Heterocycles Old and New: Carbonylazoles as Chemoselective Acylation Reagents and the Synthesis and Applications of Benzindolizinones

by

Stephen Todd Heller

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Committee in charge:

Professor Richmond Sarpong, Chair
Professor Robert G. Bergman
Professor Daniel Nomura

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Abstract

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Carbonylazole derivatives have been shown to be chemoselective and efficient acylating reagents under a variety of conditions. Catalysis with pyridinium salts, as well as with DBU or DABCO are discussed, as is the thermal reaction of imidazole carbamates with carboxylic acids to provide esters. The application of a protic solvent-mediated cycloisomerization approach to two isomers of benzindolizinone – a relatively unstudied heterocyclic system – and the syntheses of two *Erythrina* alkaloids are also discussed.

Chapter 1 provides an overview of the fundamental importance of the carbonyl group in the chemistry of life, as well as in the service of man. Key processes through which these versatile groups react are illustrated with an emphasis on the chemistry of esters. The chapter concludes with a survey of the application of carbonylimidazoles as acyl donors from their first development by Staab to the present.

Through another line of inquiry, it was discovered that imidazole carbamates and ureas are chemoselective esterification and amidation reagents. The optimization, substrate scope, and mechanism of esterification and amidation of carboxylic acids mediated by imidazole-based reagents are discussed in Chapter 2. The innate reactivity of carbonyl imidazole reagents with a range of nucleophiles is also explored.

Following this initial discovery, it was found that pyridinium salts greatly enhance the reactivity of carbonylimidazole derivatives as acylation reargents for esterification and amidation. Chapter 3 details the development of this mode of catalysis and outlines a mechanistic proposal in which pyridinium salts act as both Brønsted acid and nucleophilic catalysts. Finally, the scope of this technology in the synthesis of difficult to access oxazolidinones, as well as esters and amides, is discussed. This work was executed in partnership with Tingting Fu.

Drawing on the possibility that carbonylazole acyl donors could be potentiated through nucleophilic catalysis, a DBU-catalyzed *N*-acylation of indoles and oxazolidinones was devised. Chapter 4 covers the development of this reaction, as well as the subsequent finding that this

acylation was chemoselective even in the presence of more reactive amine and alcohol functional groups. This work was performed in collaboration with Erica Schultz.

The solvent-promoted cycloisomerization of quinoline and isoquinoline propargylic carbinols to benz[e]- and benz[g]indolizinones, respectively, is described in Chapter 5. The study of the fundamental reactivity of these new heterocyclic motifs is discussed. The formal synthesis of 3-demethoxyerythratidinone using this cycloisomerization strategy, as well as its application in studies toward the synthesis of cocculidine are also detailed.

To my loving family, for all the warmth, light, and kisses

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Acknowledgements

The Road Not Taken

Two roads diverged in a yellow wood,
And sorry I could not travel both
And be the one traveler, long I stood
And looked down one as far as I could
To where it bent in the undergrowth;

Then took the other, as just as fair,
And having perhaps the better claim,
Because it was grassy and wanted wear;
Though as for that the passing there
Had worn them really about the same,

And both that morning equally lay
In leaves no step had trodden black.
Oh, I kept the first for another day!
Yet knowing how way leads on to way,
I doubted if I should ever come back.

I shall be telling this with a sigh
Somewhere ages and ages hence:
Two roads diverged in a wood, and I—
I took the one less traveled by,
And that has made all the difference.

-Robert Frost, Mountain Interval, 1920.

It is impossible to name with certainty all of the people who have contributed to the road that I have walked to this point, but these mentors in particular have cumulatively shaped my scientific and professional outlook. Professor Richmond Sarpong provided me with a lab in a dark hour, afforded subtle and effective guidance, and provided me room to take wing. Professor Bergman has acted as an invaluable resource in planning mechanistic studies; however, he has also served as a pedagogical mentor, and my teaching will forever reflect his influence. Professors Toste and Trauner took the first cuts at an unhewn chemist, and their styles and traits are indelible. Professor Rousslang inspired a young man with too many interests and instilled a flame for chemistry. Dr. Ravi Natarajan removed the yoke of corporate science and provided a safe environment for a budding chemist to whet their curiosity through original research.

Over the years, I have had the good fortune to work in the company of a diverse and stimulating group of people. My Toste group classmates, Chris Boyd, Dan Gray, and Jane Wang made time in lab more fun than it should have been. Our different areas of expertise also provided a ready-made discussion group. I am grateful for their friendship, advice, and support.

My first fall in the Sarpong group was momentous for many reasons, but the introduction of a new cast of characters was one of the most enjoyable parts of this transition. I am deeply indebted to my labmates in the corner office of Latimer: Jesse Cortez, Amy Hamlin, David Lapointe, and Raul Leal. The entire Sarpong community gave me a warm welcome and I have continued to feel blessed to work with everyone in the group.

Though they didn't have the dubious distinction of sharing a lab with me, a number of other members of the Berkeley community were key players in my experience in graduate school. Aaron Lackner and Jeff Wu have been great friends and didn't hold it against me when I left the Toste group. They even let me come back and use the HPLC. Even though we overlapped only relatively briefly, I relished my conversations with Ethan Fisher, whether they were about old school rap, chemistry, or topics not to be mentioned in a dissertation. I want to thank Terry Lebold for all of his encouragement, kind words, and stimulating discussion. In particular, his emphasis on working collaboratively has been invaluable to the group.

My horizons have been greatly expanded by working with Erica Schultz, my partner in indole crime, and a fantastic resource for the group. I look forward to the day when we are both tenured faculty members and running into each other at conferences with students in tow. It has been great working directly with Jim Newton to win softball games, drink a bunch of bad beer, and develop the coolest ketone synthesis since Grignard. I was unbelievably lucky to work with a highly skilled undergraduate student, Tingting Fu for over a year, and her hard work and dedication are manifest in the pyridinium catalysis work. Though we got off to a rough start, working with Alison Hardin Narayan on the solvent-promoted cycloisomerization was a fantastic experience. I also greatly appreciated the good idea/bad idea interludes.

Jessica (Wood) Harrick has been a great friend, an excellent resource for solving chemical problems, and as a co-teacher – Chemistry 115 was a blast, even though we had to work our tails off. I am grateful for her suggestion to join the Sarpong lab. That invitation means more to me than she will ever know. Scott West and Rachel Zeldin have become some of my best friends. Because our bonds were forged under the intensity of graduate study, our BDEs are higher than the Si-F bond. Seeing them almost every day was such a positive aspect of my experience.

My parents put up with an AWOL son for five years and were always supportive, even at the nadir of my graduate school experience. Though they might not get what I did on a day-to-day basis, they understood what it meant to dedicate oneself to the task at hand, and what it meant to feel that you were failing at it. Indeed, without their wisdom and example, I would not have made it this far.

Five years of long hours and high stress take their toll on any relationship, but Lisa Quay put up with my perpetual exhaustion and has been a pillar of support throughout my graduate studies. I'm not sure how I got so lucky. You and Dewey mean the world to me, and coming home each day to my little family has provided me with endless happiness.

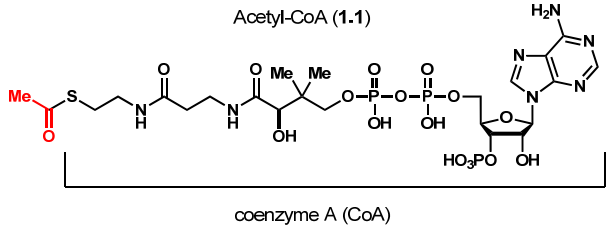
Chapter 1. Importance of the Carbonyl Group: Acylation and Its Applications

1.1 Carbonyls as Biological Lynchpins

Carbonyls underpin all life on Earth. The facile biochemical interconversion of carbonyl-based functional groups facilitates fundamental processes such as the citric acid (Krebs) cycle and the synthesis of a great number of biomolecules. In heterotrophs, these processes typically exploit the thermodynamic driving force for stepwise exhaustive oxidation of carbon to carbon dioxide (ΔH_f^o = -94.1 kcal/mol) and extract bioavailable energy along the way. This overall transformation occurs through a large number of biochemical manipulations producing a variety of intermediates of different carbon oxidation levels, the extent of which dictates the type of functional group in which the carbon atom is a part. For instance, most carbohydrates consist of carbon atoms at the alcohol and aldehyde oxidation levels. These chemical inputs provide the foundation for glycolysis, through which all heterotrophic life gains energy by oxidizing these building blocks to pyruvate.[1]

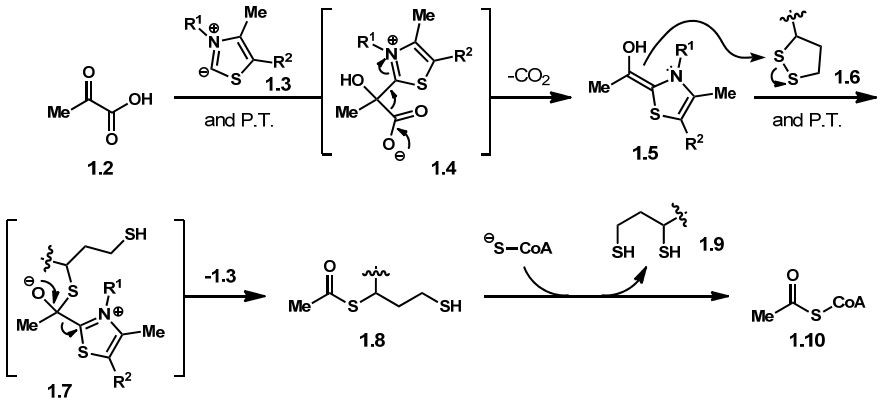
In turn, the acetyl group (in red) of acetyl-CoA (Figure 1.1, **1.1**) is formed by pyruvate decarboxylation. The central role **1.1** plays in the citric acid cycle as a carbon shuttle thus fuses these two metabolic pathways. Moreover, **1.1** is also involved in some of the main biosynthetic pathways that support life; fatty acid, isoprenoid, and polyketide synthesis, as well as post-translational modification. The implication of **1.1** in biosynthesis, the citric acid cycle, and as the ultimate product of glycolysis renders tangible the conceptual link between these processes – that they are governed by the chemistry of carbonyl groups.

Figure 1.1. Structure of Acetyl-CoA



The conversion of pyruvate to acetyl-CoA by pyruvate dehydrogenase serves as a valuable example of the wealth, but also the similarity of the biochemical reactions that can be brought to bear on a substrate. The ketone group of pyruvic acid (Scheme 1.1, **1.2**) suffers attack by thiazolium **1.3,** derived from vitamin B_1. The tetrahedral intermediate (**1.4**) arising from this reaction is transient and decomposes by decarboxylation to afford enol **1.5**. This so-called Breslow intermediate[2] is now nucleophilic at the carbon originally a part of the ketone group and can attack disulfide **1.6** to form **1.7**. A second enzyme, dihydrolipoyl transacetylase, then catalyzes a transthioesterification, the exchange of two differentiated thiol groups at a carbonyl carbon center, with CoA to afford **1.10**.

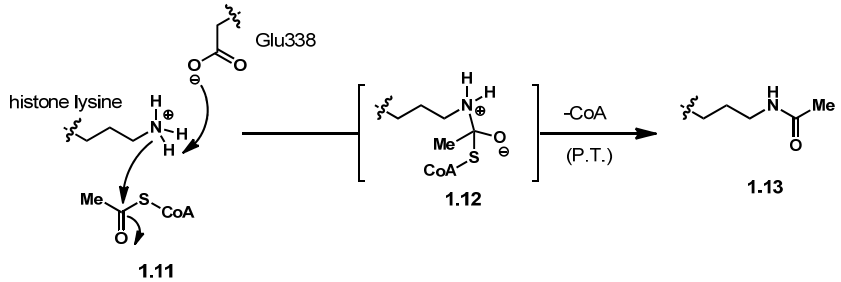
Scheme 1.1. Biosynthesis of Acetyl-CoA



Indeed, the acetylation of heteroatomic nucleophiles present in biomolecules is a fundamental biochemical transformation. For instance, the acetylation of *N*-terminal lysine residues acts as a significant post-translational modification for the regulation of histones such as those present in chromatin (involved in nucleosome formation).[3] This biochemical modification is considered by many to be a form of epigenetic tagging allowing for control over the rate of gene transcription.[4]

In this case, the acetylation reaction is catalyzed by a histone acetyltransferase, which catalyzes the transfer of an acetyl group from acetyl-CoA to the terminal lysine of histones. The mechanism of catalysis is thought to involve preorganization of the lysine and acetyl-CoA into a ternary complex (Scheme 1.2, **1.11**) such that an initial unfavorable deprotonation event (recall that lysine side chain amines are protonated under physiological conditions) is coupled to the attack of the nascent free amine onto the thioester group. A zwitterionic tetrahedral intermediate (**1.12**) forms that can then eject a thiolate anion to form the acetamide (**1.13**), completing the nucleophilic acyl substitution reaction. Though the exact protonation states of the relevant heteroatoms is apparently unknown for the enzyme mediated process outlined in Scheme 1.2, these fine details can play a crucial role in the fate of carbonyl-derived tetrahedral intermediates (see Chapter 5). Proton transfer then leads to formation of CoA and the acetylated histone lysine (**1.13**).

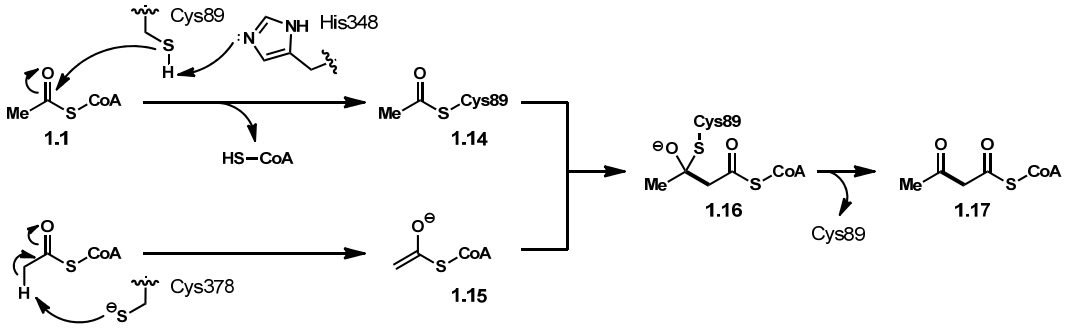
Scheme 1.2. Mechanism of Histone Acetylation



Though enzymatically distinct from post-translational acetylation, the citric acid cycle, and glycolysis; fatty acid, polyketides, and isoprenoids biosynthesis are mechanistically related through the common manipulation of carbonyl groups. The fundamental process involved in the latter three pathways is the extension of the carbon chain of acetyl-CoA by a Claisen condensation, giving rise to a ketone.[5] This transformation is most easily described in the

context of the thiolase-catalyzed synthesis of acetoacetyl-CoA (Scheme 1.3, **1.17**) from acetyl-CoA.[6] A thiolate anion generated from Cys89 and His348 undergoes transthioesterification to generate an acetylated cysteine residue (**1.14**). Meanwhile, another molecule of acetyl-CoA is deprotonated by the thiolate of Cys378 to yield enolate **1.15**. These two species are held in close proximity in the catalytic pocket of thiolase, allowing them to undergo the Claisen condensation. Therefore, through the intervention of thiolase, basic carbonyl chemistry allows for the construction of simple carbon building blocks through which the vast array of hydrocarbon-based biomolecules are produced.

Scheme 1.3. Biosynthesis of Acetoacetyl-CoA By Claisen Condensation



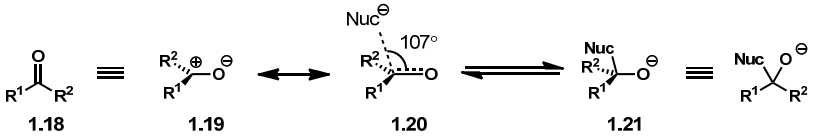
There are a staggering number of examples in which the carbonyl group is used in biochemical processes. However, just as impressive is the homology of the fundamental reactivity of this functional group. In most cases the carbonyl acts as an electrophile with an appended departing group, allowing for the chemical exchange of two substructures. A large percentage of bond-forming biochemical reactions involve the use of carbonyl groups as a tamed electrophile, stable under physiological conditions but readily freed to engage nucleophiles by way of enzyme catalysis. For instance, polypeptides – one of the pillars on which life rests – are constructed entirely from amides because of the chemical properties and stability that this linkage affords. Truly, nature stitches with carbonyls.

1.2 Carbonyls in the Service of Man: A Primer on Carbonyl Reactivity

Perhaps then, it is poetic coincidence that what took more than a billion years to evolve on Earth has been readily adopted by man as a core strategy for the manipulation of carbon-based matter. As demonstrated in the context of biochemical systems, the chemistry of carbonyl functional groups is largely one of carbon electrophilicity due to the polarization of the C-O π-bond (Scheme 1.4, see **1.18** and **1.19**). Consequently, they have been used to introduce new bonds through interaction with a nucleophilic species. This paradigm may be generalized into two broad catagories: addition and substitution.

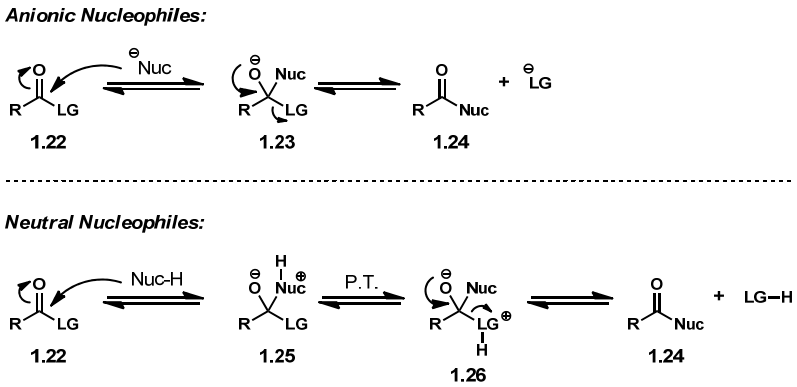
In the addition mode of reactivity, a nucleophile interacts primarily with the C-O π* LUMO, approaching at an angle that maximizes overlap between this antibonding orbital and the HOMO of the incoming nucleophile (see **1.20**).[7] The resulting adduct (**1.21**), which is tetrahedral, has a geometry distinctly different from the planar carbonyl species, reflecting the sp^3 hybridization of the carbon center. This addition process is readily reversible and weak nucleophiles tend not to form stable adducts.[8]

Scheme 1.4. Addition Reactions of Carbonyl Compounds



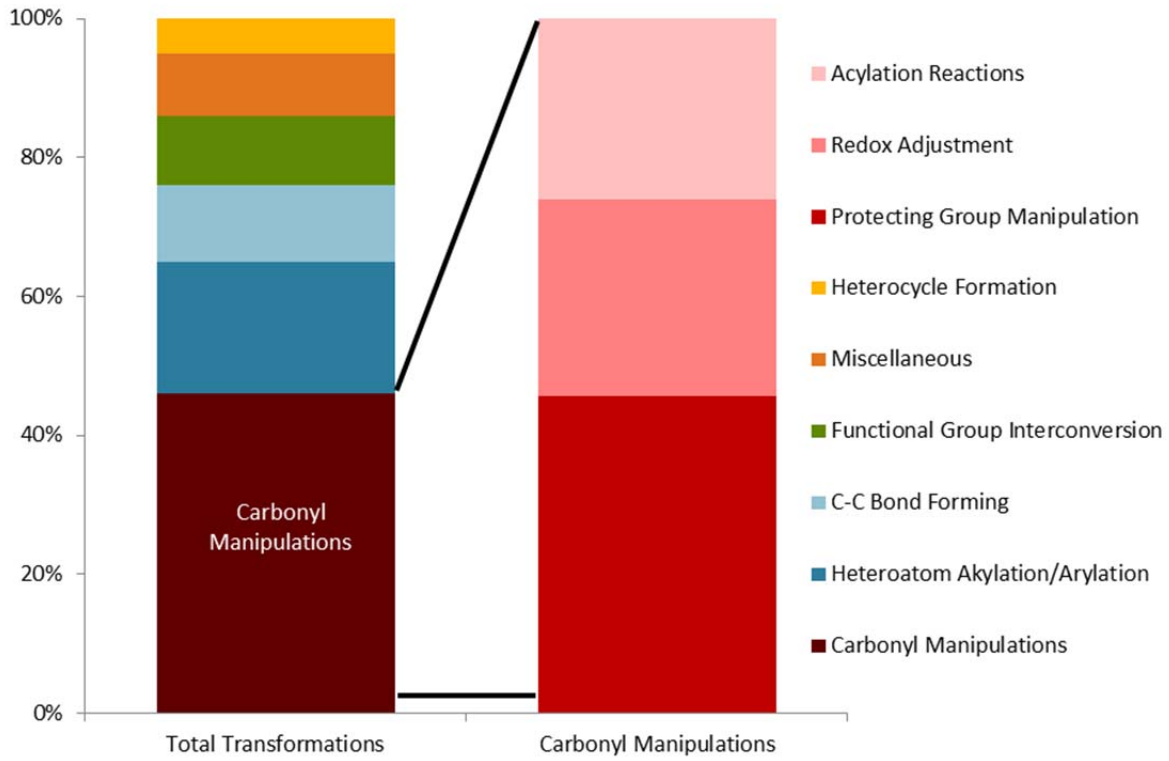
Using isotopic labels, Bender conclusively showed that if a competent nucleofuge is bound to the carbonyl substrate (Scheme 1.5, see **1.22**), a net substitution reaction occurs in what is now referred to as the "addition-elimination" mechanism.[9,10] This scenario involves an initial nucleophilic addition; however, the tetrahedral intermediate (**1.23**) is now able to restore the C-O π-bond (see **1.24**) by ejecting the nucleofuge. As before, the addition process is fully reversible, and its success in a preparative capacity is determined by the relative stabilities of the starting material and product. When a new group is introduced to the carbon of the carbonyl group, this overall process is referred to as a nucleophilic acyl substitution (S_NAc). Depending on the nature of the nucleophile, proton transfers are sometimes involved in the decomposition of tetrahedral intermediates such as **1.25**. One such possibility is shown in Scheme 1.5. While the addition reaction is commonly used for the creation of new C-C bonds,[11] it is primarily exploited as an elementary step in the S_NAc reaction. The remainder of this discussion will therefore focus on the substitution process.

Scheme 1.5. Mechanisms of Nucleophilic Acyl Substitution



Because of the rich diversity of physicochemical properties afforded by carbonyl functional groups, a great deal of effort has been expended to understand the mechanistic details of the fundamental reactions of carbonyl compounds. Furthermore, their ubiquity in commercial materials (*vide infra*) implies that a large number of synthetic operations involve the introduction and manipulation of carbonyl groups. For example, a meta-analysis of the process chemistry of three large pharmaceutical companies showed that 15% of all transformations involved acylation reactions (Figure 2).[12] When one takes into account the fact that many protecting group schemes and functional group interconversions involve the manipulation of carbonyl species, the truly overwhelming influence of carbonyl chemistry becomes apparent.[13]

Figure 1.2. Acylations As a Percentage of Reactions in the Manufacture of Pharmaceuticals



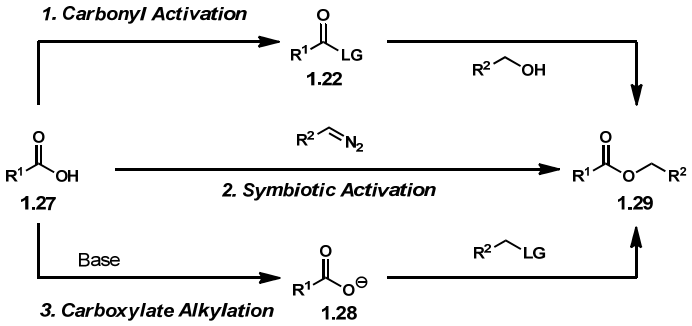
Broadly speaking, there are two modes of introducing carbonyl groups, acylation and carbonylation. In the former, a carbonyl electrophile at the carboxylic acid oxidation level is transferred to a nucleophilic species, usually through the S_NAc mechanism.[14] In the latter, an electrophile at the carbon dioxide oxidation level is interacted with *two* nucleophiles through sequential S_NAc reactions. There are variations on this mechanistic theme, including transition-metal catalyzed carbonylation reactions; however, the topology of the overall transformation remains the same. Both of these fundamental processes are widely used and a variety of synthetic tactics have been developed to effect them, as we will see through the lens of two of the most important chemical feedstocks containing carbonyl groups – acetic acid and phosgene.

1.3 Acetic Acid and the Process of Acylation

Approximately five million tons of acetic acid is produced every year,[15] of which nearly 75% come from various schemes to carbonylate methanol.[16] The bulk of this material is used in the synthesis of vinyl acetate monomer and as a solvent in the production of *o*-terephthalic acid. However, 18% of the total global supply, or approximately one million tons, of acetic acid is used as an acylating agent via S_NAc reactions. For instance, the dehydrative synthesis of acetic anhydride is used to provide a feedstock for exhaustive cellulose acetylation.[17] Commercial esters are also sometimes prepared from acetic acid using the Fischer esterification. Thus it is clear that acetic acid is a key reactant for the synthesis of industrially important esters through the acylation of an alcohol. Moreover, this transformation can serve as a representative case for the acylation of other nucleophiles.

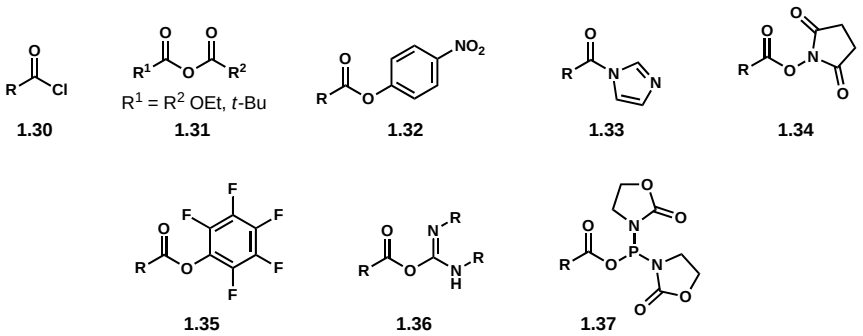
The conversion of a carboxylic acid (Scheme 1.6, **1.27**) into an ester (**1.29**) involves the exchange of water for an alcohol, a challenging S_NAc reaction due both to the reversibility of the process as well as the poor nucleophilicity associated with neutral hydroxy groups. A vast array of tactics have been designed to ameliorate these issues; however, they can be distilled into three paradigms of esterification (Scheme 1.6): (1) Carbonyl activation, (2) symbiotic activation, in which acid and and reagent form a reactive ion pair that can collapse to an ester product, and (3) conversion of an acid substrate to a carboxylate anion (**1.28**) that can be alkylated. A summary of both carbonyl activation and alkylation strategies can be found below, whereas a detailed discussion of the symbiotic pathway can be found in Chapter 2.

Scheme 1.6. Paradigms for Esterification



Carbonyl activation is typically achieved through preformation of an activated ester intermediate, that is, a carbonyl group to which a good nucleofuge is attached (**1.22**). Acyl chlorides (LG = Cl, Figure 3, **1.30**) are excellent examples of such species, as are anhydrides (**1.31**). These species are powerful electrophiles and typically offer little selectivity among nucleophilic groups, so a large body of work has emerged that details the use of moderately less reactive groups, including acyl *p*-nitrophenoxy groups (**1.32**),[18] acylimidazoles (**1.33**, *vide infra*),[19] *N*-hydroxysuccinimide esters (**1.34**),[20] and acyl pentafluorophenoxy groups (**1.35**).[21] In these cases, the reaction of alcohols (as well as other nucleophiles) proceeds through the S_NAc mechanism described above (Scheme 1.5). Modern esterification reactions often proceed through *in situ* formation of an activated ester intermediate such as *O*-acylisoureas (**1.36**),[22] mixed anhydrides (**1.31**, $R^1 \neq R^2$),[23] and acylphosphinites (**1.37**).[24]

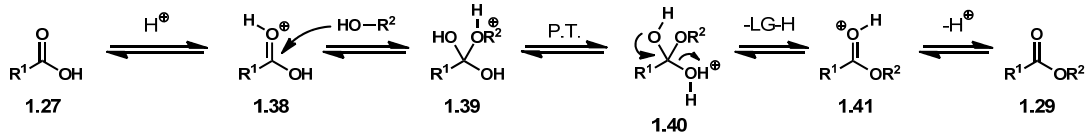
Figure 1.3. Exemplary Activated Esters Used in the Carbonyl Activation Paradigm



Many of these activated esters have been applied to the synthesis of other carboxylic acid derivatives, such as amides and thioesters, and even to the formation of new C-C bonds. In many cases, the only deviation from the general S_NAc mechanism described in this chapter is the nature of the nucleophile. As such, we refer the reader to several comprehensive reviews.[25]

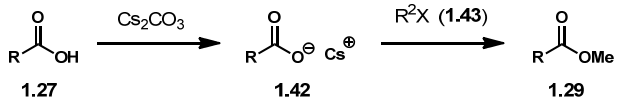
Another method of carbonyl activation involves the complexation of the carbonyl oxygen with an acid. In this case, the acid catalyzes the addition step by further polarizing the C-O π-bond. Indeed, the most widely used method for the production of esters, the Fischer-Speier esterification, exploits this mode of carbonyl activation.[26] Originally reported in 1895, Fischer observed that catalytic quantities of mineral acid allowed for successful coupling of carboxylic acids with alcohols. We now know that this reaction proceeds through Brønsted acid catalysis in which the carbonyl is protonated (Scheme 1.7, see **1.38**), followed by addition of the alcohol nucleophile to give rise to a cationic tetrahedral intermediate (**1.39**). Solvent-assisted proton transfer (not shown) then generates a nascent leaving group, water (see **1.40**). The carbonyl is restored, followed by proton loss to regenerate the catalytic acid and yield an ester (**1.29**). Therefore, acid catalyzed reactions are associated with the carbonyl activation paradigm because of the *in situ* formation of a good nucleofuge.

Scheme 1.7. Mechanism of the Fischer-Speier Esterification



However, some applications may require that the carboxylic acid be used as a nucleophile rather than attempt to render it electrophilic. In these instances, the acid can be quantitatively deprotonated, usually using a carbonate base with a weakly-coordinating countercation, to afford a nucleophilic carboxylate salt (Scheme 1.8, **1.42**).[27] Strong electrophiles such as iodomethane or allyl bromide (e.g., **1.43**) can then be introduced in order to effect an S_N2 displacement, forging the ester (**1.29**) C-O σ-bond. Of course, this tactic places significant limitations on the scope of the alkyl group introduced and in practice requires harsh conditions and high reaction temperatures. As such, carbonyl activation has remained the primary strategy for the synthesis of carboxylic acid derivatives. Further discussion of tactics for esterification and amidation can be found in Chapters 2 and 3.

Scheme 1.8. Carboxylate Alkylation



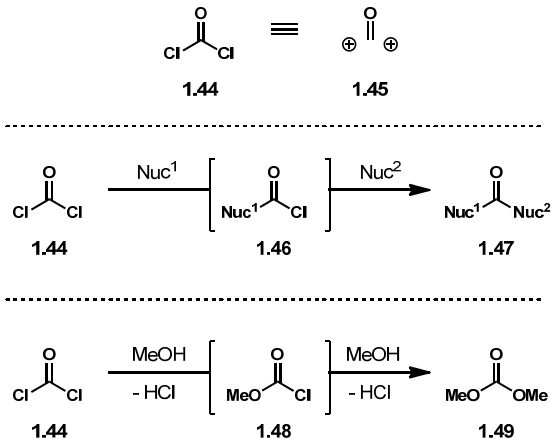
1.4 Phosgene and the Process of Carbonylation

By far the most prevalent electrophile for carbonylation in industrial chemistry, phosgene (Scheme 1.9, **1.44**) has historically played a vital role in the production of a vast array of organic compounds. Recent estimates have placed the global production of phosgene at more than 10 million tons annually.[28] However, it is difficult to assess the accuracy of such a claim as the serious safety risks that phosgene poses requires that the vast majority of phosgene is produced in co-located manufacturing plants. Though it is a powerful and economical reagent, we will see

that the hazards associated with phosgenation reactions have driven active research to find safe alternatives.

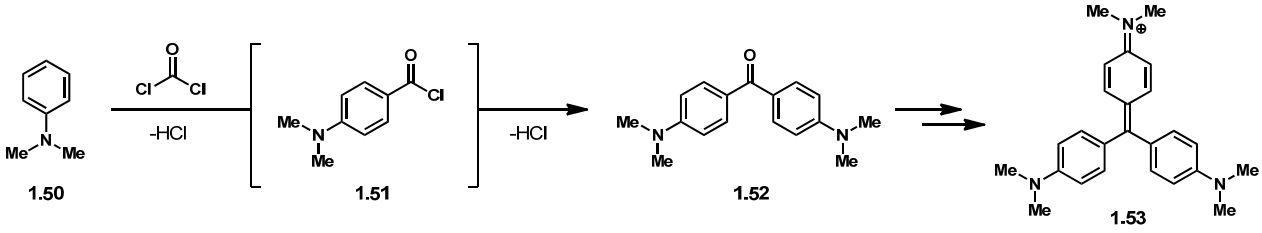
Unique among early carbonyl electrophiles, phosgene is an effective synthetic equivalent to the carbonyl dication synthon (**1.45**). In practice, **1.44** reacts with nucleophiles to form an intermediate carbonyl chloride (**1.46**), which is still sufficiently electrophilic to engage a second equivalent of nucleophile. In general, both reactions are facile and therefore synthesis of unsymmetrical carbonyl derivatives ($Nuc^1 \neq Nuc^2$) is challenging. However, phosgene has historically been the electrophile of choice for the synthesis of symmetrical ($Nuc^1 = Nuc^2$) species. For instance, until recently, dimethyl carbonate (**1.49**) was produced by the reaction of methanol with phosgene. The intermediate methyl chloroformate (**1.48**) is also produced by this route. Indeed, virtually all carbonate derivatives are produced from **1.44**.

Scheme 1.9. Phosgene as a Carbonyl Dication Synthon



One of the first industrial applications of phosgene was in the early synthetic dye industry. Michler developed a double Friedel-Crafts acylation with phosgene to synthesize the eponymous ketone (Scheme 1.10, **1.52**) from aniline derivative **1.50**. Though little was known about the mechanisms underlying this transformation at the time, it is now apparent that an acid chloride (**1.51**) is first produced, which can then go on to react with another molecule of **1.50**. Ketone **1.52** is still widely used in industrial dyes such as crystal violet (**1.53**) and is produced using the route described by Michler in 1876, one of the earliest examples of the inherent utility of the carbonyl dication synthon.[29]

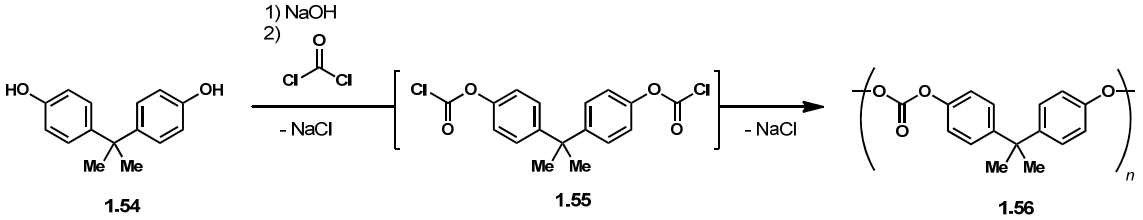
Scheme 1.10. Synthesis of Michler's Ketone



This ability to link two nucleophilic groups through the production of stable carbonyl functional groups makes phosgene a critical reagent for the synthesis of robust polymers and highlights its aptitude as a conjunctive reagent. About one billion kilograms of polycarbonate

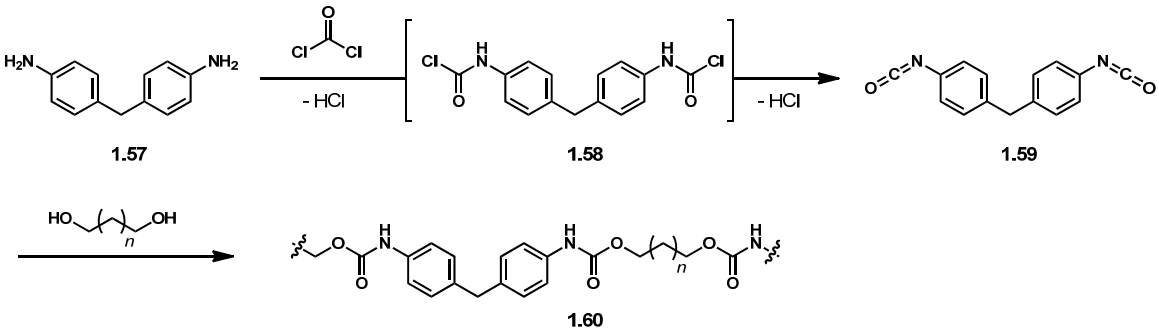
plastics are produced annually through the reaction of a diol monomer such as bisphenol A (Scheme 1.11, **1.54**) with **1.44** to produce a carbonate linkage (see **1.56**) via a transient chloroformate intermediate (**1.55**).[30]

Scheme 1.11. Production of Polycarbonates Using Phosgene



Similarly, the manufacture of polyurethanes requires large quantities of isocyanates (i.e., **1.59**, Scheme 1.12,), which are produced by the reaction of amines with phosgene. Initial nucleophilic acyl substitution occurs to yield a transient carbamyl chloride species (**1.58**), which undergoes rapid α-elimination to yield the isocyanate. For instance, over 5 million tons of methylenediphenyl diisocyanate (**1.59**) from bis-aniline (**1.57**) is produced each year using this process. Other isocyanates are also produced on a multi-ton scale, almost all of which are consumed by the production of polyurethane (**1.60**) materials by reaction with diols or polyols.

Scheme 1.12. Production of Polyurethanes from Phosgene

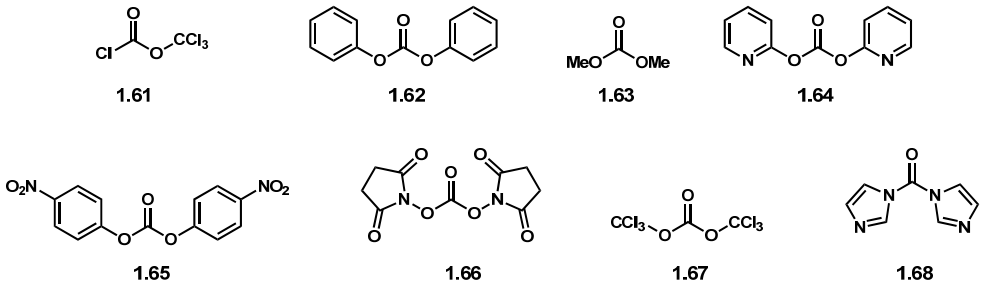


Phosgene has similar uses in bench scale chemistry, empowering the modern synthetic chemist to easily prepare a number of carbonyl-containing functional groups. However, the safety controls afforded by dedicated and specially designed plants are absent in the laboratory setting, and even on the manufacturing scale, fatal accidents still occur.[31] As such, significant effort has been directed toward development of safer phosgene equivalents. From an environmental and industrial standpoint, carbon dioxide would be the best replacement, and limited success has been achieved for the production of carbamates and carbonates from this feedstock.[32] However, it is too unreactive for many applications, and so tamed versions of phosgene continue to be used when the economics of the application allows.

The gaseous nature of phosgene makes it particularly dangerous, so the general strategy underlying these endeavors has been to retain the reactive carbonyl, but replace the nucleofuge (chlorides in phosgene) with other groups that render the reagent nonvolatile. Some of the more commonly used phosgene equivalents include **1.66**, **1.67**, and **1.68** (Figure 4).[33] Triphosgene (**1.67**), which generates phosgene *in situ* upon reaction with water, is a stable solid. *N*,*N*'-Disuccinimidyl carbonate (**1.66**) finds application in the synthesis of biochemically relevant

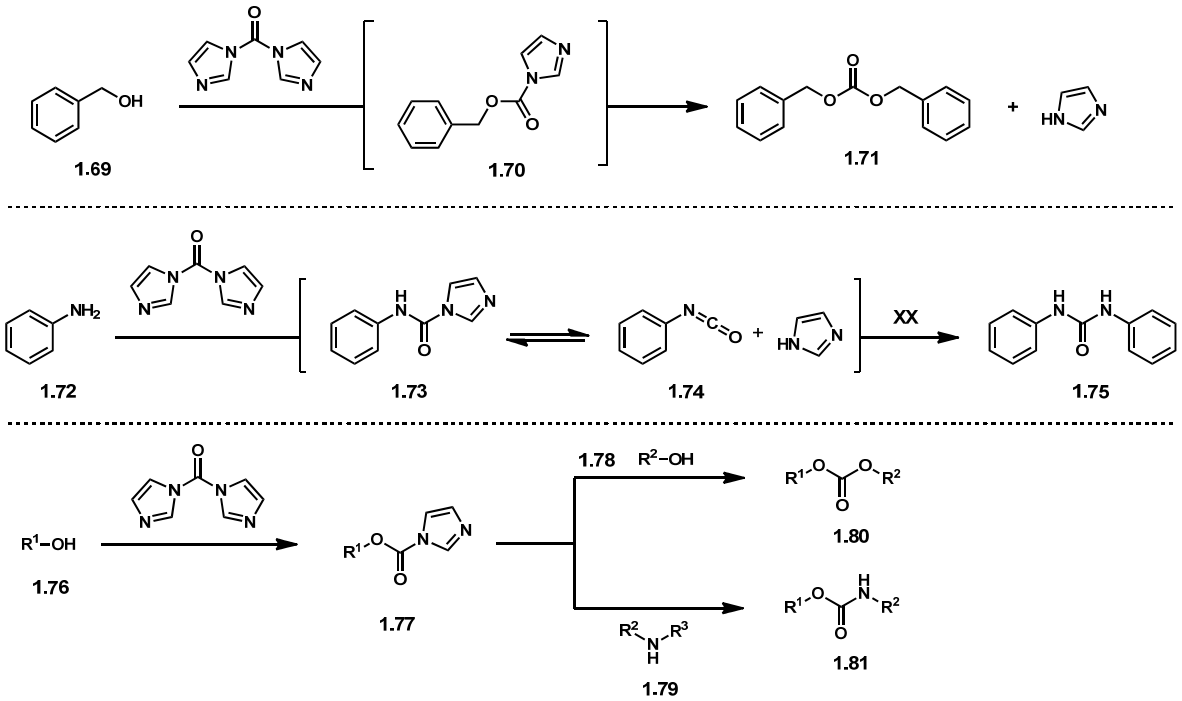
molecules, but is cost-prohibitive for large-scale syntheses. Out of this set of reagents, 1,1'-carbonyldiimidazole (CDI, **1.68**) has emerged as the most versatile and effective phosgene replacement. Originally developed by Staab,[34] CDI is now used on an industrial scale in the synthesis of high value compounds such as pharmaceuticals, fine chemicals, and some agrochemicals. For instance, as of 2006, 11% of acylation reactions performed at three large pharmaceutical companies employed CDI.[35]

Figure 1.4. Popular Phosgene Equivalents



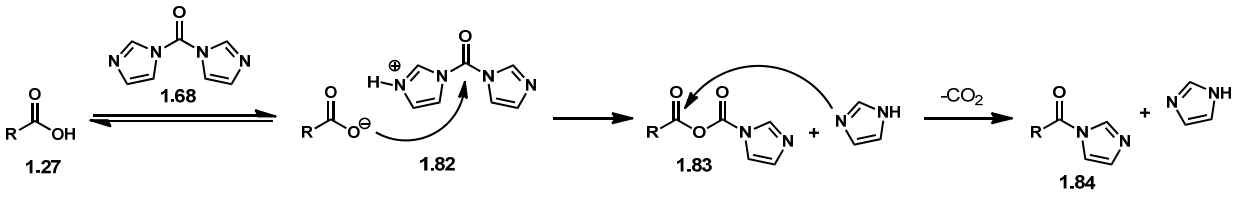
Subsequent to Staab's initial report, CDI was shown to participate readily in most of the reactions that were previously performed using phosgene, though it has been found to be somewhat less reactive. For instance, it reacts with alcohols (Scheme 1.13, **1.69**) to form symmetrical carbonates (**1.71**) and with amines (**1.72**) to form ureas (**1.75**) via an isocyanate intermediate (**1.74**).[36] Moreover, the attenuated reactivity of intermediates such as **1.77** allow for the selective mono-addition of nucleophiles to CDI, and therefore the synthesis of unsymmetrical carbonates (**1.80**) and carbamates (**1.81**) can be easily achieved by controlling the stoichiometry of the reagents.[37] Conveniently, the imidazole nucleofuge also serves as a base. Further discussion of the use of CDI as a carbonylation reagent can be found in Chapter 3.

Scheme 1.13. Reactivity of CDI as a Tamed Phosgene Equivalent



Shortly after its appearance in the literature, Anderson showed that CDI reacts with carboxylic acids to provide acylimidazoles.[38] Staab concluded that the mechanism of this transformation involved initial proton transfer to generate an ion pair (Scheme 1.14, **1.82**).[39] Subsequent attack of the carboxylate on the carbonyl of CDI through an S_NAc mechanism would lead to mixed anhydride **1.83** and a molecule of imidazole, which could then decompose to an acylimidazole (**1.84**) by another S_NAc displacement involving the acyl carbonyl of **1.83**. With a convenient way to prepare these activated esters directly from carboxylic acids in hand, a number of researchers sought to develop acylation reactions using acylimidazoles.

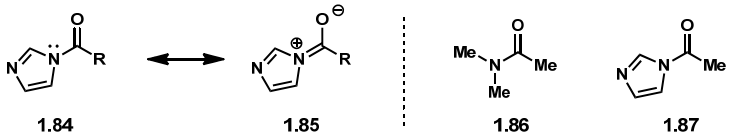
Scheme 1.14. Formation of Acylimidazoles from CDI and Carboxylic Acids



1.5 Carbonylimidazole Derivatives as Chloroformate and Acyl Chloride Substitutes

Even though the use of acylimidazoles as acyl electrophiles has been known since at least 1953,[40] it wasn't until the pioneering work of Staab and Anderson that they began to find application in synthetic organic chemistry. Formally amides, acylimidazoles have unusual structural features that make them moderately electrophilic. Of these, the most significant is the localization of the lone pair of the amide nitrogen (Scheme 1.15, see **1.84**) in the aromatic system of the imidazole ring, lowering the C-N bond order by disfavoring resonance structure **1.85**. This is inferred from the relatively high IR stretching frequency of the carbonyl of acetylimidazole (**1.87**) of 1730 cm^{-1}, nearly 70 wavenumbers greater than that of *N*,*N*-dimethylacetamide (**1.86**). Similarly, the barrier to rotation about the N-C(O) bond of **1.87** was found to be 10.5 kcal/mol, much lower than the 14-18 kcal/mol typical of an amide N-C(O) bond.[41] Thus the carbonyl does not enjoy the resonance stabilization of a typical amide and displays reactivity more akin to a destabilized ester. Accordingly, the first reactions of these derivatives that were extensively explored were simple S_NAc transformations to produce carboxylic acid derivatives.

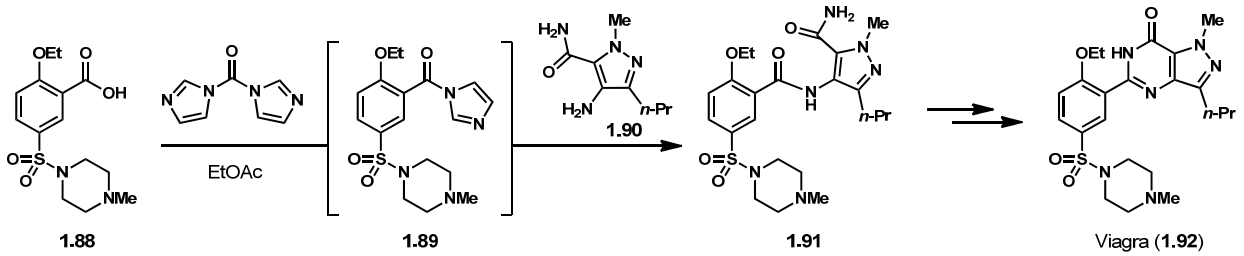
Scheme 1.15. Contrasting Carbonylimidazoles with Amides



In the period between 1957 and 1964, the synthesis of amides,[42] hydrazides,[43] hydroxamic acids,[44] and peroxy esters had been reported.[45] However, the reaction of acylimidazoles with alcohols to provide esters was found to be quite slow, with reaction temperatures in excess of 70 °C required.[46] Alternatively, catalytic amounts of alkoxides allow esterification to occur at room temperature. Even so, the use of acylimidazoles as safe, bench-stable activated esters has found widespread adoption in chemical industry, and especially in the manufacture of pharmaceuticals. The final Pfizer process for the synthesis of Viagra (Scheme

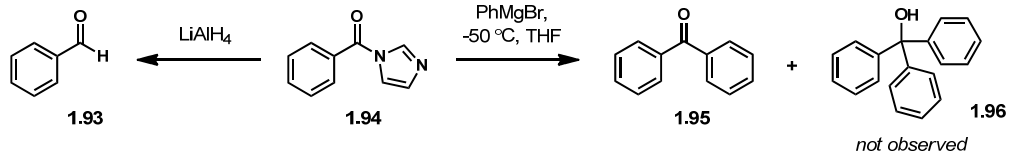
1.16, **1. 92**) involves a CDI-mediated amidation of **1.88** that proceeds via an acylimidazole intermediate (**1.89**).[47] Finally, acylimidazoles find use in biochemistry, where acetylimidazole is used as a tyrosine-selective derivatization reagent.[48]

Scheme 1.16. CDI-Mediated Amide Synthesis in the Production of Viagra



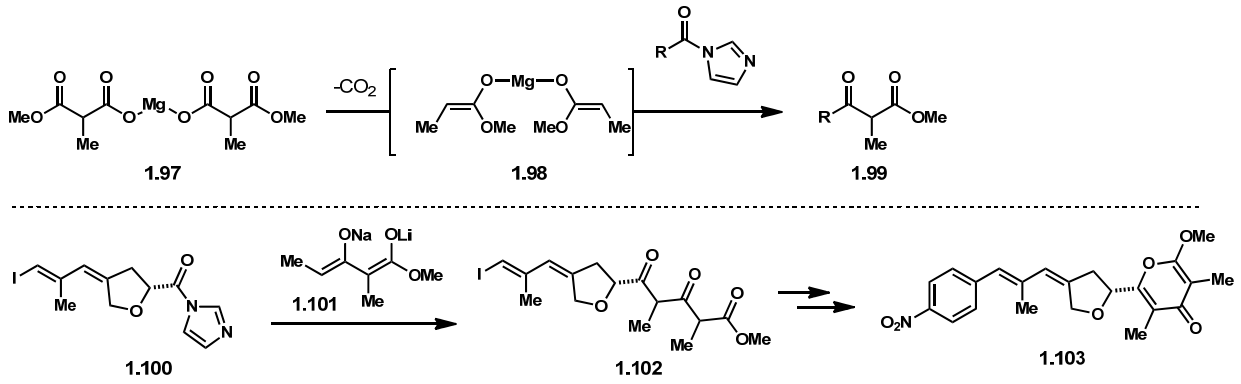
Staab also reported preliminary results on the reaction of acylimidazoles (i.e., **1.94**, Scheme 1.17) with reducing agents to afford aldehydes (**1.93**)[49] and carbon nucleophiles to yield ketones (**1.95**).[50] The finding that carbon nucleophiles could be added to acylimidazoles without overaddition was significant as it had long been known that the reaction of carbon nucleophiles with acid chlorides yielded the products of double addition (i.e., **1.96**).[51] Furthermore, this report pre-dated the development of Weinreb amides by nearly 25 years. However, for reasons that remain obscure, this method was not widely adopted.

Scheme 1.17. Addition of Carbon and Hydride Nucleophiles to Carbonylimidazoles



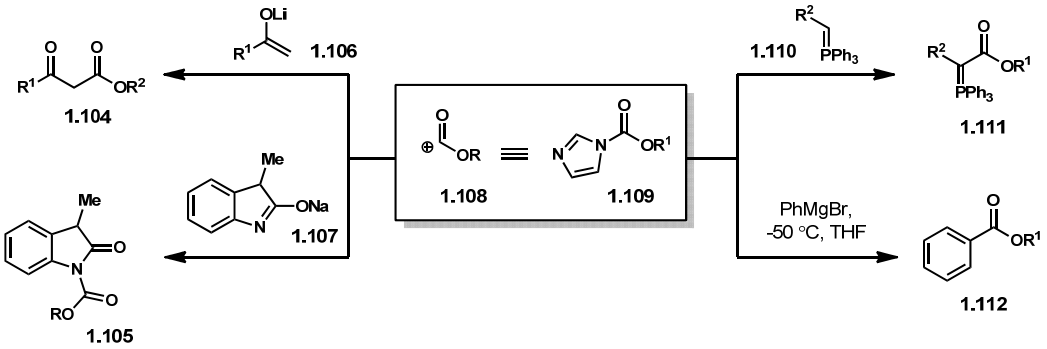
Nonetheless, the precedent that carbon nucleophiles could be used in S_NAc reactions with acylimidazoles spurred the development of a number of important and widely used carbon acylation tactics employing acylimidazoles as carbonyl electrophiles. In 1979, Masamune and coworkers established that the magnesium salts of half-malonic acid derivatives (Scheme 1.18, **1.97**) reacted cleanly with acylimidazoles to afford β-ketoester products (**1.99**) through an unknown enolate intermediate (one possible structure is **1.98**).[52] In contrast to the classical Claisen condensation, this reaction can be performed under essentially neutral conditions and thus a wide degree of functional group compatibility has been reported. Alternatively, complex enolates may be reacted with acylimidazoles to afford Claisen products in high yields.[53] Even the highly reactive dienolate **1.101** underwent smooth C-C bond formation with **1.100** to yield **1.102**, the penultimate intermediate in Trauner's synthesis of aureothin (**1.104**).[54]

Scheme 1.18. Acylimidazoles as Electrophiles in the Claisen Condensation



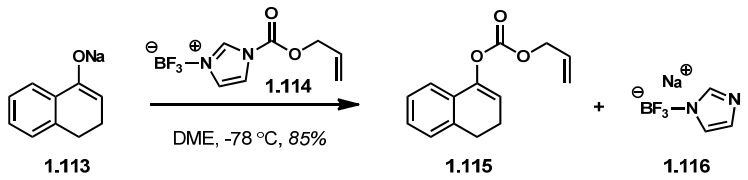
Staab's demonstration that imidazole carbamates (see **1.109**, Scheme 1.19) could be readily prepared from CDI allowed for the easy and safe preparation of a variety of formate ester cation equivalents (**1.108**). Indeed, a half-century of experimental work has proved that, as was found with acylimidazoles, the carbonylimidazole group allows for reactivity that is difficult to achieve using the analogous chloroformate. For instance, phosphoranes such as **1.110** can be acylated to afford so-called stabilized Wittig reagents (**1.111**),[55] and even Grignard reagents can be added to imidazolides to yield esters (**1.112**) selectively.[56] β-ketoesters and unsymmetrical malonates (**1.104**) can be prepared by the direct Claisen condensation of an enolate (**1.106**) with an imidazole carbamate.[57] Typically, the product of *C*-acylation predominates and so this method provides a substantial improvement to the standard *C*-acylation protocol involving cyanoformate acylation reagents (Mander reagents) by obviating cyanide.[58] Imidazolides have also proven to be excellent *N*-acylating reagents for amide anions (**1.107**) on substrates that do not react cleanly with cyanoformates.[59]

Scheme 1.19. Imidazole Carbamates as Formate Ester Cation Equivalents



On the other hand, Trost showed that the addition of enolates (eq 1, **1.113**) to allyl imidazolides pre-complexed to BF_3 (see **1.114**) provided access to *O*-acylated products such as **1.115**, which are valuable precursors for asymmetric allylation. These authors argue that selective *O*-acylation occurs as a kinetically controlled process in which coordination to imidazole would render it a harder electrophile, favoring engagement with the enolate oxygen. However, drawing on the precedent set by Mander, it may be the case that the acylation of enolates with imidazole carbamates is thermodynamically controlled. That is, *O*-acylation could be readily reversible due to the addition of imidazole anion (see **1.116**), with the reaction

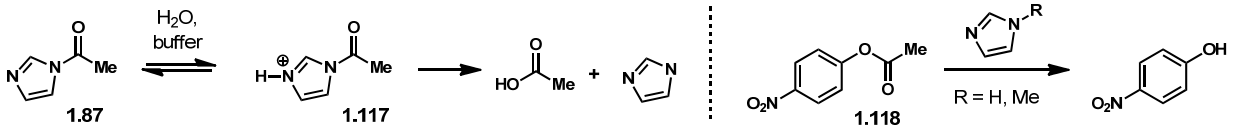
eventually favoring the *C*-acylated product due to the effectively irreversible deprotonation of the product β-dicarbonyl compound. If this was true, the addition of a Lewis acid would sequester the imidazole anion formed, preventing a reversible acyl transfer process. The possibility of thermodynamically controlled acyl donation in the presence of imidazole anion is further explored in Chapter 4.



(1)

Though not the first to exploit it, this report by Trost underscores an important structural feature of carbonylimidazole derivatives: that it is possible to interact Lewis (and Brønsted) acids with the distal nitrogen (N-3) lone pair of imidazolides in order to accentuate their reactivity. Indeed, Jencks described the acid-catalzyed hydrolysis and transacylation reactions of acetylimidazole (Scheme 1.20, **1.87**), finding that the rate of hydrolysis of **1.87** was actually lowest at pH 7, but rapidly accelerated at pH ~4 and became constant below pH 3. From this study, they concluded that acylimidazolium salts (**1.117**) have pK_as around 3.6, and the rate-determining step of hydrolysis is nucleophilic addition to the carbonyl of **1.117**.[60] Furthermore, Bender found that the rates of hydrolysis of 4-nitrophenyl acetate (**1.118**) catalyzed by imidazole and *N*-methylimidazole were similar, suggesting that the impact of protonation was roughly equivalent to exhaustive alkylation in modulating the electrophilicity of acylimidazolium salts.[61] Jencks later confirmed this finding in a detailed study with several classes of nucleophiles.[62]

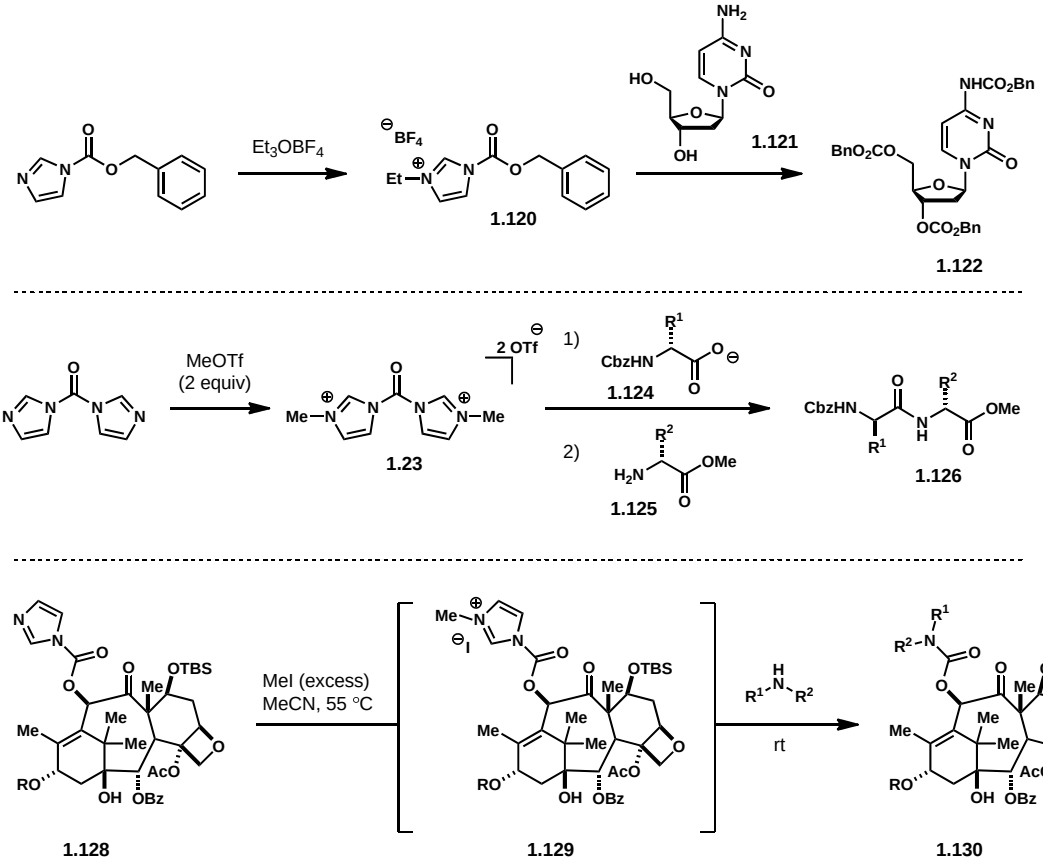
Scheme 1.20. Hydrolysis Experiments With Imidazole Species



This mechanistic insight was readily adopted by the synthetic organic chemistry community, where a number of strategies evolved that sought to activate relatively stable carbonylimidazole derivatives (e.g., **1.87**) through engagement of the distal nitrogen. A particularly interesting tactic that exploits this property is the NBS-mediated esterification of acylimidazoles, which presumably occurs through generation of small quantities of HBr.[63]

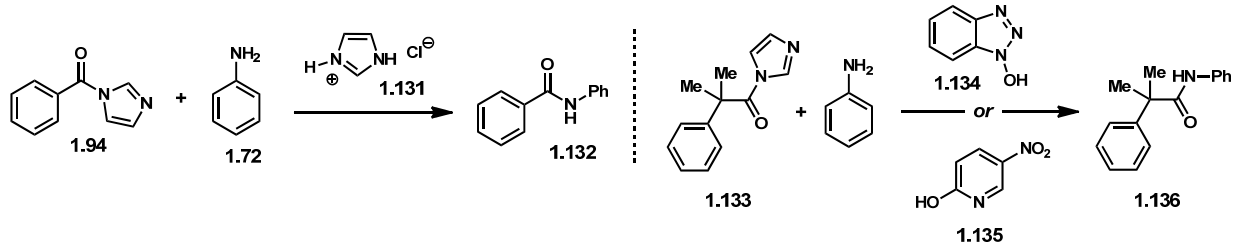
Of course, *N*-alkylation of carbonylimidazole derivatives has also been extensively explored given the precedent set by Bender and Jencks. Rapoport disclosed that *N*-ethyl imidazolium carbamate (**1.120**, Scheme 1.21) was a superior reagent for the Cbz protection of sensitive nucleoside hydroxyl groups (see **1.121**),[64] then went on to develop a highly reactive peptide coupling reagent based on exhaustively methylated CDI (**1.123**) that could be used for peptide coupling (see **1.126**).[65] This strategy can also be used to activate imidazole carbamates in complex systems such as the protected paclitaxel core (**1.128**). In this case, the imidazolium salt (**1.129**) is not typically isolated, but instead treated directly with a nucleophile to yield the S_NAc product (**1.130**).[66] Alkylative activation may be achieved *in situ* if an excess of MeI or allyl bromide is added to a solution of an acylimidazole, which then readily reacts with alcohols at room temperature.[67] Further discussion of chemistry that exploits this tactic can be found in Chapter 2.

Scheme 1.21. Carbonylimidazolium Salts are Potent Acylating Reagents



A safer and more economical approach to the activation of carbonylimidazole derivatives would thus be protonation of the distal nitrogen, just as Jencks and coworkers explored. Fittingly, Staab was the first to capitalize on this possibility, showing that acid chlorides could be produced by the treatment of acylimidazoles with anhydrous hydrochloric acid. [68] More recently, chemists at AstraZeneca developed an imidazole hydrochloride mediated amidation of acylimidazoles (e.g., **1.94**, Scheme 1.22) using aniline nucleophiles (e.g., **1.72**).[69] It has also been documented that HOBt (**1.134**) and 2-hydroxy-5-nitropyridine (**1.135**) mediate similar amidations, however, it is not clear whether these activators act as Brønsted acids or nucleophilic catalysts (see Chapters 3 and 4).[70]

Scheme 1.22. Synthesis of Amides from Acyimidazoles Using Acidic Catalysts



While much research has been devoted to the use of carbonylimidazole derivatives as acylating reagents, these activated esters are still underutilized, especially in light of the hazards

associated with the use of phosgene. Thus, we set out to develop mild, green, and inexpensive methods in which they could be used in classical acylation reactions (Chapters 2 and 3). Of particular interest was the delineation of synthetic strategies that would expand the scope of CDI as a phosgene equivalent to substrates previously observed to be recalcitrant toward carbonylimidazole electrophiles (Chapter 3). Finally, we believed that it might be possible to exploit these promising acyl electrophiles to access novel chemoselectivities (Chapter 4).

1.6 Notes and References

(1) Pyruvate derivatives can be biosynthesized from amino acids and these compounds are important building blocks in polyketide and fatty acid syntheses. However, the discussion of this method of catabolism will not be discussed in detail here.

(2) Breslow, R. *J. Am. Chem. Soc.* **1958**, *80*, 3719.

(3) Allfrey, V. G.; Faulkner, R.; Mirsky, A. E. *Proc. Natl. Sci. USA* **1964**, *51*, 786.

(4) Turner, B. M. *Bioessays* **2000**, *22*, 836.

(5) Mammals and yeasts use the mevalonic acid pathway (not shown, but involves acetyl-CoA) to biosynthesize isoprenoids. Alternatively, some species have been found to produce isopentenyl pyrophosphate from glyceraldehyde 3-phospate through a pathway involving completely different enzymatic machinery. However, this alternative biosynthetic pathway still proceeds through carbonyl functionalization.

(6) Heath, R. J.; Rock, C. O. *Nat. Prod. Rep.* **2002**, *19*, 581 and references therein.

(7) This is called the Bürgi-Dunitz angle: Bürgi, H. B.; Dunitz, J. D.; Lehn, J. M.; Wipff, G. *Tetrahedron* **1974**, *30*, 1563.

(8) The nature of the carbonyl compound also influences the favorability of the addition product.

(9) Bender, M. L. *Chem. Rev.* **1960**, *60*, 53 and references therein.

(10) There are other possible mechanisms of acyl substitution; however, they are relatively rare. See reference 9.

(11) For instance, in the venerable Grignard reaction. Grignard, V. *Compt. Rend.* **1900**, *130*, 1322.

(12) In which all or part of the appended group remained in the final product (i.e., not as part of a protecting group).

(13) Carey, J. S.; Laffan, D.; Thomson, C.; Williams, M. T. *Org. Biomol. Chem.* **2006**, *4*, 2337.

(14) There are important exceptions to this trend. For instance, the Tishchenko reaction is sometimes used industrially to produce ethyl acetate from acetaldehyde.

(15) Cheung, H.; Tanke, R. S.; Torrence, G. P. Acetic Acid. *Ullmann's Encyclopedia of Industrial Chemistry*, Wiley: Weinheim, 2002.

(16) For a review of the Cativa and Monsanto processes see: Jones, J. *Platinum Metals Rev.* **2000**, *44*, 94.

(17) See reference 15.

(18) Bodansky, M. *Nature* **1955**, *75*, 685.

(19) Wieland, T.; Schneider, G. *Liebigs Ann. Chem.* **1953**, *580*, 159. There are scattered reports of reactions that likely proceed through the intermediacy of acylimidazoles dating as far back as 1892.

(20) Anderson, J. W.; Zimmerman, J. E.; Callahan, F. M. *J. Am. Chem. Soc.* **1964**, *86*, 1839.

(21) Kisfaludy, L.; Ceprini, M. Q.; Rakoczy, B.; Kovacs, J. In *Peptides, Proceedings of the 8th European Peptide Symposium*, Beyerman, H. C.; van de Linde, A.; Maassen van den Brink, W., Eds.; North-Holland: Amsterdam: 1967, p 25.

(22) This method uses the well-known carbodiimide coupling reagents: (a) Sheehan, J. C.; Hess, G. P. *J. Am. Chem. Soc.* **1955**, *77*, 1067. A more modern approach using DMAP catalysis has been developed: (b) Hassner, A.; Alexanian, V. *Tetrahedron Lett.* **1978**, *19*, 4475.

(23) (a) Kim, S.; Kim, Y. C.; Lee, J. I. *Tetrahedron Lett.* **1983**, *24*, 3365. (b) Yamaugchi esterification: Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.

(24) From BOPCl: Diago-Meseguer, J.; Palomo-Coll, A. L.; Fernández-Lizarbe, J. R.; Zugaza-Bilbao, A. *Synthesis* **1980**, 547.

(25) (a) For the amide bond, and especially the synthesis of peptides: Benoiton, N. L. *Chemistry of Peptide Synthesis*; Taylor & Francis: Boca Raton, 2005. (b) March, J. *Advanced Organic Chemistry*, 4th ed., Wiley: New York, 1992.

(26) Fischer, E.; Speier, A. *Chem. Ber.* **1895**, *28*, 3252.

(27) Methods include: (a) MeI/Cs2CO3: Pfeffer, P. E.; Silbert, L. S. *J. Org. Chem.* **1976**, *41*, 1373. (b) Me2CO3/K2CO3: Jiang, X.; Tiwari, A.; Thompson, M.; Chen, Z.; Cleary, T. P.; Lee, T. B. K. *Org. Proc. Res.*

Dev. **2001**, *5*, 604. (c) Me2SO4/LiOH: Chakraborti, A. K.; Basak (neé Nandi), A.; Grover, V. *J. Org. Chem.* **1999**, *64*, 8014. (d) Me3OBF4/DIPEA: Raber, D. J.; Gariano, P.; Brod, A. O.; Gariano, A.; Guida, W. C.; Guida, A. R.; Herbst, M. D. *J. Org. Chem.* **1979**, *44*, 1149.

(28) Schneider, W.; Diller, W. Phosgene. *Ullmann's Encyclopedia of Industrial Chemistry*, Wiley: Weinheim, 2002.

(29) Michler, W. *Chem. Ber.* **1876**, *9*, 716.

(30) Serini, V. Polycarbonates. *Ullmann's Encyclopedia of Industrial Chemistry*, Wiley: Weinheim, 2000.

(31) Johnson, J. *Chem. Eng. News* **2011**, *89*, 34.

(32) For a good review of this green strategy, see: Sakakura, T.; Choi, J.-C.; Yasuda, H. *Chem. Rev.* **2007**, *107*, 2365.

For carbonate and carbamate synthesis from CO2, see: (a) McGhee, W.; Riley, D. *J. Org. Chem.* **1995**, *60*, 6205. (b) Shi, M.; Shen, Y. M. *Helv. Chim. Acta* **2001**, *84*, 3357. (c) Perez, E. R.; da Silva, M. O.; Costa, V. C.; Rodrigues-Filho, U. P.; Franco, D. W. *Tetrahedron Lett.* **2002**, *43*, 4091. (d) Chaturvedi, D.; Ray, S. *Monatsh. Chem.* **2006**, *137*, 127.

(33) These reagents are produced from phosgene itself, but in dedicated facilities. Therefore, smaller scale applications can effectively utilize phosgene without the need for specialized reactors or co-located phosgene plants.

(34) Staab, H. A. *Angew. Chem.* **1956**, *68*, 616.

(35) See reference 13.

(36) Staab, H. A. *Liebigs Ann. Chem.* **1957**, *609*, 75.

(37) Staab, H. A. *Liebigs Ann. Chem.* **1957**, *609*, 83.

(38) Paul, R.; Anderson, G. W. *J. Am. Chem. Soc.* **1960**, *82*, 4596.

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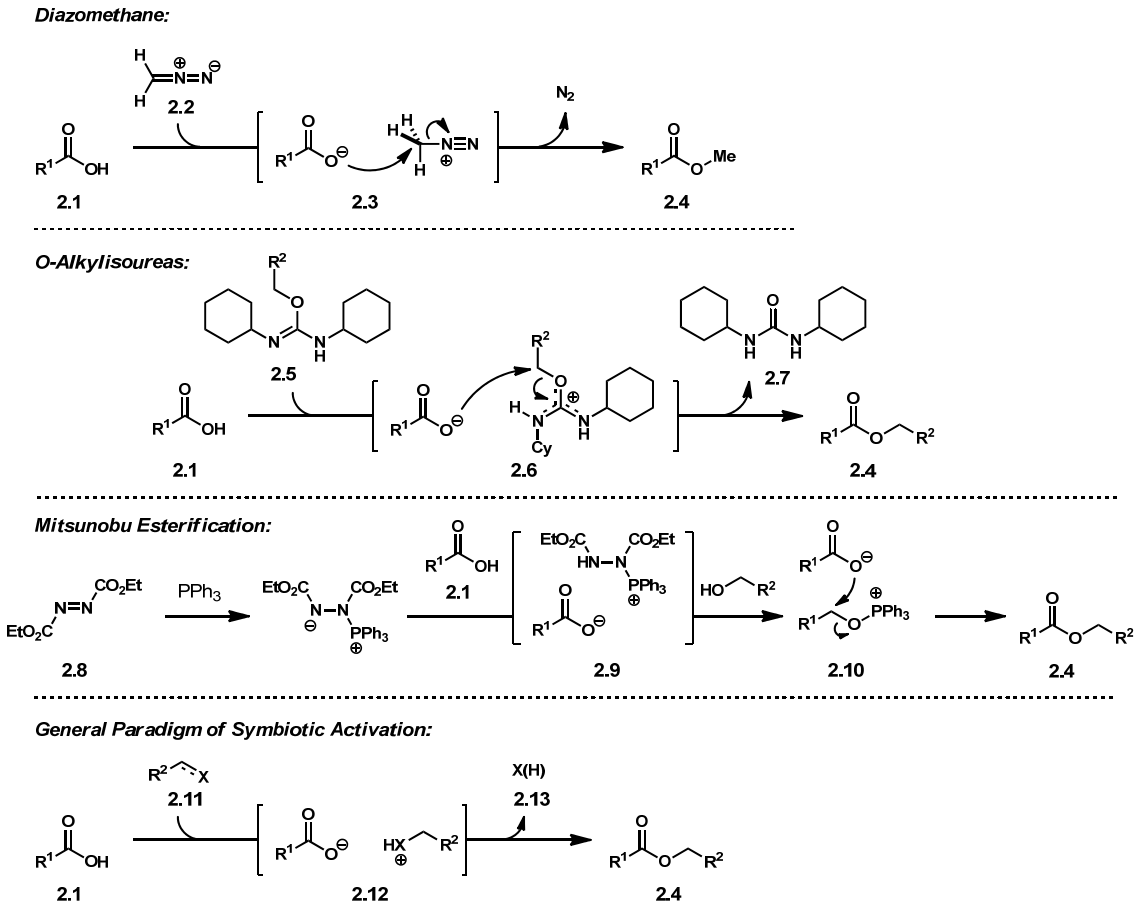
Chapter 2. Carbonylimidazoles as Reagents for Esterification and Amidation

2.1 Introduction

Esterification is a critically important process for organic synthesis, and as such, significant effort has been devoted to developing robust and mild esterification methods. Although *in situ* activation of acids and carboxylate alkylation strategies have been thoroughly explored (these paradigms are discussed in Chapter 1), reactions that proceed through symbiotic activation of both the acid and esterification agent lie relatively fallow.

One of the most recognizable examples of symbiotic activation is the reaction of diazomethane (Scheme 2.1, **2.2**) with carboxylic acids (**2.1**), which proceeds through a tight ion pair (**2.3**).[1] *O*-Alkylisoureas (**2.5**) react with carboxylic acids through the intermediacy of an analogous ion pair (**2.6**) to yield the desired ester (**2.4**) and a urea byproduct (**2.7**).[2] Finally, the mechanism of the Mitsunobu reaction shares several similarities to these processes in that triphenylphosphine and the diazodicarboxylate (**2.8**) activate each other (see **2.9**), and then go on to generate a reactive ion pair (**2.10**),[3] as in the case of diazomethane or *O*-alkylisourea esterification. The symbiotic relationships between reactants in the Mitsunobu reaction are highlighted by the fact that omission of any of the four completely inhibits the reaction.

Scheme 2.1. Symbiotic Activation as a Paradigm for Ester Synthesis

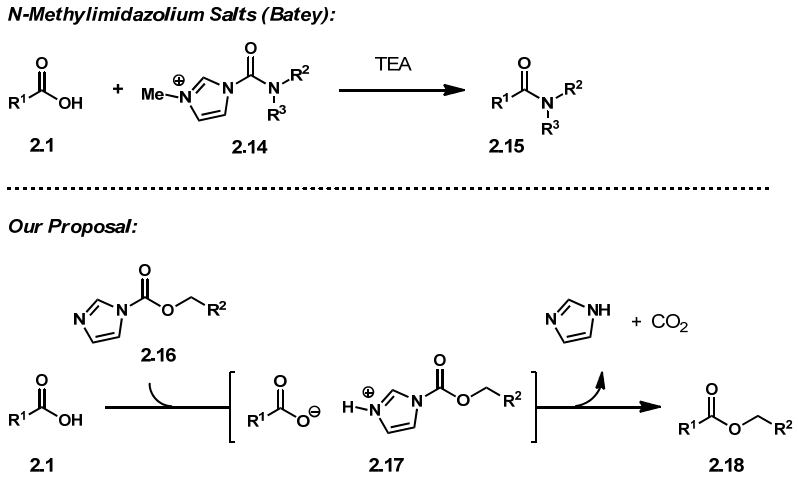


The advantages of this symbiotic activation are manifold, the most important of which is the inherent chemoselectivity imbued to the esterification process by the requirement that the reagent and substrate *activate each other* in order for the reaction to proceed. The ideal embodiment of this paradigm will use reagents that are inert unless activated, after which they will react rapidly. Diazomethane comes close to this ideal; however, the strict limitations on reagent scope and the challenge of safe handling remain significant practical barriers. Therefore, new methods that utilize this mode of activation are desirable.

The parameters required for mutual activation in esterification through an ion-pair process are typically that the esterification reagent (**2.11**) be basic enough to deprotonate a carboxylic acid (**2.1**), and that the resulting conjugate acid (see **2.12**) be electrophilic enough to react with the conjugate base (i.e., carboxylate), which acts as a nucleophile. A survey of the literature revealed that, in the case of carbonylimidazole-based reagents, these modes have been explored both in tandem and as discrete processes. Batey has demonstrated that quaternized imidazole-based ureas (Scheme 2.2, **2.14**), in which alkylation is a surrogate for protonation (see Chapter 1), react smoothly with carboxylate anions to afford amide products.[4] Moreover, Staab and Anderson have shown that 1,1'-carbonyldiimidazole (CDI) rapidly reacts with carboxylic acids to afford acylimidazoles (see Chapter 1), thereby demonstrating that for activated imidazole ureas, the initial proton transfer step from a carboxyl group, as well as collapse of the resultant conjugate pair, are facile.[5]

We sought to use the existing precedent to develop a new esterification method exploiting reagents that reacted in a fashion similar to CDI or Batey's *N*-methylimidazolium salts (**2.14**), but also carried the alkoxy constituent of the desired ester — much as diazomethane contains both a basic functional group (i.e., X in **2.11**) and an alkyl fragment that is incorporated in the ester product (**2.18**). As such, we turned our attention to imidazole carbamates (**2.16**).

Scheme 2.2. Our Proposal for Imidazole Carbamate Mediated Esterification and Existing Precedent

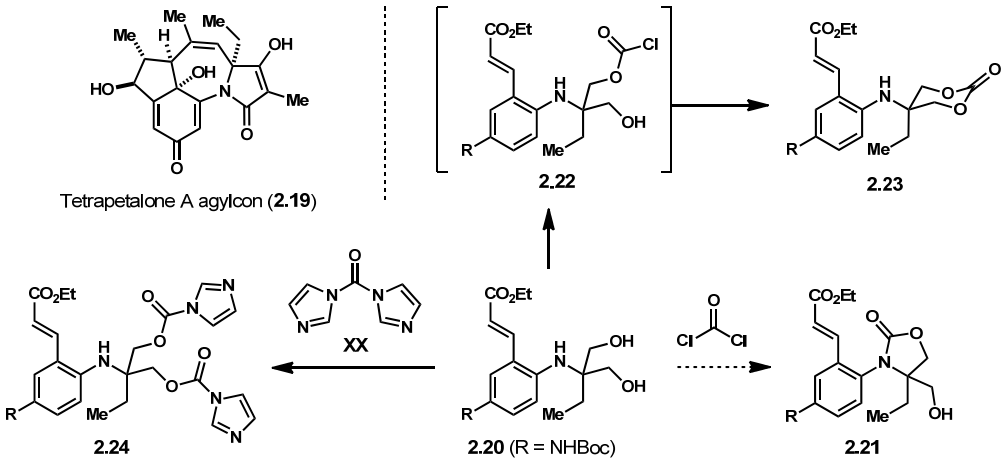


2.2 The Origin of Our Interest in Carbonylimidazoles

During our efforts toward the total synthesis of the aglycon of the natural product tetrapetalone A (Scheme 2.3, **2.19**), we needed to convert diol **2.20** into an oxazolidinone (**2.21**) in order to protect the aniline nitrogen and one of the alcohol groups. While this type of functionalization is well-documented in the literature (see Chapter 3), we found that **2.20** was

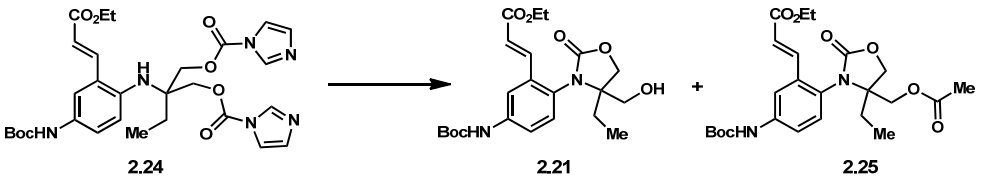
recalcitrant to the standard methods of oxazolidinone synthesis, all of which involved a carbonyl dication equivalent (e.g., phosgene). For instance, when **2.20** was treated with phosgene, cyclic carbonate **2.23** was formed as the major product. Attenuating the reactivity of the putative intermediate carbonyl electrophile (**2.22**) by using CDI allowed access to **2.24**, in which both alcohol groups had been acylated.

Scheme 2.3. Attempted Oxazolidinone Synthesis En Route to Tetrapetalone A



Having parried the problem of carbonate formation, we then sought to close the oxazolidinone ring by promoting attack of the aniline nitrogen on the electrophilic imidazole carbamate (**2.24**). However, this reaction proved to be somewhat challenging as well. Heating **2.24** did not effect cyclization, nor did attempted alkylation of the imidazole at the distal nitrogen (Table 2.1, entries 1 and 2). Treatment of **2.24** with PPTS led to slow hydrolysis, with diol **2.20** isolated as the major product (entry 3). However, simply dissolving **2.24** in acetic acid led to rapid conversion of the bis-carbamate to the desired oxazolidinone (**2.21**) along with relatively large quantities of an acetylated product (**2.25**, entry 4). Though it is known that heating mixtures of acetic acid and an alcohol leads to the formation of an ester product, this reaction is exceedingly slow at room temperature.[6] It was therefore surprising that approximately a fourth of **2.21** was acetylated at room temperature over two hours. As a control experiment, **2.21** was dissolved in acetic acid, but no acetate products were observed; a result that seemed to indicate the imidazole carbamate was participating in a hitherto unknown esterification reaction.

Table 2.1. Activation of an Imidazole Carbamate for Cyclization

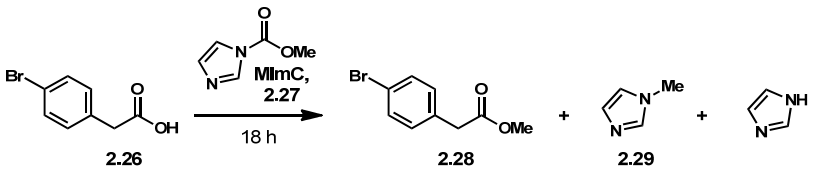


Entry	Conditions	Result
1	$CDCl_3$, 60 °C, 24 h	NR
2	4 equiv MeI, MeCN, rt	decomposition
3	50 mol% PPTS, DCM, rt, 48 h	hydrolysis (**2.20**)
4	AcOH (solvent), rt, 1 h	2.5 : 1 (**2.21** : **2.25**)

2.3 Probing Novel Reactivity of Imidazole Carbamates

Accordingly, we set out to probe this intriguing reactivity. Because of the lengthy synthetic route to **2.21**, we devised a model system consisting of methyl imidazole carbamate (**2.27**, or MImC, Table 2.2) and 4-bromophenylacetic acid (**2.26**). While no reaction between **2.26** and MImC (**2.27**) in $CDCl_3$ was observed by ^{1}H-NMR at room temperature (entry 1), heating this mixture to 60 °C led to modest conversion to methyl ester **2.28** (entry 2) along with an equivalent quantity of imidazole. Investigation of solvent effects demonstrated that polar solvents accelerate the esterification reaction (entries 3-7).[7]

Table 2.2. Optimization of Esterification with Methyl Imidazole Carbamate



Entry	Solvent	Temp (°C)	MImC (equiv)	[Acid] (M)	% Conversion (**2.28**)[a]
1	$CDCl_3$	23	1.5	0.2	0
2	$CDCl_3$	60	1.5	0.2	33
3	toluene-d_8	80	1.2	0.2	58
4	1,2-DCE	80	1.2	0.2	63
5	EtOAc	80	1.2	0.2	66
6	CD_3CN	80	1.2	0.2	72
7	DMF-d_7	80	1.2	0.2	73
8	CD_3CN	60	1.2	0.2	47
9	CD_3CN	60	1.2	0.5	70
10	CD_3CN	60	1.2	1.0	74
11	CD_3CN	60	1.2	2.0	69
12	CD_3CN	60	2.0	0.5	72
13	CD_3CN	60	3.0	0.5	80
14	CD_3CN	60	4.0	0.5	83
15	CD_3CN	80	1.2	0.5	85
16	CD_3CN	80	2.0	0.5	>95

[a] Conversions were determined by integration of resonances in ^{1}H-NMR spectra.

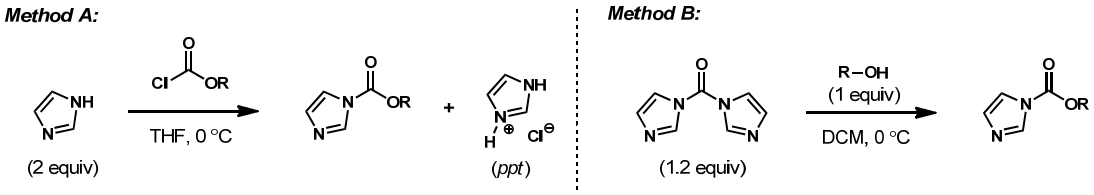
At this point, we considered that MImC might serve as a reagent for the methylation of carboxylic acids and thus might function as a replacement for the venerable, but volatile derivatization reagent – diazomethane. Thus a general investigation of the reactivity of imidazole carbamates metamorphosed into an optimization campaign aimed at identifying conditions for efficient *O*-methylation of carboxylic acids to form esters.

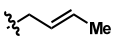
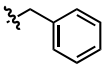
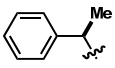
Analysis of crude reaction mixtures demonstrated that 1-methylimidazole (**2.29**) was generated during the course of the esterification reaction, presumably via an intermolecular methyl group transfer between MImC and imidazole (*vide infra*). Therefore, further optimization was aimed at suppressing this side reaction. The concentration of the acid in solution was investigated first, and a significant increase in yield (entry 9, Table 2.2) was obtained at higher concentrations. However, at very high concentrations (entries 10 and 11), the decomposition of MImC by imidazole became more pronounced. To offset this side reaction, additional equivalents of MImC were employed. Nevertheless, this modification had only a limited impact on the isolated yield of **2.28** as 1-methylimidazole formation was accelerated as

well (entries 12-14). We hypothesized that esterification must slow appreciably once a significant amount of imidazole has been generated because this byproduct is more basic than MImC, leading to sequestration of residual carboxylic acid. Eventually, success was achieved by balancing concentration and stoichiometry, along with an increase in the reaction temperature from 60 °C to 80 °C (entries 15 and 16).[8]

To help delineate the scope of this esterification reaction, we then prepared a number of imidazole carbamate reagents. If commercially available, chloroformates were reacted with imidazole to generate the desired carbonylimidazole derivative (Method A, Table 2.3). In other cases, a single equivalent of alcohol was reacted with CDI at 0 °C (Method B, discussed in Chapter 1). Yields were generally excellent, regardless of the method used, and pure products could be obtained by simple aqueous workup (Table 2.3). Only methyl imidazole carbamate was readily susceptible to hydrolysis, and as such was purified by precipitation of imidazole impurities.

Table 2.3. Synthesis of Imidazole Carbamate Reagents

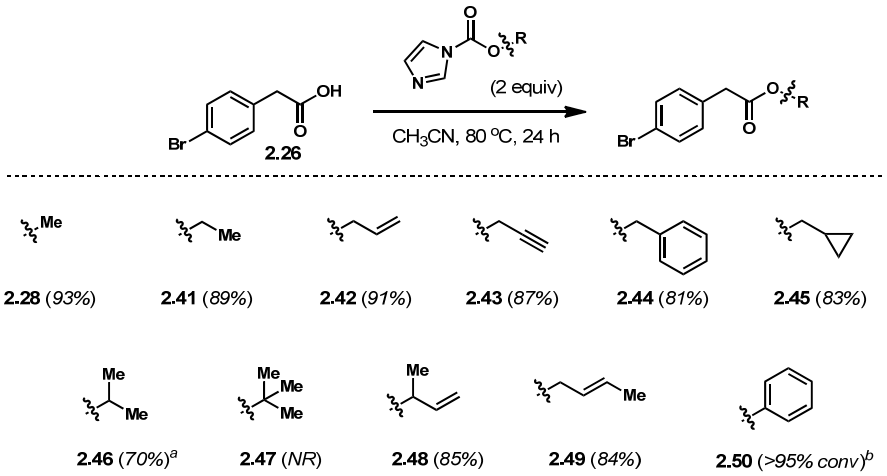


Entry	R	Carbamate	Method	Yield (%)[a]
1		**2.27**	A	84
2		**2.30**	A	92
3		**2.31**	A	71
4		**2.32**	A	94
5		**2.33**	B	92
6		**2.34**	B	90
7		**2.35**	B	89
8		**2.36**	A	88
9		**2.37**	B	96
10		**2.38**	A	92
11		**2.39**	B	90
12		**2.40**	N/A[b]	-

[a] Yields are for isolated compounds. [b] **2.40** is commercially available.

The scope of the imidazole carbamate acylation reaction was then investigated by treatment of **2.26** with a variety of imidazole carbamate esterification reagents, and the corresponding esters isolated by extraction. Methyl (Scheme 2.4, **2.28**), ethyl (**2.41**), allyl (**2.42**), and propargyl esters (**2.43**) were obtained in excellent yields, as were other primary imidazole carbamates (**2.44**, **2.45**).[9] However, the preparation of secondary esters from carbamates derived from secondary alcohols was somewhat less efficient (see **2.46**) and a tertiary carbamate (**2.40**) did not provide the ester product, but instead underwent carbamate cleavage and decarboxylation. It was therefore surprising that secondary allyl esters could be formed without event (**2.48**) and no loss of regiochemical information was observed when substituted allyl imidazole carbamates were employed (see **2.48** and **2.49**).

Scheme 2.4. Carbamate Scope in the Esterification of 4-Bromophenylacetic Acid



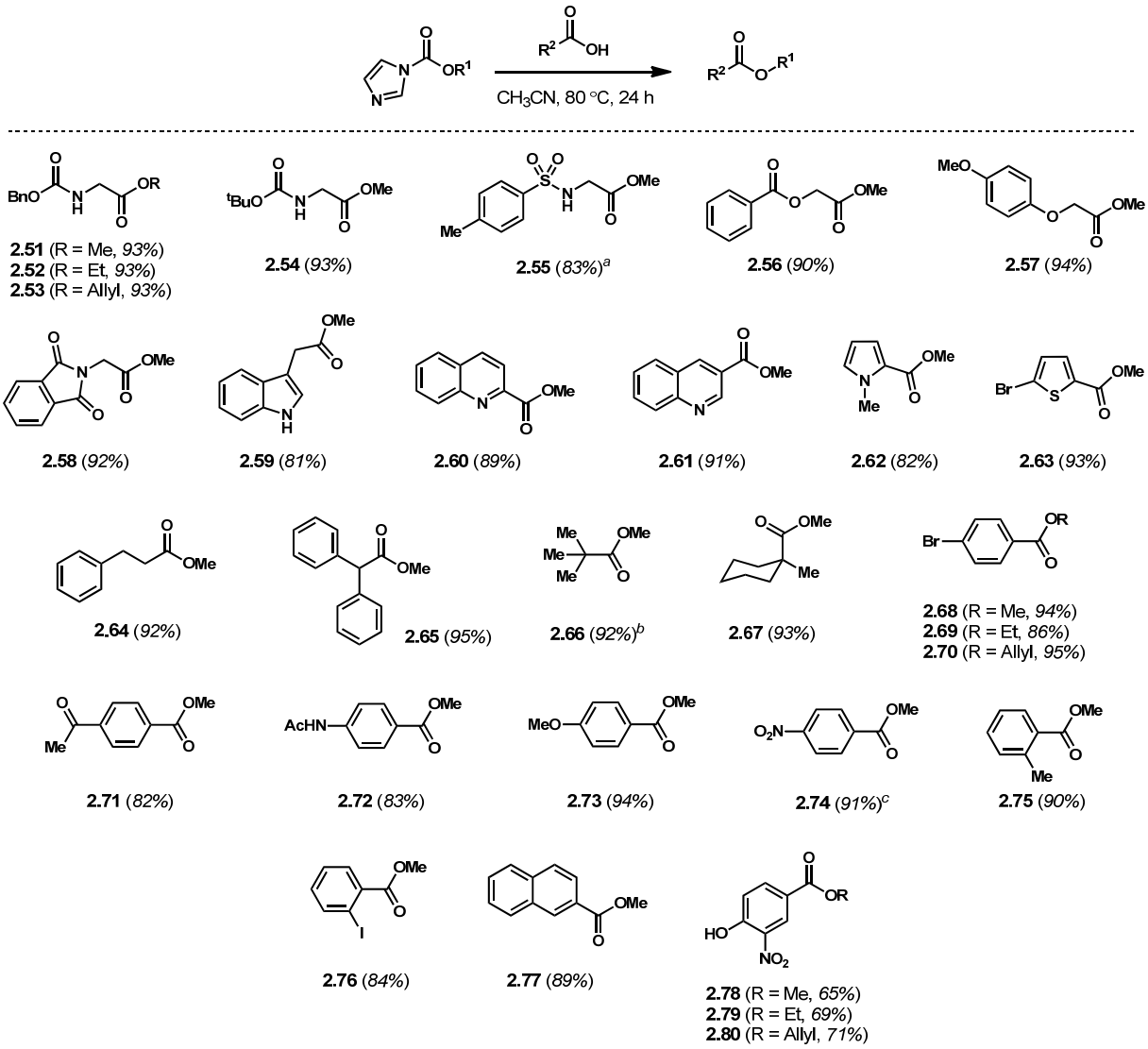
Yields in parentheses are for isolated compounds. [a] The reaction mixture was heated to 80 °C for 48 h. [b] Product was inseparable from diphenyl carbonate impurity. Conversion determined by integration of resonances in ^{1}H-NMR spectra.

Investigation of several glycine and glycolic acid derivatives demonstrated the high degree of chemoselectivity provided by esterification with MImC (**2.27**), as well as **2.30** and **2.32** (Scheme 2.5). Relatively acidic protected amines were well-tolerated (**2.51**-**2.54**), though very acidic functional groups such as tosylamides (**2.55**) were partially acylated by MImC, presumably by initial deprotonation with imidazole. Heterocyclic motifs such as quinolines (**2.60**), thiophenes (**2.63**), pyrroles (**2.62**), and even unprotected indoles (**2.59**) were untouched by the esterification procedure. Branching at the α-position was tolerated (**2.65**), and α-tertiary esters could be prepared in good yields (**2.66** and **2.67**).

MImC also efficiently mediates the esterification of benzoic acids under the standard conditions using DMF as solvent,[10] since many of these substrates exhibited limited solubility in acetonitrile under the reaction conditions. In general, the yields of benzoates increased by 10-15% when the reaction was conducted in DMF as compared with acetonitrile, though we observed little solvent dependence on isolated yields when reactions remained homogeneous throughout the process. Benzoic acids of varied acidity reacted comparably (**2.71**-**2.74**), while steric hindrance of the carboxylic acid group led to slightly lower yields (**2.75**-**2.76**). Finally, phenolic acids could be chemoselectively esterified (see **2.78**-**2.80**); we observed no phenol functionalization, regardless of the esterification reagent employed. This property of the

imidazole carbamate reagents complements diazomethane, which is known to readily methylate acidic phenols in the presence of carboxylic acids.[11]

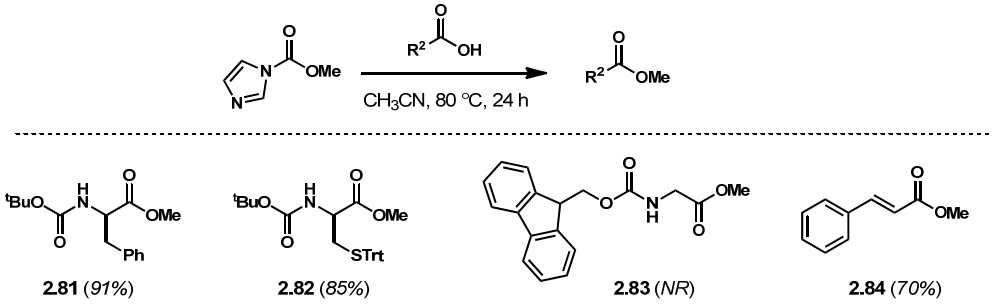
Scheme 2.5. Carboxylic Acid Scope of the Imidazole Carbamate Mediated Esterification



[a] A 7% yield of the *N*-acylated methyl ester was obtained. [b] NMR yield using piperonylonitrile as an internal standard. [c] 5% conversion to the corresponding *N*,*N*-dimethylbenzamide was observed.

Several limitations to the scope of this esterification protocol were also noted. For instance, *N*-protected amino acids were esterified in good yield (**2.81** and **2.82**, Scheme 2.6), but were partially racemized. Similarly, base-sensitive functionalities, such as the Fmoc protecting group (see **2.83**), were destroyed due to prolonged heating in the presence of imidazole. This byproduct was also found to participate in conjugate addition reactions with enoates (**2.84**) generated during the esterification of α,β-unsaturated acids (*vide infra*). Thus, we set out to deduce the mechanism by which imidazole carbamates mediate esterification in hopes that this knowledge would illuminate a strategy to address these deficiencies.

Scheme 2.6. Challenging Esterification Substrates

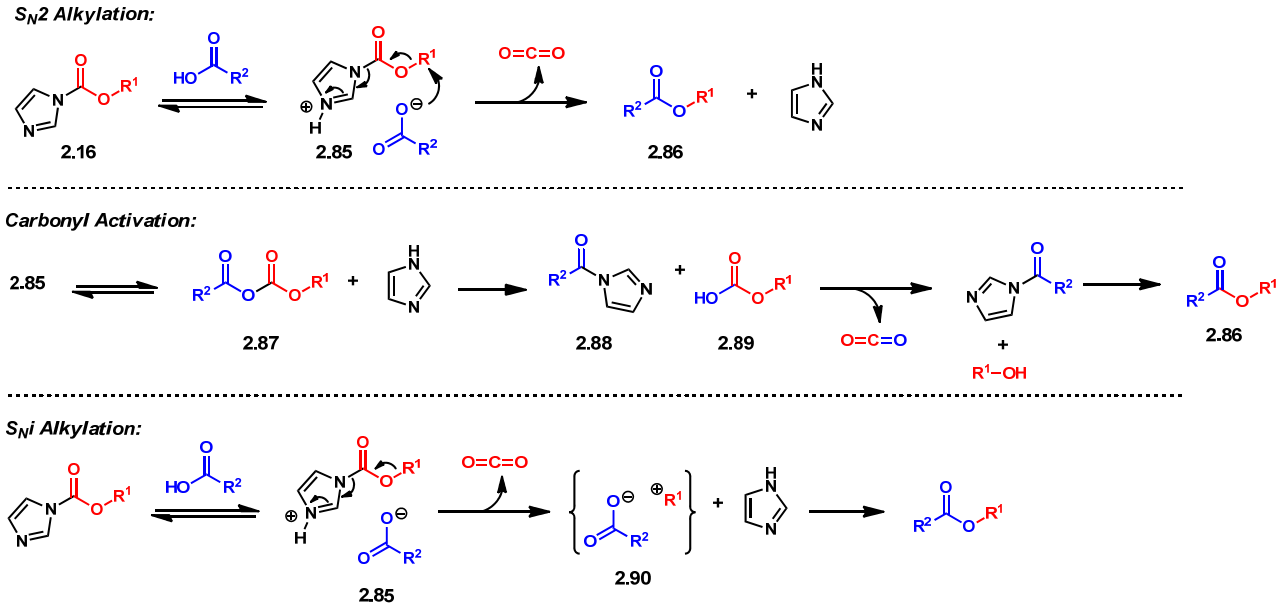


Yields in parentheses are for isolated compounds.

2.4 Mechanistic Investigations

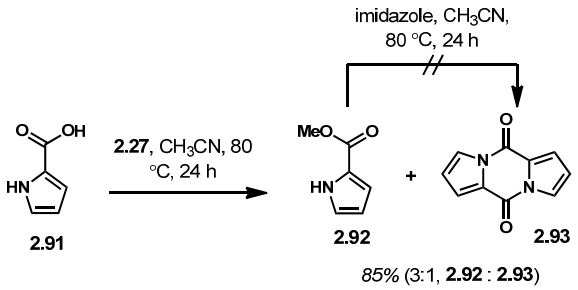
At the outset of our mechanistic studies, we considered three distinct hypotheses. Cognizant of the early work of Staab and Anderson (Chapter 1) we reasoned that the imidazole carbamate (**2.16**) could first be protonated to generate an ion pair (Scheme 2.7, **2.85**), which could decompose through attack of the carboxylate ion on the R group, expelling CO_2 and imidazole through a formal S_N2 mechanism. Alternatively, this intermediate ion pair could collapse through carboxylate attack on the carbonyl of the imidazolium carbamate (see **2.85**). The resulting acylcarbonate **2.87** could then be re-engaged by liberated imidazole to generate an acylimidazole **2.88** along with a carbonic ester (**2.89**). The latter could undergo decarboxylation to unmask an alcohol that could then react with **2.88** to provide an ester (**2.86**). Finally, we could not rule out the possibility that the postulated imidazolium carbamate intermediate (**2.85**) could ionize to a solvent-caged carbocation (**2.90**) with subsequent trapping by the tightly bound carboxylate anion, a mechanistic possibility borne out in the studies on the S_Ni mechanism by Cowdrey,[12] Lewis,[13] and Cram.[14]

Scheme 2.7. Mechanistic Hypotheses



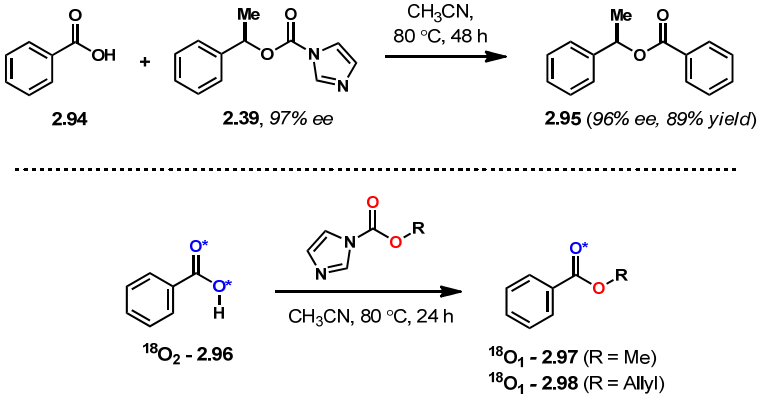
Each hypothesis was initially supported by anecdotal evidence derived from our optimization and scope studies. For instance, an activated ester intermediate such as **2.88** was implied by the isolation of **2.93** (Scheme 2.8) since only trace quantities of **2.93** were formed when ester **2.92** was heated in the presence of imidazole. On the other hand, the fact that secondary allyl imidazole carbamate **2.34** reacted with carboxylic acids more quickly than **2.31** (Scheme 2.4), suggested that ionization may be operative in some cases. Finally, observation of *N*-methylation of imidazole by MImC (*vide infra*) suggested that direct attack of a nucleophile on the alkyl fragment of imidazole carbamates is feasible.

Scheme 2.8. Side Reaction Hinting at the Intermediacy of an Activated Ester



Inspection of these possibilities suggested several experiments that could disprove one or more of our hypotheses. When enantioenriched imidazole carbamate **2.39** (Scheme 2.9) was reacted with benzoic acid (**2.94**), ester **2.95** was obtained with essentially complete retention of stereochemical configuration.[15] Furthermore, esterification of $^{18}O_2$-benzoic acid (**2.96**) with MImC, the imidazole carbamate most likely to undergo an S_N2 displacement, provided ^{18}O-methyl benzoate (**2.97**), where one isotopic oxygen label had been lost. These two results were inconsistent with an S_N2 mechanism. Similarly, allylation of **2.96** with allyl imidazole carbamate (**2.32**), a reagent expected to generate a stabilized carbocation, yielded ^{18}O-allyl benzoate (**2.98**), contradicting the operation of an S_Ni mechanism. Rather, the outcome of these isotopic labeling experiments lends strong support to a mechanism involving an activated ester intermediate, such as the carbonyl activation pathway shown in Scheme 2.7.

Scheme 2.9. Experimental Evidence for the Intermediacy of an Activated Ester

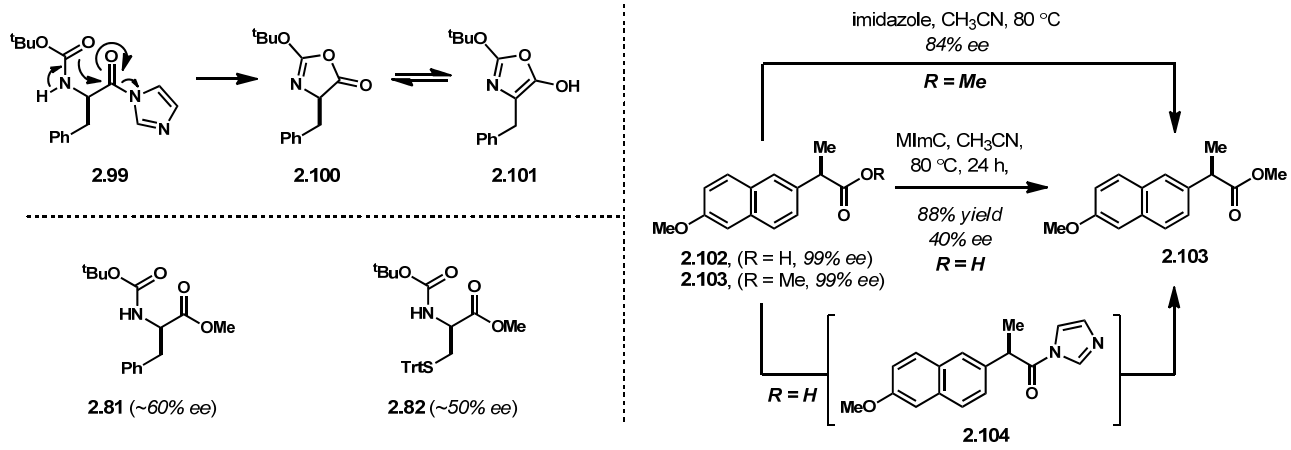


Yield in parentheses is for isolated compound. Enantiomeric excess determined by chiral HPLC analysis.

2.5 Addressing Issues of Chemoselectivity

With this mechanistic insight, we then began a systematic study of the major limitations of the imidazole carbamate mediated esterification reaction (*vide supra*), the most pressing of which was the partial racemization of amino acid substrates (see **2.81** and **2.82**, Scheme 2.10, left). Initially, it was unclear whether this process was specific to carbamate protected amino acids through the well-known oxazolone (**2.100**) pathway involving activated esters,[16] or whether α-chiral carboxylic acids in general were inappropriate substrates for imidazole carbamate-mediated esterification. Converting enantioenriched naproxen (**2.102**, Scheme 2.10, right) to its methyl ester (**2.103**) using our esterification protocol resulted in significant racemization. On the other hand, the enantiopurity of naproxen methyl ester (**2.103**) was eroded to a lesser extent when heated in the presence of imidazole. This suggested that most of the observed stereomutation during the methylation of **2.102** resulted from deprotonation of an intermediate with enhanced acidity, perhaps an activated ester such as **2.104**, by imidazole. Unfortunately, reinvestigation of solvent and concentration effects did not ameliorate this issue. A solution to this problem was later discovered through the use of an appropriate additive and these results are communicated in detail in Chapter 3.

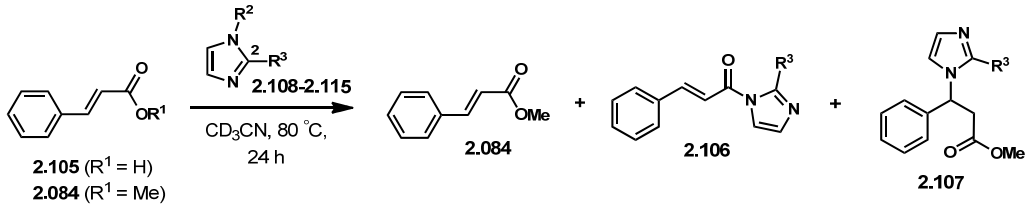
Scheme 2.10. Evaluation of Racemizable Carboxylic Acid Substrates



Yield in parentheses is for isolated compound. Enantiomeric excess determined by chiral HPLC analysis or estimated by comparing empirical and literature optical rotation values.

The esterification of α,β-unsaturated carboxylic acids (enoic acids) with imidazole carbamates was also complicated by a side reaction involving conjugate addition of free imidazole. Preliminary studies with methyl cinnamate (Table 2.4, **2.084**) showed that only small amounts of conjugate addition product (**2.107**) could be formed from the product ester, so it seemed likely that a putative activated ester intermediate was the competent Michael acceptor in the reaction mixture. Increasing the steric bulk of the C-2 substituent (R^3) on the free imidazole (**2.108-2.112**) decreased the levels of conjugate addition product (**2.107**). On the basis of this result, imidazole carbamate reagents with substitution at the C-2 position (**2.113-2.115**) were prepared and found to disfavor conjugate addition when reacted with cinnamic acid (**2.105**). However, the concomitant decrease in electrophilicity of the putative acylimidazole intermediate resulted in the observation of an appreciable amount of activated ester (**2.106**) after 24 hours. The best balance between reactivity and selectivity was achieved using 2-methylimidazole-derived carbamates such as **2.113**.

Table 2.4. Effect of Imidazole C-2 Substitution on Conjugate Addition and Esterification



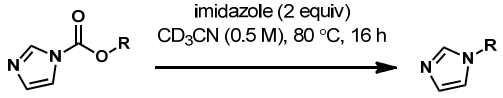
Entry	R^1	R^2	R^3	Imidazole	**2.105** (%)[a]	**2.084** (%)[a]	**2.106** (%)[a]	**2.107** (%)[a]
1	Me	H	H	**2.108**	-	93	-	7
2	Me	H	Me	**2.109**	-	92	-	8
3	Me	H	Et	**2.110**	-	>95	-	<5
4	Me	H	*i*-Pr	**2.111**	-	>99	-	Trace
5	Me	H	Ph	**2.112**	-	>99	-	Trace
6	H	CO_2Me	H	**2.27**	<5	73	0	25
7	H	CO_2Me	Me	**2.113**	<5	81	5	11
8	H	CO_2Me	Et	**2.114**	<5	69	22	5
9	H	CO_2Me	*i*-Pr	**2.115**	<5	62	32	<5

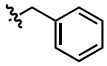
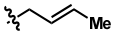
[a] Conversions were determined by integration of resonances in ^{1}H-NMR spectra.

2.6 Alternative Reaction Pathways of Imidazole Carbamates

During the optimization campaign for the esterification reaction, we noticed that an excess of imidazole carbamate reagent was required for complete consumption of the carboxylic acid substrate. Analysis of crude reaction mixtures by ^{1}H-NMR revealed that, at least in the case of MImC, imidazole alkylation was a significant side reaction, though this process did not affect the yield or complicate the purification of ester products. We chose to investigate this phenomenon by simply monitoring the reaction of an imidazole carbamate with free imidazole. Although MImC (**2.27**) and allyl imidazole carbamate (**2.32**) rapidly and completely react with imidazole (Table 2.5, entries 1 and 3), higher alkane homologs such as **2.30** (entry 2) are not competent electrophiles.[17] Curiously, 1-methylallyl imidazole carbamate (**2.34**, entry 6) resisted attack by imidazole whereas 3-methylallyl imidazole carbamate (**2.33**, entry 5) was completely consumed to provide **2.120**. This latter result suggests that an S_N2' pathway is not operative under the relevant conditions. Further experimentation demonstrated that the imidazole alkylation was highly concentration dependent, with little alkylation occurring when the concentration of imidazole was kept at or below 0.2 M. As a control experiment to probe the possibility of an intramolecular alkyl group transfer, **2.32** was heated to 80 °C in dry CD_3CN, but only starting material was observed by ^{1}H NMR.

Table 2.5. *N*-Alkylation of Imidazole By Imidazole Carbamates

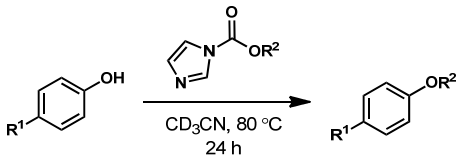


Entry	R	Carbamate	Product	Conversion (%)[a]
1		**2.27**	**2.116**	>95
2		**2.30**	**2.117**	trace
3		**2.32**	**2.118**	>95
4		**2.36**	**2.119**	>95
5		**2.33**	**2.120**	>95
6		**2.34**	**2.121**	9

[a] Conversions were determined by integration of resonances in ^{1}H-NMR spectra.

Further investigation of the reactivity of imidazole carbamates focused on understanding the nature and scope of the proton-transfer activation step that the esterification reaction appears to exploit (Scheme 2.7). Specifically, we wondered whether other acidic functional groups could be alkylated under the esterification conditions. To test this hypothesis, a series of imidazole carbamates were reacted with phenols of varying acidity under the standard esterification conditions. In most cases, phenol alkylation was negligible (Table 2.6), but imidazole alkylation proceeded as usual. Surprisingly, increasing the acidity of the phenolic hydroxyl group retarded the rates of both phenol alkylation (entries 4-6) and the *N*-alkylation of imidazole.

Table 2.6. Phenol Alkylation by Imidazole Carbamates



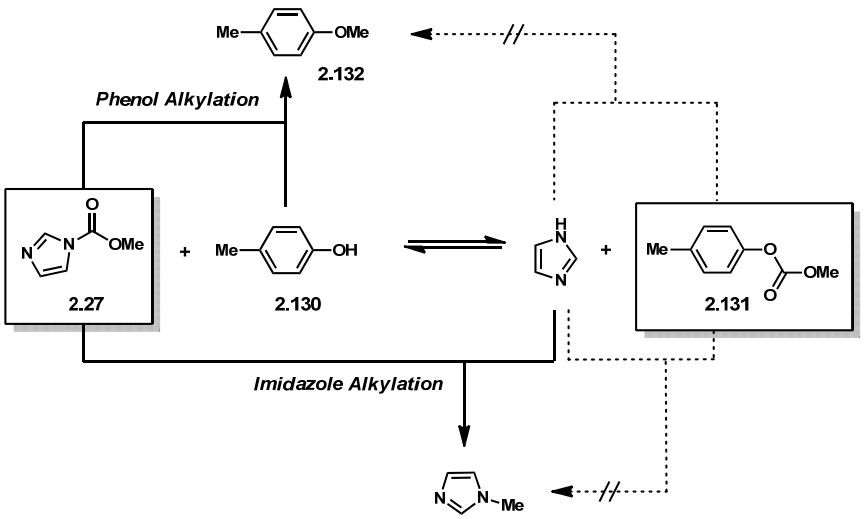
Entry	pK_a	R^1	R^2	Product	% Conversion[a]
1	10.2	OMe	Me	**2.122**	8
2	10.2	Me	Me	**2.123**	18
3	10.0	F	Me	**2.124**	11
4	9.4	Cl	Me	**2.125**	8
5	8.0	CN	Me	**2.126**	2
6	7.1	NO_2	Me	**2.127**	2
7	10.2	Me	Et	**2.128**	0[b]
8	10.2	Me	allyl	**2.129**	5[c]

[a] Conversions based on integration of resonances in ^{1}H-NMR spectra. [b] 60% conversion to 4-methylphenyl ethyl carbonate. [c] 22% conversion to 4-methylphenyl allyl carbonate. pK_a values obtained from measurements in aqueous solution: (a) Gawron, O.; Duggan, M.; Grelechi, C.J. *Anal. Chem.* **1952**, *24*, 969. (b) Sims, P. *J. Chem. Soc.* **1959**, 3648.

Alternatively, the use of ethyl imidazole carbamate (**2.30**, Table 2.6, entry 7) as an alkylating agent led to significant quantities of the phenoxycarbonate when reacted with *p*-cresol, suggesting that formation of a carbonate could be occurring as an initial step in the reaction of MImC with phenols. The possible intermediary role of such a species was investigated by allowing 4-methylphenyl methyl carbonate (**2.131**, Scheme 2.11) to react with imidazole under the relevant conditions. After two hours, 23% of the imidazole had been converted to methyl imidazole carbamate (**2.27**), while only a trace amount of *N*-methylimidazole and no 4-methylanisole (**2.132**) were observed – suggesting that the aryl carbonate is not the active methylating reagent *in situ*. After an additional 14 hours of heating, the mixture consisted primarily of *p*-cresol (**2.130**) and *N*-methylimidazole, along with trace amounts of **2.27**, **2.131**, and **2.132**. This result closely parallels that obtained from the reaction of MImC with *p*-cresol.

Thus, it seems that under the reaction conditions some amount of imidazole and phenoxycarbonate (**2.131**) is formed from the phenol (**2.130**) and imidazole carbamate (**2.27**) through a reversible acyl transfer process (see Chapter 4 for more details). The imidazole can then react with additional imidazole carbamate to generate an alkylimidazole and another molecule of imidazole. The relevant alkylating agent is therefore most likely the imidazole carbamate in both phenol and imidazole alkylation. This mechanistic hypothesis also explains the inverse correlation of gross methylation with phenol pK_a when phenols react with imidazole carbamates. More acidic phenols should disfavor the formation of the phenoxycarbonate from imidazole carbamates, leading to lower overall concentrations of imidazole and slower rates of methylation.

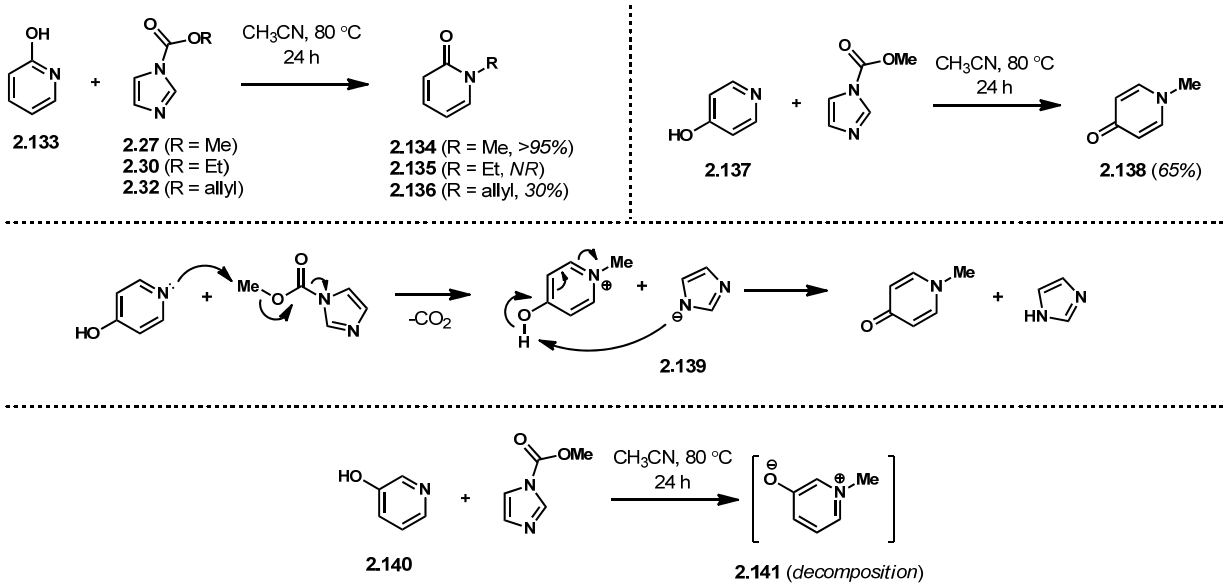
Scheme 2.11. Possible Methylating Agents for Phenol and Imiazole Alkylation



On the other hand, hydroxypyridines were efficiently *N*-alkylated by MImC (Scheme 2.12, top). Given the correlation between pK_a and the extent of phenol methylation, it seemed unlikely that the acidity of hydroxypyridine isomers was leading to alkylation.[18] Instead, an S_N2 mechanism could be envisioned (Scheme 2.12, middle), which would be analogous to the reactivity observed between imidazole and MImC (Table 2.5). This hypothesis explains the near complete regioselectivity for *N*-alkylation of both 2- and 4-hydroxypyridine (**2.133** and **2.137**) to yield *N*-methylpyridones **2.134** and **2.138**, and may account for the observation that 3-

hydroxypyridine (**2.140**) decomposes when heated with MImC as an S_N2 methylation would give rise to reactive zwitterion **2.141**.

Scheme 2.12. *N*-Alkylation of Hydroxypyridines

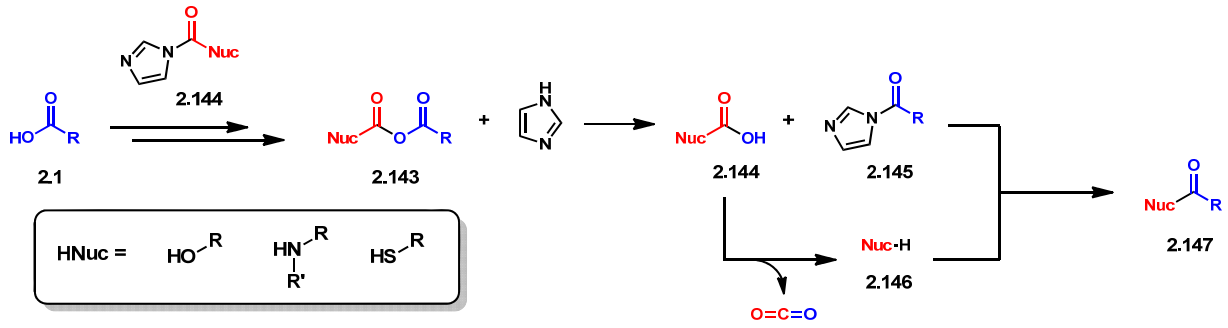


Values in parentheses represent conversions as determined by integration of resonances in ^{1}H-NMR spectra.

2.7 Extension to Amide Synthesis

With an understanding of the mechanism by which imidazole carbamates mediate the esterification of carboxylic acids, we thought it might be possible to use a similar strategy to synthesize other carboxylic acid derivatives. That is, if a mechanism proceeding through an activated intermediate (e.g., **2.143**, Scheme 2.13) was indeed operative, the group lost (**2.144**) during formation of an acylimidazole (**2.45**) could undergo decarboxylation and the resulting species, if nucleophilic (**2.146**), could engage **2.145**. Therefore, an immediate extension would be to change the heteroatom of the nucleophile from an oxygen to a nitrogen, which should result in the formation of an amide.

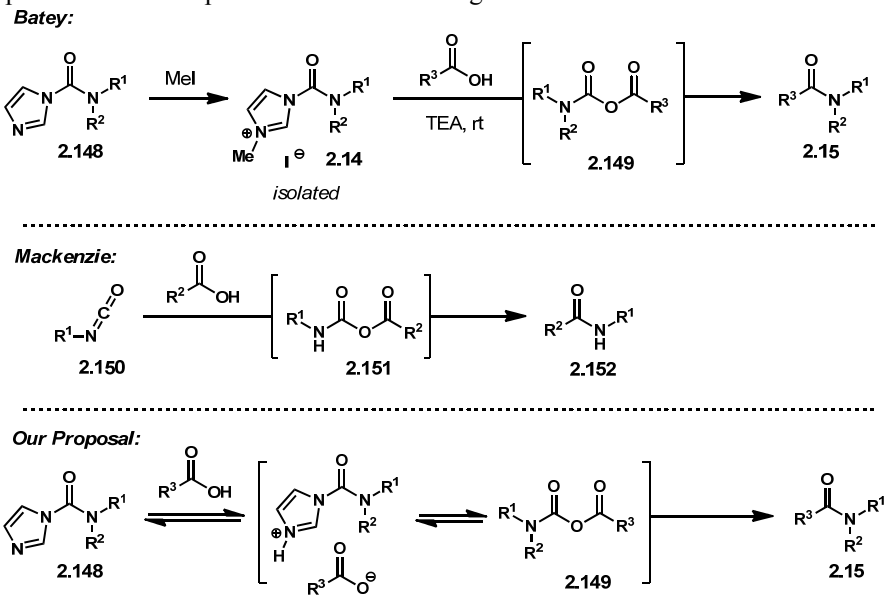
Scheme 2.13. Mechanistic Basis for Carbamylimidazole Mediated Amidation



The use of acylimidazoles as nitrogen acylating agents for the synthesis of amides is well-known, dating back to Wieland and Schneider.[19] Subsequent to this seminal work, several methods for the activation of such species have been reported; however, in all cases, the fundamental process being exploited was the reaction of a pre-formed activated ester with a nucleophilic amine. Indeed, this is the dominant paradigm for much of acylation chemistry (see Chapter 1). However, as alluded to earlier, recent work by Batey and coworkers employed a strategy similar to our proposed amidation; the *in situ* activation of a carboxylic acid with concomitant generation of the relevant amine nucleophile using a carbonylimidazole reagent. Specifically, they reported that *N*-methyl-carbamoylimidazolium salts (Scheme 2.14, **2.14**), generated from alkylation of carbamylimidazole derivatives (**2.148**) with iodomethane, react with carboxylates to generate amides (**2.15**). Perhaps surprisingly, many of the carbamylimidazole salts could be isolated from the alkylation reaction.[20]

A conceptually similar approach was described by Mackenzie et al. for the synthesis of secondary amides (**2.152**) from carboxylic acids and isocyanates (**2.150**), although the substrate scope for this reaction is hampered by the limited availability of isocyanates, which must be synthesized with phosgene or CDI (see Chapter 1), as well as the apparent poor reactivity of arylisocyanates.[21]

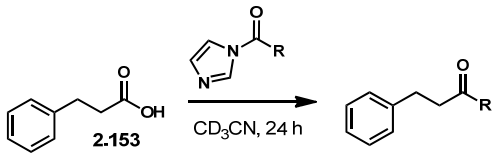
Scheme14. Comparison of Our Proposal with Similar Strategies for Amidation



Our finding that protonation of imidazole carbamates likely gives rise to an activated species analogous to **2.149** suggested that these pre-activation tactics may be unnecessary. As such, we saw an opportunity to contribute to this area by obviating the preparation of unsTable 2.acylating agents (e.g., **2.14** or **2.150**)

To test this potential outcome, a series of carbamylimidazoles (**2.148**, Table 2.7) were prepared according to the method reported by Batey.[22] These reagents were then treated with hydrocinnamic acid (**2.153**) and the reactions were monitored by ^{1}H-NMR. However, only *N*-methoxyurea **2.157** efficiently mediated amidation under typical conditions used in the esterification reaction. Increased temperature led to somewhat higher conversions for recalcitrant carbamylimidazoles such as **2.154** or **2.155** (entries 1-4) but further optimization was not pursued due to the plethora of amidation methods.

Table 2.7. Scope of Carbamylimidazoles as Amidation Reagents



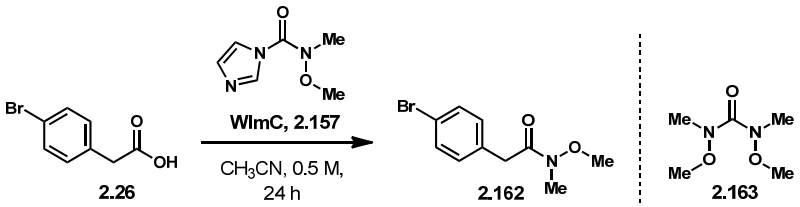
Entry	R	Carbamylimidazole	Product	Temp (°C)	% Conversion[a]
1		**2.154**	**2.158**	80	19
2				100	45
3		**2.155**	**2.159**	80	0
4				100	17
5		**2.156**	**2.160**	80	0
6		**2.157**	**2.161**	80	>95 (92)[b]

[a] Conversions based on integration of resonances in ^{1}H-NMR spectra. [b] Isolated yield in parentheses.

In all cases, only the expected hydrocinnamide products (**2.158**-**2.161**), the carbamylimidazole (**2.154**-**2.157**), and imidazole were observed during the course of the reaction, suggesting that collapse of the initial ion pair may slow as the carbonyl of the imidazole reagent becomes less electrophilic. In this regard, a parallel can be drawn between the known reactivity differences between the Weinreb amide and tertiary amides that do not possess α-heteroatoms and the observed difference between carbonyl-1-(*N*,*O*-dimethylhydroxylamino)-1-imidazole (WImC, **2.157**) and **2.155**.[23]

Given the utility of Weinreb amides,[24] we commenced an optimization campaign for the amidation of carboxylic acids with WImC (**2.157**). As before, we found the reaction to be highly temperature dependent, with no observable reaction occurring at room temperature (Table 2.8, entries 1-4). Reducing the number of equivalents of amidation reagent **2.157** led to the finding that a slight excess was sufficient for synthetically useful transformations (entry 7).[25] The mass balance of the WImC-mediated Weinreb amide synthesis was good, and the only observable products were imidazole, the desired product **2.162**, and a trace amount of symmetrical urea **2.163** arising from addition of liberated *N*,*O*-dimethylhydroxylamine to WImC.[26]

Table 2.8. Optimization of Weinreb Amide Synthesis Using WImC

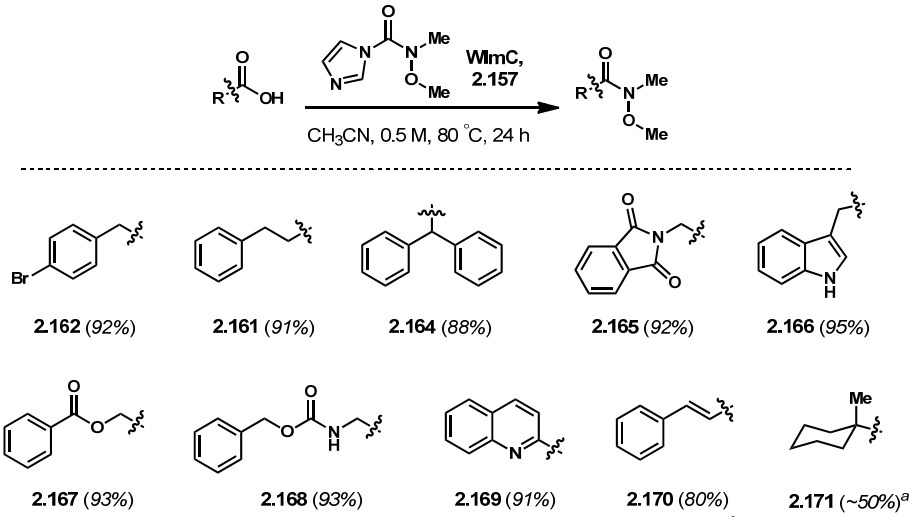


Entry	Temp (°C)	WImC (equiv)	% Conversion[a]
1	22	2.0	0
2	40	2.0	52
3	60	2.0	82
4	80	2.0	>95
5	80	1.0	80
6	80	1.1	86
7	80	1.2	93
8	80	1.3	>95

[a] Conversions based on integration of resonances in the ^{1}H-NMR spectra.

The substrate scope for amidation with WImC was broad, and a number of previously challenging substrates were converted to their Weinreb amide analogues in excellent yields (Scheme 2.15, **2.164**).[27] However, highly sterically encumbered acids, such as 1-methyl-1-cyclohexanecarboxylic acid, were converted to amides (see **2.171**) quite slowly. In general, the amidation reaction appears to be chemoselective as esters (**2.167**), unprotected indoles (**2.166**), carbamate protected amines (**2.168**), and even electrophilic carbonyls, such as those in phthalimide (**2.165**), are well tolerated.

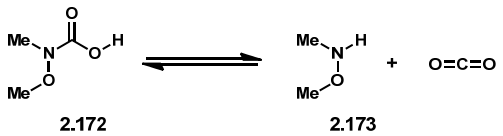
Scheme 2.15. Carboxylic Acid Scope in the WImC Mediated Synthesis of Weinreb Amides



Yields in parentheses are for isolated compounds. [a] Conversion based on integration of resonances in ^{1}H-NMR spectrum.

Even though we have not carried out a detailed mechanistic investigation of the amidation reaction, it likely proceeds through a pathway similar to that postulated for imidazole carbamate-mediated esterification. However, unlike the esterification reaction, we found that amidation is slowed by higher pressures of CO_2. This may be due to a shift in the equilibrium of

the decarboxylation of a carbamic acid intermediate (eq 1, **2.172**) to the nucleophilic free amine (**2.173**) toward the carbamic acid (**2.172**).



(1)

2.8 Large Scale Synthesis of Esterification and Amidation Reagents

After the publication of our work on this esterification reaction, we were approached by Aldrich Chemical Company about the commercialization of several carbonylimidazole reagents. In order to support their efforts, we embarked on a process optimization study to develop an efficient and scalable synthesis of ethyl imidazole carbamate (**2.30**) and WImC (**2.157**)– representative compounds in this class of reagents. At the outset, our goal was to produce 150 grams of each of these compounds.

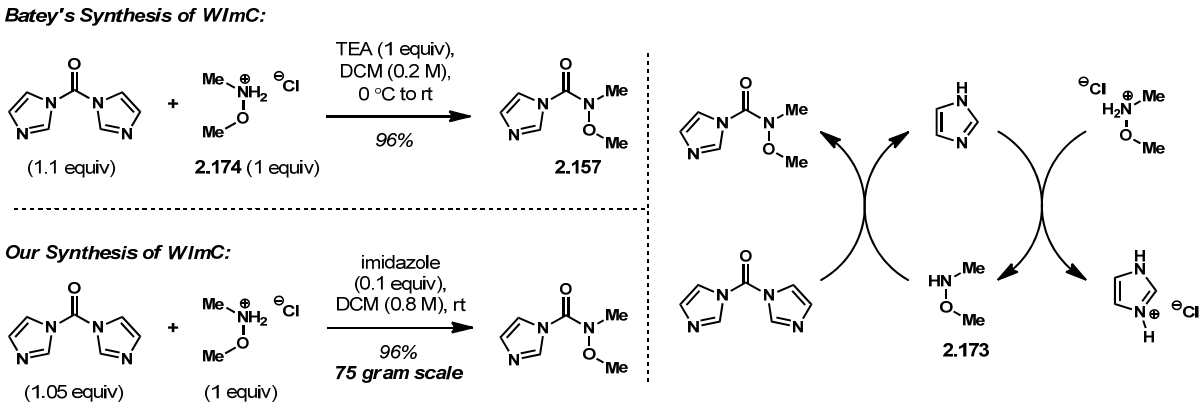
Having already prepared **2.30** on a multigram scale, we investigated the large scale synthesis of this imidazole carbamate first. The reaction of ethyl chloroformate with imidazole is a straightforward acylation reaction, and the hydrogen chloride generated from such a process could be sequestered by employing an extra equivalent of imidazole (see Table 2.3). We used this strategy in the synthesis of other carbamates, but found that some modification was required in the workup stage for large scale reactions in order to obtain reproducibly high yields. Reasoning that even brief exposure to water may lead to hydrolysis, we eschewed an aqueous wash step and chose a reaction solvent in which imidazole hydrochloride is insoluble. In the event, we found that the acylation of imidazole could be performed in anhydrous THF and the precipitated salt easily filtered off. By adding a ¼ volume of hexanes, most residual imidazole byproducts could be precipitated without loss of the product carbamate, which was isolated by concentration of the filtrate. If anhydrous solvents and a dry reaction vessel were employed, **2.30** could be isolated in 98% yield and 97% purity.[28] Additional purification could be achieved by distillation if required.

The production of **2.157** on scale proved to be a greater challenge. Our initial synthesis was adapted from the method of Batey,[29] in which CDI was reacted with *N*,*O*-dimethylhydroxylamine hydrochloride (**2.174**, Scheme 2.16) in the presence of triethylamine. However, this route has a number of attendant economic and environmental drawbacks, including the use of stoichiometric quantities of base and a chlorinated solvent (DCM). Furthermore, we found that on scale the triethylamine had to be charged slowly in order to avoid a significant exotherm, presumably due to uncontrolled reaction of the free base hydroxylamine **2.173** and CDI, leading to significant quantities of **2.163** as a side product. Consequently, our primary objective in preparing a large quantity of **2.157** was to suppress the exotherm associated with the charging of base.

We saw an opportunity to address this safety issue while simultaneously resolving one of the chief economic problems with the route of Batey by exploiting the fact that nucleophilic acyl substitution of CDI generates an equivalent of imidazole. Since imidazole (pK_a = 7.0)[30] is sufficiently basic to deprotonate *N*,*O*-dimethylhydroxylamine hydrochloride (pK_a = 4.7),[31] the synthesis of **2.157** from CDI could be rendered catalytic in imidazole (see Scheme 2.16). Such an approach would control the quantity of base available to the reaction, tempering the exotherm we observed if triethylamine was charged too quickly. This tactic was reduced to practice by

adding 10 mol% imidazole as an initiator. We were able to successfully perform this reaction at scales in excess of 100 grams with only slight loss of efficiency. Gratifyingly, no exotherm was observed at any point in the process, and as before, the imidazole hydrochloride byproduct could be removed by filtration. Further purification to remove excess imidazole was achieved by aqueous washing to afford **2.157** in 96% yield on a 75 gram scale. Experimentation to replace dichloromethane as the reaction solvent was abandoned upon finding that it was superior in the purification sequence. However, our strategy for exotherm control was sufficiently robust that the acylation could be performed at high concentrations (0.8 M), thereby reducing the quantity of chlorinated waste.

Scheme 2.11. Imidazole-Catalyzed Synthesis of WImC

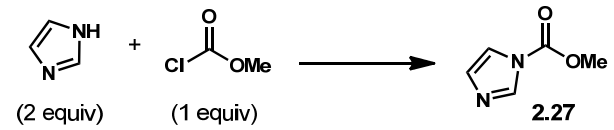


In conclusion, our efforts toward the total synthesis of tetrapetalone A led to the observation that imidazole carbamates undergo esterification in the presence of carboxylic acids. We have demonstrated that a variety of these carbonylimidazole derivatives are efficacious reagents for the esterification of carboxylic acids. The reaction is typically high yielding and generates minimal waste. Modified reagents have also been introduced for the esterification of α,β-unsaturated acids. Limitations of this method include the epimerization of achiral acid substrates and the use of tertiary imidazole carbamates. Amidation reagents have also been reported, but only relatively activated imidazole ureas afford amide products in synthetically useful yields. The mechanism of the esterification reaction was studied using stereochemical and isotopic labeling techniques, which support the intermediacy of an activated ester, such as an acylimidazole.

2.9 Experimental Section

Unless stated otherwise, reactions were performed in oven-dried glassware sealed with rubber septa under a nitrogen atmosphere and were stirred with Teflon-coated magnetic stir bars. Liquid reagents and solvents were transferred via syringe using standard Schlenk techniques. Tetrahydrofuran (THF), toluene, acetonitrile (MeCN), and dimethylformamide (DMF) were dried by passage over a column of activated alumina; dichloromethane (DCM) was distilled over calcium hydride. All other solvents and reagents were used as received unless otherwise noted. Thin layer chromatography was performed using silica gel 60 F-254 precoated plates (0.25 mm) and visualized by UV irradiation and anisaldehyde or potassium permanganate stain. Sorbent

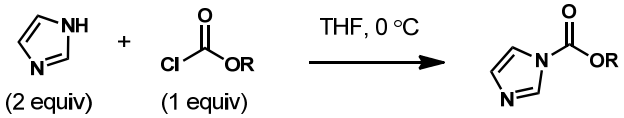
silica gel (particle size 40-63 μm) was used for flash chromatography. Enantiomeric ratios were measured by an HPLC instrument equipped with SPD-M10A microdiode array detector using a Chiral PAK OD-H or IB column. NMR experiments were performed on spectrometers operating at 300, 400 or 500 MHz for ^{1}H, and 75, 100, or 125 MHz for ^{13}C experiments. ^{1}H and ^{13}C chemical shifts (δ) are reported relative to the residual solvent signal. Data are reported as follows: chemical shift (multiplicity, coupling constants where applicable, number of hydrogens). Abbreviations are as follows: s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublet), m (multiplet), bs (broad singlet), and so forth. Spectral data is reported as obtained.



Methyl 1-imidazolecarboxylate (MImC, 2.27)
Imidazole (7.50 g, 110 mmol) was dissolved in dry THF (100 mL) and the resulting solution was stirred with cooling to 0 °C. Methyl chloroformate (4.25 mL, 55 mmol) was added dropwise and the resulting white suspension was vigorously stirred at 0 °C for 1 h and then at room temperature for 4 h. The mixture was filtered and the filtrate was concentrated *in vacuo* to approximately 50 mL and then hexanes (50 mL) was added. The resulting precipitate was filtered and the filtrate was concentrated to afford a white solid (5.69 g, 82%).
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (s, 1H), 7.41 (s, 1H), 7.06 (s, 1H), 4.03 (s, 3H). Spectra were consistent with those reported previously.[32]

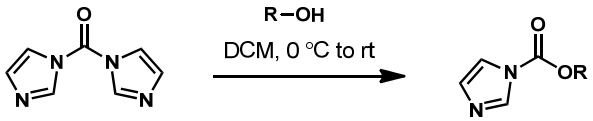
Synthesis of Imidazole Carbamates:

Method A:



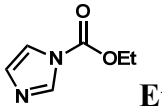
A 1.0 M solution of imidazole (2 equiv) in anhydrous THF was stirred and cooled to 0 °C. Then the chloroformate (1 equiv) was added dropwise and the resulting white suspension was vigorously stirred at 0 °C for 1 h and then at room temperature for 4 h. The mixture was filtered and the filter cake was washed with Et_2O. The filtrate was concentrated *in vacuo* and the colorless concentrate obtained was dissolved in Et_2O, washed twice with water, dried over $MgSO_4$, and concentrated *in vacuo* to afford the imidazole carbamate.

Method B:



A 0.4 M solution of 1,1'-Carbonyldiimidazole (CDI, 1.2 equiv) in anhydrous DCM was stirred and cooled to 0 °C. The alcohol (1.0 equiv) was then added dropwise. The reaction mixture was

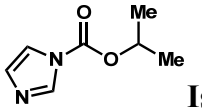
stirred at 0 °C for 1 h, and then at room temperature for 16 h. The homogeneous mixture was then diluted with DCM, washed twice with water, dried over $MgSO_4$, and concentrated *in vacuo* to afford the imidazole carbamate.



Ethyl 1-imidazolecarboxylate (2.30)

Prepared using Method A with ethyl chloroformate (2.58 mL, 27 mmol) to obtain a colorless oil (2.68 g, 92%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (s, 1H), 7.46 (t, *J* = 1.3 Hz, 1H), 7.10 (s, 1H), 4.51 (q, *J* = 7.1 Hz, 2H), 1.47 (t, *J* = 7.1 Hz, 3H). Spectra were consistent with those reported previously.[33]

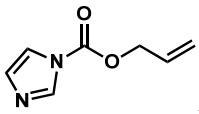


Isopropyl 1-imidazolecarboxylate (2.31)

Prepared using Method A with isopropyl chloroformate (1.0 M solution in toluene, 20 mL, 20 mmol) to obtain a colorless oil (2.19 g, 71%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.39 (s, 1H), 7.03 (s, 1H), 5.20 (hept, *J* = 6.3 Hz, 1H), 1.39 (d, *J* = 6.3 Hz, 6H).

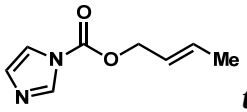
^{13}C NMR (126 MHz, $CDCl_3$) δ 148.1, 137.0, 130.3, 117.0, 73.0, 21.6.



Allyl 1-imidazolecarboxylate (2.32)

Prepared using Method A with allyl chloroformate (2.98 mL, 28 mmol) to obtain a colorless oil (3.94 g, 94%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (s, 1H), 7.42 (t, *J* = 1.3 Hz, 1H), 7.05 (s, 1H), 6.00 (ddt, *J* = 16.4, 10.4, 6.0 Hz, 1H), 5.40 (m, 2H), 4.87 (dt, *J* = 6.0, 1.1 Hz, 2H). Spectra were consistent with those reported previously.[34]

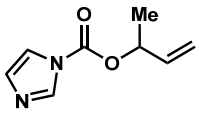


***trans*-crotyl 1-imidazolecarboxylate (2.33)**

Prepared using Method B with *trans*-crotyl alcohol (0.512 mL, 6.00 mmol) to obtain a colorless oil (0.913 g, 92%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (s, 1H), 7.42 (s, 1H), 7.04 (dd, *J* = 1.6, 0.8 Hz, 1H), 6.02 – 5.85 (m, 1H), 5.75 – 5.57 (m, 1H), 4.83 – 4.76 (m, 2H), 1.75 (ddt, *J* = 6.5, 1.8, 0.9 Hz, 3H).

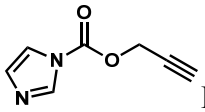
^{13}C NMR (101 MHz, $CDCl_3$) δ 148.5, 137.1, 134.0, 130.5, 123.4, 117.0, 68.8, 17.8.



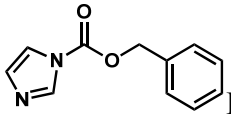
(±)-But-3-en-2-yl 1-imidazolecarboxylate (2.34)

Prepared using Method B with (±)-3-buten-2-ol (0.520 mL, 6.00 mmol) to afford a colorless oil (0.877 g, 90%).

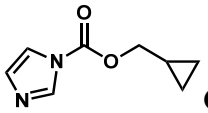
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 (s, 1H), 7.47 (t, *J* = 1.3 Hz, 1H), 7.11 (s, 1H), 5.98 (ddd, *J* = 17.0, 10.5, 6.3 Hz, 1H), 5.58 (quint, *J* = 6.5 Hz, 1H), 5.43 (d, *J* = 17.2 Hz, 1H), 5.32 (d, *J* = 10.5 Hz, 1H), 1.55 (d, *J* = 6.5 Hz, 3H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 148.0, 137.0, 135.9, 130.6, 117.9, 117.1, 76.0, 19.9.



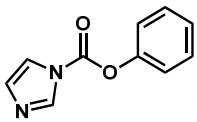
Propargyl 1-imidazolecarboxylate (2.35)
Prepared using Method B with propargyl alcohol (0.500 mL, 8.58 mmol) to obtain a pale yellow oil (1.15 g, 89%).
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 (s, 1H), 7.43 (t, *J* = 1.4 Hz, 1H), 7.06 (s, 1H), 4.98 (d, *J* = 2.5 Hz, 2H), 2.62 (t, *J* = 2.4 Hz, 1H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 148.0, 137.1, 130.8, 117.1, 76.9, 75.7, 55.3.



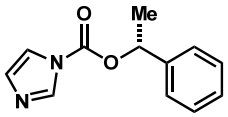
Benzyl 1-imidazolecarboxylate (2.36)
Prepared using Method A with benzyl chloroformate (4.27 mL, 30 mmol) to obtain a colorless oil (5.36 g, 88%).
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (t, *J* = 1.3 Hz, 1H), 7.49 – 7.33 (m, 6H), 7.06 (t, *J* = 1.3 Hz, 1H), 5.42 (s, 2H). Spectra were consistent with those reported previously.[35]



Cyclopropylmethyl 1-imidazolecarboxylate (2.37)
Prepared using Method B with cyclopropanemethanol (0.81 g, 11.2 mmol) to afford a colorless oil (1.78 g, 96%), contaminated with a small amount of imidazole.
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.44 (s, 1H), 7.06 (s, 1H), 4.23 (d, *J* = 7.5 Hz, 2H), 1.35 – 1.19 (m, 1H), 0.73 – 0.60 (m, 2H), 0.49 – 0.29 (m, 2H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 148.8, 137.1, 130.5, 117.1, 73.3, 9.6, 3.5.
HRMS-EI *m/z*: M+ calcd for $C_8H_{10}N_2O_2$, 166.0743; found, 166.0742.



Phenyl 1-imidazolecarboxylate (2.38)
Prepared using Method A with phenyl chloroformate (1.27 mL, 10.1 mmol) to obtain a colorless oil (1.46 g, 92%).
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (s, 1H), 7.57 (t, *J* = 1.5 Hz, 1H), 7.50 – 7.44 (m, 2H), 7.37 – 7.32 (m, 1H), 7.29 – 7.24 (m, 2H), 7.16 (dd, *J* = 1.7, 0.9 Hz, 1H). Spectra were consistent with those reported previously.[36]



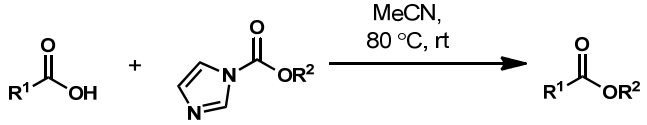
(*R*)-1-Phenylethyl 1-imidazolecarboxylate (2.39)

Prepared using Method B with (*R*)-1-phenethyl alcohol (Alfa Aesar, 97% ee) (0.50 mL, 4.1 mmol) to obtain a colorless oil (0.80 g, 90%).

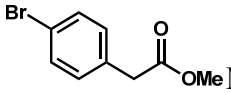
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.46 – 7.32 (m, 6H), 7.06 (s, 1H), 6.07 (q, *J* = 6.6 Hz, 1H), 1.73 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 148.0, 139.6, 137.1, 130.6, 128.8, 128.8, 126.2, 117.1, 77.2, 21.9.

General Esterification Procedure:



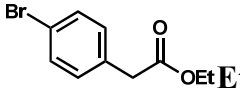
Carboxylic acid (0.5 mmol) and MImC (1.0 mmol) were placed in a dry 20 mL vial with a Teflon tape-coated thread. A magnetic stirbar was added, followed by dry MeCN (1.0 mL), and the vial was quickly sealed with a plastic cap. The reaction mixture was stirred at 23 °C for 15 minutes and then heated to 80 °C for 24 h using a heating block. The mixture was cooled to room temperature and then the vial was carefully opened (***CAUTION: vial under pressure!***). The volatiles were removed *in vacuo*, the resulting residue was dissolved in diethyl ether (20 mL), and then washed with 1 M HCl (10 mL). The aqueous layer was back-extracted with diethyl ether (20 mL) and the organic fractions were combined, washed with a saturated solution of $NaHCO_3$ and then brine, dried over $MgSO_4$, and concentrated *in vacuo* to afford the desired ester.



Methyl 2-(4-bromophenyl)acetate (2.28)

Prepared using the general esterification procedure with 4-bromophenylacetic acid (0.108 g, 0.500 mmol) and MImC (0.126 g, 1.00 mmol) to obtain a white solid (0.106 g, 93%).

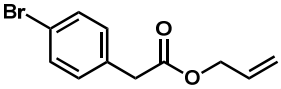
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, *J* = 8.4 Hz, 2H), 7.14 (d, *J* = 8.4 Hz, 2H), 3.69 (s, 2H), 3.68 (s, 3H). Spectra were consistent with those reported previously.[37]



Ethyl 2-(4-bromophenyl)acetate (2.41)

Prepared using the general esterification Procedure with 4-bromophenylacetic acid (0.108 g, 0.500 mmol) and ethyl 1-imidazolecarboxylate (0.140 g, 1.00 mmol) to obtain a white solid (0.109 g, 89%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.4 Hz, 2H), 7.16 (d, *J* = 8.4 Hz, 2H), 4.15 (q, *J* = 7.1 Hz, 2H), 3.56 (s, 2H), 1.25 (t, *J* = 7.1 Hz, 3H). Spectra were consistent with those reported previously.[38]



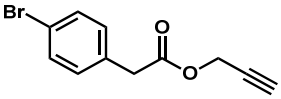
Allyl 2-(4-bromophenyl)acetate (2.42)

Prepared using the general esterification procedure with 4-bromophenylacetic acid (0.108 g, 0.500 mmol) and **2.32** (0.152 g, 1.00 mmol) to obtain a colorless oil (0.117 g, 91%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (d, *J* = 8.4 Hz, 2H), 7.20 (d, *J* = 8.4 Hz, 2H), 5.93 (ddt, *J* = 17.1, 10.5, 5.7 Hz, 1H), 5.29 (dddd, *J* = 20.8, 10.4, 2.7, 1.3 Hz, 2H), 4.63 (dt, *J* = 5.7, 1.3 Hz, 2H), 3.64 (s, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.7, 132.9, 131.9, 131.7, 131.0, 121.2, 118.51, 65.7, 40.7.

HRMS-EI *m/z*: M^+ calcd for $C_{11}H_{11}O_2Br$, 253.9942; found, 253.9937.



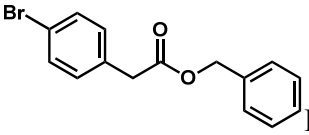
Propargyl 2-(4-bromophenyl)acetate (2.43)

Prepared using the general esterification procedure with 4-bromophenylacetic acid (0.108 g, 0.500 mmol) and (0.150 g, 1.00 mmol) to obtain a colorless oil (0.111 g, 87%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 8.1 Hz, 1H), 7.21 (d, *J* = 8.2 Hz, 2H), 4.74 (d, *J* = 0.7 Hz, 1H), 3.67 (s, 2H), 2.52 (t, *J* = 2.5 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.2, 132.3, 131.8, 131.0, 121.4, 75.2, 52.5, 40.3. One peak overlaps with solvent signal (77.3).

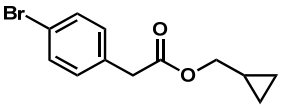
HRMS-EI *m/z*: M^+ calcd for $C_{11}H_9O_2Br$, 251.9786; found, 251.9785.



Benzyl 2-(4-bromophenyl)acetate (2.44)

Prepared using the general esterification procedure with 4-bromophenylacetic acid (0.108 g, 0.5 mmol) and **2.36** (0.202 g, 1.00 mmol) to obtain a white solid (0.124 g, 81%) after column chromatography (5 : 95 ethyl acetate : hexanes).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.4 Hz, 2H), 7.40 – 7.28 (m, 5H), 7.16 (d, *J* = 8.4 Hz, 2H), 5.13 (s, 2H), 3.62 (s, 2H). Spectra were consistent with those reported previously.[39]



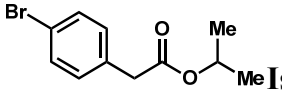
Cyclopropylmethyl 4-bromophenylacetate (2.45)

Prepared using the general esterification procedure using 4-bromophenylacetic acid (0.108 g, 0.5 mmol) and **2.37** (0.166 g, 1.00 mmol) to yield a pale yellow oil (0.112 g, 83%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.3 Hz, 2H), 7.17 (d, *J* = 8.3 Hz, 2H), 3.92 (d, *J* = 7.3 Hz, 2H), 3.59 (s, 2H), 1.21 – 1.02 (m, 1H), 0.66 – 0.45 (m, 2H), 0.30 – 0.20 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 171.2, 133.1, 131.6, 131.0, 121.0, 69.8, 40.7, 9.7, 3.2.

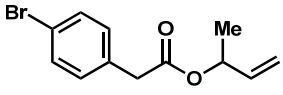
HRMS-EI *m/z*: M+ calcd for $C_{12}H_{13}O_2Br$, 268.0099; found, 268.0098.



Isopropyl 2-(4-bromophenyl)acetate (2.46)

Prepared using the general esterification procedure with 4-bromophenylacetic acid (0.108 g, 0.500 mmol) and isopropyl 1-imidazolecarboxylate (0.154 g, 1.00 mmol) to obtain a colorless oil (0.090 g, 70%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.4 Hz, 2H), 7.16 (d, *J* = 8.4 Hz, 2H), 5.00 (hept, *J* = 6.3 Hz, 1H), 3.53 (s, 1H), 1.22 (d, *J* = 6.3 Hz, 6H). Spectra were consistent with those reported previously.[40]



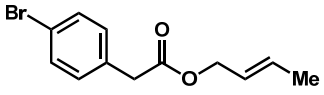
(±)-But-3-en-2-yl 2-(4-bromophenyl)acetate (2.48)

Prepared using the general esterification procedure with 4-bromophenylacetic acid (0.108 g, 0.500 mmol) and **2.34** (0.166 g, 1.00 mmol) to obtain a colorless oil (0.114 g, 85%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.3 Hz, 2H), 7.16 (d, *J* = 8.3 Hz, 2H), 5.81 (ddd, *J* = 16.6, 10.6, 5.9 Hz, 1H), 5.35 (pent, *J* = 6.4 Hz, 1H), 5.15 (m, 2H), 3.57 (s, 2H), 1.30 (d, *J* = 6.5 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.3, 137.3, 133.0, 131.6, 131.0, 121.1, 116.0, 71.7, 40.9, 19.8.

HRMS-EI *m/z*: M^+ calcd for $C_{12}H_{13}O_2Br$, 268.0099; found, 268.0097.



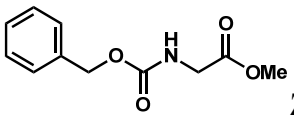
(E)-But-2-en-1-yl 2-(4-bromophenyl)acetate (2.49)

Prepared using the general esterification procedure with 4-bromophenylacetic acid (0.108 g, 0.500 mmol) and **2.35** (0.166 g, 1.00 mmol) to obtain a colorless oil (0.112 g, 84%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.4 Hz, 2H), 7.16 (d, *J* = 8.3 Hz, 2H), 5.78 (dq, *J* = 14.0, 6.5 Hz, 1H), 5.61 – 5.52 (m, 1H), 4.52 (d, *J* = 6.6 Hz, 2H), 3.57 (s, 2H), 1.72 (dd, *J* = 6.5, 1.2 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.9, 132.9, 131.8, 131.6, 131.0, 124.7, 121.1, 65.8, 40.7, 17.8.

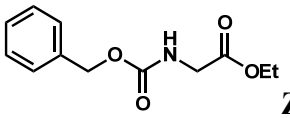
HRMS-EI *m/z*: M^+ calcd for $C_{12}H_{13}O_2Br$, 268.0099; found, 268.0091.



Z-Gly-OMe (2.51)

Prepared using the general esterification procedure with Z-Gly-OH (0.105 g, 0.5 mmol) and methyl 1-imidazolecarboxylate (0.126 g, 1.0 mmol) to obtain a white solid (0.104 g, 93%).

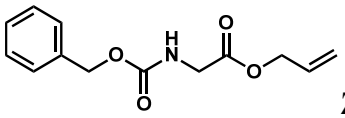
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.29 (m, 5H), 5.26 (bs, 1H), 5.13 (s, 2H), 4.00 (d, *J* = 5.5 Hz, 2H), 3.76 (s, 3H). Spectra were consistent with those reported previously.[41]



Z-Gly-OEt (2.52)

Prepared using the general esterification procedure with Z-Gly-OH (0.105 g, 0.5 mmol) and **2.30** (0.140 g, 1.00 mmol) to obtain a colorless syrup (0.106 g, 89%).

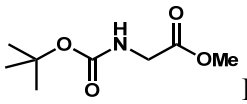
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.28 (m, 5H), 5.26 (bs, 1H), 5.13 (s, 2H), 4.21 (q, *J* = 7.2 Hz, 2H), 4.06 – 3.89 (m, 2H), 1.28 (t, *J* = 7.2 Hz, 3H). Spectra were consistent with those reported previously.[42]



Z-Gly-OAllyl (2.53)

Prepared using the general esterification procedure with Z-Gly-OH (0.105 g, 0.5 mmol) and **2.32** (0.152 g, 1.00 mmol) to obtain a colorless syrup (0.113 g, 91%).

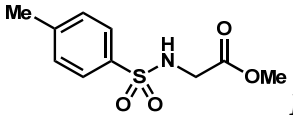
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.27 (m, 5H), 5.91 (ddt, *J* = 19.2, 10.8, 5.8 Hz, 1H), 5.43 – 5.20 (m, 3H), 5.13 (s, 2H), 4.70 – 4.59 (m, 2H), 4.02 (d, *J* = 5.6 Hz, 2H). Spectra were consistent with those reported previously.[43]



Boc-Gly-OMe (2.54)

Prepared using the general esterification procedure with Boc-Gly-OH (0.088 g, 0.5 mmol) and methyl 1-imidazolecarboxylate (0.126 g, 1.0 mmol) to obtain a white solid (0.088 g, 93%).

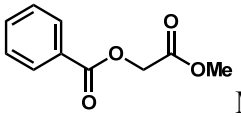
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.00 (bs, 1H), 3.92 (d, *J* = 5.5 Hz, 2H), 3.75 (s, 3H), 1.45 (s, 9H). Spectra were consistent with those reported previously.[44]



***N*-Tosylglycine methyl ester (2.55)**

Prepared using the general esterification procedure with *N*-tosylglycine (0.115 g, 0.5 mmol) and methyl 1-imidazolecarboxylate (0.126 g, 1.0 mmol) to obtain a white solid (0.109 g, 90%).

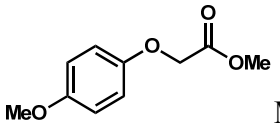
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 8.5 Hz, 2H), 5.00 (bs, 1H), 3.78 (d, *J* = 5.4 Hz, 2H), 3.64 (s, 3H), 2.43 (s, 3H). Spectra were consistent with those reported previously.[45]



Methyl benzoylglycolate (2.56)

Prepared using the general esterification procedure with *O*-benzoylglycolic acid (0.090 g, 0.5 mmol) and methyl 1-imidazolecarboxylate (0.126 g, 1.0 mmol) to obtain a white solid (0.085 g, 90%).

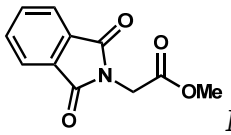
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (dd, *J* = 8.2, 1.2 Hz, 2H), 7.59 (m, 1H), 7.46 (t, *J* = 7.8 Hz, 2H), 4.87 (s, 2H), 3.80 (s, 3H). Spectra were consistent with those reported previously.[46]



Methyl 2-(4-methoxyphenoxy)acetate (2.57)

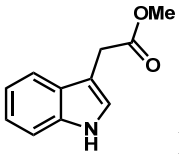
Prepared using the general esterification procedure with methyl 2-(4-methoxyphenoxy)acetic acid (0.091 g, 0.5 mmol) and methyl 1-imidazolecarboxylate (0.126 g, 1.0 mmol) to obtain a white solid (0.092 g, 94%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.92 – 6.78 (m, 4H), 4.59 (s, 2H), 3.80 (s, 3H), 3.76 (s, 3H). Spectra were consistent with those reported previously.[47]



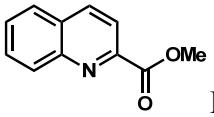
***N*-Phthaloylglycine methyl ester (2.58)**

Prepared using the general esterification procedure with *N*-phthloylglycine (0.103 g, 0.5 mmol) and methyl 1-imidazolecarboxylate (0.126 g, 1.0 mmol) to obtain a white solid (0.101 g, 92%).
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 – 7.84 (m, 2H), 7.79 – 7.71 (m, 2H), 4.45 (s, 2H), 3.77 (s, 3H). Spectra were consistent with those reported previously.[48]



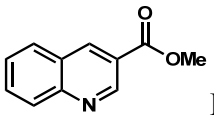
Methyl indole-3-acetate (2.59)

Prepared using the general esterification procedure with indole-3-acetic acid (0.088 g, 0.5 mmol) and methyl 1-imidazolecarboxylate (0.126 g, 1.0 mmol) to obtain a white solid (0.076 g, 81%).
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19 (bs, 1H), 7.62 (d, *J* = 8.1 Hz, 1H), 7.34 (d, *J* = 8.0 Hz, 1H), 7.21 (ddd, *J* = 8.2, 7.0, 1.3 Hz, 1H), 7.18 – 7.11 (m, 2H), 3.80 (s, 2H), 3.71 (s, 3H). Spectra were consistent with those reported previously.[49]



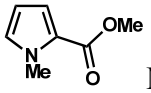
Methyl 2-quinolinecarboxylate (2.60)

Prepared using the general esterification procedure with quinaldic acid (0.087 g, 0.5 mmol) and methyl 1-imidazolecarboxylate (0.126 g, 1.0 mmol) to obtain a white solid (0.084 g, 89%).
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 – 8.29 (m, 2H), 8.21 (d, *J* = 8.5 Hz, 1H), 7.89 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.80 (ddd, *J* = 8.5, 6.9, 1.5 Hz, 1H), 7.66 (ddd, *J* = 8.1, 6.9, 1.1 Hz, 1H), 4.09 (s, 3H). Spectra were consistent with those reported previously.[50]



Methyl 3-quinolinecarboxylate (2.61)

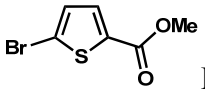
Prepared using the general esterification procedure with 3-quinolinecarboxylic acid (0.087 g, 0.5 mmol) and methyl 1-imidazolecarboxylate (0.126 g, 1.0 mmol) to obtain a white solid (0.086 g, 91%).
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.45 (d, *J* = 2.1 Hz, 1H), 8.86 (d, *J* = 2.0 Hz, 1H), 8.17 (d, *J* = 8.5 Hz, 1H), 7.94 (d, *J* = 8.2 Hz, 1H), 7.84 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 7.63 (ddd, *J* = 8.1, 7.0, 1.1 Hz, 1H), 4.02 (s, 3H). Spectra were consistent with those reported previously.[51]



Methyl 1-methyl-2-pyrrolecarboxylate (2.62)

Prepared using the general esterification procedure with 1-methyl-2-pyrrolecarboxylic acid (0.063 g, 0.5 mmol) and methyl 1-imidazolecarboxylate (0.126 g, 1.0 mmol) to obtain a white solid (0.057 g, 82%).

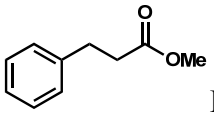
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99 – 6.89 (m, 1H), 6.78 (s, 1H), 6.11 (dd, *J* = 3.9, 2.6 Hz, 1H), 3.93 (s, 3H), 3.81 (s, 3H). Spectra were consistent with those reported previously.[52]



Methyl 5-bromo-2-thiophenecarboxylate (2.63)

Prepared using the general esterification procedure with 5-bromo-2-thiophenecarboxylic acid (0.104 g, 0.5 mmol) and methyl 1-imidazolecarboxylate (0.126 g, 1.0 mmol) to obtain a white solid (0.094 g, 85%).

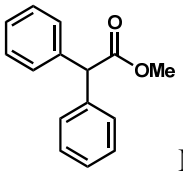
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 4.0 Hz, 1H), 7.07 (d, *J* = 4.0 Hz, 1H), 3.87 (s, 3H). Spectra were consistent with those reported previously.[53]



Methyl hydrocinnamate (2.64)

Prepared using the general esterification procedure with hydrocinnamic acid (0.075 g, 0.50 mmol) and methyl 1-imidazolecarboxylate (0.126 g, 1.0 mmol) to obtain a colorless oil (0.079 g, 96%).

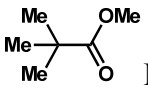
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 – 7.27 (m, 2H), 7.24 – 7.18 (m, 3H), 3.69 (s, 3H), 2.96 (t, *J* = 7.5 Hz, 2H), 2.64 (t, *J* = 7.5 Hz, 2H). Spectra were consistent with those reported previously.[54]



Methyl diphenylacetate (2.65)

Prepared using the general esterification procedure with diphenylacetic acid (0.106 g, 0.5 mmol) and methyl 1-imidazolecarboxylate (0.126 g, 1.0 mmol) to obtain a white solid (0.107 g, 95%).

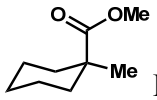
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.29 (m, 8H), 7.28 – 7.24 (m, 2H), 5.03 (s, 1H), 3.74 (s, 3H). Spectra were consistent with those reported previously.[55]



Methyl pivalate (2.66)

Prepared using the general esterification procedure with pivalic acid (0.051 g, 0.50 mmol) and methyl 1-imidazolecarboxylate (0.126 g, 1.0 mmol) to obtain a colorless oil (92%). Yield calculated by ^{1}H-NMR using piperonylonitrile as an internal standard.

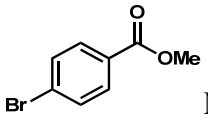
^{1}H NMR (500 MHz, $CDCl_3$) δ 3.66 (s, 3H), 1.21 (s, 9H). Spectra were consistent with those reported previously.[56]



Methyl 1-methyl-1-cyclohexanecarboxylate (2.67)

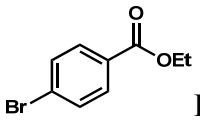
Prepared using the general esterification procedure with 1-methyl-1-cyclohexanecarboxylic acid (0.071 g, 0.5 mmol) and methyl 1-imidazolecarboxylate (0.126 g, 1.0 mmol) to obtain a colorless oil (0.073, 93%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.67 (s, 3H), 2.06 – 1.96 (m, 2H), 1.59 – 1.46 (m, 2H), 1.39 – 1.17 (m, 6H), 1.14 (s, 3H). Spectra were consistent with those reported previously.[57]



Methyl 4-bromobenzoate (2.68)

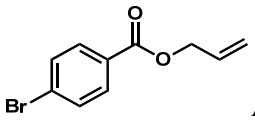
Prepared using the general esterification procedure with the exception that DMF was used as the reaction solvent along with 4-bromobenzoic acid (0.101 g, 0.5 mmol) and methyl 1-imidazolecarboxylate (0.126 g, 1.0 mmol) to obtain a white solid (0.102 g, 94%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.90 (d, J = 8.6 Hz, 2H), 7.58 (d, J = 8.6 Hz, 2H), 3.91 (s, 3H). Spectra were consistent with those reported previously.[58]



Ethyl 4-bromobenzoate (2.69)

Prepared using the general esterification procedure using 4-bromobenzoic acid (0.100 g, 0.5 mmol) and **2.30** (0.140 g, 1.00 mmol) in DMF (1 mL) to yield a colorless syrup (0.099 g, 86%).

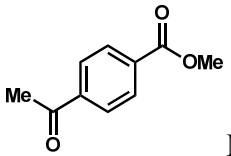
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (d, J = 8.5 Hz, 2H), 7.57 (d, J = 8.5 Hz, 2H), 4.37 (q, J = 7.1 Hz, 2H), 1.39 (t, J = 7.1 Hz, 3H). Spectra were consistent with those reported previously.[59]



Allyl 4-bromobenzoate (2.70)

Prepared using the general esterification procedure using 4-bromobenzoic acid (0.100 g, 0.5 mmol) and **2.32** (0.152 g, 1.00 mmol) in DMF (1 mL) to yield a pale yellow syrup (0.115 g, 95%).

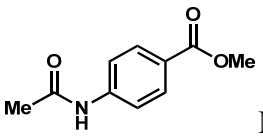
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 (d, J = 8.5 Hz, 2H), 7.58 (d, J = 8.5 Hz, 2H), 6.02 (ddt, J = 16.6, 10.9, 5.7 Hz, 1H), 5.48 – 5.18 (m, 2H), 4.81 (d, J = 5.6, 2H). Spectra were consistent with those reported previously.[60]



Methyl 4-acetylbenzoate (2.71)

Prepared using the general esterification procedure with the exception that DMF was used as the reaction solvent along with 4-acetylbenzoic acid (0.082 g, 0.5 mmol) and methyl 1-imidazolecarboxylate (0.126 g, 1.0 mmol) to obtain a white solid (0.073 g, 82%).

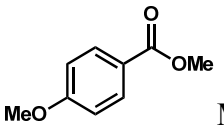
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (dd, J = 9.4, 7.6 Hz, 2H), 8.00 (dd, J = 9.1, 7.4 Hz, 2H), 3.95 (s, 3H), 2.65 (s, 3H). Spectra were consistent with those reported previously.[61]



Methyl 4-acetamidobenzoate (2.72)

Prepared using the general esterification procedure with 4-acetamidobenzoic acid (0.090 g, 0.5 mmol) and methyl 1-imidazolecarboxylate (0.126 g, 1.0 mmol) to obtain a white solid (0.080 g, 83%).

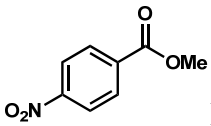
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (d, *J* = 8.7 Hz, 2H), 7.59 (d, *J* = 8.5 Hz, 2H), 7.45 (bs, 1H), 3.90 (s, 3H), 2.21 (s, 3H). Spectra were consistent with those reported previously.[62]



Methyl 4-methoxybenzoate (2.73)

Prepared using the general esterification procedure with the exception that DMF was used as the reaction solvent along with 4-methoxybenzoic acid (0.076 g, 0.5 mmol) and methyl 1-imidazolecarboxylate (0.126 g, 1.0 mmol) to obtain a white solid (0.078 g, 94%).

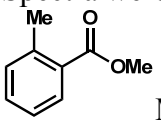
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.9 Hz, 2H), 6.92 (d, *J* = 8.9 Hz, 2H), 3.89 (s, 3H), 3.86 (s, 3H). Spectra were consistent with those reported previously.[63]



Methyl 4-nitrobenzoate (2.74)

Prepared using the general esterification procedure with the exception that DMF was used as the reaction solvent along with 4-nitrobenzoic acid (0.084 g, 0.5 mmol) and methyl 1-imidazolecarboxylate (0.126 g, 1.0 mmol) to obtain a pale yellow solid (0.083 g, 91%).

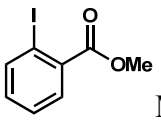
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.30 (d, *J* = 8.9 Hz, 2H), 8.22 (d, *J* = 8.9 Hz, 2H), 3.98 (s, 3H). Spectra were consistent with those reported previously.[64]



Methyl 2-methylbenzoate (2.75)

Prepared using the general esterification procedure with 2-methylbenzoic acid (0.068 g, 0.5 mmol) and methyl 1-imidazolecarboxylate (0.126 g, 1.0 mmol) to obtain a white solid (0.068 g, 90%).

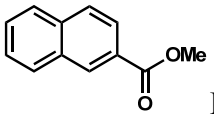
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 – 7.87 (m, 1H), 7.40 (td, *J* = 7.5, 1.4 Hz, 1H), 7.28 – 7.20 (m, 2H), 3.89 (s, 3H), 2.60 (s, 3H). Spectra were consistent with those reported previously.[65]



Methyl 2-iodobenzoate (2.76)

Prepared using the general esterification procedure with 2-iodobenzoic acid (0.124 g, 0.5 mmol) and methyl 1-imidazolecarboxylate (0.126 g, 1.0 mmol) to obtain a white solid (0.110 g, 84%).

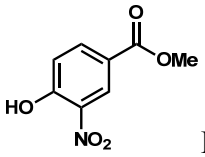
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (dd, *J* = 7.9, 1.0 Hz, 1H), 7.80 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.40 (td, *J* = 7.6, 1.2 Hz, 1H), 7.19 – 7.12 (m, 1H), 3.93 (s, 3H). Spectra were consistent with those reported previously.[66]



Methyl 2-naphthoate (2.77)

Prepared using the general esterification procedure with the exception that DMF was used as the reaction solvent along with 2-naphthoic acid (0.086 g, 0.5 mmol) and methyl 1-imidazolecarboxylate (0.126 g, 1.0 mmol) to obtain a white solid (0.090 g, 97%).

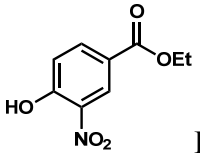
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (s, 1H), 8.06 (dd, *J* = 8.6, 1.7 Hz, 1H), 7.96 (d, *J* = 8.1 Hz, 1H), 7.89 (d, *J* = 8.7 Hz, 2H), 7.65 – 7.49 (m, 2H), 3.99 (s, 3H). Spectra were consistent with those reported previously.[67]



Methyl 4-hydroxy-3-nitrobenzoate (2.78)

Prepared using the general esterification procedure with 4-hydroxy-3-nitrobenzoic acid (0.092 g, 0.5 mmol) and methyl 1-imidazolecarboxylate (0.126 g, 1.0 mmol) to obtain a pale yellow solid (0.065 g, 65%).

