with as the silyl ether to furnish a 3:1 diastereomeric mixture of silyl **109**. The lack of stereoselectivity during the Barbier addition was determined to be inconsequential, as the newly generated stereogenic center bearing the tertiary hydroxyl group would be destroyed during subsequent steps. Thusly, RCM of diene **109** in the presence of Grubbs' first generation catalyst furnished the bicyclo[5.4.0]undecane alcohols; which could be directly exposed to thionyl chloride/pyridine leading to dehydration to give the bicyclic-1-3-dienol derivative **110**.

Deprotection of the TBS protective group of **110** furnished a dienol that could be subject to selective catalytic hydrogenation of the less substituted double bond which could be further oxidized with DMP to the enone **111**. Enone **111** underwent α -methylation in a regio- and stereoselective manner to furnish ketone **45** embodying the complete carbon framework of the frondosins. Bicyclic enone **45** had been recently elaborated to the both frondosin A and B by the Ovaska group and thus this concluded Mehta's formal synthesis of frondosin A (Scheme 1.22).

Scheme 1.22: Mehta's synthesis of (\pm)-frondosin A and B



Although, the Mehta group halted their synthetic efforts towards frondosin A, they continued their synthesis towards frondosin B. To complete the synthesis of frondosin B, Mehta selected a

deprotection/cyclization procedure, similar to that of the Ovaska group. They utilized a CAN oxidation to the corresponding quinone that could be reduced to the hydroquinone moiety that allowed for a $\text{BF}_3 \cdot \text{EtO}_2$ promoted Friedel-Crafts cyclization of the benzofuran ring of **46**. Lastly, the trisubstituted double bond of **46** was isomerized to the desired tetrasubstituted position with catalytic PTSA in refluxing benzene to deliver (\pm)-frondosin B.

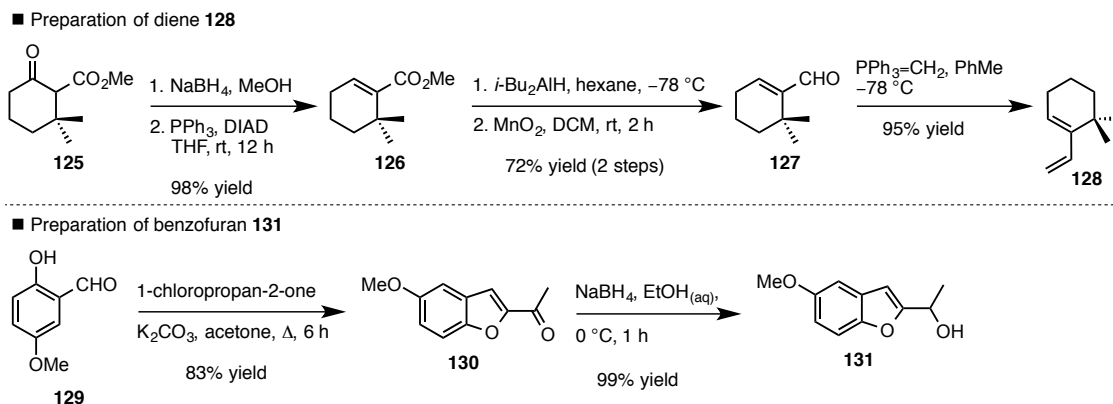
In summation of their work, the Mehta group reported on the formal synthesis of (\pm)-frondosin A and a total synthesis of (\pm)-frondosin B. The Mehta group utilized a strategy fixated on the rapid construction of the bicyclo[5.4.0]undecane core of the frondosins with an appropriate tethered aryl functionality. The key cycloheptane ring was closed in a Grubbs catalyzed RCM to generate a late stage intermediate that could be progressed to an intermediate of the Ovaska synthesis, that was shown to be elaborated to both (\pm)-frondosin A and B.

Xue and Li's synthesis of (\pm)-frondosin B

The Xue/Li synthesis was directed toward the [4+3] cycloaddition approach to the tetracyclic core of frondosin B. Thusly, starting from the known cyclic β -ketoester **125**, a sodium borohydride reduction and Mitsunobu-type dehydration gave the cyclic enoate ester **126**. A two-step redox adjustment gave the corresponding cyclohexene-carbaldehyde **127**, and subsequent Wittig methylenation gave the desired vinylcyclohexene **128**. Preparation of the benzofuran counter-part **131** was initiated with benzaldehyde **129** being reacted in a Feist-Benary type reaction with 1-chloropropan-2-one to form 2-acetylbenzofuran **130**. Borohydride reduction of acetylbenzofuran **130** produced allylic alcohol **131** as a suitable coupling partner for the ensuing [4+3] cycloaddition (Scheme 1.23).

Much synthetic effort was put into the optimization of the [4+3] cycloaddition. First was that of optimizing the cation-generating conditions, and a number of such conditions (TFA, TFAA/lutidine, SnCl_4 , TiCl_4 , BBr_3 , ZnCl_2) were screened, all failing to produce the seven-

Scheme 1.23: Xue/Li's synthesis of (±)-frondosin B: Preparation of intermediates 128 and 131

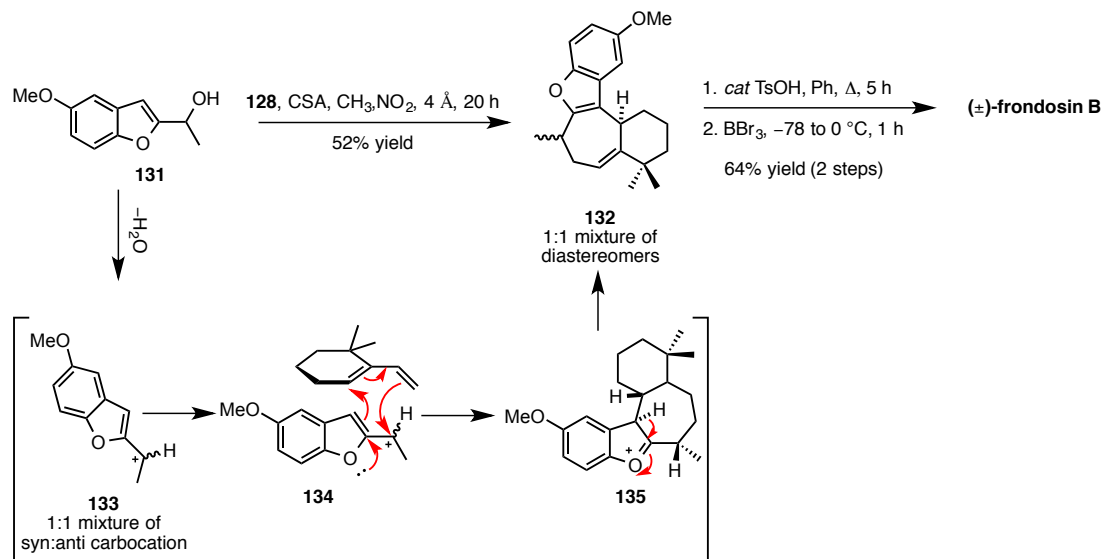


membered ring and mostly yielding diene homopolymers. The stronger protic acid CSA (camphorsulfonic acid) promoted the desired transformation, giving intermediate **132**. The group next saw that the polarity of the solvent has an obvious influence on the stability of carbocations and, nitromethane, a polar solvent, was found to be the best reaction medium. Furthermore, the group noted that the transformation was sensitive to temperature, being very slow at 0 °C, seeing accelerated the self-polymerization of dienes at higher temperatures. After a thorough investigation, the following conditions were determined to be the most efficient: allylic alcohol and diene were reacted in the presence of CSA in nitromethane at 35 to 40 °C for 20 to 22 h. Under these conditions, **131** reacted with **128** to yield **132** as a pair of diastereoisomers in a 1:1 ratio (Scheme 1.24).

The group proposed a mechanism whereby, the allylic alcohol **131** is first protonated and then dehydrated to form an allylic carbocation **133** in which the p- π conjugation produces two configurations of the carbocation, *syn*-**133** and *anti*-**133**. These carbocations are then captured by the diene **128**, yielding a pair of diastereoisomers, *anti*-**135** and *syn*-**135**. The subsequent elimination generates tetracycle **132** as an inconsequential 1:1 pair of diastereomers.

After obtaining the mixture of diastereomeric tetracycle **132**, this product was then treated with *p*-TsOH in benzene under reflux, and the double bond migrated smoothly to the more

Scheme 1.24: Xue and Li's synthesis of (±)-frondosin B: [4+3] cycloaddition approach



conjugated and thermally stable C5-C11 olefin. This product could then be deprotected with BBr₃ to generate the desired frondosin B.

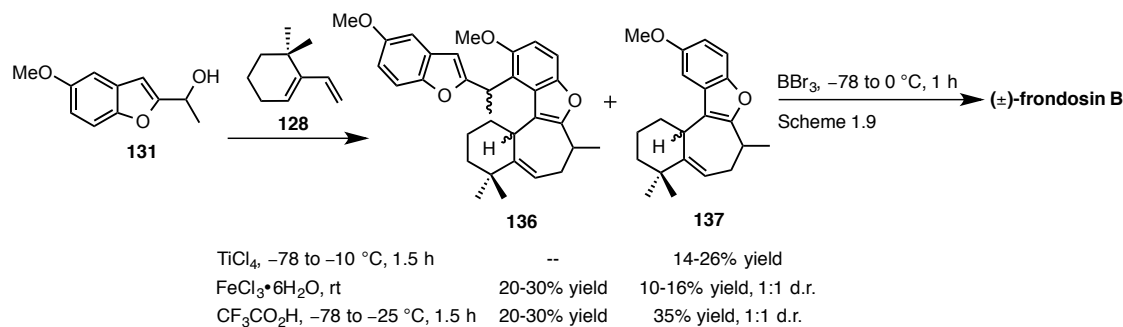
In conclusion of Xue's and Li's work, they developed a novel approach to the 6,7,5-tricyclic skeleton of frondosin B based on an acid-catalyzed intermolecular [4+3]-cycloaddition. Completing their synthesis of (±)-frondosin B from commercially available 2-acetylbenzofuran **130**.

Winne's synthesis of (±)-frondosin B

The Winne group have been working toward [4+3]-cycloaddition strategies using furfuryl alcohols as precursors for furfuryl cations, showing that they are excellent three-carbon dienophiles to be reacted with a wide range of dienes. However, in doing so their synthesis was quite mimetic to that of the Xue/Li group in that they utilized the same intermediates benzofuran **131**, and diene **128** in their key cyclization, and preparing them to that in the same method.

The group initiated studies with a titanium(IV)chloride-promoted reaction between diene **128** and benzofuran-carbinol **131**, proving to be hard to control, as a large variation in the isolated

Scheme 1.25: Winne's synthesis of (±)-frondosin B: A concise [4+3] cycloaddition approach



yield was observed. Switching to the milder Lewis acid iron(III)chloride hexahydrate, a much cleaner reaction mixture was obtained, with the O-methyl frondosin B isomer **137** being isolated as a 1:1 mixture of C-11 epimers. The group saw that the major impurity was found to contain the bis-(adduct) structure **136** (obtained as a mixture of isomers). This result confirmed that the major competing reaction was that of a Friedel–Crafts-type benzofuran–carbinol oligomerization. Winne was finally able to find a set of conditions that produced cycloadducts **137** with a modest and reproducible yield using trifluoroacetic acid as the cation-generating reagent, 35% isolated yield (Scheme 1.27). However, this reaction had previously been optimized by Xue, Li, and co-workers up to a yield of 50% in their independent studies by using camphorsulfonic acid as a reagent (Scheme 1.26).

The Winne group completed their total synthesis of (±)-frondosin B following the literature procedure and subjecting the cycloadducts **137** to the action of boron tribromide giving deprotection of the methyl ether, and concomitant isomerization of the C5–C6 double bond to C5–C11 position. This completed the Winne group's synthesis of (±)-frondosin B, demonstrating the utilization of the [4+3] cycloaddition of furfuryl cations being used to prepare the tetracyclic framework of frondosin B.

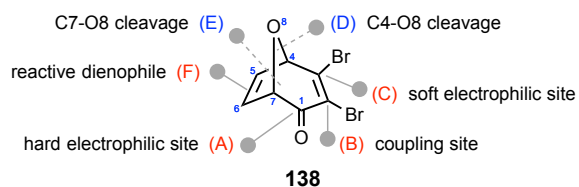
Summary and Conclusions

The first two syntheses of (+)-frondosin B by Danishefsky in 2001 and Trauner in 2002 produced conflicting assignments for the single stereogenic center at C8. These conflicting assignments of the C8 center prompted multiple subsequent asymmetric syntheses of frondosin B and frondosin A that led to the confirming Danishefsky's original assignment that (+)-frondosin B exists as the *R*-enantiomer. The deeper question extruding from this stereochemical controversy, was that there was an apparent inversion of stereochemistry that had occurred in the Trauner synthesis. The MacMillan group confirmed that a late stage chemical inversion was taking place during the Trauner synthesis and proposed a stereorelay mechanism, influenced by newly formed benzofuran C10 stereocenter, that would eventually lead to an *S*-configuration at C8 of frondosin B. The Wright group would propose an alternative inversion rationale, by carrying material, with a deuterium labeled C8 center, through to a late stage intermediate from the Trauner synthesis without inversion. Proposing a mechanism surrounding a ring contraction/expansion of a delocalized carbocation intermediate that ultimately led to inversion of the C8 center.

Natural Product Inspiration

Over the past several years, my research has focused on the synthesis of natural and non-natural small organic molecules with important biological activity; both as potential new therapeutics and complex molecules to survey interactions with biological systems. The complex and intricate structure of natural products and the wide range of biological activity associated with these compounds have motivated my synthetic efforts. Central to this work has been the oxabicyclo[3.2.1]octadiene **138** (Figure 1.8) adducts arising in a single step through formal [4+3] cyclocondensation of furans and suitably reactive dienophiles to enable rapid assembly of complex molecular building blocks. The work spent on these oxabicyclo[3.2.1]octadienes has exposed a rigid cycloheptenone backbone with functional utility at each of its seven carbons. Careful implementation of synthetic transformations allows for excellent regio- and stereochemical control over the course of synthetic elaboration. Our group's ability to effect cleavage, annulation, nucleophilic addition and rearrangement of these building blocks has allowed for the development of synthetic routes to the natural products frondosin A and B and analogs of both β -thujaplicin and platensimycin.

Figure 1.8: Elaboration on the utility of the dibromoenone building block

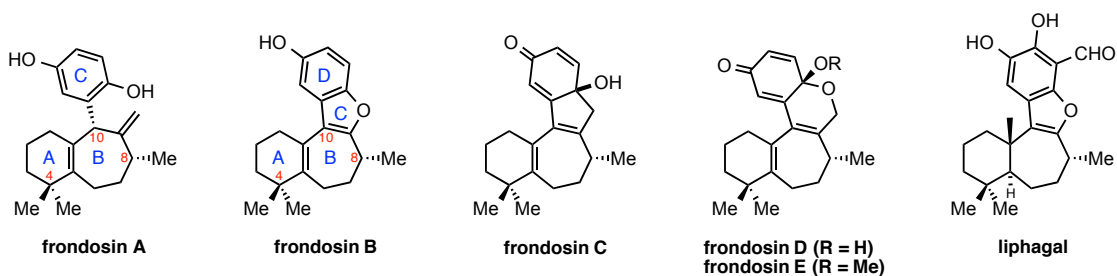


Frondosin A and B: Background and previous syntheses

Although the introduction of this work reviewed the current syntheses of the frondosins, it will be reiterated here to show their importance as natural product inspiration for my doctoral work. The marine-derived meroterpenoid natural products, frondosins A-E, were first isolated

from the marine sponge *Dysidea frondosa* in 1997 (Figure 1.9). Upon initial evaluation they were shown to exhibit significant inhibitory activity for the binding of the cytokine interleukin-8 (IL-8) to its receptor, CX-CLR1/2. The frondosins are structurally characterized as possessing a bicyclo[5.4.0]undecene core with significant structural diversity introduced through an annulated (frondosins B–E) or tethered (frondosin A) hydroquinone derivative. The structure of frondosin B is most reflective of the marine natural product liphagal as both incorporate an appended arene system in the form of a fused benzofuran motif. With liphagal showing impressive PI3K inhibition, the simplified structure of frondosin B was thought to be a promising lead-like natural product with an abridged synthetic design and a more appealing pharmacokinetic profile.

Figure 1.9: Meroterpenoid natural products



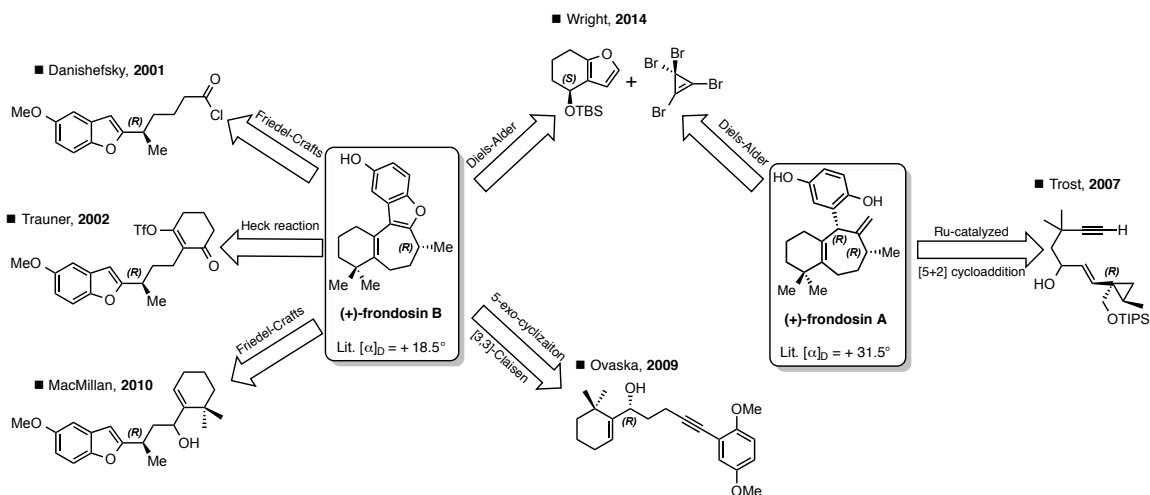
More attractive, is that several studies have associated IL-8 with various acute and chronic inflammatory conditions including sepsis syndrome, psoriasis, rheumatoid arthritis, gout, and asthma. Furthermore, various animal models of inflammation have established IL-8 as a principal leukocyte chemotactic factor directing neutrophil recruitment to and activation at the inflammatory focus. As such, the frondosins have gained interest as potential IL-8 receptor antagonists, a promising natural product target for the development of novel pharmacological agents against autoimmune hyperactivity.

With a host of biological implications surrounding IL-8 and the strong structural similarity to the potent PI3K inhibitor liphagal, frondosin B became a popular target for total synthesis, which ultimately led to assignment of the absolute stereochemistry. My synthetic interest in these complex natural products was excited with literature remarking that the first two syntheses of (+)-

frondosin B by Danishefsky in 2001 and (-)-Trauner in 2002 made a similar benzofuran (C10) disconnection yet produced conflicting assignments for the single stereogenic center at C8. These conflicting assignments of the C8 center prompted multiple subsequent asymmetric syntheses of frondosin B and frondosin A (Figure 1.10).

Succeeding asymmetric synthesis of; (+)-frondosin A by the Trost group in 2007, (-)-frondosin B by the Ovaska group in 2009, and (+)-frondosin B by the MacMillan group in 2010 gave evidence that C8 center of (+)-frondosin A and B existed as the R-enantiomer. It was not until 2010 that the MacMillan group sought to explain the discrepancy in the assignments, and proposed a scenario by which an unusual stereochemical relay mechanism during Trauner's key palladium-catalyzed cyclization caused a stereochemical inversion of the C8-center.

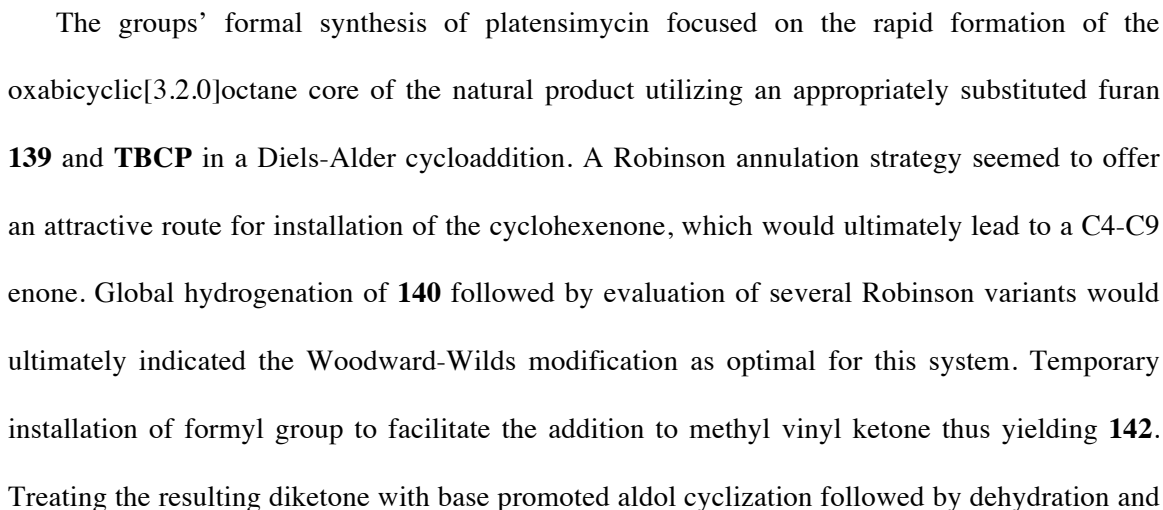
Figure 1.10: Asymmetric total syntheses of frondosin A and B: Key cycloheptane forming step



Interestingly, during the progression of our group's synthesis of (+)-frondosin B, we observed that the same stereochemical inversion as noted as in the Trauner system was seen in our synthesis. To investigate this result, we carried material with a deuterium labeled C8 center, through to a late stage intermediate from the Trauner synthesis without inversion. This result had therefore narrowed down the transformation where the inversion was thought to take place. We then proposed an inversion mechanism surrounding a ring contraction/expansion of a delocalized

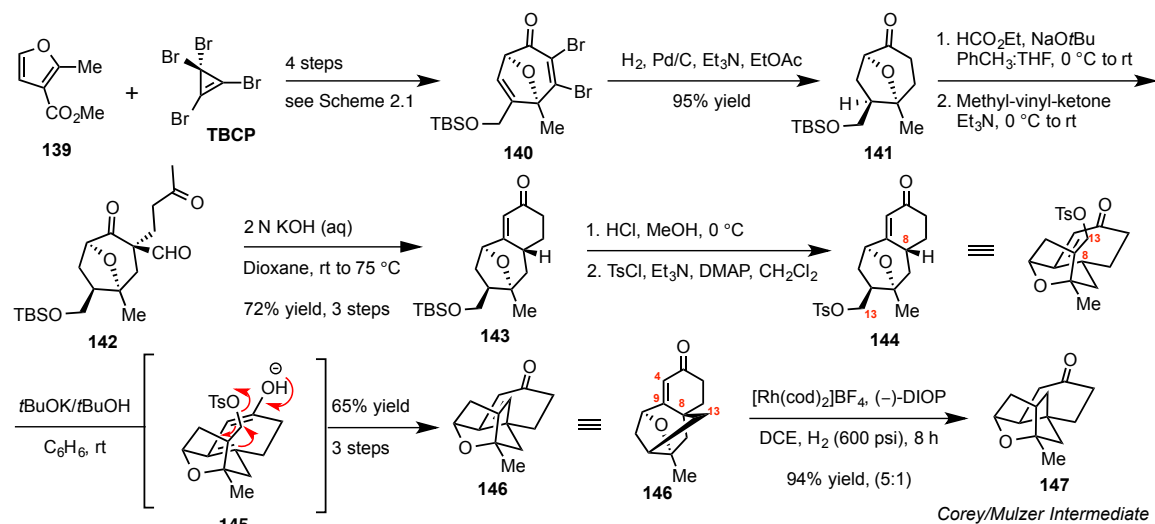
Platensimycin: Background and previous synthesis. Inspiration for analogous compounds

Figure 1.11: Platensimycin and platencin natural product



loss of the formyl group to produce the desired enone **143** in 72% overall yield from **139** and setting the stage for the formation of the final ring in the caged system (Scheme 1.26).

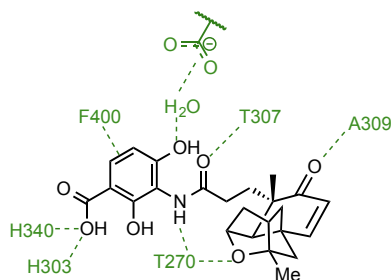
Scheme 1.26: Wright group's formal synthesis of platensimycin



The final ring to be formed would require the generation of a γ -enolate on the cyclohexenone ring followed by an intramolecular alkylation of a C13 electrophile. Initial removal of the silyl group was followed by routine conversion to the corresponding C13 tosylate **144**. We were excited to observe that exposure of **144** to *t*-butoxide triggered the desired transannular cyclization to give ketone **146** in excellent overall yield. The final key transformation necessary to complete the formal synthesis was controlled reduction of the enone to correctly set the C9 stereogenic center. Similar dienone studies by Mulzer.^{49m} Corey^{49j} and Mulzer and Pfaltz^{49t} had both reported that chiral hydrogenation catalysts were effective at mediating these reductions and could impart high levels of control at the C9 stereocenter. Employing the same chiral rhodium catalyst for **146** gave **147** in a 5:1 diastereomeric ratio which matched the reported spectral information from Corey.

With a less than ideal pharmacokinetic profile, researchers have been focused on improving the drugs medicinal chemistry profile with structural modifications to the polar benzoic acid subunit and the tricyclic lipophilic cage. However, these efforts fell short will all

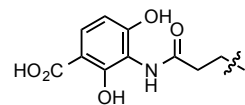
Figure 1.12: Platensimycin interactions with mutated target enzyme ecFabF(C163Q)

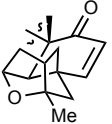
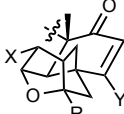
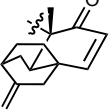
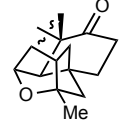

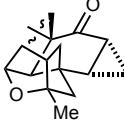
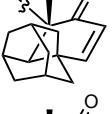
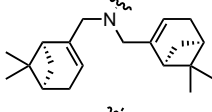
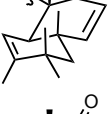
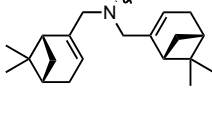
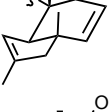
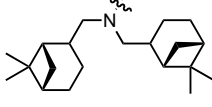



compounds expressing diminished biological results as compared to the natural product. An X-ray crystal structure of platensimycin in a complex with a mutant version of the FabF enzyme showed that these modified regions contained crucial drug-enzyme interactions (Figure 1.12).

Only a few synthetic efforts have been made towards singly altering the cyclohexenone ring, mainly based on prohibitive synthetic methods (Table 1.1). However, the chemistry developed for our platensimycin synthesis is quite amenable to alteration of this region of the natural product. Interestingly, it is clear that the carbonyl oxygen has significant interactions with A309 of the enzyme pocket crucial to the drugs efficacy; yet a majority of the poor pharmacokinetics are derived from this enone's disposition as a strong Michael acceptor. More so, analogs containing a saturated C6-C7 were shown to have poor efficacy as well, mostly likely due to a more flexible ring system. With this in consideration, we propose the synthesis of a preliminary series of compounds to answer two questions: a) Could we remove the cyclohexenone ring and use an acyclic extender to connect to the polar head group and still maintain high levels of biological activity? b) Could the cyclic enone of platensimycin be replaced with aza-rings to create a bioisostere compound? With new methodology developed for the stereodivergent resolution of the early intermediate in this synthesis, we also propose to make these analogs asymmetrically to further mimic the natural product.

Table 1.1: Minimum Inhibitory Concentration values ($\mu\text{g mL}^{-1}$) of platensimycin and biologically relevant analogs against Methicillin-resistant *Staphylococcus aureus* (MRSA) and Vancomycin-resistant *Enterococcus faecium* (VRE)



Reference	Compound	MRSA	VRE	Reference	Compound	MRSA	VRE
49a		0.2-0.4	0.01	53	 a: R=Ph, X=Y=H b: R=Me, X=H, Y=Me c: R=Me, X=H, Y=Ph d: R=Me, X=Me, Y=Ph	4 2 0.5 <0.25	≤0.5 ≤0.5 ≤0.5 ≤0.5
50		1	<0.06	54		2	NT
51		1.1-2.2	1.1-1.2	54		1	NT
49c		1.3-1.8	1.3-1.8	55		16	16
52		3.5-4.3	6.5-8.6	55		16	8
52		8.0-10	>80	55		32	32
52		17-20	>83				

NT = not tested

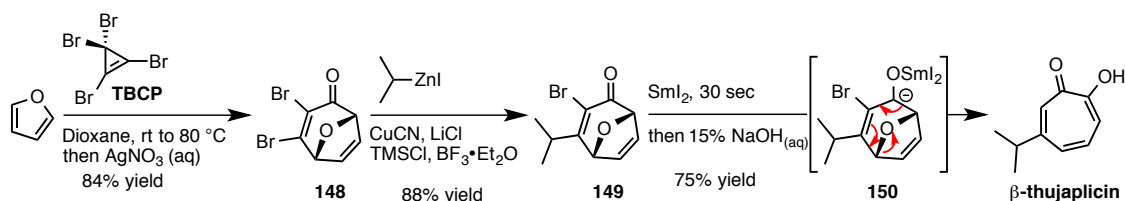
β -Thujaplicin: Background and previous synthesis. Inspiration for α -substituted tropolones as lead-like compounds

Natural products have long served as a rich source of drugs for a variety of indications ranging from anticancer to antimicrobial to neurological disorders. For the most part, natural products are commonly characterized as structurally complex molecules with a high molecular weight and potency with limited positions for structural alterations. The thujaplicins, members of the tropolone family of natural products, have set themselves apart from these complex,

unadaptable molecules and can be regarded as lead-like natural products. β -Thujaplicin (hinokitiol) is characterized by low molecular weight (MW = 164) and a simplified level of complexity, allowing for widespread structural adaptation. Thujaplicins are monoterpene natural products isolated from the heartwood of trees in the Cupressaceae family⁵⁶ that are associated with antiproliferative activity.⁵⁷ There have been few attempts to utilize these lead-like compounds in drug discovery, perhaps impaired by prohibitive synthetic methods in accessing these non-benzenoid aromatics.

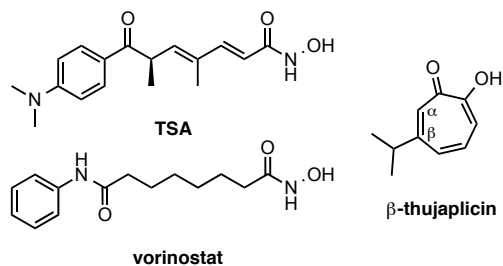
Unique to the tropolone moiety is the tendency for strong chelation of metal ions, which is questionably the foundation of biological activity for these compounds.^{57b} Substituted tropolones have emerged as an fascinating molecular architecture for the development of inhibitors of metalloenzyme drug targets. Thusly, we have directed our efforts at utilizing β -thujaplicin (Scheme 1.27) as a lead-like natural product to develop a novel class of inhibitors of histone deacetylase, a validated target in the treatment of cancer.⁶³

Scheme 1.27: Wright group's total synthesis of β -thujaplicin



Of the 18 HDAC isoforms, 11 are metalloenzymes that utilize zinc to remove a terminal acetyl group from lysine residues present in histones and other common proteins. The reversible acetylation and hydrolysis of the ϵ -acetamide in histones is associated with regulation of gene expression. Interestingly, there are a variety of natural products that inhibit HDACs such as trichostatin A (TSA), romidepsin, and trapoxin.⁵⁹ Both romidepsin and vorinostat were approved by the FDA for the treatment of cutaneous T-cell lymphoma; the latter possesses a zinc-targeting hydroxamate, similar to TSA (Figure 1.13).

Figure 1. 13: Vorinostat and the natural product, TSA, inhibit HDACs; β -thujaplicin as a lead-like natural product



Hydroxamates have been infamously labeled for their poor metabolic stability, synthetic substrates such as vorinostat suffer from relatively short metabolic half-life indebted to an easily reduced N–O bond, a hydrolytically labile amide linkage and the formation of glucuronides.⁶⁰ Therefore the development of an alternative class of HDAC inhibitors based on tropolones may have a significant impact on this metabolic profile. Whereby, the metal-chelating moiety of the tropolone scaffold can be viewed as an extended vinylogous carboxylic acid^{60a} and would not be subject to reductive or hydrolytic transformations.

More appealing, is that the tropolone scaffold provides a simplified core that is amenable to selective structural modifications allowing for synthetic elaboration to access pockets near the metal-binding site and hopefully conveying isozyme selectivity. Isozyme selectivity is believed to be associated with increased efficacy and lower toxicity,⁶¹ and although some hydroxamate-bearing compounds show some selectivity,⁶² most are considered to be pan-HDAC inhibitors, exhibiting some associated toxicity potentially related to the inhibition of the many of the HDAC isozymes.⁶¹ Based on structural analysis of HDACs,⁶³ a hydrophobic pocket near the bound Zn^{2+} ion has revealed itself as an ideal point for the synthetic incorporation of lipophilic substituents to pick up interaction near this presumed metal-binding headgroup. With this in mind, an initial series of monosubstituted tropolones were prepared, focusing on placing small lipophilic substituents at the α -positions in an attempt to obtain favorable interaction in this enzymatic region. Herein, we describe tropolones that function as potent inhibitors of the HDAC enzyme and display significant cytotoxicity against T-lymphocyte cancer cell lines.

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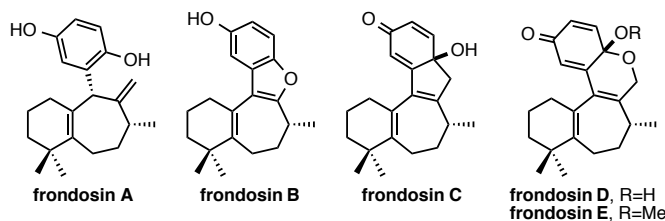
CHAPTER TWO

RESULTS AND DISCUSSION

Asymmetric total synthesis of (+)-frondosin A

Over the past decade, an interesting family of meroterpenoid natural products have emerged from marine sources characterized by a bicycle[5.4.0]undecane system containing either an annulated (frondosins B-E) or tethered (frondosin A) hydroquinone derivative. Following the isolation of the frondosins in 1997 from the Micronesian sponge *Dysidea frondosa*,¹ researchers saw that the extracts exhibited significant inhibitory activity for the binding of cytokine interleukin-8 (IL-8) to its receptor, CX- CLR1/2.²

Figure 2.1: Frondosin natural products

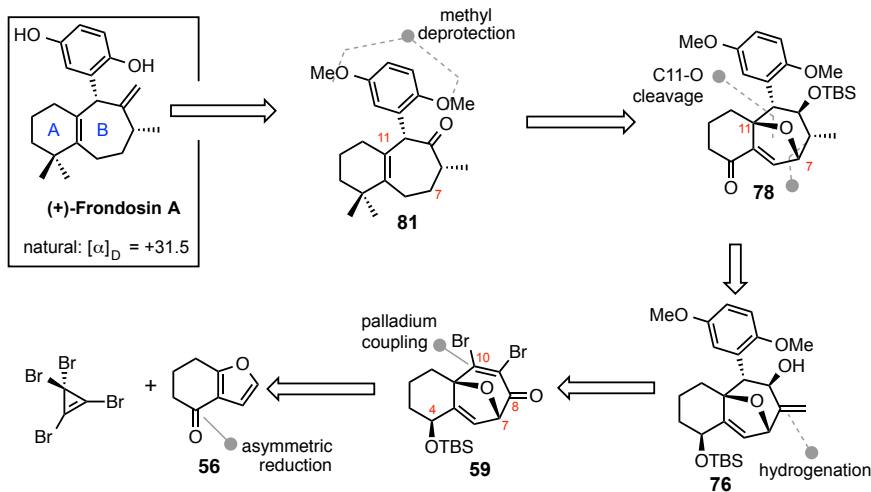


This project came about not only due the unique structural features or therapeutic potential of frondosin A, but also to supplement the total synthesis of both enantiomers of frondosin B accomplished by our lab. Over the years there has been much uncertainty concerning the absolute stereochemistry of (+)-frondosin B, with total syntheses by the Danishefsky and Trauner groups consisting of conflicting optical rotations.^{3,4} Our group's synthesis of (+)-frondosin B added additional understanding, as an unprecedented late stage stereochemical inversion was observed. As a strategy to confirm this inversion, we set out from an early intermediate of the frondosin B syntheses to see if we could accomplish the total synthesis of (+)-frondosin A without this unusual inversion.

Our retrosynthetic strategy targeted late stage intermediate **81**, containing the intact carbocyclic framework of the natural product and corresponding to the structure of a previously synthesized racemic intermediate by the Ovaska group (Scheme 2.1). Intermediate **81** was

thought to arise from manipulations of the tricyclic framework embodied in **78**, focusing on a previously developed phosphine-mediated cleavage of the temporary bridging ether spanning C7-C11 of the B-ring and transformation of C4 carbonyl to a geminal dimethyl moiety. It was envisioned that the absolute stereochemistry at C8 could be established via directed hydrogenation of allylic alcohol **76** and that the C4 protected alcohol would serve as a suitable placeholder for the ensuing carbonyl.

Scheme 2.1: (+)-Frondosin A retrosynthetic analysis

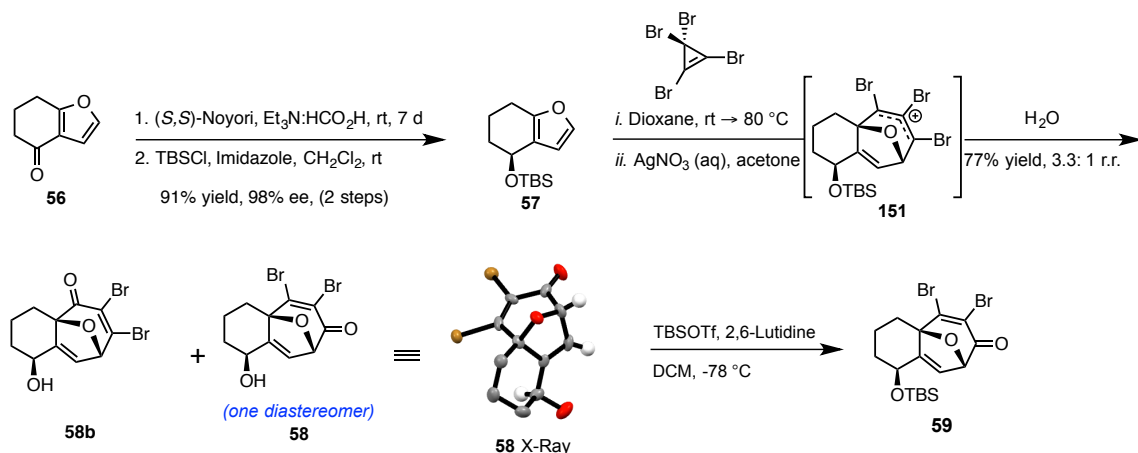


Complex intermediate **76** requires a highly functionizable starting material that was thought to come about through exploitations of dibromoenone **59**. The soft electrophilic β -vinyl bromide of the α,β -unsaturated enone of **59** provides a favorable target for palladium catalyzed reactions to incorporate the necessary aryl functionality. Additionally, the embedded oxabicyclo[3.2.1]octadiene core of **59** imparts significant concavity to the molecule, allowing our synthetic route to exploit considerable facial-selectivity and controlling diastereoselective addition of incoming functionality. The commercially available ketone **56** seemed an ideal starting point, and in fact, the asymmetric reduction of **56** to the R-alcohol had been previously reported by Noyori.^{7a}

The highly functional dibromoenone **59** is the product of a diastereoselective cycloaddition between tetrabromocyclopropene (TBCP) and an annulated furan derivative such as **57**. TBCP is readily available in a one step transformation from the commercially available tetrachlorocyclopropene, by reaction with boron tribromide. We have worked considerably with the TBCP adducts of simple substituted furans⁵ but had not previously attempted to extend this formal [4 + 3] cycloaddition to annulated furans such as **57**. Although the analogous reaction between annulated furans and oxyallyl cations are known to be difficult, with simple electrophilic substitution products arising, it was hoped that the high reactivity of TBCP toward Diels-Alder reaction with furan would have the ability to overcome the increased steric demands.⁶ Moreover, we were attracted to the notion that an asymmetric center at C4 of the A-ring could control the diastereoselectivity of the cycloaddition and that the information could be relayed throughout the synthesis to manipulate functionality in a diastereoselective manner.

In this approach to key building block **59**, we employed a single asymmetric step to effect the diastereoselective total synthesis. The commercially available ketone **56** seemed an ideal starting point and we initially prepared the requisite alcohol with reasonable selectivity (88% ee) through reduction of ketone **56** with the (R)-(+)-2-methyl-CBS-oxazaborolidine catalyst. This reduction

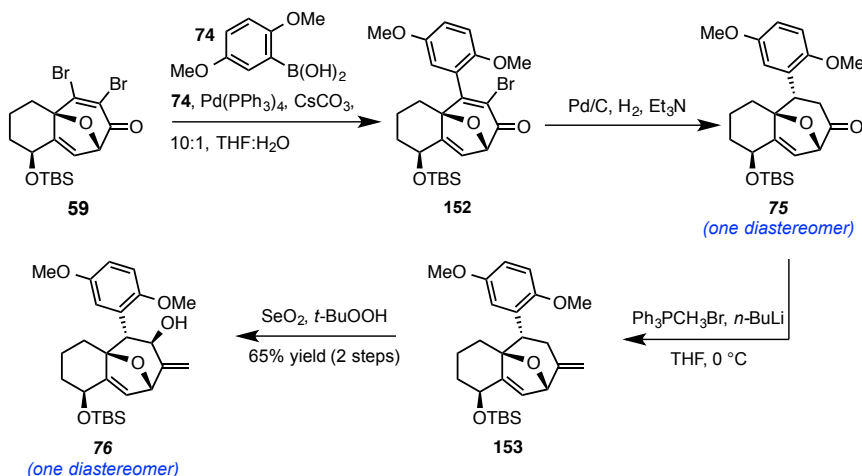
*Scheme 2.2: Diels-Alder reaction between annulated furan **57** and TBCP: X-ray crystallographic confirmation of stereochemistry*



was not amenable to a large-scale production due to the cost of the catalyst and difficult purification. Further investigation into this reduction showed that the alcohol could be produced in 98% ee with the utilization of the (*S,S*)-Noyori transfer hydrogenation catalyst (Scheme 2.2).^{7b} The reduction was much more cost effective with only a 1% catalyst load and with a significant increase in enantiomeric excess.

The alcohol was converted to the silyl ether **57** and condensed with TBCP to give a mixture of regioisomeric tetrabromides in excellent overall yield. Pleasingly, the facial selectivity was high with the C4-silyoxy group exerting a strong directing effect on the initial Diels-Alder reaction leading to a *syn*-relationship between the protected alcohol and the oxa-bridge. The bridgehead substitution at C11 provided a reasonable directing effect, which favored the formation of **58** as the major diastereomer (d.r. 3.3:1), with the standard silver-promoted hydrolysis of the tetrabromides.

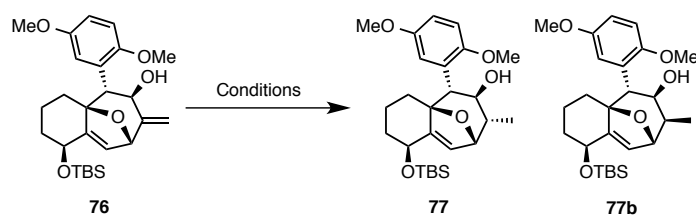
Scheme 2.3: Diastereoselective introduction of exocyclic functionality



Previous studies on this key intermediate demonstrated that the two vinylic bromides of **59** displayed substantially different levels of activity, allowing Suzuki-Miyaura cross-coupling of **59** with dimethoxyphenyl boronic acid to occur exclusively at the more electron deficient β -bromide to deliver the *dimethoxy*-hydroquinone **152** in an efficient manner (Scheme 2.3). We anticipated

that it should be possible to exploit the curvature embedded in the oxabicyclo[3.2.1]octadiene core of **152** to control the facial selectivity of incoming functionality and set the absolute stereochemistry of the natural product. With this in mind, hydrogenation of **152**, in the presence of triethylamine, effected reduction with complete facial selectivity; with palladium coordinating from the less encumbered *exo*-face to correctly set the C10 center of **75**.⁸ Further exploiting the facial bias that the temporary ether bridge provided, Wittig condensation gave exocyclic methylene **153** derivative that when subject to allylic oxidation conditions with SeO₂ to provided alcohol **76** with high diastereoselectivity, in a 97:3 mixture of *exo:endo* allylic alcohols.⁹ It was theorized that an *exo*-alcohol at C9 could serve as a suitable surrogate for the exocyclic olefin present in the natural product but also as a directing group for the stereoselective introduction of the C8 methyl group of frondosin A.

Table 2.1: Diastereoselective reduction of **76 with various hydrogenation conditions**



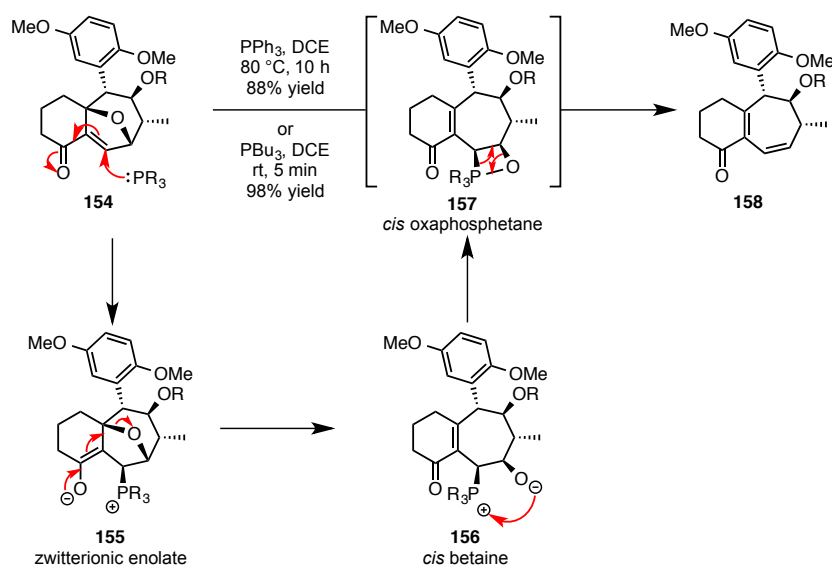
conditions	77:77b	% yield
Pd/C (10 mol %), EtOAc (0.1 M), H ₂ (1 atm)	4:1	98%
PtO ₂ (20 mol %), C ₆ H ₆ (0.1 M), H ₂ (1 atm)	4:1	96%
Crabtree's catalyst (20 mol%), CH ₂ Cl ₂ (0.05 M), H ₂ (1 atm)	5:1	94%
[Rh(nbd)(diphos-4)]BF ₄ (20 mol %), THF (0.1 M), H ₂ (600 psi)	10:1	98%
[Rh(nbd)(diphos-4)]BF ₄ (2.5 mol %), THF (0.1 M), H ₂ (600 psi)	3:1	98%
[Rh(nbd)(diphos-4)]BF ₄ , THF (0.05 M), H ₂ (600 psi)	20:1	98%
[Rh(nbd)(diphos-4)]BF ₄ , THF (0.025 M), H ₂ (600 psi)	>99:1	98%

Although it was assumed that the *exo*-alcohol in **76** would participate in a directed hydrogenation adding hydrogen in an *exo*-mode to produce the *endo*-methyl group at C8. We initiated studies to probe the natural preference for hydrogenation, subjecting alcohol **76** to hydrogenation in the presence of Pd/C and PtO₂ at 1 atmosphere of H₂ pressure (Table 2.1). In both cases, a high yielding reduction occurred to give a 4:1 mixture of diastereomers **77:77b**,

expressing the directing effect that the oxy-bridge was still imparting on the system. However, not satisfied with this diastereomeric ratio we explored a stronger hydroxyl-directed hydrogenation, exposing **76** to Crabtree's catalyst¹⁰ (20 mol%) at 1 atmosphere of H₂ pressure. Surprisingly, this catalyst had little effect on the product ratio giving only a slightly improved 5:1 mixture of diastereomers in good yield. With the ability to conduct hydrogenations at elevated pressure, the [Rh(nbd)(diphos-4)]BF₄ catalyst was employed at 600 psi of H₂ pressure.¹¹ Interestingly, it was found that a higher catalyst load (20 mol %) was needed to achieve at 10:1 mixture as the initial 2.5 mol % of catalyst gave only a 3:1 mixture of diastereomers. Furthermore, it was found that the concentration of the reaction had a dramatic effect on the diastereomeric ratio. Performing the reaction at 0.05 M in THF produced a 20:1 mixture, while further dilution (0.025 M in THF) led to a completely diastereoselective hydrogenation producing **77** exclusively in high yield.

With appropriate stereocenters of frondosin A installed, the stage was set for the cleavage of the temporary bridging ether. We extrapolated from our earlier studies on the ether bridge opening as intended for frondosin B, that **154** would be an ideal substrate on which to effect an

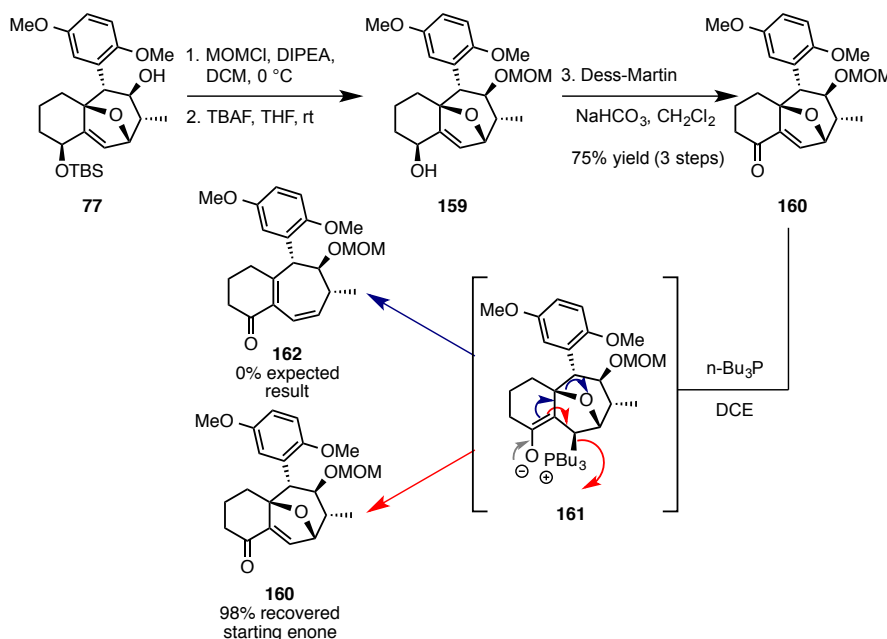
Scheme 2.4 Proposed phosphine mediated ring-opening mechanism



addition/elimination sequence with a trialkylphosphine nucleophile. A probable mechanism for this deoxygenation, akin to the phosphine induced reduction of epoxides to olefins, involves an initial conjugate addition of the phosphine to the more accessible *exo*-face of **154** to produce an initial enolate **155** followed by ejection of the β -disposed ether.¹² The elimination yields a transient betaine intermediate **156** that collapses through the intermediacy of the oxaphosphetane **157** to deliver the desired olefin **158** (Scheme 2.4).

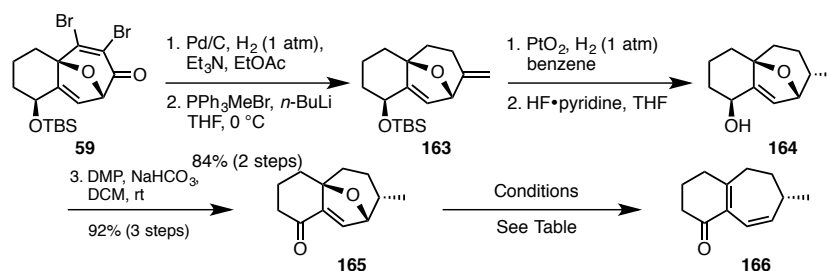
Initially, we were attracted towards a chemoselective allylic oxidation at C4 in the presence of MnO₂ to selectively construction intermediate an intermediate such as **154**. Unfortunately, after a multitude of attempts the desired enone product was never formed, returning only starting alcohol. Refocusing our efforts to generate intermediate **154**, we produced two chemically different protected alcohols for selective deprotection at the C4 alcohol. Protection of the C9 alcohol of **77** as its MOM ether derivative was followed by deprotection of the silyl ether and Dess-Martin periodinane (DMP) oxidation of the resulting C4 allylic alcohol **159** to give enone **160**. (Scheme 2.5).

Scheme 2.5: Initial attempts at ring cleavage with MOM protected enone 160



Enone **160** represented the first appropriate intermediate to probe the effectiveness of the phosphine-mediated ring opening/elimination procedure to deliver diene **162**. However, it was found that the system was not predisposed toward the addition of phosphine reagents. Addition of triphenyl- or tributylphosphine at either room temperature and elevated temperature did not produce the desired ring opened product and the starting enone was recovered unchanged. Prolonged reaction times at elevated temperatures delivered an unidentifiable compound that appears to contain a new phosphine-carbon bond with the ether bridge still intact. We assumed that 1,4-addition of phosphine to the enone occurs rapidly producing zwitterionic enolate **161**, however the resulting enolate simply releases the phosphine to produce starting material (red arrow) rather than ejecting the β -disposed ether (blue arrow).

Table 2.2: Model system: Trends in phosphine mediated ring-opening of 164



entry	phosphine ^a	Lewis acid ^b	solvent / temp	yield 165 ^c	yield 166 ^c
1	<i>n</i> -Bu ₃ P	--	DCM / 23 °C	98%	--
2	<i>n</i> -Bu ₃ P	--	DCE / 90 °C	70%	--
3	<i>n</i> -Bu ₃ P	InCl ₃	DCM / 23 °C	80%	--
4	<i>n</i> -Bu ₃ P	InCl ₃	DCE / 90 °C	--	--
5	<i>t</i> -Bu ₃ P	--	DCM / 23 °C	98%	--
6	<i>t</i> -Bu ₃ P	--	THF / 140 °C	66%	--
7	<i>t</i> -Bu ₃ P	InCl ₃	THF / 70 °C	10%	--
8	Me ₃ P	InCl ₃	DCM / 23 °C	--	25%
9	Me ₃ P	InCl ₃	DCE / 90 °C	--	55%
10	Me ₃ P	BF ₃ •Et ₂ O	DCE / 90 °C	--	88%
11	Me ₃ P	Ti(O <i>i</i> pr) ₄	DCE / 90 °C	--	85%

^a 3 equivalents of trialkylphosphines used in all reactions. ^b 6 equivalents of Lewis acid used unless otherwise stated. ^c Isolated yield.

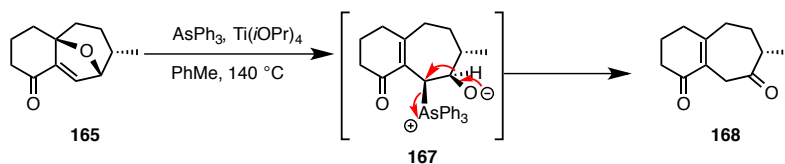
We employed a simplified model system to probe the effectiveness of the phosphine-mediated ring opening and to determine conditions necessary to effect cleavage (Table 2.2). Intermediate **59** was advanced to **166** by the series of: a) Hydrogenation of the C6-C7 olefin; b)

Wittig condensation of the C8 carbonyl producing exocyclic olefin **163** c) Hydrogenation of the newly produced methine moiety, with Adam's catalyst; d) Deprotection of the C4 silyl group in the presence of HF•pyridine to produce allylic alcohol **164**; e) Oxidation of the resulting allylic alcohol with DMP to give a **165** with complete diastereoselectivity through this series of steps.

With enone **165** in hand, it was initially observed that trialkylphosphines alone could not effect ring opening in these less strained systems. As seen in table 2.2 a series of trialkylphosphine reagents were explored, all returning starting material (entries 1 and 5). As seen earlier, prolonged reaction times at elevated temperatures delivered an unidentifiable compound that appears to contain a phosphine-carbon bond and with starting material being recovered in lower yields (entries 2 and 6).

Traditionally, Lewis acids have been employed to facilitate the opening of similar oxabicyclic intermediates and it was thought that this case might react similarly.¹³ With this in mind, we began to methodically pair Lewis acids with a series of trialkylphosphine reagents. Initial results were poor, with a variety of Lewis acid / phosphine combinations still falling short with no reactivity (entry 3), or at higher temperatures decomposition of material (entries 4 and 7). It was not until we paired the highly reactive, trimethylphosphine (Me_3P) with In(III)Cl that a productive ring-opening / elimination occurred (entry 8). Optimization of this ring opening unveiled that increased temperatures were required (entry 9) and that combination with more reactive Lewis-acids (entries 10 and 11) provided a ring-opened product **166** in acceptable yield.

*Scheme 2.6: Diketone **168** as a result of ring-opening attempt with Ph_3As nucleophile*



Interestingly, while working with our model system **165** we stumbled upon an interesting variation while screening Ph_3As with a panel of Lewis acids, whereby addition of Ph_3As

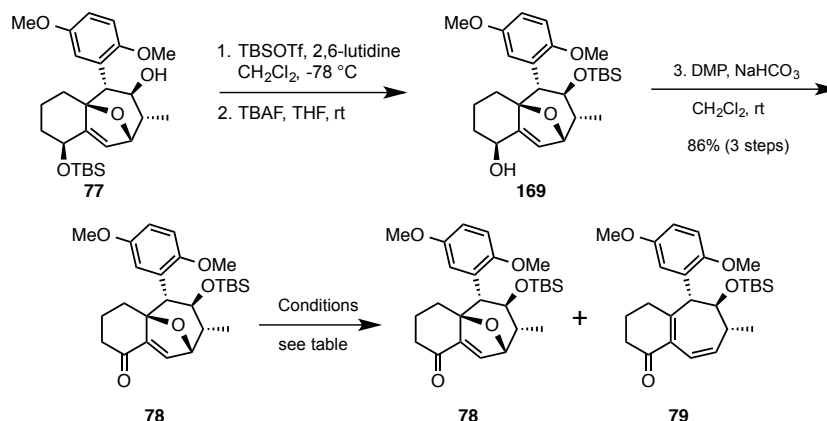
produced a ring-opened diketone product **168** in reasonable yield (Scheme 2.6). It appeared that Ph_3As added in the usual *exo*-mode to produce an enolate (**167**) that upon collapse generated oxide **168**. Given the *syn*-relationship of the oxide to the arsenic the working mechanism involves a 1,2-hydride shift following formation of the carbonyl to expunge the arsenic group. This result was interesting to us as it not only served as a productive method for cleavage of the bridging ether but it would also allow for a viable “chemical handle” for further analog generation.

Returning to our intended system, when enone **160** was exposed to a mixture of InCl_3 and Me_3P , a productive ring-opening/elimination reaction occurred, however the isolated yield was only 15% with about 10% of the unidentified phosphine product seen before. More undesirably, we were unable to account for the mass balance of the reaction mixture, as only ~25% of the material was recovered. A screen of Lewis acids determined that more reactive Lewis acids ($\text{Ti}(\text{O}i\text{pr})_4$, $\text{BF}_3 \cdot \text{Et}_2\text{O}$, AlCl_3) lead to decomposition of bridged material, most likely through deprotection and elimination of the MOM ether. Unsatisfied with these yields it was suspected that that MOM protecting group was not durable enough to withstand the Lewis acid conditions necessary for the desired transformation.

Resuming with intermediate **77** we quickly learned the C9 alcohol was significantly shielded by the proximal arene at C10 and that the bulky silyl (TBDPS, TIPS) or ester groups (PIV) needed to withstand the Lewis acid conditions could not be produced in acceptable yield. However, silylation with TBSOTf provided a disilyl product in excellent yield and to our delight the C4 allylic silyl ether could be selectively deprotected, owing to steric differences, in the presence of tetra-*n*-butylammonium fluoride (TBAF) to produce allylic alcohol **169** in good yield (Scheme 2.7).¹⁴

Oxidation of **169** utilizing DMP conditions provided intermediate **78**. The robust TBS protecting group allowed for a screen of several Lewis acid trialkylphosphine combinations. Scheme 2.7 demonstrates a trend in the trialkylphosphines whereby increasing nucleophilicity of

Scheme 2.7: Trends in phosphine mediated ring-opening of **78**



entry	Lewis acid ^a	phosphine ^b	solvent / temp	yield 78 ^c	yield 79 ^c
1	--	<i>n</i> -Bu ₃ P	DCE / 80 °C	56%	--
2	InCl ₃	<i>n</i> -Bu ₃ P	THF / 70 °C	--	25%
3	InCl ₃	Me ₃ P	THF / 70 °C	--	55%
4	Ti(O <i>i</i> Pr) ₄	<i>n</i> -Bu ₃ P	THF / 70 °C	--	62%
5	Ti(O <i>i</i> Pr) ₄	<i>t</i> -Bu ₃ P	THF / 70 °C	--	70%
6	Ti(O <i>i</i> Pr) ₄	Me ₃ P	THF / 70 °C	--	77%
7	Ti(O <i>i</i> Pr) ₄ ^d	Me ₃ P	THF / 70 °C	--	86%

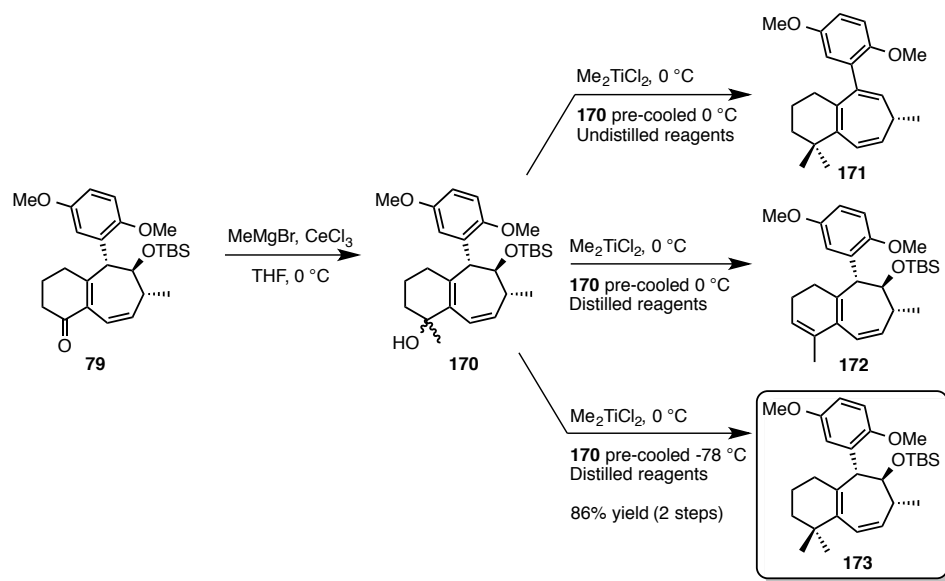
^a 6 equivalents of Lewis acid used unless otherwise stated. ^b 3 equivalents of trialkylphosphines used in all reactions. ^c Isolated yield. ^d Performed with 3 equivalents of Lewis acid.

the phosphine greatly impacts the isolated yield of ring-opened diene **78**. Treatment with Me₃P in the presence of In(III)Cl showed improved results (55% yield) but seemed to form a complex with the indium salts that could not be broken up to give desired product. However, it was apparent that the grouping of Me₃P and Ti(*i*OPr)₄ was the far superior combination to effect the desired result. With a short string of reactions to optimize the reaction conditions we were able to produce ring-opened/elimination diene **79** in a satisfying 86% yield.

Following conversion to diene **79**, our initial inclination was to saturate the C6-C7 olefin of **79**, reducing the likelihood of olefin isomerization thus eliminating the C8 chiral center. Attempts to hydrogenate were unsuccessful most likely because of the cross conjugation imparted on the diene by the C4 carbonyl. Traditional hydrogenation catalysts (Pd/C and PtO₂) resulted in a nonselective reduction of both alkenes, whereas homogenous catalysts (Wilkinson's and Crabtree's) returned only starting material.

Transformation of the C4 carbonyl to the necessary geminal dimethyl group would eliminate the cross-conjugation and allow for a selective saturation of the less substituted C6-C7 alkene. It was intended that compound **79** would be advanced with a modified 2-step procedure employed by Trauner group in their frondosin B synthesis (Scheme 2.8).^{4c,d,15} However, installation of the geminal dimethyl group proved to be more sensitive than described in that system. The C9 silyloxy was quite susceptible to elimination, producing **171** and required the use of freshly distilled reagents at the highest purity to effect the transformation and obtain optimal yields. Along the same lines the C4 dehydration product **172** was a major impurity and optimization of this procedure showed that pre-cooling **170** to -78 °C and adding it to a 0 °C solution of Me₂TiCl₂ completely suppressed elimination product **172** that was seen at higher temperatures, producing **173** in optimal yields.

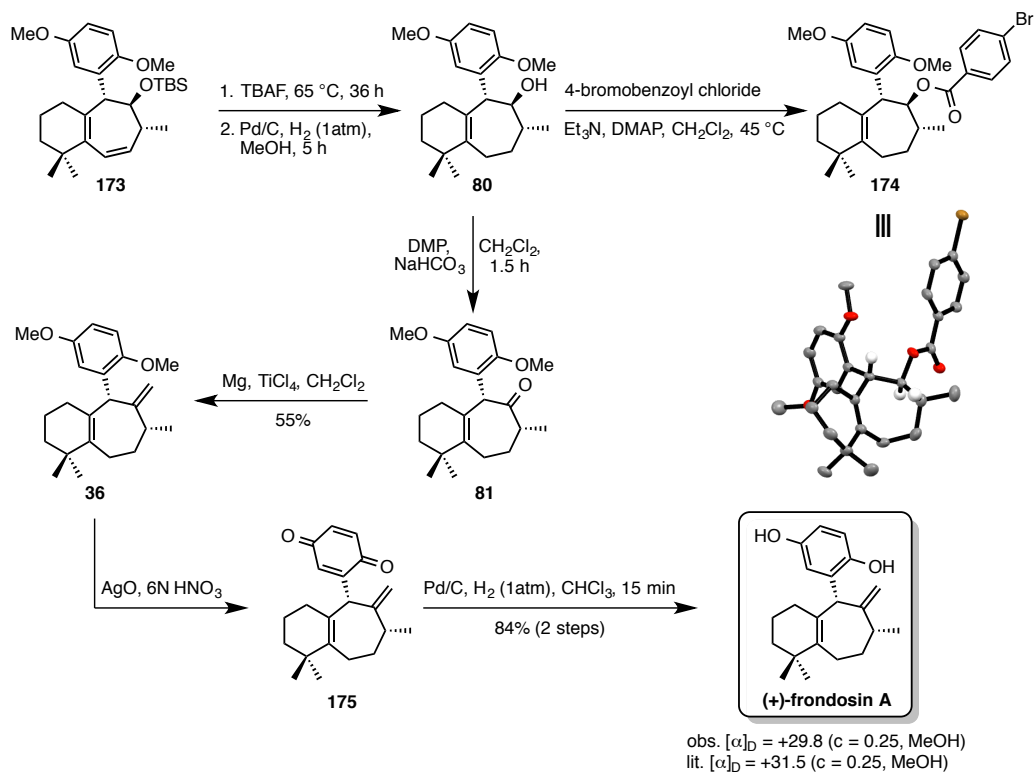
Scheme 2.8: Transformation of enone 79 to geminal dimethyl moiety



Deprotection of **173** in the presence of TBAF at elevated temperature followed by traditional hydrogenation conditions (Pd/C, MeOH, 1 atm H₂) proceeded without complications to produce intermediate **80** in a 61 % yield through this string of steps (Scheme 2.9). The three contiguous

chiral centers of alcohol **80** provided us with an ideal intermediate to validate the absolute stereochemistry. Alcohol **80** was condensed with 4-bromobenzoyl chloride to generate highly crystalline benzoate **174** that produced thin plate crystals in a simple diffusion method. X-ray crystallographic analysis of **174** allowed for the unambiguous assignment of the absolute stereochemistry confirming our diastereomeric synthesis with centers 8-(R), 9-(S), 10-(R).¹⁶ Alcohol **80** was oxidized with DMP to late stage intermediate **81** matching the spectral data reported by the Ovaska group.^{2b}

Scheme 2.9: Completion of the total synthesis of (+)-frondosin A: X-ray crystallographic confirmation of absolute stereochemistry



Having matched the Ovaska intermediate, it was still necessary to produce exocyclic alkene **36** to match the optical rotation of this common asymmetric intermediate with that reported by Trost. A variety of olefination procedures (Wittig, Petasis, Tebbe) were employed to effect the transformation to exocyclic alkene **36** but only returned unreacted starting material. The desired

olefination of the hindered B ring carbonyl carbon was then generated by applying the bimetallic $\text{TiCl}_4\text{-Mg}$ promoted methylene transfer reaction to fabricate *di-methoxy*-frondosin A in a 55% yield.¹⁷ Reports of deprotection of **36** with BBr_3 are known to result in decomposition while reports of deprotection with sodium ethanethiolate only yielded monodeprotected products. Initial attempts at final deprotection of the dimethoxy-arene **36** with $\text{CAN} / \text{Na}_2\text{S}_2\text{O}_4$, as disclosed in previous total syntheses of frondosin A, resulted in a less than effective deprotection with only around 35% recovered product. A significant improvement was made through a two-step oxidative (AgO , HNO_3) / reductive (Pd/C , H_2) procedure to provide the enantiomerically pure frondosin A in a 84% yield over the two steps and possessing optical rotation reflective of the natural product $[\alpha]_{\text{D}}^{22} = +29.8$ ($c = 0.25$, MeOH); lit. $[\alpha]_{\text{D}} = +31.5$ ($c = 0.25$, MeOH).¹⁸

Table 2.3. Inhibition of cell growth

72 hour (GI_{50} Values in μM)				
Cell Type	Cell Line	(+)-Fro A	(+)-Fro B	O-methyl-(+)-Fro A
B Cell	Daudi	2.62	N/A	N/A
	CH12	2.05	N/A	N/A
	Ba/F3 WT	4.49	N/A	N/A
	Ba/F3 WT mut IL7R (88i)	0.87	N/A	N/A
	Ba/F3 WT mut IL7R (GCins)	1.58	N/A	N/A
T Cell	HuT 78	17.23	N/A	N/A
	Jurkat	23.73	N/A	N/A
	Molt-4	25.65	N/A	N/A
Myeloid	K562	N/A	N/A	N/A

N/A = Not active at $33 \mu\text{M}$.

As the frondosins were suggested to exhibit inhibitory action on signaling through IL-8 receptor in blood cells, we evaluated both (+)-frondosin A and (+)-frondosin B (synthesis not shown)¹⁹ for effects on proliferation of a panel of leukocytes (Table 2.3).²⁰ At this point, I would like to give a special thanks to Jin Li and the Wiemer lab for conducting these biological studies. They were able to show that (+)-Frondosin A, but not frondosin B, inhibited proliferation of lymphocytic cell lines suggesting the necessity of the free hydroquinone moiety for activity. This

was further supported by the finding that the dimethyl ether analog of frondosin A (**36**) was also inactive toward the cell lines. The potency of (+)-frondosin A was an order of magnitude higher for B cell lines compared to the T-cell lines that were tested. Surprisingly, (+)-frondosin A inhibited Ba/F3 cells²¹ that express oncogenic IL-7 receptor mutations more potently than the IL-3-dependent wild-type Ba/F3 cells. Taken together, these data suggest that in addition to IL-8 in neutrophils, frondosins may have inhibitory activity against other leukocyte cytokine receptors. Further evaluations of the biological activity are currently underway.

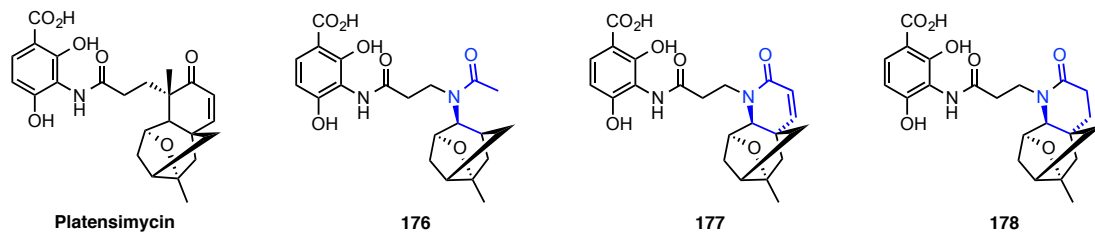
Overall, we have developed a synthesis of the natural enantiomer of frondosin A utilizing a highly selective perhalocyclopropene/furan cycloaddition reaction to access the central core of the natural product. The versatile common intermediate could be converted to two structurally distinct members of this class of marine natural product. The synthesis has also suggested the possibility of a very unusual inversion of configuration in a carbocationic intermediate that will warrant further investigation.

Efforts toward the asymmetric synthesis of platensimycin analogs: Featuring the stereodivergent resolution of oxabicyclic ketones

In 2006 researchers at Merck elucidated the structure of a the novel antibiotic platensimycin (Figure 2.2),²² attracting considerable attention from within the scientific community due to its unparalleled molecular architecture and potent antibacterial activity against Gram-positive bacteria.²³ Platensimycin's novel mode of action is trademarked by selective inhibition of the FabF enzyme, effectively blockading the biosynthesis of bacterial fatty acids. However, with a less than ideal pharmacokinetic profile, researchers have been focused on improving the drug's therapeutic potential with structural modifications to the polar benzoic acid subunit and the tricyclic lipophilic cage.²⁴ However, these efforts have thus far been disappointing with all compounds showing attenuated activity compared to the natural product.

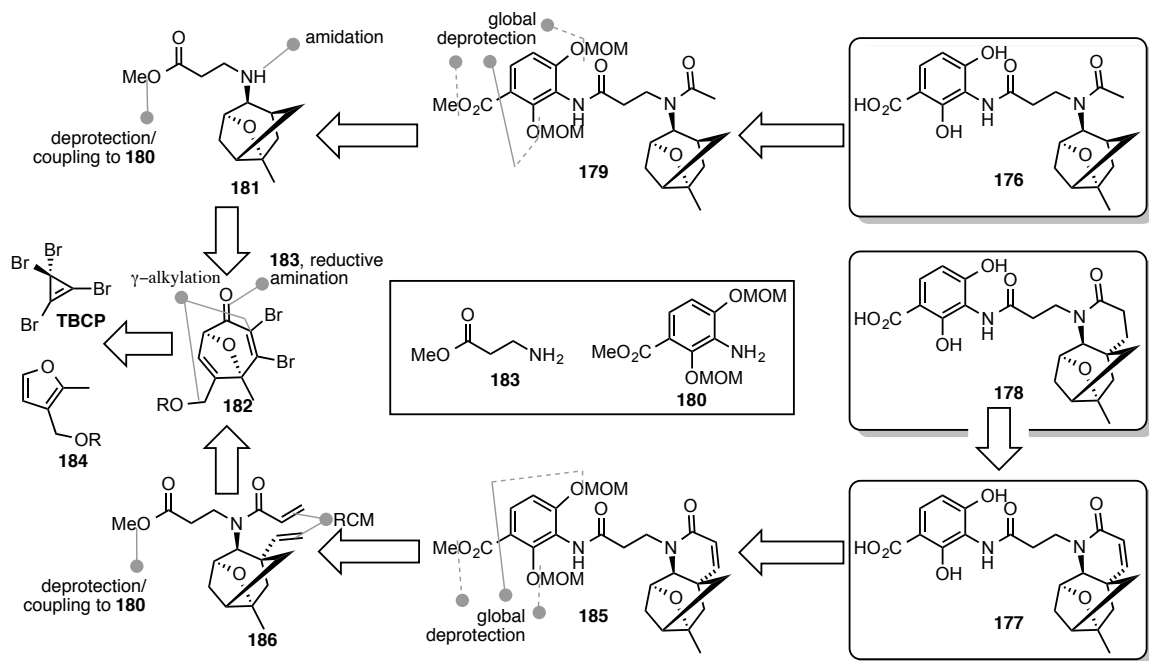
We plan to target acyclic linker compound **176** as a starting point to probe the minimal structural complexity needed to effect biological activity. A second series of compounds were devised to answer if we could create a panel of bioisotere compounds of platensimycin by substitutions of aza-rings for the cyclohexenone moiety. Thusly, we targeted δ -lactam **178** and α,β -unsaturated- δ -lactam **177** for their structural mimetic to the natural product. With these analogs we postulate that the incorporation of electron density, provided by the amide motif, to analog **177** will brand the enone less susceptible to nucleophilic addition, and saturation of this problematic olefin (**178**) will completely eliminate this electrophilic site.

Figure 2.2: Platensimycin and targeted synthetic analogs



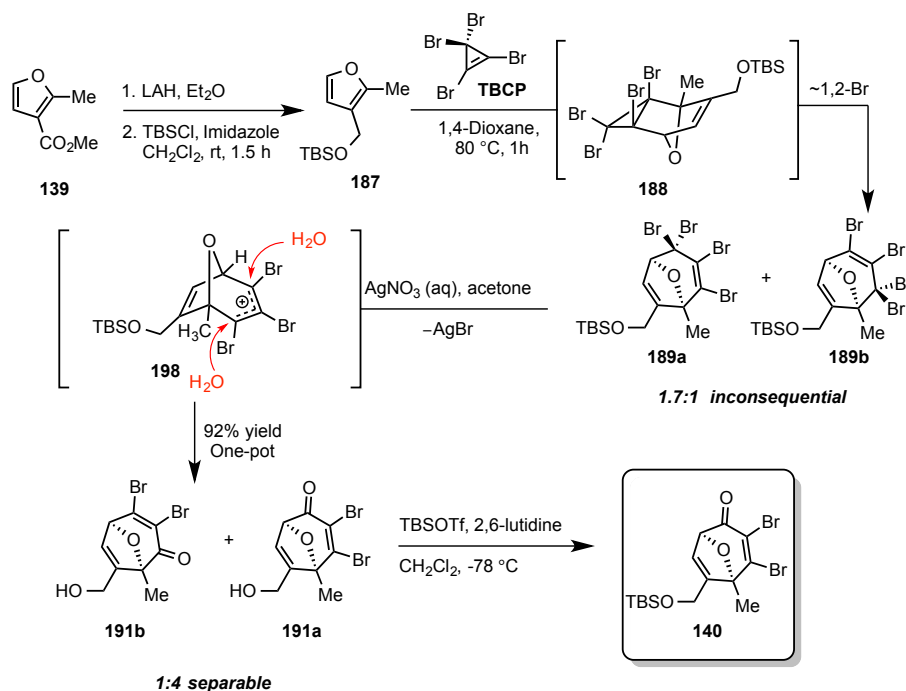
Our retrosynthesis of acyclic analog **176** targeted late stage amide **179**, containing the complete carbon skeleton of the designated analog and only requiring a global deprotection sequence to complete the synthesis. Disconnection of the acetate group followed by loss of fragment **180** allows for the design of a divergent synthetic plan utilizing known amine polar head group fragment **180** and permitting for the intersection of caged ketone **181** in our synthetic plan. Based on the group's previous formal synthesis of platensimycin, amine **181** was thought to arise from manipulations to the advanced dibromoenone building block **182** thru global hydrongenation/debromination, intramolecular γ -alkylation protocol, and reductive amination with β -alanine methyl ester **183**. Central to the overall strategy would be an efficient preparation of **182** from TBCP and a simple 2,3-disubstituted furan **184**. A stereodivergent resolution strategy would allow for intermediate **182** to be resolved into its enantiomerically pure components and effect an asymmetric synthesis.

Scheme 2.10: Retrosynthetic analysis of platensimycin analogs



Retrosynthetic design of δ -lactam analog **178** was thought to arise from saturation of α,β -unsaturated δ -lactam analog **177**. Analog **177** aimed at advanced α,β -unsaturated amide **185**, which comprised the intact carbon framework of the titled analog and needed only a global deprotection sequence to complete the synthesis. Grubbs ring-closing-metathesis (RCM) was thought to be utilized to form the lactam ring of **185** with subsequent loss of amine polar head group fragment **180** allows for the intersection of an advanced caged amide **186**. It was envisioned that amide **186** would arise through manipulations of the dibromoenone building block **182** through a similar global hydrogenation/debromination, intramolecular γ -alkylation protocol with reductive amination with β -alanine methyl ester **183**.

*Scheme 2.11: TBCP Diels-Alder with functionalized furan: Preparation of (\pm)-**140***



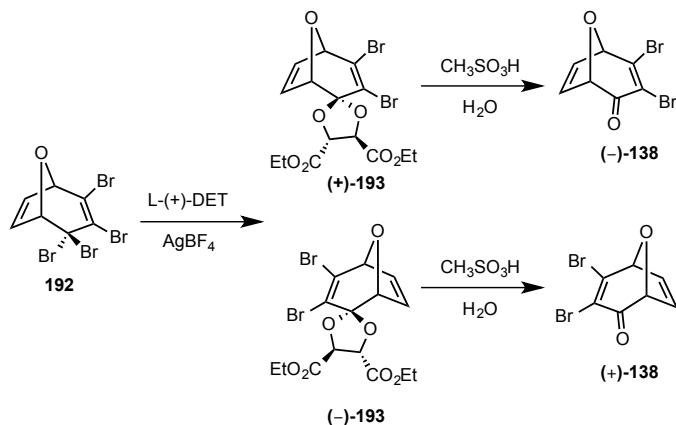
A relatively inexpensive and appropriately substituted furan **139** emerged as an attractive bulk starting material that was directly converted to the diene cycloaddition component **187** by simple reduction and protection²⁶ (Scheme 2.11). Furan **187** could be directly subject to cycloaddition with TBCP, which proceeded smoothly on a multi-gram scale despite increased

substitution on the furan ring, to produce a mixture of regioisomeric tetrabromides **189a/189b** that were converted directly to the corresponding dibromoenones **191a/191b** by action of aqueous silver nitrate. The major isomer **191a** (produced in a 4:1 ratio) arises from an intermediate tribromo-allyl cation **198** where attack of water is directed to the distal terminus of the allyl cation by the bridgehead methyl group. Reprotection of the C4 alcohol was required to give **140**, as a large amount of nitric acid is produced in the reaction, cleaving the primary silyloxy group.

Stereodivergent resolution of oxabicyclic ketones: Preparation of key intermediate (–)-**140** for the synthesis of platensimycin and analogs

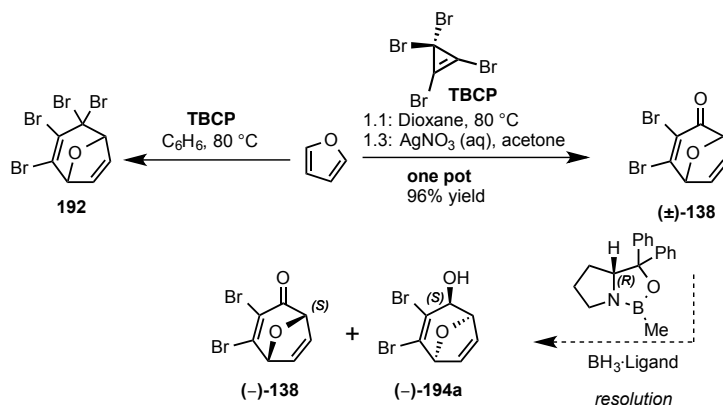
We have previously reported on the resolution of the tetrabromide (±)-**192** through formation and separation of the tartrate-derived ketals.²⁷ Although this method provided each enantiomer of **138** in high optical purity (> 95% ee) after ketal hydrolysis, the formation of the tartrate ketals involves the use of expensive air-sensitive reagents that became prohibitive on larger scale. Furthermore, cleavage of the resulting tartrate ketals required strongly acidic conditions (neat methanesulfonic acid) that would be incompatible with the incorporation of acid-sensitive functionality in more complex adducts. In order to expand the utility of these bicyclic building blocks, we set out to develop a more economical, scalable and mild method for the preparation of both enantiomers of dibromoeneone (±)-**138** and of the advanced dibromoenone **140**.

*Scheme 2.12: Resolution of dibromoenone **138** through separation of tartrate-derived ketals*



We were interested in the possibility of a classical kinetic resolution of enone (**±**)-**138** utilizing a chiral reducing agent.²⁸ Access to this key compound was initially improved by developing a one-pot process whereby thermal cycloaddition between furan and TBCP in dioxane could be directly treated with aqueous silver nitrate to deliver the enone directly in high yield on a multi-gram scale (96% on a 5 g scale, Scheme 2.13). Prior to this work, we showed that Luche reduction of (**±**)-**138** proceeds with high diastereoselectivity giving the *endo*-alcohol as the exclusive product.²⁹ In accord with these studies, we envisioned a scenario whereby this diastereoselectivity could be paired with a high degree of enantio-differentiation imparted by a chiral catalyst, leading to one enantio-enriched *endo*-alcohol (**−**)-**194a** as well as recovery of the antipode of the ketone (**−**)-**138**. The Corey-Bakshi-Shibata (CBS) oxazaborolidine had shown prior success in reductive kinetic resolutions,³⁰ and was of interest to us due to its commercial availability in both enantiomeric forms, high selectivity and a wide substrate tolerance.³¹ Furthermore, CBS reductions of cyclic α,β -unsaturated ketones have revealed that α -substitution of the enone olefin is crucial for effective steric differentiation of the carbonyl oxygen lone pairs.³² Given the α -bromo substitution in (**±**)-**138**, it appeared that it would be an ideal substrate for this reduction.

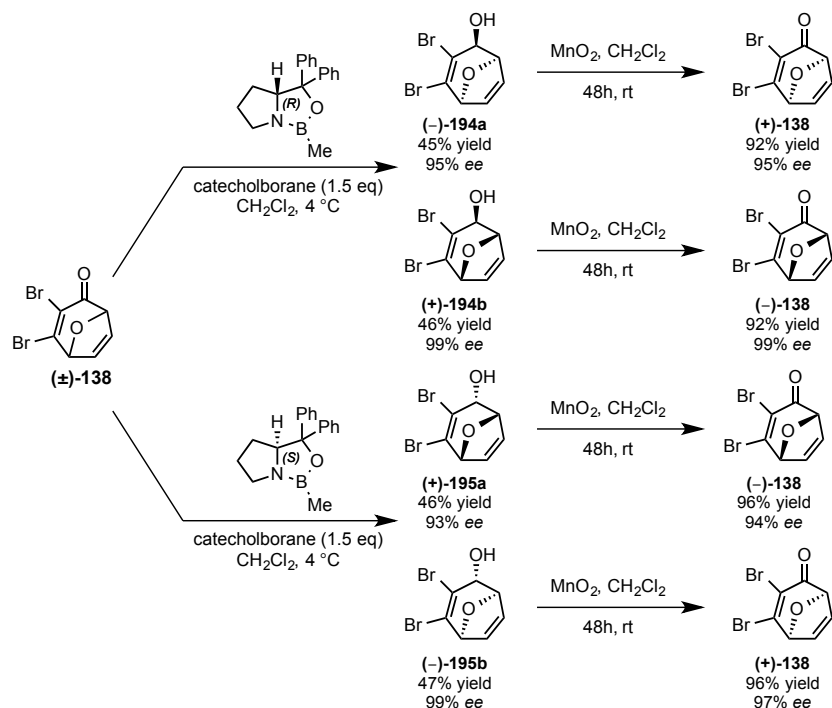
*Scheme 2.13: An improved one step synthesis of dibromoenone **138** and initial strategy for kinetic resolution*



We first examined the reduction of dibromide (**±**)-**138** with R-(+)-CBS (0.5 eq) and catecholborane (0.5 eq) at -78 °C. Preliminary studies revealed that the reaction proceeded to ~50% completion under these conditions, however the reduction led to a ~3:1 mixture of separable *endo*-**194a** and *exo*-**194b** alcohols. Each diastereomeric alcohol was isolated in high optical purity (>80% ee) while the starting dibromoenone was recovered in nearly racemic form.

This result was unusual given that the geometry of the oxabicyclo[3.2.1]octadiene **138** imparts significant concavity to the molecule, giving exclusively *endo*-products under Luche reduction conditions. These results suggested that catalyst control was overriding the directing effect embedded in the rigid bicyclic framework such that each enantiomer of **138** was reduced at similar rates by hydride attack from both faces of the ether bridge. The facile separation of the resulting diastereomeric *endo* and *exo* alcohols allowed us to exploit a stereodivergent resolution strategy to resolve the enantiomers of (**±**)-**138**.³³ Increasing the reaction temperature to 4 °C led to a noticeable increase in the enantiomeric excess (>90%) of both resulting alcohols. The elevated

Scheme 2.14: Synthesis of six non-racemic building blocks from dibromide (**±**)-**138**

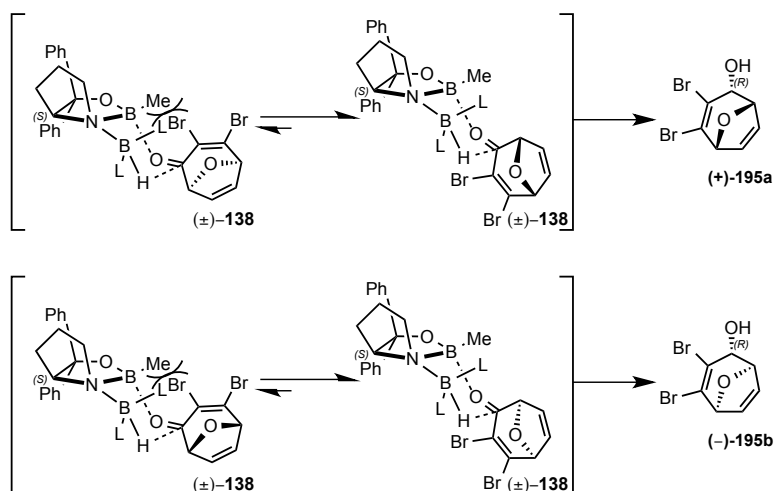


temperature allows for increased catalyst coordination to both the hydride source and the carbonyl moiety, thus suppressing any background *exo*-hydride attack.³⁴

To further optimize this process, we exposed the dibromide (\pm)-**138** to an excess of catecholborane in the presence of the CBS catalyst and allowed the reaction to proceed until complete consumption of the starting material was observed. Pleasingly, each diastereomer was isolated in high yield with even greater optical purity (**194a**, 95% and **194b**, 99% ee, Scheme 2.14). Pleased with this result, we then re-oxidized each individual diastereomer in the presence of MnO₂ to give the enantioenriched dibromoenones (+)-**138** and (-)-**138** in excellent yield (92%). The physical data and optical rotations of the enantiomers matched those reported from our previous studies. Likewise, exposure of dibromoenone (\pm)-**138** to the S-(-)-CBS catalyst proceeded in a similar fashion to provide the antipode alcohols *endo*-**195a** and *exo*-**195b**. Overall, this provides direct access to six different non-racemic building blocks in only 2-3 operations from furan, while also highlighting our first synthetic method to produce *exo*-alcohols directly from (\pm)-**138**.

Based on experimental evidence, preferred attack of the hydride on the carbonyl of both enantiomers of **138** likely occurs through related transition states as depicted in Figure 2.3. The

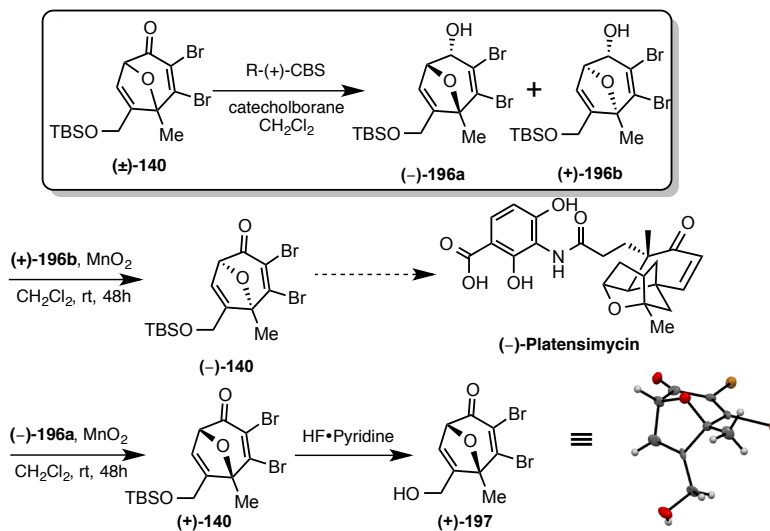
Figure 2.3: Transition state between S-(-)-CBS and (\pm)-138****



more favorable conformation positions the α -bromide *anti* to the endocyclic boron of the CBS catalyst, avoiding unfavorable steric interaction. The quasi-intramolecular hydride attack occurs from both the *endo* and *exo* face of the ether bridge, but only from a single face of the carbonyl (depending on catalyst preference). This results in a highly selective reduction without any significant control imparted from the ether bridge.

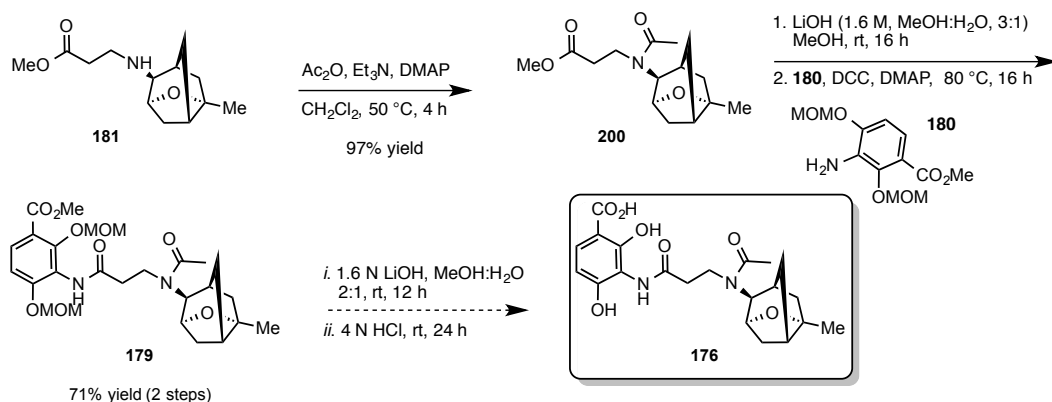
Encouraged by the success of this resolution strategy, we turned our attention to a synthetically interesting substrate that represents an early intermediate in our total synthesis of platensimycin. Subjecting (\pm)-**140** to our resolution conditions provided *endo*-alcohol (–)-**196a** and *exo*-alcohol (+)-**196b** in 49% yield (99% ee) and 47% yield (99% ee), respectively. Allylic oxidation in the presence of MnO₂ provided the enantioenriched dibromides (–)-**140** and (+)-**140** in high yield. The ability to resolve this complex material at an early stage provides entry into an asymmetric synthesis of both natural and non-natural platensimycin. To add further confirmation to our assignment of absolute stereochemistry, (+)-**140** was desilylated to the corresponding alcohol (+)-**197**. Alcohol (+)-**197** yielded thin plate crystals for X-ray crystallographic determination of absolute stereochemistry.

