UNIVERSITY OF CALIFORNIA

Santa Barbara

My Finest Work Yet:

Copper Catalyzed Single Electron Aminations *via* Nitrosoarenes:

A dissertation submitted in partial satisfaction of the

requirements for the degree Doctor of Philosophy

in Chemistry

by

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September 2022

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ACKNOWLEDGEMENTS

A PhD is no small accomplishment and it would be impossible without the support and help of countless people. First, I need to thank my family for their help in getting me to this point. I've been told I came incredibly close to falling out a second story window and/or off a cliff many times before age five. Their vigilance towards my misadventures prevented this story from going in a different direction. Thank you mom and dad for not only keeping me alive, but for giving me the support I needed to get to this point.

Further, I need to thank everyone who served as a teacher at every point in my life, starting with kindergarten/preschool, and going all the way to my current post-doctoral advisor Prof. Michael Erb. My appreciation for the pursuit of knowledge was built through the cumulative effort of all of these individuals over many years.

A special acknowledgement is due for everyone who ever served as a scientific mentor to me. This includes Dasan Thammattoor at Colby College; Martin Schnermann at the NCI in Frederick, Maryland along with the former post-docs Roger Nani, Erin Anderson and Alex Gorka who taught me everything I know about synthesis; Monika Musial-Siwek, at Pfizer's Kendall Square site in 2017, deserves a special credit for helping me apply my synthetic skills to the field of biophysics; finally, I'd like to thank Javier Read de Alaniz and David Fisher for teaching me everything I needed to know about nitroso chemistry in order to get to this point. Andre St Amant deserves a thank you as well.

I finally need to take a moment to thank those who supported me outside of my academic pursuits. Seven the rescue border collie has been my joyful companion throughout my PhD and was the best walking/running companion one could ask for. The biggest thanks and acknowledgements go to the one and only Helena Steffens, who's love and support made

this process much more enjoyable. Helena is embarrassed about this but she overall-won Montana de Oro in March 2020; please ask her about her strategy.

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• Impact of C4′-*O*-Alkyl Linker on *in Vivo* Pharmacokinetics of Near-Infrared Cyanine/Monoclonal Antibody Conjugates; Kazuhide Sato, Tadanobu Nagaya, Yuko Nakamura, Toshiko Harada, Roger R. Nani, **James B. Shaum**, Alexander P. Gorka, Insook Kim, Chang H. Paik, Peter L. Choyke, Martin J. Schnermann, and Hisataka Kobayashi; *Molecular Pharmaceutics*, **2015**, *12*, 3303–3311

• Synthesis of Hindered Anilines: Three-Component Coupling of Arylboronic Acids, *tert*-Butyl Nitrite, and Alkyl Bromides; David J. Fisher, **James B. Shaum**, C. Landon Mills, and Javier Read de Alaniz; *Organic Letters,* **2016**, *18*, 5074–5077.

• Direct Introduction of Nitrogen and Oxygen Functionality with Spatial Control Using Copper Catalysis; **James B. Shaum**, David J. Fisher, Miranda M. Sroda, Luis Limon and Javier Read de Alaniz; *Chemical Science*. **2018**, *9*, 8748–8752.

• A Single Electron Approach to C3-N Bond Formation on Pyrroloindolines; **James B. Shaum**, Andrei Nikolaev, Luis Gonzalez, Shamon Walker, Helena C. Steffens, Javier Read de Alaniz; *in preparation*

• C3-Aminated Pyrroloindolines: from Sea Sponge to Round Bottom; **James B Shaum**, Javier Read de Alaniz; *review article in preparation*

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Cancer Research Training Award, National Cancer Institute, Frederick, MD **Sept. 2013 – June 2015**

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ABSTRACT

My Finest Work Yet:

Copper Catalyzed Single Electron Aminations *via* Nitrosoarenes:

by

James Blaine Shaum IV

Carbon–nitrogen bonds abound in chemistry and biology, and, as such, it is essential for contemporary organic chemists to develop better methods for their synthesis. The current state of the art in this field is the S_N2 addition, the reductive amination and the Buchwald-Hartwig amination, among others. These approaches are widely used yet suffer, however, from overalkylation, potential tautomerizations and the use of rare transition metal catalysts, respectively.

Inspired by the materials synthesis carried out across the UCSB Campus Green from the Chemistry Department, we developed a novel single electron method for the synthesis of these bonds. Specifically, we used electron deficient alkyl halides and low valent copper catalysts to form a transient carbon-centered radical, which can add into a nitrosoarene nitrogen in a nucleophilic-like fashion, furnishing our desired C–N bond. This approach allows for high-yielding bond formation with mild conditions onto sterically congested molecules, among other benefits.

In my first example of this work, we developed an *ipso*-substitution allowing access to electron rich nitrosoarenes, which had previously been relatively inaccessible. We employed this method in a three-component-two-step-one-pot coupling to access sterically hindered anilines. We next used this method in the synthesis of N–O macrocycles and amino alcohols.

In the final application of this synthetic method, brominated pyrroloindolines were aminated in excellent yields using this radical based method. We employed this method at gram scales in the key step of a total synthesis of the natural product (+)-asperazine A.

The Want of Peace

Wendell Berry

All goes back to the earth,
and so I do not desire
pride of excess or power,
but the contentments made
by men who have had little:
the fisherman's silence
receiving the river's grace,
the gardner's musing on rows.

I lack the peace of simple things.
I am never wholly in place.
I find no peace or grace.
We sell the world to buy fire,
our way lighted by burning men,
and that has bent my mind
and made me think of darkness
and wish for the dumb life of roots.

Table of Contents

List of Abbreviations

4Å MS - 4 angstrom molecular sieves
Ac – acyl
ATRC – atom transfer radical coupling
ATRP – atom transfer radical polymerization
Ar – aromatic
ArNO – arylnitroso
AscOH – ascorbic acid
BINAP - 2,2'-bis(Diphenylphosphino)-1,1'-binaphthyl
BINOL – 1,1′-Bi-2-naphthol
Bn – benzyl
Boc – tert-butyloxycarbonyl
Bpy – bi-pyridyl
Bz – benzoyl
Cbz – Carbobenzoxy
Cy – cyclohexyl
dba – dibenzalacetone
DCC – N,N'-dicyclohexylcarbodiimide
DCE – 1,2-dichloroethane
DCM – dichloromethane
DMF – dimethylformamide
DMA – dimethylacetamide
DPPA – Diphenylphosphoryl azide
dtbbpy – 4,4′-Di-tert-butyl-2,2′-dipyridyl
DTT – dithiothreitol
E – Electrophile
ESR – electron spin resonance
EPR – electron paramagnetic resonance
Et – ethyl
EDG - electron donating group
Eq – equivalent *or* equation
EWG - electron withdrawing group
FG – functional group
HFA – hexafluoroacetone
HFIP – hexafluoroisopropanol
HMPA – hexamethylphosphoramide
HOBt – Hydroxybenzotriazole
hr – hours

hν – light
iPr – isopropyl
iPrOH – isopropanol
IR – infrared spectroscopy
L – Ligand
LA – Lewis Acid
LDA – lithium diisopropylamide
Me – methyl
Me_6TREN – Tris[2-(dimethylamino)ethyl]amine
MeCN – acetonitrile
min – minutes
MS – mass spectroscopy
Moc – methoxycarbonyl
MTAD – 4-Methyl-1,2,4-triazoline-3,5-dione
MTBE – methyl-tertbutyl ether
NBS – N-Bromosuccinimide
NMR – nuclear magnetic resonance
Nu – Nucleophile
nPrOH- n-propanol
OAc – Acetate
ONB – *ortho*-nitrobenzyl
OTf - trifluoromethanesulfonate
PIDA – phenyliodine(III) diacetate and (diacetoxyiodo)benzene,
PMDTA – N,N,N',N",N"-pentamethyldiethylenetriamine
Ph – phenyl
pin – pinacol
PPTS – Pyridinium p-toluenesulfonate
PrOH – propanol
rt – room temperature
SES – 2-(Trimethylsilyl)ethanesulfonyl
SET – single electron transfer
SPINOL – 1,1'-spirobiindane-7,7'-diol
TBS – tert-butyldimethylsilyl
t-BuOH – tert-butyl alcohol
t-BuONO – tert-butyl nitrite nitrite
TEA – triethylamine
TEMPO – (2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
Teoc – 2-(Trimethylsilyl)ethoxycarbonyl
Tf – trifluoromethylsulfonyl
TFA - Trifluoroacetic acid
TFE – trifluoroethanol
THF – tetrahydrofuran
TIPS – triisopropylsilane
TLC – thin layer chromatography
TMS – trimethylsilyl
Troc – trichloroethylcarbonyl

Ts – tosyl
Xantphos – 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene
Δ – Heat

1 Introduction

1.1a- Looking Back- A Brief History of Organic Synthesis with Cherry-picked Examples

While we today may think of organic synthesis as a purely modern science used to produce complex molecules- from medicines to plastics- human society has been optimizing organic syntheses for millennia. Our earliest success with organic synthesis was first documented on ancient Babylonian clay tablets and described a recipe for soap making from boiled fats and alkaline ashes.[1,2] About 1300 years later, an improved synthesis, recorded in Egypt on the Ebers papyrus scrolls, made use of vegetable oils and alkaline salts.[3] By 79 AD, the Romans had built a soap factory, found in the ruins of Pompeii,[4] complete with boiling basins and molds for bars.[5] Ancient civilizations were reaping the fruits of synthesis long before humanity understood the molecular processes at play. It was not until the early 1800s that a molecular understanding of the physical world was applied to the organic chemistry of soap making.[6]

Even though organic synthesis has been a human craft for millennia, the field did not reach its infancy until 1828 when Wöhler completed the first natural product synthesis, that of urea by treating silver cyanate with ammonium chloride.[7] The field would reach its maturity well into the 20th century, as advanced by the funding accompanied by two world wars and new insights into spectroscopy, which were often borrowed from physical chemistry. Synthesis in general was heavily advanced by research groups operating based on the necessity of producing compounds of importance to medicine and physiology. This is evidenced by the Woodward group's total syntheses of, among many other examples, strychnine[8] and quinine,[9] which rely on platinum or palladium assisted reductions in key

steps. Later in the 20th century many other important syntheses, such as those of taxol[10,11] and vancomycin[12,13] would continue to advance the field to targets of ever increasing complexity, continuing to make use of transition metals catalysts along the way.

1.1b- Current State of the Art

At the time of writing of this thesis, having access to hundreds of years of chemistry literature, it would seem that synthesis is a *mature science*, one where the practitioner is no longer a scientist, but an engineer, applying already discovered reactions in a linear sequence.[14] As such, by completing the correct series of synthetic steps, a contemporary chemist is seemingly capable of creating almost any organic molecule conceivable, no matter how twisted, hindered or complex it may seem.[15]

At what cost, however, do these syntheses come? What environmental and economic externalities do we as academic synthetic chemists have the privilege of ignoring as we advance our field? Further, how relevant is a total synthesis if hundreds of hours of work yield too little of a material for any practical applications?

Organic synthesis, as advanced as we are, still has two problems which require solving if we are to stay relevant: one is our reliance on toxic and rare transition metal catalysts. Palladium salts, which drove advances in synthesis for the last 75 years, are capable of catalyzing incredibly complex reactions, yet, however, they are among the most rare elements on earth's crust and their supply is hard to guarantee in the near future.[16,17] Iridium suffers from more of the same problem; iridium-bipy complexes are some of the most incredibly robust photocatalysts known to date, yet iridium is itself the most rare solid-

element found in the earth's crust. Common iridium-bipy complexes are commercially available at over $1 per milligram.

The second problem is the economies-of-scale at which academic chemists will deliver products. Impressive total syntheses, such as that of palau'amine, were the result of thousands of hours of collaborative work, carried out over years, to finally yield a rare and bizarre molecule.[18] With 0.6 milligrams isolated, however, the potential applications of this molecule will remain unknown.

1.1c- Looking Forward

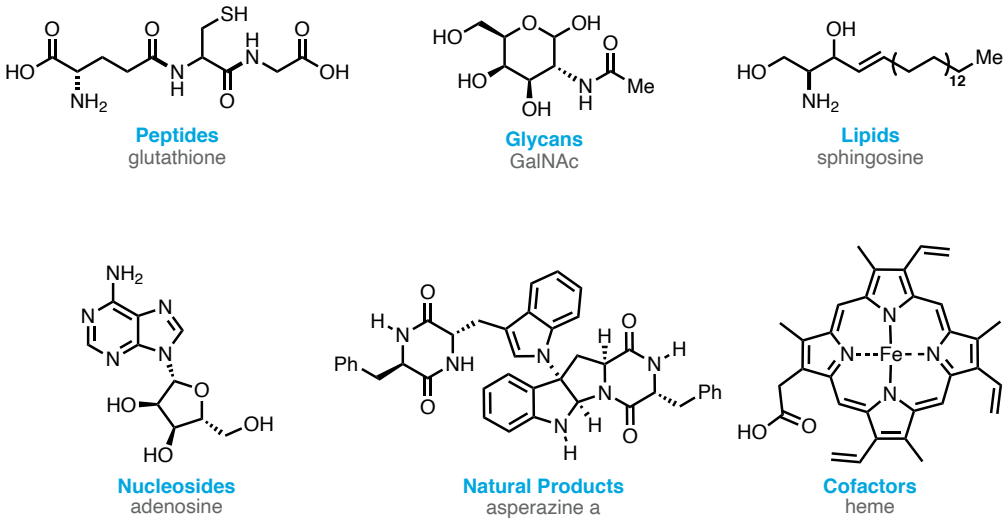
By the start of the 21st century, humans have been practicing organic synthesis for nearly five millennia and in earnest for 200 years. Yet, we still regularly employ toxic halogenated solvents in our syntheses and develop methods with *conflict catalysts* which may cease to exist within our lifetimes. Further, syntheses and methods will continue to be published which do not allow for the scalability required for them to be efficacious outside the small world of academic synthesis.

Advances arise in synthesis through individual new methodologies, improvements in one step of the linear sequence by which a practitioner builds their molecule. True benefits occur when every step of the sequence is improved. For example, in a future in which iridium salts are too rare to be used in academia, how good is a synthesis if just one step requires it? These advances must occur one at a time, however. Improving on just one single named-reaction– lowering the palladium loading or optimizing it for use in a renewable solvent– is a lofty and time-consuming goal.

Nevertheless, it is of paramount importance that today's organic chemists rise to meet these challenges, to ensure that we can still practice organic synthesis ten, 50 and 100 years into the future. Meeting the challenge laid out above, the work described in this thesis works to improve upon a future practitioner's- and my own- individual step in a linear sequence to afford a natural product. As such, the work presented here represents progress towards just one small aspect of organic synthesis: optimization of the sterically hindered carbon–nitrogen bond. We chose to meet this goal using earth abundant and non-toxic copper catalysts. Further, we employed electrophilic sources of nitrogen, which allowed us to affect these C–N bonds with mild conditions which are unorthodox in the small molecule field. Finally, after three iterative improvements with this copper catalyzed method, we applied it towards the total synthesis of a complex natural product, asperazine A, as the gram scale key-step.

1.2a- The carbon–nitrogen bond- how did we get here?

Carbon–nitrogen bonds exist all throughout Nature and area among the most essential building blocks of life. C–N bonds can be found in every class of biological molecule (Scheme 1.1). Peptides of course are amide polymers; while glycans are usually hydroxylated, some examples important in cell signaling are aminated; certain essential lipids are also aminated; the amine-based hydrogen-bonding of nucleic acids is essential to the replication of life as we know it. Certain cofactors also rely on C–N bonds for functionality.



Scheme 1.1: C–N bonds can be found in every class of biological molecule and elsewhere in nature.

Because of Nature's reliance on the C–N bond, it comes as no surprise that many of the natural products targeted by synthetic chemists feature them. In general terms, there are many viable strategies for the synthesis of C–N bonds.

The simplest approach is the S_N2. This strategy leverages the nucleophilic lone pair of electrons on the nitrogen to displace a halide on an alkyl-halide, forming the new C–N bond. This approach is difficult to control, however, as the amine becomes more nucleophilic with alkylation and thus prone to over-alkylation. Organic chemists devised a solution around this over-alkylation problem in the form of the reductive amination. How this strategy works is by once again using the nucleophilic lone pair of electrons to condense onto a carbonyl carbon, forming a hydrolytically labile imine which can be reduced to the corresponding amine with a mild reductant such as sodium cyanoborohydride. This approach comes with its own set of drawbacks, however. First, this approach will not work with easily reducible groups, as the borohydride reduction can have off target reactions. Second, you cannot have a

tertiary carbon adjacent to the amine, as you begin the reaction with an sp^2 carbon at that position which you carry into the intermediate; one can think of introducing functionality at that position with an alkyl lithium or a Grignard reagent, but these conditions are hardly mild. Third, and potentially the biggest drawback, is that secondary amines may tautomerize to form a nucleophilic enamine, which can lead to off-target reactions which lower you yield. In short, while amination *via* S_N2 and the reductive amination are tools in the tool box, there are far better tools available.

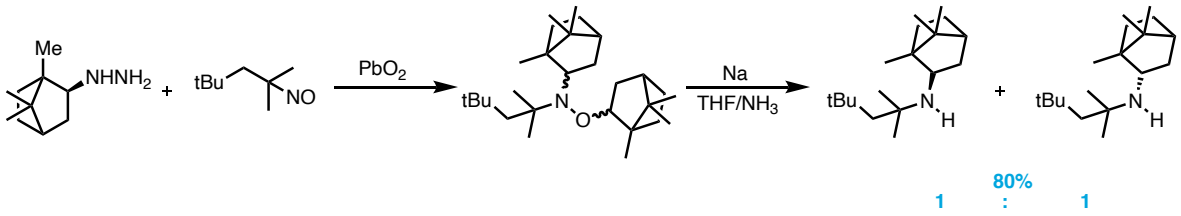
In the subsequent years, countless methodologies for the synthesis of C–N bonds have been developed, too many to survey in this introductory chapter. A considerable advance that is relevant to the community, and to this thesis, is the Buchwald-Hartwig Amination, a palladium catalyzed approach for aryl-C–N bond formation. While the first reports of palladium facilitated C–N bonds were reported by the Migita[19] and Boger[20] research groups in the early 1980s, Buchwald and Hartwig's groups optimized this approach into a robust reaction. This reaction once again employs the nucleophilic lone pair of electrons on the amine, this time to add into the palladium oxidative addition complex, prior to reductive elimination and C–N bond formation. While early examples had poor tolerance for specific substrates, such as primary amines or *o*-substituted arenes, a decade of optimization from both Buchwald and Hartwig's research groups has rendered the reaction accepting of most functionalities imaginable. While this reaction is prone to β-hydride elimination,[21] the drawback I will focus on, for the sake of this thesis, is the reliance on palladium salts, which, mentioned above, are a finite resource.

1.2b- One Electron Methods for C–N Bond Synthesis

The C–N bond forming approaches indicated above, and the vast majority in the literature, are two electron processes. That is to say, they employ the nucleophilic lone pair of electrons on nitrogen to make the new C–N bond as two-electron processes tend to be the norm in organic synthesis.

Another type of bond forming mode exists, although in the world of C–N bond formation, it tends to be underexplored. One-electron processes, making a bond from a radical precursor, have the potential to work around all of the problems indicated in the section above.

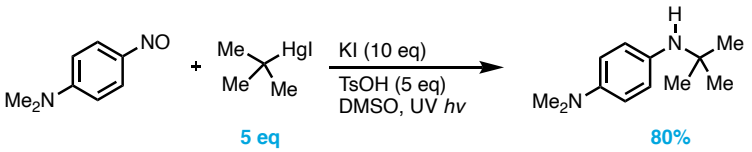
Two notable examples existed in the literature prior to the start of this work, and the common thread is that they employed the spin trapping abilities of C-nitroso compounds. The first example was published by EJ Corey's research group in 1985.[22] In this method, the hydrazine group of a camphor-hydrazine was oxidized to the corresponding radical which is trapped by the alkyl nitroso compound, affording an N–O dimer intermediate which can be reduced to the corresponding amine through Birch reduction conditions.



Scheme 1.2: EJ Corey's nitroso-based chiral amine synthesis

Eight years later, Glen Russell published a photocatalyzed method for the synthesis of substituted anilines.[23] This work employed super stoichiometric amounts of an alkyl mercury reagent as a radical precursor yet was able to affect the substituted aniline in great yield. Of

note, less electron donated examples from this work yielded an N–O dimer similar to Corey's work above.



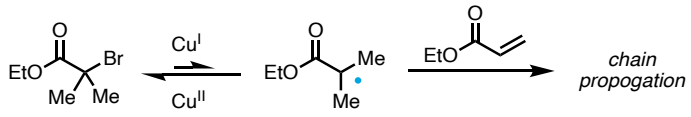
Scheme 1.3: Glen Russell's alkylation method

While these examples above indicate that C–N bonds can be forged from single electron processes, they fall short of the meeting the lofty goals indicated at the start of this chapter. Of course, lead oxides and alkyl mercury compounds are among the most toxic substances known. Further, these methods are not designed to be used on preparative scale as much as they are to initiate a new field.

These methods make use of *unusable* chemicals to craft their carbon centered radical, which then adds into the nitroso nitrogen to make the new C–N bond and subsequent N–O dimer. What these methods tell us, however, is that once the radical is formed, the process of making the C–N bond is very facile; both methods arrive at their final amine in 80%. These works, in light of the introduction to this chapter, beg the question: can carbon-radical nitroso couplings become an appealing approach if better conditions can be found? If we can find a user-friendly way to make these radicals, can optimizing this method be a viable PhD thesis in the years 2016-2020?

1.3- Lessons from Materials Science

There are many potential routes to forming carbon centered radicals, but to start this work, we were interested in options that would avoid the common problem of homo-coupling.[24] An ideal approach would generate a carbon centered radical with high chemofidelity by avoiding homo-coupling and would progress with earth-abundant catalysts. Towards this end, we were inspired by the radical forming conditions employed in atom-transfer radical polymerizations (ATRP), as summarized in Scheme 1.4.[25]

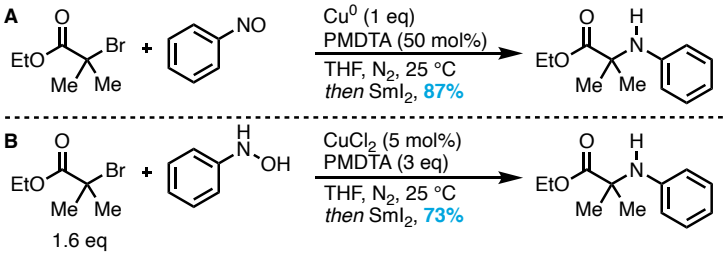


Scheme 1.4: ATRP makes use of a controlled radical to propagate polymers with low dispersities

Under ATRP conditions, an electron withdrawn and redox labile carbon–bromine bond is reduced to the corresponding carbon centered radical with Cu^{I} salts. This radical is short lived, however, as the newly formed Cu^{II} salt will quickly cap this radical to reform the starting material. The equilibrium lies such that under these conditions, around 9% of the starting material is sitting as the active radical, which can then react with monomers to propagate a polymer chain. The controlled nature of this radical formation allows practitioners to synthesize polymers with incredibly low dispersities. We looked at ATRP as a well-documented strategy for the generation of controlled carbon centered radicals, which could dramatically improve upon the published strategies indicated above.

1.5- Synthesis of hindered α-amino carbonyls

In 2015, the Read de Alaniz research group released a single electron method for the synthesis of hindered α-amino carbonyls. As the authors describe, "Given the importance of sterically hindered anilines in medicinal chemistry and the difficulties associated with their synthesis, we sought to develop a new method that was mild, practical, and highly functional-group-tolerant… With this in mind, [the authors] began by studying the reaction of ethyl α-bromoisobutyrate and nitrosobenzene in tetrahydrofuran. Using standard stoichiometric Cu^0 ATRP conditions and introducing Sm-mediated reduction of the N−O adduct afforded the desired amine in 87% yield"[26] (Scheme 1.5a). It is worth pointing out that his yield is very similar to that of Corey and Russell's examples, indicating that the efficiency of these radical couplings remains high, even while the radical generating conditions are milder.



Scheme 1.5: amide coupling reactions under (a) stoichiometric and (b) catalytic conditions

Further, the authors envisioned a redox-neutral route to render this reaction catalytic with respect to copper. As they state in the work, "By replacement of the nitrosoarene with an N-aryl hydroxylamine, the Cu^I necessary for the formation of the carbon centered radical could be regenerated via Cu^{II}-catalyzed oxidation of the N-aryl hydroxylamine. This would result in the formation of nitrosoarene, the radical trapping species." The optimized

conditions made use of only five mole percent Cu^{II} but substoichiometric alkyl bromide loadings. Excellent functional group compatibility was disclosed later in this work.

The publication of this new method set about the necessity to improve it, which will be discussed at length in subsequent chapters. This method, while robust, had a select set of drawbacks. Primarily, the substrate scope lacked electron-donated arenes (save for a single *m*-methoxy example). Second, because of the N–O dimer intermediate, half of the molecule is lost after N–O bond reduction, significantly hampering the atom economy of this approach. Finally, while impressive, this reaction lacked a significant application with which to highlight its strengths.

1.6 References

(1) Vermeil, T.; Peters, A.; Kilpatrick, C.; Pires, D.; Allegranzi, B.; Pittet, D. Hand Hygiene in Hospitals: Anatomy of a Revolution. *J. Hosp. Infect.* **2019**, *101*, 383–392. https://doi.org/https://doi.org/10.1016/j.jhin.2018.09.003.

(2) Jastrow, M. The Medicine of the Babylonians and Assyrians. *Lancet* **1913**, *182*, 1136–1142. https://doi.org/https://doi.org/10.1016/S0140-6736(01)79375-0.

(3) Reynhout, I. C.; Cornelissen, J. J. L. M.; Nolte, R. J. M. Synthesis of Polymer−Biohybrids: From Small to Giant Surfactants. *Acc. Chem. Res.* **2009**, *42*, 681–692. https://doi.org/10.1021/ar800143a.

(4) Partington, J. R. *A History of Greek Fire and Gunpowder*; Johns Hopkins University Press: Baltimore, Maryland, 1998.

(5) Blewitt, O.; Murray, J. *Handbook for Travellers in Southern Italy*; Albemarle Street: London, United Kingdom, 1853.

(6) Krafft, F.; Stern, A. Ueber Das Verhalten Der Fettsauren Alkalien Und Der Seifen in Gegenwart von Wasser. I. *Berichte der Dtsch. Chem. Gesellschaft* **1894**, *27*, 1747–1754. https://doi.org/https://doi.org/10.1002/cber.189402702116.

(7) Nicolaou, K. C.; Vourloumis, D.; Winssinger, N.; Baran, P. S. The Art and Science of Total Synthesis at the Dawn of the Twenty-First Century. *Angew. Chemie Int. Ed.* **2000**, *39*, 44–122. https://doi.org/https://doi.org/10.1002/(SICI)1521-3773(20000103)39:1<44::AID-ANIE44>3.0.CO;2-L.

(8) Woodward, R. B.; Cava, M. P.; Ollis, W. D.; Hunger, A.; Daeniker, H. U.; Schenker, K. THE TOTAL SYNTHESIS OF STRYCHNINE. *J. Am. Chem. Soc.* **1954**, *76*, 4749–4751. https://doi.org/10.1021/ja01647a088.

(9) Woodward, R. B.; Doering, W. E. THE TOTAL SYNTHESIS OF QUININE1. *J. Am. Chem. Soc.* **1944**, *66*, 849. https://doi.org/10.1021/ja01233a516.

(10) Shiina, I.; Iwadare, H.; Sakoh, H.; Hasegawa, M.; Tani, Y.; Mukaiyama, T. A New Method for the Synthesis of Baccatin III. *Chem. Lett.* **1998**, *27*, 1–2. https://doi.org/10.1246/cl.1998.1.

(11) Danishefsky, S. J.; Masters, J. J.; Young, W. B.; Link, J. T.; Snyder, L. B.; Magee, T. V; Jung, D. K.; Isaacs, R. C. A.; Bornmann, W. G.; Alaimo, C. A.; Coburn, C. A.; Di Grandi, M. J. Total Synthesis of Baccatin III and Taxol. *J. Am. Chem. Soc.* **1996**, *118*, 2843–2859. https://doi.org/10.1021/ja952692a.

(12) Boger, D. L.; Miyazaki, S.; Kim, S. H.; Wu, J. H.; Castle, S. L.; Loiseleur, O.; Jin, Q. Total Synthesis of the Vancomycin Aglycon. *J. Am. Chem. Soc.* **1999**, *121*, 10004–10011. https://doi.org/10.1021/ja992577q.
(13) Moore, M. J.; Qu, S.; Tan, C.; Cai, Y.; Mogi, Y.; Jamin Keith, D.; Boger, D. L. Next-Generation Total Synthesis of Vancomycin. *J. Am. Chem. Soc.* **2020**, *142*, 16039–16050. https://doi.org/10.1021/jacs.0c07433.
(14) Gaich, T.; Baran, P. S. Aiming for the Ideal Synthesis. *J. Org. Chem.* **2010**, *75*, 4657–4673. https://doi.org/10.1021/jo1006812.
(15) Kawano, S.; Ito, K.; Yahata, K.; Kira, K.; Abe, T.; Akagi, T.; Asano, M.; Iso, K.; Sato, Y.; Matsuura, F.; Ohashi, I.; Matsumoto, Y.; Isomura, M.; Sasaki, T.; Fukuyama, T.; Miyashita, Y.; Kaburagi, Y.; Yokoi, A.; Asano, O.; Owa, T.; Kishi, Y. A Landmark in Drug Discovery Based on Complex Natural Product Synthesis. *Sci. Rep.* **2019**, *9*, 8656. https://doi.org/10.1038/s41598-019-45001-9.
(16) Zientek, M. L.; Loferski, P. J.; Parks, H. L.; Schulte, R. F.; Seal, R. R. *Critical Mineral Resources of the United States—Economic and Environmental Geology and Prospects for Future Supply*; Reston, Virginia, 2017.
(17) Risk list 2015 — Current supply risk for chemical elements or element groups which are of economic value.
(18) Seiple, I. B.; Su, S.; Young, I. S.; Lewis, C. A.; Yamaguchi, J.; Baran, P. S. Total Synthesis of Palau'amine. *Angew. Chemie Int. Ed.* **2010**, *49*, 1095–1098. https://doi.org/https://doi.org/10.1002/anie.200907112.
(19) Kosugi, M.; Kameyama, M.; Migita, T. PALLADIUM-CATALYZED AROMATIC AMINATION OF ARYL BROMIDES WITH N,N-DI-ETHYLAMINO-TRIBUTYLTIN. *Chem. Lett.* **1983**, *12*, 927–928. https://doi.org/10.1246/cl.1983.927.
(20) Dale Boger, L.; Panek, J. S. Palladium (O) Mediated β-Carboline Synthesis: Preparation of the CDE Ring System of Lavendamycin. *Tetrahedron Lett.* **1984**, *25*, 3175–3178. https://doi.org/https://doi.org/10.1016/S0040-4039(01)91001-9.
(21) Dorel, R.; Grugel, C. P.; Haydl, A. M. The Buchwald–Hartwig Amination After 25 Years. *Angew. Chemie Int. Ed.* **2019**, *58*, 17118–17129. https://doi.org/https://doi.org/10.1002/anie.201904795.
(22) Corey, E. J.; Gross, A. W. Methods for the Synthesis of Chiral Hindered Amines. *J. Org. Chem.* **1985**, *50*, 5391–5393. https://doi.org/10.1021/jo00225a082.
(23) Russell, G. A.; Yao, C.-F. Deoxygenation of Nitro and Nitrosoaromatics by Photolysis with T-BuHgl/Kl. Regiochemistry of Tert-Butyl Radical Addition to Nitrosoaromatics [1]. *Heteroat. Chem.* **1993**, *4*, 433–444. https://doi.org/https://doi.org/10.1002/hc.520040505.
(24) Smith, M. B.; March, J. *March's Advanced Organic Chemistry*, 6th ed.; John Wiley & Sons, Ltd, 2007.
(25) Matyjaszewski, K. Atom Transfer Radical Polymerization (ATRP): Current Status and Future Perspectives. *Macromolecules* **2012**, *45*, 4015–4039. https://doi.org/10.1021/ma3001719.
(26) Fisher, D. J.; Burnett, G. L.; Velasco, R.; Read de Alaniz, J. Synthesis of Hindered α-Amino Carbonyls: Copper-Catalyzed Radical Addition with Nitroso Compounds. *J. Am. Chem. Soc.* **2015**, *137*, 11614–11617. https://doi.org/10.1021/jacs.5b07860.

2- Three-Component Coupling of Arylboronic Acids, *tert*-Butyl Nitrite, and Alkyl Bromides

2.1- Introduction

Following the highlighted methods from Chapter 1, the development of metal-catalyzed C–N bond has advanced significantly.[1] Often, the synthetic utility of these strategies is derived from their chemical robustness, generality, and availability of the starting materials. Additional features such as mildness, scalability, and use of abundant metal salts also play an important role in their widespread use. Notable examples include aforementioned palladium-catalyzed Buchwald–Hartwig[2,3] as well as the copper-catalyzed Ullman-type[4] coupling reactions between aryl halides and nitrogen nucleophiles, which have advanced the development of C_{sp}^2–N-containing molecules. Moreover, a number of novel strategies for the synthesis of sterically hindered anilines have been developed. Many research groups have published coupling reactions involving reactive organometallic intermediates, and more recently Lalic divulged a milder copper-catalyzed addition of arylboronic acids to *O*-benzoylhydroxylamines.[5,6] Moreover, Buchwald and co-workers have developed several elegant approaches for the arylation of hindered primary and secondary amines employing a novel ligand scaffold for palladium salts (Figure 2.1a).[7] Alternatively, metal-catalyzed strategies for the synthesis of C_{sp}^3–N bonds have been less flushed out and remain a fruitful area of research.[8]

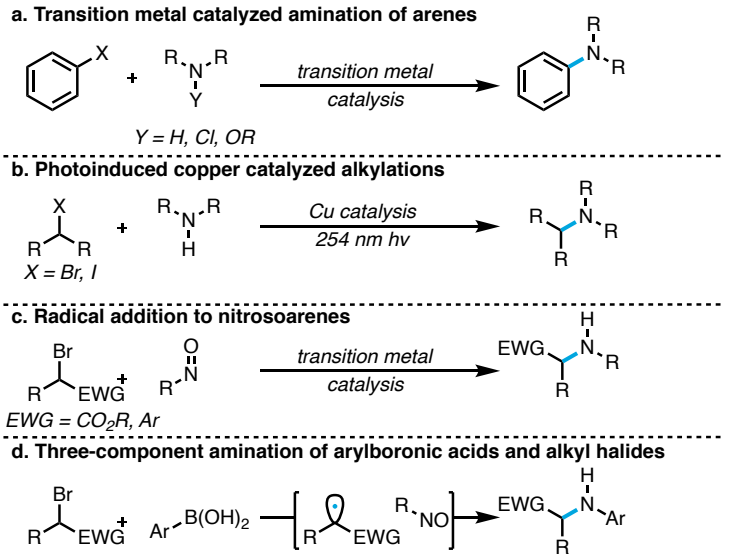


Figure 2.1: (a)–(c) general considerations and (d) the work presented in this chapter

Alkyl halides have significant potential in this reaction, as evidenced by the classic substitution reaction (S_N2) between a nitrogen nucleophile and an alkyl halide. Despite chemist's proclivity towards the S_N2, *N*-alkylation reactions have inherent limitations such as overalkylation and poor yields with less reactive alkyl halides (see Chapter 1).[9] Recently, alkyl halides unsuitable for S_N2 reactions due to steric concerns have been demonstrated as useful coupling partners for C–N bond forming reactions. For example, a 2012 collaboration by Peters, Fu, and others made use of a photoinduced, copper-catalyzed coupling between alkyl halides and amines (Figure 2.1b).[10] These amine-coupling partners have thus far been restricted to less nucleophilic options, such as carbazoles, indoles, and amides.

We[11] and others[12–15] have developed an unorthodox strategy for C–N bond formation by employing radical reactions and nitroso's inherent spin trapping ability (Figure 2.1c). This process, which has largely been limited to the field of polymer chemistry and biophysics,[16] employs two electrophiles, alkyl halides and nitroso compounds, and involves

the addition of a carbon-centered radical to the nitrosoarene. Fundamentally, this approach should have broad opportunities for synthesizing C_{sp}^3–N bonds by using the readily available alkyl halides and a range of nitroso compounds. In practice, however, nitroso chemistry has been largely restricted to the use of commercially available nitrosobenzene and 2-methyl-2-nitrosopropane, with the exception of the use of *N*-arylhydroxylamines under oxidizing conditions.[11] However, *N*-arylhydroxylamines are hardly viable coupling partners as they must be prepared prior to use as they are rarely commercially available and are often unstable when stored for even paltry amounts of time.[17,18] In this chapter, a Cu-mediated radical-based strategy has broader generality will be described, using a three-component coupling reaction with arylboronic acids, *tert*-butyl nitrite, and various alkyl halides for the synthesis of hindered aniline derivatives (Figure 2.1d). This sectional reaction strategy proceeds under mild reaction conditions, forms not one but two C–N bonds, employs commercially available starting materials, works well with α-bromocarbonyls, α-bromonitriles, and benzyl bromides, and employs earth-abundant copper salts.

2.2- *ipso*-substitution allows access to electron donated nitrosoarenes

We were inspired by independent reports from the Wu and Yan research groups describing the metal-free *ipso*-nitration of arylboronic acids with *tert*-butyl nitrite.[19,20] Ideally, we stove to find conditions to generate exclusively the nitrosoarene intermediate while avoiding the nitroarene overoxidation product. We found that by running these couplings in inert atmospheres of nitrogen gas and decreasing the of *tert*-butyl nitrite loading (1.5 equiv specifically) yielded the 4-methoxyphenylnitrosobenzene in quantitative yields. Subsequently, a one-pot, three-component coupling reaction making use of 4-

methoxyphenylboronic acid (0.6 equiv), *tert*-butyl nitrite (0.9 equiv), and ethyl α-bromoisobutyrate (1.0 equiv) was run employing well-documented stoichiometric Cu^0 ATRP conditions.[21] To our discontent, only an insignificant amount of the desired amine was produced along with a substantial amount of the nitroarene after 24 hours of reaction. We next found that simultaneous mixing of all reagents was a key problem and that the undesired formation of the nitroarene could be avoided by sequential reaction of reagents (Figure 2.2). Upon consumption of arylboronic acid (**1**), ethyl α-bromoisobutyrate, Cu^0, and PMDETA were added and allowed to react to completion. Using this strategy and subsequent treatment of the crude reaction mixture with a solution of freshly prepared SmI_2, furnished the α-amino ester (**3**) in 81% yield.

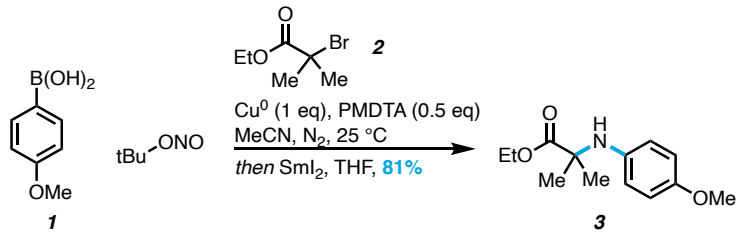
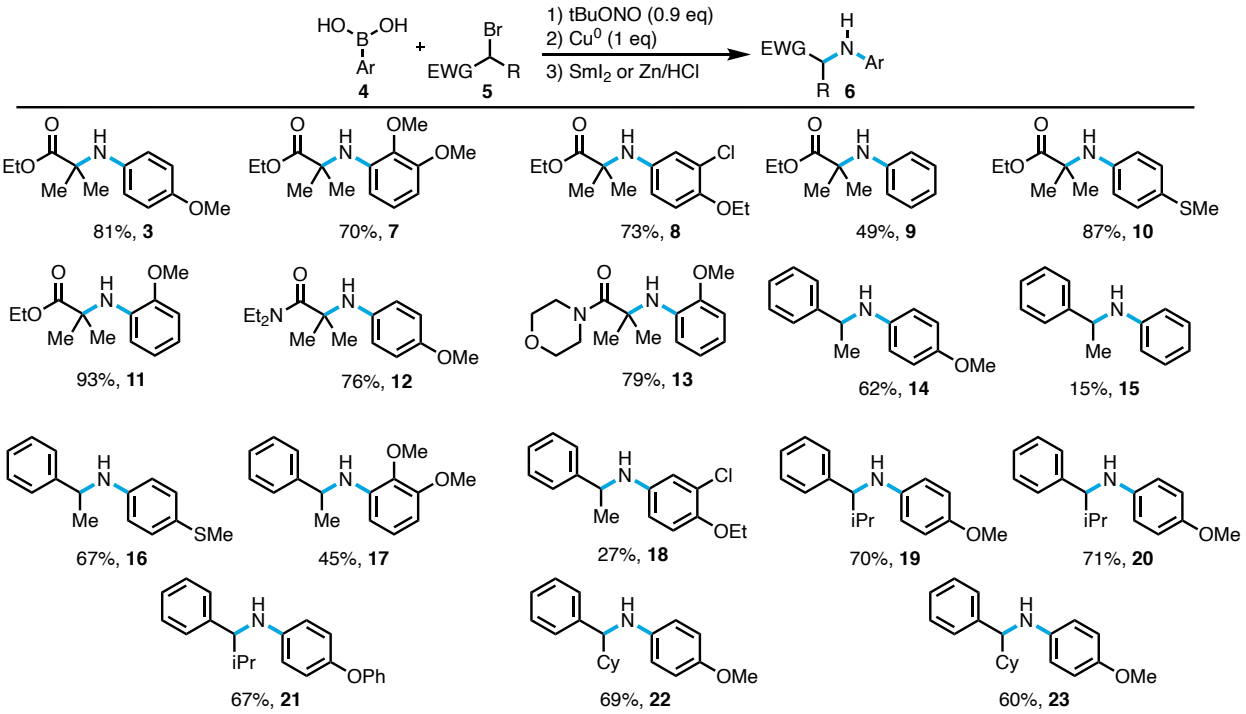


Figure 2.2: one-pot synthesis of an alpha amino ester

2.3- Substrate Scope

Having determined the optimized conditions, we next set out to explore the generality of the new methodology. To our delight, the method proved general across a range of arylboronic acids. Electron-donated arylboronic acids are tolerated on both α-bromo esters and amides. For example, those bearing O-alkyl substituents at the *ortho*, *meta*, and/or *para* positions produce products in high yield (Scheme 2.2). Difunctionalized 4-ethoxy-3-

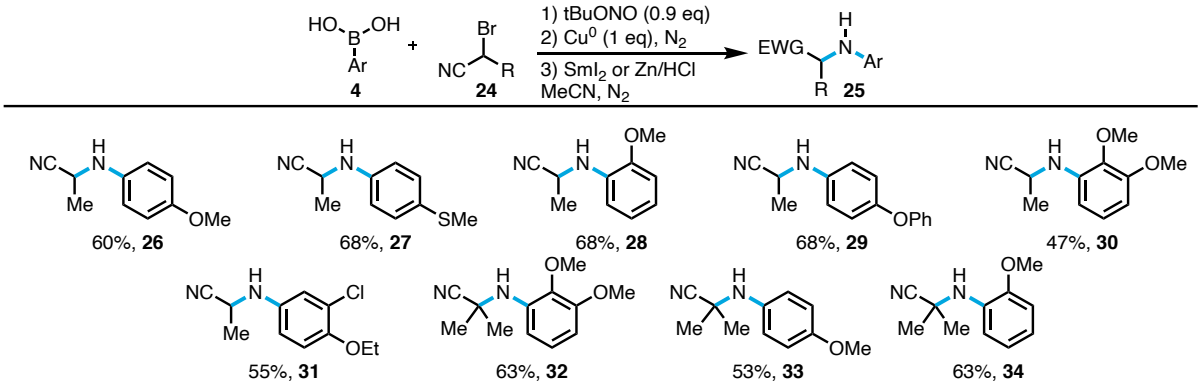
chlorophenylboronic acid reacted to give **8**, allowing incorporation of a synthetic handle for further manipulation. Aromatic thioethers were also amenable to this process as seen by **10**. Electron-neutral arylboronic acids can be used (**9**); however, excess arylboronic acid is required because oxidation of the nitrosoarene intermediate to the corresponding nitroarene could not be avoided using optimized, one-pot reaction conditions. Trace overoxidation to the corresponding nitroarene is also observed with electron-deficient arylboronic acids.



Scheme 2.2- Scope of the α-Bromocarbonyls and Benzyl Bromides with Arylboronic Acids

Utilizing the same conditions, benzyl bromides also underwent the desired three-component, Cu-mediated coupling reaction (Scheme 2.2, **14**–**23**). However, in contrast to the carbonyl derivatives, cleavage of the N–O-alkylated adduct that resulted from the radical-coupling reaction was unsuccessful with SmI_2. As such, to gain access to the desired benzylamine products, reducing Zn/HCl conditions were used to cleave the N–O bond. A

range of electron-rich arylboronic acids proved to be suitable coupling partners with the benzyl bromide substrates. In addition, sterically hindered benzyl bromide electrophiles that are typically poor substrates for substitution reactions,[22,23] including those bearing a α-branched isopropyl (**19**–**21**) and cyclohexyl (**22** and **23**) groups, showed excellent reactivity under the optimized conditions. Because this reaction presumably proceeds via radical intermediates, overalkylation products are never observed.



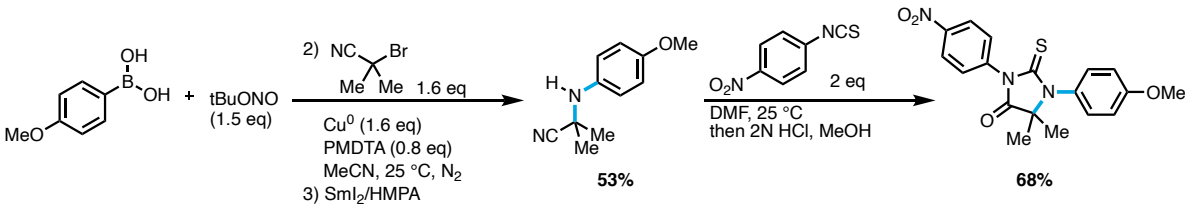
Scheme 2.3- Scope of α-Bromonitriles with Electron-Rich Arylboronic Acids

To further display the versatility of this method, it was applied to the synthesis of α-aminonitriles (Scheme 2.3),[24] valuable precursors to a wide variety of pharmacologically relevant molecules.[25] Both α-bromopropionitrile and α-bromoisobutyronitrile reacted with 4-methoxyphenylboronic acid and *tert*-butyl nitrite under the optimized reaction conditions to give the N–O alkylated adducts in 75% and 95% yield, respectively. Like the benzylamine N–O alkylated adducts, cleavage of the N–O bond for the nitrile derivatives proved challenging using SmI_2. However, the addition of HMPA, known to increase the reactivity of SmI_2,[26] enabled the cleavage and afforded the desired product in good yield. The amination

of secondary (**26**–**31**) and tertiary (**32**–**34)** α-bromonitriles was compatible with electron-rich arylboronic acids substituted in the *ortho, meta, or para* position to generate a range of α-aminonitriles (Scheme 2.3).

2.4- Thiohydantoin Synthetic Application

As proof of concept, this copper-mediated, three-component strategy was used to perform the convergent and facile synthesis of the 2-thiohydantoin scaffold, which has attracted widespread synthetic interest due in part to the chemotherapeutic activity of enzalutamide[27] and antimicrobial activity.[28] In addition, some have been developed as a possible treatment for diabetes. As depicted in Scheme 2.4, a 2-thiohydantoin can be prepared in two steps from commercially available materials. First, by using copper-mediated coupling of 4-methoxyphenylboronic acid, α-bromoisobutyronitrile, and *tert*-butyl nitrite, followed by reduction of N–O adduct, α-aminonitrile was produced in 53% yield. Treatment of this product with 4-nitrophenyl isothiocyanate followed by HCl afforded 2-phenylthiohydantoin in 68% yield.



Scheme 2.4: Synthesis of a medicinally relevant thiohydantoin scaffold

2.5- Conclusion

In conclusion, we have developed a general method for the synthesis of hindered secondary anilines through a three-component coupling of electron-rich arylboronic acids with *tert*-butyl nitrite and a variety of alkyl halides. The modularity of the process is illustrated through the synthesis of a variety of α-amino carbonyls, benzylamines, and α-amino nitriles. This method utilizes commercially available starting materials, occurs under mild reaction conditions, and forms two C–N bonds in a single protocol. Finally, the application of this method was demonstrated by convergent synthesis of a biologically active 2-thiohydantoin derivative.

2.6- References

(1) Ley, S. V; Thomas, A. W. Modern Synthetic Methods for Copper-Mediated C(Aryl)–O, C(Aryl)–N, and C(Aryl)–S Bond Formation. *Angew. Chemie Int. Ed.* **2003**, *42*, 5400–5449. https://doi.org/https://doi.org/10.1002/anie.200300594.

(2) Ruiz-Castillo, P.; Blackmond, D. G.; Buchwald, S. L. Rational Ligand Design for the Arylation of Hindered Primary Amines Guided by Reaction Progress Kinetic Analysis. *J. Am. Chem. Soc.* **2015**, *137*, 3085–3092. https://doi.org/10.1021/ja512903g.

(3) Hartwig, J. F. Carbon–Heteroatom Bond Formation Catalysed by Organometallic Complexes. *Nature* **2008**, *455*, 314–322. https://doi.org/10.1038/nature07369.

(4) Ullmann, F. Ueber Eine Neue Bildungsweise von Diphenylaminderivaten. *Berichte der Dtsch. Chem. Gesellschaft* **1903**, *36*, 2382–2384. https://doi.org/https://doi.org/10.1002/cber.190303602174.

(5) Berman, A. M.; Johnson, J. S. Copper-Catalyzed Electrophilic Amination of Diorganozinc Reagents. *J. Am. Chem. Soc.* **2004**, *126*, 5680–5681. https://doi.org/10.1021/ja049474e.

(6) Barker, T. J.; Jarvo, E. R. Umpolung Amination: Nickel-Catalyzed Coupling Reactions of N,N-Dialkyl-N-Chloroamines with Diorganozinc Reagents. *J. Am. Chem. Soc.* **2009**, *131*, 15598–15599. https://doi.org/10.1021/ja907038b.

(7) Park, N. H.; Vinogradova, E. V; Surry, D. S.; Buchwald, S. L. No Title. *Angew. Chem., Int. Ed.* **2015**, *54*, 8259.

(8) Smith, M. B.; March, J. *March's Advanced Organic Chemistry*, 6th ed.; John Wiley & Sons, Ltd, 2007.

(9) Romera, J. L.; Cid, J. M.; Trabanco, A. A. Potassium Iodide Catalysed Monoalkylation of Anilines under Microwave Irradiation. *Tetrahedron Lett.* **2004**, *45*, 8797–8800. https://doi.org/https://doi.org/10.1016/j.tetlet.2004.10.002.

(10) Creutz, S. E.; Lotito, K. J.; Fu, G. C.; Peters, J. C. Photoinduced Ullmann C–N Coupling: Demonstrating the Viability of a Radical Pathway. *Science (80)* **2012**, *338*, 647– 651.

(11) Fisher, D. J.; Burnett, G. L.; Velasco, R.; Read de Alaniz, J. Synthesis of Hindered α-Amino Carbonyls: Copper-Catalyzed Radical Addition with Nitroso Compounds. *J. Am. Chem. Soc.* **2015**, *137*, 11614–11617. https://doi.org/10.1021/jacs.5b07860.

(12) Russell, G. A.; Yao, C.-F. Deoxygenation of Nitro and Nitrosoaromatics by Photolysis with T-BuHgl/Kl. Regiochemistry of Tert-Butyl Radical Addition to Nitrosoaromatics [1]. *Heteroat. Chem.* **1993**, *4*, 433–444. https://doi.org/https://doi.org/10.1002/hc.520040505.

(13) Corey, E. J.; Gross, A. W. Methods for the Synthesis of Chiral Hindered Amines. *J. Org. Chem.* **1985**, *50*, 5391–5393. https://doi.org/10.1021/jo00225a082.

(14) Gui, J.; Pan, C.-M.; Jin, Y.; Qin, T.; Lo, J. C.; Lee, B. J.; Spergel, S. H.; Mertzman, M. E.; Pitts, W. J.; La Cruz, T. E.; Schmidt, M. A.; Darvatkar, N.; Natarajan, S. R.; Baran, P. S. No Title. *Science (80-.).*

2015, *348*, 886.
(15) Zhu, K.; Shaver, M. P.; Thomas, S. P. Chemoselective Nitro Reduction and Hydroamination Using a Single Iron Catalyst. *Chem. Sci.* **2016**, *7*, 3031–3035. https://doi.org/10.1039/C5SC04471E.
(16) Greene, A. C.; Grubbs, R. B. Synthesis and Evaluation of N-Phenylalkoxyamines for Nitroxide-Mediated Polymerization. *Macromolecules* **2009**, *42*, 4388–4390. https://doi.org/10.1021/ma900682u.
(17) Ogata, Y.; Morimoto, T. The Effects of Metallic Ions on the Autoxidation of Phenylhydroxylamine to Azoxybenzene in Methanol. *J. Org. Chem.* **1965**, *30*, 597–600. https://doi.org/10.1021/jo01013a071.
(18) Wang, K.; Guengerich, F. P. Reduction of Aromatic and Heterocyclic Aromatic N-Hydroxylamines by Human Cytochrome P450 2S1. *Chem. Res. Toxicol.* **2013**, *26*, 993–1004. https://doi.org/10.1021/tx400139p.
(19) Wu, X.-F.; Schranck, J.; Neumann, H.; Beller, M. Convenient and Mild Synthesis of Nitroarenes by Metal-Free Nitration of Arylboronic Acids. *Chem. Commun.* **2011**, *47*, 12462–12463. https://doi.org/10.1039/C1CC15484B.
(20) Wang, S.; Shu, C. C.; Wang, T.; Yu, J.; Yan, G. B. Green and Controllable Metal-Free Nitrification and Nitration of Arylboronic Acids. *Chinese Chem. Lett.* **2012**, *23*, 643–646. https://doi.org/https://doi.org/10.1016/j.cclet.2012.03.028.
(21) Matyjaszewski, K. Atom Transfer Radical Polymerization (ATRP): Current Status and Future Perspectives. *Macromolecules* **2012**, *45*, 4015–4039. https://doi.org/10.1021/ma3001719.
(22) Wang, Z. Q.; Kuo, Y. H.; Schnur, D.; Bowen, J. P.; Liu, S. Y.; Han, F. S.; Chang, J. Y.; Cheng, Y. C.; Lee, K. H. Antitumor Agents. 113. New 4.Beta.-Arylamino Derivatives of 4'-O-Demethylepipodophyllotoxin and Related Compounds as Potent Inhibitors of Human DNA Topoisomerase II. *J. Med. Chem.* **1990**, *33*, 2660–2666. https://doi.org/10.1021/jm00171a050.
(23) Hu, H.; Liu, S. Y.; Cheng, Y. C.; Lee, K. H.; Wang, Z. Q. Antitumor Agents. 123. Synthesis and Human DNA Topoisomerase II Inhibitory Activity of 2'-Chloro Derivatives of Etoposide and 4.Beta.-(Arylamino)-4'-O-Demethylpodophyllotoxins. *J. Med. Chem.* **1992**, *35*, 866–871. https://doi.org/10.1021/jm00083a009.
(24) Enders, D.; Shilvock, J. P. Some Recent Applications of α-Amino Nitrile Chemistry. *Chem. Soc. Rev.* **2000**, *29*, 359–373. https://doi.org/10.1039/A908290E.
(25) Mobaraki, A.; Movassagh, B.; Karimi, B. Magnetic Solid Sulfonic Acid Decorated with Hydrophobic Regulators: A Combinatorial and Magnetically Separable Catalyst for the Synthesis of α-Aminonitriles. *ACS Comb. Sci.* **2014**, *16*, 352–358. https://doi.org/10.1021/co500022g.
(26) Shabangi, M.; Kuhlman, M. L.; Flowers, R. A. Mechanism of Reduction of Primary Alkyl Radicals by SmI2−HMPA. *Org. Lett.* **1999**, *1*, 2133–2135. https://doi.org/10.1021/ol990329t.
(27) Jung, M. E.; Ouk, S.; Yoo, D.; Sawyers, C. L.; Chen, C.; Tran, C.; Wongvipat, J. Structure−Activity Relationship for Thiohydantoin Androgen Receptor Antagonists for Castration-Resistant Prostate Cancer (CRPC). *J. Med. Chem.* **2010**, *53*, 2779–2796. https://doi.org/10.1021/jm901488g.
(28) Bhambi, D.; Salvi, V. K.; Jat, J. L.; Ojha, S.; Talesara, G. L. Synthesis and Antimicrobial Activity of Some New Indole Containing Isoxazolines and Phthalimidoxy Derivatives of Thiazolidinone and Thiohydantoin. *J. Sulfur Chem.* **2007**, *28*, 155–163. https://doi.org/10.1080/17415990601154946.

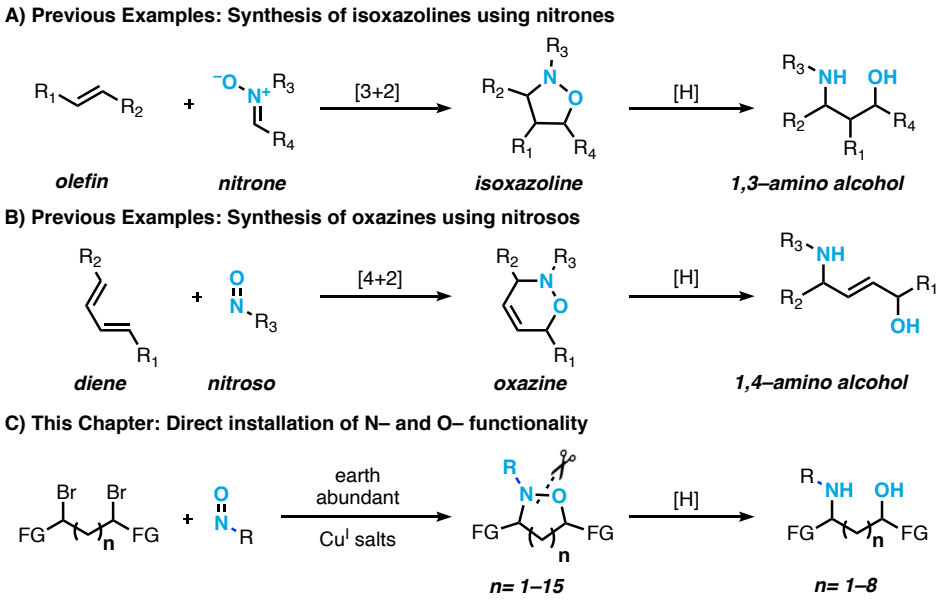
3- Direct Introduction of Nitrogen and Oxygen Functionality with Spatial Control Using Copper Catalysis

3.1- Introduction

In the past, cycloaddition reactions proved to be an efficient means to install complexity into heterocycles by constructing multiple bonds in a single reaction. Given the commonplace nature of C–N and C–O bonds in biologically relevant systems, the ability of nitrones and nitroso compounds to directly install nitrogen and oxygen character is of particular importance.[1,2] Further, due to the labile nature of the N–O bond, these transformations have also served as strategic approaches for the synthesis of amino alcohols bearing a 1,3 or 1,4-relationship[3–5]. Despite the popularity of these transformations in organic synthesis, most methods have been restricted to the construction of isoxazoline (Scheme 3.1A)[6,7] and 1,2-oxazine without much divergence (Scheme 3.1B)[8–10] heterocyclic scaffolds and the corresponding amino alcohols upon reduction. To date, there is no unified method for the synthesis of N–O heterocycles with varying ring sizes (small to large) or a direct approach to construct amino–alcohols with spatial control without independently installing the N– and O– functionality in sequential steps.

Previously, in an effort to provide alternatives to cycloaddition reactions or electrophilic functionalization of carbonyls using nitroso compounds, we[11,12] and others[13–15] described the use of radical transformations with nitroso compounds to construct sterically hindered amines. This process employs earth abundant copper salts, tolerates a range of functional groups and employs widely available radical precursors. In this Chapter, we report

the development of a generalized method to construct N–O heterocycles and amino–alcohols of any size and distribution. These studies demonstrate that bi-molecular reactions are not necessary to trap the in situ generated aminoxyl radical, despite the well-known challenges of forming larger macrocyclic rings.[16] In addition and in contrast to our previous work, this method also increases the atom economy of the nitroso additions, accessing products that incorporate both heteroatoms. Previously, the C–O bond constructed during the radical transformation was treated as part of the waste stream and discarded upon N–O bond cleavage. Combined, this radical-based process provides efficient entry into many unexplored scaffolds (Scheme 3.1C).



Scheme 3.1: examples of (a) a [3+2] nitrone-olefin and (b) a [4+2] hetero Diels-Alder cycloaddition. (c) the work presented in this chapter prepares complementary systems *via* radical additions and without olefin couplings.

3.2- Reaction Optimization and Substrate Scopes

To begin our investigations, we examined the intramolecular reaction of the 1,3-dibromide scaffold. Initially, we were able to identify conditions inspired by our previous

work and others[17–19] (5 equiv of both Cu^{I} and Cu^{0}, 2.5 equiv of PMDTA, 2 equiv of nitrosobenzene, THF, 40 ºC) that afforded the desired N–O heterocycle **1** in 70% yield. We were further encouraged to find that, in a two-step-one-pot approach, the heterocycle could be reduced to the corresponding amino–alcohol **15** (65% overall yield) by simply adding additional Cu^{I} and ascorbic acid. Further, the heterocycle was formed in a 2:1 ratio of diastereomers (dr), favouring the *cis* isomer over the *trans*, and the N–O bond reduction did not erode the selectivity. Through optimization of the reaction parameters, we found Cu^{0} could be removed entirely, Cu^{I} loading could be reduced to 2 equivalents, and nitrosobenzene loading could be lowered to 1.5 equivalents. These modifications increased the yield of the desired product (**1**) to 85%. Unfortunately, we discovered that reduction of the N–O heterocycle with Cu^{I} and ascorbic acid was only useful for five-member ring heterocycles, with incomplete reduction occurring when larger rings were investigated. A screen of various reducing conditions revealed that stronger reducing agent such as zinc in HCl and sodium-napthalenide afforded the desired amino alcohol **15** in higher yield (67% isolated yield over two steps using Zn/HCl conditions) and these methods proved general. Notably during optimization studies, we discovered that increasing the reaction temperature to 50 °C increased the dr of this transformation to 5:1 favoring the *cis*-isomer. Finally, a copper ligand screen was investigated; reactions run with the more activating ligands such as Me_6TREN provided yields very similar to those run with PMDTA. However, using a less activating ligand, such as 2,2'-bipyridyl resulted in limited or no conversion of the starting material.

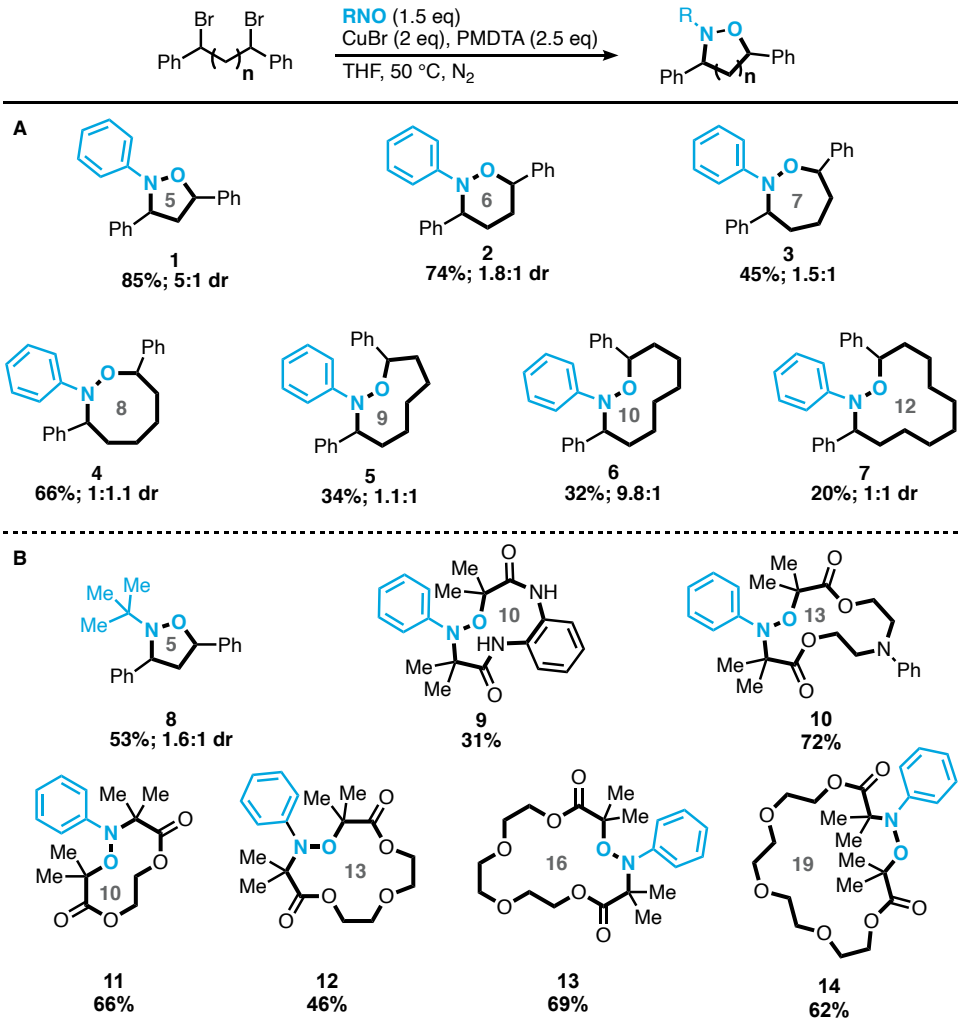


Figure 3.1: Scope of N–O heterocycles. (a) Products derived from benzyl dibromide scaffolds and nitrosobenzene. (b) Products derived from α-bromocarbonyl compounds and nitroso benzene or the 2-methyl-2-nitrosopropane dimer. Published by The Royal Society of Chemistry.

With optimized conditions established, we initially explored the generality of this method to construct N–O heterocycles with varying ring sizes (Figure 3.1A). Five (**1**) and six (**2**) membered rings were synthesized in good yields with the optimized conditions. The seven-membered ring (**3**) required more dilute reaction conditions, as increasing amounts of oligomers were observed by ^{1}H-NMR spectroscopy, presumably formed via a competitive intermolecular radical termination. The larger 8-12 membered heterocycles (**4 – 7**) required the same dilute reaction conditions, as well as the addition of 5 mol% copper (II) bromide

relative to the copper (I) bromide. Cu^{II} is known to have a strong effect on the kinetics of atom transfer radical polymerization (ATRP)[20] systems and we hypothesized that the addition of Cu^{II} decreases the concentration of carbon-centered radical, leading to a more controlled reaction. As expected when forming larger macrocyclic ring systems, the stereoselectivity of the transformation decreases as the spacer length increases. The five-membered ring **1** demonstrated a relatively high dr of 5:1 *cis:trans*, while the six- and seven-membered rings **2** and **3** demonstrated dr's of 1.8:1 and 1.5:1, respectively.[21] Rings eight-membered and greater demonstrated no selectivity. Alkyl-nitroso compounds were used to create heterocycles with yields similar to their aromatic counterparts; compound **8** was synthesized using commercially available 2-methyl-2-nitrosopropane dimer. We were pleased to find that the intramolecular reaction could be extended to readily available α-bromo carbonyl-based scaffolds. Impressively, as shown in Figure 3.1B, these scaffolds were found to cyclize very efficiently, creating up to 19-membered heterocycles in great yield (**9** – **14**). Overall, these results open the door for efficient access to a series of unexplored N–O based heterocyclic scaffolds.

We were intrigued by the large discrepancy in yields between the glycol-linked **10** – **14** and the alkyl-linked **1** – **5** substrates, and considered a Cu^{II} templating effect was responsible. Cu^{II} has been employed advantageously in a number of similar cyclizations.[22,23] To test this hypothesis, we synthesized the alkyl-linked 18-membered heterocycle that cannot benefit from templating and subjected it to optimized conditions. Compared to the closest derivatives, compound **13–14**, the yield dropped from greater than 60% to 32%. This direct comparison indicates that a templating effect might be responsible for the increased yields observed with substrates **10** – **14**.

After demonstrating the construction of N–O heterocycles with spatial control, we were now set to examine the scope of our two-step-one-pot approach to construct amino–alcohols of various distributions (Figure 3.2). We were pleased to find that many of the yields are actually higher to the amino-alcohols using the two-step-one-pot approach than those of the corresponding N–O heterocycle. For example, synthesis of an amino-alcohol (**21**) bearing a 1-10 relationship, which represents the direct installation of both N– and O–functionality over 12 angstroms of space, afforded the desired product in 48% overall yield. Notably, this is 20% higher than the corresponding N–O heterocycle (**7**, 20% yield). We speculate this is due to the in situ reduction of oligomers that also afford the desired amino–alcohol product **21**. Previously, the oligomers were removed during the heterocycle purification and isolation. For the in-situ reduction, the five-membered heterocycle affording amino-alcohol **15** and **22** was reduced using Zn/HCl conditions, but all others were reduced using sodium-napthalenide.

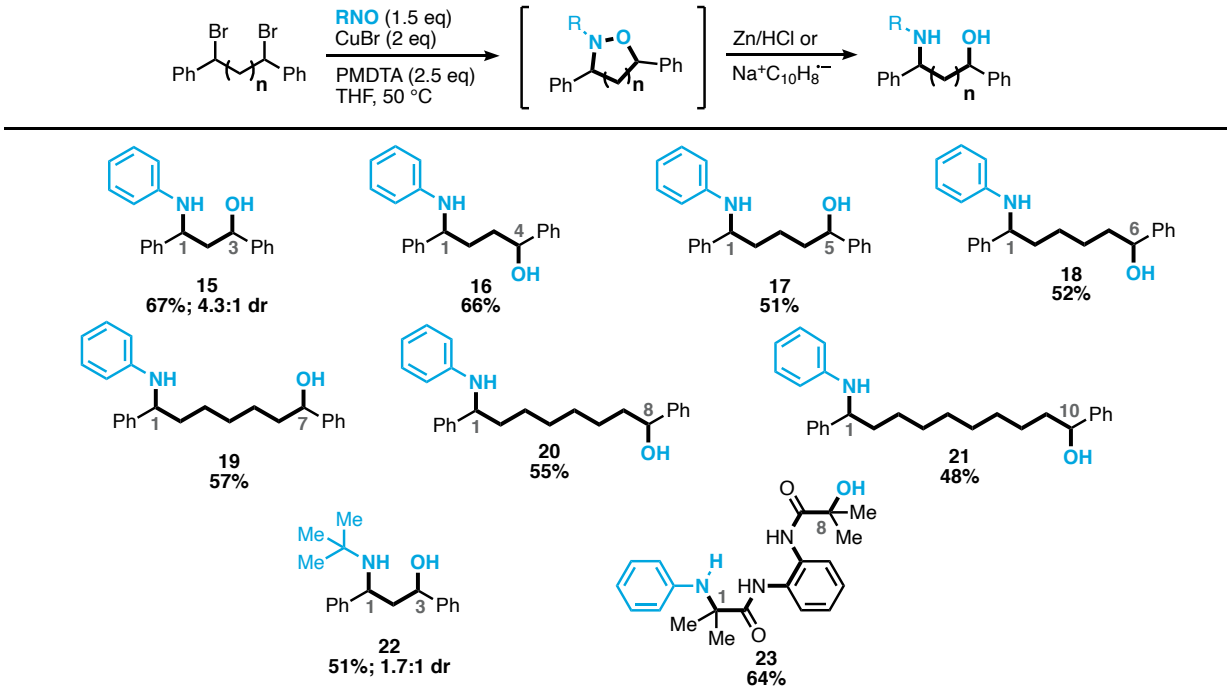


Figure 3.2: Scope of amino-alcohols synthesized with a one-pot-two-step approach. Published by The Royal Society of Chemistry.

3.3- Scaffold Modification

Next, we explored how structural modifications to the nitrosoarene and the dibromide architecture were tolerated. Given the higher yields of amino-alcohol synthesis, the two-step-one-pot approach was used for these studies. A small library of both electron-rich and deficient nitrosoarenes was synthesized and subjected to the optimized conditions (Figure 3.3a). With respect to the nitrosoarene coupling partner, the reaction was tolerant of electronic changes. Not surprisingly, the reaction tolerates halogenated compounds **26** and **28** that allow for facile downstream functionalization. Of note, the amine functional group (NH_2) group in substrate **27** is derived from the corresponding nitro group and was generated in situ upon treatment with zinc and HCl conditions. Moreover, structural changes can be made to dibromide scaffold, either the methylene linker or the aromatic rings, affording the anticipated product in moderate to good yields (40% to 66%) (Figure 3.3b). Notably, the

reaction efficiency decreased slightly when *gem*-dimethyl groups are introduced alpha to the dibromide (**30**). This is not surprising considering the costly steric interactions of forming C–N and C–O bond adjacent to a quaternary center. Interestingly, while most of the modifications to the scaffold had limited effect on the diastereomeric ratio of the products (~3:1 dr ratio was observed for **29–31**, **33**), compound **32** was formed in a 10:1 dr, suggesting diastereoselectivity can be enhanced using substitution at the *meta*-position.

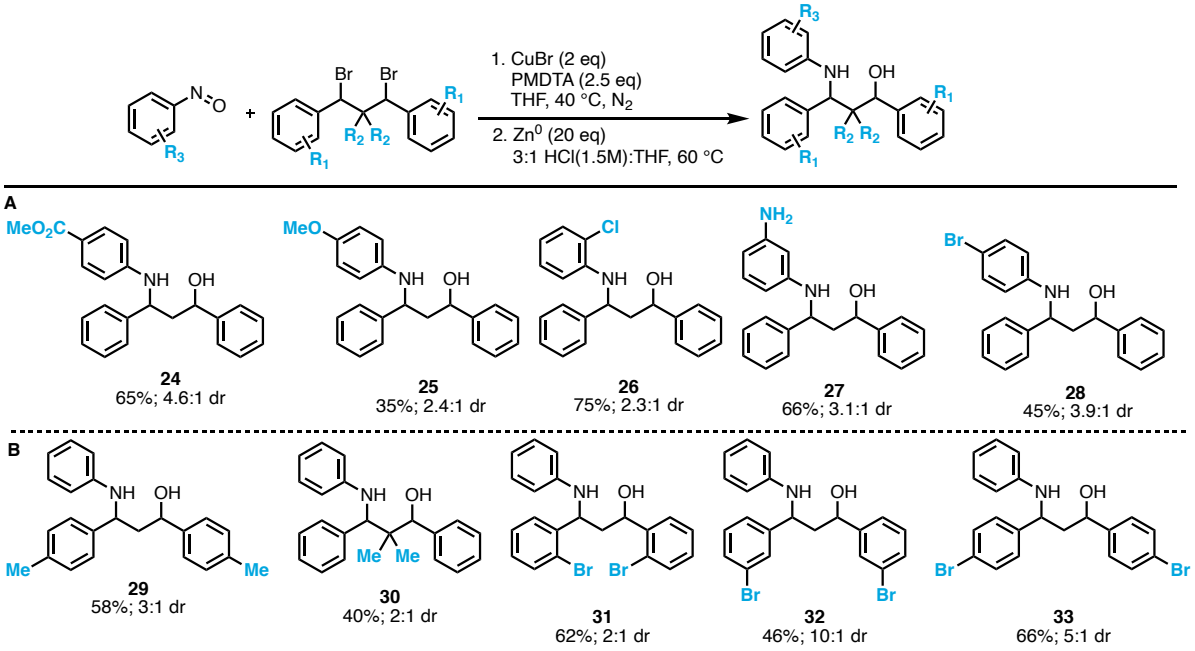


Figure 3.3: Scope of scaffold modifications. (a) Substrates derived from functionalized nitrosoarenes. (b) Substrates derived from modified dibromide scaffolds. Published by The Royal Society of Chemistry.

3.4- Unsymmetrical Scaffolds

To demonstrate the synthetic utility of this methodology beyond symmetrical substrates, we investigated strategies to construct N– and O– bonds on unsymmetrical scaffolds with regioselective control. A common feature of radical reactions with nitroso compounds is that the initial carbon centered radical reacts at nitrogen. Consequently, we hypothesized that radical initiation rates could be leveraged to control the regioselectivity.

The success of this approach would also require the second intramolecular radical reaction with the intermediate aminoxyl radical to outcompete the intermolecular reaction. Despite the challenges of balancing the reaction rates of these highly reactive radical intermediates, we were encouraged by the wealth of literature on activation rates for various initiators used for ATRP.[24]

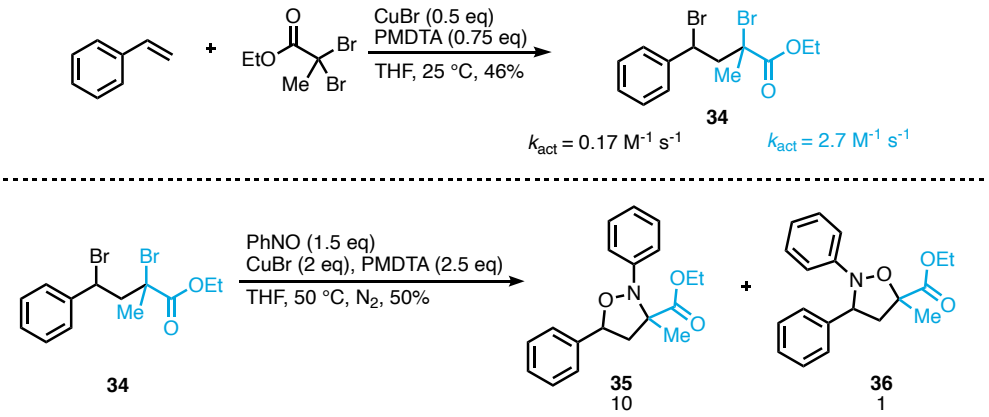


Figure 3.4: Regioselectivity of the nitroso addition onto an unsymmetrical scaffold can be predicted from relative k_{act}. Published by The Royal Society of Chemistry.

Guided by these activation studies, we designed a mixed-initiator scaffold containing both an α-bromoester and a benzyl-bromide radical precursor which could be synthesized in one step from styrene and ethyl dibromopropanoate (Figure 3.4). The k_{act} of the α-bromoester moiety is roughly an order of magnitude greater than that of the benzyl bromide under standard ATRP conditions.[25] Given this difference, we predicted that the initial radical would predominately form at the α-bromoester, leading to carbon-nitrogen bond formation α to the ester and carbon-oxygen bond formation at the less active benzyl site. To our gratification, subjection of the asymmetric scaffold to the optimized reaction conditions resulted in the N–O heterocycle with a 10:1 ratio of products **35** to **36** favouring the predicted major isomer. This result indicates that the major regioselectivity can be predicted through the relative k_{act} of each radical precursor; moreover, the approximate ratio of the regioisomers can be

predicted from the ratio of the k_{act} of the initiators. Further studies are underway to elucidate these factors in more detail and explore the scope of unsymmetrical scaffolds.

3.5- Conclusions

In summary, we have developed a new method for the direct installation of nitrogen and oxygen functionality where the N–O heterocycles and amino–alcohol scaffold size is unencumbered by traditional olefin couplings reactions. The described method is general in terms of scope and provides an efficient method capable of construction macrocycles up to 19-members in size and amino-alcohols with up to 12 Å separating the N– and O– heteroatoms. The reaction is catalysed by copper salts and leverages readily available radical precursors and nitroso compounds to generate a new C–N bond and an intermediate aminoxyl radical, which is subsequently terminated with a second intramolecularly appended radical. Moreover, we have shown that regioselectivity of the installation of nitrogen and oxygen functionality can be predicted using well-documented ATRP rate constants for radical formation. The method reported herein provides new versatile platform for the develop of N–O heterocycles and the corresponding amino-alcohols, all with high atom economy and earth-abundant catalysts.

3.6 References

(1) Frederickson, M. Optically Active Isoxazolidines via Asymmetric Cycloaddition Reactions of Nitrones with Alkenes: Applications in Organic Synthesis. *Tetrahedron* **1997**, *53*, 403–425. https://doi.org/https://doi.org/10.1016/S0040-4020(96)01095-2.

(2) Streith, J.; Defoin, A. Hetero Diels-Alder Reactions with Nitroso Dienophiles: Application to the Synthesis of Natural Product Derivatives. *Synthesis (Stuttg).* **1994**, *1994*, 1107–1117. https://doi.org/10.1055/s-1994-25647.

(3) Aoyagi, S.; Tanaka, R.; Naruse, M.; Kibayashi, C. Total Synthesis of (−)-Epibatidine Using an Asymmetric Diels−Alder Reaction with a Chiral N-Acylnitroso Dienophile. *J. Org. Chem.* **1998**, *63*, 8397–8406. https://doi.org/10.1021/jo9813078.

(4) Kibayashi, C.; Aoyagi, S. Nitrogenous Natural Products Synthesis via N-Acylnitroso Diels-Alder Methodology. *Synlett* **1995**, *1995*, 873–879. https://doi.org/10.1055/s-1995-5112.
(5) Iwasa, S.; Nishiyama, A. F. and H. Synthesis of Acylnitroso Intermediates and Their Synthetic Applications. *Mini-Reviews in Organic Chemistry*. 2005, pp 157–175. https://doi.org/http://dx.doi.org/10.2174/1570193053544445.
(6) Katagiri, N.; Okada, M.; Morishita, Y.; Kaneko, C. Synthesis of Chiral Spiro 3-Oxazolin-5-One 3-Oxides (Chiral Nitrones) via a Nitrosoketene Intermediate and Their Asymmetric 1,3-Dipolar Cycloaddition Reactions Leading to the EPC Synthesis of Modified Amino Acids. *Tetrahedron* **1997**, *53*, 5725–5746.
(7) Chackalamannil, S.; Davies, R. J.; Wang, Y.; Asberom, T.; Doller, D.; Wong, J.; Leone, D.; McPhail, A. T. Total Synthesis of (+)-Himbacine and (+)-Himbeline. *J. Org. Chem.* **1999**, *64*, 1932–1940. https://doi.org/10.1021/jo981983+.
(8) Keck, G. E.; Nickell, D. G. Synthetic Studies on Pyrrolizidine Alkaloids. 1. (.+-.)-Heliotridine and (.+-.)-Retronecine via Intramolecular Dienophile Transfer. *J. Am. Chem. Soc.* **1980**, *102*, 3632–3634. https://doi.org/10.1021/ja00530a058.
(9) McClure, K. F.; Danishefsky, S. J. A Novel Heck Arylation Reaction: Rapid Access to Congeners of FR 900482. *J. Am. Chem. Soc.* **1993**, *115*, 6094–6100. https://doi.org/10.1021/ja00067a026.
(10) Jana, C. K.; Studer, A. Total Synthesis of (+)-Trans-Dihydronarciclasine by a Catalytic Enantioselective Regiodivergent Nitroso Diels–Alder Reaction. *Chem. – A Eur. J.* **2008**, *14*, 6326–6328. https://doi.org/https://doi.org/10.1002/chem.200800903.
(11) Fisher, D. J.; Shaum, J. B.; Mills, C. L.; Read De Alaniz, J. Synthesis of Hindered Anilines: Three-Component Coupling of Arylboronic Acids, Tert-Butyl Nitrite, and Alkyl Bromides. *Org. Lett.* **2016**, *18*, 5074–5077. https://doi.org/10.1021/acs.orglett.6b02523.
(12) Fisher, D. J.; Burnett, G. L.; Velasco, R.; Read de Alaniz, J. Synthesis of Hindered α-Amino Carbonyls: Copper-Catalyzed Radical Addition with Nitroso Compounds. *J. Am. Chem. Soc.* **2015**, *137*, 11614–11617. https://doi.org/10.1021/jacs.5b07860.
(13) Gui, J.; Pan, C.-M.; Jin, Y.; Qin, T.; Lo, J. C.; Lee, B. J.; Spergel, S. H.; Mertzman, M. E.; Pitts, W. J.; La Cruz, T. E.; Schmidt, M. A.; Darvatkar, N.; Natarajan, S. R.; Baran, P. S. No Title. *Science (80).* **2015**, *348*, 886.
(14) Zhu, K.; Shaver, M. P.; Thomas, S. P. Chemoselective Nitro Reduction and Hydroamination Using a Single Iron Catalyst. *Chem. Sci.* **2016**, *7*, 3031–3035. https://doi.org/10.1039/C5SC04471E.
(15) Zhu, K.; Shaver, M. P.; Thomas, S. P. Amine-Bis(Phenolate) Iron(III)-Catalyzed Formal Hydroamination of Olefins. *Chem. – An Asian J.* **2016**, *11*, 977–980. https://doi.org/https://doi.org/10.1002/asia.201501098.
(16) Galli, C.; Mandolini, L. The Role of Ring Strain on the Ease of Ring Closure of Bifunctional Chain Molecules. *European J. Org. Chem.* **2000**, *2000*, 3117–3125. https://doi.org/https://doi.org/10.1002/1099-0690(200009)2000:18<3117::AID-EJOC3117>3.0.CO;2-5.
(17) Voter, A. F.; Tillman, E. S.; Findeis, P. M.; Radzinski, S. C. Synthesis of Macrocyclic Polymers Formed via Intramolecular Radical Trap-Assisted Atom Transfer Radical Coupling. *ACS Macro Lett.* **2012**, *1*, 1066–1070. https://doi.org/10.1021/mz300311p.
(18) Voter, A. F.; Tillman, E. S. An Easy and Efficient Route to Macrocyclic Polymers Via Intramolecular Radical−Radical Coupling of Chain Ends. *Macromolecules* **2010**, *43*, 10304–10310. https://doi.org/10.1021/ma102319r.
(19) Zhang, C.; Wang, Q. Step-Growth Radical Addition-Coupling Polymerization (RACP) for Synthesis of Alternating Copolymers. *Macromol. Rapid Commun.* **2011**, *32*, 1180–1184. https://doi.org/https://doi.org/10.1002/marc.201100208.
(20) Zhang, H.; Klumperman, B.; Ming, W.; Fischer, H.; van der Linde, R. Effect of Cu(II) on the Kinetics of the Homogeneous Atom Transfer Radical Polymerization of Methyl Methacrylate. *Macromolecules* **2001**, *34*, 6169–6173. https://doi.org/10.1021/ma0104736.
(21) Huisgen, R.; Grashey, R.; Hauck, H.; Seidl, H. 1.3-Dipolare Cycloadditionen, XLI. Anlagerung Der Nitrone an Styrol; Orientierung Und Räumlicher Ablauf. *Chem. Ber.* **1968**, *101*, 2548–2558. https://doi.org/https://doi.org/10.1002/cber.19681010734.
(22) Vance, A. L.; Alcock, N. W.; Busch, D. H.; Heppert, J. A. Copper(II) Template Synthesis of a 20-Membered [1+1] Schiff Base Macrocycle and Nickel(II) Template Synthesis of a 40-Membered [2+2] Schiff Base Macrocycle from 2,6-Pyridinedicarboxaldehyde and 1,13-Diamino-4,7,10-Trioxatridecane. *Inorg. Chem.* **1997**, *36*, 5132–5134. https://doi.org/10.1021/ic961531k.

(23) Tong, K.-L.; Yee, C.-C.; Tse, Y. C.; Au-Yeung, H. Y. Discoveries from a Phenanthroline-Based Dynamic Combinatorial Library: Catenane from a Copper(i) or Copper(Ii) Template? *Inorg. Chem. Front.* **2016**, *3*, 348–353. https://doi.org/10.1039/C5QI00227C.
(24) Matyjaszewski, K. Atom Transfer Radical Polymerization (ATRP): Current Status and Future Perspectives. *Macromolecules* **2012**, *45*, 4015–4039. https://doi.org/10.1021/ma3001719.
(25) Tang, W.; Matyjaszewski, K. Effects of Initiator Structure on Activation Rate Constants in ATRP. *Macromolecules* **2007**, *40*, 1858–1863. https://doi.org/10.1021/ma062897b.

4- Aminated Pyrroloindoline Natural Products

4.1- Introduction

Pyrroloindolines (**1**) represent the privileged core of many bioactive small molecules, including numerous natural products and therapeutic drugs. As natural products, pyrroloindolines abound in nature, as they can be isolated from settings as diverse as saltwater cultures of sea sponge fungi to rubiaceous cousins of the coffee plant. This scaffold exists in therapeutic agents with numerous examples, most importantly being the FDA approved Physostigmine[1] and structurally similar Physovenine.[2] Other natural products bearing this scaffold have promising therapeutic properties.[3]

Biosynthetically, pyrroloindolines are derived from cyclized tryptamines (**2**) or tryptophan (**3**), as demonstrated in Figure 4.1a. The structurally related furoindoline (**4**) is similarly derived from tryptophol derivatives (**5**) (Figure 4.1b). Importantly, the substituents on Carbons 2 and 3 are always observed in a *cis* relationship in pyrroloindolines, and most frequently as the *cis* product in furoindolines.

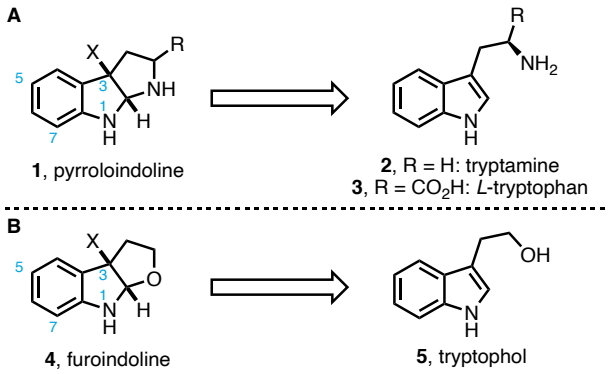


Figure 4.1- Pyrroloindolines are generally derived from cyclized tryptamines or tryptophans. The indole numbering system employed in this review is demonstrated on **1**.

Throughout Nature, pyrroloindoline based natural products can be isolated from many different species.[4] Most isolated examples bear carbon functionalization at the C3-position. Notable examples are given in Figure 4.2A, including the C3-arene functionalized asperazine and pestalazine A, the indole functionalized gliocladines and the C3 dimers of the chimonanthine family. Another common structural feature of known pyrroloindolines is prenylation at the C3 position, commonly seen in the flustramide/flustramine natural products. Fewer examples, outside of Figure 4.2A, are those bearing a C3-alcohol such as alline, flustramol B and the furoindoline products chloptosin and madindoline A.[4,5]

Many pyrroloindoline natural products are known, however, to bear a C3-N linkage, as highlighted in Figure 4.2B. Every example of this subclass of pyrroloindoline isolated to date bears an indole group at this position, the result of a biosynthetic dimerization of tryptophan residues or tryptamine subunits. Among this subclass of pyrroloindolines are many examples with known biologic activity and some with potential therapeutic applications. These aminated pyrroloindolines have been fixtures in the literature for decades, as the first example, chetomin (**9**), was isolated and identified in 1944.[6] At the same time, however, new examples continue to be discovered, as the structure of Asperazine A (**6**) was first confirmed

recently in 2014,[7] or cristazine (**10**) which was identified in 2016.[8] Further, the aminated pyrroloindoline core has been featured as a synthetic intermediate for natural products that do not bear such in the final product, specifically in Movassaghi's syntheses of the Communesin[9,10] class of alkaloids and in Baran[11,12] and Rainer's[13] syntheses of members of the Kapakahine class of natural products.

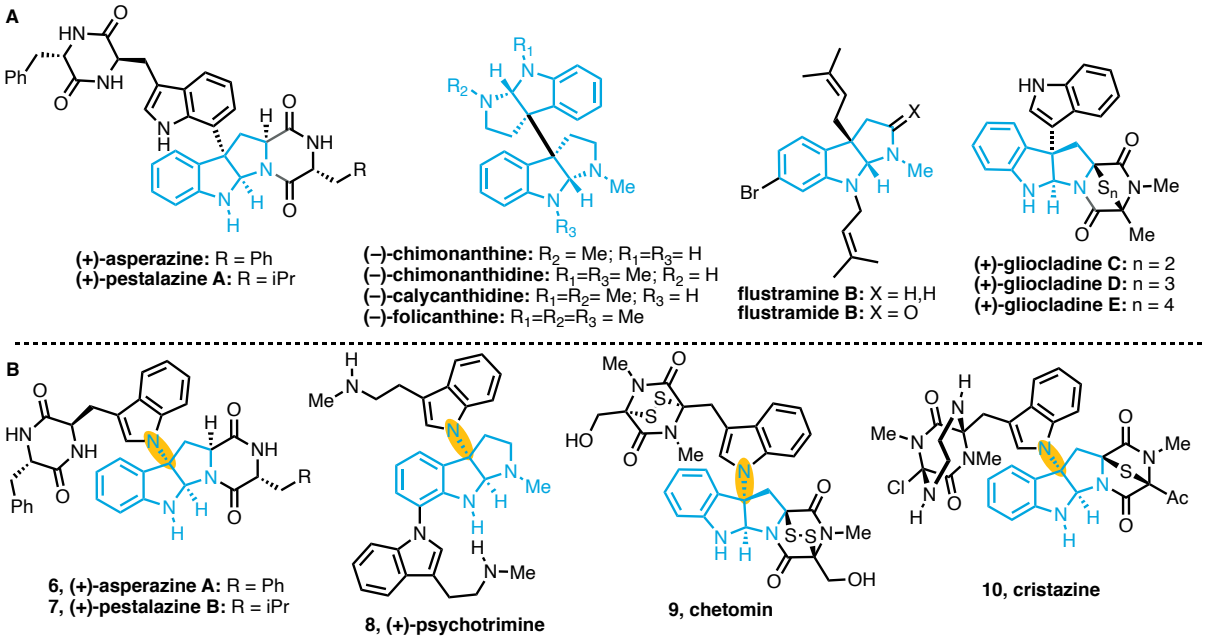


Figure 4.2- (A) Representative examples of pyrroloindolines and (B) C3-aminated pyrroloindolines in the natural product field

Despite the significance aminated pyrroloindolines bear in the natural product field and their therapeutic potential, methodologies for the direct synthesis of the key structural C–N bond is notably absent from the literature until relatively recently, beginning in earnest in 2008. In the previous decade however, dozens of complimentary methods have been reported, most of which can be neatly categorized into one of two separate strategies and further into various categories. Finally, despite the recent wealth of knowledge regarding the synthesis of this essential linkage, we found the information to be scattered in the introductory references of disparate publications.

The aim of this work is to organize the vast scientific knowledge concerning this privileged scaffold into one place. In this Chapter, we will lay out a comprehensive summary of all known natural products bearing the C3-aminated pyrroloindoline core, including the history of their isolation and any known biological activity. We will then present a comprehensive summary of every published method for the direct installation of this C–N bond onto an already developed pyrroloindoline fashion. There are many examples of installation of this key C–N bond prior to synthesis of the product scaffold in a non-biomimetic fashion, and, while potentially very elegant, this strategy will fall outside the scope of this review.[14–17]

4.2a- Known Natural Products Bearing this Core: Tryptamine Oligomers

The earliest natural product to be of wide spread interest to the synthesis community is psychotrimine (**8**), which belongs in the larger family of *N*-methyl tryptamine derived natural products. The elucidated structure of psychotrimine was first reported in 2004 by Takayama's research group at Chiba University, as isolated from *Psychotria rostrata*, an understory shrub endemic to South American rainforests.[18] The particular leafy sample from which psychotrimine was isolated in this initial report was derived from Malaysia- where *rostrata* leaves were used as a treatment for constipation- and the alkaloids were purified from the methanol extracts of these dried and powdered leaves. Two racemic syntheses for psychotrimine were published shortly thereafter in 2008; one by Baran's research group-[19] who's key step will be discussed below- and another by Takayama's group.[14] Takayama

followed up his initial studies with the first asymmetric total synthesis in 2010[15] before collaborating with Baran's lab on a more scalable synthesis.[20] While a number of formal syntheses have been reported,[17,21–23] known biological activity is scarce. Baran reported the psychotrimine had "activity against colon and lung cancers,"[12] and later demonstrated, with Floyd Romesburg's group, modest activity against Gram-positive bacteria.[24]

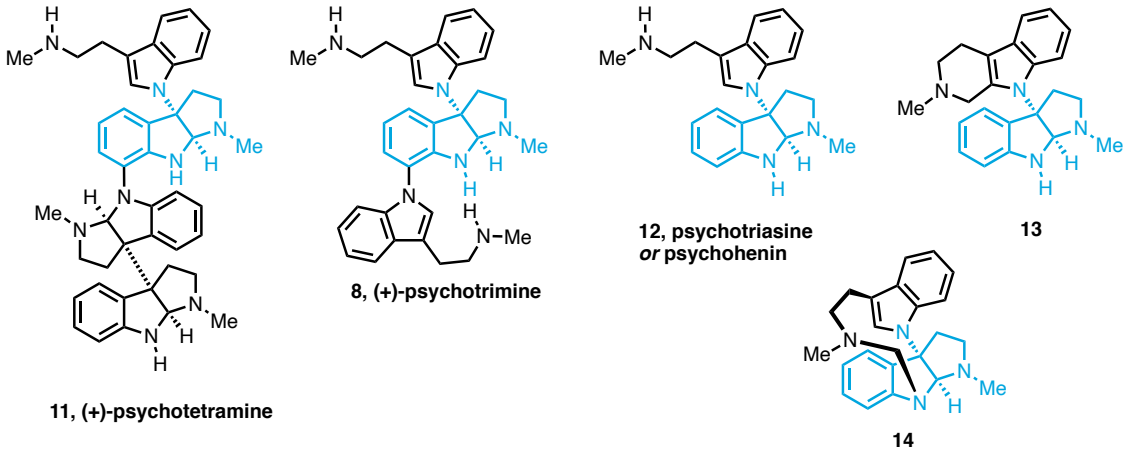


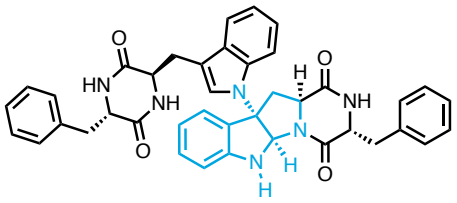
Figure 4.3- N-methyl tryptamine derived polymers are isolated from various *Psychotria* species.

The tryptamine dimer psychotriasine (**12**), also referred to as psychohenin in some publications, has also been the subject of a number of synthetic studies. Psychotriasine was identified, with relative stereochemistry, from the ethanol extracts of dried *Psychotria calocarpa* leaves,[25] and subsequently, with its absolute configuration, from ethanolic extracts of *Psychotria henryi* leaves and twigs.[26] Because psychotriasine is the least complex of all the natural products bearing a pyrroloindoline C3-N linkage, this compound has been the subject of many syntheses, serving as a proof of concept in methodology publications. As such, psychotriasine has been the subject of nine separate syntheses, either total or formal.[12,27–34] To date, there are no reports of psychotriasine's biological activity.

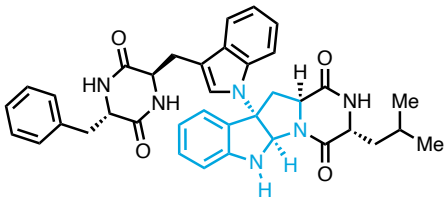
Psychotetramine (**11**) is the largest of the tryptamine polymers identified to date containing the relevant C3-N linkage, having been isolated from air dried *Psychotria rostrata* leaves by Hiromitsu Takayama's research group.[20] The absolute configuration of psychotetramine was determined *via* a synthetic collaboration with the Baran lab. No biological activity for psychotetramine has yet been reported.

Two other products in this class were reported in the same publication in 2013.[35] Tryptoline **13** and decacycle **14** were isolated from *Psychotria henryi*, similar to psychotriasine. These yet-to-be-named products have been shown to only have modest activity against human osteosarcoma cells (>10 μM IC_{50}) and tryptoline **13** has been the subject of one total synthesis.[30]

4.2b- Diketopiperazines



6, (+)-asperazine A



7, (+)-pestalazine B

Figure 4.4- Two diketopiperazines natural products exist as dimers of two amino acids

Asperazine A (**6**) and pestalazine B (**7**) are two structurally similar diketopiperazine (sometimes dioxopiperazine in the literature) natural products. The lower rings (as pictures here) exist as the cyclooxidized-*L*-tryptophan and either *D*-phenylalanine (asperazine A, **6**) or *D*-leucine (pestalazine B, **7**); the upper diketopiperazine exists as a *L*-tryptophan/*D*-phenylalanine dimer in both products. Asperazine A (**6**) with its accepted stereochemistry, was first isolated in 2014 from *Aspergillus niger* colonies growing on the liverwort

Heteroscyphus tener.[7] Interestingly, a constitutionally identical diastereomer, Q20547-A, was reported 20 years prior to be isolated from another *Aspergillus* species.[36] Pestalazine B (**7**) was also isolated from a pathogenic plant fungus, *Pestalotiopsis theae*, found on the branches of the tea plant *Camellia sinensis*.[37] Asperazine A (**6**) was also isolated from this *Pestalotiopsis* fungus. Through a modular synthetic strategy devised by the de Lera research group, the absolute structure of pestalazine B (**7**) was revised to the accepted structure reported above;[38] the position of the leucine and phenylalanine residues was reversed between the updated and originally proposed structures.

In its initial publication, asperazine A was demonstrated to have moderate activity against human ovarian carcinoma cell lines (IC_{50} = 56.7 μM against A2780 cell lines); biological activity of pestalazine B (**7**) has yet to be presented in the literature. These similar diketopiperazines have been the subject of a few total syntheses; asperazine A's initial synthesis was completed, along with one of pestalazine B (**7**), in a modular 2018 synthesis by Movassagi's research group.[39] Our research group completed a total synthesis of asperazine A (**6**) two years later in 2020.[40] Pestalazine B (**7**), given its longer standing in the literature, has been the subject of four total syntheses,[33,38,39,41] arguably the most important of which was completed by de Lera's research group which established the correct structure of the natural product *via* synthetic means,[42] as mentioned above. Of note, the absolute configuration of structurally similar pestalazine A was also revised *via* total synthesis.[43]

4.2c- Chetomin and its thio-analogues

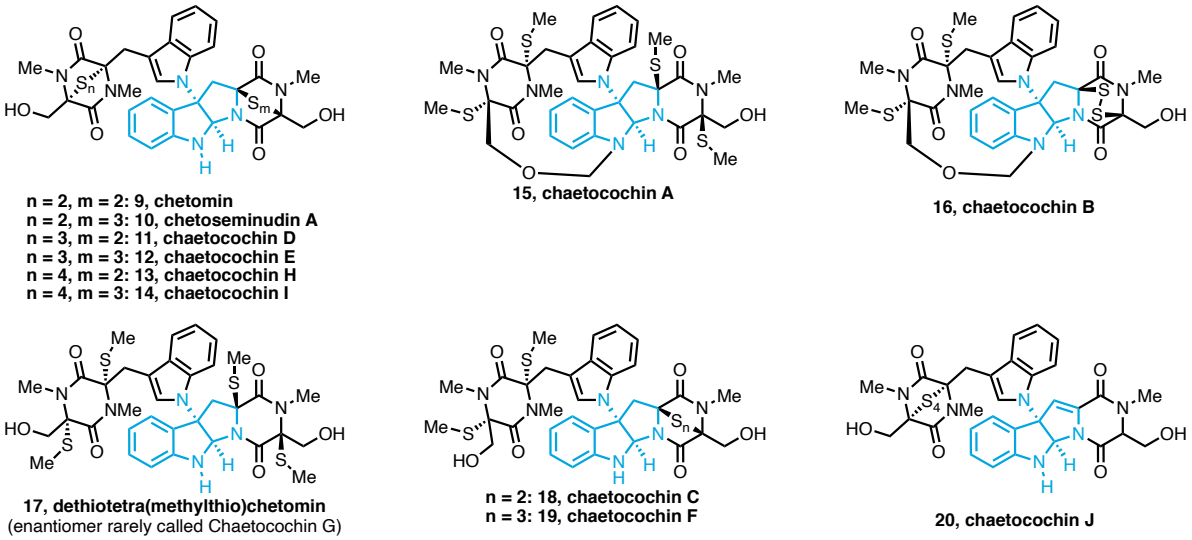


Figure 4.5- Polythiolated-C3-aminated-diketopiperazine analogues, including the chaetocochins and chetoseminudins.

Of the natural products surveyed in this review, none have been more widely studied than the mycotoxin chetomin (**9**). Chetomin was first isolated from *Chaetomium cochliodes* and identified as an antibiotic substance by Waksman and Bugie in 1944.[6] While the name was first proposed to be "chaetomin," it was shortened to "chetomin" at the request of the editor of Chemical Abstracts.[44] Since, chetomin has been identified in *Chaetomium globusum* and *Chaetomium seminudum*.[45–47] The structure remained unknown for over three decades, however, until J. A. Walter's group elucidated the exact structure,[48] after much investigation in the literature.[45] Similar in structure to asperazine A and pestalazine B, chetomin exists as a dimer of cyclooxidized *D*-tryptophan and *D*-serine. Of note, other fungi species have been demonstrated to enzymatically convert *L*-tryptophan to *D*-tryptophan *via* a nonribosomal peptide synthetase.[49] The unique feature of chetomin, and the cause of its potent biological activity, is its epidisulfide, however, which has been shown to disrupt proteins relying on zinc as a structural motif. Chetomin, long known as a Gram-positive antibiotic,[50] has been

demonstrated to inhibit HIF1α induced transcriptional activity by inhibiting HIF1α's interaction with its coactivator p300. Bogdan Olenyuk's research group demonstrated that chetomin, it its reduced thiol form, disrupts Zn^{2+} mediated folding in p300's CH1 domain, either *via* binding Zn^{2+}directly or by forming disulfide bonds with endogenous Zn^{2+}-binding cysteine residues.[51] Further work from William Figg's research group at the NIH used mass spectrometry to show that chetomin and other epidithiodiketopiperazines sequester Zinc directly from the CH1 domain of p300 without covalent addition of the small molecule to the protein of interest.[52] Due to chetomin's selectivity as a HIF1 α inhibitor, chetomin has seen recent widespread use as a molecular tool in chemical biology studies to control a cell's response to induced hypoxia.[53–60] Additionally, in the previous decade, chetomin and other epidithiodiketopiperazines have been demonstrated to inhibit histone H3K9 methyltransferases,[61] modulate mTOR/PI3K signaling,[62] inhibit proteasomal deubiquitinase Rpn11 and other JAMM proteases,[63] reactivate mutant p53 genes,[64] aid in retinal pigment epithelial cell differentiation,[65] among many other applications.

Since 2004, chetomin (**9**) has further been shown to be a viable cancer therapy *in vivo* in mouse models. Livingston and Kung's research groups at the Dana Farber Cancer Institute demonstrated Chetomin in 2 mg/kg doses had significant antitumor activities on mice implanted with both HCT116 (colorectal carcinoma) and PC3 (prostate adenocarcinoma) xenografted mice.[66] Further, these 2 mg/kg doses were tolerated by mice without significant loss of weight when injected through a central venous catheter. Similarly, the Wang research group from the Bengbu Medical College demonstrated similar results in murine models with H1299 and H460 lung cancer xenografts, as well as a "transgenic *Kras* ^{LA1} murine model that develops lung tumors spontaneously;"[67] doses in this study were significantly higher, at 50 or

100 mg/kg. In 2019, the Alani research group demonstrated a profound synergistic effect in tumor reduction of ES2 (ovarian clear cell carcinoma) xenografts when chetomin was formulated into micelles with the mTOR inhibitor everolimus.[68] Chetomin was also demonstrated to possess antitumor activity in human myeloma cell lines derived directly from patients.[3] The therapeutic potential of chetomin is, however, tempered by its known and well-studied animal toxicity.[44]

Chetomin has been thoroughly studied with a well-documented array of therapeutic biological activities both *in vitro* and *in vivo*. Due to their relatively recent discovery, other natural products in this class have been less well studied, despite their promising potential. Chaetocochins A, B and C, (**16, 17** and **19**) were first reported in 2006, isolated by the Zhang group at the Chengdu Institute of Biology from ethyl acetate extracts of *Chaetomium cochliodes*.[69] Chaetocochins A and C demonstrates inhibited cell growth in MDA-MB-231 (breast adenocarcinoma), H460 (lung carcinoma) and SF268 (brain cancer) lines; Chaetocochin A was roughly one order of magnitude less potent in these studies than chaetocochin C, which itself was one order of magnitude less active than chetomin. Chaetocochins A and C were more recently shown to be mild and somewhat potently cytotoxic, respectively, towards HL60 (leukemia), A549 (lung carcinoma), MCF7 (breast adenocarcinoma) and SW480 (colon adenocarcinoma), while also inducing cell cycle arrest at the G2/M phase in SW480 cells.[70] Chaetocochin C presumably has a stronger activity against these cell lines due to its reactive disulfides. Chaetocochin C has also been shown to be antibiotic towards Gram positive bacteria, anti-malarial activity towards *Plasmodium falciparum*, and possess activity against *Mycobacterium tuberculosis*.[71]

Chaetocochins D, E and F (**12, 13** and **20**) were reported in 2008, also by the Zhang group at the Chengdu Institute of Biology as isolated from *Chaetomium cochliodes.*[72] Interestingly, tandem mass spectrometry was employed to successfully differentiate the structurally similar chaetocochin D (**11**) from previously reported chaetoseminudin A (**11**) (*vide infra*). More recently, the structures of chaetocochins G, H, I and J (**14**, **15**, and **21**) were reported by Li's research group, also from the Chengdu Institute of Biology, as isolated from *Chaetomium globosum*.[73] While chaetocochin J has been reported to be moderately antibiotic towards hay bacillus, chaetocochins B, D, E, F, G, H and I have no known biological activity, presumably due to the lack of significant amounts of isolated material.

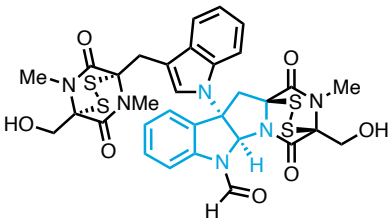
Other *Chaetomium* species have yielded natural products which fall under the scope of this review. In 2004, from *Chaetomium seminudum* was isolated chetoseminudin A (**10**), which was shown to have moderate immunosuppressive qualities.[46] Chetoseminudin A has also been isolated from *Chaetomium cochliodes*[72] and *Chaetomium globosum*,[73] the latter report further indicated that chetoseminudin A was a reasonably effective antiobiotic against the Gram-positive hay bacillus.

Dethiotetra(methylthio)chetomin (**18**) was isolated from *Chaetomium globosum* by the Kikuchi research group and reported in 1982 with antimicrobial activity against *Staphylococcus aureus* (Gram-positive) and *E. coli* (Gram-negative).[74] Further research indicated **18** as a viable antibiotic against other Gram-positive bacteria.[71] The enantiomer of this compound has also been isolated and referred to as chaetocochins G, displaying antiproliferative properties against MCF7 cells.[75]

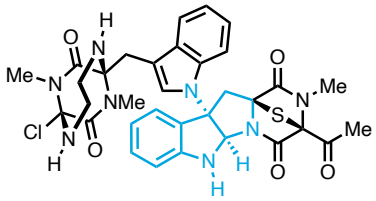
A general trend which becomes apparent when comparing the biological activity of the different members of this class of natural product is that the species containing disulfide

character are more potent biological actors than their thiomethylated counterparts. The reactivity, and thus rarity, of the polysulfide chaetocochins highlighted above can also be explained by their general photoinstability.[76]

In recent years, chetomin has been isolated from other *Chaetomium* species as the 6-formamide-analogue (Figure 4.6, **22**).[77] This product was demonstrated to possess similar bioactivity to the parent compound.



22, 6-formamide-chetomin



10, cristazine

Figure 4.6- two recently reported thiolated diketopiperazines

In 2016, Byeng Wha Son's research group released a report with the structure of a brand-new class of thiolated diketopiperazine.[8] Cristazine (Figure 4.6, **10**) bears a single sulfide and an ethane-diamine bridge. Further, cristazine is the only halogenated natural product surveyed in this review. Cristazine was demonstrated to be a powerful radical scavenger and a potent killer of HeLa cells with an IC_{50} of 500 nM.

Chetomin and its analogues present the most interesting structures and promising biological activity of the natural products surveyed in this review. Despite this potential,

none of these natural products have succumbed to a total synthesis, despite attempts from synthetic chemists.[78]

4.3- Conclusion

The privileged pyrroloindolines abound in the natural world, between terrestrial and marine environments. The scope of this chapter was limited to just a small selection of examples, those with a C3-amine (indole numbering system). The inherent diversity of these natural products imbues a range of potential therapeutic properties, most of which have yet to be discovered. Which the palpably increasing interest in this field, these products will no doubt be fully investigated in the near future.

4.4- References

(1) Proudfoot, A. The Early Toxicology of Physostigmine. *Toxicol. Rev.* **2006**, *25*, 99–138. https://doi.org/10.2165/00139709-200625020-00004.

(2) Yu, Q.; Liu, C.; Brzostowska, M.; Chrisey, L.; Brossi, A.; Greig, N. H.; Atack, J. R.; Soncrant, T. T.; Rapoport, S. I.; Radunz, H.-E. Physovenines: Efficient Synthesis of (−)- and (+)-Physovenine and Synthesis of Carbarnate Analogues of (−)-Physovenine. Anticholinesterase Activity and Analgesic Properties of Optically Active Physovenines. *Helv. Chim. Acta* **1991**, *74*, 761–766. https://doi.org/https://doi.org/10.1002/hlca.19910740409.

(3) Viziteu, E.; Grandmougin, C.; Goldschmidt, H.; Seckinger, A.; Hose, D.; Klein, B.; Moreaux, J. Chetomin, Targeting HIF-1α/P300 Complex, Exhibits Antitumour Activity in Multiple Myeloma. *Br. J. Cancer* **2016**, *114*, 519–523. https://doi.org/10.1038/bjc.2016.20.

(4) Ruiz-Sanchis, P.; Savina, S. A.; Albericio, F.; Álvarez, M. Structure, Bioactivity and Synthesis of Natural Products with Hexahydropyrrolo[2,3-b]Indole. *Chem. – A Eur. J.* **2011**, *17*, 1388–1408. https://doi.org/10.1002/chem.201001451.

(5) Gangar, M.; Kashyap, N.; Kumar, K.; Goyal, S.; Nair, V. A. Imidazolidinone Based Chiral Auxiliary Mediated Acetate Aldol Reactions of Isatin Derivatives and Stereoselective Synthesis of 3-Substituted-3-Hydroxy-2-Oxindoles. *Tetrahedron Lett.* **2015**, *56*, 7074–7081. https://doi.org/https://doi.org/10.1016/j.tetlet.2015.11.007.

(6) Waksman, S. A.; Bugie, E. Chaetomin, a New Antibiotic Substance Produced by <Em>Chaetomium Cochliodes</Em> *J. Bacteriol.* **1944**, *48*, 527 LP – 530.

(7) Li, X.-B.; Li, Y.-L.; Zhou, J.-C.; Yuan, H.-Q.; Wang, X.-N.; Lou, H.-X. A New Diketopiperazine Heterodimer from an Endophytic Fungus Aspergillus Niger. *J. Asian Nat. Prod. Res.* **2015**, *17*, 182–187. https://doi.org/10.1080/10286020.2014.959939.

(8) Yun, K.; Khong, T. T.; Leutou, A. S.; Kim, G.-D.; Hong, J.; Lee, C.-H.; Son, B. W. Cristazine, a New Cytotoxic Dioxopiperazine Alkaloid from the Mudflat-Sediment-Derived Fungus *Chaetomium Cristatum*. *Chem. Pharm. Bull.* **2016**, *64*, 59–62. https://doi.org/10.1248/cpb.c15-00525.

(9) Lathrop, S. P.; Pompeo, M.; Chang, W.-T. T.; Movassaghi, M. Convergent and Biomimetic Enantioselective Total Synthesis of (−)-Communesin F. *J. Am. Chem. Soc.* **2016**, *138*, 7763–7769. https://doi.org/10.1021/jacs.6b04072.
(10) Pompeo, M. M.; Cheah, J. H.; Movassaghi, M. Total Synthesis and Anti-Cancer Activity of All Known Communesin Alkaloids and Related Derivatives. *J. Am. Chem. Soc.* **2019**, *141*, 14411–14420. https://doi.org/10.1021/jacs.9b07397.
(11) Newhouse, T.; Lewis, C. A.; Baran, P. S. Enantiospecific Total Syntheses of Kapakahines B and F. *J. Am. Chem. Soc.* **2009**, *131*, 6360–6361. https://doi.org/10.1021/ja901573x.
(12) Newhouse, T.; Lewis, C. A.; Eastman, K. J.; Baran, P. S. Scalable Total Syntheses of N-Linked Tryptamine Dimers by Direct Indole−Aniline Coupling: Psychotrimine and Kapakahines B and F. *J. Am. Chem. Soc.* **2010**, *132*, 7119–7137. https://doi.org/10.1021/ja1009458.
(13) Espejo, V. R.; Rainier, J. D. Total Synthesis of Kapakahine E and F. *Org. Lett.* **2010**, *12*, 2154–2157. https://doi.org/10.1021/ol100672z.
(14) Matsuda, Y.; Kitajima, M.; Takayama, H. First Total Synthesis of Trimeric Indole Alkaloid, Psychotrimine. *Org. Lett.* **2008**, *10*, 125–128. https://doi.org/10.1021/ol702637r.
(15) Takahashi, N.; Ito, T.; Matsuda, Y.; Kogure, N.; Kitajima, M.; Takayama, H. Determination of Absolute Configuration of Trimeric Indole Alkaloid, Psychotrimine, by First Asymmetric Total Synthesis. *Chem. Commun.* **2010**, *46*, 2501–2503. https://doi.org/10.1039/B923918A.
(16) Hajra, S.; Bhosale, S. S.; Hazra, A. An Asymmetric Acetate-Mannich Reaction of Chiral Isatin Derived Ketimines and Its Applications. *Org. Biomol. Chem.* **2017**, *15*, 9217–9225. https://doi.org/10.1039/C7OB02407J.
(17) Wang, Y.-H.; Tian, J.-S.; Tan, P.-W.; Cao, Q.; Zhang, X.-X.; Cao, Z.-Y.; Zhou, F.; Wang, X.; Zhou, J. Regiodivergent Intramolecular Nucleophilic Addition of Ketimines for the Diverse Synthesis of Azacycles. *Angew. Chemie Int. Ed.* **2020**, *59*, 1634–1643. https://doi.org/https://doi.org/10.1002/anie.201910864.
(18) Takayama, H.; Mori, I.; Kitajima, M.; Aimi, N.; Lajis, N. H. New Type of Trimeric and Pentameric Indole Alkaloids from Psychotria Rostrata. *Org. Lett.* **2004**, *6*, 2945–2948. https://doi.org/10.1021/ol048971x.
(19) Newhouse, T.; Baran, P. S. Total Synthesis of (±)-Psychotrimine. *J. Am. Chem. Soc.* **2008**, *130*, 10886–10887. https://doi.org/10.1021/ja8042307.
(20) Foo, K.; Newhouse, T.; Mori, I.; Takayama, H.; Baran, P. S. Total Synthesis Guided Structure Elucidation of (+)-Psychotetramine. *Angew. Chemie Int. Ed.* **2011**, *50*, 2716–2719. https://doi.org/https://doi.org/10.1002/anie.201008048.
(21) Watson, E. L.; Ball, A.; Raw, S. A.; Marsden, S. P. Synthetic Studies on Psychotrimine: Palladium-Catalysed Arylation of 2-(N-Indolyl) Amides. *Synlett* **2016**, *27*, 146–150. https://doi.org/10.1055/s-0035-1560519.
(22) Araki, T.; Ozawa, T.; Yokoe, H.; Kanematsu, M.; Yoshida, M.; Shishido, K. Diastereoselective Intramolecular Carbamoylketene/Alkene [2 + 2] Cycloaddition: Enantioselective Access to Pyrrolidinoindoline Alkaloids. *Org. Lett.* **2013**, *15*, 200–203. https://doi.org/10.1021/ol303204v.
(23) Lian, X.-L.; Meng, J.; Han, Z.-Y. Ru(II)/Organo Relay Catalytic Three-Component Reaction of 3-Diazooxindoles, Amines, and Nitroalkene: Formal Synthesis of (−)-Psychotrimine. *Org. Lett.* **2016**, *18*, 4270–4273. https://doi.org/10.1021/acs.orglett.6b02019.
(24) Schallenberger, M. A.; Newhouse, T.; Baran, P. S.; Romesberg, F. E. The Psychotrimine Natural Products Have Antibacterial Activity against Gram-Positive Bacteria and Act via Membrane Disruption. *J. Antibiot. (Tokyo).* **2010**, *63*, 685–687. https://doi.org/10.1038/ja.2010.107.
(25) Zhou, H.; He, H.-P.; Wang, Y.-H.; Hao, X.-J. A New Dimeric Alkaloid from the Leaf of Psychotria Calocarpa. *Helv. Chim. Acta* **2010**, *93*, 1650–1652. https://doi.org/https://doi.org/10.1002/hlca.200900439.
(26) Liu, Y.; Wang, J.-S.; Wang, X.-B.; Kong, L.-Y. Absolute Configuration Study of a New Dimeric Indole Alkaloid from the Leaves and Twigs of Psychotria Henryi. *J. Asian Nat. Prod. Res.* **2014**, *16*, 29–33. https://doi.org/10.1080/10286020.2013.870996.
(27) Gentry, E. C.; Rono, L. J.; Hale, M. E.; Matsuura, R.; Knowles, R. R. Enantioselective Synthesis of Pyrroloindolines via Noncovalent Stabilization of Indole Radical Cations and Applications to the Synthesis of Alkaloid Natural Products. *J. Am. Chem. Soc.* **2018**, *140*, 3394–3402. https://doi.org/10.1021/jacs.7b13616.
(28) Horibe, T.; Ohmura, S.; Ishihara, K. Selenium–Iodine Cooperative Catalyst for Chlorocyclization of

Tryptamine Derivatives. *Org. Lett.* **2017**, *19*, 5525–5528. https://doi.org/10.1021/acs.orglett.7b02613.
(29) Dai, J.; Xiong, D.; Yuan, T.; Liu, J.; Chen, T.; Shao, Z. Chiral Primary Amine Catalysis for Asymmetric Mannich Reactions of Aldehydes with Ketimines: Stereoselectivity and Reactivity. *Angew. Chemie Int. Ed.* **2017**, *56*, 12697–12701. https://doi.org/https://doi.org/10.1002/anie.201706304.
(30) Gallego, S.; Lorenzo, P.; Alvarez, R.; de Lera, A. R. Total Synthesis of Naturally Occurring (+)-Psychotriasine and the Related Tetrahydro-β-Carboline, Dimeric Tryptamines with NC Connectivities. *Tetrahedron Lett.* **2017**, *58*, 210–212. https://doi.org/https://doi.org/10.1016/j.tetlet.2016.12.003.
(31) Tayu, M.; Suzuki, Y.; Higuchi, K.; Kawasaki, T. C2-Symmetric Chiral Sulfoxide-Mediated Intermolecular Interrupted Pummerer Reaction for Enantioselective Construction of C3a-Substituted Pyrroloindolines. *Synlett* **2016**, *27*, 941–945. https://doi.org/10.1055/s-0035-1560548.
(32) Liu, C.; Yi, J.-C.; Zheng, Z.-B.; Tang, Y.; Dai, L.-X.; You, S.-L. Enantioselective Synthesis of 3a-Amino-Pyrroloindolines by Copper-Catalyzed Direct Asymmetric Dearomative Amination of Tryptamines. *Angew. Chemie Int. Ed.* **2016**, *55*, 751–754. https://doi.org/10.1002/anie.201508570.
(33) Li, Q.; Xia, T.; Yao, L.; Deng, H.; Liao, X. Enantioselective and Diastereoselective Azo-Coupling/Iminium-Cyclizations: A Unified Strategy for the Total Syntheses of (−)-Psychotriasine and (+)-Pestalazine B. *Chem. Sci.* **2015**, *6*, 3599–3605. https://doi.org/10.1039/C5SC00338E.
(34) Tayu, M.; Ishizaki, T.; Higuchi, K.; Kawasaki, T. DMSO/Tf2O-Mediated Cross-Coupling of Tryptamine with Substituted Aniline to Access C3a–N1′-Linked Pyrroloindoline Alkaloids. *Org. Biomol. Chem.* **2015**, *13*, 3863–3865. https://doi.org/10.1039/C5OB00190K.
(35) Liu, Y.; Wang, J.-S.; Wang, X.-B.; Kong, L.-Y. Two Novel Dimeric Indole Alkaloids from the Leaves and Twigs of Psychotria Henryi. *Fitoterapia* **2013**, *86*, 178–182. https://doi.org/https://doi.org/10.1016/j.fitote.2013.03.013.
(36) 平本昌志; 宮田祐; 柴崎充至; 斎田裕治. P-23 不完全菌の産生するコレシストキニンBタイプ受容体アンタゴニスト、Q20547-Aに関する研究(ポスター発表の部). 天然有機化合物討論会講演要旨集 **1994**, *36*, 557–564. https://doi.org/10.24496/tennenyuki.36.0_557.
(37) Ding, G.; Jiang, L.; Guo, L.; Chen, X.; Zhang, H.; Che, Y. Pestalazines and Pestalamides, Bioactive Metabolites from the Plant Pathogenic Fungus Pestalotiopsis Theae. *J. Nat. Prod.* **2008**, *71*, 1861–1865. https://doi.org/10.1021/np800357g.
(38) Pérez-Balado, C.; de Lera, Á. R. Concise Total Synthesis and Structural Revision of (+)-Pestalazine B. *Org. Biomol. Chem.* **2010**, *8*, 5179–5186. https://doi.org/10.1039/C0OB00531B.
(39) Nelson, B. M.; Loach, R. P.; Schiesser, S.; Movassaghi, M. Concise Total Synthesis of (+)-Asperazine A and (+)-Pestalazine B. *Org. Biomol. Chem.* **2018**, *16*, 202–207. https://doi.org/10.1039/C7OB02985C.
(40) Shaum, J.; Nikolaev, A.; Steffens, H.; Gonzalez, L.; Walker, S.; Alaniz, J. R. de. A Single Electron Approach to Indoline Amination. *unpublished* **2020**.
(41) Hakamata, H.; Ueda, H.; Tokuyama, H. Construction of Indole Structure on Pyrroloindolines via AgNTf2-Mediated Amination/Cyclization Cascade: Application to Total Synthesis of (+)-Pestalazine B. *Org. Lett.* **2019**, *21*, 4205–4209. https://doi.org/10.1021/acs.orglett.9b01399.
(42) Nicolaou, K. C.; Snyder, S. A. Chasing Molecules That Were Never There: Misassigned Natural Products and the Role of Chemical Synthesis in Modern Structure Elucidation. *Angew. Chemie Int. Ed.* **2005**, *44*, 1012–1044. https://doi.org/https://doi.org/10.1002/anie.200460864.
(43) Loach, R. P.; Fenton, O. S.; Movassaghi, M. Concise Total Synthesis of (+)-Asperazine, (+)-Pestalazine A, and (+)-Iso-Pestalazine A. Structure Revision of (+)-Pestalazine A. *J. Am. Chem. Soc.* **2016**, *138*, 1057–1064. https://doi.org/10.1021/jacs.5b12392.
(44) Brewer, D.; Duncan, J. M.; Jerram, W. A.; Leach, C. K.; Safe, S.; Taylor, A.; Vining, L. C.; Archibald, R. M.; Stevenson, R. G.; Mirocha, C. J.; Christensen, C. M. Ovine Ill-Thrift in Nova Scotia. 5. The Production and Toxicology of Chetomin, a Metabolite of Chaetomium Spp. *Can. J. Microbiol.* **1972**, *18*, 1129–1137. https://doi.org/10.1139/m72-174.
(45) Safe, S.; Taylor, A. Sporidesmins. Part XIII. Ovine III-Thrift in Nova Scotia. Part III. The Characterisation of Chetomin a Toxic Metabolite of Chaetomium Cochliodes and Chaetomium Globosum. *J. Chem. Soc. Perkin Trans. 1* **1972**, No. 0, 472–479. https://doi.org/10.1039/P19720000472.
(46) Fujimoto, H.; Sumino, M.; Okuyama, E.; Ishibashi, M. Immunomodulatory Constituents from an Ascomycete, Chaetomium Seminudum. *J. Nat. Prod.* **2004**, *67*, 98–102. https://doi.org/10.1021/np0302201.

(47) Wang, X. W.; Houbraken, J.; Groenewald, J. Z.; Meijer, M.; Andersen, B.; Nielsen, K. F.; Crous, P. W.; Samson, R. A. Diversity and Taxonomy of Chaetomium and Chaetomium-like Fungi from Indoor Environments. *Stud. Mycol.* **2016**, *84*, 145–224. https://doi.org/https://doi.org/10.1016/j.simyco.2016.11.005.

(48) McInnes, A. G.; Taylor, A.; Walter, J. A. The Structure of Chetomin. *J. Am. Chem. Soc.* **1976**, *98*, 6741. https://doi.org/10.1021/ja00437a074.

(49) Hai, Y.; Jenner, M.; Tang, Y. Complete Stereoinversion of L-Tryptophan by a Fungal Single-Module Nonribosomal Peptide Synthetase. *J. Am. Chem. Soc.* **2019**, *141*, 16222–16226. https://doi.org/10.1021/jacs.9b08898.

(50) Jen, W.-C.; Jones, G. A. Effects of Chetomin on Growth and Acidic Fermentation Products of Rumen Bacteria. *Can. J. Microbiol.* **1983**, *29*, 1399–1404. https://doi.org/10.1139/m83-215.

(51) Block, K. M.; Wang, H.; Szabó, L. Z.; Polaske, N. W.; Henchey, L. K.; Dubey, R.; Kushal, S.; László, C. F.; Makhoul, J.; Song, Z.; Meuillet, E. J.; Olenyuk, B. Z. Direct Inhibition of Hypoxia-Inducible Transcription Factor Complex with Designed Dimeric Epidithiodiketopiperazine. *J. Am. Chem. Soc.* **2009**, *131*, 18078–18088. https://doi.org/10.1021/ja807601b.

(52) Cook, K. M.; Hilton, S. T.; Mecinović, J.; Motherwell, W. B.; Figg, W. D.; Schofield, C. J. Epidithiodiketopiperazines Block the Interaction between Hypoxia-Inducible Factor-1α (HIF-1α) and P300 by a Zinc Ejection Mechanism. *J. Biol. Chem.* **2009**, *284*, 26831–26838. https://doi.org/10.1074/jbc.M109.009498 .

(53) Lourenssen, S. R.; Blennerhassett, M. G. M2 Macrophages and Phenotypic Modulation of Intestinal Smooth Muscle Cells Characterize Inflammatory Stricture Formation in Rats. *Am. J. Pathol.* **2020**, *190*, 1843–1858. https://doi.org/https://doi.org/10.1016/j.ajpath.2020.05.015.

(54) Kovacsics, D.; Brózik, A.; Tihanyi, B.; Matula, Z.; Borsy, A.; Mészáros, N.; Szabó, E.; Németh, E.; Fóthi, Á.; Zámbó, B.; Szüts, D.; Várady, G.; Orbán, T. I.; Apáti, Á.; Sarkadi, B. Precision-Engineered Reporter Cell Lines Reveal ABCG2 Regulation in Live Lung Cancer Cells. *Biochem. Pharmacol.* **2020**, *175*, 113865. https://doi.org/https://doi.org/10.1016/j.bcp.2020.113865.

(55) Brennan, L.; Disatham, J.; Kantorow, M. Hypoxia Regulates the Degradation of Non-Nuclear Organelles during Lens Differentiation through Activation of HIF1a. *Exp. Eye Res.* **2020**, *198*, 108129. https://doi.org/https://doi.org/10.1016/j.exer.2020.108129.

(56) Enikő, B.; Andrea, T.; Gábor, M.; György, T.; György, P.; Viktória, J. Hypoxia Triggers Osteochondrogenic Differentiation of Vascular Smooth Muscle Cells in an HIF-1 (Hypoxia-Inducible Factor 1)–Dependent and Reactive Oxygen Species–Dependent Manner. *Arterioscler. Thromb. Vasc. Biol.* **2019**, *39*, 1088–1099. https://doi.org/10.1161/ATVBAHA.119.312509.

(57) Dongjian, H.; Annet, L.; Abir, Y.; Cláudia, C.; David, K. J.; Arman, G.; Ling, X.; J., M. D.; Peter, van der M.; Margarida, S.; M., A. P.; J., D. I. Metabolic Maturation of Human Pluripotent Stem Cell-Derived Cardiomyocytes by Inhibition of HIF1α and LDHA. *Circ. Res.* **2018**, *123*, 1066–1079. https://doi.org/10.1161/CIRCRESAHA.118.313249.

(58) Fernandez, E. V; Reece, K. M.; Ley, A. M.; Troutman, S. M.; Sissung, T. M.; Price, D. K.; Chau, C. H.; Figg, W. D. Dual Targeting of the Androgen Receptor and Hypoxia-Inducible Factor 1<Em>A</Em> Pathways Synergistically Inhibits Castration-Resistant Prostate Cancer Cells. *Mol. Pharmacol.* **2015**, *87*, 1006 LP – 1012. https://doi.org/10.1124/mol.114.097477.

(59) Watari, A.; Hashegawa, M.; Muangman, T.; Yagi, K.; Kondoh, M. Use of Cell-Based Screening to Identify Small-Molecule Compounds That Modulate Claudin-4 Expression. *Biotechnol. Lett.* **2015**, *37*, 1177–1185. https://doi.org/10.1007/s10529-015-1791-7.

(60) Ke, H.-L.; Li, W.-M.; Lin, H.-H.; Hsu, W.-C.; Hsu, Y.-L.; Chang, L.-L.; Huang, C.-N.; Li, C.-C.; Chang, H.-P.; Yeh, H.-C.; Li, C.-F.; Wu, W.-J. Hypoxia-Regulated MicroRNA-210 Overexpression Is Associated with Tumor Development and Progression in Upper Tract Urothelial Carcinoma. *Int. J. Med. Sci.* **2017**, *14*, 578–584. https://doi.org/10.7150/ijms.15699.

(61) Takahashi, M.; Takemoto, Y.; Shimazu, T.; Kawasaki, H.; Tachibana, M.; Shinkai, Y.; Takagi, M.; Shin-ya, K.; Igarashi, Y.; Ito, A.; Yoshida, M. Inhibition of Histone H3K9 Methyltransferases by Gliotoxin and Related Epipolythiodioxopiperazines. *J. Antibiot. (Tokyo).* **2012**, *65*, 263–265. https://doi.org/10.1038/ja.2012.6.

(62) Dewangan, J.; Srivastava, S.; Mishra, S.; Pandey, P. K.; Divakar, A.; Rath, S. K. Chetomin Induces Apoptosis in Human Triple-Negative Breast Cancer Cells by Promoting Calcium Overload and Mitochondrial Dysfunction. *Biochem. Biophys. Res. Commun.* **2018**, *495*, 1915–1921. https://doi.org/https://doi.org/10.1016/j.bbrc.2017.11.199.

(63) Li, J.; Zhang, Y.; Da Silva Sil Dos Santos, B.; Wang, F.; Ma, Y.; Perez, C.; Yang, Y.; Peng, J.; Cohen, S. M.; Chou, T.-F.; Hilton, S. T.; Deshaies, R. J. Epidithiodiketopiperazines Inhibit Protein Degradation by Targeting Proteasome Deubiquitinase Rpn11. *Cell Chem. Biol.* **2018**, *25*, 1350-1358.e9. https://doi.org/https://doi.org/10.1016/j.chembiol.2018.07.012.

(64) Hiraki, M.; Hwang, S.-Y.; Cao, S.; Ramadhar, T. R.; Byun, S.; Yoon, K. W.; Lee, J. H.; Chu, K.; Gurkar, A. U.; Kolev, V.; Zhang, J.; Namba, T.; Murphy, M. E.; Newman, D. J.; Mandinova, A.; Clardy, J.; Lee, S. W. Small-Molecule Reactivation of Mutant P53 to Wild-Type-like P53 through the P53-Hsp40 Regulatory Axis. *Chem. Biol.* **2015**, *22*, 1206–1216. https://doi.org/https://doi.org/10.1016/j.chembiol.2015.07.016.

(65) Maruotti, J.; Sripathi, S. R.; Bharti, K.; Fuller, J.; Wahlin, K. J.; Ranganathan, V.; Sluch, V. M.; Berlinicke, C. A.; Davis, J.; Kim, C.; Zhao, L.; Wan, J.; Qian, J.; Corneo, B.; Temple, S.; Dubey, R.; Olenyuk, B. Z.; Bhutto, I.; Lutty, G. A.; Zack, D. J. Small-Molecule–Directed, Efficient Generation of Retinal Pigment Epithelium from Human Pluripotent Stem Cells. *Proc. Natl. Acad. Sci.* **2015**, *112*, 10950 LP – 10955. https://doi.org/10.1073/pnas.1422818112.

(66) Kung, A. L.; Zabludoff, S. D.; France, D. S.; Freedman, S. J.; Tanner, E. A.; Vieira, A.; Cornell-Kennon, S.; Lee, J.; Wang, B.; Wang, J.; Memmert, K.; Naegeli, H.-U.; Petersen, F.; Eck, M. J.; Bair, K. W.; Wood, A. W.; Livingston, D. M. Small Molecule Blockade of Transcriptional Coactivation of the Hypoxia-Inducible Factor Pathway. *Cancer Cell* **2004**, *6*, 33–43. https://doi.org/https://doi.org/10.1016/j.ccr.2004.06.009.

(67) Min, S.; Wang, X.; Du, Q.; Gong, H.; Yang, Y.; Wang, T.; Wu, N.; Liu, X.; Li, W.; Zhao, C.; Shen, Y.; Chen, Y.; Wang, X. Chetomin, a Hsp90/HIF1α Pathway Inhibitor, Effectively Targets Lung Cancer Stem Cells and Non-Stem Cells. *Cancer Biol. Ther.* **2020**, *21*, 698–708. https://doi.org/10.1080/15384047.2020.1763147.

(68) Doddapaneni, B. S.; AL-Fatease, A. M.; Rao, D. A.; Alani, A. W. G. Dual-Drug Loaded Micelle for Combinatorial Therapy Targeting HIF and MTOR Signaling Pathways for Ovarian Cancer Treatment. *J. Control. Release* **2019**, *307*, 272–281. https://doi.org/https://doi.org/10.1016/j.jconrel.2019.06.036.

(69) Li, G.-Y.; Li, B.-G.; Yang, T.; Yan, J.-F.; Liu, G.-Y.; Zhang, G.-L. Chaetocochins A−C, Epipolythiodioxopiperazines from Chaetomium Cochliodes. *J. Nat. Prod.* **2006**, *69*, 1374–1376. https://doi.org/10.1021/np0602970.

(70) Wang, F.; Jiang, J.; Hu, S.; Ma, H.; Zhu, H.; Tong, Q.; Cheng, L.; Hao, X.; Zhang, G.; Zhang, Y. Secondary Metabolites from Endophytic Fungus Chaetomium Sp. Induce Colon Cancer Cell Apoptotic Death. *Fitoterapia* **2017**, *121*, 86–93. https://doi.org/https://doi.org/10.1016/j.fitote.2017.06.021.

(71) Tantapakul, C.; Promgool, T.; Kanokmedhakul, K.; Soytong, K.; Song, J.; Hadsadee, S.; Jungsuttiwong, S.; Kanokmedhakul, S. Bioactive Xanthoquinodins and Epipolythiodioxopiperazines from Chaetomium Globosum 7s-1, an Endophytic Fungus Isolated from Rhapis Cochinchinensis (Lour.) Mart. *Nat. Prod. Res.* **2020**, *34*, 494–502. https://doi.org/10.1080/14786419.2018.1489392.

(72) Wu, Z.-J.; Li, G.-Y.; Fang, D.-M.; Qi, H.-Y.; Ren, W.-J.; Zhang, G.-L. Analysis of Epipolythiodioxopiperazines in Fungus Chaetomium Cochliodes Using HPLC-ESI-MS/MS/MS. *Anal. Chem.* **2008**, *80*, 217–226. https://doi.org/10.1021/ac071447u.

(73) Xu, G.-B.; He, G.; Bai, H.-H.; Yang, T.; Zhang, G.-L.; Wu, L.-W.; Li, G.-Y. Indole Alkaloids from Chaetomium Globosum. *J. Nat. Prod.* **2015**, *78*, 1479–1485. https://doi.org/10.1021/np5007235.

(74) Kikuchi, T.; Kadota, S.; Nakamura, K.; Nishi, A.; Taga, T.; Kaji, T.; Osaki, K.; Tubaki, K. DETHIO-TETRA (METHYLTHIO) CHETOMIN, A NEW ANTIMICROBIAL METABOLITE OF CHAETOMIUM GLOBOSUM KINZE EX FR. STRUCTURE AND PARTIAL SYNTHESIS FROM CHETOMIN. *Chem. Pharm. Bull. (Tokyo).* **1982**, *30*, 3846–3848. https://doi.org/10.1248/cpb.30.3846.

(75) Wang, F.; Tong, Q.; Ma, H.; Xu, H.; Hu, S.; Ma, W.; Xue, Y.; Liu, J.; Wang, J.; Song, H.; Zhang, J.; Zhang, G.; Zhang, Y. Indole Diketopiperazines from Endophytic Chaetomium Sp 88194 Induce Breast Cancer Cell Apoptotic Death. *Sci. Rep.* **2015**, *5*, 9294. https://doi.org/10.1038/srep09294.

(76) Wang, M.-H.; Hu, Y.-C.; Sun, B.-D.; Yu, M.; Niu, S.-B.; Guo, Z.; Zhang, X.-Y.; Zhang, T.; Ding, G.; Zou, Z.-M. Highly Photosensitive Poly-Sulfur-Bridged Chetomin Analogues from Chaetomium Cochliodes. *Org. Lett.* **2018**, *20*, 1806–1809. https://doi.org/10.1021/acs.orglett.8b00304.

(77) Yu, F.-X.; Chen, Y.; Yang, Y.-H.; Li, G.-H.; Zhao, P.-J. A New Epipolythiodioxopiperazine with Antibacterial and Cytotoxic Activities from the Endophytic Fungus Chaetomium Sp. M336. *Nat. Prod. Res.* **2018**, *32*, 689–694. https://doi.org/10.1080/14786419.2017.1338285.

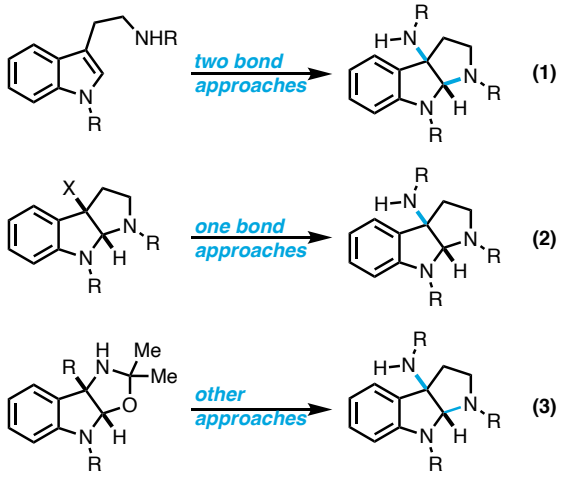
(78) Welch, T. R.; Williams, R. M. Studies on the Biosynthesis of Chetomin: Enantiospecific Synthesis of a Putative, Late-Stage Biosynthetic Intermediate. *Tetrahedron* **2013**, *69*, 770–773.

https://doi.org/https://doi.org/10.1016/j.tet.2012.10.075.

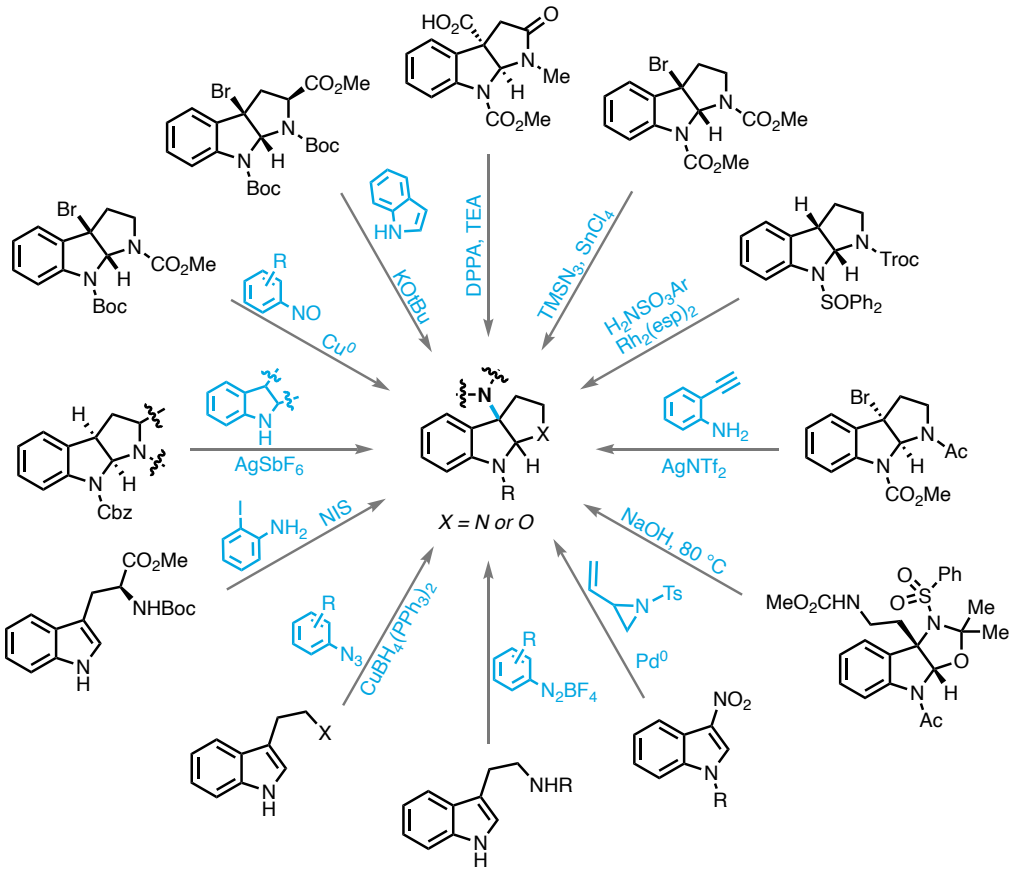
5- Aminated Pyrroloindoline Natural Products

Chapter four in this thesis summed up all of the C3-aminated pyrroloindoline natural products that have yet to be identified, as well as their biological activity. Their synthesis, however, is a whole other story however, as the construction of their key C3-N1' disconnect is anything but trivial. In this chapter, I will review every published method to install this key bond.

These 54 published methods tend to fall into one of two strategies, those which start from tryptamines, tryptophans or tryptophols and install two C–N bonds (eq 1), and those which install just one C–N bond onto an already halogenated pyrroloindoline precursor (eq 2). As of late, a number of published methods fall outside of these two broad categories (eq 3).



5.1- Synthesis: Tryptamine Cyclizations (Two Bond Approaches)



Scheme 5.1- A selection of representative methods surveyed in the synthesis section of this chapter.

5.1a- Azidization

The first reported pyrroloindole C3-N functionalization was published by Ikeda and coworkers in 1976.[1] Tryptamines (**1**) and tryptophols were found to cyclize to their corresponding 3-azidoindolines (**2**) in 43% and 30% respectively (Scheme 5.1A). 2-Methyl tryptophol gave a higher yield of 84% (Figure 5.1B). A proposed mechanism would be postulated in a 1979 follow up paper.[2] Based on their mechanistic studies, the authors propose a 3-iodoindoleninium (**4**) intermediate which undergoes cyclization to afford

intermediate **5**; attack from the azide anion affords the furoindoline **6a.** While one could postulate other pathways based on the results of the author's mechanistic studies (as later studies would), this publication laid out the foundation for almost every other difunctionalization approach surveyed in this work.

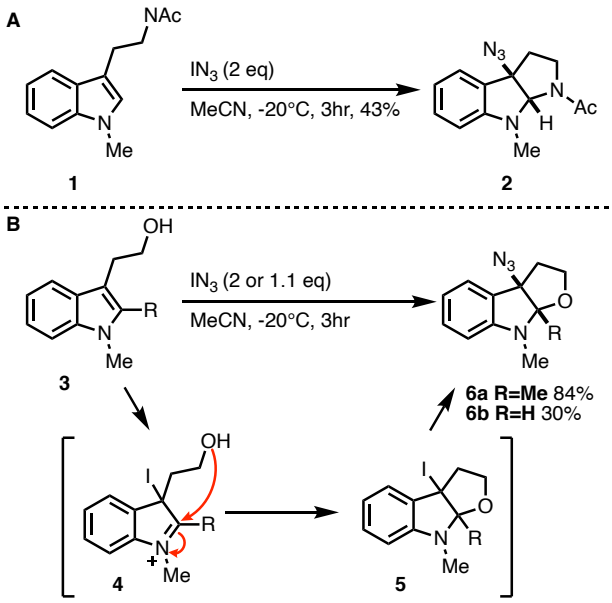


Figure 5.1- (A) The original example of tryptamine cyclization with azidization and (B) the corresponding tryptophol azidization. Below is the mechanism, as proposed by Ikeda and coworkers.

Since the original 1979 report by Ikeda and co-workers, three azidization methods have been published,[3–5] and although the proposed mechanism they describe contradicts the original work, they all build upon this pioneering contribution. The authors of these works all independently propose that C3-amination occurs via an electrophilic azide radical which is subsequently attacked by the indole **7**, resulting in a 2-indolyl species (**8**). Single electron oxidation generates the cationic intermediate **9** and **10**, analogous to **4** proposed in the previous work, which upon cyclization affords the product **11**. While all three "modern" methods are proposed to follow the same overall mechanism, they differ in their generation

of the azide radical and the oxidizing species which effects the single electron transfer. A notable example of these approaches is Wang and co-workers 2015 method (Figure 5.2). In this copper catalyzed pathway, PIDA (**12**) and Cu^{II} cooperatively facilitate the oxidation of sodium azide, furnishing an azide radical and Cu^{III}. After C3 addition of the azide radical, Cu^{III} oxidizes the indolyl intermediate to the cation (**9** and **10**), facilitating the cyclization to afford **11**.

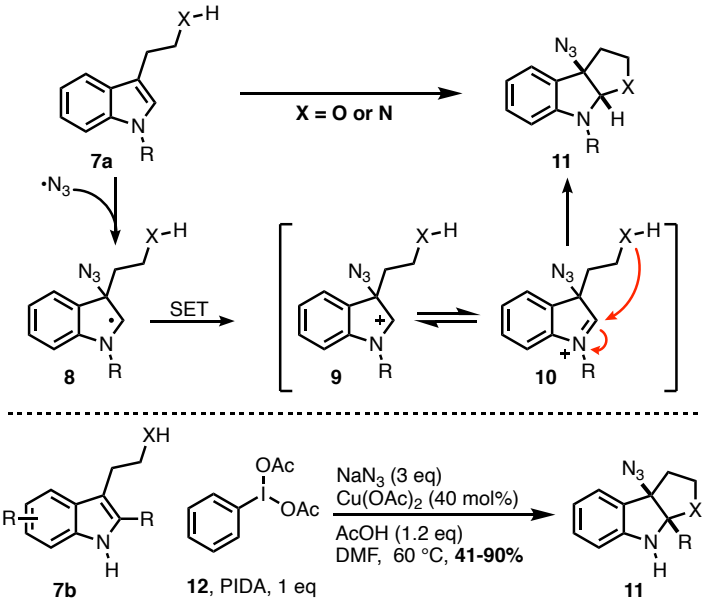


Figure 5.2- A contemporary mechanistic hypothesis with conditions, as proposed by Wang and coworkers.

5.1b- Electrophile integrating oxidative amination/cyclizations

Ikeda's electrophilic functionalizations of tryptamine and tryptophol were ground breaking in their ability to install a previously inaccessible bond. This azidization strategy, however, has enjoyed limited applications towards complex molecule synthesis; subsequent

to azidization, one must reduce the azide to the corresponding amine and then cross-couple this with a functionalized arene in order to gain access to a natural product scaffold.

To avoid these many conversions, Newhouse and Baran introduced a new method for the direct installation of aniline functionality onto minimally protected tryptamines and tryptophans (Figure 5.3).[6] As the authors discuss, the motivation for this method was to fill the previously mentioned gap in the literature of strategies that allow for the rapid syntheses of pyrroloindoline natural products containing this difficult C3–N bond.

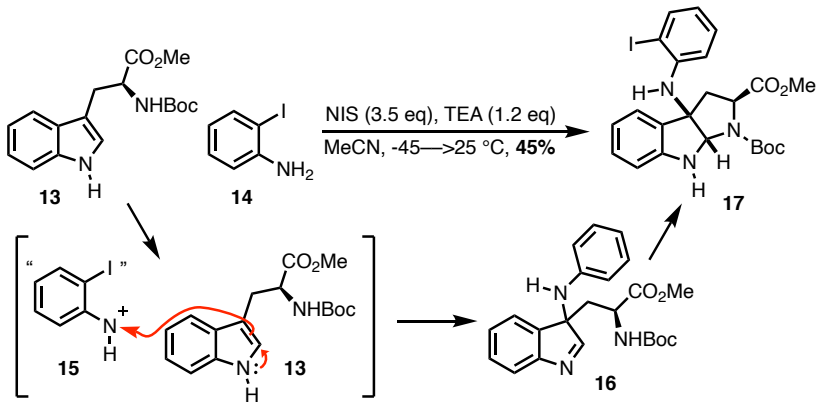
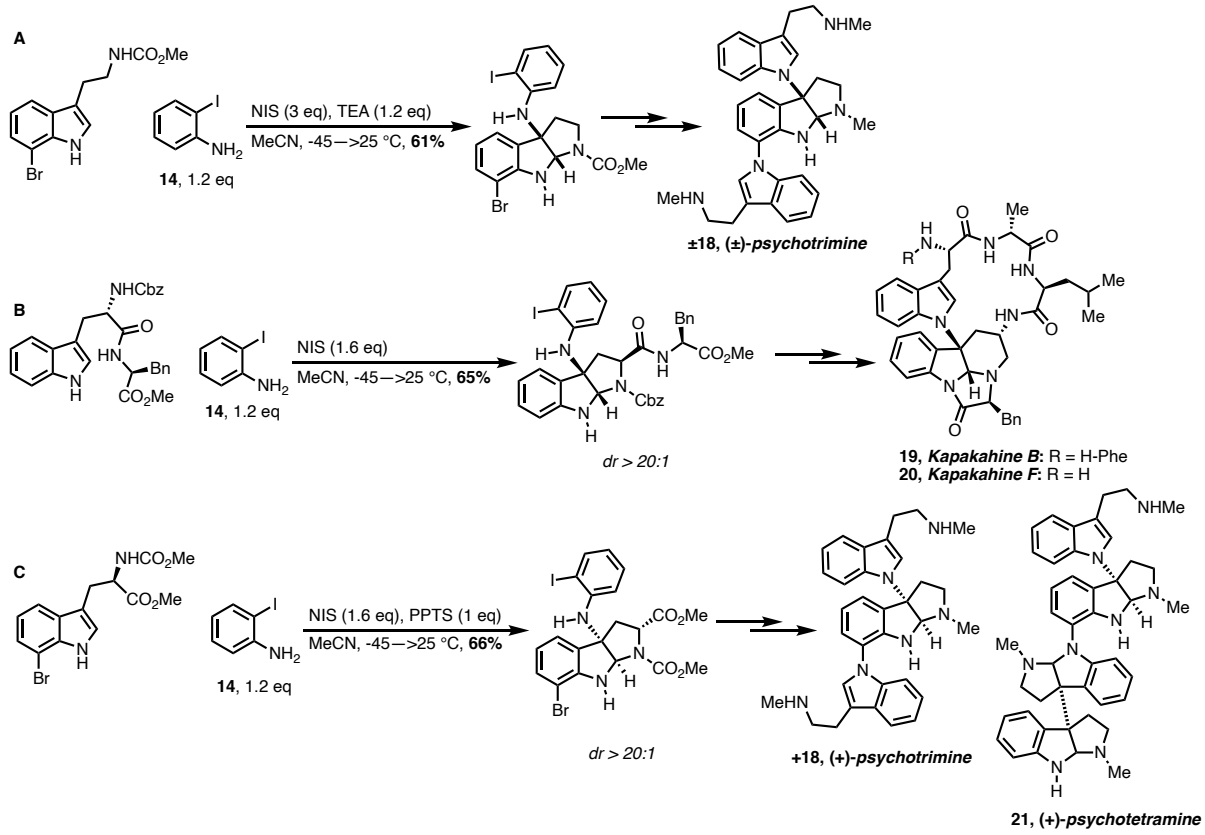


Figure 5.3- Newhouse and Baran's electrophilic functionalization with their mechanistic hypothesis.