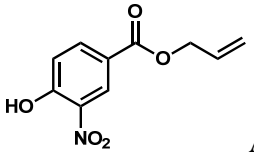
^{1}H NMR (500 MHz, $CDCl_3$) δ 10.9 (s, 1H), 8.82 (d, *J* = 2.1 Hz, 1H), 8.23 (dd, *J* = 8.8, 2.1 Hz, 1H), 7.22 (d, *J* = 8.8 Hz, 1H), 3.94 (s, 3H). Spectra were consistent with those reported previously.[68]



Ethyl 4-hydroxy-3-nitrobenzoate (2.79)

Prepared using the general esterification procedure with 4-hydroxy-3-nitrobenzoic acid (0.092 g, 0.5 mmol) and ethyl 1-imidazolecarboxylate (0.140 g, 1.0 mmol) to obtain a pale yellow solid (0.073 g, 69%).

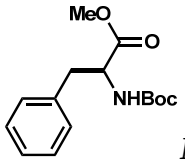
^{1}H NMR (500 MHz, $CDCl_3$) δ 10.9 (s, 1H), 8.82 (d, *J* = 2.1 Hz, 1H), 8.24 (dd, *J* = 8.8, 2.1 Hz, 1H), 7.22 (d, *J* = 8.8 Hz, 1H), 4.40 (q, *J* = 7.1 Hz, 2H), 1.41 (t, *J* = 7.1 Hz, 3H). Spectra were consistent with those reported previously.[69]



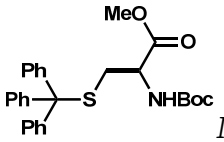
Allyl 4-hydroxy-3-nitrobenzoate (2.80)

4-Hydroxy-3-nitrobenzoic acid (0.092 g, 0.50 mmol) and allyl imidazole carbamate (0.15 g, 1.0 mmol) were placed in a dry 20 mL vial with a Teflon tape-coated thread. A magnetic stirbar was added, DMF (1.0 mL) was added, and the vial was quickly sealed with a plastic cap. The reaction mixture was then heated to 80 °C in a heating block with stirring and held at this temperature for 24 h. The mixture was cooled to room temperature and then the vial was carefully opened (***CAUTION: vial under pressure!***). The resulting mixture was dissolved in ethyl acetate (20 mL), and then washed with 1 M HCl (10 mL). The aqueous layer was back-extracted with ethyl acetate (20 mL) and the organic fractions were combined, washed with water (2 x 10 mL) and then brine, dried over $MgSO_4$, and concentrated *in vacuo* to afford a

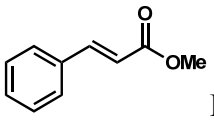
yellow solid. Chromatography (3 : 7 EtOAc : hexanes) afforded the title compound as a yellow solid (79.6 mg, 71%).
^{1}H NMR (500 MHz, $CDCl_3$) δ 10.9 (s, 1H), 8.83 (d, *J* = 2.1 Hz, 1H), 8.25 (dd, *J* = 8.8, 2.1 Hz, 1H), 7.22 (d, *J* = 8.8 Hz, 1H), 6.03 (ddt, *J* = 16.3, 10.6, 5.8 Hz, 1H), 5.42 (dd, *J* = 17.2, 1.4 Hz, 1H), 5.32 (dd, *J* = 10.4, 1.1 Hz, 1H), 4.84 (d, *J* = 5.8 Hz, 2H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 163.9, 158.1, 138.0, 133.2, 131.7, 127.4, 122.7, 120.3, 119.0, 66.2.
mp 75-76 °C.
HRMS-EI *m/z*: M^+ calcd for $C_{10}H_9NO_5$, 223.0481; found, 223.0480.



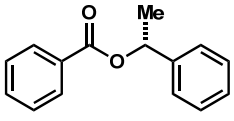
***N*-Boc-Phe-OMe (2.81)**
Prepared using the general esterification procedure with *N*-Boc-Phe-OH (0.133 g, 0.5 mmol) and methyl 1-imidazolecarboxylate (0.126 g, 1.0 mmol) to obtain a white solid (0.127 g, 91%).
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39-7.22 (m, 3H), 7.16 (m, 2H), 5.00 (d, *J* = 7.8 Hz, 1H), 4.60 (dd, *J* = 14.0, 6.5 Hz, 1H), 3.75 (s, 3H), 3.10 (dd, *J* = 14.0, 6.5 Hz, 2H), 1.44 (s, 9H).
Spectra were consistent with those reported previously.[70]



***N*-Boc-Cys(Trt)-OMe (2.82)**
Prepared using the general esterification procedure with *N*-Boc-Cys(Trt)-OH (0.231 g, 0.5 mmol) and methyl 1-imidazolecarboxylate (0.126 g, 1.0 mmol) to obtain a white solid (0.203 g, 85%).
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (d, *J* = 7.6 Hz, 6H), 7.29 (t, *J* = 7.6 Hz, 6H), 7.22 (t, *J* = 7.3 Hz, 3H), 5.01 (d, *J* = 7.9 Hz, 1H), 4.35 – 4.24 (m, 1H), 3.70 (s, 3H), 2.59 (d, *J* = 5.2 Hz, 2H), 1.40 (s, 9H). Spectra were consistent with those reported previously.[71]

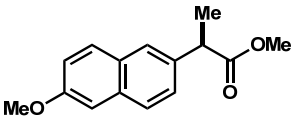


Methyl cinnamate (2.83)
Prepared using the general esterification procedure with *trans*-cinnamic acid (0.074 g, 0.5 mmol) and methyl 1-imidazolecarboxylate (0.126 g, 1.0 mmol) to obtain a glassy solid (0.057 g, 70%).
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, *J* = 16.1 Hz, 1H), 7.53-7.50 (m, 2H), 7.41-7.34 (m, 3H), 6.41 (d, *J* = 16.1 Hz, 1H), 3.79 (s, 3H). Spectra were consistent with those reported previously.[72]



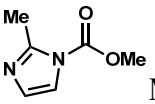
(*R*)-1-Phenylethyl benzoate (2.95)
Prepared using the general esterification procedure with benzoic acid (0.024 g, 0.195 mmol) and (*R*)-1-phenylethyl 1-imidazolecarboxylate (0.084 g, 0.39 mmol) to obtain a colorless oil (0.039 g, 89%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (d, *J* = 7.3 Hz, 2H), 7.56 (t, *J* = 7.4 Hz, 1H), 7.47-7.41 (m, 4H), 7.38 (t, *J* = 7.6 Hz, 2H), 7.31 (t, *J* = 7.3 Hz, 1H), 6.14 (q, *J* = 6.6 Hz, 1H), 1.68 (d, *J* = 6.6 Hz, 3H).
$[\alpha]^{20}_D$ -25.6 (*c* 0.99, EtOH).
HPLC Chiracel OD column (99.5 : 0.5 hexanes : isopropanol, 1.0 mL/min) t_R; 15.97 min (major); 17.52 min (minor): 96% ee. Characterization data were consistent with that reported previously.[73]



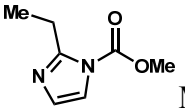
XX **(*R*)-Naproxen methyl ester (2.103)**

Prepared using the general esterification procedure with (*R*)-Naproxen (0.349 g, 1.52 mmol and methyl 1-imidazolecarboxylate (0.252 g, 3.0 mmol) to afford the title compound as a white solid (0.299 g, 88%).
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 – 7.71 (m, 2H), 7.69 (s, 1H), 7.43 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.17 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.13 (s, 1H), 3.97 – 3.85 (m, 4H), 3.69 (s, 3H), 1.61 (d, *J* = 7.1 Hz, 2H). Spectra were consistent with those reported previously.[74]
HPLC Chiracel IB column (99 : 1 hexanes : 2-propanol, 1.0 mL/min) t_R 8.29 min (major), 9.05 min (minor), 40% *ee*. This chromatographic method was used to determine the enantiomeric excess of naproxen methyl ester produced using MImC as well as that from the treatment of enantiopure ester with imidazole.



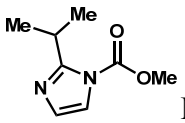
Methyl 2-methyl-1-imidazolecarboxylate (2.113)

2-Methylimidazole (10.6 g, 129 mmol) was dissolved in 120 mL dry THF and the mixture was stirred at 0 °C. Methyl chloroformate (5.0 mL, 65 mmol) was added dropwise and the resulting mixture was stirred and allowed to warm to room temperature over 16 h. The reaction mixture was concentrated to a slurry and 200 mL hexanes was added. The heterogeneous mixture was filtered through Celite, the filtrate was dried with Na_2SO_4, filtered, and concentrated *in vacuo* to afford a pale yellow oil (8.21 g, 90%).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, *J* = 1.8 Hz, 1H), 6.84 (d, *J* = 1.8 Hz, 1H), 3.97 (s, 3H), 2.63 (s, 3H). Spectra were consistent with those reported previously.[75]



Methyl 2-ethyl-1-imidazolecarboxylate (2.114)

Prepared by analogy to methyl 2-methyl-1-imidazolecarboxylate using 2-ethylimidazole to yield a pale yellow oil (3.50 g, 91%).
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (s, 1H), 6.86 (s, 1H), 3.96 (s, 3H), 3.02 (q, *J* = 7.4 Hz, 2H), 1.31 (t, *J* = 7.4 Hz, 3H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 152.8, 149.9, 127.8 118.0, 54.3, 23.2, 11.5.
HRMS-EI *m/z*: M+ calcd for $C_7H_{10}N_2O_2$, 154.0742; found, 154.0742.



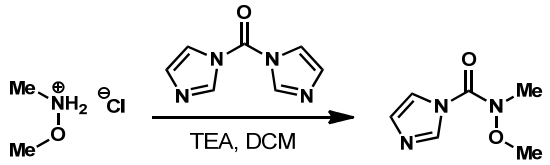
Methyl 2-isopropyl-1-imidazolecarboxylate (2.115)

Prepared by analogy to methyl 2-methyl-1-imidazolecarboxylate using 2-isopropylimidazole to yield a pale yellow oil (3.73 g, 89%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (d, *J* = 1.8 Hz, 1H), 6.87 (d, *J* = 1.7 Hz, 1H), 3.97 (s, 3H), 3.67 (hept, *J* = 6.8 Hz, 1H), 1.31 (d, *J* = 6.8 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 156.7, 149.8, 127.6, 118.0, 54.3, 28.1, 21.2.

HRMS-EI *m/z*: M+ calcd for $C_8H_{12}N_2O_2$, 168.0899; found, 166.0900.



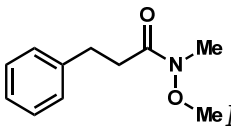
Small Scale Preparation of *N*-methoxy-*N*-methyl-1*H*-imidazole-1-carboxamide (2.157)

1,1'-Carbonyldiimidazole (2.00 g, 12.3 mmol) was dissolved in DCM (15 mL) and then *N*,*O*-dimethylhydroxylamine hydrochloride (1.09 g, 11.2 mmol) was added. The resulting suspension was stirred with cooling to 0 °C. Triethylamine (1.56 mL, 11.2 mmol) was then added dropwise. The reaction mixture was stirred at 0 °C for 1 h, and then at room temperature for 16 h. The heterogeneous mixture was then diluted with DCM (40 mL), washed with water (2 x 20 mL), dried over $MgSO_4$, and concentrated *in vacuo* to afford a colorless oil (1.48 g, 85%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (t, *J* = 1.0 Hz, 1H), 7.56 (t, *J* = 1.5 Hz, 1H), 7.04 (dd, *J* = 1.6, 0.9 Hz, 1H), 3.67 (s, 3H), 3.38 (s, 3H). Spectra were consistent with those reported previously.[76]

General Amidation Procedure:

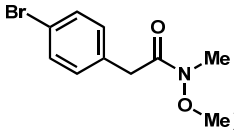
Carboxylic acid (0.5 mmol) and WImC (1.0 mmol) were placed in a dry 20 mL vial with a Teflon tape-coated thread. A magnetic stirbar was added, and then MeCN (1.0 mL) was added, and the vial was quickly sealed with a plastic cap. The reaction mixture was then heated with stirring to 80 °C and held at this temperature in a heating block for 24 h. The mixture was cooled to room temperature and then the vial was carefully opened ***(CAUTION: vial under pressure!)***. The volatiles were removed *in vacuo*, the resulting residue was dissolved in diethyl ether (20 mL), and then washed with 1 M HCl (10 mL). The aqueous layer was back-extracted with diethyl ether (20 mL) and the organic fractions were combined, washed with a saturated solution of $NaHCO_3$ and then brine, dried over $MgSO_4$, and concentrated *in vacuo* to afford the desired ester. Minor amounts of 1,3-dimethoxy-1,3-dimethylurea were removed by heating the crude product mixture at 50 °C under high vacuum for several hours. (*NOTE: 1,3-dimethoxy-1,3-dimethylurea can also be removed by column chromatography if the product amide is also volatile*).



***N*-Methoxy-*N*-methyl-3-phenylpropanamide (2.161)**

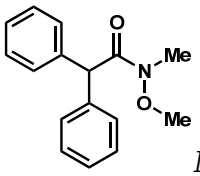
Prepared using the general amidation procedure with hydrocinnamic acid (0.075 g, 0.5 mmol) and **2.157** (0.155 g, 1.00 mmol) to obtain a colorless oil (0.088 g, 91%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.12 (m, 5H), 3.60 (s, 3H), 3.18 (s, 3H), 3.00 – 2.92 (m, 2H), 2.79 – 2.70 (m, 2H). Spectra were consistent with those reported previously.[77]



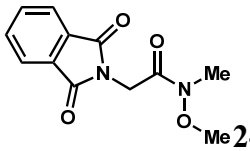
2-(4-Bromophenyl)-*N*-methoxy-*N*-methylacetamide (2.162)

Prepared using the general amidation procedure with 4-bromophenylacetic acid (0.108 g, 0.5 mmol) and **2.157** (0.155 g, 1.00 mmol) to obtain a white solid (0.118 g, 92%).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, J = 8.4 Hz, 2H), 7.17 (d, J = 8.4 Hz, 2H), 3.72 (s, 2H), 3.63 (s, 3H), 3.19 (s, 3H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 171.7, 133.8, 131.5, 131.0, 20.7, 76.9, 61.3, 38.6, 32.2.
HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{10}H_{13}BrNNaO_2$, 279.9944; found, 279.9939.
mp 59-60 °C.



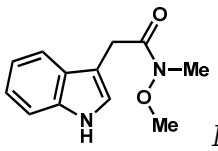
***N*-Methoxy-*N*-methyl-2,2-diphenylacetamide (2.164)**

Prepared using the general amidation procedure with diphenylacetic acid (0.106 g, 0.5 mmol) and **2.157** (0.155 g, 1.00 mmol) to obtain a white solid (0.113 g, 88%).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.21 (m, 10H), 5.55 (s, 1H), 3.49 (s, 3H), 3.24 (s, 3H). Spectra were consistent with those reported previously.[78]



2-(1,3-Dioxoisoindolin-2-yl)-*N*-methoxy-*N*-methylacetamide (2.165)

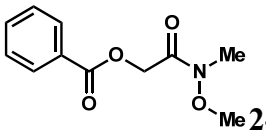
Prepared using the general amidation procedure with *N*-phthaloylglycine (0.103 g, 0.500 mmol) and **2.157** (0.155 g, 1.00 mmol) to obtain a white solid (0.114 g, 92%).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 – 7.83 (m, 2H), 7.76 – 7.68 (m, 2H), 4.62 (s, 2H), 3.82 (s, 3H), 3.21 (s, 3H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 167.9, 167.0, 134.0, 132.2, 123.4, 61.5, 38.6, 32.5.
HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{12}H_{13}N_2O_4$, 249.0870; found, 249.0869.
mp 147-148 °C.



***N*-Methoxy-*N*-methylindole-3-acetamide (2.166)**

Prepared using the general amidation procedure with 3-indoleacetic acid (0.088 g, 0.5 mmol) and **2.157** (0.155 g, 1.00 mmol) to obtain a white solid (0.104 g, 96%).

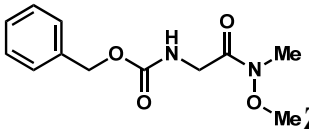
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (s, 1H), 7.65 (dd, *J* = 7.7, 1.0 Hz, 1H), 7.34 (dd, *J* = 8.1, 1.0 Hz, 1H), 7.22 – 7.08 (m, 3H), 3.92 (s, 2H), 3.67 (s, 3H), 3.22 (s, 3H). Spectra were consistent with those reported previously [79]



2-(Methoxy(methyl)amino)-2-oxoethyl benzoate (2.167)

Prepared using the general amidation procedure with *O*-benzoylglycolic acid (0.090 g, 0.5 mmol) and **2.157** (0.155 g, 1.00 mmol) to obtain a white solid (0.103 g, 92%).

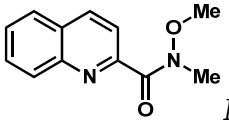
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (dd, *J* = 8.4, 1.3 Hz, 2H), 7.57 (t, *J* = 7.4 Hz, 1H), 7.45 (t, *J* = 7.7 Hz, 2H), 5.07 (s, 2H), 3.79 (s, 3H), 3.23 (s, 3H). Spectra were consistent with those reported previously.[80]



Z-Gly-N(Me)OMe (2.168)

Prepared using the general amidation procedure with Z-Gly-OH (0.105 g, 0.5 mmol) and **2.157** (0.155 g, 1.00 mmol) to obtain a colorless syrup (0.118 g, 93%).

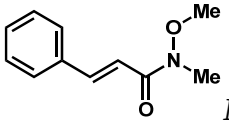
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.28 (m, 5H), 5.56 (bs, 1H), 5.13 (s, 2H), 4.15 (d, *J* = 4.5 Hz, 2H), 3.72 (s, 3H), 3.20 (s, 3H). Spectra were consistent with those reported previously.[81]



***N*-Methoxy-*N*-methylquinoline-2-carboxamide (2.169)**

Prepared using the general amidation procedure with quinaldic acid (0.087 g, 0.5 mmol) to and **2.157** (0.155 g, 1.00 mmol) obtain a tan solid (0.098 g, 91%).

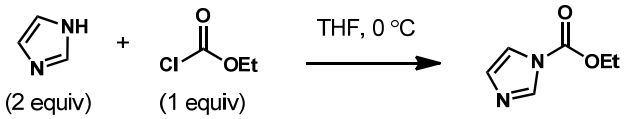
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.25 (d, *J* = 8.4 Hz, 1H), 8.14 (d, *J* = 8.5 Hz, 1H), 7.86 (d, *J* = 8.2 Hz, 1H), 7.76 (ddd, *J* = 8.3, 7.0, 1.5 Hz, 1H), 7.69 (bs, 1H) 7.61 (t, *J* = 7.5 Hz, 1H), 3.79 (bs, 3H), 3.46 (bs, 3H). Spectra were consistent with those reported previously.[82]



***N*-Methoxy-*N*-methylcinnamamide (2.170)**

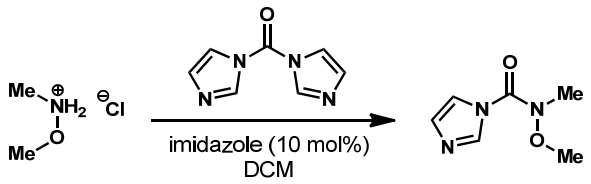
Prepared using the general amidation procedure with cinnamic acid (0.074 g, 0.5 mmol) and **2.157** (0.155 g, 1.00 mmol) to obtain a colorless oil (0.076 g, 80%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, *J* = 15.6 Hz, 1H), 7.60–7.56 (m, 2H), 7.40–7.34 (m, 3H), 7.07 (d, *J* = 15.6 Hz, 1H), 3.75 (s, 3H), 3.30 (s, 3H). Spectra were consistent with those reported previously.[83]



Large Scale Preparation of ethyl 1-imidazolecarboxylate (2.30)

To a 3-neck 2 L round bottom flask equipped with a mechanical stirrer, an internal thermometer, and a 250 mL pressure-equalizing addition funnel was added imidazole (60.0 g, 882 mmol) and then anhydrous THF (1000 mL, added by cannula). The slurry was stirred until homogeneous and then the mixture was cooled to ~0 °C. The addition funnel was charged with ethyl chloroformate (42.2 mL, 441 mmol), which was added dropwise to the stirred solution of imidazole. A white precipitate immediately began to form and the rate of addition was controlled such that the internal temperature did not rise above 10 °C. After the end of the addition, the resulting slurry was stirred for 16 h at room temperature. The precipitate was separated by filtration through a pad of Celite and the filter cake was washed with Et_2O (100 mL). The filtrate was concentrated *in vacuo* to afford **2.30** as a colorless oil (61.0 g, 98%). Care must be taken when removing residual solvent as the title compound is somewhat volatile. See above for characterization data.



Large Scale Preparation of *N*-methoxy-*N*-methyl-1*H*-imidazole-1-carboxamide (2.157)

To a 3-neck 1 L round bottom flask equipped with a large football-shaped magnetic stirbar and an internal thermometer was added CDI (75.0 g, 462 mmol), which was then dissolved in anhydrous DCM (600 mL). The mixture was stirred until homogeneous, and then *N*,*O*-dimethylhydroxylamine hydrochloride (43.1 g, 441 mmol) was added in one portion at room temperature. Imidazole (3.0 g, 44 mmol) was then added in one portion and the heterogeneous mixture was stirred vigorously for 22 h at room temperature, at which time an aliquot was removed and analyzed by ^{1}H NMR. Stirring was halted, the reaction mixture was allowed to rest for 30 minutes, and then filtered through a pad of Celite. The filter cake was then washed with DCM (100 mL). The filtrate was washed with water (250 mL) and the organic layer was dried over Na_2SO_4. Concentration of the resulting colorless solution *in vacuo* afforded the title compound as a pale yellow oil (65.8 g, 96%). See above for characterization data.

2.10 Notes and References

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(8) Initially, we attempted to avoid operating at temperatures above the boiling point of the alcohol that could be produced by hydrolysis of the imidazole carbamate reagent. However, subsequent studies have demonstrated that this was an unfounded concern.
(9) All esterification reactions were run for 24 hours. No attempt was made to optimize reaction time for individual substrates.
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(26) Though this side product is not typically removed by aqueous work up, it is volatile and can either be removed under high vacuum or by chromatography, depending on the nature of the Weinreb amide prepared. Additionally, we encountered no difficulties performing Weinreb ketone syntheses with WImC-derived amides contaminated with small amounts of the symmetrical urea.
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(77) Trost, B. M.; Machacek, M. R.; Faulk, B. D. *J. Am. Chem. Soc*. **2006**, *128*, 6745.
(78) See reference 27.
(79) Boumendjel, A.; Nuzillard, J. M.; Massiot, G. *Bull. Soc. Chim. Fr.* **1990**, 645.
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(81) Shen, M.; Beguin, C.; Golbraikh, A.; Stables, J. P.; Kohn, H.; Tropsha, A. *J. Med. Chem.* **2004**, *47*, 2356.
(82) Oscar, B.; Dawson, G. J.; Krulle, T. M.; Rowley, R. J.; Smyth, D.; Thomas, G. H. WO 2006085118.
(83) Krishnamoorthy R.; Lam, S. Q.; Manley, C. M.; Herr, R. J. *J. Org. Chem.* **2010**, *75*, 1251.

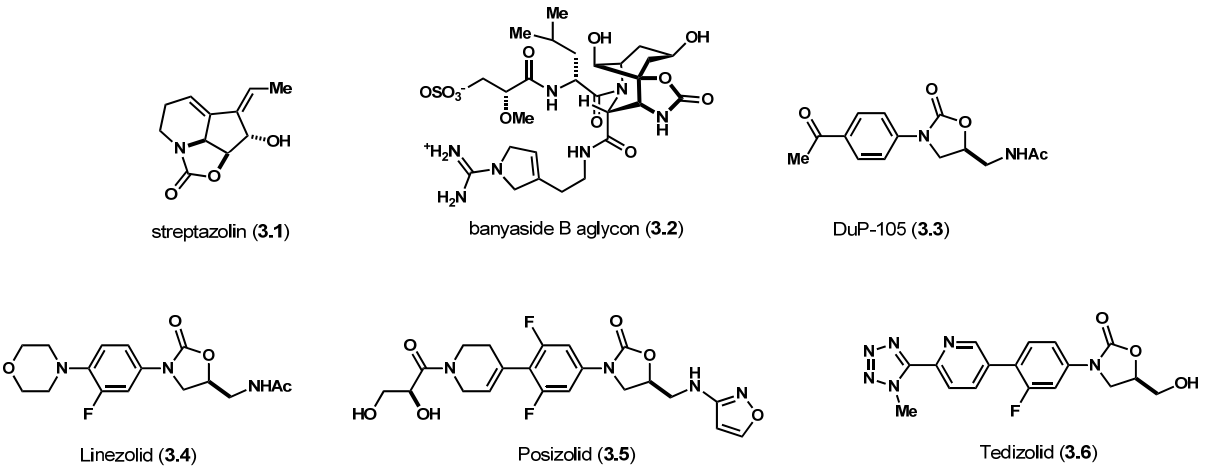
Chapter 3. Dual Brønsted Acid/Nucleophilic Activation of Carbonylimidazoles

3.1 Introduction

In addition to the discovery of a hitherto unknown esterification reaction as a result of our efforts to convert a hindered imidazole carbamate (**2.24**) into an oxazolidinone (**2.21**, see Chapter 2), the preliminary success achieved during this endeavor using Brønsted acid catalysis portended a mild and general strategy for the synthesis of oxazolidinones. The oxazolidinone moiety is present in a number of natural products, including streptazolin (Figure 3.1, **3.1**) and banyaside B (**3.2**); and has found widespread use in a variety of industrial applications. In particular, oxazolidinones play a central role in a class of chiral auxiliaries in organic synthesis and in the eponymous "oxazolidinone antibiotics".

Originally discovered by workers at DuPont, **3.3** provided proof of concept for this new class of antibiotics for the treatment of Gram positive bacterial infections (e.g., staphylococci).[1] Pharmacia and Upjohn then brought Linezolid (**3.4**, sold under the trade name Zyvox) to market in 2000.[2] Since that time, it has been used as an antibiotic of last resort for vancomycin-resistant infections and for some types of complex MRSA infections.[3] The success of **3.4** spurred investigation of other oxazolidinone-containing therapeutics. Posizolid (**3.5**) showed excellent potency in preclinical investigation, but has since been superseded by another oxazolidinone derivative (structure not yet disclosed).[4] Tedizolid (**3.6**) is currently in Phase III clinical trials and has demonstrated enhanced efficacy *in vivo* relative to **3.4**.[5]

Figure 3.1. Biologically and Industrially Significant Oxazolidinones

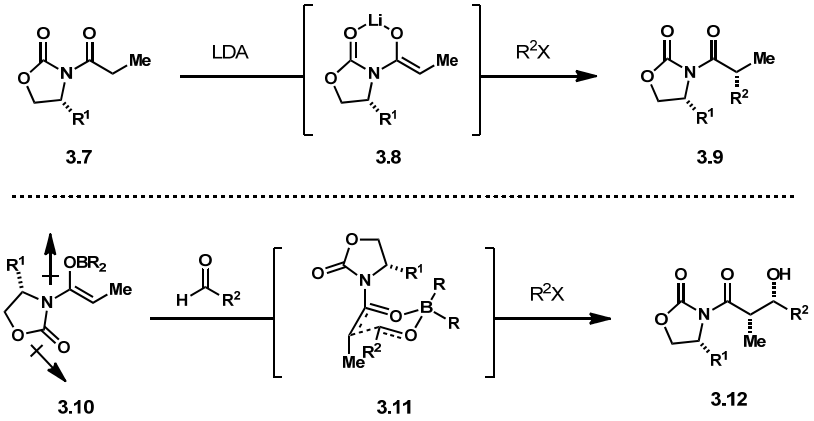


Extensive work has been performed to elucidate the mechanism of action of these antibiotics. Even though it has long been known that they act as protein synthesis inhibitors,[6] a more recent study led to the conclusion that compounds such as **3.4** disrupt this process by inhibiting formation of the 70S initiation complex.[7] This is a unique pathway and as such cross-resistance has not been documented.[8] Comprehensive SAR studies have demonstrated that the oxazolidinone ring, as well as the polar group attached to the alkyl fragment of the oxazolidinone, comprise the pharmacophore of **3.4** (and presumably of **3.5** and **3.6**).[9]

Around the time that DuPont was first developing oxazolidinone-containing antibiotics, Evans and coworkers embarked on a nearly two decade long study of their use as chiral auxiliaries.[10] The high Lewis basicity of the oxazolidinone carbonyl leads to strong chelation in

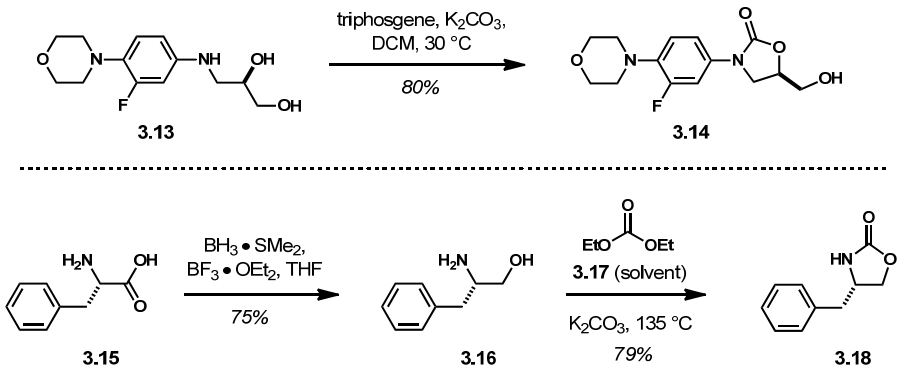
lithium enolates (Scheme 3.1, **3.8**) derived from *N*-acyloxazolidinones (**3.7**), which allows for highly diastereoselective alkylations (see **3.9**) when chiral oxazolidinones are used.[11] These same auxiliaries were also applied successfully to the first general asymmetric aldol reaction using boron enolates (**3.10**).[12] In this case, the oxazolidinone is thought to organize the Zimmerman-Traxler transition state (**3.11**) by dipole minimization (illustrated on **3.10** for clarity).[13] Excellent levels of diastereocontrol were reported, and this method has become commonplace in the synthesis of polyketide natural products and enantioenriched pharmaceutical compounds.[14] More recently, these auxiliaries have found use in a variety of synthetic transformations, including diastereoselective Diels-Alder,[15] conjugate addition,[16] and reduction reactions.[17]

Scheme 3.1. Use of Oxazolidinones as Chiral Auxiliaries



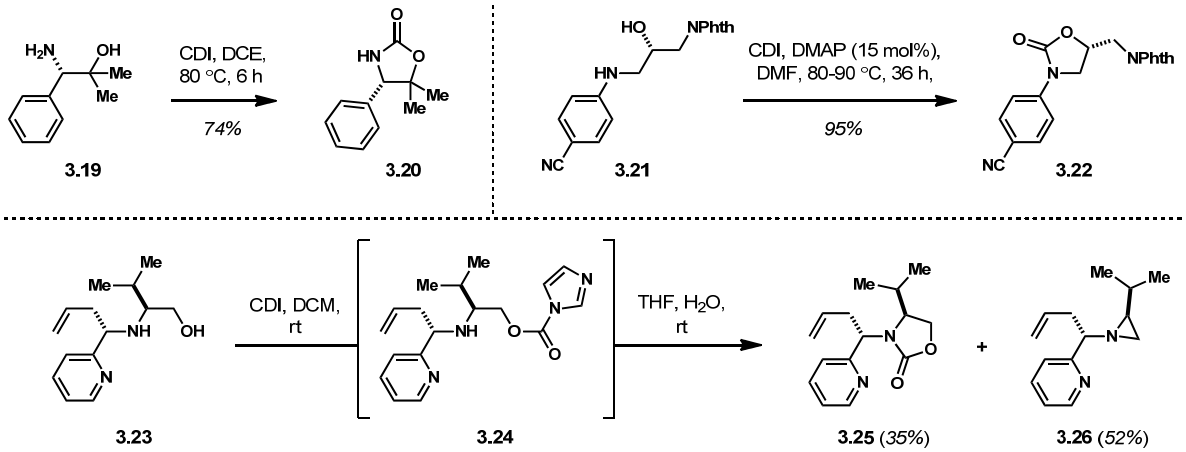
A plethora of methods for the synthesis of the oxazolidinone ring have been developed, the most common of which is the carbonylation of 1,2-amino alcohols.[18] This is typically achieved through reaction of an amino alcohol with a carbonyl bis-cation equivalent such as phosgene,[19] CDI,[20] or in some cases even dialkyl carbonates.[21] Indeed, a common route to Linezolid analogs relies on this technique to synthesize the crucial oxazolidinone ring (**3.14**, Scheme 3.2, top) from amino alcohol **3.13**.[22] Alternatively, Evans and coworkers elected to use safe and inexpensive diethyl carbonate in their large scale synthesis of a chiral auxiliary (**3.18**) from phenylalanine (**3.15**).[23] However, the poor reactivity of **3.17** as a carbonyl donor required that the reaction be run at high temperature using a vast excess of the carbonate.

Scheme 3.2. Traditional Methods for the Preparation of Oxazolidinones



Thus, if a carbonyl bis-cation synthon other than phosgene is to be employed, the choice of electrophile is heavily dependent on the stereoelectronic profile of the amino alcohol. Given the reduced reactivity of phosgene replacements, less nucleophilic substrates such as **3.19** and **3.21** (Scheme 3.3) often necessitate harsh conditions relative to those employed in traditional phosgene-mediated carbonylations.[24,25] Furthermore, CDI-mediated oxazolidinone syntheses often fail on highly hindered amines – instead affording symmetrical carbonates, or aziridines (**3.26**) if a carbamate (**3.24**) is formed first.[26] Given the increasing emphasis on the use of CDI as a safe replacement for phosgene (see Chapter 1), we sought to apply the insight gained during our investigation of the synthesis of **2.21** from imidazole carbamate **2.24** to a general and mild CDI-based oxazolidinone synthesis. However, we chose to conduct preliminary studies on a model compound because of the relatively lengthy synthetic route to bis-carbamate **2.24**.

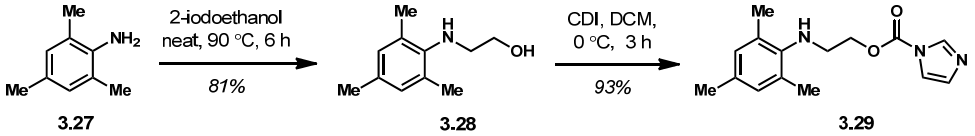
Scheme 3.3. Representative CDI-Mediated Oxazolidinone Syntheses



3.2 Model System Studies

Our primary goal in designing a model carbonylimidazole compound was to simulate the steric encumbrance of the aniline group in **2.24**, so we set out to prepare **3.29** (Scheme 3.4). This carbonylimidazole derivative was synthesized from aniline **3.27** by alkylation with iodoethanol to give the penultimate amino alcohol (**3.28**).[27] Carbamate formation was achieved using conditions developed for the preparation of some of our esterification reagents (see Chapter 2)

Scheme 3.4. Preparation of a Model System

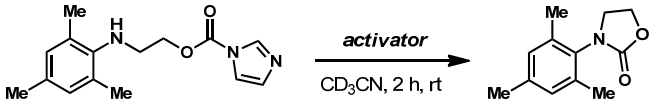


Initial explorations focused on ring closure tactics under mild, non-acidic, conditions. Simply heating **3.29** in d_7-DMF returned starting material, as did treatment with imidazole or triethylamine (Table 3.1, entries 1-3). Similarly, preliminary efforts to engage **3.29** in classical nucleophilic catalysis by addition of DMAP were unfruitful (entry 4).

We then returned to acid-promoted carbonylimidazole activation by employing imidazole hydrochloride, which has been reported to accelerate the amidation of acylimidazoles,[28] but found it to be an ineffectual activator of **3.29** (entry 7). Consistent with our work on esterification reactions mediated by imidazole carbamates, no reaction was observed when a stoichiometric amount of acetic acid was added to **3.29** at room temperature (entry 5), whereas utilization of acetic acid as solvent led to competing cyclization and esterification (entry 6). Trifluoroacetic acid (TFA) was an effective stoichiometric activator, suggesting that stronger acids may promote cyclization more readily (entry 8). However, significant quantities of trifluoroacetylated products were also obtained. Since this side reaction was likely specific to carboxylic acids, we then evaluated several other classes of acids of varying pK_a.[29] Increasing the strength of the acid promoter through the use of camphorsulfonic acid (CSA) led to 52% conversion to **3.30** over two hours (entry 9). While it was clear that the use of strong acids would allow for the synthesis of sterically crowded oxazolidinones such as **3.30**, these reaction conditions were less desirable for complex molecules that possess sensitive functional groups.

In hopes of further tuning the cyclization, we then investigated the use of acid activators with pK_as between those of TFA and CSA. The tosylate salt of *N*,*N*,-dimethylaniline (**3.31**) promoted the formation of **3.30** (entry 10), but less efficiently than either TFA or CSA – a curious result given the crude correlation we had thus far observed between acid pK_a and activator efficacy. This relationship was further weakened by the fact that, *ceteris paribus*, pyridinium tosylate (PPTS, **3.32**) was more effective than **3.31** even though it is about ten times less acidic (entries 11 and 12).

Table 3.1. Impact of Activating Species on Oxazolidinone Formation



3.29 **3.30**

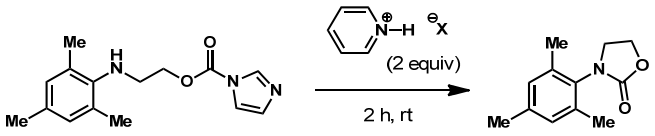
Entry	Activator	pK_a[a]	Equiv	% Conversion[b]
1	—[c]	—	—	0
2	TEA	—	1	0
3	imidazole	—	1	0
4	DMAP	—	1	0
5	AcOH	12.3	1	0
6	d_4-AcOH	12.3	~85[e]	49
7	imidazole • HCl	7.0	2	trace[d]
8	TFA	3.5	1	48[f]
9	(+)-CSA	1.6	1	53
10	*N*,*N*-dimethylaniline • HOTs (**3.31**)	2.5	2	33
11	pyridine • HOTs (**3.32**)	3.4	1	38
12	pyridine • HOTs	3.4	2	63

[a] in DMSO, see reference 29. [b] Conversions determined by integration of resonances in ^{1}H-NMR. [c] **1** was heated to 130 ºC in d_7-DMF. [d] The reaction was run in d_6-DMSO. [e] d_4-AcOH was used as solvent. [f] 2.5 : 1 ratio of **3.30** to trifluoroacetylation products obtained

While PPTS is a convenient and commercially available reagent, it is somewhat expensive ($1.95/g from Sigma-Aldrich) and has a high molecular weight, so processes using it as a stoichiometric activator tend to have poor atom economy. We reasoned that the relevant acid in such a reaction is actually pyridinium cation and that other pyridinium sources might be equally efficacious. Therefore, we assessed several pyridinium salts with varying counteranions

(Table 3.2). Gratifyingly, the least expensive and most atom-economical salt – pyridinium chloride – was a competent activator (entry 2). But to our surprise, salts with more coordinating anions were inferior to those with weakly- or non-coordinating counteranions (compare entries 1-6). In fact, pyridinium triflate was found to be a highly active promoter of the cyclization of **3.29**, with 76% conversion achieved after just two hours (entry 5).

Table 3.2. Anion Effect in the Pyridinium Salt Mediated Oxazolidinone Synthesis



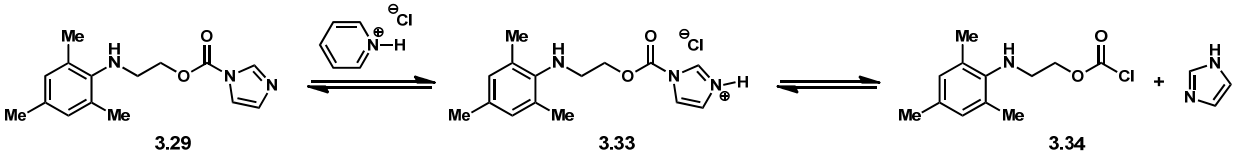
3.29 **3.30**

Entry	Counteranion (X)	Solvent	Additive	% Conversion[a]
1	OAc	CD_3CN	—	0
2	Cl	CD_3CN	—	38
3	Br	CD_3CN	—	52
4	OTs	CD_3CN	—	63
5	OTf	CD_3CN	—	76
6	BF_4	CD_3CN	—	83
7	OTf	CD_3CN	TBAC (2 equiv)	44
8	Cl	CD_3CN	TBAC (2 equiv)	38
9	Cl	$CDCl_3$	—	36
10	Cl	DMSO-d_6	—	54

[a] Conversions determined by integration of resonances in ^{1}H-NMR.

We entertained two initial hypotheses about the origin of the observed anion effect, both of which we briefly examined empirically. The first considered that chloride ion could inhibit the reaction by acting as a nucleophile toward an activated intermediate such as a protonated imidazole carbamate (**3.33**, Scheme 3.5), leading to a chloroformate (**3.34**). This would be analogous to Staab's finding that acid chlorides are produced from acylimidazoles and HCl (see Chapter 1). Alternatively, a charged intermediate (i.e., **3.33**) could be tightly bound to the counteranion by electrostatic attaction, making it a less reactive electrophile. The former proposal was tested by adding tetra-*n*-butylammonium chloride (TBAC), an exogeneous chloride source, to a reaction performed with pyridinium triflate (Table 3.2, entry 7). This experiment provided results comparable to those obtained by simply using pyridinium chloride (entry 8). A similar result was obtained by addition of TBAC to a reaction performed with pyridinium chloride. The fact that there was little difference between reactions run with differing concentrations of chloride ion (compare entries 7 and 8) lends support to our second hypothesis, but could also be the result of chloride saturation. Moreover, we did not observe a build up in the concentration of **3.34** during the reaction, suggesting that covalent inhibition may be unlikely. Comparison of entries 2 and 8 suggested the absence of a strong kinetic electrolyte effect. We also found that solvent polarity had only a moderate effect on reaction efficiency (entries 9 and 10). Unfortunately, taken together these results do not provide unambiguous support for either hypothesis. Though not explicitly investigated, it may be that the counteranion engages in a hydrogen bond with **3.23**, rendering it less electrophilic. This hypothesis would be consistent with the observed dependence on the coordinating (and hydrogen-bonding) capability of the counteranion. Nonetheless, the mechanistic basis for the observed anion effect remains an enigma.

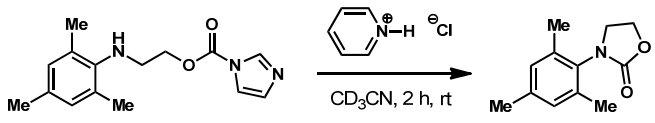
Scheme 3.5. Possible Mechanism of Chloride Inhibition



3.29 3.33 3.34

Even though it proved possible to exploit this trend to great effect, pyridinium salts with weakly coordinating counteranions such as pyridinium triflate are somewhat expensive ($3.36/g from Strem Chemicals), so we also set out to develop optimized conditions for carbonylimidazole activation using pyridinium chloride, an industrial waste product (Table 3.3, $0.26/g from Sigma-Aldrich). In principle, a single equivalent of pyridinium salt is required, but we found that reactions performed in this fashion stalled at about 70% conversion. We attribute this effect to the fact that the imidazole generated during the course of the cyclization buffers the reaction. Utilizing a second equivalent of pyridinium salt ameliorated this problem and a strong dependence on activator loading was observed with increasing quantities of pyridinium chloride (entries 1-4). The cyclization of **3.29** was then performed at varied concentrations, but only modest changes in reaction rate were observed at pyridinium cation concentrations above 0.2 M (entries 2, 5, and 6). Finally, we probed the effect of temperature on the reaction, finding that mild heating (40 °C) was sufficient to drive the reaction (entry 7). Heating to 60 °C led to very fast cyclization (entry 8), however, this additional acceleration was not necessary and all subsequent carbonylimidazole activation reactions were performed between room temperature and 40 °C.

Table 3.3. Optimization of Oxazolidone Synthesis using Pyridinium Chloride



3.29 3.30

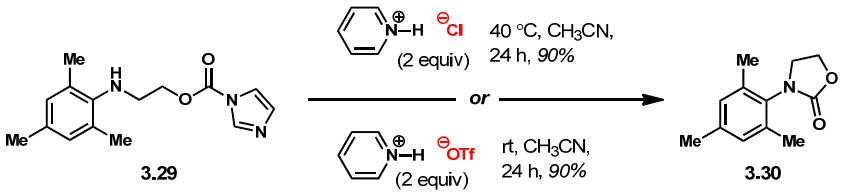
Entry	Temp (°C)	Pyridine • HCl (equiv)	Conc (M)	% Conversion[a]
1	22	1	0.2	20
2	22	2	0.2	38
3	22	3	0.2	50
4	22	4	0.2	69
5	22	2	0.1	20
6	22	2	0.5	46
7	40	2	0.2	78
8	60	2	0.2	>95

[a] Conversions determined by integration of resonances in ^{1}H-NMR.

At this point we had developed two sets of reaction conditions that efficiently promote oxazolidinone formation. Pyridinium chloride could be employed at slightly elevated temperatures, or pyridinium triflate could be used at room temperature. Each of these approaches were applied to the synthesis of **3.30** and were found to provide virtually identical yields (Scheme 3.6). The former technique is more cost-effective; however, the latter is milder

and likely to be more chemoselective because of the reduced operating temperature required. Therefore, we recommend that pyridinium triflate be used with substrates that contain particularly acid-sensitive functional groups.

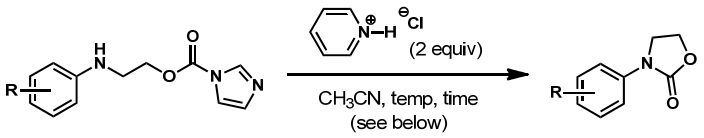
Scheme 3.6. Comparison of Pyridinium Chloride and Triflate

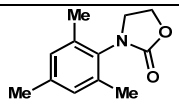
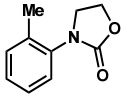
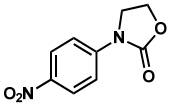
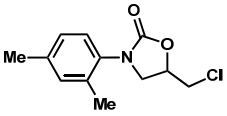
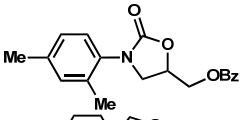
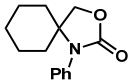
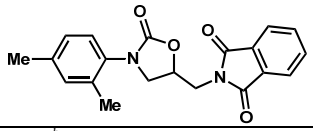


3.3 Scope and Mechanism of Oxazolidinone Synthesis Under Pyridinium Catalysis

We then applied these optimized conditions to the synthesis of other oxazolidinones that would be hard to access using standard techniques. Both sterically encumbered (Table 3.4, **3.35**, **3.36**, entries 1 and 2) and electronically deactivated aniline derivatives (**3.37**, entry 3) can be acylated to provide the corresponding oxazolidinones in good to excellent yields.

Table 3.4. Scope of the Pyridinium Salt Mediated Oxazolidinone Synthesis



Entry	Product		Temp (°C)	Time (h)	Yield (%)[a]
1		**3.35**	40	9	90
2		**3.36**	40	9	90
3		**3.37**	40	36	41[b]
4		**3.38**	22	24	89
5		**3.39**	22	24	94
6		**3.40**	22	24	93
7		**3.41**	22	24	90

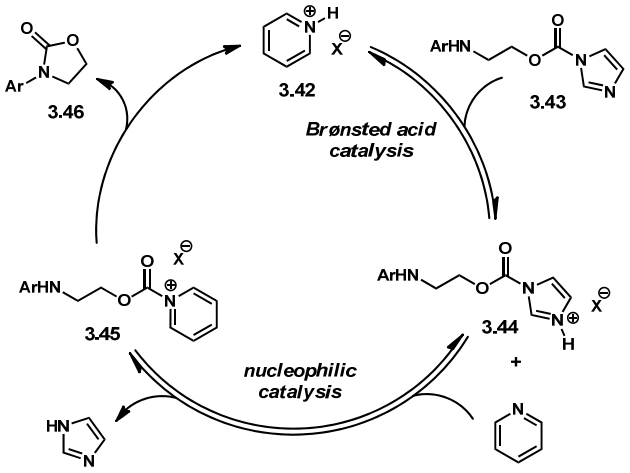
[a] Yields are for isolated compounds. [b] >90% conversion to **3.37** observed by ^{1}H-NMR

We also investigated the use of polyfunctional substrates, finding that oxazolidinone formation occurred in preference to displacement of a primary chloride (**3.38**, entry 4) or benzoyl group migration (**3.39**, entry 5). Similarly, α-tertiary anilines can be transformed to the corresponding spirocyclic oxazolidinones (**3.40**, entry 6). Finally, cyclization products appropriately functionalized for use in SAR studies related to the oxazolidinone antibiotics could be efficiently prepared (**3.41**, entry 7, compare with **3.3**, Figure 3. 1).

Turning our attention to the mechanism of action of pyridinium salts in the synthesis of oxazolidinones from imidazole carbamates, we were intrigued by the observation that the facility of oxazolidinone formation was not strictly dependent on the pK_a of the activating agent (see Table 3.1). This finding led us to further investigate the seemingly special role of pyridinium salts (Scheme 3.7, **3.42**). Early hypotheses derived from the insight that carboxylic acids react with imidazole carbamates to generate mixed anhydrides by protonation and subsequent attack on an intermediate such as **3.33** by a carboxylate ion (see Chapter 2) – a process amounting to nucleophilic activation. Thus, we wondered whether pyridine could be acting as a nucleophilic catalyst.[30]

In this scenario, an acid-base equilibrium develops to generate a carbonylimidazolium salt (**3.44**). This intermediate could then undergo an exchange reaction with pyridine (generated in the acid-base equilibrium) to form a strongly electrophilic acylpyridinium salt (**3.45**). Finally, this activated ester species could be engaged by the amine nucleophile to generate the desired amide linkage (e.g., **3.46**). Even though we propose that this reaction is formally catalytic in pyridinium salt, free imidazole formed during the reaction acts as a terminal base, thereby requiring the use of stoichiometric amounts of pyridinium salts.

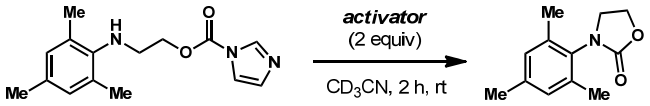
Scheme 3.7. Proposed Mechanism of Pyridinium Salt Activation of Carbonylimidazoles



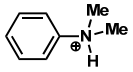
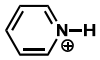
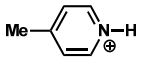
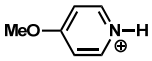
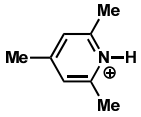
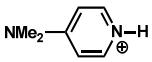
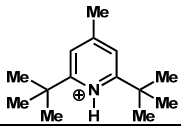
Initial inquiry into this possibility was conducted by using sterically encumbered pyridinium salts or non-nucleophilic ammonium salts as activating agents. In the event, comparison of two pyridinium salts of nearly equal acidity[31] but differing steric profiles (**3.47** and **3.48**, Table 3.5, entries 3 and 4) demonstrated that reduction of the nucleophilicity of pyridine led to dramatically decreased reactivity. This same effect can be observed by comparing **3.47** (entry 3) and **3.49** (entry 5), where the former is nearly 10 times more acidic, but still underperforms the more *nucleophilic* **3.49**. The fact that PPTS (**3.32**, entry 2) is a superior promoter relative to **3.49** (entry 5), which is much less acidic but provides a more nucleophilic

conjugate base, suggests that a balance between acidity and nucleophilicity must be achieved in order to obtain efficient carbonylimidazole activation. Thus, even pyridinium salts with highly nucleophilic conjugate bases do not promote oxazolidinone formation if they are not acidic enough to undergo an initial proton transfer step (**3.51**, entry 7). As expected, highly hindered salts are not viable activators (**3.50**, entry 6) unless the steric environment about the site of protonation renders the salt unusually acidic, in which case they can function as simple Brønsted acids (**3.52**, entry 8).[32]

Table 3.5. Effect of Acidity and Nucleophilicity on Carbonylimidazole Activation



3.29 **3.30**

Entry	Pyridinium salt		pK_a[a]	% Conversion[b]
1		**3.31**	11.4	33
2		**3.32**	12.5	63
3		**3.47**	13.3	8
4		**3.48**	~13.5[c]	48
5		**3.49**	14.2	24
6		**3.50**	15.0	trace
7		**3.51**	18.0	NR
8		**3.52**	unknown	29[d]

[a] literature pK_a values determined in MeCN [b] Conversions determined by integration of resonances in ^{1}H-NMR. [c] See reference 30. [d] The tetrafluoroborate salt was used. Unless otherwise noted, all compounds are tosylate salts (anion omitted for clarity).

These observations are consistent with pyridinium salts (**3.42**, Scheme 3.7) acting as both Brønsted acid and nucleophilic catalysts in the acylation reactions of imidazole carbamates.

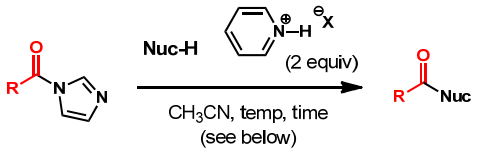
With this mechanistic insight in mind, we reasoned that this mode of activation should be applicable to any transformation in which a carbonylimidazole derivative acts as an electrophilic acylating reagent. Therefore, we sought to extend this mode of carbonylimidazole activation to intermolecular reactions, the most basic of which is the coupling of acylimidazoles with heteroatomic nucleophiles. To this end, we first investigated the effect of pyridinium salts on the reaction of acylimidazoles with alcohols.

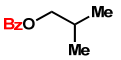
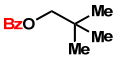
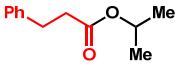
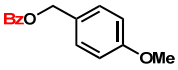
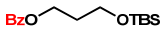
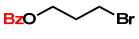
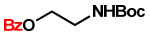
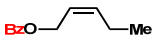
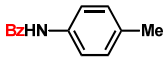
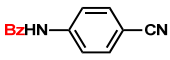
3.4 Ester Syntheses under Pyridinium Catalysis

Treatment of benzoylimidazole with a range of alcohols at room temperature in the presence of pyridinium chloride typically led to clean production of esters (Table 3.6), while no reaction occurred in the absence of an activator. More sterically congested primary alcohols such as neopentyl alcohol were efficiently esterified at room temperature using pyridinium triflate (entries 1 and 2). Similarly, secondary esters such as isopropyl 3-phenylpropanoate (**3.55**, entry 3) could be prepared in good yield, but generally required gentle heating. The mild conditions required for acylimidazole esterification allowed for a high degree of functional group tolerance. PMB, TBS, and Boc protecting groups were all unaffected (entries 4, 5 and 7), and even reactive primary bromides (entry 6)[33] survived the esterification conditions. We did not observe double bond isomerization when *Z*-alkenes were used (entry 8) or racemization when enantioenriched 1-phenylethanol was benzoylated (entry 9).[34]

Although the reaction of acylimidazoles with most amine nucleophiles need not be catalyzed, anilines can sometimes be poor nucleophiles in the synthesis of amides. So we were pleased to find that the generation of benzamides is greatly accelerated using pyridinium salt activation of the acylimidazole electrophile. For example, **3.62** formed nearly instantaneously using pyridinium chloride as a promoter (entry 10). Additionally, **3.63** (entry 11) could be prepared in 8 hours at 40 °C. In comparison, the use of imidazole hydrochloride as an activating agent for the preparation of **3.63** was reported to require heating to 100 °C for 10 hours.[35]

Table 3.6. Scope of Pyridinium Salt Mediated Esterification and Amidation of Acylimidazoles



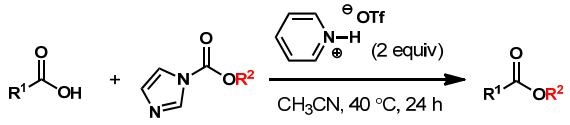
Entry	Product		Counteranion (X)	Temp (°C)	Time (h)	Yield (%)[a]
1		**3.53**	OTf	22	12	93
2		**3.54**	OTf	22	36	79
3		**3.55**	OTf	40	26	82
4		**3.56**	Cl	22	24	92
5		**3.57**	Cl	22	24	76
6		**3.58**	OTs	22	24	80
7		**3.59**	Cl	22	24	76
8		**3.60**	Cl	22	24	82
9		**3.61**	OTf	50	43	84
10		**3.62**	Cl	22	0.17	96
11		**3.63**	Cl	40	8	96

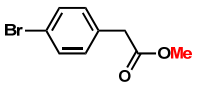
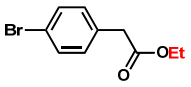
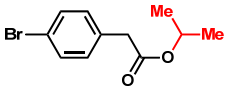
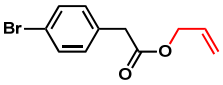
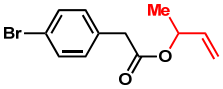
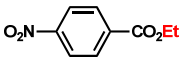
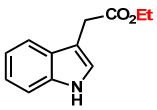
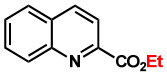
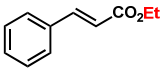
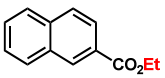
[a] Yields are for isolated compounds.

The esterification of carboxylic acids with imidazole carbamates is also accelerated by pyridinium salts, but most efficiently by pyridinium triflate (Table 3.7). Reactions that proceeded at 80 °C without a promoter can now be effectively performed at 40 °C with comparable results (entries 1-5). Notably, imidazole carbamates of secondary alcohols can now be used as esterification reagents at 40 ºC (entry 3), whereas this transformation required 48 hours at 80 ºC under our previously reported conditions (see Chapter 2). The scope of this new esterification protocol appears to be similar to that previously reported as aryl and heteroaryl

carboxylic acids were easily esterified (entries 6, 8, and 10), and acid sensitive ring systems such as indoles were well-tolerated (entry 7).

Table 3.7. Pyridinium Triflate Promoted Esterification of Carboxylic Acids By Imidazole Carbamates

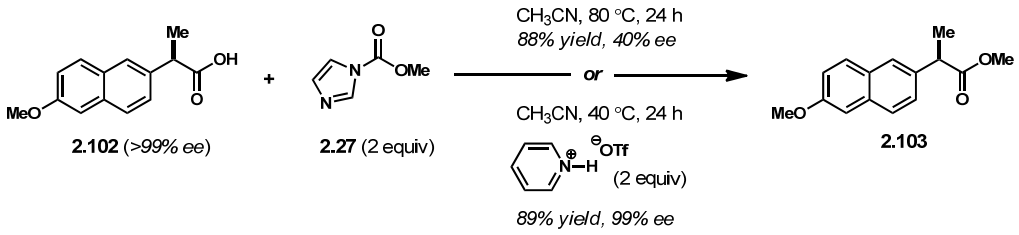


Entry	Carbamate (R^2)		Product		Yield (%)[a]
1	Me	**2.27**		**2.28**	93
2	Et	**2.30**		**2.41**	79
3	*i*-Pr	**2.31**		**2.46**	82
4	allyl	**2.32**		**2.42**	92
5	3-butenyl	**2.34**		**2.48**	76
6	Et	**2.30**		**3.64**	80
7	Et	**2.30**		**3.65**	76
8	Et	**2.30**		**3.66**	84
9	Et	**2.30**		**3.67**	96
10	Et	**2.30**		**3.68**	96

[a] Yields are for isolated compounds.

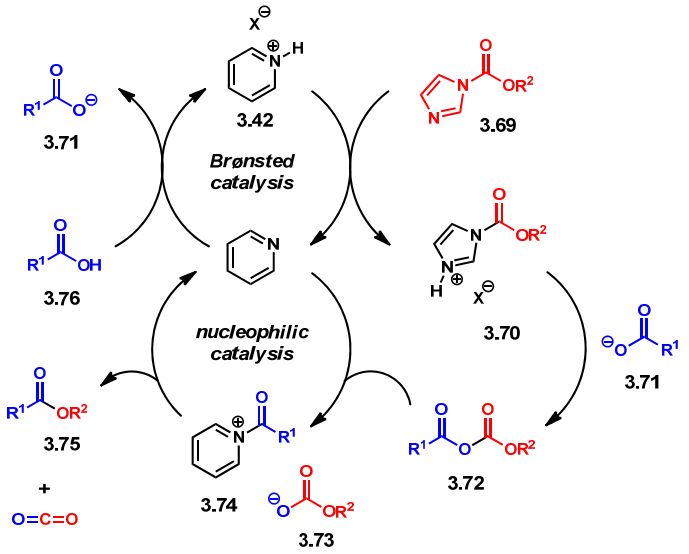
Notably, this method of carbonylimidazole activation also allowed for sequestration of imidazole through protonation, which makes possible the esterification of α-chiral carboxylic acids without racemization (Scheme 3.8, **2.103**). This was previously a serious limitation to the use of imidazole carbamates as esterification reagents (see Chapter 2). Finally, enoates such as **3.67** could be prepared in good yield (Table 3.7, entry 9). However, we observed small quantities of a side product arising from the conjugate addition of imidazole when the esterification of cinnamic acid is monitored by ^{1}H-NMR.

Scheme 3.8. Comparison of Esterification Methods on Naproxen



We are currently investigating the mechanism by which pyridinium salts promote the esterification of carboxylic acids with imidazole carbamates. One possibility involves an acid-base equilibrium between the imidazole carbamate (Scheme 3.9, **3.69**) and a pyridinium salt (**3.42**). In turn, pyridine could serve to deprotonate the carboxylic acid substrate (**3.76**), giving rise to a carboxylate anion (**3.71**). The latter could then engage electrophilic **3.70** to yield a mixed anhydride (**3.72**). Though we cannot exclude the intermediacy of an acylimidazole, we believe that pyridine, regenerated during the formation of **3.70**, could attack **3.71** to form acylpyridinium cation (**3.74**). Carbonic ester **3.73** could serve as the counteranion and undergo decarboxylation to generate an alkoxide (not shown), trapping **3.74** to afford the desired ester (**3.75**).

Scheme 3.9. Possible Mechanism of Pyridinium Salt Catalysis of Imidazole Carbamate-Based Esterifications



Thus, pyridinium cation could play the role of a Brønsted acid catalyst by distorting the equilibrium between ion pair **3.70** and neutral species **3.76** and **3.69**. In the uncatalyzed reaction, the neutral species is greatly favored; however, relatively high concentrations of both carboxylate **3.71** and electrophilic **3.70** could be accessible in the presence of pyridinium/pyridine. Furthermore, in analogy to the pyridinium salt activation of carbonylimidazole derivatives, pyridine could act as a nucleophilic catalyst toward acylcarbonate **3.72**.[36]

In conclusion, we have developed a mild and selective method for the activation of carbonylimidazole derivatives using pyridinium salts that is applicable to both intermolecular and intramolecular reactions. This activation mode was applied to the synthesis of

oxazolidinones from amino-alcohols that would be difficult to prepare without the use of phosgene, thereby providing an alternative to this less-desirable reagent. Furthermore, this method enables the preparation of esters from acylimidazoles at room temperature. Similarly, pyridinium salt additives accelerate the reaction of imidazole carbamates with carboxylic acids to yield esters and allow for esterification of easily racemizable carboxylic acid substrates. Additional studies on the mechanism by which these salts activate carbonylimidazole derivatives and application to new acylation protocols should shed more light on the subtleties of this process.

3.5 Experimental Section

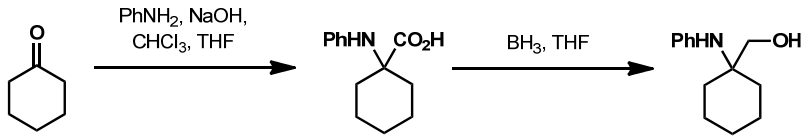
Materials and Methods:

See the experimental section of Chapter 2.

Drying Pyridinium Chloride:

Commercial pyridinium chloride (20 g) was suspended in benzene (200 mL) in a flask equipped with a Dean-Stark trap and refluxed for 12 hours. The Dean-Stark trap was then removed and the remaining benzene was removed *in vacuo* on a rotary evaporator. The resulting mass could be stored in a desiccator for several months without noticeable absorbance of moisture (NOTE: Reactions performed with dried pyridinium chloride were generally slightly higher yielding as no product arising from carbonylimidazole hydrolysis was observed. This side product was typically obtained as a 3-5% impurity in reactions run with commercial pyridinium chloride).

Synthesis of Amino Alcohol Substrates:



3.77 **3.78**

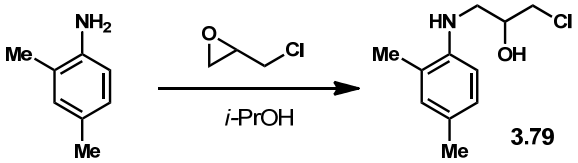
(1-(phenylamino)cyclohexyl)methanol (3.78)
Aniline (1.00 g, 10.7 mmol) and cyclohexanone (3.16 g, 32.2 mmol) were dissolved in THF (100 mL). The homogeneous mixture was stirred and cooled to 0 ºC, and then freshly powdered NaOH (2.16 g, 54.0 mmol) was added in one portion. The resulting suspension was stirred while chloroform (6.45 g, 54.0 mmol) was added dropwise at 0 ºC. The reaction mixture was allowed to warm to room temperature and was stirred overnight. During this time, a thick tan paste formed and stirring became difficult. The crude reaction mixture was filtered and the solids collected were dissolved in water. The aqueous solution was extracted with Et_2O (2 x 50 mL). The aqueous layer was acidified with AcOH and then extracted with EtOAc (3 x 50 mL). The combined EtOAc extracts were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo* to yield **3.77** as a tan powder (1.08 g, 46%) that was used without further purification.
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20 (t, J = 7.9 Hz, 2H), 6.86 (t, J = 7.3 Hz, 1H), 6.67 (d, J = 8.0 Hz, 2H), 2.06 – 1.93 (m, 4H), 1.68 – 1.58 (m, 3H), 1.50 – 1.30 (m, 3H).

3.77 was dissolved in dry THF (20 mL) and then BH_3•THF (1.0 M solution, 28 mL) was added dropwise (***CAUTION: Hydrogen gas is evolved!***) at room temperature. After gas evolution had ceased, the reaction mixture was refluxed for 14 h. Upon cooling the mixture to room temperature, water was added dropwise (***CAUTION: Hydrogen gas is evolved!***) until gas evolution ceased. The crude reaction mixture was concentrated *in vacuo* and the resulting residue was dissolved in a mixture of EtOAc and water. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 30 mL). The combined organics were washed with 1 M Na_2CO_3 (aq), then brine, dried over Na_2SO_4, and concentrated *in vacuo* to afford a pale yellow syrup. The crude product was purified by column chromatography (1 : 9, EtOAc : hexanes) to afford **3.78** as a colorless syrup (1.0 g, 87%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20-7.17 (m, 2H), 6.85-6.79 (m, 3H), 3.58 (s, 2H), 3.36 (bs, 1H), 2.53 (bs, 1H), 1.85-1.80 (m, 2H), 1.60-1.38 (m, 8H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 145.4, 129.0, 119.7, 118.4, 67.7, 57.3, 33.0, 25.8, 21.4.

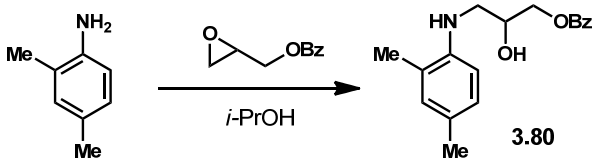
HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{13}H_{20}NO$, 206.1545; found, 206.1542.



1-chloro-3-((2,4-dimethylphenyl)amino)propan-2-ol (3.79)

A solution of 2,4-dimethylaniline (1.96 g, 16.2 mmol) in 2-propanol (25 mL) was stirred and heated to 90 ºC. Epichlorohydrin (1.80 g, 19.4 mmol) was added in three roughly equal portions, delivered 30 minutes apart. The reaction mixture was kept at 90 ºC for 1.5 h after the last addition and was then cooled and concentrated *in vacuo* to afford a red syrup. The crude product was purified by column chromatography (1 : 9, EtOAc : hexanes) to afford **3.79** as a pale yellow oil (2.13 g, 62%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.00 – 6.87 (m, 2H), 6.58 (d, *J* = 8.1 Hz, 1H), 4.16 – 4.08 (m, 1H), 3.74 – 3.63 (m, 2H), 3.40 (dd, *J* = 13.1, 4.4 Hz, 1H), 3.25 (dd, *J* = 13.1, 7.3 Hz, 1H), 2.51 (bs, 1H), 2.24 (s, 3H), 2.15 (s, 3H). Spectra were consistent with those reported previously.[37]



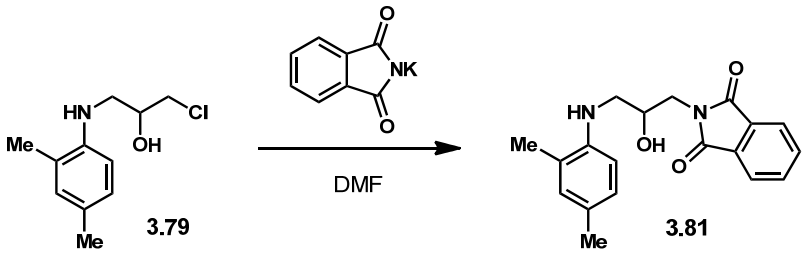
3-((2,4-dimethylphenyl)amino)-2-hydroxypropyl benzoate (3.80)

A solution of 2,4-dimethylaniline (0.140 g, 1.16 mmol) and benzoyl glycidol[38] (0.227 g, 1.27 mmol) in 2-propanol (2.5 mL) was stirred and heated to 90 ºC. After 4 h, the mixture was cooled and concentrated *in vacuo* to afford a brown oil. The crude product was purified by column chromatography (2 : 8, EtOAc : hexanes) to afford **3.80** as a pale yellow oil (0.310 g, 89%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8.3 Hz, 2H), 7.60 (t, *J* = 7.4 Hz, 1H), 7.47 (t, *J* = 7.7 Hz, 2H), 6.97 (d, *J* = 8.1 Hz, 1H), 6.94 (s, 1H), 6.62 (d, *J* = 8.1 Hz, 1H), 4.52 – 4.42 (m, 2H), 4.28 (ddd, *J* = 10.4, 8.1, 4.5 Hz, 1H), 3.43 (dd, *J* = 12.9, 4.2 Hz, 1H), 3.29 (dd, *J* = 12.9, 7.6 Hz, 1H), 2.28 (s, 3H), 2.18 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 166.7, 143.4, 133.2, 131.1, 129.6, 129.5, 128.4, 127.2, 126.8, 122.9, 110.4, 68.3, 67.0, 46.8, 20.3, 17.4.

HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{18}H_{22}NO_3$, 300.1594; found, 300.1594.



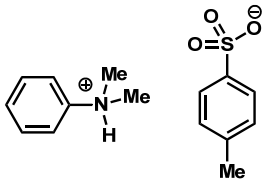
2-(3-((2,4-dimethylphenyl)amino)-2-hydroxypropyl)isoindoline-1,3-dione (3.81)

Alcohol **3.79** (0.587 g, 2.75 mmol) was dissolved in DMF (5 mL) and then potassium phthalimide (0.560 g, 3.00 mmol) was added in one portion. The resulting mixture was then heated to 100 ºC for 16 h. The reaction mixture was cooled, and water was added. The crude mixture was extracted with EtOAc (3 x 40 mL) and the combined organics were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo* to afford a yellow syrup. The crude product was purified by column chromatography (3 : 7, EtOAc : hexanes) to afford **3.81** as a bright yellow solid (0.520 g, 58%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (dd, *J* = 5.3, 3.1 Hz, 2H), 7.73 (dd, *J* = 5.5, 3.0 Hz, 2H), 6.91 (d, *J* = 8.0 Hz, 1H), 6.88 (s, 1H), 6.58 (d, *J* = 8.1 Hz, 1H), 4.20 (pent, *J* = 5.0 Hz, 1H), 3.99 (bs, 1H) 3.97 – 3.87 (m, 2H), 3.33 – 3.26 (m, 1H), 3.25 – 3.18 (m, 1H), 2.97 (bs, 1H), 2.22 (s, 3H), 2.17 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 169.0, 143.5, 134.2, 131.8, 131.1, 127.3, 126.7, 123.5, 122.8, 110.3, 68.7, 47.3, 42.0, 20.3, 17.4.

HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{19}H_{21}N_2O_3$, 325.1547; found, 325.1546.

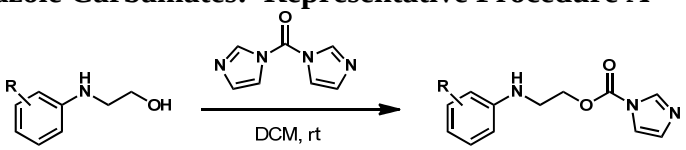


***N,N*-Dimethylanilinium tosylate (3.31)**

N,*N*-dimethylaniline (0.989 g, 8.16 mmol) was dissolved in THF (20 mL) and the resulting solution was cooled to 0 °C and stirred. *p*-Toluenesulfonic acid monohydrate (1.55 g, 8.16 mmol) was then added in one portion. The resulting homogeneous mixture was stirred and warmed to room temperature over 1 h, and then concentrated *in vacuo*. The purple solid so obtained was recrystallized from acetone/hexanes to afford the title compound (1.94 g, 81%) as a pale purple solid.

^{1}H NMR (500 MHz, CD_3CN) δ ^{1}H NMR (500 MHz, CD_3CN) δ 7.73 – 7.64 (m, 4H), 7.58 – 7.48 (m, 3H), 7.23 (d, *J* = 7.7 Hz, 2H), 3.18 (s, 6H), 2.36 (s, 3H).

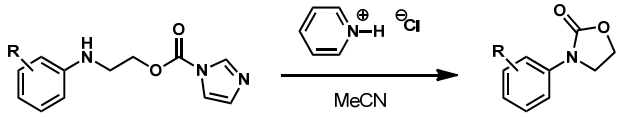
Preparation of Imidazole Carbamates: Representative Procedure A



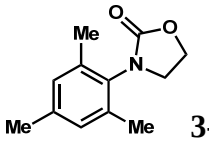
Amino alcohol (1 mmol) was dissolved in dichloromethane (5 mL) and the resulting homogeneous mixture was stirred at room temperature. 1,1'-Carbonyldiimidazole (CDI) (1.2 mmol) was added in one portion and the reaction mixture was stirred at room temperature until TLC analysis indicated that the starting alcohol had been completely consumed (typically 2

hours after addition of CDI). The crude reaction mixture was diluted with dichloromethane (20 mL) and washed with water. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo* to afford crude imidazole carbamate that was used without further purification.

Preparation of Oxazolidinones: Representative Procedure B



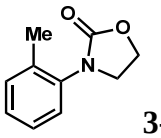
Imidazole carbamate (0.3 mmol) was dissolved in dry MeCN (1.5 mL) and pyridinium chloride (0.6 mmol) was added in one portion at room temperature. The homogeneous mixture was then stirred at room temperature. Imidazole hydrochloride precipitated as the reaction proceeded. After 24 hours, the reaction was quenched with 1 M HCl and then extracted with dichloromethane. The combined organics were dried over Na_2SO_4 and then concentrated *in vacuo*. If necessary, the crude product could be purified by column chromatography.



3-Mesityloxazolidin-2-one (3.35)

Prepared from 2-(mesitylamino)ethanol (**3.28**) by conversion to the imidazole carbamate using representative procedure A, which was then cyclized using representative procedure B to obtain a brown solid (0.090 g, 90%). The reaction mixture was heated to 40 ºC for 9 h.

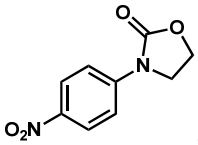
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.93 (s, 2H), 4.54 (t, *J* = 8.1 Hz, 2H), 3.82 (t, *J* = 8.1 Hz, 2H), 2.28 (s, 3H), 2.25 (s, 6H). Spectra were consistent with those reported previously.[39]



3-(*o*-Tolyl)oxazolidin-2-one (3.36)

Prepared from 2-(o-tolylamino)ethanol[40] by conversion to the imidazole carbamate using representative procedure A, which was then cyclized using representative procedure B to obtain a light yellow oil (0.054 g, 90%). The reaction mixture was heated to 40 ºC for 9 h. The crude product was purified by column chromatography (1 : 1, EtOAc : hexanes).

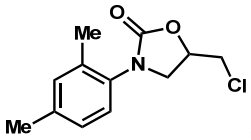
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.21 (m, 4H), 4.51 (t, *J* = 8.0 Hz, 2H), 3.98 – 3.89 (m, 2H), 2.32 (s, 3H). Spectra were consistent with those reported previously.[41]



3-(4-Nitrophenyl)oxazolidin-2-one (3.37)

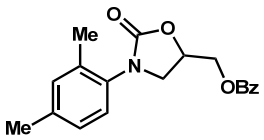
Prepared from 2-((4-nitrophenyl)amino)ethanol[42] using representative procedure A to form the imidazole carbamate (0.138 g, 0.5 mmol). The imidazole carbamate was combined with a 0.4 M solution of pyridinium chloride in dry DMF (2.5 mL, 1.0 mmol) at room temperature. The

homogeneous mixture was stirred at room temperature for 10 minutes and then heated to 40 °C. After 36 h, the reaction was cooled to room temperature and then a saturated aqueous $CuSO_4$ solution (15 mL) was added. The aqueous layer was extracted with Et_2O (3×15 mL). The combined organic fractions were washed with water (3 x 10 mL) and then dried over $MgSO_4$ and concentrated *in vacuo* to afford a yellow oil. The product obtained was purified by column chromatography (2 : 1, heptane : acetone) to obtain a pale yellow solid (0.043 g, 41%).
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.27 (d, *J* = 9.3 Hz, 2H), 7.74 (d, *J* = 9.3 Hz, 2H), 4.65 – 4.49 (m, 2H), 4.22 – 4.08 (m, 2H). Spectra were consistent with those reported previously.[43]

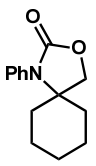


5-(Chloromethyl)-3-(2,4-dimethylphenyl)oxazolidin-2-one (3.38)

Prepared from **3.79** by conversion to the imidazole carbamate using representative procedure A, which was then cyclized using representative procedure B to obtain a colorless oil (0.058 g, 89%).
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.14 – 7.07 (m, 2H), 7.06 – 7.02 (m, 1H), 4.95-4.86 (m, 1H), 4.03 (t, *J* = 9.0 Hz, 1H), 3.85 – 3.72 (m, 3H), 2.32 (s, 3H), 2.27 (s, 3H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 155.5, 138.4, 135.6, 132.8, 132.0, 127.7, 126.4, 71.5, 50.5, 44.9, 21.0, 17.7.
HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{12}H_{14}ClNNaO_2$, 262.0605; found, 262.0606.

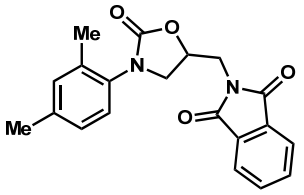


(3-(2,4-Dimethylphenyl)-2-oxooxazolidin-5-yl)methyl benzoate (3.39)
Prepared from **3.80** by conversion to the imidazole carbamate using representative procedure A, which was then cyclized using representative procedure B to obtain a colorless syrup (0.063 g, 94%).
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (d, *J* = 6.7 Hz, 2H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.45 (t, *J* = 7.7 Hz, 2H), 7.10 – 7.05 (m, 2H), 7.00 (d, *J* = 8.0 Hz, 1H), 5.02 (ddt, *J* = 9.0, 6.1, 4.3 Hz, 1H), 4.59 (d, *J* = 4.3 Hz, 2H), 4.05 (t, *J* = 9.1 Hz, 1H), 3.77 (dd, *J* = 9.0, 6.1 Hz, 1H), 2.30 (s, 3H), 2.23 (s, 3H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 166.1, 155.8, 138.2, 135.4, 133.4, 132.8, 131.9, 129.7, 129.1, 128.4, 127.6, 126.3, 70.8, 64.6, 49.5, 20.9, 17.6.
HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{19}H_{19}NNaO_4$, 348.1207; found, 348.1210.

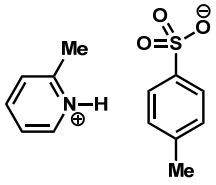


1-Phenyl-3-oxa-1-azaspiro[4.5]decan-2-one (3.40)
Prepared from **3.78** by conversion to the imidazole carbamate using representative procedure A, which was then cyclized using representative procedure B to obtain a white solid (0.086 g, 93%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 – 7.34 (m, 3H), 7.20 (dd, *J* = 7.5, 1.8 Hz, 2H), 4.29 (s, 2H), 1.87 (d, *J* = 13.3 Hz, 2H), 1.77 (d, *J* = 14.6 Hz, 2H), 1.59 (d, *J* = 13.6 Hz, 1H), 1.52 – 1.42 (m, 2H), 1.27 (m, 2H), 0.95 (m, 1H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 157.3, 134.6, 130.0, 129.2, 128.4, 72.2, 63.0, 34.9, 24.2, 22.8.
HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{14}H_{17}NNaO_2$, 254.1151; found, 254.1152.

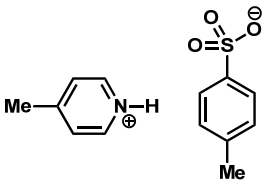


2-((3-(2,4-Dimethylphenyl)-2-oxooxazolidin-5-yl)methyl)isoindoline-1,3-dione (3.41)
Prepared from **3.81** by conversion to the imidazole carbamate using representative procedure A, which was then cyclized using representative procedure B to obtain a white solid (0.154 g, 90%).
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 (dd, *J* = 5.4, 3.0 Hz, 2H), 7.75 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.11 (d, *J* = 7.9 Hz, 1H), 7.07 (s, 1H), 7.03 (d, *J* = 8.0 Hz, 1H), 5.01 (dtd, *J* = 8.3, 6.5, 5.4 Hz, 1H), 4.16 (dd, *J* = 14.0, 6.8 Hz, 1H), 4.03 – 3.96 (m, 2H), 3.73 (dd, *J* = 9.2, 5.4 Hz, 1H), 2.31 (s, 3H), 2.27 (s, 3H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 168.0, 155.5, 138.3, 135.6, 134.4, 132.8, 132.0, 131.7, 127.7, 126.3, 123.6, 70.2, 50.8, 40.6, 21.0, 17.7.
HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{20}H_{18}N_2NaO_4$, 373.1164; found, 373.1161.



2-Methylpyridinium tosylate (3.47)

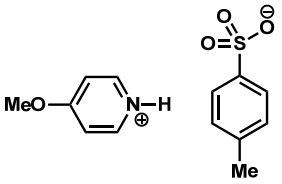
A solution of 2-picoline (0.896 g, 9.63 mmol) in THF (15 mL) was stirred and cooled to 0 °C. *p*-toluenesulfonic acid monohydrate (1.83 g, 9.63 mmol) was added in one portion and the resulting cloudy mixture was stirred and allowed to warm to room temperature over 1 h, at which time it was concentrated *in vacuo* to yield a solid. Recrystallization from hot acetone afforded the title compound (2.23 g, 87%) as white needles.
^{1}H NMR (400 MHz, CD_3CN) δ 8.63 (d, *J* = 6 Hz, 1H), 8.34 (t, *J* = 8 Hz, 1H), 7.76-7.70 (m, 2H), 7.68 (d, *J* = 8 Hz, 2H), 7.20 (d, *J* = 8 Hz, 2H), 2.74 (s, 3H), 2.34 (s, 3H).



4-Methylpyridinium tosylate (3.48)

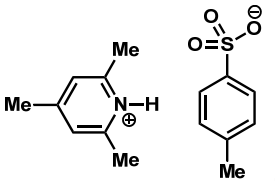
A solution of 4-picoline (0.986 g, 10.6 mmol) in THF (20 mL) was stirred and cooled to 0 °C. *p*-toluenesulfonic acid monohydrate (2.01 g, 10.6 mmol) was added in one portion. A white precipitate formed and was collected by filtration and dried *in vacuo* to afford the title compound (2.38 g, 85%) as a flocculent white solid.

^{1}H NMR (500 MHz, CD_3CN) δ 8.62 (d, *J* = 6.6 Hz, 2H), 7.78 (d, *J* = 5.9 Hz, 2H), 7.68 (d, *J* = 8.1 Hz, 2H), 7.21 (d, *J* = 7.8 Hz, 2H), 2.60 (s, 3H), 2.34 (s, 3H).



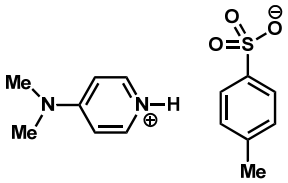
4-Methoxypyridinium tosylate (3.49)

A solution of 4-methoxypyridine (1.11 g, 10.2 mmol) in THF (20 mL) was stirred and cooled to 0 °C. *p*-toluenesulfonic acid monohydrate (1.94 g, 10.2 mmol) was added in one portion. A white precipitate formed and was collected by filtration. The crude product was then recrystallized from hot acetone to afford the title compound (2.44 g, 85%) as white needles.
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.77 (d, *J* = 7.3 Hz, 2H), 7.81 (d, *J* = 8.2 Hz, 2H), 7.33 (d, *J* = 7.3 Hz, 2H), 7.17 (d, *J* = 7.7 Hz, 2H), 4.05 (s, 3H), 2.34 (s, 3H).



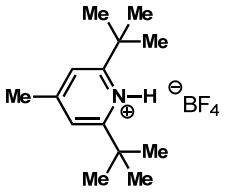
2,4,6-Trimethylpyridinium tosylate (3.50)

A solution of 2,4,6-trimethylpyridine (0.459 g, 3.78 mmol) in Et_2O (10 mL) and MeOH (1 mL) was stirred and cooled to 0 °C. *p*-toluenesulfonic acid monohydrate (0.720 g, 3.78 mmol) was added in one portion and the resulting cloudy mixture was stirred and allowed to warm to room temperature over 1 h, at which time it was concentrated *in vacuo* to yield a solid. Recrystallization from hot acetone afforded the title compound (0.80 g, 72%) as colorless cubes.
^{1}H NMR (500 MHz, CD_3CN) δ 7.68 (d, *J* = 8.1 Hz, 2H), 7.38 (s, 2H), 7.22 (d, *J* = 7.8 Hz, 2H), 2.66 (s, 6H), 2.49 (s, 3H), 2.37 (s, 3H).



4-(*N*,*N*-Dimethylamino)pyridinium tosylate (3.51)

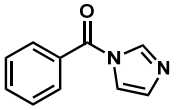
A solution of 4-(*N*,*N*-dimethylamino)pyridine (0.642 g, 5.26 mmol) in THF (10 mL) was stirred and cooled to 0 °C. *p*-toluenesulfonic acid monohydrate (1.00 g, 5.26 mmol) was added in one portion. A white precipitate formed and was collected by filtration. (1.43 g, 92%) as a white powder.
^{1}H NMR (500 MHz, CD_3CN) δ 8.05 (d, *J* = 6.8 Hz, 2H), 7.64 (d, *J* = 7.6 Hz, 2H), 7.17 (d, *J* = 7.6 Hz, 2H), 6.81 (d, *J* = 6.8 Hz, 2H), 3.13 (s, 6H), 2.33 (s, 3H).



2,6-Di-*tert*-butyl-4-methylpyridinium tetrafluoroborate (3.52)

A solution of 2,6-di-*tert*-butyl-4-methylpyridinium (0.118 g, 0.575 mmol) in Et_2O (1.5 mL) was cooled to 0 °C and HBF_4 etherate (0.104 g, 0.632 mmol) was added dropwise. A white precipitate formed and was collected by filtration to yield the title compound (0.156 g, 92%) as an off-white solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 7.82 (s, 2H), 2.50 (s, 3H), 1.44 (s, 18H). Spectra were consistent with those reported previously.[44]



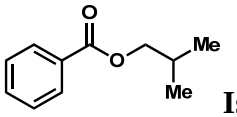
1-Benzoylimidazole (1.94)

A solution of imidazole (0.797 g, 11.7 mmol) in THF (20 mL) was cooled to 0 °C and benzoyl chloride (0.823 g, 5.85 mmol) was added dropwise. The resulting heterogeneous mixture was stirred at room temperature for 16 h, and then hexanes (10 mL) was added. The white precipitate was removed by filtration and the filtrate was concentrated *in vacuo* to afford the title compound (0.951 g, 94%) as a viscous colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (s, 1H), 7.83 – 7.77 (m, 2H), 7.72 – 7.65 (m, 1H), 7.60 – 7.53 (m, 3H), 7.17 (s, 1H). Spectra were consistent with those reported previously.[45]

Preparation of Esters from Acylimidazoles: Representative Procedure C

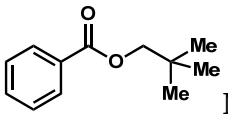
Alcohol (1.0 mmol) and benzoyl imidazole (1.1 mmol)[46] were placed in a dry 20 mL screw cap vial with a magnetic stir bar. A 1.0 M solution of pyridinium salt in dry MeCN (2.20 mL, 2.2 mmol) was added in one portion at room temperature. The vial was quickly sealed with a plastic cap. The reaction mixture was then stirred at 20 °C for 24 h. The reaction was quenched with 1 M NaOH (10 mL) and then extracted with hexane (4 × 15 mL). The organic fractions were combined and washed with 1 M HCl (15 mL) and brine. The organic fraction was dried over $MgSO_4$ and concentrated *in vacuo* to afford the desired ester. Though typically unnecessary, further purification could be achieved by column chromatography.



Isobutyl benzoate (3.53)

Prepared using representative procedure C with isobutanol (0.080 g, 1.08 mmol) and pyridinium triflate to afford a light yellow oil (0.179 g, 93%). The reaction was stirred at room temperature for 12 h.

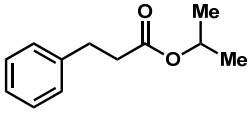
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (d, J = 7.0 Hz, 2H), 7.56 (t, J = 7.5 Hz, 1H), 7.44 (dd, J = 7.5, 8.0 Hz, 2H), 4.11 (d, J = 6.6 Hz, 2H), 2.18 – 2.00 (m, 1H), 1.03 (d, J = 6.8 Hz, 6H). Spectra were consistent with those reported previously.[47]



Neopentyl benzoate (3.54)

Prepared using representative procedure C with neopentyl alcohol (0.100 g, 1.13 mmol) and pyridinium triflate to afford a light yellow oil (0.1726 g, 79%). The reaction mixture was stirred at room temperature for 36 h.

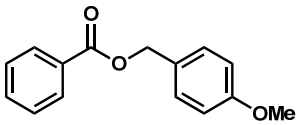
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (d, *J* = 7.0 Hz, 2H), 7.60 – 7.53 (m, 1H), 7.50 – 7.41 (m, 2H), 4.02 (s, 2H), 1.05 (s, 9H). Spectra were consistent with those reported previously.[48]



Isopropyl 3-phenylpropanoate (3.55)

Prepared using representative procedure C with 3-phenylpropanoyl imidazole[49] (prepared by analogy to **3.82,** 0.288 g, 1.44 mmol), dry isopropanol (0.079 g, 1.31 mmol) and pyridinium triflate to afford a colorless oil (0.207 g, 82%). The reaction was heated to 40 °C for 26 h using a heating block.

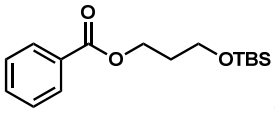
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.26 (m, 2H), 7.23 – 7.17 (m, 3H), 5.00 (hept, *J* = 6.3 Hz, 1H), 2.94 (t, *J* = 7.8 Hz, 2H), 2.59 (t, *J* = 7.8 Hz, 2H), 1.20 (d, *J* = 6.2 Hz, 6H). Spectra were consistent with those reported previously.[50]



4-Methoxybenzyl benzoate (3.56)

Prepared using representative procedure C with 4-methoxybenzyl alcohol (0.178 g, 1.29 mmol) and pyridinium triflate to obtain a colorless oil (0.288 g, 92%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (d, *J* = 6.9 Hz, 2H), 7.55 (t, *J* = 7.5 Hz, 1H), 7.46 – 7.37 (m, 4H), 6.92 (d, *J* = 8.6 Hz, 2H), 5.30 (s, 2H), 3.82 (s, 3H). Spectra were consistent with those reported previously.[51]



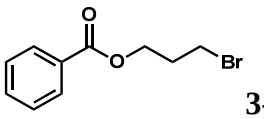
3-((tert-Butyldimethylsilyl)oxy)propyl benzoate (3.57)

Prepared following representative procedure C with 3-((*tert*-butyldimethylsilyl)oxy)propan-1-ol[52] (0.129 g, 0.679 mmol) and pyridinium chloride to afford a light yellow oil (0.147 g, 73%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 7.0 Hz, 2H), 7.59 – 7.52 (m, 1H), 7.47 – 7.40 (m, 2H), 4.42 (t, *J* = 6.3 Hz, 2H), 3.79 (t, *J* = 6.1 Hz, 2H), 1.98 (pent, *J* = 6.2 Hz, 2H), 0.90 (s, 9H), 0.06 (s, 6H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 166.6, 132.8, 130.5, 129.5, 128.3, 61.9, 59.5, 31.9, 25.9, 18.3, -5.4.

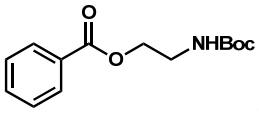
HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{16}H_{27}O_3Si$, 295.1724; found, 295.1727.



3-Bromopropyl benzoate (3.58)

Prepared using representative procedure C with 3-bromopropan-1-ol (0.159 g, 1.14 mmol) and pyridinium tosylate to obtain a light yellow oil (0.221 g, 80%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 7.8 Hz, 2H), 7.62 – 7.53 (m, 1H), 7.45 (t, *J* = 7.8 Hz, 2H), 4.47 (t, *J* = 5.9 Hz, 2H), 3.56 (t, *J* = 6.5 Hz, 2H), 2.33 (pent, *J* = 6.2 Hz, 2H). Spectra were consistent with those reported previously.[53]



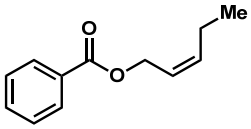
2-((tert-Butoxycarbonyl)amino)ethyl benzoate (3.59)

Prepared using representative procedure C with *tert*-butyl (2-hydroxyethyl)carbamate (0.162 g, 1.00 mmol) and pyridinium chloride. Diethyl ether was used as the extraction solvent instead of hexane. The crude product was purified by column chromatography (30 : 70, ethyl acetate : hexane) to obtain a white solid (0.202 g, 76%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, *J* = 7.1 Hz, 2H), 7.58 (t, *J* = 7.7 Hz, 1H), 7.45 (t, *J* = 7.6 Hz, 2H), 4.84 (bs, 1H), 4.38 (t, *J* = 5.3 Hz, 2H), 3.54 (q, *J* = 5.5 Hz, 2H), 1.44 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.5, 155.8, 133.1, 129.8, 129.6, 128.3, 79.5, 64.2, 39.7, 28.3.

HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{14}H_{19}NNaO_4$, 288.1206; found, 288.1209.



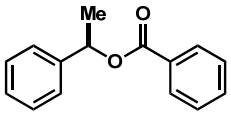
(Z)-Pent-2-en-1-yl benzoate (3.60)

Prepared using representative procedure C with (Z)-pent-2-en-1-ol (0.088 g, 1.02 mmol) and pyridinium chloride to afford a yellow oil (0.160 g, 82% yield)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (d, *J* = 6.9 Hz, 2H), 7.55 (t, *J* = 7.4 Hz, 1H), 7.44 (t, *J* = 7.8 Hz, 2H), 5.76 – 5.59 (m, 2H), 4.88 (d, *J* = 6.7 Hz, 2H), 2.26 – 2.13 (m, 2H), 1.03 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 166.3, 137.1, 132.8, 130.3, 129.5, 128.2, 122.7, 60.8, 20.9, 13.8.

HRMS-EI *m/z*: M^+ calcd for $C_{12}H_{14}O_2$, 190.0994; found, 190.0994.

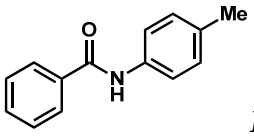


(*R*)-1-Phenylethyl benzoate (2.95)

Prepared using representative procedure C with (*R*)-1-phenylethanol (0.061 g, 0.50 mmol) and pyridinium triflate. The homogenous solution was heated to 50 °C for 43 h using a heating block. A colorless oil was obtained (0.095 g, 84%) after column chromatography (5 : 95, ethyl acetate : hexane).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 7.0 Hz, 2H), 7.56 (t, *J* = 7.4 Hz, 1H), 7.49 – 7.41 (m, 4H), 7.37 (t, *J* = 7.4 Hz, 2H), 7.31 (t, *J* = 7.4 Hz, 1H), 6.14 (q, *J* = 6.6 Hz, 1H), 1.68 (d, *J* = 6.6 Hz, 3H). Spectra were consistent with those reported in Chapter 2.

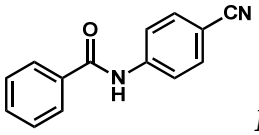
HPLC Chiracel OD column (99.5 : 0.5 hexanes : isopropanol, 1.0 mL/min) t_R; 15.95 min (major); 17.57 min (minor): 96% ee.



***N*-(*p*-Tolyl)benzamide (3.62)**

Prepared using representative procedure C with *p*-toluidine (0.113 g, 1.05 mmol) and pyridinium chloride to afford a white solid (0.213 g, 96%). The reaction mixture was stirred at room temperature for 10 minutes.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 6.9 Hz, 2H), 7.76 (bs, 1H), 7.60 – 7.43 (m, 5H), 7.18 (d, *J* = 7.7 Hz, 2H), 2.35 (s, 3H). Spectra were consistent with those reported previously.[54]



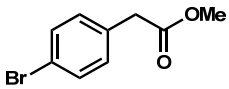
***N*-(4-Cyanophenyl)benzamide (3.63)**

Prepared using representative procedure C with 4-aminobenzonitrile (0.094 g, 0.794 mmol) and pyridinium chloride to afford a white solid (0.170 g, 96%). The mixture was heated to 40 °C for 8 h.

^{1}H NMR (500 MHz, $CDCl_3$ with 1 drop of CD_3OD) δ 7.86 (d, *J* = 7.1 Hz, 2H), 7.83 – 7.79 (m, 2H), 7.60 (d, *J* = 8.8 Hz, 2H), 7.56 – 7.49 (m, 1H), 7.46 (d, *J* = 8.1 Hz, 2H) Spectra were consistent with those reported previously.[55]

Preparation of Esters from Carboxylic Acids: Representative Procedure D

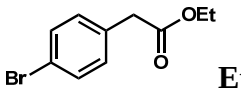
Carboxylic acid (0.5 mmol) and imidazole carbamate (1.0 mmol) were placed in a dry 20 mL vial with a Teflon tape-coated thread and a magnetic stir bar, followed by addition of 1.0 mL of 1.0 M solution of pyridinium triflate in dry MeCN in one portion at room temperature. The vial was quickly sealed with a plastic cap (***CAUTION: gas is evolved during the course of the reaction! All experiments should be performed behind a blast shield if a sealed container is used!*).** The reaction mixture was then stirred at room temperature for 10 minutes and then heated to 40 °C using a heating block for 24 h. The mixture was cooled to room temperature and then the vial was carefully opened. (***CAUTION: vial under pressure!***). The reaction was diluted with diethyl ether (15 mL) and washed with 1 M HCl (15 mL). The aqueous layer was back-extracted with diethyl ether (3 × 15 mL) and the organic fractions were combined, washed with saturated $NaHCO_3$ (aq) and brine. The organic fraction was dried over anhydrous $MgSO_4$, and concentrated *in vacuo* to afford the desired ester.



Methyl 2-(4-bromophenyl)acetate (2.28)

Prepared using representative procedure D with methyl 1-imidazolecarboxylate (0.097 g, 0.778 mmol) and 2-(4-bromophenyl)acetic acid (0.084 g, 0.389 mmol) to obtain a yellow oil (0.082 g, 93%).

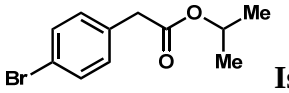
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.3 Hz, 2H), 7.16 (d, *J* = 8.3 Hz, 2H), 3.69 (s, 3H), 3.58 (s, 2H). Spectra were consistent with those reported in Chapter 2.



Ethyl 2-(4-bromophenyl)acetate (2.41)

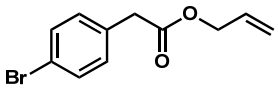
Prepared using representative procedure D with ethyl 1-imidazolecarboxylate (0.109 g, 0.778 mmol) and 2-(4-bromophenyl)acetic acid (0.084 g, 0.389 mmol) to obtain a yellow oil (0.083 g, 88%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.3 Hz, 2H), 7.16 (d, *J* = 8.4 Hz, 2H), 4.15 (q, *J* = 7.2 Hz, 2H), 3.56 (s, 2H), 1.25 (t, *J* = 7.1 Hz, 3H). Spectra were consistent with those reported in Chapter 2.



Isopropyl 2-(4-bromophenyl)acetate (2.46)

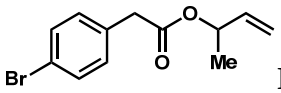
Prepared using representative procedure D with isopropyl 1-imidazolecarboxylate (0.120 g, 0.778 mmol) and 2-(4-bromophenyl)acetic acid (0.084 g, 0.389 mmol) to obtain a yellow oil (0.081 g, 81%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.4 Hz, 2H), 7.16 (d, *J* = 8.3 Hz, 2H), 5.00 (hept, *J* = 6.3 Hz, 1H), 3.53 (s, 2H), 1.22 (d, *J* = 6.3 Hz, 6H). Spectra were consistent with those reported in Chapter 2.



Allyl 2-(4-bromophenyl)acetate (2.42)

Prepared using representative procedure D with allyl 1-imidazolecarboxylate (0.118 g, 0.778 mmol) and 2-(4-bromophenyl)acetic acid (0.084 g, 0.389 mmol) to obtain a yellow oil (0.081 g, 82%).

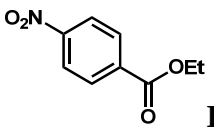
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.3 Hz, 2H), 7.17 (d, *J* = 8.3 Hz, 2H), 5.89 (ddt, *J* = 17.1, 10.4, 5.8 Hz, 1H), 5.32 – 5.19 (m, 2H), 4.59 (d, *J* = 5.8 Hz, 2H), 3.60 (s, 2H). Spectra were consistent with those reported in Chapter 2.



But-3-en-2-yl 2-(4-bromophenyl)acetate (2.48)

Prepared using representative procedure D with but-3-en-2-yl 1-imidazolecarboxylate (0.129 g, 0.778 mmol) and 2-(4-bromophenyl)acetic acid (0.084 g, 0.389 mmol) to obtain a yellow oil (0.091 g, 87%).

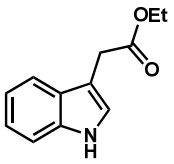
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.1 Hz, 2H), 7.16 (d, *J* = 8.0 Hz, 2H), 5.81 (ddd, *J* = 16.8, 10.6, 5.9 Hz, 1H), 5.35 (pent, *J* = 6.4 Hz, 1H), 5.23 – 5.07 (m, 2H), 3.57 (s, 2H), 1.30 (d, *J* = 6.5 Hz, 3H). Spectra were consistent with those reported in Chapter 2.



Ethyl 4-nitrobenzoate (3.64)

Prepared using representative procedure D with ethyl 1-imidazolecarboxylate (0.140 g, 1.00 mmol) and 4-nitrobenzoic acid (0.084 g, 0.500 mmol) to obtain a yellow solid (0.0726 g, 74%). DMF was used as the solvent for this reaction instead of MeCN.

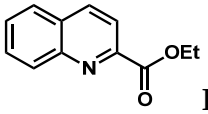
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, *J* = 8.8 Hz, 2H), 8.22 (d, *J* = 8.8 Hz, 2H), 4.43 (q, *J* = 7.1 Hz, 2H), 1.46 (t, *J* = 7.5 Hz, 3H). Spectra were consistent with those reported previously.[56]



Ethyl 2-(1*H*-indol-3-yl)acetate (3.65)

Prepared using representative procedure D with ethyl 1-imidazolecarboxylate (0.200 g, 1.43 mmol) and 2-(1*H*-indol-3-yl)acetic acid (0.125 g, 0.713 mmol) to obtain a yellow oil (0.131 g, 90%) after column chromatography (20 : 80, ethyl acetate : hexane).

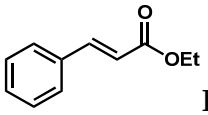
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (bs, 1H), 7.63 (dd, *J* = 7.9, 1.0 Hz, 1H), 7.37 (d, *J* = 8.0 Hz, 1H), 7.23 – 7.17 (m, 2H), 7.16 – 7.11 (m, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 3.78 (s, 2H), 1.27 (t, *J* = 7.1 Hz, 3H). Spectra were consistent with those reported previously.[57]



Ethyl quinoline-2-carboxylate (3.66)

Prepared using representative procedure D with ethyl 1-imidazolecarboxylate (0.140 g, 1.00 mmol) and quinoline-2-carboxylic acid (0.087 g, 0.500 mmol) to obtain colorless oil (0.081 g, 80%).

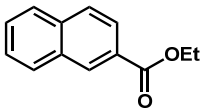
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 – 8.27 (m, 2H), 8.19 (d, *J* = 8.4 Hz, 1H), 7.88 (d, *J* = 8.0 Hz, 1H), 7.79 (dd, *J* = 8.4Hz, 1H), 7.65 (dd, *J* = 7.2 Hz, 1H), 4.56 (q, *J* = 7.1 Hz, 2H), 1.49 (t, *J* = 7.1 Hz, 3H). Spectra were consistent with those reported previously.[58]



Ethyl cinnamate (3.67)

Prepared using representative procedure D with ethyl 1-imidazolecarboxylate (0.258 g, 1.84 mmol) and cinnamic acid (0.136 g, 0.919 mmol) to obtain a yellow oil (0.128 g, 79%).

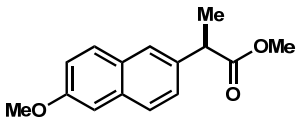
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (d, *J* = 16.1 Hz, 1H), 7.56 – 7.50 (m, 2H), 7.42 – 7.35 (m, 3H), 6.44 (d, *J* = 16.0 Hz, 1H), 4.27 (q, *J* = 7.1 Hz, 2H), 1.34 (t, *J* = 7.1 Hz, 3H). Spectra were consistent with those reported previously.[59]



Ethyl 2-naphthoate (3.68)

Prepared using representative procedure D with ethyl 1-imidazolecarboxylate (0.112 g, 0.800 mmol) and 2-naphthoic acid (0.069 g, 0.40 mmol) to obtain a light yellow oil (0.058 g, 72%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.62 (s, 1H), 8.07 (dd, *J* = 8.6, 1.7 Hz, 1H), 7.96 (d, *J* = 8.2 Hz, 1H), 7.88 (d, *J* = 8.5 Hz, 2H), 7.62 – 7.52 (m, 2H), 4.45 (q, *J* = 7.1 Hz, 2H), 1.45 (t, *J* = 7.1 Hz, 3H). Spectra were consistent with those reported previously.[60]



(*R*)-Methyl 2-(6-methoxynaphthalen-2-yl)propanoate (2.103)

Prepared using representative procedure D with methyl 1-imidazolecarboxylate (0.126 g, 1.00 mmol) and (*R*)-2-(6-methoxynaphthalen-2-yl)propanoic acid (0.115 g, 0.500 mmol) to obtain a white solid (0.109 g, 89%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.6 Hz, 2H), 7.66 (d, *J* = 1.8 Hz, 1H), 7.40 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.16 – 7.10 (m, 2H), 3.91 (s, 3H), 3.86 (q, *J* = 7.2 Hz, 1H), 3.67 (s, 3H), 1.59 (s, 3H). Spectra were consistent with those reported in Chapter 2.

HPLC Chiracel IB column (99 : 1 hexanes : 2-propanol, 1.0 mL/min, t_R 8.31 min (major), 9.08 min (minor), 99% *ee*.

3.6 Notes and References

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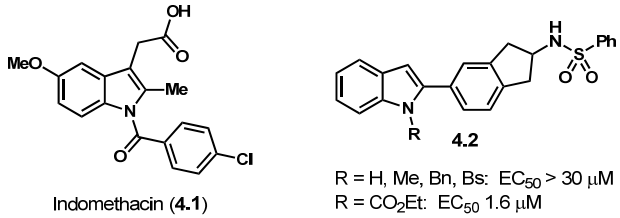
Chapter 4. Chemoselective *N*-Acylation of Indoles with Carbonylazoles

4.1 Introduction

Despite our discovery of an operationally simple and efficient strategy for acylation and carbonylation using carbonylimidazole derivatives in the presence of a pyridinium salt activator (Chapter 3), we felt that we had yet to tap the true value of these acyl electrophiles. Because of their stability relative to other common acylating agents, we reasoned that unprecedented chemoselectivity might be obtainable if carbonylimidazoles were used in conjunction with novel methods for activation. Of particular interest was the ability to chemoselectively acylate heteropolyfunctional molecules at their *inherently least nucleophilic site*, a difficult and therefore underdeveloped reaction. Specifically, we wondered whether common non-nucleophilic azacycles such as indoles, pyrroles, and oxazolidinones could be *N*-acylated in the presence of stronger nucleophiles such as amine or hydroxyl groups. The ability to *N*-functionalize a heterocycle bearing multiple nucleophilic sites, which is often the case at a late stage of a synthesis campaign, would significantly simplify the preparation of pharmaceuticals, functional materials, and complex natural products by obviating the need for protecting groups (*vide infra*).[1]

Aside from their well-known use as protecting groups, *N*-carbonylindoles have been adopted as key structural elements in pharmaceuticals. For example, indomethacin (Figure 4.1, **4.1**), a non-selective COX inhibitor used as an anti-inflammatory agent,[2] contains an *N*-benzoyl moiety. Surprisingly, the *N*-benzoylindole is relatively stable under physiological conditions as evidenced by the major observed catabolic pathway of **4.1**, which is *O*-demethylation rather than amide hydrolysis.[3] More recently, workers at Tanabe found that liver X receptor (LXR) agonist activity, which could be a valuable treatment for type II diabetes, required an *N*-acylated indole moiety (**4.2**).[4] *N*-Acylpyrroles have emerged as a versatile class of activated amides in stereoselective synthesis and in the construction of C-C bonds (see Chapter 5). Similarly, *N*-acyloxazolidinones are a privileged class of chiral auxiliaries (see Chapter 3).

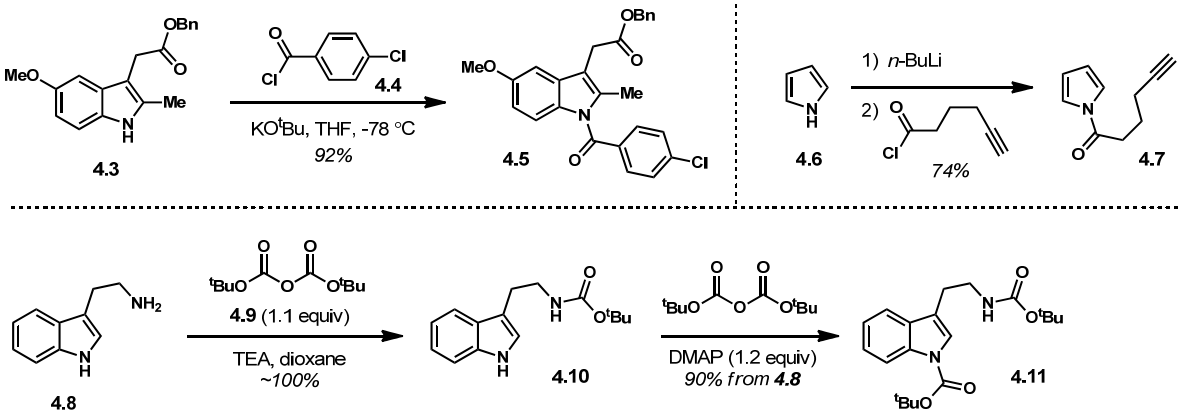
Figure 4.1. *N*-Carbonylindoles in Medicinal Chemistry



Indomethacin (**4.1**)

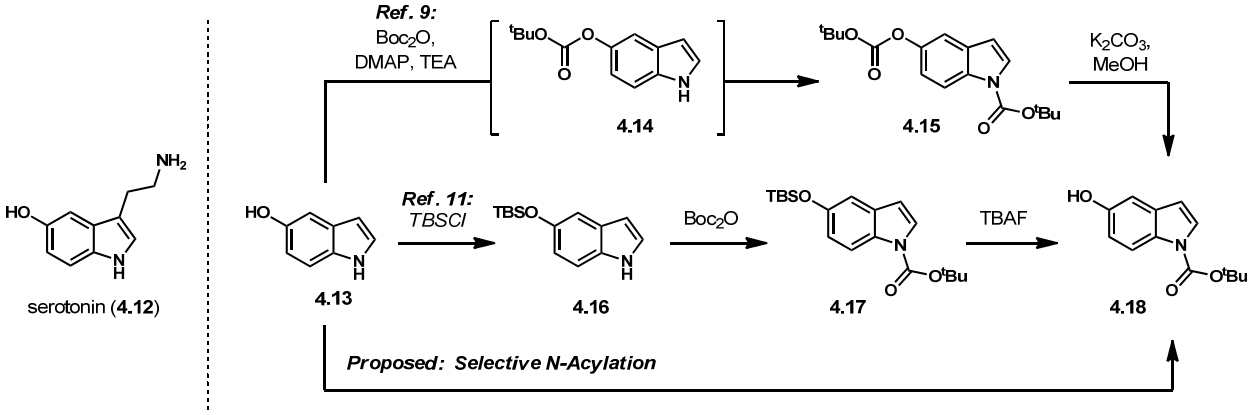
Non-nucleophilic heterocyclic amines (e.g., **4.3** and **4.6**, Scheme 4.1) are typically acylated through quantitative deprotonation followed by treatment with activated esters or carbonyl halides (i.e., **4.4**).[5] However, the use of strong bases limits the functional group tolerance of this general method. Sufficiently reactive electrophiles such as acid chlorides are occasionally used in tandem with weak base and a nucleophilic catalyst (i.e., triethylamine and DMAP) to acylate indoles, or under phase transfer conditions.[6] Alternatively, a wide variety of heterocyclic amines react with pyrocarbonates (e.g., **4.9**) in the presence of DMAP to afford carbamates (**4.10** or **4.11**).[7]

Scheme 4.1. Classical Methods of Non-Nucleophilic Amine Acylation



In all of these cases, the acylation reagent engages the most nucleophilic site first (see bottom of Scheme 4.1).[8] Similarly, under basic conditions it is often the case that the most acidic site is acylated first due to the resulting competition between anionic and neutral nucleophiles. For instance, the circuitous synthetic approach to *N*-Boc-5-hydroxyindole (the most common approach is shown in Scheme 4.2, **4.13**),[9] a widely employed intermediate to a variety of pharmaceutically relevant compounds because of its relationship to serotonin (**4.12**),[10] is plagued by the requirement that the more acidic phenol group be masked (see **4.16**) before the indole nitrogen is engaged. The bis-Boc derivative **4.15** could also be prepared and the *O*-Boc group removed to afford **4.18**, but this tactic wastes an equivalent of acylating agent and still adds synthetic steps.[11] Thus, the synthesis of **4.18** would be greatly simplified by selective *N*-acylation.

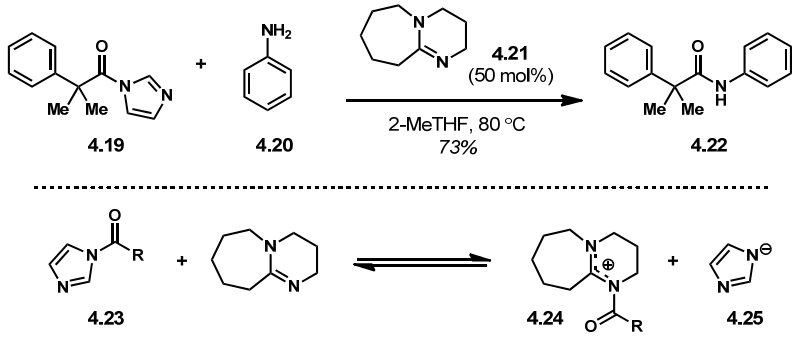
Scheme 4.2. Existing Strategies for the Synthesis of *N*-Boc-Indole



Our finding that carbonylimidazoles could be activated through nucleophilic catalysis after an initial protonation event (Chapter 3) led us to question whether novel reactivity or selectivity could be obtained from *direct* nucleophilic catalysis. It has been shown that carbonylimidazole species can be engaged by Lewis bases such as 1-hydroxybenzotriazole (HOBt).[12] However, we were especially intrigued by the finding that DBU (Scheme 4.3, **4.21**) performed similarly to HOBt as an amidation promoter in the reaction of anilines (**4.20**) with acylimidazoles (**4.19**), presumably through nucleophilic displacement of imidazole (Scheme 4.3,

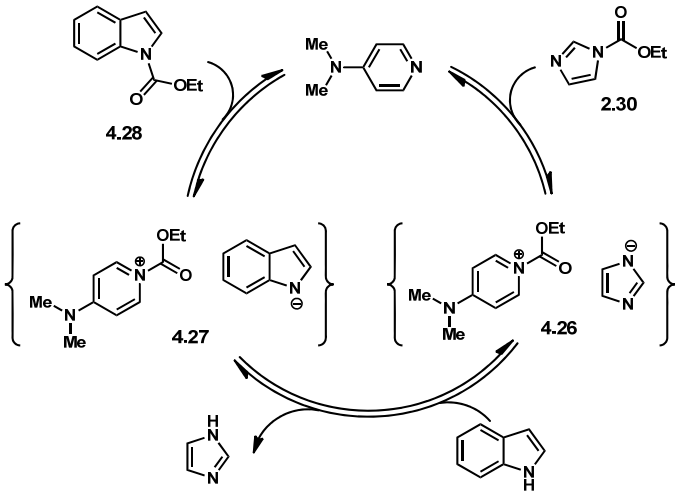
bottom).[13] Even though no evidence for the mechanism of catalysis of either HOBt or DBU had been reported, these proposals inspired us to consider that imidazolide (**4.25**, imidazole anion) generated by putative nucleophilic attack by DBU, or some other nucleophilic species, on a carbonylimidazole (**4.23**) might provide a path toward our aforementioned goal of unprecendented chemoselectivity.

Scheme 4.3. DBU-Catalyzed Amidation with Acylimidazoles



From a mechanistic perspective, the proposed mode of nucleophilic catalysis would rely on equilibration between a bench stable carbonylimidazole species (e.g., **2.30**, Scheme 4.4) and an activated intermediate (**4.26**). The counteranion of the electrophilic species would be imidazolide (**4.25**), disfavoring the forward reaction, but the basicity of imidazolide could also be exploited to accelerate the acylation of relatively acidic nucleophiles by initial deprotonation. Consequently, less nucleophilic functional groups such as indole, which are typically more acidic, could potentially be selectively acylated in the presence of more nucleophilic, but less acidic, groups. This exciting possibility would represent one of the first examples of a direct functionalization of the least inherently nucleophilic site of a polyfunctional substrate, though several methods have been developed that mask more reactive sites *in situ*.[14]

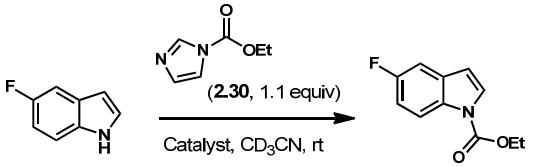
Scheme 4.4. Mechanistic Hypothesis for Carbonylimidazole Mediated Acylation of Indoles



4.2 Reaction Optimization and Initial Scope

We modeled the desired acylation process by investigating the reaction of ethyl imidazole carbamate (**2.30**) with 5-fluoroindole (Table 1, **4.29**), chosen as it allowed for easy monitoring of the reaction by ^{19}F-NMR, to produce indole carbamate **4.30**. No reaction was observed when a stoichiometric quantity of triethylamine was used as an activator at room temperature. This control experiment illustrated that non-nucleophilic weak bases do not lead to indole acylation, presumably due to the pK_a difference between indole (pK_a = 21 in DMSO)[15] and triethylamine (pK_a of $HNEt_3^+$ = 9.0 in DMSO).[16] Classical nucleophilic catalysts such as 4-methoxypyridine *N*-oxide (MPO) and tributylphosphine were unpromising (Table 4.1, entries 2 and 3), but consistent with our hypothesis, small amounts of **4.30** were observed when DMAP was employed as a catalyst (entry 4). DABCO catalysis led to 52% conversion in less than 3 hours (entry 5). Moreover, employment of DBU, which has recently been recognized as an excellent nucleophilic catalyst,[17] led to rapid acylation of **4.29** (entry 6).

Table 4.1. Optimization of Acylation Using Ethyl Imidazole Carbamate



4.29 **4.30**

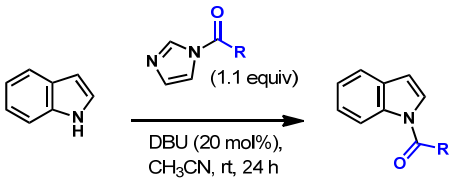
Entry	Catalyst	Mol %	Time (h)	% Conversion[a]
1	NEt_3	100	24	NR
2	PBu_3	20	24	trace
3	MPO	20	24	NR
4	DMAP	20	24	10
5	DABCO	20	2.5	52
6	DBU	20	1	>95

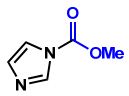
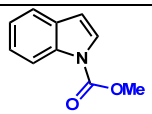
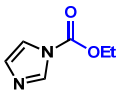
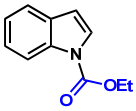
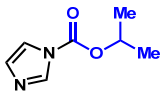
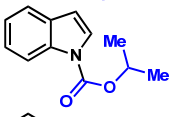
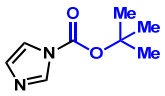
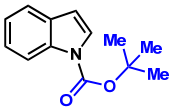
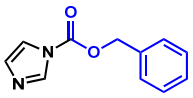
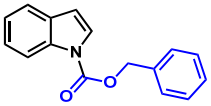
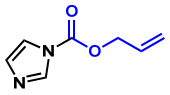
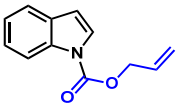
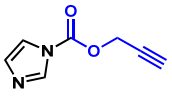
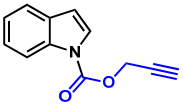
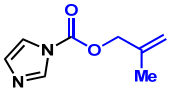
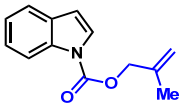
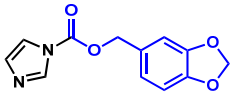
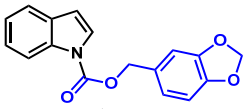
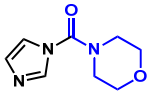
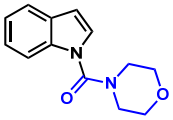
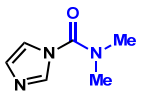
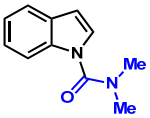
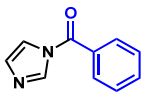
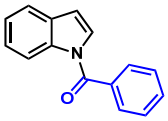
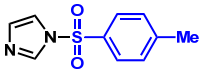
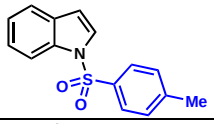
[a] Conversion determined by integration of ^{19}F-NMR resonances.

Several functionalized imidazole carbamates were then explored as acyl donors, and were found to cleanly afford the desired *N*-acylated indoles in excellent yield. Primary, secondary, and even tertiary alkyl groups were tolerated, though in the last case, the reaction was somewhat slower (entries 1-4, Table 4.2). Carbamylimidazoles and acylimidazoles are also competent reagents for the *N*-functionalization of indoles. However, optimal reaction conditions vary between classes of carbonylimidazole derivatives. For instance, while carbamylindoles such as **4.43** and **4.44** can be prepared from carbamylimidazoles (**2.154** and **4.33**), longer reaction times and higher catalyst loadings are required (entries 10 and 11). Similarly, **4.46** may be prepared from indole and *N*-tosylimidazole (**4.34**), but in this case, heating to 50 ºC was required (entry 13).

At the outset, we were concerned that the generation of imidazolide in the presence of imidazole carbamates could lead to imidazole alkylation, as observed when species such as **2.32** were heated in the presence of free imidazole (see Chapter 2). Exacerbating this worry, Shieh reported that DABCO, and to a lesser extent DBU, mediate azole alkylation by dimethyl carbonate through initial alkyl transfer to the nucleophilic catalyst.[18] However, imidazole carbamates that were well-suited to effect *N*-alkylation afforded only the *N*-acyl product (i.e.,

Table 4.2. Carbonylimidazole Scope as Indole Acylation Reagents



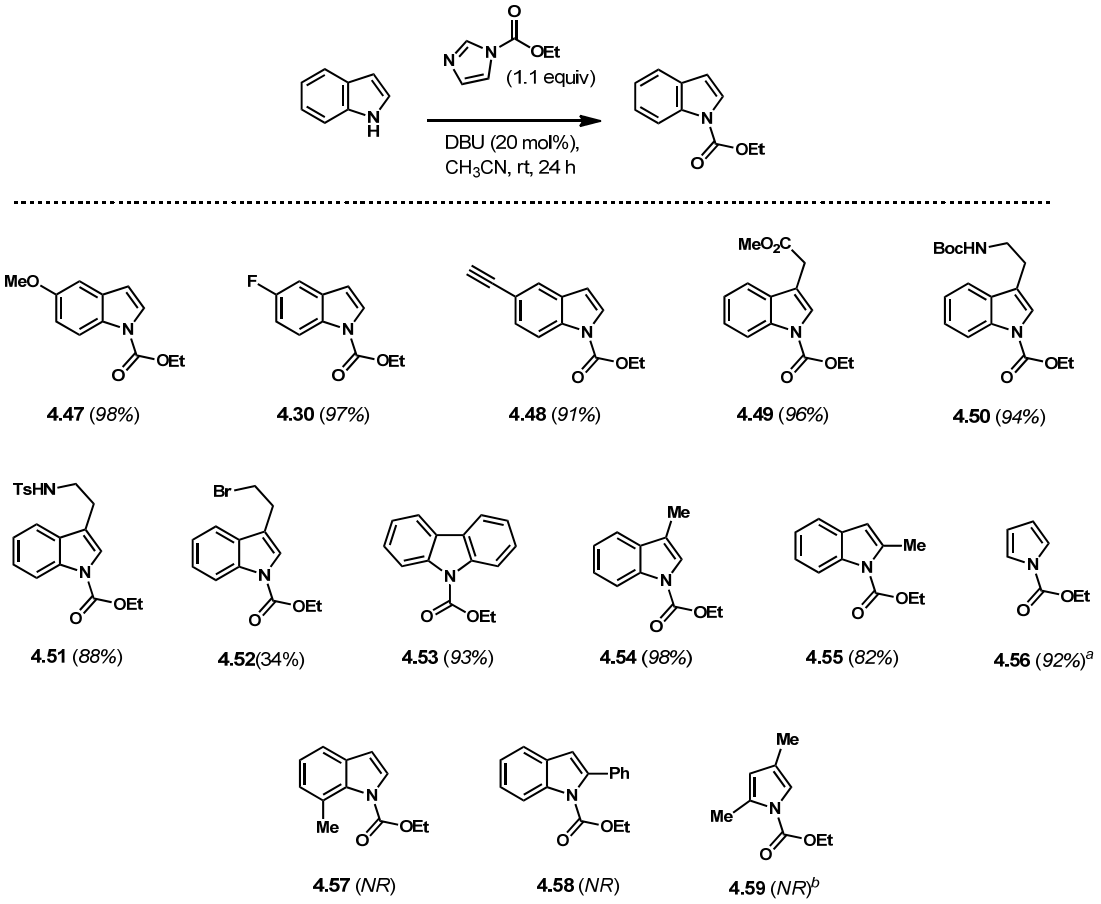
Entry	Carbonylimidazole		Product		% Yield[a]
1		**2.27**		**4.35**	95
2		**2.30**		**4.28**	96
3		**2.31**		**4.36**	88
4		**2.40**		**4.37**	90
5		**2.36**		**4.38**	92
6		**2.32**		**4.39**	91
7		**2.35**		**4.40**	97
8		**4.31**		**4.41**	92
9		**4.32**		**4.42**	97
10		**2.154**		**4.43**	89[b]
11		**4.33**		**4.44**	76[c]
12		**1.94**		**4.45**	90
13		**4.34**		**4.46**	95[c]

[a] Yields are for isolated compounds. [b] Reaction performed with 50 mol% DBU. [c] Reaction performed at 50 °C and with 50 mol% DBU.

2.27, **2.32**, and **2.36**). As in our earlier work with imidazole carbamates, the only byproduct of indole acylation was free imidazole, which could be removed by aqueous workup.

We then sought to further define the scope of this mild acylation reaction by employing a variety of functionalized indole substrates along with **2.30** as the acylation reagent. Groups such as mono-protected amines (Scheme 4.5, **4.50** and **4.51**), acidic esters (**4.49**), and terminal alkynes (**4.48**) were tolerated. Alkyl halides (**4.52**) did not engage in imidazole or indole alkylation, nor was any elimination observed. The low yield of **4.52** may presumably arise from initial cyclopropane formation, followed by an as yet uncharacterized process. As expected, 2-, and 3-alkylated indoles were also efficiently engaged to afford the desired *N*-acylated indoles (**4.54** and **4.55**), as were annulated indole ring systems such as carbazoles (**4.53**). However, large groups at C-2 (**4.58**) or C-7 (see **4.57**) impede acylation. Pyrrole could also be acylated using ethyl imidazole carbamate (**2.30**) along with a stoichiometric quantity of DBU, but substituted pyrroles were poor substrates. For instance, 2,4-dimethylpyrrole was not acylated, even when exposed to **2.30** and DBU at 80 °C.

Scheme 4.5. Indole Scope in Carbonylimidazole Mediated Acylation

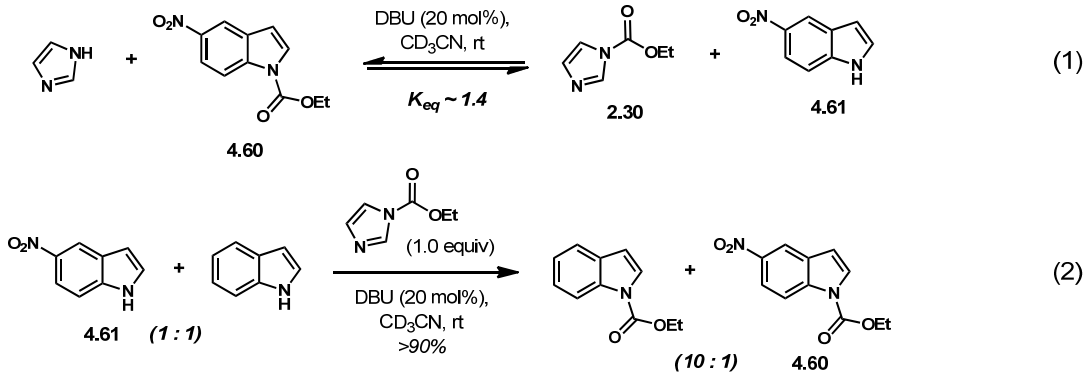


[a] 100 mol% DBU used. [b] Reaction performed at 80 °C and with 100 mol% DBU. Yields in parentheses are of isolated products.

4.3 Thermodynamic Control: Implications for Selectivity and Reagent Design

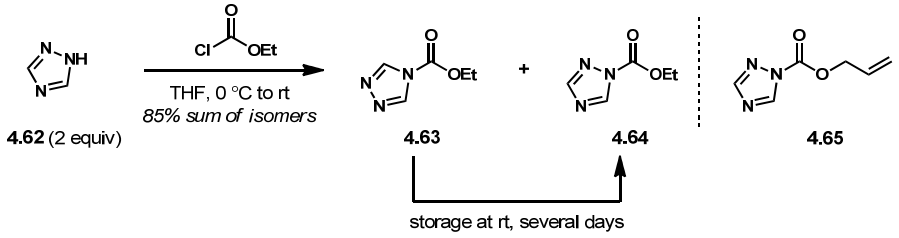
Curiously, attempts to acylate 5-nitroindole (**4.61**) or 3-acetylindole were stymied by an inability to drive the reaction to completion, regardless of catalyst loading or reaction

temperature, suggesting that the acylation may be reversible and under thermodynamic control. This suspicion was confirmed by observation of 5-nitroindole and ethyl imidazole carbamate (**2.30**) when **4.60** was treated with imidazole and DBU (eq 1). As expected, evaluation of both sides of this equilibrium revealed that the obtained product distribution was path-independent. Competition experiments between indole (eq 2) and 5-nitroindole (**4.61**) demonstrated that the less acidic indole species was selectively acylated in overall excellent yield, providing further evidence of thermodynamic control in the carbonylimidazole mediated acylation of indoles.



The fact that 5-nitroindole (**4.61**) has a pK_a similar to that of imidazole (14.6 versus 14.5 in H_2O)[19] suggested that carbonyl stability might be easily approximated by the pK_a of the free heterocycle to which it is attached. On this basis, we prepared 1,2,4-triazole carbamates **4.64** and **4.65** because of the high acidity of the parent 1,2,4-triazole (Scheme 4.6, **4.62**, pK_a = 10.3 in H_2O)[20] by reaction of this heterocycle with ethyl and allyl chloroformate respectively. Preparation of **4.64** was initially complicated by the formation of a mixture of two regioisomers, of which the main constituent was the symmetrical carbonyltriazole **4.63** (a 4*H*-1,2,4-triazole). However, it was found that this mixture equilibrated upon storage to the thermodynamic product, **4.64**.

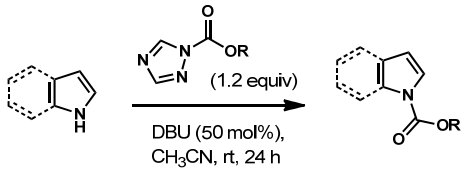
Scheme 4.6. Preparation of 1,2,4-Carbonyltriazoles

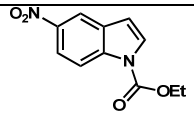
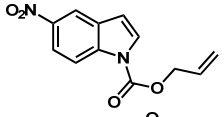
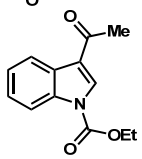
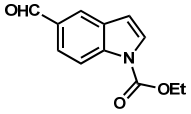
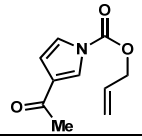


Reaction of **4.64** or **4.65** with 50 mol% DBU and 5-nitroindole led to nearly quantitative conversion to **4.60** or **4.66** (Table 3, entries 1 and 2) respectively. However, lower catalyst loadings resulted in incomplete reactions due to competitive protonation of DBU by free triazole. The use of carbonyltriazoles as acylation reagents for acidic azacycles seemed to be general, and yields were good to excellent. Ketones and aldehydes were well-tolerated (see **4.67-4.69**, entries 4-6). Analysis of the mass balance of the reaction of **4.64** with **4.70** showed that a small quantity of a side product was formed, which we have tentatively assigned as the triazole addition adduct, **4.71** (eq 3). Finally, while investigating the use of these carbonyltriazole species as acyl donors,

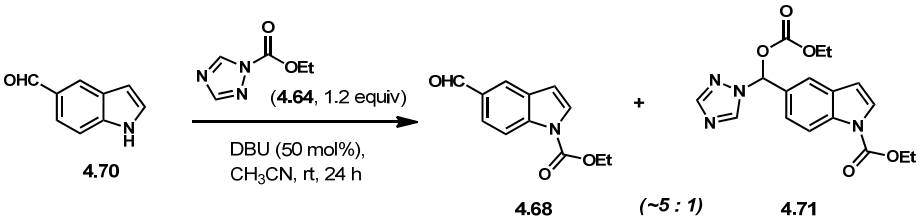
it was found that the initially formed regioisomeric mixture was equally efficacious to pure **4.63** or **4.64** as DBU promotes rapid equilibration.

Table 4.3. Acylation of Acidic Indoles and Pyrroles with 1,2,4-Carbonyltriazoles



Entry	Carbonyltriazole (R)		Product		% Yield[a]
1	Et	**4.64**		**4.60**	92
2	Allyl	**4.65**		**4.66**	93
3	Et	**4.64**		**4.67**	69
4	Et	**4.64**		**4.68**	79
5	Allyl	**4.65**		**4.69**	85

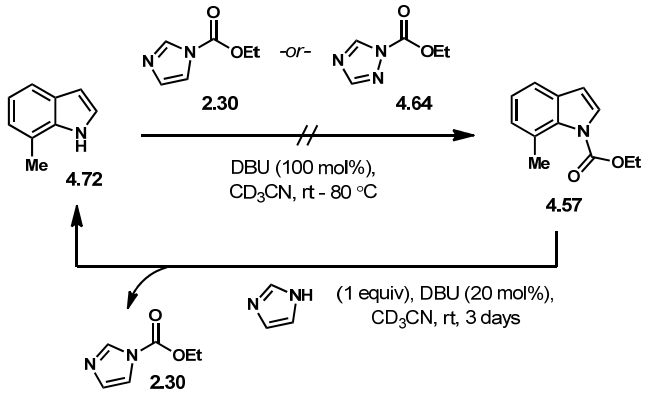
[a] Yields are for isolated compounds.



(3)

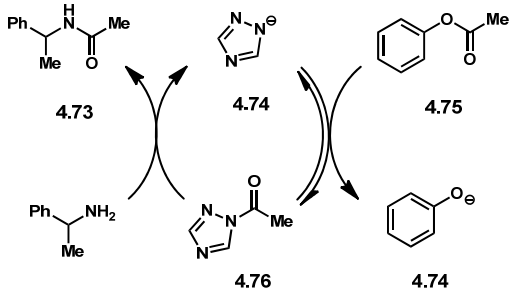
Given the reversibility of the acylation of particularly acidic indoles, we considered that the acylation of sterically encumbered indoles failed because the retro-acylation was favored, and that the use of carbonyltriazoles such as **4.64** could facilitate their acylation by suppressing the reverse reaction. However, treatment of 7-methylindole (Scheme 4.7, **4.72**) with **4.64** and DBU at a variety of temperatures, did not effect indole acylation. In order to test the hypothesis that steric compression could destabilize an acylindole, **4.57** was prepared by other means and was treated with DBU and imidazole or 1,2,4-triazole. Surprisingly, no reaction occurred between **4.57** and free triazole. Thus, it appears that the acylation of sterically encumbered indoles (e.g., **4.72**) by carbonyltriazoles, and potentially carbonyimidazoles, is kinetically unfavorable. On the other hand, **2.30** was slowly generated from the reaction between **4.57** and imidazole.

Scheme 4.7. Steric Compression Affects Equilibrium Between Indole and Imidazole Carbamtes



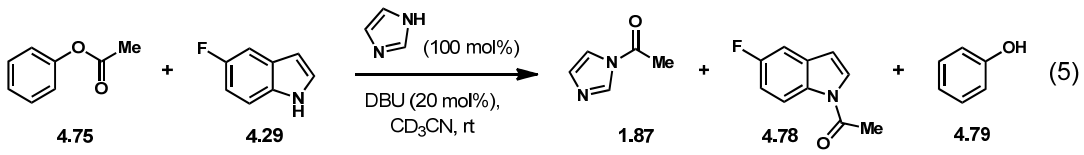
The finding that acylation of indoles is thermodynamically controlled in the presence of DBU and azole heterocycles suggested a strategy for selectively acylating indoles in the presence of more acidic functional groups. By exploiting an equilibration process, the kinetic selectivity for acidic groups like phenols could be overturned and directed toward acylation of the less acidic indole moiety. Such a process would have the potential to greatly accelerate the synthesis of polyfunctional indole derivatives such as 5-hydroxyindole (**4.13**, Scheme 4.2).

There are several examples of the reversible acylation of phenols in the presence of azoles.[21] Most recently, Birman and co-workers have disclosed that 1,2,4-triazolide (the anion of 1,2,4-triazole, **4.74**, eq 4) was an excellent acyl transfer catalyst when used in conjunction with phenyl acetate (**4.75**).[22] Presumably, the active acyl electrophile in this system is acyltriazole **4.76**. Furthermore, we had previously observed that free imidazole reacts with phenyl carbonates at high temperatures to afford imidazole carbamates (Chapter 2).



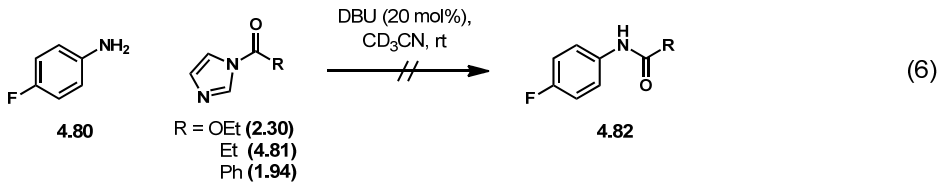
(4)

We then sought to apply this precedent to the chemoselective acylation of indole by employing a model system in which equilibration between an *O*-acylphenol and an *N*-acylindole could be studied by NMR spectroscopy. Treating phenyl acetate (eq 5, **4.75**) with 5-fluoroindole (**4.29**), imidazole, and DBU at room temperature led to initial formation of *N*-acetylimidazole (**1. 87**) with lagging formation of **4.78** (observed by ^{1}H and ^{19}F-NMR). After 24 hours, **4.75** had been completely converted to **4.78** and a small amount of acetic acid. Therefore, it seemed feasible that indoles could be acylated in the presence of phenols through an azolide-mediated equilibration process. Indeed, this is likely the same phenomenon that led to selective acylation of the less acidic of two indole species (see eq 2).

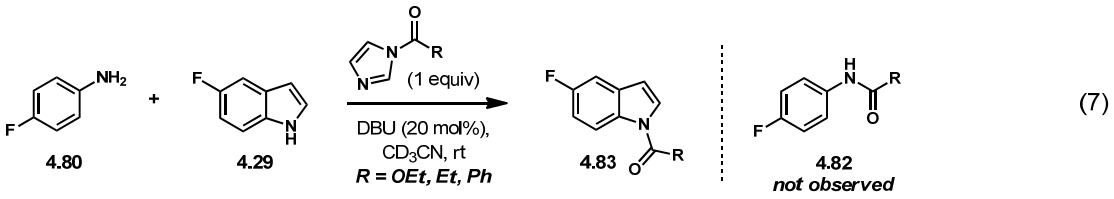


4.4 Kinetic Control: Putting the Chemoselectivity Puzzle Together

Selectivity over functional groups more nucleophilic, but less acidic, than neutral indole was also thought to be accessible if our initial mechanistic hypothesis was correct – that imidazolide ion was being generated through a nucleophilic catalysis event between DBU and carbonylimidazoles – since this would allow for competition for an acyl donor between a neutral nucleophile and the indole *anion* generated through deprotonation by imidazolide. However, any attempt at this type of reaction would require that the carbonylindole product not be a competent acyl donor itself. Preliminary experimentation showed that this was indeed a problem for many aliphatic amines, so we restricted our study to anilines, which do not readily react with *N*-acylindoles. Initial investigations were based on competition experiments between 4-fluoroaniline (eq 6, **4.80**) and 5-fluoroindole (**4.29**) directly monitored by ^{19}F-NMR, as simple ^{1}H-NMR analysis was confounded by multiple overlapping signals. No reaction between carbonylimidazoles and **4.80** was observed in the absence of DBU, the addition of which led to very slow aniline acylation by **4.81**, but not **1.94** or **2.30**.



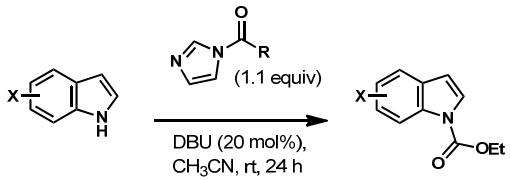
Having established that the background reaction was negligible, we then performed a complete competition experiment by adding 5-fluoroindole (eq 7, **4.29**) to a mixture of **4.80**, a carbonylimidazole, and catalytic quantities of DBU. Rapid acylation of **4.29** was observed, with complete conversion to **4.83** achieved in about one hour for all three carbonylimidazole acyl donors. Aging for 48 hours did not lead to any acyl transfer from **4.83** to aniline **4.80**.

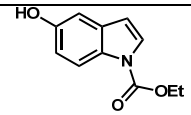
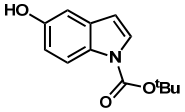
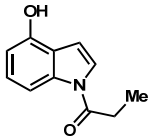
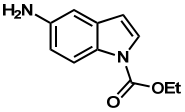
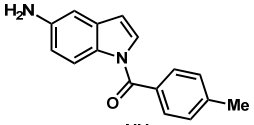
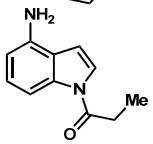
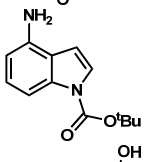
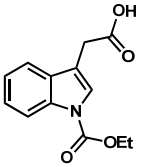
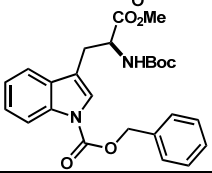


Though we had established that DBU-mediated acylation with carbonylimidazoles was selective for indoles in the presence of anilines and phenols through competition experiments, we wanted to demonstrate that this chemoselectivity could be accessed in a variety of polyfunctional substrates and with a broad class of carbonylimidazoles. Gratifyingly, ethoxycarbonyl, Boc, benzoyl, and propionyl groups could be introduced at the indole nitrogen with excellent selectivity (Table 4.4). For example, the *N*-acylated product **4.84** was obtained in greater than 20:1 selectivity (entry 1). Similarly, acylation of the indole nitrogen could be accomplished in the presence of an amino group (see **4.86-4.88** with good to excellent selectivity (entries 4-6). Moreover, aniline acylation was not observed when 1-(*tert*-butoxycarbonyl)imidazole (**2.40**) was

employed as an acyl donor (entry 7, **4.89**). Acidic functional groups such as carboxylic acids (entry 8, **4.90**) were tolerated in the *N*-acylation of the indole nucleus, although superstoichiometric quantities of DBU were required to overcome catalyst sequestration by protonation. Finally, the indole of Boc-Trp-OMe could be protected with a Cbz group without loss of optical activity (see **4.91**, entry 9).[23]

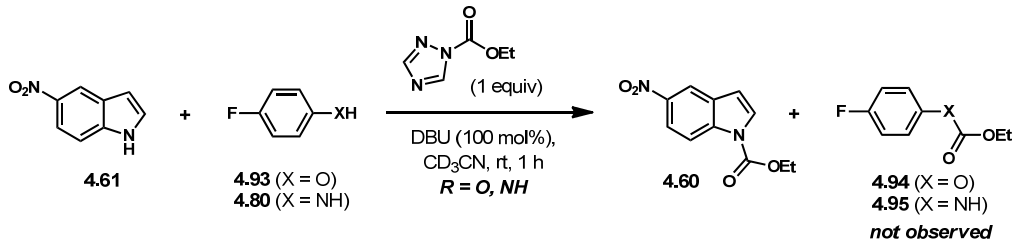
Table 4.4. Chemoselective Indole Acylation by Carbonylimidazole Derivatives



Entry	Carbonylimidazole (R)		Product		Selectivity[a]	Yield (%)[b]
1	OEt	**2.30**		**4.84**	>20 : 1	83
2	O^{t}Bu	**2.40**		**4.18**	12 : 1	85[c]
3	Et	**4.81**		**4.85**	10 : 1	86[d]
4	OEt	**2.30**		**4.86**	10 : 1	81
5	*p*-tolyl	**4.92**		**4.87**	9 : 1	82
6	Et	**4.81**		**4.88**	13 : 1	88
7	O^{t}Bu	**2.40**		**4.89**	>20 : 1	94
8	OEt	**2.30**		**4.90**	>20 : 1	96[e]
9	OBn	**2.36**		**4.91**	>20 : 1	91[f]

[a] Ratios reflect indole nitrogen versus competing nucleophile acylation. [b] Yields are for isolated compounds. [c] 50 mol% DBU used. [d] **4.85** was obtained as an 11:1 inseparable mixture with the starting material. [e] 120 mol% DBU used. [f] No racemization was observed.

Though excellent chemoselectivity could be achieved using carbonylimidazoles, this strategy exploited the stability of these acyl donors toward nucleophiles such as anilines. It was not immediately obvious whether the same selectivity could be expected in cases where carbonyltriazoles were used, so we monitored the acylation of **4.61** with **4.64** in the presence of either 4-fluorophenol (**4.93**) or 4-fluoroaniline (**4.80**, eq 8). Gratifyingly, clean and complete indole acylation was observed to yield (**4.60**) and no phenol or aniline acylation products were detected by ^{1}H or ^{19}F-NMR. Thus, even using the more reactive carbonyltriazole species, virtually complete selectivity could be achieved for the indole nitrogen over phenols or anilines.

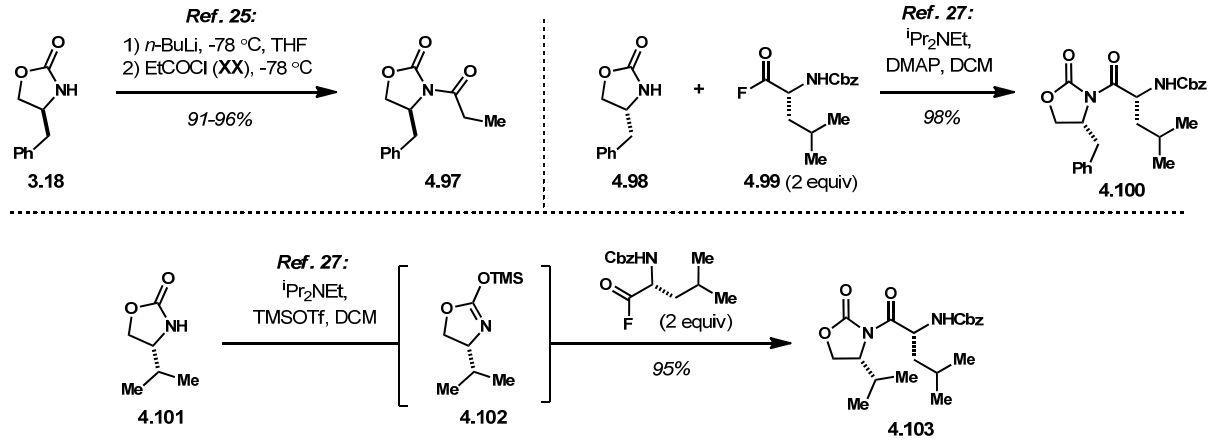


(8)

4.5 Application to the Acylation of Oxazolidinones

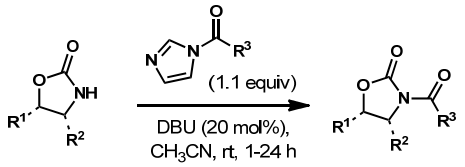
Because pK_a appeared to correlate strongly with relative acyl group stability, we reasoned that other functional groups with a pK_a similar to that of indole, such as oxazolidinones, might be efficiently acylated. The significance of these heterocycles is discussed in detail in Chapter 3. To be sure, a number of methods already exist for the synthesis of *N*-acyloxazolidinones (e.g., **4.97**, **4.100**, **4.103**, Scheme 4.8).[24] The most widely applied technique involves quantitative deprotonation of the free oxazolidinone (**3.18**) with strong base, followed by addition of an active acyl electrophile, typically an acid chloride (e.g., **4.96**).[25] A singular report exists on the use of an acylimidazole as the acyl electrophile.[26] Recent work by Carreira demonstrated that acyl fluorides (**4.99**) could react with oxazolidinones (**4.98** or **4.101**) in the presence of weak bases.[27] This method is particularly well-suited for the acylation of highly sterically congested oxazolidinones; however, significant safety hazards are associated with the preparation of acyl fluorides, and in many cases, prior *O*-silylation (see **4.102**) of the oxazolidinone is required for successful *N*-acylation. On the other hand, acylimidazoles are substantially more stable, as well as easier and safer to prepare than acyl fluorides. Accordingly, we set ourselves to the task of developing a catalytic, chemoselective, and mild *N*-acylation of oxazolidinones.

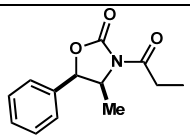
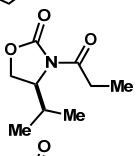
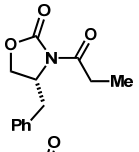
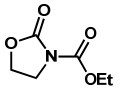
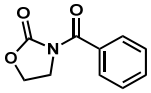
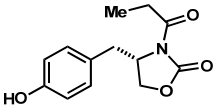
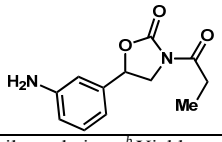
Scheme 4.8. Exemplary Methods for *N*-Acylation of Oxazolidinones



We were therefore pleased to find that the optimal conditions for indole acylation could be directly applied to the synthesis of *N*-acyloxazolidinones. That is, simply treating an oxazolidinone with a carbonylimidazole derivative in the presence of catalytic DBU at room temperature led to rapid *N*-acylation. Though the reactions for many oxazolidinones only required two or three hours, we chose to allow for complete conversion by allowing the reaction to proceed for 24 hours. A variety of carbonylimidazoles have been found to acylate both the parent oxazolidinone (Table 4.5, entries 4 and 5), as well as several commonly used chiral auxiliaries (see **4.103-4.105,** entries 1-3). Furthermore, like indoles, oxazolidinones could be acylated in the presence of phenol (**4.108**) and aniline (**4.109**) groups (entries 6 and 7).

Table 4.5. Carbonylimidazole Mediated *N*-Acylation of Oxazolidinones



Entry	Carbonylimidazole (R)		Product		Selectivity[a]	Yield (%)[b]
1	Et	**4.81**		**4.103**	—	97
2	Et	**4.81**		**4.104**	—	83
3	Et	**4.81**		**4.105**	—	94
4	OEt	**2.30**		**4.106**	—	79
5	Ph	**1.94**		**4.107**	—	91
6	Et	**4.81**		**4.108**	7 : 1	72
7	Et	**4.81**		**4.109**	14 : 1	92

[a] Ratios reflect indole nitrogen versus competing nucleophile acylation. [b] Yields are for isolated compounds.

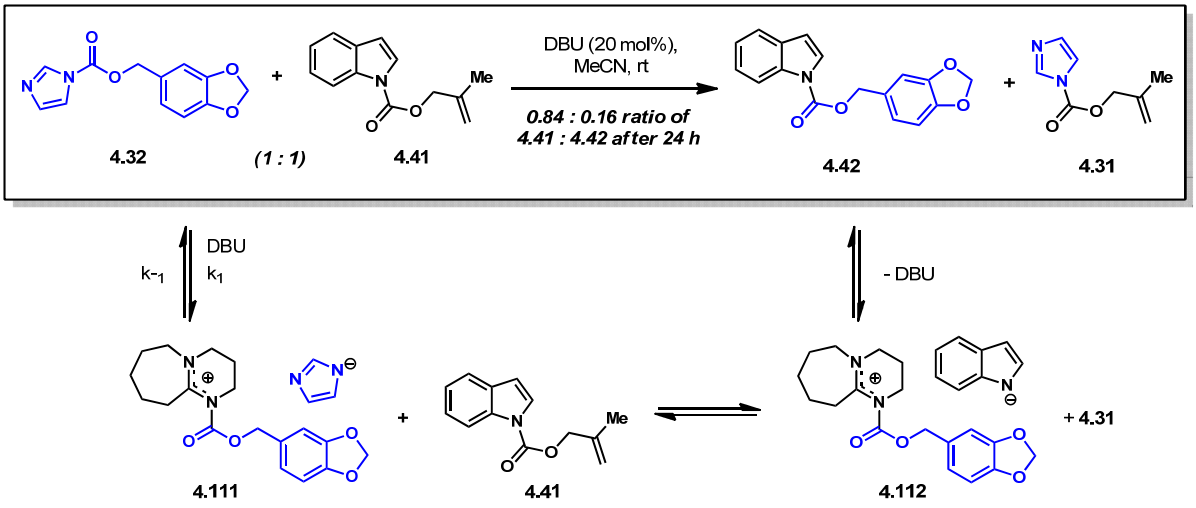
4.6 Preliminary Mechanistic Investigations

Preliminary mechanistic investigations have focused on elucidating the role of DBU in the acylation of acidic pronucleophiles. Rather than simply acting as a base, we postulated that DBU might instead react as a nucleophilic catalyst to produce imidazolide (see Scheme 4.3).[28]

Therefore, we directed our efforts at detecting this intermediate. When **4.32** and **4.41** were allowed to react with DBU (Scheme 4.9), slow acyl group exchange was observed, suggesting that imidazolide was indeed generated directly (as part of ion pair **4.111**) from **4.32** and could engage **4.41** in an acyl transfer reaction. The putative product, **4.112**, would likely then collapse to the crossover product, **4.42**.

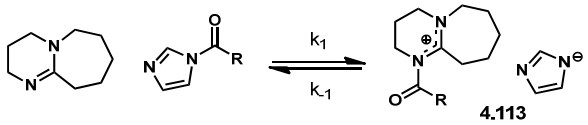
Though this experiment provided direct evidence that DBU can act as a nucleophilic catalyst toward carbonylimidazole derivatives, we could not rule out that DBU was simply acting as a Brønsted base toward indoles with an acidic hydrogen.

Scheme 4.9. Crossover Experiment Supporting Role of DBU as a Nucleophilic Catalyst



However, simple Brønsted catalysis is inconsistent with the observation that DABCO is a better catalyst than triethylamine or DMAP, even though it is less basic (see Table 4.1).[29] Instead, this reactivity trend is strongly correlated with nucleophilicity, as the former is by far the most nucleophilic of the three.[30] It was somewhat perplexing then that DBU, which has been estimated to be less nucleophilic than DABCO, was found to be a superior catalyst for carbonylazole acyl transfer reactions.[31]

On the other hand, Mayr has shown that DBU is more carbon basic than DABCO.[32] Thus we believe that the carbon basicity of the catalyst, an often overlooked property referring to the stability of a Lewis adduct of an sp^2-carbon acid, is at play in this acylation. This property is analogous to Brønsted basicity and the ratio of [**4.111**] to [**4.32**][DBU] can be described with an equilibrium constant.[33] Assuming that the nucleophilic attack of DBU on **4.32** is reversible, it appears that the ratio of the rate constants k_1 and k_{-1}, or K_{eq}, significantly impacts the rate of indole acylation. DMAP is also highly carbon basic, but not as nucleophilic as DBU or DABCO and proved to be ineffective in the reaction under study, suggesting that the magnitude of k_1 is also important. Nucleophilic catalysis by DABCO is likely quite fast (large k_1) given the findings of Mayr and coworkers; however, its low carbon basicity implies that K_{eq} may be small relative to the other amine catalyst systems. Thus, a balance of nucleophilicity – a kinetic parameter – and carbon basicity – a thermodynamic parameter – is important in the catalysis of acylations with carbonylimidazoles due to their relatively weak electrophilicity.



(9)

This mechanistic hypothesis also accounts for the observation that pronucleophiles with a pKa substantially higher than imidazole are not acylated under the conditions described here. In these cases deprotonation by imidazolide, which is the active base in the reaction, is inefficient. Therefore, we tentatively propose that pronucleophiles with pK_as (in DMSO) greater than pyrrole (~23) will be relatively inert to the DBU-catalyzed acylation with carbonylimidazoles. Conversely, functional groups or azacycles that are more acidic than imidazole will be rapidly acylated because they can be easily deprotonated by imidazolide. However, if the product of this acylation is less or similarly stable relative to the imidazole carbamate, the acylation may be readily reversible. As a consequence, there is a functional lower limit to the pK_a of the pronucleophile, which we tentatively assign to be ~19 (in DMSO).

In conclusion, we have demonstrated that DBU reacts with a series of carbonylazoles to generate an ion pair with azolide as the counteranion. The basicity of the azolide allows the chemoselective N-acylation of pronucleophiles, such as indoles and oxazolidinones, in a certain pK_a range (approximately 19‑23 for carbonylimidazoles) in the presence of carboxylic acids, phenols, and anilines − a selectivity that has never before been observed in acylation reactions.

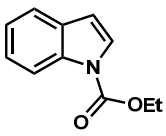
4.7. Experimental Section

Materials and Methods:

See the experimental section of Chapter 2.

Indole Acylation: Representative Procedure A

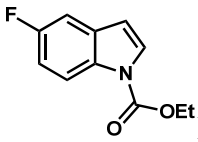
Indole (0.117 g, 1.00 mmol) was dissolved in anhydrous acetonitrile (3 mL) and then ethyl 1*H*-imidazole-1-carboxylate (**2.30**, 0.154 g, 1.10 mmol) was added at room temperature, followed by DBU (0.03 g, 0.2 mmol). The mixture was then allowed to stand (or stirred if heterogeneous) until complete consumption of indole was observed by TLC (typically 1-2 hours). The reaction was quenched by addition of 1 M HCl (5 mL) and then the mixture was extracted with EtOAc (3 x 30 mL). The pooled organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to afford **4** (0.181 g, 96%). If necessary, the crude product was purified by flash chromatography using a mixture of EtOAc and hexanes as eluent.



Ethyl 1*H*-indole-1-carboxylate (4.28)

Prepared from indole and **2.30** using Representative Procedure A.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19 (d, *J* = 8.1 Hz, 1H), 7.63 (d, *J* = 3.8 Hz, 1H), 7.56 (d, *J* = 7.8 Hz, 1H), 7.31 (t, *J* = 7.8 Hz, 1H), 7.28 – 7.23 (m, 1H), 6.58 (d, *J* = 4.3 Hz, 1H), 4.50 (q, *J* = 7.1 Hz, 2H), 1.44 (t, *J* = 7.1 Hz, 3H). Spectra were consistent with those reported previously.[34]



Ethyl 5-fluoro-1*H*-indole-1-carboxylate (4.30)

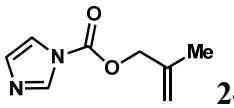
Prepared from 5-fluoroindole and **2.30** using Representative Procedure A.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (s, 1H), 7.65 (s, 1H), 7.22 (dt, *J* = 8.8, 2.4 Hz, 1H), 7.10 – 7.00 (m, 1H), 6.55 (t, *J* = 2.6 Hz, 1H), 4.49 (q, *J* = 6.8 Hz, 2H), 1.47 (t, *J* = 6.9 Hz, 1H).

^{19}F NMR (400 MHz, $CDCl_3$) δ -120.0

^{13}C NMR (126 MHz, $CDCl_3$) δ 159.3 (d, *J* = 238.9 Hz), 150.7, 131.5, 131.3 (d, *J* = 9.9 Hz), 127.0, 116.0 (d, *J* = 9.2 Hz), 112.1 (d, *J* = 25.1 Hz), 107.5 (d, *J* = 4.0 Hz), 106.4 (d, *J* = 23.8 Hz), 63.3, 14.3

HRMS-EI (*m/z*): M^+ calcd for $C_{11}H_{10}FNO_2$, 207.0696; found, 207.0697.

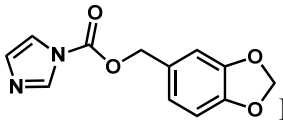


2-Methylallyl 1*H*-imidazole-1-carboxylate (4.31)

Prepared from 2-methallyl alcohol and CDI using Representative Procedure B from Chapter 2.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.43 (d, *J* = 0.9 Hz, 1H), 7.07 (s, 1H), 5.08 (s, 1H), 5.05 (s, 1H), 4.80 (s, 2H), 1.82 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 148.6, 138.4, 137.2, 130.8, 117.2, 115.1, 71.4, 19.5.

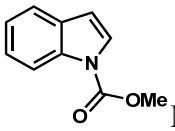


Benzo[d][1,3]dioxol-5-ylmethyl 1*H*-imidazole-1-carboxylate (4.32)

Prepared from piperonol and CDI using Representative Procedure B from Chapter 2.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (s, 1H), 7.12 (s, 2H), 6.86 – 6.83 (m, 2H), 6.77 (d, *J* = 7.8 Hz, 1H), 5.96 (d, *J* = 0.6 Hz, 2H), 5.05 (s, 2H).

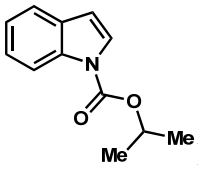
^{13}C NMR (126 MHz, $CDCl_3$) δ 155.1, 148.0, 147.9, 135.2, 129.7, 129.0, 122.7, 122.1, 109.3, 108.4, 101.3, 69.8.



Methyl 1*H*-indole-1-carboxylate (4.35)

Prepared from indole and methyl 1*H*-imidazole-1-carboxylate (**2.27**) using Representative Procedure A.

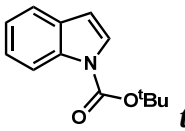
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19 (d, *J* = 8.8 Hz, 1H), 7.68 – 7.52 (m, 2H), 7.39 – 7.29 (m, 1H), 7.29 – 7.22 (m, 1H), 6.61 (d, *J* = 3.8 Hz, 1H), 4.05 (s, 3H). Spectra were consistent with those reported previously.[35]



Isopropyl 1*H*-indole-1-carboxylate (4.36)

Prepared from indole and isopropyl 1*H*-imidazole-1-carboxylate (**2.31**) using Representative Procedure A.

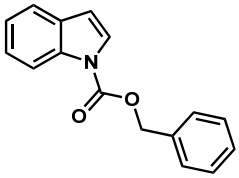
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19 (d, *J* = 8.1 Hz, 1H), 7.63 (d, *J* = 3.8 Hz, 1H), 7.57 (d, *J* = 7.8 Hz, 1H), 7.33 (t, *J* = 7.8 Hz, 1H), 7.28 – 7.21 (m, 1H), 6.60 (d, *J* = 4.3 Hz, 1H), 5.28 (hept, *J* = 6.3 Hz, 1H), 1.47 (d, *J* = 6.2 Hz, 6H). Spectra were consistent with those reported previously.[36]



***tert*-Butyl 1*H*-indole-1-carboxylate (4.37)**

Prepared from indole and *tert*-butyl 1*H*-imidazole-1-carboxylate using (**2.40**) Representative Procedure A.

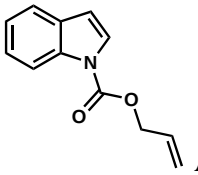
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 (bs, 1H), 7.66 (bs, 1H), 7.62 (d, *J* = 7.7 Hz, 1H), 7.38 (t, *J* = 7.7 Hz, 1H), 7.33 – 7.25 (m, 1H, overlapping with solvent), 6.62 (d, *J* = 3.7 Hz, 1H), 1.72 (s, 9H). Spectra were consistent with those reported previously.[37]



Benzyl 1*H*-indole-1-carboxylate (4.38)

Prepared from indole and benzyl 1*H*-imidazole-1-carboxylate (**2.36**) using Representative Procedure A.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20 (s, 1H), 7.64 (d, *J* = 3.8 Hz, 1H), 7.57 (d, *J* = 7.8 Hz, 1H), 7.53-7.47 (m, 2H), 7.46 – 7.30 (m, 5H), 7.29 – 7.22 (m, 1H, overlapping with solvent), 6.60 (d, *J* = 3.7 Hz, 1H), 5.46 (s, 2H). Spectra were consistent with those reported previously.[38]



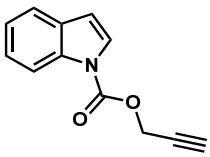
Allyl 1*H*-indole-1-carboxylate (4.39)

Prepared from indole and allyl 1*H*-imidazole-1-carboxylate (**2.32**) using Representative Procedure A.

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.27 (s, 1H), 7.67 (d, *J* = 2.4 Hz, 1H), 7.61 (d, *J* = 7.7 Hz, 1H), 7.39 (t, *J* = 7.7 Hz, 1H), 7.30 (t, *J* = 7.7 Hz, 1H), 6.64 (d, *J* = 3.7 Hz, 1H), 6.11 (app. dq, *J* = 10.9, 5.7 Hz, 1H), 5.50 (d, *J* = 17.2 Hz, 1H), 5.39 (d, *J* = 10.4 Hz, 1H), 4.95 (d, *J* = 5.7 Hz, 2H).

^{13}C NMR (150 MHz, $CDCl_3$) δ 150.8, 135.3, 131.6, 130.6, 125.5, 124.6, 123.1, 121.1, 119.3, 115.2, 108.2, 67.51.

HRMS-EI (*m/z)*: M^+ calcd for $C_{12}H_{11}NO_2$, 201.0790; found, 201.0789.



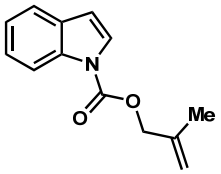
Propargyl 1*H*-indole-1-carboxylate (4.40)

Prepared from indole and propargyl 1*H*-imidazole-1-carboxylate (**2.35**) using Representative Procedure A.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.63 (s, 1H), 7.61 (d, *J* = 7.8 Hz, 1H), 7.39 (t, *J* = 7.8 Hz, 1H), 7.30 (t, *J* = 7.8 Hz, 1H), 5.02 (d, *J* = 2.3 Hz, 2H), 2.65 (t, *J* = 2.3 Hz, 1H).

^{13}C NMR (150 MHz, $CDCl_3$) δ 150.1, 135.3, 130.6, 125.4, 124.8, 123.3, 121.1, 115.3, 108.7, 77.0, 76.1, 54.3.

HRMS-EI (*m/z)*: M^+ calcd for $C_{12}H_9NO_2$, 199.0633; found, 199.0630.



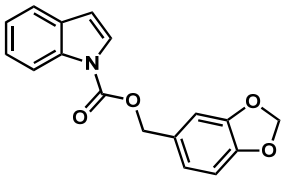
2-Methylallyl 1*H*-indole-1-carboxylate (4.41)

Prepared from indole and 2-methylallyl 1*H*-imidazole-1-carboxylate (**4.31**) using Representative Procedure A.

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.27 (s, 1H), 7.68 (d, *J* = 2.5 Hz, 1H), 7.62 (d, *J* = 7.7 Hz, 1H), 7.39 (t, *J* = 7.7 Hz, 1H), 7.30 (t, *J* = 7.7 Hz, 1H), 6.65 (d, *J* = 3.7 Hz, 1H), 5.17 (s, 1H), 5.09 (s, 1H), 4.88 (s, 2H), 1.91 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$) δ 150.8, 139.3, 135.3, 130.6, 125.5, 124.6, 123.1, 121.1, 115.2, 114.0, 108.2, 70.2, 19.6.

HRMS-EI (*m/z)*: M^+ calcd for $C_{13}H_{13}NO_2$, 215.0946; found, 215.0946.



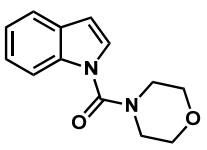
Benzo[*d*][1,3]dioxol-5-ylmethyl 1*H*-indole-1-carboxylate (4.42)

Prepared from indole and benzo[*d*][1,3]dioxol-5-ylmethyl 1*H*-imidazole-1-carboxylate (**4.32**) using Representative Procedure A.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.61 (s, 1H), 7.56 (d, *J* = 7.7 Hz, 1H), 7.32 (t, *J* = 7.7 Hz, 1H), 7.24 (t, *J* = 7.5 Hz, 1H), 6.99 - 6.95 (m, 2H), 6.83 (d, *J* = 7.8 Hz, 1H), 6.59 (d, *J* = 3.6 Hz, 1H), 5.99 (s, 2H), 5.35 (s, 2H).

^{13}C NMR (150 MHz, $CDCl_3$) δ 151.0, 148.2, 148.1, 135.4, 130.7, 129.0, 125.7, 124.7, 123.2, 122.9, 121.1, 115.3, 109.4, 108.5, 108.3, 101.4, 68.85.

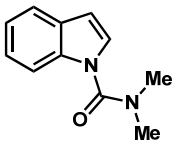
HRMS-EI (*m/z)*: M^+ calcd for $C_{17}H_{13}NO_4$, 295.0845; found, 295.0840.



(1*H*-Indol-1-yl)(morpholino)methanone (4.43)

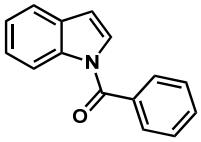
Prepared from indole and **2.154** using Representative Procedure A, but 50 mol% DBU was used.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.3 Hz, 1H), 7.61 (d, *J* = 7.8 Hz, 1H), 7.37 – 7.27 (m, 2H), 7.22 (t, *J* = 7.5 Hz, 1H), 6.62 (d, *J* = 3.5 Hz, 1H), 3.76 (t, *J* = 4.8 Hz, 4H), 3.59 (t, *J* = 4.8 Hz, 4H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 154.1, 135.0, 129.5, 126.0, 123.6, 121.9, 120.98, 113.1, 106.1, 66.5, 46.9.
HRMS-EI (*m/z)*: M^+ calcd for $C_{12}H_{13}NO_3$, 230.1055; found, 230.1060.



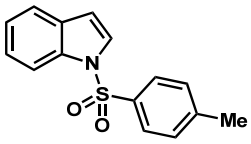
***N*,*N*-Dimethyl-1*H*-indole-1-carboxamide (4.44)**

Prepared from indole and *N*,*N*-dimethyl-1*H*-imidazole-1-carboxamide (**4.33**)[39] using Representative Procedure A except the reaction was heated to 50 ºC with 50 mol% DBU.
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.2 Hz, 1H), 7.63 (d, *J* = 7.8 Hz, 1H), 7.35-7.28 (m, 2H), 7.22 (t, 7.5 Hz, 1H), 6.63 (d, *J* = 3.5 Hz, 1H), 3.08 (s, 3H). Spectra were consistent with those reported previously.[40]



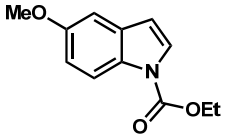
1-Benzoylindole (4.45)

Prepared from indole and 1-benzoyl-1*H*-imidazole (**1.94**)[41] using Representative Procedure A.
^{1}H NMR ($CDCl_3$, 400MHz) δ 8.38 (d, *J* = 8.2 Hz, 1H), 7.73 (d, *J* = 7.5 Hz, 2H), 7.60-7.43 (m, 4H), 7.40-7.29 (m, 3H), 6.61 (d, *J* = 7.6 Hz, 1H). Spectra were consistent with those reported previously.[42]



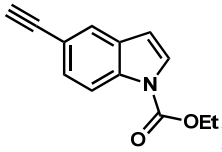
1-Tosylindole (4.46)

Prepared from indole and 1-tosyl-1*H*-imidazole (**4.34**) using Representative Procedure A except the reaction was heated to 50 °C with 50 mol% DBU.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 8.3 Hz, 1H), 7.76 (d, *J* = 8.1 Hz, 2H), 7.56 (d, *J* = 3.6 Hz, 1H), 7.52 (d, *J* = 7.8 Hz, 1H), 7.30 (t, *J* = 7.8 Hz, 1H), 7.24 – 7.16 (m, 3H), 6.65 (d, *J* = 3.6 Hz, 1H), 2.33 (s, 3H). Spectra were consistent with those reported previously.[43]



Ethyl 5-methoxy-1*H*-indole-1-carboxylate (4.47)

Prepared from 5-methoxyindole and **2.30** using Representative Procedure A.
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (s, 1H), 7.60 (s, 1H), 7.04 (d, *J* = 2.4 Hz, 1H), 6.95 (dd, *J* = 8.9, 2.5 Hz, 1H), 6.53 (d, *J* = 3.6 Hz, 1H), 4.48 (q, *J* = 7.1 Hz, 2H), 3.85 (s, 3H), 1.46 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 155.9, 150.9, 131.3, 126.1, 115.8, 113.1, 107.7, 103.4, 63.0, 55.6, 14.4.
HRMS-EI (*m/z*): M^+ calcd for $C_{12}H_{13}NO_3^+$, 219.0895; found, 219.0901.



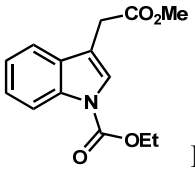
Ethyl 5-ethynyl-1*H*-indole-1-carboxylate (4.48)

Prepared from 5-ethynylindole[44] and **2.30** using Representative Procedure A.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, *J* = 8.5 Hz, 1H), 7.72 (s, 1H), 7.62 (d, *J* = 3.5 Hz, 1H), 7.45 (d, *J* = 8.5 Hz, 1H), 6.55 (d, *J* = 3.6 Hz, 1H), 4.48 (q, *J* = 7.2 Hz, 2H), 3.05 (s, 1H), 1.46 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 150.7, 135.0, 130.3, 128.2, 126.5, 125.0, 116.4, 115.0, 107.5, 84.2, 75.9, 63.4, 14.3.