Scheme 2.15: Resolution of early intermediate 140 for (–)-platensimycin synthesis and X-ray crystal structure of (+)-197



With the caged ketone **199** in hand, the synthetic plan was aimed at introducing the polar head group with a β -alanine linker. To that end, a simple set of reductive amination conditions were put into place whereby a mixture of ketone **199** and β -alanine methylester **183** in DCE (adjusted to pH 3.5 with HCl) rapidly formed the intermediate imine species that could be reduced with exposure to sodium cyanoborohydride to produce amine **181** in modest yields.³⁵ Previous work by Sintim and coworkers suggested that only one diastereomer would be the product of the reduction, with hydride attack occurring from the *endo*-face as the protons of the carbon bridge would prohibit *exo*-attack. This hypothesis was confirmed with strong n.O.e. enhancements correlating the proton of C9 with the protons of C14.

Scheme 2.17: Completion of synthesis of acyclic analog **176**



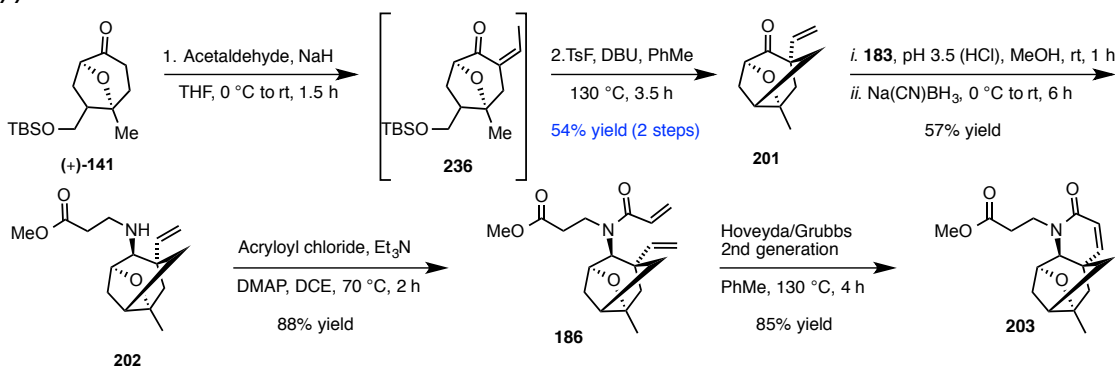
The synthesis was then progressed toward completion with protection of the amine of **181** with an acetate group to produce amide **200** in 97% yield. This acetate group was thought to help retain enzyme activity by interacting with A309 of the active site as shown in Figure 2.2. Following saponification of the methyl ester of **200**, the resulting carboxylic acid could be coupled to aniline **180** to construct amide **179** and complete the carbon skeleton of the desired analog. At this point, we focused our efforts toward a global deprotection of the aryl ring, as was seen in other syntheses of platensimycin. The devised scheme incorporated initial exposure of amide **179** to 1.6 N lithium hydroxide effected saponification of the benzoate group and then a

pH adjustment with 4 N hydrochloric acid allowed for the deprotection of the two MOM groups to produce acyclic analog **176**. However, these acid/base conditions resulted in decomposition of the titled compound. We concluded that since we had performed saponification of methyl ester **181** under the same basic conditions, that the decomposition must be a result of the strong acidic conditions needed to remove the MOM ethers.

Efforts toward synthesis of saturated and α,β -unsaturated δ -lactam analogs **178** and **177**

Efforts toward the synthesis of acyclic analog **176** left a precise blueprint to follow for the synthesis of the α,β -unsaturated δ -lactam analog **177** and its saturated counterpart **178**. Thusly, the synthesis originated with chiral ketone (+)-**141** being condensed with acetaldehyde in an aldol reaction generating exocyclic enone **236**, as an 8:1 inconsequential mixture of isomers, in modest yields. However, exocyclic enone **236** was shown to be quite sensitive with isomerization to the more stable cyclic enone predominating over time. Thusly, the crude material was progressed directly to the subsequent γ -alkylation step. A significant improvement was devised for the intramolecular γ -alkylation step, with literature reporting the transformation of primary siloxyl groups to the corresponding tosylate group in a single transformation utilizing tosylflouride and catalytic diazabicyclo[5.4.0]undec-7-ene (DBU).^{36,37} We were able to adapt these conditions to our substrate, and with the use of excess tosylflouride and DBU we were able to develop a one-

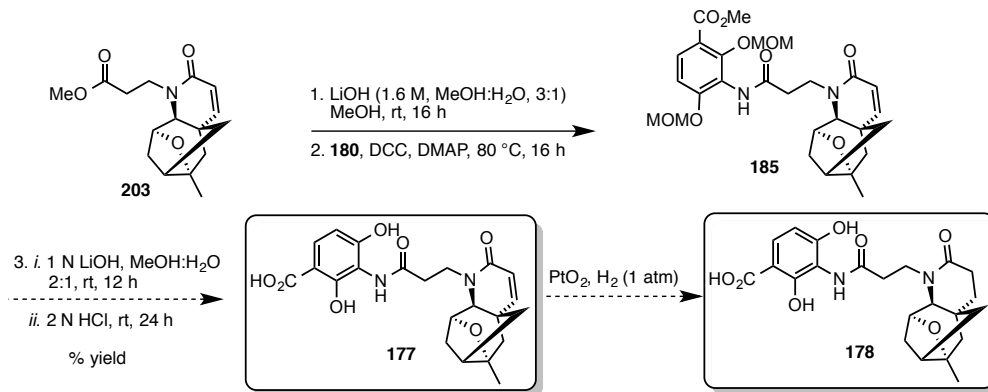
*Scheme 2.18: Initiation of synthesis of saturated and α,β -unsaturated δ -lactam analogs **178** and **177***



step deprotection/sulfonation/cyclization protocol to generate caged ketone intermediate **201** in an 54% overall yield (2 steps, Scheme 2.18).

With ketone **201** in hand, we were able to utilize the same reductive amination conditions as described earlier to join together ketone **201** and β -alanine methylester **183**. The vinyl group on the *endo*-face of C8 provided sufficient steric bulk to shift the diastereomeric ratio of the reduction to a 1:20 ratio (*endo*-disfavored:*exo*-favored) of separable diastereomers. Confirmation of the *exo*-amine was provided by strong n.O.e. enhancements correlating the proton of C9 with the protons of C14. With amine **202** available to us, it could then be reacted with an acryloyl chloride in the presence of base to generate α,β -unsaturated amide **186** in an 88% yield. The terminal olefin moiety of the α,β -unsaturated amide **186** provided an ideal intermediate to perform ring-closing metathesis (RCM) to form the requisite α,β -unsaturated δ -lactam. However, initial results were poor while utilizing common conditions (0.03eq catalyst loading at 0.05 M solution at room temperature) for the RCM. Thusly, more forcing conditions (0.1eq catalyst loading at 1 M concentration at 130 °C) were utilized to produce optimal yields of the desired α,β -unsaturated δ -lactam **203**.

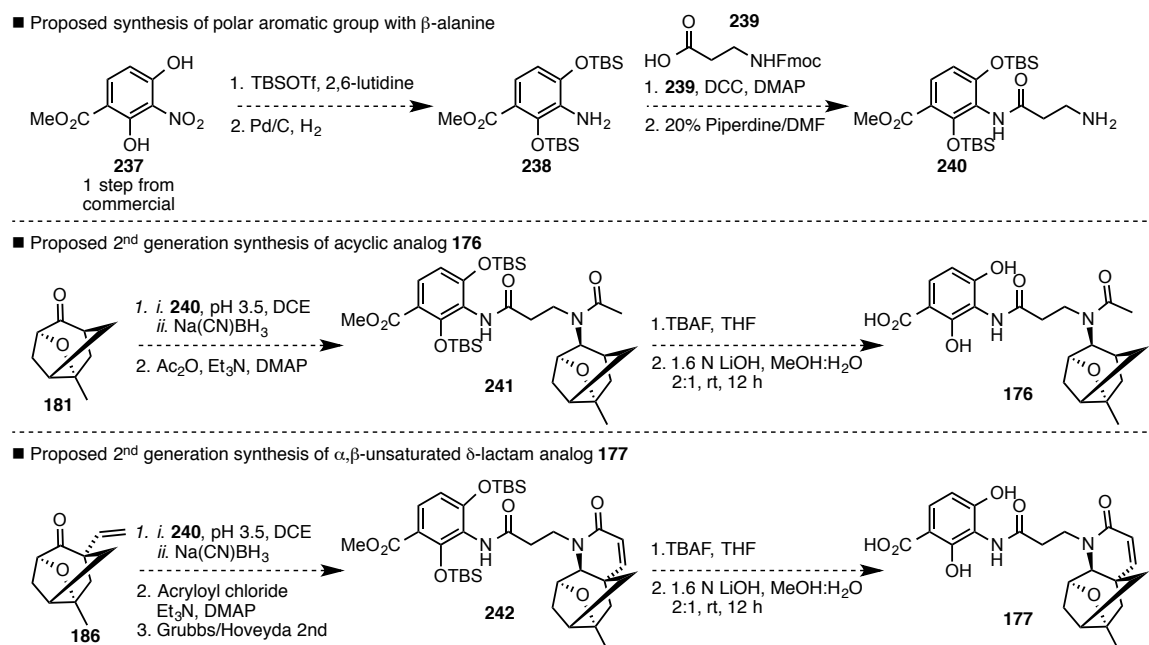
*Scheme 2.19: Completion of synthesis of saturated and α,β -unsaturated δ -lactam analogs **178** and **177***



Following saponification of the methyl ester of **203**, the resulting carboxylic acid could be coupled to aniline **180** to construct amide **185** and complete the carbon skeleton of the desired

analog. Although we had seen decomposition of acyclic analog **176** with exposure to an acid/base deprotection scheme, we thought this cyclic system might behave differently. Unfortunately, the result of the acid/base deprotection scheme resulted in decomposition, indicating that our system is not accepting of strenuous pH conditions, and needed a new synthetic design (Scheme 2.20). Had we been able to successfully produce analog **177**, we have layed out a synthetic plan towards reducing δ -lactam analog **177** to give α,β -unsaturated δ -lactam **178**. The proposed method here would be to use Adam's catalyst (PtO_2) to saturate this electron poor olefin.

Scheme 2.20: Proposed 2nd generation synthesis of platensimycin analogs



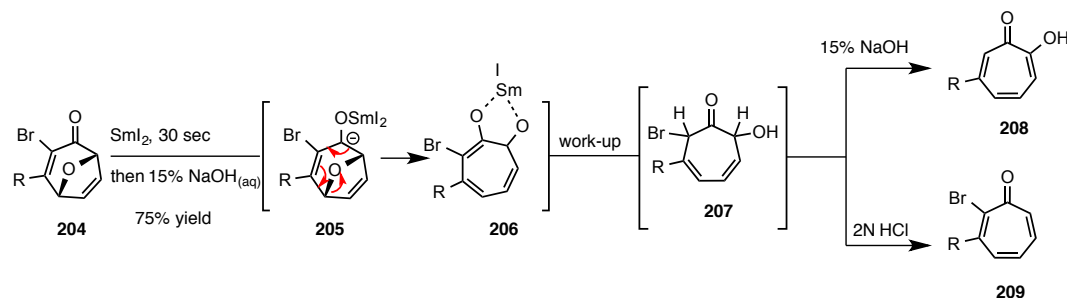
In conclusion we described a concise and direct methods towards the synthesis of two asymmetric platensimycin analogs based on the key use of a furan-TBCP cycloaddition reaction. These routes showcase a somewhat unique synthetic scheme in allowing late-stage functionality to be introduced to the oxabicyclo[3.2.1]octane core of **141**.

Development of potent α -tropolones as lead-like natural products

Natural products containing a tropolone core have been known since the early 1950s when the novel non-benzenoid aromatic structure was proposed by Dewar and Nozoe for the plant derived metabolite β -thujaplicin (hinokitiol).³⁸ Thujaplicins are monoterpene natural products isolated from the heartwood of trees in the Cupressaceae family³⁹ that are associated with antiproliferative activity.⁴⁰ Based on their therapeutic potential, the thujaplicins, members of the tropolone family of natural products, can be regarded as lead-like natural products. However, there have been few attempts to utilize these lead-like compounds in drug discovery, perhaps impaired by prohibitive synthetic methods in accessing these non-benzenoid aromatics. From the perspective of a drug development effort, thujaplicin is much more reminiscent of a lead structure, characterized by low molecular weight, minimal functionalization and metal-binding functionality primed for targeting a range of metalloenzyme drug targets.⁴¹ Thusly, we planed to expand our current library of β -tropolones to incorporate α -tropolones, to further probe these potential biological implications.

Initial synthetic design toward the synthesis of novel α -tropolones was aimed at utilizing the formal [4+3] cycloadduct **138** produced from the reaction of furan and TBCP as seen in our past synthesis of β -thujaplicin.⁴² The product of these investigations unveiled that exposure of β -substituted enone (such as **204**) to samarium diiodide exclusively opened the ether bridge producing an extended enolate **206**. What was interesting about these investigations was that

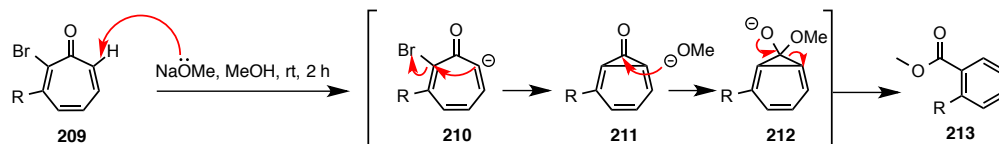
*Scheme 2.21: Initial synthetic design toward α -tropolones from β -substituted enone **204***



kinetic protonation of the enolate **206** led to a diene species **207** that was poised for easy aromatization either through dehydrohalogenation to give β -tropolone **208** or dehydration to give α -bromo tropone **209** (Scheme 2.21).

With α -bromo tropone **209** in hand, we directed our efforts toward a basic hydrolysis of the α -bromide with NaOMe. Unfortunately, the strong basic conditions resulted in the deprotonation of the α -proton which ultimately proceeded through a Favorskii rearrangement to yield benzyl ester **213**.⁴³ Disappointed with this result, it was clear that all subsequent reactions would result in the same rearrangement and we had to abandon our initial synthetic design (Scheme 2.22).

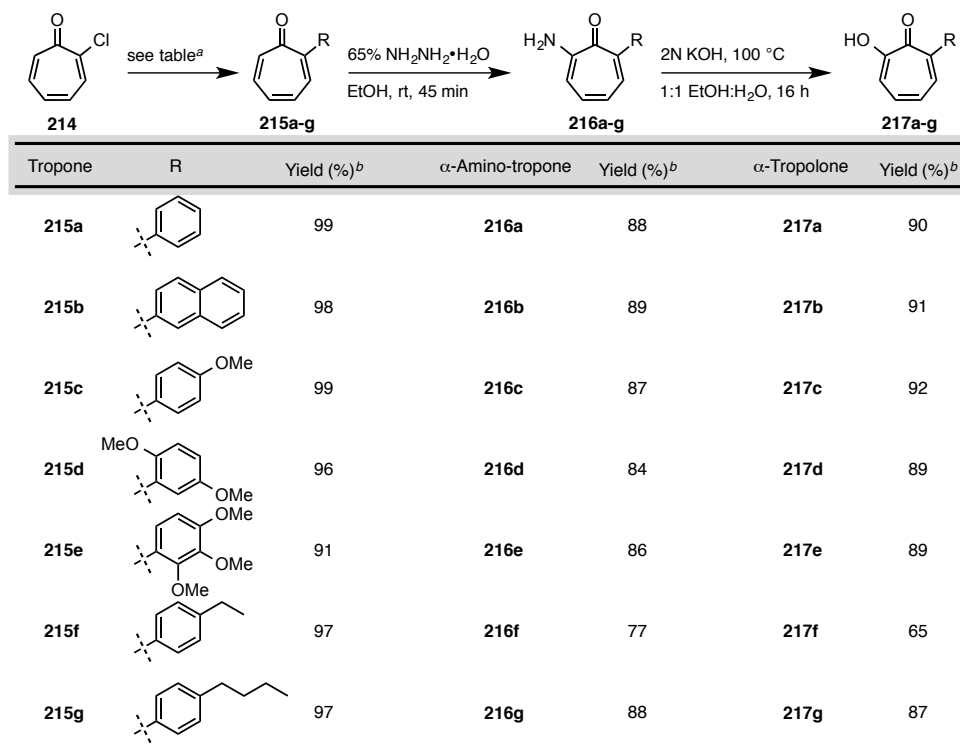
*Scheme 2.22: Favorskii rearrangement of α -bromo tropone **209***



Commercially available 2-chlorotropone **214** presented itself to be an ideal starting material to develop a brief route for the synthesis of α -substituted tropolones. Palladium-catalyzed cross-coupling conditions with this α -chloro substituent proved to be quite amenable, such that a series of 2-aryl tropones (**215a–g**) could be easily prepared by Suzuki reactions. Following a protocol initially reported for the synthesis of α -thujaplicin,⁴⁴ we saw that the addition of hydrazine to our 2-aryl tropones (**215a–g**) led directly to the corresponding 7-aryl-2-amino tropones (**216a–e**). These amino-tropones could be subject to basic conditions to perform a final hydrolysis, yielded the α -substituted tropolones (**217a–g**) in good overall yield (Scheme 2.23).

In order to precisely compare inhibition values of different HDAC isozymes, we first performed a detailed Michaelis-Menten analysis of six different HDAC isozymes: 1, 2, 4, 5, 6, and 8. At this point I would like to thank Sophia Ononye and the Anderson lab in their detailed investigations into the biological potential of these novel synthetic compounds. They evaluated 5

Scheme 2.23: Synthesis of tropolones from commercially available 2-chlorotropone **214**



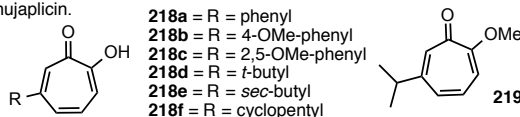
^a RB(OH)₂, Pd(PPh₃)₂Cl₂, Cs₂CO₃, 10:1 THF:H₂O, 75 °C, 16 h; ^b Yield of isolated products.

α -substituted tropolones (**217a–e**) and 6 β -substituted tropolones (**218a–f**) and show that these compounds function as inhibitors of HDACs. Seven (**217b–e**, **218c**, **218d**, and **218f**) show high levels of selectivity (>100-fold) for the inhibition of HDAC2 relative to HDACs 1, 4, 5, 6, and 8 (Table 2.4). All of the tropolones, with the exception of β -thujaplicin, were more potent inhibitors of HDAC2 than TSA, which inhibited HDACs 1, 2, and 6 with similar levels of potency. As confirmation to our hypothesis that the tropolone motif may facilitate strong metal (Zn²⁺) chelation in the HDAC active site, it was noteworthy to report that methylated tropolone **219** showed significantly lower activity than the free tropolones. It was interesting to see that with substitutions larger than the isopropyl group, which is found in β -thujaplicin, at both the α - and β -positions, these compounds function as very potent inhibitors of HDAC2. More importantly, is that it was clear to us that in contrast to the pan-HDAC inhibition exhibited by the hydroxamates TSA and vorinostat, our tropolone analogs showed modest levels of isozyme selectivity.⁴⁵

Table 2.4: Inhibition of HDAC isozymes^a

HDAC isozyme (K _i values in nM)						
Compound	1	2	8	4	5	6
TSA	0.87	1.06	69.65	14547	4120	3.02
217a	NA	0.26	1.09	NA	NA	527
217b	NA	0.25	186.30	NA	NA	NA
217c	NA	0.81	83.80	NA	NA	NA
217d	NA	0.42	811.50	NA	NA	NA
217e	NA	0.23	123.65	NA	NA	NA
218a	NA	0.06	1.47	10860	NA	NA
218b	NA	0.12	2.38	8361	NA	NA
218c	NA	0.51	266.30	11204	NA	NA
218d	NA	0.13	12.81	806.13	NA	NA
218e	NA	0.22	2.27	6115	NA	NA
218f	NA	0.04	122.70	990.23	NA	NA
β -tj	NA	15.44	177.95	NA	NA	NA
219	NA	NA	7.87	11,641	NA	NA

^aFor all HDAC isozymes except HDAC4, not active (NA) refers to K_i values >2500 nM, the highest concentration of inhibitor; for HDAC4, NA refers to K_i values >20,000 nM, the highest concentration of inhibitor. β -tj refers to β -thujaplicin.



As the overexpression of the HDAC2 isozyme has been shown to be significant in aggressive forms of some cancers, it was thrilling to see that our tropolones analogs showed potent inhibition of this isozyme.⁴⁶ However, it was also exciting to see that the tropolones did not inhibit HDAC5; this preferential isozyme selectivity could be potentially beneficial to the tropolone's therapeutic potential, as deletion of HDAC5 may impair cardiac function.⁴⁷ Some SAR was also obtained from these preliminary biological results, whereby inhibition of HDAC8 was more sensitive to patterns of substitution with only one α -substituted compound (**217a**). Compound **217a** showed good inhibition (K_i = 1.09 nM); however, increasing steric bulk at this position (**217b-e**) directly led to loss of potency for HDAC8. With TSA and vorinostat having much higher K_i values at 69.65 and 480 nM,⁴⁵ respectively for HDAC8 it was encouraging to see that some of the tropolones (**217a**, **218a**, **218b**, and **218e**) were able to effectively inhibit this isozyme.

Although several of the substituted tropolones proved to be excellent HDAC inhibitors, it was important to evaluate if this enzymatic inhibition could be translated to cellular effects to further probe whether these compounds are indeed drug-like. Two T-cell lymphocyte lines (HuT-78 and

Jurkat) were chosen for analysis based on the well-known fact that HDAC inhibitors have pronounced antiproliferative effects against hematological cancer cell lines.⁴⁸ To survey solid tumor lines, we added a colon cancer cell line (HCT116) and a pancreatic cancer line (BxPC-3). Tropolone analogues **217c**, **217d**, **218a**, and **218e** showed significant half maximal growth inhibition (GI₅₀) values in both T-lymphocyte cell lines with increased activity relative to vorinostat (vorin.) with GI₅₀ values below 1 μ M against the Jurkat cell line (Table 2.5). Results of tropolones against HCT-116 were demonstrated to be less active, however, two derivatives (**217a** and β -tj) did show GI₅₀ values less than 20 μ M. In contrast, tropolone derivatives (**217b**, **217d**, **218a**, and β -tj) displayed GI₅₀ values less than 20 μ M against the BxPC-3 cells. For further evaluation, we tested the tropolones against a nonmalignant human dermal fibroblast (hDF) line as an indicator of general cytotoxicity, and encouragingly most of the products (except **217b**) showed no activity at 100 μ M.

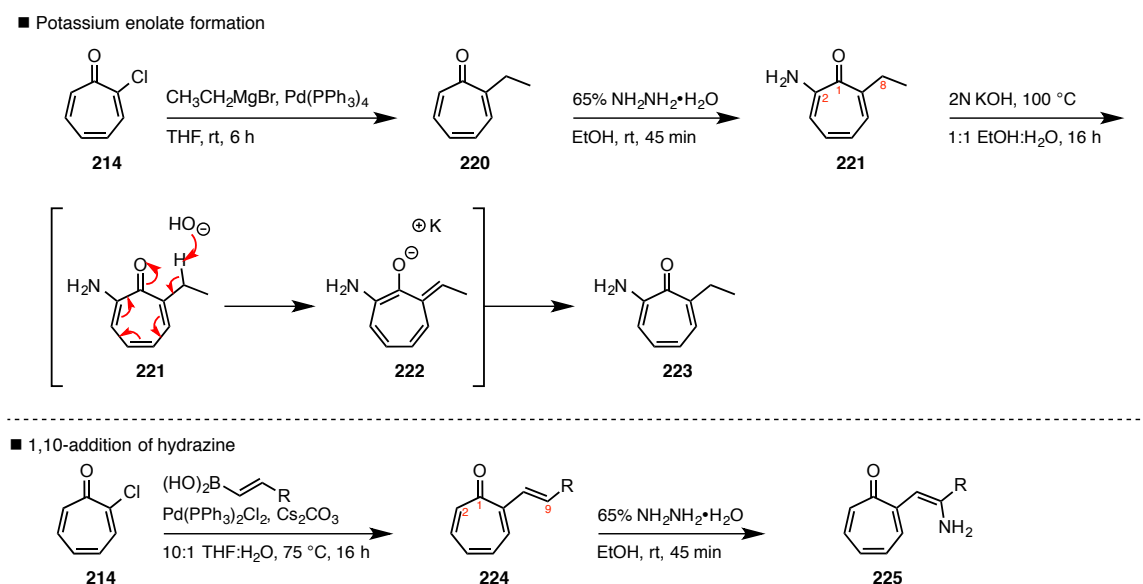
Table 2.5: Inhibition of cell growth

Compound	cell line (GI ₅₀ values in μ M)				
	Jurkat	Hut-78	HCT-116	BxPC-3	hDF
217a	3.33	7.83	15.24	29.39	96.46
217b	1.15	4.11	32.06	17.1	93.07
217c	0.62	2.87	56.99	35.93	>100
217d	0.76	3.05	46.65	14.1	>100
217e	1.86	4.74	34.98	21	>100
218a	0.67	4.14	53.44	18.5	>100
218b	4.62	8.95	43.67	91.6	>100
218c	5.89	17.09	>100	34.79	>100
218d	4.45	13.11	62.61	43.02	>100
218e	0.59	3.25	26.86	104	>100
218f	6.30	11.36	>100	180	>100
β -tj	1.10	4.99	6.92	19	>100
219	>100	>100	>100	>100	>100
Vorin.	0.90	2.10	2.50	5.56	18.95

With encouraging biological findings surrounding our initial series of α -substituted tropolone analogs, our goals shifted toward extending the aryl functionality with a flexible aliphatic linker as seen in other active compounds (TSA, vorinostat, Figure 1. 13). Toward these goals, we initiated synthesis as seen previously only using Kumada coupling conditions to introduce the aliphatic moiety. We targeted a simplified substitution to probe the effectiveness of this new

route, and toward that end we initiated studies with incorporation of an ethyl group with palladium-catalyzed coupling conditions with 2-chlorotropone **214** to produce α -ethyl-tropone **220**. Tropone **220** could be sequentially treated with hydrazine to progress the synthesis to α -ethyl-aminotropone **221** in good yield. Unfortunately, basic hydrolysis of the amino group resulted in quantitative recovery of starting material. It was presumed that the hydrolysis was halted by the propensity for the base to deprotonate the C8 proton and form a stabilized potassium enolate **222**. To circumvent these complications, we added alkene functionality (via Suzuki couplings) to effectively unsaturate this susceptible position (**224**). However, it was found that treatment of **224** with hydrazine resulted in a 1,10-conjugate addition of hydrazine, producing vinyl amine tropone **225** (Scheme 2.24).

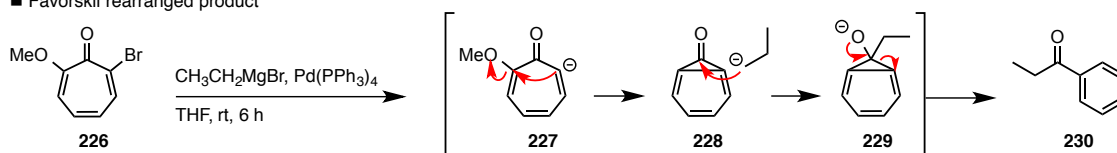
*Scheme 2.24: Complications in aliphatic α -tropolone synthesis initiated with 2-chlorotropone **214***



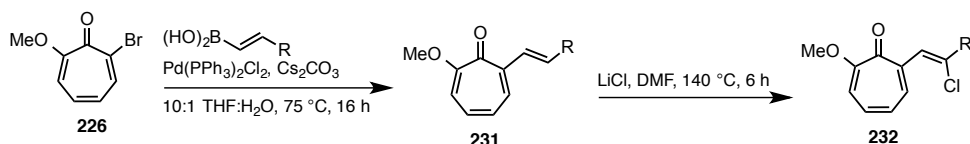
With a series of issues arising while using 2-chlorotropone **214** to synthesize α -aliphatic tropolone analogs we shifted our starting material to known α -bromo-methoxytropolone **226**, prepared in 2 steps from commercially available tropolone. However, more obstacles arose, whereby Kumada coupling conditions resulted in favorskii rearrangement, as seen previously, yielding ethyl-benzyl ketone **230**. Moving forward from this result, we introduced alkene

*Scheme 2.25: Complications in aliphatic α -tropolone synthesis initiated with α -bromo-methoxytropolone **226***

■ Favorskii rearranged product



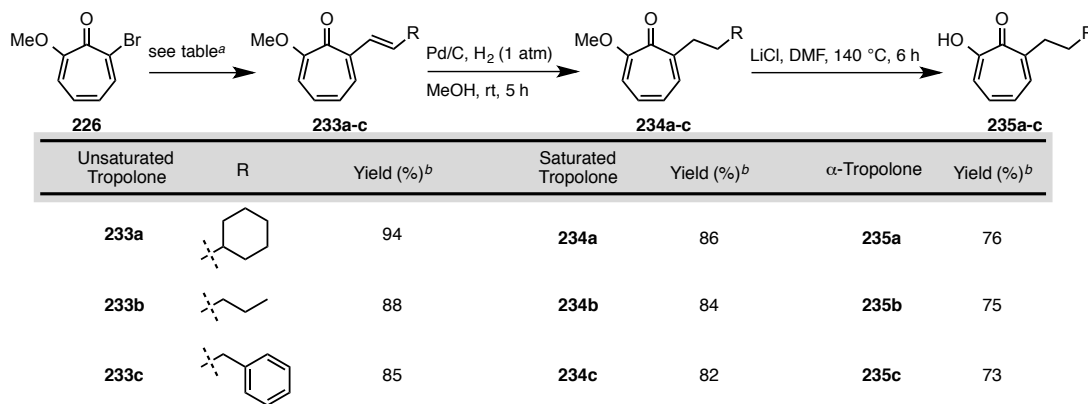
■ 1,10-addition of chloride



functionality, via Suzuki coupling conditions, to effectively produce α -alkenyl-methoxytropolone **231**. However as seen previously, treatment of **231** under nucleophilic cleavage conditions (LiCl) resulted in a 1,10-conjugate addition of chloride, producing vinyl chloride tropone **232** (Scheme 2.25).

We were delighted to see that saturation of the C8-C9 olefin allowed for a productive deprotection to yield α -aliphatic-tropolones in an efficient manner. To this end, an initial series of α -aliphatic-tropolones were derived from α -bromo-methoxytropolone **226** being subject to palladium-catalyzed cross-coupling conditions such that a series of α -alkenyl methoxytropolones (**233a-c**) were easily prepared by Suzuki reactions. Hydrogenation of the resulting α -alkenyl

*Scheme 2.26: Synthesis of tropolones from known α -bromo-methoxytropolone **226***



^a RB(OH)₂, Pd(PPh₃)₂Cl₂, Cs₂CO₃, 10:1 THF:H₂O, 75 °C, 16 h; ^b Yield of isolated products.

methoxytropolones, with standard conditions of Pd/C and H₂ (1 atm), yielded the corresponding α -alkyl-methoxytropolones (**234a-e**). Final nucleophilic cleavage of the α -alkyl methoxytropolones with LiCl yielded the α -aliphatic tropolones (**235a-g**) in good overall yield (Scheme 2.26). These compounds are under current biological evaluation.

In conclusion, we investigated whether thujaplicins could serve as powerful lead-like natural products targeting HDACs as they possess relatively low molecular weight, ample sites of diversification, and a key metal-directing functional group. In addition to activity at the enzyme level, further evaluation shows that the compounds exhibit significant cytotoxicity in cancer cells and modulate histone acetylation levels. These initial investigations into tropolone-based HDAC inhibitors suggest that this new chemotype could give rise to potent and selective inhibitors that may find application in the study of HDAC function or even as versatile leads for new therapeutic development.

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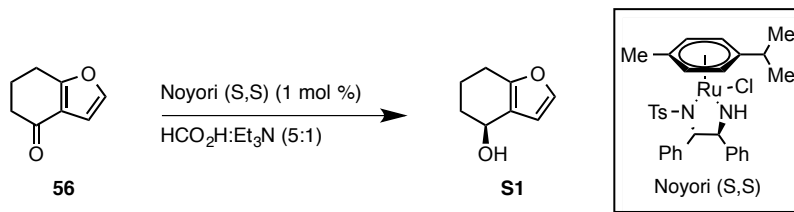
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CHAPTER THREE

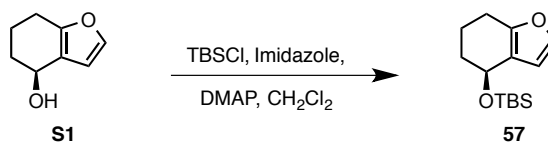
EXPERIMENTAL SECTION

General procedures. All reactions were carried out under an inert argon atmosphere with dry solvents under anhydrous conditions unless otherwise stated. Commercial grade reagents and solvents were used without further purification except as indicated below. Hexanes, tetrahydrofuran (THF), diethyl ether (Et₂O), and dichloromethane (CH₂Cl₂) were used directly from a Baker cycle-tainer system. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise noted. Yields refer to chromatographically and spectroscopically (¹H NMR) homogenous materials, unless otherwise stated. Reactions were monitored by thin layer chromatography (TLC) carried out on Whatman silica 60 Å precoated plates using UV light as the visualizing agent and an acidic mixture of anisaldehyde or basic aqueous potassium permanganate (KMnO₄) and heated as developing agents. Flash chromatography was performed using Baker silica gel (60 Å particle size). NMR spectra were recorded on Bruker-500 and 400 instruments and calibrated using residual undeuterated solvent as internal reference (CHCl₃ at δ 7.26 ppm ¹H NMR, δ 77.0 ppm ¹³C NMR). The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad. IR spectra were recorded on Shimadzu FT-IR 8400 spectrometer. Melting points (m.p.) are uncorrected and were recorded on a Mel-Temp digital melting point apparatus. High resolution mass spectra (HRMS) were obtained from the University of Connecticut Spectral Facility by electrospray ionization of flight reflectron experiments. Optical rotations were measured with a Jasco P-2000 polarimeter using a 50 mm path-length cell. Enantiomeric excess was measured on a Shimadzu 20 Series high-pressure liquid chromatograph (HPLC) using a Daicel Chemical Industries, LTD. Chiralcel -OJ chiral column with detection at 254 nm.

Experimental procedures: Asymmetric total synthesis of (+) and (-)-frondosin B



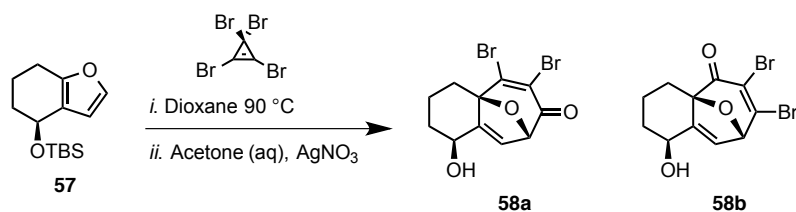
Alcohol (-)-S1: Tetrahydrobenzofuranone **5** (5.00 g, 36.7 mmol) and $\text{RuCl}[1S,2S)\text{-p-TsNCH}(\text{C}_6\text{H}_5)\text{CH}(\text{C}_6\text{H}_5)\text{NH}_2](\eta^6\text{-p-cymene})$ (223 mg, 0.367 mmol, 1 mol %) were dissolved in a 5:2 formic acid:triethylamine azeotropic mixture (18.4 mL) and stirred at room temperature for 7 days. After this time, the mixture was poured into water and extracted with ethyl acetate (3 x 100 mL). The combined organics were washed with sat. aq. NaHCO_3 (50 mL), H_2O (50 mL) and brine (50 mL) then dried over Na_2SO_4 and the solvent removed in vacuo to provide crude alcohol **S1** as a brown oil. The crude alcohol was used without further purification. A small portion was purified by column chromatograph for determination of enantiomeric excess. IR, NMR, and HRMS are consistent with the literature.¹ $[\alpha]_{\text{D}}^{23} = -28.8$ ($c = 1.00$, CHCl_3); Observed 98% ee as determined by chiral HPLC analysis (Chiralcel OJ, 3% *i*PrOH/hexanes, 1 mL/min, 209 nm).



Furan (-)-57: A solution of crude alcohol **S1** (63.3 mmol) in CH_2Cl_2 (70 mL) was treated sequentially with imidazole (6.46 g, 95.0 mmol) and DMAP (770 mg, 6.3 mmol). The solution was cooled to 0 °C and TBDMSCl (9.9 g, 65.9 mmol) was added portionwise over 15 min. Upon complete addition, the mixture was warmed to room temperature and stirred for 5 h before quenching the reaction with H_2O . The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed with H_2O (2 x 50 mL) and brine (100 mL), dried over Na_2SO_4 , and concentrated *in vacuo*. The crude oil was

purified by flash chromatography (SiO₂, 200 g, 10% EtOAc in Hexanes) to afford furan **57** (13.9 g, 55.1 mmol, 87% yield) as a clear oil.

R_f = 0.47 (5% EtOAc in hexanes); IR (KBr): ν : 2948, 2858, 1256, 1074 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.25 – 7.23 (m, 1H), 6.32 (d, J = 1.9 Hz, 1H), 4.76 (dd, J = 5.9, 4.6 Hz, 1H), 2.63 (dt, J = 12.4, 6.0 Hz, 1H), 2.52 (dt, J = 12.0, 5.8 Hz, 1H), 2.08 – 2.01 (m, 1H), 1.94 – 1.88 (m, 1H), 1.78 – 1.68 (m, 2H), 0.94 (s, 9H), 0.14 (d, J = 3.1 Hz, 6H); ¹³C NMR (126 MHz, CDCl₃) δ 151.8, 140.6, 120.9, 109.2, 65.2, 33.4, 25.9, 23.0, 19.6, 18.2, -4.4, -4.6; HRMS (ESI) calcd for C₁₄H₂₅O₂Si [M+H]⁺: 253.1624; found: 253.1618; $[\alpha]_D^{21}$ = -9.5 (c = 1.00, CHCl₃).

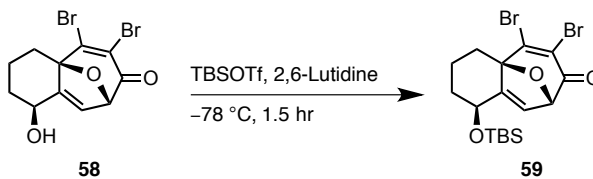


Dibromoenone (–)-58: To a flame dried pressure tube was added furan **57** (5.00 g, 19.8 mmol) and dioxane (4 mL) under argon. The solution was treated with freshly distilled tetrabromocyclopropene² (7.00 g, 19.8 mmol) at room temperature and the tube was sealed. The sealed tube was placed in an oil bath at room temperature then gradually heated to 90 °C for 5 h. After this time, the flask was cooled to room temperature, diluted with acetone-H₂O (2:1, 66 mL) and treated with AgNO₃ (6.73 g, 39.6 mmol). The reaction mixture was allowed to stir at room temperature for 8 h before being poured over solid NaHCO₃ (7 g). The solids were filtered through a pad of Celite and washed with acetone (300 mL). The acetone was removed under reduced pressure and the resulting aqueous layer was extracted with EtOAc (3 x 100 mL). The combined organics were washed with NaHCO₃ (100 mL), H₂O (100 mL), brine (100 mL), dried over Na₂SO₄, and concentrated to give the crude dibromoenone as a mixture of regioisomers (3.3 : 1, ¹H NMR). The crude material was purified by flash chromatography (SiO₂, 200 g, 25%

EtOAc in hexanes) to provide 1.23 g of **58b** (3.52 mmol, 18%) and 4.10 g of **58a** (11.7 mmol, 59%) as a pale yellow solid; recrystallized with hexanes and EtOAc.

58a: R_f = 0.24 (25% EtOAc in hexanes); mp = 162.4-164 °C; IR (KBr): ν : 3425, 1706 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 6.18 (t, J = 2.1 Hz, 1H), 5.10 (dd, J = 2.4, 0.9 Hz, 1H), 4.42 (ddd, J = 11.7, 4.7, 1.9 Hz, 1H), 2.58 – 2.51 (m, 1H), 2.22 – 2.15 (m, 1H), 2.06 (tt, J = 14.1, 3.6 Hz, 2H), 2.00 – 1.92 (m, 1H), 1.80 (tt, J = 12.1, 6.0 Hz, 1H), 1.49 – 1.39 (m, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ 183.6, 158.1, 151.2, 122.7, 119.1, 91.4, 86.1, 69.2, 34.4, 34.3, 21.9; HRMS (ESI) calcd for $\text{C}_{11}\text{H}_{10}\text{Br}_2\text{NaO}_3$ $[\text{M}+\text{Na}]^+$: 370.8894; found: 370.8899; $[\alpha]_{\text{D}}^{21} = -253.7$ (c = 1.00, CHCl_3).

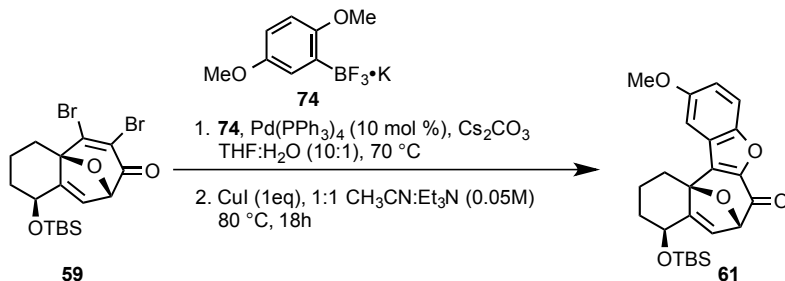
58b: R_f = 0.27 (25% EtOAc in hexanes), mp = 163.5-165; IR (KBr): ν 3523, 1697; ^1H NMR (500 MHz, CDCl_3) δ 6.74 (ddd, J = 2.8, 1.9, 0.8 Hz, 1H), 5.31 (dd, J = 2.1, 0.9 Hz, 1H), 4.24 (ddd, J = 11.8, 5.8, 2.7 Hz, 1H), 2.45 (dddd, J = 12.1, 4.0, 2.7, 1.4 Hz, 1H), 2.19 – 2.12 (m, 1H), 2.04 – 1.94 (m, 2H), 1.94 – 1.81 (m, 1H), 1.58 – 1.47 (m, 1H), 1.39 (dtd, J = 13.1, 11.9, 3.5 Hz, 1H). ^{13}C NMR (126 MHz, CDCl_3) δ 186.2, 150.9, 149.9, 127.8, 120.2, 92.3, 86.6, 68.9, 34.9, 31.1, 21.2; HRMS (ESI) calcd for $\text{C}_{11}\text{H}_{11}\text{Br}_2\text{O}_3$ $[\text{M}+\text{H}]^+$: 350.9055; found: 350.9036.



Dibromoenone (–)-59: Dibromoenone **58a** (4.00 g, 11.4 mmol) was dissolved in CH_2Cl_2 (23 mL), cooled to -78 °C, and treated with 2,6-lutidine (2.00 mL, 17.1 mmol). To the cooled solution was added TBSOTf (2.62 mL, 11.4 mmol) and stirring was continued for 1 h. Upon completion, the reaction was quenched by addition of H_2O and the biphasic mixture was allowed to warm to room temperature. The layers were separated and the aqueous layer extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were washed with brine (50 mL), dried over

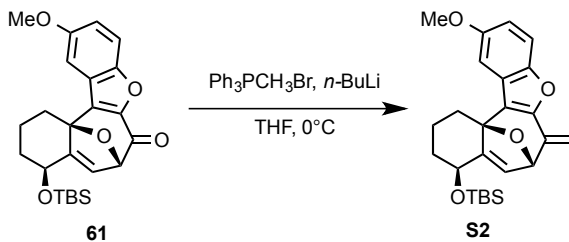
Na₂SO₄, and concentrated *in vacuo*. The crude material was purified by flash chromatography (SiO₂, 50 g, 10% EtOAc in hexanes) to afford dibromoenone **59** (5.18 g, 98%) as a pale yellow solid:

R_f = 0.68 (15% EtOAc in hexanes); mp = 108.1-109.2 °C; IR (KBr): ν : 2952, 1711, 836 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 6.11 (td, J = 2.5, 0.6 Hz, 1H), 5.07 (dd, J = 2.4, 1.0 Hz, 1H), 4.35 – 4.30 (m, 1H), 2.56 – 2.47 (m, 1H), 2.09 – 2.00 (m, 2H), 2.00 – 1.88 (m, 1H), 1.78 (td, J = 14.0, 5.5 Hz, 1H), 1.53 – 1.41 (m, 1H), 0.91 – 0.88 (m, 9H), 0.08 – 0.06 (m, 6H); ¹³C NMR (126 MHz, CDCl₃) δ 183.8, 158.9, 152.2, 122.5, 119.5, 91.3, 86.0, 69.9, 34.8, 34.4, 25.7, 21.9, 18.2, -4.6, -5.0; HRMS (ESI) calcd for C₁₇H₂₄Br₂KO₃Si [M+K]⁺: 500.9499; found: 500.9493; [α]_D²¹ = -153.5 (*c* 1.00, CHCl₃)



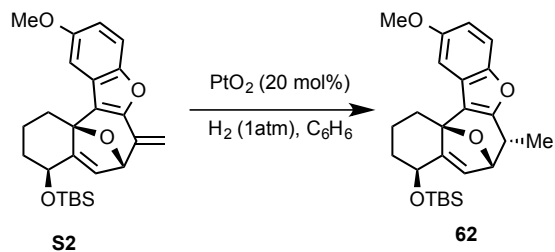
Benzofuran (-)-61: [α]_D²³ = -214.6 (*c* 1.00, CHCl₃)

Benzofuran (+)-61: [α]_D²³ = +213.9 (*c* 1.00, CHCl₃)



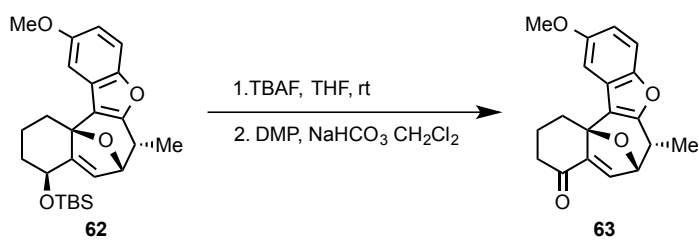
Olefin (+)-S2: [α]_D²³ = +46.7 (*c* 1.00, CHCl₃)

Olefin (-)-S2: [α]_D²³ = -47.1 (*c* 1.00, CHCl₃)



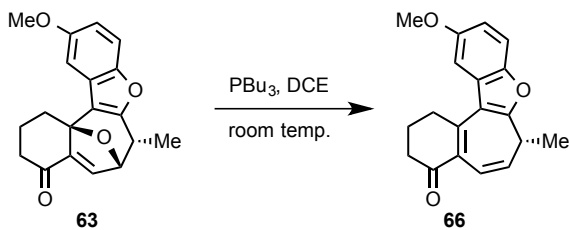
Tetracycle (+)-62: $[\alpha]_{\text{D}}^{23} = +149.2$ (*c* 1.00, CHCl_3)

Tetracycle (–)-62: $[\alpha]_{\text{D}}^{23} = -151.7$ (*c* 1.00, CHCl_3)



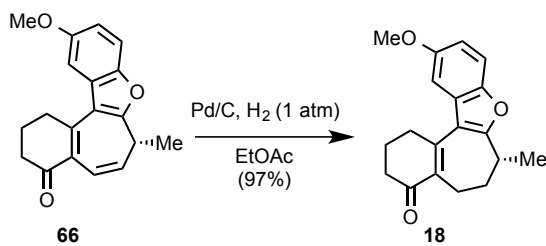
Enone (+)-63: $[\alpha]_{\text{D}}^{22} = +215.0$ (*c* 1.00, CHCl_3)

Enone (–)-63: $[\alpha]_{\text{D}}^{22} = -213.8$ (*c* 1.00, CHCl_3)



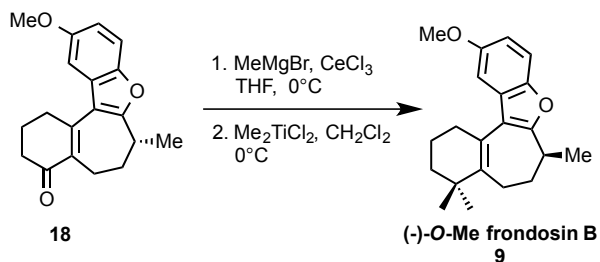
Cycloheptatriene (+)-66: $[\alpha]_{\text{D}}^{22} = +60.8$ (*c* 1.00, CHCl_3)

Cycloheptatriene (–)-66: $[\alpha]_{\text{D}}^{22} = -59.8$ (*c* 1.00, CHCl_3).



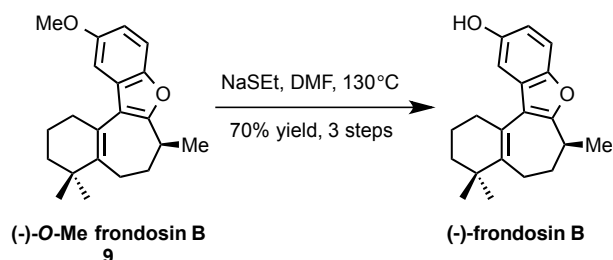
Enone (–)-18: $[\alpha]_{\text{D}}^{23} = -39.4$ (*c* 1.00, CHCl_3)

Enone (+)-18: $[\alpha]_D^{22} = +38.4$ (*c* 1.00, CHCl₃)



(-)-O-Methyl Frondosin B 9: $[\alpha]_D^{23} = -11.1$ (*c* 1.00, CHCl₃)

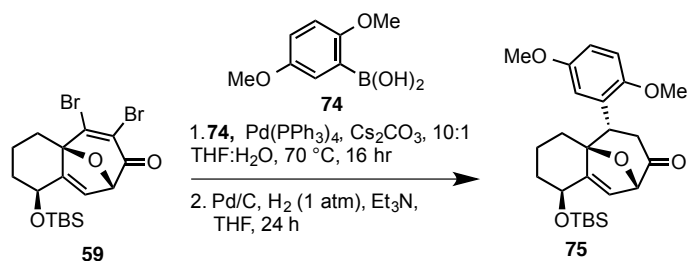
(+)-O-Methyl Frondosin B 9: $[\alpha]_D^{23} = +11.7$ (*c* 1.00, CHCl₃)



(-)-Frondosin B: $[\alpha]_D^{23} = -16.7$ (*c* 0.13, MeOH)

(+)-Frondosin B: $[\alpha]_D^{23} = +16.4$ (*c* 0.13, MeOH)

Experimental procedures: Asymmetric total synthesis of (+)-frondosin A

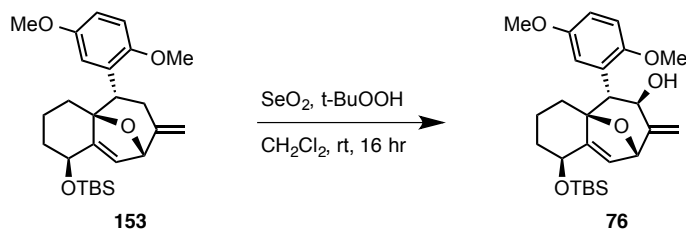


Ketone (-)-75: A flame dried pressure vessel under argon was charged with dibromoenone **59** (2.00g, 4.3 mmol), boronic acid (1.26 g, 5.16 mmol), and Cs₂CO₃ (1.7 g, 5.16 mmol). The solids were dissolved in THF-H₂O (10:1, 47 mL) and the mixture was degassed by bubbling argon

through the solution for 20 min. After this time, Pd(PPh₃)₄ (500 mg, 0.43 mmol, 10 mol%) was added and the mixture was again degassed (argon) for 10 min. The flask was sealed and the reaction was heated at 70 °C for 4 h. Following the completion of the coupling as monitored by TLC, the reaction mixture was cooled to room temperature, diluted with EtOAc (100 mL) and poured into H₂O. The aqueous layer was extracted with EtOAc (3 x 50 mL) and the combined organic layers were washed with brine (100 mL), dried over Na₂SO₄, and concentrated to give the crude hydroquinone as yellow foam. The crude material was passed through a plug of silica gel (25 g) eluting with 15% EtOAc in hexanes and used without further purification.

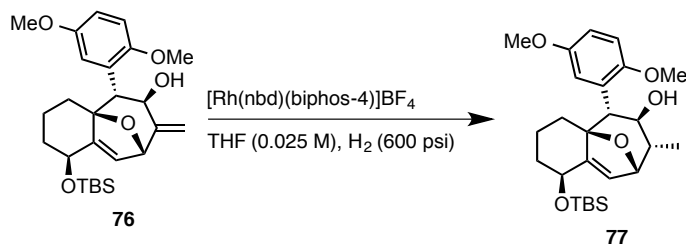
The crude hydroquinone obtained above was dissolved in EtOAc (10 mL) and treated with Et₃N (4.17 mL, 30.1 mmol). To the solution was added 10% Pd/C (1.00 g) and the flask was evacuated and backfilled with H₂ (3 cycles). The reaction mixture was stirred under an atmosphere of H₂ (balloon) for 24 h before being filtered through a pad of SiO₂ eluting with EtOAc (250 mL). The solvent was removed under vacuum and the residue was purified by flash chromatography (SiO₂, 100g, 15% EtOAc in hexanes) to give ketone **75** (1.45 g, 3.26 mmol, 76% yield, 2 steps) as a white foam.

R_f = 0.30 (5% EtOAc in hexanes); IR (KBr): ν : 2948, 1728, 1488, 1232, 1117, cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 6.80 (d, *J* = 8.8 Hz, 1H), 6.74 (dd, *J* = 8.9, 2.9 Hz, 1H), 6.67 (d, *J* = 2.8 Hz, 1H), 6.14 (s, 1H), 4.60 (s, 1H), 4.38 (t, *J* = 8.3 Hz, 1H), 4.09 (ddd, *J* = 11.1, 5.6, 1.4 Hz, 1H), 3.78 (dd, *J* = 23.3, 13.4 Hz, 7H), 2.99 (dd, *J* = 17.9, 8.9 Hz, 1H), 2.66 (ddd, *J* = 17.9, 7.6, 1.2 Hz, 1H), 2.40 (d, *J* = 13.2 Hz, 1H), 1.68 – 1.61 (m, 2H), 1.43 (ddd, *J* = 10.7, 6.0, 3.7 Hz, 1H), 1.28 – 1.17 (m, 1H), 0.91 (s, 9H), 0.44 – 0.32 (m, 1H), 0.12 – 0.05 (m, 6H); ¹³C NMR (126 MHz, CDCl₃) δ 203.6, 153.5, 152.9, 152.0, 128.8, 122.4, 116.7, 111.4, 110.9, 90.4, 85.6, 70.7, 56.0, 55.5, 40.3, 39.5, 35.8, 35.6, 25.7, 21.1, 18.2, -4.8, -5.0; HRMS (ESI) calcd for C₂₅H₃₇O₅Si [M+H]⁺: 445.2410; found: 445.2389; [α]_D²² = -130.5 (*c* = 1.00, CHCl₃).



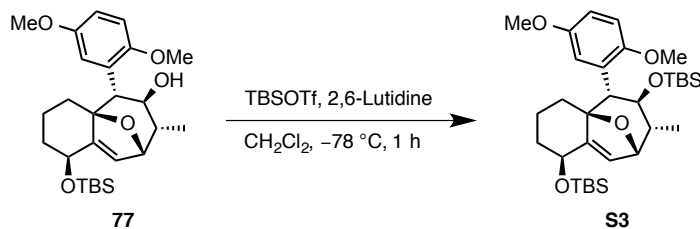
Allylic alcohol (+)-76: Selenium (IV) oxide (205 mg, 1.85 mmol) was suspended in dichloromethane (18.5 mL) and *tert*-butylhydroperoxide (70% solution in H₂O, 1.53 mL, 11.1 mmol) was added. After stirring the mixture for 20 min, a solution of olefin **153** (1.63 g, 3.69 mmol) in dichloromethane (10 mL) was added and the reaction mixture was allowed to stir at room temperature for 16 h before being quenched with sat. aq. sodium sulfite (10 mL). The aqueous layer was extracted with CH₂Cl₂ (3 x 25 mL) and the combined organics were washed with H₂O (20 mL) and brine (20 mL) then dried over Na₂SO₄ and the solvent removed in vacuo. The crude alcohol was purified by flash chromatography (SiO₂, 35 g, 5% EtOAc in hexanes) to provide allylic alcohol **76** (1.37 g, 2.99 mmol, 81% yield, 97:3 mixture of diastereomers) as a white foam.

$R_f = 0.25$ (25% EtOAc in hexanes); IR (KBr): ν : 3444, 2938, 1498, 1235, 1099, 838 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 6.84 (d, $J = 8.8$ Hz, 1H), 6.80 (d, $J = 3.0$ Hz, 1H), 6.75 (dd, $J = 8.8$, 3.0 Hz, 1H), 6.08 (t, $J = 2.1$ Hz, 1H), 5.23 – 5.20 (m, 1H), 5.08 (dd, $J = 2.1$, 1.3 Hz, 1H), 4.94 (d, $J = 2.0$ Hz, 1H), 4.75 (d, $J = 2.3$ Hz, 1H), 4.34 (ddd, $J = 11.3$, 5.6, 2.1 Hz, 1H), 3.77 (s, 3H), 3.76 (s, 3H), 3.67 (d, $J = 9.9$ Hz, 1H), 2.29 (d, $J = 13.3$ Hz, 1H), 1.68 – 1.62 (m, 1H), 1.56 (d, $J = 6.5$ Hz, 1H), 1.42 (td, $J = 13.8$, 5.0 Hz, 1H), 1.36 – 1.29 (m, 1H), 1.24 – 1.15 (m, 1H), 0.93 (s, 9H), 0.14 (dd, $J = 11.6$, 8.6 Hz, 6H); ¹³C NMR (126 MHz, CDCl₃) δ 153.6, 153.4, 149.9, 145.8, 127.5, 124.1, 115.8, 112.0, 111.0, 107.2, 88.9, 83.2, 70.3, 70.1, 56.2, 55.6, 49.8, 35.8, 34.4, 25.8, 21.0, 18.3, -4.8, -4.9. HRMS (ESI) calcd for C₂₆H₃₈O₅Si [M+H]⁺: 458.2489; found: 458.2475; $[\alpha]_D^{22} = +84.0$ ($c = 1.00$, CHCl₃).



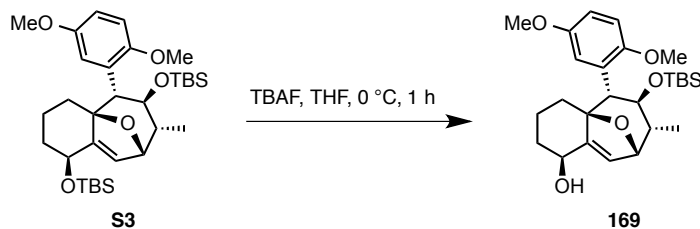
Alcohol (+)-77: Allylic alcohol **76** (100 mg, 0.218 mmol) and $[\text{Rh}(\text{nbd})(\text{diphos-4})]\text{BF}_4$ (31 mg, 0.20 equiv, 0.044 mmol) were placed in a dry plastic vial and dissolved in THF (8.7 mL, 0.025 M). The vial was placed in a hydrogenation apparatus and purged three times (H_2) prior to pressurizing the reaction vessel with H_2 (600 psi). The reaction mixture was allowed to stir under hydrogen pressure for 2 hours before carefully releasing the pressure. The solvent was removed under reduced pressure and the crude material was passed through a pad of SiO_2 (3 g) eluting with 50% EtOAc in hexanes (50 mL) to provide alcohol **77** (98 mg, 98% yield) as a white foam.

$R_f = 0.38$ (25% EtOAc in hexanes, eluted twice); IR (KBr): ν : 3459, 2933, 1496, 1115, 838 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 6.84 (d, $J = 8.5$ Hz, 1H), 6.76 – 6.72 (m, 2H), 6.05 (s, 1H), 4.53 (s, 1H), 4.32 (ddd, $J = 11.3, 5.5, 2.2$ Hz, 1H), 3.78 (s, 3H), 3.77 – 3.74 (m, 4H), 3.60 (d, $J = 6.9$ Hz, 1H), 2.29 (d, $J = 13.1$ Hz, 1H), 1.89 (dq, $J = 13.7, 6.9, 3.8$ Hz, 1H), 1.64–1.61 (m, 1H), 1.56 (s, OH, 1H), 1.41–1.15 (m, 3H), 1.22 – 1.13 (m, 1H), 1.04 (d, $J = 6.9$ Hz, 3H), 0.95 – 0.93 (m, 9H), 0.16 – 0.12 (m, 6H); ^{13}C NMR (126 MHz, CDCl_3) δ 153.7, 153.6, 150.2, 127.8, 122.2, 115.9, 112.0, 110.7, 88.5, 82.2, 74.9, 70.2, 56.2, 55.6, 47.8, 39.9, 35.8, 34.4, 25.8, 21.0, 18.3, 14.4, -4.9, -4.8; HRMS (ESI) calcd for $\text{C}_{26}\text{H}_{31}\text{O}_5\text{Si}$ $[\text{M}+\text{H}]^+$: 461.2723; found: 461.2725; $[\alpha]_D^{22} = +95.8$ ($c = 1.00$, CHCl_3).



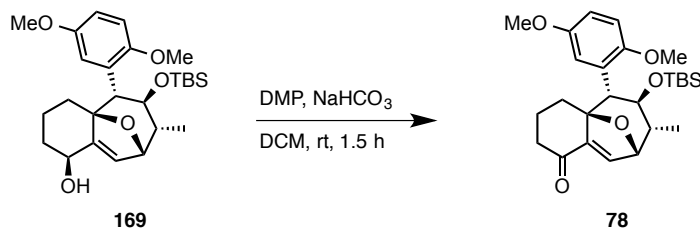
DiSilyl (+)-S3: To a flame dried flask was added alcohol **77** (510 mg, 1.1 mmol) in CH_2Cl_2 (5.5 mL) and cooled to -78°C . 2,6-Lutidine was added (0.19 mL, 1.66 mmol) followed by TBSOTf (0.28 mL, 1.1 mmol) stirred at -78°C for one hour. The reaction was quenched with sat. aq. NH_4Cl at -78°C and allowed to warm to rt before being extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed with sat. aq. NaHCO_3 (3 X 50 mL), H_2O (3 x 50 mL), brine (100 mL), dried over Na_2SO_4 and concentrated. The resulting DiSilyl **S3** was purified by flash chromatography (SiO_2 , 25 g) using 10% EtOAc in hexanes as the eluent to afford product as a clear oil (600 mg, 1.04 mmol, 95% yield).

$R_f = 0.8$ (5% EtOAc in hexanes); IR (KBr) ν : 2926, 1587, 1091, 835, cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 6.81 – 6.76 (m, 1H), 6.71 – 6.64 (m, 2H), 6.07 – 6.03 (m, 1H), 4.48 (s, 1H), 4.37 (dd, $J = 5.4$ Hz, 1H), 3.78 (t, $J = 8.4$ Hz, 1H), 3.76 (s, 3H), 3.75 (s, 3H), 3.62 (d, $J = 9.4$ Hz, 1H), 2.24 (d, $J = 13.5, 2.9$ Hz, 1H), 1.95 – 1.85 (m, 1H), 1.61 (dq, $J = 11.8, 4.0$ Hz, 1H), 1.37 (td, $J = 13.4, 4.7$ Hz, 1H), 1.28 (d, $J = 16.2$, Hz, 1H), 1.24 – 1.10 (m, 1H), 0.98 (d, $J = 6.8$ Hz, 3H), 0.95 (s, 9H), 0.64 (s, 9H), 0.17 (s, 3H), 0.13 (s, 3H), 0.11 – 0.03 (m, 1H), -0.07 (s, 3H), -0.63 (s, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 153.8, 153.5, 150.4, 129.8, 122.6, 117.2, 112.4, 110.3, 88.4, 82.2, 77.2, 70.5, 56.5, 55.7, 47.9, 40.6, 35.9, 34.6, 25.8, 25.8, 21.1, 18.4, 18.2, 15.2, -4.5, -4.8, -4.9, -4.9; HRMS (ESI) calcd for $\text{C}_{32}\text{H}_{54}\text{O}_5\text{Si}_2[\text{M}]^+$: 574.3510; found: 574.3480. $[\alpha]_D^{22} = +81.5$ ($c = 1.00$, CHCl_3).



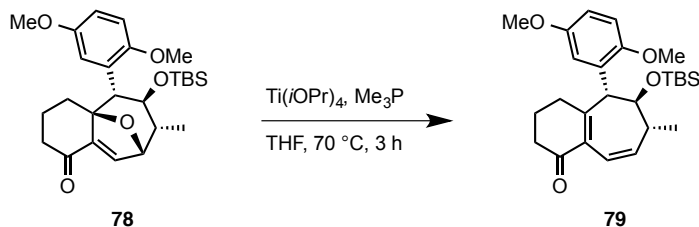
Enol (+)-169: To a flame dried flask was added disilyl **S3** (1.74 g, 3.03 mmol) in THF (10 mL) and cooled to 0 °C. To this solution was added TBAF (3.63 mL, 3.6 mmol, 1 M in THF) and stirred at this temperature for 20 min before being allowed to warm to rt and stirred for an additional 6 hr. Following the consumption of all starting material the reaction was concentrated and absorbed onto SiO₂ (5 g). Flash chromatography (SiO₂, 150 g) using 25% EtOAc in hexanes as the eluent afforded alcohol **169** as a white foam (1.33 g, 2.87 mmol, 95% yield).

R_f = 0.18 (25% EtOAc in hexanes); IR (KBr): ν ; br 3387, 2936, 1216, 1082, 883 cm^{-1} ; ¹H NMR (500 MHz, CDCl₃) δ 6.75 (d, J = 8.7 Hz, 1H), 6.68 - 6.62 (m, 2H), 6.11 (s, 1H), 4.47 (s, 1H), 4.33 (dd, J = 16.2, 4.8 Hz, 1H), 3.76 (t, J = 8.6 Hz, 1H), 3.71 (s, 3H), 3.70 (s, 3H), 3.59 (d, J = 9.2 Hz, 1H), 2.33 (s, 1H), 2.24 (d, J = 13.0 Hz, 1H), 1.87 (td, J = 7.2, 4.1 Hz, 1H), 1.77 - 1.71 (m, 1H), 1.36 (dd, J = 13.8, 5.0 Hz, 1H), 1.28 (d, J = 19.0 Hz, 1H), 1.08 - 0.98 (m, 1H), 0.95 (d, J = 6.6 Hz, 3H), 0.59 (s, 9H), 0.11 (qt, J = 14.0, 3.3 Hz, 1H), -0.12 (s, 3H), -0.71 (s, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 153.7, 153.3, 150.5, 129.3, 122.2, 115.8, 112.6, 111.6, 88.4, 82.3, 77.0, 69.6, 56.4, 55.7, 48.0, 40.5, 35.9, 34.6, 25.7, 21.0, 18.0, 15.0, -4.5, -5.0; HRMS (ESI) calcd for C₂₆H₃₉O₅Si [M+H]⁺: 459.2567; found: 459.2607; $[\alpha]_D^{22}$ = +82.5 (c = 2.00, CHCl₃).



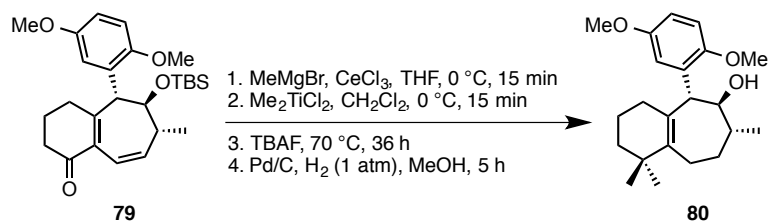
Enone (+)-78: To a flame dried flask was added alcohol **169** (630 mg, 1.36 mmol) in CH_2Cl_2 (13.5 mL) and cooled to 0 °C. The solution was treated sequentially with NaHCO_3 (1.15 g, 13.6 mmol) and Dess-Martin periodinane (1.16 g, 2.7 mmol) and stirred at 0 °C before being allowed to warm to rt. After 1.5 hr the reaction was quenched with sat. aq. $\text{Na}_2\text{S}_2\text{O}_3$, diluted with CH_2Cl_2 and stirred for 1 hr. The aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL) and the combined organics were washed with H_2O (50 mL), brine (50 mL), dried over Na_2SO_4 and the solvent removed in vacuo. The crude enone was purified by flash chromatography (SiO_2 , 30 g, 15% EtOAc in hexanes) to provide enone **78** as a mixture of non-interconverting atropisomers (595 mg, 1.30 mmol, 95% yield). The major atropisomer is reported.

$R_f = 0.33$ (15% EtOAc in hexanes); IR (KBr): ν ; 2950, 1686, 1500, 1215, 835 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.04 (s, 1H), 6.82 – 6.59 (m, 2H), 6.41 (d, $J = 3.0$ Hz, 1H), 4.65 (dd, $J = 4.2, 2.3$ Hz, 1H), 3.77 (s, 3H), 3.67 (s, 3H), 3.61 (t, $J = 8.5$ Hz, 1H), 2.11 (ddd, $J = 17.4, 8.3, 4.8$ Hz, 1H), 2.05 – 1.87 (m, 3H), 1.83 – 1.65 (m, 2H), 1.53 – 1.45 (m, 1H), 1.01 (d, $J = 7.0$ Hz, 3H), 0.92 – 0.82 (m, 1H), 0.67 (s, 9H), -0.14 (s, 3H), -0.78 (s, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 198.2, 153.9, 153.3, 144.8, 137.9, 129.2, 114.2, 113.0, 112.3, 87.8, 82.5, 77.8, 56.4, 55.7, 47.5, 40.1, 31.7, 25.7, 19.3, 18.0, 15.3, -4.6, -5.0; HRMS (ESI) calcd for $\text{C}_{26}\text{H}_{39}\text{O}_5\text{Si}$ $[\text{M}+\text{H}]^+$: 459.2567; found: 459.2602; $[\alpha]_D^{22} = +80.2$ ($c = 1.00$, CHCl_3).



Diene (+)-79: To a flame dried pressure tube was added enone **78** (405 mg, 0.88 mmol) in THF (8.8 mL) followed sequentially by $\text{Ti}(i\text{-OPr})_4$ (0.78 mL, 2.6 mmol) and Me_3P (2.65 mL, 2.6 mmol, 1 M in THF). The mixture was sealed and stirred at 70 °C for 3 hr. Following the consumption of all starting material the vessel was cooled to 0 °C quenched with 2 N HCl, diluted with EtOAc then allowed to warm to rt. The aqueous layer was extracted with EtOAc (3 x 40 mL) and the combined organic layers were washed with 2 N HCl (2 x 40 mL), H_2O (2 X 40), brine (40 mL) then dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography (SiO_2 , 20 g, 10% EtOAc in hexanes) to provide diene **79** (336mg, 0.76 mmol, 86% yield).

R_f = 0.44 (15% EtOAc in hexanes); IR (KBr): ν ; 2947, 1668, 1503, 1497, 1226, 1052, 864, 734 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 6.73 (d, J = 8.8 Hz, 1H), 6.70 (d, J = 8.8 Hz, 1H), 6.66 (s, 1H), 6.59 (d, J = 11.6 Hz, 1H), 5.69 (dd, J = 11.6, 5.2 Hz, 1H), 4.16 (d, J = 5.9 Hz, 1H), 4.07 (t, J = 6.3 Hz, 1H), 3.77 (s, 3H), 3.69 (s, 3H), 2.50 – 2.29 (m, 5H), 1.96 – 1.86 (m, 1H), 1.86 – 1.76 (m, 1H), 0.86 – 0.81 (m, 12H), -0.05 (s, 3H), -0.37 (s, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 199.0, 160.9, 153.4, 152.0, 136.1, 131.8, 129.6, 122.2, 116.4, 111.9, 110.9, 80.2, 56.1, 55.5, 41.1, 37.7, 33.7, 25.8, 22.4, 18.0, 17.9, -4.3, -5.4; HRMS (ESI) calcd for $\text{C}_{26}\text{H}_{39}\text{O}_4\text{Si}$ $[\text{M}+\text{H}]^+$: 443.2617; found: 443.2640; $[\alpha]_D^{23}$ = +174.8 (c = 1.00, CHCl_3).



Alcohol (+)-80: To a dry schlenk flask was added freshly ground $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ (740 mg, 1.9 mmol). The flask was heated under vacuum to 150°C for 3 h. The flask was flushed with argon, cooled to room temperature and enone **79** (278 mg, 0.62 mmol) in THF (31 mL) was added. The suspension was stirred at room temperature for 15 min before being cooled to 0°C . To the cooled mixture was rapidly added a solution of MeMgBr (1.3 mL, 3.8 mmol, 3 M in diethylether) and stirring continued for 15 min before addition of MeOH (5 mL). The solution was diluted with H_2O (20 mL), brine (20 mL) and extracted with Et_2O (3 x 40 mL). The combined organics were washed with brine, dried over Na_2SO_4 , and concentrated to give the crude alcohol as a yellow oil; $R_f = 0.37$ (15% EtOAc in hexanes).

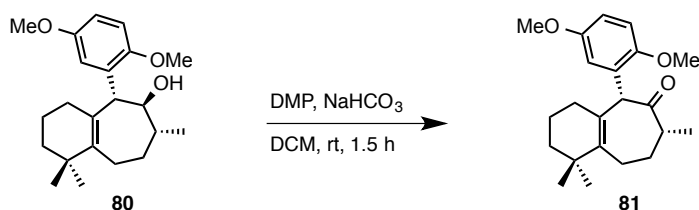
To a cooled (0°C) solution of TiCl_4 (0.64 mL, 0.62 mmol, 1M) in CH_2Cl_2 was slowly added a 2.2 M solution of dimethyl zinc in toluene (1.08 mL, 1.3 mmol). The deep red solution was stirred at 0°C for 15 min before a solution of the crude alcohol (pre-cooled to -78°C) obtained above (0.62 mmol) in CH_2Cl_2 (6.2 mL) was added dropwise via cannula. After 30 min, the reaction was quenched by dropwise addition of MeOH (5 mL) and diluted with Et_2O . The mixture was poured into H_2O (20 mL) and the aqueous layer was extracted with Et_2O (3 x 50 mL). The combined organics were washed with brine (50 mL) then dried over NaSO_4 and the solvent removed in vacuo. The crude material was pushed through a plug of silica (25g, 5% EtOAc in hexanes) and used without further purification.

The crude material obtained above (0.62 mmol) was added to a flame dried pressure vessel followed by TBAF (5.6 mL, 5.6 mmol, 1 M in THF). The vessel was sealed and heated to 65°C for a period of 36 hr. Following the consumption of all starting material the solvent was removed

in vacuo and passed through a plug of SiO₂ (15 g, 25% EtOAc in hexanes). The resulting alcohol was used without further purification.

To a flame dried flask was added crude alcohol obtained above (0.62 mmol) in MeOH (6.2 mL) and degassed by bubbling argon through solution for 15 min. To the solution was added 10% Pd/C (66 mg, 0.062 mmol) and the flask was evacuated and backfilled with H₂ (3 cycles). The reaction mixture was stirred under an atmosphere of H₂ (balloon) for 5 h before being filtered through a pad of celite eluting with CH₂Cl₂ (25 mL). The solvent was removed under vacuum and the residue was purified by flash chromatography (SiO₂, 15g, 15% EtOAc in hexanes) to provide alcohol **80** (132 mg, 0.38 mmol, 61% yield, 4 steps) as a cloudy oil.

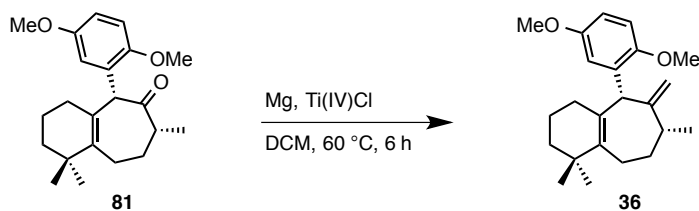
R_f = 0.29 (10% EtOAc in hexanes); IR (KBr): ν; br 3514, 2926, 1497, 1215, 1047, 805 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 6.85 (d, J = 8.8 Hz, 1H), 6.78 (d, J = 3.0 Hz, 1H), 6.73 (dd, J = 8.8, 3.1 Hz, 1H), 3.83 (s, 3H), 3.72 (s, 3H), 3.64 (d, J = 7.0 Hz, 1H), 3.59 – 3.51 (m, 1H), 2.10 (dd, J = 8.3, 4.2 Hz, 2H), 1.93 – 1.70 (m, 3H), 1.69 – 1.59 (m, 1H), 1.56 – 1.39 (m, 4H), 1.30 – 1.19 (m, 2H), 1.08 (s, 3H), 1.06 (s, 3H), 0.98 (d, J = 6.6 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 154.3, 151.5, 138.7, 132.2, 131.0, 114.5, 112.1, 112.0, 78.5, 56.3, 55.8, 55.5, 39.2, 35.9, 35.1, 34.8, 31.8, 28.2, 27.7, 25.3, 20.1, 18.6; HRMS (ESI) calcd for C₂₂H₃₂O₃ [M]⁺: 334.2351; found: 344.2349; [α]_D²² = +138.2 (c = 1.00, CH₂Cl₂).



Ketone (+)-81: To a flame dried flask was added alcohol **80** (160 mg, 0.46 mmol) in CH₂Cl₂ (4.6 mL) and cooled to 0 °C. The solution was treated sequentially with NaHCO₃ (390 g, 4.6 mmol) and Dess-Martin periodinane (395 g, 0.92 mmol) and stirred at 0 °C before being allowed to warm to rt. After 1.5 hr the reaction was quenched with sat. aq. Na₂S₂O₃, diluted with CH₂Cl₂ and

stirred for 1 hr. The aqueous layer was extracted with CH₂Cl₂ (3 x 20 mL) and the combined organics were washed with H₂O (25 mL), brine (25 mL), dried over Na₂SO₄ and the solvent removed in vacuo. The crude enone was purified by flash chromatography (SiO₂, 7.5 g, 15% EtOAc in hexanes) to provide ketone **81** (151 mg, 0.44 mmol, 95% yield). IR, NMR, and HRMS are consistent with the literature.⁵

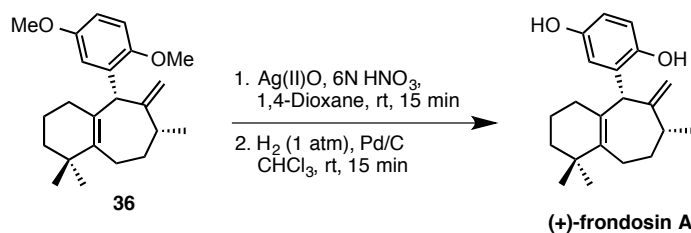
R_f = 0.32 (10% EtOAc in hexanes); IR; (KBr): ν; 2928, 1715, 1498, 1239, 1051 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 6.84 (d, J = 8.8 Hz, 1H), 6.76 (dd, J = 8.8, 3.1 Hz, 1H), 6.59 (d, J = 3.1 Hz, 1H), 4.31 (s, 1H), 3.76 (s, 3H), 3.71 (s, 3H), 3.20 – 3.09 (m, 1H), 2.23 – 2.08 (m, 2H), 2.08 – 1.93 (m, 2H), 1.84 – 1.73 (m, 1H), 1.64 – 1.47 (m, 5H), 1.14 (s, 3H), 1.10 (s, 3H), 1.06 (d, J = 6.5 Hz, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 212.4, 153.6, 152.9, 139.7, 129.7, 126.8, 113.7, 112.4, 111.8, 59.6, 56.5, 55.4, 41.7, 39.3, 37.3, 35.4, 31.5, 28.4, 27.8, 25.7, 19.9, 15.1; HRMS (ESI) calcd for C₂₂H₃₁O₃ [M+H]⁺: 343.2273; found: 343.2244; [α]_D²² = +139.8 (c = 1.00, CH₂Cl₂).



O-Methyl frondosin A (+)-36: A suspension of Mg (120 mg, 4.9 mmol) in CH₂Cl₂ (4.9 mL) in a flame dried pressure vessel was degassed by bubbling argon through it for a period of 15 min. TiCl₄ (1.22 mL, 1.22 mmol, 1 M in CH₂Cl₂) was added and to the suspension and stirred for 10 min. A solution of ketone **81** (105 mg, 0.307 mmol) in CH₂Cl₂ (2.4 mL) and THF (1.6 mL) was added dropwise to the suspension and the resulting mixture was heated at reflux for 6 h. Saturated aq. K₂CO₃ was then added to quench the reaction and the mixture was diluted with diethyl ether. The organic layer was separated, washed with brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude product was then purified by flash column chromatography

(SiO₂, 7.5 g, 2.5% EtOAc in hexanes) to give alkene **36** as a pale yellow oil (52 mg, 0.153 mmol, 74% yield brsm 35 mg). IR, NMR, and HRMS are consistent with the literature .⁶

R_f = 0.55 (5% EtOAc in hexanes); IR (KBr): ν ; 2920, 1636, 1494, 1455, 1218, 1052, 887 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 6.83 (d, J = 8.6 Hz, 1H), 6.77 (d, J = 3.0 Hz, 1H), 6.74 (dd, J = 8.5, 3.0 Hz, 1H), 4.64 (s, 1H), 4.25 (s, 1H), 4.15 (s, 1H), 3.76 (s, 3H), 3.72 (s, 3H), 2.55 – 2.45 (m, 2H), 2.00 – 1.94 (m, 1H), 1.91 – 1.83 (m, 2H), 1.65 – 1.43 (m, 4H), 1.31 – 1.22 (m, 2H), 1.10 (d, J = 7.0 Hz, 3H), 1.07 (s, 3H), 1.04 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 156.3, 154.0, 152.7, 137.6, 132.6, 130.5, 114.3, 112.0 (2C), 105.1, 56.8, 55.4, 52.8, 39.6, 39.4, 35.4, 35.3, 31.8, 28.1, 27.9, 25.0, 20.1, 19.5; HRMS (ESI) calcd for C₂₃H₃₂O₂ [M+H]⁺: 341.2481; found: 341.2459; $[\alpha]_D^{21}$ = +185.6 (*c* = 0.72, CH₂Cl₂).

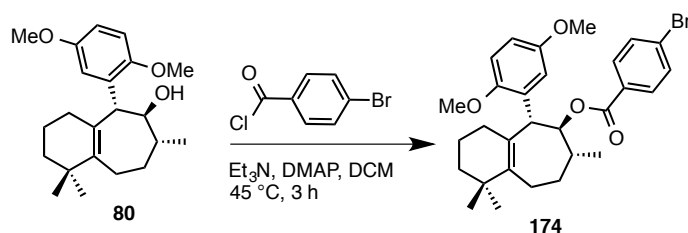


(+)-Frondosin A: To a flame dried flask was added alkene **36** (21.5 mg, 0.063 mmol) in Dioxane (1.7 mL). The solution was sequentially treated with AgO (15.5 mg, 0.13 mmol) and 6N HNO₃ (31 μ m, 0.19 mmol). The reaction was stirred for 15 min at rt before being quenched by the addition of sat. aq. NaHCO₃ and diluted with Et₂O. The aqueous layer was extracted with Et₂O (2 X 10 mL), the combined organic layers were washed with H₂O (3 X 20 mL) and brine (2 X 20 mL), dried over Na₂SO₄, concentrated and used without further purification.

The crude quinone obtained above was dissolved in CHCl₃ (2 mL). To the solution was added 10% Pd/C (7.1 mg) and the flask was evacuated and backfilled with H₂ (3 cycles). The reaction mixture was stirred under an atmosphere of H₂ (balloon) for 15 min before being filtered through a pad of SiO₂ eluting with Et₂O (3 mL). The solvent was removed under vacuum and the residue was purified by flash chromatography (SiO₂, 2g, 5%/10%/15% EtOAc in hexanes) to give

(+)-Frondosin A (17 mg, 0.054 mmol, 84% yield, 2 steps) as a white foam. IR, NMR, and HRMS were consistent to that of the original isolation literature.⁷

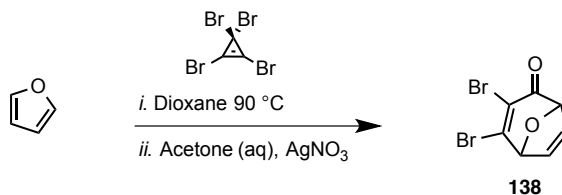
R_f = 0.33 (25% EtOAc in hexanes); IR (KBr): ν ; br 3400, 2926, 2908, 2870, 1652, 1495, 1456, 1359, 1207, 1192, 888, 741 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 6.74 (d, J = 8.6 Hz, 1H), 6.65 (dd, J = 8.6, 3.0 Hz, 1H), 6.56 (d, J = 3.0 Hz, 1H), 4.83 (dd, J = 0.8, 1.1 Hz, 1H), 4.50 (dd, J = 0.8, 1.1 Hz, 1H), 3.93 (dd, J = 1.1 Hz, 1H), 2.51 – 2.43 (m, 2H), 2.02 (dt, J = 14.7, 4.2 Hz, 1H), 1.89 – 1.82 (m, 3H), 1.58 – 1.33 (m, 5H), 1.07 (s, 3H), 1.06 (s, 3H), 1.04 (d, J = 6.9 Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 155.3, 149.4, 149.3, 140.6, 129.5, 128.4, 117.2, 116.6, 114.6, 107.9, 56.4, 39.5, 37.7, 37.0, 35.7, 32.1, 28.0, 27.8, 25.4, 20.1, 19.8; HRMS (ESI) calcd for $\text{C}_{21}\text{H}_{29}\text{O}_2$ $[\text{M}+\text{H}]^+$, 313.2167, found: 313.2177; $[\alpha]_D^{22}$ = +29.8 (c = 0.25, MeOH); Lit: $[\alpha]_D$ = +31.5 (c = 0.25, MeOH)



BromoBenzoate (+)-174: To a flame dried pressure vessel was added alcohol **80** (18 mg, 0.052 mmol) in CH_2Cl_2 (0.04 M). The solution was sequentially treated with Et_3N (0.022ml, 0.156 mmol), DMAP (6.4 mg, 0.052 mmol) and 4-bromobenzoyl chloride (34.4 mg, 0.156 mmol). The reaction vessel was sealed and heated at 45 °C for 3 hr. Following the consumption of all starting material the reaction was allowed to return to rt and quenched with H_2O . The aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL), the combined organic layers were then washed with sat. aq. NaHCO_3 (15 mL), H_2O (2 x 15 mL), brine (25 mL), dried over Na_2SO_4 and concentrated. The crude benzoate was subject to flash chromatography (SiO_2 , 2.5g, 5% EtOAc in hexanes) to yield a white crystalline solid (22 mg, 0.041 mmol, 80% yield). Benzoate **174** crystals were grown using CHCl_3 and pentane in a vapor diffusion method.

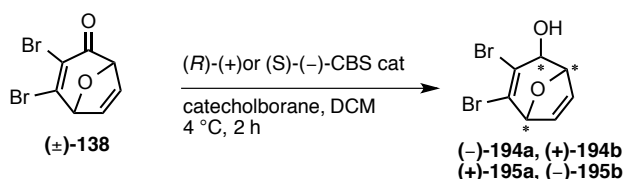
$R_f = 0.39$ (5% EtOAc in hexanes); mp = 129.1 – 130.4 °C IR (KBr): ν ; 2927, 1715, 1589, 1494, 1271, 1012, 755 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.78 – 7.71 (m, 2H), 7.53 – 7.47 (m, 2H), 6.81 (d, $J = 2.8$ Hz, 1H), 6.68 – 6.57 (m, 2H), 5.47 (t, $J = 16.6, 8.7, 8.3$ Hz, 1H), 4.07 (d, $J = 8.6$ Hz, 1H), 3.68 (s, 3H), 3.56 (b s, 3H), 2.55 – 2.45 (m, 1H), 2.24 (ddd, $J = 15.2, 6.3, 3.7$ Hz, 1H), 2.16 – 2.06 (m, 1H), 1.91 – 1.80 (m, 1H), 1.80 – 1.66 (m, 2H), 1.56 – 1.38 (m, 5H), 1.07 (s, 3H), 1.06 (s, 3H), 0.81 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 165.2, 153.4, 152.0, 131.3, 131.1, 130.7, 129.9, 127.4, 115.7, 112.0, 111.1, 55.7, 55.5, 50.8, 39.4, 37.2, 35.5, 31.2, 29.6, 28.2, 27.8, 25.3, 19.9, 18.8, 18.6; HRMS (ESI) calcd for $\text{C}_{29}\text{H}_{35}\text{BrO}_4$ $[\text{M}]^+$: 526.1919; found: 526.1897; $[\alpha]_D^{22} = +90.8$ ($c = 0.5$, CHCl_3).

Experimental procedures: Stereodivergent resolution of dibromoenone intermediates



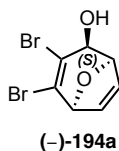
General procedure for one-pot Diels Alder and silver hydrolysis: To a flame dried pressure vessel was added furan (24.6 mmol) and solvated with 1,4-dioxane (5 mL). The solution was treated with freshly distilled TBCP (8.7 g, 24.6 mmol) at rt and the vessel was sealed. The vessel was stirred overnight at rt before being gradually heated to 80 °C and held at that temperature until all starting material was consumed ~1 hr. After this time, the reaction was allowed to cool to rt, diluted with acetone (46 mL) and treated with 2 portions of $\text{AgNO}_{3(\text{aq})}$ (8.3 g, 49.2 mmol, in 23 mL of H_2O) over 20 min. The suspension was allowed to stir at rt for 3 hr before being poured over solid NaHCO_3 (6.2 g, 73.8 mmol). The solids were removed by filtration through Celite and washed with acetone (300 mL). The filtrate was concentrated and then extracted with Et_2O (4 x 100 mL). The combined organic layers were washed with sat. NaHCO_3 (2 x 100 mL), H_2O (3 x

100 mL), brine (2 x 100 mL) dried over sodium sulfate and concentrated. The resulting crude dibromoenone was purified by flash chromatography using 25% EtOAc in hexanes as the eluent to afford products as yellow solids. The spectral data of (\pm)-**138** and (\pm)-**140** were consistent to previous work done in the lab. Isolated with yields of (\pm)-**138** (96%, 23.6 mmol) and (\pm)-**140** (94%, 23.1 mmol).

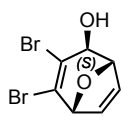


General procedure for CBS reduction: To a flame dried flask was added substrate in CH_2Cl_2 (0.2 M) followed by the (R)-(+)- or (S)-(-)-CBS catalyst (50 mol%). The solution was stirred at rt for a period of 20 minutes at which time the reaction was cooled to 4 °C and catecholborane (150 mol%) was added. Following the consumption of all starting material the reaction was quenched with 15 % NaOH and allowed to stir at rt for 1h. The aqueous layer was extracted with CH_2Cl_2 (3x 0.05 M). The combined organic layers were washed with 15% NaOH (3 x 0.05 M) and brine (0.05 M), dried over sodium sulfate and concentrated. The resulting diastereomers were separated and purified by flash chromatography (SiO_2 , 1:200 g) using 15% EtOAc in hexanes as the eluent to afford products as white solids.

Endo-alcohol-(-)-194a: Prepared by utilizing the (R)-(+)-CBS catalyst; yield based on 500 mg scale of (\pm)-**138**; yield = 226 mg, 45%; $[\alpha]_{\text{D}}^{23} = -63.6$ (c 1.00, CHCl_3) with 95.4% ee for the major enantiomer having a $T_{\text{r}} = 44$ min.



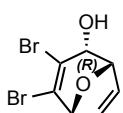
Exo-alcohol-(+)-194b: Prepared by utilizing the (R)-(+)-CBS catalyst; yield based on 500 mg



(+)-194b

scale of (\pm)-**138**; yield = 232 mg, 47%; R_f = 0.26 (Hex:EtOAc, 3:1); IR (KBr) ν : 3406, 3094, 2970, 2868, 1603, 1299, 1080, 1054, 919, 741, 692, 597 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 6.88 (dd, J = 5.9, 1.2 Hz, 1H), 6.29 (dd, J = 5.9, 2.1 Hz, 1H), 5.01 (d, J = 2.1 Hz, 1H), 4.97 (d, J = 1.8 Hz, 1H), 3.85 (d, J = 8.4 Hz, 1H), 2.75 (d, J = 8.8 Hz, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ 140.2, 131.3, 129.0, 121.6, 84.5, 83.6, 72.5; Enantiomeric excess of (**+**)-**194b** was determined by conversion to its Mosher ester; ^{19}F NMR (376 MHz, CDCl_3) δ -71.87 (s, 3F) >99% ee; HRMS (ESI) calcd for $\text{C}_7\text{H}_6\text{Br}_2\text{O}_2$ $[\text{M}+\text{H}]^+$: 280.8813; found: 280.8839; $[\alpha]_D^{23}$ = +80.5 (c 1.00, CHCl_3).

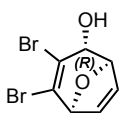
Endo-alcohol-(+)-195a: Prepared by utilizing the (S)-(-)-CBS catalyst; yield based on 500 mg



(+)-195a

scale of (\pm)-**138**; yield = 230 mg, 46%; $[\alpha]_D^{23}$ = +70.2 (c 1.00, CHCl_3) with 93.3% ee for the major enantiomer having a T_r = 36 min.

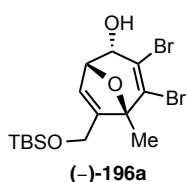
Exo-alcohol-(-)-195b: Prepared by utilizing the (S)-(-)-CBS catalyst; yield based on 500 mg



(-)-195b

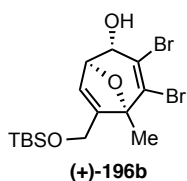
scale of (\pm)-**138**; yield = 236 mg, 47%. R_f = 0.26 (Hex:EtOAc, 3:1); IR (KBr) ν : 3406, 2975, 2868, 2389, 1606, 1296, 1088, 1042, 874, 722, 694, 597 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 6.88 (dd, J = 5.9, 1.5 Hz, 1H), 6.29 (dd, J = 5.9, 2.0 Hz, 1H), 5.01 (d, J = 2.0 Hz, 1H), 4.97 (d, J = 1.8 Hz, 1H), 3.84 (d, J = 8.8 Hz, 1H), 2.90 (d, J = 9.0 Hz, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ 140.1, 131.2, 129.0, 121.6, 84.6, 83.5, 72.5; Enantiomeric excess of (**-**)-**195b** was determined by conversion to its Mosher ester; ^{19}F NMR (376 MHz, CDCl_3) δ -71.39 (s, 3F) >99% ee; HRMS (ESI) calcd for $\text{C}_7\text{H}_6\text{Br}_2\text{O}_2$ $[\text{M}+\text{H}]^+$: 280.8813; found: 280.8842; $[\alpha]_D^{23}$ = -79.2 (c 1.00, CHCl_3).

Endo-Silyl-alcohol-(–)-196a: Prepared by utilizing the (R)-(+)-CBS catalyst; yield based on 1.75

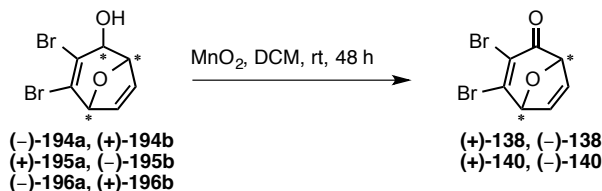


g scale of (\pm)-**140**; yield = 875 mg, 49%; R_f = 0.50 (Hex:EtOAc, 3:1); IR (KBr) ν ; 3446, 2953, 2928, 2856, 1592, 1254, 1068, 844, 778 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 5.99 – 5.89 (m, 1H), 5.14 (d, J = 5.8 Hz, 1H), 4.53 (t, J = 5.8 Hz, 1H), 4.38 (s, 2H), 2.25 (dd, J = 9.0, 5.2 Hz, 1H, OH), 1.56 (s, 3H), 0.92 (s, 9H), 0.09 (s, 6H); ^{13}C NMR (126 MHz, CDCl_3) δ 157.0, 133.6, 126.0, 122.5, 88.1, 80.8, 70.7, 59.3, 25.8, 21.2, 18.4, -5.4; HRMS (ESI) calcd for $\text{C}_{15}\text{H}_{24}\text{Br}_2\text{O}_3\text{Si}$ $[\text{M}+\text{H}]^+$: 438.9940; found: 438.9952; $[\alpha]_D^{22}$ = -51.6 (c 1.00, CHCl_3).