The authors envisioned the reaction of the nucleophilic tryptamine with an "indole cation equivalent." While a direct union of the tryptamine and indole was unsuccessful, the authors were able to ligate tryptophans (**13**) with *o*-iodoaniline (**14**) following its presumed oxidation with *N*-iodosuccinimide. Oxidation of the aniline nitrogen facilitates an electrophile-induced cyclization similar to earlier reports by Wiktop in terms of electrophile addition to the C3 position.[7] Further, while the authors did not meet their original goal of a direct indole addition, they demonstrate that the newly installed *o*-iodoaniline **17** can be easily transformed into a functionalized indole via a high yielding Larock annulation,

providing the most direct synthetic approach for these pyrroloindoline natural products to date. Moreover, this method was also demonstrated on gram scale and applied to the total synthesis of (±)-psychotrimine (**±18**, scheme 5.4A) and Kapakahines B and F (**19** and **20**, Scheme 5.4B).[8] Of note, the synthesis of psychotetramine (**21**, Scheme 5.4C) occurred three years after the first disclosure of this method, and was reported using one equivalent of the mild acid PPTS in place of the mild base triethylamine, which had been employed in the 2008 method; the use of PPTS bears similarity to many other dearomative and oxidative tryptamine cyclizations. Moreover, the authors used the inherent *exo* selectivity of their cyclizations and a chiral tryptophan scaffold to render this reaction asymmetric, providing access to (+)-psychotetramine.[9] The absolute diastereoselectivity is governed by the stereochemistry of the tryptophan employed (compare Scheme 5.4B with 5.4C). The authors also disclosed an expansive analysis of the reaction's development which revealed the installed aniline must have electron withdrawing groups in the *o*-position (*p*-nitroaniline was also tolerated).[10] Further, mechanistic studies indicated the active electrophile was most likely an aryl nitrenium, not the halogenated aniline as was initially postulated in 2008.



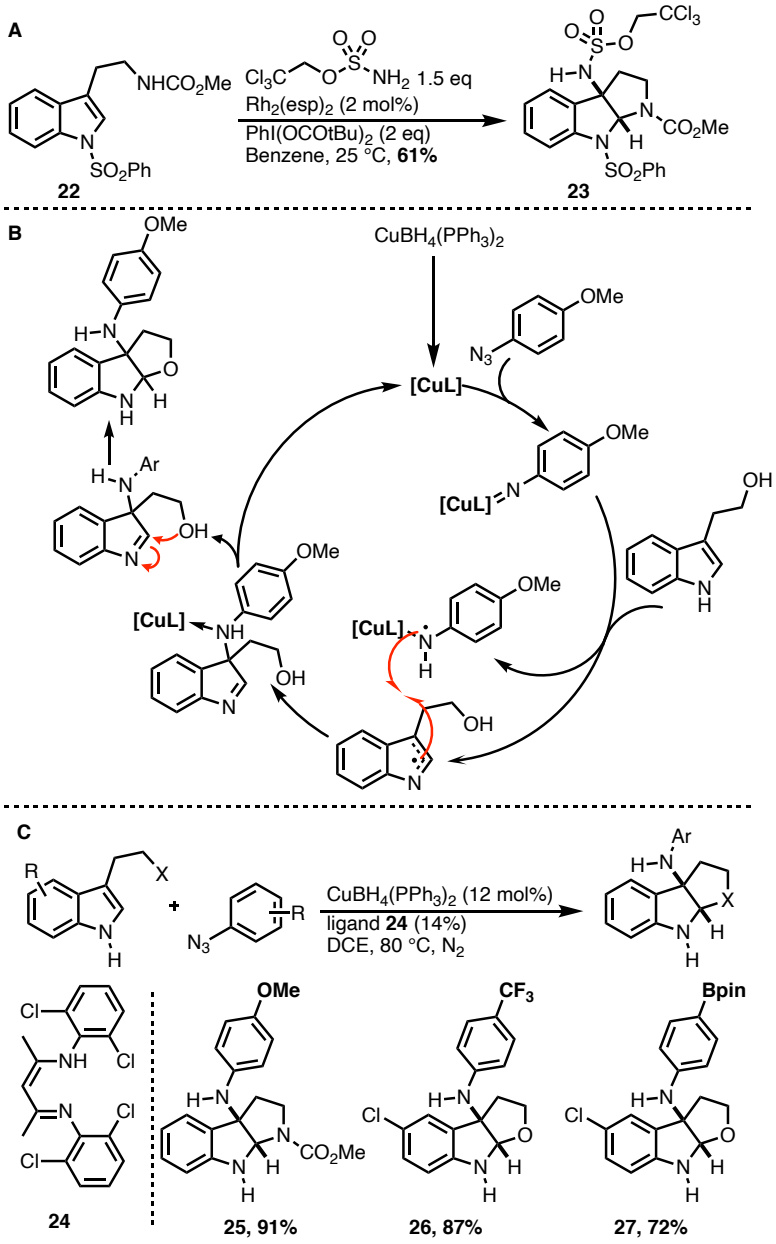
Scheme 5.4- (A) Indole aminating conditions allowed for a concise synthesis of (±)-psychotrimine and (B) Kapakahines B and F. (C) An asymmetric approach allowed for syntheses of both (+)-psychotrimine and (+)-psychotetramine.

In subsequent years Ji and Wang[11] and Yuan and Liu[12] independently reported tryptamine cyclizations with *N*-arylation at the C3 position of the newly formed pyrroloindoline. Although no mechanistic speculation appears in these papers, one could postulate they proceed through a similar pathway as Baran's strategy.

5.1c- Methods with intermediate nitrenes

Although Baran and Newhouse's method presumably involves a nitrene intermediate, this was not the goal of the method at the outset. Beaumont and Dauban and co-workers targeting this specifically and reported a formal nitrene mediated tryptamine cyclization using rhodium catalyzed nitrene-forming conditions similar to those developed by Du Bois and co-workers (scheme 5.5A).[13] Previously, acyl and sulfonyl nitrenes have been demonstrated to form C3-indole spirocycles,[14–16] but this was the first report of cyclization with olefin difunctionalization. In this work, the authors present a range of indole C3-sulfamoylations; one example is given with concomitant tryptamine cyclization (**23**).

Zhang, Deng and co-workers revisited tryptamine cyclization via nitrene intermediates with their 2019 study using a copper catalyzed route.[17] The authors employed bidentate copper ligand complexes, known to efficiently catalyze a wide variety of nitrene transfers, in order to generate a copper-nitrene complex from aryl azides. The optimal β-diketiminate ligand the authors employ requires a low yielding synthesis, however.[18,19] After hydrogen atom transfer, the two intermediate radical species combine, facilitating cyclization (Scheme 5.5B). In addition to an elegant catalytic cycle, this method also offers excellent yields on many substrates (selected substrates are in Scheme 5.5C). A range of electron donating and withdrawing functionality is well tolerated as demonstrated in the selected substrate scope (**25**-**27**).

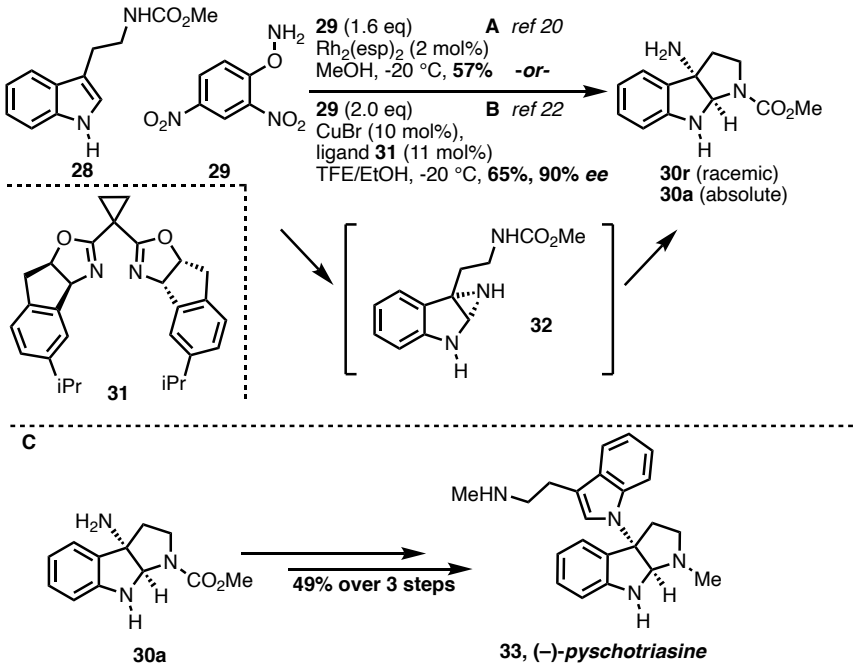


Scheme 5.5- (A) Daubin and coworkers sulfamation conditions. (B) Zhang, Deng and coworker's mechanistic hypothesis and (C) their conditions and selected examples of substrates.

5.1d- Transition Metal Catalyzed Direct-Aminations

Among the most difficult transformations is the installation of a primary amine onto the pyrroloindoline C3 position and Lai, Zhu, Xie and coworkers tackled this problem with a rhenium catalyzed approach (Scheme 5.6A).[20] While methods exist for this amine's synthesis from brominated precursors (*vide infra*), this group sought to find the first direct route from acyclic tryptamines to maximize step-efficiency. Using $Rh_2(esp)_2$ and hydroxylamine **29** as an amination reagent, the authors report a moderate substrate scope of 3-amino pyrroloindolines (such as **30r**) and furoindolines in yields between 23 and 57%. Citing previous work from the Kurti group, the authors postulate this reaction operates through an aziridine intermediate, which in turn is formed through a nitrene mediated ring closure.[21] The authors further report a lack of diastereoselectivity on reactions bearing a chiral precursor.

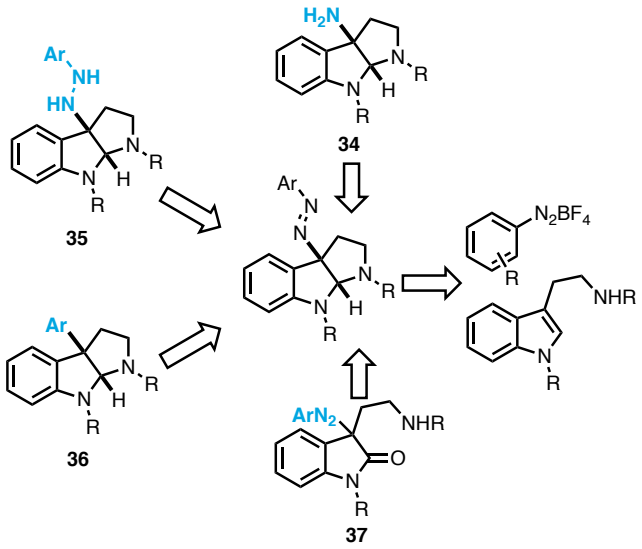
The following year, Tang, Yu and coworkers greatly improved on this methodology (Scheme 5.6B).[22] By employing the same hydroxylamine, catalytic Copper (II) Bromide and chiral BOX ligand **31**, the authors were able to install the same amine asymmetrically *via* intermediate **32**. The copper catalyzed approach, while requiring fivefold higher catalyst loadings, forms the product in appreciably higher yields than the rhenium-based method. A large substrate scope was presented, demonstrating good reactivity on substrates bearing withdrawing and donating functionality on the indole ring, as well as a range of protecting groups on the tryptamine's N_b. To showcase the abilities of this method, the authors completed a total synthesis of (–)-psychotriasine (**33**) in three steps from **30a**.



Scheme 5.6- (A) Lai, Zhu, and Xie's and (B) Tang and Yu's direct amination conditions. (c) Tang and Yu used this amine in an asymmetric total synthesis of (–)-psychotriasine.

5.1e- Azocoupling Cyclizations

Indole functionalization by electrophilic azocoupling has been known for decades, and has been used for direct C3 addition, or C2 *via* rearrangement.[23] Beginning in 2014, research groups have been adapting azo-coupling strategies to tryptamines as route toward pyrroloindoline syntheses. These approaches closely mimic the high yielding electrophilic cyclizations that have been gainfully employed in the past. The drawback, however, is that the product must be further functionalized before it can become biologically useful; azo-coupled tryptamines have been produced as intermediates for aminated or arylated products, as seen in scheme 5.7. The upshot is that these approaches tend to be relatively high yielding while requiring little in the way of additives or harsh conditions.

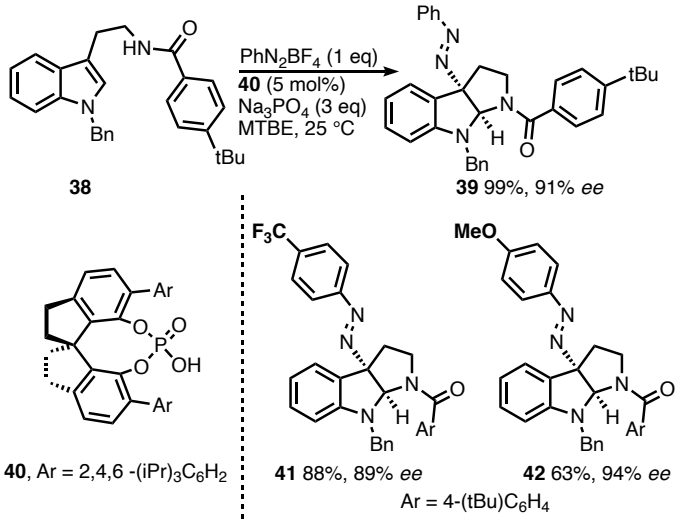


Scheme 5.7: Functional opportunities from 3-diazopyrroloindolines.

Nelson, Toste and coworkers were the first to open up this field.[24] Building from previous work from their lab, this approach involved chiral anion phase transfer (CAPT) to affect an asymmetric cyclization.[25–28] Granted their previous work with CAPT catalysis on benzamide precursors, the authors began exploring reaction conditions with acyclic benzoyl-protected tryptamines and found good results with phenyldiazonium tetrafluoroborate and trisodium phosphate. SPINOL-derived phosphoric acids afforded the highest levels of enantiomeric excess.[29] After optimization, the desired azo-coupled product was afforded in high yield and enantioselectivity (Scheme 5.8). The employment of nonpolar solvents maximized the phase-transfer component of the reaction; enantio-selectivity was eroded in media that fully dissolved the phenyldiazonium salt.

This reaction afforded pyrroloindolines in high yields and enantiomeric excess. Electron deficient (**41**) and electron rich (**42**) aryldiazonium salts were well tolerated, as well

as difunctionalized substrates. The employed-tryptamine could also be functionalized, as decorating the indole with withdrawing and donating functionality had no significant effect on the yield or enantioselectivity. As the authors state in the manuscript, "protection of the exocyclic tryptamine-N atom as a carbamate or the endocyclic indole-N atom with an allyl group resulted in diminished, but synthetically useful enantioselectivities." The ultimate goal for this azo-coupling is not to yield C–N bond, however. The subjugation of substrate **39** to UV light affords C3-aryl substrate (**36**) in 42% but with retention of stereochemistry.



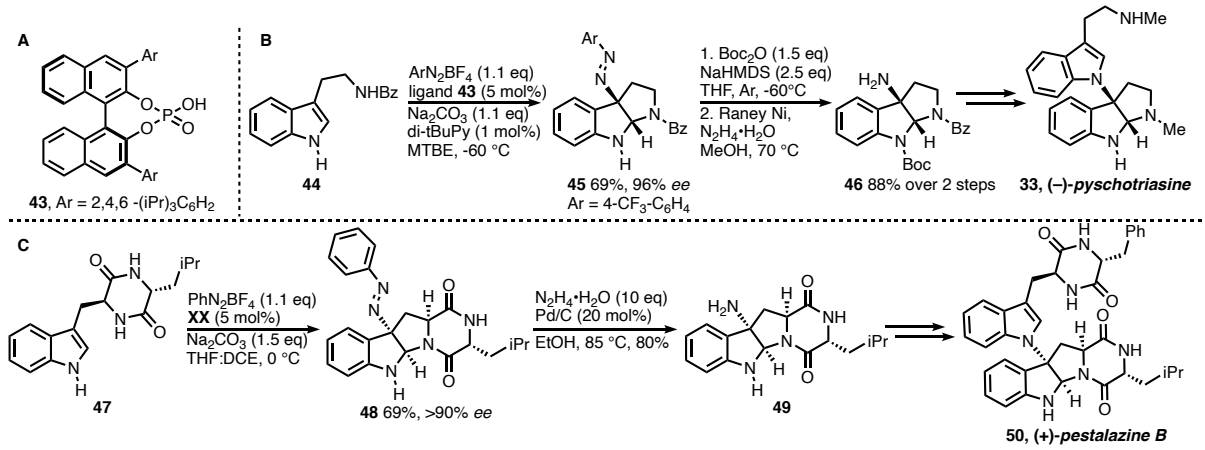
Scheme 5.8-Nelson and Toste's azocoupling conditions, and representative examples from their substrate scope.

Later in 2014 year, Stephens and Larinov released their azo-coupling conditions from tryptamine precursors.[30] The goal of this work was not to affect an asymmetric reaction, which allowed the authors more latitude in their substrate scope; the optimized conditions used acetonitrile, which fully solubilized the aryldiazonium salts; the substrates used protecting groups with a range of sterics, always in good yield. The authors note that

arenediazonium salts bearing withdrawing functionality proceeded in a cleaner fashion than their less electrophilic counterparts. This point was further demonstrated with a Hammet Plot which afforded a ρ value of 0.59. The small ρ value indicates that diazonium addition may be reversible and that deprotonation of the amide could be the rate limiting step, as observed in similar electrophilic cyclizations.[31]

To expand the utility of these azo-coupled pyrroloindolines, the authors demonstrate a high yielding hydrazine-based reduction of a range of substrates to compounds like **35** as well as a photo-induced nitrogen extrusion to **36.** Notably, this arylation yield is identical to that of the Toste group's work.

The tryptamine azo-coupling's utility in total synthesis was demonstrated in Deng and Liao in 2015, by reducing the azo-coupled products to amines like **34**.[32] The azo-coupling conditions employed in this work are very similar to those optimized by the Toste group; the best enantioselectivities were observed with BINOL derived phosphoric acid **43** (Scheme 5.9). This reaction allowed for a unified strategy for the synthesis of psychotriasine (**33**, Scheme 5.9B) and pestalazine B (**50**, Scheme 5.9C). Tryptamine products **44** and **47** reacted with arenediazonium salts to give azocoupled products **45** and **48**. Reduction afforded the corresponding amines (**46**, **49**). Sequential Buchwald-Hartiwg couplings and Larock annulations, and finally removal of protecting groups, afforded the natural products. Trypamine azo-couplings continue to appear in the literature. In 2019, Haijun Chen and coworkers published a method for the direct synthesis of azo-substituted oxindoles like **37**.[33] Mechanistic studies indicated the azo-coupled intermediate was formed in quantitative yields, prior to nickel mediated oxidation.



Scheme 5.9- (A) Deng and Liao employed phosphoric acid **43** in their total syntheses of (B) (–)-psychotriasine and (C)(+)-Pestalazine B

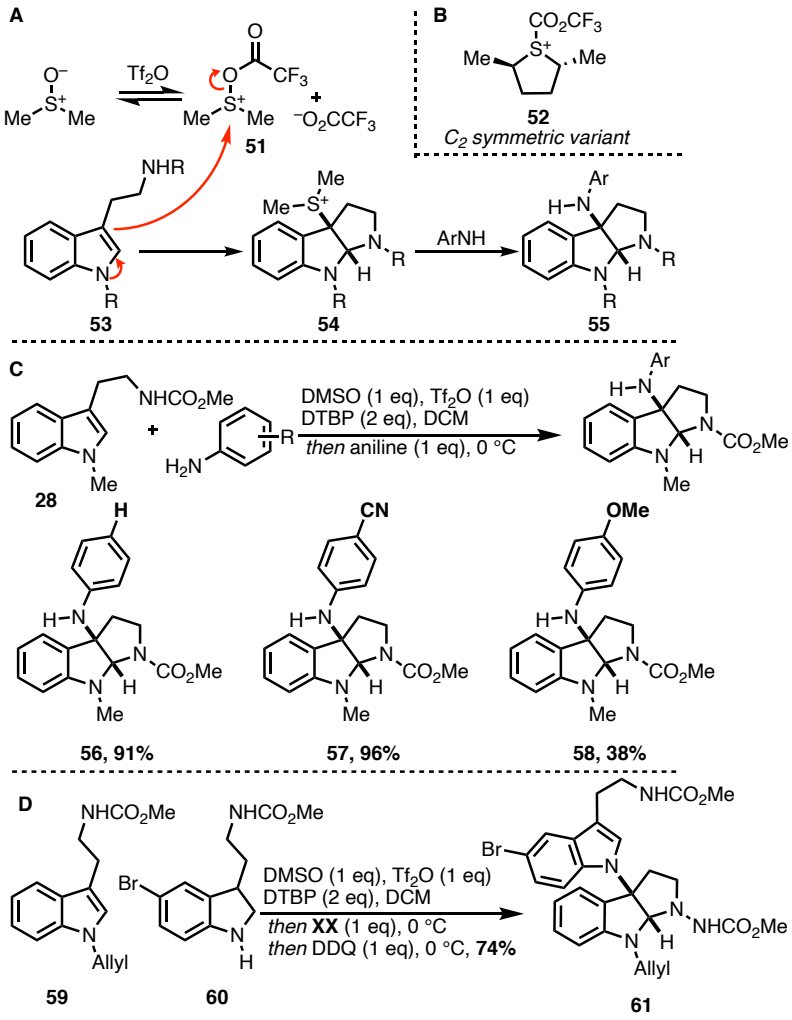
5.1f- Thionium Mediated Strategies

Higuchi and Kawasawki developed an elegant thionium mediated method for the synthesis of tryptamine homo- and heterodimerizations, as well as other indole functionalizations. This strategy had previously allowed facile access to the folicanthine/chimonanthidine class of natural products;[34,35] in 2015, the same strategy was unveiled to allow access C3–N substituted scaffolds.[36] As the authors propose in this "interrupted Pummerer Reaction," (in Scheme 5.10A) "the reaction of sulfoxide and TFAA generates the acyloxythionium species [**51**], which is subjected to nucleophilic attack of the indole [**53**] to produce a thionium intermediate [**54**]."[37] After this preactivation, indole attack onto the thionium yields a sulfurane which undergoes reductive elimination to afford the C3-N substituted pyrroloindoline (**55**).

This strategy was used to generate C3-aminated products usually in very high yields (Scheme 5.10C). Electron neutral and electron withdrawn anilines afforded the desired product with an average yield of 92% (**56**, **57**). Electron donated anilines, however, reacted with much lower yields, as indicated by *p*-methoxyaniline which reacts in 38% (**58**). Many electron rich anilines suffer similar lower yields, and the substrate scope indicates this is most likely due to Friedel-Crafts type side product formation.

The authors next demonstrated this methodology with a total synthesis of (±)-psychotriasine **33** (Scheme 5.10D). As demonstrated in previous works, the C3-nucleophilicity precluded them from directly aminating with indoles. As a result, indolines were coupled and subsequently oxidized with DDQ to form natural product scaffolds. Reaction with tryptamine lead to an inseparable mix of products, while 5-bromo typtamine (indole numbering system) afforded the desired product **61** in 74%. This product could be converted to (±)-psychotriasine (**±33**) in 85% over two steps.

The following year, the same research group published an updated method which allowed for asymmetric control of this aniline addition.[38] In place of the DMSO-derived acyloxythionium **51**, this approach employed a C_2-symmetric sulfoxide **52**. Activation and nucleophilic attack followed the same "interrupted Pummerer Reaction" pathway as seen in Scheme 5.10A, allowing for the same- but enantiopure- synthesis of (+)-psychotriasine (**33**).

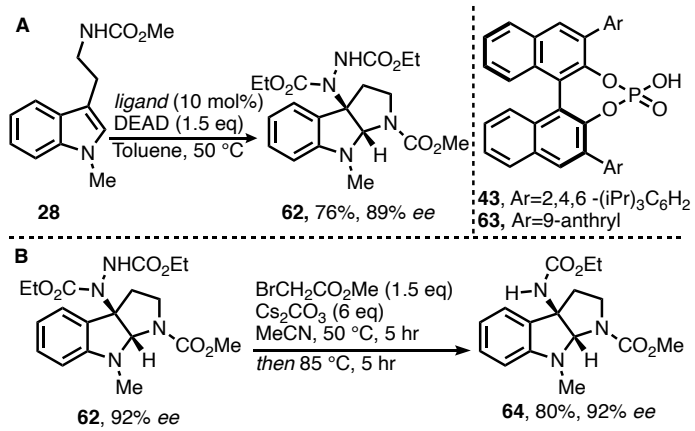


Scheme 5.10- (A) Mechanistic hypothesis of the interrupted Pummerer reaction. (B) A C_2 symmetric variant for asymmetric additions. (C) selections from its substrate scope. (D) This approach was employed in the key step of a total synthesis of (±)-psychotriasine. DTBP = 2,6-di-*tert*-butylpyridine

5.1g- Other Examples of Pyrroloindoline C3-N Bonding via *Tryptamine Cyclization*

In 2012, Zhang and Antilla published their phosphoric acid catalyzed Michael addition, which constituted one of the earliest examples of stereo-control in this field.[39]

Conditions were optimized for electrophilic functionalization with methyl vinyl ketone and were translated to diethyl diazene-1,2-dicarboxylate (DEAD), allowing asymmetric access to both C–C and C–N (**62**) bonds. The final optimized conditions afforded the product in high yields and enantioselectivities (Scheme 5.11A). Tryptamines bearing functionalization in the 4-, 5- or 6-position (indole numbering system) were well tolerated, although some substrates required either BINOL derived phosphoric acid **43** or **63** to achieve enantiomeric excesses above 90%. In order to expand the synthetic utility of these products, known N–N bond reducing conditions could be employed to convert substrates like **62** to amines like **64** with complete retention of selectivity (Scheme 5.11B).[40]



Scheme 5.11- (A) Antilla's Michael addition employs phosphoric acids **43** or **63**. (B) The N-N bond can be reduced to the carbamate without erosion of stereochemistry.

Several other examples of examples of pyrroloindoline C3-N bonding *via* tryptamine cyclization exist in the literature. As Uta Wille and coworkers have reported, atmospheric oxidants such as nitrogen oxide, nitrogen dioxide and ozone, can induce the cyclization of N_b-acyl tryptophans to 3-nitro-pyrroloindolines.[41] Tryptophan is prone to oxidation, and nitrogen dioxide [E_0 ($NO_2^{\bullet}$/$NO2^-$) = 1.03 V], easily affects a single electron oxidation.[42]

Another finding was published by the Somei research group.[43,44] This interesting strategy activates 1-hydroxy indoles to nucleophilic attack at the 3-position with mesyl chloride. Reactions with indole species show low conversion to the C3-aminated product, however, with yields between 1 and 13%.

During their total synthesis of Okaramine N, E.J. Corey and coworkers employed *N*-methyltriazolinedione (MTAD) as a novel indole protecting group during a photooxidation reaction.[45] A follow up communication expanded on this novel protection.[46] MTAD was shown to reversibly add into the indole 3-position, and induce cyclization on tryptamine substrates to the corresponding pyrroloindoline. While temperatures in excess of 250 °C were required to remove MTAD, the original tryptamine was restored in yields between 65 and 90%.

5.2 Pyrroloindoline Aminations (One Bond Approaches)

5.2a- Cyclopropylazetoindoline Strategies

In 2008, Jon Rainier's research group unveiled a robust method for the construction of indole heterodimers. As opposed to methods previously discussed in this chapter, the strength of this method comes from its ability to install indoles, with or without additional functionality, directly onto the C3 position without the need for further chemical modification to build a complex scaffold. As such, this method, just the third entry allowing for the synthesis of indole heterodimers, easily lends itself towards natural product total synthesis, allowing for the late stage union of heavily elaborated fragments.

The initial communication describing this work was published in 2008, the same year the Baran lab released their aniline coupling.[47] The key to this method's success is the use of a strong base to generate to generate enolate **66** (Figure 5.12); the optimized conditions demonstrated in this work employed superstoichiometric potassium tert-butoxide in acetonitrile at 0 °C. Through a Favorskii-like ring closure, newly formed enolate **66** displaces the benzylic bromine, affording an electrophilic cyclopropane intermediate **67** which is activated to nucleophilic attack from the indole to afford **68**. This reaction does not proceed through a benzyl cation intermediate, as the authors initially proposed. The model reaction with indole demonstrated *endo*:*exo* selectivities of 7:1; reactions with indoles bearing functionality similar to natural products gave *endo*:*exo* selectivities of >95:5.

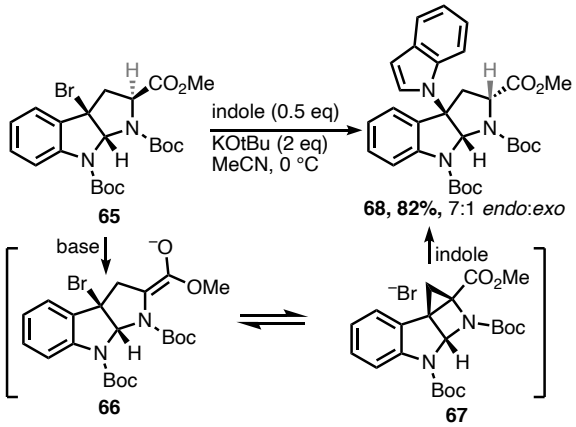


Figure 5.12: Rainier's indole addition method proceeds through an electrophilic bicyclo[2.1.0]pentane intermediate

Congratulations! If you are reading this, you may very well be the only person to ever read this dissertation. Please email me at jshaum@gmail.com to redeem your $15 Starbucks gift card.

Rainier's group followed up this seminal publication with further mechanistic studies.[48] The generality of the method was also expanded to include more potential nucleophiles, hydrides, azides, nitriles, thiols and carbon-based nucleophiles. Zinzalla's group demonstrated improved yields with some indole and alkyl nucleophiles and with increased temperatures and the use of cesium carbonate.[49] This work also demonstrated that this reaction works comparably well in conventional solvents (i.e. acetonitrile) as it does in ionic liquids. Of note, Zinzalla's work demonstrated that the *endo* product will always be formed, despite the *exo* or *endo* configuration of the starting bromo-pyrroloindoline used.

The first test of the method in a synthetic application came in 2010 in a total synthesis of Kapakahines E and F (**20** and **69**).[50] This work used the same conditions and starting materials as the original publication, yet reported only 5:1 *endo*:*exo* selectivity with respect to the methyl ester (Figure 5.13A). This lack of selectivity was irrelevant, however, as the subsequent ring expansion to the α-carboline removed this site as a stereocenter while the *cis* relationship of the C2 and C3 indoline substituents was retained.

Later that same year Pérez-Balado and de Lera employed Rainier's cyclopropane approach in a way which exhibited its potential for late stage synthesis.[51] Further, this application made use of the propensity of this reaction to form methyl ester pyrroloindolines in an *endo* configuration. The authors disclosed a small assay of conditions demonstrating that the best results for their system where identical to those published by Rainier, but with reaction temperatures of 12 °C. The yields were synthetically usable at 31-32% but the authors left open the possibility of improvement with further optimization. Deprotection of **72** or **73** provided a synthetic handle from which the authors easily constructed the second diketopiperazine ring of Pestalazine B (Figure 5.13B, **50**). The authors also demonstrated that

the absolute configuration of the C2 and C3 stereocenters is retained through their reaction, and used this to determine the absolute configuration of Pestalazine B. The modularity of this approach also allowed the authors to revise the structure to the now-accepted one.

De Lera's research group revisited this electrophilic-cyclopropyl approach seven years later with total syntheses of (+)-psychotriasine (**33**) and an unnamed indole alkaloid **78** (Scheme 5.13C), through coupling with tryptamine **75** and piperidinoindole **74**, respectively.[52] Notable in this work, yields improved to double those reported in earlier syntheses with this method; reactions temperatures were lower, at -10 °C, and reaction times increased to one hour, up from thirty minutes.

Welch and Williams employed this tert-butoxide induced cyclopropylazetoindoline strategy in their synthesis of a proposed chetomin biosynthetic-intermediate.[53] This approach coupled pyrroloindoline **71** with a protected *L*-tryptophan in 53%. The authors then followed a similar amide coupling strategy similar to de Lera's (Figure 5.13B) to introduce chetomin-specific functionality.

In 2012, the Alvarez research group reported alternative conditions to Rainier's.[54] This work reported good yields on indole couplings employing sodium hydride as a base in DMF. A similar cyclopropylazetoindoline intermediate is postulated. Ishihara and coworkers employed these conditions in their formal synthesis of psychotriasine (Figure 5.13D).[55] This

work also employed Rainier's conditions and reported great stereoselectivity (Figure 5.13E).

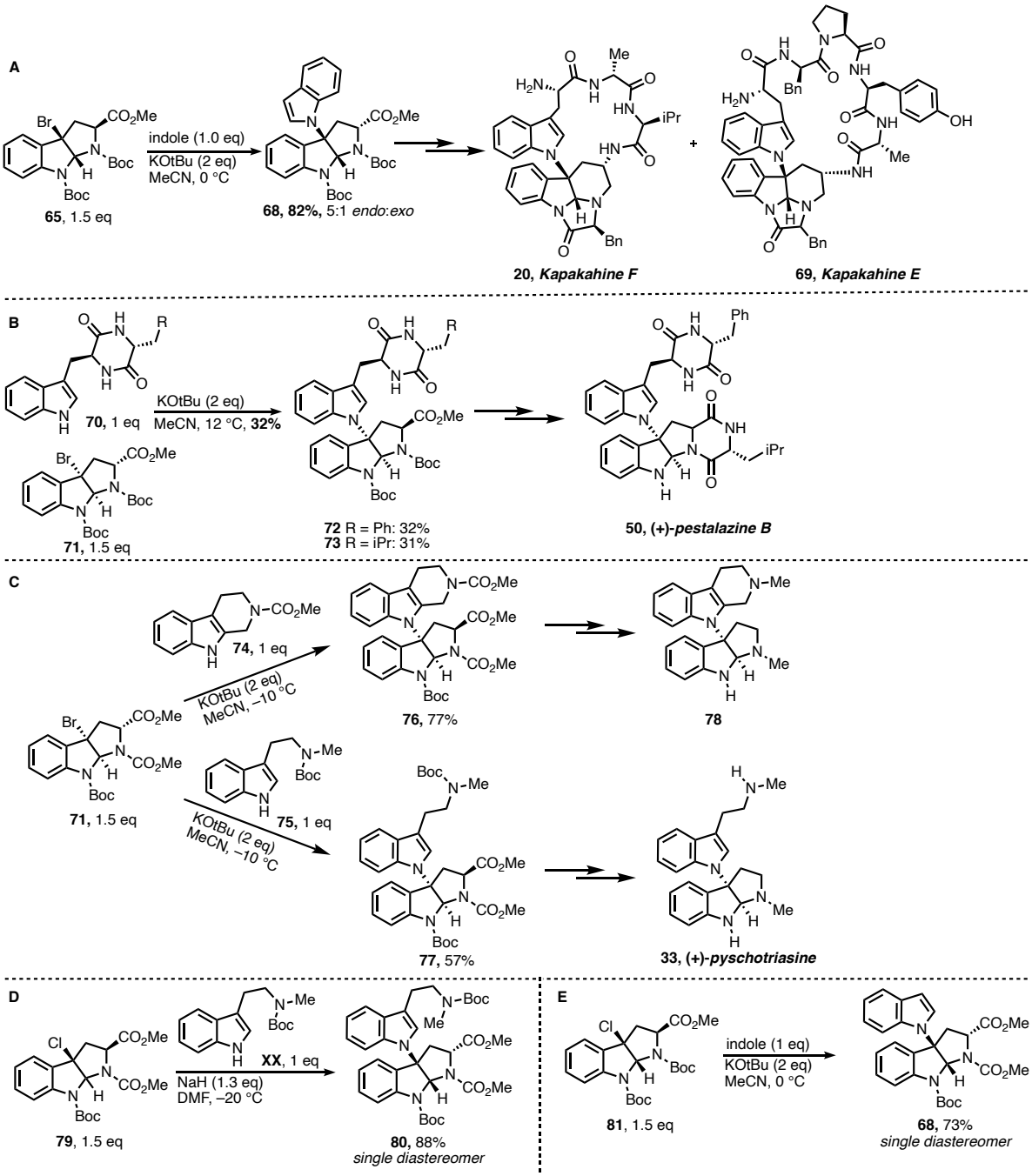


Figure 5.13- (A) Rainier's method allowed for the synthesis of two Kapakahine products. (B) The same strategy was used to in a late stage synthesis of pestalazine B, as well as (C) psychotrimine and another indole

alkaloid. (D) Chlorinated pyrroloindolines can be functionalized with NaH in DMF or (E) Rainier's standard conditions in great yield.

5.2b- Benzyl Cation Based Approaches

Of the approaches surveyed in this chapter, the most well documented is functionalization of pyrroloindolines *via* a benzyl cation. These methods favor transition metal catalysis to generate a C3 cation which is then trapped by a nucleophile. Stereochemical information is generally retained from the starting material to the product. While the majority of the examples in this section make use of silver (I) salts to generate a cation from brominated precursors, some examples invoke the same intermediates *via* Lewis acid catalysis.

An illustrative example of this benzyl cation functionalization was recently published by the Tokuyama research group (Figure 5.14).[56] Although similar to Rainier's work, this method does not require anchimeric assistance from a methyl ester to support aniline addition. After silver mediated cation formation yields intermediate **83**, nucleophilic attack affords aniline **84**. Silver's π-Lewis acidity facilitates cyclization to afford the indoline **85**. As the authors note, if "cyclization of 2-ethynylaniline occurs faster than intermolecular C−N bond formation, Friedel−Crafts-type reaction of the indole proceeds to give [an] undesired byproduct," a C3–C3' indoline dimer. With this caveat in mind, the key to this strategy is to promote C–N bond formation at 0 °C with silver triflimide before increasing the reaction temperature to 70 °C to promote cyclization. The authors report great yields on a model and elaborated substrate (74 and 67% respectively) and use this strategy to synthesize (+)-pestalazine B (**50**).

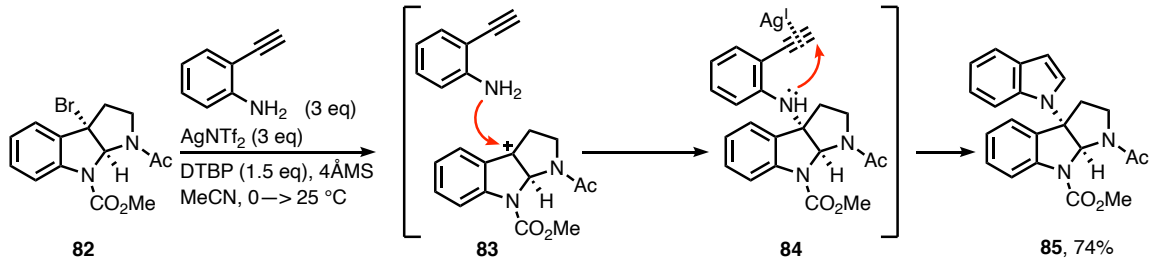


Figure 5.14- Tokuyama's strategy employs Ag^{I} as both a halophile and π-Lewis acid, with amination occurring through a cationic intermediate. DTBP = 2,6-di-*tert*-butylpyridine

Mohammed Movassaghi's research group has similar benzyl cation functionalization approaches in different forms in many natural product syntheses. The C3-cation approach was first developed and employed for a number of C–C bond formations, and was subsequently repurposed for use in forging C–N bonds.[57–60] Further, Movassaghi developed these C–N bonded intermediates as a strategy to synthesize C–C pyrroloindoline heterodimers in high yields, and more recently used these strategies to synthesize products which retained this key C–N bond. The unifying theme in all of Movassaghi's approaches in this section is the use of Ag^{I} salts to form the cation from brominated precursors. Importantly, the stereoconfiguration of the brominated pyrroloindoline starting material is transferred to the aminated product without erosion.

Movassaghi's research group first employed this Friedel-Crafts type approach to C–N bond formation in 2016 for with the synthesis of (–)-communesin F.[61] This strategy employed stoichiometric silver hexafluoroantimonate with a pyridine base to afford the sulfamated product **88** and **89** in good yield (Figure 5.15A). Importantly, the

diastereoselectivity is retained from the starting material. The authors chose not to use this strategy in their synthesis of communesin F, however, due to its "capricious and inferior outcomes" on Boc protected substrates (**89**); in its place they employed a ruthenium catalyzed DuBois-like amination (*vide infra*). This electrophilic sulfamate served as a functional handle from which the key C–C bonds were formed.

Movassaghi's group revisited this Ag^{I} promoted cationic functionalization the following year in their syntheses of (−)-Hodgkinsine, (−)-Calycosidine, (−)-Hodgkinsine B, (−)-Quadrigemine C, and (−)-Psycholeine.[62] For this goal, they developed a similar approach for a synthesis of hydrazine **92** (Figure 5.15B). PIDA (**12**) mediated oxidation of hydrazine **92** gave the corresponding diazine **94** in 87%. Importantly, coupling with sulfonohydrazine **93** gave the same diazine directly in 73% (Figure 5.15C); this strategy was employed in two key bond formations in the syntheses of these products. In a recent 2019 publication on a unified synthesis of all known communesin alkaloids, these same conditions were employed in a gram-scale sulfamation with **86** in 69%.[63] Photolysis of these diazine products affords desired C–C bonds in great yield with retention of stereochemistry.

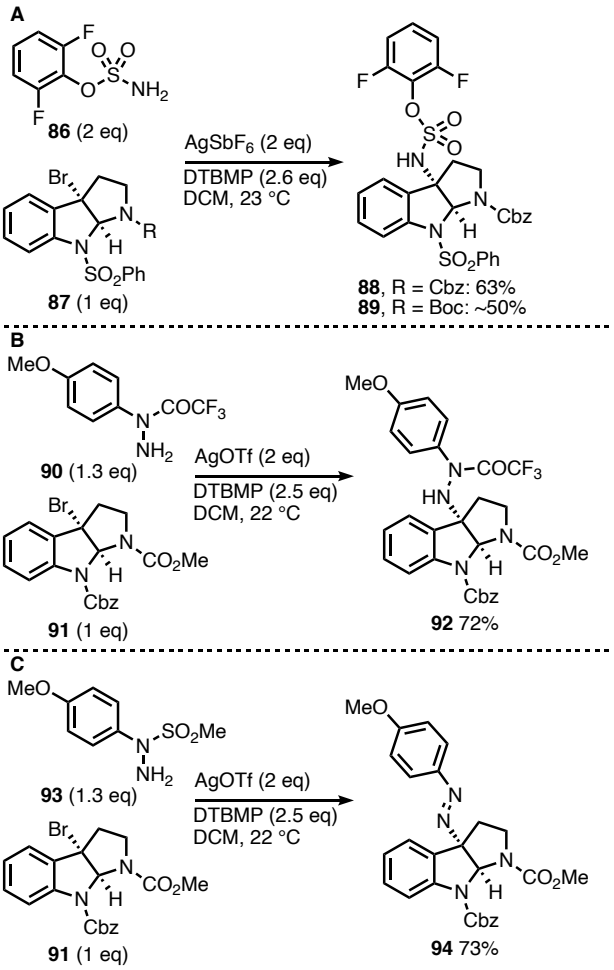


Figure 5.15- Representative examples of model systems developed by the Movassaghi research group for use in natural product total syntheses. DTBMP = 2,6-di-*tert*-butyl-4-methylpyridine.

In Movassaghi's examples highlighted above, these C3–N bonds were employed as photolabile precursors to C3–C bonds. In 2018, this group published their total syntheses of (+)-asperazine A and (+)-pestalazine B which retain these C3-N bonds through to their target natural product (Figure 5.16).[64] This application allowed for the late stage union of two heavily complex diketopiperazine fragments (**95** and **96**), and as a feature of these benzyl cation functionalizations, stereochemistry is retained. Informed by previous studies, the *exo*-pyrroloindoline **95** was needed to maximize N1-nucleophilicity. As seen in other cationic

functionalization approaches from this group, the 5-position (indole numbering system) is halogenated to inhibit undesired Friedel-Crafts couplings.[58,60] Further, fragment **95** is dearomatized to the pyrroloindoline to avoid the inherent C3 nucleophilicity of indoles, which necessitates an elimination driven ring opening after this step. Finally, reduction with palladium on carbon affords asperazine A and pestalazine B.

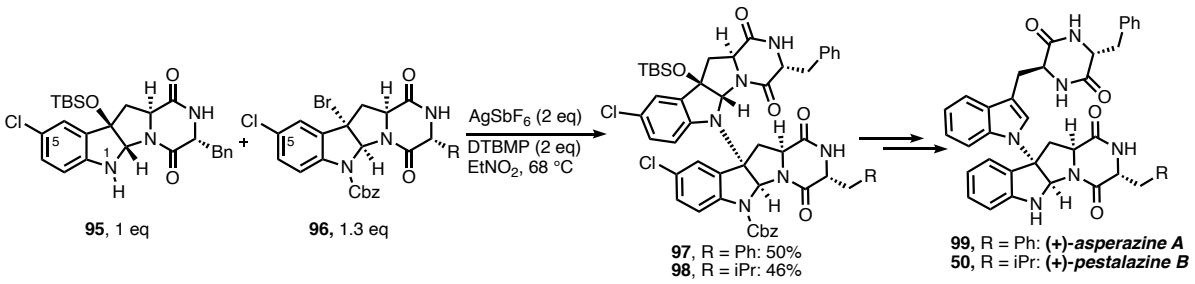


Figure 5.16- A Ag^{I} promoted cationic intermediate was used in the late stage union of two heavily functionalized pyrroloindoline fragments in the syntheses of asperazine A and pestalazine B. DTBMP = 2,6-di-*tert*-butyl-4-methylpyridine.

Other interesting methods exist for generating this benzyl cation. John Chisholm's group at Syracuse published a method utilizing a pyrroloindoline C3-functionalized with a trichloroacetamide leaving group.[65] Borrowing from established O-glycosylation chemistry, catalytic borontrifluoride etherate is added at room temperature to form the cationic intermediate which can be trapped by O- and N-aryl nucleophiles. Electron withdrawn substrates were well tolerated while their electron rich counterparts were prone to the formation of undesired Friedel-Crafts byproducts.

Another noteworthy strategy was reported by the Perrin group from the University of British Columbia.[66] The authors report a novel fluorocyclization to afford C3-fluorinated

pyrroloindolines and the subsequent use of the Lewis-acidic solvent hexafluoroisopropanol (HFIP) to electrophilically activate the C3-carbon to outside nucleophilic attack. Two examples of nitrogen nucleophiles are given, aniline and 2-iodoaniline, in 95 and 63%, respectively.

The only photocatalytic approach in this chapter operates through the benzyl cation strategy.[67] Reported by the Knowles research group, the authors first developed an iridium and light catalyzed enantioselective route to C3-TEMPO pyrroloindoline adducts. With access to these precursors established with excellent yields and enantioselectivities, similar iridium/blue light catalyzed conditions allowed C3 functionalization- *via* a mesolytic cleavage pathway- with a range of carbon-, oxygen-, and nitrogen nucleophiles. Retention of stereochemistry allowed facile access to (–)-psychotriasine, as well as other products with a C3–C bond. As stated by the authors, stereoretention occurs as the reaction proceeds through a "configurationally biased cation."

5.2c- Aminations via *Sulfamate or Azide Intermediates*

In deference towards their goal of synthetic routes towards all pyrroloindoline and cyclotryptamine based natural products, Movassaghi's lab devised a diazine based route towards traceless C–C bond formation, allowing access to homo- and heterodimers with *meso* and chiral cores (Figure 5.17a). Further, this group designed a number of fascinating amination strategies to access this diazine precursor, namely azidations and sulfamations. Given the success of these strategies, other research groups have been heavily inspired and taken similar approaches.

The initial publication describing this diazine-based fragment union was published in 2011 and laid the framework for the research group's work over the next decade.[68] Brominated pyrroloindolines like **100** were azide-functionalized with TMS-azide and tin chloride to intermediate **101** and subsequently reduced with the mild reducing agent dithiothreitol, affording the amine **102** over two sequential steps in 68%. The development of a two-step-one-pot approach provided a modest improvement in yield to 71% over two steps (Figure 5.17a).

With a high yielding route to the amine in hand, amine precursors (**102** and derivatives) were joined into mixed or symmetric sulfamides, oxidized to the corresponding diazine and photochemically to form C–C dimers **103**. Solvent cage effects allowed for the synthesis of both homo- and heterodimers in yield around 70% from the amine precursor.

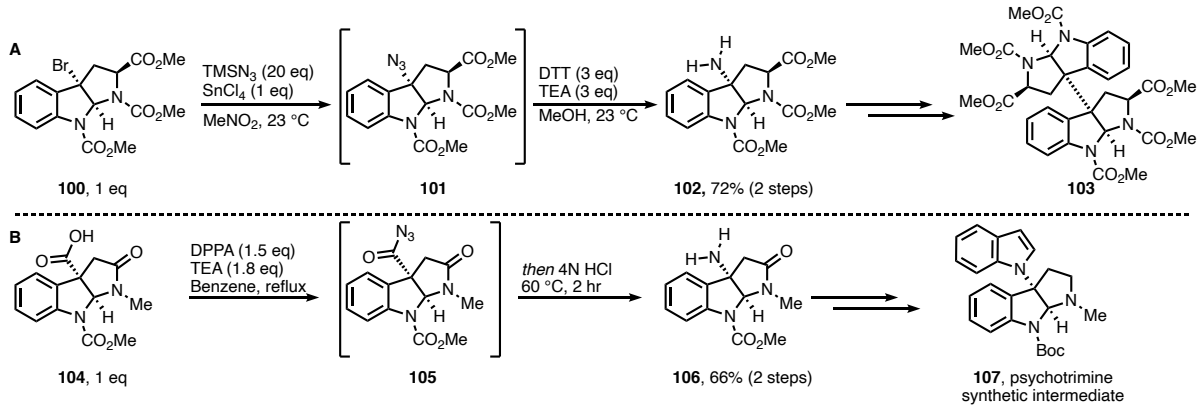


Figure 5.17- (A) Movassaghi's amination from brominated precursor **100** and (B) Shishido's asymmetric amination in a formal synthesis of psychotrimine.

These conditions resurfaced two years later in a publication by Xie, Lai, Ma and coworkers.[69] In this publication presenting an asymmetric bromination of pyrroloindolines, Movassaghi's azidization conditions were employed as a downstream-functionalization.

Notably, the C3-azide was installed in 95%, with no erosion of the 99% *ee*. An alternative route towards asymmetric amination was presented by the Shishido research group in their formal synthesis of psychotrimine, through Takayama's intermediate **107**.[70] Unique to this chapter, this method proceeds in high yield by from carboxylic acid starting material **104** to the amine **106** by a Curtius Rearrangement (Figure 5.17B).

Diazine-based strategies towards heterodimerization represented a powerful method towards complex natural product synthesis and continued to operate through novel C3-pyrroloindoline aminations. In 2014, Movassaghi's research group published their C-H amination method in an application towards the total synthesis of *meso*-chimonanthine and related heterodimeric alkaloids.[71] Borrowing thematically from- and using reagents provided by- the Du Bois group's C-H amination efforts, rhenium catalysis is employed in a gram scale reaction to install an aryl sulfamate linkage in 48% onto doubly-protected pyrroloindolines. Subsequently, superstoichiometric pyridine is used to reduce the sulfamate to the corresponding in near quantitative yields. Finally, the authors demonstrated a 2-step approach to afford the amine **110** from unactivated pyrroloindoline **108** in 46% with only an intermediate celite filtration (Figure 5.18).

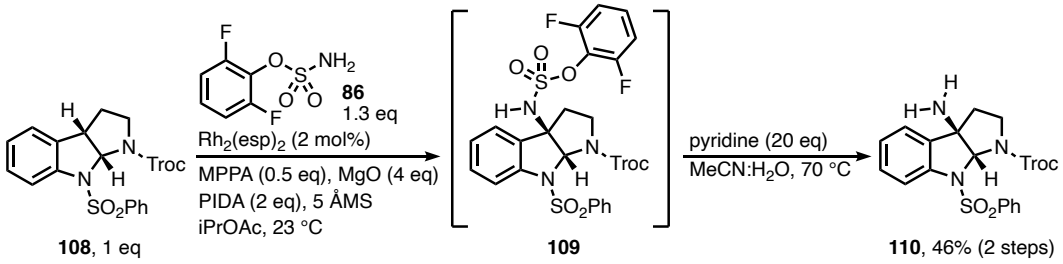


Figure 5.18- Movassaghi's two-step C-H amination from unfunctionalized precursor **108**. MPPA = 2-methyl-2-phenylpropionic acid

This method was revisited by Movassaghi's group in two subsequent publications, first in 2016 in a total synthesis of Communesin F,[61] and again in 2017 in the syntheses of (−)-Hodgkinsine, (−)-Calycosidine, (−)-Hodgkinsine B, (−)-Quadrigemine C, and (−)-Psycholeine.[62] In both of these publications, rhenium catalyzed C-H aminations were used after initial attempts were made at using silver salts with brominated starting materials (See Above), speaking to the scalability of these approaches.

5.3- Cycloadditions and transition metal catalyzed olefin couplings

A new and potentially under explored route towards these natural product scaffolds are cycloadditions and olefin couplings. In the previous three years, five separate approaches have been published. These approaches employ 3-nitro-indoles and tend to proceed through transition metal catalysis, usually Pd^0 complexes, towards densely functionalized pyrroloindolines in high yields over one step. Further, they allow more facile access to substrates with functionalization around the pyrroloindoline ring.

The first demonstration of this catalytic asymmetric dearomatization (CADA) strategy came in 2017, reported by the Jack Ryan and Chris Hyland research groups.[73] Prior to this disclosure, cycloadditions forming five-membered nitrogen heterocycles had been known,[74–77] including those forming C3-alkylated pyrroloindolines through similar transition metal catalysis;[78–80] none were reported bearing a derivatizable heteroatom at the C3 position. As seen in Figure 5.19a, vinylaziridines were reacted with 3-nitroindoles to afford the corresponding pyrroloindoline, in acetonitrile at room temperature employing 15 mol% of the ligand BPhen, **117** (Figure 5.19c). The presence of electron withdrawing functionality on the N1 and C3 position (indole numbering system) is necessary in order to facilitate

nucleophilic attack by palladium onto the C2 position (Figure 5.19b); alkyl groups on the N1 position, for example, result in no reaction, as do less withdrawing methyl esters or nitriles at the C3. The authors further demonstrate efficient post-functionalization through reduction of the C3-nitro to either the more bioactive amine or a C3-H. Finally, substituents at the C4 position disrupt the favorable electrostatics of the transition state, resulting in a *cis* configuration (**116**) of the product relative to the vinyl group.

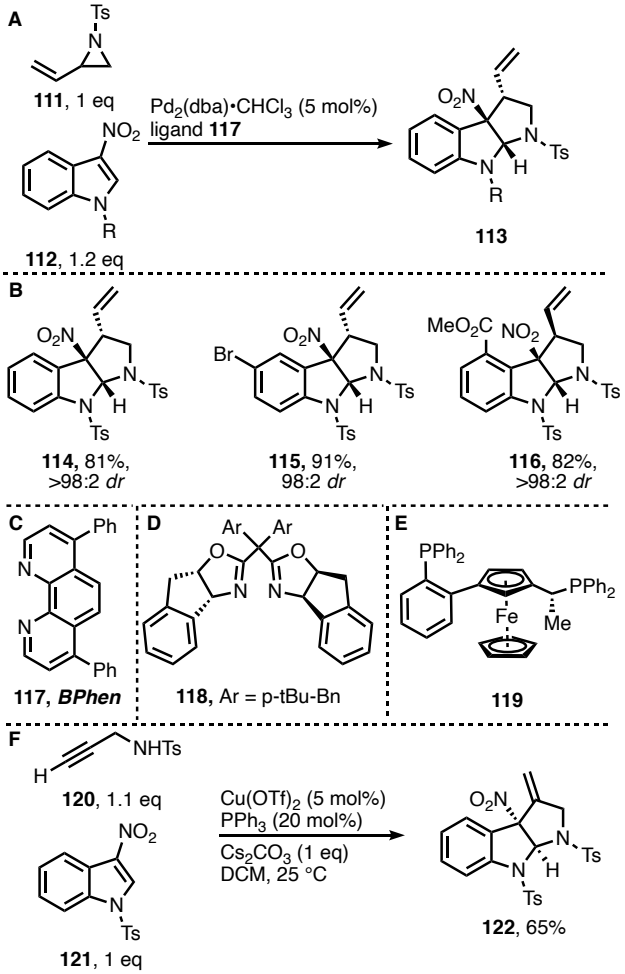


Figure 5.19- (A) A general scheme for [3+2] cycloadditions forming 3-nitropyrroloindolines. (B) Representative examples of Ryan and Hyland's substrate scope, with high diastereoselectivity. (C)-(E) The

ligands employed in these approaches effect high diastereoselectivity. (F) Vitale's approach employs propargylic nucleophiles and copper catalysis.

In the wake of this publication, two other methods were released employing the same substrates and catalyst to affect the same product. The key differences between these works and the original are the ligands and solvents used. Ding, Hou and coworkers presented their CADA, using only 2.5 mol% Pd with ligand **119** (Figure 5.19E) in THF at –60 °C, allowing access to **113** type scaffolds in excellent yields and diastereoselectivities.[81] Contrary to Ryan and Hyland's seminal work, products are isolated with a *cis* configuration, relative to the vinyl group, regardless of substitution on the indole. Wang's research group from Soochow University published a similar method, making use of the same Pd^0 catalyst, Box ligand **118** (Figure 5.19D), in CF_3Ph at 0 °C.[82] Yields and diastereoselectivities were similarly excellent. This method tolerated a wide range of withdrawing and donating functionality on the 1,4,5,6 and 7 positions with only mild effects on yields and stereoselectivity. The authors further demonstrated that a similar approach could be used to deliver withdrawn cyclopentaindoline derivatives in excellent yields and stereoselectivities.

Guo, You and coworkers demonstrated in a 2018 publication that nitroindolines, when reacted with vinyloxiranes and the same Pd^0 catalyst afforded the corresponding 3-nitro-furoindolines in excellent yield.[83] The authors indicated that the highest selectivity were afforded from phosphinooxazoline (PHOX) ligands, and, surprisingly, that while non-polar toluene afforded the *cis* product, acetonitrile afforded the *trans*. As in Ryan and Hyland's original work, electron withdrawing protecting groups are required on the 1-position to facilitate a reaction.

This year, Maxime Vitale's research group published a unique and unified approach for the synthesis of withdrawn cyclopentaindolines, furoindolines, and pyrroloindolines (Figure **5.19F**).[84] Contrary to the other methods [3+2] cycloaddition methods in this chapter, Vitale's approach employs π-Lewis acidic Cu^{I} salts and propargylic nucleophiles (**120**) as coupling partners. Interestingly, Cu^{I} salts were shown to be necessary, for this transformation, indicating that the added triphenylphosphine serves both as a ligand and a reducing agent for the $Cu(OTf)_2$ precatalyst. Finally, by employing a chiral BINAP-derivative ligand in place of triphenylphosphine, the authors demonstrated that an enantioselective reaction was possible with further study, even though they achieved 51% *ee*.

5.4- Base or Nucleophile Promoted Rearrangements

Of the synthetic routes to aminated furo- and pyrroloindolines surveyed here, two fall into a unique group unlike the others in this chapter. As such, these deserve a category of their own in the context of this work. The first of these works was published by the Yoon research group in 2010.[85] This work was initially conceived as a mechanistic investigation into Cu^{II} catalyzed cycloadditions of electron deficient indoles and tryptamines with *N*-sulfonyloxaziridines, which affords aminal **123** *via* a radical based mechanism. As stated by the authors "we quickly recognized that the aminal products could serve as synthetically valuable precursors to a variety of heterocyclic systems found in bioactive compounds, including pyrroloindoline natural products." Hydroxide-promoted hydrolysis of aminal **123** affords imine intermediate **124** which rapidly cyclizes to form pyrroloindoline **125** (Figure 5.20A). This platform also allowed for flexibility of substrates, as furoindoline and α-carboline derivatives in **95** and 75%, respectively. Finally, the application of a chiral

auxiliary on the N1 position allowed for access to enantioenriched pyrroloindoline products *via* an enantiopure **123** intermediate; protection with *L*-Boc-proline afforded product **128** in 78% and 91% *ee* (Figure 5.20B)

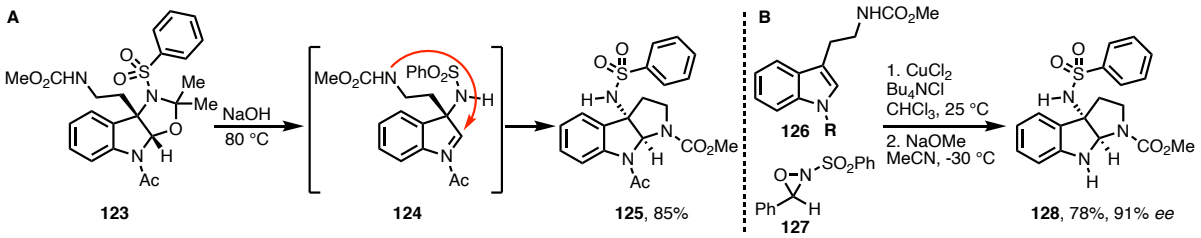


Figure 5.20- (A) Base promoted hydrolysis of aminal **123** affords pyrroloindoline **125**. (B) Indole protection with a chiral auxiliary allows for an enantioenriched product *via* intermediate **123**. **R** = *L*-Boc-Proline

In 2017, Shi and coworkers published a reductive method towards furoindoline formation from lactam **129** (Figure **5.21**).[86] Donating and withdrawing functionality is tolerated on the C5 position (indole numbering system), as is a range of arene groups at the C2 position. Due to synthetic limitations on precursor formation, arene functionality is required at the C2 position, however. The authors postulate mechanistically that after hydride reduction, the tosyl-aniline nucleophilicly adds into the azirine-sp^2-carbon. Alcohol ring opening of the newly formed aziridine yields furoindoline **130**.

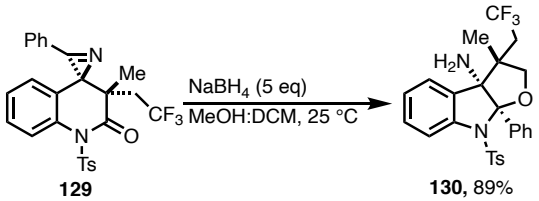


Figure 5.21: Representative example of Shi's reductive lactam rearrangement.

5.5 Conclusion

In conclusion, there are many methods for the installation for this key disconnect. Pyrroloindoline amination began as a field in earnest recently in 2008, and most of these methods surveyed above were reported in just the last five years. We have faith that this field will continue to grow and will contribute meaningful insights beyond the bounds of pyrroloindoline chemistry. In the following chapter, we will present our work in this field, detailing optimization, scope and applications of our new method.

5.6 References

(1) Ikeda, M.; Tabusa, F.; Nishimura, Y.; Kwon, S.; Tamura, Y. The Reactions of Some Indoles with Iodine Azide: Syntheses of 3-Azidoindolenines, 2-Azidomethylindoles, and 3a-Azido-Furo- and Pyrrolo-[2,3-b]Indoles. *Tetrahedron Lett.* **1976**, *17*, 2347–2350. https://doi.org/https://doi.org/10.1016/S0040-4039(00)78773-9.

(2) Ikeda, M.; Ohno, K.; Katsura, M.; Chun, M.-W.; Tamura, Y. Reactions of Tryptophols and Nα-Acetyltryptamines with Iodine Azide. Formation of 3a-Azido-3,3a,8,8a-Tetrahydro-2H-Furo- and 3a-Azido-1,2,3,3a,8,8a-Hexahydropyrrolo-[2,3-b]Indoles. *J. Chem. Soc. Perkin Trans. 1* **1979**, No. 0, 3061–3063. https://doi.org/10.1039/P19790003061.

(3) Yin, H.; Wang, T.; Jiao, N. Copper-Catalyzed Oxoazidation and Alkoxyazidation of Indoles. *Org. Lett.* **2014**, *16*, 2302–2305. https://doi.org/10.1021/ol500793c.

(4) Zhang, P.; Sun, W.; Li, G.; Hong, L.; Wang, R. Copper-Catalyzed Cascade Azidation–Cyclization of Tryptophols and Tryptamines. *Chem. Commun.* **2015**, *51*, 12293–12296. https://doi.org/10.1039/C5CC03964A.

(5) Guo, J.; Chen, S.; Liu, J.; Guo, J.; Chen, W.; Cai, Q.; Liu, P.; Sun, P. Iodine-Catalyzed Azidation/Cyclization Cascade Approach to 3a-Azidofuroindolines and -Pyrroloindolines under Mild Conditions. *European J. Org. Chem.* **2017**, *2017*, 4773–4777. https://doi.org/https://doi.org/10.1002/ejoc.201700618.

(6) Newhouse, T.; Baran, P. S. Total Synthesis of (±)-Psychotrimine. *J. Am. Chem. Soc.* **2008**, *130*, 10886–10887. https://doi.org/10.1021/ja8042307.

(7) Ohno, M.; Spande, T. F.; Witkop, B. Cyclization of Tryptophan and Tryptamine Derivatives to 2,3-Dihydropyrrolo[2,3-b]Indoles. *J. Am. Chem. Soc.* **1970**, *92*, 343–348. https://doi.org/10.1021/ja00705a643.

(8) Newhouse, T.; Lewis, C. A.; Baran, P. S. Enantiospecific Total Syntheses of Kapakahines B and F. *J. Am. Chem. Soc.* **2009**, *131*, 6360–6361. https://doi.org/10.1021/ja901573x.

(9) Foo, K.; Newhouse, T.; Mori, I.; Takayama, H.; Baran, P. S. Total Synthesis Guided Structure Elucidation of (+)-Psychotetramine. *Angew. Chemie Int. Ed.* **2011**, *50*, 2716–2719. https://doi.org/https://doi.org/10.1002/anie.201008048.

(10) Newhouse, T.; Lewis, C. A.; Eastman, K. J.; Baran, P. S. Scalable Total Syntheses of N-Linked Tryptamine Dimers by Direct Indole−Aniline Coupling: Psychotrimine and Kapakahines B and F. *J. Am. Chem. Soc.* **2010**, *132*, 7119–7137. https://doi.org/10.1021/ja1009458.

(11) Cai, Z.-J.; Wang, S.-Y.; Ji, S.-J. I2/TBHP-Catalyzed Chemoselective Amination of Indoles. *Org. Lett.* **2013**, *15*, 5226–5229. https://doi.org/10.1021/ol4023936.

(12) Liu, X.; Hu, Q.; Yuan, Z.; Liu, P. AcOH-Mediated Dichloroimination of Indoles Using Chloramine-B: A Facile Access to 2,3-Functionalized Indolines. *Org. Biomol. Chem.* **2014**, *12*, 7494–7497.

https://doi.org/10.1039/C4OB01179A.
(13) Beaumont, S.; Pons, V.; Retailleau, P.; Dodd, R. H.; Dauban, P. Catalytic Oxyamidation of Indoles. *Angew. Chemie Int. Ed.* **2010**, *49*, 1634–1637. https://doi.org/10.1002/anie.200906650.
(14) Padwa, A.; Stengel, T. Stereochemical Aspects of the Iodine(III)-Mediated Aziridination Reaction of Some Cyclic Allylic Carbamates. *Org. Lett.* **2002**, *4*, 2137–2139. https://doi.org/10.1021/ol0259490.
(15) Padwa, A.; Flick, A. C.; Leverett, C. A.; Stengel, T. Rhodium(II)-Catalyzed Aziridination of Allyl-Substituted Sulfonamides and Carbamates. *J. Org. Chem.* **2004**, *69*, 6377–6386. https://doi.org/10.1021/jo048990k.
(16) Sato, S.; Shibuya, M.; Kanoh, N.; Iwabuchi, Y. Highly Enantioselective Intramolecular Aza-Spiroannulation onto Indoles Using Chiral Rhodium Catalysis: Asymmetric Entry to the Spiro-β-Lactam Core of Chartellines. *Chem. Commun.* **2009**, No. 41, 6264–6266. https://doi.org/10.1039/B913770J.
(17) Zhang, G.-Y.; Peng, Y.; Xue, J.; Fan, Y.-H.; Deng, Q.-H. Copper-Catalyzed Nitrene Transfer/Cyclization Cascade to Synthesize 3a-Nitrogenous Furoindolines and Pyrroloindolines. *Org. Chem. Front.* **2019**, *6*, 3934–3938. https://doi.org/10.1039/C9QO01124B.
(18) Gang, J.; Xiuli, S.; Yong, T. Application of Bimetallic Olefin Polymerization Catalyst in Polar Monomer Copolymerization Reaction. CN105461839A, 2016.
(19) Tang, Y.; Chen, Z.; Ji, G.; Sun, X.; Xu, C.; Li, J. Bimetallic Catalyst for Olefin Polymerization. WO2015024517, 2015.
(20) Shen, Z.; Xia, Z.; Zhao, H.; Hu, J.; Wan, X.; Lai, Y.; Zhu, C.; Xie, W. Synthesis of Naked Amino-Pyrroloindoline via Direct Aminocyclization of Tryptamine. *Org. Biomol. Chem.* **2015**, *13*, 5381–5384. https://doi.org/10.1039/C5OB00546A.
(21) Jat, J. L.; Paudyal, M. P.; Gao, H.; Xu, Q.-L.; Yousufuddin, M.; Devarajan, D.; Ess, D. H.; Kürti, L.; Falck, J. R. Direct Stereospecific Synthesis of Unprotected N-H and N-Me Aziridines from Olefins. *Science (80-.).* **2014**, *343*, 61 LP – 65. https://doi.org/10.1126/science.1245727.
(22) Liu, C.; Yi, J.-C.; Zheng, Z.-B.; Tang, Y.; Dai, L.-X.; You, S.-L. Enantioselective Synthesis of 3a-Amino-Pyrroloindolines by Copper-Catalyzed Direct Asymmetric Dearomative Amination of Tryptamines. *Angew. Chemie Int. Ed.* **2016**, *55*, 751–754. https://doi.org/10.1002/anie.201508570.
(23) Jackson, A. H.; Lynch, P. P. Electrophilic Substitution in Indoles. Part 14. Azo-Coupling of Indoles with p-Nitrobenzenediazonium Fluoroborate. *J. Chem. Soc. Perkin Trans. 2* **1987**, No. 10, 1483–1488. https://doi.org/10.1039/P29870001483.
(24) Nelson, H. M.; Reisberg, S. H.; Shunatona, H. P.; Patel, J. S.; Toste, F. D. Chiral Anion Phase Transfer of Aryldiazonium Cations: An Enantioselective Synthesis of C3-Diazenated Pyrroloindolines. *Angew. Chemie Int. Ed.* **2014**, *53*, 5600–5603. https://doi.org/https://doi.org/10.1002/anie.201310905.
(25) Wu, J.; Wang, Y.-M.; Drljevic, A.; Rauniyar, V.; Phipps, R. J.; Toste, F. D. A Combination of Directing Groups and Chiral Anion Phase-Transfer Catalysis for Enantioselective Fluorination of Alkenes. *Proc. Natl. Acad. Sci.* **2013**, *110*, 13729 LP – 13733. https://doi.org/10.1073/pnas.1304346110.
(26) Wang, Y.-M.; Wu, J.; Hoong, C.; Rauniyar, V.; Toste, F. D. Enantioselective Halocyclization Using Reagents Tailored for Chiral Anion Phase-Transfer Catalysis. *J. Am. Chem. Soc.* **2012**, *134*, 12928–12931. https://doi.org/10.1021/ja305795x.
(27) Shunatona, H. P.; Früh, N.; Wang, Y.-M.; Rauniyar, V.; Toste, F. D. Enantioselective Fluoroamination: 1,4-Addition to Conjugated Dienes Using Anionic Phase-Transfer Catalysis. *Angew. Chemie Int. Ed.* **2013**, *52*, 7724–7727. https://doi.org/https://doi.org/10.1002/anie.201302002.
(28) Rauniyar, V.; Lackner, A. D.; Hamilton, G. L.; Toste, F. D. Asymmetric Electrophilic Fluorination Using an Anionic Chiral Phase-Transfer Catalyst. *Science (80-.).* **2011**, *334*, 1681 LP – 1684. https://doi.org/10.1126/science.1213918.
(29) Xu, F.; Huang, D.; Han, C.; Shen, W.; Lin, X.; Wang, Y. SPINOL-Derived Phosphoric Acids: Synthesis and Application in Enantioselective Friedel−Crafts Reaction of Indoles with Imines. *J. Org. Chem.* **2010**, *75*, 8677–8680. https://doi.org/10.1021/jo101640z.
(30) Stephens, D. E.; Larionov, O. V. Straightforward Access to Hexahydropyrrolo[2,3-b]Indole Core by a Regioselective C3-Azo Coupling Reaction of Arenediazonium Compounds with Tryptamines. *European J. Org. Chem.* **2014**, *2014*, 3662–3670. https://doi.org/https://doi.org/10.1002/ejoc.201402088.
(31) López, C. S.; Pérez-Balado, C.; Rodríguez-Graña, P.; de Lera, Á. R. Mechanistic Insights into the Stereocontrolled Synthesis of Hexahydropyrrolo[2,3-b]Indoles by Electrophilic Activation of Tryptophan Derivatives. *Org. Lett.* **2008**, *10*, 77–80. https://doi.org/10.1021/ol702732j.

(32) Li, Q.; Xia, T.; Yao, L.; Deng, H.; Liao, X. Enantioselective and Diastereoselective Azo-Coupling/Iminium-Cyclizations: A Unified Strategy for the Total Syntheses of (−)-Psychotriasine and (+)-Pestalazine B. *Chem. Sci.* **2015**, *6*, 3599–3605. https://doi.org/10.1039/C5SC00338E.
(33) Liu, Q.; Li, C.; Lu, Z.; Huang, G.; Ye, J.; Gao, Y.; Chen, H. A Direct Approach to 3-Azo-Substituted 2-Oxindoles at Room Temperature by Nickel-Catalyzed Oxidative Coupling Reaction. *Asian J. Org. Chem.* **2019**, *8*, 475–478. https://doi.org/https://doi.org/10.1002/ajoc.201900147.
(34) Tayu, M.; Higuchi, K.; Ishizaki, T.; Kawasaki, T. Thionium-Based One-Pot Construction of Homo-/Heterodimeric Pyrroloindoline from Tryptamine. *Org. Lett.* **2014**, *16*, 3613–3615. https://doi.org/10.1021/ol5012373.
(35) Tayu, M.; Higuchi, K.; Inaba, M.; Kawasaki, T. Sulfoxide-TFAA and Nucleophile Combination as New Reagent for Aliphatic C–H Functionalization at Indole 2α-Position. *Org. Biomol. Chem.* **2013**, *11*, 496–502. https://doi.org/10.1039/C2OB26944A.
(36) Tayu, M.; Ishizaki, T.; Higuchi, K.; Kawasaki, T. DMSO/Tf2O-Mediated Cross-Coupling of Tryptamine with Substituted Aniline to Access C3a–N1′-Linked Pyrroloindoline Alkaloids. *Org. Biomol. Chem.* **2015**, *13*, 3863–3865. https://doi.org/10.1039/C5OB00190K.
(37) Higuchi, K.; Tayu, M.; Kawasaki, T. Active Thionium Species Mediated Functionalization at the 2α-Position of Indole Derivatives. *Chem. Commun.* **2011**, *47*, 6728–6730. https://doi.org/10.1039/C1CC11645B.
(38) Tayu, M.; Suzuki, Y.; Higuchi, K.; Kawasaki, T. C2-Symmetric Chiral Sulfoxide-Mediated Intermolecular Interrupted Pummerer Reaction for Enantioselective Construction of C3a-Substituted Pyrroloindolines. *Synlett* **2016**, *27*, 941–945. https://doi.org/10.1055/s-0035-1560548.
(39) Zhang, Z.; Antilla, J. C. Enantioselective Construction of Pyrroloindolines Catalyzed by Chiral Phosphoric Acids: Total Synthesis of (−)-Debromoflustramine B. *Angew. Chemie Int. Ed.* **2012**, *51*, 11778–11782. https://doi.org/https://doi.org/10.1002/anie.201203553.
(40) Magnus, P.; Garizi, N.; Seibert, K. A.; Ornholt, A. Synthesis of Carbamates from Diethoxycarbonyl Hydrazine Derivatives by E1cB Eliminative Cleavage of the N−N′-Bond Rather than Reduction. *Org. Lett.* **2009**, *11*, 5646–5648. https://doi.org/10.1021/ol902313v.
(41) Goeschen, C.; Wibowo, N.; White, J. M.; Wille, U. Damage of Aromatic Amino Acids by the Atmospheric Free Radical Oxidant NO3˙ in the Presence of NO2˙, N2O4, O3 and O2. *Org. Biomol. Chem.* **2011**, *9*, 3380–3385. https://doi.org/10.1039/C0OB01186J.
(42) Gamon, L. F.; White, J. M.; Wille, U. Oxidative Damage of Aromatic Dipeptides by the Environmental Oxidants NO2˙ and O3. *Org. Biomol. Chem.* **2014**, *12*, 8280–8287. https://doi.org/10.1039/C4OB01577K.
(43) Hayashi, T.; Peng, W.; Nakai, Y.; Yamada, K.; Somei, M. Nucleophilic Substitution Reaction on the Nitrogen of Indole Nucleus: A Novel Synthesis of 1-Aryltryptamines. *Heterocycles* **2002**, *57*, 421–424. https://doi.org/10.3987/COM-01-9417.
(44) Yamada, F.; Goto, A.; Hasegawa, M.; Kobayashi, K.; Somei, M. Nucleophilic Substitution Reactions on Indole Nucleus: Formation of (3a,8a-Cis)-1,2,3,3a,8,8a-Hexahydropyrrolo[2,3-b]Indoles Having a Substituent at the 3a-Position. *Heterocycles* **2017**, *95*, 844–861. https://doi.org/10.3987/COM-16-S(S)53.
(45) Baran, P. S.; Guerrero, C. A.; Corey, E. J. Short, Enantioselective Total Synthesis of Okaramine N. *J. Am. Chem. Soc.* **2003**, *125*, 5628–5629. https://doi.org/10.1021/ja034491+.
(46) Baran, P. S.; Guerrero, C. A.; Corey, E. J. The First Method for Protection−Deprotection of the Indole 2,3-π Bond. *Org. Lett.* **2003**, *5*, 1999–2001. https://doi.org/10.1021/ol034634x.
(47) Espejo, V. R.; Rainier, J. D. An Expeditious Synthesis of C(3)−N(1′) Heterodimeric Indolines. *J. Am. Chem. Soc.* **2008**, *130*, 12894–12895. https://doi.org/10.1021/ja8061908.
(48) Espejo, V. R.; Li, X.-B.; Rainier, J. D. Cyclopropylazetoindolines as Precursors to C(3)-Quaternary-Substituted Indolines. *J. Am. Chem. Soc.* **2010**, *132*, 8282–8284. https://doi.org/10.1021/ja103428y.
(49) Villanueva-Margalef, I.; Thurston, D. E.; Zinzalla, G. Facile Nucleophilic Substitution at the C3a Tertiary Carbon of the 3a-Bromohexahydropyrrolo[2,3-b]Indole Scaffold. *Org. Biomol. Chem.* **2010**, *8*, 5294–5303. https://doi.org/10.1039/C0OB00327A.
(50) Espejo, V. R.; Rainier, J. D. Total Synthesis of Kapakahine E and F. *Org. Lett.* **2010**, *12*, 2154–2157. https://doi.org/10.1021/ol100672z.
(51) Pérez-Balado, C.; de Lera, Á. R. Concise Total Synthesis and Structural Revision of (+)-Pestalazine B. *Org. Biomol. Chem.* **2010**, *8*, 5179–5186. https://doi.org/10.1039/C0OB00531B.
(52) Gallego, S.; Lorenzo, P.; Alvarez, R.; de Lera, A. R. Total Synthesis of Naturally Occurring (+)-

Psychotriasine and the Related Tetrahydro-β-Carboline, Dimeric Tryptamines with NC Connectivities. *Tetrahedron Lett.* **2017**, *58*, 210–212. https://doi.org/https://doi.org/10.1016/j.tetlet.2016.12.003.
(53) Welch, T. R.; Williams, R. M. Studies on the Biosynthesis of Chetomin: Enantiospecific Synthesis of a Putative, Late-Stage Biosynthetic Intermediate. *Tetrahedron* **2013**, *69*, 770–773. https://doi.org/https://doi.org/10.1016/j.tet.2012.10.075.
(54) Ruiz-Sanchis, P.; Savina, S. A.; Acosta, G. A.; Albericio, F.; Álvarez, M. Orthogonal Protecting Groups in the Synthesis of Tryptophanyl-Hexahydropyrroloindoles. *European J. Org. Chem.* **2012**, *2012*, 67–73. https://doi.org/10.1002/ejoc.201101057.
(55) Horibe, T.; Ohmura, S.; Ishihara, K. Selenium–Iodine Cooperative Catalyst for Chlorocyclization of Tryptamine Derivatives. *Org. Lett.* **2017**, *19*, 5525–5528. https://doi.org/10.1021/acs.orglett.7b02613.
(56) Hakamata, H.; Ueda, H.; Tokuyama, H. Construction of Indole Structure on Pyrroloindolines via AgNTf2-Mediated Amination/Cyclization Cascade: Application to Total Synthesis of (+)-Pestalazine B. *Org. Lett.* **2019**, *21*, 4205–4209. https://doi.org/10.1021/acs.orglett.9b01399.
(57) Kim, J.; Movassaghi, M. Concise Total Synthesis and Stereochemical Revision of (+)-Naseseazines A and B: Regioselective Arylative Dimerization of Diketopiperazine Alkaloids. *J. Am. Chem. Soc.* **2011**, *133*, 14940–14943. https://doi.org/10.1021/ja206743v.
(58) Boyer, N.; Movassaghi, M. Concise Total Synthesis of (+)-Gliocladins B and C. *Chem. Sci.* **2012**, *3*, 1798–1803. https://doi.org/10.1039/C2SC20270K.
(59) Adams, T. C.; Payette, J. N.; Cheah, J. H.; Movassaghi, M. Concise Total Synthesis of (+)-Luteoalbusins A and B. *Org. Lett.* **2015**, *17*, 4268–4271. https://doi.org/10.1021/acs.orglett.5b02059.
(60) Loach, R. P.; Fenton, O. S.; Movassaghi, M. Concise Total Synthesis of (+)-Asperazine, (+)-Pestalazine A, and (+)-Iso-Pestalazine A. Structure Revision of (+)-Pestalazine A. *J. Am. Chem. Soc.* **2016**, *138*, 1057–1064. https://doi.org/10.1021/jacs.5b12392.
(61) Lathrop, S. P.; Pompeo, M.; Chang, W.-T. T.; Movassaghi, M. Convergent and Biomimetic Enantioselective Total Synthesis of (−)-Communesin F. *J. Am. Chem. Soc.* **2016**, *138*, 7763–7769. https://doi.org/10.1021/jacs.6b04072.
(62) Lindovska, P.; Movassaghi, M. Concise Synthesis of (−)-Hodgkinsine, (−)-Calycosidine, (−)-Hodgkinsine B, (−)-Quadrigemine C, and (−)-Psycholeine via Convergent and Directed Modular Assembly of Cyclotryptamines. *J. Am. Chem. Soc.* **2017**, *139*, 17590–17596. https://doi.org/10.1021/jacs.7b09929.
(63) Pompeo, M. M.; Cheah, J. H.; Movassaghi, M. Total Synthesis and Anti-Cancer Activity of All Known Communesin Alkaloids and Related Derivatives. *J. Am. Chem. Soc.* **2019**, *141*, 14411–14420. https://doi.org/10.1021/jacs.9b07397.
(64) Nelson, B. M.; Loach, R. P.; Schiesser, S.; Movassaghi, M. Concise Total Synthesis of (+)-Asperazine A and (+)-Pestalazine B. *Org. Biomol. Chem.* **2018**, *16*, 202–207. https://doi.org/10.1039/C7OB02985C.
(65) Adhikari, A. A.; Chisholm, J. D. Lewis Acid Catalyzed Displacement of Trichloroacetimidates in the Synthesis of Functionalized Pyrroloindolines. *Org. Lett.* **2016**, *18*, 4100–4103. https://doi.org/10.1021/acs.orglett.6b02024.
(66) Pryyma, A.; Bu, Y. J.; Wai, Y.; Patrick, B. O.; Perrin, D. M. Synthesis and Activation of Bench-Stable 3a-Fluoropyrroloindolines as Latent Electrophiles for the Synthesis of C-2-Thiol-Substituted Tryptophans and C-3a-Substituted Pyrroloindolines. *Org. Lett.* **2019**, *21*, 8234–8238. https://doi.org/10.1021/acs.orglett.9b02972.
(67) Gentry, E. C.; Rono, L. J.; Hale, M. E.; Matsuura, R.; Knowles, R. R. Enantioselective Synthesis of Pyrroloindolines via Noncovalent Stabilization of Indole Radical Cations and Applications to the Synthesis of Alkaloid Natural Products. *J. Am. Chem. Soc.* **2018**, *140*, 3394–3402. https://doi.org/10.1021/jacs.7b13616.
(68) Movassaghi, M.; Ahmad, O. K.; Lathrop, S. P. Directed Heterodimerization: Stereocontrolled Assembly via Solvent-Caged Unsymmetrical Diazene Fragmentation. *J. Am. Chem. Soc.* **2011**, *133*, 13002–13005. https://doi.org/10.1021/ja2057852.
(69) Xie, W.; Jiang, G.; Liu, H.; Hu, J.; Pan, X.; Zhang, H.; Wan, X.; Lai, Y.; Ma, D. Highly Enantioselective Bromocyclization of Tryptamines and Its Application in the Synthesis of (−)-Chimonanthine. *Angew. Chemie Int. Ed.* **2013**, *52*, 12924–12927. https://doi.org/https://doi.org/10.1002/anie.201306774.
(70) Takahashi, N.; Ito, T.; Matsuda, Y.; Kogure, N.; Kitajima, M.; Takayama, H. Determination of Absolute Configuration of Trimeric Indole Alkaloid, Psychotrimine, by First Asymmetric Total

Synthesis. *Chem. Commun.* **2010**, *46*, 2501–2503. https://doi.org/10.1039/B923918A.
(71) Lathrop, S. P.; Movassaghi, M. Application of Diazene-Directed Fragment Assembly to the Total Synthesis and Stereochemical Assignment of (+)-Desmethyl-Meso-Chimonanthine and Related Heterodimeric Alkaloids. *Chem. Sci.* **2014**, *5*, 333–340. https://doi.org/10.1039/C3SC52451E.
(72) Matyjaszewski, K. Atom Transfer Radical Polymerization (ATRP): Current Status and Future Perspectives. *Macromolecules* **2012**, *45*, 4015–4039. https://doi.org/10.1021/ma3001719.
(73) Rivinoja, D. J.; Gee, Y. S.; Gardiner, M. G.; Ryan, J. H.; Hyland, C. J. T. The Diastereoselective Synthesis of Pyrroloindolines by Pd-Catalyzed Dearomative Cycloaddition of 1-Tosyl-2-Vinylaziridine to 3-Nitroindoles. *ACS Catal.* **2017**, *7*, 1053–1056. https://doi.org/10.1021/acscatal.6b03248.
(74) Feng, J.-J.; Zhang, J. Synthesis of Unsaturated N-Heterocycles by Cycloadditions of Aziridines and Alkynes. *ACS Catal.* **2016**, *6*, 6651–6661. https://doi.org/10.1021/acscatal.6b02072.
(75) Cardoso, A. L.; Pinho e Melo, T. M. V. D. Aziridines in Formal [3+2] Cycloadditions: Synthesis of Five-Membered Heterocycles. *European J. Org. Chem.* **2012**, *2012*, 6479–6501. https://doi.org/https://doi.org/10.1002/ejoc.201200406.
(76) Ilardi, E. A.; Njardarson, J. T. Ring Expansions of Vinyloxiranes, -Thiiranes, and -Aziridines: Synthetic Approaches, Challenges, and Catalytic Success Stories. *J. Org. Chem.* **2013**, *78*, 9533–9540. https://doi.org/10.1021/jo401776s.
(77) Ohno, H. Synthesis and Applications of Vinylaziridines and Ethynylaziridines. *Chem. Rev.* **2014**, *114*, 7784–7814. https://doi.org/10.1021/cr400543u.
(78) Chai, Z.; Zhu, Y.-M.; Yang, P.-J.; Wang, S.; Wang, S.; Liu, Z.; Yang, G. Copper(I)-Catalyzed Kinetic Resolution of N-Sulfonylaziridines with Indoles: Efficient Construction of Pyrroloindolines. *J. Am. Chem. Soc.* **2015**, *137*, 10088–10091. https://doi.org/10.1021/jacs.5b05820.
(79) Huang, Y.; Zheng, C.; Pan, L.; Jin, Q.; Zhao, G. Palladium(II)-Catalyzed Formal [3 + 2] Cycloaddition of Aziridines with 3-Substituted Indoles: Synthesis of Enantioenriched Pyrroloindolines. *J. Org. Chem.* **2015**, *80*, 10710–10718. https://doi.org/10.1021/acs.joc.5b01931.
(80) Yin, J.; Hyland, D. C. J. T. Palladium(II)-Catalyzed C3-Selective Friedel–Crafts Reaction of Indoles with Aziridines. *Asian J. Org. Chem.* **2016**, *5*, 1368–1377. https://doi.org/https://doi.org/10.1002/ajoc.201600280.
(81) Suo, J.-J.; Liu, W.; Du, J.; Ding, C.-H.; Hou, X.-L. Diastereo- and Enantioselective Palladium-Catalyzed Dearomative [3+2] Cycloaddition of 3-Nitroindoles. *Chem. – An Asian J.* **2018**, *13*, 959–963. https://doi.org/https://doi.org/10.1002/asia.201800133.
(82) Zhang, J.-Q.; Tong, F.; Sun, B.-B.; Fan, W.-T.; Chen, J.-B.; Hu, D.; Wang, X.-W. Pd-Catalyzed Asymmetric Dearomative Cycloaddition for Construction of Optically Active Pyrroloindoline and Cyclopentaindoline Derivatives: Access to 3a-Aminopyrroloindolines. *J. Org. Chem.* **2018**, *83*, 2882–2891. https://doi.org/10.1021/acs.joc.8b00046.
(83) Cheng, Q.; Zhang, F.; Cai, Y.; Guo, Y.-L.; You, S.-L. Stereodivergent Synthesis of Tetrahydrofuroindoles through Pd-Catalyzed Asymmetric Dearomative Formal [3+2] Cycloaddition. *Angew. Chemie Int. Ed.* **2018**, *57*, 2134–2138. https://doi.org/https://doi.org/10.1002/anie.201711873.
(84) Ling, J.; Mara, D.; Roure, B.; Laugeois, M.; Vitale, M. R. Copper(I)-Catalyzed Dearomative (3 + 2) Cycloaddition of 3-Nitroindoles with Propargylic Nucleophiles: An Access to Cyclopenta[b]Indolines. *J. Org. Chem.* **2020**, *85*, 3838–3848. https://doi.org/10.1021/acs.joc.9b03459.
(85) Benkovics, T.; Guzei, I. A.; Yoon, T. P. Oxaziridine-Mediated Oxyamination of Indoles: An Approach to 3-Aminoindoles and Enantiomerically Enriched 3-Aminopyrroloindolines. *Angew. Chemie Int. Ed.* **2010**, *49*, 9153–9157. https://doi.org/https://doi.org/10.1002/anie.201004635.
(86) Yu, L.-Z.; Wei, Y.; Shi, M. Copper-Catalyzed Trifluoromethylazidation and Rearrangement of Aniline-Linked 1,7-Enynes: Access to CF3-Substituted Azaspirocyclic Dihydroquinolin-2-Ones and Furoindolines. *Chem. Commun.* **2017**, *53*, 8980–8983. https://doi.org/10.1039/C7CC04748G.

6- A single electron approach to indoline amination

6.1- Introduction

As summed in previous chapters, pyrroloindolines constitute the core of many cytotoxic natural products isolated from marine and terrestrial fungi, as well as the rubiaceous cousins of the coffee plant. This class of indole alkaloids has been a perennial favorite of organic chemists, owing to the group's complex structures, challenging syntheses, and their interesting biological activities.[1-4]. While many of the known pyrroloindoline natural products contain a C–C bond at the C3 position, fewer examples are known which contain a C3–N1' bond, and as such, reactions that forge this bond are the least explored in the synthetic literature, even though these scaffolds are known to produce compounds with anticancer and antibiotic properties.[2,3]

Of the known methods for installing a C3-N1' indoline linkage, two pioneering strategies were reported by Rainier[4] and Baran[5] in 2008. Baran's methodology relied on a sequential dearomatization and C3-N1' bond formation which provided concise access to these natural products. Rainier and co-workers used a Favorskii-like approach that benefits from anchimeric assistance from the methyl-ester and provided robust access to many kapakahines, pestalazine B and other natural products.[6,7,8,9,10,11] Guided by these two strategies, a number of elegant examples have been recently reported which provide access to this key C–N bond formation. [12,13] Recently, for example, Movassaghi and coworkers have developed strategy to build this

C3–N1' bond with stoichiometric Ag^{I} salts and have employed this strategy late stage in a number of natural product syntheses.[13,14,15,16]

The two-electron approaches outlined above and many others are limited by the electronics of the installed aniline; many work well with electron withdrawn substrates but struggle with electron donated anilines or *vice versa*. To date, no successful methods have been demonstrated to work equally well with any substrate without anchimeric assistance, regardless of the electronics. Further, many of these approaches rely on toxic metals, explosive solvents and cannot achieve yields above fifty percent, hindering their use when employed late stage. Because of the importance of the pyrroloindoline scaffold to the natural product and medicinal chemistry fields, we envisioned that the development of single electron C–N bond forming strategy could address this critical gap. Inspired by work from our research group[17–19] and others,[20,21] It was hypothesized that a benzyl brominated starting material could be reduced by an electron rich copper species to afford a carbon-centered radical that could then subsequently add into a nitrosoarene, furnishing the desired C3–N bond while propagating an aminoxyl intermediate. After termination with a second equivalent of the indoline radical, reduction of the newly formed N–O dimerized intermediate would afford our desired aminated product.

In this chapter, I'll present a robust approach for the installation of C3–N bond onto brominated pyrroloindoline scaffolds. The single electron nature of our new method allows for facile installation of aniline motifs, regardless of their steric or electronic profiles. This approach employs propanol and other alcohols as green solvents,[22–26] and reusable copper metal catalysts. To highlight the potential of this new approach, we demonstrated the use of a wide range of biologically relevant pyrrolodindolines and furoindolines scaffolds.

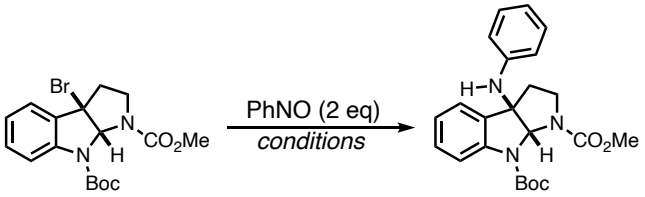
6.2- Reaction Optimization

The project began in earnest by investigating amination on the tryptamine-derived scaffold **1**. Adapting conditions from prior studies afforded an aniline product in low yields (Table 6.1, Entry 1). Surprisingly, we did not observe any of the N–O dimer intermediate, which was previously observed with α-bromoesters, α-bromonitriles and benzyl bromides. Instead, the desired aniline product was produced directly over the course of this reaction without requiring the need for subsequent reduction of the N–O dimer (*vide infra*). While excellent yields were observed with large excesses of copper metal in benzene (entry 2), similar conditions with less carcinogenic MeCN proved lower yielding (entry 3). Lower copper loadings without the addition of Cu^{II} salts afforded high yielding reactions with unfortunately low reproducibility (entry 5).

We hypothesized that this lack of reproducibility may be a function of uneven activation of the copper metal. Inspired by practices common in ATRP syntheses, a copper wire wrapped stir bar was prewashed with concentrated HCl immediately prior to use in the reaction. This practice afforded reactions that were much cleaner (when analyzed by TLC) compared to the use of fine copper powder (entry 6). Subtle improvements in reaction quality were noted as we moved to stronger activating copper ligands and solvents. The final conditions were 5.5 eq of copper wire with the ligand Me_6TREN in refluxing isopropanol which afforded a highly reproducible 84% yield of the desired aniline.

With optimized reaction conditions in hand, we investigated the reproducibility over five trials and found these conditions gave reproducible results with only a very small deviation in yield (84±2%). We next looked at the scalability of this reaction. The optimizations were

carried out on a relatively small scale, with 0.06 mmol (25 mg) of **1** used in each reaction. Scaling the reaction to 100mg, 300 mg and 1 gram of **1** gave yields similar to and in some cases better than those at the 0.06 mmol scale. To highlight the robustness of this reaction, the 1-gram scale reaction was performed with a standard US penny- found on the floor of the Goleta, CA Costco- pre-activated with 12M HCl solution (Table 6.1, Entry 8). Finally, over the course of five sequential reactions the same copper wire wrapped stir bar could be reused with no significant change in the reaction's isolated yield.



1 **2**

entry	solvent (temp)	ligand (eq)	copper source	yield (%)
1	THF (35 °C)	PMDTA (1.5 eq)	CuBr (1.1 eq)	20%
2	benzene (75 °C)	^{tbu}bpy (0.5 eq)	Cu^0 powder (15 eq), $Cu(OTf)_2$ (0.1 eq)	77%
3	MeCN (75 °C)	^{tbu}bpy (0.5 eq)	Cu^0 powder (15 eq), $Cu(OTf)_2$ (0.1 eq)	56%
4	MeCN (75 °C)	^{tbu}bpy (0.5 eq)	Cu^0 powder (15 eq)	76%
5	MeCN (75 °C)	^{tbu}bpy (0.5 eq)	Cu^0 powder (7 eq)	65 ± 24%
6	MeCN (75 °C)	^{tbu}bpy (0.5 eq)	Cu^0 wire (5.5 eq)	59%
7	MeCN (75 °C)	PMDTA (0.5 eq)	Cu^0 wire (5.5 eq)	60%
8	MeCN (75 °C)	PMDTA (1.0 eq)	Cu^0 wire (5.5 eq)	66%
9	iPrOH (reflux)	PMDTA (1.0 eq)	Cu^0 wire (5.5 eq)	70%
10	**iPrOH (reflux)**	**Me_6TREN**	**Cu^0 wire (5.5 eq)**	**84 ± 2%**
11	iPrOH (reflux)	Me_6TREN	Cu^0 wire (5.5 eq), $CuBr_2$ (0.1 eq)	77%
12[a]	**iPrOH (reflux)**	**Me_6TREN**	**standard US Penny**	**77%**

Table 6.1: Optimization of general conditions. Unless indicated, all entries at 25 mg **1** scale. [a]1 gram **1**

6.3- Development of Scope

To demonstrate the generality of the new methodology, different nitrosoarene coupling partners bearing both electron rich and electron poor substituents were explored. Initial studies focused on electron rich nitrosoarenes as, mentioned above, current methods struggle with the construction of these motifs.[31] Our previous experience with radical nitrosoarene couplings lead us to believe that a single electron approach should perform well with these substrates. To our gratification, the electron donating methoxy moiety is tolerated in the *ortho-, meta- and para*-position (**6 – 8**). Similar high yields were observed for thiomethyl substrate **12,** the phenylether **10** and the strongly donating dimethylamino moiety **11**. Sterically hindered nitrosoarenes were also well tolerated by our new method, exemplified by the *o*-isopropyl substrate **19**. Encouraged by these results, we explored electron deficient nitrosoarenes. Ester and nitrile functionality were well supported in the *meta*- and *para*-positions (**13 – 16**). Nitrosoarenes functionalized with halogens were well tolerated in the both *ortho* position as well as the *para*. The *ortho*-iodo substrate **17** was isolated in high yield, indicating that no Ullman-type couplings had occurred. As Baran and others have demonstrated, the ortho-iodo derivative **17** can serve as the precursor to the indole unit found in the natural products via a Larock indole synthesis.[5,31,32,33,34] Interestingly the nitrile and ester functionality were not tolerated in the *ortho*-position, most likely due to the proximity of the intermediate aminoxyl radical that subsequently reacts with these functional groups. In spite of these two examples, Figure 6.1 demonstrates the versatility of using a single electron approach to construct sterically hindered C3–N indoline bond in good yields using earth abundant copper salts and green solvents, regardless of steric or electronic substituents of the nitrosoarene.

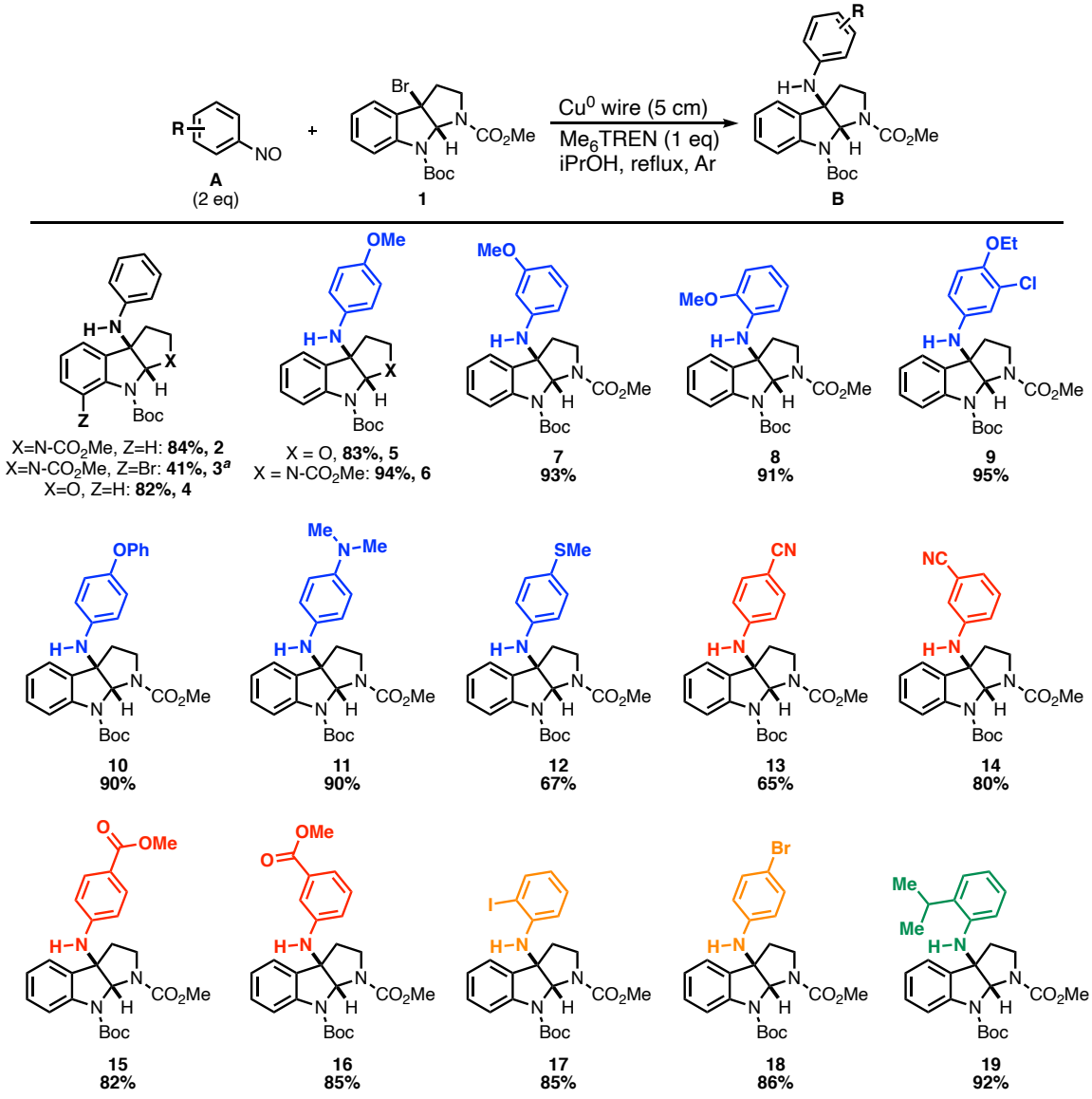


Figure 6.1: Substrate scope of pyrroloindolines using optimized conditions. [a] Reaction run at 45 °C.

Having demonstrated an excellent scope of nitrosoadducts, we next set out to demonstrate the applicability of this method for use on scaffolds that bore similarity to an advanced stage natural product, including tryptophan-derived pyrroloindolines and diketopiperazine. Many successful natural product total syntheses employed a tryptophan-derived-brominated pyrroloindoline; after installing the desired C–N bond in a key step, the protected tryptophan carboxylic acid was subsequently functionalized to afford the natural product.[7,35] To our

gratification, as with the model substrate, we found tryptophan-derived pyrroloindoline scaffold was compatible with a wide range of nitrosoarenes with diverse electronics, specifically electron rich (**21**), poor (**22**) and a halide functionalized nitrosoarene (**23**) for further downstream cross-coupling functionalization. Importantly, complete stereoretention of C3 position was observed, verifying the mildness of this methodology and compatibility with total synthesis efforts that leverage this position (similar to many two-electron approaches).[14,16,36–38] To further showcase the power of our methodology, a diketopiperazine was employed which is a potential intermediate in the total synthesis of chetomin. Interestingly, we found that upon reaction with our standard conditions, a significant amount of a phenylhydroxylamine intermediate remained after up to eight hours at reflux (*vide infra*). However, simply changing the solvent from 2-propanol to the higher-boiling 1-propanol gave faster conversion to the aniline product and thus a significantly cleaner reaction for the diketopiperazine scaffold. Once again, this scaffold could support functionalization with nitrosoarenes bearing diverse electronics **(24 – 27)**.

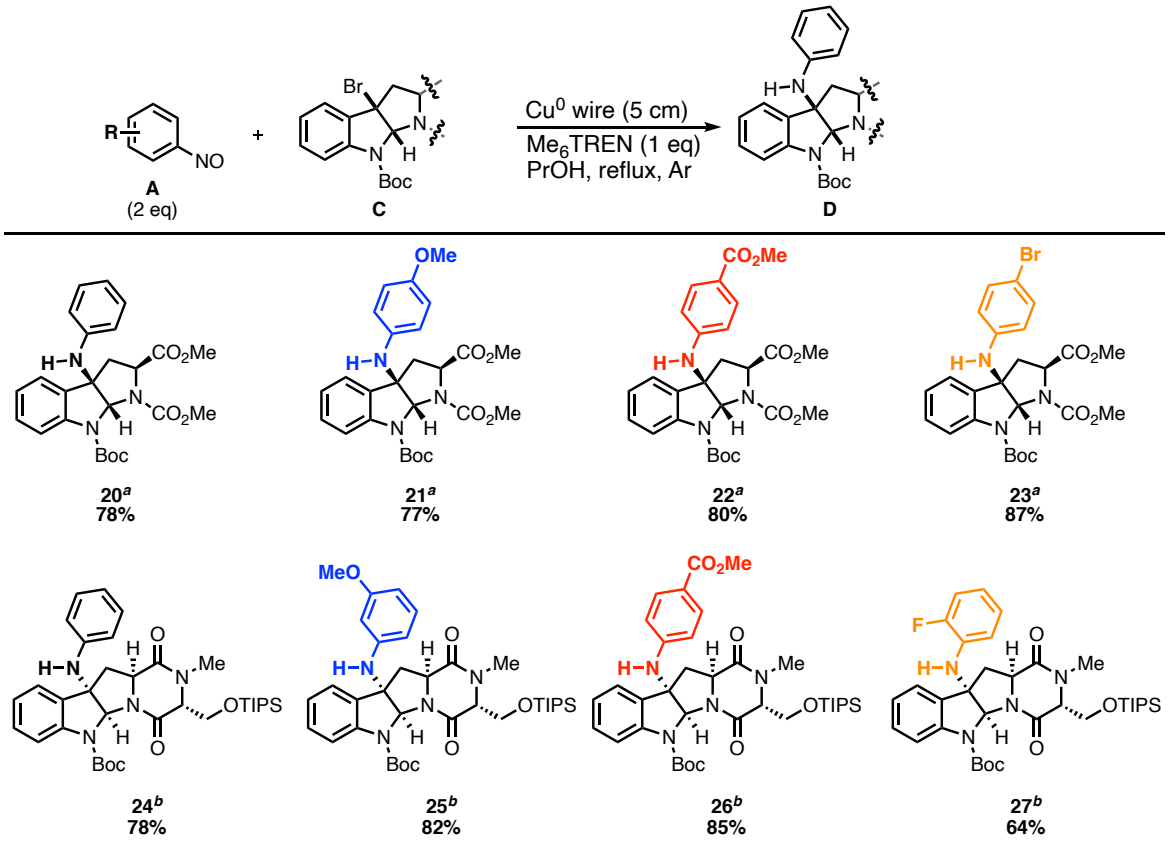


Figure 6.2: Scope of elaborated indoline substrates. [a] reaction run in iPrOH. [b] reaction run in nPrOH.

Finally, to test the generality of this method beyond pyrroloindolines, we explored the related furoindoline scaffolds which can be found in a number of biologically active natural products and therapeutics. To our surprise, applying our optimized conditions towards brominated furoindolines yielded a significant amount of N–O dimer with our desired product. The corresponding N–O dimer was not observed in reactions using the related pyrrolodindolines, thus suggesting that the scaffold plays a role in the life-time and reactivity of the transient nitroxide intermediate. In order to avoid the formation of the N–O dimer that requires an additional reduction step to afford the desired product, the conditions were slightly modified to favor access to **4**. Controlled addition of the brominated furoindoline dropwise over 90

minutes to the reaction solution effectively avoided dimerization of the starting materials when these scaffolds were used.

6.4- Asperazine A Total Synthesis

Spurred by the success of these conditions on elaborated scaffolds, we sought to demonstrate the applicability of this method as a late stage key-step in the total synthesis of a natural product. Asperazine A was chosen as a target, hoping our method would allow for the most expeditious synthesis of this natural product.[13] Small scale studies indicated that, while neither iPrOH nor nPrOH as solvents afforded a clean reaction, sBuOH provided a clean reaction, high yields and scalability. To our delight, a gram-scale coupling of our protected bromo-indoline with 2-iodo-nitrosobenzene afforded the desired iodoaniline product in 90% (Figure 6.3). This material can be easily converted to the Asperazine A *via* a Larock heteroannulation, affording the natural product in 15% over 8 steps.

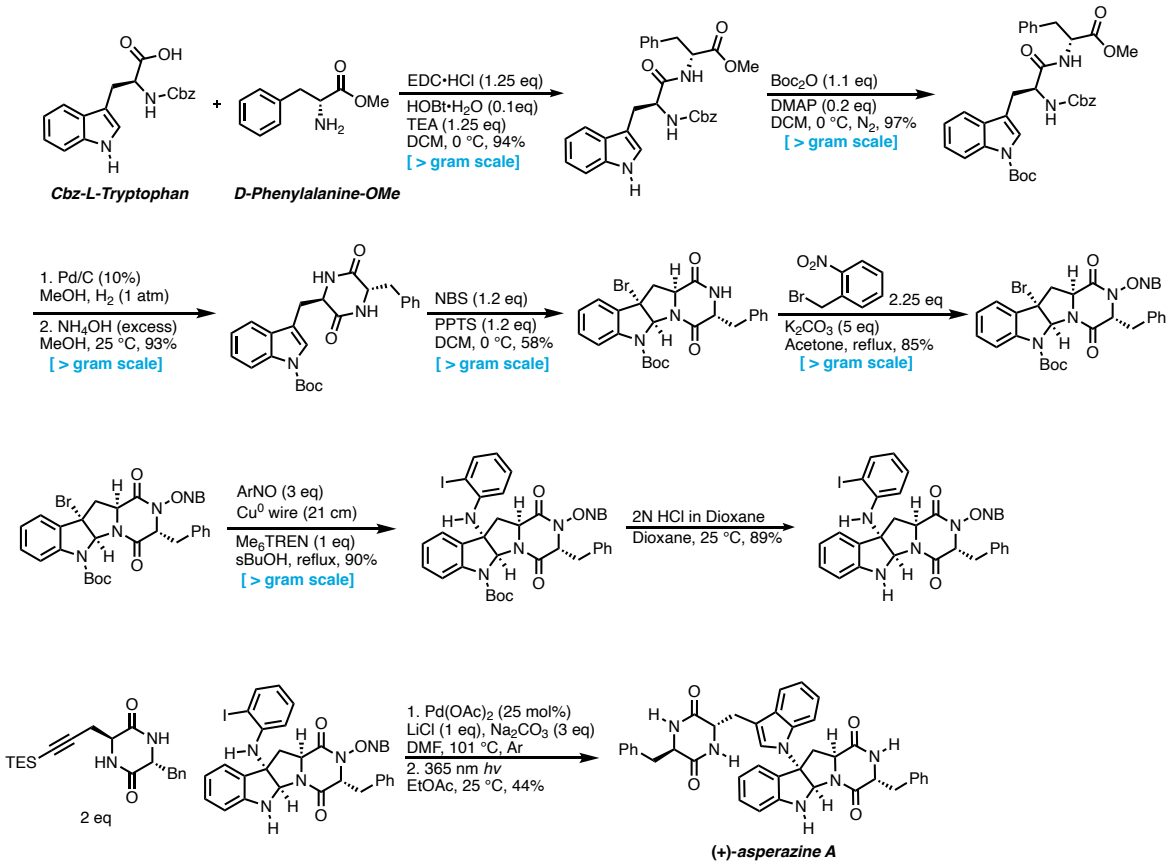


Figure 6.3: Overview of the total synthesis of (+)-asperazine A. ONB = *ortho*-nitrobenzyl

6.5- Mechanistic Investigations

With a thorough demonstration of the scope and synthetic applications completed, attention was moved to investigate the reaction's mechanism. Because an N–O dimer like intermediate was not observed with most substrates, this reaction's mechanism must deviate from that of our previous work in this field. Our first step in probing this proposed mechanism was to verify that we were indeed generating an accessible carbon-centered radical at the C3 position. Replacing nitrosobenzene with TEMPO provided the corresponding TEMPO adduct (**28**) in 82%, a yield similar to those with nitrosobenzene. This observation directly implicates carbon-

centered radical **32** as a mechanistic intermediate. Next, we sought to verify the presence of the intermediate aminoxyl radical. Perpendicular-mode X-band electron paramagnetic resonance (EPR) spectra were collected on a Bruker EMX EPR spectrometer of our reaction running in an EPR tube at 70 °C. The EPR spectrum in Figure 6.4B shows three equal resonances which is consistent with a coupling of a S= ½ spin to a I = 1 spin (^{14}N), typical of the well-studied aminoxyl radical.[39] For definitive evidence of an aminoxyl based radical, the spectrum was simulated and fit using the EasySpin software.[40] The fitting parameters consisted of standard g and A parameters for an aminoxyl radical as a starting point and a Heisenberg exchange constant of 14.4212 MHz.[41] Given that the first two steps of the proposed mechanism were consistent with prior work, we speculated that in the presence of Cu^{II} salts, the aminoxyl radical could become oxidized to an oxoammonium which would then be reduced by the protic solvent to afford the aryl hydroxylamine we observed with compound **24**.[42,43] Reduction of the corresponding hydroxylamine with copper salts and heat would then afford the observed aniline. Due to the transient nature of the proposed oxoammonium intermediate, probing this species directly is difficult, however, related species are known to readily oxidize primary and secondary alcohols under similar conditions. We hypothesized that under our reaction conditions, one equivalent of acetone– relative to our pyrroloindoline starting material– was generated from the oxidation of the 2-propanol solvent. Given the challenges of monitoring the formation of acetone at 80 ºC, we substituted 2-propanol for hexafluoroisopropanol (HFIP) and used F^{19} NMR to monitor the formation of hexafluoroacetone. Taking aliquots of the reaction, hexafluoroacetone was clearly observed by F^{19} NMR, indicating the presence of an oxidizing species in solution. Although indirect, thus supports the presence of the oxoammonium intermediate. Finally, we investigated the role of the hydroxylamine in this

mechanism to answer the question of whether or not this was a mechanistic intermediate. Working up the reaction in Scheme 6.2D at various time points indicated that increasing time yielded a decreasing amount of hydroxylamine with a concomitant increase in the aniline **24** yield. This observation concludes that the hydroxylamine is formed en-route to the desired product **24**.

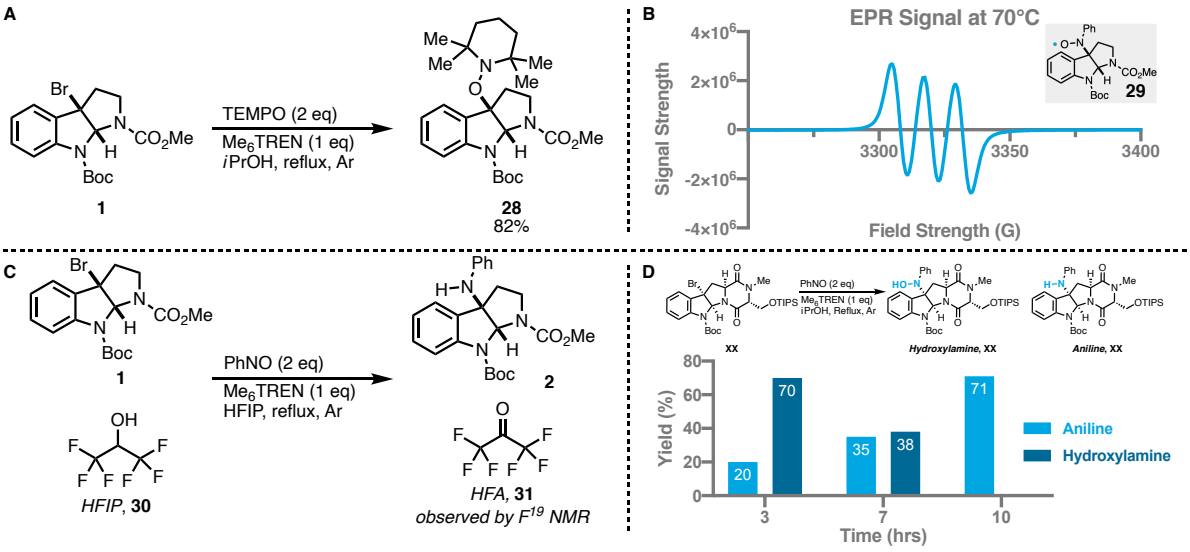
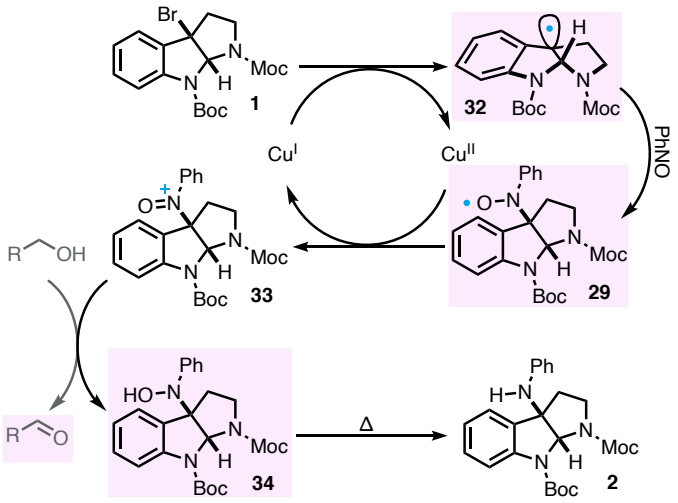


Figure 6.4: Key findings from mechanistic studies

These observations lead us to the proposed mechanism in Scheme 6.4 when the reaction is performed in a primary or secondary alcohol solvent. Cu^{I} salts reduce the C3 carbon-bromine bond on **1** to the corresponding radical **32**, generating Cu^{II} which is subsequently converted to Cu^{I} through the oxidation of the intermediate aminoxyl radical (**29**). Reduction of the formed oxoammonium species (**33**) affords a transient aryl hydroxylamine which is subsequently converted to the desired aniline **2**.[44]



Scheme 6.1: Proposed mechanism in protic solvents. The highlighted intermediates were observed either spectroscopically or by chemical derivatization. Moc = methoxycarbamoyl

6.6- Conclusions

In conclusion, I have developed a single electron-based method for the direct installation of aryl C3–N linkages onto C3-brominated pyrroloindoline and furoindoline scaffolds. By leveraging a single electron pathway, we were able to functionalize our desired scaffolds under mild conditions with a wide range of relevant functionality, regardless of steric or electronic nature of the aryl nitroso derivative. These substrates formed are of interest to the medicinal chemistry and natural product synthesis communities. We have further demonstrated the applicability of this new method with a concise total synthesis of (+)–asperazine A. Through this work, we have pushed for a reaction that uses an earth abundant catalyst (copper metal), green solvents (propanols and butanols) and high yields. Moving forward, we aim investigating the kinetics of the radical formation step and applying this new methodology towards improving the atom economy of our general approach to copper catalyzed carbon–nitrogen bond formation.

6.7- References

(1) Ruiz-Sanchis, P.; Savina, S. A.; Albericio, F.; Álvarez, M. Structure, Bioactivity and Synthesis of Natural Products with Hexahydropyrrolo[2,3-b]Indole. *Chem. – A Eur. J.* **2011**, *17*, 1388–1408. https://doi.org/10.1002/chem.201001451.

(2) Staab, A.; Loeffler, J.; Said, H. M.; Diehlmann, D.; Katzer, A.; Beyer, M.; Fleischer, M.; Schwab, F.; Baier, K.; Einsele, H.; Flentje, M.; Vordermark, D. Effects of HIF-1 Inhibition by Chetomin on Hypoxia-Related Transcription and Radiosensitivity in HT 1080 Human Fibrosarcoma Cells. *BMC Cancer* **2007**, *7*, 213. https://doi.org/10.1186/1471-2407-7-213.

(3) Schallenberger, M. A.; Newhouse, T.; Baran, P. S.; Romesberg, F. E. The Psychotrimine Natural Products Have Antibacterial Activity against Gram-Positive Bacteria and Act via Membrane Disruption. *J. Antibiot. (Tokyo).* **2010**, *63*, 685–687. https://doi.org/10.1038/ja.2010.107.

(4) Espejo, V. R.; Rainier, J. D. An Expeditious Synthesis of C(3)−N(1′) Heterodimeric Indolines. *J. Am. Chem. Soc.* **2008**, *130*, 12894–12895. https://doi.org/10.1021/ja8061908.

(5) Newhouse, T.; Baran, P. S. Total Synthesis of (±)-Psychotrimine. *J. Am. Chem. Soc.* **2008**, *130*, 10886–10887. https://doi.org/10.1021/ja8042307.

(6) Pérez-Balado, C.; de Lera, Á. R. Concise Total Synthesis and Structural Revision of (+)-Pestalazine B. *Org. Biomol. Chem.* **2010**, *8*, 5179–5186. https://doi.org/10.1039/C0OB00531B.

(7) Espejo, V. R.; Rainier, J. D. Total Synthesis of Kapakahine E and F. *Org. Lett.* **2010**, *12*, 2154–2157. https://doi.org/10.1021/ol100672z.

(8) Welch, T. R.; Williams, R. M. Studies on the Biosynthesis of Chetomin: Enantiospecific Synthesis of a Putative, Late-Stage Biosynthetic Intermediate. *Tetrahedron* **2013**, *69*, 770–773. https://doi.org/https://doi.org/10.1016/j.tet.2012.10.075.

(9) Horibe, T.; Ohmura, S.; Ishihara, K. Selenium–Iodine Cooperative Catalyst for Chlorocyclization of Tryptamine Derivatives. *Org. Lett.* **2017**, *19*, 5525–5528. https://doi.org/10.1021/acs.orglett.7b02613.

(10) Gallego, S.; Lorenzo, P.; Alvarez, R.; de Lera, A. R. Total Synthesis of Naturally Occurring (+)-Psychotriasine and the Related Tetrahydro-β-Carboline, Dimeric Tryptamines with NC Connectivities. *Tetrahedron Lett.* **2017**, *58*, 210–212. https://doi.org/https://doi.org/10.1016/j.tetlet.2016.12.003.

(11) Villanueva-Margalef, I.; Thurston, D. E.; Zinzalla, G. Facile Nucleophilic Substitution at the C3a Tertiary Carbon of the 3a-Bromohexahydropyrrolo[2,3-b]Indole Scaffold. *Org. Biomol. Chem.* **2010**, *8*, 5294–5303. https://doi.org/10.1039/C0OB00327A.

(12) Beaumont, S.; Pons, V.; Retailleau, P.; Dodd, R. H.; Dauban, P. Catalytic Oxyamidation of Indoles. *Angew. Chemie Int. Ed.* **2010**, *49*, 1634–1637. https://doi.org/10.1002/anie.200906650.

(13) Nelson, B. M.; Loach, R. P.; Schiesser, S.; Movassaghi, M. Concise Total Synthesis of (+)-Asperazine A and (+)-Pestalazine B. *Org. Biomol. Chem.* **2018**, *16*, 202–207. https://doi.org/10.1039/C7OB02985C.

(14) Lathrop, S. P.; Pompeo, M.; Chang, W.-T. T.; Movassaghi, M. Convergent and Biomimetic Enantioselective Total Synthesis of (−)-Communesin F. *J. Am. Chem. Soc.* **2016**, *138*, 7763–7769. https://doi.org/10.1021/jacs.6b04072.

(15) Lindovska, P.; Movassaghi, M. Concise Synthesis of (−)-Hodgkinsine, (−)-Calycosidine, (−)-Hodgkinsine B, (−)-Quadrigemine C, and (−)-Psycholeine via Convergent and Directed Modular Assembly of Cyclotryptamines. *J. Am. Chem. Soc.* **2017**, *139*, 17590–17596. https://doi.org/10.1021/jacs.7b09929.

(16) Pompeo, M. M.; Cheah, J. H.; Movassaghi, M. Total Synthesis and Anti-Cancer Activity of All Known Communesin Alkaloids and Related Derivatives. *J. Am. Chem. Soc.* **2019**, *141*, 14411–14420. https://doi.org/10.1021/jacs.9b07397.

(17) Fisher, D. J.; Shaum, J. B.; Mills, C. L.; Read de Alaniz, J. Synthesis of Hindered Anilines: Three-Component Coupling of Arylboronic Acids, Tert-Butyl Nitrite, and Alkyl Bromides. *Org. Lett.* **2016**, *18*, 5074–5077. https://doi.org/10.1021/acs.orglett.6b02523.

(18) Fisher, D. J.; Burnett, G. L.; Velasco, R.; Read de Alaniz, J. Synthesis of Hindered α-Amino Carbonyls: Copper-Catalyzed Radical Addition with Nitroso Compounds. *J. Am. Chem. Soc.* **2015**, *137*, 11614–11617. https://doi.org/10.1021/jacs.5b07860.

(19) Shaum, J. B.; Fisher, D. J.; Sroda, M. M.; Limon, L.; Read de Alaniz, J. Direct Introduction of Nitrogen

and Oxygen Functionality with Spatial Control Using Copper Catalysis. *Chem. Sci.* **2018**, *9*, 8748–8752. https://doi.org/10.1039/C8SC03288B.
(20) Voter, A. F.; Tillman, E. S.; Findeis, P. M.; Radzinski, S. C. Synthesis of Macrocyclic Polymers Formed via Intramolecular Radical Trap-Assisted Atom Transfer Radical Coupling. *ACS Macro Lett.* **2012**, *1*, 1066–1070. https://doi.org/10.1021/mz300311p.
(21) Gockel, S. N.; Buchanan, T. L.; Hull, K. L. Cu-Catalyzed Three-Component Carboamination of Alkenes. *J. Am. Chem. Soc.* **2018**, *140*, 58–61. https://doi.org/10.1021/jacs.7b10529.
(22) Doble, M.; Kruthiventi, A. K. CHAPTER 5 - Alternate Solvents; Doble, M., Kruthiventi, A. K. B. T.-G. C. and E., Eds.; Academic Press: Burlington, 2007; pp 93–104. https://doi.org/https://doi.org/10.1016/B978-012372532-5/50006-7.
(23) Gupta, J.; Wilson, B. W.; Vadlani, P. V. Evaluation of Green Solvents for a Sustainable Zein Extraction from Ethanol Industry DDGS. *Biomass and Bioenergy* **2016**, *85*, 313–319. https://doi.org/https://doi.org/10.1016/j.biombioe.2015.12.020.
(24) Zhang, X.; Zhou, X.; Xiao, H.; Li, X. A Catalyst-Free System for 3-Sulfenylation of Free (N–H) Indoles with Mercaptobenzoic Acid under Alkaline Conditions. *RSC Adv.* **2013**, *3*, 22280–22284. https://doi.org/10.1039/C3RA44484H.
(25) Zhou, X.; Li, X. Catalyst-Free System for Sulfenylation of Free (N–H) Indoles with 2,2′-Dithiosalicylic Acid under Alkaline Conditions. *RSC Adv.* **2014**, *4*, 1241–1245. https://doi.org/10.1039/C3RA46361C.
(26) Jang, J.; Nam, Y. T.; Kim, D.; Kim, Y.-J.; Kim, D. W.; Jung, H.-T. Turbostratic Nanoporous Carbon Sheet Membrane for Ultrafast and Selective Nanofiltration in Viscous Green Solvents. *J. Mater. Chem. A* **2020**, *8*, 8292–8299. https://doi.org/10.1039/D0TA00804D.
(27) Matyjaszewski, K. Atom Transfer Radical Polymerization (ATRP): Current Status and Future Perspectives. *Macromolecules* **2012**, *45*, 4015–4039. https://doi.org/10.1021/ma3001719.
(28) Magenau, A. J. D.; Kwak, Y.; Matyjaszewski, K. ATRP of Methacrylates Utilizing CuIIX2/L and Copper Wire. *Macromolecules* **2010**, *43*, 9682–9689. https://doi.org/10.1021/ma102051q.
(29) Boyer, C.; Corrigan, N. A.; Jung, K.; Nguyen, D.; Nguyen, T.-K.; Adnan, N. N. M.; Oliver, S.; Shanmugam, S.; Yeow, J. Copper-Mediated Living Radical Polymerization (Atom Transfer Radical Polymerization and Copper(0) Mediated Polymerization): From Fundamentals to Bioapplications. *Chem. Rev.* **2016**, *116*, 1803–1949. https://doi.org/10.1021/acs.chemrev.5b00396.
(30) Urbani, C. N.; Bell, C. A.; Whittaker, M. R.; Monteiro, M. J. Convergent Synthesis of Second Generation AB-Type Miktoarm Dendrimers Using “Click” Chemistry Catalyzed by Copper Wire. *Macromolecules* **2008**, *41*, 1057–1060. https://doi.org/10.1021/ma702707e.
(31) Newhouse, T.; Lewis, C. A.; Eastman, K. J.; Baran, P. S. Scalable Total Syntheses of N-Linked Tryptamine Dimers by Direct Indole−Aniline Coupling: Psychotrimine and Kapakahines B and F. *J. Am. Chem. Soc.* **2010**, *132*, 7119–7137. https://doi.org/10.1021/ja1009458.
(32) Newhouse, T.; Lewis, C. A.; Baran, P. S. Enantiospecific Total Syntheses of Kapakahines B and F. *J. Am. Chem. Soc.* **2009**, *131*, 6360–6361. https://doi.org/10.1021/ja901573x.
(33) Li, Q.; Xia, T.; Yao, L.; Deng, H.; Liao, X. Enantioselective and Diastereoselective Azo-Coupling/Iminium-Cyclizations: A Unified Strategy for the Total Syntheses of (−)-Psychotriasine and (+)-Pestalazine B. *Chem. Sci.* **2015**, *6*, 3599–3605. https://doi.org/10.1039/C5SC00338E.
(34) Liu, C.; Yi, J.-C.; Zheng, Z.-B.; Tang, Y.; Dai, L.-X.; You, S.-L. Enantioselective Synthesis of 3a-Amino-Pyrroloindolines by Copper-Catalyzed Direct Asymmetric Dearomative Amination of Tryptamines. *Angew. Chemie Int. Ed.* **2016**, *55*, 751–754. https://doi.org/10.1002/anie.201508570.
(35) Xu, J.; Tong, R. An Environmentally Friendly Protocol for Oxidative Halocyclization of Tryptamine and Tryptophol Derivatives. *Green Chem.* **2017**, *19*, 2952–2956. https://doi.org/10.1039/C7GC01341H.
(36) Kim, J.; Movassaghi, M. Concise Total Synthesis and Stereochemical Revision of (+)-Naseseazines A and B: Regioselective Arylative Dimerization of Diketopiperazine Alkaloids. *J. Am. Chem. Soc.* **2011**, *133*, 14940–14943. https://doi.org/10.1021/ja206743v.
(37) Coste, A.; Kim, J.; Adams, T. C.; Movassaghi, M. Concise Total Synthesis of (+)-Bionectins A and C. *Chem. Sci.* **2013**, *4*, 3191–3197. https://doi.org/10.1039/C3SC51150B.
(38) Kim, J.; Ashenhurst, J. A.; Movassaghi, M. Total Synthesis of (+)-11,11'-Dideoxyverticillin A. *Science (80-.).* **2009**, *324*, 238 LP – 241. https://doi.org/10.1126/science.1170777.
(39) Clark, A.; Sedhom, J.; Elajaili, H.; Eaton, G. R.; Eaton, S. S. Dependence of Electron Paramagnetic Resonance Spectral Lineshapes on Molecular Tumbling: Nitroxide Radical in Water:Glycerol Mixtures. *Concepts Magn. Reson. Part A* **2016**, *45A*, e21423. https://doi.org/10.1002/cmr.a.21423.
(40) Stoll, S.; Schweiger, A. EasySpin, a Comprehensive Software Package for Spectral Simulation and

Analysis in EPR. *J. Magn. Reson.* **2006**, *178*, 42–55. https://doi.org/https://doi.org/10.1016/j.jmr.2005.08.013.
(41) Bowman, P. B.; Puett, D. Electron Paramagnetic Resonance Spectroscopy of Nitroxide-Labeled Calmodulin. *Protein J.* **2014**, *33*, 267–277. https://doi.org/10.1007/s10930-014-9559-9.
(42) Walroth, R. C.; Miles, K. C.; Lukens, J. T.; MacMillan, S. N.; Stahl, S. S.; Lancaster, K. M. Electronic Structural Analysis of Copper(II)–TEMPO/ABNO Complexes Provides Evidence for Copper(I)–Oxoammonium Character. *J. Am. Chem. Soc.* **2017**, *139*, 13507–13517. https://doi.org/10.1021/jacs.7b07186.
(43) Badalyan, A.; Stahl, S. S. Cooperative Electrocatalytic Alcohol Oxidation with Electron-Proton-Transfer Mediators. *Nature* **2016**, *535*, 406–410. https://doi.org/10.1038/nature18008.
(44) Zhong, G. Tandem Aminoxylation–Allylation Reactions: A Rapid, Asymmetric Conversion of Aldehydes to Mono-Substituted 1,2-Diols. *Chem. Commun.* **2004**, No. 5, 606–607. https://doi.org/10.1039/B314356B.

7- A Yet Unfinished Total Synthesis of Chetomin

7.1- Introduction

Chetomin (**1**) is a cytotoxic mycotoxin known to occur in three species of the *Chaetomium* genus, and possibly more. Its fascinating structure exists as a diketopiperazine dimer of *D*-tryptophan with *D*-serine with one cyclo-oxidized tryptophan sitting as a pyrroloindoline aminated at the C3 position (indole numbering system). Further, the diketopiperazines moieties each contain an epidithio-bridge, making chetomin a significantly more difficult synthetic target than other diketopiperazine natural products in its class, such as Asperazine A (**1**) and Pestalazine B (**2**). This epidithio bridge, however, has been tackled by synthetic chemists on related natural products, such as chaetocin (**3**), the verticillins, sirodesmins, leptosins, bionectins and gliotoxins.[1]

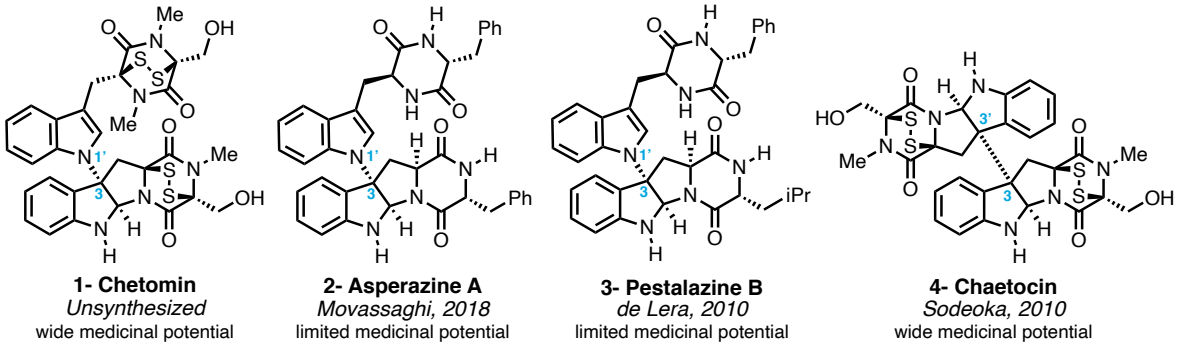


Figure 7.1- Chetomin with a selection of other diketopiperazines. Despite well documented therapeutic potential, chetomin is still isolated from *Chaetomium* extracts.

As discussed in chapter four, chetomin has been known to be antibiotic primarily to gram positive bacteria since 1944.[2] In recent years, its role as a potent HIF1α has been discovered,[3] and studies by William Figg's research group at the NIH indicated that chetomin works by ejecting structurally-required zinc atoms from HIF1α's binding partner p300.[4] Due to this activity against an important transcription factor, chetomin is widely employed in the chemical biology field[5–9] and has been demonstrated as a potent antitumor agent in mouse xenograft studies.[10,11] Chetomin has also demonstrated therapeutic potential in a number of other cancer-related phenotypes.[12–16] Chetomin's disulfide bonds are essential for its activity; thiomethylated equivalents have been demonstrated to have much attenuated activity against both bacterial and cancer cells.[17] Moreover, the scientific community's interest in chetomin is growing, as clearly demonstrated by the increasing cumulative mentions in peer reviewed literature (Figure 7.2).

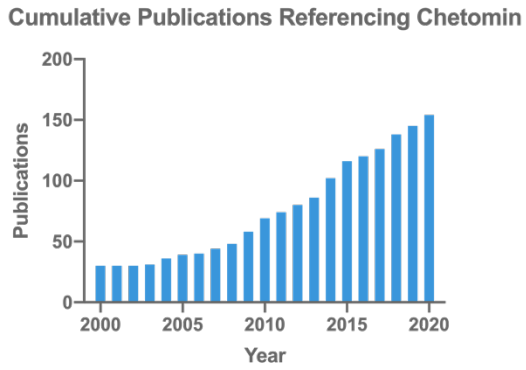


Figure 7.2- Chetomin continues to be employed and studied by the chemical sciences community

Despite the well-documented evidence of therapeutic and clinical potential, we were surprised to see that chetomin has yet to be the subject of a total synthesis. As of 2020, this widely employed molecule is isolated in much the same fashion as it was 80 years ago, *via* extraction from cultured *Chaetomium.* The common price for this natural product is currently hundreds of dollars per milligram, limiting its study and application for lifesaving therapeutics. Given the clear demand, and the unique nature of its chemical structure, we thought chetomin was overdue for a synthetic route.

7.2- Our Proposed Synthesis

Given the Read lab's knowledge and experience with similar natural products, and our robust method for installing the key disconnect in this natural product, we imagined a synthetic route for chetomin would greatly improve its accessibility and medicinal potential. Further, much of chetomin's scaffold can be assembled through robust and high yielding synthetic methods, such as amide couplings, our demonstrated nitroso coupling, and a Larock heteroannulation, which should render a highly scalable synthesis (Figure 7.3). The epidithio bonds can finally be installed with Nicolau's 2012 epidithio methodology.[18]

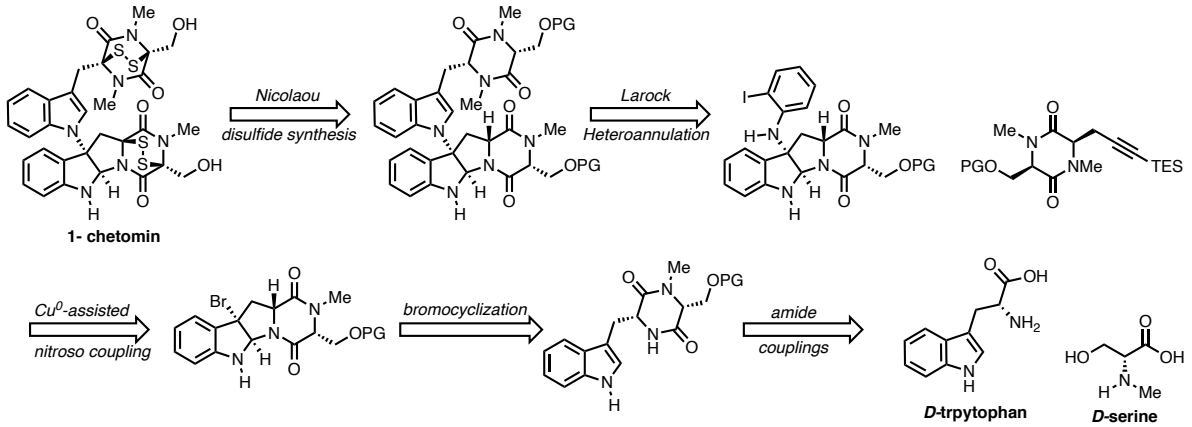


Figure 7.3- Proposed retrosynthesis of chetomin.

We began our synthesis of the chetomin scaffold with an amide coupling of protected *D*-tryptophan (**5**) and *D*-serine (**6**) in 69%. This material was Boc-protected and cyclized to the corresponding diketopiperazine *via* a three-step-one-pot approach to afford **8** in 54% over three steps. Notably, to avoid over acylation on one of substrate **7**'s amide bonds, boc-anhydride was added to the reaction solution in a DCM solution *via* syringe pump over 90 minutes. This approach avoided the over-acylation problem we observed during the asperazine A scaffold synthesis. Oxidative halocyclization afforded bromopyrrolindoline **9** which was methylated to afford key building block **10.**

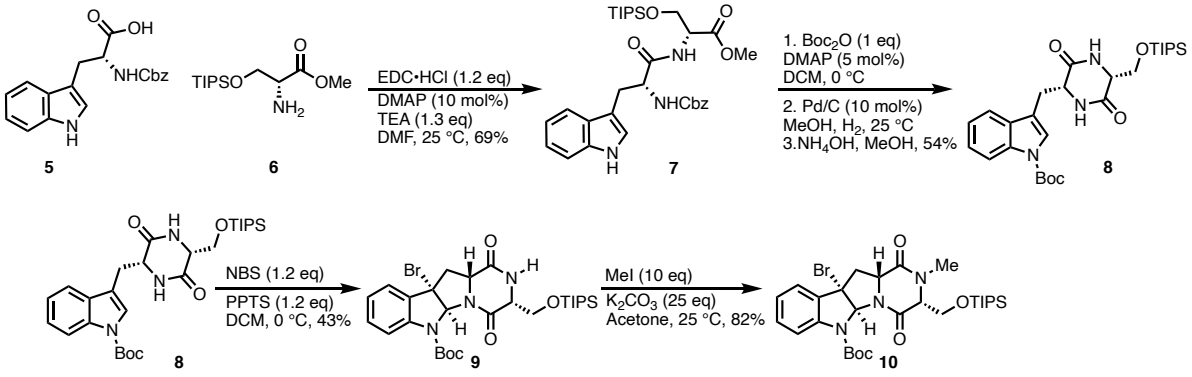


Figure 7.4- Synthesis of the chetomin scaffold from the corresponding *D*-amino acids

Substrate **10** was now set up for our copper-assisted nitroso coupling, the key step in the chetomin total synthesis. A 0.1mmol scale coupling with 2-iodonitrosobenzene, Cu^0 wire and Me_6TREN in 1-propanol afforded the desired product in 74% (Figure 7.5).

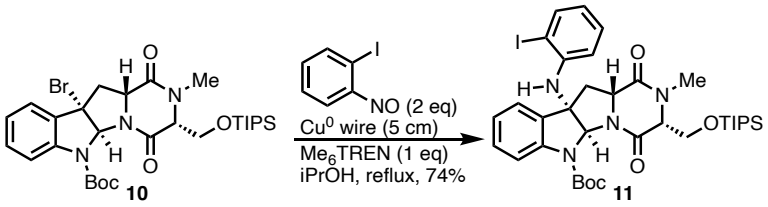


Figure 7.5- The key step in a potential total synthesis of chetomin.

At this point, the key step in the synthesis had been completed, yet much more work had to be done to get this product to chetomin. Unfortunately, due to time constraints, this work was left uncompleted. The rest of the synthesis will be outlined below, as it was planned.

With the key step completed, the next component would be the synthesis of the Larock alkyne coupling partner **16**. As proposed in Scheme 7.4, Knoechel's conditions can be used to create the alkyne **13** from the serine derived alkyl-iodide **12**. This reaction works well at 67% on a 5-gram scale. Next, amide coupling with Cbz-protected *D*-serine affords **14** which can be cyclized through sequential hydrogenation and basification to diketopiperazine **15**. Finally, alkylation with methyl iodide will afford the Larock coupling partner **16**.

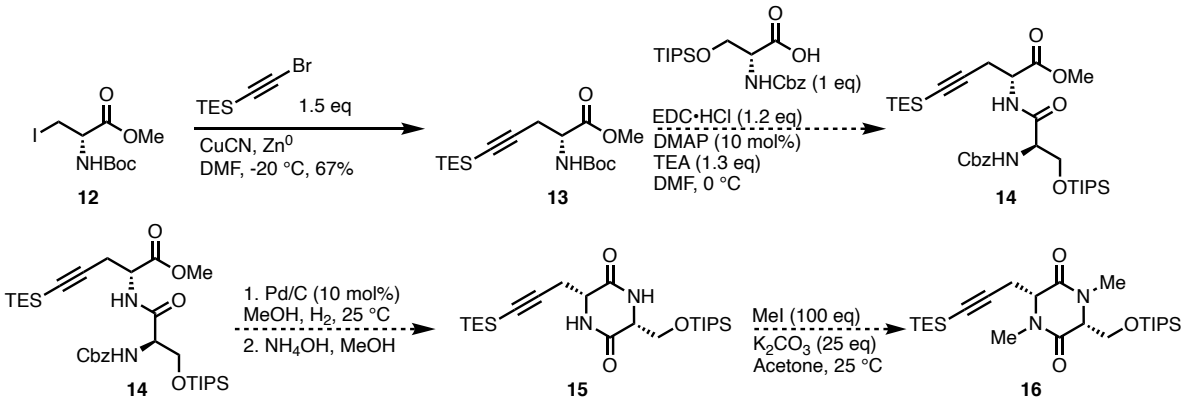


Figure 7.6- The hardest part of the alkyne coupling partner synthesis has already been completed

With alkyne **16** in hand, Larock heteroannulation with **11** can be carried out using the same conditions to afford diketopiperazine dimer **17**. Deprotection of **17** with HCl and TBAF would afford dethio-chetomin **18**, the same intermediate Welch and Williams arrived at in their 2013 synthesis.[19] Finally, we would employ conditions from Nicolaou's epidithio method to complete our synthesis of chetomin[18]

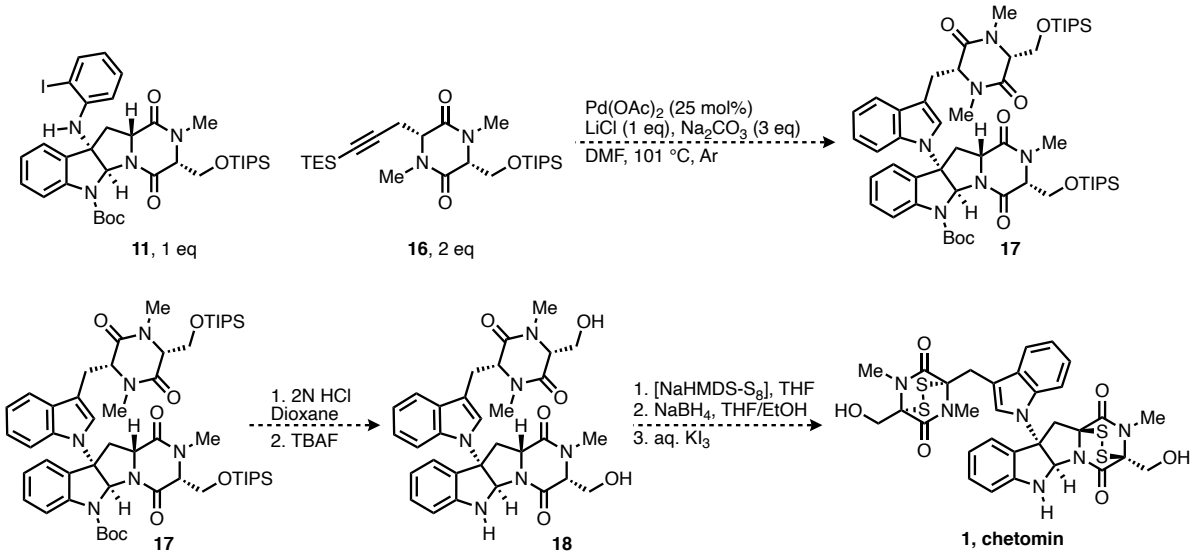


Figure 7.7- A potential late stage synthesis of chetomin

Due to the proven scalability of each step of this method through intermediate **18**, not only should this method prove successful, it should also be able to deliver chetomin on a multiple gram scale. This eight-step synthetic route would lower the cost of chetomin to researchers from hundreds of dollars per milligram and, given more access, could help open up new applications for this unique natural product.

7.3 Conclusion

Chetomin is a power mycotoxin with many biotherapeutic and chemical biological applications. Despite being well studied, it was yet to be synthesized by organic chemists. In this chapter, I propose a concise, convergent, and scalable eight step total synthesis which would provide the first synthetic route towards chetomin.

7.4 References

(1) Kim, J.; Movassaghi, M. Biogenetically-Inspired Total Synthesis of Epidithiodiketopiperazines and Related Alkaloids. *Acc. Chem. Res.* **2015**, *48*, 1159–1171. https://doi.org/10.1021/ar500454v.

(2) Waksman, S. A.; Bugie, E. Chaetomin, a New Antibiotic Substance Produced by Chaetomium Cochliodes: I. Formation and Properties. *J. Bacteriol.* **1944**, *48*, 527–530. https://doi.org/10.1128/JB.48.5.527-530.1944.

(3) Viziteu, E.; Grandmougin, C.; Goldschmidt, H.; Seckinger, A.; Hose, D.; Klein, B.; Moreaux, J. Chetomin, Targeting HIF-1α/P300 Complex, Exhibits Antitumour Activity in Multiple Myeloma. *Br. J. Cancer* **2016**, *114*, 519–523. https://doi.org/10.1038/bjc.2016.20.

(4) Cook, K. M.; Hilton, S. T.; Mecinović, J.; Motherwell, W. B.; Figg, W. D.; Schofield, C. J. Epidithiodiketopiperazines Block the Interaction between Hypoxia-Inducible Factor-1α (HIF-1α) and P300 by a Zinc Ejection Mechanism. *J. Biol. Chem.* **2009**, *284*, 26831–26838. https://doi.org/10.1074/jbc.M109.009498 .

(5) Lourenssen, S. R.; Blennerhassett, M. G. M2 Macrophages and Phenotypic Modulation of Intestinal Smooth Muscle Cells Characterize Inflammatory Stricture Formation in Rats. *Am. J. Pathol.* **2020**, *190*, 1843–1858. https://doi.org/https://doi.org/10.1016/j.ajpath.2020.05.015.

(6) Kovacsics, D.; Brózik, A.; Tihanyi, B.; Matula, Z.; Borsy, A.; Mészáros, N.; Szabó, E.; Németh, E.; Fóthi, Á.; Zámbó, B.; Szüts, D.; Várady, G.; Orbán, T. I.; Apáti, Á.; Sarkadi, B. Precision-Engineered Reporter Cell Lines Reveal ABCG2 Regulation in Live Lung Cancer Cells. *Biochem. Pharmacol.* **2020**, *175*, 113865. https://doi.org/https://doi.org/10.1016/j.bcp.2020.113865.

(7) Brennan, L.; Disatham, J.; Kantorow, M. Hypoxia Regulates the Degradation of Non-Nuclear Organelles during Lens Differentiation through Activation of HIF1a. *Exp. Eye Res.* **2020**, *198*, 108129. https://doi.org/https://doi.org/10.1016/j.exer.2020.108129.

(8) Enikő, B.; Andrea, T.; Gábor, M.; György, T.; György, P.; Viktória, J. Hypoxia Triggers Osteochondrogenic Differentiation of Vascular Smooth Muscle Cells in an HIF-1 (Hypoxia-Inducible Factor 1)–Dependent and Reactive Oxygen Species–Dependent Manner. *Arterioscler. Thromb. Vasc. Biol.* **2019**, *39*, 1088–1099. https://doi.org/10.1161/ATVBAHA.119.312509.

(9) Dongjian, H.; Annet, L.; Abir, Y.; Cláudia, C.; David, K. J.; Arman, G.; Ling, X.; J., M. D.; Peter, van der M.; Margarida, S.; M., A. P.; J., D. I. Metabolic Maturation of Human Pluripotent Stem Cell-Derived Cardiomyocytes by Inhibition of HIF1α and LDHA. *Circ. Res.* **2018**, *123*, 1066–1079. https://doi.org/10.1161/CIRCRESAHA.118.313249.

(10) Kung, A. L.; Zabludoff, S. D.; France, D. S.; Freedman, S. J.; Tanner, E. A.; Vieira, A.; Cornell-Kennon, S.; Lee, J.; Wang, B.; Wang, J.; Memmert, K.; Naegeli, H.-U.; Petersen, F.; Eck, M. J.; Bair, K. W.; Wood, A. W.; Livingston, D. M. Small Molecule Blockade of Transcriptional Coactivation of the Hypoxia-Inducible Factor Pathway. *Cancer Cell* **2004**, *6*, 33–43. https://doi.org/https://doi.org/10.1016/j.ccr.2004.06.009.

(11) Min, S.; Wang, X.; Du, Q.; Gong, H.; Yang, Y.; Wang, T.; Wu, N.; Liu, X.; Li, W.; Zhao, C.; Shen, Y.; Chen, Y.; Wang, X. Chetomin, a Hsp90/HIF1α Pathway Inhibitor, Effectively Targets Lung Cancer

Stem Cells and Non-Stem Cells. *Cancer Biol. Ther.* **2020**, *21*, 698–708. https://doi.org/10.1080/15384047.2020.1763147.

(12) Takahashi, M.; Takemoto, Y.; Shimazu, T.; Kawasaki, H.; Tachibana, M.; Shinkai, Y.; Takagi, M.; Shin-ya, K.; Igarashi, Y.; Ito, A.; Yoshida, M. Inhibition of Histone H3K9 Methyltransferases by Gliotoxin and Related Epipolythiodioxopiperazines. *J. Antibiot. (Tokyo).* **2012**, *65*, 263–265. https://doi.org/10.1038/ja.2012.6.

(13) Dewangan, J.; Srivastava, S.; Mishra, S.; Pandey, P. K.; Divakar, A.; Rath, S. K. Chetomin Induces Apoptosis in Human Triple-Negative Breast Cancer Cells by Promoting Calcium Overload and Mitochondrial Dysfunction. *Biochem. Biophys. Res. Commun.* **2018**, *495*, 1915–1921. https://doi.org/https://doi.org/10.1016/j.bbrc.2017.11.199.

(14) Li, J.; Zhang, Y.; Da Silva Sil Dos Santos, B.; Wang, F.; Ma, Y.; Perez, C.; Yang, Y.; Peng, J.; Cohen, S. M.; Chou, T.-F.; Hilton, S. T.; Deshaies, R. J. Epidithiodiketopiperazines Inhibit Protein Degradation by Targeting Proteasome Deubiquitinase Rpn11. *Cell Chem. Biol.* **2018**, *25*, 1350-1358.e9. https://doi.org/https://doi.org/10.1016/j.chembiol.2018.07.012.

(15) Hiraki, M.; Hwang, S.-Y.; Cao, S.; Ramadhar, T. R.; Byun, S.; Yoon, K. W.; Lee, J. H.; Chu, K.; Gurkar, A. U.; Kolev, V.; Zhang, J.; Namba, T.; Murphy, M. E.; Newman, D. J.; Mandinova, A.; Clardy, J.; Lee, S. W. Small-Molecule Reactivation of Mutant P53 to Wild-Type-like P53 through the P53-Hsp40 Regulatory Axis. *Chem. Biol.* **2015**, *22*, 1206–1216. https://doi.org/https://doi.org/10.1016/j.chembiol.2015.07.016.