HRMS-EI (*m/z*): M^+ calcd for $C_{13}H_{11}NO_2$, 213.0790; found, 213.0792.



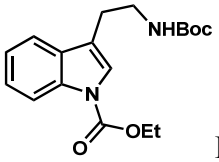
Ethyl (methyl 1*H*-indole-3-acetate)-1-carboxylate (4.49)

Prepared from methyl indole-3-acetate (**2.59**) and **2.30** using Representative Procedure A.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 (s, 1H), 7.62 (s, 1H), 7.54 (d, *J* = 7.7 Hz, 1H), 7.35 (t, *J* = 8.3 Hz, 1H), 7.31 – 7.23 (m, 1H), 4.48 (q, *J* = 7.1 Hz, 2H), 3.73 (d, *J* = 1.1 Hz, 2H), 3.72 (s, 3H), 1.46 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 171.3, 150.7, 135.3, 129.9, 124.7, 124.0, 122.8, 118.9, 115.2, 113.6, 63.1, 52.1, 30.7, 14.3.

HRMS-EI (*m/z*): M^+ calcd for $C_{14}H_{15}NO_4$, 261.1001; found, 261.1004.



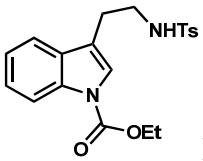
Ethyl 3-(2-((*tert*-butoxycarbonyl)amino)ethyl)-1*H*-indole-1-carboxylate (4.50)

Prepared from *N*-Boc-tryptamine[45] and **2.30** using Representative Procedure A.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17 (s, 1H), 7.55 (d, *J* = 7.7 Hz, 1H), 7.45 (s, 1H), 7.38 – 7.30 (m, 1H), 7.30 – 7.18 (m, 2H), 4.65 (s, 1H), 4.48 (q, *J* = 7.1 Hz, 2H), 3.47 (q, *J* = 6.7 Hz, 2H), 2.90 (t, *J* = 7.0 Hz, 2H), 1.53 – 1.35 (m, 12H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 155.8, 151.0, 135.5, 130.4, 124.6, 122.7, 119.0, 118.4, 115.2, 79.3, 63.1, 40.0, 28.4, 25.5, 14.4.

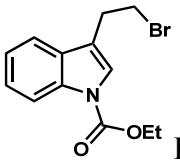
HRMS-EI (*m/z*): M^+ calcd for $C_{18}H_{24}N_2O_4$, 332.1736; found, 332.1740.



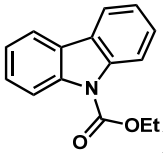
Ethyl 3-(2-(4-methylphenylsulfonamido)ethyl)-1*H*-indole-1-carboxylate (4.51)

Prepared from *N*-tosyltryptamine[46] and **2.30** using Representative Procedure A.

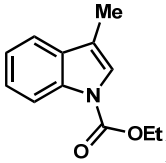
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (s, 1H), 7.66 (d, *J* = 8.1 Hz, 2H), 7.42 – 7.33 (m, 2H), 7.30 (t, *J* = 7.8 Hz, 1H), 7.22 – 7.13 (m, 3H), 5.18 (t, *J* = 6.2 Hz, 1H), 4.41 (q, *J* = 7.1 Hz, 2H), 3.27 (q, *J* = 6.7 Hz, 2H), 2.85 (t, *J* = 6.9 Hz, 2H), 2.37 (s, 3H), 1.43 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 150.6, 143.2, 136.6, 135.4, 129.8, 129.4, 126.8, 124.5, 123.0, 122.6, 118.6, 117.1, 115.1, 63.0, 42.3, 25.3, 21.3, 14.3.
HRMS-EI (*m/z*): M^+ calcd for $C_{20}H_{22}N_2O_4S$, 386.1300; found, 386.1308.



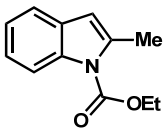
Ethyl 3-(2-bromoethyl)-1*H*-indole-1-carboxylate (4.52)
Prepared from 3-(2-bromoethyl)indole and **2.30** using Representative Procedure A.
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.19 (s, 1H), 7.53 (d, *J* = 7.6 Hz, 1H), 7.52 (s, 1H), 7.36 (t, *J* = 7.6 Hz, 1H), 7.28 (t, *J* = 7.6 Hz, 1H), 4.49 (q, *J* = 7.0 Hz, 1H), 3.65 (t, *J* = 7.4 Hz, 1H), 3.28 (t, *J* = 7.5 Hz, 1H), 1.48 (t, *J* = 7.1 Hz, 2H).
^{13}C NMR (150 MHz, $CDCl_3$) δ 151.0, 135.6, 130.0, 124.9, 123.2, 123.0, 118.7, 118.6, 115.5, 63.3, 31.4, 29.0, 14.6.



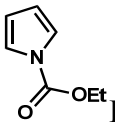
Ethyl 9*H*-carbazole-9-carboxylate (4.53)
Prepared from carbazole and **2.30** using Representative Procedure A.
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.33 (d, *J* = 8.1 Hz, 2H), 8.02 – 7.97 (m, 2H), 7.52 – 7.46 (m, 2H), 7.40 – 7.35 (m, 2H), 4.61 (q, *J* = 7.2 Hz, 2H), 1.57 (t, *J* = 7.1 Hz, 3H). Spectra were consistent with those reported previously.[47]



Ethyl 3-methyl-1*H*-indole-1-carboxylate (4.54)
Prepared from 3-methylindole and **2.30** using Representative Procedure A.
^{1}H NMR (600 MHz, CD_3CN) δ 7.86 (d, *J* = 8.1 Hz, 1H), 7.29 (d, *J* = 7.7 Hz, 1H), 7.16 (s, 1H), 7.07 (t, *J* = 7.6 Hz, 1H), 7.00 (t, *J* = 7.5 Hz, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 2.00 (s, 3H), 1.15 (t, *J* = 7.1 Hz, 3H). Spectra were consistent with those reported previously.[48]



Ethyl 2-methyl-1*H*-indole-1-carboxylate (4.55)
Prepared from 2-methylindole and **2.30** using Representative Procedure A.
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 (d, *J* = 8.2 Hz, 1H), 7.48 (d, *J* = 7.4 Hz, 1H), 7.29 (t, *J* = 7.4 Hz, 1H), 7.24 (t, *J* = 7.4 Hz, 1H), 6.36 (s, 1H), 4.51 (q, *J* = 7.2 Hz, 2H), 2.64 (s, 3H), 1.51 (t, *J* = 7.2 Hz, 3H). Spectra were consistent with those reported previously.[49]


Ethyl 1*H*-pyrrole-1-carboxylate (4.56)

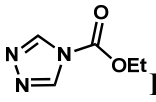
Prepared from pyrrole and **2.30** using Representative Procedure A, but 100 mol% DBU was used.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 (t, *J* = 2.3 Hz, 2H), 6.30 – 6.19 (m, 2H), 4.41 (q, *J* = 7.1 Hz, 2H), 1.38 (s, 1H). Spectra were consistent with those reported previously.[50]

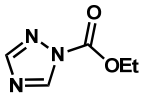
Preparation of 1,2,4-Triazole Carbamates: Representative Procedure B

A solution of 1,2,4-triazole (1.38 g, 20.0 mmol) in anhydrous THF (20 mL) was stirred at 0 °C. Ethyl chloroformate (1.09 g, 10.0 mmol) was added dropwise. The reaction mixture was then stirred and allowed to warm to room temperature overnight. The resultant white precipitate was removed by filtration and the filtrate was concentrated *in vacuo* to afford **S3** (1.20 g, 85%) as a colorless oil which was sufficiently pure for further use.

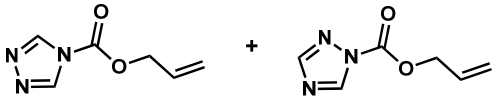
NOTE: The 1-carbonyltriazoles described below were obtained as regioisomeric mixtures of 1*H*-triazole-1-carboxylate and 4*H*-triazole-4-carboxylate species which initially favored the latter isomer. In the presence of trace 1,2,4-triazole or other nucleophilic bases, the mixture equilibrates to the 1*H*-triazole-1-carboxylate isomer. However, the obtained regioisomeric mixtures were used directly in the acylation reaction.


Ethyl 4*H*-1,2,4-triazole-4-carboxylate (4.63)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.64 (s, 2H), 4.53 (q, *J* = 7.2 Hz, 2H), 1.46 (t, *J* = 7.1 Hz, 3H).

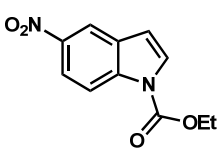

Ethyl 1*H*-1,2,4-triazole-1-carboxylate (4.64)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.82 (s, 1H), 8.05 (s, 1H), 4.57 (q, *J* = 7.2 Hz, 2H), 1.53 – 1.40 (m, 3H).


Allyl 4*H*-1,2,4-triazole-4-carboxylate (4.65)

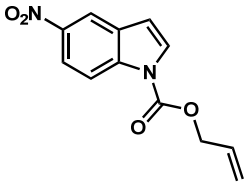
Prepared from allyl chloroformate using Representative Procedure B and was isolated as a mixture with allyl 1*H*-1,2,4-triazole-1-carboxylate:

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.80 (s, 0.2H), 8.62 (s, 1.6H), 8.01 (s, 0.2H), 6.08 – 5.90 (m, 1H), 5.49 – 5.34 (m, 2H), 4.92 (dt, *J* = 6.5, 1.0 Hz, 0.4), 4.89 (dt, *J* = 6.5, 1.0 Hz, 0.6H).


Ethyl 5-nitro-1*H*-indole-1-carboxylate (4.61)

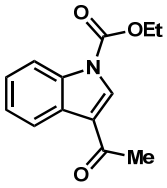
Prepared from 5-nitroindole and ethyl 1*H*-1,2,4-triazole-1-carboxylate (regioisomeric mixture) using Representative Procedure A, but 50 mol% DBU was used.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.50 (d, *J* = 2.2 Hz, 1H), 8.30 (d, *J* = 9.1 Hz, 1H), 8.23 (dd, *J* = 9.1, 2.2 Hz 1H), 7.78 (d, *J* = 3.8 Hz, 1H), 6.75 (d, *J* = 3.8 Hz, 1H), 4.54 (q, *J* = 7.1 Hz, 2H), 1.50 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 150.3, 143.8, 138.3, 130.3, 128.5, 119.7, 117.2, 115.3, 108.4, 64.1, 14.3.
HRMS-EI (*m/z*): M^+ calcd for $C_{11}H_{10}N_2O_4$, 234.0641; found, 234.0640.



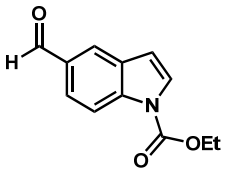
Allyl 5-nitro-1*H*-indole-1-carboxylate (4.66)

Prepared from 5-nitroindole and allyl 1*H*-1,2,4-triazole-1-carboxylate (regioisomeric mixture) using Representative Procedure B, but 50 mol% DBU was used.
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.42 (d, *J* = 2.2 Hz, 1H), 8.23 (d, *J* = 9.1 Hz, 1H), 8.15 (dd, *J* = 9.1, 2.2 Hz, 1H), 7.74 (d, *J* = 3.7 Hz, 1H), 6.70 (d, *J* = 3.7 Hz, 1H), 6.07 (ddt, *J* = 16.6, 10.3, 6.0 Hz, 1H), 5.48 (dd, *J* = 17.2, 1.4 Hz, 1H), 5.39 (dd, *J* = 10.4, 1.5 Hz, 1H), 4.94 (d, *J* = 5.8 Hz, 2H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 149.7, 143.5, 137.9, 130.5, 129.9, 128.1, 119.9, 119.4, 116.9, 114.9, 108.3, 68.0.
HRMS-EI (*m/z*): M^+ calcd for $C_{12}H_{10}N_2O_4$, 246.0641; found, 246.0645.



Ethyl 3-acetyl-1*H*-indole-1-carboxylate (4.67)

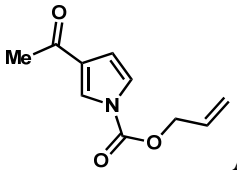
Prepared from 3-acetylindole and ethyl 1*H*-1,2,4-triazole-1-carboxylate (regioisomeric mixture) using Representative Procedure B, but 50 mol% DBU was used.
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.34 (d, *J* = 7.8 Hz, 1H), 8.16 (s, 1H), 8.11 (d, *J* = 7.7 Hz, 1H), 7.39 - 7.32 (m, 2H), 4.53 (q, *J* = 7.1 Hz, 2H), 2.53 (s, 3H), 1.50 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (150 MHz, $CDCl_3$) δ 193.8, 150.5, 135.6, 132.0, 127.3, 125.7, 124.6, 122.7, 121.1, 115.0, 64.3, 27.8, 14.4.
HRMS-EI (*m/z)*: M^+ calcd for $C_{13}H_{13}NO_3$, 231.0895; found, 231.0893.



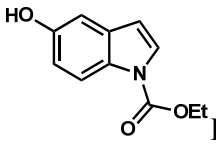
Ethyl 5-formyl-1*H*-indole-1-carboxylate (4.68)

Prepared from 5-indolecarboxaldehyde and ethyl 1*H*-1,2,4-triazole-1-carboxylate (regioisomeric mixture) using Representative Procedure B, but 50 mol% DBU was used.
^{1}H NMR (500 MHz, $CDCl_3$) δ 10.01 (s, 1H), 8.25 (d, *J* = 8.6 Hz, 1H), 8.03 (s, 1H), 7.81 (d, *J* = 8.5 Hz, 1H), 7.66 (d, *J* = 3.8 Hz, 1H), 6.65 (d, *J* = 3.6 Hz, 1H), 4.48 (q, *J* = 7.1 Hz, 2H), 1.45 (t, *J* = 7.1 Hz, 3H).

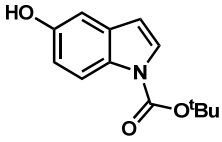
^{13}C NMR (126 MHz, $CDCl_3$) δ 191.9, 150.4, 138.6, 131.7, 130.5, 127.2, 125.2, 124.1, 115.4, 108.2, 63.6, 14.2.
HRMS-EI (*m/z*): M^+ calcd for $C_{12}H_{11}NO_3$, 217.0739; found, 217.0745.



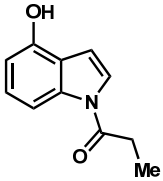
Allyl 3-acetyl-1*H*-pyrrole-1-carboxylate (4.69)
Prepared from 3-acetylpyrrole and allyl 1*H*-1,2,4-triazole-1-carboxylate (regioisomeric mixture) using Representative Procedure B, but 50 mol% DBU was used.
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (t, *J* = 1.7 Hz, 1H), 7.30 (t, *J* = 1.8 Hz, 1H), 6.68 (dd, *J* = 3.3, 1.6 Hz, 1H), 6.04 (ddt, *J* = 16.6, 10.3, 6.0 Hz, 1H), 5.48 (dd, *J* = 17.1, 1.4 Hz, 1H), 5.40 (dd, *J* = 10.4, 1.5 Hz, 1H), 4.90 (d, *J* = 5.8 Hz, 2H), 2.46 (s, 3H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 193.3, 149.5, 130.5, 128.8, 124.6, 121.3, 120.2, 111.4, 68.5, 27.2.
HRMS-EI (*m/z*): M^+ calcd for $C_{10}H_{11}NO_3$, 193.0739; found, 193.0743.



Ethyl 5-hydroxy-1*H*-indole-1-carboxylate (4.84)
Prepared from 5-hydroxyindole and **2.30** using Representative Procedure A.
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (bs, 1H), 7.58 (s, 1H), 7.03 (t, *J* = 1.9 Hz, 1H), 6.91 (dt, *J* = 9.0, 2.2 Hz, 1H), 6.46 (d, *J* = 3.7 Hz, 1H), 6.34 – 5.98 (m, 1H), 4.47 (q, *J* = 7.1 Hz, 2H), 1.45 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 151.8, 151.8, 151.2, 131.6, 129.8, 126.3, 115.8, 113.2, 107.7, 106.2, 63.3, 14.3.
IR (film) ν_{max} 3400, 2983, 1737 cm^{-1}
HRMS-EI (*m/z*): M^+ calcd for $C_{11}H_{11}NO_3$, 205.0739; found, 205.0743.

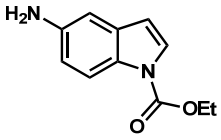


***tert*-butyl 5-hydroxy-1*H*-indole-1-carboxylate (4.18)**
Prepared from 5-hydroxyindole and **2.40** using Representative Procedure A, but with 50 mol% DBU.
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (bs, 1H), 7.56 (bs, 1H), 7.00 (d, *J* = 2.5 Hz, 1H), 6.87 (dd, *J* = 8.9, 2.5 Hz, 1H), 6.74 (s, 1H), 6.44 (d, *J* = 3.7 Hz, 1H), 1.66 (s, 9H). Spectra were consistent with those reported previously.[51]



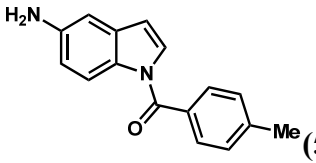
1-propionyl-(4-hydroxy-1*H*-indole) (4.85)
Prepared from 4-hydroxyindole and **4.81**[52] using Representative Procedure A.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, *J* = 8.3 Hz, 1H), 7.40 (d, *J* = 3.9 Hz, 1H), 7.20 (t, *J* = 8.1 Hz, 1H), 6.76 (d, *J* = 3.8 Hz, 1H), 6.69 (d, *J* = 7.8 Hz, 1H), 5.32 (bs, 1H), 2.96 (q, *J* = 7.3 Hz, 2H), 1.35 (t, *J* = 7.4 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 172.4, 148.6, 137.3, 126.1, 123.3, 119.3, 109.7, 108.7, 105.4, 29.3, 8.7.
IR (film) ν_{max} 3369, 1683, 1591, 1446, 1361, 1245, 1205 cm^{-1}
HRMS-EI (*m/z*): M^+ calcd for $C_{11}H_{11}NO_2$, 189.0790; found, 189.0793.



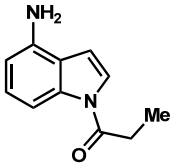
Ethyl 5-amino-1*H*-indole-1-carboxylate (4.86)

Prepared from 5-aminoindole and **2.30** using Representative Procedure A.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (bs, 1H), 7.54 (bd, *J* = 4.0 Hz, 1H), 6.85 (d, *J* = 2.2 Hz, 1H), 6.73 (dd, *J* = 8.7, 2.2 Hz, 1H), 6.43 (d, *J* = 3.6 Hz, 1H), 4.46 (q, *J* = 7.1 Hz, 2H), 3.68 (s, 2H), 1.45 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 150.9, 142.2, 131.5, 129.1, 125.9, 115.6, 113.7, 107.3, 105.9, 62.9, 14.4.
IR (film) ν_{max} 3450, 3360, 1732 cm^{-1}
HRMS-EI (*m/z*): M^+ calcd for $C_{11}H_{12}N_2O_2$, 204.0899; found, 204.0903.



(5-amino-1*H*-indol-1-yl)(*p*-tolyl)methanone (4.87)

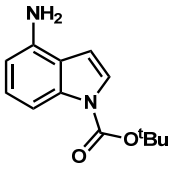
Prepared from 5-aminoindole and (1*H*-imidazol-1-yl)(*p*-tolyl)methanone[53] using Representative Procedure B.
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.20 (d, *J* = 8.7 Hz, 1H), 7.61 (d, *J* = 8.2 Hz, 2H), 7.30 (d, *J* = 7.8 Hz, 2H), 7.22 (d, *J* = 3.8 Hz, 1H), 6.85 (d, *J* = 2.6 Hz, 1H), 6.75 (dd, *J* = 8.4, 2.5 Hz, 1H), 6.43 (d, *J* = 3.8 Hz, 1H), 3.69 (s, 2H), 2.44 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 168.2, 143.0, 142.2, 131.9, 131.9, 129.9, 129.2, 129.1, 128.1, 117.1, 113.9, 107.9, 105.6, 21.5.
IR (film) ν_{max} 3451, 3364, 1651, 1623, 1477, 1455, 1384, 1356, 1279, 1193 cm^{-1}
HRMS-EI (*m/z*): M^+ calcd for $C_{16}H_{14}N_2O$, 250.1106; found, 250.1109.



1-propionyl-(4-amino-1*H*-indole) (4.88)

Prepared from 4-aminoindole and **4.81** using Representative Procedure A.
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.2 Hz, 1H), 7.34 (d, *J* = 4.0 Hz, 1H), 7.16 (t, *J* = 8.0 Hz, 1H), 6.63 – 6.50 (m, 2H), 3.93 (s, 2H), 2.90 (q, *J* = 7.3 Hz, 2H), 1.32 (t, *J* = 7.3 Hz, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 172.2, 139.1, 136.5, 126.2, 122.6, 118.5, 108.6, 107.4, 105.1, 105.0, 29.1, 8.6.
IR (film) ν_{max} 3445, 3367, 2980, 2939, 1698 cm^{-1}

HRMS-EI (*m/z*): M^+ calcd for $C_{11}H_{12}N_2O$, 188.0950; found, 188.0954.



***tert*-butyl 4-amino-1*H*-indole-1-carboxylate (4.89)**

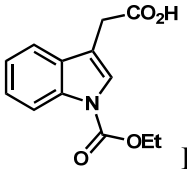
Prepared from 4-aminoindole and **2.40** using Representative Procedure A.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (bd, *J* = 8.4 Hz, 1H), 7.52 (d, *J* = 3.8 Hz, 1H), 7.12 (t, *J* = 8.0 Hz, 5H), 6.54 (d, *J* = 7.7 Hz, 1H), 6.51 (d, *J* = 3.8 Hz, 1H), 3.90 (bs, 2H), 1.59 (s, 9H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 149.9, 139.2, 136.2, 125.3, 124.1, 119.0, 107.7, 106.2, 103.3, 83.5, 28.2.

IR (film) ν_{max} 3460, 3377, 2979, 2933, 1731 cm^{-1}

HRMS-EI (*m/z*): M^+ calcd for $C_{13}H_{16}N_2O_2$, 232.1212; found, 232.1213.



Ethyl (1*H*-indole-1-carboxylate)-3-acetic acid (4.90)

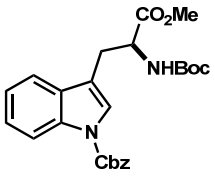
Prepared from indole-3-acetic acid and **2.30** using Representative Procedure A, but 120 mol% DBU was used.

^{1}H NMR (600 MHz, $CDCl_3$) δ 11.71 (bs, 1H), 8.20 (bs, 1H), 7.63 (s, 1H), 7.55 (d, *J* = 7.7 Hz, 1H), 7.37 (t, *J* = 7.7 Hz, 1H), 7.29 (t, *J* = 7.7 Hz, 1H), 4.48 (q, *J* = 7.1 Hz, 2H), 3.76 (s, 2H), 1.47 (t, *J* = 7.1 Hz, 4H).

^{13}C NMR (150 MHz, $CDCl_3$) δ 177.2, 150.9, 135.4, 130.0, 124.9, 124.3, 123.0, 119.1, 115.3, 113.2, 63.3, 30.8, 14.4.

IR (film) ν_{max} 2983, 1736, 1716, 1456, 1405, 1381, 1254 cm^{-1}.

HRMS-EI (*m/z)*: M^+ calcd for $C_{13}H_{13}NO_4$, 247.0845; found, 247.0849.



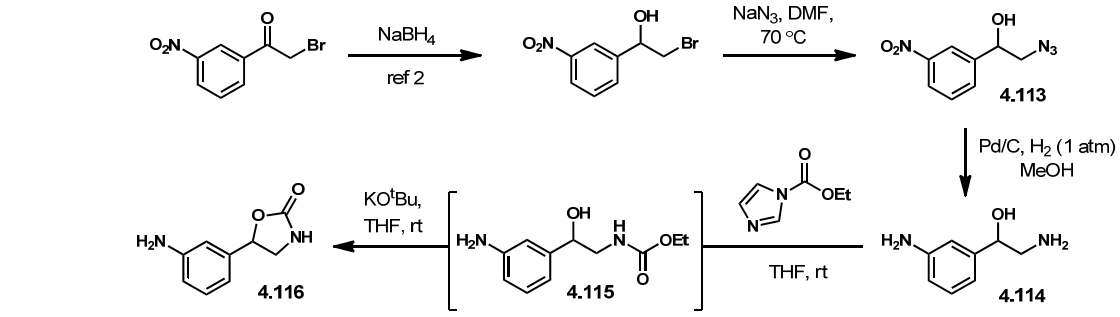
(*S*)-benzyl 3-(2-((*tert*-butoxycarbonyl)amino)-3-methoxy-3-oxopropyl)-1*H*-indole-1-carboxylate (4.91)

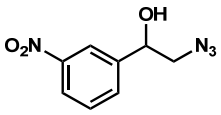
Prepared from Boc-Trp-OMe and **2.36** using Representative Procedure A. The reaction was allowed to proceed for 1 hour.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17 (s, 1H), 7.55-7.43 (m, 3H), 7.41-7.33 (m, 4H), 7.32 (t, *J* = 7.5 Hz, 1H), 7.24 (t, *J* = 8.0 Hz, 1H), 5.43 (s, 2H), 5.10 (d, *J* = 7.5 Hz, 1H), 4.66 (q, *J* = 5.5 Hz, 1H), 3.67 (s, 3H), 3.25 (dd, *J* = 15.0, 5.5 Hz, 1H), 3.17 (dd, *J* = 15.0, 6.0 Hz, 1H), 1.42 (s, 1H). Spectra were consistent with those reported previously for the enantiomer.[54]

[α^{25}_D] = +42.0 (c = 1.2, $CHCl_3$), lit. (enantiomer): [α^{25}_D] = -40.2 (c = 1.2, $CHCl_3$).[17]

Synthesis of Substrates:

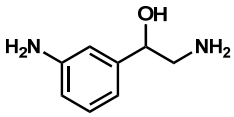




2-Azido-1-(3-nitrophenyl)ethanol (4.113)

A solution of 2-bromo-1-(3-nitrophenyl)ethanol[55] (0.70 g, 2.84 mmol) in anhydrous DMF (6 mL) was prepared and then sodium azide (0.37 g, 5.7 mmol) was added at room temperature. The reaction mixture was heated to 70 °C for 8 h, during which time a white precipitate formed. The mixture was cooled to room temperature, 20 mL water was added, and the aqueous solution was extracted with Et_2O (4 x 20 mL). The pooled organic layers were washed with water (2 x 20 mL) then brine, dried over $MgSO_4$, and concentrated *in vacuo*. The title compound (0.371 g, 63%) was obtained as a colorless syrup and was used without further purification.

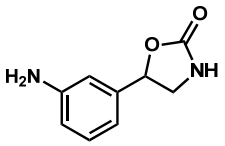
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.27 (s, 1H), 8.18 (dd, *J* = 8.2, 2.3 Hz, 1H), 7.73 (d, *J* = 7.6 Hz, 1H), 7.57 (t, *J* = 7.9 Hz, 1H), 5.00 (dt, *J* = 7.7, 3.8 Hz, 1H), 3.63 – 3.44 (m, 2H), 2.63 (d, *J* = 3.7 Hz, 1H).



2-Amino-1-(3-aminophenyl)ethanol (4.114)

Pd/C (10 wt%, 0.06 g) was suspended in MeOH (8 mL), and then a solution of **4.113** (0.371 g, 1.78 mmol) in MeOH (2 mL) was added. The heterogeneous mixture was stirred at room temperature and the atmosphere of the reaction mixture was exchanged for H_2 using a balloon equipped with a needle adapter. The slurry was stirred for 5 h at room temperature. The crude reaction mixture was diluted with EtOAc (10 mL) and filtered through Celite. The filtrate was concentrated *in vacuo* to afford pure **4.115** (0.270 g, 99%) as a colorless oil that solidified on standing.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.13 (t, *J* = 7.8 Hz, 1H), 6.73-6.65 (m, 2H), 6.60 (d, *J* = 7.8 Hz, 1H), 4.55 (dd, *J* = 7.8, 4.2 Hz), 3.68 (bs, 2H), 3.49 (s, 2H), 3.00 (dd, *J* = 12.6, 4.2 Hz, 1H), 2.80 (dd, *J* = 13.0, 7.8 Hz, 1H).



5-(3-Aminophenyl)oxazolidin-2-one (4.116)

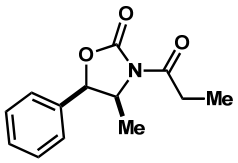
A solution of **4.114** (0.270 g, 1.77 mmol) was dissolved in anhydrous THF (10 mL). Ethyl 1*H*-imidazole-1-carboxylate (0.250 g, 1.77 mmol) was added dropwise at room temperature and the

resulting mixture was stirred for 24 h. An aliquot from the reaction was removed, concentrated *in vacuo*, and analyzed by ^{1}H-NMR, indicating that **4.114** had been completely consumed. The reaction was quenched with 1 M HCl (10 mL) and the aqueous mixture was extracted with DCM (3 x 20 mL). The pooled organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to afford the intermediate carbamate **4.115** as a yellow syrup. This crude material was redissolved in anhydrous THF (13 mL) and then KO^{t}Bu was added (1.0 M solution in THF, 1.25 mL) at room temperature. The resulting heterogeneous orange mixture was stirred for 3 h, during which time the reaction mixture became gelatinous. The reaction was quenched with sat. NH_4Cl and the mixture extracted with DCM (3 x 20 mL). The pooled organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to afford a pale yellow oil, which was purified by column chromatography (EtOAc) to yield **4.116** as a pale yellow syrup (0.201 g, 90%).

^{1}H NMR (600 MHz, $CDCl_3$ + $(CD_3)_2CO$, 4:1) δ 6.99 (t, *J* = 7.7 Hz, 1H), 6.60 – 6.45 (m, 3H), 5.97 (s, 1H), 5.35 (t, *J* = 8.1 Hz, 1H), 3.86 (s, 2H), 3.79 (t, *J* = 8.7 Hz, 1H), 3.35 (t, *J* = 8.2 Hz, 1H).

^{13}C NMR (151 MHz, $CDCl_3$ + $(CD_3)_2CO$, 4:1) δ 159.3, 147.1, 139.7, 129.4, 114.8, 114.7, 111.4, 77.4, 47.9.

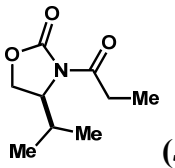
HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_9H_{11}N_2O_2^+$, 179.0815; found, 179.0815.



(4*S*,5*R*)-4-methyl-5-phenyl-3-propionyloxazolidin-2-one (4.103)

Prepared from (4*S*,5*R*)-4-methyl-5-phenyloxazolidin-2-one and **4.81** using Representative Procedure A.

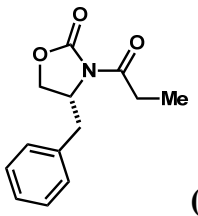
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 – 7.34 (m, 3H), 7.34 – 7.28 (m, 2H), 5.67 (d, *J* = 7.3 Hz, 1H), 4.77 (p, *J* = 6.8 Hz, 1H), 2.97 (app qq, *J* = 17.8, 7.4 Hz, 2H), 1.19 (t, *J* = 7.3 Hz, 3H), 0.90 (d, *J* = 6.6 Hz, 3H). Spectra were consistent with those reported previously.[56]



(*S*)-4-isopropyl-3-propionyloxazolidin-2-one (4.104)

Prepared from (S)-4-isopropyloxazolidin-2-one and **4.81** using Representative Procedure A.

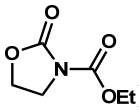
^{1}H NMR (500 MHz, $CDCl_3$) δ 4.45−4.40 (m, 1H), 4.29 – 4.18 (m, 2H), 3.03 – 2.85 (m, 2H), 2.42 – 2.32 (m, 1H), 1.16 (t, *J* = 7.4 Hz, 3H), 0.92 (d, *J* = 7.0 Hz, 3H), 0.87 (d, *J* = 7.0 Hz, 3H). Spectra were consistent with those reported previously.[57]



(*R*)-4-benzyl-3-propionyloxazolidin-2-one (4.105)

Prepared from (R)-4-benzyloxazolidin-2-one and **4.81** using Representative Procedure A.

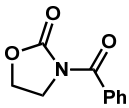
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.31 (m, 2H), 7.31 – 7.27 (m, 1H), 7.24 – 7.18 (m, 2H), 4.67 (ddt, *J* = 10.5, 7.4, 3.2 Hz, 1H), 4.26 – 4.15 (m, 2H), 3.31 (dd, *J* = 13.3, 3.3 Hz, 1H), 3.07 – 2.87 (m, 2H), 2.77 (dd, *J* = 13.3, 9.7 Hz, 1H), 1.21 (t, *J* = 7.3 Hz, 3H). Spectra were consistent with those reported previously.[58]



Ethyl 2-oxooxazolidine-3-carboxylate (4.106)

Prepared from oxazolidin-2-one and **2.30** using Representative Procedure A.

^{1}H NMR (500 MHz, CDCl3) δ 4.32 (t, *J* = 8.0 Hz, 2H), 4.25 (q, *J* = 7.1 Hz, 2H), 3.96 (t, *J* = 8.0 Hz, 2H), 1.27 (t, *J* = 7.1 Hz, 3H). Spectra were consistent with those reported previously.[59]

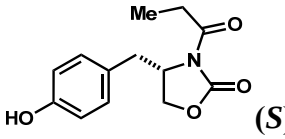


3-benzoyloxazolidin-2-one (4.107)

Prepared from oxazolidin-2-one and **1.94** using Representative Procedure A.

^{1}H NMR (500 MHz, CDCl3) δ 8.00-7.41 (m, 5H), 4.55-4.44 (m, 2H), 4.30-3.91 (m, 2H)

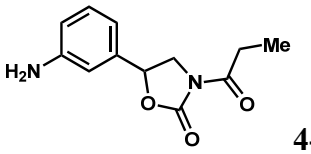
Spectra were consistent with those reported previously.[60]



(*S*)-4-(4-hydroxybenzyl)-3-propionyloxazolidin-2-one (4.108)

Prepared from (*S*)-4-(4-hydroxybenzyl)oxazolidin-2-one[61] and **4.81** using Representative Procedure A.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 (d, *J* = 8.3 Hz, 2H), 6.80 (d, *J* = 8.3 Hz, 2H), 5.18 (s, 1H), 4.63 (ddd, *J* = 12.5, 7.0, 3.0 Hz, 1H), 4.29 – 4.11 (m, 2H), 3.18 (dd, *J* = 13.5, 3.3 Hz, 1H), 3.07 – 2.85 (m, 2H), 2.73 (dd, *J* = 13.6, 9.3 Hz, 1H), 1.20 (t, *J* = 7.3 Hz, 3H). Spectra were consistent with those reported previously.[62]



4-(3-aminophenyl)-3-propionyloxazolidin-2-one (4.109)

Prepared from 4-(3-aminophenyl)-oxazolidin-2-one (**4.116**) and **4.81** using Representative Procedure A.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (t, *J* = 7.7 Hz, 1H), 6.71 – 6.60 (m, 3H), 5.45 (t, *J* = 8.1 Hz, 1H), 4.33 (dd, *J* = 11.1, 8.8 Hz, 1H), 3.92 – 3.70 (m, 3H), 2.95 (q, *J* = 7.3 Hz, 2H), 1.16 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 174.0, 153.1, 147.1, 138.4, 130.0, 115.6, 115.1, 111.5, 74.8, 49.7, 28.8, 8.2.

IR (film) ν_{max} 3459, 3370, 2980, 2941, 1778, 1701 cm^{-1}

HRMS-EI (*m/z*): M^+ calcd for $C_{12}H_{14}N_2O_3$, 234.1004; found, 234.1010.

4.8 Notes and References

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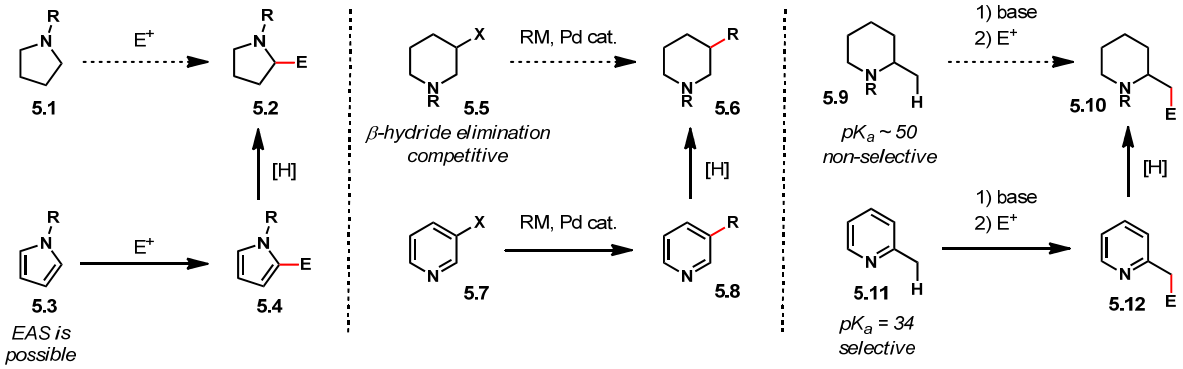
Chapter 5. Study and Synthesis of Benzindolizinones: Applications to Alkaloid Synthesis

5.1 Introduction

The ability to imbue hydrocarbon rings with varied physicochemical properties by heteroatomic substitution has led to the widespread adoption of heterocyclic motifs in functional materials such as pharmaceuticals and polymers. The ability to tune these properties also underpins many strategies in organic synthesis. As such, the synthesis and study of heterocycles has long been a central activity in organic chemistry. The fruits of this labor are a vast literature describing an enormous variety of heteroatomic ring systems — some of which are so common they are incorporated into introductory organic chemistry courses, while others are quite exotic. Yet of the nearly limitless possible structural arrangements, nitrogen-containing ring systems hold privileged status in medicinal and natural-products chemistry. For instance, alkaloids continue to serve as a platform for the in-depth study of many heterocyclic intermediates, leading to fundamental contributions on, for example, the reactivity of pyridines, indoles and pyrroles.[1] Indeed, these heteroaromatic systems, which have reactivity and physical properties differing substantially from their saturated counterparts, have been used with profound effect in the synthesis of complex molecules.

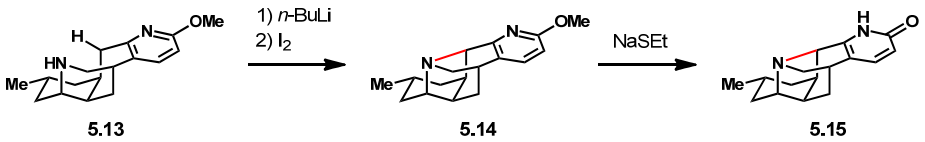
Myriad strategies exist that exploit these reactivity differences, but three approaches in particular have found their way into the basic lexicon of organic synthesis. The use of electron-rich aromatic azacycles such as pyrroles (**5.3**) allows for facile C-C bond construction through electrophilic aromatic substitution (EAS). Though an additional reduction step must be introduced in this strategy, the overall effect can be greatly simplifying in the synthesis of complex saturated heterocycles (**5.2**).[2] Similarly, C-C bonds may be forged through powerful transition metal catalyzed cross-coupling reactions; however, in many cases sp^3-hybridized carbon-halogen groups (as in **5.5**) have remained challenging substrates for this transformation due to the facile β-hydride elimination of intermediate organometallic species as well as slow oxidative addition to alkyl halides.[3] On the other hand, the use of heteroaromatic halides (**5.7**) in cross-coupling reactions is well-documented.[4] Finally, the dramatic acidity differences between pseudobenzylic C-H groups of electron-poor heterocycles (i.e., 2-picoline, **5.11**) and unconjugated C-H groups allow for easy deprotonation and functionalization at an otherwise remote position (see **5.9**).[5] As before, coupling with a reduction step allows for quick access to complex saturated azacyclic systems.

Scheme 5.1. Common Applications of Aromatic Heterocycles in the Synthesis of Saturated Azacycles



The use of heteroaromatic systems to install saturated or highly basic heterocycles is also a well-worn paradigm in the synthesis of complex natural products, especially alkaloids. One advantage conferred by this strategy is the ease of handling of many heteroaromatic amines. As described above, the aromaticity of these systems can also capacitate bond-forming processes not available to their non-aromatic congeners. For instance, our group has exploited the acidity of the picolinic position of 2-methoxypicolines (see **5.14**) to secure a strategically important C-N bond at a late stage in the synthesis of Lyconadin A (**5.15**).[6]

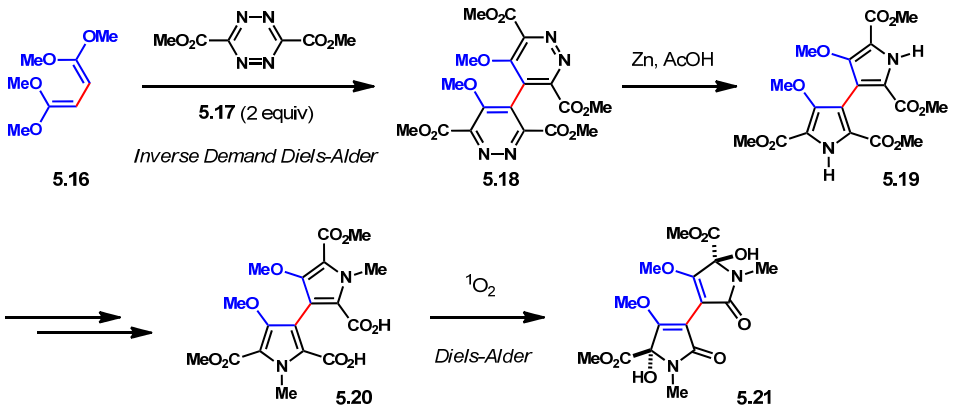
Scheme 5.2. Total Synthesis of Lyconadin A using a Key Lateral Deprotonation Step



The rich, but sometimes esoteric, chemistry of aromatic nitrogen heterocycles can be leveraged in order to effect powerful reorganizations of the carbon framework of complex molecules. In particular, the ability of some of these systems to undergo cycloaddition reactions involving C-C bond formation has been harnessed in the synthesis of alkaloid natural products.

The Boger synthesis of the dimeric bis-pyrrole natural product, isochrysohermidin (Scheme 5.3, **5.21**), utilizes such a strategy to translate a challenging homodimerization transform (see bond in red) into a much more tractable diene synthesis (see **5.16**) by exploiting the chemistry of tetrazines (**5.17**).[7] These azacycles are excellent dienes for inverse electron demand Diels-Alder reaction, and the product diazenes (**5.18**) are readily reduced to bis-imines (not shown) that intercept the Paal-Knorr pyrrole synthesis. Thus the requisite pyrrole (**20**) could be installed from an accessible diene through sequential manipulation of heteroaromatic systems. Additionally, the lactam groups found in **5.21** were generated by recognition that pyrroles participate in Diels-Alder cycloadditions with singlet oxygen. The Boger synthesis of **21** is a *tour de force* of the manipulation of aromatic heterocycles in the service of alkaloid synthesis.

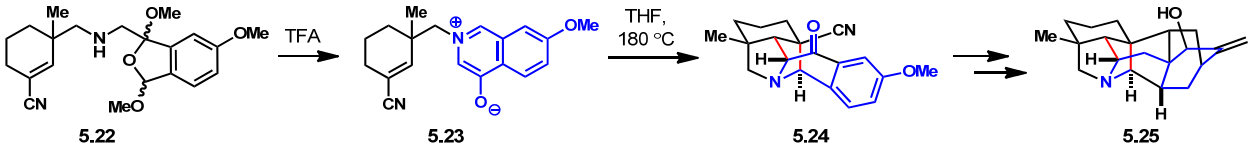
Scheme 5.3. Boger's Synthesis of Isochrysohermidin



However, the power of this logic is perhaps best conveyed in the total synthesis of nominine (Scheme 5.4, **5.25**) by Gin, in which the innate reactivity of a dipolar compound (**5.23**) was used to generate the congested core of **5.25**. In this case, an aromatic amine was used as a

platform by which a saturated azacycle could be installed using chemistry unavailable to a saturated heterocycle.[8]

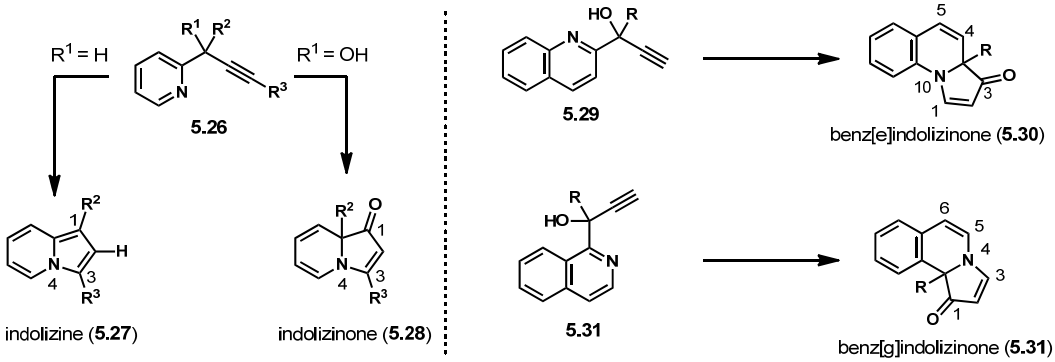
Scheme 5.4. Gin's Synthesis of Nominine



Coincidentally, the same physical properties that make saturated azacycles difficult to manipulate also make them ideal substructures in pharmaceutical compounds. For example, 68% of the 40 best-selling drugs in 2010 contain an aliphatic azacycle (90% contain some sort of amine).[9] In the arena of medicinal chemistry, modulation of basicity, lipophilicity, and three-dimensional structure is achieved in part through the use of heteroaromatic amines such as pyridines, pyrazoles, and imidazoles.[10] However, the use of a relatively small number of heterocyclic substructures has led to congested intellectual property space, impeding the development of new therapeutics. In an attempt to circumvent this issue, new functional groups have been developed and hitherto under-appreciated ring systems adopted.

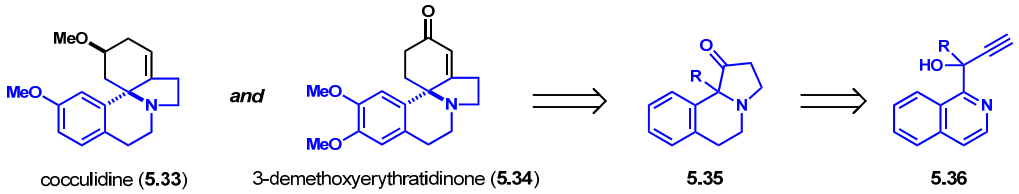
To this end, we have been interested in the development of practical methods to access promising but understudied heterocycles. Stemming from our work on the metal-catalyzed cycloisomerization of 2-propargylpyridine substrates (Scheme 5.5, **5.26**) to indolizines (**5.27**) and indolizinones (**5.28**),[11] we wondered whether the stability and physicochemical properties of these systems could be beneficially modulated through benzannulation, giving rise to what we colloquially refer to as "benzindolizinones". Of course, multiple isomers are possible, but we restricted our study to benz[e]indolizinones (**5.30**) and benz[g]indolizinones (**5.32**) that would be derived from quinolines (**5.29**) and isoquinolines (**5.31**) respectively.

Scheme 5.5. Cycloisomerizations Leading to Indolizines and Their Derivatives



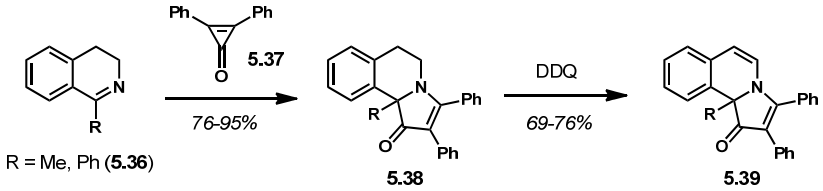
This exploration was also motivated by the observation that the *Erythrina* alkaloids, a prominent class of natural products, contained a nearly intact tetrahydrobenz[g]indolizinone core (Scheme 5.6, **5.35**, core in blue). Drawing on the synthetic logic described above, facile preparation of unsaturated benzindolizinone scaffolds from simple aromatic heterocycles might allow for the efficient synthesis of 3-demethoxyerythratidinone (**5.34**) and cocculidine (**5.33**), two representative members of this family of alkaloids, by utilizing the unique reactivity of a heteroaromatic system such as **5.31** in order to potentiate unconventional retrosynthetic disconnections (*vide infra*).

Scheme 5.6. Logic for the Use of Benzindolizinones in the Synthesis of Erythrina Alkaloids



Surprisingly, prior to our studies, only a single report of a benz[g]indolizinone has appeared in the literature. In 1986, Eicher demonstrated that diphenylcyclopropenone (Scheme 5.7, **5.37**) reacted with 3,4-dihydroisoquinolines (**5.36**) to afford 5,6-dihydrobenzindolizinones (see numbering system in Scheme 5.5, **5.38**), which could be oxidized by DDQ to afford simple benz[g]indolizinones (**5.39**).[12] Though this sequence is high yielding, it is severely limited by the availability of cyclopropenones. Since this initial report, the benz[g]indolizinone nucleus has lain dormant.

Scheme 5.7. Eicher's Synthesis of a Benz[g]indolizinone

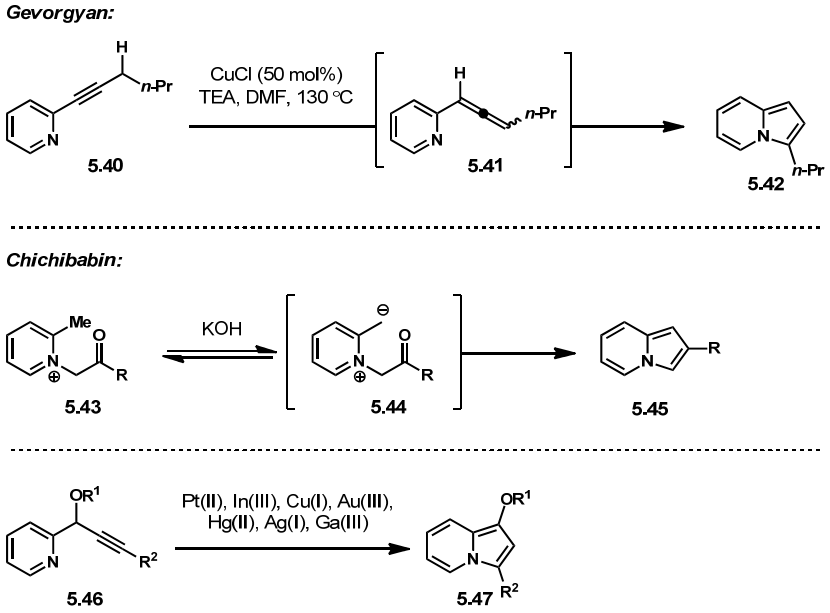


Similarly, the isomeric benz[e]indolizinone (e.g., **5.30**) has received little attention. Our group demonstrated one example of Pt(II)-catalyzed cycloisomerization of a propargyl quinoline carbinol (**5.29**), and Liu and coworkers showed that Cu(I)-catalysis effects the same cycloisomerization on a single quinoline substrate (*vide infra*).[13] Given this precedent, as well as earlier work by Gevorgyan and others, transition metal catalysis seemed like a promising tactic in our campaign to develop robust routes to the benzindolizinone cores.

5.2 Synthesis of Indolizines and Indolizinones: A Point of Embarkation

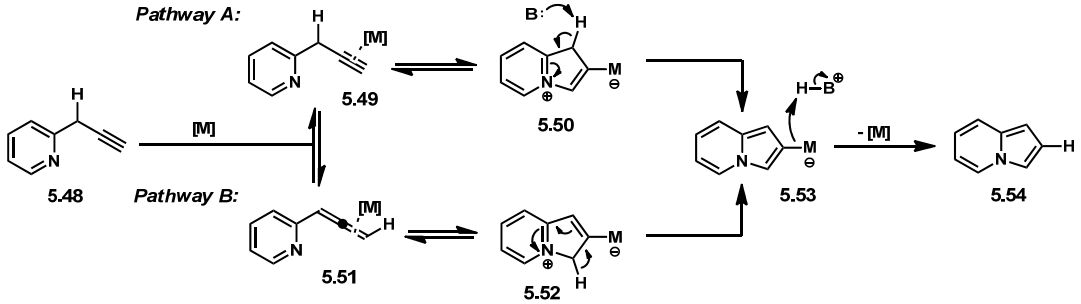
In 2001, Gevorgyan reported that Cu(I) salts promote the cycloisomerization of alkynyl pyridines (Scheme 5.8, **5.40**) to the corresponding indolizines (**5.42**) by an allene intermediate (**5.41**).[14] Prior to this work, the only widely applicable route to this intriguing heterocyclic motif was the Chichibabin synthesis in which pyridinium salts such as **5.43** could be cyclized under basic conditions. The confluence of Gevorgyan's initial disclosure and the emerging field of π-acid activation of alkynes[15] resulted in a large number of reports detailing cycloisomerization approaches to indolizines with a variety of metals, including Ag(I),[16] Au(III),[17] and Cu(I) salts.[18] In 2007, our group reported both Pt(II)- and In(III)-catalyzed transformations yielding 1-alkoxyindolizines (**5.47**)[19] as well as the isomeric 2-alkoxyindolizinones.[20]

Scheme 5.8. Strategies for the Synthesis of Indolizines

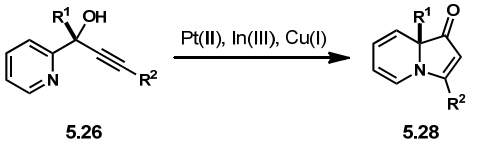


While detailed mechanistic analysis of these metal-catalyzed cyclizations has remained unrealized, two distinct possibilities have been marshaled in the literature. In both cases, initial association of the metal catalyst to the alkyne would provide η^2 metal-alkyne complex **5.49** (Scheme 5.9). In one pathway, the pyridine nitrogen could then engage in 5-*endo*-dig cyclization to afford zwitterion **5.50** and rearomatization could then be achieved through a proton transfer pathway. Alternatively, **5.49** could isomerize to a metal-bound allene (**5.51**), which could then undergo cyclization and proton transfer.[21]

Scheme 5.9. Possible Mechanisms for the Metal-Catalyzed Cycloisomerization of Propargylpyridines



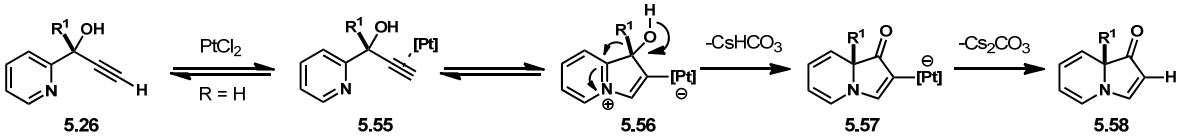
We were also interested in the reaction of alkynylpyridine substrates in which a C-C bond migration rather than the loss of a proton might be possible. The lack of benzylic hydrogens in a suitable substrate would preclude alkyne-allene isomerization, and thus would provide incidental support for the feasibility of pathway A in the indolizine cycloisomerization. In the event, treatment of pyridine-containing propargylic carbinols (i.e., **5.26**, eq 1) with a Pt(II)-catalyst along with catalytic amounts of cesium carbonate led to the formation of indolizinones (**5.28**), a relatively unexplored heterocyclic motif.[22]



5.26 5.28 (1)

As in the Pt(II)-catalyzed indolizine synthesis, we believe that the reaction proceeds by initial coordination of the alkyne (Scheme 5.10, **5.55**), which is activated as an electrophile. Addition of the pyridine nitrogen in a 5-*endo*-dig fashion would then yield vinylplatinum species **5.56**. Rather than a subsequent cleavage of a C-H bond to generate the heteroaromatic system, an α-hydroxyimine rearrangement (a variant of the α-ketol rearrangement) could then take place, shifting the acyclic carbon group (R^1) to the ring fusion carbon and generating platinated indolizinone **5.57**. Finally, protodeplatination would lead to the desired heterocycle (**5.58**).

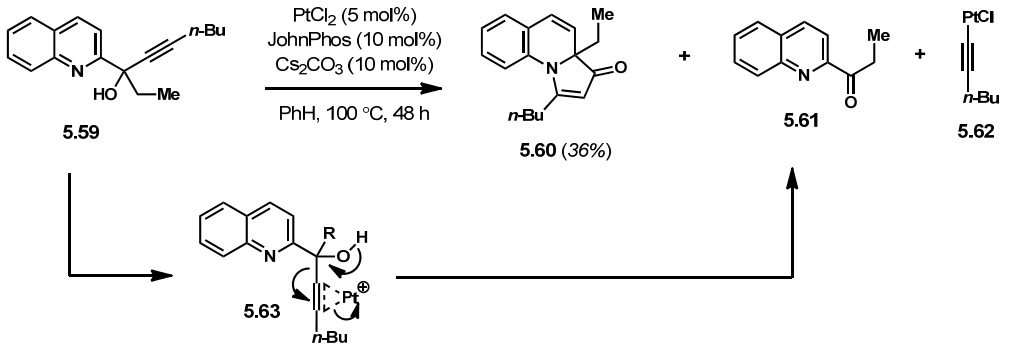
Scheme 5.10. Possible Mechanism for Indolizinone Formation Involving a Wagner-Meerwein Shift



5.26 5.55 5.56 5.57 5.58

While platinum catalysis provided rapid access to both indolizines and indolizinones, a number of significant limitations plagued this strategy. Terminal alkynes (R^2 = H) were poor substrates, presumably due to their ability to undergo facile Pt(II)-acetylide formation. Furthermore, these cycloisomerizations required long reaction times as well as an expensive metal and ligand set. However, most significantly, benzannulated substrates (see **5.59**, Scheme 5.11) seemed to undergo loss of the alkyne group to provide a ketone as the major product. We tentatively propose that, rather than engagement of the pyridine nitrogen, the η^2-alkynylplatinum complex (**5.63**) undergoes a retro-acetylide addition to generate a ketone (**5.61**) and platinium(II)-acetylide (**5.62**), which is protonated *in situ*.

Scheme 5.11. Failure of Pt(II)-Catalysis in Benzannulated Cycloisomerization Substrates

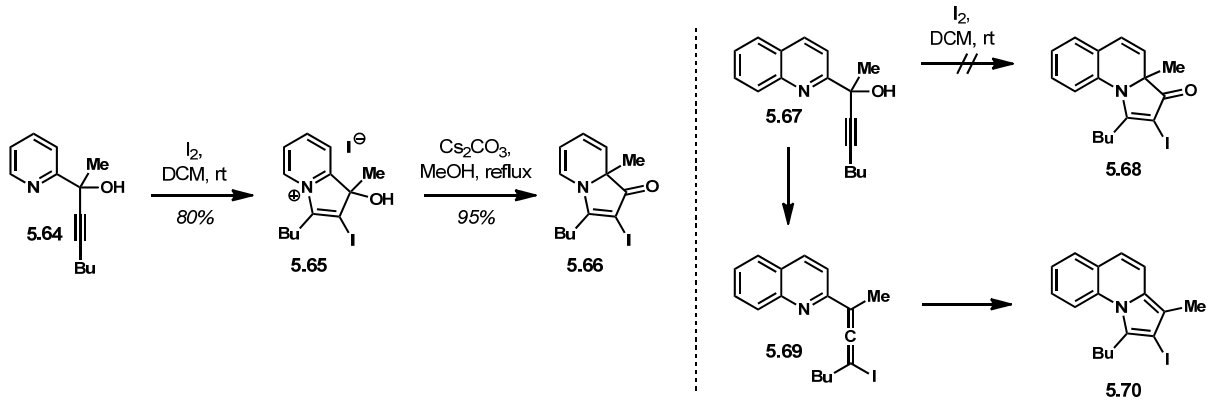


5.59 5.60 (*36%*) 5.61 5.62 5.63

Non-metal π-acids have also been applied to the synthesis of indolizinones from pyridine carbinols. For instance, Kim showed that the interaction of molecular iodine and pyridine carbinols (Scheme 5.12, **5.64**) gave rise to iodopyridinium salts (**5.65**), which could be transformed to 2-iodoindolizinones by heating in basic alcoholic media.[23] However, this strategy failed to provide benz[e]indolizinones, instead giving rise to benz[e]indolizines (**5.70**), in which

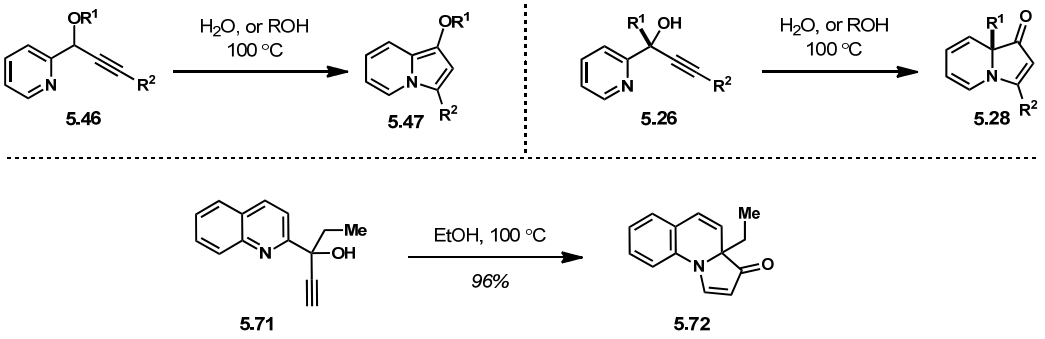
the hydroxyl group had been lost. The mechanism of this surprising transformation is unknown, but was proposed to proceed through an allenyl iodide (**5.69**).

Scheme 5.12. Iodine-Mediated Synthesis of 2-Iodoindolizinones



Because of the recalcitrance of benzannulated substrates (i.e., **5.64**) to participate in cycloisomerization reactions under the conditions that afford the corresponding indolizinones, we sought to apply another cycloisomerization strategy developed in our lab – the protic solvent promoted cyclization of pyridyl propargylic carbinols – to access benzindolizinones. Concurrent with the Kim group, we discovered that simply heating alkynylpyridines such as **5.46** or **5.26** (Scheme 5.13) in protic solvents effects efficient cycloisomerization to indolizines (**5.47**) and indolizinones (**5.28**) respectively.[24] While this result was surprising, it became clear that in many respects the solvent-promoted cyclization was superior to any of the reported metal-catalyzed processes. Importantly, terminal alkynes were well-tolerated, indeed, they were the best substrates for the so-called "metal-free" cycloisomerization. Proof-of-concept that this tactic could be used in the synthesis of benzindolizinones was obtained when quinoline carbinol **5.71** was cleanly converted to benzindolizinone **5.72** by heating in ethanol. We then embarked on an exploration of the scope of this method to access benzindolizinones.

Scheme 5.13. The Protic Solvent-Mediated Cycloisomerization

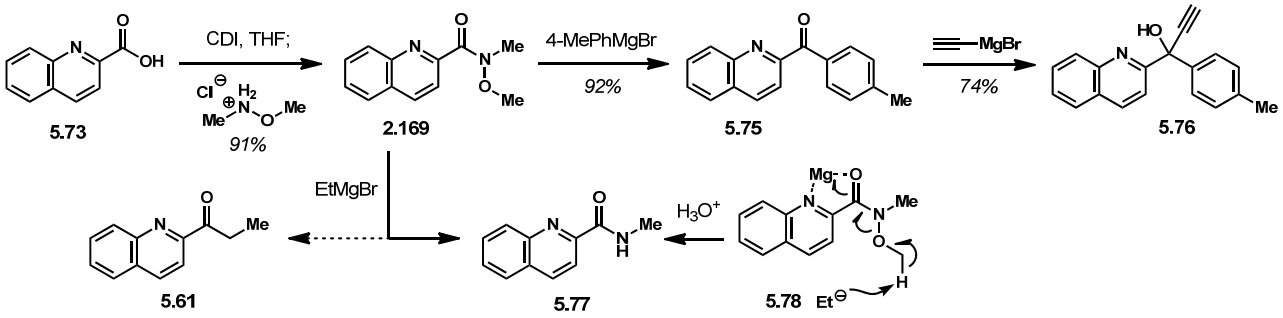


5.3 Substrate Synthesis

Preparation of the tertiary alcohol cycloisomerization substrates commenced with conversion of quinaldic acid (Scheme 5.14, **5.73**) into Weinreb amide **2.169** using a CDI-mediated amidation. This transformation could also be achieved by heating **5.73** with WImC

(see Chapter 2); however, this was not cost-effective on scale up. Addition of arylmagnesium halides (i.e., *p*-tolylmagnesium bromide) to **5.75** was uneventful. However, treatment of **2.169** with sp^3-Grignard reagents led predominantly to benzamide **5.77**. Reductive cleavage of the N-O bond of Weinreb amides has been documented in sterically congested systems with Grignard reagents or by treatment with strong Lewis acids in the presence of amine bases.[25] In both cases, it has been shown that net reduction occurs through deprotonation of the methoxy group, followed by elimination of formaldehyde to generate the stabilized amide anion. This process has not been documented in cases involving sterically unencumbered nucleophiles, but we reasoned that the ring nitrogen may allow for the formation of a magnesium chelate (**78**), which could greatly stabilize the amide anion resulting from N-O bond cleavage. Presumably sp^2-Grignard reagents do not effect this reduction because of their reduced basicity.

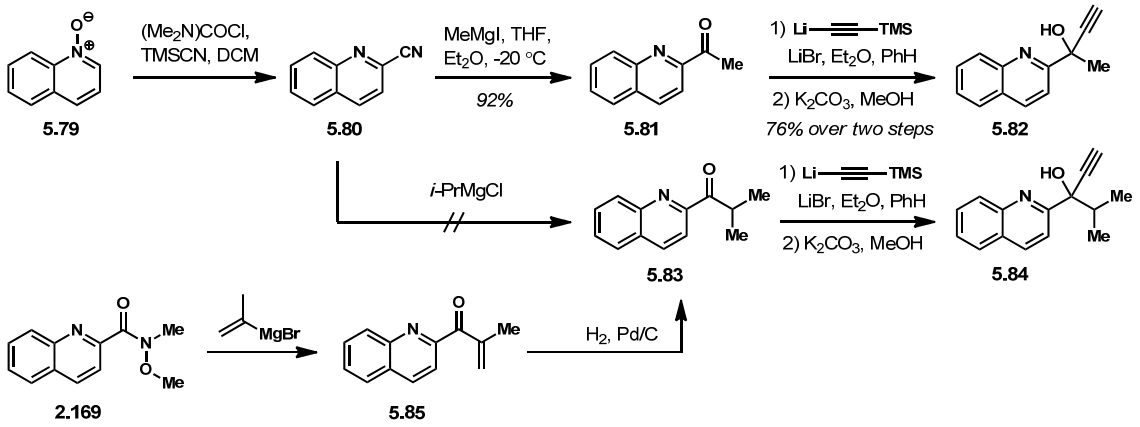
Scheme 5.14. The Use of Weinreb Amides in the Synthesis of Quinoline Carbinol Substrates



In order to avoid the undesired reduction process, 2-cyanoquinoline (**5.80**, Scheme 5.15) was employed as an electrophile with sp^3-Grignard reagents. Addition of sterically unencumbered organomagnesium nucleophiles cleanly afforded quinoline ketones such as **5.81**. Adapting a strategy developed in our lab for the addition of acetylides to 2-pyridylketones, propargylic carbinols such as **5.82** could be prepared using lithium acetylides in the presence of a large excess of lithium bromide in non-polar, less-coordinating solvents.

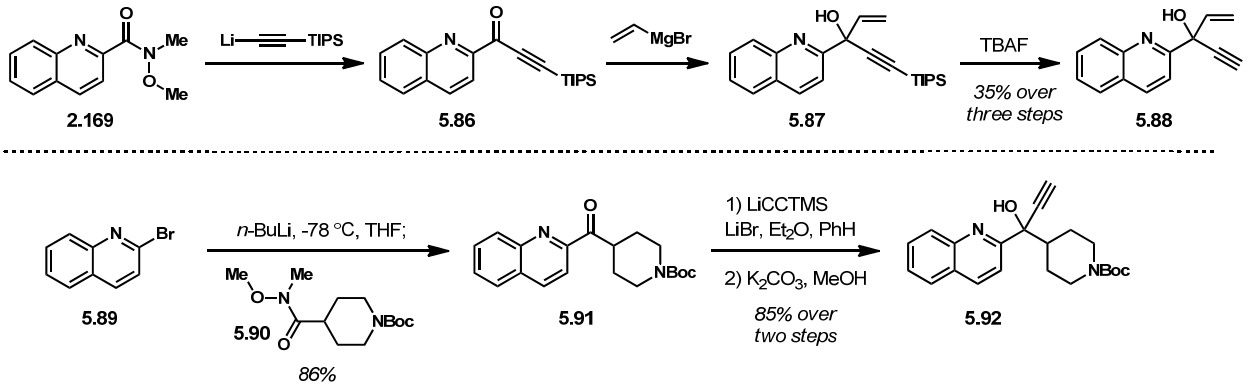
Unfortunately, α-branched ketones (e.g., **5.83**) could not be synthesized using this approach, as a complex mixture of ring addition products was obtained when **5.74** was treated with sterically encumbered Grignard reagents. Instead, an indirect route to these substrates was developed that exploited the clean reaction of sp^2-organomagesium species with Weinreb amides. In the event, 2-propenylmagnesium bromide was coupled with **2.169** and the crude product was immediately hydrogenated to afford ketone **5.83**.[26] Acetylide addition was then accomplished using the strategy described above to provide **5.84**, albeit in lower yield.

Scheme 5.15. Alternative Strategies for the Synthesis of Alkyl Quinoline Ketones



Even though the most direct route to a diverse set of quinoline carbinols would be through an ynone (e.g., **5.86**, Scheme 5.16), it was found that **5.86** was unstable on prolonged storage and that the overall yield of the route was too low for subsequent adoption in the synthesis of other substrates. Reversal of the polarity of the ketone synthesis was also explored using 2-lithioquinoline (generated from 2-bromoquinoline) and an appropriate Weinreb amide such as **5.90**. While this strategy was successfully applied to the synthesis of **5.92**, it was not cost-effective for other substrates.

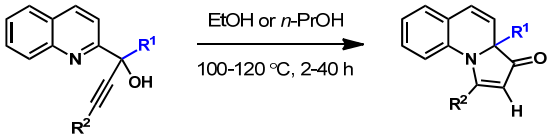
Scheme 5.16. Even More Substrate Syntheses

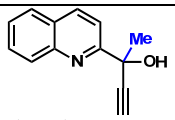
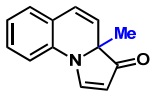
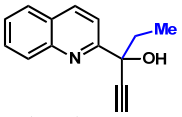
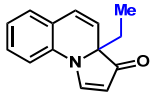
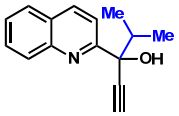
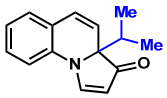
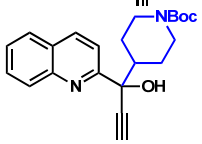
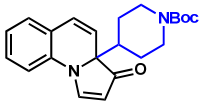
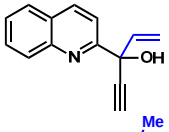
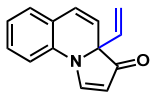
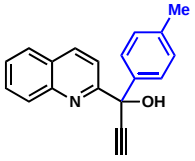
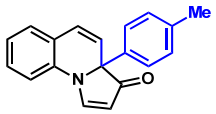
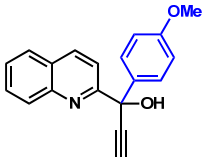
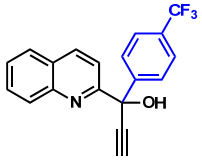
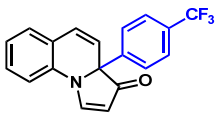
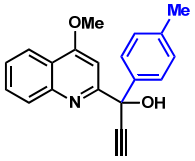
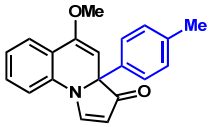
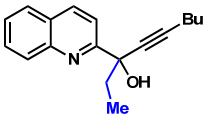
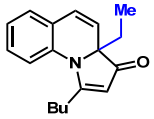


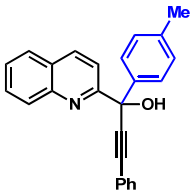
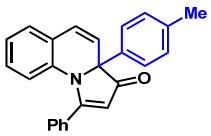
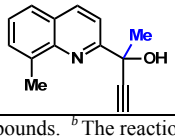
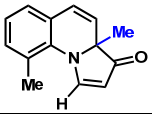
5.4 Synthesis of Benz[e]indolizinones

With a range of tertiary propargylic carbinols in hand, the scope of the solvent-promoted cycloisomerization was explored. The reaction was generally high-yielding and provided clean benzindolizinone products. Aliphatic migrating groups were well-tolerated, but required several hours at 100 °C to reach completion (Table 5.1). Cyclization of substrates with aryl migrating groups were appreciably faster; however, little difference was observed between electron-rich and electron-poor aryl groups. Heating enyne carbinol **5.88** in ethanol led to a single product arising from cycloisomerization with the alkyne group to yield **5.101**. Subsequent investigation showed that alkenes do not participate in the cycloisomerization reaction even when heated to 190 °C in *n*-butanol. Finally, substituents on the parent quinoline were readily incorporated into the benz[e]indolizinone product (see **5.105**).

Table 5.1. Scope of Cycloisomerization Approach to Benz[e]indolizinones



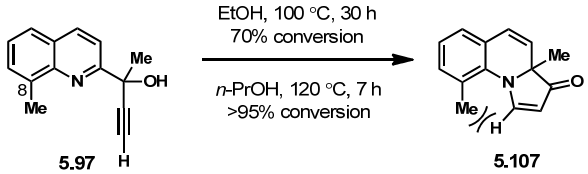
Entry	Substrate		Product		Time (h)	Yield (%)[a]
1		**5.82**		**5.98**	7	92
2		**5.71**		**5.72**	6	96
3		**5.84**		**5.99**	6	88
4		**5.92**		**5.100**	6	95
5		**5.88**		**5.101**	4	94
6		**5.76**		**5.102**	2	93
7		**5.93**		**5.103**	2	91
8		**5.94**		**5.104**	2	94
9		**5.95**		**5.105**	2	93
10		**5.59**		**5.60**	40	91[b]

11		**5.96**		**5.106**	9	95[b]
12		**5.97**		**5.107**	7	87[b]

[a] Yields refer to isolated compounds. [b] The reaction was performed in *n*-PrOH at 120 °C.

Internal alkynes were competent substrates, but required significantly longer reaction times for full conversion. For instance, only 50% conversion to **5.60** was observed after heating to 100 °C in ethanol for 40 hours. Increasing the reaction temperature to 120 °C and using **5.59** *n*-propanol as solvent (due to its higher boiling point) allowed for complete conversion to **5.60**, albeit sluggishly. Arylalkynes such as **5.96** could also be used in the cycloisomerization, but required higher reaction temperatures.

The large difference in reactivity between terminal and internal alkynes was somewhat surprising, but was believed to be primarily driven by steric clashing between the C8-H and the distal group of the alkyne (R^2 in Table 5.1). To test this hypothesis, a terminal alkyne substrate with a group larger than hydrogen at C8 was synthesized and then subjected to the cycloisomerization conditions. Thus, **5.97** cycloisomerized only slowly at 100 °C but could be completely transformed at 120 °C in 7 hours (see eq 2). The retardation of cyclization observed in both **5.59** and **5.97** suggests that development of peri-strain (see **5.107**) in the transition state of the C-N bond-forming step, rather than an electronic difference between internal and terminal alkynes, is primarily responsible for the observed rate differences.

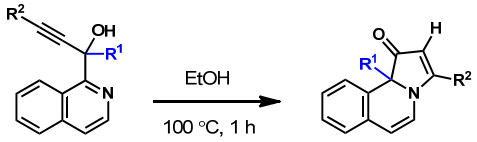


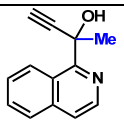
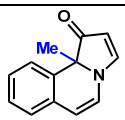
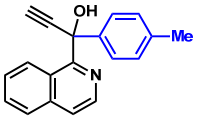
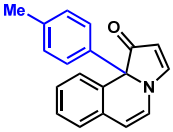
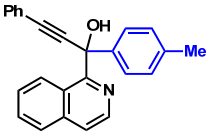
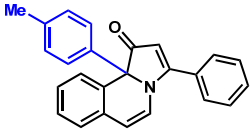
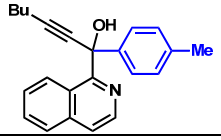
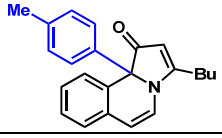
(2)

5.5 Synthesis of Benz[g]indolizinones

Application of the solvent-promoted cycloisomerization to isoquinoline propargylic carbinols was also explored to access the isomeric benz[g]indolizinone core. Substrates were prepared by analogy to the isomeric quinoline compounds; aryl and alkyl isoquinoline ketones could be prepared from isoquinoline-1-carboxylic acid or isoquinoline *N*-oxide respectively. Intriguingly, the cycloisomerization of **5.108** (Table 5.2) was found to be extremely facile, with complete conversion observed in less than one hour. In these cases, internal alkynes were found to react at qualitatively similar rates to terminal alkynes. Because there is no peri-interaction between substituents on the isoquinoline ring and the alkyne, this observation further supported our hypothesis that internal alkynes were challenging substrates in quinoline systems (see **5.59**) due to peri-strain buildup during cyclization.

Table 5.2. Scope of Cycloisomerization Approach to Benz[g]indolizinones



Entry	Substrate		Product		Time (h)	Yield (%)[a]
1		**5.108**		**5.112**	1	91
2		**5.109**		**5.113**	1	93
3		**5.110**		**5.114**	1	98
4		**5.111**		**5.115**	1	91

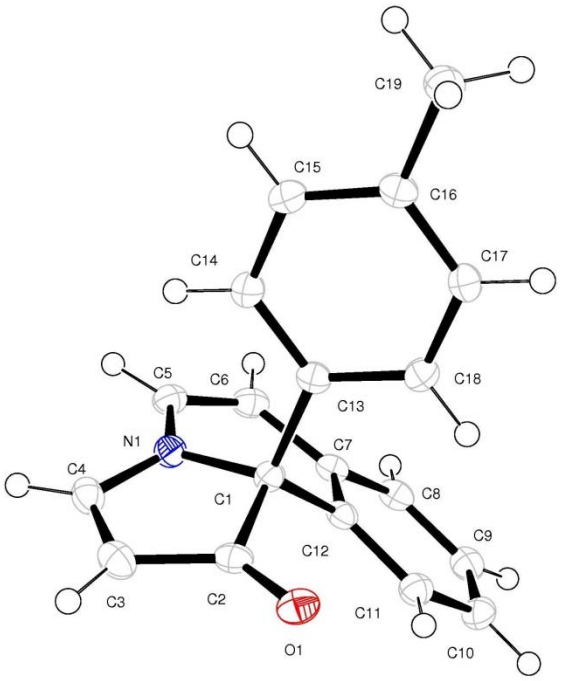
[a] Yields refer to isolated compounds.

The connectivity of the cycloisomerization products was confirmed by X-ray crystallographic analysis of **5.113** and the crystal structure (see Figure 5.1) was studied in order to gain a better understanding of the bonding in benz[g]indolizinones. Of particular interest was the qualitative bond order between the atoms comprising the dienamine portion of **5.113**. Unsurprisingly, the bond angles and distances about the nitrogen suggest that it is completely sp^2 hybridized. However, on the basis of the differing N^1-C^5 and N^1-C^4 bond lengths, the nitrogen participates more fully in the vinylogous amide π-system than it does with the styrenic enamine (C^5=C^6). This effect can also be observed by the relatively long C^3=C^4 bond and apparent shortening of the C^2-C^3 bond, reflecting some contribution from a charge-separated resonance structure of the vinylogous amide. Interestingly, the C^2=O^1 bond is longer than would be expected for a cyclopentenone, but neatly matches the average length of a γ-lactam.[27] Finally, the angular nature of the migrating group (*p*-tolyl in **5.113**) is put into stark relief in the crystal structure, and highlights the potential utility of benz[g]indolizinones in medicinal chemistry as they allow for simultaneous tuning of three-dimensional space filling interactions and modulation of the basicity of an amine nitrogen, a dualism that is essentially impossible with simple heteroaromatic motifs.

With facile access to both the benz[e]- and benz[g]indolizinone cores, we then turned our attention to the basic reactivity of these novel heterocycles. The benz[e]indolizinone system contains two electronically differentiated alkenes, so it was anticipated that the vinylogous amide would be the most nucleophilic of the pair, but would not participate in other classical reactions of alkenes. Indeed, when **5.102** (Scheme 5.17) was treated with *N*-iodosuccinimide (NIS), 3-iodobenz[e]indolizinone **5.116** was obtained as the sole identifiable product. The vinylogous amide could also be selectively reduced by sodium cyanoborohydride under acidic conditions to yield **5.118** as its high electron density renders C3 and the carbonyl oxygen unusually basic.

Alternatively, catalytic hydrogenation conditions led to selective reduction of the styrenic double bond of **5.102** and provided **5.117** in good yield.[28]

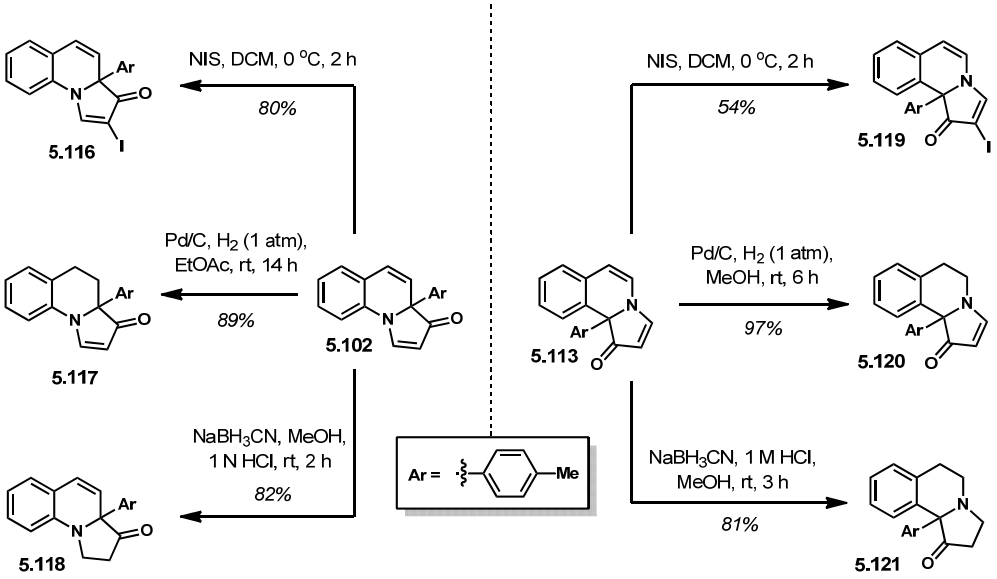
Figure 5.1. Crystal Structure and Selected Bond Lengths and Angles for Benz[g]indolizinone **5.113**



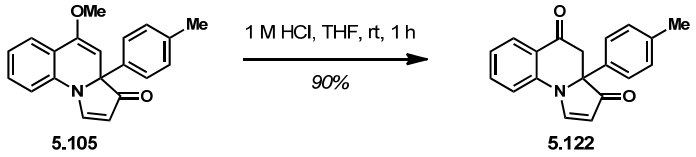
Bond	Length (Å)	Angle	(º)
C^5=C^6	1.3391	C^6-**C^5**-N^1	118.97
N^1-C^5	1.3886	C^5-**N^1**-C^1	120.69
N^1-C^4	1.3530	C^4-**N^1**-C^1	110.39
C^3=C^4	1.3585	N^1-**C^4**-C^3	112.93
C^2-C^3	1.4368	C^4-**C^3**-C^2	108.50
C^2=O^1	1.2277	C^3-**C^2**-C^1	106.20

However, as we have seen, the benz[g]indolizinone ring system contains two slightly differentiated enamines. As such, avenues for achieving chemoselective transformations were less obvious. Exposure of **5.113** to NIS led to iodination of the vinylogous amide to yield **5.119**, the structure of which was assigned by analysis of the coupling constants of the alkene protons. This finding supports the conclusion derived from the crystal structure of **5.113** that nitrogen lone pair participates more with the vinylogous amide system, making it more nucleophilic. Similarly, the styrenic enamine could be selectively hydrogenated under mild conditions to afford dihydrobenz[g]indolizinone **5.120**. Alternatively, ionic reduction of **5.113** led to tetrahydrobenz[g]indolizinone **5.121** when two equivalents of sodium cyanoborohydride were used. Efforts to selectively reduce the vinylogous amide double bond by tuning the amount of reductant were unsuccessful, leading instead to decomposition products. Interestingly, when triethylsilane was used as the reductant, only the styrenic enamine was reduced to afford **5.120** (the same product obtained from hydrogenation).

Scheme 5.11. Functionalization of Benzindolizinones



Functional groups could also be incorporated into the benzindolizinone scaffolds by employing the corresponding (iso)quinoline starting material. In turn, this functionality could be used as a synthetic handle to prepare compounds that would be difficult to access using other methods. For instance, **5.105** could be used as a surrogate for oxo-benz[e]indolizinone **5.122** as the enol ether derived from the cycloisomerization reaction could be easily hydrolyzed under acidic conditions (eq 3).



(3)

5.6 Mechanistic Considerations

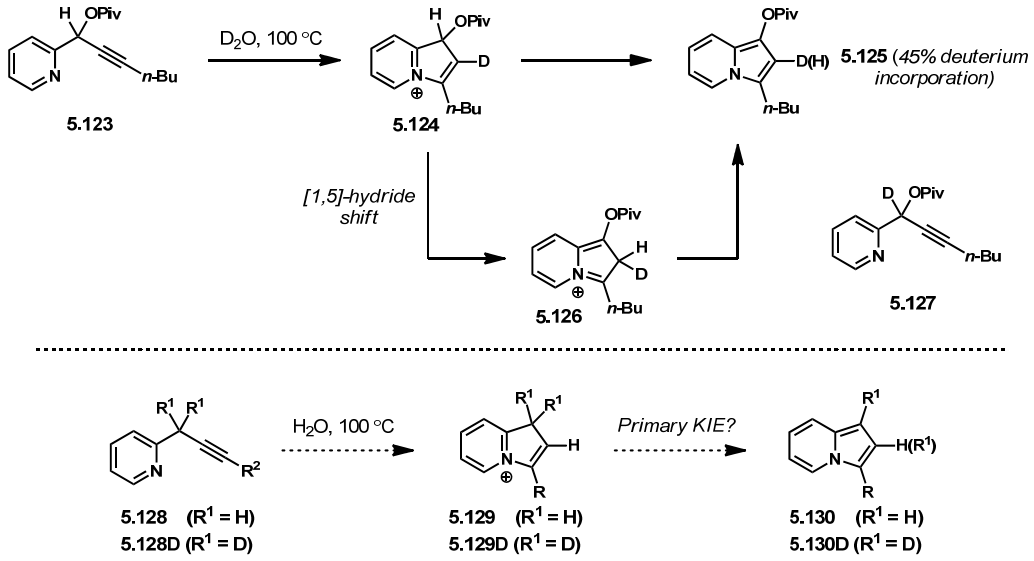
The protic solvent mediated cycloisomerization has proved to be a robust tactic in the preparation of indolizines, indolizinones, and benzindolizinones, yet very little is currently known about how the reaction proceeds. Nonetheless, we have been interested in elucidating the mechanism of these cycloisomerizations. Given the topological similarities between the solvent-mediated and Pt(II)-catalyzed reactions, we formulated a number of hypotheses aimed at explaining the observed differences between these two methods for the cycloisomerization of azacyclic propargylic carbinols, as well as between classes of carbinol substrates. Observations made in the course of scope studies (*vide supra*) that may be relevant to mechanistic studies on the solvent-promoted cycloisomerization are discussed below, as are preliminary experiments in the indolizine series. Experiments that may eventually shed light on the mechanistic details of this process are also proposed, but have not yet been performed.

Upon the discovery of the solvent-promoted cycloisomerization to prepare indolizines, we attempted to rationalize the reaction using a mechanistic framework derived from known metal-catalyzed processes (see Scheme 5.7). However, it was unclear whether a discrete

intermediate such as **5.50** formed, and if so, how it was consumed to provide the indolizine. We thus considered both a stepwise process that was analogous to metal-catalyzed reactions as well as some sort of concerted process in which cyclization and aromatization occur asynchronously. Preliminary studies involving deuterium labeling performed by Dr. Hardin-Narayan showed that a deuterated solvent gave rise to C2-D indolizines (Scheme 5.18, **5.125**).[29] The relatively low deuterium incorporation was puzzling and may be indicative of a mechanism in which a 1,5-hydride shift precedes deprotonation to afford the indolizine.[30] Gevorgyan considered a similar mechanism in a Ag(I)-catalyzed cycloisomerization to afford indolizines, but argued that another pathway was operative.[31]

With respect to the indolizine synthesis, we propose that more insight could be gained by subjecting a deuterated pyridine substrate (i.e., **5.128D**, R^1=D) to an H_2O-mediated cycloisomerization, where deuterium incorporation at C-2 could imply the intermediacy of **5.126**. Furthermore, we propose that measurement of the rate of cycloisomerization of bis-deuterated **5.128D** (R^1=D) relative to that of **5.128** (R^1=H) in parallel experiments could shed light on the process by which indolizines are formed by providing kinetic information. That is, if an absolute primary kinetic isotope effect (KIE) was observed, we could conclude that either a C-H bond breaking step prior to the rate determining step, perhaps through a reversible 1,3-hydride shift to form an allene from the propargyl group, was occurring or that the rate determining step of the cycloisomerization involved C-H/D bond breaking in **5.128**. Because we believe that a pre-rate determing step giving rise to a KIE is unlikely in this reaction, such an observation would implicate either aromatization by proton (deuteron) loss or a hydride (deuteride) shift as the rate determining step. Conversely, the absence of an observed KIE would exculpate a concerted process and suggest that initial cyclization was rate determining.

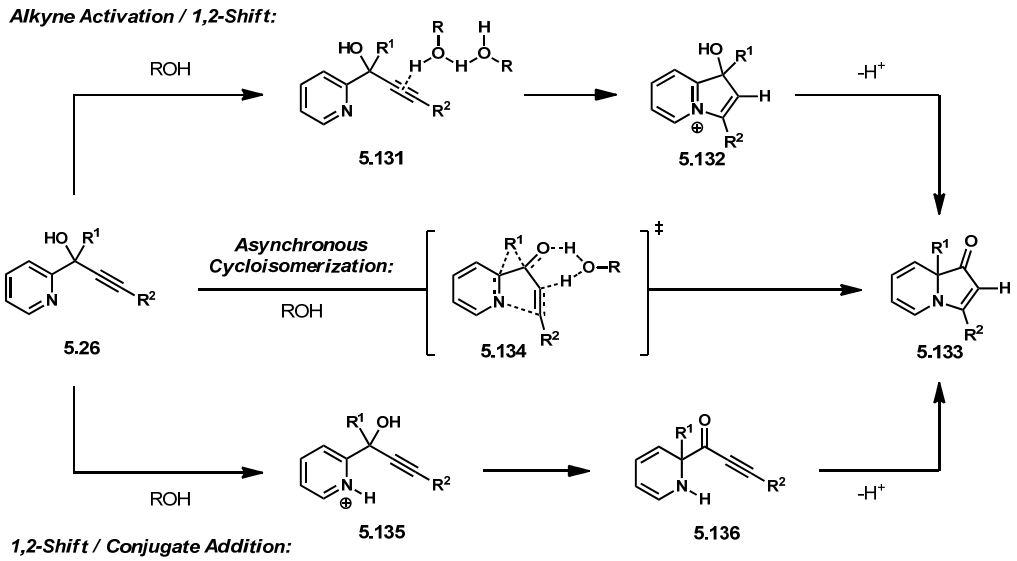
Scheme 5.18. Deuterium Incorporation During Solvent-Promoted Cycloisomerization



Regardless of the potential outcomes of the proposed isotope effects study, the finding that a deuterated solvent gave rise to C2-deuterated products such as **5.125** led us to hypothesize that the alkyne of **5.26** could interact with a solvent-based hydrogen bonding network (see **5.131**, Scheme 5.19), which would activate it as an electrophile. Cyclization by attack of the heterocyclic nitrogen would then give rise to zwitterion **5.132**. Subsequent loss of a proton

would then yield an indolizinone (**5.133**). However, the presence of a hydroxyl group in the pyridine substrate giving rise to indolizinones (see **5.26**) raised several possibilities that seemed unlikely in the indolizine system. For instance, the synthesis of indolizinones could potentially proceed through a concerted, but asynchronous cycloisomerization (see **5.134**). Finally, we cannot rule out the possibility that pyridine protonation occurs in the first step to yield a salt (**5.135**), which can undergo a 1,2-migration of the R^1 group. The ynone (**5.136**) so obtained could then undergo a conjugate addition to yield the indolizinone product.

Scheme 5.19. Potential Mechanisms of Solvent-Mediated Cycloisomerization



Our observations during substrate scope studies for the benzindolizinone synthesis have further piqued our curiosity about the mechanism(s) of cycloisomerization in these reactions, but so far have not provided unambiguous support for one of these hypotheses. The finding that quinoline-containing substrates (see **5.98**-**5.107**, Table 5.1) with aryl migrating groups showed very limited qualitative rate dependence on the migratory aptitude was surprising and seemed to suggest that, if the cycloisomerization is a two-step process, the 1,2-shift may occur after the rate determining step. On the other hand, some dependence on the nature of the migrating group was inferred from the fact that substrates with alkyl migrating groups were consumed at a significantly lower rate. These seemingly contradictory observations may instead point to a change of mechanism between substrates with aryl and alkyl migrating groups. It should be mentioned that careful kinetic analyses have yet to be performed, so small differences in overall reaction rate were not detected.

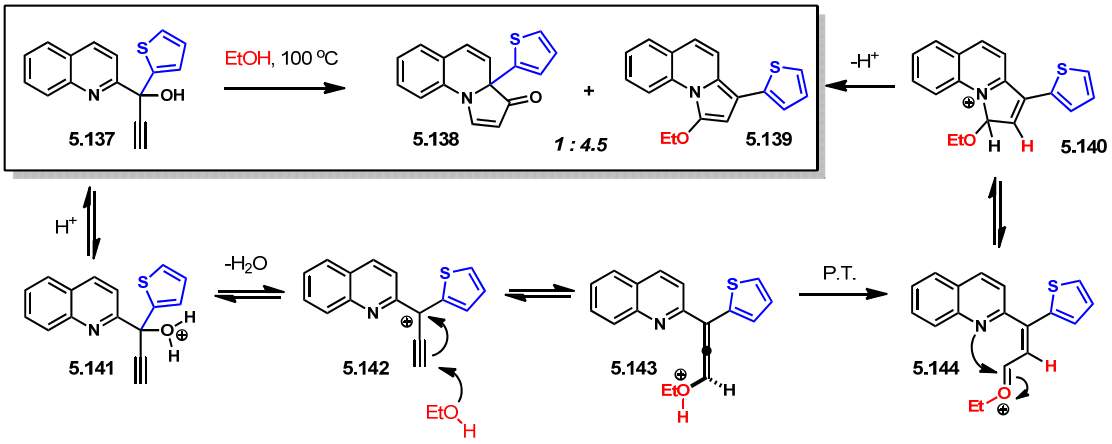
Despite the impact of the migrating group, it was clear that the parent heterocycle was playing an important role in the rate of cycloisomerization, as benz[g]indolizinones were generated more rapidly than benz[e]indolizinones from isomeric substrates (compare **5.108** and **5.82**). However, the exact nature of this influence was opaque. While quinoline and isoquinoline are of similar basicity (pK_as of conjugate acids = 4.85 and 5.46 respectively),[32] the former is substantially more aromatic than the latter.[33] Therefore, it may be the case that isoquinoline carbinols cyclize more rapidly than their quinoline isomers because the transition state leading to a benz[g]indolizinone is less affected by the loss of aromaticity than that leading to the benz[e]indolizinone. If this were the case, it would be expected that the relative reactivities of

the three heterocycles would descend in the order isoquinoline > quinoline > pyridine. On the other hand, steric interactions between the C8-group of the quinoline and the distal group of the alkyne may retard the cycloisomerization relative to that of pyridine, which does not experience a peri-interaction. Isoquinoline substrates experience a small interaction between the C8-group and the carbonyl formed in the cycloisomerization. Accordingly, we would expect to find that the order of reactivity would be pyridine > isoquinoline > quinoline. We propose that relative reactivities could be determined spectroscopically by subjecting three substrates that vary only in their parent heterocycle to the cycloisomerization reaction. Of course, both internal and terminal alkynes would need to be evaluated.

A major limitation to the scope of this solvent-promoted cycloisomerization is the formation of indolizine byproducts that have incorporated a solvent molecule, leading predominantly to the formation of benzindolizine products such as **5.139** (Scheme 5.20). While this is usually a trace byproduct, when the migrating group is sufficiently electron-rich, such as in thiophene carbinol **5.137**, ionization becomes facile and the benzindolizine (**5.139**) becomes the major product. A potential mechanism for this deleterious side reaction involves initial ionization of the carbinol to the propargylic carbocation (**5.142**), which could then be trapped by solvent to afford an alkoxyallene (**5.143**). Protonation at the sp-hybridized carbon would then lead to an oxocarbenium ion (**5.144**) that could engage the ring nitrogen to form **5.140**. Loss of a proton to rearomatize the ring system would then lead to benzindolizine **5.139**.

Initially, we reasoned that carbon dioxide dissolved in the solvent could acidify the mixture to make ionization to **5.142** favorable; however, neither careful degassing of the solvent prior to heating nor the addition of triethylamine had any discernible effect. The fact that basifying the reaction mixture did not inhibit the ionization process is curious, and may hint at a reaction mechanism substantially different from that proposed here. Nonetheless, most migrating groups were well-tolerated, with only strongly electron-donating heterocycles giving rise to appreciable quantities of 1-alkoxybenzindolizine products.

Scheme 5.20. Possible Mechanism of Alkoxybenz[e]indolizine Formation During Cycloisomerization



To be sure, a more fundamental understanding of the activation of an alkyne with neutral protic media has the potential to open new avenues of inquiry in cycloisomerization reactions, as well as industrially important processes such as the hydration of alkynes. Specifically, in the future we hope to identify and structurally assign reaction intermediates (if they exist), determine the fundamental processes by which they are formed and converted to product, and establish

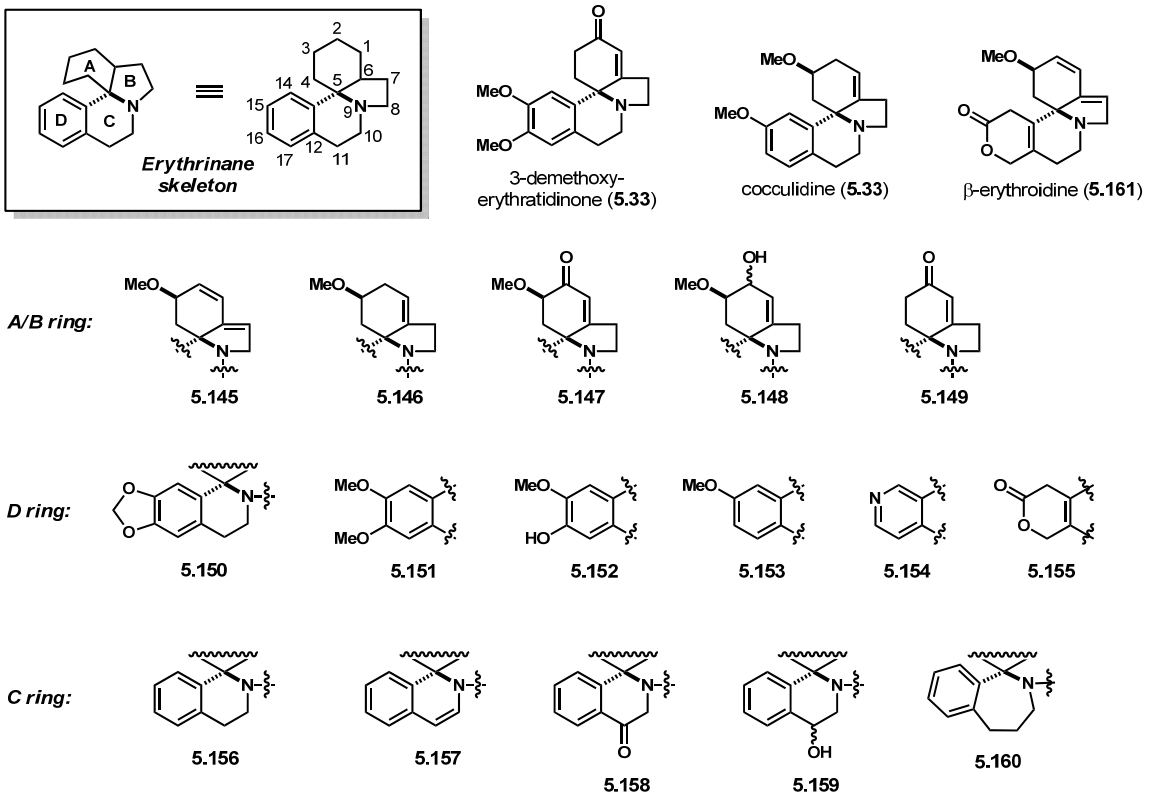
whether these mechanistic details were conserved across substrate classes (i.e., quinoline, pyridine, and isoquinoline substrates). As such, both experimental and *in silico* study of the mechanism by which indolizines and indolizinones form from heterocyclic carbinols is ongoing in the Sarpong laboratory.

5.7 Application of the Benz[g]indolizinone Core to the Synthesis of Erythrina Alkaloids

Having developed a rudimentary understanding of the fundamental reactivity of the benz[g]indolizinone system, we then sought to employ the solvent promoted cycloisomerization in the total synthesis of several members of the *Erythrina* alkaloid family. There are hundreds of unique compounds in this class of natural products, but their structural diversity arises from variance in four distinct regions of the molecule, commonly referred to as the A/B azahydrindane, the typically aromatic D ring, and the piperidine C ring (Scheme 5.21).[34]

While the carbon skeleton of these alkaloids is highly conserved, a wide range of oxygenation patterns has been found in various members of the family. This is particularly evident in the A/B ring system, where alkaloids with diols (see **5.148**), ethers (**5.148**), and carbonyls have all been isolated (**5.149**). The majority of the *Erythrina* alkaloids contain a 1,3-diene function extending across the A-B ring fusion (**5.147**), yet several reduced compounds have been isolated that possess only a single trisubstituted double bond (**5.148**). To date, only alkaloids with a *cis* stereochemical relationship between the amino group and oxygenation at C2 – usually a methoxy group – have been isolated.

Scheme 5.21. Structural Diversity of Erythrina Alkaloids



The D ring of the *Erythrina* alkaloids is typically an oxygenated arene, with phenol as well as methoxy functional groups most commonly found at C11 and C12 (see **5.150**-**5.152**). Intriguingly, select alkaloids contain rearranged ring scaffolds, presumably arising from oxidative ring opening of catechol-derived D ring systems (**5.152**). Ring closure via condensation of these putative over-oxidized intermediates then leads to lactones such as those found in β-erythroidine (**5.163**), or even azacyclic scaffolds (**5.154**).

The site of relatively high structural homology, the C ring is typically a simple piperidine, and thus these compounds are often classified as members of the tetrahydroisoquinoline alkaloids (e.g., morphine). However, there are a few reports of compounds containing oxygenation at the benzylic carbon (**5.158**-**5.159**). Similarly, compounds containing an enamine function have been isolated (**5.157**). A related set of alkaloids, called the homoerythrina alkaloids, contain a tetrahydrobenzazepine (**5.160**).

The *Erythrina* alkaloids exhibit a wide variety of biological activity, but were first described as demonstrating "curare-like" effects when crude extracts of *Erythrina americana* were investigated by Rey,[35] Altamirano,[36] and Greshoff.[37] The term "curare" (named after the curare alkaloids) describes a class of paralytics used by indigenous South Americans as arrow poisons as well as hypnotic and antiepileptic medicines.[38] As such, a systematic study of these alkaloids was undertaken by Folkers and coworkers in hopes of understanding the molecular basis of these myriad pharmacological effects. In a series of publications, these researchers described the isolation, partial structural elucidation, and biological activities of dozens of unique compounds.[39] However, it was not until the 1950s that Prelog and Boekelheide, working separately, were able to complete the structural assignment of several *Erythrina* alkaloids.[40]

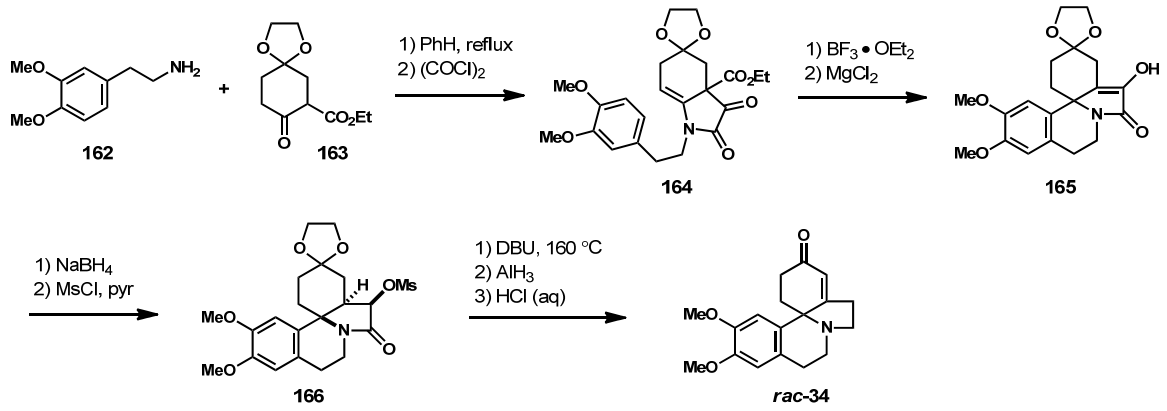
Subsequent research with pure samples of the various alkaloids in this family has led to a detailed understanding of their interactions with biological systems. The most widely studied *Erythrina* alkaloid seems to be dihydro-β-erythroidine, which is an antagonist of nicotinic acetylcholine receptors with moderate selectivity for the neuronal α4 subunit. Consequently, this compound has found use as a mechanistic probe for the study of nicotine addiction.[41] Erysodine, another widely studied member of the family, has been shown to be more potent than dihydro-β-erythroidine as an inhibitor of cytosine binding at neuronal nicotinic acetylcholine receptors. Significantly, when administered systemically, erysodine was observed in the brains of mice and exhibited pronounced behavioral effects in standard maze assays.[42] These results, and especially the finding that many alkaloids of this type pass through the blood-brain barrier, make them ideal candidates for SAR studies. As such, and because of their interesting polycyclic structures, the *Erythrina* alkaloids have enjoyed significant attention from the synthetic community.

5.8 Formal Synthesis of (+)-3-Demethoxyerythratidinone

First isolated in 1973 by Barton and coworkers, (+)-3-demethoxyerythratidinone (**5.34**) has one of the least complex structures of all the *Erythrina* alkaloids isolated to date.[43] Though there are no reports on its biological activity, a number of total syntheses have been reported — three of which are discussed in detail here.[44] Tsuda and coworkers were the first to complete a synthesis of **5.34**, reporting several related approaches in 1984.[45] Scheme 5.22 details their most concise approach, relying on an enamine annulation strategy to generate the B ring. The resulting enamine (not shown) could then undergo a Pictet-Spengler reaction and subsequent decarboxylation to set the α-tertiary amine present in **5.165**. Sodium borohydride reduction and mesylate formation afforded **5.166**. DBU-mediated elimination generated an α,β-unsaturated

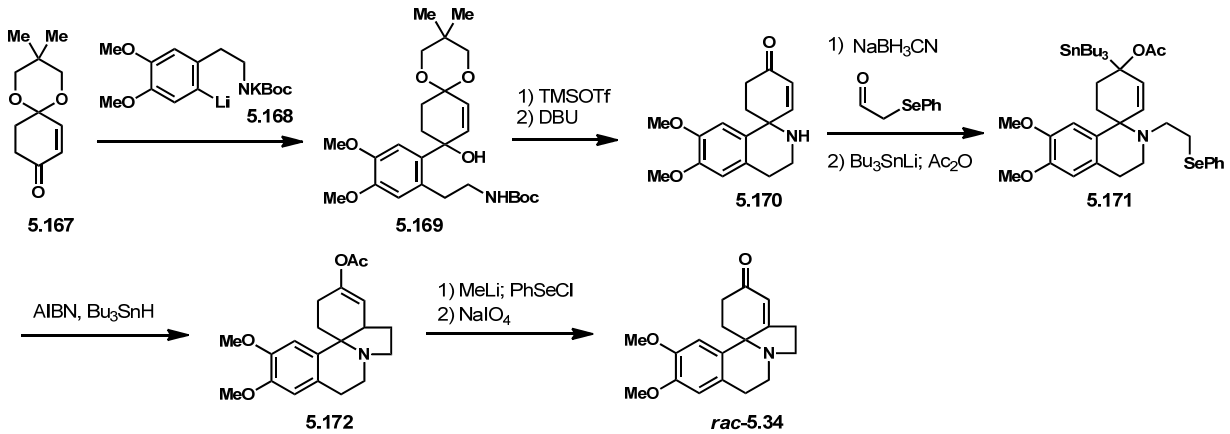
lactam, which could undergo selective 1,2-reduction with alane (AlH_3). Simultaneous ketal cleavage and alkene isomerization under acidic conditions provided racemic **5.34**.

Scheme 5.22. The Tsuda Synthesis of 3-Demethoxyerythratidinone



Just three years later, Danishefsky and Panek reported a synthesis of **5.34** relying on late-stage construction of the B-ring pyrrolidine through the 1,4-addition of an alkyl radical to a masked enone.[46] The penultimate substrate for this reaction was secured through addition of aryllithium **5.168** (Scheme 5.23) to enone **5.167** to yield **5.169**, followed by trimethylsilyl triflate mediated amination to afford **5.170**. Reductive amination of 2-phenylselenylacetaldehyde, followed by 1,2-addition of tri-*n*-butylstannyllithium led to **5.171**. At this stage, selenium abstraction and subsequent ring closure afforded **5.172** through loss of a tin radical. The enol acetate formed could then be converted to 3-demethoxyerythratidinone via a Reich oxidation sequence involving a creative enolate formation step.

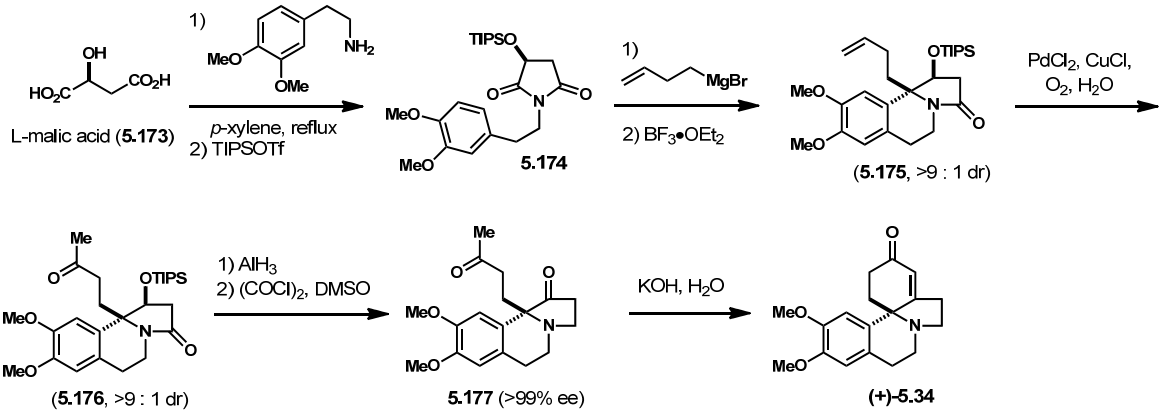
Scheme 5.23. Total Synthesis of 3-Demethoxyerythratidinone by Danishefsky



A more recent enantioselective approach to **5.34** was developed by Simpkins and workers.[47] Starting from natural malic acid (**5.173**), condensation with 3,4-dimethoxyphenethylamine yielded succinimide **5.174** (Scheme 5.24). Regioselective Grignard addition followed by Lewis acid mediated Pictet-Spengler cyclization afforded **5.175** in greater than 9:1 diastereoselectivity. Wacker oxidation then facilitated the installation of the pendant ketone found in **5.176**. Global reduction with alane led to complete deoxygenation of the amide

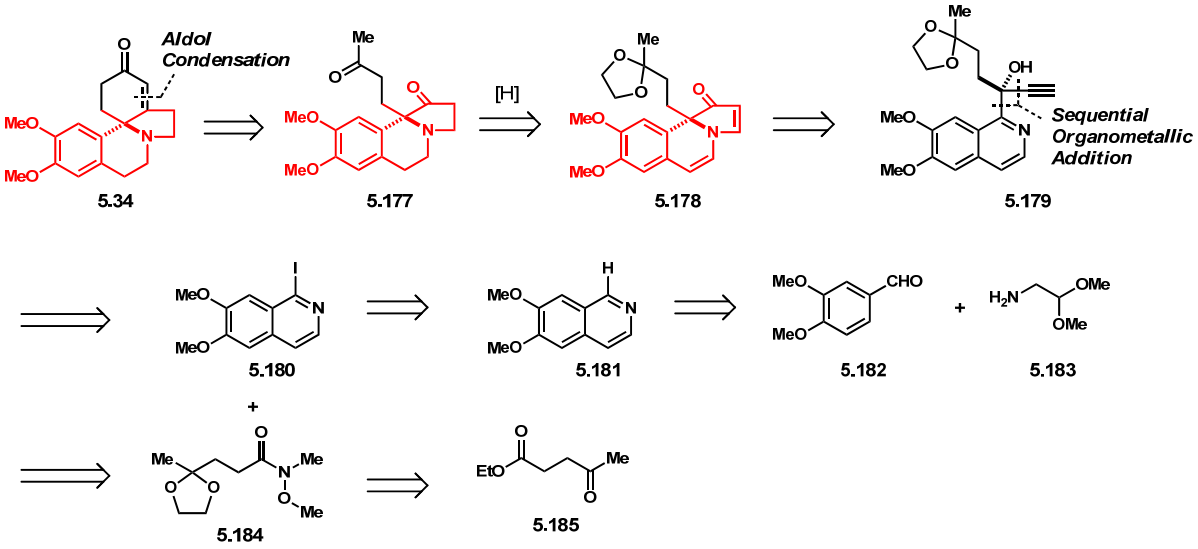
group as well as removal of the TIPS group. Readjustment of the oxidation level of the resulting diol (not shown) led to diketone **5.177**. An aldol condensation previously reported by Wasserman[48] then provided (+)-**5.34**.

Scheme 5.24. The Simpkins Synthesis of (+)-3-Demethoxyerythratidinone



We noted that 3-demethoxyerythratidinone contained a nearly intact tetrahydrobenz[g]indolizinone core (in red, **5.34**, Scheme 5.25), and thus presented a significant opportunity to demonstrate the utility of this heterocyclic system as a scaffold for the synthesis of complex alkaloids. Furthermore, we believed that the solvent-promoted cycloisomerization would facilitate a brief and efficient synthesis of **5.34** that would compare favorably with most existing synthetic routes.

Scheme 5.25. Retrosynthetic Analysis of 3-Demethoxyerythratidinone

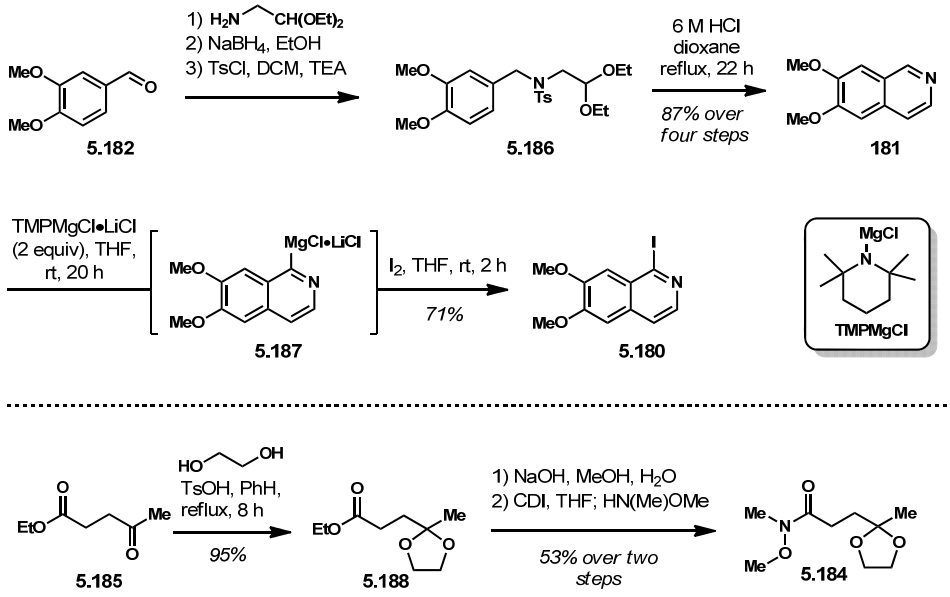


Our retrosynthetic analysis of **5.34** took advantage of the precedent set by Simpkins and Wasserman that 3-demethoxyerythratidinone could be accessed through an intramolecular aldol condensation of **5.177**. This diketone could be prepared through a double reduction and deprotection of **5.178**. In turn, the benz[g]indolizinone core of **5.178** could be secured by the

solvent-promoted cycloisomerization described above. The requisite carbinol substrate **5.179** was envisioned to arise from a sequential addition of **5.180** (after metal-halogen exchange) and an acetylide to known Weinreb amide **5.184**.[49] Iodoisoquinoline **5.180** could be generated from known 6,7-dimethoxyisoquinoline (**5.181**) using a strategy outlined by Knochel.[50]

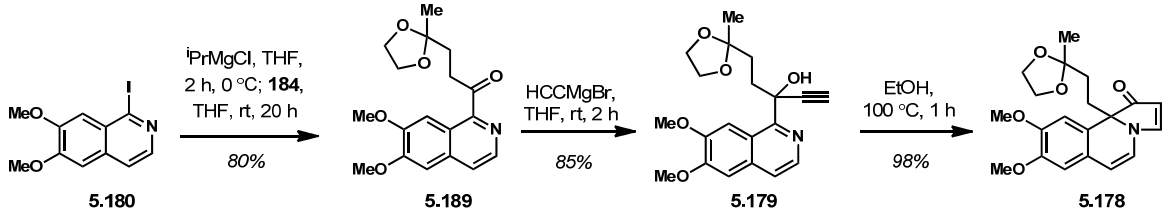
In the forward sense, 6,7-dimethoxyisoquinoline was prepared according to a literature procedure involving a modified Pomeranz-Fritsch reaction.[51] It was found that the use of a sulfonamide (see **5.186**, Scheme 5.26) was crucial for efficient oxidative aromatization to the isoquinoline nucleus as it can serve as an internal redox element (by loss of a sulfinate). In practice, the acid-mediated cyclization reaction mixture turned a deep red, indicative of the presence of *p*-toluenesulfinic acid, which could be isolated in nearly quantitative yield. Iodination of **5.181** was achieved by treatment with the lithium chloride complex of 2,2,6,6-tetramethylpiperidinylmagnesium chloride (TMPMgCl) to yield **5.187** as a putative intermediate, the iodinolysis of which afforded **5.180** in 71% yield.[52] The requisite Weinreb amide was generated by a known three step procedure wherein the ketone group of ethyl levulinate (**5.185**) was protected as the dioxolane (**5.188**), the ester saponified, and the amide (**5.184**) synthesized by CDI-mediated coupling with *N*,*N*-dimethylhydroxylamine.[53]

Scheme 5.26. Synthesis of Building Blocks for 3-Demethoxyerythratidinone



At this stage, iodoisoquinoline **5.180** was converted to the corresponding Grignard reagent by magnesium-iodine exchange using isopropylmagnesium chloride, and the resulting nucleophilic species was trapped with **5.184** to afford ketone **5.189** (Scheme 5.27). Initial investigations utilized a lithium-halogen exchange to provide a 1-lithioisoquinoline, however, substantial **5.181** was observed, presumably generated by α-deprotonation of **5.184**. Alkynylation of ketone **5.189** using ethynylmagnesium bromide in THF proceeded uneventfully to afford carbinol **5.179** in 85% yield. Gratifyingly, heating a solution of **5.179** in ethanol to 100 °C for one hour led to clean and nearly quantitative conversion to the desired benz[g]indolizinone (**5.178**).

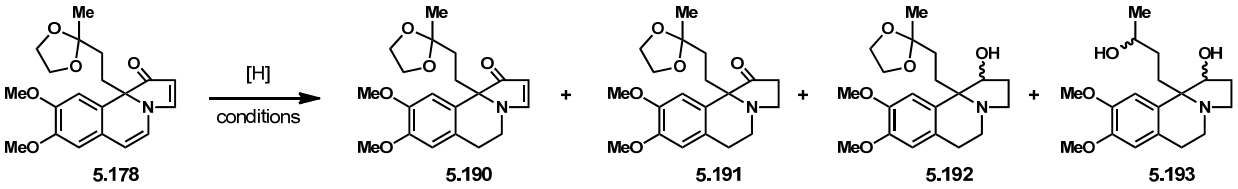
Scheme 5.27. Union of Building Blocks to Provide a Benz[g]indolizinone



We then turned our attention to the double reduction of the benz[g]indolizinone system. Hydrogenation using a variety of heterogeneous catalysts provided either the partially hydrogenated product (**5.190**), or a complex mixture of reduction products (Table 5.3). Though there was precedent for the reduction of the vinylogous amide under acidic aqueous conditions,[54] applied to **5.178**, this approach led to rapid ketal cleavage as well as overreduction to the tetrahydrobenz[g]indolizinol (**5.193**). Rapid decomposition was observed when less than two equivalents of $NaBH_3CN$ were employed. In many cases, small amounts of an aldehyde were noted in the crude reduction mixtures, suggesting that the benz[g]indolizinone core was undergoing acid catalyzed ring-opening hydrolysis.

From these observations, it became apparent that the two major challenges of a global reduction process – ketal cleavage and enamine hydrolysis – were promoted by water. Furthermore, Gribble and coworkers have shown that the reduction of ketones with $NaBH_3CN$ is strongly pH-dependent.[55] Therefore, anhydrous conditions were investigated using TFA instead of HCl. In the event, treatment of **5.178** with $NaBH_3CN$ and TFA in methanol led to controlled double reduction. Only trace amounts of tetrahydrobenz[g]indolizinol were observed by LCMS. Furthermore, the labile ketal group was retained (along with a small amount of dimethyl ketal).

Table 5.3. Exploration of the Double Reduction of the Benz[g]indolizinone Core

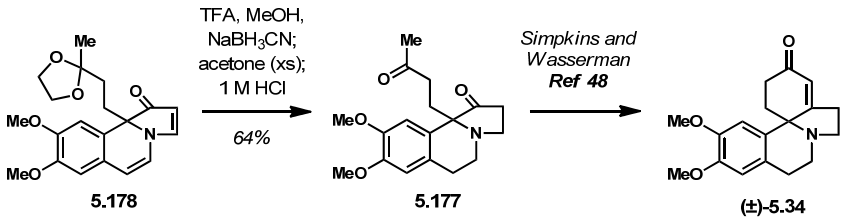


Entry	Reductant	Equiv	Conditions	Major Products
1	H_2	1 atm	Pd/C (100 mol%), MeOH	**5.190**
2	H_2	1 atm	Rh/Al_2CO_3 (100 mol%), MeOH	**5.191** and **192**
3	$NaBH_3CN$	0.5	MeOH, 1 M HCl (1:1)	decomposition
4	$NaBH_3CN$	1	MeOH, 1 M HCl (1:1)	decomposition
5	$NaBH_3CN$	2	MeOH, 1 M HCl (1:1)	Mixture of **5.190**-**5.193**
6	$NaBH_3CN$	3	MeOH, 1 M HCl (1:1)	**5.192** and deprotected **5.191**
7	$NaBH_3CN$	2	TFA, MeOH (anh)	**5.191**

With the experience gained in the optimization campaign of the global reduction of **5.178**, restoration of the ketone via ketal cleavage was trivial. Simply dissolving **5.191** in aqueous hydrochloric acid provided clean diketone **5.177** (see Scheme 5.28). However, the irony of performing a carefully controlled acid-mediated reduction in order to retain the ketal, only to cleave it under essentially identical conditions in a subsequent step was not lost on us. We attempted to telescope this process by adding water to the reduction reaction once complete

conversion to **5.191** was noted by LCMS, but partial ketone reduction was unexpectedly encountered. This problem was surmounted by adding a sacrificial ketone (acetone) to the reduction prior to the addition of water, allowing for a one-pot global reduction-ketone deprotection leading to diketone **5.177** in 64% yield and completing the formal total synthesis of (±)-3-demethoxyerythratidinone.

Scheme 5.28. Completion of the Formal Synthesis of 3-Demethoxyerythratidinone

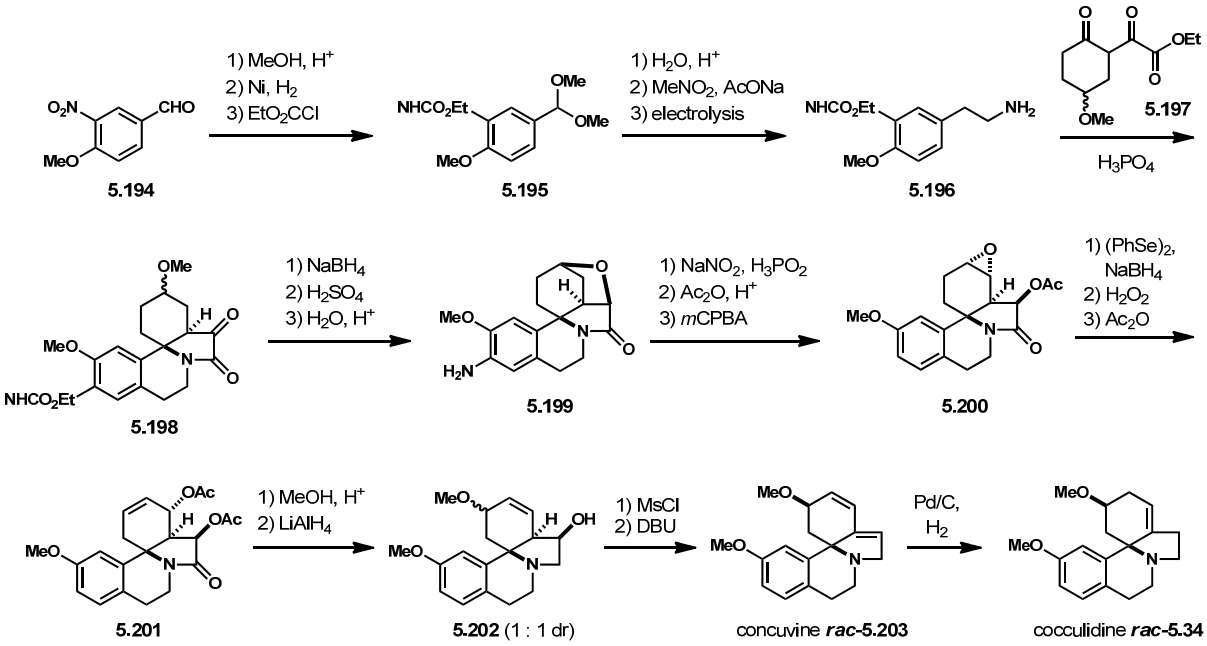


Though our synthesis of **5.34** provided racemic material, this drawback begged the question of whether the solvent-promoted cycloisomerization was stereospecific. That is, whether the stereochemistry of the tertiary alcohol center is translated into the C5 α-tertiary amine center. We anticipated that enantioselective addition of an acetylide to **5.189** could be quite challenging, so we elected to separate the enantiomers of carbinol **5.179** by chiral chromatography.[56] Subjecting enantioenriched **5.179** (>99% ee) to the cycloisomerization reaction conditions led to clean and complete conversion to benz[g]indolizinone **5.178** without loss of optical activity (>99% ee). Though we cannot discount the possibility that the cycloisomerization proceeds with stereoinversion, to the best of our knowledge, there is no known mechanism by which a Wagner-Meerwein-type shift proceeds with this stereochemical outcome in a cyclic system. Thus the challenging ring fusion center of the *Erythrina* alkaloids could be set stereoselectively through the use of a stereodefined carbinol precursor. In essence, the cycloisomerization approach to this family of natural products allows for the substitution of a particularly challenging stereochemical problem – a polycyclic α-tertiary amine - for a well-studied one – a stereogenic carbinol center.

5.9 Toward the Total Synthesis of Cocculidine

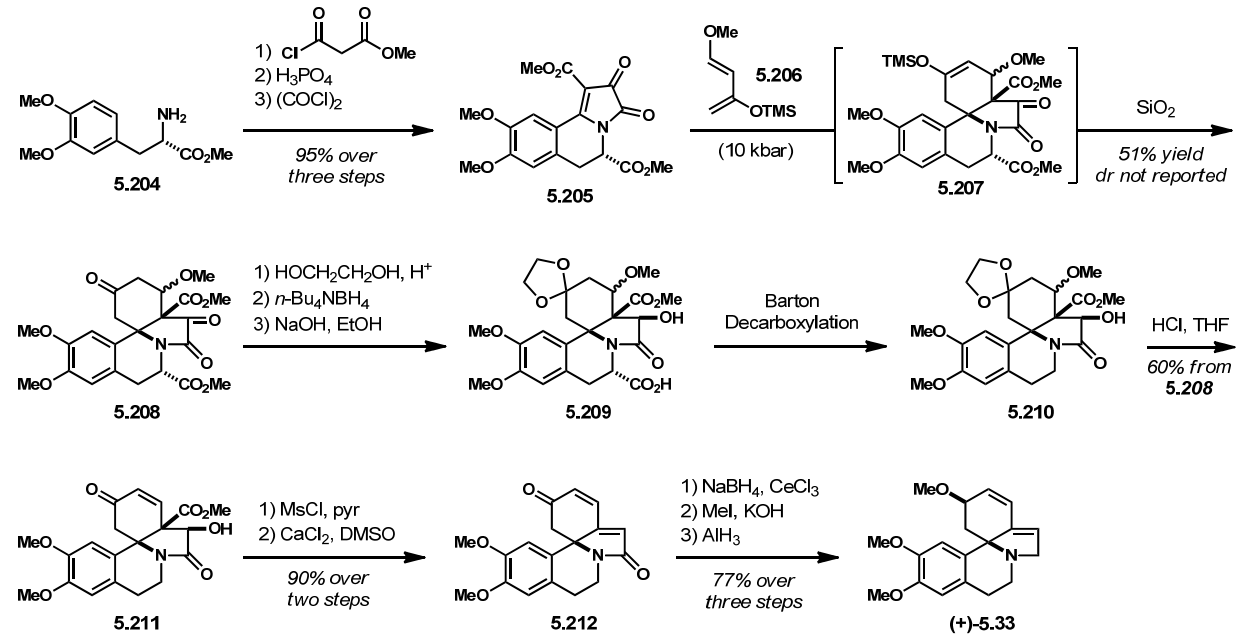
To further demonstrate the power of this strategy, we targeted cocculidine (**5.33**), a more representative member of the *Erythria* alkaloid family. Unlike 3-demethoxyerythratidinone (**5.34**), cocculidine contains two stereocenters, and as such has provided a more stringent synthetic challenge. Accordingly, there have been only a handful of total syntheses of *Erythrina* alkaloids containing multiple stereocenters, and the routes established thus far are largely racemic. As in the case of 3-demethoxyerythratidinone, most approaches rely on an early stage Pictet-Spengler cyclization to secure the C ring. For instance, the synthesis of cocculidine (**5.33**) and coccuvinine (**5.203**, Scheme 5.29) by Ando and coworkers commences with a Pictet-Spengler reaction of aniline derivative **5.196**, which must be prepared by a six-step sequence, and the β-diketone **5.197**. Concomitant lactam formation then gives **5.198**. A number of manipulations were then required to access allylic acetate **5.201**. Transposition by solvolysis of **5.201** then gave an erythrinan with the requisite C3 oxygenation (see **5.202**), but with no diastereocontrol. Separation of the stereoisomers of **5.202** followed by elimination then provided coccuvinine (**5.203**), the semi-hydrogenation of which gave cocculidine (**5.33**).

Scheme 5.29. Ando's Synthesis of (±)-Cocculidine



Tsuda and coworkers established one of the only enantioselective syntheses of a complex *Erythrina* alkaloid in 1993 by utilizing a diastereoselective Diels-Alder cycloaddition between dienophile **5.205** and diene **5.206**. Unfortunately, removal of the directing group ester required four steps (**5.208** to **5.210**). Transformation of ketal **5.210** to dienone **5.212** was accomplished using a Krapcho decarboxylation. Substrate-controlled Luche reduction, methylation, and lactam deoxygenation then afforded (+)-**5.33** in 15 steps from **5.204**.

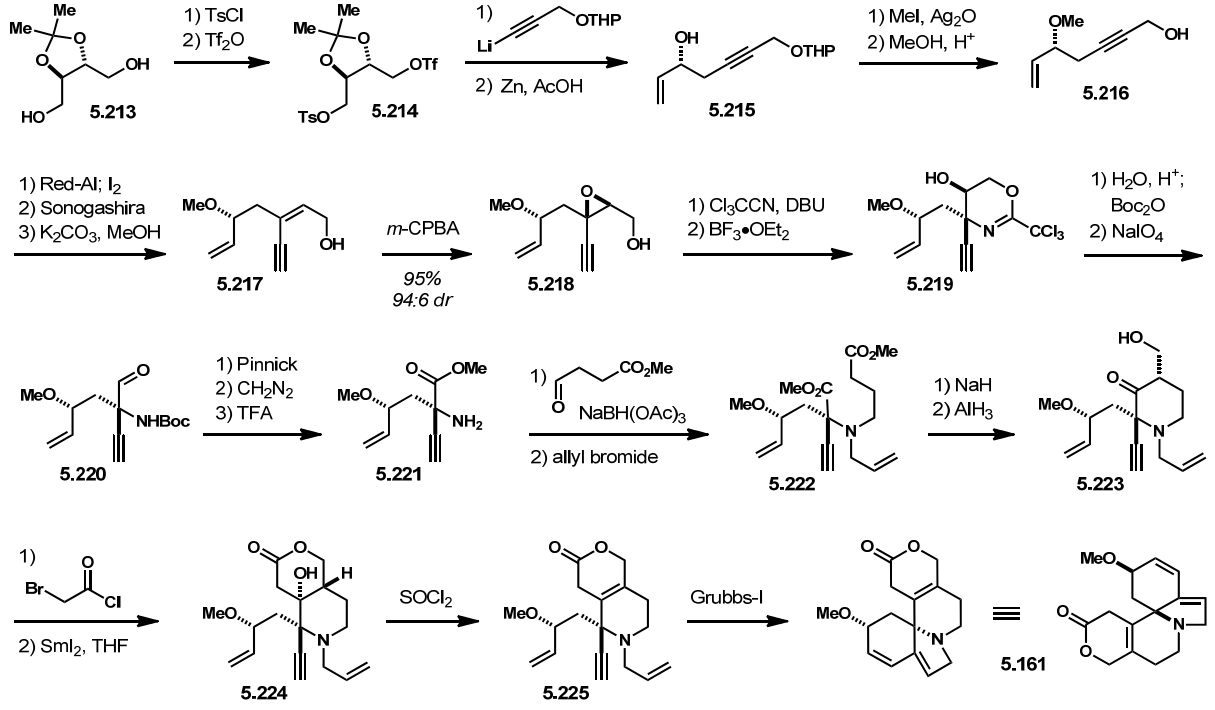
Scheme 5.28. Enantioselective Synthesis of Erysotrine by Tsuda



This early work accentuates the inherent challenge associated with the synthesis of *Erythrina* alkaloids containing stereogenic oxygen functional groups on the A ring – the largest subgroup of this family of natural products. Furthermore, only certain aromatic D ring substrates react efficiently in the Pictet-Spengler cyclization, precluding the synthesis of the so-called abnormal alkaloids (those lacking oxygenation at C15). As such, electron-deficient or nonaromatic D rings have proved completely inaccessible until recently.

In 2006, Hatakeyama and coworkers reported the first enantioselective synthesis of a nonaromatic *Erythrina* alkaloid by exploiting an enyne metathesis cascade to forge the diene present in β-erythroidine (**5.161**) as well as the A and B rings. Starting from the chiral pool (tartaric acid, not shown), diol **5.213** was differentiated through sequential sulfonation to yield triflate **5.214**. Alkynylation, reductive elimination, etherification, and deprotection then provided **5.216**. Enyne **5.217** was then prepared and subjected to epoxidation under standard conditions. Surprisingly, the desired diastereomer of **5.218** was formed nearly exclusively. The authors propose a hydrogen-bonding interaction between the homoallylic ether of **5.217** and *m*-CPBA, but do not provide any evidence to support this hypothesis. Lewis acid mediated epoxide opening via intramolecular engagement by an imidate then provided **5.219**. With the required stereochemical elements in place, functional group manipulation completed the first phase of the synthesis of **5.161**. The α-tertiary amine of **5.221** was sequentially alkylated to provide **5.222**. Cyclization under classical Dieckmann condensation conditions followed by selective reduction of the ester with alane afforded **5.223**. Acylation with bromoacetyl chloride and a SmI_2-mediated aldol reaction gave rise to **5.224**. Elimination of the resulting tertiary alcohol group returned two olefin isomers; however, only the desired β,γ-lactone (see **5.225**) underwent successful enyne metathesis.

Scheme 5.29. Enantiospecific Synthesis of β-Erythroidine

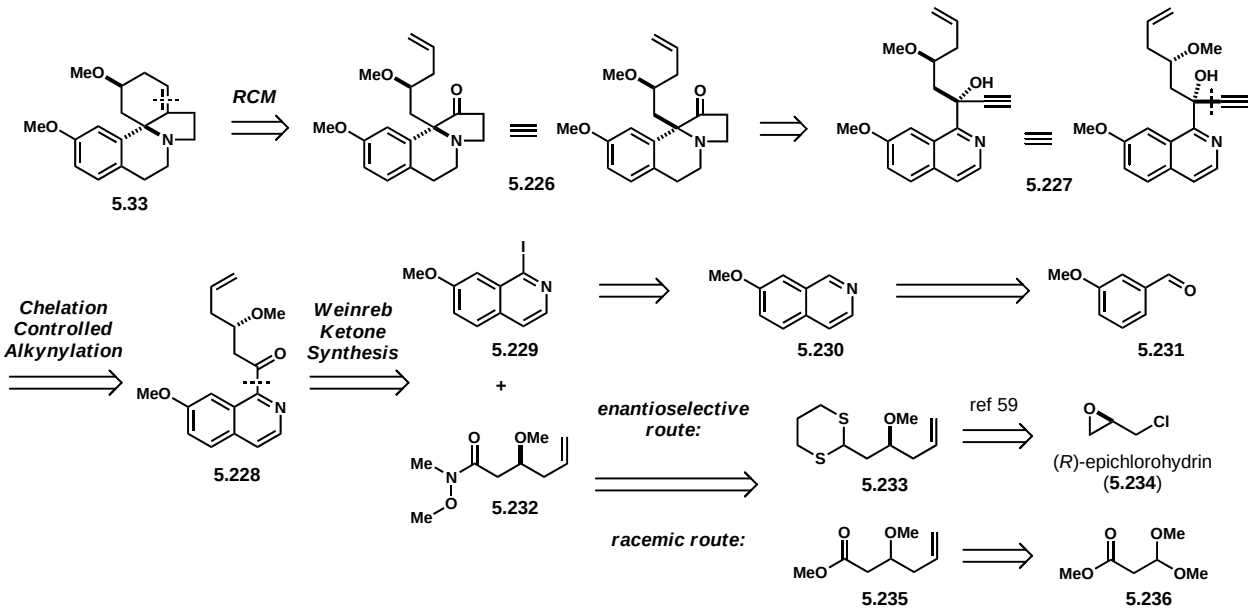


The difficulty associated with a stereoselective synthesis of the α-tertiary amine, which is amplified by the requisite *cis* stereochemical relationship between the α-tertiary amine and the methoxy group in the A ring, is evidenced by this relatively lengthy approach. Indeed, nearly two-thirds of the steps in this route serve to address these stereogenic centers. Nonetheless, Hatakeyama's work has set the current standard for the synthesis of complex *Erythrina* alkaloids.[57]

Alternatively, the use of the solvent-mediated cycloisomerization could facilitate the synthesis of these alkaloids, and potentially make obsolete the Pictet-Spengler strategy, as it would tolerate virtually any D ring. Moreover, the difficulty associated with the C3 and C5 stereocenters would be simplified as the C3 center could be installed prior to cycloisomerization, and the C5 center, the α-tertiary amine, is stereospecifically generated from the propargylic carbinol. That is, the heretofore thorny stereochemical problem of a 1,3-*cis* angular α-tertiary amino ether is translated into that of a 1,3-diol.[58] To demonstrate the power of this simplifying strategy, we embarked on the total synthesis of cocculidine (**5.33**), a representative *Erythrina* alkaloid that had previously been shown to be recalcitrant to the Pictet-Spengler strategy.

In the retrosynthetic sense, the A ring of **5.33** could be secured by a ring-closing metathesis reaction of a diene derived from ketone **5.226** (Scheme 5.30) by way of a Wittig olefination. The desired stereoisomer of the tetrahydrobenz[g]indolizinone core could be secured via a solvent-promoted cycloisomerization of *cis* carbinol **5.227**. It was anticipated that a β-chelation controlled addition of an ethynyl group to ketone **5.228** would afford the desired carbinol diastereomer. In turn, **5.228** could be prepared by analogy to ketone **5.189**, which was a key intermediate in the total synthesis of 3-demethoxyerythratidinone. The requisite 1-iodoisoquinoline **5.229** could be generated from *m*-anisaldehyde via a Pomeranz-Frisch reaction followed by iodination of the product 7-methoxyisoquinoline (**5.230**). Weinreb amide **5.232** was envisioned to arise from known dithiane **5.233**, which could be prepared from epichlorohydrin (**5.234**).[59] Alternatively, **5.232** could be prepared in racemic form from dimethyl acetal **5.236** by way of homoallyl ether **5.235**, generated from a Sakurai allylation.

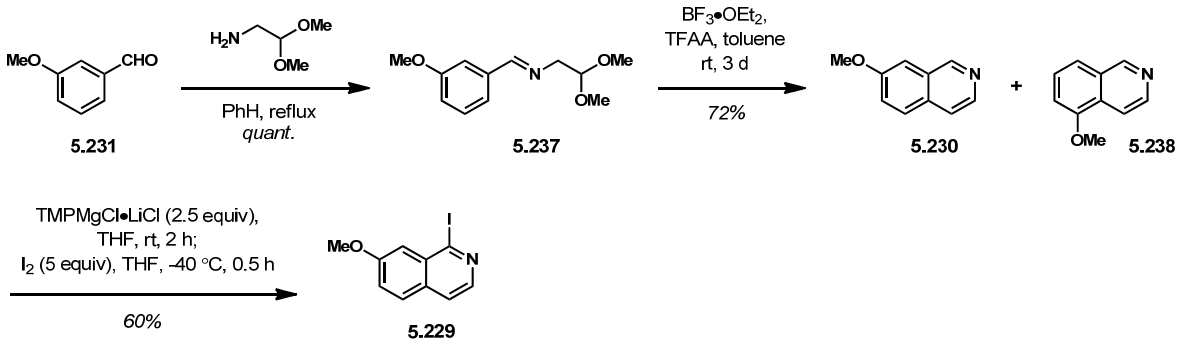
Scheme 5.30. Retrosynthetic Analysis of Cocculidine



We initially focused on the synthesis of iodoisoquinoline **5.229** using the precedent established by workers at Böhringer Mannheim.[60] Condensation of *m*-anisaldehyde with aminoacetaldehyde dimethyl acetal provided imine **5.237** (Scheme 5.31), which was treated with a mixture of trifluoroacetic anhydride (TFAA) and boron trifluoride diethyl etherate to effect cyclization. The synthesis of **5.230** was straightforward; however, a 95:5 mixture of regioisomers (**5.230**: **5.238**) was obtained and was found to be quite difficult to separate. While small amounts of regiopure **230** could be produced using this route, we found that the isomeric mixture could be used to establish the bulk of the synthetic route.

Treatment of **5.230** with TMPMgCl•LiCl and iodinolysis of the resulting organomagnesium species provided **5.229** in 60% yield. A variety of reaction conditions were explored in an effort to increase the efficiency of the iodination of 7-methoxyisoquinoline (**5.230**); however, we were never able to drive the initial deprotonation to completion (as measured by quenching with CD_3OD). Unfortunately, the regioisomeric iodides were chromatographically inseparable.

Scheme 5.31. Synthesis of 1-Iodo-7-methoxyisoquinoline



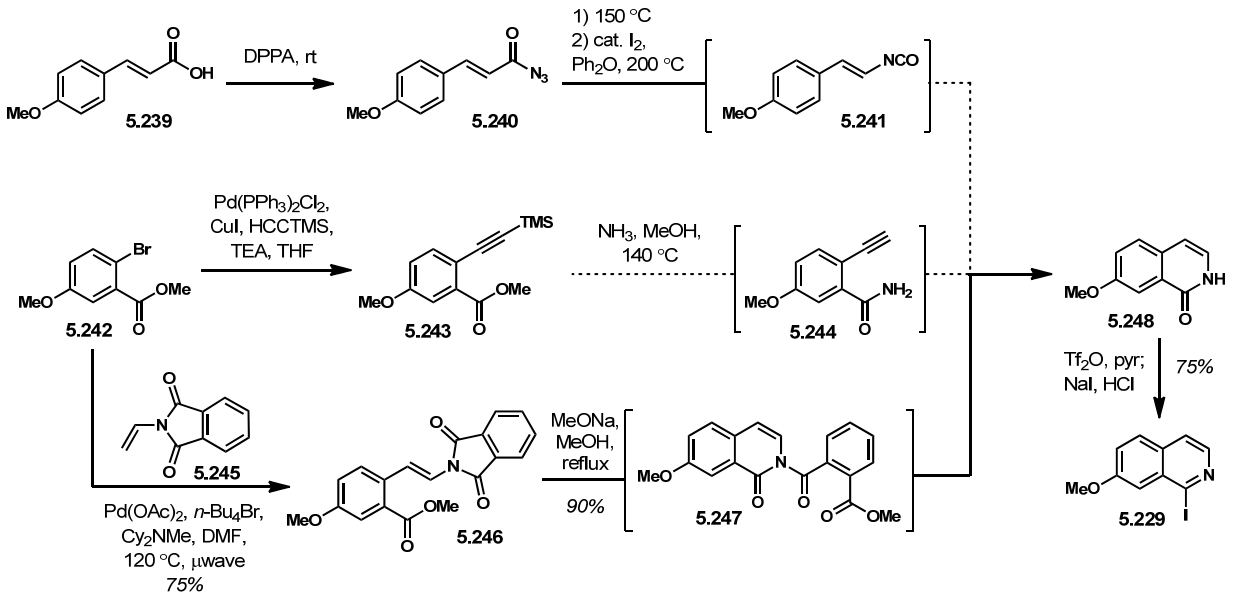
Though we had successfully established a route to **5.229**, its weaknesses led us to explore regiospecific approaches to 1-iodo-7-methoxyisoquinoline. We planned to exploit a sequence recently disclosed by process chemists at Merck in which iodopyridines and quinolines were synthesized from the corresponding hydroxypyridines and quinolinones.[61] As such, we targeted isoquinolinone **5.248** (Scheme 5.32). There are two reports of the synthesis of **5.248** from 4-methoxycinnamic acid (**5.239**) by cyclization of a styrylisocyanate (**5.241**) generated from the Curtius rearrangement of an acyl azide (**5.240**).[62] However, the reported yields of **5.248** are low and it has been claimed that electron-rich arenes are poor substrates for this process.[63] In our hands, this transformation was low-yielding and somewhat capricious, so we explored other approaches to **5.248**.

Because we desired a regiodefined synthesis of **5.248**, we attempted to develop a route stemming from bromo-ester **5.242** by utilizing a cross-coupling reaction to secure the two-carbon fragment that comprises C3 and C4 of the isoquinolinone core. We thought that a Sonogashira coupling of **5.242** with trimethylsilylacetylene could lead to **5.243**, which may be able to undergo amidation a 6-*endo*-dig cyclization to afford **5.248**.[64] In the event, the Sonogashira reaction was surprisingly sluggish, even under forcing conditions.[65]

Fortunately, we had simultaneously been investigating another cross-coupling approach involving the Heck coupling of **5.242** and *N*-vinylphthalimide (**5.245**).[66] Typically, electron-rich alkenes undergo α-selective migratory insertion to give branched products; however, the

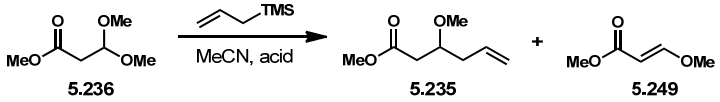
deactivating nature of the phthalimide group allows for highly selective formation of the linear (β-substituted) insertion product (**5.246**).[67] Methanolysis of the phthalimide group under basic conditions rapidly led to an intermediate tentatively assigned to be *N*-acylisoquinolinone **5.247**, which slowly formed the desired isoquinolinone **5.248** in excellent yield with concomitant formation of dimethyl phthalate. Conversion of **5.248** to **5.229** using the procedure outlined by Maloney and coworkers proceeded uneventfully.

Scheme 5.32. In Search of a Robust Route to 7-Methoxyisoquinolone



A racemic synthesis of Weinreb amide was then developed starting from methyl 3,3-dimethoxypropionate (**5.236**). We were initially drawn to a report by List of a mild Brønsted acid-catalyzed Sakurai allylation of dimethyl acetals using allyltrimethylsilane as we were concerned about facile elimination in the presence of classical conditions employing strong Lewis acids.[68] However, application of the conditions reported by List to the allylation of **5.236** resulted in low conversion to β-methoxyacrylate **5.249** (entry 1). Methanesulfonic acid provided **5.235** as the minor product (entry 2), but with significant formation of **5.249**. On the other hand, TFA proved to be an effective promoter of the Sakurai allylation (entries 3-5), but, owing to its reduced acidity relative to sulfonic acids, a large volume of TFA was required for complete conversion to **5.235**. It was eventually found that using TFA as a co-solvent with acetonitrile allowed for efficient allylation (entries 4 and 5). The enrichment of the product mixture in favor of **5.235** with higher acid loading suggests that enoate **5.249** may be a competent electrophile or is in equilibrium with **5.236**.

Table 5.4. Optimization of the Brønsted Acid-Catalyzed Sakurai Allylation

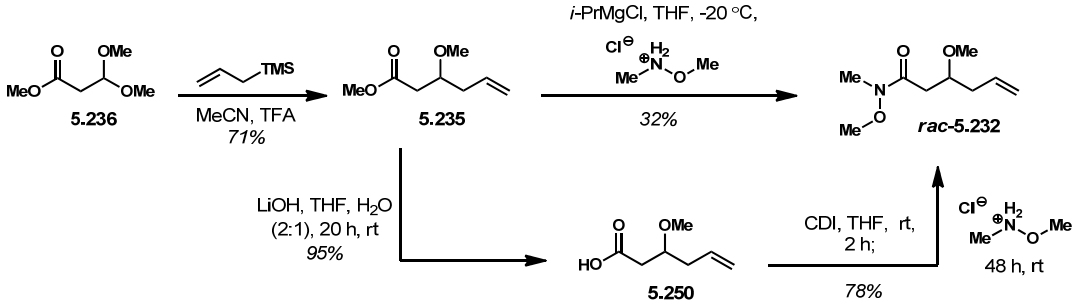


Entry	Acid	Equiv Acid	% Conversion[a]	**235** : **249**
1	TsOH	10 mol%	25	1 : >20
2	CH_3SO_3H	10 mol%	35	1 : 2
3	TFA	10 mol%	30	2.5 : 1
4	TFA	20% v/v	80	4 : 1
5	TFA	40% v/v	>95	14 : 1

[a] Conversions determined by integration of resonances in 1H-NMR.

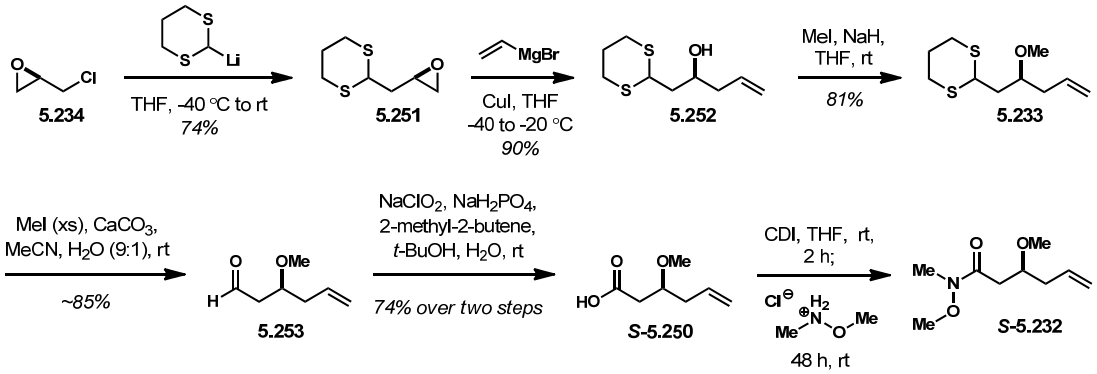
Subjection of **5.235** to direct amidation with an *in situ* generated magnesium amide provided the desired Weinreb amide in low yield (Scheme 5.33).[69] Alternatively, hydrolysis of methyl ester **5.235** with lithium hydroxide led cleanly to acid **5.250**, which could be transformed to Weinreb amide **5.232** by CDI-mediated amidation. Thus, racemic **5.232** could be accessed in 53% yield over three steps; the brevity and atom economy of this sequence was a boon to the rapid development of a synthetic route to cocculidine.

Scheme 5.33. Short Route to Racemic Weinreb Amide **5.232**



As we were interested in preparing the natural enantiomer of cocculidine, an enantioselective route to amide **5.232** was developed from readily available (*R*)-epichlorohydrin. Nucleophilic epoxide opening with 2-lithio-1,3-dithiane with subsequent Payne rearrangement led to **5.251** (Scheme 5.34), which upon treatment with divinylcuprate (generated *in situ*) led to homoallylic alcohol **5.252**. Methylation of the sodium salt of **5.252** with iodomethane afforded **5.233**. Cleavage of the dithiane proved to be somewhat challenging as most oxidative methods failed. However, *S*-alkylation in a basic aqueous medium led to aldehyde **5.253**. This compound proved to be volatile and was used without purification. Pinnick oxidation in the presence of a large excess of 2-methyl-2-butene led to enantioenriched carboxylic acid **5.250** in 74% yield over two steps. Weinreb amide **5.232** was then prepared as before.

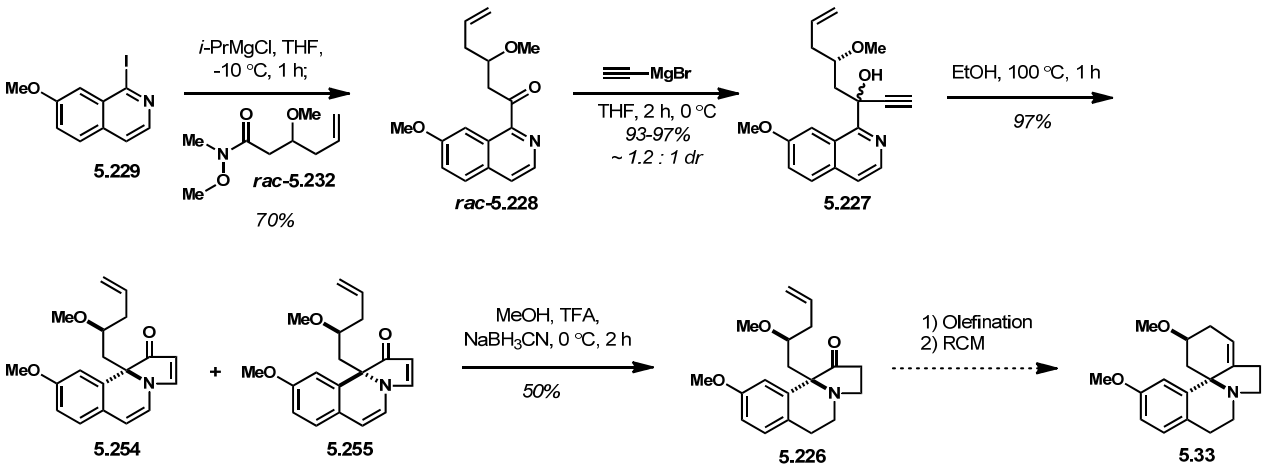
Scheme 5.34. Enantioselective Synthesis of Weinreb Amide **5.232**



The union of **5.232** and iodoisoquinoline **5.229** was achieved via a Weinreb ketone synthesis following generation of a Grignard reagent by iodine-magnesium exchange. Surprisingly, ketone **5.228** was always accompanied by small amounts of 7-methoxyisoquinoline (**5.230**), but under optimized conditions, **5.228** could be generated in 70% yield and the unreacted Weinreb amide isolated and recycled. Acetylide addition using ethynylmagnesium bromide provided **5.227** as an inseparable 1.2:1 mixture of diastereomers. Investigation of different solvents and reaction temperatures failed to provide significantly higher levels of stereocontrol. Nevertheless, the diastereomeric pair of carbinols was heated in ethanol to afford benz[g]indolizinones **5.254** and **5.255** in a 1.2:1 ratio — identical to the ratio of the two carbinol stereoisomers. Fortunately, **5.254** and **5.255** could be separated by silica gel chromatography. Elucidation of the relative stereochemistry of these diastereomers proved challenging, so we elected to continue forward with the more polar of the benz[g]indolizinone stereoisomers.

Reduction of both enamine π-systems could be achieved as before; however, over-reduction of the resultant ketone was a significant problem. Preliminary findings suggest that one of the diastereomers (**5.254** or **5.255**) is more prone to over-reduction. We anticipate that cocculidine can be accessed through olefination of ketone **5.226** followed by ring-closing metathesis to afford **5.33**. At 12 steps from epichlorohydrin or nine steps from known dithiane **5.233**, this route would be the most concise enantioselective synthesis of an "abnormal" *Erythrina* alkaloid.[70]

Scheme 5.35. Toward the Completion of the Synthesis of ±-Cocculidine



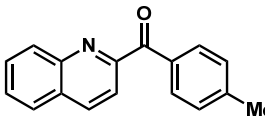
In summary, the synthesis of benzindolizinones was accomplished using a protic solvent-mediated cycloisomerization, overcoming the limitations imposed on both the iodine- and metal-mediated cyclizations. The fundamental reactivity of benz[e]- and benz[g]indolizinones was then briefly explored. Finally, the benz[g]indolizinones were found to be highly efficacious scaffolds for the synthesis of *Erythrina* alkaloids. Mechanistic investigations on the cycloisomerization reaction and the completion of the total synthesis of cocculidine are currently underway by others in the Sarpong laboratory.

5.10 Experimental Section

Materials and Methods:

See the experimental section of Chapter 2. Complete spectral data is only reported for substrates and products from scope studies on the benzindolizinone synthesis, and of new compounds generated in the total syntheses reported above.

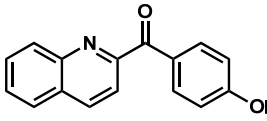
Substrate Synthesis: Preparation Quinolinyl Ketones



Quinolin-2-yl(p-tolyl)methanone (5.75)

The Weinreb amide (**2.169**, 0.640 g, 2.96 mmol) was dissolved in 15 mL dry THF and the resulting solution was cooled to -78 °C. *p*-Tolylmagnesium bromide (1.0 M in THF, 4.44 mmol) was added dropwise and the reaction mixture was stirred at -78 °C for 1 hr. The reaction was quenched with sat. NH_4Cl and the mixture extracted three times with EtOAc. The pooled organics were washed with brine, dried over $MgSO_4$, and concentrated to afford a yellow oil which was purified by flash chromatography (10% EtOAc in hexanes). The title compound (0.676 g, 92%) was obtained as a pale yellow oil.

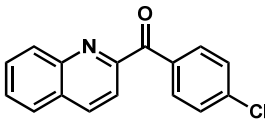
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (d, *J* = 8.1 Hz, 1H), 8.25 (d, *J* = 8.5 Hz, 1H), 8.13 (d, *J* = 8.3 Hz, 2H), 8.08 (d, *J* = 8.5 Hz, 1H), 7.92 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.80 (ddd, *J* = 8.5, 6.9, 1.5 Hz, 1H), 7.67 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 7.32 (d, *J* = 7.7 Hz, 2H), 2.46 (s, 3H).



(4-Methoxyphenyl)(quinolin-2-yl)methanone (5.256)

A solution of 4-bromoanisole (0.623 g, 3.33 mmol) in anhydrous THF (10 mL) was cooled to -78 °C and stirred. *n*-BuLi (2.5 M, 1.33 mL) was added dropwise and the resulting solution was stirred at -78 °C for 0.75 h. A solution of **2.169** (0.60 g, 2.78 mmol) in anhydrous THF (5 mL) was added dropwise and the reaction mixture was stirred at -78 °C for 1 h. The reaction was quenched by addition of sat. NH_4Cl (aq) and the mixture was extracted with EtOAc. The pooled organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by flash chromatography (10% → 20% EtOAc in hexanes) to afford the title compound (0.458 g, 63%) as a yellow oil that solidifies on standing.

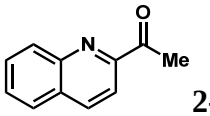
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (d, *J* = 8.6 Hz, 1H), 8.29 (d, *J* = 8.7 Hz, 2H), 8.21 (d, *J* = 8.5 Hz, 1H), 8.06 (d, *J* = 8.5 Hz, 1H), 7.89 (d, *J* = 8.0 Hz, 1H), 7.83 – 7.74 (m, 1H), 7.69 – 7.60 (m, 1H), 6.99 (d, *J* = 8.8 Hz, 2H), 3.90 (s, 3H).



Quinolin-2-yl(4-(trifluoromethyl)phenyl)methanone (5.257)

Prepared by analogy to **5.256** using 4-Iodobenzotrifluoride (0.88 g, 3.23 mmol) and **2.169** (0.635 g, 2.94 mmol) to afford the title compound (0.497 g, 54%) as a white solid.

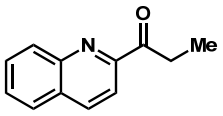
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (d, *J* = 8.4 Hz, 1H), 8.35 (d, *J* = 8.0 Hz, 2H), 8.20 (d, *J* = 6.8 Hz, 1H), 8.17 (d, *J* = 6.4 Hz, 1H), 7.94 (d, *J* = 8.0 Hz, 1H), 7.84-7.76 (m, 3H), 7.70 (ddd, *J* = 8.1, 6.8, 1.2 Hz, 1H),



2-Acetylquinoline (5.81)

Quinoline-2-carbonitrile (**5.80**, 0.300 g, 1.90 mmol) was dissolved in a 1:1 mixture of anhydrous THF (3 mL) and Et_2O (3 mL) and then the mixture was cooled to -20 °C. Methylmagnesium bromide (3.0 M solution in Et_2O, 0.78 mL) was added dropwise with stirring, during which an orange precipitate formed. The reaction mixture was allowed to warm to 0 °C over approximately 0.5 h. The reaction was then quenched with 1 M HCl (aq), followed by basification with sat. $NaHCO_3$ (aq). The resulting mixture was extracted with EtOAc. The pooled extracts were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to afford the title compound (0.308 g, 92%) as an orange oil that solidified on standing.

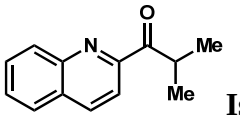
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.27 (d, *J* = 7.7 Hz, 1H), 8.21 (d, *J* = 8.5 Hz, 1H), 8.13 (d, *J* = 8.5 Hz, 1H), 7.88 (d, *J* = 8.1 Hz, 1H), 7.79 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 7.65 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 2.88 (s, 3H). Spectrum matched previously reported data.[71]



2-Propionylquinoline (5.61)

Prepared by analogy to **5.81** using ethylmagnesium bromide (3.0 M solution in Et_2O, 0.78 mL) and **5.80** (0.300 g, 1.95 mmol) to obtain the title compound (0.268 g, 74%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, *J* = 8.6 Hz, 1H), 8.19 (d, *J* = 8.4 Hz, 1H), 8.13 (d, *J* = 8.5 Hz, 1H), 7.87 (dd, *J* = 8.3, 1.4 Hz, 1H), 7.78 (ddd, *J* = 8.5, 6.9, 1.5 Hz, 1H), 7.64 (ddd, *J* = 8.2, 6.9, 1.2 Hz, 1H), 3.43 (q, *J* = 7.3 Hz, 2H), 1.28 (t, *J* = 7.3 Hz, 3H).

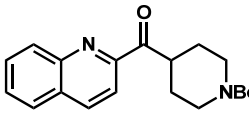


Isopropyl 2-quinolinyl ketone (5.83)

Weinreb amide **2.169** (0.461 g, 2.13 mmol) was dissolved in anhydrous THF (7 mL) and the solution was cooled to -78 °C and 2-propenylmagnesium bromide (0.5 M solution in THF, 6.4 mL) was added dropwise. The reaction mixture was stirred at -78 °C for 1 h and then allowed to warm to room temperature over 2 h. The reaction was quenched with sat. NH_4Cl (aq) and the mixture was extracted with EtOAc. The pooled organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. Crude enone **5.85** was redissolved in EtOAc (10 mL) and Pd/C (10 wt%, 0.04 g) was carefully added. The reaction vessel was fitted with a hydrogen balloon and the atmosphere was exchanged by brief application of vacuum. The heterogeneous

mixture was then stirred vigorously overnight and then filtered through Celite. The filtrate was concentrated to an oily residue, which was purified by flash chromatography (10% EtOAc in hexanes) to afford the title compound (0.120 g, 30% over two steps) as a colorless oil.

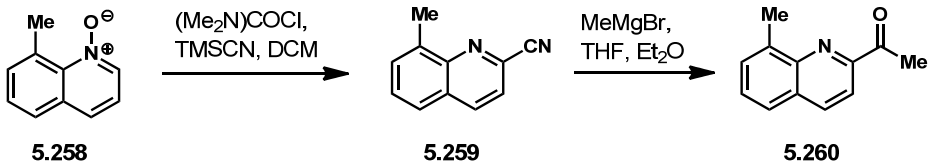
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.27 (d, *J* = 8.5 Hz, 1H), 8.21 (d, *J* = 8.5 Hz, 1H), 8.13 (d, *J* = 8.5 Hz, 1H), 7.90 – 7.85 (m, 1H), 7.78 (ddd, *J* = .2, 6.7, 1.3 Hz, 1H), 7.65 (t, *J* = 7.5 Hz, 1H), 4.40 (hept, *J* = 6.9 Hz, 1H), 1.28 (d, *J* = 6.9 Hz, 6H).



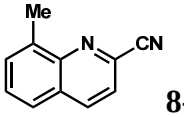
***tert*-butyl 4-(quinoline-2-carbonyl)piperidine-1-carboxylate (5.91)**

2-bromoquinoline (0.200 g, 0.961 mmol) was dissolved in anhydrous THF (5 mL). The solution was cooled to -78 °C and then *n*-BuLi (2.5 M solution in hexanes, 0.422 mL) was added dropwise. The resulting dark red solution was stirred for 0.5 h at -78 °C and then a solution of **5.90**[1] (0.262 g, 0.961) in anhydrous THF (1 mL) was added rapidly dropwise. The reaction mixture was then stirred at -78 °C for 4 h, at which time the reaction was quenched with sat. NH_4Cl (aq). The mixture was extracted with EtOAc and the pooled organics were washed with brine, dried over $MgSO_4$, and dried *in vacuo*. The crude product was purified by column chromatography (20% EtOAc in hexanes) to afford the title compound (0.280 g, 86%) as an orange oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, *J* = 8.4 Hz, 1H), 8.17 (d, *J* = 8.5 Hz, 1H), 8.09 (d, *J* = 8.5 Hz, 1H), 7.85 (d, *J* = 8.1 Hz, 1H), 7.77 (ddd, *J* = 8.4, 6.9, 1.5 Hz, 1H), 7.63 (ddd, *J* = 8.1, 6.8, 1.2 Hz, 1H), 4.35 – 4.04 (m, 3H), 3.06 – 2.88 (m, 2H), 2.03 – 1.89 (m, 2H), 1.77 – 1.62 (m, 2H), 1.52 – 1.39 (m, 9H).



5.258 **5.259** **5.260**

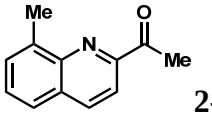


8-Methylquinoline-2-carbonitrile (5.259)

N-oxide **5.258** (0.900 g, 5.65 mmol) was dried by azeotropic distillation from benzene and then dissolved in anhydrous DCM (30 mL). TMSCN (1.12 g, 11.3 mmol) was added at room temperature, followed immediately by dropwise addition of dimethylcarbamyl chloride (1.21 g, 11.3 mmol). The resulting solution was allowed to age for 48 h at room temperature, and was then poured into sat. $NaHCO_3$ (aq). The mixture was extracted with DCM and the pooled organics were dried over Na_2SO_4 and concentrated *in vacuo*. The crude nitrile was purified by column chromatography (10% EtOAc in hexanes) to yield the title compound (0.760 g, 80%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, *J* = 8.4 Hz, 1H), 7.76 – 7.64 (m, 3H), 7.63 – 7.54 (m, 1H), 2.82 (s, 3H).

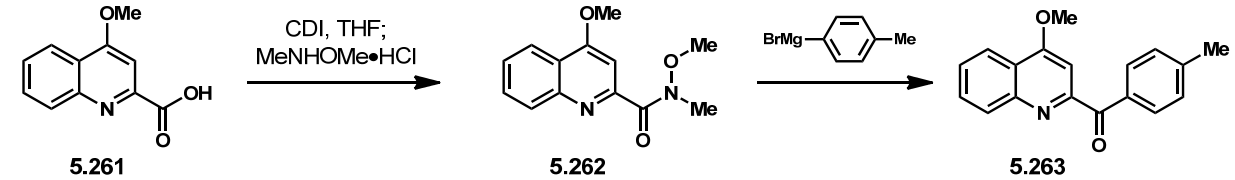
[1] Maynard, G. D.; Cheng, H. G.; Kane, J. M.; Staeger, M. A. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 753.



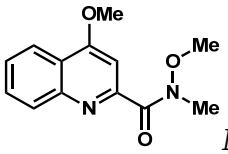
2-Acetyl-8-methylquinoline (5.260)

Prepared by analogy to **5.81** using methylmagnesium bromide (3.0 M, 1.09 mL) and **5.259** (0.423 g, 2.51 mmol) to obtain the title compound (0.164 g, 35%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 (d, *J* = 8.5 Hz, 1H), 8.12 (d, *J* = 8.5 Hz, 1H), 7.70 (d, *J* = 8.1 Hz, 1H), 7.63 (d, *J* = 7.0 Hz, 1H), 7.53 (t, *J* = 7.6 Hz, 1H), 2.89 (s, 3H), 2.88 (s, 3H).



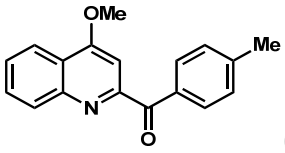
5.261 **5.262** **5.263**



***N*,4-dimethoxy-*N*-methylquinoline-2-carboxamide (5.262)**

To a stirred solution of 4-methoxyquinoline-2-carboxylic acid (**5.261**, 1.00 g, 4.92 mmol) in anhydrous DMF (15 mL) was added CDI (0.838 g, 5.17 mmol) in two portions over 5 minutes at room temperature. The mixture was stirred at room temperature for 10 h, at which time *N*,*O*-dimethylhydroxylamine hydrochloride (0.525 g, 5.41 mmol) was added in one portion. The mixture was stirred at room temperature for 14 h and then poured into water (100 mL). The aqueous solution was extracted with EtOAc, washed with water (x2) and then brine, dried over $MgSO_4$, and concentrated *in vacuo* to afford the title compound (1.02 g, 84%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (dd, *J* = 8.4, 1.4 Hz, 1H), 8.05 (d, *J* = 8.4 Hz, 1H), 7.73 (ddd, *J* = 8.4, 6.9, 1.5 Hz, 1H), 7.55 (ddd, *J* = 8.3, 6.9, 1.2 Hz, 1H), 7.08 (bs, 1H), 4.09 (s, 3H), 3.84 (bs, 3H), 3.47 (bs, 3H).



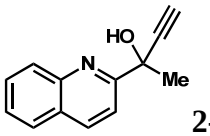
(4-methoxyquinolin-2-yl)(p-tolyl)methanone (5.263)

A stirred solution of 4-bromotoluene (0.347 g, 2.03 mmol) in anhydrous THF (4 mL) was cooled to -78 °C and then *n*-BuLi (2.5 M solution in hexanes, 0.89 mL) was added dropwise. The reaction mixture was stirred for 0.75 h at -78 °C and then a solution of **5.262** (0.500 g, 2.03 mmol) in anhydrous THF (8 mL) was added dropwise. The resulting mixture was stirred and slowly warmed to room temperature by allowing the cooling bath to expire (ca. 4 h). The reaction was quenched with sat. NH_4Cl (aq) and the mixture was extracted with EtOAc. The pooled organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by flash chromatography (10 → 20% EtOAc in hexanes) to afford the title compound (0.510 g, 91%) as a white solid.

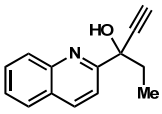
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.26 (d, *J* = 8.3 Hz, 1H), 8.16 (d, *J* = 7.9 Hz, 2H), 8.13 (d, *J* = 8.4 Hz, 1H), 7.78 – 7.72 (m, 1H), 7.65 – 7.55 (m, 1H), 7.46 (s, 1H), 7.31 (d, *J* = 7.8 Hz, 2H), 4.14 (s, 3H), 2.45 (s, 3H).

Substrate Synthesis: Preparation of (Iso)quinolinyl Propargylic Alcohols

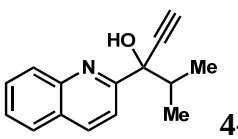
Representative Procedure A: Alkynylation with TMS-acetylide
Trimethylsilylacetylene (0.421 g, 4.29 mmol) was dissolved in anhydrous Et_2O (4 mL) and cooled to 0 °C. *n*-Butyllithium (2.5 M solution in hexanes, 1.43 mL) was added dropwise and the resulting solution was stirred for 1 h at 0 °C. Meanwhile, lithium bromide (0.50 g, 5.8 mmol) was flame-dried under vacuum in a 50 mL Schlenk flask until it became free-flowing. A solution of **5.81** (0.245 g, 1.43 mmol) in anhydrous Et_2O (4 mL) and benzene (5 mL) was added to the flask and stirring was initiated. The solution of lithium acetylide was added dropwise via cannula at room temperature and the resulting heterogeneous mixture was stirred overnight. The reaction was quenched with sat. NH_4Cl (aq) and the mixture was extracted with EtOAc. The pooled organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude carbinol was then dissolved in MeOH (30 mL) and K_2CO_3 (0.395 g, 2.86 mmol) was added. The mixture was stirred at room temperature for 12 h. Approximately half of the solvent was removed *in vacuo* and then H_2O was added. The mixture was extracted with EtOAc. The pooled extracts were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to afford a waxy residue that was purified by column chromatography (20 → 30% EtOAc in hexanes) to afford the title compound (0.213 g, 76% over two steps) as a white solid.



2-(quinolin-2-yl)but-3-yn-2-ol (5.82)
Prepared from **5.81** using Representative Procedure A.
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24 (d, *J* = 8.5 Hz, 1H), 8.09 (d, *J* = 8.6 Hz, 1H), 7.88 – 7.82 (m, 1H), 7.75 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 7.69 (d, *J* = 8.5 Hz, 1H), 7.58 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 6.28 (s, 1H), 2.56 (s, 1H), 1.87 (s, 3H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 160.8, 145.4, 138.0, 130.1, 128.8, 127.6, 127.5, 127.0, 117.8, 86.9, 71.9, 68.3, 31.7.
HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{13}H_{12}NO^+$, 198.0913; found, 198.0917.