Exo-Silyl-alcohol-(+)-196b: Prepared by utilizing the (R)-(+)-CBS catalyst; yield based on 1.75



g scale of (\pm)-**140**; yield = 827 mg, 47%; R_f = 0.43 (Hex:EtOAc, 3:1); IR (KBr) ν ; 3444, 2953, 2927, 2858, 1594, 1256, 1067, 844, 776 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 5.97 – 5.88 (m, 1H), 4.94 – 4.88 (m, 1H), 4.40 – 4.30 (m, 2H), 3.81 (d, J = 8.8 Hz, 1H), 2.83 (d, J = 8.8 Hz, 1H), 1.61 (s, 3H), 0.91 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 157.7, 135.45, 123.4, 121.1, 87.7, 83.6, 73.4, 59.4, 25.8, 20.7, 18.3, -5.4, -5.5; HRMS (ESI) calcd for $\text{C}_{15}\text{H}_{24}\text{Br}_2\text{O}_3\text{Si}$ $[\text{M}+\text{H}]^+$: 438.9940; found: 438.9923; $[\alpha]_D^{22}$ = +65.7 (c 1.00, CHCl_3).



General procedure for MnO_2 oxidation of separated diastereomers. To a flame dried flask was added alcohol substrate in CH_2Cl_2 (0.1 M). MnO_2 (300 mol%) was added to the flask and was stirred at rt until starting material was consumed ~48 h. Solids were filtered off through a plug of silica and the resulting organics were condensed under reduced pressure. The solids were purified by flash chromatography (SiO_2 , 2.5 g) using 10% EtOAc in hexanes as the eluent to

afford the (+) or (–) dibromoenones as a white solid. Spectral data was consistent to that of work previously done in our lab. Enantiomeric excess of all compounds were determined by HPLC analysis in hexanes:isopropanol (99.5:0.5) at a column flow rate of 1.0 mL/min with detection at 254 nm.

Dibromoenone-(+)-138: Yield based on 50 mg scale of (–)-194a; Oxidation yielded (+)-138 in

46 mg (92 %) with an $[\alpha]_D^{23} = +266.3$ (c 1.00, CHCl₃); HPLC analysis showed that (+)-138 was formed with 94.7% ee. Yield based on 50 mg scale of (–)-195b; Oxidation yielded (+)-138 in 48 mg (96 %) with an $[\alpha]_D^{23} = +269.4$ (c 1.00, CHCl₃);

HPLC analysis showed that (+)-138 was formed with 96.8% ee.

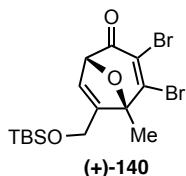
Dibromoenone-(–)-138: Yield based on 50 mg scale of (+)-195a; Oxidation yielded (–)-138 in

48 mg (96 %) with an $[\alpha]_D^{23} = -268.6$ (c 1.00, CHCl₃); HPLC analysis showed that (–)-138 was formed with 94.1% ee. Yield based on 50 mg scale of (+)-194b; Oxidation yielded (–)-138 in 46 mg (92 %) with an $[\alpha]_D^{23} = -295.1$ (c 1.00, CHCl₃);

HPLC analysis showed that (–)-138 was formed with 98.6% ee..

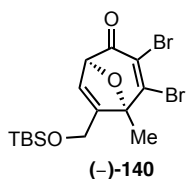
Silyl-dibromoenone-(+)-140: Yield based on 875 mg scale of (–)-196a; Oxidation yielded (+)-

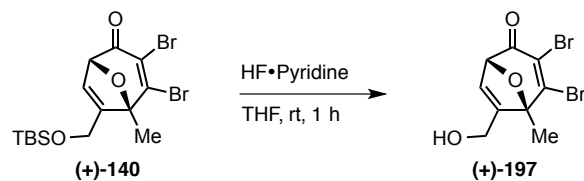
140 in 818 mg (94 %) with an $[\alpha]_D^{21} = +179.7$ (c 1.00, CHCl₃).



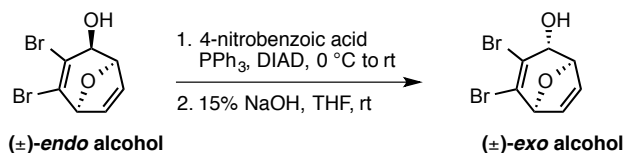
Silyl-dibromoenone-(–)-140: Yield based on 827 mg scale of (+)-196b; Oxidation yielded (–)-

140 in 790 mg (96 %) with an $[\alpha]_D^{21} = -182.3$ (c 1.00, CHCl₃).





Alcohol-(+)-197: To a plastic vial was added **(+)-140** (25 mg, 0.057 mmol) and diluted with THF (0.075 mL). The solution was treated with HF•pyridine (0.03 mL, 1.14 mmol, 70% in pyridine) and stirred at rt until all starting material was consumed ~1 h. The reaction was quenched with by the slow addition of NaHCO₃ and diluted with EtOAc (10 mL). The aqueous layer was extracted with EtOAc (2 x 20 mL) and the combined organic layers were washed with NaHCO₃ (20 mL), H₂O (20 mL), brine (20 mL) dried over sodium sulfate and concentrated. The crude alcohol was purified by flash chromatography (SiO₂, 2.5 g) using 10% EtOAc in hexanes as the eluent to afford the alcohol **(+)-197** (18 mg, 0.055 mmol, 97% yield) as a white solid. The solid was crystallized by a simple diffusion method using CHCl₃ and pentane as diffusing solvents. All spectra were consistent with work previously done in our lab.

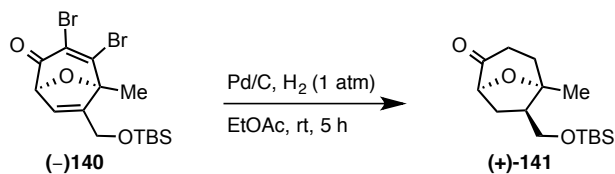


(±)-dibromo-*exo*-alcohol for HPLC analysis only: Triphenylphosphine (TPP) (327 mg, 1.25 mM) was added to a 10 mL flame dried flask, dissolved in benzene (3 mL) and cooled to 0 °C. Diisopropyl azodicarboxylate (DIAD) (0.24 mL, 1.25 mM) was added dropwise and the solution was stirred at 0 °C for 10 minutes. To the resulting red solution was added 4-nitrobenzoic acid (103 mg, 0.64 mM) followed by **(±)-endo-alcohol** (118 mg, 0.42 mM) in benzene (0.4 mL). The reaction was allowed to warm to rt and stirred until all starting material was consumed. The solvent was removed under reduced pressure and the resulting orange solids were dissolved in Et₂O (20 mL). The organic layer was washed with sodium bicarbonate (2×15 mL), water (2×15 mL) and brine (2×15 mL). The organics were then dried over sodium sulfate and the solvent was

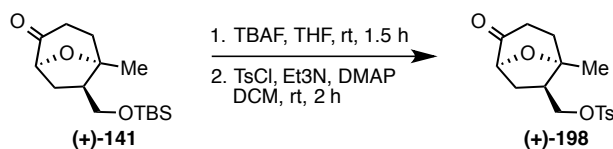
removed under reduced pressure. The resulting solids were purified by flash chromatography (SiO₂, 6 g) using 5% EtOAc in hexanes as the eluent to afford the **exo-nitrobenzoate** as a white solid.

The resulting **exo-nitrobenzoate** was taken up with THF (2 mL) and stirred with 15% NaOH at rt until all starting material was consumed. The reaction was quenched with water (3 mL) and the aqueous layer was extracted with EtOAc (3×10 mL). The combined organic layers were washed with sodium bicarbonate (2×15 mL) and brine (2×15 mL) and all solvent was removed under reduced pressure. The resulting solids were purified by flash chromatography (SiO₂, 6 g) using 25% EtOAc in hexanes as the eluent to afford (**±**)-**exo-alcohol** as a white solid. (95 mg, 80% over 2 steps). To develop a standard set of peaks for analysis (**±**)-**exo-alcohol** was converted to its Mosher ester using known procedures.

Experimental procedures: Efforts toward symmetric synthesis of platensimycin analogs



Saturated ketone (+)-141: Yield based on 13.5 g scale of **(-)-140**; Reduction yielded **(+)-141** in 8.3 g (95 %) with an $[\alpha]_D^{21} = +9.4$ (c 1.00, CHCl₃).

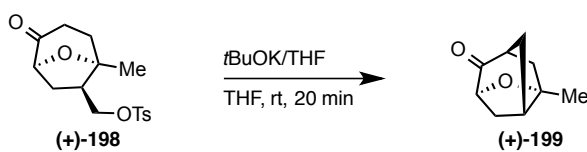


Tosylate (+)-198: To a solution (rt) of silyl ether **141** (2.28 g, 8.0 mmol) in THF (40 mL, 0.2 M) was slowly added TBAF (16 mL, 16 mmol, 1 M in THF). The solution was stirred at room temperature for 1.5 h before being concentrated *in vacuo*. The reaction materials were flushed

through a plug of SiO₂ (50 g) eluting with 100% EtOAc to give the crude alcohol as a clear oil: [R_f = 0.15 (4:1 EtOAc in hexanes)].

The crude alcohol (8.0 mmol) obtained above was dissolved in CH₂Cl₂ (40 mL, 0.2 mL) and treated sequentially with Et₃N (2.2 mL, 16 mmol), DMAP (1.95 g, 16 mmol) and p-toluenesulfonylchloride (2.0 g, 10.5 mmol). The mixture was stirred at room temperature for 2 h before it was diluted with CH₂Cl₂ (20 mL) and poured into H₂O (100 mL). The aqueous layer was extracted with CH₂Cl₂ (3 X 50 mL) and the combined organics were washed with H₂O (2 X 50 mL) and brine (50 mL), dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The crude residue was purified by flash chromatography (SiO₂, 100 g, 15% EtOAc in hexanes) to afford tosylate **198** (2.37 g, 7.3 mmol, 91% yield 2 steps) as a white amorphous solid.

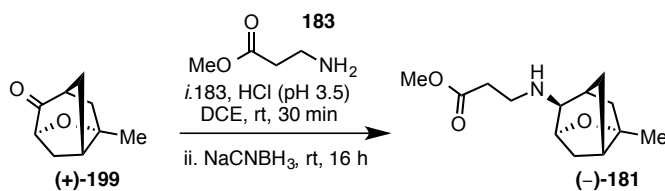
R_f = 0.17 (1:3 EtOAc in hexanes). ¹H NMR (400 MHz, CDCl₃) δ 7.77 (d, J = 8.4 Hz, 2H), 7.35 (d, J = 7.8 Hz, 2H), 4.24 – 4.00 (m, 3H), 2.49 (d, J = 12.9 Hz, 1H), 2.44 (s, 3H), 2.41 – 2.22 (m, 3H), 2.05 – 1.83 (m, 2H), 1.45 (dd, J = 12.5, 6.9 Hz, 1H), 1.37 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 206.61, 145.24, 132.44, 129.96, 127.76, 81.12, 80.44, 69.20, 45.74, 32.15, 31.88, 31.36, 26.13, 21.58. HRMS (ESI) calcd for C₁₆H₂₁O₅S [M+H]⁺: 325.1110; found: 325.1124; [α]_D²¹ = +12.2 (c 1.00, CHCl₃).



Ketone (+)-199: To a solution of tosylate **198** (2.1 g, 6.47 mmol) in THF (125 mL, 0.05 M) was slowly added a 1.0 M solution of *t*BuOK in THF (32 mL) at room temperature. The alkaline solution was stirred for an additional 20 min before the addition of sat. aq. NaHCO₃ (100 mL). The solvent was removed under reduced pressure and the remaining aqueous layer was extracted with Et₂O (3 X 50 mL). The combined organics were washed with brine (100 mL), dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The crude residue was purified by flash

chromatography (SiO₂, g, EtOAc in hexanes) to afford ketone **199** (653mg, 4.29 mmol, 66%) as a clear oil.

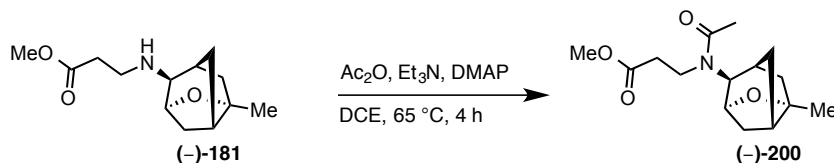
$R_f = 0.27$ (1:3 EtOAc in hexanes). ¹H NMR (400 MHz, CDCl₃) δ 4.19 (d, $J = 4.6$ Hz, 1H), 2.81 (dq, $J = 5.1, 1.8$ Hz, 1H), 2.54 (t, $J = 6.3$ Hz, 1H), 2.34 (dd, $J = 12.0, 3.1$ Hz, 1H), 2.29 – 2.19 (m, 1H), 2.10 – 1.99 (m, 1H), 1.92 – 1.83 (m, 2H), 1.82 – 1.74 (m, 1H), 1.54 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 208.86, 99.97, 86.33, 84.13, 52.17, 49.41, 44.12, 42.80, 42.63, 22.12. HRMS (ESI) calcd for C₉H₁₃O₂ [M+H]⁺: 153.0916; found: 153.0901; $[\alpha]_D^{21} = +12.3$ (c 1.00, CHCl₃).



Amine (–)-181: To a flame dried flask containing ketone **199** (228 mg, 1.5 mmol) was added a solution of β -alanine methyl ester **183** (619 mg, 6.0 mmol) in DCE (6 mL) followed by 0.16 mL of HCl/MeOH (0.006 M). This solution was allowed to stir at room temperature for 30 min before NaCNBH₃ was added and the solution was allowed to stir a further 16 h. following the consumption of all starting material the reaction mixture was diluted with DCM (25 mL) and poured over NaHCO₃ (50 mL). The aqueous layer was extracted with DCM (3 X 25 mL) and the combined extracts were then washed with brine (2 X 50 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography (SiO₂, 15 g, 99:1 EtOAc:Et₃N) to afford amine **181** (204 mg, 0.85 mmol, 54%) as a clear oil.

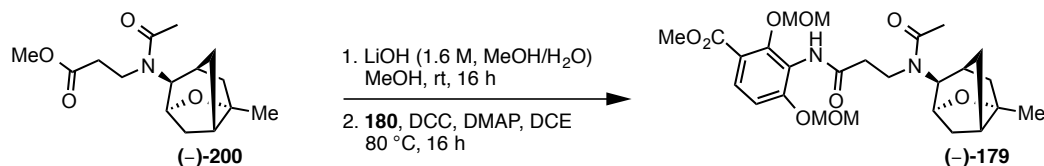
$R_f = 0.05$ (100% EtOAc). ¹H NMR (400 MHz, CDCl₃) δ 4.20 – 4.13 (m, 1H), 3.67 (s, 3H), 2.97 – 2.85 (m, 1H), 2.85 – 2.75 (m, 2H), 2.48 (td, $J = 6.3, 2.0$ Hz, 2H), 2.27 (s, 1H), 2.10 (td, $J = 6.7, 2.0$ Hz, 1H), 1.98 – 1.91 (m, 1H), 1.88 (dd, $J = 11.5, 3.6$ Hz, 1H), 1.80 (dd, $J = 11.9, 3.9$ Hz, 2H), 1.55 – 1.46 (m, 2H), 1.38 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 173.51, 85.95, 79.53,

58.30, 51.79, 46.09, 44.41, 42.96, 40.89, 38.76, 37.50, 35.20, 23.09. HRMS (ESI) calcd for $C_{13}H_{22}NO_3 [M+H]^+$: 240.1600; found: 240.1610; $[\alpha]_D^{21} = -10.6$ (c 1.00, $CHCl_3$).



Amide (-)-200: To a flame dried flask containing amine **181** (96 mg, 0.4 mmol) in DCE (3 mL) was sequentially added Ac_2O (0.075 mL, 0.8 mmol), Et_3N (0.11 mL, 0.8 mmol) and DMAP (98 mg, 0.8 mmol). This solution was heated to 65 °C and was allowed to stir at this temperature for 4 h. following the consumption of all starting material the reaction mixture was diluted with DCM (25 mL) and poured over NaHCO_3 (50 mL). The aqueous layer was extracted with DCM (3 X 25 mL) and the combined extracts were then washed with brine (2 X 50 mL), dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography (SiO_2 , 7.5 g, 4:1 EtOAc in hexanes) to afford amide **200** (109 mg, 0.39 mmol, 97%) as a clear oil. Based on conformational dynamics about the amide bond, the ^1H spectra showed broadened signals and not all carbon singnals in the ^{13}C spectra were seen.

$R_f = 0.43$ (100% EtOAc). ^1H NMR (500 MHz, CDCl_3 , 50 °C) δ 4.32 (s, 1H), 4.10 (s, 1H), 3.88 – 3.75 (m, 2H), 3.68 (s, 3H), 2.61 (td, $J = 8.3, 7.9, 3.7$ Hz, 2H), 2.42 (s, 1H), 2.27 (q, $J = 5.6, 4.7$ Hz, 1H), 2.13 (s, 3H), 2.07 – 1.95 (m, 4H), 1.76 (t, $J = 8.8$ Hz, 1H), 1.61 (dd, $J = 11.8, 4.2$ Hz, 1H), 1.43 (s, 3H). ^{13}C NMR (126 MHz, CDCl_3) δ 171.68, 86.39, 51.65, 51.61, 48.15, 43.58, 39.76, 38.83, 22.63, 22.27. HRMS (ESI) calcd for $C_{15}H_{24}NO_4 [M+H]^+$: 282.1705; found: 282.1722; $[\alpha]_D^{21} = -19.7$ (c 1.00, $CHCl_3$).

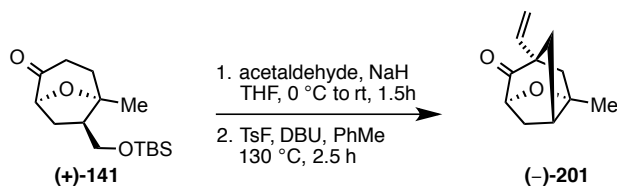


Protected acyclic analog (-)-179: To a round bottom flask charged with amide **200** (19 mg, 0.067 mmol) in MeOH (0.14 mL) was added 1.6 M LiOH (0.13 mL, MeOH:H₂O, 3:1, 0.21 mmol). The reaction mixture was stirred at room temperature for 16 h, at which point all starting material had been consumed and the reaction mixture was diluted with DCM (2 mL) and quenched with 2 N HCl (0.17 mL, 0.34 mmol) and the mixture was allowed to stir for a further 30 min. The aqueous layer was extracted with DCM (3 X 10 mL), and the combined organic layers were then washed with brine (2 X 15 mL), dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The crude acid was used without further purification. [*R*_f = 0.34 (1:9 MeOH in DCM)].

The crude acid (0.067 mmol) obtained above was dissolved in DCE (0.22 mL), and to this solution was sequentially added aniline **180** (36 mg, 0.13 mmol), DCC (20 mg, 0.1 mmol) and DMAP (1.6 mg, 0.013 mmol). The reaction mixture was heated to 80 °C and stirred at this temperature for a duration of 16 h. At this point the reaction mixture was diluted with DCM and quenched with NaHCO₃. The aqueous layer was extracted with DCM (3 X 15 mL) and the combined extracts were then washed with brine (2 X 25 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography (SiO₂, 3 g, 100% EtOAc to 1:9 MeOH:EtOAc) to afford protected acyclic analog **179** (25 mg, 0.048 mmol, 71% yield (2 steps)) as a white amorphous solid.

*R*_f = 0.26 (1:19 MeOH in EtOAc); ¹H NMR (500 MHz, CD₃CN, 70 °C) δ 7.76 (d, *J* = 8.8 Hz, 1H), 7.65 (s, 1H), 7.02 (d, *J* = 8.9 Hz, 1H), 5.25 (s, 2H), 5.03 (s, 2H), 4.37 (s, 1H), 4.14 (d, *J* = 4.2 Hz, 1H), 3.91 – 3.85 (m, 5H), 3.52 (s, 3H), 3.49 (s, 3H), 2.68 (s, 2H), 2.50 (s, 1H), 2.29 (t, *J* = 6.7 Hz, 1H), 2.09 – 2.02 (m, 4H), 2.00 – 1.97 (m, 1H), 1.90 – 1.77 (m, 2H), 1.76 – 1.57 (m, 2H), 1.42 (s, 3H). ¹³C NMR (126 MHz, CD₃CN, 70 °C) δ 172.95, 166.92, 158.35, 155.96, 131.68, 123.11,

120.33, 111.80, 111.75, 101.95, 96.27, 87.42, 79.53, 58.19, 57.20, 52.77, 49.90, 49.16, 45.08, 40.85, 39.88, 34.81, 26.85, 26.04, 23.36, 23.01. HRMS (ESI) calcd for $C_{26}H_{37}N_2O_9$ $[M+H]^+$: 521.2499; found: 521.2519; $[\alpha]_D^{21} = -6.2$ (c 0.81, MeOH).

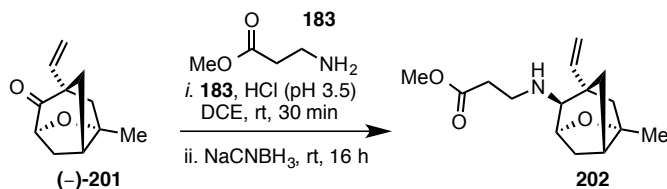


Caged Ketone (–)-201: To a solution of NaH (93 mg, 3.9 mmol) in THF (10 mL) at 0 °C was slowly added a solution of ketone **141** (1.0 g, 3.5 mmol) in 7 mL of THF over a 10 min period. After the addition was complete the solution was allowed to warm to room temperature and stirred at that temperature for 1.5 h before being quenched with brine (50 mL). The material was extracted with EtOAc (3 X 50 mL) and the combined extracts were washed with brine (2 X 100 mL), dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. The crude material was used without further purification. [R_f = 0.48 (1:9 EtOAc in hexanes)].

The crude alcohol (3.9 mmol) obtained above was dissolved in PhMe (6 mL) and treated sequentially with TsF (1.56 g, 9.0 mmol) and DBU (1.35 mL, 9.0 mmol). The mixture was stirred at 130 °C for 2.5 h before it was diluted with Et_2O (20 mL) and poured into Brine (50 mL). The aqueous layer was extracted with Et_2O (3 X 50 mL) and the combined organics were washed with sat. $NH_4Cl_{(aq)}$ (50 mL) and brine (2 X 50 mL), dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. The crude residue was purified by flash chromatography (SiO_2 , 35 g, 10% EtOAc in hexanes) to afford caged ketone **201** (374 mg, 2.1 mmol, 54% yield 2 steps) as a slight yellow oil.

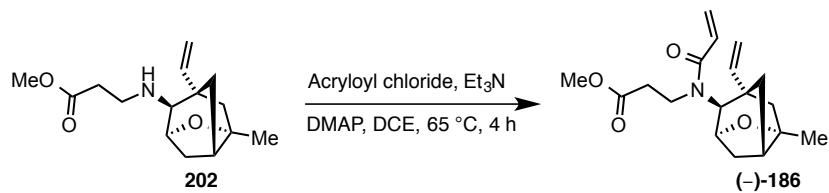
R_f = 0.36 (1:9 EtOAc in hexanes). 1H NMR (500 MHz, $CDCl_3$) δ 6.21 (dd, J = 17.7, 10.9 Hz, 1H), 5.17 (d, J = 10.9 Hz, 1H), 5.04 (d, J = 17.6 Hz, 1H), 4.28 (d, J = 4.8 Hz, 1H), 2.62 (t, J = 6.3 Hz, 1H), 2.33 (dd, J = 11.7, 3.4 Hz, 1H), 2.26 (dq, J = 10.7, 5.0 Hz, 1H), 2.07 (ddd, J = 12.0, 6.5, 3.9 Hz, 1H), 1.97 (d, J = 11.6 Hz, 1H), 1.87 (d, J = 11.8 Hz, 1H), 1.76 (dd, J = 11.9, 3.5 Hz, 1H), 1.56 (d, J = 5.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 207.77, 135.59, 114.53, 86.56, 83.52,

60.51, 52.89, 47.00, 44.21, 42.25, 22.17. HRMS (ESI) calcd for $C_{11}H_{15}O_2 [M+H]^+$: 179.1072; found: 179.1103; $[\alpha]_D^{21} = -12.6$ (c 1.00, $CHCl_3$).



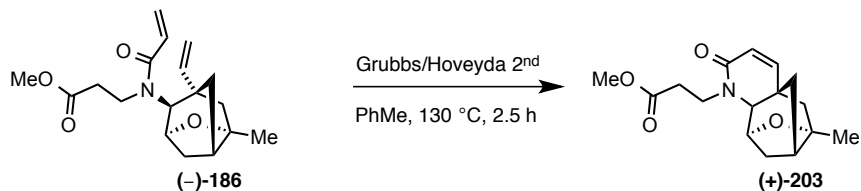
Amine 202: To a flame dried flask containing ketone **201** (374 mg, 2.1 mmol) was added a solution of β -alanine methyl ester **183** (666 mg, 8.4 mmol) in DCE (8.4 mL) followed by 0.23 mL of HCl/MeOH (0.006 M). This solution was allowed to stir at room temperature for 30 min before $NaCNBH_3$ was added and the solution was allowed to stir a further 16 h. following the consumption of all starting material the reaction mixture was diluted with DCM (30 mL) and poured over $NaHCO_3$ (60 mL). The aqueous layer was extracted with DCM (3 X 30 mL) and the combined extracts were then washed with brine (2 X 60 mL), dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography (SiO_2 , 20 g, 99:1 EtOAc:Et₃N) to afford amine **202** (317 mg, 1.2 mmol, 57%) as a clear oil.

$R_f = 0.1$ (100% EtOAc). 1H NMR (400 MHz, $CDCl_3$) δ 5.90 (dd, $J = 17.6, 10.8$ Hz, 1H), 5.03 – 4.88 (m, 2H), 4.27 (d, $J = 4.8$ Hz, 1H), 3.64 (s, 3H), 3.00 (dt, $J = 11.8, 6.7$ Hz, 1H), 2.78 (tt, $J = 11.9, 7.4$ Hz, 1H), 2.46 (ddd, $J = 8.1, 6.6, 1.5$ Hz, 2H), 2.29 (s, 1H), 2.22 (t, $J = 6.6$ Hz, 1H), 2.02 – 1.92 (m, 2H), 1.63 (dq, $J = 11.7, 3.4, 2.6$ Hz, 2H), 1.58 – 1.50 (m, 1H), 1.47 (dd, $J = 11.8, 3.4$ Hz, 1H), 1.36 (s, 3H), 1.30 (d, $J = 11.6$ Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.02, 141.91, 113.12, 86.19, 77.57, 61.48, 52.33, 51.43, 45.86, 45.50, 44.10, 43.72, 40.00, 34.90, 23.21. HRMS (ESI) calcd for $C_{15}H_{24}NO_3 [M+H]^+$: 266.1756; found: 266.1781.



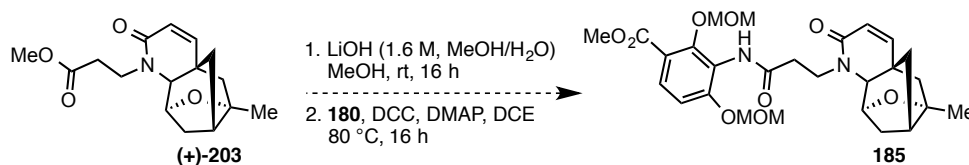
Amide (-)-186: To a flame dried flask containing amine **202** (43 mg, 0.16 mmol) in DCE (1.6 mL) was sequentially added Acryloyl chloride (0.027 mL, 0.32 mmol), Et₃N (0.045 mL, 0.32 mmol) and DMAP (40 mg, 0.32 mmol). This solution was heated to 65 °C and was allowed to stir at this temperature for 3 h. following the consumption of all starting material the reaction mixture was diluted with DCM (10 mL) and poured over NaHCO₃ (25 mL). The aqueous layer was extracted with DCM (3 X 15 mL) and the combined extracts were then washed with brine (2 X 25 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography (SiO₂, 5 g, 1:1 EtOAc in hexanes) to afford amide **186** (45 mg, 0.14 mmol, 88%) as a mixture of non-interconverting atropisomers (the major isomer is reported).

R_f = 0.37 (1:1 EtOAc in hexanes). ¹H NMR (400 MHz, CDCl₃, 50 °C) δ 6.59 (dd, J = 16.6, 10.3 Hz, 1H), 6.40 – 6.29 (m, 1H), 5.87 (dd, J = 17.2, 11.1 Hz, 1H), 5.70 (dd, J = 10.3, 2.2 Hz, 1H), 4.98 – 4.88 (m, 2H), 4.73 (s, 1H), 4.27 (d, J = 4.7 Hz, 1H), 4.11 – 4.03 (m, 2H), 3.74 – 3.61 (m, 4H), 2.83 – 2.73 (m, 1H), 2.67 – 2.54 (m, 1H), 2.33 (t, J = 6.5 Hz, 1H), 2.21 – 2.12 (m, 1H), 2.00 – 1.89 (m, 1H), 1.88 – 1.77 (m, 1H), 1.77 – 1.65 (m, 1H), 1.57 (d, J = 12.4 Hz, 1H), 1.42 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 171.42, 167.27, 140.57, 128.85, 127.56, 113.13, 86.27, 80.20, 55.69, 52.93, 51.72, 48.23, 45.52, 44.67, 41.20, 39.90, 35.75, 23.29. HRMS (ESI) calcd for C₁₈H₂₆NO₄ [M+H]⁺: 320.1862; found: 320.1849; $[\alpha]_D^{22}$ = -24.8 (c = 1.00, CHCl₃).



α , β -Unsaturated δ -lactam (+)-203**:** To a flame dried pressure vessel was added amide **186** (35 mg, 0.11 mmol) in 0.22 mL of PhMe. To this solution was added Grubbs/Hoveyda 2nd generation catalyst (15 mg, 0.022 mmol) and the mixture was then sealed and heated to 130 °C for a period of 2.5 h. At this point all starting material had been consumed and the reaction mixture was concentrated *in vacuo* and preabsorbed on SiO₂ and subject to purification. The crude residue was purified by flash chromatography (SiO₂, 3 g, 1:1 EtOAc in hexanes) to afford α , β -unsaturated δ -lactam **203**: (27 mg, 0.09 mmol, 85%)

R_f = 0.22 (1:1 EtOAc in hexanes). ¹H NMR (400 MHz, CDCl₃) δ 6.24 (d, J = 9.7 Hz, 1H), 5.86 (d, J = 9.7 Hz, 1H), 4.75 (d, J = 5.0 Hz, 1H), 4.02 (ddd, J = 14.7, 9.0, 6.0 Hz, 1H), 3.79 (ddd, J = 14.7, 8.8, 6.3 Hz, 1H), 3.65 (s, 3H), 3.39 (s, 1H), 2.75 – 2.52 (m, 2H), 2.36 (t, J = 6.5 Hz, 1H), 2.14 – 2.04 (m, 2H), 1.82 (ddd, J = 11.9, 6.6, 2.6 Hz, 1H), 1.74 (d, J = 11.5 Hz, 1H), 1.62 (dd, J = 11.8, 3.4 Hz, 1H), 1.42 – 1.35 (m, 4H). ¹³C NMR (101 MHz, CDCl₃) δ 172.23, 165.82, 144.70, 124.58, 86.56, 75.45, 58.97, 51.63, 46.79, 46.68, 44.72, 44.26, 40.38, 36.91, 32.59, 22.64. HRMS (ESI) calcd for C₁₆H₂₂NO₄ [M+H]⁺: 292.1549; found: 292.1565; [α]_D²¹ = +59.7 (c 1.00, CHCl₃).



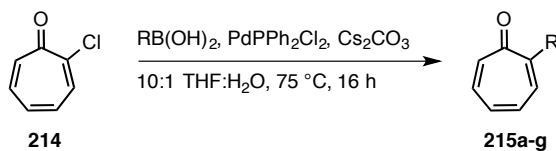
Protected α,β -unsaturated δ -lactam analog **185:** To a round bottom flask charged with α , β -unsaturated δ -lactam **203** (27 mg, 0.09 mmol) in MeOH (0.2 mL) was added 1.6 M LiOH (0.17 mL, MeOH:H₂O, 3:1, 0.27 mmol). The reaction mixture was stirred at room temperature for 16 h, at which point all starting material had been consumed and the reaction mixture was diluted with DCM (2 mL) and quenched with 2 N HCl (0.125 mL, 0.25 mmol) and the mixture was allowed to stir for a further 30 min. The aqueous layer was extracted with DCM (3 X 10 mL), and the combined organic layers were then washed with brine (2 X 15 mL), dried over Na₂SO₄,

filtered, and concentrated *in vacuo*. The crude acid was used without further purification. [R_f = 0.27 (1:9 MeOH in DCM)].

The crude acid (0.09 mmol) obtained above was dissolved in DCE (0.25 mL), and to this solution was sequentially added aniline **180** (45 mg, 0.17 mmol), DCC (26 mg, 0.12 mmol) and DMAP (2 mg, 0.016 mmol). The reaction mixture was heated to 80 °C and stirred at this temperature for a duration of 16 h. At this point the reaction mixture was diluted with DCM and quenched with NaHCO₃. The aqueous layer was extracted with DCM (3 X 15 mL) and the combined extracts were then washed with brine (2 X 25 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography (SiO₂, 3 g, 100% EtOAc to 1:99 MeOH:EtOAc) to afford protected acyclic analog **185** as a white foam. However there was an inseparable impurity that eluted with the titled compound. The major product is reported.

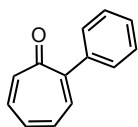
R_f = 0.24 (1:99 MeOH:EtOAc), ¹H NMR (400 MHz, CDCl₃) δ 7.77 (d, J = 9.0 Hz, 1H), 7.51 (q, J = 3.1 Hz, 1H), 7.00 (d, J = 9.0 Hz, 1H), 6.24 (d, J = 9.7 Hz, 1H), 5.88 (d, J = 9.7 Hz, 1H), 5.22 (s, 2H), 5.10 – 5.02 (m, 2H), 4.92 (d, J = 5.1 Hz, 1H), 4.09 – 3.90 (m, 2H), 3.86 (s, 3H), 3.56 (s, 3H), 3.49 (s, 3H), 3.43 (s, 1H), 2.75 (d, J = 6.6 Hz, 2H), 2.40 – 2.28 (m, 1H), 2.14 – 2.04 (m, 2H), 1.82 (ddt, J = 11.8, 6.1, 2.4 Hz, 1H), 1.73 (dd, J = 11.5, 4.1 Hz, 1H), 1.66 – 1.56 (m, 2H), 1.38 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 169.57, 166.21, 156.96, 144.81, 130.70, 124.72, 122.08, 118.30, 110.88, 101.54, 95.01, 86.46, 79.82, 77.20, 75.60, 59.35, 57.44, 56.49, 51.87, 47.06, 46.80, 44.95, 44.43, 40.48, 37.77, 24.98, 22.70.

Experimental Procedures: Synthesis of α -Tropolone analogs.



General Procedure For Suzuki Couplings to 2-Chlorotropone 214: 2-Chloro-2,4,6-cycloheptatrien-1-one (1.0 eq), aryl boronic acid (2.0 eq), and cesium carbonate (4.0 eq) were added to 10:1 THF/H₂O (0.2 M) and the mixture was thoroughly degassed by bubbling argon through solution (10 min). Bis(triphenylphosphine)palladium(II) dichloride (0.1 eq) was added and the mixture was again degassed with argon (5 min). The homogenous solution was heated at 75 °C for 16 h before being cooled to room temperature. Water was added and the mixture was extracted with EtOAc (3x). The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated in vacuo. Flash chromatography of the crude residue (SiO₂, EtOAc in hexanes) provided the desired 2-aryl-tropones.

2-phenyl tropone 215a: 99% yield; R_f = 0.5 (1:1 EtOAc:Hexanes); mp = 77.9-79.2 °C; IR

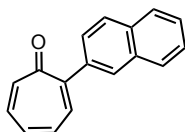


215a

(KBr): ν : 3101, 3022, 1895, 1808, 1625, 1547, 1441, 1261, 784, 698. ¹H NMR (500 MHz, CDCl₃) δ 7.51-7.49 (m, 2H), 7.43- 7.36 (m, 4H), 7.20 (d, J = 12.2 Hz, 1H), 7.14 (ddd, J = 19.8, 1.3, 1.3, 1.3, 1.4 Hz, 1H), 7.07-7.03 (m, 1H), 6.99-6.95

(m, 1H). ¹³C NMR (126 MHz, CDCl₃) δ 186.4, 152.4, 142.2, 139.9, 136.5, 135.2, 133.7, 133.2, 129.0, 128.3, 128.0. HRMS (ESI) calcd for C₁₃H₁₁O [M+H]⁺: 183.0810; found: 183.0788.

2-naphthyl tropone 215b: 98% yield isolated with inseparable impurity that is removed during

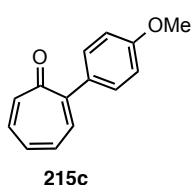


215b

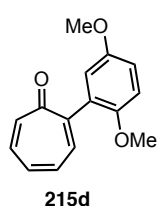
amination; R_f = 0.58 (1:1 EtOAc:Hexanes); mp = N/A; IR (KBr): ν : 3056, 3009, 2359, 1926, 1876, 1771, 1703, 1626, 1574, 800, 777, 733, 697. ¹H NMR (500 MHz, CDCl₃) δ 7.92 (d, J = 1.45 Hz, 1H), 7.90 (d, J = 2.0 Hz, 1H), 7.71

(d, J = 8.3 Hz, 1H), 7.57-7.45 (m, 3H), 7.41 (dd, J = 6.9, 0.85, 0.90 Hz, 1H), 7.38-7.36 (m, 1H), 7.26 (d, J = 12.1 Hz, 1H), 7.20-7.16 (m, 1H), 6.99-6.97 (m, 2H). ¹³C NMR (126 MHz, CDCl₃) δ 186.4, 152.6, 141.7, 138.3, 137.6, 135.5, 133.8, 133.5, 133.2, 130.7, 128.3, 128.2, 126.4, 125.9, 125.6, 125.2, 125.2. HRMS (ESI) calcd for C₁₇H₁₃O [M+H]⁺: 233.0966; found: 233.0945.

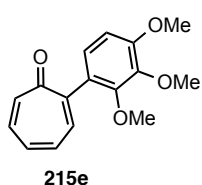
2-(4-methoxy-phenyl) tropone 215c: 99% yield; $R_f = 0.59$, (1:1 EtOAc:Hexanes); mp = 52.2-



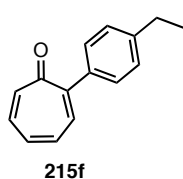
53.6 °C; IR (KBr): ν : 2958, 2835, 2541, 2041, 1974, 1883, 1622, 1564, 1175, 1031, 830, 780, 686. ^1H NMR (500 MHz, CDCl_3) δ 7.51 (d, $J = 2.0$ Hz, 1H), 7.50 (d, $J = 2.0$ Hz, 1H), 7.40 (d, $J = 9.0$ Hz, 1H), 7.23 (d, $J = 12.1$ Hz, 1H), 7.15 (ddd, $J = 21.5, 1.2, 1.2, 1.2, 1.2$ Hz, 1H), 7.06 (t, $J = 20.0, 10.1, 9.5$ Hz, 1H), 6.99-6.94 (m, 3H), 3.85 (s, 3H). ^{13}C NMR (126 MHz, CDCl_3) δ 186.5, 159.9, 152.0, 142.0, 136.0, 135.3, 133.8, 132.8, 132.1, 130.6, 113.6, 55.3. HRMS (ESI) calcd for $\text{C}_{14}\text{H}_{13}\text{O}_2$ $[\text{M}+\text{H}]^+$: 213.0916; found: 213.0898.



2-(2,5-methoxy-phenyl) tropone 215d: 96% yield; $R_f = 0.29$ (1:1 EtOAc:Hexanes); mp = 102.2-103.2 °C; IR (KBr): ν : 2940, 2832, 2351, 1628, 1588, 1218, 1046, 808, 748, 694. ^1H NMR (500 MHz, CDCl_3) δ 7.30 (dd, $J = 8.4, 1.0, 1.1$ Hz, 1H), 7.15-7.13 (m, 2H), 7.03-6.94 (m, 2H), 6.88 (s, 1H), 6.88 (s, 1H), 6.82 (t, $J = 3.2, 1.6, 1.6$ Hz, 1H), 3.79 (s, 3H), 3.74 (s, 3H). ^{13}C NMR (126 MHz, CDCl_3) δ 186.5, 153.7, 150.9, 150.3, 141.0, 136.3, 134.9, 133.5, 133.3, 130.9, 116.4, 114.1, 112.5, 56.5, 55.7. HRMS (ESI) calcd for $\text{C}_{15}\text{H}_{15}\text{O}_3$ $[\text{M}+\text{H}]^+$: 243.1021; found: 243.1016.



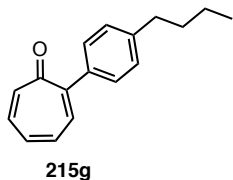
2-(2,3,4-methoxy-phenyl) tropone 215e: 91% yield; $R_f = 0.29$ (1:1 EtOAc:Hexanes); mp = 98.3-99.6 °C; IR (KBr): ν : 2946, 2841, 2825, 1947, 1883, 1626, 1583, 1458, 1103, 1072, 1013, 799, 684. ^1H NMR (500 MHz, CDCl_3) δ 7.28 (dd, $J = 9.6, 1.1, 1.1$ Hz, 1H), 7.18-7.12 (m, 2H), 7.03-6.93 (m, 3H), 6.72 (d, $J = 8.5$ Hz, 1H), 3.89 (s, 3H), 3.88 (s, 3H), 3.82 (s, 3H). ^{13}C NMR (126 MHz, CDCl_3) δ 187.0, 154.2, 150.7, 150.6, 141.9, 140.6, 136.3, 135.1, 133.6, 133.1, 127.7, 124.6, 107.3, 60.9, 60.7, 56.0. HRMS (ESI) calcd for $\text{C}_{16}\text{H}_{17}\text{O}_4$ $[\text{M}+\text{H}]^+$: 273.1127; found: 273.1118.



2-(4-ethylphenyl) tropone 215f: 97% yield. $R_f = 0.29$ (25% EtOAc in Hexanes). mp = N/A. IR (KBr): ν : 3024, 2964, 2931, 2873, 1638, 1575, 1464, 1384, 1261, 833, 791,

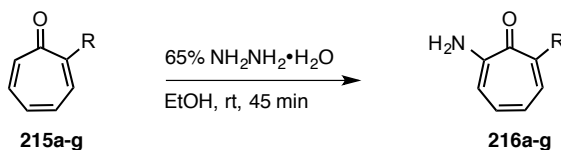
690. ^1H NMR (500 MHz, CDCl_3) δ 7.49 – 7.44 (m, 2H), 7.38 (dd, J = 8.8, 1.0 Hz, 1H), 7.28 – 7.24 (m, 2H), 7.20 (dt, J = 12.1, 1.1 Hz, 1H), 7.13 (ddd, J = 12.1, 7.6, 1.3 Hz, 1H), 7.05 (dddd, J = 11.0, 8.9, 1.4, 0.8 Hz, 1H), 6.96 (ddt, J = 10.9, 7.7, 1.2 Hz, 1H), 2.71 (q, J = 7.6 Hz, 2H), 1.29 (t, J = 7.6 Hz, 3H). ^{13}C NMR (126 MHz, CDCl_3): δ 186.8, 175.5, 152.7, 144.9, 142.3, 137.4, 136.3, 136.0, 135.3, 133.9, 133.1, 129.3, 127.8, 41.4, 29.4, 28.9, 15.6. HRMS (ESI) calcd for $\text{C}_{16}\text{H}_{16}\text{O}_2$ $[\text{M}+\text{H}]^+$: 211.1124; found 211.1152.

2-(4-butylphenyl) tropone 215g: yield: 97%. R_f = 0.47 (25% EtOAc in Hexanes). mp = N/A.



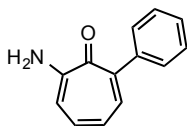
IR (KBr): ν : 3024, 2956, 2929, 2869, 2856, 1630, 1582, 1508, 1463, 1382, 1259, 1230, 1183, 902, 830, 781, 687, 558. ^1H NMR (500 MHz, CDCl_3) δ 7.43 (d, J = 7.9 Hz, 2H), 7.29 (d, J = 8.8 Hz, 1H), 7.20 (d, J = 7.9 Hz, 2H), 7.12 (d, J = 12.0 Hz, 1H), 7.03 (dd, J = 12.1, 7.8 Hz, 1H), 6.94 (t, J = 9.8

Hz, 1H), 6.85 (dd, J = 11.2, 8.2 Hz, 1H), 2.63 (t, J = 7.7 Hz, 2H), 1.62 (p, J = 7.6 Hz, 2H), 1.38 (h, J = 7.4 Hz, 2H), 0.94 (t, J = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, CDCl_3): δ 186.6, 152.4, 143.4, 142.1, 137.5, 136.3, 135.3, 133.9, 133.1, 129.3, 128.3, 35.6, 33.7, 22.6, 14.2. HRMS (ESI) calcd for $\text{C}_{18}\text{H}_{20}\text{O}_2$ $[\text{M}+\text{H}]^+$: 239.1437; found: 239.1498.



General Procedure For α -Amination of 2-aryl tropone: To a solution of α -aryl-tropone (1.0 eq) in EtOH (0.2 M) was added 65% hydrazine monohydrate (25 eq). The solution was allowed to stir at room temperature until all starting material was consumed by monitoring on TLC (~45 min). The reaction was concentrated in vacuo and then taken up in EtOAc (0.05 M) and washed with H_2O (3x). The organic layer was then washed with brine, dried over Na_2SO_4 , filtered and concentrated in vacuo. Flash chromatography of the crude residue (SiO_2 , EtOAc in hexanes) provided the desired α -amino-tropones.

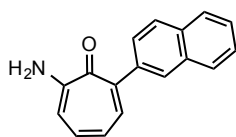
7-amino-2-phenyl tropone 216a: 88% yield; R_f = 0.61 (4:1 EtOAc:Hexanes); mp = 209.3-



216a

210.4 °C; IR (KBr): ν : 3403, 3251, 3122, 1604, 1515, 1428, 1336, 1235, 1054, 919, 686. ^1H NMR (500 MHz, CD_2Cl_2) δ 7.50- 7.38 (m, 5H), 7.33 (t, J = 14.4, 7.1, 7.3 Hz, 1H), 7.14 (t, J = 20.2, 10.1, 10.1 Hz, 1H), 6.93 (d, J = 10.0 Hz, 1H), 6.77 (t, J = 19.6, 9.8, 9.8 Hz, 1H), 6.12 (s, 2H). ^{13}C NMR (126 MHz, CD_2Cl_2) δ 174.9, 158.5, 143.4, 142.5, 139.0, 135.8, 130.1, 128.3, 127.7, 123.4, 112.7. HRMS (ESI) calcd for $\text{C}_{13}\text{H}_{12}\text{NO}$ $[\text{M}+\text{H}]^+$: 198.0919; found: 198.0900.

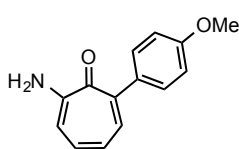
7-amino-2-naphthyl tropone 216b: 89% yield; R_f = 0.63 (4:1 EtOAc:Hexanes); mp = 221.7-



216b

222.5 °C; IR (KBr): ν : 3443, 3280, 3150, 1604, 1511, 1446, 1062, 780, 737. ^1H NMR (500 MHz, CD_2Cl_2) δ 7.90 (d, J = 8.2 Hz, 1H), 7.87 (d, J = 8.3 Hz, 1H), 7.55-7.45 (m, 4H), 7.38-7.35 (m, 2H), 7.23 (td, J = 20.2, 10.1, 10.1, 1.1, 1.1, 1.1 Hz, 1H), 6.98 (d, J = 9.9 Hz, 1H), 6.80 (t, J = 19, 9.5, 9.5 Hz, 1H), 6.13 (s, 2H). ^{13}C NMR (126 MHz, CD_2Cl_2) δ 175.2, 157.9, 141.8, 141.8, 139.6, 136.5, 134.0, 132.2, 128.8, 128.1, 126.9, 126.4, 126.3, 126.2, 126.1, 123.2, 112.8. HRMS (ESI) calcd for $\text{C}_{17}\text{H}_{14}\text{NO}$ $[\text{M}+\text{H}]^+$: 248.1075; found: 248.1065.

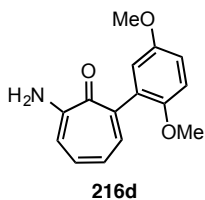
7-amino-2-(4-methoxy-phenyl) tropone 216c: 87% yield; R_f = 0.55 (4:1 EtOAc:Hexanes); mp



216c

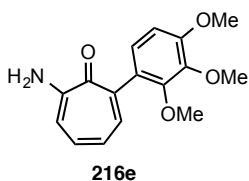
= 153.8-155.2 °C; IR (KBr): ν : 3434, 3269, 3233, 2962, 1601, 1511, 1450, 1244, 1023, 829, 781. ^1H NMR (500 MHz, CD_2Cl_2) δ 7.49 (dd, J = 9.6, 1.0, 0.9 Hz, 1H), 7.44-7.41 (m, 2H), 7.10 (td, J = 20.0, 1.0, 1.0, 1.0 Hz, 1H), 6.96- 6.93 (m, 2H), 6.89 (d, J = 10.0 Hz, 1H), 6.24 (s, 2H), 3.83 (s, 3H). ^{13}C NMR (126 MHz, CD_2Cl_2) δ 174.9, 159.5, 158.4, 141.9, 138.7, 135.6, 135.4, 131.3, 123.3, 113.7, 112.9, 55.8. HRMS (ESI) calcd for $\text{C}_{14}\text{H}_{14}\text{NO}_2$ $[\text{M}+\text{H}]^+$: 228.1025; found: 228.1018.

7-amino-2-(2,5-methoxy-phenyl) tropone 216d: 84% yield; $R_f = 0.39$ (4:1 EtOAc:Hexanes);



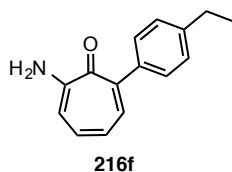
mp = 109.6- 110.7 °C; IR (KBr): ν : 3278, 3191, 2939, 2831, 1601, 1519, 1455, 1219, 1047, 783, 725. ^1H NMR (500 MHz, CD_2Cl_2) δ 7.39 (d, $J = 9.5$ Hz, 1H), 7.12 (t, $J = 20.2, 10.1, 10.1$ Hz, 1H), 6.92-6.87 (m, 3H), 6.80 (d, $J = 2.9$ Hz, 1H), 6.72 (t, $J = 19.5, 9.7, 9.8$ Hz, 1H), 6.42 (s, 2H), 3.77 (s, 3H), 3.69 (s, 3H). ^{13}C NMR (126 MHz, CD_2Cl_2) δ 174.5, 158.1, 154.1, 151.5, 139.8, 138.9, 136.2, 133.9, 122.6, 117.1, 113.4, 112.9, 112.6, 56.7, 56.2. HRMS (ESI) calcd for $\text{C}_{15}\text{H}_{16}\text{NO}_3$ $[\text{M}+\text{H}]^+$: 258.1130; found: 258.1151.

7-amino-2-(2,3,4-methoxy-phenyl) tropone 216e: 86% yield; $R_f = 0.42$ (4:1 EtOAc:Hexanes);



mp = 175.3- 176.5 °C; IR (KBr): ν : 3367, 2939, 2825, 1599, 1514, 1455, 1097, 1019, 770. ^1H NMR (500 MHz, CDCl_3) δ 7.41 (d, $J = 9.5$ Hz, 1H), 7.09 (t, $J = 20.1, 10.0, 10.1$ Hz, 1H), 6.91 (d, $J = 8.5$ Hz, 1H), 6.87 (d, $J = 10$ Hz, 1H), 6.72-6.68 (m, 2H), 6.28 (s, 2H), 3.99 (s, 3H), 3.87 (s, 3H), 3.73 (s, 3H). ^{13}C NMR (126 MHz, CDCl_3) δ 174.4, 157.2, 153.1, 151.3, 142.0, 139.3, 138.7, 135.4, 129.7, 124.5, 122.4, 112.4, 107.4, 60.9, 60.7, 55.9. HRMS (ESI) calcd for $\text{C}_{16}\text{H}_{18}\text{NO}_4$ $[\text{M}+\text{H}]^+$: 288.1236; found: 288.1217.

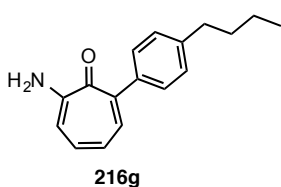
7-amino-2-(4-ethylphenyl) tropone 216f: 77% yield. $R_f = 0.44$ (1:1 EtOAc: Hexanes). mp =



131.0-132.2. IR (KBr): ν : 3388, 3254, 3242, 3233, 3206, 3176, 3152, 3147, 3118, 2960, 1606, 1512, 1453, 1433, 1410, 1343, 1273, 1240, 1180, 1113, 915, 833, 757, 707, 584. ^1H NMR (500 MHz, CD_2Cl_2) δ 7.48 (dd, $J = 9.6, 1.1$ Hz, 1H), 7.37 (d, $J = 8.2$ Hz, 2H), 7.24 (d, $J = 7.9$ Hz, 2H), 7.12 (td, $J = 10.0, 1.1$ Hz, 1H), 6.91 (dd, $J = 10.0, 0.8$ Hz, 1H), 6.79 – 6.73 (m, 1H), 6.10 (s, 2H), 2.70 (q, $J = 7.6$ Hz, 2H), 1.28 (t, $J = 7.6$ Hz, 3H). ^{13}C NMR (126 MHz, CD_2Cl_2): δ 174.6, 157.9, 143.6, 142.2, 140.2,

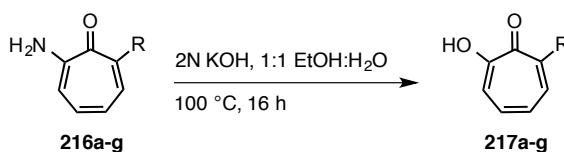
138.4, 135.1, 129.6, 127.4, 123.0, 112.3, 28.8, 15.6. HRMS (ESI) calcd for C₁₅H₁₅NO [M+H]⁺: 226.1236; found 226.1262.

7-amino-2-(4-butylphenyl) tropone 216g: 88% yield. R_f = 0.50 (1:1 EtOAc: Hexanes). mp =



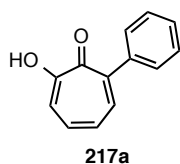
133.7-135.0. IR (KBr): ν: 3398, 3240, 3232, 3200, 3140, 3124, 3118, 2954, 2925, 1607, 1520, 1507, 1433, 1335, 1266, 1239, 916, 759, 706, 573. ¹H NMR (500 MHz, CDCl₃) δ 7.51 (d, J = 9.6 Hz, 1H), 7.43 (d, J

= 8.0 Hz, 2H), 7.25 (d, J = 7.9 Hz, 2H), 7.06 (t, J = 10.0 Hz, 1H), 6.84 (d, J = 10.1 Hz, 1H), 6.74 (t, J = 9.8 Hz, 1H), 6.25 (s, 2H), 2.75 – 2.59 (m, 2H), 1.65 (p, J = 8.5, 7.9 Hz, 2H), 1.41 (h, J = 7.4 Hz, 2H), 0.96 (t, J = 7.3 Hz, 3H). ¹³C NMR (126 MHz, CD₂Cl₂): δ 174.0, 158.1, 141.8, 141.6, 139.7, 138.4, 135.1, 129.2, 127.8, 122.6, 112.8, 35.3, 33.4, 22.3, 13.8. HRMS (ESI) calcd for C₁₇H₁₉NO [M+H]⁺: 254.1545; found: 254.1526.



General Procedure For α-amino-2-aryl tropone Hydrolysis: α-amino-2-aryl tropone (1.0 eq) was dissolved in 1:1 EtOH:H₂O (2.0 M) to which was added 2N KOH (20 eq). The reaction was heated to 100 °C and stirred for 16 h. The reaction was returned to room temperature and diluted with 15% NaOH. The aqueous layer was washed with Et₂O (3x) and CH₂Cl₂ (3x) and then acidified to pH 2.0 and extracted with CH₂Cl₂ (3x) washed with brine, dried over Na₂SO₄, filtered, and concentrated in vacuo.

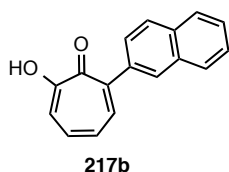
α-phenyl tropolone 217a: 90% yield; R_f = 0.52 (1:19 *i*PrOH:CH₂Cl₂); mp = N/A; IR (KBr): ν:



3200-2800 broad, 2917, 2848, 1721, 1712, 1615, 1595, 1548, 1417, 1247, 737, 698. ¹H NMR (500 MHz, CD₂Cl₂) δ 7.60 (d, J = 9.9 Hz, 1H), 7.51 (d, J = 7.4 Hz, 2H), 7.46 (t, J = 14.8, 7.2, 7.6 Hz, 2H), 7.42-7.39 (m, 3H), 7.10 (t, J = 17.2,

7.7, 9.5 Hz, 1H). ^{13}C NMR (126 MHz, CD_2Cl_2) δ 171.9, 170.8, 141.1, 140.7, 139.5, 137.3, 129.8, 128.7, 128.6, 127.9, 122.0. HRMS (ESI) calcd for $\text{C}_{13}\text{H}_{11}\text{O}_2$ $[\text{M}+\text{H}]^+$: 199.0759; found: 199.0749.

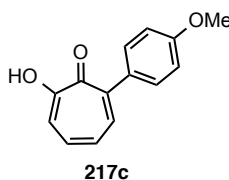
α -naphthyl tropolone 217b: 91% yield; R_f = 0.52 (1:19 *i*PrOH: CH_2Cl_2); mp = N/A; IR (KBr): ν :



3200-2800 broad, 3173, 3044, 2925, 1614, 1593, 1548, 1470, 1367, 1258, 1242, 1210, 800, 773, 689. ^1H NMR (500 MHz, CD_2Cl_2) δ 7.96 (d, J = 7.3 Hz, 2H), 7.61-7.50 (m, 6H), 7.44 (t, J = 14.0, 6.9, 7.1 Hz, 2H), 7.13-7.09

(m, 1H). ^{13}C NMR (126 MHz, CD_2Cl_2) δ 171.6, 170.8, 141.6, 138.6, 138.2, 137.2, 134.1, 131.5, 129.0, 128.9, 127.8, 127.0, 126.7, 126.5, 126.0, 125.9, 123.8. HRMS (ESI) calcd for $\text{C}_{17}\text{H}_{13}\text{O}_2$ $[\text{M}+\text{H}]^+$: 249.0916; found: 249.0928.

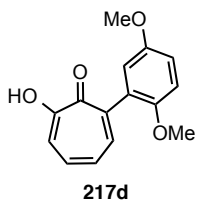
α -(4-methoxy-phenyl) tropolone 217c: 92% yield; R_f = 0.52 (1:19 *i*PrOH: CH_2Cl_2); mp = N/A;



IR (KBr): ν : 3200-2800 broad, 3128, 3927, 1920, 1802, 1615, 1593, 1499, 1367, 1039, 802, 728. ^1H NMR (500 MHz, CD_2Cl_2) δ 7.49 (d, J = 10.0 Hz, 1H), 7.42-7.39 (m, 3H), 7.22 (dd, J = 7.4, 1.5, 1.5 Hz, 1H), 7.07-7.02 (m, 3H), 3.76 (s, 3H).

^{13}C NMR (126 MHz, CD_2Cl_2) δ 171.2, 170.9, 157.1, 141.4, 137.5, 136.5, 13.7, 130.1, 129.8, 127.4, 122.6, 121.0, 111.7, 56.1. HRMS (ESI) calcd for $\text{C}_{14}\text{H}_{13}\text{O}_3$ $[\text{M}+\text{H}]^+$: 229.0865; found: 229.0854.

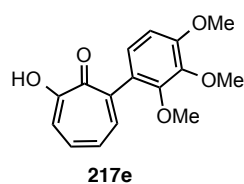
α -(2,5-methoxy-phenyl) tropolone 217d: 89% yield; R_f = 0.52 (1:19 *i*PrOH: CH_2Cl_2); mp = N/A;



IR (KBr): ν : 3200-2800 broad, 2930, 2832, 2002, 1925, 1797, 1615, 1595, 1548, 1496, 1398, 1201, 1044, 1024, 805, 728. ^1H NMR (500 MHz, CD_2Cl_2) δ 7.49 (d, J = 10 Hz, 1H), 7.39-7.37 (m, 2H), 7.07-7.03 (m, 1H), 6.97-6.92 (m, 2H), 6.82 (d, J = 2.7 Hz, 1H), 3.79 (s, 3H), 3.71 (s, 3H).

^{13}C NMR (126 MHz, CD_2Cl_2) δ 171.1, 170.9, 154.1, 151.3, 141.3, 137.6, 136.3, 130.7, 127.4, 122.6, 116.7, 114.4, 112.9, 56.8, 56.2. HRMS (ESI) calcd for $\text{C}_{15}\text{H}_{15}\text{O}_4$ $[\text{M}+\text{H}]^+$: 259.0970; found: 259.0956.

α -(2,3,4-methoxy-phenyl) tropolone 217e: 89% yield; R_f = 0.55 (1:19 *i*PrOH:CH₂Cl₂); mp =



N/A; IR (KBr): ν : 3200-2800 broad, 2994, 2938, 2837, 1992, 1920, 1713,

1614, 1596, 1408, 1301, 1108, 1046, 793, 735. ¹H NMR (500 MHz,

CD₂Cl₂) δ 7.49 (d, *J* = 10 Hz, 1H), 7.40-7.36 (m, 2H), 7.07-7.01 (m, 1H),

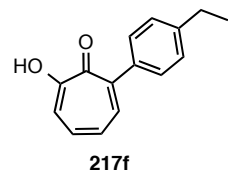
6.93 (d, *J* = 8.6 Hz, 1H), 6.77 (d, *J* = 8.6 Hz, 1H), 3.89 (s, 3H), 3.89 (s, 3H), 3.74 (s, 3H). ¹³C

NMR (126 MHz, CD₂Cl₂) δ 171.9, 170.4, 154.6, 151.8, 142.7, 141.4, 173.3, 136.8, 127.5, 127.4,

124.8, 122.2, 107.8, 61.4, 61.1, 56.5. HRMS (ESI) calcd for C₁₆H₁₇O₅ [M+H]⁺: 289.1076; found:

289.1103.

α -(4-ethylphenyl) tropolone 217f: 65% yield. R_f = 0.47 (1:1 EtOAc: Hexanes). mp = 60.7-



61.9. IR (KBr): ν : 3168, 3022, 2964, 2929, 2872, 1615, 1595, 1549, 1474,

1418, 1380, 1365, 1276, 1247, 914, 835, 751. ¹H NMR (500 MHz, CD₂Cl₂)

δ 9.70 (bs, 1H), 7.59 (d, *J* = 10.0 Hz, 1H), 7.48 – 7.43 (m, 2H), 7.42 – 7.36

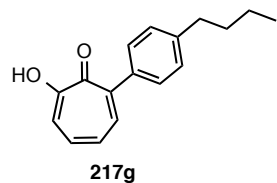
(m, 2H), 7.30 (d, *J* = 8.3 Hz, 2H), 7.09 (ddd, *J* = 10.5, 8.7, 2.1 Hz, 1H), 2.73 (q, *J* = 7.6 Hz, 2H),

1.30 (t, *J* = 7.6 Hz, 3H). ¹³C NMR (126 MHz, CD₂Cl₂): δ 171.6, 170.3, 144.7, 140.6, 139.1, 137.6,

136.6, 129.4, 127.8, 121.5, 28.8, 15.5. HRMS (ESI) calcd for C₁₅H₁₄O₂ [M+H]⁺: 227.1072; found

227.1103.

α -(4-butylphenyl) tropolone 217g: 87% yield. R_f = 0.37 (1:1 EtOAc: Hexanes). mp = N/A. IR



(KBr): ν : 2957, 2928, 2856, 1613, 1595, 1549, 1474, 1466, 1455, 1419,

1376, 1363, 1291, 1276, 1246, 1182, 730. ¹H NMR (400 MHz, CD₂Cl₂)

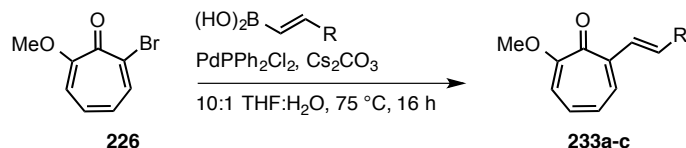
δ 9.80 (bs, 1H), 7.60 (d, *J* = 10.1 Hz, 1H), 7.50 – 7.36 (m, 4H), 7.27 (d,

J = 8.1 Hz, 2H), 7.09 (ddd, *J* = 10.4, 7.7, 3.1 Hz, 1H), 2.67 (ddt, *J* = 14.9, 15.7, 7.9, 7.3 Hz,

2H), 1.65 (p, *J* = 7.5 Hz, 2H), 1.40 (dq, *J* = 14.7, 7.3 Hz, 2H), 0.96 (t, *J* = 7.3 Hz, 3H). ¹³C NMR

(101 MHz, CD₂Cl₂): δ 172.0, 170.7, 143.8, 141.0, 139.6, 137.9, 137.0, 129.8, 128.7, 127.9, 121.9,

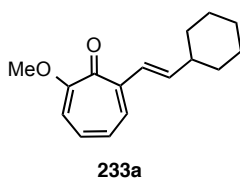
35.9, 34.3, 23.0, 14.3. HRMS (ESI) calcd for C₁₇H₁₈O₂ [M+H]⁺: 255.1385; found: 255.1390.



General Procedure for Suzuki couplings to 2-bromo-7-methoxy-2,4,6-cycloheptatrien-1-one:

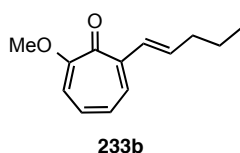
2-bromo-7-methoxy-2,4,6-cycloheptatrien-1-one (1.0 eq), aryl boronic acid (2.0 eq), and cesium carbonate (4.0 eq) were added to 10:1 THF/H₂O (0.2 M) and the mixture was thoroughly degassed by bubbling argon through solution (10 min). Bis(triphenylphosphine)palladium(II) dichloride (0.1 eq) was added and the mixture was again degassed with argon (5 min). The homogenous solution was heated at 75 °C for 16 h before being cooled to room temperature. Water was added and the mixture was extracted with EtOAc (3x). The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated in vacuo. Flash chromatography of the crude residue (SiO₂, EtOAc in hexanes) provided the desired 2-aryl-tropolones.

7-methoxy-2-cyclohexylethene tropolone 233a: 94% yield. *R*_f = 0.26 (1:1 EtOAc: Hexanes).



mp = N/A. IR (KBr): ν : 2925, 2918, 2849, 1632, 1610, 1595, 1570, 1488, 1466, 1448, 1364, 1270, 1249, 1217, 1178, 1043, 969, 750. ¹H NMR (500 MHz, CDCl₃): δ 7.54 (d, *J* = 9.2 Hz, 1H), 6.96-6.93 (m, 2H), 6.80 (t, *J* = 19.7, 9.7, 10 Hz, 1H), 6.68 (d, *J* = 9.7 Hz, 1H), 6.24 (dd, *J* = 16, 7.2, 7.2 Hz, 1H), 3.88 (s, 3H), 2.17-2.13 (m, 1H), 1.79-1.62 (m, 5H), 1.32-1.11 (m, 5H). ¹³CNMR (126 MHz, CDCl₃): δ 178.8, 164.0, 143.9, 141.3, 132.3, 130.6, 126.8, 126.6, 112.1, 56.2, 41.6, 32.6, 25.8. HRMS (ESI) calcd for C₁₆H₂₀O₂ [M+H]⁺: 245.1542; found: 245.1533.

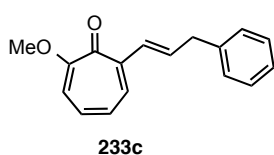
7-methoxy-2-(1-pentene) tropolone 233b: 88% yield. *R*_f = 0.25 (1:1 EtOAc: Hexanes). mp =



N/A. IR (KBr): ν : 2958, 2929, 2870, 1633, 1610, 1590, 1570, 1560, 1489, 1465, 1438, 1364, 1270, 1250, 1218, 1177, 1057, 1039, 969, 782, 750,

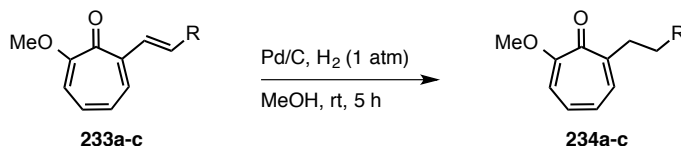
671. ^1H NMR (500 MHz, CDCl_3): δ 7.40 (d, J = 9.1 Hz, 1H), 6.84-6.79 (m, 2H), 6.68 (t, J = 19.7, 9.7, 10 Hz, 1H), 6.58 (d, J = 9.7 Hz, 1H), 6.22-6.16 (m, 1H), 3.74 (s, 3H), 2.05 (q, J = 23.1, 7.3, 7.4, 8.4 Hz, 2H), 1.33 (h, J = 36.9, 7.4, 7.4, 7.4, 7.4, 7.4 Hz, 2H), 0.77 (t, J = 14.8, 7.4, 7.4 Hz, 3H). ^{13}C NMR (126 MHz, CDCl_3): δ 178.3, 163.7, 143.2, 135.2, 132.2, 130.5, 128.8, 126.5, 111.9, 55.9, 35.1, 21.9, 13.3. HRMS (ESI) calcd for $\text{C}_{13}\text{H}_{16}\text{O}_2$ $[\text{M}+\text{H}]^+$: 205.1229; found: 205.1247.

7-methoxy-2-allylphenyl tropolone 233c: 85% yield. R_f = 0.28 (1:1 EtOAc: Hexanes). mp =



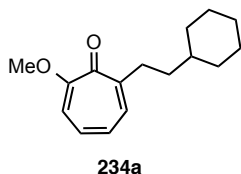
77.4-79.0. IR (KBr): ν : 3057, 3024, 3005, 2964, 2936, 2897, 2835, 1632, 1587, 1564, 1489, 1466, 1452, 1438, 1409, 1364, 1272, 1247, 1217, 1175, 1154, 1059, 1042, 1030, 971, 937, 819, 799, 751, 700, 674.

^1H NMR (500 MHz, CDCl_3) δ 7.46 (d, J = 9.1 Hz, 1H), 7.23 (t, J = 7.4 Hz, 2H), 7.19 – 7.10 (m, 3H), 7.04 (d, J = 15.7 Hz, 1H), 6.89 (t, J = 10.0 Hz, 1H), 6.77 – 6.68 (m, 1H), 6.63 (d, J = 9.7 Hz, 1H), 6.39 (dt, J = 15.6, 7.2 Hz, 1H), 3.82 (s, 3H), 3.51 (d, J = 6.9 Hz, 2H). ^{13}C NMR (126 MHz, CDCl_3): δ 178.3, 163.9, 142.8, 139.4, 133.3, 132.6, 130.9, 129.9, 128.2, 128.1, 126.5, 125.8, 111.9, 55.9, 39.4. HRMS (ESI) calcd for $\text{C}_{17}\text{H}_{16}\text{O}_2$ $[\text{M}+\text{H}]^+$: 253.1229; found: 253.1258.



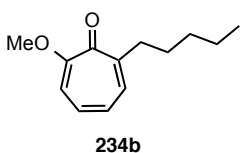
General Procedure for Reduction of C8-C9 conjugated olefin: To a flame dried flask was added the coupled product obtained above MeOH (1.0 M) and degassed by bubbling argon through solution for 15 min. To the solution was added 10% Pd/C (0.5 w/w) and the flask was evacuated and backfilled with H_2 (3 cycles). The reaction mixture was stirred under an atmosphere of H_2 (balloon) for 5 h before being filtered through a pad of celite eluting with CH_2Cl_2 (25 mL). The solvent was removed under vacuum and the residue was purified by flash chromatography (SiO_2 , EtOAc in hexanes) to provide desired saturated tropolones.

7-methoxy-2-cyclohexylethyl tropolone 234a: 86% yield. $R_f = 0.27$ (1:1 EtOAc: Hexanes). mp



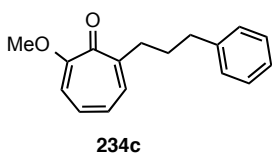
= N/A. IR (KBr): ν : 3053, 2945, 2842, 2662, 1738, 1575, 1568, 1556, 1504, 1455, 1372, 1128, 1062, 1055, 1042, 1037, 837, 798, 748. ^1H NMR (500 MHz, CDCl_3): δ 7.37 (d, $J = 8.9$ Hz, 1H), 6.99 (t, $J = 20.2, 10.5, 9.8$ Hz, 1H), 6.82 (t, $J = 19.5, 9.5, 10.0$ Hz, 1H), 6.74 (d, $J = 9.7$ Hz, 1H), 3.92 (s, 3H), 2.79-2.76 (m, 2H), 1.81-1.62 (m, 5H), 1.48-1.44 (m, 2H), 1.36-1.11 (m, 4H), 0.99-0.91 (m, 2H). ^{13}C NMR (126 MHz, CDCl_3): δ 179.2, 163.4, 150.5, 135.2, 130.3, 126.8, 111.7, 55.9, 37.5, 36.5, 33.6, 26.4, 26.0. HRMS (ESI) calcd for $\text{C}_{16}\text{H}_{22}\text{O}_2$ $[\text{M}+\text{H}]^+$: 247.1698; found: 247.1696.

7-methoxy-2-pentyl tropolone 234b: 84% yield. $R_f = 0.26$ (1:1 EtOAc: Hexanes). mp = N/A.

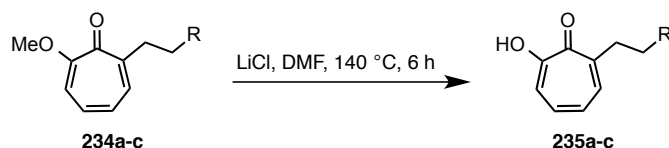


IR (KBr): ν : 2954, 2923, 2869, 2855, 1595, 1567, 1556, 1496, 1466, 1463, 1446, 1435, 1413, 1375, 1270, 1254, 1218, 1175, 1114, 1045, 1022, 795, 748. ^1H NMR (500 MHz, CDCl_3): δ 7.34 (d, $J = 8.9$ Hz, 1H), 6.96 (t, $J = 20.3, 10.6, 9.8$ Hz, 1H), 6.79 (t, $J = 19.6, 10.5, 9.1$ Hz, 1H), 6.70 (d, $J = 9.7$ Hz, 1H), 3.90 (s, 3H), 2.75-2.72 (m, 2H), 1.56 (m, 2H), 1.32 (m, 4H), 0.86 (m, 3H). ^{13}C NMR (126 MHz, CDCl_3): δ 179.5, 163.7, 150.3, 135.6, 130.5, 127.0, 111.9, 56.2, 36.3, 31.8, 28.7, 22.4, 13.9. HRMS (ESI) calcd for $\text{C}_{13}\text{H}_{18}\text{O}_2$ $[\text{M}+\text{H}]^+$: 207.1385; found: 207.1410.

7-methoxy-2-propylphenyl tropolone 234c: 82% yield. $R_f = 0.29$ (1:1 EtOAc: Hexanes). mp =

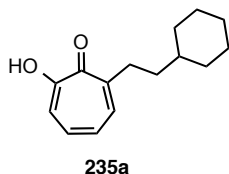


N/A. IR (KBr): ν : 3024, 2929, 2913, 2853, 1594, 1574, 1497, 1466, 1453, 1374, 1271, 1219, 1177, 751, 700. ^1H NMR (500 MHz, CDCl_3): δ 7.33 (d, $J = 8.9$ Hz, 1H), 7.26 (t, $J = 7.4$ Hz, 2H), 7.22 – 7.14 (m, 3H), 6.97 (t, $J = 10.1$ Hz, 1H), 6.82 – 6.75 (m, 1H), 6.71 (d, $J = 9.7$ Hz, 1H), 3.92 (s, 3H), 2.89 – 2.75 (m, 2H), 2.74 – 2.62 (m, 2H), 1.97 – 1.89 (m, 2H). ^{13}C NMR (126 MHz, CDCl_3): δ 179.4, 163.8, 149.7, 142.1, 135.7, 130.7, 128.3, 128.2, 126.9, 125.6, 56.2, 36.1, 35.7, 30.5. HRMS (ESI) calcd for $\text{C}_{17}\text{H}_{18}\text{O}_2$ $[\text{M}+\text{H}]^+$: 255.1385; found: 255.1406.



General Procedure of Deprotection of 7-methoxy Tropolones: To a flame dried pressure vessel was added 7-methoxy tropolone in DMF (0.5 M) followed by LiCl (3 eq). The vessel was heated to 140 °C for a period of 6 h when all starting material had been consumed. The crude material was diluted with Et₂O and brine. The mixture was then extracted with Et₂O (3x). The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated in vacuo. Flash chromatography of the crude residue (SiO₂, EtOAc in hexanes) provided the tropolones as clear oils.

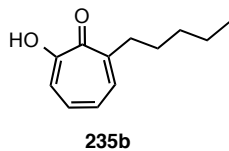
2-cyclohexylethyl tropolone 235a: 76% yield. *R*_f = 0.54 (1:1 EtOAc: Hexanes). mp = N/A. IR



(KBr): ν : 3204, 2919, 2901, 2848, 1599, 1547, 1537, 1475, 1418, 1380, 1229, 1205, 1125, 996, 731. ¹H NMR (500 MHz, CD₂Cl₂): δ 9.65 (bs, 1H), 7.47 (d, *J* = 9.9 Hz, 1H), 7.32-7.25 (m, 2H), 7.00-6.96 (m, 1H), 2.84-2.80 (m, 2H), 1.80 (d, *J* = 13.6 Hz, 2H), 1.72-1.64 (m, 3H), 1.50-1.46 (m, 2H),

1.36-1.13 (m, 5H), 1.00-0.92 (m, 2H). ¹³C NMR (126 MHz, CD₂Cl₂): δ 172.7, 168.9, 142.6, 139.9, 136.2, 127.9, 121.7, 38.4, 37.5, 33.8, 33.3, 27.3, 26.9. HRMS (ESI) calcd for C₁₅H₂₀O₂ [M+H]⁺: 233.1541; found: 233.1550.

2-pentyl tropolone 235b: 75% yield. *R*_f = 0.6 (1:1 EtOAc: Hexanes). mp = N/A. IR (KBr): ν :

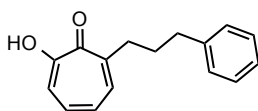


3172, 3161, 3153, 3140, 2957, 2927, 2924, 2869, 2857, 1616, 1601, 1549, 1488, 1477, 1468, 1422, 1381, 1293, 1240, 1232, 850, 799, 743, 718, 696.

¹H NMR (500 MHz, CD₂Cl₂): δ 9.60 (bs, 1H), 7.46 (d, *J* = 9.9 Hz, 1H), 7.31-7.24 (m, 2H), 6.96 (t, *J* = 18.7, 9.0, 9.7 Hz, 1H), 2.80 (t, *J* = 15.5, 7.6, 7.9 Hz, 2H), 1.61 (m, 2H), 1.35 (m, 4H), 0.89 (m, 3H). ¹³C NMR (126 MHz, CDCl₃): δ 172.9, 169.1, 142.1, 139.9,

136.2, 127.7, 121.8, 35.9, 32.4, 29.4, 23.1, 14.4. HRMS (ESI) calcd for $C_{12}H_{16}O_2$ $[M+H]^+$: 193.1229; found: 193.1249.

2-propylphenyl tropolone 235c: 73% yield. R_f = 0.35 (1:1 EtOAc: Hexanes). mp = N/A. IR



235c

(KBr): ν : 3026, 2927, 2923, 2857, 1616, 1600, 1550, 1473, 1459, 1453,

1424, 1382, 1293, 1263, 1247, 1233, 1214, 738, 699. 1H NMR (500

MHz, CD_2Cl_2) δ 9.61 (bs, 1H), 7.47 (d, J = 9.9 Hz, 1H), 7.30 (t, J = 15.3

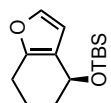
Hz, 4H), 7.20 (d, J = 29.3 Hz, 3H), 6.98 (td, J = 9.9, 1.5 Hz, 1H), 2.96 – 2.82 (m, 2H), 2.80 – 2.66

(m, 2H), 1.96 (p, J = 7.8 Hz, 2H). ^{13}C NMR (126 MHz, CD_2Cl_2): δ 173.0, 168.7, 142.8, 141.8,

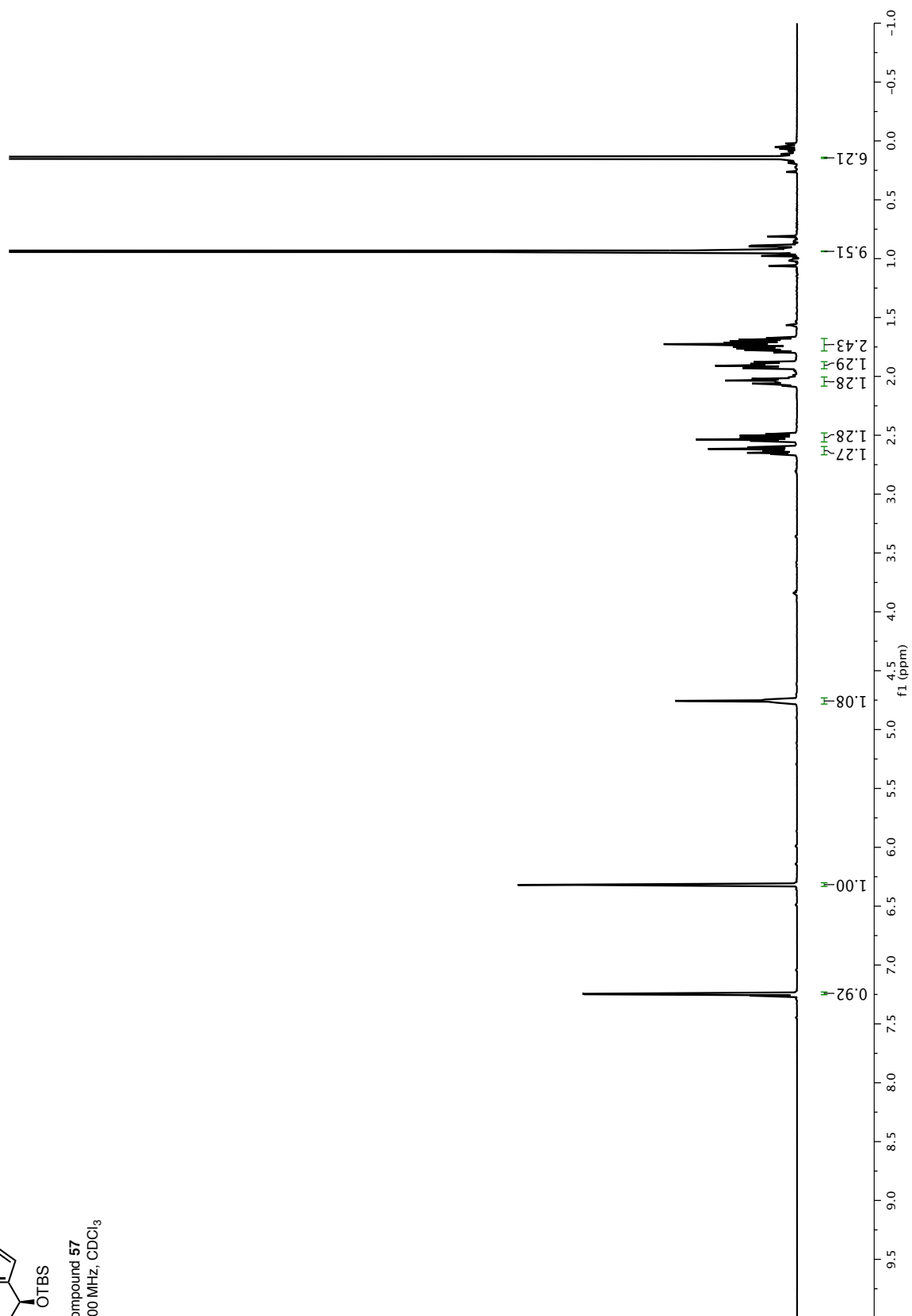
140.0, 136.4, 129.0, 128.8, 127.9, 126.3, 121.5, 36.3, 35.7, 31.2. HRMS (ESI) calcd for $C_{16}H_{16}O_2$

$[M+H]^+$: 241.1229; found: 241.1253.