(16) Maruotti, J.; Sripathi, S. R.; Bharti, K.; Fuller, J.; Wahlin, K. J.; Ranganathan, V.; Sluch, V. M.; Berlinicke, C. A.; Davis, J.; Kim, C.; Zhao, L.; Wan, J.; Qian, J.; Corneo, B.; Temple, S.; Dubey, R.; Olenyuk, B. Z.; Bhutto, I.; Lutty, G. A.; Zack, D. J. Small-Molecule–Directed, Efficient Generation of Retinal Pigment Epithelium from Human Pluripotent Stem Cells. *Proc. Natl. Acad. Sci.* **2015**, *112*, 10950 LP – 10955. https://doi.org/10.1073/pnas.1422818112.

(17) Tantapakul, C.; Promgool, T.; Kanokmedhakul, K.; Soytong, K.; Song, J.; Hadsadee, S.; Jungsuttiwong, S.; Kanokmedhakul, S. Bioactive Xanthoquinodins and Epipolythiodioxopiperazines from Chaetomium Globosum 7s-1, an Endophytic Fungus Isolated from Rhapis Cochinchinensis (Lour.) Mart. *Nat. Prod. Res.* **2020**, *34*, 494–502. https://doi.org/10.1080/14786419.2018.1489392.

(18) Nicolaou, K. C.; Lu, M.; Totokotsopoulos, S.; Heretsch, P.; Giguère, D.; Sun, Y.-P.; Sarlah, D.; Nguyen, T. H.; Wolf, I. C.; Smee, D. F.; Day, C. W.; Bopp, S.; Winzeler, E. A. Synthesis and Biological Evaluation of Epidithio-, Epitetrathio-, and Bis-(Methylthio)Diketopiperazines: Synthetic Methodology, Enantioselective Total Synthesis of Epicoccin G, 8,8′-Epi-Ent-Rostratin B, Gliotoxin, Gliotoxin G, Emethallicin E, and Haematocin and Discovery of New Antiviral and Antimalarial Agents. *J. Am. Chem. Soc.* **2012**, *134*, 17320–17332. https://doi.org/10.1021/ja308429f.

(19) Welch, T. R.; Williams, R. M. Studies on the Biosynthesis of Chetomin: Enantiospecific Synthesis of a Putative, Late-Stage Biosynthetic Intermediate. *Tetrahedron* **2013**, *69*, 770–773. https://doi.org/https://doi.org/10.1016/j.tet.2012.10.075.

8- Supporting Information for Chapter 2: Three-Component Coupling of Arylboronic Acids, *tert*-Butyl Nitrite, and Alkyl Bromides

Materials and Methods Unless stated otherwise, reactions were conducted in flame dried glassware under an atmosphere of N_2 using reagent grade solvents. All commercially obtained reagents were used as received. Reaction temperatures were controlled using a Heidolph temperature modulator, and unless stated otherwise, reactions were performed at room temperature (rt, approximately 23 °C). Thin-layer chromatography (TLC) was conducted with E. Merck silica gel 60 F254 pre-coated plates, (0.25 mm) and visualized by exposure to UV light (254 nm) or stained with potassium permanganate or anisaldehyde. Flash column chromatography was performed using normal phase silica gel (60 Å, 230-240 mesh, Geduran®). ^{1}H NMR spectra were recorded on Varian Spectrometers (at 400, 500 and 600 MHz) and are reported relative to deuterated solvent signals. Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz) and integration. ^{13}C NMR spectra were recorded on Varian Spectrometers (at 100, 125 and 150 MHz). Data for ^{13}C NMR spectra are reported in terms of chemical shift. IR spectra were recorded on a Perkin Elmer Spectrum 100 FT/IR and a Bruker Alpha FT/IR and are reported in terms of frequency of absorption (cm^{-1}). High resolution mass spectra were obtained from the UC Santa Barbara Mass Spectrometry Facility and the Materials Research Laboratory Polymer Characterization Facility at UC Santa Barbara.

Starting materials **S1** was prepared according to literature procedure and **S14–S18** using a modified procedure.[1] Starting materials **S2–S7** were prepared according to a literature

procedure using a modified procedure.[2] Nitrosoarenes **S19**–**S22** were prepared according to modified literature procedures.[3,4]

General Procedure A for N–O Heterocycles (5-6 membered rings)

To a 25 mL oven dried round bottom flask is added CuBr (28 mg, 0.2 mmol, 2 eq) and PMDTA (52 μL, 0.25 mmol, 2.5 eq) in THF (anhydrous, 7 mL). This suspension is sonicated for one minute and sparged with nitrogen for seven minutes. A second solution of nitrosobenzene (16 mg, 0.15 mmol, 1.5 eq) and dibromide (0.1 mmol, 1 eq) is prepared in THF (anhydrous, 3 mL) in a 10 mL conical flask. This solution is sparged with nitrogen for three minutes. The copper suspension is stirred at 50 °C under nitrogen while the nitroso solution is added dropwise to the copper suspension via syringe pump over ten hours. Upon completion of addition, the reaction is allowed to continue stirring under nitrogen for an additional six hours.

The solution is concentrated *in vacuo* and reconstituted in DCM (10 mL). The DCM solution is washed with EDTA (0.5 M, pH 8, 20 mL) and extracted with DCM (3 x 15 mL). The organic layers are combined and sequentially dried with brine (20 mL) and sodium sulfate. The crude product was dry loaded onto Celite and purified via flash chromatography with an increasing gradient of DCM in hexane (0 —> 35%). Diastereomeric ratio was determined from the crude ^{1}H NMR.

General Procedure B for N–O Heterocycles (7 membered rings)

To a 100 mL oven dried round bottom flask is added CuBr (28 mg, 0.2 mmol, 2 eq) and PMDTA (52 μL, 0.25 mmol, 2.5 eq) in THF (anhydrous, 30 mL). This suspension is sonicated for one minute and sparged with nitrogen for thirty minutes. A second solution of nitrosobenzene (16 mg, 0.15 mmol, 1.5 eq) and dibromide (0.1 mmol, 1 eq) is prepared in THF (anhydrous, 10 mL) in a 10 mL conical flask. This solution is sparged with nitrogen for ten minutes. The copper suspension is stirred at 50 °C under nitrogen while the nitroso solution is added dropwise to the copper suspension via syringe pump over ten hours. Upon completion of addition, the reaction is allowed to continue stirring under nitrogen for an additional six hours.

The solution is concentrated *in vacuo* and reconstituted in DCM (10 mL). The DCM solution is washed with EDTA (0.5 M, pH 8, 20 mL) and extracted with DCM (3 x 15 mL). The organic layers are combined and sequentially dried with brine (20 mL) and sodium sulfate. The crude product was dry loaded onto Celite and purified via flash chromatography with an increasing gradient of DCM in hexane (0 —> 35%). Diastereomeric ratio was determined from the crude ^{1}H NMR.

General Procedure C for N–O Heterocycles (8 membered ring)

To a 100 mL oven dried round bottom flask is added CuBr (28 mg, 0.2 mmol, 2 eq), $CuBr_2$ (4 mg, 0.02 mmol, 10 mol% relative to CuBr) and PMDTA (52 μL, 0.25 mmol, 2.5 eq) in THF (anhydrous, 30 mL). This suspension is sonicated for one minute and sparged with nitrogen for thirty minutes. A second solution of nitrosobenzene (16 mg, 0.15 mmol, 1.5 eq) and

dibromide (0.1 mmol, 1 eq) is prepared in THF (anhydrous, 10 mL) in a 10 mL conical flask. This solution is sparged with nitrogen for ten minutes. The copper suspension is stirred at 50 °C under nitrogen while the nitroso solution is added dropwise to the copper suspension via syringe pump over ten hours. Upon completion of addition, the reaction is allowed to continue stirring under nitrogen for an additional six hours.

The solution is concentrated *in vacuo* and reconstituted in DCM (10 mL). The DCM solution is washed with EDTA (0.5 M, pH 8, 20 mL) and extracted with DCM (3 x 15 mL). The organic layers are combined and sequentially dried with brine (20 mL) and sodium sulfate. The crude product was dry loaded onto Celite and purified via flash chromatography with an increasing gradient of DCM in hexane (0 —> 35%). Diastereomeric ratio was determined from the crude ^{1}H NMR.

General Procedure D for N–O Heterocycles (9+ membered rings)

To a 100 mL oven dried round bottom flask is added CuBr (28 mg, 0.2 mmol, 2 eq), $CuBr_2$ (4 mg, 0.02 mmol, 10 mol% relative to CuBr) and PMDTA (52 μL, 0.25 mmol, 2.5 eq) in THF (anhydrous, 30 mL). This suspension is sonicated for one minute and sparged with nitrogen for thirty minutes. A second solution of nitrosobenzene (16 mg, 0.15 mmol, 1.5 eq) and dibromide (0.1 mmol, 1 eq) is prepared in THF (anhydrous, 10 mL) in a 10 mL conical flask. This solution is sparged with nitrogen for ten minutes. The copper suspension is stirred at 50 °C under nitrogen while the nitroso solution is added dropwise to the copper suspension via syringe pump over ten hours. Upon completion of addition, the reaction is allowed to continue stirring under nitrogen for an additional eight hours.

The solution is concentrated *in vacuo* and reconstituted in DCM (10 mL). The DCM solution is washed with EDTA (0.5 M, pH 8, 20 mL) and extracted with DCM (3 x 15 mL). The organic layers are combined and sequentially dried with brine (20 mL) and sodium sulfate. The crude solution is loaded onto a prep TLC plate and purified with an isocratic mobile phase of 3:7 DCM:Hexane. Diastereomeric ratio was determined from the crude ^{1}H NMR.

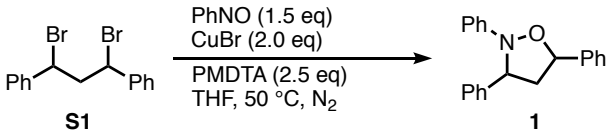
General Procedure for N–O Bond Reduction *via* Zn/HCl

A 1-dram vial containing the resulting crude N–O alkylated adduct and a stir bar was charged with activated Zn^{0} (130 mg, 2 mmol, 20 equiv) and 4:1 solution of 1.5 M HCl and THF (1.5 mL) and heated to 60 °C. The solution was stirred until consumption of the starting material was observed by TLC, upon which the crude reaction mixture was quenched with an aqueous solution of saturated $NaHCO_3$ (20 mL). The resulting precipitate was removed through vacuum filtration and the filtrate was extracted with EtOAc (3x 15 mL). The combined organic layers were washed with water (1x 15 mL) and once with brine (1x 15 mL) and then dried over sodium sulfate. The crude product was dry loaded onto Celite and purified via flash chromatography with an increasing gradient of DCM in hexane (0 —> 50%)

General Procedure for N–O Bond Reduction *via* Sodium Naphthalenide

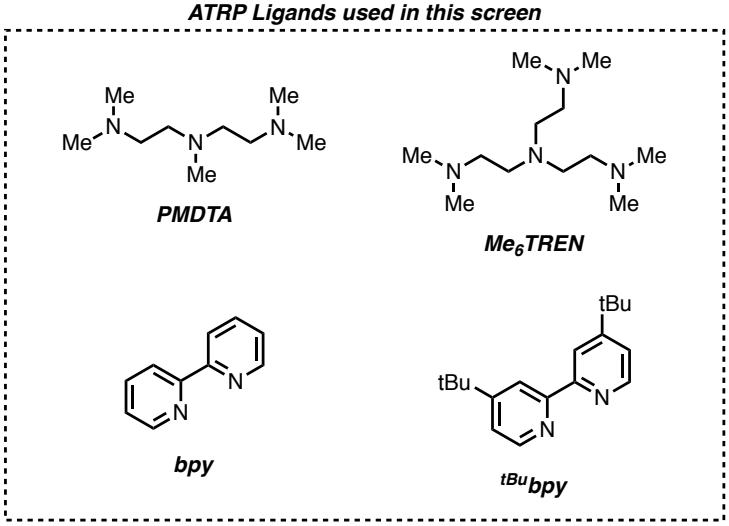
A 500 mM solution of Sodium Naphthalenide was freshly prepared in THF while the substrate to be reduced was dissolved in 1 mL of THF in a 1-dram vial and briefly degassed with N_2. The napthalenide was titrated slowly until the substrate solution remained dark green. After three minutes, the reaction was quenched with isopropanol (~5 mL), washed with saturated

sodium bicarbonate (10 mL) and extracted with ethyl acetate (2 x 10 mL). Organic layers were combined and dried sequentially with brine (10 mL) and sodium sulfate. The crude product was dry loaded onto Celite and purified via flash chromatography with an increasing gradient of DCM in hexane (0 —> 50%).



entry	deviation from conditions	temp (°C)	result
1	5 eq CuBr, 5 eq Cu^0, 2 eq PhNO	40	70%
2	5 eq Cu^0, 5 eq PhNO	40	46%
3	5 eq CuBr, 1 eq PhNO	40	66%
4	5 eq CuBr, 2 eq PhNO	40	80%
5	5 eq CuBr, 1.5 eq PhNO	40	85%
6	None	40	84%
7	1.5 eq CuBr, 1.5 eq PhNO	40	75%
8	**None**	**50**	**85%**
9	MeCN as solvent	40	66%
10	DMF as solvent	40	61%
11	2.5 eq Me_6TREN	40	82%
12	2.5 eq bpy	40	>1%
13	2.5 eq ^{tBu}bpy	40	>1%

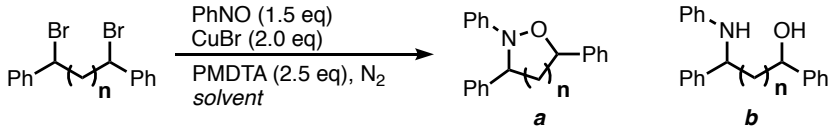
ATRP Ligands used in this screen



Relevant Optimization Data

Table S1: Relevant heterocycle synthesis optimization data

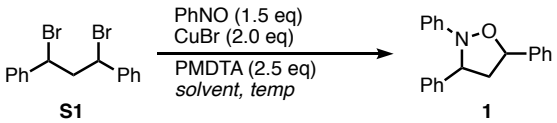
Table S2: Relevant data from the two-step-one-pot optimization



entry	deviation from conditions	n	a	b
1	THF, 50 °C, 18 hr	1	85%	0%
2	EtOH, 50 °C, 18 hr	1	42%	36%
3	EtOH, 50 °C, 48 hr	1	12%	68%
4	EtOH, 50 °C, 4 eq CuBr, 38 hr	1	0%	71%
5	EtOH, reflux, 2 eq CuBr, 14 hr	1	0%	73%
6	EtOH, reflux, 1 eq CuBr, 14 hr	1	0%	68%
7	EtOH, reflux, 2 eq CuBr, 14 hr	2	56%	0%
8	EtOH, reflux, 2 eq CuBr, 14 hr	3	43%	0%
9	THF, 50 °C, 16 hr; then 2 eq AscOH, excess Cu^0 in 1.5 mL MeCN, 80 °C, 14 hr	1	0%	65%
10	DMF, 40 °C, excess Cu^0, 16 hr; then 5 eq AscOH, DMF, 80 °C, 24 hr	1	6%	61%
11	MeCN, 40 °C, 16 hr; then 5 eq AscOH, 2 eq Cu^0, 80°C, 8hr	1	0%	64%
12	MeCN, 40 °C, 16 hr; then 5 eq AscOH, 2 eq Cu^0, 80°C, 8hr	2	35%	0%
13	MeCN, 40 °C, 16 hr; then 5 eq AscOH, 2 eq Cu^0, 80°C, 8hr	3	51%	0%
13	MeCN, 40 °C, 16 hr; then 5 eq AscOH, 2 eq Cu^0, 80°C, 8hr	4	24%	0%

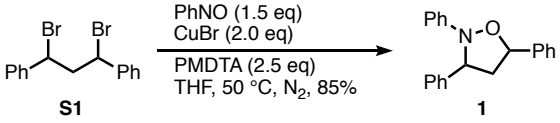
Table S3:

Temperature and solvent effects on diastereoselectivity



entry	solvent	temp (°C)	dr of product
1	MeCN	40	1.5:1
2	THF	40	4:1
3	THF	50	5:1

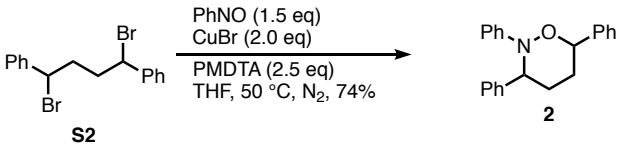
Experimental Procedures and Data:



2,3,5-triphenylisoxazolidine (1): To a 25 mL oven dried round bottom flask is added CuBr (28 mg, 0.2 mmol, 2 eq) and PMDTA (52 µL, 0.25 mmol, 2.5 eq) in THF (anhydrous, 7 mL).

This suspension is sonicated for one minute and sparged with nitrogen for seven minutes. A second solution of nitrosobenzene (16 mg, 0.15 mmol, 1.5 eq) and dibromide **S1** (35 mg, 0.1 mmol, 1 eq, 1.1:1 mix of diastereomers) is prepared in THF (anhydrous, 3 mL) in a 10 mL conical flask. This solution is sparged with nitrogen for three minutes. The copper suspension is stirred at 50 °C under nitrogen while the nitroso solution is added dropwise to the copper suspension via syringe pump over ten hours. Upon completion of addition, the reaction is allowed to continue stirring under nitrogen for an additional six hours.

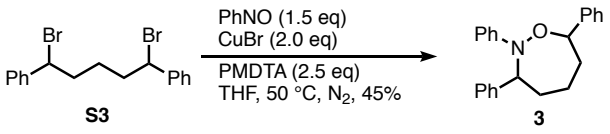
The solution is concentrated *in vacuo* and reconstituted in DCM (10 mL). The DCM solution is washed with EDTA (0.5 M, pH 8, 20 mL) and extracted with DCM (3 x 15 mL). The organic layers are combined and sequentially dried with brine (20 mL) and sodium sulfate. The crude product was dry loaded onto Celite and purified via flash chromatography with an increasing gradient of DCM in hexane (0 —> 35%) to afford **1** as a clear oil and a 5:1 mix of diastereomers (26 mg, 85%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.62 – 7.53 (m, 2H), 7.45 (d, *J* = 8.1 Hz, 2H), 7.43 – 7.17 (m, 8H), 7.13 – 6.91 (m, 3H), 5.38 (dd, *J* = 9.0, 6.5 Hz, 1H minor), 5.20 (dd, *J* = 10.1, 5.7 Hz, 1H major), 4.94 (t, *J* = 7.9 Hz, 1H major), 4.70 (dd, *J* = 9.1, 4.6 Hz, 1H minor), 3.20 (ddd, *J* = 12.2, 8.0, 5.7 Hz, 1H major), 2.81 (dt, *J* = 12.2, 9.0 Hz, 1H minor), 2.69 (ddd, *J* = 12.3, 6.6, 4.6 Hz, 1H minor), 2.50 (ddd, *J* = 12.2, 10.2, 7.8 Hz, 1H major); ^{13}C NMR (125 MHz, Chloroform-*d*) δ 152.6, 142.9, 137.9, 129.0, 128.9, 128.8, 128.6, 128.6, 128.3, 128.2, 127.6, 127.4, 126.9, 126.8, 126.8, 126.3, 121.9, 121.4, 115.9, 114.0, 80.6, 78.8, 71.6, 69.8, 48.8, 47.3; IR (thin film) 3061, 3029, 2940, 2878, 1596, 1487, 1451, 1248, 1026, 753, 696 cm $^{-1}$; HRMS (ESI), calculated for $C_{21}H_{19}NO$: ($M+Na^{+}$) 324.1364, observed 324.1369. [56]



2,3,6-triphenyl-1,2-oxazinane (**2**): To a 25 mL oven dried round bottom flask is added CuBr (28 mg, 0.2 mmol, 2 eq) and PMDTA (52 µL, 0.25 mmol, 2.5 eq) in THF (anhydrous, 7 mL). This suspension is sonicated for one minute and sparged with nitrogen for seven minutes. A second solution of nitrosobenzene (16 mg, 0.15 mmol, 1.5 eq) and dibromide **S2** (37 mg, 0.1 mmol, 1 eq) is prepared in THF (anhydrous, 3 mL) in a 10 mL conical flask. This solution is sparged with nitrogen for three minutes. The copper suspension is stirred at 50 °C under nitrogen while the nitroso solution is added dropwise to the copper suspension via syringe pump over ten hours. Upon completion of addition, the reaction is allowed to continue stirring under nitrogen for an additional six hours.

The solution is concentrated *in vacuo* and reconstituted in DCM (10 mL). The DCM solution is washed with EDTA (0.5 M, pH 8, 20 mL) and extracted with DCM (3 x 15 mL). The organic layers are combined and sequentially dried with brine (20 mL) and sodium sulfate. The crude product was dry loaded onto Celite and purified via flash chromatography with an increasing gradient of DCM in hexane (0 —> 50%) to afford **2** as a clear oil with a 1.8:1 mix of diastereomers (23 mg, 74%). *trans (minor) isomer:* ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.44 (d, *J* = 7.0 Hz, 2H), 7.35 (t, *J* = 7.4 Hz, 2H), 7.33 – 7.04 (m, 10H), 6.98 (d, *J* = 9.2 Hz, 1H), 5.19 (dd, *J* = 11.2, 2.3 Hz, 1H), 4.17 (dd, *J* = 11.2, 2.8 Hz, 1H), 2.45 – 2.30 (m, 1H), 2.23 – 2.10 (m, 2H), 2.04 – 1.92 (m, 1H); ^{13}C NMR (125 MHz, Chloroform-*d*) δ 149.8, 141.3, 141.1, 128.3, 128.3, 128.2, 128.0, 127.7, 127.4, 126.4, 125.6, 124.0, 81.4, 77.4, 77.1, 76.9, 76.8, 69.9, 33.8, 32.5; IR (thin film) 3052, 3020, 2909, 2840, 1529, 1484, 1447, 1059, 745, 692; HRMS

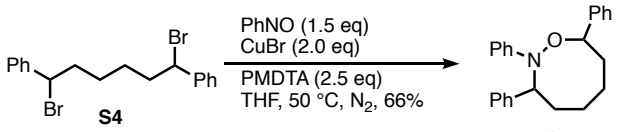
(ESI), calculated for $C_{22}H_{21}NO$: ($M+H^+$) 316.1701, observed 316.1723. *cis (major) isomer*: ^1H NMR (500 MHz, Chloroform-*d*) δ 7.56 (d, *J* = 7.4 Hz, 2H), 7.47 – 7.24 (m, 7H), 7.20 (t, *J* = 7.4 Hz, 3H), 7.03 (d, *J* = 8.2 Hz, 2H), 6.82 (t, *J* = 7.3, 1.1 Hz, 1H), 5.15 (dd, *J* = 5.5, 2.5 Hz, 1H), 5.05 (dd, *J* = 11.2, 2.7 Hz, 1H), 2.54 (tt, *J* = 13.1, 5.1 Hz, 1H), 2.31 – 2.23 (m, 1H), 2.01 – 1.91 (m, 1H), 1.83 (ddt, *J* = 13.5, 4.3, 3.0 Hz, 1H); ^{13}C NMR (125 MHz, Chloroform-*d*) δ 148.9, 140.7, 140.3, 128.9, 128.4, 128.3, 128.1, 128.0, 126.6, 126.4, 120.2, 114.2, 80.5, 58.7, 30.0, 29.7, 27.3; IR (thin film) 3019, 2913, 1591, 1486, 1445, 1215, 1028, 936, 747; HRMS (ESI), calculated for $C_{22}H_{21}NO$: ($M+H^+$) 316.1701, observed 316.1723.



2,3,7-triphenyl-1,2-oxazepane (**3**): To a 100 mL oven dried round bottom flask is added CuBr (28 mg, 0.2 mmol, 2 eq) and PMDTA (52 µL, 0.25 mmol, 2.5 eq) in THF (anhydrous, 30 mL). This suspension is sonicated for one minute and sparged with nitrogen for thirty minutes. A second solution of nitrosobenzene (16 mg, 0.15 mmol, 1.5 eq) and dibromide **S3** (38 mg, 0.1 mmol, 1 eq) is prepared in THF (anhydrous, 10 mL) in a 10 mL conical flask. This solution is sparged with nitrogen for ten minutes. The copper suspension is stirred at 50 °C under nitrogen while the nitroso solution is added dropwise to the copper suspension via syringe pump over ten hours. Upon completion of addition, the reaction is allowed to continue stirring under nitrogen for an additional six hours.

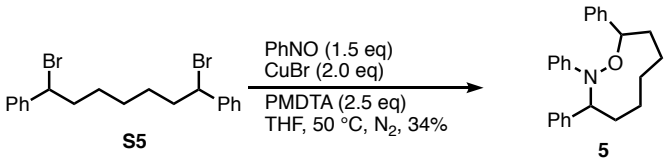
The solution is concentrated *in vacuo* and reconstituted in DCM (10 mL). The DCM solution is washed with EDTA (0.5 M, pH 8, 20 mL) and extracted with DCM (3 x 15 mL). The organic

layers are combined and sequentially dried with brine (20 mL) and sodium sulfate. The crude product was dry loaded onto Celite and purified via flash chromatography with an increasing gradient of DCM in hexane (0 —> 50%) to afford **3** as a clear oil with a 1.5:1 mix of diastereomers (14 mg, 45%) ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.53 – 7.30 (m, 8H), 7.25 – 7.00 (m, 4H), 6.84 – 6.62 (m, 3H), 5.27 – 4.91 (m, 1H), 4.86 – 4.73 (m, 1H), 2.73 – 2.61 (m, 1H), 2.51 – 2.39 (m, 1H), 2.21 – 1.82 (m, 3H), 1.76 – 1.64 (m, 1H); ^{13}C NMR (125 MHz, Chloroform-*d*) δ 148.8, 142.8, 141.5, 128.7, 128.5, 128.4, 128.4, 128.3, 128.3, 127.6, 127.5, 127.4, 127.0, 126.9, 126.6, 126.3, 121.3, 119.1, 116.9, 113.5, 90.7, 88.6, 69.8, 66.4, 40.1, 38.2, 37.5, 36.3, 24.7, 20.9; IR (thin film) 3060, 3072, 2931, 2858, 1597, 1490, 1449, 748, 697 cm^{-1}; HRMS (ESI), calculated for $C_{23}H_{23}NO$: ($M+H^{+}$) 330.1858, observed 330.1859.



2,3,8-triphenyl-1,2-oxazocane (**4**): To a 100 mL oven dried round bottom flask is added CuBr (28 mg, 0.2 mmol, 2 eq), $CuBr_2$ (4 mg, 0.02 mmol, 10 mol% relative to CuBr) and PMDTA (52 µL, 0.25 mmol, 2.5 eq) in THF (anhydrous, 30 mL). This suspension is sonicated for one minute and sparged with nitrogen for thirty minutes. A second solution of nitrosobenzene (16 mg, 0.15 mmol, 1.5 eq) and dibromide **S4** (40 mg, 0.1 mmol, 1 eq) is prepared in THF (anhydrous, 10 mL) in a 10 mL conical flask. This solution is sparged with nitrogen for ten minutes. The copper suspension is stirred at 50 °C under nitrogen while the nitroso solution is added dropwise to the copper suspension via syringe pump over ten hours. Upon completion of addition, the reaction is allowed to continue stirring under nitrogen for an additional six hours.

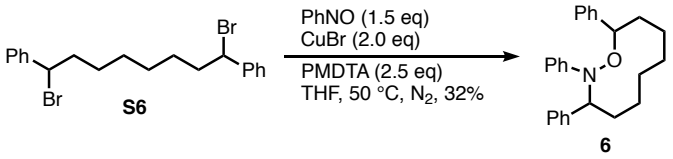
The solution is concentrated *in vacuo* and reconstituted in DCM (10 mL). The DCM solution is washed with EDTA (0.5 M, pH 8, 20 mL) and extracted with DCM (3 x 15 mL). The organic layers are combined and sequentially dried with brine (20 mL) and sodium sulfate. The crude product was dry loaded onto Celite and purified via flash chromatography with an increasing gradient of DCM in hexane (0 —> 35%) to afford **4** as a clear oil with a 1.1:1 mix of diastereomers (22.5 mg, 66%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.49 (d, *J* = 8.7 Hz, 2H), 7.42 (t, *J* = 7.7 Hz, 2H), 7.33 (d, *J* = 11.4 Hz, 3H), 7.15 (t, *J* = 7.0 Hz, 2H), 7.12 – 7.05 (m, 3H), 6.90 (d, *J* = 7.7 Hz, 2H), 6.73 (t, *J* = 7.0 Hz, 1H), 4.88 (dd, *J* = 6.7, 3.9 Hz, 1H), 4.71 (dd, *J* = 11.7, 3.8 Hz, 1H), 2.63 (q, *J* = 12.8 Hz, 1H), 2.29 (ddd, *J* = 14.8, 10.3, 3.8 Hz, 1H), 2.06 – 1.89 (m, 4H), 1.83 – 1.66 (m, 2H); ^{13}C NMR (125 MHz, Chloroform-*d*) δ 149.8, 141.9, 141.7, 128.6, 128.2, 127.9, 127.9, 127.3, 126.6, 126.5, 120.4, 116.0, 82.0, 70.2, 35.5, 33.4, 27.8, 23.6; IR (thin film) 3085, 3027, 2922, 2853, 1597, 1489, 1449, 1359, 755, 696 cm $^{-1}$; HRMS (ESI), calculated for $C_{24}H_{25}NO$: ($M+H^{+}$) 344.2014, observed 344.2022.



2,3,9-triphenyl-1,2-oxazonane (**5**): To a 100 mL oven dried round bottom flask is added CuBr (28 mg, 0.2 mmol, 2 eq) and PMDTA (52 µL, 0.25 mmol, 2.5 eq) in THF (anhydrous, 7 mL). This suspension is sonicated for one minute and sparged with nitrogen for seven minutes. A second solution of nitrosobenzene (16 mg, 0.15 mmol, 1.5 eq) and dibromide **S5** (41 mg, 0.1 mmol, 1 eq) is prepared in THF (anhydrous, 3 mL) in a 10 mL conical flask. This solution is sparged with nitrogen for three minutes. The copper suspension is stirred at 50 °C under nitrogen while the nitroso solution is added dropwise to the copper suspension via syringe

pump over ten hours. Upon completion of addition, the reaction is allowed to continue stirring under nitrogen for an additional eight hours.

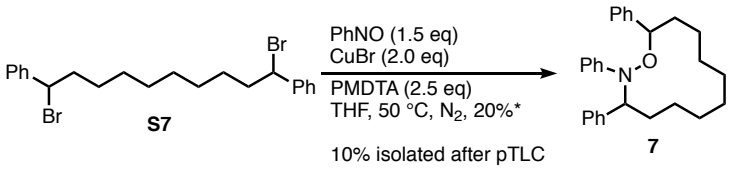
The solution is concentrated *in vacuo* and reconstituted in DCM (10 mL). The DCM solution is washed with EDTA (0.5 M, pH 8, 20 mL) and extracted with DCM (3 x 15 mL). The organic layers are combined and sequentially dried with brine (20 mL) and sodium sulfate. The crude solution is loaded onto a prep TLC plate and purified with an isocratic mobile phase of 3:7 DCM:Hexane to afford **5** as a clear oil with a 1.1:1 mix of diasteroemers (12 mg, 34%). *Major Diastereomer* **5a** ^{1}H NMR (500 MHz, Chloroform-*d*, 50 °C) δ 7.41 (d, *J* = 7.6 Hz, 2H), 7.36 (t, *J* = 7.9, 7.4 Hz, 2H), 7.31 – 7.23 (m, 1H), 7.22 – 7.18 (m, 2H), 7.17 – 7.06 (m, 6H), 6.89 (d, *J* = 7.4 Hz, 2H), 6.83 (tt, *J* = 7.5, 1.2 Hz, 1H), 4.77 (t, *J* = 3.8 Hz, 1H), 4.38 (dd, *J* = 12.3, 3.9 Hz, 1H), 2.66 – 2.55 (m, 1H), 2.47 (dq, *J* = 15.1, 4.2 Hz, 1H), 2.25 – 2.15 (m, 1H), 1.99 – 1.74 (m, 6H), 1.62 – 1.45 (m, 5H); ^{13}C NMR (125 MHz, Chloroform-*d,* 50 °C) δ 150.5, 142.1, 139.8, 128.6, 128.4, 128.0, 127.4, 126.8, 126.7, 126.1, 122.0, 118.9, 80.2, 73.5, 30.5, 28.4, 27.1, 22.3, 18.7; IR (thin film) 3018, 2917, 2839, 1590, 1481, 1446, 1256, 1026, 946, 805, 749; HRMS (ESI), calculated for $C_{25}H_{27}NO$: ($M+H^+$) 358.2171, observed 358.2219. *Minor Diastereomer* **5b** ^{1}H NMR (500 MHz, Chloroform-*d,* 50 °C) δ 7.22 – 7.05 (m, 10H), 6.94 (d, *J* = 4.5 Hz, 4H), 6.90 – 6.78 (m, 1H), 5.03 (dd, *J* = 7.7, 3.6 Hz, 1H), 4.31 (t, *J* = 5.1 Hz, 1H), 2.44 – 1.69 (m, 10H); ^{13}C NMR (125 MHz, Chloroform-*d,* 50 °C) δ 128.4, 127.7, 127.6, 127.5, 126.8, 126.7, 85.7, 74.4, 29.6, 27.5, 24.0, 22.8; IR (thin film) 3018, 2914, 2841, 1590, 1483, 1446, 1067, 1025, 761; HRMS (ESI), calculated for $C_{25}H_{27}NO$: ($M+H^+$) 358.2171, observed 358.2219.



2,3,10-triphenyl-1,2-oxazecane (**6**): To a 100 mL oven dried round bottom flask is added CuBr (28 mg, 0.2 mmol, 2 eq), $CuBr_2$ (4 mg, 0.02 mmol, 10 mol% relative to CuBr) and PMDTA (52 μL, 0.25 mmol, 2.5 eq) in THF (anhydrous, 30 mL). This suspension is sonicated for one minute and sparged with nitrogen for thirty minutes. A second solution of nitrosobenzene (16 mg, 0.15 mmol, 1.5 eq) and dibromide **S6** (42 mg, 0.1 mmol, 1 eq) is prepared in THF (anhydrous, 10 mL) in a 10 mL conical flask. This solution is sparged with nitrogen for ten minutes. The copper suspension is stirred at 50 °C under nitrogen while the nitroso solution is added dropwise to the copper suspension via syringe pump over ten hours. Upon completion of addition, the reaction is allowed to continue stirring under nitrogen for an additional eight hours.

The solution is concentrated *in vacuo* and reconstituted in DCM (10 mL). The DCM solution is washed with EDTA (0.5 M, pH 8, 20 mL) and extracted with DCM (3 x 15 mL). The organic layers are combined and sequentially dried with brine (20 mL) and sodium sulfate. The crude solution is loaded onto a prep TLC plate and purified with an isocratic mobile phase of 3:7 DCM:Hexane to afford **6** as a clear oil, isolated as a 9.8:1 mixture of diastereomers (12 mg, 32%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.17 – 7.04 (m, 1H), 6.93 – 6.74 (m, 9H), 6.69 – 6.52 (m, 4H), 4.71 (dd, *J* = 8.8, 3.2 Hz, 1H), 4.02 (dd, *J* = 6.5, 2.7 Hz, 1H), 2.00 (dtd, *J* = 15.2, 7.8, 2.7 Hz, 1H), 1.90 – 1.45 (m, 8H), 1.36 (dddt, *J* = 28.2, 14.4, 9.7, 5.2 Hz, 3H); ^{13}C NMR (125 MHz, Chloroform-*d*) δ 152.0, 142.7, 142.3, 128.7, 128.5, 128.2, 127.9, 127.6, 127.5, 127.4, 127.3, 126.9, 126.6, 126.4, 126.0, 125.0, 124.5, 120.5, 83.8, 78.9, 74.9, 74.4, 34.6, 32.3,

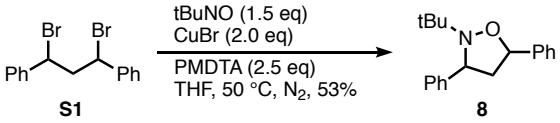
31.1, 30.9, 29.6, 26.7, 26.4, 26.1, 25.8, 23.5, 23.2, 22.4; IR (thin film) 3020, 2917, 2844, 1451, 1449, 1069, 1027, 753 cm $^{-1}$; HRMS (ESI), calculated for $C_{26}H_{29}NO$: ($M+H^+$) 372.2327, observed 372.2343.



2,3,12-triphenyl-1-oxa-2-azacyclododecane (**7**): To a 100 mL oven dried round bottom flask is added CuBr (28 mg, 0.2 mmol, 2 eq), $CuBr_2$ (4 mg, 0.02 mmol, 10 mol% relative to CuBr) and PMDTA (52 μL, 0.25 mmol, 2.5 eq) in THF (anhydrous, 30 mL). This suspension is sonicated for one minute and sparged with nitrogen for thirty minutes. A second solution of nitrosobenzene (16 mg, 0.15 mmol, 1.5 eq) and dibromide **S7** (45 mg, 0.1 mmol, 1 eq) is prepared in THF (anhydrous, 10 mL) in a 10 mL conical flask. This solution is sparged with nitrogen for ten minutes. The copper suspension is stirred at 50 °C under nitrogen while the nitroso solution is added dropwise to the copper suspension via syringe pump over ten hours. Upon completion of addition, the reaction is allowed to continue stirring under nitrogen for an additional eight hours.

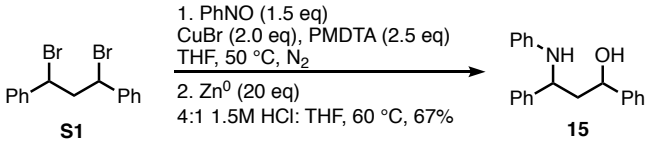
The solution is concentrated *in vacuo* and reconstituted in DCM (10 mL). The DCM solution is washed with EDTA (0.5 M, pH 8, 20 mL) and extracted with DCM (3 x 15 mL). The organic layers are combined and sequentially dried with brine (20 mL) and sodium sulfate. NMR analysis of the crude sample versus an internal standard (0.1 mmol of dimethylterephthalate) indicated 20% conversion to the heterocycle. The crude solution is loaded onto a prep TLC

plate and purified with an isocratic mobile phase of 3:7 DCM:Hexane to afford **7** as a clear oil with a 1:1 mix of diastereomers (4mg, 10%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.18 – 6.95 (m, 10H), 6.90 (t, *J* = 7.6 Hz, 2H), 6.83 – 6.74 (m, 3H), 4.85 (dd, *J* = 6.5, 4.2 Hz, 1H), 4.45 (dd, *J* = 7.6, 5.6 Hz, 1H), 2.27 (dq, *J* = 13.6, 6.6 Hz, 1H), 2.06 (dd, *J* = 13.2, 6.6 Hz, 1H), 1.94 (dq, *J* = 13.5, 6.7 Hz, 1H), 1.88 – 1.43 (m, 13H); ^{13}C NMR (125 MHz, Chloroform-*d*) δ 150.4, 142.3, 140.3, 129.0, 127.5, 127.5, 127.4, 126.8, 126.7, 126.6, 124.2, 123.4, 84.0, 72.6, 33.3, 32.7, 29.6, 26.4, 25.6, 24.7, 23.3, 22.9; IR (thin film) 3019, 2914, 2847, 1591, 1483, 1448, 1025, 752; HRMS (ESI), calculated for $C_{28}H_{33}NO$: ($M+H^+$) 400.2640, observed 400.2672.



2-(*tert*-butyl)-3,5-diphenylisoxazolidine (**8**): To a 25 mL oven dried round bottom flask is added CuBr (28 mg, 0.2 mmol, 2 eq) and PMDTA (52 µL, 0.25 mmol, 2.5 eq) in THF (anhydrous, 7 mL). This suspension is sonicated for one minute and sparged with nitrogen for seven minutes. A second solution of 2-methyl-2-nitrosopropane dimer (13 mg, 0.075 mmol, 1.5 eq) and dibromide **S1** (35 mg, 0.1 mmol, 1 eq, 1.1:1 mix of diastereomers) is prepared in THF (anhydrous, 3 mL) in a 10 mL conical flask. This solution is sparged with nitrogen for three minutes. The copper suspension is stirred at 50 °C under nitrogen while the nitroso solution is added dropwise to the copper suspension via syringe pump over ten hours. Upon completion of addition, the reaction is allowed to continue stirring under nitrogen for an additional fourteen hours.

The solution is concentrated *in vacuo* and reconstituted in DCM (10 mL). The DCM solution is washed with EDTA (0.5 M, pH 10, 20 mL) and extracted with DCM (3 x 15 mL). The organic layers are combined and sequentially dried with brine (20 mL) and sodium sulfate. The crude product was dry loaded onto Celite and purified via flash chromatography on a Yamazen brand amino-column with an increasing gradient of DCM in hexane (0 —> 35%) to afford **8** as a 1.6:1 mix of diastereomers (15 mg, 53%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.58 – 7.17 (m, 10H), 5.13 (ddd, *J* = 14.4, 9.9, 5.7 Hz, 1H), 4.53 – 4.33 (m, 1H), 2.96 (ddd, *J* = 12.2, 6.9, 5.3 Hz, 1H), 2.52 (dt, *J* = 12.1, 9.8 Hz, 1H), 2.44 (ddd, *J* = 12.1, 6.2, 3.9 Hz, 1H), 2.36 (dt, *J* = 12.2, 10.0 Hz, 1H), 1.15 (s, 4H), 1.13 (s, 5H); ^{13}C NMR (125 MHz, Chloroform-*d*) δ 145.4, 143.9, 139.9, 128.4, 128.3, 128.3, 128.3, 127.7, 127.7, 127.2, 127.0, 126.8, 126.8, 126.5, 126.4, 80.2, 64.5, 62.9, 60.3, 58.7, 51.2, 49.2, 26.7, 26.2; IR (thin film) 3061, 3028, 2968, 2925, 2870, 1451, 1214, 754, 698 ; HRMS (ESI), calculated for $C_{19}H_{23}NO$: ($M+H^+$) 282.1858, observed 282.1885.[7]



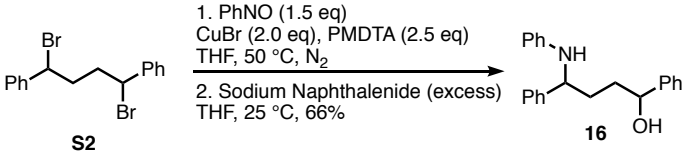
1,3-diphenyl-3-(phenylamino)propan-1-ol (**16**): To a 25 mL oven dried round bottom flask is added CuBr (28 mg, 0.2 mmol, 2 eq) and PMDTA (52 µL, 0.25 mmol, 2.5 eq) in THF (anhydrous, 7 mL). This suspension is sonicated for one minute and sparged with nitrogen for seven minutes. A second solution of nitrosobenzene (16 mg, 0.15 mmol, 1.5 eq) and dibromide **S1** (35 mg, 0.1 mmol, 1 eq, 1.1:1 mix of diastereomers) is prepared in THF (anhydrous, 3 mL) in a 10 mL conical flask. This solution is sparged with nitrogen for three minutes. The copper suspension is stirred at 50 °C under nitrogen while the nitroso solution is added dropwise to

the copper suspension via syringe pump over ten hours. Upon completion of addition, the reaction is allowed to continue stirring under nitrogen for an additional six hours.

The solution is concentrated *in vacuo* and reconstituted in DCM (10 mL). The DCM solution is washed with EDTA (0.5 M, pH 8, 20 mL) and extracted with DCM (3 x 15 mL). The organic layers are combined and sequentially dried with brine (20 mL) and sodium sulfate.

A 1-dram vial containing the resulting crude N–O alkylated adduct and a stir bar was charged with activated Zn^0 (130 mg, 2 mmol, 20 equiv) and 4:1 solution of 1.5 M HCl and THF (1.5 mL) and heated to 60 °C. The solution was stirred until consumption of the starting material was observed by TLC, upon which the crude reaction mixture was quenched with an aqueous solution of saturated $NaHCO_3$ (20 mL). The resulting precipitate was removed through vacuum filtration and the filtrate was extracted with EtOAc (3x 15 mL). The combined organic layers were washed with water (1x 15 mL) and once with brine (1x 15 mL) and then dried over sodium sulfate. The crude product was dry loaded onto Celite and purified via flash chromatography with an increasing gradient of DCM in hexane (0 —> 50%) to afford **15** as a 4.3:1 mix of diastereomers (20 mg, 67%). ^{1}H NMR (600 MHz, CDCl3) δ 7.43 – 7.25 (m, 9H), 7.23 – 7.18 (m, 1H), 7.08 (q, J = 8.1 Hz, 2H), 6.72 – 6.61 (m, 1.36H major), 6.57 (d, J = 8.0 Hz, 0.66H minor), 6.52 (d, J = 8.0 Hz, 1H), 4.86 (dd, J = 9.2, 3.3 Hz, 1H), 4.65 – 4.53 (m, 1H), 2.28 (ddt, J = 18.4, 14.6, 9.7 Hz, 1H), 2.16 (ddd, J = 14.1, 8.4, 3.5 Hz, 0.36H minor), 2.05 (dt, J = 14.5, 4.2 Hz, 0.78H major); ^{13}C NMR (100 MHz, CDCl3) δ 129.1, 128.7, 128.6, 128.6, 127.8, 127.7, 127.2, 127.0, 126.3, 126.2, 125.7, 118.2, 114.5, 113.9, 73.8, 71.8, 58.2, 47.3,

46.6; IR (thin film) 3533, 3390, 3057, 3026, 2922, 2853, 1601, 1502, 749, 699 cm^{-1}; HRMS (ESI), calculated for $C_{21}H_{21}NO$: ($M+H^+$) 304.1701, observed 304.1706.[8]

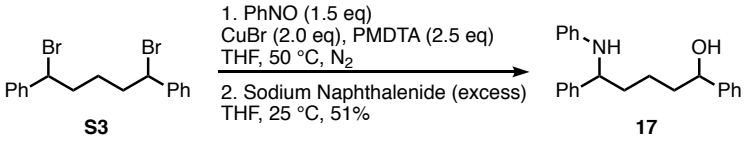


1,4-diphenyl-4-(phenylamino)butan-1-ol (**16**): To a 25 mL oven dried round bottom flask is added CuBr (28 mg, 0.2 mmol, 2 eq) and PMDTA (52 µL, 0.25 mmol, 2.5 eq) in THF (anhydrous, 7 mL). This suspension is sonicated for one minute and sparged with nitrogen for seven minutes. A second solution of nitrosobenzene (16 mg, 0.15 mmol, 1.5 eq) and dibromide **S2** (37 mg, 0.1 mmol, 1 eq) is prepared in THF (anhydrous, 3 mL) in a 10 mL conical flask. This solution is sparged with nitrogen for three minutes. The copper suspension is stirred at 50 °C under nitrogen while the nitroso solution is added dropwise to the copper suspension via syringe pump over ten hours. Upon completion of addition, the reaction is allowed to continue stirring under nitrogen for an additional six hours.

The solution is concentrated *in vacuo* and reconstituted in DCM (10 mL). The DCM solution is washed with EDTA (0.5 M, pH 8, 20 mL) and extracted with DCM (3 x 15 mL). The organic layers are combined and sequentially dried with brine (20 mL) and sodium sulfate.

A 500 mM solution of Sodium Naphthalenide was freshly prepared in THF while the substrate to be reduced was dissolved in 1 mL of THF in a 1-dram vial and briefly degassed with N_2. The napthalenide was titrated slowly until the substrate solution remained dark green. After three minutes, the reaction was quenched with isopropanol (~5 mL), washed with saturated

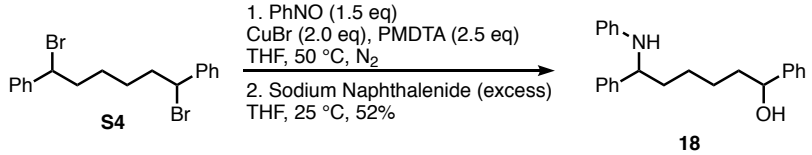
sodium bicarbonate (10 mL) and extracted with ethyl acetate (2 x 10 mL). Organic layers were combined and dried sequentially with brine (10 mL) and sodium sulfate. The crude product was dry loaded onto Celite and purified via flash chromatography with an increasing gradient of DCM in hexane (0 —> 50%) to afford **16** as a 2:1 mix of diastereomers (21 mg, 66%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.40 – 7.28 (m, 9H), 7.26 – 7.19 (m, 1H), 7.08 (ddt, *J* = 9.6, 6.7, 2.4 Hz, 2H), 6.64 (tdd, *J* = 7.3, 2.6, 1.3 Hz, 1H), 6.58 – 6.45 (m, 2H), 4.73 – 4.66 (m, 1H), 4.37 – 4.30 (m, 1H), 2.05 – 1.72 (m, 4H); ^{13}C NMR (125 MHz, Chloroform-*d*) δ 147.2, 144.3, 143.8, 143.7, 129.1, 128.6, 128.6, 128.5, 127.7, 127.7, 127.0, 126.4, 126.4, 125.9, 125.8, 117.3, 117.3, 113.4, 113.4, 74.3, 74.3, 58.3, 58.2, 35.7, 35.6, 34.9, 34.7, 29.7; IR (thin film) 3423, 3028, 2929, 2855, 1601, 1504, 1490, 1317, 750, 702; HRMS (ESI), calculated for $C_{22}H_{23}NO$: ($M+H^{+}$) 318.1858 observed 318.1870.



1,5-diphenyl-5-(phenylamino)pentan-1-ol (**17**): To a 100 mL oven dried round bottom flask is added CuBr (28 mg, 0.2 mmol, 2 eq) and PMDTA (52 µL, 0.25 mmol, 2.5 eq) in THF (anhydrous, 30 mL). This suspension is sonicated for one minute and sparged with nitrogen for thirty minutes. A second solution of nitrosobenzene (16 mg, 0.15 mmol, 1.5 eq) and dibromide **S3** (38 mg, 0.1 mmol, 1 eq) is prepared in THF (anhydrous, 10 mL) in a 10 mL conical flask. This solution is sparged with nitrogen for ten minutes. The copper suspension is stirred at 50 °C under nitrogen while the nitroso solution is added dropwise to the copper suspension via syringe pump over ten hours. Upon completion of addition, the reaction is allowed to continue stirring under nitrogen for an additional six hours.

The solution is concentrated *in vacuo* and reconstituted in DCM (10 mL). The DCM solution is washed with EDTA (0.5 M, pH 8, 20 mL) and extracted with DCM (3 x 15 mL). The organic layers are combined and sequentially dried with brine (20 mL) and sodium sulfate.

A 500 mM solution of Sodium Naphthalenide was freshly prepared in THF while the substrate to be reduced was dissolved in 1 mL of THF in a 1-dram vial and briefly degassed with N_2. The napthalenide was titrated slowly until the substrate solution remained dark green. After three minutes, the reaction was quenched with isopropanol (~5 mL), washed with saturated sodium bicarbonate (10 mL) and extracted with ethyl acetate (2 x 10 mL). Organic layers were combined and dried sequentially with brine (10 mL) and sodium sulfate. The crude product was dry loaded onto Celite and purified via flash chromatography with an increasing gradient of DCM in hexane (0 —> 50%) to afford **17** as a 1.5:1 mix of diastereomers (17 mg, 51%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.41 – 7.15 (m, 10H), 7.07 (t, *J* = 7.7 Hz, 2H), 6.62 (t, *J* = 7.3 Hz, 1H), 6.49 (d, *J* = 8.0 Hz, 2H), 4.65 (dd, *J* = 7.7, 5.6 Hz, 1H), 4.29 (t, *J* = 6.8 Hz, 1H), 1.93 – 1.29 (m, 6H); ^{13}C NMR (100 MHz, Chloroform-*d*) δ 147.3, 144.6, 144.1, 144.0, 129.0, 128.5, 128.5, 127.6, 126.9, 126.3, 125.8, 117.1, 113.2, 74.4, 74.4, 58.1, 58.0, 38.7, 38.7, 22.8, 22.6; IR (thin film) 3404, 2913, 2856, 1599, 1501, 1451, 1315, 1027, 748, 696 cm $^{-1}$; HRMS (ESI), calculated for $C_{23}H_{25}NO$: ($M+H^+$) 322.2014 observed 332.2321.

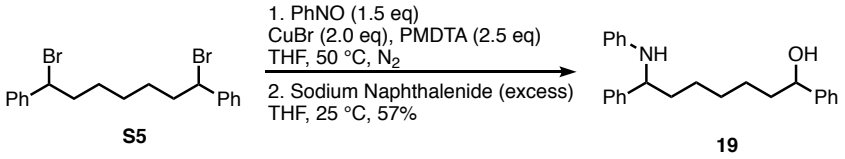


1,6-diphenyl-6-(phenylamino)hexan-1-ol (**18**): To a 100 mL oven dried round bottom flask is added CuBr (28 mg, 0.2 mmol, 2 eq), $CuBr_2$ (4 mg, 0.02 mmol, 10 mol% relative to CuBr) and PMDTA (52 μL, 0.25 mmol, 2.5 eq) in THF (anhydrous, 30 mL). This suspension is sonicated for one minute and sparged with nitrogen for thirty minutes. A second solution of nitrosobenzene (16 mg, 0.15 mmol, 1.5 eq) and dibromide **S4** (40 mg, 0.1 mmol, 1 eq) is prepared in THF (anhydrous, 10 mL) in a 10 mL conical flask. This solution is sparged with nitrogen for ten minutes. The copper suspension is stirred at 50 °C under nitrogen while the nitroso solution is added dropwise to the copper suspension via syringe pump over ten hours. Upon completion of addition, the reaction is allowed to continue stirring under nitrogen for an additional six hours.

The solution is concentrated *in vacuo* and reconstituted in DCM (10 mL). The DCM solution is washed with EDTA (0.5 M, pH 8, 20 mL) and extracted with DCM (3 x 15 mL). The organic layers are combined and sequentially dried with brine (20 mL) and sodium sulfate.

A 500 mM solution of Sodium Naphthalenide was freshly prepared in THF while the substrate to be reduced was dissolved in 1 mL of THF in a 1-dram vial and briefly degassed with N_2. The napthalenide was titrated slowly until the substrate solution remained dark green. After three minutes, the reaction was quenched with isopropanol (~5 mL), washed with saturated sodium bicarbonate (10 mL) and extracted with ethyl acetate (2 x 10 mL). Organic layers were combined and dried sequentially with brine (10 mL) and sodium sulfate. The crude product was dry loaded onto Celite and purified via flash chromatography with an increasing gradient of DCM in hexane (0 —> 50%) to afford **18** as a 1:1 mix of diasteromers (18 mg, 52%). ^1H

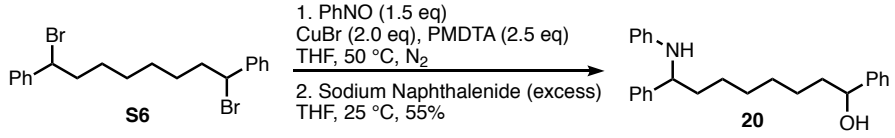
NMR (400 MHz, Chloroform-*d*) δ 7.42 – 7.27 (m, 8H), 7.25 – 7.18 (m, 1H), 7.07 (t, *J* = 8.5 Hz, 2H), 6.63 (t, *J* = 7.3 Hz, 1H), 6.49 (d, *J* = 7.7 Hz, 2H), 4.64 (dd, *J* = 7.4, 5.8 Hz, 1H), 4.37 – 4.19 (m, 1H), 4.04 (bs, 1H), 1.89 – 1.63 (m, 5H), 1.59 (bs, 1H), 1.53 – 1.23 (m, 4H); ^{13}C NMR (100 MHz, Chloroform-*d*) δ 147.4, 144.7, 144.1, 129.0, 128.6, 128.5, 128.5, 127.6, 126.9, 126.3, 125.8, 125.8, 117.1, 113.2, 74.5, 74.5, 58.1, 38.8, 38.8, 38.8, 26.2, 25.7, 25.6; IR (thin film) 3353, 2980, 2931, 2857, 1655, 1529, 1156, 702 cm $^{-1}$; HRMS (ESI), calculated for $C_{24}H_{27}NO$: ($M+Na^+$) 346.2171 observed 346.2175.



1,7-diphenyl-7-(phenylamino)heptan-1-ol (**19**): To a 100 mL oven dried round bottom flask is added CuBr (28 mg, 0.2 mmol, 2 eq) and PMDTA (52 µL, 0.25 mmol, 2.5 eq) in THF (anhydrous, 7 mL). This suspension is sonicated for one minute and sparged with nitrogen for seven minutes. A second solution of nitrosobenzene (16 mg, 0.15 mmol, 1.5 eq) and dibromide **S5** (41 mg, 0.1 mmol, 1 eq) is prepared in THF (anhydrous, 3 mL) in a 10 mL conical flask. This solution is sparged with nitrogen for three minutes. The copper suspension is stirred at 50 °C under nitrogen while the nitroso solution is added dropwise to the copper suspension via syringe pump over ten hours. Upon completion of addition, the reaction is allowed to continue stirring under nitrogen for an additional eight hours.

The solution is concentrated *in vacuo* and reconstituted in DCM (10 mL). The DCM solution is washed with EDTA (0.5 M, pH 8, 20 mL) and extracted with DCM (3 x 15 mL). The organic layers are combined and sequentially dried with brine (20 mL) and sodium sulfate.

A 500 mM solution of Sodium Naphthalenide was freshly prepared in THF while the substrate to be reduced was dissolved in 1 mL of THF in a 1-dram vial and briefly degassed with N_2. The napthalenide was titrated slowly until the substrate solution remained dark green. After three minutes, the reaction was quenched with isopropanol (~5 mL), washed with saturated sodium bicarbonate (10 mL) and extracted with ethyl acetate (2 x 10 mL). Organic layers were combined and dried sequentially with brine (10 mL) and sodium sulfate. The crude product was dry loaded onto Celite and purified via flash chromatography with an increasing gradient of DCM in hexane (0 —> 50%) to afford **19** as a mix of diastereomers (20 mg, 57%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.40 – 7.25 (m, 10H), 7.22 (ddd, *J* = 8.5, 5.7, 2.3 Hz, 1H), 7.12 – 7.04 (m, 2H), 6.67 – 6.60 (m, 1H), 6.56 – 6.46 (m, 2H), 4.65 (dd, *J* = 7.5, 5.8 Hz, 1H), 4.28 (t, *J* = 6.8 Hz, 1H), 4.06 (bs, 1H), 1.90 – 1.63 (m, 3H), 1.57 (bs, 1H), 1.36 (tdd, *J* = 30.4, 16.6, 7.4 Hz, 7H); ^{13}C NMR (125 MHz, Chloroform-*d*) δ 144.8, 144.8, 129.1, 128.5, 128.4, 127.5, 126.9, 126.4, 125.9, 117.2, 113.3, 74.6, 74.6, 58.3, 38.9, 38.8, 29.3, 26.2, 26.2, 25.6, 25.6; IR (thin film) 3399, 3028, 2929, 2845, 1600, 1502, 1451, 1317, 1027, 749, 699; HRMS (ESI), calculated for $C_{25}H_{29}NO$: ($M+H^+$) 360.2372 observed 360.2290.

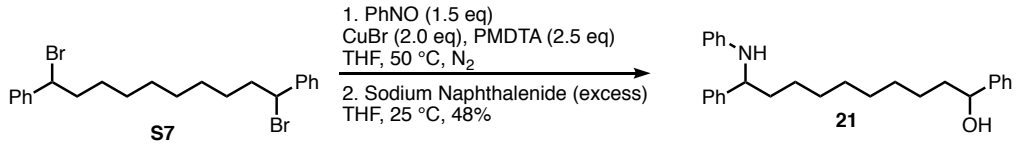


1,8-diphenyl-8-(phenylamino)octan-1-ol (**20**): To a 100 mL oven dried round bottom flask is added CuBr (28 mg, 0.2 mmol, 2 eq), $CuBr_2$ (4 mg, 0.02 mmol, 10 mol% relative to CuBr) and PMDTA (52 μL, 0.25 mmol, 2.5 eq) in THF (anhydrous, 30 mL). This suspension is sonicated for one minute and sparged with nitrogen for thirty minutes. A second solution of nitrosobenzene (16 mg, 0.15 mmol, 1.5 eq) and dibromide **S6** (42 mg, 0.1 mmol, 1 eq) is prepared in THF (anhydrous, 10 mL) in a 10 mL conical flask. This solution is sparged with nitrogen for ten minutes. The copper suspension is stirred at 50 °C under nitrogen while the nitroso solution is added dropwise to the copper suspension via syringe pump over ten hours. Upon completion of addition, the reaction is allowed to continue stirring under nitrogen for an additional eight hours.

The solution is concentrated *in vacuo* and reconstituted in DCM (10 mL). The DCM solution is washed with EDTA (0.5 M, pH 8, 20 mL) and extracted with DCM (3 x 15 mL). The organic layers are combined and sequentially dried with brine (20 mL) and sodium sulfate.

A 500 mM solution of Sodium Naphthalenide was freshly prepared in THF while the substrate to be reduced was dissolved in 1 mL of THF in a 1-dram vial and briefly degassed with N_2. The napthalenide was titrated slowly until the substrate solution remained dark green. After three minutes, the reaction was quenched with isopropanol (~5 mL), washed with saturated sodium bicarbonate (10 mL) and extracted with ethyl acetate (2 x 10 mL). Organic layers were combined and dried sequentially with brine (10 mL) and sodium sulfate. The crude product was dry loaded onto Celite and purified via flash chromatography with an increasing gradient of DCM in hexane (0 —> 50%) to afford **20** (20 mg, 55%). ^{1}H NMR (500 MHz, Chloroform-

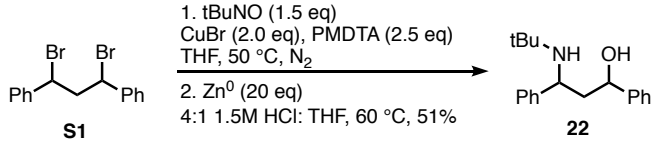
d) δ 7.38 – 7.27 (m, 10H), 7.24 – 7.19 (m, 1H), 7.11 – 7.02 (m, 2H), 6.62 (t, J = 7.4 Hz, 1H), 6.54 – 6.45 (m, 2H), 4.68 – 4.61 (m, 1H), 4.27 (t, J = 6.8 Hz, 1H), 4.03 (bs, 1H), 1.84 – 1.63 (m, 5H), 1.45 – 1.24 (m, 7H); ^{13}C NMR (100 MHz, Chloroform-*d*) δ 147.4, 144.8, 144.2, 129.1, 128.5, 128.4, 127.5, 126.8, 126.3, 125.9, 117.1, 113.2, 74.6, 58.2, 39.0, 38.9, 29.3, 29.3, 26.2, 25.7; IR (thin film) 3402, 3026, 2927, 2853, 1600, 1503, 1452, 1316, 1179, 1027, 749, 700; HRMS (ESI), calculated for $C_{26}H_{31}NO$: ($M+H^+$) 374.2484 observed 374.2978.



1,10-diphenyl-10-(phenylamino)decan-1-ol (**21**): To a 100 mL oven dried round bottom flask is added CuBr (28 mg, 0.2 mmol, 2 eq), $CuBr_2$ (4 mg, 0.02 mmol, 10 mol% relative to CuBr) and PMDTA (52 µL, 0.25 mmol, 2.5 eq) in THF (anhydrous, 30 mL). This suspension is sonicated for one minute and sparged with nitrogen for thirty minutes. A second solution of nitrosobenzene (16 mg, 0.15 mmol, 1.5 eq) and dibromide **S7** (45 mg, 0.1 mmol, 1 eq) is prepared in THF (anhydrous, 10 mL) in a 10 mL conical flask. This solution is sparged with nitrogen for ten minutes. The copper suspension is stirred at 50 °C under nitrogen while the nitroso solution is added dropwise to the copper suspension via syringe pump over ten hours. Upon completion of addition, the reaction is allowed to continue stirring under nitrogen for an additional eight hours.

The solution is concentrated *in vacuo* and reconstituted in DCM (10 mL). The DCM solution is washed with EDTA (0.5 M, pH 8, 20 mL) and extracted with DCM (3 x 15 mL). The organic layers are combined and sequentially dried with brine (20 mL) and sodium sulfate.

A 500 mM solution of Sodium Naphthalenide was freshly prepared in THF while the substrate to be reduced was dissolved in 1 mL of THF in a 1-dram vial and briefly degassed with N_2. The napthalenide was titrated slowly until the substrate solution remained dark green. After three minutes, the reaction was quenched with isopropanol (~5 mL), washed with saturated sodium bicarbonate (10 mL) and extracted with ethyl acetate (2 x 10 mL). Organic layers were combined and dried sequentially with brine (10 mL) and sodium sulfate. The crude product was dry loaded onto Celite and purified via flash chromatography with an increasing gradient of DCM in hexane (0 —> 50%) to afford **21** (19 mg, 48%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.42 – 7.17 (m, 10H), 7.13 – 7.04 (m, 2H), 6.63 (t, *J* = 7.3 Hz, 1H), 6.51 (d, *J* = 7.9 Hz, 2H), 4.66 (dd, *J* = 7.5, 5.7 Hz, 1H), 4.28 (t, *J* = 6.8 Hz, 1H), 4.07 (s, 1H), 1.88 – 1.63 (m, 4H), 1.57 (bs, 1H), 1.48 – 1.17 (m, 12H); ^{13}C NMR (125 MHz, Chloroform-*d*) δ 147.5, 144.9, 144.3, 129.1, 128.5, 128.4, 127.5, 126.8, 126.4, 125.9, 125.9, 117.1, 113.2, 74.7, 58.2, 39.1, 39.0, 29.5, 29.5, 29.4, 29.4, 26.3, 25.8; IR (thin film) 3421, 3028, 2927, 2851, 1600, 1501, 1451, 1027, 748, 697 cm $^{-1}$; HRMS (ESI), calculated for $C_{28}H_{35}NO$: ($M+H^+$) 402.2797 observed 402.2787.



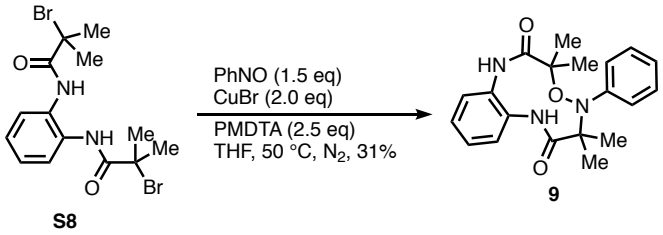
3-(*tert*-butylamino)-1,3-diphenylpropan-1-ol (**22**): To a 25 mL oven dried round bottom flask is added CuBr (28 mg, 0.2 mmol, 2 eq) and PMDTA (52 µL, 0.25 mmol, 2.5 eq) in THF (anhydrous, 7 mL). This suspension is sonicated for one minute and sparged with nitrogen for

seven minutes. A second solution of 2-methyl-2-nitrosopropane dimer (13 mg, 0.075 mmol, 1.5 eq) and dibromide **S1** (35 mg, 0.1 mmol, 1 eq, 1.1:1 mix of diastereomers) is prepared in THF (anhydrous, 3 mL) in a 10 mL conical flask. This solution is sparged with nitrogen for three minutes. The copper suspension is stirred at 50 °C under nitrogen while the nitroso solution is added dropwise to the copper suspension via syringe pump over ten hours. Upon completion of addition, the reaction is allowed to continue stirring under nitrogen for an additional fourteen hours.

The solution is concentrated *in vacuo* and reconstituted in DCM (10 mL). The DCM solution is washed with EDTA (0.5 M, pH 10, 20 mL) and extracted with DCM (3 x 15 mL). The organic layers are combined and sequentially dried with brine (20 mL) and sodium sulfate.

A 1-dram vial containing the resulting crude N–O alkylated adduct and a stir bar was charged with activated Zn^0 (130 mg, 2 mmol, 20 equiv) and 4:1 solution of 1.5 M HCl and THF (1.5 mL) and heated to 60 °C. The solution was stirred until consumption of the starting material was observed by TLC, upon which the crude reaction mixture was quenched with an aqueous solution of saturated $NaHCO_3$ (20 mL). The resulting precipitate was removed through vacuum filtration and the filtrate was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with water (1 x 15 mL) and once with brine (1 x 15 mL) and then dried over sodium sulfate. The crude product was dry loaded onto Celite and purified via flash chromatography on a Yamazen brand amino-column with an increasing gradient of EtOAc in hexane (0 —> 50%) to afford **22** as a 1.7:1 mix of diasteromers (14 mg, 51%). *Major Diastereomer **22-a***: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.37 (d, *J* = 7.3 Hz, 2H), 7.34 – 7.26

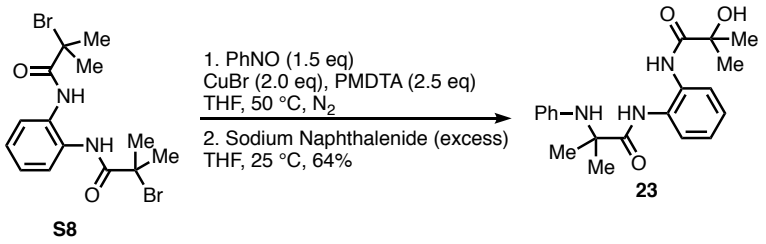
(m, 4H), 7.25 – 7.17 (m, 4H), 5.00 (dd, *J* = 9.6, 2.9 Hz, 1H), 4.16 (dd, *J* = 10.4, 4.0 Hz, 1H), 1.89 – 1.73 (m, 2H), 1.07 (s, 9H); ^{13}C NMR (125 MHz, Chloroform-*d*) δ 146.7, 145.1, 128.7, 128.2, 127.0, 126.9, 125.8, 125.5, 75.2, 58.9, 52.0, 48.1, 30.3; IR (thin film) 3287, 3026, 2963, 2805, 1453, 1206, 1063, 751, 699 cm $^{-1}$; HRMS (ESI), calculated for $C_{19}H_{25}NO$: ($M+H^+$) 284.2014 observed 284.2027. *Minor Diastereomer* ***22-b***: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.42 – 7.39 (m, 2H), 7.38 – 7.28 (m, 4H), 7.25 – 7.18 (m, 2H), 7.17 – 7.13 (m, 2H), 5.02 (t, *J* = 4.7 Hz, 1H), 3.93 (dd, *J* = 8.9, 3.2 Hz, 1H), 2.14 (ddd, *J* = 14.5, 8.9, 3.9 Hz, 1H), 2.00 (ddd, *J* = 14.5, 5.5, 3.2 Hz, 1H), 0.98 (s, 9H); ^{13}C NMR (125 MHz, Chloroform-*d*) δ 146.2, 145.2, 128.7, 128.1, 126.9, 126.6, 126.0, 125.7, 72.1, 54.9, 51.9, 45.3, 30.2; IR (thin film) 3260, 3057, 3026, 2961, 2924, 2854, 1601, 1453, 1365, 1210, 1064, 1029, 759, 700, 668 cm $^{-1}$; HRMS (ESI), calculated for $C_{19}H_{25}NO$: ($M+H^+$) 284.2014 observed 284.2024.



3,3,6,6-tetramethyl-5-phenyl-1,5,6,8-tetrahydro-7*H*-benzo[*f*][1,2,5,8]oxatriazecine-2,7(3*H*)-dione (**9**): To a 100 mL oven dried round bottom flask is added CuBr (28 mg, 0.2 mmol, 2 eq) and PMDTA (52 μL, 0.25 mmol, 2.5 eq) in THF (anhydrous, 30 mL). This suspension is sonicated for one minute and sparged with nitrogen for thirty minutes. A second solution of nitrosobenzene (16 mg, 0.15 mmol, 1.5 eq) and dibromide **S8** (40 mg, 0.1 mmol, 1 eq) is prepared in THF (anhydrous, 10 mL) in a 10 mL conical flask. This solution is sparged with nitrogen for ten minutes. The copper suspension is stirred at 50 °C under nitrogen while the nitroso solution is added dropwise to the copper suspension via syringe pump over ten

hours. Upon completion of addition, the reaction is allowed to continue stirring under nitrogen for an additional six hours.

The solution is concentrated *in vacuo* and reconstituted in DCM (10 mL). The DCM solution is washed with EDTA (0.5 M, pH 8, 20 mL) and extracted with DCM (3 x 15 mL). The organic layers are combined and sequentially dried with brine (20 mL) and sodium sulfate. The crude product was dry loaded onto Celite and purified via flash chromatography on a Yamazen brand amino-column with an increasing gradient of DCM in hexane (0 —> 35%) to afford **9** as a white crystalline solid (11 mg, 31%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.72 (s, 1H), 7.58 (s, 1H), 7.44 – 7.32 (m, 5H), 7.28 (s, 1H), 7.21 (tt, *J* = 7.3, 1.3 Hz, 1H), 7.09 (s, 1H), 1.45 (s, 3H), 1.36 (s, 3H), 1.18 (s, 3H), 1.05 (s, 3H); ^{13}C NMR (125 MHz, Chloroform-*d*) δ 177.5, 176.5, 148.6, 136.1, 135.5, 129.2, 129.2, 128.9, 128.8, 128.3, 127.7, 126.3, 126.1, 124.7, 82.4, 68.5, 26.6, 25.1, 22.4, 14.9; IR (thin film) 3333, 3274, 2922, 2853, 1669, 1501, 1164, 750, 706 cm^{-1}; HRMS (ESI), calculated for $C_{20}H_{23}N_3O_3$: (M+Na^{+}) 376.1637 observed 376.1637.



S8 **23**

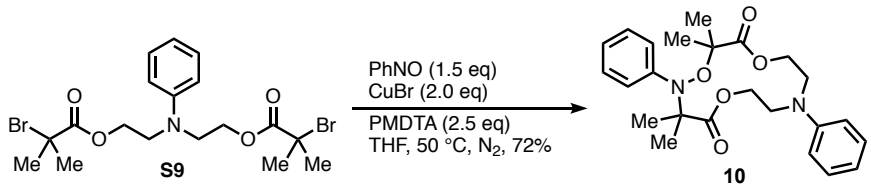
2-hydroxy-2-methyl-*N*-(2-(2-methyl-2-(phenylamino)propanamido)phenyl)propanamide (**23**): To a 100 mL oven dried round bottom flask is added CuBr (28 mg, 0.2 mmol, 2 eq) and PMDTA (52 µL, 0.25 mmol, 2.5 eq) in THF (anhydrous, 30 mL). This suspension is sonicated for one minute and sparged with nitrogen for thirty minutes. A second solution of nitrosobenzene (16 mg, 0.15 mmol, 1.5 eq)

and dibromide **S8** (40 mg, 0.1 mmol, 1 eq) is prepared in THF (anhydrous, 10 mL) in a 10 mL conical flask. This solution is sparged with nitrogen for ten minutes. The copper suspension is stirred at 50 °C under nitrogen while the nitroso solution is added dropwise to the copper suspension via syringe pump over ten hours. Upon completion of addition, the reaction is allowed to continue stirring under nitrogen for an additional six hours.

The solution is concentrated *in vacuo* and reconstituted in DCM (10 mL). The DCM solution is washed with EDTA (0.5 M, pH 8, 20 mL) and extracted with DCM (3 x 15 mL). The organic layers are combined and sequentially dried with brine (20 mL) and sodium sulfate.

A 500 mM solution of Sodium Naphthalenide was freshly prepared in THF while the substrate to be reduced was dissolved in 1 mL of THF in a 1-dram vial and briefly degassed with N_2. The napthalenide was titrated slowly until the substrate solution remained dark green. After three minutes, the reaction was quenched with isopropanol (~5 mL), washed with saturated sodium bicarbonate (10 mL) and extracted with ethyl acetate (2 x 10 mL). Organic layers were combined and dried sequentially with brine (10 mL) and sodium sulfate. The crude product was dry loaded onto Celite and purified via flash chromatography on a Yamazen brand amino-column with an increasing gradient of DCM in hexane (0 —> 50%) to afford **23** (27 mg, 64%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 9.17 (s, 1H), 8.83 (s, 1H), 7.59 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.37 (dd, *J* = 7.7, 1.9 Hz, 1H), 7.24 – 7.13 (m, 4H), 6.84 (tt, *J* = 7.3, 1.0 Hz, 1H), 6.64 (d, *J* = 8.5 Hz, 2H), 3.94 (bs, 1H), 2.30 (bs, 1H), 1.59 (s, 6H), 1.39 (s, 6H); ^{13}C NMR (125 MHz, Chloroform-*d*) δ 175.6, 175.4, 144.7, 130.3, 130.1, 129.5 126.4, 126.4, 126.2, 125.1, 125.1, 124.8, 119.8, 116.5, 73.7, 58.9, 27.7, 26.0; IR (thin film) 3337, 3054, 2976, 2930, 2866, 1661,

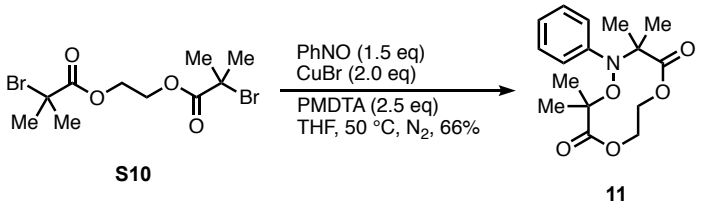
1597, 1499, 1445, 1364, 1298, 1258, 1184, 1148, 749, 734, 695 cm $^{-1}$; HRMS (ESI), calculated for $C_{20}H_{25}N_3O_3$: ($M+H^+$) 356.1974 observed 356.1968.



3,3,13,13-tetramethyl-2,8-diphenyl-1,5,11-trioxa-2,8-diazacyclotridecane-4,12-dione (**10**): To a 100 mL oven dried round bottom flask is added CuBr (28 mg, 0.2 mmol, 2 eq) and PMDTA (52 μL, 0.25 mmol, 2.5 eq) in THF (anhydrous, 30 mL). This suspension is sonicated for one minute and sparged with nitrogen for thirty minutes. A second solution of nitrosobenzene (16 mg, 0.15 mmol, 1.5 eq) and dibromide **S9** (48 mg, 0.1 mmol, 1 eq) is prepared in THF (anhydrous, 10 mL) in a 10 mL conical flask. This solution is sparged with nitrogen for ten minutes. The copper suspension is stirred at 50 °C under nitrogen while the nitroso solution is added dropwise to the copper suspension via syringe pump over ten hours. Upon completion of addition, the reaction is allowed to continue stirring under nitrogen for an additional six hours.

The solution is concentrated *in vacuo* and reconstituted in DCM (10 mL). The DCM solution is washed with EDTA (0.5 M, pH 8, 20 mL) and extracted with DCM (3 x 15 mL). The organic layers are combined and sequentially dried with brine (20 mL) and sodium sulfate. The crude product was dry loaded onto Celite and purified via flash chromatography with an increasing gradient of DCM in hexane (0 —> 35%) to afford **10** (30 mg, 72%). ^{1}H NMR (500 MHz,

Chloroform-*d*) δ 7.32 – 7.23 (m, 4H), 7.22 – 7.15 (m, 2H), 7.15 – 7.07 (m, 3H), 6.85 – 6.76 (m, 3H), 4.53 – 4.38 (m, 2H), 4.27 (tt, J = 11.6, 4.0 Hz, 2H), 3.74 (tq, J = 3.9, 2.3, 1.5 Hz, 4H), 1.31 (s, 3H), 1.28 (s, 3H), 1.14 (s, 3H), 1.10 (s, 3H); ^{13}C NMR (125 MHz, Chloroform-*d*) δ 174.3, 173.5, 148.9, 148.2, 129.2, 127.7, 125.8, 125.3, 117.7, 114.0, 83.1, 68.0, 63.8, 62.9, 51.5, 50.0, 25.8, 25.0, 23.1, 19.3; IR (thin film) 3060, 2982, 2927, 2852, 1732, 1598, 1504, 1286, 1173, 1154, 749, 700 cm^{-1}; HRMS (ESI), calculated for $C_{24}H_{30}N_2O_5$: (M+Na$^+$) 449.2052 observed 449.2067.

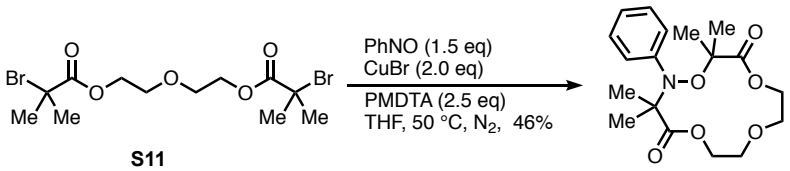


S10 **11**

3,3,10,10-tetramethyl-2-phenyl-1,5,8,2-trioxazecane-4,9-dione (**11**): To a 100 mL oven dried round bottom flask is added CuBr (28 mg, 0.2 mmol, 2 eq) and PMDTA (52 µL, 0.25 mmol, 2.5 eq) in THF (anhydrous, 30 mL). This suspension is sonicated for one minute and sparged with nitrogen for thirty minutes. A second solution of nitrosobenzene (16 mg, 0.15 mmol, 1.5 eq) and dibromide **S10** (36 mg, 0.1 mmol, 1 eq) is prepared in THF (anhydrous, 10 mL) in a 10 mL conical flask. This solution is sparged with nitrogen for ten minutes. The copper suspension is stirred at 50 °C under nitrogen while the nitroso solution is added dropwise to the copper suspension via syringe pump over ten hours. Upon completion of addition, the reaction is allowed to continue stirring under nitrogen for an additional six hours.

The solution is concentrated *in vacuo* and reconstituted in DCM (10 mL). The DCM solution is washed with EDTA (0.5 M, pH 8, 20 mL) and extracted with DCM (3 x 15 mL). The organic

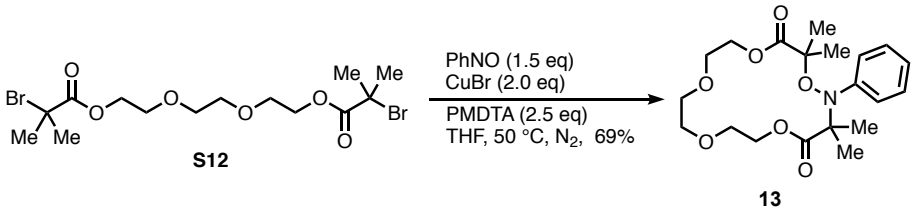
layers are combined and sequentially dried with brine (20 mL) and sodium sulfate. The crude product was dry loaded onto Celite and purified via flash chromatography with an increasing gradient of EtOAc in hexane (0 —> 50%) to afford **11** (20 mg, 66%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.49 – 7.00 (m, 5H), 5.25 (tdd, *J* = 10.6, 5.3, 0.7 Hz, 1H), 5.16 (tdd, *J* = 10.9, 5.3, 0.7 Hz, 1H), 3.94 – 3.84 (m, 2H), 1.37 (s, 3H), 1.32 (s, 3H), 1.12 (s, 3H), 0.97 (s, 3H); ^{13}C NMR (125 MHz, Chloroform-*d*) δ 173.7, 172.3, 148.4, 127.7, 126.1, 125.8, 82.5, 67.8, 59.1, 58.8, 24.9, 24.3, 23.9, 16.2; IR (thin film) 2998, 2967, 2924, 2852, 1748, 1277, 1162, 1123, 705 cm $^{-1}$; HRMS (ESI), calculated for $C_{16}H_{21}NO_5$: ($M+Na^+$) 330.1317 observed 330.1331.



S11 **12**

3,3,13,13-tetramethyl-2-phenyl-1,5,8,11-tetraoxa-2-azacyclotridecane-4,12-dione (**12**): To a 100 mL oven dried round bottom flask is added CuBr (28 mg, 0.2 mmol, 2 eq) and PMDTA (52 μL, 0.25 mmol, 2.5 eq) in THF (anhydrous, 30 mL). This suspension is sonicated for one minute and sparged with nitrogen for thirty minutes. A second solution of nitrosobenzene (16 mg, 0.15 mmol, 1.5 eq) and dibromide **S11** (40 mg, 0.1 mmol, 1 eq) is prepared in THF (anhydrous, 10 mL) in a 10 mL conical flask. This solution is sparged with nitrogen for ten minutes. The copper suspension is stirred at 50 °C under nitrogen while the nitroso solution is added dropwise to the copper suspension via syringe pump over ten hours. Upon completion of addition, the reaction is allowed to continue stirring under nitrogen for an additional six hours.

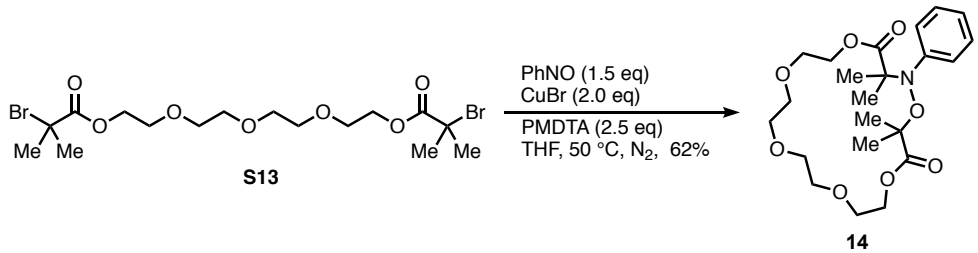
The solution is concentrated *in vacuo* and reconstituted in DCM (10 mL). The DCM solution is washed with EDTA (0.5 M, pH 8, 20 mL) and extracted with DCM (3 x 15 mL). The organic layers are combined and sequentially dried with brine (20 mL) and sodium sulfate. The crude product was dry loaded onto Celite and purified via flash chromatography with an increasing gradient of EtOAc in hexane (0 —> 50%) to afford **12** (16 mg, 46 %). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.36 – 7.23 (m, 4H), 7.15 (ddd, *J* = 8.5, 6.8, 1.8 Hz, 1H), 4.56 (ddd, *J* = 11.7, 9.1, 2.2 Hz, 1H), 4.41 (ddd, *J* = 12.0, 4.8, 2.4 Hz, 1H), 4.22 (ddd, *J* = 11.9, 8.1, 2.4 Hz, 1H), 4.12 (ddd, *J* = 12.2, 4.0, 2.4 Hz, 1H), 3.96 – 3.87 (m, 2H), 3.71 (ddd, *J* = 12.2, 4.0, 2.3 Hz, 1H), 3.65 (ddd, *J* = 11.4, 4.8, 2.4 Hz, 1H), 1.49 (s, 3H), 1.35 (s, 3H), 1.22 (s, 3H), 1.15 (s, 3H); ^{13}C NMR (125 MHz, Chloroform-*d*) δ 174.1, 173.5, 149.4, 127.7, 125.7, 125.5, 83.0, 68.6, 67.8, 67.6, 63.6, 62.5, 62.5, 26.7, 26.2, 22.3, 19.3; IR (thin film) 3060, 2985, 2945, 2865, 1732, 1466, 1381, 1281, 1138, 1091, 1027, 783, 761, 703 cm^{-1} ; HRMS (ESI), calculated for $C_{18}H_{25}NO_6$: ($M+Na^+$) 374.1580 observed 374.1594.



3,3,16,16-tetramethyl-2-phenyl-1,5,8,11,14-pentaoxa-2-azacyclohexadecane-4,15-dione (**13**): To a 100 mL oven dried round bottom flask is added CuBr (28 mg, 0.2 mmol, 2 eq) and PMDTA (52 μL, 0.25 mmol, 2.5 eq) in THF (anhydrous, 30 mL). This suspension is sonicated for one minute and sparged with nitrogen for thirty minutes. A second solution of nitrosobenzene (16 mg, 0.15 mmol, 1.5 eq) and dibromide **S12** (45 mg, 0.1 mmol, 1 eq) is prepared in THF (anhydrous, 10 mL) in a 10 mL conical flask. This solution is sparged with

nitrogen for ten minutes. The copper suspension is stirred at 50 °C under nitrogen while the nitroso solution is added dropwise to the copper suspension via syringe pump over ten hours. Upon completion of addition, the reaction is allowed to continue stirring under nitrogen for an additional six hours.

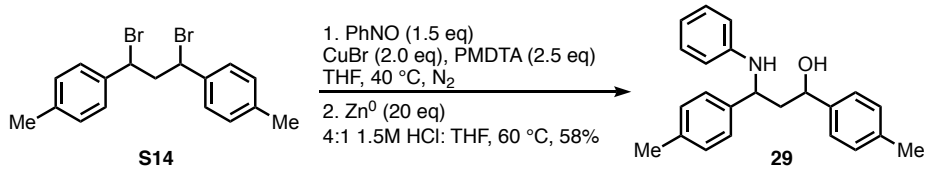
The solution is concentrated *in vacuo* and reconstituted in DCM (10 mL). The DCM solution is washed with EDTA (0.5 M, pH 8, 20 mL) and extracted with DCM (3 x 15 mL). The organic layers are combined and sequentially dried with brine (20 mL) and sodium sulfate. The crude product was dry loaded onto Celite and purified via flash chromatography with an increasing gradient of EtOAc in hexane (0 —> 50%) to afford **13** (27 mg, 69%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.37 (d, *J* = 7.9 Hz, 2H), 7.23 (t, *J* = 7.7 Hz, 2H), 7.09 (t, *J* = 7.3 Hz, 1H), 4.46 – 4.35 (m, 1H), 4.17 – 4.06 (m, 2H), 3.99 – 3.89 (m, 1H), 3.85 – 3.67 (m, 8H), 1.40 – 1.30 (m, 12H); ^{13}C NMR (125 MHz, Chloroform-*d*) δ 174.0, 173.0, 149.0, 127.6, 125.5, 125.6, 81.8, 81.8, 70.9, 70.9, 69.0, 68.9, 68.0, 64.5, 64.3, 24.3, 24.1, 24.0, 23.6; IR (thin film) 3061, 2982, 2942, 2869, 1732, 1451, 1280, 1172, 1142, 702 cm $^{-1}$; HRMS (ESI), calculated for $C_{20}H_{29}NO_7$: ($M+Na^+$) 418.1842 observed 462.1828.



3,3,19,19-tetramethyl-2-phenyl-1,5,8,11,14,17-hexaoxa-2-azacyclononadecane-4,18-dione (**14**): To a 100 mL oven dried round bottom flask is added CuBr (28 mg, 0.2 mmol, 2

eq) and PMDTA (52 μL, 0.25 mmol, 2.5 eq) in THF (anhydrous, 30 mL). This suspension is sonicated for one minute and sparged with nitrogen for thirty minutes. A second solution of nitrosobenzene (16 mg, 0.15 mmol, 1.5 eq) and dibromide **S13** (49 mg, 0.1 mmol, 1 eq) is prepared in THF (anhydrous, 10 mL) in a 10 mL conical flask. This solution is sparged with nitrogen for ten minutes. The copper suspension is stirred at 50 °C under nitrogen while the nitroso solution is added dropwise to the copper suspension via syringe pump over ten hours. Upon completion of addition, the reaction is allowed to continue stirring under nitrogen for an additional six hours.

The solution is concentrated *in vacuo* and reconstituted in DCM (10 mL). The DCM solution is washed with EDTA (0.5 M, pH 8, 20 mL) and extracted with DCM (3 x 15 mL). The organic layers are combined and sequentially dried with brine (20 mL) and sodium sulfate. The crude product was dry loaded onto Celite and purified via flash chromatography with an increasing gradient of EtOAc in hexane (0 —> 50%) to afford **14** as a mix of rotamers (27 mg, 62%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.39 – 7.31 (m, 2H), 7.23 (dd, *J* = 8.3, 7.1 Hz, 2H), 7.09 (td, *J* = 7.2, 1.3 Hz, 1H), 4.31 (dt, *J* = 9.2, 4.5 Hz, 1H), 4.20 (dd, *J* = 10.6, 5.9 Hz, 1H), 3.80 (t, *J* = 4.4 Hz, 4H), 3.78 – 3.74 (m, 2H), 3.72 (q, *J* = 4.2 Hz, 4H), 3.67 (dt, *J* = 5.6, 2.3 Hz, 2H), 3.61 – 3.44 (m, 2H), 1.47 (s, 3H), 1.36 (s, 3H), 1.33 (s, 6H); ^{13}C NMR (125 MHz, Chloroform-*d*) δ 173.7, 172.7, 148.4, 127.6, 125.7, 125.7, 80.9, 80.9, 77.2, 71.2, 71.1, 71.1, 70.9, 69.1, 68.7, 68.1, 64.6, 64.0, 24.5, 23.4, 23.3, 23.2; IR (thin film) 2983, 2943, 2872, 1733, 1467, 1281, 1172, 1137, 953, 703 cm^{-1}; HRMS (ESI), calculated for $C_{22}H_{33}NO_8$ ($M+Na^+$): 462.2104 observed 462.2096.

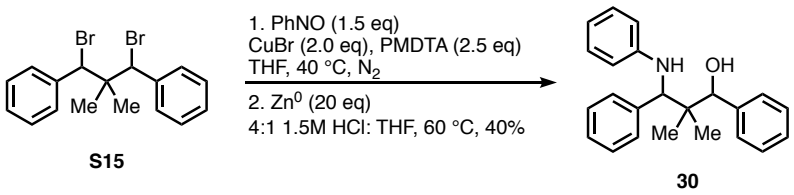


3-(phenylamino)-1,3-di-*p*-tolylpropan-1-ol (**29**): To a 25 mL oven dried round bottom flask is added CuBr (28 mg, 0.2 mmol, 2 eq) and PMDTA (52 µL, 0.25 mmol, 2.5 eq) in THF (anhydrous, 7 mL). This suspension is sonicated for one minute and sparged with nitrogen for seven minutes. A second solution of nitrosobenzene (16 mg, 0.15 mmol, 1.5 eq) and dibromide **S14** (38 mg, 0.1 mmol, 1 eq) is prepared in THF (anhydrous, 3 mL) in a 10 mL conical flask. This solution is sparged with nitrogen for three minutes. The copper suspension is stirred at 40 °C under nitrogen while the nitroso solution is added dropwise to the copper suspension via syringe pump over ten hours. Upon completion of addition, the reaction is allowed to continue stirring under nitrogen for an additional six hours.

The solution is concentrated *in vacuo* and reconstituted in DCM (10 mL). The DCM solution is washed with EDTA (0.5 M, pH 8, 20 mL) and extracted with DCM (3 x 15 mL). The organic layers are combined and sequentially dried with brine (20 mL) and sodium sulfate.

A 1-dram vial containing the resulting crude N–O alkylated adduct and a stir bar was charged with activated Zn^0 (130 mg, 2 mmol, 20 equiv) and 4:1 solution of 1.5 M HCl and THF (1.5 mL) and heated to 60 °C. The solution was stirred until consumption of the starting material was observed by TLC, upon which the crude reaction mixture was quenched with an aqueous solution of saturated $NaHCO_3$ (20 mL). The resulting precipitate was removed through vacuum filtration and the filtrate was extracted with EtOAc (3x 15 mL). The combined organic layers were washed with water (1x 15 mL) and once with brine (1x 15 mL) and then dried over

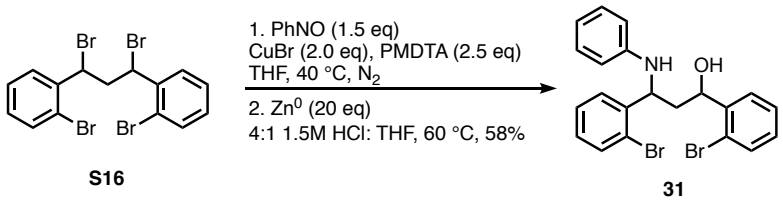
sodium sulfate. The crude product was dry loaded onto Celite and purified via flash chromatography with an increasing gradient of DCM in hexane (0 —> 50%) to afford **29** as a 3:1 mix of diastereomers (19 mg, 58%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.19 (m, 5H), 7.19 – 7.03 (m, 6H), 6.73 – 6.62 (m, 1H), 6.62 – 6.49 (m, 2H), 4.82 (dt, *J* = 6.9, 3.4 Hz, 1H), 4.57 (dt, *J* = 9.0, 5.2 Hz, 1H), 2.40 – 2.20 (m, 7H), 2.03 (ddd, *J* = 14.5, 5.1, 3.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.2, 141.5, 140.6, 137.4, 136.6, 129.4, 129.3, 129.3, 129.2, 129.1, 129.1, 126.2, 126.1, 125.7, 125.7, 117.9, 117.4, 114.3, 113.6, 73.6, 71.7, 57.7, 55.1, 47.4, 46.6, 21.1, 21.1; IR (thin film) 3366, 3011, 2912, 1596, 1499, 812, 689 cm^{-1}; HRMS (CI), calculated for $C_{23}H_{25}NO$ (M^+): 331.1936 observed 331.1935.



2,2-dimethyl-1,3-diphenyl-3-(phenylamino)propan-1-ol (**30**): To a 25 mL oven dried round bottom flask is added CuBr (28 mg, 0.2 mmol, 2 eq) and PMDTA (52 µL, 0.25 mmol, 2.5 eq) in THF (anhydrous, 7 mL). This suspension is sonicated for one minute and sparged with nitrogen for seven minutes. A second solution of nitrosobenzene (16 mg, 0.15 mmol, 1.5 eq) and dibromide **S15** (38 mg, 0.1 mmol, 1 eq) is prepared in THF (anhydrous, 3 mL) in a 10 mL conical flask. This solution is sparged with nitrogen for three minutes. The copper suspension is stirred at 40 °C under nitrogen while the nitroso solution is added dropwise to the copper suspension via syringe pump over ten hours. Upon completion of addition, the reaction is allowed to continue stirring under nitrogen for an additional six hours.

The solution is concentrated *in vacuo* and reconstituted in DCM (10 mL). The DCM solution is washed with EDTA (0.5 M, pH 8, 20 mL) and extracted with DCM (3 x 15 mL). The organic layers are combined and sequentially dried with brine (20 mL) and sodium sulfate.

A 1-dram vial containing the resulting crude N–O alkylated adduct and a stir bar was charged with activated Zn^0 (130 mg, 2 mmol, 20 equiv) and 4:1 solution of 1.5 M HCl and THF (1.5 mL) and heated to 60 °C. The solution was stirred until consumption of the starting material was observed by TLC, upon which the crude reaction mixture was quenched with an aqueous solution of saturated $NaHCO_3$ (20 mL). The resulting precipitate was removed through vacuum filtration and the filtrate was extracted with EtOAc (3x 15 mL). The combined organic layers were washed with water (1x 15 mL) and once with brine (1x 15 mL) and then dried over sodium sulfate. The crude product was dry loaded onto Celite and purified via flash chromatography with an increasing gradient of DCM in hexane (0 —> 50%) to afford **30** as a 2:1 mix of diastereomers (13 mg, 40%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 – 7.27 (m, 9H), 7.24 – 7.18 (m, 1H), 7.12 – 7.04 (m, 2H), 6.71 – 6.65 (m, 0.67 H, minor), 6.64 – 6.58 (m, 1.63H, major + minor), 6.57 – 6.53 (m, 0.7H, minor), 4.80 (s, 0.67H, major), 4.70 (s, 0.33H, minor), 4.46 (s, 0.67H, major), 4.36 (s, 0.33H, minor), 1.13 (s, 2H major), 0.96 (s, 1H minor), 0.92 (s, 1H minor), 0.62 (s, 2H major); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.8, 141.6, 140.1, 129.0, 128.9, 128.6, 128.0, 127.9, 127.8, 127.8, 127.7, 127.6, 127.5, 127.0, 126.9, 118.3, 116.9, 114.8, 113.5, 81.0, 80.4, 65.7, 65.4, 42.2, 29.7, 22.8, 22.2, 22.0, 15.8; IR (thin film) 3553, 3379, 3058, 3027, 2972, 2928, 2875, 1600, 1501, 1452, 1317, 1042, 750, 735, 703 cm^{-1}; HRMS (EI) calculated for $C_{23}H_{25}NO$ (M^+): 331.1936 observed 331.1934.



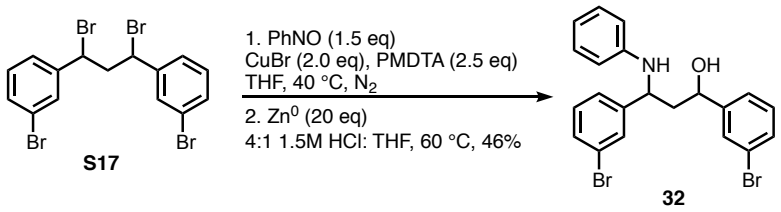
S16 **31**

1,3-bis(2-bromophenyl)-3-(phenylamino)propan-1-ol (**31**): To a 25 mL oven dried round bottom flask is added CuBr (28 mg, 0.2 mmol, 2 eq) and PMDTA (52 µL, 0.25 mmol, 2.5 eq) in THF (anhydrous, 7 mL). This suspension is sonicated for one minute and sparged with nitrogen for seven minutes. A second solution of nitrosobenzene (16 mg, 0.15 mmol, 1.5 eq) and dibromide **S16** (51 mg, 0.1 mmol, 1 eq) is prepared in THF (anhydrous, 3 mL) in a 10 mL conical flask. This solution is sparged with nitrogen for three minutes. The copper suspension is stirred at 40 °C under nitrogen while the nitroso solution is added dropwise to the copper suspension via syringe pump over ten hours. Upon completion of addition, the reaction is allowed to continue stirring under nitrogen for an additional six hours.

The solution is concentrated *in vacuo* and reconstituted in DCM (10 mL). The DCM solution is washed with EDTA (0.5 M, pH 8, 20 mL) and extracted with DCM (3 x 15 mL). The organic layers are combined and sequentially dried with brine (20 mL) and sodium sulfate.

A 1-dram vial containing the resulting crude N–O alkylated adduct and a stir bar was charged with activated Zn^0 (130 mg, 2 mmol, 20 equiv) and 4:1 solution of 1.5 M HCl and THF (1.5 mL) and heated to 60 °C. The solution was stirred until consumption of the starting material was observed by TLC, upon which the crude reaction mixture was quenched with an aqueous solution of saturated $NaHCO_3$ (20 mL). The resulting precipitate was removed through vacuum

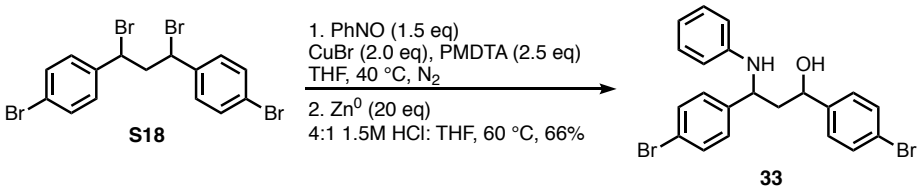
filtration and the filtrate was extracted with EtOAc (3x 15 mL). The combined organic layers were washed with water (1x 15 mL) and once with brine (1x 15 mL) and then dried over sodium sulfate. The crude product was dry loaded onto Celite and purified via flash chromatography with an increasing gradient of DCM in hexane (0 —> 50%) to afford **31** as a 2:1 mix of diastereomers (27 mg, 58%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 – 6.85 (m, 10H), 6.87 – 6.47 (m, 3H), 5.44 – 5.20 (m, 1H), 5.07 (ddd, J = 23.6, 8.9, 3.8 Hz, 0.5H), 4.74 – 4.69 (m, 0.5H), 2.37 – 1.78 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.1, 143.4, 133.1, 132.6, 129.1, 128.9, 128.7, 12, 127.8, 127.2, 127.0, 126.2, 118.2, 114.5, 114.2, 113.3, 73.2, 72.9, 58.8, 57.7, 45.8, 44.2; IR (thin film) 3377, 2913, 1597, 1500, 1020, 748 cm^{-1}; HRMS (CI), calculated for $C_{21}H_{19}NOBr_2$ (M^+): 458.9833 observed 458.9819.



1,3-bis(3-bromophenyl)-3-(phenylamino)propan-1-ol (**32**): To a 25 mL oven dried round bottom flask is added CuBr (28 mg, 0.2 mmol, 2 eq) and PMDTA (52 µL, 0.25 mmol, 2.5 eq) in THF (anhydrous, 7 mL). This suspension is sonicated for one minute and sparged with nitrogen for seven minutes. A second solution of nitrosobenzene (16 mg, 0.15 mmol, 1.5 eq) and dibromide **S17** (51 mg, 0.1 mmol, 1 eq) is prepared in THF (anhydrous, 3 mL) in a 10 mL conical flask. This solution is sparged with nitrogen for three minutes. The copper suspension is stirred at 40 °C under nitrogen while the nitroso solution is added dropwise to the copper suspension via syringe pump over ten hours. Upon completion of addition, the reaction is allowed to continue stirring under nitrogen for an additional six hours.

The solution is concentrated *in vacuo* and reconstituted in DCM (10 mL). The DCM solution is washed with EDTA (0.5 M, pH 8, 20 mL) and extracted with DCM (3 x 15 mL). The organic layers are combined and sequentially dried with brine (20 mL) and sodium sulfate.

A 1-dram vial containing the resulting crude N–O alkylated adduct and a stir bar was charged with activated Zn^0 (130 mg, 2 mmol, 20 equiv) and 4:1 solution of 1.5 M HCl and THF (1.5 mL) and heated to 60 °C. The solution was stirred until consumption of the starting material was observed by TLC, upon which the crude reaction mixture was quenched with an aqueous solution of saturated $NaHCO_3$ (20 mL). The resulting precipitate was removed through vacuum filtration and the filtrate was extracted with EtOAc (3x 15 mL). The combined organic layers were washed with water (1x 15 mL) and once with brine (1x 15 mL) and then dried over sodium sulfate. The crude product was dry loaded onto Celite and purified via flash chromatography with an increasing gradient of DCM in hexane (0 —> 50%) to afford **32** as a 10:1 mix of diastereomers (21 mg, 46%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 – 7.46 (m, 2H), 7.38 (m, 2H), 7.32 – 7.08 (m, 6H), 6.77 – 6.69 (m, 1H), 6.61 – 6.50 (m, 2H), 4.82 (dd, *J* = 9.6, 3.1 Hz, 1H), 4.62 (dd, *J* = 8.7, 3.4 Hz, 0.12H minor), 4.55 (dd, *J* = 9.1, 5.0 Hz, 0.88H major), 2.20 (dt, *J* = 14.5, 9.3 Hz, 1H), 1.98 (ddd, *J* = 14.5, 5.0, 3.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.6, 146.5, 146.0, 130.9, 130.4, 130.4, 130.2, 129.3, 129.2, 128.7, 124.8, 124.3, 122.9, 122.7, 118.4, 114.3, 73.1, 57.8, 47.2; IR (thin film) 3376, 3044, 2914, 1596, 1500, 1066, 780, cm^{-1}; HRMS (EI), calculated for $C_{21}H_{19}NOBr_2$ (M^+): 458.9833 observed 458.9840

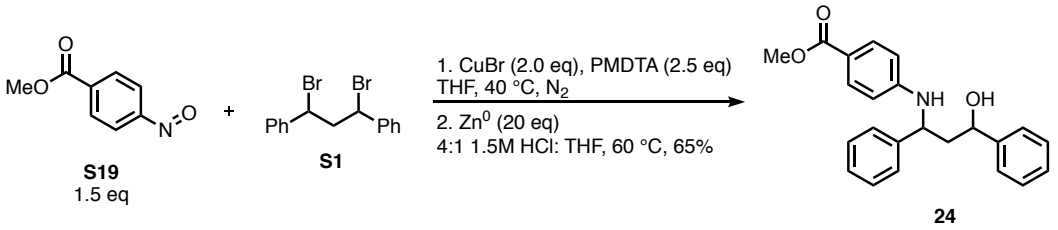


1,3-bis(4-bromophenyl)-3-(phenylamino)propan-1-ol (**33**): To a 25 mL oven dried round bottom flask is added CuBr (28 mg, 0.2 mmol, 2 eq) and PMDTA (52 µL, 0.25 mmol, 2.5 eq) in THF (anhydrous, 7 mL). This suspension is sonicated for one minute and sparged with nitrogen for seven minutes. A second solution of nitrosobenzene (16 mg, 0.15 mmol, 1.5 eq) and dibromide **S18** (51 mg, 0.1 mmol, 1 eq) is prepared in THF (anhydrous, 3 mL) in a 10 mL conical flask. This solution is sparged with nitrogen for three minutes. The copper suspension is stirred at 40 °C under nitrogen while the nitroso solution is added dropwise to the copper suspension via syringe pump over ten hours. Upon completion of addition, the reaction is allowed to continue stirring under nitrogen for an additional six hours.

The solution is concentrated *in vacuo* and reconstituted in DCM (10 mL). The DCM solution is washed with EDTA (0.5 M, pH 8, 20 mL) and extracted with DCM (3 x 15 mL). The organic layers are combined and sequentially dried with brine (20 mL) and sodium sulfate.

A 1-dram vial containing the resulting crude N–O alkylated adduct and a stir bar was charged with activated Zn^0 (130 mg, 2 mmol, 20 equiv) and 4:1 solution of 1.5 M HCl and THF (1.5 mL) and heated to 60 °C. The solution was stirred until consumption of the starting material was observed by TLC, upon which the crude reaction mixture was quenched with an aqueous solution of saturated $NaHCO_3$ (20 mL). The resulting precipitate was removed through vacuum filtration and the filtrate was extracted with EtOAc (3x 15 mL). The combined organic layers

were washed with water (1x 15 mL) and once with brine (1x 15 mL) and then dried over sodium sulfate. The crude product was dry loaded onto Celite and purified via flash chromatography with an increasing gradient of DCM in hexane (0 —> 50%) to afford **33** as a 5:1 mix of diastereomers (30 mg, 66%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 – 7.39 (m, 4H), 7.25 – 7.16 (m, 4H), 7.15 – 7.06 (m, 2H), 6.76 – 6.66 (m, 1H), 6.52 (ddt, *J* = 16.1, 6.9, 1.1 Hz, 2H), 4.80 (dd, *J* = 9.4, 3.4 Hz, 1H), 4.53 (dd, *J* = 9.1, 5.1 Hz, 1H), 2.19 (dt, *J* = 14.5, 9.2 Hz, 1H), 1.95 (ddd, *J* = 14.4, 5.1, 3.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.6, 143.2, 143.0, 142.5, 131.9, 131.8, 131.7, 129.2, 129.2, 128.0, 128.0, 127.4, 121.6, 121.5, 120.9, 118.4, 117.9, 114.3, 113.7, 73.0, 71.2, 57.4, 54.8, 47.2, 46.4; IR (thin film) 3374, 3042, 2913, 1596, 1480, 1067, 1006, 822, 748 cm^{-1}; HRMS (ESI), calculated for $C_{21}H_{19}Br_2NO$ ($M+H^+$): 459.9911 observed 459.9905.

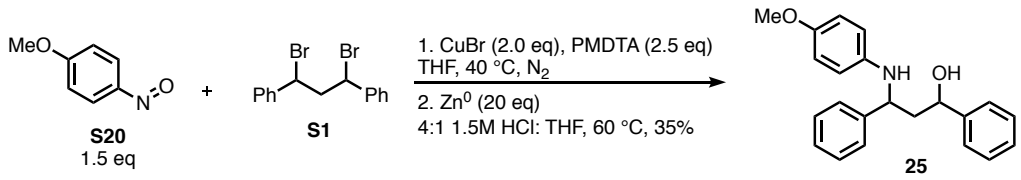


Methyl 4-((3-hydroxy-1,3-diphenylpropyl)amino)benzoate (**24**): To a 25 mL oven dried round bottom flask is added CuBr (28 mg, 0.2 mmol, 2 eq) and PMDTA (52 µL, 0.25 mmol, 2.5 eq) in THF (anhydrous, 7 mL). This suspension is sonicated for one minute and sparged with nitrogen for seven minutes. A second solution of nitrosoarene **S19** (25 mg, 0.15 mmol, 1.5 eq) and dibromide **S1** (35 mg, 0.1 mmol, 1 eq, 1.1:1 mix of diastereomers) is prepared in THF (anhydrous, 3 mL) in a 10 mL conical flask. This solution is sparged with nitrogen for three minutes. The copper suspension is stirred at 40 °C under nitrogen while the nitroso solution is added dropwise to the copper suspension via syringe pump over ten hours. Upon

completion of addition, the reaction is allowed to continue stirring under nitrogen for an additional six hours.

The solution is concentrated *in vacuo* and reconstituted in DCM (10 mL). The DCM solution is washed with EDTA (0.5 M, pH 8, 20 mL) and extracted with DCM (3 x 15 mL). The organic layers are combined and sequentially dried with brine (20 mL) and sodium sulfate.

A 1-dram vial containing the resulting crude N–O alkylated adduct and a stir bar was charged with activated Zn^0 (130 mg, 2 mmol, 20 equiv) and 4:1 solution of 1.5 M HCl and THF (1.5 mL) and heated to 60 °C. The solution was stirred until consumption of the starting material was observed by TLC, upon which the crude reaction mixture was quenched with an aqueous solution of saturated $NaHCO_3$ (20 mL). The resulting precipitate was removed through vacuum filtration and the filtrate was extracted with EtOAc (3x 15 mL). The combined organic layers were washed with water (1x 15 mL) and once with brine (1x 15 mL) and then dried over sodium sulfate. The crude product was dry loaded onto Celite and purified via flash chromatography with an increasing gradient of DCM in hexane (0 —> 50%) to afford **24** as a 4.6:1 mix of diastereomers (23.5 mg, 65%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.5 Hz, 2H), 7.40 – 7.25 (m, 9H), 6.46 (d, *J* = 8.5 Hz, 2H), 4.79 (dd, *J* = 9.2, 3.3 Hz, 1H), 4.61 (dd, *J* = 8.7, 5.6 Hz, 1H), 3.79 (s, 3H), 2.30 (dt, *J* = 14.5, 9.0 Hz, 1H), 2.06 (ddd, *J* = 14.5, 5.6, 3.4 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.3, 151.1, 144.2, 142.9, 131.3, 128.8, 128.7, 128.0, 127.4, 126.1, 125.6, 118.5, 112.6, 73.4, 57.2, 51.5, 47.2; IR (thin film) 3368, 3029, 2948, 1685, 1601, 1523, 1434, 1274, 1172, 836, 771 cm^{-1}; HRMS (EI) calculated for $C_{23}H_{23}NO_3$ (M^+): 361.1670 observed 361.1674.

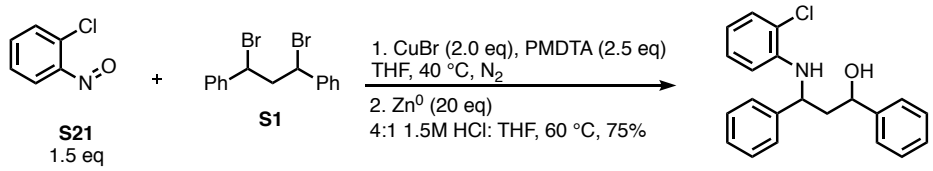


3-((4-methoxyphenyl)amino)-1,3-diphenylpropan-1-ol (**25**): To a 25 mL oven dried round bottom flask is added CuBr (28 mg, 0.2 mmol, 2 eq) and PMDTA (52 µL, 0.25 mmol, 2.5 eq) in THF (anhydrous, 7 mL). This suspension is sonicated for one minute and sparged with nitrogen for seven minutes. A second solution of nitrosoarene **S20** (20 mg, 0.15 mmol, 1.5 eq) and dibromide **S1** (35 mg, 0.1 mmol, 1 eq, 1.1:1 mix of diastereomers) is prepared in THF (anhydrous, 3 mL) in a 10 mL conical flask. This solution is sparged with nitrogen for three minutes. The copper suspension is stirred at 40 °C under nitrogen while the nitroso solution is added dropwise to the copper suspension via syringe pump over ten hours. Upon completion of addition, the reaction is allowed to continue stirring under nitrogen for an additional six hours.

The solution is concentrated *in vacuo* and reconstituted in DCM (10 mL). The DCM solution is washed with EDTA (0.5 M, pH 8, 20 mL) and extracted with DCM (3 x 15 mL). The organic layers are combined and sequentially dried with brine (20 mL) and sodium sulfate.

A 1-dram vial containing the resulting crude N–O alkylated adduct and a stir bar was charged with activated Zn^0 (130 mg, 2 mmol, 20 equiv) and 4:1 solution of 1.5 M HCl and THF (1.5 mL) and heated to 60 °C. The solution was stirred until consumption of the starting material was observed by TLC, upon which the crude reaction mixture was quenched with an aqueous solution of saturated $NaHCO_3$ (20 mL). The resulting precipitate was removed through vacuum

filtration and the filtrate was extracted with EtOAc (3x 15 mL). The combined organic layers were washed with water (1x 15 mL) and once with brine (1x 15 mL) and then dried over sodium sulfate. The crude product was dry loaded onto Celite and purified via flash chromatography with an increasing gradient of EtOAc in hexane (0 —> 50%) to afford **25** as a 2.4:1 mix of diastereomers (17 mg, 51%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37 – 7.25 (m, 9H), 7.19 (tt, *J* = 6.1, 2.2 Hz, 1H), 6.70 – 6.65 (m, 2H), 6.58 – 6.54 (m, 1.31H major), 6.50 – 6.46 (m, 0.65H minor), 4.91 (td, *J* = 9.3, 8.8, 3.4 Hz, 1H), 4.53 (dd, *J* = 9.5, 4.5 Hz, 0.64H major), 4.50 (dd, *J* = 8.8, 3.8 Hz, 0.32H minor), 3.68 (d, *J* = 5.4 Hz, 3H), 2.30 – 2.14 (m, 1H), 2.04 (ddd, *J* = 14.5, 4.5, 3.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.8, 144.5, 143.6, 140.9, 128.7, 128.6, 128.6, 128.5, 127.6, 127.6, 127.2, 127.0, 126.3, 126.2, 125.7, 125.7, 116.3, 115.4, 114.7, 114.7, 74.2, 72.0, 59.7, 56.4, 55.7, 55.7, 47.3, 46.5; IR (thin film) 3377, 3027, 2919, 2850, 1501, 1452, 1233, 1028, 818, 751 cm^{-1}; HRMS (CI) calculated for $C_{22}H_{23}NO_2$ (M^+): 333.1729; observed 333.1731.[8]



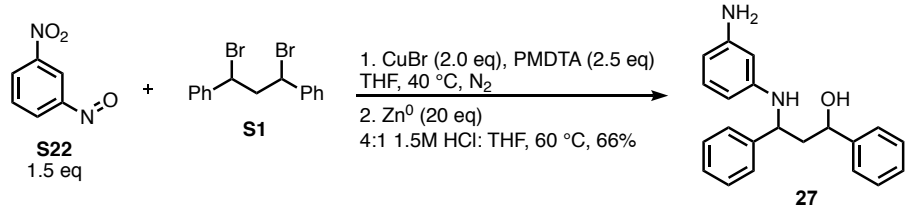
3-((2-chlorophenyl)amino)-1,3-diphenylpropan-1-ol (**26**): To a 25 mL oven dried round bottom flask is added CuBr (28 mg, 0.2 mmol, 2 eq) and PMDTA (52 µL, 0.25 mmol, 2.5 eq) in THF (anhydrous, 7 mL). This suspension is sonicated for one minute and sparged with nitrogen for seven minutes. A second solution of nitrosoarene **S21** (21 mg, 0.15 mmol, 1.5 eq) and dibromide **S1** (35 mg, 0.1 mmol, 1 eq, 1.1:1 mix of diastereomers) is prepared in THF (anhydrous, 3 mL) in a 10 mL conical flask. This solution is sparged with nitrogen for three

minutes. The copper suspension is stirred at 40 °C under nitrogen while the nitroso solution is added dropwise to the copper suspension via syringe pump over ten hours. Upon completion of addition, the reaction is allowed to continue stirring under nitrogen for an additional six hours.

The solution is concentrated *in vacuo* and reconstituted in DCM (10 mL). The DCM solution is washed with EDTA (0.5 M, pH 8, 20 mL) and extracted with DCM (3 x 15 mL). The organic layers are combined and sequentially dried with brine (20 mL) and sodium sulfate.

A 1-dram vial containing the resulting crude N–O alkylated adduct and a stir bar was charged with activated Zn^0 (130 mg, 2 mmol, 20 equiv) and 4:1 solution of 1.5 M HCl and THF (1.5 mL) and heated to 60 °C. The solution was stirred until consumption of the starting material was observed by TLC, upon which the crude reaction mixture was quenched with an aqueous solution of saturated $NaHCO_3$ (20 mL). The resulting precipitate was removed through vacuum filtration and the filtrate was extracted with EtOAc (3x 15 mL). The combined organic layers were washed with water (1x 15 mL) and once with brine (1x 15 mL) and then dried over sodium sulfate. The crude product was dry loaded onto Celite and purified via flash chromatography with an increasing gradient of DCM in hexane (0 —> 50%) to afford **26** as a 2.3:1 mix of diastereomers (25 mg, 75%). *Major diastereomer*: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.20 (m, 9H), 7.16 (dt, *J* = 6.4, 2.1 Hz, 1H), 6.91 (t, *J* = 8.0 Hz, 1H), 6.55 (dd, *J* = 7.9, 2.0 Hz, 1H), 6.46 (t, *J* = 2.2 Hz, 1H), 6.32 (dd, *J* = 8.1, 2.4 Hz, 1H), 4.75 (dd, *J* = 9.2, 3.3 Hz, 1H), 4.47 (dd, *J* = 8.8, 5.3 Hz, 1H), 2.20 (dt, *J* = 14.6, 9.0 Hz, 1H), 1.98 (ddd, *J* = 14.5, 5.4, 3.3 Hz, 1H); *Minor diastereomer*: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 – 7.20 (m, 9H), 7.19 –

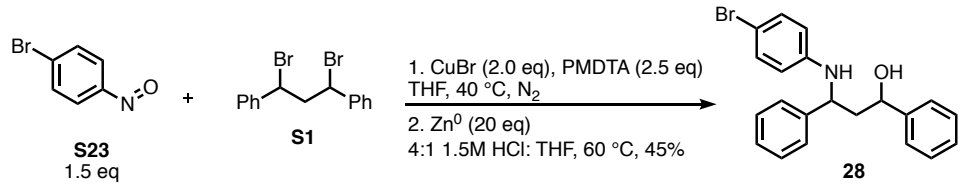
7.14 (m, 1H), 6.91 (t, J = 8.0 Hz, 1H), 6.55 (ddd, J = 7.9, 2.0, 0.9 Hz, 1H), 6.46 (t, J = 2.1 Hz, 1H), 6.32 (ddd, J = 8.2, 2.3, 0.9 Hz, 1H), 4.76 (dd, J = 9.3, 3.3 Hz, 1H), 4.47 (dd, J = 8.8, 5.3 Hz, 1H), 2.20 (dt, J = 14.5, 9.1 Hz, 1H), 1.98 (ddd, J = 14.5, 5.3, 3.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.3, 143.2, 130.0, 128.8, 128.7, 127.9, 127.3, 126.2, 125.7, 117.6, 113.8, 112.1, 105.0, 73.6, 57.7, 47.4; IR (thin film) 3382, 3028, 2921, 1595, 1482, 1323, 988, 908, 761 cm^{-1}; HRMS (EI), calculated for $C_{21}H_{20}NOCl$ (M^+): 337.1229; observed 337.1229.



3-((3-aminophenyl)amino)-1,3-diphenylpropan-1-ol (**27**): To a 25 mL oven dried round bottom flask is added CuBr (28 mg, 0.2 mmol, 2 eq) and PMDTA (52 µL, 0.25 mmol, 2.5 eq) in THF (anhydrous, 7 mL). This suspension is sonicated for one minute and sparged with nitrogen for seven minutes. A second solution of nitrosoarene **S22** (23 mg, 0.15 mmol, 1.5 eq) and dibromide **S1** (35 mg, 0.1 mmol, 1 eq, 1.1:1 mix of diastereomers) is prepared in THF (anhydrous, 3 mL) in a 10 mL conical flask. This solution is sparged with nitrogen for three minutes. The copper suspension is stirred at 40 °C under nitrogen while the nitroso solution is added dropwise to the copper suspension via syringe pump over ten hours. Upon completion of addition, the reaction is allowed to continue stirring under nitrogen for an additional six hours.

The solution is concentrated *in vacuo* and reconstituted in DCM (10 mL). The DCM solution is washed with EDTA (0.5 M, pH 8, 20 mL) and extracted with DCM (3 x 15 mL). The organic layers are combined and sequentially dried with brine (20 mL) and sodium sulfate.

A 1-dram vial containing the resulting crude N–O alkylated adduct and a stir bar was charged with activated Zn^0 (130 mg, 2 mmol, 20 equiv) and 4:1 solution of 1.5 M HCl and THF (1.5 mL) and heated to 60 °C. The solution was stirred until consumption of the starting material was observed by TLC, upon which the crude reaction mixture was quenched with an aqueous solution of saturated $NaHCO_3$ (20 mL). The resulting precipitate was removed through vacuum filtration and the filtrate was extracted with EtOAc (3x 15 mL). The combined organic layers were washed with water (1x 15 mL) and once with brine (1x 15 mL) and then dried over sodium sulfate. The crude product was dry loaded onto Celite and purified via flash chromatography with an increasing gradient of DCM in hexane (0 —> 50%) to afford **27** as a 3.1:1 mix of diastereomers (21 mg, 66%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 – 7.19 (m, 9H), 7.15 – 7.11 (m, 1H), 6.84 – 6.77 (m, 1H), 6.00 – 5.91 (m, 2H), 5.84 (t, *J* = 2.2 Hz, 1H 0.84 major), 5.77 (t, *J* = 2.2 Hz, 0.16H minor), 4.77 (dt, *J* = 8.7, 3.4 Hz, 1H), 4.50 (ddd, *J* = 17.3, 8.8, 4.5 Hz, 1H), 2.26 – 2.11 (m, 1H), 2.00 – 1.94 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.4, 147.3, 144.5, 143.8, 129.9, 129.9, 128.7, 128.6, 128.6, 128.6, 127.7, 127.7, 127.1, 126.9, 126.3, 126.2, 125.8, 125.7, 105.6, 105.5, 105.1, 104.9, 101.1, 100.3, 73.8, 71.8, 57.9, 55.2, 47.5, 46.8; IR (thin film) 3340, 3019, 2914, 1610, 1489, 1334, 1210, 824, 757, 698 cm^{-1}; HRMS (ESI), calculated for $C_{21}H_{22}N_2O$: ($M+H^+$) 319.1810; observed 319.1818.

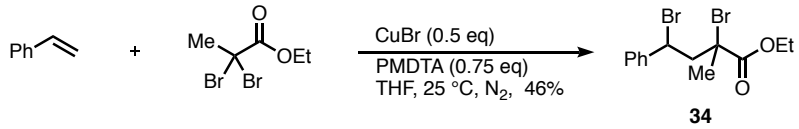


3-((4-bromophenyl)amino)-1,3-diphenylpropan-1-ol (**28**): To a 25 mL oven dried round bottom flask is added CuBr (28 mg, 0.2 mmol, 2 eq) and PMDTA (52 µL, 0.25 mmol, 2.5 eq) in THF (anhydrous, 7 mL). This suspension is sonicated for one minute and sparged with nitrogen for seven minutes. A second solution of nitrosoarene **S22** (27.5 mg, 0.15 mmol, 1.5 eq) and dibromide **S1** (35 mg, 0.1 mmol, 1 eq, 1.1:1 mix of diastereomers) is prepared in THF (anhydrous, 3 mL) in a 10 mL conical flask. This solution is sparged with nitrogen for three minutes. The copper suspension is stirred at 40 °C under nitrogen while the nitroso solution is added dropwise to the copper suspension via syringe pump over ten hours. Upon completion of addition, the reaction is allowed to continue stirring under nitrogen for an additional six hours.

The solution is concentrated *in vacuo* and reconstituted in DCM (10 mL). The DCM solution is washed with EDTA (0.5 M, pH 8, 20 mL) and extracted with DCM (3 x 15 mL). The organic layers are combined and sequentially dried with brine (20 mL) and sodium sulfate.

A 1-dram vial containing the resulting crude N–O alkylated adduct and a stir bar was charged with activated Zn^0 (130 mg, 2 mmol, 20 equiv) and 4:1 solution of 1.5 M HCl and THF (1.5 mL) and heated to 60 °C. The solution was stirred until consumption of the starting material was observed by TLC, upon which the crude reaction mixture was quenched with an aqueous solution of saturated $NaHCO_3$ (20 mL). The resulting precipitate was removed through vacuum

filtration and the filtrate was extracted with EtOAc (3x 15 mL). The combined organic layers were washed with water (1x 15 mL) and once with brine (1x 15 mL) and then dried over sodium sulfate. The crude product was dry loaded onto Celite and purified via flash chromatography with an increasing gradient of DCM in hexane (0 —> 50%) to afford **28** as a 3.9:1 mix of diastereomers (17 mg, 45%). Major Diastereomer ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.27 (m, 10H), 7.18 – 7.14 (m, 2H), 6.45 – 6.40 (m, 2H), 4.84 (dd, *J* = 9.2, 3.4 Hz, 1H), 4.53 (dd, *J* = 8.9, 5.3 Hz, 1H), 2.28 (dt, *J* = 14.4, 9.0 Hz, 1H), 2.06 (ddd, *J* = 14.5, 5.3, 3.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.3, 144.3, 143.2, 131.8, 128.8, 128.7, 127.9, 127.3, 126.2, 125.6, 115.9, 105.0, 73.7, 57.8, 47.4, 29.7; IR (thin film) 3372, 2924, 1594, 1491, 1454, 1072, 813, 757 cm^{-1}; HRMS (ESI), calculated for $C_{21}H_{20}BrNO$: ($M+H^+$) 382.0807 and 384.0789; observed 382.0807 and 384.084096.

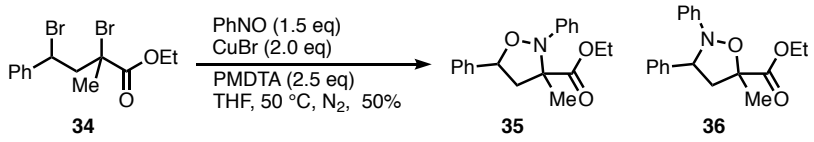


34

Ethyl 2,4-dibromo-2-methyl-4-phenylbutanoate (**34**): To a flame dried 50 mL round bottom flask is added styrene (124 µL, 1 mmol, 1 eq), ethyl 2,2-dibromopropanoate[9] (260 mg, 1 mmol, 1 eq) and CuBr (72 mg, 0.5 mmol, 0.5 eq) in THF (20 mL, anhydrous) and sparged for ten minutes through a runner septum. Next, PMDTA (129 µL, 0.75 mmol, 0.75 eq) is added through the septum to initiate the reaction. After three hours, NMR of an aliquot indicates consumption of the ester. The solution is washed with EDTA (0.5 M, pH 8) and extracted with EtOAc (3 x 15 mL) and dried sequentially with brine and sodium sulfate.

The material was dissolved in a minimal amount (~3 mL) of hexane and loaded directly onto a silica column and purified with an increasing gradient of DCM in hexane (10 —> 40 %) to

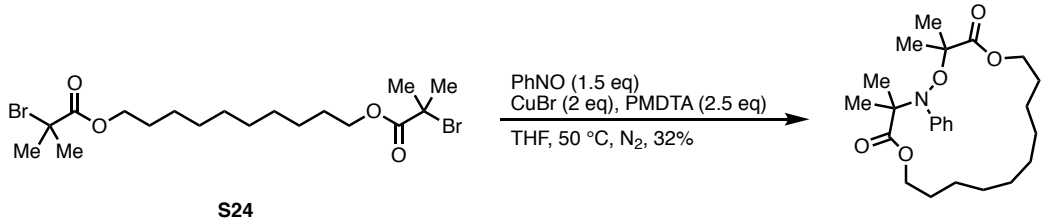
yield **34** as a yellow oil (150 mg, 42%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.41 (d, *J* = 7.0 Hz, 2H), 7.33 (d, *J* = 7.2 Hz, 2H), 7.30 – 7.24 (m, 1H), 5.17 (q, *J* = 6.4, 5.9 Hz, 1H), 4.04 (dq, *J* = 10.9, 7.1 Hz, 1H), 3.93 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.26 – 3.19 (m, 2H), 1.84 (s, 3H), 1.23 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, Chloroform-*d*) δ 170.2, 141.1, 128.7, 128.7, 127.7, 62.34, 59.2, 51.43, 49.9, 28.5, 13.7; IR (thin film) 3027, 2975, 2932, 1732, 1454, 1381, 1254, 1200, 1166, 1109, 1061, 1024, 759, 697 cm^{-1}; HRMS (EI) calculated for $C_{13}H_{16}Br_2O_2$: $(M–Br^–)^+$ 283.0334; observed 283.0323. EI is reported as –Br- due to ionization of bromine which occurs in the mass spec source.



Ethyl 5-methyl-2,3-diphenylisoxazolidine-5-carboxylate and ethyl 3-methyl-2,5-diphenylisoxazolidine-3-carboxylate (**35** and **36**): To a 25 mL oven dried round bottom flask is added CuBr (28 mg, 0.2 mmol, 2 eq) and PMDTA (52 µL, 0.25 mmol, 2.5 eq) in THF (anhydrous, 11 mL). This suspension is sonicated for one minute and sparged with nitrogen for ten minutes. A second solution of nitrosobenzene (16 mg, 0.15 mmol, 1.5 eq) and dibromide **34** (0.1 mmol, 1 eq) is prepared in THF (anhydrous, 4 mL) in a 10 mL conical flask. This solution is sparged with nitrogen for three minutes. The copper suspension is stirred at 50 °C under nitrogen while the nitroso solution is added dropwise to the copper suspension via syringe pump over ten hours. Upon completion of addition, the reaction is allowed to continue stirring under nitrogen for an additional six hours.

The solution is concentrated *in vacuo* and reconstituted in EtOAc (10 mL). The EtOAc solution is washed with EDTA (0.5 M, pH 8, 20 mL) and extracted with EtOAc (3 x 15 mL). The organic layers are combined and sequentially dried with brine (20 mL) and magnesium sulfate. The crude product was dry loaded onto Celite and purified via flash chromatography with an increasing gradient of DCM in hexane (0 —> 35%) to afford **35** + **36** as an inseparable mix of regioisomers and diastereomers (15.5 mg, 50%).

Major regioisomer as a mix of diastereomers: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.57 (d, *J* = 7.2 Hz, 1H), 7.48 (d, *J* = 7.2 Hz, 1H), 7.40 (t, *J* = 7.4 Hz, 2H), 7.36 – 7.30 (m, 1H), 7.31 – 7.20 (m, 2H), 7.20 – 7.13 (m, 1H), 7.10 (d, *J* = 7.8 Hz, 1H), 7.02 (d, *J* = 7.3 Hz, 1H), 5.40 (dd, *J* = 8.8, 7.1 Hz, 1H), 5.27 (dd, *J* = 8.8, 7.0 Hz, 1H), 4.22 (d, 1H), 3.94 (q, *J* = 7.1 Hz, 1H), 3.21 (dd, *J* = 12.4, 7.1 Hz, 0.5H), 3.01 (dd, *J* = 12.2, 8.9 Hz, 0.5H), 2.62 (dd, *J* = 12.3, 7.0 Hz, 0.5H), 2.33 (dd, *J* = 12.4, 8.8 Hz, 0.5H), 1.70 (s, 1.5H), 1.46 (s, 1.5H), 1.23 (t, *J* = 7.1 Hz, 1.5H), 1.01 (t, *J* = 7.1 Hz, 1.5H); *minor regioisomer, as differentiable from the major:* ^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.87 (t, *J* = 7.4 Hz, 1H), 4.77 (dd, *J* = 9.2, 7.4 Hz, 1H), 4.48 (dd, *J* = 9.1, 6.5 Hz, 2H), 4.02 (q, *J* = 7.2 Hz, 2H), 3.36 (dd, *J* = 12.4, 7.3 Hz, 0.5H), 3.09 – 3.01 (m, 0.5H), 2.68 (dd, *J* = 12.7, 9.2 Hz, 0.5H), 2.40 – 2.29 (m, 0.5H), 1.09 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, Chloroform-*d*) δ 172.8, 172.4, 147.0, 147.0, 139.3, 138.8, 128.8, 128.8, 128.7, 128.5, 128.5, 128.4, 128.4, 128.3, 128.1, 127.0, 126.9, 126.4, 123.2, 123.0, 117.6, 117.6, 117.0, 78.4, 78.2, 71.5, 70.9, 61.6, 61.2, 51.5, 50.7, 29.7, 23.3, 21.3, 14.0, 13.8; IR (thin film) 2927, 2850, 1726, 1598, 1448, 1259, 1158, 1096, 1027, 756, 699 cm $^{-1}$; HRMS (ESI) calculated for $C_{19}H_{21}NO_3$: ($M+Na^+$) 334.1419; observed 334.1425.



S24 **S25**

3,3,18,18-tetramethyl-2-phenyl-1,5,16-trioxa-2-azacyclooctadecane-4,17-dione (S25): To a 100 mL oven dried round bottom flask is added CuBr (28 mg, 0.2 mmol, 2 eq) and PMDTA (52 µL, 0.25 mmol, 2.5 eq) in THF (anhydrous, 30 mL). This suspension is sonicated for one minute and sparged with nitrogen for thirty minutes. A second solution of nitrosobenzene (16 mg, 0.15 mmol, 1.5 eq) and dibromide **S24** (47 mg, 0.1 mmol, 1 eq) is prepared in THF (anhydrous, 10 mL) in a 25 mL conical flask. This solution is sparged with nitrogen for ten minutes. The copper suspension is stirred at 50 °C under nitrogen while the nitroso solution is added dropwise to the copper suspension via syringe pump over ten hours. Upon completion of addition, the reaction is allowed to continue stirring under nitrogen for an additional six hours.

The solution is concentrated *in vacuo* and reconstituted in DCM (10 mL). The DCM solution is washed with EDTA (0.5 M, pH 8, 20 mL) and extracted with DCM (3 x 15 mL). The organic layers are combined and sequentially dried with brine (20 mL) and sodium sulfate. The crude product was dry loaded onto Celite and purified via flash chromatography with an increasing gradient of DCM in hexane to yield **S25** as a clear oil (13.4 mg, 32%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.24 – 7.19 (m, 4H), 7.14 – 7.08 (m, 1H), 4.23 – 4.03 (m, 2H), 3.65 – 3.54 (m, 2H), 1.74 (p, *J* = 6.6 Hz, 2H), 1.54 – 1.20 (m, 26H); ^{13}C NMR (125 MHz, Chloroform-*d*) δ 173.5, 172.8, 148.50 , 127.5, 125.8, 125.4, 81.1, 67.9, 64.7, 64.6, 28.1, 27.5, 27.2, 27.0, 26.9, 26.7, 25.5, 24.7, 24.6, 23.5, 23.4, 23.3; IR (thin film) 2938, 2854, 1734, 1460, 1377, 1362,

1280, 1169, 1143, 767 cm $^{-1}$; HRMS (ESI) calculated for $C_{14}H_{37}NO_6$: ($M+Na^+$) 442.2570; observed 442.2557.

References

1 G. W. Kabalka, Z. Wu, Y. Ju and M. L. Yao, *J. Org. Chem.*, 2005, **70**, 10285–10291.
2 V. Mojr, E. Svobodová, K. Straková, T. Neveselý, J. Chudoba, H. Dvořáková and R. Cibulka, *Chem. Commun.*, 2015, **51**, 12036–12039.
3 B. Priewisch and K. Rück-Braun, *J. Org. Chem.*, 2005, **70**, 2350–2352.
4 D. J. Fisher, J. B. Shaum, C. L. Mills and J. Read De Alaniz, *Org. Lett.*, 2016, **18**, 5074–5077.
5 R. Huisgen, R. Grashey, H. Hauck and H. Seidl, *Chem. Ber.*, 1968, **101**, 2548–2558.
6 K. B. Simonsen, P. Bayón, R. G. Hazell, K. V Gothelf and K. A. Jørgensen, *J. Am. Chem. Soc.*, 1999, **121**, 3845–3853.
7 A. N. Artemov, E. V Sazonova, E. A. Mavrina and N. Y. Zarovkina, *Russ. Chem. Bull.*, 2012, **61**, 2076–2081.
8 J. Barluenga, F. J. Fananas, J. Villamana and M. Yus, *J. Org. Chem.*, 1982, **47**, 1560–1564.
9 M. Shindo, K. Masumoto and K. Shishido, *Org. Synth.*, 2007, **84**, 11.

9- Supporting information for Chapter 6: A single electron approach for pyrroloindoline amination

Section 1- Materials and Methods

All commercially obtained reagents were used as received. Flash column chromatography was performed using normal phase silica gel (60 Å, 230-240 mesh, Geduran®) with a Yamazen chromatograph. ^{1}H NMR spectra were recorded on Varian (at

400, 500 and 600 MHz) or Bruker (400 and 500 MHz) Spectrometers and are reported relative to deuterated solvent signals. Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz) and integration. ^{13}C NMR spectra were recorded on Varian (at 100, 125 and 150 MHz) or Bruker (at 125 MHz) Spectrometers. Data for ^{13}C NMR spectra are reported in terms of chemical shift. These NMRs are housed at the UCSB Department of Chemistry and Biochemistry and the Materials Research Laboratory. Unless otherwise stated, NMR spectroscopy was carried out at an unregulated ambient temperature.

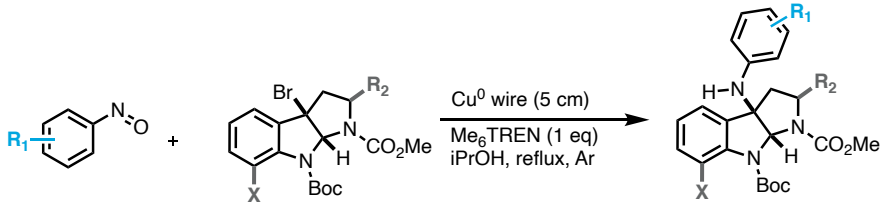
IR spectra were recorded on a Perkin Elmer Spectrum 100 FT/IR and a Bruker Alpha FT/IR and are reported in terms of frequency of absorption (cm-1). Low- and high-resolution mass spectra were obtained from the UC Santa Barbara Mass Spectrometry Facility within the Department of Chemistry and Biochemistry with a Waters LCT Premier ESI TOF instrument.

Unless otherwise stated, all reactions are run in round bottom flasks equipped with Teflon coated magnetic stirbars and sealed with rubber septa. Reactions were conducted in flame-dried or oven-dried glassware under an atmosphere of N_2 using reagent grade solvents. Reaction temperatures were controlled using a Heidolph temperature modulator, and unless stated otherwise, reactions were performed at room temperature (rt, approximately 25 °C). Thin-layer chromatography (TLC) was conducted with E. Merck silica gel 60 F254 pre-coated plates, (0.25 mm) and visualized by exposure to UV light (254 and 280 nm) or stained with Hanessian's stain or anisaldehyde. Purification was performed with Geduran SI 60,

0.040-0.063 μm silica, purchased from MilliporeSigma, or with C18-bonded silica obtained from Biotage.

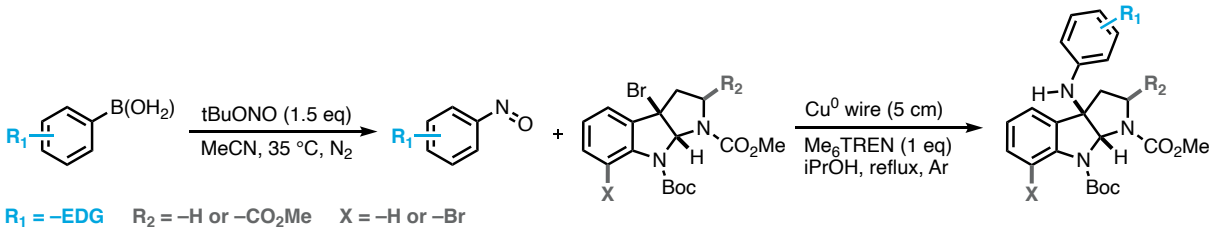
Section 2- General Experimental Procedures

2a- General Procedures for C–N bond formation



General Procedure 1a for electron deficient or neutral nitroso adducts

To a 10 mL round bottom flask is added pyrroloindoline **x** (0.06 mmol, 1 eq), nitrosoarene (0.012 mmol, 2 eq), Me_6TREN (16 µL, 0.06 mmol, 1 eq), and anhydrous isopropanol (3 mL) with a stir bar wrapped in 5 cm of freshly activated copper wire. The flask is capped with a reflux condenser and heated to 110 °C for sixteen hours under an atmosphere of argon. The reaction mixture was allowed to cool to RT and then the solution was concentrated and reconstituted in DCM. This solution was loaded directly onto a flash column (15 g silica). The product is purified with an increasing gradient of ethyl acetate in hexane (5—> 45%).

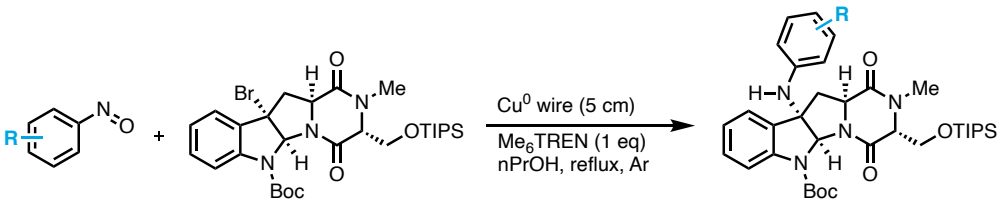


General Procedure 1b for electron rich nitroso adducts

To a 10 mL round bottom flask is added arylboronic acid **x** (0.15 mmol, 2.5 eq) and MeCN (1.5 mL) and a Teflon coated stir bar. After the reaction vial is capped with a rubber septum and sparged with anhydrous nitrogen (three minutes), *t*BuONO (27 µL, 0.23 mmol, 3.75 eq) is added through the septum. The reaction is then heated to 35 °C and stirred under nitrogen until consumption of the starting material is observed by TLC (~2 hours). The reaction is

then concentrated *in vacuo* resulting in a green solid; this resulting nitrosoarene is carried forward to the next step without purification.

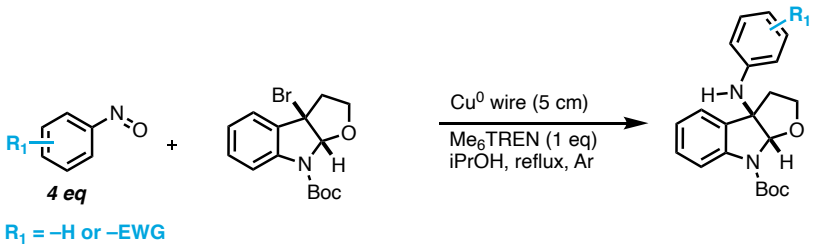
To this round bottom flask is added pyrroloindoline **x** (0.06 mmol, 1 eq), Me_6TREN (16 µL, 0.06 mmol, 1 eq) and anhydrous isopropanol (3 mL) with a stir bar wrapped in 5 cm of freshly activated copper wire. The flask is capped with a reflux condenser and heated to 110 °C for sixteen hours under an atmosphere of argon. The reaction mixture was allowed to cool to RT and then the solution was concentrated and reconstituted in DCM. This solution was loaded directly onto a flash column (15 g silica). The product is purified with an increasing gradient of ethyl acetate in hexane (5 —> 45%).



General Procedure 2 for chetomin scaffold adducts

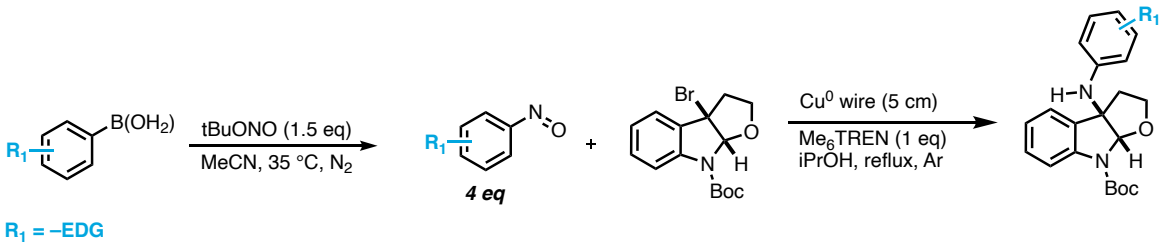
To a 15 mL two neck round bottom flask is added bromo-indoline **1** (38 mg, 0.06 mmol, 1 eq), nitrosoarene (0.12 mmol, 2 eq), Me_6TREN (16 µL, 0.06 mmol, 1 eq), and anhydrous n-propanol (3 mL) with a stir bar wrapped in 5 cm of freshly activated copper wire. The flask is capped with a reflux condenser and heated to a vigorous reflux (120 °C) until TLC indicates consumption of starting material and the more-polar hydroxylamine intermediate (9 hours) under an atmosphere of argon. The reaction mixture was allowed to cool to room temperature

and then the solution was concentrated and reconstituted in DCM. This solution was loaded directly onto a flash column (15 g silica). The product is purified with an increasing gradient of ethyl acetate in dichloromethane (5—> 25%) to afford the product.



General Procedure 3a for Furoindoline scaffold adducts

To a 15 mL two neck round bottom flask is added nitrosoarene (0.24 mmol, 4 eq), Me_6TREN (16 µL, 0.06 mmol, 1 eq), and anhydrous n-propanol (3 mL) with a stir bar wrapped in 5 cm of freshly activated copper wire. The flask is capped with a reflux condenser and heated to a vigorous reflux (120 °C) under an atmosphere of argon while bromo-furoindoline (20 mg, 0.06 mmol, 1 eq) in 10% EtOAc in isopropanol (1 mL) is added dropwise via syringe pump over 90 minutes. After TLC indicates completion of the reaction (about 6 hours after the initiation of indoline addition), the reaction is cooled to room temperature and then the solution was concentrated and reconstituted in DCM. This solution was loaded directly onto a flash column (15 g silica). The product is purified with an increasing gradient of ethyl acetate in hexane (5 —> 45%).



General Procedure 3b for electron-rich Furoindoline scaffold adducts

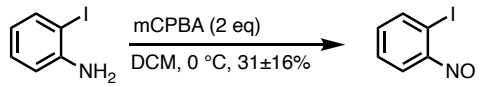
To a 15 mL two-neck round bottom flask is added arylboronic acid (0.3 mmol, 5 eq) and MeCN (1.5 mL) and a Teflon coated stir bar. After the reaction vial is capped with a rubber septum and sparged with anhydrous nitrogen (three minutes), *t*BuONO (27 mL, 0.23 mmol, 7.5 eq) is added through the septum. The reaction is then heated to 35 °C and stirred under nitrogen until consumption of the starting material is observed by TLC (~2 hours). The reaction is then concentrated *in vacuo* resulting in a green solid; this resulting nitrosoarene is carried forward to the next step without purification.

To this vial is added Me_6TREN (16 μL, 0.06 mmol, 1 eq), and anhydrous n-propanol (3 mL) with a stir bar wrapped in 5 cm of freshly activated copper wire. The flask is capped with a reflux condenser and heated to a vigorous reflux (120 °C) under an atmosphere of argon while bromo-furoindoline (20 mg, 0.06 mmol, 1 eq) in 10% EtOAc in isopropanol (1 mL) is added dropwise via syringe pump over 90 minutes. After TLC indicates completion of the reaction (about 6 hours after the initiation of indoline addition), the reaction is cooled to room temperature and then the solution was concentrated and reconstituted in DCM. This solution was loaded directly onto a flash column (15 g silica). The product is purified with an increasing gradient of ethyl acetate in hexane (5 —> 45%).

2b- Preparation of Nitrosoarenes

Unless otherwise stated, all nitroso arenes used in this work were prepared according to the literature.[1,2,3] *N*,*N*-dimethyl-4-nitrosoaniline is commercially available from a number of sources.

Literature syntheses for 1-iodo-2-nitrosobenzene provided results that lacked reproducibility and scalability. Due to the essential nature of this nitrosoarene for latter parts of this work, a reproducible and scalable synthesis was developed to provide high purity material. This synthesis is reported below:



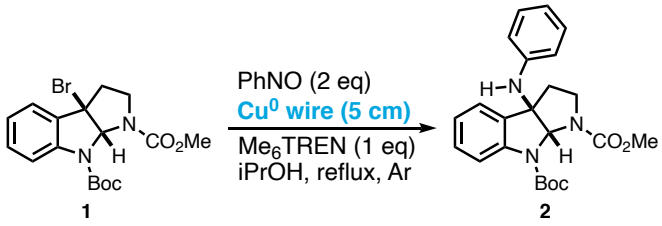
1-iodo-2-nitrosobenzene

To a flame-dried 250 mL round bottom flask is added 2-iodoaniline (2.44 grams, 11.16 mmol, 1 eq) and DCM (50 mL, anhydrous). This flask is placed under an atmosphere of argon and cooled on an ice bath for 10 min. Meanwhile, a solution of mCPBA (70%, 3.83 grams, 22.32 mmol, 2 eq) and DCM (50 mL) is filtered through a plug of sodium sulfate (25 grams) and added to the aniline solution *via* syringe pump dropwise over one hour. After completin of addition, the solution is quickly washed with saturated aqueous sodium bicarbonate (2 x 35 mL) and 1M aqueous HCl (2 x 35 mL) and brine (1 x 30 mL).

The crude material is adsorbed onto celite and purified *via* flash chromatography with an increasing gradient of DCM in hexane (0 —> 40%). The fractions containing primarily the nitroso product (verified by TLC, R_f =0.75 in 40% DCM in hexane) were collected and concentrated.

The enriched nitrosoarene product was then further purified *via* sublimation with gentle heating from a heat gun to yield pure product whose characterization matched the literature.

Section 3- Relevant Data and Initial Mechanistic Hypothesis



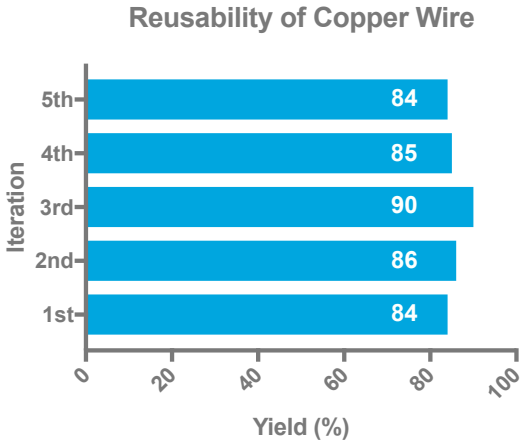


Chart S1: over five iterative reactions with the same copper wire, no significant reduction in yield is observed. Prior to each reaction, the copper wire wrapped stirbar is washed with conc. HCl. Reaction was run on a 0.06 mmol scale (27 mg bromo-indoline) in each reaction.

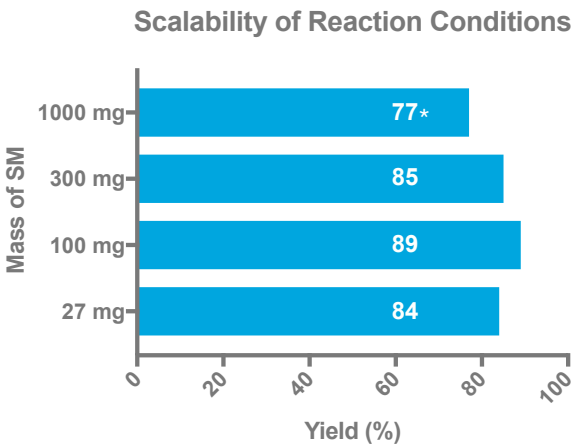
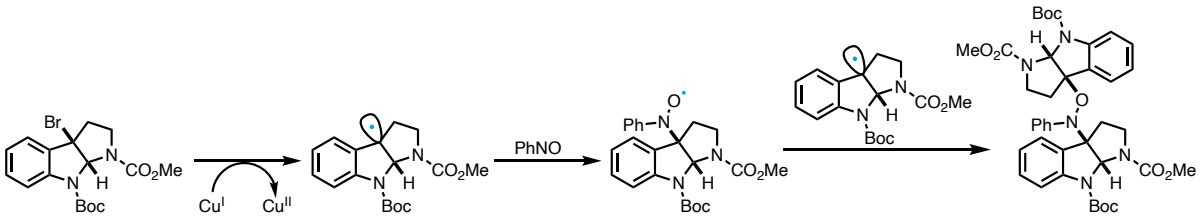


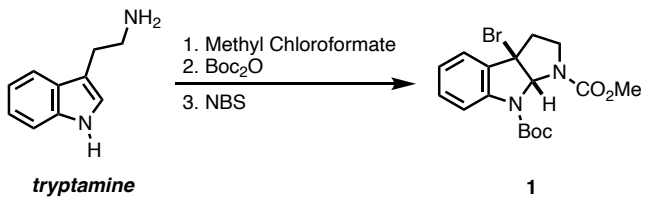
Chart S2: Scalability of the model reaction. 7 cm copper wire was used for the 100 mg scale and 10 cm was used for the 300 mg scale. 1 standard US penny was used for the 1-gram scale reaction after being washed in conc. HCl.



Scheme S1: Our originally hypothesized product and reaction pathway. Note, our newly proposed scheme deviates at the aminoxyl radical step.

