

THE UNIVERSITY OF CHICAGO

ASYMMETRIC ACCESS TO COMPLEX ALKALOID FRAMEWORKS

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“In order to rise from its own ashes a phoenix first must burn.”

— Octavia Butler, Parable of the Talents

“We cannot always do great things, but we can do small things with great love”

— Gauri Varadhachary

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List of Abbreviations

Ac	acetyl
AIBN	1,1'-azobisisobutyronitrile
Alloc	Allyloxycarbonyl
Ar	aryl
BDSB	bromodiethylsulfonium bromopentachloroantimonate(V)
BINAP	(2,2'-bis(diphenylphosphino)-1,1'-binaphthyl)
bipy	2,2'-Bipyridine
Boc	<i>tert</i> -butoxycarbonyl
BOX	bis(oxazoline)
Bn	benzyl
brsm	based on recovered starting material

Bz	Benzoyl
COSY	correlated spectroscopy
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	N,N'-Dicyclohexylcarbodiimide
DCE	1,2-dichloroethane
DIC	<i>N,N'</i> -diisopropylcarbodiimide
DIBAL-H	Diisobutylaluminum hydride
dioxane	1,4-dioxane
DIPEA	diisopropylethylamine
DMAP	4-(<i>N,N</i> -dimethylamino)pyridine
DMF	<i>N,N</i> -dimethylformamide
DMP	Dess-Martin periodininane
DMPU	N, N'-Dimethylpropyleneurea
DMSO	dimethylsulfoxide
<i>dr</i>	diastereomeric ratio
EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
<i>ee</i>	enantiomeric excess
Et	ethyl
HAT	hydrogen-atom transfer
HOBt	1-Hydroxybenzotriazole
HMDS	hexamethyldisilazide
HMPA	hexamethylphosphoramide
HRMS	high-resolution mass spectrometry
IndaBOX	((3aR,8aR)-3a,8a-dihydro-8H-indeno[1,2-d]oxazol-2-yl)((3aR,8aS)-3a,8a-dihydro-8H-indeno[1,2-d]oxazol-2-yl)methane
IBX	2-iodoxybenzoic acid
<i>i</i> -Pr	<i>iso</i> -propyl
IR	infrared

LDA	lithium diisopropylamide
<i>m</i> CPBA	<i>meta</i> -chloroperoxybenzoic acid
Me	methyl
Mes	mesityl
Ms	methanesulfonyl
MS	molecular sieves
<i>n</i> -Bu	<i>n</i> -butyl
NMO	<i>N</i> -methylmorpholine oxide
NMR	nuclear magnetic resonance
NOESY	nuclear Overhauser effect spectroscopy
nr	no reaction
Ph	phenyl
pin	pinacolato
PPTS	pyridinium <i>para</i> -toluenesulfonate
<i>p</i> -TsOH	<i>para</i> -Toluenesulfonic acid
PyBOX	2,6-bis(oxazolinyl)pyridine
Raney-Ni	Raney Nickel
Redox	Reduction-Oxidation
SXRD	single crystal x-ray diffraction
<i>t</i> -Bu	<i>tert</i> -Butyl
TBS	<i>tert</i> -Butyldimethylsilyl
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic acid anhydride
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl

List of Schemes

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Abstract

ASYMMETRIC ACCESS TO COMPLEX ALKALOID FRAMEWORKS

Russell Kielawa

Bioactive natural products have historically played an essential role at the interface of chemistry and biology. Their complex architectures are the result of unknowable years of evolution and natural selection, often resulting in scaffolds with privileged biological properties in regards to both potency, and pharmacokinetics. The unintended consequence of Nature's unique frameworks is the provision of both formidable challenges and inspiration for the synthetic chemist. Alkaloids research in particular has been a field of both great import, and innovation, dating back to the necessity for quinine with early chemical endeavors toward the anti-malarial cinchona alkaloids resulting in the birth of the synthetic dye industry. Some of the most notable and historically relevant alkaloids (ex. morphine, strychnine, & tropanes) are famous beyond the chemical community, and have provided sufficient impetus for the pursuit of new alkaloid-centric synthetic methodologies to further probe their biological impact. As further evidenced by the history of quinine, the confluence of heteroatom-rich frameworks and stereochemical complexity impedes the asymmetric synthesis of these natural products. Herein we present efforts towards two distinct natural product classes and a number of intricate frameworks, tied together by their functional density, all of which we are able to access in an enantioselective manner.