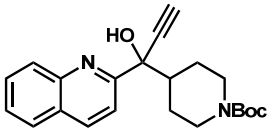


3-(quinolin-2-yl)pent-1-yn-3-ol (5.71)
Prepared from **5.61** (0.50 g, 2.70 mmol) using Representative Procedure A to obtain the title compound (0.477 g, 92%) as a colorless oil.
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24 (d, *J* = 8.6 Hz, 1H), 8.10 (d, *J* = 8.5 Hz, 1H), 7.90 – 7.83 (m, 1H), 7.75 (ddd, *J* = 8.4, 7.0, 1.5 Hz, 1H), 7.67 (d, *J* = 8.6 Hz, 1H), 7.58 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 6.17 (bs, 1H), 2.56 (s, 1H), 2.20 (dq, *J* = 14.6, 7.4 Hz, 1H), 1.98 (dq, *J* = 14.4, 7.3 Hz, 1H), 0.99 (t, *J* = 7.3 Hz, 3H).
HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{14}H_{14}NO^+$, 212.1070; found, 212.1066.

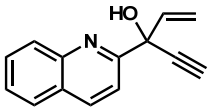


4-methyl-3-(quinolin-2-yl)pent-1-yn-3-ol (5.84)

Prepared from **5.83** (0.120 g, 0.602 mmol) using Representative Procedure A to obtain the title compound (0.111 g, 82% over two steps) as a colorless oil.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, *J* = 8.5 Hz, 1H), 8.09 (d, *J* = 8.4 Hz, 1H), 7.85 (d, *J* = 8.3 Hz, 1H), 7.74 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 7.68 (d, *J* = 8.6 Hz, 1H), 7.57 (ddd, *J* = 8.0, 6.9, 1.2 Hz, 1H), 6.09 (s, 1H), 2.56 (s, 1H), 2.29 (hept, *J* = 6.7 Hz, 1H), 1.24 (d, *J* = 6.7 Hz, 4H), 0.72 (d, *J* = 6.7 Hz, 3H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 160.0, 145.3, 137.5, 130.0, 128.8, 127.6, 127.5, 126.9, 118.6, 86.0, 74.5, 73.0, 39.7, 17.7, 16.0.
HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{15}H_{16}NO^+$, 226.1226; found, 226.1227.

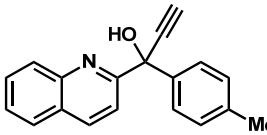


***tert*-butyl 4-(1-hydroxy-1-(quinolin-2-yl)prop-2-yn-1-yl)piperidine-1-carboxylate (5.92)**
Prepared from **5.91** (0.230 g, 0.68 mmol) using Representative Procedure A to obtain the title compound (0.171 g, 85% over two steps) as a colorless oil.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, *J* = 8.5 Hz, 1H), 8.08 (d, *J* = 8.5 Hz, 1H), 7.86 (d, *J* = 8.1 Hz, 1H), 7.76 (ddd, *J* = 8.5, 6.9, 1.5 Hz, 1H), 7.68 (d, *J* = 8.5 Hz, 1H), 7.59 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 6.10 (s, 1H), 4.47 – 3.82 (m, 2H), 2.75 – 2.43 (s, 3H), 2.09 – 1.95 (m, 2H), 1.70 – 1.52 (m, 1H), 1.49 – 1.30 (m, 1H), 1.20 – 1.08 (m, 1H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 158.8, 154.5, 145.2, 137.5, 130.1, 128.6, 127.5, 127.4, 126.9, 118.4, 85.0, 79.1, 77.2, 73.5, 47.7, 28.3, 26.6, 25.4.
HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{22}H_{27}N_2O_3^+$, 367.2016; found, 367.2017.

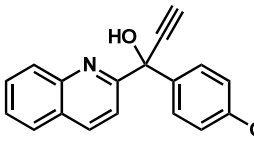


1-(quinolin-2-yl)-3-(triisopropylsilyl)prop-2-yn-1-one (5.88)
Triisopropylsilylacetylene (0.37 g, 2.04 mmol) was dissolved in anhydrous THF (2 mL) and then the solution was stirred and cooled to -78 °C. *n*-Butyllithium (2.5 M solution in hexanes, 0.82 mL) was added dropwise and stirred for 1.5 h. A solution of **5.169** (0.400 g, 1.85 mmol) in anhydrous THF (2 mL) was added dropwise at -78 °C and then the reaction mixture was stirred at that temperature for 2 h. The reaction was quenched by addition of sat. NH_4Cl (aq) and the mixture was extracted with EtOAc. The pooled organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to afford **5.86** as an orange residue that was used immediately without further purification.
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.29 (d, *J* = 8.5 Hz, 1H), 8.23 (dd, *J* = 8.5, 1.1 Hz, 1H), 8.19 (d, *J* = 8.5 Hz, 1H), 7.93 – 7.85 (m, 1H), 7.80 (ddd, *J* = 8.4, 6.8, 1.4 Hz, 1H), 7.67 (ddd, *J* = 8.2, 6.8, 1.2 Hz, 1H), 1.32 – 1.14 (m, 21H).
The crude ynone was dissolved in anhydrous THF (6 mL) and cooled to -20 °C. To the stirred solution was added vinylmagnesium bromide (0.7 M solution in THF, 4.0 mL) and the resulting milky suspension was stirred and allowed to warm to room temperature over approximately 2 h. The reaction was quenched with sat. NH_4Cl (aq) and the mixture was extracted with EtOAc. The pooled organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. Crude enyne **5.87** was redissolved in THF (6 mL) and then TBAF (1.0 M solution in THF, 3.7 mL) was added in one portion at room temperature. The resulting solution was allowed to stand overnight at room temperature and was then poured into sat. $NaHCO_3$ (aq). The mixture was

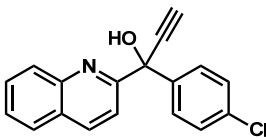
extracted with EtOAc, washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to afford a yellow residue that was purified by column chromatography (10 → 20% EtOAc in hexanes. The title compound (0.100 g, 26% over three steps) as a colorless oil.
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.22 (d, *J* = 8.6 Hz, 1H), 8.10 (d, *J* = 8.5 Hz, 1H), 7.86 (d, *J* = 8.1 Hz, 1H), 7.76 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 7.64 – 7.55 (m, 2H), 6.62 (s, 1H), 6.00 (d, *J* = 17.0, 10.0 Hz, 1H), 5.91 (d, *J* = 17.0, 1.0 Hz), 1H), 5.35 (dd, *J* = 9.8, 1.3 Hz, 1H), 2.70 (s, 1H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 158.5, 145.3, 139.7, 137.9, 130.2, 128.8, 128.3, 127.7, 127.5, 127.1, 118.7, 116.3, 83.9, 74.7, 72.0.
HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{14}H_{12}NO$, 210.0913; found, 210.0913.



1-(Quinolin-2-yl)-1-(p-tolyl)prop-2-yn-1-ol (5.76)
quinolin-2-yl(p-tolyl)methanone (**5.75**, 0.676 g, 2.73 mmol) was dissolved in 7 mL dry THF and the resulting solution was cooled to 0 °C. Ethynylmagnesium bromide (0.5 M, 3.6 mmol) was added dropwise and the reaction mixture was stirred at 0 °C for 1 h and then at rt for 2 h. The reaction was quenched with sat. NH_4Cl and the mixture was extracted three times with EtOAc. The pooled organics were washed with brine, dried over $MgSO_4$, and concentrated to afford a brown syrup which was purified by flash chromatography (10% EtOAc in hexanes). The title compound (0.549 g, 74%) was obtained as an off-white solid.
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 (d, *J* = 8.4 Hz, 1H), 8.11 (d, *J* = 8.6 Hz, 1H), 7.84 – 7.75 (m, 2H), 7.61 – 7.55 (m, 3H), 7.44 (d, *J* = 8.6 Hz, 1H), 7.22 (s, 1H), 7.15 (d, *J* = 8.7 Hz, 2H), 2.82 (s, 1H), 2.33 (s, 3H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 160.1, 145.0, 140.0, 138.0, 137.9, 130.2, 129.1, 128.7, 127.6, 127.5, 127.1, 126.5, 119.3, 85.3, 75.1, 73.1, 21.1.
HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{19}H_{16}NO^+$, 274.1226; found, 274.1234.

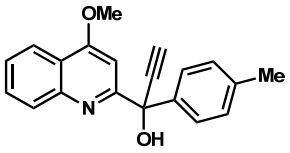


1-(4-Methoxyphenyl)-1-(quinolin-2-yl)prop-2-yn-1-ol (5.93)
Prepared by analogy to **5.76** using ethynylmagnesium bromide (0.5 M solution in THF, 4.44 mL) and **2.169** (0.390 g, 1.48 mmol) to obtain the title compound (0.358 g, 84%) as a pale yellow syrup.
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 (d, *J* = 8.4 Hz, 1H), 8.12 (d, *J* = 9.1 Hz, 1H), 7.82 (d, *J* = 7.9 Hz, 1H), 7.78 (t, *J* = 7.8 Hz, 1H), 7.62 – 7.57 (m, 3H), 7.42 (d, *J* = 8.7 Hz, 1H), 7.19 (s, 1H), 6.86 (dd, *J* = 8.5, 1.6 Hz, 2H), 3.78 (s, 3H), 2.81 (s, 1H).
^{13}C NMR (150 MHz, $CDCl_3$) δ 159.8, 159.2, 144.7, 137.7, 134.9, 130.0, 128.4, 127.7, 127.3 (two peaks), 126.8, 119.0, 113.5, 85.2, 75.0, 72.6, 55.0
HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{19}H_{16}NO_2^+$, 290.1176; found, 290.1180.



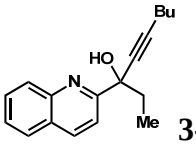
1-(Quinolin-2-yl)-1-(4-(trifluoromethyl)phenyl)prop-2-yn-1-ol (5.94)

Prepared by analogy to **5.76** using ethynylmagnesium bromide (0.5 M solution in THF, 4.94 mL) and **5.257** (0.477 g, 1.48 mmol) to obtain the title compound (0.479 g, 89%) as an off-white solid.
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 (dd, *J* = 8.5, 2.9 Hz, 2H), 7.84 (d, *J* = 8.1 Hz, 3H), 7.80 (ddd, *J* = 8.5, 6.9, 1.5 Hz, 1H), 7.64 – 7.57 (m, 3H), 7.43 (d, *J* = 8.6 Hz, 1H), 7.32 (s, 1H), 2.87 (s, 1H).
^{13}C NMR (125 MHz, $CDCl_3$) δ 158.9, 146.8, 145.1, 138.3, 130.5, 130.4, 130.2, 128.8, 127.7, 127.6, 127.4, 127.0, 125.4, 124.9, 123.1, 118.9, 84.5, 75.7, 72.9.
HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{19}H_{13}F_3NO^+$, 328.0944; found, 328.0951.



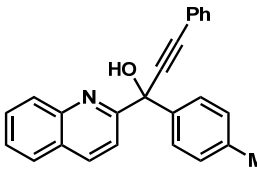
1-(4-methoxyquinolin-2-yl)-1-(p-tolyl)prop-2-yn-1-ol (5.95)

Prepared by analogy to **5.76** using ethynylmagnesium bromide (0.5 M solution in THF, 7.2 mL) and **5.263** (0.50 g, 1.8 mmol) to obtain the title compound (0.51 g, 93%) as a white solid.
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.1 Hz, 1H), 7.96 (d, *J* = 8.2 Hz, 1H), 7.61 (t, *J* = 7.7 Hz, 1H), 7.56 7.48 (m, 2H), 7.39 (t, *J* = 7.6 Hz, 1H), 7.31 (s, 1H), 7.06 (d, *J* = 7.6 Hz, 2H), 6.65 (dt, *J* = 4.4, 2.1 Hz, 1H), 3.82 (s, 3H), 2.73 (s, 1H), 2.23 (s, 3H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 163.2, 161.3, 145.7, 140.2, 137.7, 130.2, 128.9, 128.2, 126.4, 126.0, 121.8, 120.8, 97.5, 85.6, 74.7, 73.0, 55.7, 21.0.
HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{20}H_{18}NO_2^+$, 304.1332; found, 304.1335.



3-(quinolin-2-yl)non-4-yn-3-ol (5.59)

Prepared from **5.61** (0.50 g, 2.70 mmol) using Representative Procedure A, but 1-hexyne was used in place of TMS-acetylene. Accordingly, the subsequent desilation step was not performed. The title compound (0.477 g, 92%) was obtained as a colorless oil.
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.20 (d, *J* = 8.5 Hz, 1H), 8.07 (d, *J* = 8.4 Hz, 1H), 7.84 (d, *J* = 8.1 Hz, 1H), 7.75 – 7.70 (m, 1H), 7.66 (d, *J* = 8.6 Hz, 1H), 7.55 (t, *J* = 7.5 Hz, 1H), 6.09 (bs, 1H), 2.29 – 2.20 (m, 2H), 2.13 (dq, *J* = 14.5, 7.4 Hz, 1H), 1.93 (dq, *J* = 14.4, 7.3 Hz, 1H), 1.55 – 1.47 (m, 2H), 1.40 (h, *J* = 7.3 Hz, 2H), 0.97 (t, *J* = 7.3 Hz, 3H), 0.90 (t, *J* = 7.4 Hz, 3H). Spectrum matched previously reported data.[72]



3-Phenyl-1-(quinolin-2-yl)-1-(p-tolyl)prop-2-yn-1-ol (5.96)

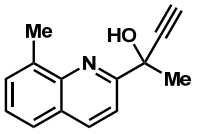
Phenylacetylene (0.166 g, 1.62 mmol) was dissolved in 2 mL dry THF and the resulting solution was cooled to 0 °C. Ethylmagnesium bromide (3.0 M, 0.35 mL) was added dropwise and the resulting mixture was stirred at room temperature for 1 h. This solution was then added dropwise to a solution of quinolin-2-yl(p-tolyl)methanone (**5.75**, 0.200 g, 0.81 mmol) in 4 mL dry THF that was cooled to 0 °C. The reaction mixture was stirred for 1 h at 0 °C and 3 h at

room temperature, at which time the reaction was quenched with sat. NH_4Cl (aq). The mixture was extracted three times with EtOAc. The pooled organics were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to afford an orange syrup, which was purified by flash chromatography (10% EtOAc in hexanes). The title compound (0.247 g, 87%) was obtained as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 (d, *J* = 8.4 Hz, 1H), 8.12 (d, *J* = 8.6 Hz, 1H), 7.82 (d, *J* = 8.1 Hz, 1H), 7.78 (t, *J* = 7.6 Hz, 1H), 7.67 (d, *J* = 8.0 Hz, 2H), 7.62 – 7.47 (m, 4H), 7.38 – 7.29 (m, 4H), 7.19 (d, *J* = 7.8 Hz, 2H), 2.35 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 160.5, 145.0, 140.7, 137.8, 137.7, 131.8, 130.1, 129.0, 128.8, 128.6, 128.2, 127.6, 127.5, 127.0, 126.6, 122.5, 119.5, 90.7, 86.8, 73.6, 21.1.

HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{25}H_{20}NO^+$, 350.1539; found, 350.1543.



2-(8-methylquinolin-2-yl)but-3-yn-2-ol (5.97)

Prepared from **5.260** (0.164 g, 0.886 mmol) using Representative Procedure A to obtain the title compound (0.140 g, 75% over two steps) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 (d, *J* = 8.5 Hz, 1H), 7.74 – 7.64 (m, 2H), 7.60 (d, *J* = 7.0 Hz, 1H), 7.47 (t, *J* = 7.6 Hz, 1H), 6.55 (s, 1H), 2.81 (s, 3H), 2.56 (s, 1H), 1.87 (s, 3H).

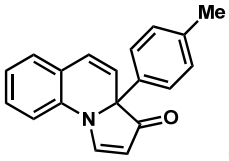
^{13}C NMR (126 MHz, $CDCl_3$) δ 159.5, 144.1, 138.4, 136.6, 130.4, 127.6, 126.8, 125.5, 117.5, 87.1, 71.8, 68.3, 31.7, 17.8.

HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{14}H_{13}NO^+$, 212.1070; found, 212.1068.

Synthesis of Benz[e]indolizinones

Representative Procedure B: Alcohol-Mediated Cycloisomerization

A solution of **5.76** (0.029 g, 0.106 mmol) in absolute EtOH (1.1 mL) was heated to 100 °C for 2 h. The crude reaction mixture was concentrated *in vacuo* and the resulting residue was purified by flash chromatography (20% EtOAc in hexanes) to afford **5.102** (0.027 g, 93%) as a yellow syrup.



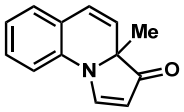
3a-(*p*-tolyl)pyrrolo[1,2-*a*]quinolin-3(3a*H*)-one (5.102)

Prepared from **5.76** using Representative Procedure B.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.26 (d, *J* = 3.6 Hz, 1H), 7.33 – 7.18 (m, 4H), 7.13 – 6.99 (m, 4H), 6.54 (d, 1H), 6.51 – 6.44 (m, 1H), 5.23 (d, *J* = 3.5 Hz, 1H), 2.24 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 200.9, 162.7, 137.7, 136.3, 136.0, 129.4, 129.4, 128.0, 127.1, 126.8, 125.5, 124.7, 124.5, 116.7, 98.7, 70.9, 21.0.

HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{19}H_{16}NO^+$, 274.1226; found, 274.1230.



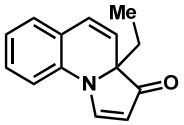
3a-methylpyrrolo[1,2-*a*]quinolin-3(3a*H*)-one (5.98)

Prepared from **5.82** (0.026 g, 0.115 mmol) using Representative Procedure B to obtain the title compound (0.024 g, 92%) as a colorless oil that solidified on standing.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (d, *J* = 3.6 Hz, 1H), 7.31 – 7.21 (m, 1H), 7.19 – 7.00 (m, 3H), 6.40 (d, *J* = 9.5 Hz, 1H), 6.08 (d, *J* = 9.5 Hz, 1H), 5.23 (d, *J* = 3.6 Hz, 1H), 1.35 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 202.6, 160.7, 135.3, 129.1, 127.9, 127.4, 126.5, 124.6, 124.3, 116.4, 98.4, 67.4, 24.1.

HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{13}H_{12}NO^+$, 198.0913; found, 198.0914.



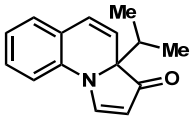
3a-methylpyrrolo[1,2-*a*]quinolin-3(3a*H*)-one (5.72)

Prepared from **5.71** (0.026 g, 0.115 mmol) using Representative Procedure B to obtain the title compound (0.024 g, 92%) as a colorless oil that solidified on standing.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 (d, *J* = 3.6 Hz, 1H), 7.28 (td, *J* = 7.7, 1.3 Hz, 1H), 7.14 (d, *J* = 7.9 Hz, 2H), 7.08 (t, *J* = 7.5 Hz, 1H), 6.45 (d, *J* = 9.5 Hz, 1H), 6.05 (*J* = 9.5 Hz, 1H), 5.27 (d, *J* = 3.6 Hz, 1H), 1.89 (dq, *J* = 14.1, 7.2 Hz, 1H), 1.71 (dq, *J* = 14.1, 7.2 Hz, 1H), 0.79 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 202.4, 162.5, 136.1, 129.1, 127.8, 127.2, 126.9, 125.0, 124.4, 116.5, 100.5, 71.0, 31.6, 6.9.

HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{14}H_{14}NO^+$, 212.1075; found, 212.1067.



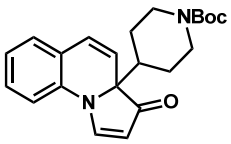
3a-isopropylpyrrolo[1,2-*a*]quinolin-3(3a*H*)-one (5.99)

Prepared from **5.84** (0.026 g, 0.115 mmol) using Representative Procedure B to obtain the title compound (0.023 g, 88%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (d, *J* = 3.7 Hz, 1H), 7.29 – 7.21 (m, 1H), 7.16 – 7.00 (m, 4H), 6.49 (d, *J* = 9.6 Hz, 1H), 6.00 (d, *J* = 9.6 Hz, 1H), 5.23 (d, *J* = 3.6 Hz, 1H), 2.09 (hept, *J* = 6.8 Hz, 1H), 0.94 (d, *J* = 6.8 Hz, 3H), 0.84 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 202.8, 163.8, 137.5, 129.1, 127.6, 127.6, 126.9, 125.5, 124.4, 116.7, 100.8, 73.3, 37.3, 16.3, 14.8.

HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{15}H_{16}NO^+$, 226.1226; found, 226.1227.

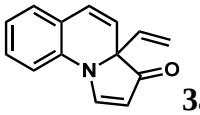


***tert*-butyl 4-(3-oxo-3,3a-dihydropyrrolo[1,2-*a*]quinolin-3a-yl)piperidine-1-carboxylate (5.100)**

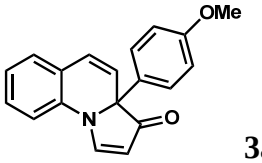
Prepared from **5.92** (0.043 g, 0.118 mmol) using Representative Procedure B to obtain the title compound (0.041 g, 95%) as a white foam.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (d, *J* = 3.7 Hz, 1H), 7.29 – 7.21 (m, 1H), 7.13 – 7.02 (m, 3H), 6.51 (d, *J* 9.6 Hz, 1H), 5.91 (d, *J* = 9.5 Hz, 1H), 5.24 (d, *J* = 3.7 Hz, 1H), 4.04 (bs, 2H),

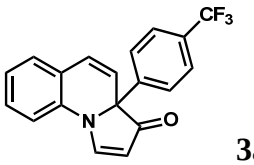
2.62 – 2.37 (m, 2H), 1.95 – 1.82 (m, 1H), 1.76 (bd, *J* = 13.0 Hz, 1H), 1.59 – 1.28 (m, 13H), 1.17 – 1.02 (m, 1H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 202.3, 164.6, 154.5, 137.5, 129.4, 127.8, 127.3, 126.2, 125.4, 124.6, 116.8, 100.9, 79.4, 77.2, 72.6, 45.4, 28.4, 25.3, 24.1.
HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{22}H_{27}N_2O_3^+$, 367.2016; found, 367.2022.



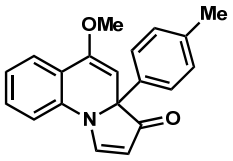
3a-vinylpyrrolo[1,2-*a*]quinolin-3(3a*H*)-one (5.101)
Prepared from **5.88** (0.0218 g, 0.1042 mmol) using Representative Procedure B to obtain the title compound (0.0205 g, 88%) as a yellow oil.
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21 (d, *J* = 3.6 Hz, 1H), 7.32 (td, *J* = 7.7, 1.5 Hz, 1H), 7.19 (t, *J* = 7.9 Hz, 2H), 7.14 – 7.07 (m, 1H), 6.54 (d, *J* = 9.5 Hz, 1H), 6.19 (d, *J* = 9.5 Hz, 1H), 5.76 (dd, *J* = 17.1, 10.3 Hz, 1H), 5.27 – 5.19 (m, 2H), 5.12 (d, *J* = 10.3 Hz, 1H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 200.0, 161.8, 135.8, 134.0, 129.4, 128.0, 126.6, 125.6, 124.7, 124.4, 116.3, 114.8, 98.7, 71.5.
HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{14}H_{12}NO$, 210.0913; found, 210.0913.



3a-(*p*-tolyl)pyrrolo[1,2-*a*]quinolin-3(3a*H*)-one (5.103)
Prepared from **5.76** (0.108 g, 0.373 mmol) using Representative Procedure B to obtain the title compound (0.098 g, 91%) as a colorless foam.
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.27 (d, *J* = 3.5 Hz, 1H), 7.32-7.27 (m, 3H), 7.22 (d, *J* = 8.0 Hz, 1H), 7.11 (d, *J* = 7.0 Hz, 1H), 7.05 (t, *J* = 7.0 Hz, 1H), 6.80 (d, *J* = 9.0 Hz, 2H), 6.55 (d, *J* = 9.5 Hz, 1H), 6.46 (d, *J* = 9.5 Hz, 1H), 5.25 (d, *J* = 3.5 Hz, 1H), 3.72 (s, 3H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 201.2, 162.9, 159.2, 136.2, 130.9, 129.4, 128.0, 127.1, 126.8, 126.1, 125.5, 124.6, 116.8, 114.1, 70.6, 55.2.
HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{19}H_{16}NO_2^+$, 290.1176; found, 290.1179.



3a-(4-(trifluoromethyl)phenyl)pyrrolo[1,2-*a*]quinolin-3(3a*H*)-one (5.104)
Prepared from **5.257** (0.036 g, 0.110 mmol) using Representative Procedure B to obtain the title compound (0.034 g, 94%) as a yellow foam.
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (d, *J* = 3.6 Hz, 1H), 7.10 – 6.95 (m, 2H), 6.90 – 6.76 (m, 2H), 6.32 (d, *J* = 9.4 Hz, 1H), 6.22 (d, *J* = 9.4 Hz, 1H), 5.00 (d, *J* = 3.6 Hz, 1H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 199.8, 163.3, 142.7, 136.0, 130.1, 129.9, 129.8, 128.2, 126.8, 126.3, 125.9, 125.7, 125.7, 125.7, 125.6, 125.2, 125.0, 124.9, 122.8, 116.8, 98.9, 70.5.
HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{19}H_{13}F_3NO^+$, 328.0944; found, 328.0949.



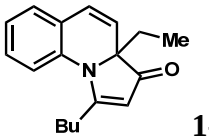
5-methoxy-3a-(*p*-tolyl)pyrrolo[1,2-*a*]quinolin-3(3a*H*)-one (5.105)

Prepared from **5.95** (0.0275 g, 0.0906 mmol) using Representative Procedure B to obtain the title compound (0.0255 g, 93%) as a white foam.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.26 (d, *J* = 3.6 Hz, 1H), 7.52 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.32 (td, *J* = 7.7, 1.5 Hz, 1H), 7.30 – 7.26 (m, 1H), 7.22 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.11 – 7.05 (m, 3H), 5.55 (s, 1H), 5.32 (d, *J* = 3.6 Hz, 1H), 3.80 (s, 3H), 2.26 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 202.2, 162.3, 151.6, 137.5, 136.6, 136.3, 129.9, 129.3, 124.9, 124.7, 124.3, 123.9, 116.5, 99.5, 96.1, 70.6, 55.3, 21.0.

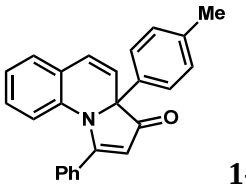
HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{20}H_{18}NO_2$, 304.1332; found, 304.1330.



1-butyl-3a-ethylpyrrolo[1,2-*a*]quinolin-3(3a*H*)-one (5.60)

Prepared by analogy to **5.106** using **5.59** (0.018 g, 0.118 mmol) to obtain the title compound (0.016 g, 95%) as a colorless syrup.

^{1}H NMR (500 MHz, C_6D_6) δ (dt, *J* = 7.6, 1.7 Hz, 1H), 6.82-6.66 (m, 3H), 6.18 (d, *J* = 9.4 Hz, 1H), 6.00 (d, *J* = 9.4 Hz, 1H), 2.17-2.05 (m, 1H), 2.02-1.92 (m, 2H), 1.63-1.54 (m, 1H), 1.22-1.05 (m, 1H), 1.10-0.87 (m, 3H), 0.77 (t, *J* = 7.4 Hz, 3H), 0.59 (t, *J* = 7.3 Hz, 3H). Spectrum matched previously reported data.[73]



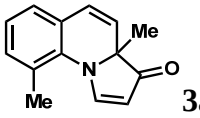
1-phenyl-3a-(*p*-tolyl)pyrrolo[1,2-*a*]quinolin-3(3a*H*)-one (5.106)

A solution of **5.96** (0.024 g, 0.069 mmol) in nitrogen sparged 1-propanol (0.69 mL) was heated to 120 °C for 9 h. The crude reaction mixture was concentrated *in vacuo* and the resulting residue was purified by flash chromatography (10% EtOAc in hexanes) to obtain the title compound (0.023 g, 95%) as a yellow solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 – 7.45 (m, 1H), 7.41 (t, *J* = 7.5 Hz, 2H), 7.31 (d, *J* = 8.2 Hz, 2H), 7.27 (d, *J* = 7.0 Hz, 2H), 7.14 – 7.05 (m, 3H), 6.98 (td, *J* = 7.6, 1.2 Hz, 1H), 6.88 (td, *J* = 7.8, 1.5 Hz, 1H), 6.72 – 6.65 (m, 2H), 6.47 (d, *J* = 8.0 Hz, 1H), 5.23 (s, 1H), 2.26 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 198.5, 174.5, 137.5, 135.3, 133.7, 130.7, 130.2, 129.3, 129.2, 128.9, 128.4, 128.2, 127.6, 127.4, 126.4, 125.3, 124.9, 122.9, 99.6, 73.0, 21.0.

HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{25}H_{20}NO$, 350.1539; found, 350.1539.

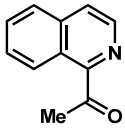


3a,9-dimethylpyrrolo[1,2-*a*]quinolin-3(3a*H*)-one (5.107)

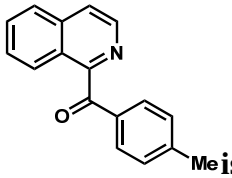
Prepared by analogy to **5.106** using **5.97** (0.021 g, 0.099 mmol) to obtain the title compound (0.0183 g, 87%) as a pale yellow solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 (d, *J* = 3.4 Hz, 1H), 7.15 (d, *J* = 7.5 Hz, 1H), 7.03 (t, *J* = 7.5 Hz, 1H), 7.00 – 6.96 (m, 1H), 6.37 (d, *J* = 9.3 Hz, 1H), 6.02 (d, *J* = 9.2 Hz, 1H), 5.24 (d, *J* = 3.4 Hz, 1H), 2.40 (s, 3H), 1.34 (s, 3H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 201.9, 162.7, 134.0, 131.6, 129.1, 128.5, 128.0, 125.5, 124.9, 124.9, 98.1, 68.5, 22.1, 17.9.
HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{14}H_{14}NO$, 212.1070; found, 212.1069.

Substrate Synthesis: Preparation of Isoquinolinyl Ketones

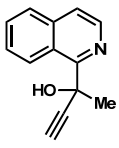


1-acetylisoquinoline (5.264)
Prepared by analogy to **5.81** using methylmagnesium bromide (3.0 M, 0.78 mL) and 1-isoquinolinecarbonitrile (0.300 g, 1.95 mmol) to obtain the title compound (0.271 g, 81%) as a colorless oil.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.96 (d, *J* = 8.2 Hz, 1H), 8.58 (d, *J* = 5.5 Hz, 1H), 7.92 – 7.77 (m, 2H), 7.77 – 7.63 (m, 2H), 2.87 (s, 3H).



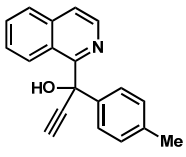
isoquinolin-1-yl(p-tolyl)methanone (5.265)
A stirred solution of *N*-methoxy-*N*-methylisoquinoline-1-carboxamide[74] (0.400 g, 1.85 mmol) in anhydrous THF (10 mL) was cooled to -78 °C and then 4-tolylmagnesium bromide (1.0 M solution in THF, 2.8 mL) was added dropwise. The resulting yellow solution was stirred for 1 h at -78 °C and then allowed to warm to room temperature over 1 h. The reaction was quenched with sat. NH_4Cl (aq) and then the mixture was extracted with EtOAc. The pooled organics were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by flash chromatography (10% EtOAc in hexanes) to afford the title compound (0.341 g, 74%) as a white solid.
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.60 (d, *J* = 5.6 Hz, 1H), 8.19 (dd, *J* = 8.6, 1.1 Hz, 1H), 7.93 (d, *J* = 8.3 Hz, 1H), 7.87 – 7.79 (m, 3H), 7.75 (ddd, *J* = 8.2, 6.9, 1.2 Hz, 1H), 7.62 (ddd, *J* = 8.2, 6.8, 1.2 Hz, 1H), 7.28 (d, *J* = 7.9 Hz, 2H), 2.43 (s, 3H).

Substrate Synthesis: Preparation of Isoquinolinyl Propargylic Alcohols



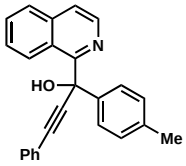
2-(isoquinolin-1-yl)but-3-yn-2-ol (5.108)
Prepared from **5.264** (0.270 g, 1.58 mmol) using Representative Procedure A to obtain the title compound (0.143 g, 46% over two steps) as a white solid.
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.74 (d, *J* = 8.4 Hz, 1H), 8.41 (d, *J* = 5.6 Hz, 1H), 7.90 (d, *J* = 8.1 Hz, 1H), 7.74 (ddd, *J* = 8.1, 6.8, 1.2 Hz, 1H), 7.70 – 7.63 (m, 2H), 2.65 (s, 1H), 1.98 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 158.6, 138.7, 137.5, 130.4, 127.7, 127.1, 126.5, 124.2, 122.1, 87.2, 72.8, 67.0, 31.9.
HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{13}H_{12}NO^+$, 198.0913; found, 198.0913.



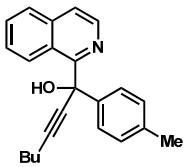
1-(isoquinolin-1-yl)-1-(p-tolyl)prop-2-yn-1-ol (5.109)

Ketone **5.265** was dried by azeotropic distillation from benzene and then dissolved in anhydrous THF (3 mL). The resulting solution was stirred at 0 °C and ethynylmagnesium bromide (0.5 M solution in THF, 5.3 mL) was added rapidly. The reaction mixture became heterogeneous and was allowed to warm to room temperature by letting the cooling bath expire and then stirred for 4 h at room temperature. The reaction was quenched with sat. NH_4Cl (aq) and then the mixture was extracted with EtOAc. The pooled organics were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo.* The crude product was purified by flash chromatography (20% EtOAc in hexanes) to afford the title compound (0.330 g, 91%) as a white solid.
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.52 (d, *J* = 5.7 Hz, 1H), 8.13 (d, *J* = 8.6 Hz, 1H), 7.85 (d, *J* = 8.3 Hz, 1H), 7.74 (d, *J* = 5.7 Hz, 1H), 7.63 (ddd, *J* = 8.1, 6.9, 1.1 Hz, 1H), 7.45 – 7.37 (m, 3H), 7.10 (d, *J* = 7.9 Hz, 2H), 2.84 (s, 1H), 2.29 (s, 3H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 157.6, 140.5, 138.3, 137.9, 137.6, 130.3, 129.2, 127.3, 127.1, 127.1, 126.7, 124.5, 122.5, 85.1, 75.9, 71.9, 21.1.
HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{19}H_{16}NO^+$, 274.1226; found, 274.1233.



1-(isoquinolin-1-yl)-3-phenyl-1-(p-tolyl)prop-2-yn-1-ol (5.110)

Prepared by analogy to **5.111** using phenylacetylene (0.310 g, 3.03 mmol), ethylmagnesium bromide (3.0 M solution in Et_2O, 0.68 mL), and **5.265** (0.250 g, 1.01 mmol) to obtain the title compound (0.315 g, 89%) as a white foam.
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.53 (d, *J* = 5.7 Hz, 1H), 8.28 (d, *J* = 8.6 Hz, 1H), 7.99 (b, 1H), 7.85 (d, *J* = 8.2 Hz, 1H), 7.74 (d, *J* = 5.6 Hz, 1H), 7.62 (dd, *J* = 8.2, 6.8 Hz, 1H), 7.53 – 7.38 (m, 5H), 7.33 – 7.22 (m, 3H), 7.11 (d, *J* = 7.8 Hz, 2H), 2.31 (s, 3H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 158.2, 141.3, 138.4, 137.8, 137.6, 131.7, 130.2, 129.2, 128.5, 128.2, 127.3, 127.2, 127.0, 126.8, 124.7, 122.6, 122.4, 90.8, 87.5, 72.4, 21.1.
HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{25}H_{20}NO^+$, 350.1539; found, 350.1539.

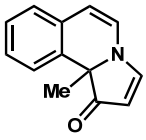


1-(isoquinolin-1-yl)-1-(p-tolyl)hept-2-yn-1-ol (5.111)

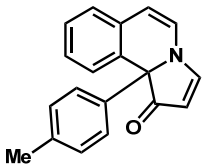
A stirred solution of 1-hexyne (0.251 g, 0.306 mmol) in anhydrous THF (4 mL) was cooled to 0 °C and then ethylmagnesium bromide (3.0 M solution in Et_2O, 0.68 mL) was added dropwise. The resulting grey solution was stirred at 0 °C for 2 h and then a solution of **5.265** (0.250 g, 1.01 mmol) in anhydrous THF (4 mL) was added dropwise. The reaction mixture was warmed to

room temperature by allowing the cooling bath to expire and then stirred for a further 2 h. The reaction was quenched with sat. NH_4Cl (aq) and the mixture was extracted with EtOAc. The pooled organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by flash chromatography (15% EtOAc in hexanes) to afford the title compound (0.283, 86%) as a colorless syrup.
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.50 (d, *J* = 5.6 Hz, 1H), 8.19 (d, *J* = 8.7 Hz, 1H), 7.83 (d, *J* = 8.2 Hz, 1H), 7.71 (d, *J* = 5.7 Hz, 1H), 7.61 (ddd, *J* = 8.2, 6.9, 1.2 Hz, 1H), 7.45 – 7.34 (m, 3H), 7.07 (d, *J* = 7.9 Hz, 2H), 2.38 – 2.20 (m, 5H), 1.55 – 1.45 (m, 2H), 1.41 – 1.30 (m, 2H), 0.85 (t, *J* = 7.3 Hz, 3H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 158.7, 141.6, 138.2, 137.3, 137.3, 129.9, 128.9, 127.2, 127.1, 126.6, 126.5, 124.4, 122.0, 88.5, 81.7, 71.9, 30.4, 21.8, 20.9, 18.5, 13.4.
HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{23}H_{24}NO^+$, 330.1852; found, 330.1858.

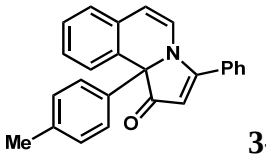
Synthesis of Benz[g]indolizinones



10b-methylpyrrolo[2,1-*a*]isoquinolin-1(10b*H*)-one (5.112)
Prepared from **5.108** (0.0259 g, 0.1313 mmol) using Representative Procedure B to obtain the title compound (0.0236 g, 91%) as a brilliant orange residue.
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 – 8.00 (m, 1H), 7.77 (d, *J* = 3.6 Hz, 1H), 7.23 – 7.15 (m, 2H), 7.08 – 7.01 (m, 1H), 6.47 (d, *J* = 7.2 Hz, 1H), 5.93 (d, *J* = 7.2 Hz, 1H), 5.23 (d, *J* = 3.6 Hz, 1H), 1.52 (s, 3H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 202.7, 157.7, 132.8, 130.6, 127.6, 126.8, 125.8, 123.7, 123.5, 110.8, 99.3, 65.7, 27.6.
HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{13}H_{12}NO^+$, 198.0913; found, 198.0917.

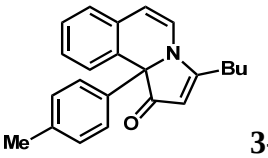


10b-methylpyrrolo[2,1-*a*]isoquinolin-1(10b*H*)-one (5.113)
Prepared from **5.109** (1.80 g, 0.1313 mmol) using Representative Procedure B to obtain the title compound (1.67 g, 93%) as a yellow powder.
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.30 (d, *J* = 7.8 Hz, 1H), 8.01 (d, *J* = 3.6 Hz, 1H), 7.31 (t, *J* = 7.8 Hz, 1H), 7.27-7.24 (m, 1H), 7.13 (d, *J* = 7.2 Hz, 1H), 7.07-7.04 (m, 3H), 6.59 (d, *J* = 7.2 Hz, 1H), 5.91 (d, *J* = 7.2 Hz, 1H), 5.23 (d, *J* = 3.6 Hz, 1H), 2.26 (s, 3H).
HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{19}H_{16}NO^+$, 274.1226; found, 274.1228.



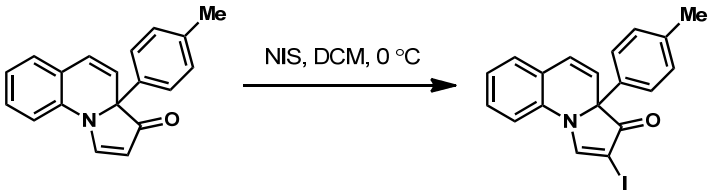
3-butyl-10b-(*p*-tolyl)pyrrolo[2,1-*a*]isoquinolin-1(10b*H*)-one (5.114)
Prepared from **5.110** (0.0292 g, 0.0836 mmol) using Representative Procedure B to obtain the title compound (0.0285 g, 98%) as a yellow solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.40 (d, *J* = 8.4 Hz, 1H), 7.64 – 7.59 (m, 2H), 7.58 – 7.52 (m, 3H), 7.36 – 7.31 (m, 1H), 7.31 – 7.27 (m, 1H), 7.22 – 7.15 (m, 2H), 7.13 – 7.04 (m, 3H), 6.73 (d, *J* = 7.3 Hz, 1H), 5.90 (d, *J* = 7.3 Hz, 1H), 5.32 (s, 1H), 2.27 (s, 3H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 198.5, 172.0, 137.6, 135.9, 131.7, 131.3, 131.1, 129.3, 129.2, 129.0, 129.0, 128.2, 128.0, 126.5, 126.0, 125.3, 125.3, 125.1, 122.8, 112.4, 100.6, 71.8, 21.0.
HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{25}H_{20}NO$, 350.1539; found, 350.1539.

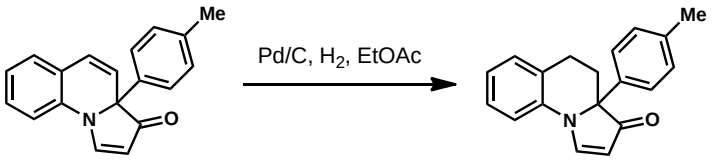


3-phenyl-10b-(*p*-tolyl)pyrrolo[2,1-*a*]isoquinolin-1(10b*H*)-one (5.115)
Prepared from **5.111** (0.0303 g, 0.0920 mmol) using Representative Procedure B to obtain the title compound (0.0275 g, 91%) as a yellow residue.
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.44 (d, *J* = 7.5 Hz, 1H), 7.37-7.29 (m, 2H), 7.16 (d, *J* = 8.5 Hz, 2H), 7.12-7.10 (m, 3H), 6.71 (d, *J* = 7.5 Hz, 1H), 5.15 (s, 1H), 2.70-2.58 (m, 2H), 2.31 (s, 3H), 1.78-1.75 (m, 2H), 1.548 (p, *J* = 7.5 Hz, 2H), 1.05 (t, *J* = 7.5 Hz, 3H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 198.9, 175.5, 137.5, 136.0, 131.8 (two peaks), 129.2, 128.0, 126.5, 126.1, 125.4, 125.1, 121.8, 112.6, 98.7, 71.4, 28.8, 27.2, 22.6, 21.1, 13.9.
HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{23}H_{24}NO$, 330.1852; found, 330.1853.

Derivatization Reactions:



2-iodo-3a-(*p*-tolyl)pyrrolo[1,2-*a*]quinolin-3(3a*H*)-one (5.116)
Benzindolizinone **5.102** (0.035 g, 0.129 mmol) was dissolved in anhydrous DCM (1.3 mL) and then the solution was stirred and cooled to 0 °C. NIS (0.032 g, 0.142 mmol) was added in one portion and the initially heterogeneous mixture was stirred for 2 h at 0 °C. The reaction was quenched with sat. $Na_2S_2O_3$ (aq) and the organic layer was collected. The aqueous layer was extracted with DCM and the pooled organic fractions were dried over Na_2SO_4 followed by concentration *in vacuo*. The crude product was purified by flash chromatography (10% EtOAc in hexanes) to afford the title compound (0.041 g, 80%) as a bright yellow foam.
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.35 (s, 1H), 7.35 – 7.19 (m, 4H, overlapping with solvent), 7.14 – 7.01 (m, 5H), 6.54 (d, *J* = 9.5 Hz, 1H), 6.48 (d, *J* = 9.5 Hz, 1H), 2.25 (s, 3H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 196.1, 165.3, 138.1, 135.4, 135.3, 129.6, 129.5, 128.0, 126.6, 126.3, 125.5, 125.1, 124.7, 116.7, 70.4, 58.1, 21.0.
HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{19}H_{15}INO$, 400.0193; found, 400.0198.



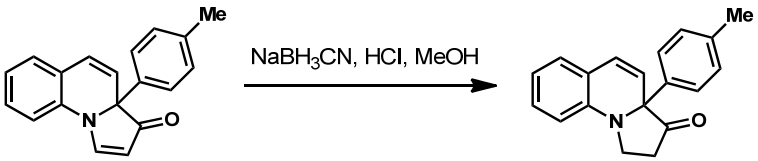
3a-(*p*-tolyl)-4,5-dihydropyrrolo[1,2-*a*]quinolin-3(3a*H*)-one (5.117)

Pd/C (10 wt%, 0.0023 g) was suspended in EtOAc (0.30 mL) and then a solution of **5.102** (0.0231 g, 0.0845 mmol) in EtOAc (0.55 mL) was added and the mixture was stirred at room temperature. A hydrogen atmosphere was introduced by evacuating the reaction flask and then affixing a hydrogen balloon. Vigorous stirring was maintained for 20 h and then the mixture was filtered using a syringe filter. The filtrate was concentrated and the crude material was purified by flash chromatography (10% EtOAc in hexanes). The title compound (0.0208 g, 89%) was obtained as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.42 (d, *J* = 3.6 Hz, 1H), 7.34 – 7.23 (m, 3H), 7.09 (d, *J* = 8.0 Hz, 2H), 7.04 (d, *J* = 7.5 Hz, 1H), 6.98 (td, *J* = 7.5, 1.5 Hz, 1H), 2.79 – 2.68 (m, 2H), 2.61 – 2.50 (m, 1H), 2.27 (s, 3H), 1.92 (td, *J* = 13.5, 5.0 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 202.5, 159.2, 137.4, 137.0, 132.4, 129.9, 129.5, 127.5, 126.4, 125.3, 123.1, 115.0, 100.8, 70.2, 30.2, 24.0, 21.0.

HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{19}H_{18}NO$, 276.1383; found, 276.1380.



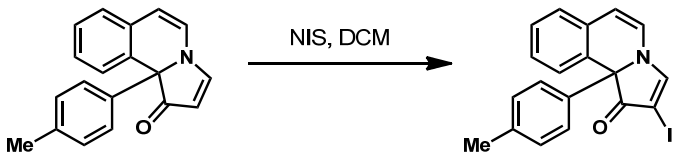
3a-(*p*-tolyl)-1,2-dihydropyrrolo[1,2-*a*]quinolin-3(3a*H*)-one (5.118)

To a solution of **5.102** (0.0206 g, 0.0754 mmol) in MeOH (0.8 mL) at room temperature was added $NaBH_3CN$ (0.0057 g, 0.090 mmol). The mixture was stirred until homogeneous and then 1 M HCl (0.8 mL) was added at room temperature in one portion. The mixture was stirred at room temperature for 2 h and then neutralized by addition of sat. $NaHCO_3$ (aq). The mixture was extracted with DCM and the pooled organics were dried over Na_2SO_4. The crude product was purified by flash chromatography (10% EtOAc in hexanes) to afford the title compound (0.017 g, 82%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 – 7.17 (m, 3H), 7.08 (d, *J* = 7.8 Hz, 2H), 6.99 (d, *J* = 7.4 Hz, 1H), 6.79 (d, *J* = 8.0 Hz, 1H), 6.72 (t, *J* = 7.4 Hz, 1H), 6.43 (d, *J* = 9.5 Hz, 1H), 6.05 (d, *J* = 9.6 Hz, 1H), 3.92 (ddd, *J* = 9.8, 3.7 Hz, 1H), 3.86 – 3.76 (m, 1H), 2.70 – 2.52 (m, 2H), 2.27 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 209.8, 143.1, 138.3, 137.5, 129.6, 129.4, 127.6, 124.9, 124.6, 122.7, 121.1, 117.6, 110.8, 68.4, 42.2, 33.4, 21.0.

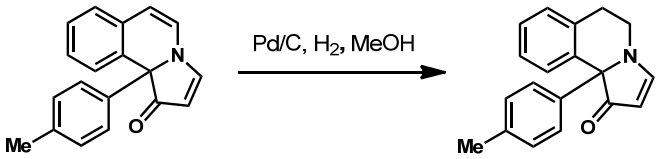
HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{19}H_{18}NO$, 276.1383; found, 276.1387



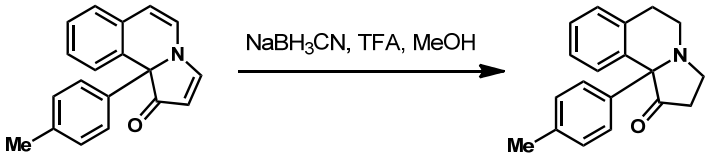
2-iodo-10b-(p-tolyl)pyrrolo[2,1-a]isoquinolin-1(10bH)-one (5.119)

A solution of **5.113** (0.039 g, 0.143 mmol) in DCM (1 mL) was cooled to -10 °C and then a solution of NIS (0.032 g, 0.143 mmol) in DCM (1 mL) was added dropwise. The resulting homogeneous mixture was stirred at -10 °C for 1 h and then at 0 °C for 1 h. The reaction was quenched by addition of sodium thiosulfate (aq). The aqueous layer was extracted with DCM, the pooled organics were dried over $MgSO_4$, and then concentrated *in vacuo*. The crude product was purified by column chromatography (10% to 20% EtOAc in hexanes) to afford the title compound (0.031 g, 54%) as a yellow solid.

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.28 (d, *J* = 7.7 Hz, 1H), 8.11 (s, 1H), 7.31 (td, *J* = 7.8, 1.5 Hz, 1H), 7.29 – 7.24 (m, 2H), 7.13 (d, *J* = 8.4 Hz, 2H), 7.09 – 7.03 (m, 3H), 6.59 (d, *J* = 7.1 Hz, 1H), 5.90 (d, *J* = 7.1 Hz, 1H), 2.26 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 195.4, 162.1, 138.0, 135.0, 131.1, 130.4, 129.3, 128.3, 127.0, 126.4, 125.2 (overlapping peaks), 123.5, 112.7, 69.8, 59.5, 21.0.
HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{19}H_{15}INO$, 400.0193; found, 400.0192.

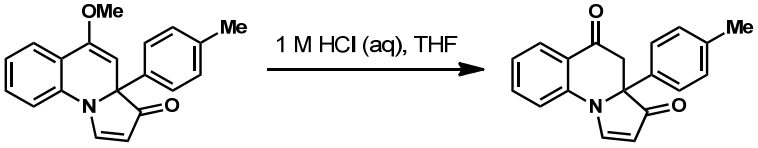


10b-(*p*-tolyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinolin-1(10b*H*)-one (5.120)
Pd/C (5 wt%, 0.004 g) was suspended in MeOH (1.0 mL) and then a solution of **5.113** (0.0235 g, 0.0860 mmol) in MeOH (1.2 mL) was added and the mixture was stirred at room temperature. A hydrogen atmosphere was introduced by evacuating the reaction flask and then affixing a hydrogen balloon. Vigorous stirring was maintained for 4 h and then the mixture was filtered using a syringe filter. The filtrate was concentrated and the crude material was purified by flash chromatography (50% EtOAc in hexanes). The title compound (0.0230 g, 97%) was obtained as a white solid.
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (d, *J* = 3.3 Hz, 1H), 7.90 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.33 – 7.22 (m, 2H), 7.16 (d, *J* = 6.6 Hz, 1H), 7.08 (d, *J* = 8.1 Hz, 2H), 6.96 (d, *J* = 8.3 Hz, 2H), 5.34 (d, *J* = 3.4 Hz, 1H), 3.69 (ddd, *J* = 13.5, 6.5, 3.5 Hz, 1H), 3.58 (ddd, *J* = 13.3, 10.7, 4.8 Hz, 1H), 3.04 – 2.93 (m, 1H), 2.93 – 2.83 (m, 1H), 2.30 (s, 3H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 202.8, 165.0, 137.7, 137.6, 133.5, 133.3, 129.2, 128.4, 128.4, 127.6, 127.3, 126.6, 100.2, 72.7, 43.4, 30.5, 21.0.
HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{19}H_{18}NO$, 276.1383; found, 276.1383



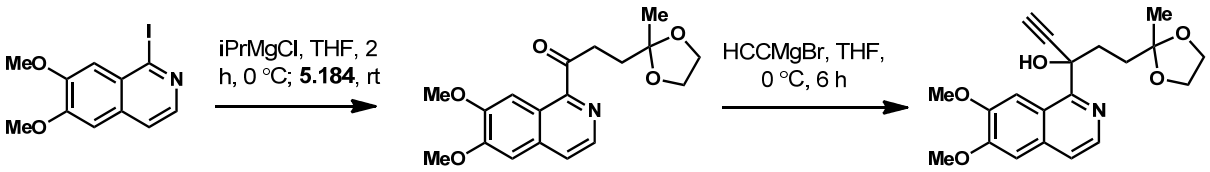
10b-(*p*-tolyl)-2,3,5,6-tetrahydropyrrolo[2,1-*a*]isoquinolin-1(10b*H*)-one (5.121)
A solution of **5.113** (1.40 g, 5.12 mmol) in methanol (60 mL) was cooled to 0 °C and then $NaBH_3CN$ (0.640 g, 10.2 mmol) was added, followed immediately by dropwise addition of trifluoroacetic acid (5.7 g, 3.83 mL, 50 mmol). The reaction mixture was stirred and allowed to warm to room temperature over 3 h, at which time the reaction was quenched by the addition of a small quantity of acetone as well as $NaHCO_3$ (aq). The organics were removed *in vacuo* and the remaining aqueous layer was extracted with DCM. The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo* to afford a crude solid that was further purified by column chromatography (40% EtOAc in hexanes) to afford the title compound (1.16 g, 81%) as a colorless solid.
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.47 (d, *J* = 7.8 Hz, 1H), 7.26 (td, *J* = 7.8, 1.8 Hz, 1H), 7.23 – 7.16 (m, 2H), 7.10 (d, *J* = 8.0 Hz, 2H), 7.04 (d, *J* = 8.0 Hz, 2H), 3.29 (td, *J* = 9.2, 2.0 Hz, 1H), 3.22 – 3.12 (m, 3H), 3.12 – 3.06 (m, 1H), 2.74 (dt, *J* = 18.6, 9.3 Hz, 1H), 2.67 – 2.58 (m, 1H), 2.55 (ddd, *J* = 18.5, 7.0, 2.0 Hz, 1H), 2.32 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 214.3, 140.3, 137.0, 135.1, 130.4, 129.6, 129.5, 128.7 (overlapping peaks), 127.3, 125.9, 72.9, 44.0, 41.5, 36.5, 22.4, 21.0.
HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{19}H_{20}NO^+$, 278.1539; found, 278.1534.



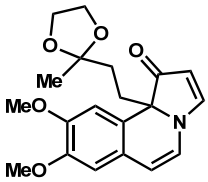
3a-(p-tolyl)-3a,4-dihydropyrrolo[1,2-a]quinoline-3,5-dione (5.122)
Enol ether **5.105** (0.030 g, 0.099 mmol) was dissolved in THF (1 mL) and 1 M HCl (1 mL) was added in one portion at room temperature. After 3 h at room temperature, the reaction was quenched with $NaHCO_3$ (aq) and the resulting mixture was extracted with EtOAc. The pooled organic fractions were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude material so obtained was purified by column chromatography (30% EtOAc in hexanes) to afford the title compound (0.027 g, 90%) of a colorless residue.
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.58 (d, J = 3.8 Hz, 1H), 7.83 (dd, J = 7.9, 1.6 Hz, 1H), 7.60 (ddd, J = 8.6, 7.3, 1.6 Hz, 1H), 7.34 (dd, J = 8.2, 1.0 Hz, 1H), 7.18 (d, J = 8.4 Hz, 2H), 7.11 – 7.03 (m, 3H), 5.63 (d, J = 3.7 Hz, 1H), 3.59 (d, J = 16.2 Hz, 1H), 2.95 (d, J = 16.2 Hz, 1H), 2.24 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 201.5, 190.8, 157.0, 140.5, 138.4, 135.9, 130.6, 129.8, 128.3, 125.5, 123.3, 122.3, 115.0, 103.6, 71.0, 43.9, 20.9.
HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{19}H_{16}NO_2^+$, 290.1176; found, 290.1179.

Total Synthesis of 3-Demethoxyerythratidinone

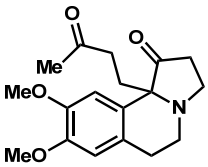


3-(6,7-dimethoxyisoquinolin-1-yl)-5-(2-methyl-1,3-dioxolan-2-yl)pent-1-yn-3-ol (5.179): Iodoisoquinoline **5.180**[75] (0.707 g, 2.24 mmol) was dissolved in THF (12 mL) in a Schlenk flask. The solution was cooled to 0 °C, isopropylmagnesium chloride (2.0 M in THF, 1.23 mL) was added dropwise and the solution was stirred at 0 °C for 2 h. A solution of **5.184**[76] (0.455 g, 2.24 mmol) in THF (6 mL) was then added dropwise at 0 °C. The resulting solution was stirred at room temperature overnight, after which time the reaction was quenched with saturated NH_4Cl solution. The mixture was extracted with EtOAc three times and the pooled organics were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to afford a yellow syrup. The crude material obtained was used in the next step without further purification.
Crude ketone **5.189** was dissolved in THF (6 mL) and the resulting solution was cooled to 0 °C. Ethynylmagnesium bromide (0.5 M in THF, 9.6 mL) was added rapidly down the side of the flask. The reaction mixture was stirred for 2 h at 0 °C and then at room temperature for 1 h. After that time, saturated NH_4Cl solution was added and the crude mixture was extracted with EtOAc three times. The pooled organics were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to afford a pale yellow oil. The crude material was purified by flash

chromatography (1:2 acetone/hexanes) to yield **5.179** (0.545 g, 68% over two steps) of a pale yellow oil.
^{1}H NMR (500 MHz, CDCl3) δ 8.28 (d, *J* = 5.5 Hz, 1H), 8.01 (s, 1H), 7.52 (d, *J* = 5.5 Hz, 1H), 7.19 (bs, 1H), 7.12 (s, 1H), 4.04 (s, 3H), 4.03 (s, 3H), 3.91 – 3.72 (m, 4H), 2.69 (s, 1H), 2.53-2.44 (m, 1H), 2.13 – 2.01 (m, 2H), 1.57-1.52 (m, 1H), 1.25 (s, 3H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 155.1, 152.8, 149.6, 137.8, 134.6, 120.7, 120.2, 109.7, 105.5, 105.0, 86.2, 73.5, 69.5, 64.5, 64.5, 56.1, 56.0, 37.8, 32.9, 23.9.
HRMS (*m*/*z*): $[M+H]^+$ calcd for $C_{20}H_{18}O_5N$, 358.1649; found 358.1644.



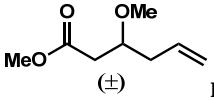
8,9-dimethoxy-10b-(2-(2-methyl-1,3-dioxolan-2-yl)ethyl)-2,3,5,6 tetrahydropyrrolo[2,1-*a*]isoquinolin-1(10b*H*)-one (5.178)
Alcohol **5.179** (0.545 g, 1.52 mmol) was dissolved in absolute ethanol (15 mL). The solution was heated to 100 °C for 1 h, during which time the reaction mixture became goldenrod in color. The ethanol was removed *in vacuo* to afford 0.537 g (98%) of a yellow oil that solidified on standing.
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (d, *J* = 3.5 Hz, 1H), 7.63 (s, 1H), 6.56 (s, 1H), 6.39 (d, *J* = 7.1 Hz, 1H), 5.84 (d, *J* = 7.1 Hz, 1H), 5.22 (d, *J* = 3.5 Hz, 1H), 3.92 (s, 3H), 3.89 – 3.78 (m, 7H), 2.07 – 1.91 (m, 2H), 1.66 – 1.50 (m, 2H), 1.21 (s, 3H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 202.3, 159.6, 148.2, 147.9, 125.2, 123.5, 122.6, 111.8, 109.4, 109.0, 107.5, 100.4, 68.3, 64.6, 64.5, 56.1, 55.9, 35.6, 31.9, 23.8.
HRMS (*m*/*z*): $[M+H]^+$ calcd for $C_{20}H_{18}O_5N$, 358.1649; found 358.1643.



8,9-dimethoxy-10b-(3-oxobutyl)-2,3,5,6-tetrahydropyrrolo[2,1-*a*]isoquinolin-1(10b*H*)-one (5.177)
Benzindolizinone **5.178** (0.115 g, 0.322 mmol) was dissolved in MeOH (7 mL) and sodium cyanoborohydride (0.046 g, 0.741 mmol) was added. The resulting solution was cooled to 0 °C and trifluoroacetic acid (0.404 g, 3.54 mmol) was added dropwise. The reaction mixture was stirred and allowed to come to room temperature over 1 h. Acetone (0.2 mL) was added at room temperature and the mixture was stirred for 5 minutes, followed by the addition of 1 M HCl (7 mL). The mixture was then stirred for 5 h at room temperature. The reaction was quenched with saturated $NaHCO_3$ and the crude mixture was extracted three times with DCM. The pooled organics were dried over Na_2SO_4 and concentrated *in vacuo* to afford a yellow oil. The crude material was purified by flash chromatography (2:1 EtOAc/hexanes) to yield 0.065 g (64%) of a pale yellow oil.
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.90 (s, 1H), 6.51 (s, 1H), 3.83 (s, 3H), 3.82 (s, 3H), 3.27-3.13 (m, 1H), 3.11-2.99 (m, 4H), 2.58-2.45 (m, 1H), 2.42-2.33 (m, 3H), 2.28-2.19 (m, 2H), 2.17-2.09 (m, 4H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 215.9, 208.0, 148.1, 147.6, 125.9, 124.9, 111.6, 109.5, 68.1, 55.9, 55.7, 43.4, 41.2, 39.2, 36.2, 32.5, 30.2, 21.1.

HRMS (*m*/*z*): $[M+H]^+$ calcd for $C_{18}H_{24}O_4N^+$, 318.1700; found 318.1696.

Total Synthesis of Cocculidine



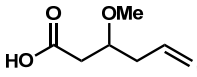
methyl 3-methoxyhex-5-enoate (5.235)

To a solution of methyl 3,3-dimethoxypropanoate (8.0 g, 54 mmol) in dry MeCN (120 mL) was added allyltrimethylsilane (12.3 g, 108 mmol), followed by careful addition of trifluoroacetic acid (60 mL). The resulting solution was aged for 48 h at room temperature and was then added dropwise to an excess of sat. aq. $NaHCO_3$ such that the final pH of the solution was ~9. During this operation, the solution turned purple and then bright yellow. The aqueous mixture was extracted with Et_2O (5 x 50 mL). The pooled organics were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure to afford the title compound (6.1 g, 71%) as a pale yellow oil and was used without further purification.

^{1}H NMR (600 MHz, $CDCl_3$) δ 5.80 (ddt, *J* = 17.0, 9.8, 7.3 Hz, 1H), 5.13-5.08 (m, 2H), 3.73-3.65 (m, 4H), 3.35 (s, 3H), 2.52 (dd, *J* = 15.8, 7.3 Hz, 1H), 2.47 (dd, *J* = 15.4, 5.1 Hz), 2.36 (dt, *J* = 13.7, 6.6 Hz, 1Hz), 2.30 (dt, *J* = 14.1 Hz, 7.0 Hz)

^{13}C NMR (151 MHz, $CDCl_3$) δ 172.1, 133.7, 117.8, 57.0, 51.6, 38.9, 37.8

HRMS (*m*/*z*): $[M+H]^+$ calcd for $C_8H_{15}O_3^+$, 159.1016; found 159.1011.



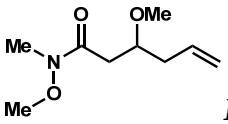
3-methoxyhex-5-enoic acid (5.250)

Methyl ester **5.235** (5.54 g, 35 mmol) was dissolved in THF (120 mL). A solution of lithium hydroxide monohydrate (2.94 g, 70 mmol) in water (60 mL) was then added and the mixture was stirred for 20 h at room temperature. The mixture was then acidified to pH ~2 with 2 M HCl. The mixture was extracted with EtOAc (4 x 50 mL) and the pooled organics were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to afford the title compound (4.79 g, 95%) as a yellow oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 5.80 (app dq, *J* = 17.1, 8.5 Hz, 1H), 5.16-5.13 (m, 2H), 3.75 (quint, *J* = 6.0 Hz, 1H), 3.42 (s, 3H), 2.56-2.55 (m, 2H), 2.41 (dt, *J* = 13.7, 6.6 Hz, 1H), 2.33 (dt, *J* = 14.1, 7.0 Hz, 1H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 177.2, 133.4, 118.1, 57.0, 38.8, 37.6, 31.0.

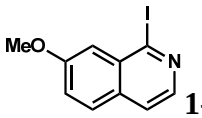
HRMS (*m*/*z*): $[M+H]^+$ calcd for $C_7H_{13}O_3^+$, 145.0859; found 145.0860.



***N*,3-dimethoxy-*N*-methylhex-5-enamide (5.232)**

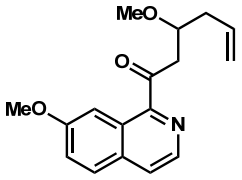
Acid **5.250** (4.79 g, 33.2 mmol) was dissolved in THF (20 mL) was added to a solution of CDI (6.19 g, 38.2 mmol) in THF (90 mL) via cannula. The resulting solution was stirred for 2 h at room temperature and then *N*,*O*-dimethylhydroxylamine hydrochloride (4.88 g, 49.8 mmol) was added in one portion. The heterogeneous mixture was stirred vigorously for 40 h at room temperature, during which time a thick precipitate forms. The crude mixture was added to 1 M HCl (50 mL) and the resulting solution was extracted with EtOAc. The organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to afford the title compound (4.88 g, 78%) as an orange oil that was used without further purification.

^{1}H NMR (600 MHz, $CDCl_3$) δ 5.72 (ddt, *J* = 17.2, 10.2, 7.1 Hz, 1H), 5.03-4.98 (m, 2H), 3.73 (dq, *J* = 7.6, 5.6 Hz, 1H), 3.59 (s, 3H), 3.28 (s, 3H), 3.09 (s, 3H), 2.65 (dd, *J* = 15.1, 7.3 Hz, 1H), 2.35 (dd, *J* = 15.6, 4.7 Hz, 1H), 2.28-2.21 (m, 2H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 172.4, 134.2, 117.5, 61.2, 57.1, 38.1, 36.3, 32.02
HRMS (*m*/*z*): $[M+H]^+$ calcd for $C_9H_{18}NO_3^+$, 188.1281; found 188.1279.



1-iodo-7-methoxyisoquinoline (5.229)

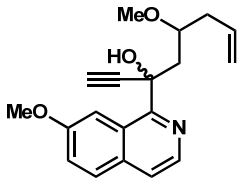
A 25 mL round-bottom flask was charged with 7-methoxyisoquinolin-1(2*H*)-one[77] (**5.248**, 0.100 g, 0.571 mmol) and MeCN (5.7 mL). Pyridine (0.050 g, 0.656 mmol) was added in one portion, and the reaction mixture was cooled to 0 °C. Tf_2O (0.180 g, 0.628 mmol) was added dropwise. The resulting light yellow solution was stirred at room temperature for 2 h. A small aliquot was removed for NMR analysis to confirm complete consumption of starting material. Sodium iodide (0.430 g, 2.85 mmol) was added in one portion followed by dropwise addition of 4.0 M HCl in dioxane (0.16 mL). The reaction mixture was warmed to room temperature and stirred for 20 h. The reaction was quenched with saturated $NaHCO_3$, and then the mixture was diluted with EtOAc (30 mL) and washed with sodium thiosulfate (1 x 20 mL). The aqueous phase was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine and dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude mixture was purified by column chromatography (20% EtOAc in hexane) to afford **5.229** (0.120 g, 75%) as a white solid.
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.15 (d, J = 5.4 Hz, 1H), 7.65 (d, J = 9.6 Hz, 1H), 7.49 (d, J = 5.4 Hz, 1H), 7.37 – 7.32 (m, 2H), 4.02 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 159.8, 141.3, 133.3, 131.6, 128.9, 125.7, 124.1, 121.0, 110.5, 55.6.
HRMS (*m*/*z*): $[M+H]^+$ calcd for $C_{10}H_9INO^+$, 285.9723; found 285.9726.



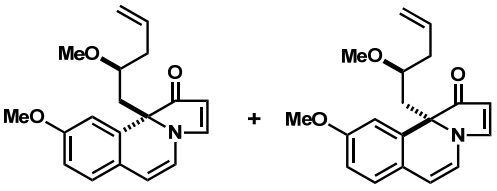
3-methoxy-1-(7-methoxyisoquinolin-1-yl)hex-5-en-1-one (5.228)

Iodide **5.229** (0.705 g, 2.47 mmol) was dissolved in THF (8 mL) and cooled to -10 °C. Isopropylmagnesium chloride (2.0 M in THF, 1.36 mL) was added dropwise and the resulting mixture was stirred for 2 h, during which time a fine brown precipitate formed. The heterogeneous mixture was cooled to -50 °C and then amide **5.232** (0.463 g, 2.47 mmol) was added slowly dropwise as a solution in THF (3 mL). The reaction mixture was allowed to warm to room temperature over ~2 h and then stirred at room temperature for 4 h. The reaction was quenched with sat. aq. NH_4Cl and the mixture was extracted with EtOAc. The pooled organics were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to afford a brown residue that was purified by column chromatography (20% EtOAc in hexanes) to afford a pale yellow oil (0.491 g, 70%).
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.54 (d, *J* = 5.4 Hz, 1H), 8.46 (*J* = 2.4 Hz, 1H), 7.83-7.79 (m, 2H), 7.41 (dd, *J* = 9.0, 2.4 Hz, 1H), 5.94 (ddt, *J* = 17.2, 10.1, 7.1 Hz, 1H), 5.20-5.13 (m, 2H), 4.07 (quint, *J* = 6.6 Hz, 1H), 4.01 (s, 3H), 3.71 (dd, *J* = 16.3, 7.8 Hz, 1H), 3.46 (dd, *J* = 16.3, 4.8 Hz, 1H), 3.38 (s, 3H), 2.48-2.37 (m, 2H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 203.2, 160.1, 150.5, 139.3, 134.3, 133.0, 128.4, 127.5, 124.5, 123.8, 117.5, 103.8, 56.9, 55.5, 44.5, 38.3.
HRMS (*m*/*z*): $[M+H]^+$ calcd for $C_{17}H_{20}NO_3^+$, 286.1438; found 286.1443.



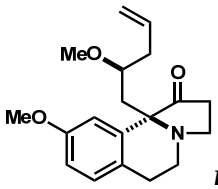
mixture of diastereomers **5-methoxy-3-(7-methoxyisoquinolin-1-yl)oct-7-en-1-yn-3-ol (5.227)**
Ketone **5.228** (0.470 g, 1.65 mmol) was dissolved in THF (4 mL) and cooled to -10 °C. Ethynylmagnesium bromide (0.5 M solution in THF, 6.6 mL) was added in one portion and the mixture was allowed to stir and warm to room temperature over 1 h. The reaction was quenched with sat. aq. NH_4Cl and then the mixture was extracted with EtOAc. The pooled organics were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to afford a yellow residue (0.477 g, 93%) that was used without further purification. Spectroscopic analysis showed that this material was a roughly 1.2 : 1 mixture of inseparable diastereomers.
HRMS (*m*/*z*): $[M+H]^+$ calcd for $C_{19}H_{22}NO_3^+$, 312.1594; found 312.1595.
Major diastereomer:
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.32 (d, *J* = 5.5 Hz, 1H), 8.09 (d, *J* = 2.3 Hz, 1Hz), 7.81 (d, *J* = 9.0 Hz, 1H), 7.62 (d, *J* = 5.5 Hz, 1H), 7.40 (dd, *J* = 9.0, 2.5 Hz, 1H), 7.25 (bs, 1H), 5.85 (ddt, *J* = 17.2, 10.1, 7.1 Hz, 1H), 5.20-5.12 (m, 2H), 4.00 (s, 3H), 3.66, (dtd, *J* = 8.2, 5.7, 2.5 Hz, 1H), 2.79 (s, 3H), 2.68 (s, 1H), 2.63 (dd, *J* = 14.7, 2.9 Hz, 1H), 2.56 (dd, *J* = 14.7, 8.3 Hz, 1H). 2.37-2.35 (m, 1H), 2.15-2.11 (m, 1H).
Minor diastereomer:
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.39 (d, *J* = 5.5 Hz, 1H), 8.12 (d, *J* = 2.3 Hz, 1Hz), 7.84 (d, *J* = 9.0 Hz, 1H), 7.65 (d, *J* = 5.5 Hz, 1H), 7.43 (dd, *J* = 9.0, 2.5 Hz, 1H), 7.18 (bs, 1H), 5.76 (ddt, *J* = 17.2, 10.2, 7.0 Hz, 1H), 5.00-4.91 (m, 2H), 4.00 (s, 3H), 3.82, (quint, 1H), 2.79 (s, 3H), 2.68 (s, 1H), 2.67 (dd, *J* = 14.7, 6.0 Hz, 1H), 2.37-2.35 (m, 2H), 2.25-2.21 (m, 1H).



254 **255** ***rac*-9-methoxy-10b-(-2-methoxypent-4-en-1-yl)pyrrolo[2,1-*a*]isoquinolin-1(10b*H*)-one (5.254 and 5.255)**
A mixture of carbinol **5.227** diastereomers (0.122 g, 0.392 mmol) was dissolved in 4 mL EtOH. The solution was degassed and then heated to 100 °C in a sealed container for 1 h. The solvent was removed *in vacuo* and the resulting dark yellow residue (0.118 g, 97%) was used without further purification on the basis of its high purity (adjudged by NMR). Separation of diastereomers could be achieved by flash chromatography (20% EtOAc in hexanes).
*NOTE: The more polar of the two stereoisomers has been <u>arbitrarily</u> assigned the relative stereochemistry shown in **5.254** above.*
5.254:

^{1}H NMR (600 MHz, C_6D_6) δ 8.16 (d, *J* = 2.3 Hz, 1H), 6.75-6.71 (m, 3H), 5.70 (ddt, *J* = 17.2, 10.2, 7.0 Hz, 1H), 5.63, (d, *J* = 7.1 Hz, 1H), 5.54 (d, *J* = 7.1 Hz, 1H), 5.05 (d, *J* = 3.7 Hz, 1H), 4.935-4.91 (m, 2H), 3.38 (s, 3H), 3.26-3.21 (m, 1H), 3.01 (s, 3H), 2.39 (dd, *J* = 14.5, 7.7 Hz, 1H), 2.14 (dd, *J* = 14.5, 3.4 Hz, 1H), 2.11-2.05 (m, 2H).
^{13}C NMR (151 MHz, C_6D_6) δ 200.7, 159.1, 157.8, 134.4, 124.3, 126.8, 123.7, 122.4, 116.9, 114.3, 110.6, 109.3, 100.2, 75.6, 66.8, 55.5, 54.7, 45.7, 37.9.
HRMS (*m*/*z*): $[M+H]^+$ calcd for $C_{19}H_{22}NO_3^+$, 312.1594; found 312.1598.

5.255:
^{1}H NMR (600 MHz, C_6D_6) δ 8.11 (d, *J* = 2.3 Hz, 1H), 6.74-6.69 (m, 3H), 5.80-5.72 (m, 1H), 5.70 (d, *J* = 7.1 Hz, 1H), 5.57 (d, *J* = 7.1 Hz, 1H), 5.03 (d, *J* = 3.6 Hz, 1H) 4.98-4.95 (m, 2H), 3.37-3.33 (m, 4H), 2.99 (s, 3H), 2.37 (dd, *J* = 14.5, 6.8 Hz, 1H), 2.21 (dd, *J* = 14.5, 3.6 Hz, 1H), 2.09 (t, *J* = 6.2 Hz, 2H).
^{13}C NMR (151 MHz, C_6D_6) δ 200.6, 159.0, 158.8, 134.5, 134.3, 126.9, 123.7, 122.4, 116.9, 114.3, 110.9, 109.0, 99.5, 76.3, 67.5, 55.7, 54.6, 45.0, 38.7.
HRMS (*m*/*z*): $[M+H]^+$ calcd for $C_{19}H_{22}NO_3^+$, 312.1594; found 312.1592.



***rac*-9-methoxy-10b-(-2-methoxypent-4-en-1-yl)-2,3,5,6-tetrahydropyrrolo[2,1-*a*]isoquinolin-1(10b*H*)-one (5.226)**
Benz[g]indolizinone **5.254** (0.040 g, 0.128 mmol) was dissolved in MeOH (2 mL) and then $NaBH_3CN$ was added, followed by TFA (0.088 mL). The resulting solution was stirred at 0 °C for 1.5 h. The reaction was quenched by the addition of sat. aq. $NaHCO_3$ and extracted with DCM. The organics were dried over Na_2SO_4 and then concentrated *in vacuo* to afford a residue that was purified by flash chromatography (50% EtOAc in hexanes) to afford the title compound (0.020 g, 50%) as a colorless oil.
^{1}H NMR (600 MHz, $CDCl_3$) δ 6.97-6.94 (m, 2H), 6.72 (dd, *J* = 8.4, 2.5 Hz, 1H), 5.81 (ddt, *J* = 17.1, 10.1, 7.0 Hz, 1H), 5.09-5.04 (m, 2H), 3.76 (s, 3H), 3.41 (td, *J* = 13.3, 5.0 Hz, 1H), 3.31 (quint, *J* = 5.4 Hz, 1H), 3.25 (s, 3H), 3.16 (m, 2H), 3.09-3.03 (m, 2H), 2.51-2.44 (m, 2H), 2.37 (dd, *J* = 18.3, 6.9 Hz, 1H), 2.26-2.21 (m, 3H), 2.01 (dd, *J* = 15.0, 5.9 Hz, 1H).

X-ray Diffraction Analysis of 5.113:
A yellow block 0.20 x 0.15 x 0.15 mm in size was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using phi and omega scans. Crystal-to-detector distance was 60 mm and exposure time was 10 seconds per frame using a scan width of 0.3°. Data collection was 100.0% complete to 25.00° in □. A total of 20146 reflections were collected covering the indices, -14<=*h*<=14, -13<=*k*<=13, -25<=*l*<=25. 2545 reflections were found to be symmetry independent, with an R_{int} of 0.0180. Indexing and unit cell refinement indicated a C-centered, monoclinic lattice. The space group was found to be C2/c (No. 15). The data were integrated using the Bruker SAINT software program and scaled using the SADABS software program. Solution by direct methods (SIR-2011) produced a complete heavy-atom phasing model consistent with the proposed structure. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-97). All hydrogen atoms were placed

using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-97.

Table 1. Crystal data and structure refinement for sarpong30.

X-ray ID	sarpong30	
Sample/notebook ID	sth8.046	
Empirical formula	C19 H15 N O	
Formula weight	273.32	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	C2/c	
Unit cell dimensions	a = 11.6769(7) Å	α= 90°.
	b = 11.3906(6) Å	β= 100.4240(10)°.
	c = 21.2800(12) Å	γ = 90°.
Volume	2783.7(3) $Å^3$	
Z	8	
Density (calculated)	1.304 Mg/m^3	
Absorption coefficient	0.080 mm^{-1}	
F(000)	1152	
Crystal size	0.20 x 0.15 x 0.15 mm^3	
Crystal color/habit	yellow block	
Theta range for data collection	1.95 to 25.33°.	
Index ranges	-14<=h<=14, -13<=k<=13, -25<=l<=25	
Reflections collected	20146	
Independent reflections	2545 [R(int) = 0.0180]	
Completeness to theta = 25.00°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9880 and 0.9841	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2545 / 0 / 191	
Goodness-of-fit on F^2	1.006	
Final R indices [I>2sigma(I)]	R1 = 0.0334, wR2 = 0.0839	
R indices (all data)	R1 = 0.0348, wR2 = 0.0854	
Largest diff. peak and hole	0.241 and -0.227 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for sarpong30. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	1490(1)	3895(1)	1713(1)	18(1)
C(2)	1687(1)	2756(1)	2125(1)	19(1)
C(3)	1781(1)	3124(1)	2778(1)	24(1)
C(4)	1588(1)	4300(1)	2787(1)	22(1)
C(5)	989(1)	5906(1)	2017(1)	21(1)
C(6)	356(1)	6076(1)	1434(1)	22(1)
C(7)	-58(1)	5070(1)	1030(1)	19(1)
C(8)	-997(1)	5173(1)	521(1)	22(1)
C(9)	-1461(1)	4195(1)	183(1)	23(1)
C(10)	-1002(1)	3090(1)	350(1)	23(1)
C(11)	-60(1)	2967(1)	852(1)	21(1)
C(12)	419(1)	3949(1)	1186(1)	18(1)
C(13)	2623(1)	4098(1)	1454(1)	17(1)

C(14)	3503(1)	4804(1)	1782(1)	22(1)
C(15)	4548(1)	4932(1)	1564(1)	23(1)
C(16)	4743(1)	4368(1)	1014(1)	19(1)
C(17)	3849(1)	3670(1)	684(1)	20(1)
C(18)	2807(1)	3529(1)	903(1)	19(1)
C(19)	5899(1)	4479(1)	798(1)	23(1)
N(1)	1376(1)	4781(1)	2196(1)	19(1)
O(1)	1799(1)	1777(1)	1902(1)	23(1)

Table 3. Bond lengths [Å] and angles [°] for sarpong30.

C(1)-N(1)	1.4647(14)	C(9)-H(9)	0.9500
C(1)-C(12)	1.5221(15)	C(10)-C(11)	1.3942(16)
C(1)-C(13)	1.5389(15)	C(10)-H(10)	0.9500
C(1)-C(2)	1.5593(15)	C(11)-C(12)	1.3876(16)
C(2)-O(1)	1.2277(14)	C(11)-H(11)	0.9500
C(2)-C(3)	1.4368(16)	C(13)-C(14)	1.3897(16)
C(3)-C(4)	1.3585(17)	C(13)-C(18)	1.3906(16)
C(3)-H(3)	0.9500	C(14)-C(15)	1.3900(16)
C(4)-N(1)	1.3530(15)	C(14)-H(14)	0.9500
C(4)-H(4)	0.9500	C(15)-C(16)	1.3891(17)
C(5)-C(6)	1.3391(17)	C(15)-H(15)	0.9500
C(5)-N(1)	1.3886(15)	C(16)-C(17)	1.3969(16)
C(5)-H(5)	0.9500	C(16)-C(19)	1.5084(15)
C(6)-C(7)	1.4610(16)	C(17)-C(18)	1.3884(16)
C(6)-H(6)	0.9500	C(17)-H(17)	0.9500
C(7)-C(8)	1.3996(16)	C(18)-H(18)	0.9500
C(7)-C(12)	1.4086(16)	C(19)-H(19A)	0.9800
C(8)-C(9)	1.3830(17)	C(19)-H(19B)	0.9800
C(8)-H(8)	0.9500	C(19)-H(19C)	0.9800
C(9)-C(10)	1.3891(17)		

N(1)-C(1)-C(12)	108.75(9)	C(9)-C(8)-C(7)	120.89(11)
N(1)-C(1)-C(13)	109.93(9)	C(9)-C(8)-H(8)	119.6
C(12)-C(1)-C(13)	112.11(9)	C(7)-C(8)-H(8)	119.6
N(1)-C(1)-C(2)	101.61(8)	C(8)-C(9)-C(10)	119.98(10)
C(12)-C(1)-C(2)	117.73(9)	C(8)-C(9)-H(9)	120.0
C(13)-C(1)-C(2)	106.10(8)	C(10)-C(9)-H(9)	120.0
O(1)-C(2)-C(3)	130.07(10)	C(9)-C(10)-C(11)	120.14(11)
O(1)-C(2)-C(1)	123.59(10)	C(9)-C(10)-H(10)	119.9
C(3)-C(2)-C(1)	106.20(9)	C(11)-C(10)-H(10)	119.9
C(4)-C(3)-C(2)	108.50(10)	C(12)-C(11)-C(10)	120.01(11)
C(4)-C(3)-H(3)	125.7	C(12)-C(11)-H(11)	120.0
C(2)-C(3)-H(3)	125.7	C(10)-C(11)-H(11)	120.0
N(1)-C(4)-C(3)	112.93(10)	C(11)-C(12)-C(7)	120.30(10)
N(1)-C(4)-H(4)	123.5	C(11)-C(12)-C(1)	123.08(10)
C(3)-C(4)-H(4)	123.5	C(7)-C(12)-C(1)	116.58(10)
C(6)-C(5)-N(1)	118.97(10)	C(14)-C(13)-C(18)	118.71(10)
C(6)-C(5)-H(5)	120.5	C(14)-C(13)-C(1)	120.86(10)
N(1)-C(5)-H(5)	120.5	C(18)-C(13)-C(1)	120.36(9)
C(5)-C(6)-C(7)	120.05(10)	C(15)-C(14)-C(13)	120.45(10)
C(5)-C(6)-H(6)	120.0	C(15)-C(14)-H(14)	119.8
C(7)-C(6)-H(6)	120.0	C(13)-C(14)-H(14)	119.8
C(8)-C(7)-C(12)	118.66(10)	C(16)-C(15)-C(14)	121.39(10)
C(8)-C(7)-C(6)	121.24(10)	C(16)-C(15)-H(15)	119.3
C(12)-C(7)-C(6)	119.84(10)	C(14)-C(15)-H(15)	119.3

C(15)-C(16)-C(17)	117.74(10)	C(16)-C(19)-H(19A)	109.5
C(15)-C(16)-C(19)	120.66(10)	C(16)-C(19)-H(19B)	109.5
C(17)-C(16)-C(19)	121.57(10)	H(19A)-C(19)-H(19B)	109.5
C(18)-C(17)-C(16)	121.16(10)	C(16)-C(19)-H(19C)	109.5
C(18)-C(17)-H(17)	119.4	H(19A)-C(19)-H(19C)	109.5
C(16)-C(17)-H(17)	119.4	H(19B)-C(19)-H(19C)	109.5
C(17)-C(18)-C(13)	120.54(10)	C(4)-N(1)-C(5)	128.64(10)
C(17)-C(18)-H(18)	119.7	C(4)-N(1)-C(1)	110.39(9)
C(13)-C(18)-H(18)	119.7	C(5)-N(1)-C(1)	120.69(9)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$)for sarpong30. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2 a^{*2} U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	18(1)	17(1)	18(1)	-2(1)	4(1)	-1(1)
C(2)	13(1)	21(1)	24(1)	3(1)	3(1)	-2(1)
C(3)	23(1)	28(1)	21(1)	5(1)	5(1)	2(1)
C(4)	18(1)	30(1)	18(1)	-1(1)	5(1)	0(1)
C(5)	19(1)	18(1)	26(1)	-3(1)	8(1)	-1(1)
C(6)	21(1)	17(1)	28(1)	2(1)	7(1)	0(1)
C(7)	17(1)	21(1)	21(1)	2(1)	7(1)	-2(1)
C(8)	19(1)	24(1)	23(1)	5(1)	7(1)	2(1)
C(9)	16(1)	32(1)	21(1)	2(1)	3(1)	-1(1)
C(10)	19(1)	27(1)	24(1)	-4(1)	5(1)	-4(1)
C(11)	18(1)	21(1)	23(1)	-1(1)	6(1)	0(1)
C(12)	15(1)	21(1)	17(1)	2(1)	6(1)	-1(1)
C(13)	17(1)	16(1)	19(1)	3(1)	3(1)	1(1)
C(14)	23(1)	24(1)	21(1)	-4(1)	6(1)	-4(1)
C(15)	20(1)	24(1)	25(1)	-3(1)	4(1)	-6(1)
C(16)	19(1)	18(1)	22(1)	4(1)	4(1)	1(1)
C(17)	21(1)	20(1)	18(1)	0(1)	4(1)	3(1)
C(18)	18(1)	18(1)	20(1)	0(1)	1(1)	-1(1)
C(19)	20(1)	25(1)	26(1)	0(1)	7(1)	0(1)
N(1)	18(1)	20(1)	19(1)	-2(1)	5(1)	-1(1)
O(1)	22(1)	18(1)	28(1)	1(1)	3(1)	-1(1)

Table 5. Hydrogen coordinates ($x\ 10^4$) and isotropic displacement parameters ($Å^2 x\ 10^3$) for sarpong30.

	x	y	z	U(eq)
H(3)	1950	2629	3142	29
H(4)	1602	4738	3168	26
H(5)	1171	6546	2305	25
H(6)	176	6850	1282	26
H(8)	-1321	5925	408	26
H(9)	-2092	4278	-165	28
H(10)	-1331	2416	123	28
H(11)	255	2210	965	25
H(14)	3390	5202	2159	27
H(15)	5142	5415	1795	28
H(17)	3955	3285	302	24

H(18)	2215	3040	674	23
H(19A)	6297	5191	981	35
H(19B)	5771	4526	331	35
H(19C)	6381	3792	941	35

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(58) For a review on the stereoselective synthesis of 1,3-diols, see: Bode, S. E.; Wolberg, M.; Müller, M. *Synthesis* **2006**, 557.
(59) Guo, J.; Duffy, K. J.; Stevens, K. L.; Dalko, P. I.; Roth, R. M.; Hayward, M. M.; Kishi, Y. *Angew. Chem. Int. Ed.* **1998**, *37*, 187.
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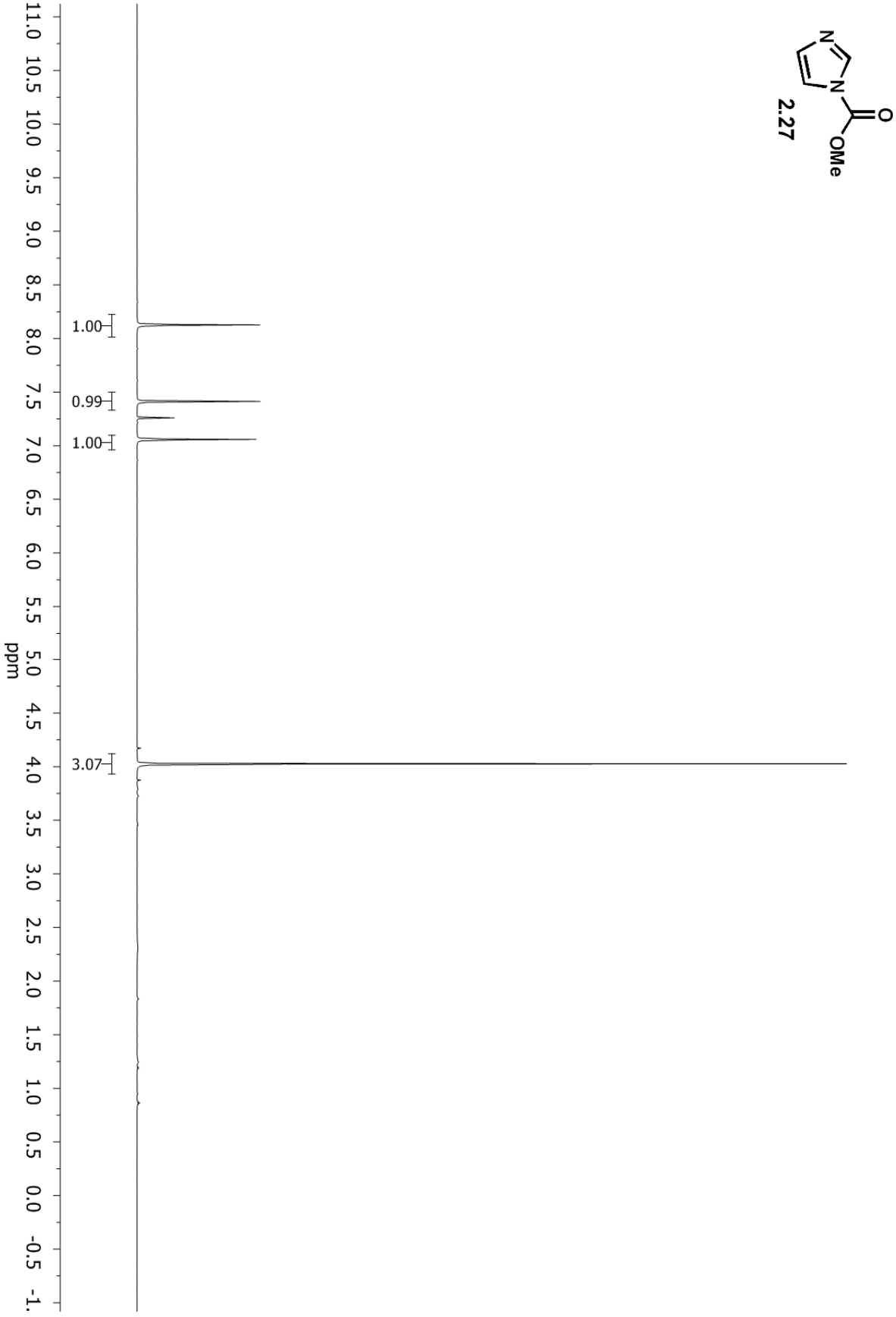
(61) Maloney, K. M.; Nwakpuda, E.; Kuethe, J. T.; Yin, J. *J. Org. Chem.* **2009**, *74*, 5111.
(62) Eloy, F.; Deryckere, A. *Helv. Chim. Acta* **1969**, *52*, 1755.
(63) Trost, B. M.; Pulley, S. R. *J. Am. Chem. Soc.* **1995**, *117*, 10143.
(64) (a) Ru(II)-catalyzed cyclization: Varela-Fernandez, A.; Varela, J. A.; Saa, C. *Adv. Synth. Catal.* **2011**, *353*, 1933. (b) Pd(II)-catalyzed cyclization: Sashida, H.; Kawamukai, A. *Synthesis* **1999**, 1145. (c) Thermal cyclization: Jouvenot, D.; Glazer, E. C.; Tor, Y. *Org. Lett.* **2006**, *8*, 1987.
(65) The low boiling point of trimethylsilylacetylene (55 °C) may have contributed to the challenge of this reaction and limited our ability to facilitate the Sonogashira reaction by increasing the temperature at which it was run.

(66) Alacid, E.; Najera, C. *Adv. Synth. Catal.* **2008**, *350*, 1316.
(67) Ziegler, C. B.; Heck, R. F. *J. Org. Chem.* **1978**, *43*, 2949.
(68) (a) Kampen, D.; List, B. *Synlett* **2006**, 2589. (b) The Lewis acid-catalyzed Sakurai allylation of acetals is well known: Fleming, I.; Dunogues, J.; Smithers, R. *Org. React.* **1989**, *37*, 1.
(69) For a review, see: Mentzel, M.; Hoffmann, H. M. R. *J. Prakt. Chem.* **1997**, *339*, 517.
(70) The racemic synthesis would also be nine steps from **236**.
(71) Tan, Q.; Hayashi, M. *Adv. Synth. Catal.* **2008**, *350*, 2639.
(72) See reference 11b.
(73) See reference 11b.
(74) Friel, D. K.; Snapper, M. L.; Hoyveda, A. H. *J. Am. Chem. Soc.* **2008**, *130*, 9942.
(75) See reference 50.
(76) See reference 49.
(77) See reference 62.

Appendix 1: Selected Spectra for Compounds Disclosed in Chapter 2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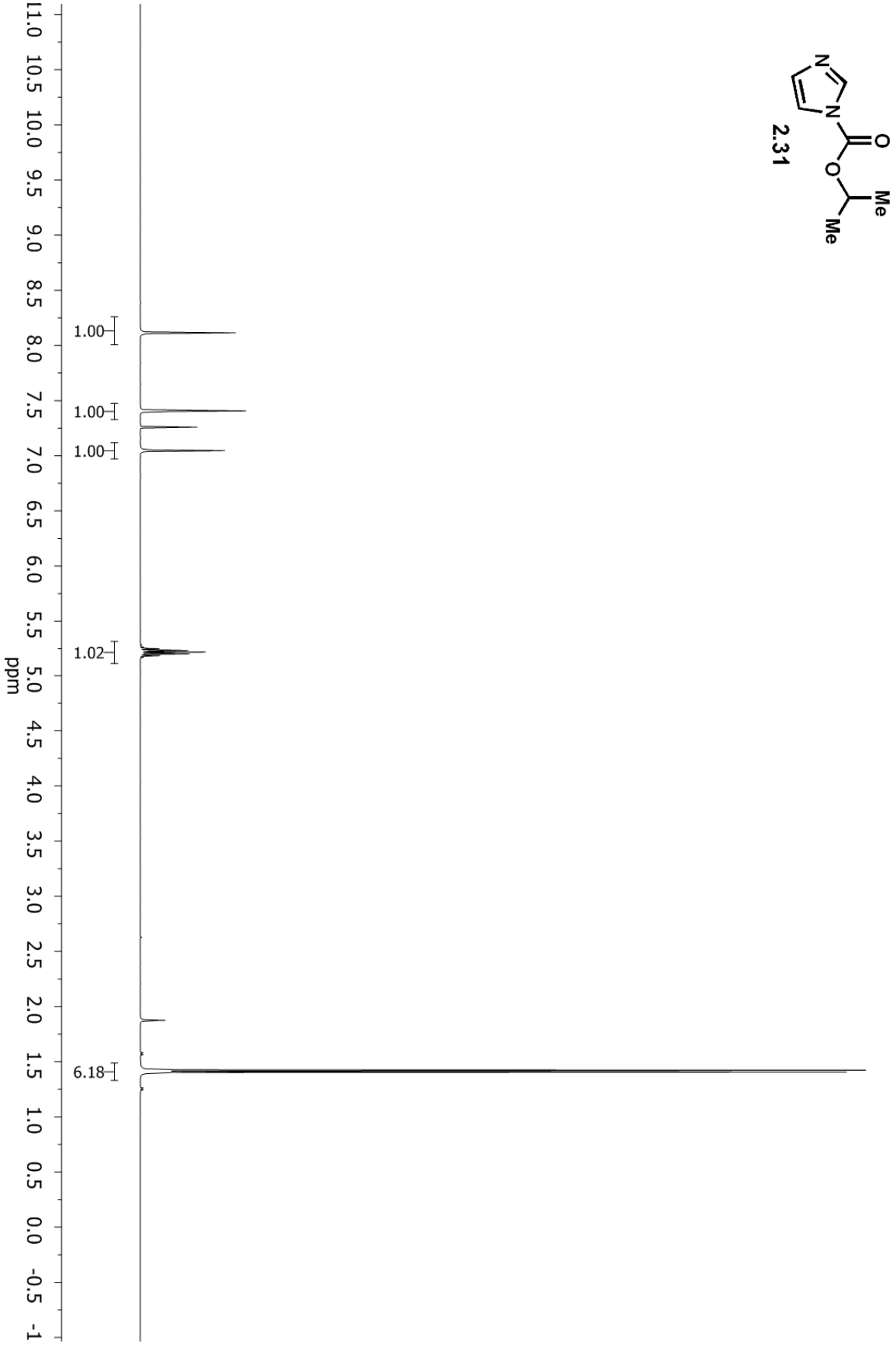
OMe
1.00
0.99
1.00
3.07
ppm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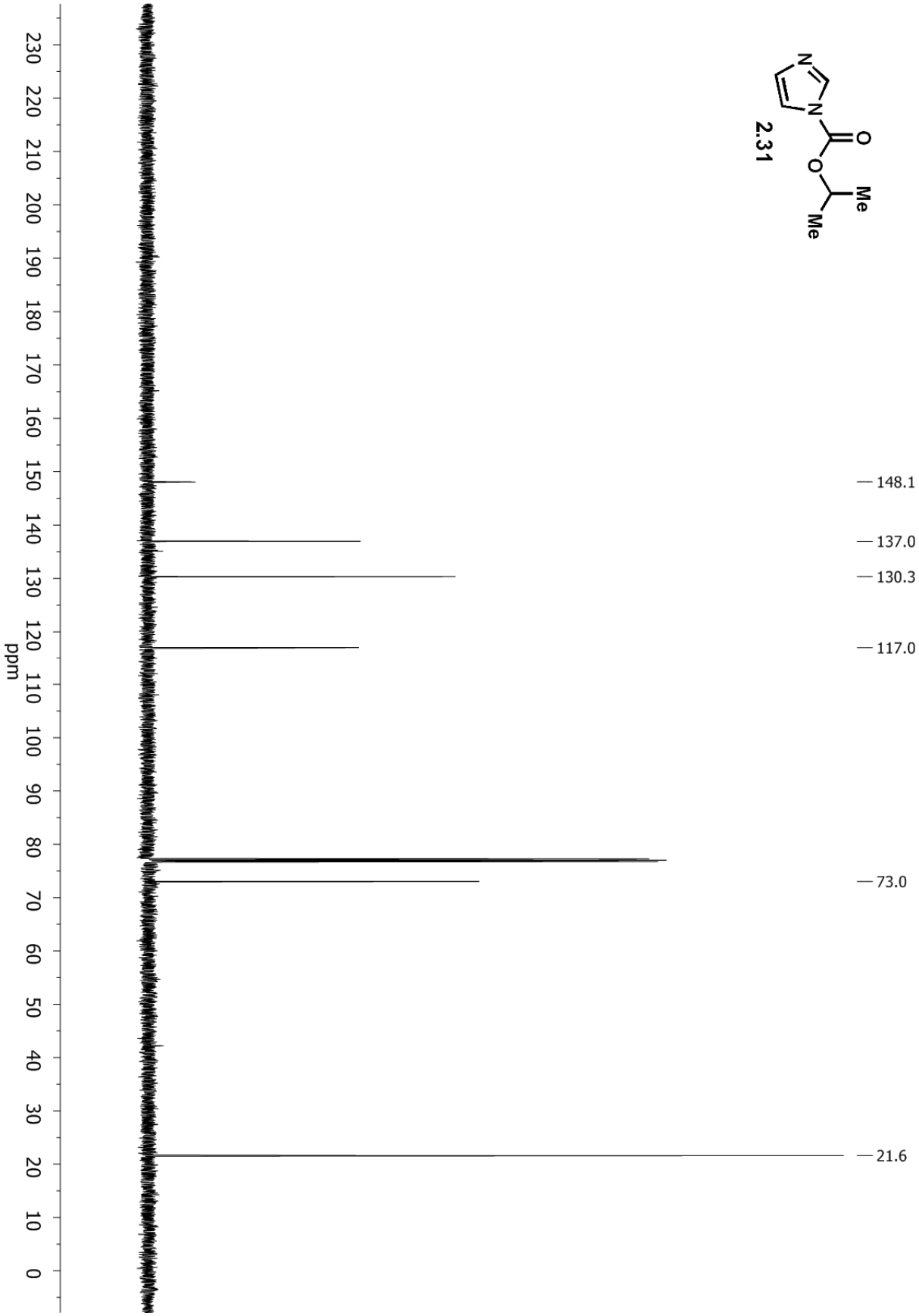
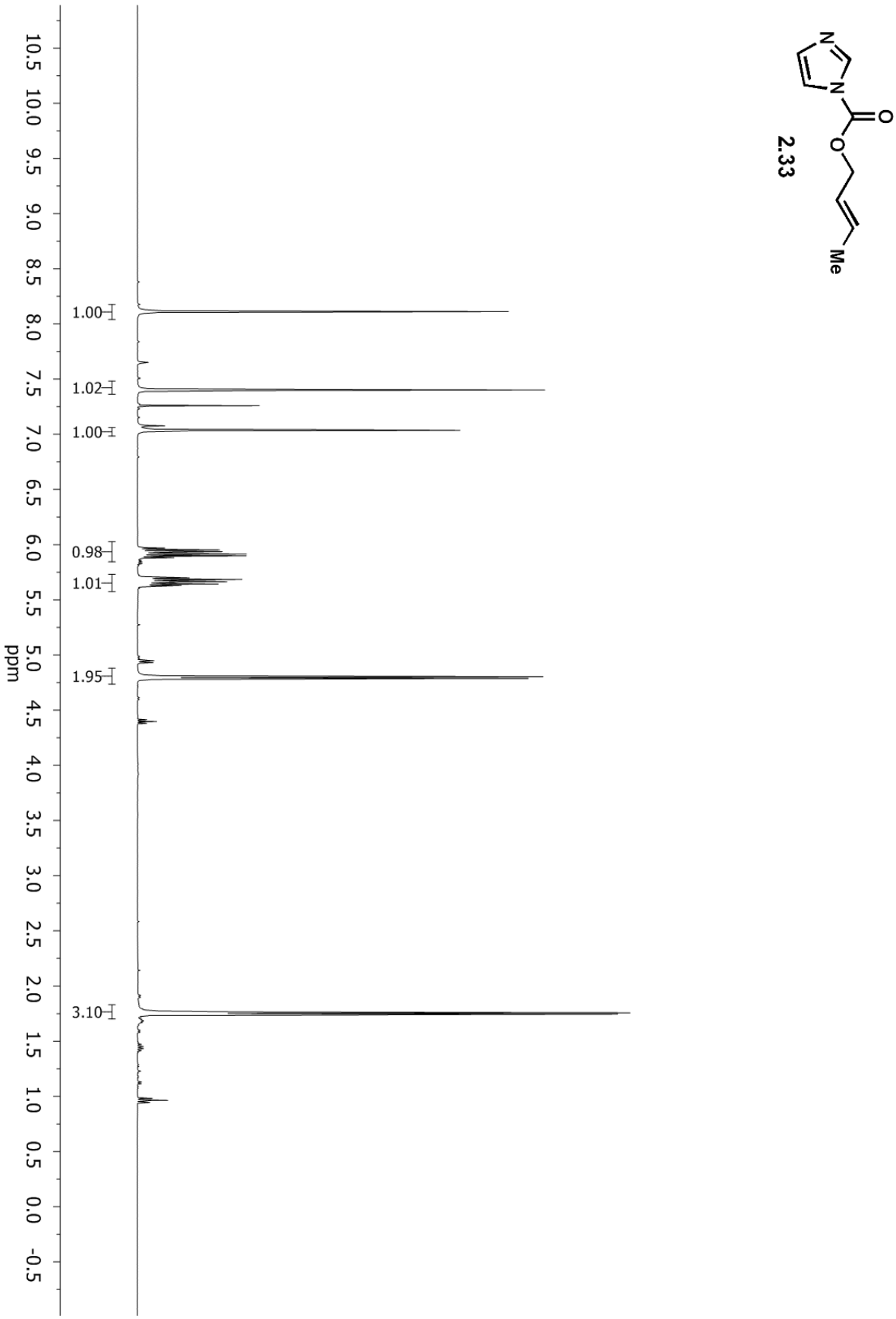
Me
1.00
1.00
1.00
1.02
6.18
ppm


2.31
Me
Me
148.1
137.0
130.3
117.0
73.0
21.6
ppm
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0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ppm
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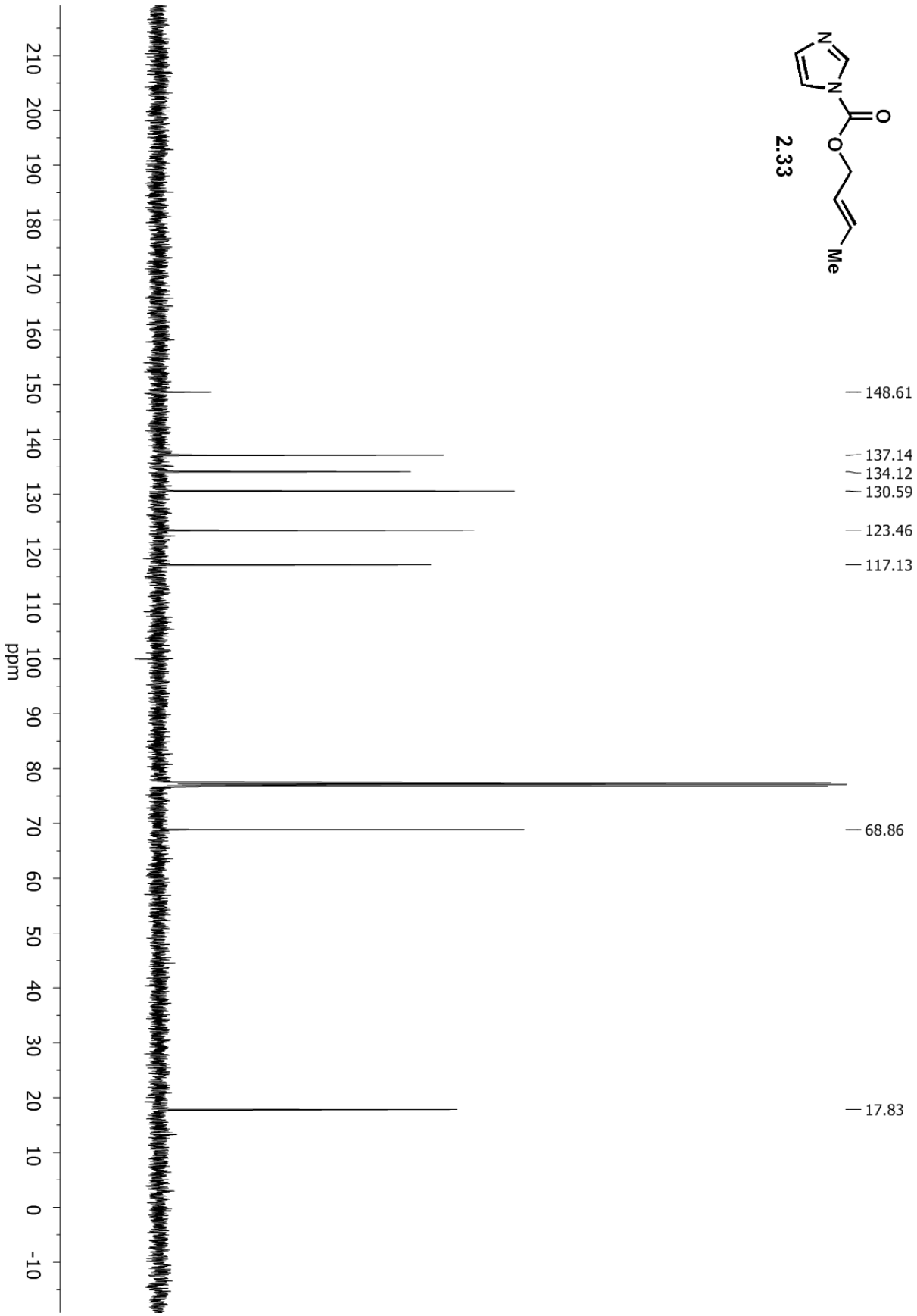
1.02
1.00
0.98
1.01
1.95
3.10
N
N
O
O
Me
2.33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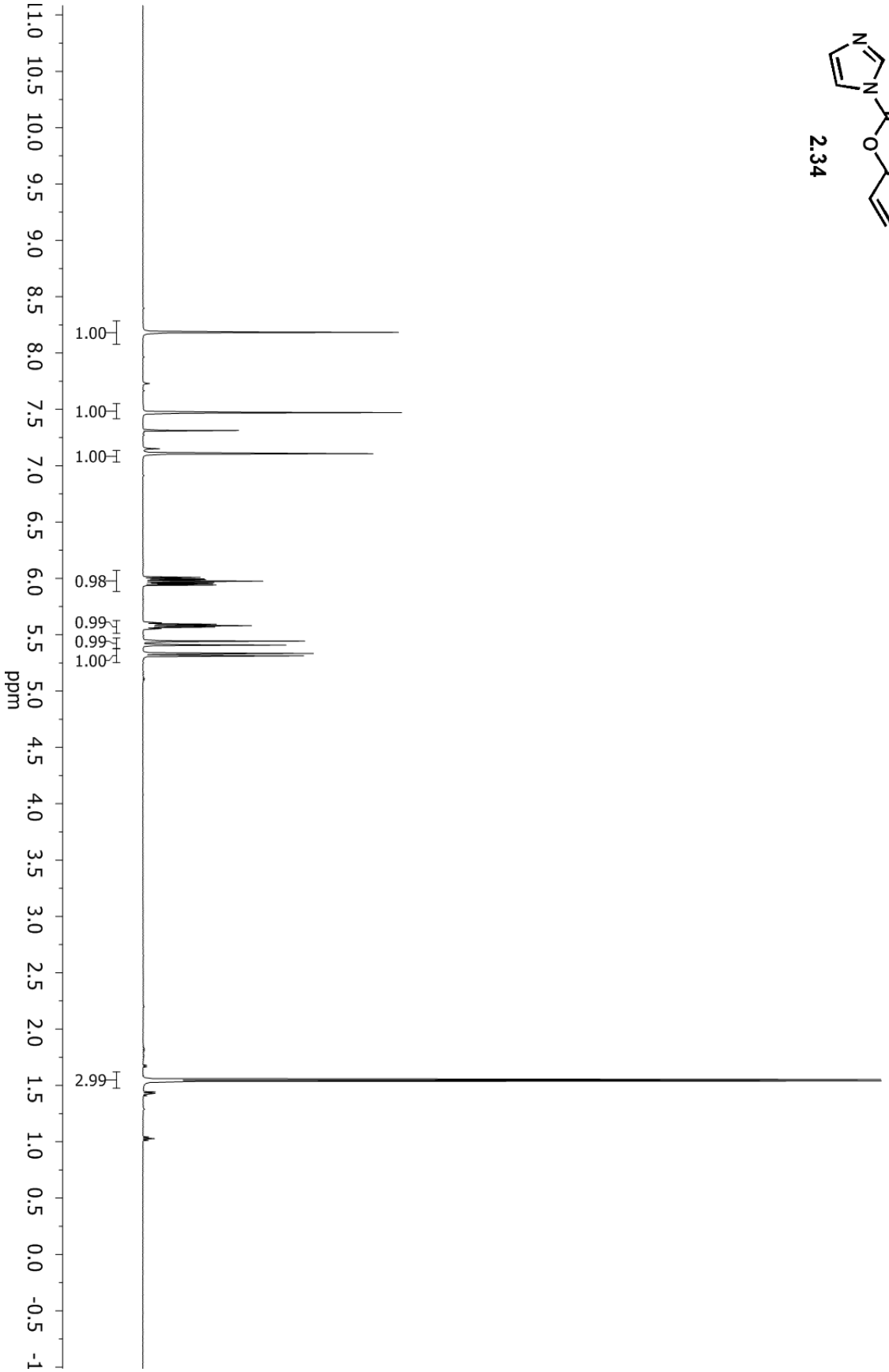
Me
148.61
137.14
134.12
130.59
123.46
117.13
68.86
17.83
ppm
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10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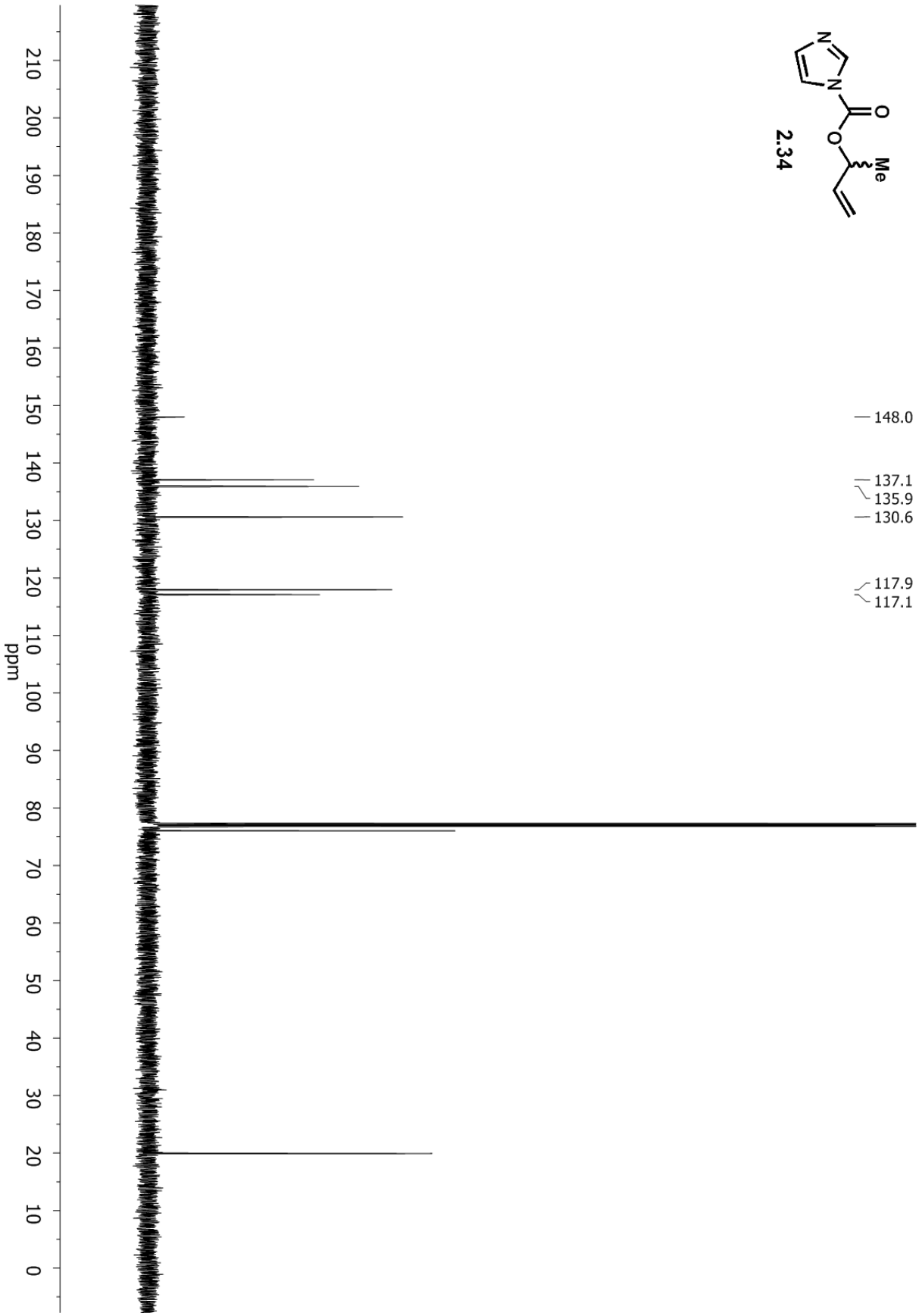
1.00
1.00
0.98
0.99
0.99
1.00
2.99
N
N
O
O
Me
2.34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Me
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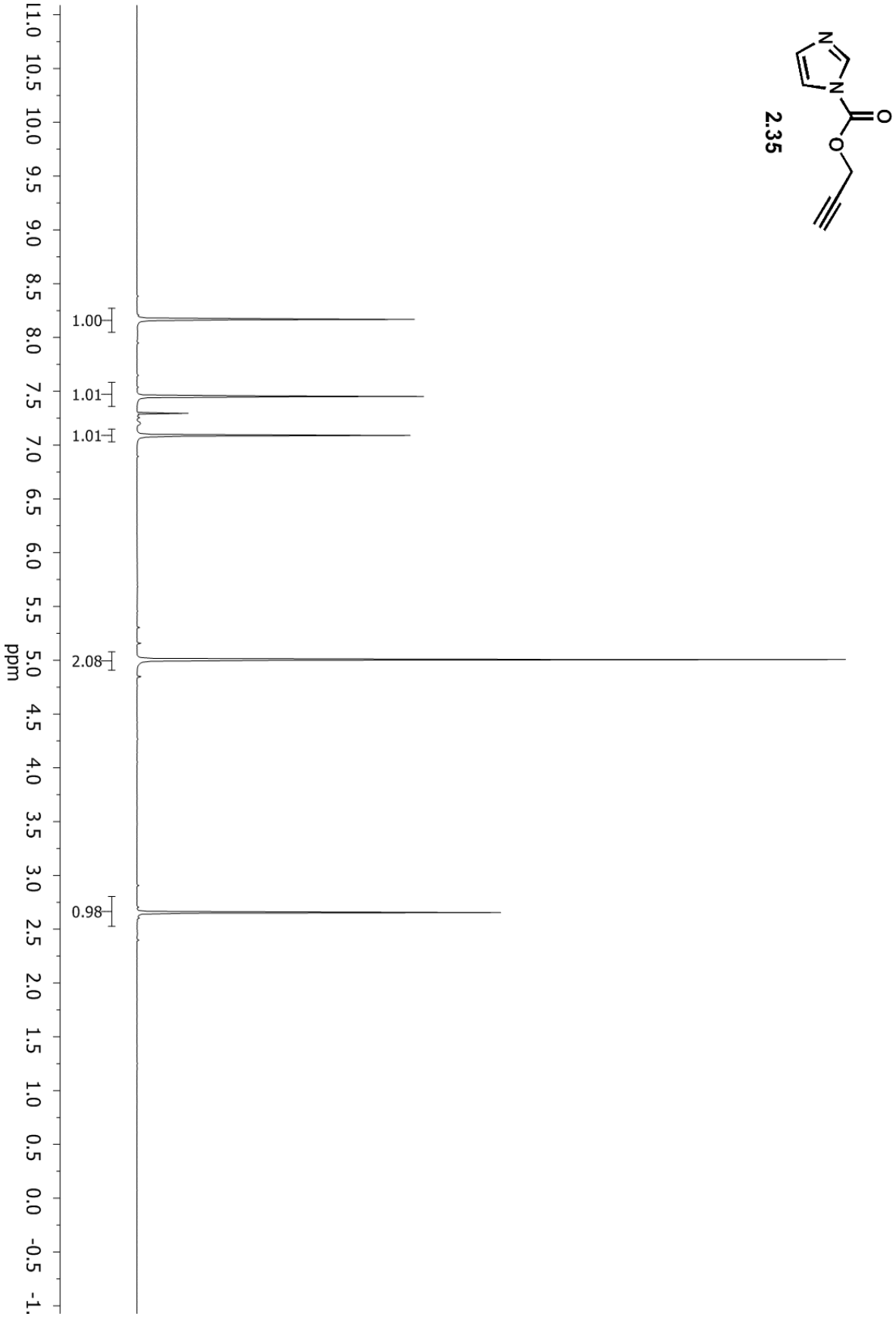
137.1
135.9
130.6
117.9
117.1
ppm
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0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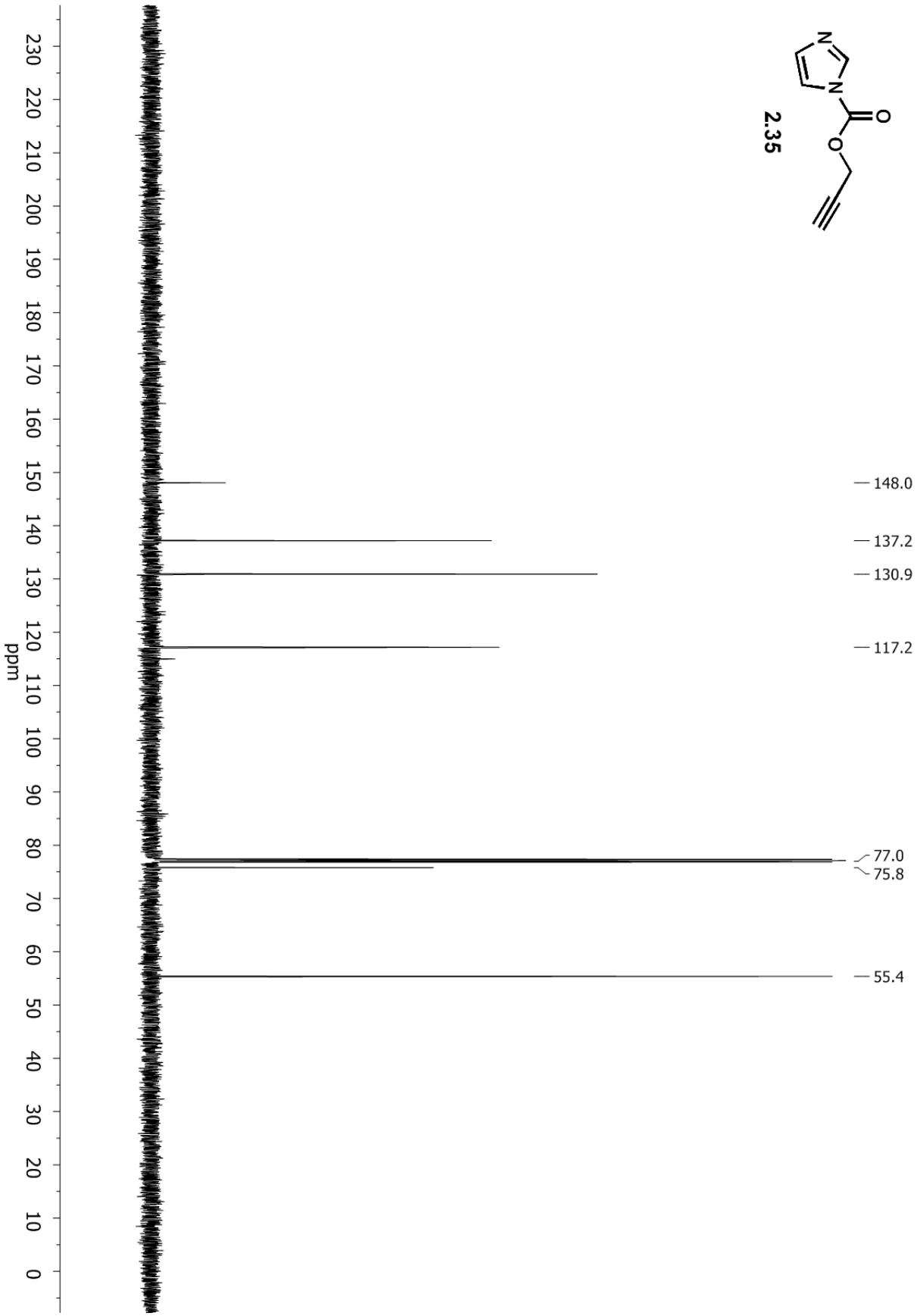
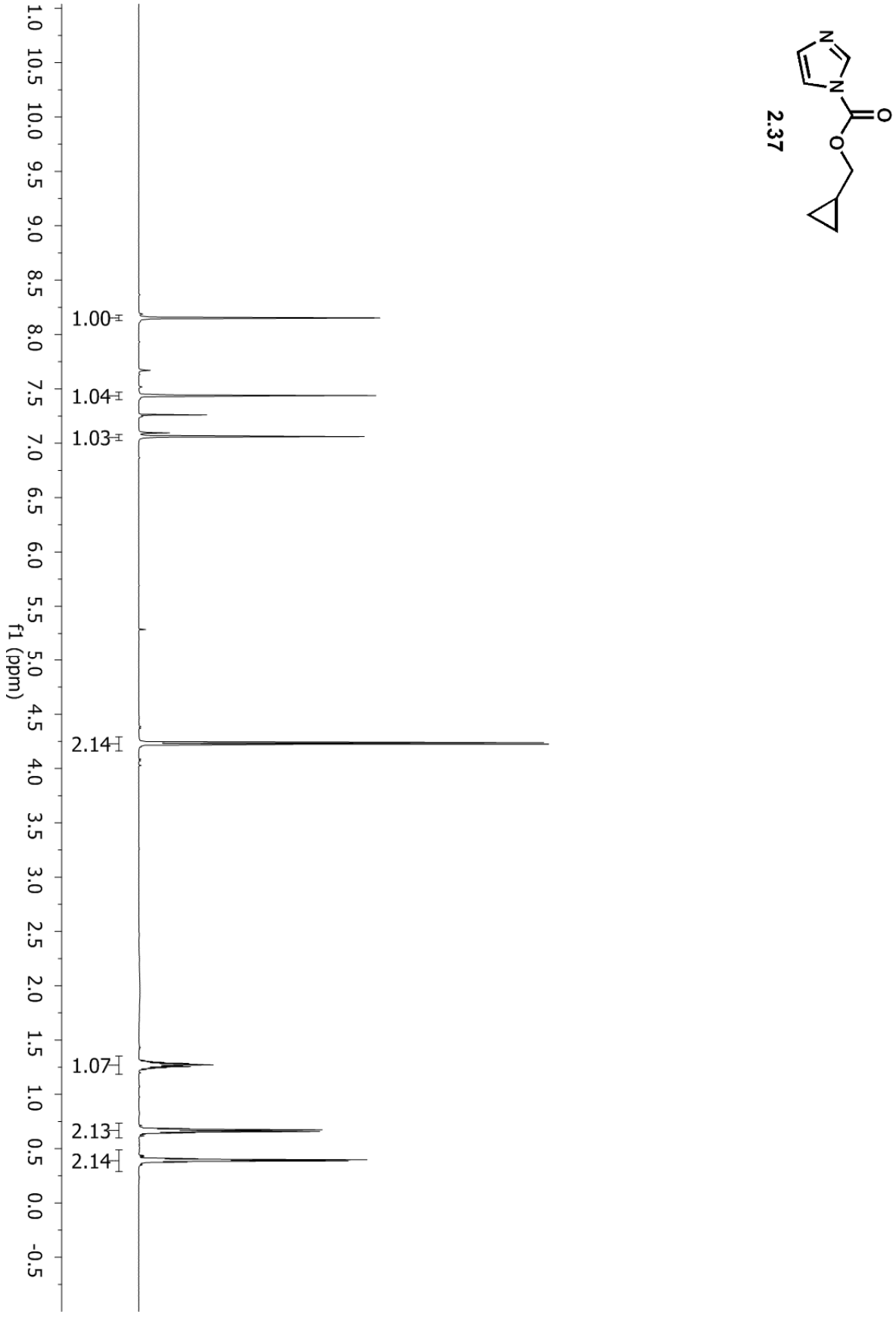
1.01
1.01
2.08
0.98
ppm


2.35
148.0
137.2
130.9
117.2
77.0
75.8
55.4
ppm
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0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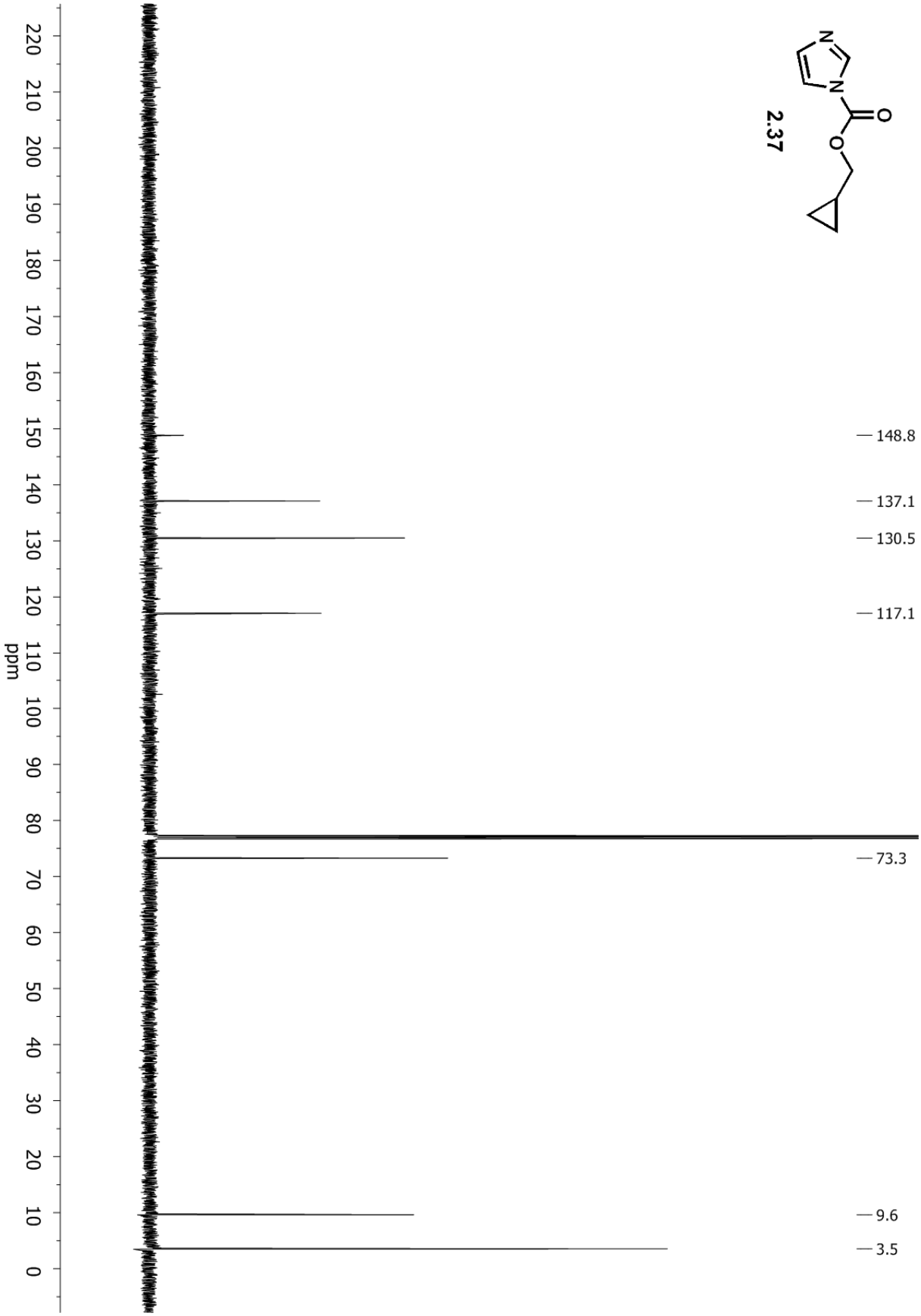
1.04
1.03
2.14
1.07
2.13
2.14
f1 (ppm)
2.37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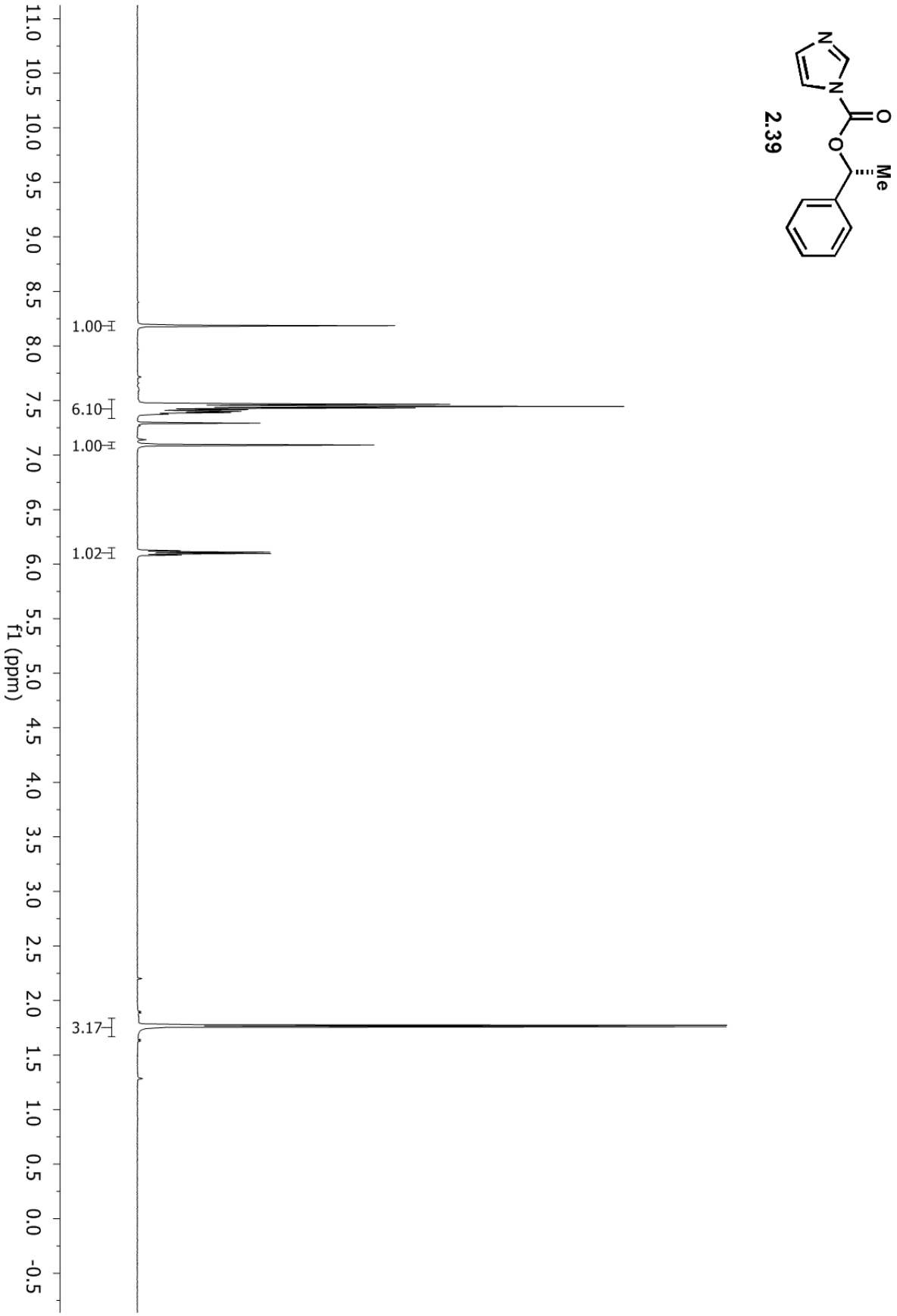
148.8
137.1
130.5
117.1
73.3
9.6
3.5
ppm
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0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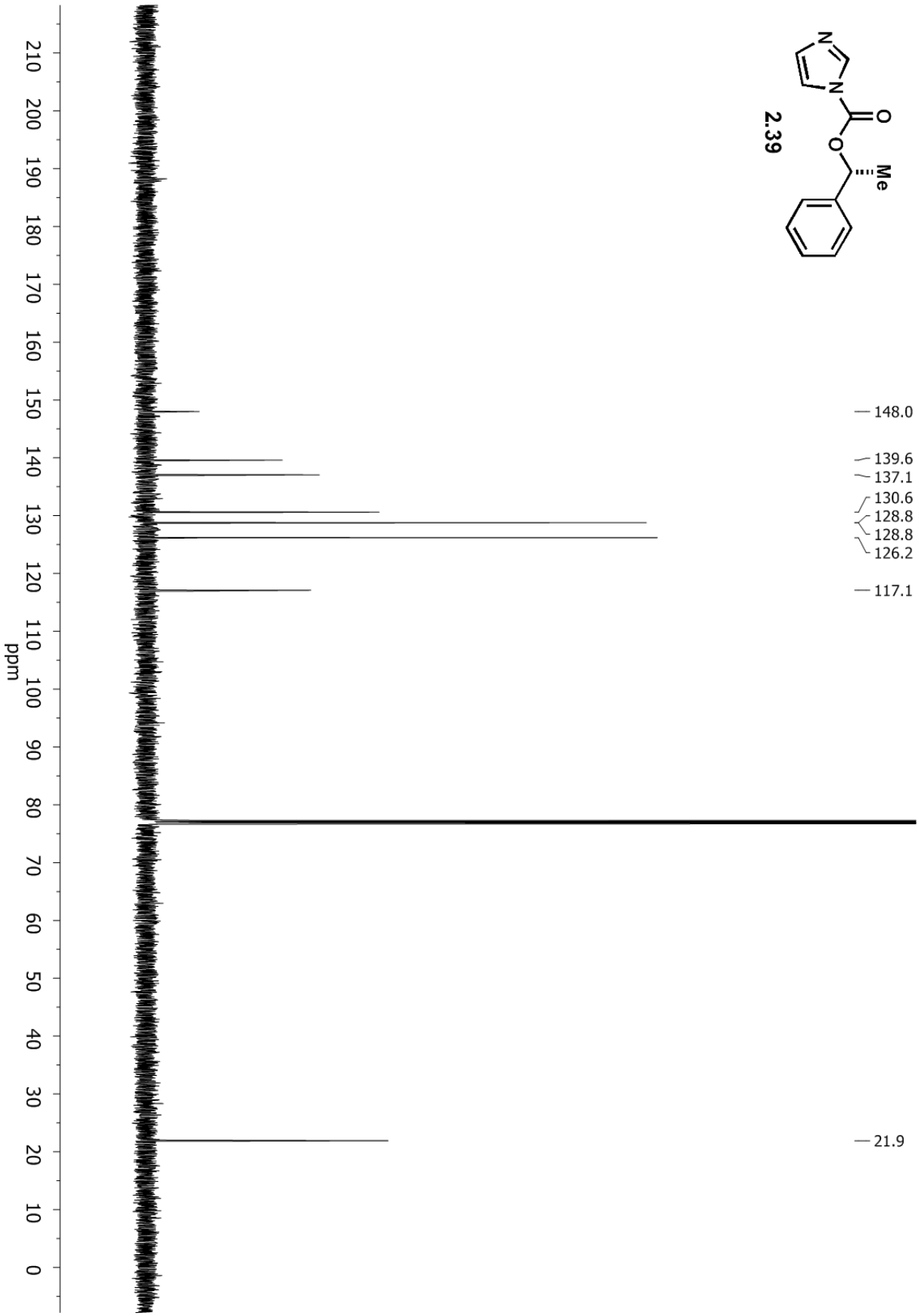
1.02
3.17
f1 (ppm)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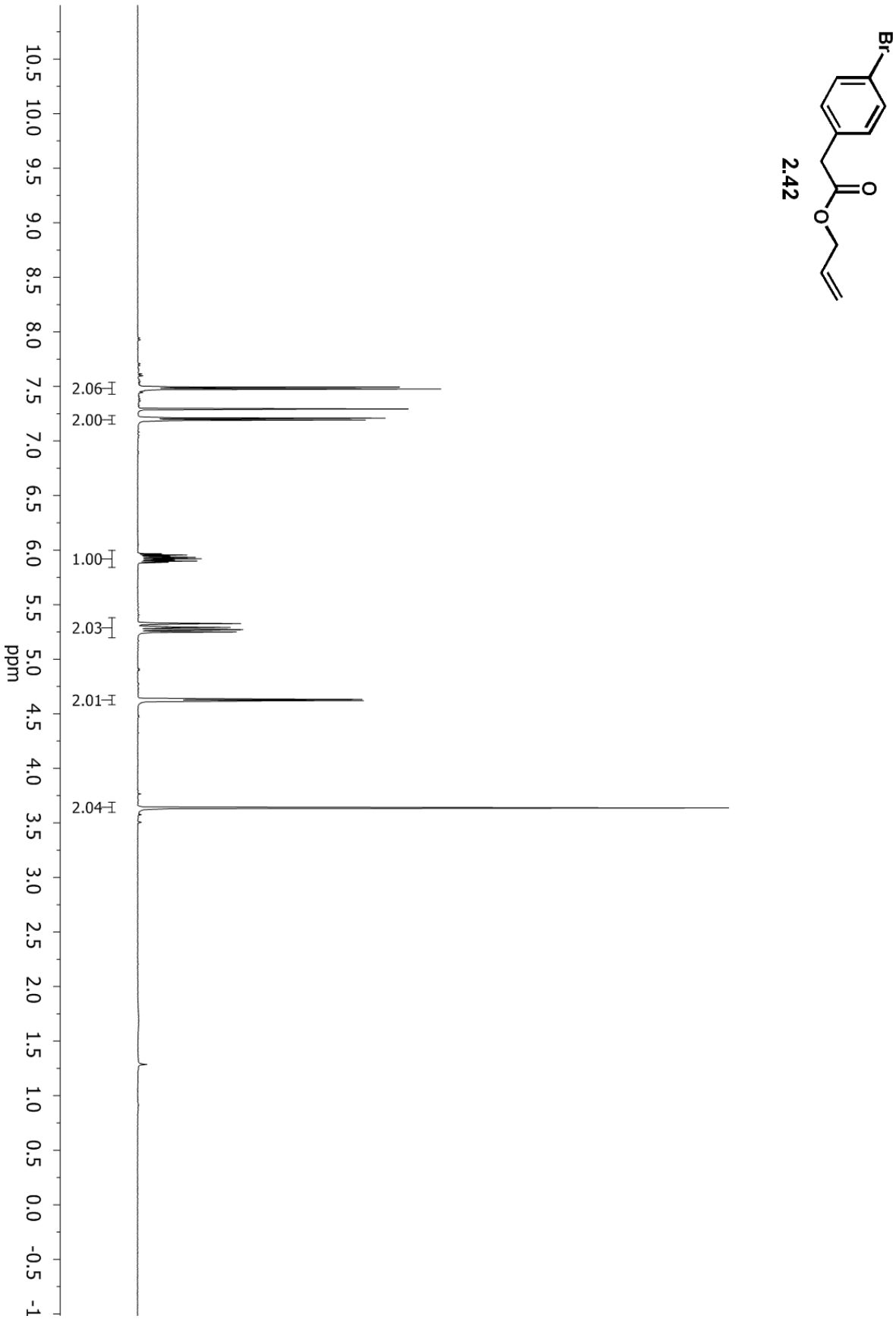
139.6
137.1
130.6
128.8
128.8
126.2
117.1
21.9
ppm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O
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ppm
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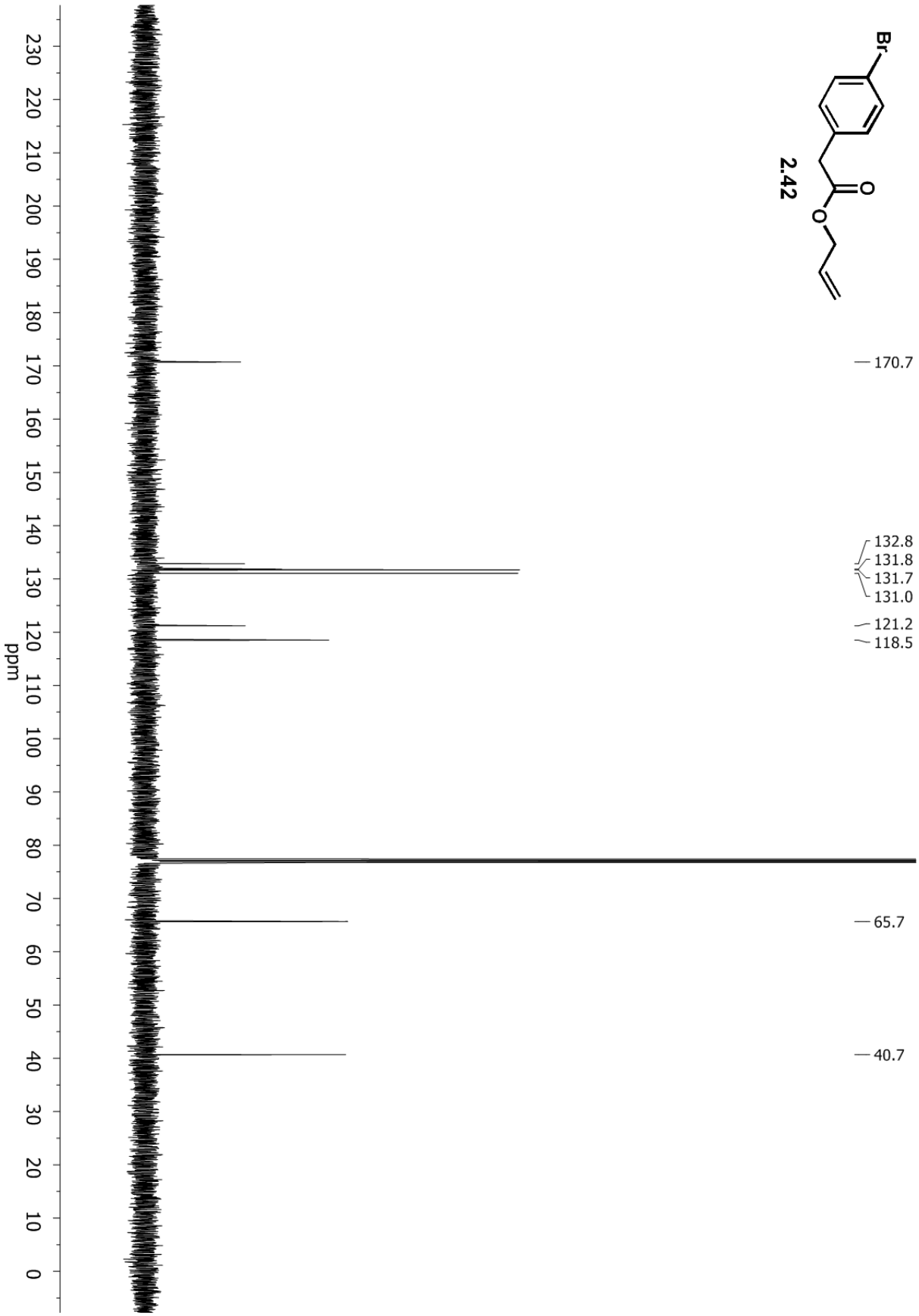
2.00
1.00
2.03
2.01
2.04


Br
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O
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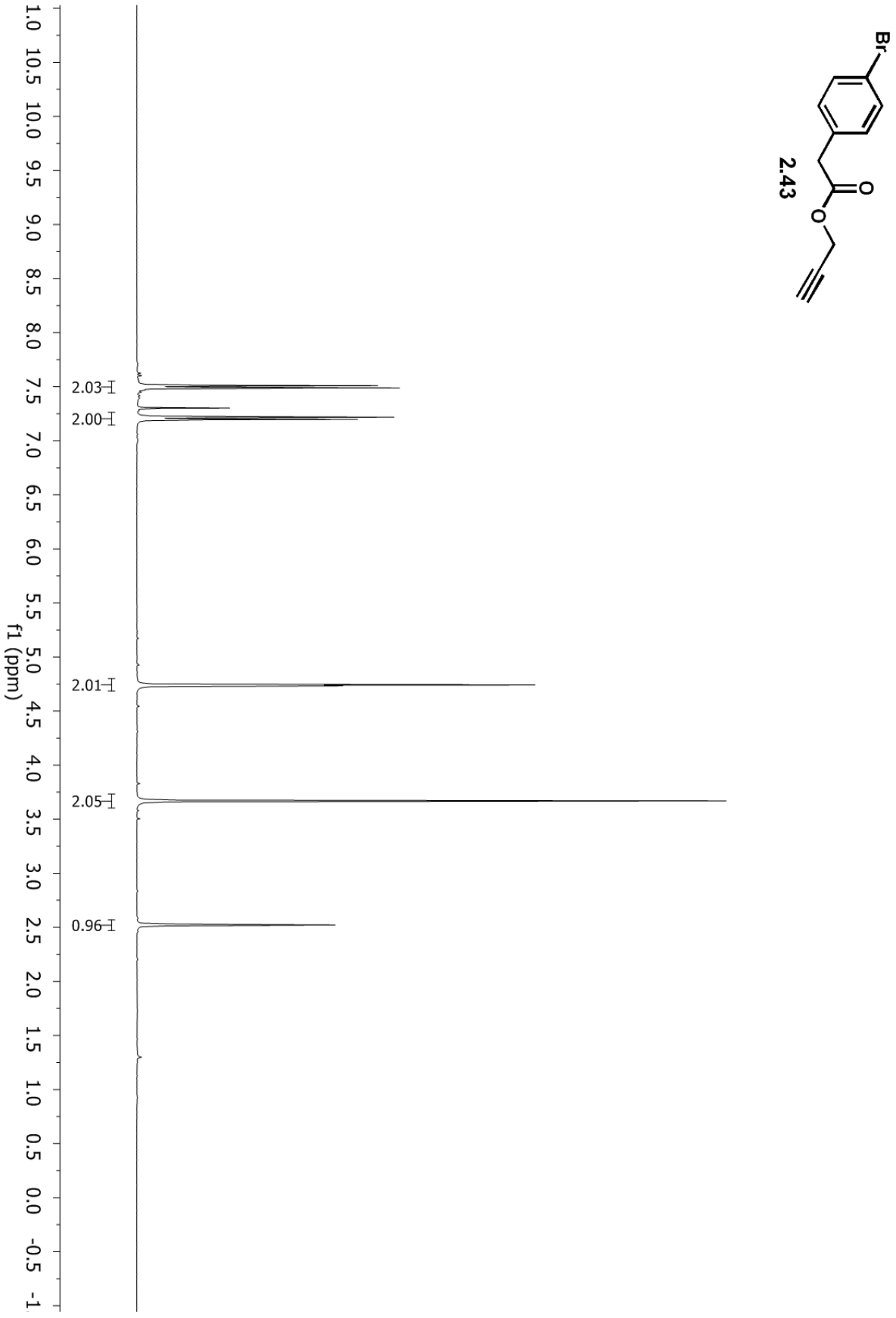
132.8
131.8
131.7
131.0
121.2
118.5
65.7
40.7
ppm
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0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O
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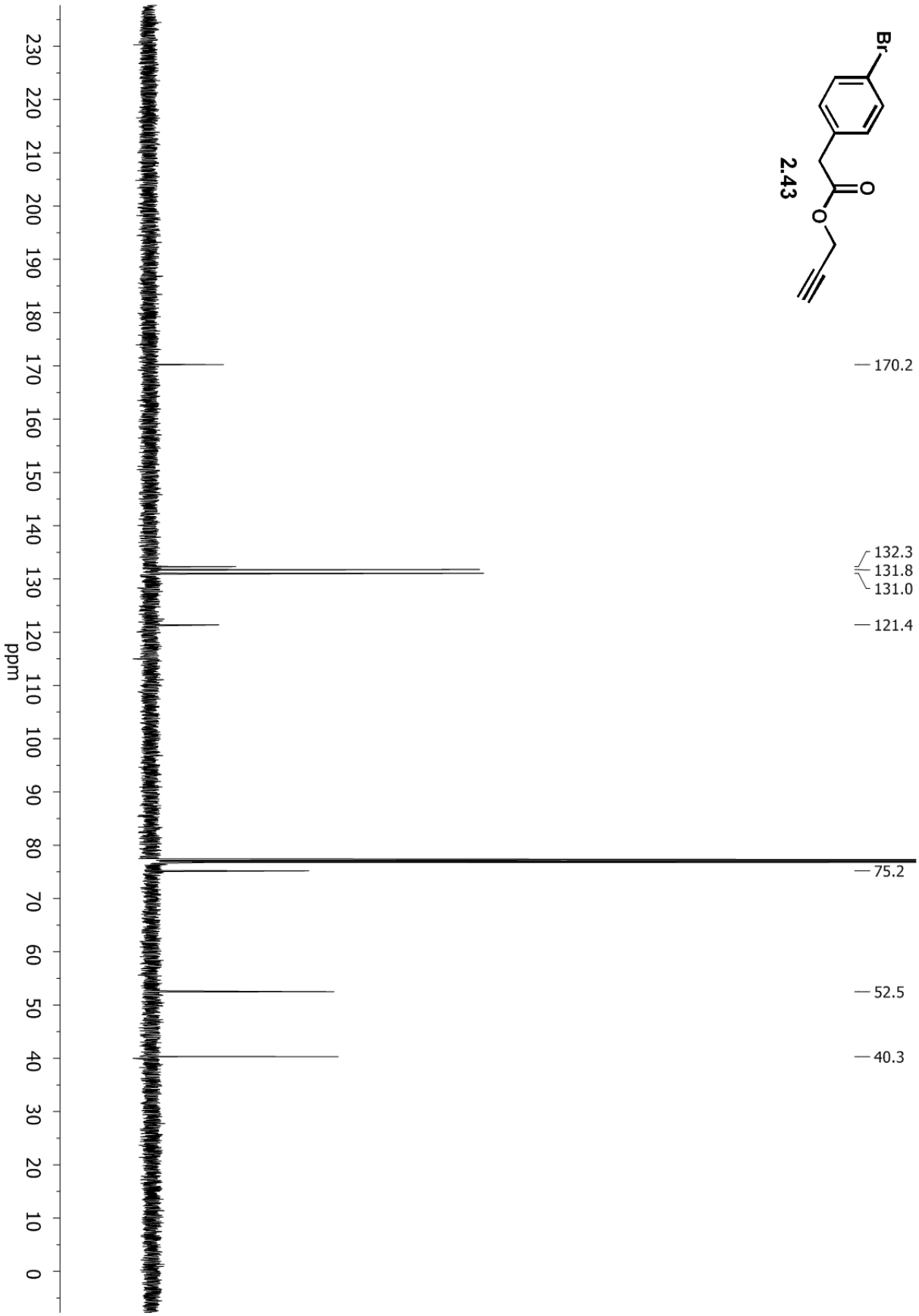
2.00
2.01
2.05
0.96
f1 (ppm)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O
O
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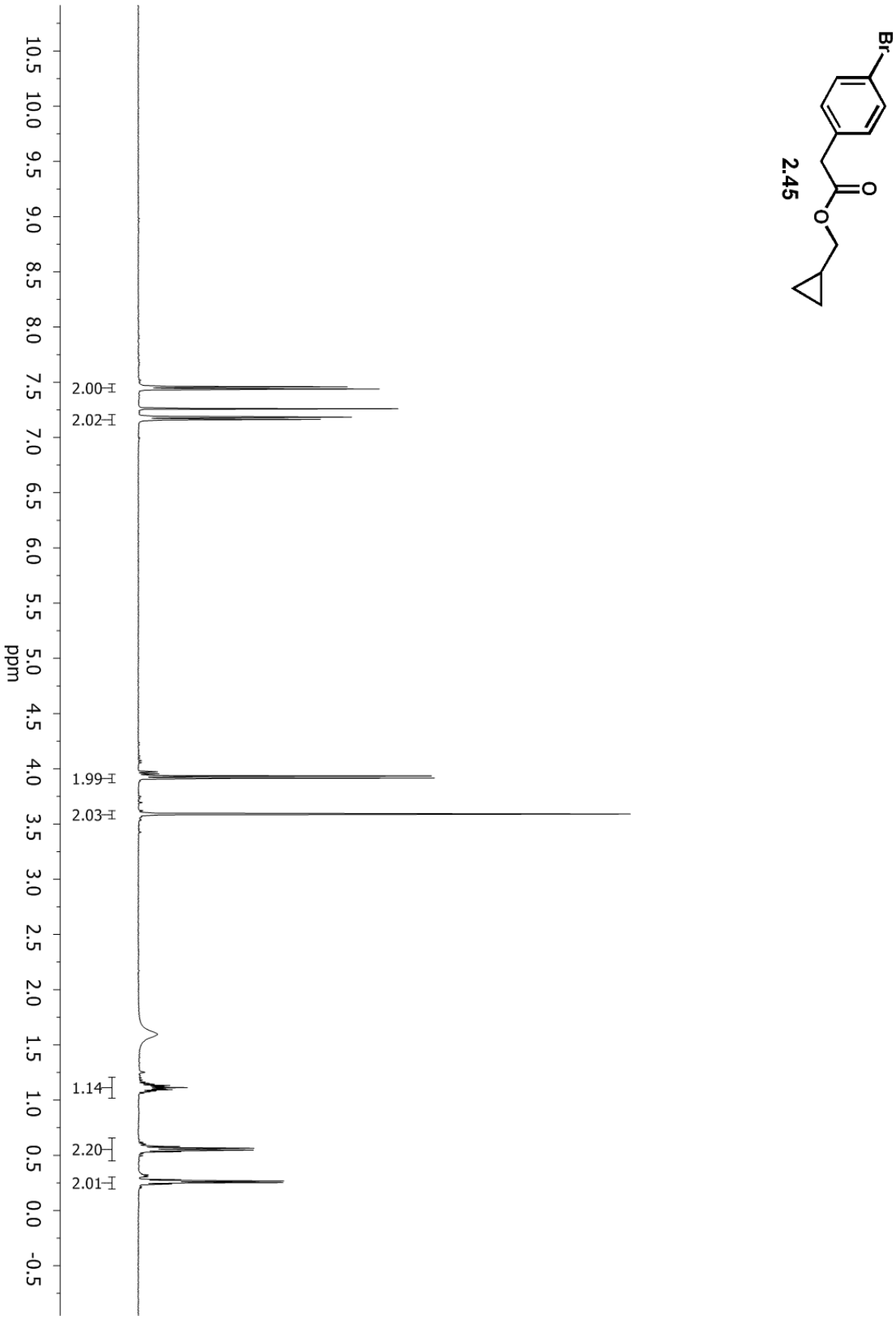
132.3
131.8
131.0
121.4
75.2
52.5
40.3
ppm
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0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O
O
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ppm
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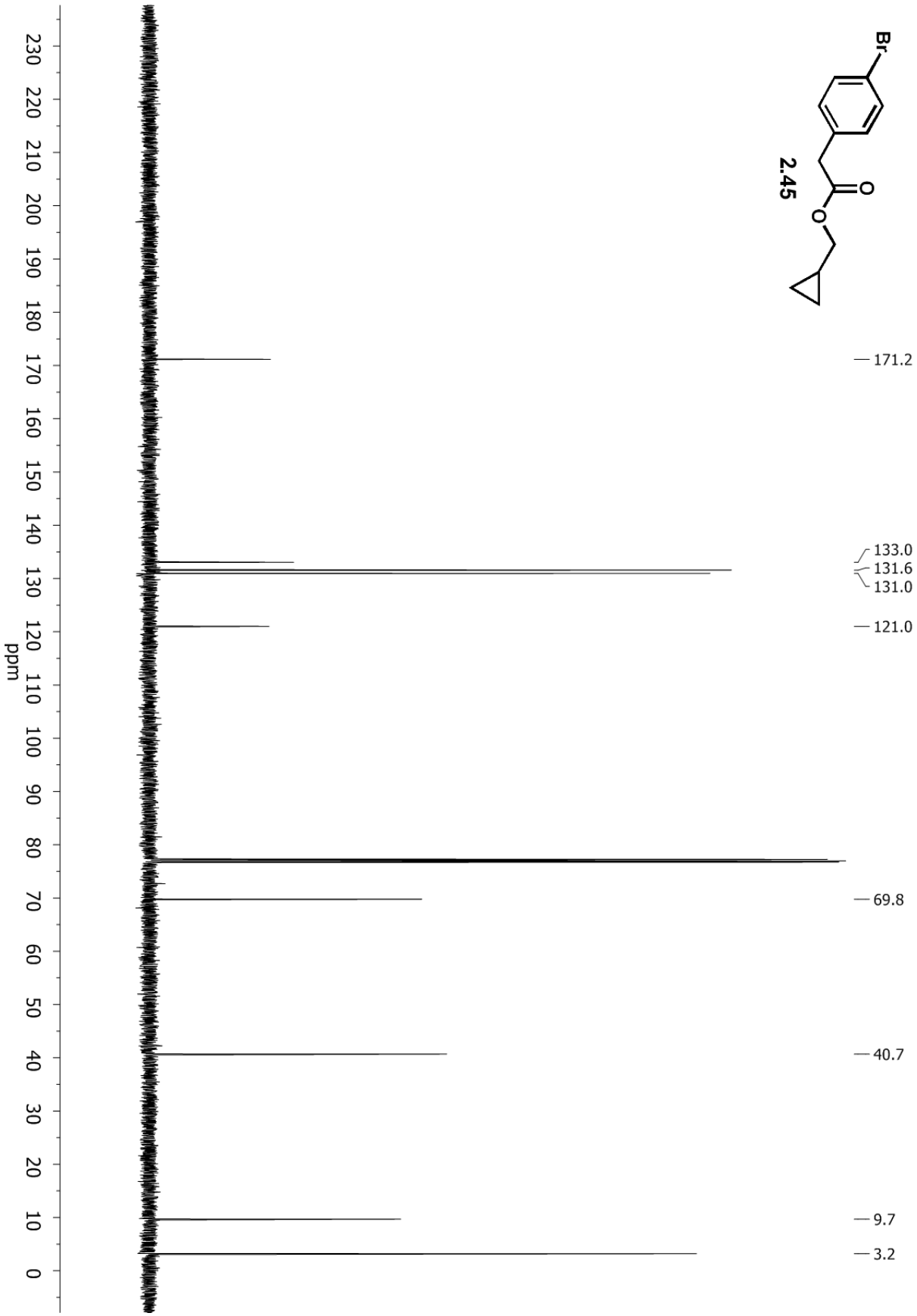
2.02
1.99
2.03
1.14
2.20
2.01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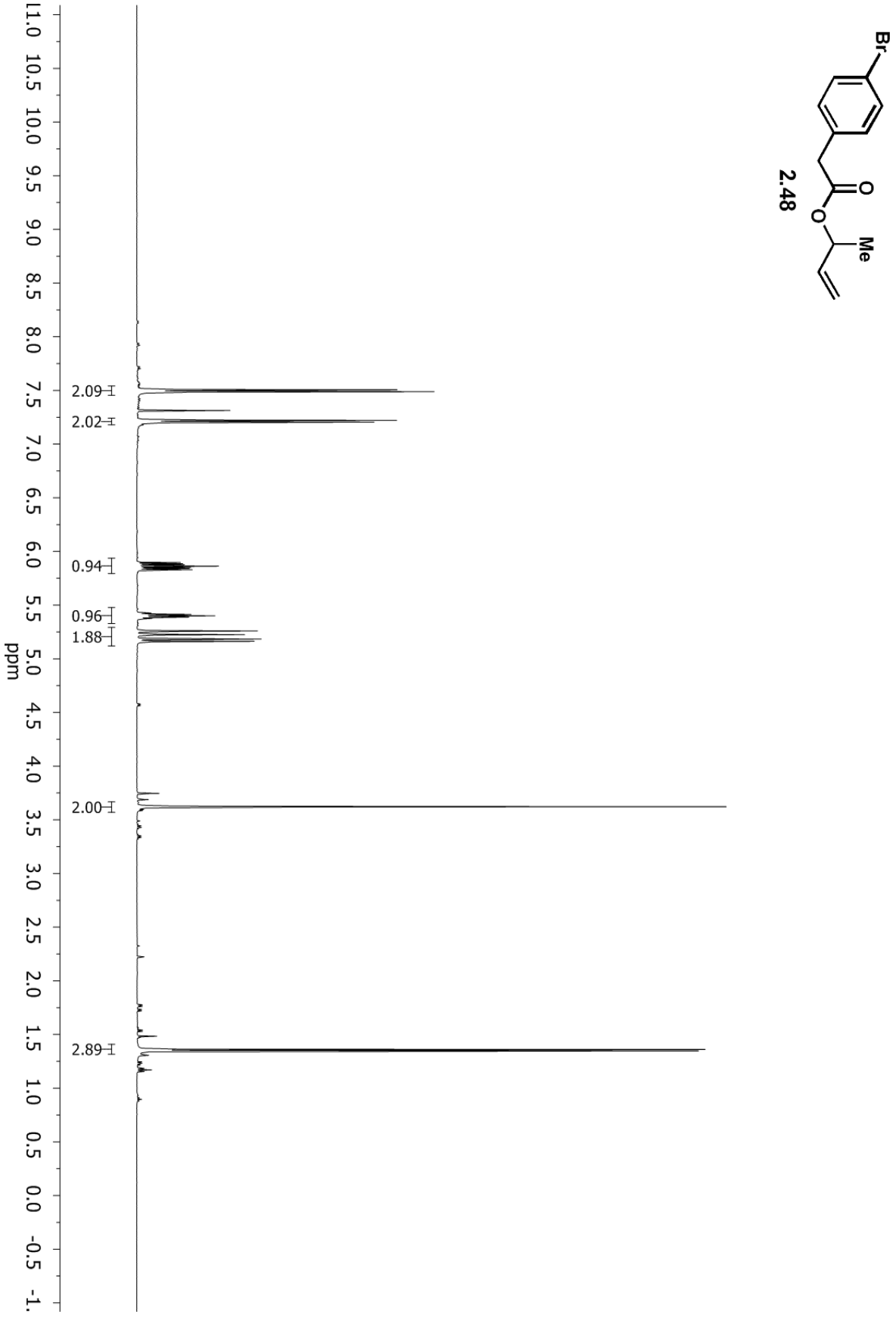
O
O
2.45
171.2
133.0
131.6
131.0
121.0
69.8
40.7
9.7
3.2
ppm
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0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O
O
Me
2.48
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ppm
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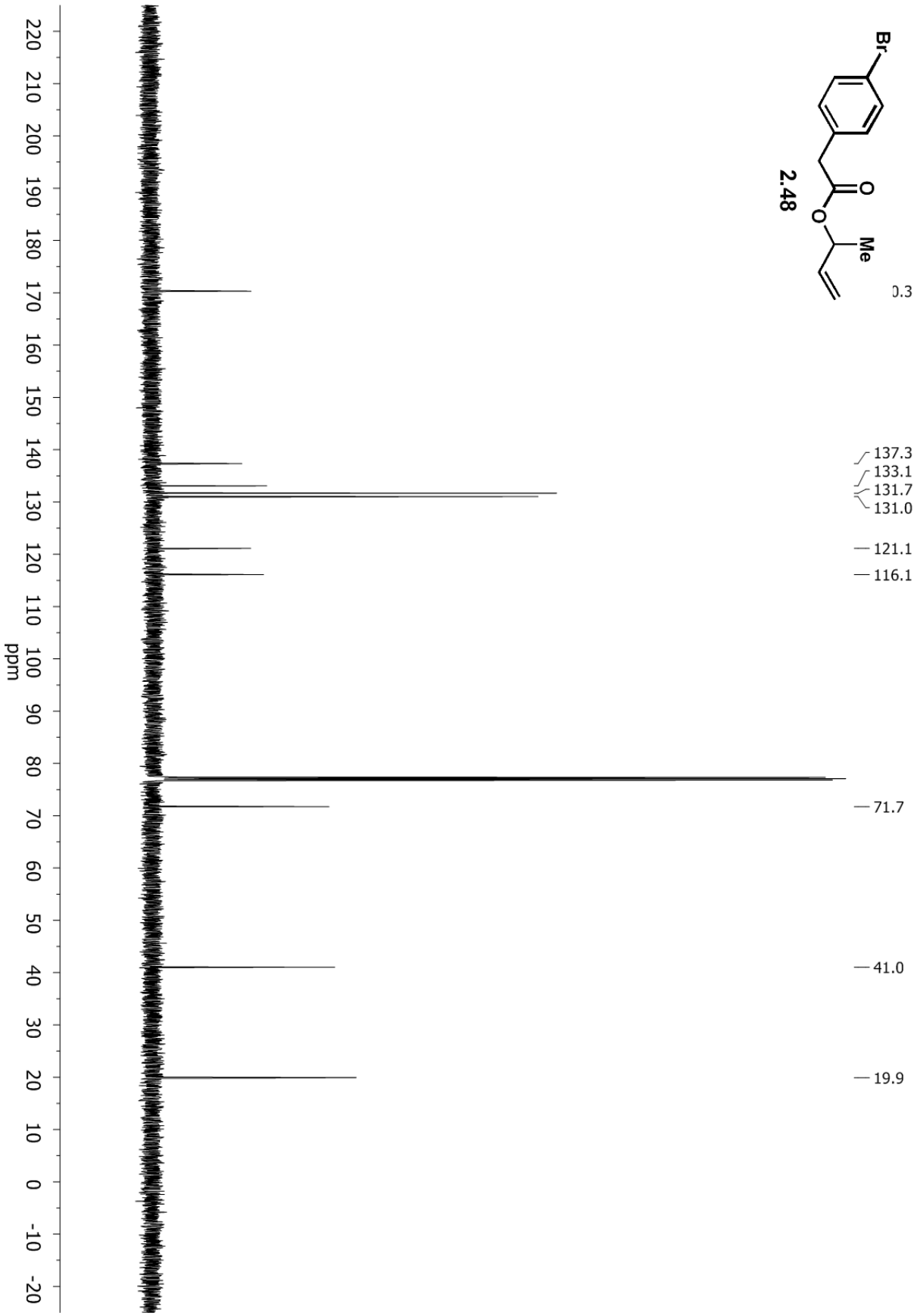
2.02
0.94
0.96
1.88
2.00
2.89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O
O
Me
2.48
0.3
137.3
133.1
131.7
131.0
121.1
116.1
71.7
41.0
19.9
ppm
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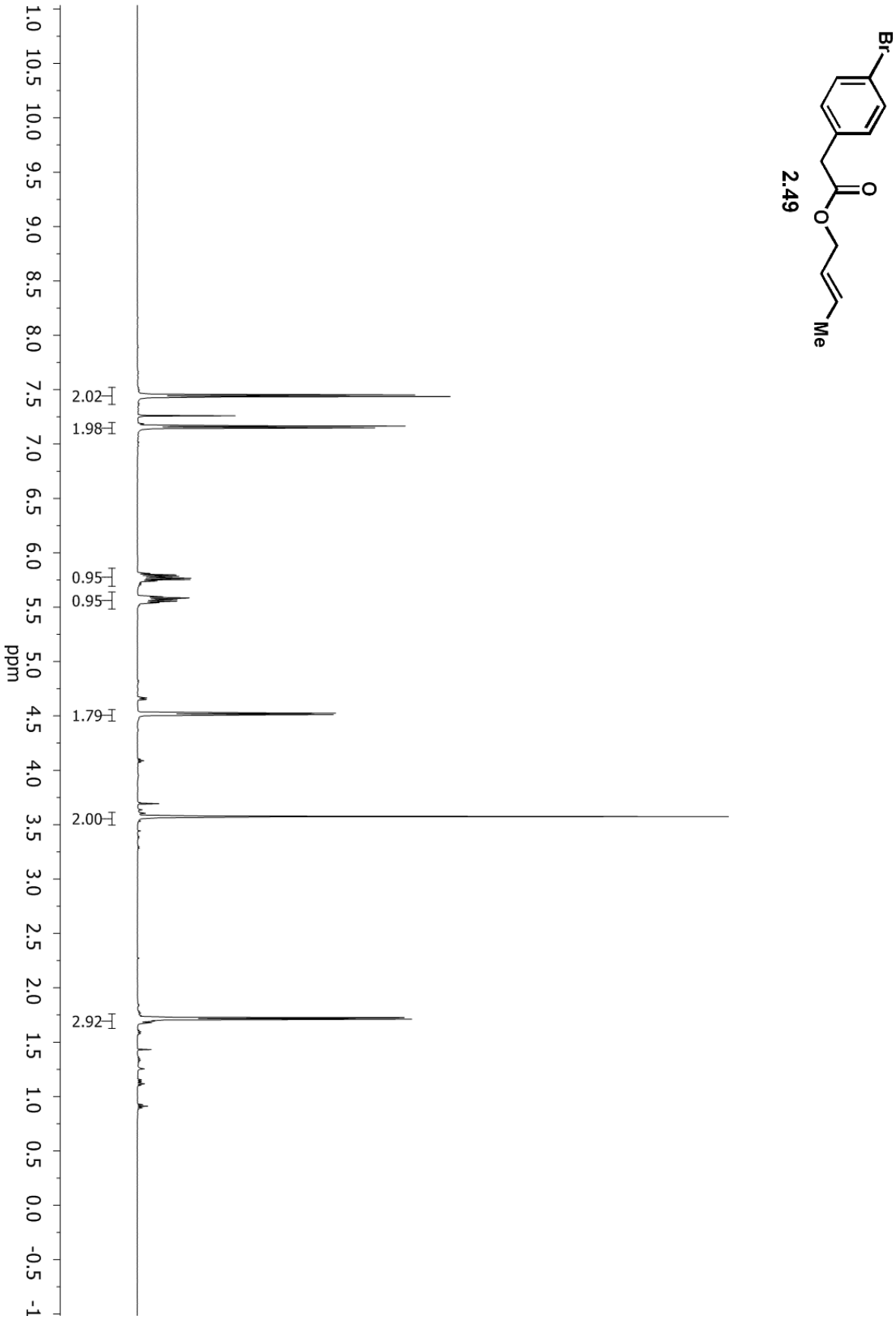
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O
O
Me
2.49
2.02
1.98
0.95
0.95
1.79
2.00
2.92
ppm
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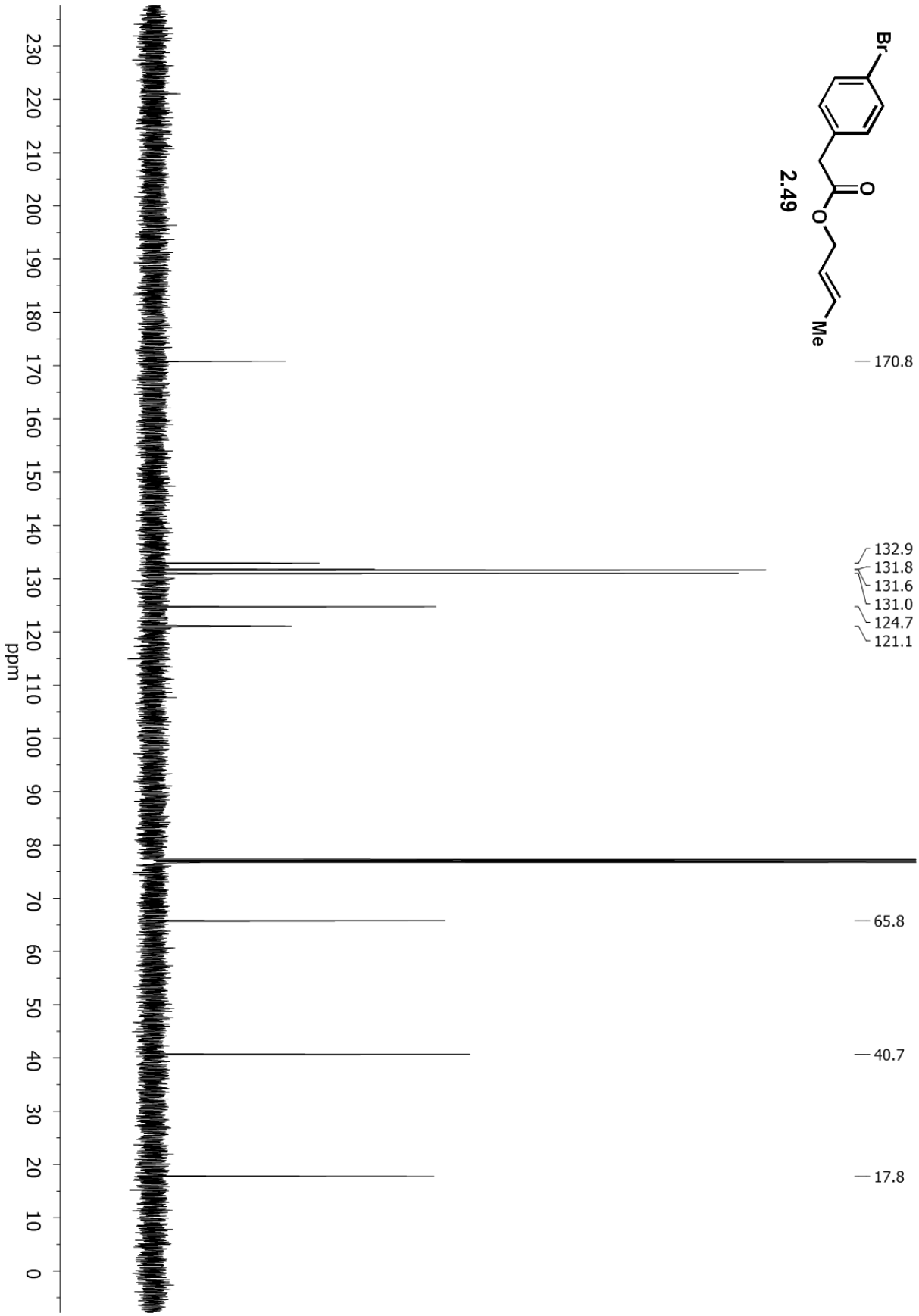
Br
O
O
Me
2.49
170.8
132.9
131.8
131.6
131.0
124.7
121.1
65.8
40.7
17.8
ppm
230
220
210
200
190
180
170
160
150
140
130
120
110
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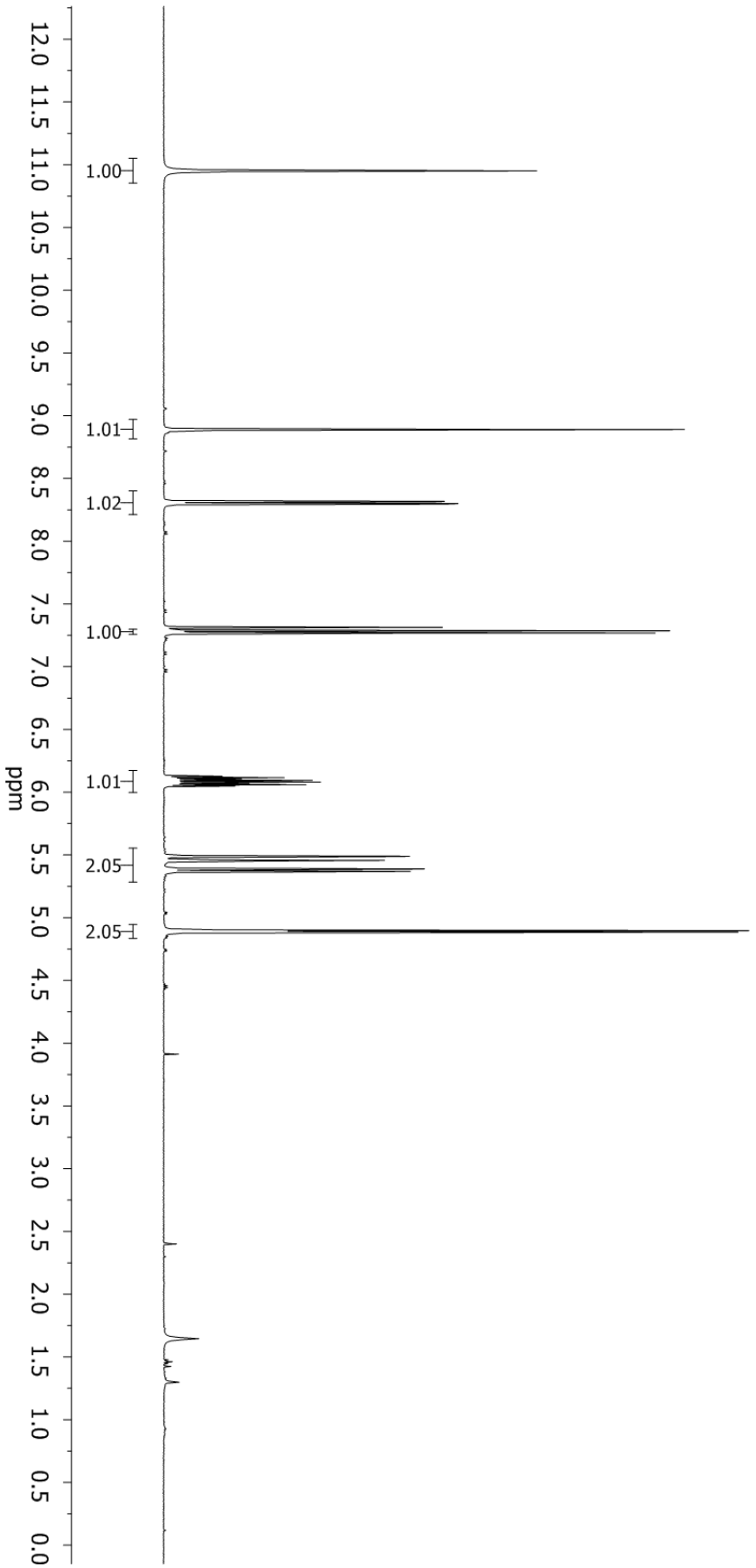
90
80
70
60
50
40
30
20
10
0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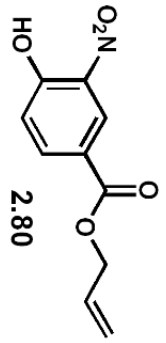
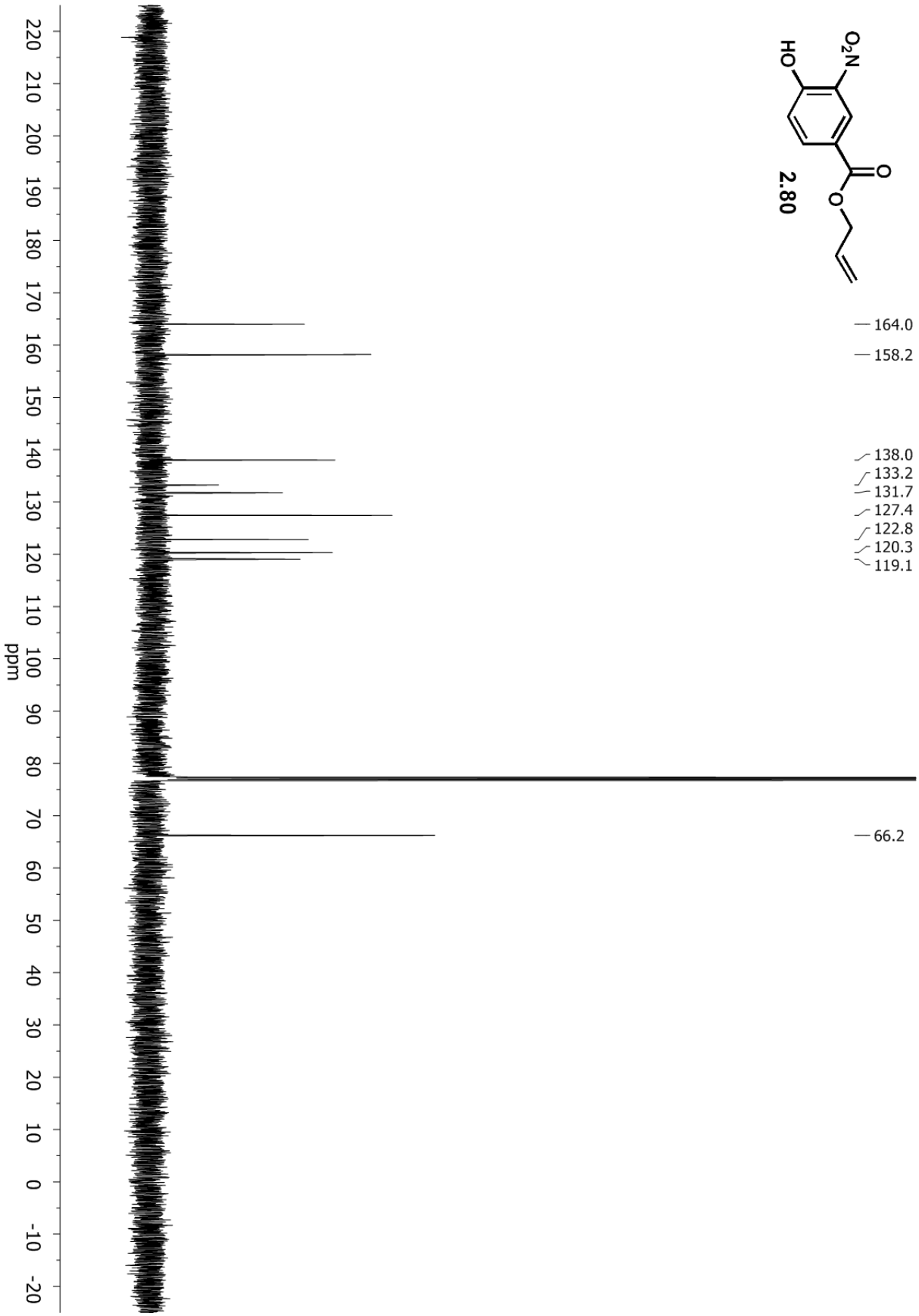
ppm
1.00
1.01
1.02
1.00
1.01
2.05
2.05