Section 4- Preparation of Synthetic Intermediates and Starting Materials

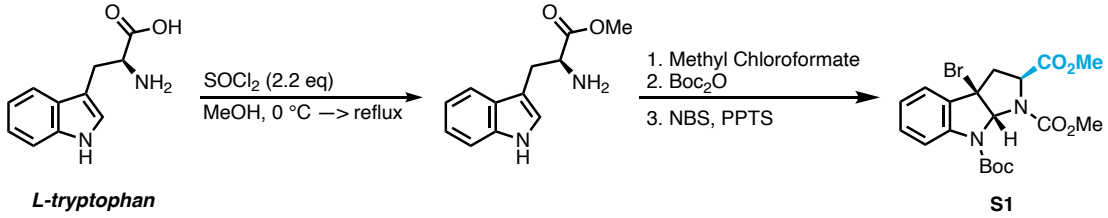
4a- Synthesis of the tryptamine-derived pyrroloindoline scaffold



tryptamine **1**

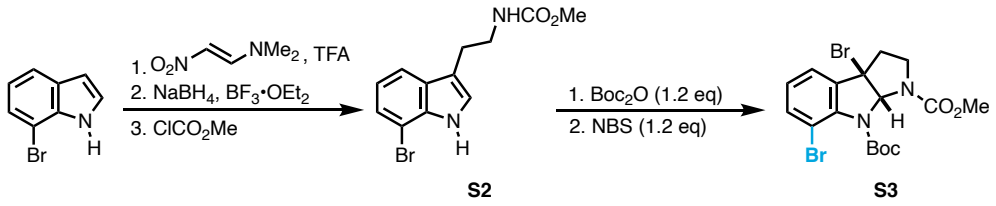
Bromo-pyrroloindole **1** was prepared from commercially available tryptamine in three steps, according to literature procedures.[4,5] Before use, N-Bromosuccinimide was purified according to the literature[6].

4b- Synthesis of the tryptophan-derived pyrroloindoline scaffold

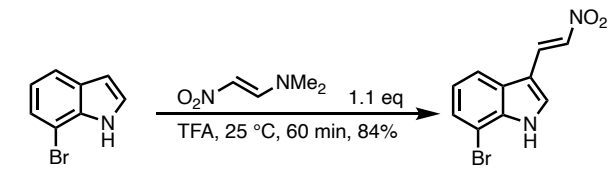


Bromo-pyrroloindole **S1** was prepared from commercially available *L*-tryptophan in four steps, with the initial esterification prepared according to the literature. [7] The subsequent protections and halocyclization were performed similarly to the tryptamine-derived scaffold. Before use, N-Bromosucinimide was purified according to the literature[6].

4c- Synthesis of the 7-bromopyrroloindoline scaffold



Carbamate **S2** was prepared according to the literature.[8] The initial step to form the intermediate nitro-olefin, was carried out with slight modifications, as recorded below. The subsequent protection and cyclization were performed as recorded below.



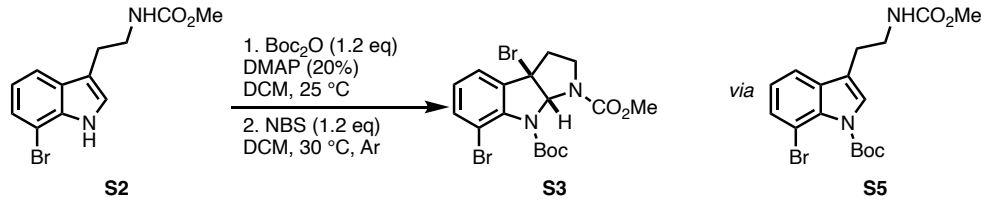
7-bromoindole **S4**

7-bromo-3-(2-nitrovinyl)-1*H*-indole (S4)

To a 250 mL round bottom flask is added 7-bromoindole (3.36 g, 17.1 mmol, 1 eq) and 1-dimethylamino-2-nitroethylene (2.16 g, 18.6 mmol, 1.1 eq), followed by TFA (35 mL, 0.5 M relative to 7-bromoindole). The reaction vessel is sealed with rubber septum and stirred at room under a balloon of argon.

After 60 minutes, the dark brown/black reaction solution is cooled to 0 °C with ice. The septum is pierced with two vent needles and saturated aqueous potassium carbonate is added dropwise to the reaction until effervescence ceases (about 120 mL). As the solution is quenched, the brown color fades and a yellow chunky precipitate is formed. The resulting suspension is poured into a 500 mL separatory funnel with more saturated aqueous potassium carbonate (80 mL) and ethyl acetate. The layers are separated and the aqueous layer is extracted with EtOAc (4 x 50 mL). The organic layers are combined, dried with sodium sulfate and concentrated *in vacuo*.

This material is further purified through a plug of silica and eluted with a 1:1 solution of EtOAc:Hexane (only the yellow eluent is collected; the solution which eluted before is discarded) to afford the title compound in high purity (3.8 grams, 84%) with characterization in agreement with the literature. [9]



8-(*tert*-butyl) 1-methyl (3a*R*,8a*R*)-3a,7-dibromo-2,3,3a,8a-tetrahydropyrrolo[2,3-*b*]indole-1,8-dicarboxylate (S3)

To a 100 mL round bottom flask is added carbamate **S2** (410 mg, 1.4 mmol, 1 eq), Boc-anhydride (360 mg, 1.65 mmol, 1.2 eq) and DMAP (35 mg, 0.27 mmol, 0.2 eq) in DCM (20 mL, anhydrous). The reaction is stirred at room temperature for two hours until TLC indicates consumption of starting material. The reaction solution is washed with saturated sodium bicarbonate (20 mL) and extracted with DCM (4 x 10 mL). The organic layers are combined and dried sequentially with brine (20 mL) and sodium sulfate. This material is subsequently cyclized without further purification.

Note: If necessary, this material can be purified by silica column chromatography with an increasing gradient of 10 —> 50% EtOAc in Hexane. *tert*-butyl 7-bromo-3-(2-((methoxycarbonyl)amino)ethyl)-1H-indole-1-carboxylate (**S5**)**:** ^{1}H NMR (500 MHz, Chloroform-*d*, **50 °C**) δ 7.53 (d, *J* = 7.7 Hz, 1H), 7.49 (d, *J* = 7.8 Hz, 1H), 7.35 (s, 1H), 7.10 (t, *J* = 7.7 Hz, 1H), 4.72 (s, 1H), 3.71 – 3.64 (m, 6H), 3.48 (q, *J* = 6.7 Hz, 2H), 2.88 (t, *J* = 7.0 Hz, 2H), 1.65 (s, 10H);

^{13}C NMR (125 MHz, Chloroform-*d*, **50 °C**) δ 157.0, 148.5, 134.3, 133.9, 130.0, 126.7, 123.9, 118.1, 117.0, 108.2, 84.3, 52.1, 40.6, 28.0, 25.5;

IR (thin film) 3267, 2987, 1727, 1710, 1683, 1413, 1367, 1339, 1268, 1249, 1142, 1029, 836, 765, 739 cm^{-1}

HRMS (ESI), calculated for $C_{17}H_{21}BrN_2O_4$: ($M+Na^+$) 419.0586, observed 419.0582.

To a 100 mL round bottom flask is added the Boc-protected indole (**S5**), N-bromosuccinimide (freshly recrystallized according to the literature[6], 270 mg, 1.51 mmol, 1.2 eq) and DCM (15 mL, anhydrous). The reaction vessel is heated to 30 °C under an atmosphere of argon for 16 hours until consumption of starting material is observed by TLC. The reaction solution is washed with 10% aqueous sodium thiosulfate (20 mL) and extracted with DCM (4 x 10 mL). The organic layers are combined and dried with sodium sulfate. The crude organic solution is concentrated and loaded directly onto a silica column and purified with an increasing gradient of ethyl acetate in hexane (10 —> 50%) to afford pyrroloindole **S3** (380 mg, 64%, 58% over two steps).

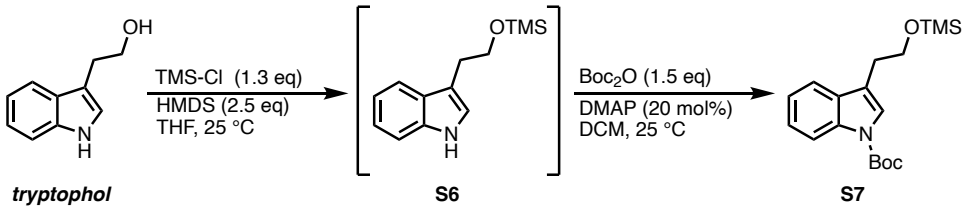
^{1}H NMR (500 MHz, Chloroform-*d,* **50 °C**) δ 7.51 (d, *J* = 8.0 Hz, 1H), 7.32 (d, *J* = 7.6 Hz, 1H), 7.07 (t, *J* = 7.8 Hz, 1H), 6.28 (s, 1H), 3.78 (s, 3H), 3.69 (dd, *J* = 9.5, 7.6 Hz, 1H), 2.84 – 2.69 (m, 3H), 1.57 (s, 9H);

^{13}C NMR (125 MHz, Chloroform-*d,* **50 °C**) δ 154.6, 152.3, 142.1, 137.4, 134.8, 127.1, 122.0, 115.1, 87.0, 82.4, 61.6, 52.6, 46.0, 39.4, 28.1;

IR (thin film) 2979, 2892, 1706, 1442, 1366, 1295, 1232, 1150, 1085, 768 cm^{-1};

HRMS (ESI), calculated for $C_{17}H_{20}Br_2N_2O_4$: ($M+Na^+$)498.9668, observed 498.9645.

4d- Synthesis of the Furoindolenine Scaffold



***tert*-butyl 3-(2-((trimethylsilyl)oxy)ethyl)-1*H*-indole-1-carboxylate (S7):** To a 50 mL round bottom flask is added, sequentially, commercially available tryptophol (500 mg, 3.10 mmol, 1 eq) in THF (anhydrous, 15 mL) hexamethyldisilazane (1.61 mL, 7.75 mmol, 2.5 eq) and trimethylsilyl chloride (510 µL, 4.04 mmol, 1.3 eq). The flask is sealed with a rubber septum and allowed to stir at room temperature under an atmosphere of nitrogen gas for 16 hours before TLC indicates consumption of starting material. The solution is then diuted with diethyl ether (20 mL), washed with saturated aqueous $NaHCO_3$ (30 mL) and extracted with additional diethyl ether (3 x 20 mL). The organic layers are combined and dried with sodium sulfate and concentrated in vacuo. The crude TMS-protected tryptophol **S6** is used without further purification.

To a 50 mL round bottom flask is added intermediate **S6** from the previous step, DCM (anhydrous, 6 mL), Boc-anhydride (1.01 grams, 4.65 mmol, 1.5 eq), and 4-dimethylaminopyridine (75 mg, 0.62 mmol, 0.2 eq). The flask is sealed with a rubber septum and allowed to stir at room temperature under an atmosphere of nitrogen gas for 16 hours before TLC indicates consumption of starting material. The solution is then washed with saturated aqueous $NaHCO_3$ (30 mL) and extracted with DCM (3 x 20 mL). The organic layers are combined and dried with sodium sulfate, concentrated in vacuo, and loaded onto a

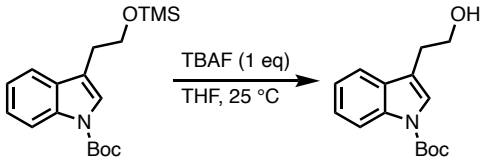
silica column for purification via chromatography with an increasing gradient of ethyl acetate in hexane (0 —> 40%) to afford **S7** (747 mg, 72%).

^{1}H NMR (600 MHz, cdcl$_3$, **26 °C**) δ 8.15 (s, 1H), 7.55 (d, *J* = 7.8 Hz, 1H), 7.44 (s, 1H), 7.32 (d, *J* = 7.8 Hz, 1H), 7.25 (d, *J* = 8.1 Hz, 1H), 3.88 (t, *J* = 7.2 Hz, 2H), 2.95 (t, *J* = 7.8 Hz, 2H), 1.68 (s, 9H), 0.13 (s, 9H);

^{13}C NMR (150 MHz, cdcl$_3$, **26 °C**) δ 149.8, 135.4, 130.8, 124.2, 123.2, 122.3, 119.0, 117.7, 115.2, 83.3, 62.3, 28.5, 28.2, -0.5;

IR (thin film) 2955, 1728, 1452, 1366, 1248, 1156, 1091, 837, 753 cm^{-1}

HRMS (ESI), calculated for $C_{18}H_{27}NO_3Si$: (M+Na$^+$) 356.1658, observed 356.1661.

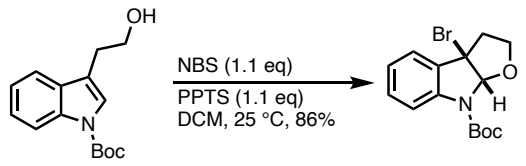


S7 **S8**

***tert*-butyl 3-(2-hydroxyethyl)-1*H*-indole-1-carboxylate (S8)**

To a 10 mL round bottom flask is added TMS-Boc-protected tryptophol **S7** (720 mg, 3.10 mmol, 1 eq) and tetrabutylammonium fluoride (3.10 mL of a 1.0 M solution in THF). The solution is stirred at room temperature under an atmosphere of nitrogen for 20 hours before being quenched with saturated aqueous $NaHCO_3$ and extracted with EtOAc (3 x 50 mL). The organic layers were combined, dried with sodium sulfate, and concentrated in vacuo before being loaded onto a silica column for flash purification (25 g of silica, increasing gradient of

5 —> 65% EtOAc in hexane) to yield the product **S8** as a clear oil (620 mg, 77%). Characterization was consistent with the literature. [10]

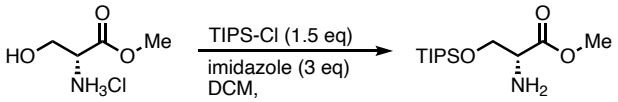


S8 **S9**

***tert*-butyl 3a,8a-dibromo-2,3,3a,8a-tetrahydro-8*H*-furo[2,3-*b*]indole-8-carboxylate (S9)**

To a 10 mL round bottom flask equipped with a teflon coated stir bar is added Boc-tryptophol (**S8**) (1.85 g, 7.09 mmol, 1 eq) and DCM (anhydrous, 50 mL), and the flask if allowed to cool to 0 °C in an ice bath for ten minutes, after which freshly recrystallized[6] NBS (1.38 g, 7.8 mmol, 1.1 eq) and Pyridinium p-toluenesulfonate (PPTS) (1.96 g, 7.8 mmol, 1.1 eq) are added through the stopper. The reaction is stirred under nitrogen for two hours before TLC indicates consumption of starting material. The reaction is quenched with a saturated aqueous solution of sodium thiosulfate (100 mL) and extracted with DCM (3 x 50 mL). The organic layers are combined, dried with sodium sulfate and concentrated. The crude organic is then purified by silica flash column chromatography with an increasing gradient of 0 —> 65% EtOAc in hexane to afford the product **S9** as a while solid (2.08 grams, 86%) consistent with literature characterization.[11]

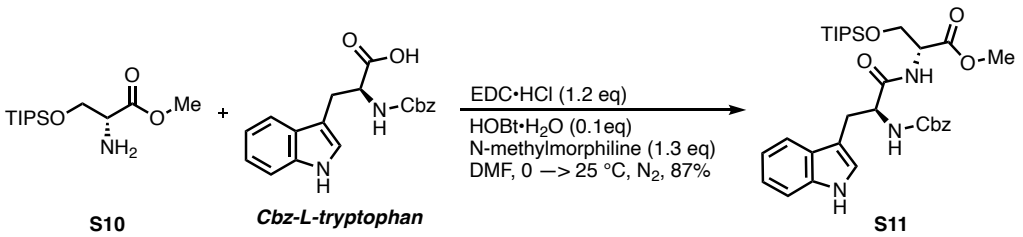
4e- Synthesis of the Chetomin Scaffold



D-serine methyl ester **S10**

TIPS protected *D*-serine methyl ester **(S10)** was prepared from commercially available *d*-Serine methyl ester hydrochloride according to an adapted literature procedure.[12] This material was used without purification via column chromatography.

Cbz-protected *L*-tryptophan is commercially available and was acquired from Alfa Aesar.



methyl *N*-(((benzyloxy)carbonyl)-*L*-tryptophyl)-*O*-(triisopropylsilyl)-*D*-serinate (S11): To a flame dried 250 mL round bottom flask equipped with a Teflon stir bar is added **S10** (4.3 g, 15.6 mmol, 1 eq), Cbz-*L*-tryptophan (5 g, 15.6 mmol, 1 eq) HOBt hydrate (240 mg, 1.56 mmol, 0.1 eq), N-methyl morphiline (2.22 mL, 20.3 mmol, 1.3 eq) and DMF (stored under N_2 over sieves, 30 mL). The flask is sealed with a rubber septum, backfilled with N_2 and cooled to 0 °C with ice for ten minutes, at which point EDC•HCl (3.6 g, 18.7 mmol, 1.2 eq) is added quickly through the neck of the flask. The rubber septum is quickly replaced and the reaction is stirred overnight under nitrogen as the reaction temperature is slowly allowed to climb to room temperature. After 16 hours, the reaction is washed with saturated aqueous $NaHCO_3$ (75 mL) and extracted with EtOAc (4 x 50 mL). The organic layers are combined, dried sequentially with brine (75 mL) and sodium sulfate and concentrated *in vacuo*.

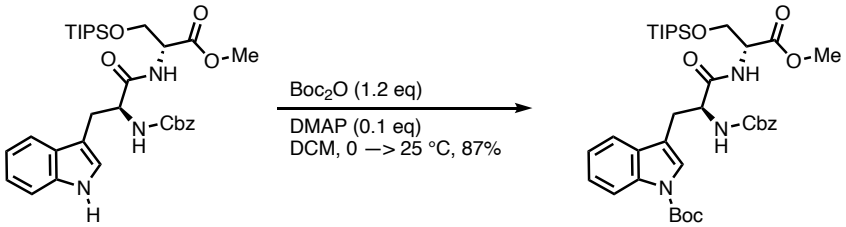
The crude organics are reconstituted in DCM, loaded directly onto a silica column (100 grams of silica) and purified with an increasing gradient of EtOAc in DCM (0 —> 25%) to afford **S11** (7.9 g, 87%).

^{1}H NMR (600 MHz, Chloroform-*d*, **50 °C**) δ 8.05 (s, 1H), 7.60 (d, *J* = 7.9 Hz, 1H), 7.36 – 7.26 (m, 6H), 7.18 (t, *J* = 7.6 Hz, 1H), 7.09 (t, *J* = 7.6 Hz, 1H), 7.06 (s, 1H), 6.68 (d, *J* = 8.2 Hz, 1H), 5.32 (s, 1H), 5.12 (d, *J* = 12.4 Hz, 1H), 5.03 (d, *J* = 12.3 Hz, 1H), 4.61 – 4.54 (m, 2H), 4.08 (dd, *J* = 9.9, 2.6 Hz, 1H), 3.67 (s, 4H), 3.36 – 3.23 (m, 2H), 1.05 – 0.96 (m, 21H);

^{13}C NMR (150 MHz, Chloroform-*d,* **50 °C**) δ 171.2, 170.4, 155.9, 136.2, 128.4, 128.0, 127.9, 127.7, 123.0, 122.2, 119.7, 118.7, 111.1, 110.5, 67.0, 63.7, 55.70, 54.4, 52.1, 28.2, 17.7, 17.7, 11.8.

IR (thin film) 3328, 2942, 2865, 1738, 1708, 1660, 1511, 1243, 1210, 881, 736, 682 cm^{-1}

HRMS (ESI), calculated for $C_{32}H_{45}N_3O_6Si$: ($M+Na^+$) 618.2975, observed 618.2978.



S11 **S12**

***tert*-butyl 3-((*S*)-2-(((benzyloxy)carbonyl)amino)-3-(((*R*)-1-methoxy-1-oxo-3-((triisopropylsilyl)oxy)propan-2-yl)amino)-3-oxopropyl)-1*H*-indole-1-carboxylate (S12):**

To a flame dried 250 mL round bottom flask equipped with a Teflon stir bar is added **S11** (7.7 g, 12.9 mmol, 1 eq), Boc-anhydride (3.6 g, 16.3 mmol, 1.25 eq) and DCM (stored over sieves, 65 mL). The flask is sealed with a rubber septum, backfilled with N_2 and cooled to 0 °C with ice for ten minutes, at which point 4-DMAP (180 mg, 1.47 mmol, 0.11 eq) is added in 3 mL of DCM via syringe through the septum. The reaction is stirred overnight under nitrogen as the reaction temperature is slowly allowed to climb to room temperature. After 16 hours, the reaction is washed with saturated aqueous $NaHCO_3$ (75 mL) and extracted with DCM (3 x 50 mL). The organic layers are combined, dried sequentially with brine (75 mL) and sodium sulfate and concentrated *in vacuo*.

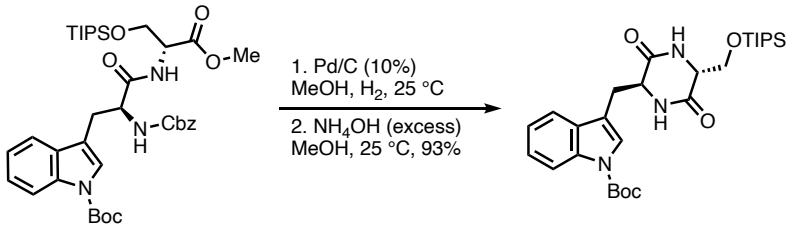
The crude organics are reconstituted in DCM, loaded directly onto a silica column (100 grams of silica) and purified with an increasing gradient of EtOAc in DCM (0 —> 20%) to afford **S12** (7.78 g, 87%)

^{1}H NMR (600 MHz, Chloroform-*d*, **50 °C**) δ 8.12 (d, *J* = 8.3 Hz, 1H), 7.54 (d, *J* = 7.8 Hz, 1H), 7.47 (s, 1H), 7.31 (dt, *J* = 20.8, 7.3 Hz, 6H), 7.20 (t, *J* = 7.6 Hz, 1H), 6.67 (d, *J* = 8.3 Hz, 1H), 5.33 (s, 1H), 5.12 (d, *J* = 12.5 Hz, 1H), 5.05 (d, *J* = 12.2 Hz, 1H), 4.65 – 4.49 (m, 2H), 4.08 (d, *J* = 9.5 Hz, 1H), 3.68 (s, 3H), 3.58 (d, *J* = 9.3 Hz, 1H), 3.27 – 3.16 (m, 2H), 1.66 (d, *J* = 2.3 Hz, 9H), 0.96 (d, *J* = 3.0 Hz, 21H);

^{13}C NMR (150 MHz, Chloroform-*d*, **50 °C**) δ 170.8, 170.3, 155.8, 149.4, 136.1, 135.5, 130.4, 128.4, 128.1, 127.9, 125.0, 124.3, 124.3, 122.6, 118.8, 115.3, 115.3, 83.5, 68.0, 63.6, 55.4, 54.4, 52.2, 28.2, 17.7, 11.8

IR (thin film) 3309, 2942, 2865, 1727, 1673, 1505, 1367, 1154, 1084, 742, 683 cm^{-1}

HRMS (ESI), calculated for $C_{37}H_{53}N_3O_8Si$: ($M+Na^+$) 718.3500, observed 718.3497.



S12 **S13**

To a 250 mL round bottom flask is added coupling product **S12** (7.68 g, 11.05 mmol, 1 eq) and Pd/C (10%, 1.17 g, 10 mol %). The flask is sealed with a rubber septum and the atmosphere removed under vacuum and replaced with nitrogen three times. To this flask is added anhydrous methanol (110 mL). The resulting suspension is vigourously sparged with hydrogen gas and the solution is allowed to stir under an atmosphere of hydrogen for three hours, at which point the solution is filtered through celite and concentrated *in vacuo*. Care was taken to only pull minimal air through the plug containing the palladium on carbon.

The afforded white oil is reconstituted in methanol (30 mL) and aqueous ammonium hydroxide (28-30%, 2 mL) is added. This solution is allowed to stir for 16 hours at room temperature. After 16 hours, the reaction is concentrated *in vacuo* to afford the desired

product (5.75 g, 93%). This material was used in the subsequent halocyclization without further purification.

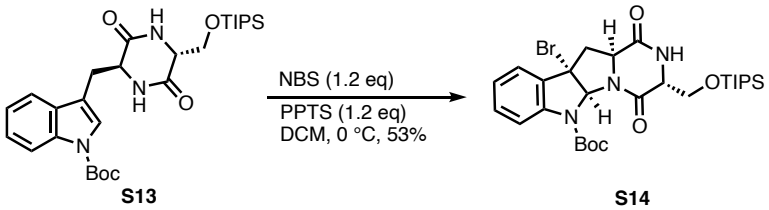
Note: if necessary, this material can be purified through silica gel chromatography with an increasing gradient of EtOAc in DCM (5 —> 35%).

^{1}H NMR (600 MHz, Chloroform-*d*, **50 °C**) δ 8.14 (d, *J* = 8.3 Hz, 1H), 7.55 (d, *J* = 7.9 Hz, 1H), 7.50 (s, 1H), 7.31 (d, *J* = 7.5 Hz, 1H), 7.22 (t, *J* = 7.6 Hz, 1H), 6.68 (s, 1H), 6.47 (s, 1H), 4.35 (d, *J* = 7.5 Hz, 1H), 3.99 – 3.89 (m, 2H), 3.79 – 3.73 (m, 1H), 3.49 (dd, *J* = 14.6, 2.5 Hz, 1H), 3.06 (dd, *J* = 14.8, 9.1 Hz, 1H), 1.66 (s, 9H), 1.12 – 0.96 (m, 21H);

^{13}C NMR (150 MHz, Chloroform-*d,* **50 °C**) δ 168.0, 166.6, 149.3, 135.8, 129.6, 124.9, 124.8, 122.8, 118.9, 115.3, 114.4, 83.9, 65.3, 57.0, 54.5, 29.8, 28.2, 17.8, 11.8.

IR (thin film) 3209, 2941, 2865, 1731, 1678, 1451, 1368, 1324, 1252, 1156, 1084, 743 cm^{-1}

HRMS (ESI), calculated for $C_{28}H_{43}N_3O_5Si$: ($M+Na^+$) 552.2870, observed 552.2874.



A 100 mL round bottom flask is charged with diketopiperazine **S13** (2.1 grams, 3.97 mmol, 1 eq) and is azeotropically dried with anhydrous toluene (50 mL) two times. To this flask is

added DCM (anhydrous, 35 mL), a teflon coated stir bar and is sealed with a rubber septum. The head space of the flask is evacuated and replaced with N_2 three times. The slurry contained flask is cooled to 0 °C with an ice bath for fifteen minutes before solid N-bromosuccinimide (freshly recrystallized[6], 920 mg, 5.16 mmol, 1.2 eq) and pyridinium p-toluenesulfonate (1.3 grams, 5.16 mmol, 1.2 eq) are added. The reaction is allowed to stir at 0 °C under an atmosphere of N_2 for 18 hours before the reaction is warmed to room temperature and quenched with 10% aqueous sodium thiosulfate (100 mL) and extracted with DCM (6 x 20 mL). The organic layers are combined, dried sequentially with brine and sodium sulfate, concentrated and reconstituted in minimal DCM. This solution was loaded directly onto a flash column (100 grams of silica) to afford **S14** as white foam (1,284 mg, 2.1 mmol, 53%).

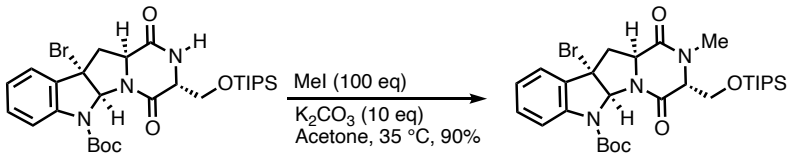
Note: the same conditions, but at room temperature, yield the product in 40%.

^{1}H NMR (400 MHz, Chloroform-*d*, **25 °**) δ 7.67 (d, *J* = 8.2 Hz, 1H), 7.39 (d, *J* = 7.6 Hz, 1H), 7.26 (t, *J* = 8.5 Hz, 1H), 7.08 (t, *J* = 7.5 Hz, 1H), 6.50 (s, 1H), 6.19 (s, 1H), 4.66 (dd, *J* = 9.5, 7.4 Hz, 1H), 4.21 (dd, *J* = 10.7, 4.0 Hz, 1H), 3.88 – 3.77 (m, 2H), 3.29 (dd, *J* = 14.5, 7.4 Hz, 1H), 3.15 (dd, *J* = 14.5, 9.6 Hz, 1H), 1.61 (s, 9H), 1.15 – 0.92 (m, 21H);

^{13}C NMR (100 MHz, Chloroform-*d*, **25 °**) δ 168.5, 164.7, 151.7, 140.0, 133.9, 130.4, 124.4, 116.8, 85.3, 85.2, 82.6, 66.5, 60.2, 59.6, 55.74, 41.2, 28.2, 17.8, 11.8;

IR (thin film) 3258, 2936, 2866, 1687, 1646, 1368, 1332, 1155, 1115, 883, 753 cm^{-1}

HRMS (ESI), calculated for $C_{28}H_{42}BrN_3O_5Si$: ($M+Na^+$) 630.1975, observed 630.1983.



S14 **S15**

Note: Iodomethane was purified according to the literature via percolation through activated alumina and silica gel and stored over HCl washed copper wire prior to use.[13]

To an oven dried 50 mL round bottom flask is added pyrroloindole-diketopiperazine **S14** (600 mg, 1 mmol, 1 eq) K_2CO_3 (finely divided and stored under vacuum at 110 °C, 4140 mg, 30 mmol, 30 eq) and acetone (stored over sieves and under nitrogen, 3 mL). The vial is equipped with a teflon coated, a reflux condenser fitted with a pierceable septum and a teflon coated stir bar. To this solution is added Iodomethane (6.18 mL, 100 mmol, 100 eq) through the septum. The solution is stirred at 35 °C for 14 hours before TLC indicates the consumption of starting material and the solution is quenched with aqueous sodium bicarbonate (saturated, 50 mL) and extracted with DCM (3 x 30 mL). The organic layers are combined, dried sequentially with sodium sulfate and brine, concentrated and reconstituted in DCM. This solution was loaded directly onto a flash column (25 g silica). The product was purified with an increasing gradient of ethyl acetate in DCM (0 —> 12%), affording **S15** (570 mg, 90%)**.**

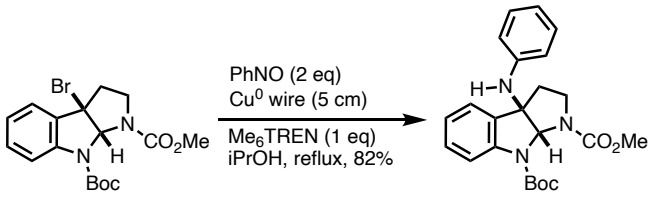
^{1}H NMR (500 MHz, $CDCl_3$, **25 °**) δ 7.73 (d, *J* = 8.2 Hz, 1H), 7.43 (d, *J* = 7.6 Hz, 1H), 7.31 (d, *J* = 7.8 Hz, 1H), 7.12 (t, *J* = 7.5 Hz, 1H), 6.22 (s, 1H), 4.70 (t, *J* = 8.7 Hz, 1H), 4.23 (dd, *J*

= 10.4, 2.7 Hz, 1H), 4.02 (dd, *J* = 10.4, 2.6 Hz, 1H), 3.72 (s, 1H), 3.34 (dd, *J* = 14.6, 7.7 Hz, 1H), 3.22 (dd, *J* = 14.6, 9.5 Hz, 1H), 2.87 (s, 3H), 1.65 (s, 9H), 1.19 – 1.05 (m, 21H).

^{13}C NMR (125 MHz, $CDCl_3$, **25 °**) δ 166.7, 164.9, 151.8, 140.1, 134.2, 130.4, 124.5, 124.4, 116.8, 85.3, 82.6, 67.0, 63.2, 59.9, 56.0, 41.9, 32.1, 28.2, 17.9, 11.8.

HRMS (ESI), calculated for $C_{29}H_{44}BrN_3O_5Si$: ($M+Na^+$) 644.2131, observed 644.2131.

Section 5– Synthetic Procedures and Characterization Data

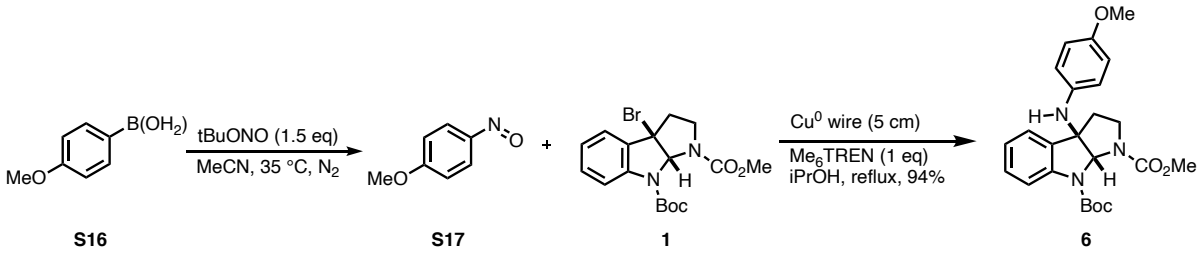


1 **2**

8-(*tert*-butyl) 1-methyl 3a-(phenylamino)-2,3,3a,8a-tetrahydropyrrolo[2,3-*b*]indole-1,8-dicarboxylate (2)

To a 10 mL round bottom flask is added bromo-indoline **1** (24 mg, 0.06 mmol, 1 eq), nitrosobenzene (13 mg, 0.12 mmol, 2 eq), Me_6TREN (16 μL, 0.06 mmol, 1 eq), and anhydrous isopropanol (3 mL) with a stir bar wrapped in 5 cm of freshly activated copper wire. The flask is capped with a reflux condenser and heated to a vigorous reflux (110 °C) for sixteen hours under an atmosphere of argon. The reaction mixture was allowed to cool to RT and then the solution was concentrated and reconstituted in DCM. This solution was loaded directly onto a flash column (15 g silica). The product is purified with an increasing gradient

of ethyl acetate in hexane (5—> 45%), to afford **2** (20.2 mg, 82%) as a white foam. Characterization is consistent with the literature.[4]



S16 **S17** **1** **6**

8-(*tert*-butyl) 1-methyl 3a-((4-methoxyphenyl)amino)-2,3,3a,8a-tetrahydropyrrolo[2,3-*b*]indole-1,8-dicarboxylate (6)

To a 10 mL round bottom flask is added boronic acid **S16** (23 mg, 0.15 mmol, 1 eq) and MeCN (1.5 mL) and a Teflon coated stir bar. After the reaction vial is capped with a rubber septum and sparged with anhydrous nitrogen (three minutes), *t*BuONO (27 mL, 0.23 mmol, 1.5 eq) is added through the septum. The reaction is then heated to 35 °C and stirred under nitrogen until consumption of the starting material is observed by TLC (~2 hours). The reaction is then concentrated *in vacuo* resulting in a green solid; this resulting nitrosoarene **S17** is carried forward to the next step without purification.

To a 10 mL round bottom flask is added bromo-indole **1** (24 mg, 0.06 mmol, 1 eq), nitrosoarene **S17** (17 mg, 0.12 mmol, 2 eq), Me_6TREN (16 µL, 0.06 mmol, 1 eq), and anhydrous isopropanol (3 mL) with a stir bar wrapped in 5 cm of freshly activated copper wire. The flask is capped with a reflux condenser and heated to a vigorous reflux (110 °C) for sixteen hours under an atmosphere of argon. The reaction mixture was allowed to cool to RT and then the solution was concentrated and reconstituted in DCM. This solution was loaded

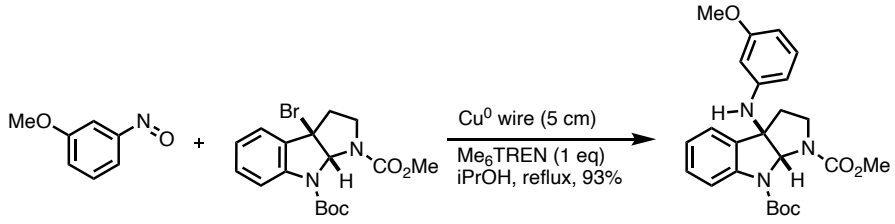
directly onto a flash column (15 g silica). The product is purified with an increasing gradient of ethyl acetate in hexane (10—> 50%), to afford **6** (24.7 mg, 94%) as a white foam.

^{1}H NMR (500 MHz, cdcl$_3$, **25 °C**) δ 7.63 (d, *J* = 8.1 Hz, 1H), 7.26 – 7.21 (m, 2H), 7.00 (t, *J* = 7.5 Hz, 1H), 6.61 – 6.55 (m, 2H), 6.39 – 6.33 (m, 2H), 6.17 (s, 1H), 3.85 (dd, *J* = 11.5, 7.5 Hz, 1H), 3.65 (s, 3H), 3.62 (s, 3H), 2.84 (td, *J* = 11.7, 5.7 Hz, 1H), 2.35 – 2.20 (m, 2H), 1.44 (s, 9H);

^{13}C NMR (125 MHz, cdcl$_3$, **25 °C**) δ 155.2, 154.7, 152.2, 143.5, 137.5, 132.1, 129.7, 123.6, 120.2, 116.6, 114.7, 81.5, 78.4, 73.2, 55.5, 52.5, 44.7, 38.4, 28.3;

IR (thin film) 3369, 3055, 2977, 1704, 1601, 1502, 1203, 788 cm^{-1};

HRMS (ESI), calculated for $C_{24}H_{29}N_3O_5$: (M+Na$^+$) 462.2005, observed 462.2020.



S18 1 7

8-(*tert*-butyl) 1-methyl 3a-((3-methoxyphenyl)amino)-2,3,3a,8a-tetrahydropyrrolo[2,3-*b*]indole-1,8-dicarboxylate (7)

To a 10 mL round bottom flask is added bromo-indole **1** (24 mg, 0.06 mmol, 1 eq), nitrosoarene **S18** (17 mg, 0.12 mmol, 2 eq), Me$_6$TREN (16 µL, 0.06 mmol, 1 eq), and anhydrous isopropanol (3 mL) with a stir bar wrapped in 5 cm of freshly activated copper

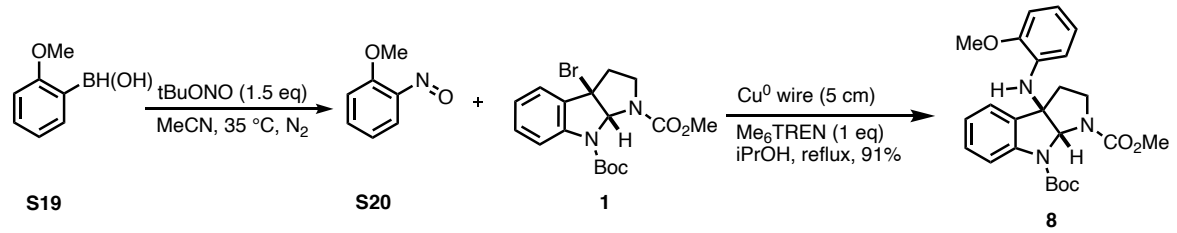
wire. The flask is capped with a reflux condenser and heated to a vigorous reflux (110 °C) for sixteen hours under an atmosphere of argon. The reaction mixture was allowed to cool to RT and then the solution was concentrated and reconstituted in DCM. This solution was loaded directly onto a flash column (15 g silica). The product is purified with an increasing gradient of ethyl acetate in hexane (10—> 50%), to afford **7** (24.5 mg, 93%) as a white foam.

^{1}H NMR (500 MHz, cdcl$_3$, **50 °C**) δ 7.80 (d, *J* = 8.1 Hz, 1H), 7.33 – 7.26 (m, 2H), 7.05 (t, *J* = 7.4 Hz, 1H), 6.97 (t, *J* = 8.0 Hz, 1H), 6.37 (s, 1H), 6.29 (d, *J* = 8.5 Hz, 1H), 6.04 (d, *J* = 8.1 Hz, 1H), 5.89 (t, *J* = 2.2 Hz, 1H), 4.02 (dd, *J* = 11.8, 7.7 Hz, 1H), 3.74 (d, *J* = 1.9 Hz, 3H), 3.58 (d, *J* = 1.9 Hz, 3H), 2.92 (td, *J* = 11.9, 5.4 Hz, 1H), 2.39 (td, *J* = 12.0, 7.7 Hz, 1H), 2.27 (dd, *J* = 12.1, 5.4 Hz, 1H), 1.53 (s, 9H);

^{13}C NMR (125 MHz, cdcl$_3$, **50 °C**) δ 160.7, 155.3, 152.4, 146.3, 143.4, 132.1, 129.9, 129.7, 116.1, 108.4, 105.2, 101.1, 81.8, 78.7, 72.1, 54.8, 52.6, 44.3, 40.3, 28.3;

IR (thin film) 3371, 3089, 2975, 1708, 1597, 1500, 1250, 805 cm^{-1};

HRMS (ESI), calculated for $C_{24}H_{29}N_3O_5$: (M+Na$^+$) 462.2005, observed 462.2008.



S19 **S20** **1** **8**

8-(*tert*-butyl) 1-methyl 3a-((2-methoxyphenyl)amino)-2,3,3a,8a-tetrahydropyrrolo[2,3-*b*]indole-1,8-dicarboxylate (XX)

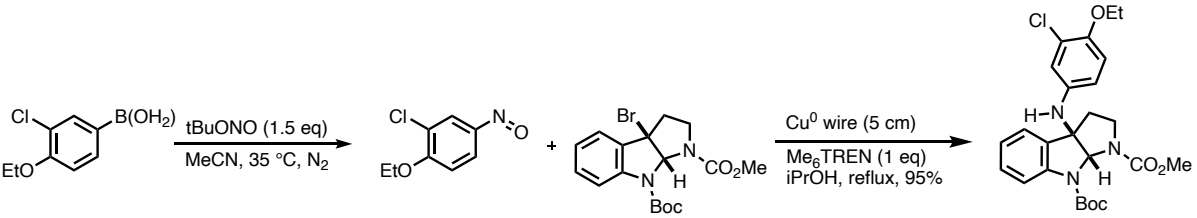
To a 10 mL round bottom flask is added boronic acid **S19** (23 mg, 0.15 mmol, 1 eq) and MeCN (1.5 mL) and a Teflon coated stir bar. After the reaction vial is capped with a rubber septum and sparged with anhydrous nitrogen (three minutes), *t*BuONO (27 mL, 0.23 mmol, 1.5 eq) is added through the septum. The reaction is then heated to 35 °C and stirred under nitrogen until consumption of the starting material is observed by TLC (~2 hours). The reaction is then concentrated *in vacuo* resulting in a green solid; this resulting nitrosoarene **S20** is carried forward to the next step without purification.

To a 10 mL round bottom flask is added bromo-indole **1** (24 mg, 0.06 mmol, 1 eq), nitrosoarene **S20** (17 mg, 0.12 mmol, 2 eq), Me_6TREN (16 µL, 0.06 mmol, 1 eq), and anhydrous isopropanol (3 mL) with a stir bar wrapped in 5 cm of freshly activated copper wire. The flask is capped with a reflux condenser and heated to a vigorous reflux (110 °C) for sixteen hours under an atmosphere of argon. The reaction mixture was allowed to cool to RT and then the solution was concentrated and reconstituted in DCM. This solution was loaded directly onto a flash column (15 g silica). The product is purified with an increasing gradient of ethyl acetate in hexane (10—> 50%), to afford **8** (24.0 mg, 91%) as a white foam.
^{1}H NMR (600 MHz, cdcl$_3$, **50 °C**) δ 7.79 (d, *J* = 8.2 Hz, 1H), 7.34 – 7.18 (m, 2H), 7.04 (d, *J* = 7.3 Hz, 1H), 6.76 (d, *J* = 7.7 Hz, 1H), 6.67 (d, *J* = 7.3 Hz, 1H), 6.63 (d, *J* = 7.7 Hz, 1H), 6.35 (s, 1H), 6.14 (d, *J* = 8.0 Hz, 1H), 4.72 (s, 1H), 4.02 (dd, *J* = 11.8, 7.9 Hz, 1H), 3.83 (s, 3H), 3.73 (s, 3H), 2.94 (td, *J* = 11.9, 5.5 Hz, 1H), 2.46 (td, *J* = 12.1, 7.8 Hz, 1H), 2.28 (dd, *J* = 12.2, 5.4 Hz, 1H), 1.53 (s, 8H);

^{13}C NMR (150 MHz, cdcl$_3$, **50 °C**) δ 155.3, 152.4, 147.9, 143.3, 134.7, 132.2, 129.5, 123.5, 123.3, 121.1, 118.4, 116.1, 113.3, 109.9, 81.6, 78.7, 71.8, 55.5, 52.5, 44.4, 40.1, 28.3;

IR (thin film) 3419, 2954, 1701, 1601, 1510, 1443, 1372, 1141, 1014, 733 cm^{-1}

HRMS (ESI), calculated for $C_{24}H_{29}N_3O_5$: (M+Na$^+$) 462.2005, observed 462.2012.



S21 **S22** **1** **9**

8-(*tert*-butyl) 1-methyl 3a-((3-chloro-4-ethoxyphenyl)amino)-2,3,3a,8a-tetrahydropyrrolo[2,3-*b*]indole-1,8-dicarboxylate (9)

To a 10 mL round bottom flask is added boronic acid **S21** (30 mg, 0.15 mmol, 1 eq) and MeCN (1.5 mL) and a Teflon coated stir bar. After the reaction vial is capped with a rubber septum and sparged with anhydrous nitrogen (three minutes), *t*BuONO (27 mL, 0.23 mmol, 1.5 eq) is added through the septum. The reaction is then heated to 35 °C and stirred under nitrogen until consumption of the starting material is observed by TLC (~2 hours). The reaction is then concentrated *in vacuo* resulting in a green solid; this resulting nitrosoarene **S22** is carried forward to the next step without purification.

To this round bottom flask is added bromo-indole **1** (27 mg, 0.06 mmol, 1 eq), Me$_6$TREN (16 μL, 0.06 mmol, 1 eq) and anhydrous isopropanol (3 mL) with a stir bar wrapped in 5 cm of freshly activated copper wire. The flask is capped with a reflux condenser and heated to a vigorous reflux (110 °C) for sixteen hours under an atmosphere of argon. The reaction

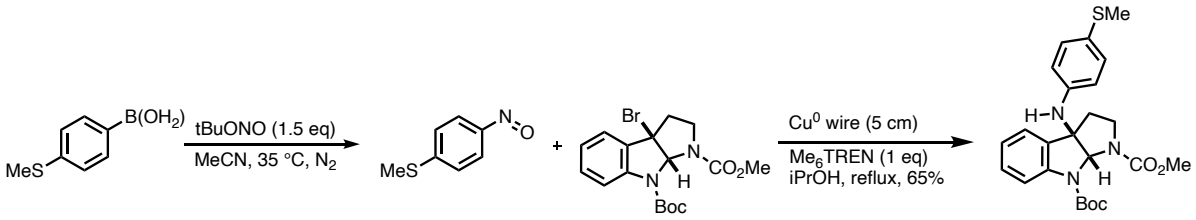
mixture was allowed to cool to RT and then the solution was concentrated and reconstituted in DCM. This solution was loaded directly onto a flash column (15 g silica). The product is purified with an increasing gradient of ethyl acetate in hexane (5 —> 45%), affording **9** (27.7 mg, 95%).

^{1}H NMR (500 MHz, Chloroform-*d*, **50 °C**) δ 7.74 (d, *J* = 8.2 Hz, 1H), 7.30 (d, *J* = 7.5 Hz, 1H), 7.26 (d, *J* = 6.8 Hz, 1H), 7.07 (t, *J* = 7.4 Hz, 1H), 6.67 (d, *J* = 8.7 Hz, 1H), 6.55 (d, *J* = 2.8 Hz, 1H), 6.28 – 6.24 (m, 2H), 4.00 – 3.91 (m, 3H), 3.74 (s, 3H), 2.91 (td, *J* = 11.7, 5.6 Hz, 1H), 2.36 (td, *J* = 11.9, 7.7 Hz, 1H), 2.28 (dd, *J* = 12.1, 5.6 Hz, 1H), 1.53 (s, 9H), 1.37 (t, *J* = 7.0 Hz, 3H);

^{13}C NMR (126 MHz, Chloroform-*d*, **50 °C**) δ 155.2, 152.2, 148.8, 143.4, 139.0, 131.9, 129.8, 123.9, 123.6, 123.3, 120.1, 116.6, 116.5, 115.5, 81.7, 78.5, 72.7, 65.6, 52.6, 44.6, 39.0, 28.3, 14.8;

IR (thin film) 3367, 2979, 2889, 1698 ,1499, 1368, 1039,754, 736 cm^{-1};

HRMS (ESI), calculated for $C_{25}H_{30}N_3O_5Cl$: ($M+Na^+$)510.1772, observed 512.1779.



S23 **S24** **1** **12**

8-(*tert*-butyl) 1-methyl 3a-((4-(methylthio)phenyl)amino)-2,3,3a,8a-tetrahydropyrrolo[2,3-*b*]indole-1,8-dicarboxylate (12)

To a 10 mL round bottom flask is added boronic acid **S23** (42 mg, 0.25 mmol, 1 eq) and MeCN (2 mL) and a Teflon coated stir bar. After the reaction vial is capped with a rubber septum and sparged with anhydrous nitrogen (three minutes), *t*BuONO (45 mL, 0.375 mmol, 1.5 eq) is added through the septum. The reaction is then heated to 35 °C and stirred under nitrogen until consumption of the starting material is observed by TLC (~2 hours). The reaction is then concentrated *in vacuo* resulting in a green solid; this resulting nitrosoarene **S24** is carried forward to the next step without purification.

To this round bottom flask is added bromo-indole **1** (40 mg, 0.1 mmol, 1 eq), Me_6TREN (26 μL, 0.1 mmol, 1 eq) and anhydrous isopropanol (5 mL) with a stir bar wrapped in 5 cm of freshly activated copper wire. The flask is capped with a reflux condenser and heated to a vigorous reflux (110 °C) for sixteen hours under an atmosphere of argon. The reaction mixture was allowed to cool to RT and then the solution was concentrated and reconstituted in DCM. This solution was loaded directly onto a flash column (15 g silica). The product is purified with an increasing gradient of ethyl acetate in hexane (5 —> 45%), affording **12** (29.8 mg, 65%).

Note: the same reaction on a 0.06 mmol scale afforded the product in 67%.

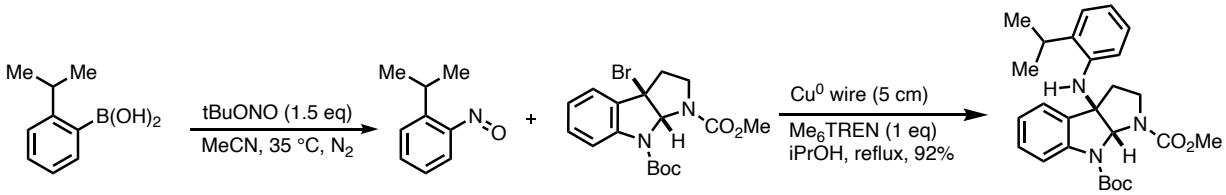
^{1}H NMR (500 MHz, cdcl$_3$, **50 °C**) δ 7.78 (d, *J* = 8.2 Hz, 1H), 7.30 (d, *J* = 7.5 Hz, 1H), 7.27 – 7.22 (m, 1H), 7.10 – 7.01 (m, 3H), 6.37 – 6.31 (m, 3H), 3.99 (dd, *J* = 11.8, 7.7 Hz, 1H), 3.74

(s, 3H), 2.93 (td, J = 11.9, 5.5 Hz, 1H), 2.44 – 2.34 (m, 4H), 2.26 (dd, J = 12.1, 5.5 Hz, 1H), 1.53 (s, 9H).

^{13}C NMR (125 MHz, cdcl$_3$, **50 °C**) δ 155.3, 152.34, 143.3, 132.0, 130.4, 129.8, 127.2, 123.6, 123.3, 116.5, 116.3, 81.8, 78.5, 72.1, 52.6, 44.4, 39.9, 28.3, 18.1.

IR (thin film) 3366, 2977, 1708, 1597, 1478, 1442, 1390, 1365, 1313, 1242, 1143, 952, 751 cm^{-1}

HRMS (ESI), calculated for $C_{24}H_{29}N_3O_4S$: (M+Na$^+$) 478.1776, observed 478.1765.



8-(*tert*-butyl) 1-methyl 3a-((2-isopropylphenyl)amino)-2,3,3a,8a-tetrahydropyrrolo[2,3-*b*]indole-1,8-dicarboxylate (19)

To a 10 mL round bottom flask is added boronic acid **S25** (41 mg, 0.25 mmol, 1 eq) and MeCN (2 mL) and a Teflon coated stir bar. After the reaction vial is capped with a rubber septum and sparged with anhydrous nitrogen (three minutes), *t*BuONO (45 mL, 0.375 mmol, 1.5 eq) is added through the septum. The reaction is then heated to 35 °C and stirred under nitrogen until consumption of the starting material is observed by TLC (~2 hours). The reaction is then concentrated *in vacuo* resulting in a green solid; this resulting nitrosoarene **S26** is carried forward to the next step without purification.

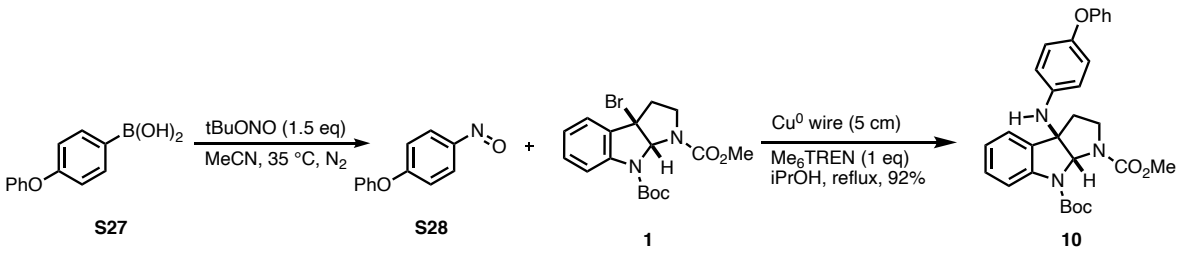
To this 10 mL round bottom flask is added bromo-indole **1** (24 mg, 0.06 mmol, 1 eq), nitrosoarene **S26** (18 mg, 0.12 mmol, 2 eq), Me_6TREN (16 µL, 0.06 mmol, 1 eq), and anhydrous isopropanol (3 mL) with a stir bar wrapped in 5 cm of freshly activated copper wire. The flask is capped with a reflux condenser and heated to a vigorous reflux (110 °C) for sixteen hours under an atmosphere of argon. The reaction mixture was allowed to cool to room temperature and then the solution was concentrated and reconstituted in DCM. This solution was loaded directly onto a flash column (15 g silica). The product is purified with an increasing gradient of ethyl acetate in hexane (10—> 50%), to afford **19** (24.9 mg, 92%) as a white foam.

^{1}H NMR (600 MHz, cdcl$_3$, **50 °C**) δ 7.80 (d, *J* = 8.2 Hz, 1H), 7.31 – 7.28 (m, 1H), 7.22 (d, *J* = 7.3 Hz, 1H), 7.14 (d, *J* = 7.6 Hz, 1H), 7.04 (d, *J* = 7.3 Hz, 1H), 6.90 (t, *J* = 7.6 Hz, 1H), 6.76 (d, *J* = 7.3 Hz, 1H), 6.39 (s, 1H), 6.26 (d, *J* = 8.1 Hz, 1H), 4.03 (dd, *J* = 11.8, 7.8 Hz, 2H), 3.74 (s, 3H), 2.94 (td, *J* = 11.9, 5.5 Hz, 1H), 2.85 (hept, *J* = 6.8 Hz, 1H), 2.48 (td, *J* = 12.0, 7.8 Hz, 1H), 2.26 (dd, *J* = 12.1, 5.4 Hz, 1H), 1.54 (s, 9H), 1.24 (dd, *J* = 8.3, 6.8 Hz, 6H);

^{13}C NMR (150 MHz, cdcl$_3$, **50 °C**) δ 155.6, 152.7, 143.4, 141.8, 134.7, 132.8, 129.8, 126.6, 125.6, 123.9, 123.3, 119.6, 116.5, 114.8, 81.9, 78.8, 72.4, 44.6, 40.2, 31.7, 28.5, 27.7, 22.6.

IR (thin film) 3377, 3010, 2988, 1699, 1600, 1498, 1209, 1100 cm $^{-1}$

HRMS (ESI), calculated for $C_{26}H_{33}N_3O_4$: ($M+Na^+$) 474.2369, observed 474.2369.



S27 S28 1 10

8-(*tert*-butyl) 1-methyl 3a-((4-phenoxyphenyl)amino)-2,3,3a,8a-tetrahydropyrrolo[2,3-*b*]indole-1,8-dicarboxylate (10):

To a 10 mL round bottom flask is added boronic acid **S27** (41 mg, 0.25 mmol, 1 eq) and MeCN (2 mL) and a Teflon coated stir bar. After the reaction vial is capped with a rubber septum and sparged with anhydrous nitrogen (three minutes), *t*BuONO (45 mL, 0.375 mmol, 1.5 eq) is added through the septum. The reaction is then heated to 35 °C and stirred under nitrogen until consumption of the starting material is observed by TLC (~2 hours). The reaction is then concentrated *in vacuo* resulting in a green solid; this resulting nitrosoarene **S28** is carried forward to the next step without purification.

To a 10 mL round bottom flask is added bromo-indole **1** (24 mg, 0.06 mmol, 1 eq), nitrosoarene **S28** (18 mg, 0.12 mmol, 2 eq), Me_6TREN (16 µL, 0.06 mmol, 1 eq), and anhydrous isopropanol (3 mL) with a stir bar wrapped in 5 cm of freshly activated copper wire. The flask is capped with a reflux condenser and heated to a vigorous reflux (110 °C) for sixteen hours under an atmosphere of argon. The reaction mixture was allowed to cool to room temperature and then the solution was concentrated and reconstituted in DCM. This solution was loaded directly onto a flash column (15 g silica). The product is purified with an increasing gradient of ethyl acetate in hexane (10—> 50%), to afford **10** (24.9 mg, 92%) as a white foam.

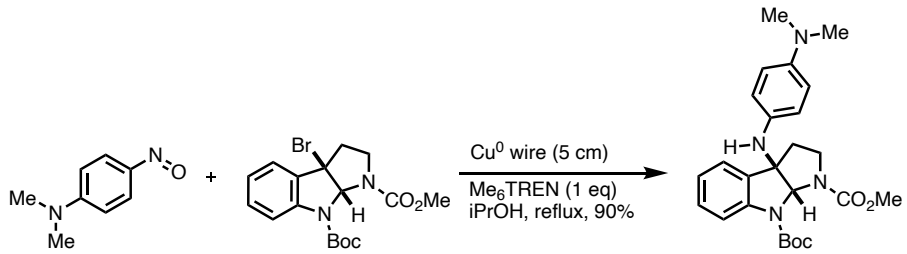
^{1}H NMR (500 MHz, cdcl$_3$, **50 °C**) δ 7.75 (d, *J* = 8.2 Hz, 1H), 7.33 – 7.21 (m, 4H), 7.09 – 7.05 (m, 1H), 7.01 (t, *J* = 7.2 Hz, 1H), 6.90 (d, *J* = 7.9 Hz, 2H), 6.77 (d, *J* = 8.9 Hz, 2H), 6.46 – 6.39 (m, 2H), 6.33 (s, 1H), 3.97 (dd, *J* = 11.7, 7.8 Hz, 1H), 3.87 (d, *J* = 13.3 Hz, 1H), 3.74 (d, *J* = 1.2 Hz, 3H), 2.93 (td, *J* = 11.7, 5.5 Hz, 1H), 2.41 (td, *J* = 12.0, 7.9 Hz, 1H), 2.29 (dd, *J* = 12.1, 5.4 Hz, 1H), 1.53 (d, *J* = 1.2 Hz, 8H).

^{13}C NMR (125 MHz, cdcl$_3$, **50 °C**) δ 158.29, 155.25, 152.34, 150.17, 143.35, 140.90, 132.18, 129.75, 129.47, 123.60, 123.35, 122.41, 120.39, 118.08, 117.86, 116.44, 81.73, 78.49, 72.54, 52.55, 44.49, 39.37, 28.31;

IR (thin film) 3383, 2978, 1700, 1483, 1390, 1229, 1151, 752cm $^{-1}$

HRMS (ESI), calculated for $C_{29}H_{31}N_3O_5$: (M+Na$^+$) 524.2161, observed 524.2158

.



8-(*tert*-butyl) 1-methyl 3a-((4-(dimethylamino)phenyl)amino)-2,3,3a,8a-tetrahydropyrrolo[2,3-*b*]indole-1,8-dicarboxylate (11)

To a 10 mL round bottom flask is added bromo-indole **1** (24 mg, 0.06 mmol, 1 eq), nitrosoarene **S29** (18 mg, 0.12 mmol, 2 eq), Me_6TREN (16 µL, 0.06 mmol, 1 eq), and anhydrous isopropanol (3 mL) with a stir bar wrapped in 5 cm of freshly activated copper wire. The flask is capped with a reflux condenser and heated to a vigorous reflux (110 °C) for sixteen hours under an atmosphere of argon. The reaction mixture was allowed to cool to room temperature and then the solution was concentrated and reconstituted in DCM. This solution was loaded directly onto a flash column (15 g silica). The product is purified with an increasing gradient of ethyl acetate in hexane (10—> 50%), to afford **11** (24.4 mg, 90%) as a white foam.

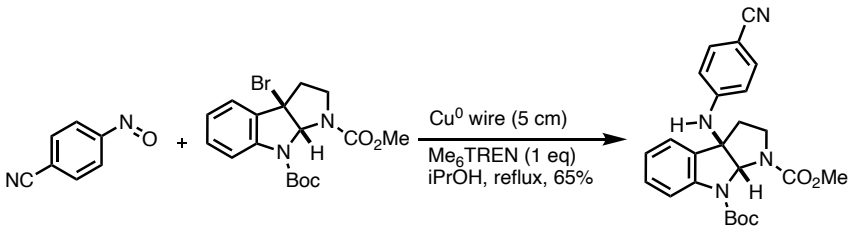
Note: Due to an apparent instability in deuterated chloroform, this compound was characterized in deuterated DCM

^{1}H NMR (600 MHz, cd_2cl_2, **25 °C**) δ 7.69 (d, *J* = 8.1 Hz, 1H), 7.32 – 7.26 (m, 2H), 7.07 (t, *J* = 7.3 Hz, 1H), 6.54 (d, *J* = 8.9 Hz, 2H), 6.45 (d, *J* = 9.0 Hz, 2H), 6.20 (s, 1H), 3.87 (dd, *J* = 11.4, 7.9 Hz, 1H), 3.69 (s, 3H), 3.58 (s, 1H), 2.87 (td, *J* = 11.7, 5.7 Hz, 1H), 2.80 (s, 6H), 2.35 (td, *J* = 12.0, 7.8 Hz, 1H), 2.28 (dd, *J* = 12.1, 5.6 Hz, 1H), 1.52 (s, 9H);

^{13}C NMR (151 MHz, cd_2cl_2, **25 °C**) δ 155.8, 152.9, 146.8, 144.2, 136.1, 133.6, 129.9, 124.1, 123.9, 121.0, 116.9, 114.7, 81.9, 79.3, 73.7, 45.2, 41.5, 39.3, 28.6;

IR (thin film) 3368, 3102, 2984, 1697, 1601, 1498, 1258, 866 cm $^{-1}$

HRMS (ESI), calculated for $C_{25}H_{32}N_4O_4$: ($M+Na^+$) 475.2321, observed 475.2309.



S30 **1** **13**

8-(*tert*-butyl) 1-methyl 3a-((4-cyanophenyl)amino)-2,3,3a,8a-tetrahydropyrrolo[2,3-*b*]indole-1,8-dicarboxylate (**13**)

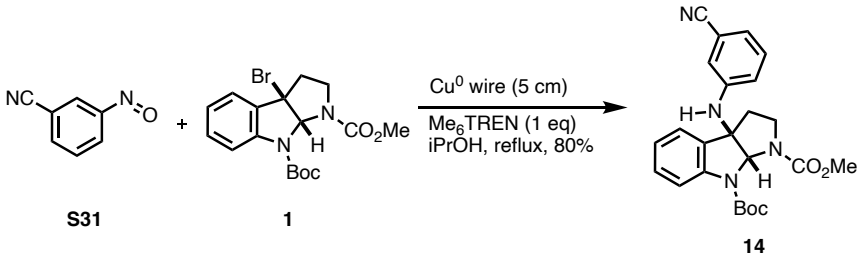
To a 10 mL round bottom flask is added bromo-indole **1** (24 mg, 0.06 mmol, 1 eq), nitrosoarene **S30** (16 mg, 0.12 mmol, 2 eq), Me_6TREN (16 µL, 0.06 mmol, 1 eq), and anhydrous isopropanol (3 mL) with a stir bar wrapped in 5 cm of freshly activated copper wire. The flask is capped with a reflux condenser and heated to a vigorous reflux (110 °C) for sixteen hours under an atmosphere of argon. The reaction mixture was allowed to cool to RT and then the solution was concentrated and reconstituted in DCM. This solution was loaded directly onto a flash column (15 g silica). The product is purified with an increasing gradient of ethyl acetate in hexane (10—> 50%), to afford **13** (16.9 mg, 65%) as a white foam.

^{1}H NMR (500 MHz, Chloroform-*d*, **50 °C**) δ 7.82 (d, *J* = 8.2 Hz, 1H), 7.37 – 7.31 (m, 3H), 7.22 (d, *J* = 7.6 Hz, 1H), 7.06 (t, *J* = 7.6 Hz, 1H), 6.37 (s, 1H), 6.35 (d, *J* = 8.6 Hz, 2H), 4.53 (s, 1H), 4.06 (dd, *J* = 12.0, 7.6 Hz, 1H), 3.76 (s, 3H), 2.95 (td, *J* = 11.9, 5.5 Hz, 1H), 2.40 (td, *J* = 11.9, 7.7 Hz, 1H), 2.30 (dd, *J* = 12.1, 5.5 Hz, 1H), 1.55 (s, 9H);

^{13}C NMR (125 MHz, Chloroform-*d*, **50 °C**) δ 155.1, 148.3, 143.2, 133.6, 130.6, 130.3, 123.8, 123.1, 119.5, 116.3, 114.3, 101.1, 82.3, 71.5, 52.7, 44.2, 40.6, 29.6, 28.3;

IR (thin film) 3358, 2958, 2929, 1705, 1606, 1446, 1393, 1369, 1334, 1255, 1201, 755, 735 cm^{-1}

HRMS (ESI), calculated for $C_{24}H_{26}N_4O_4$: ($M+Na^+$) 457.1852, observed 457.1847.



S31 1 14

8-(*tert*-butyl) 1-methyl 3a-((3-cyanophenyl)amino)-2,3,3a,8a-tetrahydropyrrolo[2,3-*b*]indole-1,8-dicarboxylate (14)

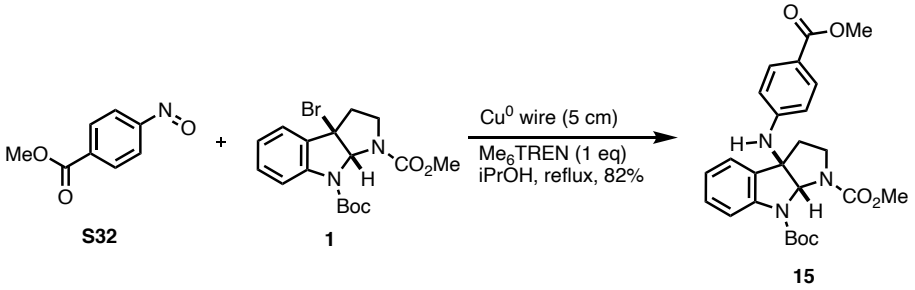
To a 10 mL round bottom flask is added bromo-indole **1** (24 mg, 0.06 mmol, 1 eq), nitrosoarene **S31** (16 mg, 0.12 mmol, 2 eq), Me_6TREN (16 µL, 0.06 mmol, 1 eq), and anhydrous isopropanol (3 mL) with a stir bar wrapped in 5 cm of freshly activated copper wire. The flask is capped with a reflux condenser and heated to a vigorous reflux (110 °C) for sixteen hours under an atmosphere of argon. The reaction mixture was allowed to cool to RT and then the solution was concentrated and reconstituted in DCM. This solution was loaded directly onto a flash column (15 g silica). The product is purified with an increasing gradient of ethyl acetate in hexane (10—> 50%), to afford **14** (20.8 mg, 87%) as a white foam.

^{1}H NMR (500 MHz, Chloroform-*d*, **50 °C**) δ 7.79 (d, *J* = 8.2 Hz, 1H), 7.32 (t, *J* = 7.9 Hz, 1H), 7.23 (d, *J* = 7.6 Hz, 1H), 7.11 (t, *J* = 8.0 Hz, 1H), 7.06 (t, *J* = 7.8 Hz, 1H), 6.97 (d, *J* = 7.5 Hz, 1H), 6.63 (s, 1H), 6.52 (d, *J* = 8.5 Hz, 1H), 6.34 (s, 1H), 4.31 (s, 1H), 4.03 (dd, *J* = 11.8, 7.7 Hz, 1H), 3.76 (s, 3H), 2.95 (td, *J* = 11.9, 5.5 Hz, 1H), 2.39 (td, *J* = 12.0, 7.8 Hz, 1H), 2.29 (dd, *J* = 12.1, 5.5 Hz, 1H), 1.55 (s, 9H);

^{13}C NMR (126 MHz, Chloroform-*d*, **50 °C**) δ 155.1, 152.2, 145.4, 143.3, 130.8 130.2, 130.0, 123.8, 123.2, 122.3, 119.0, 118.7, 118.0, 116.3, 113.2, 82.2, 78.4, 71.7, 52.7, 44.3, 40.1, 28.3;

IR (thin film) 3369, 3055, 2982, 1699, 1603, 1264, 1151, 731 cm $^{-1}$

HRMS (ESI), calculated for $C_{24}H_{26}N_4O_4$: (M+Na$^+$)457.1852, observed 457.1856.



8-(*tert*-butyl) 1-methyl 3a-((4-(methoxycarbonyl)phenyl)amino)-2,3,3a,8a-tetrahydropyrrolo[2,3-*b*]indole-1,8-dicarboxylate (15)

To a 10 mL round bottom flask is added bromo-indole **1** (24 mg, 0.06 mmol, 1 eq), nitrosoarene **S32** (20 mg, 0.12 mmol, 2 eq), Me_6TREN (16 µL, 0.06 mmol, 1 eq), and anhydrous isopropanol (3 mL) with a stir bar wrapped in 5 cm of freshly activated copper wire. The flask is capped with a reflux condenser and heated to a vigorous reflux (110 °C) for sixteen hours under an atmosphere of argon. The reaction mixture was allowed to cool to room temperature and then the solution was concentrated and reconstituted in DCM. This solution was loaded directly onto a flash column (15 g silica). The product is purified with an increasing gradient of ethyl acetate in hexane (10—> 50%), to afford **15** (23.0 mg, 82%).

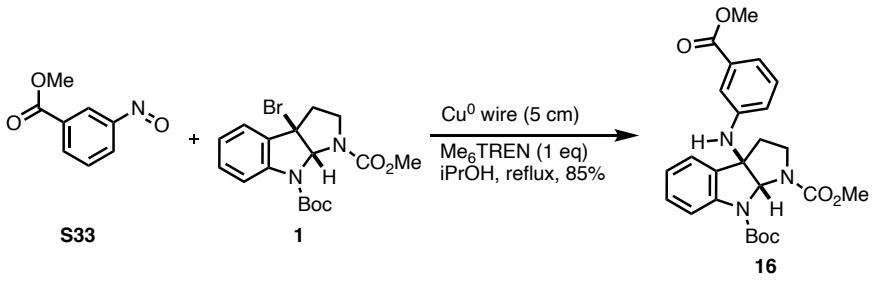
^{1}H NMR (500 MHz, cdcl$_3$, **50 °C**) δ 7.81 (d, *J* = 8.2 Hz, 1H), 7.76 (d, *J* = 8.7 Hz, 2H), 7.32 (d, *J* = 7.9 Hz, 1H), 7.23 (d, *J* = 7.5 Hz, 1H), 7.05 (d, *J* = 7.4 Hz, 1H), 6.40 (s, 1H), 6.35 (d, *J* = 8.8 Hz, 2H), 4.47 (s, 1H), 4.05 (dd, *J* = 11.9, 7.8 Hz, 1H), 3.82 (s, 3H), 3.75 (s, 3H), 2.95

(td, J = 11.8, 5.4 Hz, 1H), 2.44 (td, J = 12.0, 7.8 Hz, 1H), 2.28 (dd, J = 12.1, 5.4 Hz, 1H), 1.54 (s, 9H).

^{13}C NMR (126 MHz, cdcl$_3$, **50 °C**) δ 167.1, 152.5, 149.0, 143.5, 136.7, 131.6, 130.3, 124.0, 123.3, 120.5, 116.4, 113.9, 82.3, 81.2, 78.7, 71.9, 51.7, 47.6, 44.5, 40.5, 28.6.

IR (thin film) 3368, 2980, 2953, 1697, 1604, 1444, 1391, 1368, 1333, 1271, 1176, 701 cm^{-1};

HRMS (ESI), calculated for $C_{25}H_{29}N_3O_6$: (M+Na$^+$) 490.1954, observed 490.1947



8-(*tert*-butyl) 1-methyl 3a-((3-(methoxycarbonyl)phenyl)amino)-2,3,3a,8a-tetrahydropyrrolo[2,3-*b*]indole-1,8-dicarboxylate (16)

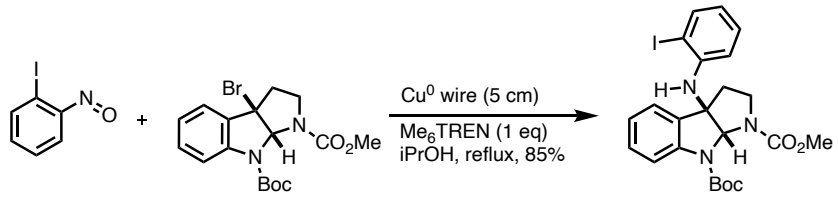
To a 10 mL round bottom flask is added bromo-indole **1** (24 mg, 0.06 mmol, 1 eq), nitrosoarene **S33** (20 mg, 0.12 mmol, 2 eq), Me$_6$TREN (16 µL, 0.06 mmol, 1 eq), and anhydrous isopropanol (3 mL) with a stir bar wrapped in 5 cm of freshly activated copper wire. The flask is capped with a reflux condenser and heated to a vigorous reflux (110 °C) for sixteen hours under an atmosphere of argon. The reaction mixture was allowed to cool to RT and then the solution was concentrated and reconstituted in DCM. This solution was loaded directly onto a flash column (15 g silica). The product is purified with an increasing gradient of ethyl acetate in hexane (10—> 50%), to afford **16** (23.8 mg, 85%) as a white foam. ^{1}H

NMR (500 MHz, Chloroform-*d*, **50 °C**) δ 7.81 (d, *J* = 8.2 Hz, 1H), 7.39 (d, *J* = 7.6 Hz, 1H), 7.30 (t, *J* = 7.8 Hz, 1H), 7.24 (d, *J* = 7.4 Hz, 1H), 7.13 (t, *J* = 2.0 Hz, 1H), 7.10 (t, *J* = 7.9 Hz, 1H), 7.04 (t, *J* = 7.6 Hz, 1H), 6.51 (d, *J* = 8.2 Hz, 1H), 6.35 (s, 1H), 4.03 (dd, *J* = 11.8, 7.7 Hz, 1H), 3.83 (s, 3H), 3.74 (s, 3H), 2.94 (td, *J* = 11.9, 5.5 Hz, 1H), 2.40 (td, *J* = 12.0, 7.7 Hz, 1H), 2.29 (dd, *J* = 12.1, 5.4 Hz, 1H), 1.52 (s, 10H);

^{13}C NMR (126 MHz, cdcl$_3$, **50 °C**)) δ 170.9, 166.8, 155.2, 152.3, 144.9, 143.4, 131.5, 131.2, 129.9, 129.2, 123.6, 123.2, 120.2, 119.3, 116.9, 116.2, 81.8, 78.7, 72.1, 60.2, 52.6, 51.8, 44.4, 40.1, 28.3, 20.8, 14.1;

IR (thin film) 3375, 2981, 2953, 1701, 1605, 1479, 1443, 1392, 1243, 1145, 752 cm $^{-1}$

HRMS (ESI), calculated for $C_{25}H_{29}N_3O_6$: (M+Na$^+$)490.1954, observed 490.1964.



S34 **1** **17**

8-(*tert*-butyl) 1-methyl 3a-((2-iodophenyl)amino)-2,3,3a,8a-tetrahydropyrrolo[2,3-*b*]indole-1,8-dicarboxylate (17)

To a 10 mL round bottom flask is added bromo-indole **1** (24 mg, 0.06 mmol, 1 eq), nitrosoarene **S34** (28 mg, 0.12 mmol, 2 eq), Me$_6$TREN (16 µL, 0.06 mmol, 1 eq), and anhydrous isopropanol (3 mL) with a stir bar wrapped in 5 cm of freshly activated copper wire. The flask is capped with a reflux condenser and heated to a vigorous reflux (110 °C) for sixteen hours under an atmosphere of argon. The reaction mixture was allowed to cool to room temperature and then the solution was concentrated and reconstituted in DCM. This solution was loaded directly onto a flash column (15 g silica). The product is purified with an

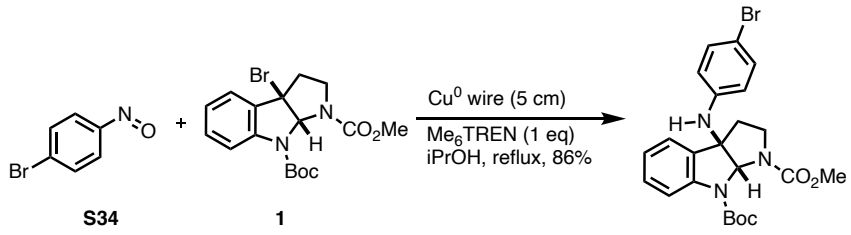
increasing gradient of ethyl acetate in hexane (10—> 50%), to afford **17** (27.3 mg, 85%) as a white foam.

^{1}H NMR (500 MHz, cdcl$_3$, **50 °C**) δ 7.81 (d, *J* = 8.2 Hz, 1H), 7.67 (d, *J* = 8.0 Hz, 1H), 7.35 – 7.30 (m, 1H), 7.27 (d, *J* = 7.0 Hz, 1H), 7.07 (t, *J* = 7.5 Hz, 1H), 7.02 – 6.95 (m, 1H), 6.49 – 6.42 (m, 1H), 6.37 (s, 1H), 6.12 (d, *J* = 8.2 Hz, 1H), 4.64 (s, 1H), 4.07 (t, *J* = 9.9 Hz, 1H), 3.77 (s, 3H), 2.95 (td, *J* = 11.9, 5.4 Hz, 1H), 2.47 (td, *J* = 12.0, 7.7 Hz, 1H), 2.39 – 2.29 (m, 1H), 1.55 (s, 9H).

^{13}C NMR (125 MHz, cdcl$_3$, **50 °C**) δ 155.3, 152.4, 144.4, 143.3, 139.4, 131.2, 129.9, 129.3, 123.8, 123.3, 120.3, 116.0, 113.4, 88.1, 82.0, 78.6, 72.2, 52.8, 44.2, 40.8, 28.4;

IR (thin film) 3366, 3001, 2981, 1705, 1605, 1500, 1210, 880 cm $^{-1}$

HRMS (ESI), calculated for $C_{23}H_{26}IN_3O_4$: (M+Na$^+$) 558.0866, observed 558.0865.



S34 1 18

8-(*tert*-butyl) 1-methyl 3a-((4-bromophenyl)amino)-2,3,3a,8a-tetrahydropyrrolo[2,3-*b*]indole-1,8-dicarboxylate (18)

To a 10 mL round bottom flask is added bromo-indole **1** (24 mg, 0.06 mmol, 1 eq), nitrosoarene **S34** (22 mg, 0.12 mmol, 2 eq), Me$_6$TREN (16 µL, 0.06 mmol, 1 eq), and

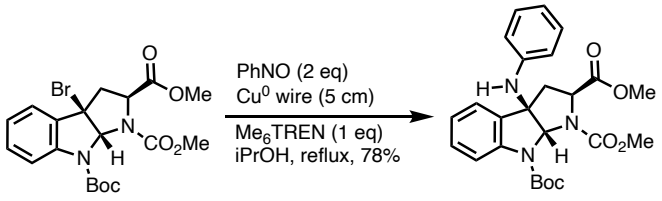
anhydrous isopropanol (3 mL) with a stir bar wrapped in 5 cm of freshly activated copper wire. The flask is capped with a reflux condenser and heated to a vigorous reflux (110 °C) for sixteen hours under an atmosphere of argon. The reaction mixture was allowed to cool to RT and then the solution was concentrated and reconstituted in DCM. This solution was loaded directly onto a flash column (15 g silica). The product is purified with an increasing gradient of ethyl acetate in hexane (10—> 50%), to afford **18** (25.1 mg, 86%) as a white foam.

^{1}H NMR (500 MHz, Chloroform-*d*, **50 °C**) δ 7.77 (d, *J* = 8.2 Hz, 1H), 7.30 (t, *J* = 8.4, 7.4, 1.3 Hz, 1H), 7.24 (d, *J* = 7.7, 1.3 Hz, 1H), 7.15 (d, 2H), 7.05 (d, *J* = 7.5 Hz, 1H), 6.32 (s, 1H), 6.30 – 6.24 (m, 2H), 4.00 (dd, *J* = 11.8, 7.7 Hz, 1H), 2.93 (td, *J* = 11.8, 5.6 Hz, 1H), 2.37 (td, *J* = 12.0, 7.7 Hz, 1H), 2.28 (dd, *J* = 12.1, 5.5 Hz, 1H), 1.53 (s, 9H);

^{13}C NMR (125 MHz, Chloroform-*d*, **50 °C**) δ 155.2, 152.3, 143.8, 143.3, 132.0, 131.4, 129.9, 123.7, 123.2, 117.4, 116.3, 111.5, 81.9, 78.5, 72.1, 52.6, 44.3, 40.0, 28.3.

IR (thin film) 3373, 2979, 2931, 1696, 1594, 1445, 1392, 1368, 1321, 1146, 703cm $^{-1}$

HRMS (ESI), calculated for $C_{23}H_{26}BrN_3O_4$: ($M+Na^+$) 510.1004, observed 510.1002.



S1 **20**

8-(*tert*-butyl) 1,2-dimethyl (2*S*,3a*R*,8a*R*)-3a-(phenylamino)-2,3,3a,8a-tetrahydropyrrolo[2,3-*b*]indole-1,2,8-tricarboxylate (20)

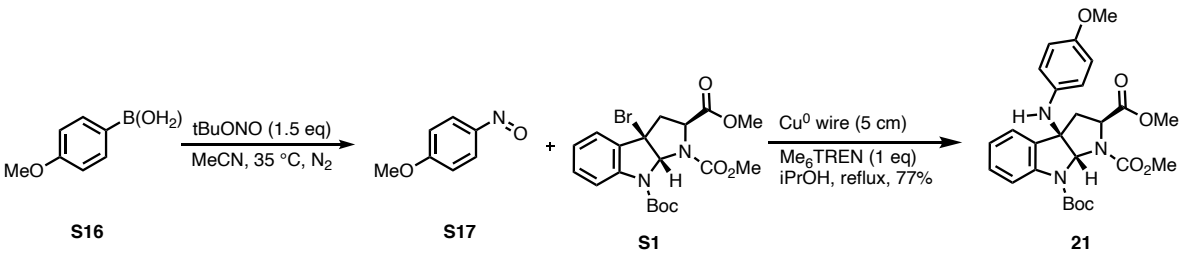
To a 10 mL round bottom flask is added bromo-indole **S1** (27 mg, 0.06 mmol, 1 eq), nitrosobenzene (13 mg, 0.12 mmol, 2 eq), Me_6TREN (16 μL, 0.06 mmol, 1 eq), and anhydrous isopropanol (3 mL) with a stir bar wrapped in 5 cm of freshly activated copper wire. The flask is capped with a reflux condenser and heated to a vigorous reflux (110 °C) for sixteen hours under an atmosphere of argon. The reaction mixture was allowed to cool to RT and then the solution was concentrated and reconstituted in DCM. This solution was loaded directly onto a flash column (15 g silica). The product is purified with an increasing gradient of ethyl acetate in hexane (5—> 45%), to afford **20** (21.8 mg, 78%) as a white foam.

^{1}H NMR (500 MHz, Chloroform-*d*, **50 °C**) δ 7.65 (d, *J* = 8.2 Hz, 1H), 7.34 (t, *J* = 7.5 Hz, 2H), 7.16 – 7.08 (m, 3H), 6.82 (t, *J* = 7.4 Hz, 1H), 6.61 (d, *J* = 8.0 Hz, 2H), 6.43 (s, 1H), 4.06 (dd, *J* = 9.2, 7.4 Hz, 1H), 3.78 (s, 3H), 3.69 (s, 3H), 2.82 (dd, *J* = 13.1, 9.2 Hz, 1H), 2.67 (dd, *J* = 13.1, 7.5 Hz, 1H), 1.49 (s, 9H);

^{13}C NMR (125 MHz, Chloroform-*d*, **50 °C**) δ 172.4, 154.8, 152.2, 144.1, 142.3, 133.3, 130.2, 129.2, 124.0, 123.1, 120.3, 118.0, 117.4, 81.7, 77.4, 70.5, 58.6, 52.6, 52.3, 37.1, 28.2;

IR (thin film) 3365, 2955, 1698, 1602, 1447, 1390, 1327, 1147, 752, 699 cm^{-1};

HRMS (ESI), calculated for $C_{25}H_{29}N_3O_6$: (M+Na$^+$)490.1954, observed 490.1970.



S16 S17 S1 21

8-(*tert*-butyl) 1,2-dimethyl (2*S*,3a*R*,8a*R*)-3a-((4-methoxyphenyl)amino)-2,3,3a,8a-tetrahydropyrrolo[2,3-*b*]indole-1,2,8-tricarboxylate (21)

To a 10 mL round bottom flask is added boronic acid **S16** (23 mg, 0.15 mmol, 1 eq) and MeCN (1.5 mL) and a Teflon coated stir bar. After the reaction vial is capped with a rubber septum and sparged with anhydrous nitrogen (three minutes), *t*BuONO (27 mL, 0.23 mmol, 1.5 eq) is added through the septum. The reaction is then heated to 35 °C and stirred under nitrogen until consumption of the starting material is observed by TLC (~2 hours). The reaction is then concentrated *in vacuo* resulting in a green solid; this resulting nitrosoarene **S17** is carried forward to the next step without purification.

To this round bottom flask is added bromo-indole **S1** (27 mg, 0.06 mmol, 1 eq), Me_6TREN (16 μL, 0.06 mmol, 1 eq) and anhydrous isopropanol (3 mL) with a stir bar wrapped in 5 cm of freshly activated copper wire. The flask is capped with a reflux condenser and heated to a vigorous reflux (110 °C) for sixteen hours under an atmosphere of argon. The reaction mixture was allowed to cool to RT and then the solution was concentrated and reconstituted in DCM. This solution was loaded directly onto a flash column (15 g silica). The product is purified with an increasing gradient of ethyl acetate in hexane (10 —> 55%), affording **21** (22.9 mg, 77%) as a white solid.

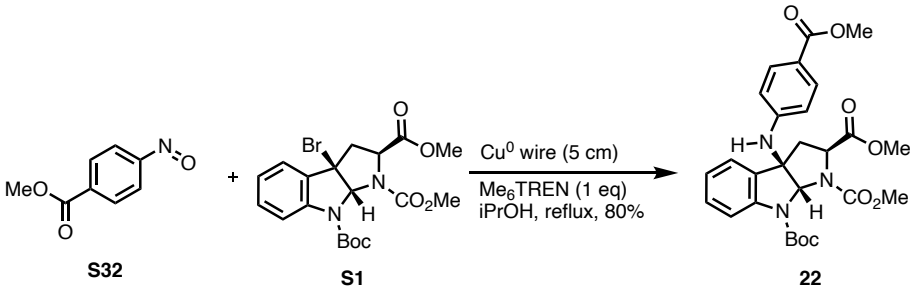
^{1}H NMR (500 MHz, Chloroform-*d*, **50 °C**) δ 7.60 (d, *J* = 8.1 Hz, 1H), 7.37 – 7.28 (m, 2H), 7.11 (t, *J* = 7.5, 1.0 Hz, 1H), 6.68 (d, *J* = 9.0 Hz, 2H), 6.57 (d, *J* = 9.4 Hz, 2H), 6.27 (s, 1H),

4.01 (dd, J = 9.5, 7.1 Hz, 1H), 3.76 (s, 3H), 3.70 (s, 3H), 3.67 (s, 3H), 2.71 (dd, J = 12.8, 7.2 Hz, 1H), 2.62 (dd, J = 12.8, 9.5 Hz, 1H), 1.49 (s, 9H);

^{13}C NMR (125 MHz, $CDCl_3$, **50 °C**) δ 172.4, 155.2, 154.7, 152.0, 142.5, 137.1, 133.0, 130.01, 123.8, 123.3, 121.7, 117.8, 114.5, 81.5, 78.0, 71.6 58.6, 55.4, 52.5, 52.3, 37.9, 28.1;

IR (thin film) 3326, 2954, 1736, 1703, 1607, 1509, 1455, 1447, 1388, 1330, 1154, 1030, 907, 733;

HRMS (ESI), calculated for $C_{26}H_{31}N_3O_7$: ($M+Na^+$) 520.2060, observed 520.2041.



8-(tert-butyl) 1,2-dimethyl (2S,3aR,8aR)-3a-((4-(methoxycarbonyl)phenyl)amino)-2,3,3a,8a-tetrahydropyrrolo[2,3-*b*]indole-1,2,8-tricarboxylate (22)

To a 10 mL round bottom flask is added bromo-indole **S1** (27 mg, 0.06 mmol, 1 eq), nitrosoarene **S32** (20 mg, 0.12 mmol, 2 eq), Me_6TREN (16 µL, 0.06 mmol, 1 eq), and anhydrous isopropanol (3 mL) with a stir bar wrapped in 5 cm of freshly activated copper wire. The flask is capped with a reflux condenser and heated to a vigorous reflux (110 °C) for sixteen hours under an atmosphere of argon. The reaction mixture was allowed to cool to RT and then the solution was concentrated and reconstituted in DCM. This solution was loaded directly onto a flash column (15 g silica). The product is purified with an increasing gradient of ethyl acetate in hexane (10—> 55%), to afford **22** (25.2 mg, 80%) as a white foam.

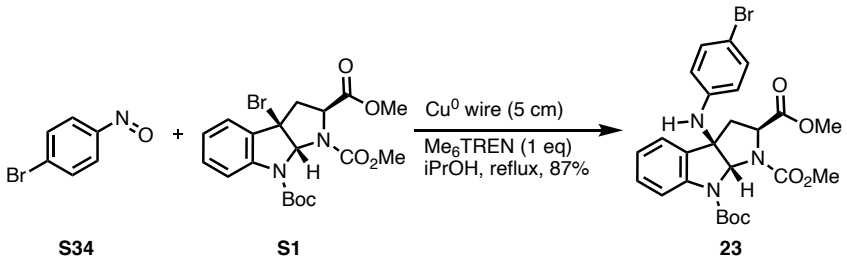
^{1}H NMR (500 MHz, Chloroform-*d*, **50 °C**) δ 7.84 (d, J = 8.8 Hz, 2H), 7.69 (d, J = 8.1 Hz, 1H), 7.40 – 7.30 (m, 2H), 7.12 (d, J = 7.6 Hz, 1H), 6.65 – 6.56 (m, 2H), 6.50 (s, 1H), 4.13 –

4.08 (m, 1H), 3.84 (s, 3H), 3.79 (s, 3H), 3.70 (s, 3H), 2.86 (dd, *J* = 13.3, 8.8 Hz, 1H), 2.65 (dd, *J* = 13.3, 7.7 Hz, 1H), 1.50 (s, 9H);

^{13}C NMR (125 MHz, Chloroform-*d*, **50 °C**) δ 172.4, 166.8, 154.7, 152.3, 148.2, 142.1, 132.8, 131.4, 130.5, 124.1, 122.8, 120.7, 118.0, 114.5, 82.0, 77.1, 69.7, 58.6, 52.7, 52.4, 51.5, 36.7, 28.2;

IR (thin film) 3361, 2951, 1699, 1604, 1446, 1390, 1331, 1273, 1150, 733 cm $^{-1}$;

HRMS (ESI), calculated for $C_{25}H_{29}N_3O_6$: ($M+Na^+$) 548.2009, observed 548.2015.



S34 **S1** **23**

8-(*tert*-butyl) 1,2-dimethyl (2*S*,3a*R*,8a*R*)-3a-((4-bromophenyl)amino)-2,3,3a,8a-tetrahydropyrrolo[2,3-*b*]indole-1,2,8-tricarboxylate (23)

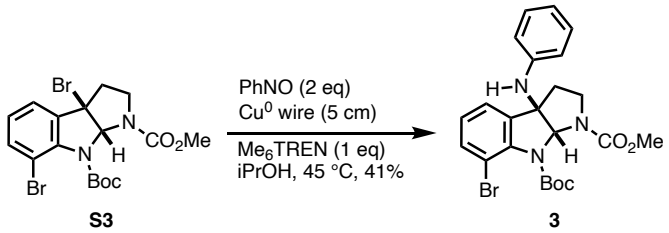
To a 10 mL round bottom flask is added bromo-indole **S1** (27 mg, 0.06 mmol, 1 eq), nitrosoarene **S34** (22 mg, 0.12 mmol, 2 eq), Me_6TREN (16 µL, 0.06 mmol, 1 eq), and anhydrous isopropanol (3 mL) with a stir bar wrapped in 5 cm of freshly activated copper wire. The flask is capped with a reflux condenser and heated to a vigorous reflux (110 °C) for sixteen hours under an atmosphere of argon. The reaction mixture was allowed to cool to RT and then the solution was concentrated and reconstituted in DCM. This solution was loaded directly onto a flash column (15 g silica). The product is purified with an increasing gradient of ethyl acetate in hexane (10—> 50%), to afford **23** (28.5 mg, 87%) as a white foam.

^{1}H NMR (500 MHz, Chloroform-*d*, **50 °C**) δ 7.66 (d, *J* = 8.1 Hz, 1H), 7.41 – 7.31 (m, 2H), 7.23 (d, *J* = 8.5 Hz, 2H), 7.13 (t, *J* = 7.3 Hz, 1H), 6.47 (d, *J* = 9.1 Hz, 2H), 6.39 (s, 1H), 4.09 (t, *J* = 7.8 Hz, 1H), 3.79 (s, 3H), 3.71 (s, 3H), 2.70 (qd, *J* = 13.1, 8.2 Hz, 2H), 1.52 (s, 9H);

^{13}C NMR (125 MHz, Chloroform-*d*, **50 °C**) δ 172.5, 154.7, 152.2, 143.2, 142.3, 132.8, 132.1, 130.3, 124.0, 123.0, 118.8, 118.0, 112.6, 81.9, 77.5, 70.4, 58.6, 52.6, 52.4, 37.5, 28.2.

IR (thin film) 3367, 2978, 2954, 1702, 1595, 1481, 1365, 1151, 702 cm $^{-1}$

HRMS (ESI), calculated for $C_{25}H_{28}BrN_3O_6$: ($M+Na^+$) 568.1059, observed 568.1064.



8-(*tert*-butyl) 1-methyl 7-bromo-3a-(phenylamino)-2,3,3a,8a-tetrahydropyrrolo[2,3-*b*]indole-1,8-dicarboxylate (3)

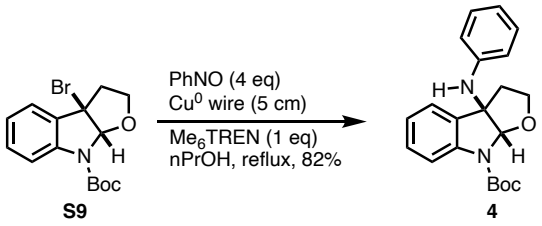
To a 10 mL round bottom flask is added bromo-indole **S3** (28 mg, 0.06 mmol, 1 eq), nitrosobenzene (13 mg, 0.12 mmol, 2 eq), Me_6TREN (16 μL, 0.06 mmol, 1 eq), and anhydrous isopropanol (3 mL) with a stir bar wrapped in 5 cm of freshly activated copper wire. The flask is capped with a rubber septum, sparged with argon and heated to 50 °C for sixteen hours under an atmosphere of argon. The reaction mixture was allowed to cool to RT and then the solution was concentrated and reconstituted in DCM. This solution was loaded directly onto a flash column (15 g silica). The product is purified with an increasing gradient

of ethyl acetate in hexane (10—> 50%), to afford **3** (12.1 mg, 41%) as an off-white (taupe) foam.

^{1}H NMR (600 MHz, Chloroform-*d*, **50 °C**) δ 7.55 (d, *J* = 8.2 Hz, 1H), 7.28 (d, *J* = 7.5 Hz, 1H), 7.12 (d, *J* = 7.7 Hz, 2H), 7.06 (t, *J* = 7.7 Hz, 1H), 6.78 (t, *J* = 7.4 Hz, 1H), 6.50 (d, *J* = 7.9 Hz, 2H), 6.28 (s, 1H), 3.84 (dd, *J* = 11.3, 8.2 Hz, 1H), 3.77 (s, 3H), 2.80 (td, *J* = 11.6, 5.5 Hz, 1H), 2.58 (td, *J* = 12.1, 8.2 Hz, 1H), 2.23 (dd, *J* = 12.5, 5.5 Hz, 1H), 1.41 (s, 9H);

^{13}C NMR (150 MHz, cdcl$_3$, **50 °C**) δ 155.2 152.2, 144.6, 142.9, 137.8, 134.5, 129.4, 126.6, 122.1, 119.8, 116.2, 114.4, 81.9, 80.0, 73.1, 52.5, 44.3, 36.1, 28.0.

HRMS (ESI), calculated for $C_{23}H_{26}N_3O_4Br$: ($M+Na^+$) 510.1004, observed 510.1023.



***tert*-butyl-3a-(phenylamino)-2,3,3a,8a-tetrahydro-8*H*-furo[2,3-*b*]indole-8-carboxylate (4):** To a 15 mL two neck round bottom flask is added nitrosobenzene (0.24 mmol, 4 eq), Me_6TREN (16 µL, 0.06 mmol, 1 eq), and anhydrous n-propanol (3 mL) with a stir bar wrapped in 5 cm of freshly activated copper wire. The flask is capped with a reflux condenser and heated to a vigorous reflux (120 °C) under an atmosphere of argon while bromo-furoindoline **S9** (20 mg, 0.06 mmol, 1 eq) in 10% EtOAc in isopropanol (1 mL) is added dropwise via syringe pump over 90 minutes. After TLC indicates completion of the

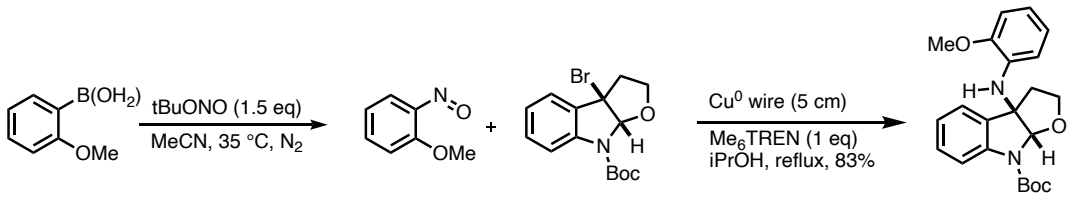
reaction (about 6 hours after the initiation of indoline addition), the reaction is cooled to room temperature and then the solution was concentrated and reconstituted in DCM. This solution was loaded directly onto a flash column (15 g silica). The product is purified with an increasing gradient of ethyl acetate in hexane (5 —> 45%), affording **4** as a clear oil.

^{1}H NMR (600 MHz, cdcl$_3$, **50 °C**) δ 7.78 (s, 1H), 7.29 (d, *J* = 7.5 Hz, 2H), 7.07 (t, *J* = 7.6 Hz, 2H), 7.02 (t, *J* = 7.5 Hz, 1H), 6.70 (t, *J* = 7.3 Hz, 1H), 6.46 (d, *J* = 7.9 Hz, 2H), 6.13 (s, 1H), 4.11 (t, *J* = 8.4 Hz, 1H), 3.56 (ddd, *J* = 11.6, 9.4, 4.8 Hz, 1H), 2.69 (td, *J* = 12.0, 7.8 Hz, 1H), 2.23 (dd, *J* = 12.0, 4.8 Hz, 1H), 1.56 (s, 9H);

^{13}C NMR (151 MHz, cdcl$_3$, **50 °C**) δ 152.3, 145.0, 143.0, 132.2, 129.7, 129.3, 123.5, 123.3, 118.5, 114.7, 95.0, 94.9, 81.8, 71.5, 66.3, 40.9, 28.3;

IR (thin film) 3376, 2932, 2883, 1716, 1604, 1484, 1372, 1332, 1152, 1039, 744 cm-1

HRMS (ESI), calculated for $C_{21}H_{24}N_2O_3$: ($M+Na^+$) 375.1685, observed 375.1686;



S19 **S20** **S9** **5**

***tert*-butyl 3a-((2-methoxyphenyl)amino)-2,3,3a,8a-tetrahydro-8*H*-furo[2,3-*b*]indole-8-carboxylate (5)** To a 15 mL two-neck round bottom flask is added arylboronic acid **S19** (0.3 mmol, 5 eq) and MeCN (1.5 mL) and a Teflon coated stir bar. After the reaction vial is

capped with a rubber septum and sparged with anhydrous nitrogen (three minutes), *t*BuONO (27 mL, 0.23 mmol, 7.5 eq) is added through the septum. The reaction is then heated to 35 °C and stirred under nitrogen until consumption of the starting material is observed by TLC (~2.5 hours). The reaction is then concentrated *in vacuo* resulting in a green solid; this resulting nitrosoarene **S20** is carried forward to the next step without purification.

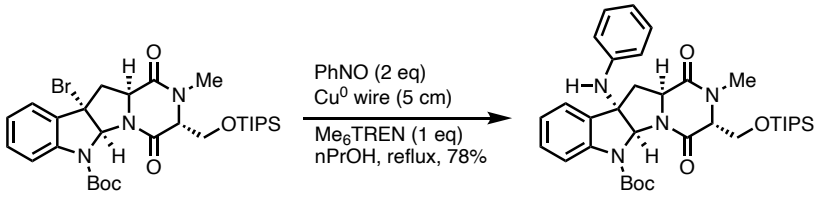
To this vial is added Me_6TREN (16 µL, 0.06 mmol, 1 eq), and anhydrous n-propanol (3 mL) with a stir bar wrapped in 5 cm of freshly activated copper wire. The flask is capped with a reflux condenser and heated to a vigorous reflux (120 °C) under an atmosphere of argon while bromo-furoindoline **S9** (20 mg, 0.06 mmol, 1 eq) in 10% EtOAc in isopropanol (1 mL) is added dropwise via syringe pump over 90 minutes. After TLC indicates completion of the reaction (about 6 hours after the initiation of indoline addition), the reaction is cooled to room temperature and then the solution was concentrated and reconstituted in DCM. This solution was loaded directly onto a flash column (15 g silica). The product is purified with an increasing gradient of ethyl acetate in hexane (5 —> 45%) to afford **5** as a clear oil.

^{1}H NMR (600 MHz, $cdcl_3$, **50 °C**) δ 7.80 (s, 1H), 7.32 (d, *J* = 7.5 Hz, 1H), 7.29 (t, *J* = 7.8 Hz, 1H), 7.04 (t, *J* = 7.5 Hz, 1H), 6.77 (d, *J* = 7.9 Hz, 1H), 6.67 (d, *J* = 5.8 Hz, 2H), 6.31 (d, *J* = 7.2 Hz, 1H), 6.14 (s, 1H), 4.77 (s, 1H), 4.13 (t, *J* = 8.4 Hz, 1H), 3.84 (s, 3H), 3.59 (ddd, *J* = 12.1, 9.3, 4.9 Hz, 1H), 2.74 (td, *J* = 11.9, 7.6 Hz, 1H), 2.27 (dd, *J* = 12.0, 4.8 Hz, 1H), 1.58 (s, 9H);

^{13}C NMR (150 MHz, cdcl$_3$, **50 °C**) δ 152.4, 147.4, 143.0, 135.0, 132.3, 129.6, 123.5, 123.3, 121.3, 117.6, 114.6, 112.0, 109.8, 95.1, 81.7, 71.2, 66.3, 55.4, 41.1, 28.3;

IR (thin film) 3429, 3049, 2977, 1706, 1601, 1510, 1480, 1382, 1244, 1144, 1046, 1027, 908, 728 cm $^{-1}$;

HRMS (ESI), calculated for $C_{22}H_{26}N_2O_4$: (M+Na$^+$) 405.1790, observed 405.1792.



***tert*-butyl (3*R*,5a*S*,10b*S*,11a*S*)-2-methyl-1,4-dioxo-10b-(phenylamino)-3 (((triisopropylsilyl)oxy)methyl)-1,2,3,4,5a,10b,11,11a-octahydro-6*H*-pyrazino[1',2':1,5]pyrrolo[2,3-*b*]indole-6-carboxylate (24):**

To a 15 mL two neck round bottom flask is added bromo-indole **S15** (38 mg, 0.06 mmol, 1 eq), nitrosobenzene (13 mg, 0.12 mmol, 2 eq), Me$_6$TREN (16 µL, 0.06 mmol, 1 eq), and anhydrous n-propanol (3 mL) with a stir bar wrapped in 5 cm of freshly activated copper wire. The flask is capped with a reflux condenser and heated to a vigorous reflux (120 °C) until TLC indicates consumption of starting material and the more-polar hydroxylamine intermediate (9 hours) under an atmosphere of argon. The reaction mixture was allowed to cool to room temperature and then the solution was concentrated and reconstituted in DCM. This solution was loaded directly onto a flash column (15 g silica). The product is purified

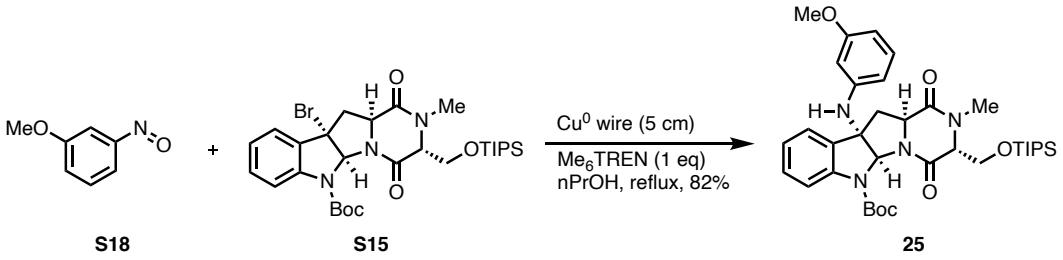
with an increasing gradient of ethyl acetate in dichloromethane (5—> 25%), to afford **24** (27.1 mg, 71%) as an off-white oil.

^{1}H NMR (600 MHz, cdcl$_3$, **26 °C**) δ 7.75 (d, *J* = 8.1 Hz, 1H), 7.36 (d, *J* = 7.5, 1.3 Hz, 1H), 7.31 (t, *J* = 7.8, 1.3 Hz, 1H), 7.13 (d, *J* = 8.5, 7.3 Hz, 2H), 7.09 (t, *J* = 7.5, 1.0 Hz, 1H), 6.80 (t, *J* = 7.3 Hz, 1H), 6.49 (d, *J* = 7.8 Hz, 2H), 6.21 (s, 1H), 4.79 (t, *J* = 9.1 Hz, 1H), 4.26 (dd, *J* = 10.4, 2.3 Hz, 1H), 4.02 (dd, *J* = 10.4, 2.5 Hz, 1H), 3.79 (s, 1H), 3.74 (d, *J* = 2.3 Hz, 1H), 3.03 (dd, *J* = 14.4, 9.6 Hz, 1H), 2.87 (s, 3H), 2.83 (dd, *J* = 14.4, 8.6 Hz, 1H), 1.54 (s, 9H), 1.16 – 1.03 (m, 21H);

^{13}C NMR (150 MHz, cdcl$_3$, **26 °C**) δ 167.5, 165.6, 152.3, 144.0, 141.3, 135.4, 129.8, 129.3, 124.1, 123.7, 119.4, 117.0, 115.6, 82.0, 77.8, 68.5, 66.9, 63.2, 56.0, 35.9, 31.9, 28.1, 17.9, 11.9;

IR (thin film) 3376, 2943, 2866, 2839, 1731, 1681, 1648, 1602, 1481, 1323, 1158, 1112, 727 cm^{-1};

HRMS (ESI), calculated for $C_{35}H_{50}N_4O_5Si$: (M+Na$^+$) 657.3448, observed 657.3449.



S18 **S15** **25**

***tert*-butyl (3*R*,5a*S*,10b*S*,11a*S*)-10b-((3-methoxyphenyl)amino)-2-methyl-1,4-dioxo-3-(((triisopropylsilyl)oxy)methyl)-1,2,3,4,5a,10b,11,11a-octahydro-6*H*-pyrazino[1',2':1,5]pyrrolo[2,3-*b*]indole-6-carboxylate (25)**

Procedure in nPrOH

To a 15 mL two-neck-round bottom flask is added bromo-indole (38 mg, 0.06 mmol, 1 eq), nitrosoarene **S18** (16 mg, 0.12 mmol, 2 eq), Me_6TREN (16 µL, 0.06 mmol, 1 eq), and anhydrous **n-propanol** (3 mL) with a stir bar wrapped in 5 cm of freshly activated copper wire. The flask is capped with a reflux condenser and heated to a vigorous reflux (120 °C) until TLC indicates consumption of starting material and the more-polar hydroxylamine intermediate (7 hours) under an atmosphere of argon. The reaction mixture was allowed to cool to room temperature and then the solution was concentrated and reconstituted in DCM. This solution was loaded directly onto a flash column (15 g silica). The product is purified with an increasing gradient of ethyl acetate in dichloromethane (5—> 30%), to afford **25** (22.8 mg, 82%) as an off-white oil.

Procedure in iPrOH

To a 10 mL round bottom flask is added bromo-indole **x** (38 mg, 0.06 mmol, 1 eq), nitrosoarene **S18** (16 mg, 0.12 mmol, 2 eq), Me_6TREN (16 µL, 0.06 mmol, 1 eq), and anhydrous **isopropanol** (3 mL) with a stir bar wrapped in 5 cm of freshly activated copper wire. The flask is capped with a reflux condenser and heated to a vigorous reflux (110 °C) for 10 hours under an atmosphere of argon. The reaction mixture was allowed to cool to room temperature and then the solution was concentrated and reconstituted in DCM. This solution

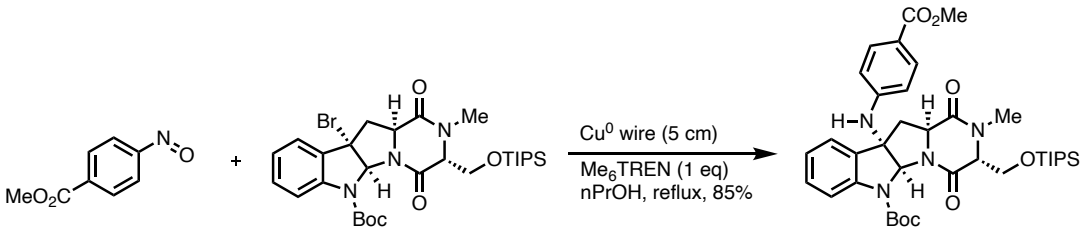
was loaded directly onto a flash column (15 g silica). The product is purified with an increasing gradient of ethyl acetate in dichloromethane (5—> 30%), to afford **25** (22.8 mg, 55%) as an off-white oil.

^{1}H NMR (600 MHz, cdcl$_3$, **26 °C**) δ 7.76 (d, *J* = 7.9 Hz, 1H), 7.36 (d, *J* = 7.8 Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 1H), 7.10 (d, *J* = 6.9 Hz, 1H), 7.03 (t, *J* = 8.1 Hz, 1H), 6.35 (dd, *J* = 7.9, 2.2 Hz, 1H), 6.19 (s, 1H), 6.09 (dd, *J* = 7.8, 1.9 Hz, 1H), 5.99 (t, *J* = 2.3 Hz, 1H), 4.76 (t, *J* = 9.1 Hz, 1H), 4.25 (dd, *J* = 10.3, 2.4 Hz, 1H), 4.02 (dd, *J* = 10.4, 2.6 Hz, 1H), 3.81 (s, 1H), 3.73 (d, *J* = 2.8 Hz, 1H), 3.66 (s, 3H), 3.02 (dd, *J* = 14.3, 9.4 Hz, 1H), 2.87 (s, 3H), 2.80 (dd, *J* = 14.3, 8.9 Hz, 1H), 1.54 (s, 10H), 1.08 (d, *J* = 6.7 Hz, 21H);

^{13}C NMR (150 MHz, cdcl$_3$, **26 °C**) δ 167.6, 165.6, 160.9, 152.4, 145.5, 141.5, 135.4, 130.1, 130.0, 124.2, 123.9, 117.1, 108.1, 104.9, 102.1, 82.2, 78.2, 68.7, 67.1, 63.3, 56.1, 55.1, 36.7, 32.0, 28.2, 18.0, 12.0;

IR (thin film) 3359, 2942, 2866, 1659, 1600, 1460, 1337, 1248, 1158, 1110, 729, 685 cm^{-1};

HRMS (ESI), calculated for $C_{36}H_{52}N_4O_6Si$: ($M+Na^+$) 687.3554, observed 687.3546.



S32 **S15** **26**

***tert*-butyl (3*R*,5a*S*,10b*S*,11a*S*)-10b-((4-(methoxycarbonyl)phenyl)amino)-2-methyl-1,4-dioxo-3-(((triisopropylsilyl)oxy)methyl)-1,2,3,4,5a,10b,11,11a-octahydro-6*H*-pyrazino[1',2':1,5]pyrrolo[2,3-*b*]indole-6-carboxylate (26)**

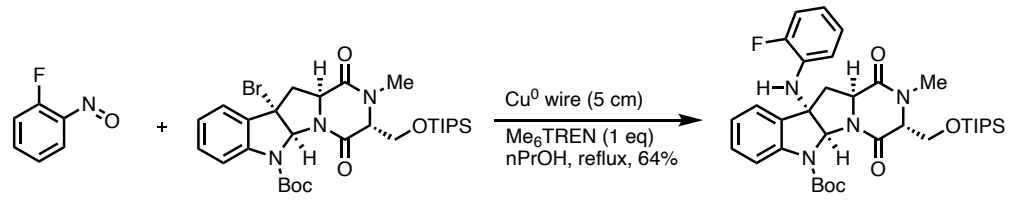
To a 15 mL two neck round bottom flask is added bromo-indole **S15** (38 mg, 0.06 mmol, 1 eq), nitrosoarene **S32** (20 mg, 0.12 mmol, 2 eq), Me_6TREN (16 µL, 0.06 mmol, 1 eq), and anhydrous n-propanol (3 mL) with a stir bar wrapped in 5 cm of freshly activated copper wire. The flask is capped with a reflux condenser and heated to a vigorous reflux (120 °C) until TLC indicates consumption of starting material and the more-polar hydroxylamine intermediate (9.5 hours) under an atmosphere of argon. The reaction mixture was allowed to cool to room temperature and then the solution was concentrated and reconstituted in DCM. This solution was loaded directly onto a flash column (15 g silica). The product is purified with an increasing gradient of ethyl acetate in dichloromethane (0—> 25%), to afford **26** (35.4 mg, 85%) as an off-white foam.

^{1}H NMR (600 MHz, cdcl$_3$, **26 °C**) δ 7.82 (d, *J* = 8.5 Hz, 2H), 7.76 (d, *J* = 8.1 Hz, 1H), 7.37 – 7.29 (m, 2H), 7.09 (t, *J* = 7.5 Hz, 1H), 6.44 (d, *J* = 9.0 Hz, 2H), 6.24 (s, 1H), 4.83 (t, *J* = 9.1 Hz, 1H), 4.30 (s, 1H), 4.26 (dd, *J* = 10.4, 2.2 Hz, 1H), 4.03 (dd, *J* = 10.4, 2.5 Hz, 1H), 3.85 (s, 3H), 3.75 (t, *J* = 2.4 Hz, 1H), 3.02 (dd, *J* = 14.5, 9.5 Hz, 1H), 2.89 – 2.82 (m, 4H), 1.54 (s, 9H), 1.13 – 1.04 (m, 21H);

^{13}C NMR (150 MHz, cdcl$_3$, **26 °C**) δ 167.25, 166.89, 165.61, 152.18, 147.88, 141.29, 134.57, 131.43, 130.20, 124.22, 123.60, 120.22, 117.06, 113.35, 82.31, 77.51, 67.91, 66.94, 63.19, 55.94, 51.68, 35.71, 31.91, 28.20, 17.86, 11.92.

IR (thin film) 3356, 2943, 2866, 1713, 1690, 1672, 1604, 1335, 1274, 1155, 731,

HRMS (ESI), calculated for $C_{37}H_{52}N_4O_7Si$ Na: ($M+Na^+$) 715.3503, observed 715.3511.



S35 **S15** **27**

***tert*-butyl (3*R*,5a*S*,10b*S*,11a*S*)-10b-((2-fluorophenyl)amino)-2-methyl-1,4-dioxo-3-(((triisopropylsilyl)oxy)methyl)-1,2,3,4,5a,10b,11,11a-octahydro-6*H*-pyrazino[1',2':1,5]pyrrolo[2,3-*b*]indole-6-carboxylate (27)**

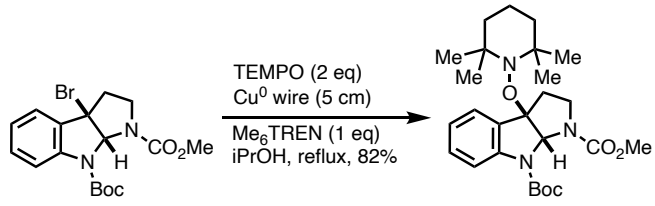
To a 15 mL two neck round bottom flask is added bromo-indole **S15** (38 mg, 0.06 mmol, 1 eq), nitrosoarene **S35** (15 mg, 0.12 mmol, 2 eq), Me_6TREN (16 µL, 0.06 mmol, 1 eq), and anhydrous n-propanol (3 mL) with a stir bar wrapped in 5 cm of freshly activated copper wire. The flask is capped with a reflux condenser and heated to a vigorous reflux (120 °C) until TLC indicates consumption of starting material and the more-polar hydroxylamine intermediate (9 hours) under an atmosphere of argon. The reaction mixture was allowed to cool to room temperature and then the solution was concentrated and reconstituted in DCM. This solution was loaded directly onto a flash column (15 g silica). The product is purified with an increasing gradient of ethyl acetate in dichloromethane (5—> 30%), to afford **27** (25.2 mg, 64%) as an of white foam.

^{1}H NMR (600 MHz, cdcl$_3$, **26 °C**) δ 7.73 (d, *J* = 8.1 Hz, 1H), 7.36 (d, *J* = 7.9 Hz, 1H), 7.31 (t, *J* = 7.6 Hz, 1H), 7.10 (t, *J* = 7.6 Hz, 1H), 6.99 (ddd, *J* = 11.6, 8.1, 1.5 Hz, 1H), 6.84 (d, *J* = 7.9 Hz, 1H), 6.73 (tdd, *J* = 7.9, 4.9, 1.5 Hz, 1H), 6.39 (t, *J* = 8.2 Hz, 1H), 6.16 (s, 1H), 4.76 (t, *J* = 9.2 Hz, 1H), 4.25 (dd, *J* = 10.4, 2.3 Hz, 1H), 4.10 (d, *J* = 4.0 Hz, 1H), 4.02 (dd, *J* = 10.4, 2.6 Hz, 1H), 3.75 (t, *J* = 2.4 Hz, 1H), 2.97 (dd, *J* = 14.4, 9.3 Hz, 1H), 2.88 (s, 3H), 2.81 (dd, *J* = 14.4, 9.1 Hz, 1H), 1.54 (s, 9H), 1.17 – 1.04 (m, 21H);

^{13}C NMR (150 MHz, cdcl$_3$, **26 °C**) δ 167.36, 165.58, 153.67, 152.24, 152.09, 141.48, 134.68, 132.51, 129.94, 124.24, 124.17, 123.70, 119.53, 116.96, 115.41, 115.16, 82.06, 78.48, 68.48, 66.95, 63.15, 55.95, 37.40, 31.88, 28.10, 17.84, 11.89;

IR (thin film) 3351, 2942, 2866, 1717, 1665, 1478, 1335, 1248, 1154, 1106, 882, 737;

HRMS (ESI), calculated for $C_{35}H_{49}FN_4O_5Si$: ($M+Na^+$) 675.3354, observed 675.3362.



1 **28**

8-(*tert*-butyl) 1-methyl 3a-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)-2,3,3a,8a-tetrahydropyrrolo[2,3-*b*]indole-1,8-dicarboxylate (28): To a 10 mL round bottom flask is added pyrroloindoline **1** (24 mg, 0.06 mmol, 1 eq), TEMPO (18 mg, 0.012 mmol, 2 eq), Me_6TREN (16 μL, 0.06 mmol, 1 eq), and anhydrous isopropanol (3 mL) with a stir bar wrapped in 5 cm of freshly activated copper wire. The flask is capped with a reflux condenser and heated to 110 °C for 1 hour under an atmosphere of argon. The reaction mixture was allowed to cool to RT and then the solution was concentrated and reconstituted in DCM. This solution was loaded directly onto a flash column (15 g silica). The product is purified with an increasing gradient of ethyl acetate in hexane (8—> 35%) to afford **28** as a clear oil (23.3 mg, 82%).

^{1}H NMR (500 MHz, cdcl$_3$, **50 °C**) δ 7.64 (d, J = 8.1 Hz, 1H), 7.36 (d, J = 7.5 Hz, 1H), 7.27 (d, J = 7.6 Hz, 1H), 7.07 (t, J = 7.5 Hz, 1H), 6.81 (s, 1H), 3.96 (dd, J = 11.4, 8.0 Hz, 1H),

3.75 (s, 3H), 2.82 (td, *J* = 12.0, 5.3 Hz, 1H), 2.55 (td, *J* = 12.2, 8.0 Hz, 1H), 2.30 (dd, *J* = 11.9, 5.3 Hz, 1H), 1.58 (s, 9H), 1.56 – 1.21 (m, 6H), 1.12 (s, 3H), 1.02 (s, 3H), 0.95 (s, 3H), 0.54 (s, 3H);

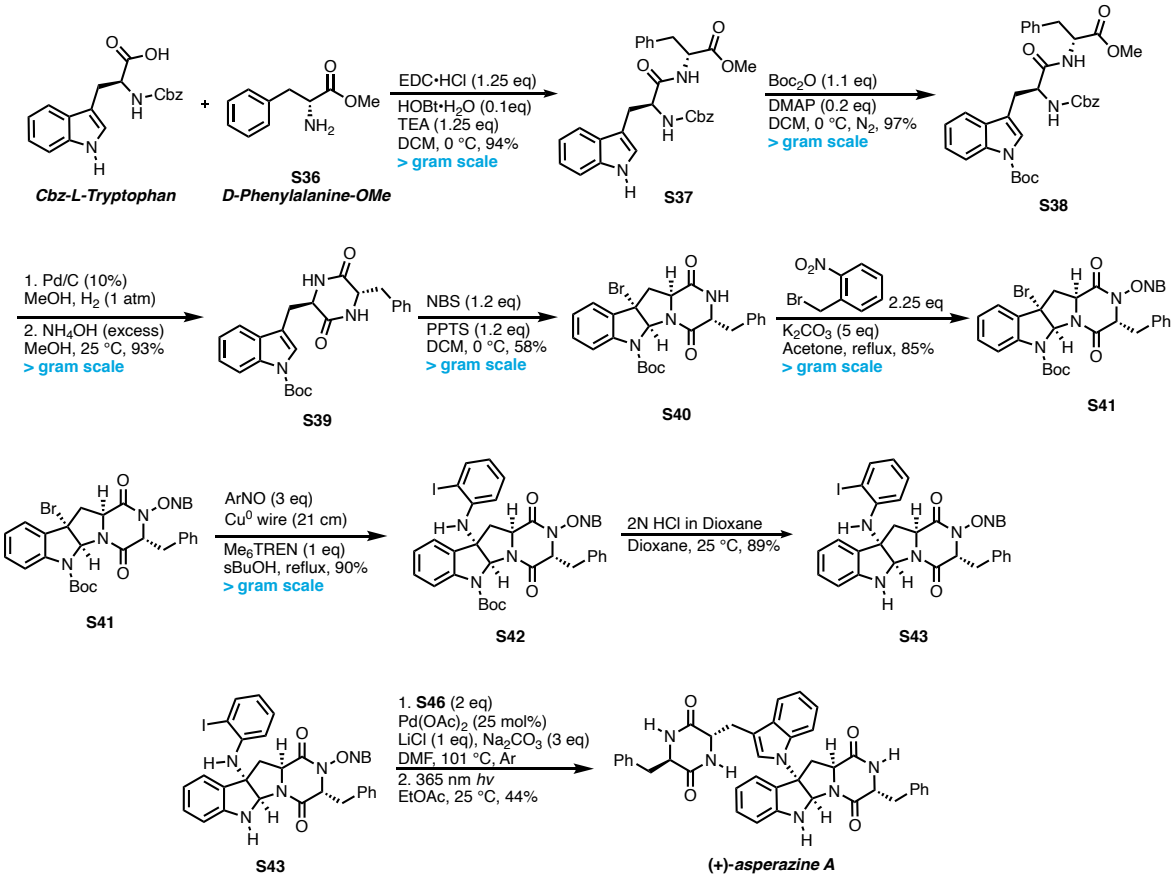
^{13}C NMR (125 MHz, cdcl$_3$, **50 °C**) δ 152.6, 144.2, 133.2, 129.6, 124.8, 123.2, 116.5, 95.4, 81.2, 78.2, 60.3, 59.5, 52.3, 45.8, 40.9, 40.5, 39.4, 32.9, 28.4, 20.6, 20.3, 17.0;

IR (thin film) 2974, 2931, 1701, 1452, 1445, 1248, 1144, 1023, 907, 726, cm-1

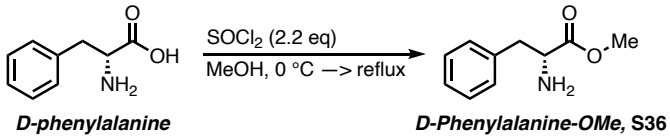
HRMS (ESI), calculated for $C_{26}H_{39}N_3O_5$: ($M+Na^+$) 496.2787, observed 496.2779;

Section 6- Synthesis of Asperazine A

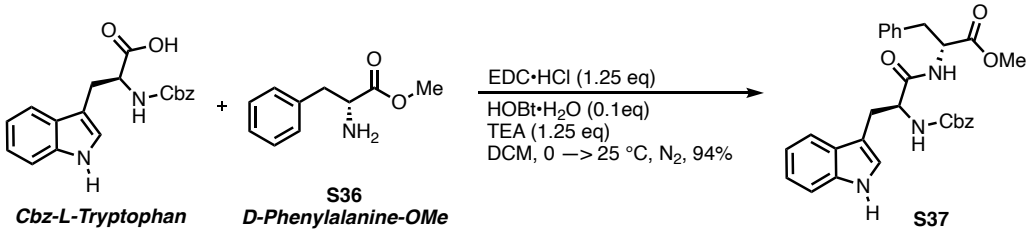
Overview– *14.7% overall yield over 8 steps*



D-Phenylalanine-OMe



D-phenylalanine methyl ester was prepared in one step from commercially available D-phenylalanine according to a modified literature procedure.[7]



methyl ((benzyloxy)carbonyl)-*L*-tryptophyl-*D*-phenylalaninate (S37)

To a flame dried 1L round bottom flask equipped with a Teflon stir bar is added Cbz-L-Tryptophan (28 g, 87.5 mmol, 1.05 eq) and DCM (400 mL). After this solution is cooled to 0 °C, the suspension is charged EDC•HCl (20 g, 104 mmol, 1.25 eq), HOBt•H_2O (1.1 g, 8.3 mmol, 0.1 eq) and triethylamine (14.5 mL, 104 mmol, 1.25 eq). Subsequently, D-phenylalanine methyl ester **S36** (14.9 g, 83.3 mmol, 1.0 eq) is added. The flask is sealed with a rubber septum and the reaction is stirred at 0 °C and allowed to warm slowly to room temperature.

After 16 hours, the reaction is washed with saturated aqueous $NaHCO_3$ (300 mL) and extracted with DCM (3 x 100 mL). The organic layers are combined, dried sequentially with brine (75 mL) and sodium sulfate and concentrated *in vacuo*. A 350 mL fritted funnel is filled with silica while the crude material is dissolved in minimal 3:1 EtOAc:DCM. The crude material is passed through the silica and eluted with EtOAc. The resulting solution is concentrated in vacuo to yield **S37** (37.5 grams, 94%).

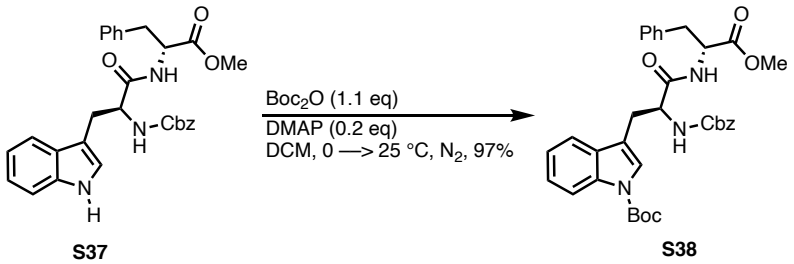
^{1}H NMR (600 MHz, cdcl$_3$, **50 °C**) δ 7.96 (s, 1H), 7.60 (s, 1H), 7.33 – 7.24 (m, 6H), 7.19 – 7.06 (m, 5H), 6.85 (s, 1H), 6.80 (d, *J* = 7.1 Hz, 2H), 6.11 (d, *J* = 7.9 Hz, 1H), 5.30 (s, 1H), 5.06 (s, 2H), 4.75 (q, *J* = 6.2 Hz, 1H), 4.47 (q, *J* = 7.2 Hz, 1H), 3.57 (d, *J* = 3.1 Hz, 3H), 3.24 (dd, *J* = 14.4, 5.6 Hz, 1H), 3.13 (dd, *J* = 14.6, 7.6 Hz, 1H), 2.90 (dd, *J* = 13.9, 5.8 Hz, 1H), 2.79 (dd, *J* = 14.0, 5.9 Hz, 1H);

^{13}C NMR (151 MHz, cdcl$_3$, **50 °C**) δ 171.5, 171.2, 136.5, 136.4, 135.8, 129.3, 128.7, 128.3, 128.2, 127.7, 127.2, 123.3, 122.5, 120.0, 118.9, 111.4, 110.6, 67.2, 55.8, 53.3, 52.2, 37.9, 28.7;

IR (thin film) 3407, 3295, 3034, 1735, 1687, 1643, 1533, 1280, 1231, 1058, 742 cm^{-1}

HRMS (ESI), calculated for $C_{29}H_{29}N_3O_5$: (M+Na$^+$) 522.2005, observed 522.2001.

$R_f \approx 0.15$ in 5% EtOAc in DCM



S37 **S38**

methyl ((benzyloxy)carbonyl)-*L*-tryptophyl-*D*-phenylalaninate (S38)

To a 250 mL round bottom flask is added amide-coupled product **S37** (4.17 grams, 8.67 mmol, 1.0 eq) and DCM (80 mL, anhydrous). After the flask is sealed with a rubber septum, the atmosphere is removed *in vacuo* and replaced with nitrogen three times, after which the flask is cooled in ice water for ten minutes. Boc-anhydride (2.08 grams, 9.56 mmol, 1.1 eq) and 4-DMAP (212 mg, 1.73 mmol, 0.2 eq) is dissolved in DCM (1 mL, anhydrous) and added via syringe through the septum. The reaction is allowed to stir for eight hours while the reaction slowly warms to room temperature. The reaction is poured into a separatory

funnel, washed with saturated $NaHCO_3$ (50 mL) and extracted with DCM (3 x 30 mL). The organic layers are combined, dried sequentially with brine and sodium sulfate. The crude organic solution is concentrated and loaded directly onto a silica column and purified with an increasing gradient of ethyl acetate in hexane (10 —> 50%) to afford the product **S38** as a white foamy solid (4.91 grams, 97%).

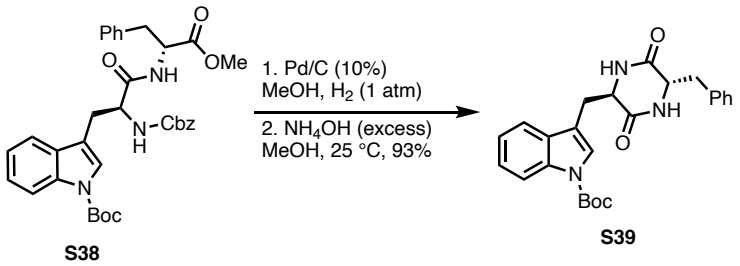
^{1}H NMR (600 MHz, cdcl$_3$, **50 °C**) δ 8.14 (s, 1H), 7.59 (d, *J* = 7.8 Hz, 1H), 7.43 (s, 1H), 7.38 – 7.28 (m, 6H), 7.26 – 7.23 (m, 1H), 7.18 – 7.10 (m, 3H), 6.77 (d, *J* = 7.1 Hz, 2H), 6.21 (d, *J* = 7.8 Hz, 1H), 5.38 (d, *J* = 6.5 Hz, 1H), 5.09 (s, 2H), 4.78 (dt, *J* = 8.1, 5.7 Hz, 1H), 4.52 – 4.48 (m, 1H), 3.60 (s, 3H), 3.19 – 3.11 (m, 2H), 2.97 (dd, *J* = 13.8, 5.4 Hz, 1H), 2.76 (dd, *J* = 13.8, 6.0 Hz, 1H), 1.62 (s, 9H);

^{13}C NMR (150 MHz, cdcl$_3$, **50 °C**) δ 171.2, 170.5, 155.8, 149.5, 136.0, 135.5, 135.3, 130.1, 129.0, 128.5, 128.2, 128.1, 127.2, 124.7, 124.3, 122.8, 119.1, 115.4, 115.2, 83.7, 67.1, 55.1, 53.0, 52.2, 37.7, 28.3, 28.2;

IR (thin film) 3303, 2977, 1727, 1656, 1527, 1452, 1366, 1253, 1220, 1153, 1084, 743, 697 cm^{-1}

HRMS (ESI), calculated for $C_{34}H_{37}N_3O_7$: ($M+Na^+$) 622.2529, observed 622.2543.

$R_f \approx 0.4$ in 5% EtOAc in DCM



S38 **S39**

***tert*-butyl 3-(((2*R*,5*S*)-5-benzyl-3,6-dioxopiperazin-2-yl)methyl)-1*H*-indole-1-carboxylate (S39)**

To a 50 mL round bottom flask is added the Trp-*d*Phe coupling product **S38** (660 mg, 1.16 mmol, 1 eq) and Pd/C (10%, 122 mg, 10 mol %). The flask is sealed with a rubber septum and the atmosphere removed under vacuum and replaced with nitrogen three times. To this flask is added anhydrous methanol (15 mL). The resulting suspension is briefly sparged with hydrogen gas and the solution is allowed to stir under an atmosphere of hydrogen for two hours, at which point the solution is filtered through celite and concentrated *in vacuo*.

The afforded white oil is reconstituted in methanol (5 mL) and aqueous ammonium hydroxide (28-30%, 300 μL) is added. This solution is allowed to stir for 16 hours while a white precipitate is formed. After 16 hours, the reaction is briefly chilled to 0 °C and filtered. The filter cake is washed with cold methanol (30 mL, three times) to afford the desired product **S39** (470 mg, 93%).

^{1}H NMR (500 MHz, Chloroform-*d,* **25 °C**) δ 8.15 (d, *J* = 8.2 Hz, 1H), 7.42 (s, 1H), 7.39 – 7.27 (m, 5H), 7.25 – 7.21 (m, 1H), 7.17 – 7.14 (m, 2H), 6.18 (s, 1H), 5.90 (s, 1H), 4.13 – 4.06 (m, 1H), 3.52 (dd, *J* = 10.0, 3.5 Hz, 1H), 3.40 (dd, *J* = 14.7, 3.6 Hz, 1H), 3.18 (dd, *J* =

13.9, 4.1 Hz, 1H), 3.03 (dd, *J* = 13.9, 7.2 Hz, 1H), 2.86 (dd, *J* = 14.7, 10.0 Hz, 1H), 1.68 (s, 9H);

^{1}H NMR (600 MHz, Chloroform-*d*, **50 °C**) δ 8.16 (d, *J* = 8.3 Hz, 1H), 7.43 (s, 1H), 7.40 (d, *J* = 7.9 Hz, 1H), 7.35 (t, *J* = 7.8 Hz, 1H), 7.31 – 7.28 (m, 3H), 7.23 (t, *J* = 7.5 Hz, 1H), 7.18 – 7.13 (m, 2H), 5.97 (s, 1H), 5.82 (s, 1H), 4.07 (dt, *J* = 6.8, 3.0 Hz, 1H), 3.61 (d, *J* = 9.8 Hz, 1H), 3.41 (dd, *J* = 14.8, 2.5 Hz, 1H), 3.19 (dd, *J* = 14.0, 4.0 Hz, 1H), 3.02 (dd, *J* = 13.9, 7.5 Hz, 1H), 2.90 (dd, *J* = 14.9, 9.8 Hz, 1H), 1.69 (s, 9H);

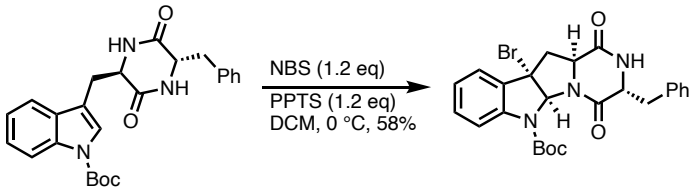
^{13}C NMR (150 MHz, Chloroform-*d,* **50 °C**) δ 167.5, 167.2, 149.3, 135.8, 134.9, 129.6, 129.3, 129.0, 127.6, 125.0, 124.7, 122.8, 118.8, 115.5, 114.1, 84.0, 56.5, 53.5, 40.2, 29.3, 28.2;

IR (thin film) 3064, 2975, 1728, 1678, 1450, 1371, 1254, 1154, 1076, 761 cm^{-1};

HRMS (ESI), calculated for $C_{25}H_{27}N_3O_4$: (M+Na^{+}) 456.1899, observed 456.1905.

R_f of the intermediate amine ≈ 0.05 in 10% EtOAc in DCM

R_f of the diketopiperazine product ≈ 0.25 in 25% EtOAc in DCM



S39 **S40**

***tert*-butyl (3*R*,5a*S*,10b*S*,11a*S*)-3-benzyl-10b-bromo-1,4-dioxo-1,2,3,4,5a,10b,11,11a-octahydro-6*H*-pyrazino[1',2':1,5]pyrrolo[2,3-*b*]indole-6-carboxylate (S40)**

A one-liter round bottom flask is charged with diketopiperazine **S39** (13.88 grams, 31.9 mmol, 1 eq) and is azeotropically dried with anhydrous benzene (150 mL) two times. To this flask is added DCM (anhydrous, 400 mL), a teflon coated stir bar and is sealed with a rubber septum. The head space of the flask is evacuated and replaced with N_2 three times. The slurry contained flask is cooled to 0 °C with an ice bath for fifteen minutes before solid N-bromosuccinimide (freshly recrystallized[6], 6.8 grams, 38.24 mmol, 1.2 eq) and pyridinium p-toluenesulfonate (9.59 grams, 38.24 mmol, 1.2 eq) are added. The reaction is allowed to stir at 0 °C under an atmosphere of N_2 for 18 hours before the reaction is warmed to room temperature and quenched with 10% aqueous sodium thiosulfate (300 mL) and extracted with DCM (6 x 50 mL). The organic layers are combined, dried sequentially with brine and sodium sulfate, concentrated and reconstituted in minimal DCM. This solution was loaded directly onto a flash column (350 g silica). The product was purified with an increasing gradient of ethyl acetate in DCM (0 —> 25%), affording **S40** (9.45 grams, 58%)

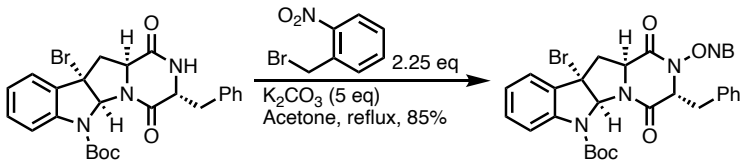
^{1}H NMR (500 MHz, Acetone-d_6, **25 °C**) δ 7.71 (d, J = 8.1 Hz, 1H), 7.49 (d, J = 8.6 Hz, 1H), 7.37 – 7.23 (m, 7H), 7.10 (d, J = 7.3 Hz, 1H), 6.10 (s, 1H), 4.00 (dt, J = 6.7, 4.4 Hz, 1H), 3.57 (dd, J = 9.9, 6.3 Hz, 1H), 3.30 (dd, J = 14.3, 6.4 Hz, 1H), 3.18 (dd, J = 13.5, 6.8 Hz, 1H), 3.02 (dd, J = 13.5, 4.7 Hz, 1H), 2.95 (dd, J = 14.3, 9.8 Hz, 1H), 1.66 (s, 9H);

^{13}C NMR (125 MHz, Acetone-d_6, **25 °C**) δ 166.8, 165.5, 151.4, 140.2, 136.3, 134.3, 130.4, 129.9, 128.5, 127.2, 124.7, 124.1, 116.3, 85.1, 81.7, 60.7, 58.9, 55.1, 39.7, 39.3, 27.7;

IR (thin film) 3242, 2976, 2930, 1720, 1682, 1477, 1368, 1325, 1244, 1150, 1100, 1059, 749, 700 cm^{-1};

HRMS (ESI), calculated for $C_{25}H_{26}BrN_3O_4$: ($M+Na^+$) 534.1005, observed 534.1006.

R_f of the brominated pyrroloindoline ≈ 0.45 in 25% EtOAc in DCM



***tert*-butyl (3*R*,5a*S*,10b*S*,11a*S*)-3-benzyl-10b-bromo-2-(2-nitrobenzyl)-1,4-dioxo-1,2,3,4,5a,10b,11,11a-octahydro-6*H*-pyrazino[1',2':1,5]pyrrolo[2,3-*b*]indole-6-carboxylate (S41)**

Note: K_2CO_3 was stored in a vacuum oven at 100 °C prior to use. Acetone was stored on sieves and under nitrogen, and passed through a plug of activated alumina prior to use.

To a 10 mL round bottom flask is added **SX** (1,150 mg, 2.25 mmol, 1 eq), acetone (23 mL, filtered through a plug of activated alumina prior to use), 2-nitrobenzyl bromide (1215 mg, 5.6 mmol, 2.5 eq) and potassium carbonate (anhydrous, 1520 mg, 11.25 mmol, 5 eq). The flask is equipped with a reflux condenser and Teflon coated stir bar, and the reaction is stirred at reflux for 8 hours at which time the solution is cooled to room temperature. The reaction is diluted with DCM (30 mL) and washed with saturated aqueous sodium bicarbonate (50 mL). The aqueous solution is extracted with DCM (3 x 30 mL), the organic

layers are combined and dried sequentially with brine and sodium sulfate. The crude organic solution is concentrated *in vacuo* and loaded directly onto a silica column for purification with an increasing gradient of DCM in Hexane (50—> 100%) then EtOAc in DCM (0 —> 15%) to afford **SX** as an off-white foam (1,234 mg, 85%).

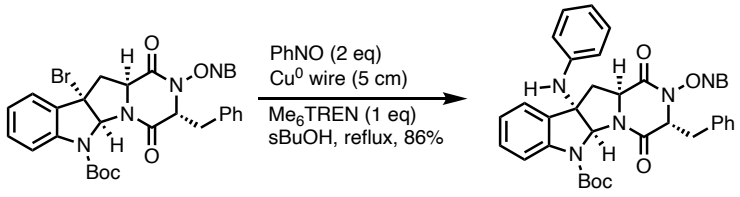
^{1}H NMR (500 MHz, Acetone-*d*$_6$, **25 °C**) δ 7.94 (d, *J* = 8.1 Hz, 1H), 7.84 (d, *J* = 7.8 Hz, 1H), 7.56 – 7.50 (m, 2H), 7.41 (d, *J* = 7.6 Hz, 1H), 7.37 – 7.30 (m, 5H), 7.23 (d, *J* = 7.7 Hz, 1H), 7.13 (d, *J* = 7.4 Hz, 1H), 6.29 (s, 1H), 5.86 (d, *J* = 7.8 Hz, 1H), 5.14 (d, *J* = 17.4 Hz, 1H), 4.12 (dd, *J* = 10.6, 3.1 Hz, 1H), 3.95 – 3.87 (m, 2H), 3.80 (dd, *J* = 13.9, 3.1 Hz, 1H), 3.26 (d, *J* = 6.6 Hz, 2H), 3.11 (dd, *J* = 13.9, 10.6 Hz, 1H), 1.63 (s, 9H);

^{13}C NMR (125 MHz, Acetone-*d*$_6$, **25 °C**) δ 166.7, 164.7, 151.2, 148.6, 140.5, 136.1, 134.0, 133.2, 131.7, 130.8, 129.7, 128.7, 128.0, 127.4, 126.4, 124.9, 124.1, 116.4, 85.0, 81.7, 64.3, 61.0, 56.9, 44.7, 37.3, 36.2, 27.6;

IR (thin film) 2976, 1718, 1676, 1523, 1367, 1157, 1080, 855, 782, 725, 700, cm^{-1}

HRMS (ESI), calculated for $C_{32}H_{31}BrN_4O_6$: (M+Na$^+$) 671.1310 observed 671.1313.

R_f of the protected scaffold ≈ 0.8 in 5% EtOAc in DCM



S41 **S46**

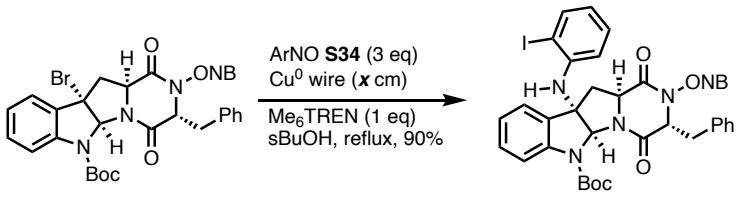
***tert*-butyl (3*R*,5a*S*,10b*S*,11a*S*)-3-benzyl-2-(2-nitrobenzyl)-1,4-dioxo-10b-(phenylamino)-1,2,3,4,5a,10b,11,11a-octahydro-6*H*-pyrazino[1',2':1,5]pyrrolo[2,3-*b*]indole-6-carboxylate (46)**

To a 15 mL two neck round bottom flask is added bromo-indoline **S41** (39 mg, 0.06 mmol, 1 eq), nitrosobenzene (13 mg, 0.12 mmol, 2 eq), Me_6TREN (16 µL, 0.06 mmol, 1 eq), and anhydrous *sec*-butanol (5 mL) with a stir bar wrapped in 5 cm of freshly activated copper wire. The flask is capped with a reflux condenser and heated to a vigorous reflux (120 °C) under an atmosphere of argon until TLC indicates consumption of starting material and the more-polar hydroxylamine intermediate (9 hours). The reaction mixture was allowed to cool to room temperature and then the solution was concentrated and reconstituted in DCM. This solution was loaded directly onto a flash column (15 g silica). The product is purified with an increasing gradient of ethyl acetate in dichloromethane (0—> 12%) to afford the product **S46** (34.2 mg, 86%).

^{1}H NMR (500 MHz, cdcl$_3$, **50 °C**) δ 7.92 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.72 (d, *J* = 8.2 Hz, 1H), 7.44 – 7.29 (m, 7H), 7.25 – 7.21 (m, 2H), 7.16 (ddd, *J* = 8.7, 7.5, 2.3 Hz, 3H), 7.06 (td, *J* = 7.5, 1.0 Hz, 1H), 6.88 (t, *J* = 7.4 Hz, 1H), 6.48 (d, *J* = 7.8 Hz, 2H), 6.35 (d, *J* = 7.9 Hz, 1H), 6.15 (s, 1H), 5.33 (d, *J* = 16.9 Hz, 1H), 4.12 (d, *J* = 17.0 Hz, 1H), 3.96 (dd, *J* = 5.5, 4.4 Hz, 1H), 3.30 (dd, *J* = 13.9, 5.6 Hz, 1H), 3.21 – 3.05 (m, 2H), 2.96 (dd, *J* = 14.2, 6.1 Hz, 1H), 2.84 – 2.75 (m, 1H), 1.59 (s, 9H);

^{13}C NMR (126 MHz, cdcl$_3$, **50 °C**) δ 167.5, 165.6, 151.8, 148.6, 141.3, 135.4, 133.9, 131.1, 130.0, 129.8, 129.2, 129.1, 128.2, 127.9, 127.6, 125.0, 124.3, 123.9, 120.8, 117.4, 116.9, 82.2, 78.4, 68.84, 64.06, 54.88, 44.26, 36.99, 33.92, 28.22.

HRMS (ESI), calculated for $C_{38}H_{37}N_5O_6$: (M+Na$^+$) 682.2642, observed 682.2642.



S41 **S42**

***tert*-butyl (3*R*,5a*S*,10b*S*,11a*S*)-3-benzyl-10b-((2-iodophenyl)amino)-2-(2-nitrobenzyl)-1,4-dioxo-1,2,3,4,5a,10b,11,11a-octahydro-6*H*-pyrazino[1',2':1,5]pyrrolo[2,3-*b*]indole-6-carboxylate (S42)**

Small Scale Synthesis

To a 15 mL two neck round bottom flask is added bromo-indoline **S41** (38 mg, 0.06 mmol, 1 eq), 2-iodo nitrosobenzene (41 mg, 0.18mmol, 3 eq), Me$_6$TREN (16 μL, 0.06 mmol, 1 eq), and anhydrous *sec*-butanol (3 mL) with a stir bar wrapped in 5 cm of freshly activated copper wire. The flask is capped with a reflux condenser and heated to a vigorous reflux (120 °C) under an atmosphere of argon until TLC indicates consumption of starting material and the more-polar hydroxylamine intermediate (9 hours, TLC was run from an aliquot removed through a septum to minimize introduction of ambient atmosphere). The reaction mixture was allowed to cool to room temperature and then the solution was concentrated and

reconstituted in DCM. This solution was loaded directly onto a flash column (15 g silica). The product is purified with an increasing gradient of ethyl acetate in dichloromethane (0—> 12%) to afford the product (41 mg, 88%).

Gram Scale Synthesis

To a 100 mL round bottom flask is added bromo-indoline **S41** (1066 mg, 1.65 mmol, 1 eq), nitrosobenzene (1150 mg, 4.95 mmol, 3 eq), Me_6TREN (440 µL, 1.65 mmol, 1 eq), and anhydrous *sec*-butanol (30 mL) with a stir bar wrapped in 21 cm of freshly activated copper wire. The flask is capped with a reflux condenser and heated to a vigorous reflux (120 °C) under an atmosphere of argon for 8.5 hours. The reaction mixture was allowed to cool to room temperature and then the solution was concentrated and reconstituted in minimal DCM. This solution was loaded directly onto a flash column (45 g silica). The product is purified with an increasing gradient of ethyl acetate in dichloromethane (0—> 12%). The product was collected and concentrated and the resulting solid was quickly washed with pentane to afford the product (1168 mg, 90%).

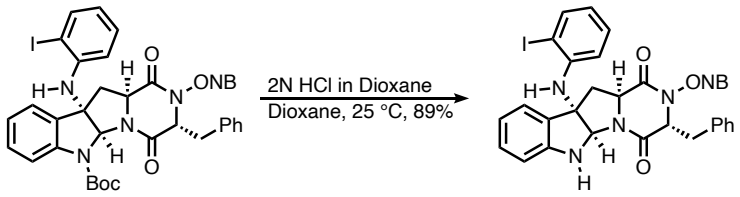
^{1}H NMR (500 MHz, $CDCl_3$, **25 °C**) δ 7.99 (d, *J* = 8.3 Hz, 1H), 7.75 (d, *J* = 8.1 Hz, 1H), 7.72 (d, *J* = 7.8 Hz, 1H), 7.48 – 7.44 (m, 1H), 7.42 – 7.38 (m, 3H), 7.36 (d, *J* = 7.5 Hz, 2H), 7.28 – 7.22 (m, 3H), 7.14 – 7.09 (m, 2H), 6.59 (t, *J* = 7.7 Hz, 1H), 6.44 (d, *J* = 7.8 Hz, 1H), 6.21 (d, *J* = 8.1 Hz, 1H), 6.11 (s, 1H), 5.40 (d, *J* = 17.0 Hz, 1H), 4.27 (s, 1H), 4.20 (d, *J* = 17.0 Hz, 1H), 4.03 (t, *J* = 4.7 Hz, 1H), 3.35 (dd, *J* = 13.9, 5.2 Hz, 1H), 3.20 (dd, *J* = 14.0, 4.3 Hz, 1H), 2.98 (dd, *J* = 9.6, 6.9 Hz, 1H), 2.87 (dd, *J* = 14.2, 6.9 Hz, 1H), 2.72 (dd, *J* = 14.2, 9.6 Hz, 1H), 1.64 (s, 9H);

^{13}C NMR (125 MHz, $CDCl_3$, **25 °C**) δ 167.5, 165.6, 152.0, 148.4, 143.8, 141.3, 139.7, 135.2, 134.2, 133.8, 131.1, 130.1, 129.9, 129.2, 129.1, 128.4, 128.2, 127.6, 125.3, 124.2, 124.1, 121.5, 117.0, 114.5, 89.8, 82.4, 78.8, 68.7, 63.9, 54.9, 44.2, 37.0, 35.7, 28.3.

IR (thin film) 2976, 1714, 1672, 1605, 1522, 1345, 1157, 858, 756, 733, 704, cm $^{-1}$

HRMS (ESI), calculated for $C_{38}H_{36}IN_5O_6$: ($M+Na^+$) 808.1608, observed 808.1625.

R_f = 0.7 in 5% EtOAc in DCM



S42 **S43**

(3*R*,5a*R*,10b*S*,11a*S*)-3-benzyl-10b-((2-iodophenyl)amino)-2-(2-nitrobenzyl)-2,3,6,10b,11,11a-hexahydro-4*H*-pyrazino[1',2':1,5]pyrrolo[2,3-*b*]indole-1,4(5a*H*)-dione (S43)

To an oven dried 15 mL round bottom flask is added **S42** (125 mg, 0.159 mmol, 1 eq), dioxane (2 mL, anhydrous) and a hydrogen chloride solution in dioxane (4N, 2 mL). The resulting 2N solution of hydrogen chloride in dioxane with **S42** was stirred under an atmosphere of argon for five hours before it was diluted ethyl acetate (20 mL) and quenched with saturated aqueous sodium bicarbonate (20 ml). The phases were separated and the aqueous layer was extracted with ethyl acetate (3 x 20 mL). The organic layers were

combined, dried with sodium sulfate and concentrated. The resulting crude material was dissolved in minimal DCM and loaded directly onto a flash column (16 g silica). The product is purified with an increasing gradient of ethyl acetate in dichloromethane (0—> 20%). The product was collected and concentrated to afford the product **S43** (97.3 mg, 89%).