Appendix A: Selected Spectra



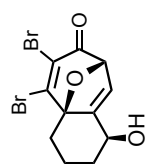
Compound **57**
 ^1H , 500 MHz, CDCl_3



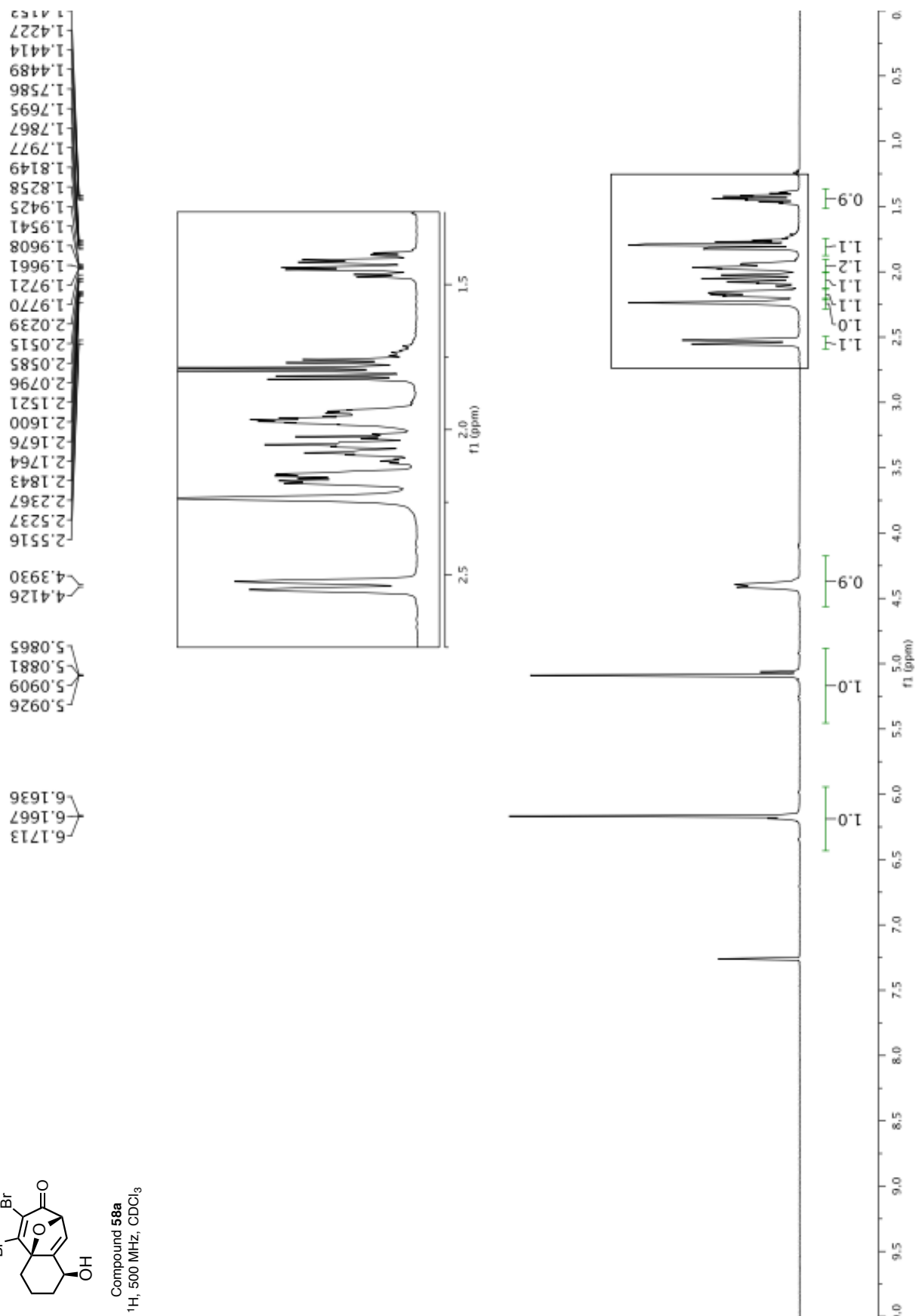


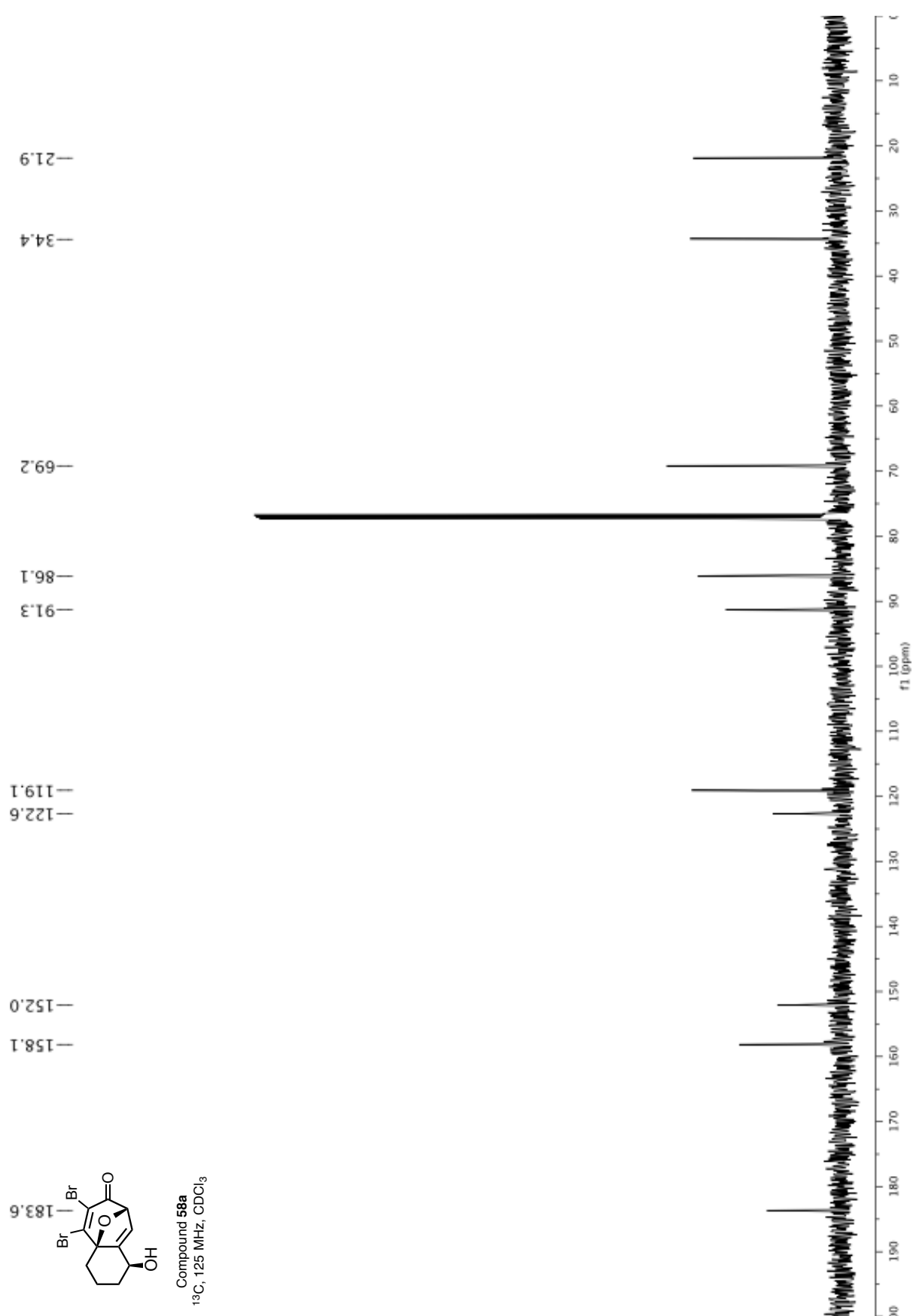
Compound **57**
 ^{13}C , 125 MHz, CDCl_3

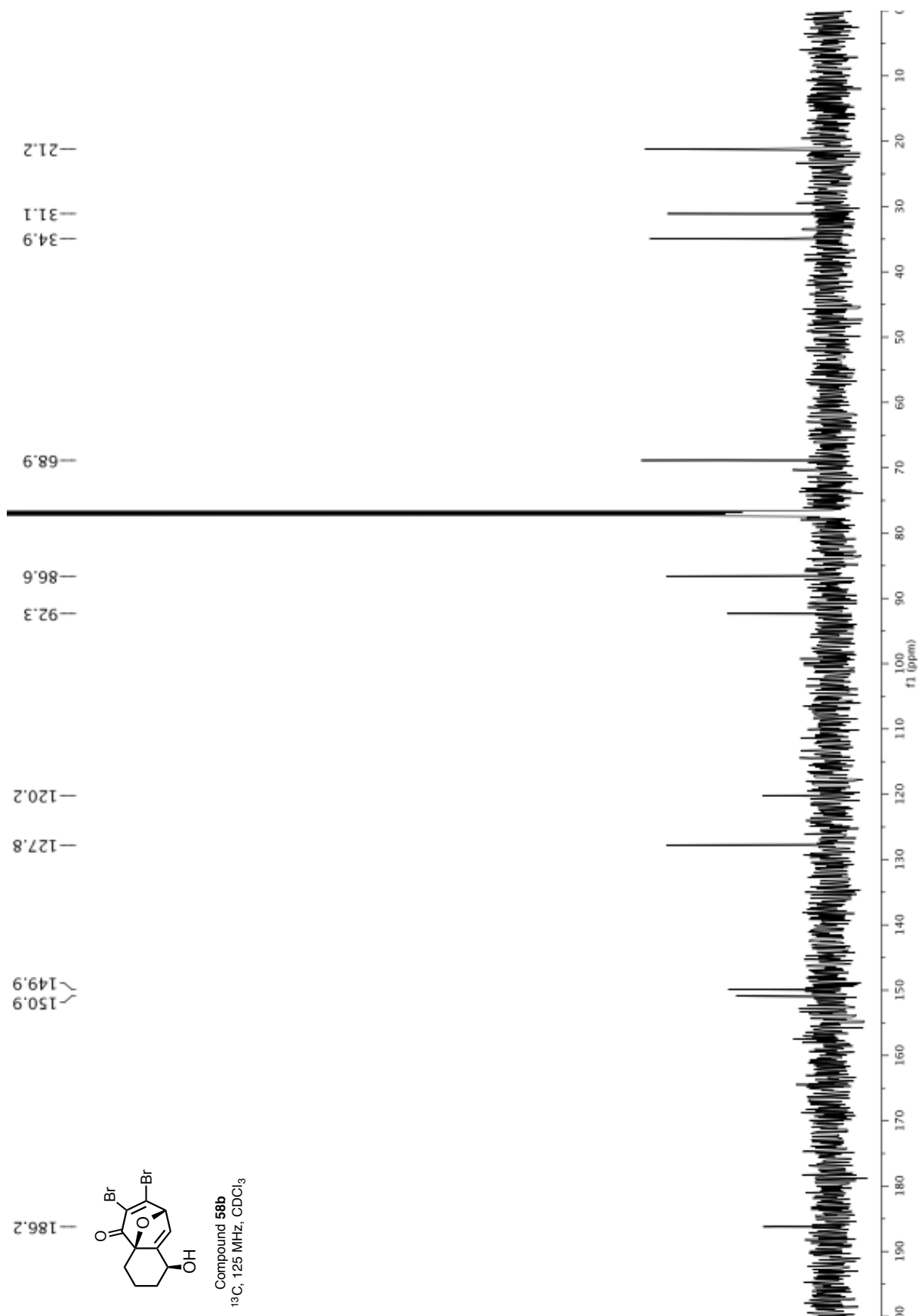


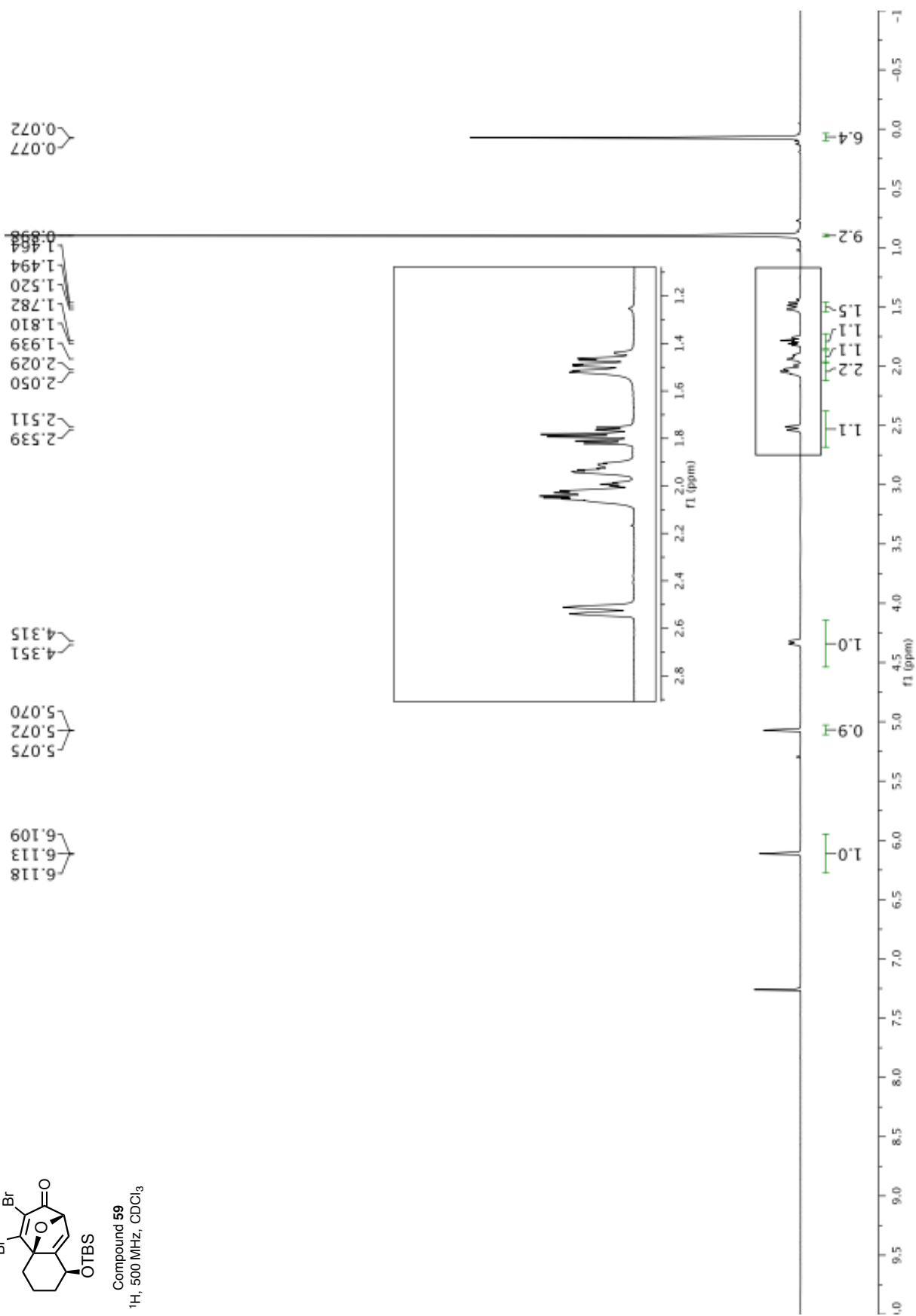
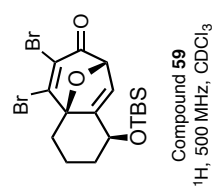


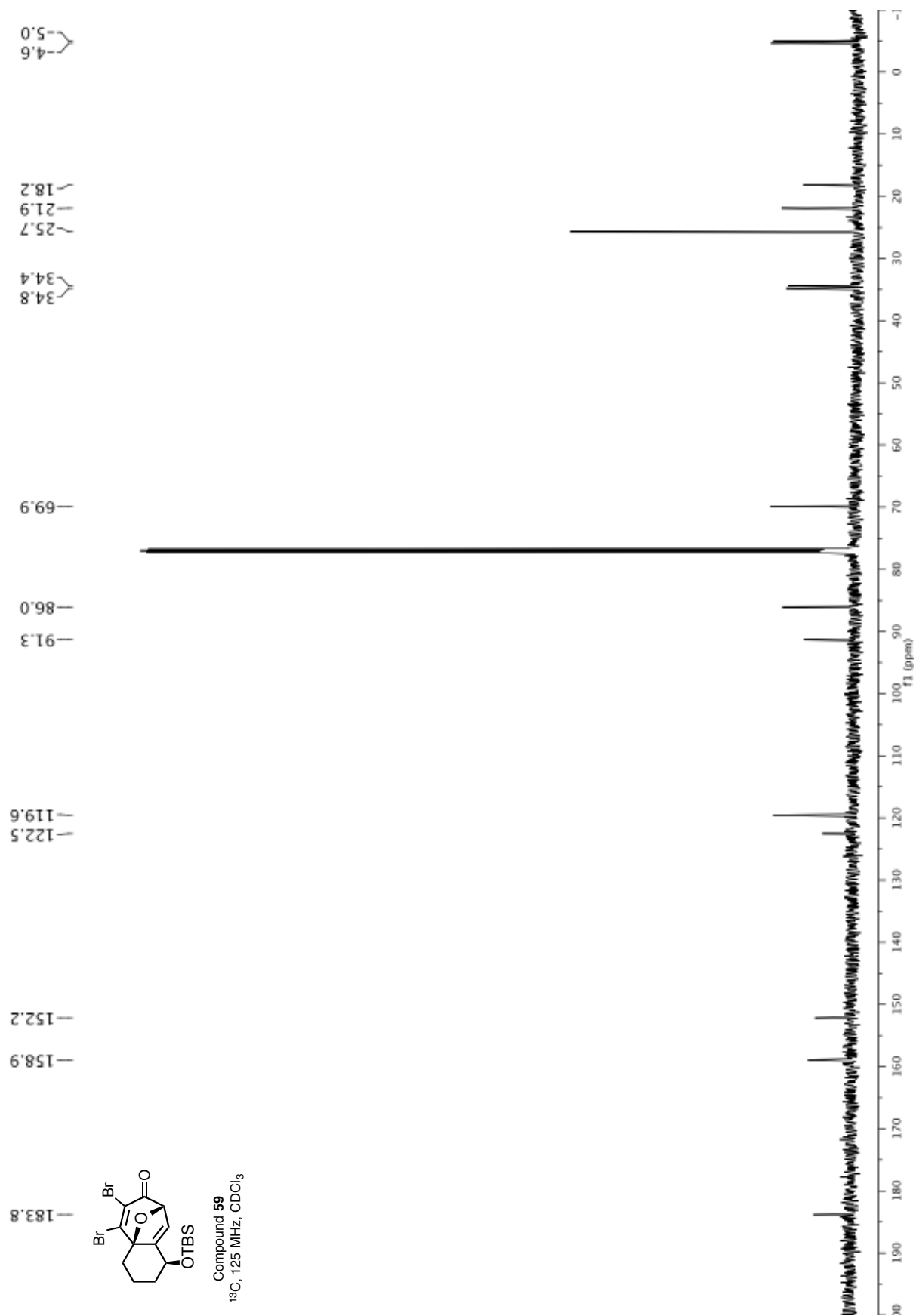
Compound **58a**
 ^1H , 500 MHz, CDCl_3

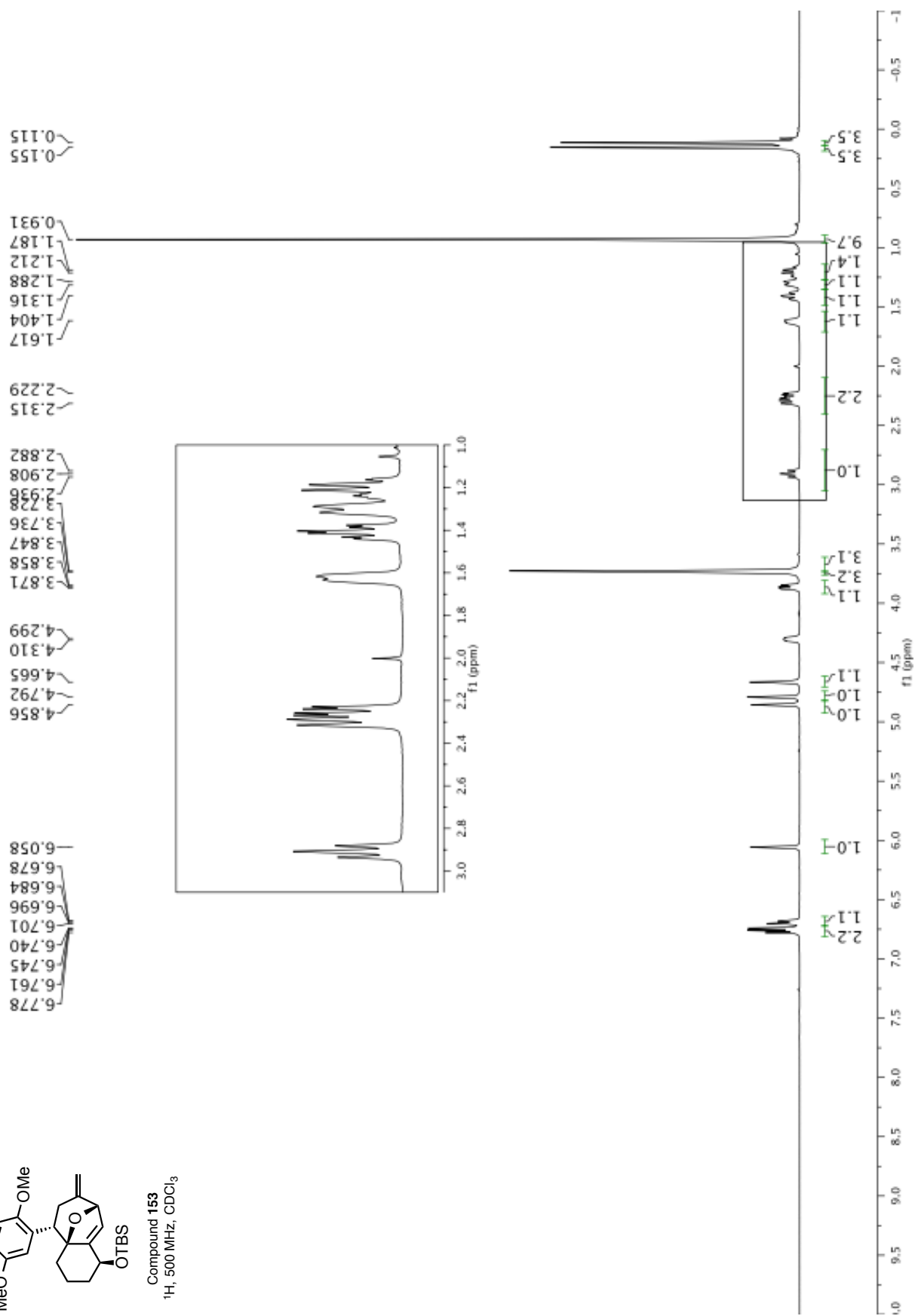
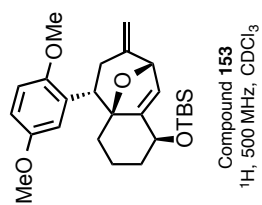


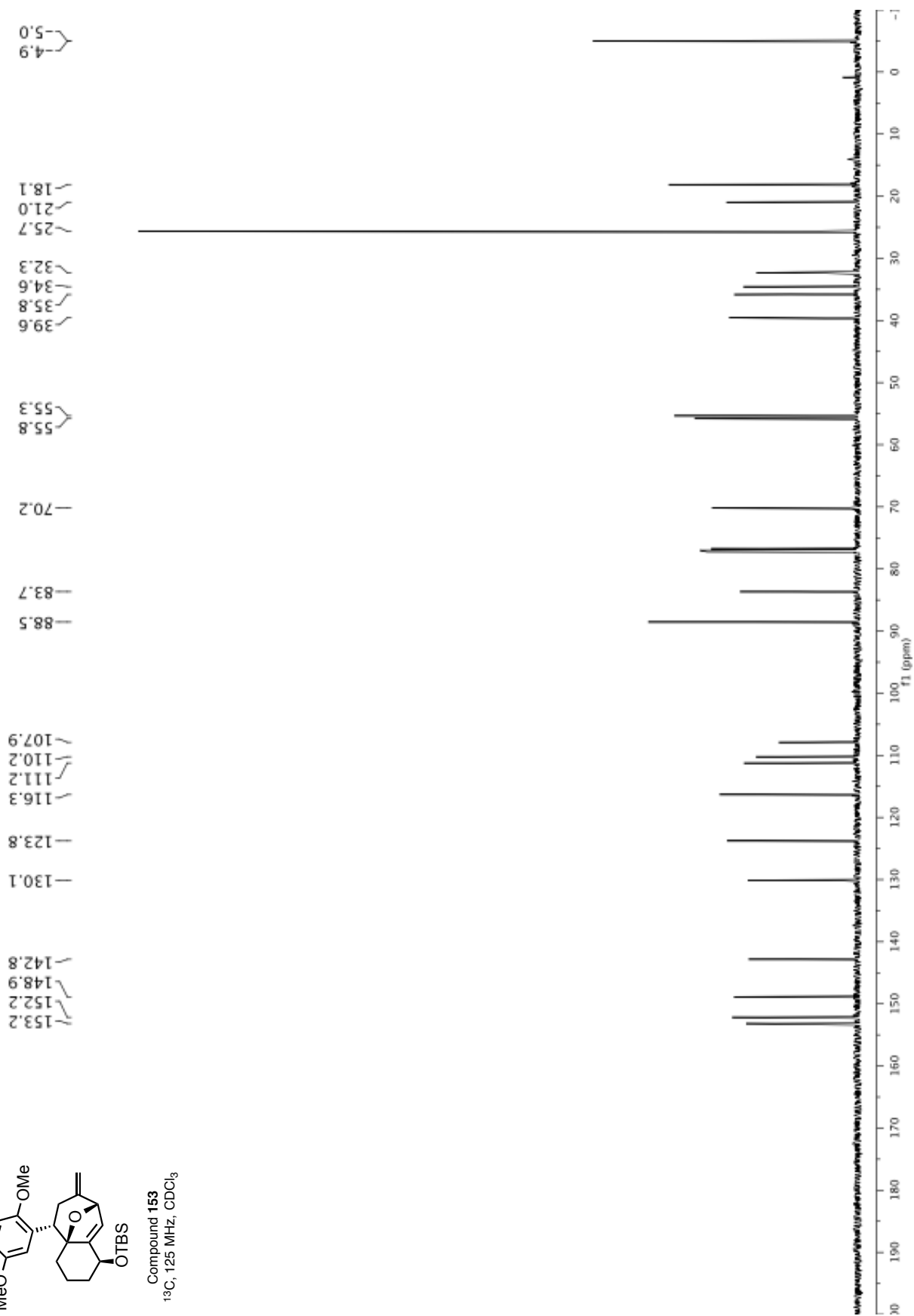
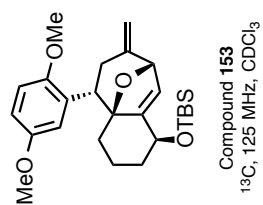


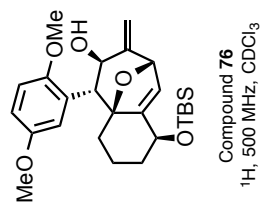




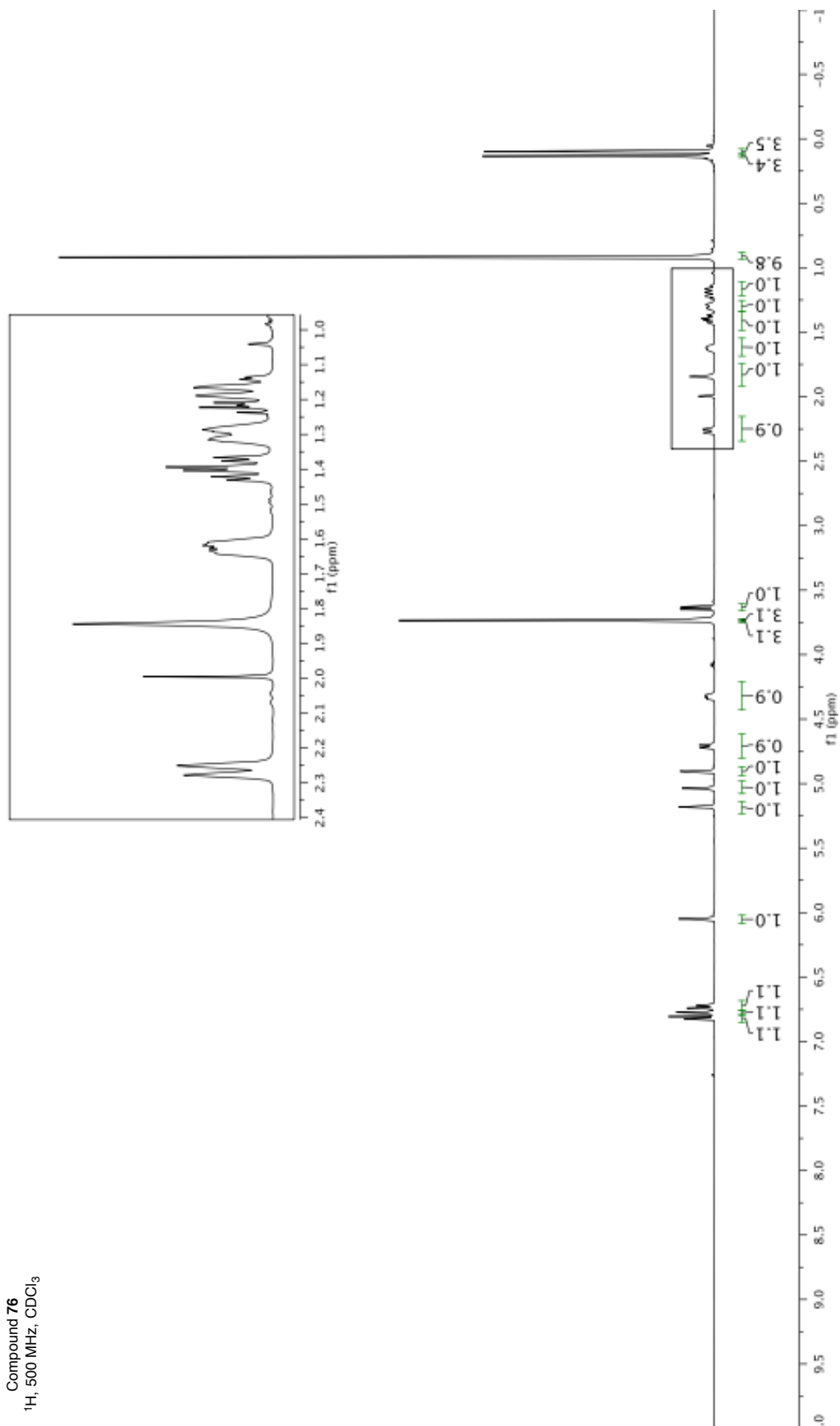


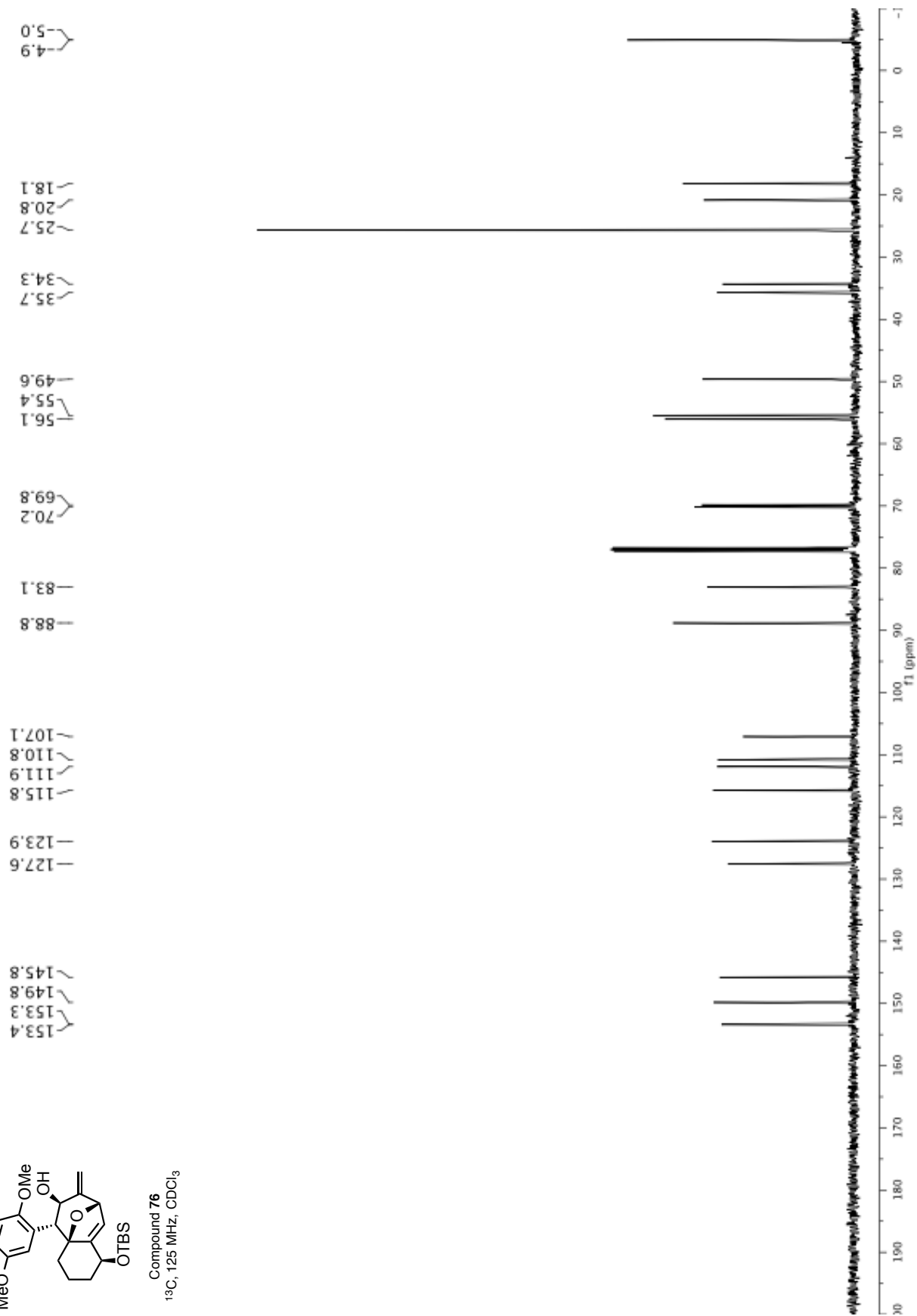
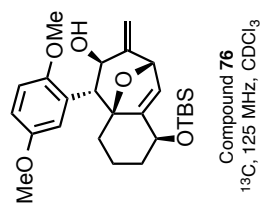


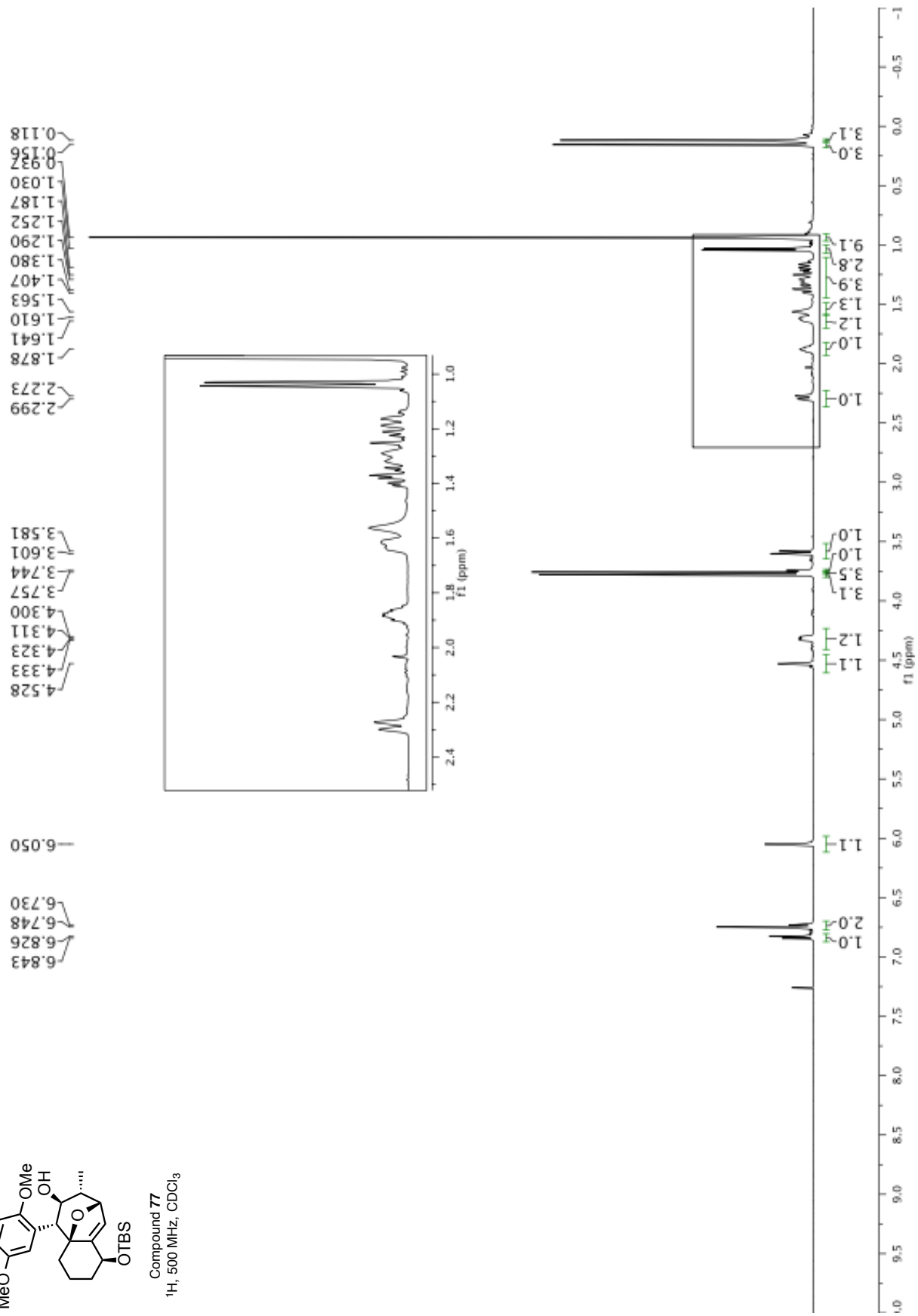
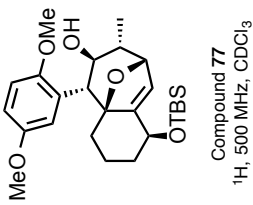


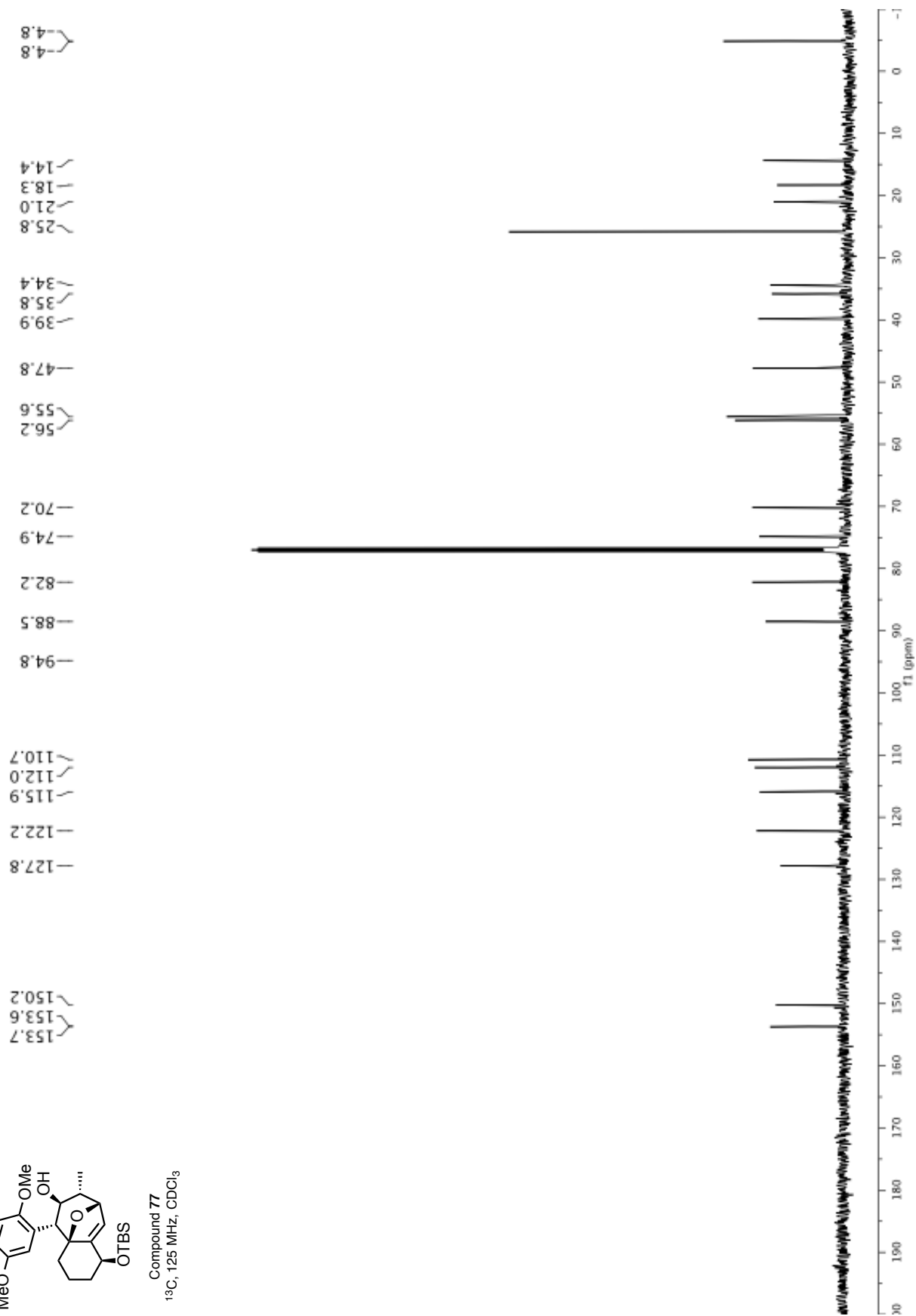
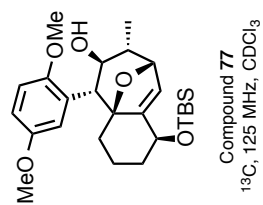


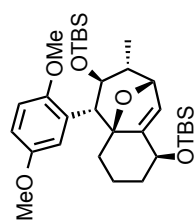
6.823, 6.806, 6.779, 6.774, 6.740, 6.734, 6.723, 6.717, 6.053, 6.049, 6.045, 5.181, 5.037, 4.907, 4.904, 4.721, 4.702, 4.340, 4.329, 4.307, 3.734, 3.732, 3.648, 3.629, 2.277, 2.251, 1.844, 1.642, 1.609, 1.431, 1.404, 1.366, 1.312, 1.284, 1.189, 1.165, 0.917, 0.134, 0.097



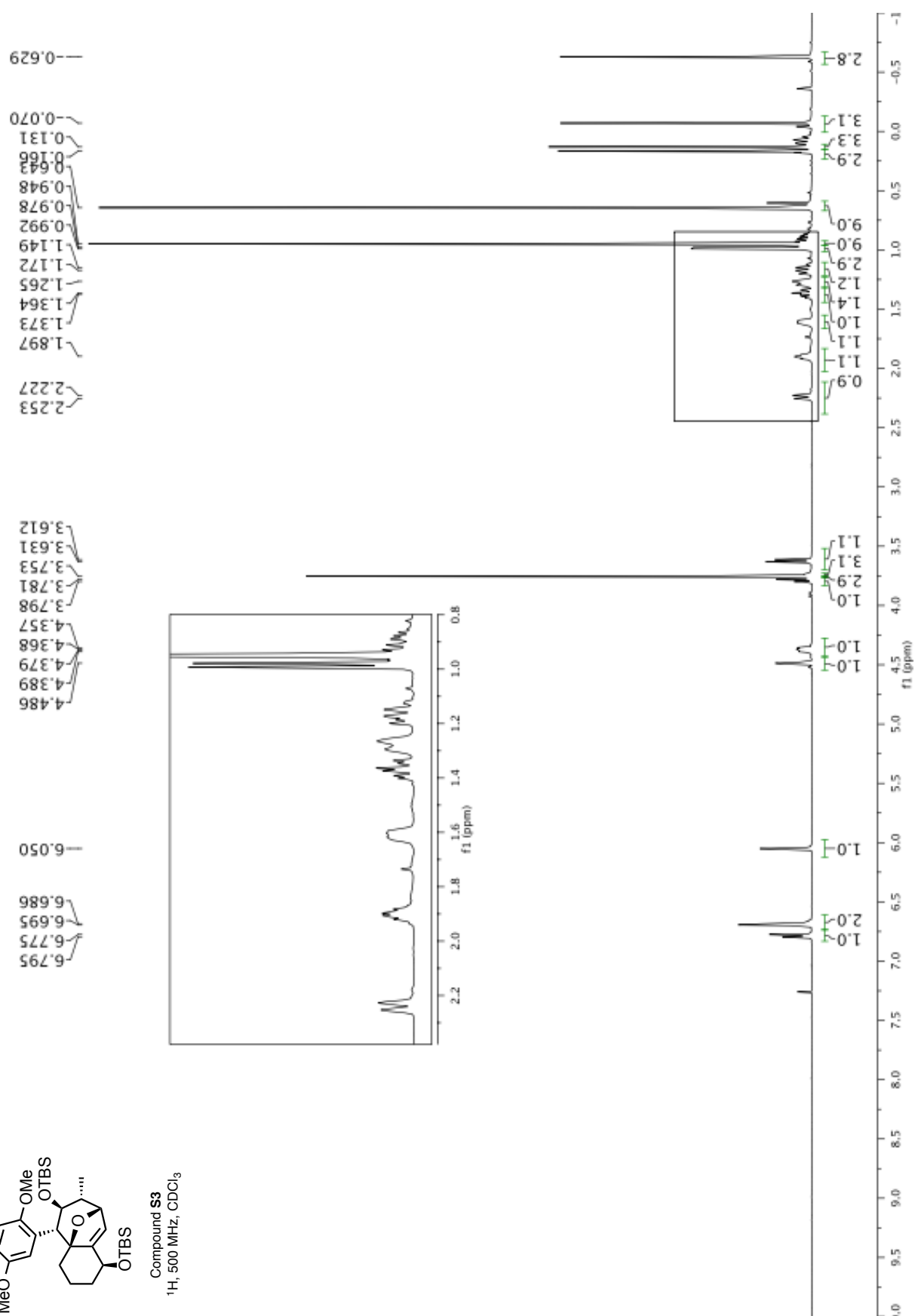


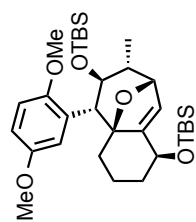




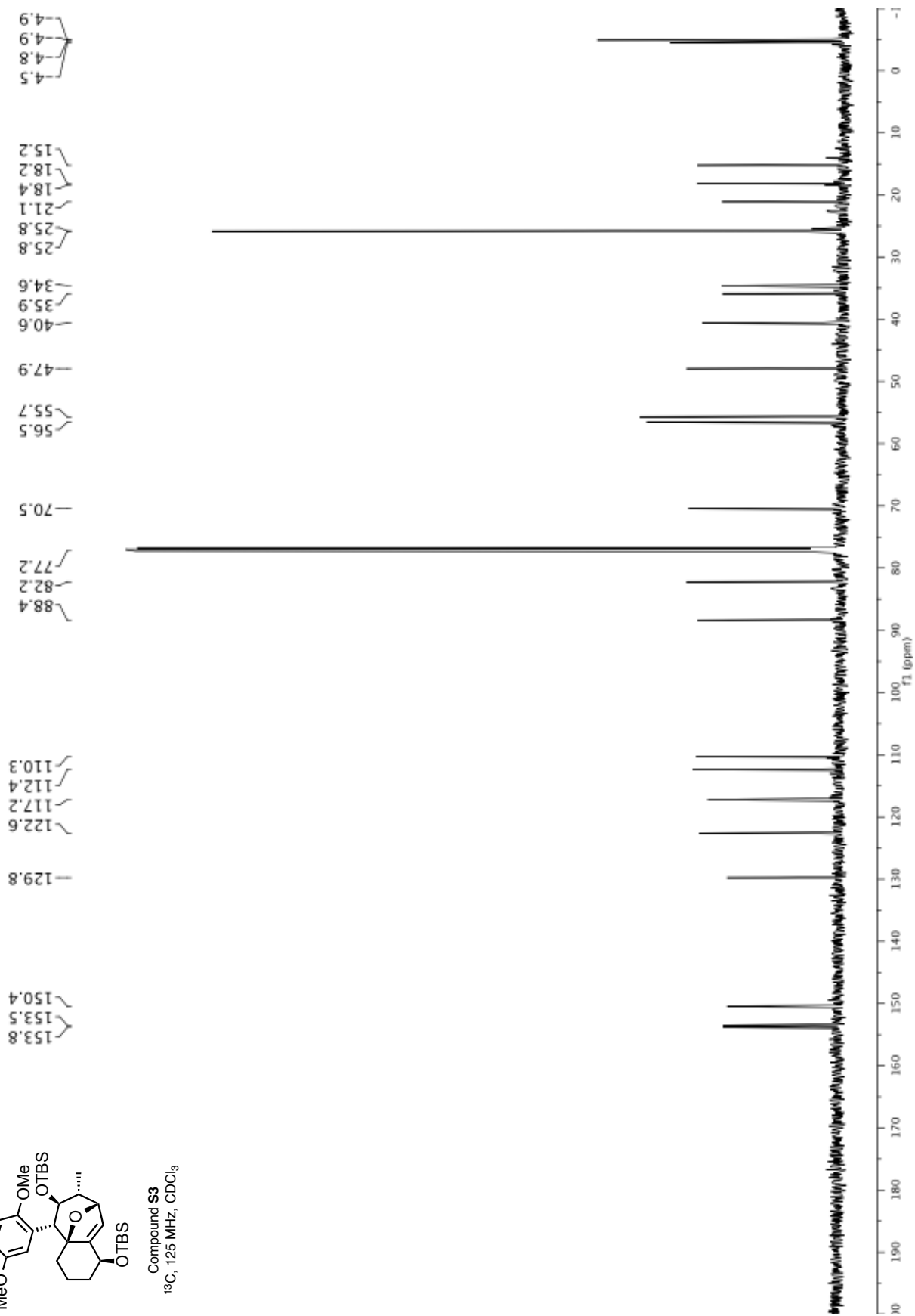


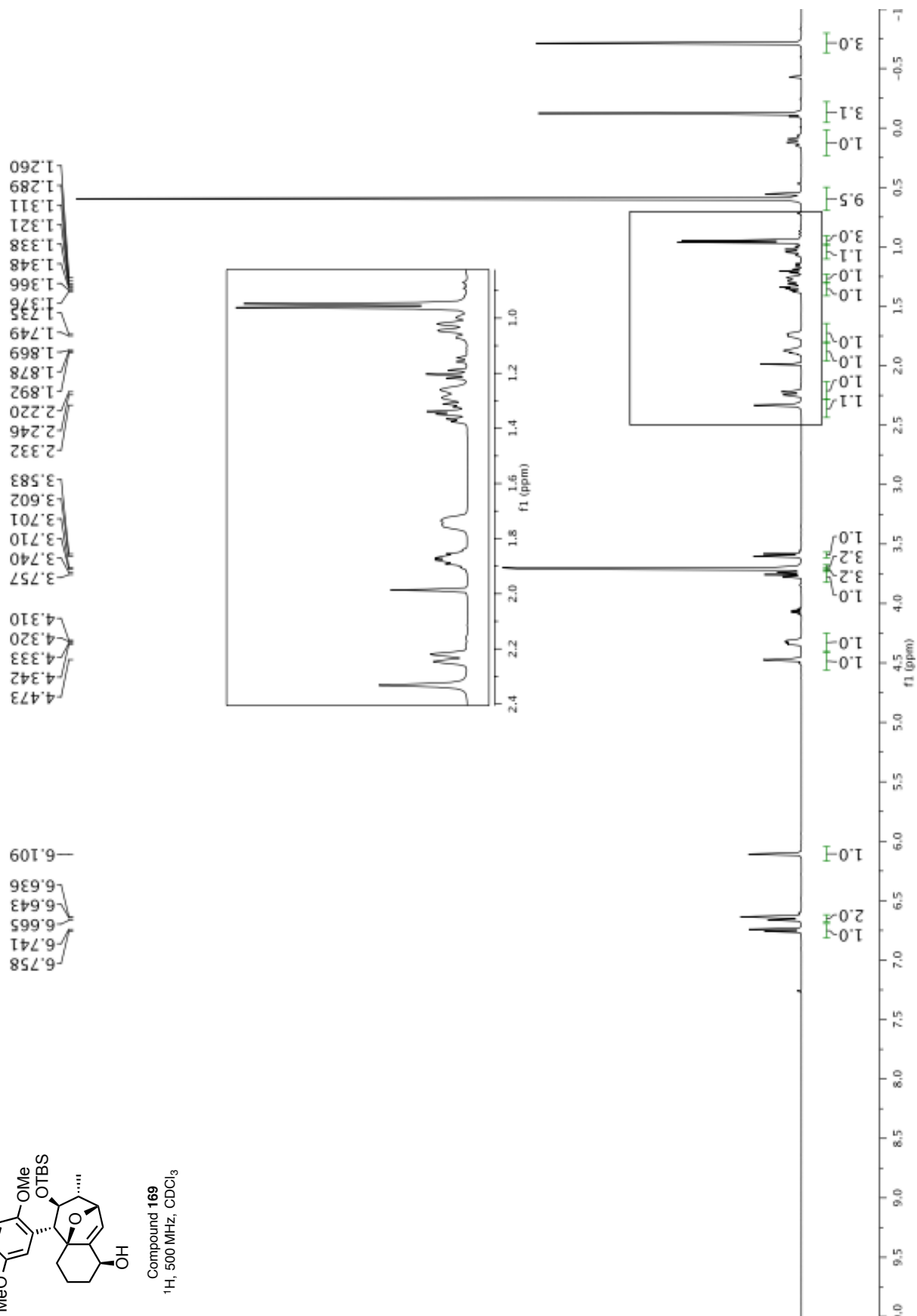
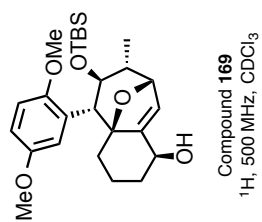
Compound **S3**
 ^1H , 500 MHz, CDCl_3

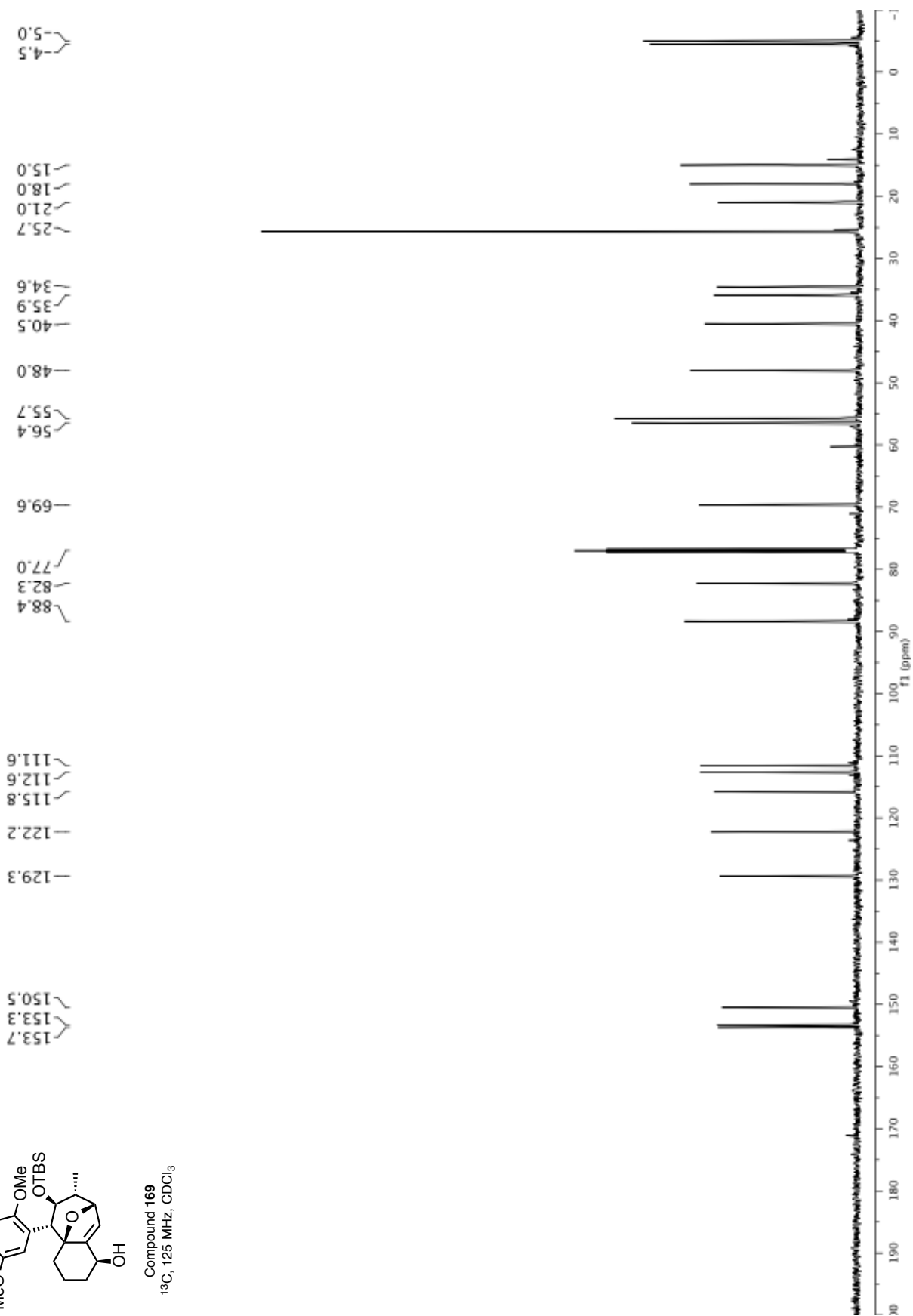
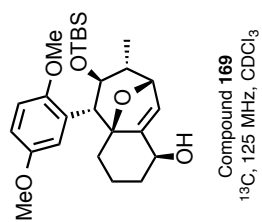


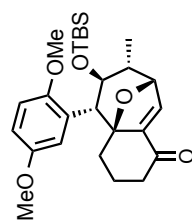


Compound **S3**
 ^{13}C , 125 MHz, CDCl_3

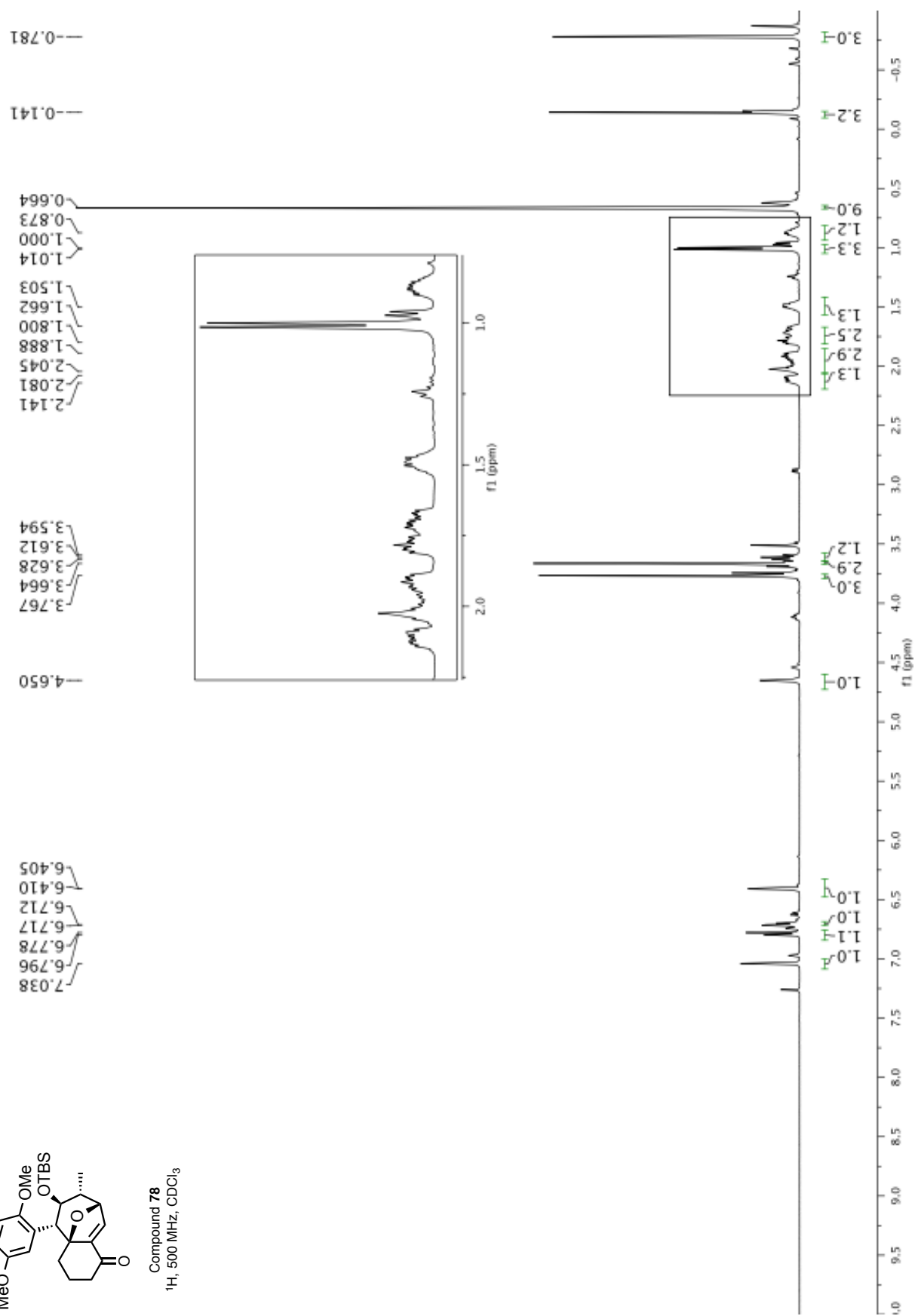


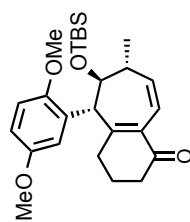




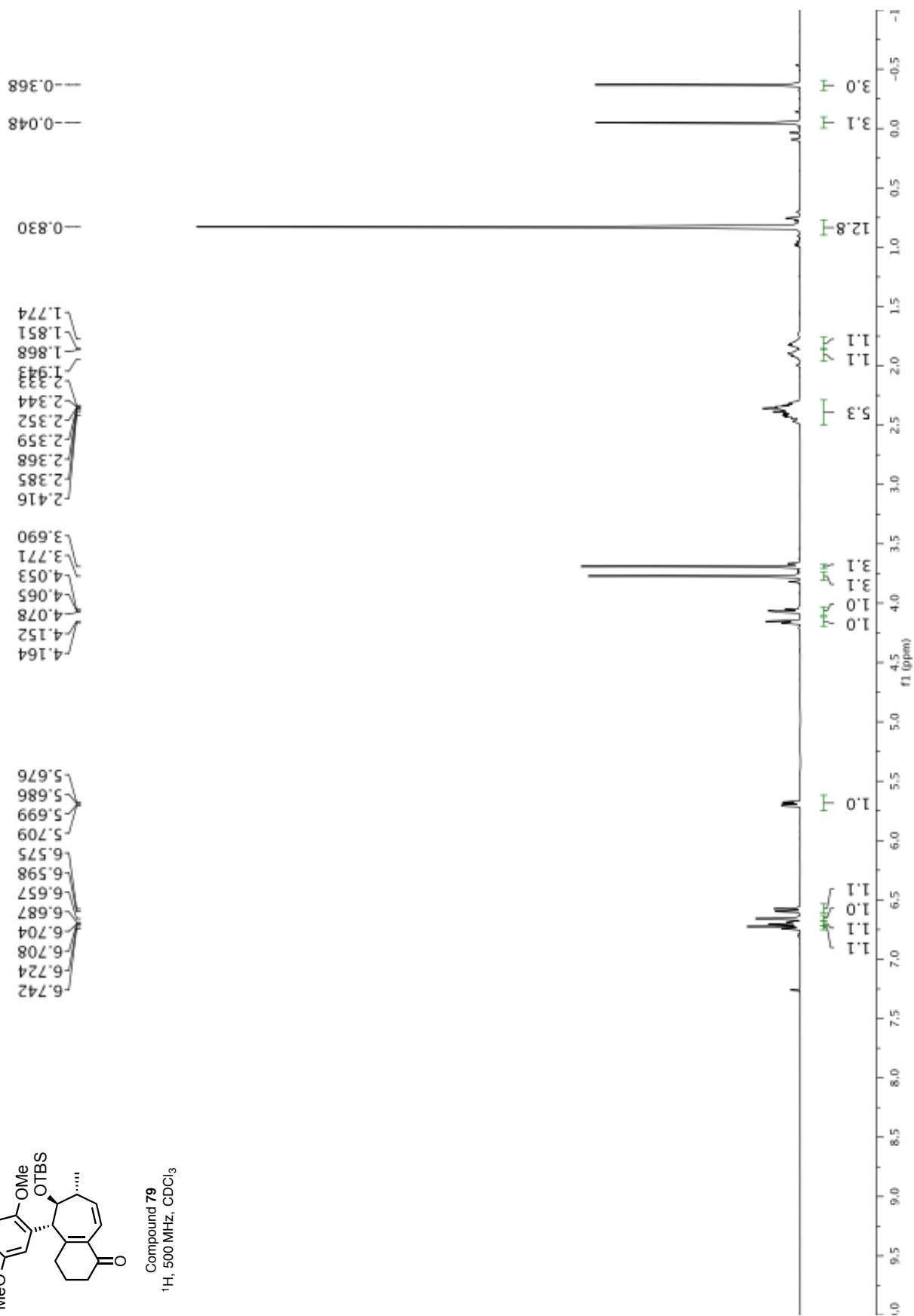


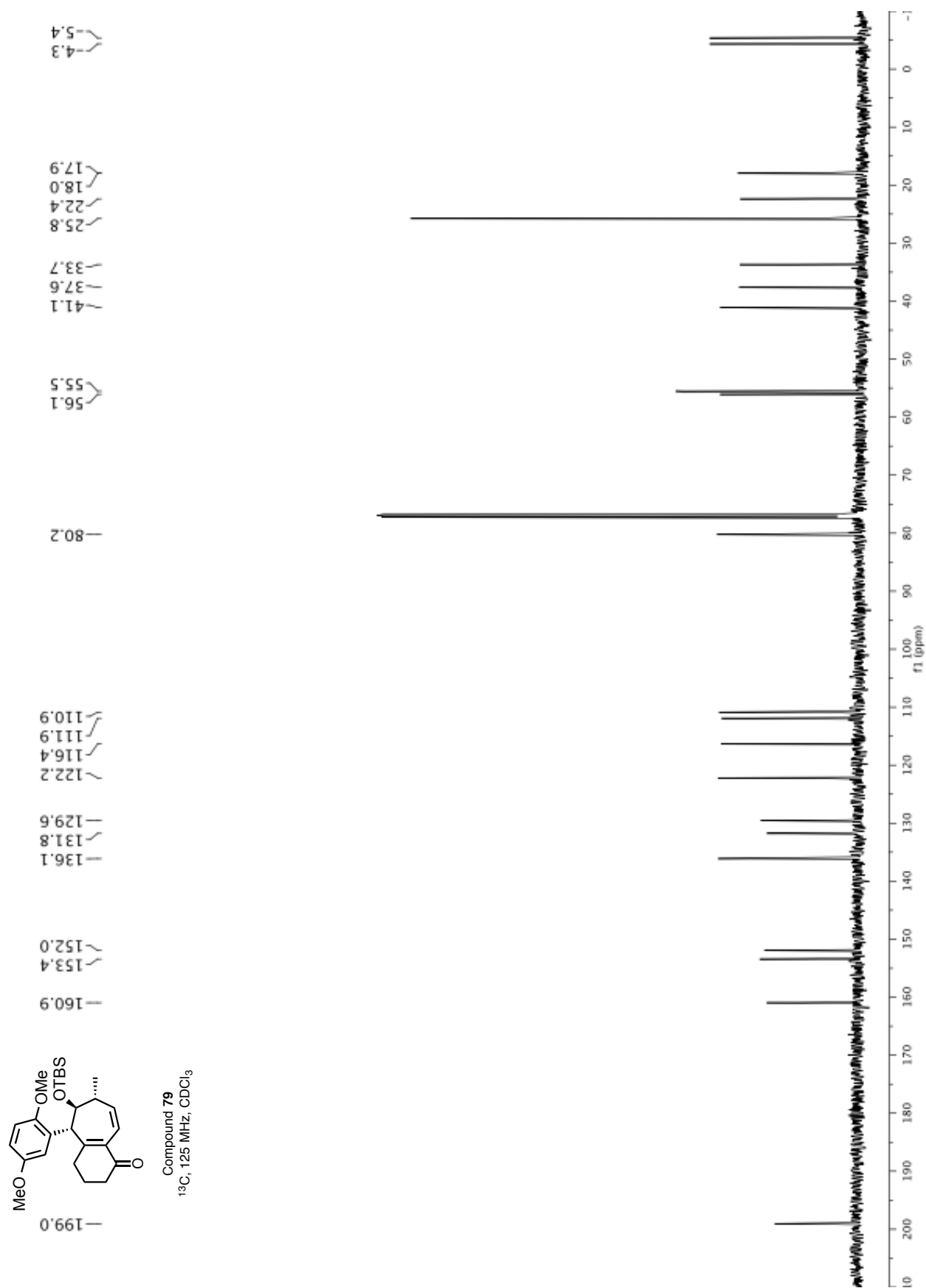
Compound **78**
 ^1H , 500 MHz, CDCl_3

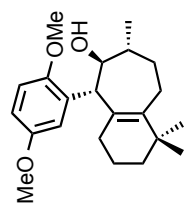




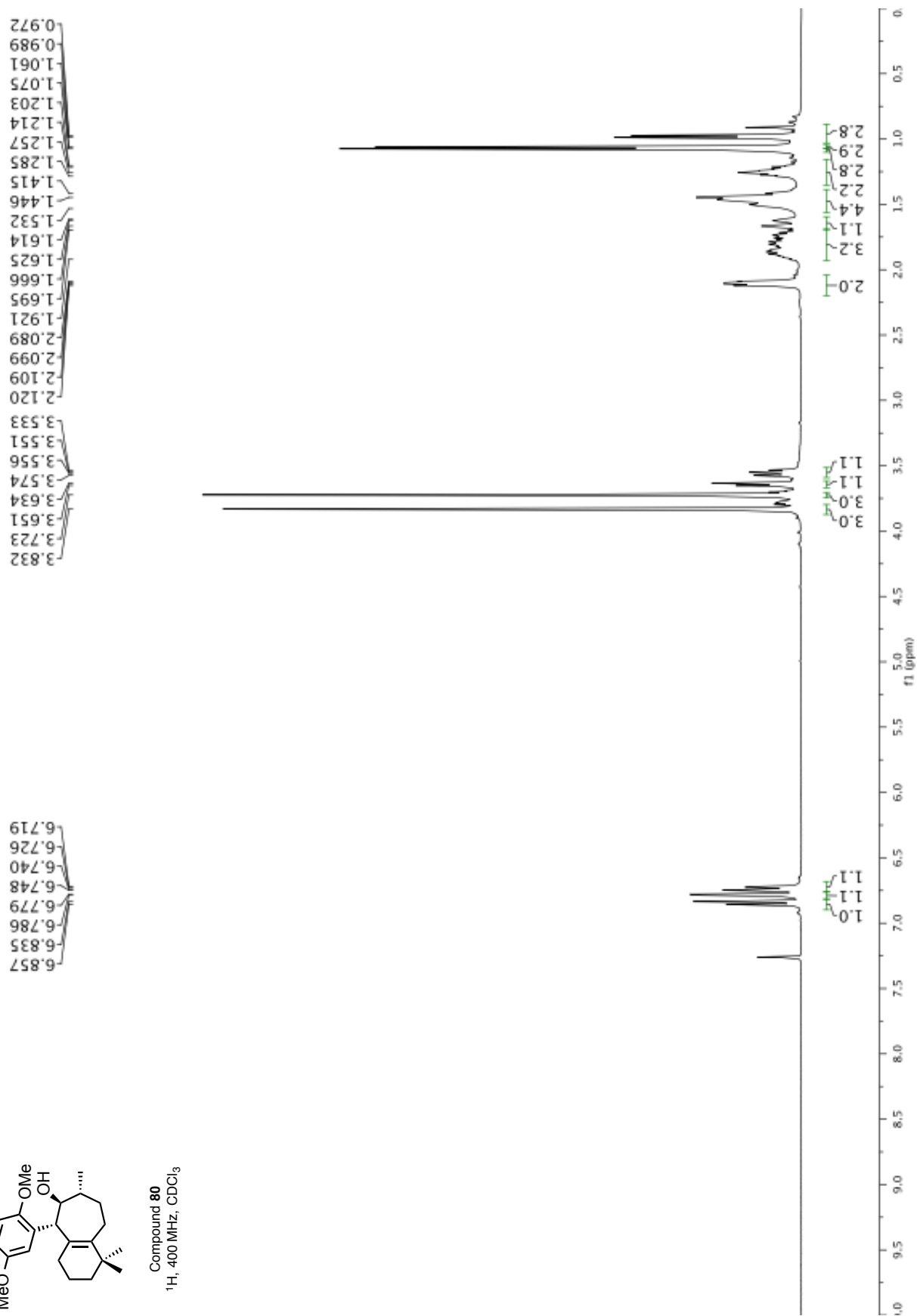
Compound **79**
 ^1H , 500 MHz, CDCl_3

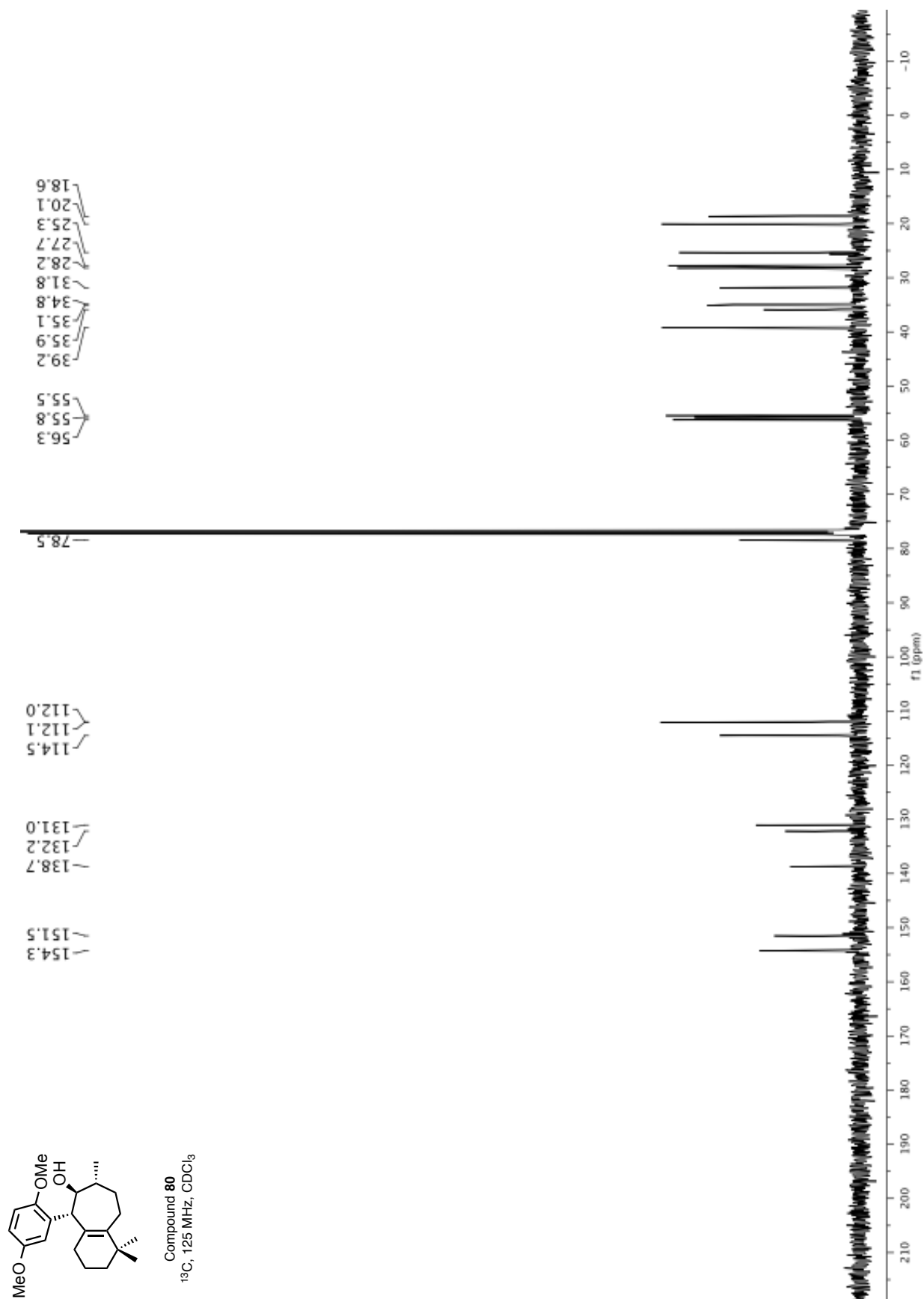


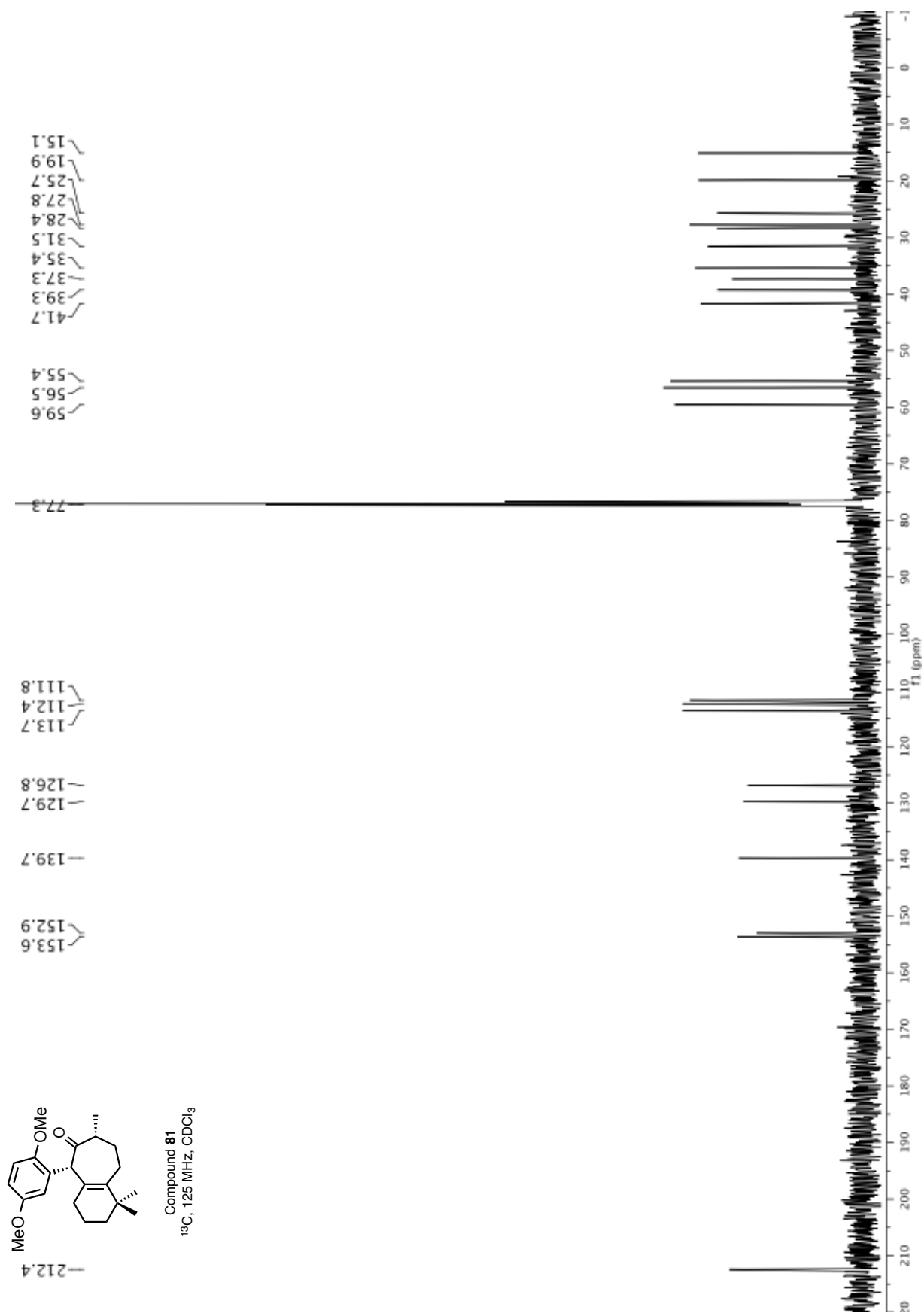


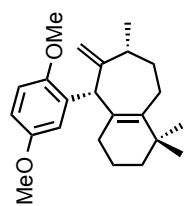


Compound **80**
 ^1H , 400 MHz, CDCl_3

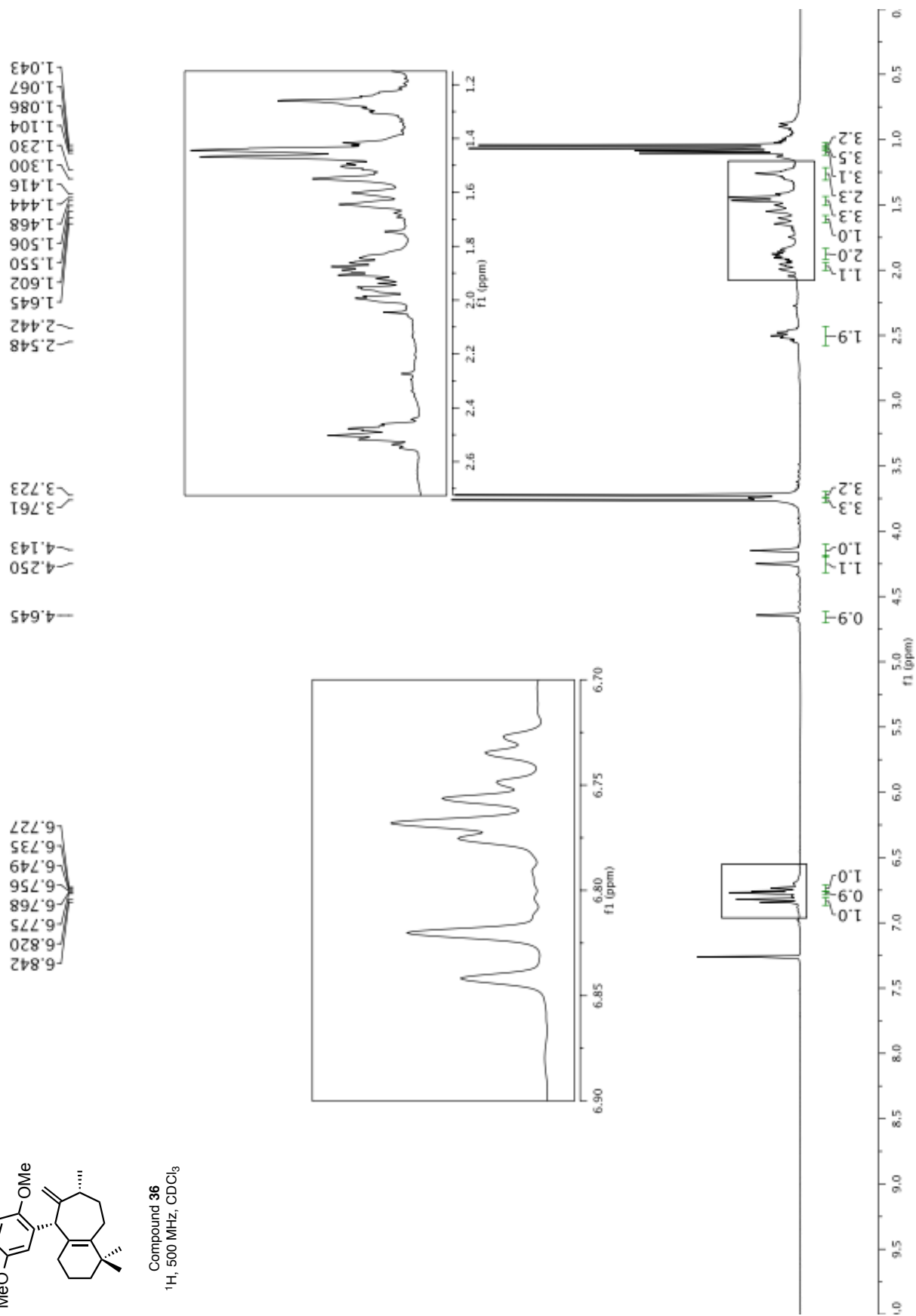


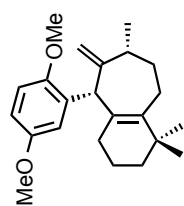




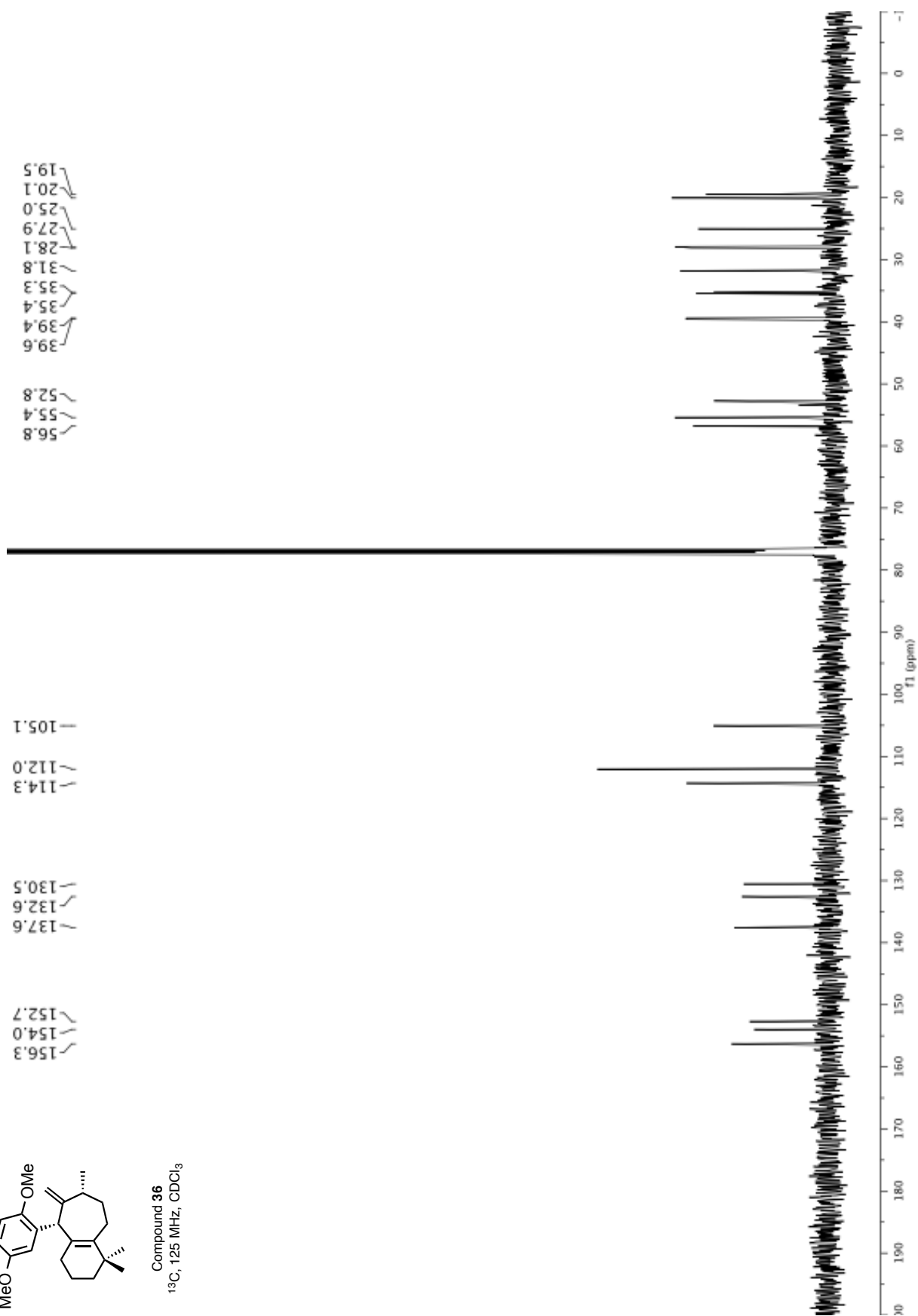


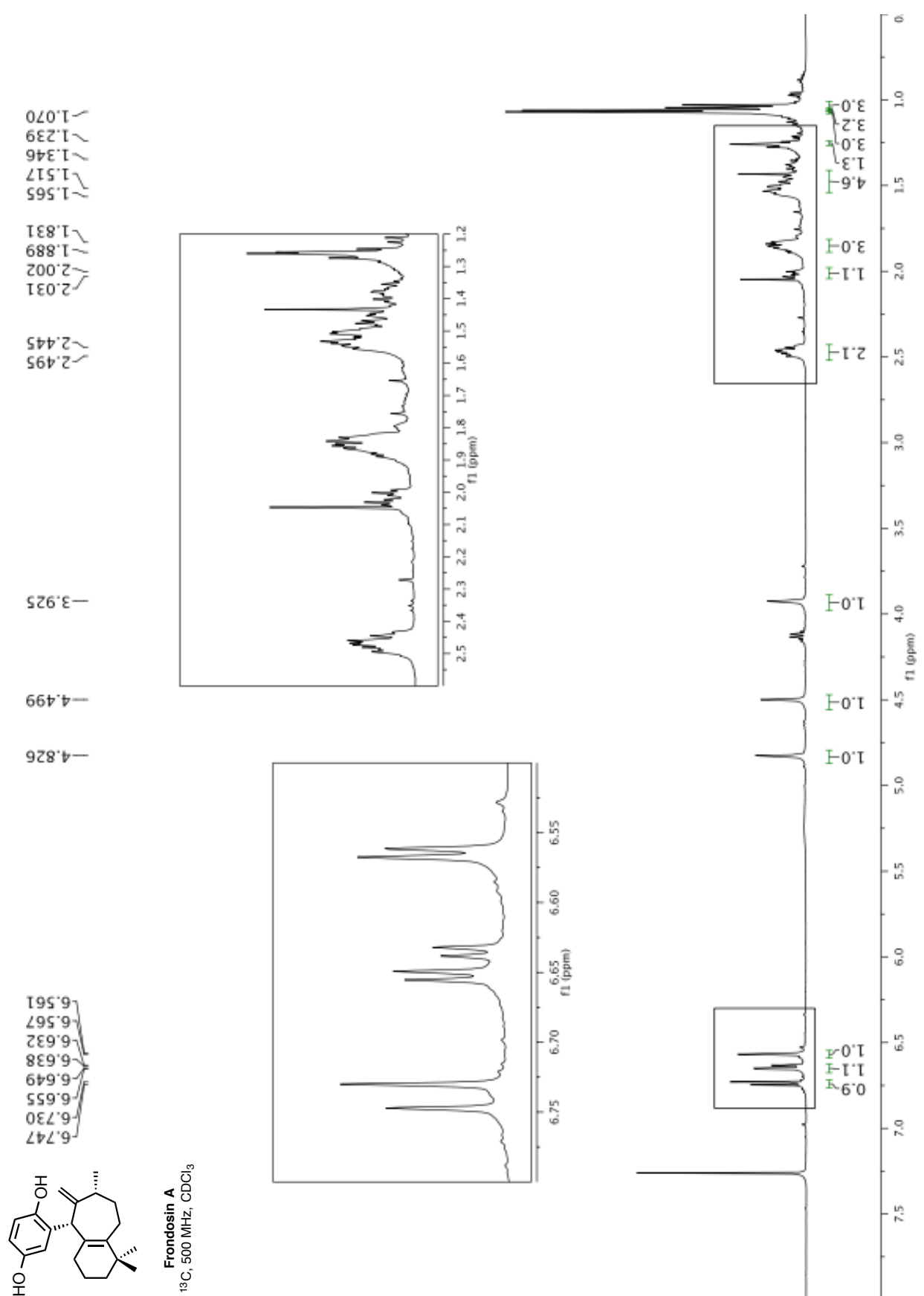
Compound **36**
 ^1H , 500 MHz, CDCl_3

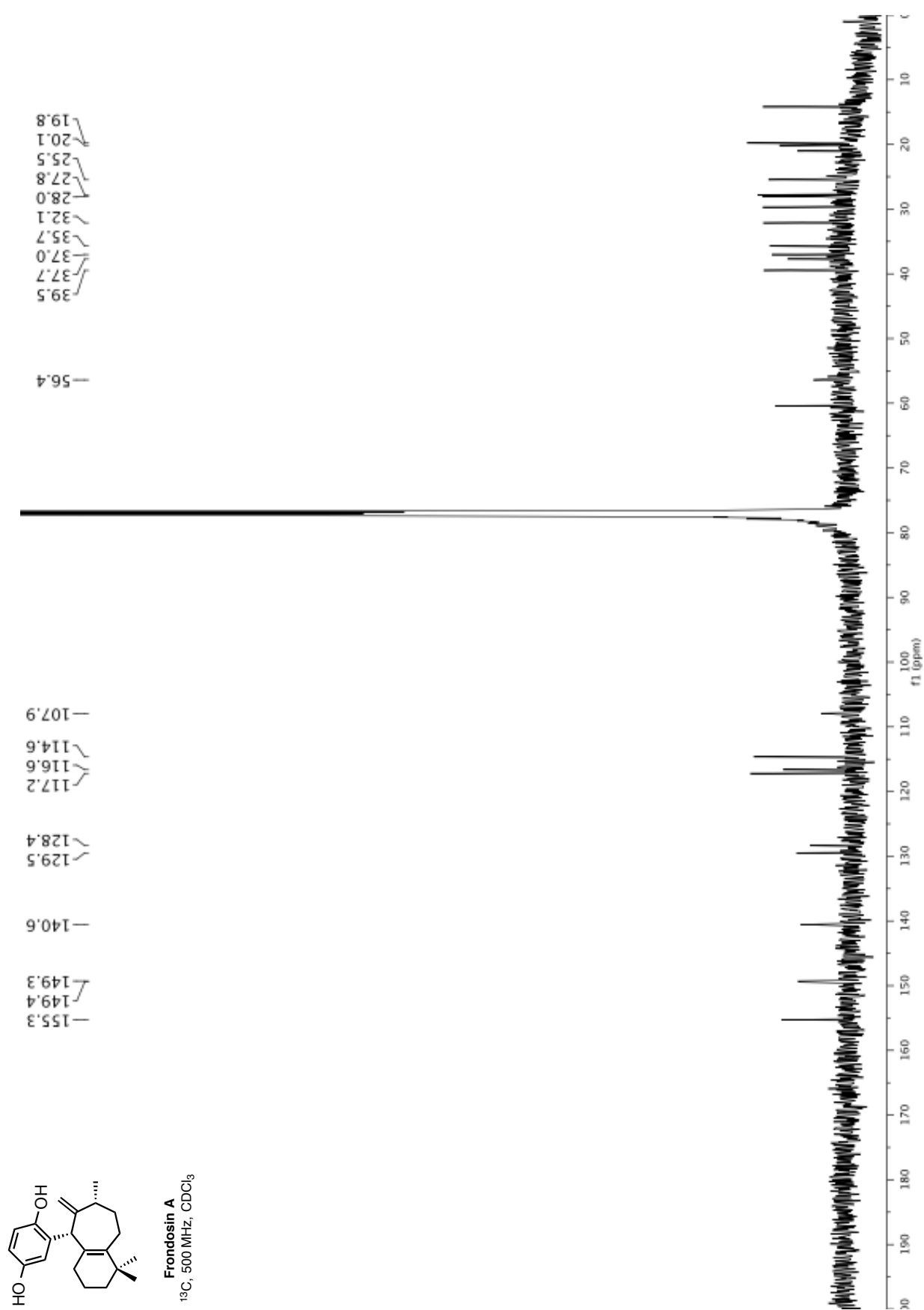


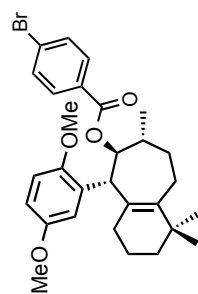


Compound **36**
 ^{13}C , 125 MHz, CDCl_3

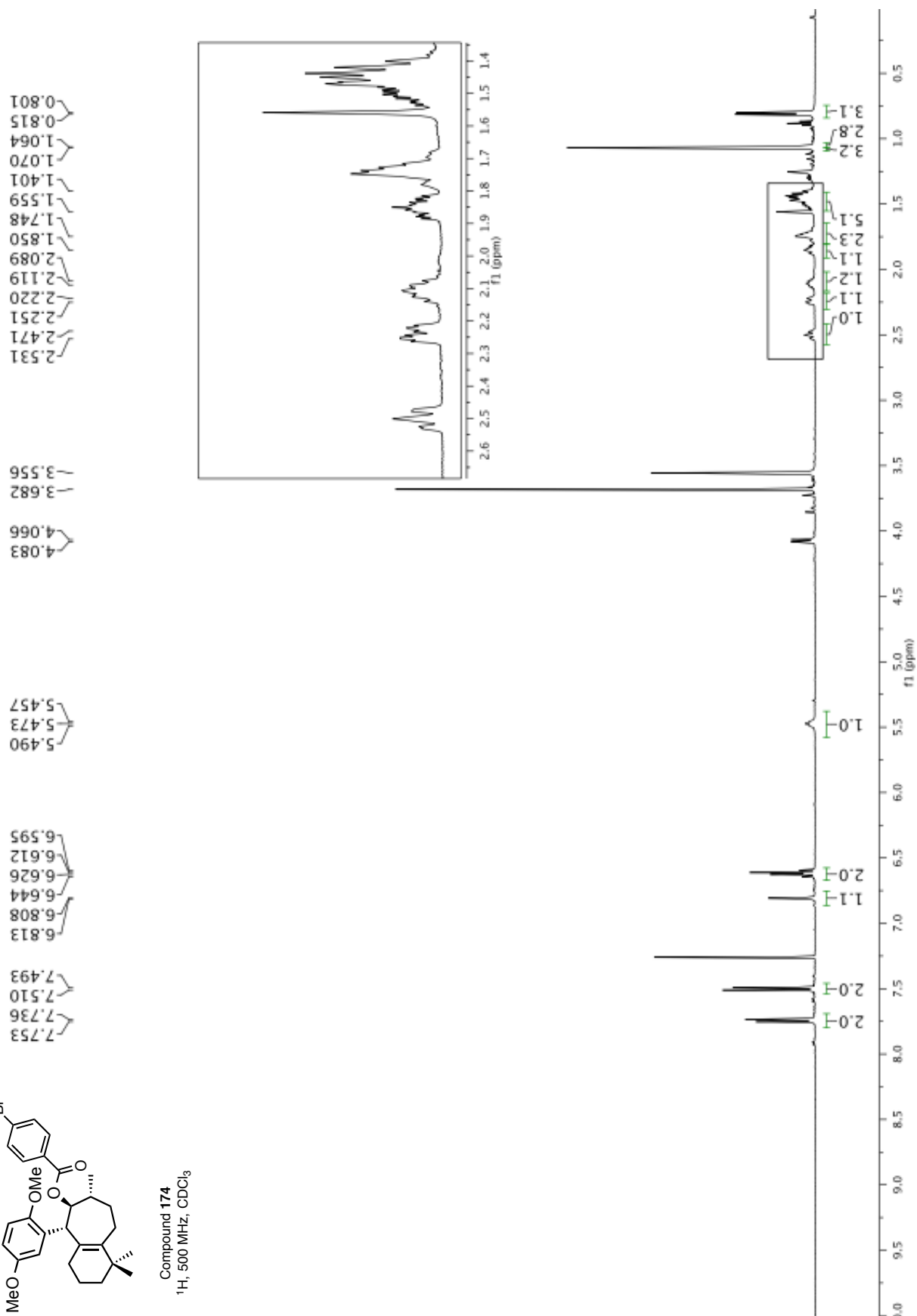


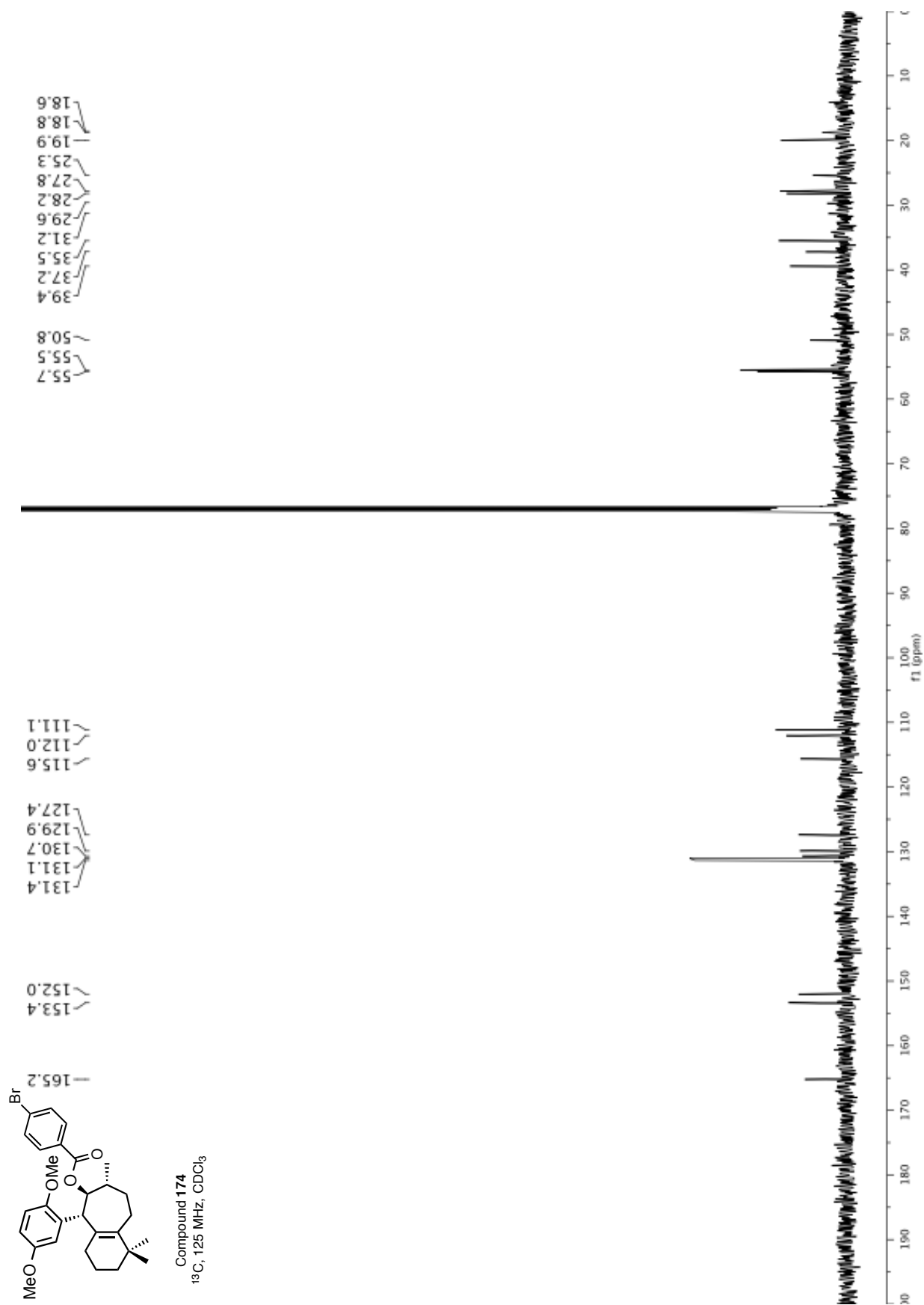


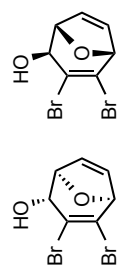




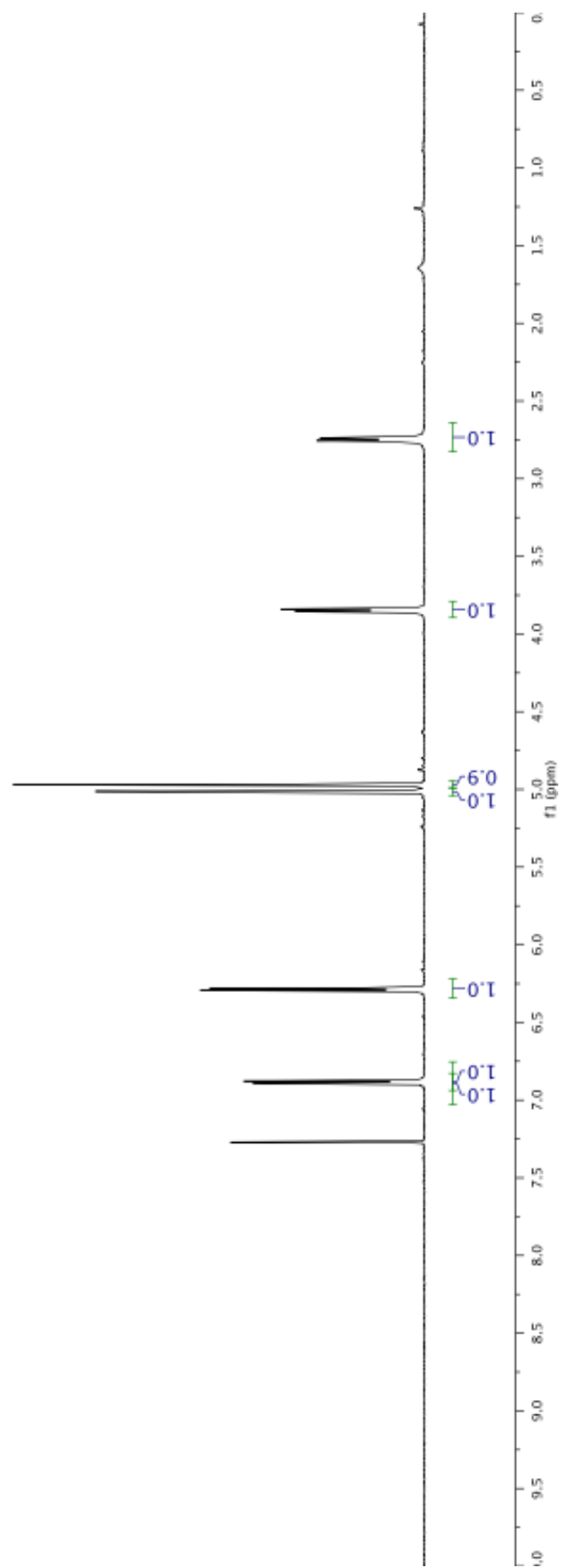
Compound 174
 ^1H , 500 MHz, CDCl_3

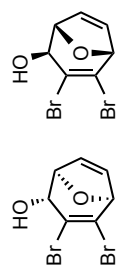




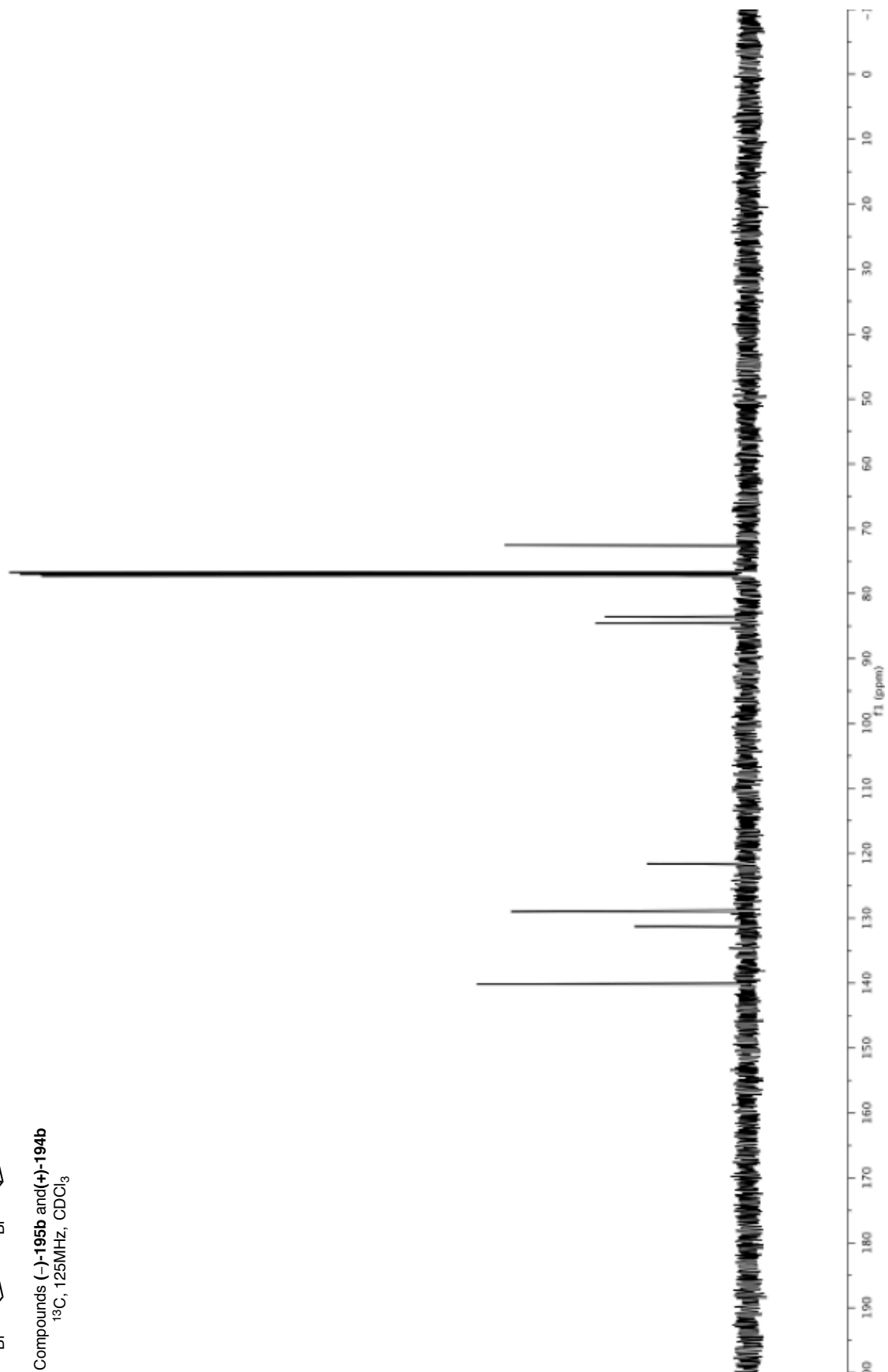


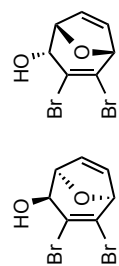
Compounds **(-)-195b** and **(+)-194b**
 ^1H , 500MHz, CDCl_3