HO
O2N
O
O
2.80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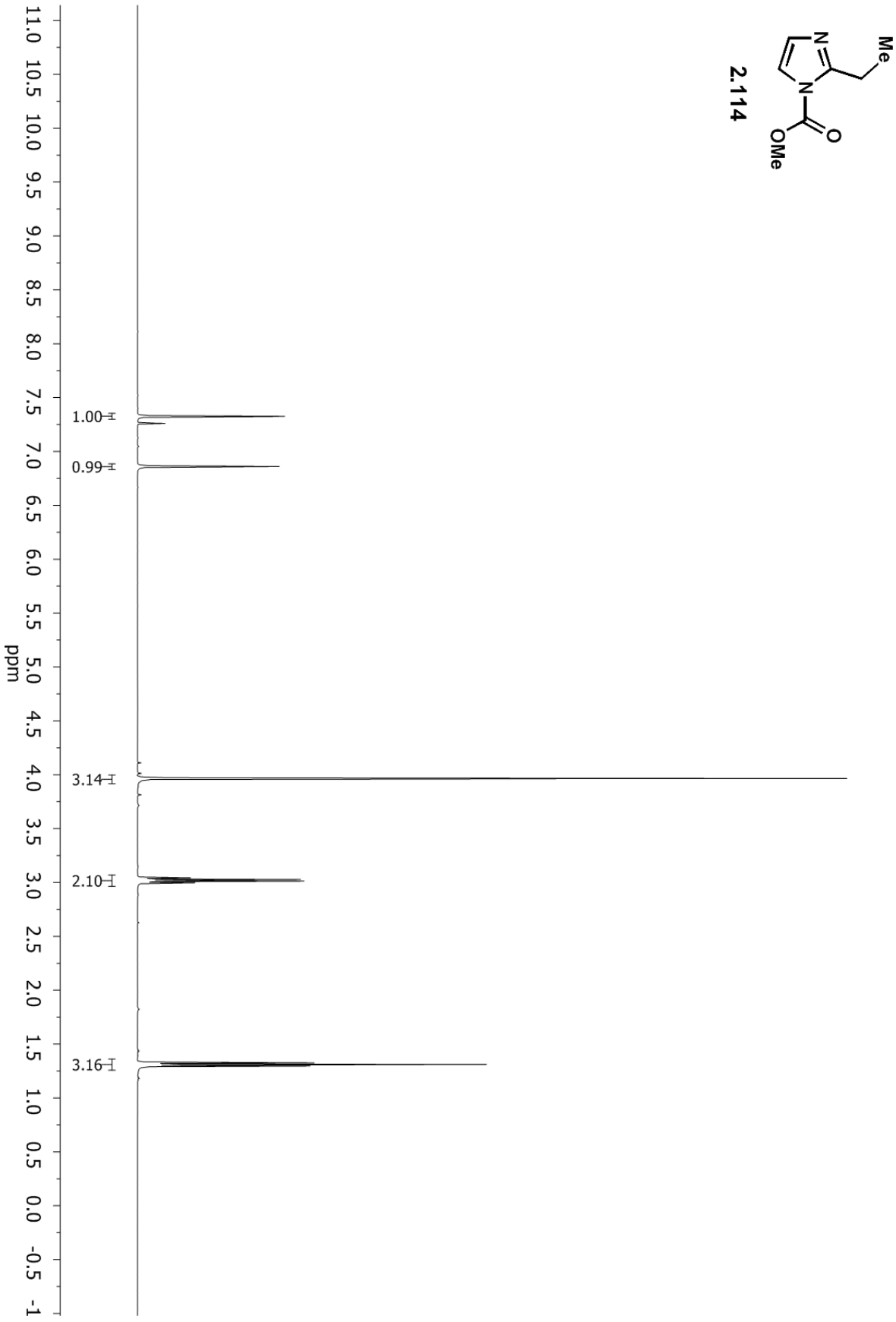
ppm
HO
O2N
O
O
2.80
164.0
158.2
138.0
133.2
131.7
127.4
122.8
120.3
119.1
66.2


Me
N
N
O
OMe
2.114
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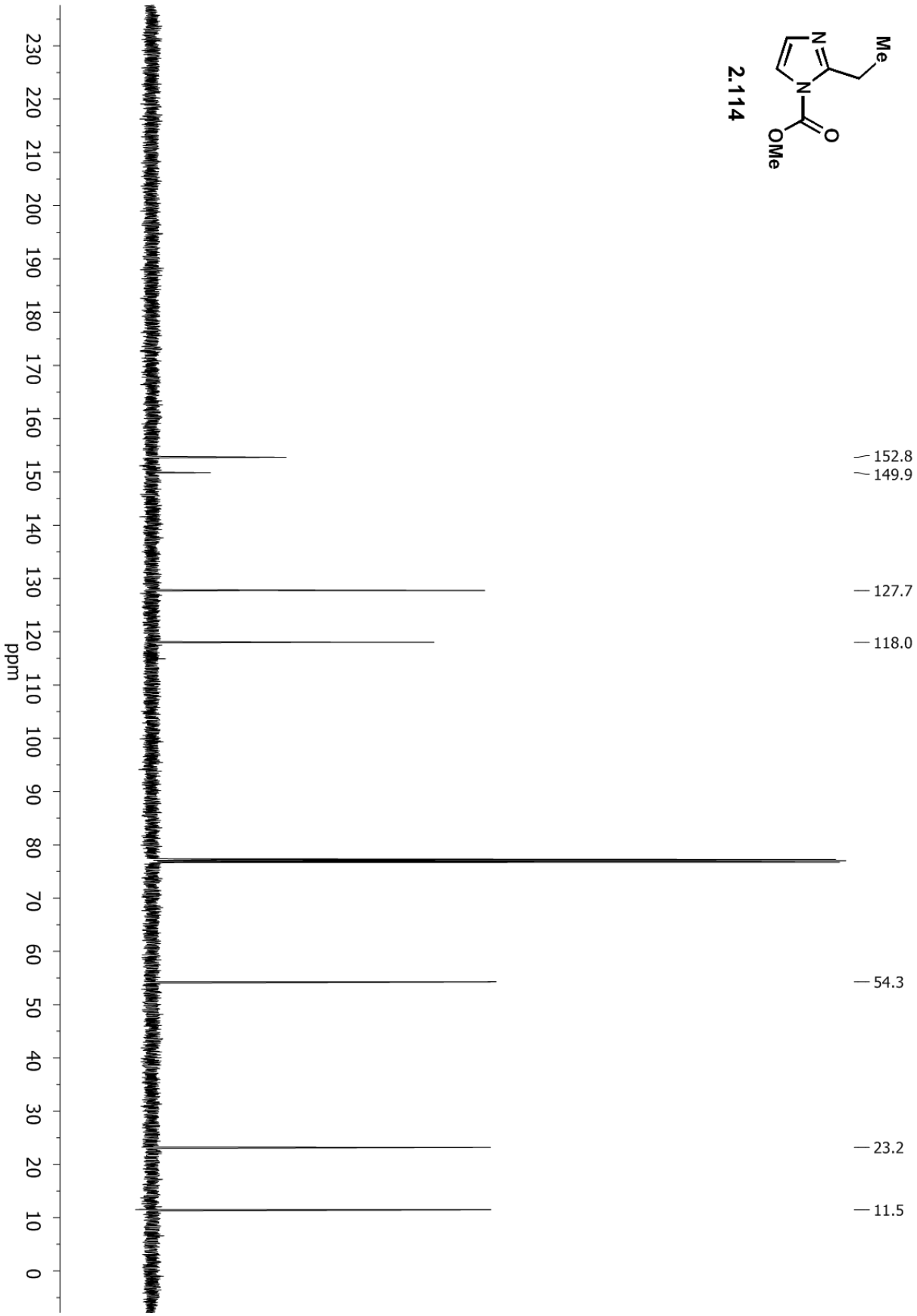
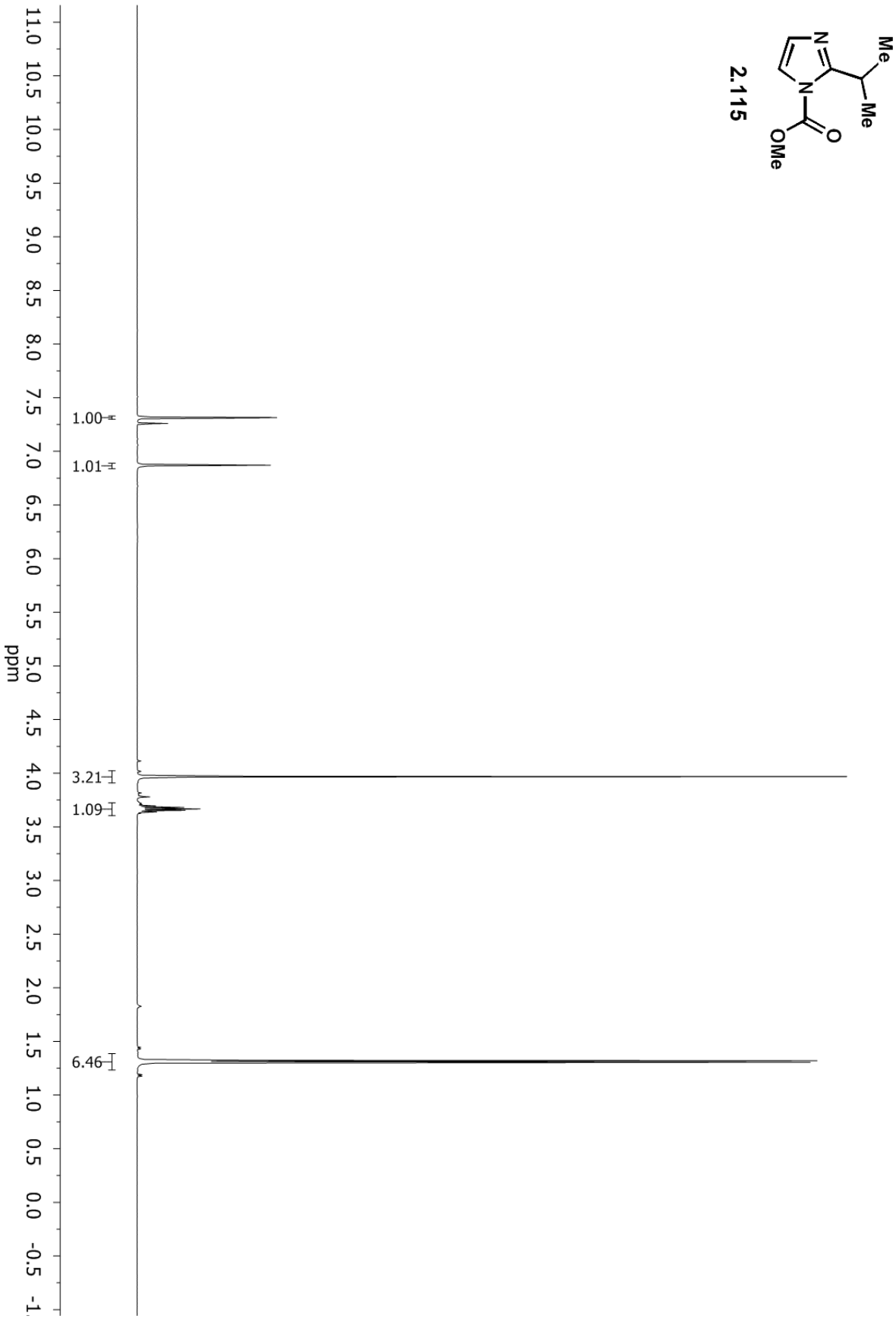
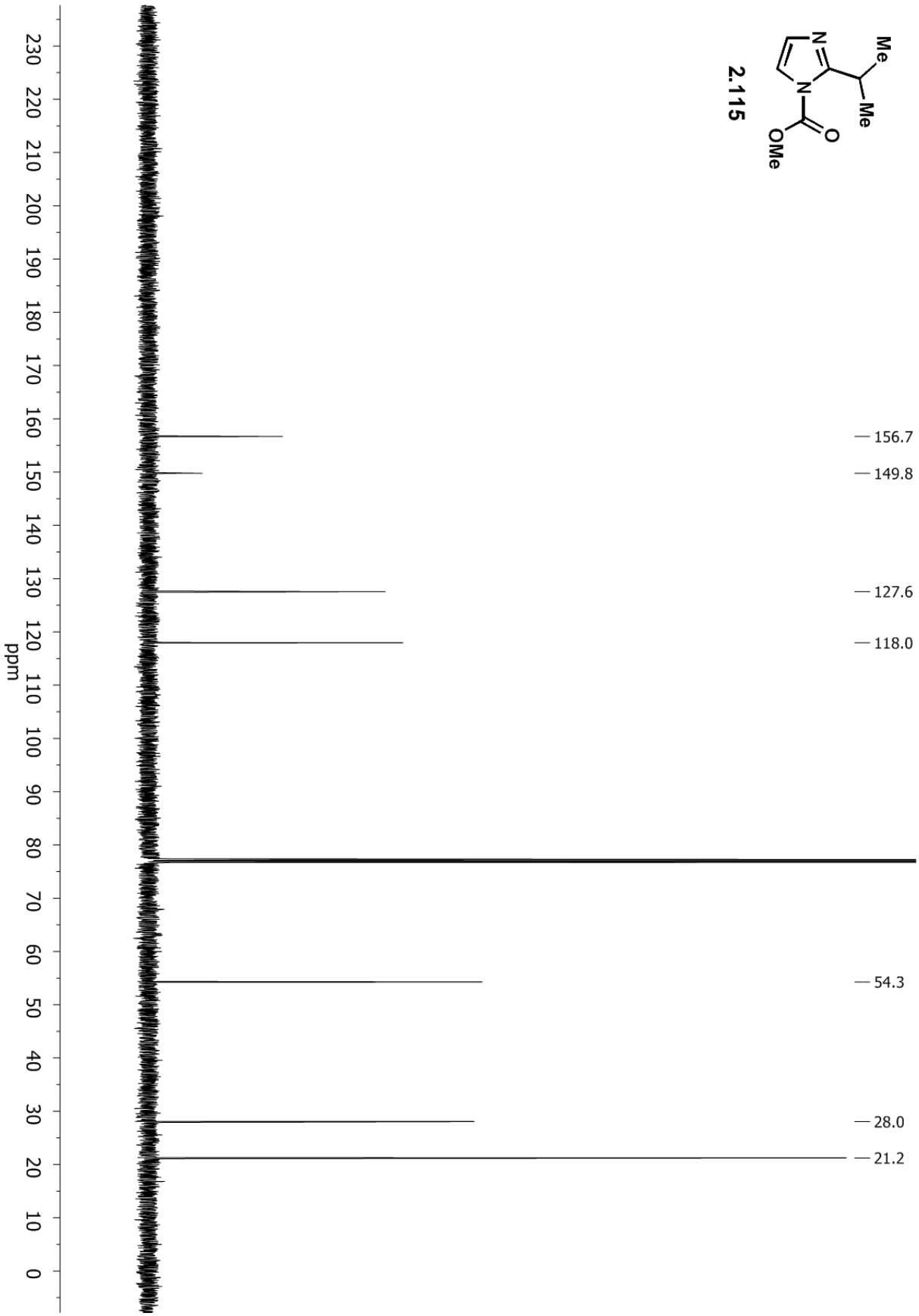
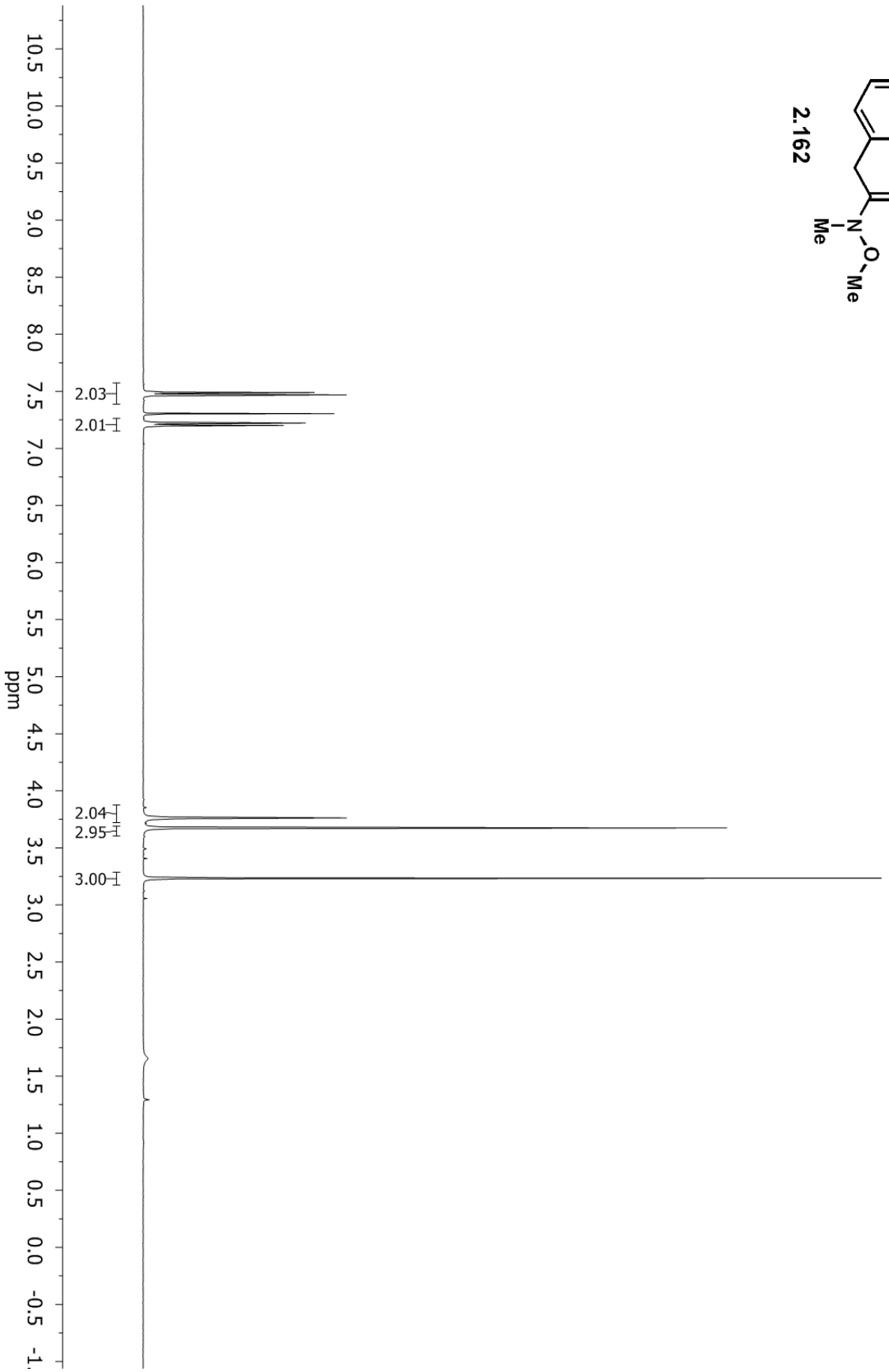
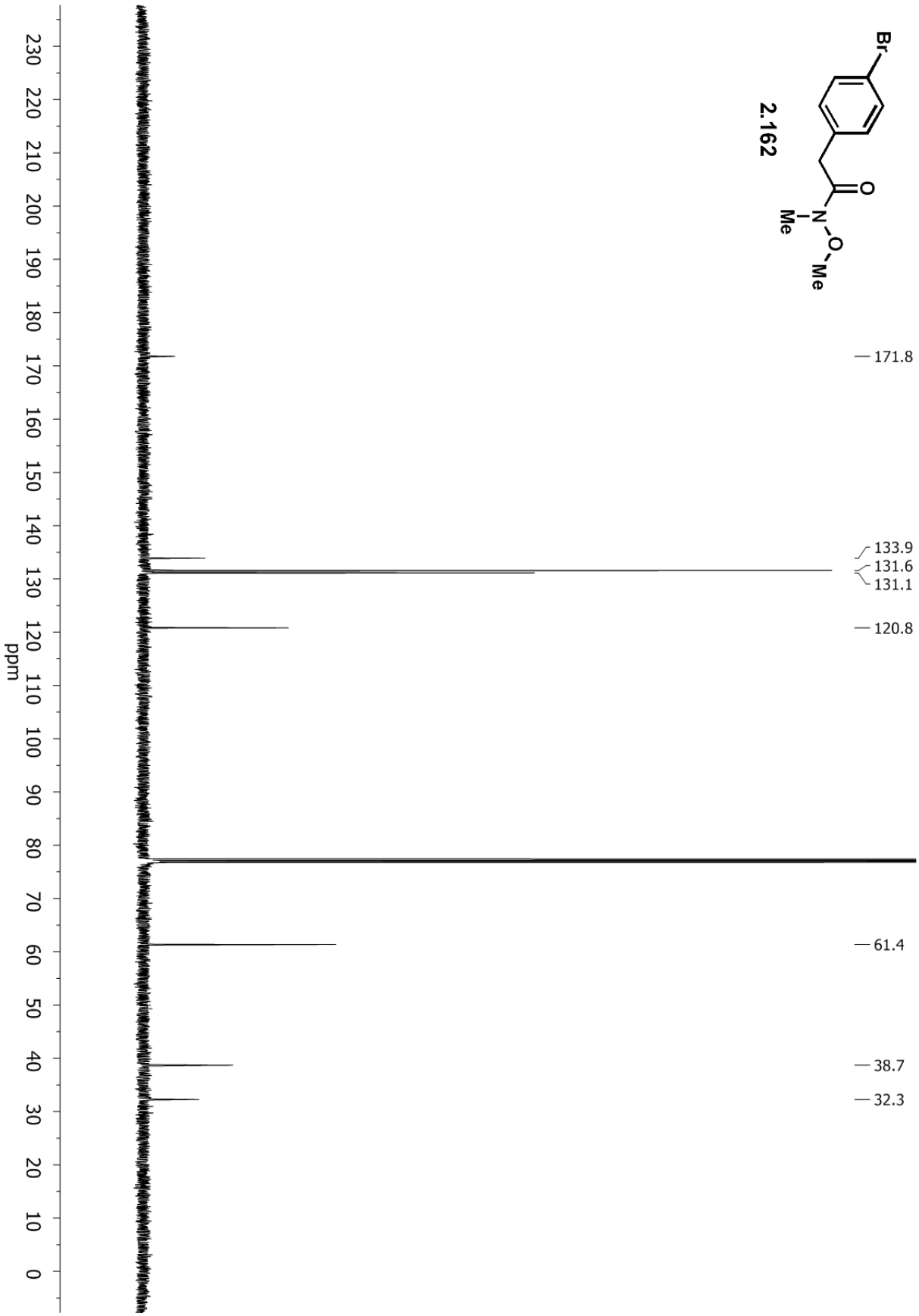
ppm
1.00
0.99
3.14
2.10
3.16

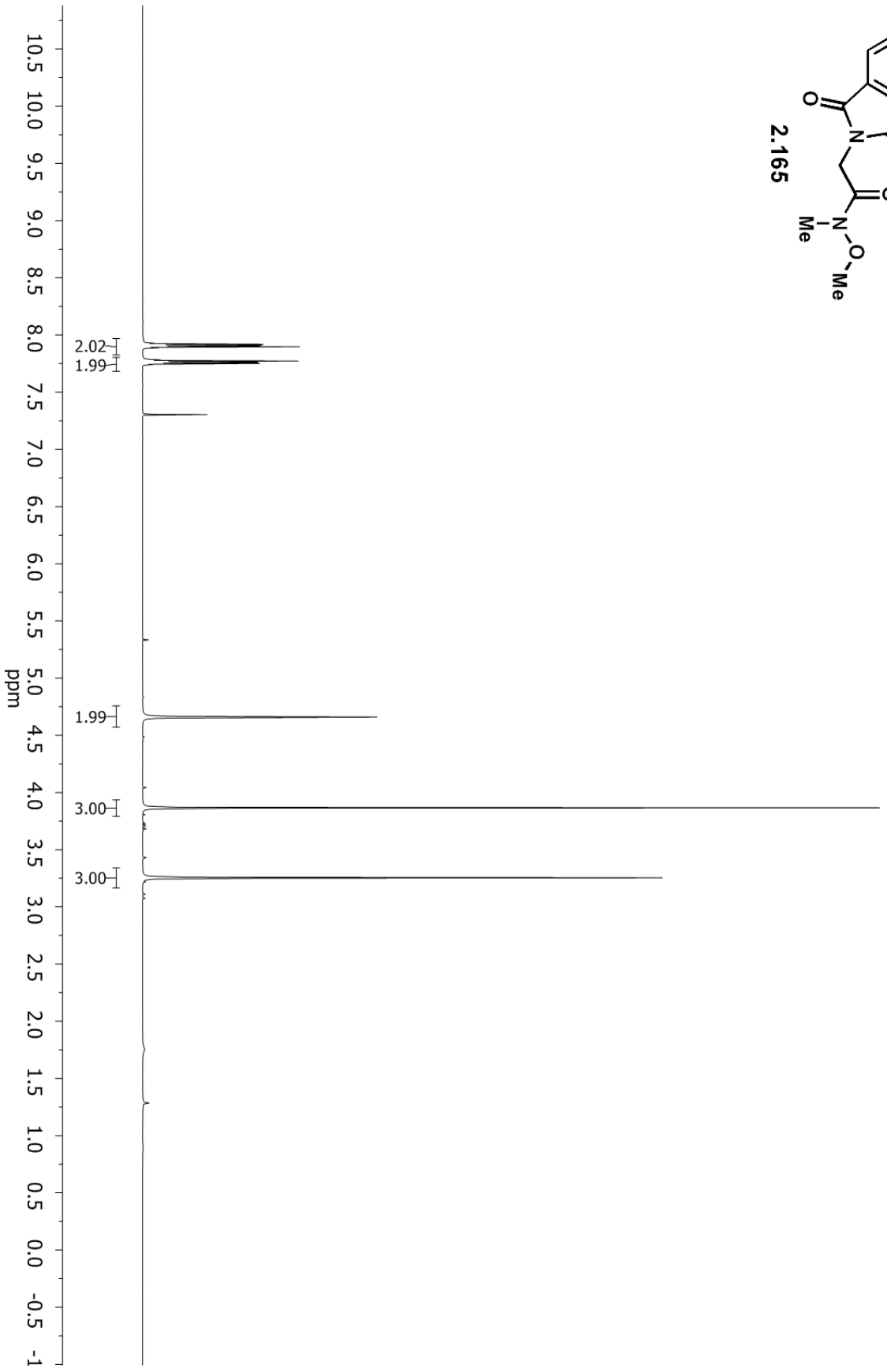

2.114
Me
N
N
O
OMe
152.8
149.9
127.7
118.0
54.3
23.2
11.5
ppm
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

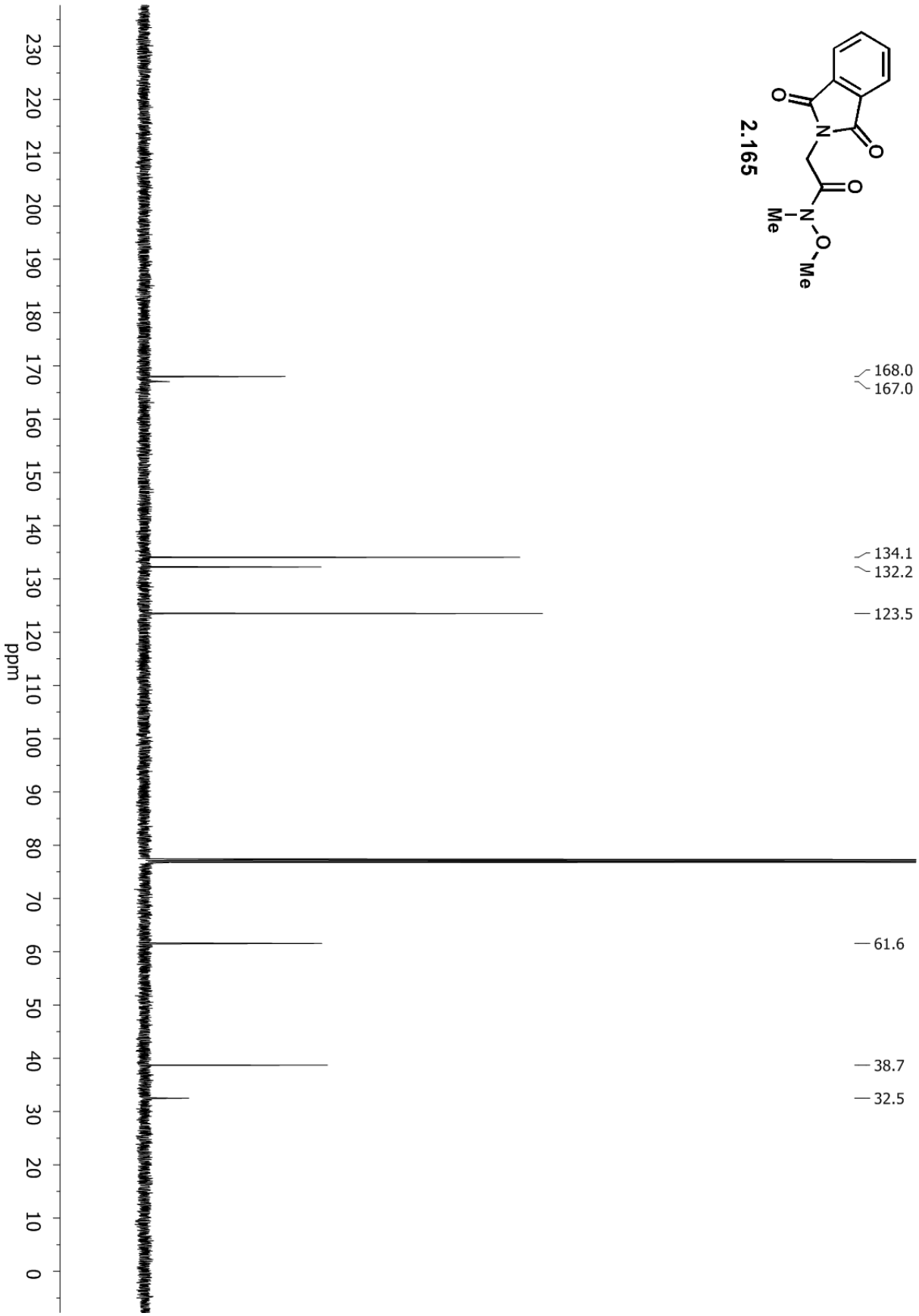

2.115
Me
Me
N
N
O
OMe
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.
ppm
1.00
1.01
3.21
1.09
6.46


2.115
Me
Me
N
N
O
OMe
156.7
149.8
127.6
118.0
54.3
28.0
21.2
ppm
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

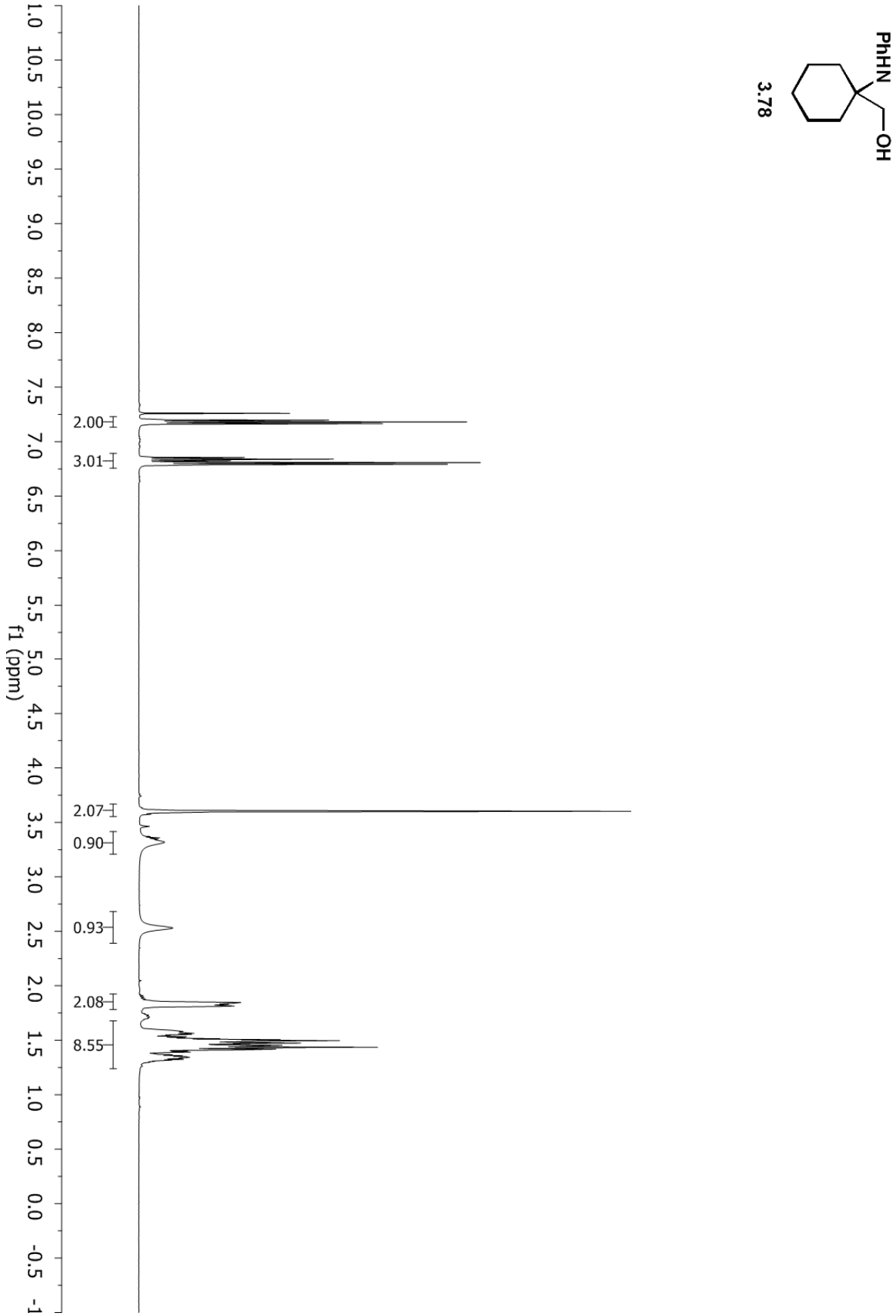

Br
O
N
Me
O
Me
2.162
2.03
2.01
2.04
2.95
3.00
ppm
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.

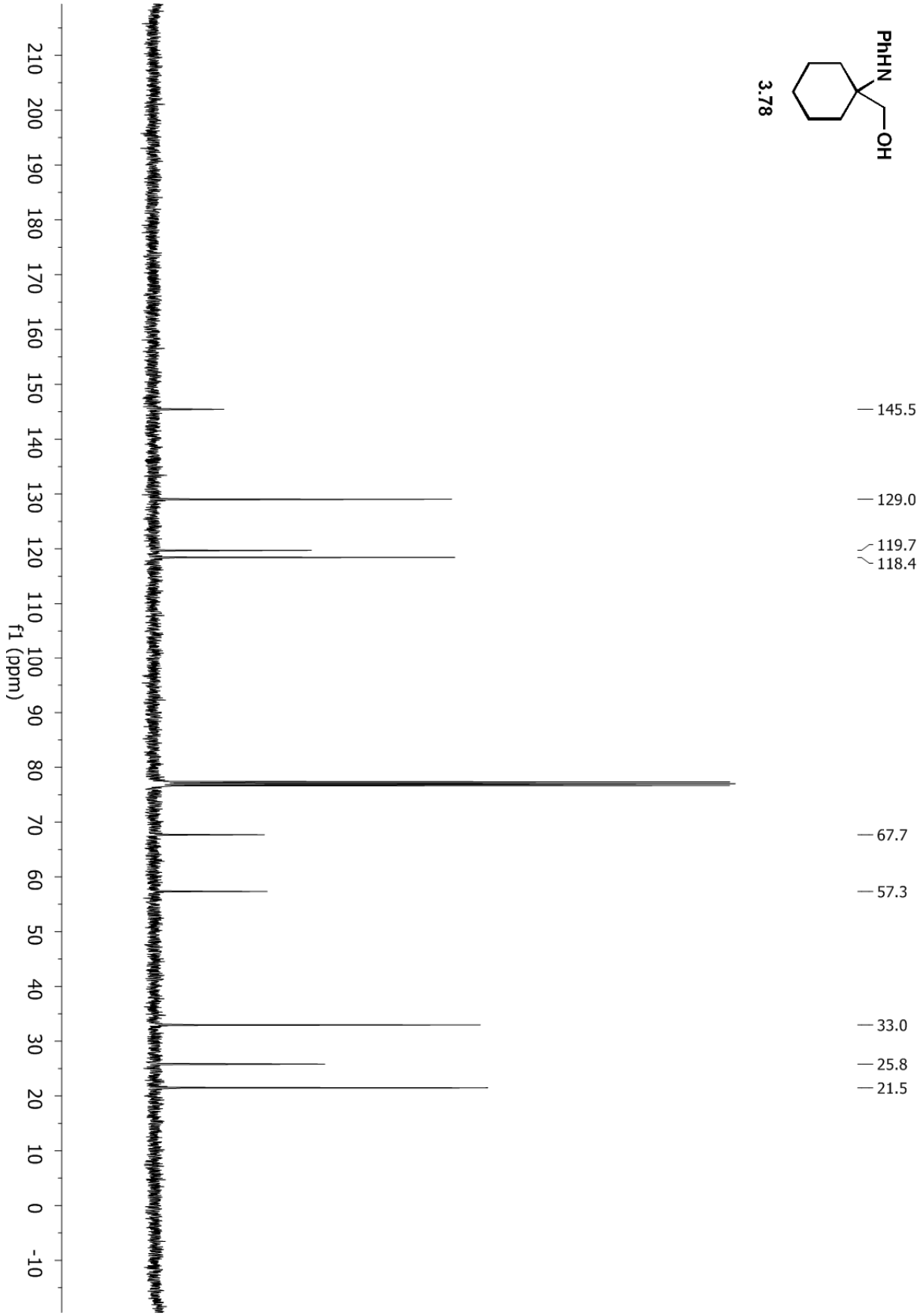

Br
O
N
Me
O
Me
2.162
171.8
133.9
131.6
131.1
120.8
61.4
38.7
32.3
ppm
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

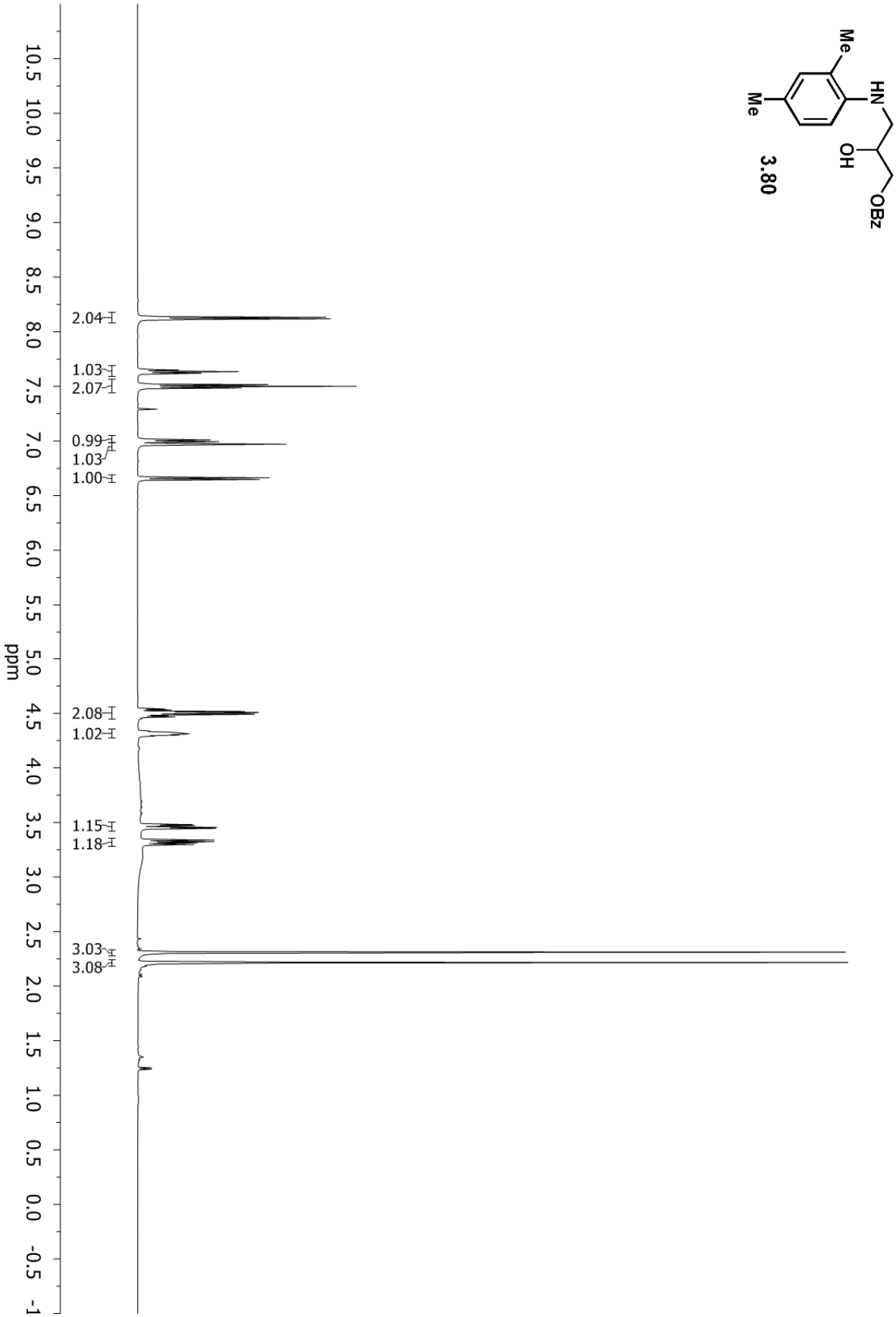

2.165
2.02
1.99
1.99
3.00
3.00
ppm

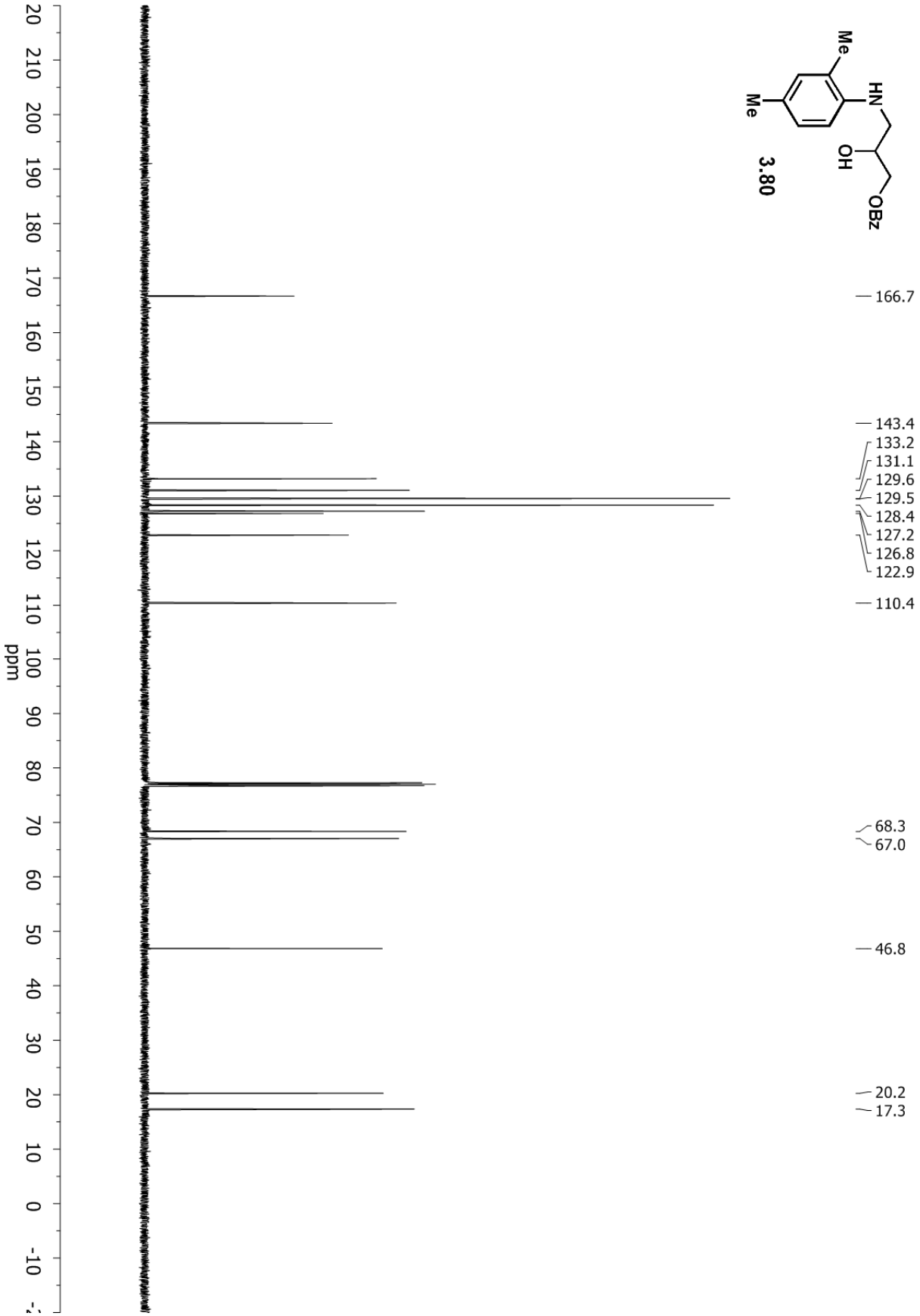

2.165
168.0
167.0
134.1
132.2
123.5
61.6
38.7
32.5
ppm
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

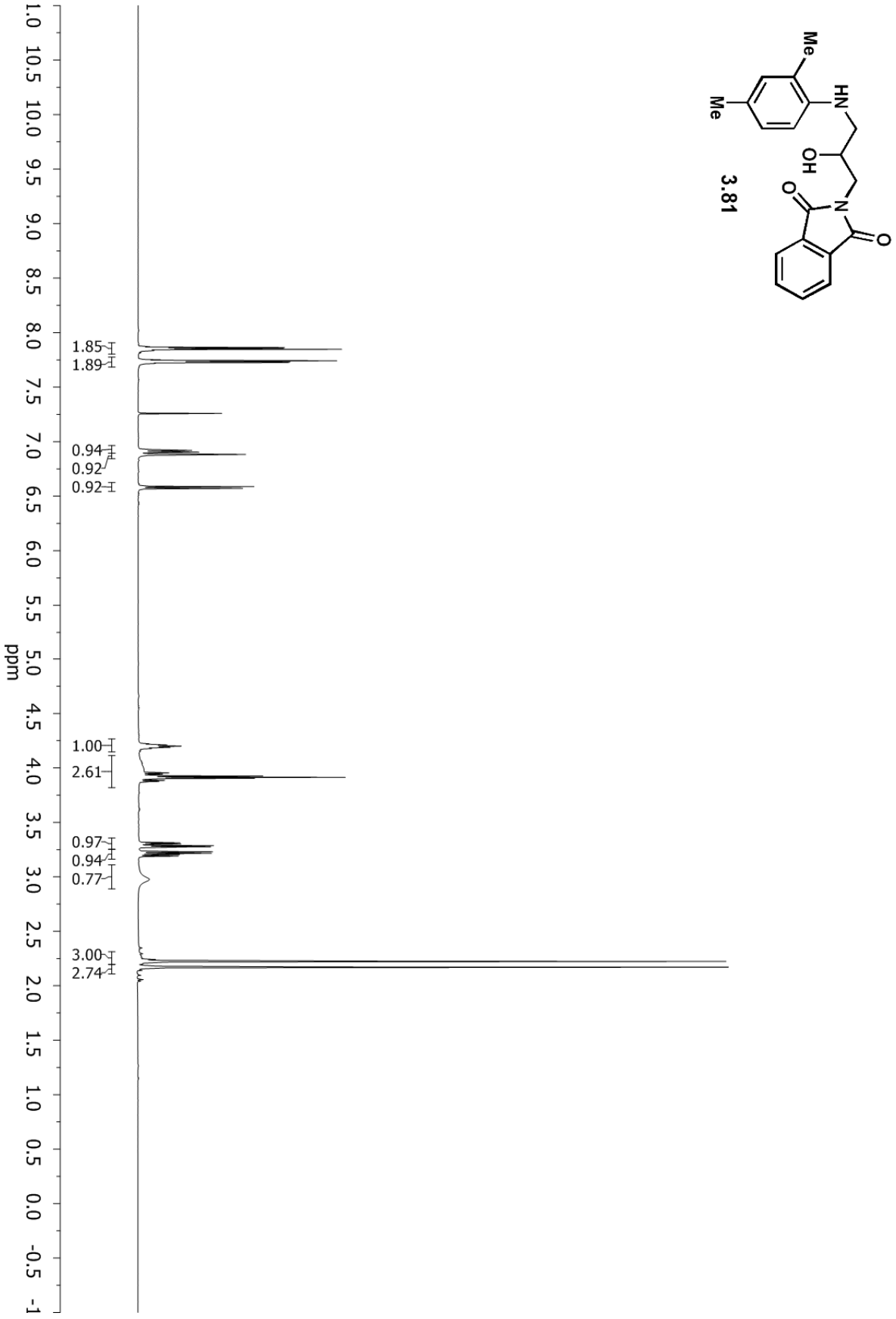
Appendix 2: Selected Spectra for Compounds Disclosed in Chapter 3

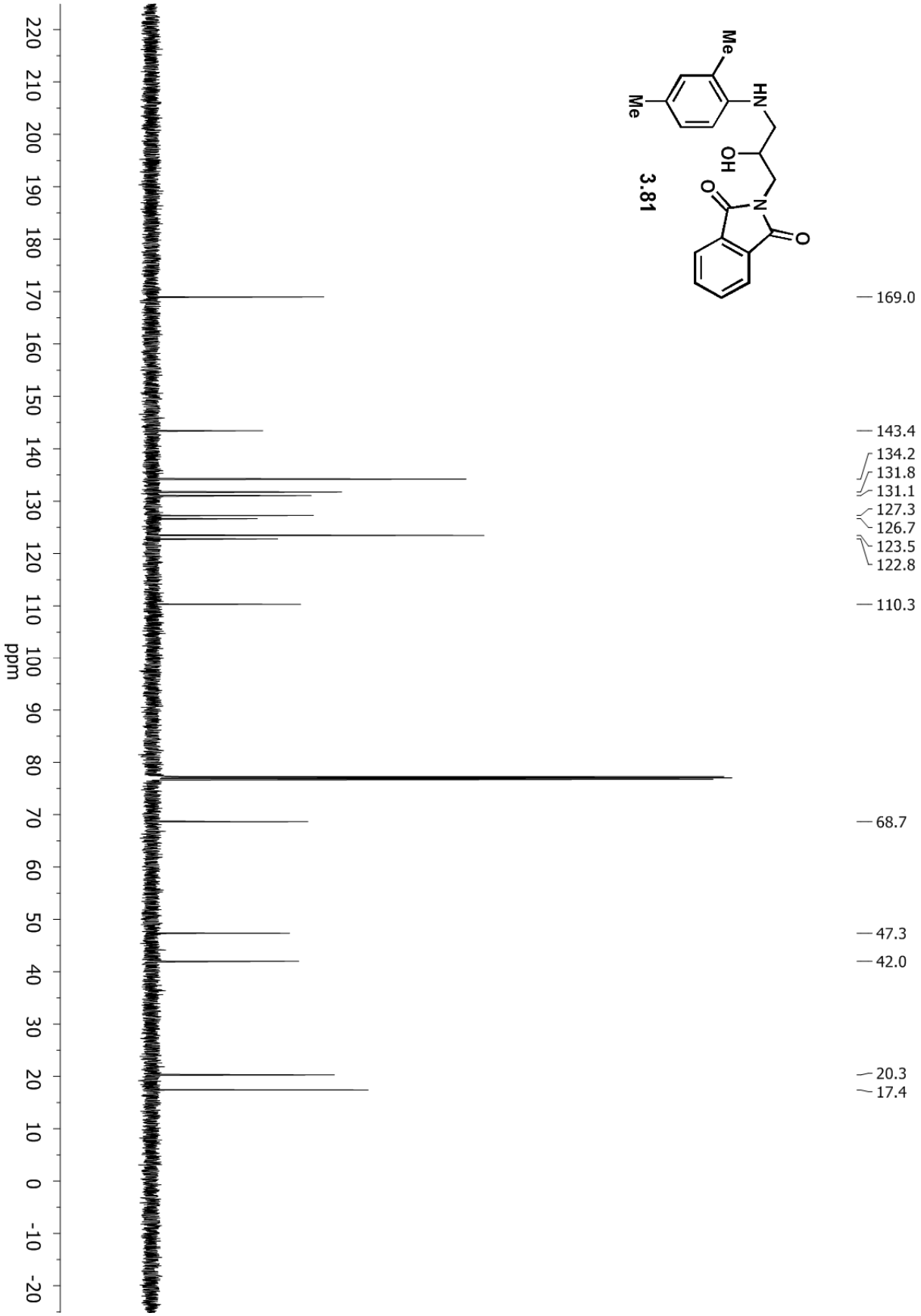

PhHN
OH
3.78
2.00
3.01
2.07
0.90
0.93
2.08
8.55
f1 (ppm)

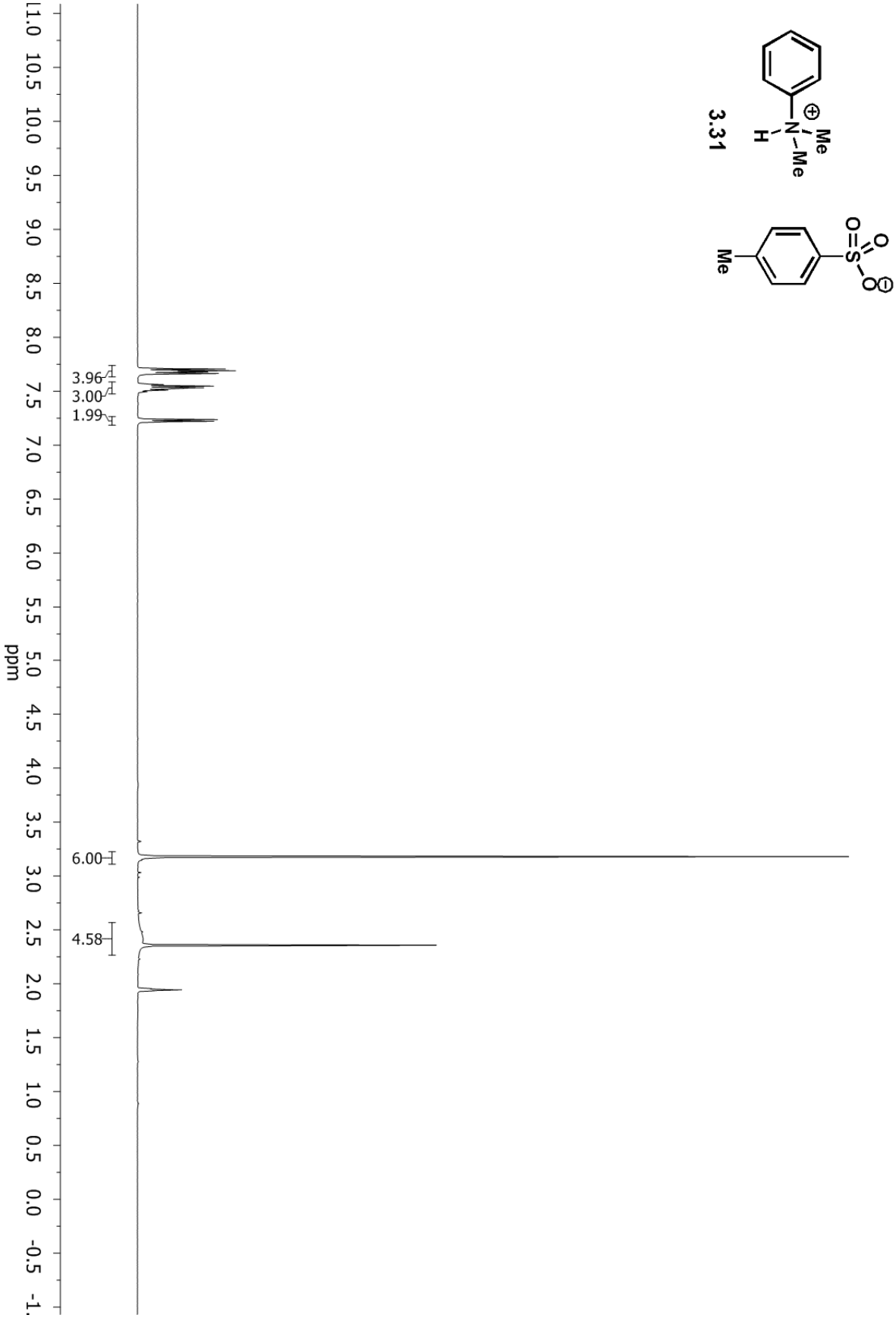

PhHN
OH
3.78
145.5
129.0
119.7
118.4
67.7
57.3
33.0
25.8
21.5
f1 (ppm)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

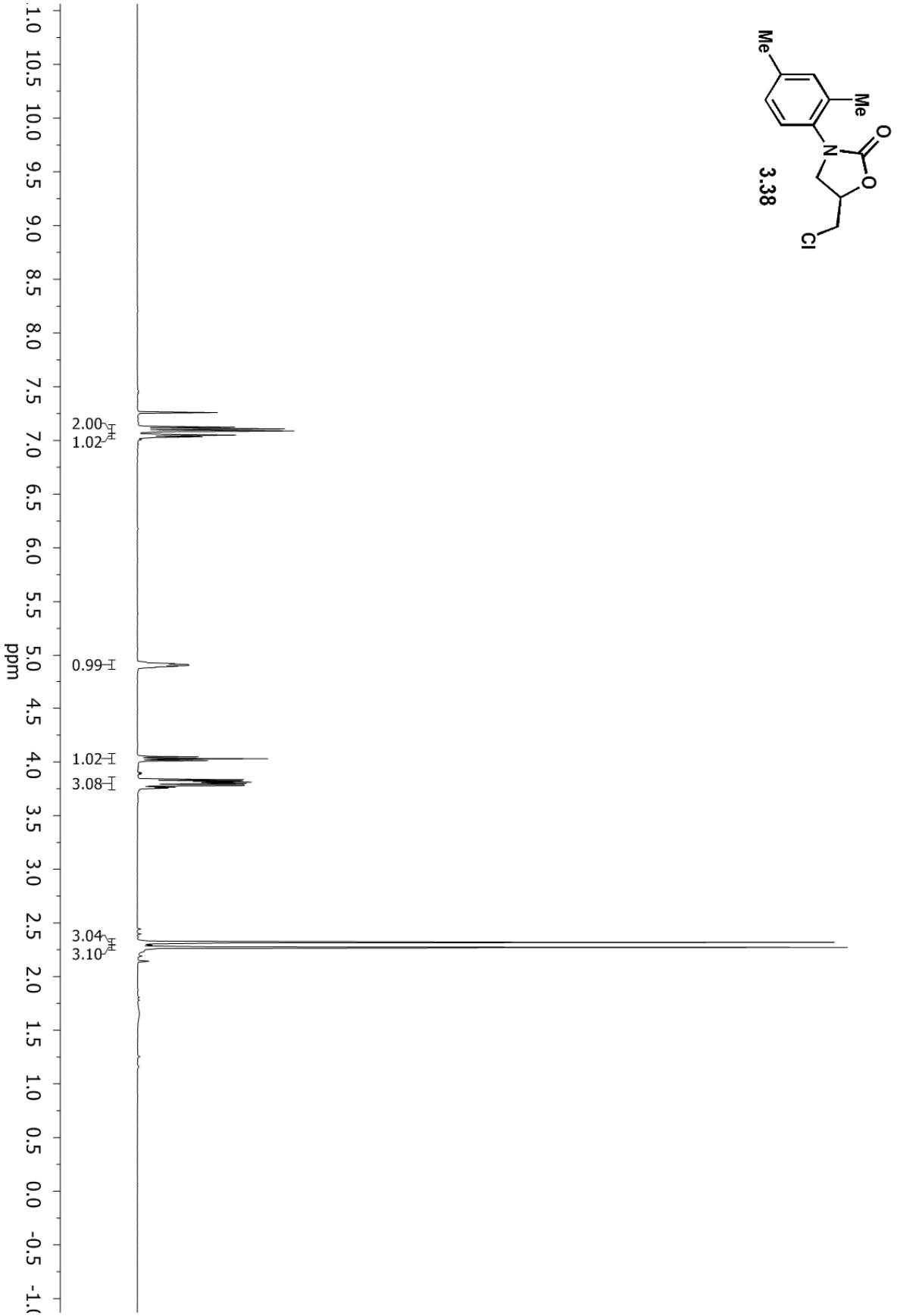

Me
HN
Me
OH
OBz
3.80
2.04
1.03
2.07
0.99
1.03
1.00
2.08
1.02
1.15
1.18
3.03
3.08
ppm

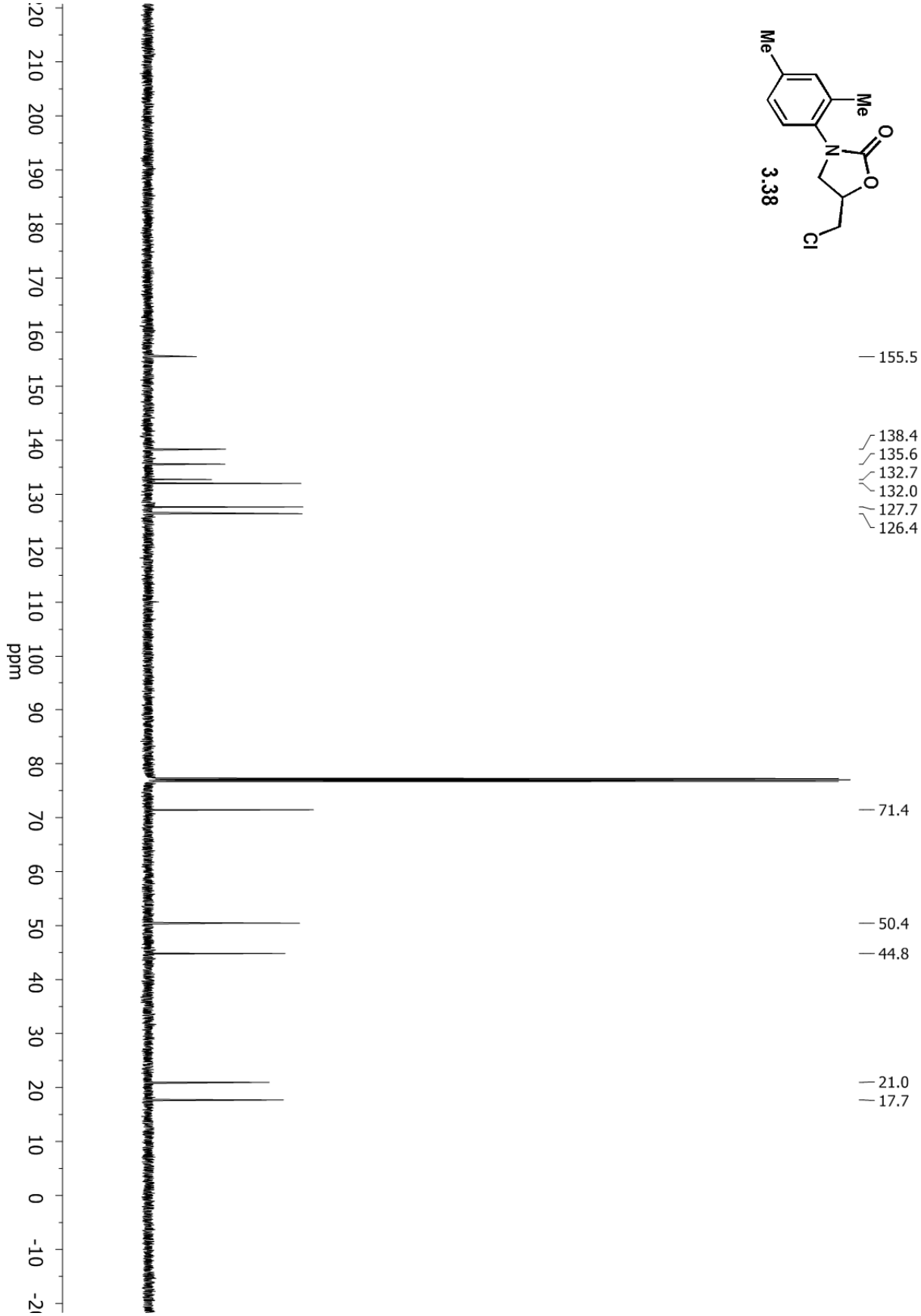

Me
HN
Me
OH
OBz
3.80
166.7
143.4
133.2
131.1
129.6
129.5
128.4
127.2
126.8
122.9
110.4
68.3
67.0
46.8
20.2
17.3
ppm

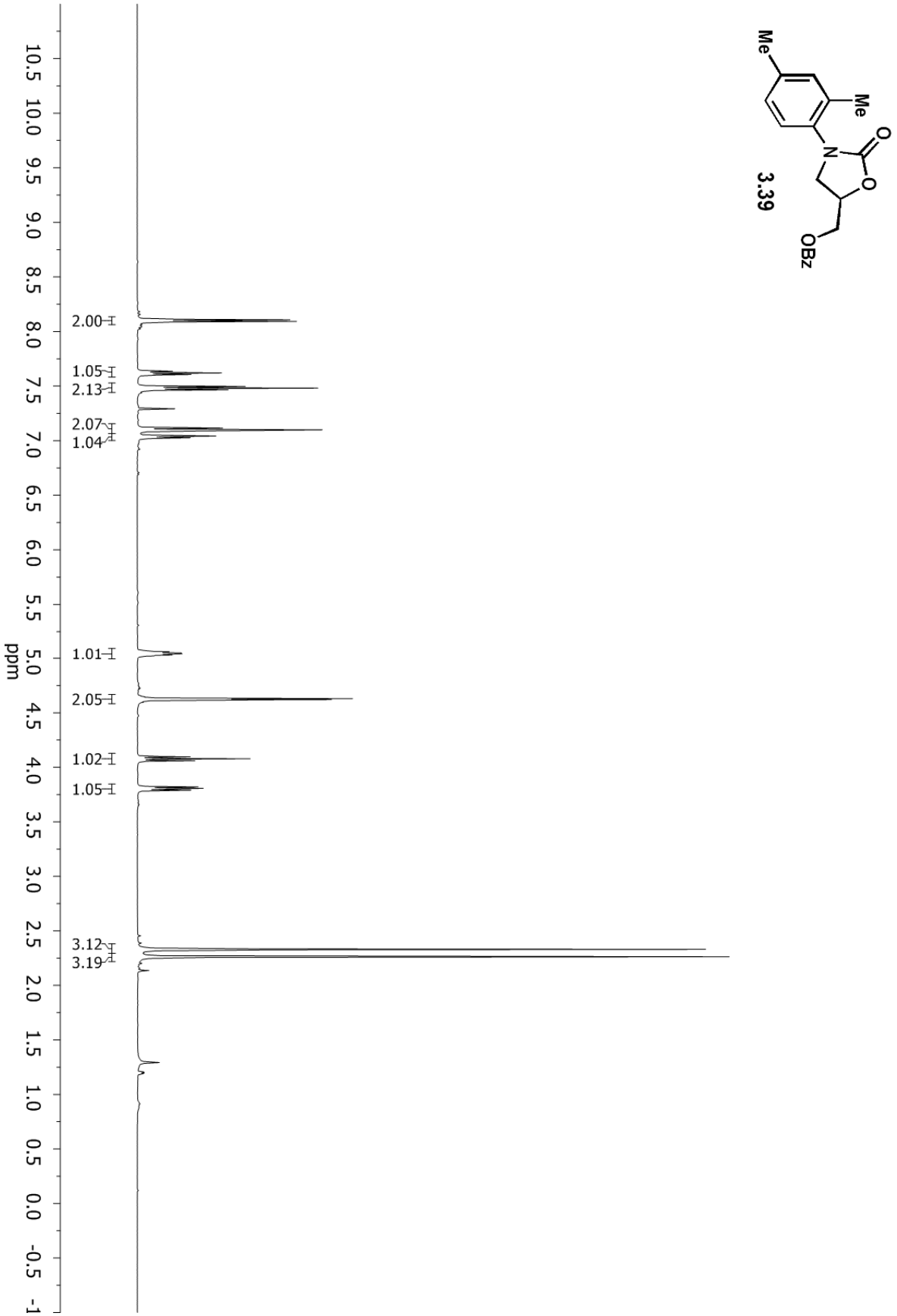

Me
Me
HN
OH
O
N
O
3.81
1.85
1.89
0.94
0.92
0.92
1.00
2.61
0.97
0.94
0.77
3.00
2.74
ppm
1.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1

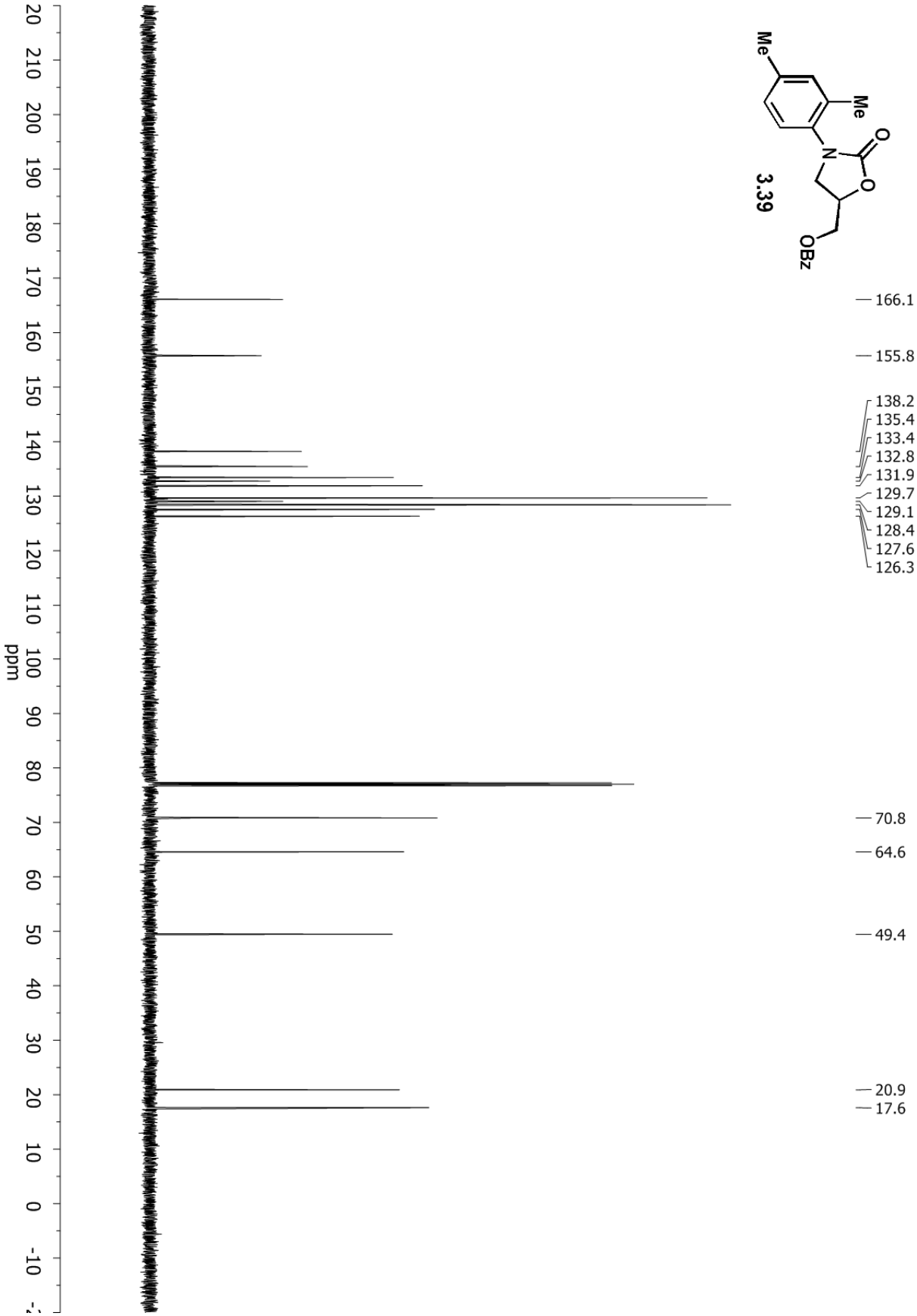

Me
Me
HN
OH
O
N
O
3.81
169.0
143.4
134.2
131.8
131.1
127.3
126.7
123.5
122.8
110.3
68.7
47.3
42.0
20.3
17.4
ppm
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20

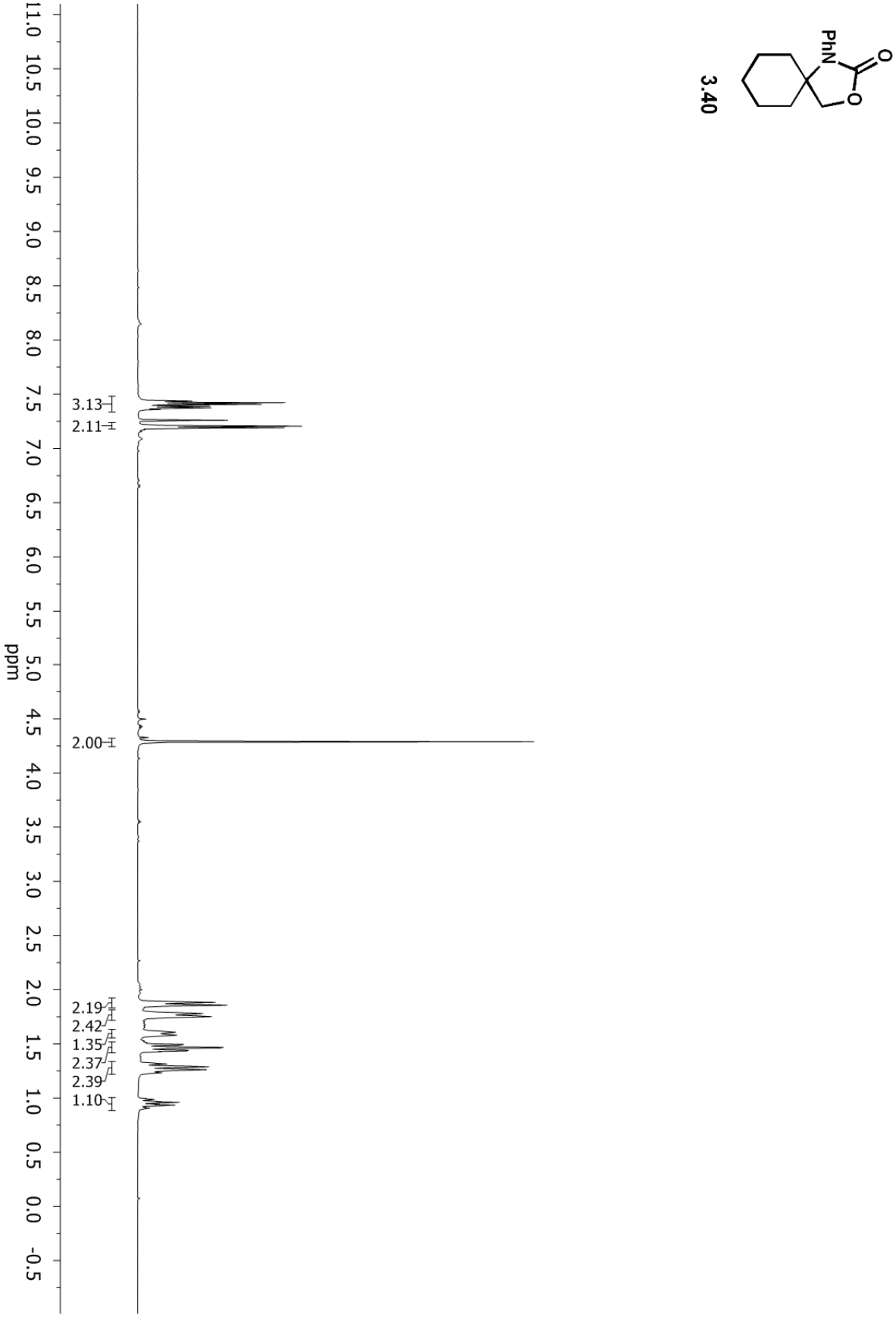

3.31
Me
N
H
Me
Me
O
S
O
O
Me
3.96
3.00
1.99
6.00
4.58
ppm
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.

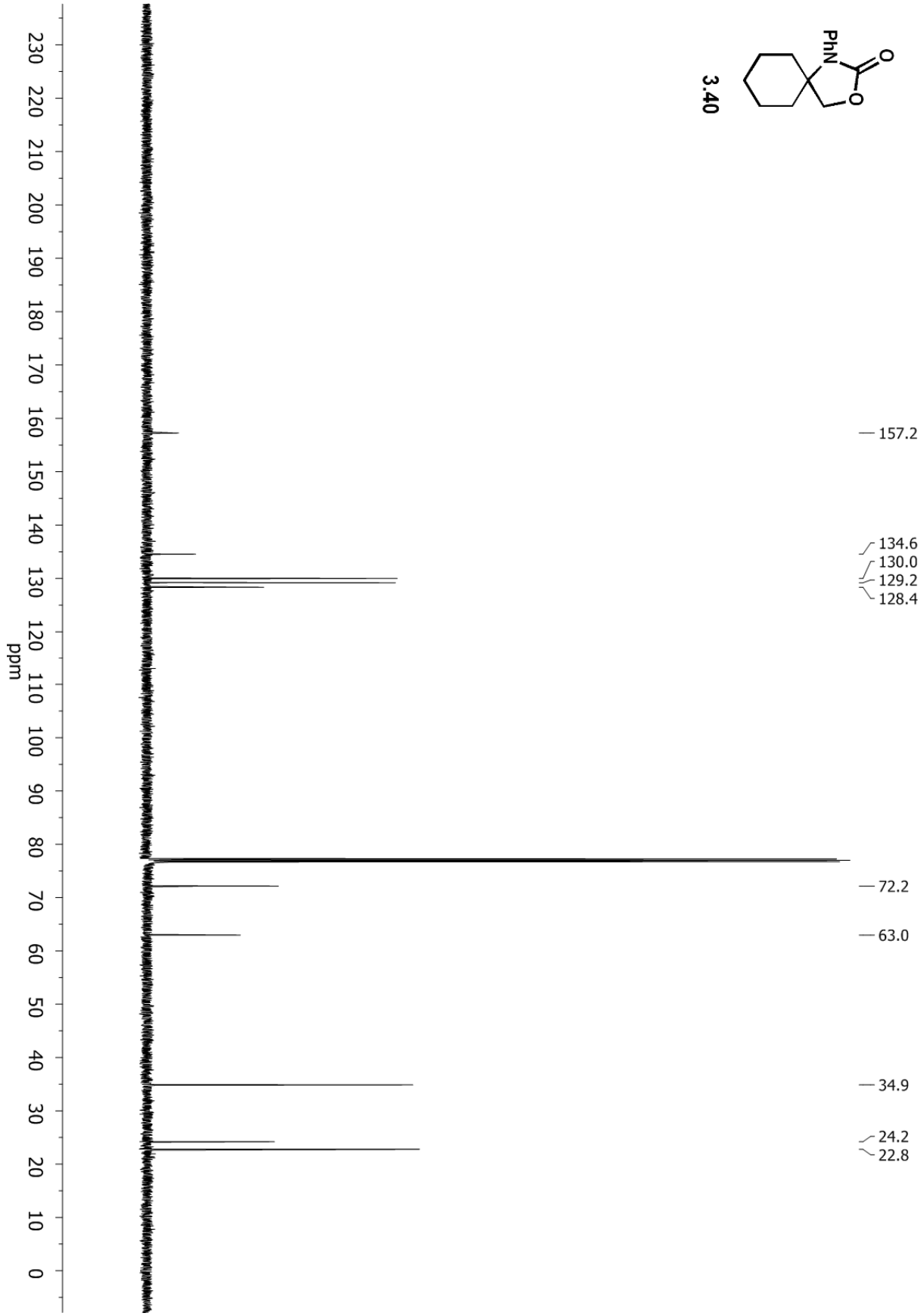

Me
Me
O
N
O
Cl
3.38
2.00
1.02
0.99
1.02
3.08
3.04
3.10
ppm

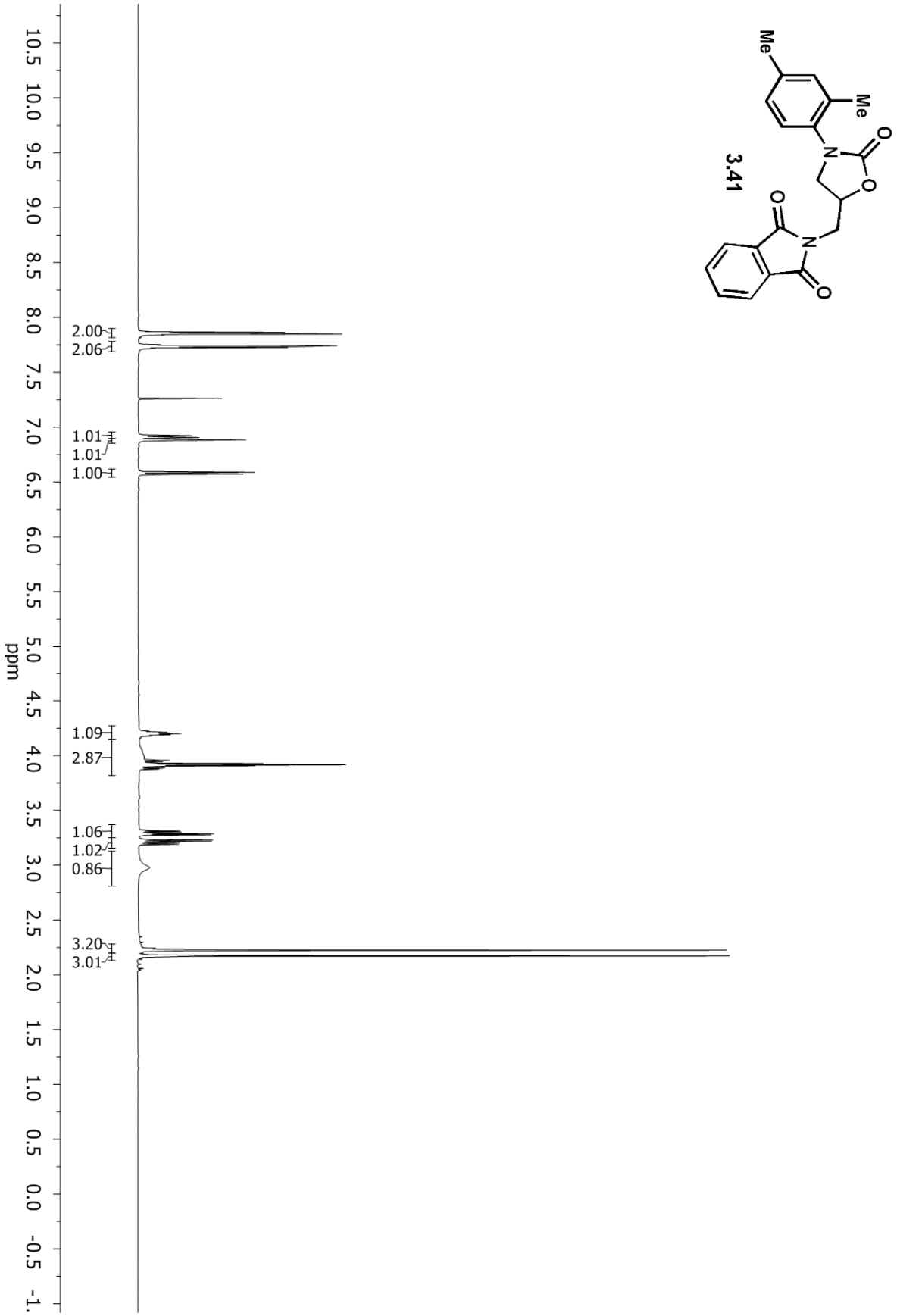

Me
Me
O
N
O
Cl
3.38
155.5
138.4
135.6
132.7
132.0
127.7
126.4
71.4
50.4
44.8
21.0
17.7
ppm

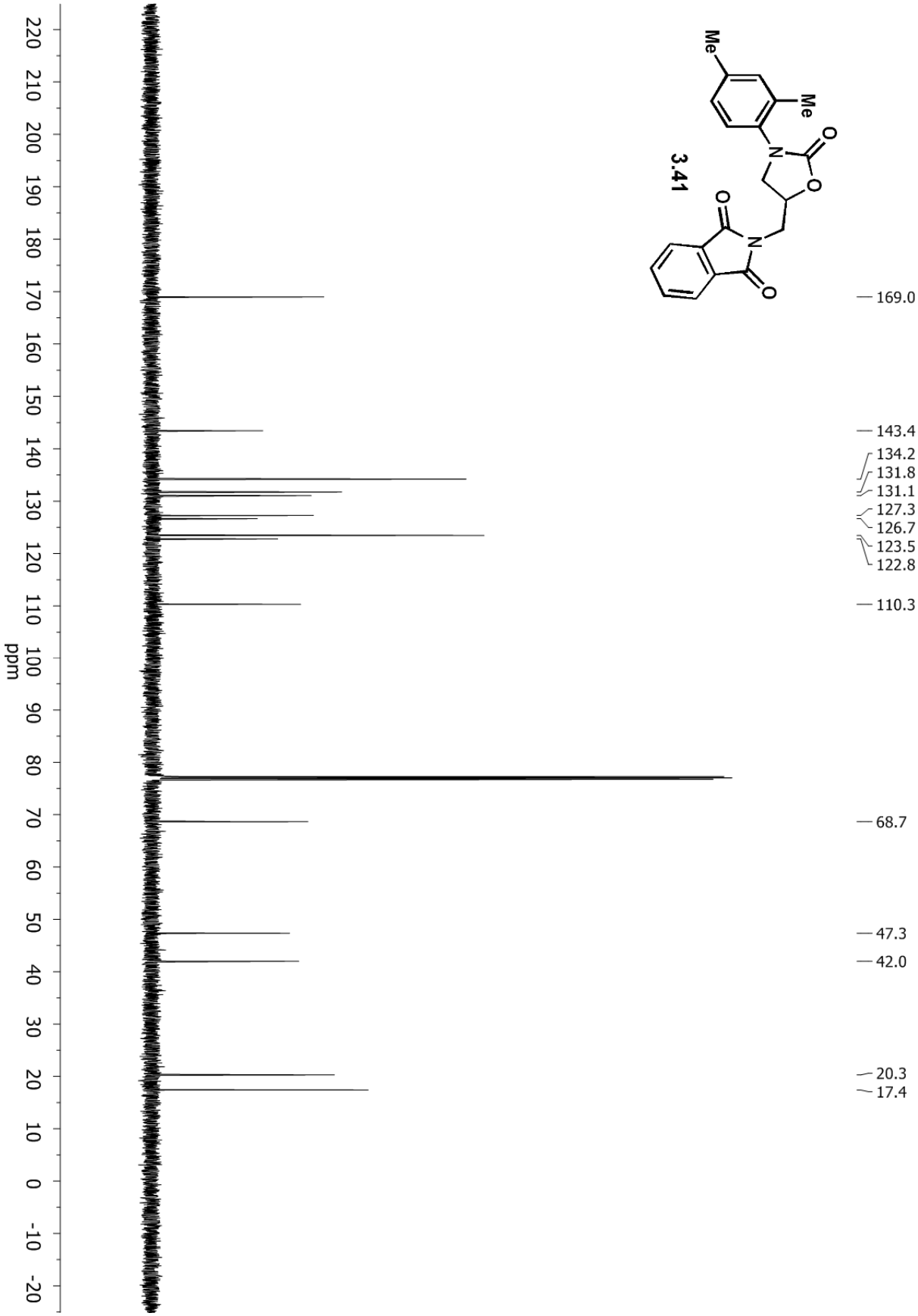

Me
Me
O
N
O
O
OBz
3.39
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
ppm
2.00
1.05
2.13
2.07
1.04
1.01
2.05
1.02
1.05
3.12
3.19

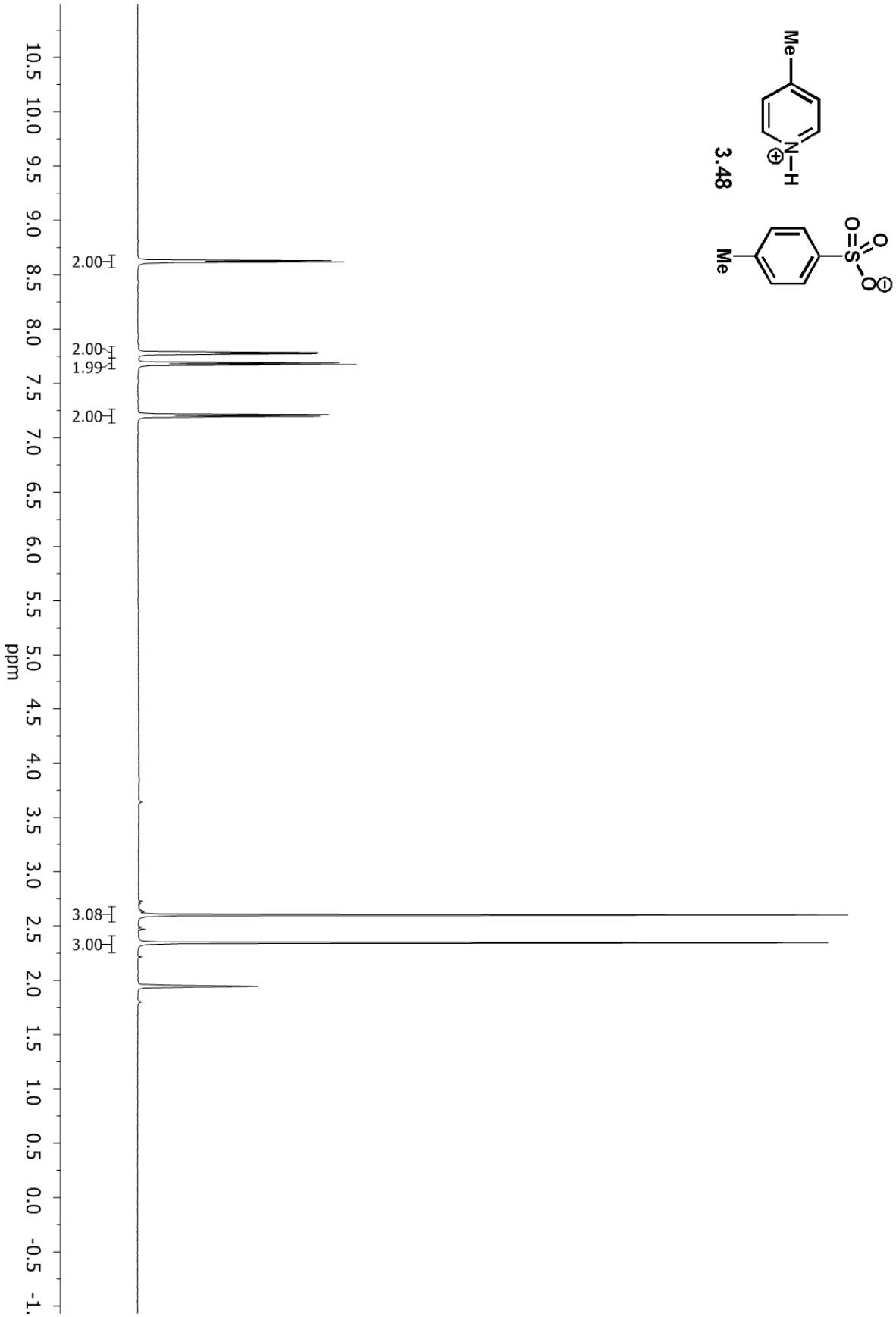

Me
Me
O
N
O
OBz
3.39
166.1
155.8
138.2
135.4
133.4
132.8
131.9
129.7
129.1
128.4
127.6
126.3
70.8
64.6
49.4
20.9
17.6
ppm

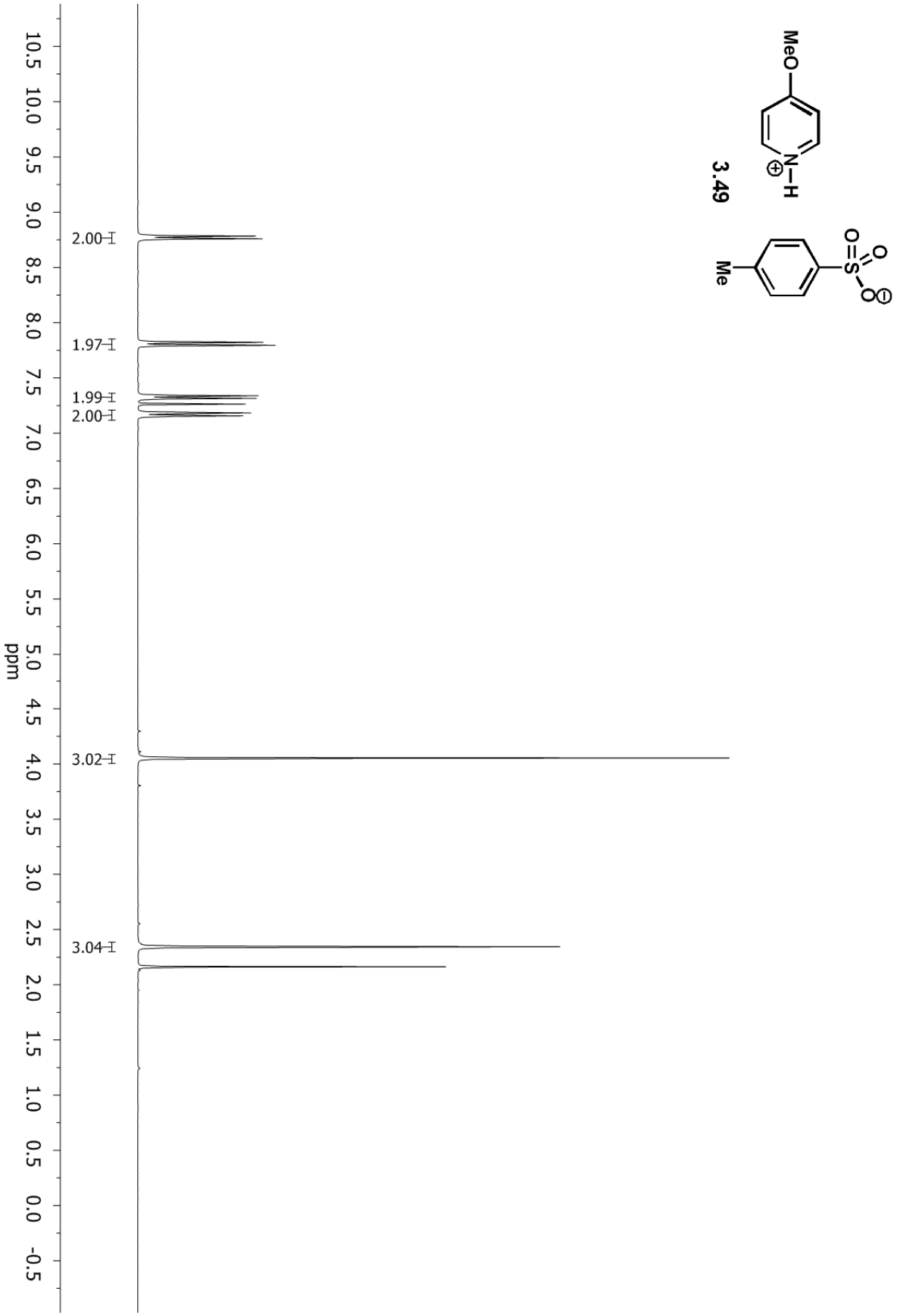

3.40
PhN
O
O
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
ppm
3.13
2.11
2.00
2.19
2.42
1.35
2.37
2.39
1.10

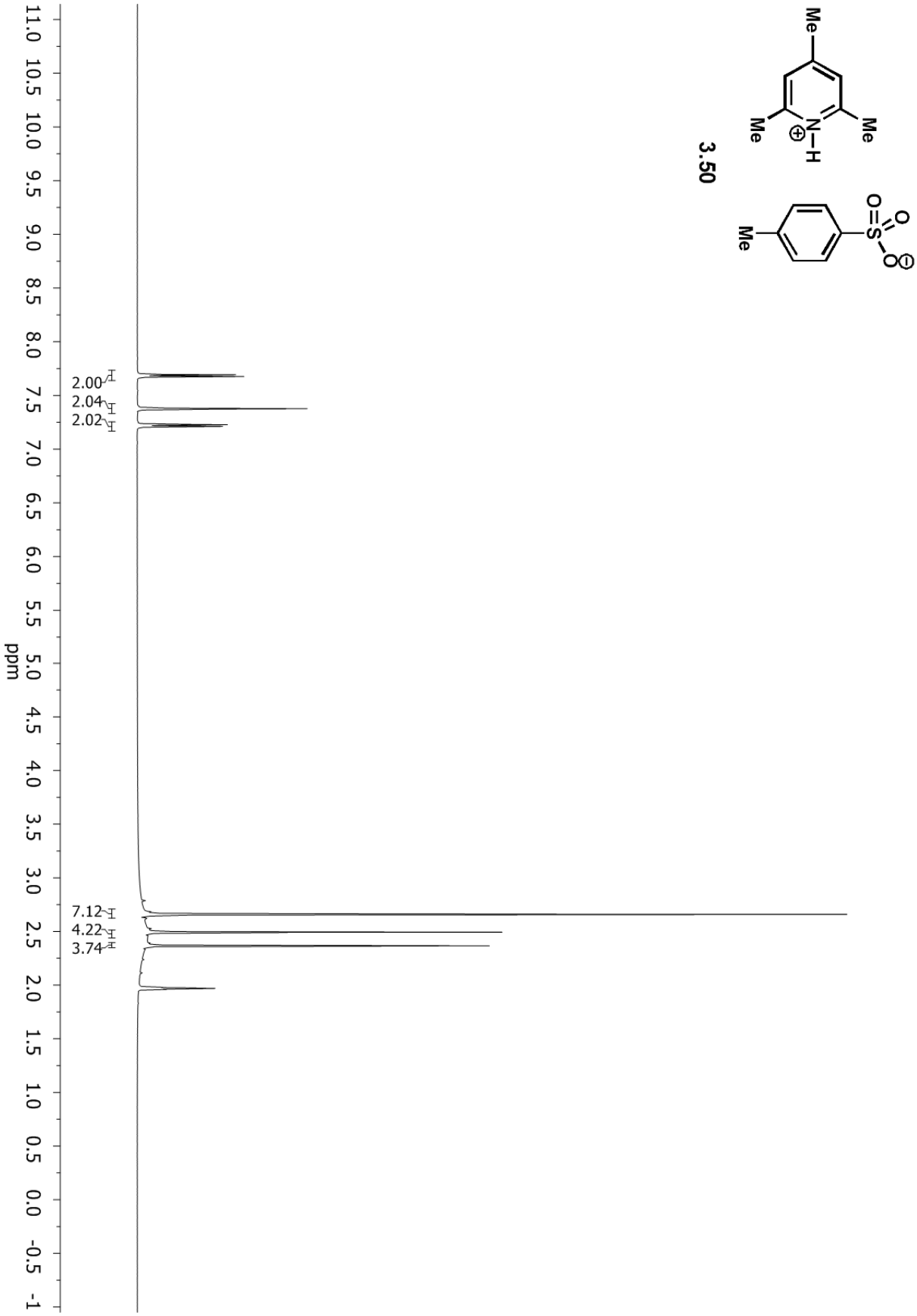

3.40
PhN
O
O
O
157.2
134.6
130.0
129.2
128.4
72.2
63.0
34.9
24.2
22.8
ppm
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

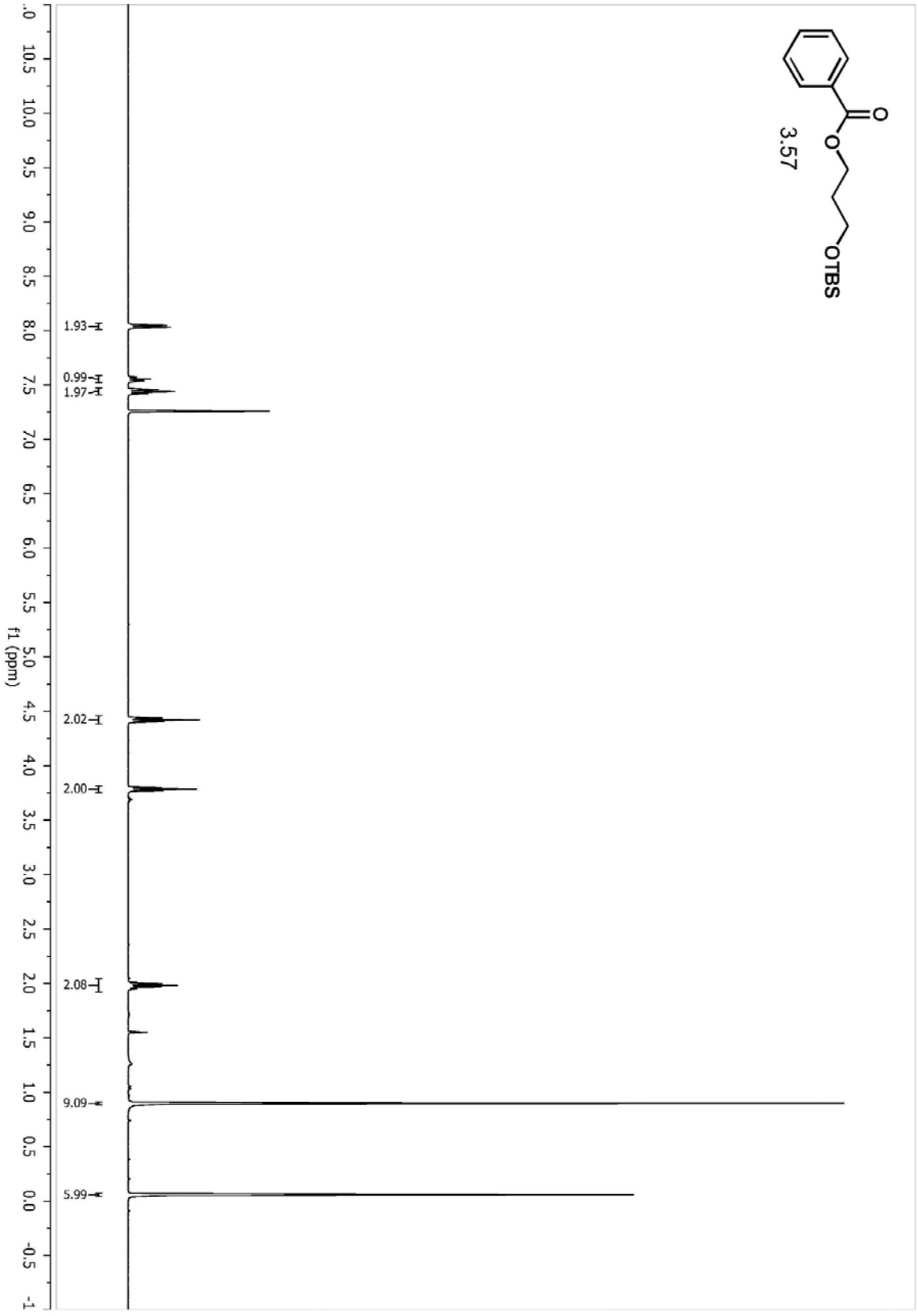

Me
Me
O
O
N
O
O
N
O
3.41
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.
ppm
2.00
2.06
1.01
1.01
1.00
1.09
2.87
1.06
1.02
0.86
3.20
3.01

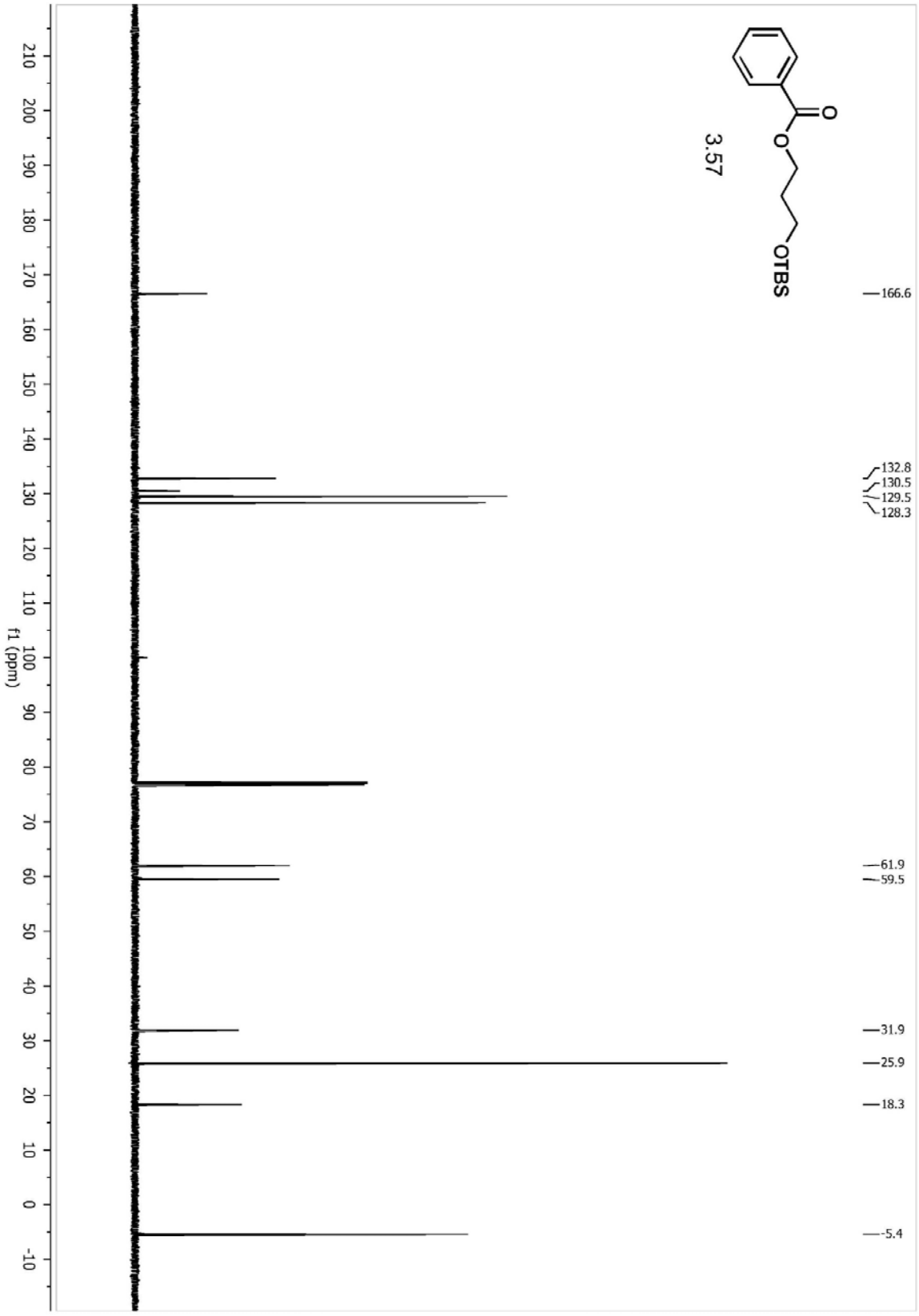

Me
Me
3.41
O
O
N
O
O
N
O
169.0
143.4
134.2
131.8
131.1
127.3
126.7
123.5
122.8
110.3
68.7
47.3
42.0
20.3
17.4
ppm
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20

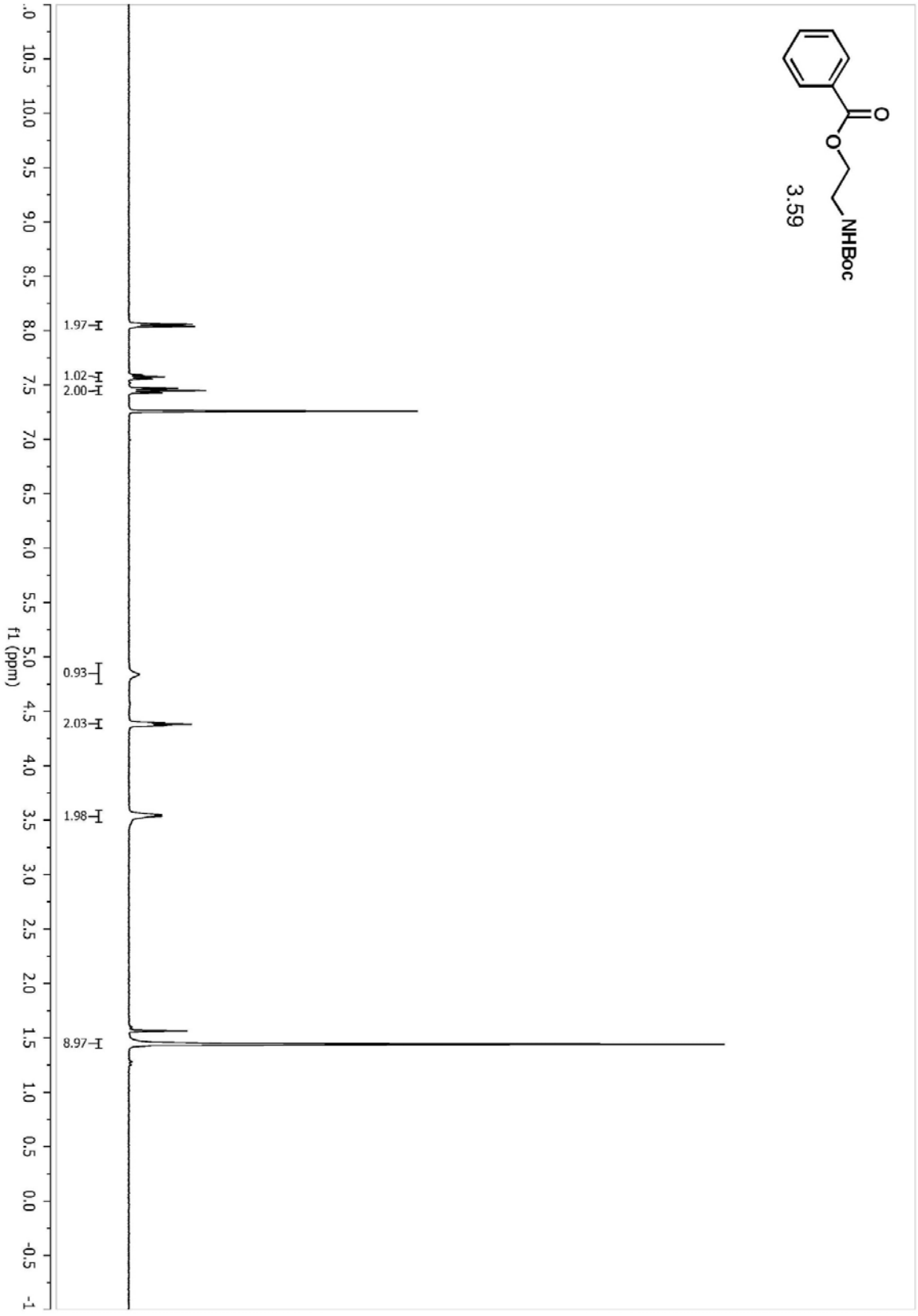

3.48
Me
N–H
Me
O=S
O
O
2.00
2.00
1.99
2.00
3.08
3.00
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.
ppm

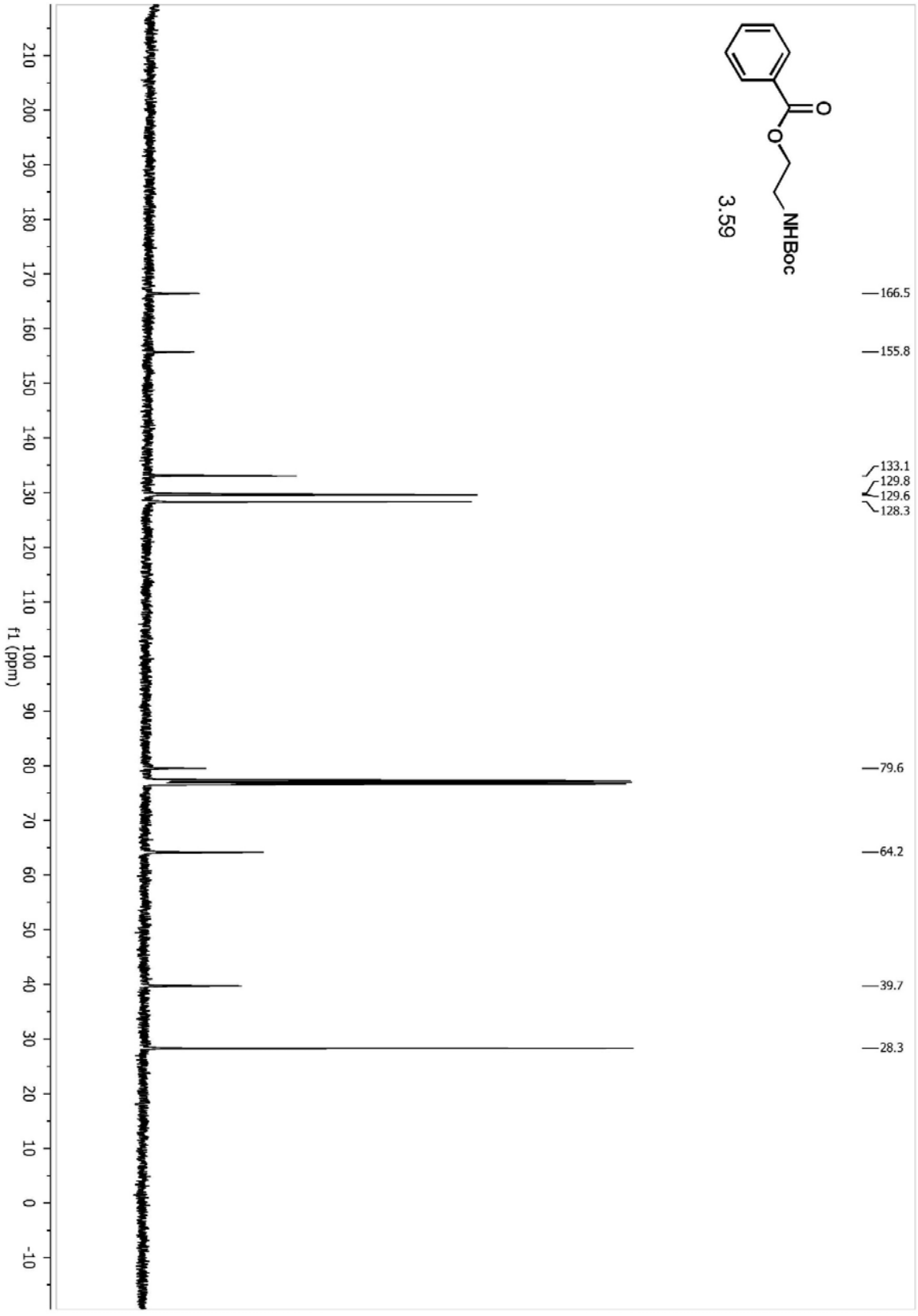

MeO
N–H
3.49
Me
O=S
O
O
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
ppm
2.00
1.97
1.99
2.00
3.02
3.04

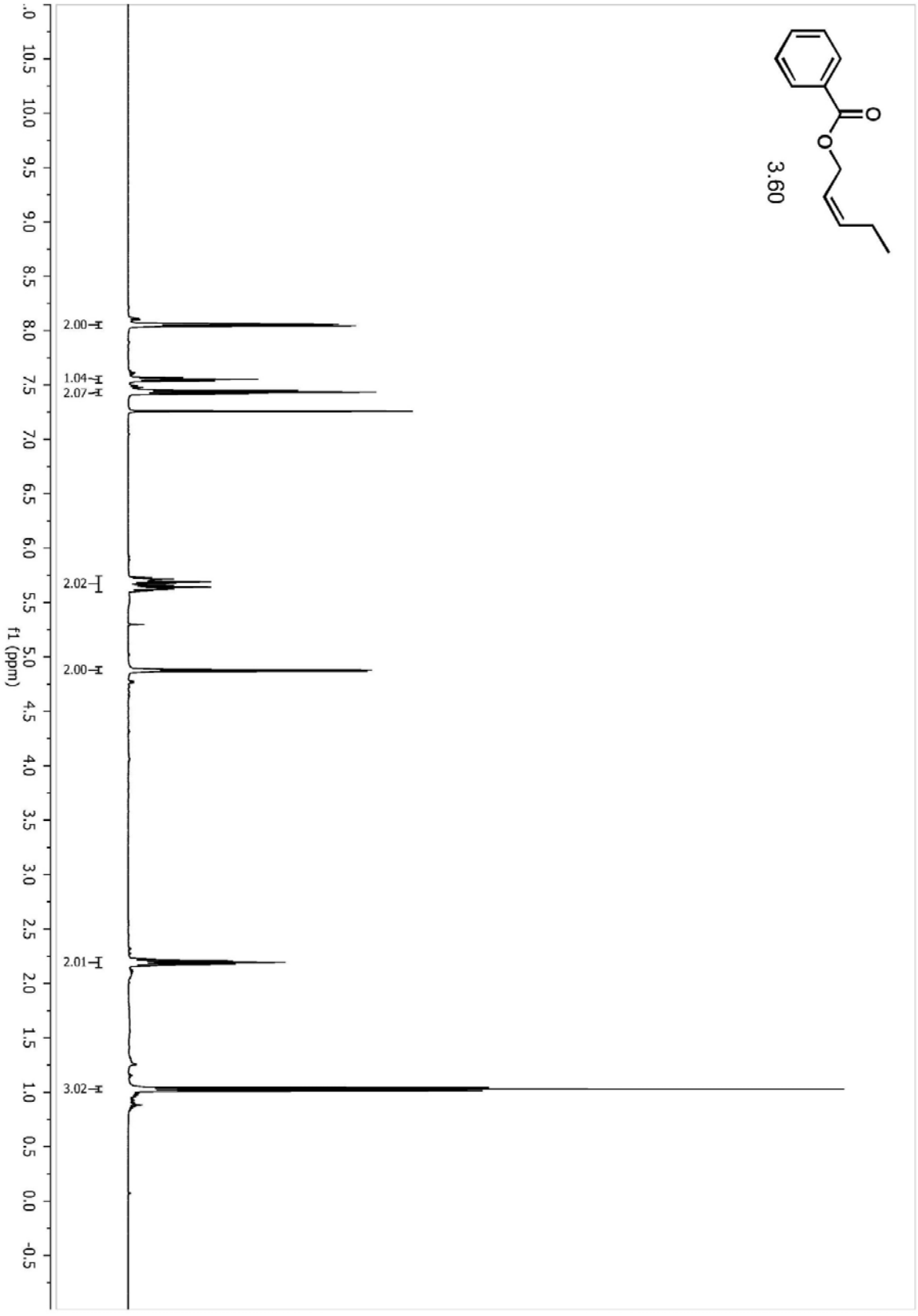

3.50
Me
Me
Me
N
H
Me
O
S
O
O
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
ppm
2.00
2.04
2.02
7.12
4.22
3.74

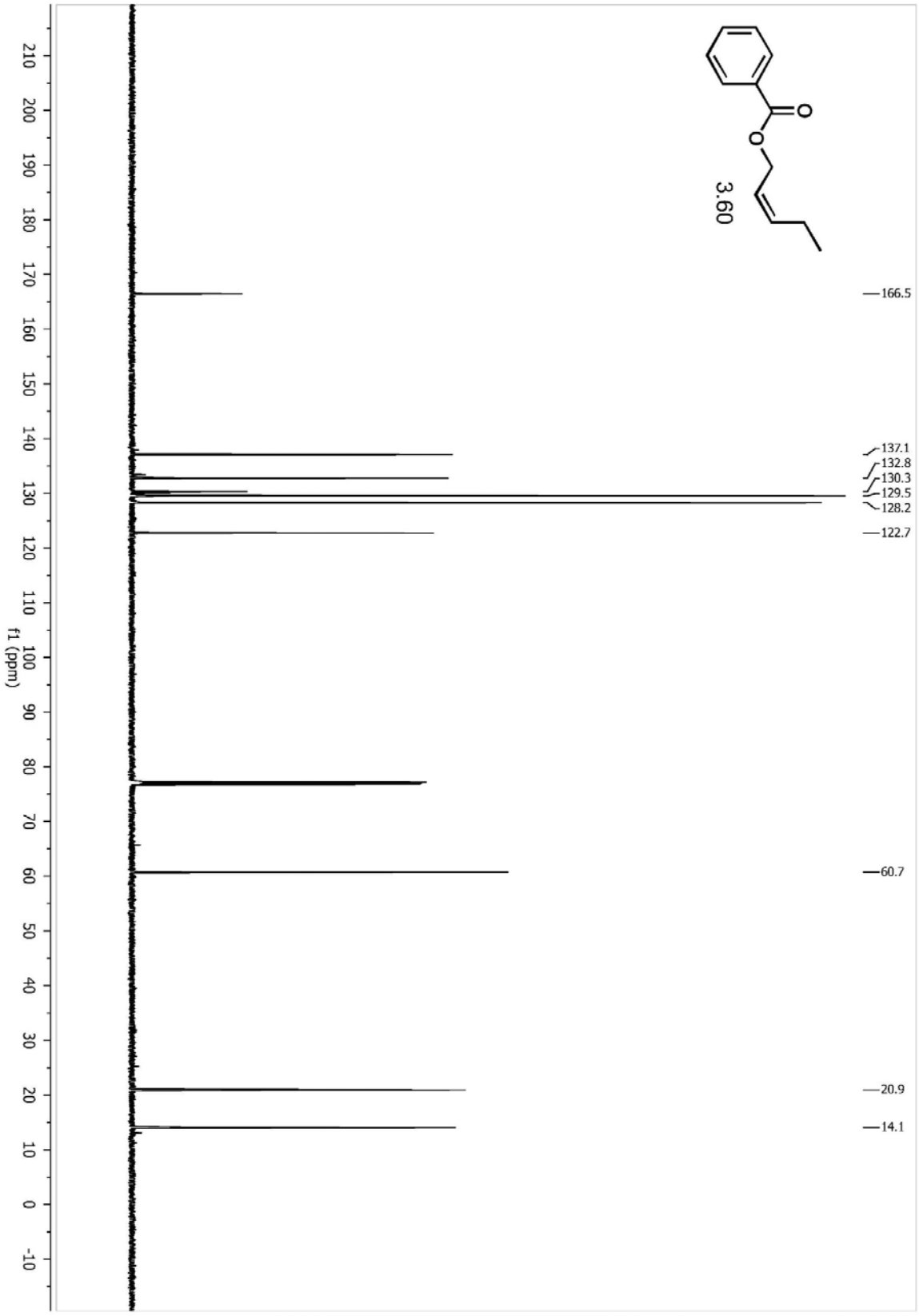

OTBS
3.57
1.93
0.99
1.97
2.02
2.00
2.08
9.09
5.99
f1 (ppm)


3.57
OTBS
166.6
132.8
130.5
129.5
128.3
61.9
59.5
31.9
25.9
18.3
-5.4
f1 (ppm)

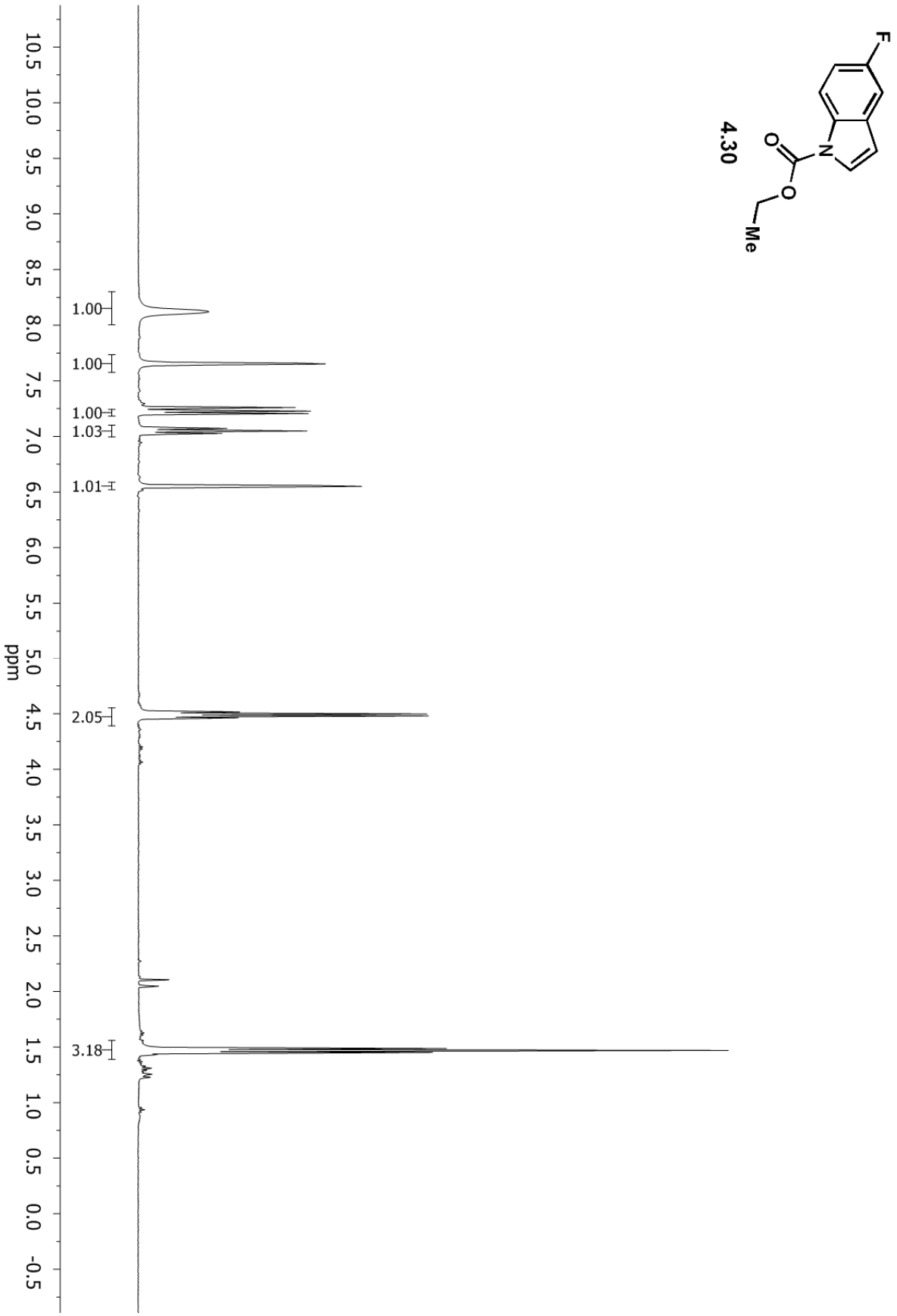

O
O
NHBoc
3.59
1.97
1.02
2.00
0.93
2.03
1.98
8.97
f1 (ppm)

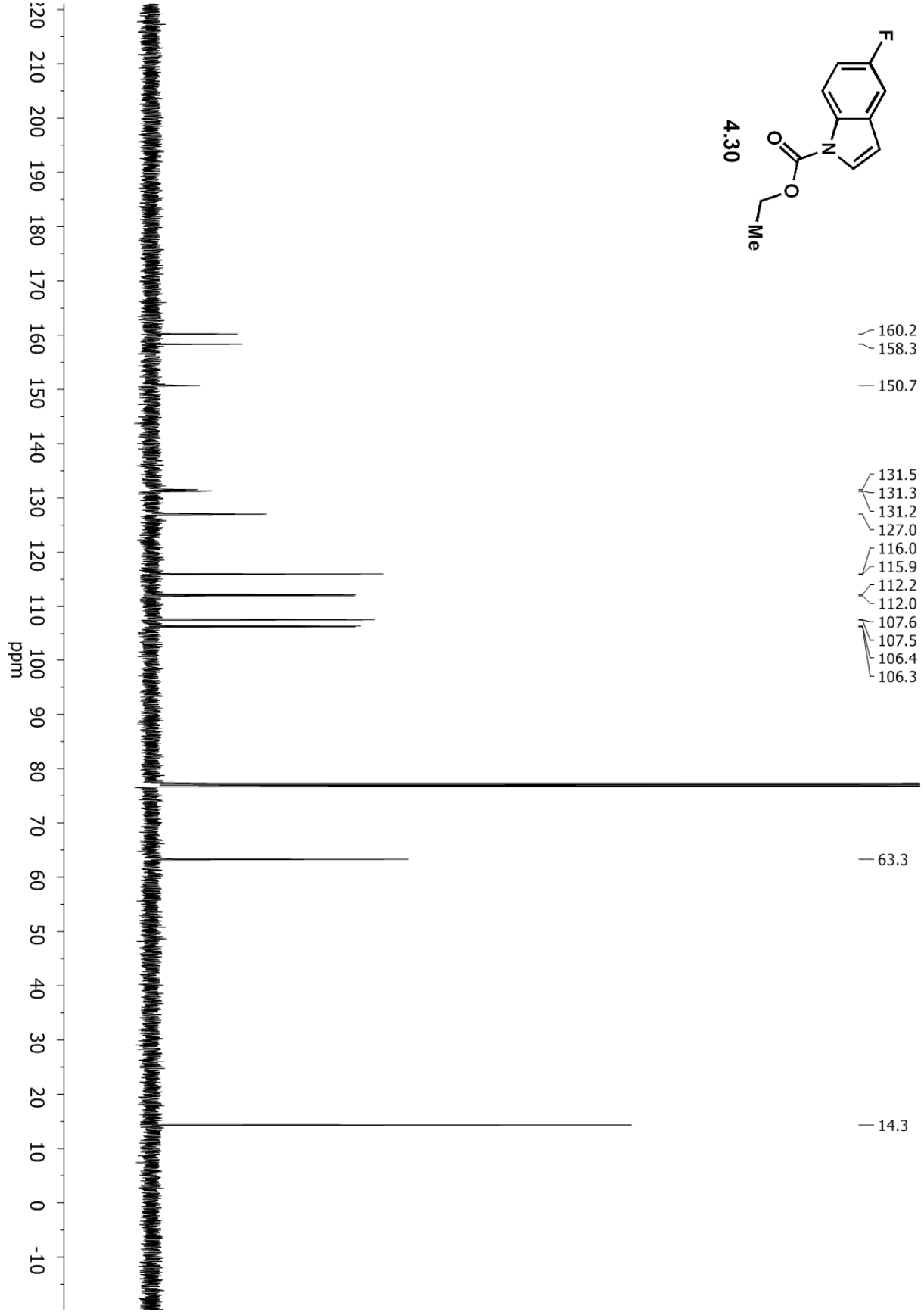

O
O
NHBoc
3.59
166.5
155.8
133.1
129.8
129.6
128.3
79.6
64.2
39.7
28.3
f1 (ppm)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10


3.60
2.00
1.04
2.07
2.02
2.00
2.01
3.02
f1 (ppm)


3.60
166.5
137.1
132.8
130.3
129.5
128.2
122.7
60.7
20.9
14.1
f1 (ppm)

Appendix 3: Selected Spectra for Compounds Disclosed in Chapter 4

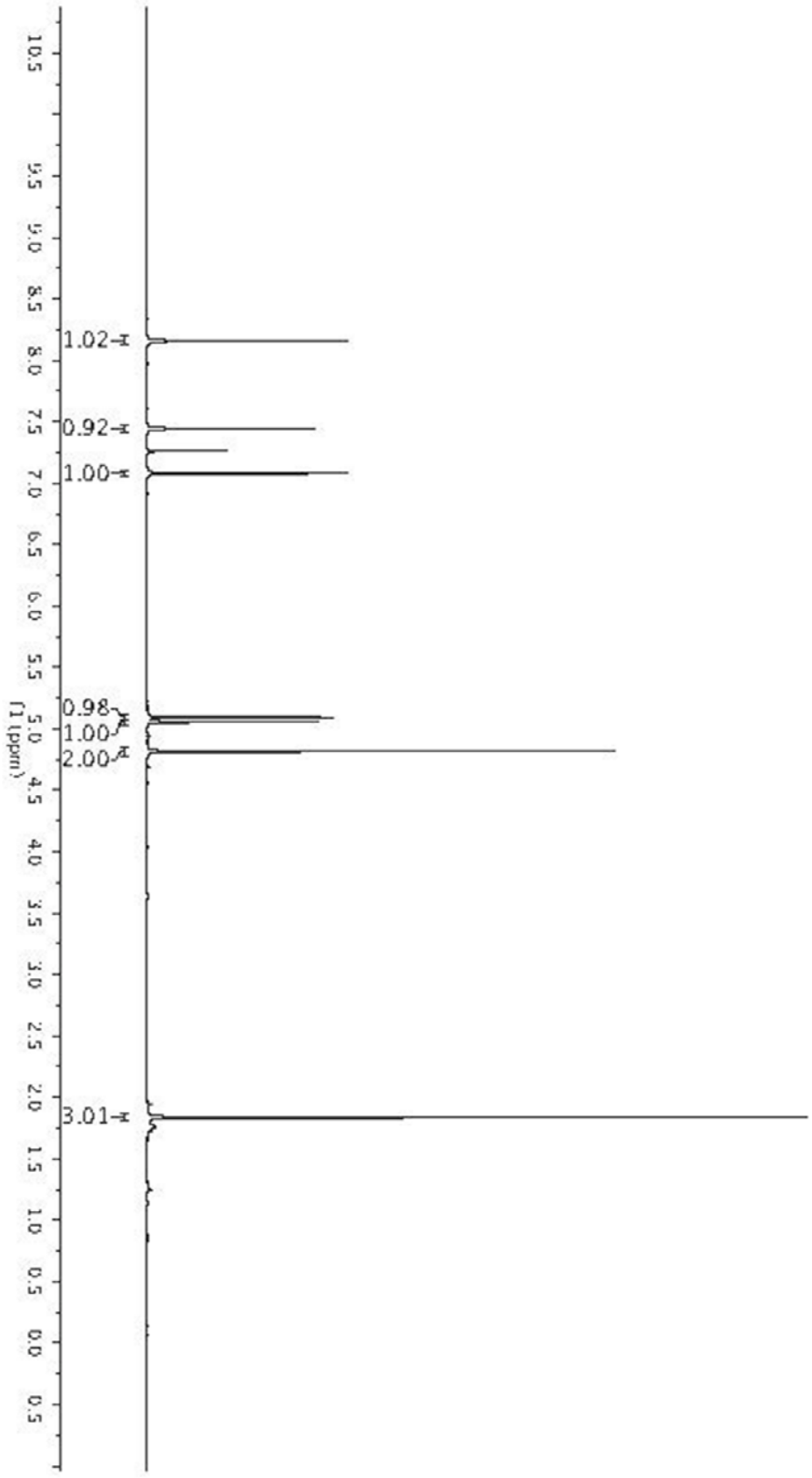

4.30
F
O
N
O
Me
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
ppm
1.00
1.00
1.00
1.03
1.01
2.05
3.18

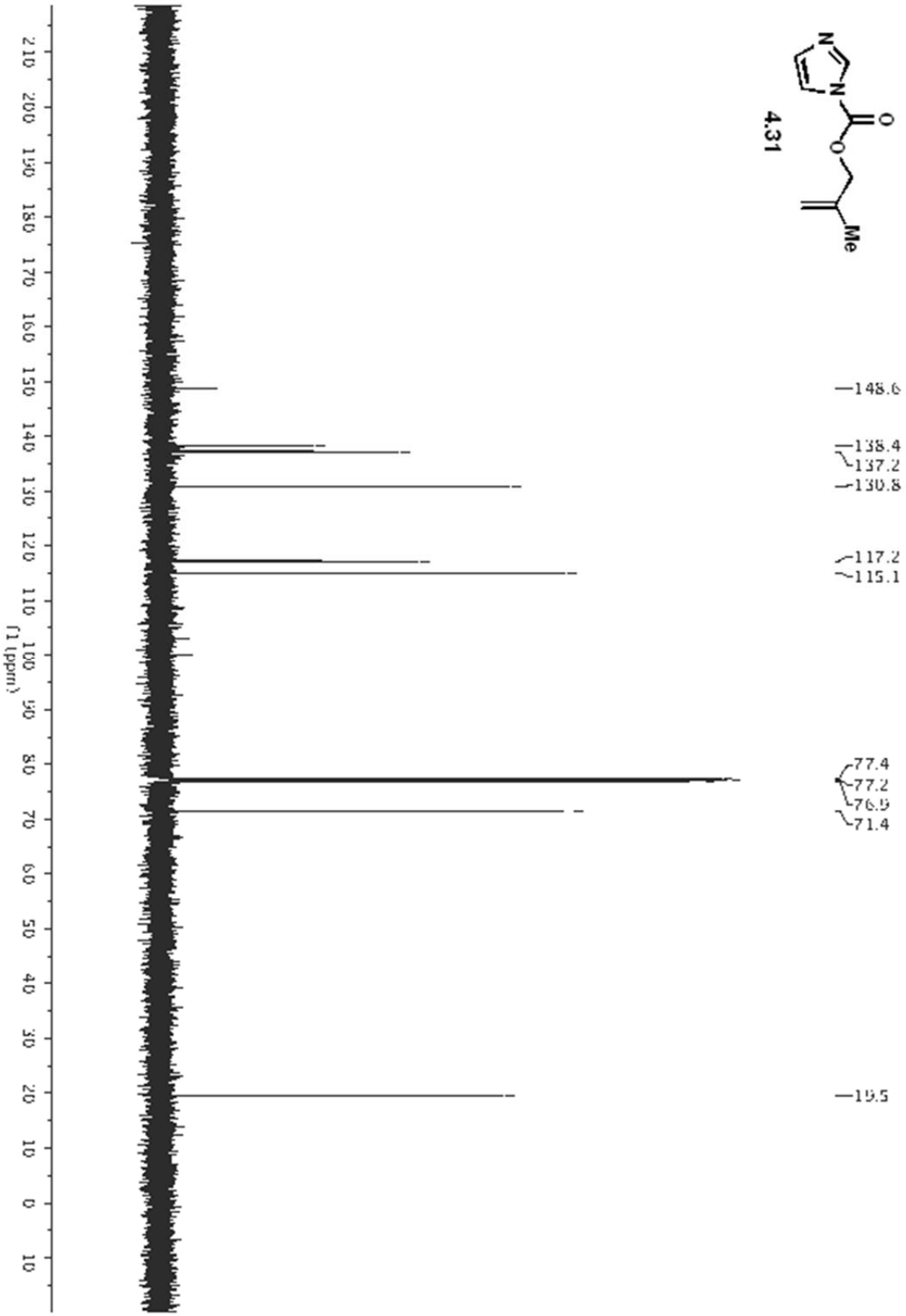

4.30
F
O
N
O
Me
160.2
158.3
150.7
131.5
131.3
131.2
127.0
116.0
115.9
112.2
112.0
107.6
107.5
106.4
106.3
63.3
14.3
ppm
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

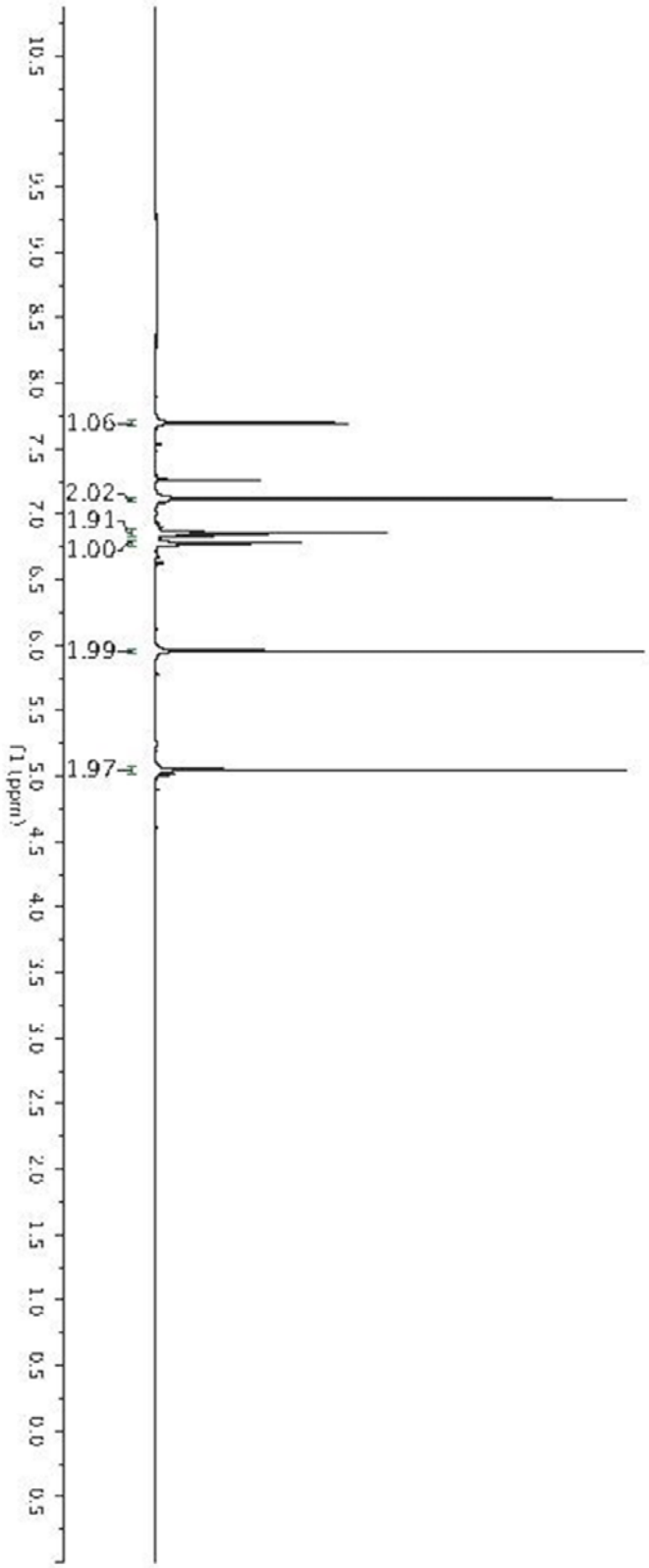
F
O
N
O
Me

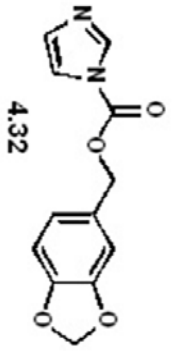
4.30

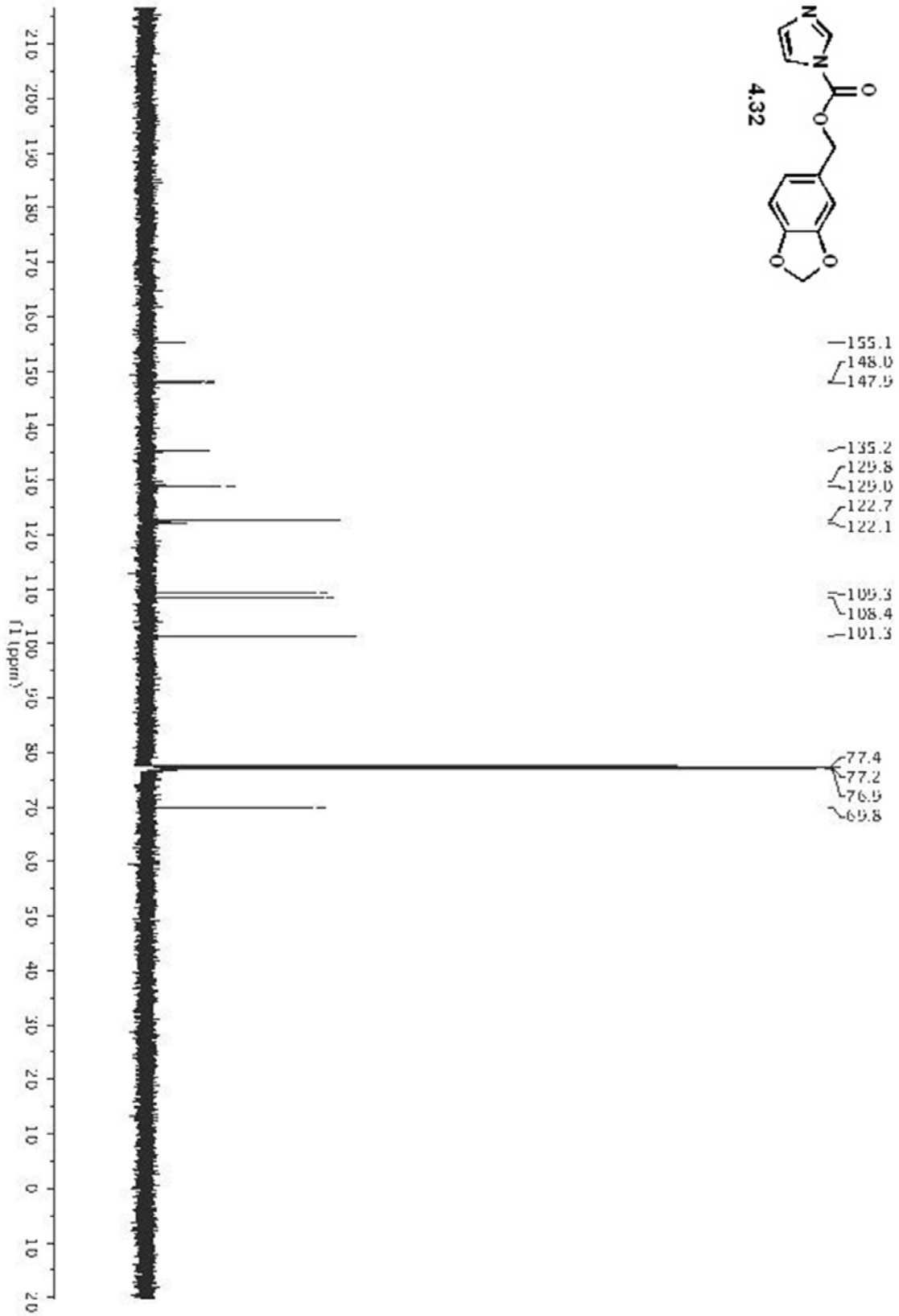
130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -13
ppm
-120.0

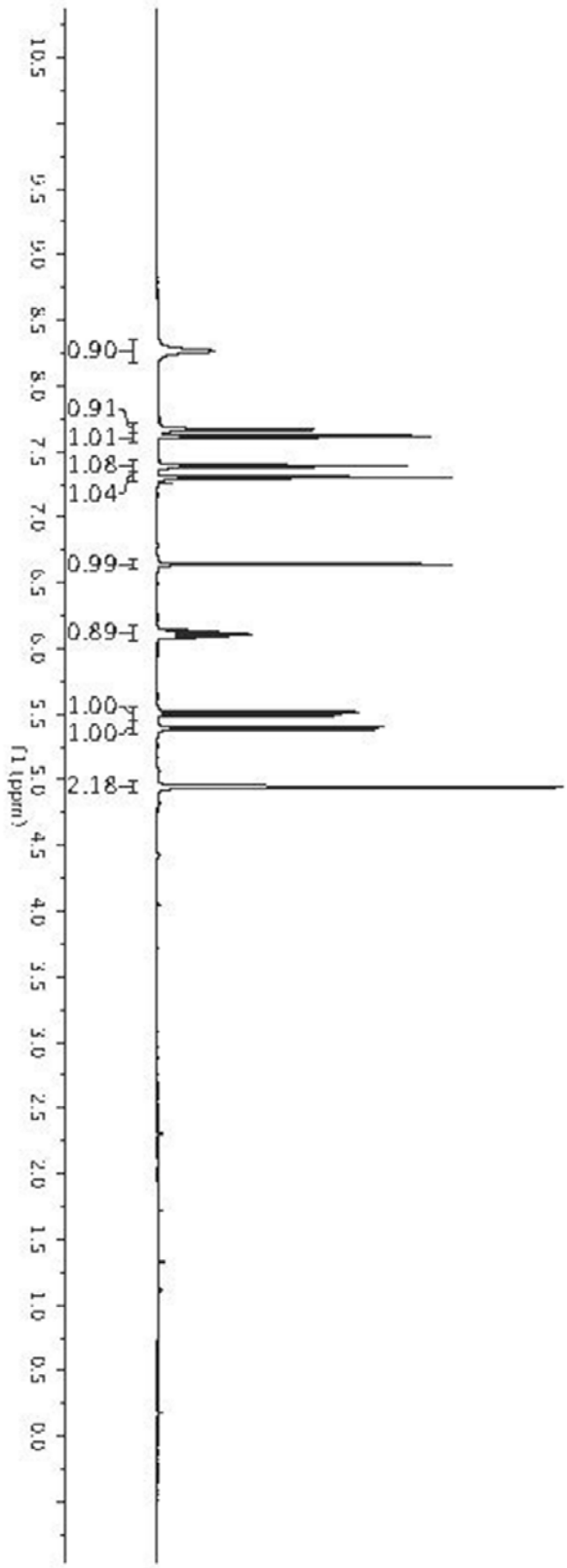

4.31
Me
1.02
0.92
1.00
0.98
1.00
2.00
3.01
f1 (ppm)

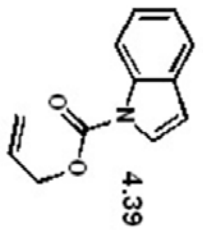

4.31
Me
148.6
138.4
137.2
130.8
117.2
115.1
77.4
77.2
76.9
71.4
19.5
f1 (ppm)

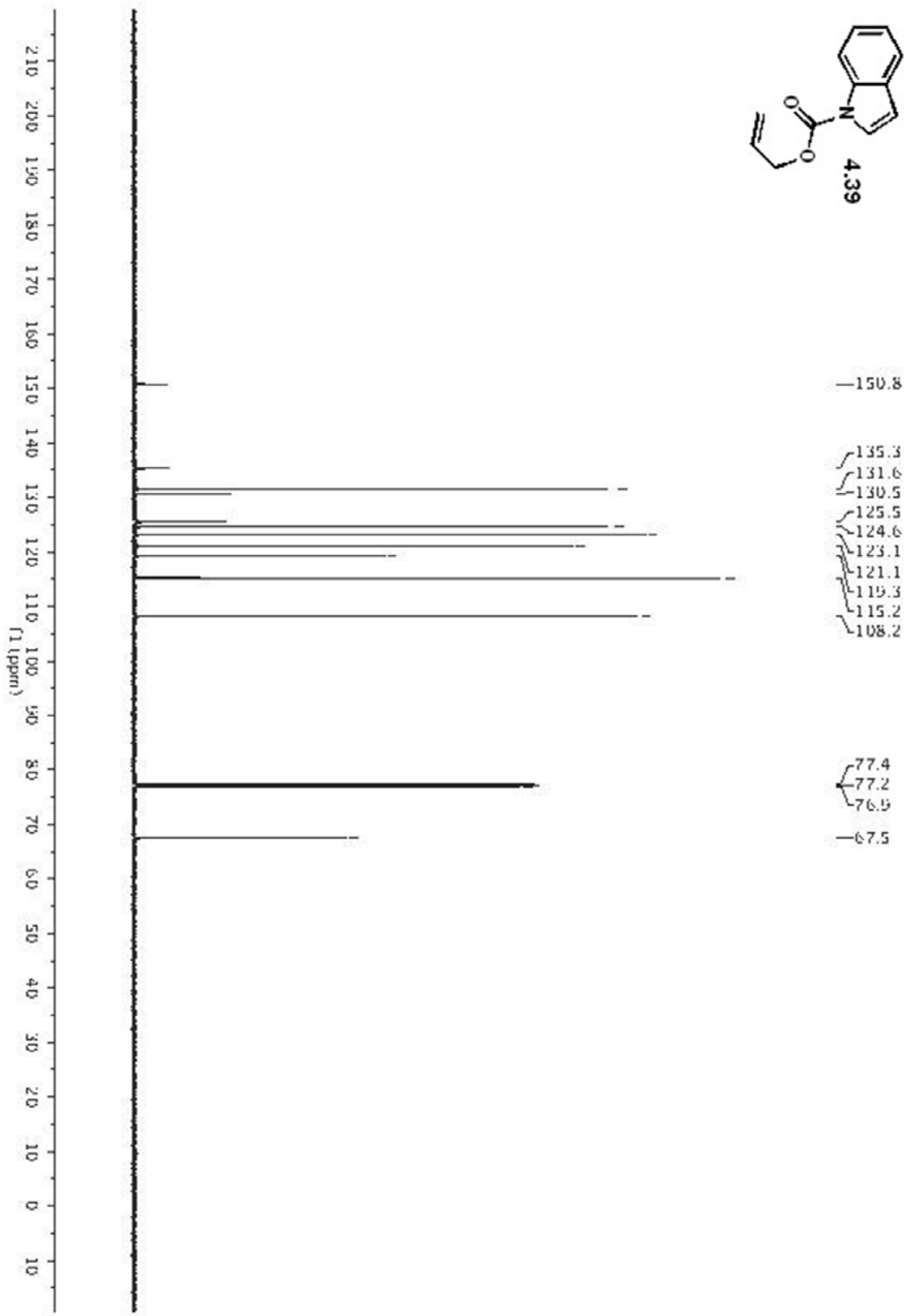

1.06
2.02
1.91
1.00
1.99
1.97
f1 (ppm)

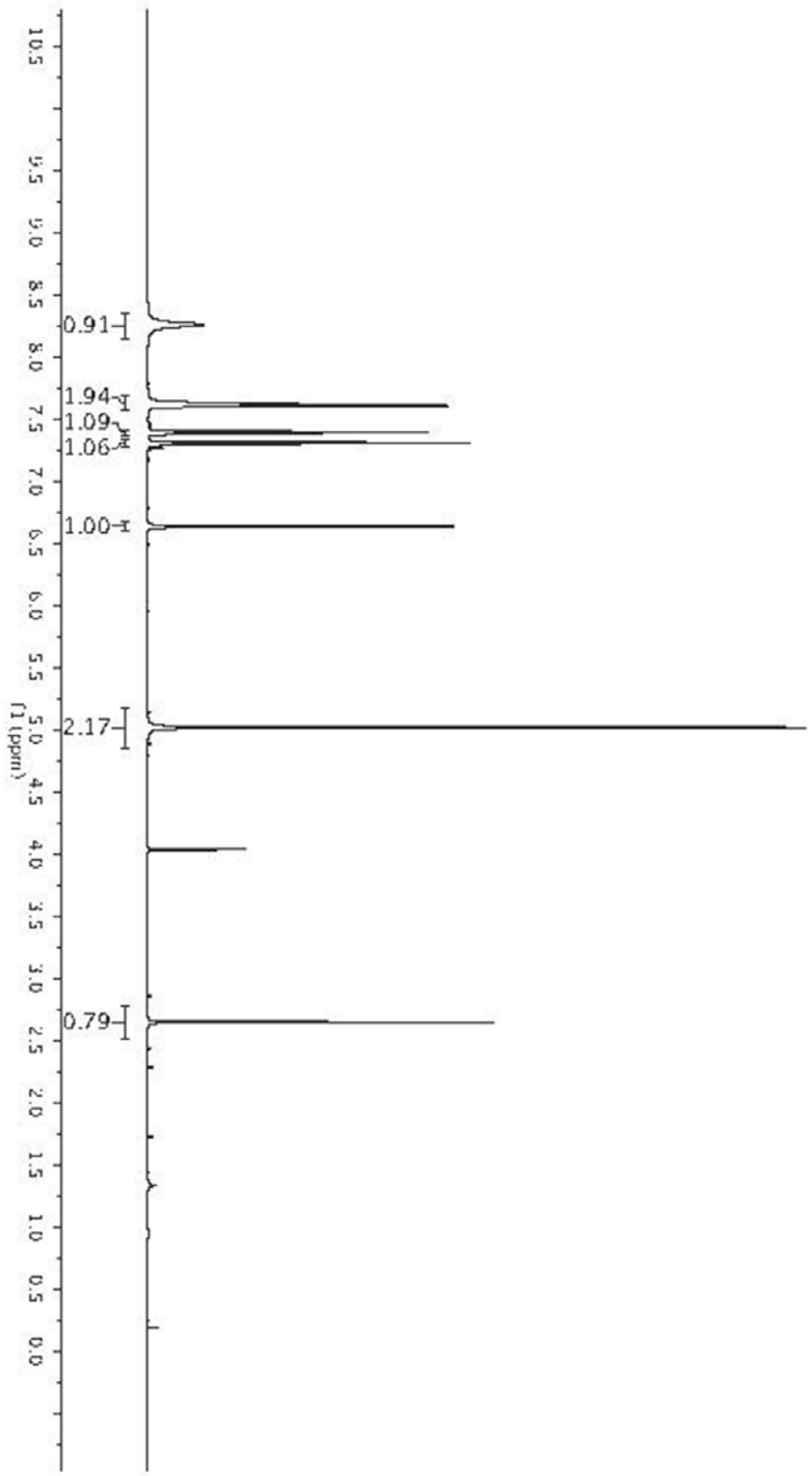

4.32

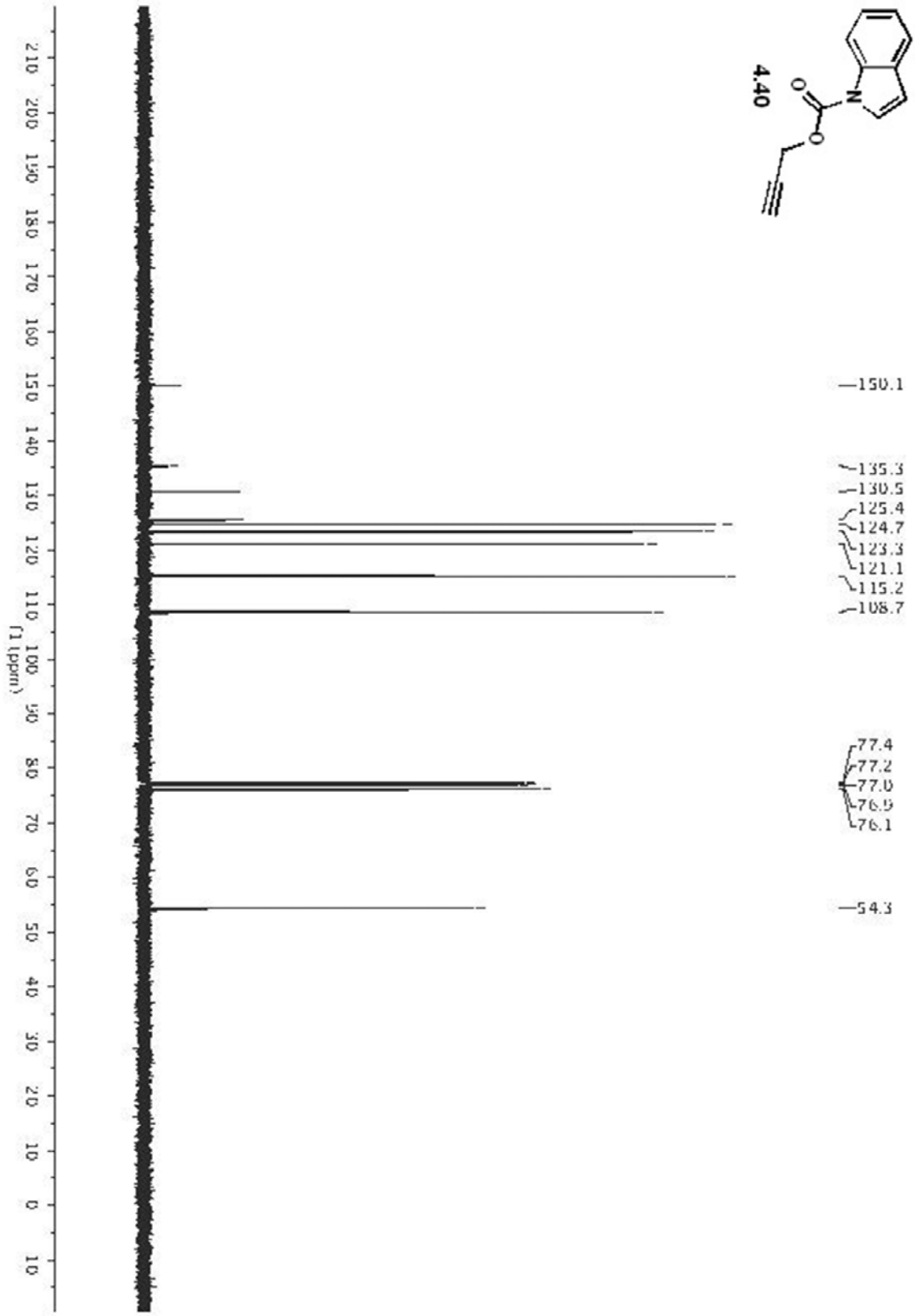

4.32
155.1
148.0
147.9
135.2
129.8
129.0
122.7
122.1
109.3
108.4
101.3
77.4
77.2
76.9
69.8
f1 (ppm)

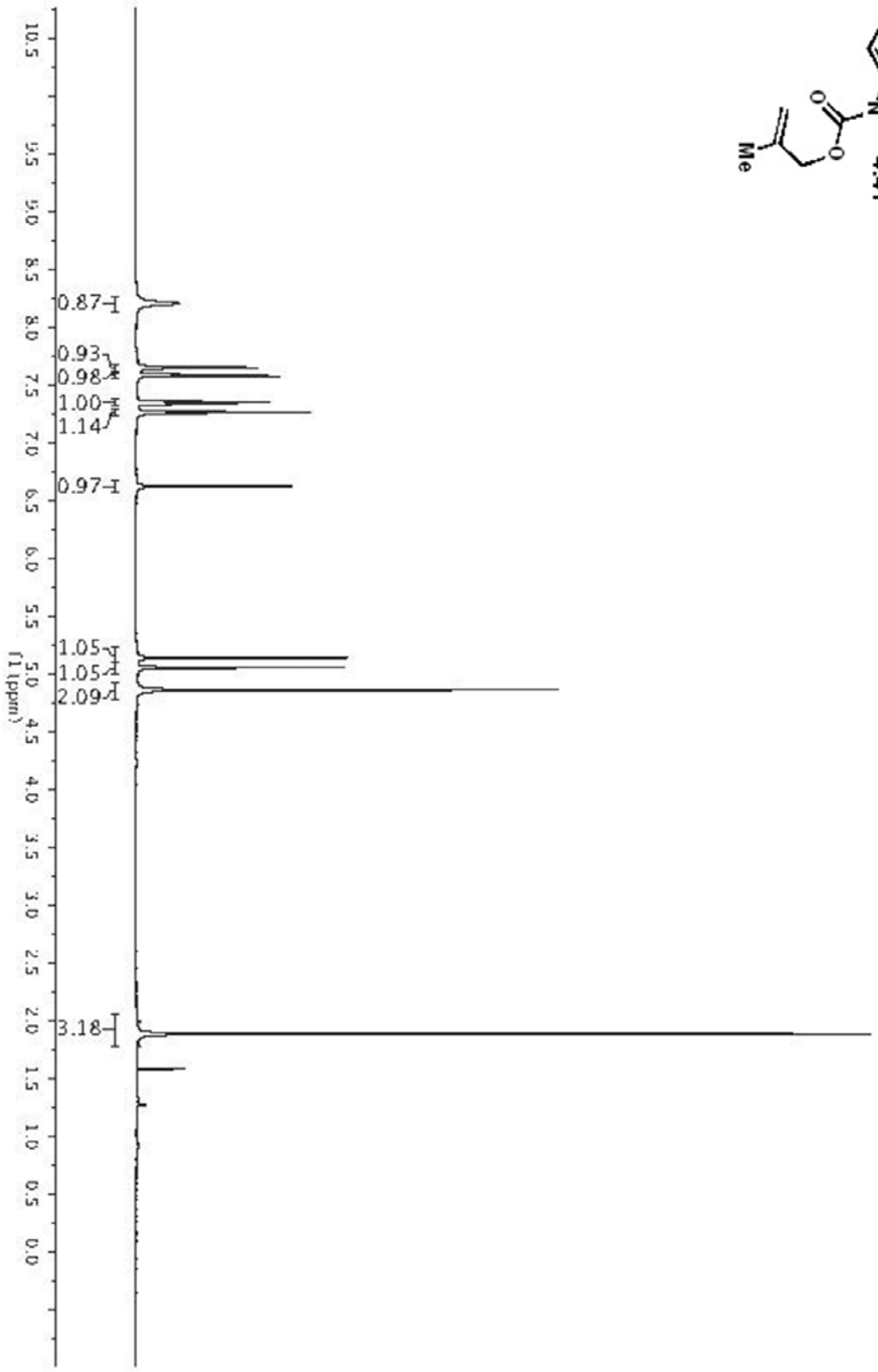

0.90
0.91
1.01
1.08
1.04
0.99
0.89
1.00
1.00
2.18
f1 (ppm)