^{1}H NMR (500 MHz, $CDCl_3$**, 25 °C**) δ 8.05 (d, *J* = 8.1 Hz, 1H), 7.72 (d, *J* = 7.2 Hz, 1H), 7.56 (t, *J* = 7.5 Hz, 1H), 7.44 (t, *J* = 7.7 Hz, 2H), 7.27 (t, *J* = 7.7 Hz, 2H), 7.21 (d, *J* = 7.8 Hz, 1H), 7.16 (t, *J* = 7.8 Hz, 1H), 7.12 (d, *J* = 7.6 Hz, 2H), 7.04 (d, *J* = 7.4 Hz, 1H), 6.94 (t, *J* = 7.6 Hz, 1H), 6.72 (t, *J* = 7.4 Hz, 1H), 6.67 (d, *J* = 7.9 Hz, 1H), 6.45 (t, *J* = 7.3 Hz, 1H), 5.79 (d, *J* = 3.4 Hz, 1H), 5.56 (d, *J* = 16.6 Hz, 1H), 5.36 (d, *J* = 3.7 Hz, 1H), 4.51 (d, *J* = 16.6 Hz, 1H), 4.41 (s, 1H), 4.23 (t, *J* = 4.3 Hz, 1H), 3.31 (dd, *J* = 14.1, 3.9 Hz, 1H), 3.22 (dd, *J* = 14.0, 4.6 Hz, 1H), 2.82 (dd, *J* = 11.9, 5.9 Hz, 1H), 2.56 (dd, *J* = 13.9, 6.0 Hz, 1H);

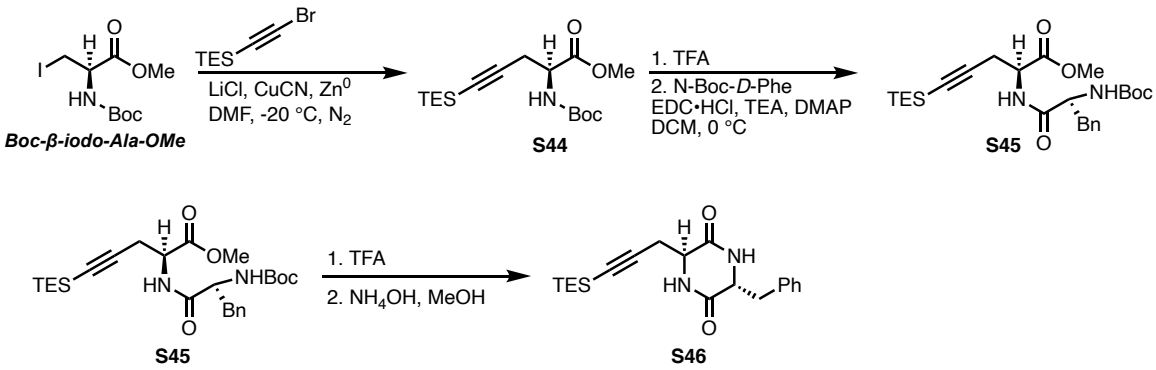
^{13}C NMR (125 MHz, $CDCl_3$**, 25 °C**) δ 167.7, 166.1, 148.7, 147.2, 143.4, 139.5, 134.4, 134.2, 131.2, 129.8, 129.7, 129.2, 129.0, 129.0, 128.7, 128.6, 127.7, 125.4, 122.8, 119.9, 119.6, 112.8, 109.8, 86.8, 78.6, 70.7, 63.5, 55.8, 45.0, 43.8, 37.0;

IR (thin film) 3381, 2925, 2323, 1646, 1613, 1585, 1522, 1453, 1339, 1314, 725, 701 cm^{-1}

HRMS (ESI), calculated for $C_{33}H_{28}IN_5O_4$: ($M+Na^+$) 708.1084, observed 708.1084.

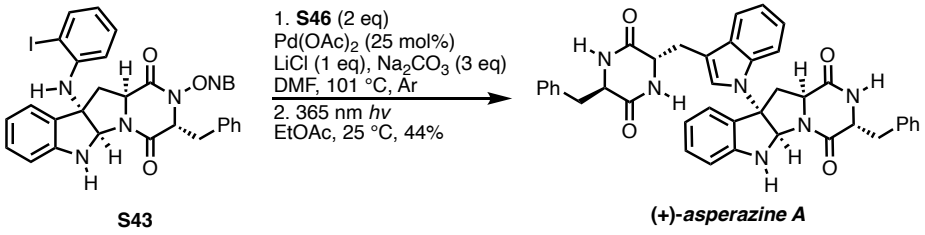
R_f = 0.75 in 15% EtOAc in DCM

Synthesis of the Asperazine A Alkyne Coupling Partner



The *L*-serine derived alkyl iodide, Boc-β-iodo-Ala-OMe, was purchased directly from ACROS organics. It can also be prepared according to the literature.[14] TES-protected alkyne **S44** was prepared from the *L*-serine derived alkyl iodide **Boc-beta-iodoalanine-OMe** using Knochel's conditions, according to the literature.[15,16,17] The subsequent synthesis of TES-protected diketopiperazine was carried out according to the literature.[18]

Synthesis of Asperazine A *via* Larock Annulation



Note: Prior to use, LiCl and Na_2CO_3 are flame dried and stored in a vacuum oven at 100 °C for 72 hours or more. The DMF was degassed *via* freeze-pump-thaw five times immediately prior to use in this reaction and maintained under an atmosphere of argon during reaction set

up. This reaction was most successful when relative humidity in the lab was at or lower than 36%.

To a 5 mL conical flask was added LiCl (3.1 mg, 0.073 mmol, 1 eq) and Na_2CO_3 (23 mg, 0.219 mmol, 3 eq). This flask is sealed with a rubber septum, evacuated *via* high-vac, and rigorously flame dried. After the flask cools to room temperature, a Teflon coated stir bar, iodo-aniline **S43** (50 mg, 0.073 mmol, 1 eq), TES-protected alkyne **S46** (52 mg, 0.146 mmol, 2 eq), and $Pd(OAc)_2$ (4 mg, 0.0182 mmol, 25 mol%) are quickly added. The septum is replaced and the atmosphere in the flask is removed *via* high-vac for five minutes before the flask is refilled with argon and DMF (1 mL, degassed as indicated above) is added through the septum. The flask is vigorously sparged with argon for one minute, then sparged while sonicating for an additional 10 minutes, at which point the flask is heated in an oil bath to 101 °C.

After stirring at elevated temperature for 3 hours under an atmosphere of argon, the reaction is cooled to room temperature, diluted with EtOAc (5 mL) and filtered through a small plug of celite into a 25 mL round bottom flask. This flask is irradiated with 365 nm light from a collimated light source (light intensity is 8.70 mW/cm^2) under an atmosphere of argon for eight hours before aqueous HCl (1M, 5 mL) is added.

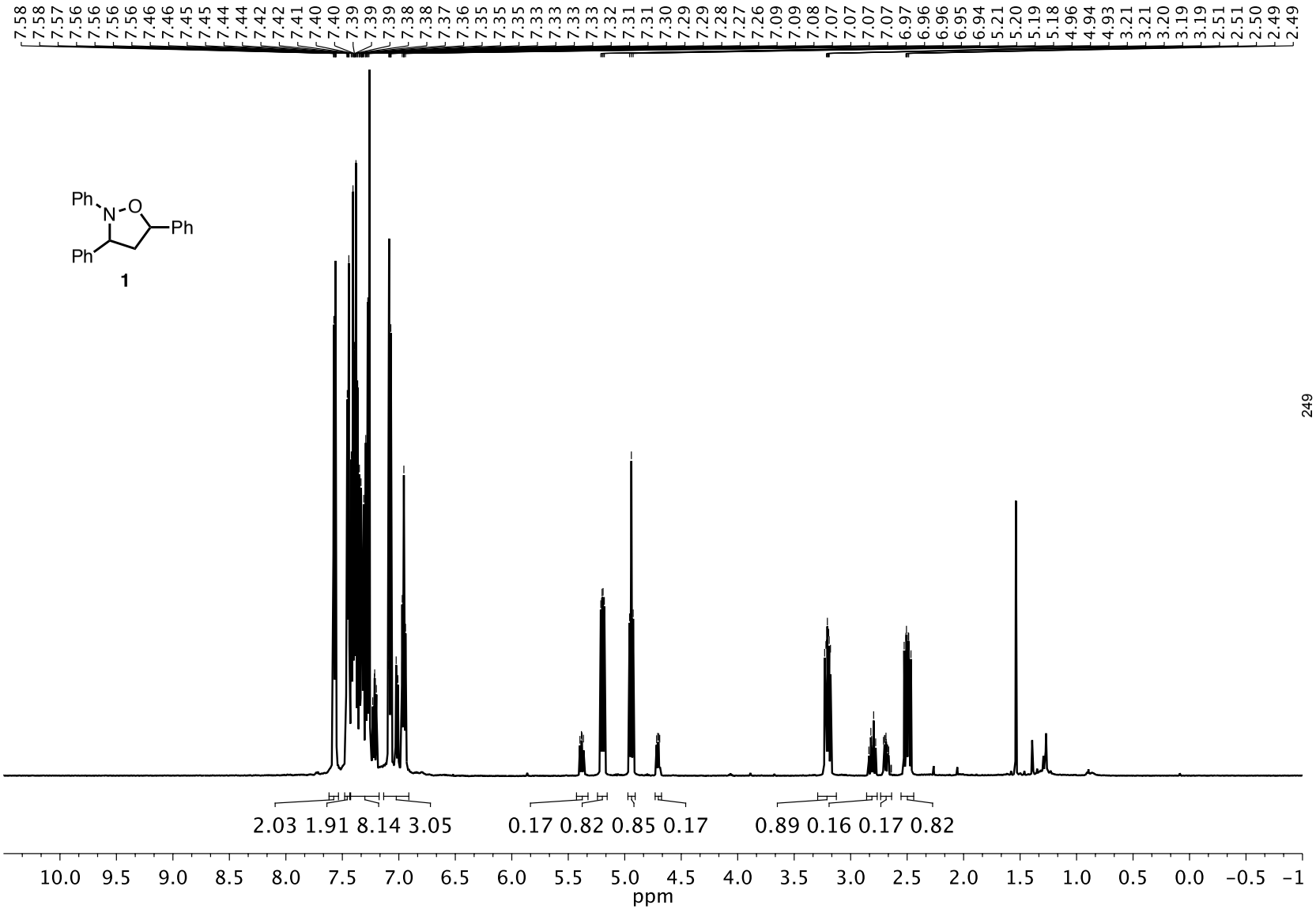
After vigorous stirring for 20 minutes, the reaction is diluted with EtOAc (20 mL) and slowly quenched with saturated aqueous sodium bicarbonate (20 mL). The phases were separated and the aqueous layer was extracted with ethyl acetate (3 x 20 mL). The organic layers were

combined, dried with sodium sulfate and concentrated. The resulting crude material was adsorbed onto celite purified by reverse phase flash chromatography (16 grams C18) with an increasing gradient of acetonitrile in water (15 —> 65%, with 0.1% TFA) to afford asperazine A (21.4 mg, 44% over two steps) as the TFA salt. The TFA salt can be freebased *via* multiple rounds of azeotropic removal with DMSO and matches characterization from the literature.[19]

Section 7- References

(1) Yanagisawa, A.; Fujinami, T.; Oyokawa, Y.; Sugita, T.; Yoshida, K. *Org. Lett.* **2012**, *14* (10), 2434.
(2) Priewisch, B.; Rück-Braun, K. *J. Org. Chem.* **2005**, *70* (6), 2350.
(3) Fisher, D. J.; Shaum, J. B.; Mills, C. L.; Read De Alaniz, J. *Org. Lett.* **2016**, *18* (19), 5074.
(4) Newhouse, T.; Lewis, C. A.; Eastman, K. J.; Baran, P. S. *J. Am. Chem. Soc.* **2010**, *132* (20), 7119.
(5) Wada, M.; Murata, T.; Oikawa, H.; Oguri, H. *Org. Biomol. Chem.* **2014**, *12* (2), 298.
(6) Virgil, S. C.; Jenkins, P. R.; Wilson, A. J.; García Romero, M. D. *Encyclopedia of Reagents for Organic Synthesis*. September 15, 2006,.
(7) Arjomandi, O. K.; Hussein, W. M.; Vella, P.; Yusof, Y.; Sidjabat, H. E.; Schenk, G.; McGeary, R. P. *Eur. J. Med. Chem.* **2016**, *114*, 318.
(8) Newhouse, T.; Baran, P. S. *J. Am. Chem. Soc.* **2008**, *130* (33), 10886.
(9) Olsen, E. K.; Hansen, E.; W. K. Moodie, L.; Isaksson, J.; Sepčić, K.; Cergolj, M.; Svenson, J.; Andersen, J. H. *Org. Biomol. Chem.* **2016**, *14* (5), 1629.
(10) Ghosh, N.; Nayak, S.; Sahoo, A. K. *J. Org. Chem.* **2011**, *76* (2), 500.
(11) Xu, J.; Tong, R. *Green Chem.* **2017**, *19* (13), 2952.
(12) Nappi, M.; He, C.; Whitehurst, W. G.; Chappell, B. G. N.; Gaunt, M. J. *Angew. Chemie Int. Ed.* **2018**, *57* (12), 3178.
(13) Sulikowski, G. A.; Sulikowski, M. M.; Haukaas, M. H.; Moon, B. *Encyclopedia of Reagents for Organic Synthesis*. October 15, 2005,.
(14) Trost, B. M.; Rudd, M. T. *Org. Lett.* **2003**, *5* (24), 4599.
(15) Newhouse, T.; Lewis, C. A.; Baran, P. S. *J. Am. Chem. Soc.* **2009**, *131* (18), 6360.
(16) Yeh, M. C. P.; Knochel, P. *Tetrahedron Lett.* **1989**, *30* (36), 4799.
(17) Jsselstijn, M. I.; Kaiser, J.; van Delft, F. L.; Schoemaker, H. E.; Rutjes, F. P. J. T. *Amino Acids* **2003**, *24* (3), 263.
(18) Li, Q.; Xia, T.; Yao, L.; Deng, H.; Liao, X. *Chem. Sci.* **2015**, *6* (6), 3599.
(19) Nelson, B. M.; Loach, R. P.; Schiesser, S.; Movassaghi, M. *Org. Biomol. Chem.* **2018**, *16* (2), 202.

Chapter 10- NMR Spectra of New Compounds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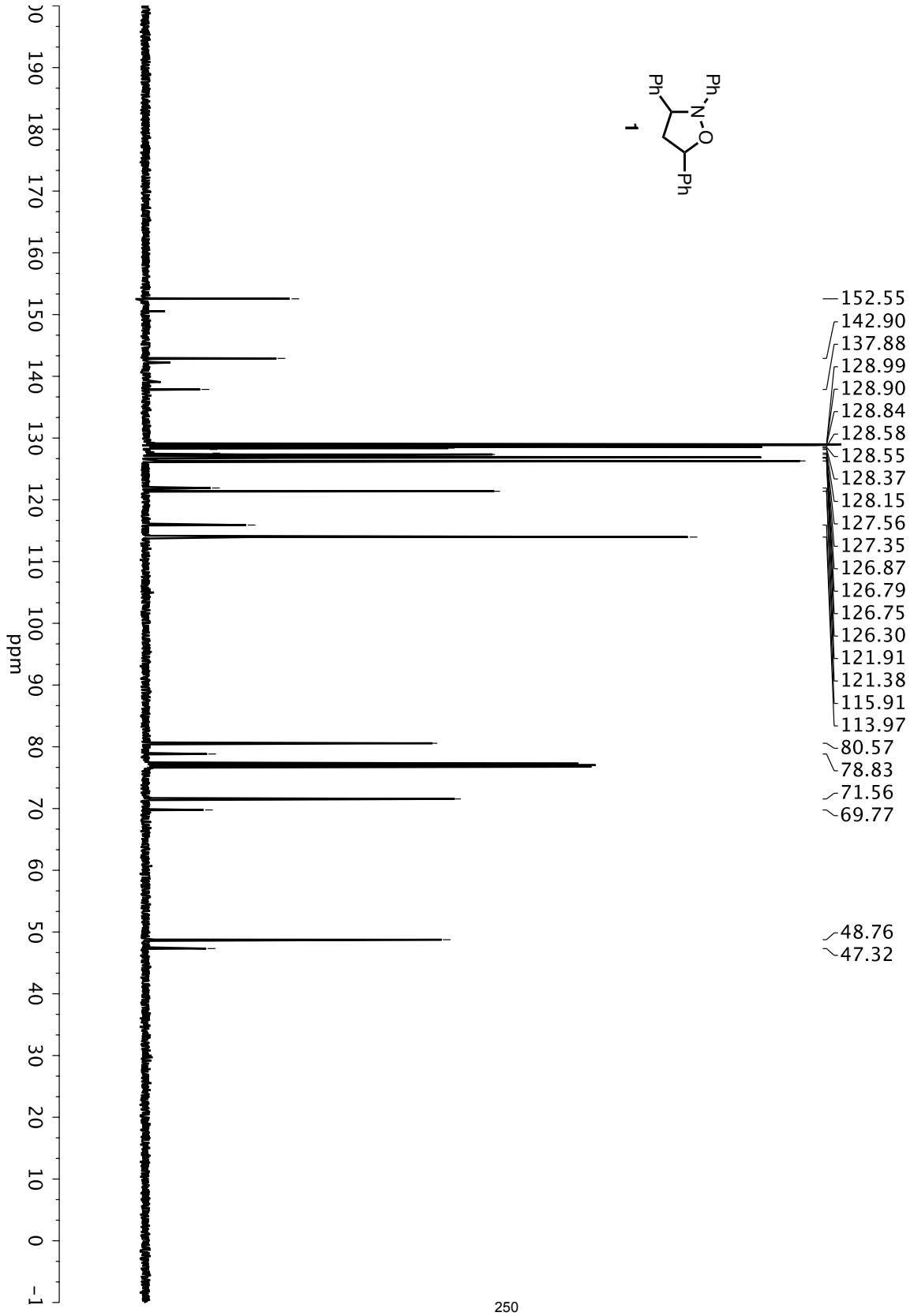
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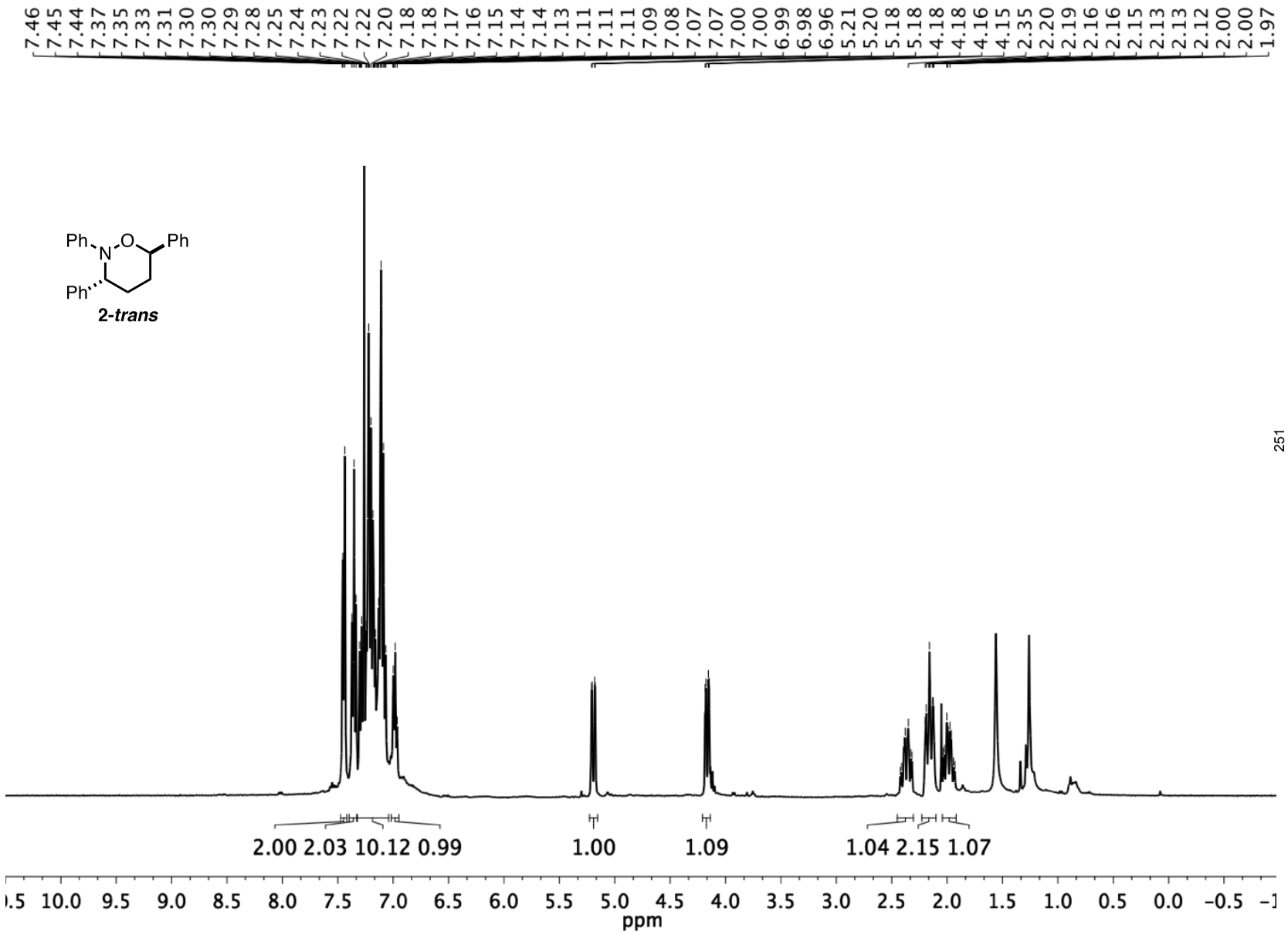
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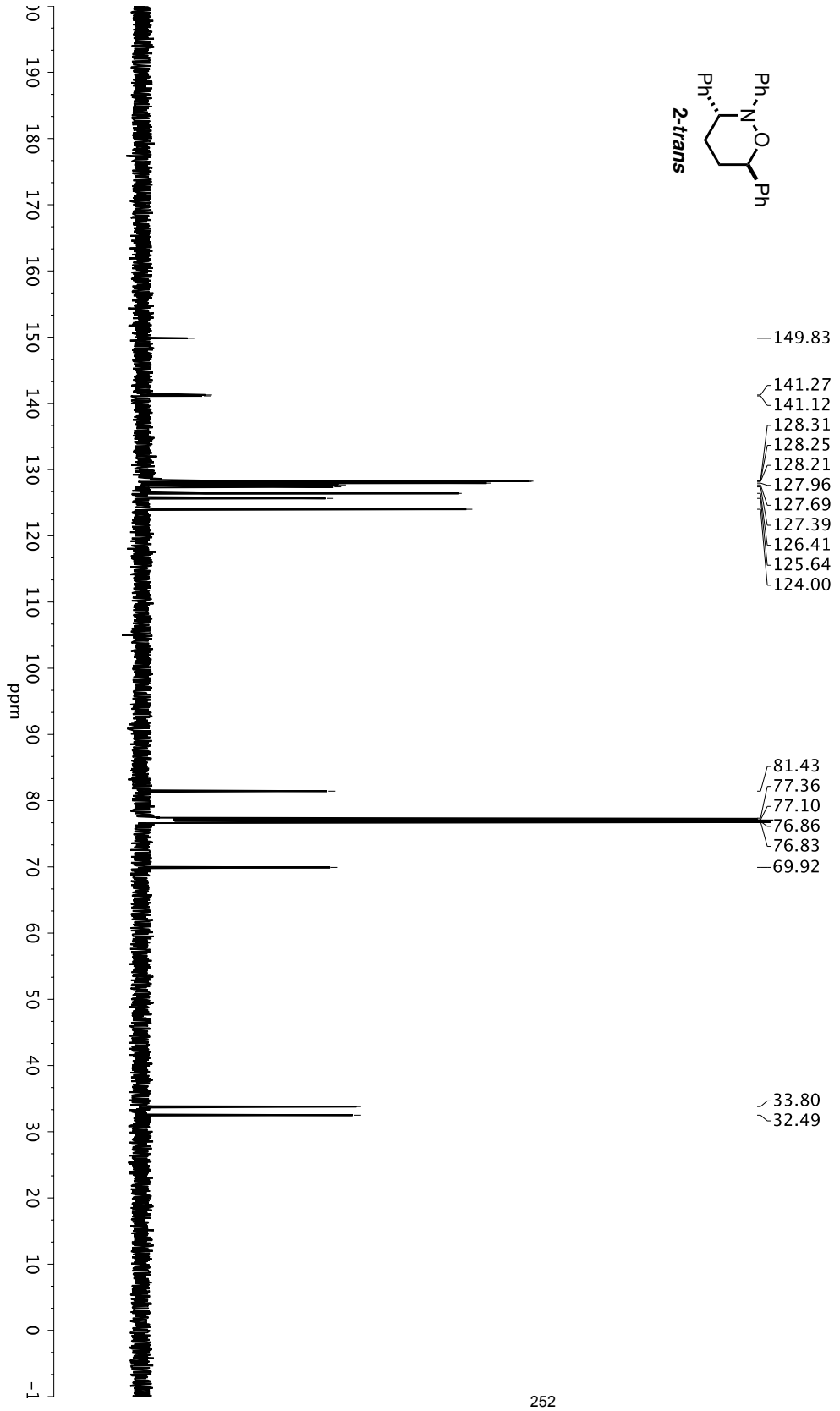
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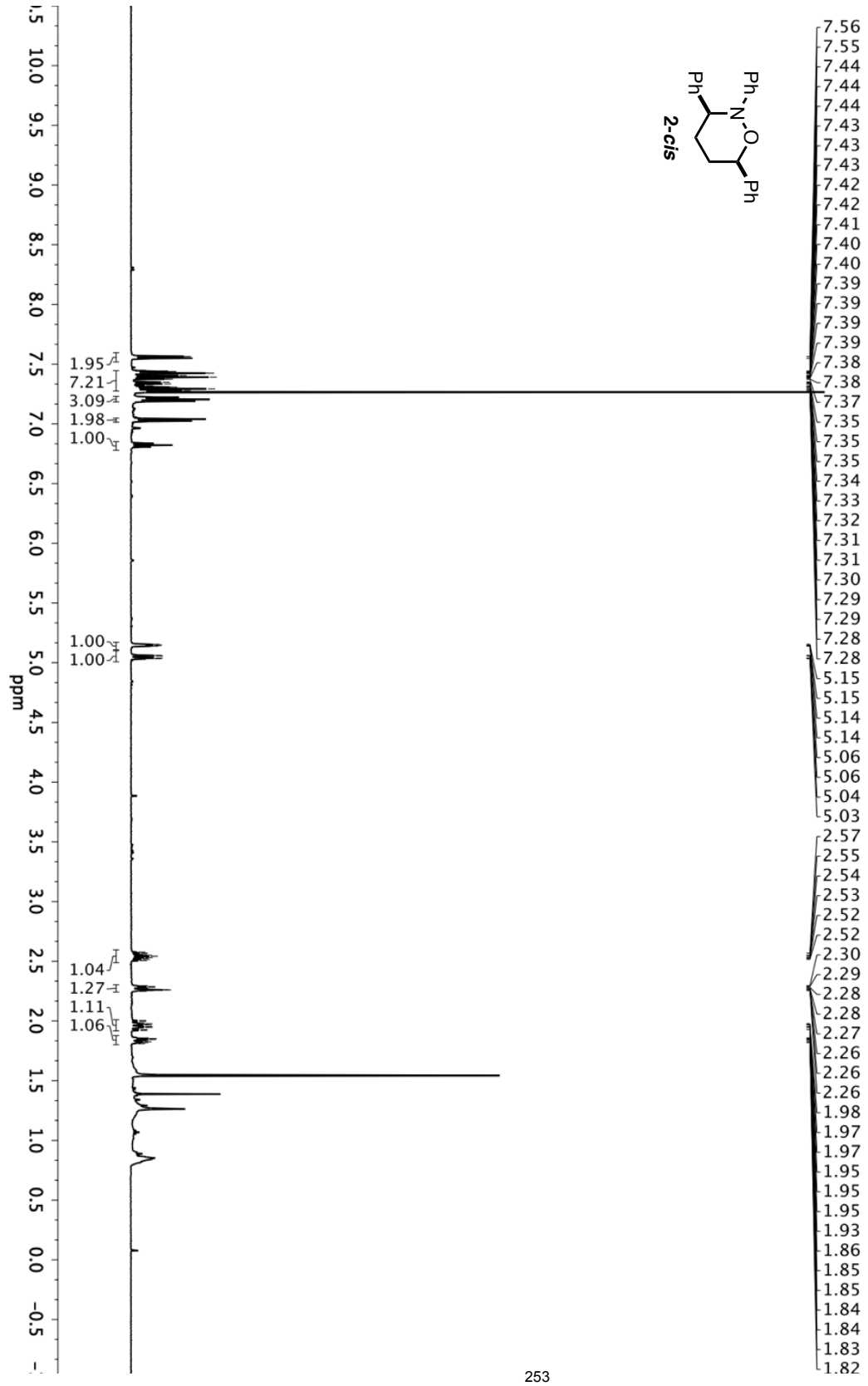
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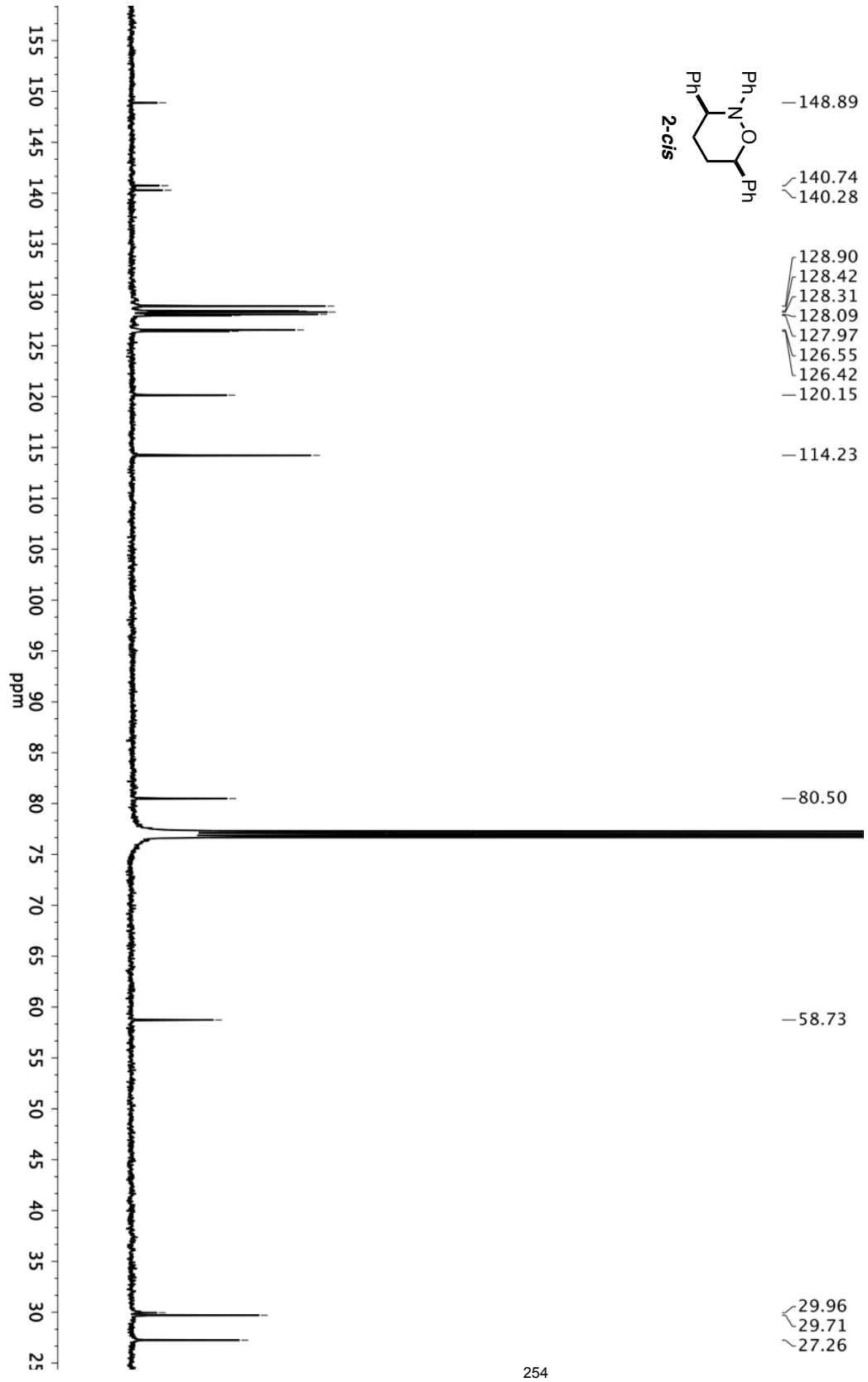
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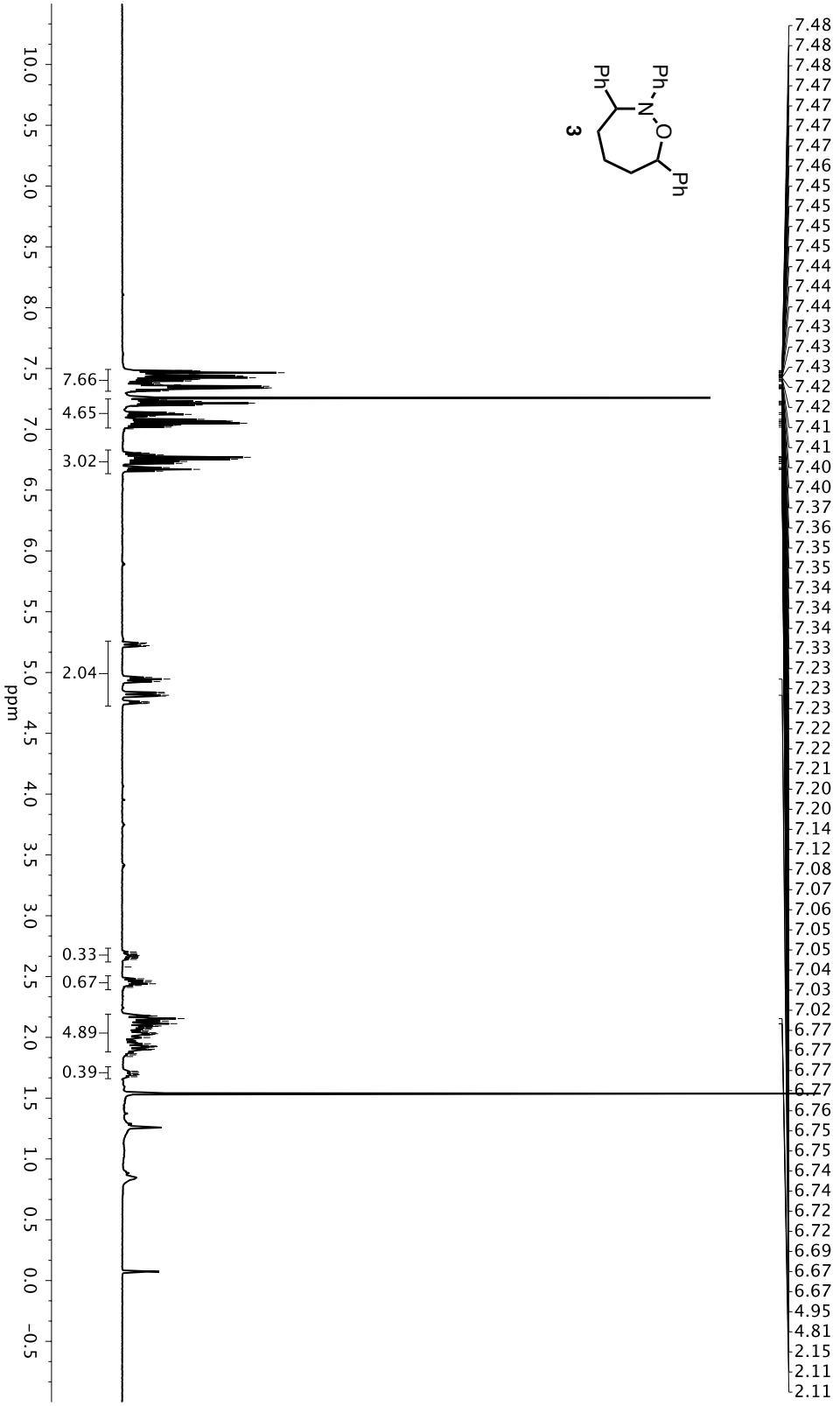
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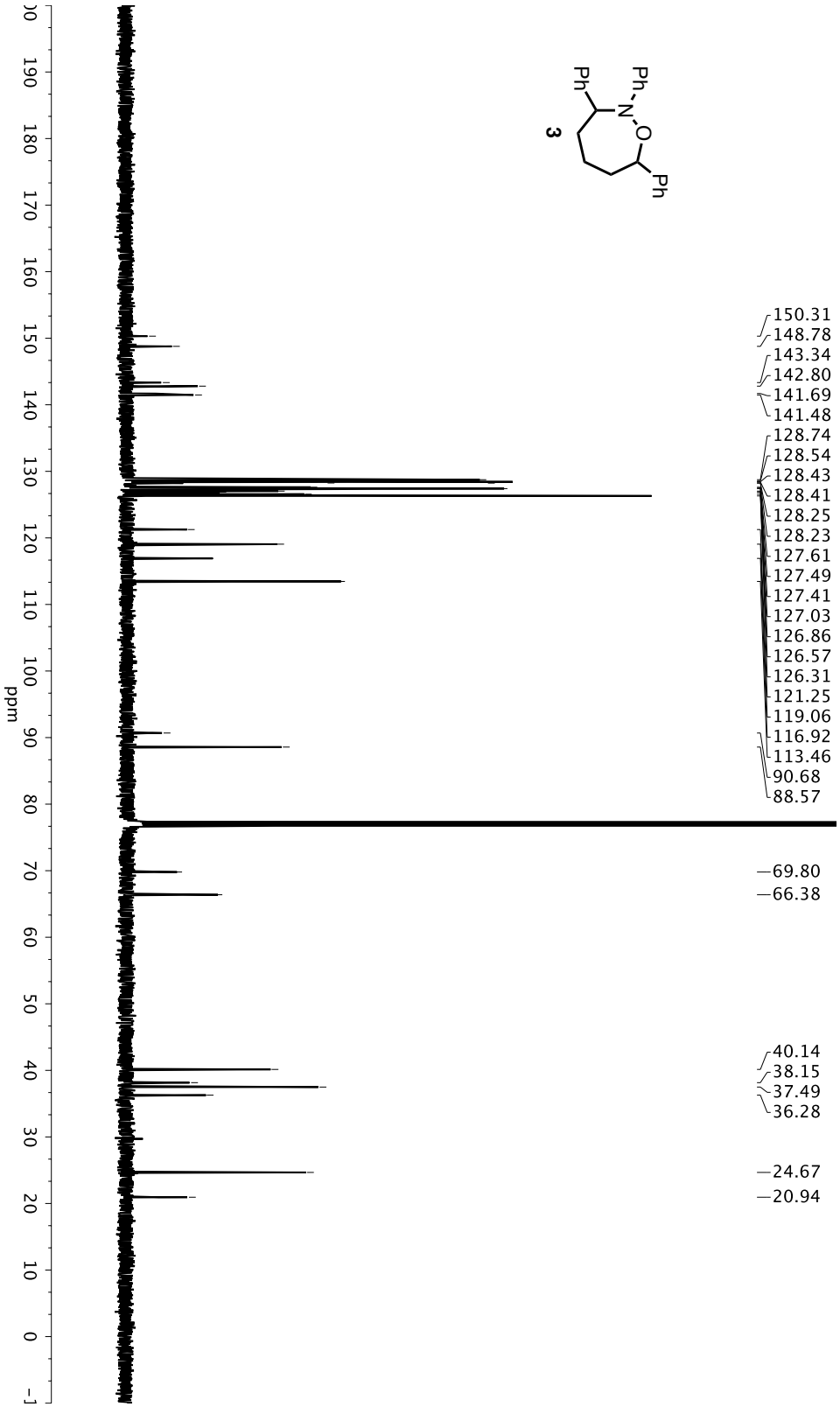
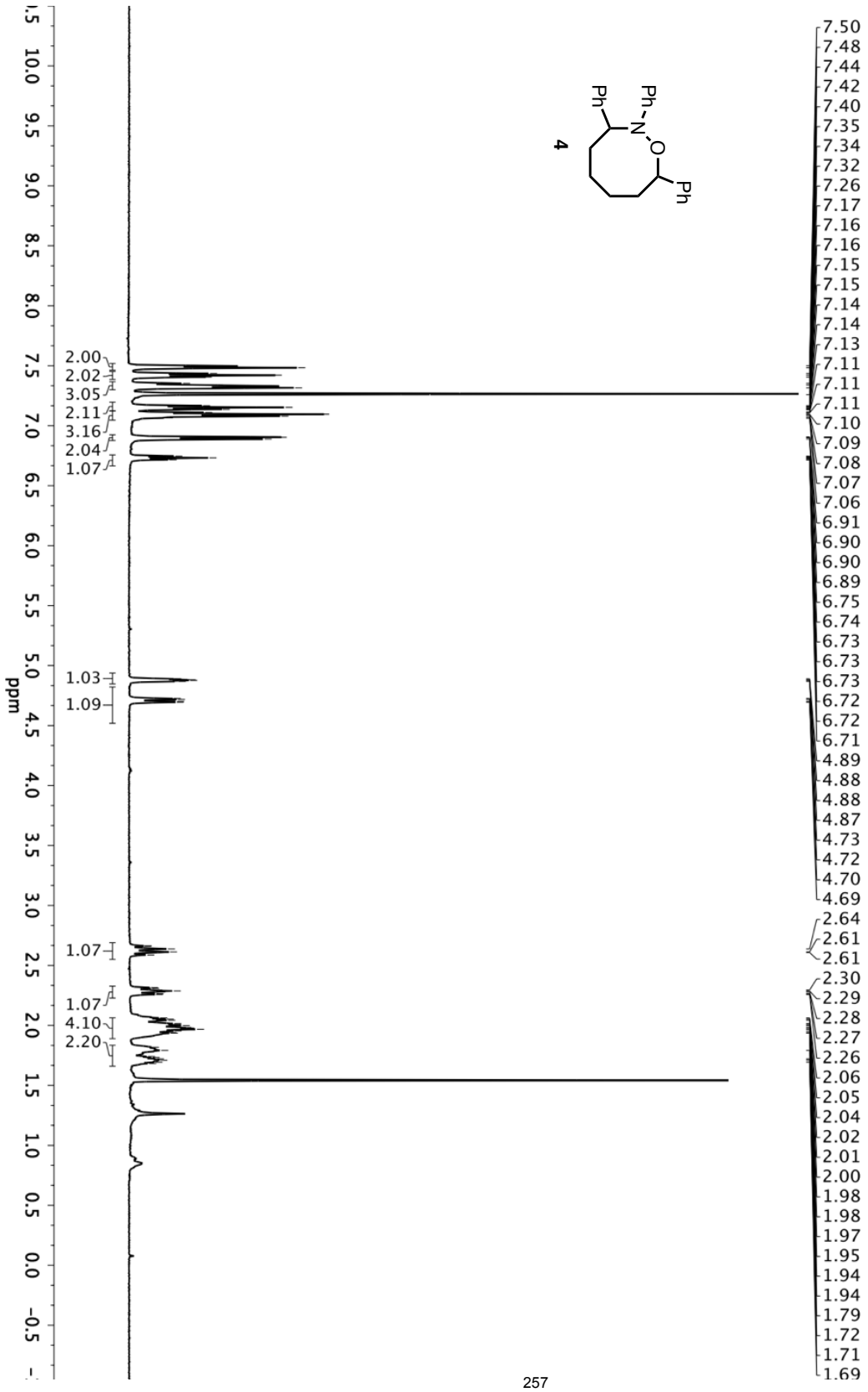
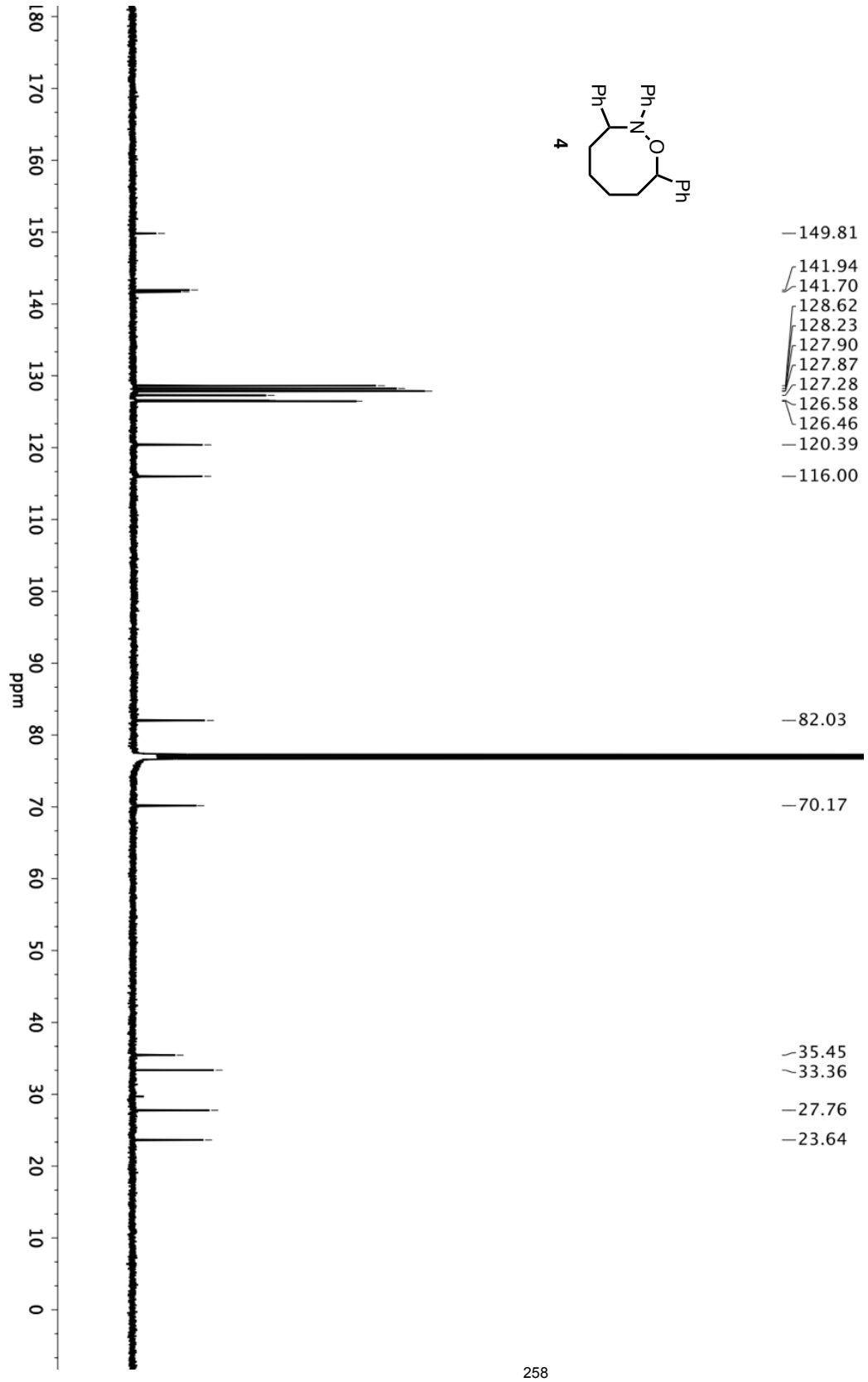
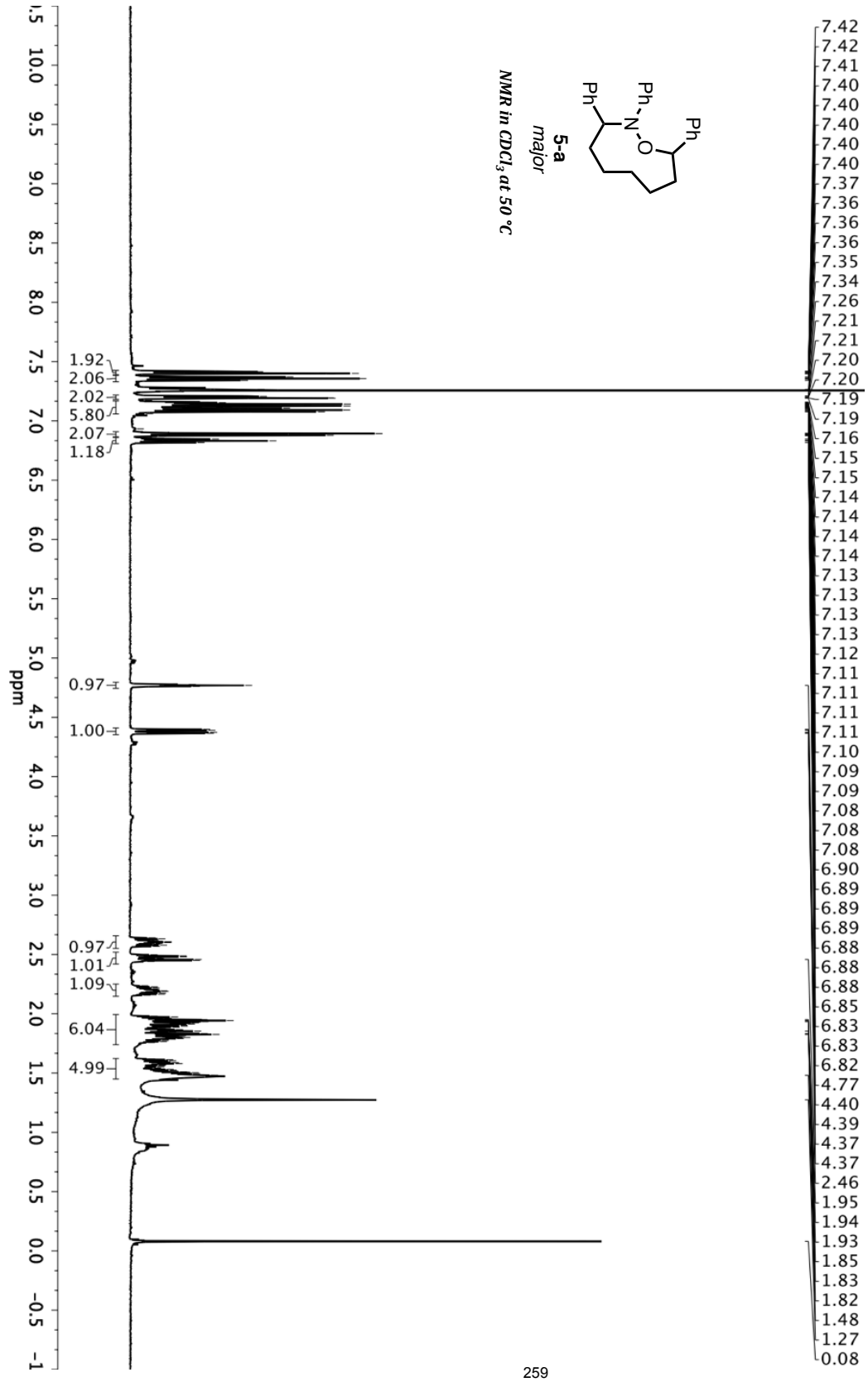
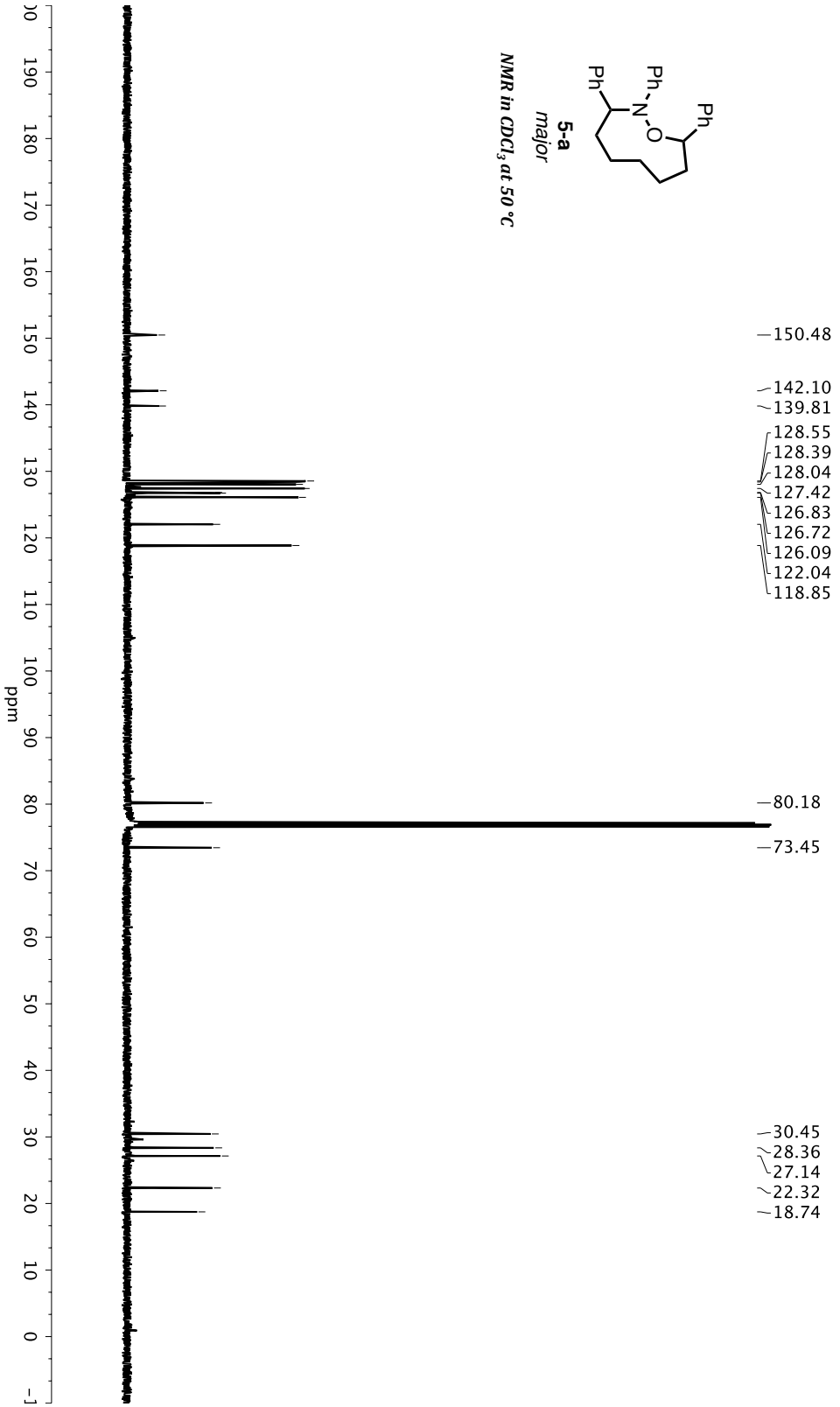
7.48 7.48 7.48 7.47 7.47 7.47 7.47 7.47 7.46 7.45 7.45 7.45 7.45 7.45 7.44 7.44 7.44 7.43 7.43 7.43 7.42 7.42 7.41 7.41 7.40 7.40 7.37 7.36 7.35 7.35 7.34 7.34 7.34 7.33 7.23 7.23 7.23 7.22 7.22 7.21 7.20 7.20 7.14 7.12 7.08 7.07 7.06 7.05 7.05 7.04 7.03 7.02 6.77 6.77 6.77 6.77 6.76 6.75 6.75 6.74 6.74 6.72 6.72 6.69 6.67 6.67 4.95 4.81 2.15 2.11 2.11

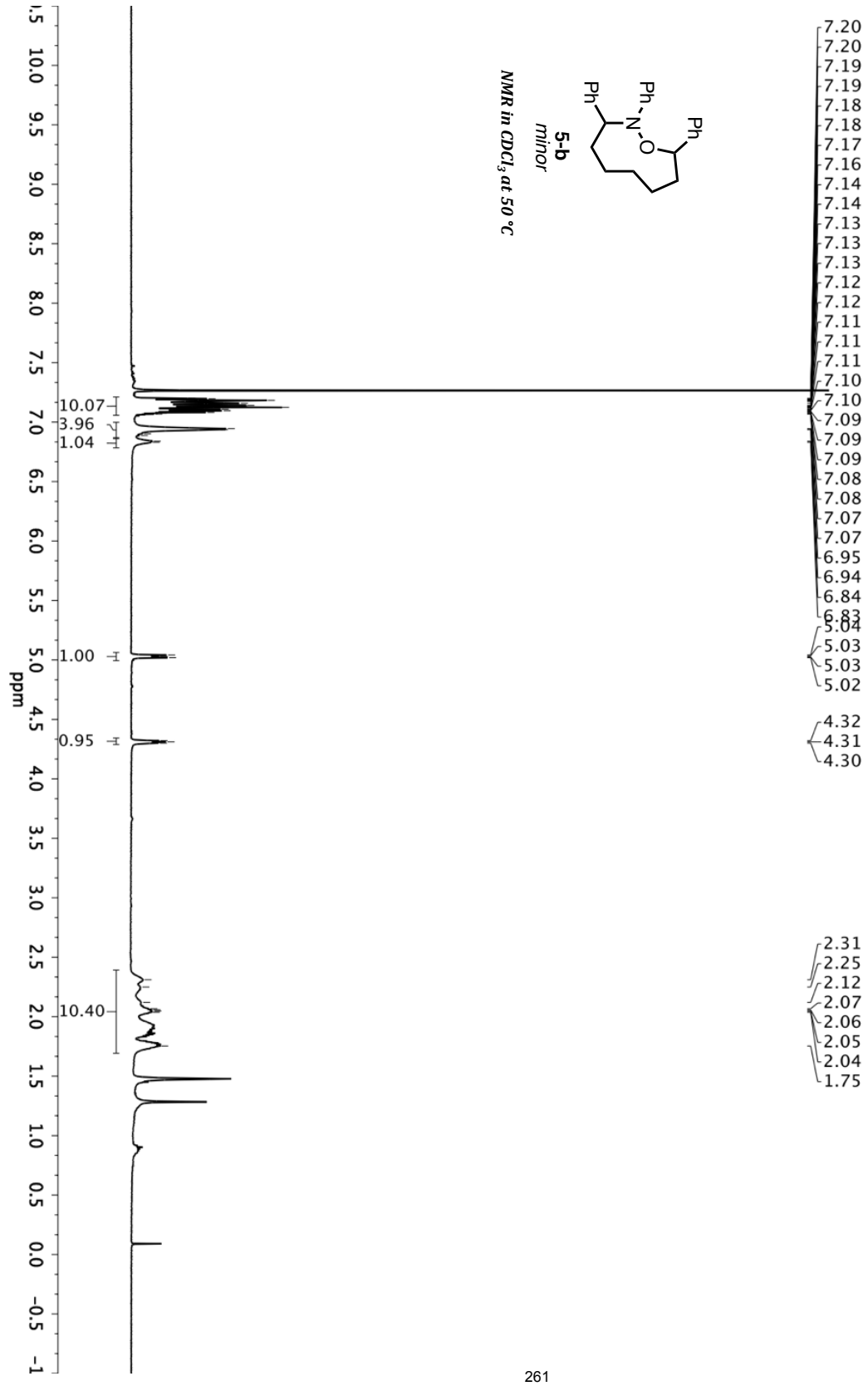

Ph
Ph
N
O
Ph
3
150.31
148.78
143.34
142.80
141.69
141.48
128.74
128.54
128.43
128.41
128.25
128.23
127.61
127.49
127.41
127.03
126.86
126.57
126.31
121.25
119.06
116.92
113.46
90.68
88.57
69.80
66.38
40.14
38.15
37.49
36.28
24.67
20.94
ppm

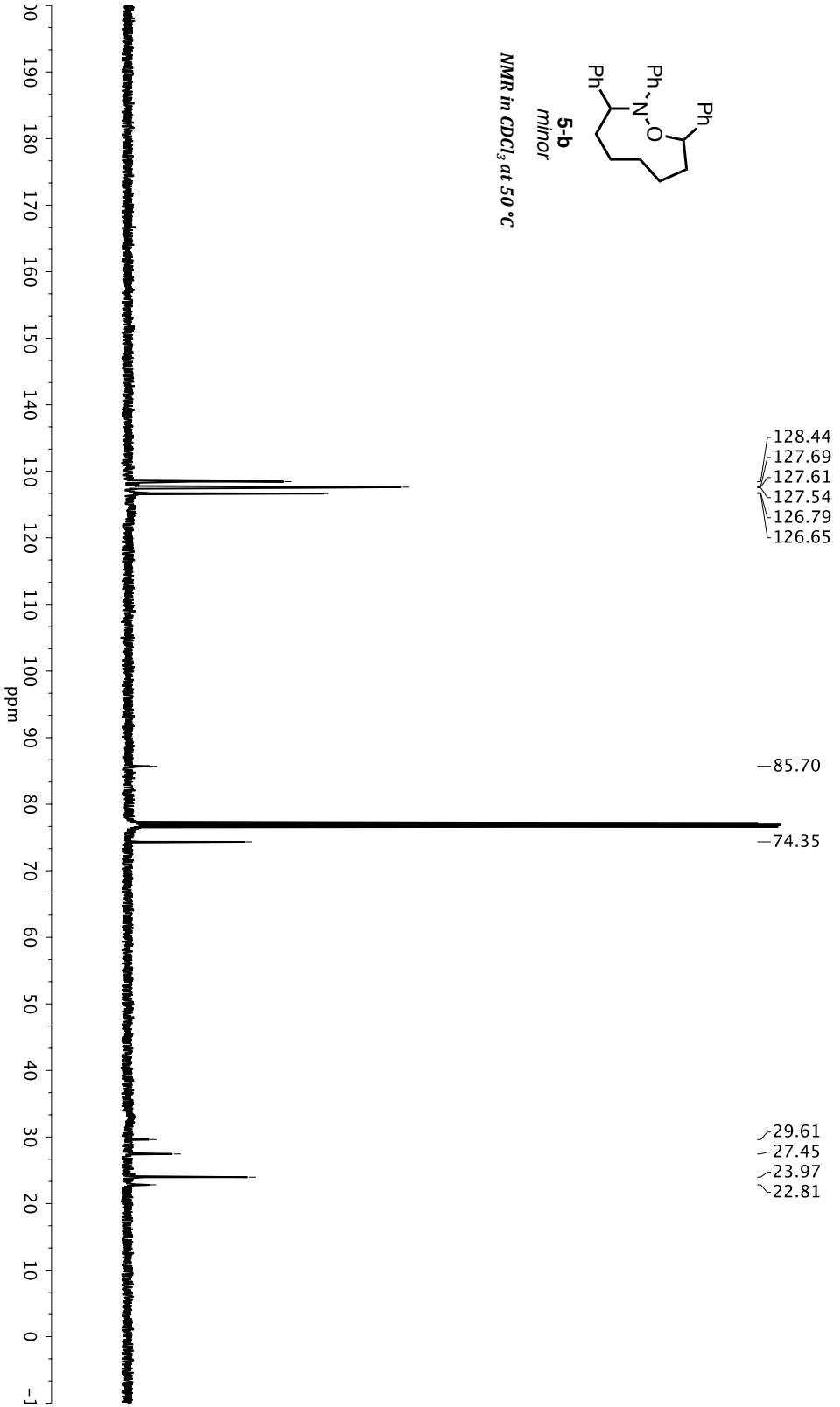

4
Ph
Ph
N
O
Ph
ppm
2.00
2.02
3.05
2.11
3.16
2.04
1.07
1.03
1.09
1.07
1.07
4.10
2.20
7.50
7.48
7.44
7.42
7.40
7.35
7.34
7.32
7.26
7.17
7.16
7.16
7.15
7.15
7.14
7.14
7.13
7.11
7.11
7.11
7.10
7.09
7.08
7.07
7.06
6.91
6.90
6.90
6.89
6.75
6.74
6.73
6.73
6.73
6.72
6.72
6.71
4.89
4.88
4.88
4.87
4.73
4.72
4.70
4.69
2.64
2.61
2.61
2.30
2.29
2.28
2.27
2.26
2.06
2.05
2.04
2.02
2.01
2.00
1.98
1.98
1.97
1.95
1.94
1.94
1.79
1.72
1.71
1.69

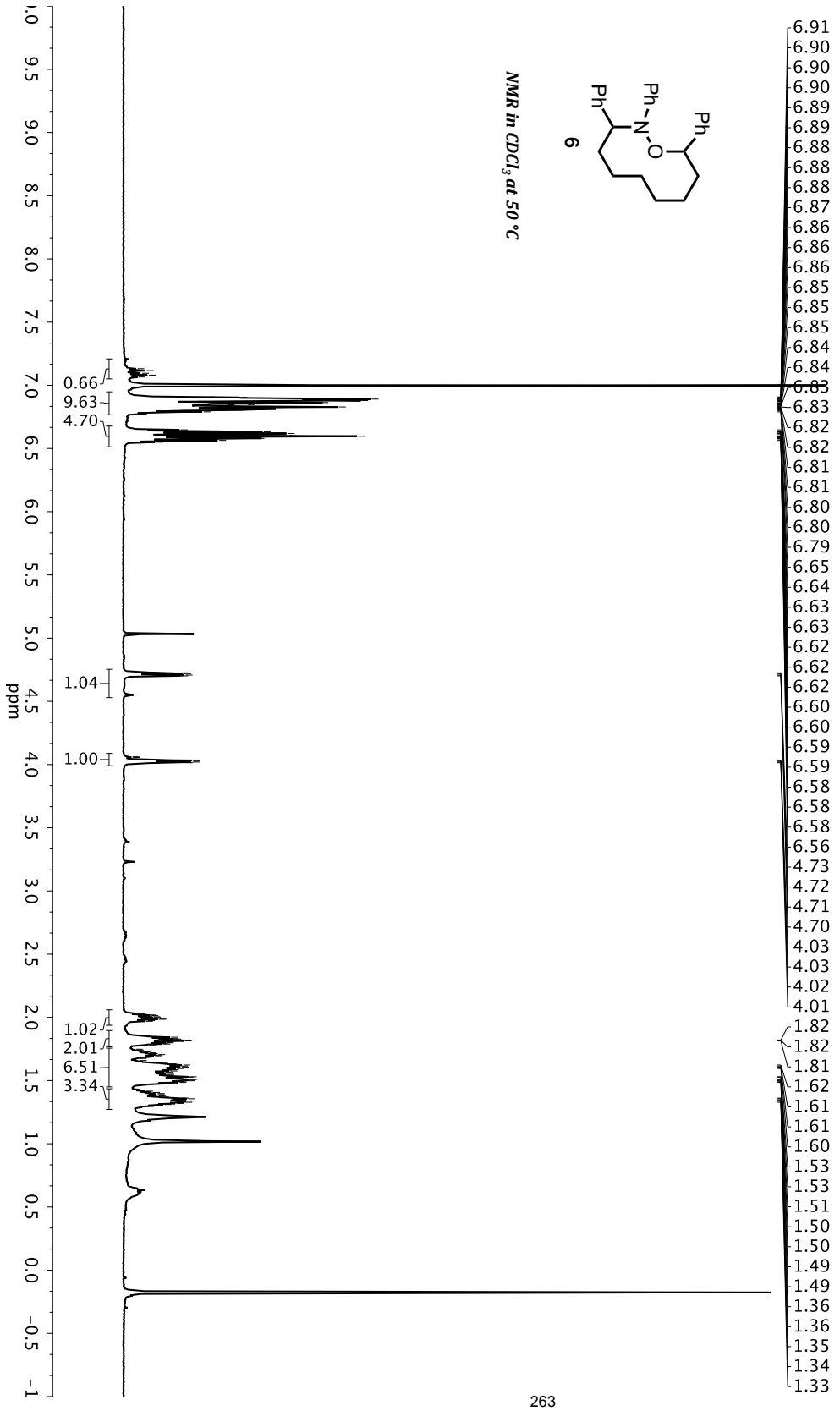

Ph
Ph
N
O
Ph
4
149.81
141.94
141.70
128.62
128.23
127.90
127.87
127.28
126.58
126.46
120.39
116.00
82.03
70.17
35.45
33.36
27.76
23.64
ppm

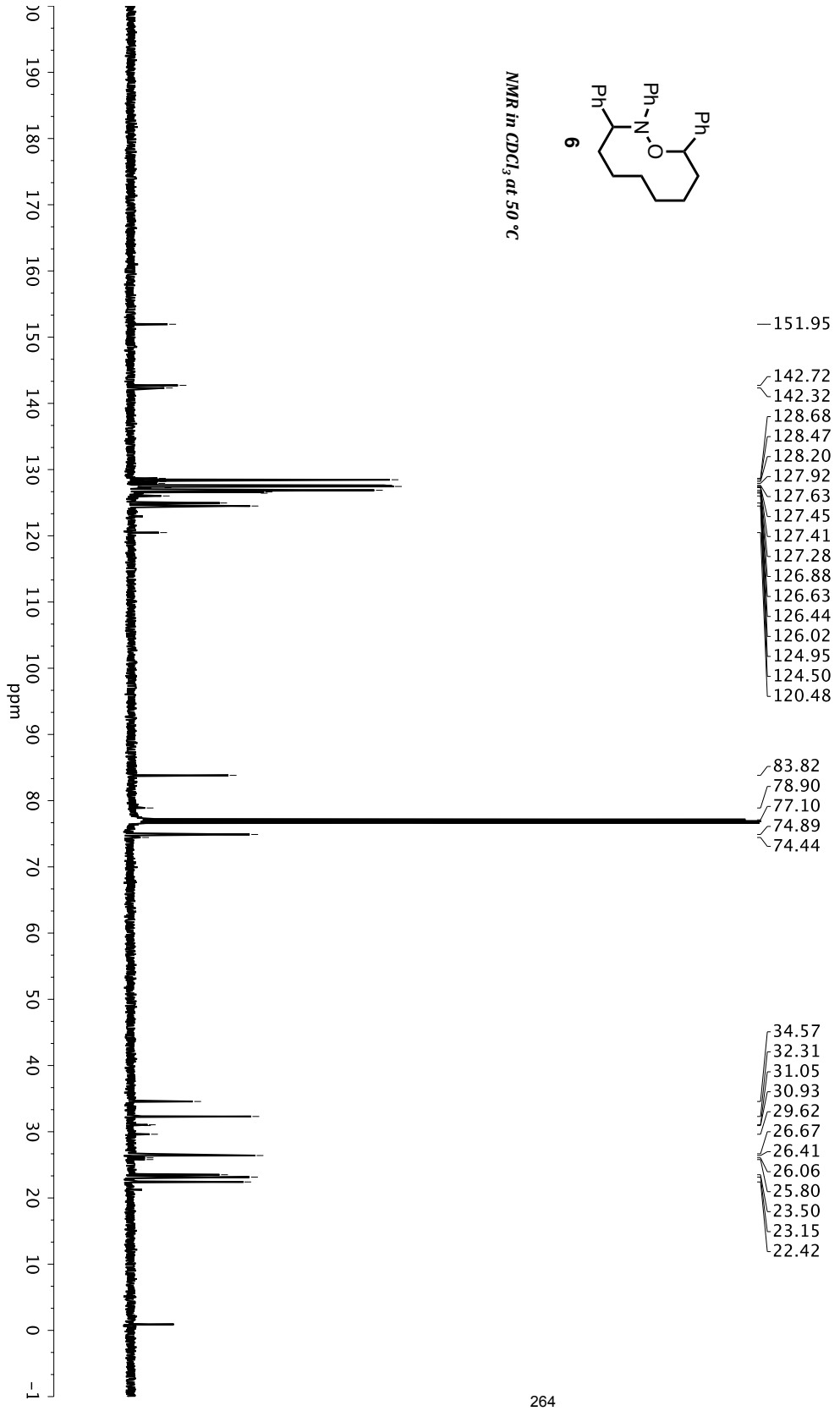

NMR in CDCl3 at 50 °C
5-a
major
Ph
Ph
N
O
Ph
ppm
1.92
2.06
2.02
5.80
2.07
1.18
0.97
1.00
0.97
1.01
1.09
6.04
4.99
7.42
7.42
7.41
7.40
7.40
7.40
7.40
7.40
7.40
7.37
7.36
7.36
7.36
7.35
7.34
7.26
7.21
7.21
7.20
7.20
7.19
7.19
7.16
7.15
7.15
7.14
7.14
7.14
7.14
7.14
7.13
7.13
7.13
7.13
7.12
7.11
7.11
7.11
7.11
7.10
7.09
7.09
7.08
7.08
7.08
6.90
6.89
6.89
6.89
6.88
6.88
6.88
6.85
6.83
6.83
6.82
4.77
4.40
4.39
4.37
4.37
2.46
1.95
1.94
1.93
1.85
1.83
1.82
1.48
1.27
0.08

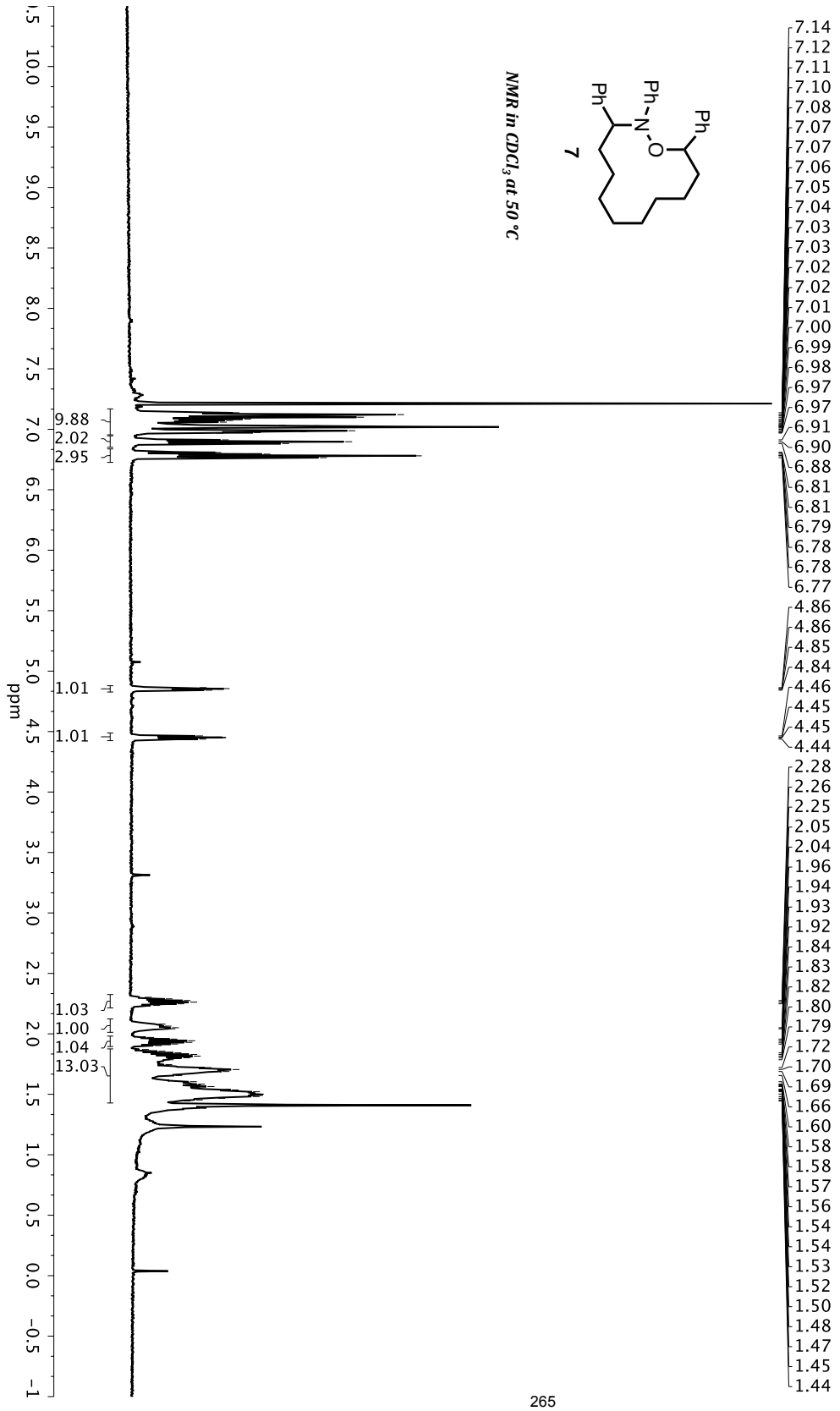

NMR in CDCl3 at 50 °C
5-a
major
Ph
Ph
N
O
Ph
150.48
142.10
139.81
128.55
128.39
128.04
127.42
126.83
126.72
126.09
122.04
118.85
80.18
73.45
30.45
28.36
27.14
22.32
18.74
ppm
210
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10


NMR in CDCl3 at 50 °C
5-b
minor
Ph
Ph
N
O
Ph
7.20
7.20
7.19
7.19
7.18
7.18
7.17
7.16
7.14
7.14
7.13
7.13
7.13
7.12
7.12
7.11
7.11
7.11
7.10
7.10
7.09
7.09
7.09
7.08
7.08
7.07
7.07
6.95
6.94
6.84
6.83
5.04
5.03
5.03
5.02
4.32
4.31
4.30
2.31
2.25
2.12
2.07
2.06
2.05
2.04
1.75
10.07
3.96
1.04
1.00
0.95
10.40
ppm


Ph
Ph
N
O
Ph
5-b
minor
NMR in CDCl3 at 50 °C
128.44
127.69
127.61
127.54
126.79
126.65
85.70
74.35
29.61
27.45
23.97
22.81
ppm


NMR in CDCl3 at 50 °C
6
Ph
Ph-N-O
Ph
0.66
9.63
4.70
1.04
1.00
1.02
2.01
6.51
3.34
ppm
6.91
6.90
6.90
6.90
6.89
6.89
6.88
6.88
6.88
6.87
6.86
6.86
6.86
6.86
6.85
6.85
6.85
6.84
6.84
6.83
6.83
6.82
6.82
6.81
6.81
6.80
6.80
6.79
6.65
6.64
6.63
6.63
6.62
6.62
6.62
6.60
6.60
6.59
6.59
6.58
6.58
6.58
6.56
4.73
4.72
4.71
4.70
4.03
4.03
4.02
4.01
1.82
1.82
1.81
1.62
1.61
1.61
1.60
1.53
1.53
1.51
1.50
1.50
1.49
1.49
1.36
1.36
1.35
1.34
1.33


NMR in CDCl3 at 50 °C
6
Ph
Ph-N-O
Ph
151.95
142.72
142.32
128.68
128.47
128.20
127.92
127.63
127.45
127.41
127.28
126.88
126.63
126.44
126.02
124.95
124.50
120.48
83.82
78.90
77.10
74.89
74.44
34.57
32.31
31.05
30.93
29.62
26.67
26.41
26.06
25.80
23.50
23.15
22.42
ppm


NMR in CDCl3 at 50 °C
7
Ph
Ph-N-O
Ph
ppm
9.88
2.02
2.95
1.01
1.01
1.03
1.00
1.04
13.03
7.14
7.12
7.11
7.10
7.08
7.07
7.07
7.06
7.05
7.04
7.03
7.03
7.02
7.02
7.01
7.00
6.99
6.98
6.97
6.97
6.91
6.90
6.88
6.81
6.81
6.79
6.78
6.78
6.77
4.86
4.86
4.85
4.84
4.46
4.45
4.45
4.44
2.28
2.26
2.25
2.05
2.04
1.96
1.94
1.93
1.92
1.84
1.83
1.82
1.80
1.79
1.72
1.70
1.69
1.66
1.60
1.58
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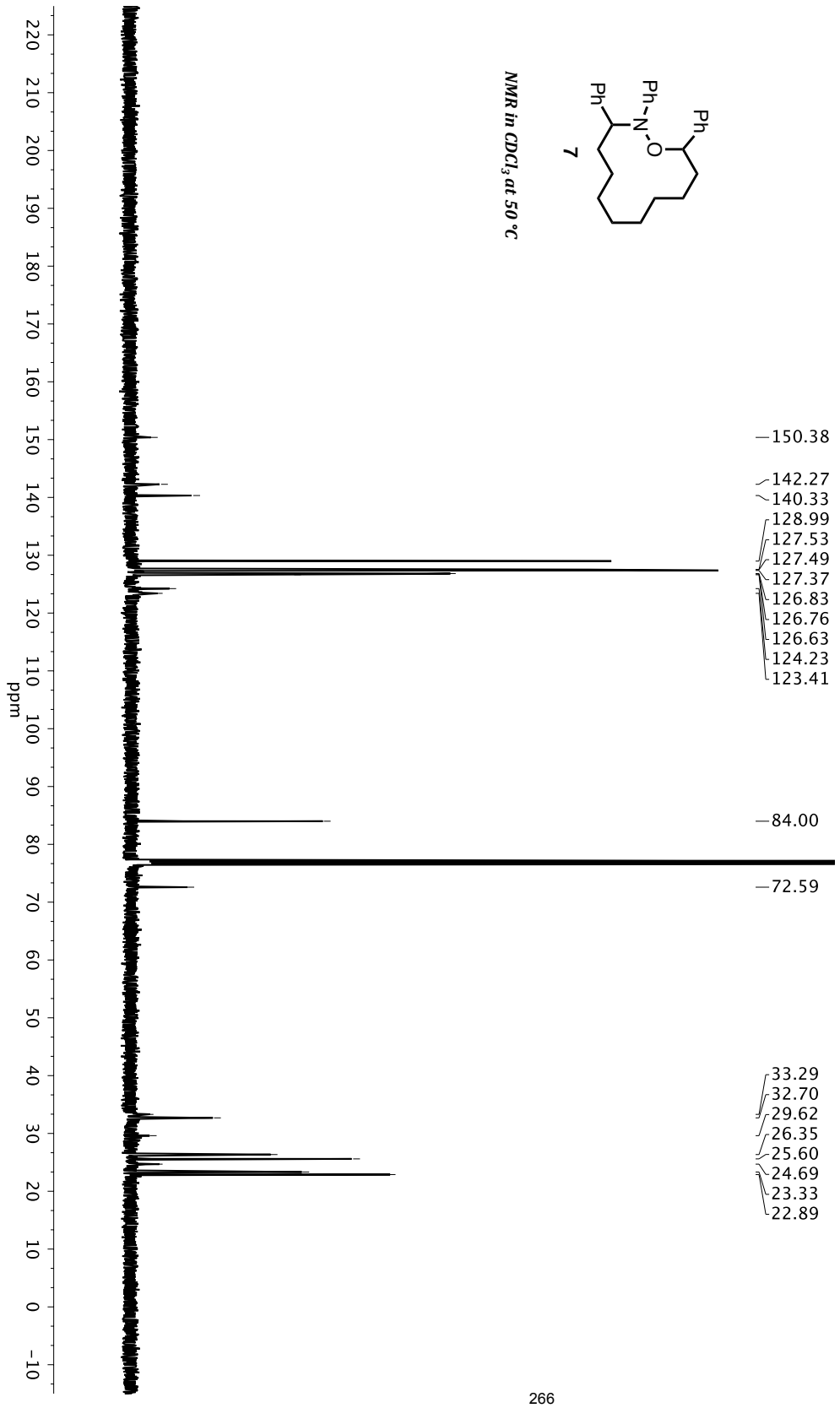
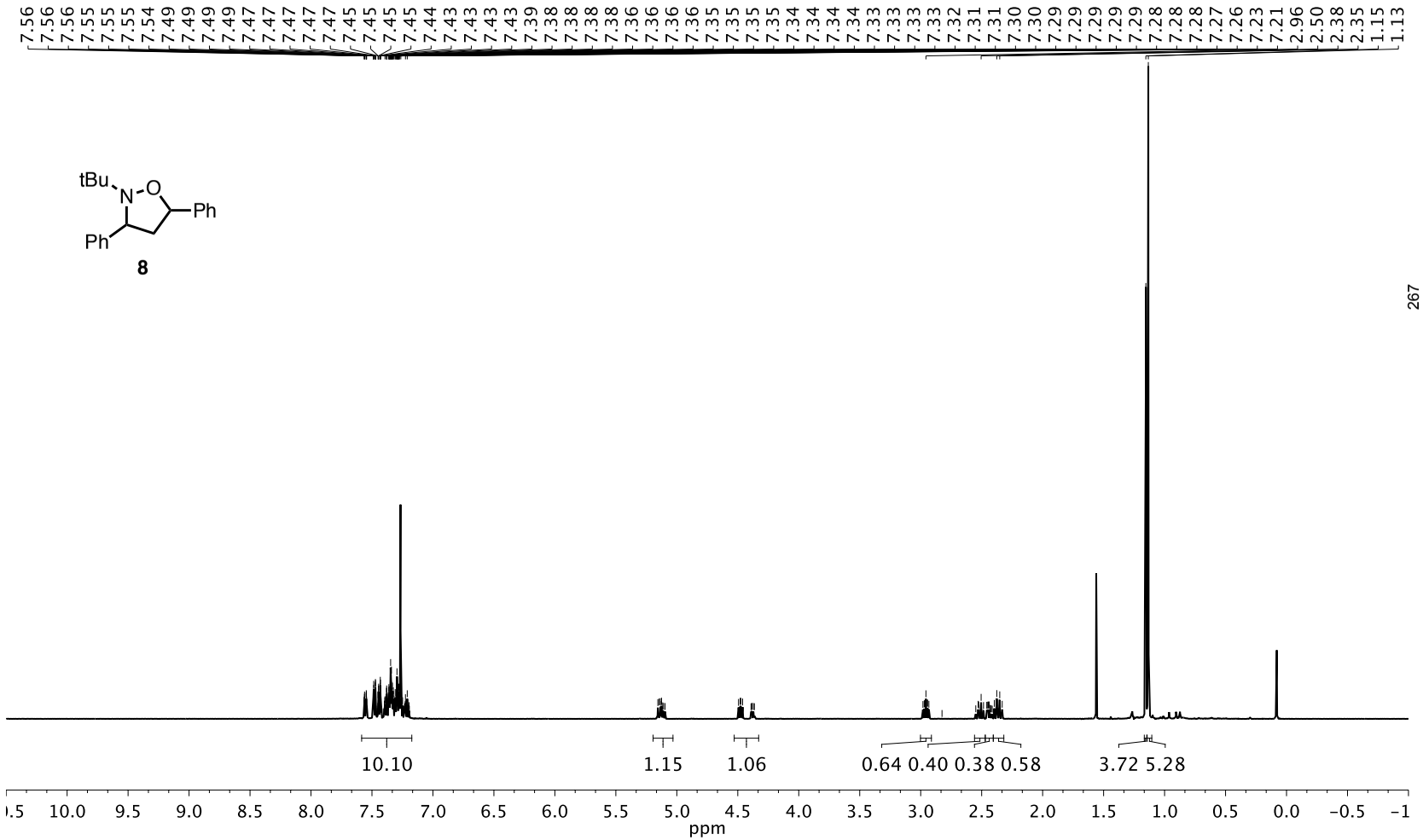
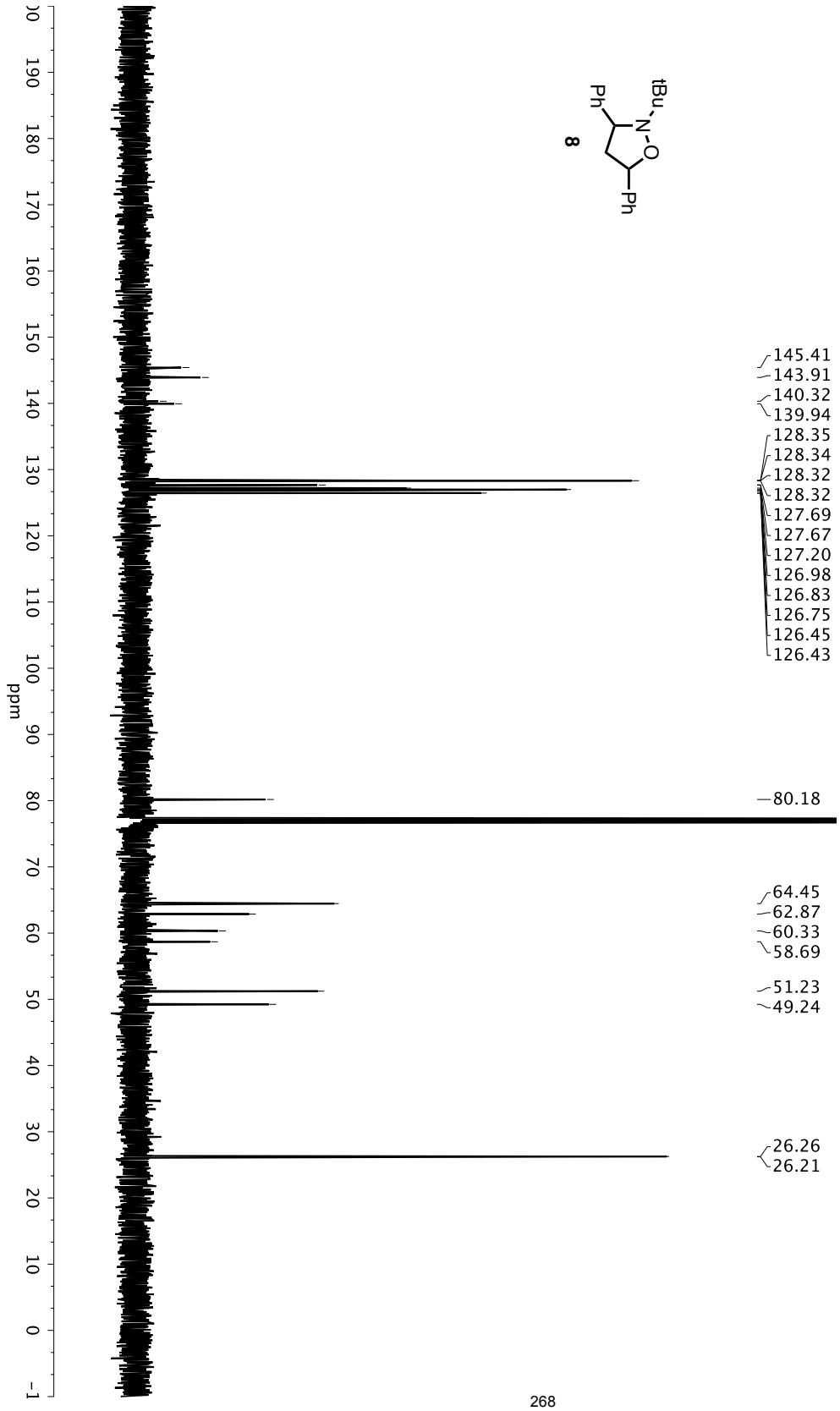
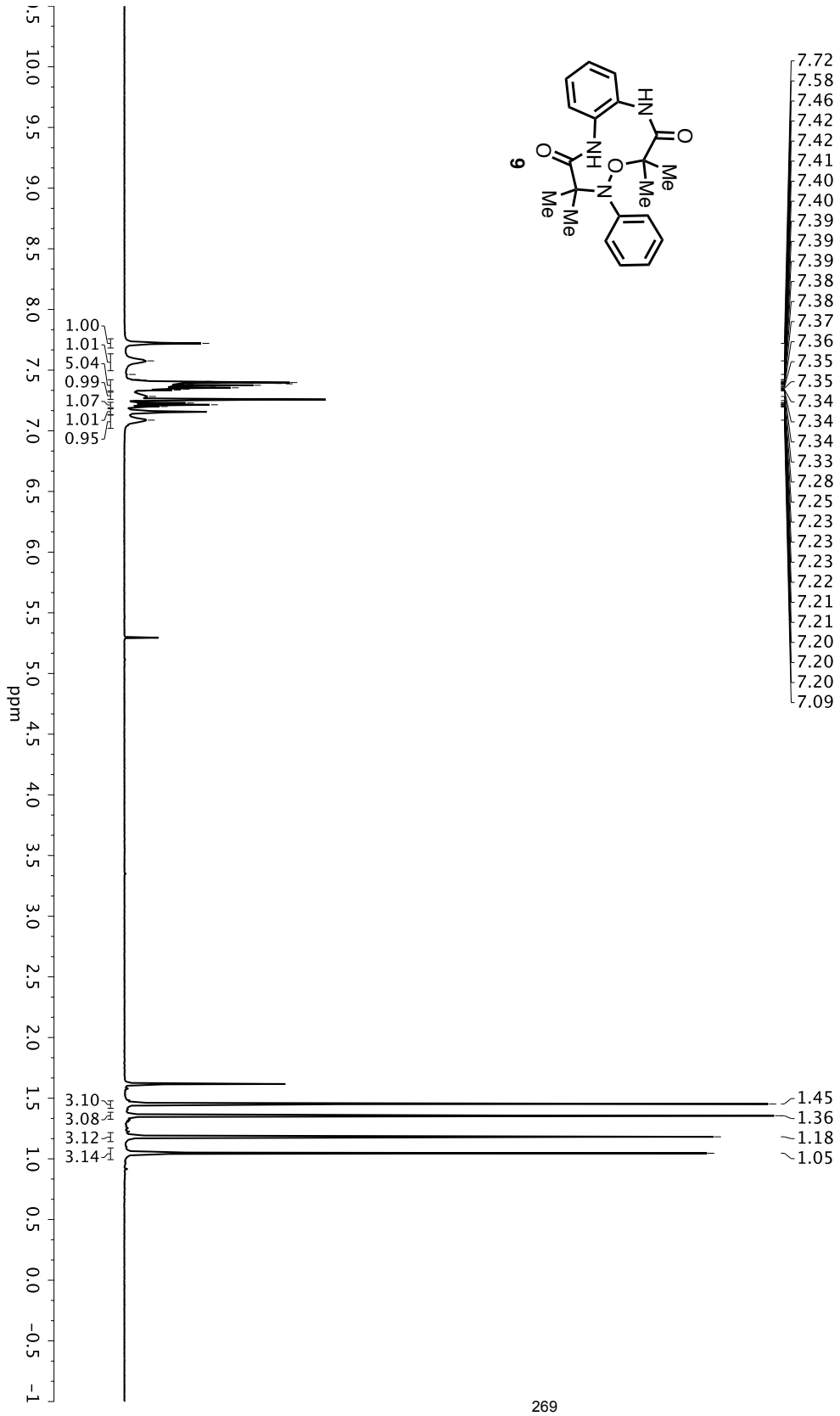
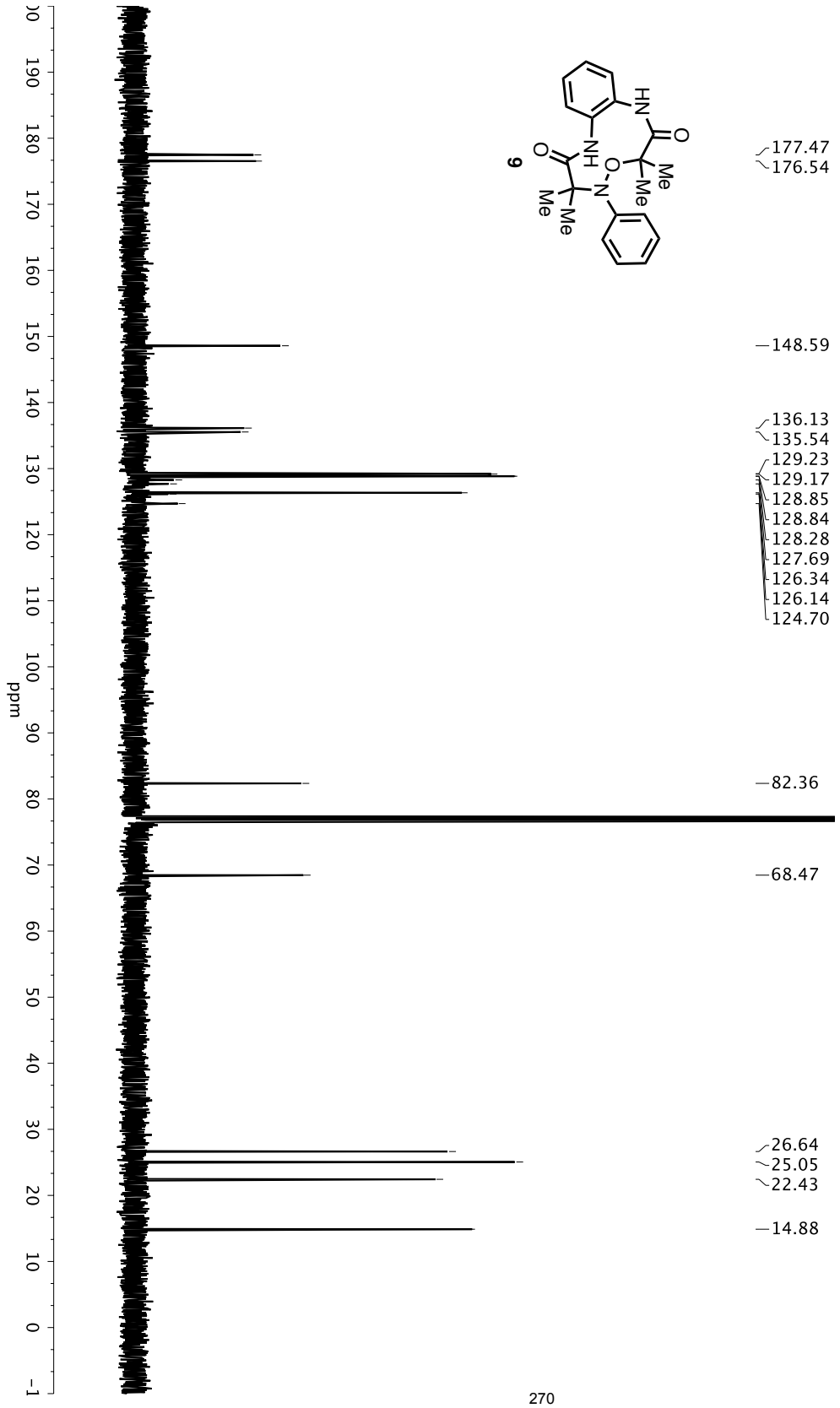
1.52
1.50
1.48
1.47
1.45
1.44

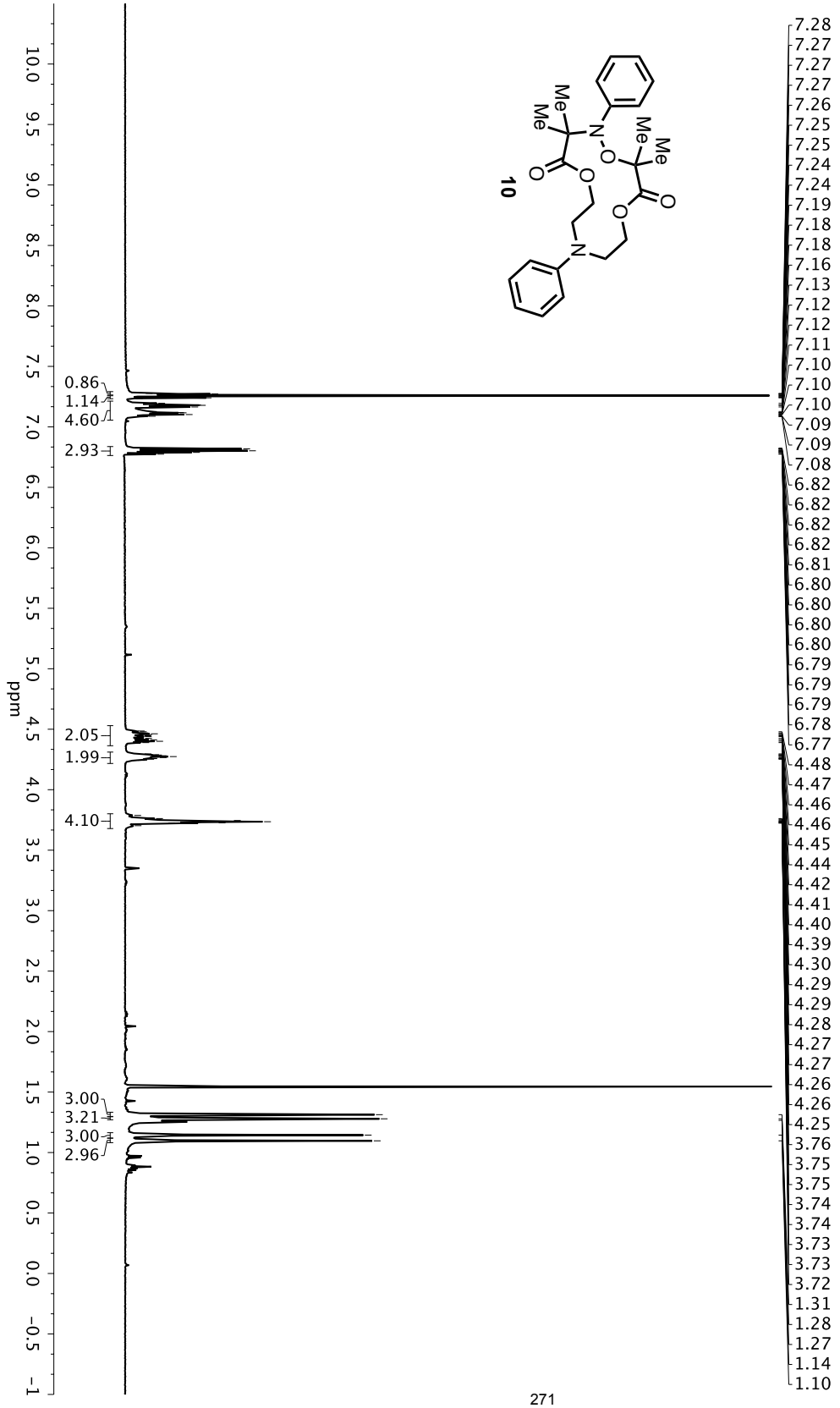

NMR in CDCl3 at 50 °C
7
Ph
Ph-N-O
Ph
150.38
142.27
140.33
128.99
127.53
127.49
127.37
126.83
126.76
126.63
124.23
123.41
84.00
72.59
33.29
32.70
29.62
26.35
25.60
24.69
23.33
22.89
ppm

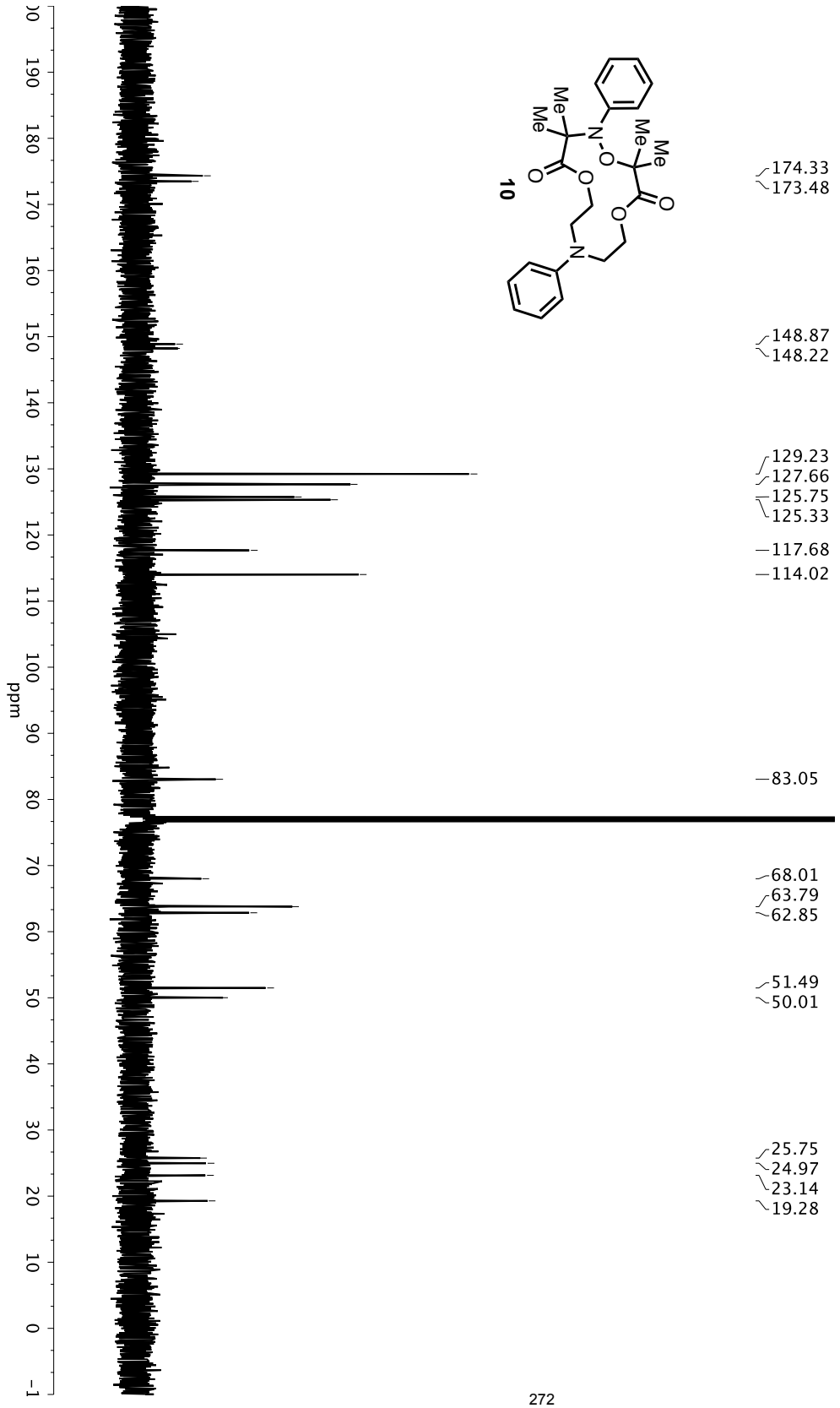

7.56 7.56 7.56 7.55 7.55 7.55 7.54 7.49 7.49 7.49 7.49 7.47 7.47 7.47 7.47 7.45 7.45 7.45 7.45 7.44 7.43 7.43 7.43 7.43 7.39 7.38 7.38 7.38 7.38 7.36 7.36 7.36 7.35 7.35 7.35 7.35 7.34 7.34 7.34 7.33 7.33 7.33 7.33 7.32 7.31 7.31 7.30 7.30 7.29 7.29 7.29 7.29 7.28 7.28 7.28 7.27 7.26 7.23 7.21 2.96 2.50 2.38 2.35 1.15 1.13
tBu
N
O
Ph
Ph
8
267
10.10
1.15
1.06
0.64 0.40 0.38 0.58
3.72 5.28
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

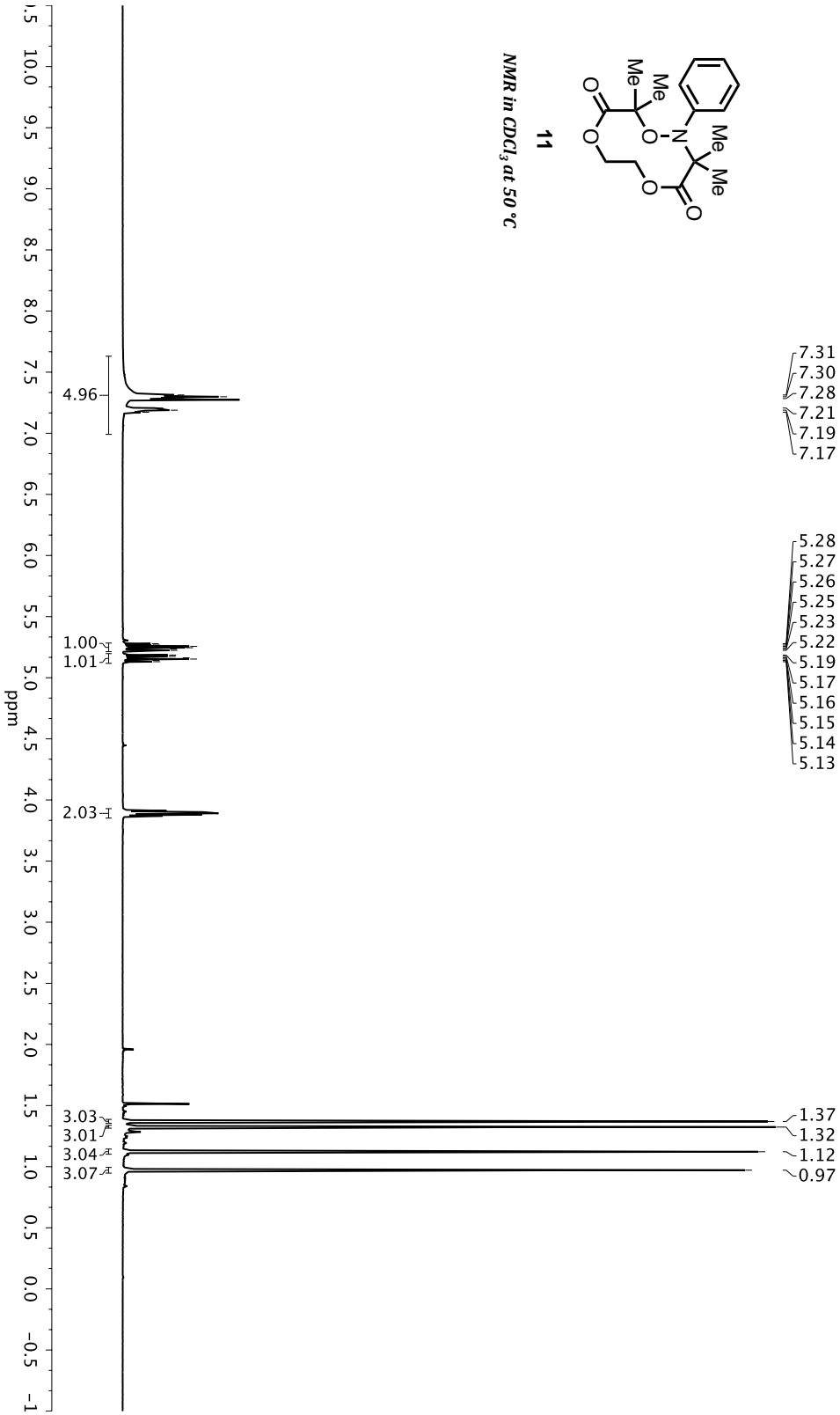

tBu
N
O
Ph
Ph
8
145.41
143.91
140.32
139.94
128.35
128.34
128.32
128.32
127.69
127.67
127.20
126.98
126.83
126.75
126.45
126.43
80.18
64.45
62.87
60.33
58.69
51.23
49.24
26.26
26.21
ppm

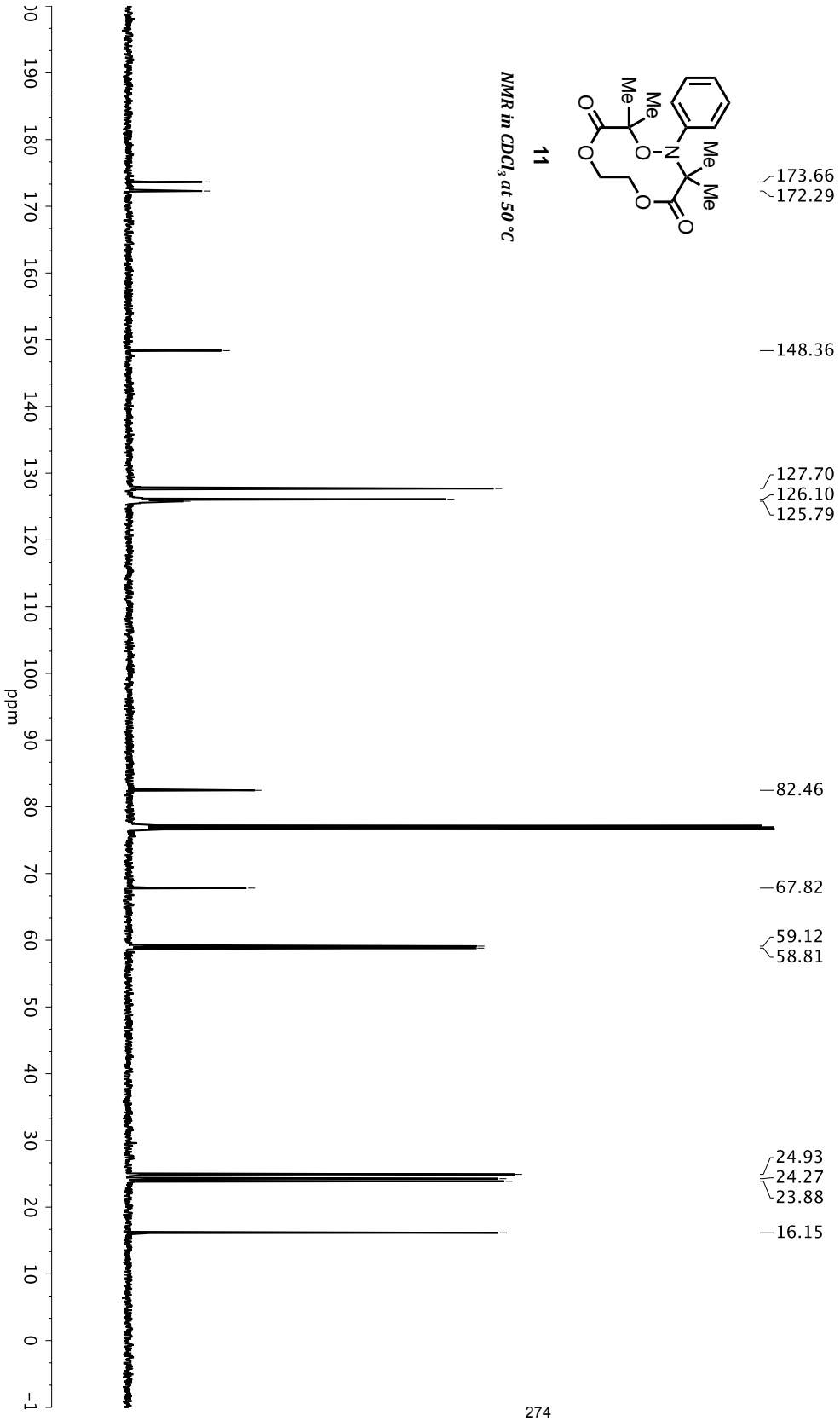

9
NH
HN
O
O
Me
Me
Me
Me
O
N
7.72
7.58
7.46
7.42
7.42
7.41
7.40
7.40
7.39
7.39
7.39
7.38
7.38
7.37
7.36
7.35
7.35
7.34
7.34
7.34
7.33
7.28
7.25
7.23
7.23
7.23
7.22
7.21
7.21
7.20
7.20
7.20
7.09
1.00
1.01
5.04
0.99
1.07
1.01
0.95
3.10
3.08
3.12
3.14
1.45
1.36
1.18
1.05
ppm

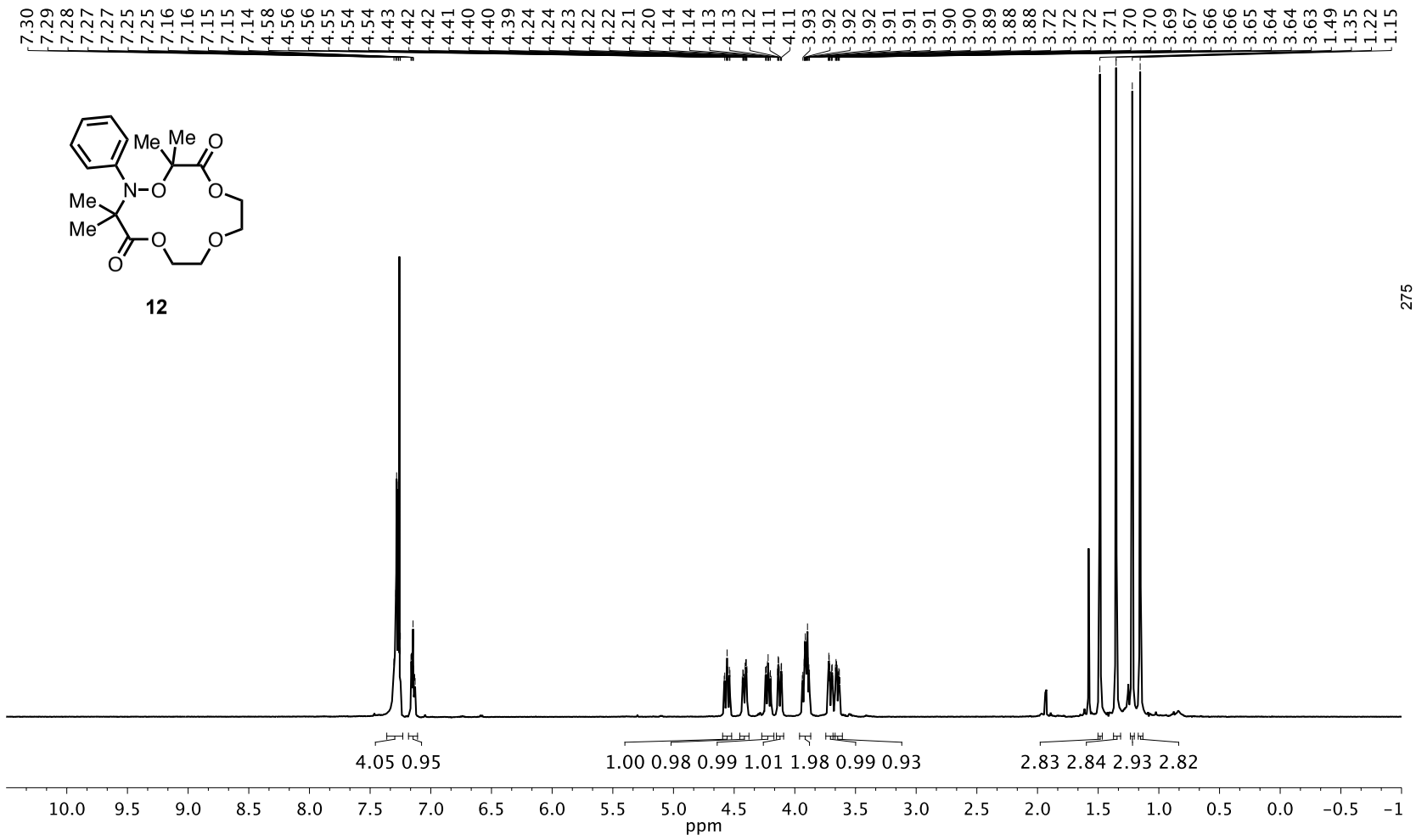

9
177.47
176.54
148.59
136.13
135.54
129.23
129.17
128.85
128.84
128.28
127.69
126.34
126.14
124.70
82.36
68.47
26.64
25.05
22.43
14.88
ppm


10
Me
Me
Me
Me
N
O
O
O
O
O
N
0.86
1.14
4.60
2.93
2.05
1.99
4.10
3.00
3.21
3.00
2.96
ppm
7.28
7.27
7.27
7.27
7.26
7.25
7.25
7.24
7.24
7.19
7.18
7.18
7.16
7.13
7.12
7.12
7.11
7.10
7.10
7.10
7.09
7.09
7.08
6.82
6.82
6.82
6.82
6.81
6.80
6.80
6.80
6.80
6.79
6.79
6.79
6.78
6.77
4.48
4.47
4.46
4.46
4.45
4.44
4.42
4.41
4.40
4.39
4.30
4.29
4.29
4.28
4.27
4.27
4.26
4.26
4.25
3.76
3.75
3.75
3.74
3.74
3.73
3.73
3.72
1.31
1.28
1.27
1.14
1.10


10
Me
Me
Me
Me
N
O
O
O
O
O
N
174.33
173.48
148.87
148.22
129.23
127.66
125.75
125.33
117.68
114.02
83.05
68.01
63.79
62.85
51.49
50.01
25.75
24.97
23.14
19.28
ppm


11
NMR in CDCl3 at 50 °C
Me
Me
Me
Me
Me
O
O
O
O
O
O
N
7.31
7.30
7.28
7.21
7.19
7.17
5.28
5.27
5.26
5.25
5.23
5.22
5.19
5.17
5.16
5.15
5.14
5.13
1.37
1.32
1.12
0.97
4.96
1.00
1.01
2.03
3.03
3.01
3.04
3.07
ppm


11
NMR in CDCl3 at 50 °C
Me
Me
Me
Me
Me
O
O
O
O
O
O
N
173.66
172.29
148.36
127.70
126.10
125.79
82.46
67.82
59.12
58.81
24.93
24.27
23.88
16.15
ppm
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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Me Me O
N O O
Me
Me
O O O
O
12
275
4.05 0.95
1.00 0.98 0.99 1.01 1.98 0.99 0.93
2.83 2.84 2.93 2.82
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
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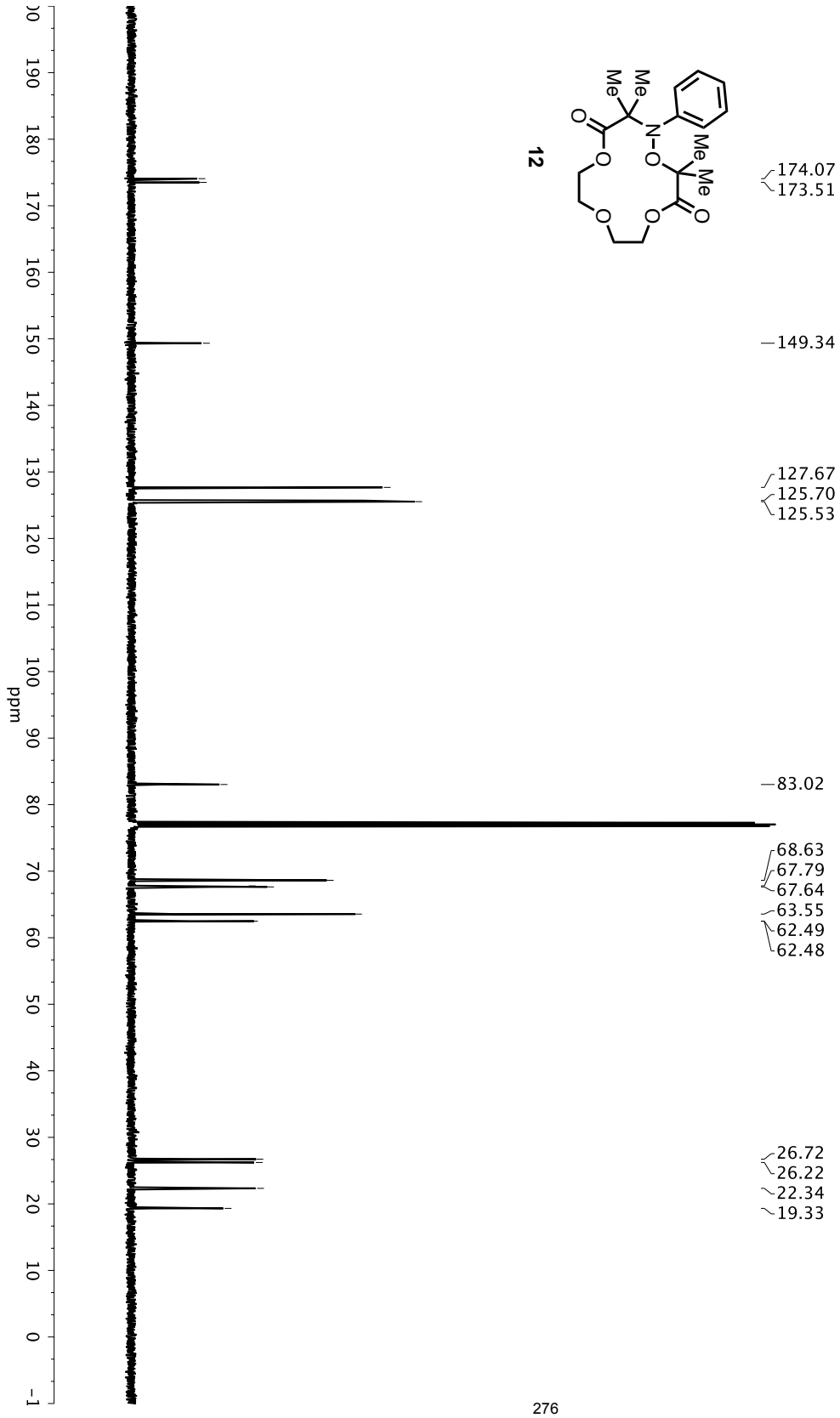
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Me
Me
Me
O
O
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O
O
O
O
O
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173.51
149.34
127.67
125.70
125.53
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67.64
63.55
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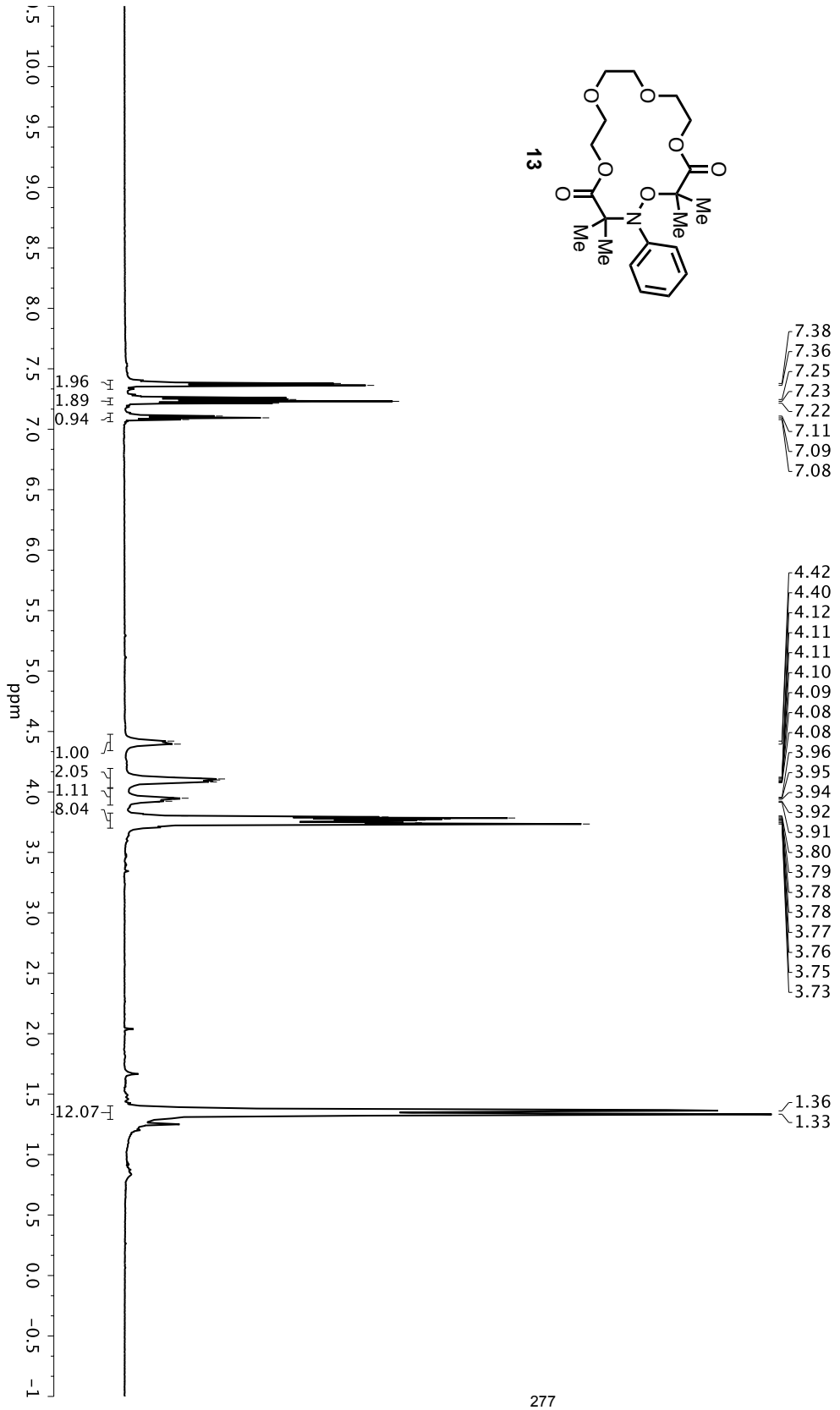
26.72
26.22
22.34
19.33
ppm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Me
Me
Me
Me
O
O
O
O
O
O
O
O
N
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7.36
7.25
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7.22
7.11
7.09
7.08
4.42
4.40
4.12
4.11
4.11
4.10
4.09
4.08
4.08
3.96
3.95
3.94
3.92
3.91
3.80
3.79
3.78
3.78
3.77
3.76
3.75
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1.33
1.96
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2.05
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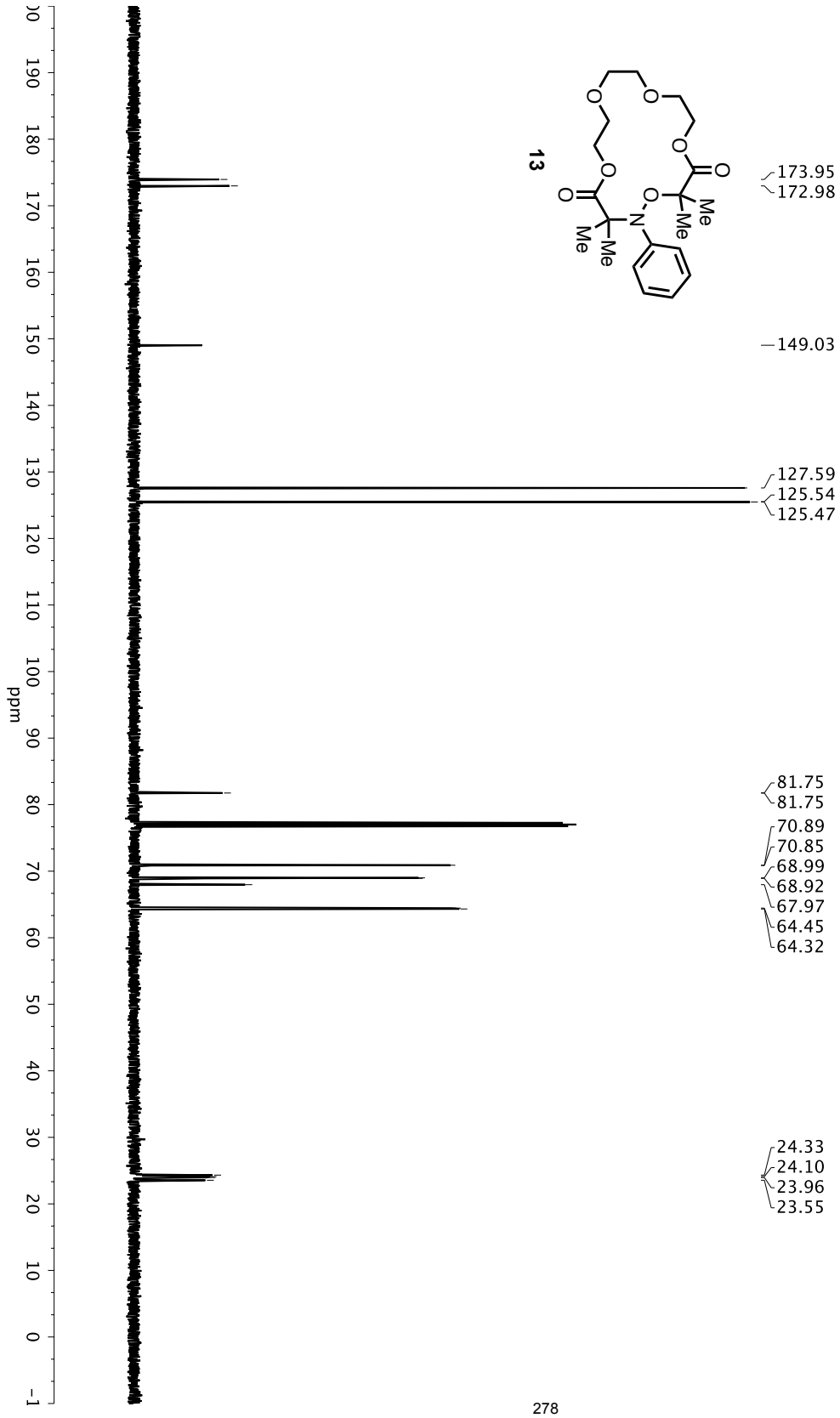
8.04
12.07
ppm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68.99
68.92
67.97
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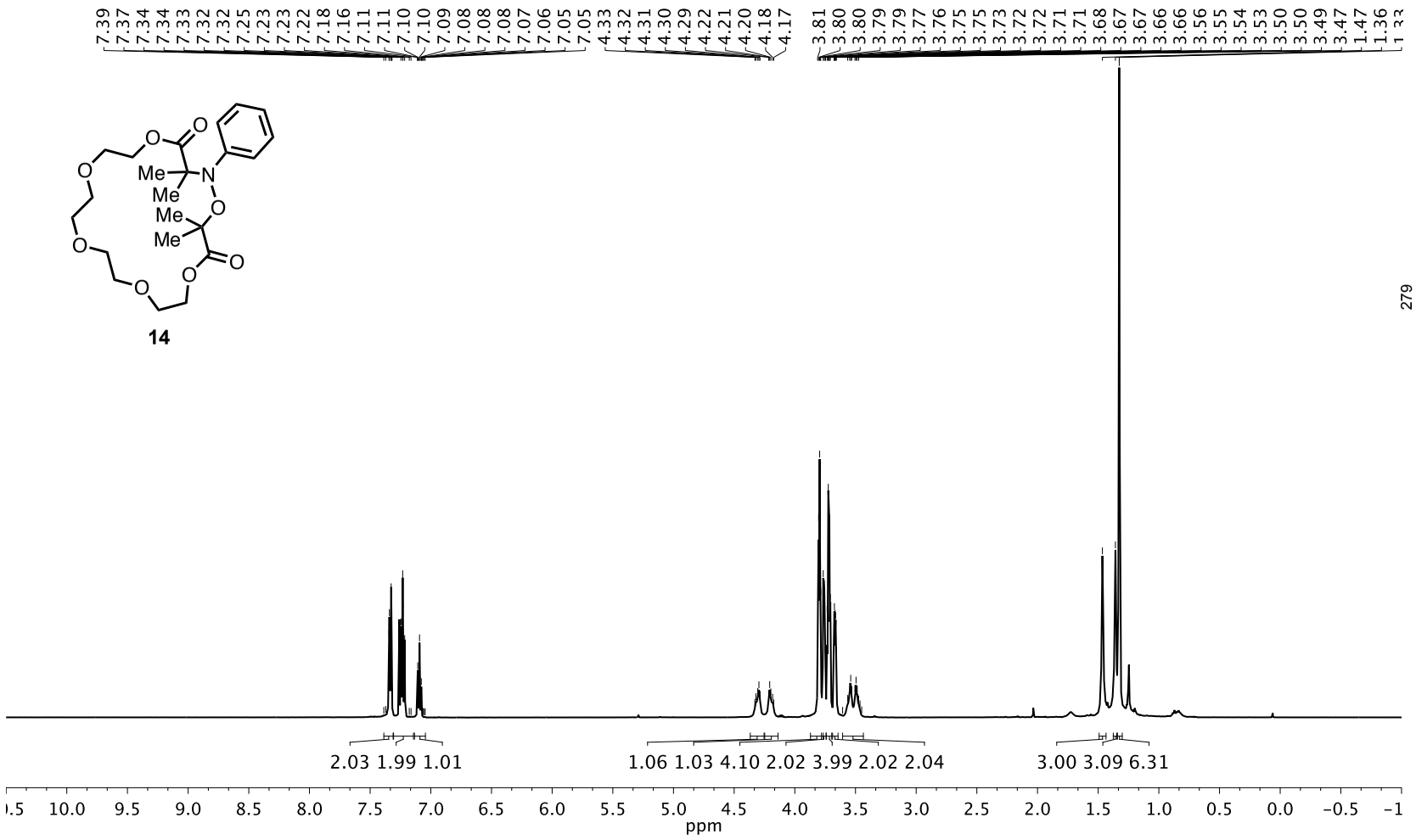
64.32
24.33
24.10
23.96
23.55
ppm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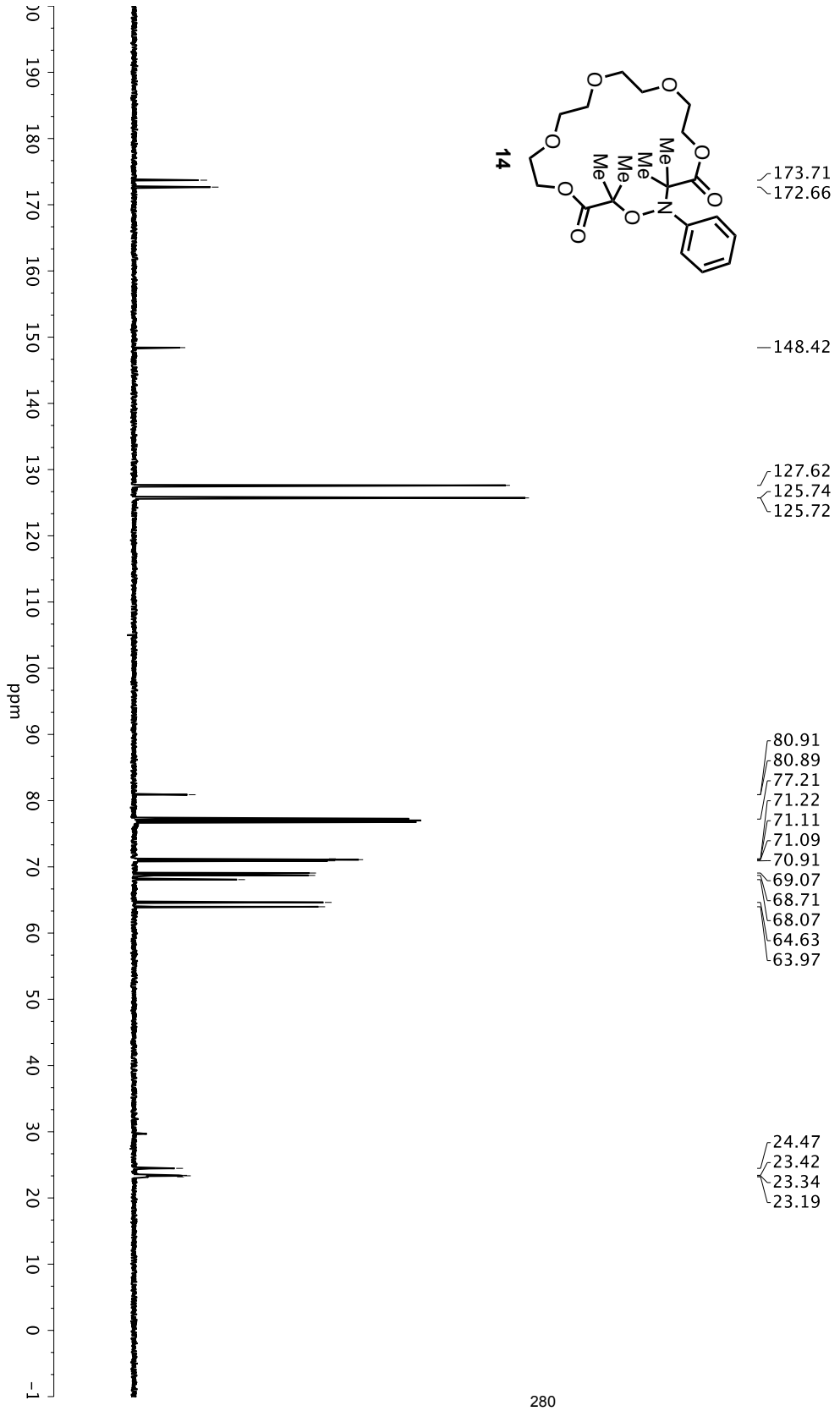
4.33 4.32 4.31 4.30 4.29 4.22 4.21 4.20 4.18 4.17
3.81 3.80 3.80 3.79 3.79 3.77 3.76 3.75 3.75 3.73 3.72 3.72 3.71 3.71 3.68 3.67 3.67 3.66 3.66 3.56 3.55 3.54 3.53 3.50 3.50 3.49 3.47 1.47 1.36
Me
Me
Me
Me
N
O
O
O
O
O
O
O
O
O
O
14
279
2.03 1.99 1.01
1.06 1.03 4.10 2.02 3.99 2.02 2.04
3.00 3.09 6.31
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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Me
Me
Me
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127.62
125.74
125.72
80.91
80.89
77.21
71.22
71.11
71.09
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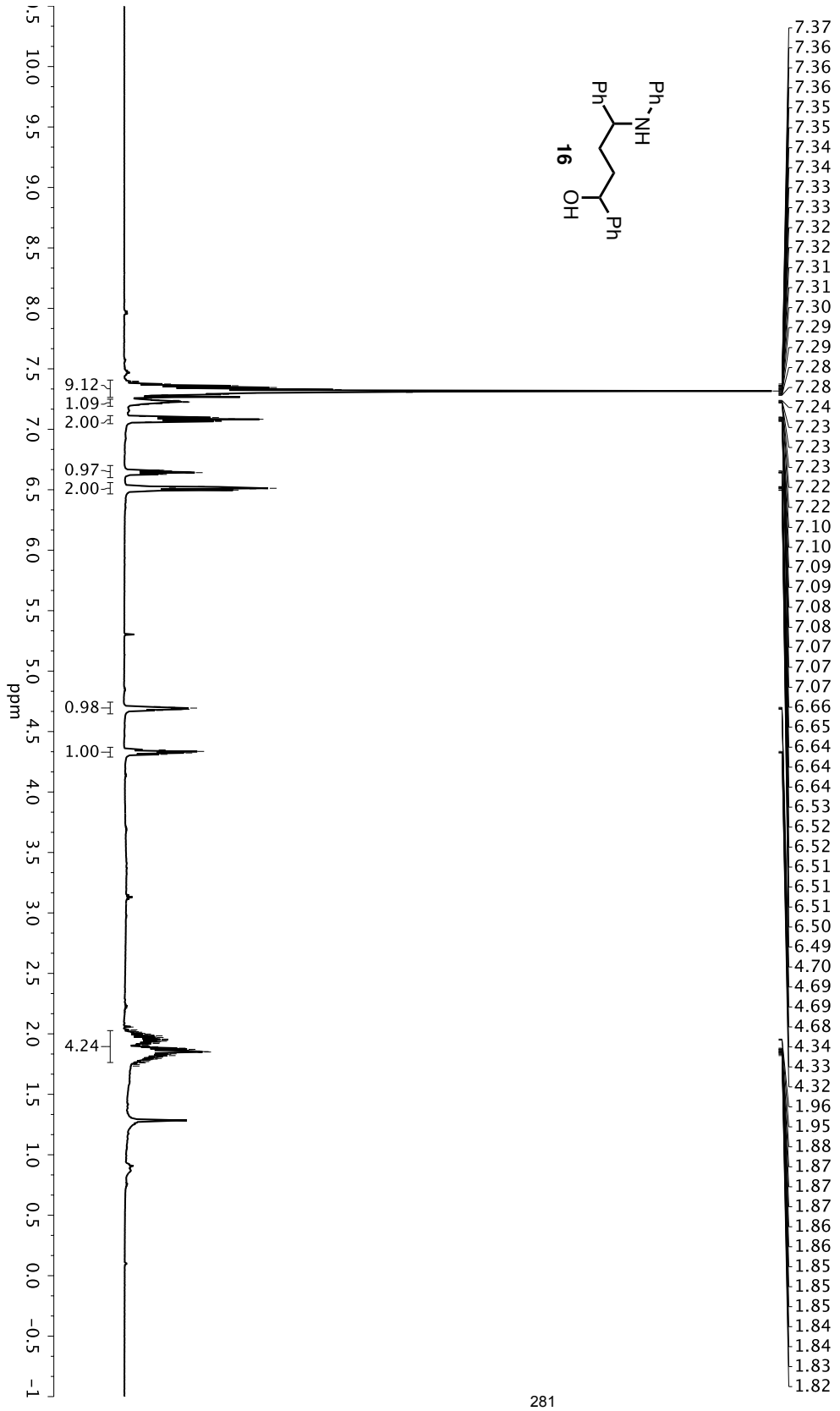
69.07
68.71
68.07
64.63
63.97
24.47
23.42
23.34
23.19
ppm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Ph
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Ph
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1.09
2.00
0.97
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0.98
1.00
4.24
ppm
7.37
7.36
7.36
7.36
7.35
7.35
7.34
7.34
7.33
7.33
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7.23
7.23
7.23
7.22
7.22
7.10
7.10
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7.09
7.08
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7.07
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6.52
6.52
6.51
6.51
6.51
6.50
6.49
4.70
4.69
4.69
4.68
4.34
4.33
4.32
1.96
1.95
1.88
1.87
1.87
1.87
1.86
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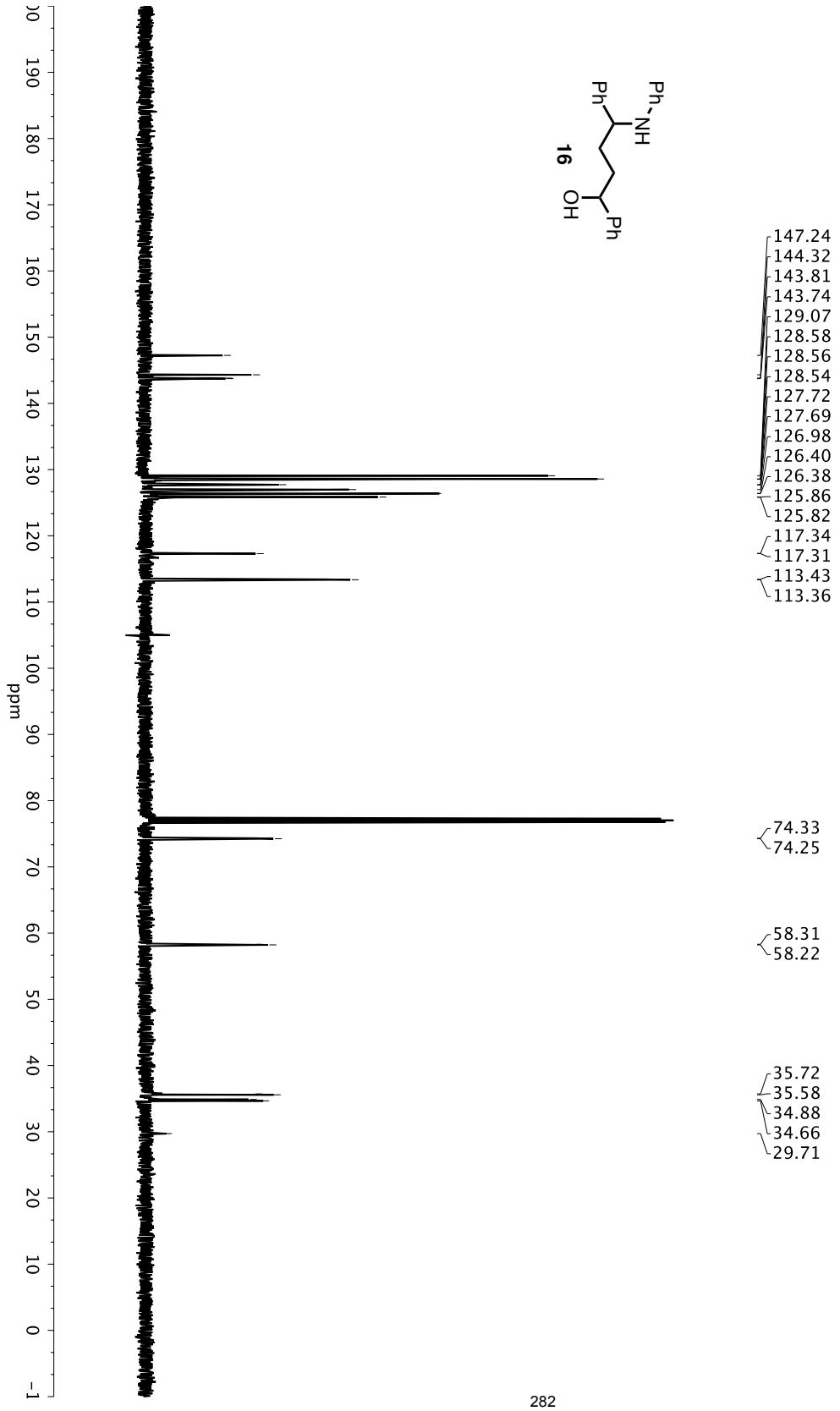
1.85
1.85
1.85
1.84
1.84
1.83
1.82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Ph
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OH
Ph
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144.32
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128.56
128.54
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126.98
126.40
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117.34
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74.33
74.25
58.31
58.22
35.72
35.58
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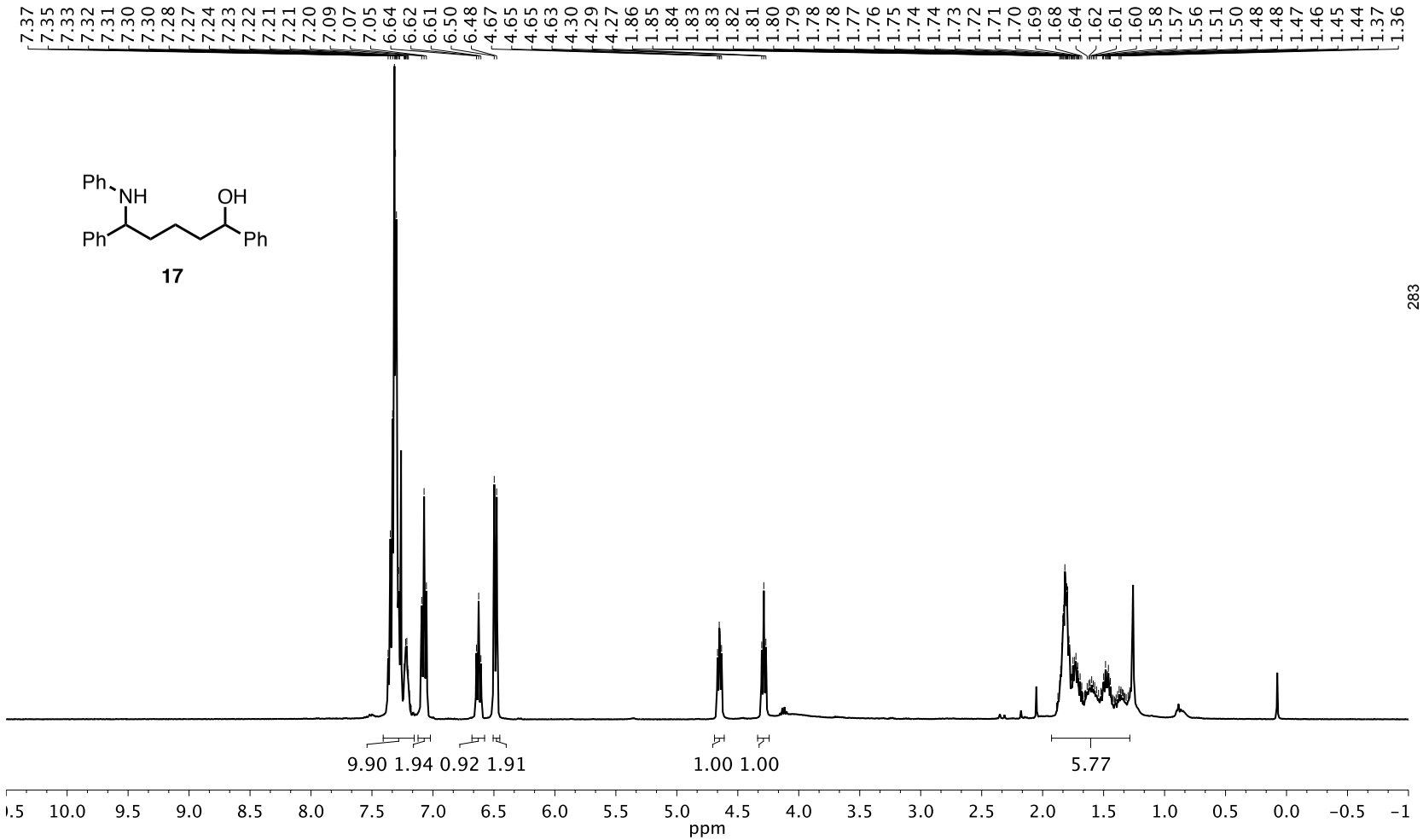
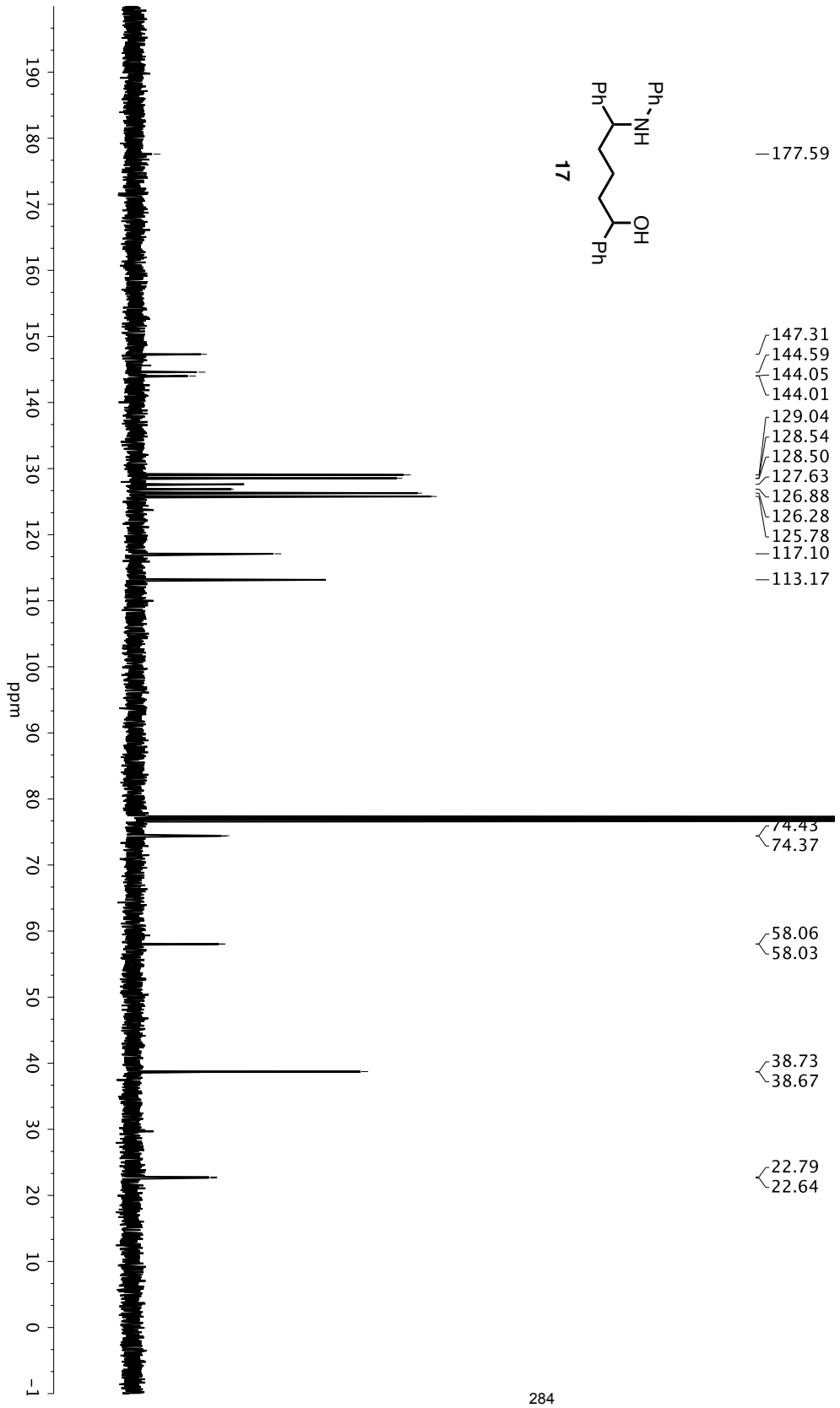
34.66
29.71
ppm