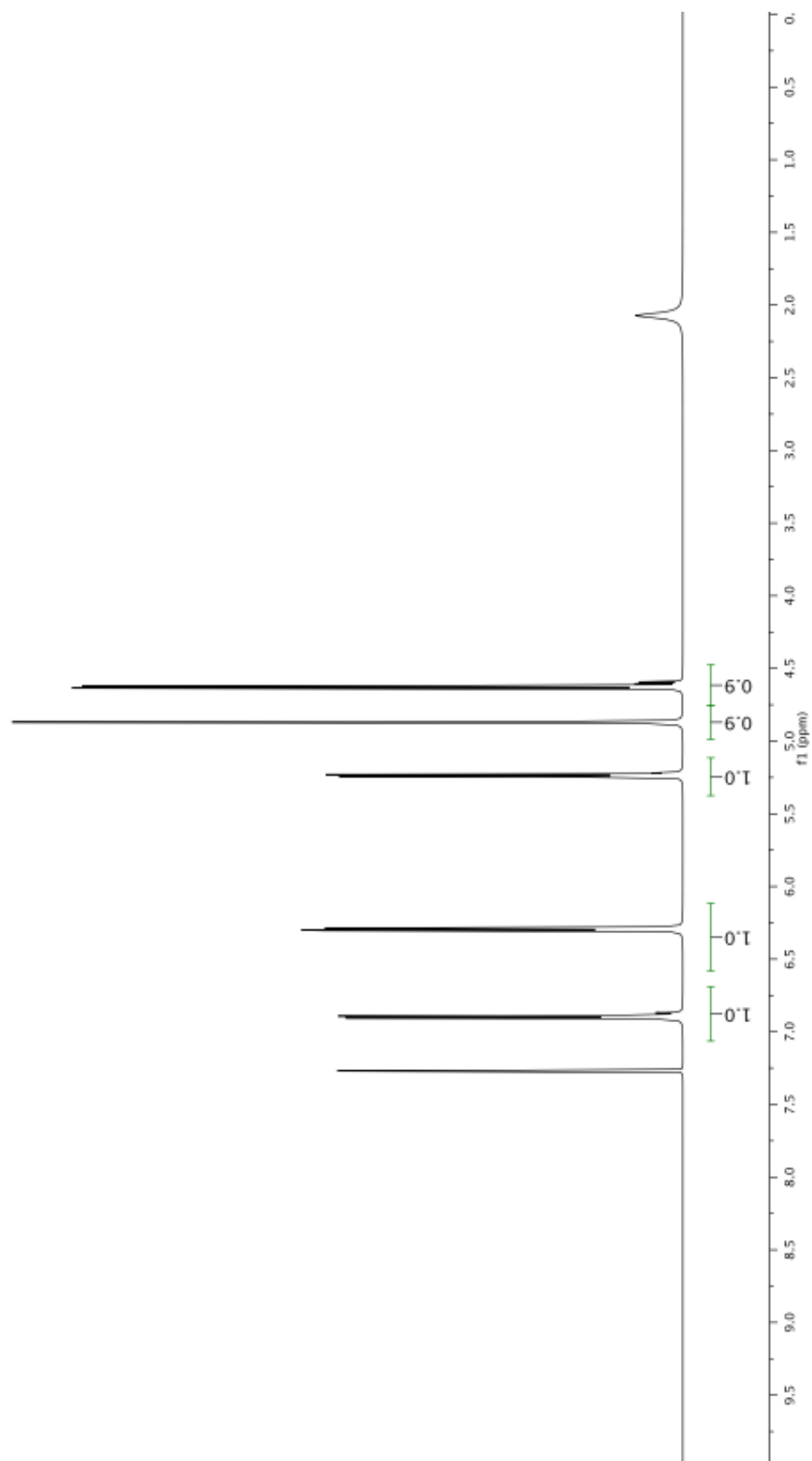


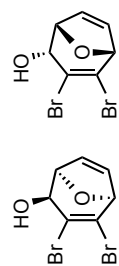
Compounds **(-)-195b** and **(+)-194b**
 ^{13}C , 125MHz, CDCl_3



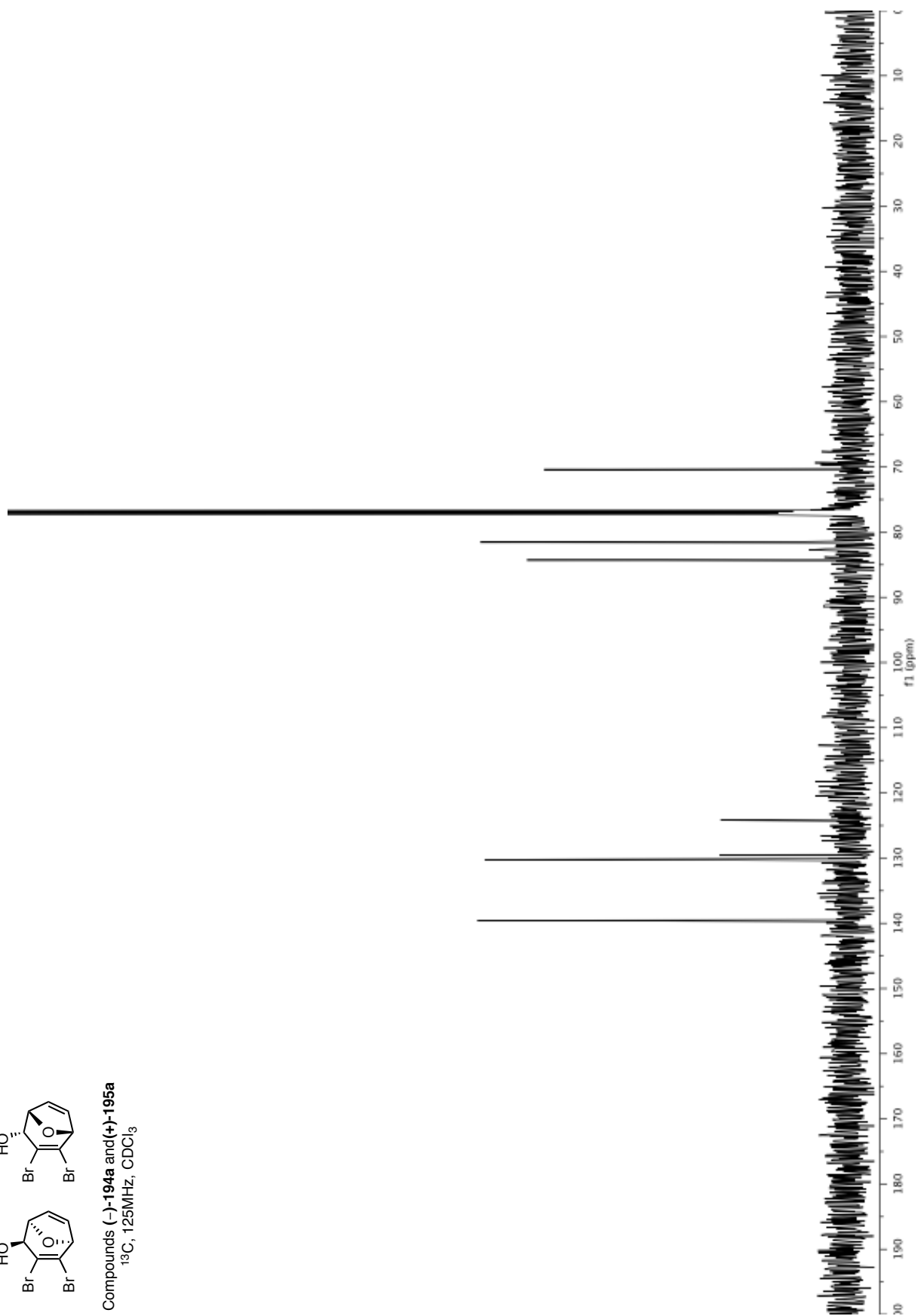


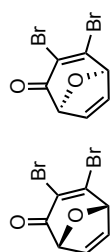
Compounds **(-)-194a** and **(+)-195a**
 ^1H , 500MHz, CDCl_3



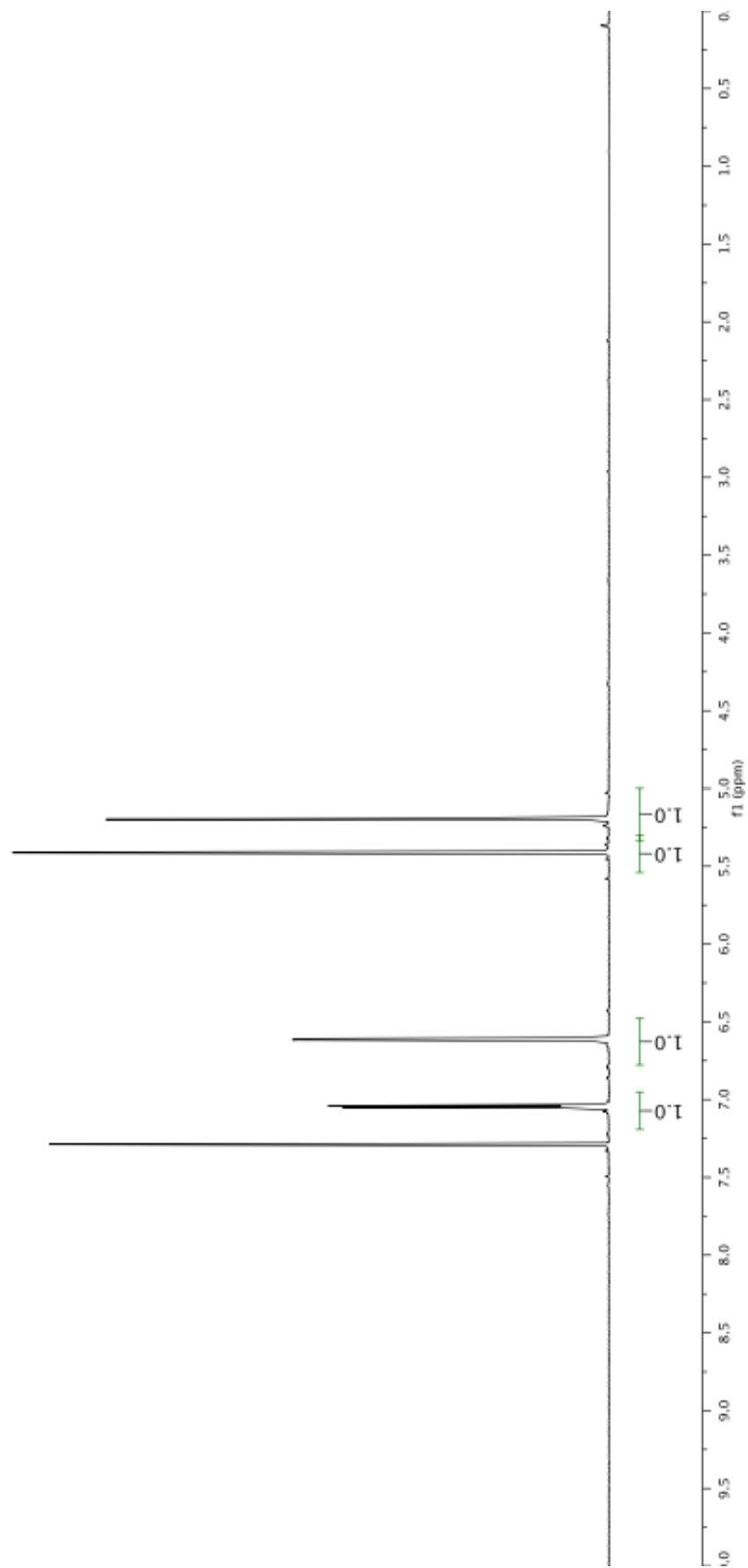


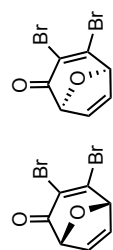
Compounds **(-)-194a** and **(+)-195a**
 ^{13}C , 125MHz, CDCl_3



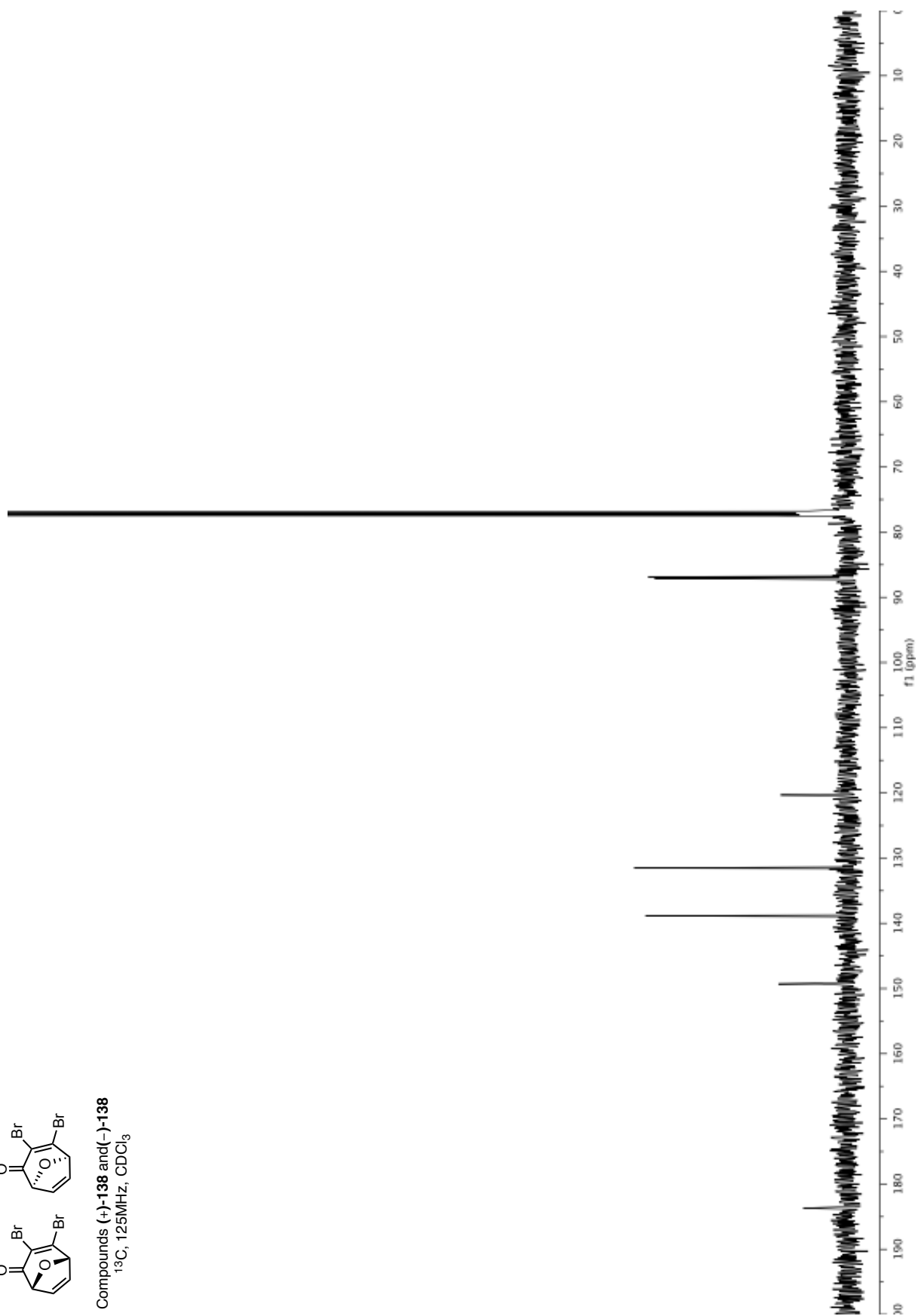


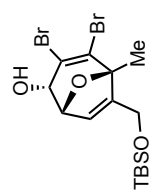
Compounds (+)-**138** and (-)-**138**
 ^1H , 500MHz, CDCl_3



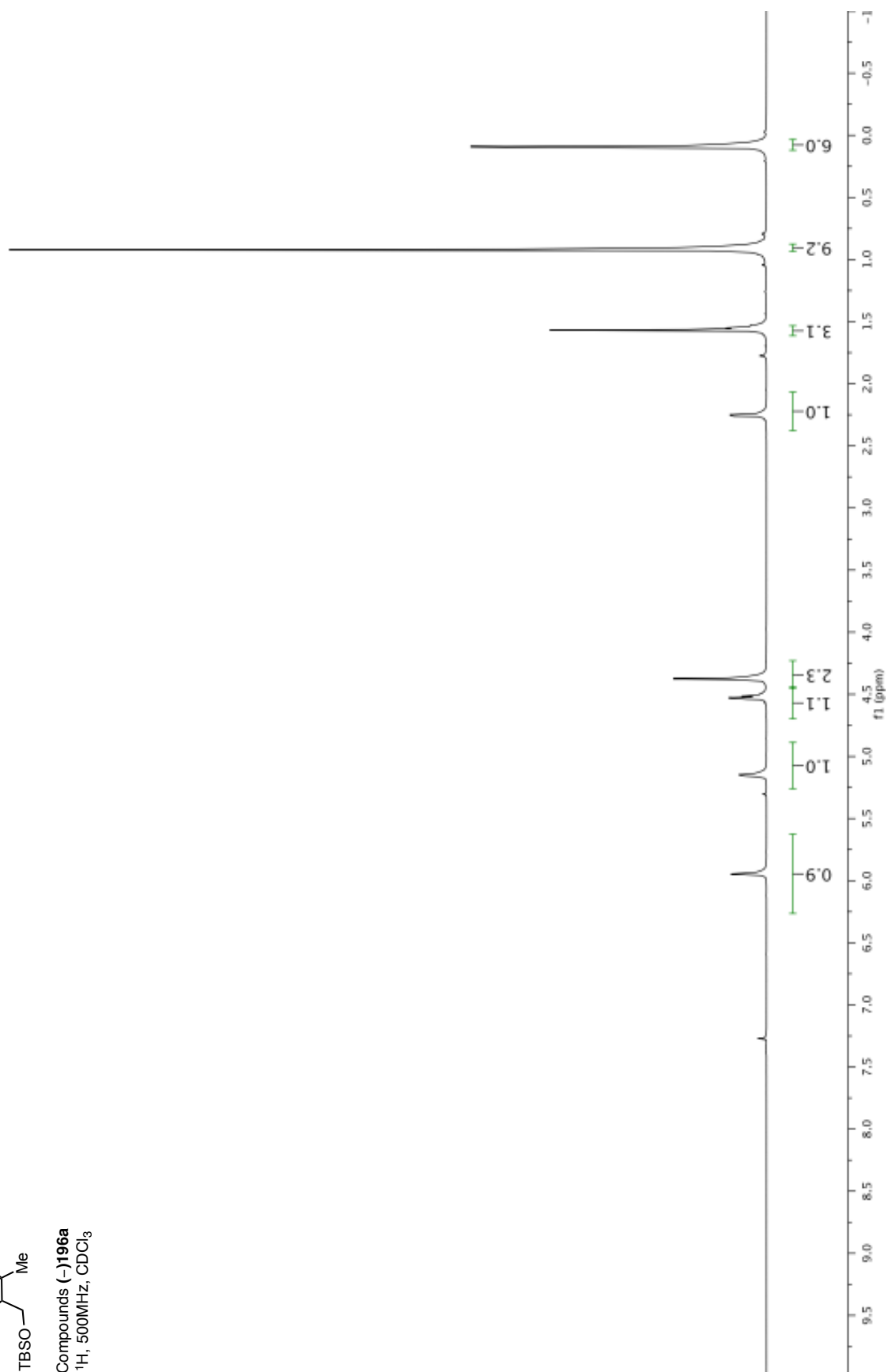


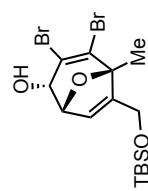
Compounds (+)-**138** and (-)-**138**
 ^{13}C , 125MHz, CDCl_3



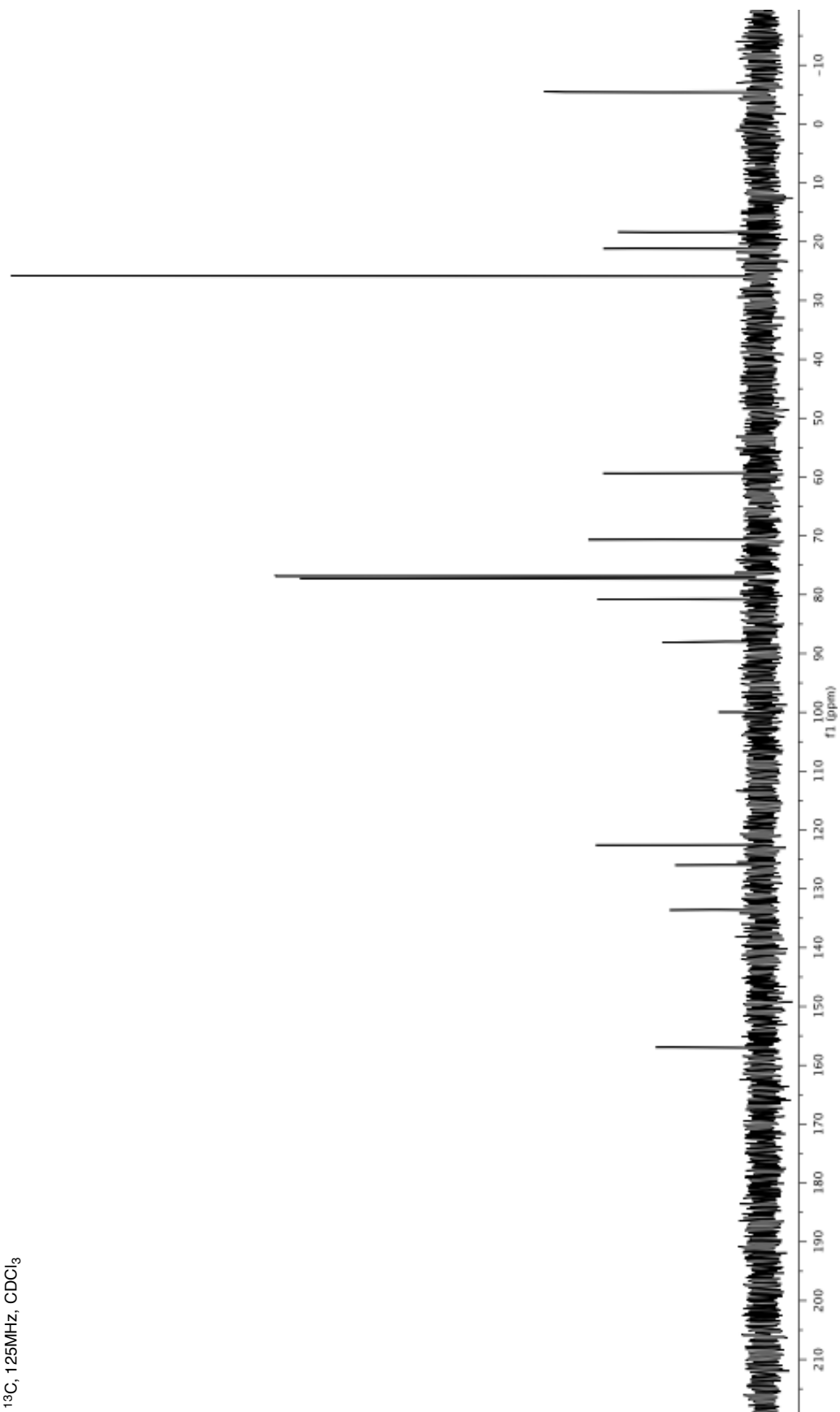


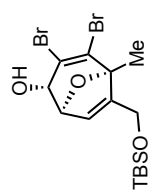
Compounds (-)-**196a**
¹H, 500MHz, CDCl₃



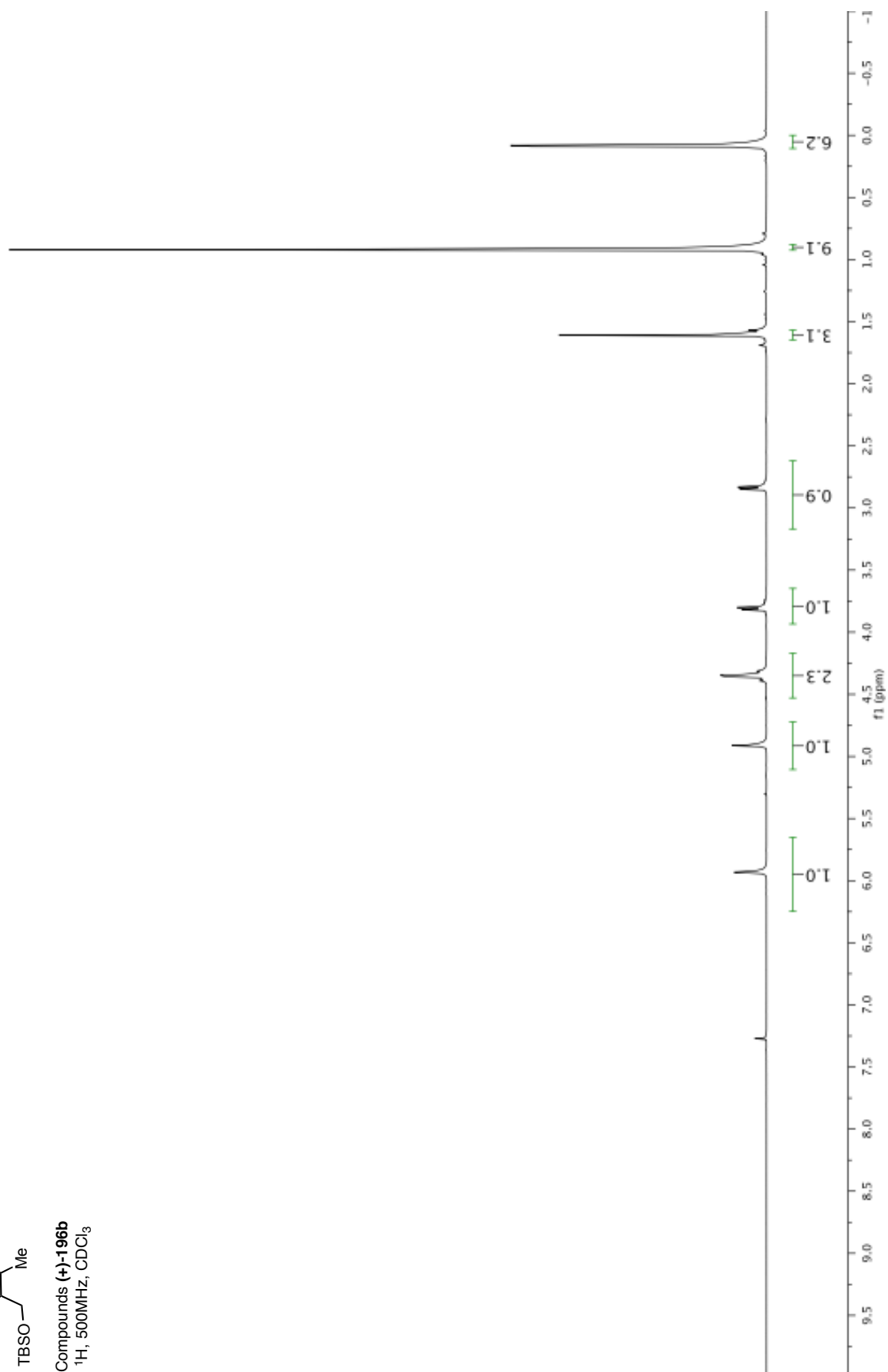


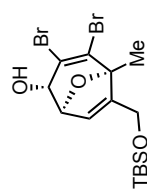
Compounds **(-)-196a**
 ^{13}C , 125MHz, CDCl_3



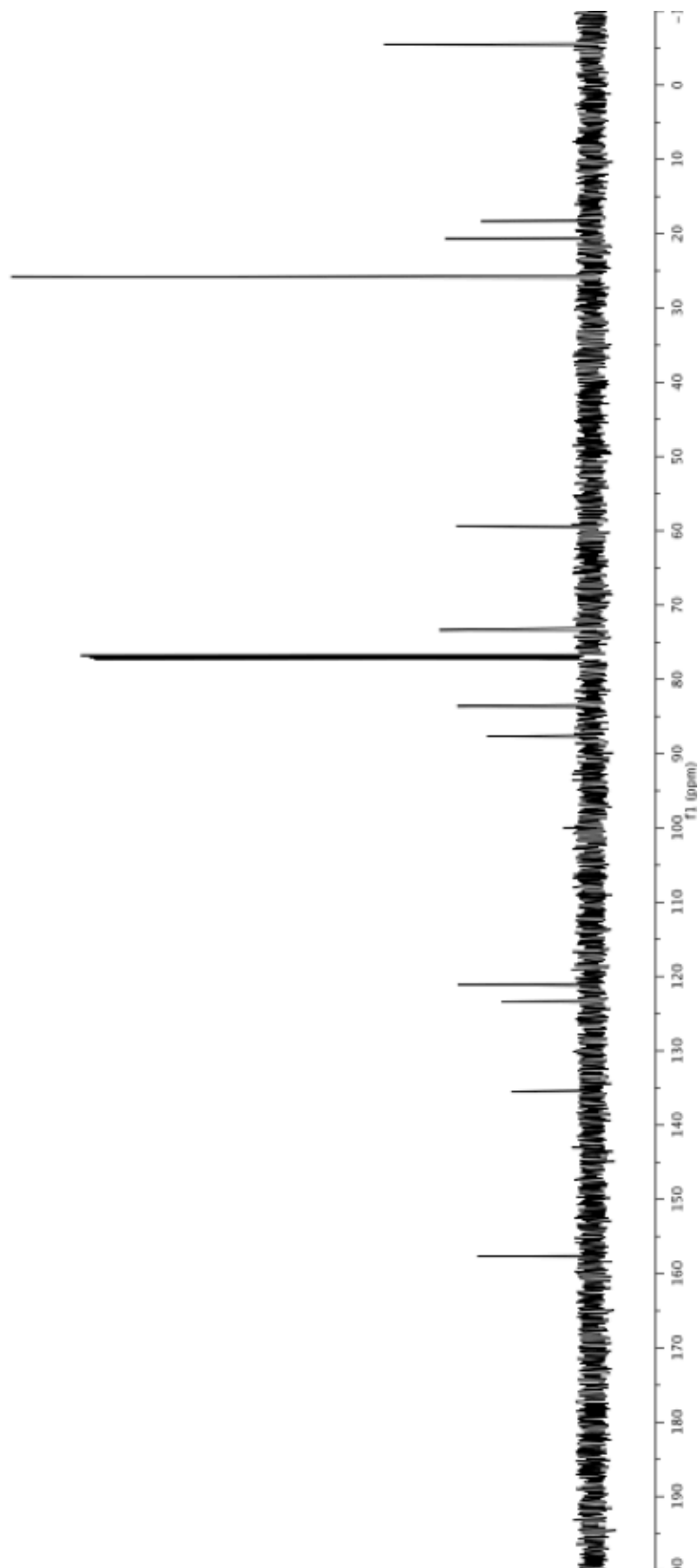


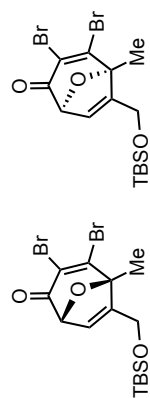
Compounds (+)-196b
¹H, 500MHz, CDCl₃



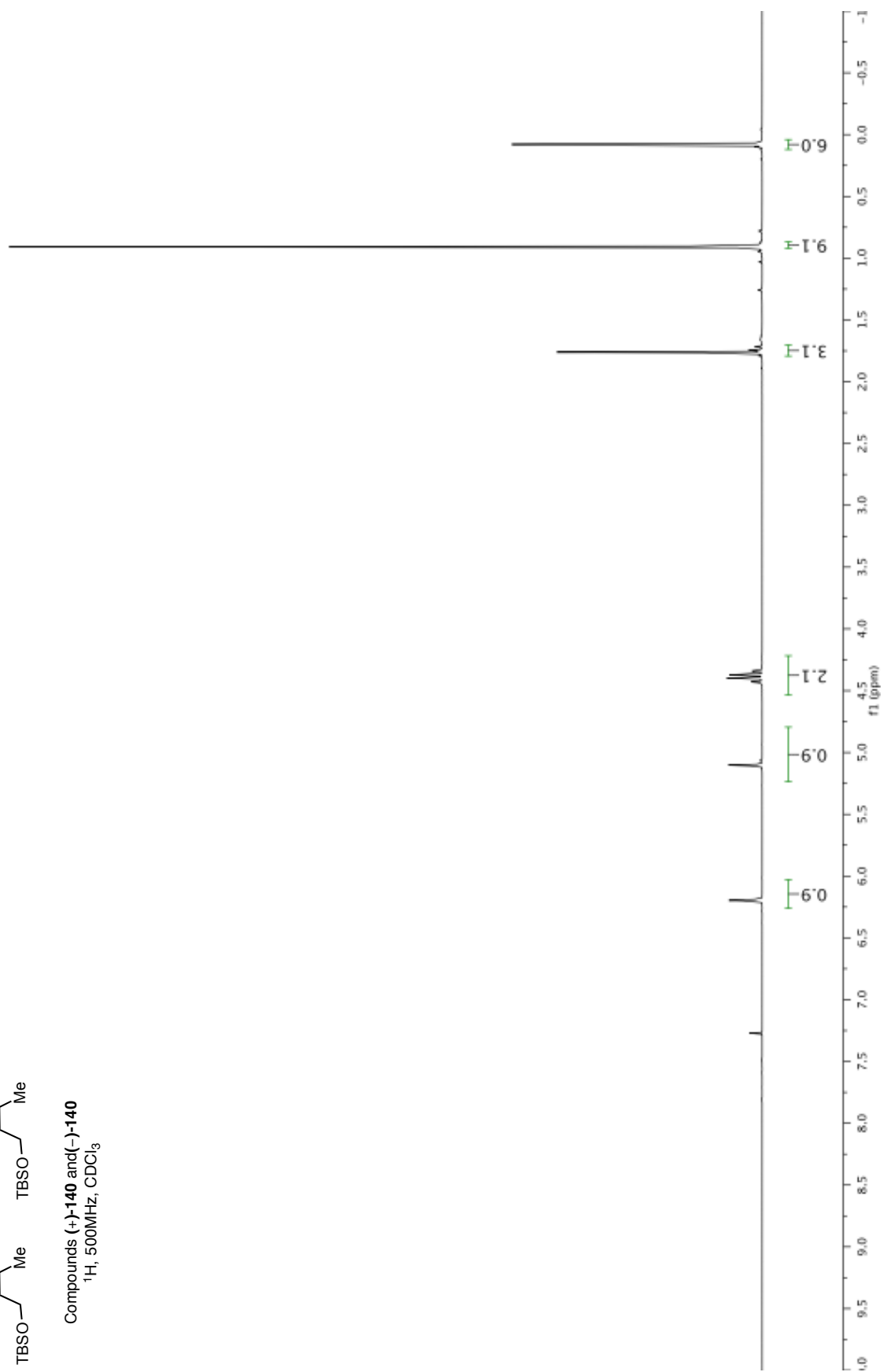


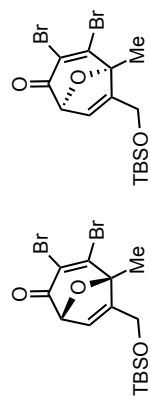
Compounds **(+)-196b**
 ^{13}C , 125MHz, CDCl_3



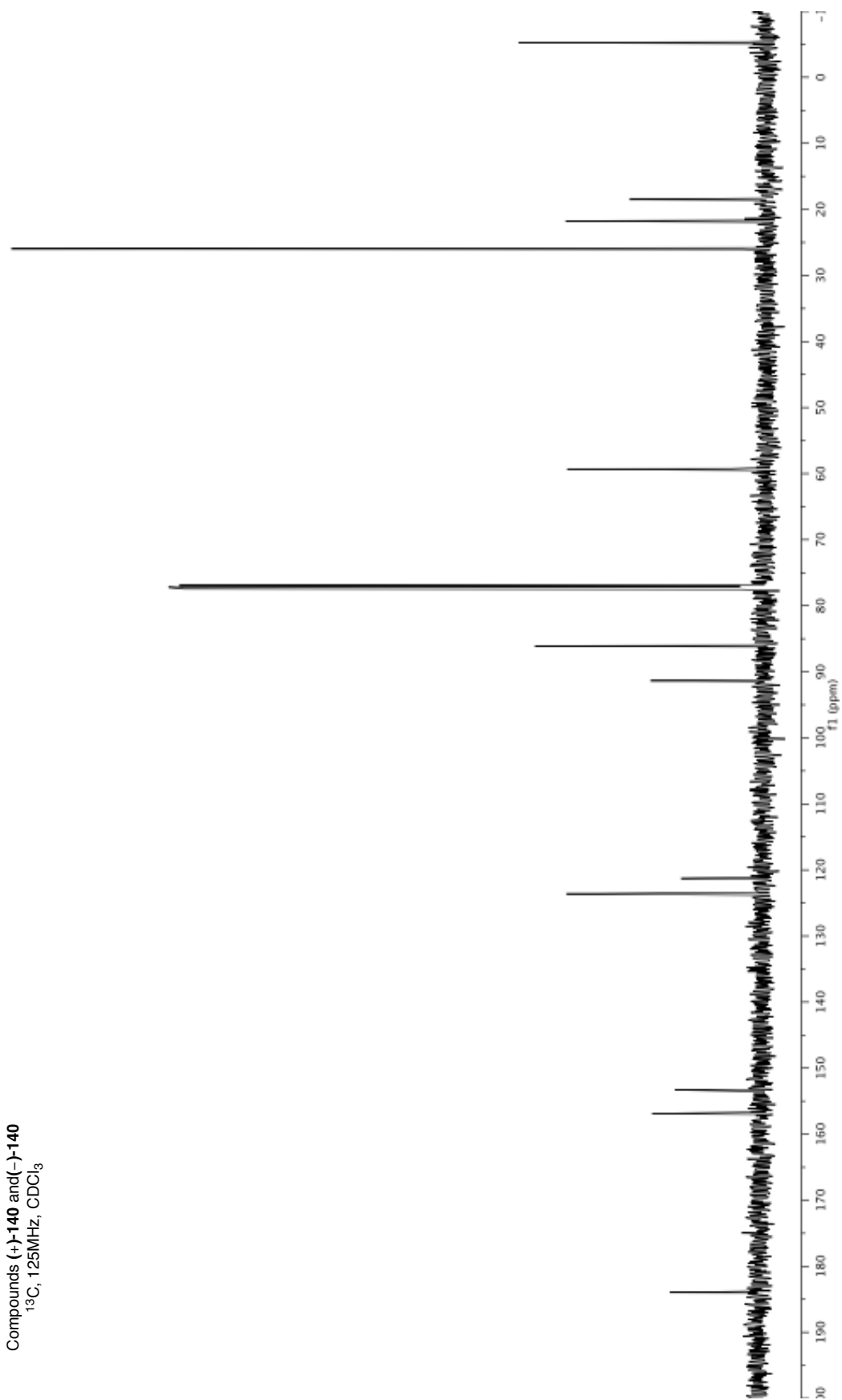


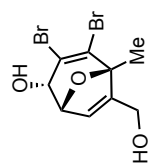
Compounds (+)-140 and (-)-140
 ^1H , 500MHz, CDCl_3



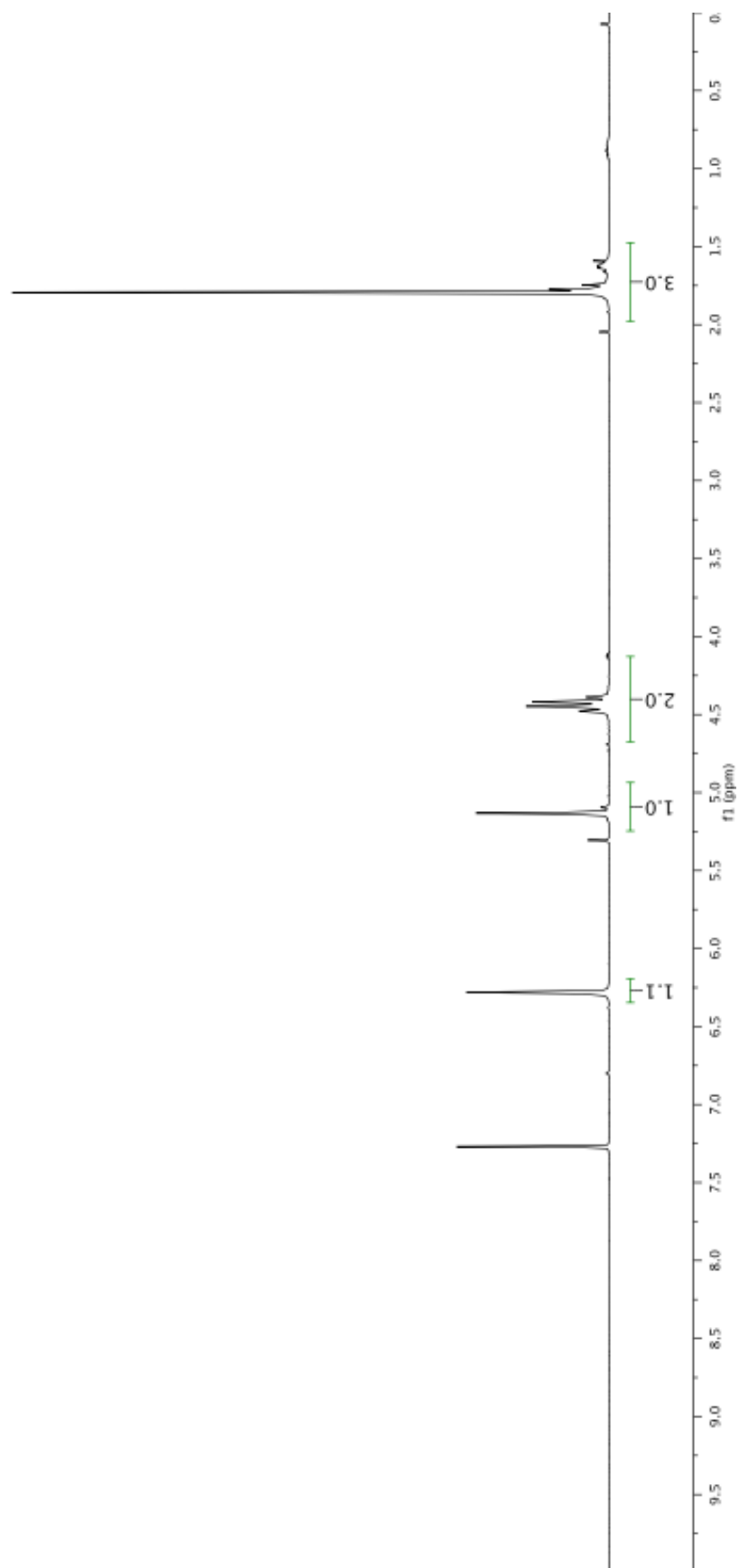


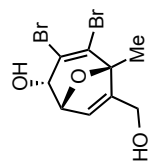
Compounds (+)-140 and (-)-140
¹³C, 125MHz, CDCl₃



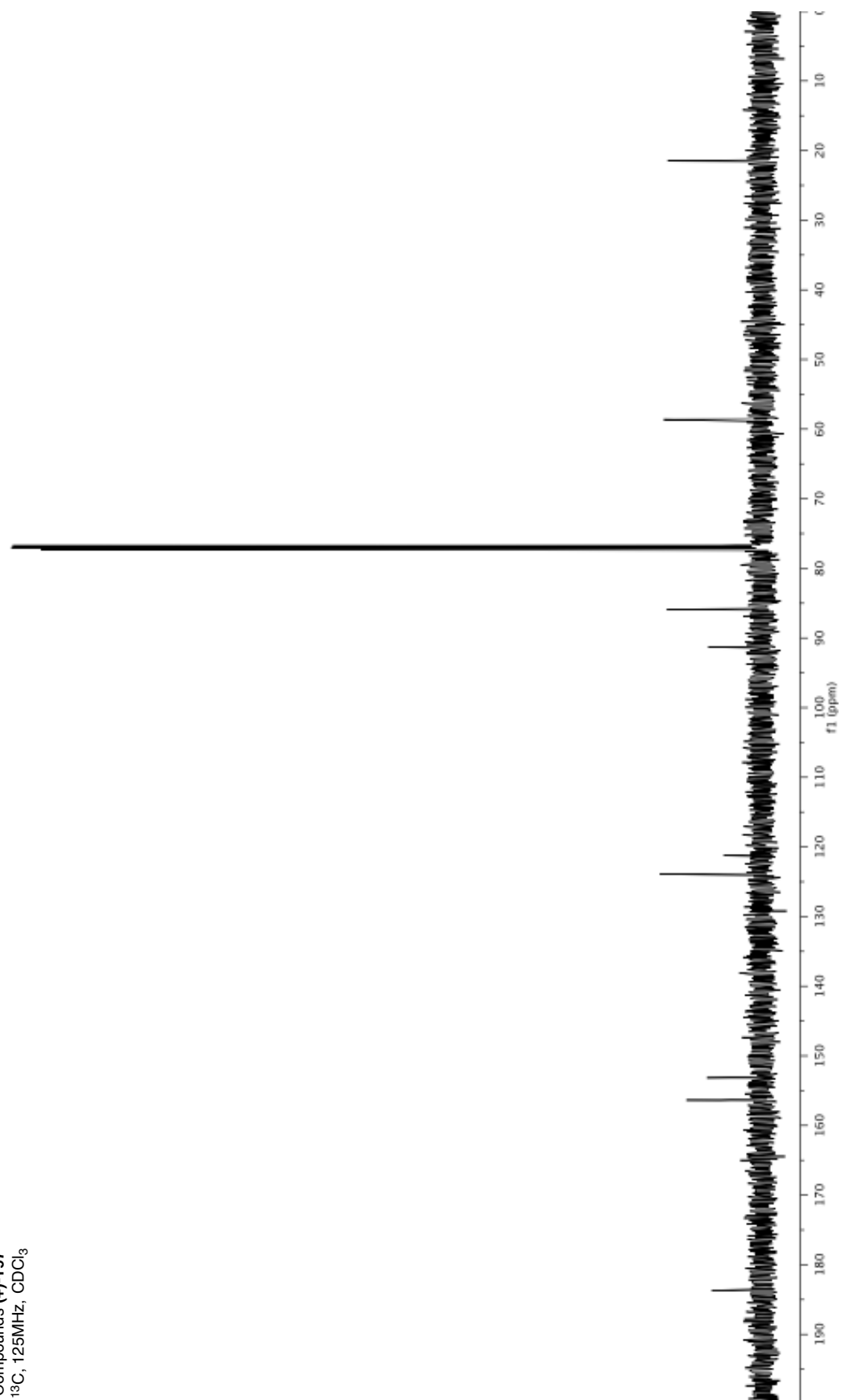


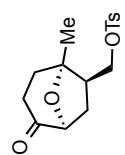
Compounds (+)-197
 ^1H , 500MHz, CDCl_3



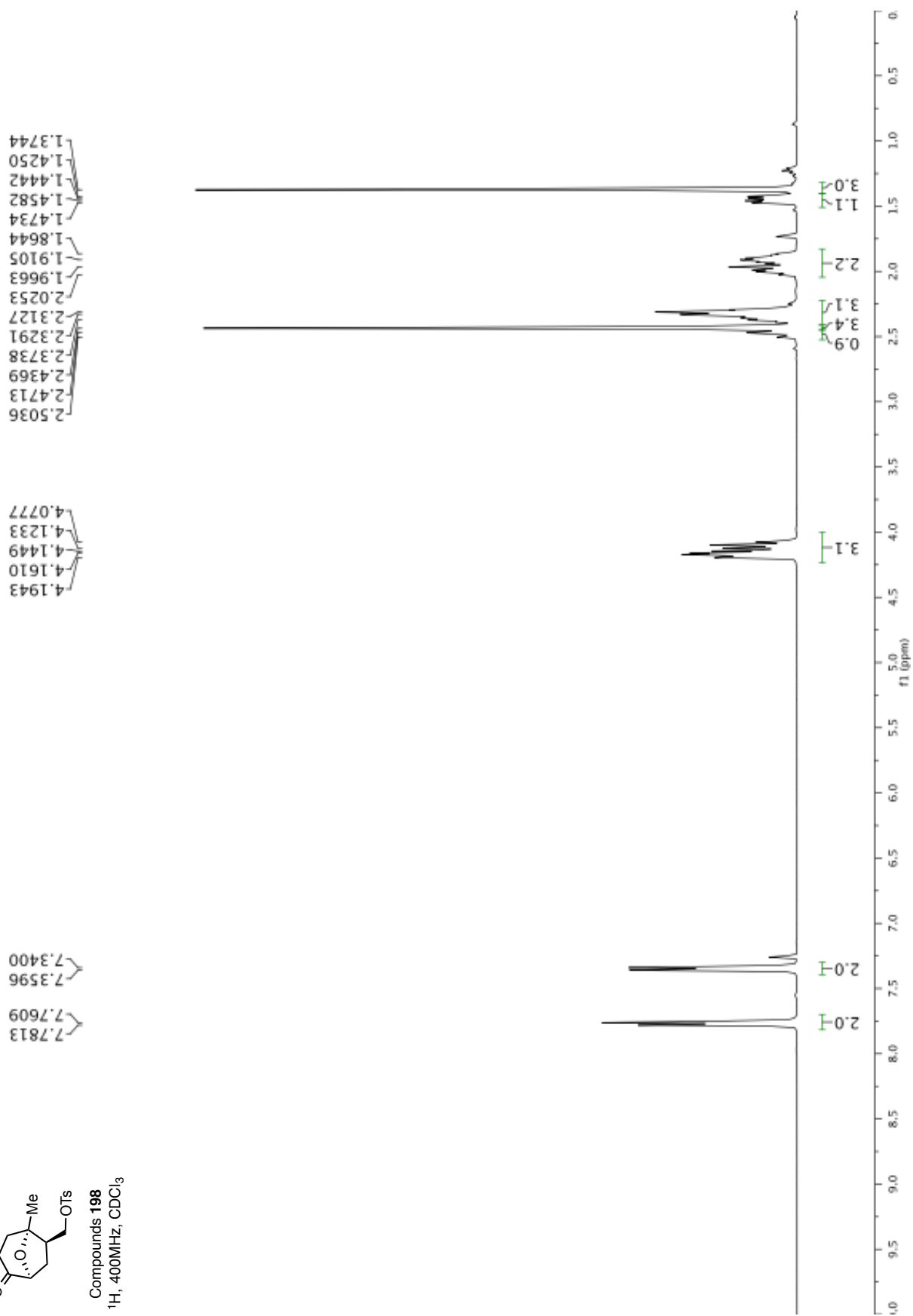


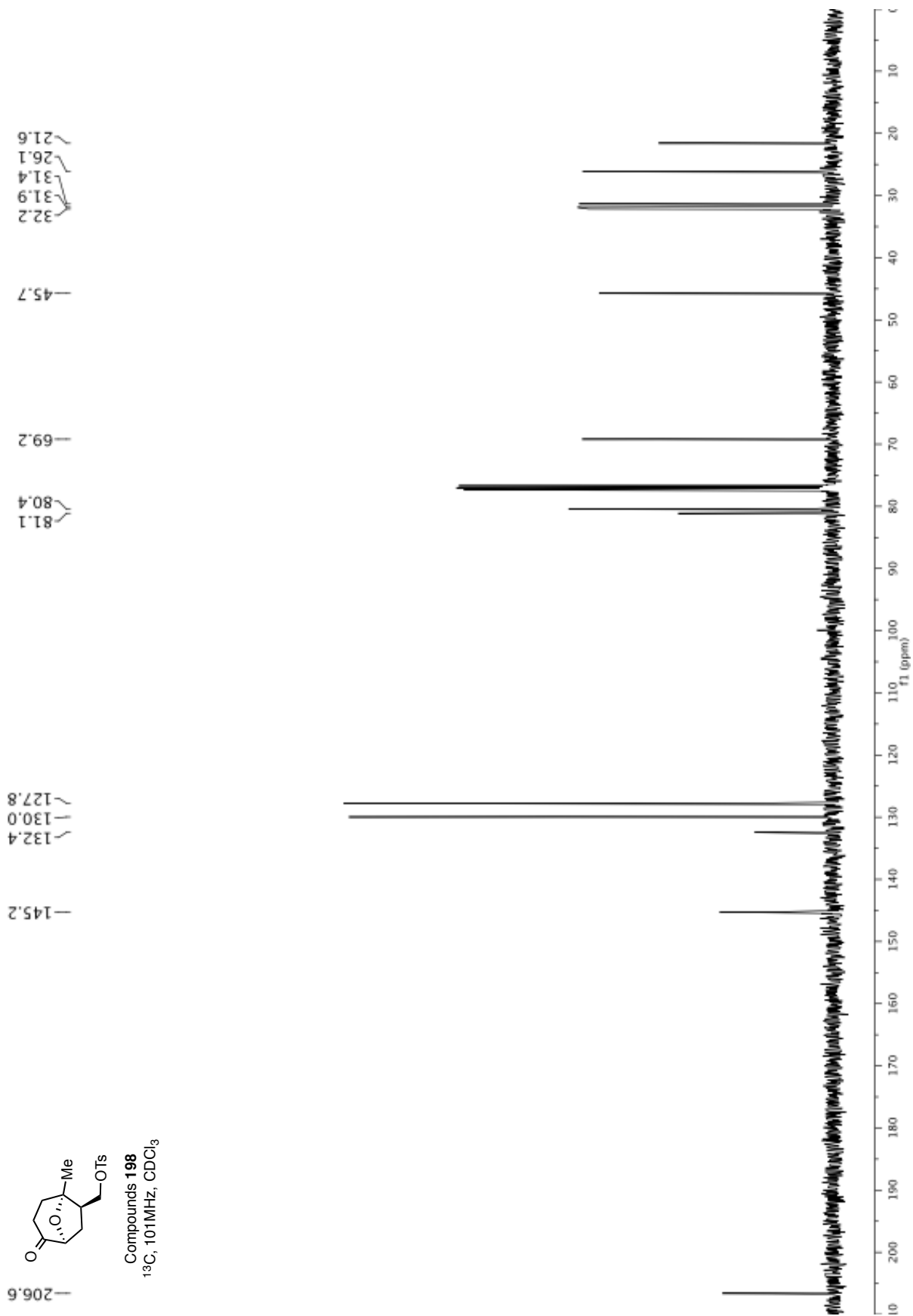
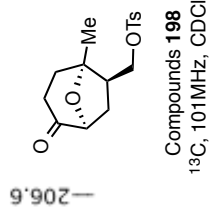
Compounds **(+)-197**
 ^{13}C , 125MHz, CDCl_3



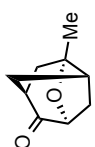


Compounds **198**
¹H, 400MHz, CDCl₃

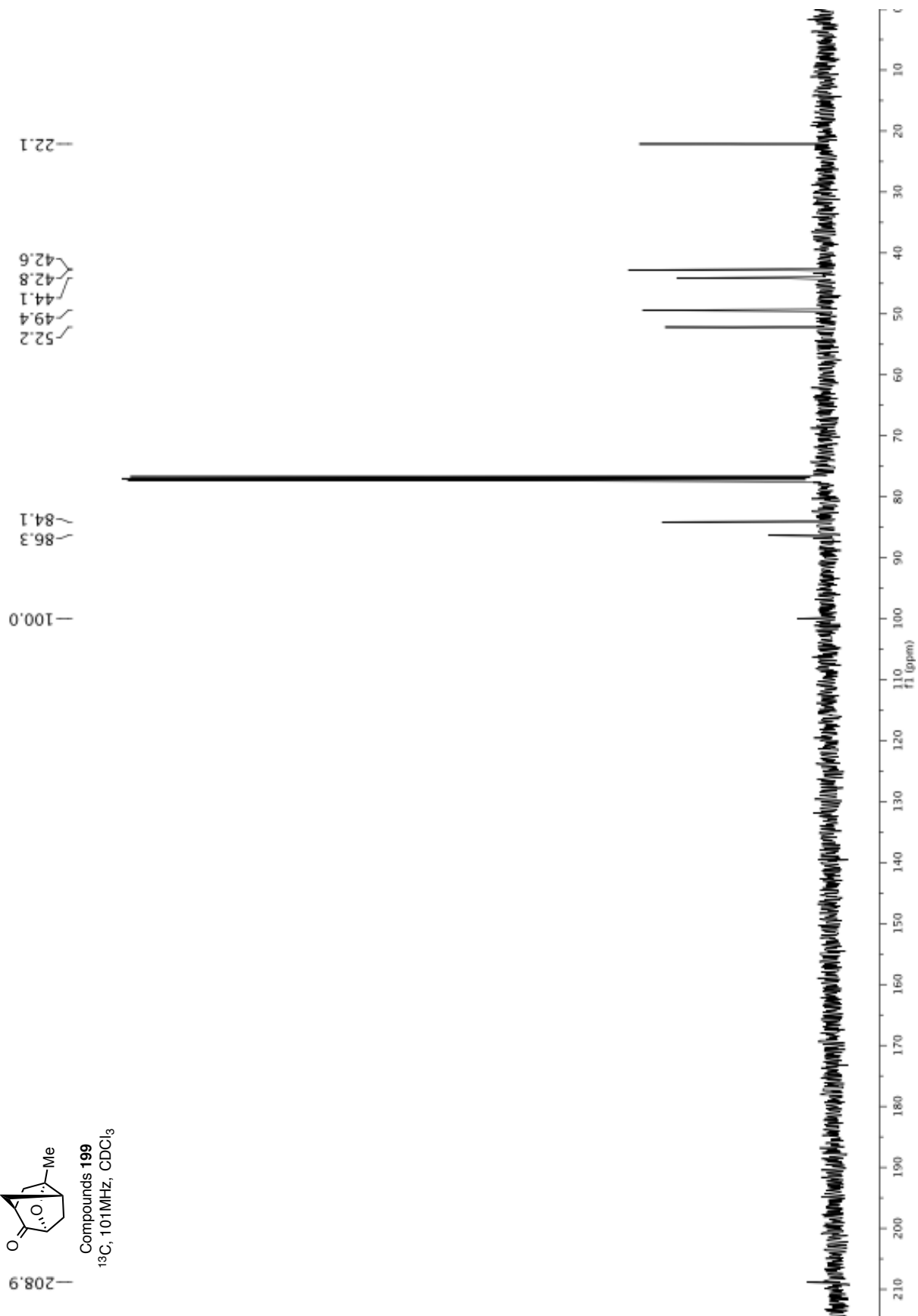


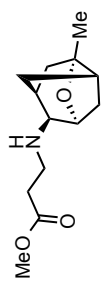




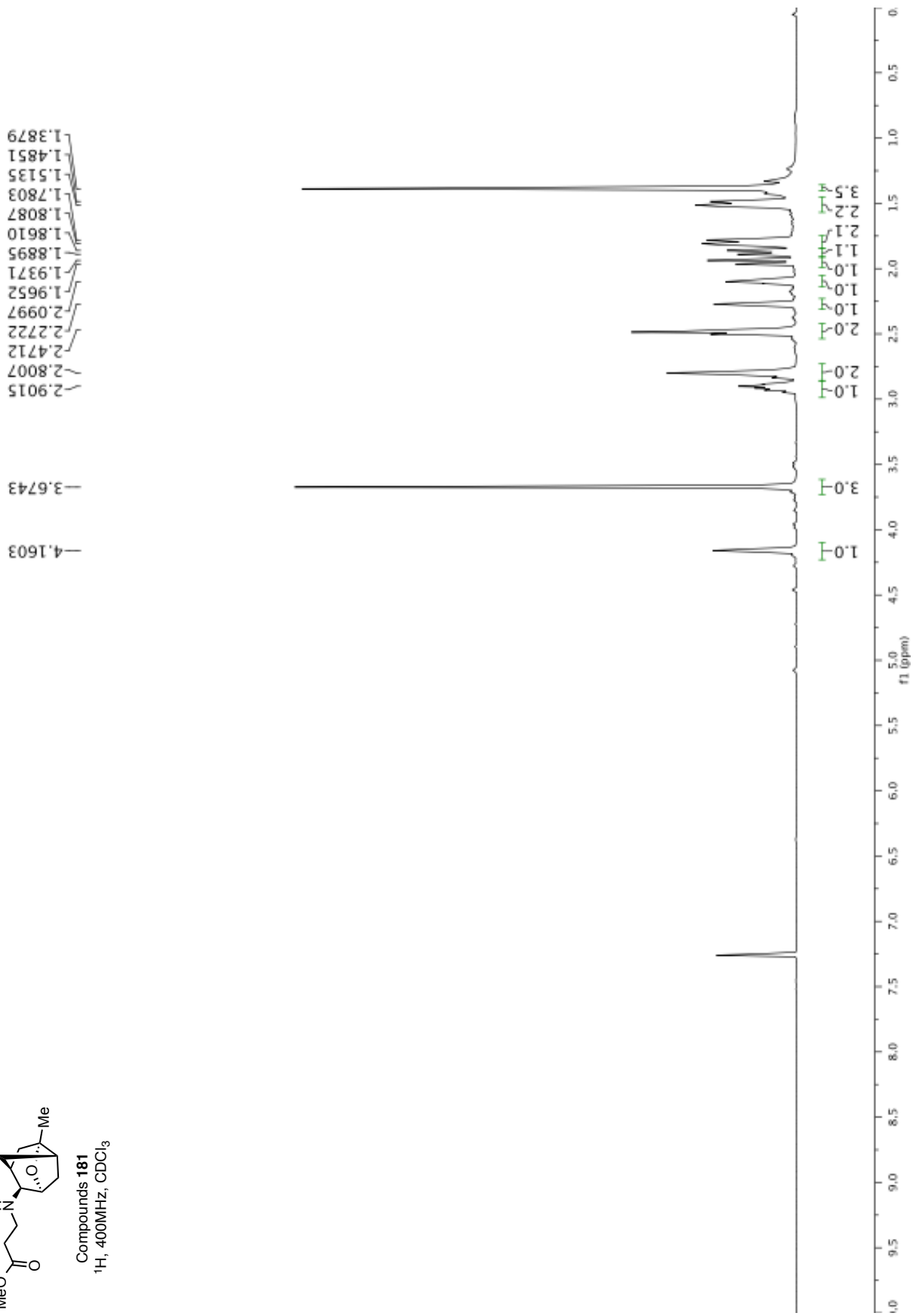


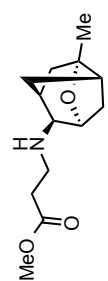
Compounds **199**
 ^{13}C , 101MHz, CDCl_3



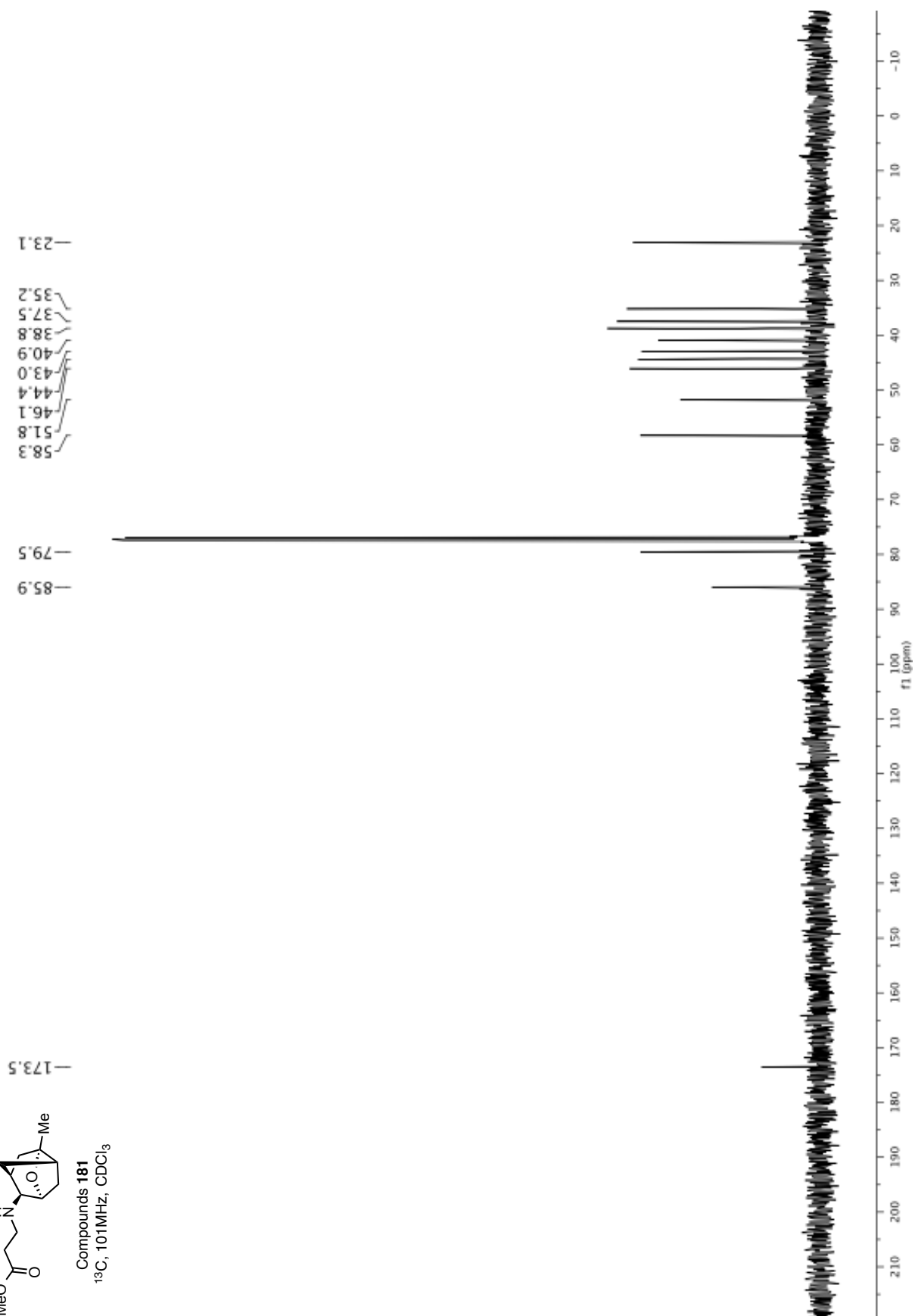


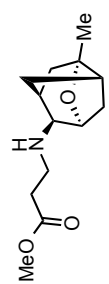
Compounds **181**
 ^1H , 400MHz, CDCl_3



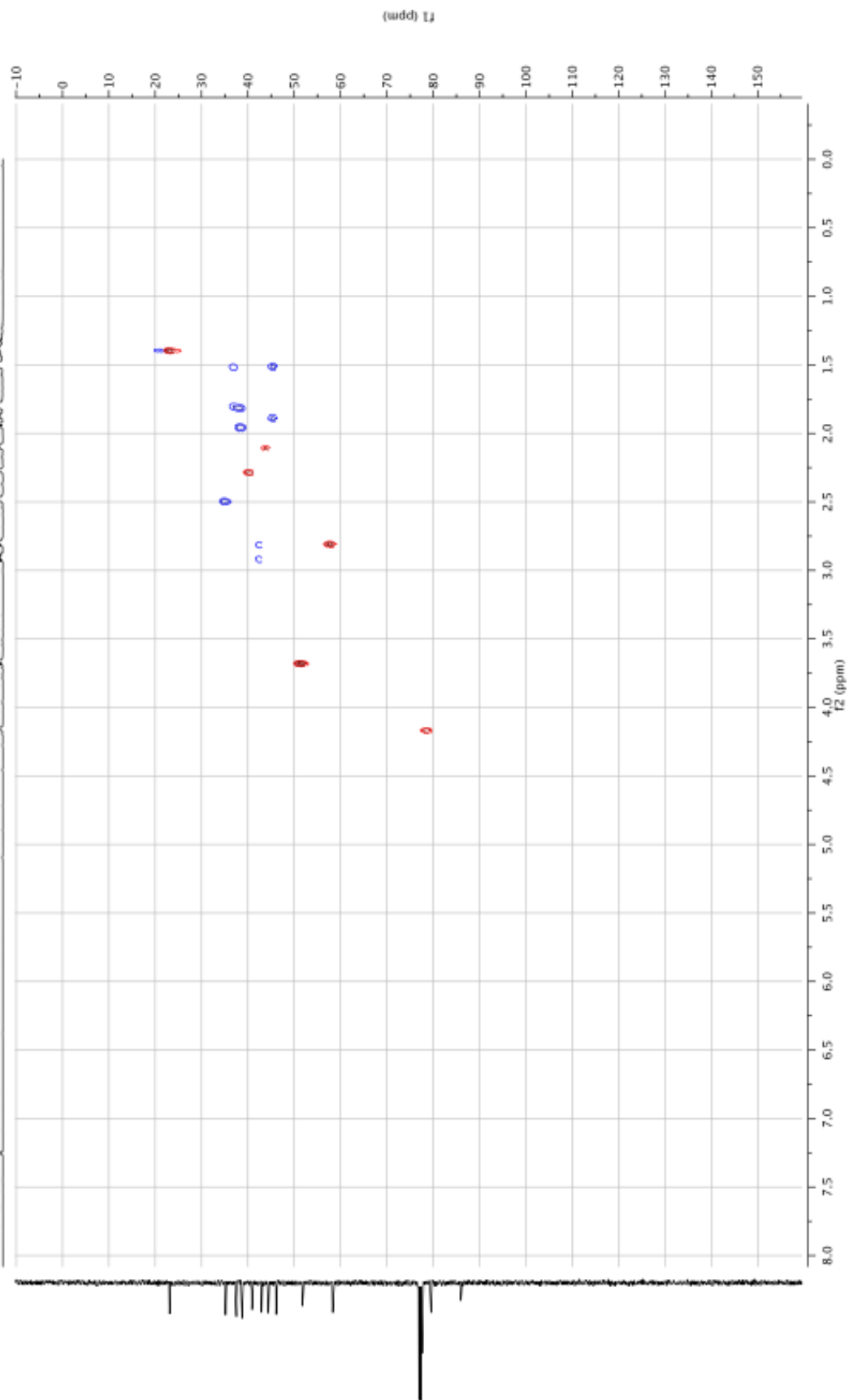


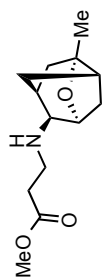
Compounds **181**
 ^{13}C , 101MHz, CDCl_3



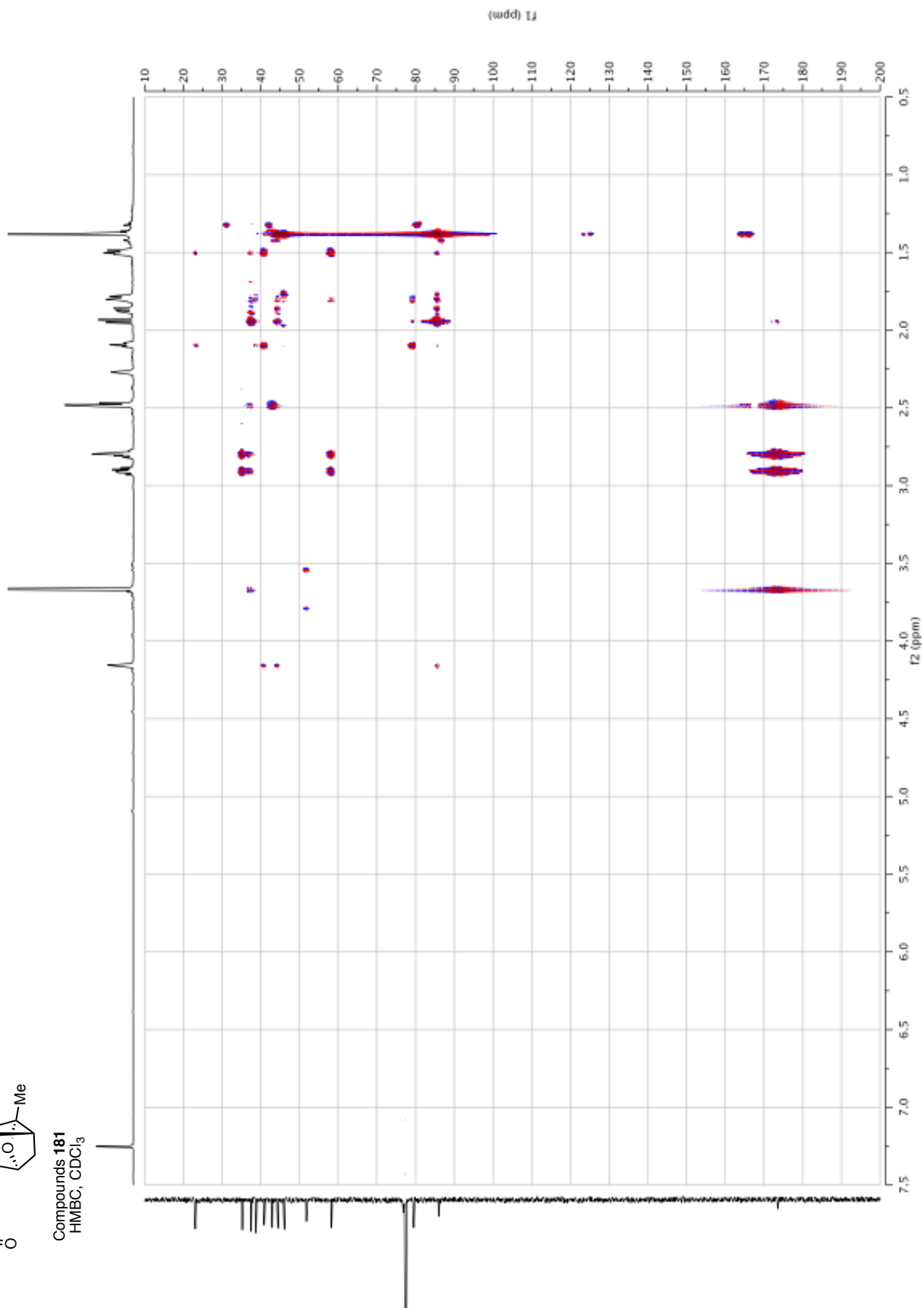


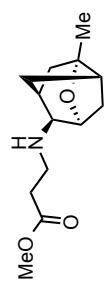
Compounds **181**
HSQC, CDCl₃



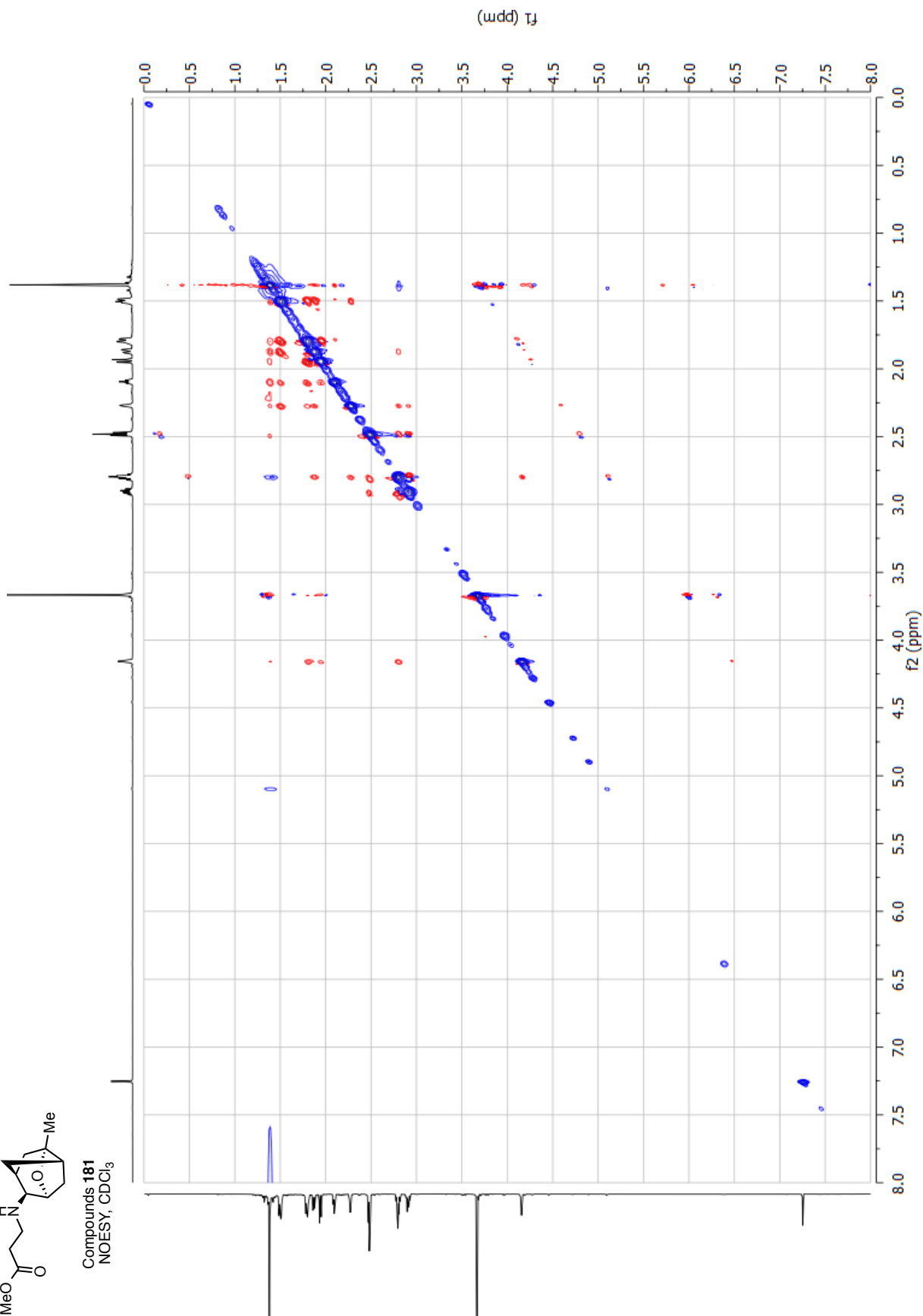


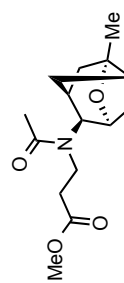
Compound **181**
HMBC, CDCl₃





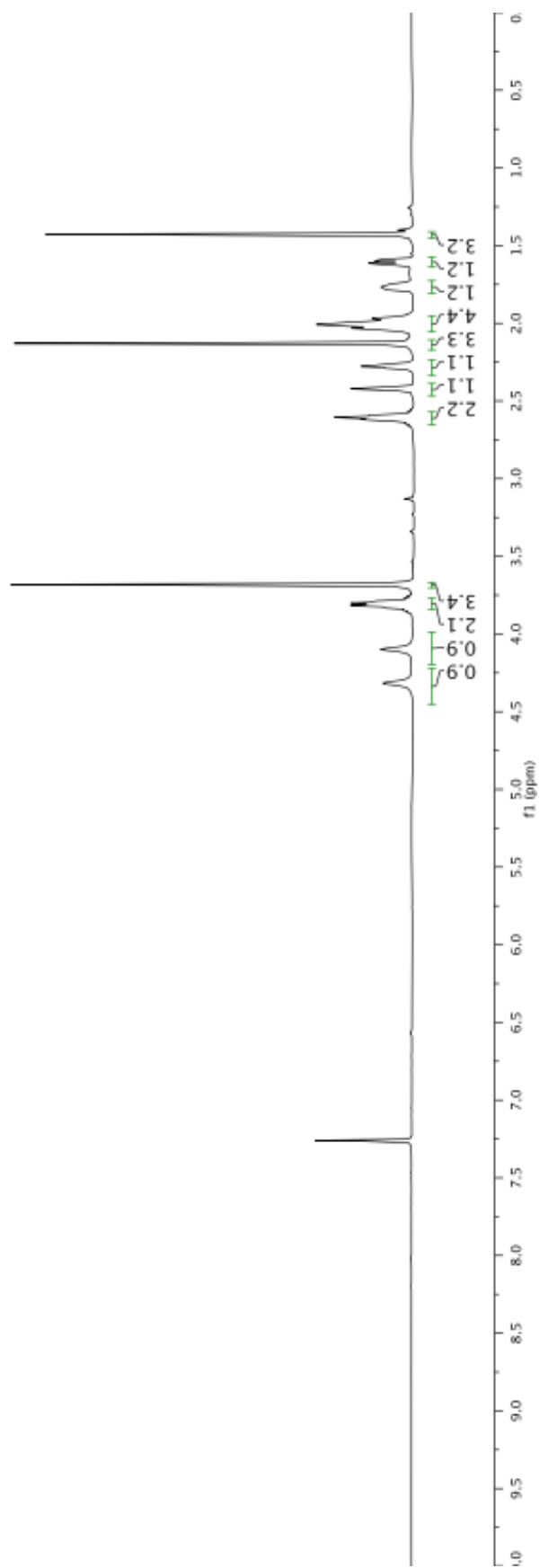
Compounds **181**
NOESY, CDCl₃

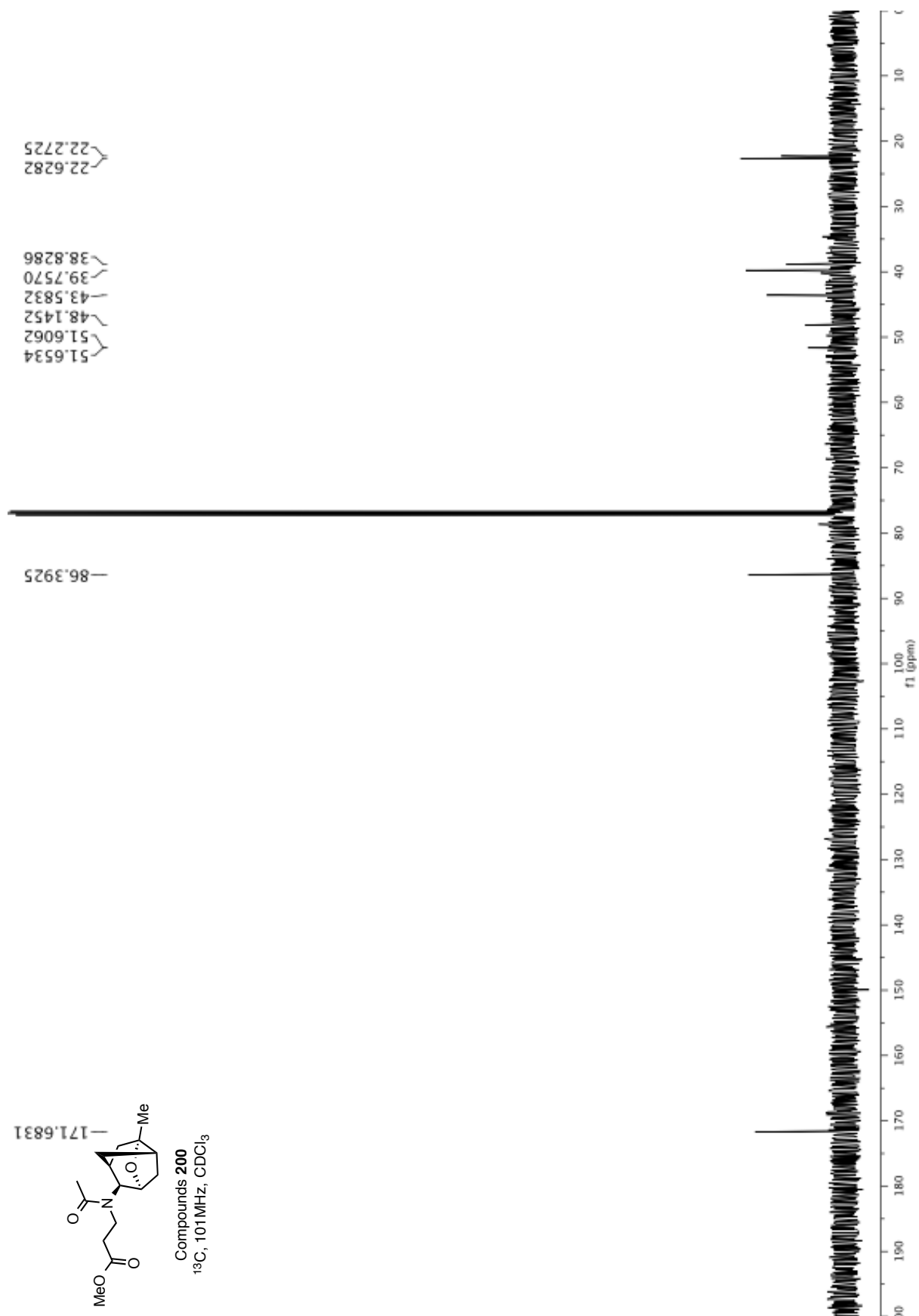


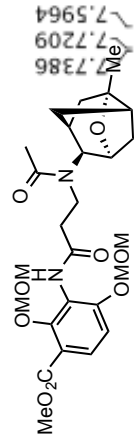


Compounds **200**
¹H, 400MHz, CDCl₃

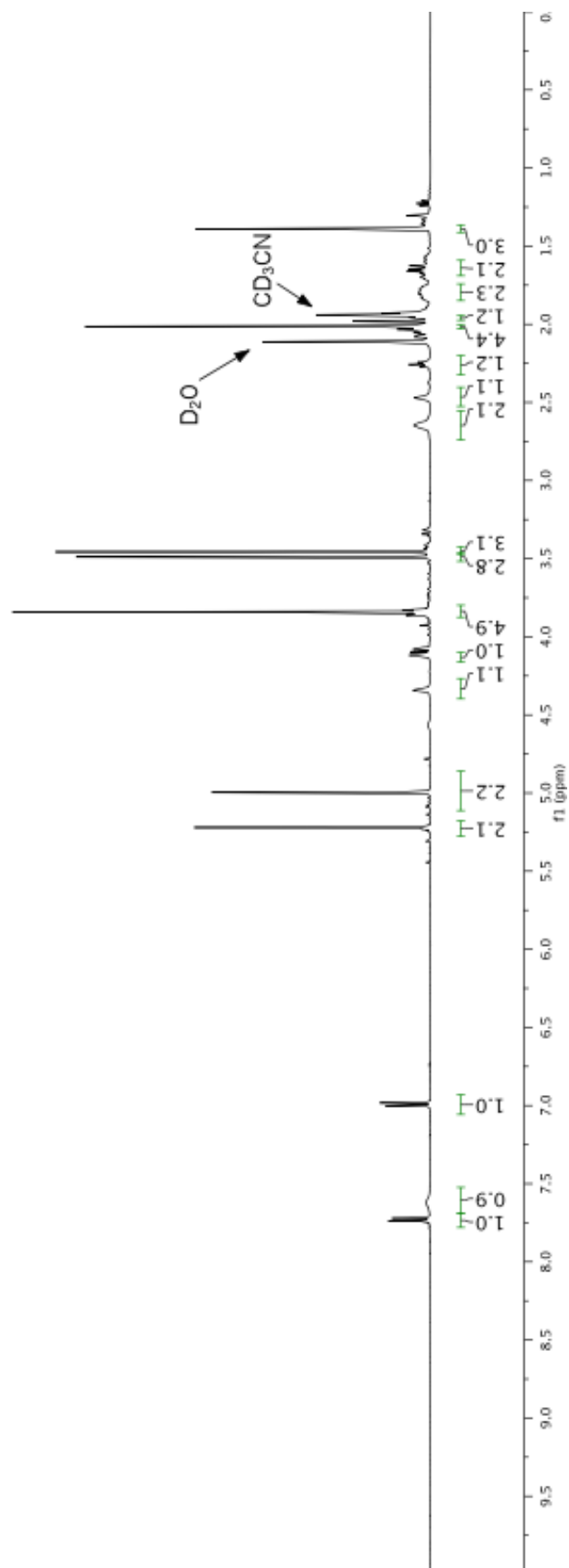
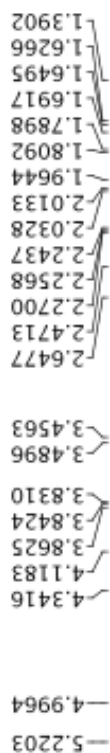
4.3166
 4.0981
 3.8295
 3.8172
 3.8003
 3.7872
 3.6816
 2.6240
 2.6061
 2.5887
 2.4207
 2.2776
 2.1302
 2.0313
 2.0086
 1.9702
 1.7656
 1.6210
 1.5909
 1.4271