Chapter 1 delineates the inaugural total synthesis of strychnochromine, a cage-like pentacyclic alkaloid from the *strychnos* family. This molecule is comprised of a tetrahydroquinoline core rarely seen in this family, a total of five chiral centers, and a pyramidal nitrogen which also serves as the junction of multiple interlocked rings. In order to access the natural product asymmetrically, we then developed a copper catalyzed enantioselective α -amination methodology which subsequently enabled the formal asymmetric synthesis of strychnochromine. Furthermore, we demonstrated the extensive synthetic utility

of this method by divergently synthesizing five different alkaloid frameworks from a common functional motif.

Finally, the 2nd chapter of this thesis begins with a synopsis of synthetic efforts towards the akuammiline class of natural products, and the evolution of a chiral pool strategy towards picrinine. Of particular note is the nuanced stereochemical and conformational analysis which was ultimately key to the development of a viable synthetic strategy towards the incredibly challenging methanoquinolizidine core of this class of natural products. This successful radical based strategy marks a significant divergence from the akuammiline alkaloid literature, enabled by a transient quaternization induced Thorpe-Ingold accelerated strategy. Later efforts detail the challenges of a late-stage olefin isomerization, and the decision to target a related alkaloid which is reported to exhibit alternate olefin geometry to the majority of this class.

Chapter 1:

The Asymmetric Total Synthesis of Strychnochromine & Other Alkaloid Frameworks

1.1 Introduction

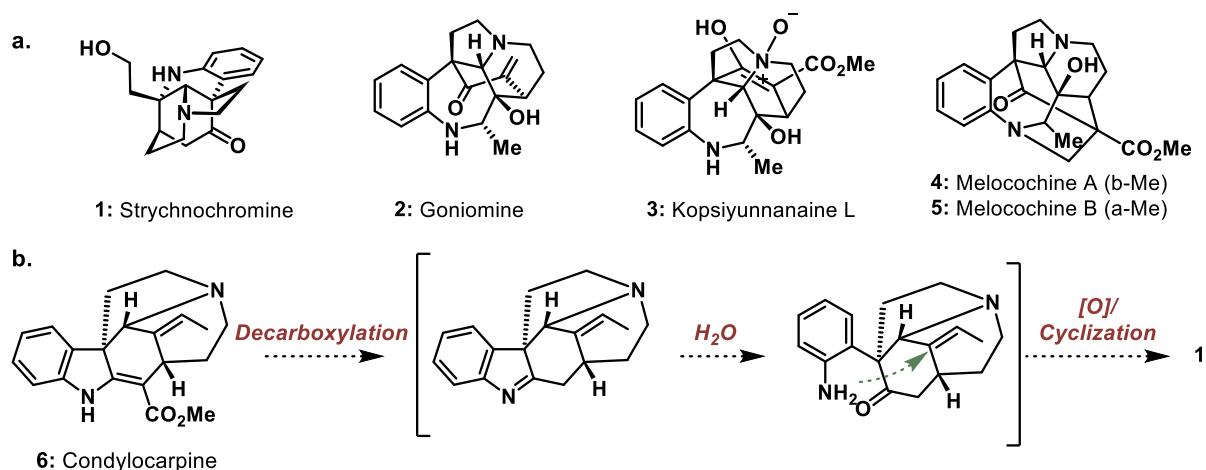
1.1.1 History & Biosynthesis

The total synthesis of alkaloid natural products has a remarkably rich tradition in the field of organic chemistry, with some of the most notable synthetic achievements falling within in this subclass.¹⁻⁷ Perhaps one of the most famed alkaloid targets is none other than Strychnine, first synthesized by Woodward in 1954.⁸ Yet, despite the extensive academic attention this landmark synthesis brought to the *strychnos* family, one rather unique member, strychnochromine (**1**), has evaded chemical synthesis since its discovery in 1988.^{4,7,9,10}