7.37 7.35 7.33 7.32 7.31 7.30 7.30 7.28 7.27 7.24 7.23 7.22 7.21 7.21 7.20 7.09 7.07 7.05 6.64 6.62 6.61 6.50 6.48 4.67 4.65 4.65 4.63 4.30 4.29 4.27 1.86 1.85 1.84 1.83 1.83 1.82 1.81 1.80 1.79 1.78 1.78 1.77 1.76 1.75 1.74 1.74 1.73 1.72 1.71 1.70 1.69 1.68 1.64 1.62 1.61 1.60 1.58 1.57 1.56 1.51 1.50 1.48 1.48 1.47 1.46 1.45 1.44 1.37 1.36
Ph
NH
OH
Ph
Ph
17
283
9.90 1.94 0.92 1.91
1.00 1.00
5.77
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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Ph
OH
Ph
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144.01
129.04
128.54
128.50
127.63
126.88
126.28
125.78
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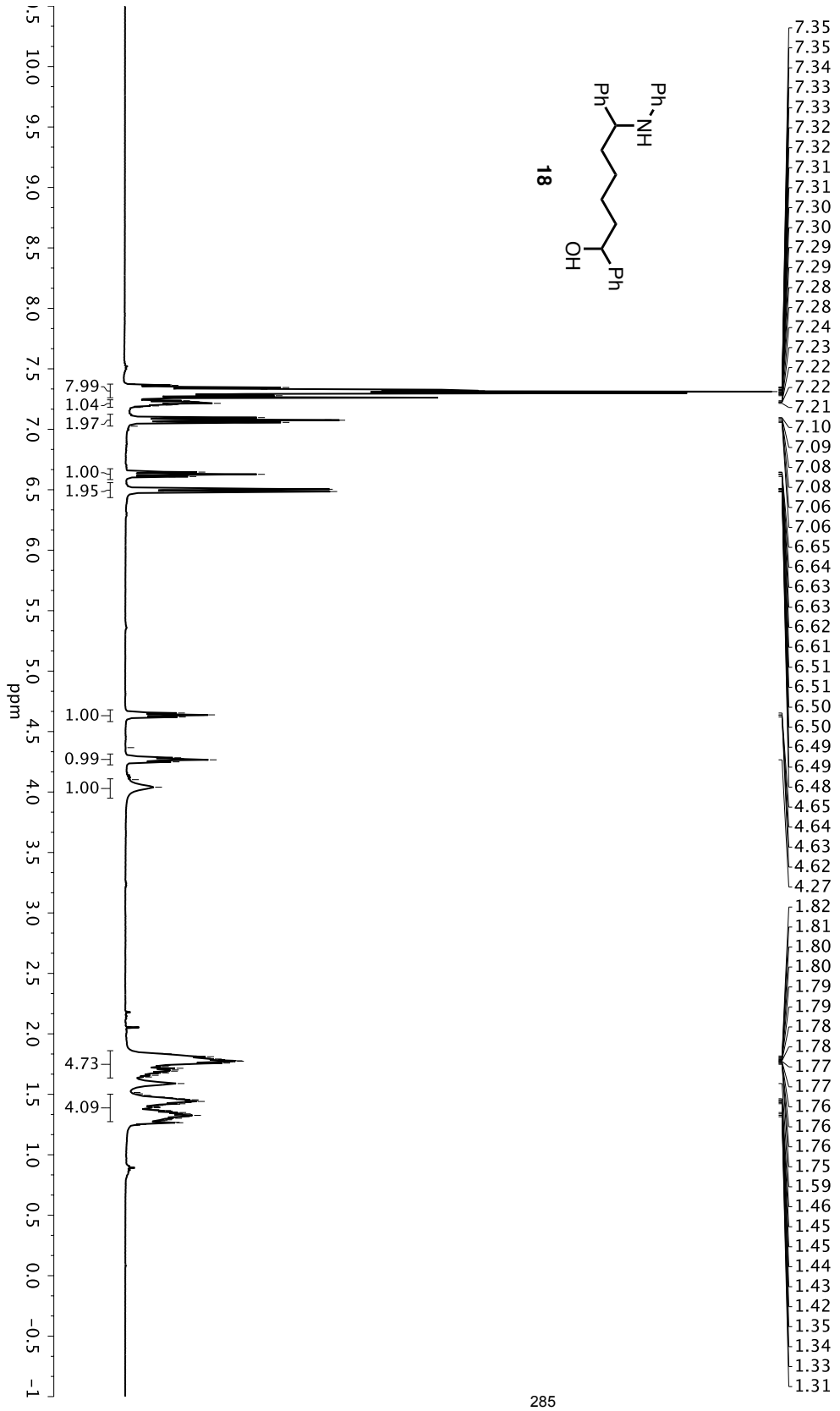
113.17
74.43
74.37
58.06
58.03
38.73
38.67
22.79
22.64
ppm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NH
Ph
OH
Ph
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1.00
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1.00
0.99
1.00
4.73
4.09
ppm
7.35
7.35
7.34
7.33
7.33
7.32
7.32
7.31
7.31
7.30
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7.29
7.28
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7.22
7.21
7.10
7.09
7.08
7.08
7.06
7.06
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6.64
6.63
6.63
6.62
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6.51
6.51
6.50
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6.49
6.49
6.48
4.65
4.64
4.63
4.62
4.27
1.82
1.81
1.80
1.80
1.79
1.79
1.78
1.78
1.77
1.77
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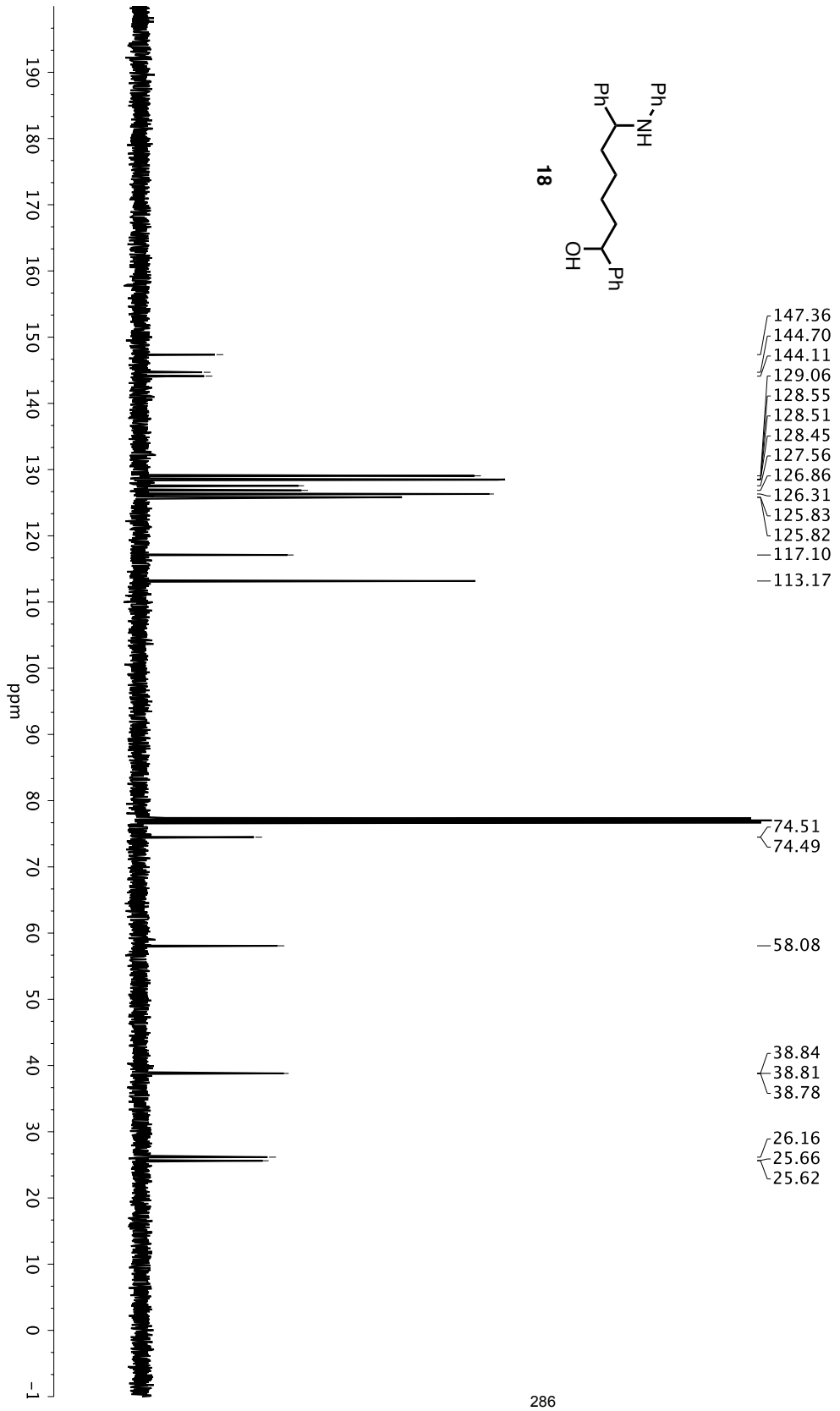
1.31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128.45
127.56
126.86
126.31
125.83
125.82
117.10
113.17
74.51
74.49
58.08
38.84
38.81
38.78
26.16
25.66
25.62
ppm
190
180
170
160
150
140
130
120
110
100
90
80
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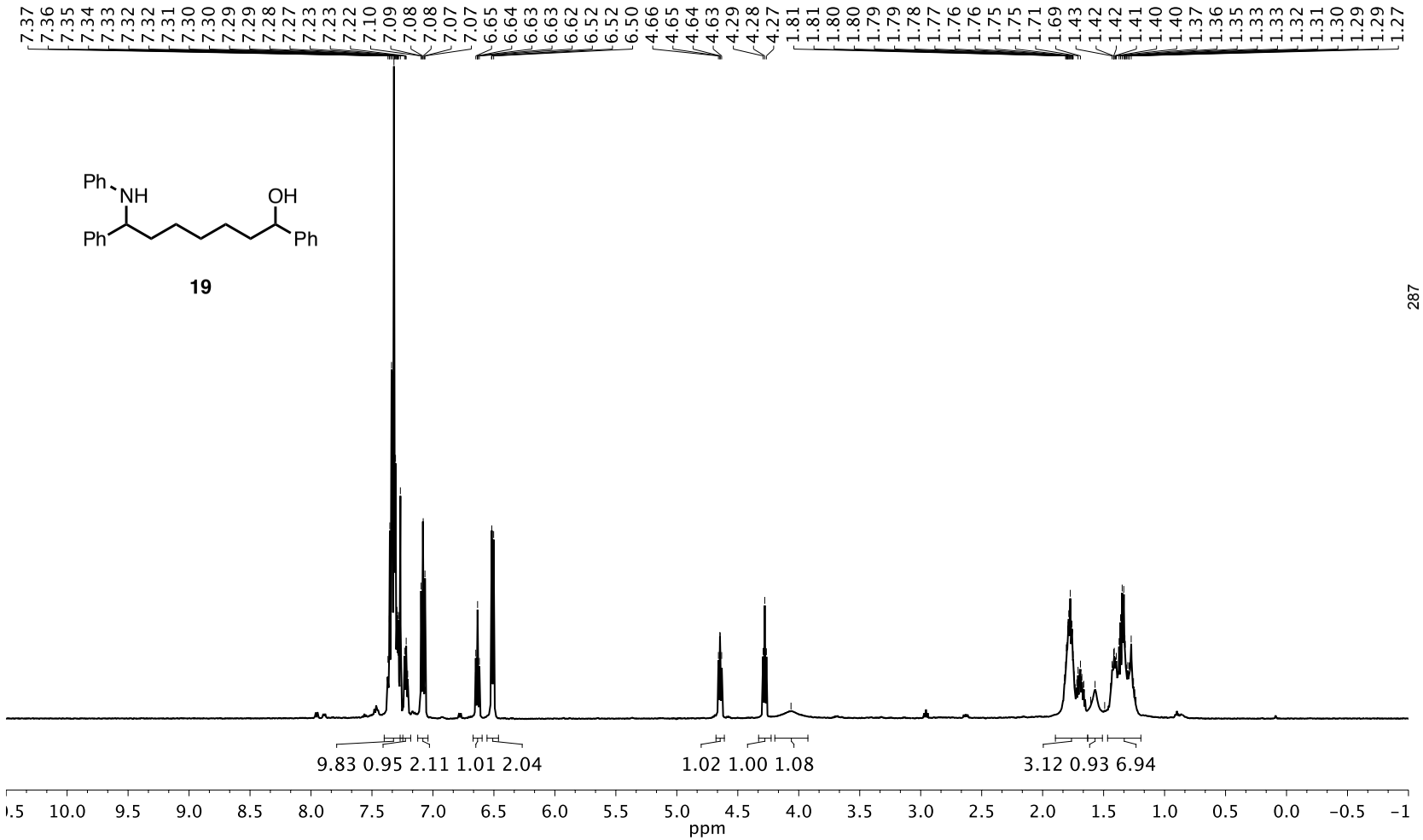
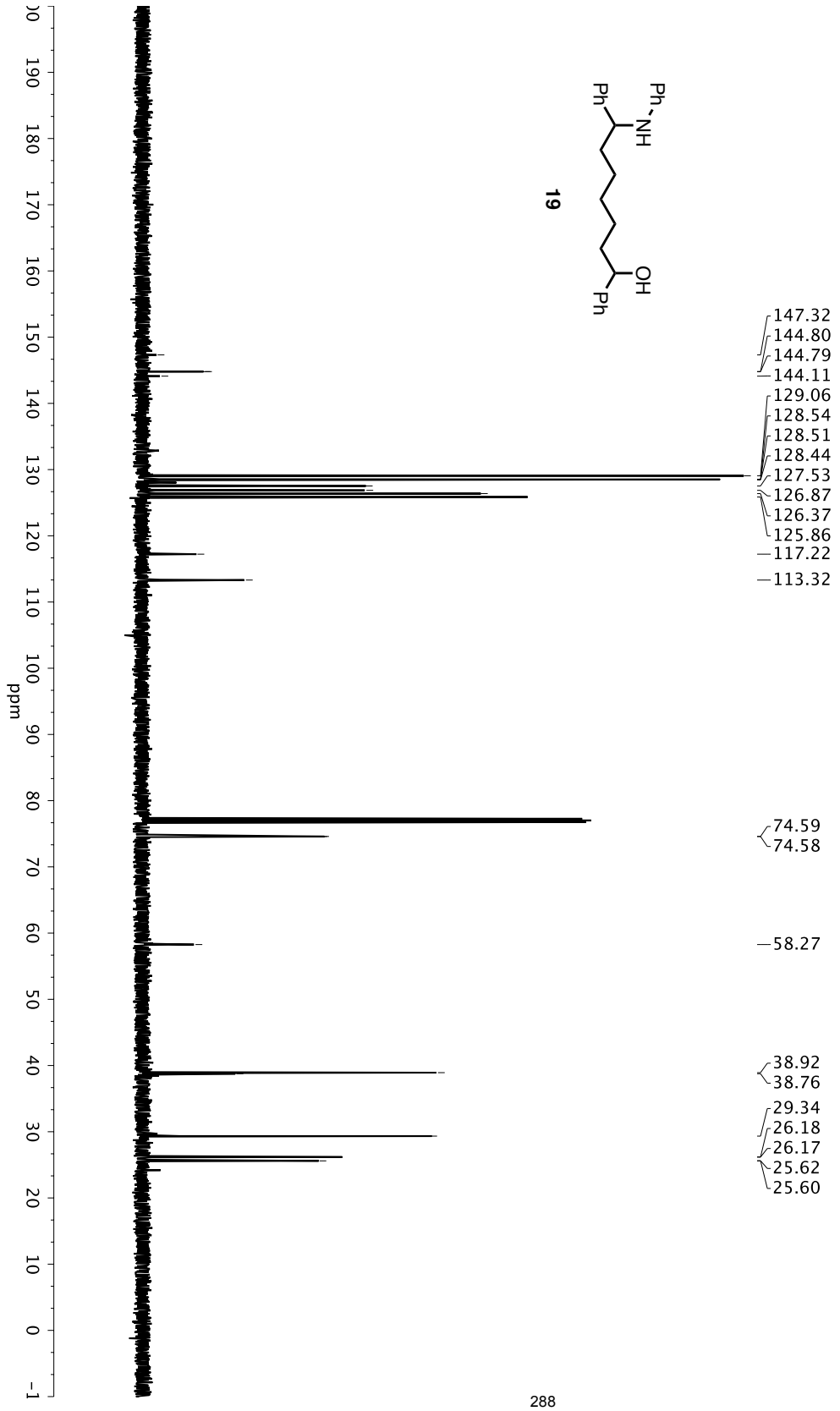
60
50
40
30
20
10
0
-1


7.37 7.36 7.35 7.34 7.33 7.32 7.32 7.31 7.30 7.30 7.29 7.29 7.28 7.27 7.23 7.23 7.22 7.10 7.09 7.08 7.08 7.07 7.07 6.65 6.64 6.63 6.63 6.62 6.52 6.52 6.50 4.66 4.65 4.64 4.63 4.29 4.28 4.27 1.81 1.81 1.80 1.80 1.79 1.79 1.78 1.77 1.76 1.76 1.75 1.75 1.71 1.69 1.43 1.42 1.42 1.41 1.40 1.40 1.37 1.36 1.35 1.33 1.33 1.32 1.31 1.30 1.29 1.29 1.27
Ph
NH
OH
Ph
Ph
19
287
9.83 0.95 2.11 1.01 2.04
1.02 1.00 1.08
3.12 0.93 6.94
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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125.86
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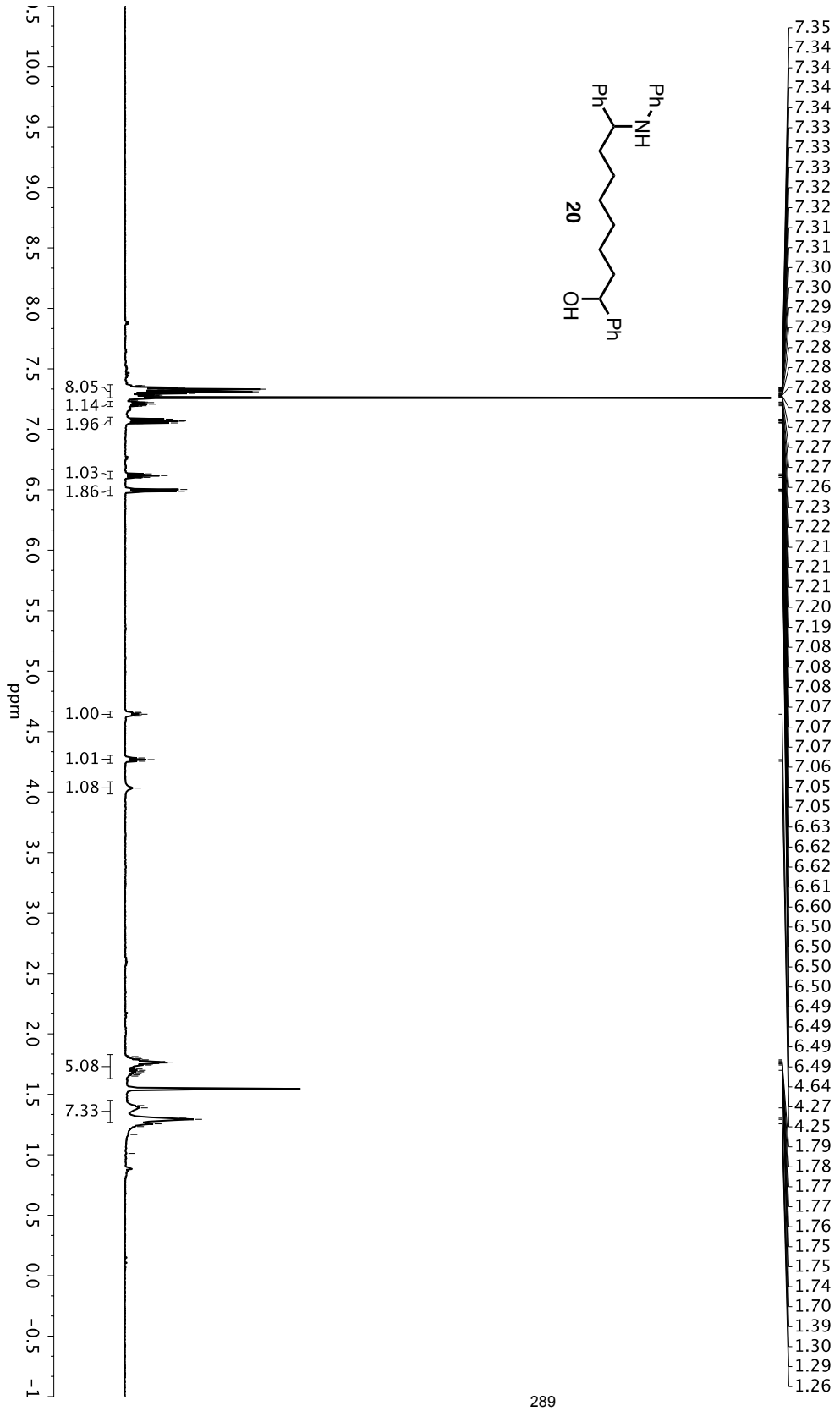
ppm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1.01
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ppm
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7.19
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7.08
7.08
7.07
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7.06
7.05
7.05
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6.62
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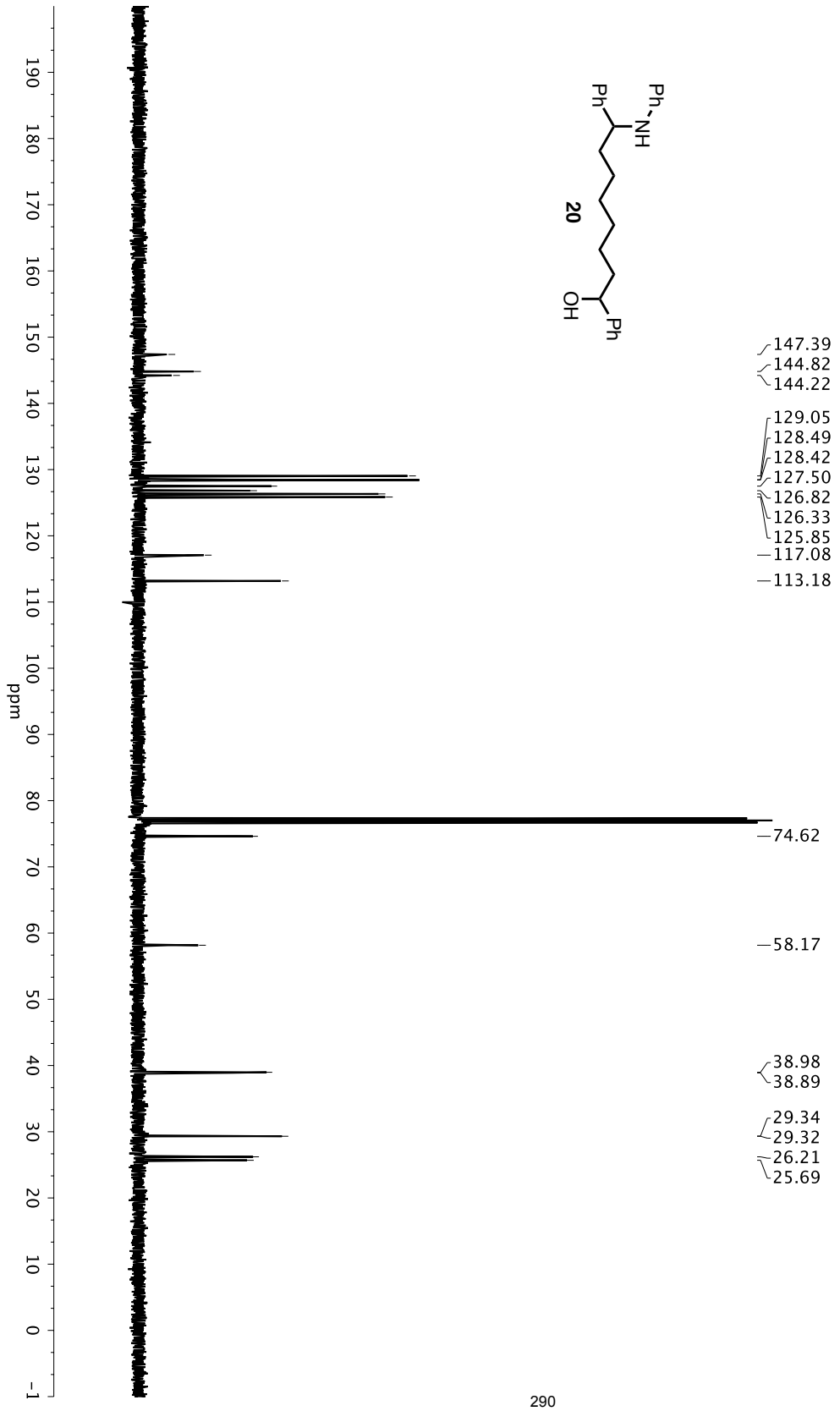
1.29
1.26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OH
Ph
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126.82
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125.85
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113.18
74.62
58.17
38.98
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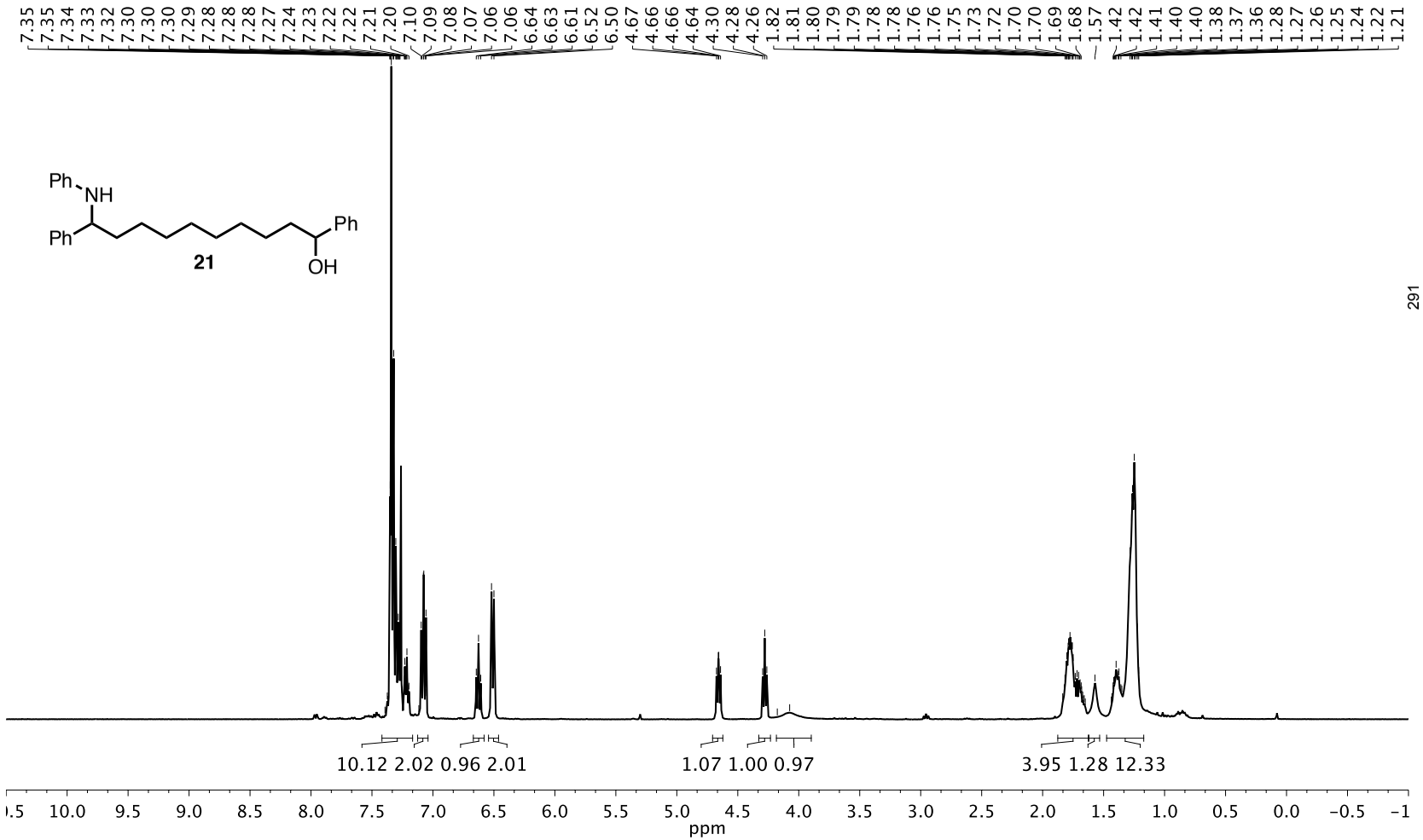
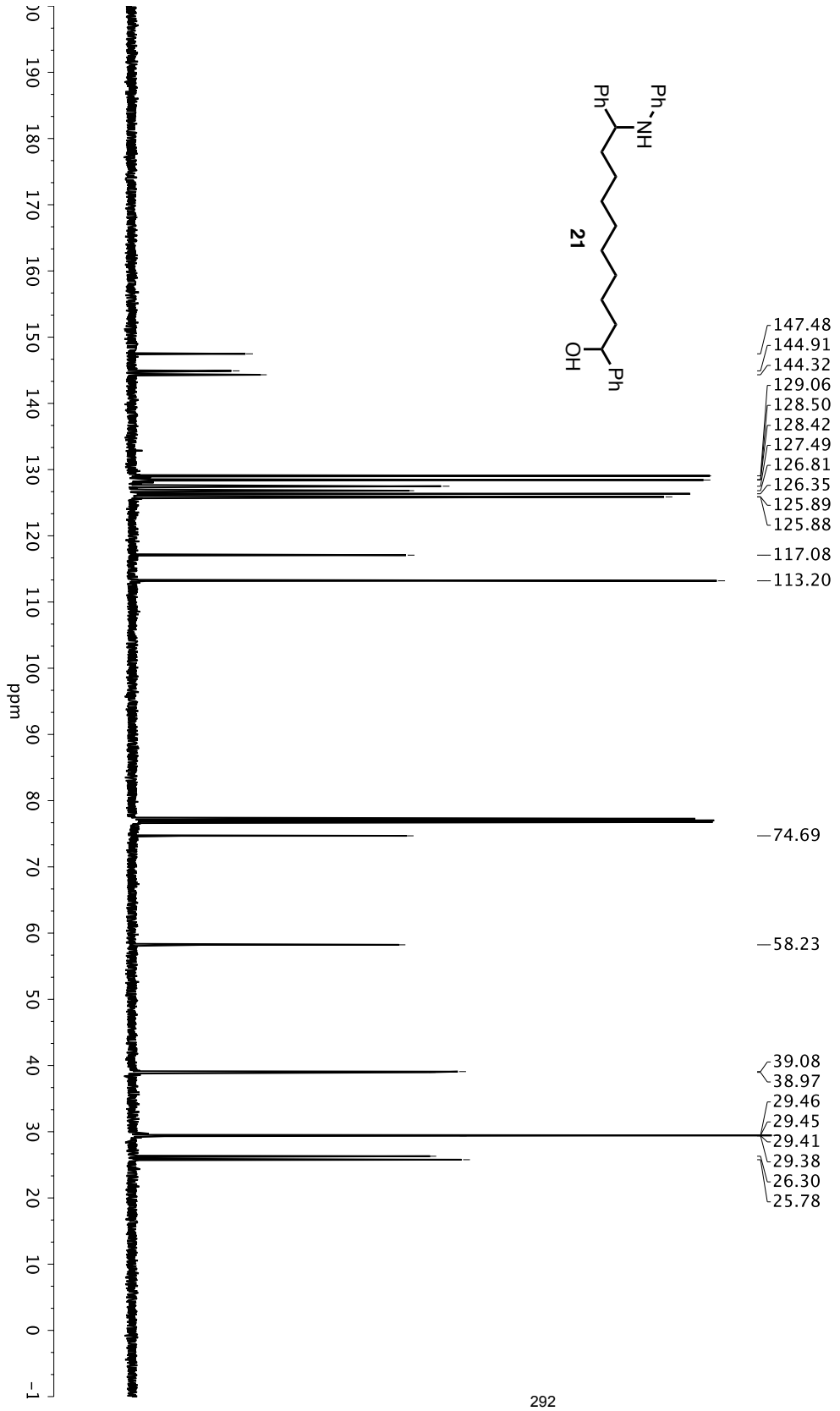
29.34
29.32
26.21
25.69
ppm


7.35 7.35 7.34 7.33 7.32 7.30 7.30 7.30 7.29 7.28 7.28 7.28 7.27 7.24 7.23 7.22 7.22 7.21 7.20 7.10 7.09 7.08 7.07 7.06 7.06 6.64 6.63 6.61 6.52 6.50 4.67 4.66 4.66 4.64 4.30 4.28 4.26 1.82 1.81 1.80 1.79 1.79 1.78 1.78 1.76 1.76 1.75 1.73 1.72 1.70 1.70 1.69 1.68 1.57 1.42 1.42 1.41 1.40 1.40 1.38 1.37 1.36 1.28 1.27 1.26 1.25 1.24 1.22 1.21
Ph
NH
Ph
Ph
OH
21
291
10.12 2.02 0.96 2.01
1.07 1.00 0.97
3.95 1.28 12.33
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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OH
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127.49
126.81
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125.89
125.88
117.08
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58.23
39.08
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29.41
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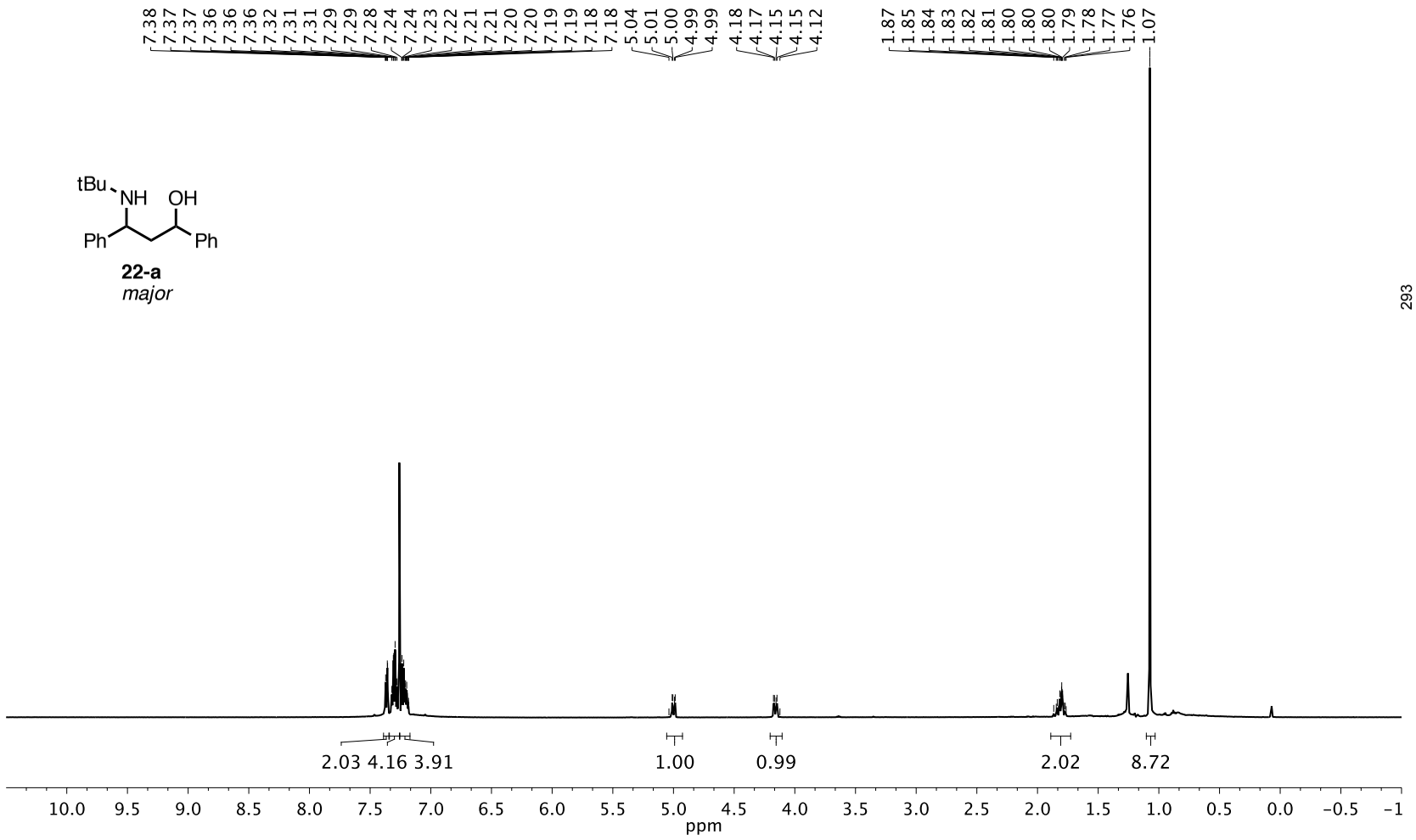
26.30
25.78
ppm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7.18
7.18
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5.01
5.00
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4.18
4.17
4.15
4.15
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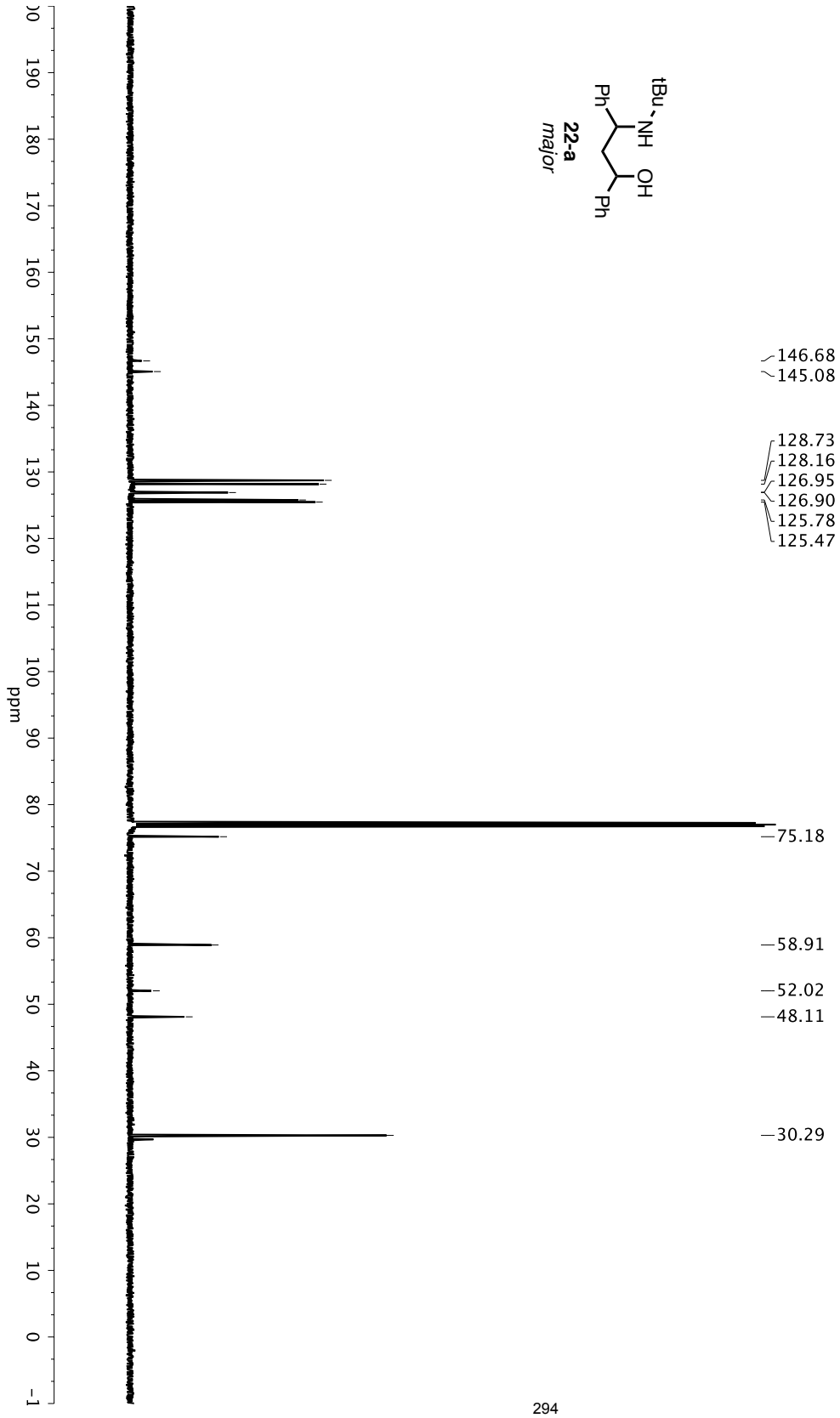
1.78
1.77
1.76
1.07
tBu
NH
OH
Ph
Ph
22-a
major
293
2.03 4.16 3.91
1.00
0.99
2.02
8.72
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
ppm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OH
Ph
Ph
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125.47
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58.91
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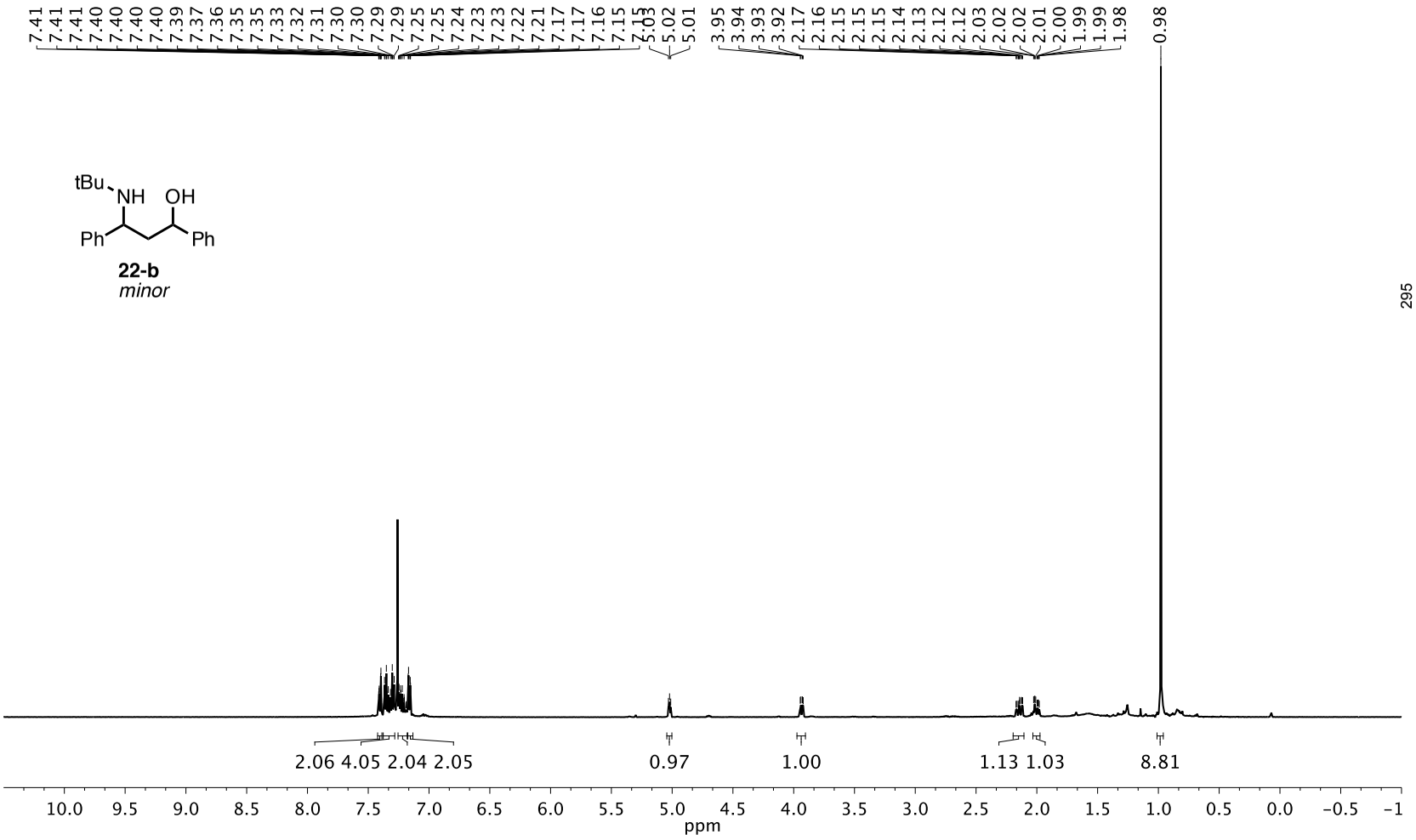
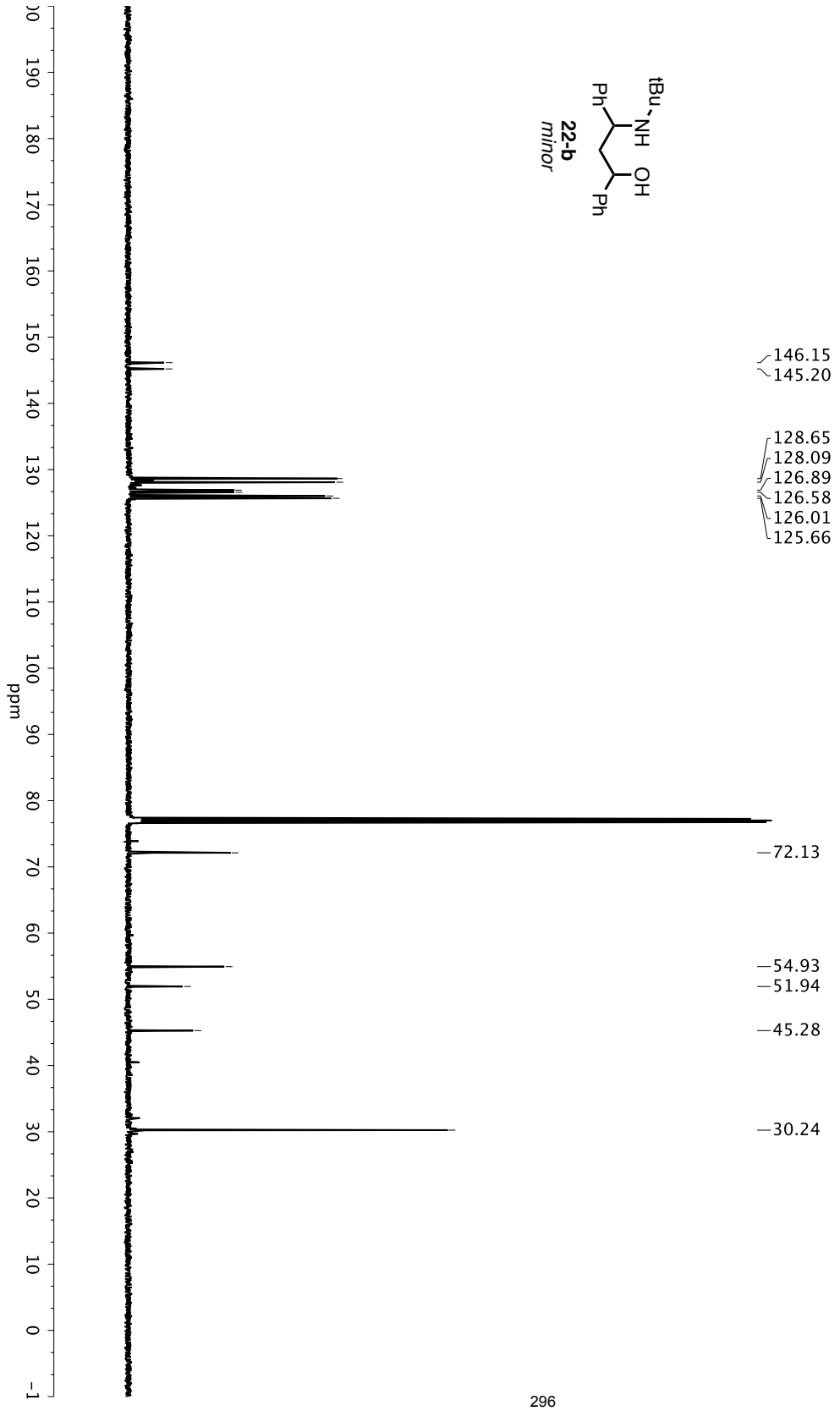
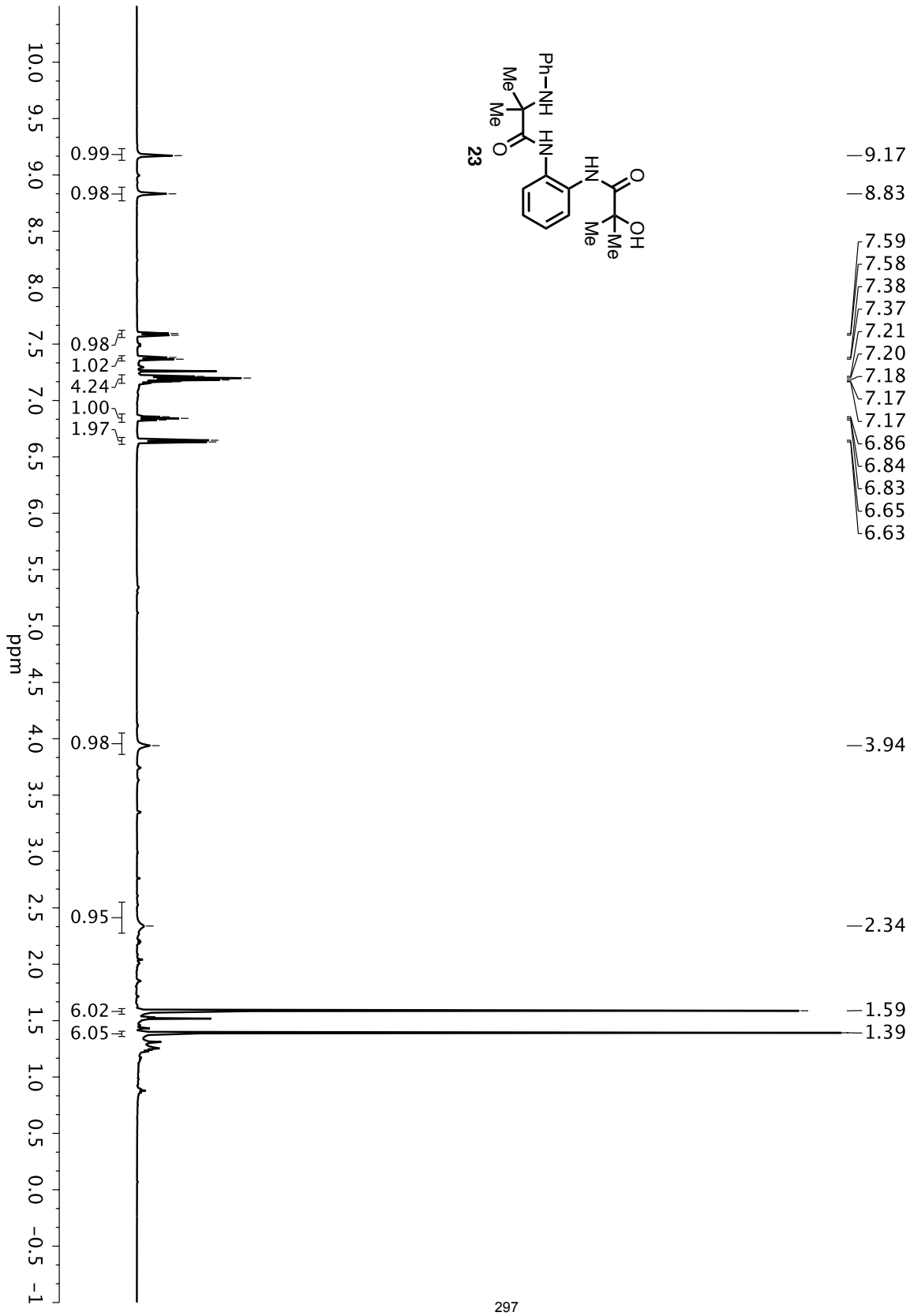
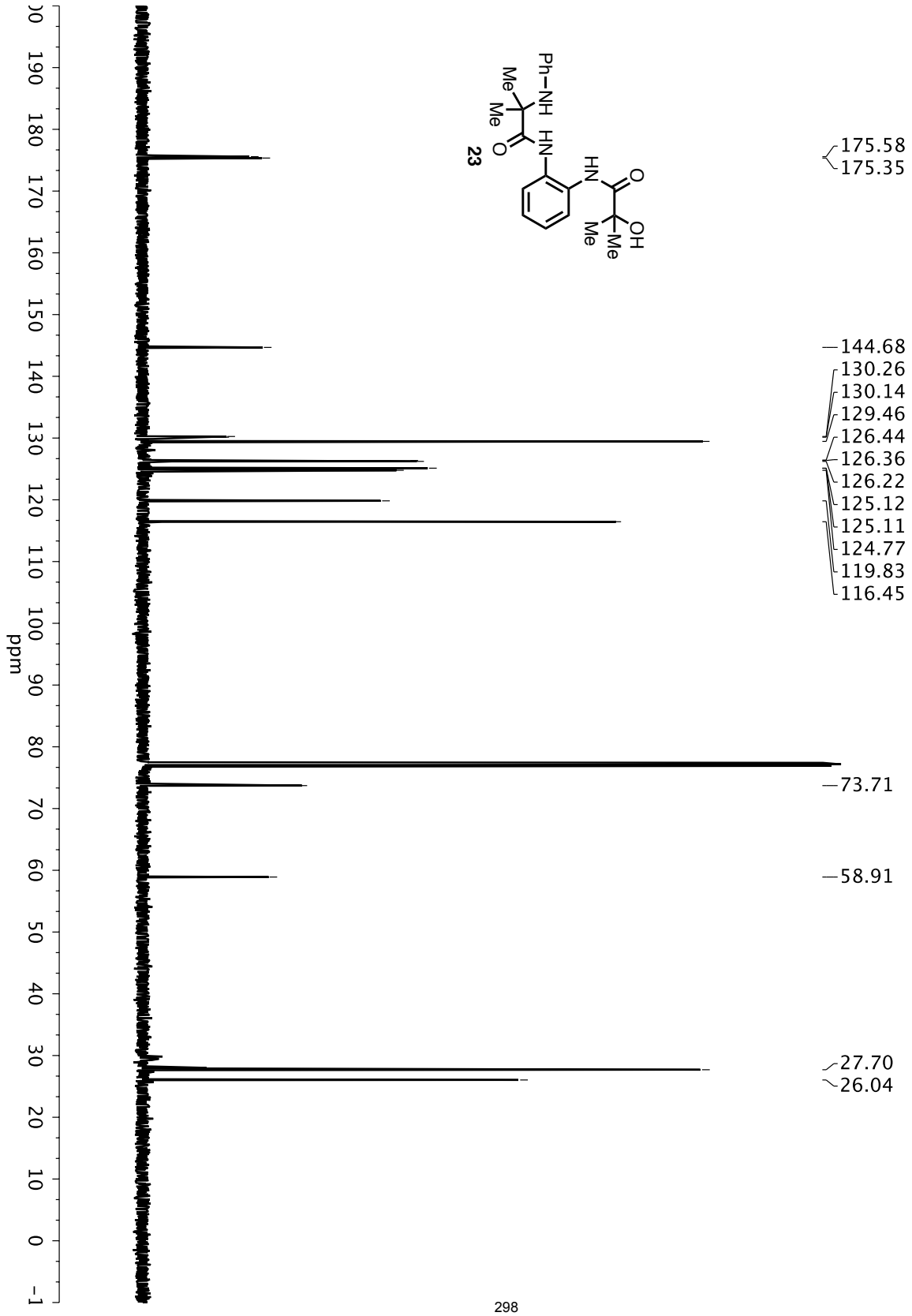
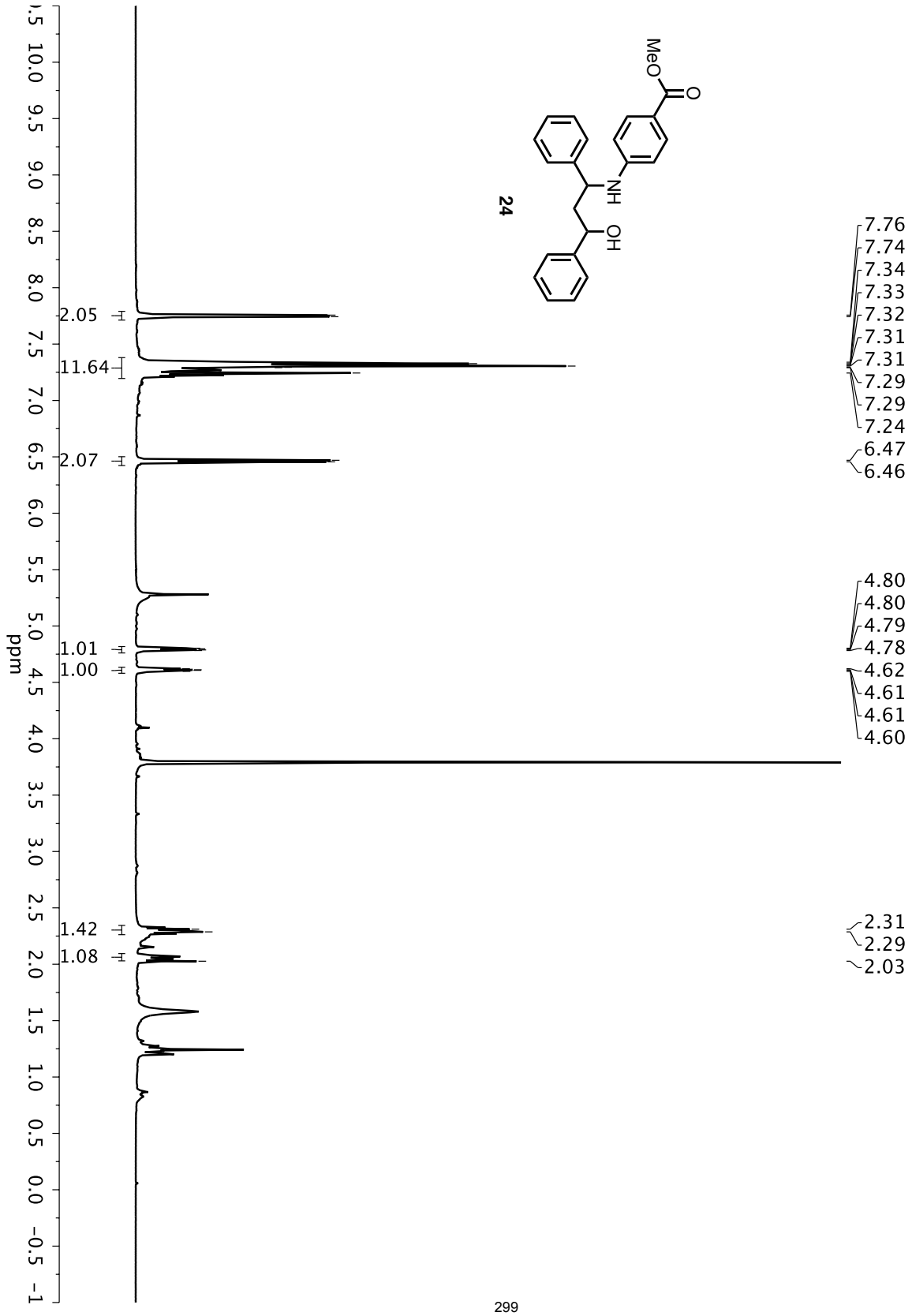
48.11
30.29
ppm

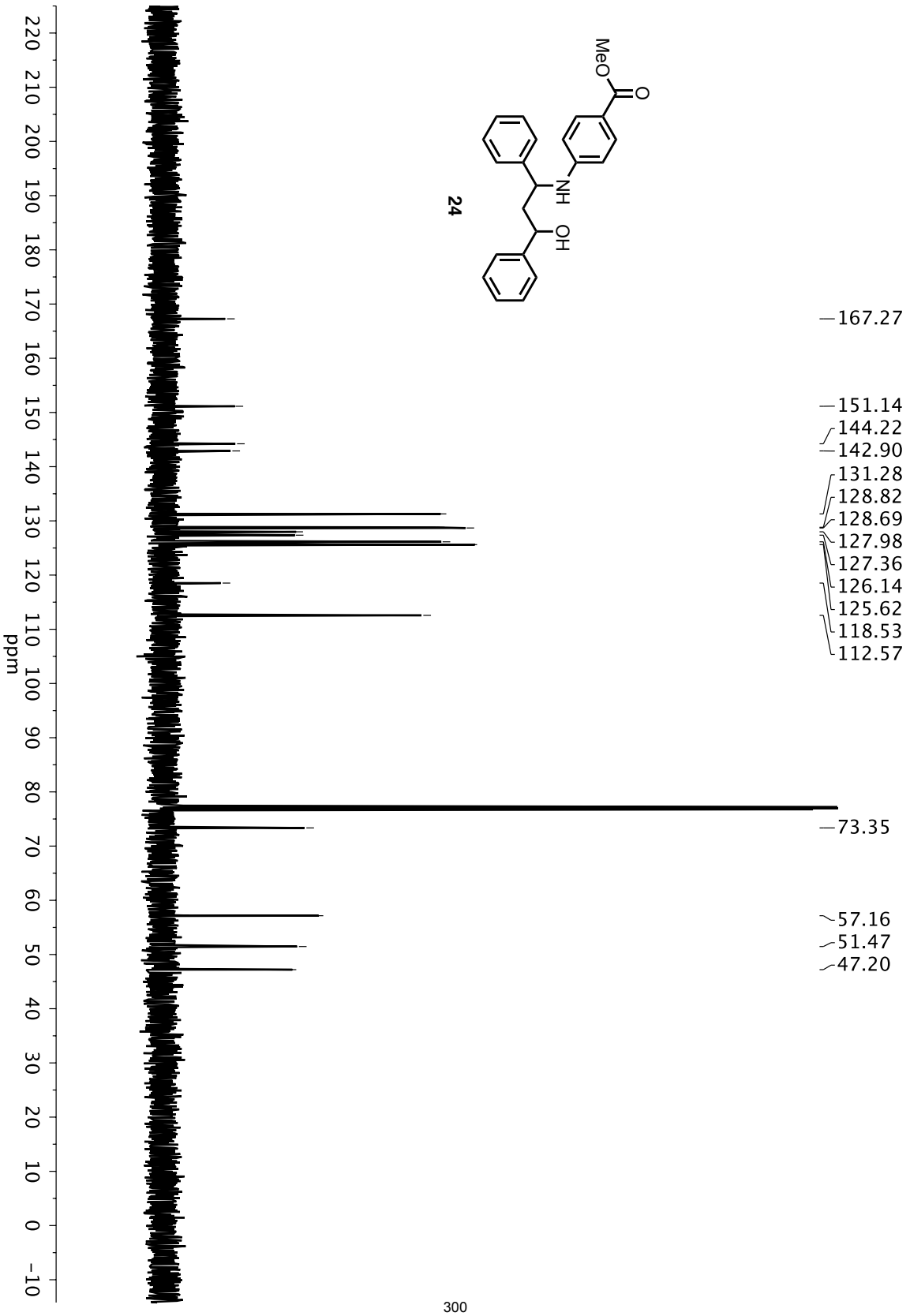

7.41 7.41 7.41 7.40 7.40 7.40 7.39 7.37 7.36 7.35 7.35 7.33 7.32 7.31 7.30 7.30 7.29 7.29 7.25 7.25 7.24 7.23 7.23 7.22 7.21 7.17 7.17 7.16 7.15 7.15 5.03 5.02 5.01
3.95 3.94 3.93 3.92 2.17 2.16 2.15 2.15 2.15 2.14 2.13 2.12 2.12 2.03 2.02 2.02 2.01 2.00 1.99 1.99 1.98
0.98
tBu
NH
OH
Ph
Ph
22-b
minor
295
2.06 4.05 2.04 2.05
0.97
1.00
1.13 1.03
8.81
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

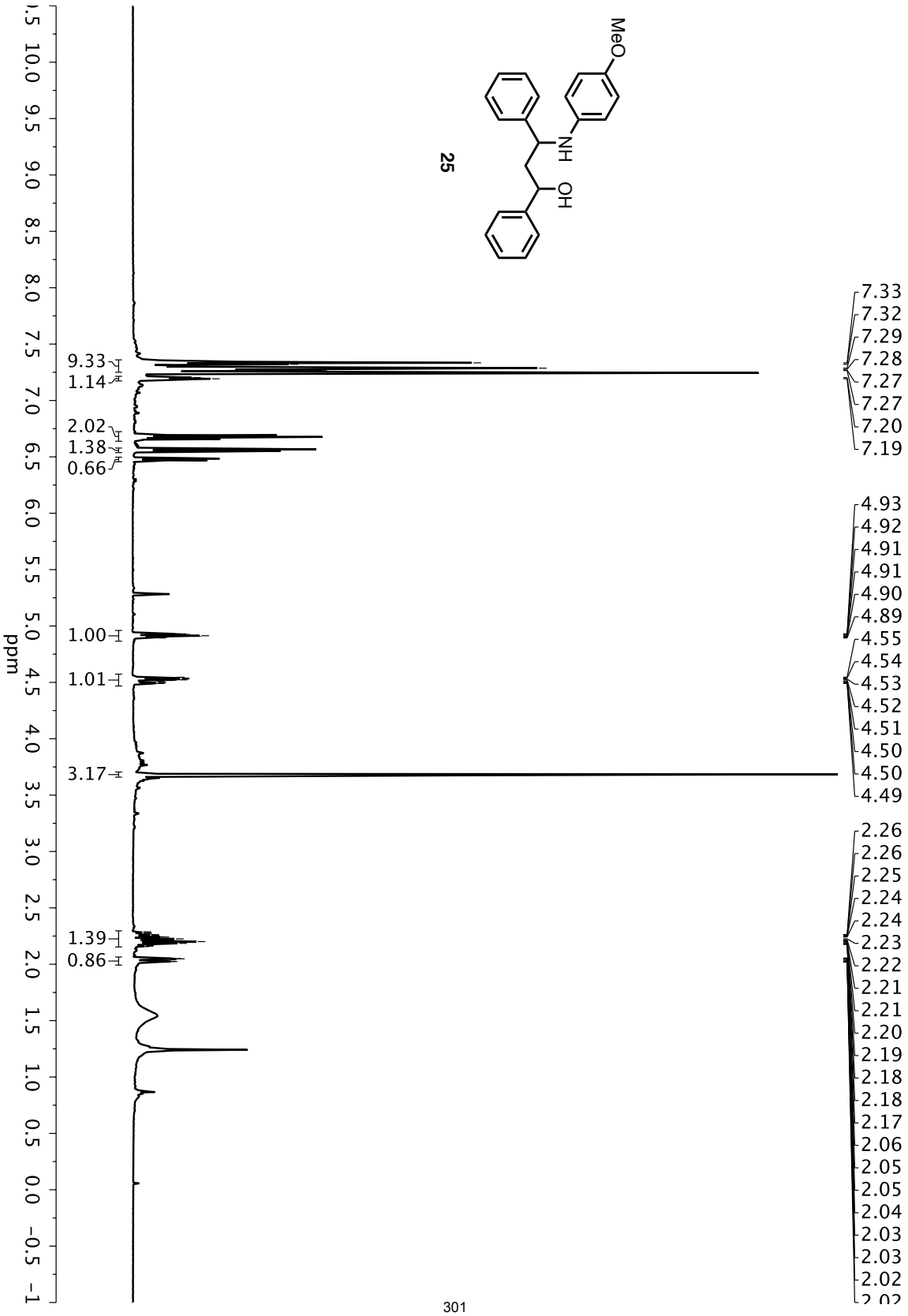

tBu
NH
OH
Ph
Ph
22-b
minor
146.15
145.20
128.65
128.09
126.89
126.58
126.01
125.66
72.13
54.93
51.94
45.28
30.24
ppm

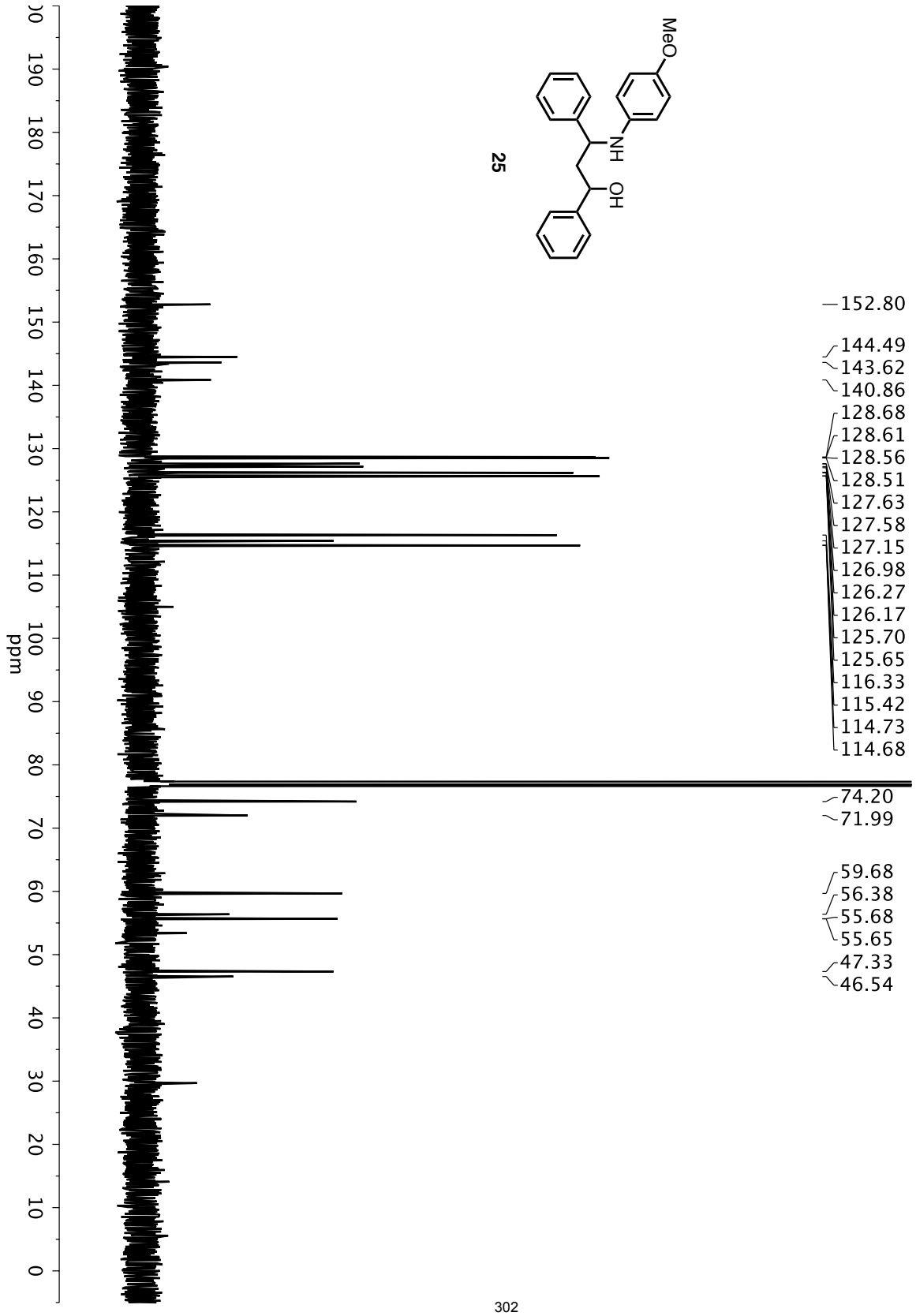

Ph–NH HN
Me
Me
O
23
HN
O
OH
Me
Me
ppm
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
0.99
0.98
0.98
1.02
4.24
1.00
1.97
0.98
0.95
6.02
6.05
9.17
8.83
7.59
7.58
7.38
7.37
7.21
7.20
7.18
7.17
7.17
6.86
6.84
6.83
6.65
6.63
3.94
2.34
1.59
1.39

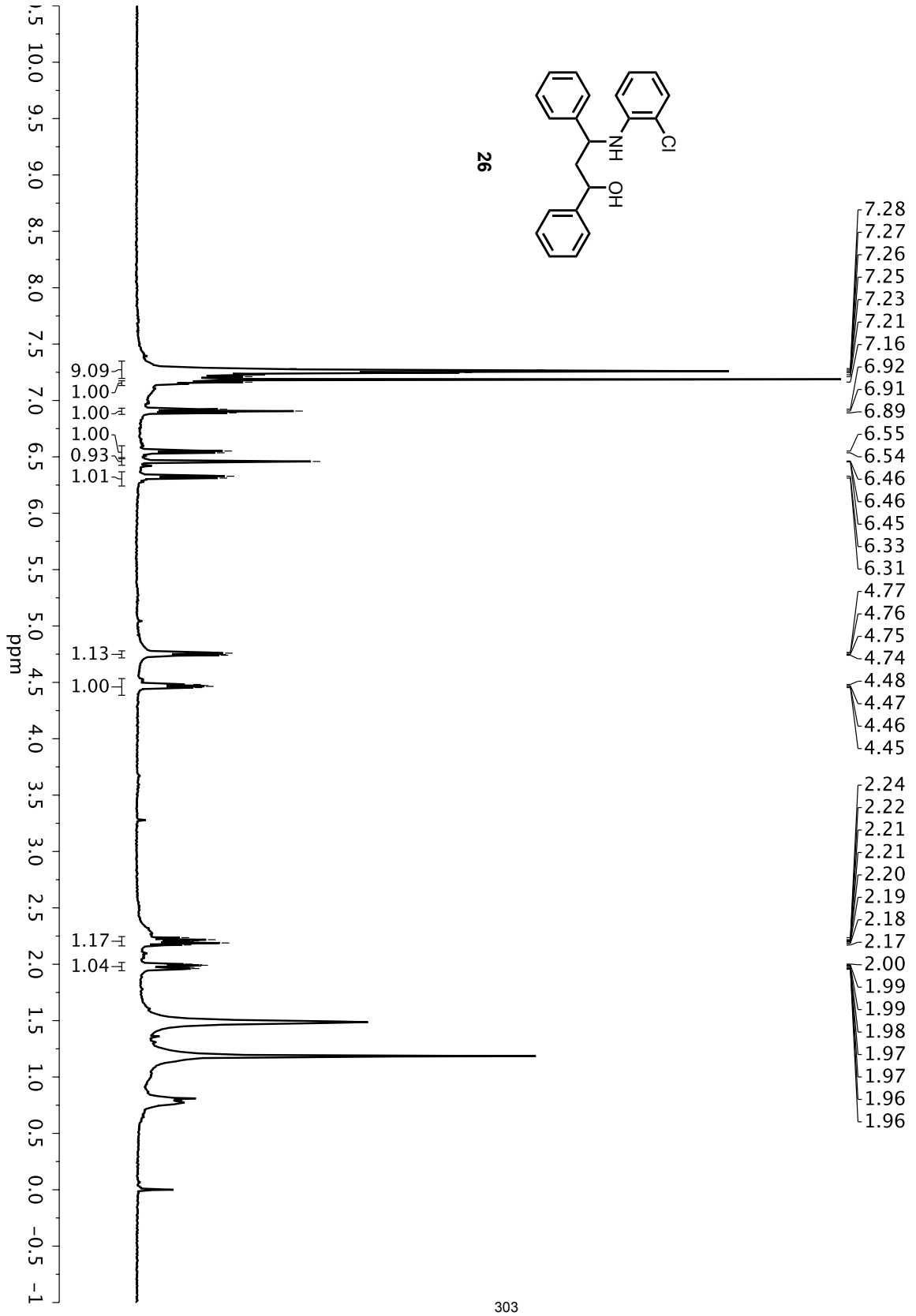

Ph–NH
HN
Me
Me
O
23
HN
O
OH
Me
Me
175.58
175.35
144.68
130.26
130.14
129.46
126.44
126.36
126.22
125.12
125.11
124.77
119.83
116.45
73.71
58.91
27.70
26.04
ppm

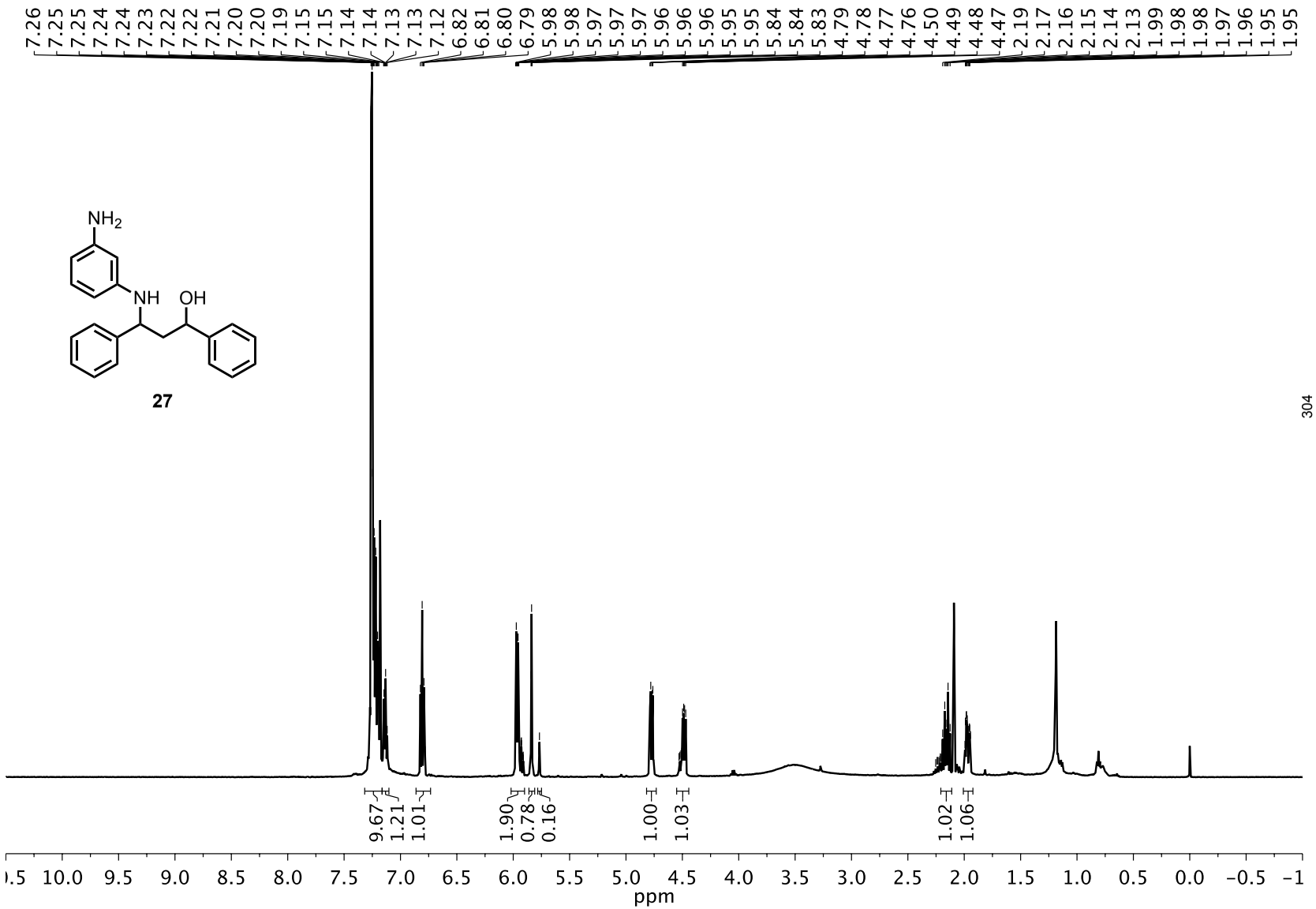

MeO
O
NH
OH
24
7.76
7.74
7.34
7.33
7.32
7.31
7.31
7.29
7.29
7.24
6.47
6.46
4.80
4.80
4.79
4.78
4.62
4.61
4.61
4.60
2.31
2.29
2.03
2.05
11.64
2.07
1.01
1.00
1.42
1.08
ppm

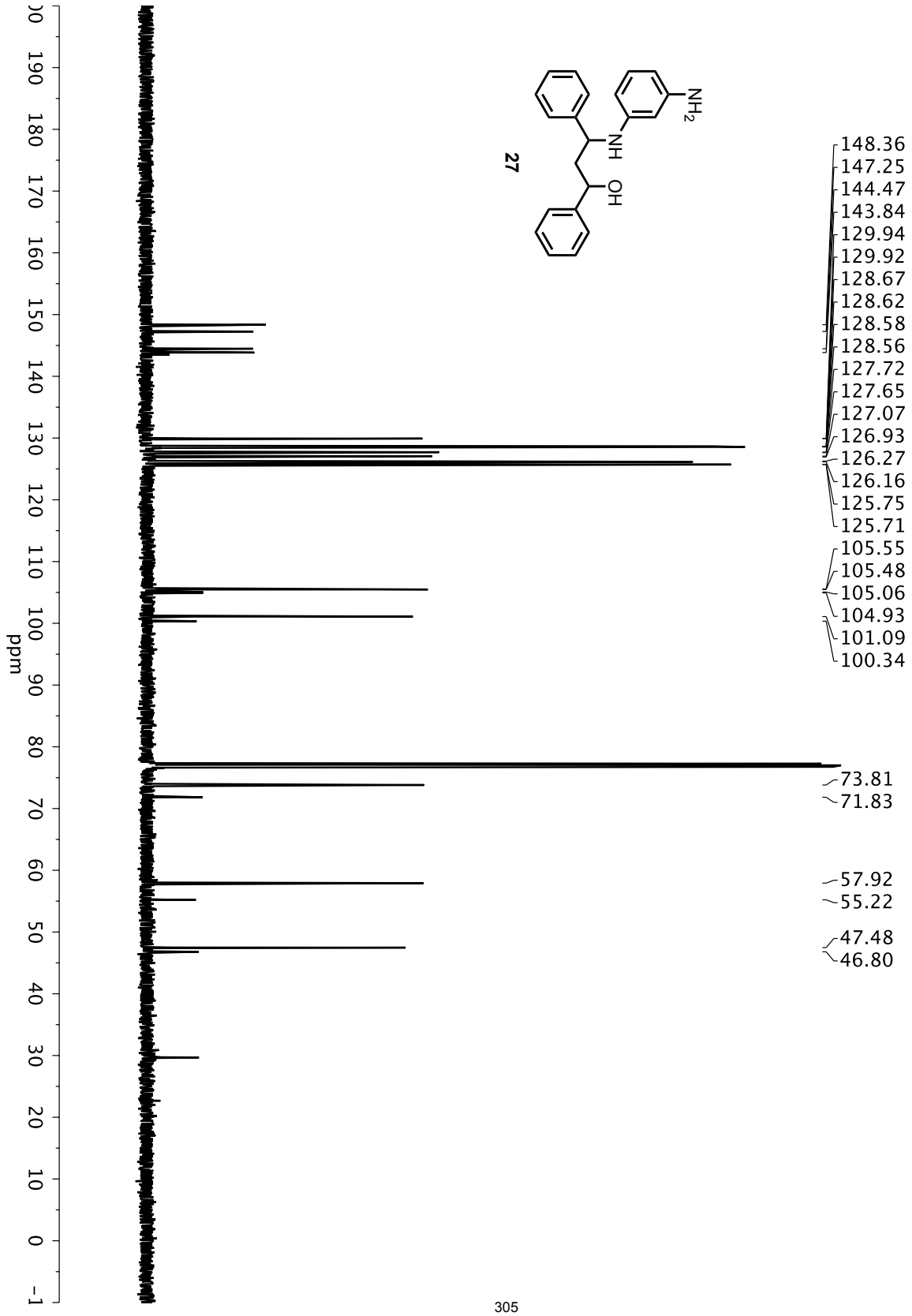

MeO
O
NH
OH
24
167.27
151.14
144.22
142.90
131.28
128.82
128.69
127.98
127.36
126.14
125.62
118.53
112.57
73.35
57.16
51.47
47.20
ppm
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

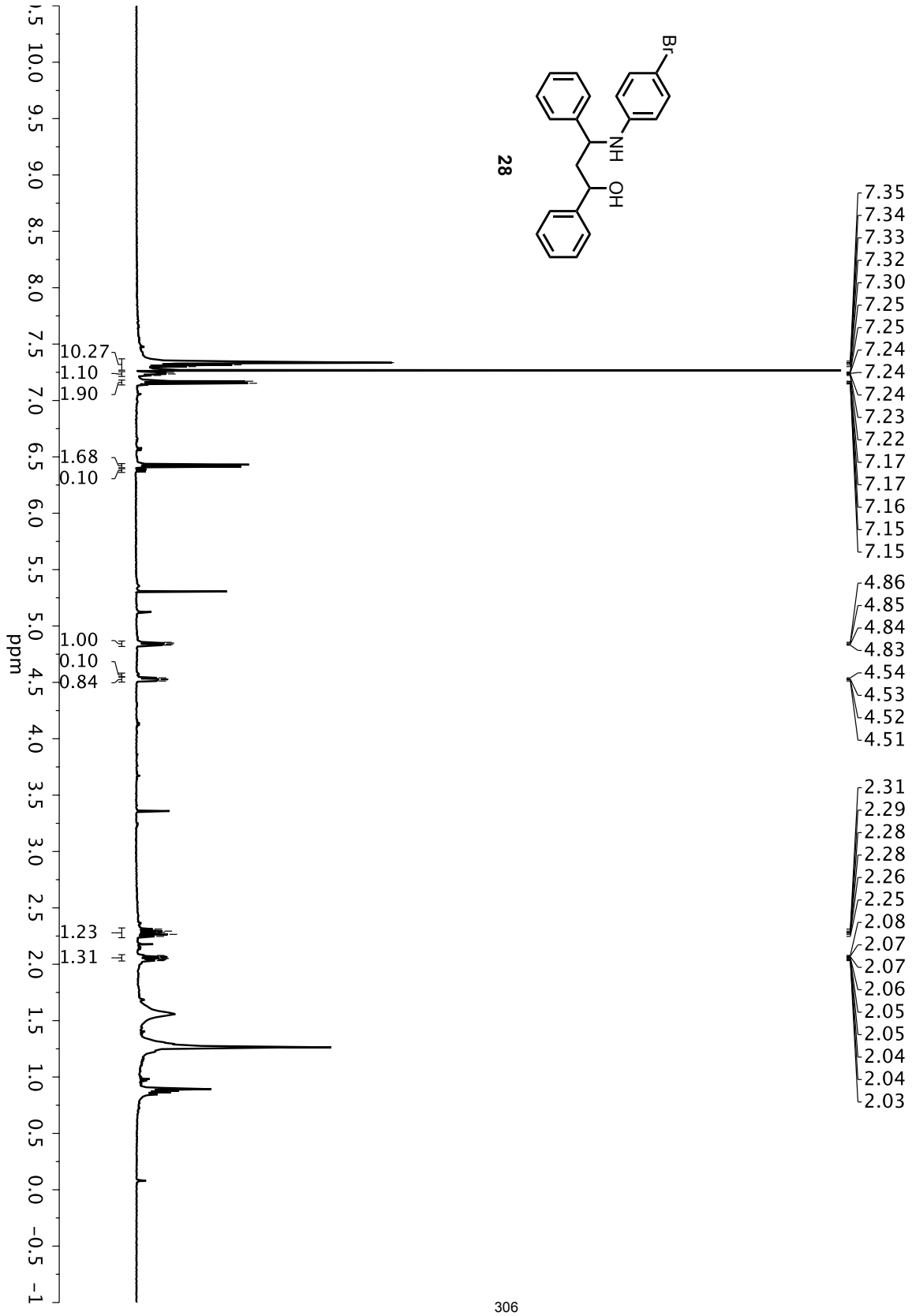

MeO
NH
OH
25
9.33
1.14
2.02
1.38
0.66
1.00
1.01
3.17
1.39
0.86
7.33
7.32
7.29
7.28
7.27
7.27
7.20
7.19
4.93
4.92
4.91
4.91
4.90
4.89
4.55
4.54
4.53
4.52
4.51
4.50
4.50
4.49
2.26
2.26
2.25
2.24
2.24
2.23
2.22
2.21
2.21
2.20
2.19
2.18
2.18
2.17
2.06
2.05
2.05
2.04
2.03
2.03
2.02
ppm

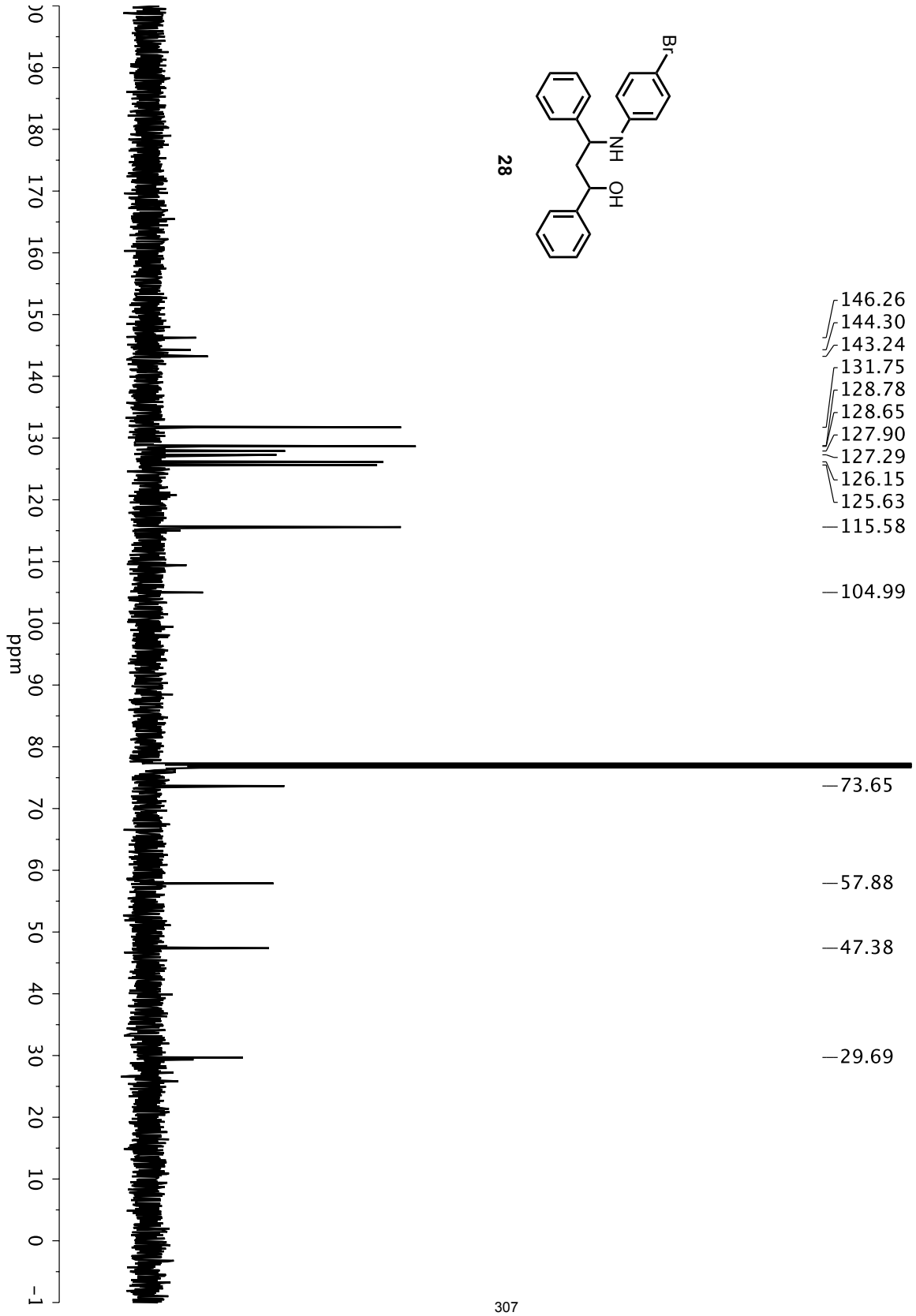

25
MeO
NH
OH
152.80
144.49
143.62
140.86
128.68
128.61
128.56
128.51
127.63
127.58
127.15
126.98
126.27
126.17
125.70
125.65
116.33
115.42
114.73
114.68
74.20
71.99
59.68
56.38
55.68
55.65
47.33
46.54
ppm

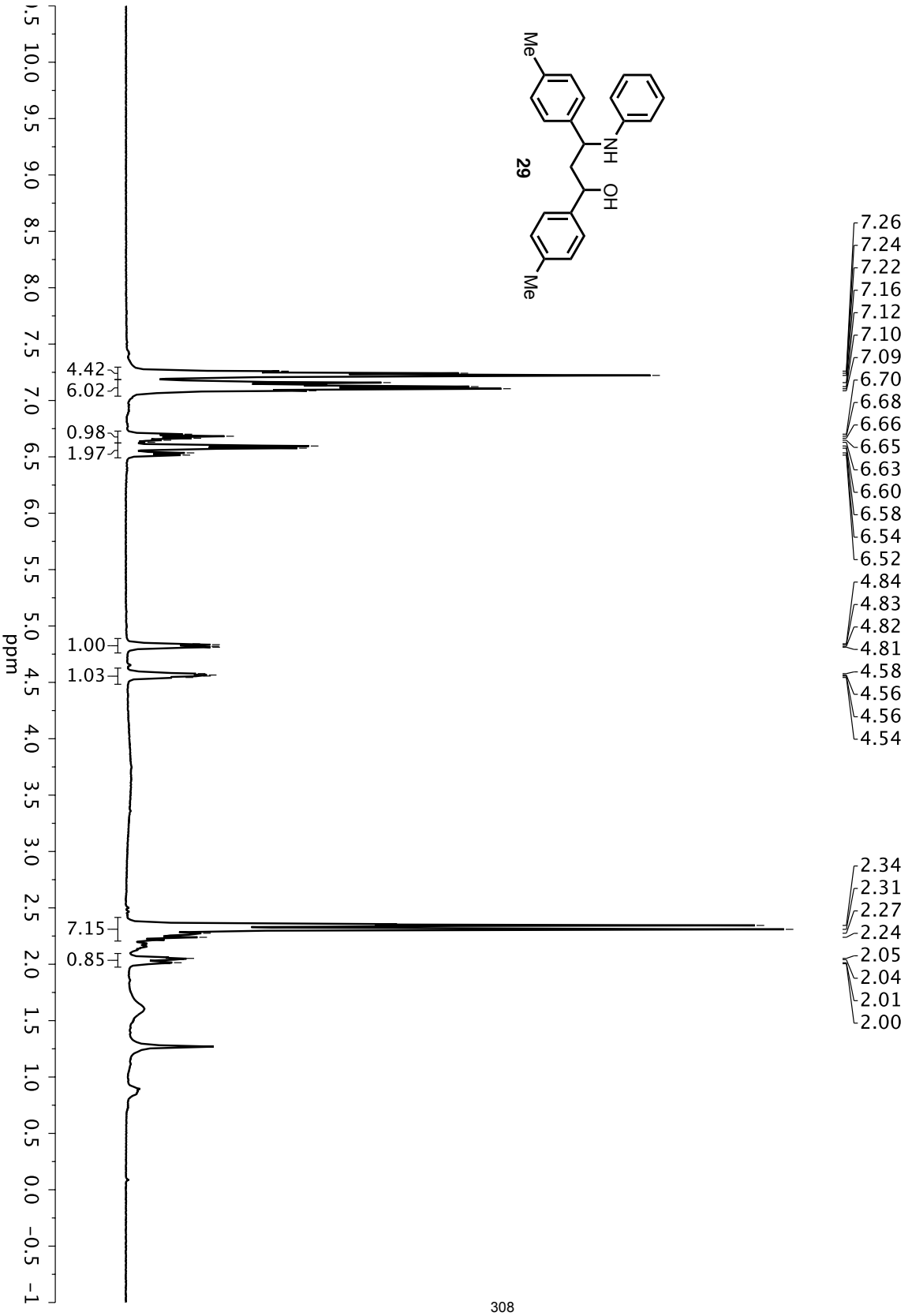

26
NH
OH
Cl
ppm
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
−0.5
−1
9.09
1.00
1.00
1.00
0.93
1.01
1.13
1.00
1.17
1.04
7.28
7.27
7.26
7.25
7.23
7.21
7.16
6.92
6.91
6.89
6.55
6.54
6.46
6.46
6.45
6.33
6.31
4.77
4.76
4.75
4.74
4.48
4.47
4.46
4.45
2.24
2.22
2.21
2.21
2.20
2.19
2.18
2.17
2.00
1.99
1.99
1.98
1.97
1.97
1.96
1.96

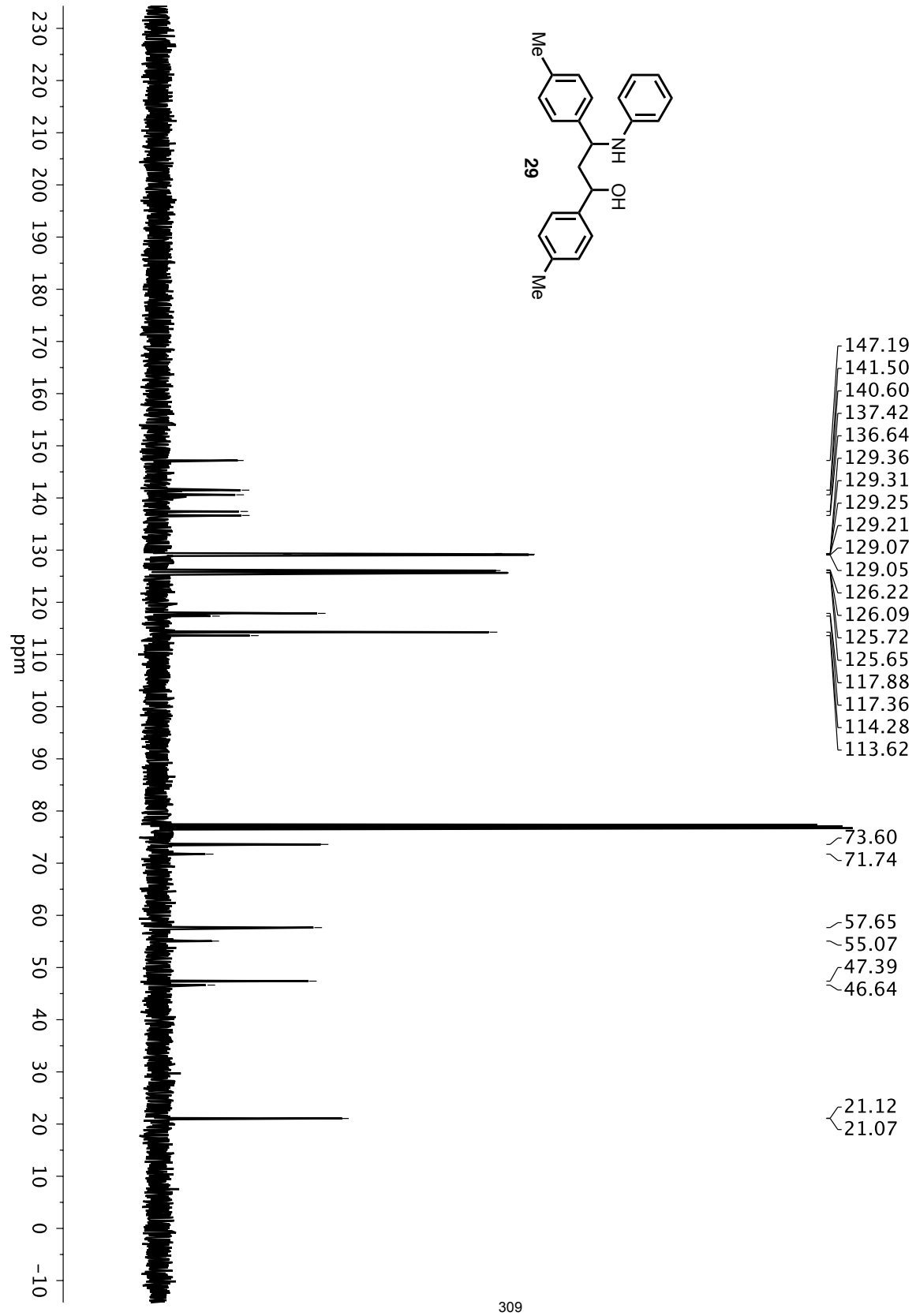

7.26 7.25 7.25 7.24 7.24 7.23 7.22 7.22 7.21 7.20 7.20 7.19 7.15 7.15 7.14 7.14 7.13 7.13 7.12 6.82 6.81 6.80 6.79 5.98 5.98 5.97 5.97 5.97 5.96 5.96 5.96 5.95 5.95 5.84 5.84 5.83 4.79 4.78 4.77 4.76 4.50 4.49 4.48 4.47 2.19 2.17 2.16 2.15 2.14 2.13 1.99 1.98 1.98 1.97 1.96 1.95 1.95
NH2
NH
OH
27
304
9.67
1.21
1.01
1.90
0.78
0.16
1.00
1.03
1.02
1.06
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


27
NH2
NH
OH
148.36
147.25
144.47
143.84
129.94
129.92
128.67
128.62
128.58
128.56
127.72
127.65
127.07
126.93
126.27
126.16
125.75
125.71
105.55
105.48
105.06
104.93
101.09
100.34
73.81
71.83
57.92
55.22
47.48
46.80
ppm


28
Br
NH
OH
10.27
1.10
1.90
1.68
0.10
1.00
0.10
0.84
1.23
1.31
7.35
7.34
7.33
7.32
7.30
7.25
7.25
7.24
7.24
7.24
7.23
7.22
7.17
7.17
7.16
7.15
7.15
4.86
4.85
4.84
4.83
4.54
4.53
4.52
4.51
2.31
2.29
2.28
2.28
2.26
2.25
2.08
2.07
2.07
2.06
2.05
2.05
2.04
2.04
2.03
ppm


28
Br
NH
OH
146.26
144.30
143.24
131.75
128.78
128.65
127.90
127.29
126.15
125.63
115.58
104.99
73.65
57.88
47.38
29.69
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
NH
OH
Me
29
7.26
7.24
7.22
7.16
7.12
7.10
7.09
6.70
6.68
6.66
6.65
6.63
6.60
6.58
6.54
6.52
4.84
4.83
4.82
4.81
4.58
4.56
4.56
4.54
2.34
2.31
2.27
2.24
2.05
2.04
2.01
2.00
4.42
6.02
0.98
1.97
1.00
1.03
7.15
0.85
ppm


Me
NH
OH
29
Me
147.19
141.50
140.60
137.42
136.64
129.36
129.31
129.25
129.21
129.07
129.05
126.22
126.09
125.72
125.65
117.88
117.36
114.28
113.62
73.60
71.74
57.65
55.07
47.39
46.64
21.12
21.07
ppm
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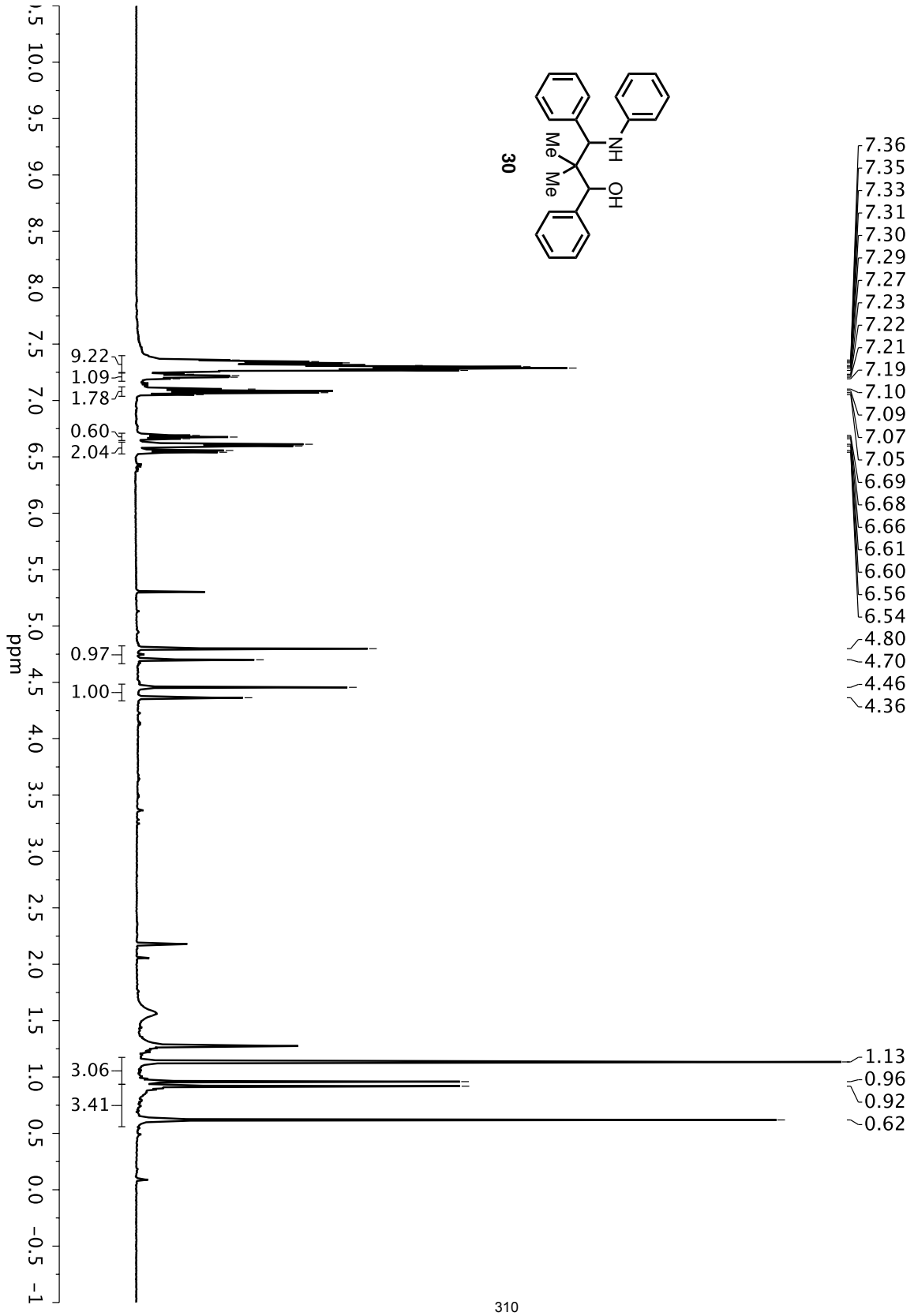
30
Me
Me
NH
OH
9.22
1.09
1.78
0.60
2.04
0.97
1.00
3.06
3.41
7.36
7.35
7.33
7.31
7.30
7.29
7.27
7.23
7.22
7.21
7.19
7.10
7.09
7.07
7.05
6.69
6.68
6.66
6.61
6.60
6.56
6.54
4.80
4.70
4.46
4.36
1.13
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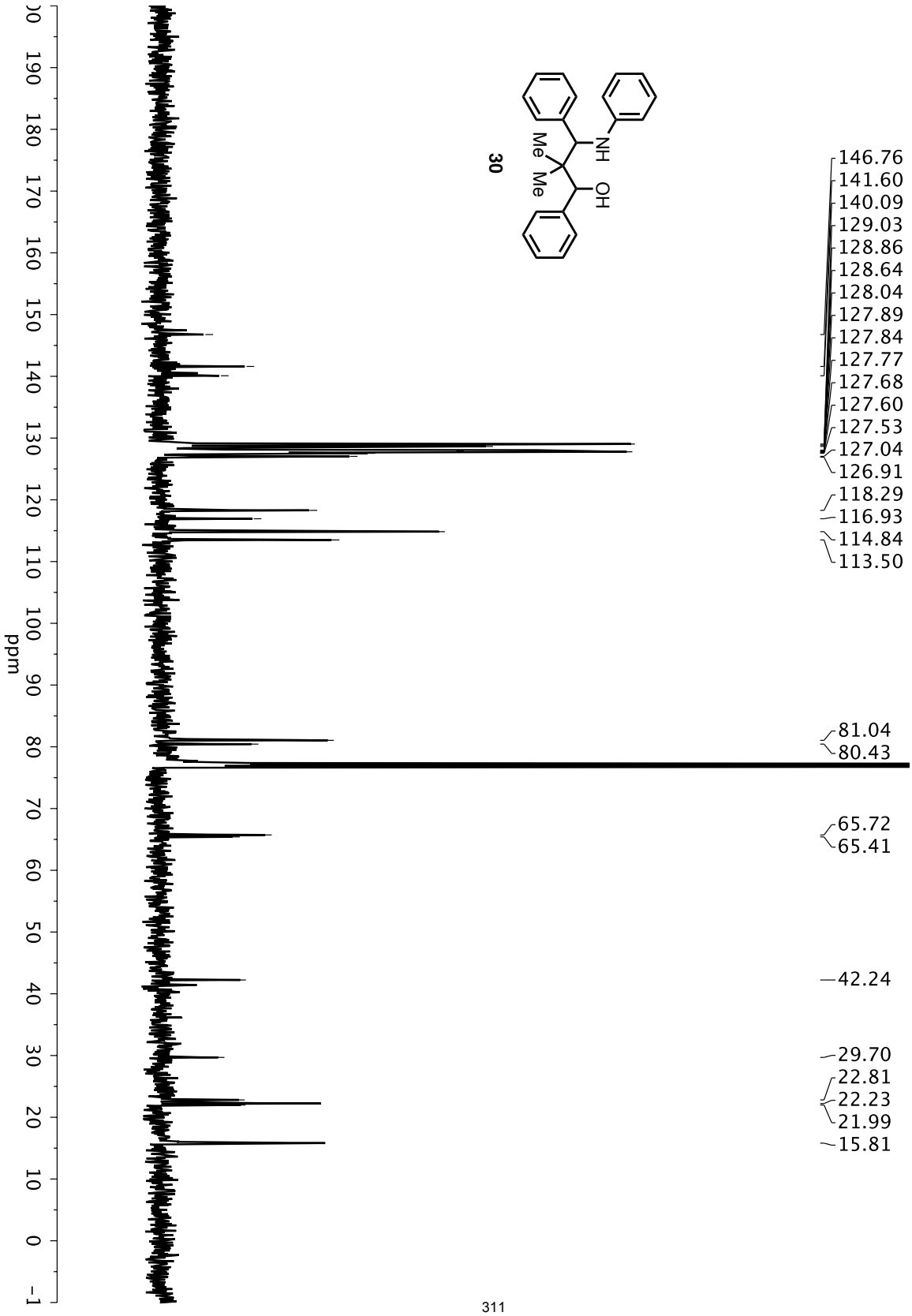
0.92
0.62
ppm


30
Me
Me
NH
OH
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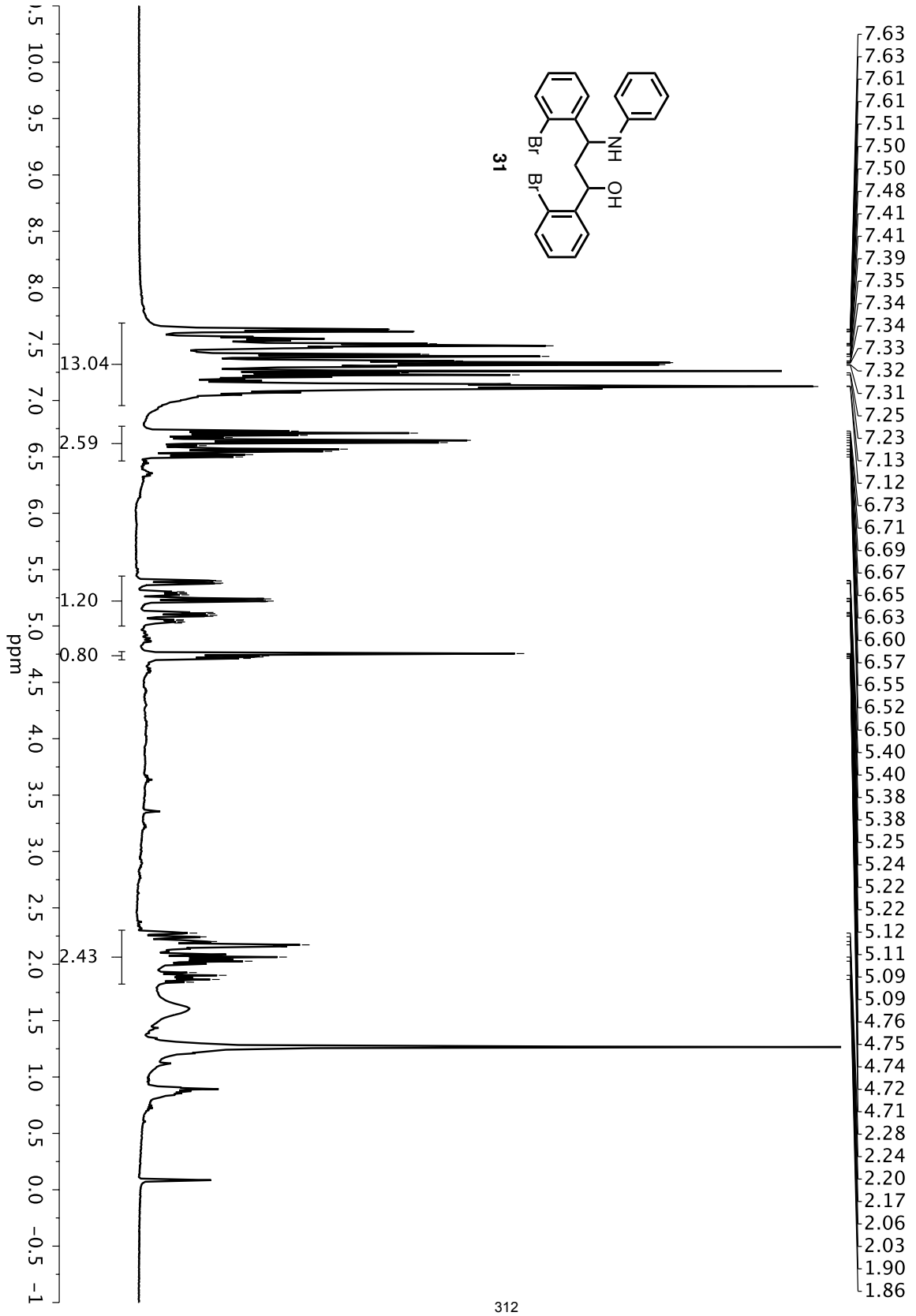
141.60
140.09
129.03
128.86
128.64
128.04
127.89
127.84
127.77
127.68
127.60
127.53
127.04
126.91
118.29
116.93
114.84
113.50
81.04
80.43
65.72
65.41
42.24
29.70
22.81
22.23
21.99
15.81
ppm


31
Br
Br
NH
OH
13.04
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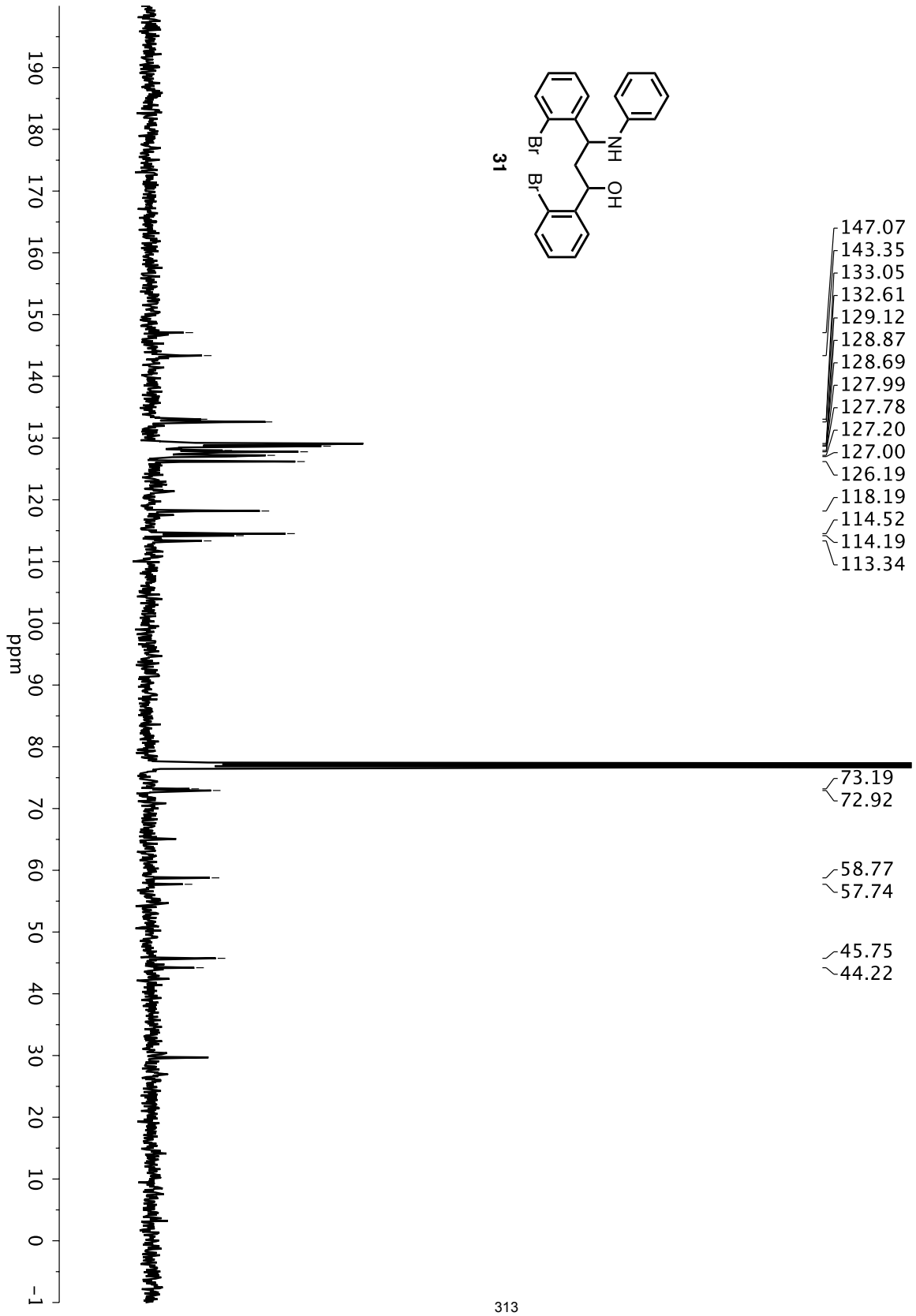
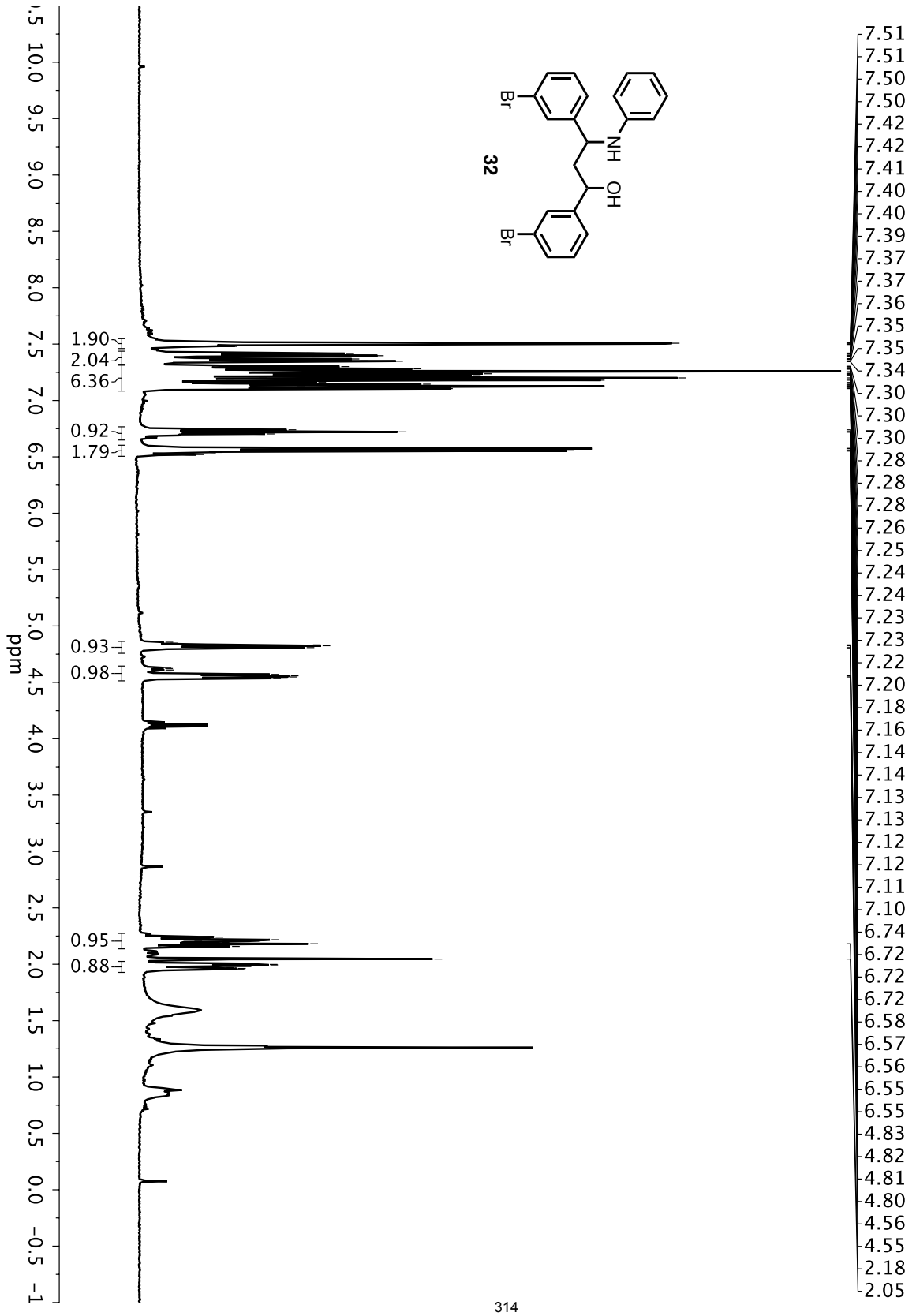
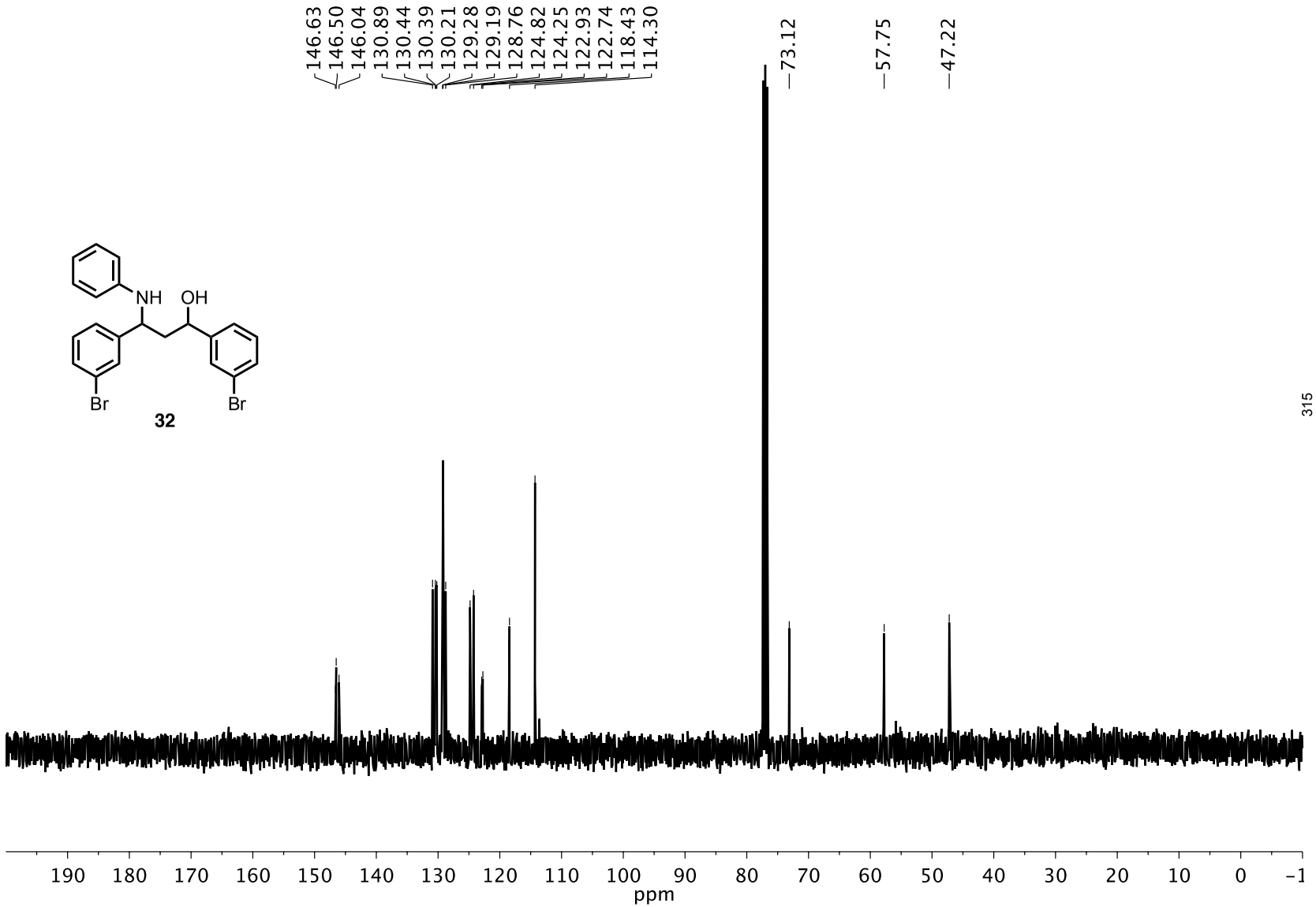
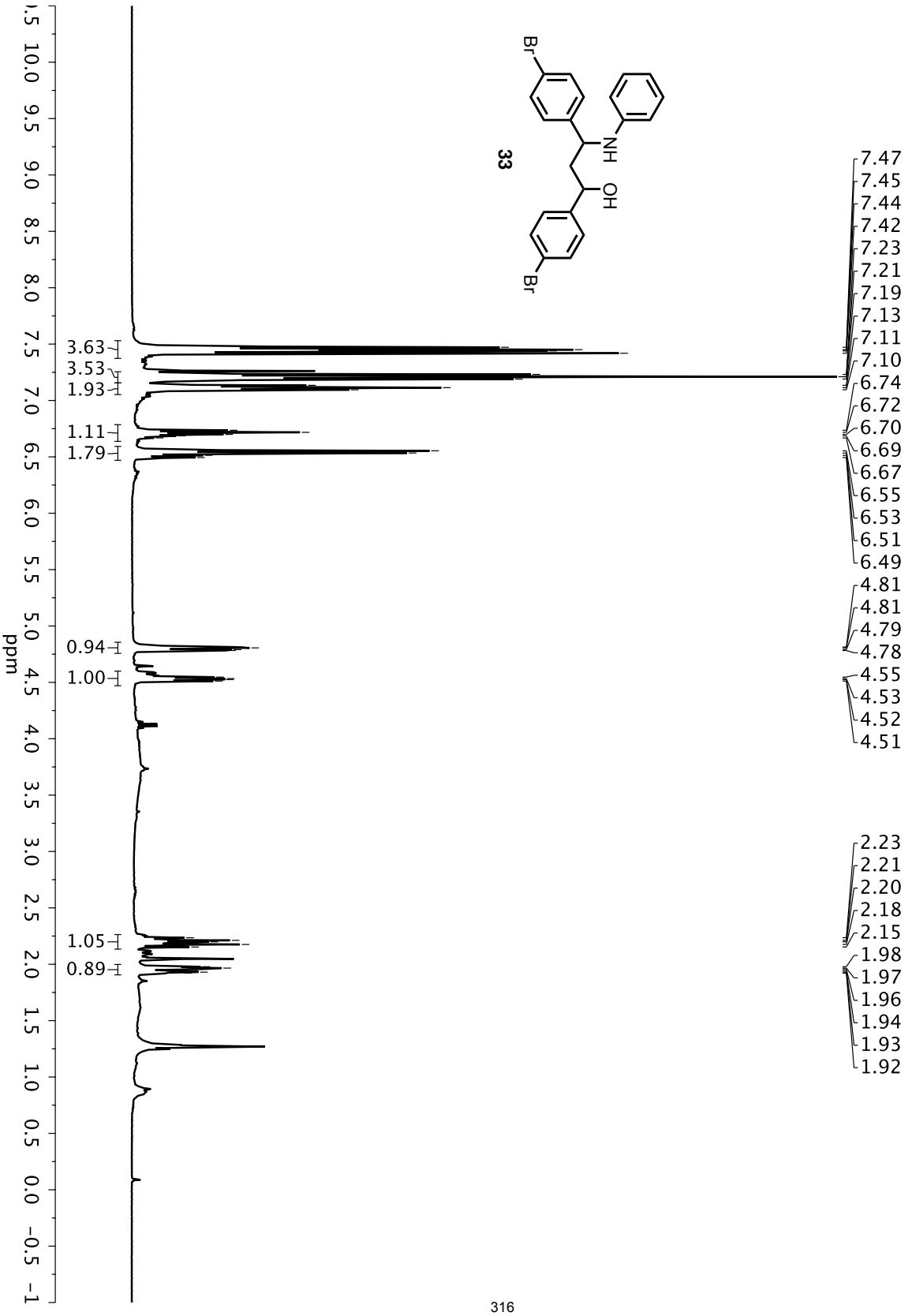
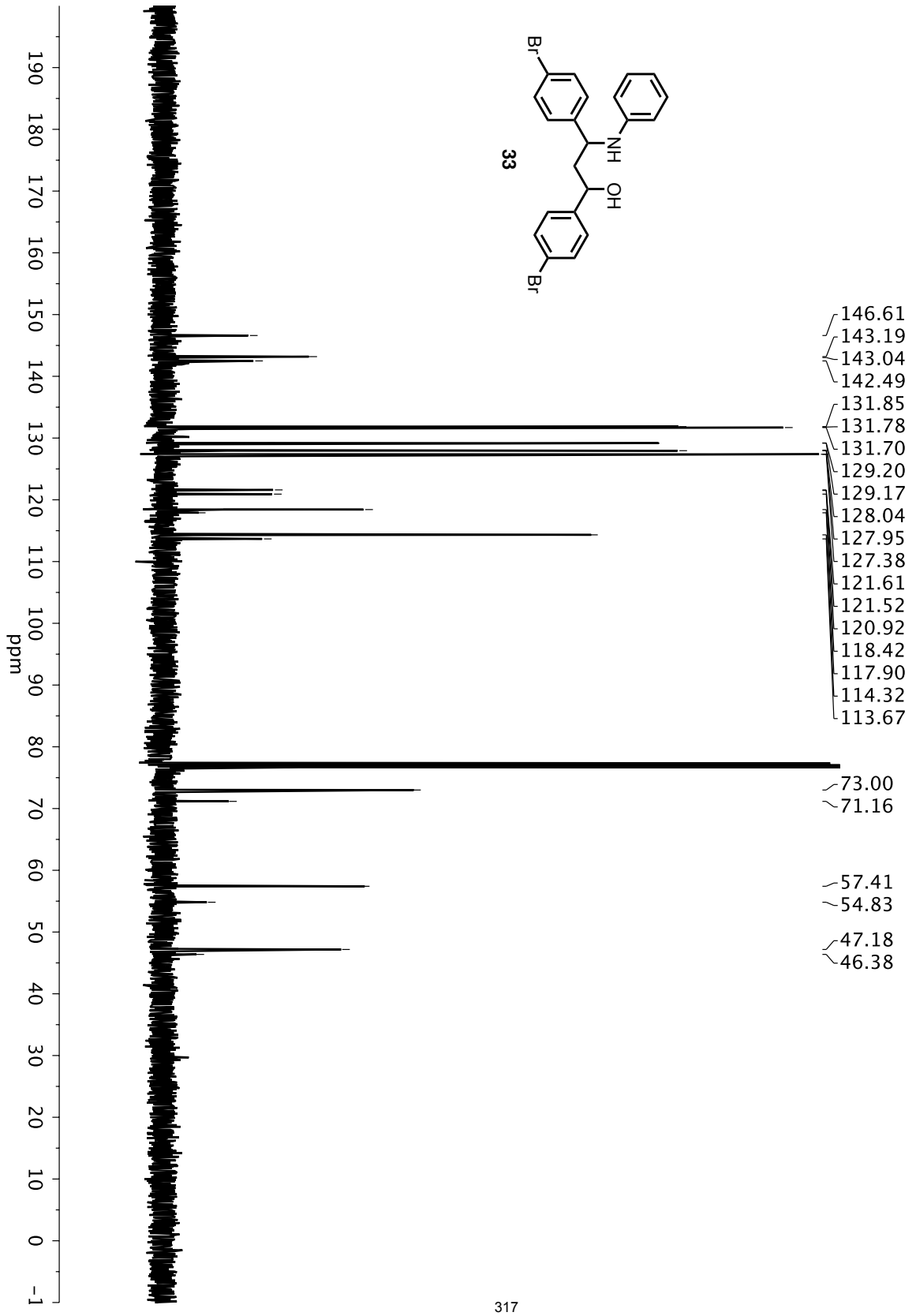
1.20
0.80
2.43
ppm
7.63
7.63
7.61
7.61
7.51
7.50
7.50
7.48
7.41
7.41
7.39
7.35
7.34
7.34
7.33
7.32
7.31
7.25
7.23
7.13
7.12
6.73
6.71
6.69
6.67
6.65
6.63
6.60
6.57
6.55
6.52
6.50
5.40
5.40
5.38
5.38
5.25
5.24
5.22
5.22
5.12
5.11
5.09
5.09
4.76
4.75
4.74
4.72
4.71
2.28
2.24
2.20
2.17
2.06
2.03
1.90
1.86

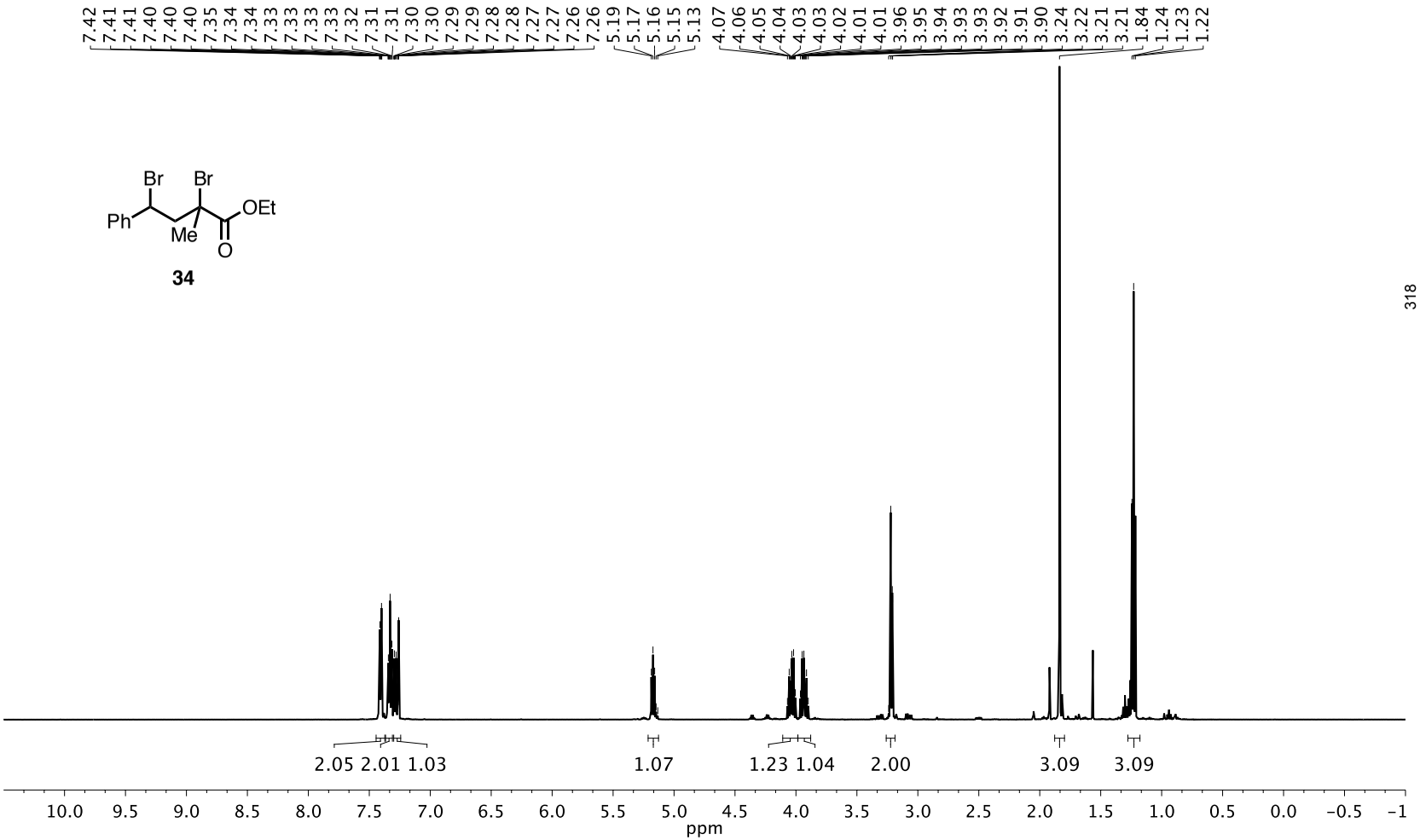

147.07
143.35
133.05
132.61
129.12
128.87
128.69
127.99
127.78
127.20
127.00
126.19
118.19
114.52
114.19
113.34
73.19
72.92
58.77
57.74
45.75
44.22
Br
Br
NH
OH
31
ppm
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-1

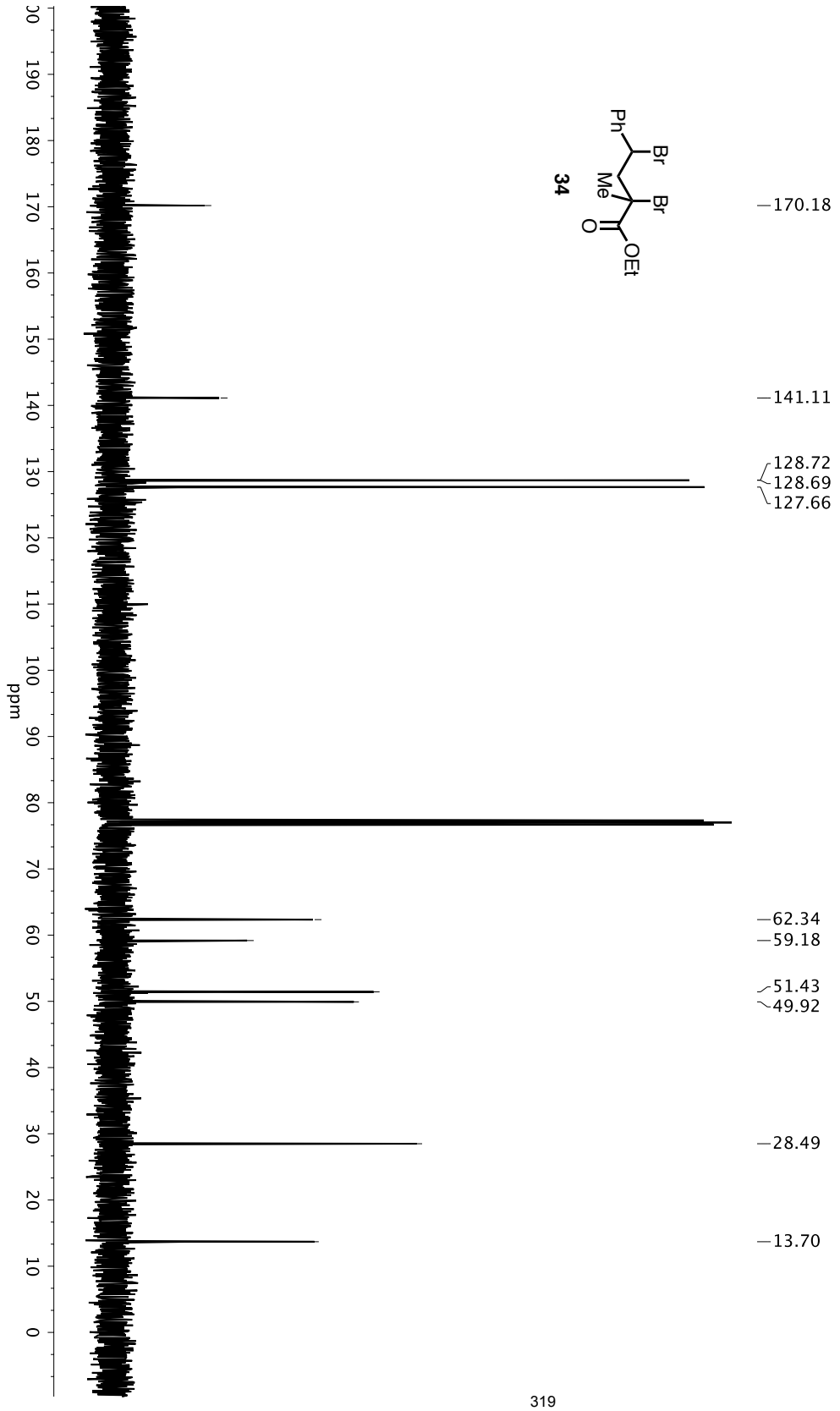

Br
NH
OH
Br
32
1.90
2.04
6.36
0.92
1.79
0.93
0.98
0.95
0.88
ppm
7.51
7.51
7.50
7.50
7.42
7.42
7.41
7.40
7.40
7.39
7.37
7.37
7.36
7.35
7.35
7.34
7.30
7.30
7.30
7.28
7.28
7.28
7.26
7.25
7.24
7.24
7.23
7.23
7.22
7.20
7.18
7.16
7.14
7.14
7.13
7.13
7.12
7.12
7.11
7.10
6.74
6.72
6.72
6.72
6.58
6.57
6.56
6.55
6.55
4.83
4.82
4.81
4.80
4.56
4.55
2.18
2.05

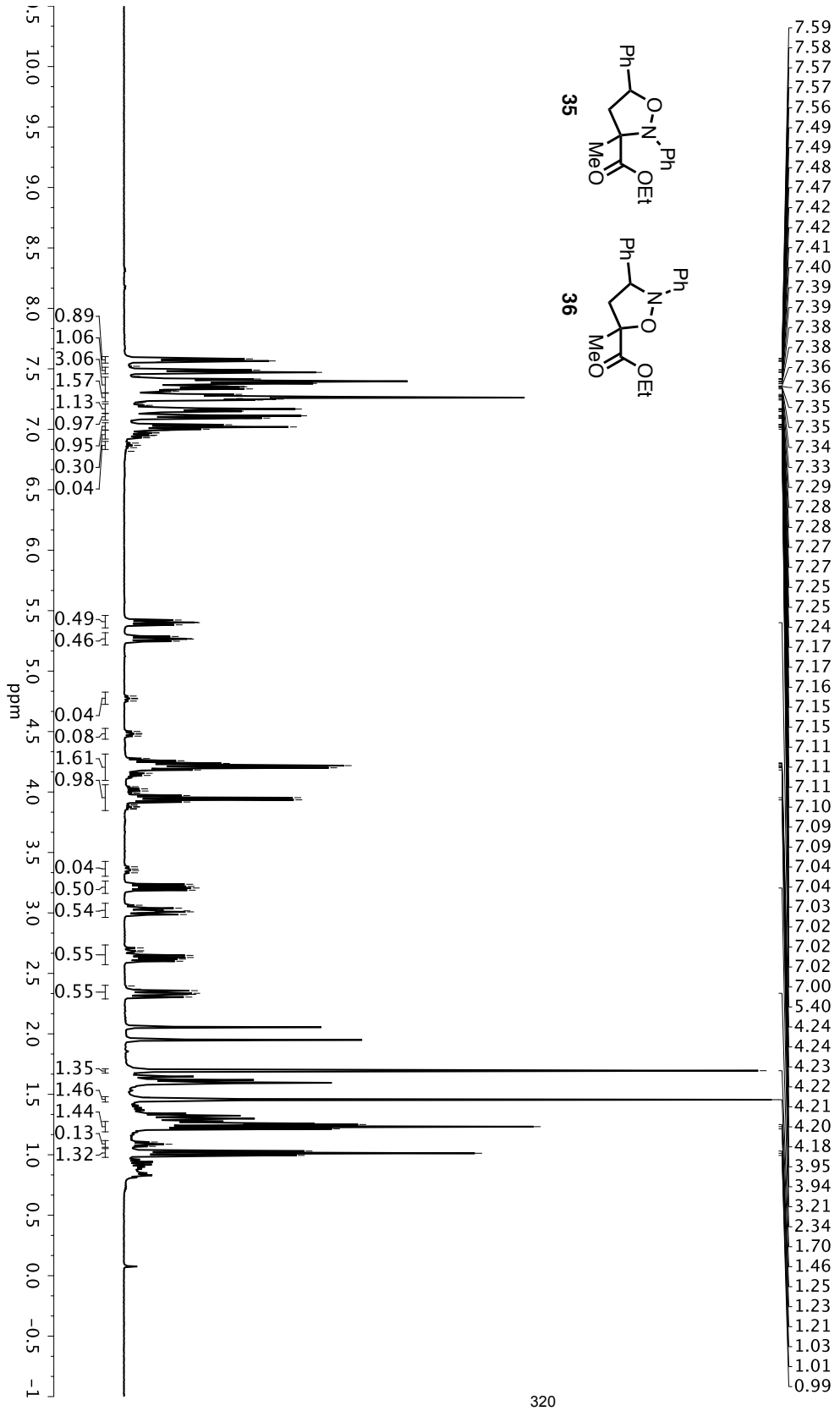

146.63
146.50
146.04
130.89
130.44
130.39
130.21
129.28
129.19
128.76
124.82
124.25
122.93
122.74
118.43
114.30
73.12
57.75
47.22
NH
OH
Br
Br
32
315
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
−1
ppm

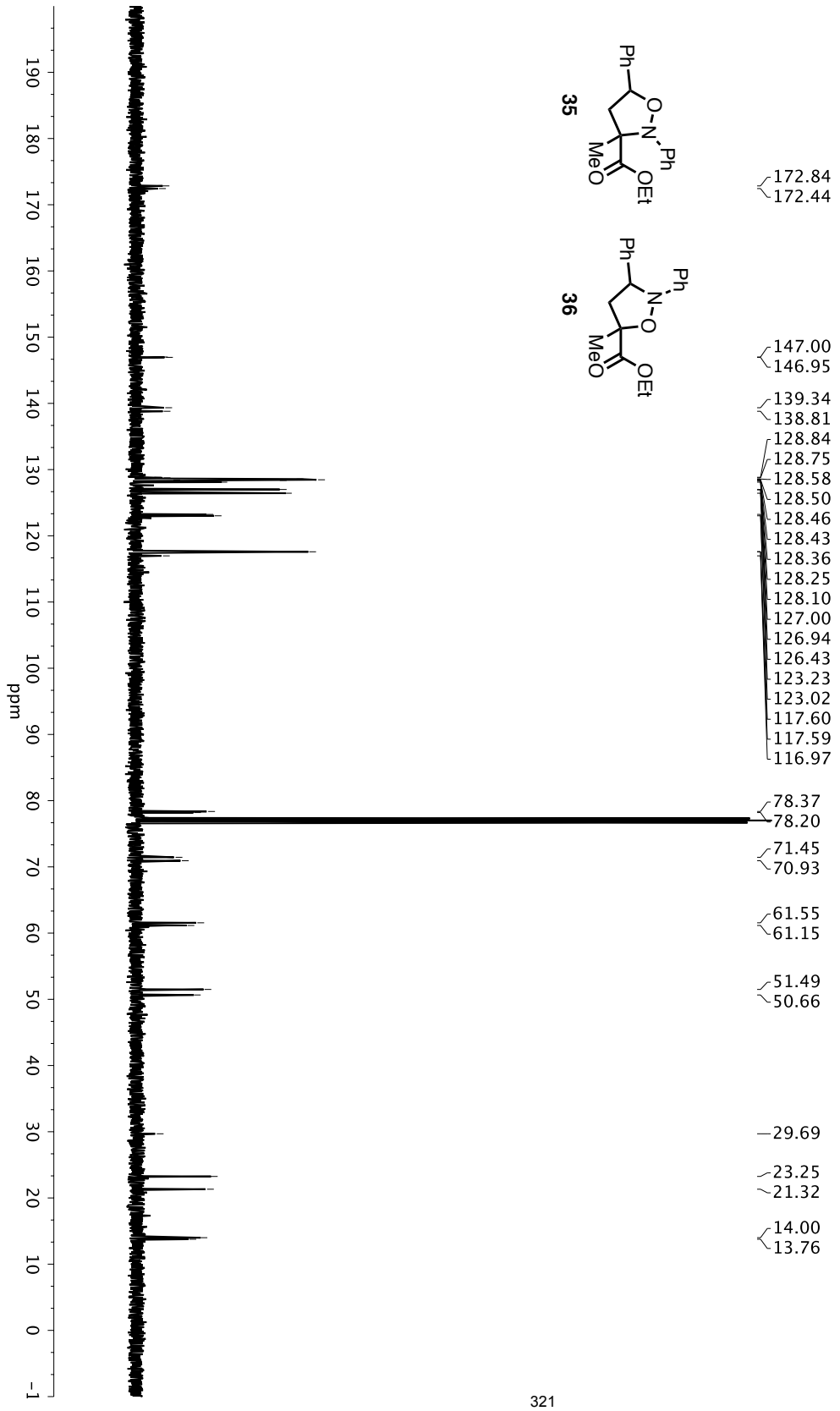

Br
NH
OH
Br
33
7.47
7.45
7.44
7.42
7.23
7.21
7.19
7.13
7.11
7.10
6.74
6.72
6.70
6.69
6.67
6.55
6.53
6.51
6.49
4.81
4.81
4.79
4.78
4.55
4.53
4.52
4.51
2.23
2.21
2.20
2.18
2.15
1.98
1.97
1.96
1.94
1.93
1.92
3.63
3.53
1.93
1.11
1.79
0.94
1.00
1.05
0.89
ppm

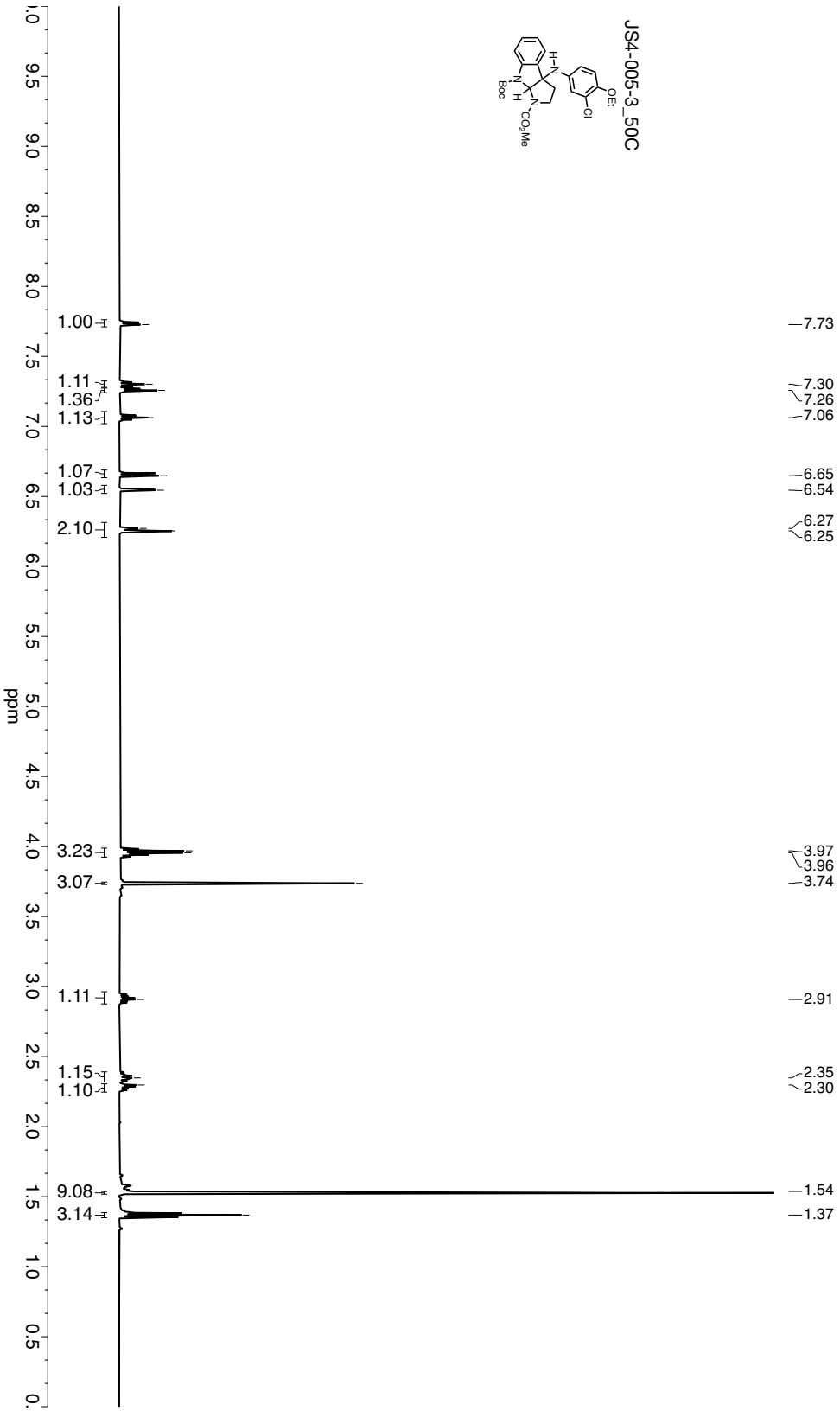

Br
NH
OH
Br
33
146.61
143.19
143.04
142.49
131.85
131.78
131.70
129.20
129.17
128.04
127.95
127.38
121.61
121.52
120.92
118.42
117.90
114.32
113.67
73.00
71.16
57.41
54.83
47.18
46.38
ppm
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-1

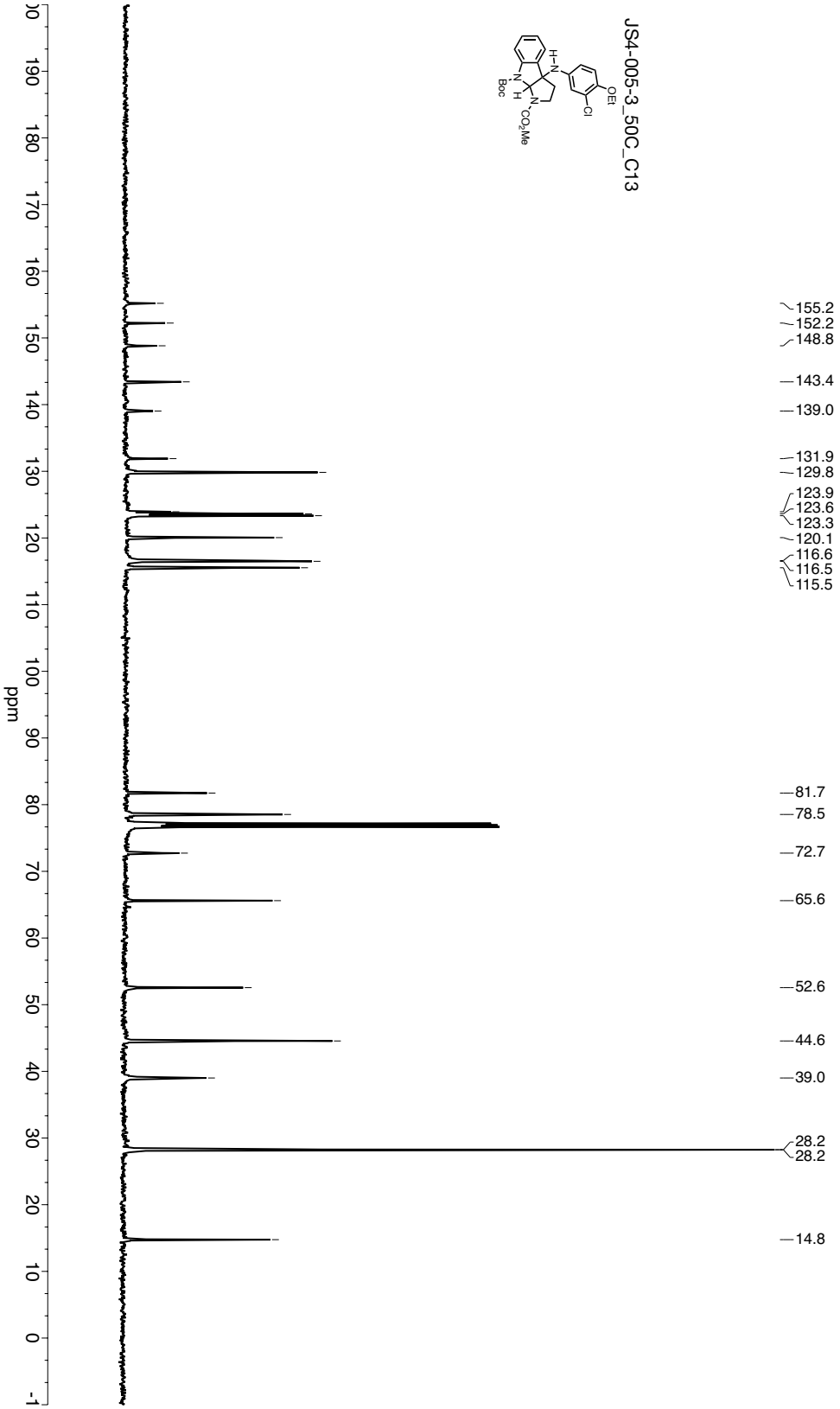

7.42 7.41 7.41 7.40 7.40 7.40 7.35 7.34 7.34 7.33 7.33 7.33 7.33 7.32 7.31 7.31 7.30 7.30 7.29 7.29 7.28 7.28 7.27 7.27 7.26 7.26
5.19 5.17 5.16 5.15 5.13
4.07 4.06 4.05 4.04 4.03 4.03 4.02 4.01 4.01 3.96 3.95 3.94 3.93 3.93 3.92 3.91 3.90
3.24 3.22 3.21 3.21
1.84 1.24 1.23 1.22
Br
Br
Ph
Me
OEt
O
34
318
2.05 2.01 1.03
1.07
1.23 1.04
2.00
3.09
3.09
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