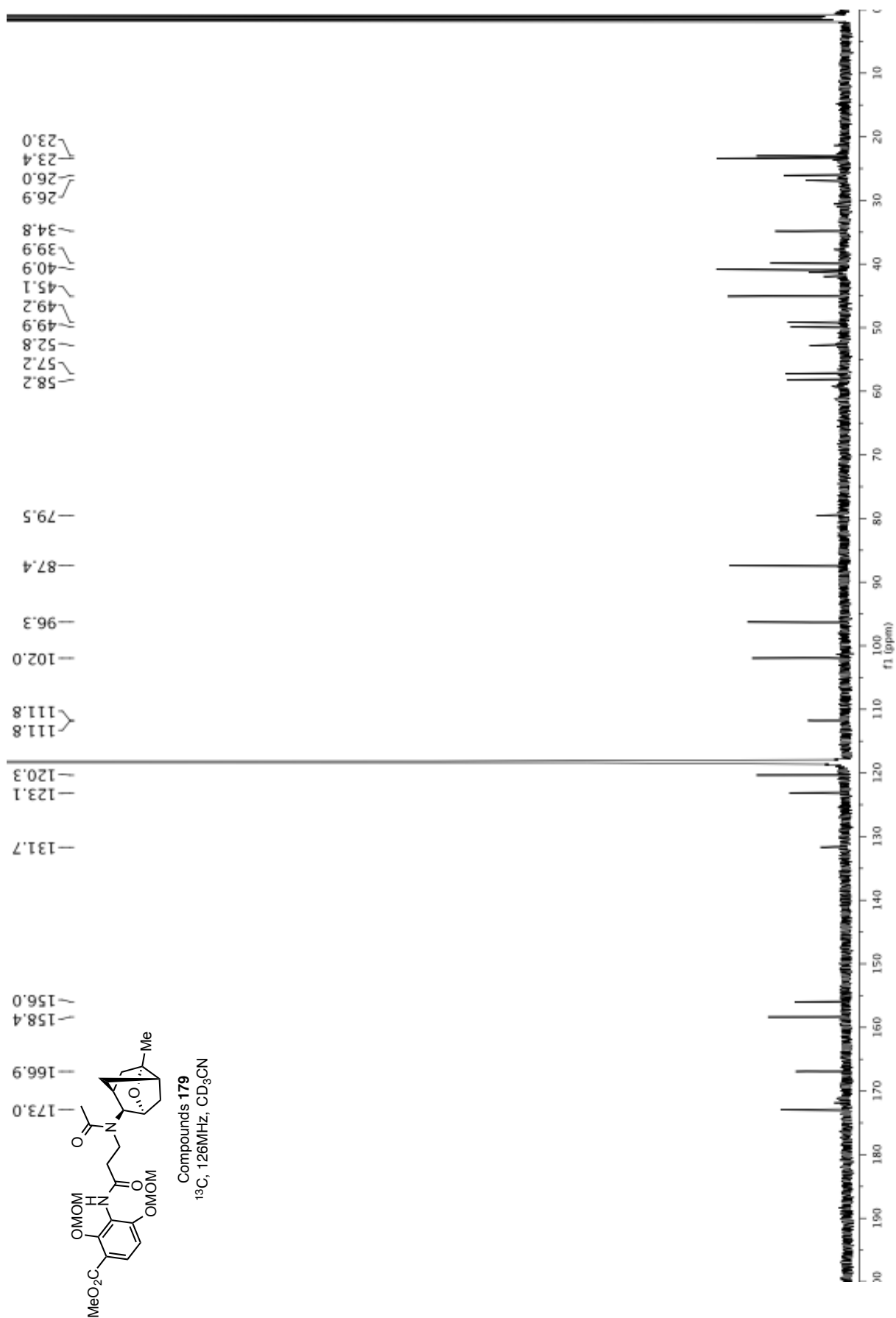


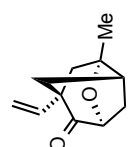




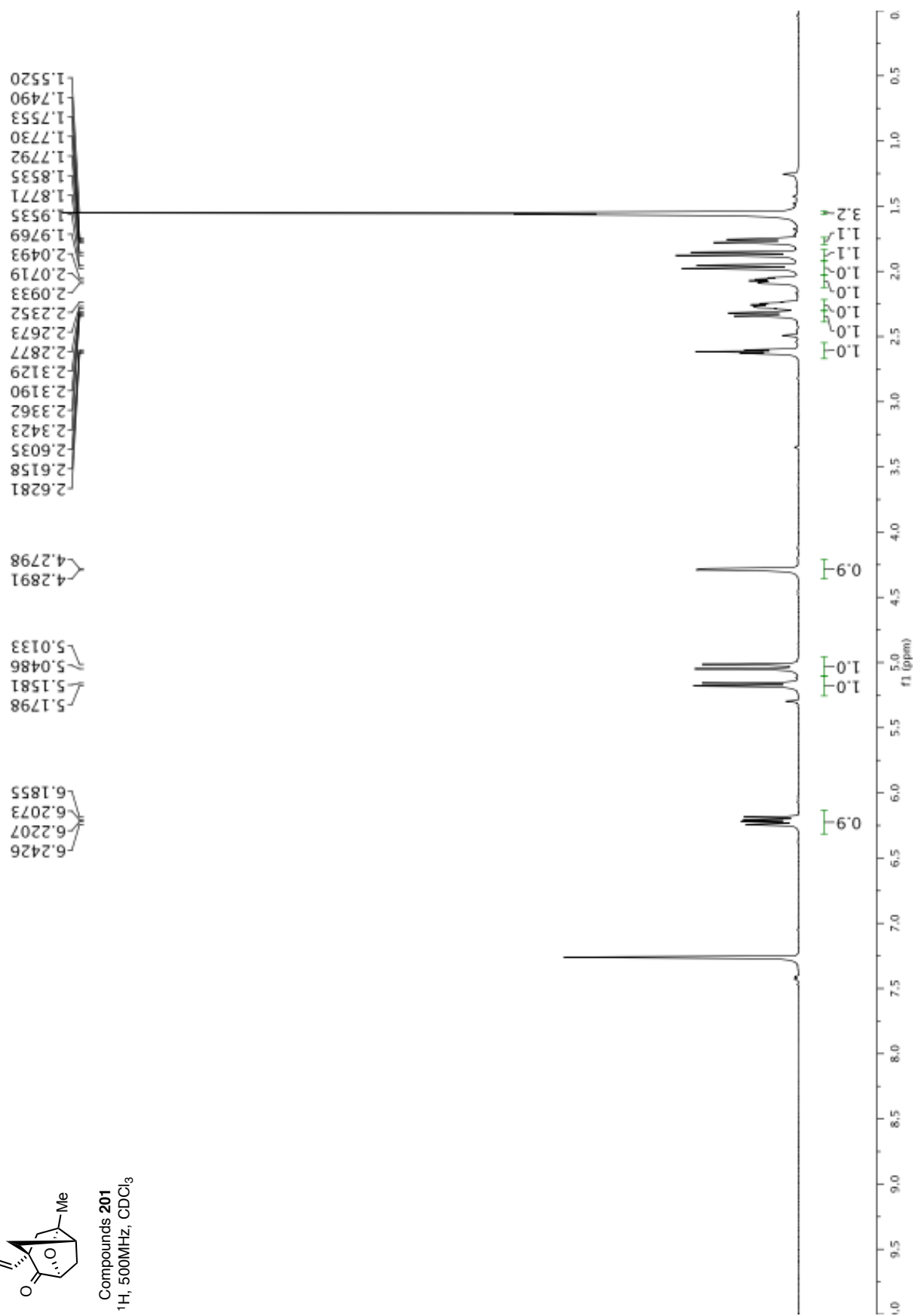
Compounds **179**
 ^1H , 500MHz, CD_3CN

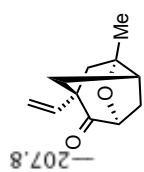




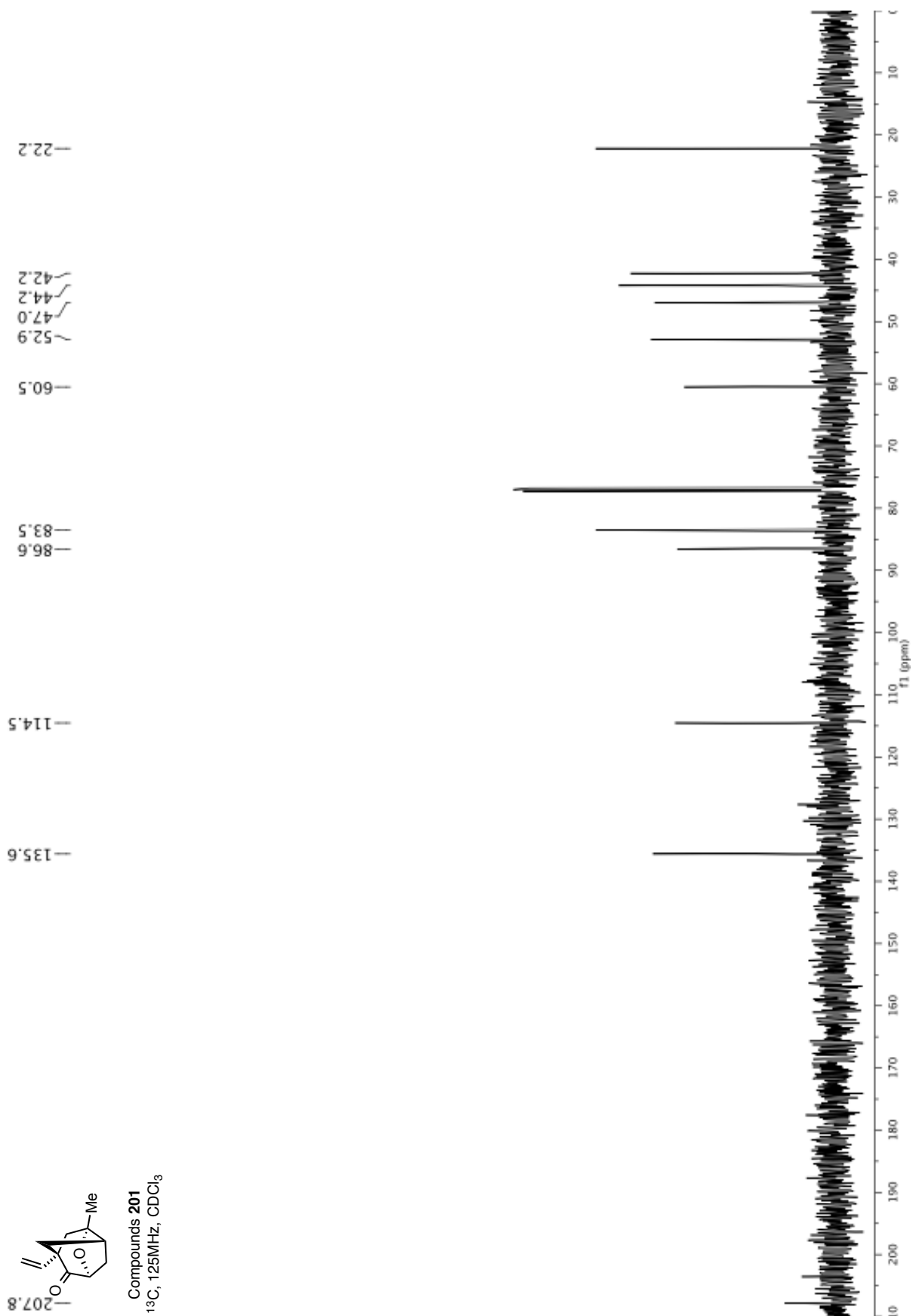


Compounds **201**
 ^1H , 500MHz, CDCl_3



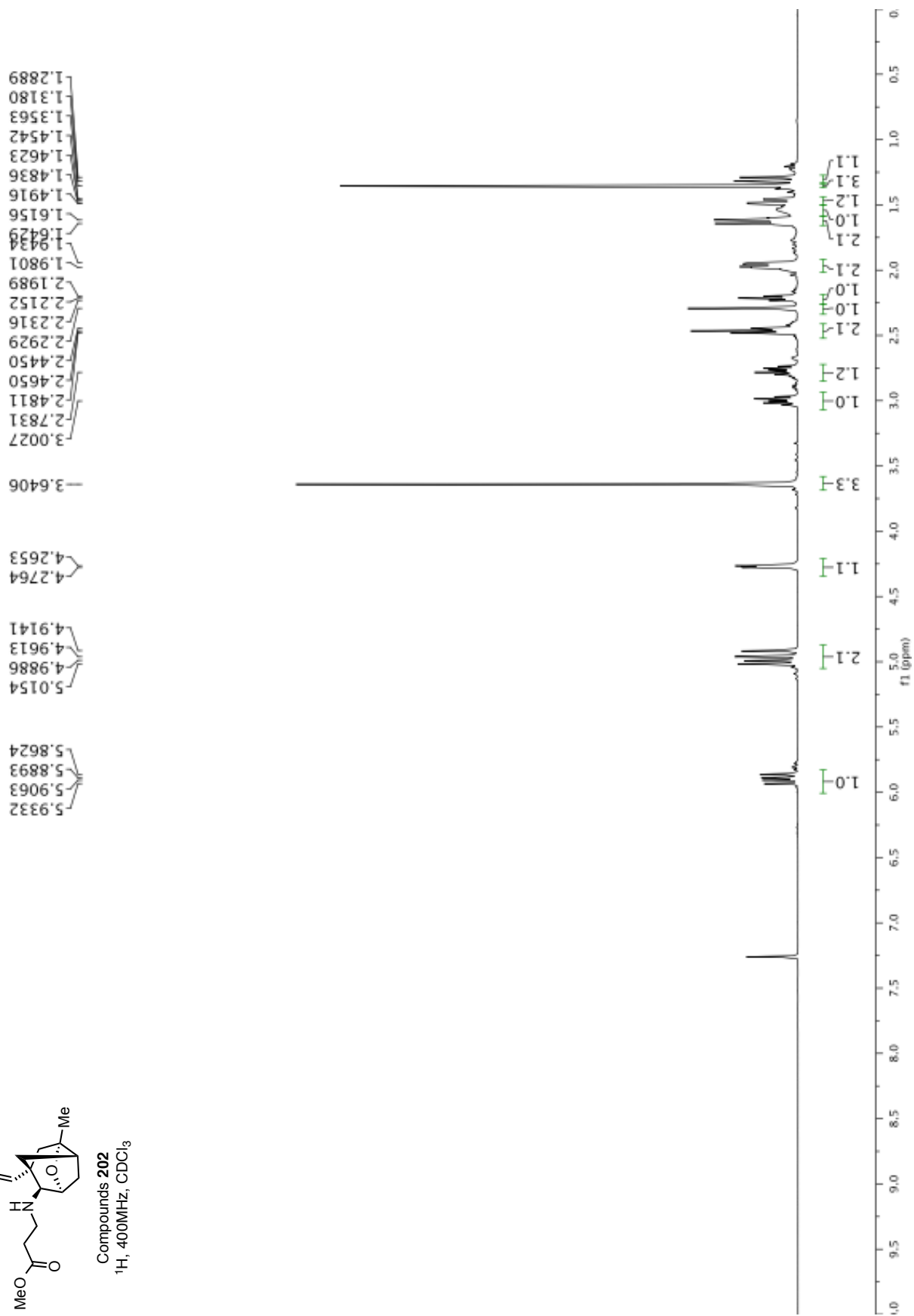


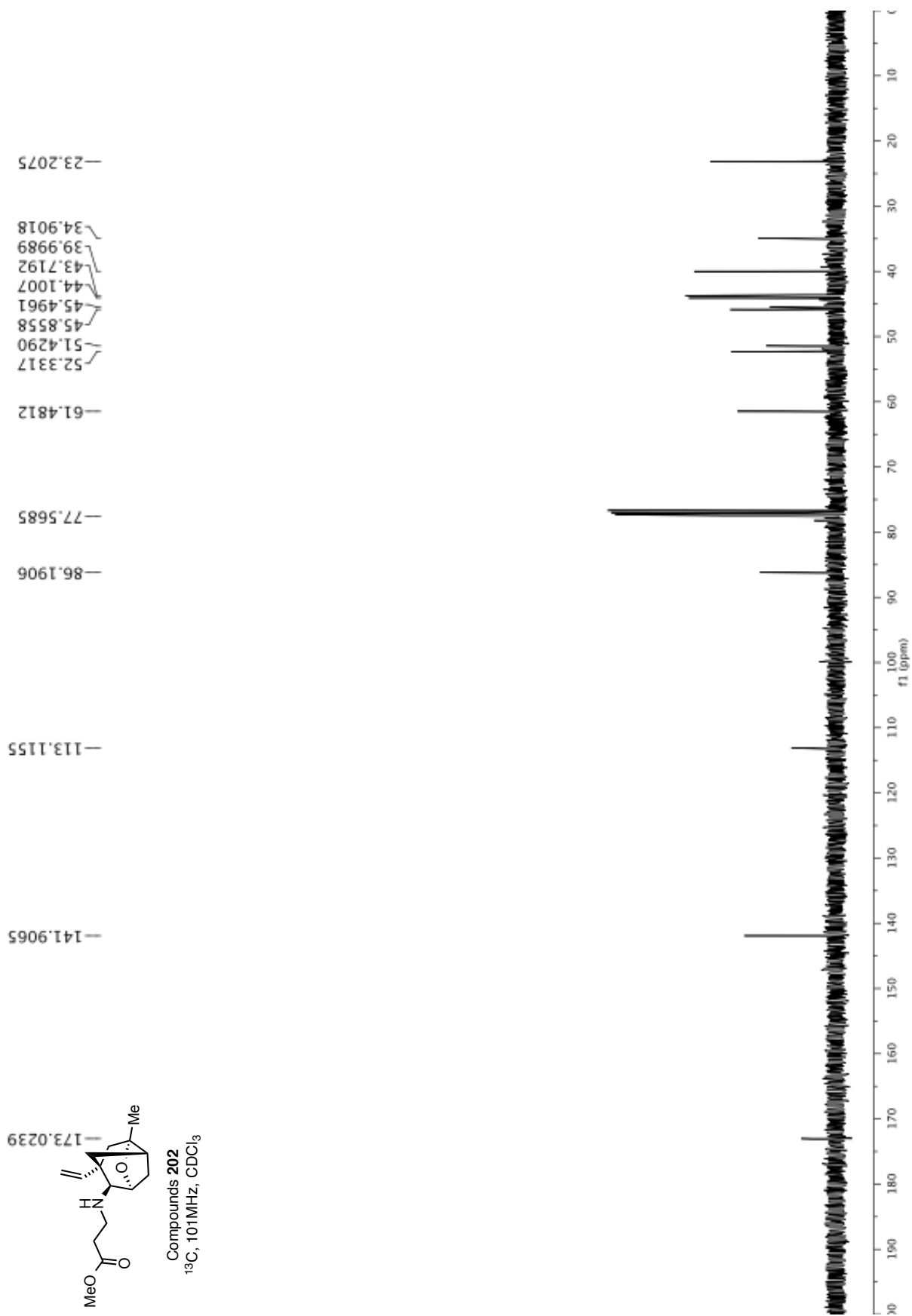
Compound **201**
 ^{13}C , 125MHz, CDCl_3

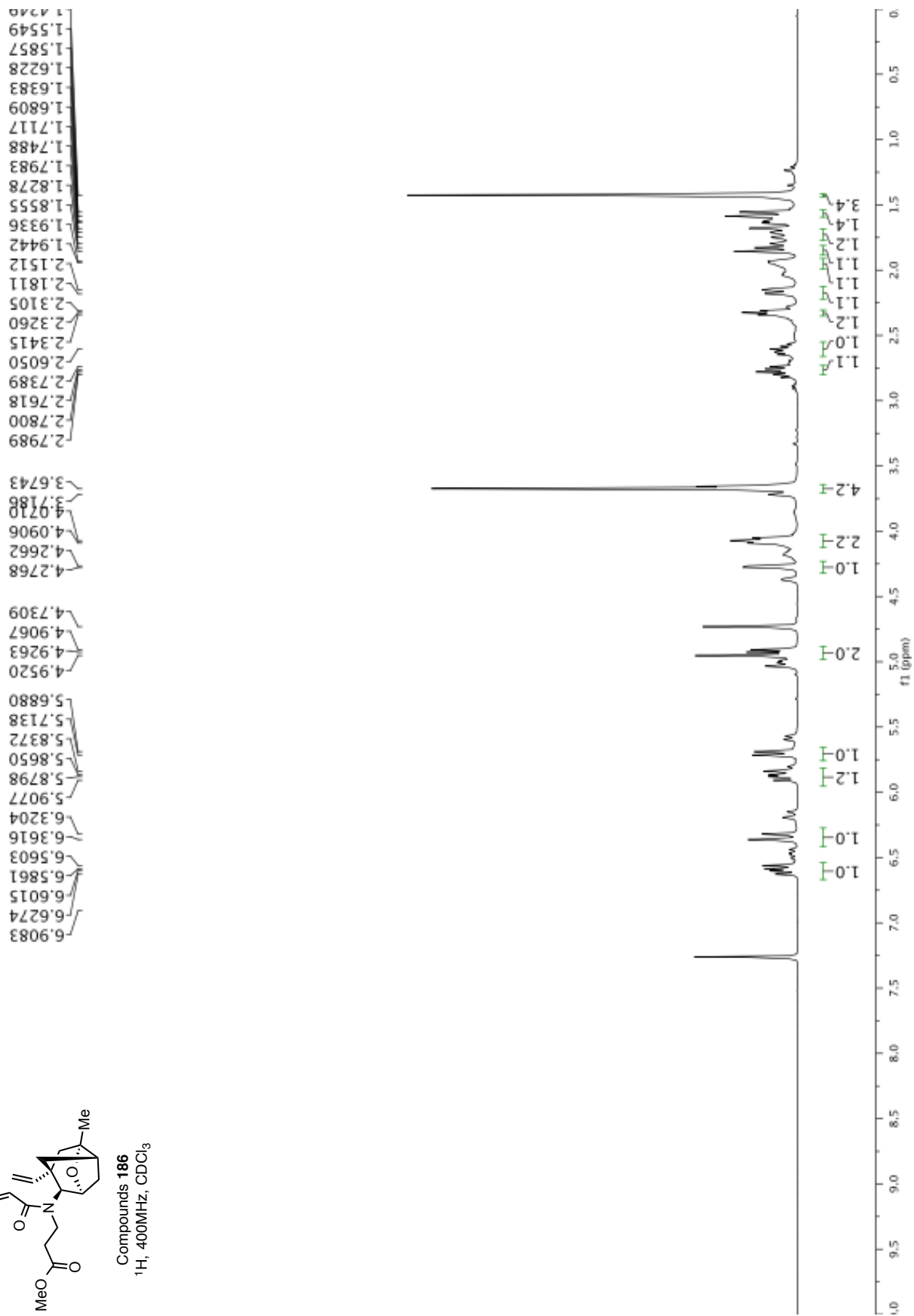
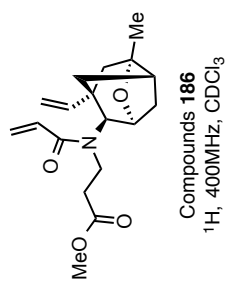


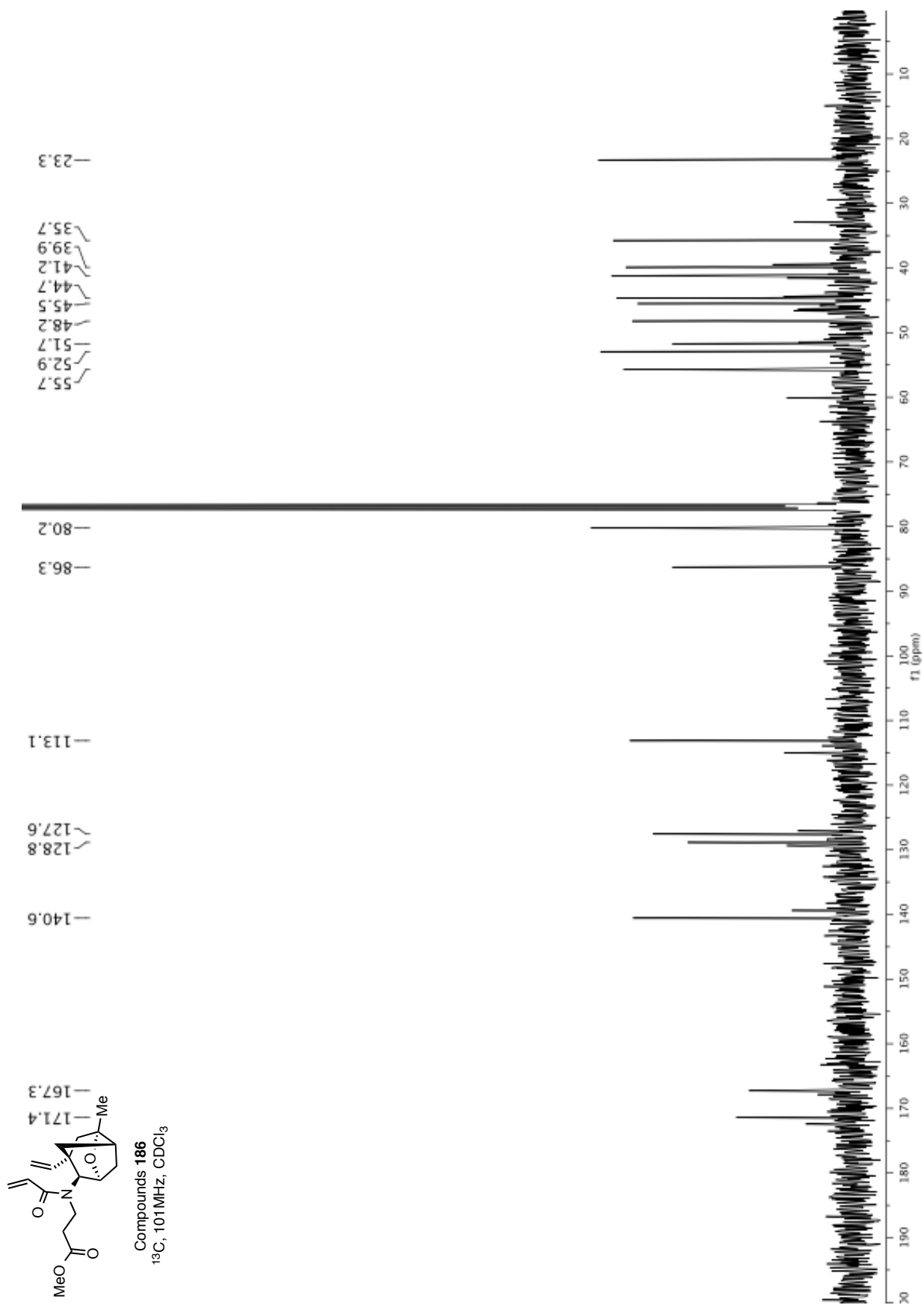


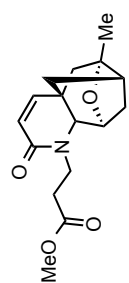
Compound **202**
 ^1H , 400MHz, CDCl_3



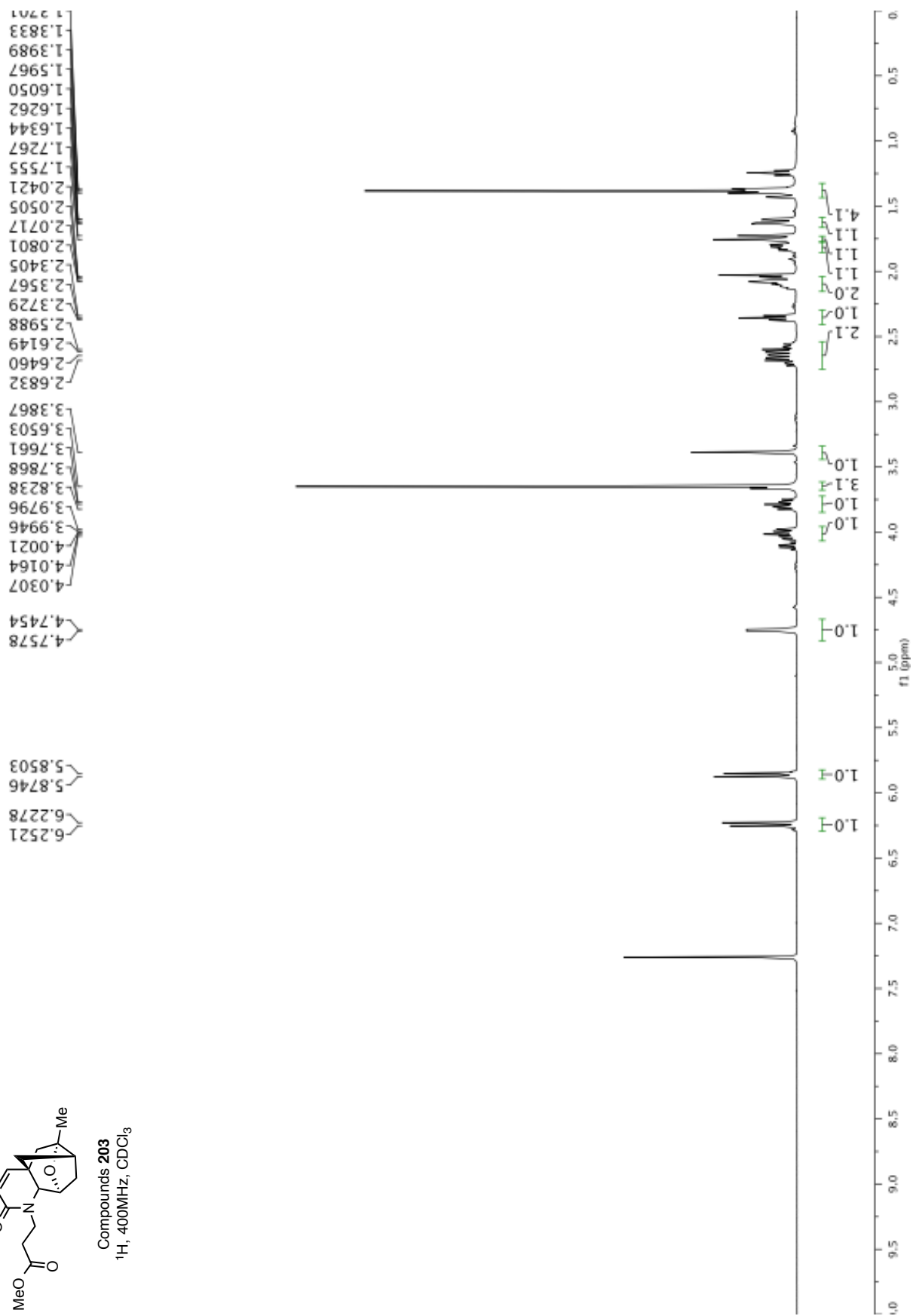


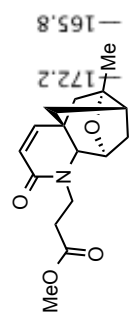




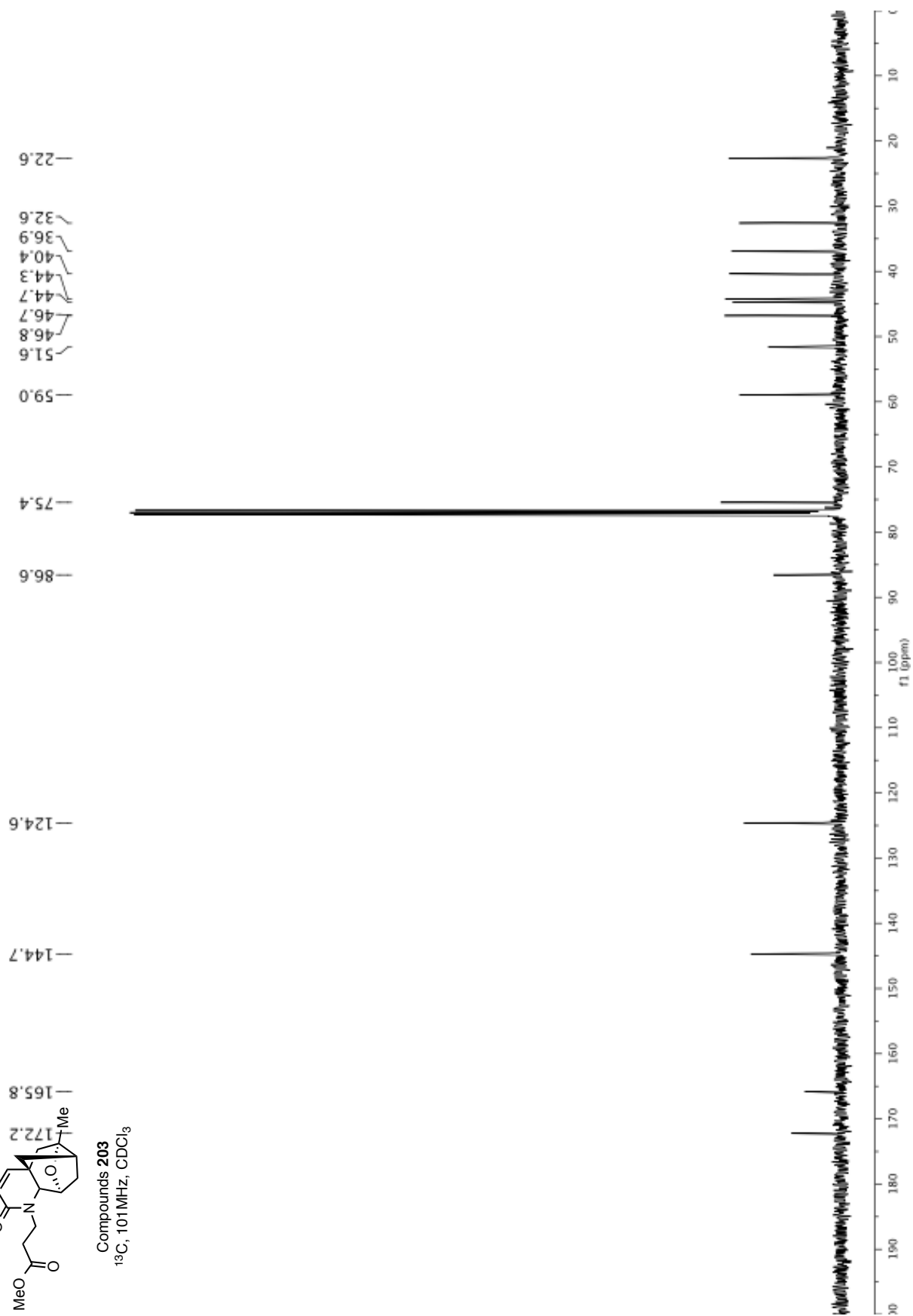


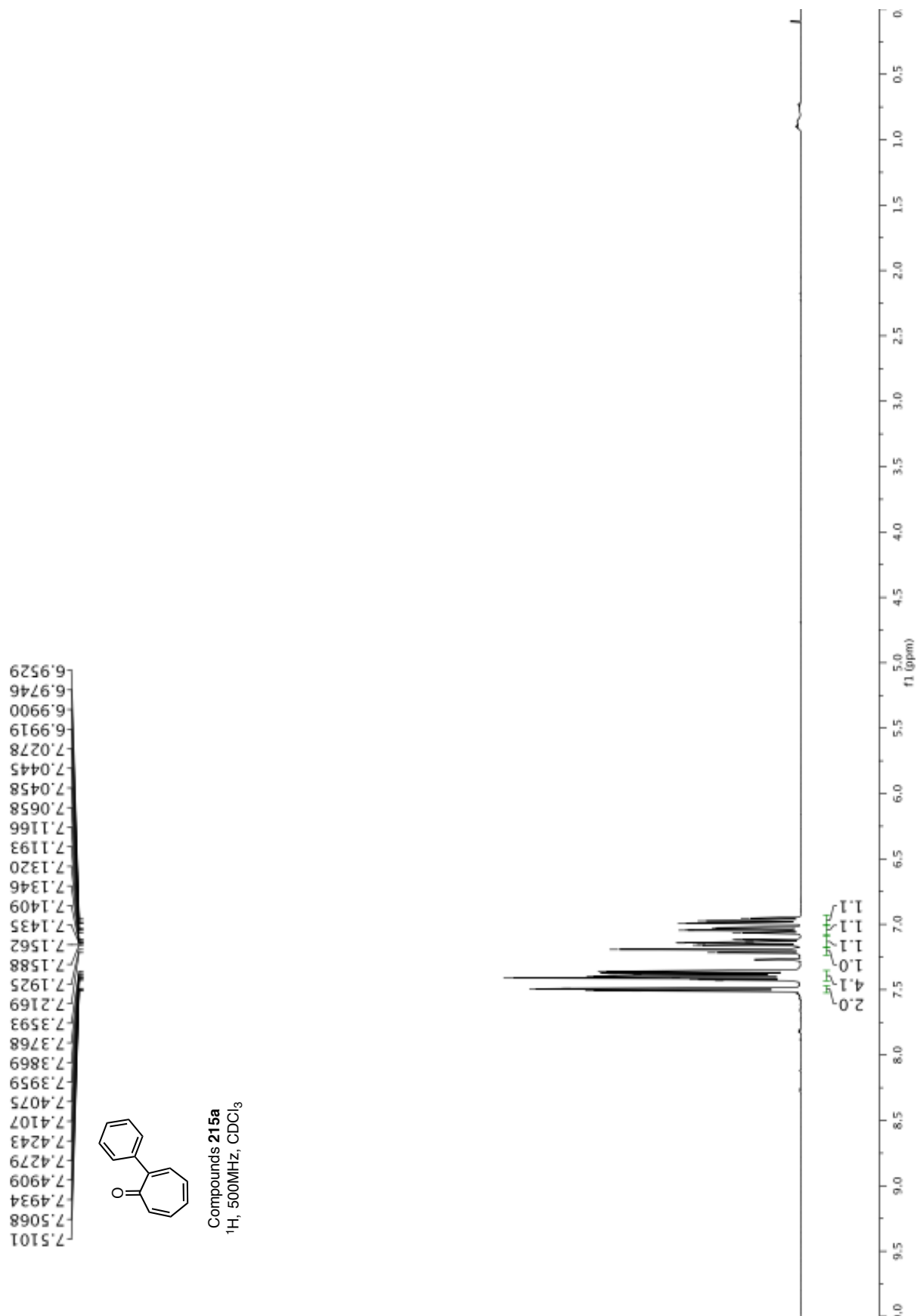
Compounds **203**
 ^1H , 400MHz, CDCl_3

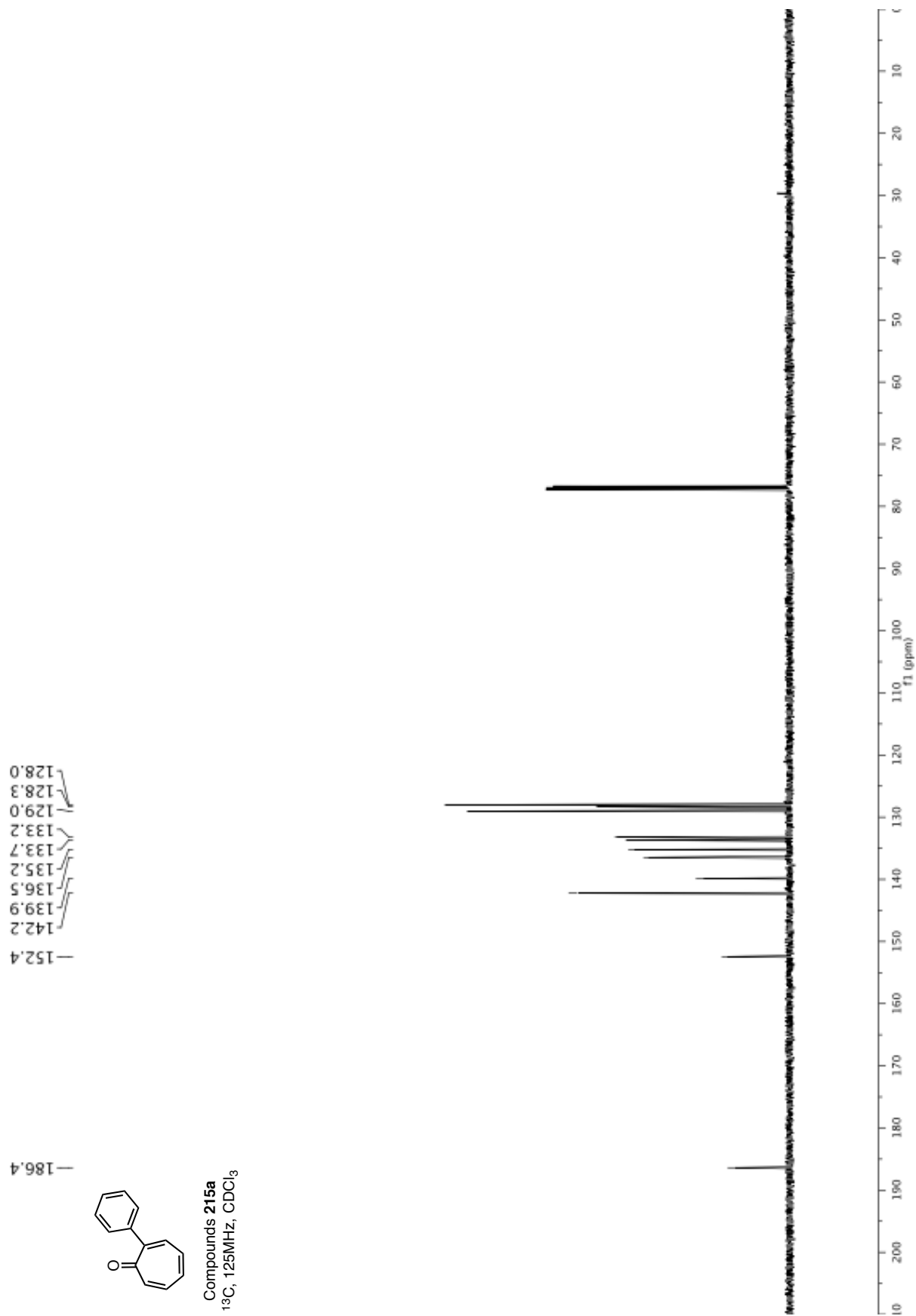


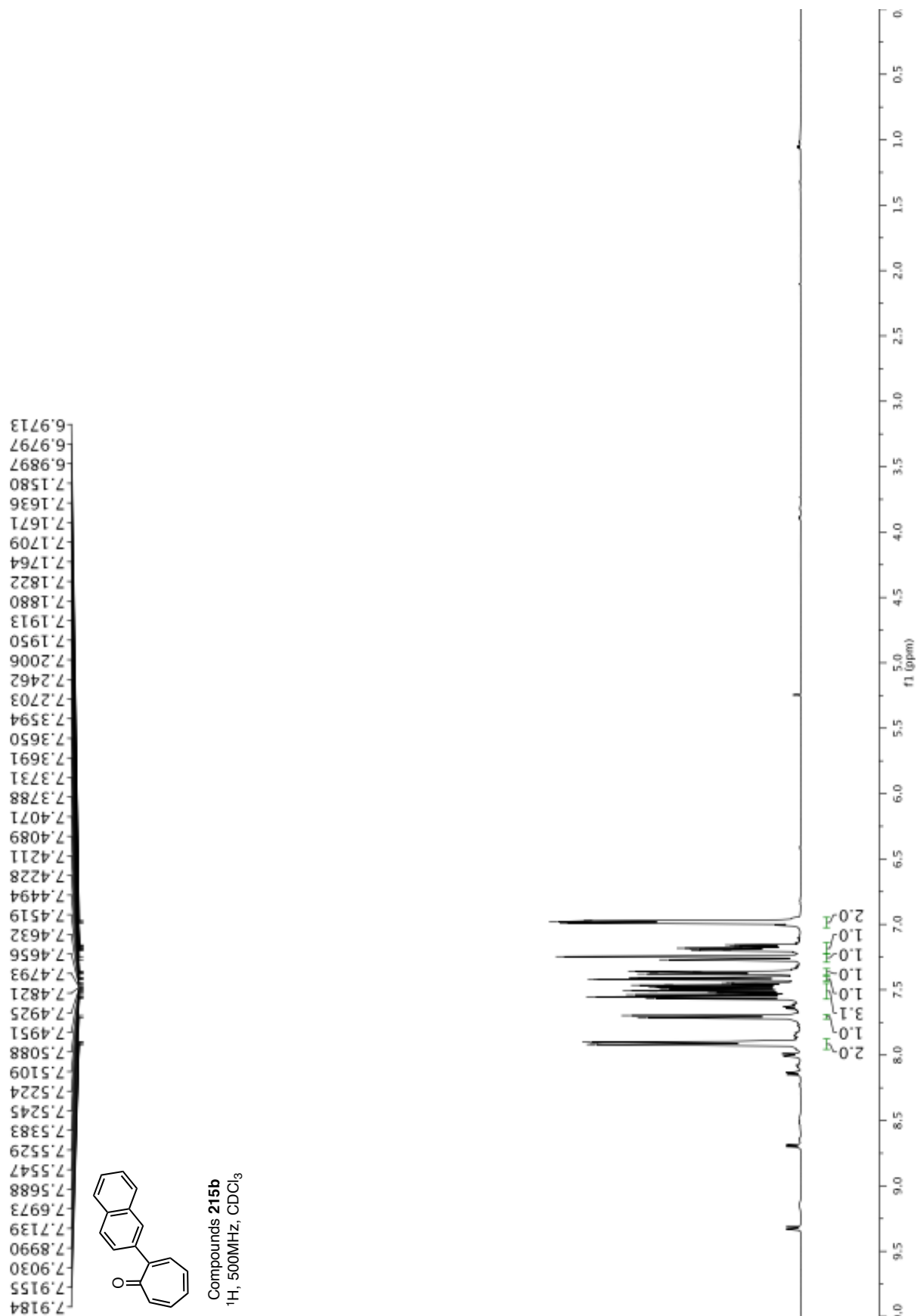


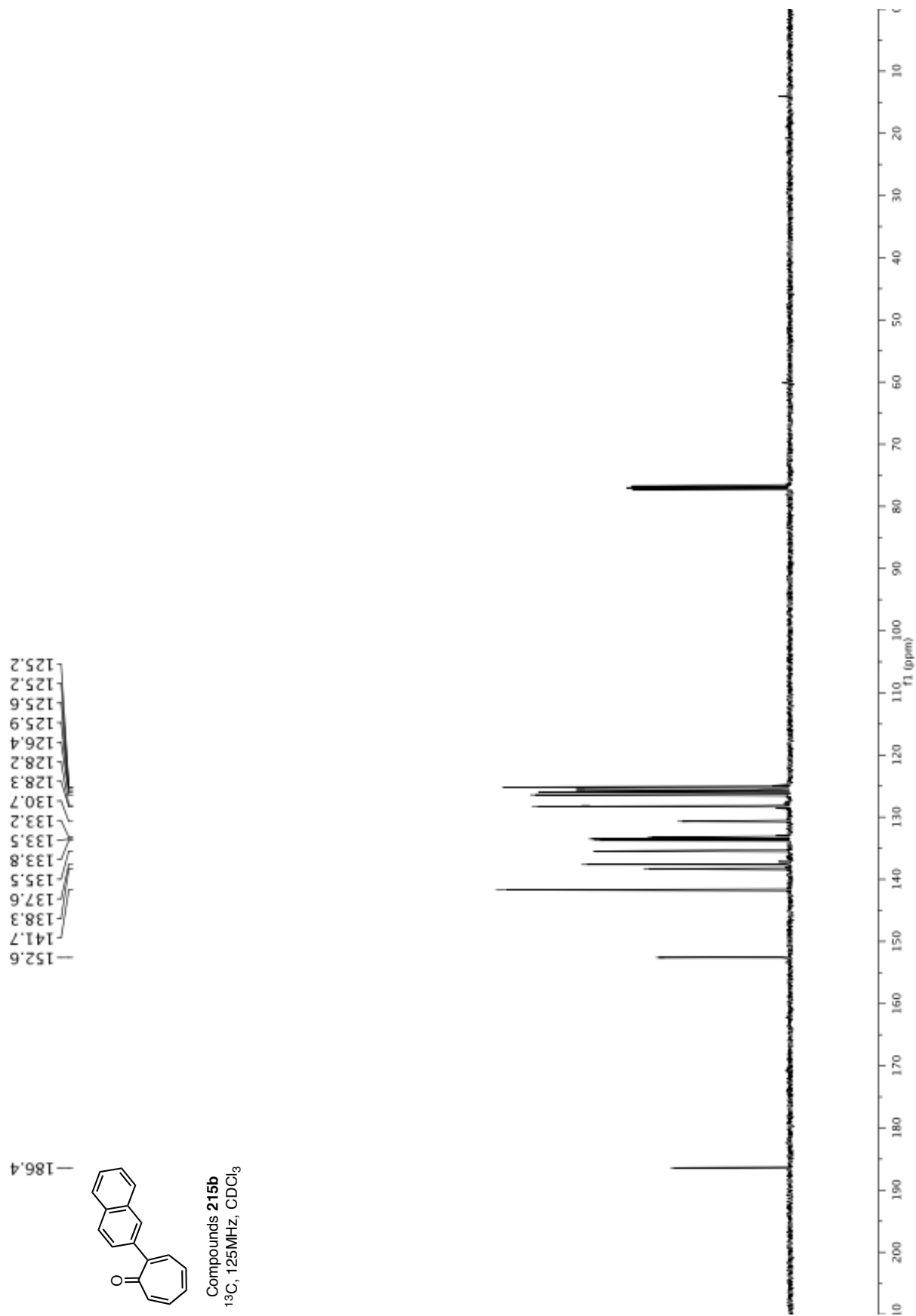
Compounds **203**
 ^{13}C , 101 MHz, CDCl_3

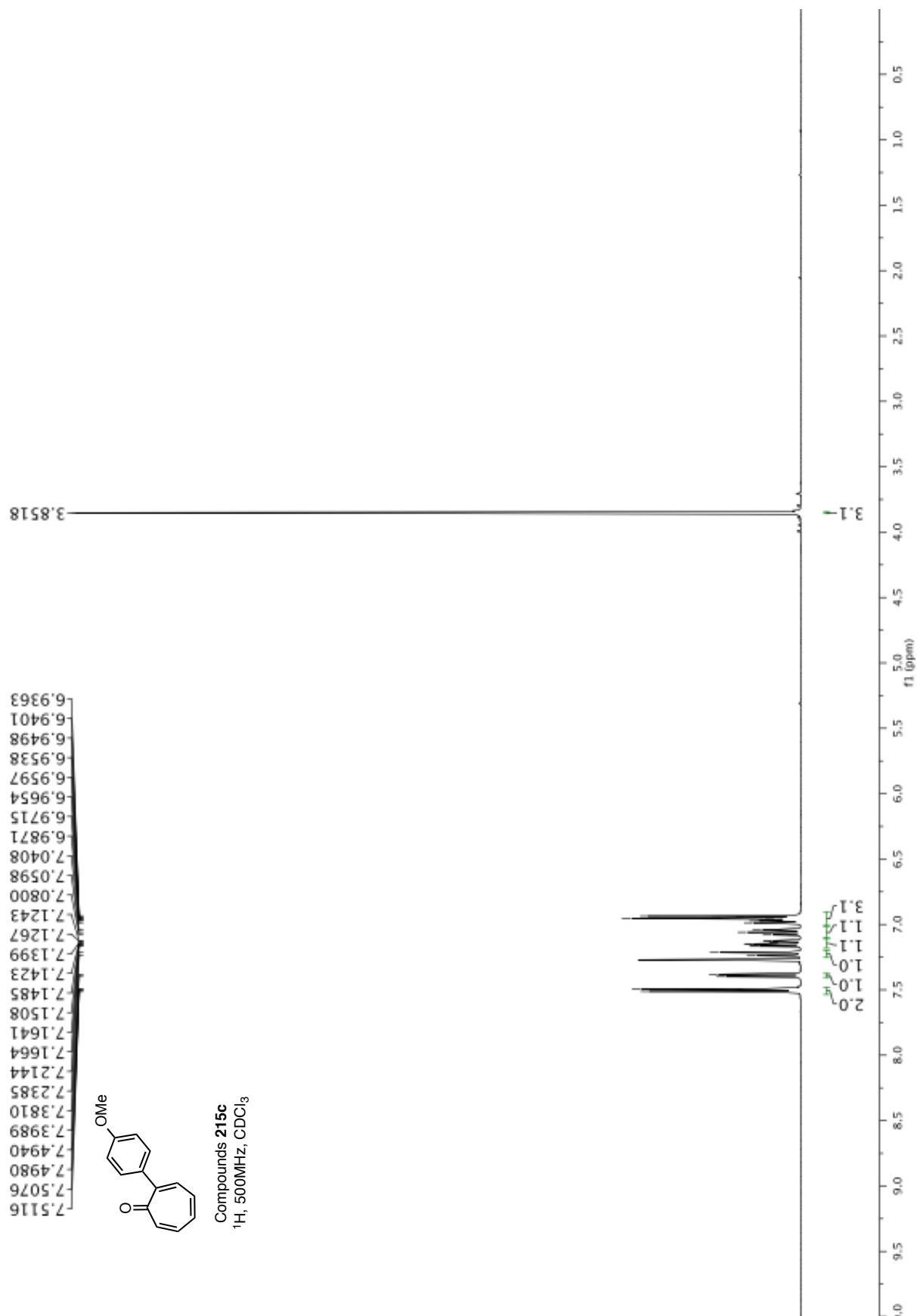


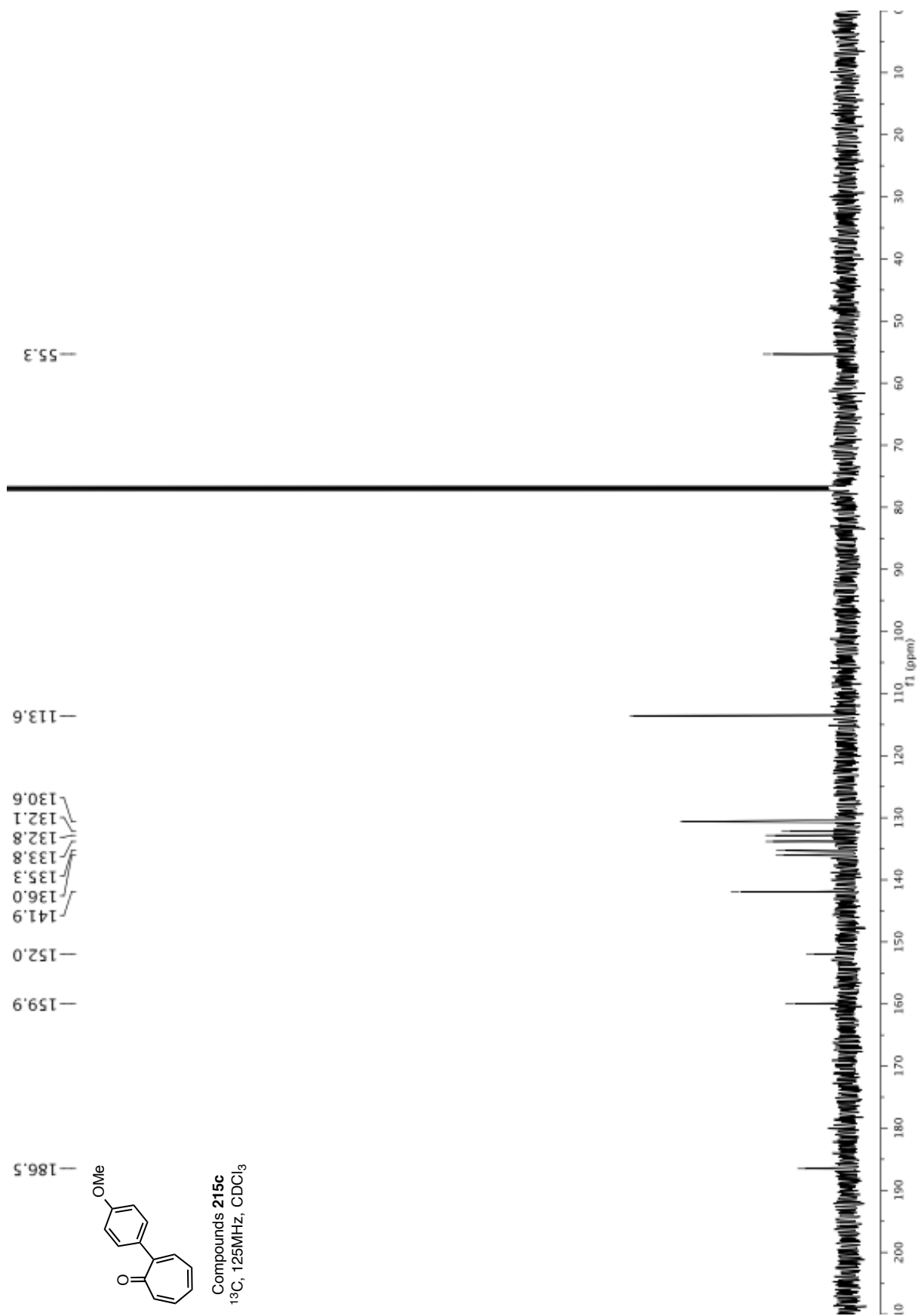


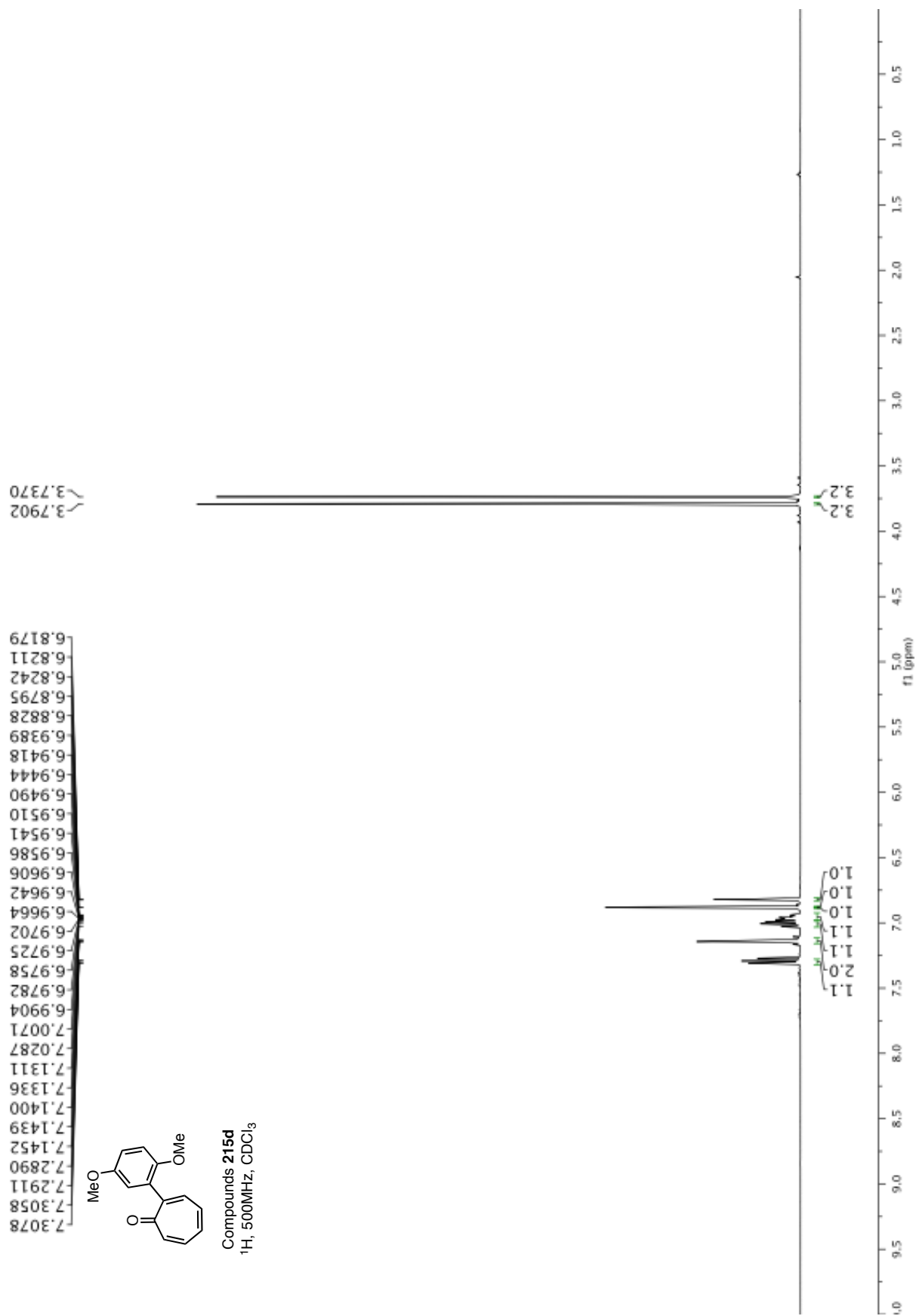


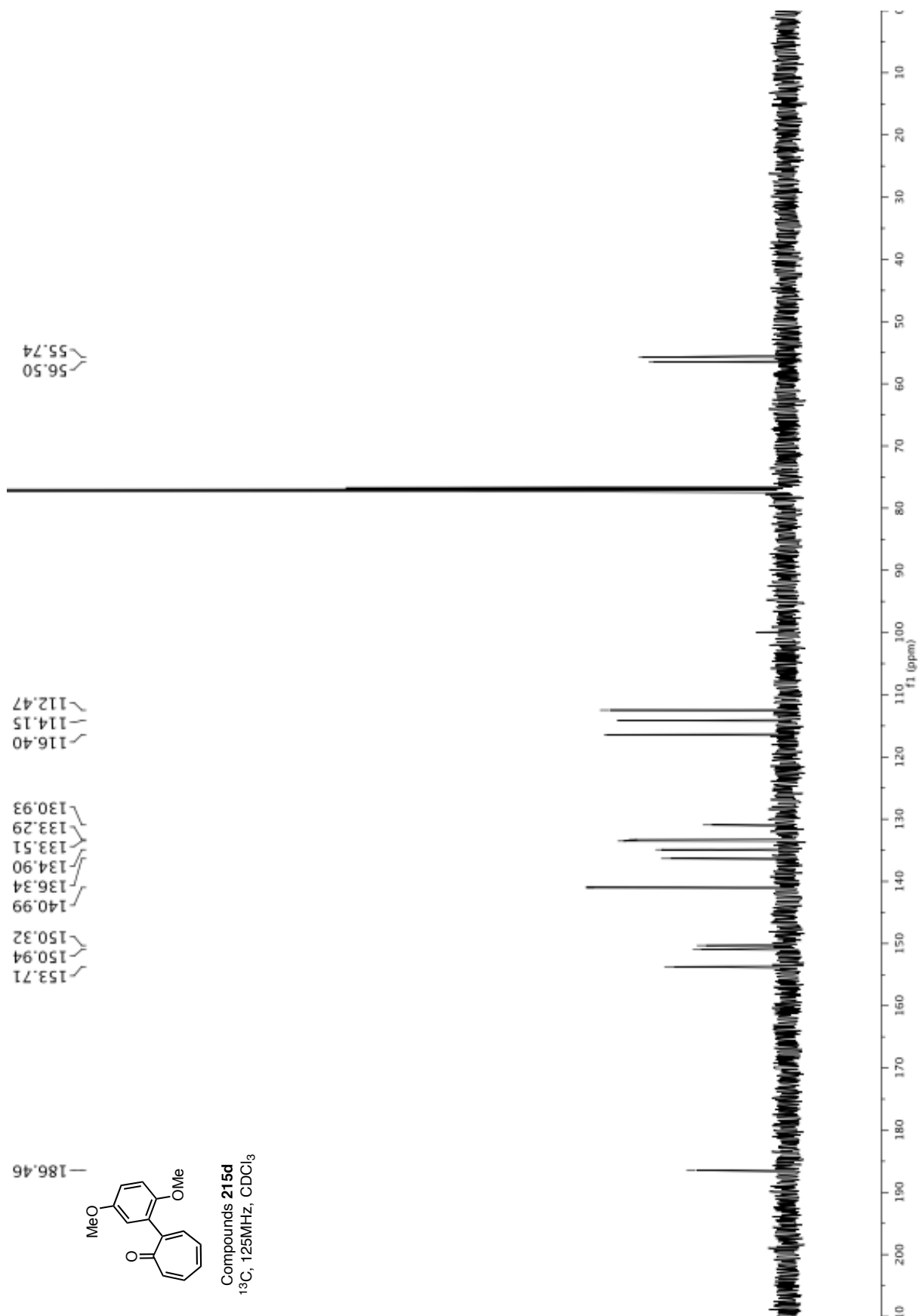


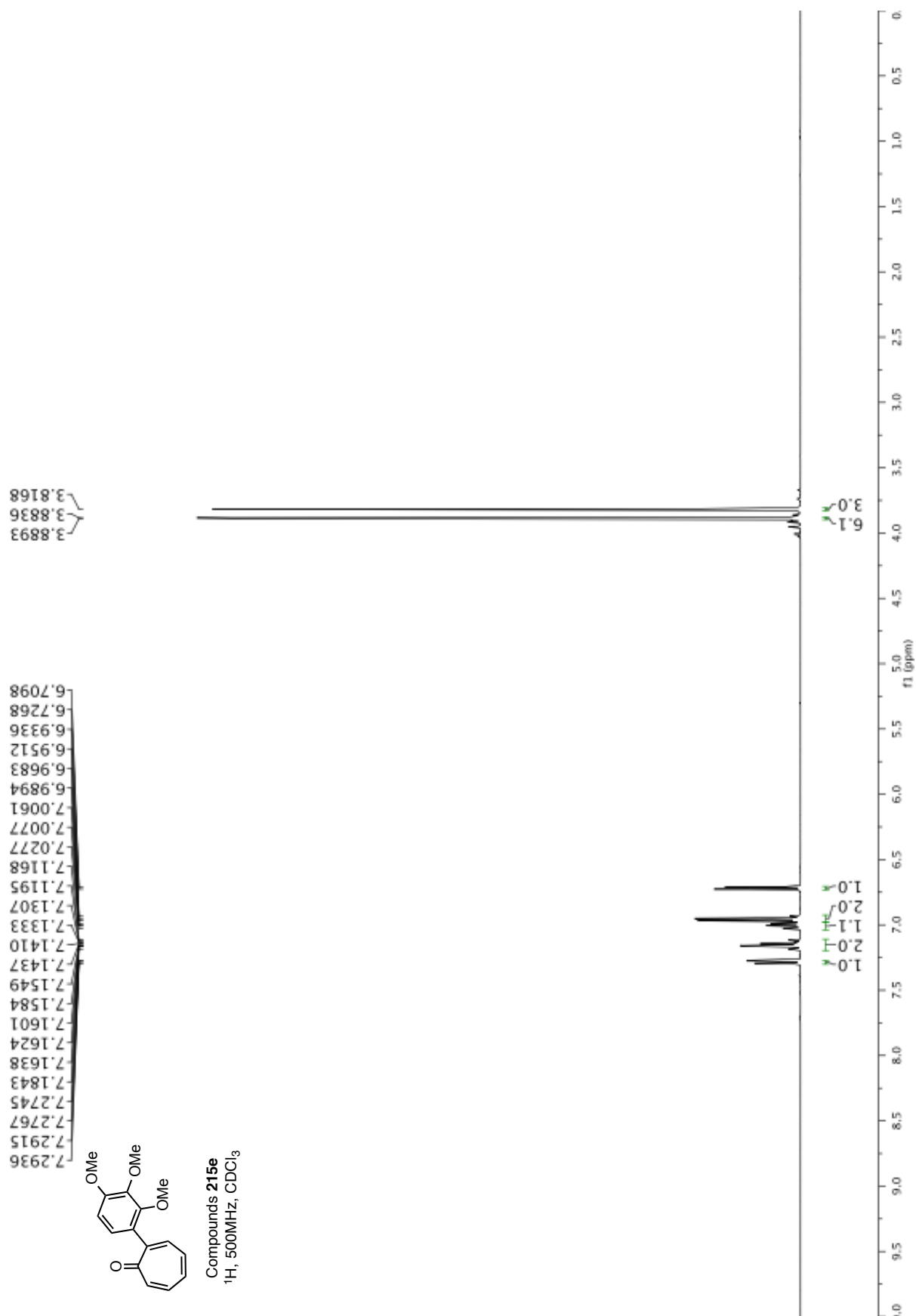


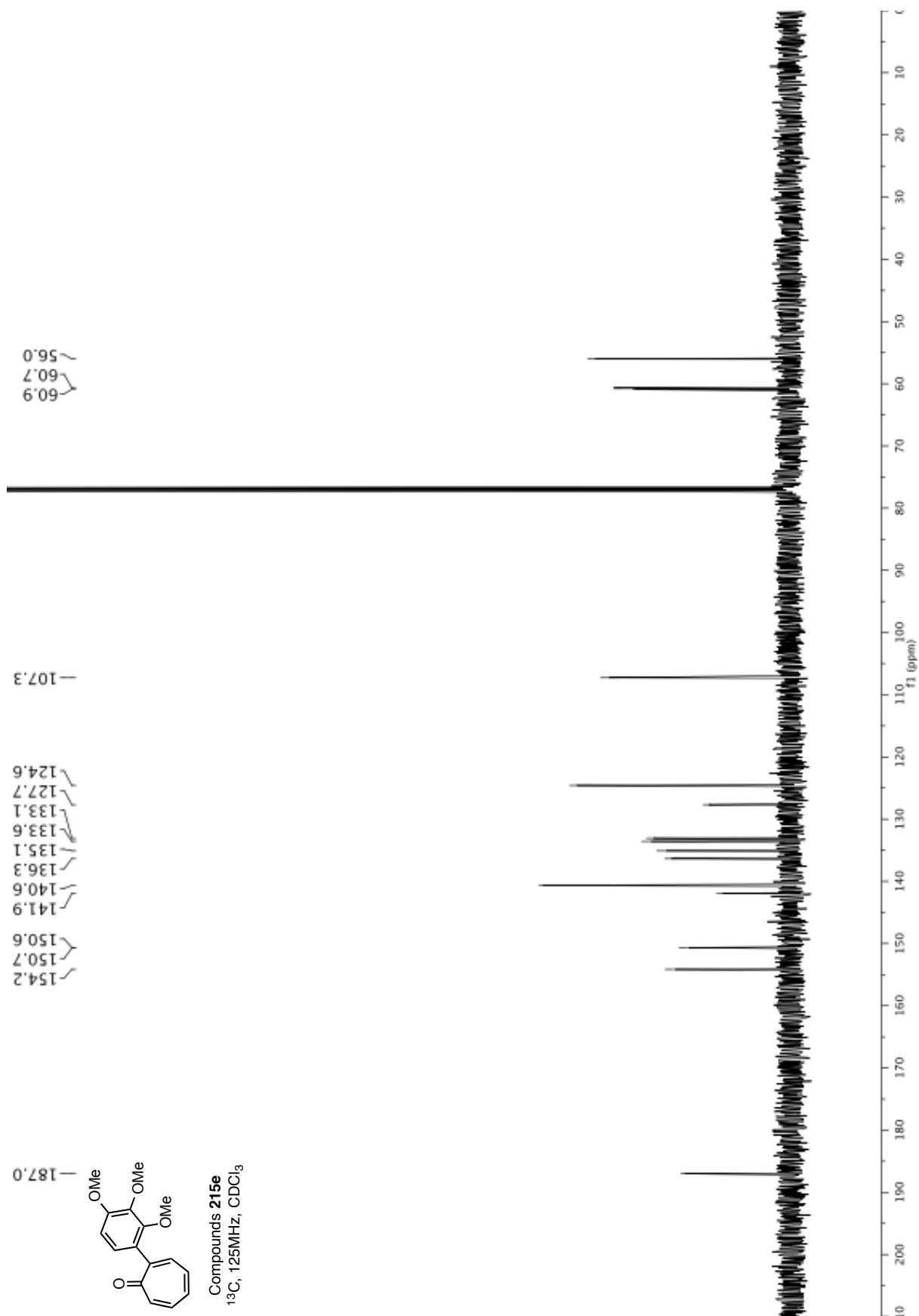


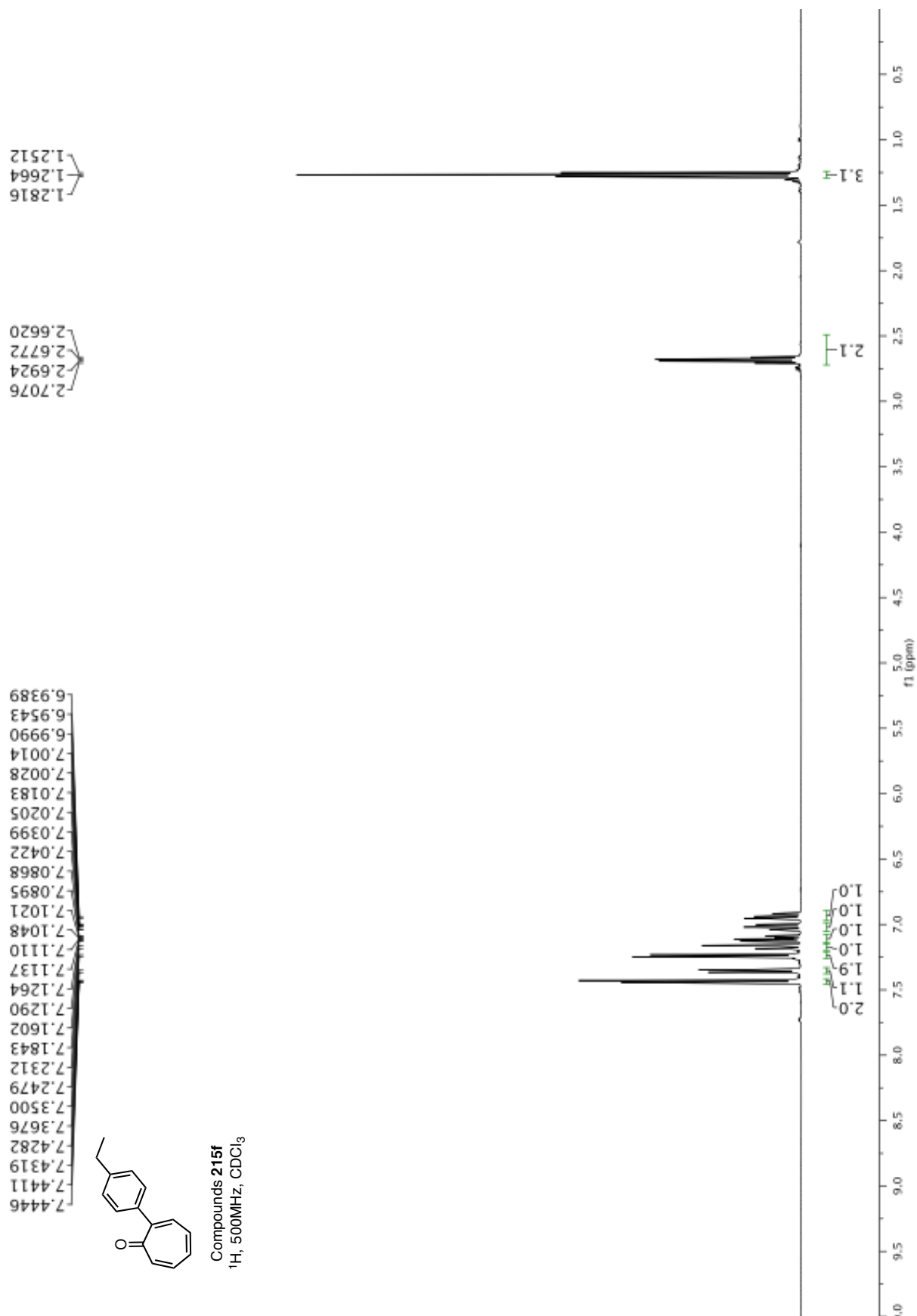


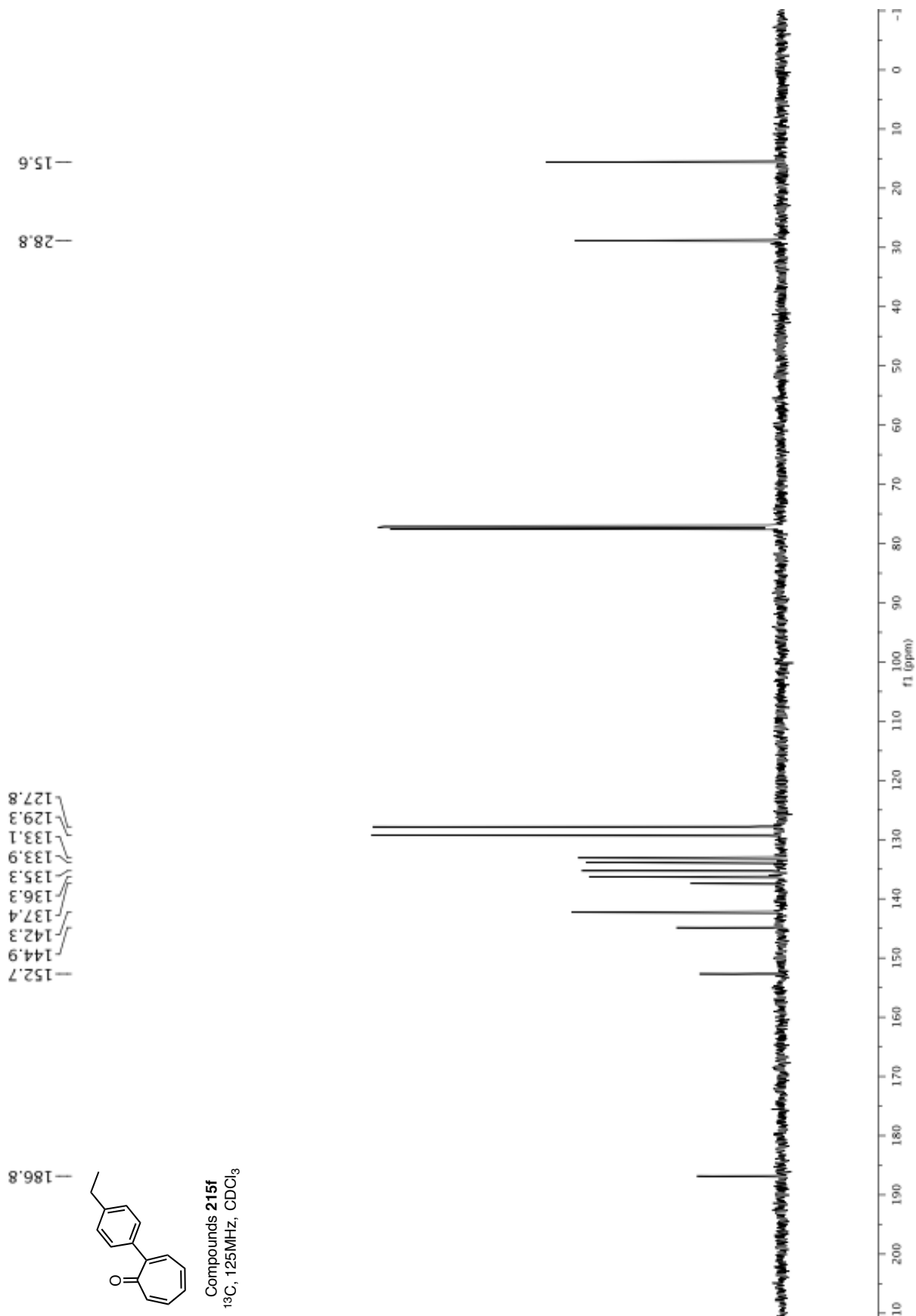


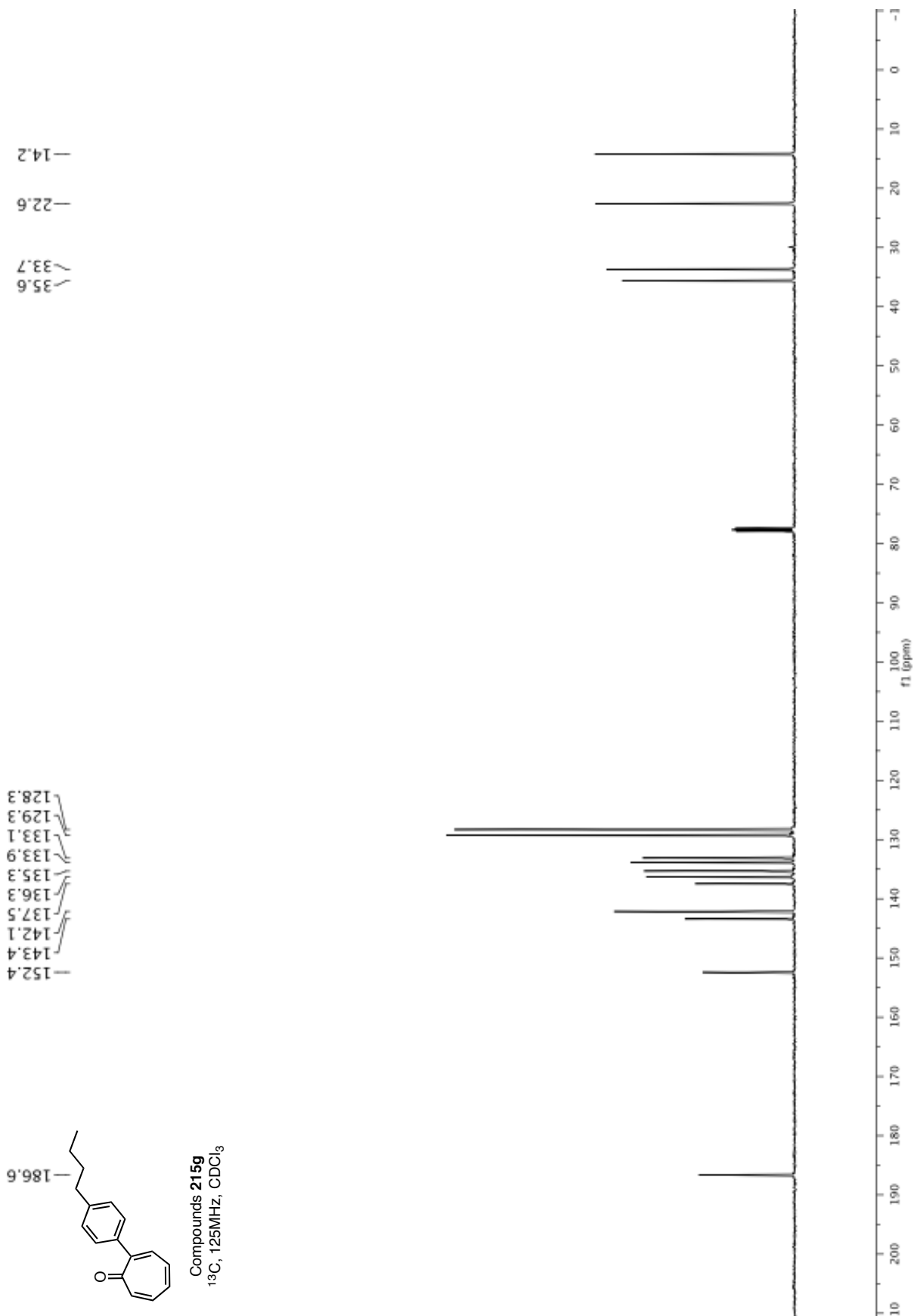


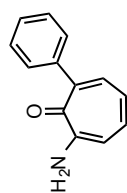




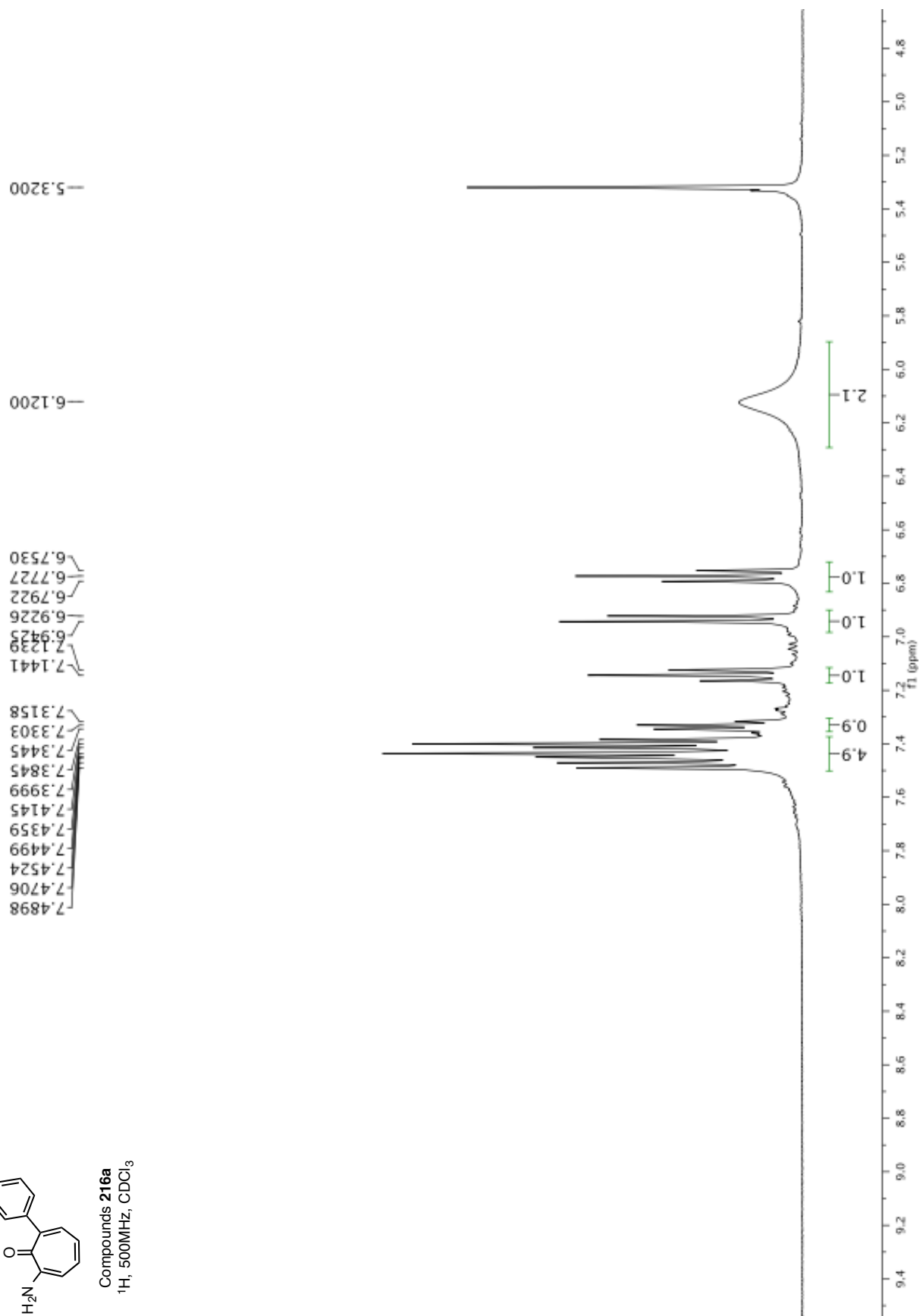


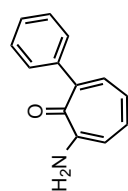




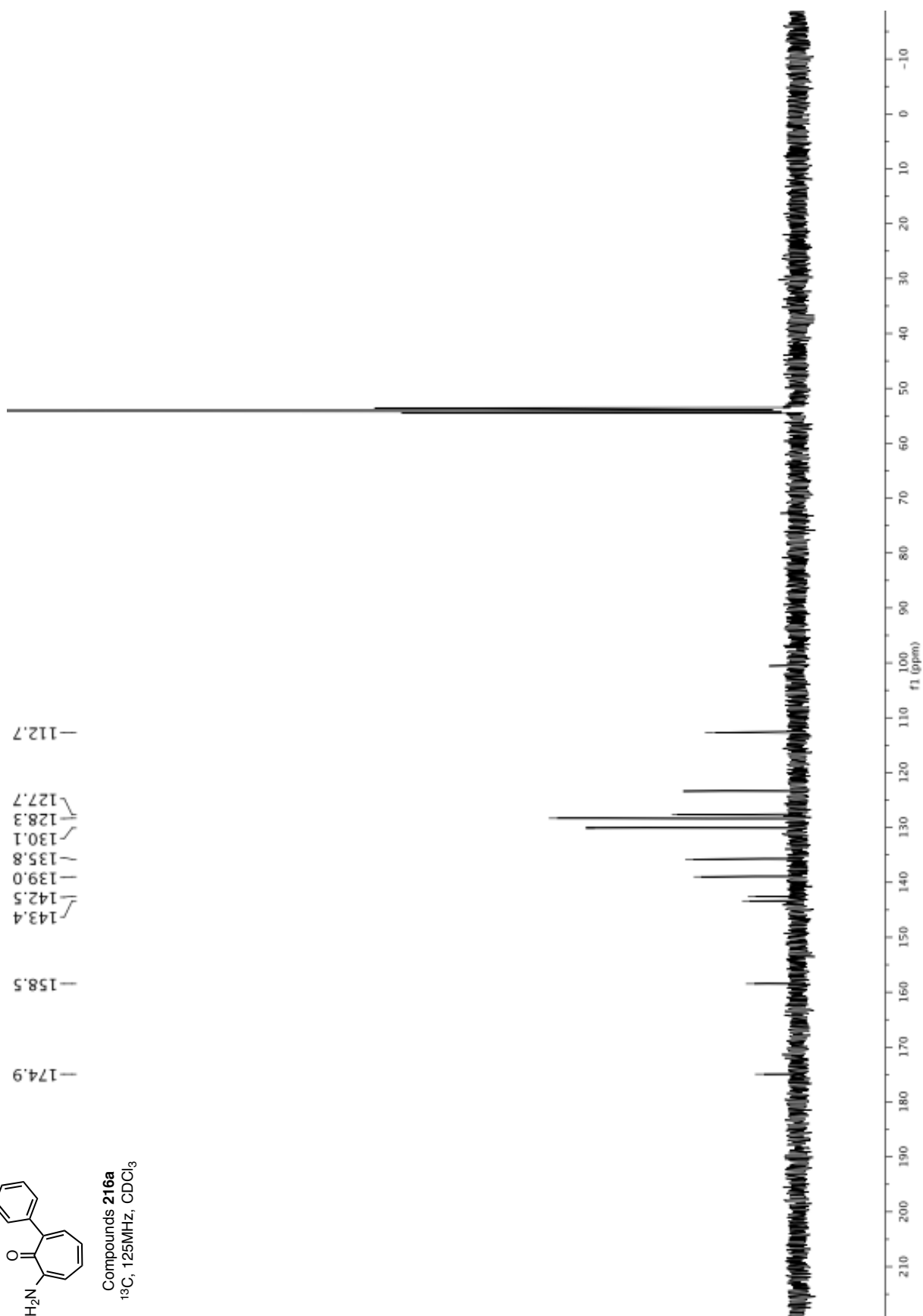


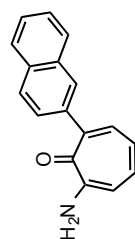
Compounds **216a**
¹H, 500MHz, CDCl₃





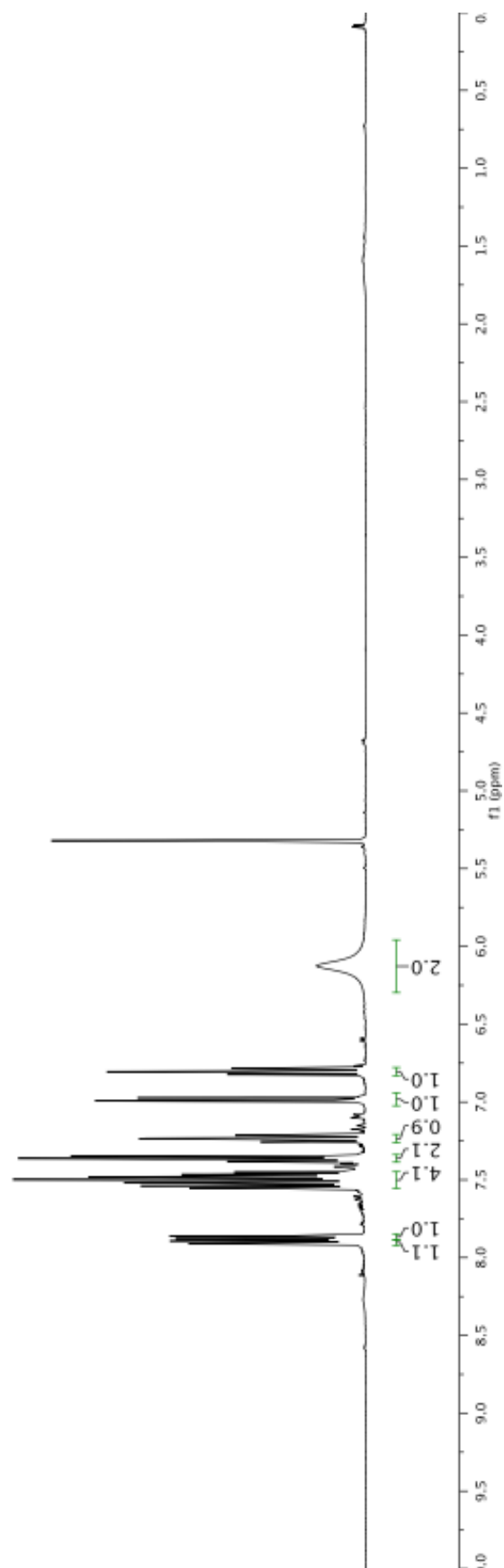
Compounds **216a**
 ^{13}C , 125MHz, CDCl_3