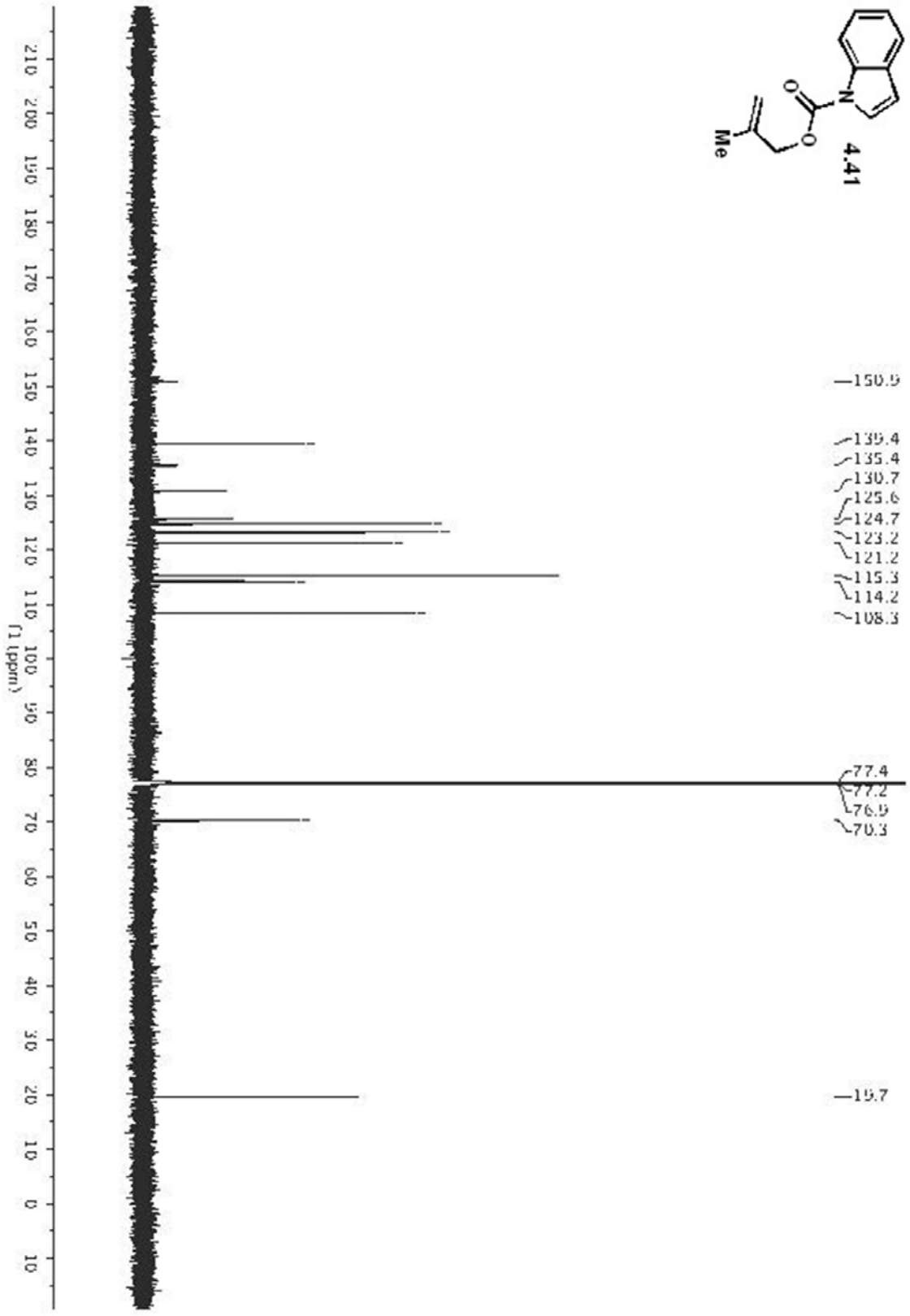

4.39

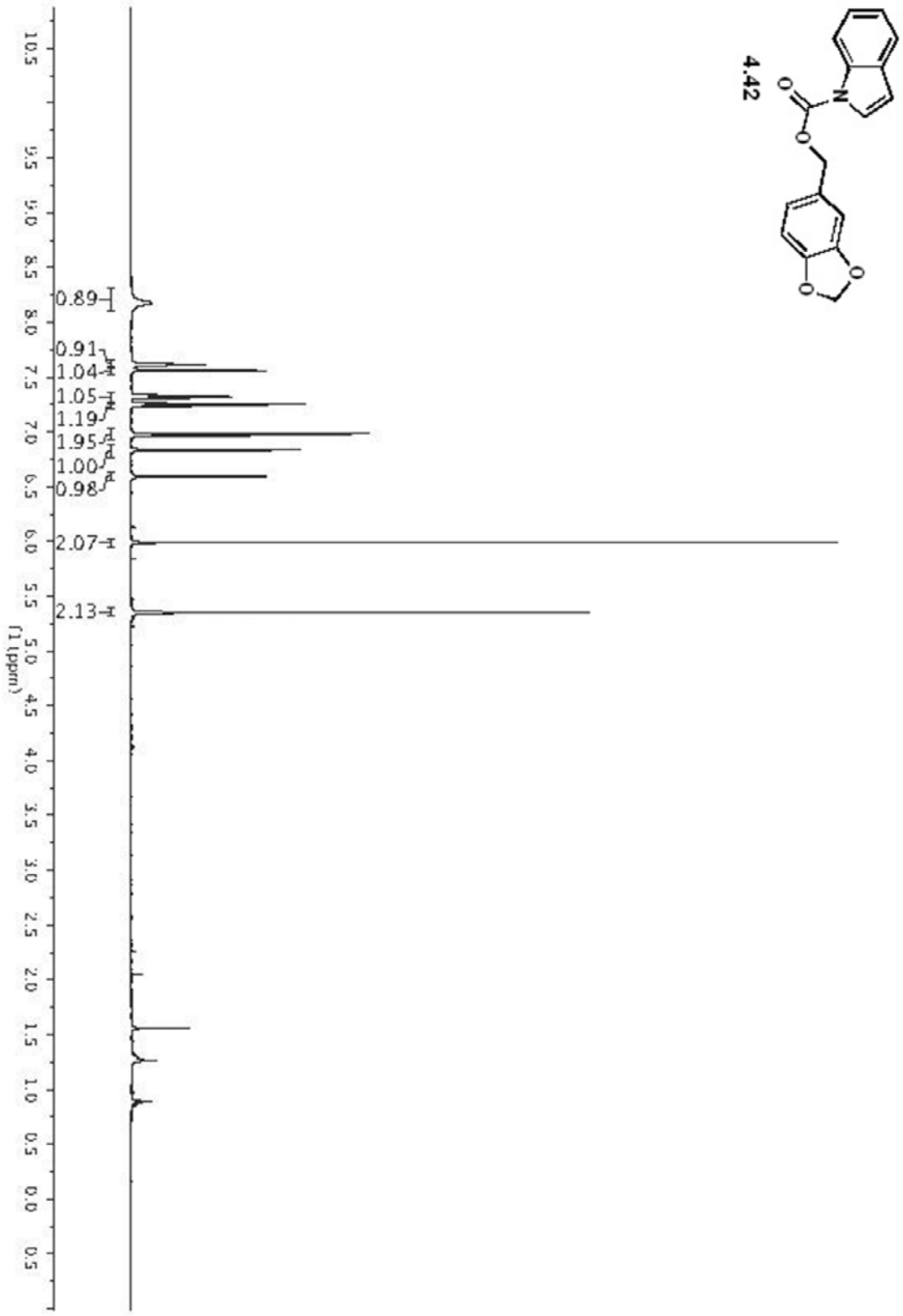

4.39
150.8
135.3
131.6
130.5
125.5
124.6
123.1
121.1
119.3
115.2
108.2
77.4
77.2
76.9
67.5
f1 (ppm)

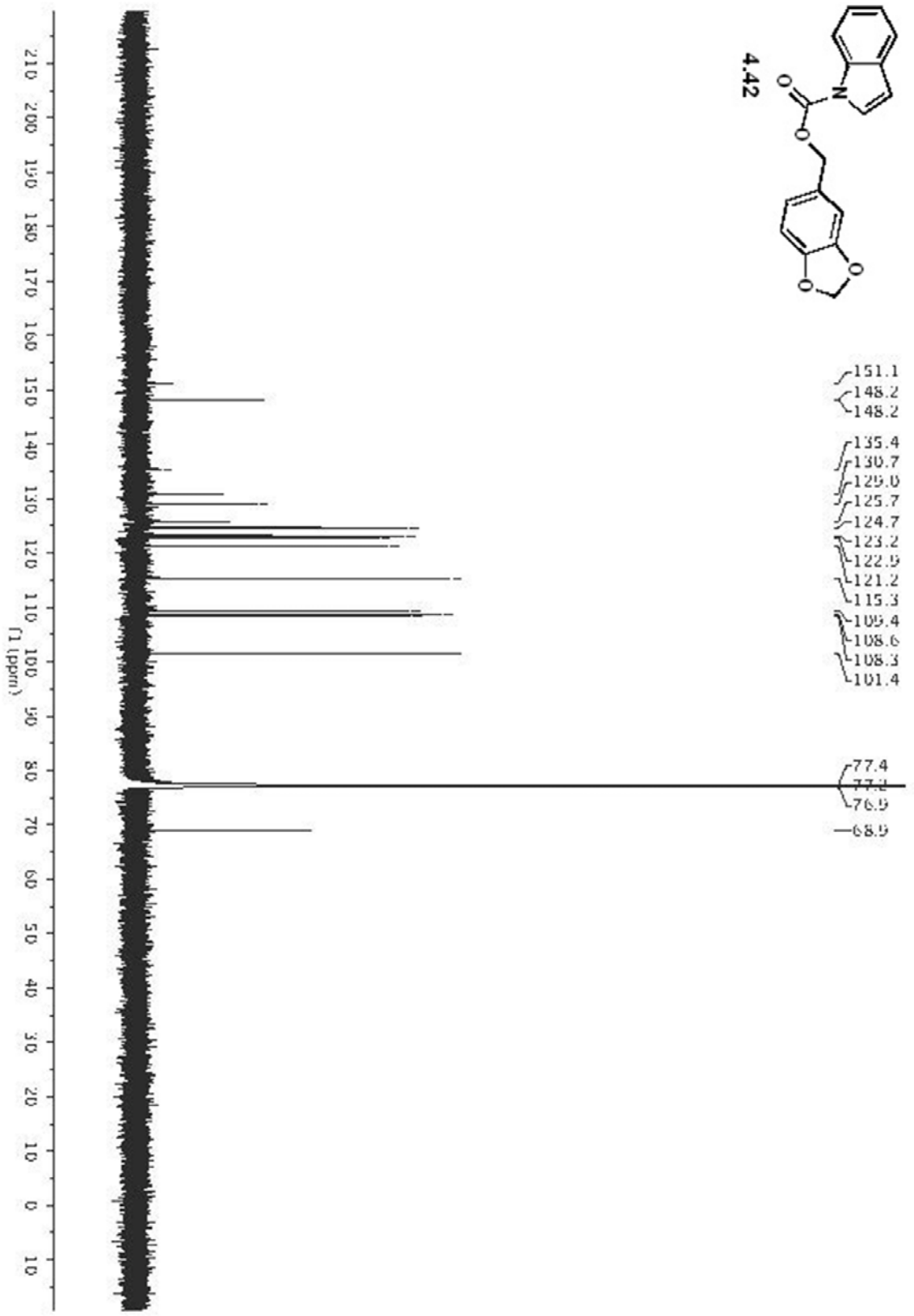

4.40
0.91
1.94
1.09
1.06
1.00
2.17
0.79
f1 (ppm)

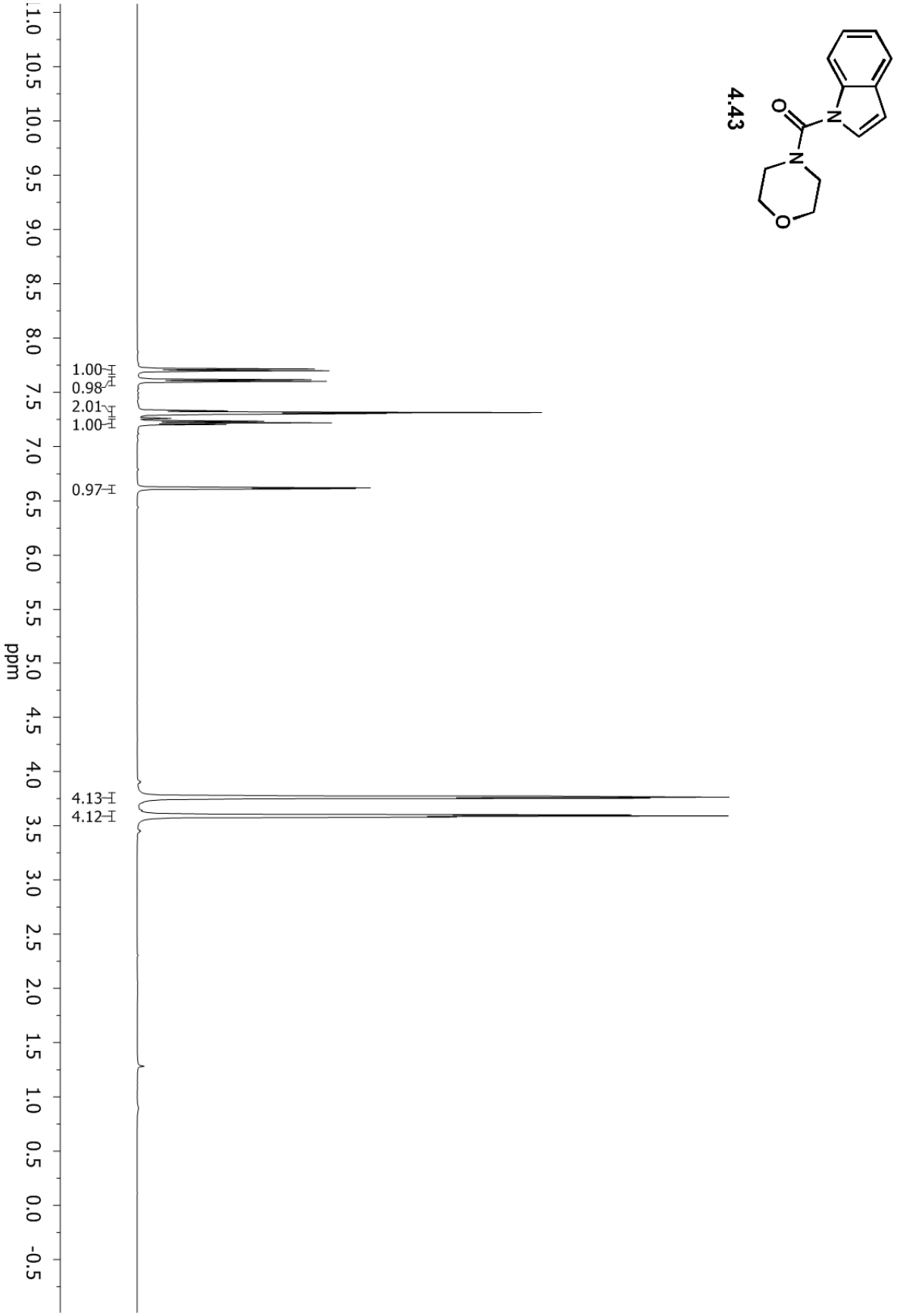

4.40
O
O
N
150.1
135.3
130.5
125.4
124.7
123.3
121.1
115.2
108.7
77.4
77.2
77.0
76.9
76.1
54.3
f1 (ppm)

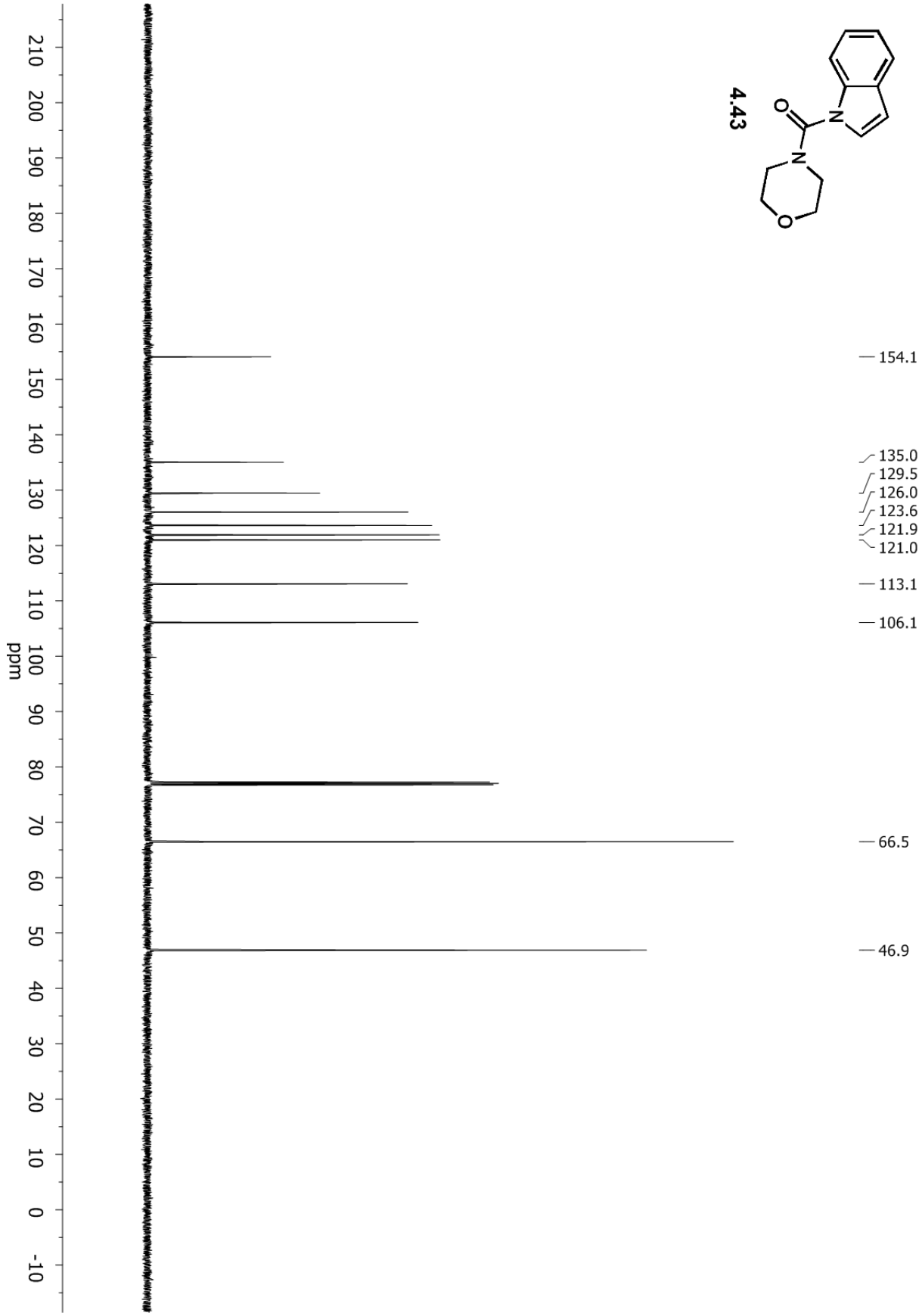

0.87
0.93
0.98
1.00
1.14
0.97
1.05
1.05
2.09
3.18
f1 (ppm)
Me
4.41

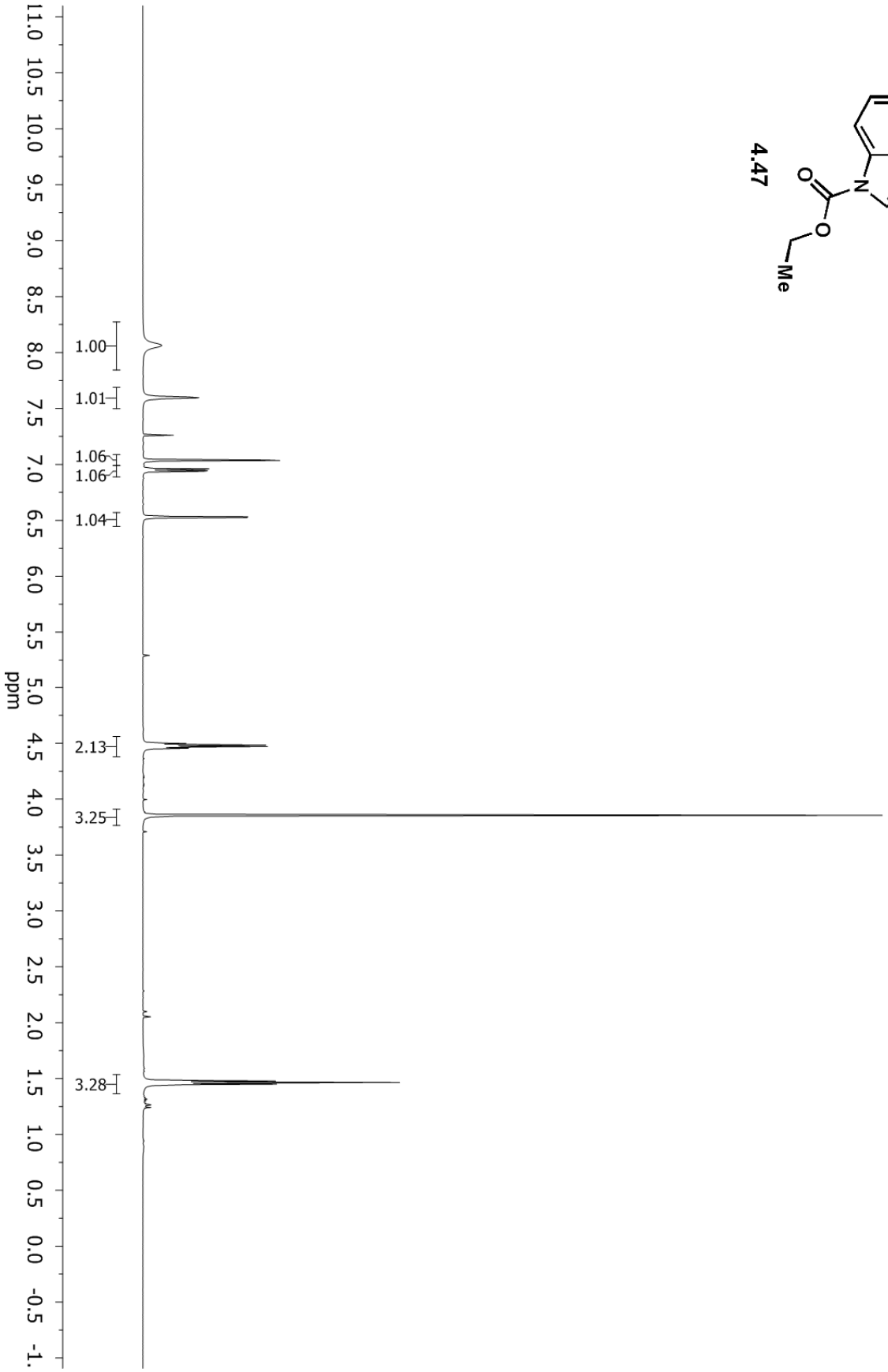

4.41
Me
150.9
139.4
135.4
130.7
125.6
124.7
123.2
121.2
115.3
114.2
108.3
77.4
77.2
76.9
70.3
19.7
f1 (ppm)

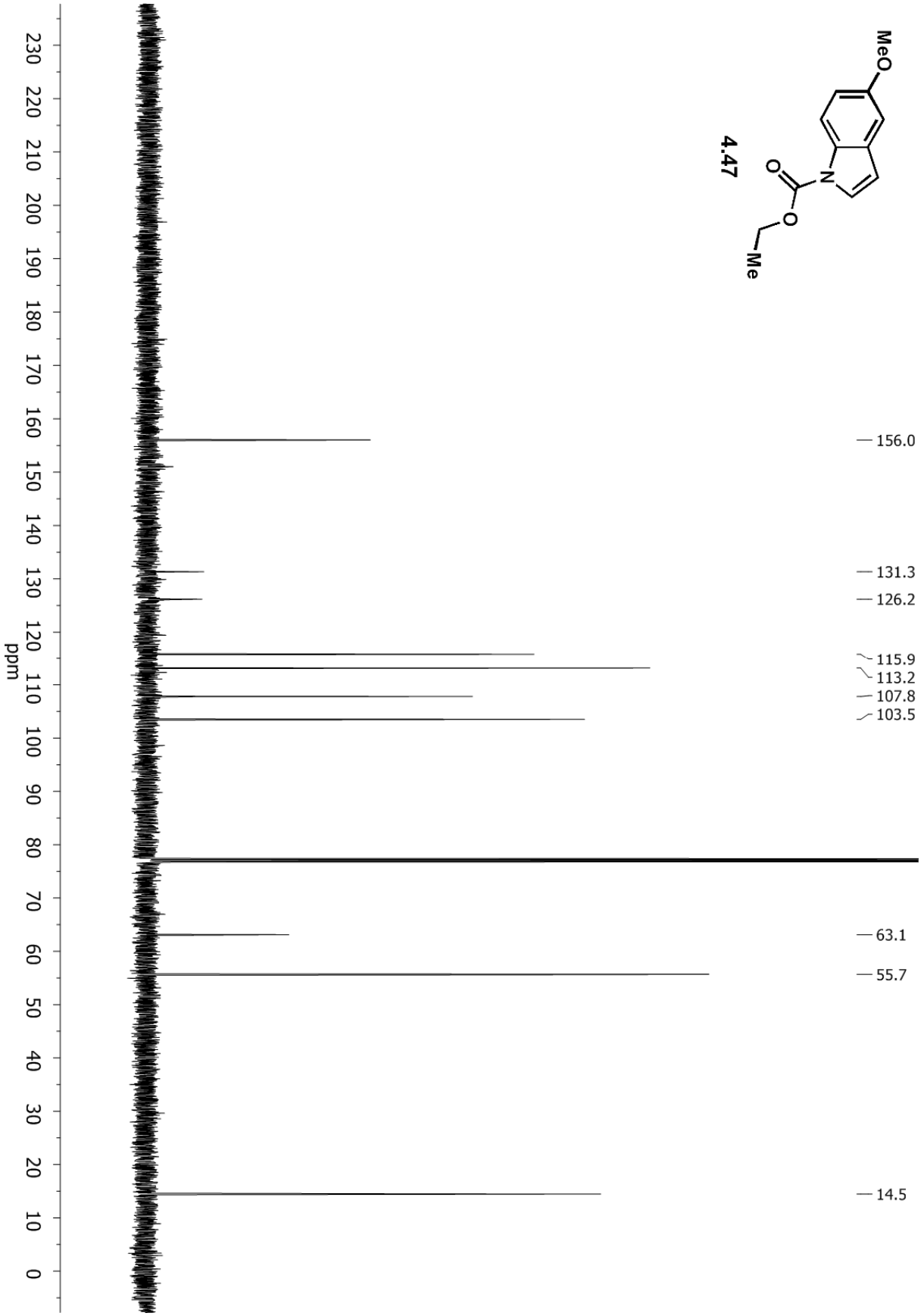

4.42
0.89
0.91
1.04
1.05
1.19
1.95
1.00
0.98
2.07
2.13
f1 (ppm)

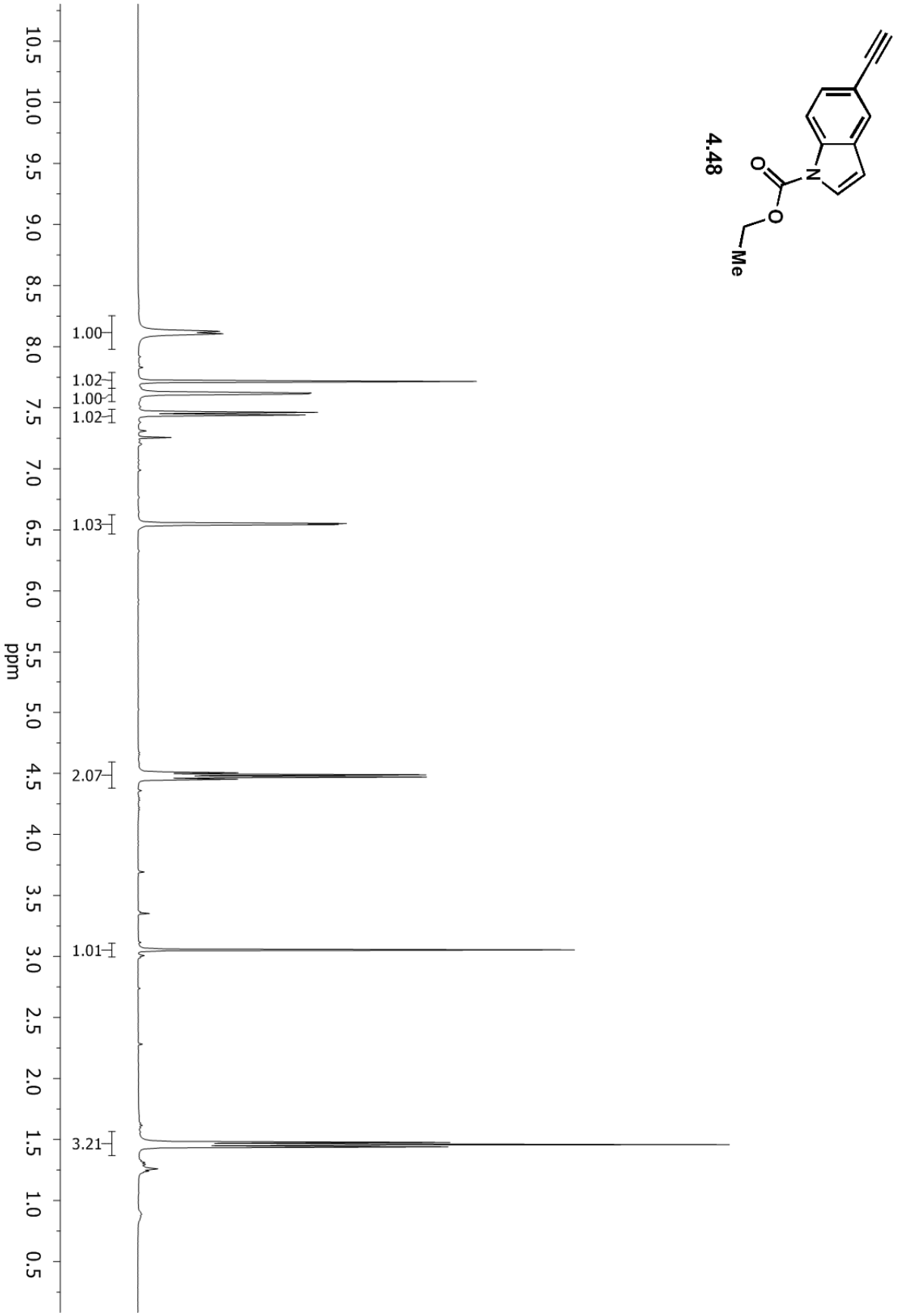

4.42
151.1
148.2
148.2
135.4
130.7
129.0
125.7
124.7
123.2
122.9
121.2
115.3
109.4
108.6
108.3
101.4
77.4
76.9
68.9
f1 (ppm)

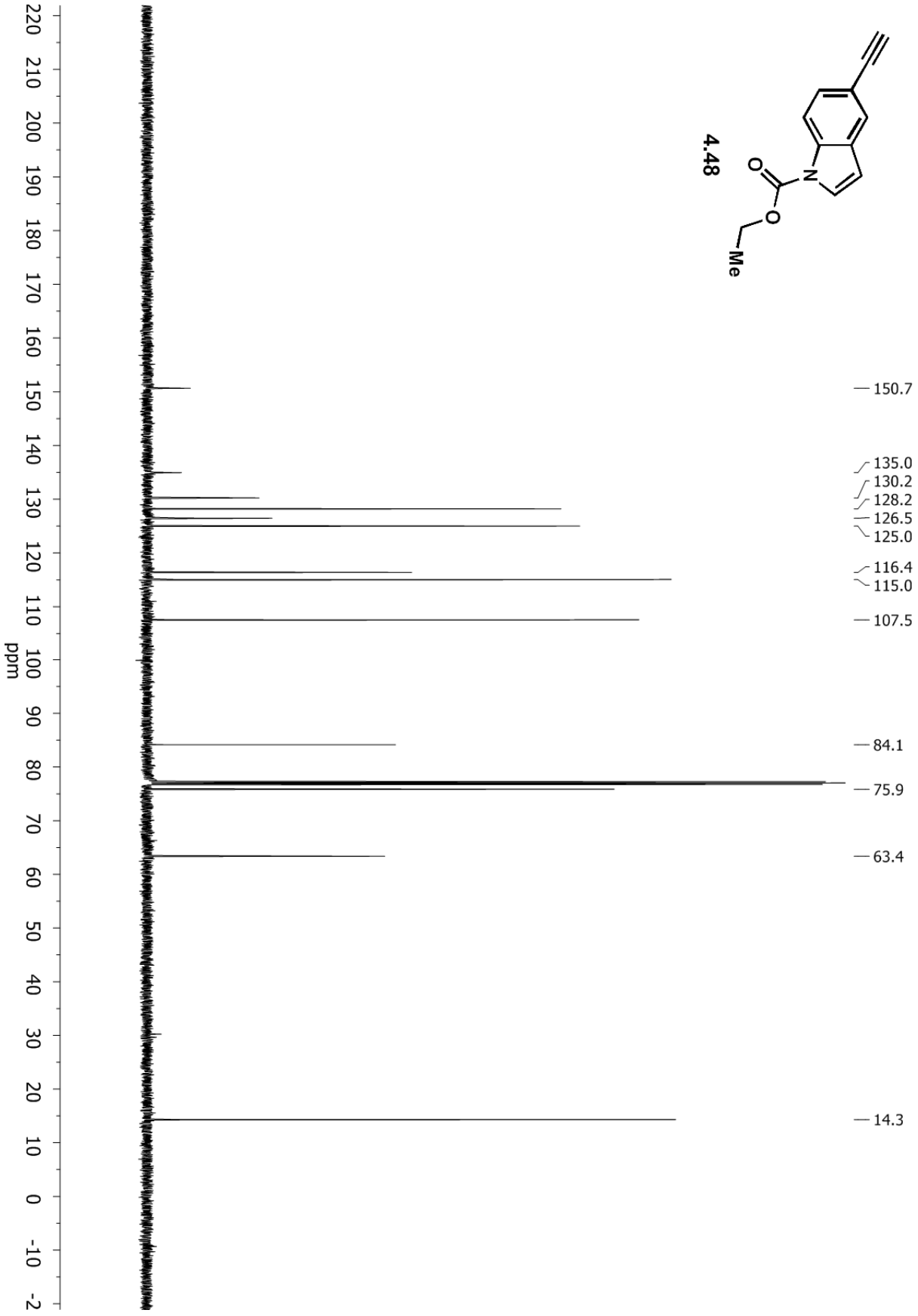

4.43
1.00
0.98
2.01
1.00
0.97
4.13
4.12
ppm

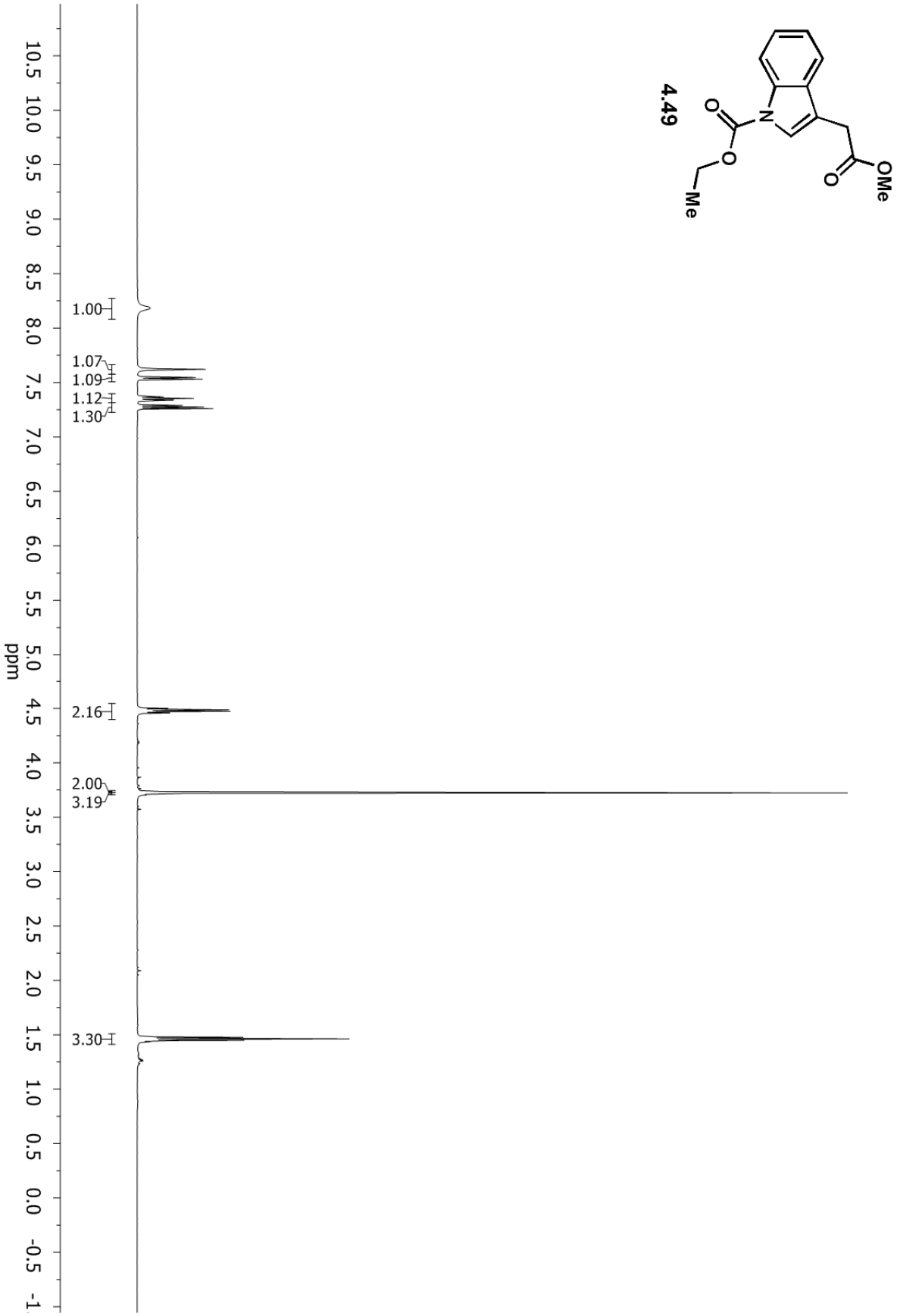

4.43
154.1
135.0
129.5
126.0
123.6
121.9
121.0
113.1
106.1
66.5
46.9
ppm

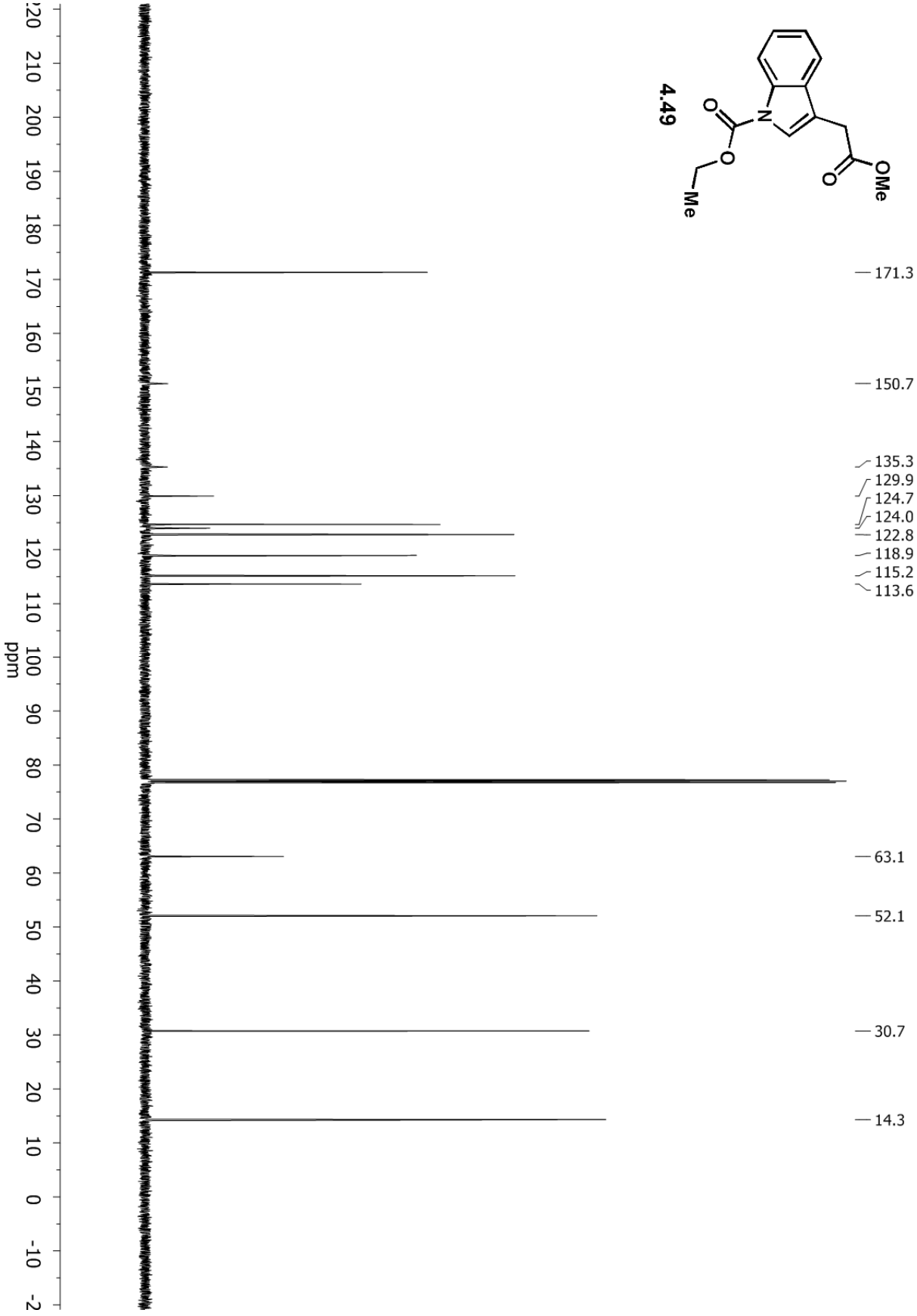

MeO
N
O
O
Me
4.47
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.
ppm
1.00
1.01
1.06
1.06
1.04
2.13
3.25
3.28

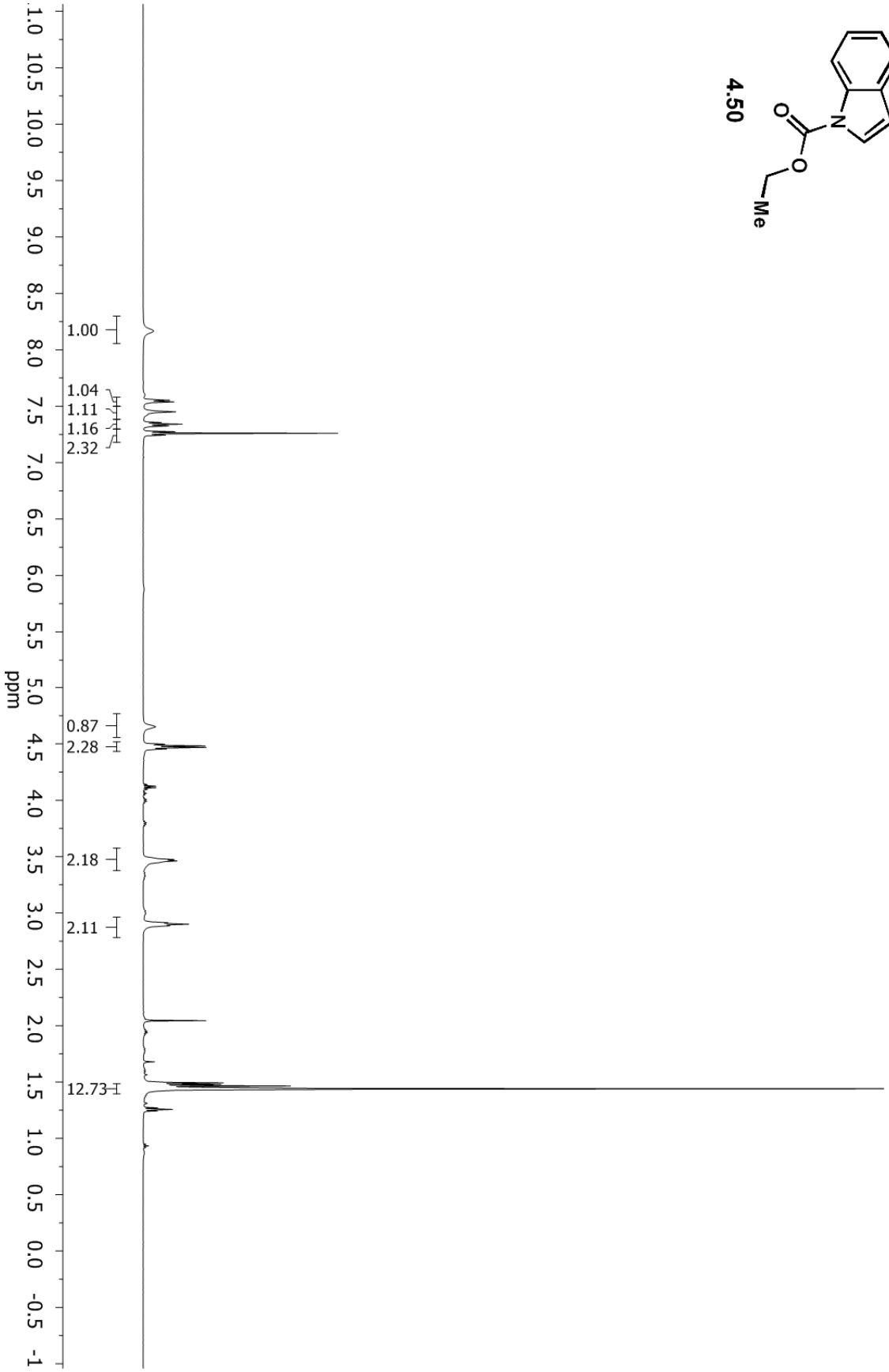

4.47
MeO
N
O
O
Me
156.0
131.3
126.2
115.9
113.2
107.8
103.5
63.1
55.7
14.5
ppm
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

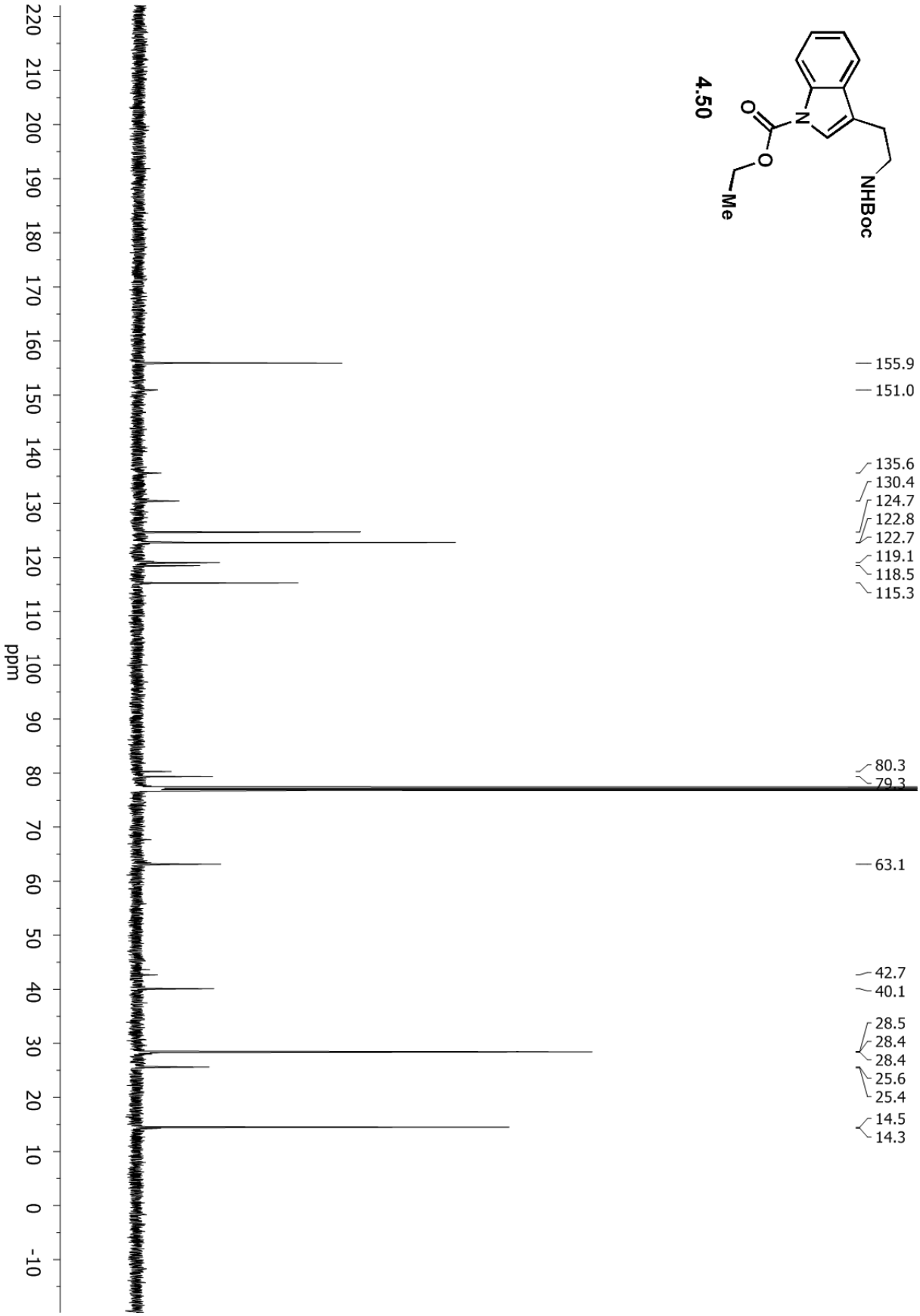

4.48
Me
O
N
O
ppm
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
1.00
1.02
1.00
1.02
1.03
2.07
1.01
3.21

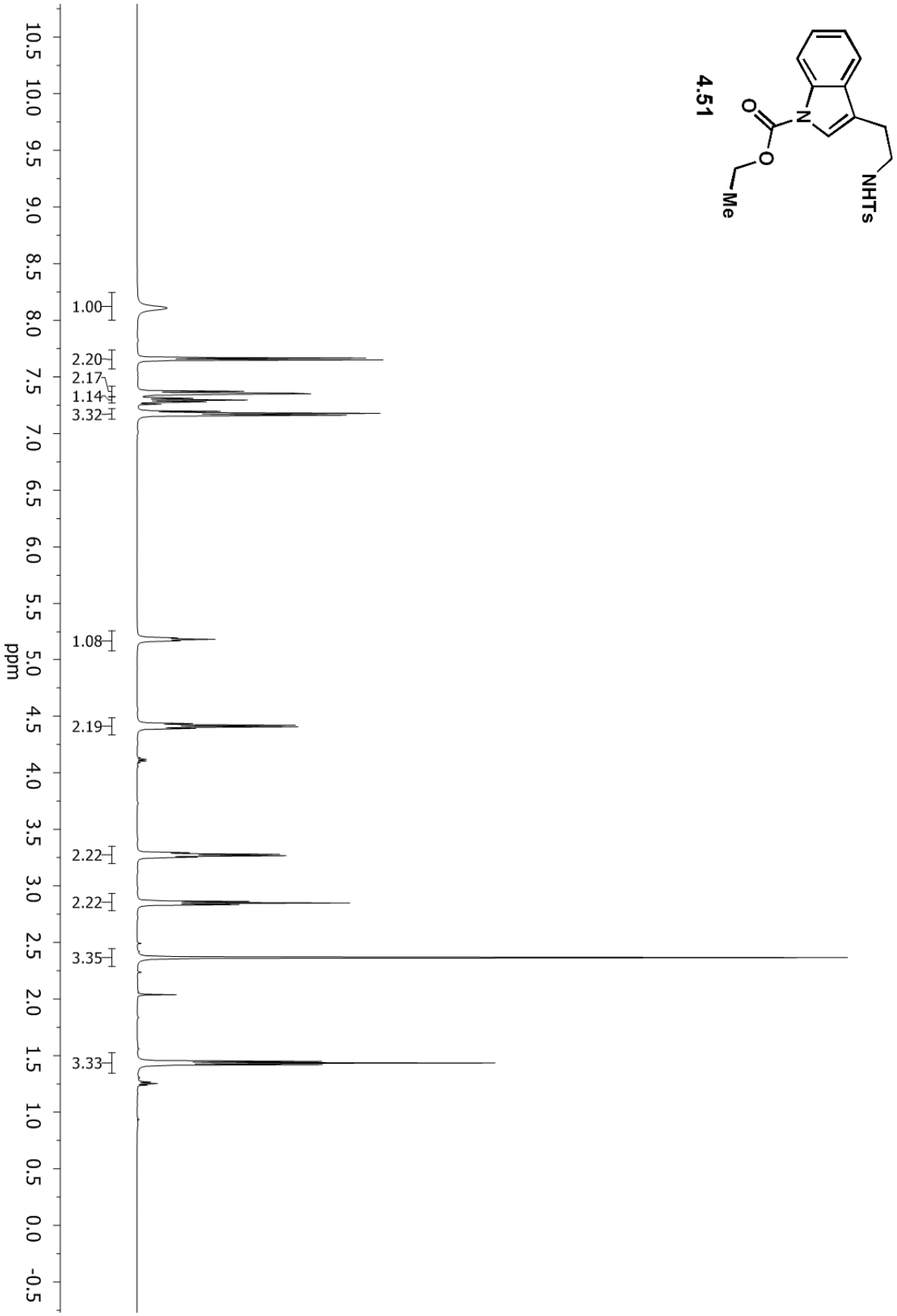

4.48
Me
150.7
135.0
130.2
128.2
126.5
125.0
116.4
115.0
107.5
84.1
75.9
63.4
14.3
ppm

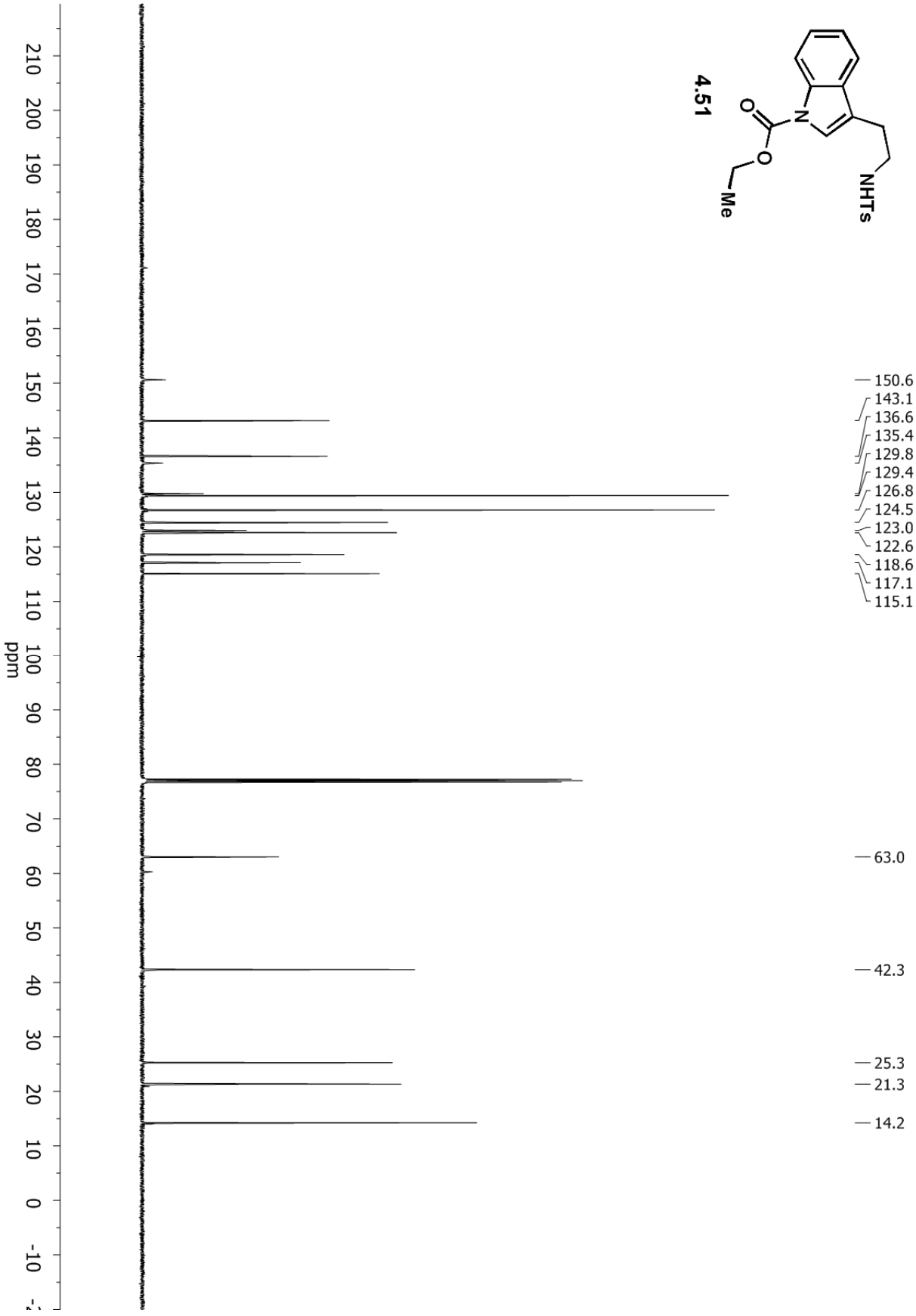

4.49
OMe
Me
1.00
1.07
1.09
1.12
1.30
2.16
2.00
3.19
3.30
ppm

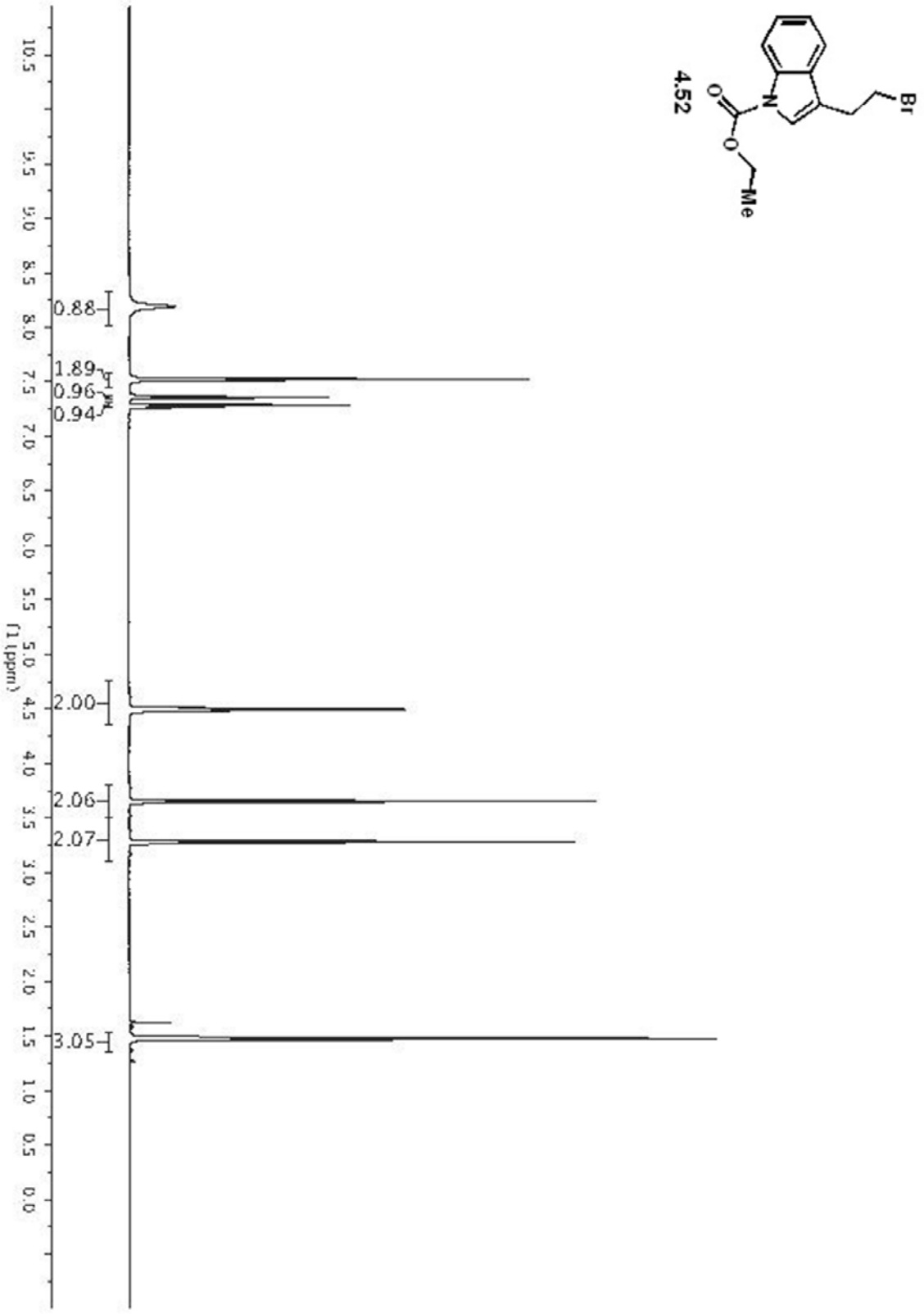

4.49
Me
O
O
N
O
O
OMe
171.3
150.7
135.3
129.9
124.7
124.0
122.8
118.9
115.2
113.6
63.1
52.1
30.7
14.3
ppm
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -2

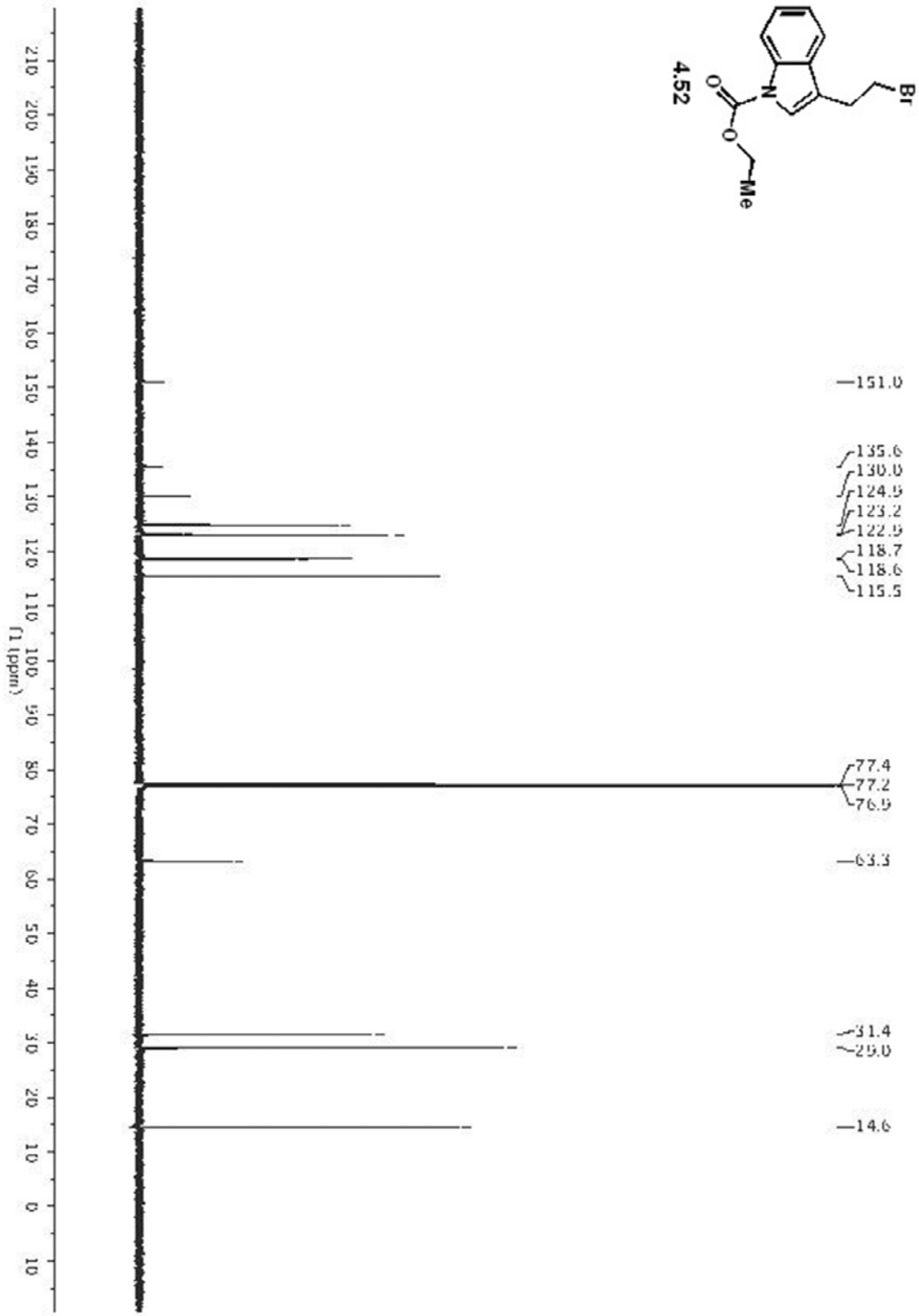

4.50
NHBoc
Me
O
O
N
1.00
1.04
1.11
1.16
2.32
0.87
2.28
2.18
2.11
12.73
ppm
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1

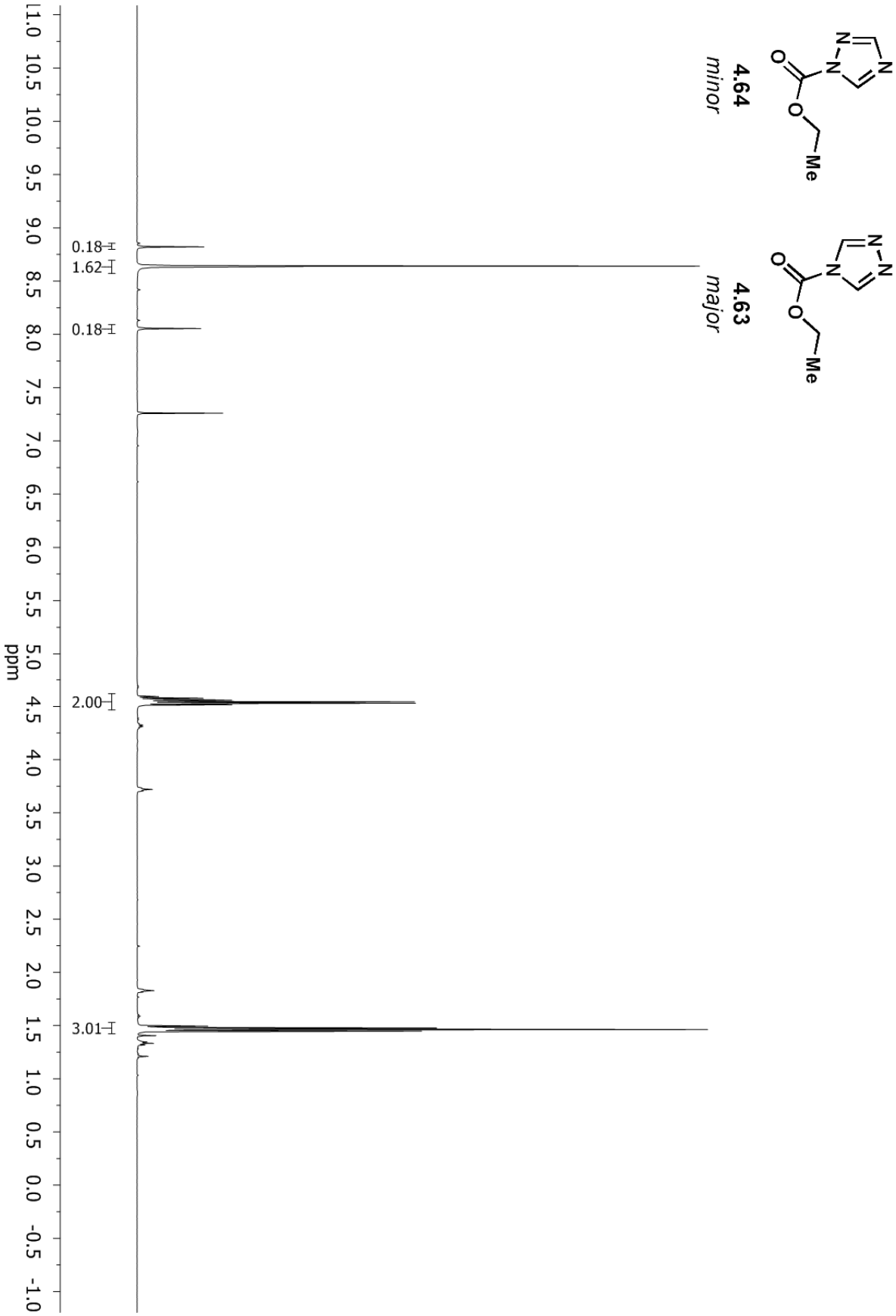

4.50
Me
NHBoc
155.9
151.0
135.6
130.4
124.7
122.8
122.7
119.1
118.5
115.3
80.3
79.3
63.1
42.7
40.1
28.5
28.4
28.4
25.6
25.4
14.5
14.3
ppm

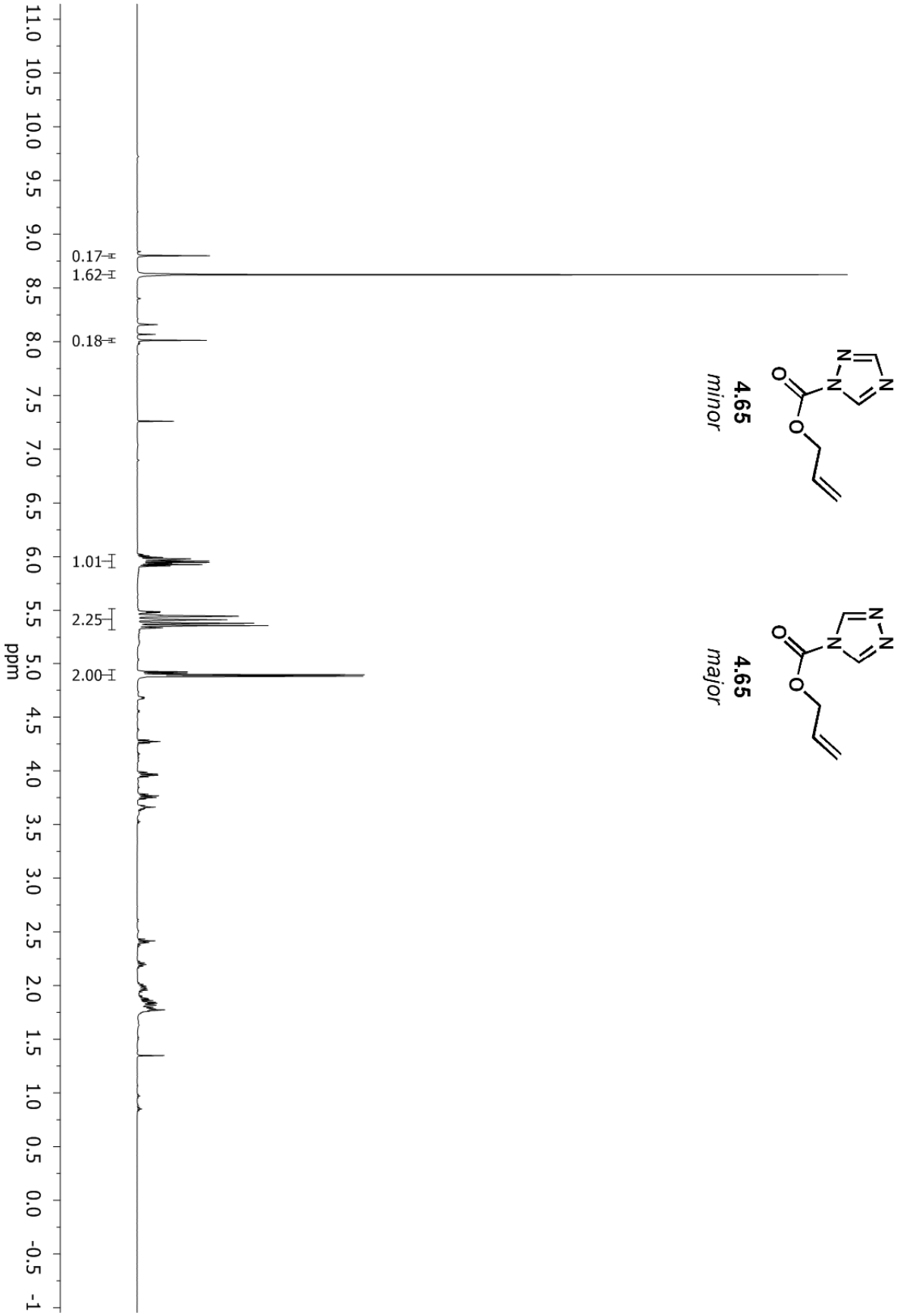

4.51
N
O
O
Me
NHTs
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
ppm
1.00
2.20
2.17
1.14
3.32
1.08
2.19
2.22
2.22
3.35
3.33

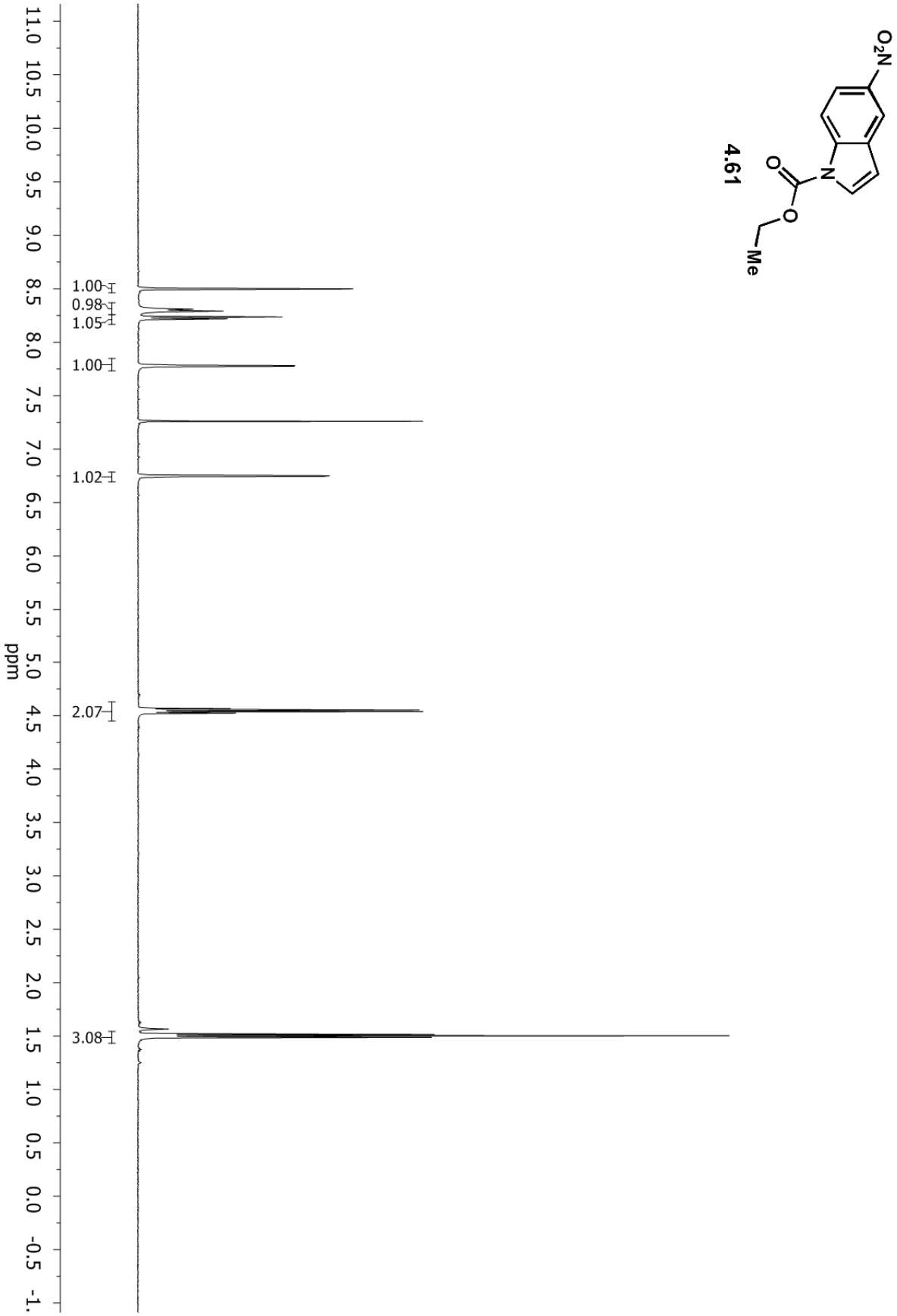

4.51
N
O
O
Me
NHTs
150.6
143.1
136.6
135.4
129.8
129.4
126.8
124.5
123.0
122.6
118.6
117.1
115.1
63.0
42.3
25.3
21.3
14.2
ppm
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

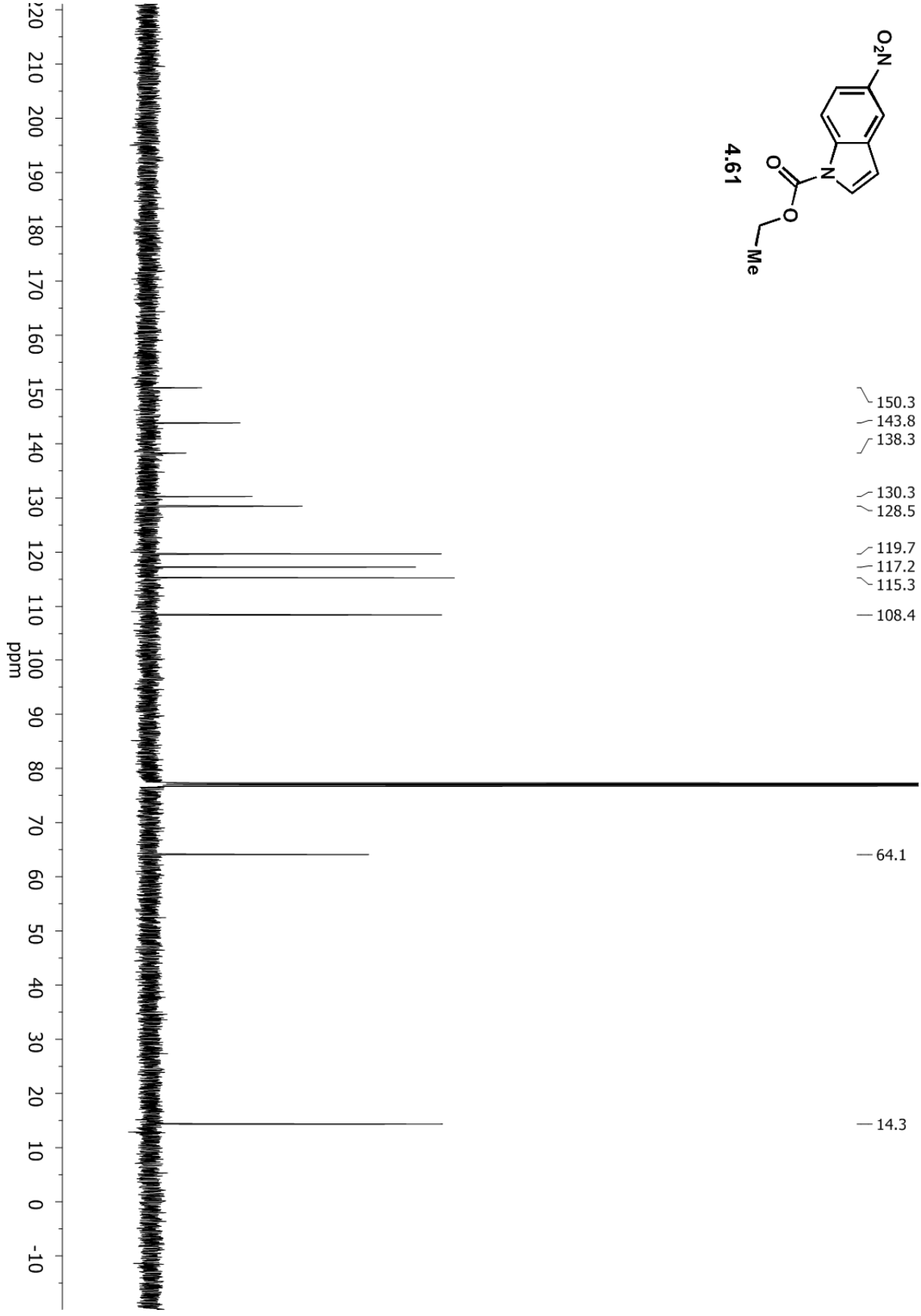

4.52
Br
N
O
O
Me
0.88
1.89
0.96
0.94
2.00
2.06
2.07
3.05
f1 (ppm)

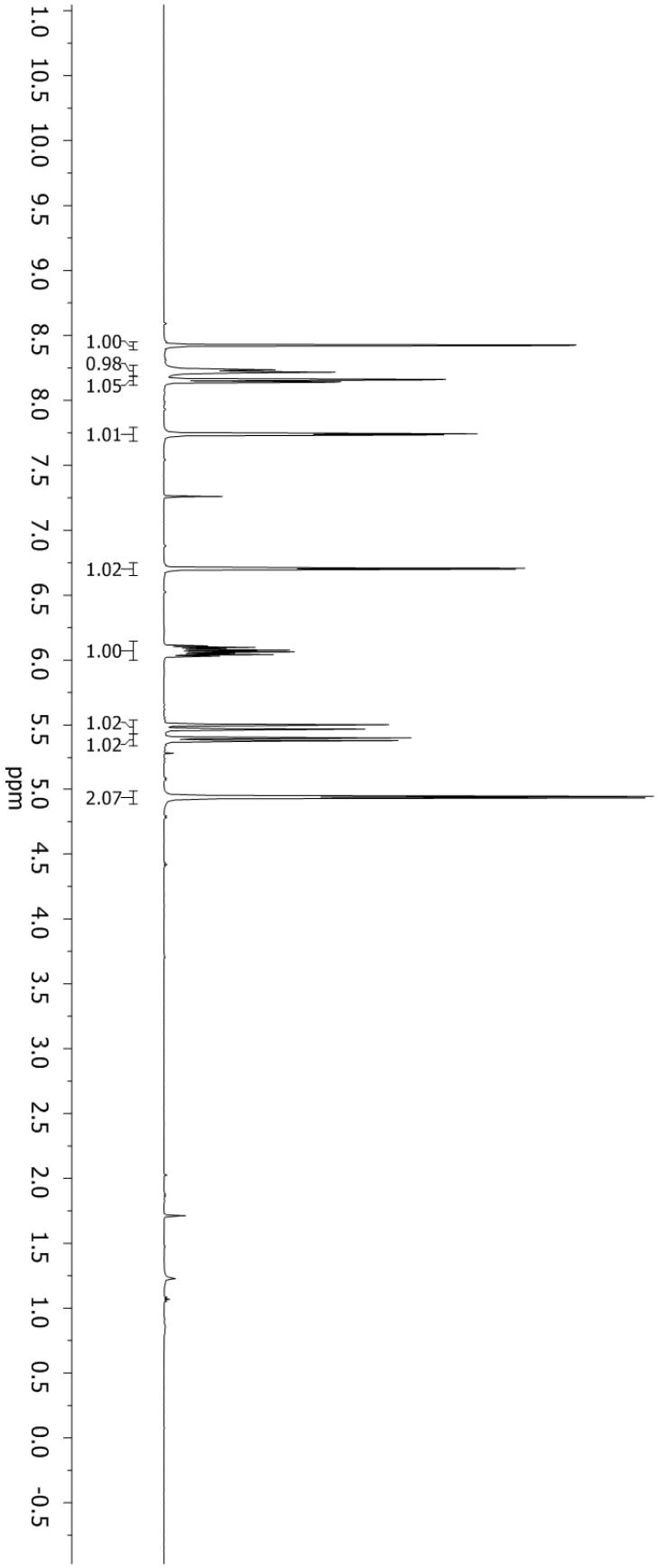

4.52
Br
N
O
O
Me
151.0
135.6
130.0
124.9
123.2
122.9
118.7
118.6
115.5
77.4
77.2
76.9
63.3
31.4
29.0
14.6
f1 (ppm)

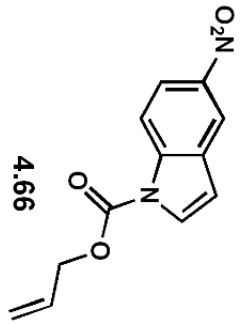

4.64
minor
4.63
major
Me
Me
0.18
1.62
0.18
2.00
3.01
ppm
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0

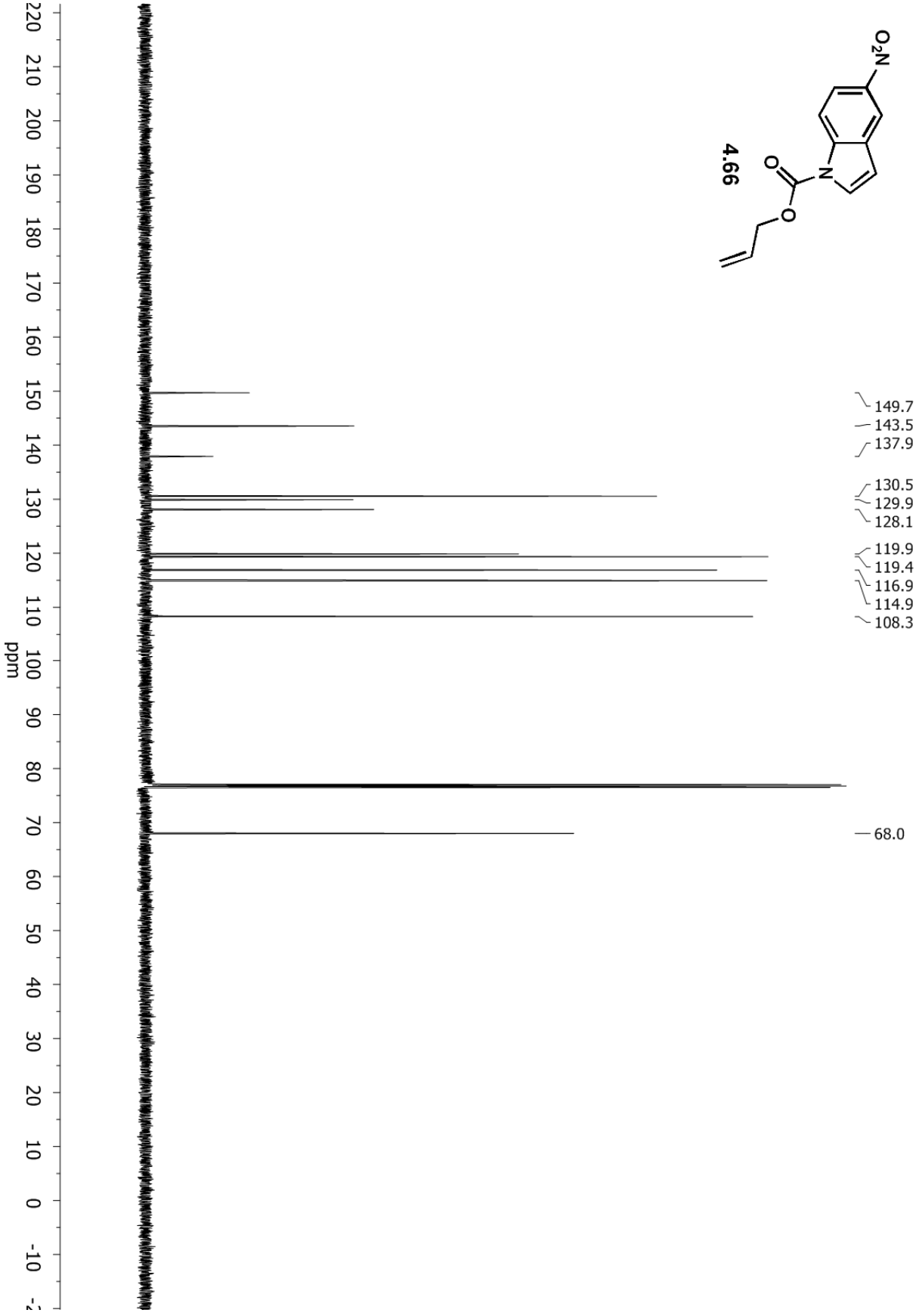

11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
ppm
0.17
1.62
0.18
1.01
2.25
2.00
4.65
minor
4.65
major

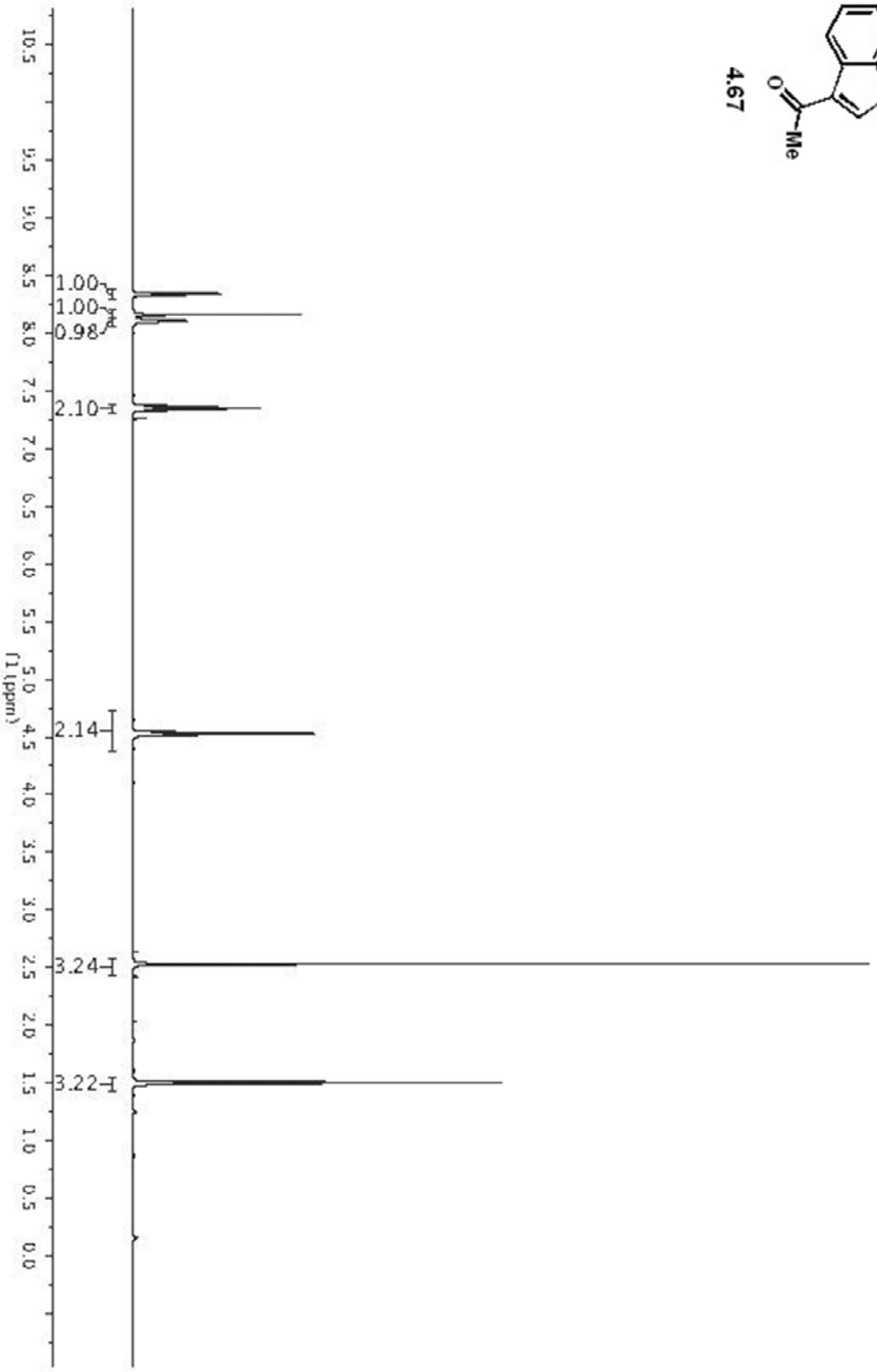

4.61
O2N
O
N
O
Me
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.
ppm
1.00
0.98
1.05
1.00
1.02
2.07
3.08

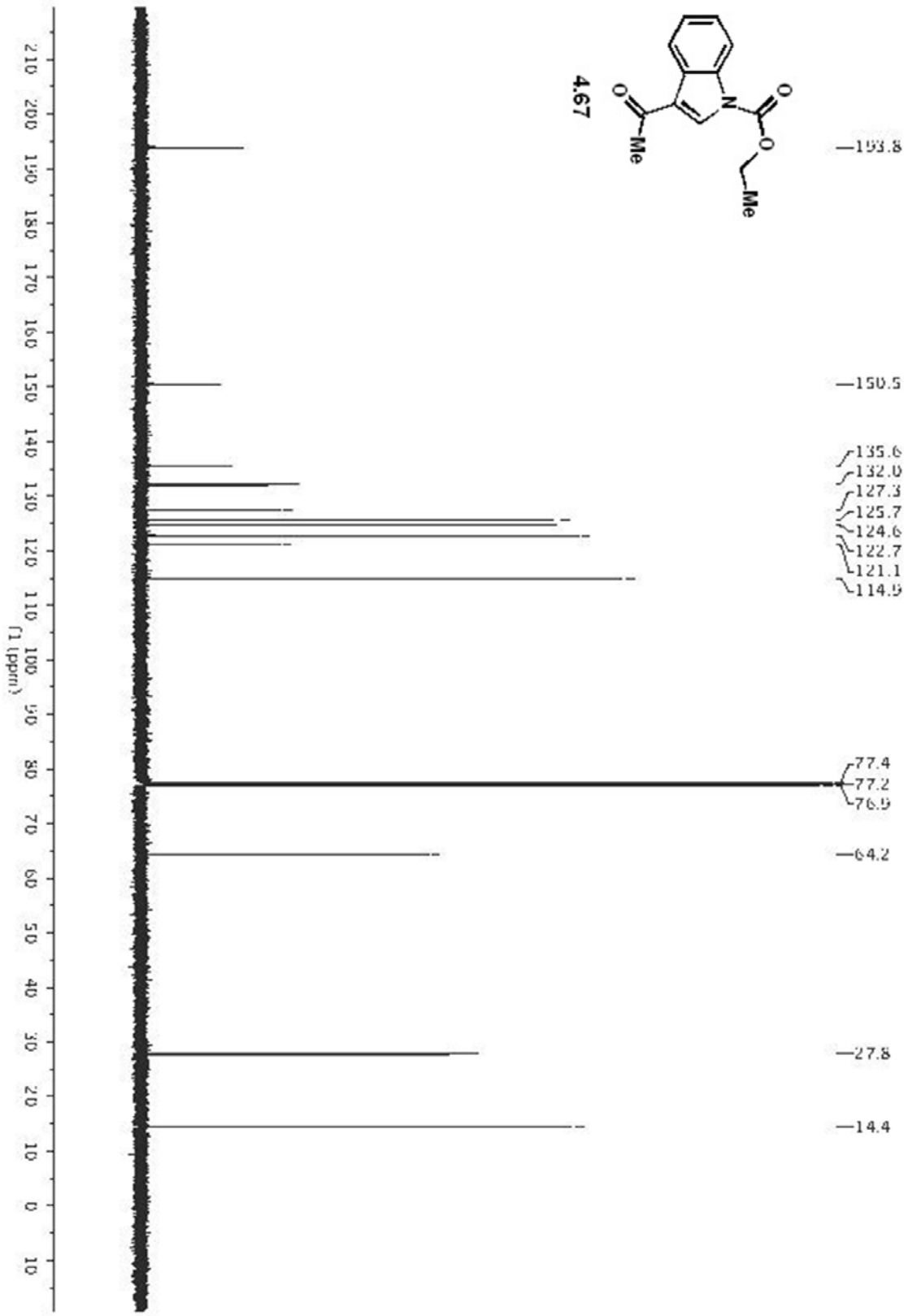

4.61
O2N
O
N
O
Me
150.3
143.8
138.3
130.3
128.5
119.7
117.2
115.3
108.4
64.1
14.3
ppm
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

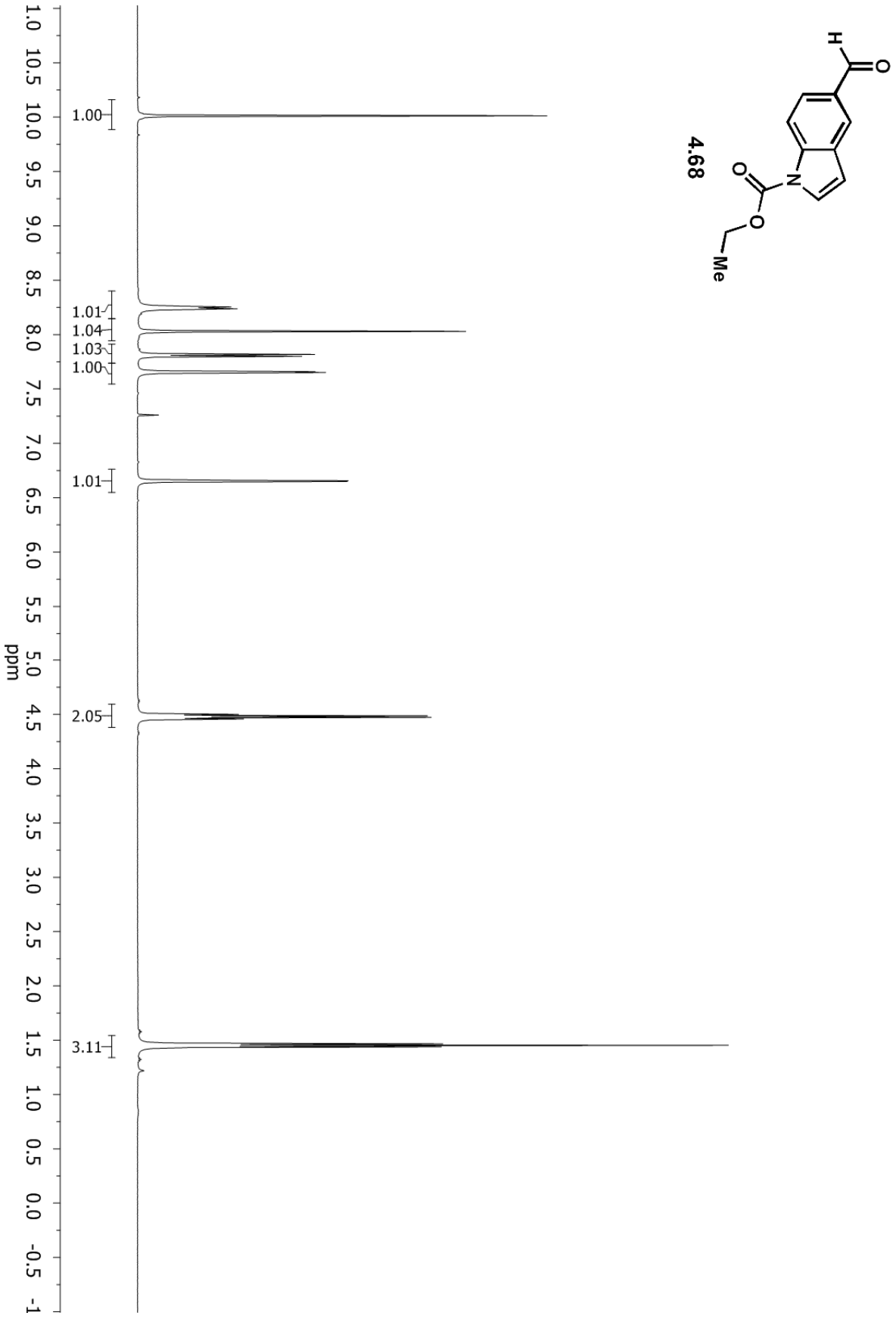

1.00
0.98
1.05
1.01
1.02
1.00
1.02
1.02
2.07
ppm

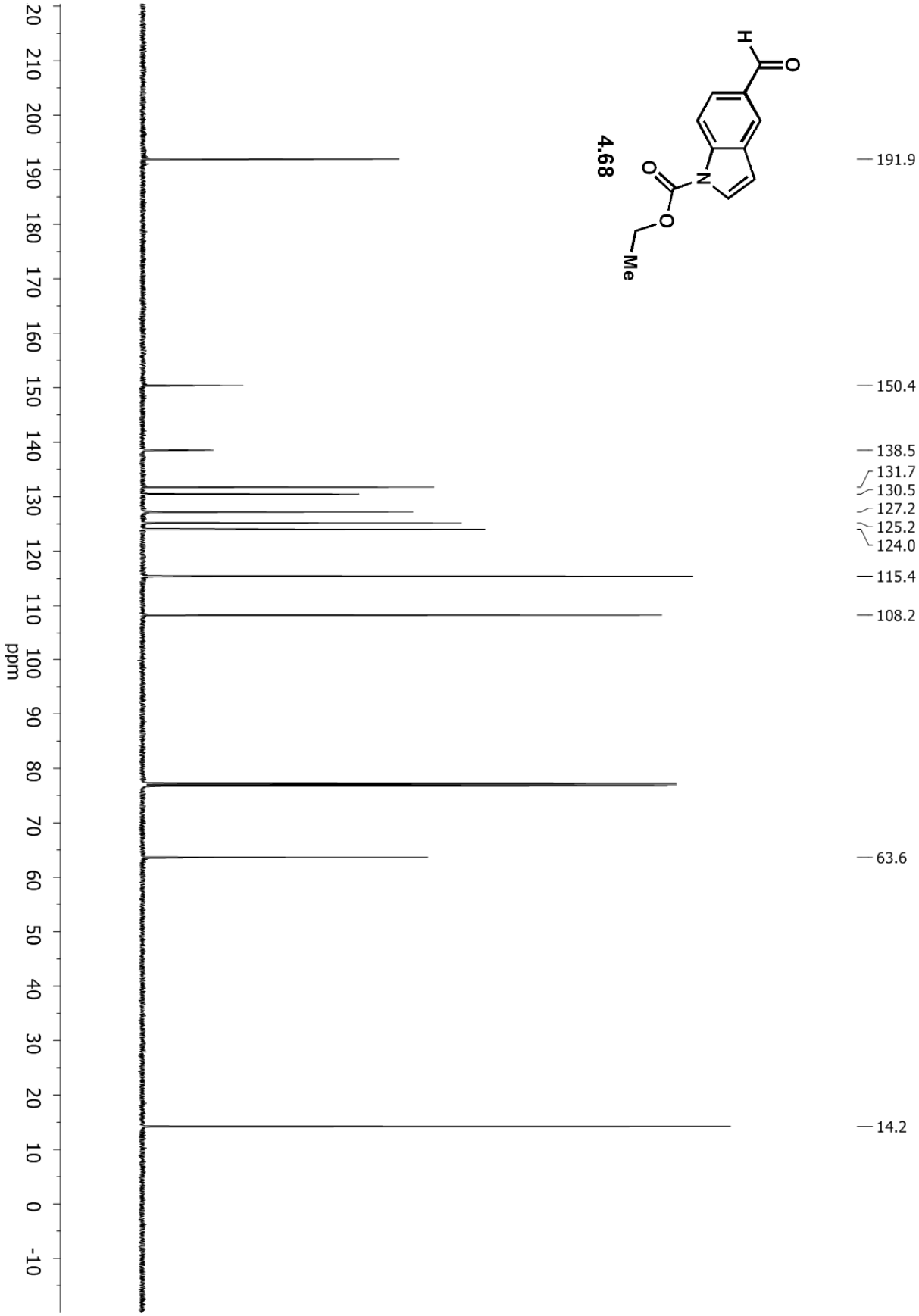

O2N
O
N
O
4.66

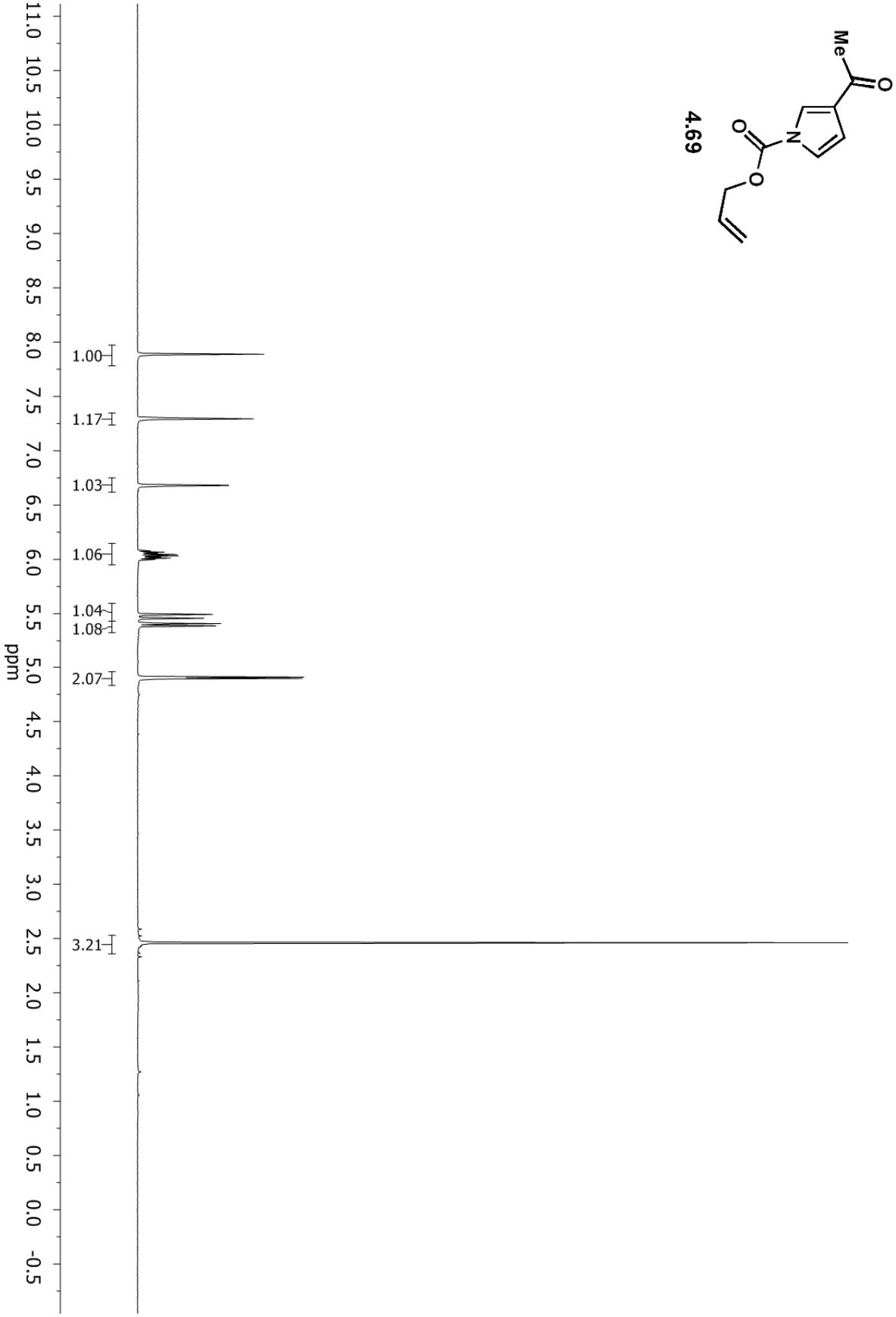

4.66
149.7
143.5
137.9
130.5
129.9
128.1
119.9
119.4
116.9
114.9
108.3
68.0
ppm

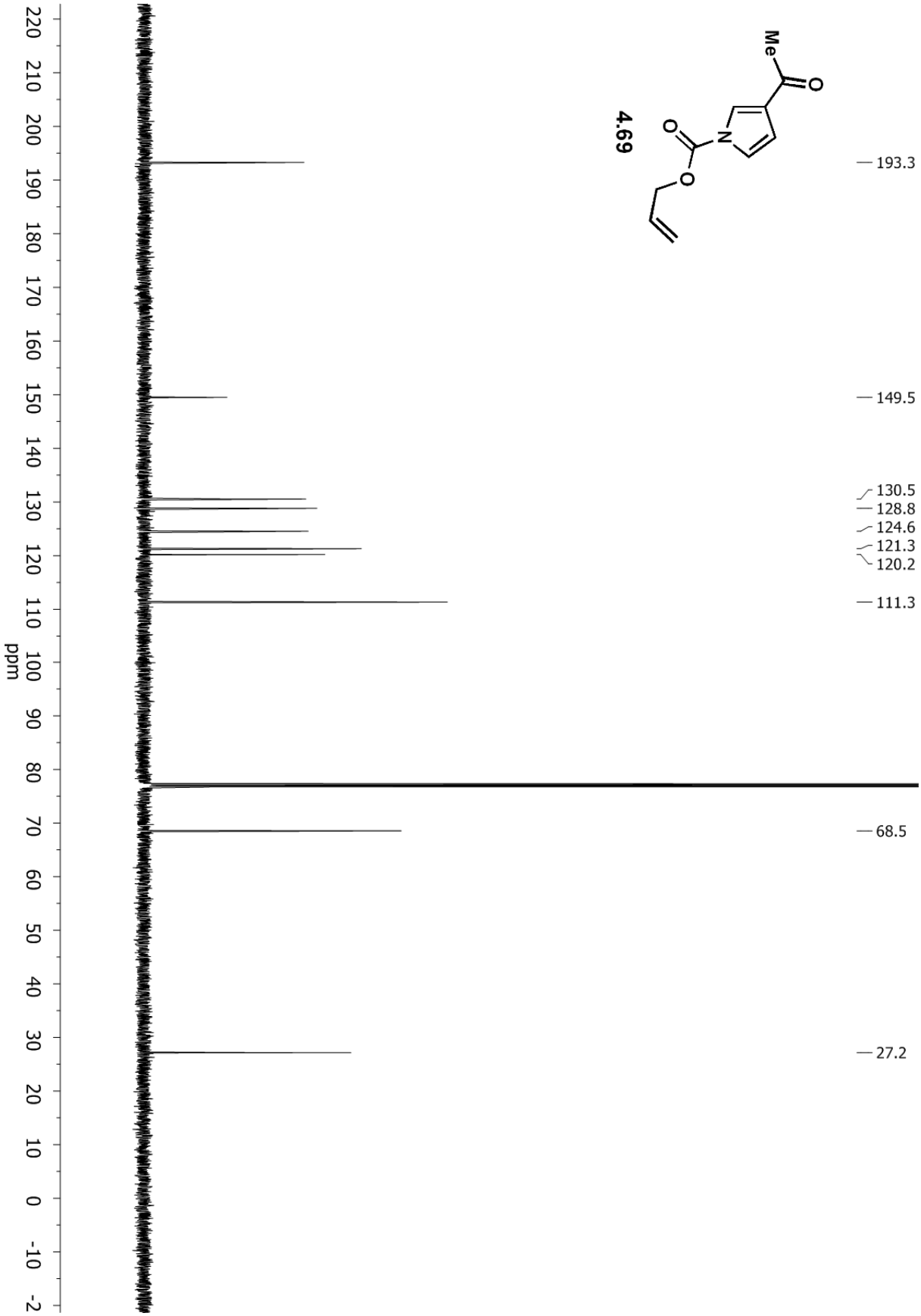

4.67
Me
Me
O
O
O
N
O
1.00
1.00
0.98
2.10
2.14
3.24
3.22
f1 (ppm)

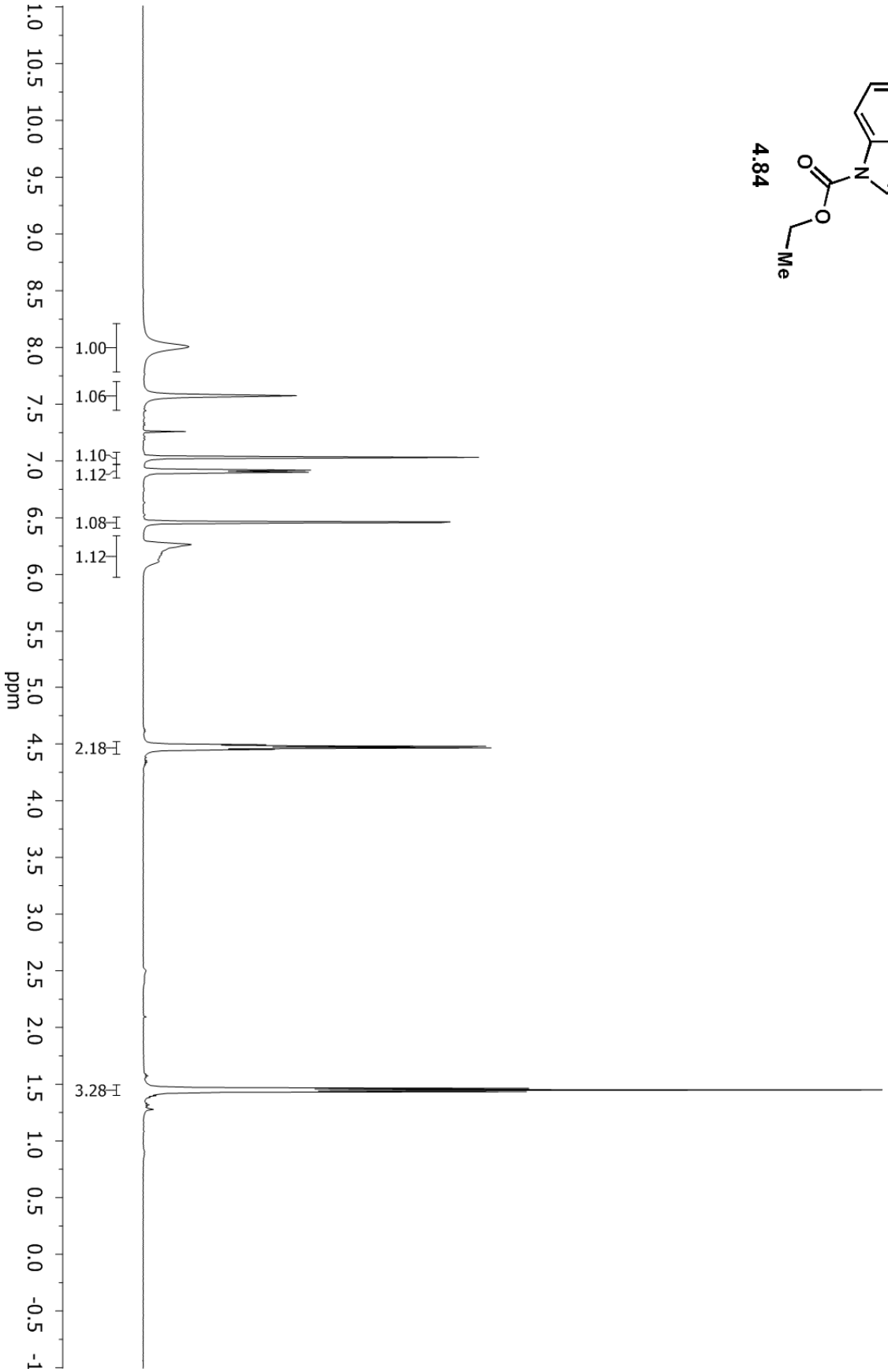

4.67
Me
O
N
O
O
Me
193.8
150.5
135.6
132.0
127.3
125.7
124.6
122.7
121.1
114.9
77.4
77.2
76.9
64.2
27.8
14.4
f1 (ppm)

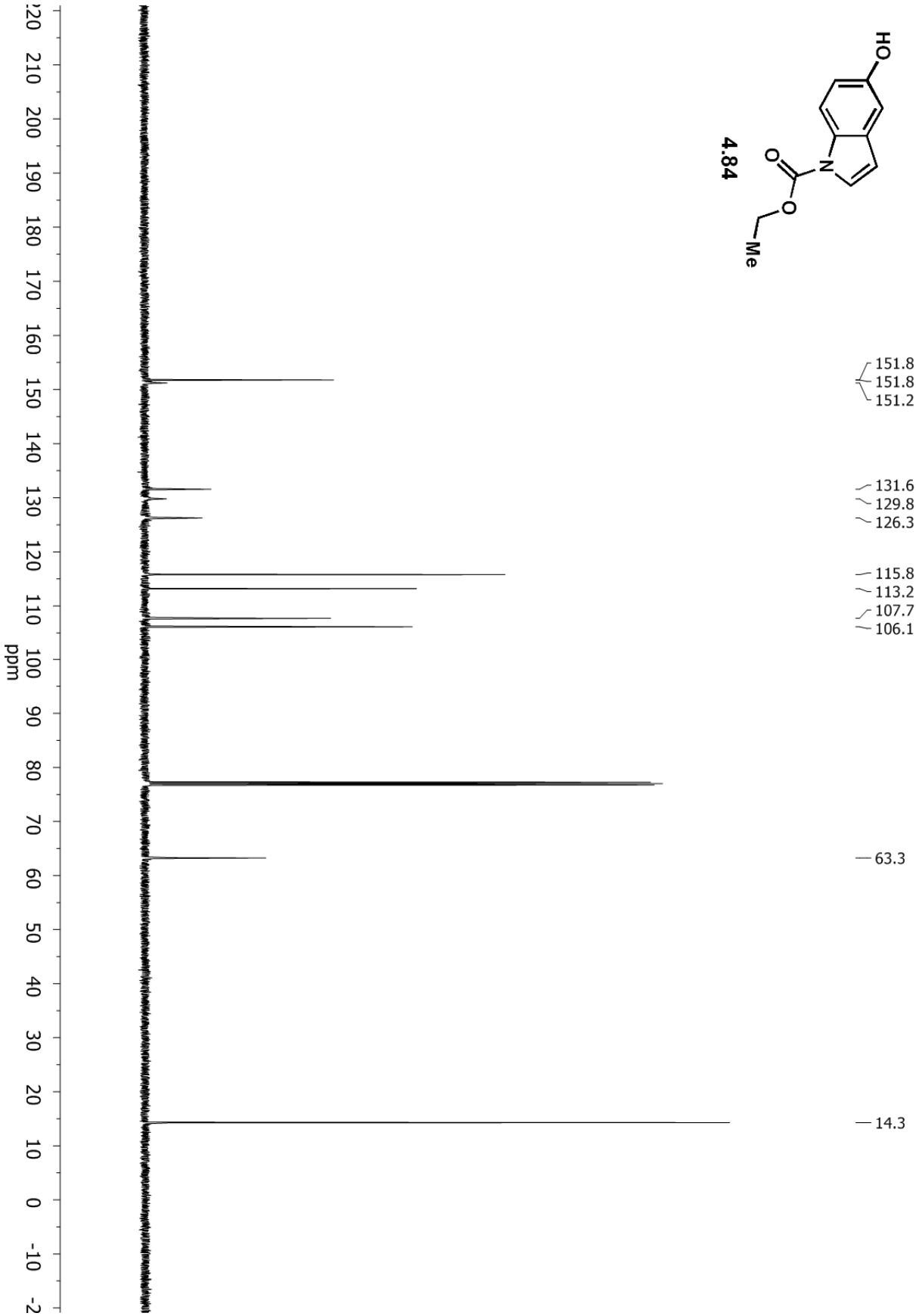

4.68
1.00
1.01
1.04
1.03
1.00
1.01
2.05
3.11
ppm

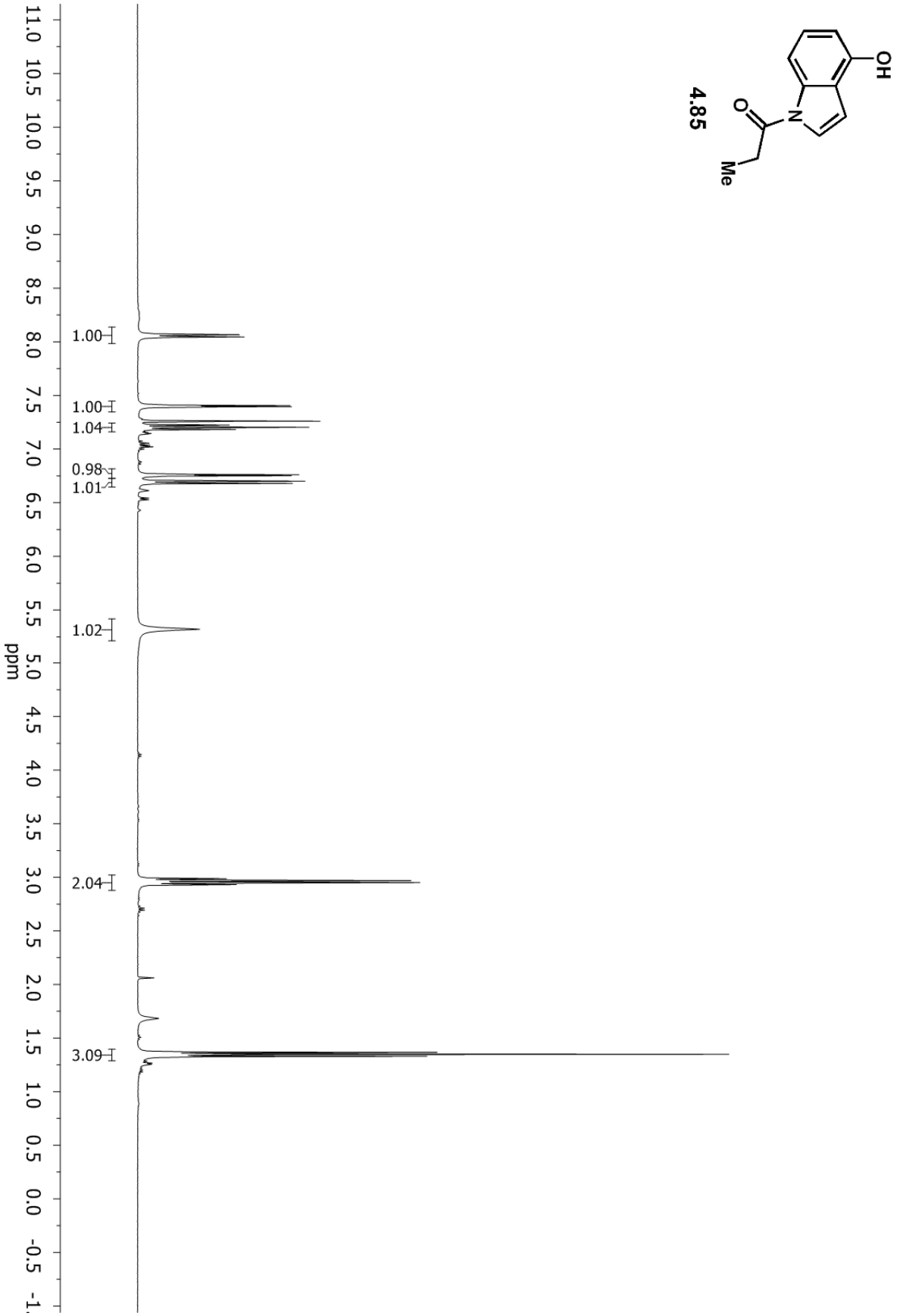

4.68
191.9
150.4
138.5
131.7
130.5
127.2
125.2
124.0
115.4
108.2
63.6
14.2
ppm

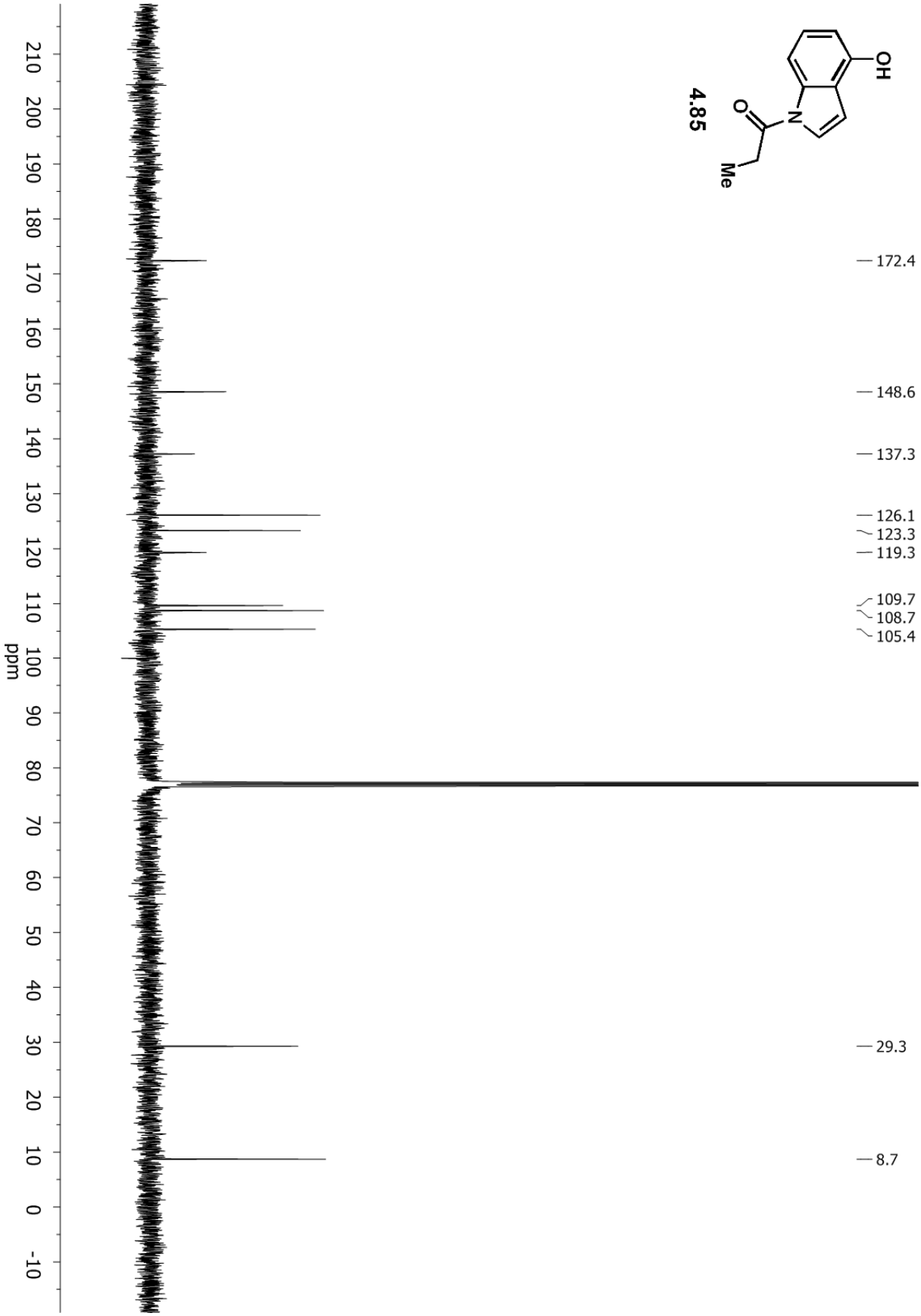

4.69
Me
O
O
N
O
O
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
ppm
1.00
1.17
1.03
1.06
1.04
1.08
2.07
3.21

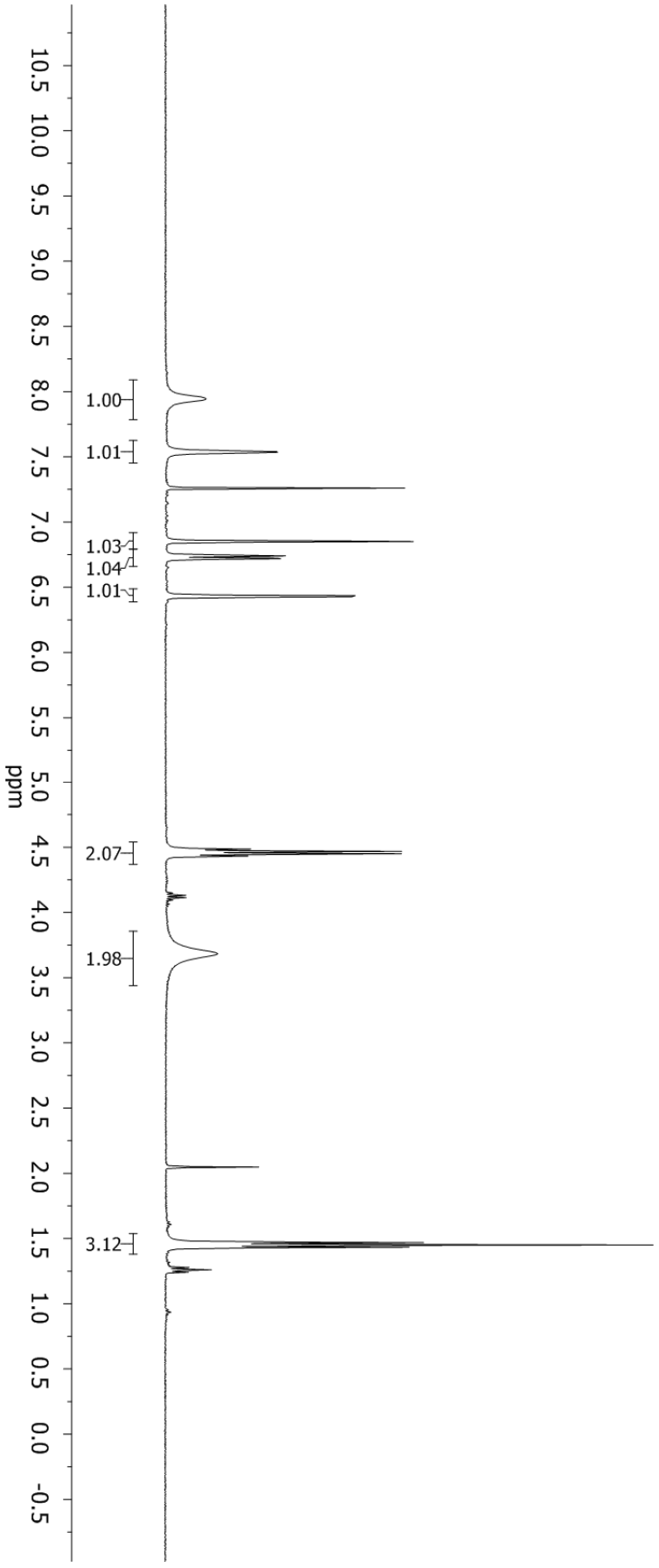

4.69
Me
O
O
N
O
193.3
149.5
130.5
128.8
124.6
121.3
120.2
111.3
68.5
27.2
ppm
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -2

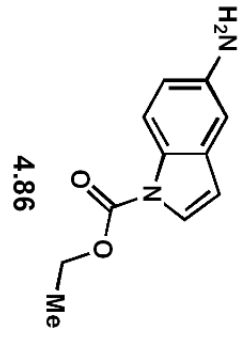

4.84
HO
O
N
O
Me
1.00
1.06
1.10
1.12
1.08
1.12
2.18
3.28
ppm
1.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1


4.84
HO
O
N
O
Me
151.8
151.8
151.2
131.6
129.8
126.3
115.8
113.2
107.7
106.1
63.3
14.3
ppm
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -2

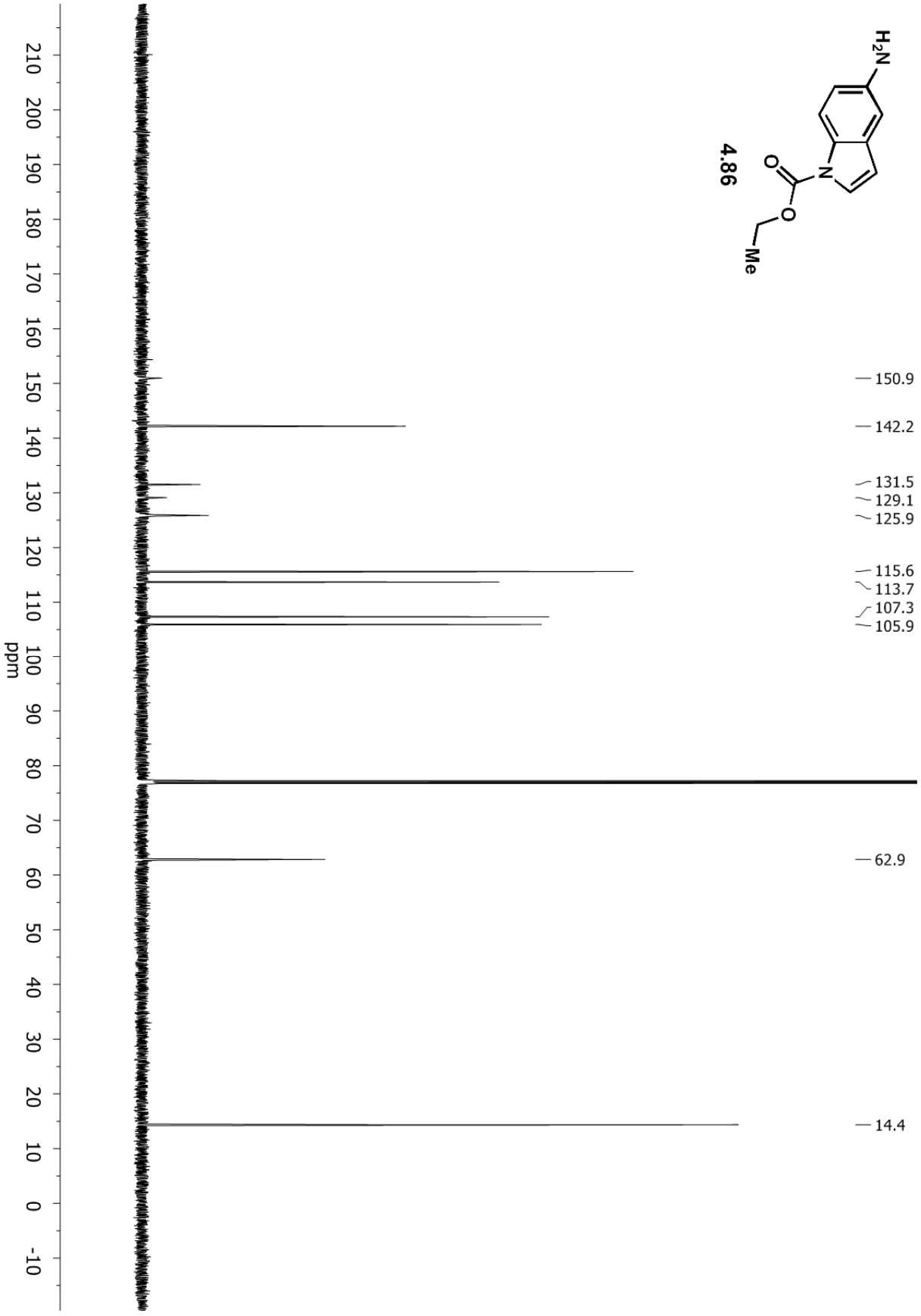

4.85
OH
O
N
Me
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.
ppm
1.00
1.00
1.04
0.98
1.01
1.02
2.04
3.09

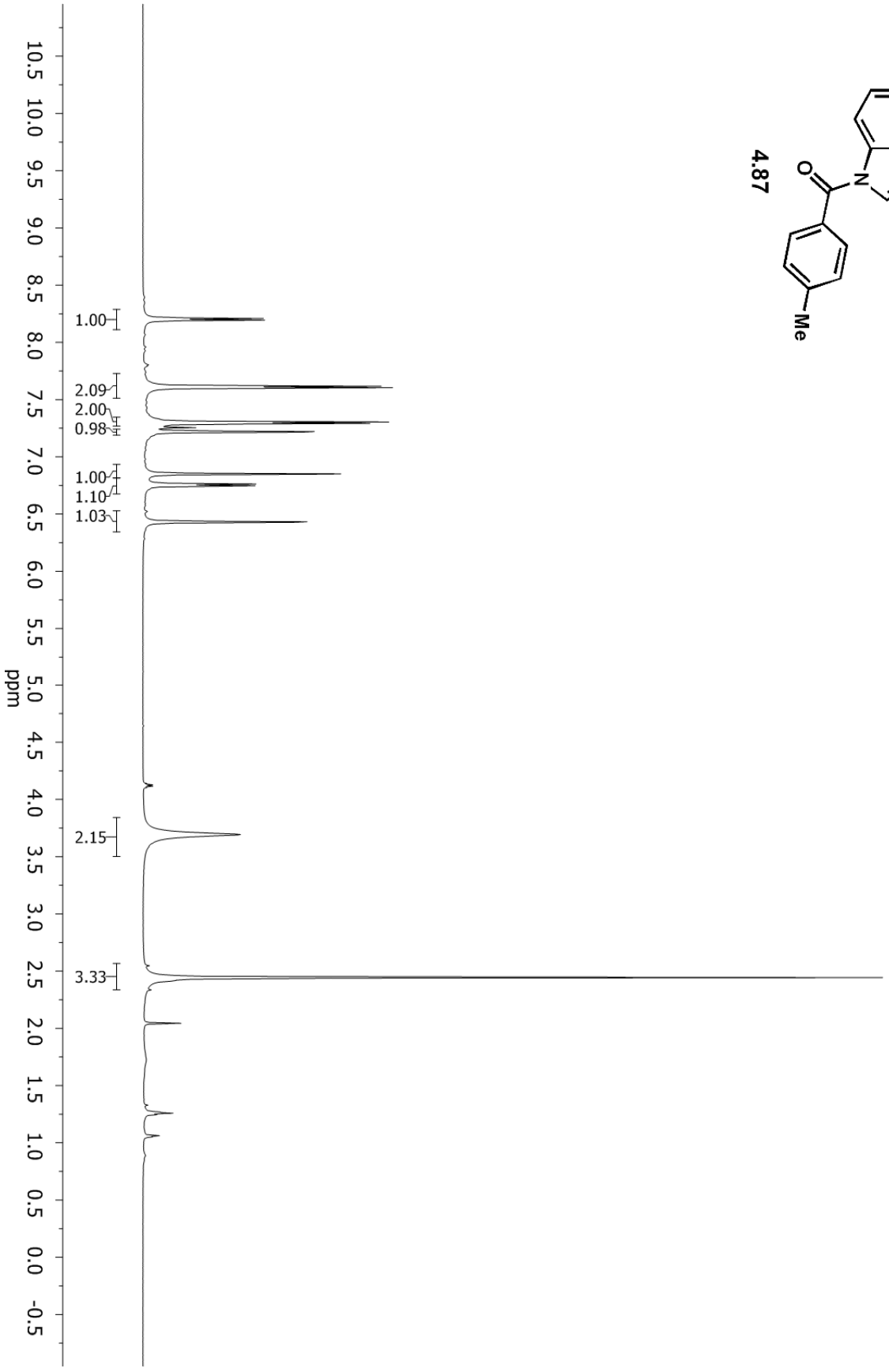

4.85
OH
N
O
Me
172.4
148.6
137.3
126.1
123.3
119.3
109.7
108.7
105.4
29.3
8.7
ppm
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

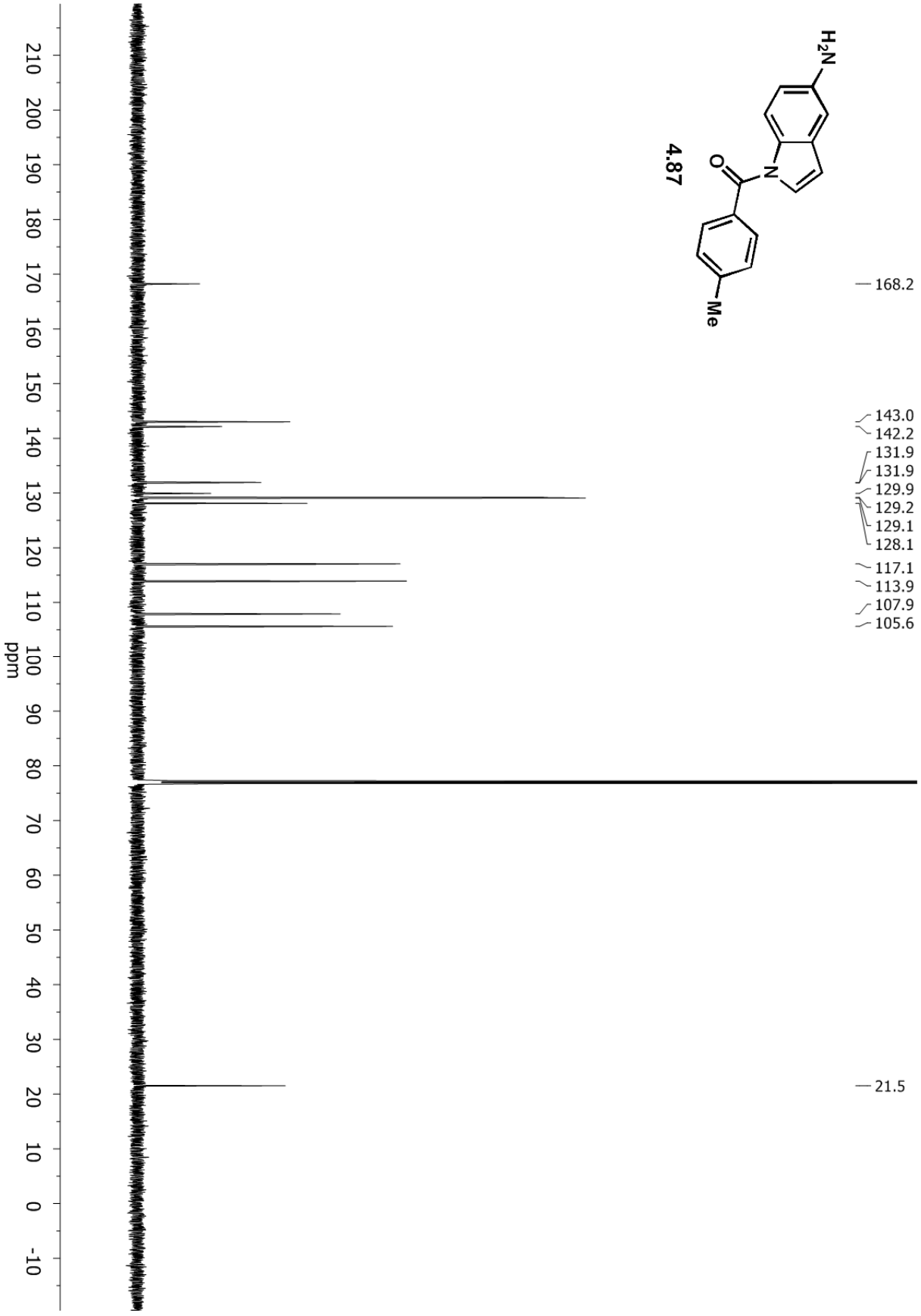

10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
ppm
1.00
1.01
1.03
1.04
1.01
2.07
1.98
3.12

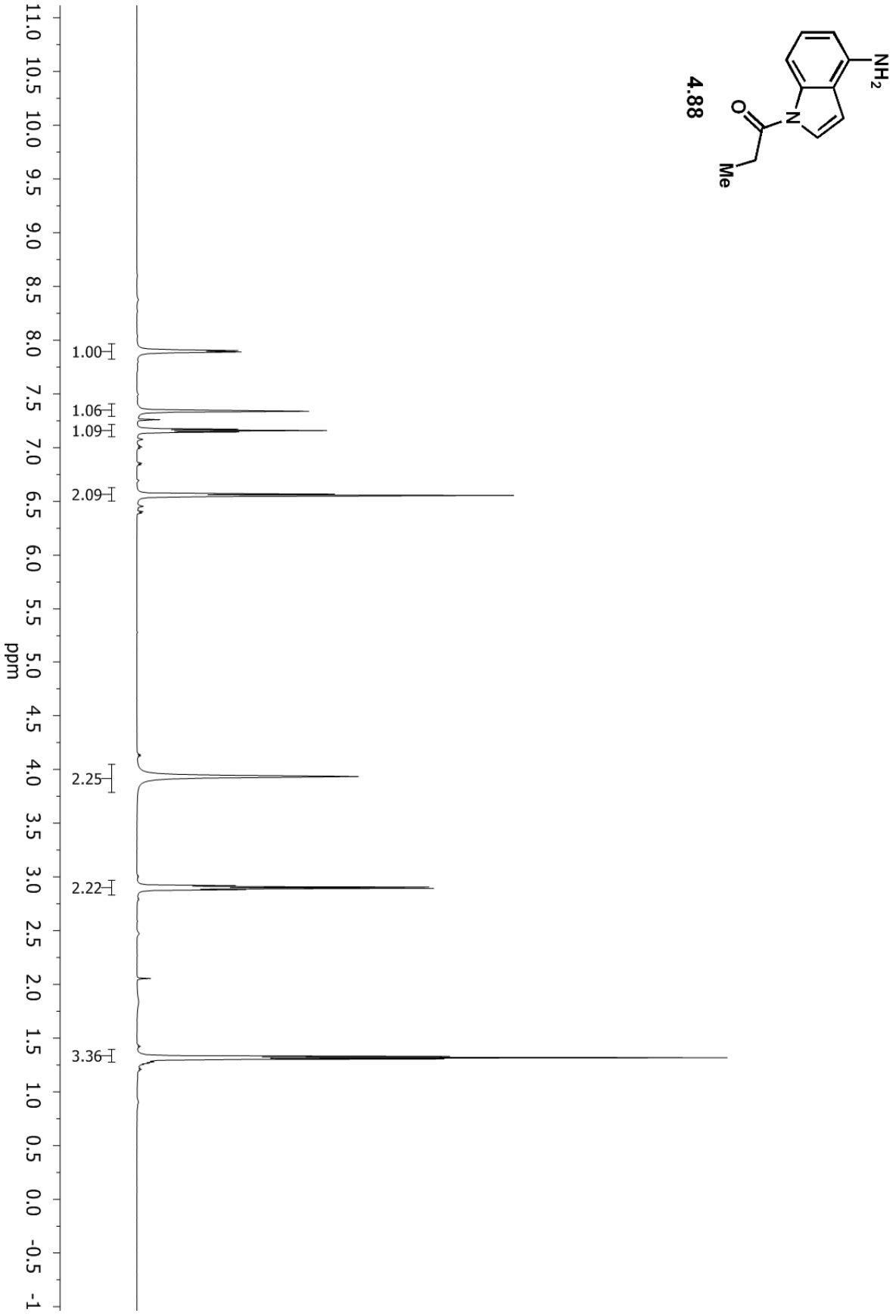

H2N
O
N
O
Me

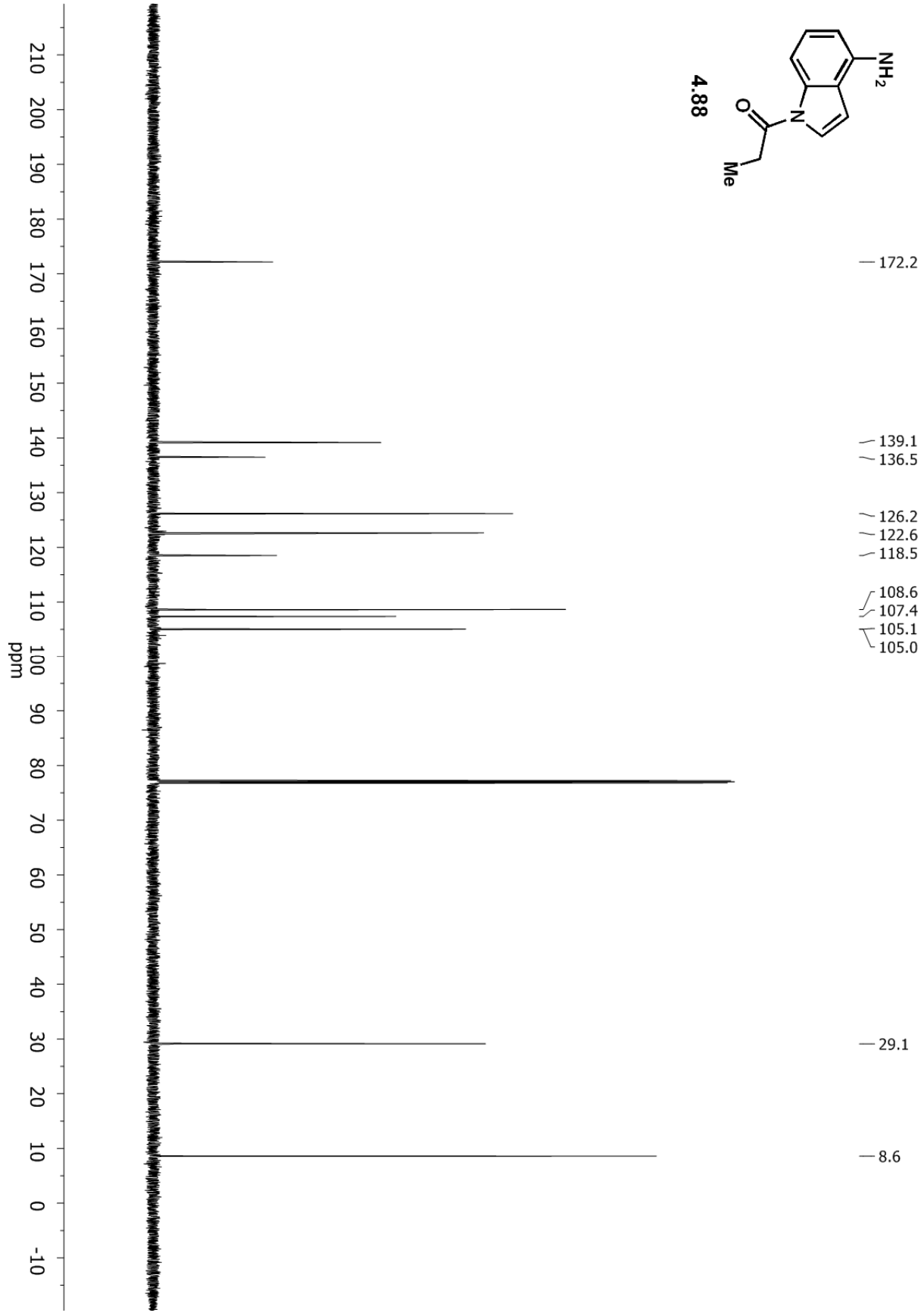
4.86

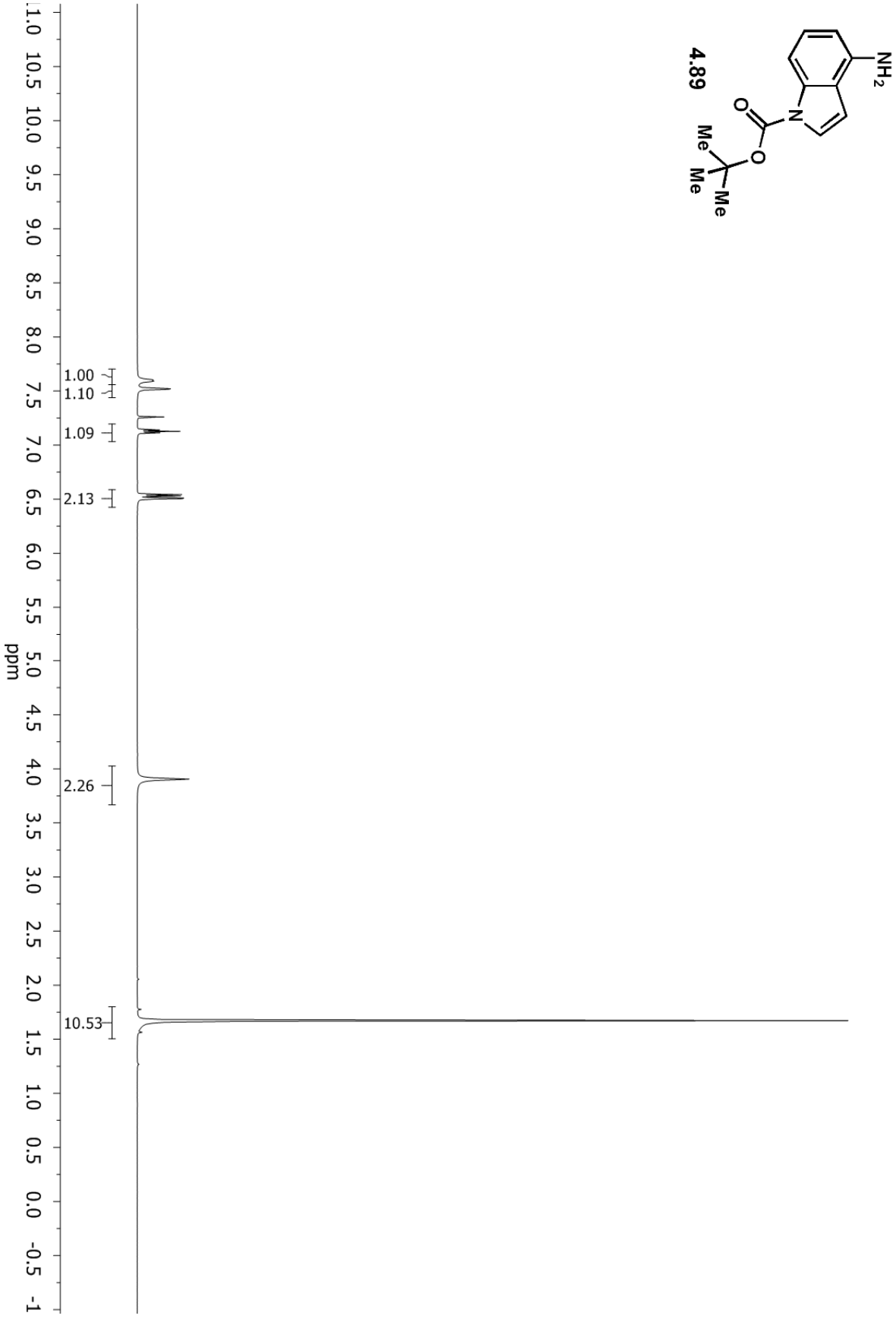

H2N
4.86
O
N
O
Me
150.9
142.2
131.5
129.1
125.9
115.6
113.7
107.3
105.9
62.9
14.4
ppm
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

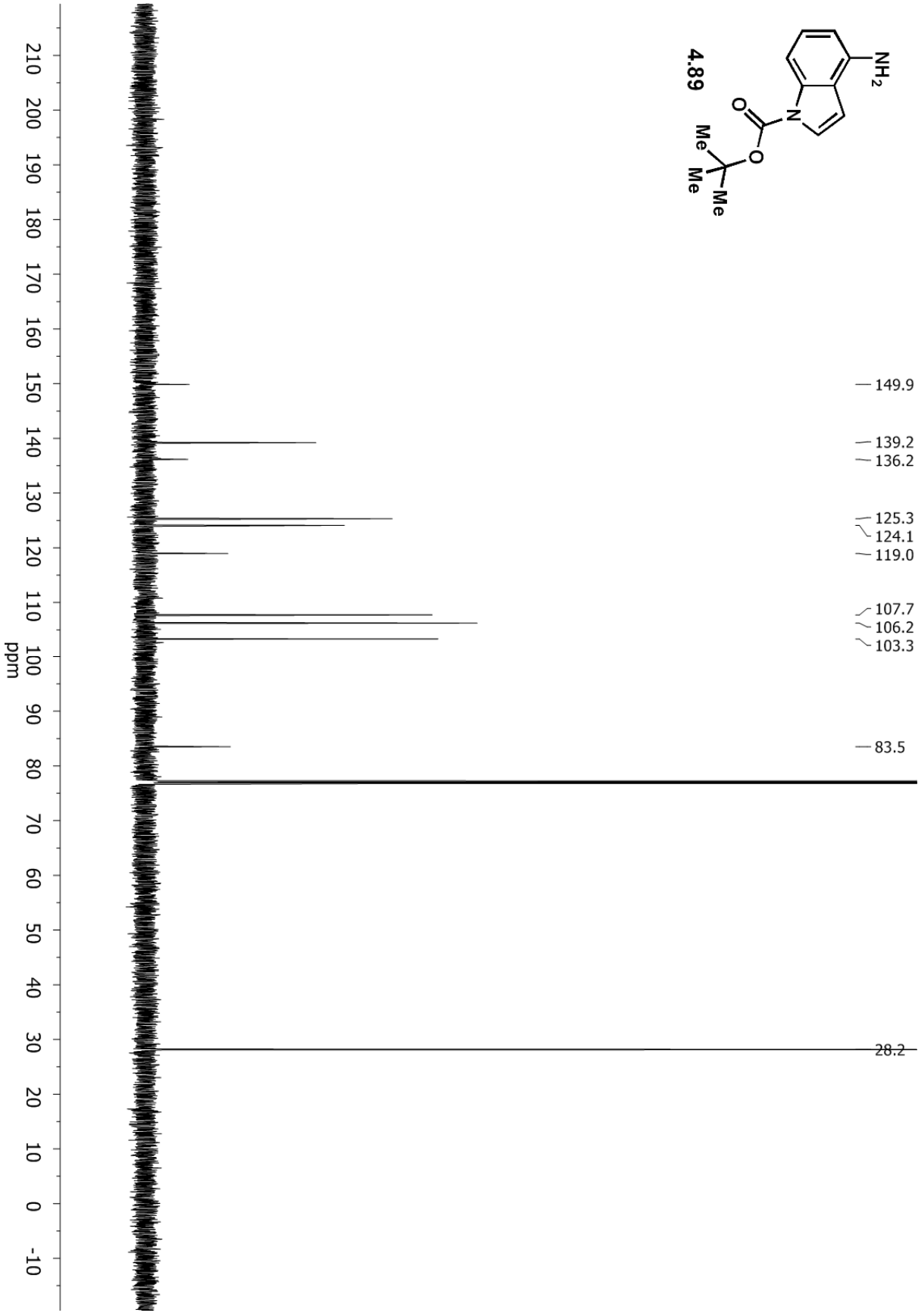

4.87
H2N
O
N
Me
1.00
2.09
2.00
0.98
1.00
1.10
1.03
2.15
3.33
ppm

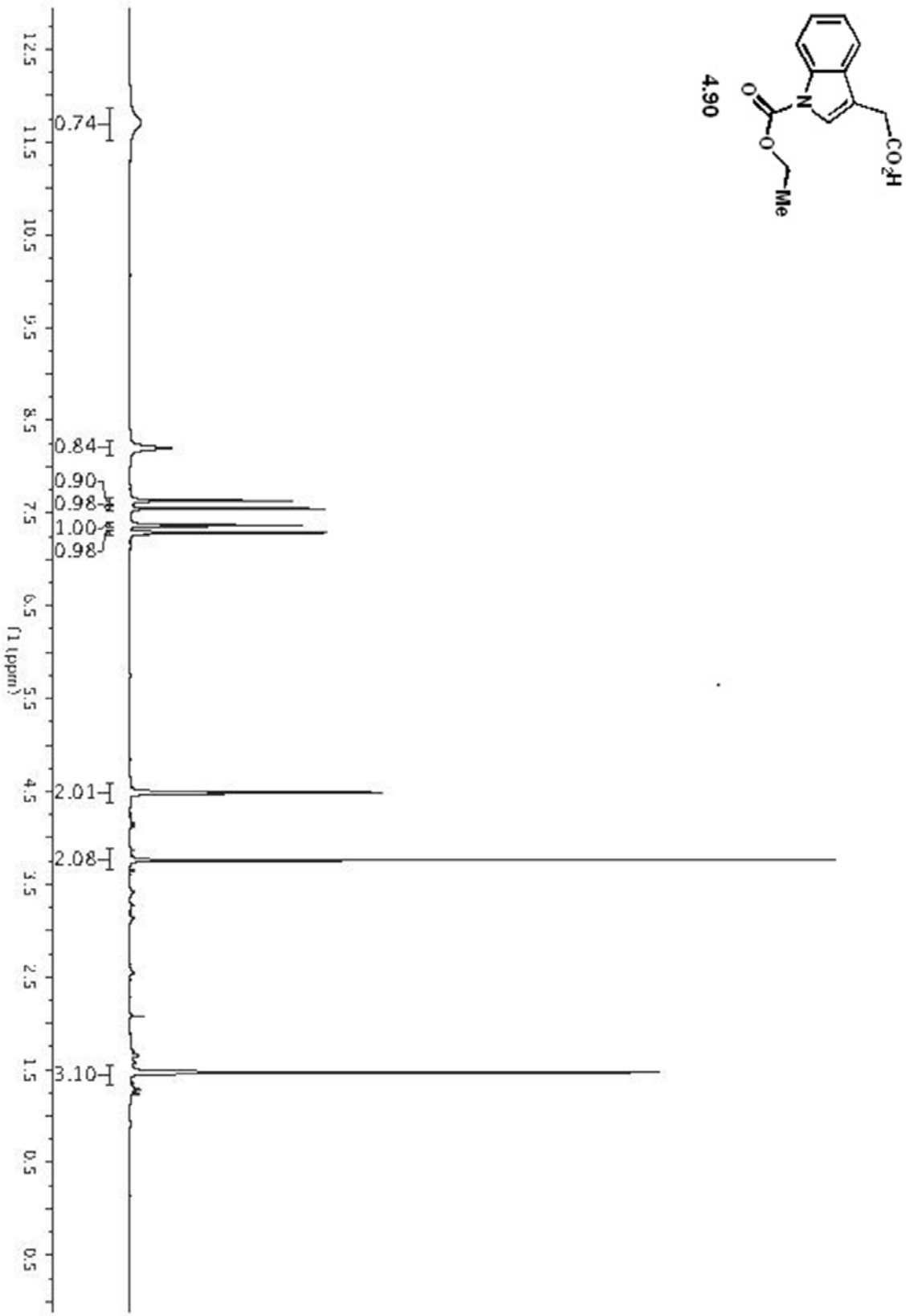

4.87
H2N
O
N
Me
168.2
143.0
142.2
131.9
131.9
129.9
129.2
129.1
128.1
117.1
113.9
107.9
105.6
21.5
ppm
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

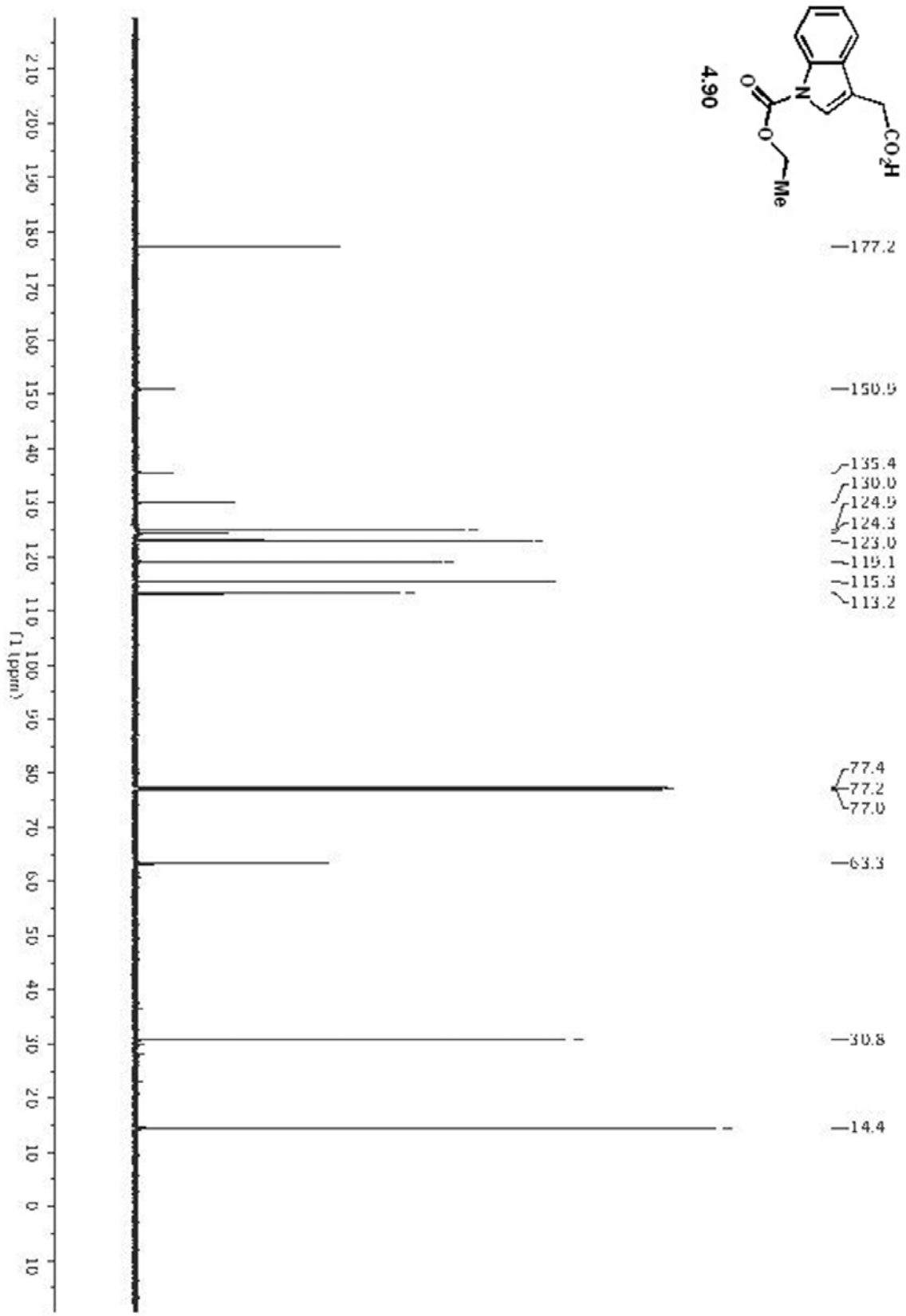

4.88
NH2
O
N
Me
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
ppm
1.00
1.06
1.09
2.09
2.25
2.22
3.36

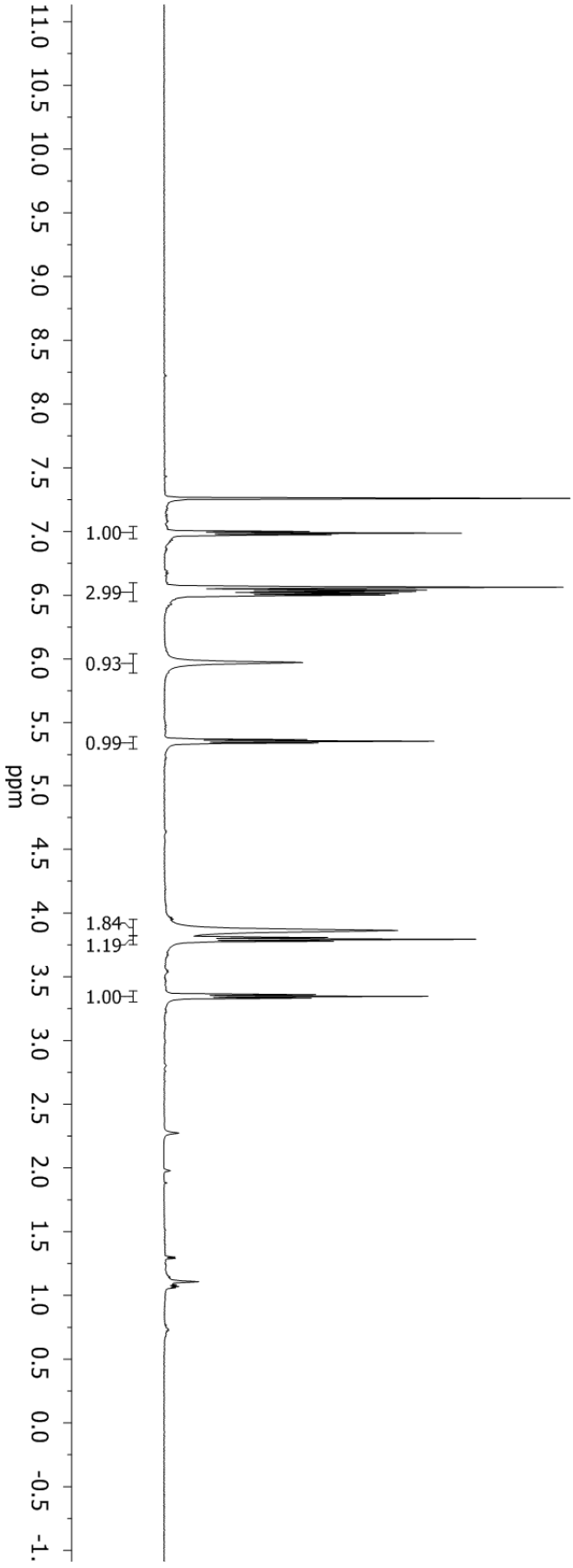

4.88
NH2
O
N
Me
172.2
139.1
136.5
126.2
122.6
118.5
108.6
107.4
105.1
105.0
29.1
8.6
ppm
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

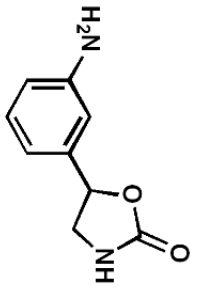

4.89
NH2
O
N
O
Me
Me
Me
1.00
1.10
1.09
2.13
2.26
10.53
ppm
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1


4.89
NH2
O
N
O
Me
Me
Me
149.9
139.2
136.2
125.3
124.1
119.0
107.7
106.2
103.3
83.5
28.2
ppm
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

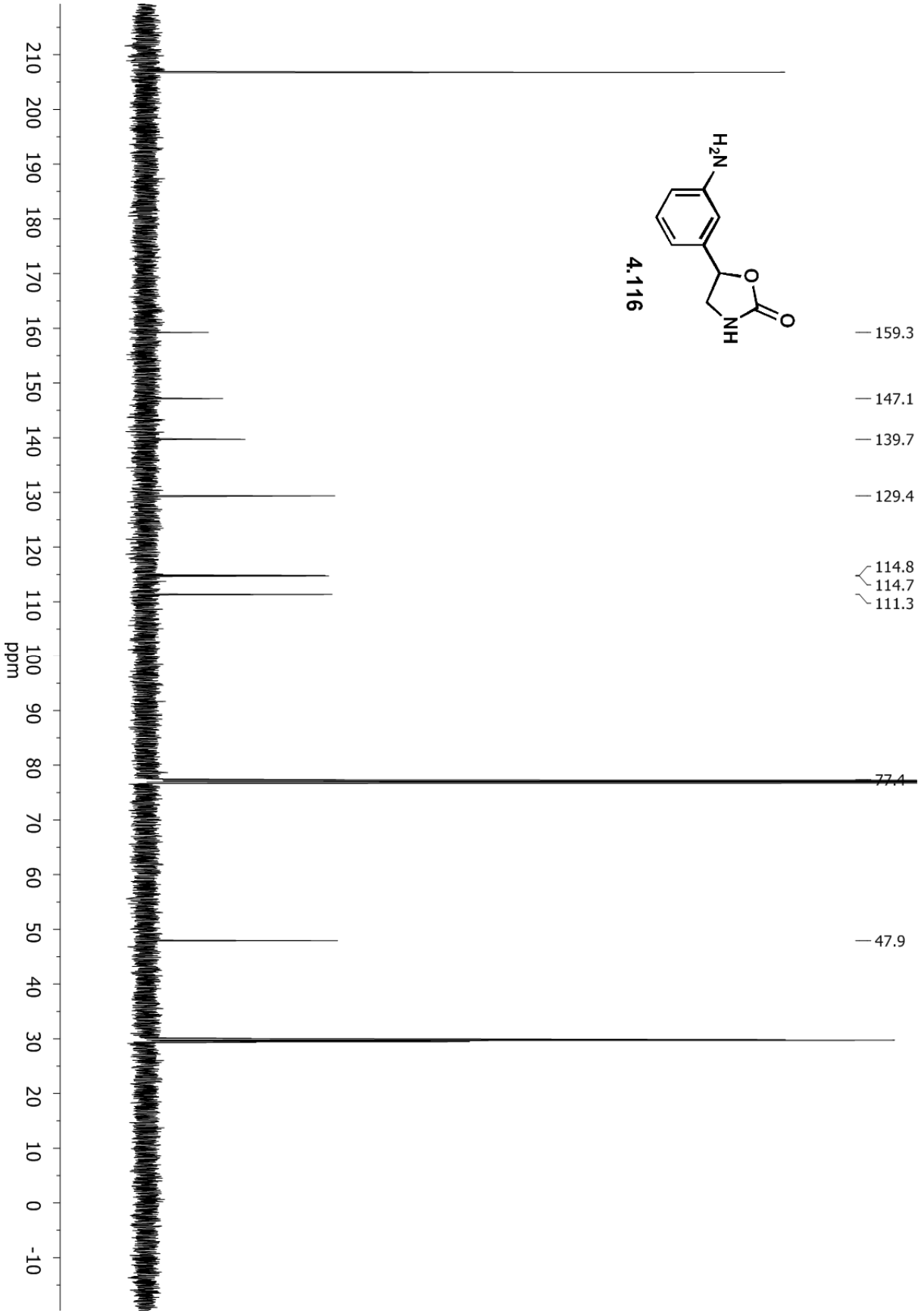

4.90
0.74
0.84
0.90
0.98
1.00
0.98
2.01
2.08
3.10
f1 (ppm)

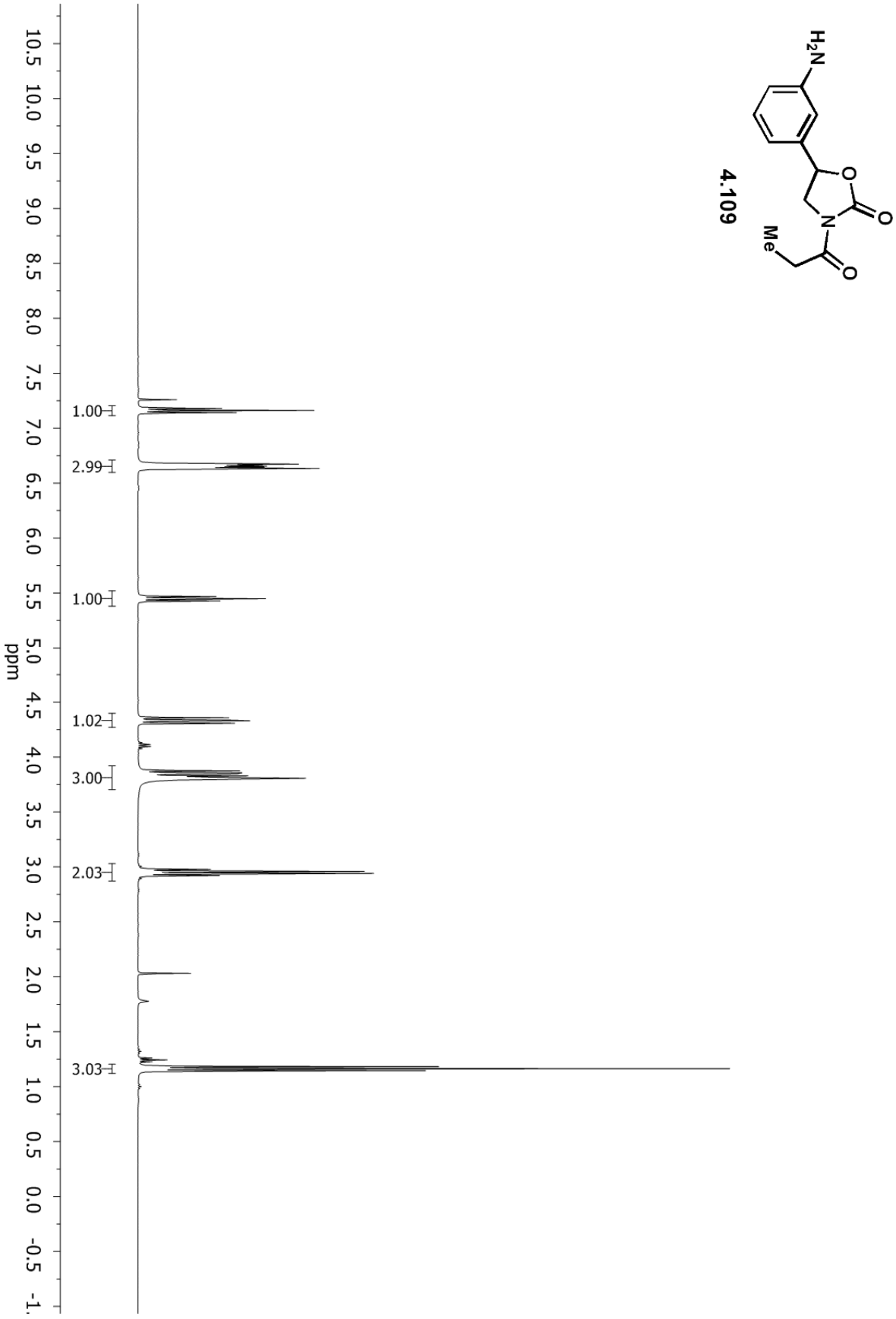

4.90
N
O
O
Me
CO2H
177.2
150.9
135.4
130.0
124.9
124.3
123.0
119.1
115.3
113.2
77.4
77.2
77.0
63.3
30.8
14.4
f1 (ppm)

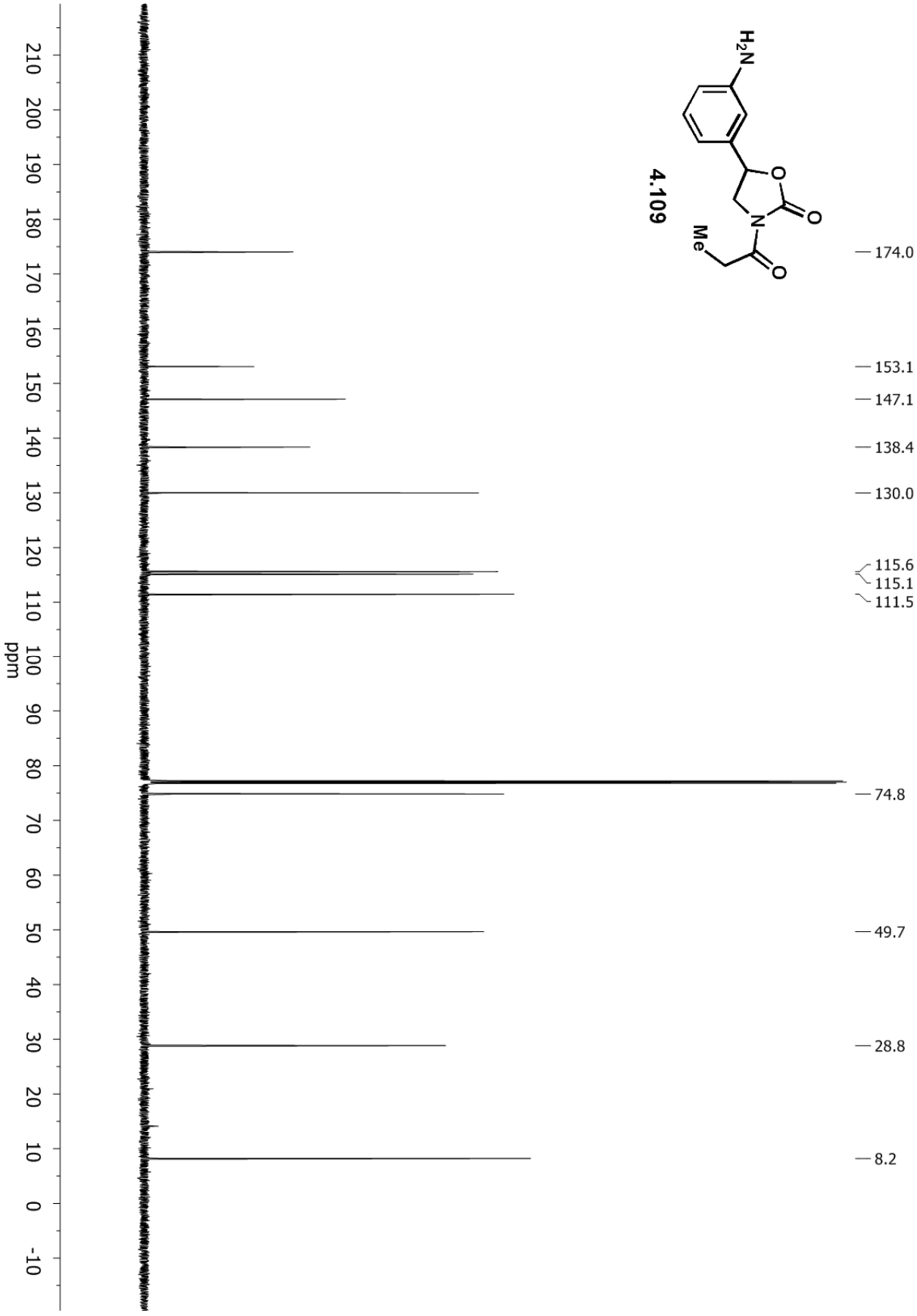

11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.
ppm
1.00
2.99
0.93
0.99
1.84
1.19
1.00