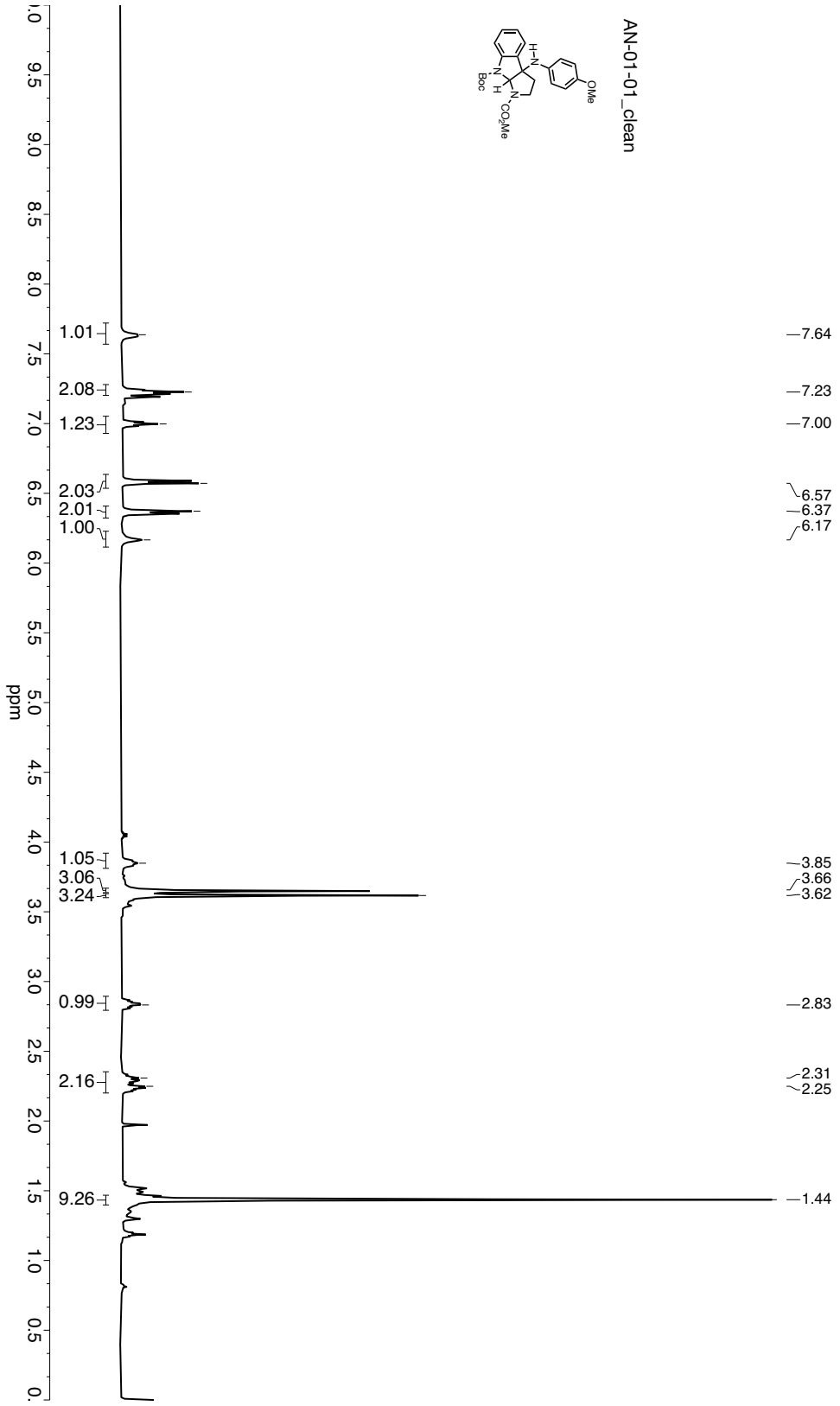

34
Ph
Br
Me
Br
O
OEt
170.18
141.11
128.72
128.69
127.66
62.34
59.18
51.43
49.92
28.49
13.70
ppm

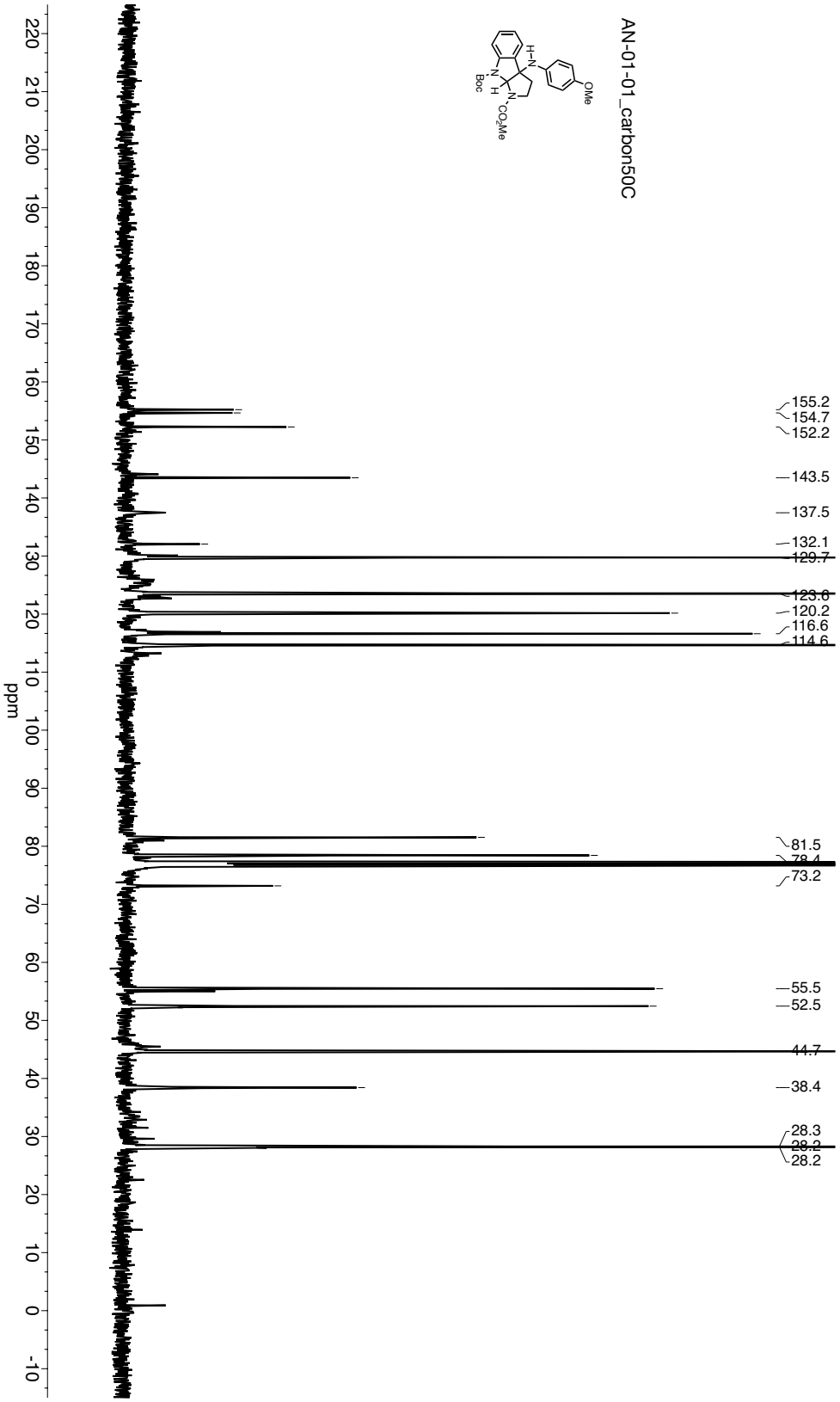

35
36
Ph
O
N
Ph
MeO
OEt
ppm

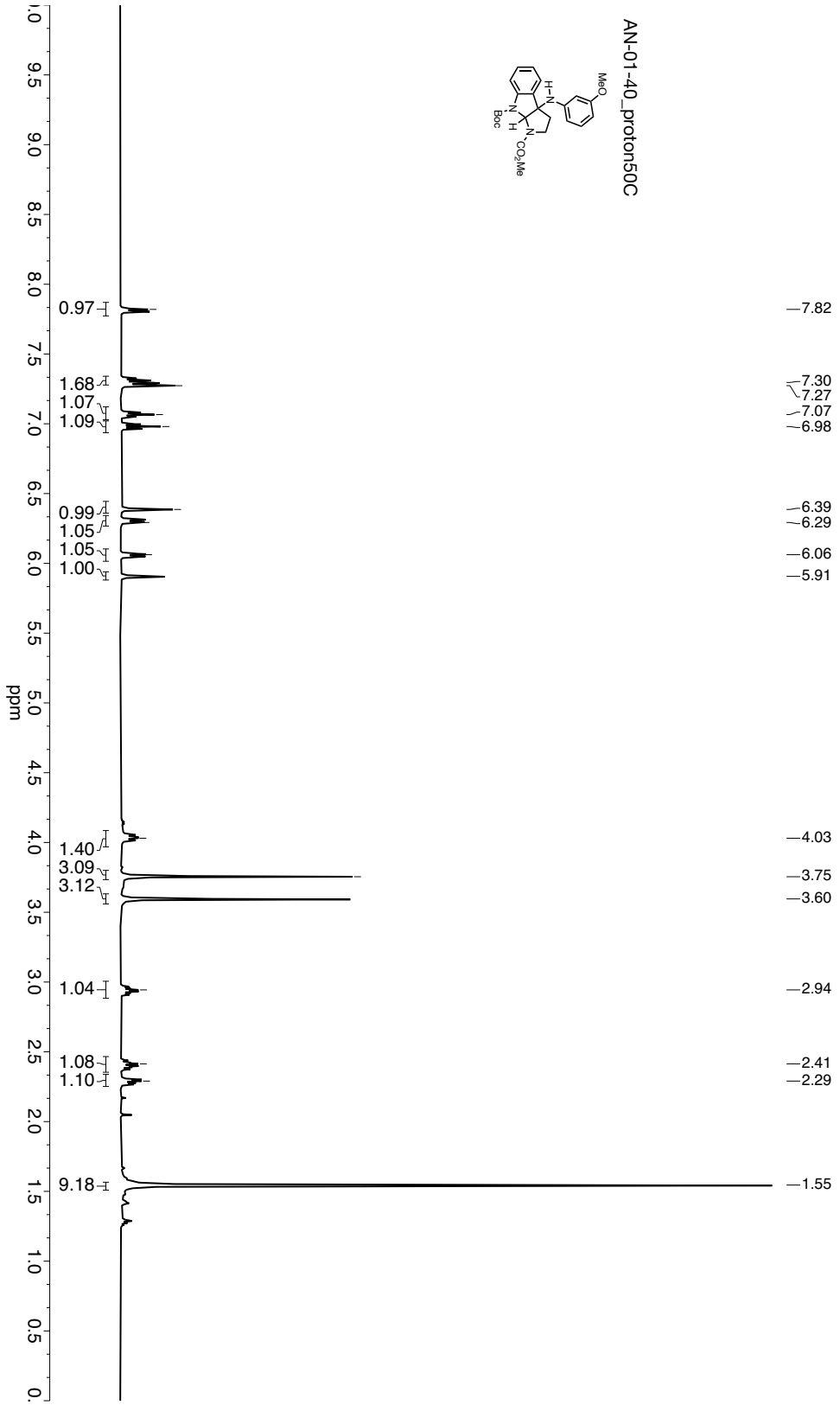

35
36
Ph
O
N
Ph
MeO
OEt
172.84
172.44
147.00
146.95
139.34
138.81
128.84
128.75
128.58
128.50
128.46
128.43
128.36
128.25
128.10
127.00
126.94
126.43
123.23
123.02
117.60
117.59
116.97
78.37
78.20
71.45
70.93
61.55
61.15
51.49
50.66
29.69
23.25
21.32
14.00
13.76
ppm

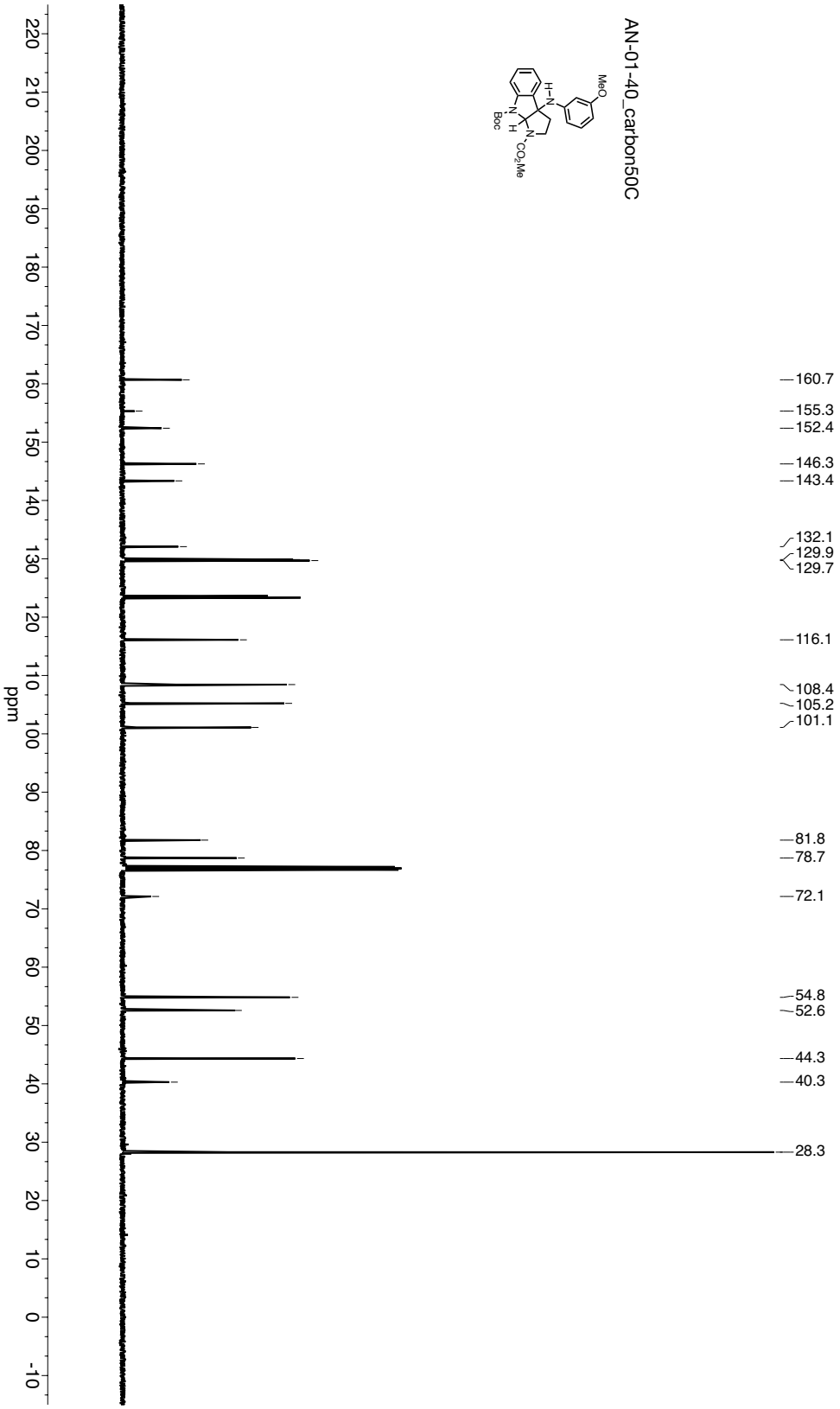

JS4-005-3_50C
ppm
1.00
1.11
1.36
1.13
1.07
1.03
2.10
3.23
3.07
1.11
1.15
1.10
9.08
3.14
7.73
7.30
7.26
7.06
6.65
6.54
6.27
6.25
3.97
3.96
3.74
2.91
2.35
2.30
1.54
1.37

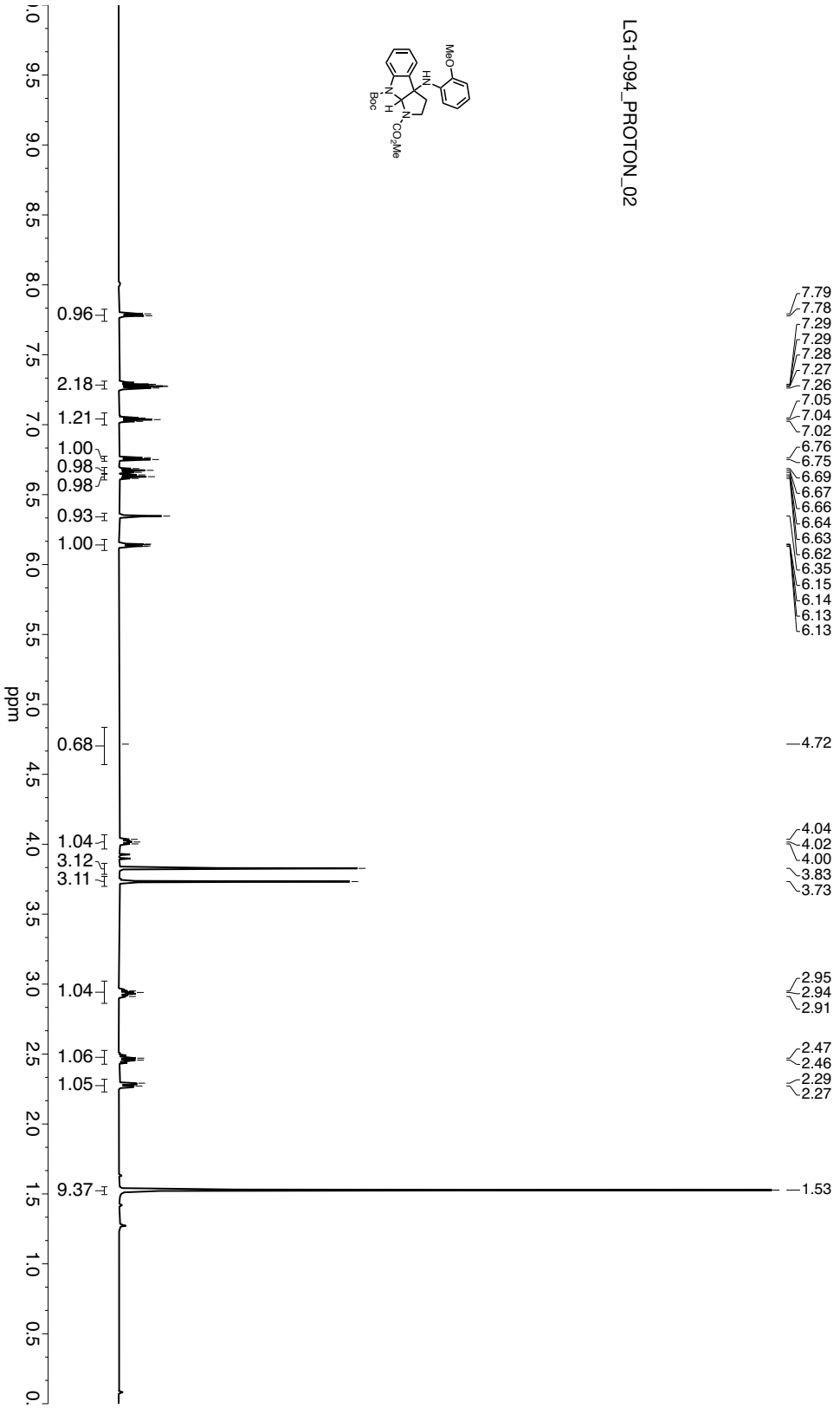

JS4-005-3_50C_C13
155.2
152.2
148.8
143.4
139.0
131.9
129.8
123.9
123.6
123.3
120.1
116.6
116.5
115.5
81.7
78.5
72.7
65.6
52.6
44.6
39.0
28.2
28.2
14.8
ppm

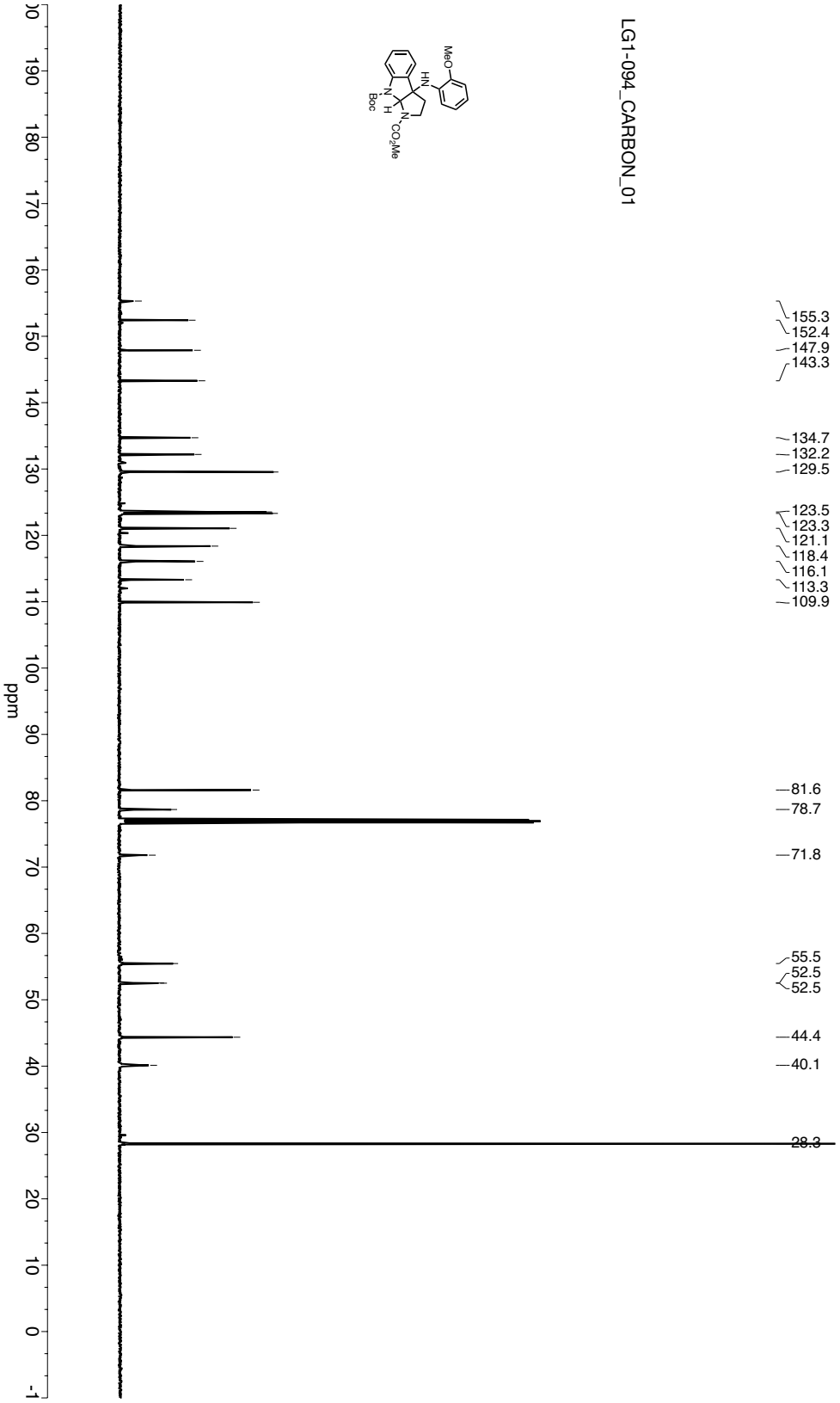

AN-01-01_clean
ppm
1.01
2.08
1.23
2.03
2.01
1.00
1.05
3.06
3.24
0.99
2.16
9.26
7.64
7.23
7.00
6.57
6.37
6.17
3.85
3.66
3.62
2.83
2.31
2.25
1.44

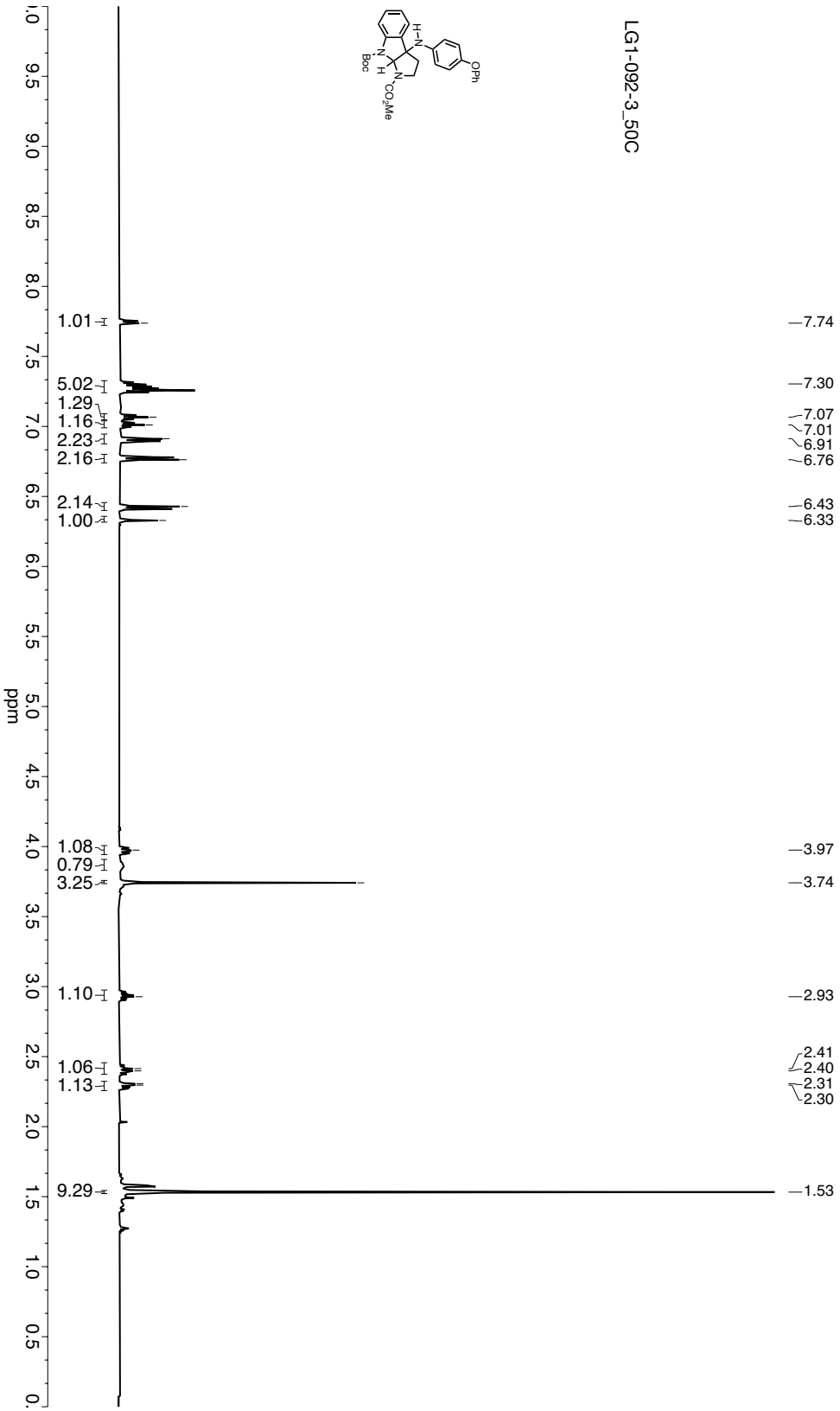

AN-01-01_carbon50C
155.2
154.7
152.2
143.5
137.5
132.1
129.7
123.6
120.2
116.6
114.6
81.5
78.4
73.2
55.5
52.5
44.7
38.4
28.3
28.2
28.2
ppm

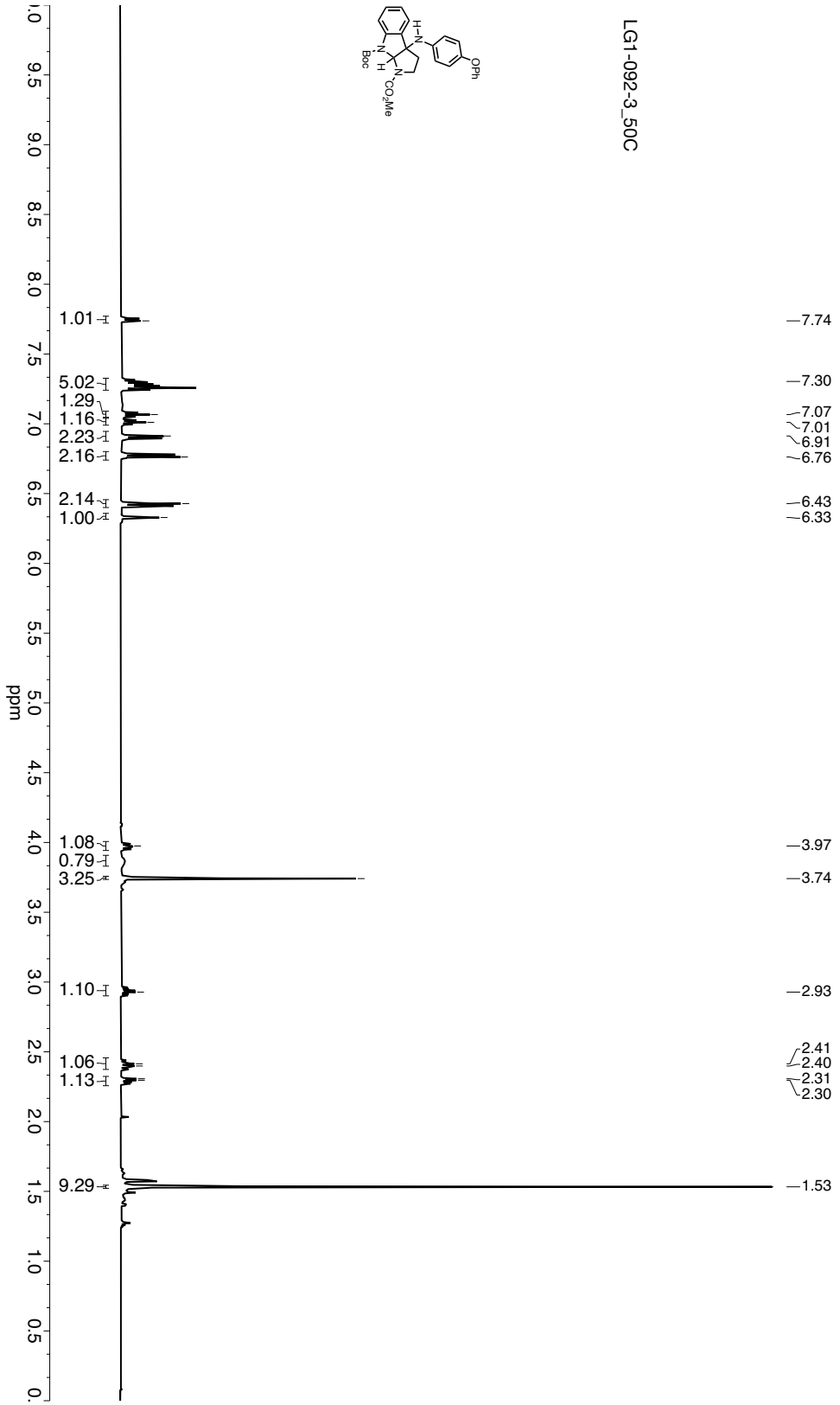

AN-01-40_proton50C
MeO
H–N
N
H
Boc
N
CO2Me
ppm
0.97
1.68
1.07
1.09
0.99
1.05
1.05
1.00
1.40
3.09
3.12
1.04
1.08
1.10
9.18
7.82
7.30
7.27
7.07
6.98
6.39
6.29
6.06
5.91
4.03
3.75
3.60
2.94
2.41
2.29
1.55

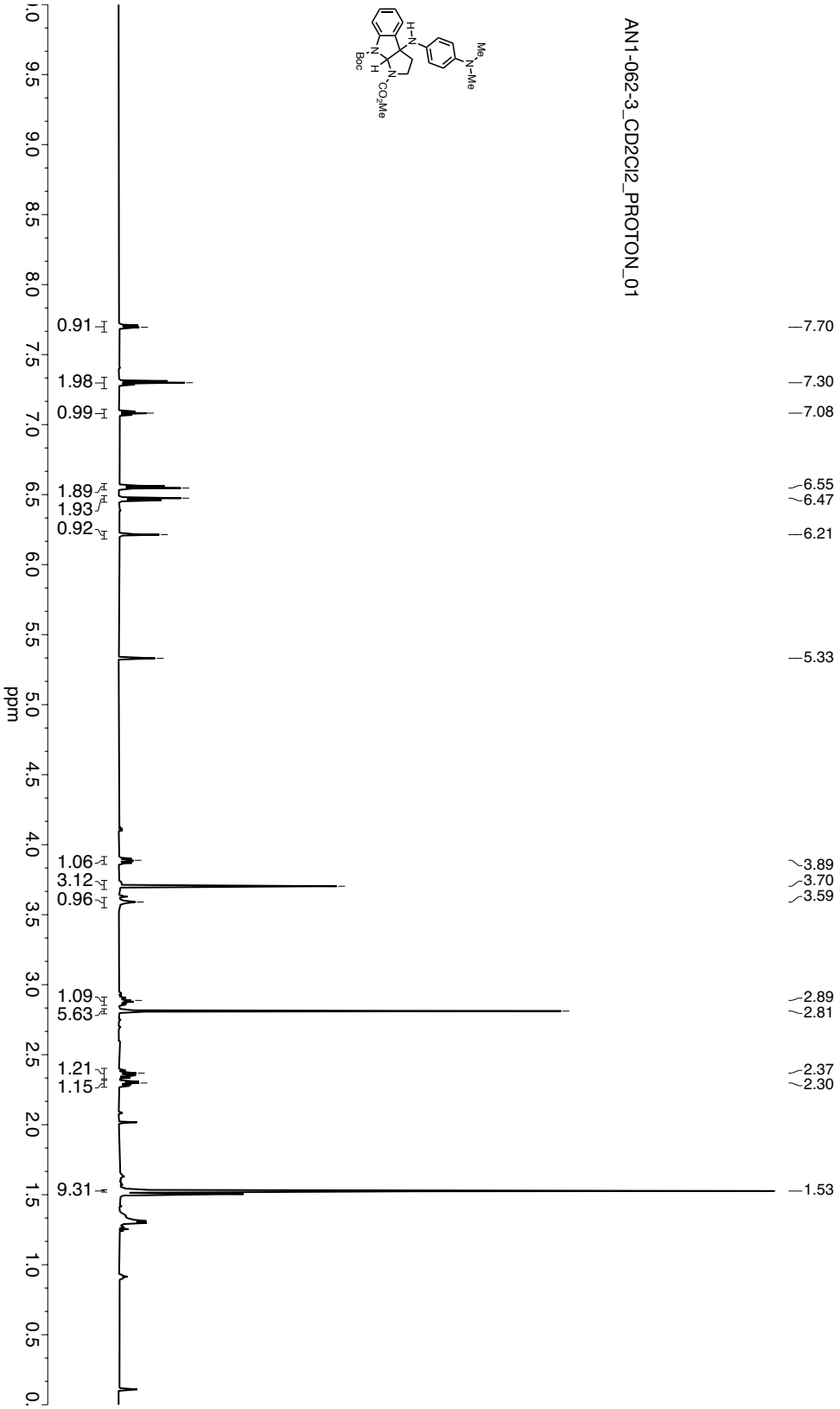

AN-01-40_carbon50C
160.7
155.3
152.4
146.3
143.4
132.1
129.9
129.7
116.1
108.4
105.2
101.1
81.8
78.7
72.1
54.8
52.6
44.3
40.3
28.3
ppm

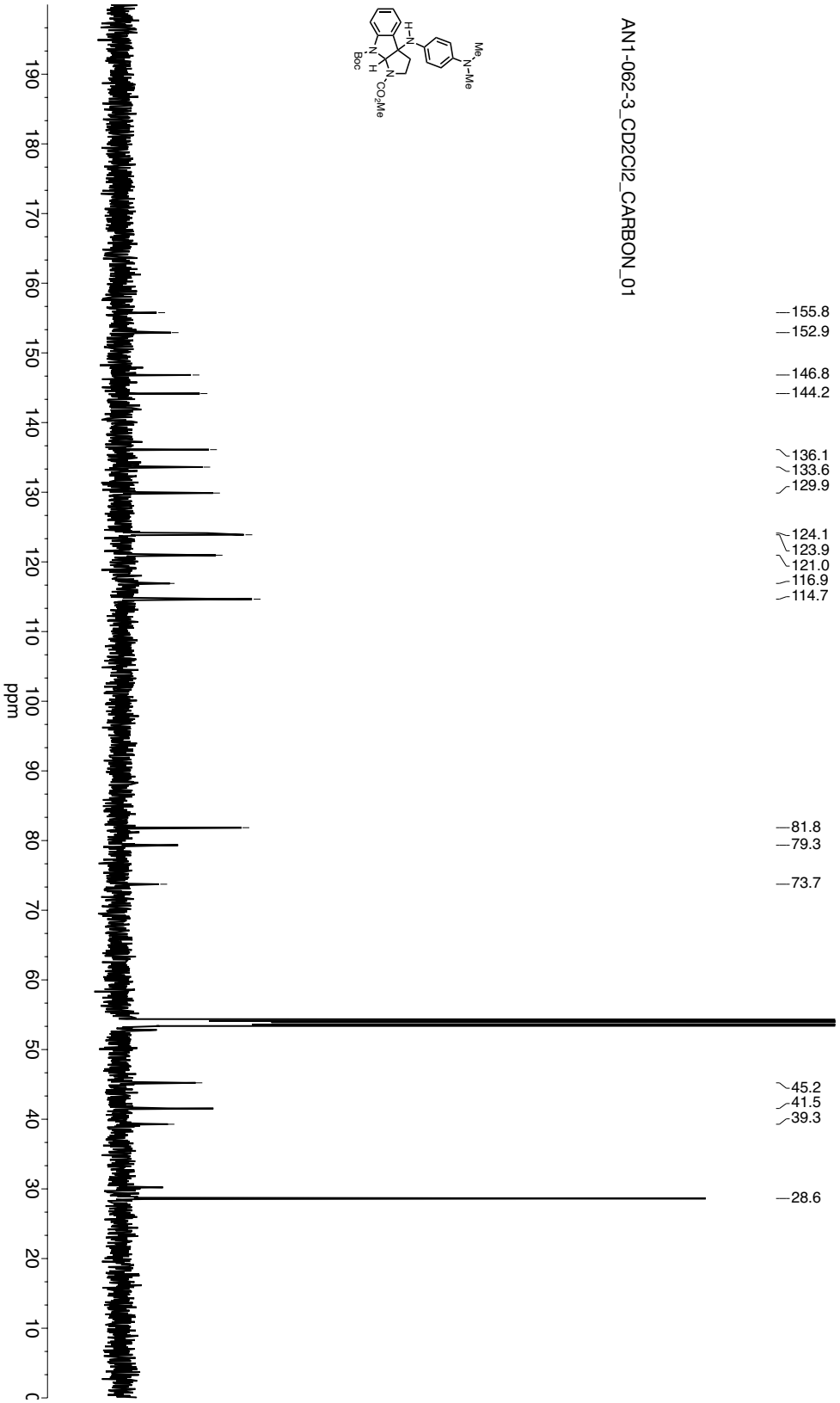

LG1-094_PROTON_02
MeO
HN
N
H
Boc
N
CO2Me
ppm
0.96
2.18
1.21
1.00
0.98
0.98
0.93
1.00
0.68
1.04
3.12
3.11
1.04
1.06
1.05
9.37
7.79
7.78
7.29
7.29
7.28
7.27
7.26
7.05
7.04
7.02
6.76
6.75
6.69
6.67
6.66
6.64
6.63
6.62
6.35
6.15
6.14
6.13
6.13
4.72
4.04
4.02
4.00
3.83
3.73
2.95
2.94
2.91
2.47
2.46
2.29
2.27
1.53

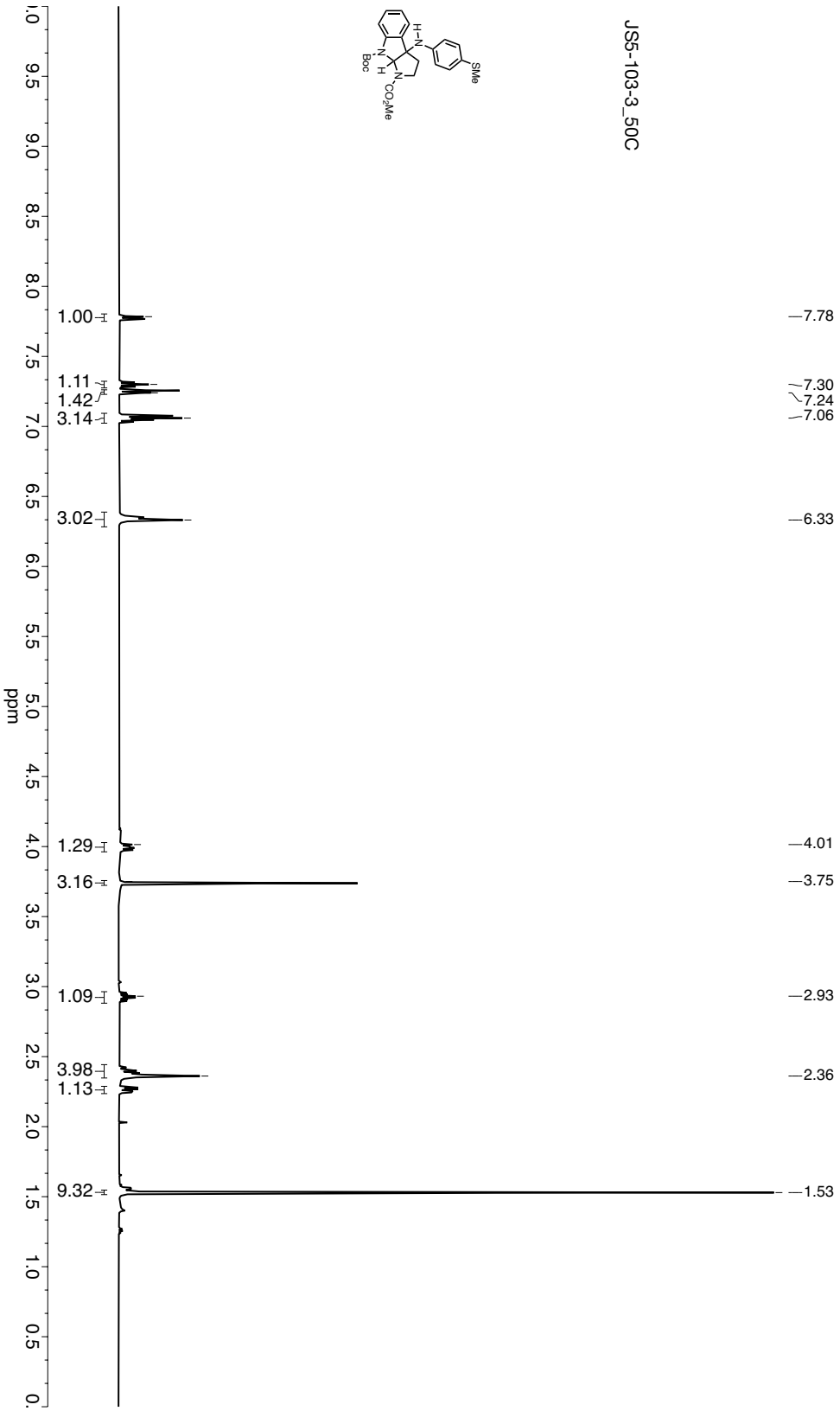

LG1-094_CARBON_01
MeO
HN
N
H
Boc
N
CO2Me
155.3
152.4
147.9
143.3
134.7
132.2
129.5
123.5
123.3
121.1
118.4
116.1
113.3
109.9
81.6
78.7
71.8
55.5
52.5
52.5
44.4
40.1
28.3
ppm
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

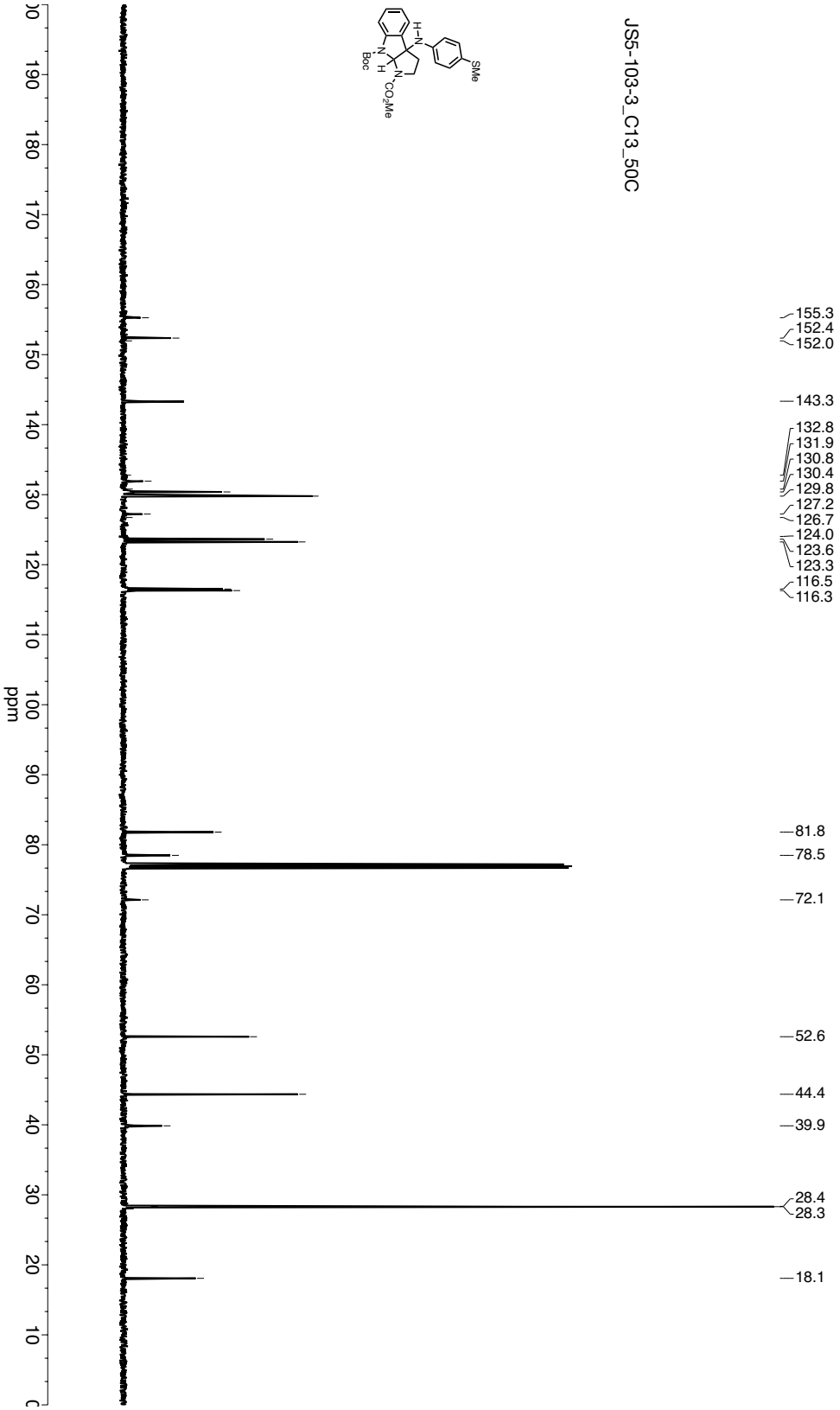

LG1-092-3_50C
ppm
1.01
5.02
1.29
1.16
2.23
2.16
2.14
1.00
1.08
0.79
3.25
1.10
1.06
1.13
9.29
7.74
7.30
7.07
7.01
6.91
6.76
6.43
6.33
3.97
3.74
2.93
2.41
2.40
2.31
2.30
1.53

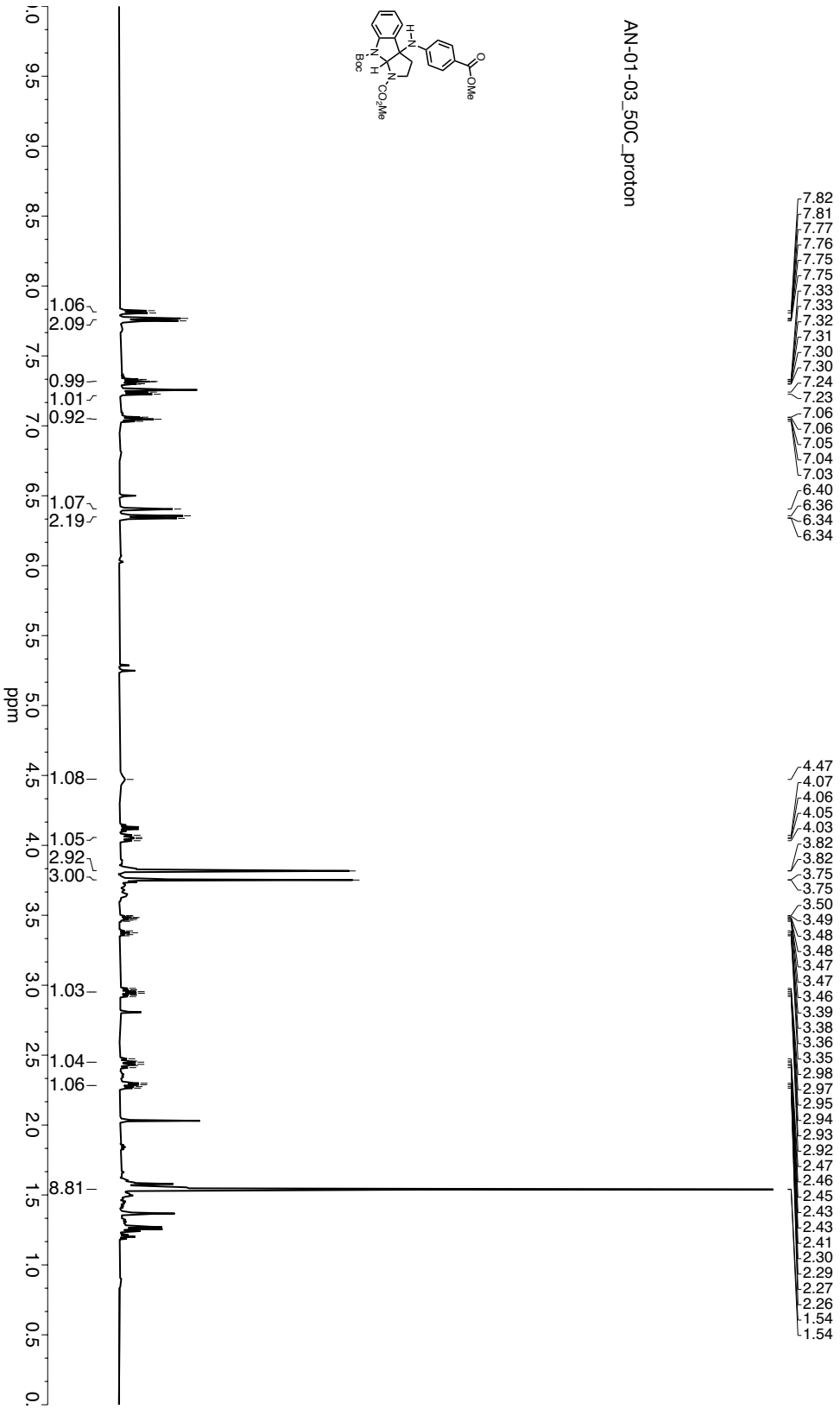

LG1-092-3_50C
ppm
1.01
5.02
1.29
1.16
2.23
2.16
2.14
1.00
1.08
0.79
3.25
1.10
1.06
1.13
9.29
7.74
7.30
7.07
7.01
6.91
6.76
6.43
6.33
3.97
3.74
2.93
2.41
2.40
2.31
2.30
1.53

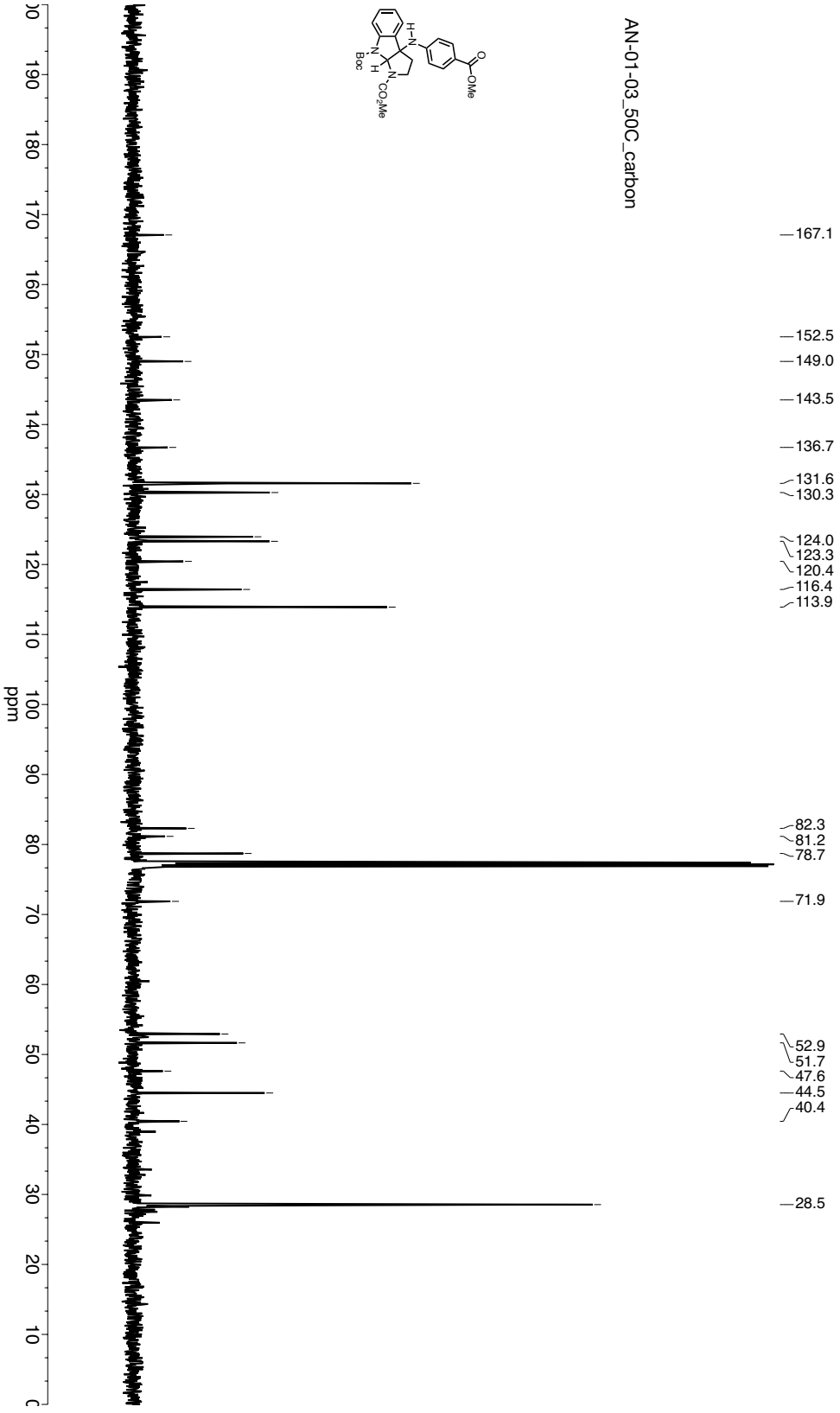

AN1-062-3_CD2Cl2_PROTON_01
ppm
0.91
1.98
0.99
1.89
1.93
0.92
1.06
3.12
0.96
1.09
5.63
1.21
1.15
9.31
7.70
7.30
7.08
6.55
6.47
6.21
5.33
3.89
3.70
3.59
2.89
2.81
2.37
2.30
1.53

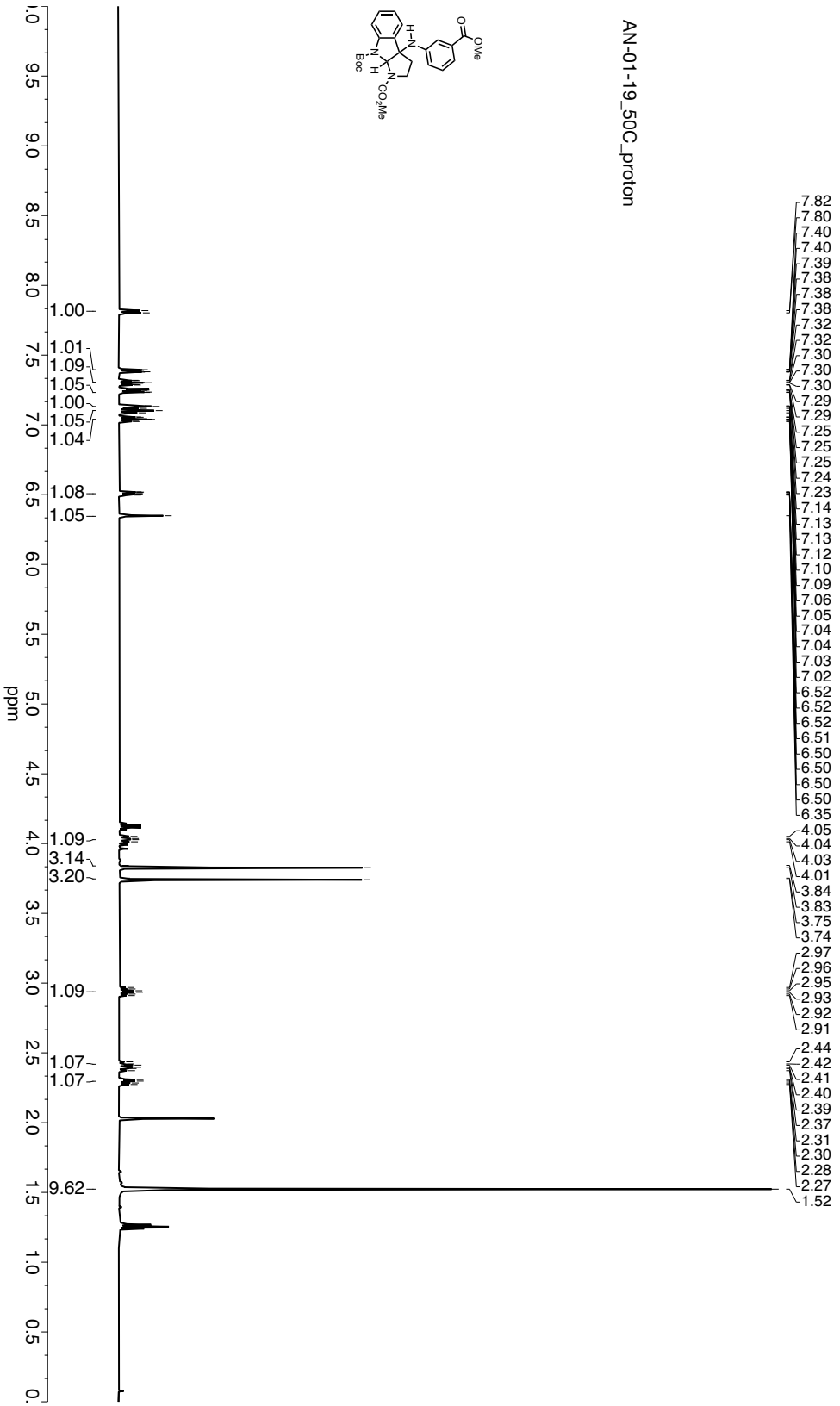

AN1-062-3_CD2Cl2_CARBON_01
155.8
152.9
146.8
144.2
136.1
133.6
129.9
124.1
123.9
121.0
116.9
114.7
81.8
79.3
73.7
45.2
41.5
39.3
28.6
ppm


JS5-103-3_50C
SMe
Boc
CO2Me
ppm
1.00
1.11
1.42
3.14
3.02
1.29
3.16
1.09
3.98
1.13
9.32
7.78
7.30
7.24
7.06
6.33
4.01
3.75
2.93
2.36
1.53


JS5-103-3_C13_50C
155.3
152.4
152.0
143.3
132.8
131.9
130.8
130.4
129.8
127.2
126.7
124.0
123.6
123.3
116.5
116.3
81.8
78.5
72.1
52.6
44.4
39.9
28.4
28.3
18.1
ppm


AN-01-03_50C_proton
ppm
1.06
2.09
0.99
1.01
0.92
1.07
2.19
1.08
1.05
2.92
3.00
1.03
1.04
1.06
8.81
7.82
7.81
7.77
7.76
7.75
7.75
7.33
7.33
7.32
7.31
7.30
7.30
7.24
7.23
7.06
7.06
7.05
7.04
7.03
6.40
6.36
6.34
6.34
4.47
4.07
4.06
4.05
4.03
3.82
3.82
3.75
3.75
3.50
3.49
3.48
3.48
3.47
3.47
3.46
3.39
3.38
3.36
3.35
2.98
2.97
2.95
2.94
2.93
2.92
2.47
2.46
2.45
2.43
2.43
2.41
2.30
2.29
2.27
2.26
1.54
1.54


AN-01-03_50C_carbon
ppm
167.1
152.5
149.0
143.5
136.7
131.6
130.3
124.0
123.3
120.4
116.4
113.9
82.3
81.2
78.7
71.9
52.9
51.7
47.6
44.5
40.4
28.5


AN-01-19_50C_proton
ppm
1.00
1.01
1.09
1.05
1.00
1.05
1.04
1.08
1.05
1.09
3.14
3.20
1.09
1.07
1.07
9.62
7.82
7.80
7.40
7.40
7.39
7.38
7.38
7.38
7.32
7.32
7.30
7.30
7.30
7.29
7.29
7.25
7.25
7.25
7.24
7.23
7.14
7.13
7.13
7.12
7.10
7.09
7.06
7.05
7.04
7.04
7.03
7.02
6.52
6.52
6.52
6.51
6.50
6.50
6.50
6.50
6.50
6.35
4.05
4.04
4.03
4.01
3.84
3.83
3.75
3.74
2.97
2.96
2.95
2.93
2.92
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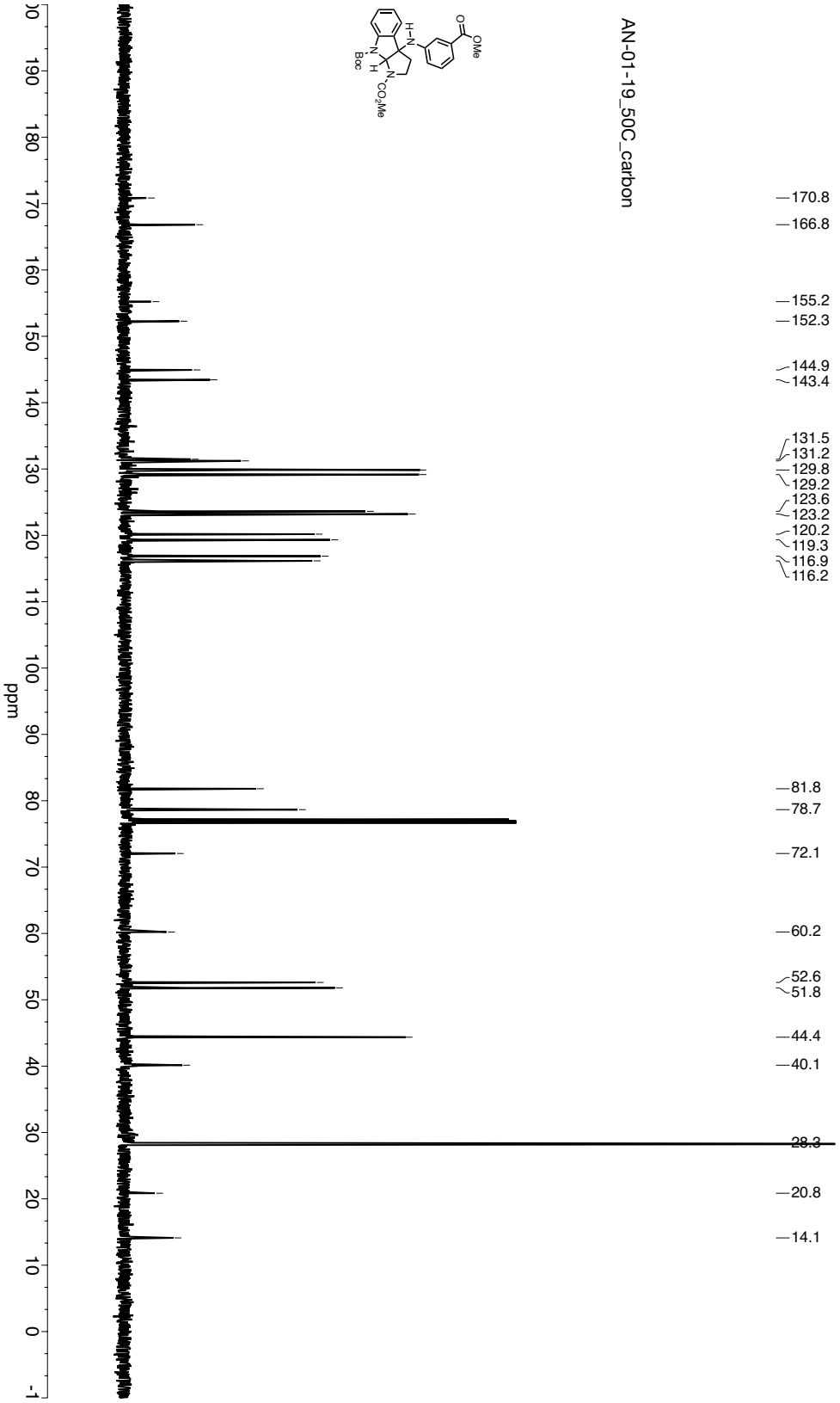
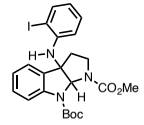
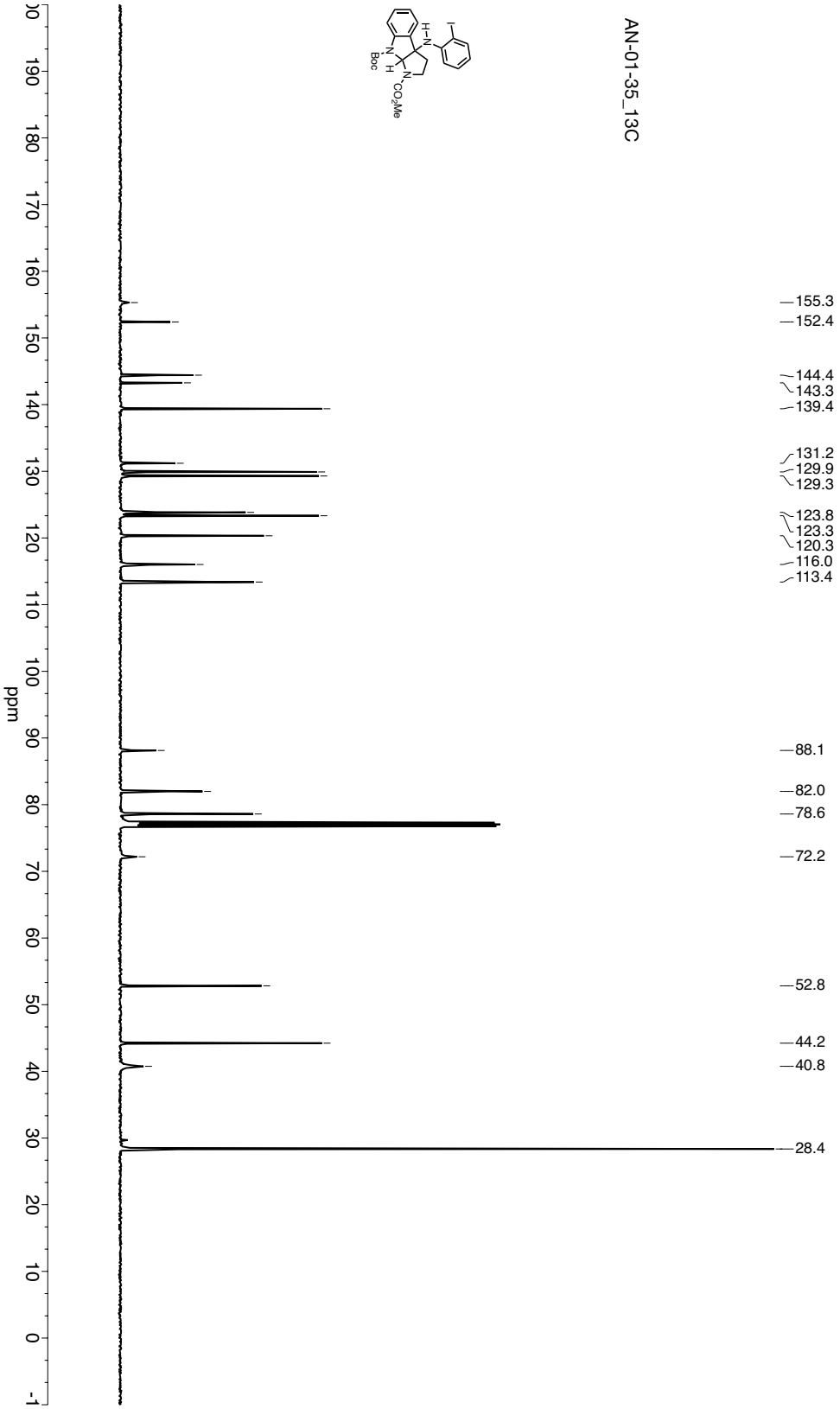
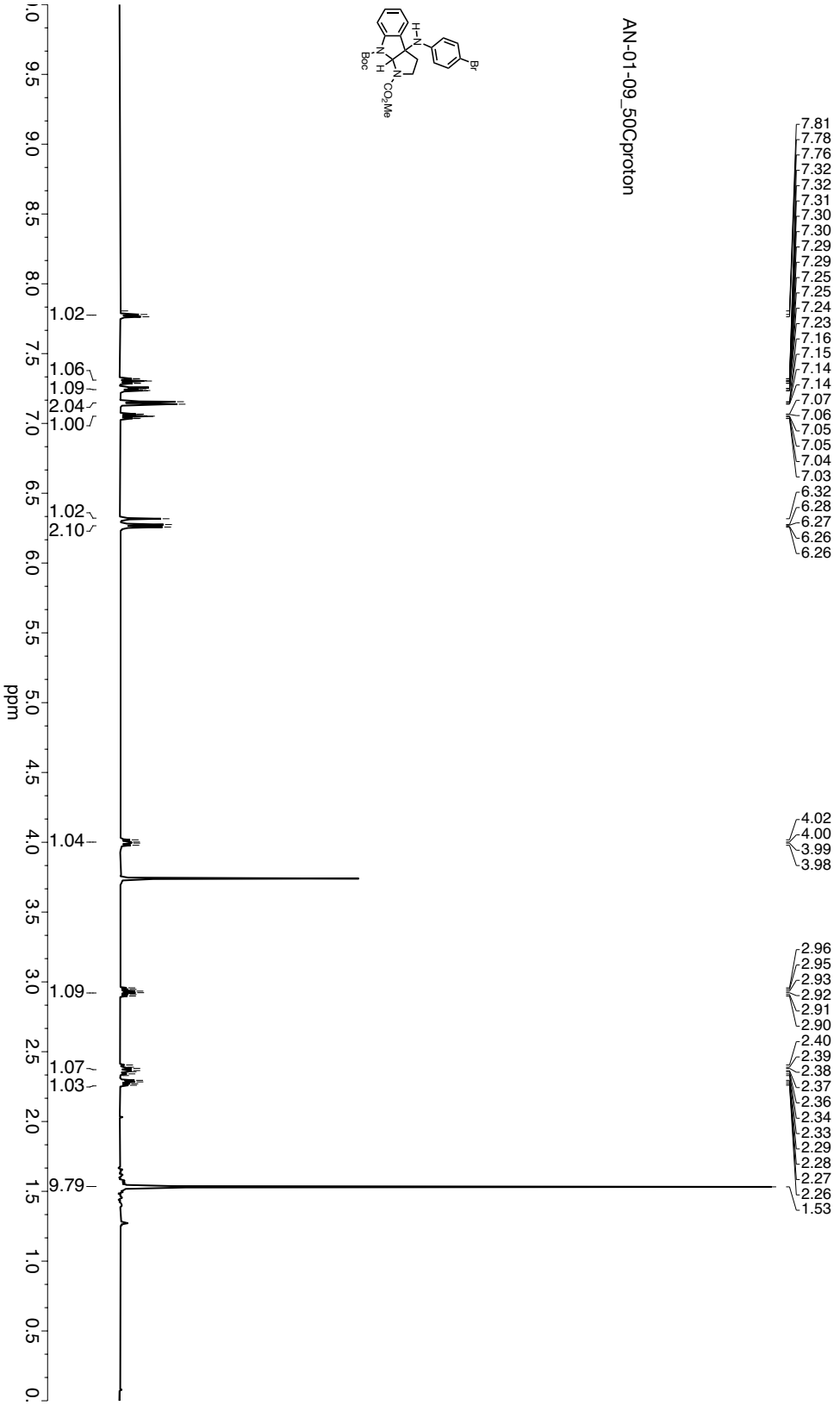
2.37
2.31
2.30
2.28
2.27
1.52

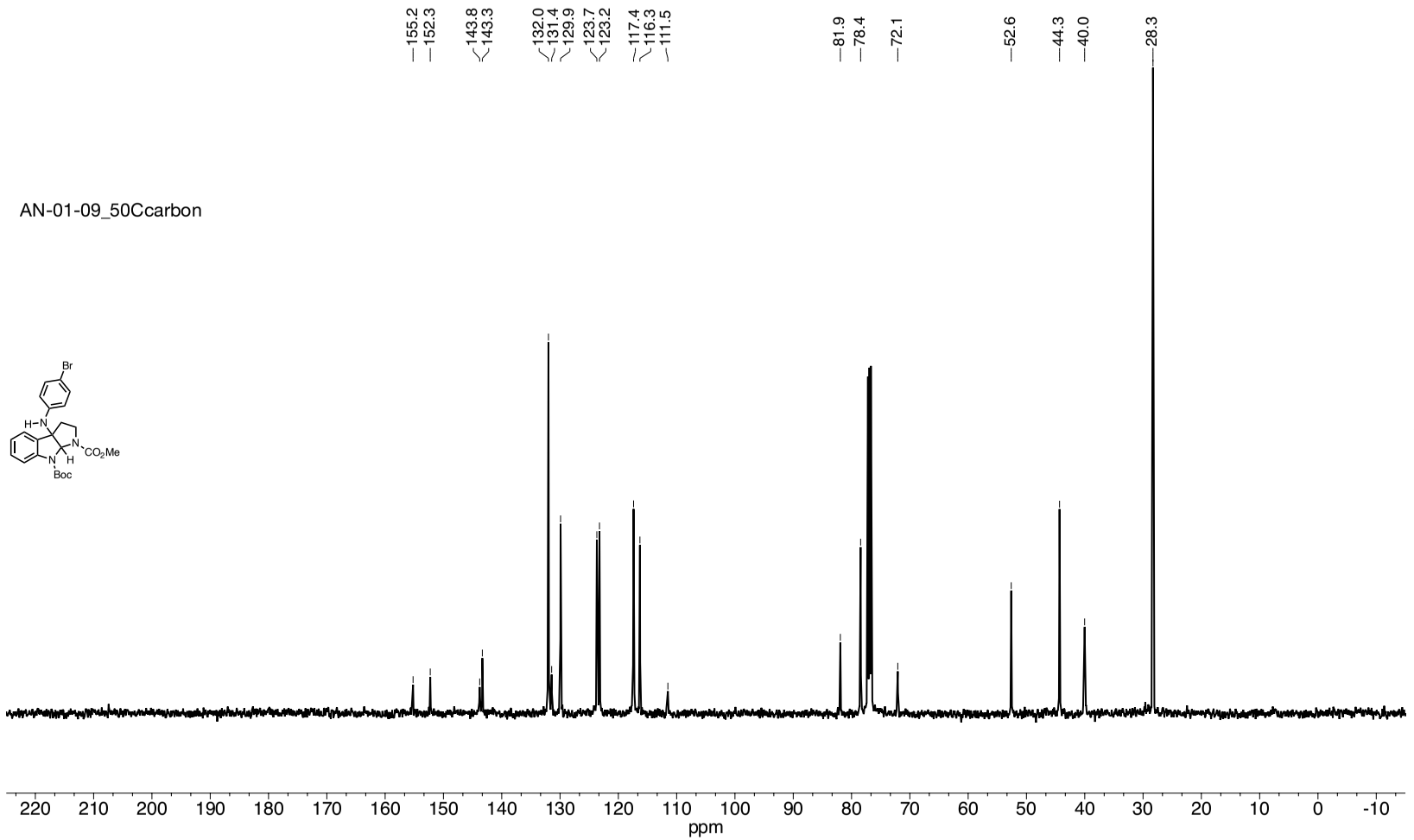

AN-01-19_50C_carbon
ppm
170.8
166.8
155.2
152.3
144.9
143.4
131.5
131.2
129.8
129.2
123.6
123.2
120.2
119.3
116.9
116.2
81.8
78.7
72.1
60.2
52.6
51.8
44.4
40.1
28.3
20.8
14.1

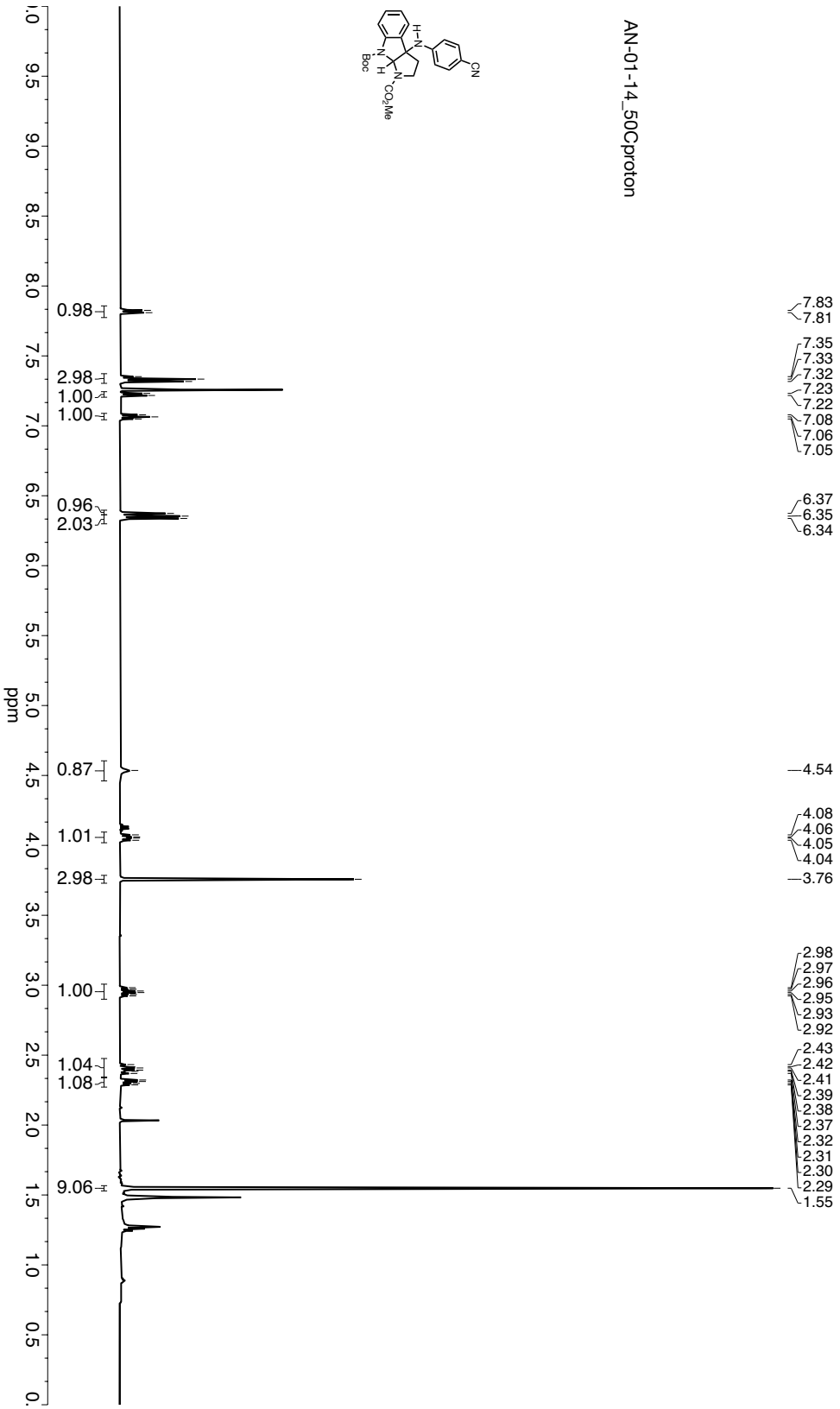
AN-01-35_Clean

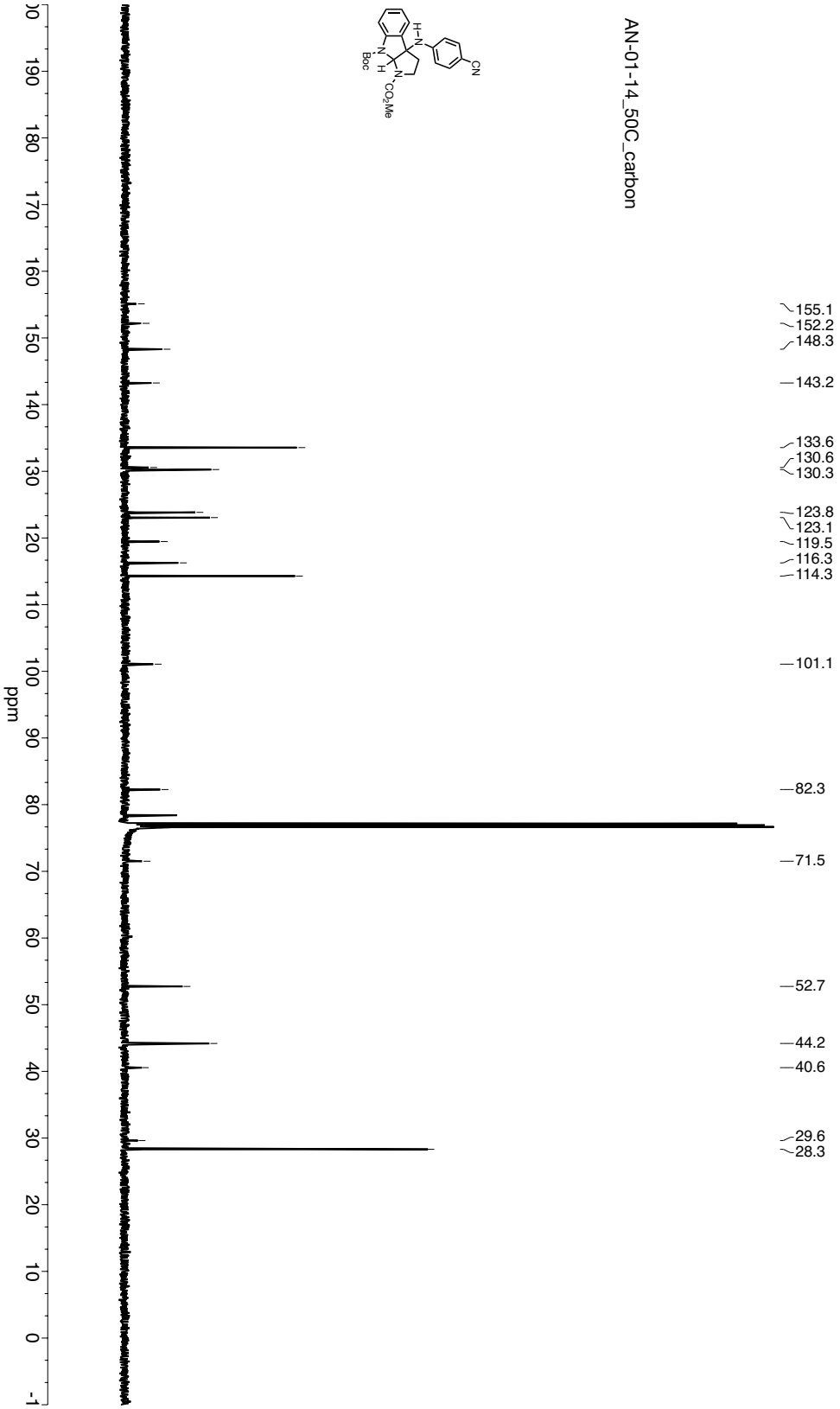


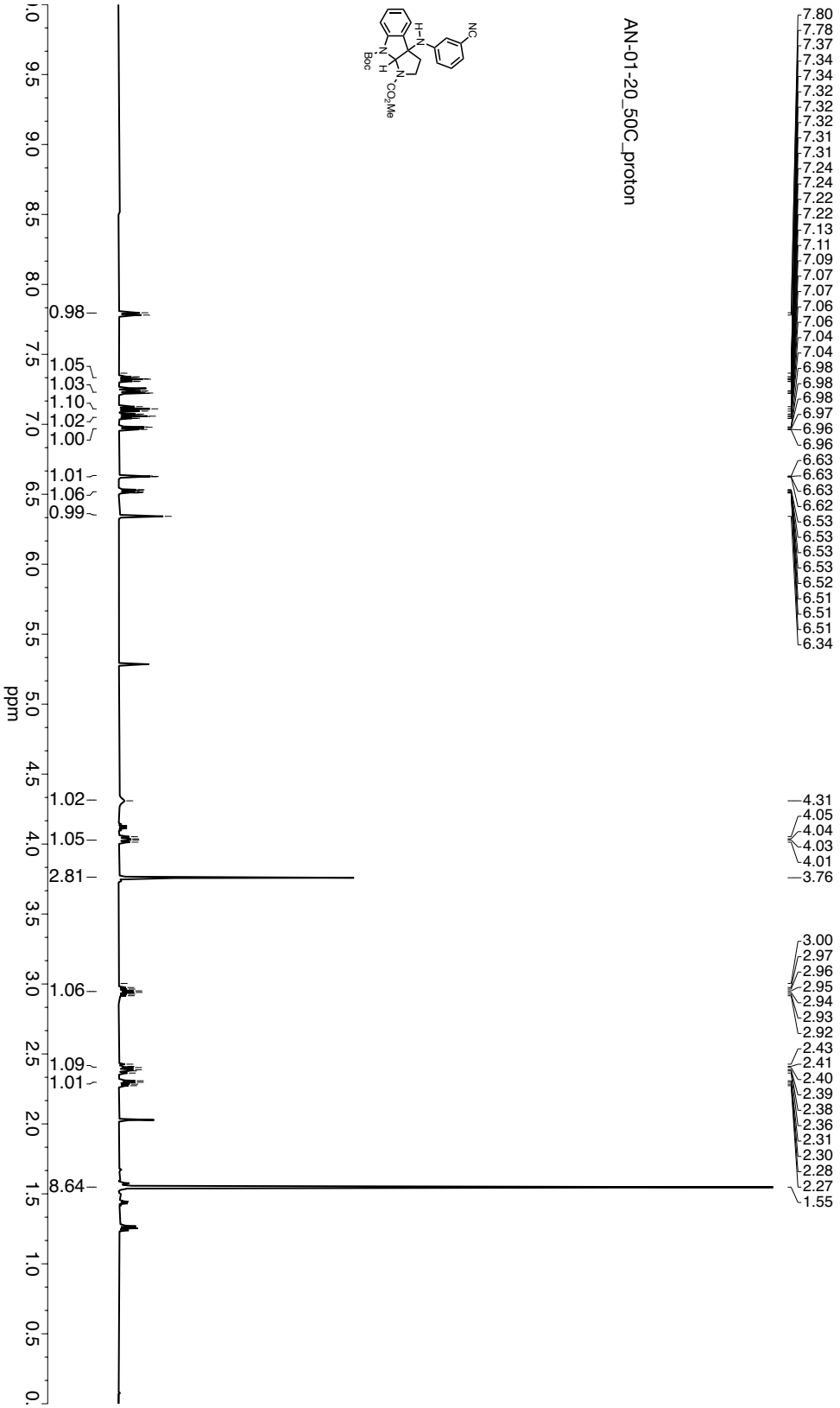

AN-01-35_13C
155.3
152.4
144.4
143.3
139.4
131.2
129.9
129.3
123.8
123.3
120.3
116.0
113.4
88.1
82.0
78.6
72.2
52.8
44.2
40.8
28.4
ppm

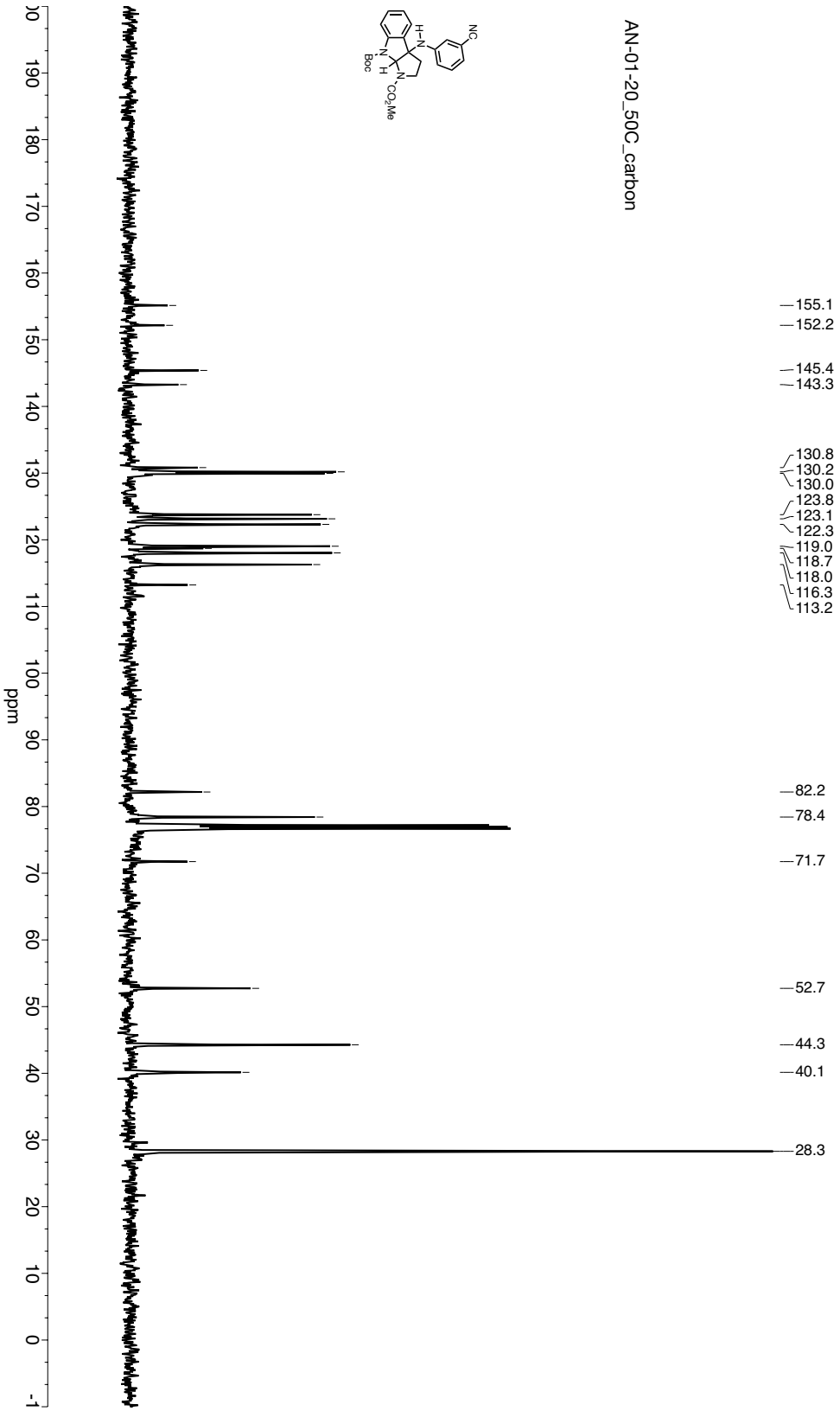

AN-01-09_50Cproton
ppm
1.02
1.06
1.09
2.04
1.00
1.02
2.10
1.04
1.09
1.07
1.03
9.79
7.81
7.78
7.76
7.32
7.32
7.31
7.30
7.30
7.29
7.29
7.25
7.25
7.24
7.23
7.16
7.15
7.14
7.14
7.07
7.06
7.05
7.05
7.04
7.03
6.32
6.28
6.27
6.26
6.26
4.02
4.00
3.99
3.98
2.96
2.95
2.93
2.92
2.91
2.90
2.40
2.39
2.38
2.37
2.36
2.34
2.33
2.29
2.28
2.27
2.26
1.53

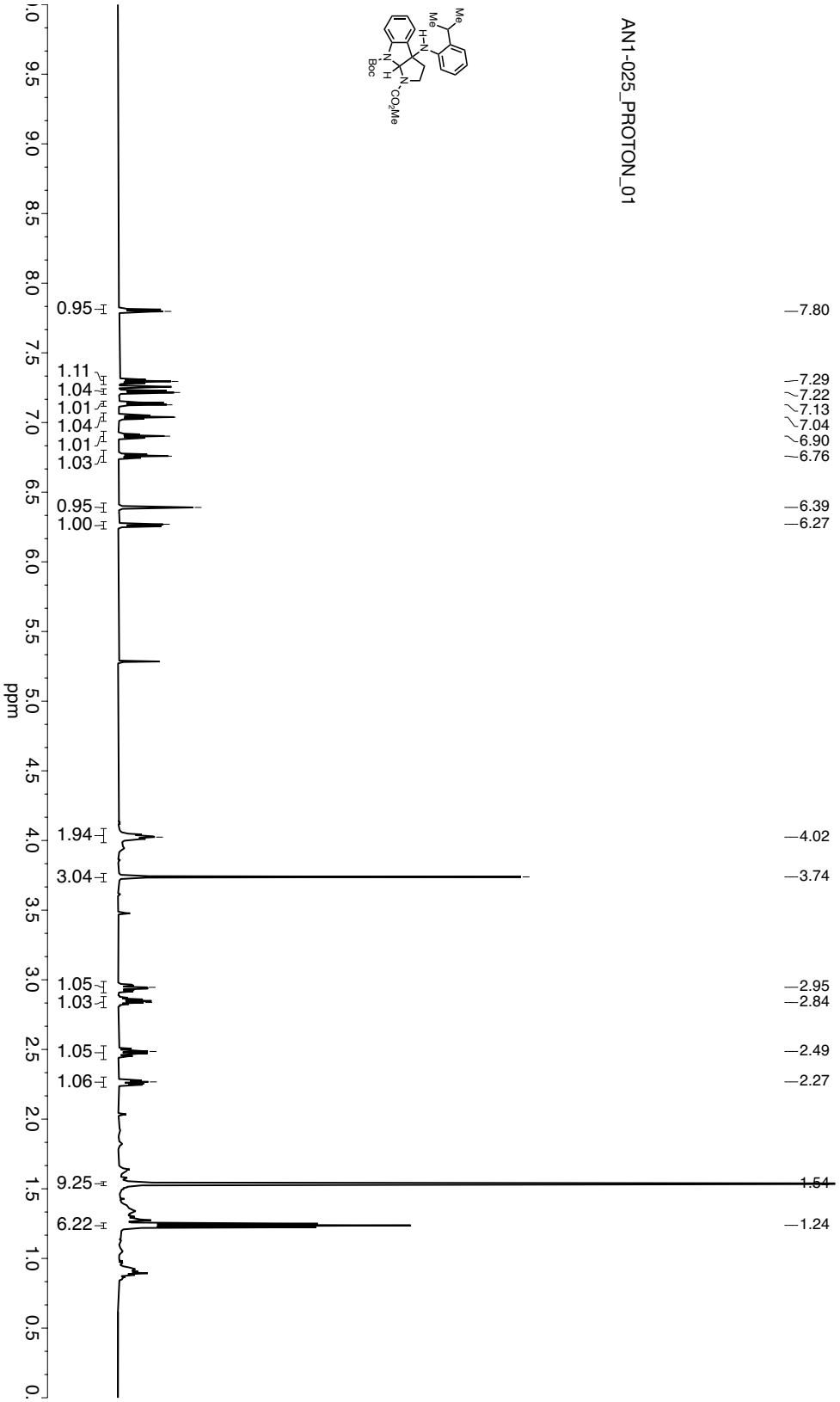

155.2
152.3
143.8
143.3
132.0
131.4
129.9
123.7
123.2
117.4
116.3
111.5
81.9
78.4
72.1
52.6
44.3
40.0
28.3
AN-01-09_50Ccarbon
343
Br
H-N
N
CO2Me
N
H
Boc
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
ppm

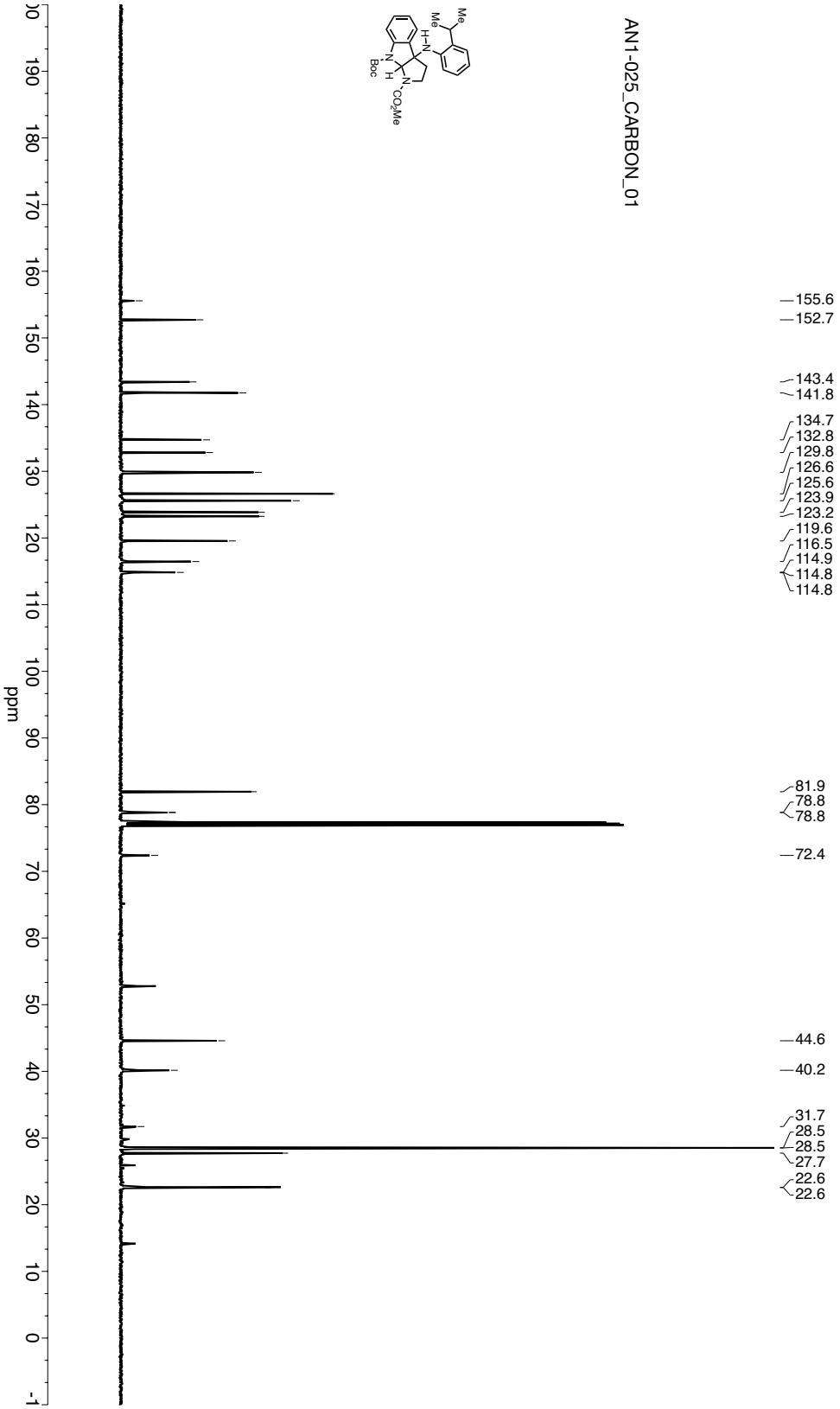

AN-01-14_50Cproton
ppm
0.98
2.98
1.00
1.00
0.96
2.03
0.87
1.01
2.98
1.00
1.04
1.08
9.06
7.83
7.81
7.35
7.33
7.32
7.23
7.22
7.08
7.06
7.05
6.37
6.35
6.34
4.54
4.08
4.06
4.05
4.04
3.76
2.98
2.97
2.96
2.95
2.93
2.92
2.43
2.42
2.41
2.39
2.38
2.37
2.32
2.31
2.30
2.29
1.55

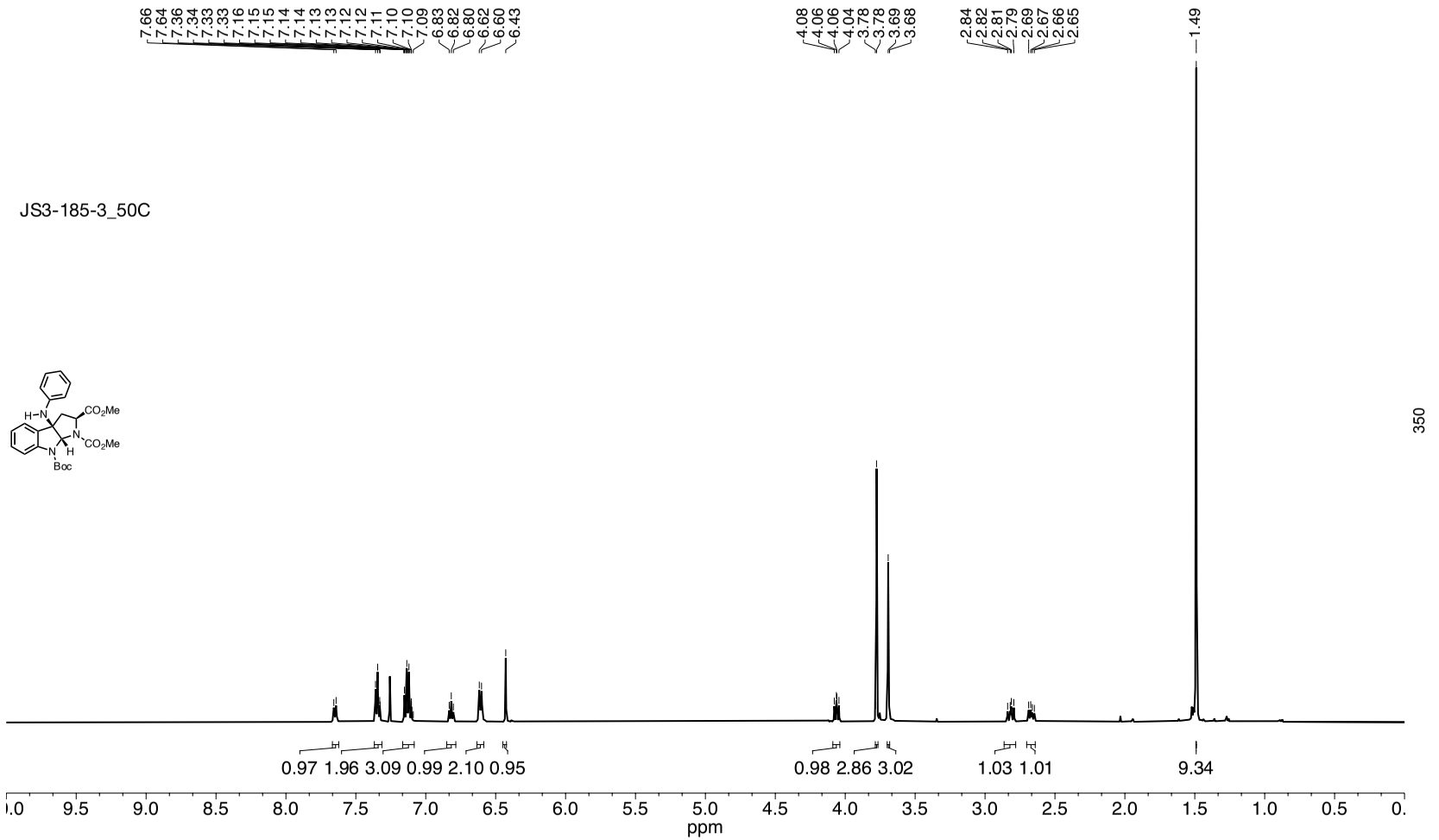

AN-01-14_50C_carbon
155.1
152.2
148.3
143.2
133.6
130.6
130.3
123.8
123.1
119.5
116.3
114.3
101.1
82.3
71.5
52.7
44.2
40.6
29.6
28.3
ppm

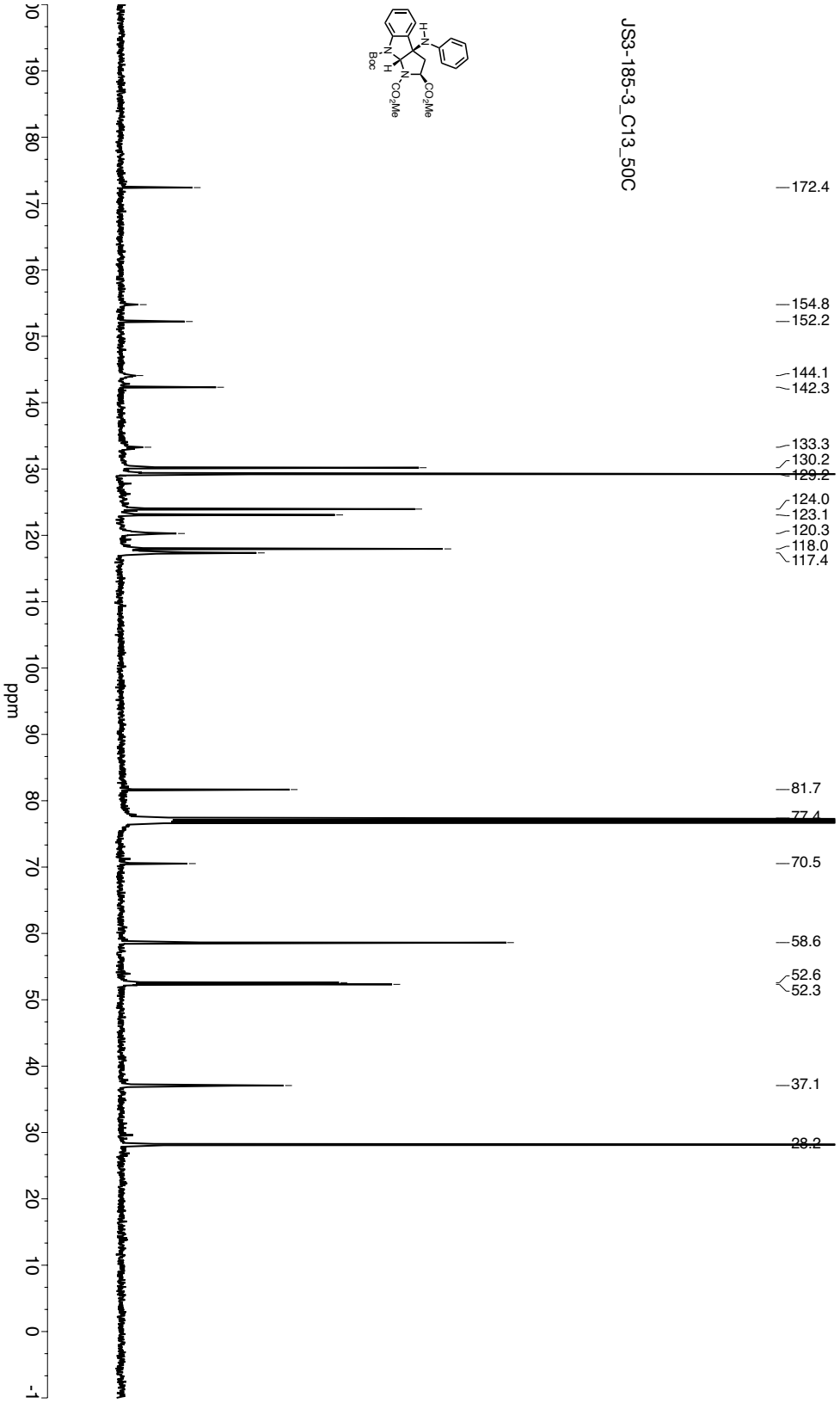

AN-01-20_50C_proton
ppm
0.98
1.05
1.03
1.10
1.02
1.00
1.01
1.06
0.99
1.02
1.05
2.81
1.06
1.09
1.01
8.64
7.80
7.78
7.37
7.34
7.34
7.32
7.32
7.32
7.31
7.31
7.24
7.24
7.22
7.22
7.13
7.11
7.09
7.07
7.07
7.06
7.06
7.04
7.04
6.98
6.98
6.98
6.97
6.96
6.96
6.63
6.63
6.63
6.62
6.53
6.53
6.53
6.53
6.53
6.52
6.51
6.51
6.51
6.34
4.31
4.05
4.04
4.03
4.01
3.76
3.00
2.97
2.96
2.95
2.94
2.93
2.92
2.43
2.41
2.40
2.39
2.38
2.36
2.31
2.30
2.28
2.27
1.55

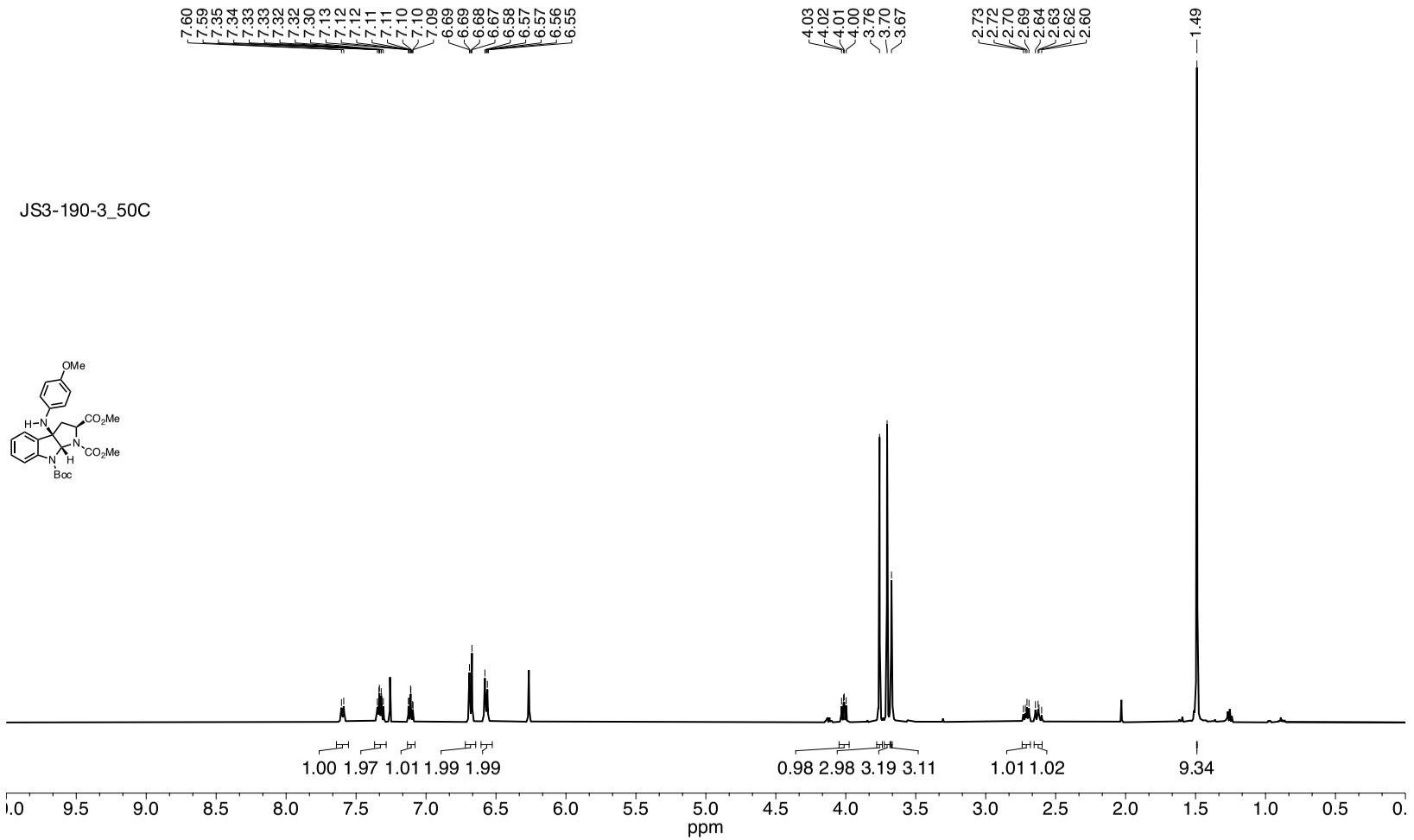

AN-01-20_50C_carbon
155.1
152.2
145.4
143.3
130.8
130.2
130.0
123.8
123.1
122.3
119.0
118.7
118.0
116.3
113.2
82.2
78.4
71.7
52.7
44.3
40.1
28.3
ppm

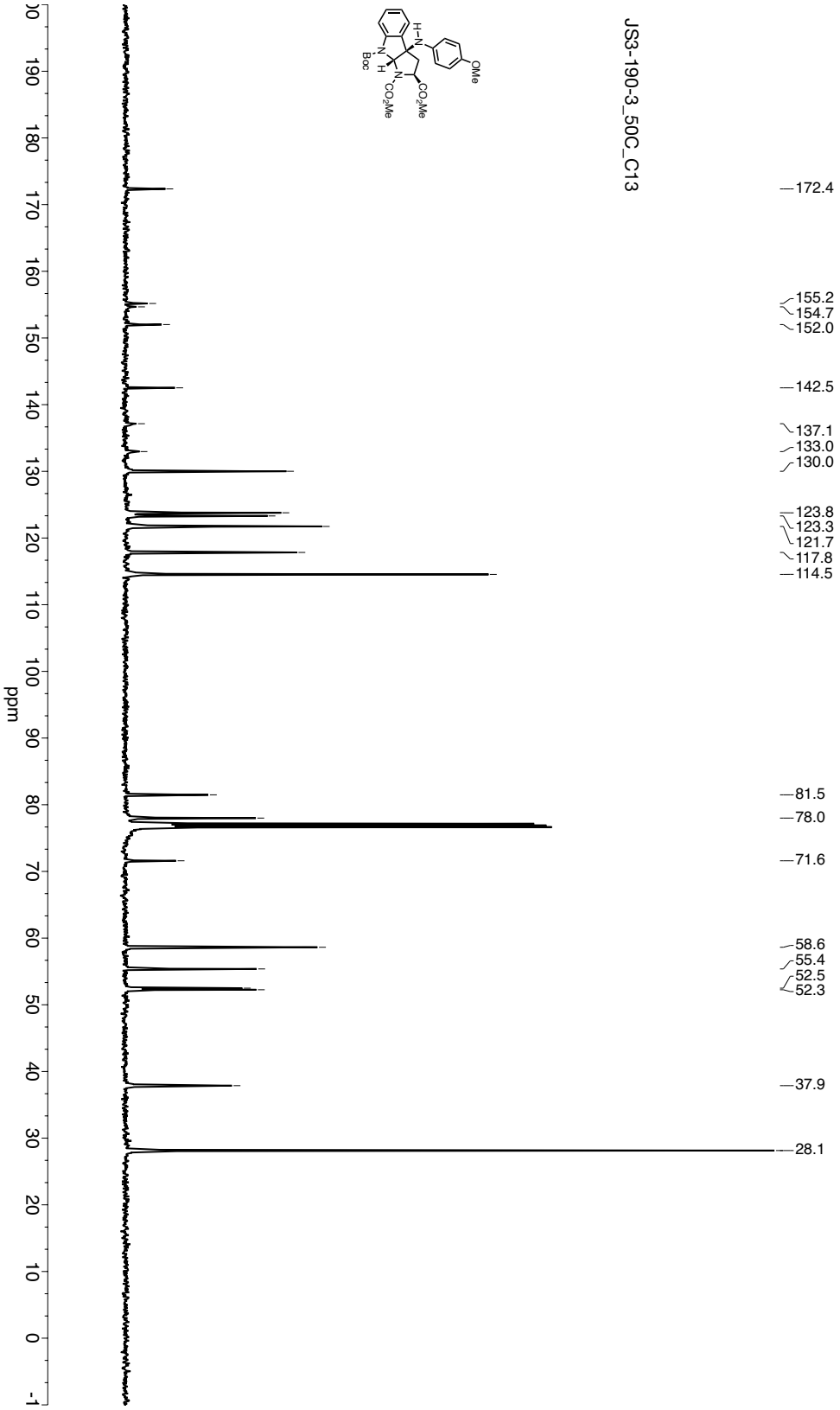

AN1-025_PROTON_01
ppm
0.95
1.11
1.04
1.01
1.04
1.01
1.03
0.95
1.00
1.94
3.04
1.05
1.03
1.05
1.06
9.25
6.22
7.80
7.29
7.22
7.13
7.04
6.90
6.76
6.39
6.27
4.02
3.74
2.95
2.84
2.49
2.27
1.54
1.24

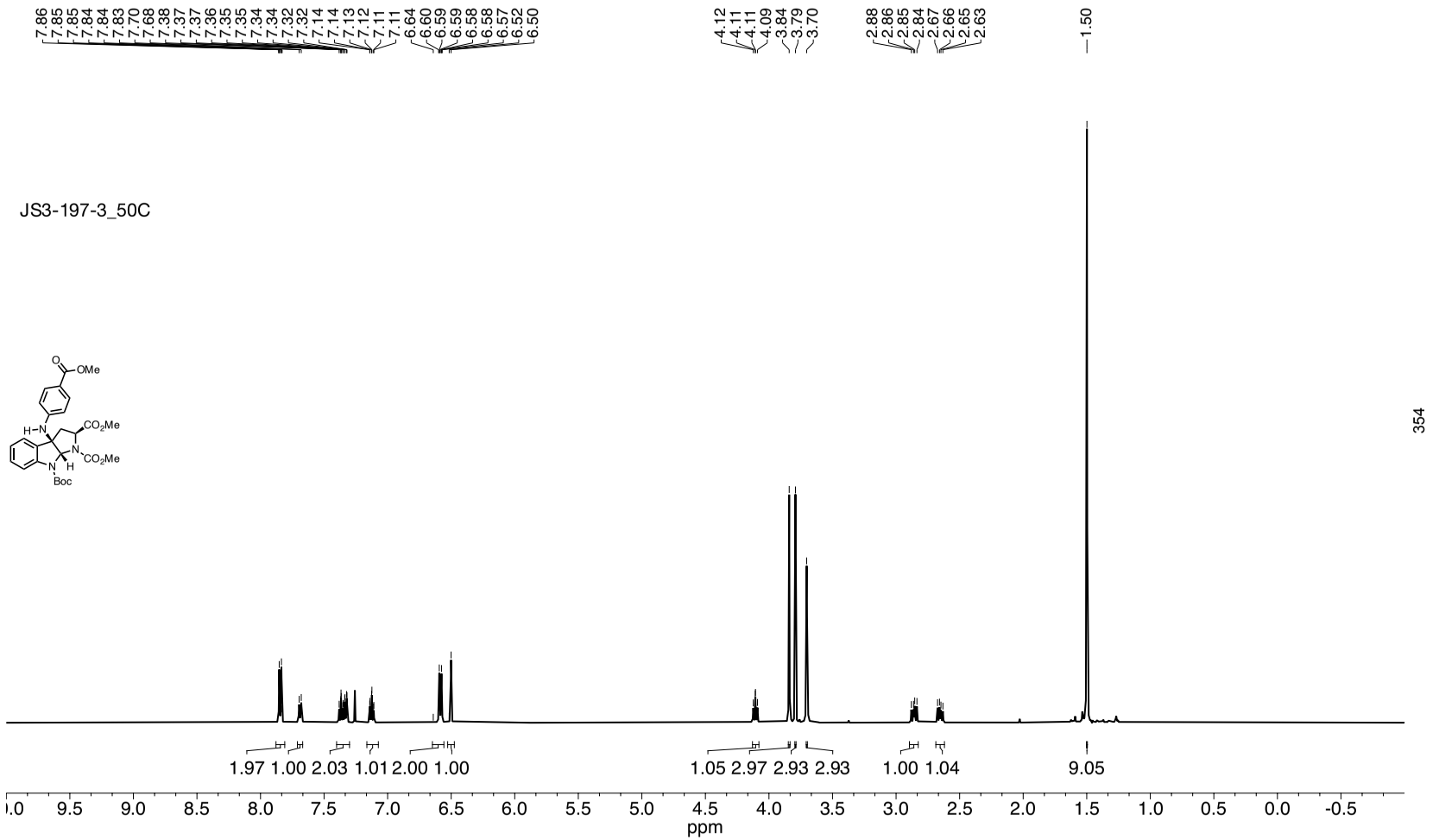

AN1-025_CARBON_01
155.6
152.7
143.4
141.8
134.7
132.8
129.8
126.6
125.6
123.9
123.2
119.6
116.5
114.9
114.8
114.8
81.9
78.8
78.8
72.4
44.6
40.2
31.7
28.5
28.5
27.7
22.6
22.6
ppm

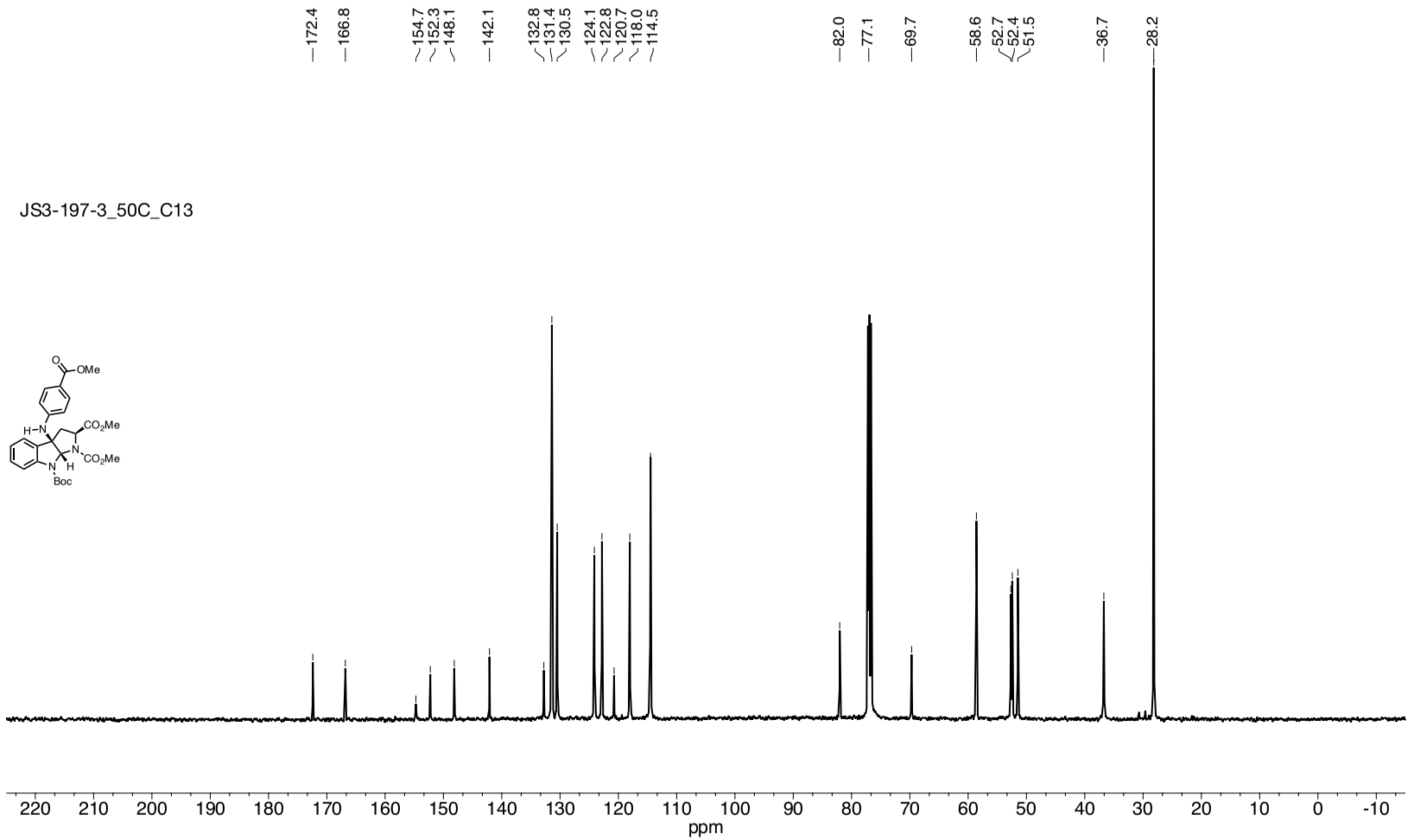

7.66
7.64
7.36
7.34
7.33
7.33
7.16
7.15
7.15
7.14
7.14
7.13
7.13
7.12
7.12
7.11
7.10
7.10
7.09
6.83
6.82
6.80
6.62
6.60
6.43
4.08
4.06
4.06
4.04
3.78
3.69
3.68
2.84
2.82
2.81
2.79
2.69
2.67
2.66
2.65
1.49
JS3-185-3_50C
CO2Me
CO2Me
Boc
350
0.97 1.96 3.09 0.99 2.10 0.95
0.98 2.86 3.02
1.03 1.01
9.34
ppm

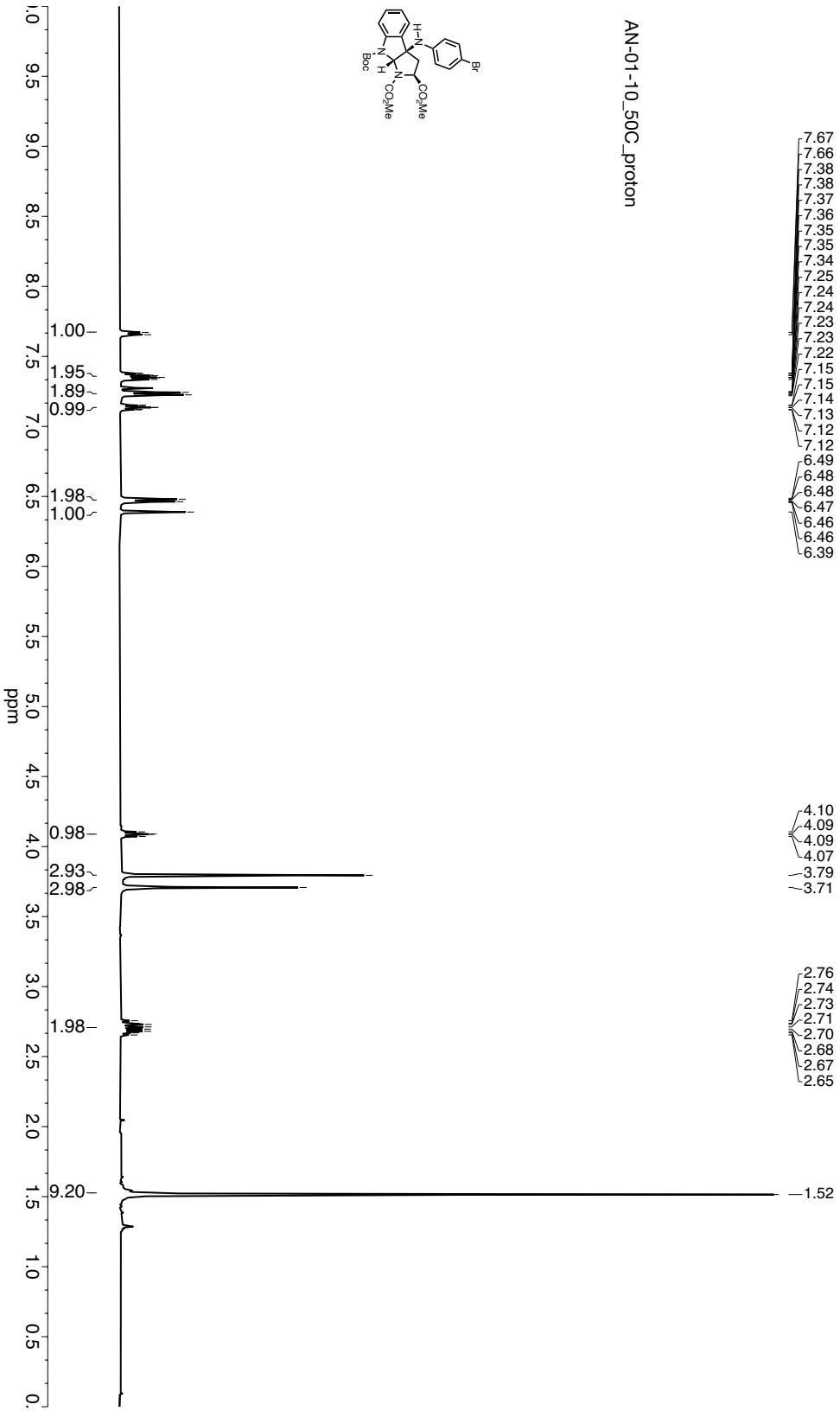

JS3-185-3_C13_50C
172.4
154.8
152.2
144.1
142.3
133.3
130.2
129.2
124.0
123.1
120.3
118.0
117.4
81.7
77.4
70.5
58.6
52.6
52.3
37.1
28.2
ppm
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

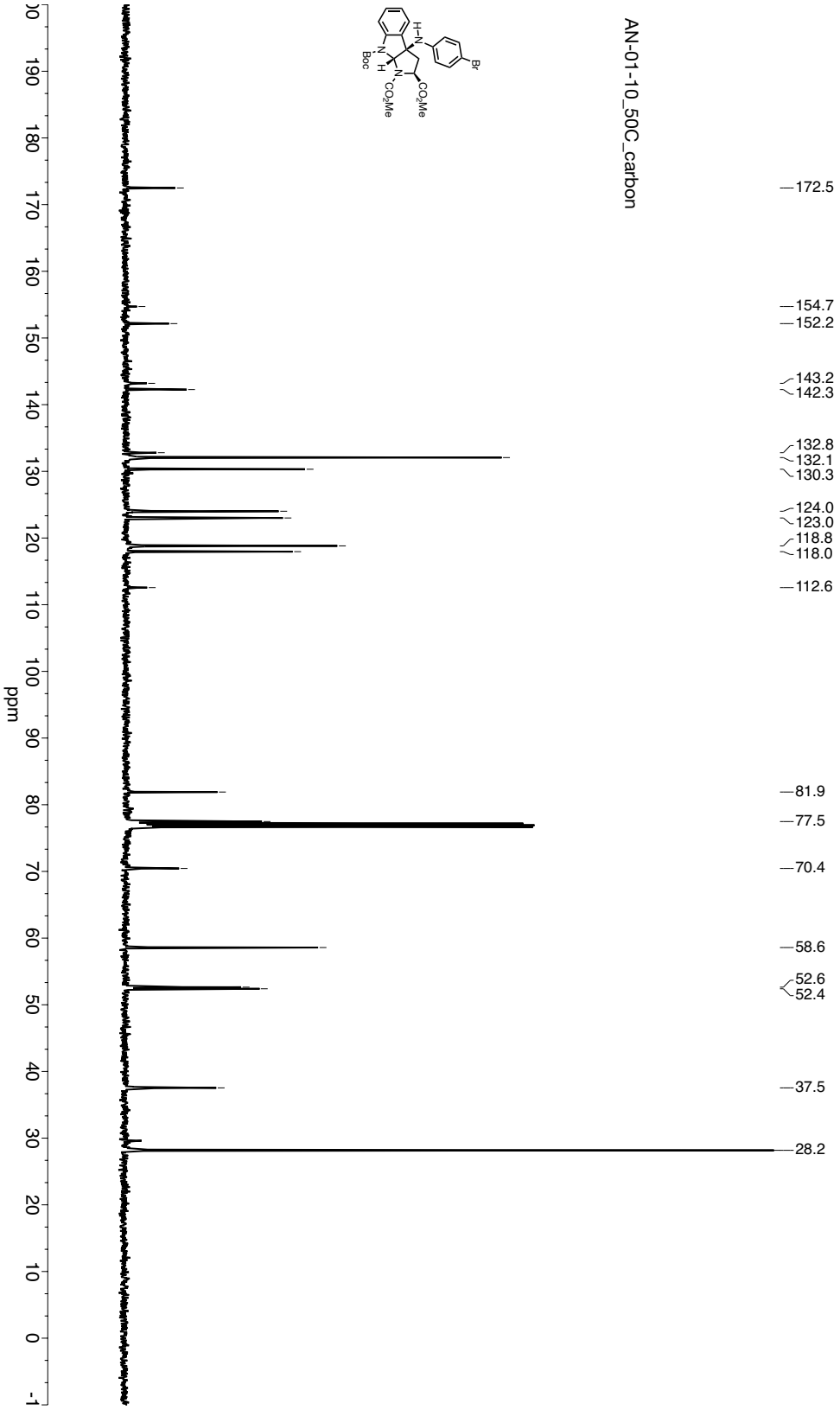

7.60
7.59
7.35
7.34
7.33
7.33
7.32
7.32
7.30
7.13
7.12
7.12
7.11
7.11
7.10
7.10
7.09
6.69
6.69
6.68
6.67
6.58
6.57
6.57
6.56
6.55
4.03
4.02
4.01
4.00
3.76
3.70
3.67
2.73
2.72
2.70
2.69
2.64
2.63
2.62
2.60
1.49
JS3-190-3_50C
OMe
H–N
CO2Me
N
CO2Me
N
H
Boc
352
1.00 1.97 1.01 1.99 1.99
0.98 2.98 3.19 3.11
1.01 1.02
9.34
ppm

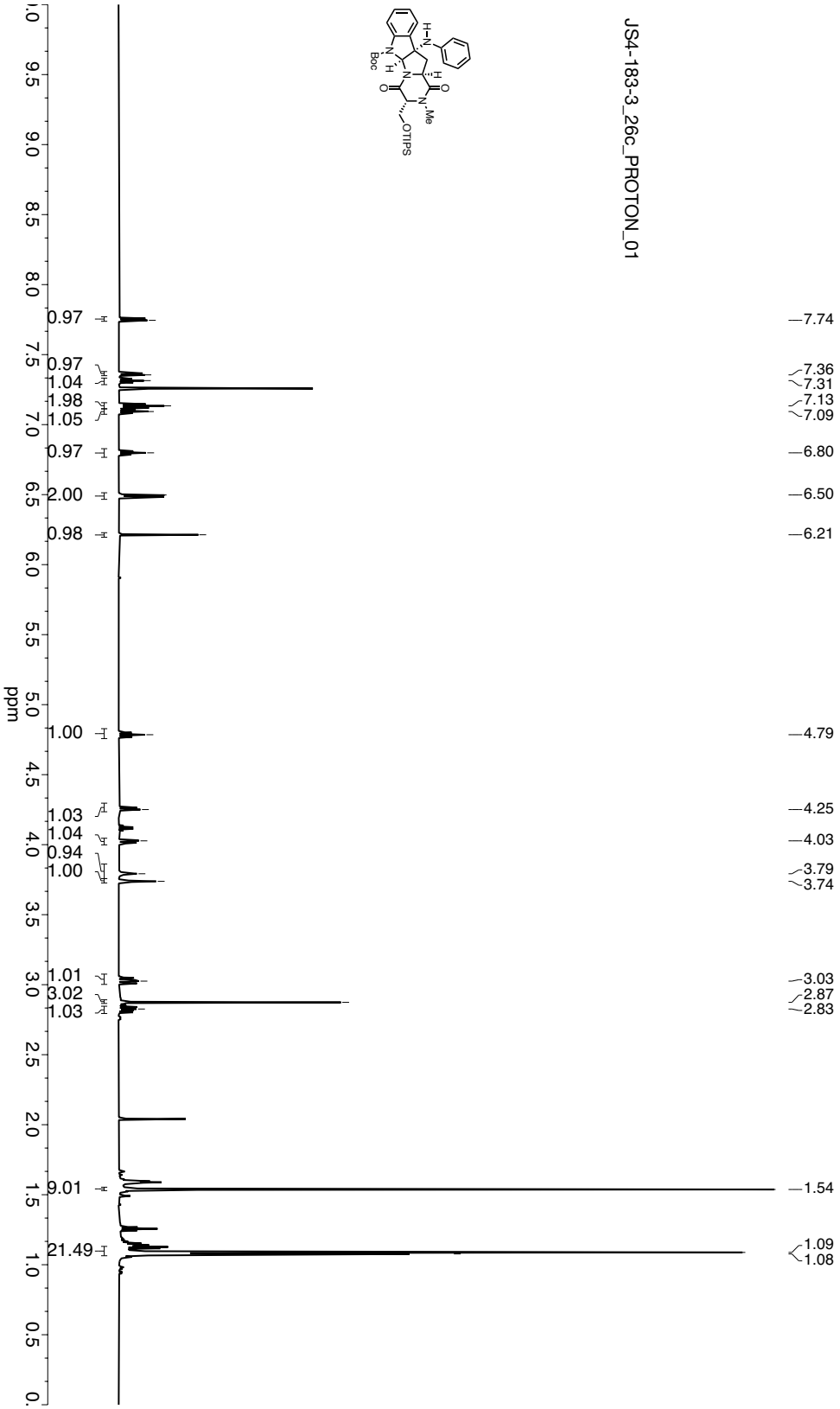

JS3-190-3_50C_C13
ppm
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-1
172.4
155.2
154.7
152.0
142.5
137.1
133.0
130.0
123.8
123.3
121.7
117.8
114.5
81.5
78.0
71.6
58.6
55.4
52.5
52.3
37.9
28.1
OMe
CO2Me
CO2Me
Boc

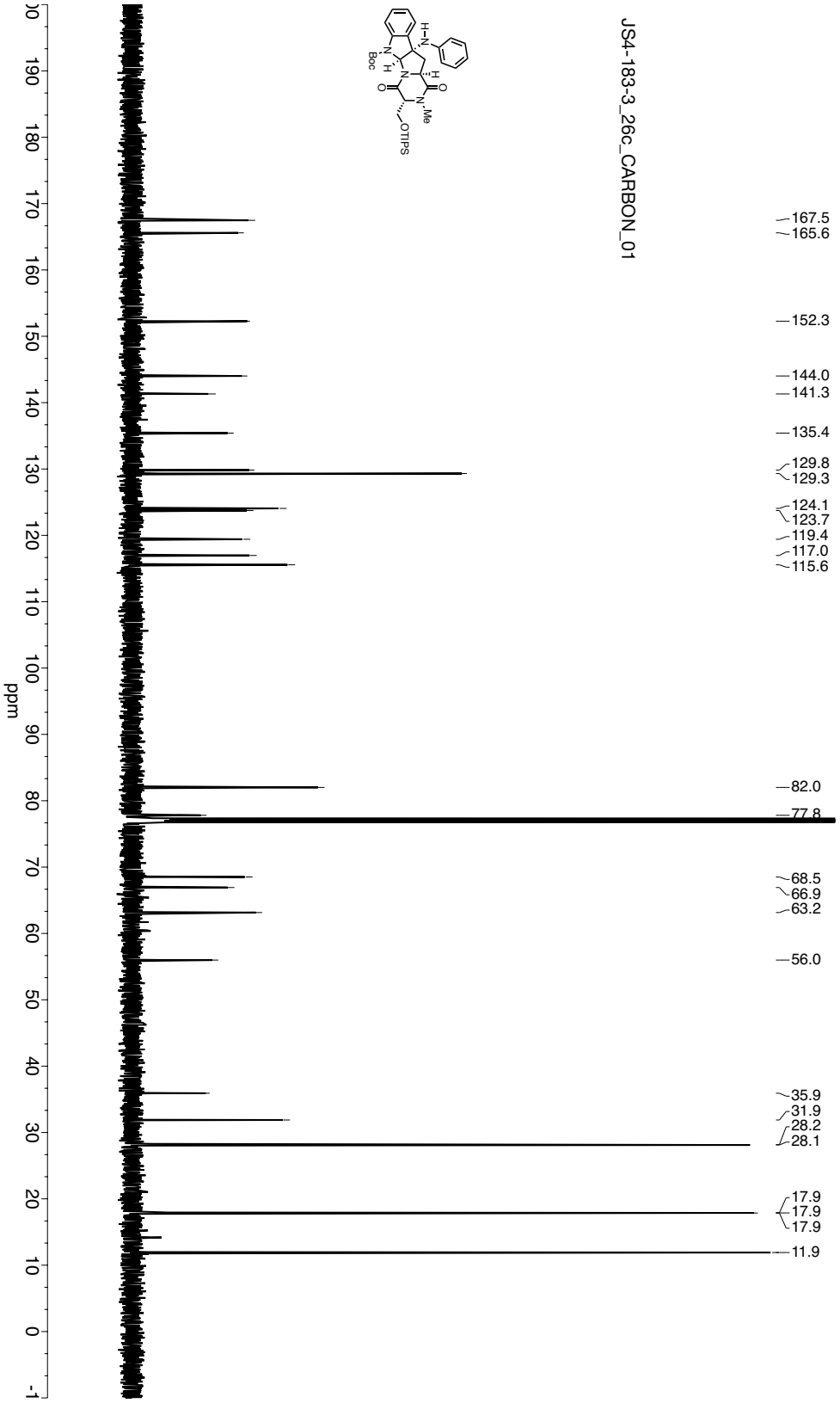

7.86
7.85
7.85
7.84
7.84
7.83
7.70
7.68
7.38
7.37
7.37
7.36
7.35
7.35
7.34
7.34
7.32
7.32
7.14
7.14
7.13
7.12
7.11
7.11
6.64
6.60
6.59
6.59
6.58
6.58
6.57
6.52
6.50
4.12
4.11
4.11
4.09
3.84
3.79
3.70
2.88
2.86
2.85
2.84
2.67
2.66
2.65
2.63
1.50
JS3-197-3_50C
OMe
CO2Me
CO2Me
Boc
354
1.97 1.00 2.03 1.01 2.00 1.00
1.05 2.97 2.93 2.93
1.00 1.04
9.05
ppm

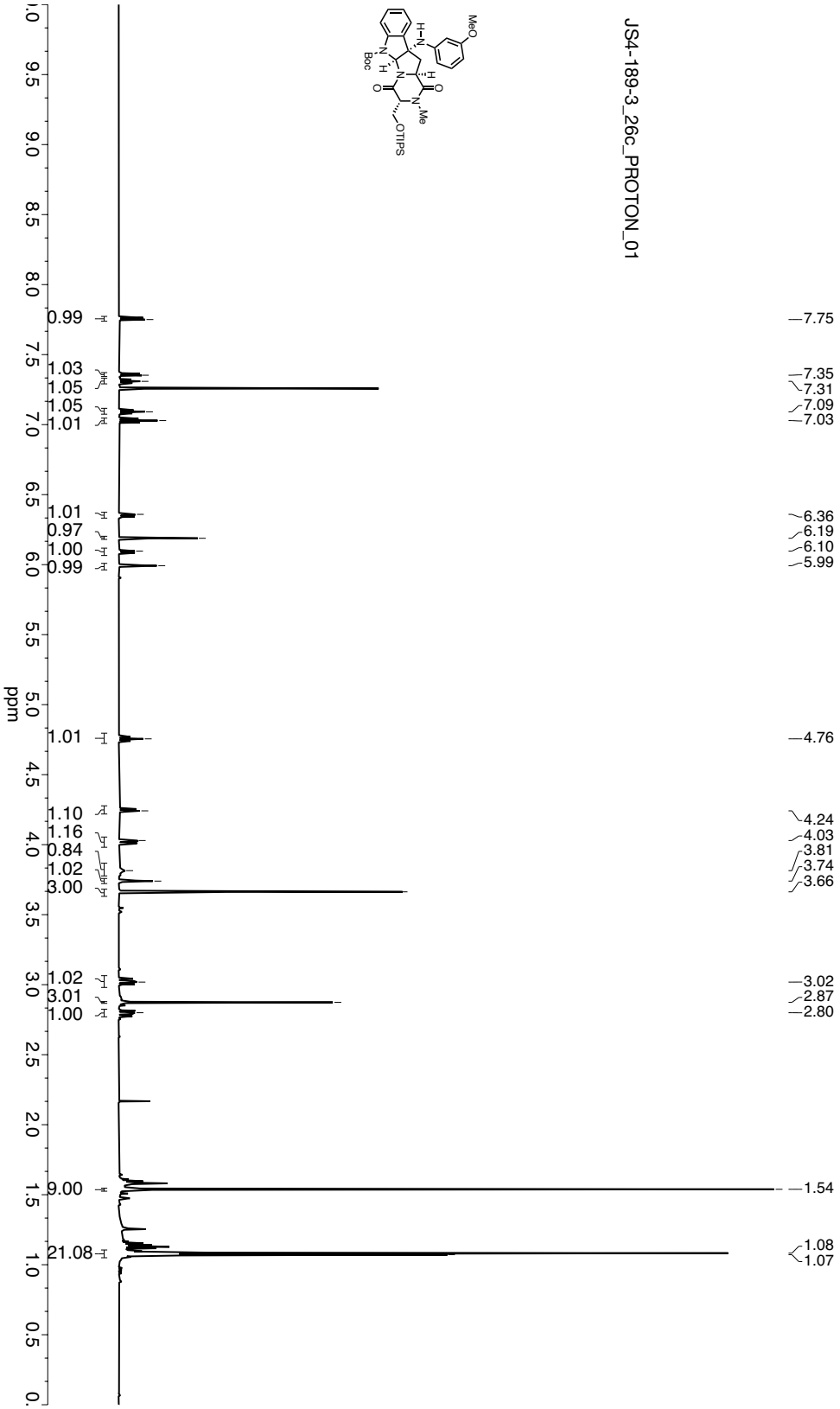

172.4
166.8
154.7
152.3
148.1
142.1
132.8
131.4
130.5
124.1
122.8
120.7
118.0
114.5
82.0
77.1
69.7
58.6
52.7
52.4
51.5
36.7
28.2
JS3-197-3_50C_C13
355
OMe
CO2Me
CO2Me
Boc
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
ppm

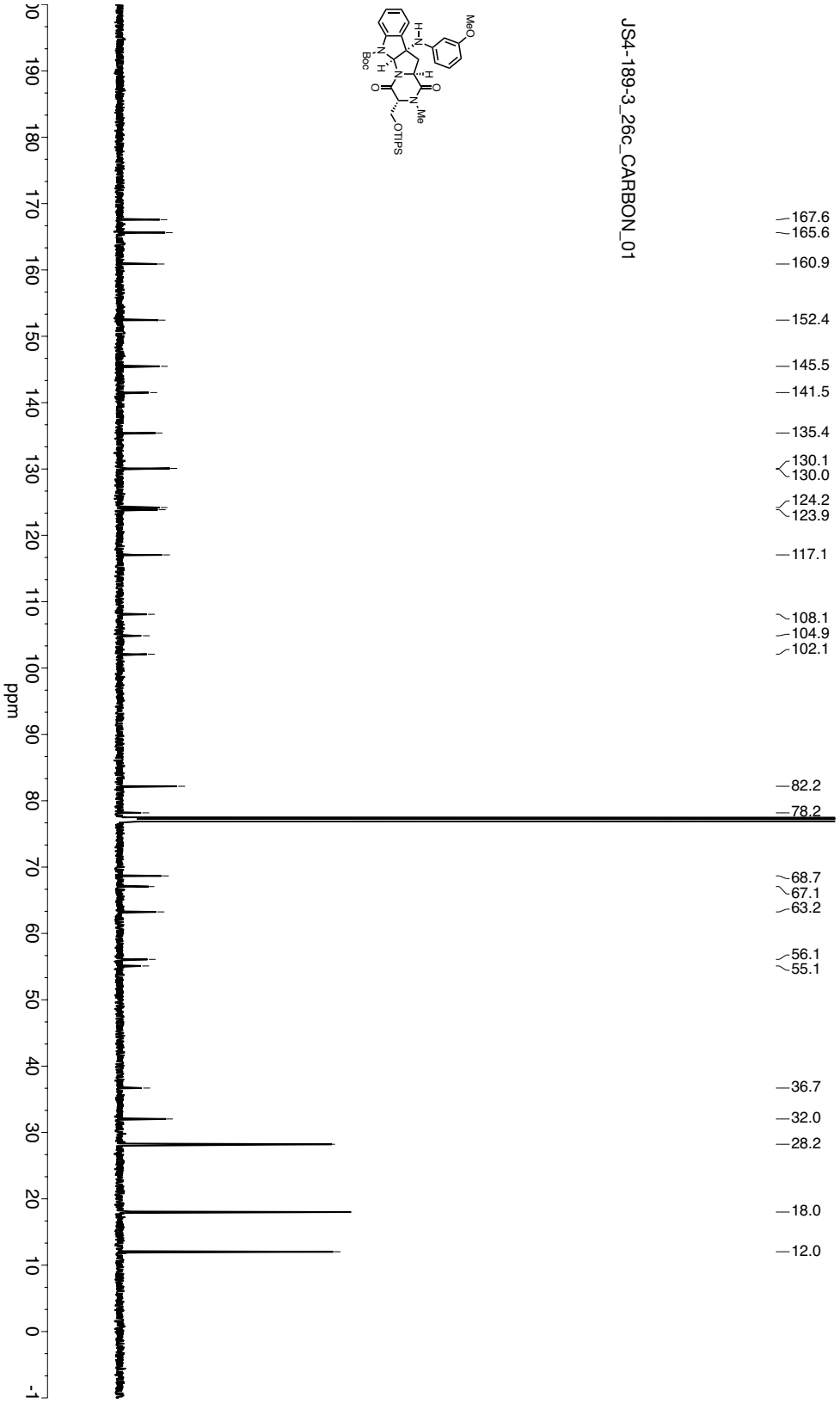

AN-01-10_50C_proton
ppm
1.00
1.95
1.89
0.99
1.98
1.00
0.98
2.93
2.98
1.98
9.20
7.67
7.66
7.38
7.38
7.37
7.36
7.35
7.35
7.34
7.25
7.24
7.24
7.23
7.23
7.22
7.15
7.15
7.14
7.13
7.12
7.12
6.49
6.48
6.48
6.47
6.46
6.46
6.39
4.10
4.09
4.09
4.07
3.79
3.71
2.76
2.74
2.73
2.71
2.70
2.68
2.67
2.65
1.52

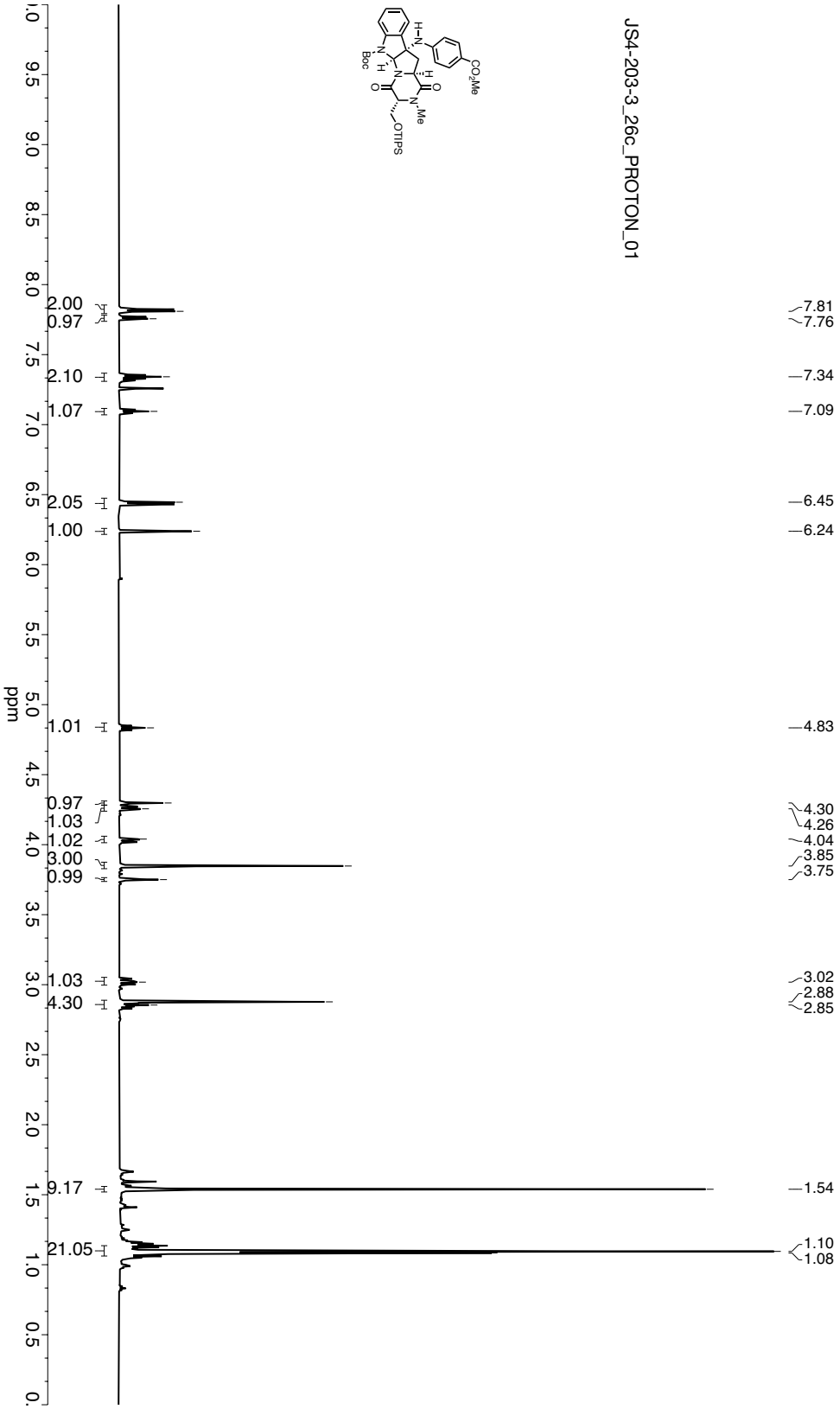

AN-01-10_50C_carbon
ppm
172.5
154.7
152.2
143.2
142.3
132.8
132.1
130.3
124.0
123.0
118.8
118.0
112.6
81.9
77.5
70.4
58.6
52.6
52.4
37.5
28.2

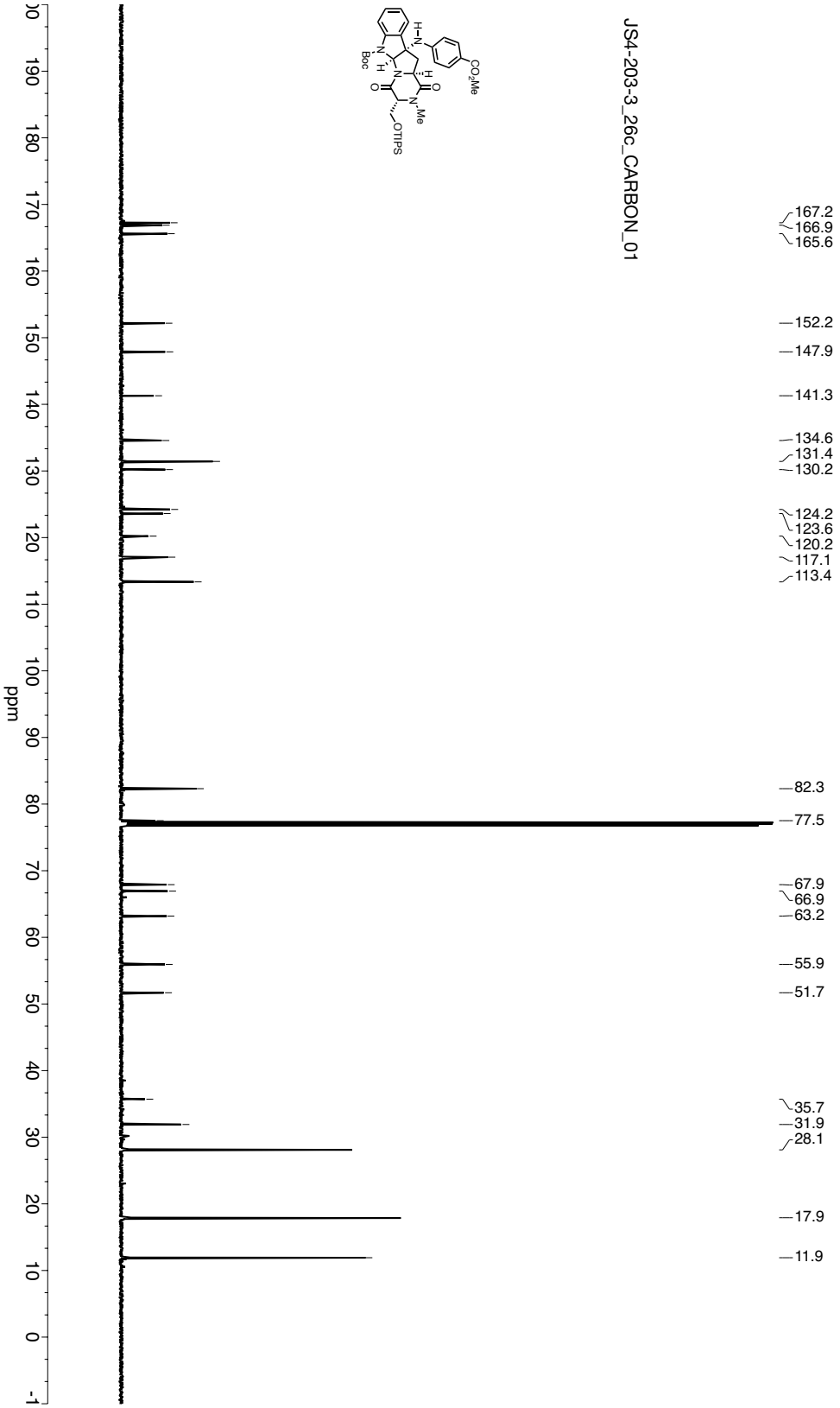

JS4-183-3_26c_PROTON_01
ppm
0.97
0.97
1.04
1.98
1.05
0.97
2.00
0.98
1.00
1.03
1.04
0.94
1.00
1.01
3.02
1.03
9.01
21.49
7.74
7.36
7.31
7.13
7.09
6.80
6.50
6.21
4.79
4.25
4.03
3.79
3.74
3.03
2.87
2.83
1.54
1.09
1.08