Inspired by the unusual colors (**1**) exhibits upon exposure to a variety of TLC staining solutions, strychnochromine's name is a portmanteau of its taxonomy and this chromatic phenomenon. The structure was originally proposed by Angenot to contain an indole core, however this was later revised by the same group *via* SXRD analysis to incorporate a pentacyclic tetrahydroquinoline framework.¹⁰ This structural reassignment makes strychnochromine an exceptionally attractive synthetic target as it is the only *strychnos* member isolated to date to feature a tetrahydroquinoline moiety. This unique feature in addition to the dense cage-like framework composed of the multiple conjoined *aza*-bicyclic systems impose a substantial and alluring synthetic challenge. Additionally, we hope that our endeavors will provide materials for further biological screening, as thus far only limited efforts have disclosed mild antimalarial activity (IC₅₀ = 16 mM).¹¹

Strychnochromine, along with other structurally related natural products are proposed to arise divergently from condylocarpine (**4**, Scheme 1.1).¹⁰⁻¹⁴ Following an initial decarboxylation, hydrolysis of the resulting enamine function to the keto-aniline structure provides the putative

biosynthetic precursor towards the various natural products (1-5). The determining feature then is the final oxidation and ring-closure processes to afford the differentially functionalized targets.



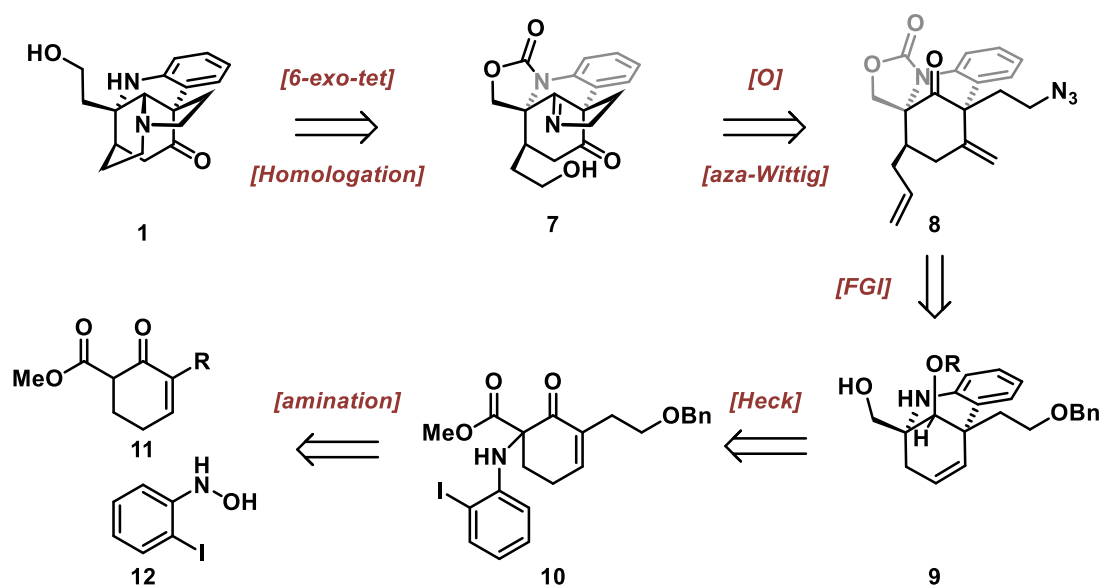
Scheme 1.1 a) Strychnochromine and biosynthetically related natural products. b) Biosynthesis as proposed by Angenot *et. al.*

Prior to our successful total synthesis, there had been some reports detailing results towards various polycyclic substructures, primarily by the Bonjoch group, however the lessons learned from these endeavors have been both implemented prior to my arrival on the project, and elegantly discussed by my mentor Dr. Fangjie Yin.^{15–20} As such, the following analysis will instead focus more specifically on the components of the synthesis upon which my efforts were focused.