H2N
O
O
NH

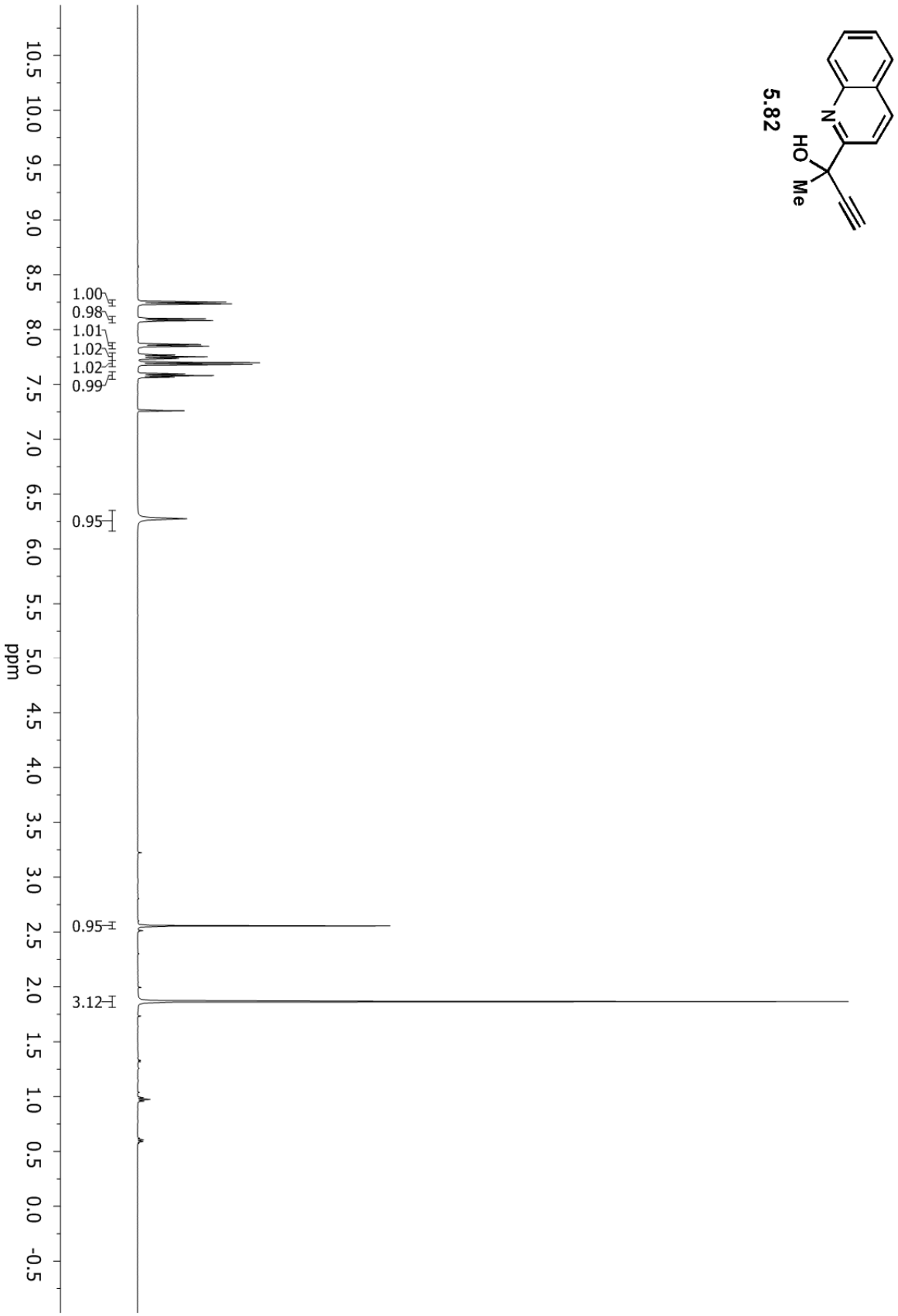
4.116

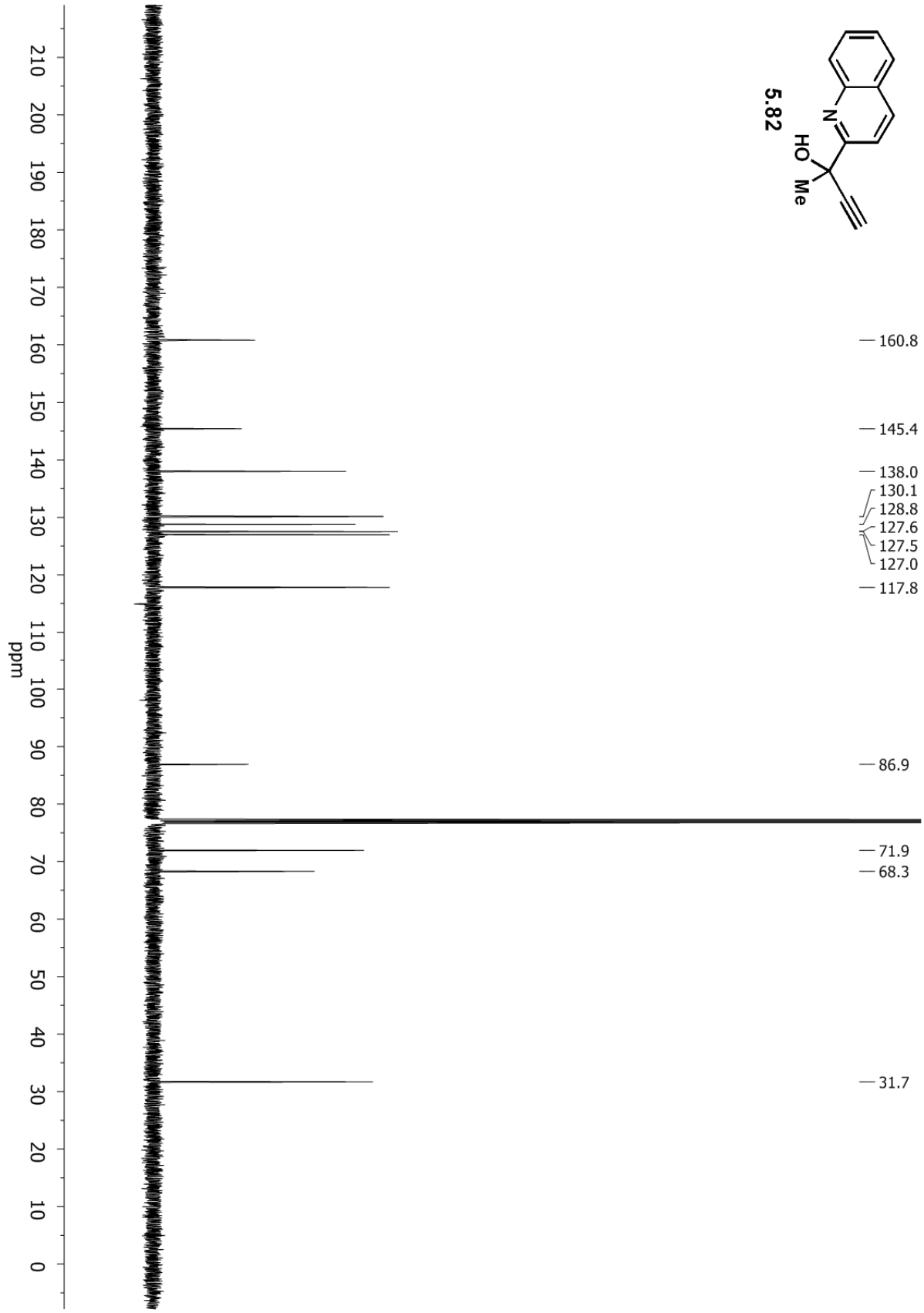

4.116
H2N
O
O
NH
159.3
147.1
139.7
129.4
114.8
114.7
111.3
77.4
47.9
ppm
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

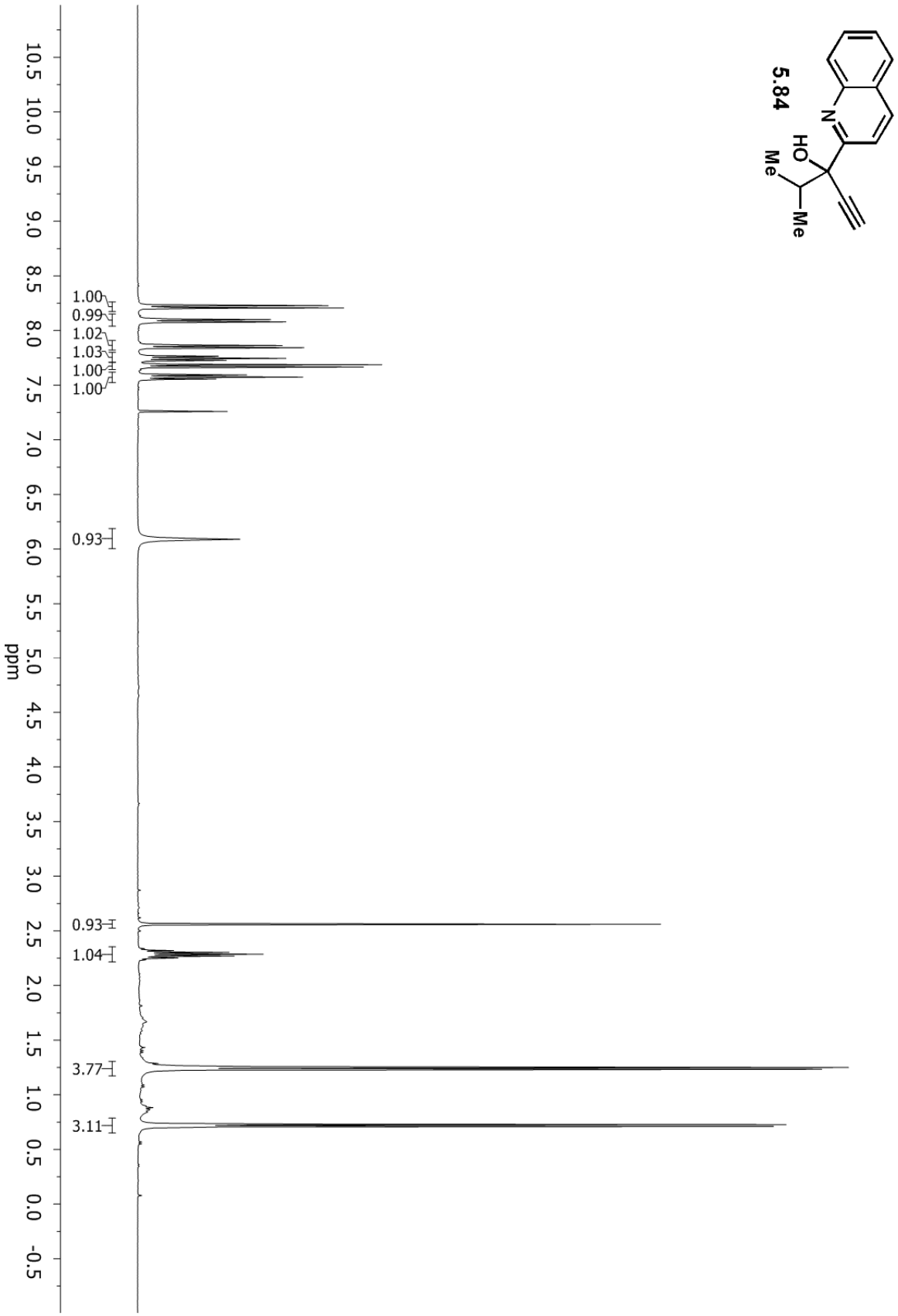

4.109
H2N
O
O
N
Me
O
1.00
2.99
1.00
1.02
3.00
2.03
3.03
ppm
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.

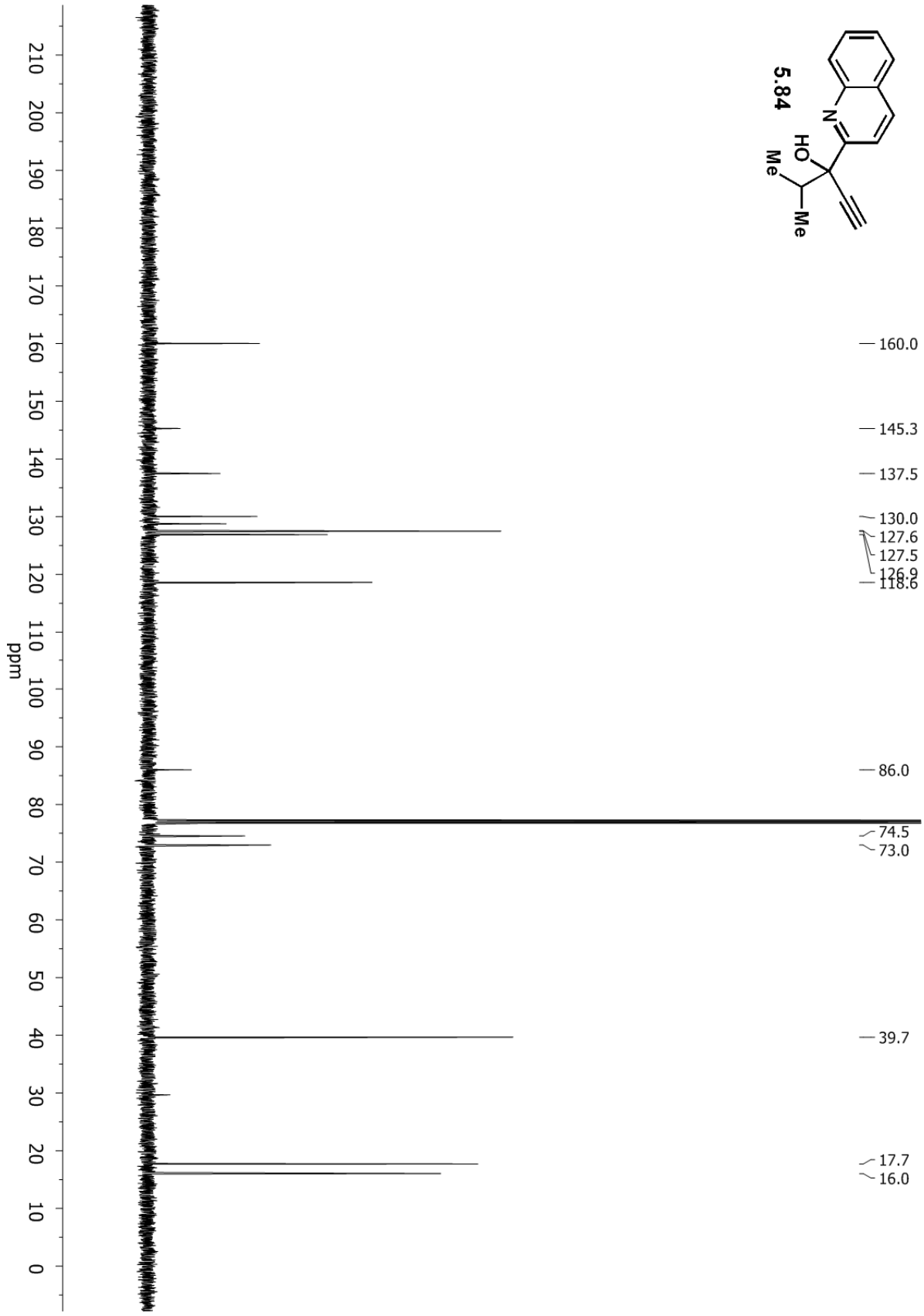

4.109
174.0
153.1
147.1
138.4
130.0
115.6
115.1
111.5
74.8
49.7
28.8
8.2
ppm

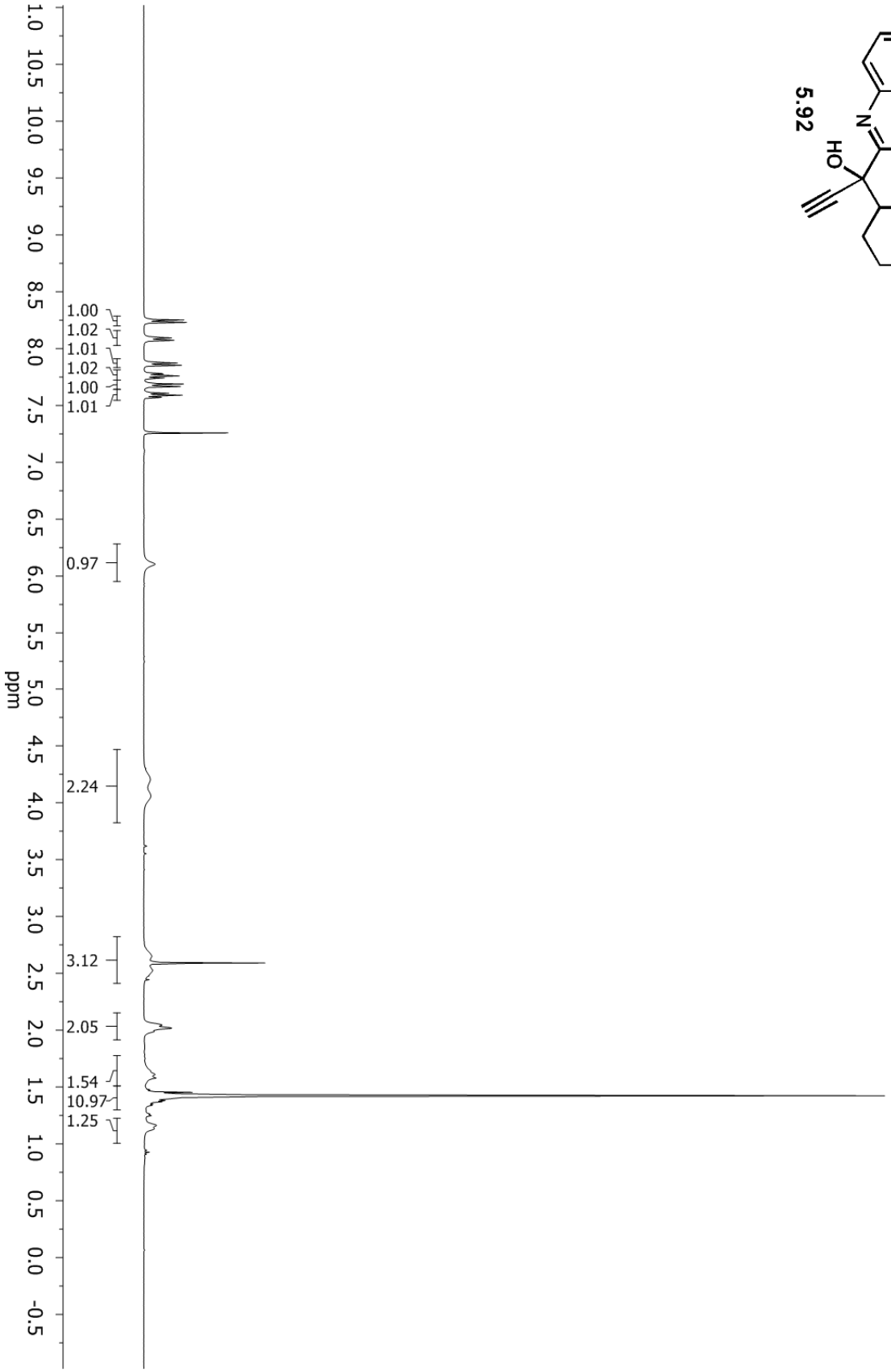
Appendix 4: Selected Spectra for Compounds Disclosed in Chapter 5

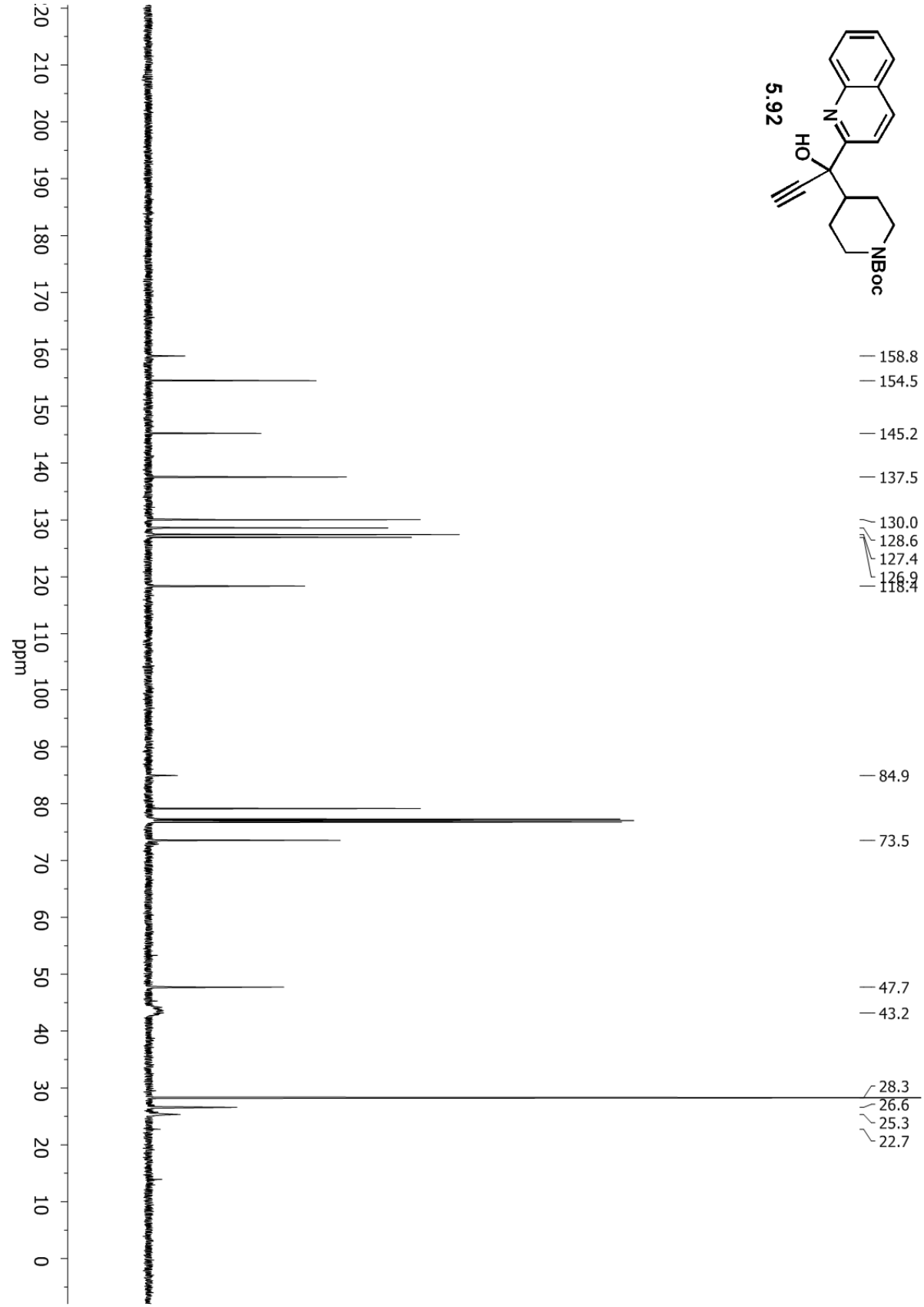

5.82
HO
Me
N
1.00
0.98
1.01
1.02
1.02
0.99
0.95
0.95
3.12
ppm
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5


5.82
HO
Me
N
160.8
145.4
138.0
130.1
128.8
127.6
127.5
127.0
117.8
86.9
71.9
68.3
31.7
ppm
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

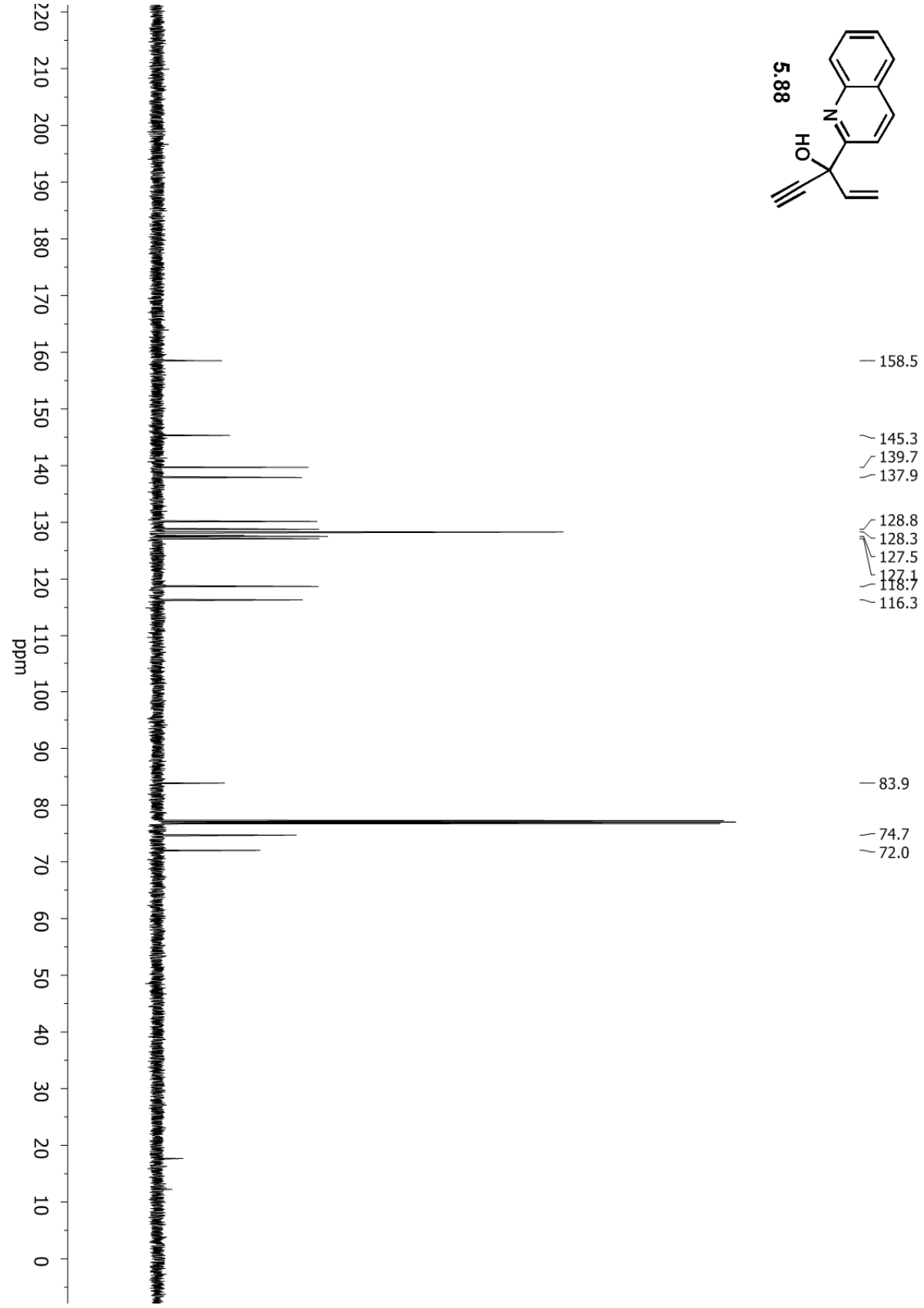

5.84
N
HO
Me
Me
1.00
0.99
1.02
1.03
1.00
1.00
0.93
0.93
1.04
3.77
3.11
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
ppm

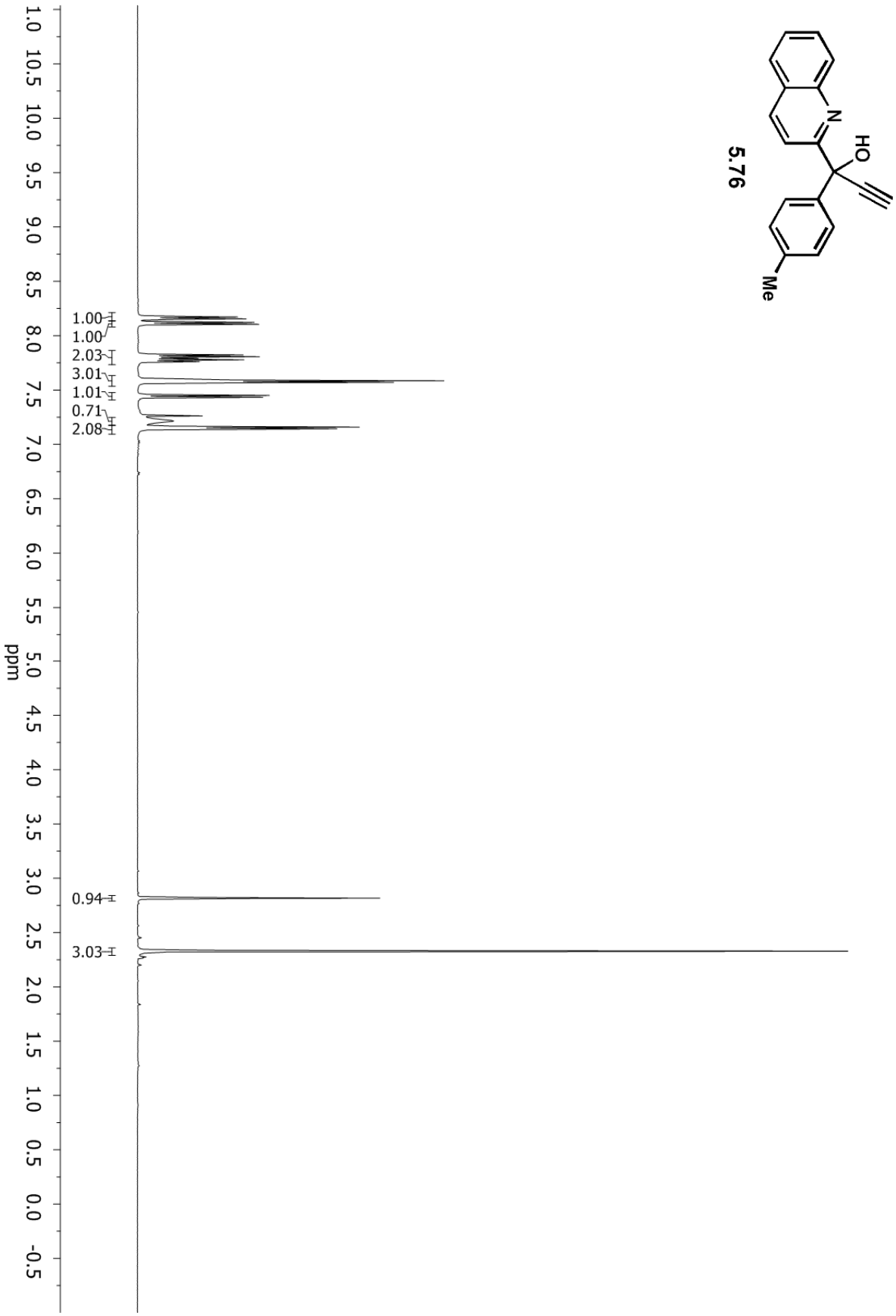

5.84
N
HO
Me
Me
160.0
145.3
137.5
130.0
127.6
127.5
126.9
118.6
86.0
74.5
73.0
39.7
17.7
16.0
ppm
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

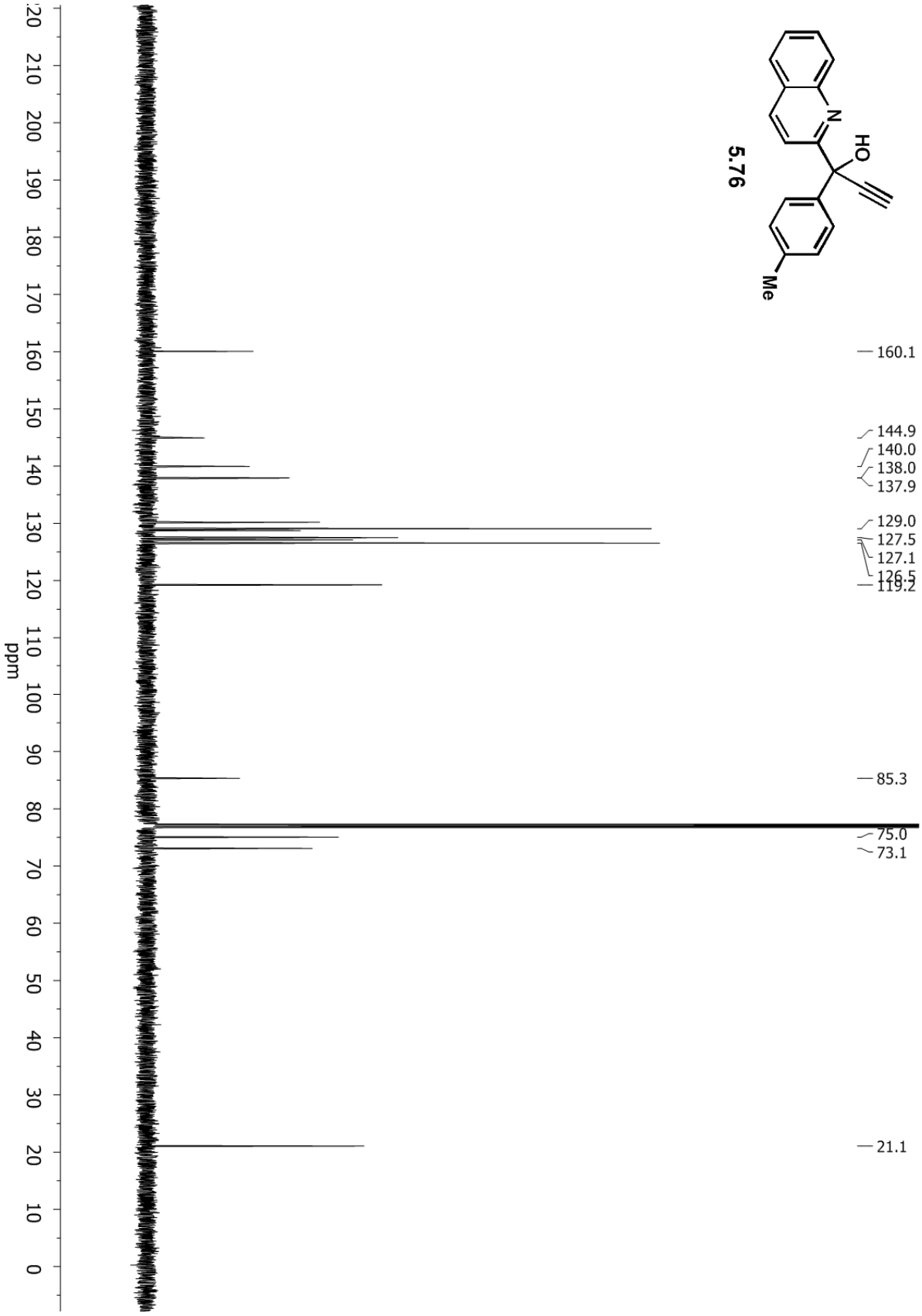

5.92
HO
N
NBoc
1.00
1.02
1.01
1.02
1.00
1.01
0.97
2.24
3.12
2.05
1.54
10.97
1.25
ppm
1.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5

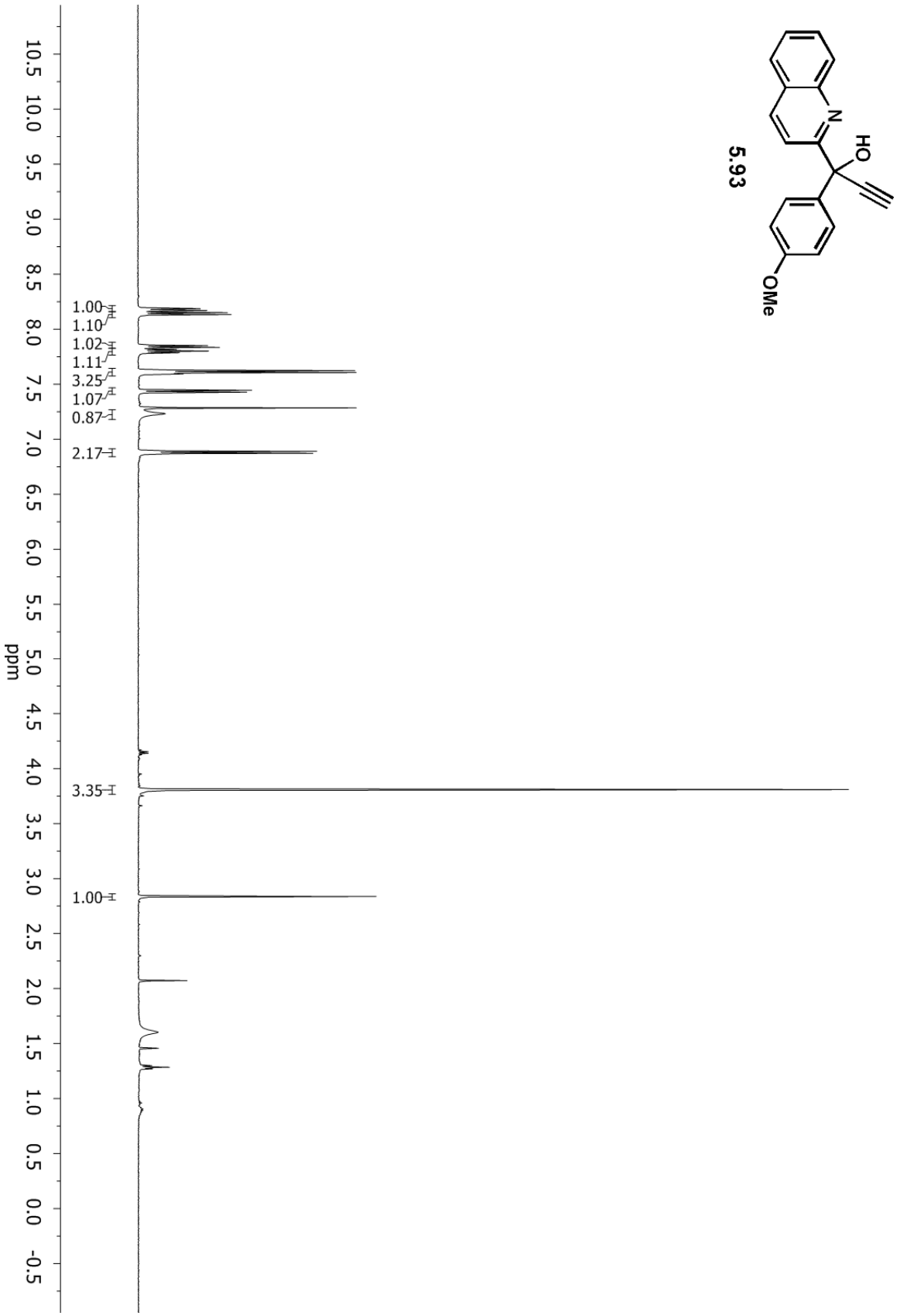

5.92
HO
N
NBoc
158.8
154.5
145.2
137.5
130.0
128.6
127.4
126.9
118.4
84.9
73.5
47.7
43.2
28.3
26.6
25.3
22.7
ppm
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

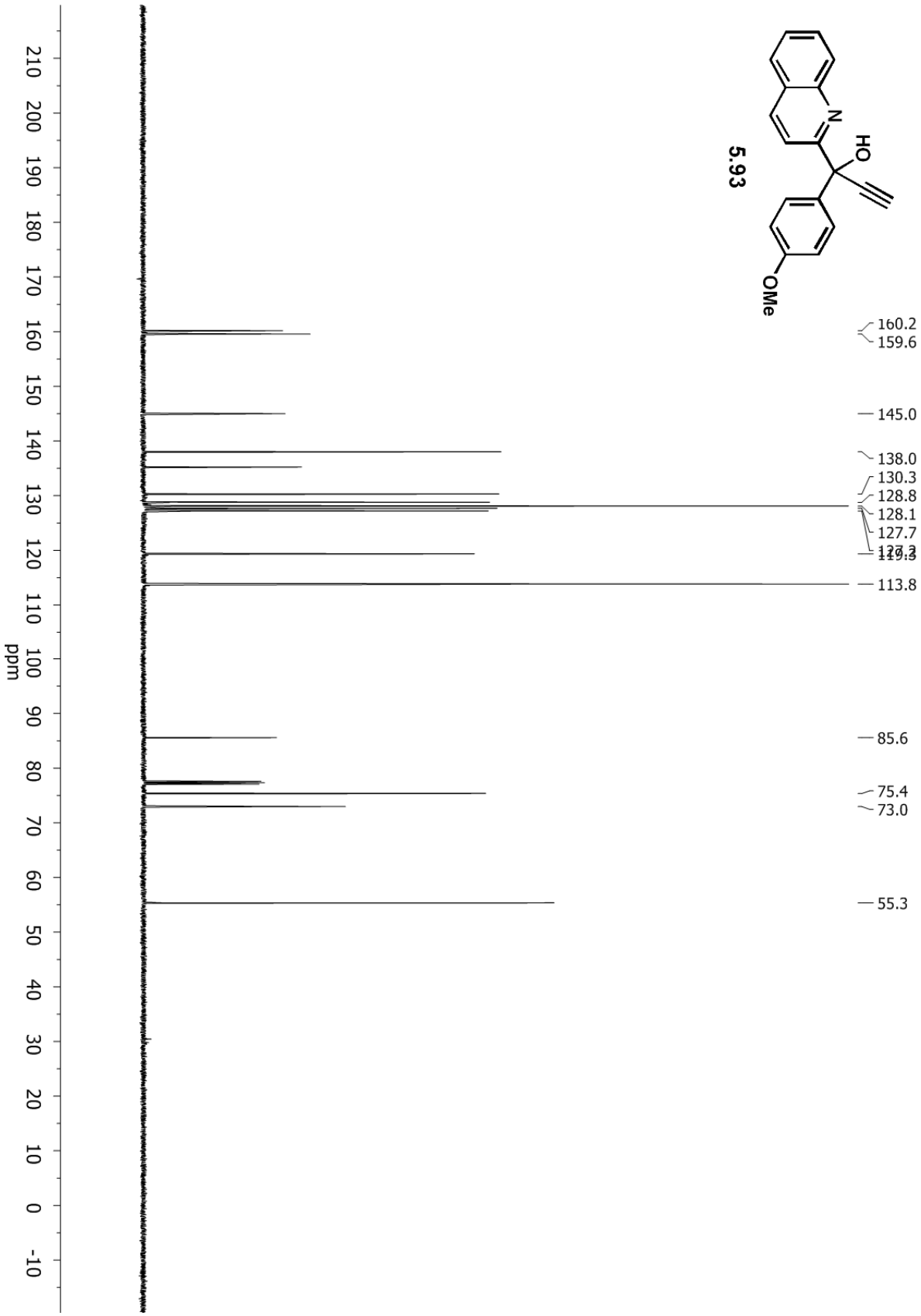
5.88
N
HO
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
ppm

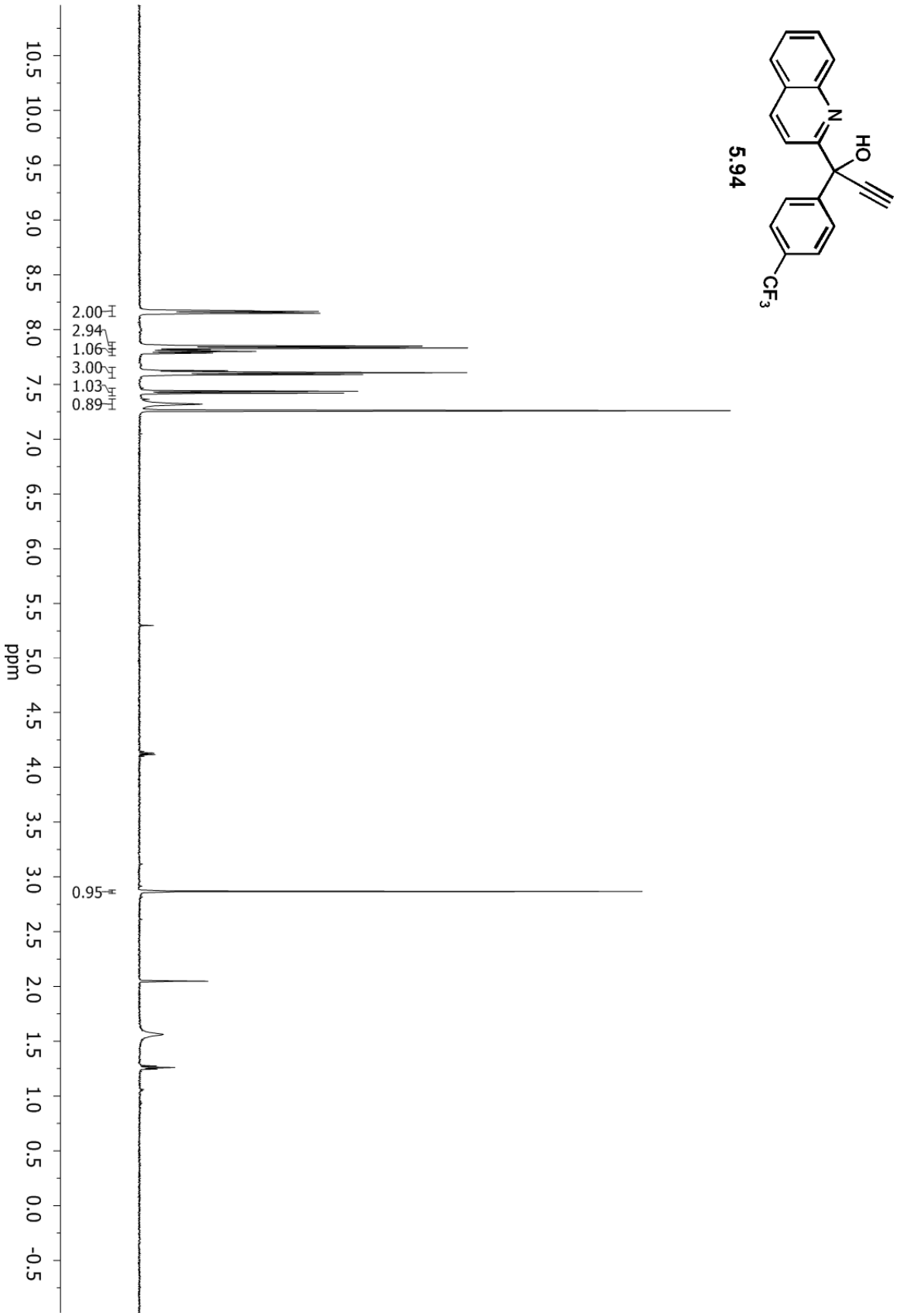

5.88
HO
N
158.5
145.3
139.7
137.9
128.8
128.3
127.5
127.1
118.7
116.3
83.9
74.7
72.0
ppm
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

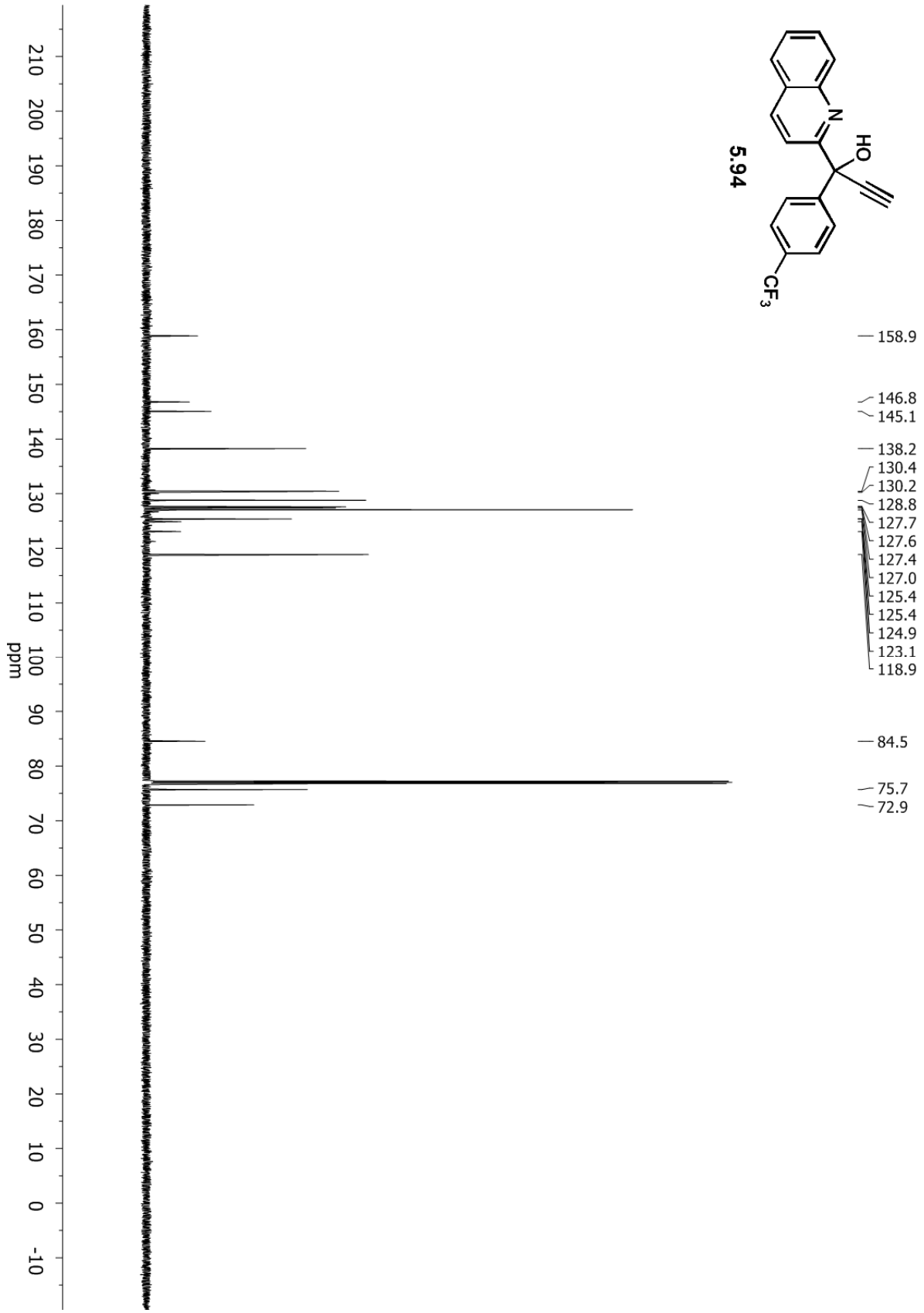

5.76
HO
N
Me
1.00
1.00
2.03
3.01
1.01
0.71
2.08
0.94
3.03
ppm
1.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5

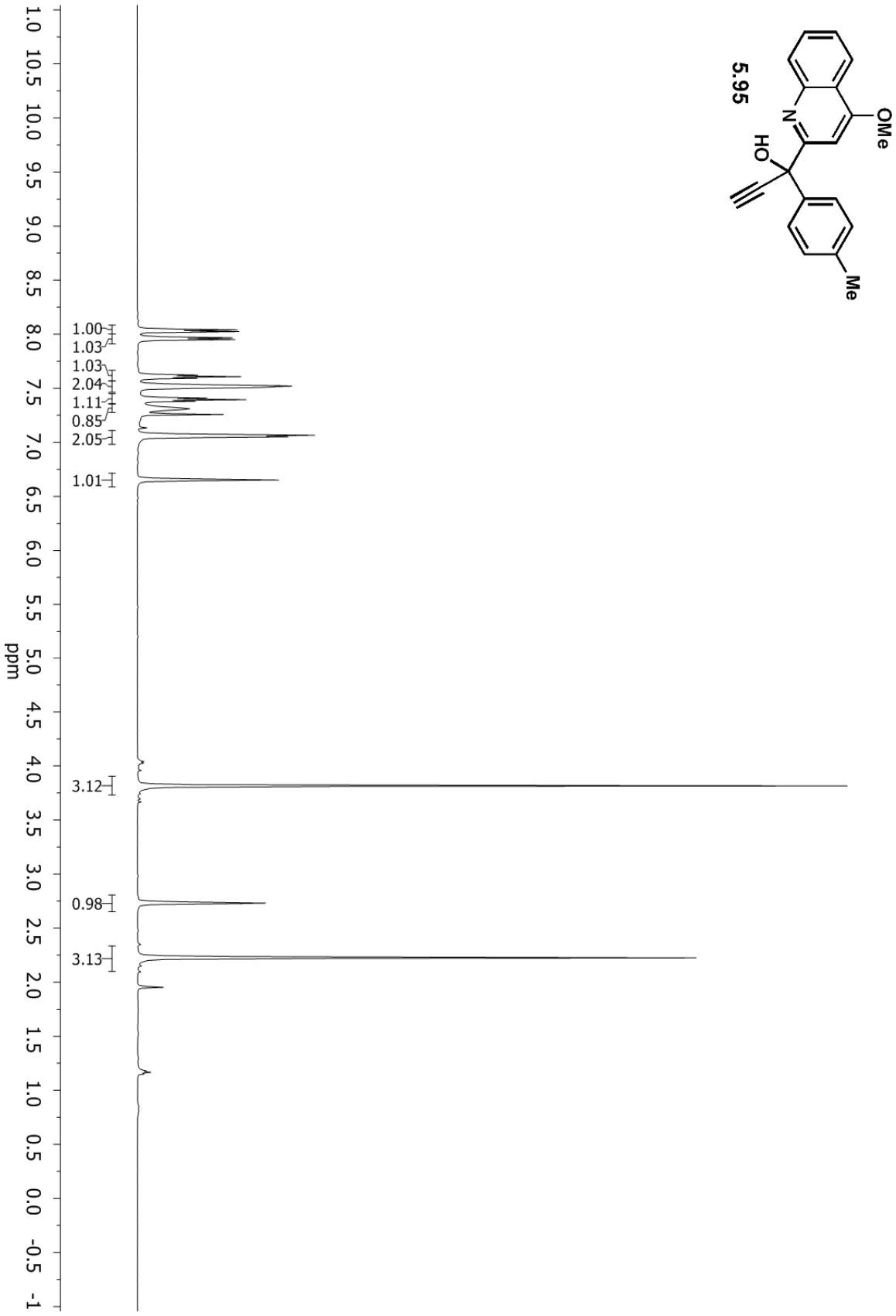

5.76
N
HO
Me
160.1
144.9
140.0
138.0
137.9
129.0
127.5
127.1
126.5
119.2
85.3
75.0
73.1
21.1
ppm

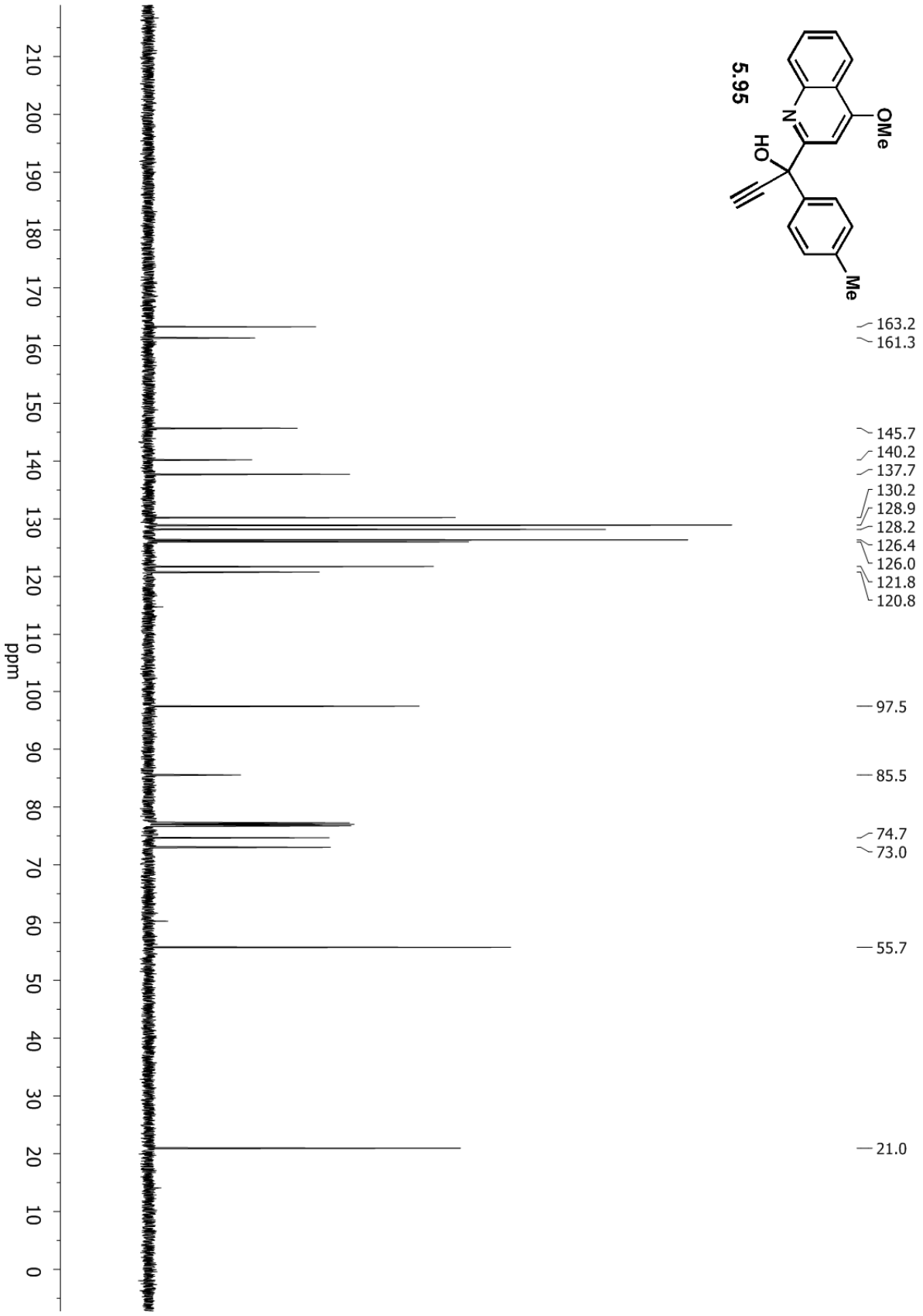

5.93
HO
N
OMe
1.00
1.10
1.02
1.11
3.25
1.07
0.87
2.17
3.35
1.00
ppm
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5

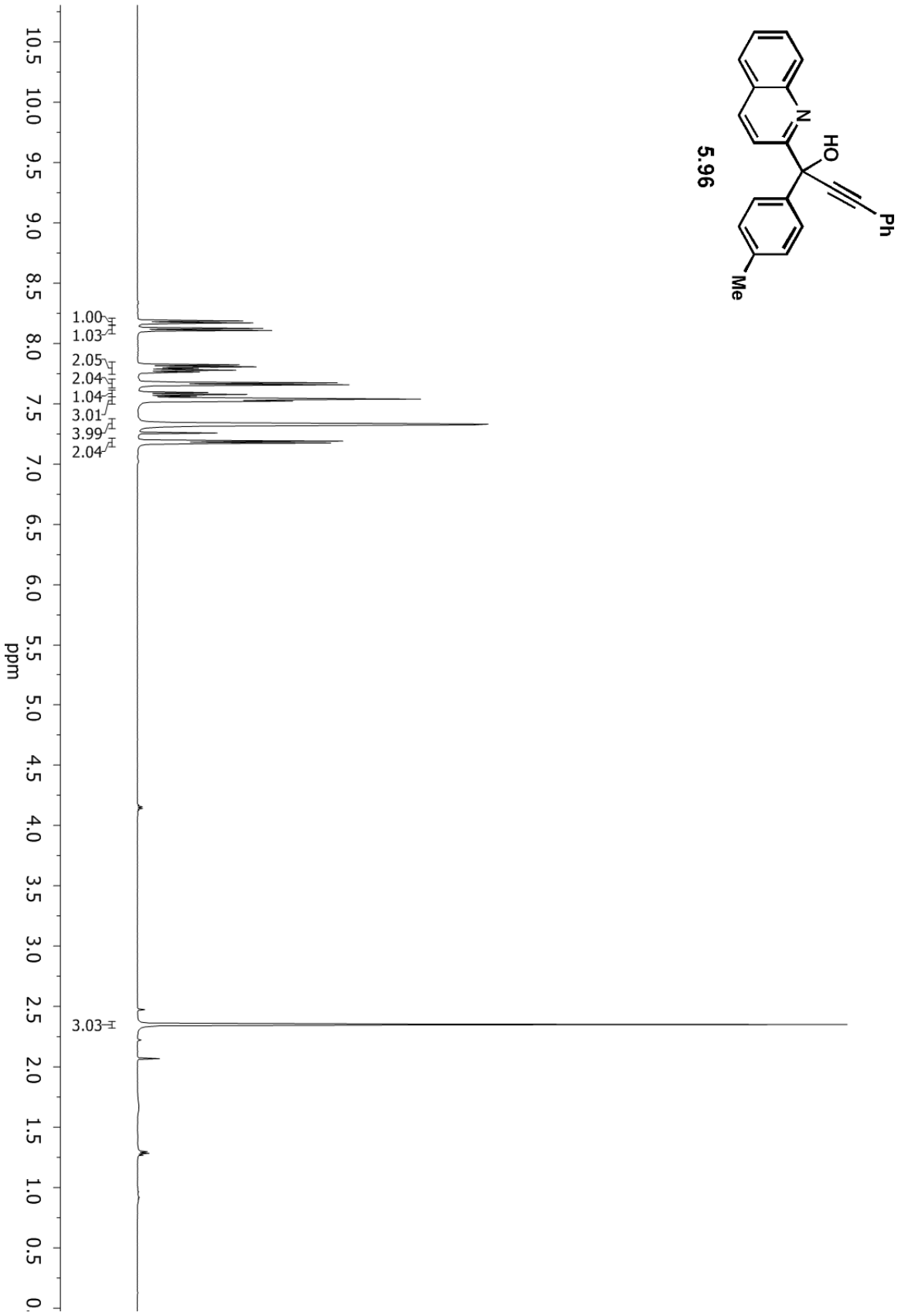

5.93
HO
N
OMe
160.2
159.6
145.0
138.0
130.3
128.8
128.1
127.7
113.8
85.6
75.4
73.0
55.3
ppm
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

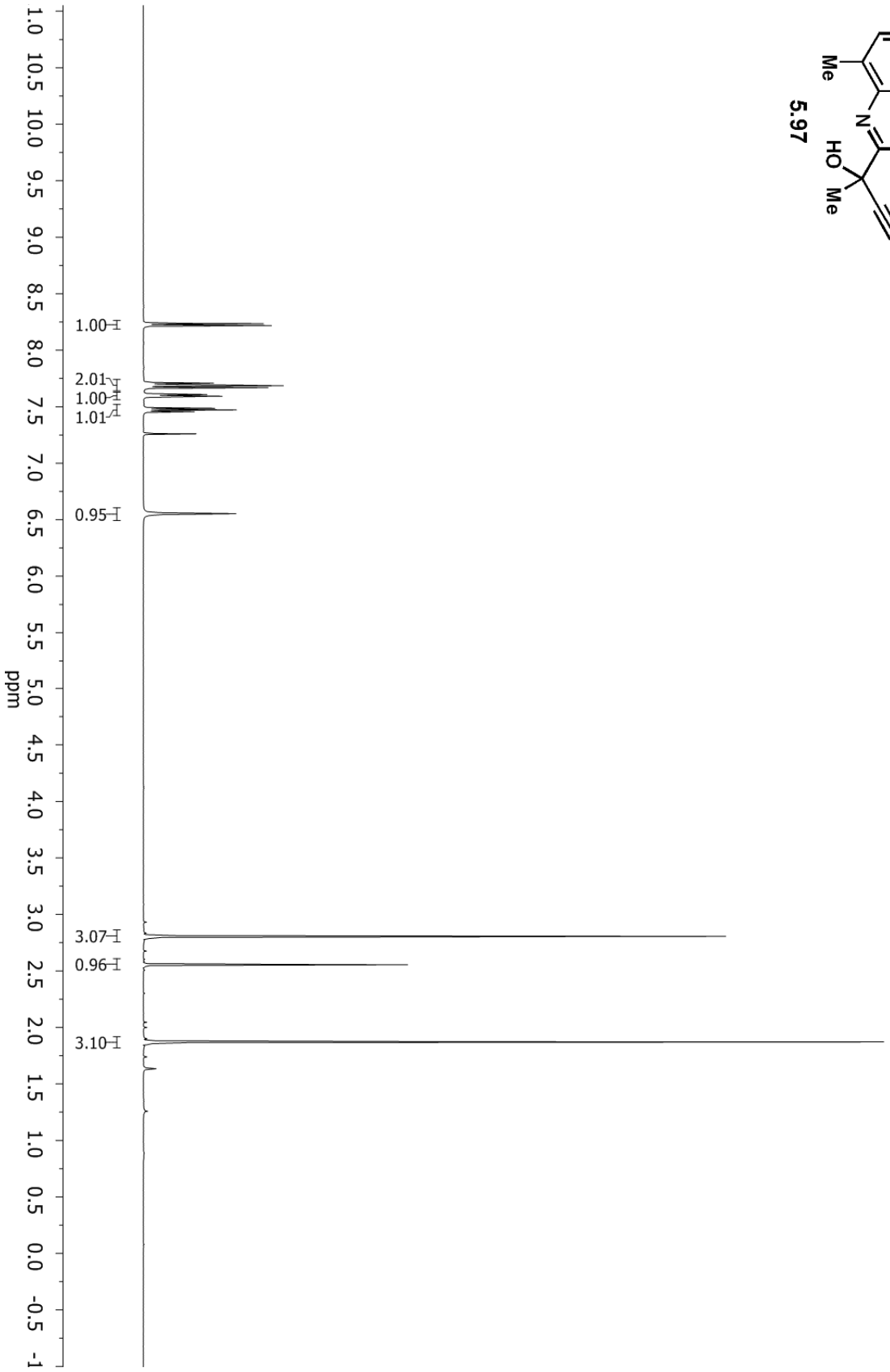

5.94
HO
N
CF3
2.00
2.94
1.06
3.00
1.03
0.89
0.95
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
ppm

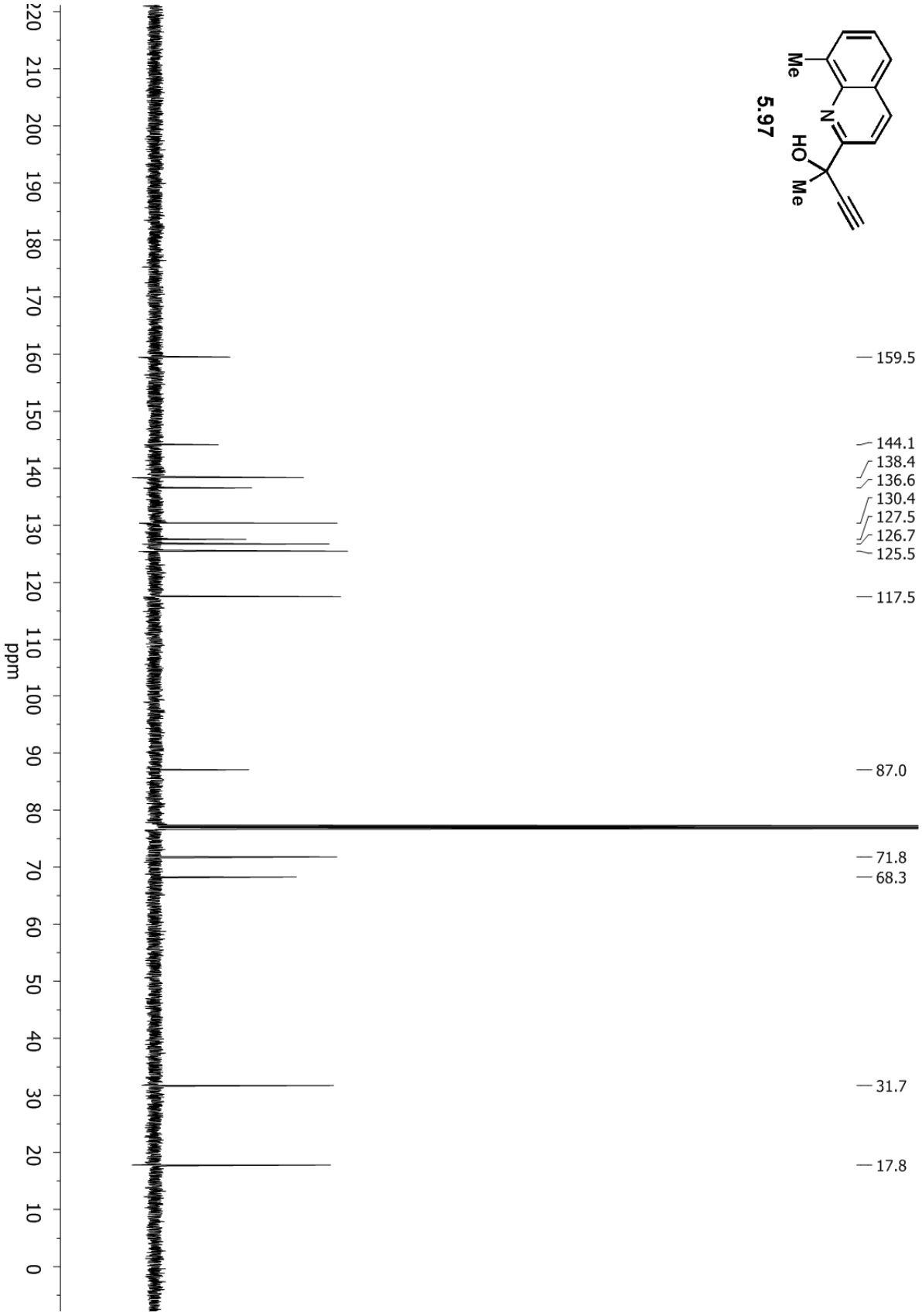

5.94
HO
N
CF3
158.9
146.8
145.1
138.2
130.4
130.2
128.8
127.7
127.6
127.4
127.0
125.4
125.4
124.9
123.1
118.9
84.5
75.7
72.9
ppm
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

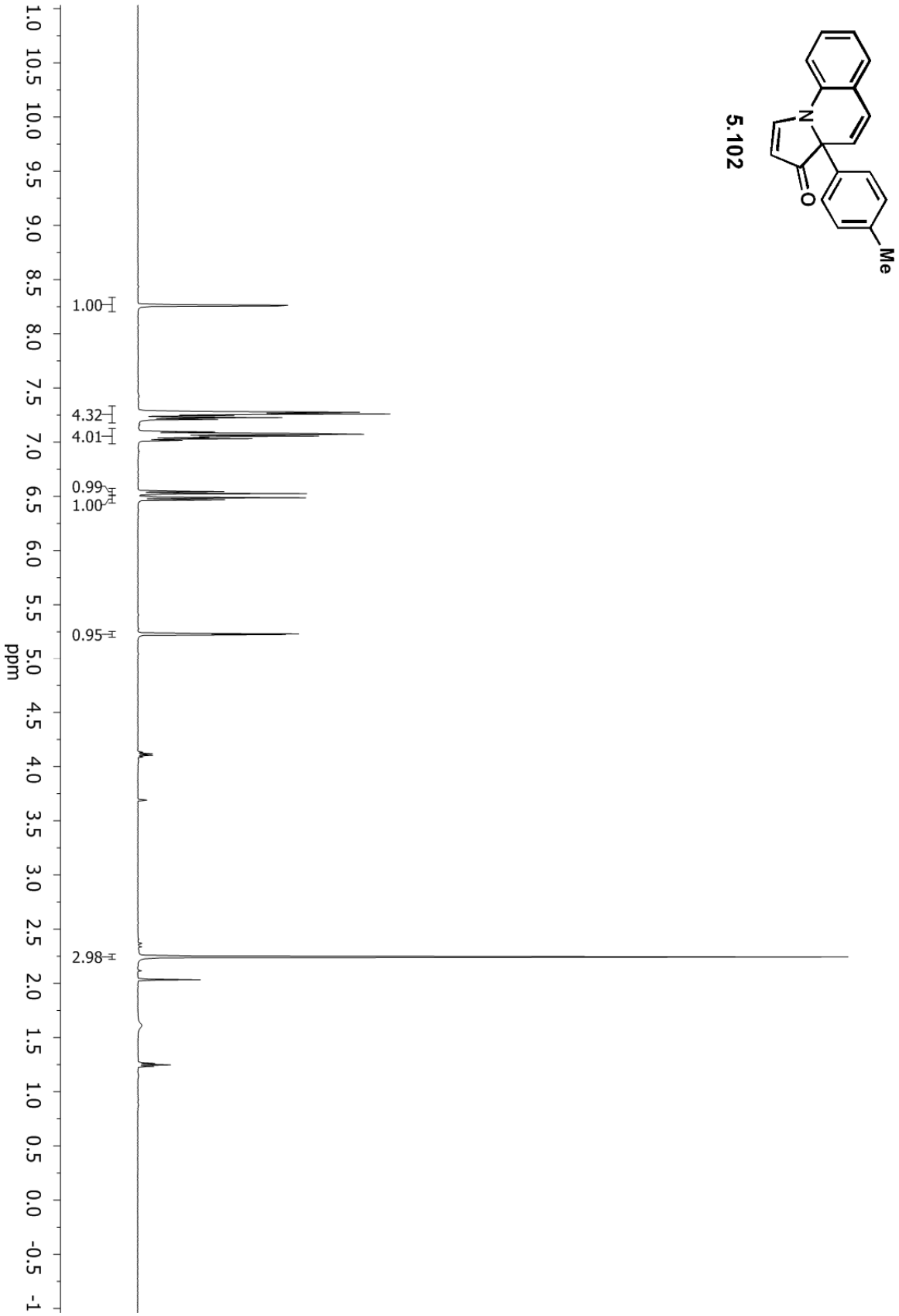

5.95
OMe
HO
N
Me
1.00
1.03
1.03
2.04
1.11
0.85
2.05
1.01
3.12
0.98
3.13
ppm
1.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1

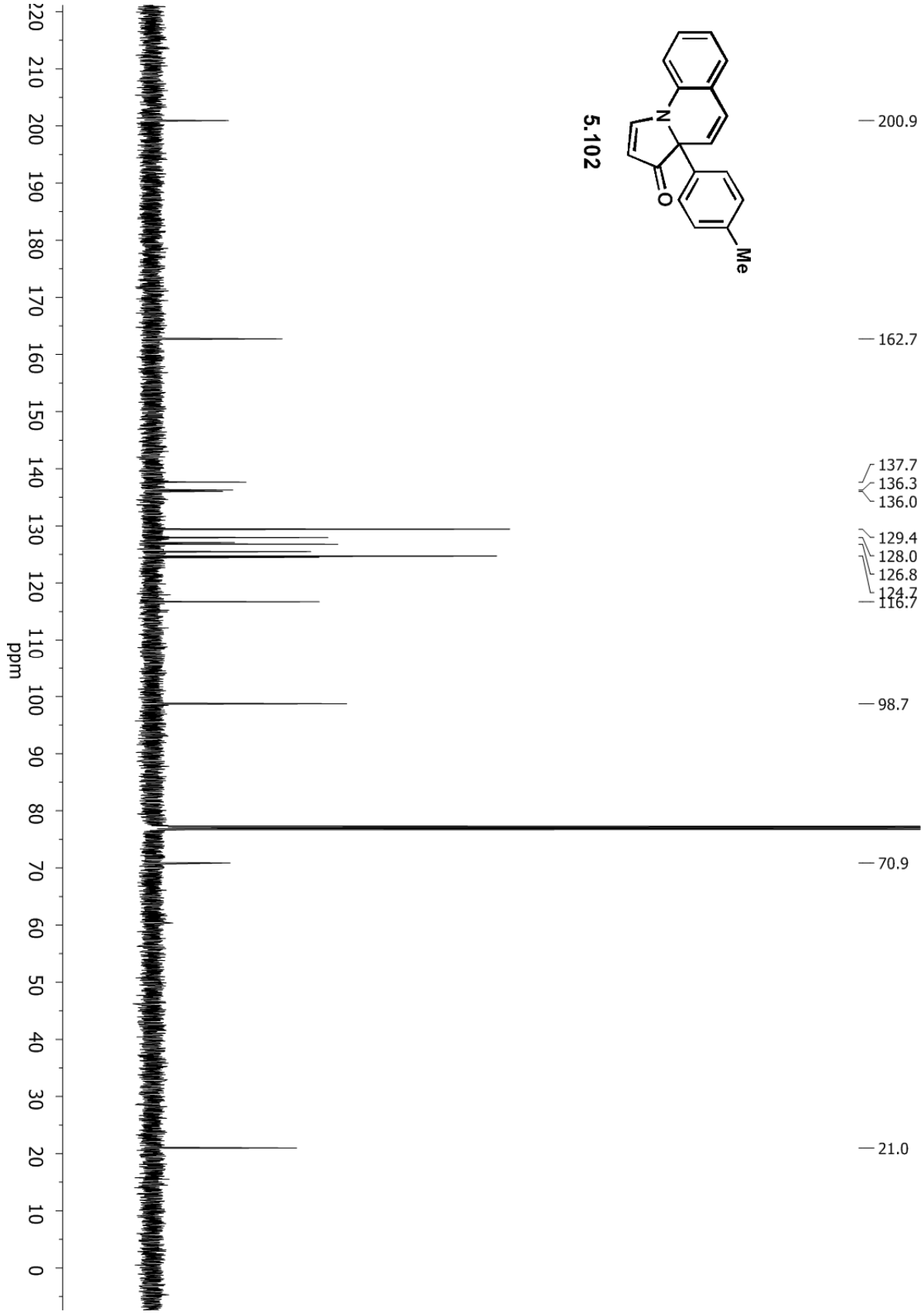

5.95
OMe
HO
N
Me
163.2
161.3
145.7
140.2
137.7
130.2
128.9
128.2
126.4
126.0
121.8
120.8
97.5
85.5
74.7
73.0
55.7
21.0
ppm
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

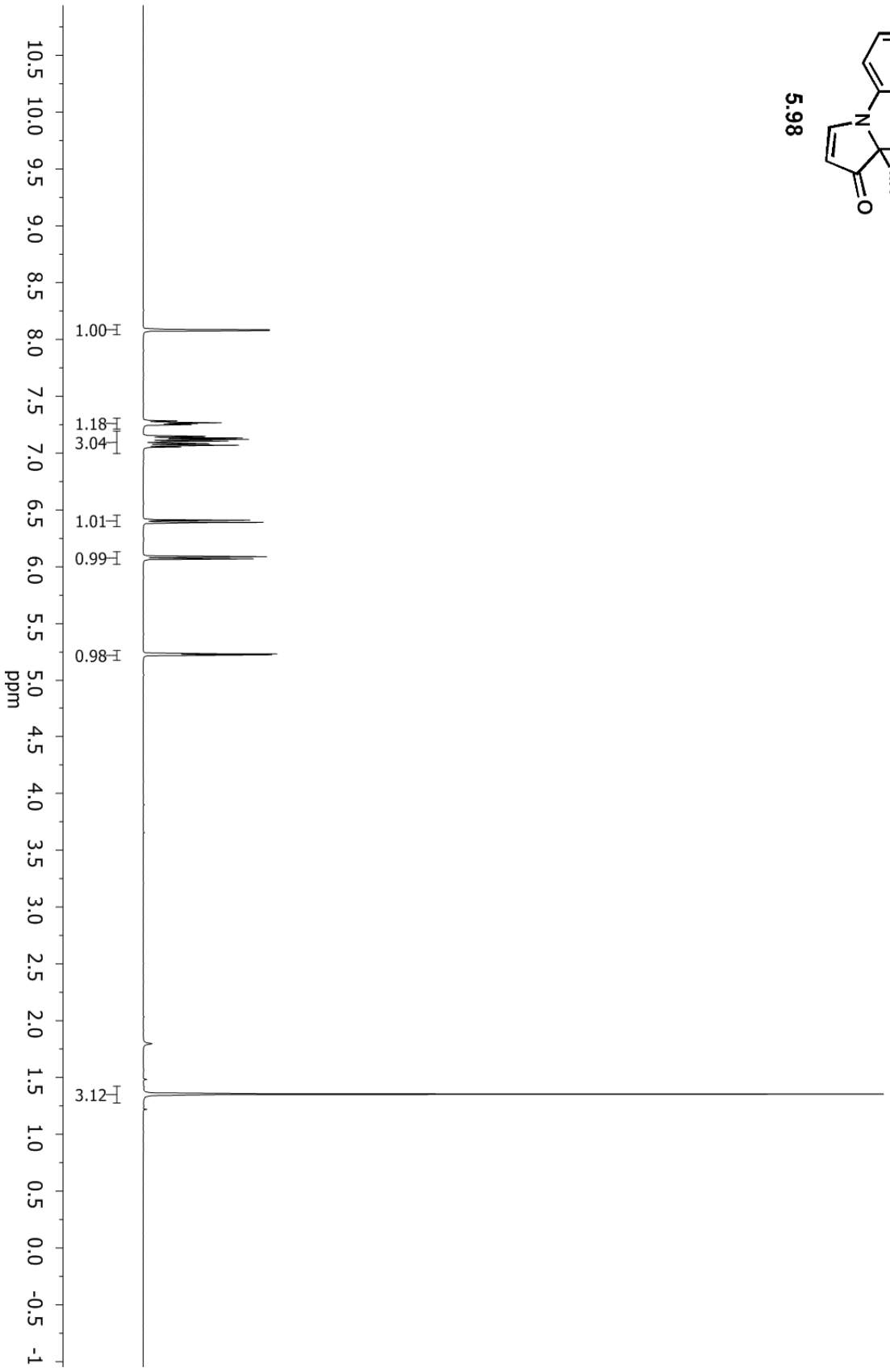

5.96
N
HO
Ph
Me
1.00
1.03
2.05
2.04
1.04
3.01
3.99
2.04
3.03
ppm
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.

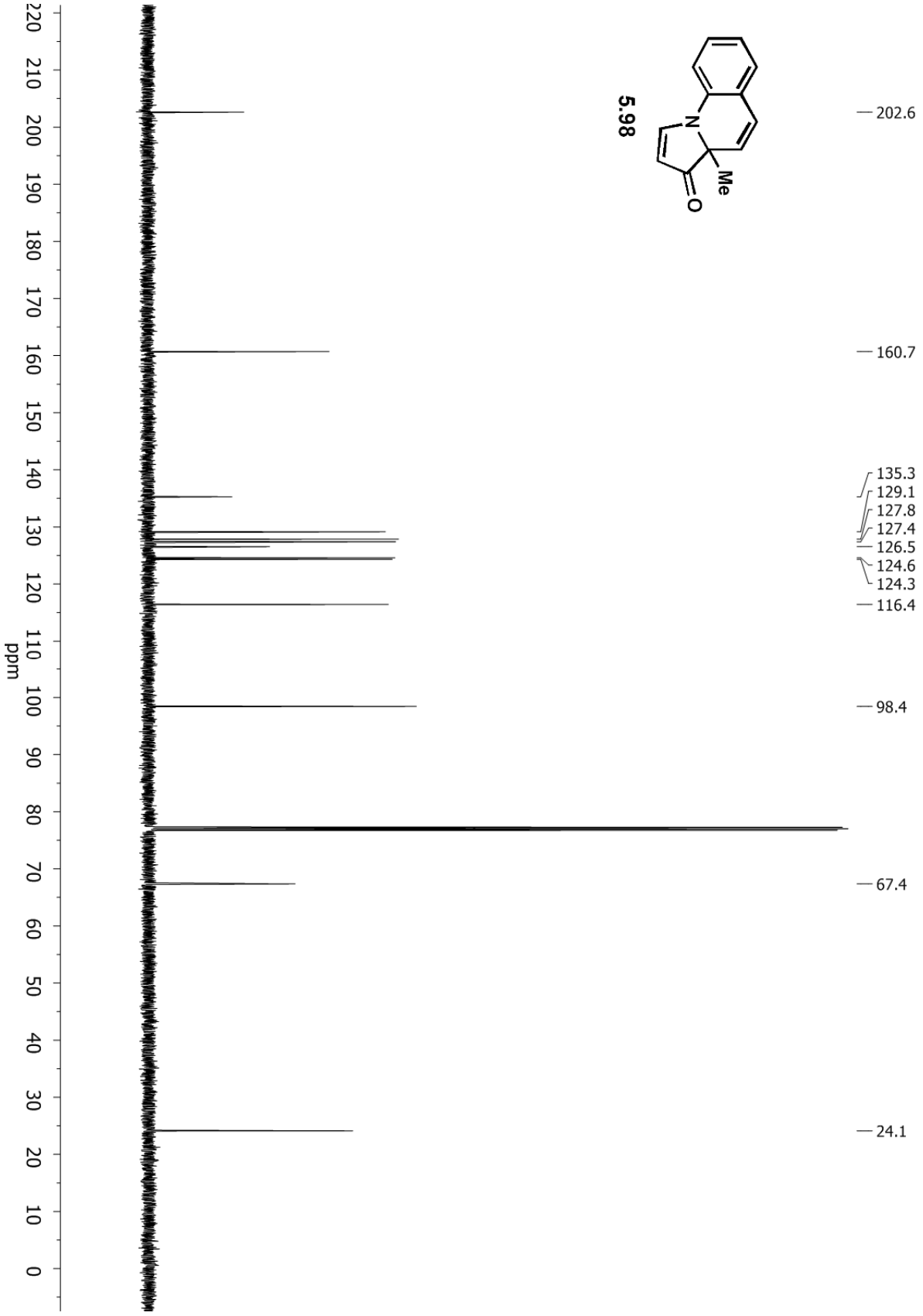

Me
N
HO
Me
5.97
1.00
2.01
1.00
1.01
0.95
3.07
0.96
3.10
ppm

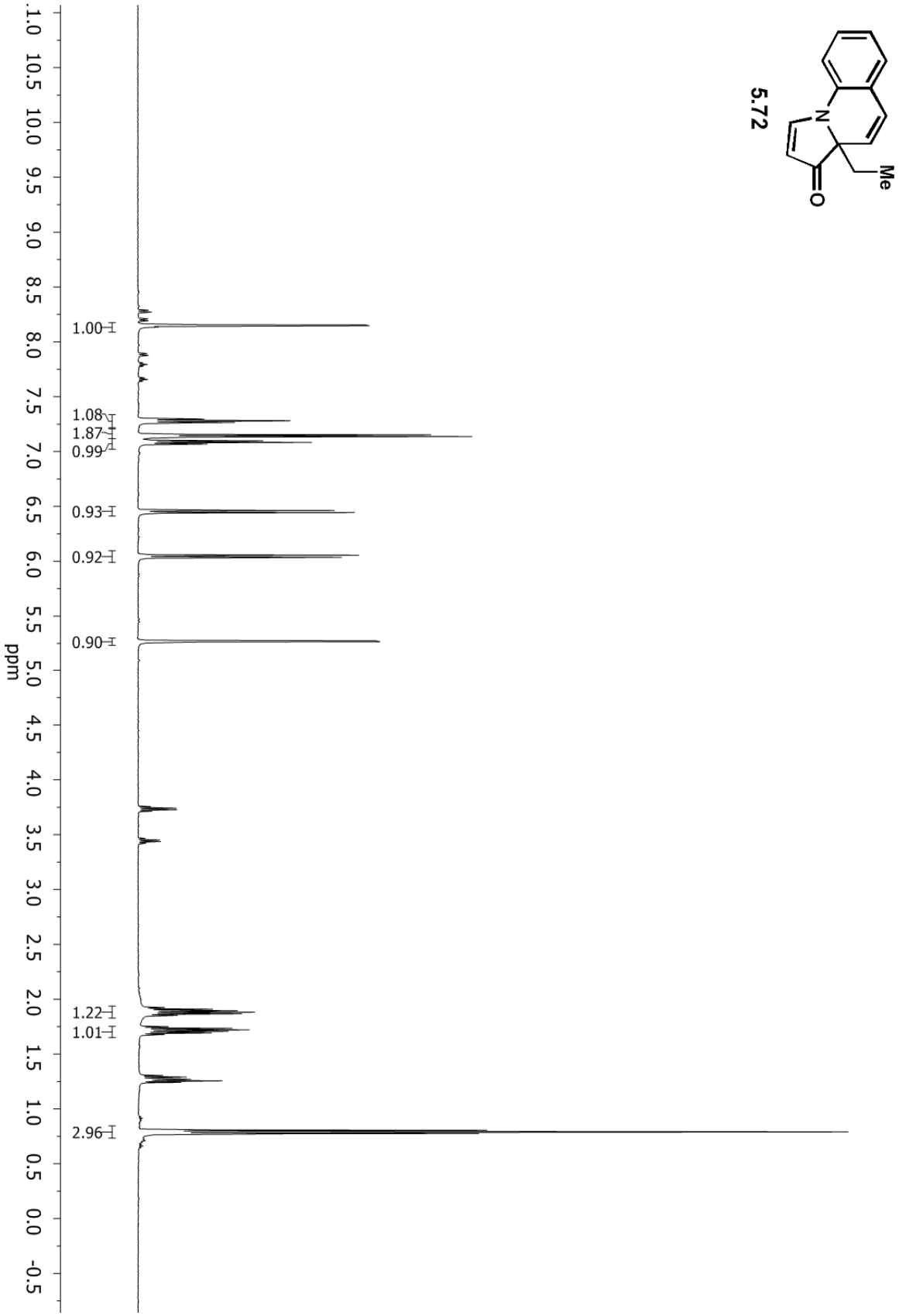

Me
N
HO
Me
5.97
159.5
144.1
138.4
136.6
130.4
127.5
126.7
125.5
117.5
87.0
71.8
68.3
31.7
17.8
ppm
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

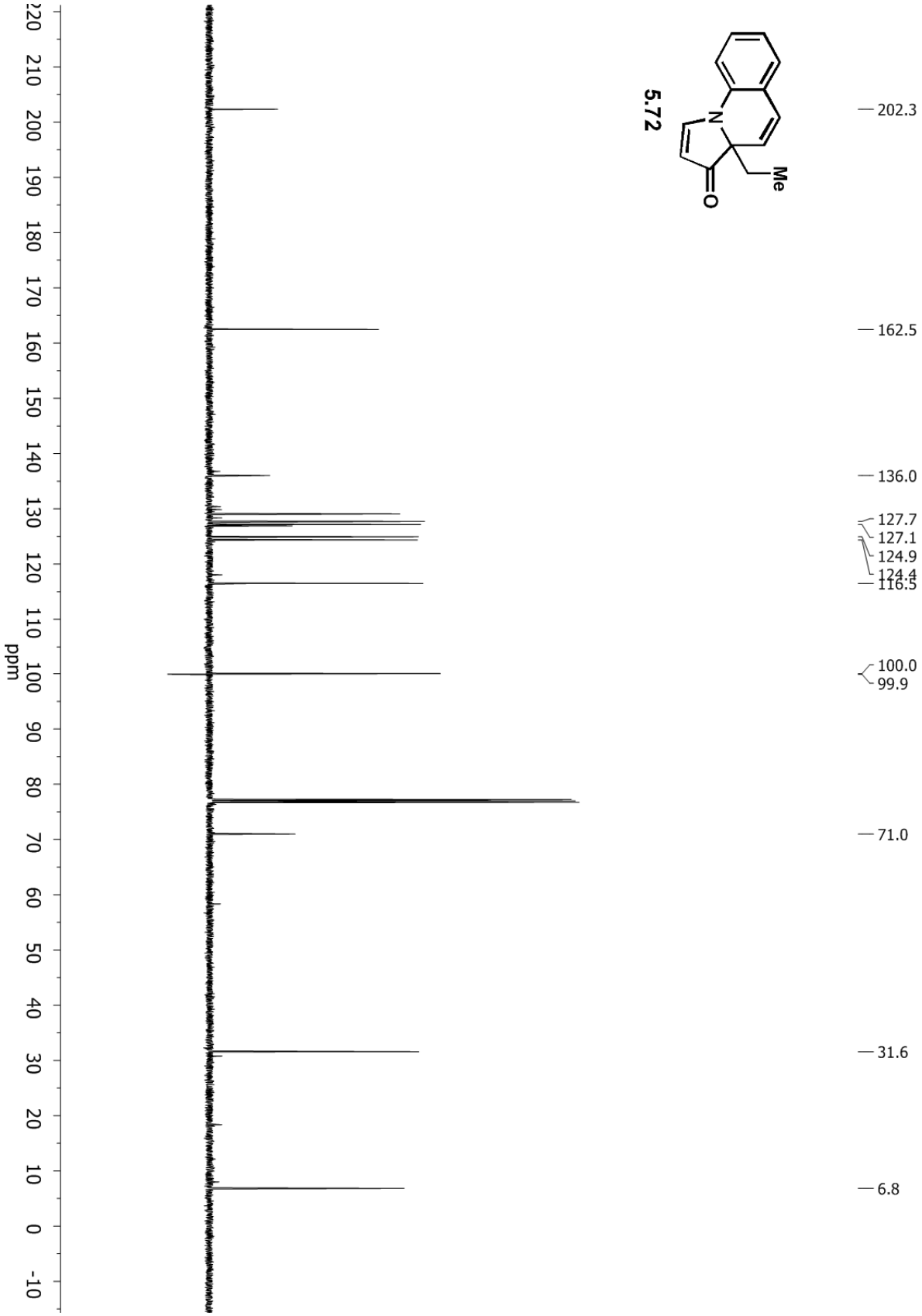

5.102
N
O
Me
1.00
4.32
4.01
0.99
1.00
0.95
2.98
ppm
1.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1

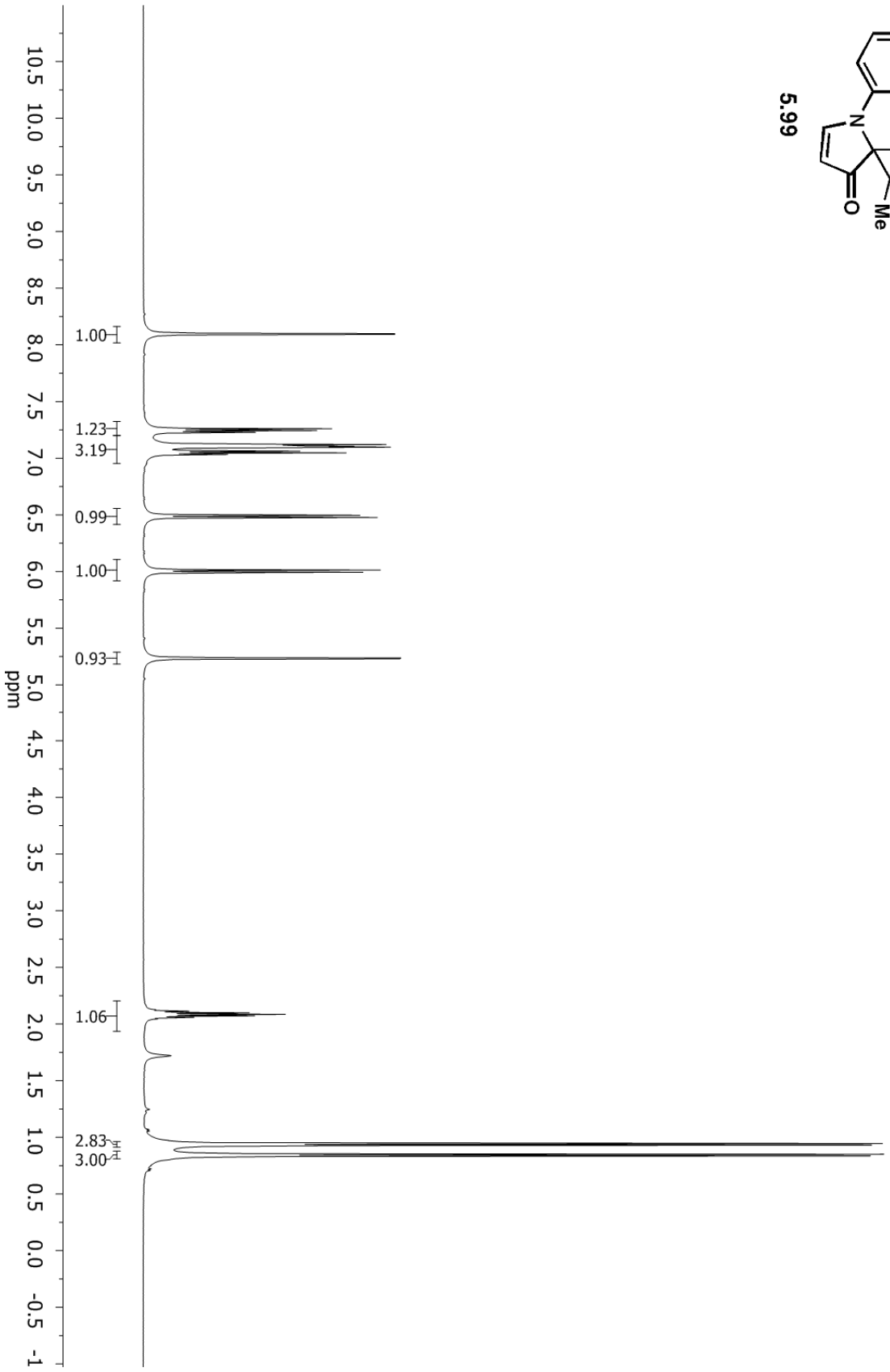

5.102
N
O
Me
200.9
162.7
137.7
136.3
136.0
129.4
128.0
126.8
124.7
116.7
98.7
70.9
21.0
ppm
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

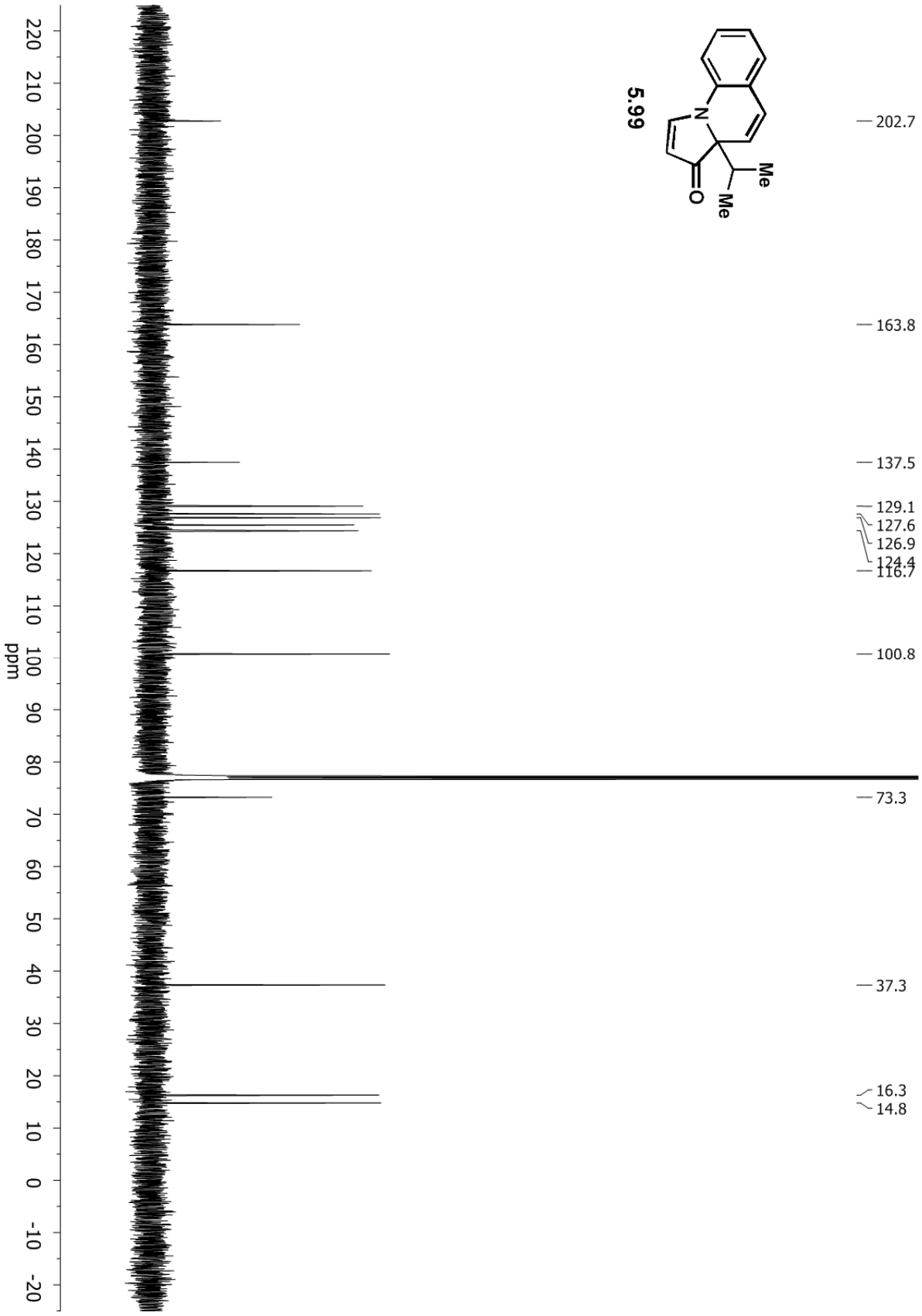

5.98
N
Me
O
1.00
1.18
3.04
1.01
0.99
0.98
3.12
ppm
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1

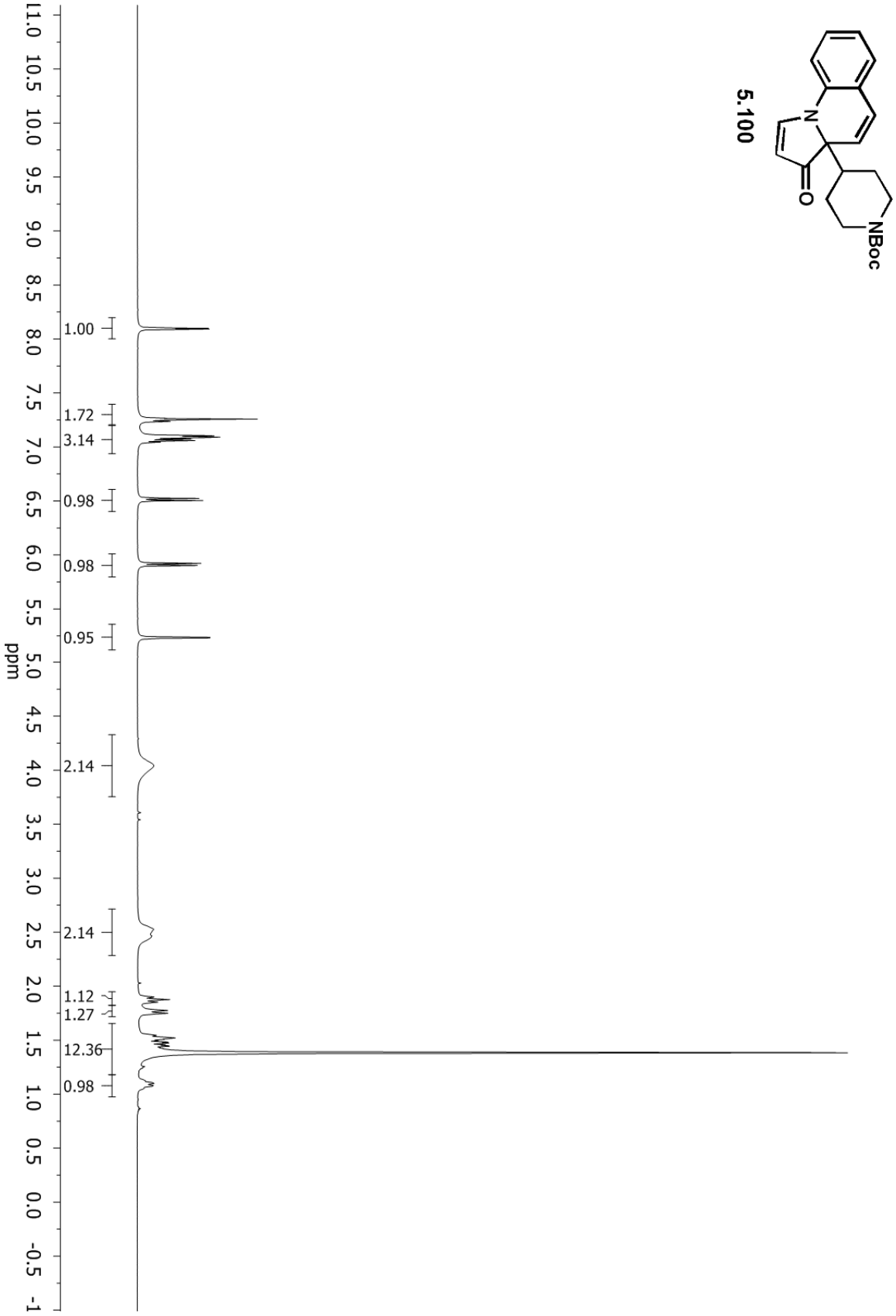

5.98
N
Me
O
202.6
160.7
135.3
129.1
127.8
127.4
126.5
124.6
124.3
116.4
98.4
67.4
24.1
ppm
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

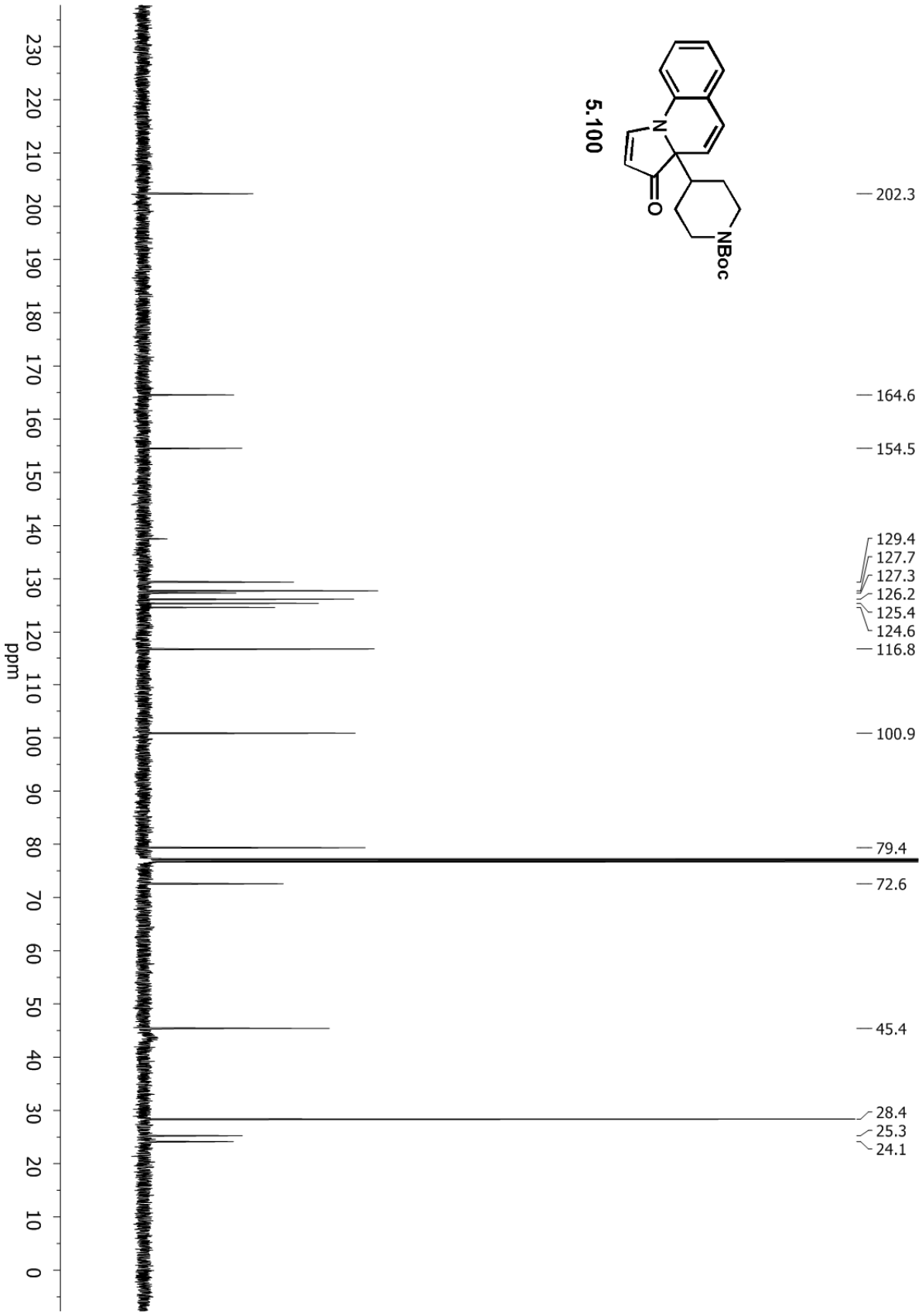

5.72
N
O
Me
1.00
1.08
1.87
0.99
0.93
0.92
0.90
1.22
1.01
2.96
ppm


5.72
Me
O
N
202.3
162.5
136.0
127.7
127.1
124.9
124.4
116.5
100.0
99.9
71.0
31.6
6.8
ppm
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10


5.99
N
O
Me
Me
1.00
1.23
3.19
0.99
1.00
0.93
1.06
2.83
3.00
ppm
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1


5.99
Me
Me
O
N
202.7
163.8
137.5
129.1
127.6
126.9
124.4
116.7
100.8
73.3
37.3
16.3
14.8
ppm
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20


5.100
NBoc
O
N
ppm
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
1.00
1.72
3.14
0.98
0.98
0.95
2.14
2.14
1.12
1.27
12.36
0.98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N
O
NBoc
202.3
164.6
154.5
129.4
127.7
127.3
126.2
125.4
124.6
116.8
100.9
79.4
72.6
45.4
28.4
25.3
24.1
ppm
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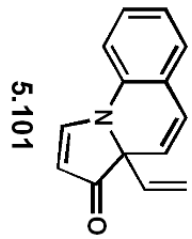
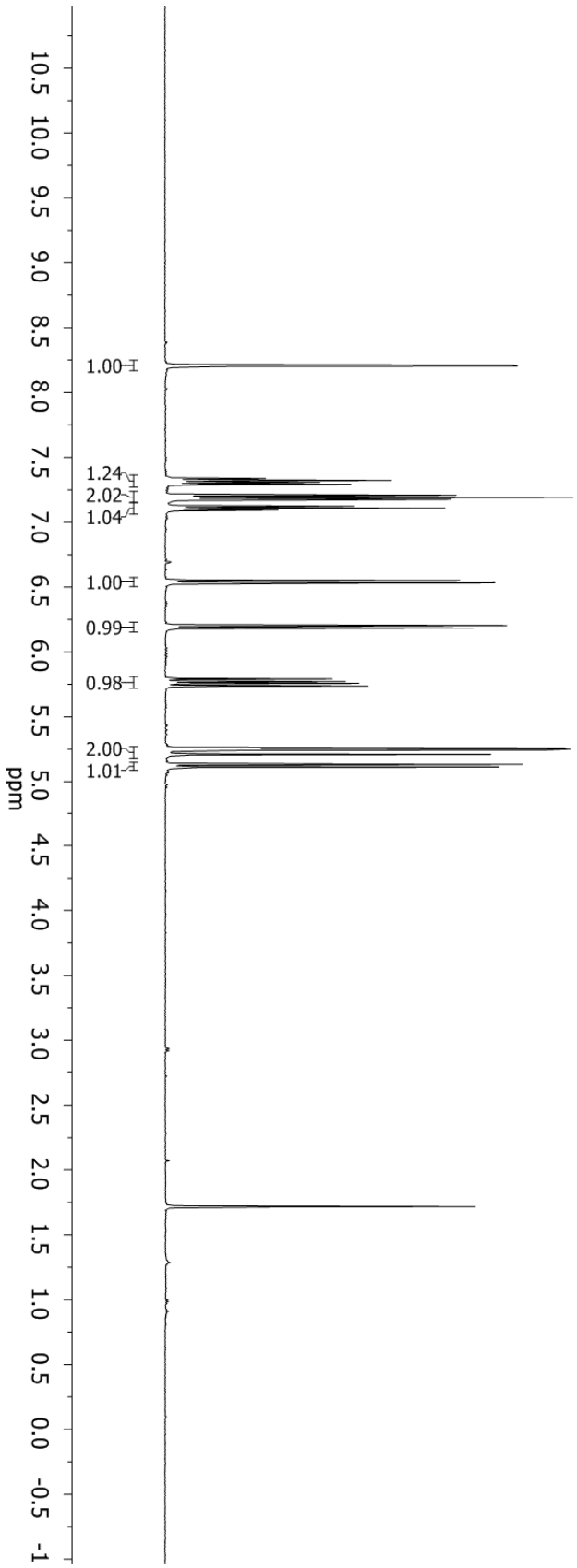

N
O

5.101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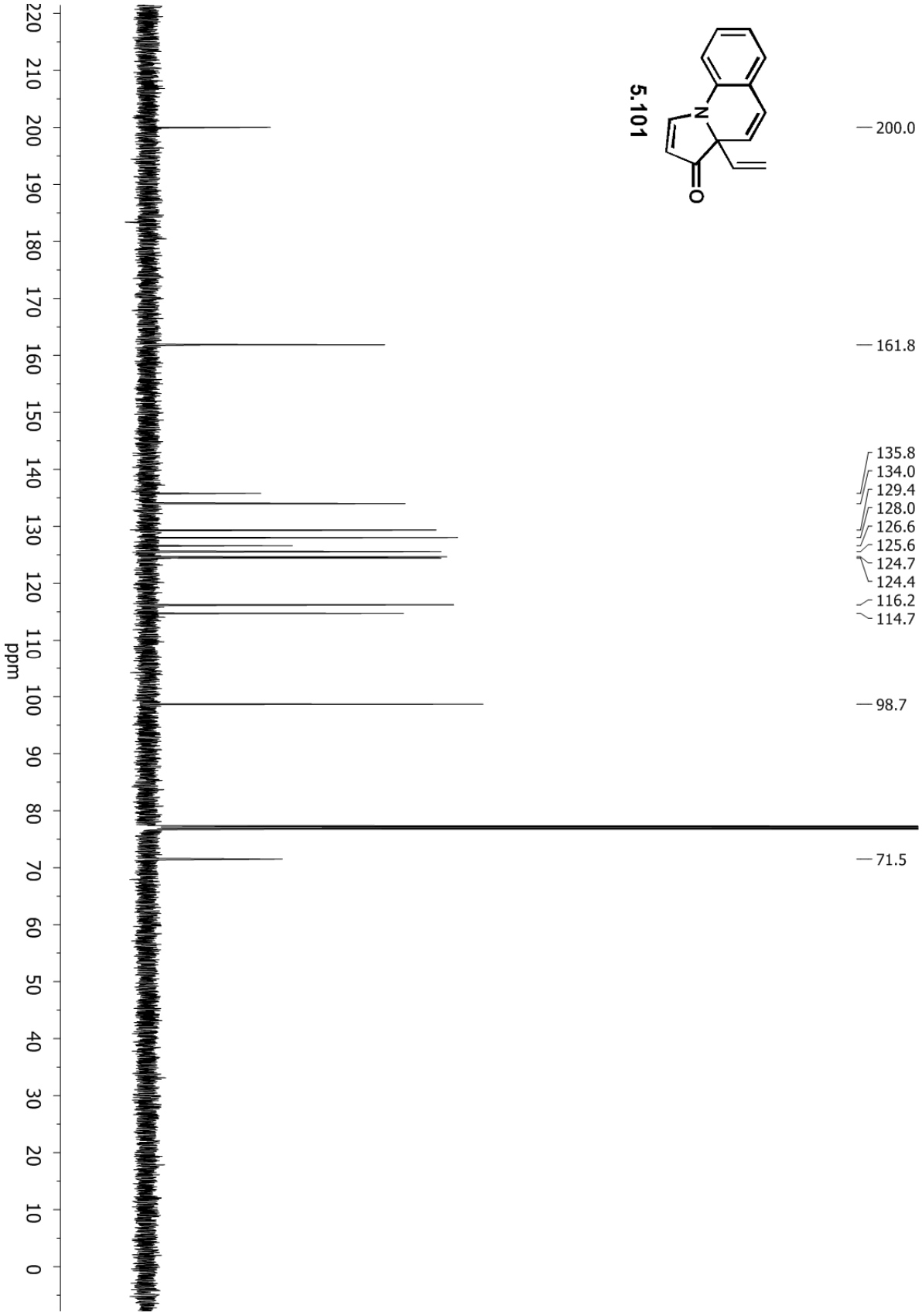
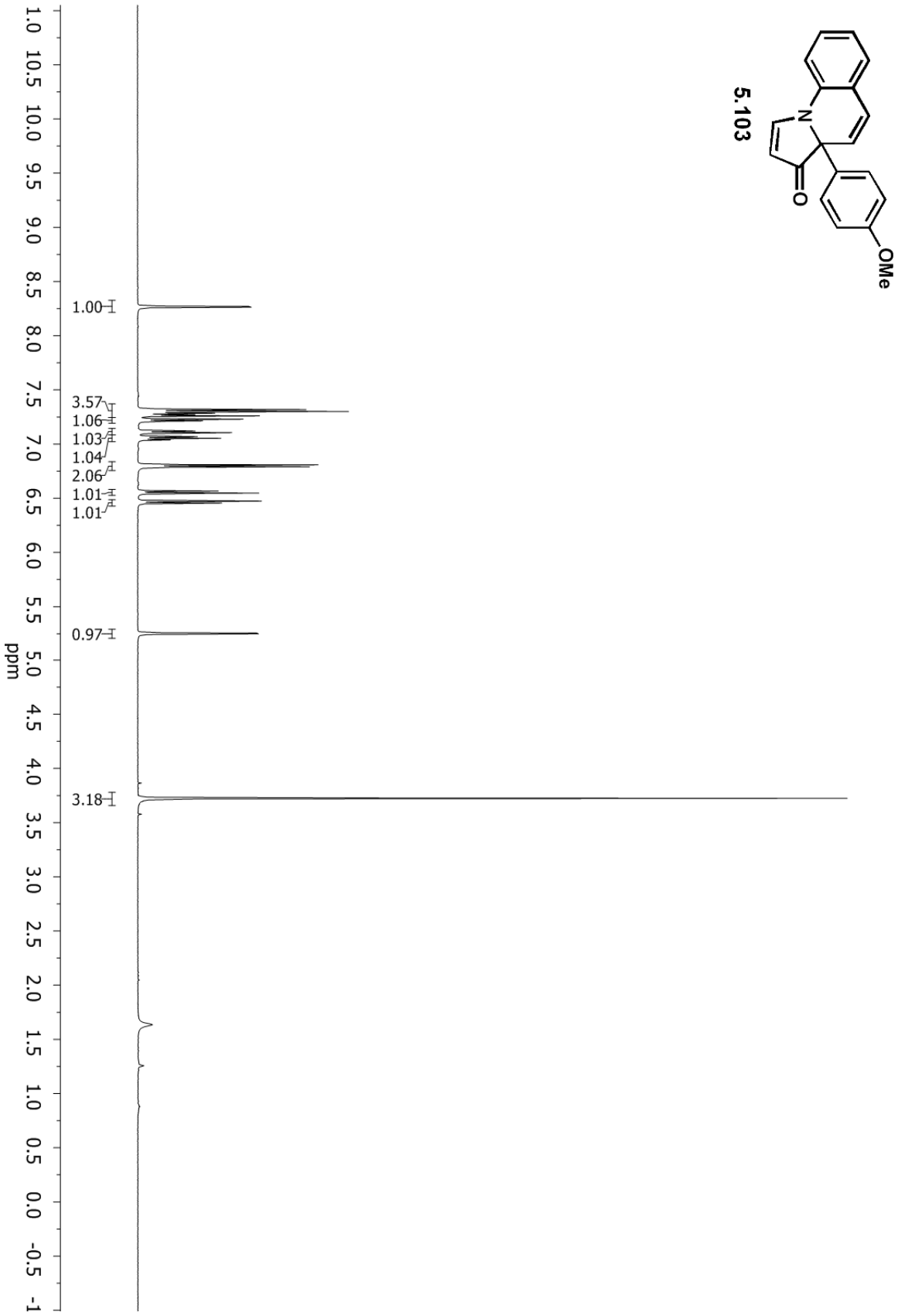
1.24
2.02
1.04
1.00
0.99
0.98
2.00
1.01
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
ppm


5.101
200.0
161.8
135.8
134.0
129.4
128.0
126.6
125.6
124.7
124.4
116.2
114.7
98.7
71.5
ppm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N
O
OMe
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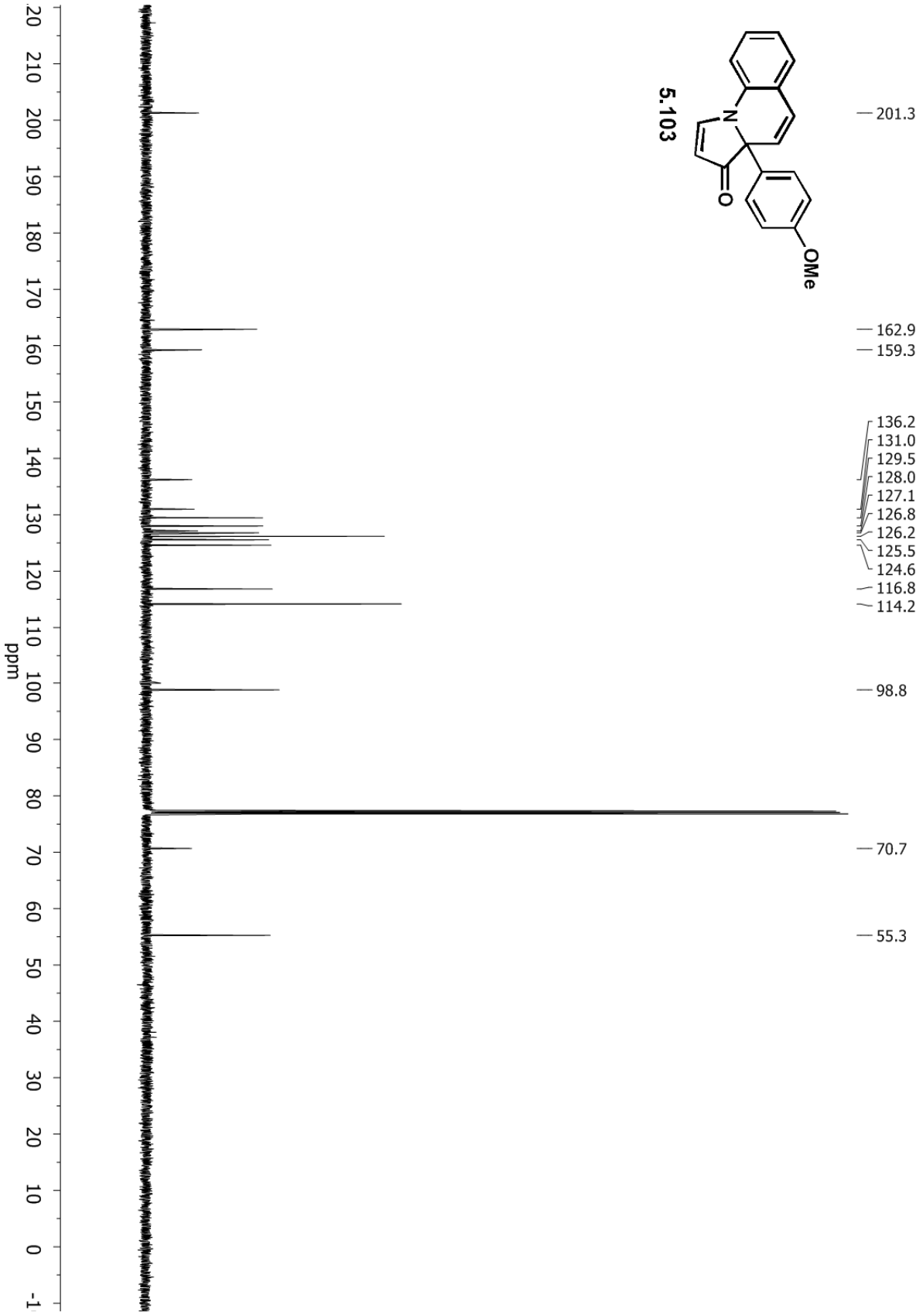
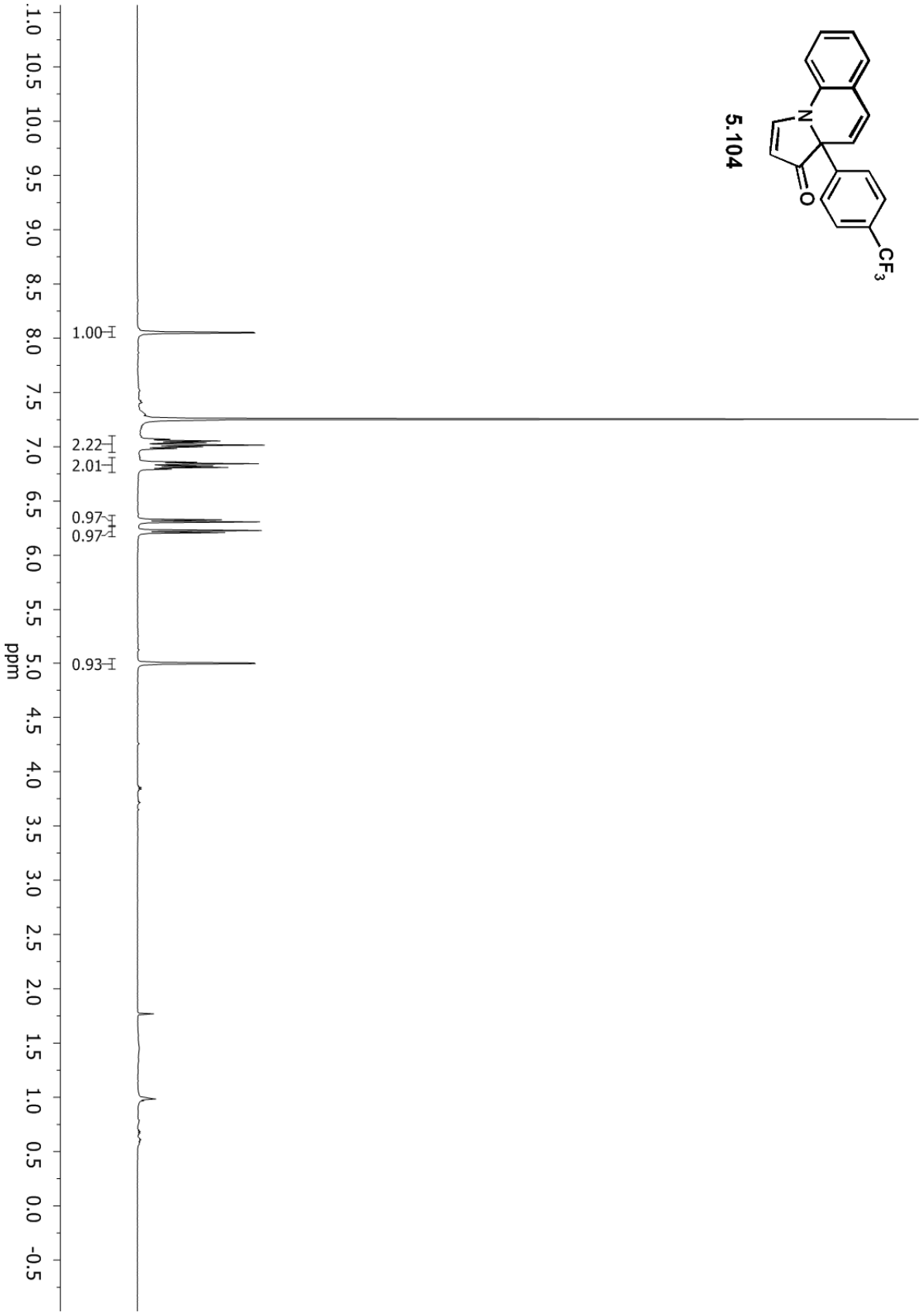
3.57
1.06
1.03
1.04
2.06
1.01
1.01
0.97
3.18
ppm
1.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1


5.103
N
O
OMe
201.3
162.9
159.3
136.2
131.0
129.5
128.0
127.1
126.8
126.2
125.5
124.6
116.8
114.2
98.8
70.7
55.3
ppm
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-1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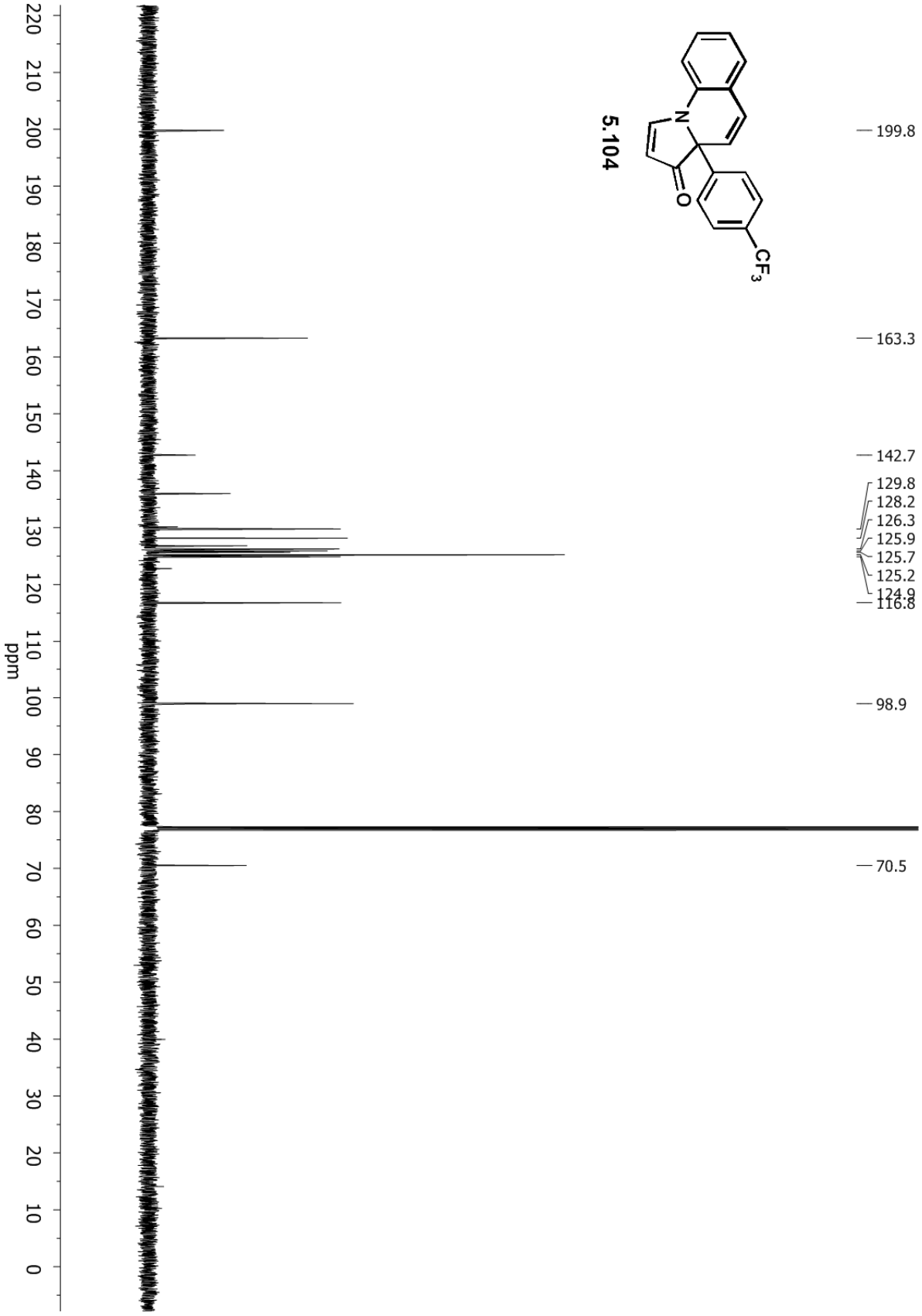
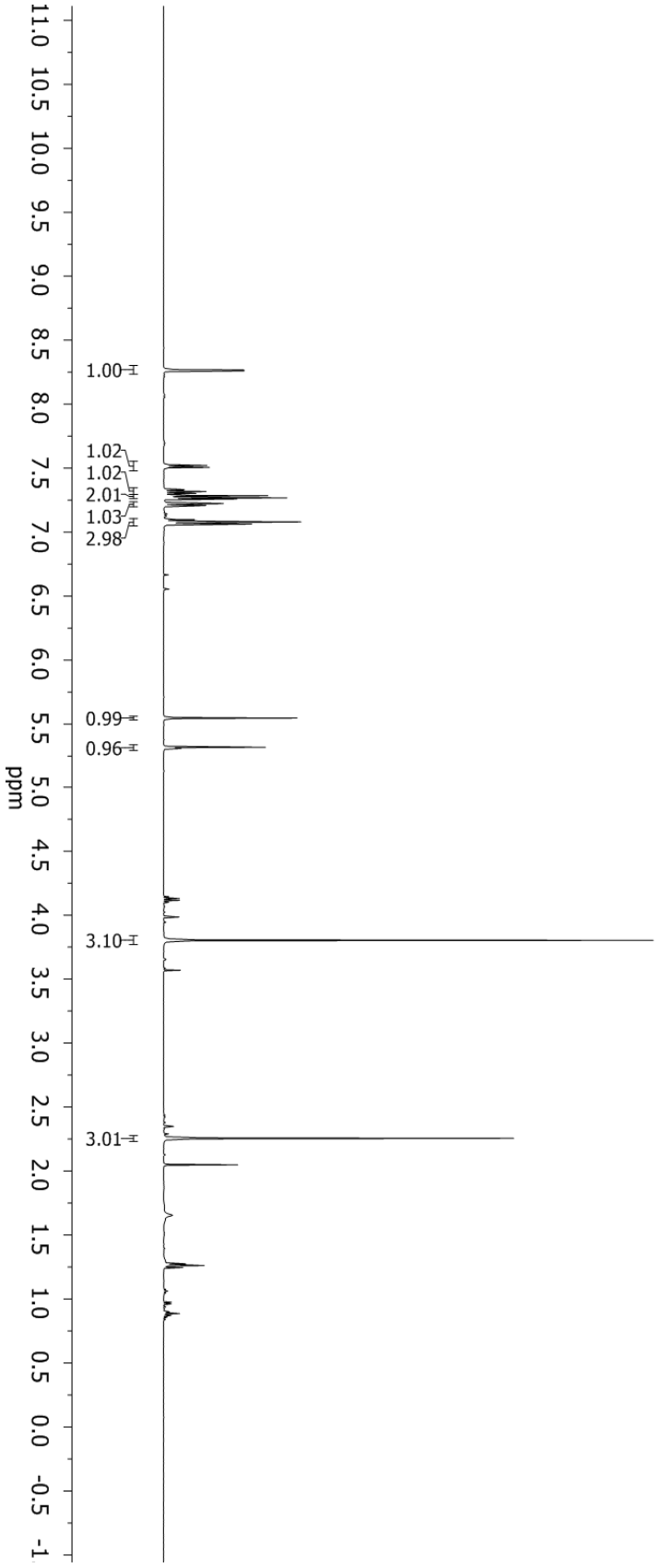
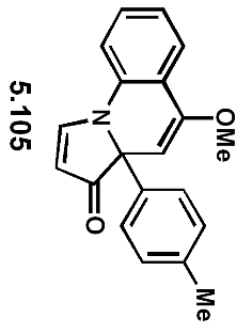
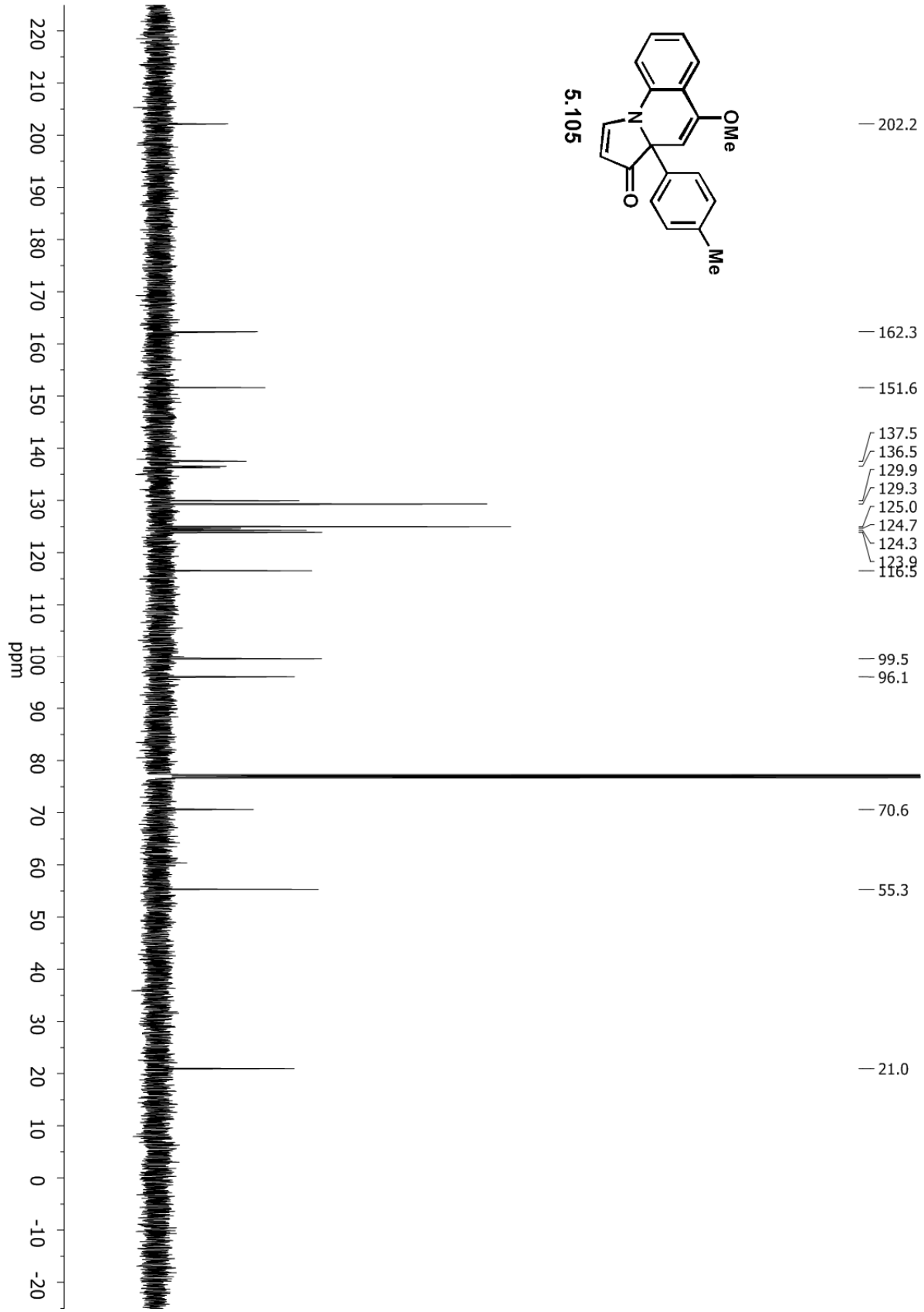
N
O
CF3
1.00
2.22
2.01
0.97
0.97
0.93
ppm
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5

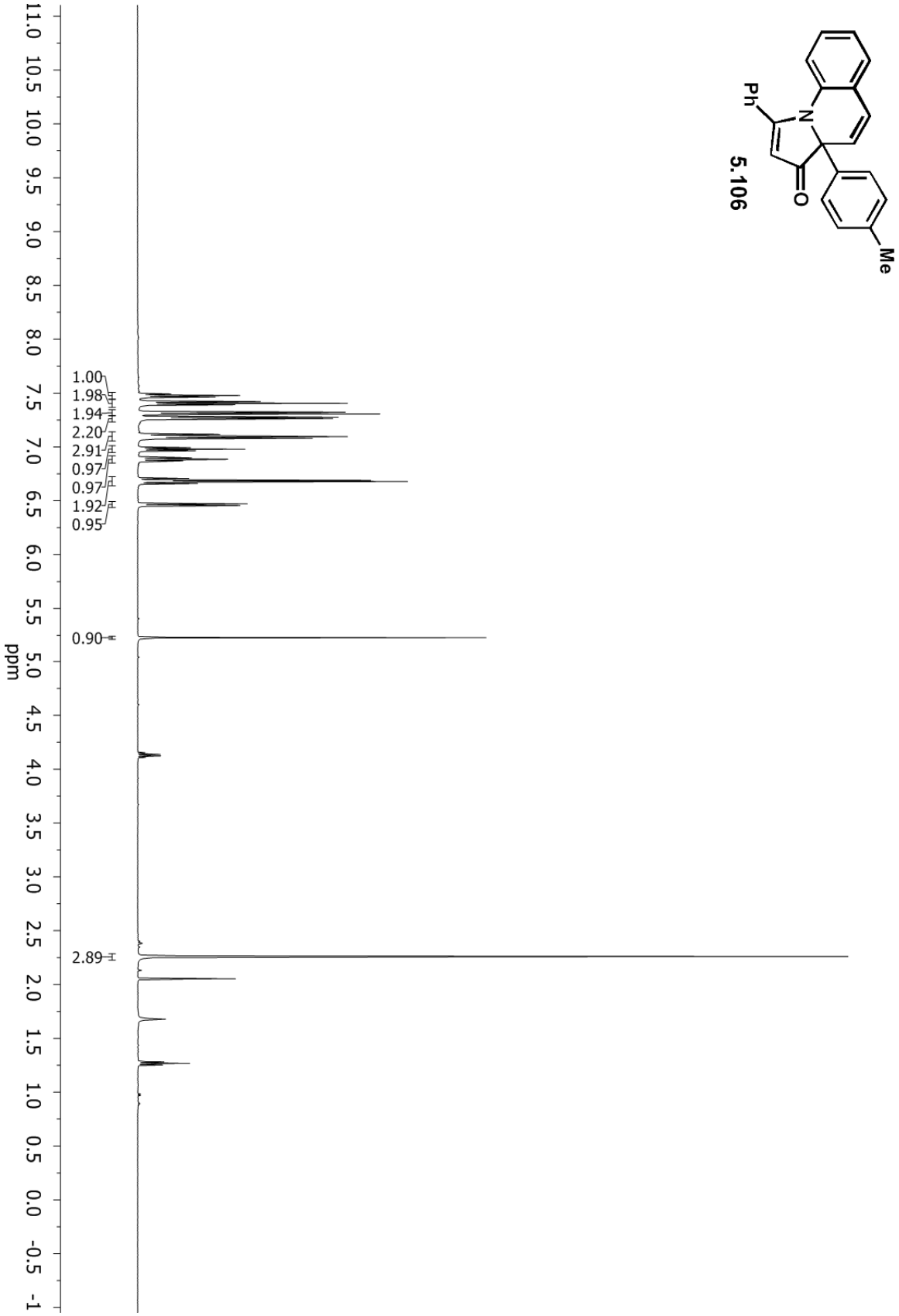

5.104
O
N
CF3
199.8
163.3
142.7
129.8
128.2
126.3
125.9
125.7
125.2
124.9
116.8
98.9
70.5
ppm
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

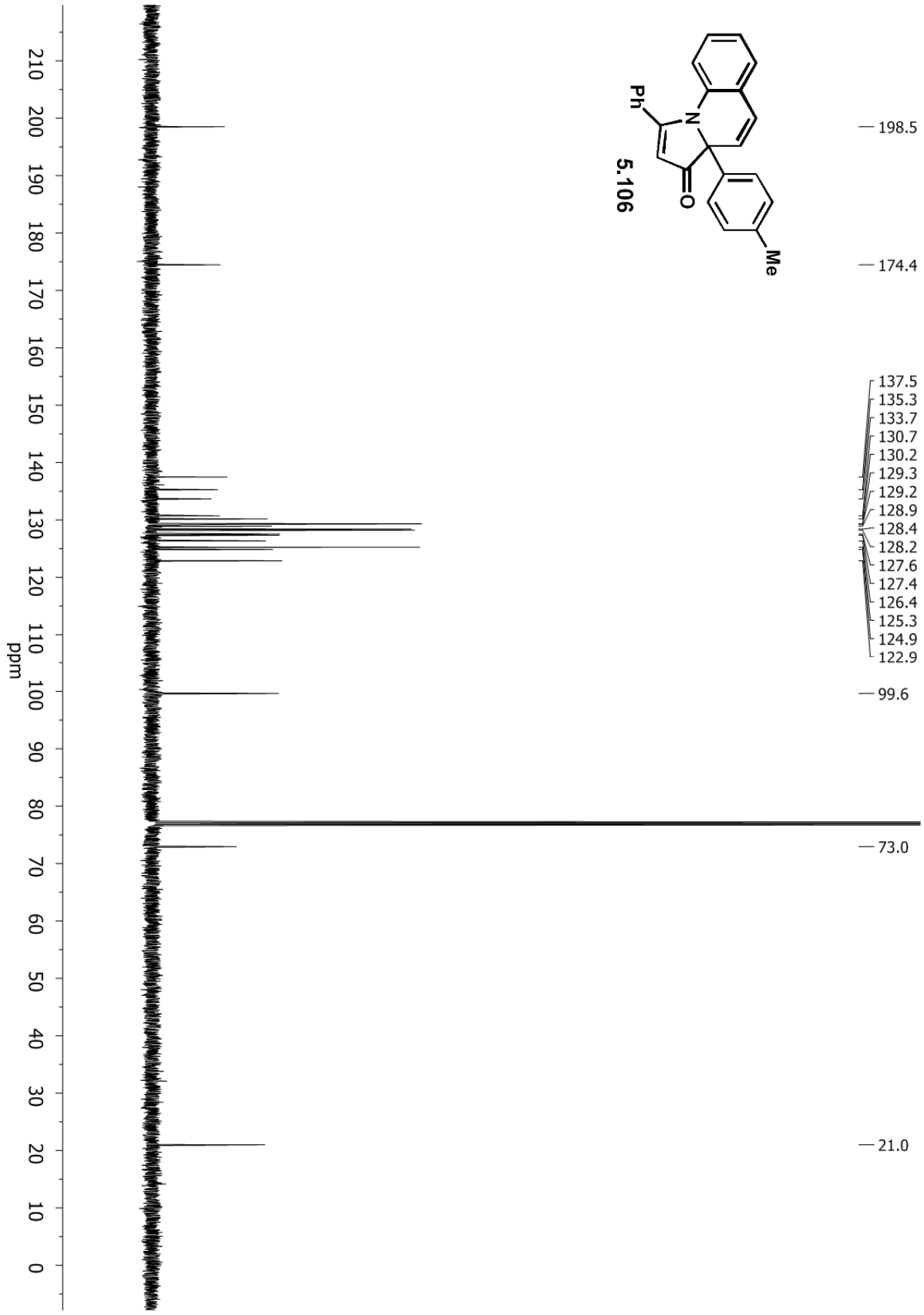

11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
ppm
1.00
1.02
1.02
2.01
1.03
2.98
0.99
0.96
3.10
3.01

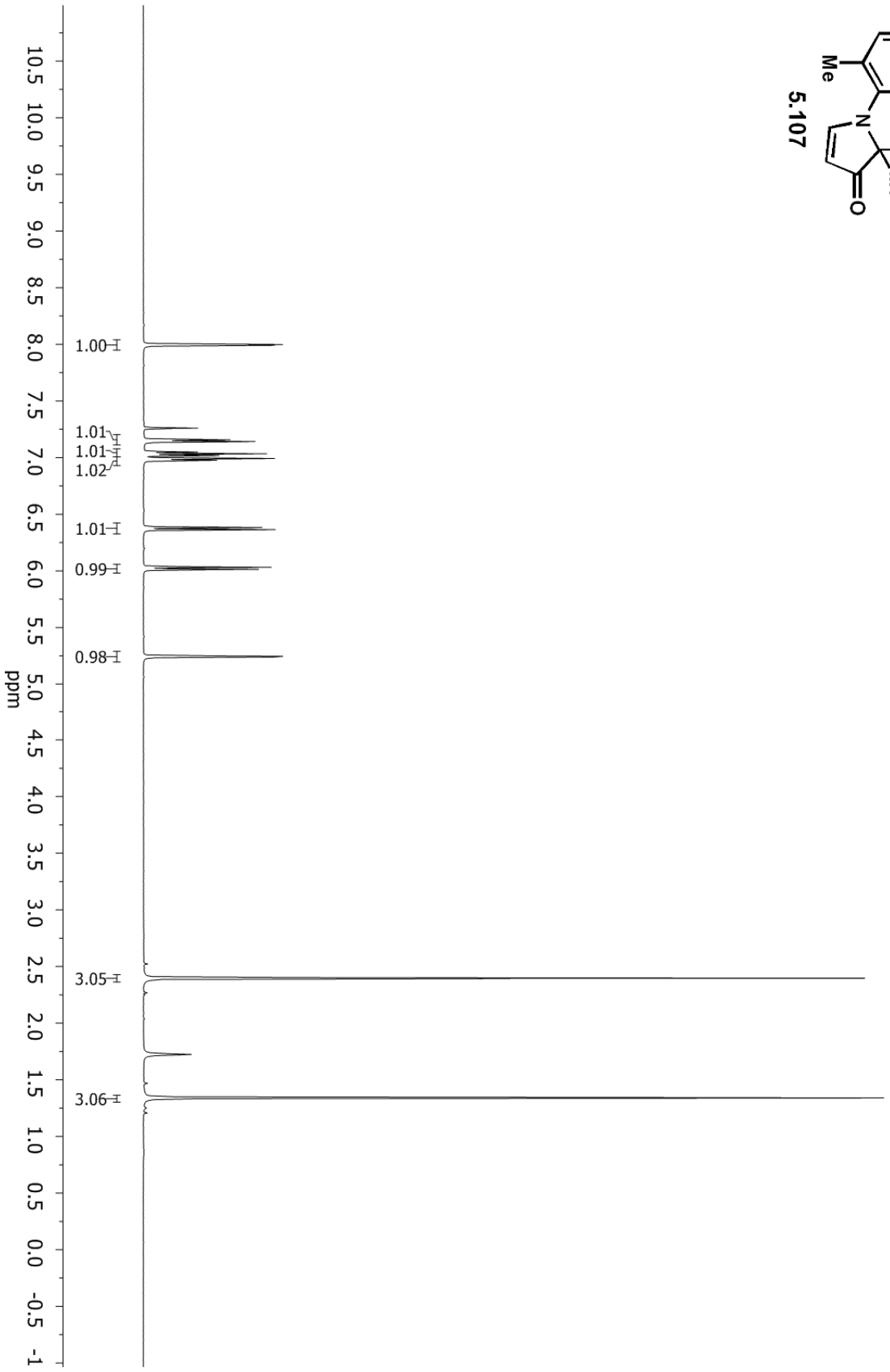

OMe
N
O
Me

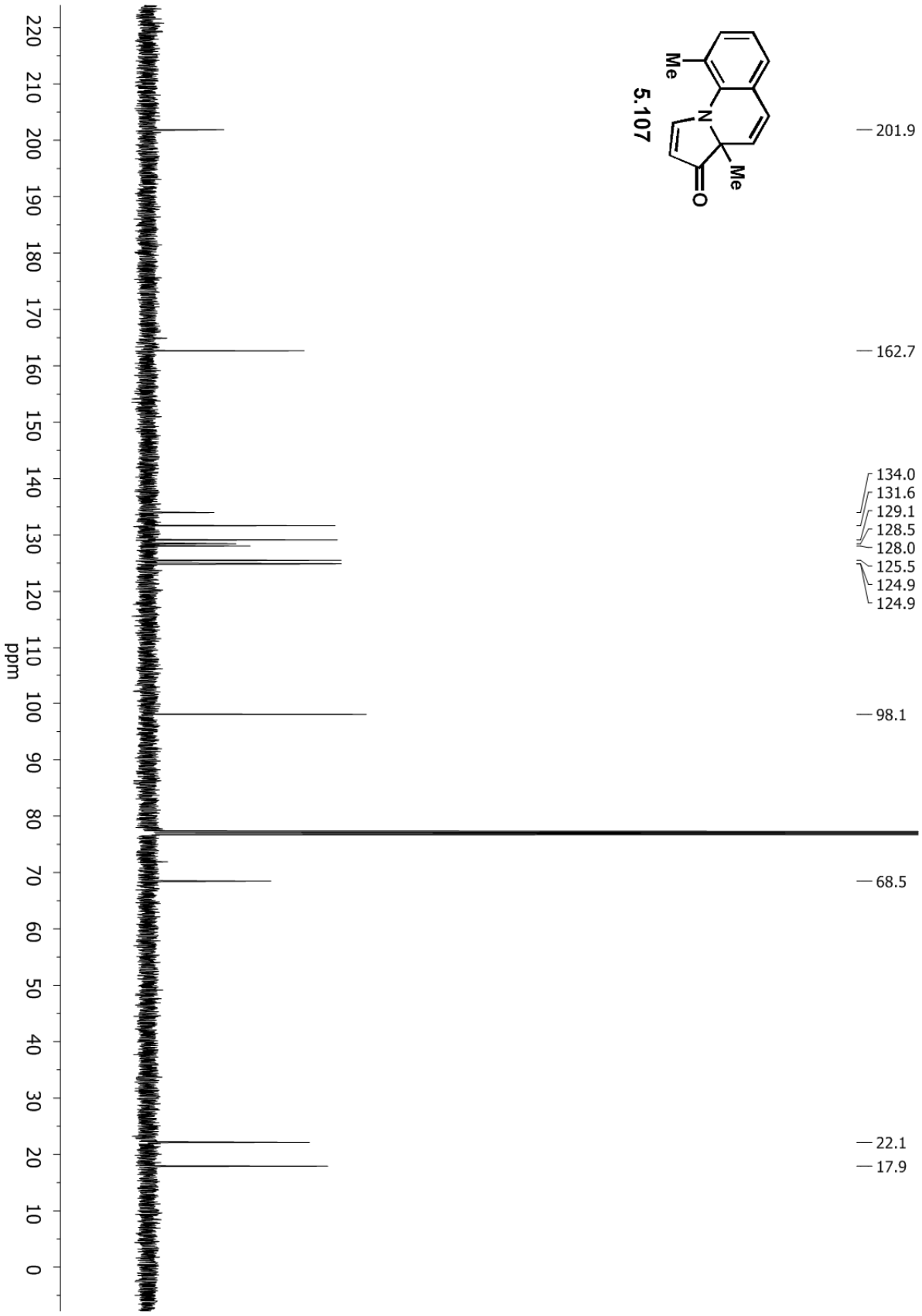
5.105

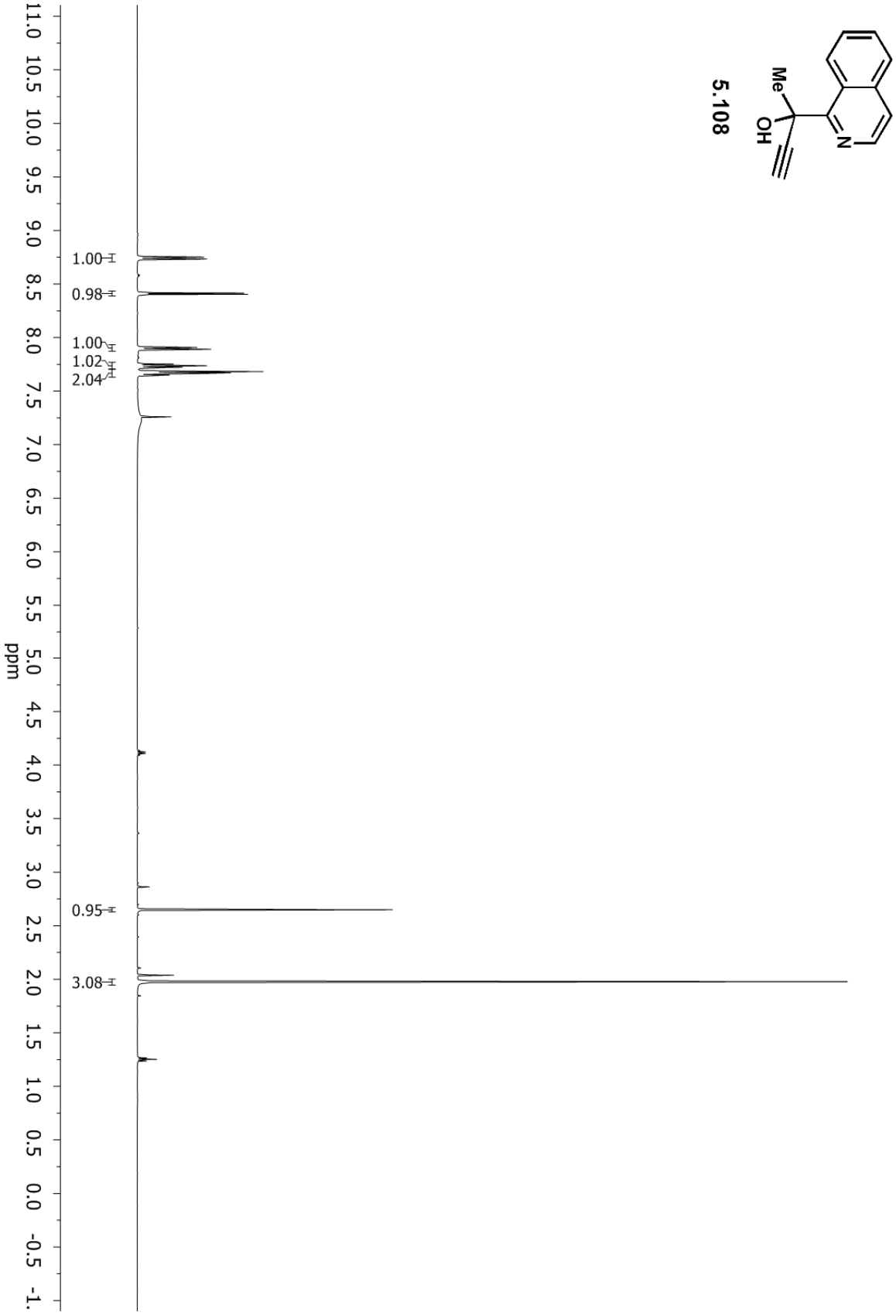

5.105
OMe
Me
N
O
202.2
162.3
151.6
137.5
136.5
129.9
129.3
125.0
124.7
124.3
123.9
116.5
99.5
96.1
70.6
55.3
21.0
ppm
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20


Ph
N
O
Me
5.106
1.00
1.98
1.94
2.20
2.91
0.97
0.97
1.92
0.95
0.90
2.89
ppm
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1


5.106
Ph
N
O
Me
198.5
174.4
137.5
135.3
133.7
130.7
130.2
129.3
129.2
128.9
128.4
128.2
127.6
127.4
126.4
125.3
124.9
122.9
99.6
73.0
21.0
ppm
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


5.107
Me
N
Me
O
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
ppm
1.00
1.01
1.01
1.02
1.01
0.99
0.98
3.05
3.06


5.107
Me
N
Me
O
201.9
162.7
134.0
131.6
129.1
128.5
128.0
125.5
124.9
124.9
98.1
68.5
22.1
17.9
ppm
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0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Me
OH
N
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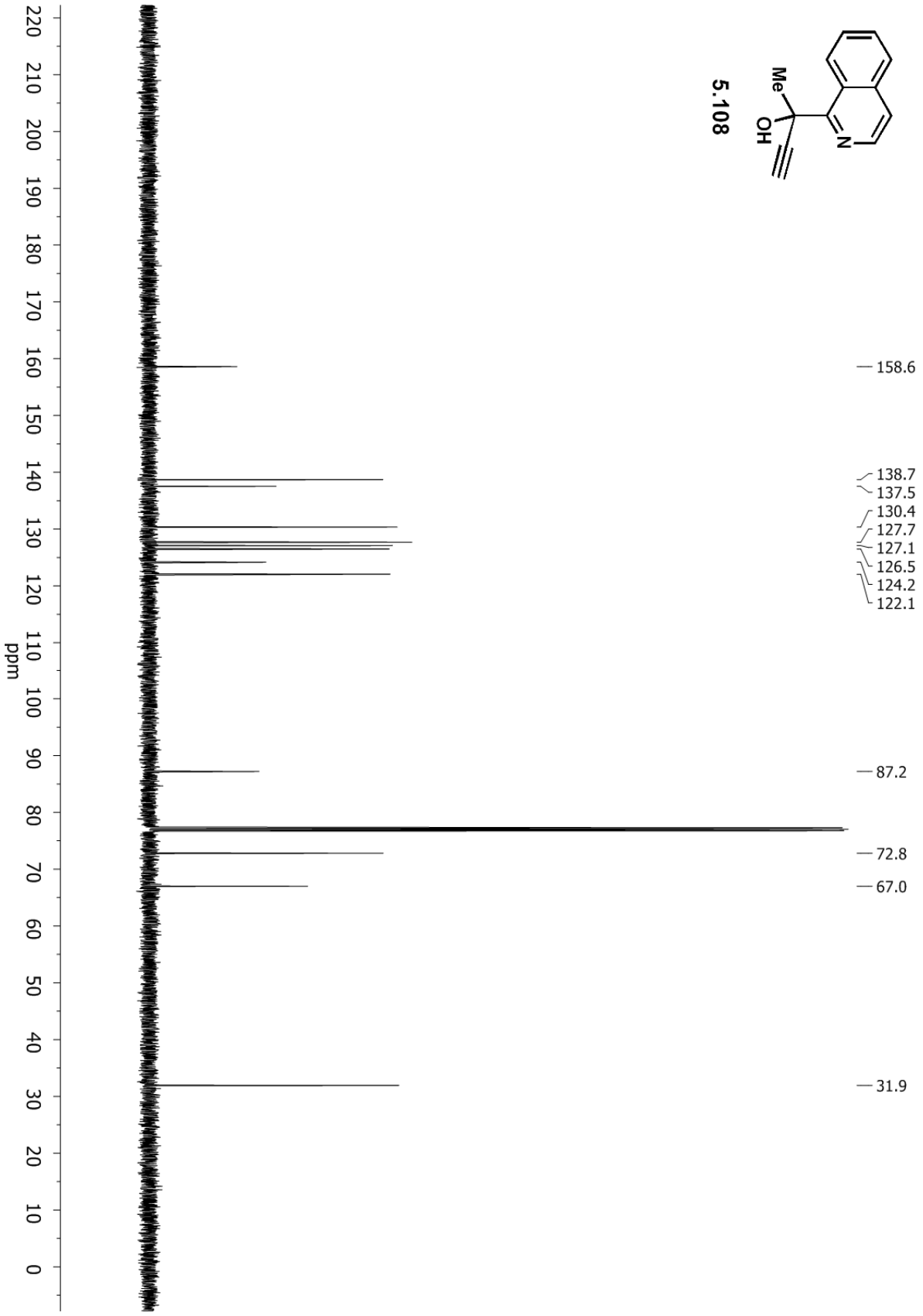
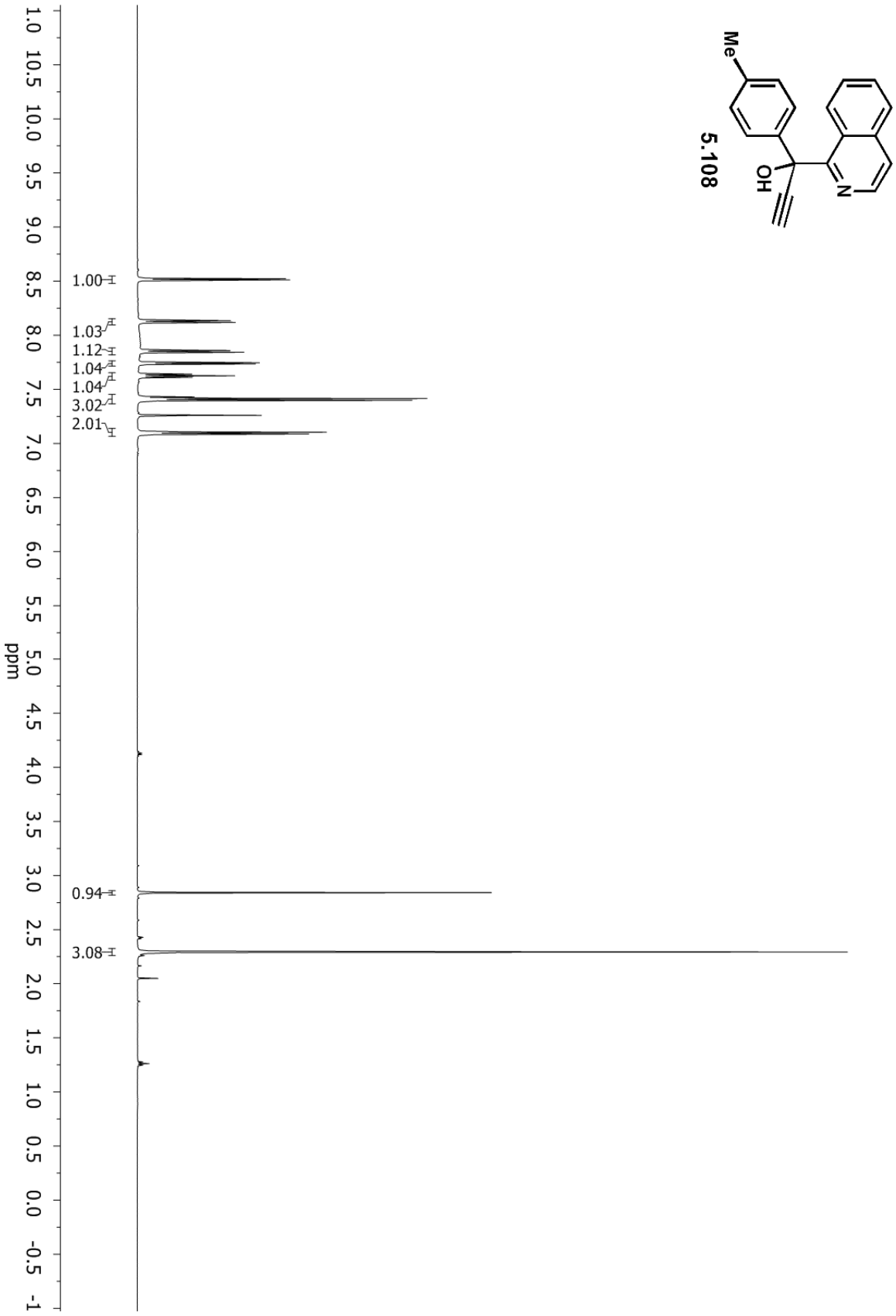
0.98
1.00
1.02
2.04
0.95
3.08
ppm


5.108
Me
OH
N
158.6
138.7
137.5
130.4
127.7
127.1
126.5
124.2
122.1
87.2
72.8
67.0
31.9
ppm
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0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OH
N
5.108
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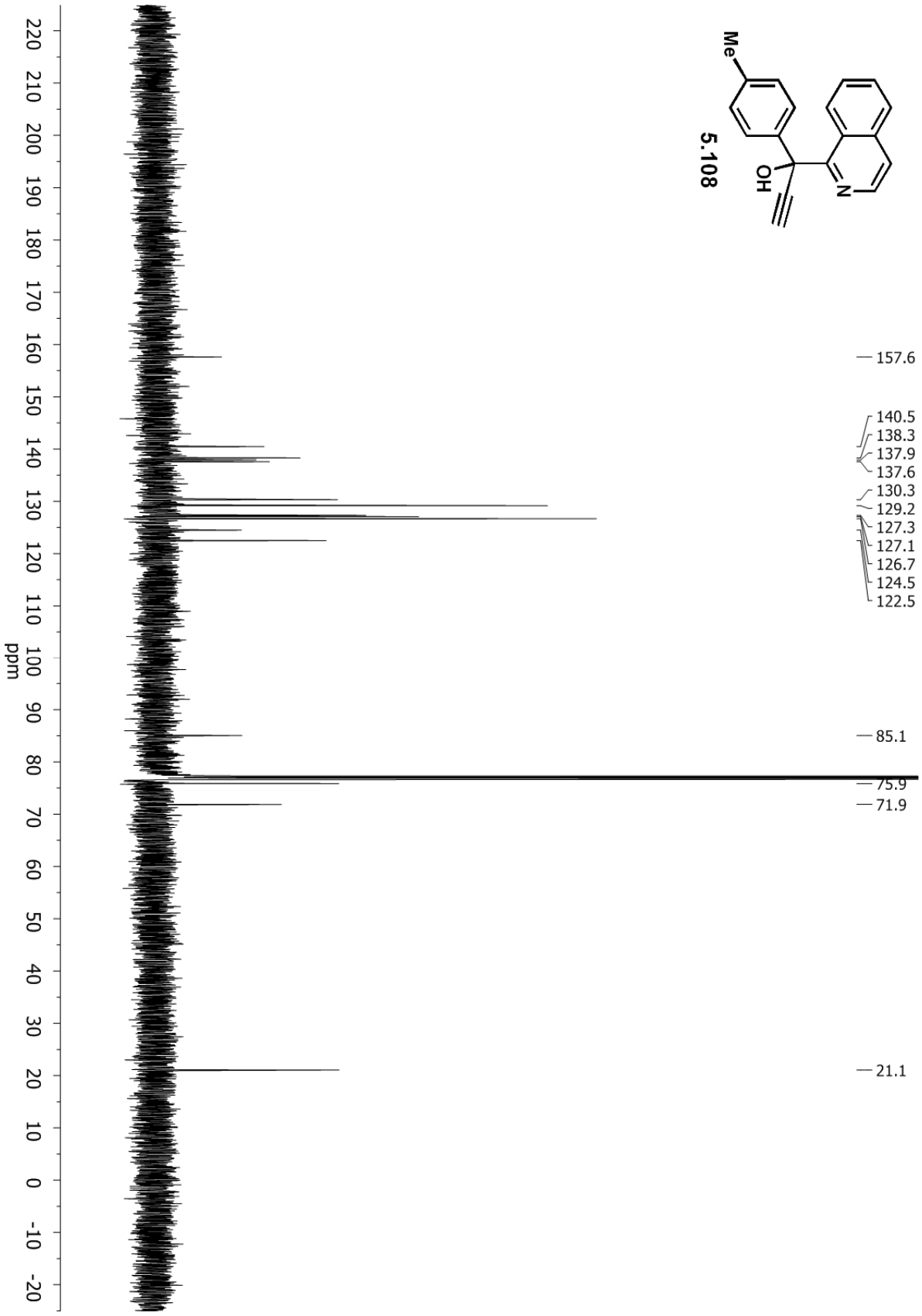
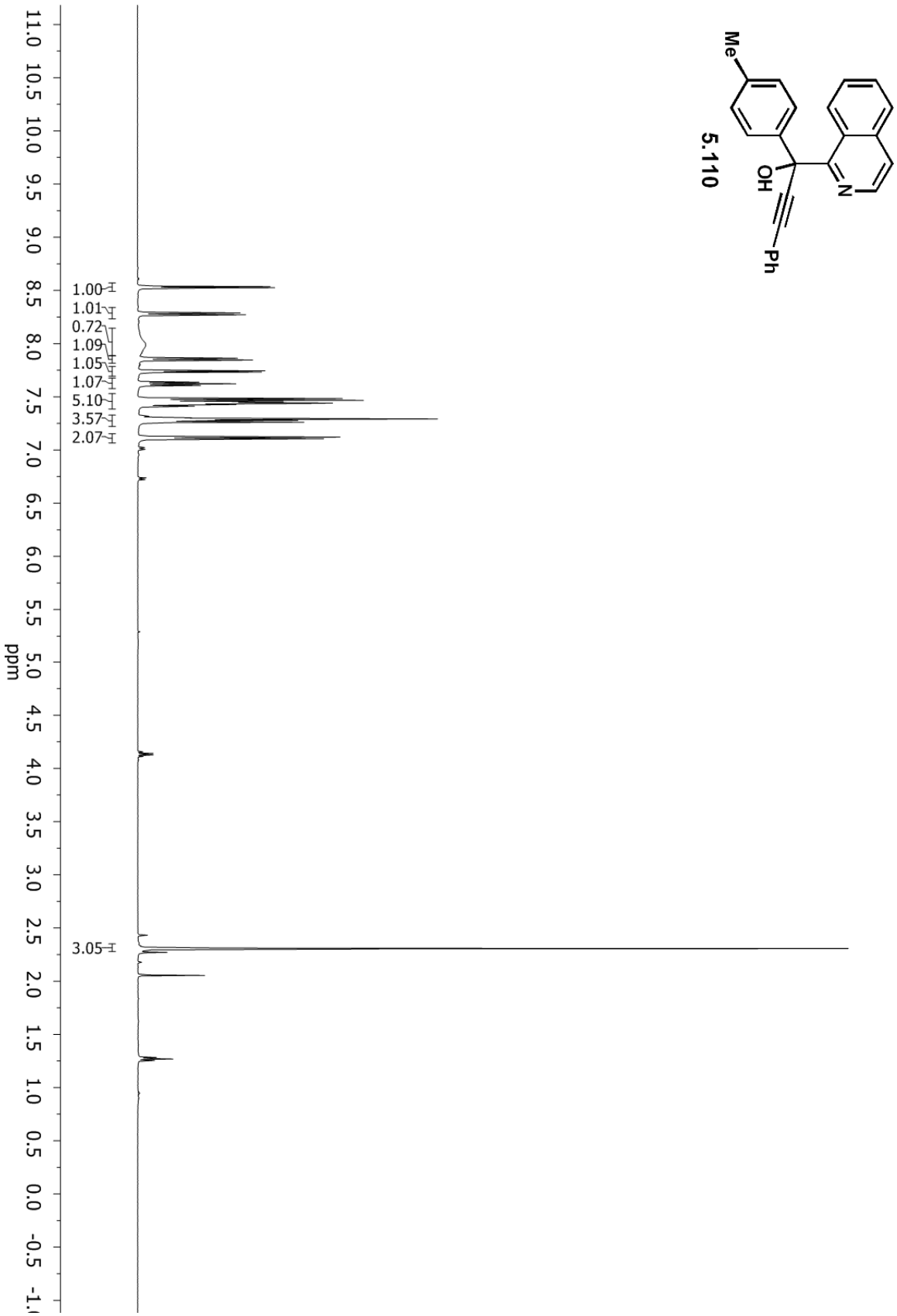
1.03
1.12
1.04
1.04
3.02
2.01
0.94
3.08
ppm
1.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1