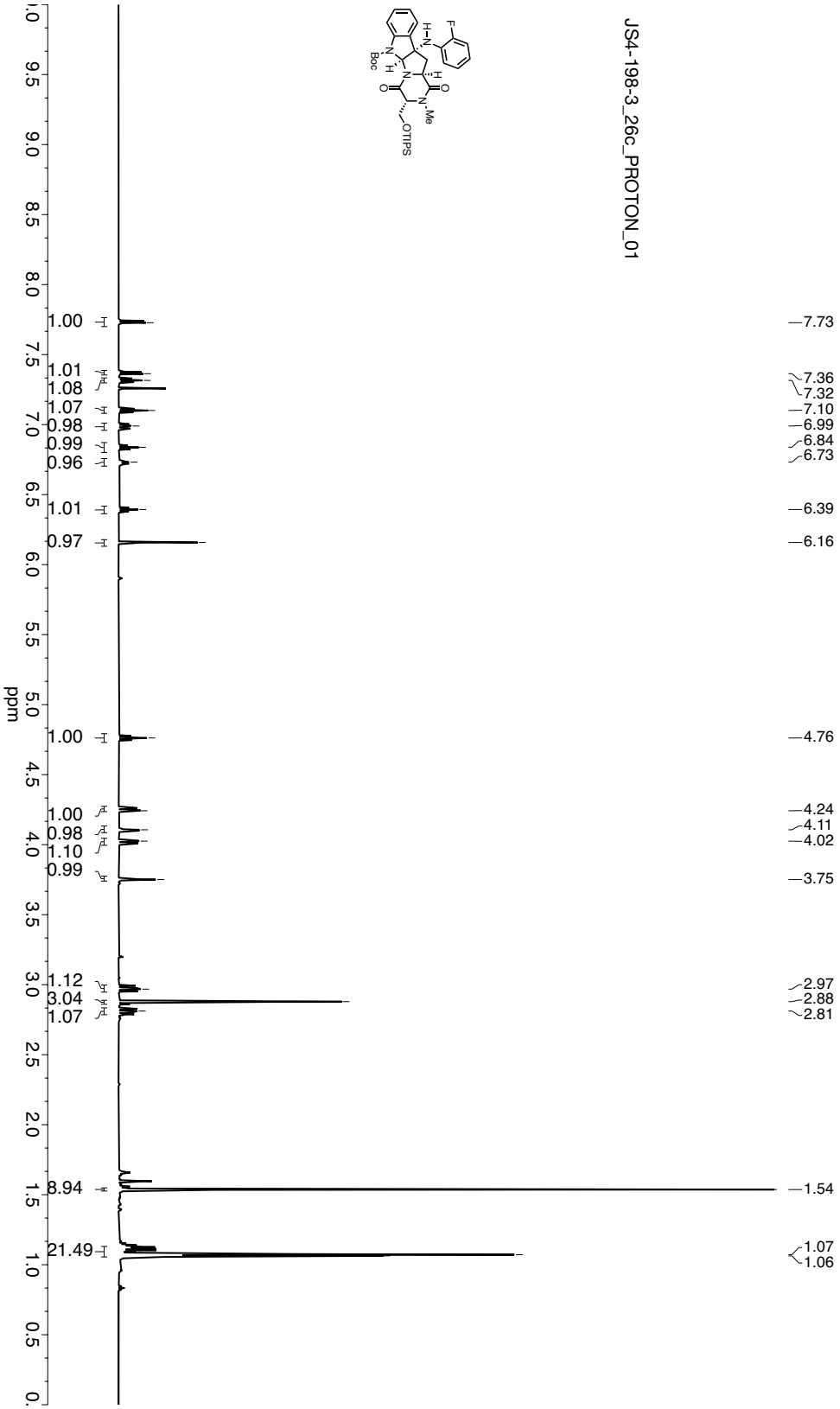

JS4-183-3_26c_CARBON_01
ppm
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-1
167.5
165.6
152.3
144.0
141.3
135.4
129.8
129.3
124.1
123.7
119.4
117.0
115.6
82.0
77.8
68.5
66.9
63.2
56.0
35.9
31.9
28.2
28.1
17.9
17.9
17.9
11.9
H-N
N
H
Boc
O
N
Me
OTIPS

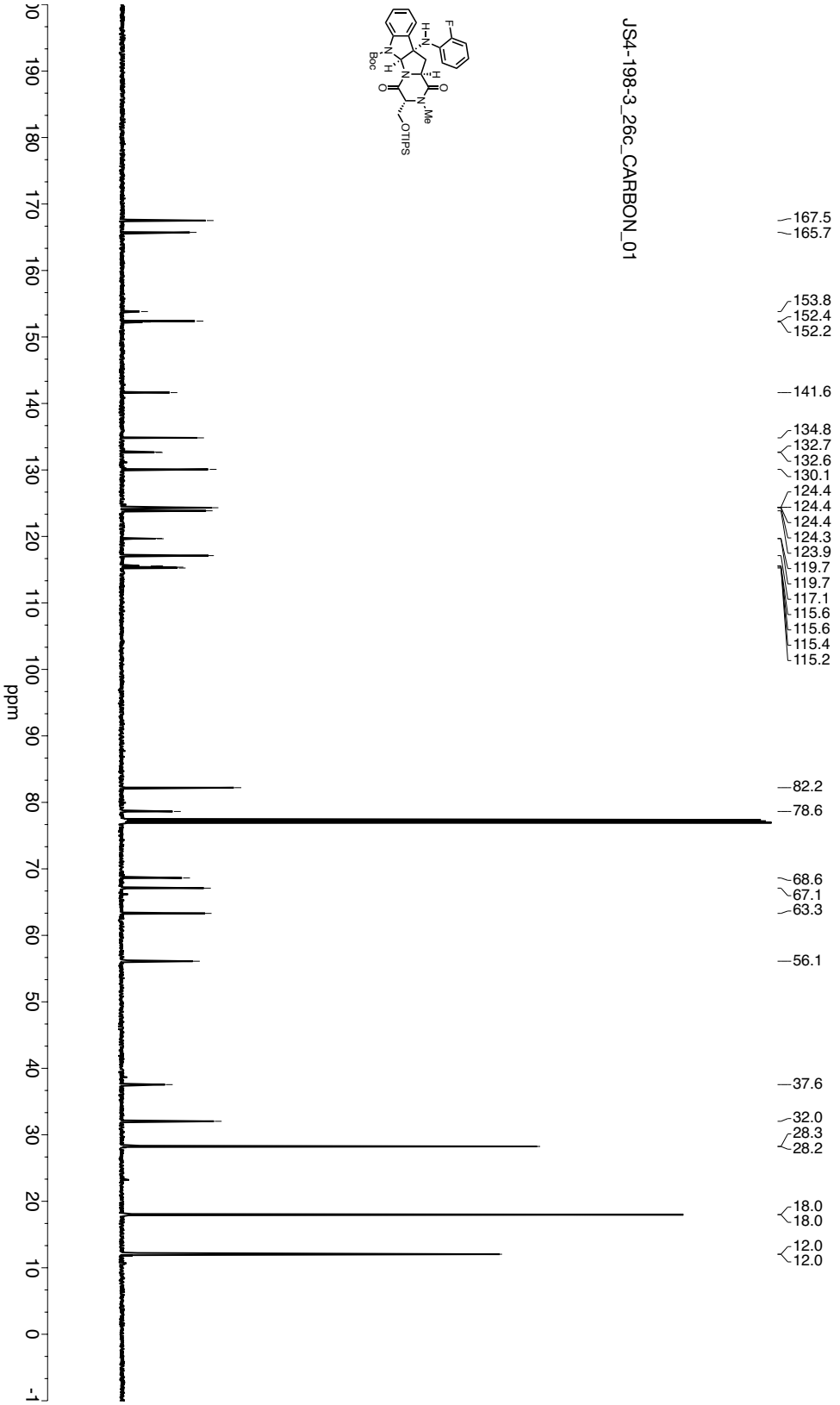

JS4-189-3_26c_PROTON_01
ppm
0.99
1.03
1.05
1.05
1.01
1.01
0.97
1.00
0.99
1.01
1.10
1.16
0.84
1.02
3.00
1.02
3.01
1.00
9.00
21.08
7.75
7.35
7.31
7.09
7.03
6.36
6.19
6.10
5.99
4.76
4.24
4.03
3.81
3.74
3.66
3.02
2.87
2.80
1.54
1.08
1.07

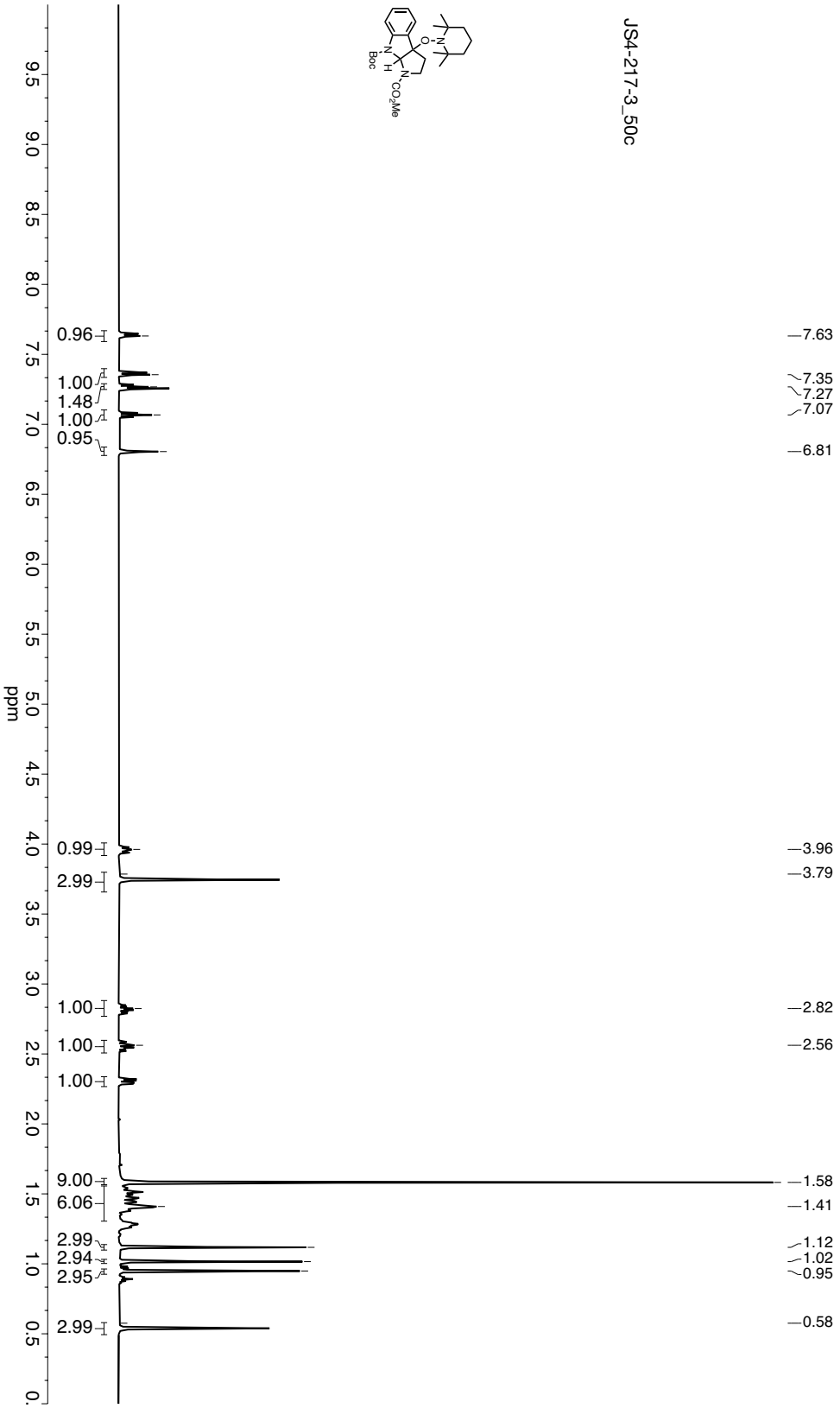

JS4-189-3_26c_CARBON_01
ppm
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-1
167.6
165.6
160.9
152.4
145.5
141.5
135.4
130.1
130.0
124.2
123.9
117.1
108.1
104.9
102.1
82.2
78.2
68.7
67.1
63.2
56.1
55.1
36.7
32.0
28.2
18.0
12.0
MeO
H-N
N
H
Boc
N
H
O
O
N
Me
OTIPS

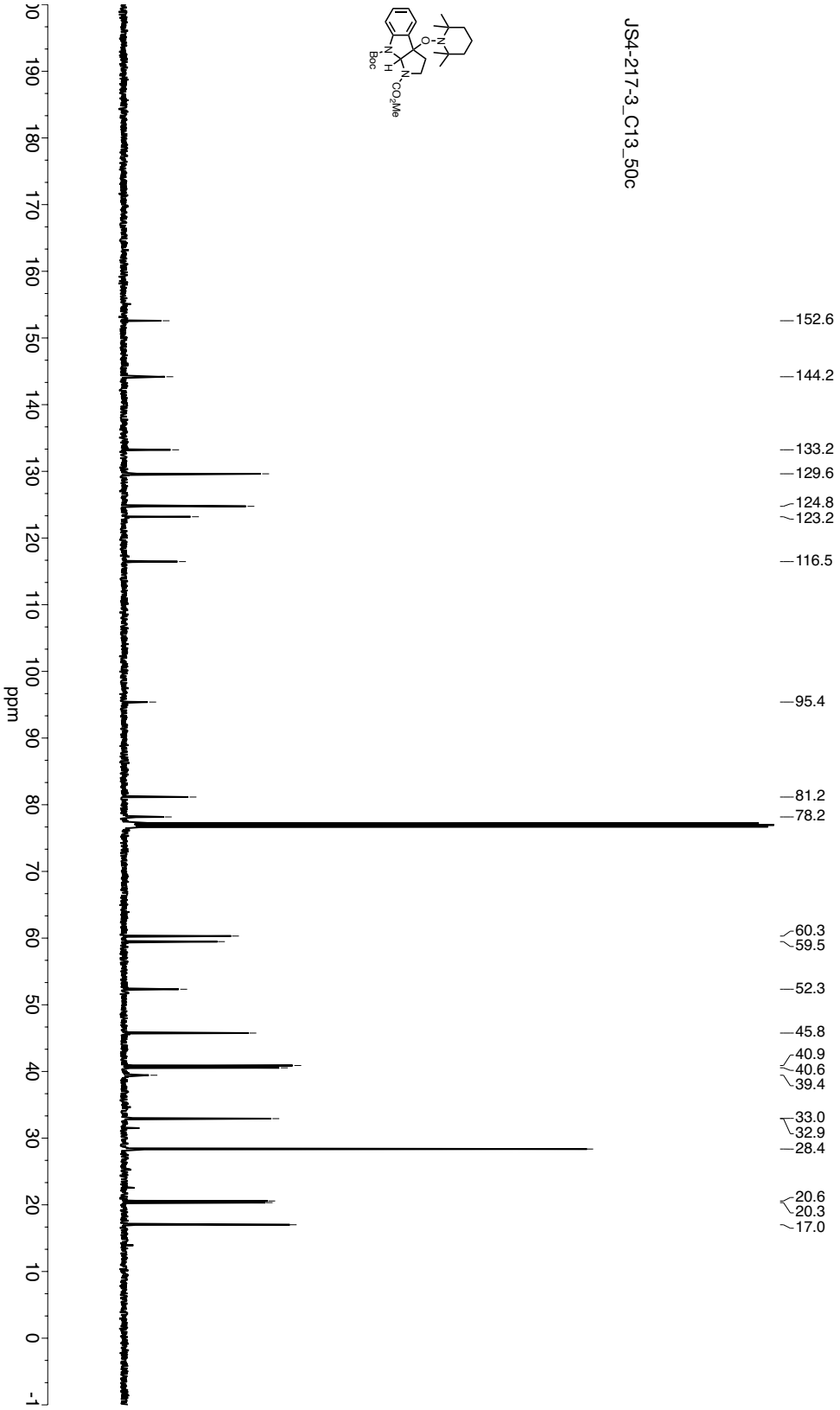

JS4-203-3_26c_PROTON_01
ppm
2.00
0.97
2.10
1.07
2.05
1.00
1.01
0.97
1.03
1.02
3.00
0.99
1.03
4.30
9.17
21.05
7.81
7.76
7.34
7.09
6.45
6.24
4.83
4.30
4.26
4.04
3.85
3.75
3.02
2.88
2.85
1.54
1.10
1.08

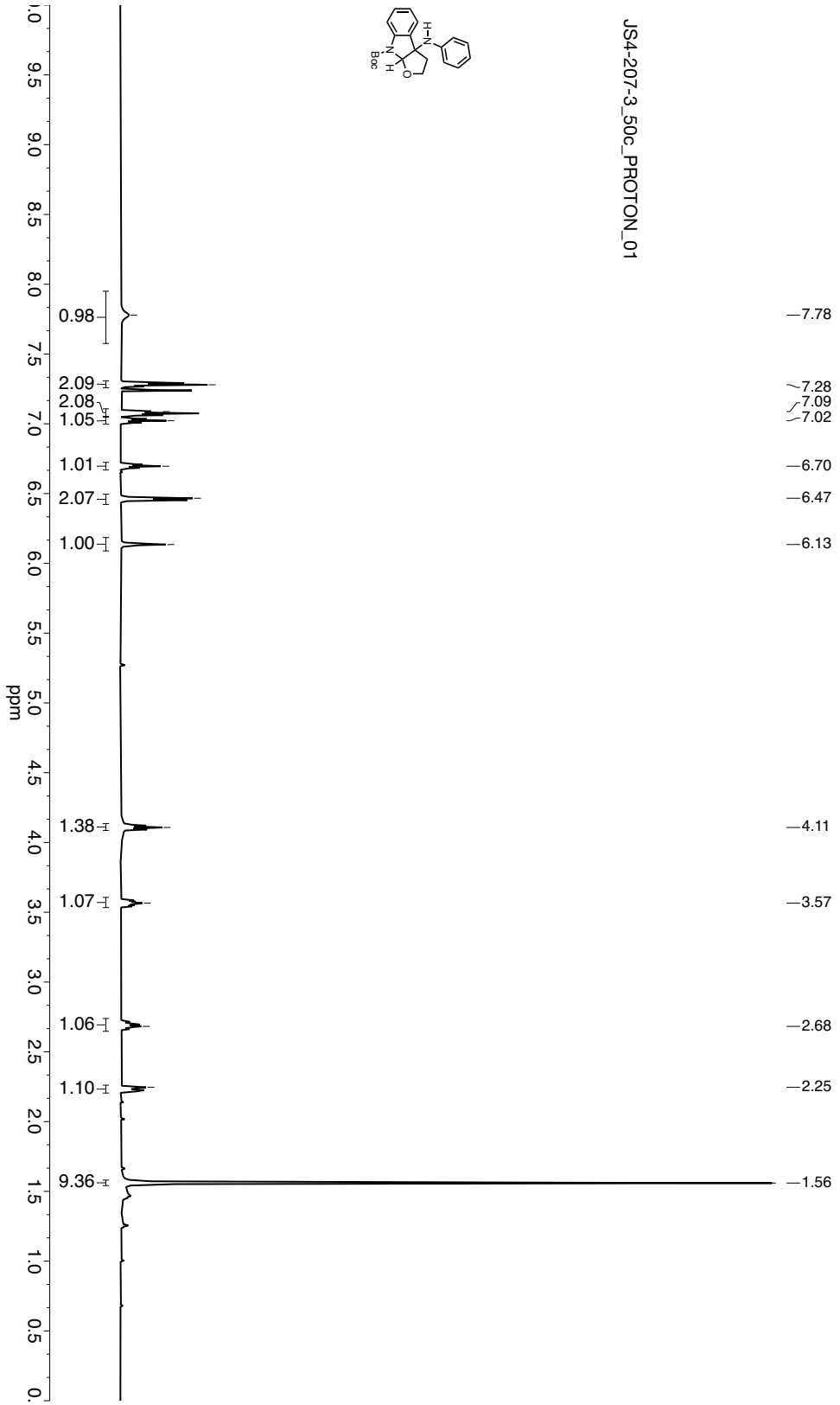

JS4-203-3_26c_CARBON_01
ppm
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-1
167.2
166.9
165.6
152.2
147.9
141.3
134.6
131.4
130.2
124.2
123.6
120.2
117.1
113.4
82.3
77.5
67.9
66.9
63.2
55.9
51.7
35.7
31.9
28.1
17.9
11.9
Boc
OTIPS
Me
CO2Me

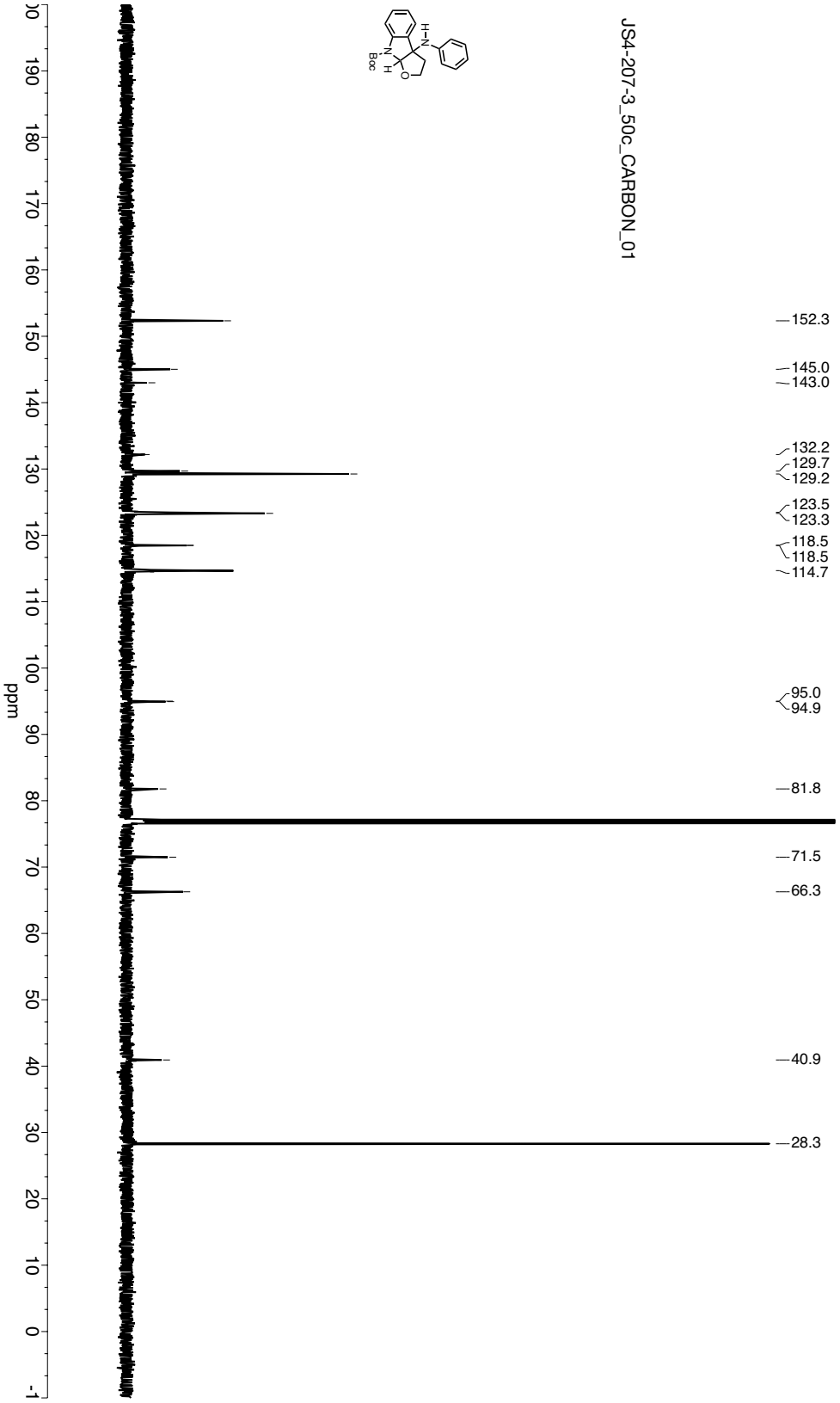

JS4-198-3_26c_PROTON_01
ppm
1.00
1.01
1.08
1.07
0.98
0.99
0.96
1.01
0.97
1.00
1.00
0.98
1.10
0.99
1.12
3.04
1.07
8.94
21.49
7.73
7.36
7.32
7.10
6.99
6.84
6.73
6.39
6.16
4.76
4.24
4.11
4.02
3.75
2.97
2.88
2.81
1.54
1.07
1.06

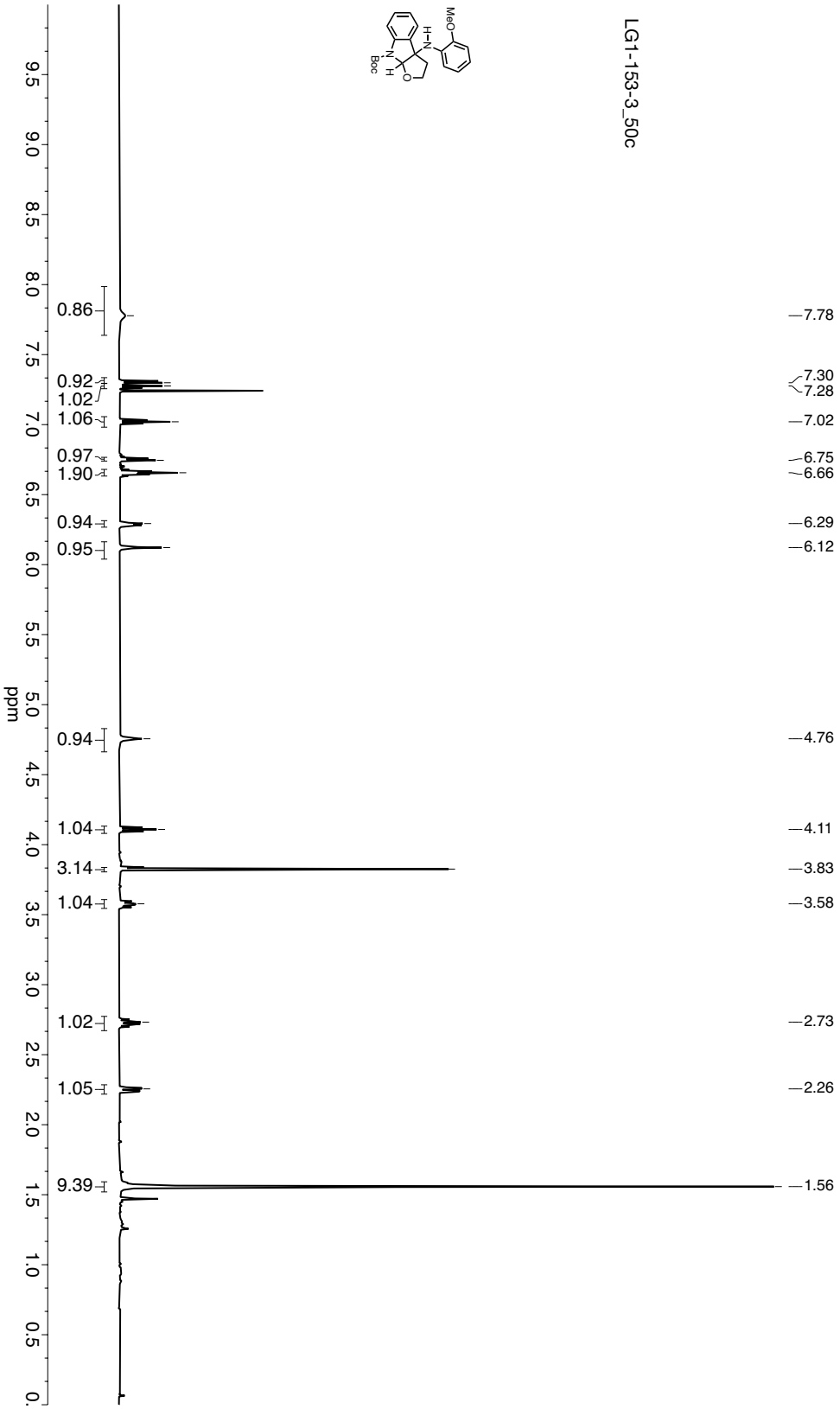

JS4-198-3_26c_CARBON_01
ppm
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-1
167.5
165.7
153.8
152.4
152.2
141.6
134.8
132.7
132.6
130.1
124.4
124.4
124.4
124.3
123.9
119.7
119.7
117.1
115.6
115.6
115.4
115.2
82.2
78.6
68.6
67.1
63.3
56.1
37.6
32.0
28.3
28.2
18.0
18.0
12.0
12.0

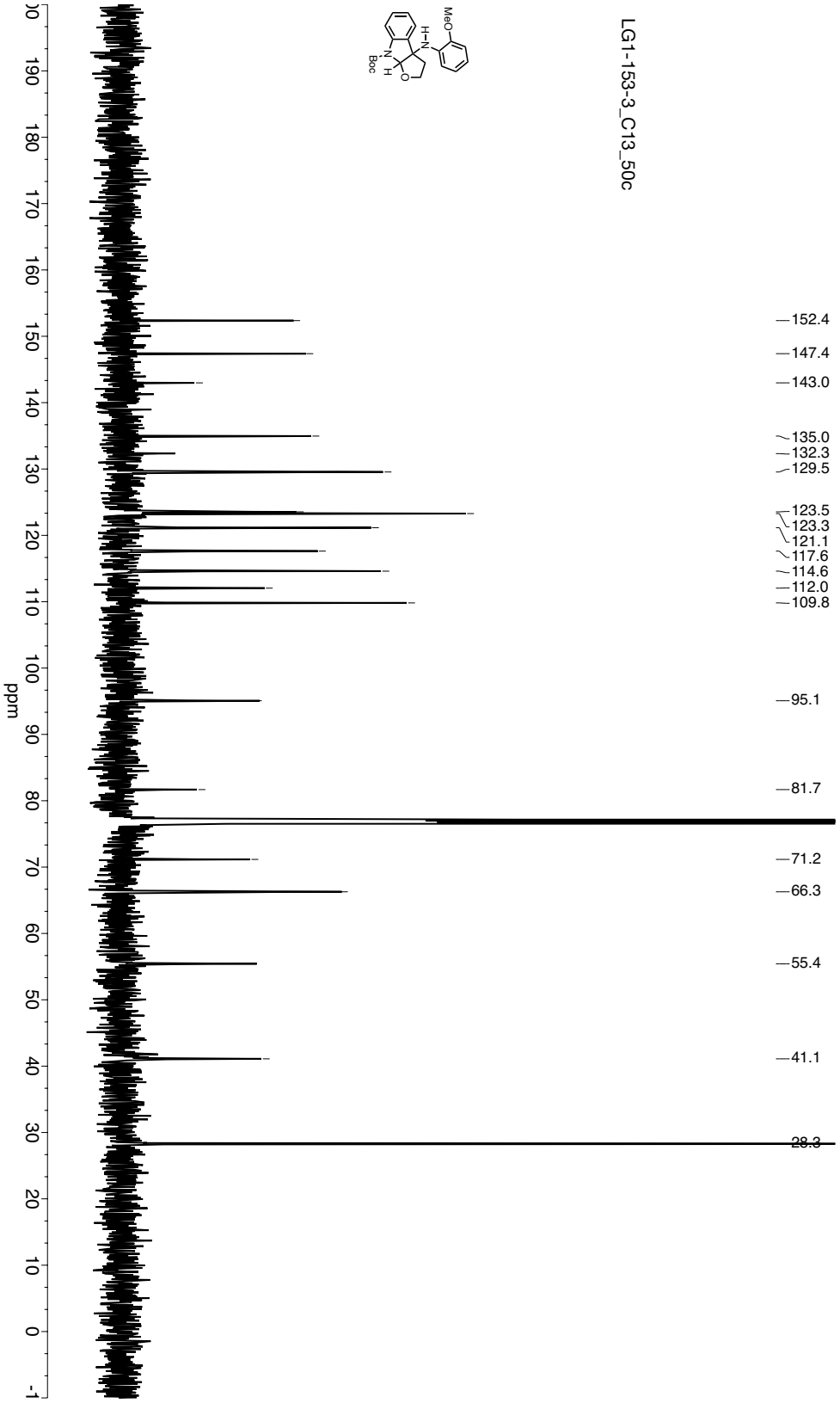

JS4-217-3_50c
ppm
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.
0.96
1.00
1.48
1.00
0.95
0.99
2.99
1.00
1.00
1.00
9.00
6.06
2.99
2.94
2.95
2.99
7.63
7.35
7.27
7.07
6.81
3.96
3.79
2.82
2.56
1.58
1.41
1.12
1.02
0.95
0.58

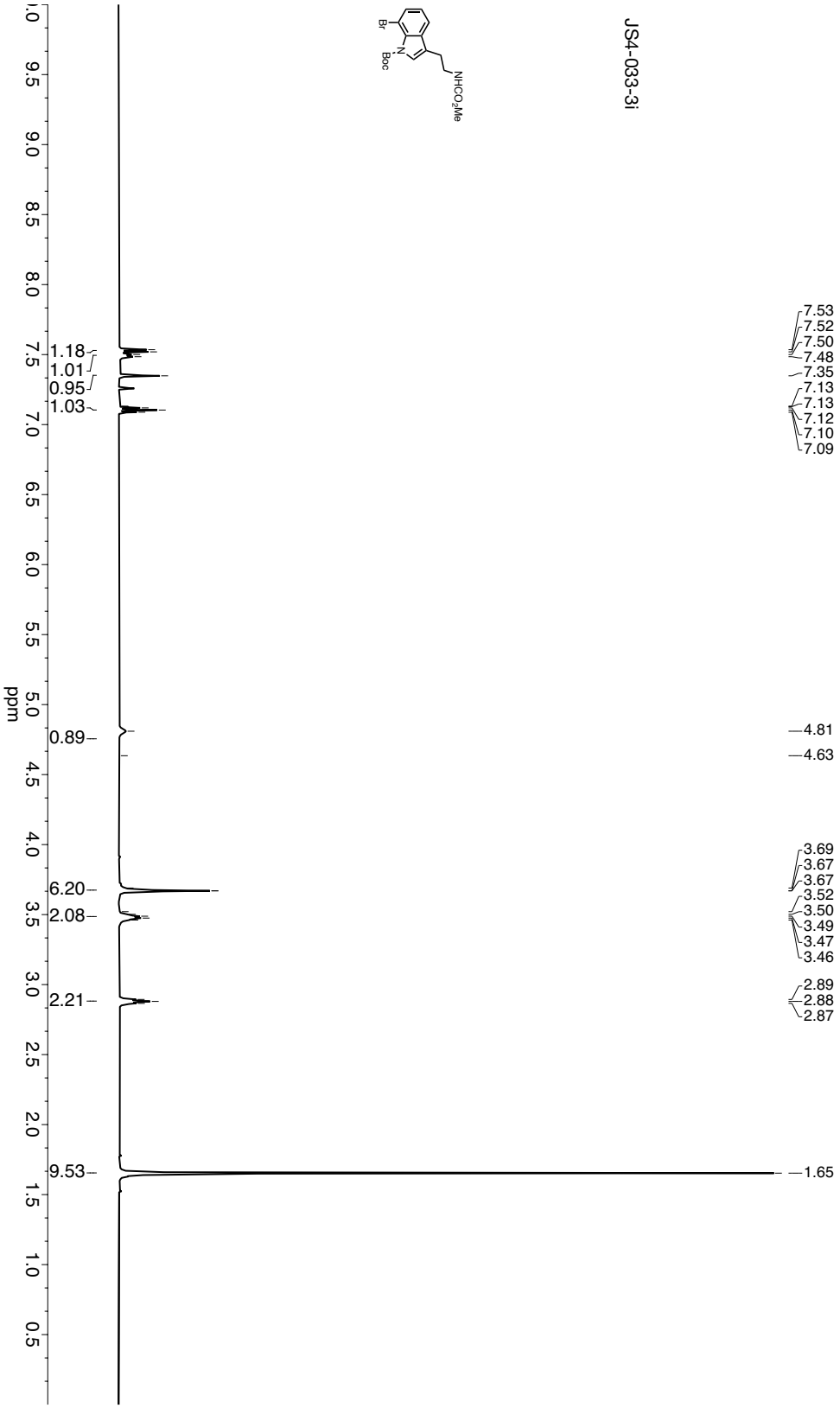

JS4-217-3_C13_50c
ppm
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-1
152.6
144.2
133.2
129.6
124.8
123.2
116.5
95.4
81.2
78.2
60.3
59.5
52.3
45.8
40.9
40.6
39.4
33.0
32.9
28.4
20.6
20.3
17.0

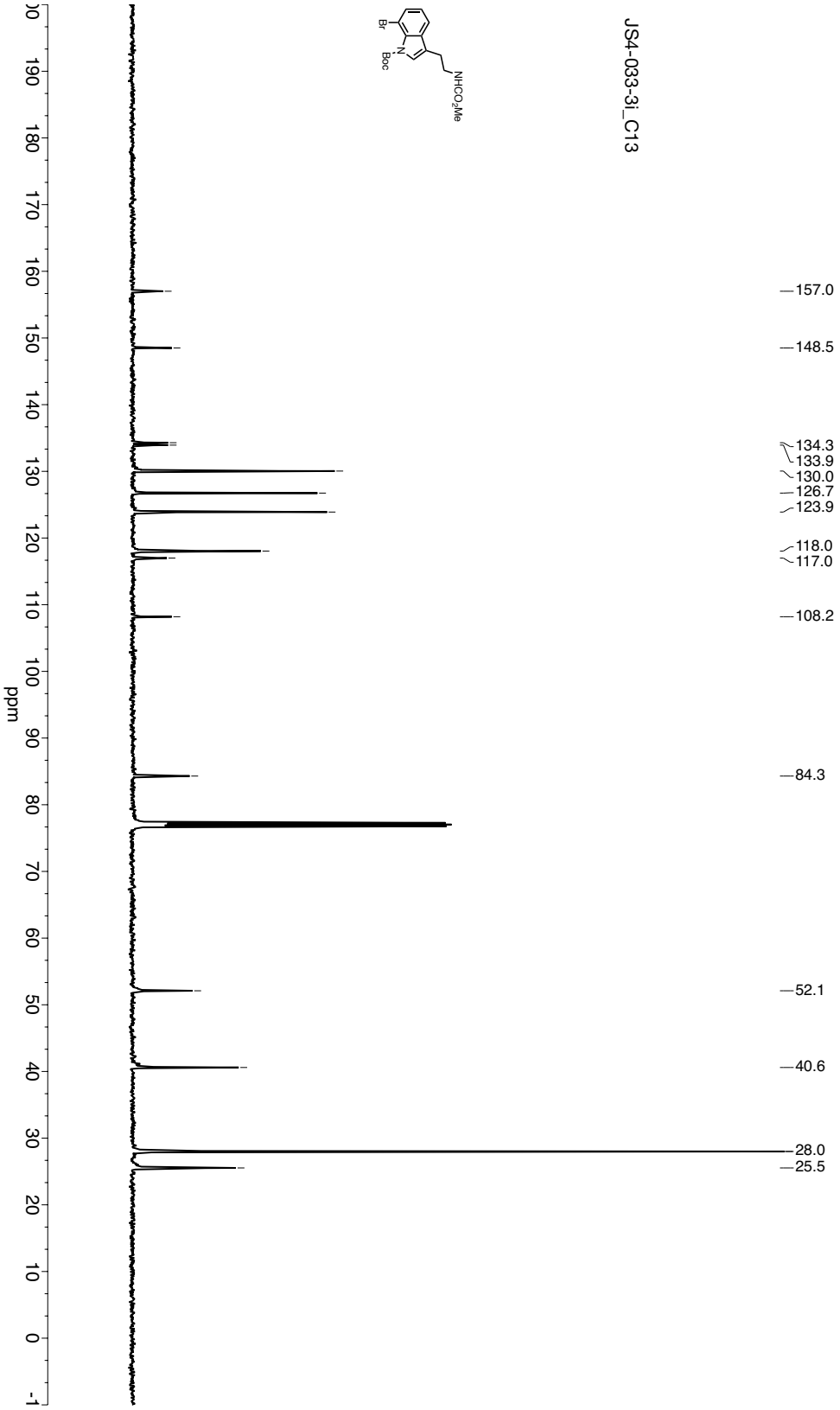

JS4-207-3_50c_PROTON_01
ppm
0.98
2.09
2.08
1.05
1.01
2.07
1.00
1.38
1.07
1.06
1.10
9.36
7.78
7.28
7.09
7.02
6.70
6.47
6.13
4.11
3.57
2.68
2.25
1.56

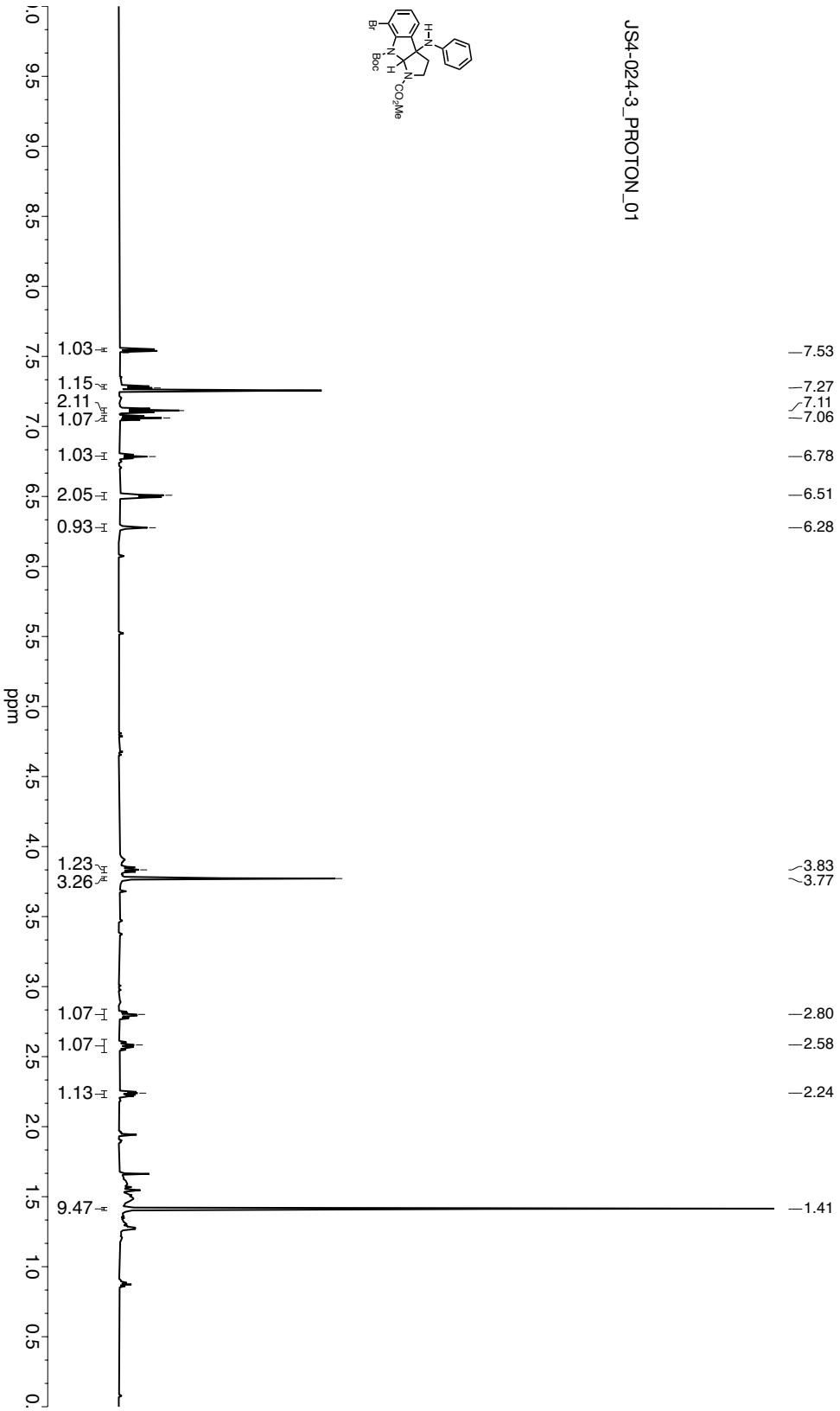

JS4-207-3_50c_CARBON_01
152.3
145.0
143.0
132.2
129.7
129.2
123.5
123.3
118.5
118.5
114.7
95.0
94.9
81.8
71.5
66.3
40.9
28.3
ppm
Boc

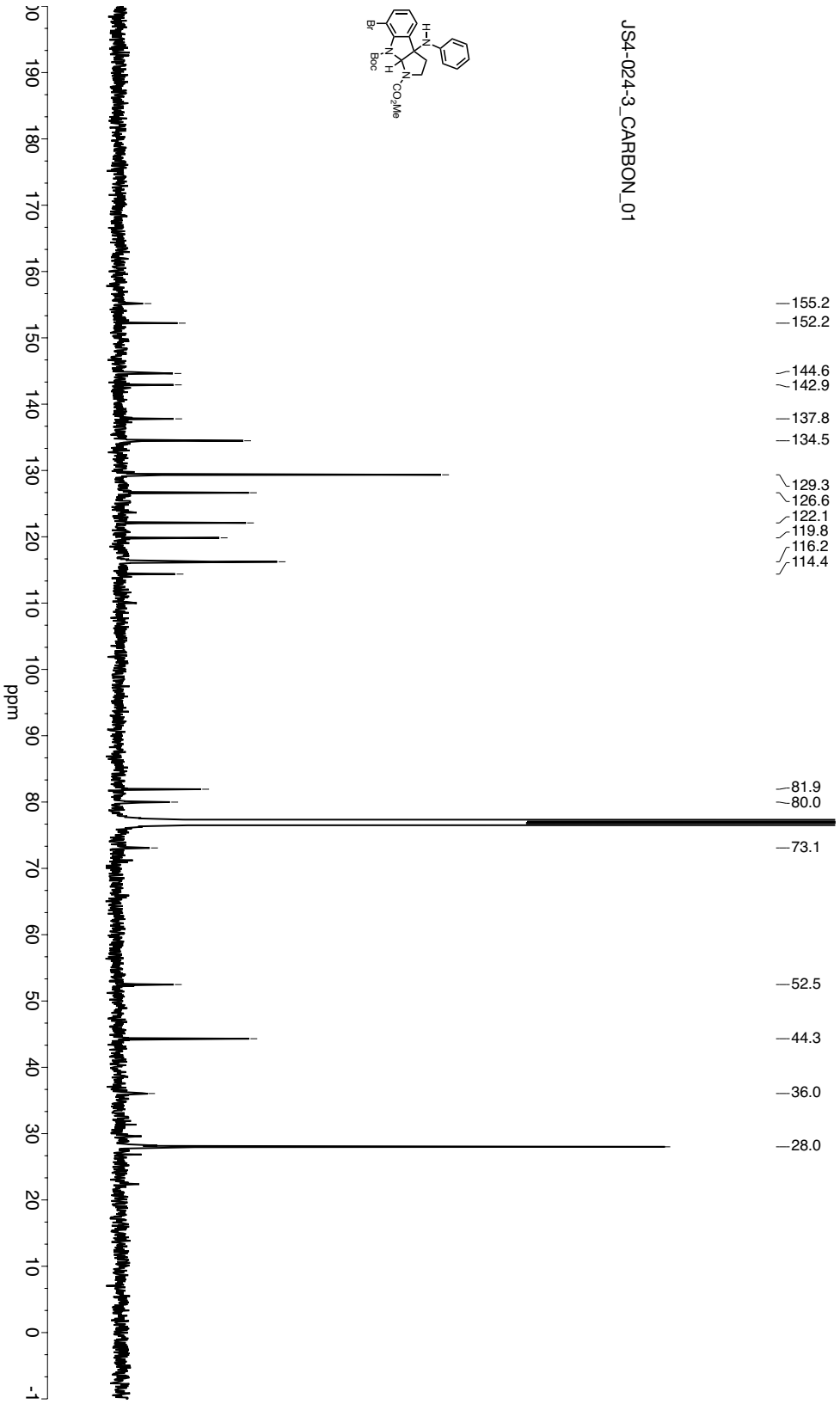

LG1-153-3_50c
MeO
H
N
N
H
Boc
O
ppm
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.
0.86
0.92
1.02
1.06
0.97
1.90
0.94
0.95
0.94
1.04
3.14
1.04
1.02
1.05
9.39
7.78
7.30
7.28
7.02
6.75
6.66
6.29
6.12
4.76
4.11
3.83
3.58
2.73
2.26
1.56

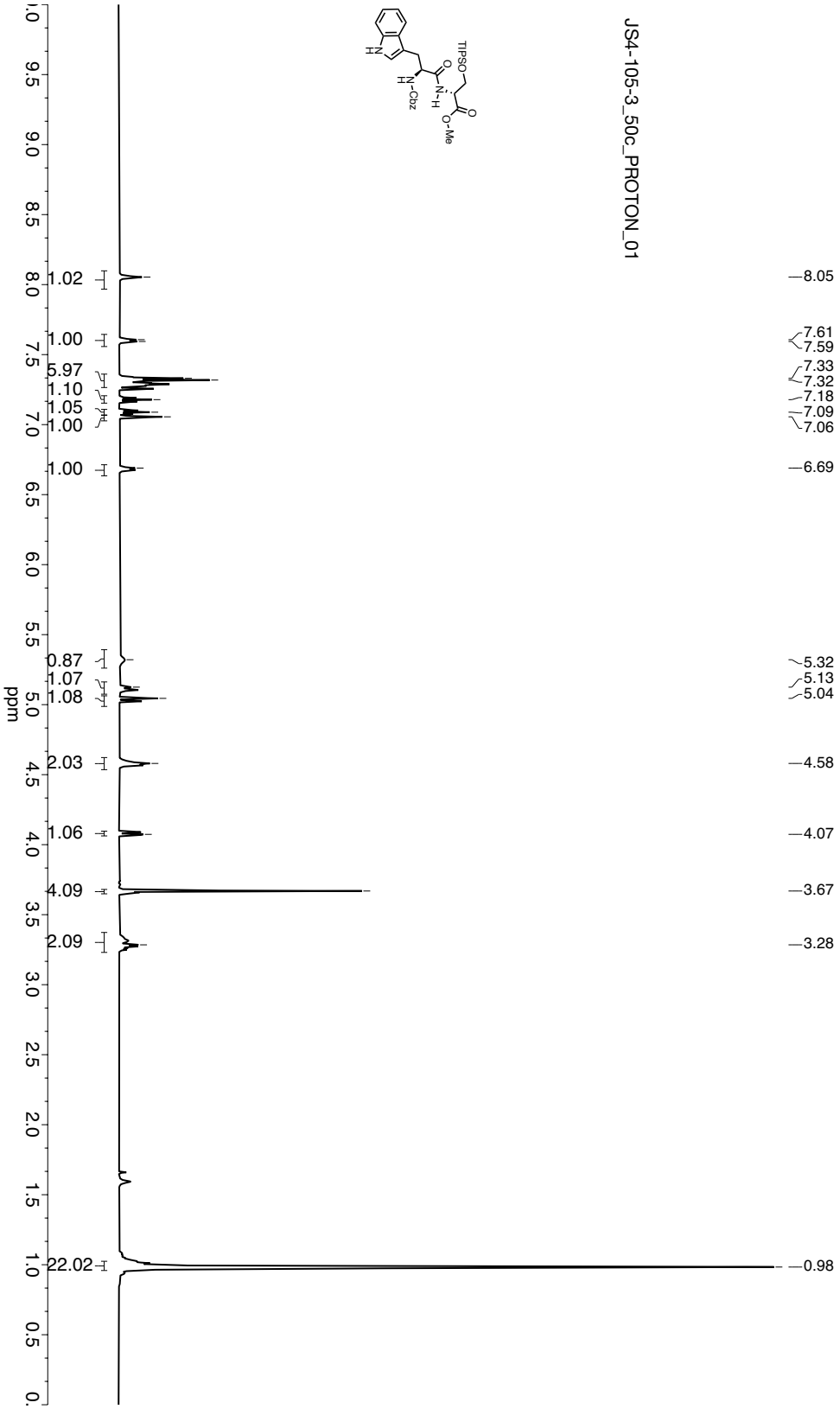

LG1-153-3_C13_50c
MeO
H
N
N
H
Boc
O
ppm
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
152.4
147.4
143.0
135.0
132.3
129.5
123.5
123.3
121.1
117.6
114.6
112.0
109.8
95.1
81.7
71.2
66.3
55.4
41.1
28.3

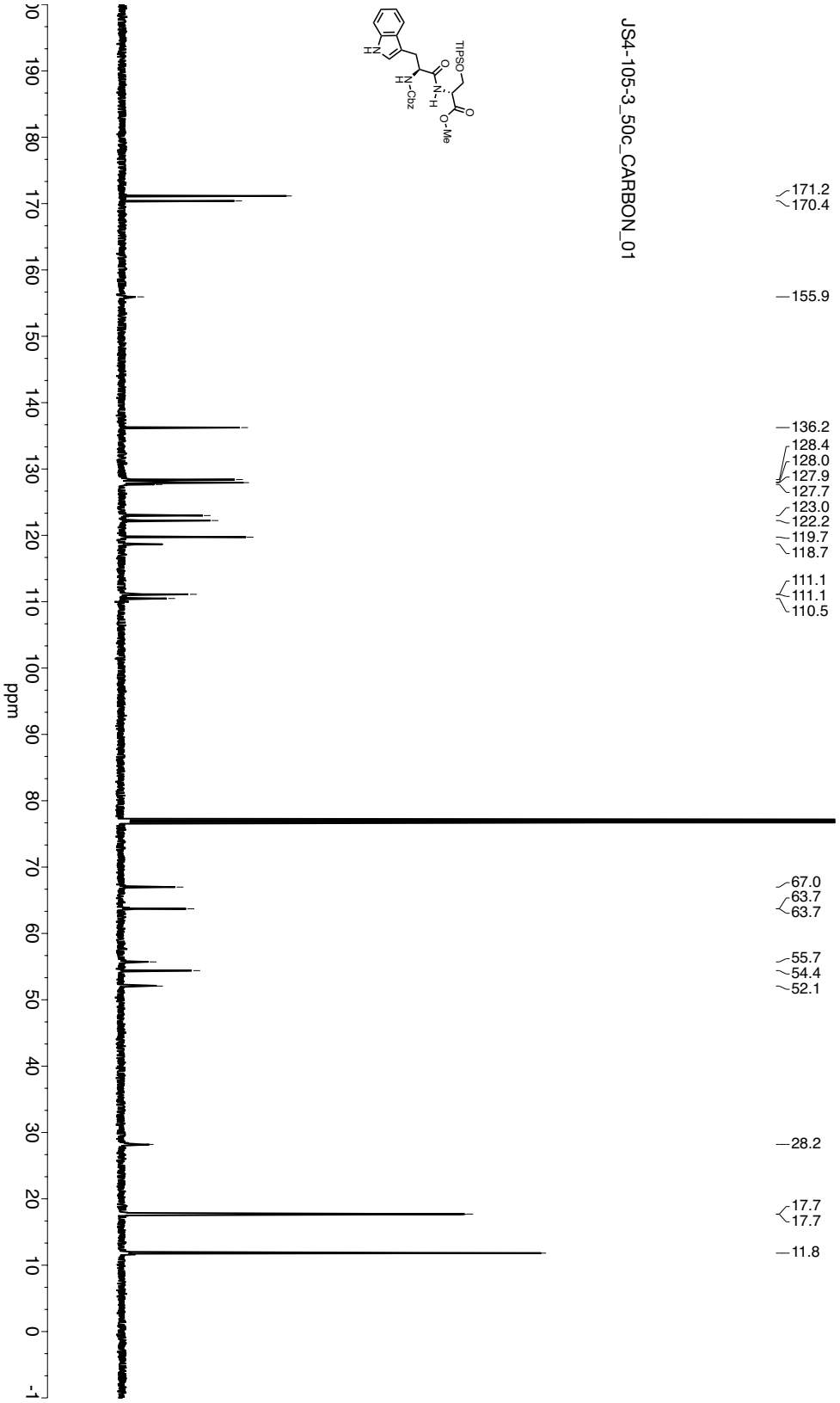

JS4-033-3i
Br
N
Boc
NHCO2Me
ppm
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
1.18
1.01
0.95
1.03
0.89
6.20
2.08
2.21
9.53
7.53
7.52
7.50
7.48
7.35
7.13
7.13
7.12
7.10
7.09
4.81
4.63
3.69
3.67
3.67
3.52
3.50
3.49
3.47
3.46
2.89
2.88
2.87
1.65

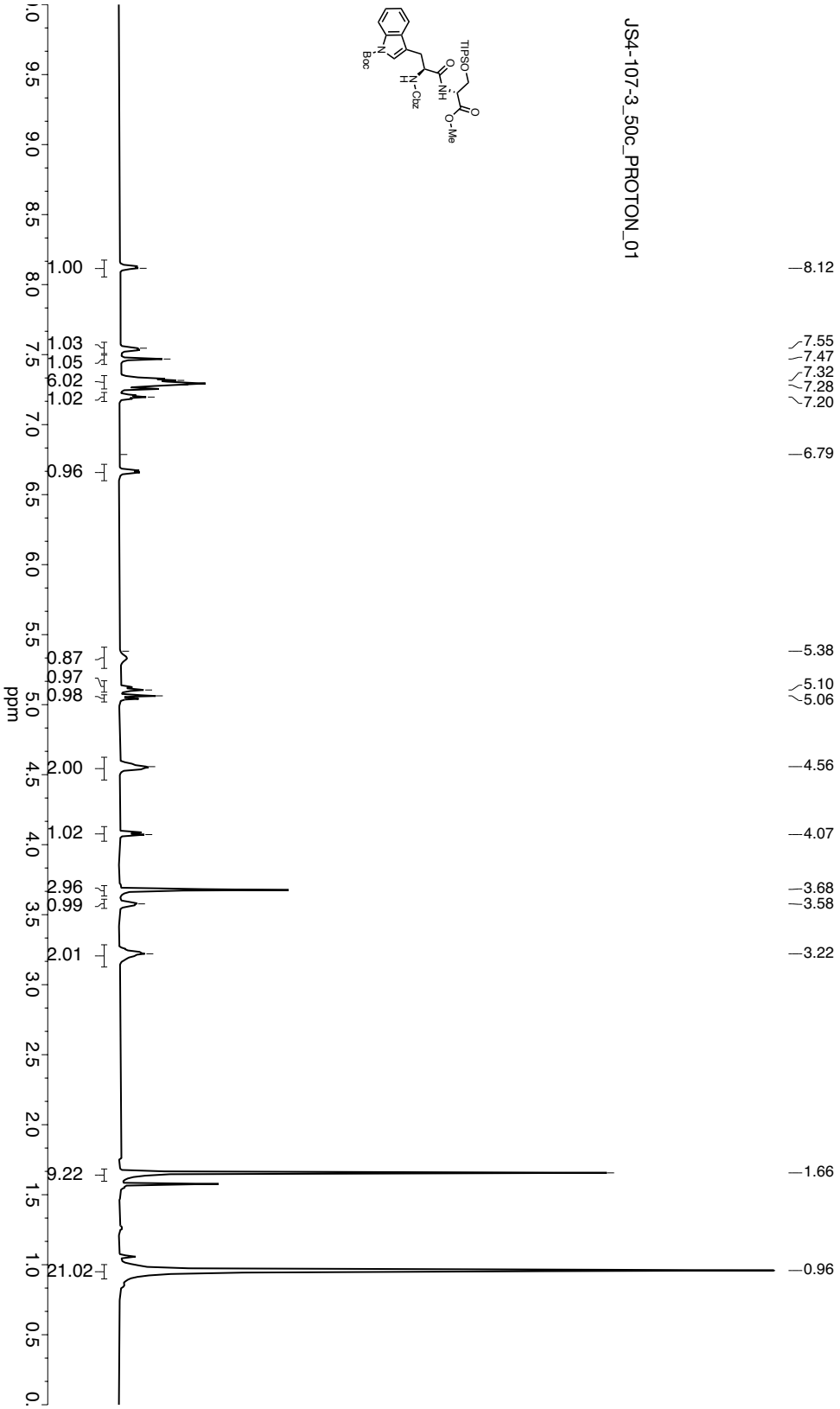

JS4-033-3i_C13
Br
N
Boc
NHCO2Me
157.0
148.5
134.3
133.9
130.0
126.7
123.9
118.0
117.0
108.2
84.3
52.1
40.6
28.0
25.5
ppm
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

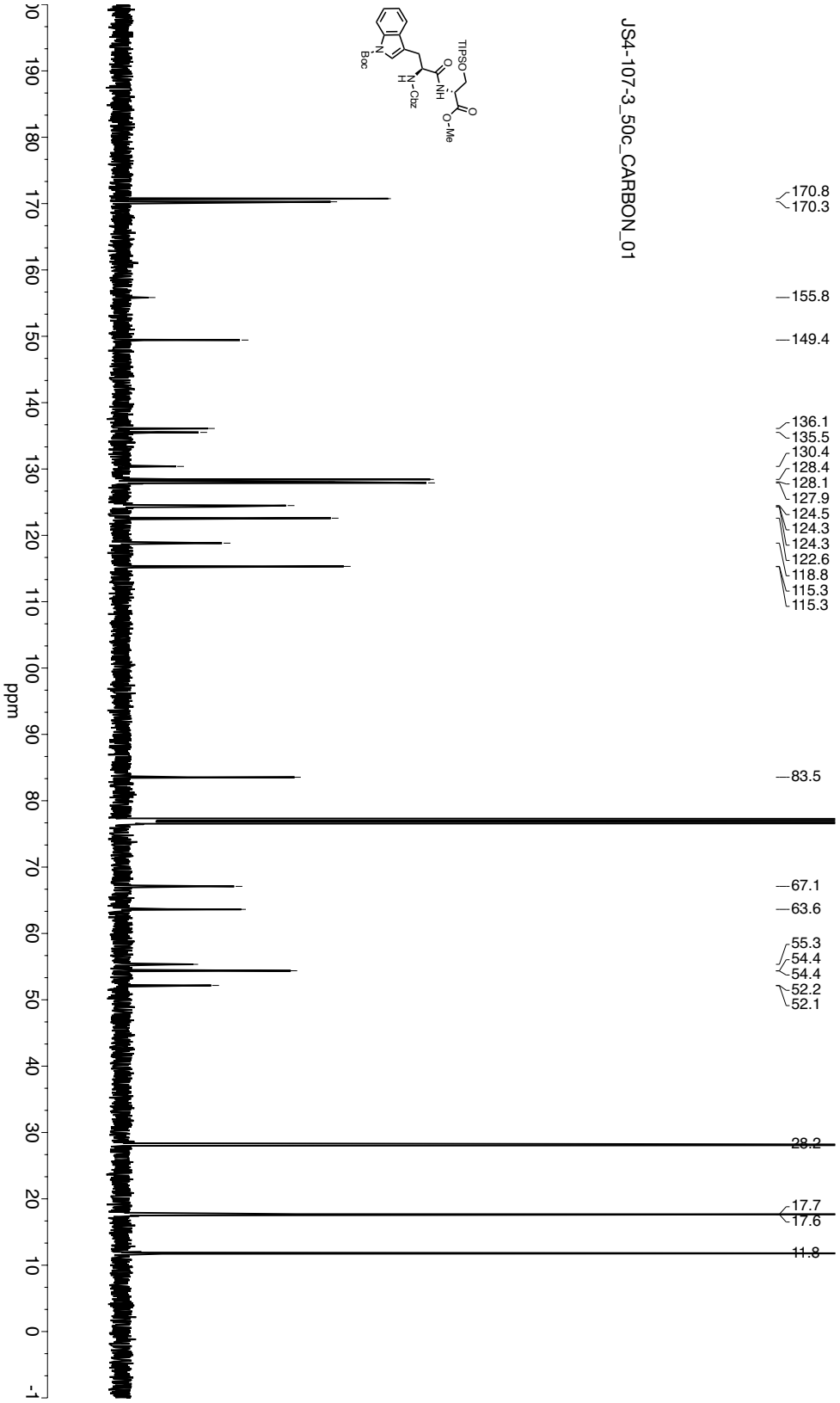

JS4-024-3_PROTON_01
ppm
1.03
1.15
2.11
1.07
1.03
2.05
0.93
1.23
3.26
1.07
1.07
1.13
9.47
7.53
7.27
7.11
7.06
6.78
6.51
6.28
3.83
3.77
2.80
2.58
2.24
1.41

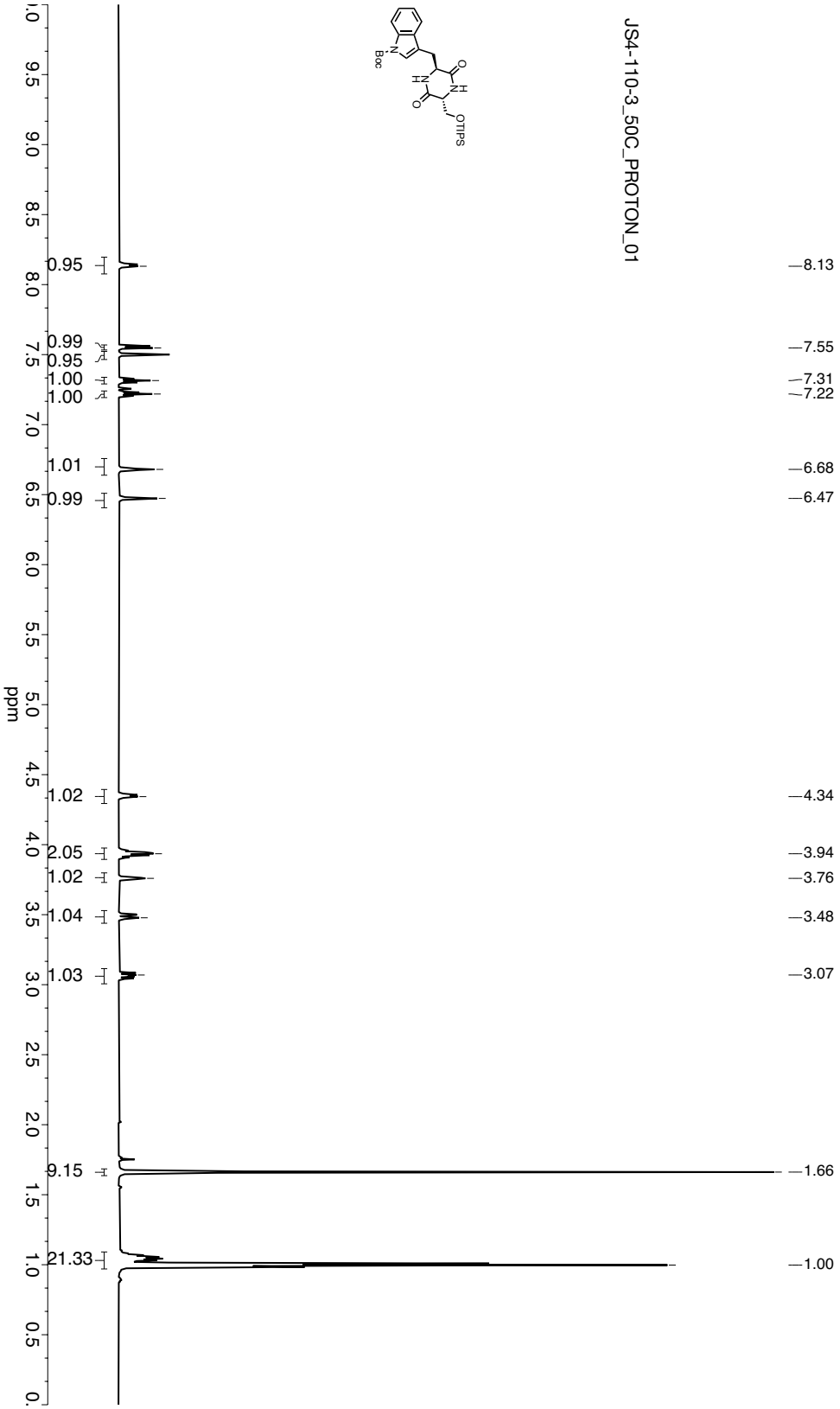

JS4-024-3_CARBON_01
155.2
152.2
144.6
142.9
137.8
134.5
129.3
126.6
122.1
119.8
116.2
114.4
81.9
80.0
73.1
52.5
44.3
36.0
28.0
ppm
Br
Boc
CO2Me

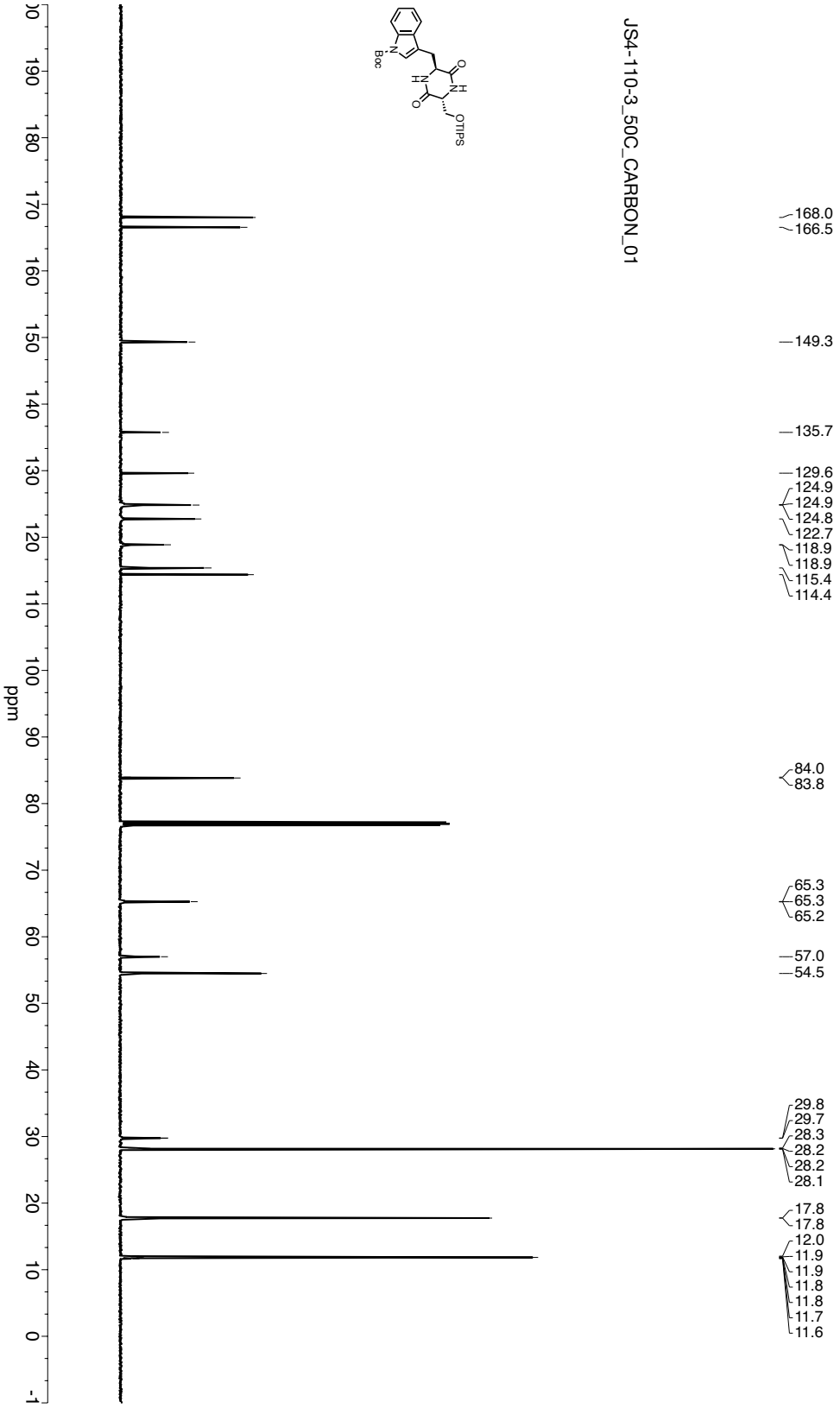

JS4-105-3_50c_PROTON_01
ppm
1.02
1.00
5.97
1.10
1.05
1.00
1.00
0.87
1.07
1.08
2.03
1.06
4.09
2.09
22.02
8.05
7.61
7.59
7.33
7.32
7.18
7.09
7.06
6.69
5.32
5.13
5.04
4.58
4.07
3.67
3.28
0.98

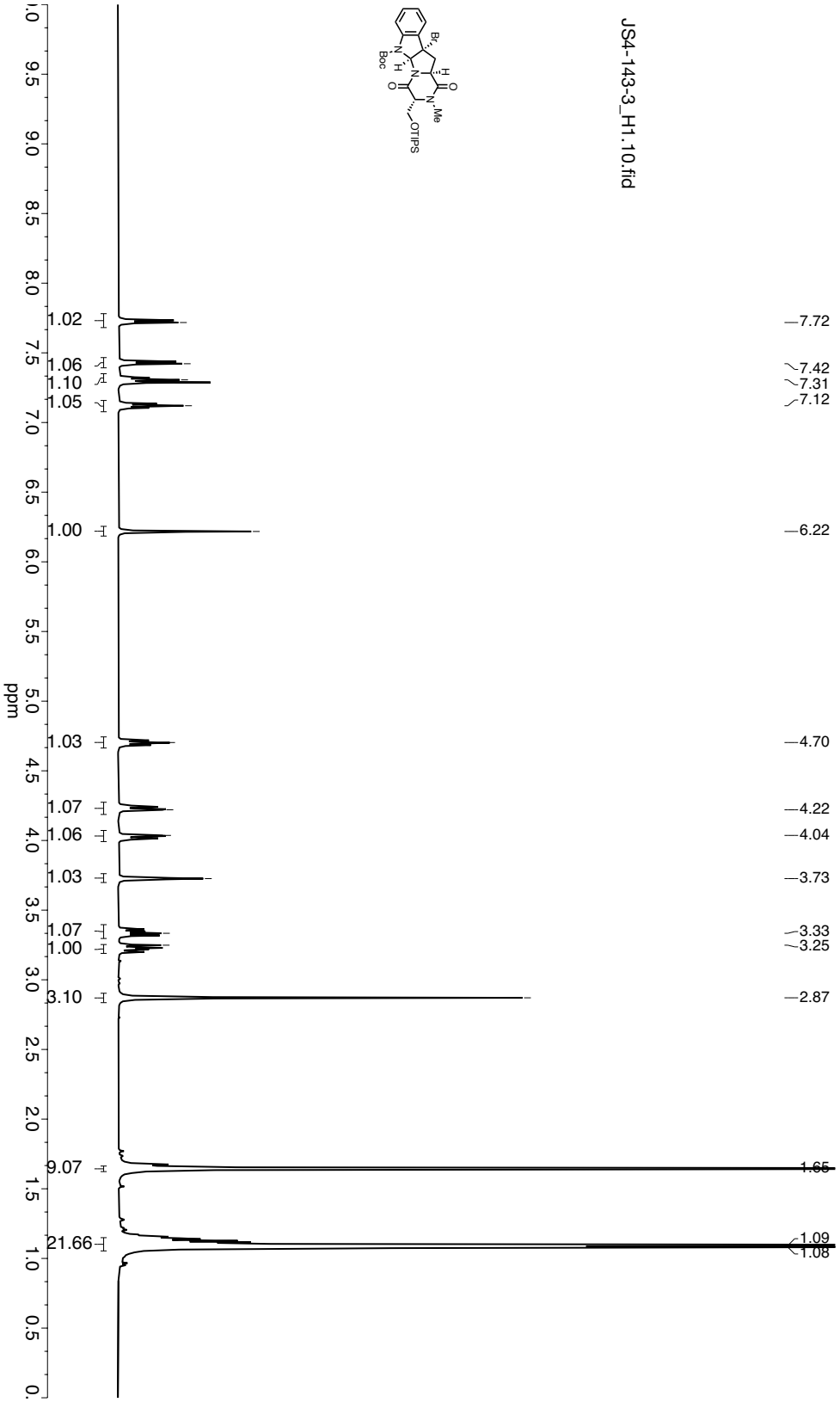

JS4-105-3_50c_CARBON_01
TIPSO
O
N-H
O
O-Me
H
N
N-Cbz
171.2
170.4
155.9
136.2
128.4
128.0
127.9
127.7
123.0
122.2
119.7
118.7
111.1
111.1
110.5
67.0
63.7
63.7
55.7
54.4
52.1
28.2
17.7
17.7
11.8
ppm
210
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

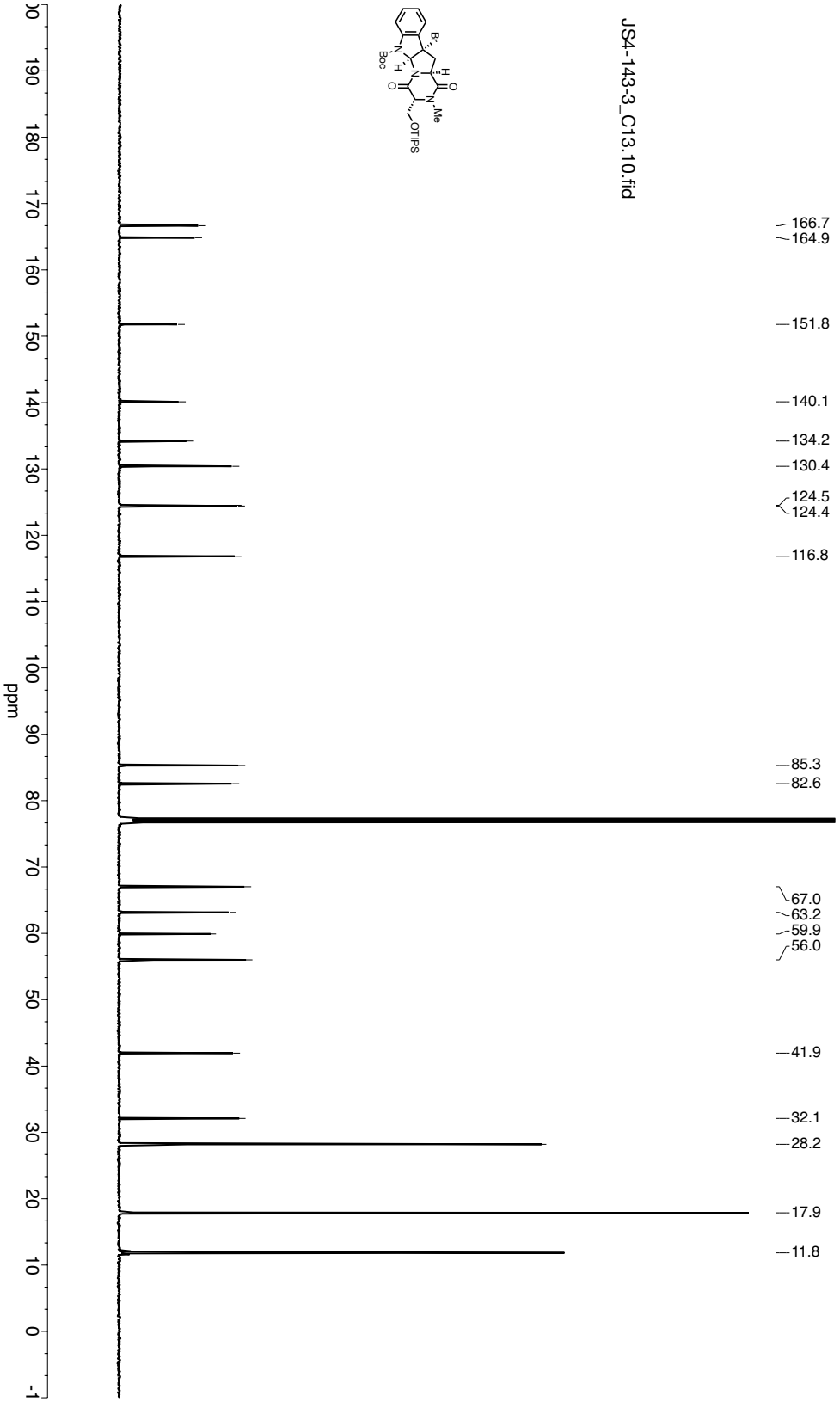

JS4-107-3_50c_PROTON_01
TIPSO
O
NH
O
O-Me
N
H
N-Cbz
N
Boc
ppm
1.00
1.03
1.05
6.02
1.02
0.96
0.87
0.97
0.98
2.00
1.02
2.96
0.99
2.01
9.22
21.02
8.12
7.55
7.47
7.32
7.28
7.20
6.79
5.38
5.10
5.06
4.56
4.07
3.68
3.58
3.22
1.66
0.96

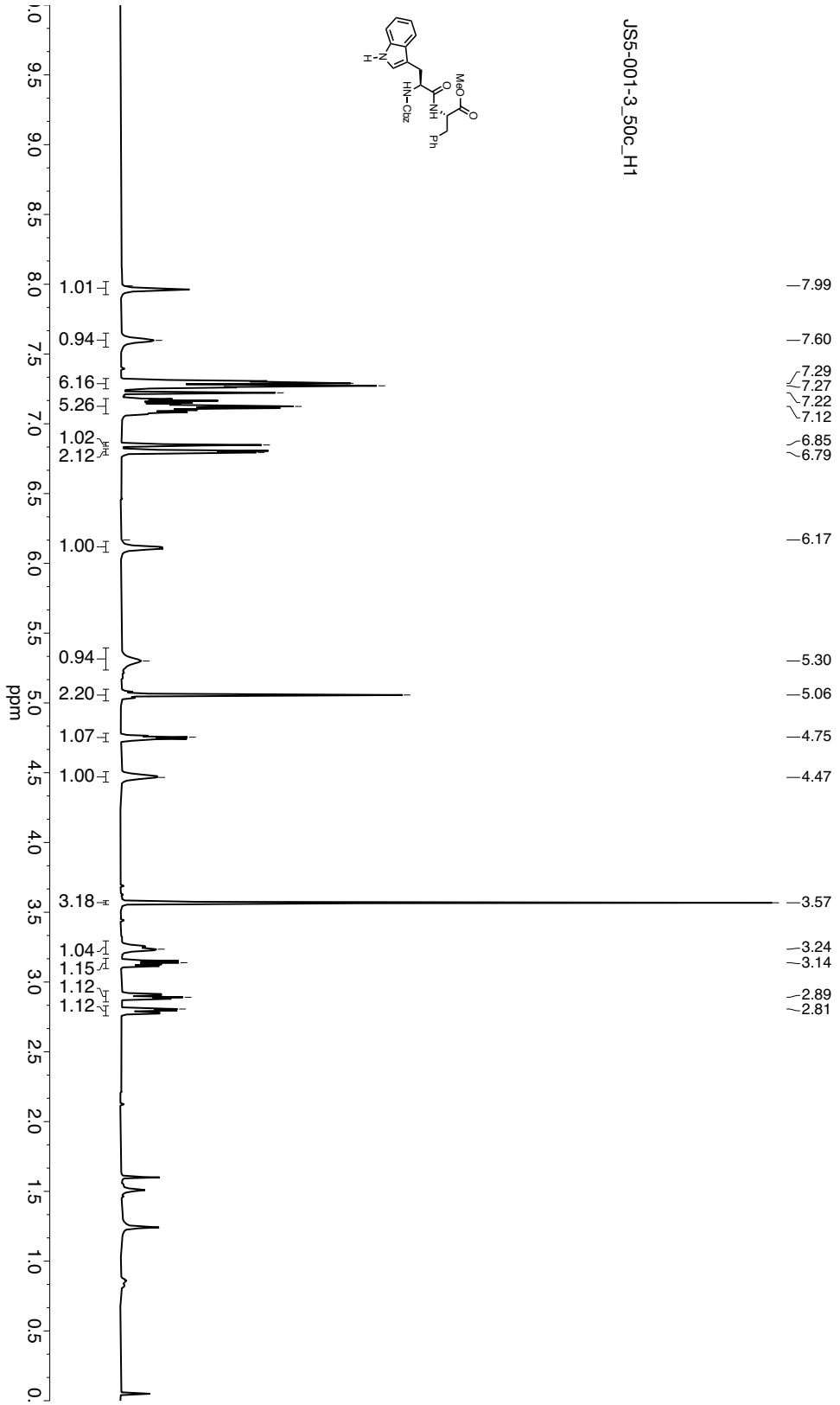

JS4-107-3_50c_CARBON_01
170.8
170.3
155.8
149.4
136.1
135.5
130.4
128.4
128.1
127.9
124.5
124.3
124.3
122.6
118.8
115.3
115.3
83.5
67.1
63.6
55.3
54.4
54.4
52.2
52.1
28.2
17.7
17.6
11.8
ppm

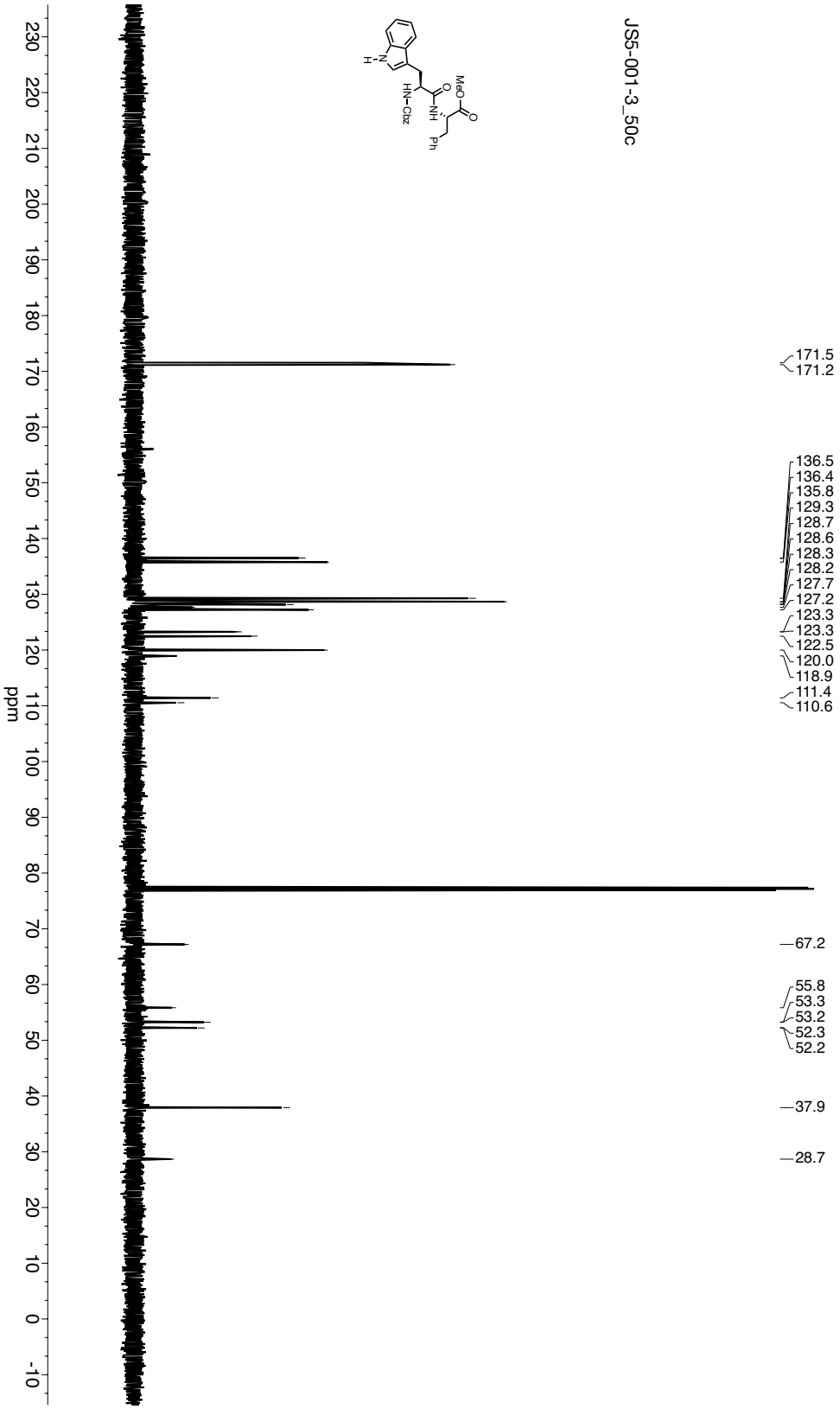

JS4-110-3_50C_PROTON_01
ppm
0.95
0.99
0.95
1.00
1.00
1.01
0.99
1.02
2.05
1.02
1.04
1.03
9.15
21.33
8.13
7.55
7.31
7.22
6.68
6.47
4.34
3.94
3.76
3.48
3.07
1.66
1.00

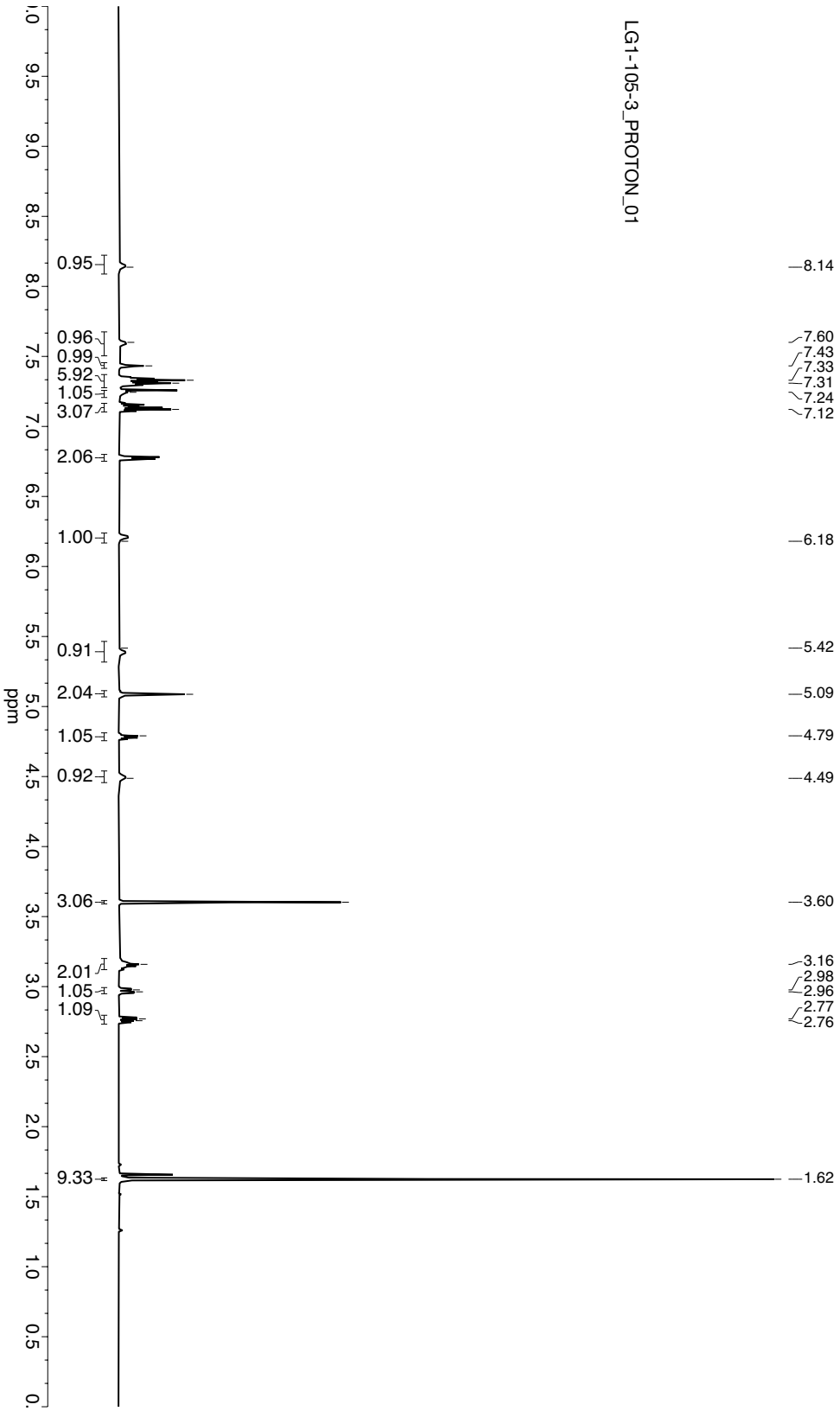

JS4-110-3_50C_CARBON_01
Boc
OTIPS
168.0
166.5
149.3
135.7
129.6
124.9
124.9
124.8
122.7
118.9
118.9
115.4
114.4
84.0
83.8
65.3
65.3
65.2
57.0
54.5
29.8
29.7
28.3
28.2
28.2
28.1
17.8
17.8
12.0
11.9
11.9
11.8
11.8
11.7
11.6
ppm


JS4-143-3_H1.10.fid
ppm
1.02
1.06
1.10
1.05
1.00
1.03
1.07
1.06
1.03
1.07
1.00
3.10
9.07
21.66
7.72
7.42
7.31
7.12
6.22
4.70
4.22
4.04
3.73
3.33
3.25
2.87
1.65
1.09
1.08


JS4-143-3_C13.10.fid
ppm
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-1
166.7
164.9
151.8
140.1
134.2
130.4
124.5
124.4
116.8
85.3
82.6
67.0
63.2
59.9
56.0
41.9
32.1
28.2
17.9
11.8


JS5-001-3_50c_H1
ppm
1.01
0.94
6.16
5.26
1.02
2.12
1.00
0.94
2.20
1.07
1.00
3.18
1.04
1.15
1.12
1.12
7.99
7.60
7.29
7.27
7.22
7.12
6.85
6.79
6.17
5.30
5.06
4.75
4.47
3.57
3.24
3.14
2.89
2.81


JS5-001-3_50c
171.5
171.2
136.5
136.4
135.8
129.3
128.7
128.6
128.3
128.2
127.7
127.2
123.3
123.3
122.5
120.0
118.9
111.4
110.6
67.2
55.8
53.3
53.2
52.3
52.2
37.9
28.7
ppm


LG1-105-3_PROTON_01
ppm
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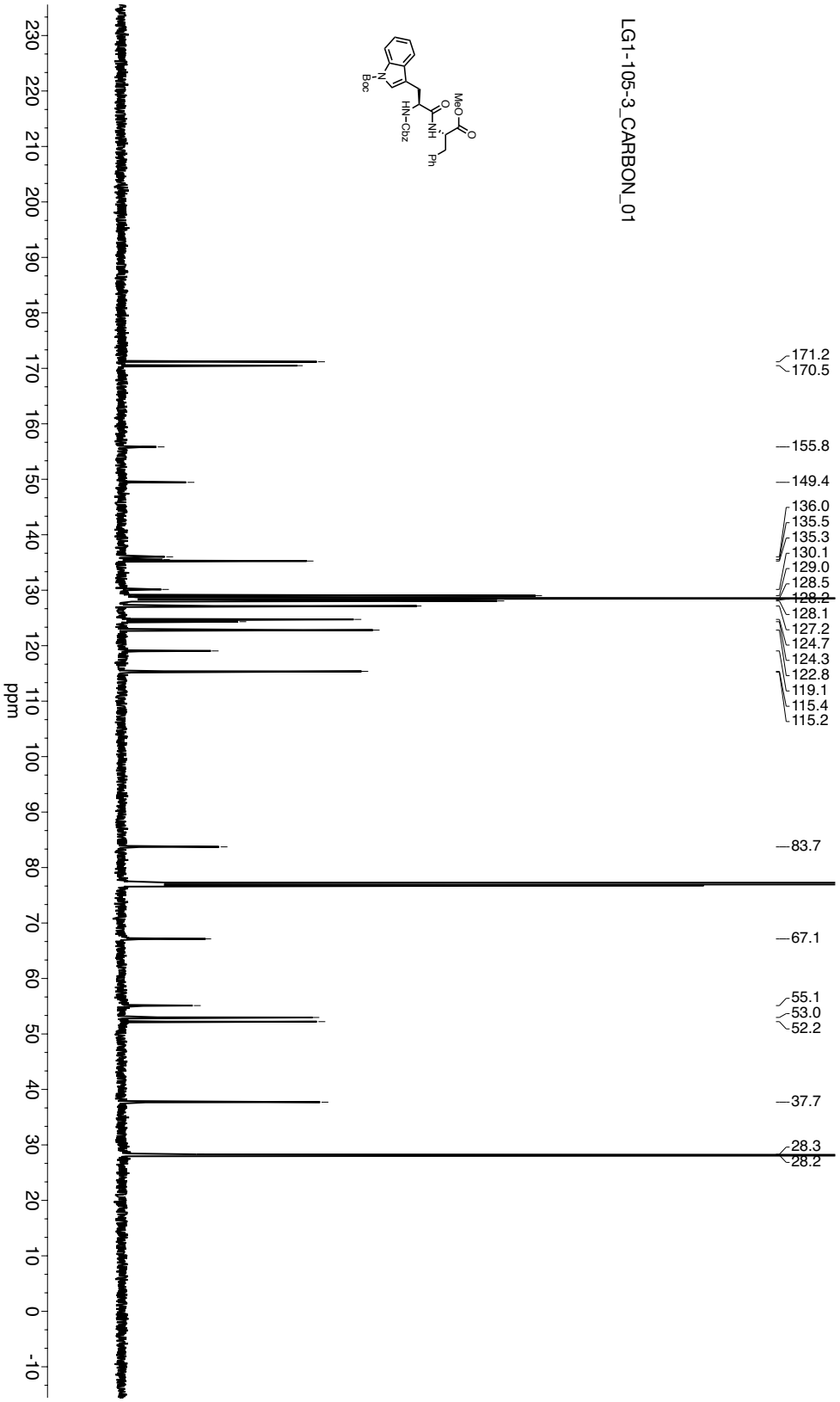
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.
0.95
0.96
0.99
5.92
1.05
3.07
2.06
1.00
0.91
2.04
1.05
0.92
3.06
2.01
1.05
1.09
9.33
8.14
7.60
7.43
7.33
7.31
7.24
7.12
6.18
5.42
5.09
4.79
4.49
3.60
3.16
2.98
2.96
2.77
2.76
1.62


LG1-105-3_CARBON_01
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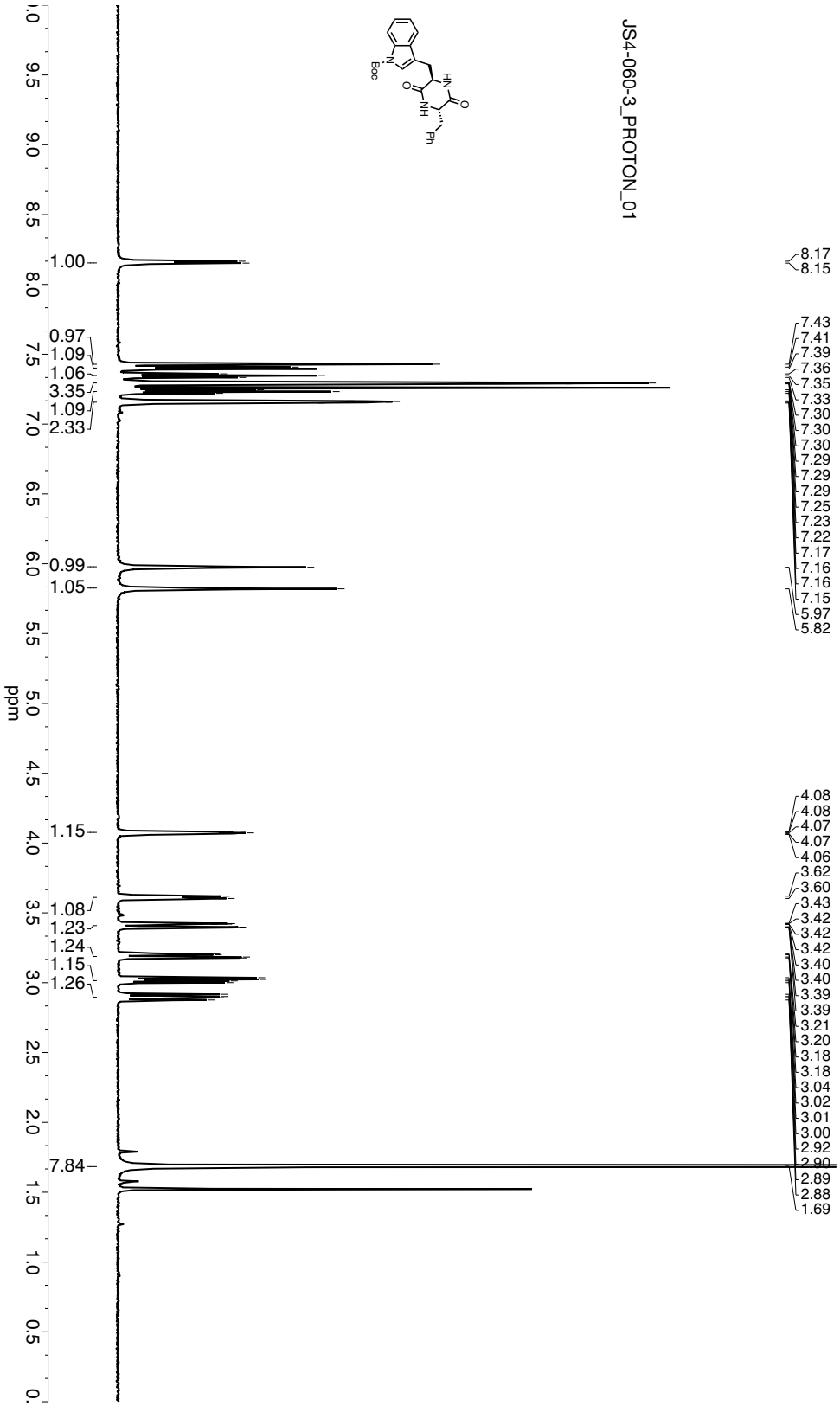
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
171.2
170.5
155.8
149.4
136.0
135.5
135.3
130.1
129.0
128.5
128.2
128.1
127.2
124.7
124.3
122.8
119.1
115.4
115.2
83.7
67.1
55.1
53.0
52.2
37.7
28.3
28.2
N
Boc
HN-Cbz
O
NH
MeO
O
O
Ph


JS4-060-3_PROTON_01
ppm
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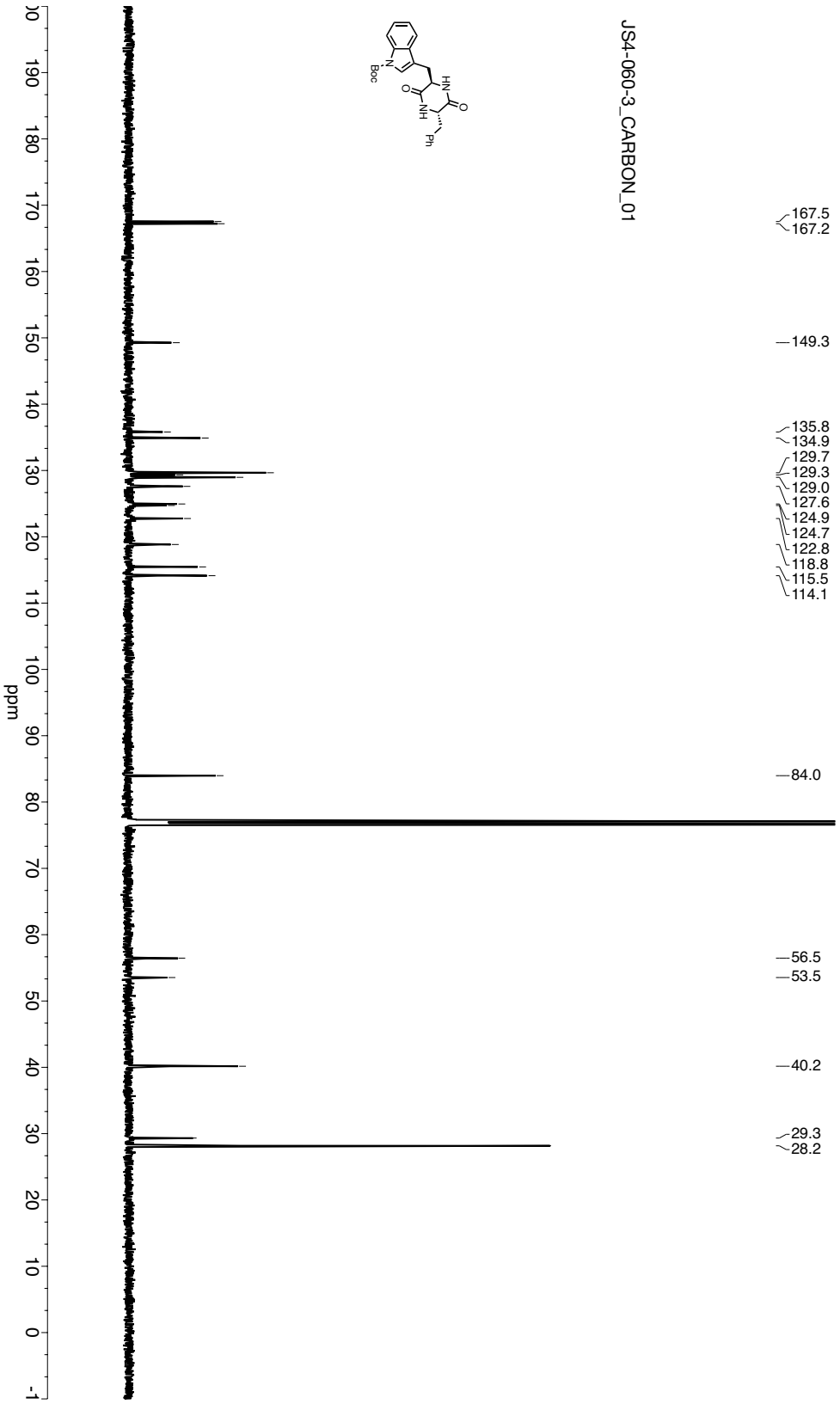
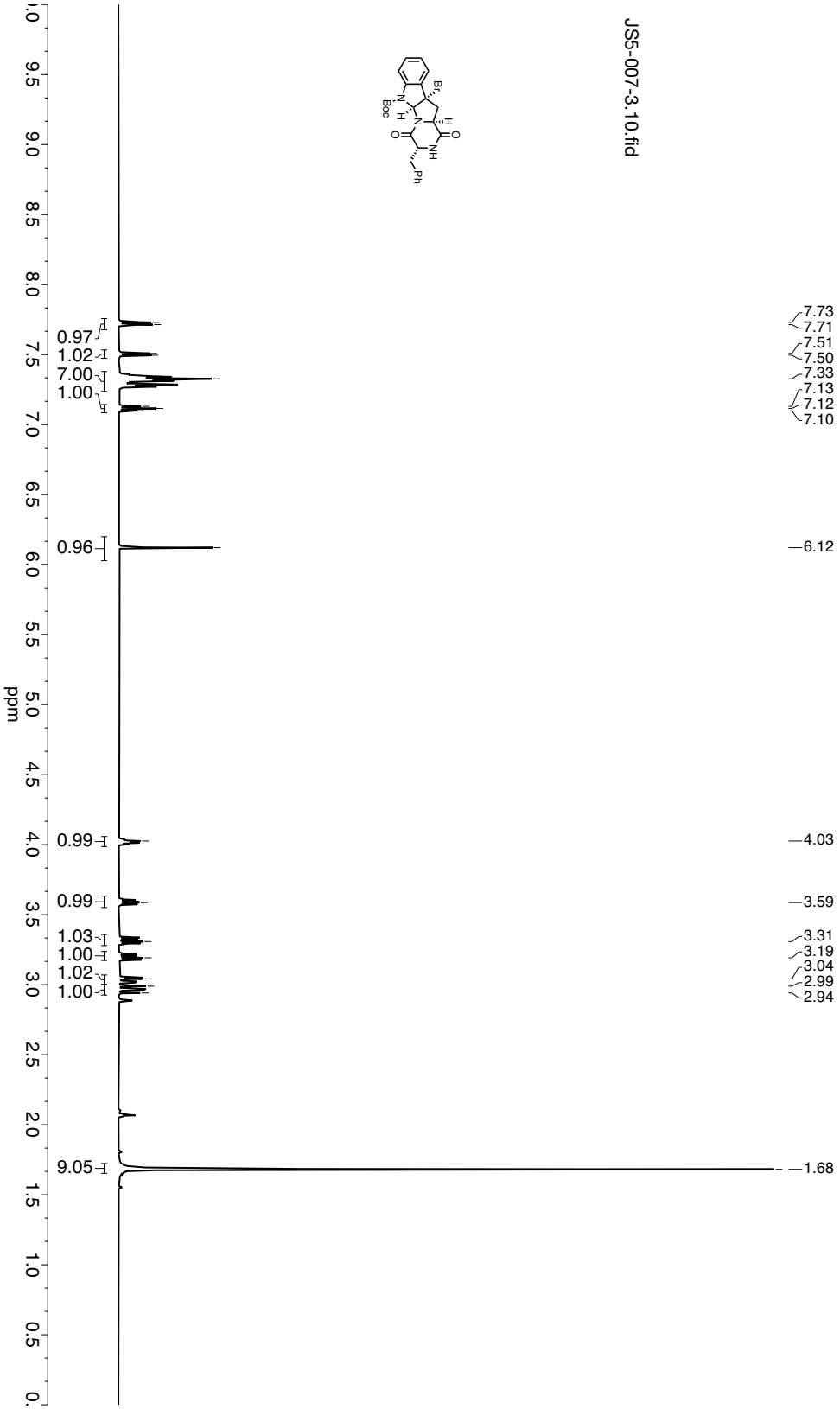
1.09
1.06
3.35
1.09
2.33
0.99
1.05
1.15
1.08
1.23
1.24
1.15
1.26
7.84
8.17
8.15
7.43
7.41
7.39
7.36
7.35
7.33
7.30
7.30
7.30
7.29
7.29
7.29
7.25
7.23
7.22
7.17
7.16
7.16
7.15
5.97
5.82
4.08
4.08
4.07
4.07
4.06
3.62
3.60
3.43
3.42
3.42
3.42
3.40
3.40
3.39
3.39
3.21
3.20
3.18
3.18
3.04
3.02
3.01
3.00
2.92
2.90
2.89
2.88
1.69


JS4-060-3_CARBON_01
Boc
HN
O
NH
Ph
167.5
167.2
149.3
135.8
134.9
129.7
129.3
129.0
127.6
124.9
124.7
122.8
118.8
115.5
114.1
84.0
56.5
53.5
40.2
29.3
28.2
ppm


JS5-007-3.10.fid
ppm
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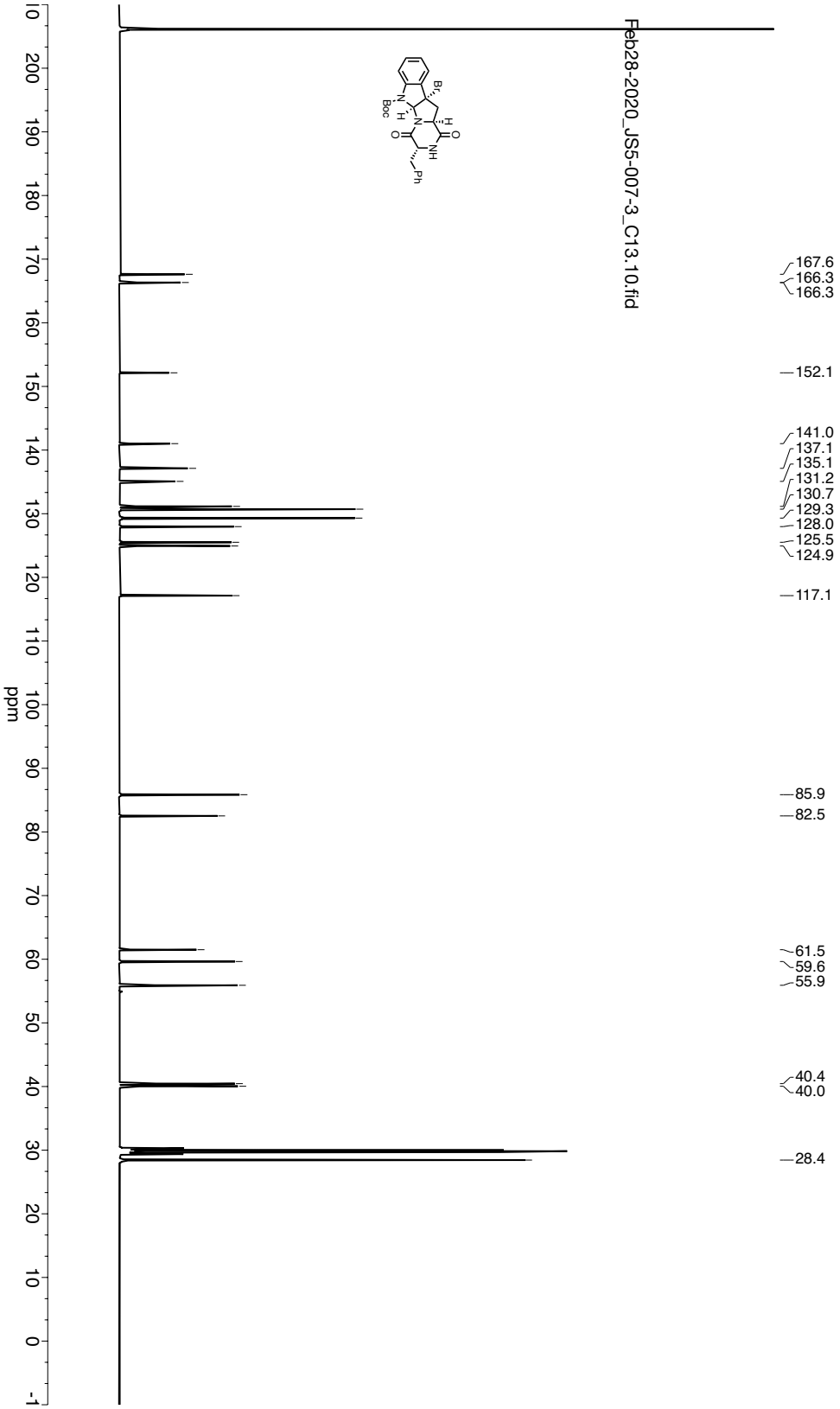
7.00
1.00
0.96
0.99
0.99
1.03
1.00
1.02
1.00
9.05
7.73
7.71
7.51
7.50
7.33
7.13
7.12
7.10
6.12
4.03
3.59
3.31
3.19
3.04
2.99
2.94
1.68


Feb28-2020_JS5-007-3_C13.10.fid
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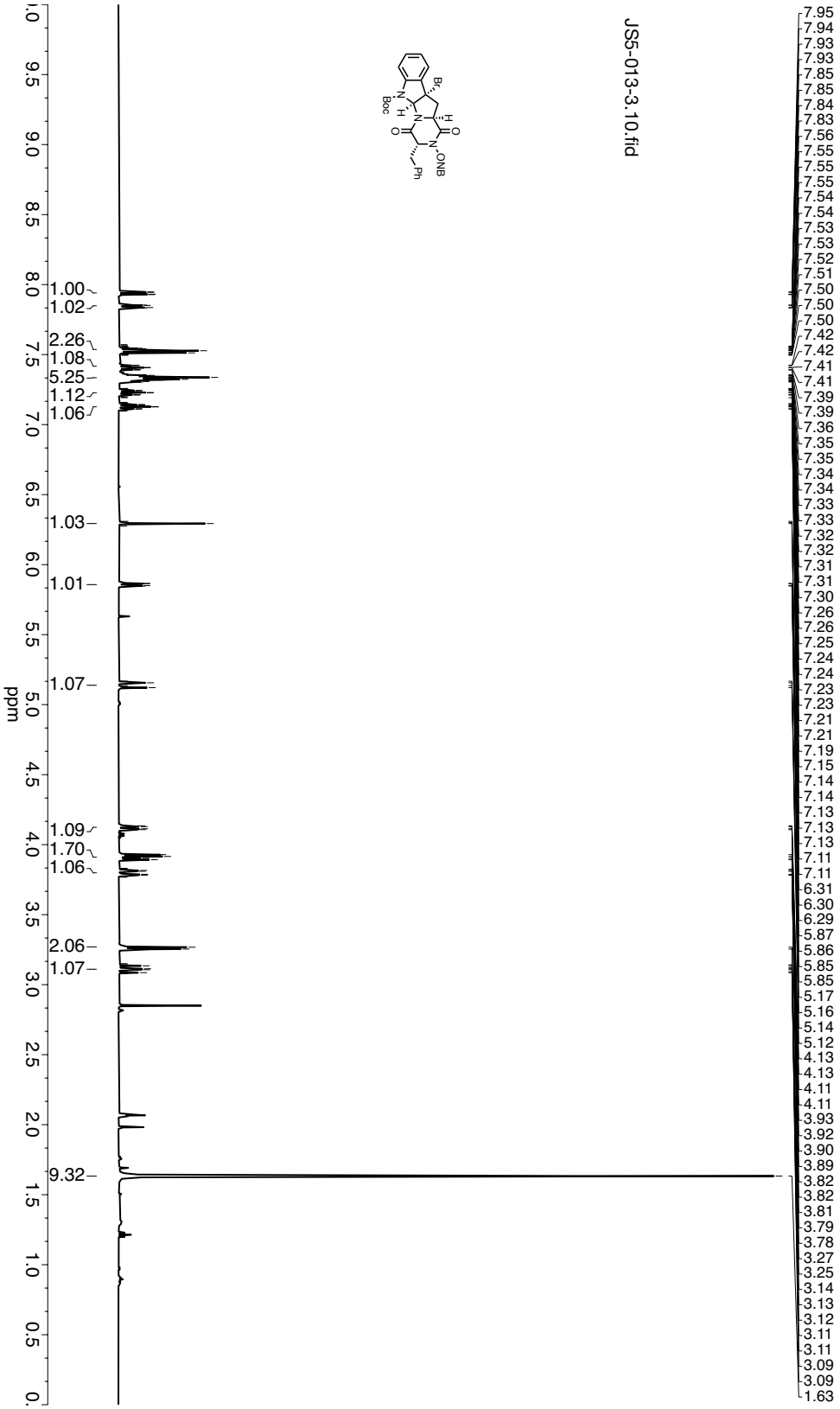
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-1
167.6
166.3
166.3
152.1
141.0
137.1
135.1
131.2
130.7
129.3
128.0
125.5
124.9
117.1
85.9
82.5
61.5
59.6
55.9
40.4
40.0
28.4
Br
N
H
Boc
O
O
H
O
NH
Ph


JS5-013-3.10.fid
ppm
1.00
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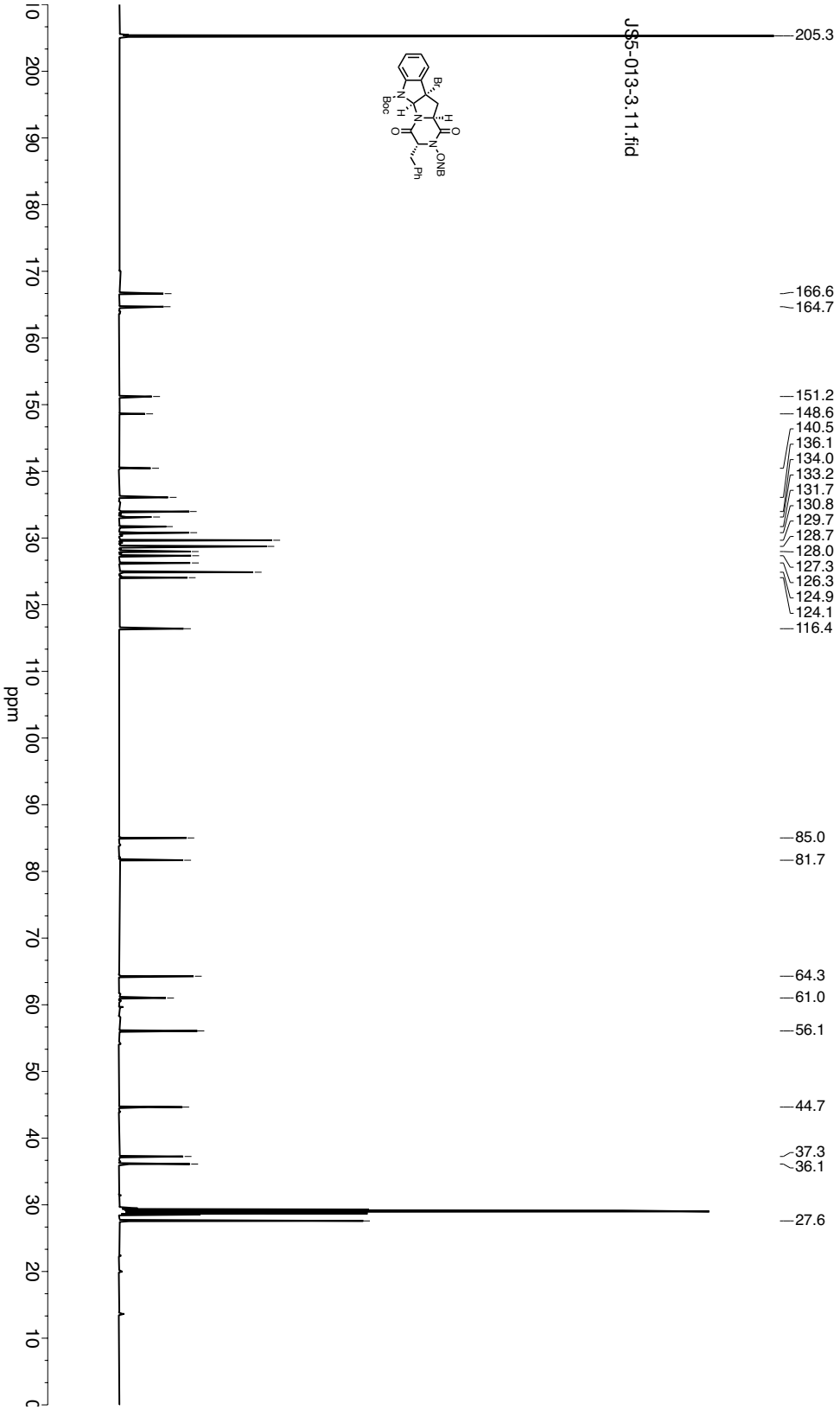
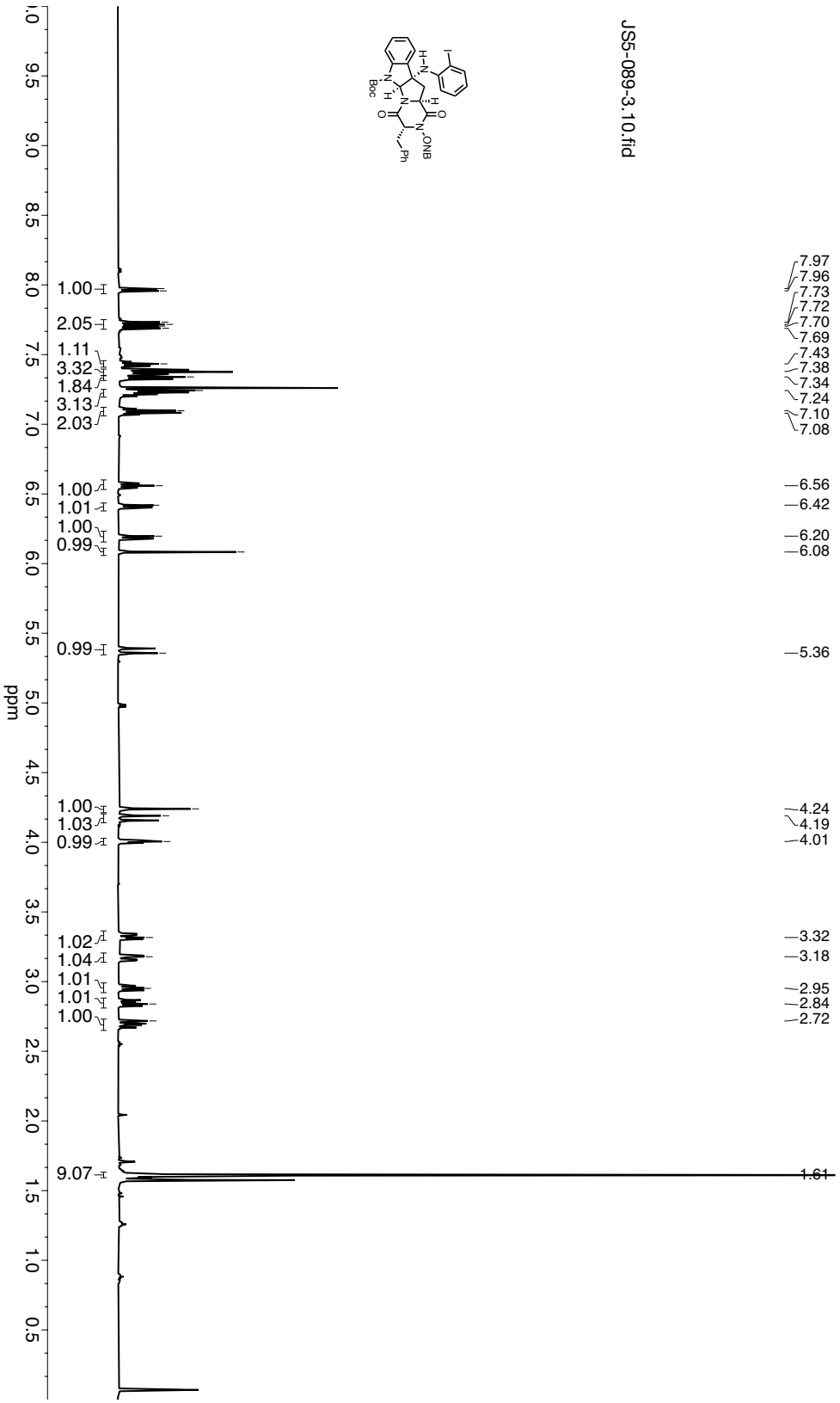
2.26
1.08
5.25
1.12
1.06
1.03
1.01
1.07
1.09
1.70
1.06
2.06
1.07
9.32
7.95
7.94
7.93
7.93
7.85
7.85
7.84
7.83
7.56
7.55
7.55
7.55
7.54
7.54
7.53
7.53
7.52
7.51
7.50
7.50
7.50
7.42
7.42
7.41
7.41
7.39
7.39
7.36
7.35
7.35
7.34
7.34
7.33
7.33
7.32
7.32
7.31
7.31
7.30
7.26
7.26
7.25
7.24
7.24
7.23
7.23
7.21
7.21
7.19
7.15
7.14
7.14
7.13
7.13
7.13
7.11
7.11
6.31
6.30
6.29
5.87
5.86
5.85
5.85
5.17
5.16
5.14
5.12
4.13
4.13
4.11
4.11
3.93
3.92
3.90
3.89
3.82
3.82
3.81
3.79
3.78
3.27
3.25
3.14
3.13
3.12
3.11
3.11
3.09
3.09
1.63


JS5-013-3.11.fid
205.3
166.6
164.7
151.2
148.6
140.5
136.1
134.0
133.2
131.7
130.8
129.7
128.7
128.0
127.3
126.3
124.9
124.1
116.4
85.0
81.7
64.3
61.0
56.1
44.7
37.3
36.1
27.6
ppm
Boc
Ph
ONB


JS5-089-3.10.fid
ppm
1.00
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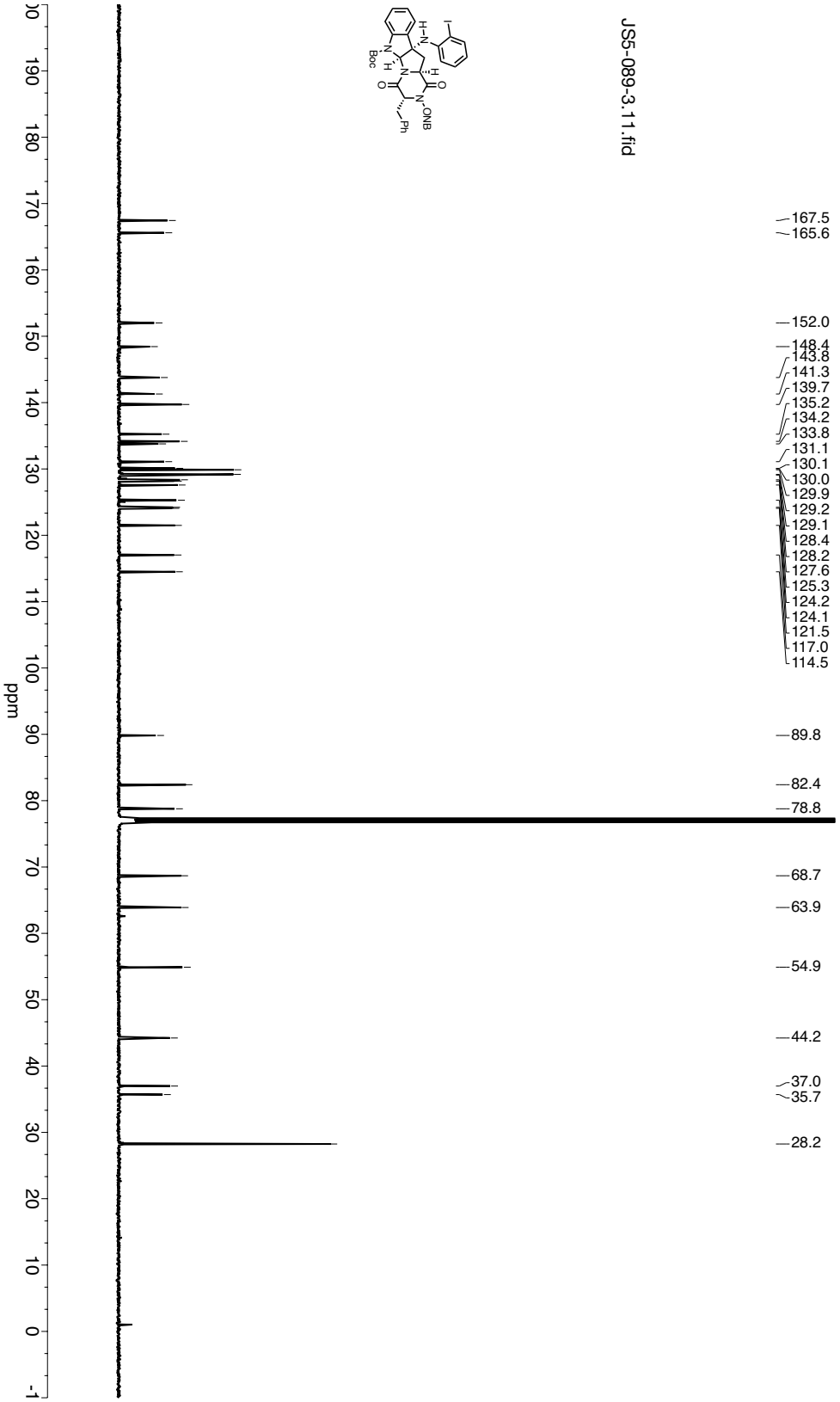
1.11
3.32
1.84
3.13
2.03
1.00
1.01
1.00
0.99
0.99
1.00
1.03
0.99
1.02
1.04
1.01
1.01
1.00
9.07
7.97
7.96
7.73
7.72
7.70
7.69
7.43
7.38
7.34
7.24
7.10
7.08
6.56
6.42
6.20
6.08
5.36
4.24
4.19
4.01
3.32
3.18
2.95
2.84
2.72
1.61


JS5-089-3.11.fid
ppm
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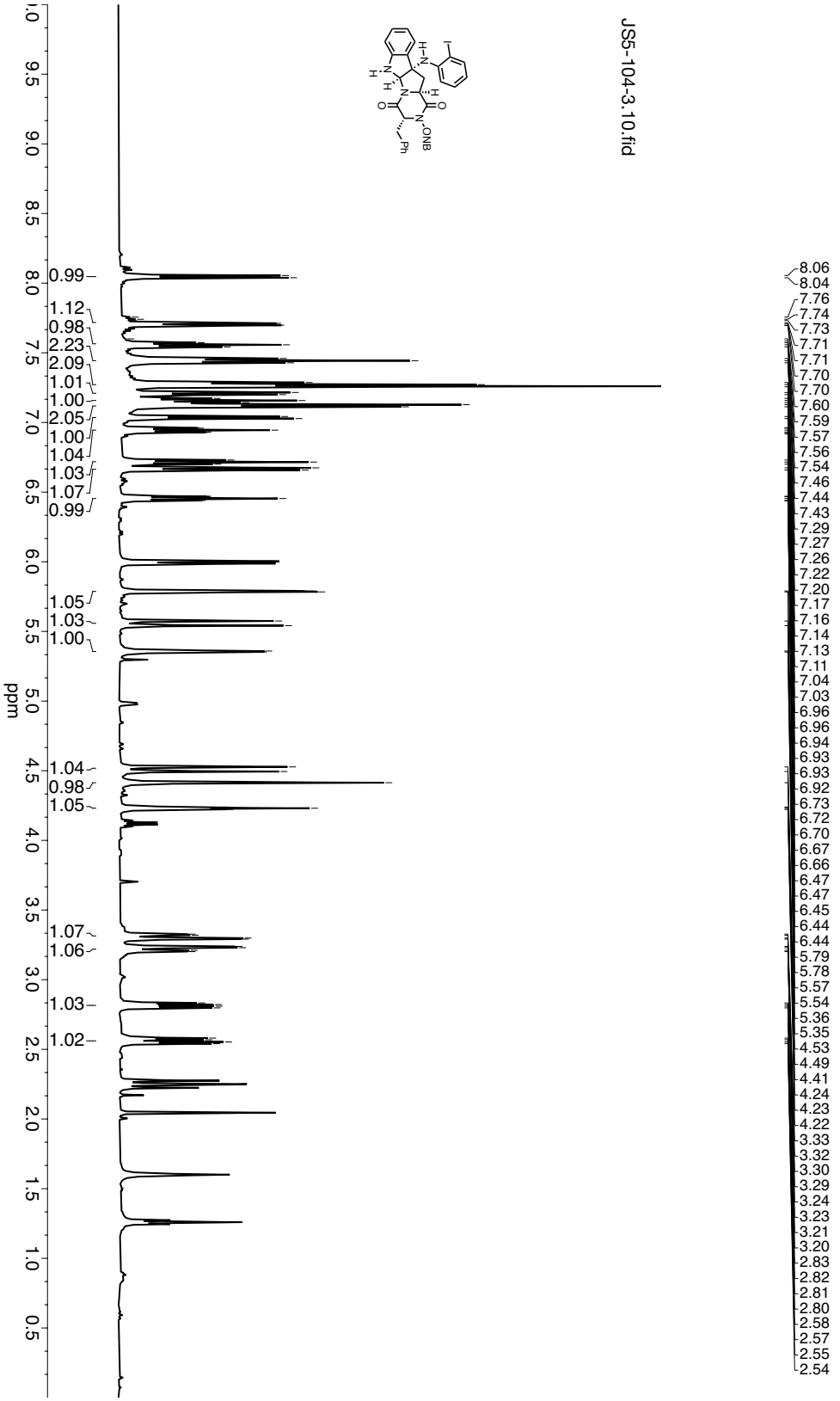
152.0
148.4
143.8
141.3
139.7
135.2
134.2
133.8
131.1
130.1
130.0
129.9
129.2
129.1
128.4
128.2
127.6
125.3
124.2
124.1
121.5
117.0
114.5
89.8
82.4
78.8
68.7
63.9
54.9
44.2
37.0
35.7
28.2


JS5-104-3.10.fid
ppm
0.99
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0.98
2.23
2.09
1.01
1.00
2.05
1.00
1.04
1.03
1.07
0.99
1.05
1.03
1.00
1.04
0.98
1.05
1.07
1.06
1.03
1.02
8.06
8.04
7.76
7.74
7.73
7.71
7.71
7.70
7.70
7.60
7.59
7.57
7.56
7.54
7.46
7.44
7.43
7.29
7.27
7.26
7.22
7.20
7.17
7.16
7.14
7.13
7.11
7.04
7.03
6.96
6.96
6.94
6.93
6.93
6.92
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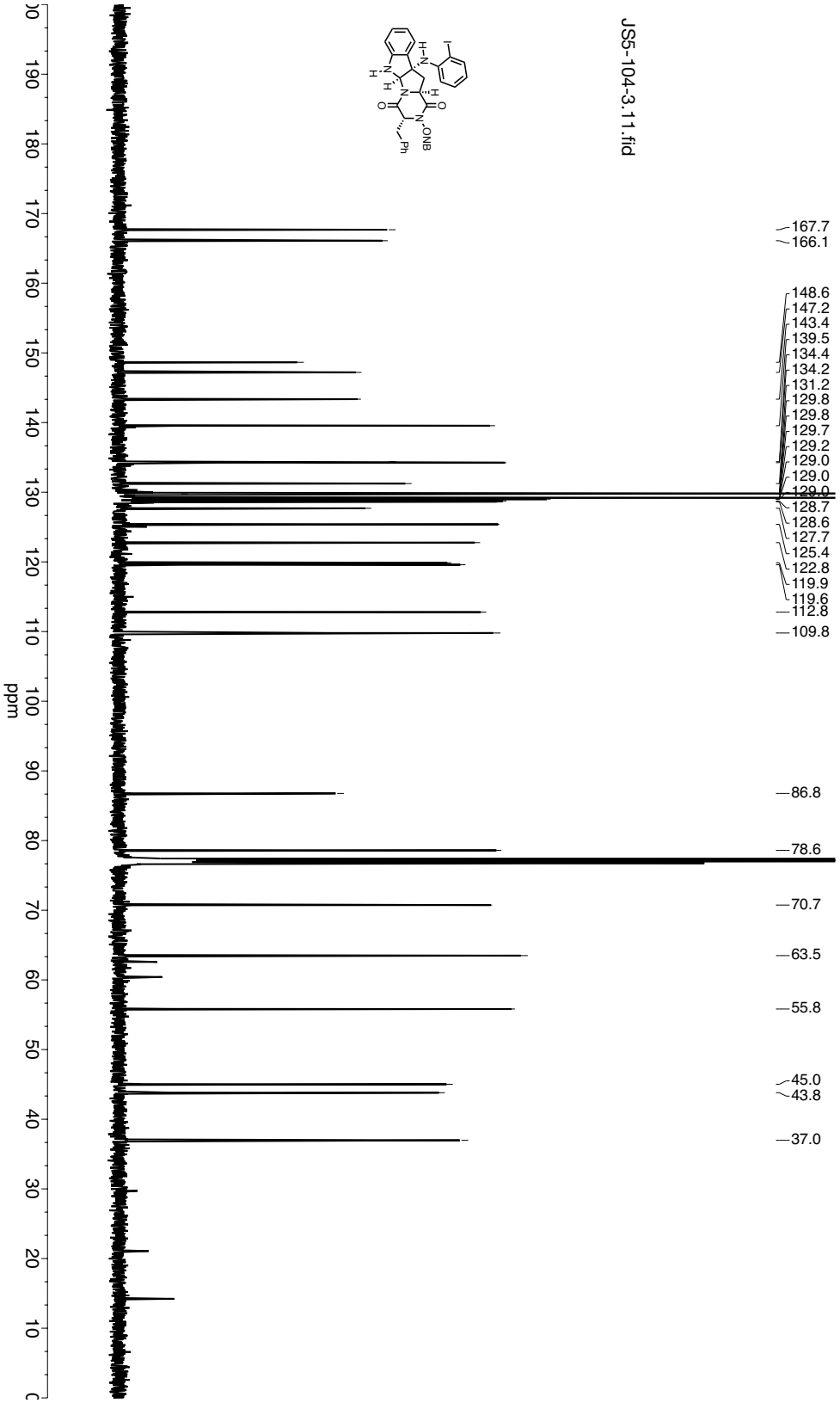
6.72
6.70
6.67
6.66
6.47
6.47
6.45
6.44
6.44
5.79
5.78
5.57
5.54
5.36
5.35
4.53
4.49
4.41
4.24
4.23
4.22
3.33
3.32
3.30
3.29
3.24
3.23
3.21
3.20
2.83
2.82
2.81
2.80
2.58
2.57
2.55
2.54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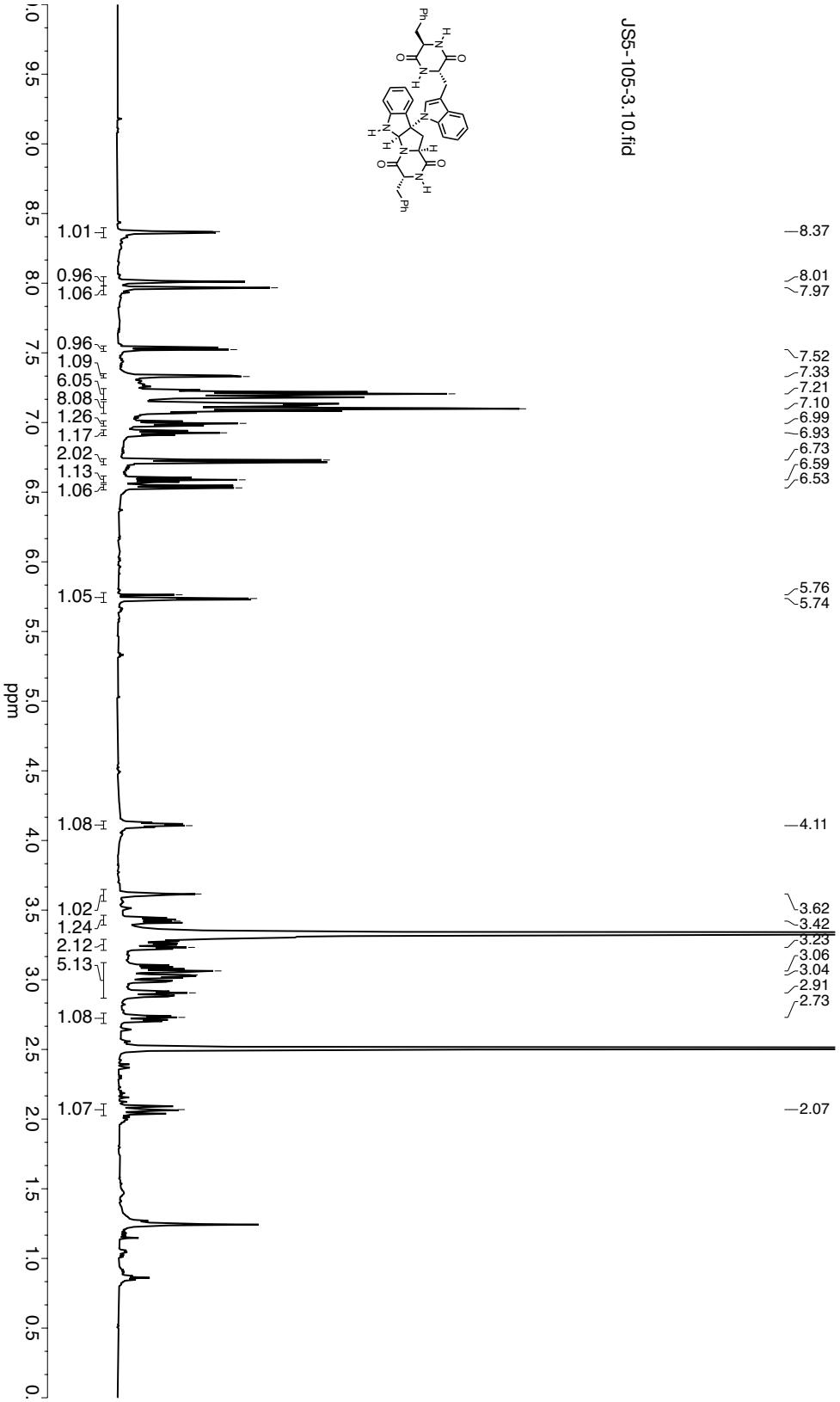
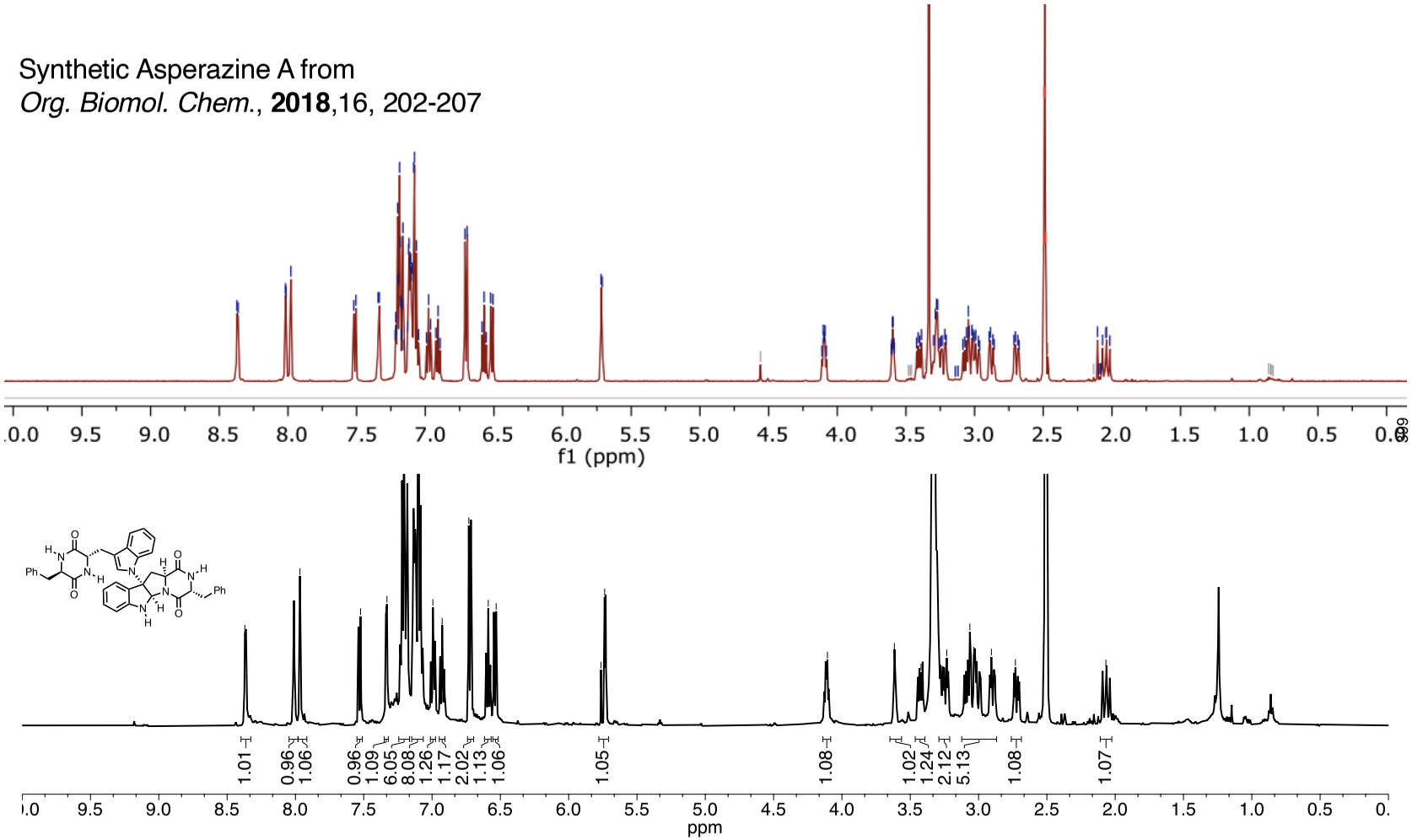
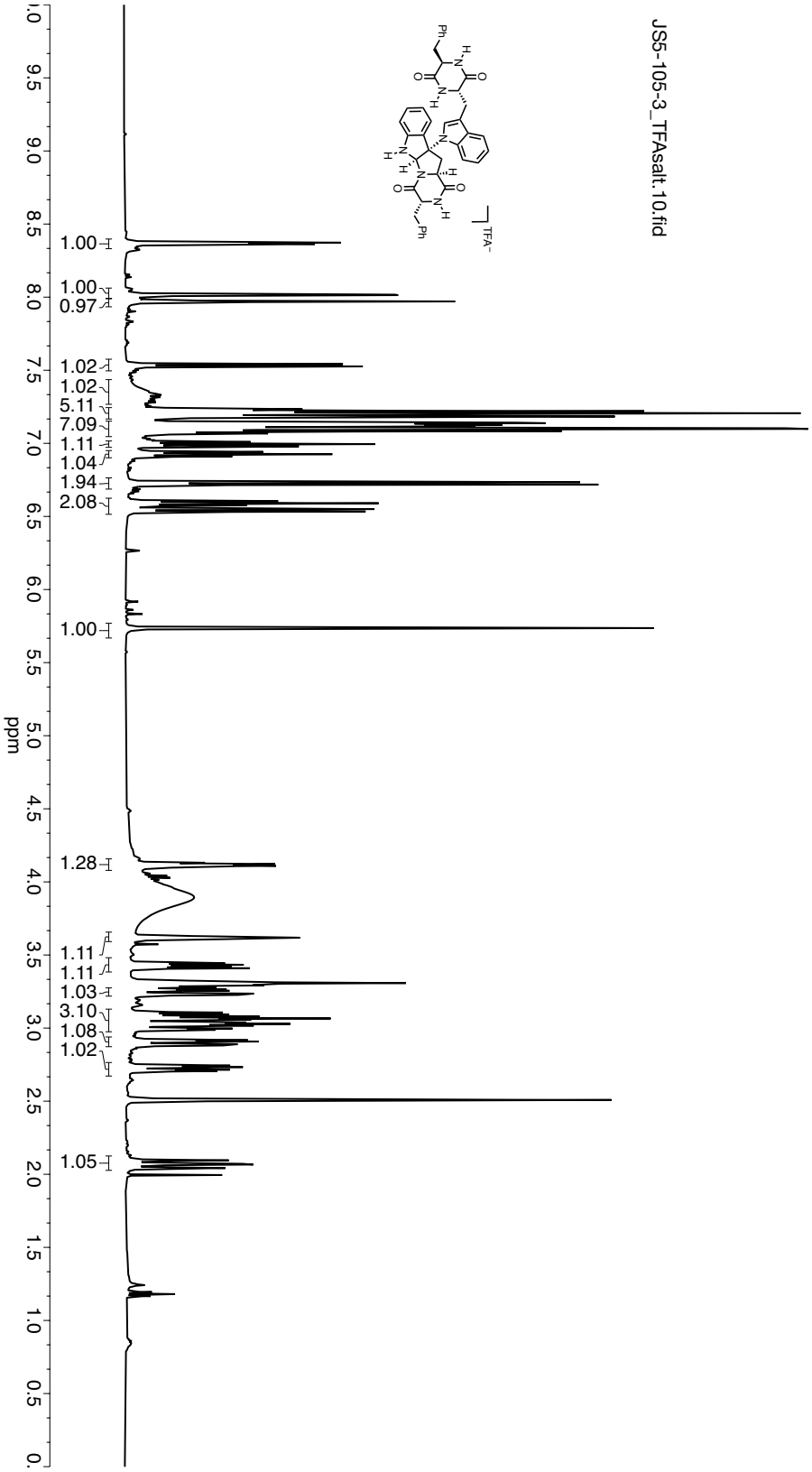
148.6
147.2
143.4
139.5
134.4
134.2
131.2
129.8
129.8
129.7
129.2
129.0
129.0
128.7
128.6
127.7
125.4
122.8
119.9
119.6
112.8
109.8
86.8
78.6
70.7
63.5
55.8
45.0
43.8
37.0


JS5-105-3.10.fid
ppm
1.01
0.96
1.06
0.96
1.09
6.05
8.08
1.26
1.17
2.02
1.13
1.06
1.05
1.08
1.02
1.24
2.12
5.13
1.08
1.07
8.37
8.01
7.97
7.52
7.33
7.21
7.10
6.99
6.93
6.73
6.59
6.53
5.76
5.74
4.11
3.62
3.42
3.23
3.06
3.04
2.91
2.73
2.07

Synthetic Asperazine A from
Org. Biomol. Chem., **2018**,16, 202-207

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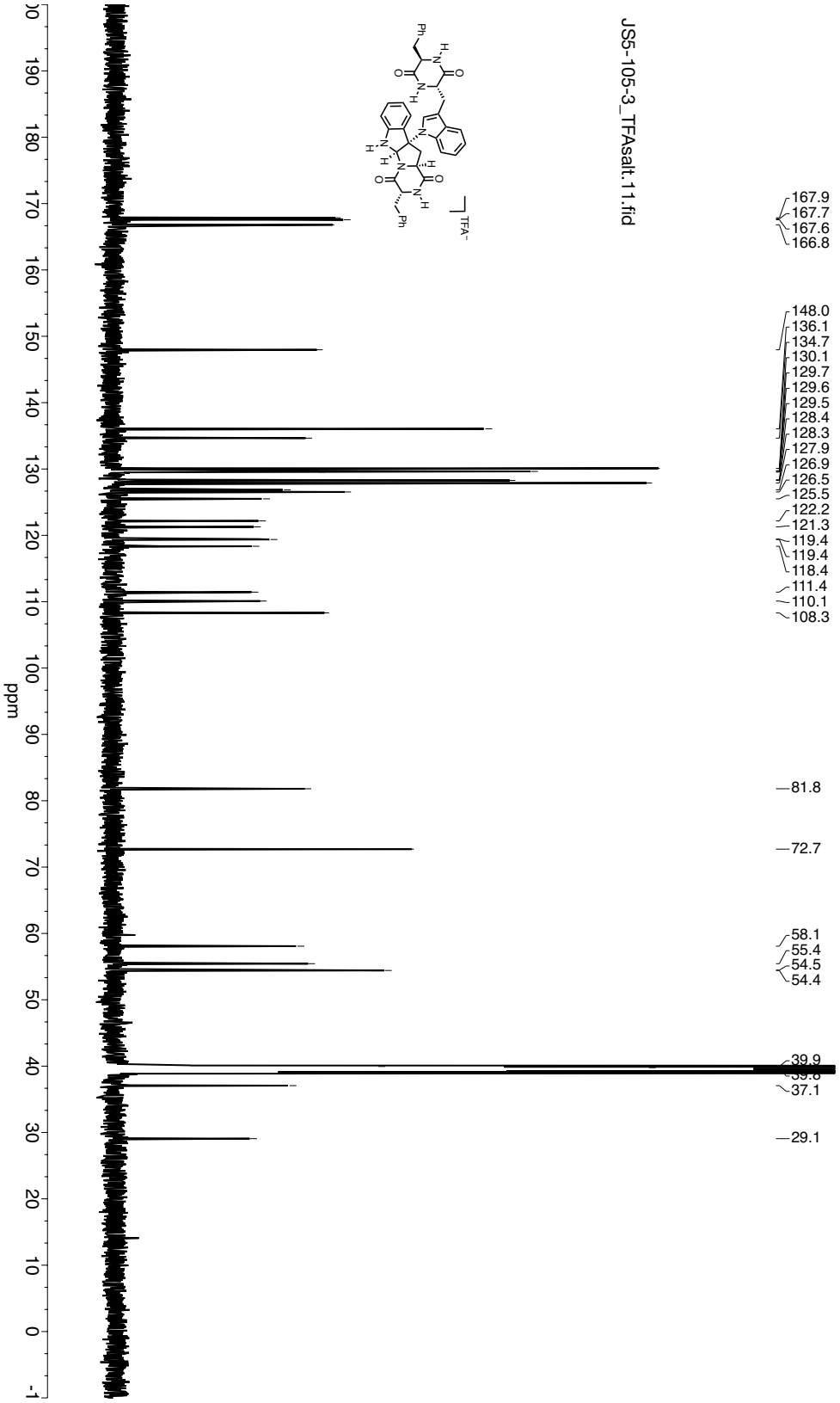
1.00
0.97
1.02
1.02
5.11
7.09
1.11
1.04
1.94
2.08
1.00
1.28
1.11
1.11
1.03
3.10
1.08
1.02
1.05
TFA⁻


JS5-105-3_TFAsalt.11.fid
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167.7
167.6
166.8
148.0
136.1
134.7
130.1
129.7
129.6
129.5
128.4
128.3
127.9
126.9
126.5
125.5
122.2
121.3
119.4
119.4
118.4
111.4
110.1
108.3
81.8
72.7
58.1
55.4
54.5
54.4
39.9
37.1
29.1
ppm
TFA⁻