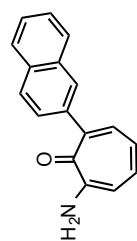




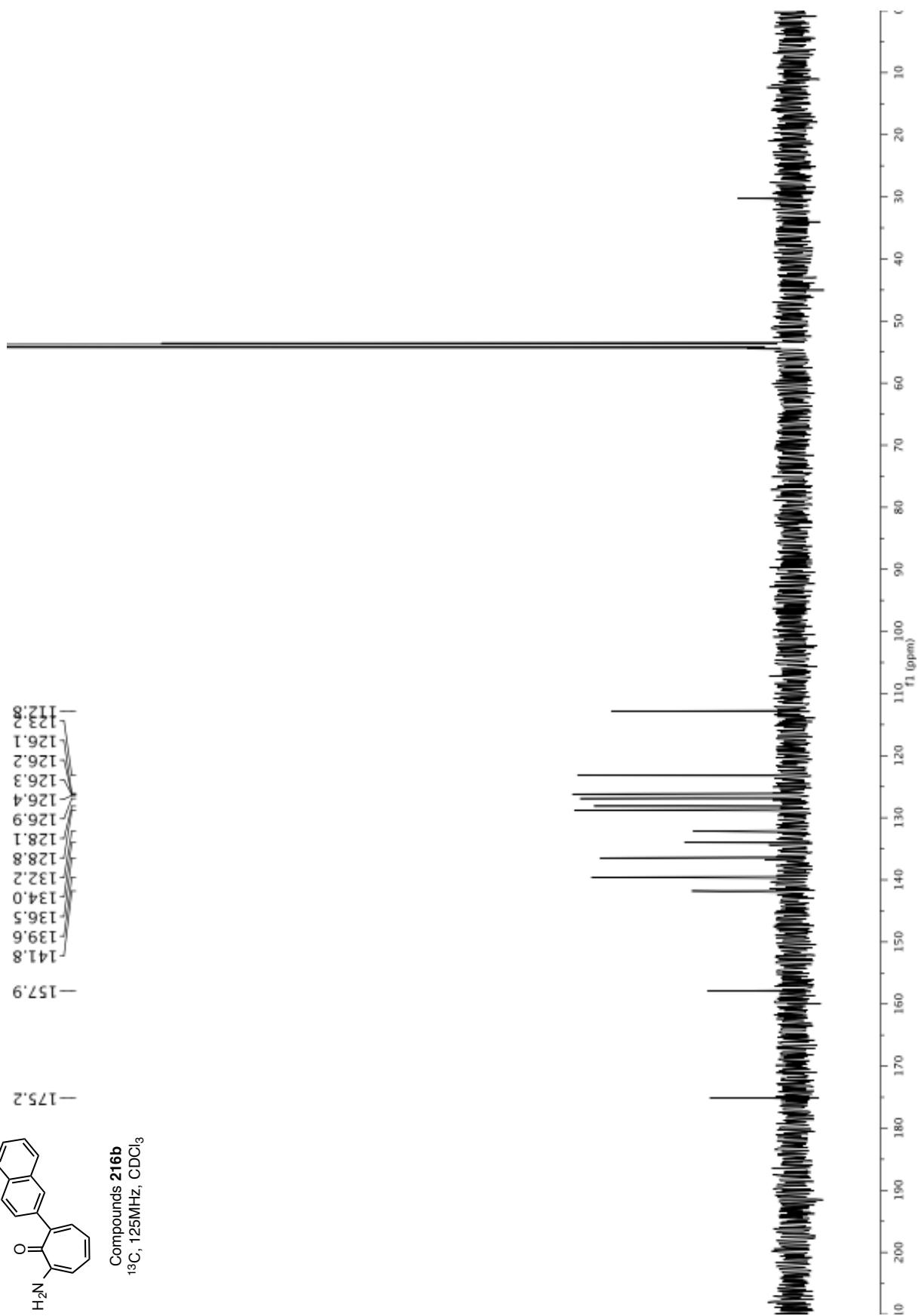
Compounds **216b**
¹H, 500MHz, CDCl₃

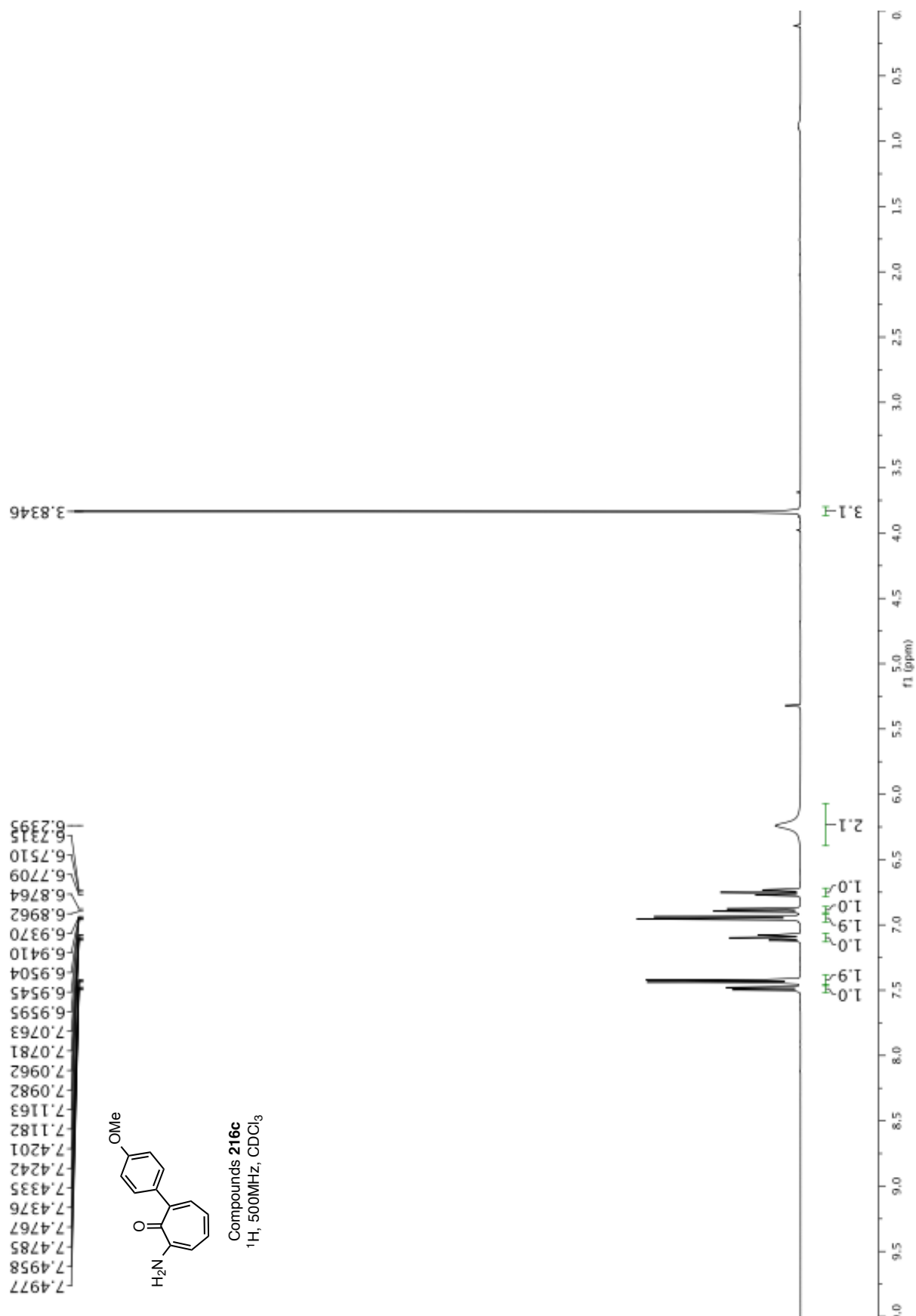
7.9089
 7.8926
 7.8789
 7.8623
 7.5193
 7.5171
 7.5002
 7.4983
 7.4810
 7.3630
 7.3611
 7.3492
 6.9929
 6.8043
 6.1291

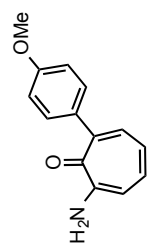




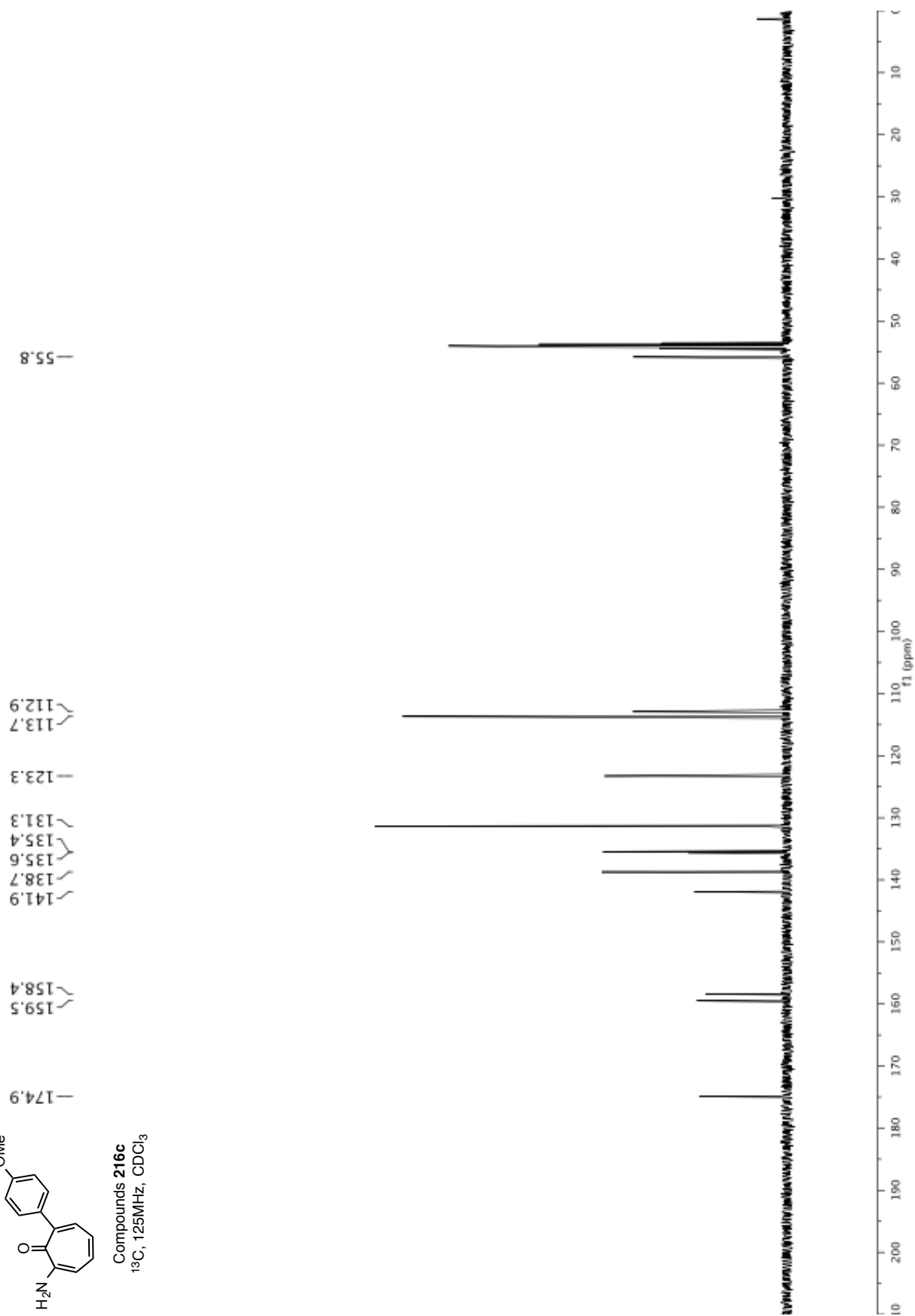
Compound **216b**
 ^{13}C , 125MHz, CDCl_3

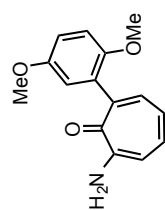






Compounds **216c**
 ^{13}C , 125MHz, CDCl_3

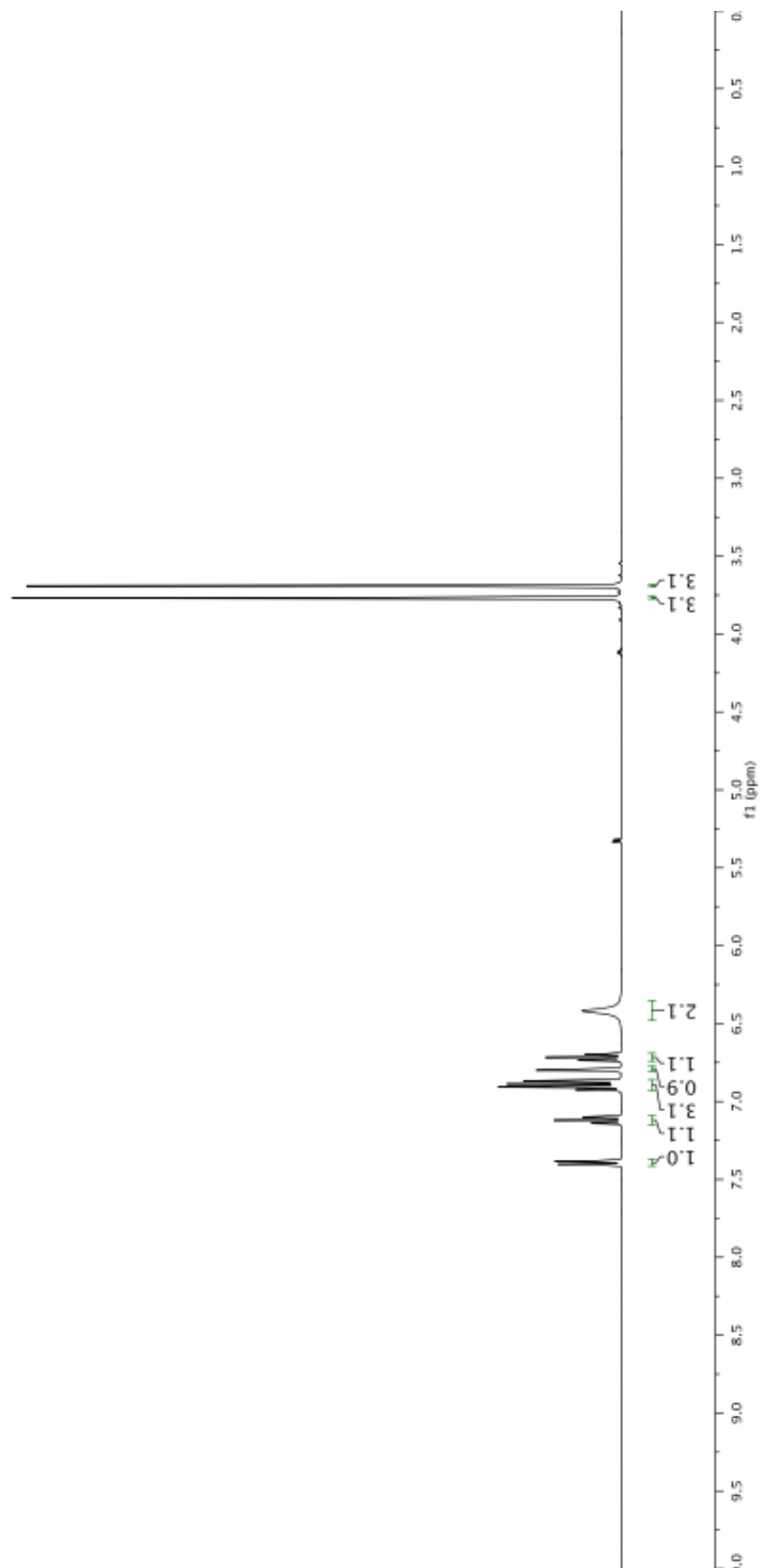


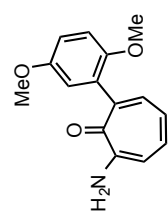


Compounds **216d**
¹H, 500MHz, CDCl₃

3.7685
 3.6913

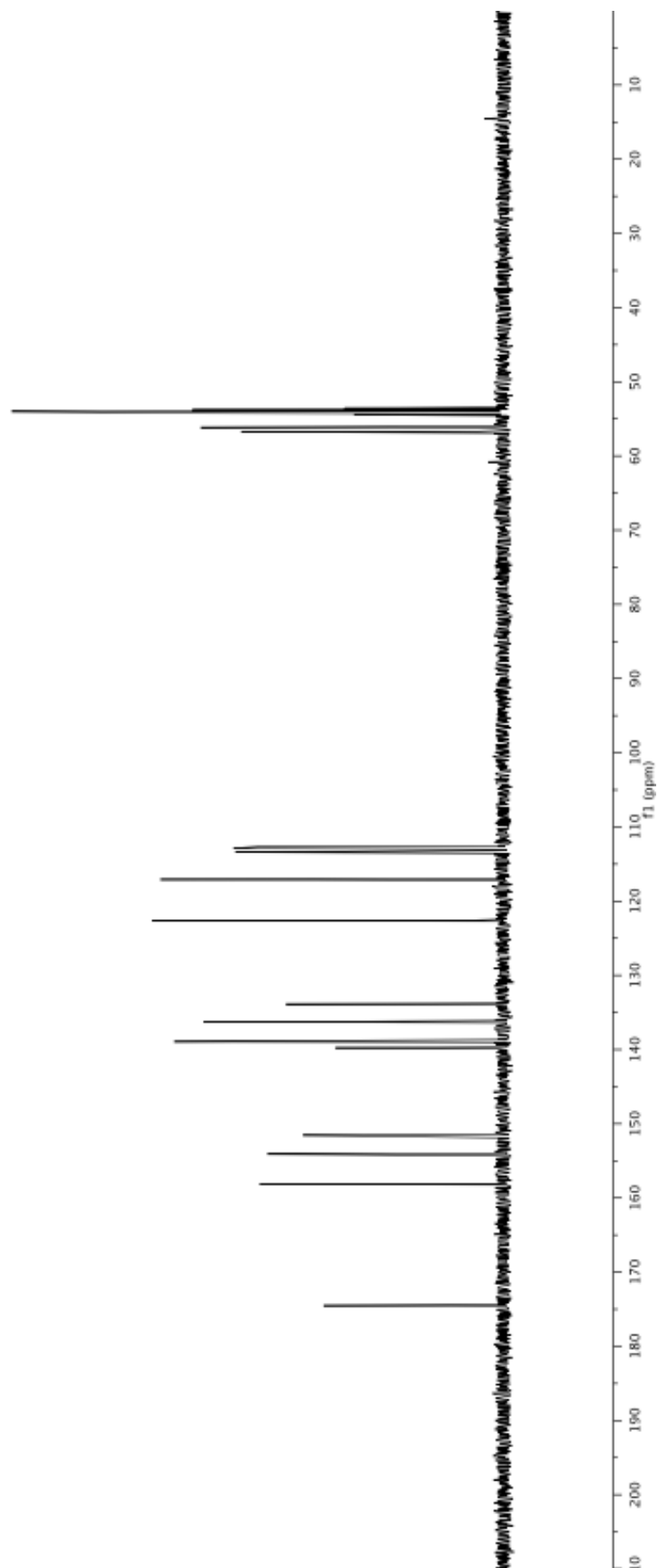
7.4029
 7.3839
 7.1403
 7.1201
 7.1000
 6.9246
 6.9068
 6.8879
 6.8850
 6.8724
 6.8671
 6.8002
 6.7944
 6.7362
 6.7169
 6.6972
 6.4194

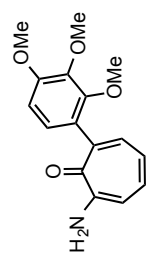




Compounds **216d**
¹³C, 125MHz, CDCl₃

174.5
 158.1
 154.1
 151.5
 139.8
 138.9
 136.2
 133.9
 122.6
 117.1
 113.4
 112.9
 112.6
 56.7
 56.2

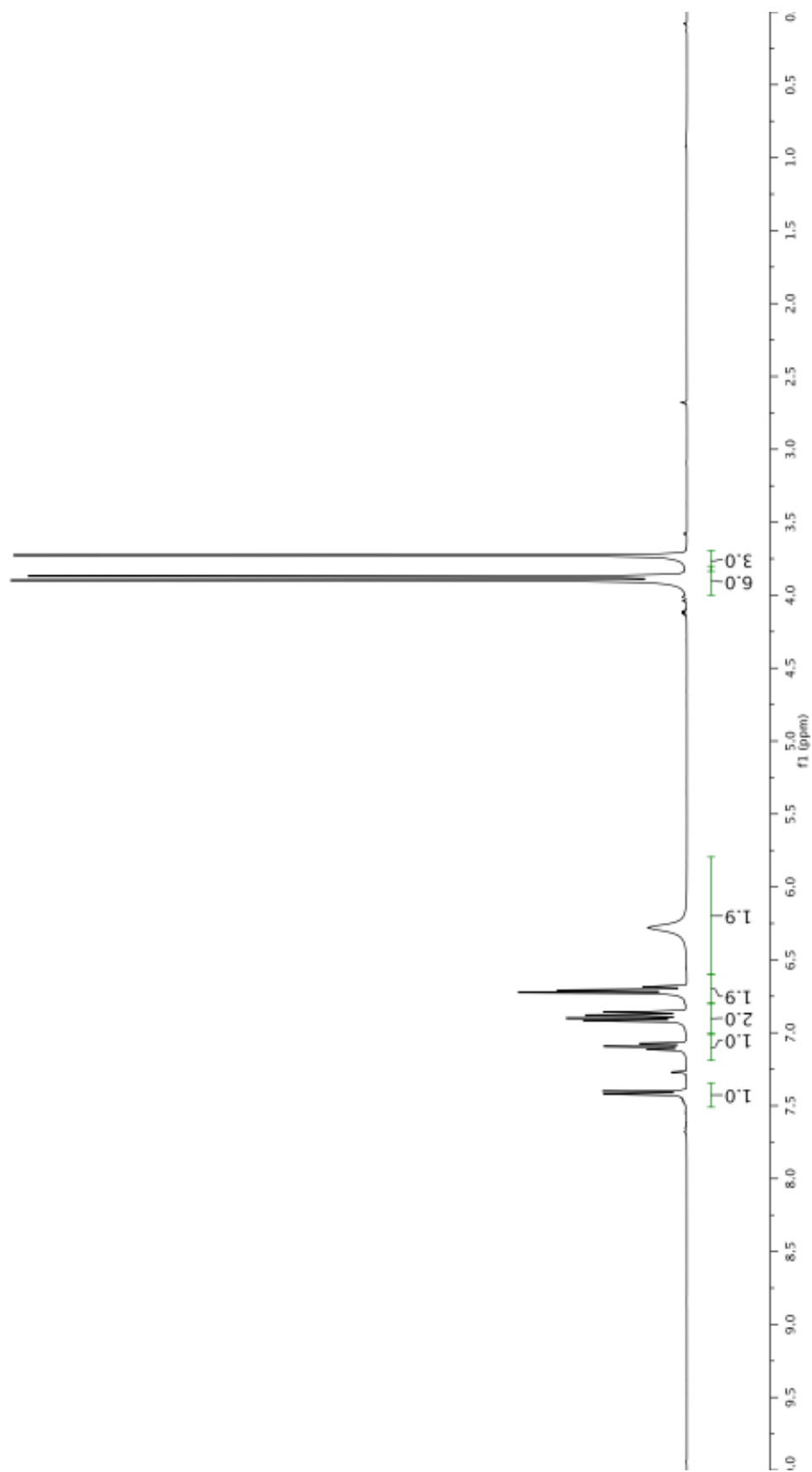


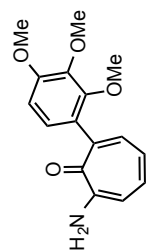


Compounds **216e**
¹H, 500MHz, CDCl₃

3.8975
 3.8700
 3.7254

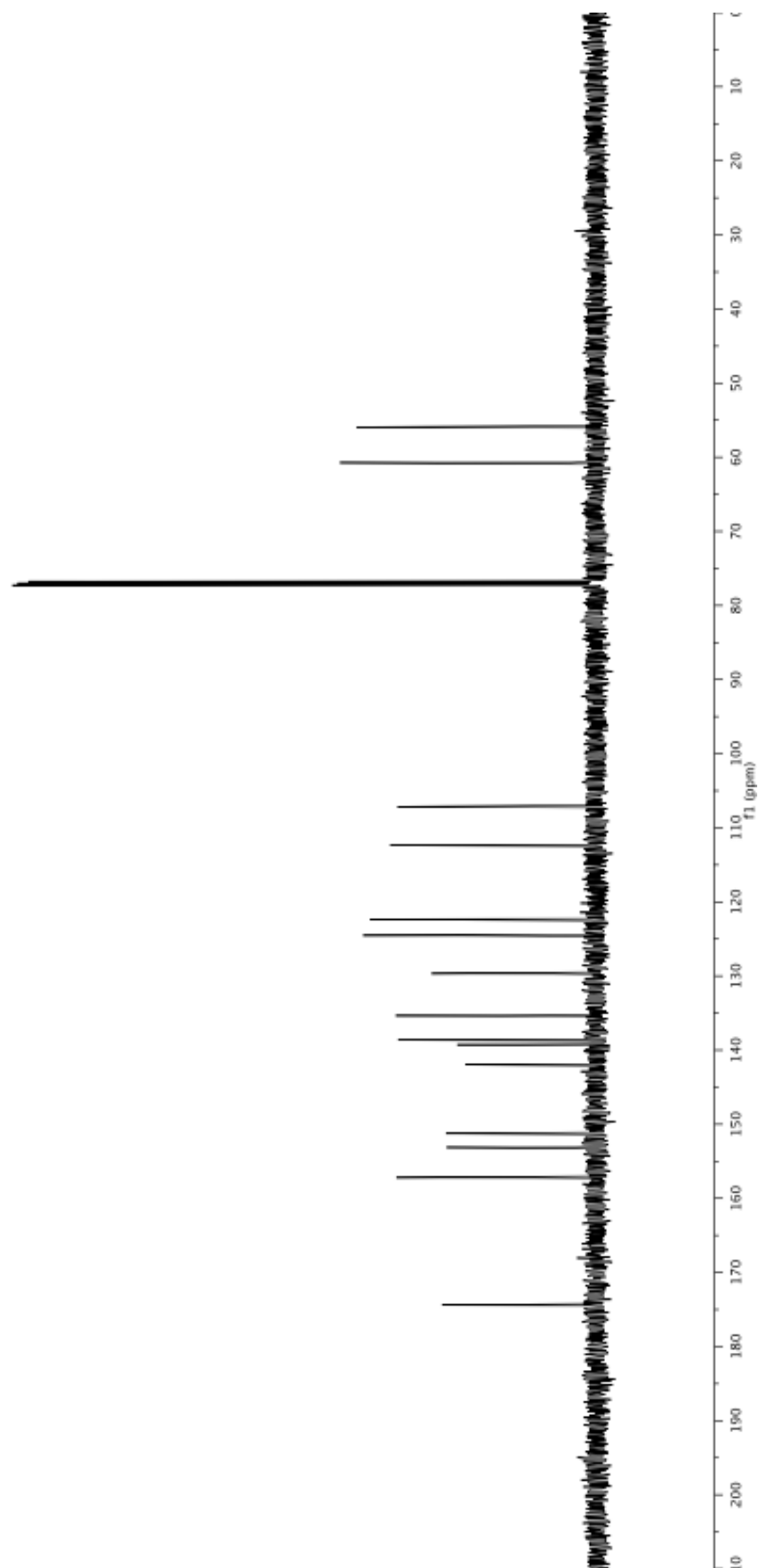
7.4201
 7.4011
 7.1137
 7.0937
 7.0736
 6.9169
 6.9000
 6.8778
 6.8578
 6.7247
 6.7075
 6.6847
 6.2793

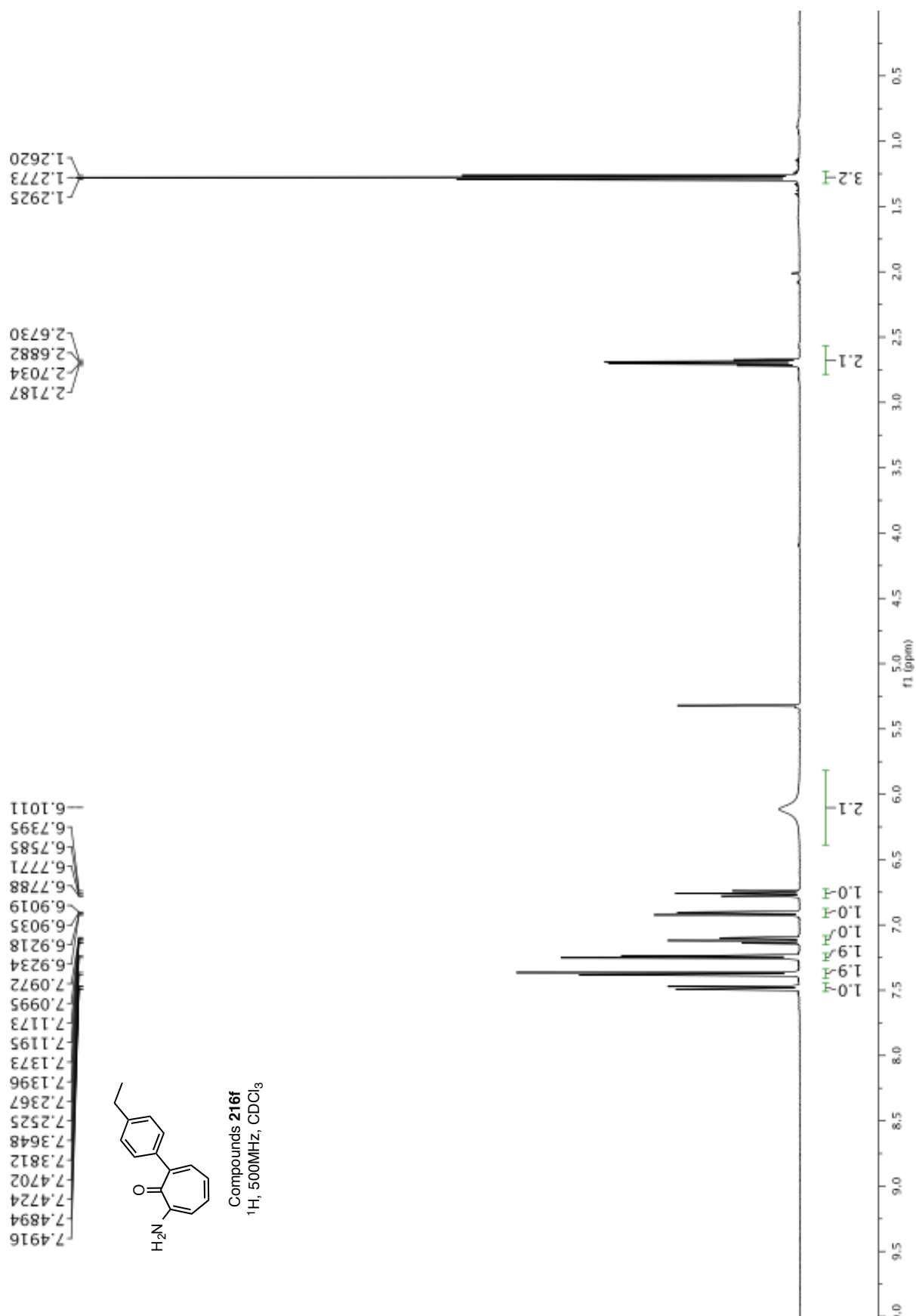


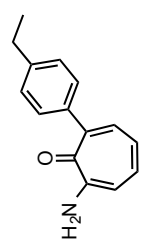


Compounds **216e**
 ^{13}C , 125MHz, CDCl_3

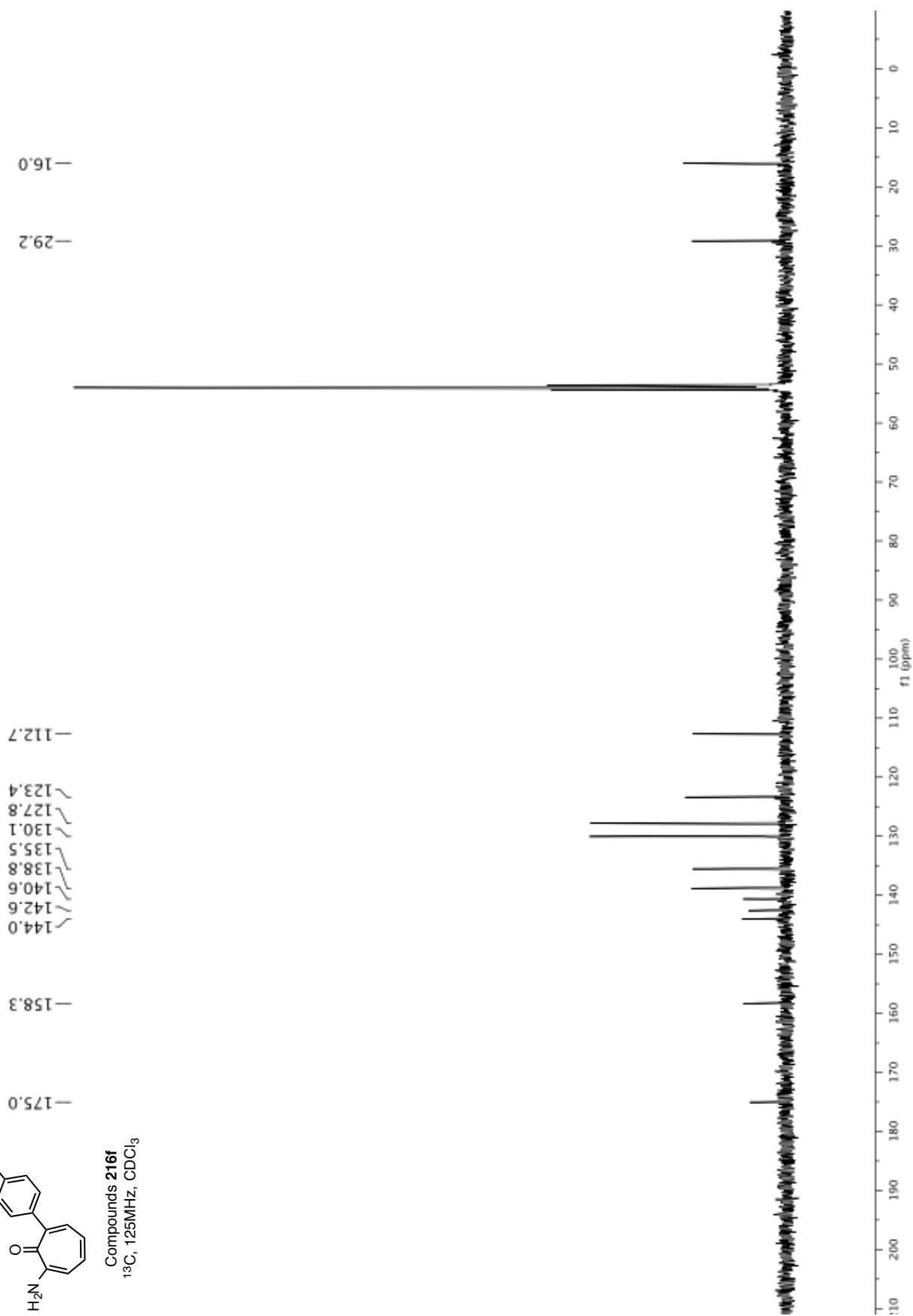
— 174.4
 — 157.2
 — 153.1
 — 151.3
 — 142.0
 — 139.3
 — 138.6
 — 135.4
 — 129.7
 — 124.5
 — 122.3
 — 112.4
 — 107.1
 — 60.8
 — 60.7
 — 55.9

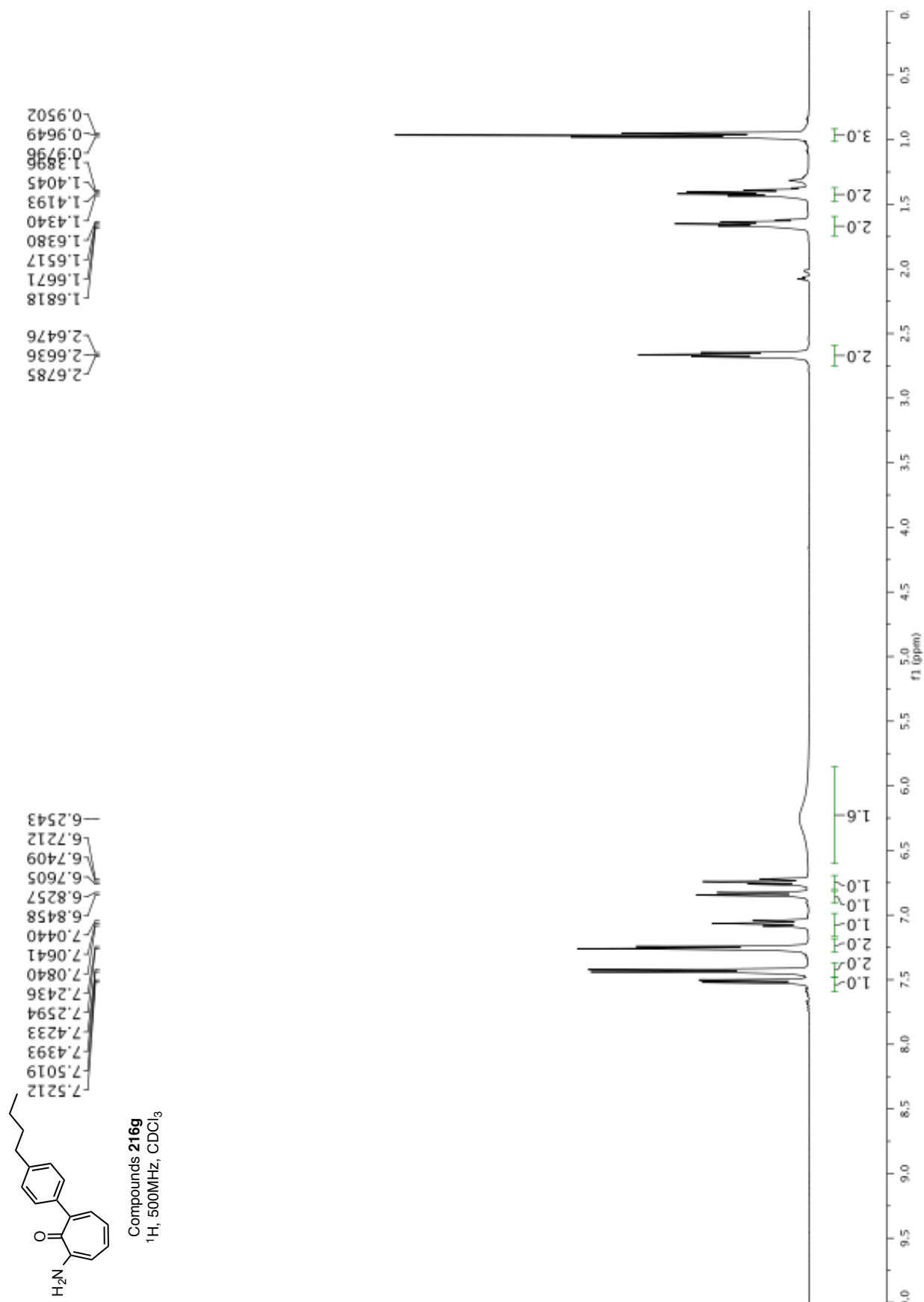


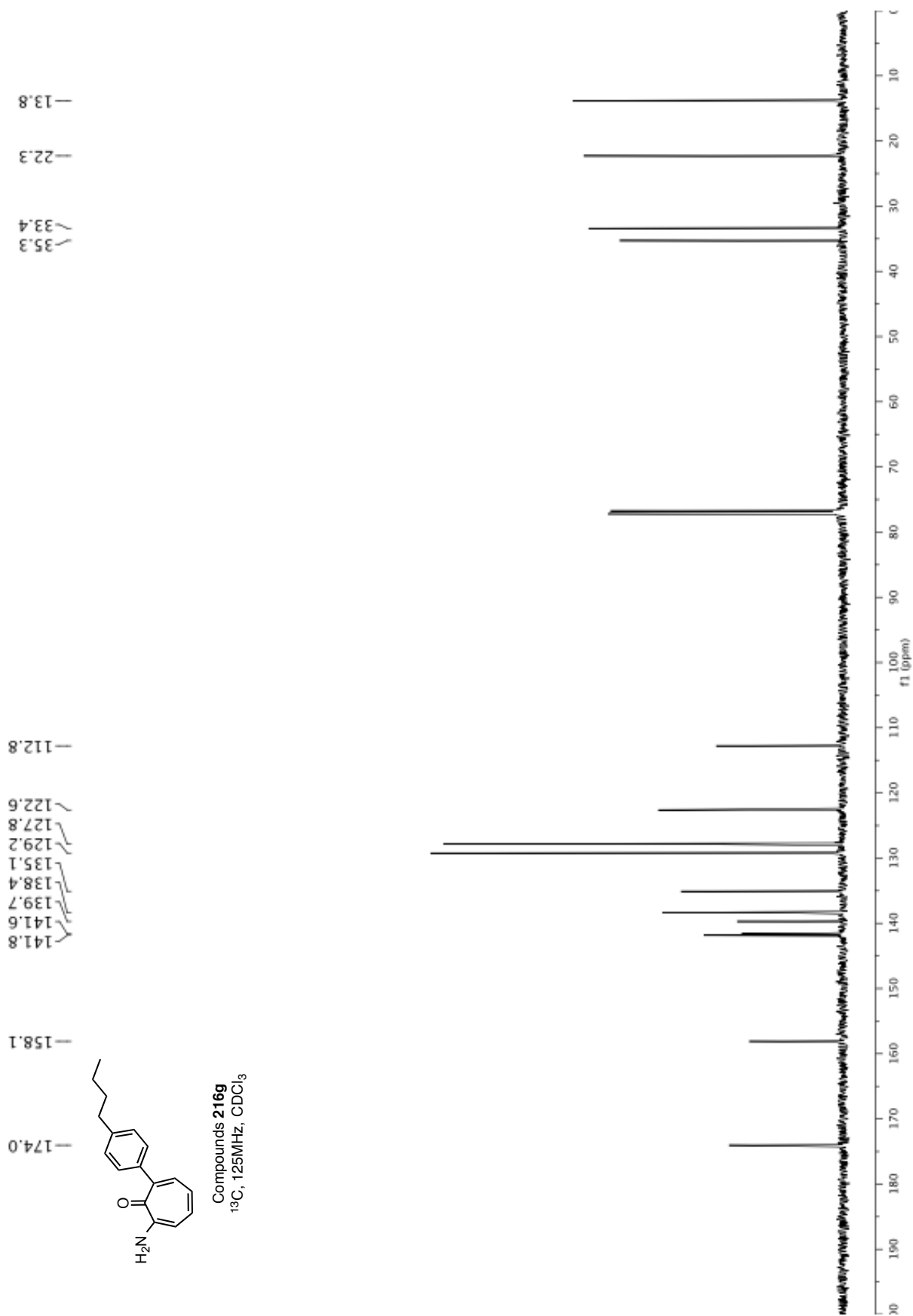


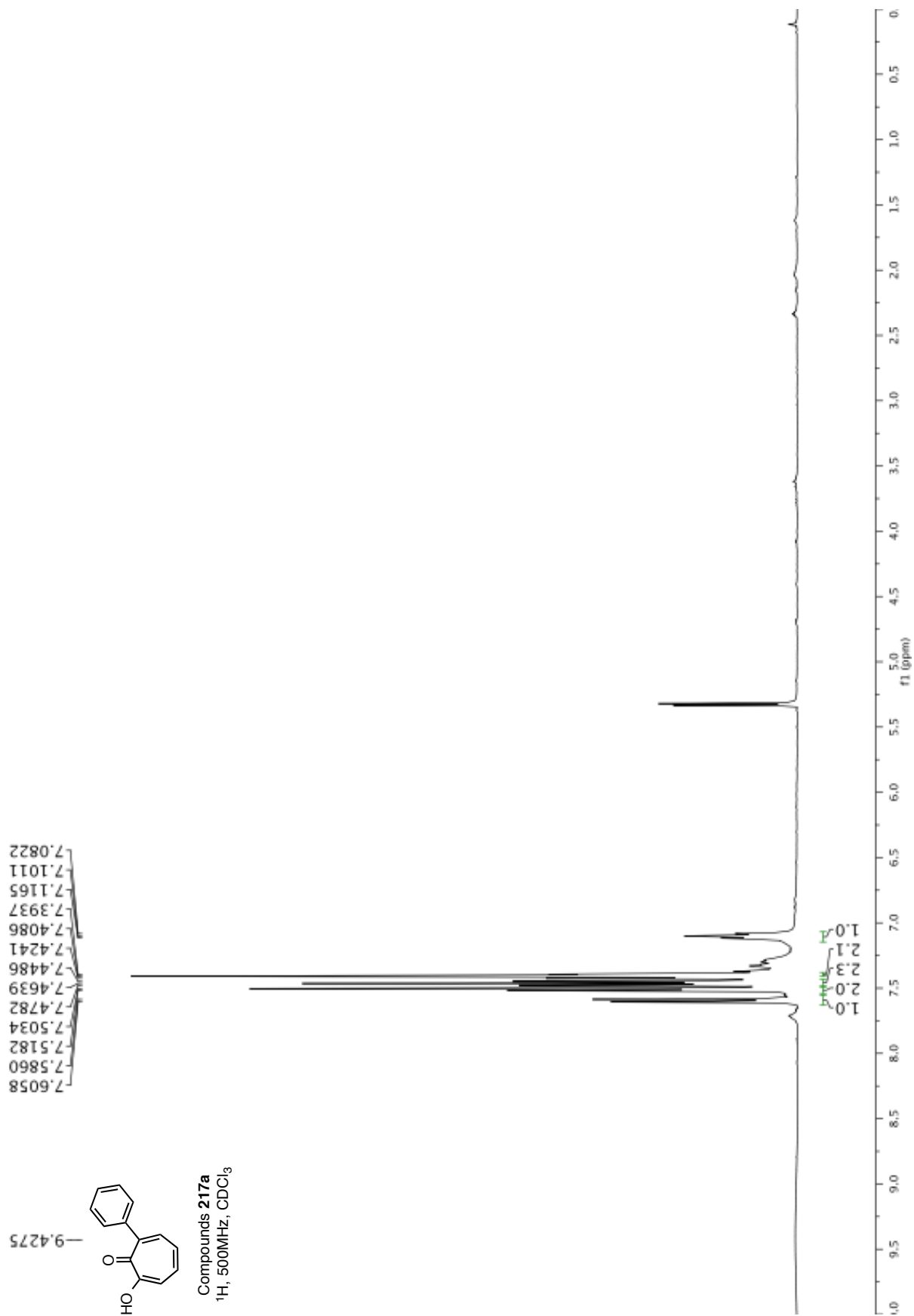


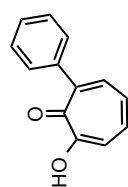
Compound **216f**
 ^{13}C , 125MHz, CDCl_3







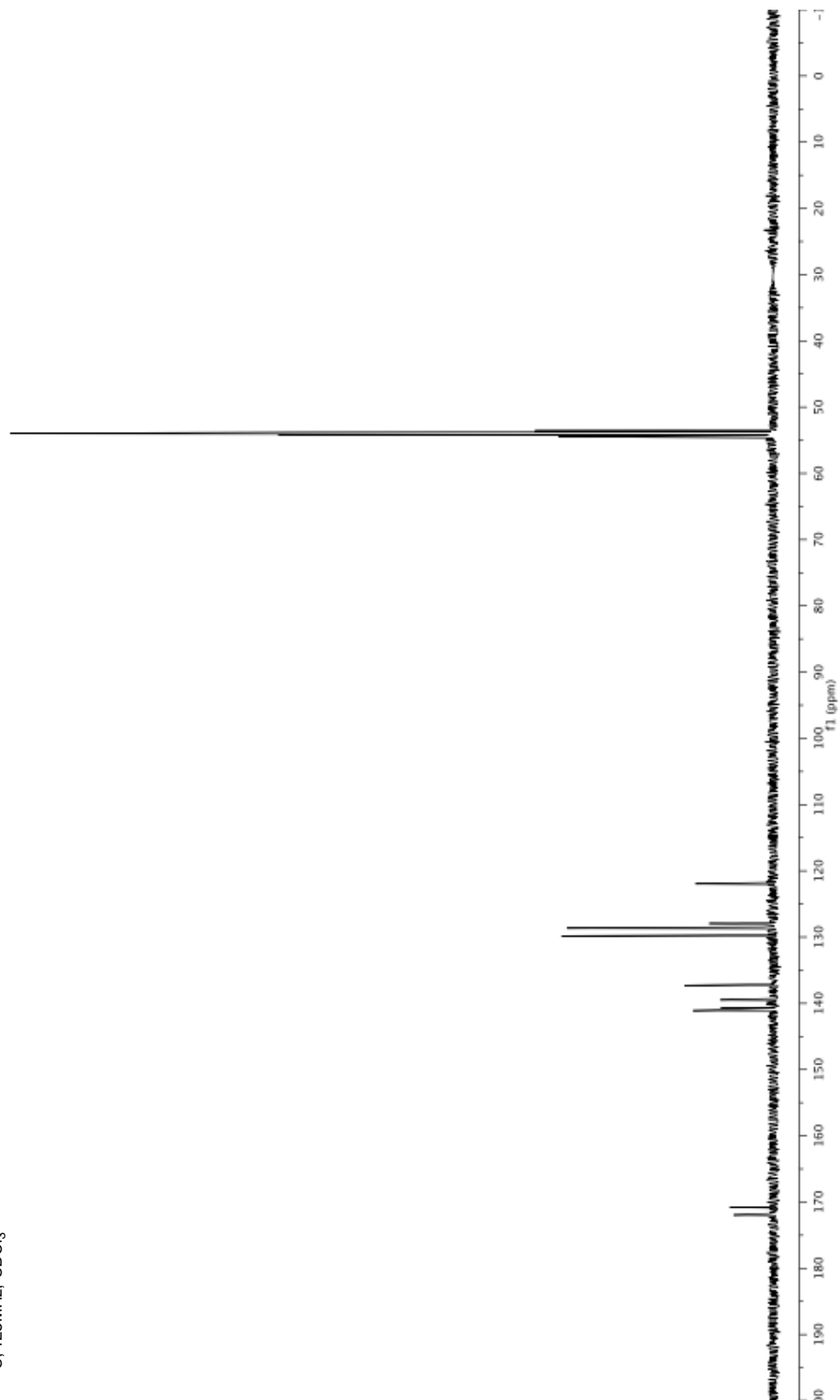


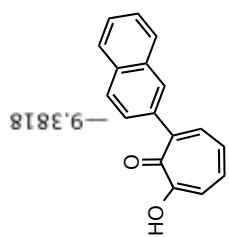


171.9
170.8

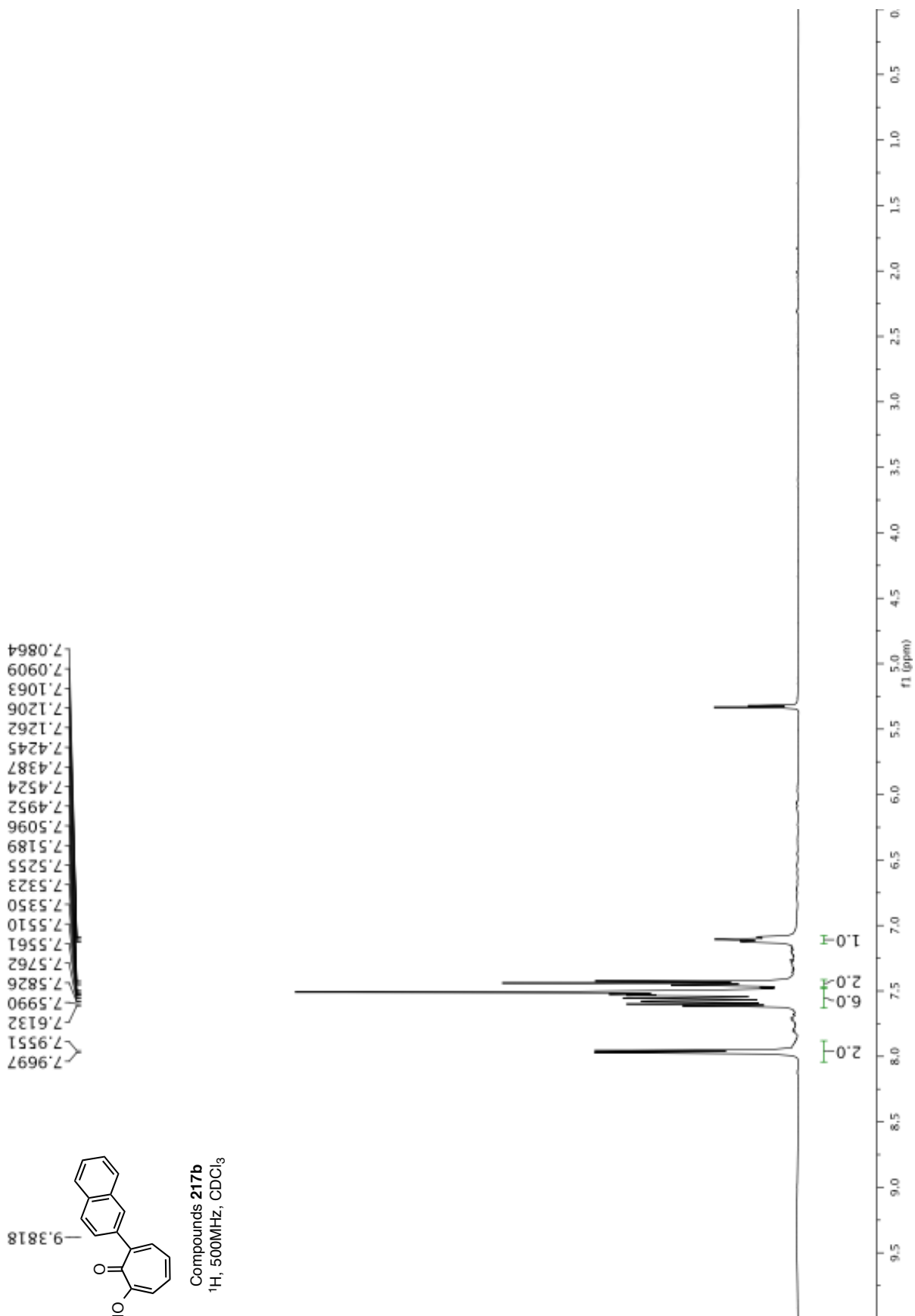
141.1
140.7
139.5
137.3
129.8
128.7
128.6
127.9
122.0

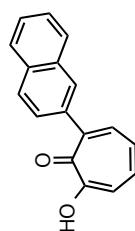
Compounds **217a**
 ^{13}C , 125MHz, CDCl_3





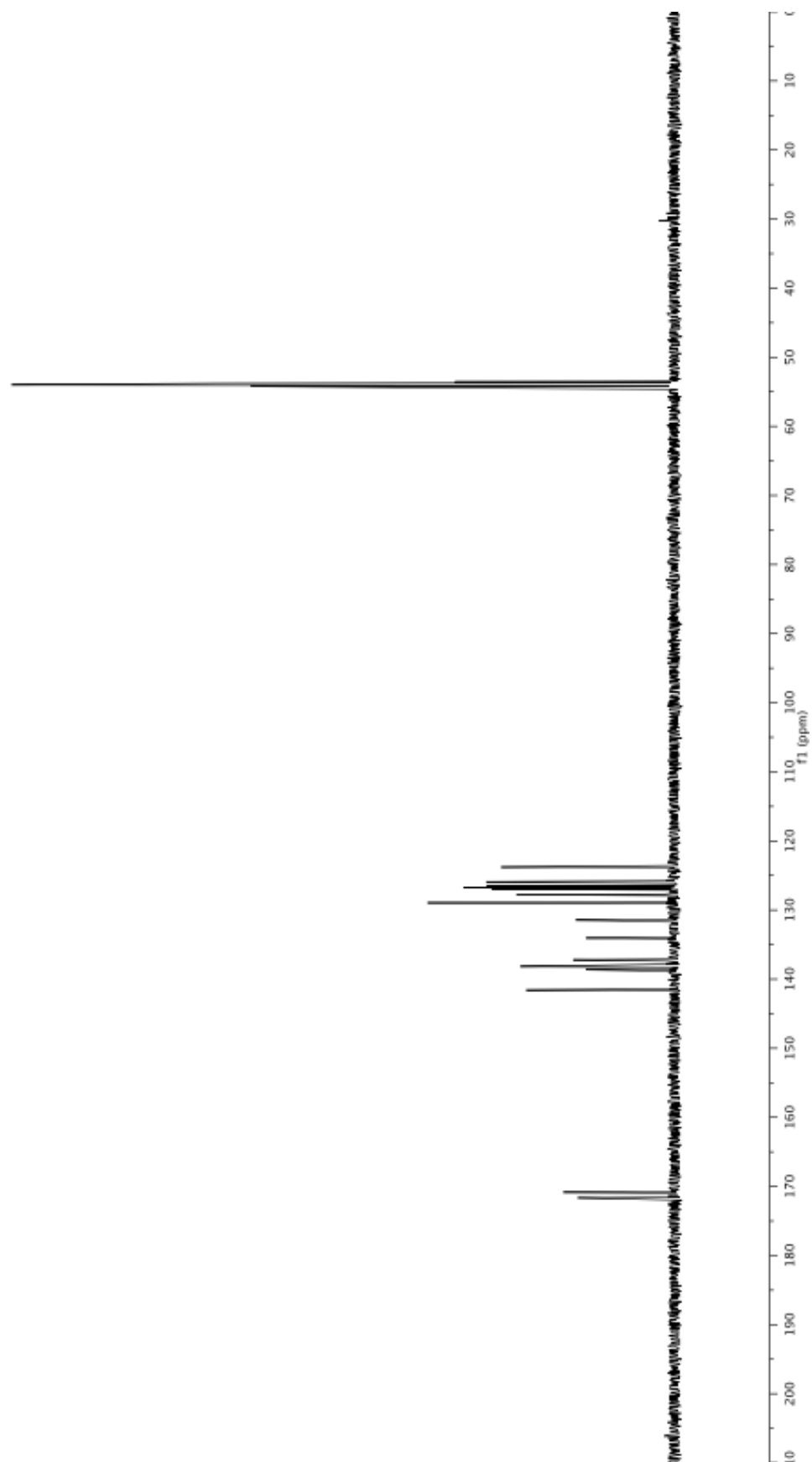
Compound **217b**
 ^1H , 500MHz, CDCl_3

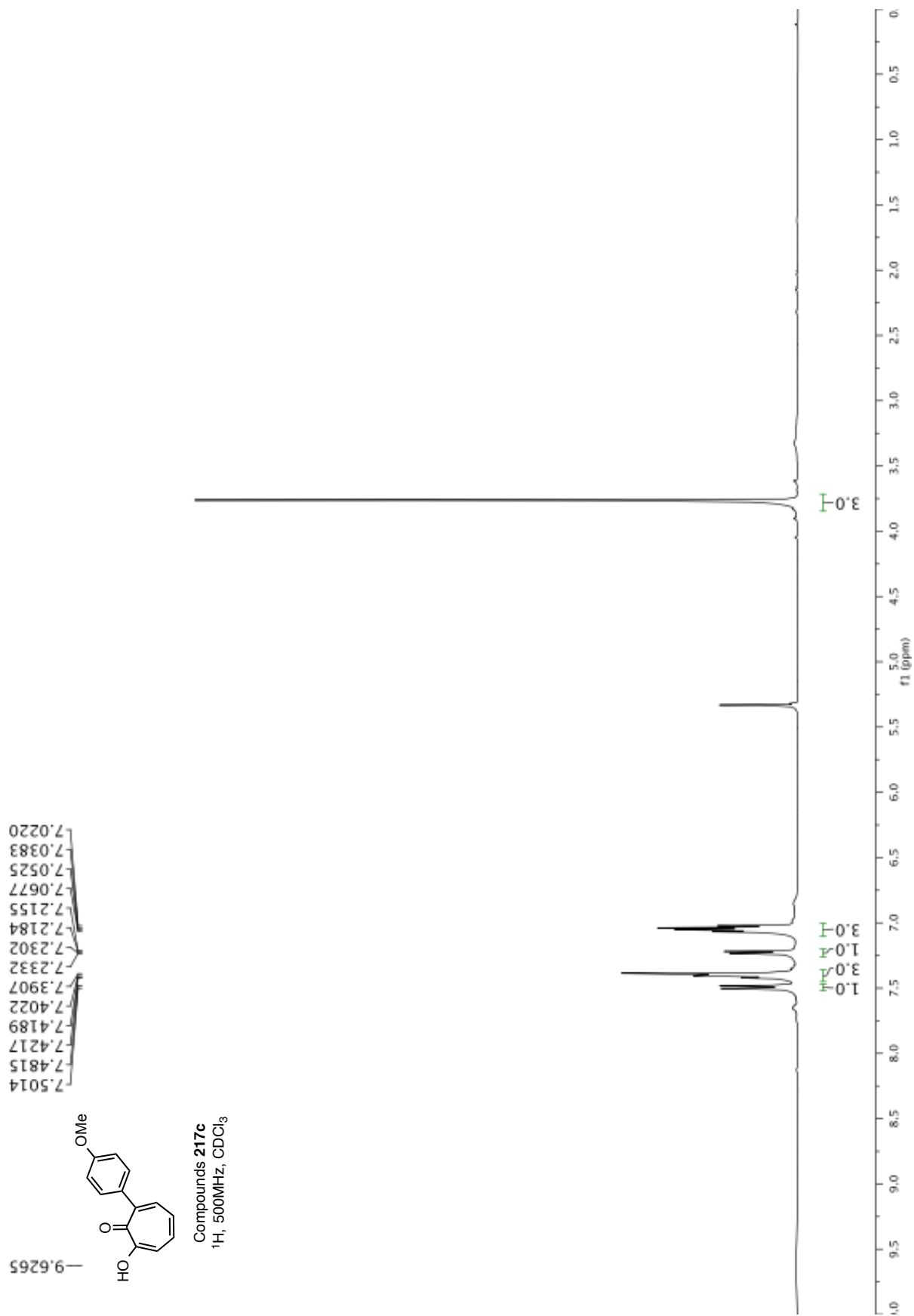


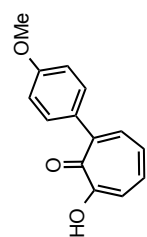


Compounds **217b**
 ^{13}C , 125MHz, CDCl_3

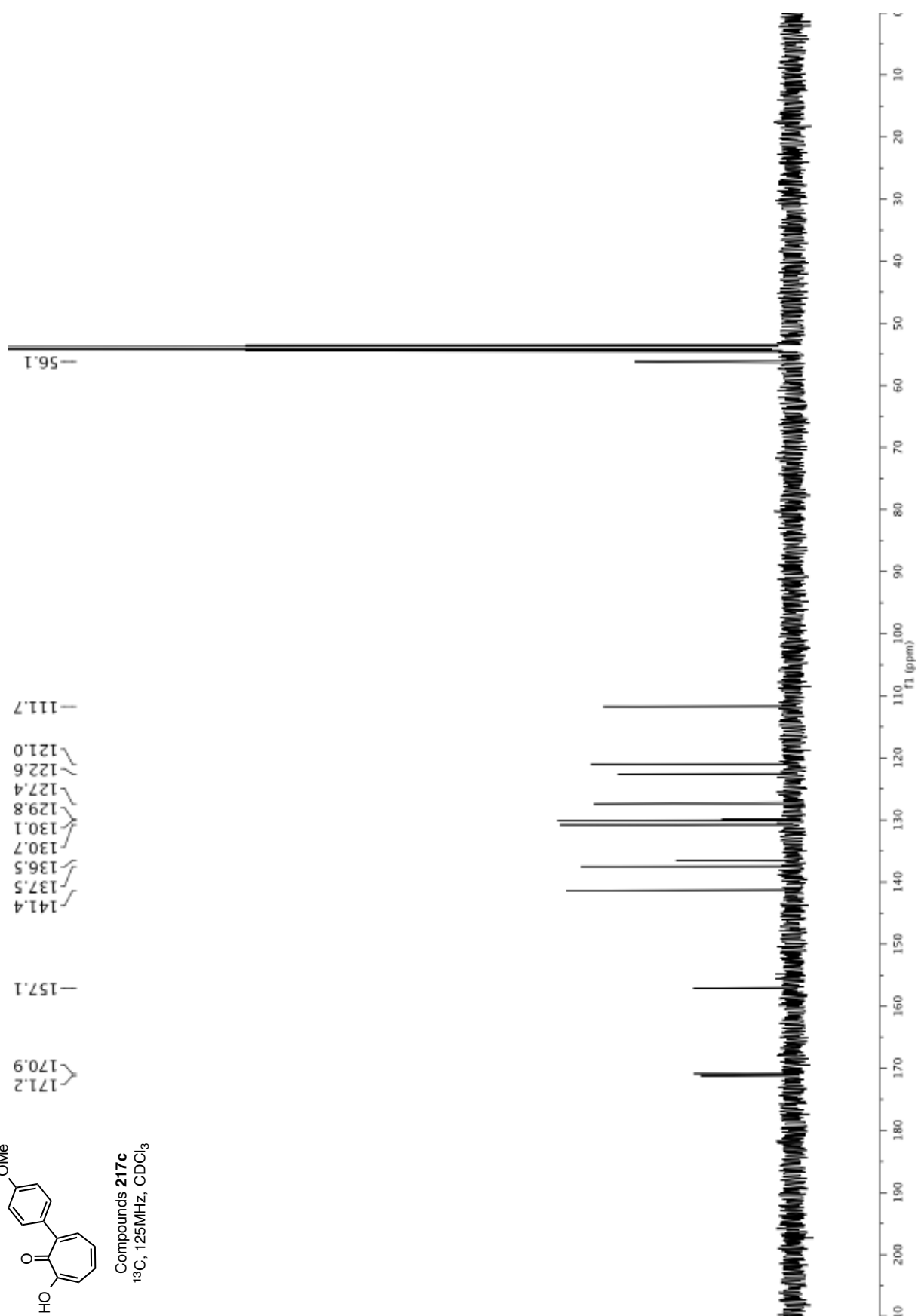
171.6
 170.8
 141.6
 138.6
 138.2
 137.2
 134.1
 131.5
 129.0
 128.9
 127.8
 127.0
 126.7
 126.5
 126.0
 125.9
 123.8

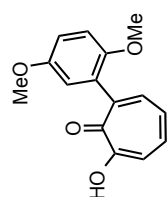




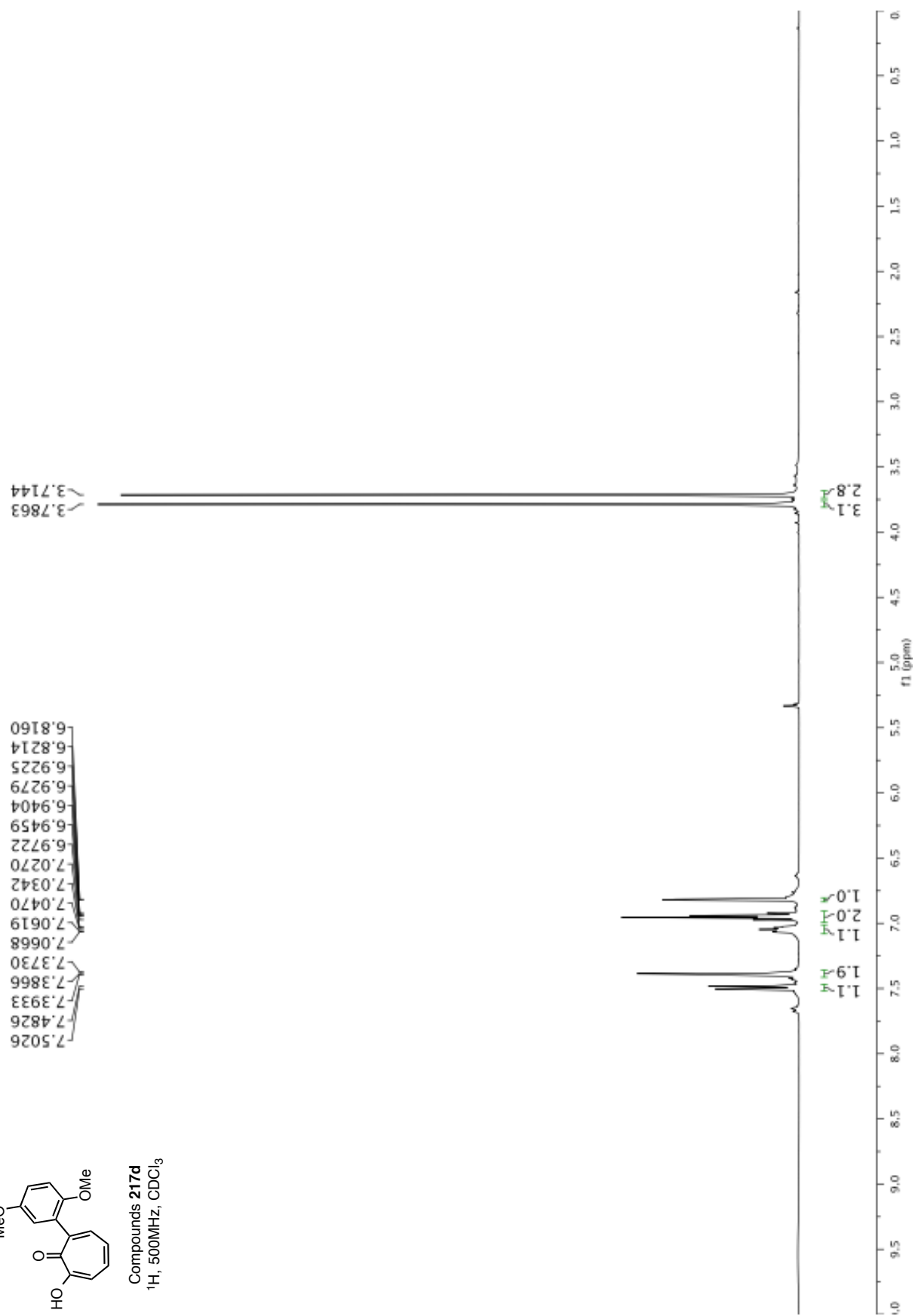


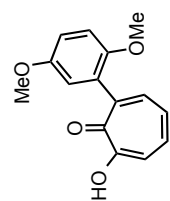
Compounds **217c**
 ^{13}C , 125MHz, CDCl_3





Compounds **217d**
¹H, 500MHz, CDCl₃





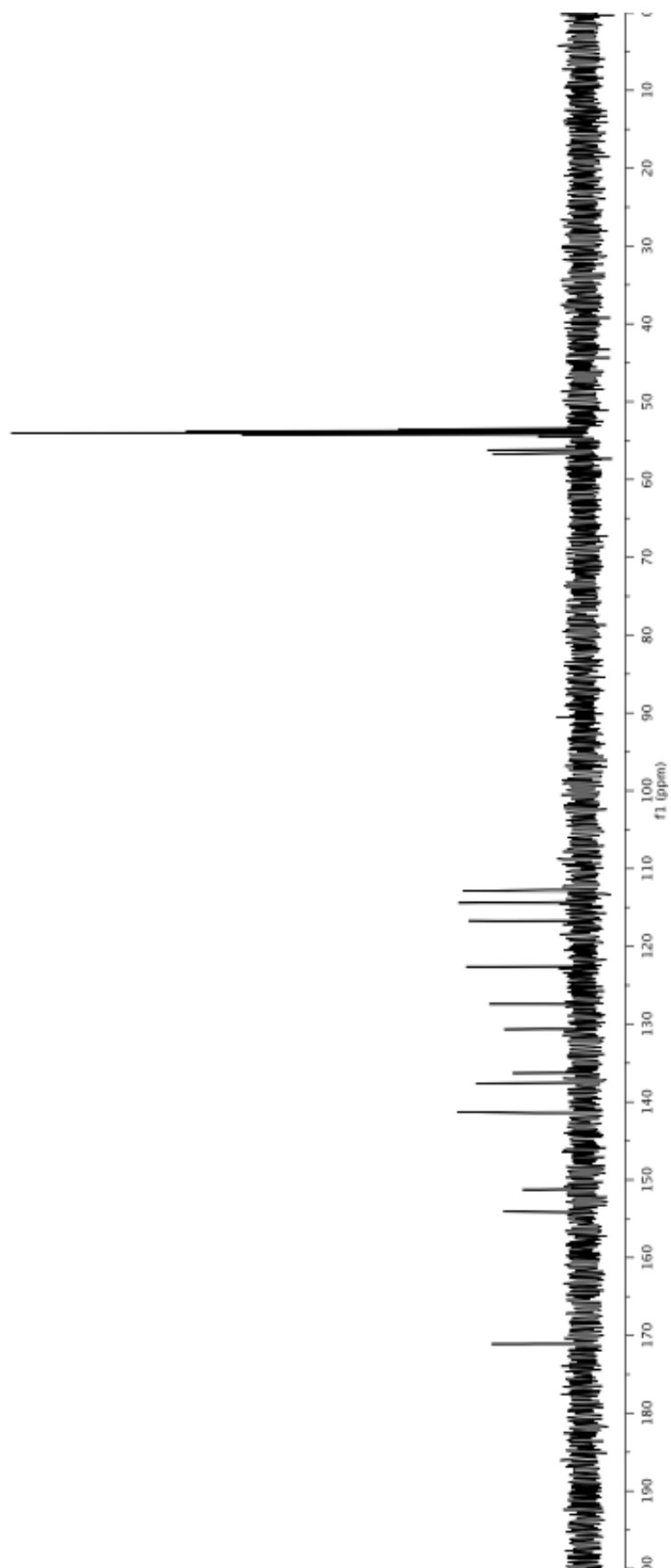
Compound **217d**
¹³C, 125MHz, CDCl₃

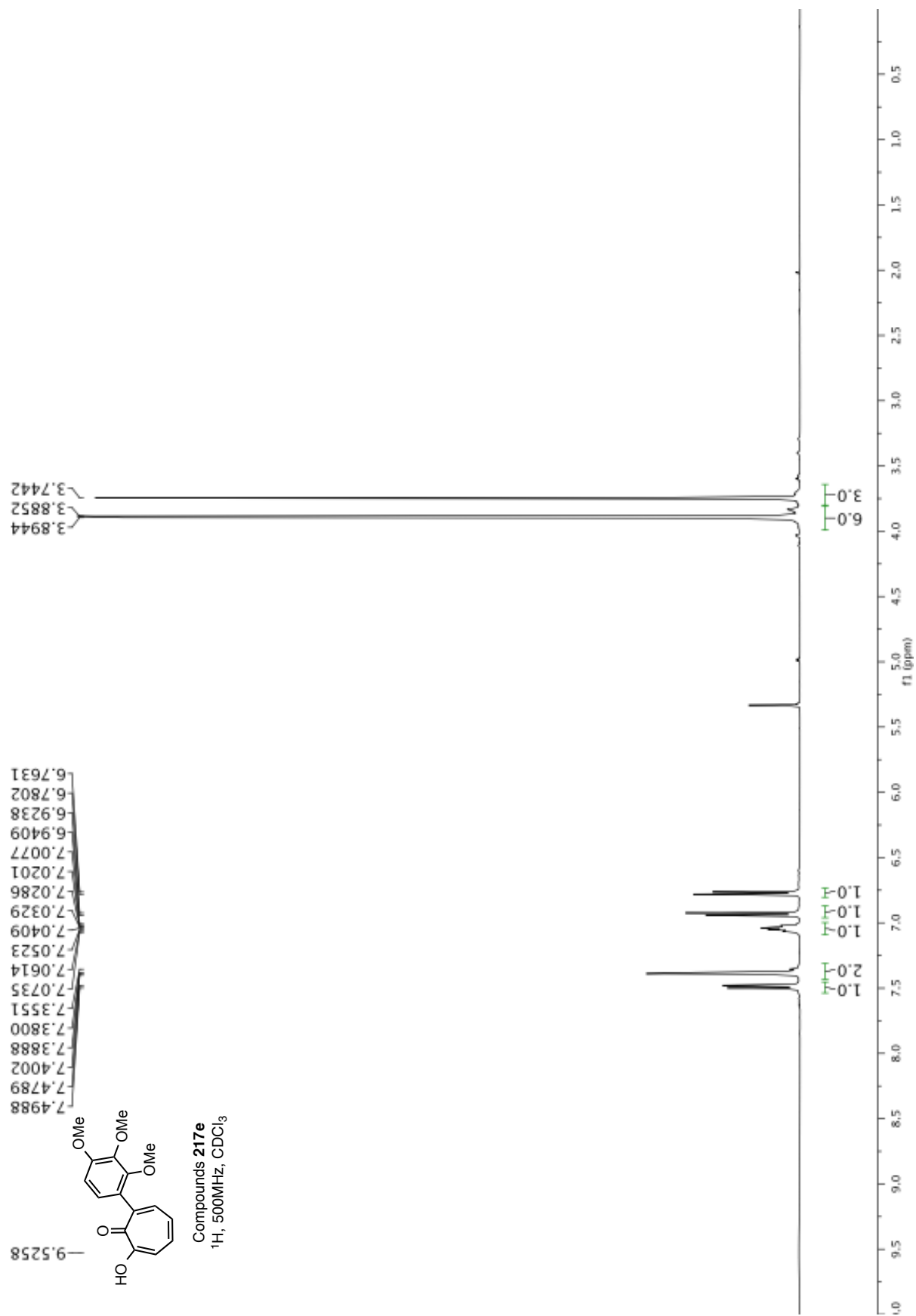
171.1
170.9

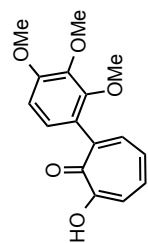
154.1
151.3

141.3
137.6
136.3
130.7
127.4
122.6
116.7
114.4
112.9

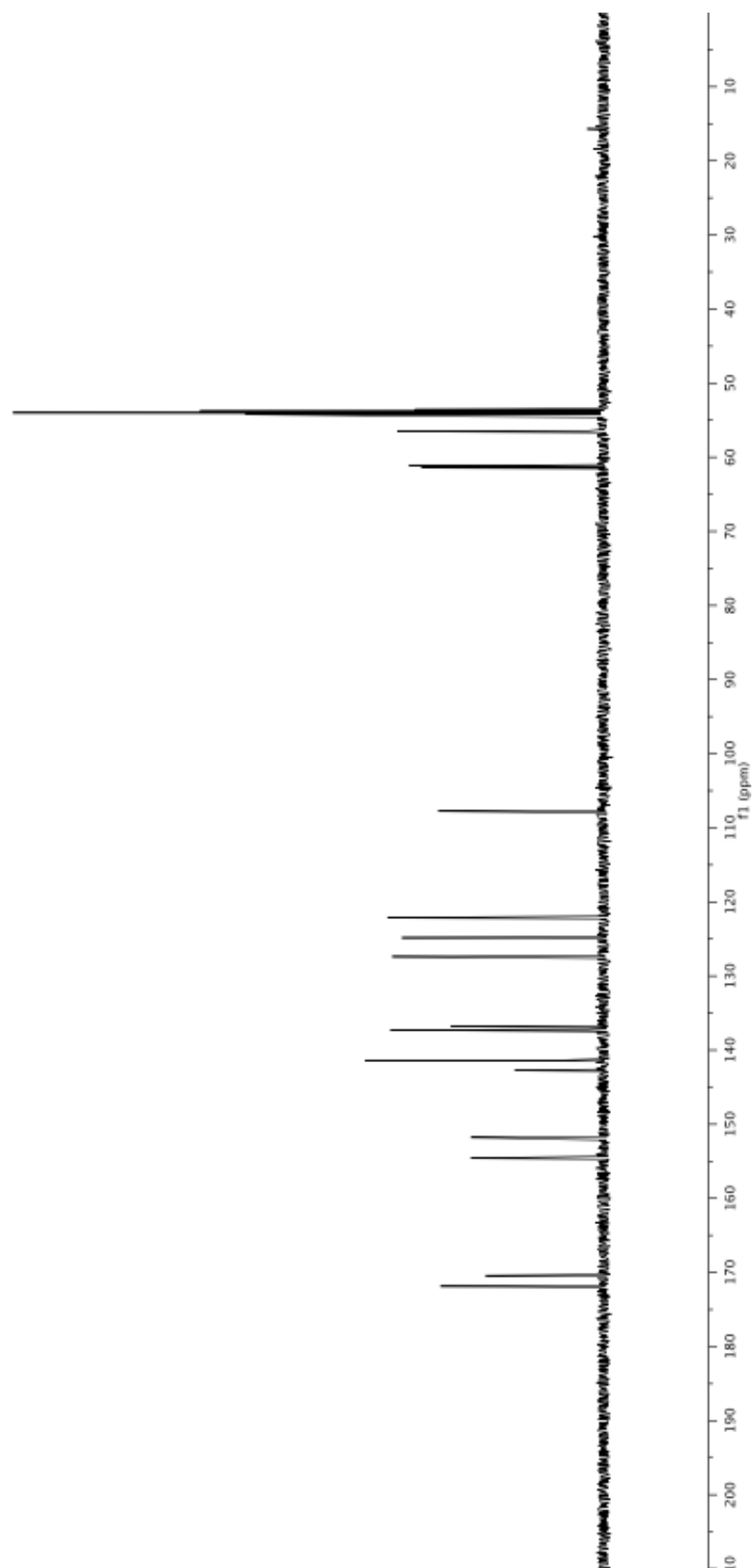
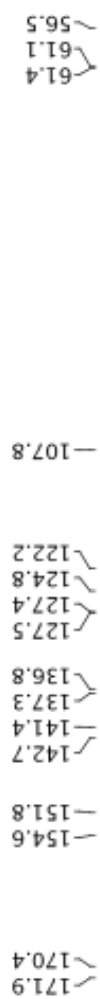
56.8
56.2

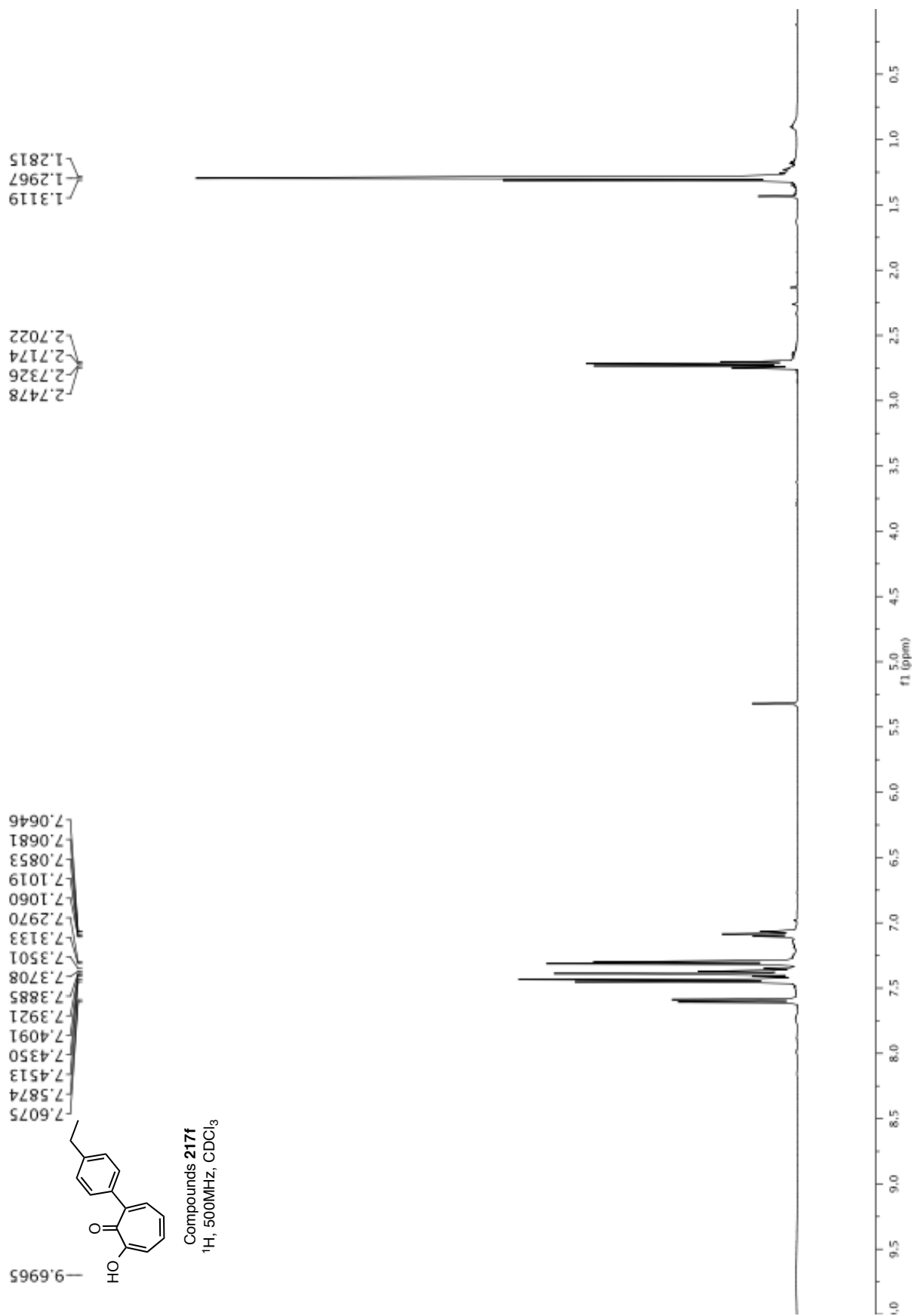


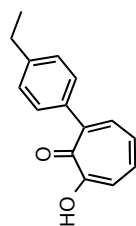




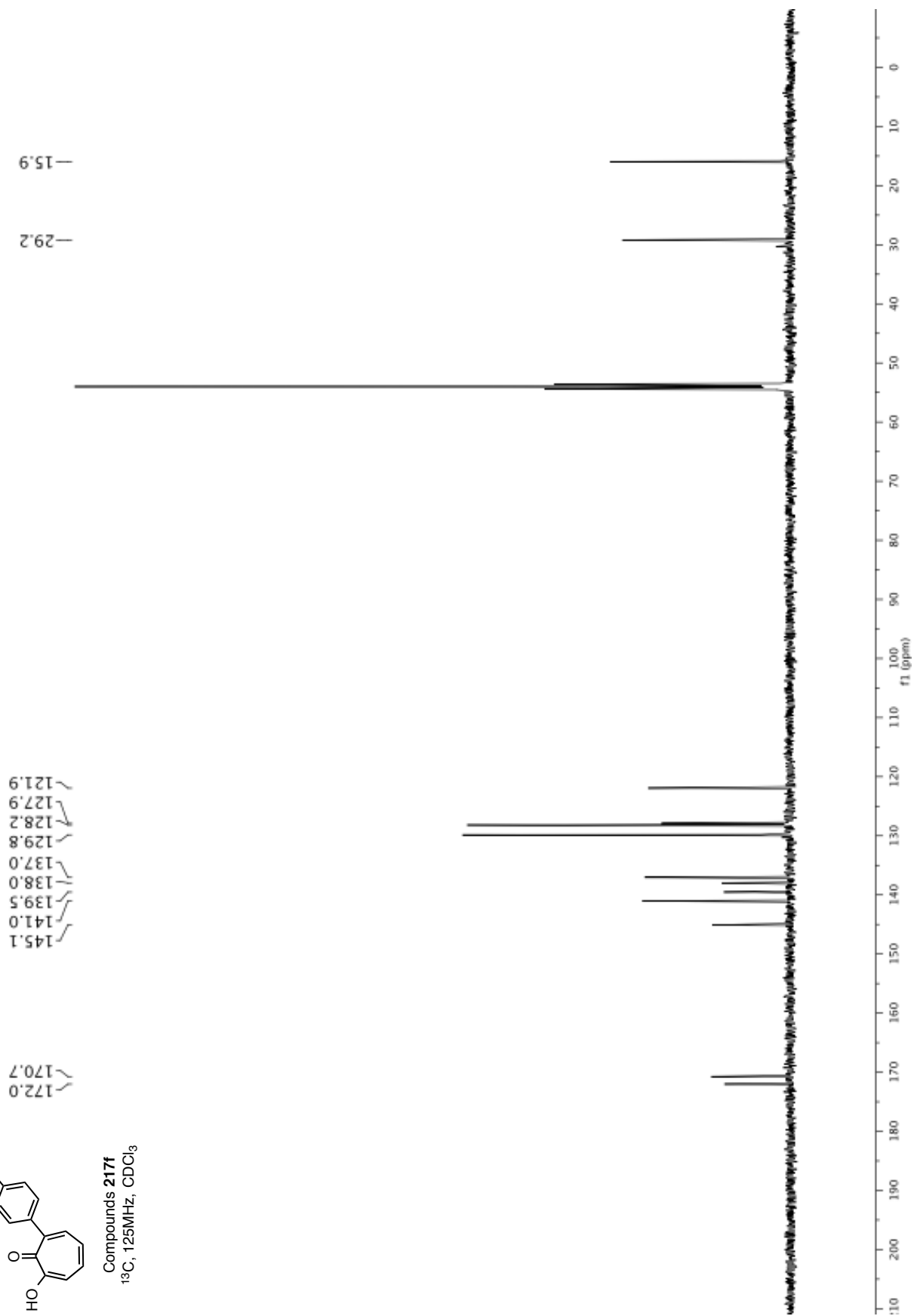
Compounds **217e**
 ^{13}C , 125MHz, CDCl_3