5.108
Me
OH
N
157.6
140.5
138.3
137.9
137.6
130.3
129.2
127.3
127.1
126.7
124.5
122.5
85.1
75.9
71.9
21.1
ppm
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20


Me
OH
N
Ph
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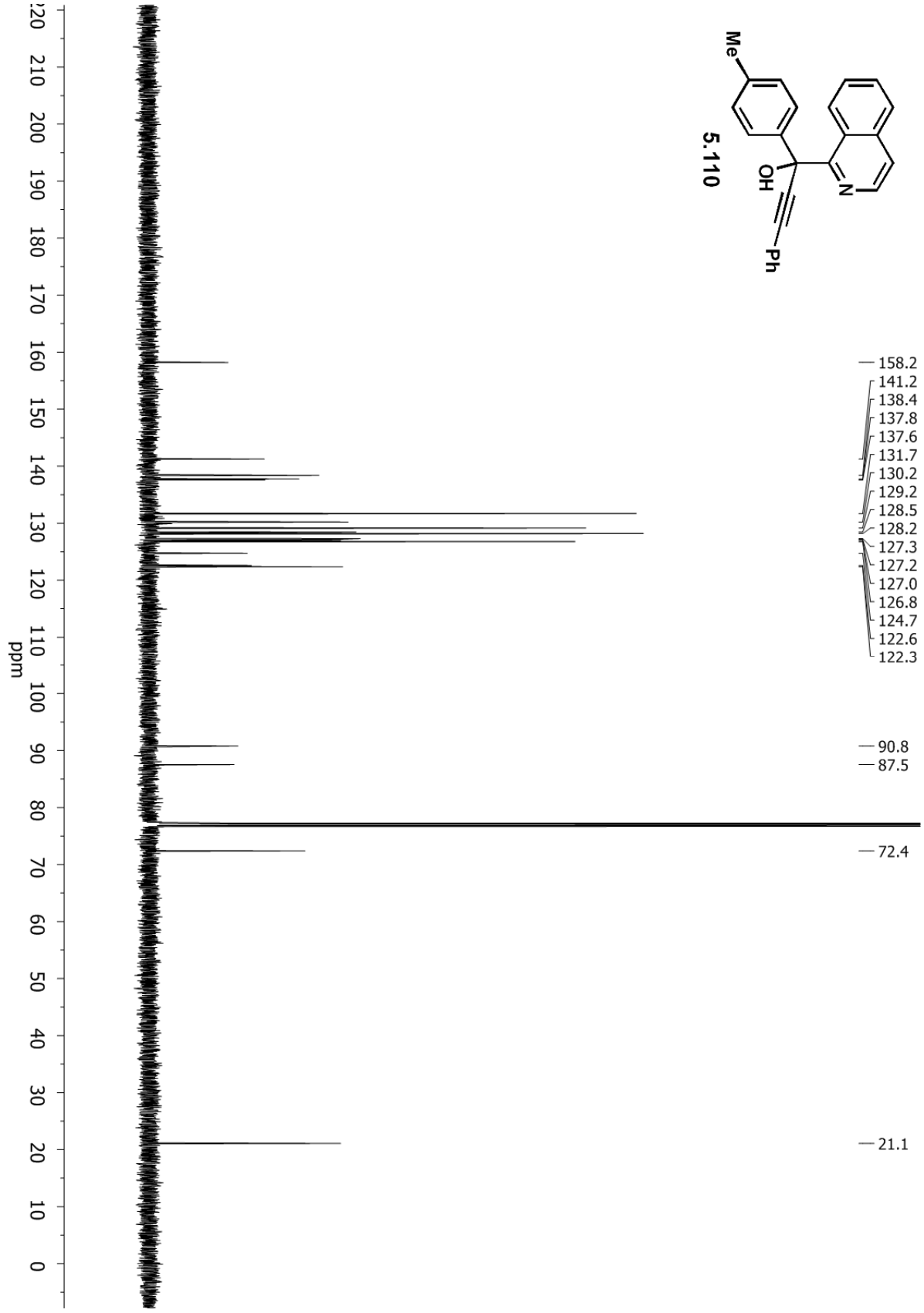
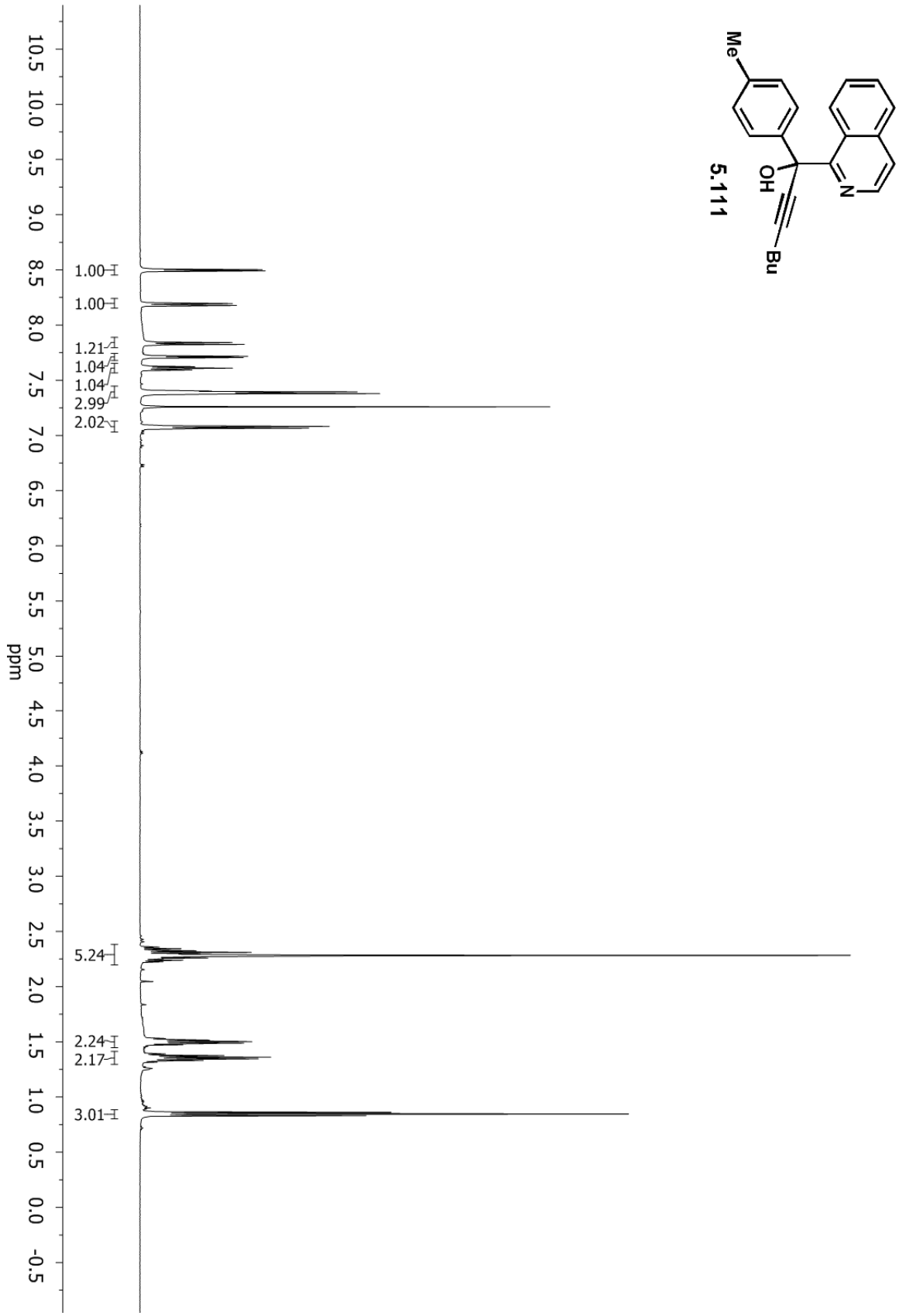
1.01
0.72
1.09
1.05
1.07
5.10
3.57
2.07
3.05
ppm


Me
OH
N
Ph
5.110
158.2
141.2
138.4
137.8
137.6
131.7
130.2
129.2
128.5
128.2
127.3
127.2
127.0
126.8
124.7
122.6
122.3
90.8
87.5
72.4
21.1
ppm


Me
OH
N
Bu
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1.21
1.04
1.04
2.99
2.02
5.24
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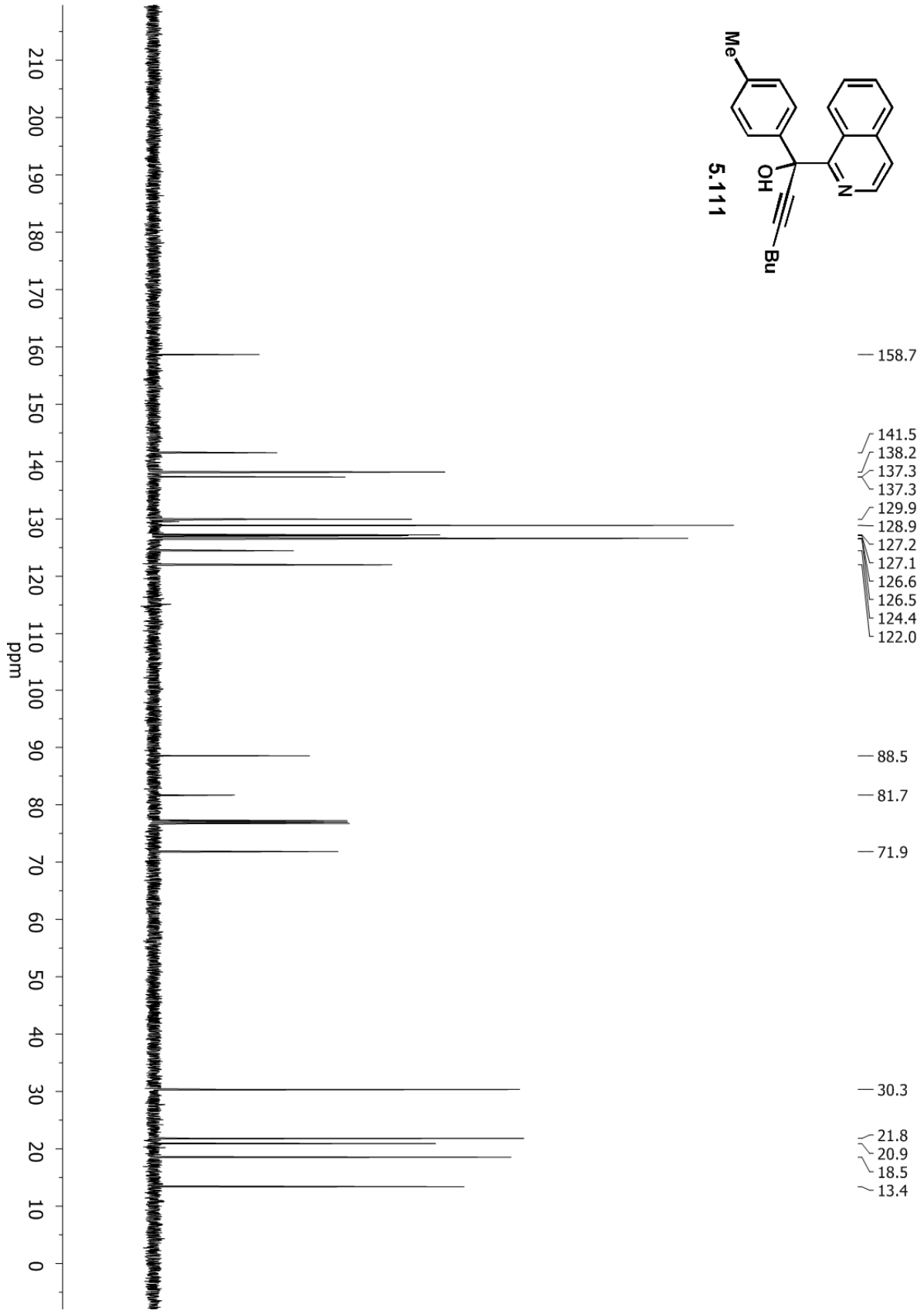
2.17
3.01
ppm


Me
OH
N
Bu
5.111
158.7
141.5
138.2
137.3
137.3
129.9
128.9
127.2
127.1
126.6
126.5
124.4
122.0
88.5
81.7
71.9
30.3
21.8
20.9
18.5
13.4
ppm
210
200
190
180
170
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150
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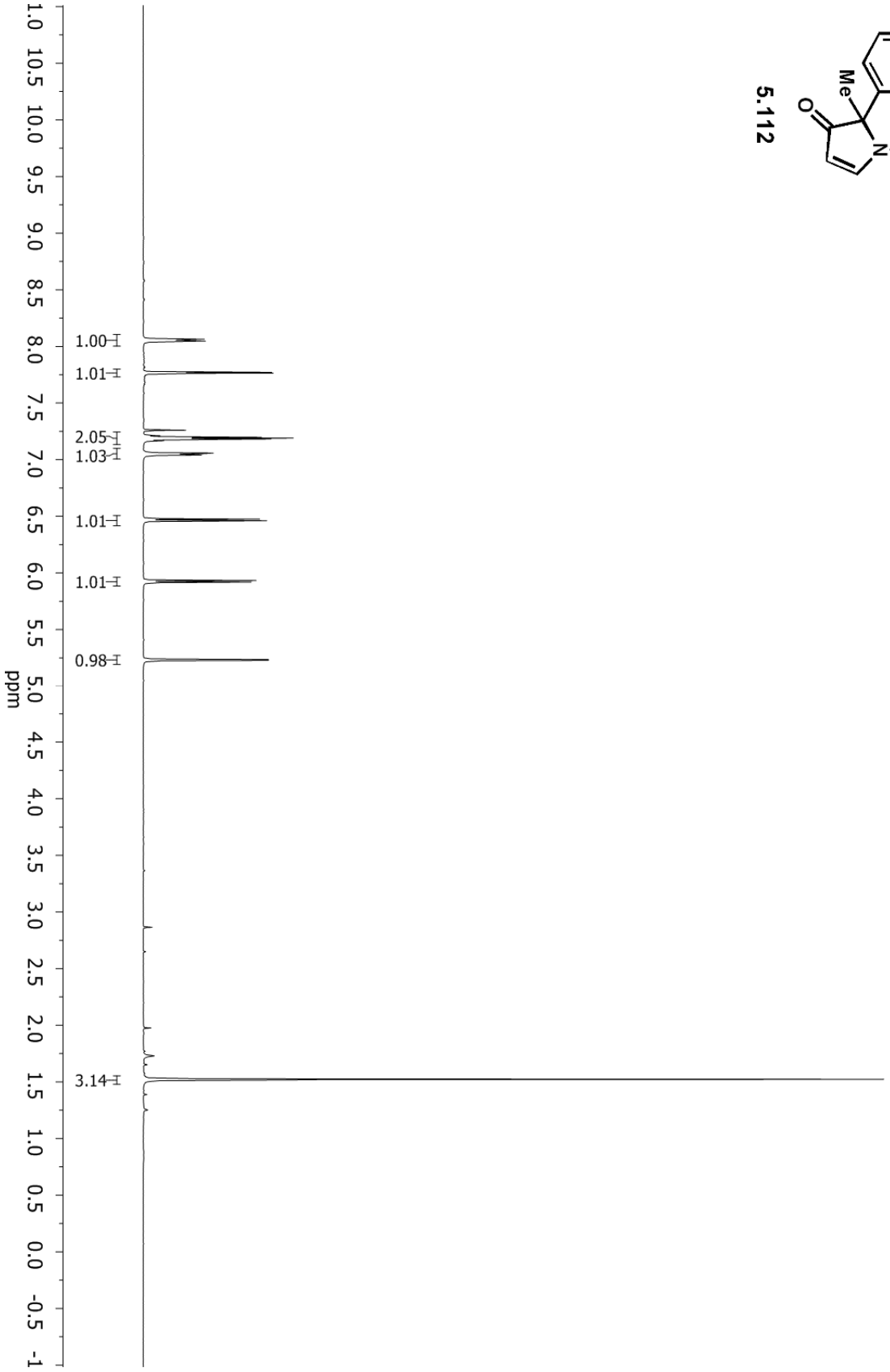
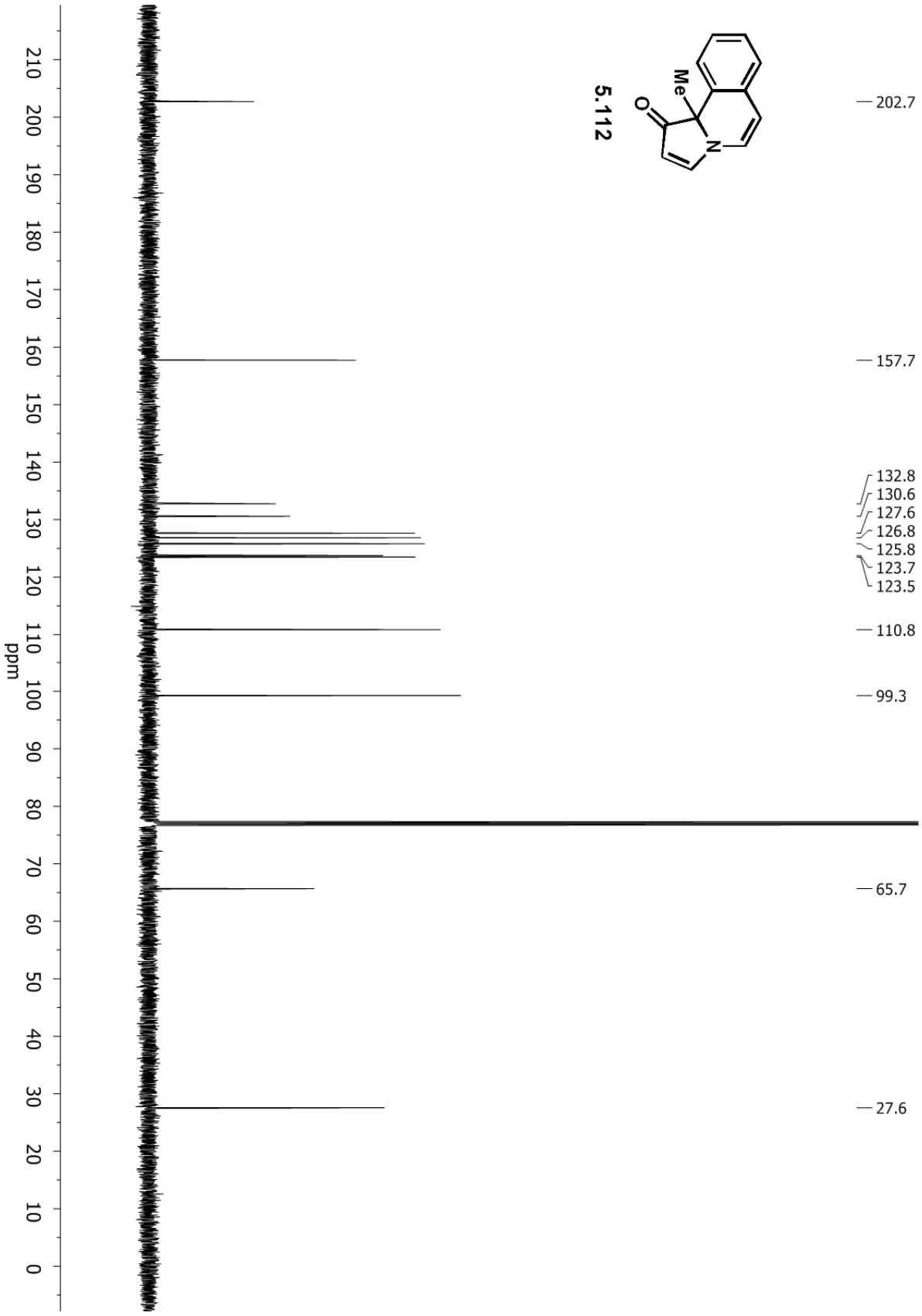
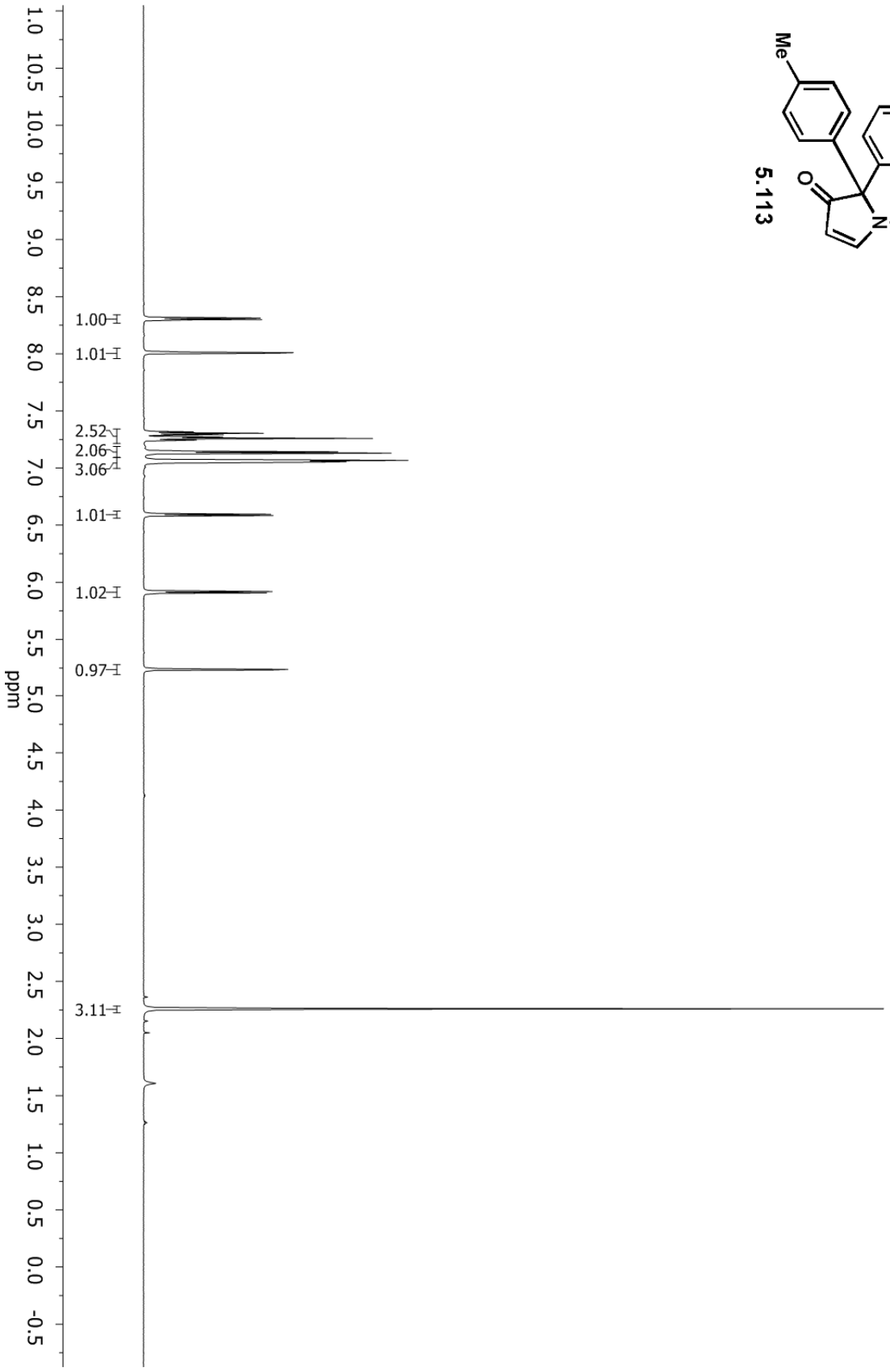
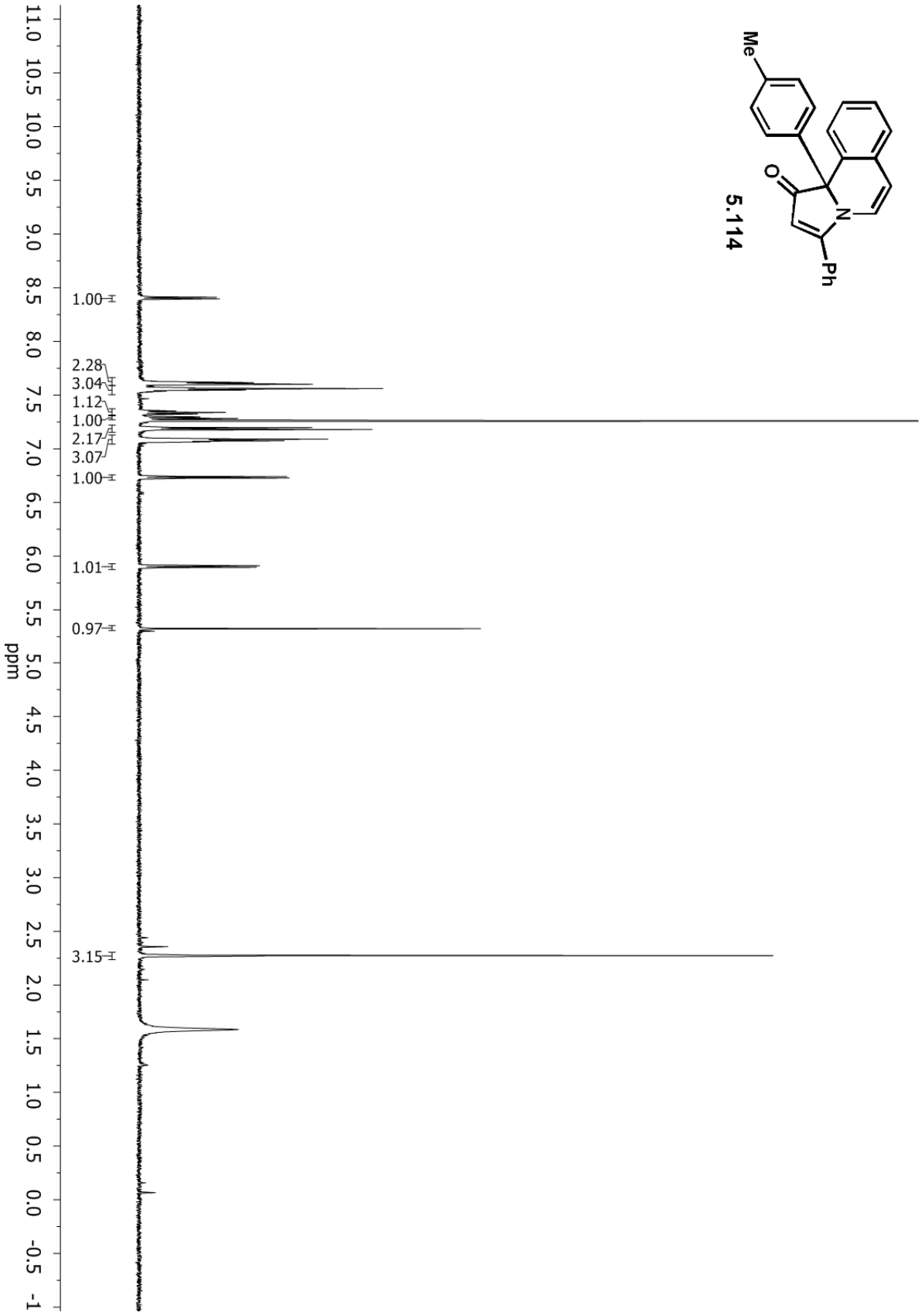
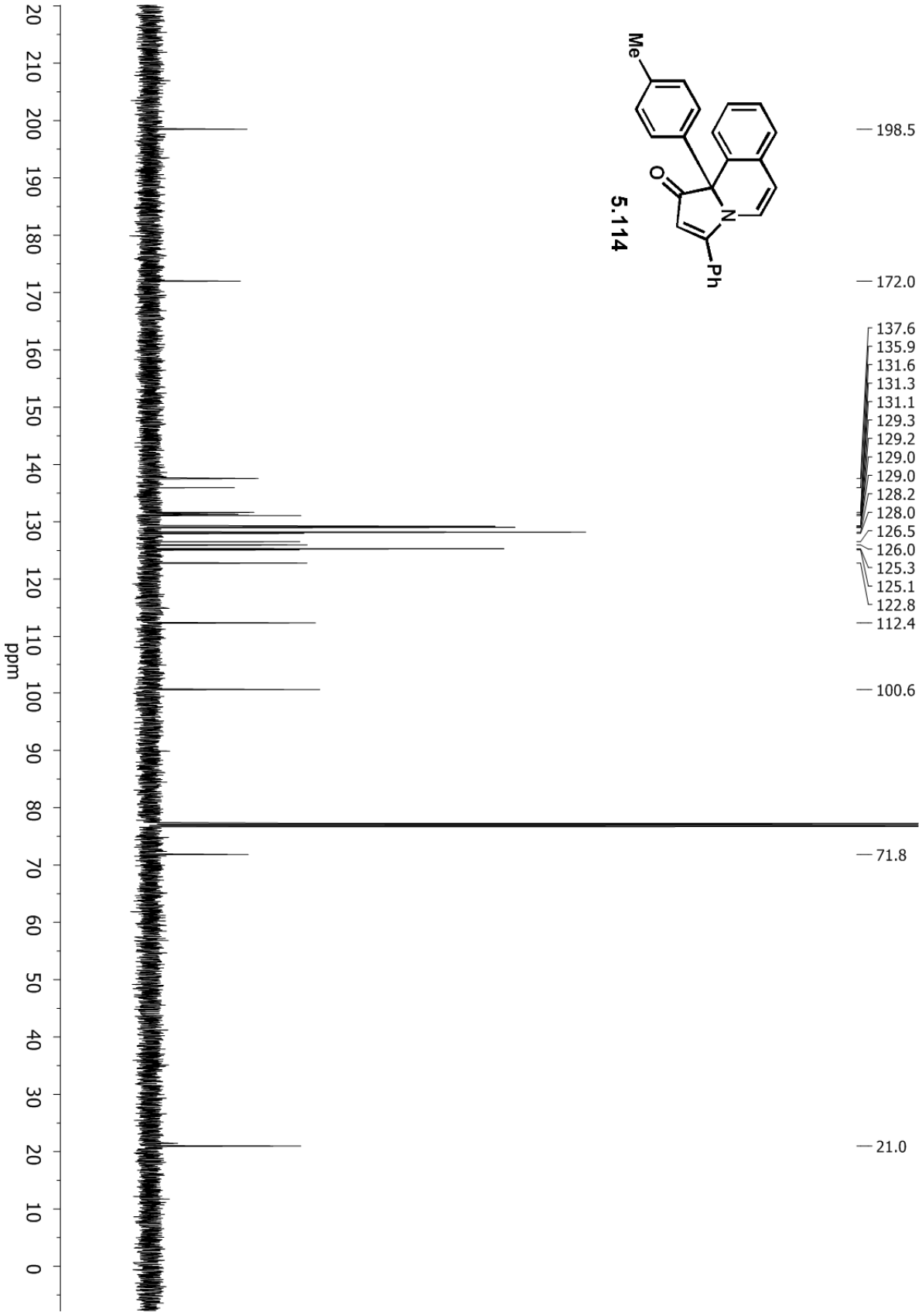
90
80
70
60
50
40
30
20
10
0

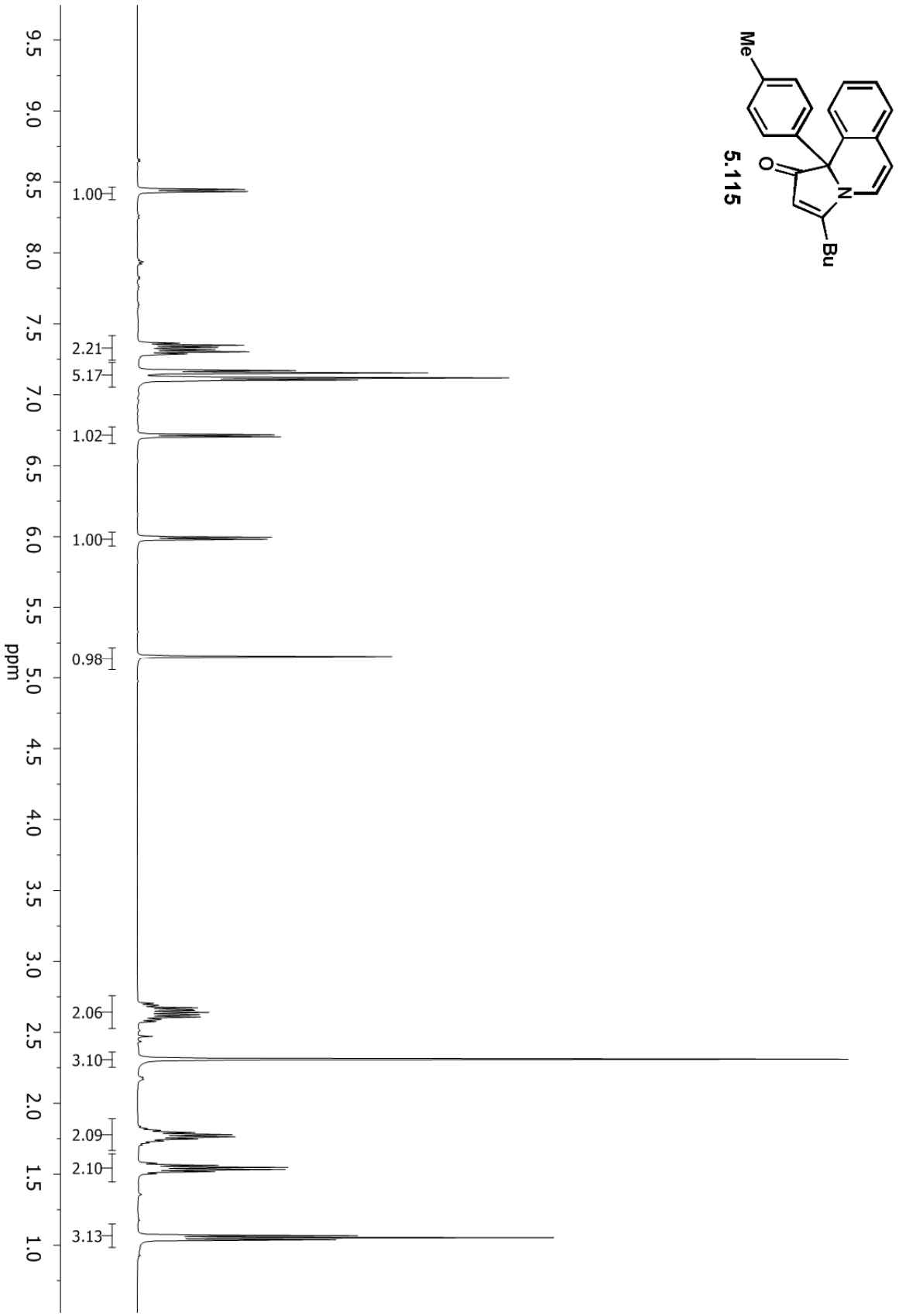

5.112
Me
O
N
1.00
1.01
2.05
1.03
1.01
1.01
0.98
3.14
ppm
1.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1


5.112
Me
O
N
202.7
157.7
132.8
130.6
127.6
126.8
125.8
123.7
123.5
110.8
99.3
65.7
27.6
ppm
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


Me
O
N
5.113
1.00
1.01
2.52
2.06
3.06
1.01
1.02
0.97
3.11
ppm
1.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5


Me
O
N
Ph
5.114
1.00
2.28
3.04
1.12
1.00
2.17
3.07
1.00
1.01
0.97
3.15
ppm
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1


Me
O
N
Ph
5.114
198.5
172.0
137.6
135.9
131.6
131.3
131.1
129.3
129.2
129.0
129.0
128.2
128.0
126.5
126.0
125.3
125.1
122.8
112.4
100.6
71.8
21.0
ppm
20 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0


Me
O
N
Bu
5.115
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
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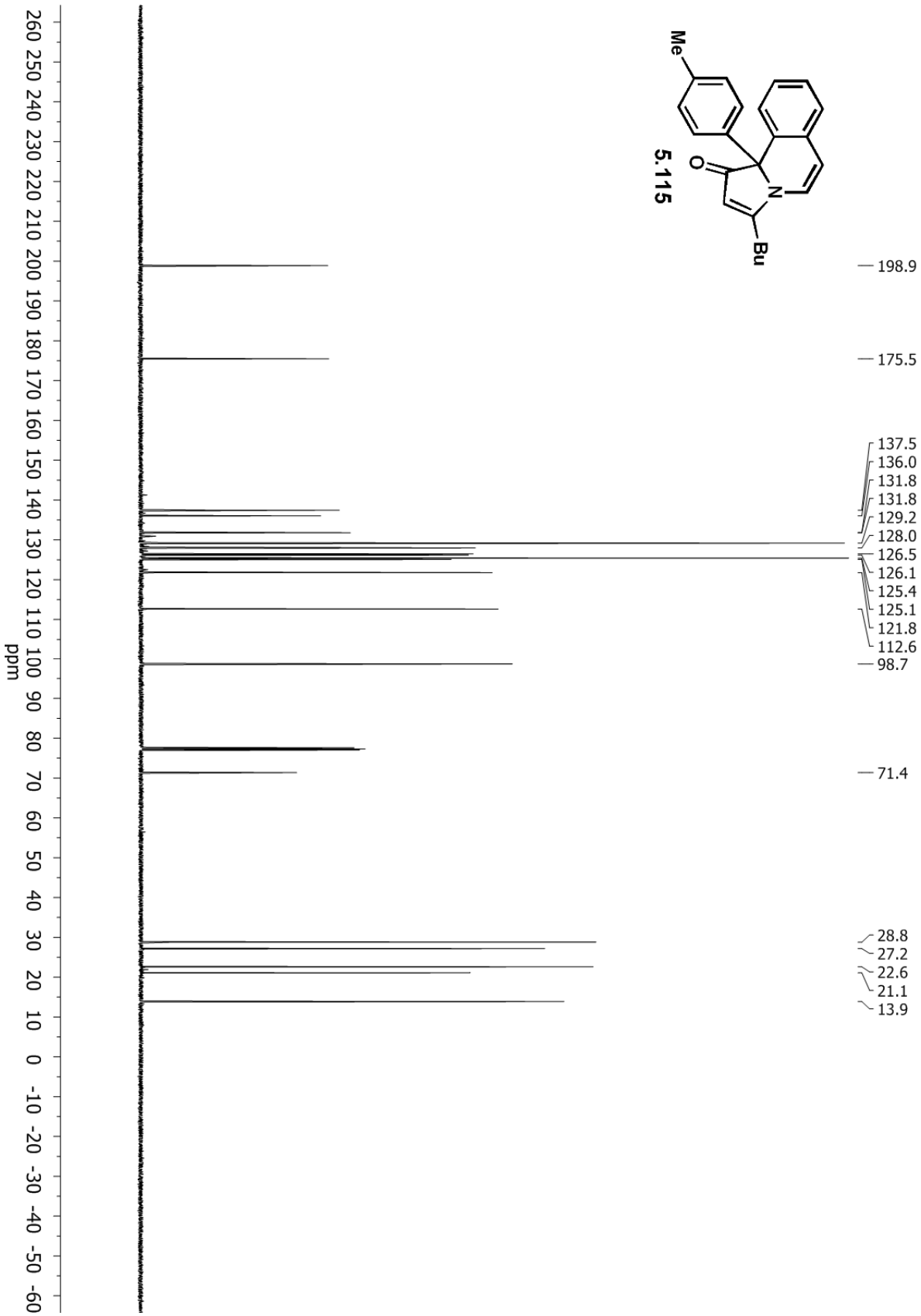
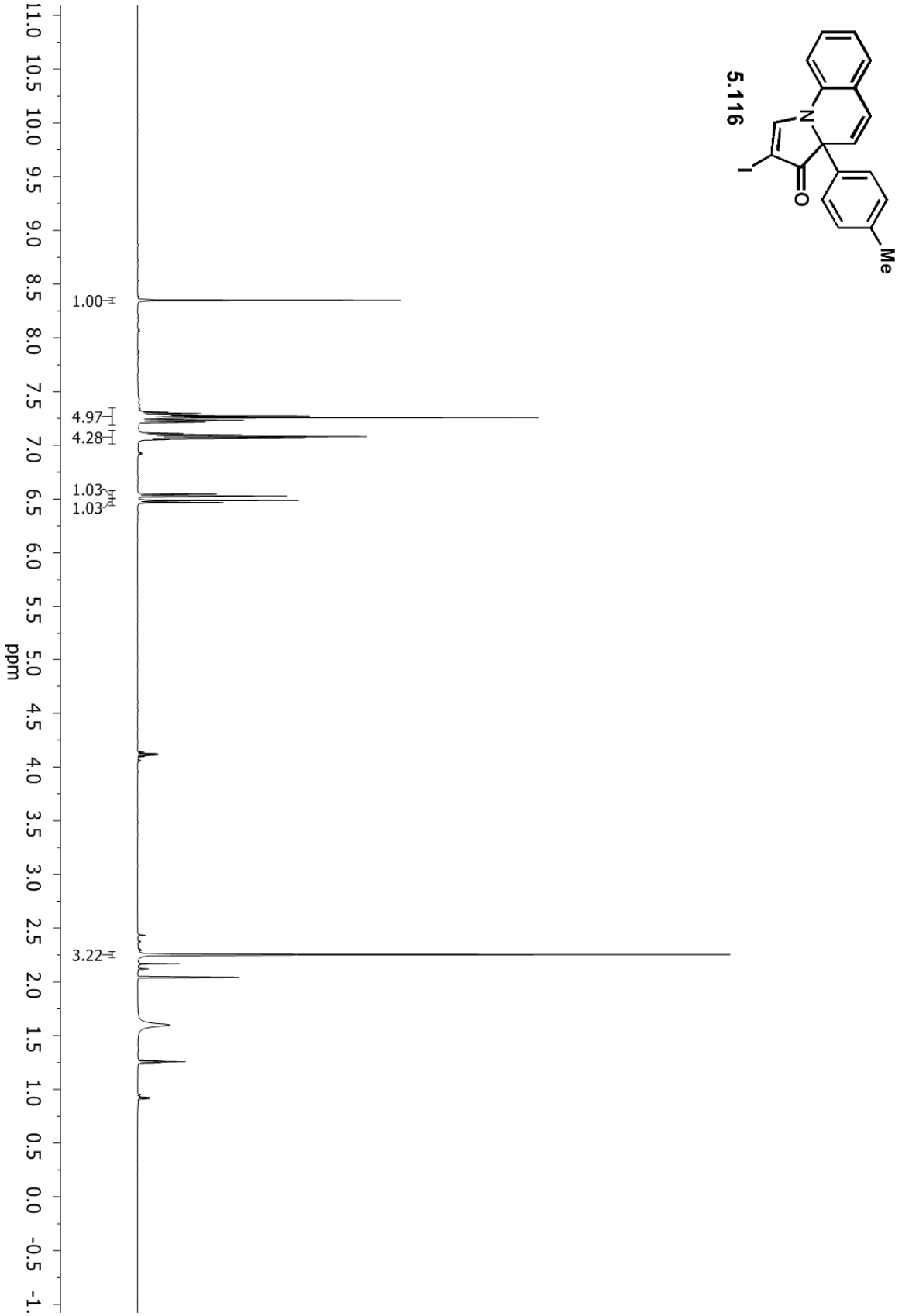
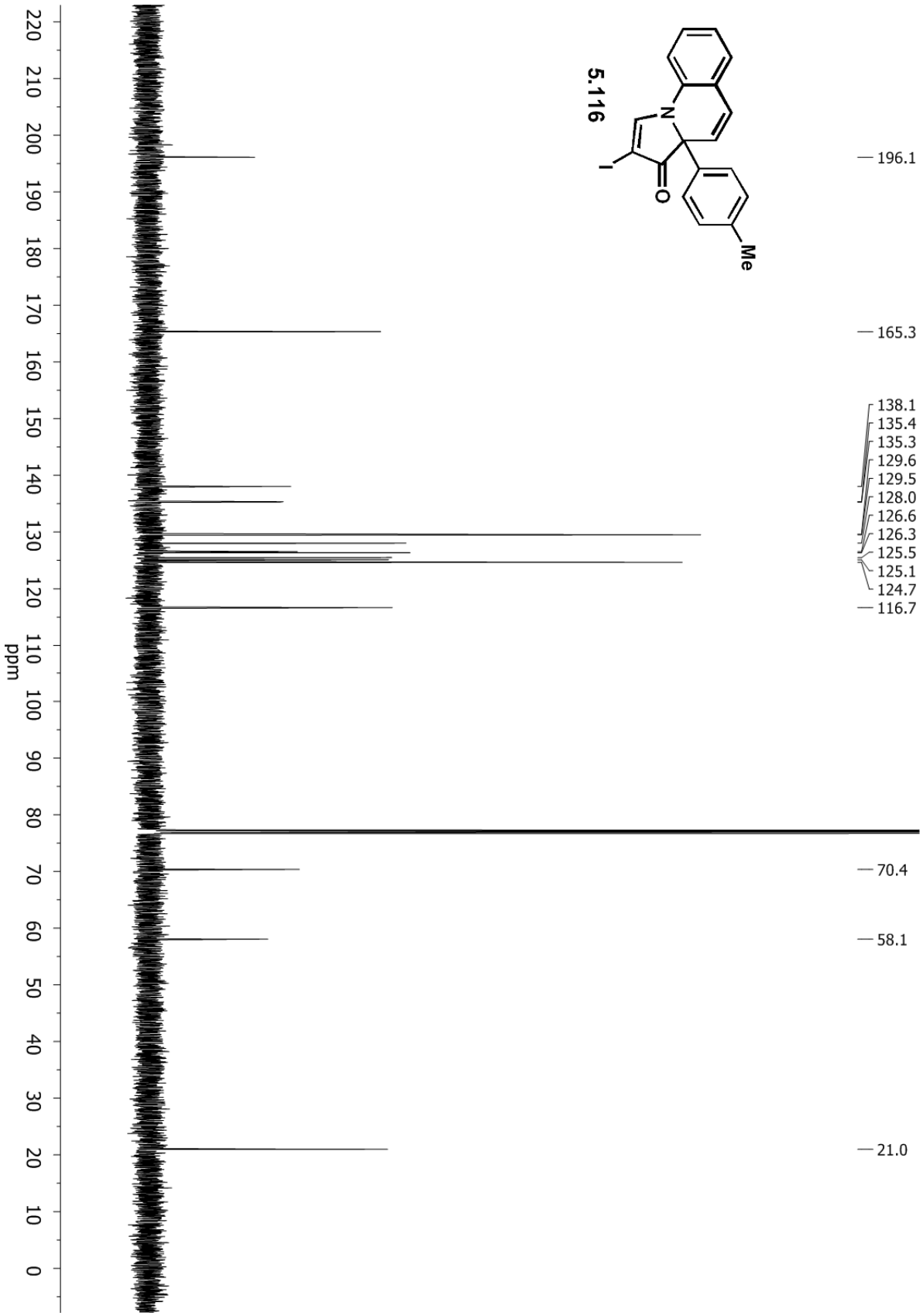
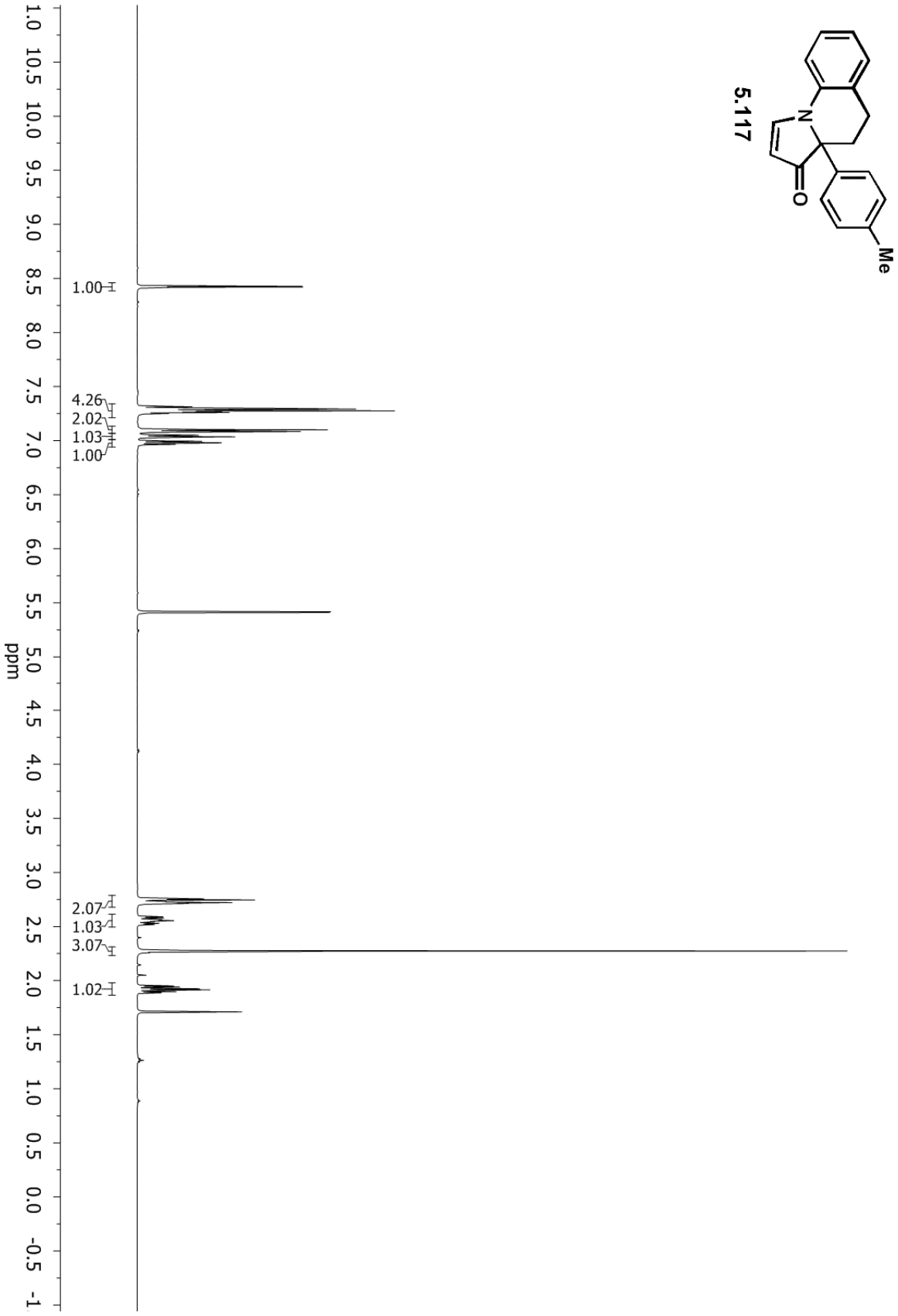
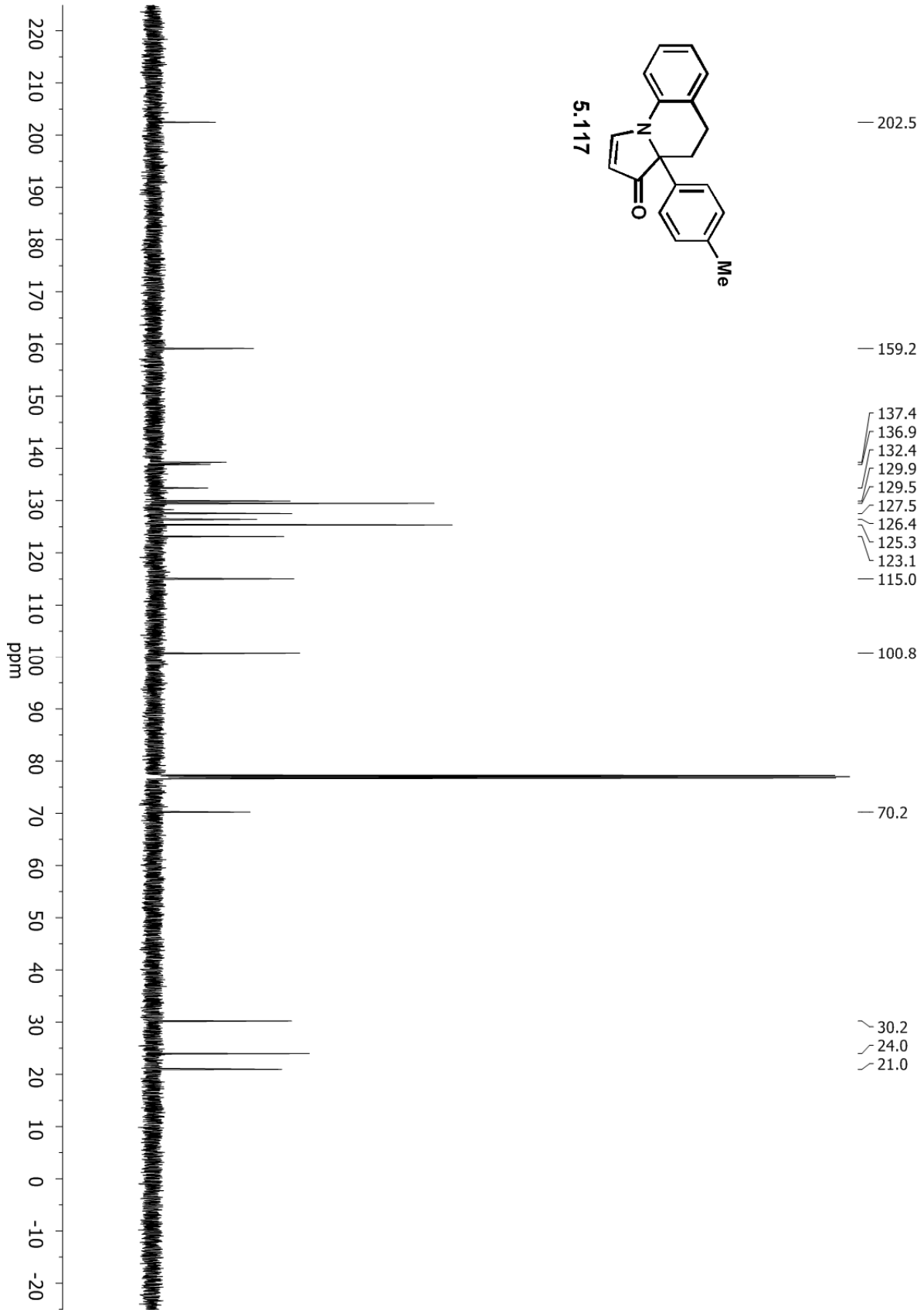
2.21
5.17
1.02
1.00
0.98
2.06
3.10
2.09
2.10
3.13

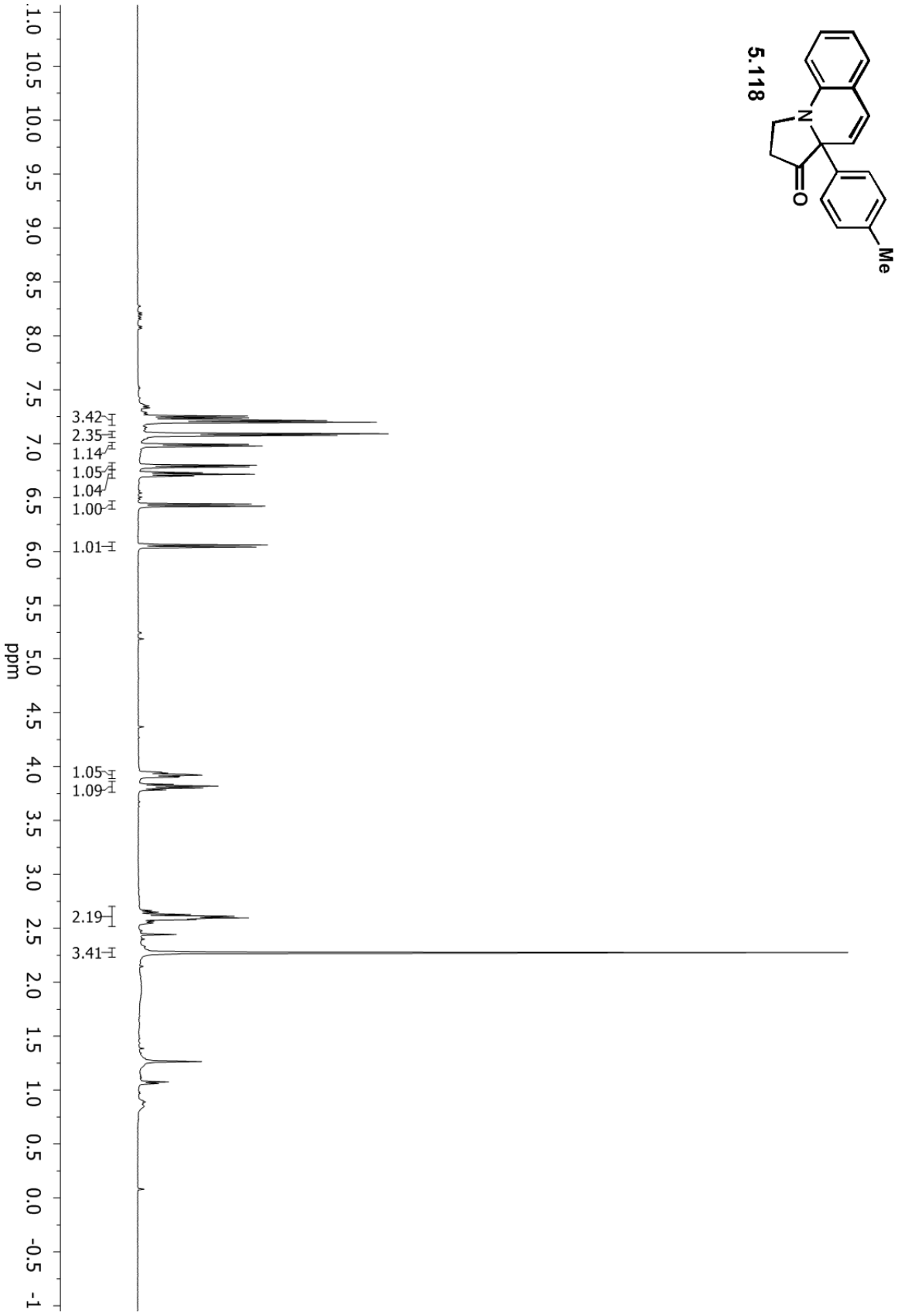

Me
O
N
Bu
5.115
198.9
175.5
137.5
136.0
131.8
131.8
129.2
128.0
126.5
126.1
125.4
125.1
121.8
112.6
98.7
71.4
28.8
27.2
22.6
21.1
13.9
260 250 240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60
ppm

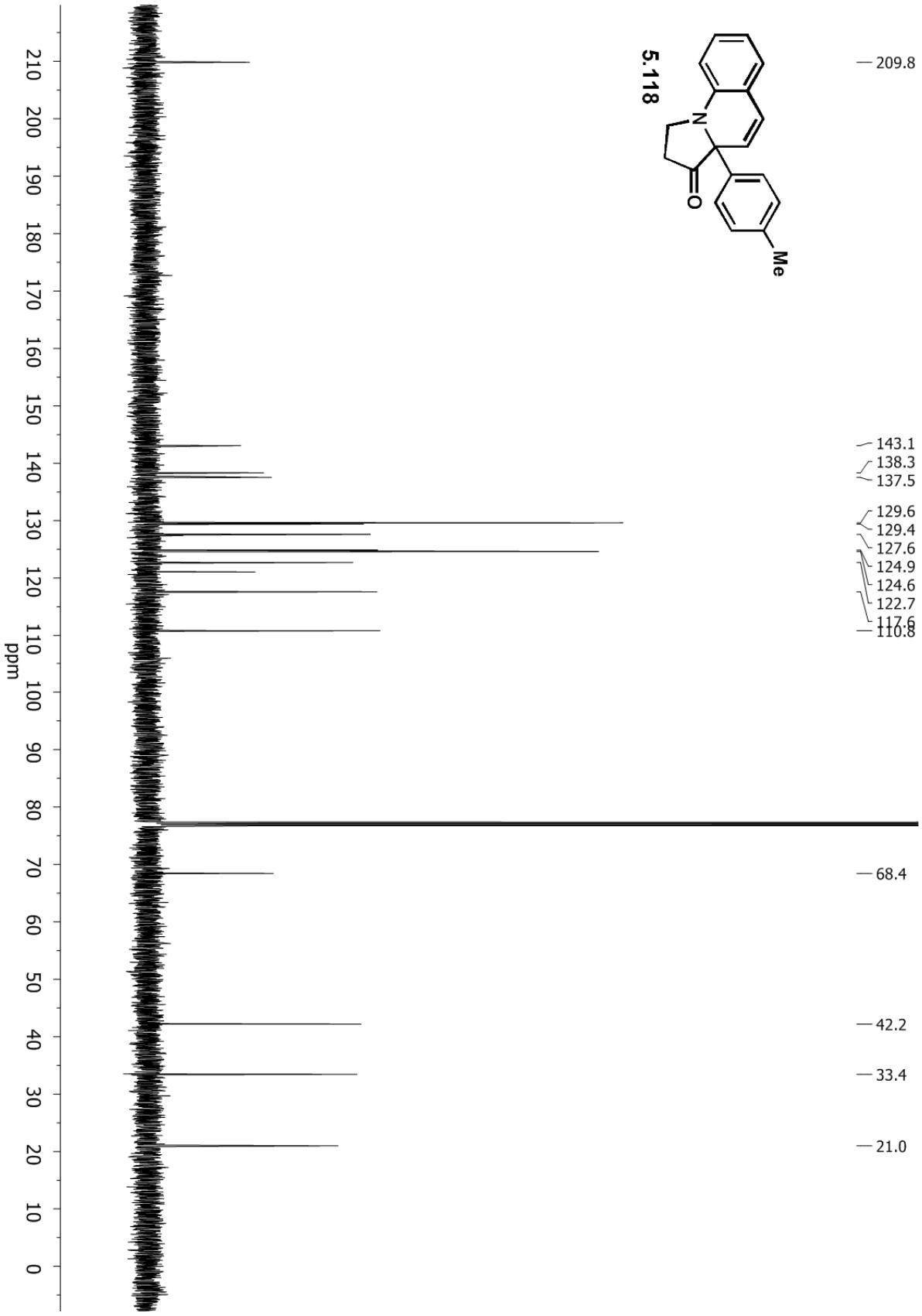

5.116
N
I
O
Me
1.00
4.97
4.28
1.03
1.03
3.22
ppm
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.

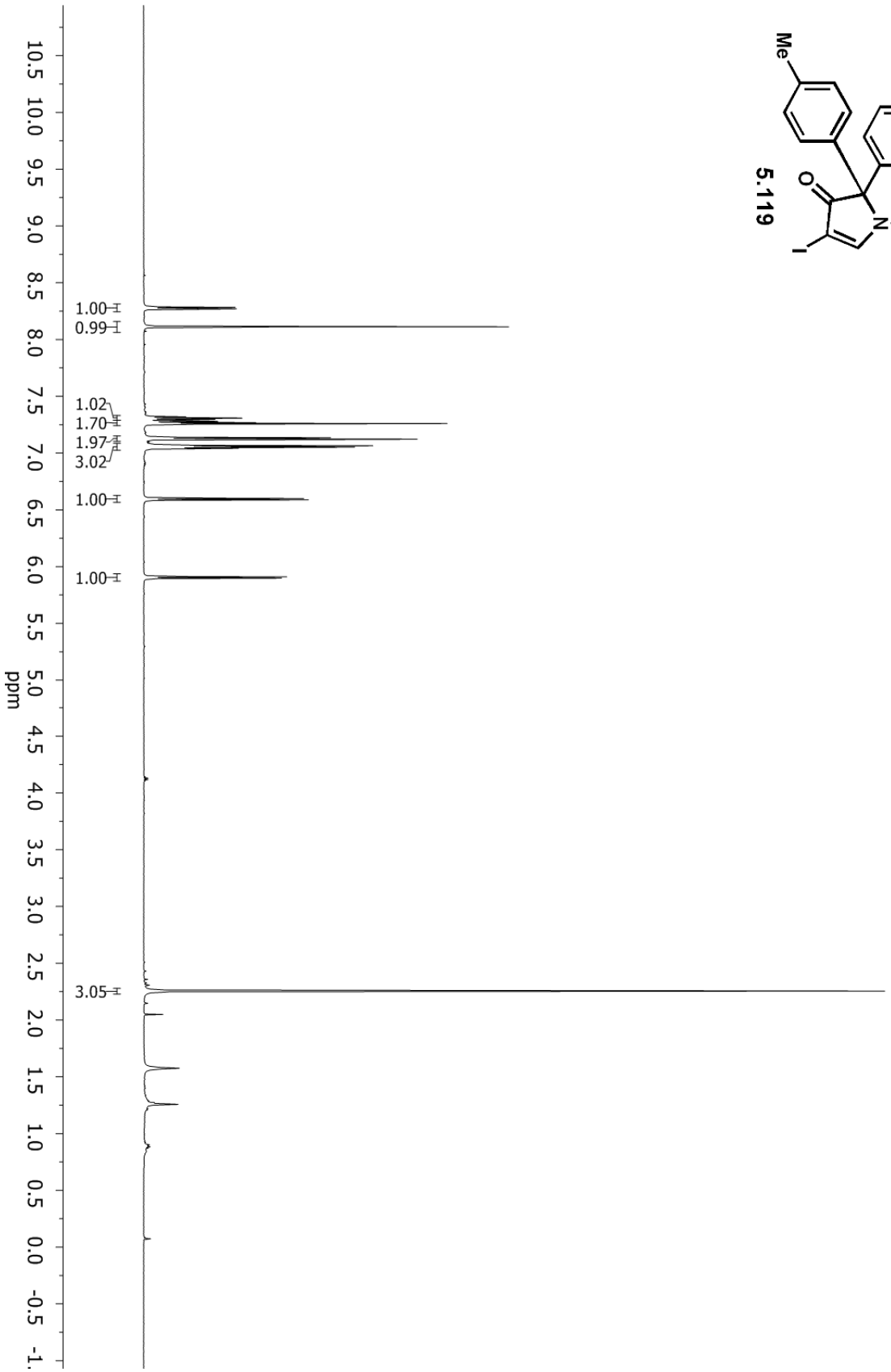

5.116
N
I
O
Me
196.1
165.3
138.1
135.4
135.3
129.6
129.5
128.0
126.6
126.3
125.5
125.1
124.7
116.7
70.4
58.1
21.0
ppm
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

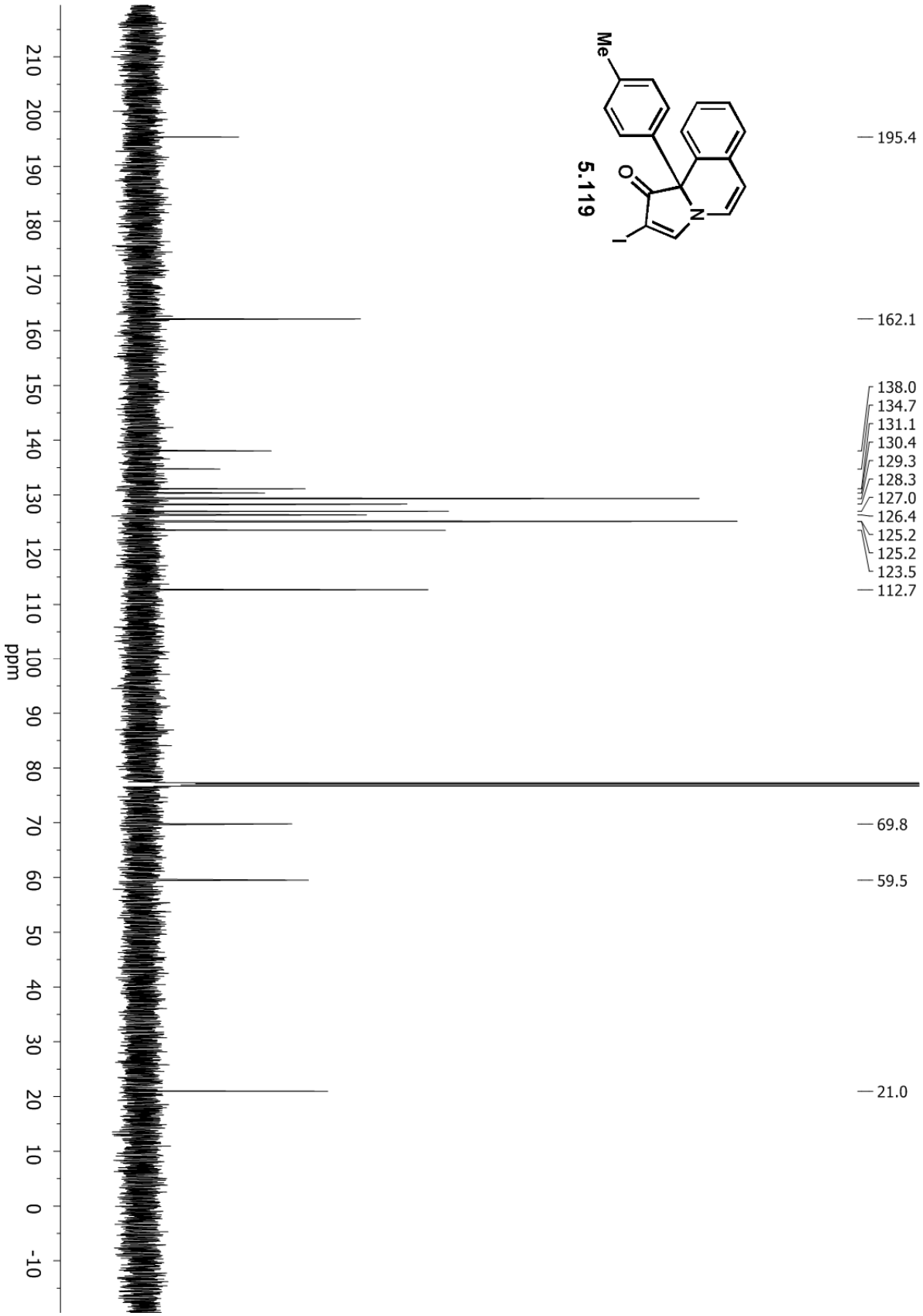

5.117
N
O
Me
1.00
4.26
2.02
1.03
1.00
2.07
1.03
3.07
1.02
ppm
1.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1

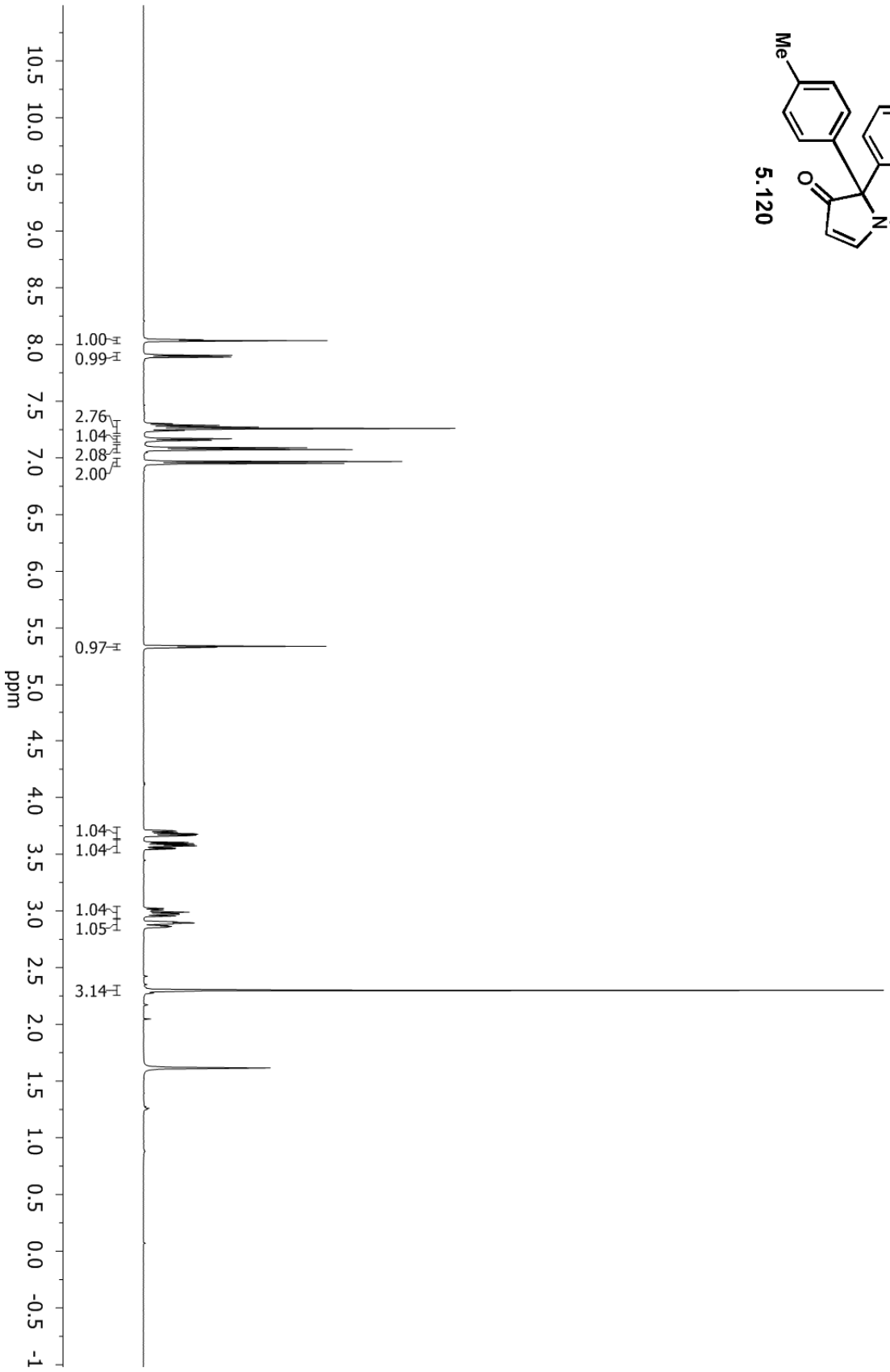

5.117
Me
O
N
202.5
159.2
137.4
136.9
132.4
129.9
129.5
127.5
126.4
125.3
123.1
115.0
100.8
70.2
30.2
24.0
21.0
ppm
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20

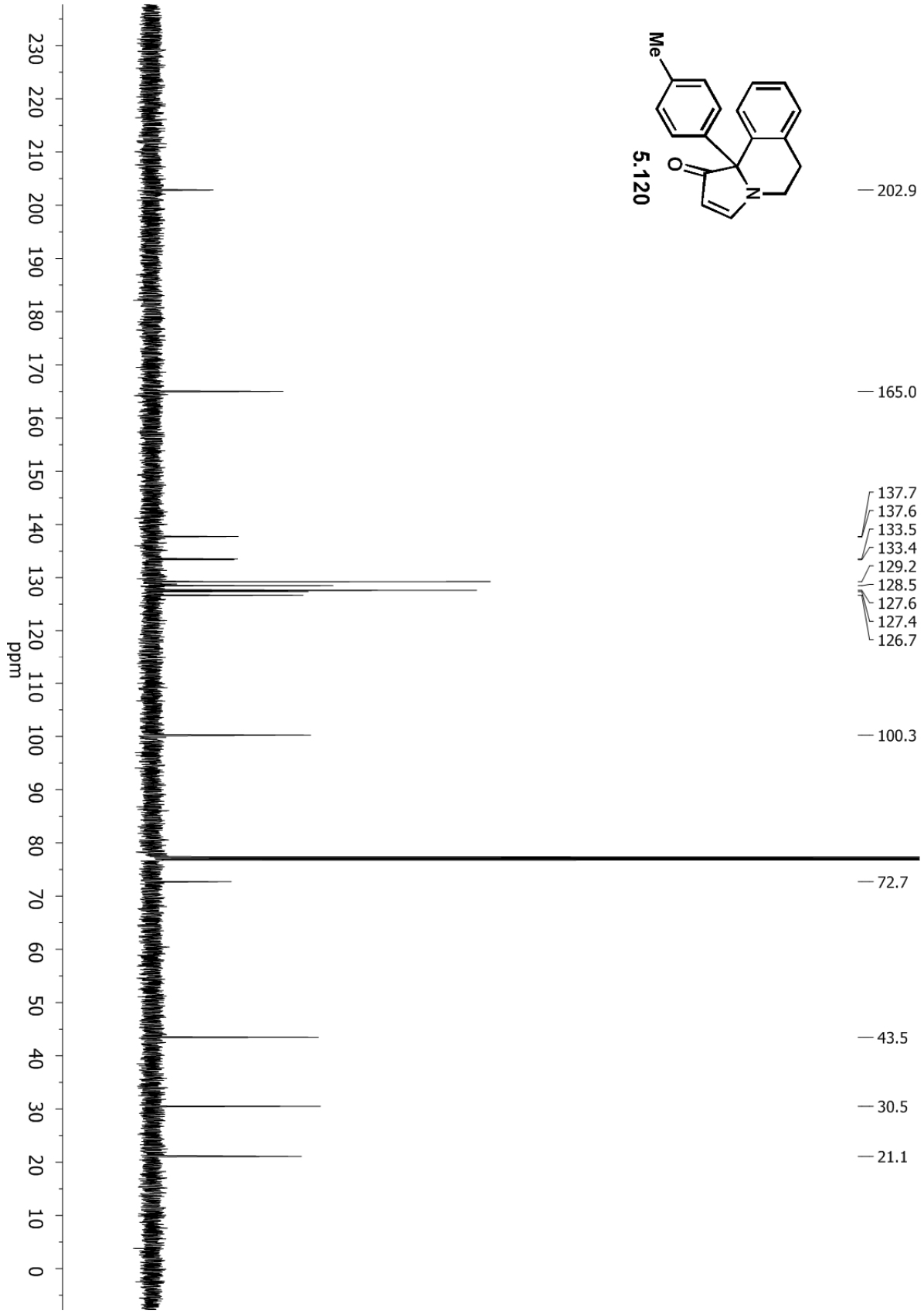

5.118
N
O
Me
3.42
2.35
1.14
1.05
1.04
1.00
1.01
1.05
1.09
2.19
3.41
ppm
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1

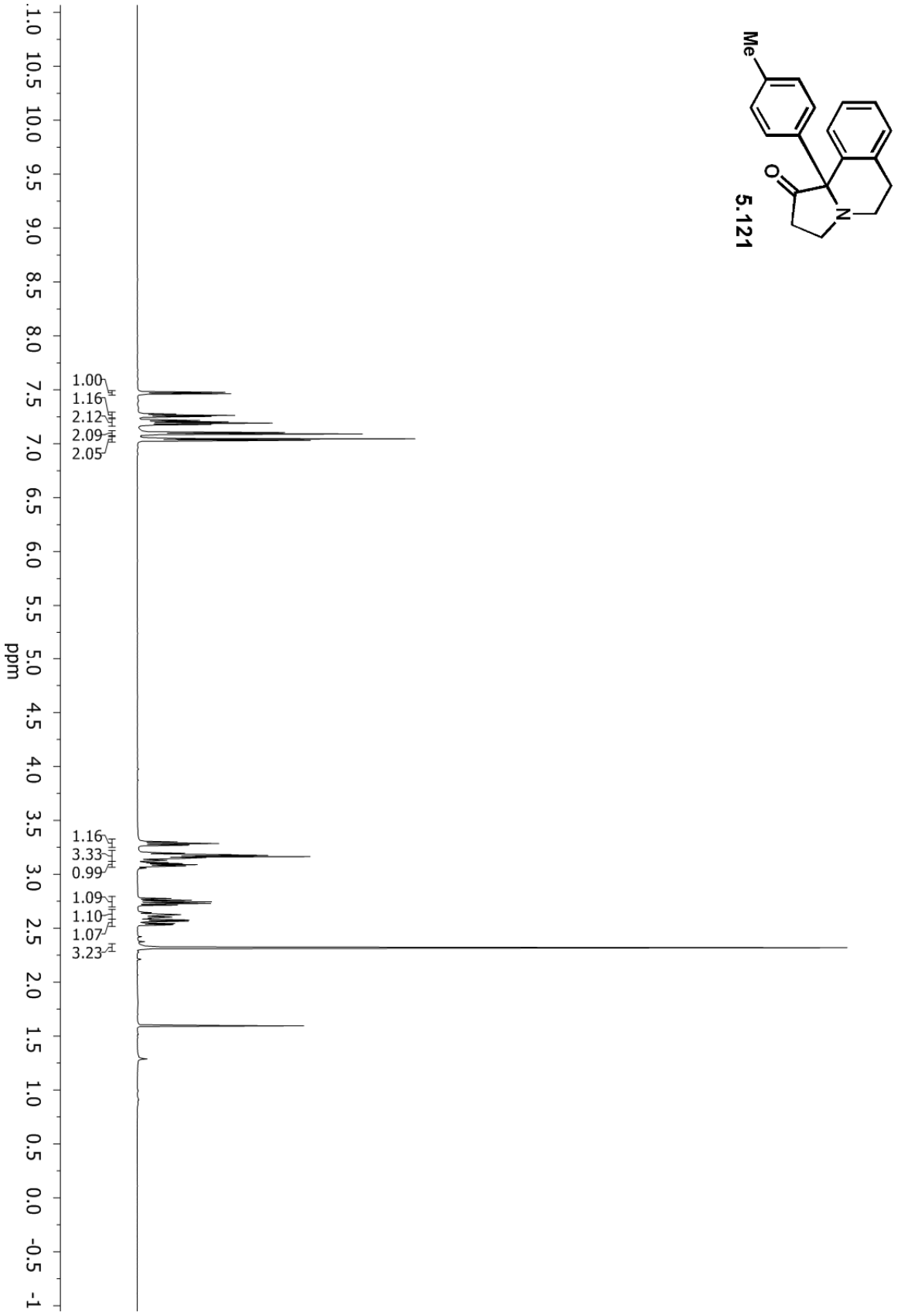

5.118
N
O
Me
209.8
143.1
138.3
137.5
129.6
129.4
127.6
124.9
124.6
122.7
117.6
110.8
68.4
42.2
33.4
21.0
ppm
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

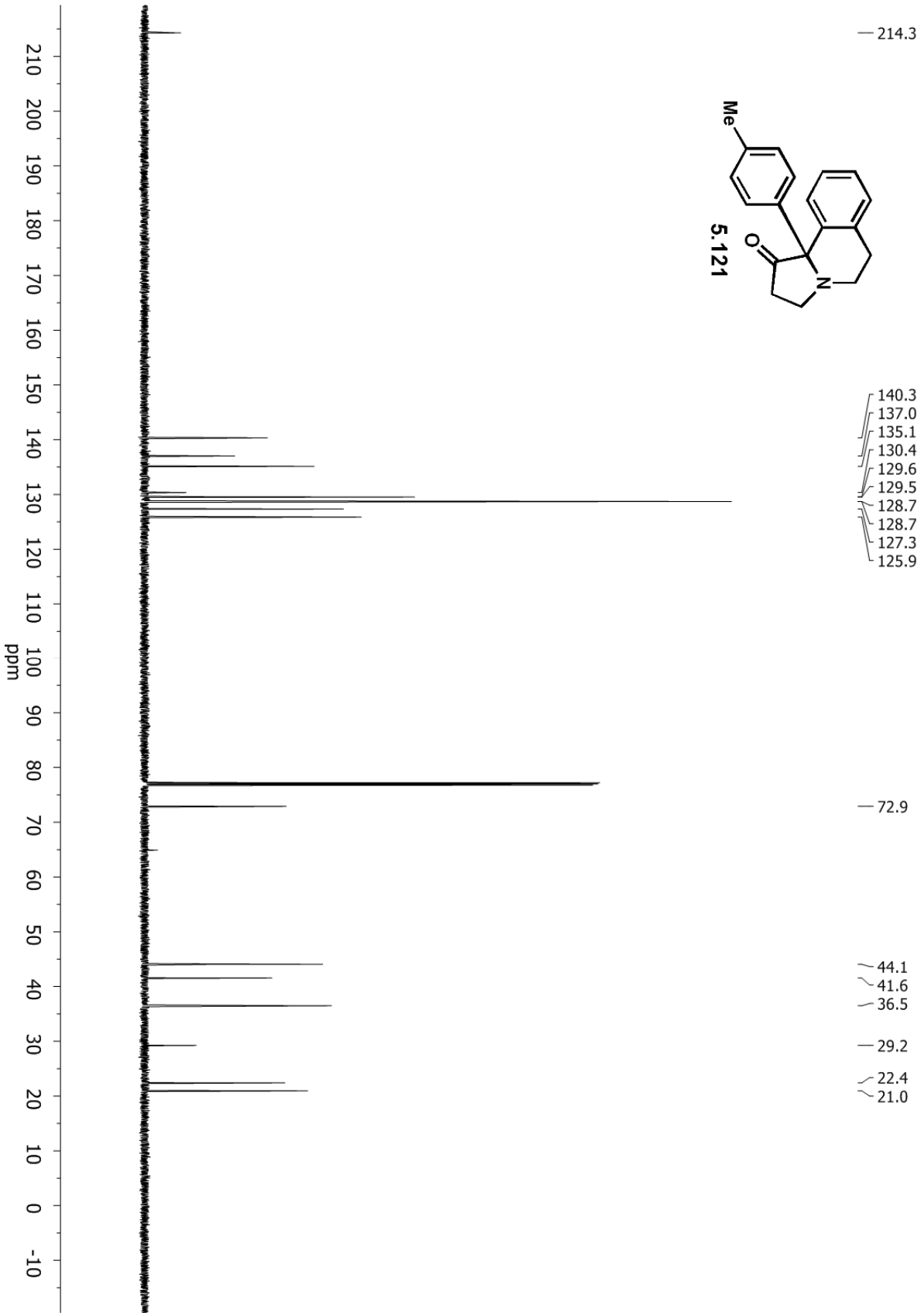

Me
O
N
I
5.119
1.00
0.99
1.02
1.70
1.97
3.02
1.00
1.00
3.05
ppm

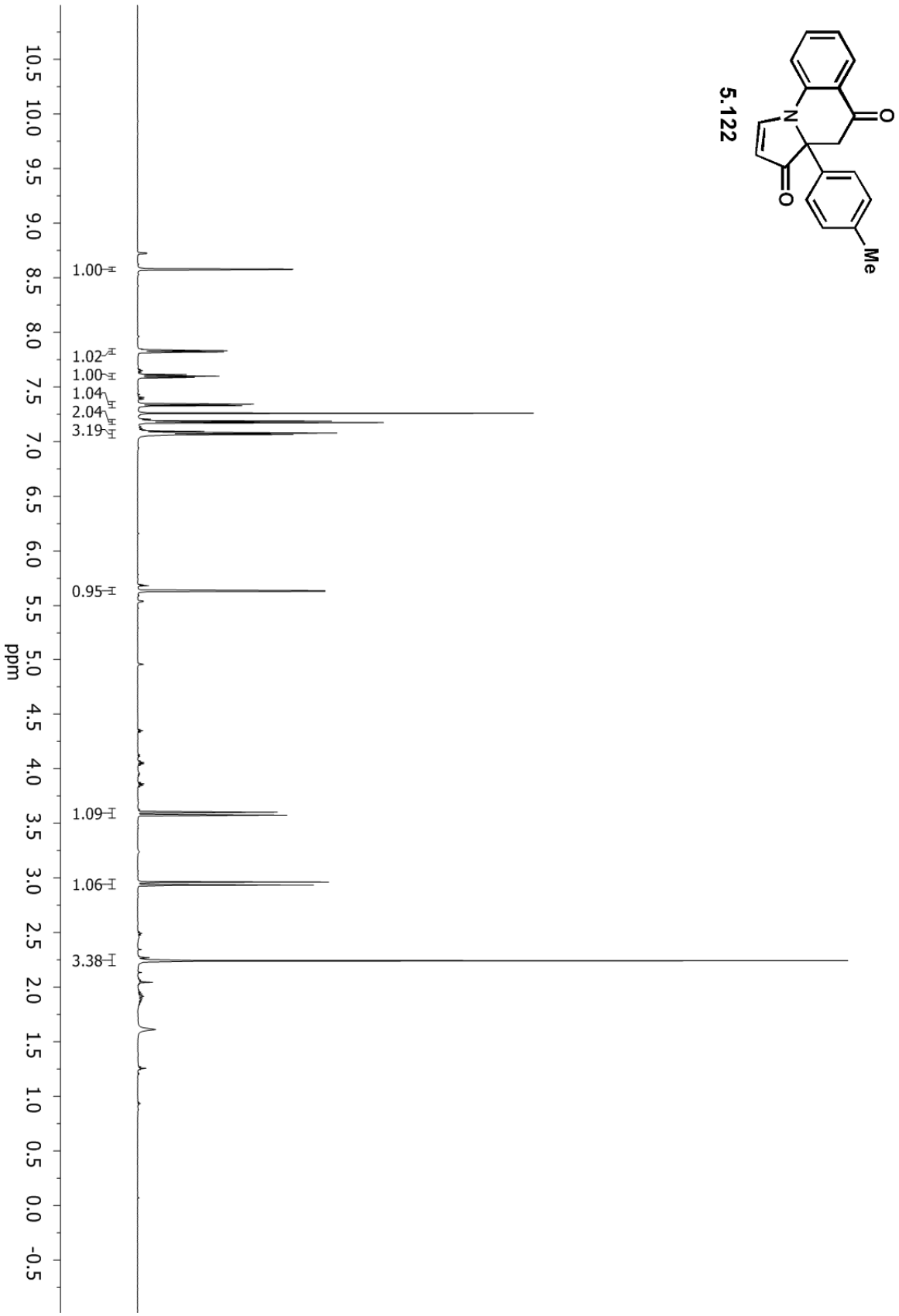

Me
O
N
I
5.119
195.4
162.1
138.0
134.7
131.1
130.4
129.3
128.3
127.0
126.4
125.2
125.2
123.5
112.7
69.8
59.5
21.0
ppm
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

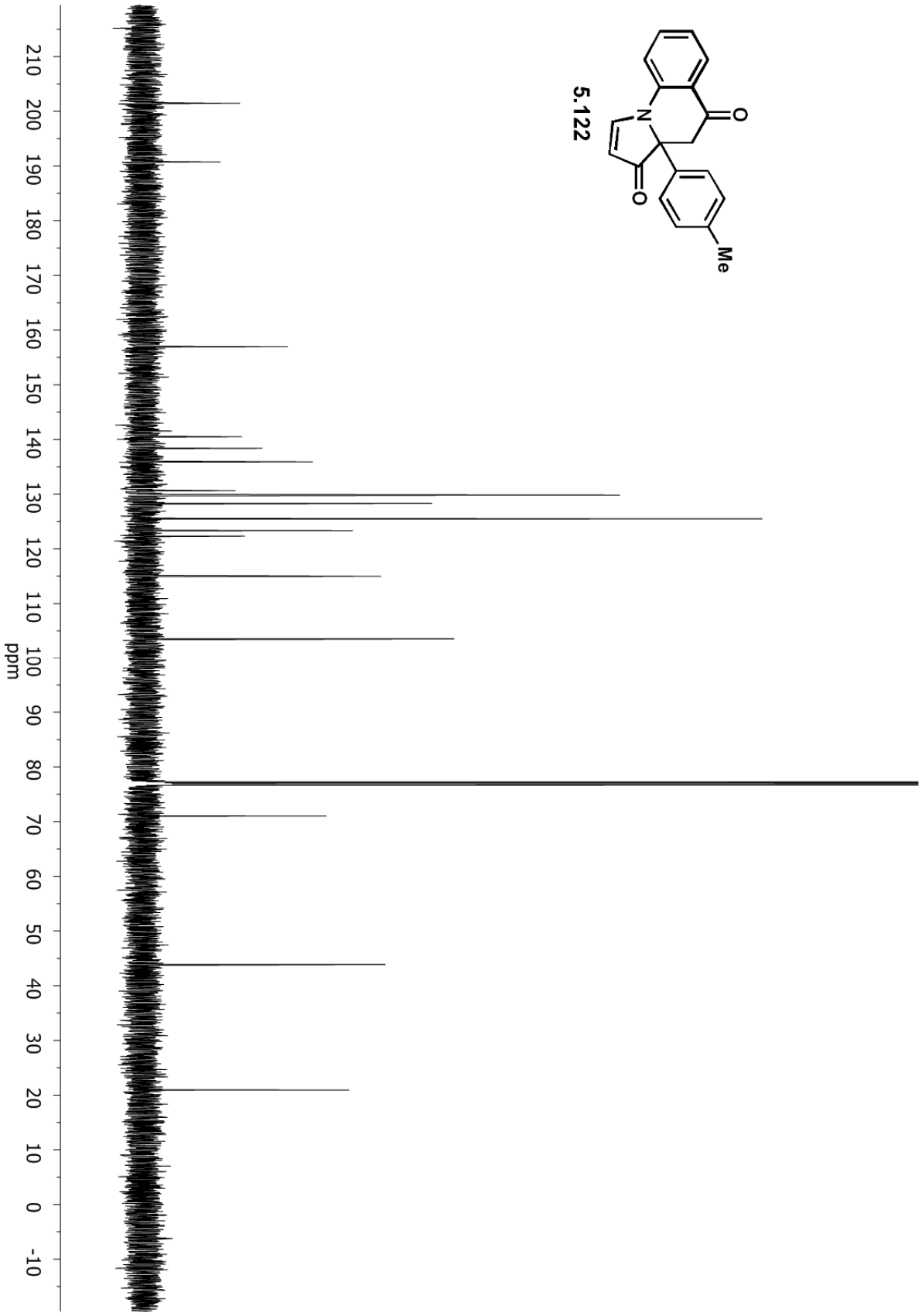

Me
O
N
5.120
1.00
0.99
2.76
1.04
2.08
2.00
0.97
1.04
1.04
1.04
1.05
3.14
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
ppm

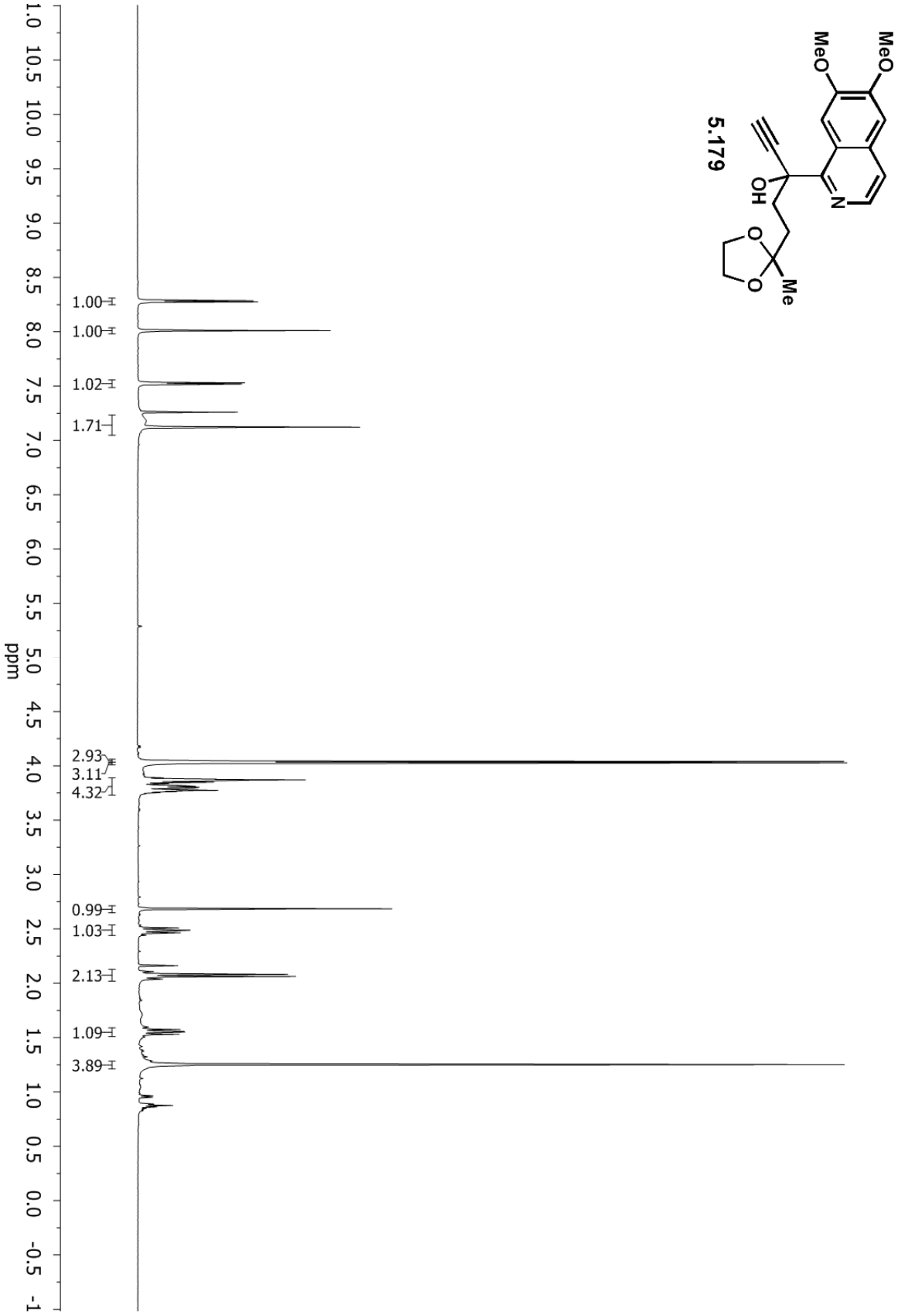

Me
O
N
5.120
202.9
165.0
137.7
137.6
133.5
133.4
129.2
128.5
127.6
127.4
126.7
100.3
72.7
43.5
30.5
21.1
ppm
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

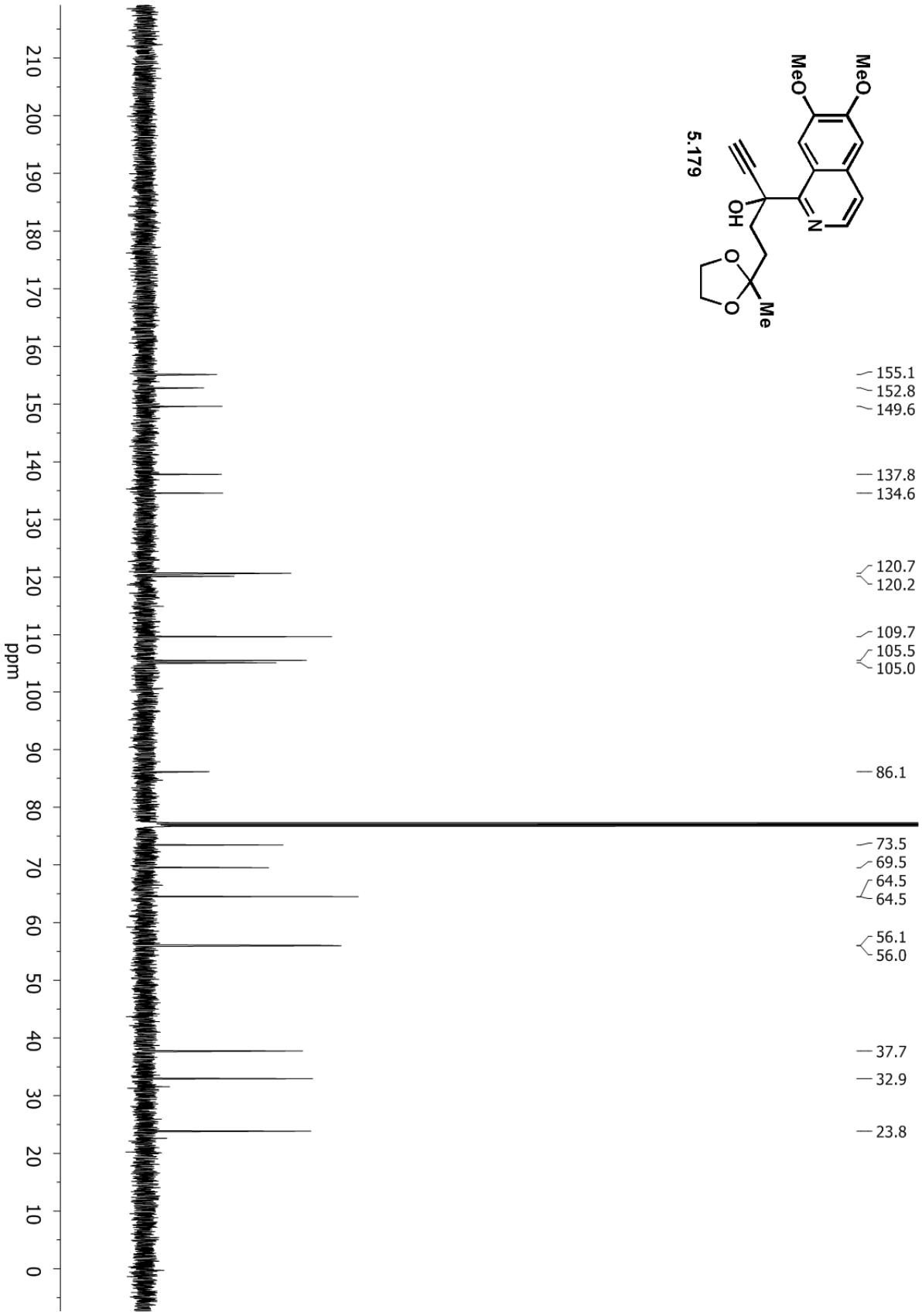

Me
O
N
5.121
1.00
1.16
2.12
2.09
2.05
1.16
3.33
0.99
1.09
1.10
1.07
3.23
ppm

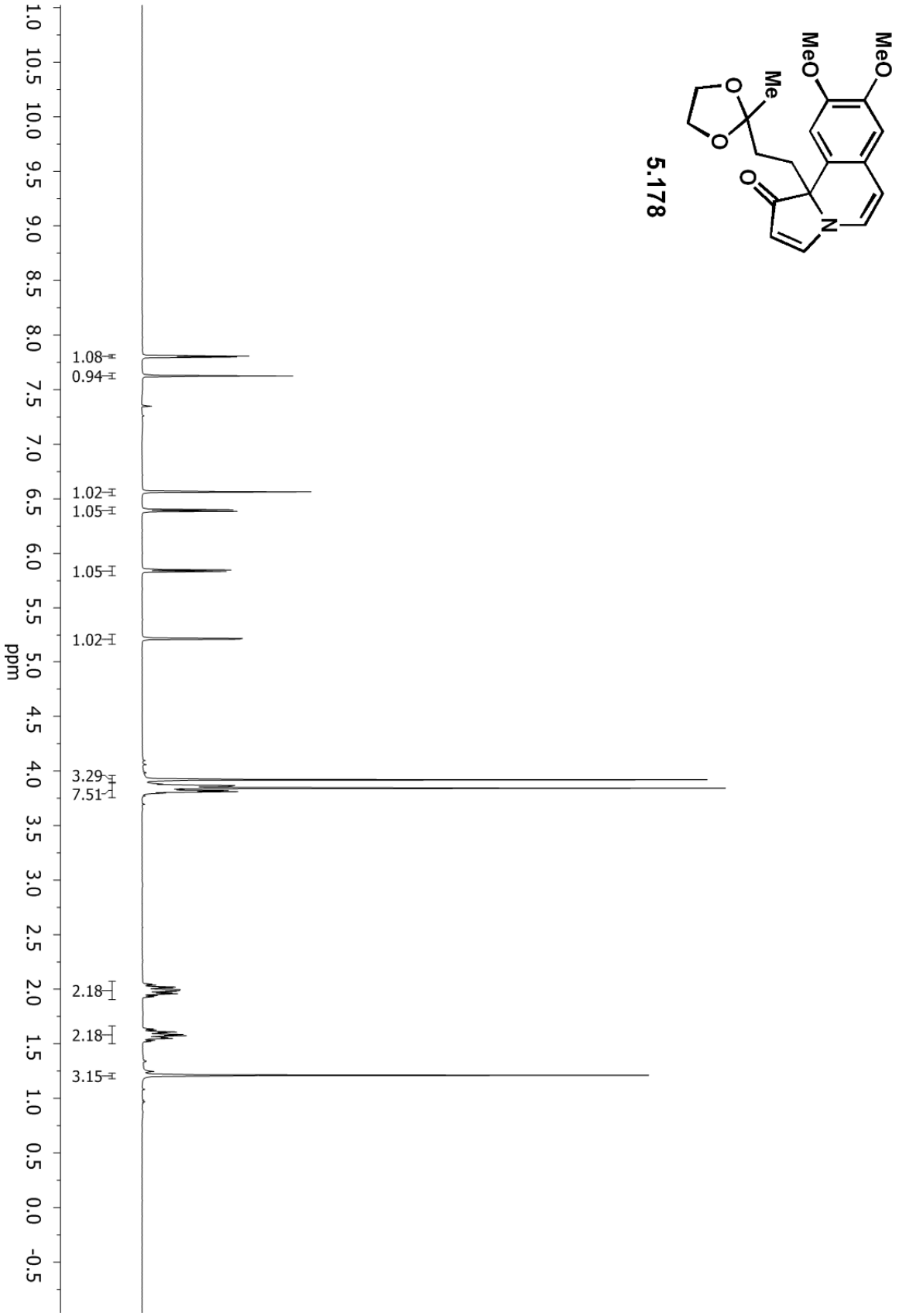

214.3
140.3
137.0
135.1
130.4
129.6
129.5
128.7
128.7
127.3
125.9
72.9
44.1
41.6
36.5
29.2
22.4
21.0
Me
O
N
5.121
ppm
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10


5.122
Me
O
O
N
1.00
1.02
1.00
1.04
2.04
3.19
0.95
1.09
1.06
3.38
ppm
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5


5.122
Me
O
O
N
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
ppm


5.179
MeO
MeO
OH
N
O
O
Me
1.00
1.00
1.02
1.71
2.93
3.11
4.32
0.99
1.03
2.13
1.09
3.89
ppm


MeO
MeO
OH
N
O
O
Me
5.179
155.1
152.8
149.6
137.8
134.6
120.7
120.2
109.7
105.5
105.0
86.1
73.5
69.5
64.5
64.5
56.1
56.0
37.7
32.9
23.8
ppm
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


5.178
MeO
MeO
Me
O
O
O
N
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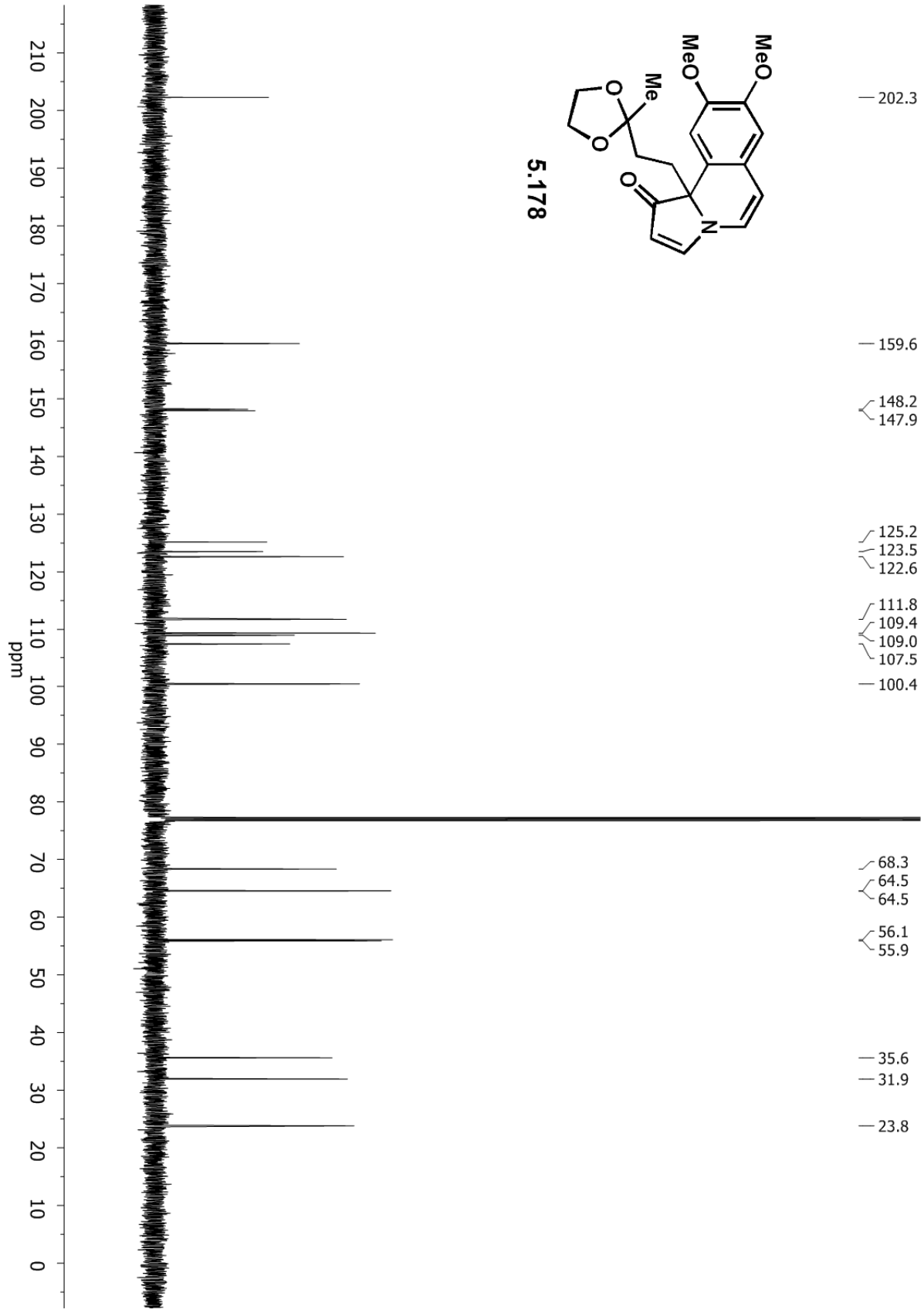
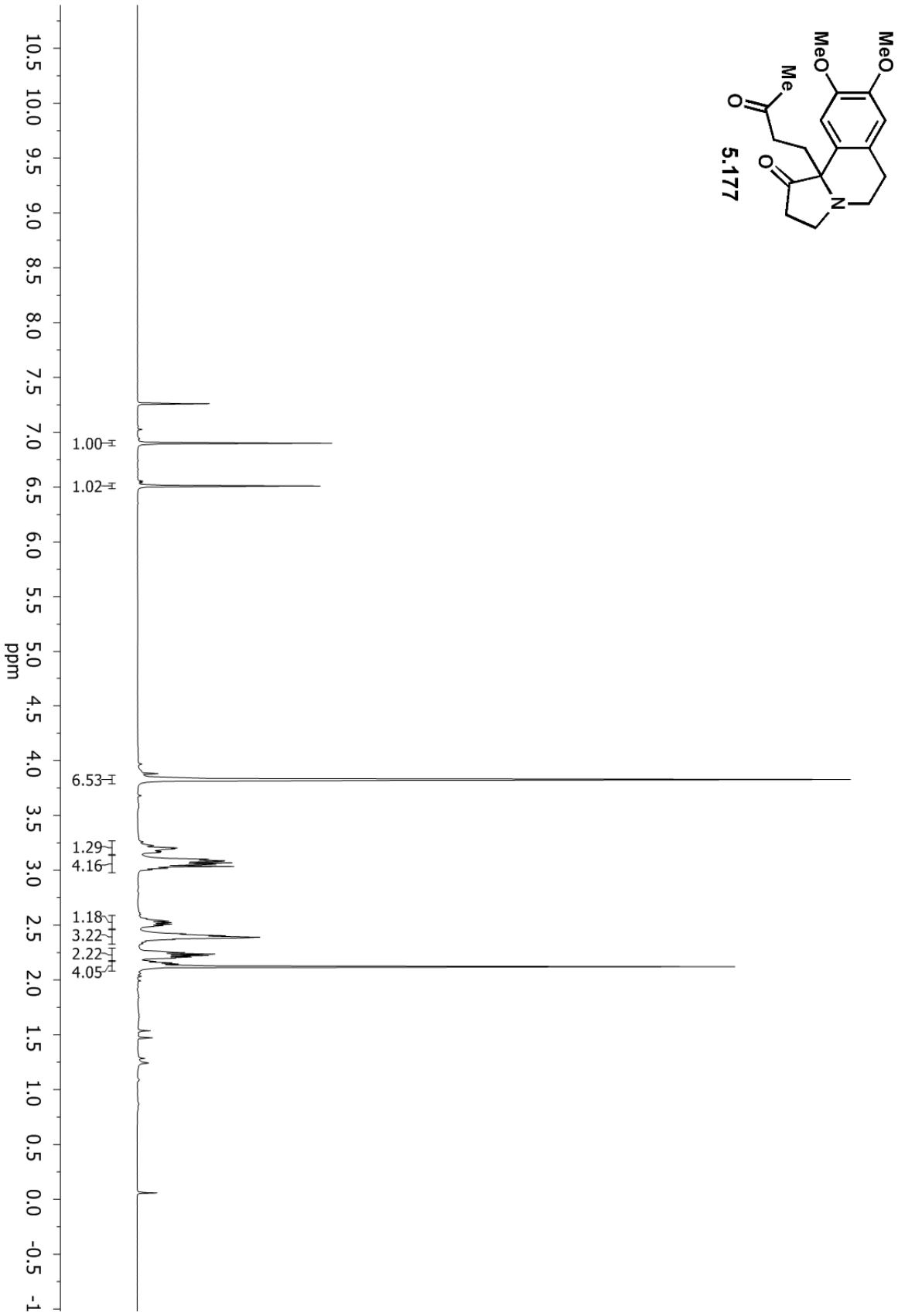
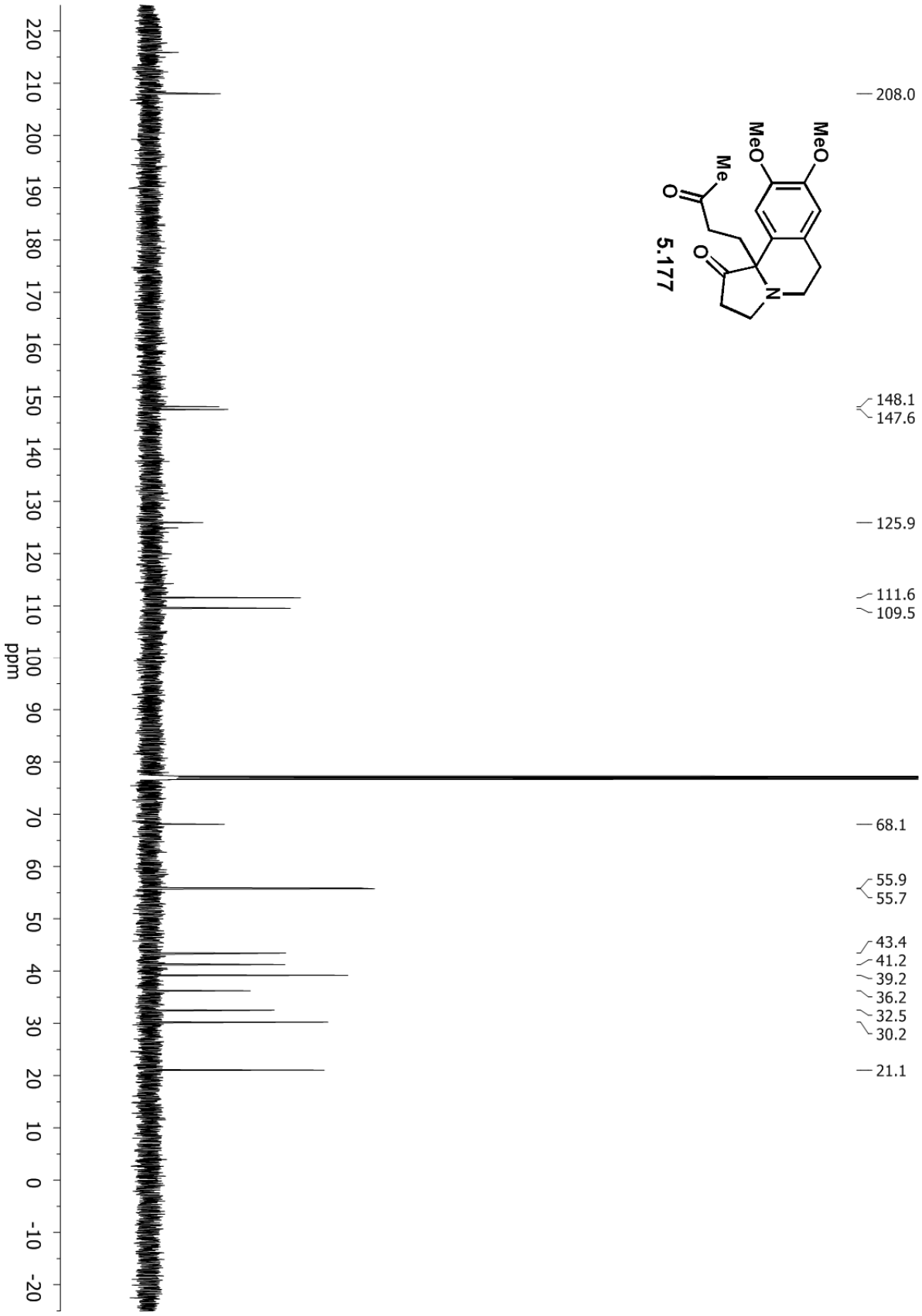
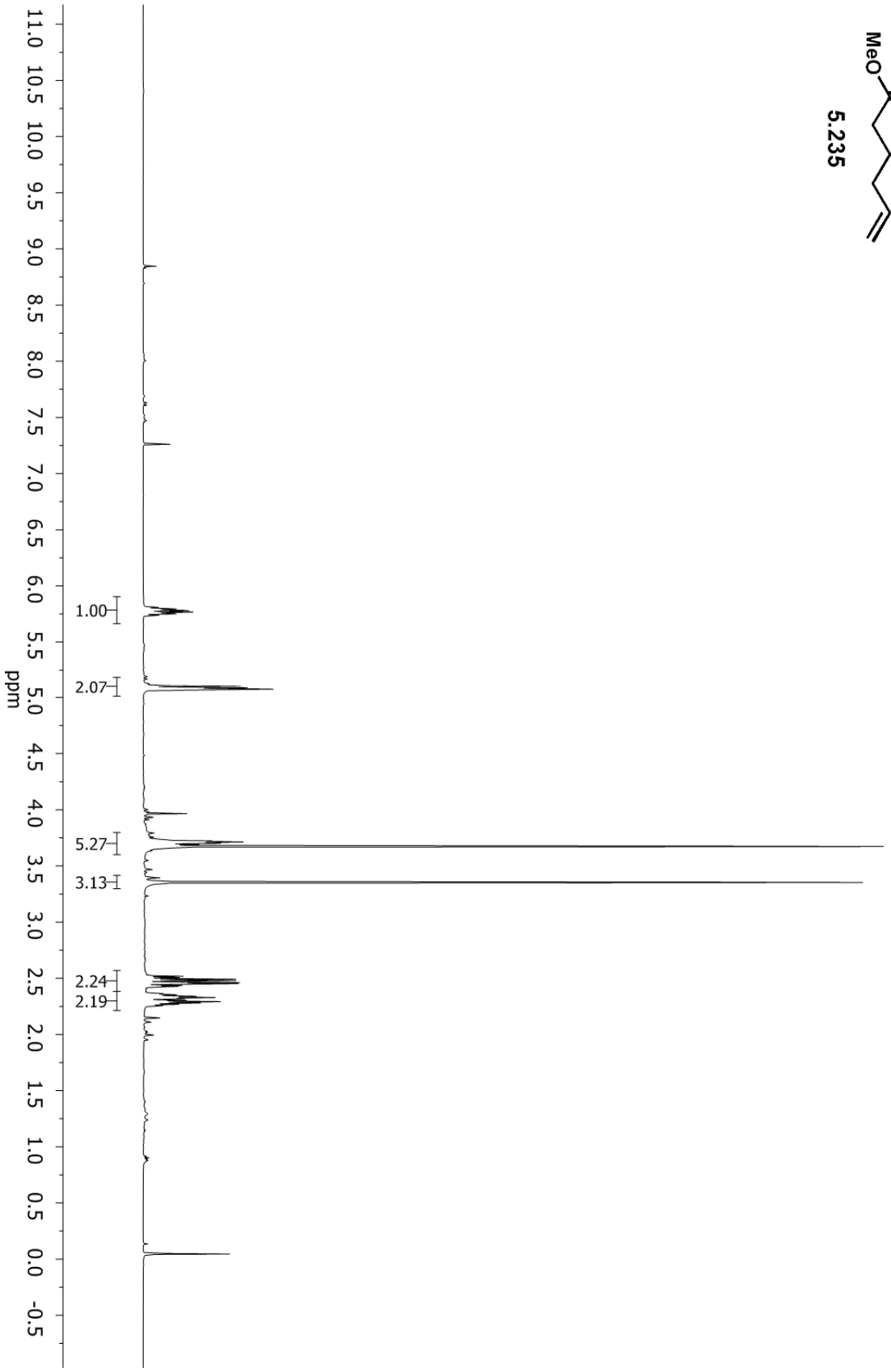
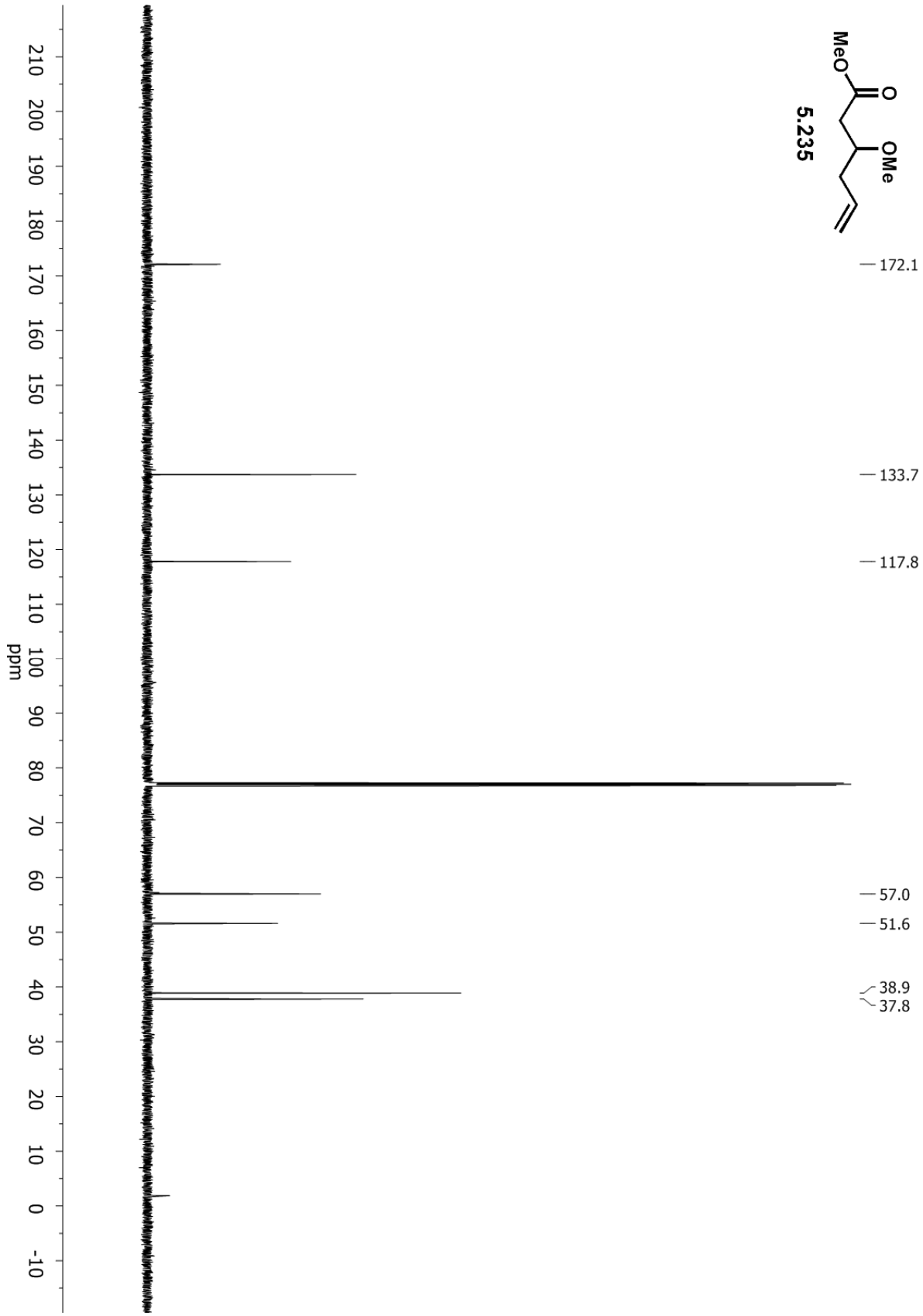
0.94
1.02
1.05
1.05
1.02
3.29
7.51
2.18
2.18
3.15
ppm
1.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5

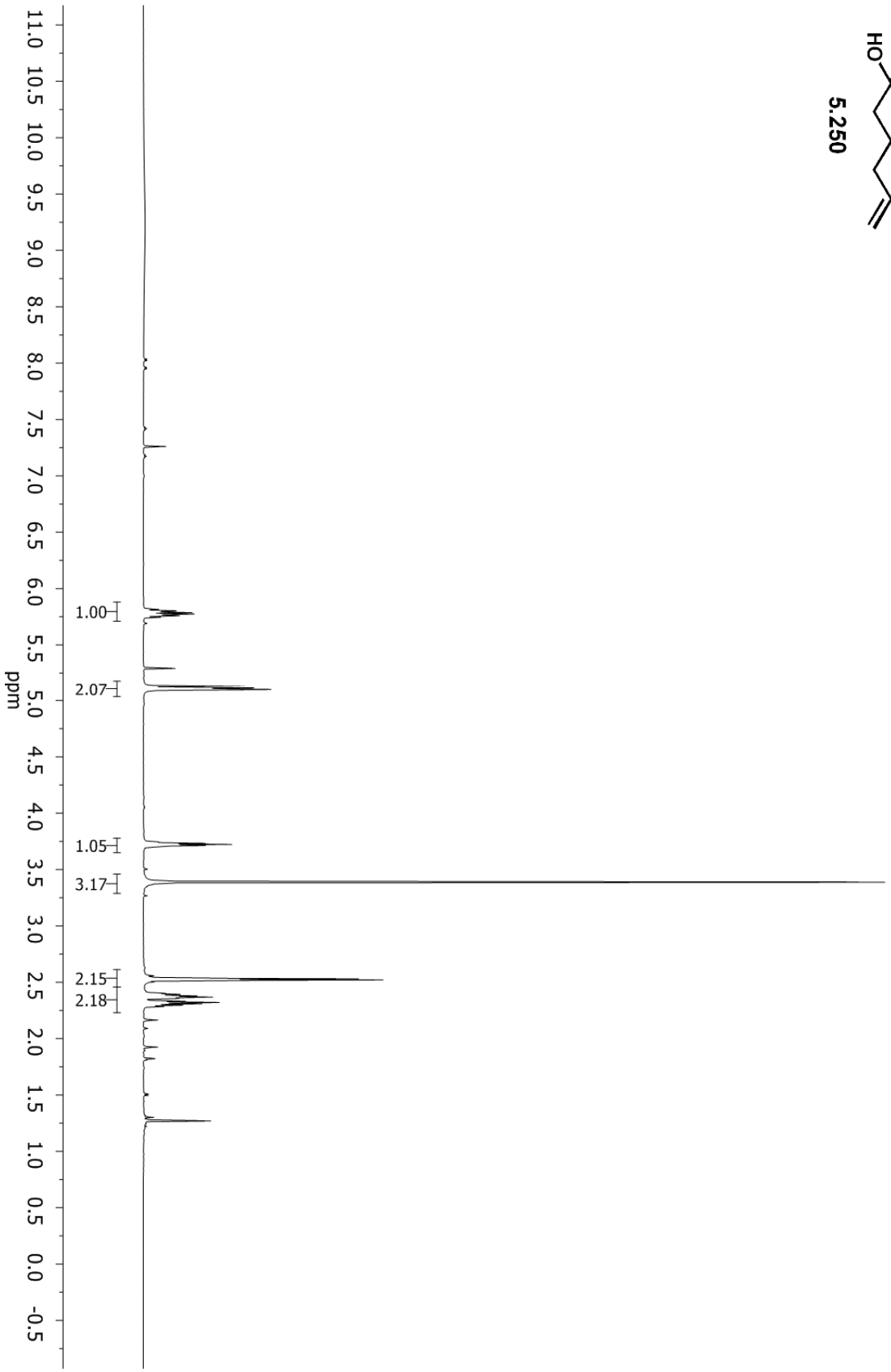

5.178
MeO
MeO
Me
O
O
O
N
202.3
159.6
148.2
147.9
125.2
123.5
122.6
111.8
109.4
109.0
107.5
100.4
68.3
64.5
64.5
56.1
55.9
35.6
31.9
23.8
ppm
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

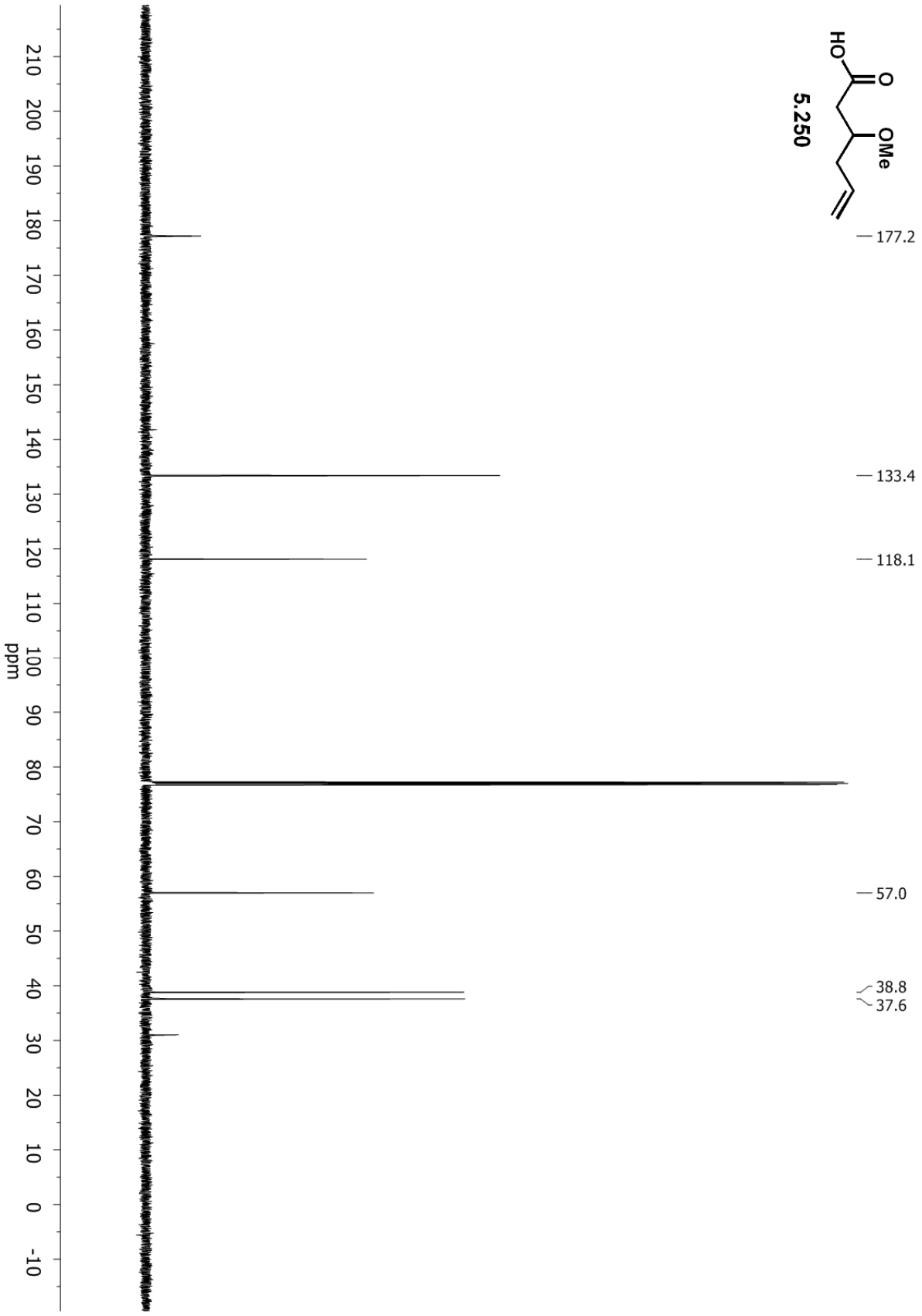

MeO
MeO
MeO
Me
O
O
N
5.177
1.00
1.02
6.53
1.29
4.16
1.18
3.22
2.22
4.05
ppm
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1

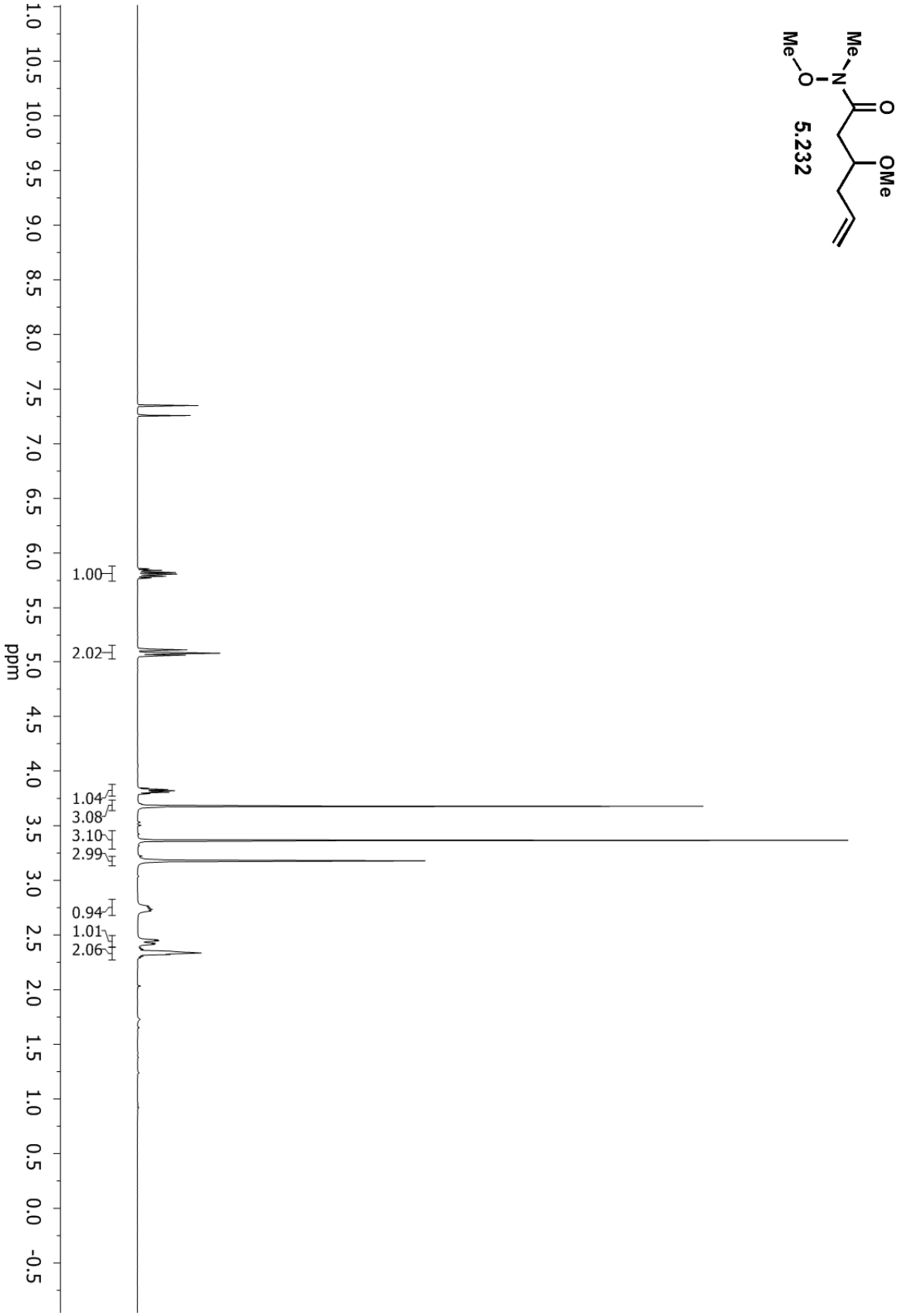

208.0
148.1
147.6
125.9
111.6
109.5
68.1
55.9
55.7
43.4
41.2
39.2
36.2
32.5
30.2
21.1
MeO
MeO
Me
O
O
N
5.177
ppm

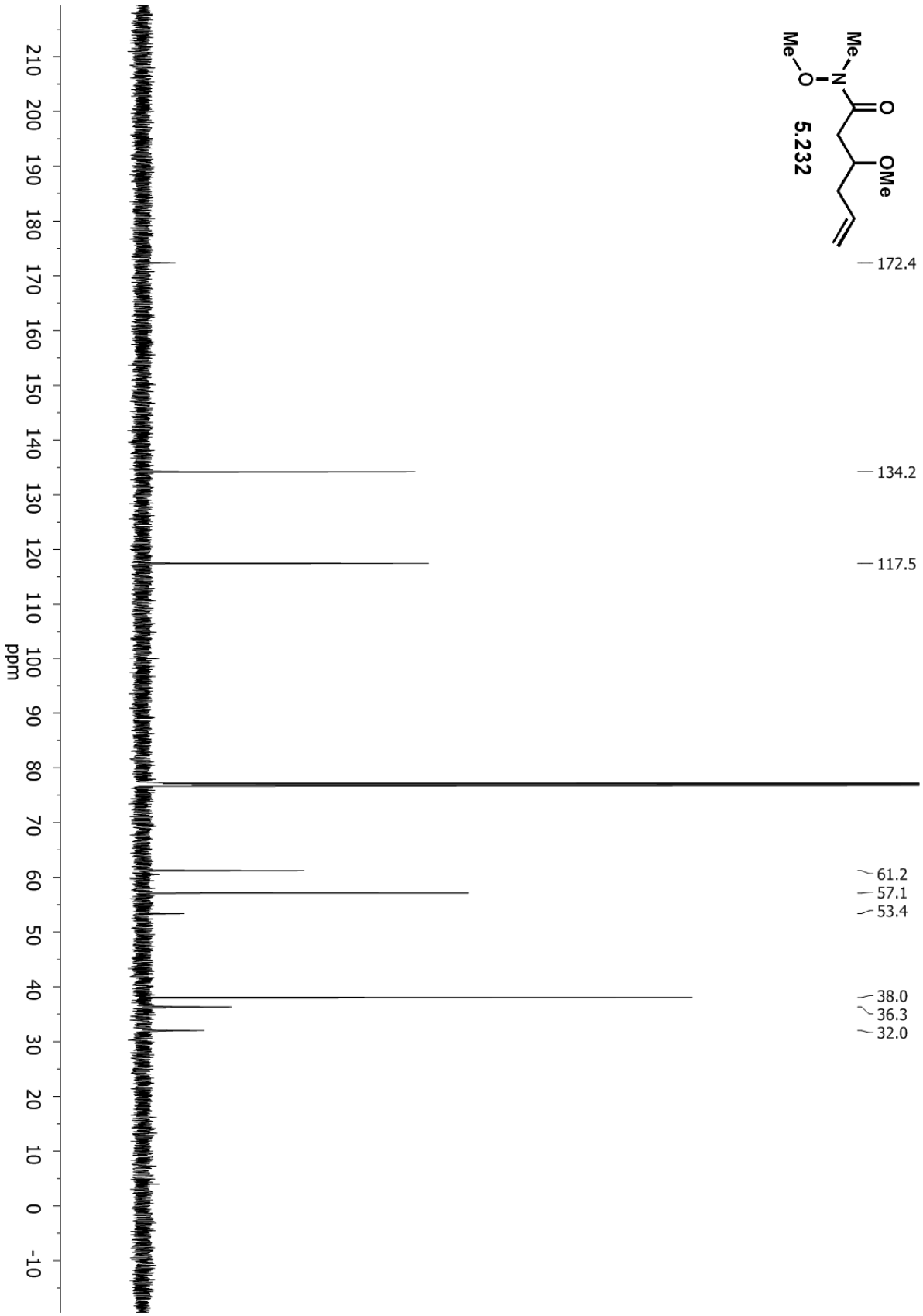

MeO
O
OMe
5.235
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
ppm
1.00
2.07
5.27
3.13
2.24
2.19

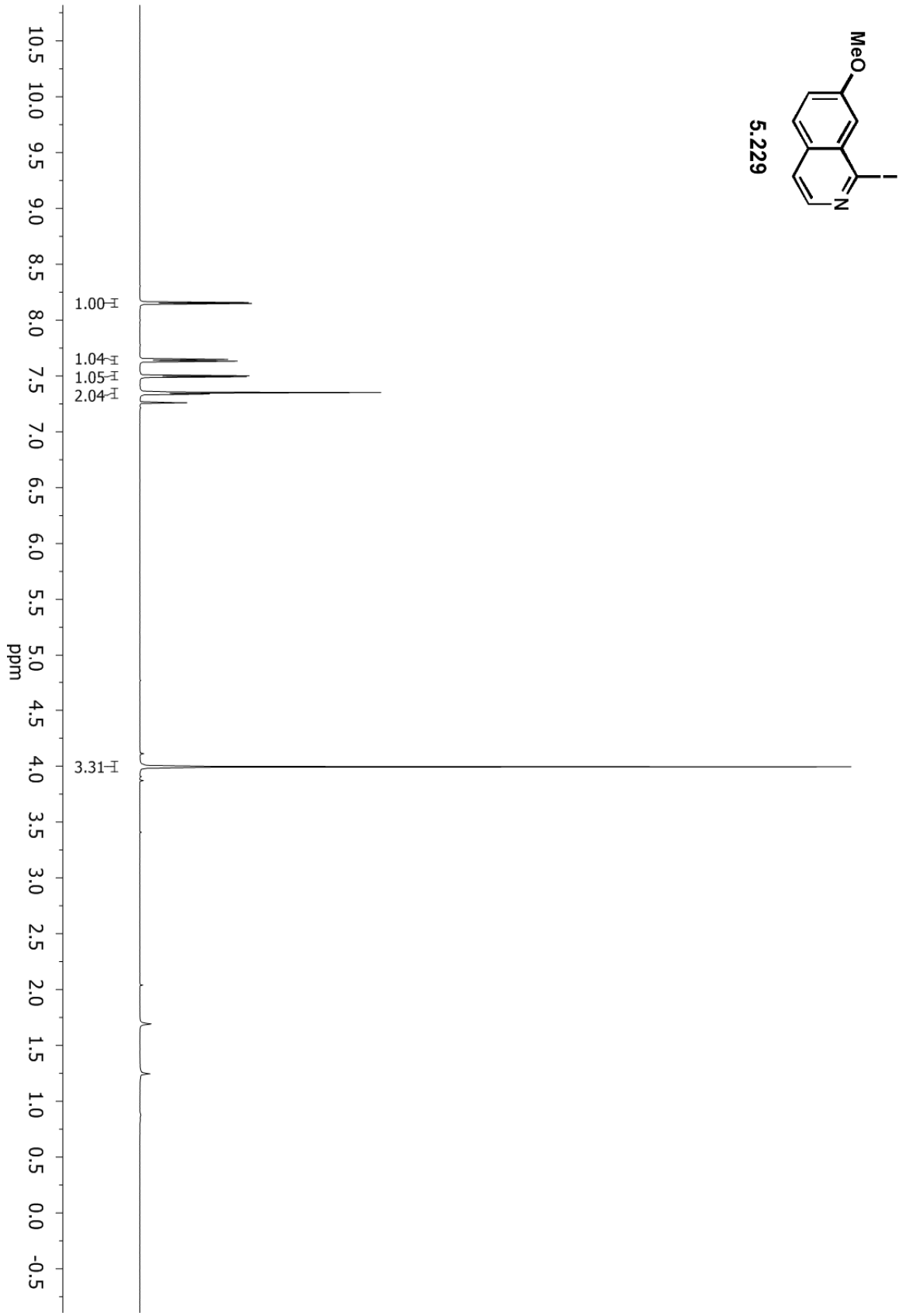

MeO
O
OMe
5.235
172.1
133.7
117.8
57.0
51.6
38.9
37.8
ppm
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

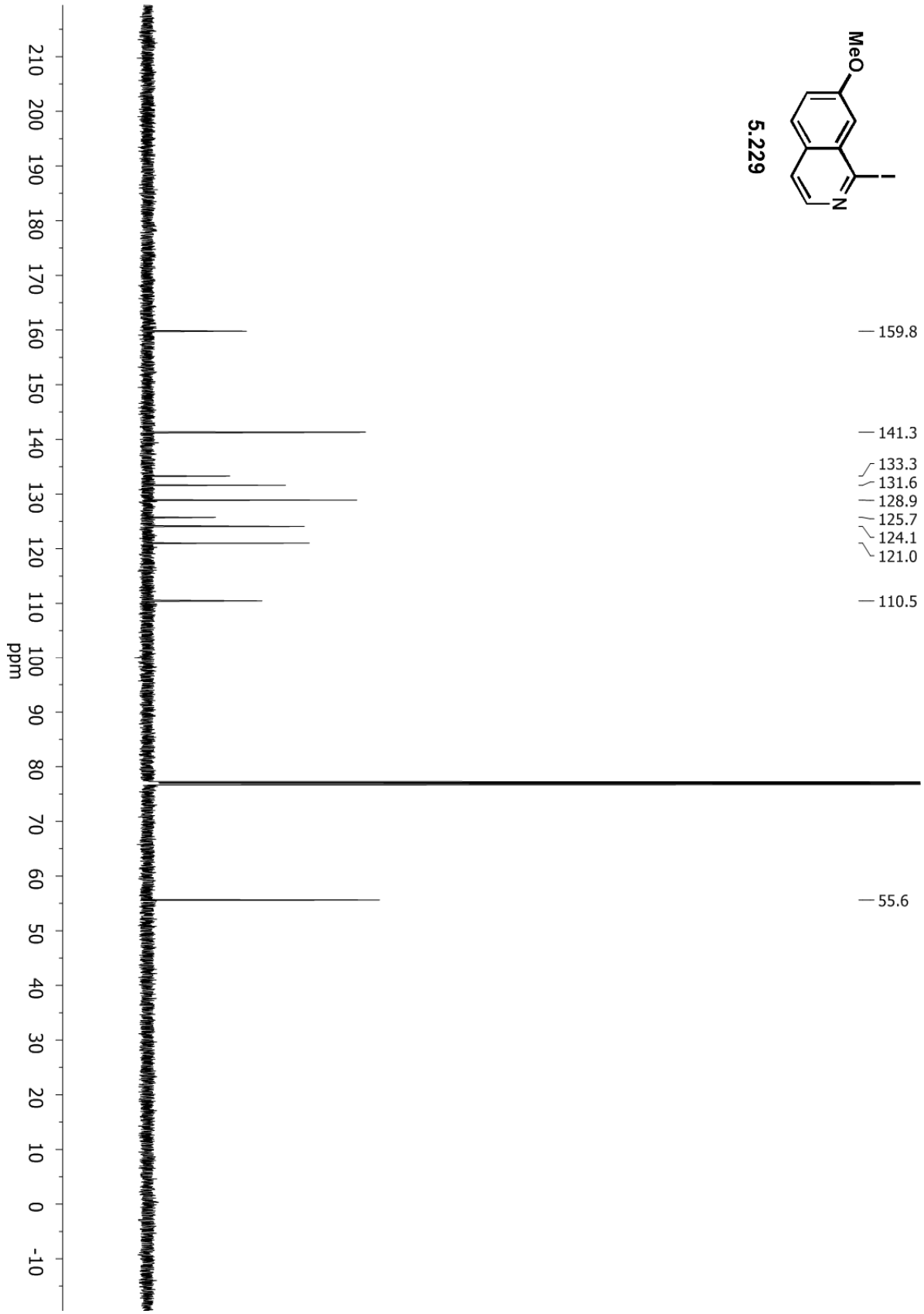

HO
O
OMe
5.250
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
ppm
1.00
2.07
1.05
3.17
2.15
2.18

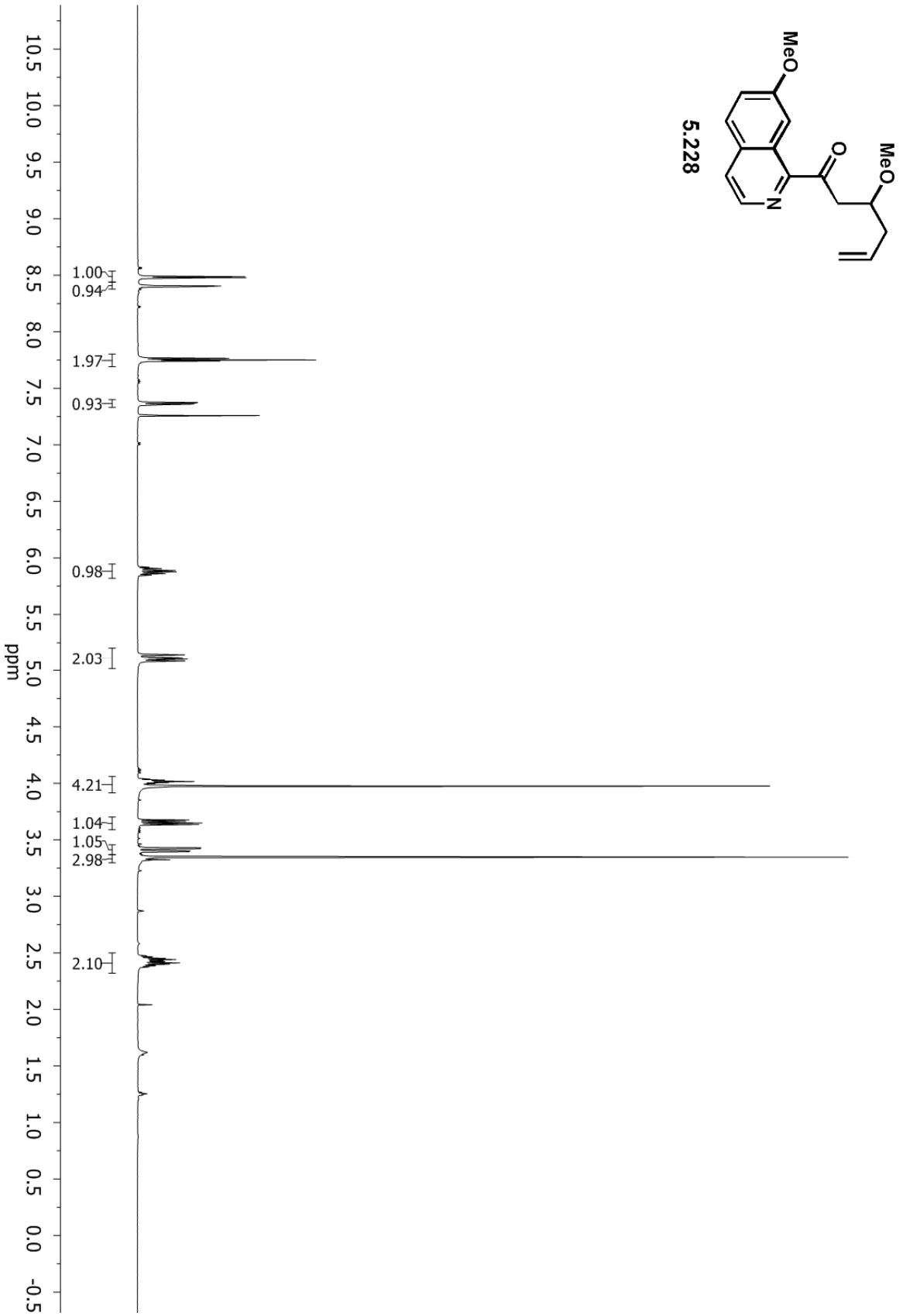

HO
O
OMe
5.250
177.2
133.4
118.1
57.0
38.8
37.6
ppm
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

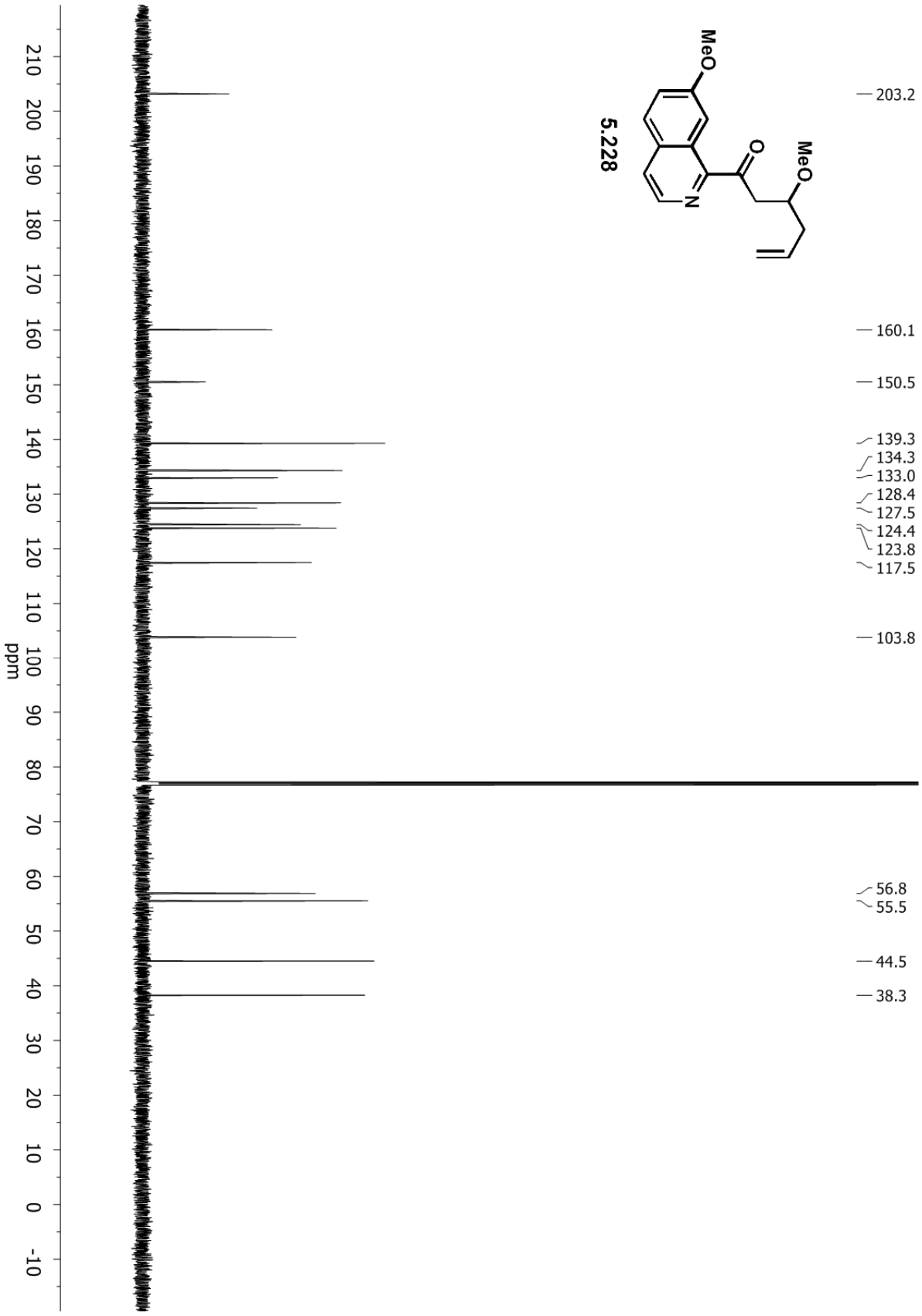

Me
N
O
Me
O
OMe
5.232
1.00
2.02
1.04
3.08
3.10
2.99
0.94
1.01
2.06
ppm
1.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5

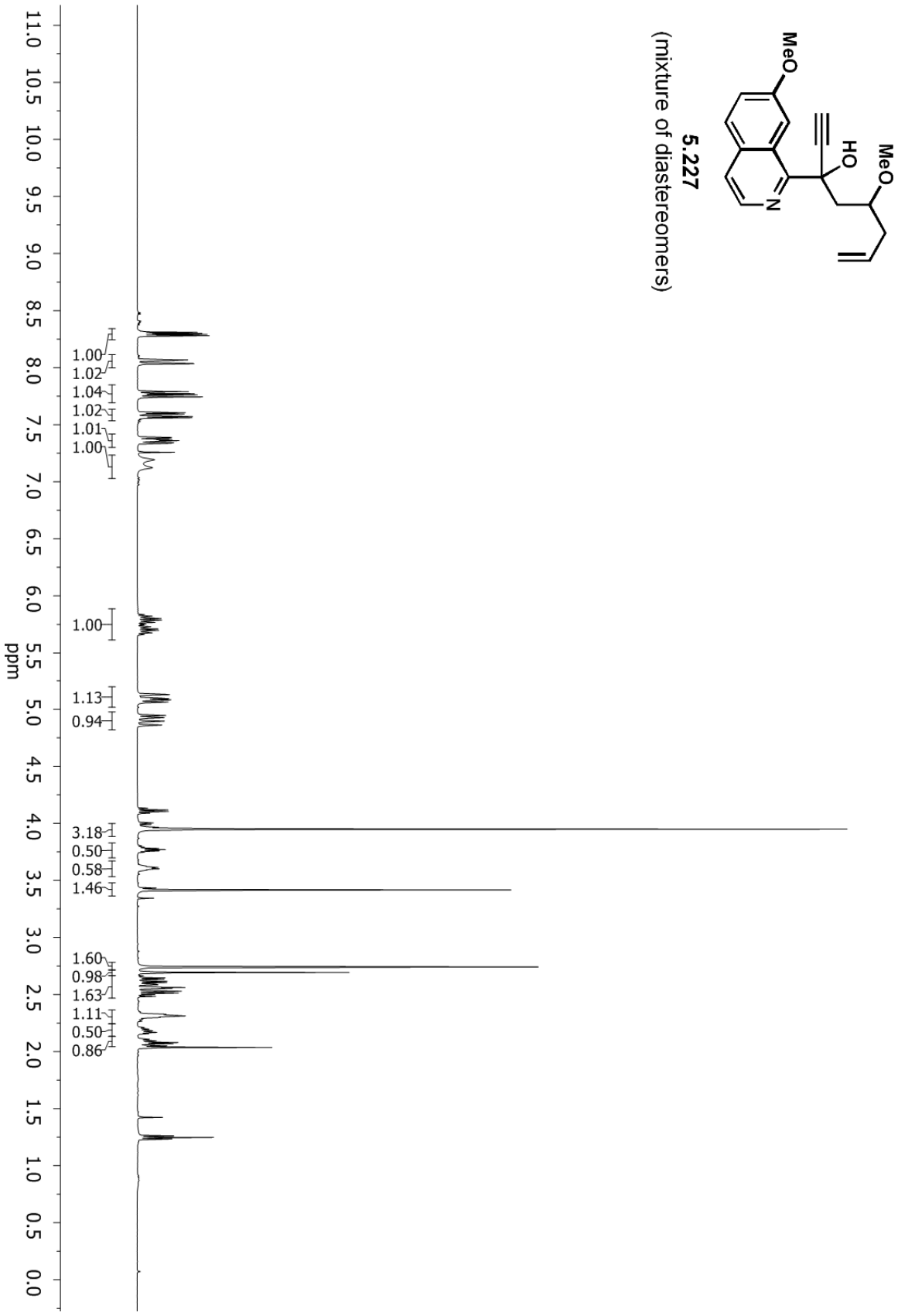

Me
N
O
Me
O
OMe
5.232
172.4
134.2
117.5
61.2
57.1
53.4
38.0
36.3
32.0
ppm
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

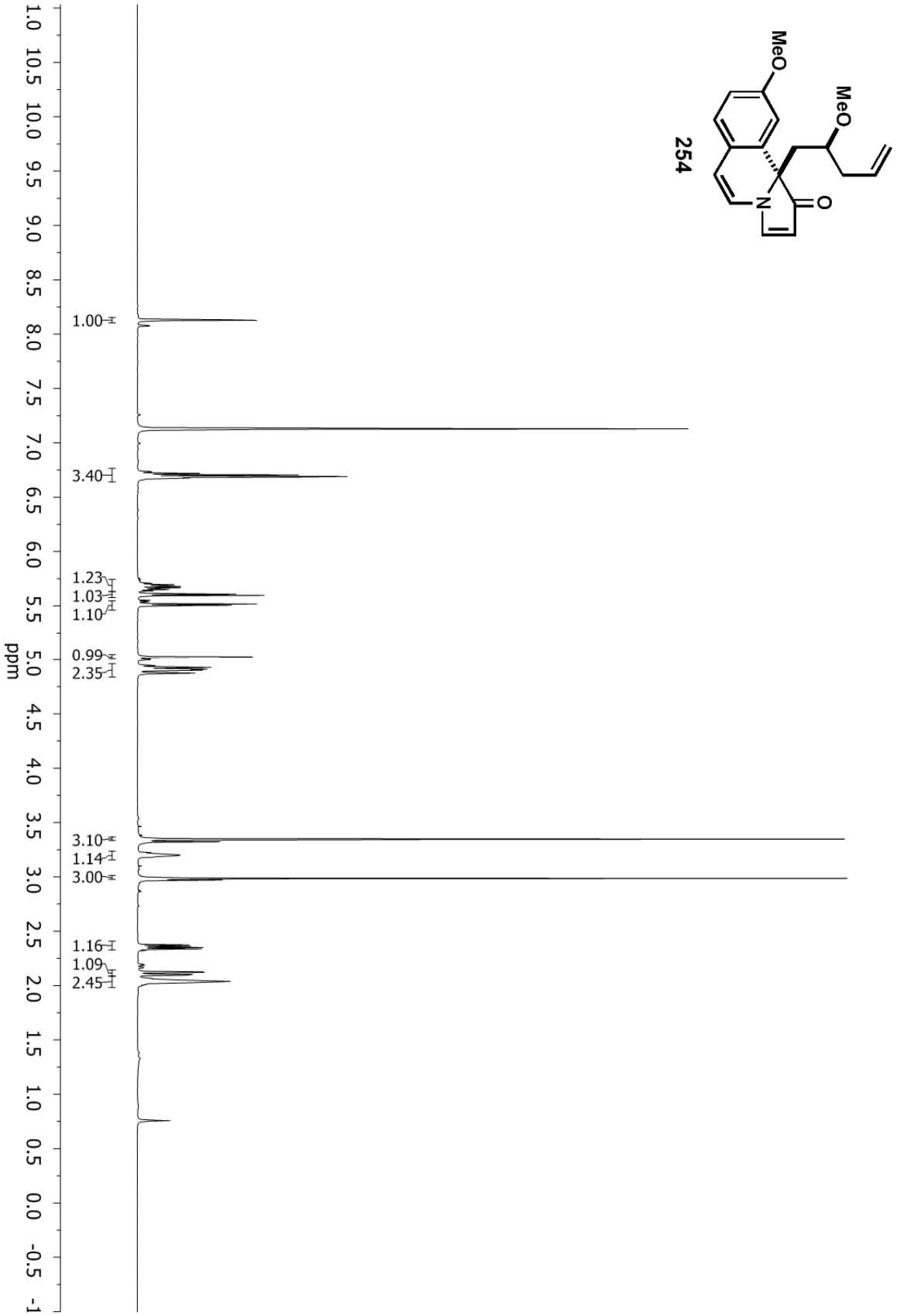

MeO
I
N
5.229
1.00
1.04
1.05
2.04
3.31
ppm
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5

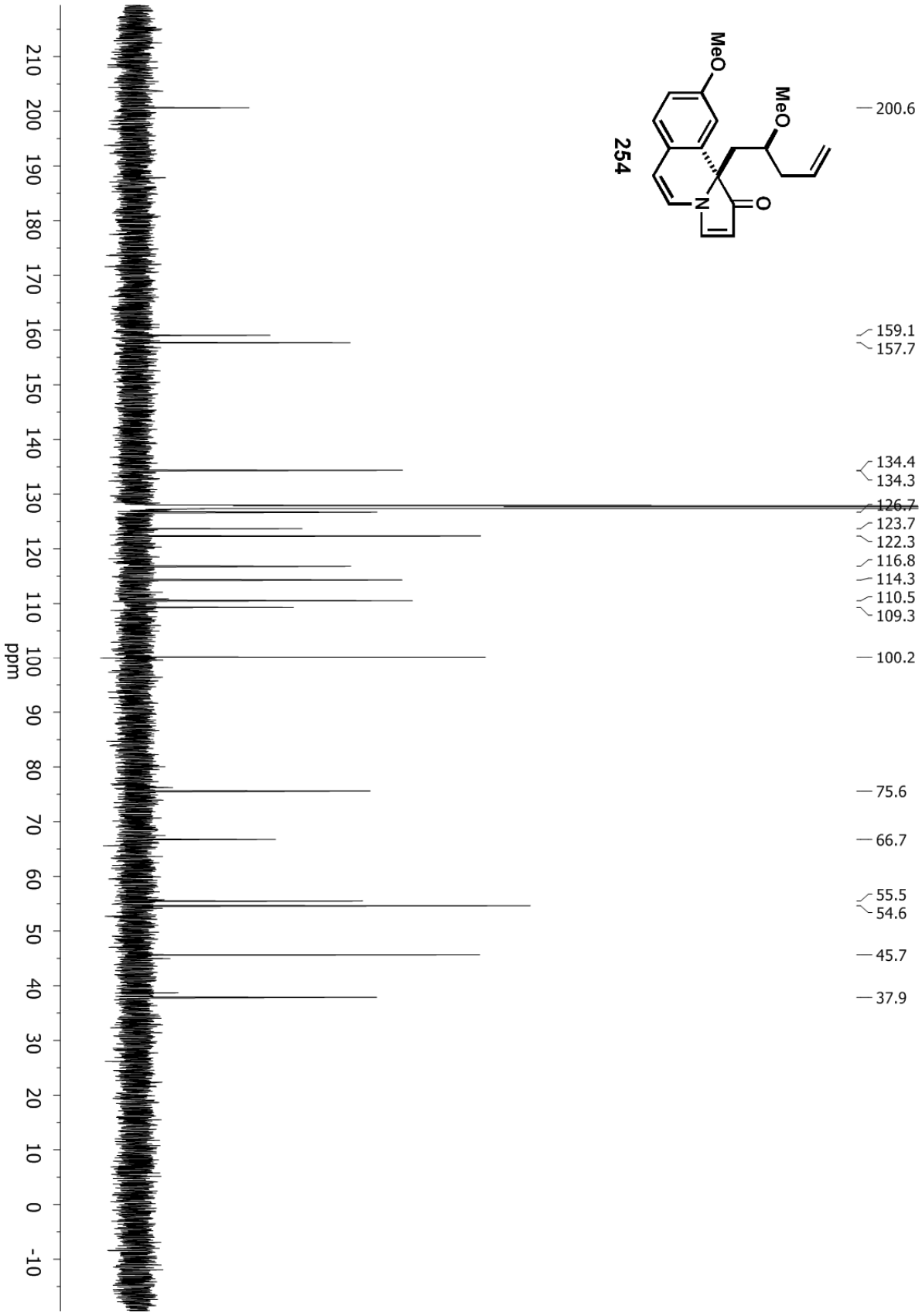

MeO
I
N
5.229
159.8
141.3
133.3
131.6
128.9
125.7
124.1
121.0
110.5
55.6
ppm
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

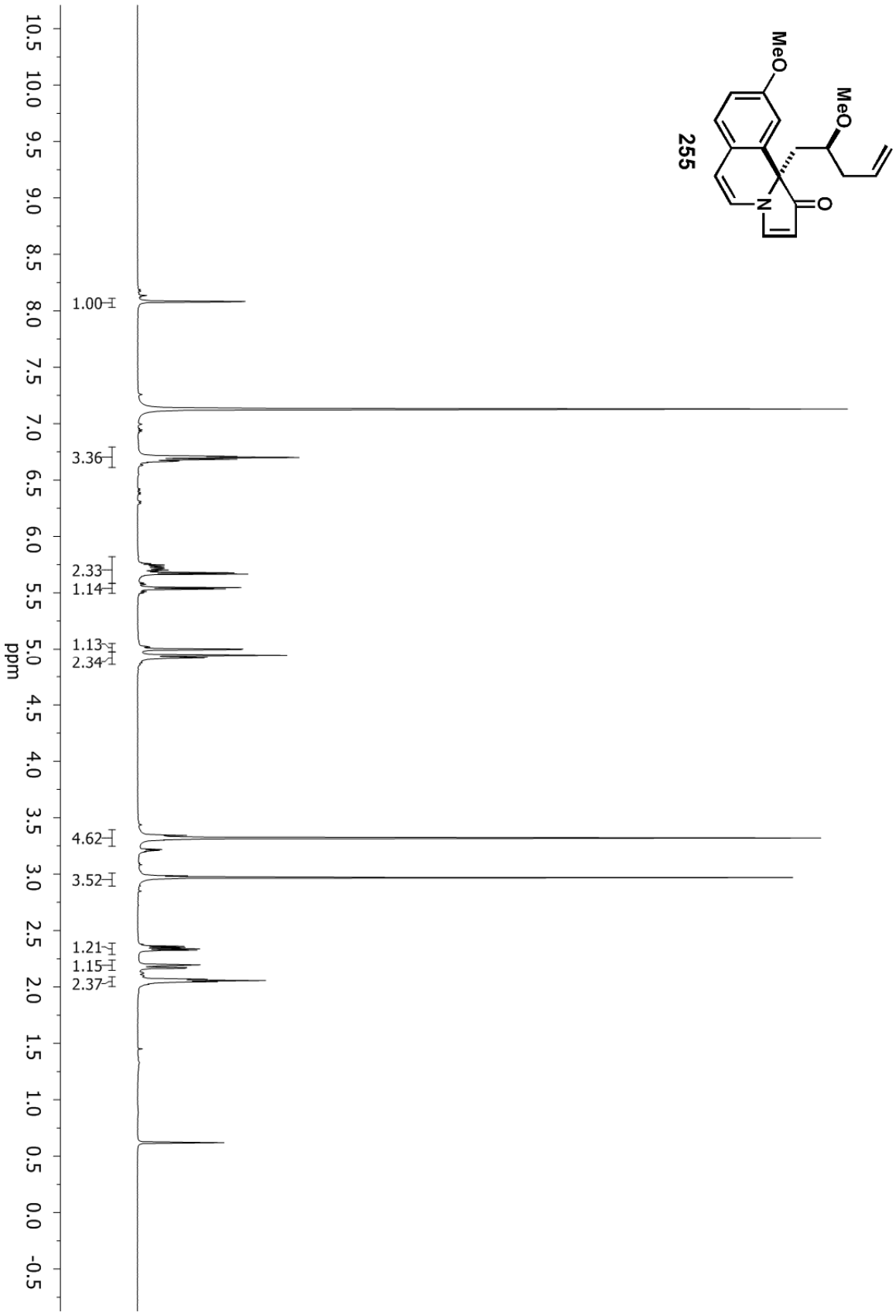

5.228
MeO
MeO
O
N
1.00
0.94
1.97
0.93
0.98
2.03
4.21
1.04
1.05
2.98
2.10
ppm
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5

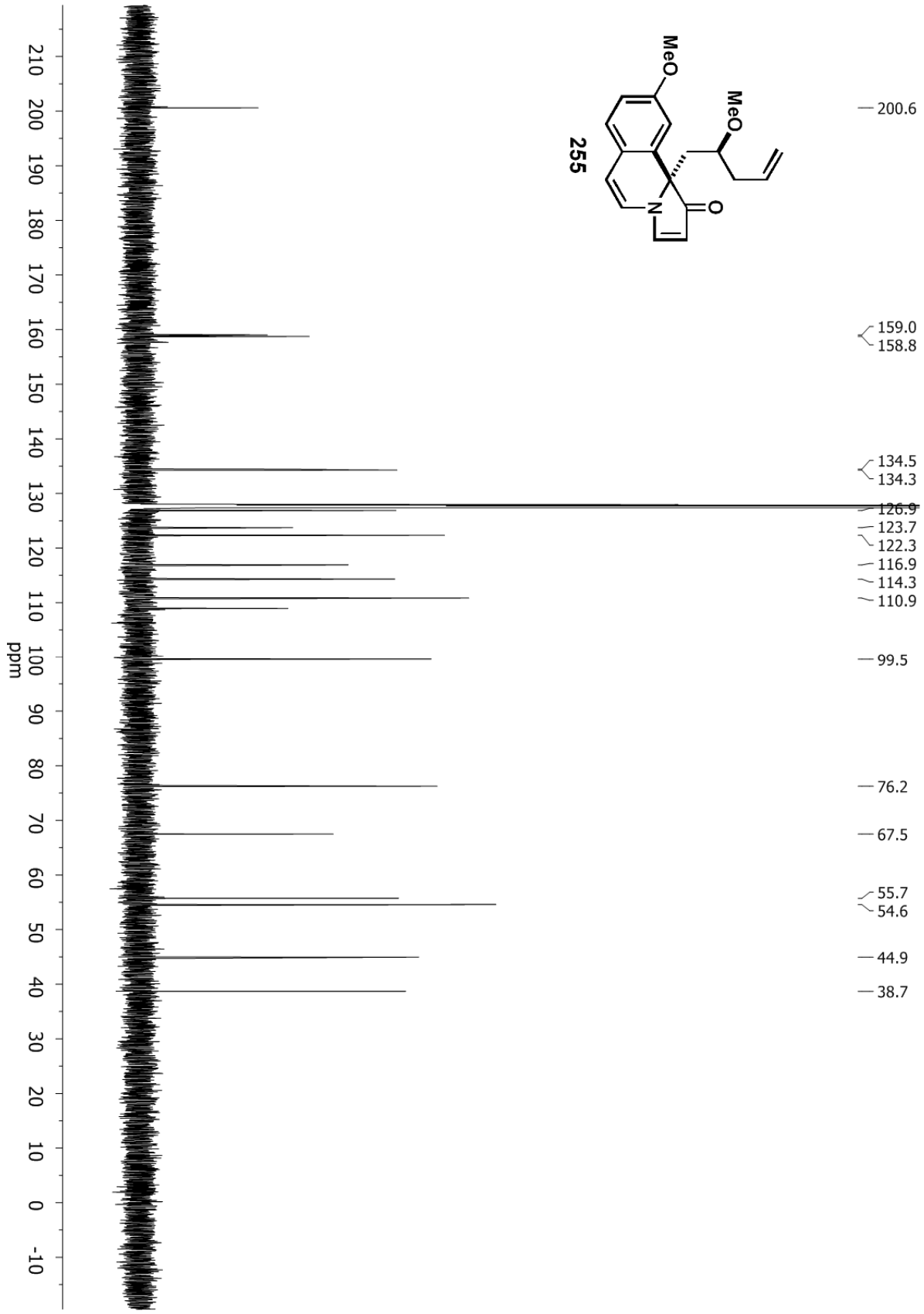

MeO
O
MeO
N
5.228
203.2
160.1
150.5
139.3
134.3
133.0
128.4
127.5
124.4
123.8
117.5
103.8
56.8
55.5
44.5
38.3
ppm
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10


MeO
HO
MeO
N
5.227
(mixture of diastereomers)
1.00
1.02
1.04
1.02
1.01
1.00
1.00
1.13
0.94
3.18
0.50
0.58
1.46
1.60
0.98
1.63
1.11
0.50
0.86
ppm
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0


MeO
MeO
O
N
254
1.00
3.40
1.23
1.03
1.10
0.99
2.35
3.10
1.14
3.00
1.16
1.09
2.45
ppm
1.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1


MeO
MeO
O
N
254
200.6
159.1
157.7
134.4
134.3
126.7
123.7
122.3
116.8
114.3
110.5
109.3
100.2
75.6
66.7
55.5
54.6
45.7
37.9
ppm
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10


MeO
MeO
O
N
255
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
ppm
1.00
3.36
2.33
1.14
1.13
2.34
4.62
3.52
1.21
1.15
2.37


MeO
MeO
N
O
255
200.6
159.0
158.8
134.5
134.3
126.9
123.7
122.3
116.9
114.3
110.9
99.5
76.2
67.5
55.7
54.6
44.9
38.7
ppm
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10