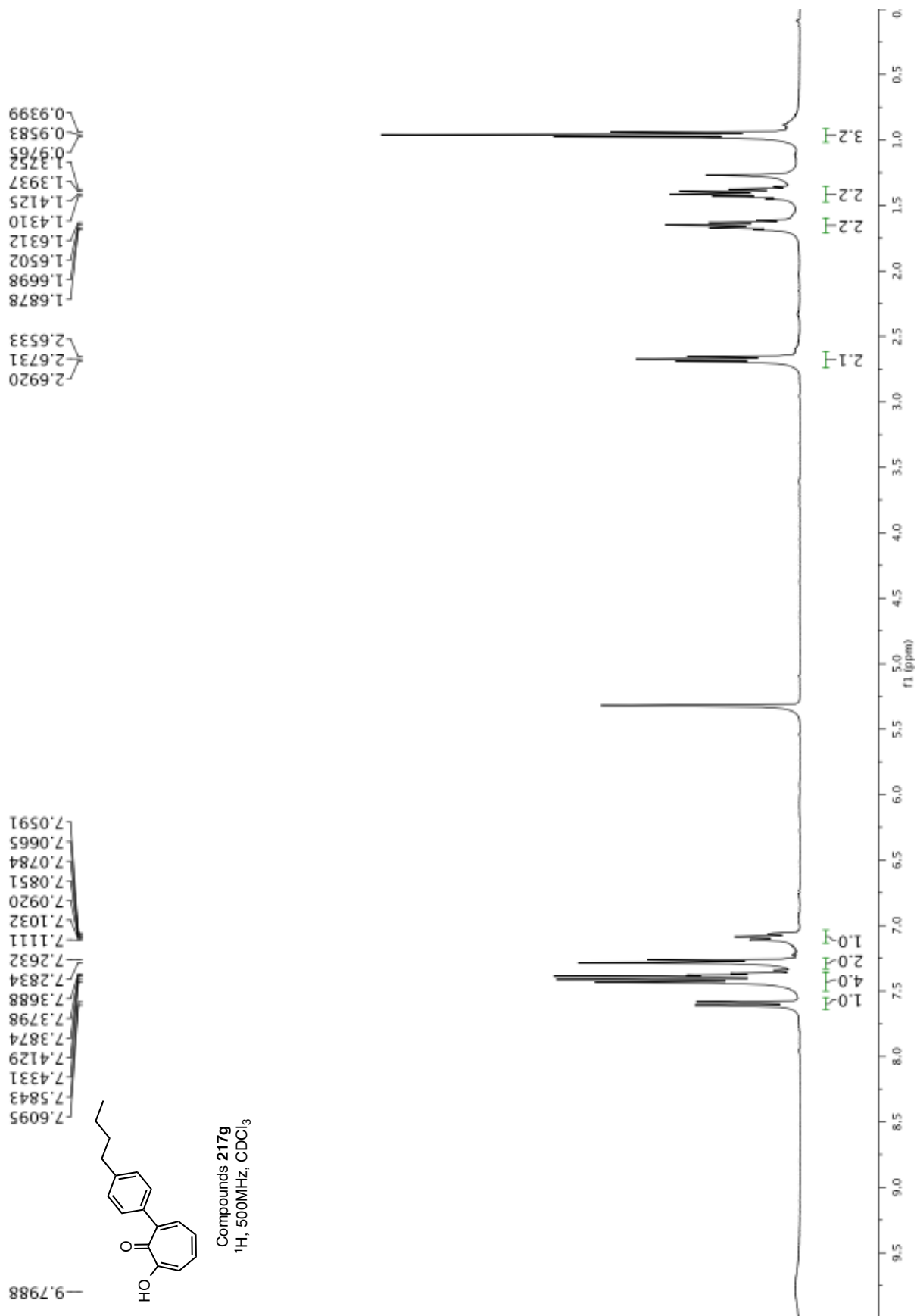


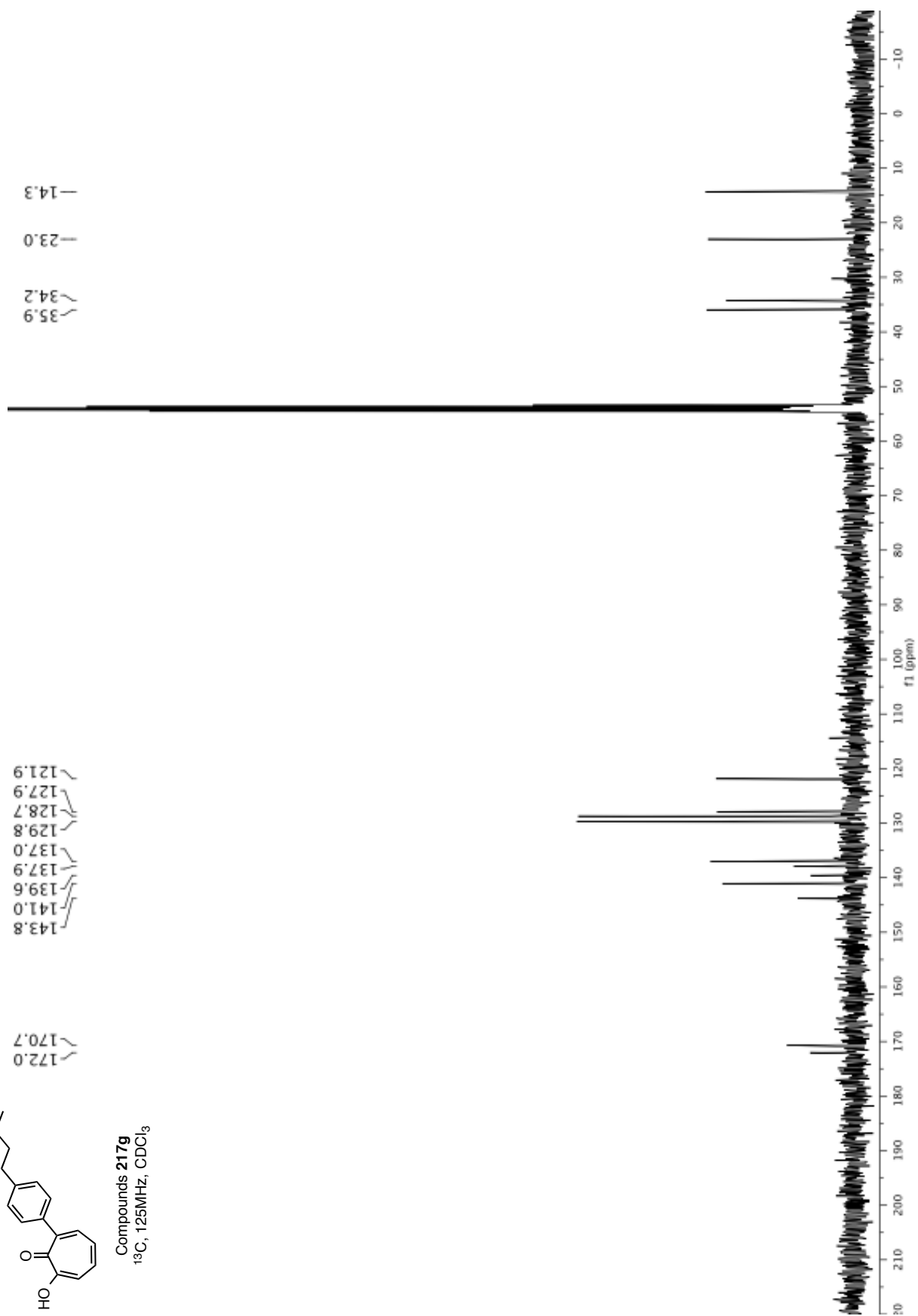


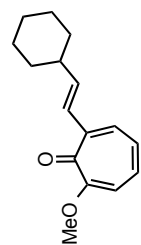


Compounds **217f**
 ^{13}C , 125MHz, CDCl_3

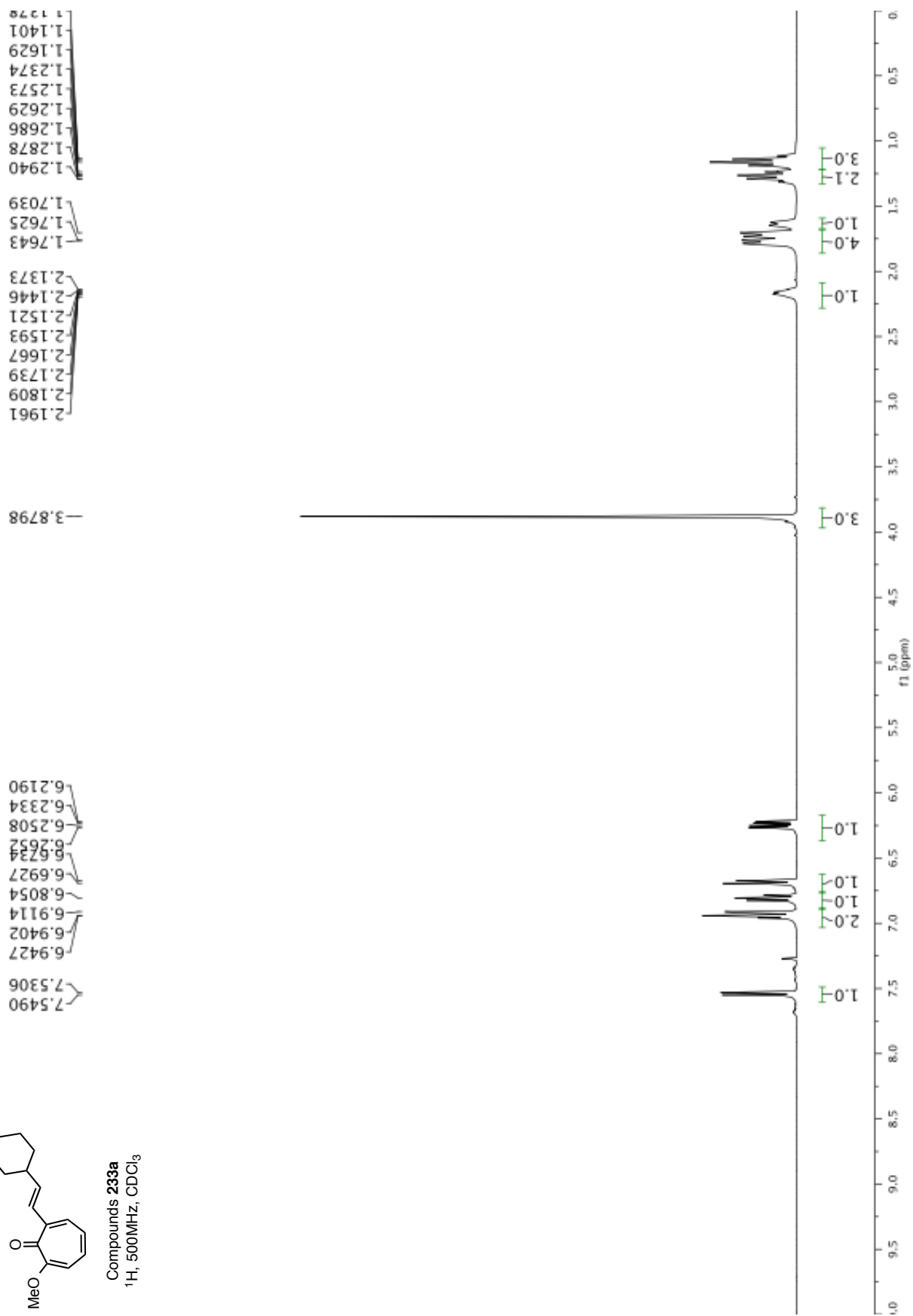


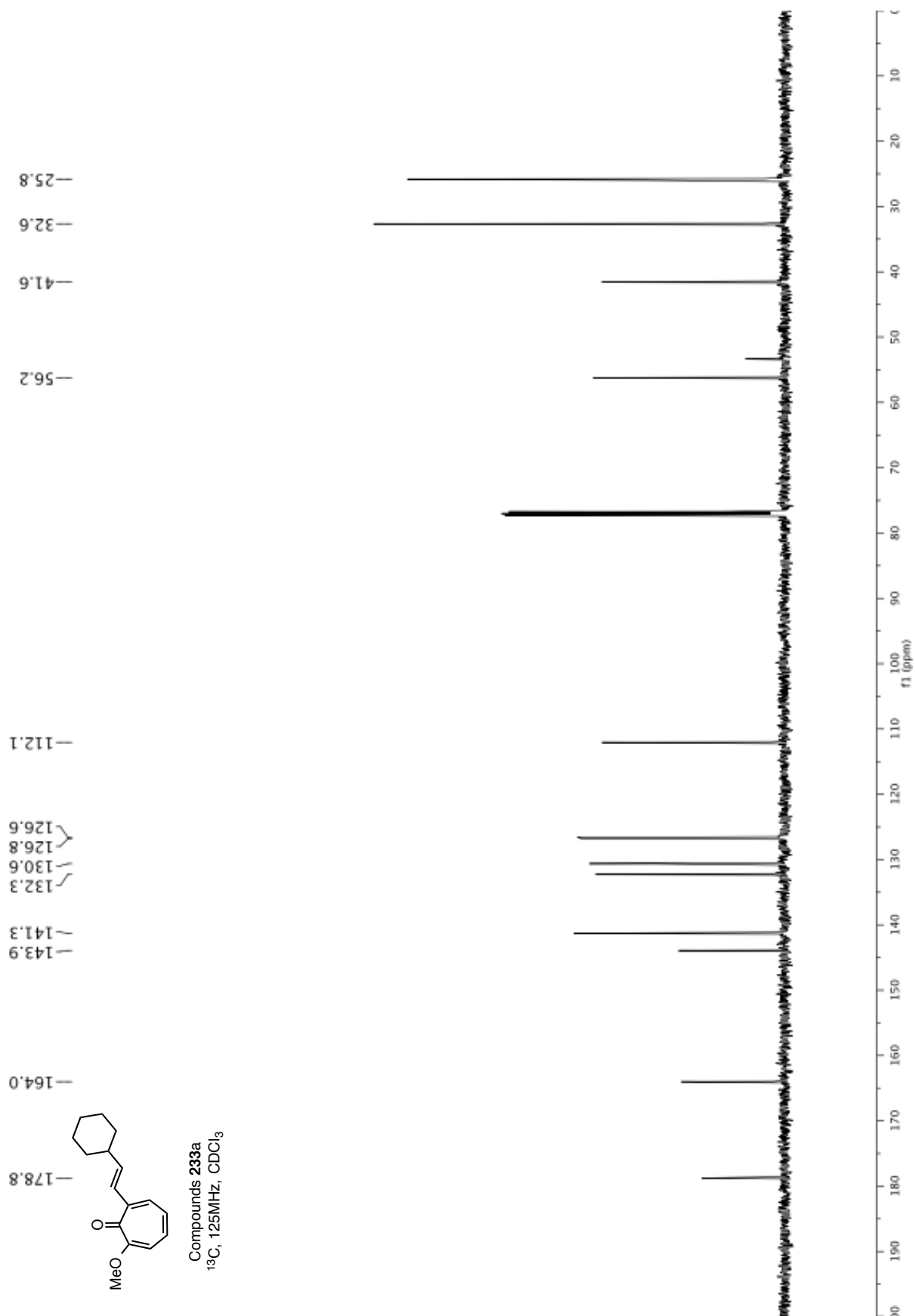


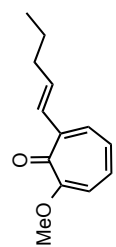




Compounds **233a**
 ^1H , 500MHz, CDCl_3

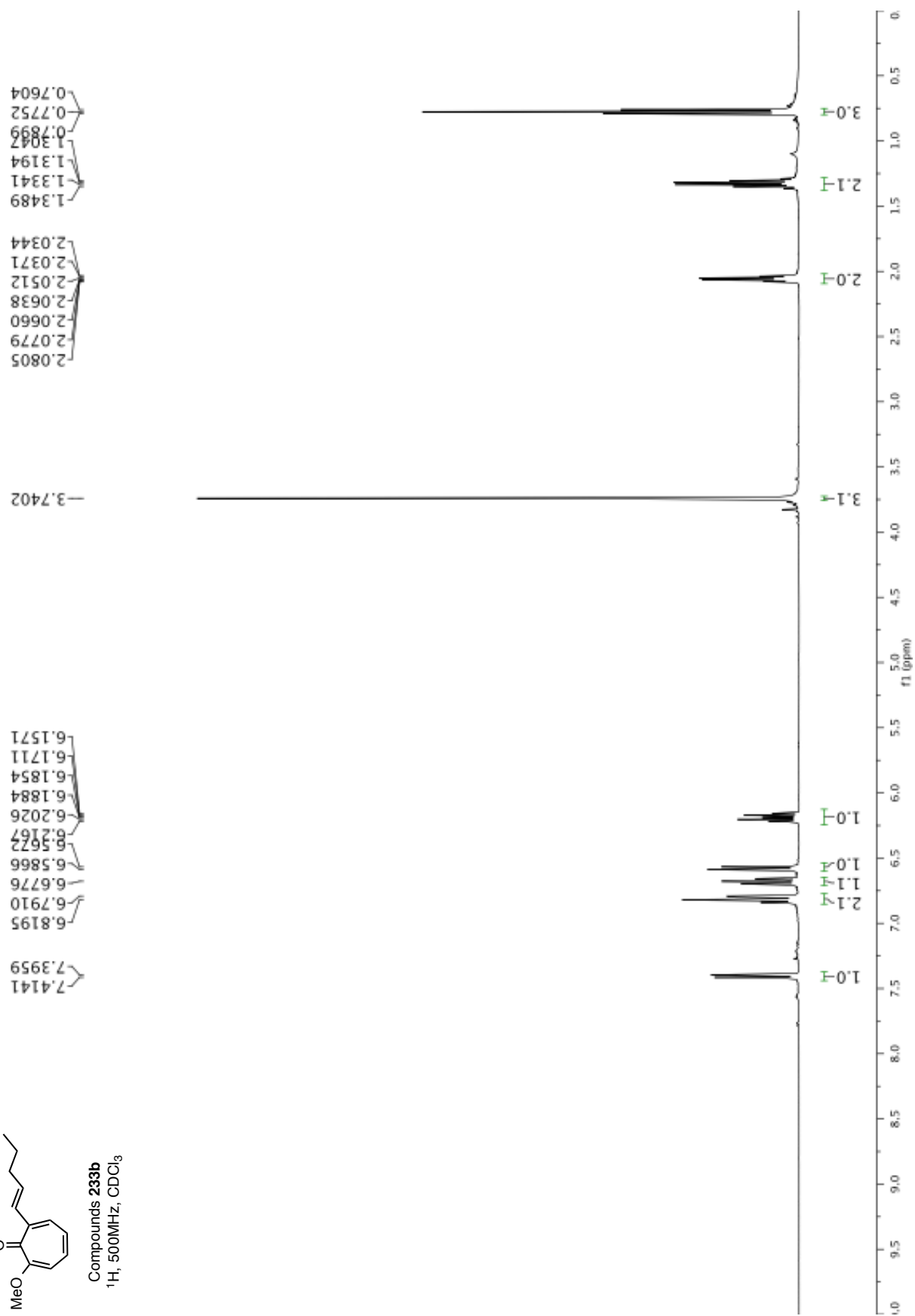


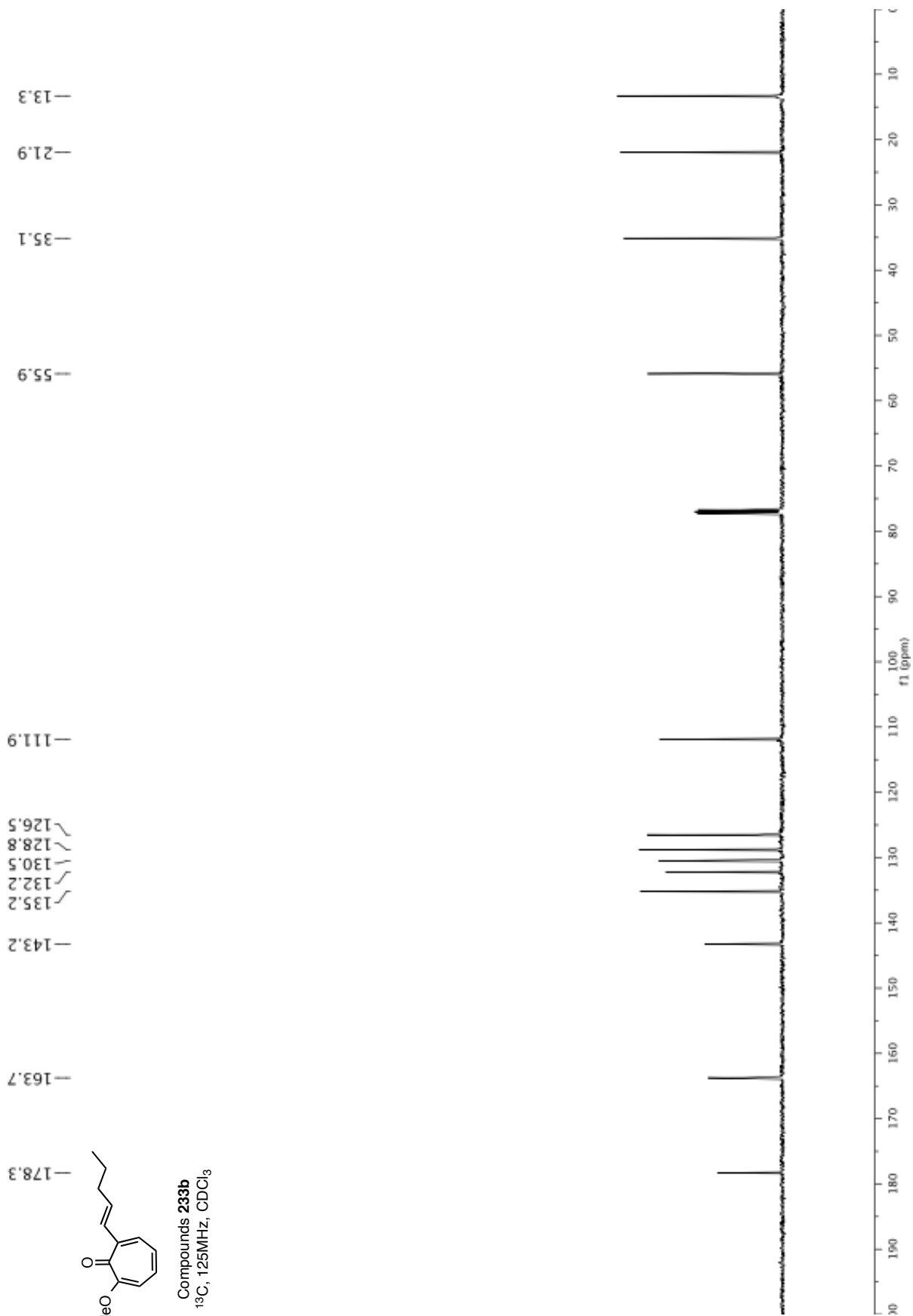


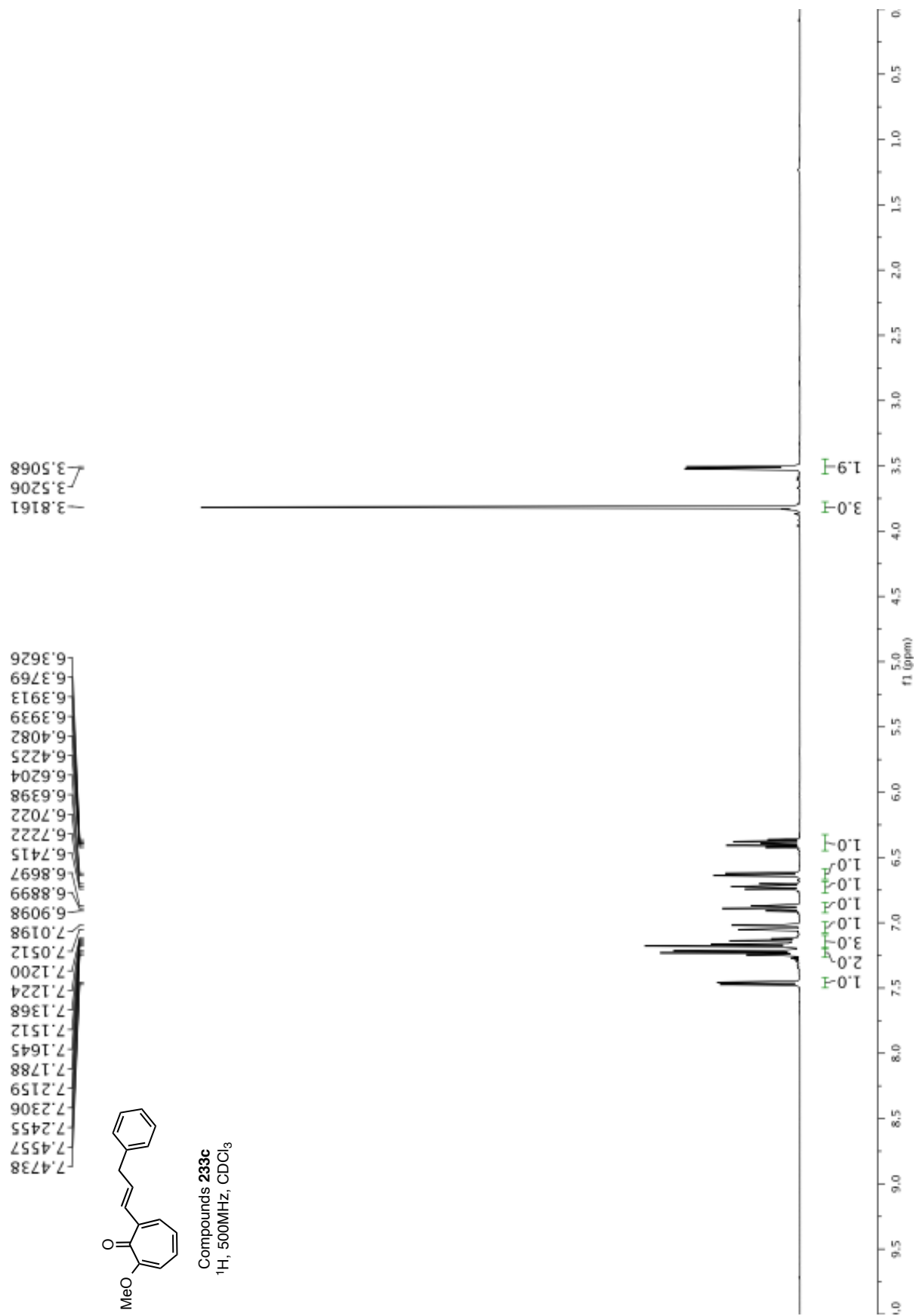


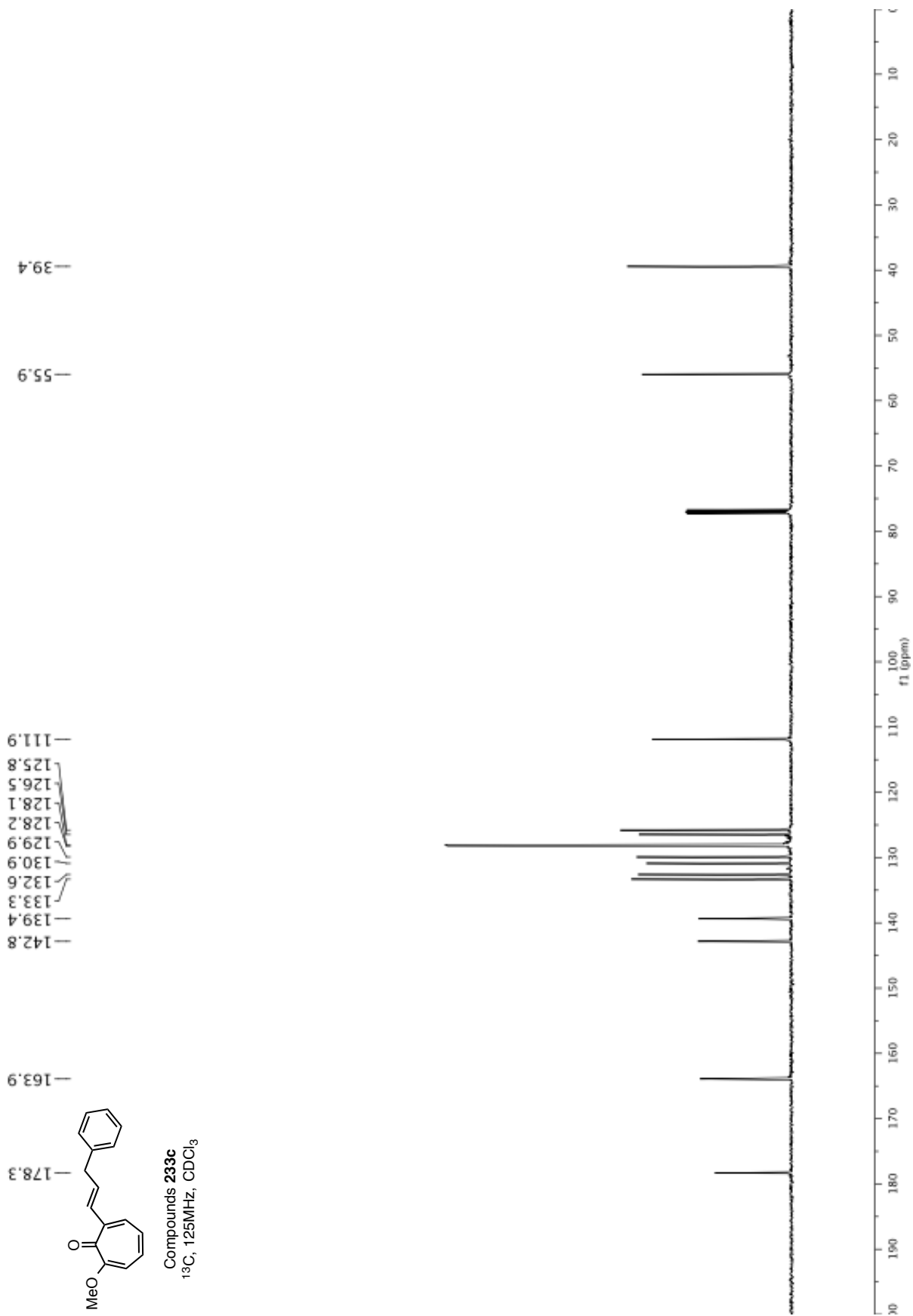
Compounds **233b**

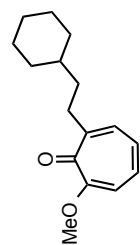
^1H , 500MHz, CDCl_3



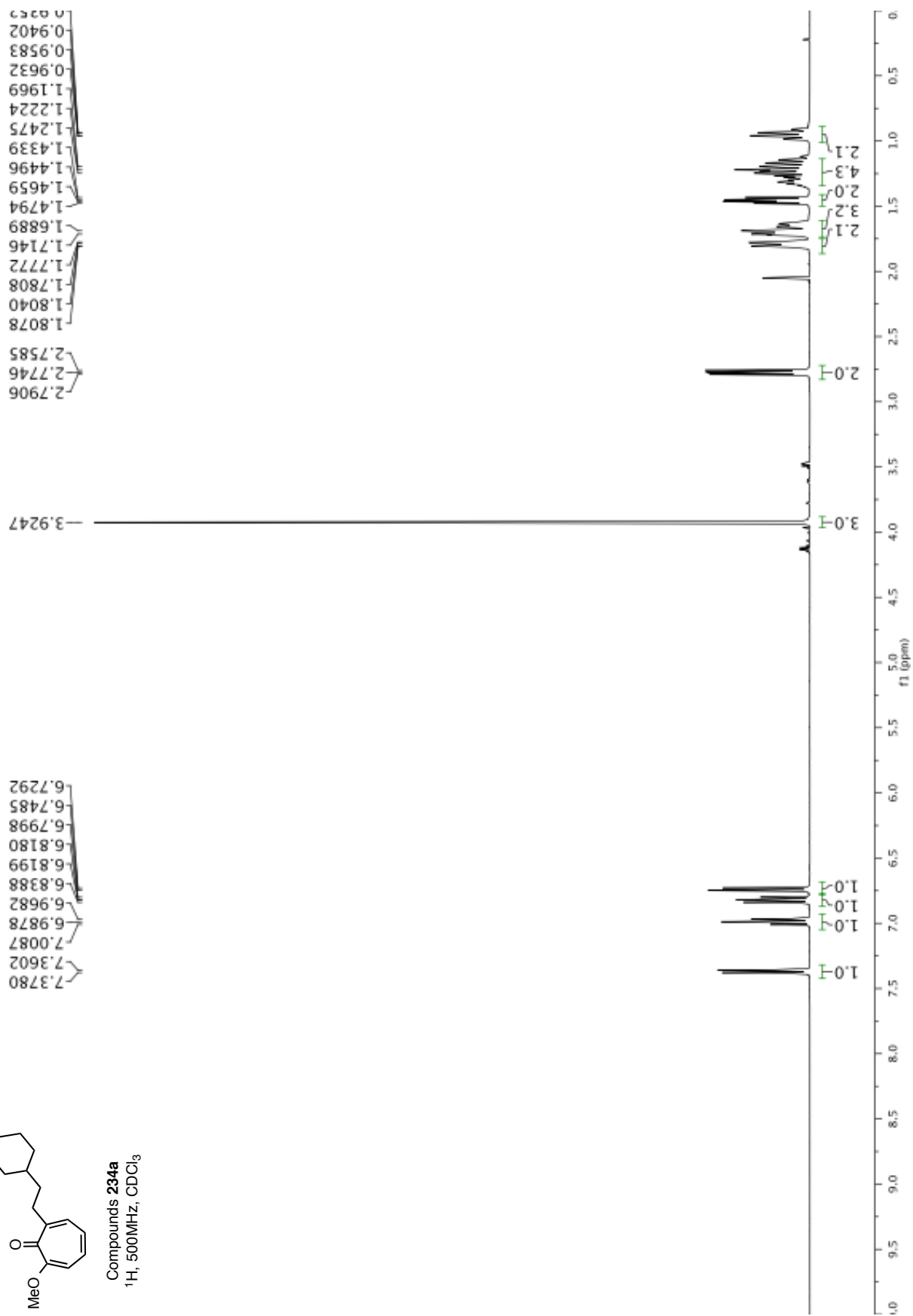


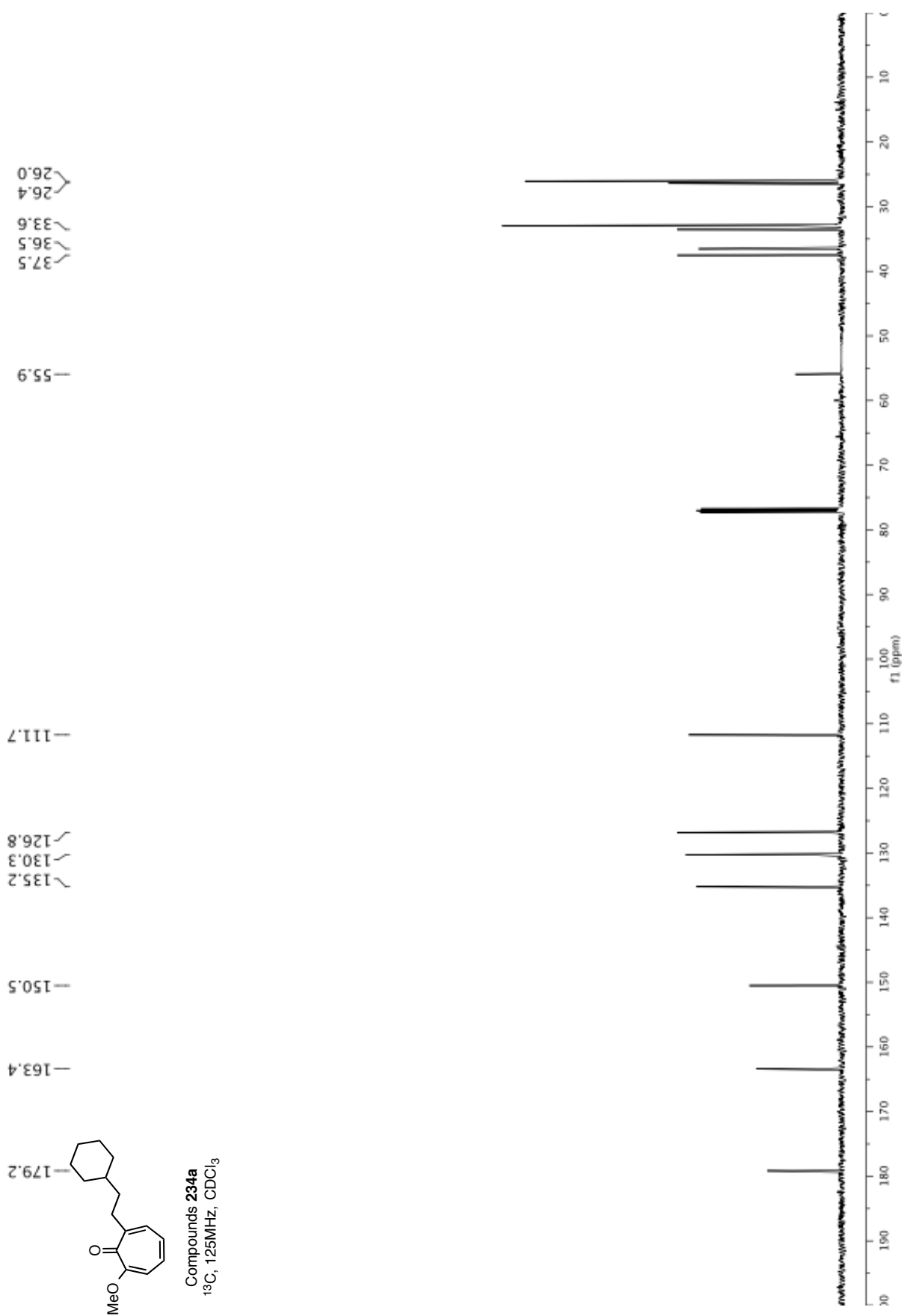


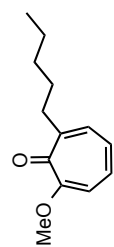




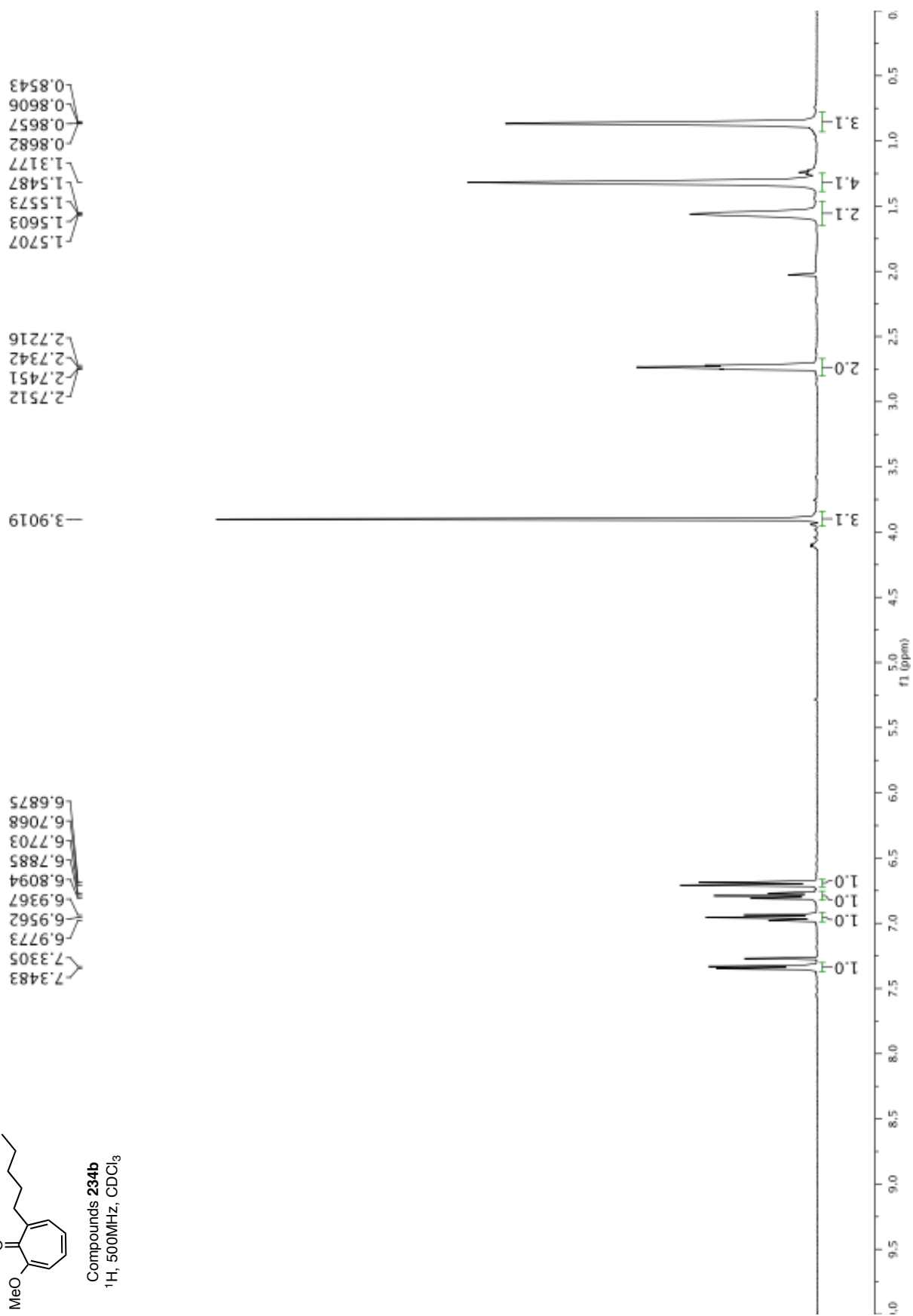
Compounds **234a**
 ^1H , 500MHz, CDCl_3

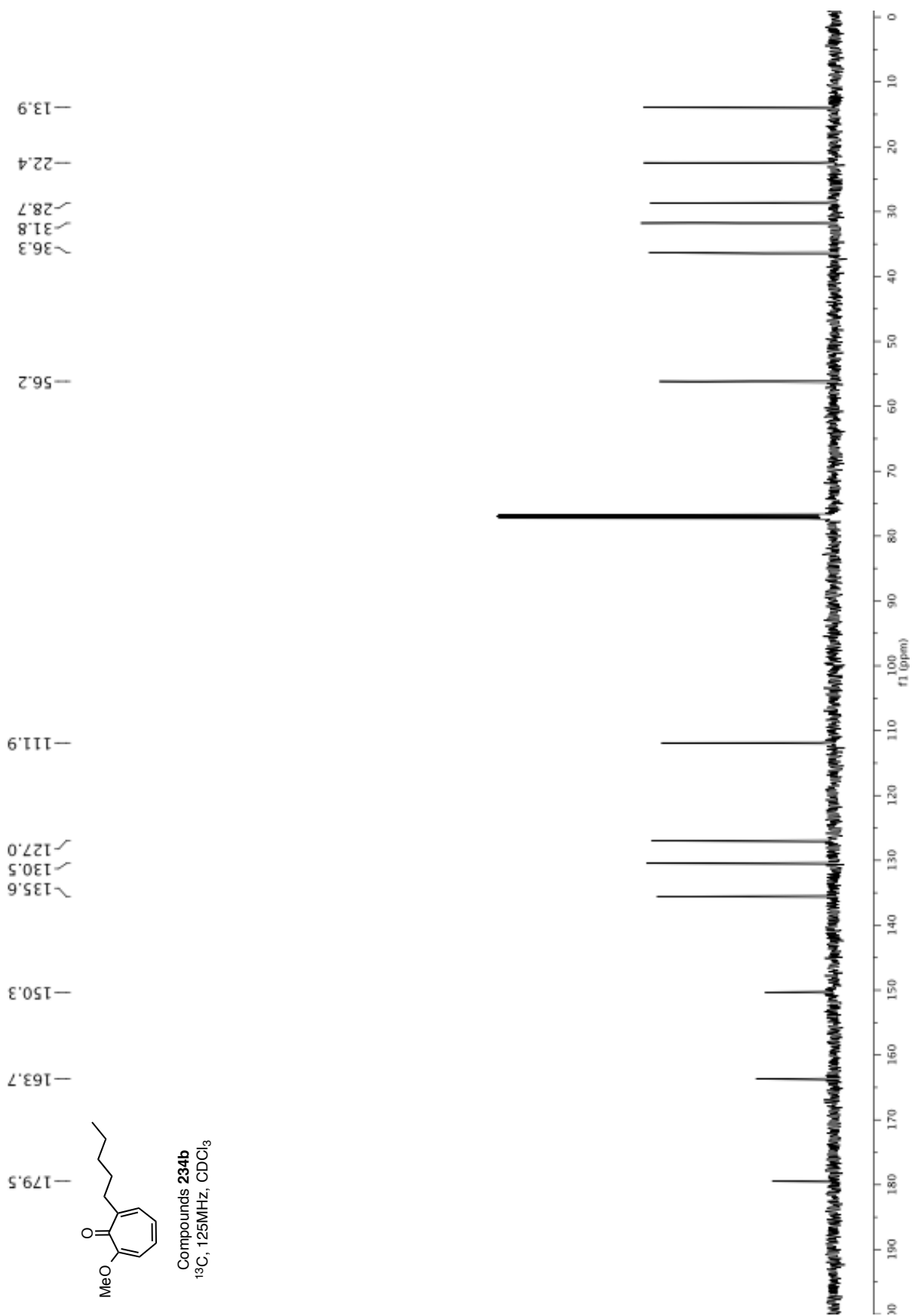


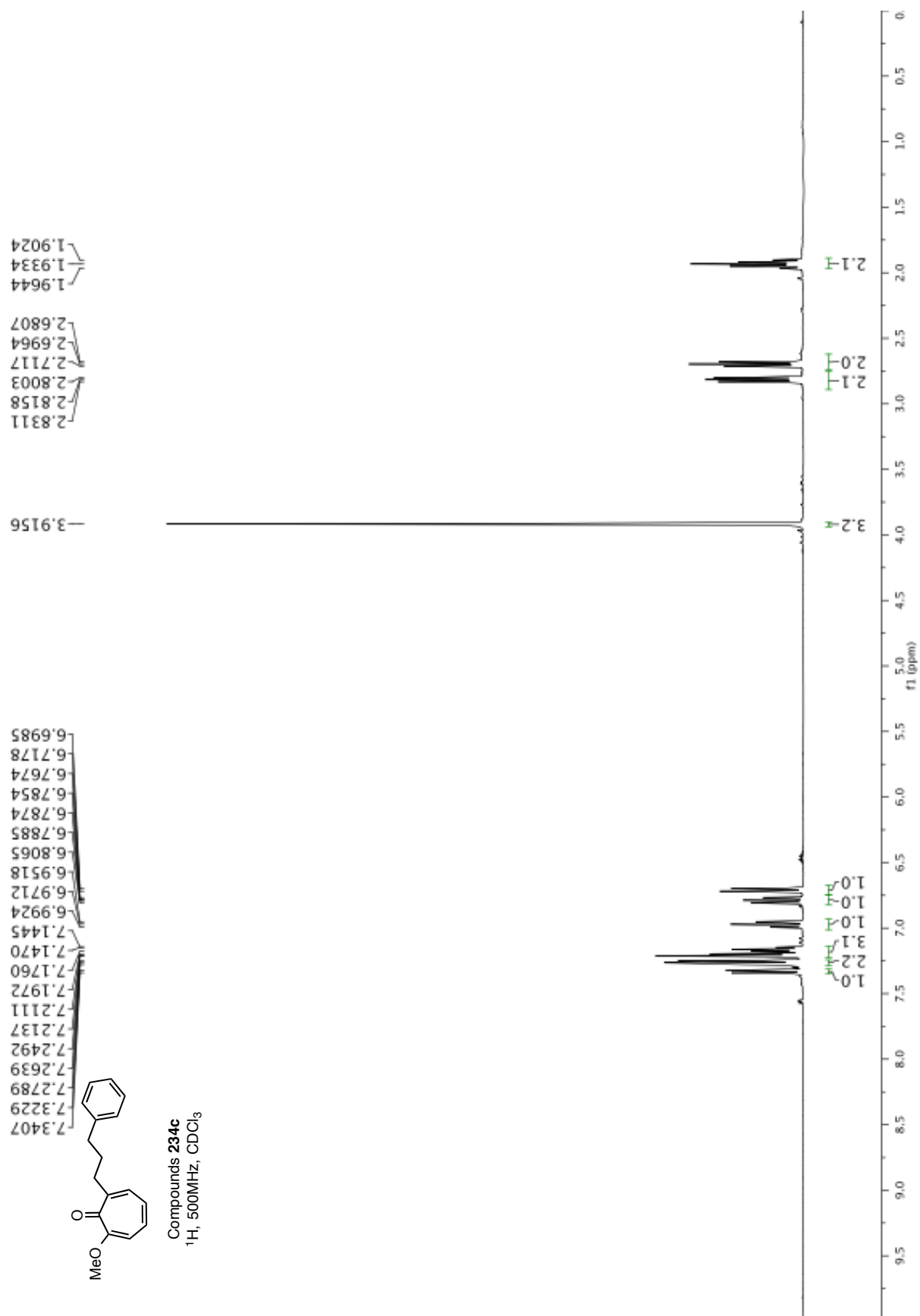


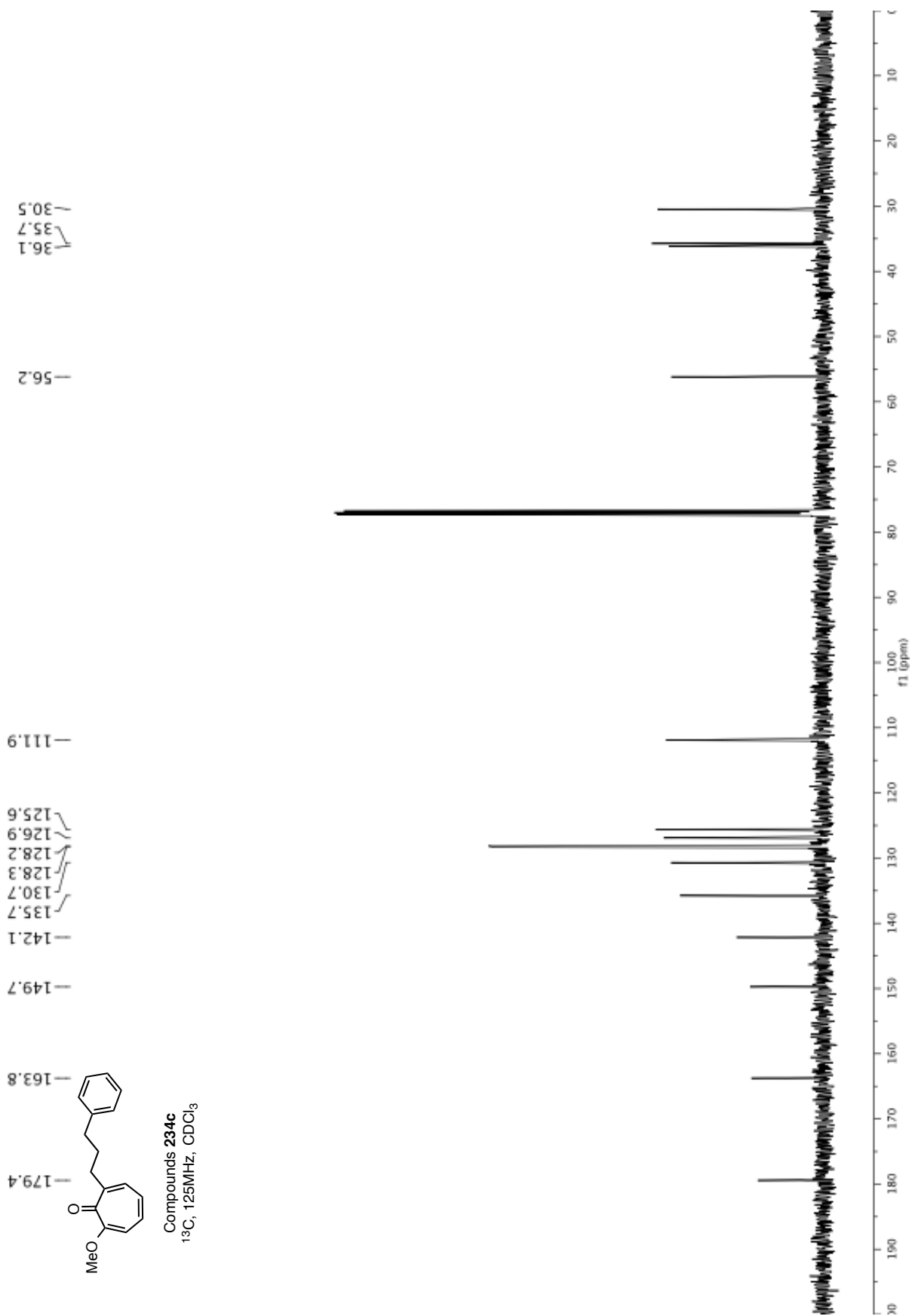


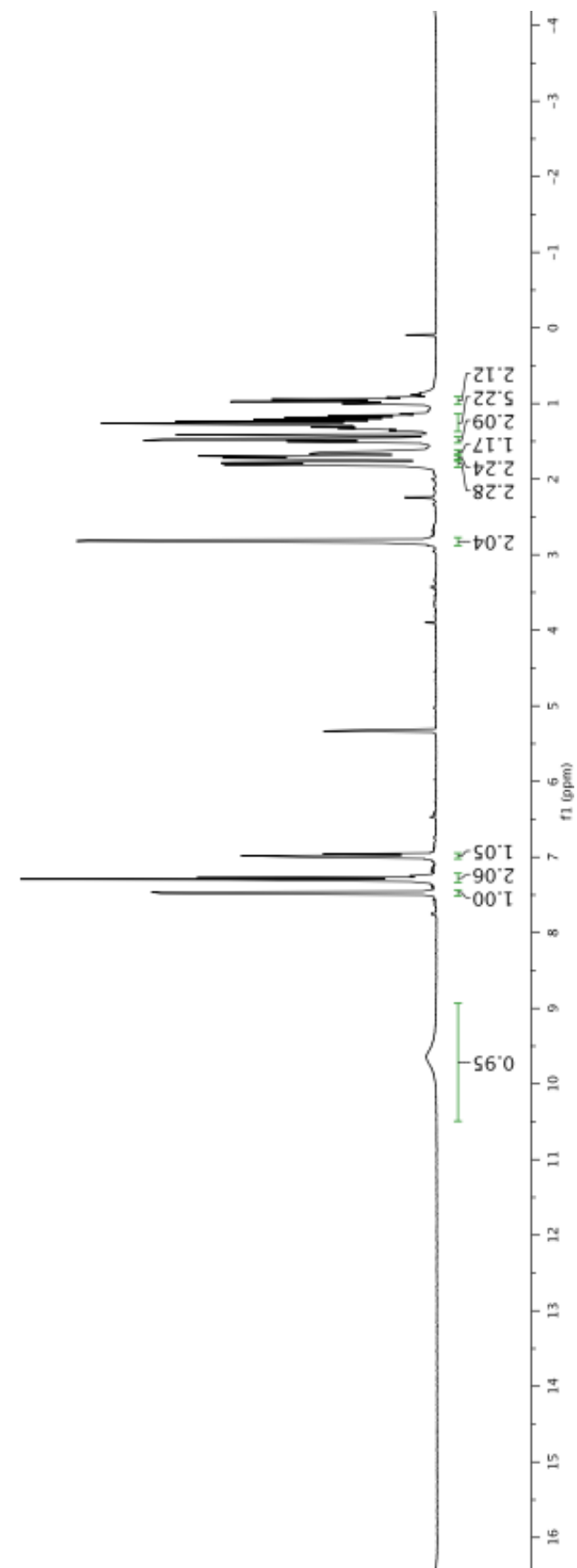
Compounds **234b**
 ^1H , 500MHz, CDCl_3





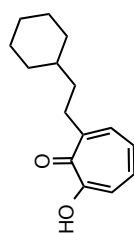




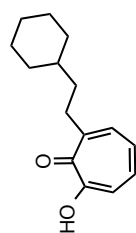


2.8353
2.8241
2.8192
2.8138
2.8029
1.8119
1.7854
1.7226
1.7035
1.6970
1.6615
1.6393
1.5008
1.4874
1.4710
1.4551
1.4128
1.3593
1.3168
1.1271
0.9996
0.9217

9.6505
7.4809
7.4611
7.3169
7.3135
7.2964
7.2927
7.2724
7.2518
7.0000
6.9963
6.9799
6.9620
6.9586



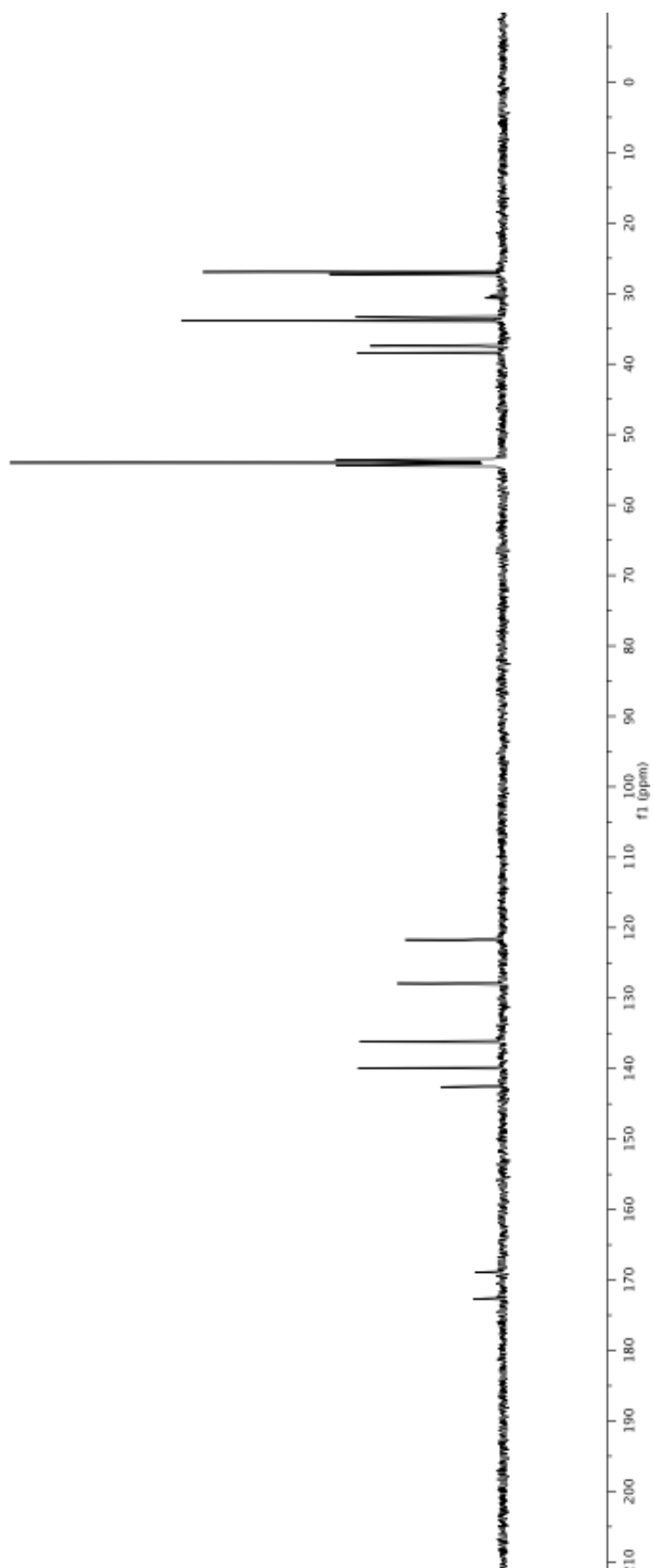
Compounds **235a**
¹H, 500MHz, CDCl₃

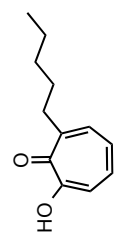


Compound **235a**
 ^{13}C , 125MHz, CDCl_3

— 172.7
 — 168.9
 — 142.6
 — 139.9
 — 136.2
 — 127.9
 — 121.7

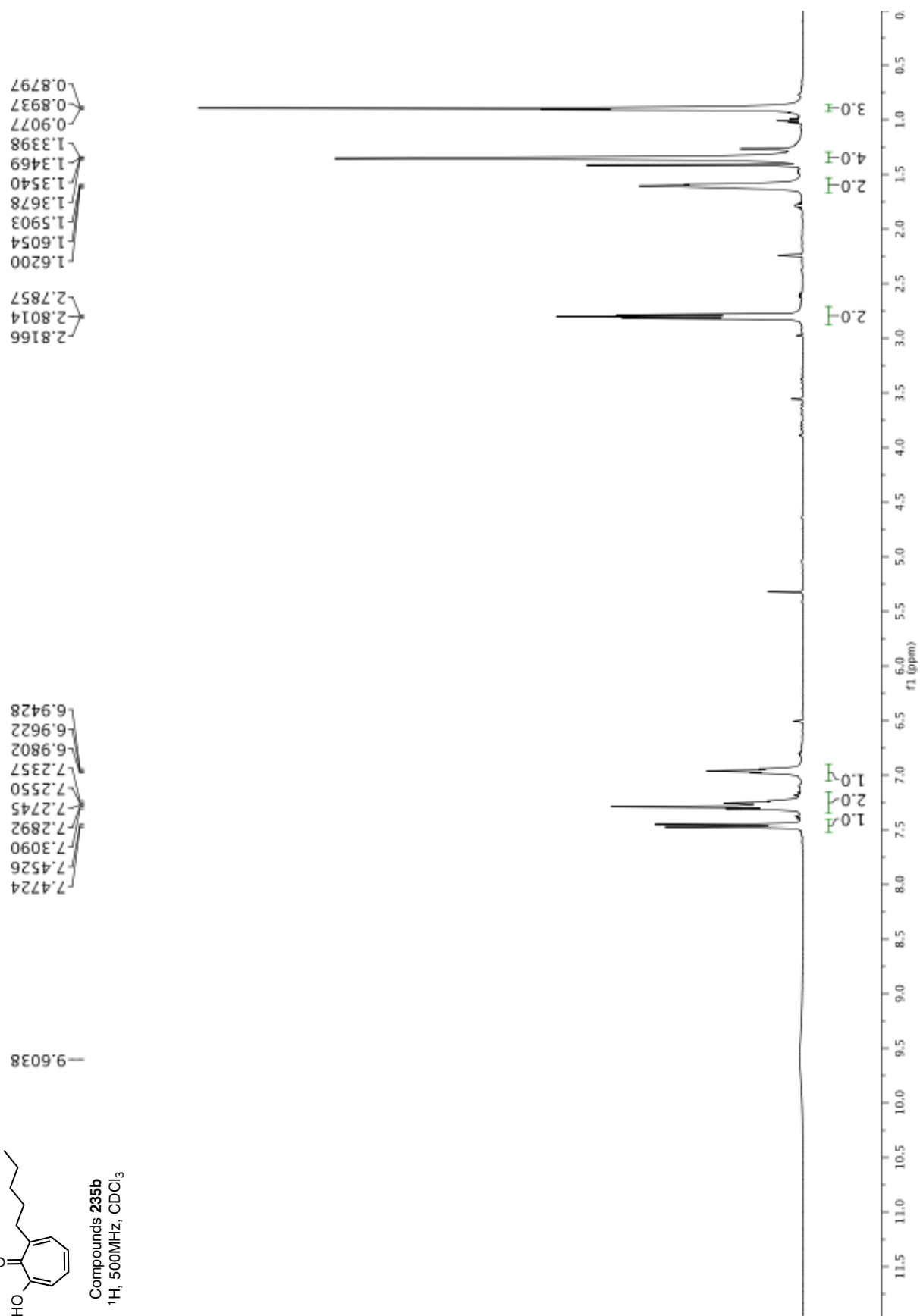
38.4
 37.5
 33.8
 33.3
 27.3
 26.9

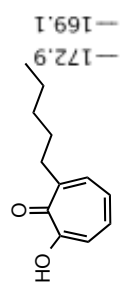




Compounds **235b**

¹H, 500MHz, CDCl₃





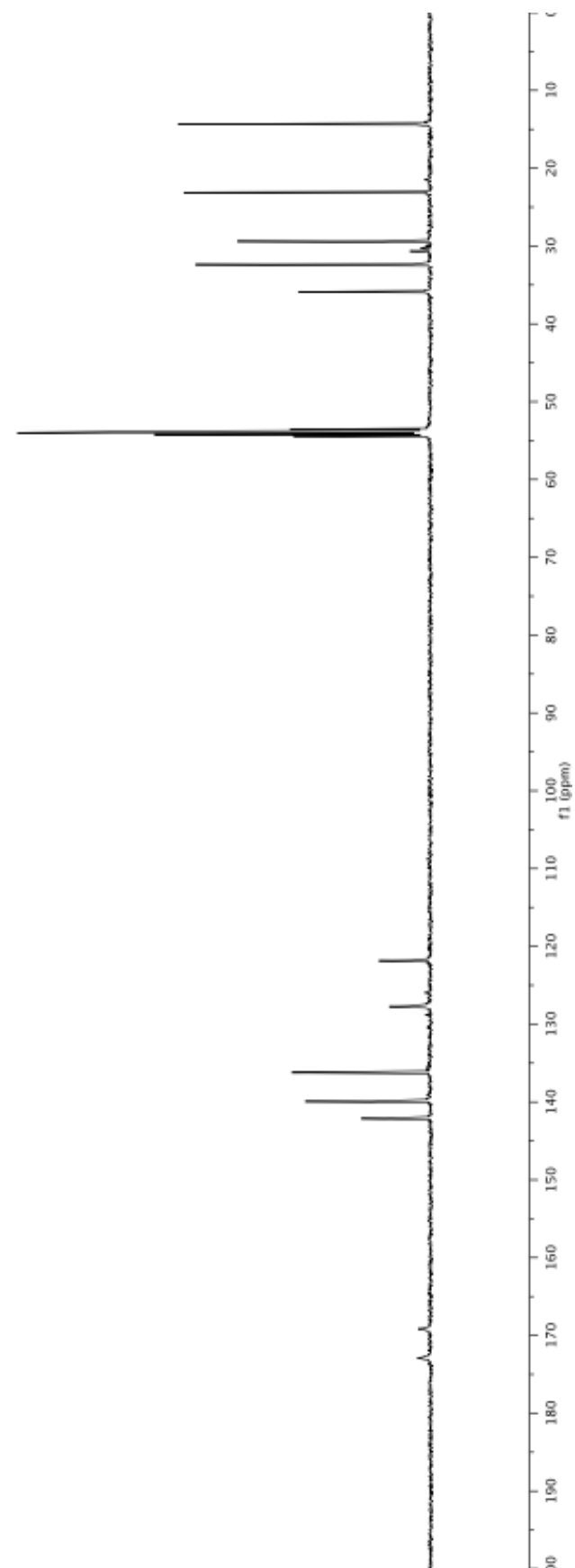
Compounds **235b**

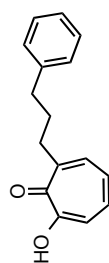
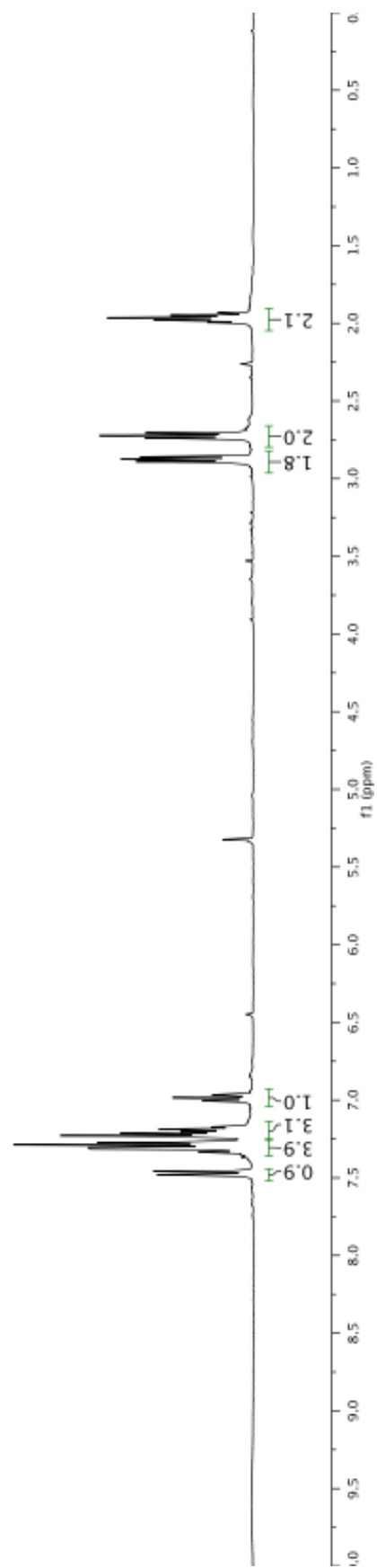
^{13}C , 125MHz, CDCl_3

—172.9
—169.1

—142.1
—139.9
—136.2
—127.7
—121.8

—35.9
—32.4
—29.4
—23.1
—14.4



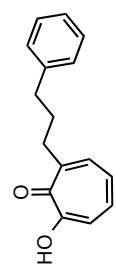


Compounds **235c**
¹H, 500MHz, CDCl₃

2.8905
 2.8753
 2.8595
 2.7370
 2.7218
 2.7061
 1.9948
 1.9790
 1.9637
 1.9481
 1.9326

7.5104
 7.4794
 7.4597
 7.3351
 7.3050
 7.2740
 7.2309
 7.1722
 7.0040
 7.0009
 6.9842
 6.9826
 6.9657
 6.9627

9.6067



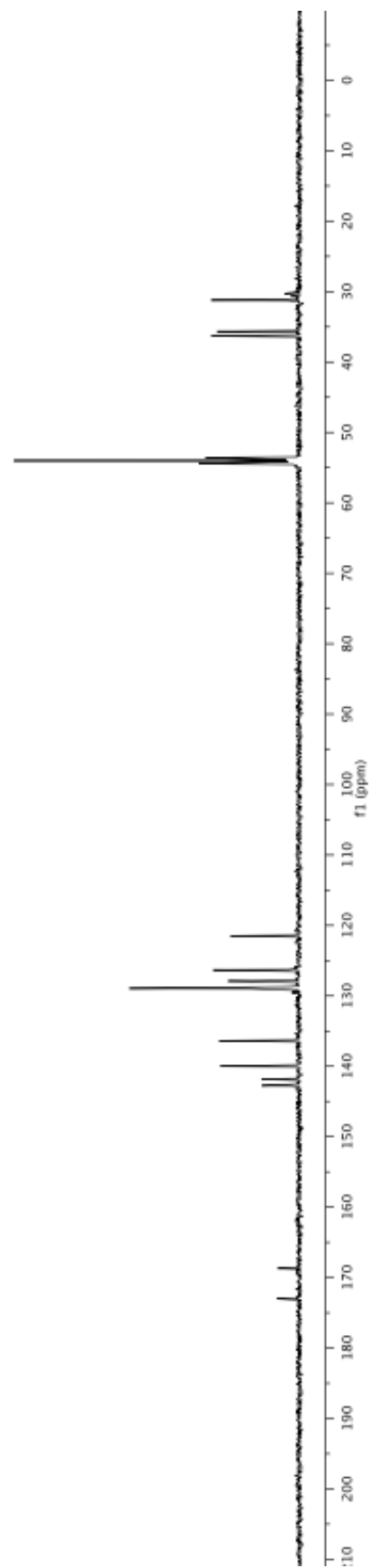
Compounds **235c**

^{13}C , 125MHz, CDCl_3

173.0
168.7

142.8
141.8
140.0
136.4
129.0
128.8
127.9
126.3
121.5

36.3
35.7
31.2



Appendix B: Crystal Structure Data

A. Crystal Data for (+)-174

Empirical formula	C ₂₉ H ₃₅ Br O ₄	
Formula weight	527.48	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 7.5438(6) Å	a = 90°.
	b = 10.6784(9) Å	b = 90°.
	c = 32.488(3) Å	g = 90°.
Volume	2617.1(4) Å ³	
Z	4	
Density (calculated)	1.339 Mg/m ³	
Absorption coefficient	2.391 mm ⁻¹	
F(000)	1104	
Crystal size	0.23 x 0.13 x 0.01 mm ³	
Theta range for data collection	2.72 to 68.32°.	
Index ranges	-9<=h<=7, -8<=k<=12, -39<=l<=37	
Reflections collected	14077	
Independent reflections	4572 [R(int) = 0.0347]	
Completeness to theta = 66.00°	99.8 %	
Absorption correction	Multi-scan	
Max. and min. transmission	1.000 and 0.733	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	4572 / 0 / 312	
Goodness-of-fit on F ²	1.028	
Final R indices [I>2sigma(I)]	R1 = 0.0283, wR2 = 0.0731	
R indices (all data)	R1 = 0.0290, wR2 = 0.0737	
Absolute structure parameter	0.048(13)	
Largest diff. peak and hole	0.661 and -0.510 e.Å ⁻³	

Table 1. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for C₂₉H₃₅BrO₄. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Br	-1640(1)	-3946(1)	1850(1)	35(1)
O(1)	106(2)	2448(2)	1580(1)	33(1)
O(2)	5667(2)	4756(2)	2393(1)	40(1)
O(3)	3277(2)	897(1)	1154(1)	30(1)
O(4)	5550(2)	-196(2)	1428(1)	33(1)
C(1)	3546(3)	4281(2)	870(1)	25(1)
C(2)	3172(3)	3085(2)	1116(1)	26(1)
C(3)	4421(3)	1951(2)	1050(1)	28(1)
C(4)	5120(4)	1836(2)	607(1)	35(1)
C(5)	6824(4)	2631(2)	569(1)	41(1)
C(6)	6775(3)	3865(2)	805(1)	35(1)
C(7)	5118(3)	4634(2)	723(1)	28(1)
C(8)	5372(3)	5812(2)	459(1)	32(1)
C(9)	3591(4)	6337(2)	317(1)	36(1)
C(10)	2204(3)	6357(2)	656(1)	36(1)
C(11)	1864(3)	5024(2)	805(1)	28(1)
C(12)	2951(3)	3370(2)	1575(1)	25(1)
C(13)	1421(3)	3043(2)	1796(1)	27(1)
C(14)	1284(3)	3334(2)	2214(1)	31(1)
C(15)	2675(3)	3916(2)	2419(1)	32(1)
C(16)	4199(3)	4224(2)	2207(1)	30(1)
C(17)	4314(3)	3972(2)	1787(1)	27(1)
C(18)	-1311(3)	1937(2)	1814(1)	40(1)
C(19)	5333(4)	5814(3)	2641(1)	47(1)
C(20)	3993(3)	-86(2)	1351(1)	28(1)
C(21)	2598(3)	-1006(2)	1468(1)	28(1)
C(22)	3100(3)	-2082(2)	1681(1)	32(1)
C(23)	1846(3)	-2964(2)	1788(1)	32(1)
C(24)	84(3)	-2755(2)	1688(1)	30(1)

C(25)	-455(3)	-1686(2)	1481(1)	32(1)
C(26)	817(3)	-812(2)	1372(1)	32(1)
C(27)	5511(4)	493(3)	473(1)	46(1)
C(28)	6407(4)	6799(2)	704(1)	39(1)
C(29)	6424(4)	5482(3)	66(1)	46(1)

Table 2. Bond lengths [Å] and angles [°] for C₂₉H₃₅BrO₄.

Br-C(24)	1.894(2)	C(8)-C(28)	1.536(3)
O(1)-C(13)	1.372(3)	C(8)-C(29)	1.542(3)
O(1)-C(18)	1.420(3)	C(9)-C(10)	1.519(4)
O(2)-C(16)	1.383(3)	C(9)-H(9A)	0.9900
O(2)-C(19)	1.411(3)	C(9)-H(9B)	0.9900
O(3)-C(20)	1.343(3)	C(10)-C(11)	1.526(3)
O(3)-C(3)	1.459(2)	C(10)-H(10A)	0.9900
O(4)-C(20)	1.206(3)	C(10)-H(10B)	0.9900
C(1)-C(7)	1.334(3)	C(11)-H(11A)	0.9900
C(1)-C(11)	1.512(3)	C(11)-H(11B)	0.9900
C(1)-C(2)	1.531(3)	C(12)-C(17)	1.394(3)
C(2)-C(12)	1.533(3)	C(12)-C(13)	1.404(3)
C(2)-C(3)	1.550(3)	C(13)-C(14)	1.396(3)
C(2)-H(2)	1.0000	C(14)-C(15)	1.390(3)
C(3)-C(4)	1.537(3)	C(14)-H(14)	0.9500
C(3)-H(3)	1.0000	C(15)-C(16)	1.380(3)
C(4)-C(27)	1.527(3)	C(15)-H(15)	0.9500
C(4)-C(5)	1.545(4)	C(16)-C(17)	1.394(3)
C(4)-H(4)	1.0000	C(17)-H(17)	0.9500
C(5)-C(6)	1.525(3)	C(18)-H(18A)	0.9800
C(5)-H(5A)	0.9900	C(18)-H(18B)	0.9800
C(5)-H(5B)	0.9900	C(18)-H(18C)	0.9800
C(6)-C(7)	1.519(3)	C(19)-H(19A)	0.9800
C(6)-H(6A)	0.9900	C(19)-H(19B)	0.9800
C(6)-H(6B)	0.9900	C(19)-H(19C)	0.9800
C(7)-C(8)	1.534(3)	C(20)-C(21)	1.489(3)
C(8)-C(9)	1.527(4)	C(21)-C(26)	1.394(3)

C(21)-C(22)	1.394(3)	C(2)-C(3)-H(3)	109.9
C(22)-C(23)	1.380(3)	C(27)-C(4)-C(3)	114.0(2)
C(22)-H(22)	0.9500	C(27)-C(4)-C(5)	109.4(2)
C(23)-C(24)	1.388(3)	C(3)-C(4)-C(5)	108.4(2)
C(23)-H(23)	0.9500	C(27)-C(4)-H(4)	108.3
C(24)-C(25)	1.385(3)	C(3)-C(4)-H(4)	108.3
C(25)-C(26)	1.385(3)	C(5)-C(4)-H(4)	108.3
C(25)-H(25)	0.9500	C(6)-C(5)-C(4)	114.5(2)
C(26)-H(26)	0.9500	C(6)-C(5)-H(5A)	108.6
C(27)-H(27A)	0.9800	C(4)-C(5)-H(5A)	108.6
C(27)-H(27B)	0.9800	C(6)-C(5)-H(5B)	108.6
C(27)-H(27C)	0.9800	C(4)-C(5)-H(5B)	108.6
C(28)-H(28A)	0.9800	H(5A)-C(5)-H(5B)	107.6
C(28)-H(28B)	0.9800	C(7)-C(6)-C(5)	113.5(2)
C(28)-H(28C)	0.9800	C(7)-C(6)-H(6A)	108.9
C(29)-H(29A)	0.9800	C(5)-C(6)-H(6A)	108.9
C(29)-H(29B)	0.9800	C(7)-C(6)-H(6B)	108.9
C(29)-H(29C)	0.9800	C(5)-C(6)-H(6B)	108.9
C(13)-O(1)-C(18)	116.68(19)	H(6A)-C(6)-H(6B)	107.7
C(16)-O(2)-C(19)	115.8(2)	C(1)-C(7)-C(6)	121.01(19)
C(20)-O(3)-C(3)	118.44(17)	C(1)-C(7)-C(8)	123.0(2)
C(7)-C(1)-C(11)	123.15(19)	C(6)-C(7)-C(8)	116.0(2)
C(7)-C(1)-C(2)	126.0(2)	C(9)-C(8)-C(7)	111.1(2)
C(11)-C(1)-C(2)	110.86(18)	C(9)-C(8)-C(28)	110.6(2)
C(1)-C(2)-C(12)	111.18(17)	C(7)-C(8)-C(28)	109.6(2)
C(1)-C(2)-C(3)	117.86(18)	C(9)-C(8)-C(29)	106.6(2)
C(12)-C(2)-C(3)	110.84(17)	C(7)-C(8)-C(29)	109.9(2)
C(1)-C(2)-H(2)	105.3	C(28)-C(8)-C(29)	109.0(2)
C(12)-C(2)-H(2)	105.3	C(10)-C(9)-C(8)	113.09(19)
C(3)-C(2)-H(2)	105.3	C(10)-C(9)-H(9A)	109.0
O(3)-C(3)-C(4)	111.06(18)	C(8)-C(9)-H(9A)	109.0
O(3)-C(3)-C(2)	102.18(16)	C(10)-C(9)-H(9B)	109.0
C(4)-C(3)-C(2)	113.60(19)	C(8)-C(9)-H(9B)	109.0
O(3)-C(3)-H(3)	109.9	H(9A)-C(9)-H(9B)	107.8
C(4)-C(3)-H(3)	109.9	C(9)-C(10)-C(11)	109.5(2)

C(9)-C(10)-H(10A)	109.8	O(2)-C(19)-H(19A)	109.5
C(11)-C(10)-H(10A)	109.8	O(2)-C(19)-H(19B)	109.5
C(9)-C(10)-H(10B)	109.8	H(19A)-C(19)-H(19B)	109.5
C(11)-C(10)-H(10B)	109.8	O(2)-C(19)-H(19C)	109.5
H(10A)-C(10)-H(10B)	108.2	H(19A)-C(19)-H(19C)	109.5
C(1)-C(11)-C(10)	113.20(19)	H(19B)-C(19)-H(19C)	109.5
C(1)-C(11)-H(11A)	108.9	O(4)-C(20)-O(3)	124.5(2)
C(10)-C(11)-H(11A)	108.9	O(4)-C(20)-C(21)	124.9(2)
C(1)-C(11)-H(11B)	108.9	O(3)-C(20)-C(21)	110.61(19)
C(10)-C(11)-H(11B)	108.9	C(26)-C(21)-C(22)	119.7(2)
H(11A)-C(11)-H(11B)	107.8	C(26)-C(21)-C(20)	121.8(2)
C(17)-C(12)-C(13)	117.9(2)	C(22)-C(21)-C(20)	118.5(2)
C(17)-C(12)-C(2)	119.5(2)	C(23)-C(22)-C(21)	120.1(2)
C(13)-C(12)-C(2)	122.6(2)	C(23)-C(22)-H(22)	119.9
O(1)-C(13)-C(14)	123.18(19)	C(21)-C(22)-H(22)	119.9
O(1)-C(13)-C(12)	116.6(2)	C(22)-C(23)-C(24)	119.1(2)
C(14)-C(13)-C(12)	120.2(2)	C(22)-C(23)-H(23)	120.4
C(15)-C(14)-C(13)	120.7(2)	C(24)-C(23)-H(23)	120.4
C(15)-C(14)-H(14)	119.7	C(25)-C(24)-C(23)	121.9(2)
C(13)-C(14)-H(14)	119.7	C(25)-C(24)-Br	119.16(18)
C(16)-C(15)-C(14)	119.7(2)	C(23)-C(24)-Br	118.92(17)
C(16)-C(15)-H(15)	120.1	C(26)-C(25)-C(24)	118.4(2)
C(14)-C(15)-H(15)	120.1	C(26)-C(25)-H(25)	120.8
C(15)-C(16)-O(2)	123.2(2)	C(24)-C(25)-H(25)	120.8
C(15)-C(16)-C(17)	119.6(2)	C(25)-C(26)-C(21)	120.7(2)
O(2)-C(16)-C(17)	117.2(2)	C(25)-C(26)-H(26)	119.7
C(16)-C(17)-C(12)	121.8(2)	C(21)-C(26)-H(26)	119.7
C(16)-C(17)-H(17)	119.1	C(4)-C(27)-H(27A)	109.5
C(12)-C(17)-H(17)	119.1	C(4)-C(27)-H(27B)	109.5
O(1)-C(18)-H(18A)	109.5	H(27A)-C(27)-H(27B)	109.5
O(1)-C(18)-H(18B)	109.5	C(4)-C(27)-H(27C)	109.5
H(18A)-C(18)-H(18B)	109.5	H(27A)-C(27)-H(27C)	109.5
O(1)-C(18)-H(18C)	109.5	H(27B)-C(27)-H(27C)	109.5
H(18A)-C(18)-H(18C)	109.5	C(8)-C(28)-H(28A)	109.5
H(18B)-C(18)-H(18C)	109.5	C(8)-C(28)-H(28B)	109.5

H(28A)-C(28)-H(28B)	109.5	C(8)-C(29)-H(29B)	109.5
C(8)-C(28)-H(28C)	109.5	H(29A)-C(29)-H(29B)	109.5
H(28A)-C(28)-H(28C)	109.5	C(8)-C(29)-H(29C)	109.5
H(28B)-C(28)-H(28C)	109.5	H(29A)-C(29)-H(29C)	109.5
C(8)-C(29)-H(29A)	109.5	H(29B)-C(29)-H(29C)	109.5

Symmetry transformations used to generate equivalent atoms:

Table 3. Anisotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for C₂₉H₃₅BrO₄. 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
Br	31(1)	27(1)	45(1)	2(1)	4(1)	-7(1)
O(1)	22(1)	37(1)	40(1)	7(1)	-1(1)	-9(1)
O(2)	31(1)	40(1)	49(1)	-7(1)	1(1)	-9(1)
O(3)	24(1)	17(1)	48(1)	3(1)	-5(1)	-2(1)
O(4)	24(1)	25(1)	50(1)	3(1)	-2(1)	0(1)
C(1)	24(1)	20(1)	31(1)	3(1)	0(1)	1(1)
C(2)	20(1)	20(1)	36(1)	3(1)	0(1)	-2(1)
C(3)	22(1)	19(1)	42(1)	2(1)	-1(1)	-3(1)
C(4)	37(1)	29(1)	39(1)	-1(1)	2(1)	5(1)
C(5)	36(1)	37(1)	50(1)	3(1)	14(1)	9(1)
C(6)	24(1)	33(1)	48(1)	8(1)	6(1)	-3(1)
C(7)	25(1)	24(1)	36(1)	3(1)	1(1)	-2(1)
C(8)	32(1)	29(1)	36(1)	8(1)	6(1)	-6(1)
C(9)	40(2)	30(1)	39(1)	12(1)	-3(1)	-5(1)
C(10)	31(1)	26(1)	50(1)	12(1)	0(1)	4(1)
C(11)	22(1)	26(1)	37(1)	7(1)	0(1)	0(1)
C(12)	20(1)	18(1)	36(1)	6(1)	-2(1)	0(1)
C(13)	20(1)	22(1)	39(1)	8(1)	2(1)	-1(1)
C(14)	24(1)	30(1)	39(1)	8(1)	4(1)	-2(1)
C(15)	34(1)	27(1)	35(1)	6(1)	3(1)	-2(1)
C(16)	26(1)	22(1)	40(1)	1(1)	-3(1)	-2(1)
C(17)	23(1)	22(1)	36(1)	4(1)	4(1)	-2(1)

C(18)	23(1)	44(1)	52(2)	11(1)	4(1)	-9(1)
C(19)	48(2)	60(2)	34(1)	-13(1)	-4(1)	-10(1)
C(20)	26(1)	20(1)	40(1)	-2(1)	-3(1)	1(1)
C(21)	26(1)	19(1)	38(1)	0(1)	-2(1)	-2(1)
C(22)	23(1)	25(1)	48(1)	3(1)	-3(1)	1(1)
C(23)	31(1)	25(1)	39(1)	5(1)	-1(1)	1(1)
C(24)	29(1)	25(1)	35(1)	-4(1)	3(1)	-1(1)
C(25)	23(1)	26(1)	47(1)	-2(1)	-2(1)	0(1)
C(26)	29(1)	18(1)	48(1)	3(1)	-4(1)	1(1)
C(27)	54(2)	39(1)	46(1)	-9(1)	3(1)	10(1)
C(28)	39(2)	29(1)	50(1)	9(1)	-1(1)	-11(1)
C(29)	49(2)	45(1)	44(1)	10(1)	16(1)	-2(1)

Table 4. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for C29H35BrO4.

	x	y	z	U(eq)
H(2)	1979	2796	1021	31
H(3)	5437	1996	1247	33
H(4)	4209	2192	416	42
H(5A)	7838	2129	671	49
H(5B)	7038	2813	275	49
H(6A)	6850	3686	1103	42
H(6B)	7828	4368	728	42
H(9A)	3769	7201	214	44
H(9B)	3145	5824	85	44
H(10A)	1089	6725	550	43
H(10B)	2625	6881	887	43
H(11A)	1199	5059	1068	34
H(11B)	1114	4585	601	34
H(14)	230	3132	2360	37
H(15)	2577	4101	2704	38

H(17)	5348	4217	1641	32
H(18A)	-2073	1435	1634	59
H(18B)	-2006	2618	1936	59
H(18C)	-832	1406	2033	59
H(19A)	6437	6083	2774	71
H(19B)	4458	5600	2853	71
H(19C)	4872	6496	2470	71
H(22)	4308	-2208	1752	38
H(23)	2185	-3706	1930	38
H(25)	-1668	-1556	1415	38
H(26)	473	-72	1230	38
H(27A)	4443	-19	507	69
H(27B)	6466	150	644	69
H(27C)	5875	486	184	69
H(28A)	6605	7538	532	59
H(28B)	7551	6450	790	59
H(28C)	5724	7038	949	59
H(29A)	6472	6216	-115	69
H(29B)	5837	4790	-78	69
H(29C)	7631	5232	141	69

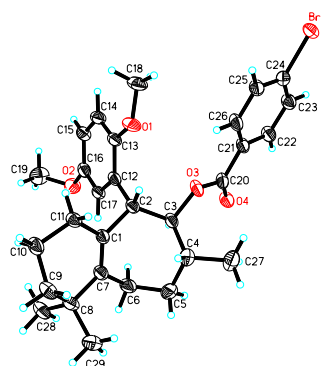
Table 5. Torsion angles [°] for C₂₉H₃₅BrO₄.

C(7)-C(1)-C(2)-C(12)	103.7(3)	C(2)-C(3)-C(4)-C(27)	-150.4(2)
C(11)-C(1)-C(2)-C(12)	-77.6(2)	O(3)-C(3)-C(4)-C(5)	-158.00(18)
C(7)-C(1)-C(2)-C(3)	-25.8(3)	C(2)-C(3)-C(4)-C(5)	87.5(2)
C(11)-C(1)-C(2)-C(3)	152.90(19)	C(27)-C(4)-C(5)-C(6)	-163.1(2)
C(20)-O(3)-C(3)-C(4)	95.2(2)	C(3)-C(4)-C(5)-C(6)	-38.3(3)
C(20)-O(3)-C(3)-C(2)	-143.31(19)	C(4)-C(5)-C(6)-C(7)	-49.7(3)
C(1)-C(2)-C(3)-O(3)	-153.81(18)	C(11)-C(1)-C(7)-C(6)	178.7(2)
C(12)-C(2)-C(3)-O(3)	76.5(2)	C(2)-C(1)-C(7)-C(6)	-2.7(4)
C(1)-C(2)-C(3)-C(4)	-34.1(3)	C(11)-C(1)-C(7)-C(8)	-2.1(4)
C(12)-C(2)-C(3)-C(4)	-163.79(19)	C(2)-C(1)-C(7)-C(8)	176.5(2)
O(3)-C(3)-C(4)-C(27)	-35.9(3)	C(5)-C(6)-C(7)-C(1)	71.6(3)

C(5)-C(6)-C(7)-C(8)	-107.6(2)	C(13)-C(14)-C(15)-C(16)	0.8(3)
C(1)-C(7)-C(8)-C(9)	-12.0(3)	C(14)-C(15)-C(16)-O(2)	-177.2(2)
C(6)-C(7)-C(8)-C(9)	167.2(2)	C(14)-C(15)-C(16)-C(17)	1.4(3)
C(1)-C(7)-C(8)-C(28)	110.5(3)	C(19)-O(2)-C(16)-C(15)	-50.3(3)
C(6)-C(7)-C(8)-C(28)	-70.3(3)	C(19)-O(2)-C(16)-C(17)	131.1(2)
C(1)-C(7)-C(8)-C(29)	-129.8(3)	C(15)-C(16)-C(17)-C(12)	-2.5(3)
C(6)-C(7)-C(8)-C(29)	49.4(3)	O(2)-C(16)-C(17)-C(12)	176.18(19)
C(7)-C(8)-C(9)-C(10)	43.6(3)	C(13)-C(12)-C(17)-C(16)	1.4(3)
C(28)-C(8)-C(9)-C(10)	-78.3(2)	C(2)-C(12)-C(17)-C(16)	-178.32(19)
C(29)-C(8)-C(9)-C(10)	163.4(2)	C(3)-O(3)-C(20)-O(4)	-4.5(3)
C(8)-C(9)-C(10)-C(11)	-60.9(3)	C(3)-O(3)-C(20)-C(21)	174.46(18)
C(7)-C(1)-C(11)-C(10)	-14.9(3)	O(4)-C(20)-C(21)-C(26)	179.3(3)
C(2)-C(1)-C(11)-C(10)	166.27(19)	O(3)-C(20)-C(21)-C(26)	0.4(3)
C(9)-C(10)-C(11)-C(1)	44.8(3)	O(4)-C(20)-C(21)-C(22)	-0.1(4)
C(1)-C(2)-C(12)-C(17)	-57.0(3)	O(3)-C(20)-C(21)-C(22)	-179.1(2)
C(3)-C(2)-C(12)-C(17)	76.1(2)	C(26)-C(21)-C(22)-C(23)	1.5(4)
C(1)-C(2)-C(12)-C(13)	123.3(2)	C(20)-C(21)-C(22)-C(23)	-179.0(2)
C(3)-C(2)-C(12)-C(13)	-103.6(2)	C(21)-C(22)-C(23)-C(24)	-1.1(4)
C(18)-O(1)-C(13)-C(14)	-10.5(3)	C(22)-C(23)-C(24)-C(25)	0.2(4)
C(18)-O(1)-C(13)-C(12)	170.12(19)	C(22)-C(23)-C(24)-Br	-178.20(18)
C(17)-C(12)-C(13)-O(1)	-179.78(19)	C(23)-C(24)-C(25)-C(26)	0.3(4)
C(2)-C(12)-C(13)-O(1)	-0.1(3)	Br-C(24)-C(25)-C(26)	178.66(18)
C(17)-C(12)-C(13)-C(14)	0.8(3)	C(24)-C(25)-C(26)-C(21)	0.1(4)
C(2)-C(12)-C(13)-C(14)	-179.49(19)	C(22)-C(21)-C(26)-C(25)	-1.0(4)
O(1)-C(13)-C(14)-C(15)	178.7(2)	C(20)-C(21)-C(26)-C(25)	179.5(2)
C(12)-C(13)-C(14)-C(15)	-1.9(3)		

Symmetry transformations used to generate equivalent atoms:

Thermal Ellipsoid plot of (+)-174



A. Crystal Data for (+)-197

Empirical formula	C ₉ H ₈ Br ₂ O ₃	
Formula weight	323.97	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	P2(1)	
Unit cell dimensions	a = 6.9650(3) Å	α = 90°.
	b = 8.1765(3) Å	β = 99.0010(10)°.
	c = 8.7646(3) Å	γ = 90°.
Volume	492.99(3) Å ³	
Z	2	
Density (calculated)	2.182 Mg/m ³	
Absorption coefficient	10.275 mm ⁻¹	
F(000)	312	
Crystal size	0.13 x 0.09 x 0.06 mm ³	
Theta range for data collection	6.43 to 69.07°.	
Index ranges	-8 ≤ h ≤ 8, -9 ≤ k ≤ 6, -10 ≤ l ≤ 8	
Reflections collected	3719	
Independent reflections	1239 [R(int) = 0.0371]	
Completeness to theta = 66.00°	96.3 %	
Absorption correction	Multi-scan	
Max. and min. transmission	1.000 and 0.448	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	1239 / 1 / 127	
Goodness-of-fit on F ²	1.160	
Final R indices [I > 2σ(I)]	R1 = 0.0440, wR2 = 0.1144	
R indices (all data)	R1 = 0.0440, wR2 = 0.1144	
Absolute structure parameter	0.04(5)	
Largest diff. peak and hole	1.092 and -1.189 e.Å ⁻³	

Table 6. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for C₉H₈Br₂O₃. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Br(1)	3044(1)	3225(1)	7215(1)	23(1)
Br(2)	2626(1)	0(1)	4692(1)	21(1)
O(1)	181(6)	3858(7)	2274(5)	20(1)
O(2)	2334(6)	6339(8)	5315(5)	23(1)
O(3)	6225(7)	3534(9)	595(6)	29(1)
C(1)	3323(8)	3423(10)	1771(7)	17(1)
C(2)	3117(8)	5007(11)	1970(8)	21(2)
C(3)	1355(10)	5257(10)	2747(7)	21(2)
C(4)	2021(9)	5140(11)	4497(8)	19(2)
C(5)	2318(9)	3444(10)	5049(9)	17(1)
C(6)	2181(10)	2197(10)	4080(8)	20(2)
C(7)	1592(10)	2534(10)	2335(8)	19(1)
C(8)	4919(10)	2489(11)	1203(7)	23(2)
C(9)	709(10)	1139(11)	1352(8)	27(2)

Table 7. Bond lengths [\AA] and angles [$^\circ$] for C₉H₈Br₂O₃.

Br(1)-C(5)	1.895(8)	C(3)-C(4)	1.534(9)
Br(2)-C(6)	1.886(8)	C(3)-H(3A)	1.0000
O(1)-C(3)	1.430(10)	C(4)-C(5)	1.473(12)
O(1)-C(7)	1.457(9)	C(5)-C(6)	1.321(10)
O(2)-C(4)	1.214(10)	C(6)-C(7)	1.545(8)
O(3)-C(8)	1.411(10)	C(7)-C(9)	1.502(11)
O(3)-H(3O)	0.8400	C(8)-H(8A)	0.9900
C(1)-C(2)	1.318(13)	C(8)-H(8B)	0.9900
C(1)-C(8)	1.496(10)	C(9)-H(9D)	0.9800
C(1)-C(7)	1.553(10)	C(9)-H(9A)	0.9800
C(2)-C(3)	1.508(10)	C(9)-H(9B)	0.9800
C(2)-H(2A)	0.9500	C(3)-O(1)-C(7)	103.4(5)

C(8)-O(3)-H(3O)	109.5	C(5)-C(6)-Br(2)	124.1(6)
C(2)-C(1)-C(8)	130.4(7)	C(7)-C(6)-Br(2)	117.2(6)
C(2)-C(1)-C(7)	108.2(6)	O(1)-C(7)-C(9)	109.3(6)
C(8)-C(1)-C(7)	121.4(7)	O(1)-C(7)-C(6)	104.0(6)
C(1)-C(2)-C(3)	107.8(7)	C(9)-C(7)-C(6)	117.0(7)
C(1)-C(2)-H(2A)	126.1	O(1)-C(7)-C(1)	101.2(6)
C(3)-C(2)-H(2A)	126.1	C(9)-C(7)-C(1)	116.2(6)
O(1)-C(3)-C(2)	103.3(6)	C(6)-C(7)-C(1)	107.4(5)
O(1)-C(3)-C(4)	108.0(6)	O(3)-C(8)-C(1)	111.9(7)
C(2)-C(3)-C(4)	107.6(5)	O(3)-C(8)-H(8A)	109.2
O(1)-C(3)-H(3A)	112.4	C(1)-C(8)-H(8A)	109.2
C(2)-C(3)-H(3A)	112.4	O(3)-C(8)-H(8B)	109.2
C(4)-C(3)-H(3A)	112.4	C(1)-C(8)-H(8B)	109.2
O(2)-C(4)-C(5)	124.3(6)	H(8A)-C(8)-H(8B)	107.9
O(2)-C(4)-C(3)	122.5(8)	C(7)-C(9)-H(9D)	109.5
C(5)-C(4)-C(3)	113.1(7)	C(7)-C(9)-H(9A)	109.5
C(6)-C(5)-C(4)	121.6(7)	H(9D)-C(9)-H(9A)	109.5
C(6)-C(5)-Br(1)	123.5(6)	C(7)-C(9)-H(9B)	109.5
C(4)-C(5)-Br(1)	114.8(5)	H(9D)-C(9)-H(9B)	109.5
C(5)-C(6)-C(7)	118.7(7)	H(9A)-C(9)-H(9B)	109.5

Symmetry transformations used to generate equivalent atoms:

Table 8. Anisotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for C₉H₈Br₂O₃. 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
Br(1)	36(1)	22(1)	12(1)	1(1)	3(1)	4(1)
Br(2)	29(1)	16(1)	18(1)	2(1)	5(1)	2(1)
O(1)	22(2)	20(3)	17(2)	-1(2)	-2(2)	3(2)
O(2)	28(2)	21(4)	19(3)	0(2)	7(2)	0(2)
O(3)	27(2)	41(4)	19(2)	6(3)	4(2)	1(2)
C(1)	22(2)	18(4)	10(3)	6(3)	-4(2)	-2(3)
C(2)	26(3)	28(5)	8(2)	2(3)	2(2)	-4(3)

C(3)	33(3)	21(5)	9(3)	-1(3)	-1(2)	0(3)
C(4)	21(2)	26(5)	11(3)	-4(3)	3(2)	4(3)
C(5)	24(3)	15(4)	13(3)	-3(3)	5(2)	1(3)
C(6)	27(3)	23(4)	13(3)	1(3)	7(3)	-2(3)
C(7)	25(3)	22(4)	7(3)	1(3)	-3(3)	-1(3)
C(8)	28(3)	24(4)	15(3)	3(3)	3(3)	0(3)
C(9)	32(3)	32(5)	18(4)	1(3)	4(3)	-9(3)

Table 9. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($\text{\AA}^2 \times 10^{-3}$) for C₉H₈Br₂O₃.

	x	y	z	U(eq)
H(3O)	7307	3518	1173	43
H(2A)	3933	5843	1676	25
H(3A)	669	6308	2438	25
H(8A)	5639	1849	2066	27
H(8B)	4345	1711	392	27
H(9D)	388	1502	276	41
H(9A)	-477	773	1721	41
H(9B)	1639	233	1416	41

Table 10. Torsion angles [$^\circ$] for C₉H₈Br₂O₃.

C(8)-C(1)-C(2)-C(3)	-173.4(6)	O(2)-C(4)-C(5)-C(6)	-171.6(7)
C(7)-C(1)-C(2)-C(3)	3.4(7)	C(3)-C(4)-C(5)-C(6)	5.8(9)
C(7)-O(1)-C(3)-C(2)	39.6(6)	O(2)-C(4)-C(5)-Br(1)	5.0(9)
C(7)-O(1)-C(3)-C(4)	-74.2(6)	C(3)-C(4)-C(5)-Br(1)	-177.7(4)
C(1)-C(2)-C(3)-O(1)	-26.9(7)	C(4)-C(5)-C(6)-C(7)	-3.2(10)
C(1)-C(2)-C(3)-C(4)	87.2(8)	Br(1)-C(5)-C(6)-C(7)	-179.5(5)
O(1)-C(3)-C(4)-O(2)	-149.8(6)	C(4)-C(5)-C(6)-Br(2)	177.8(5)
C(2)-C(3)-C(4)-O(2)	99.3(8)	Br(1)-C(5)-C(6)-Br(2)	1.5(9)
O(1)-C(3)-C(4)-C(5)	32.8(7)	C(3)-O(1)-C(7)-C(9)	-159.8(5)
C(2)-C(3)-C(4)-C(5)	-78.1(8)	C(3)-O(1)-C(7)-C(6)	74.5(6)

C(3)-O(1)-C(7)-C(1)	-36.8(6)
C(5)-C(6)-C(7)-O(1)	-36.3(8)
Br(2)-C(6)-C(7)-O(1)	142.7(5)
C(5)-C(6)-C(7)-C(9)	-156.9(7)
Br(2)-C(6)-C(7)-C(9)	22.2(8)
C(5)-C(6)-C(7)-C(1)	70.4(8)
Br(2)-C(6)-C(7)-C(1)	-110.6(6)
C(2)-C(1)-C(7)-O(1)	20.7(7)
C(8)-C(1)-C(7)-O(1)	-162.3(5)
C(2)-C(1)-C(7)-C(9)	138.8(7)
C(8)-C(1)-C(7)-C(9)	-44.2(8)
C(2)-C(1)-C(7)-C(6)	-88.0(7)
C(8)-C(1)-C(7)-C(6)	89.0(7)
C(2)-C(1)-C(8)-O(3)	-10.0(9)
C(7)-C(1)-C(8)-O(3)	173.6(5)

Symmetry transformations used to generate equivalent atoms:

Table 11. Hydrogen bonds for C₉H₈Br₂O₃ [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(3)-H(3O)...O(1)#1	0.84	2.10	2.926(6)	167.4

Symmetry transformations used to generate equivalent atoms:

#1 x+1,y,z

Thermal Ellipsoid plot of **(+)-197**