1.1.2 Evolution of the Successful Synthetic Route

Our retrosynthetic disconnections which ultimately led to the first total synthesis of strychnochromine begins with a late-stage homologation sequence (scheme 1.2). We devised this disconnection because although the biosynthesis indicates divergency *via* cyclization at the pendant olefin, replicating that formal hydroamination and oxidation process abiotically is non-trivial. Moreover, the consonant 1,3-dicarbonyl synthon of **7** begets a plethora of options both for its own synthesis, and any other transformations originating at that center. From **1**, retrosynthetic disconnection of the piperidine and pyrrolidine rings *via* either S_N2 or suprafacial reactions where

mechanistically appropriate provides the functionalized tricyclic core **8**. The remaining synthetic challenge then becomes to establish the core of **9** in a stereospecific fashion while maintaining the alkene as a handle for subsequent functionalization. To affect this transformation a Heck reaction was envisioned, tracing back to the greatly simplified aryl iodide **10**. From here, retrosynthetic disconnection in the form of an α -amination reveals a functionalized γ - δ -unsaturated- β -ketoester **11**, and the halogenated hydroxylamine **12**. These disconnections, interspersed with any necessary functional group interconversions and protecting group manipulations serve to gradually instill molecular complexity towards **1**.

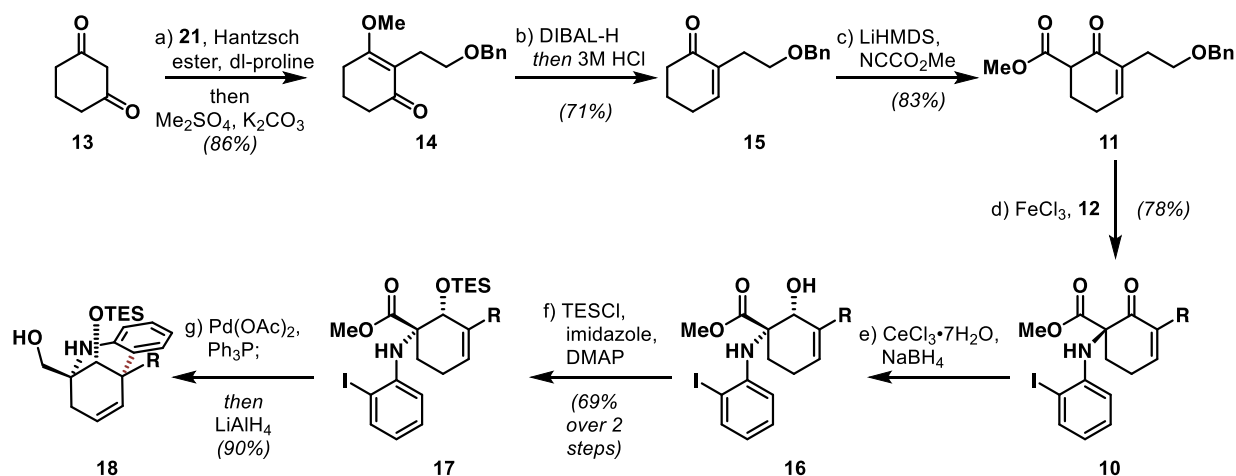


Scheme 1.2 Retrosynthesis of strychnochromine

1.2 Route Scouting & Optimization Towards Strychnochromine

1.2.1 Early Optimization & Model Studies

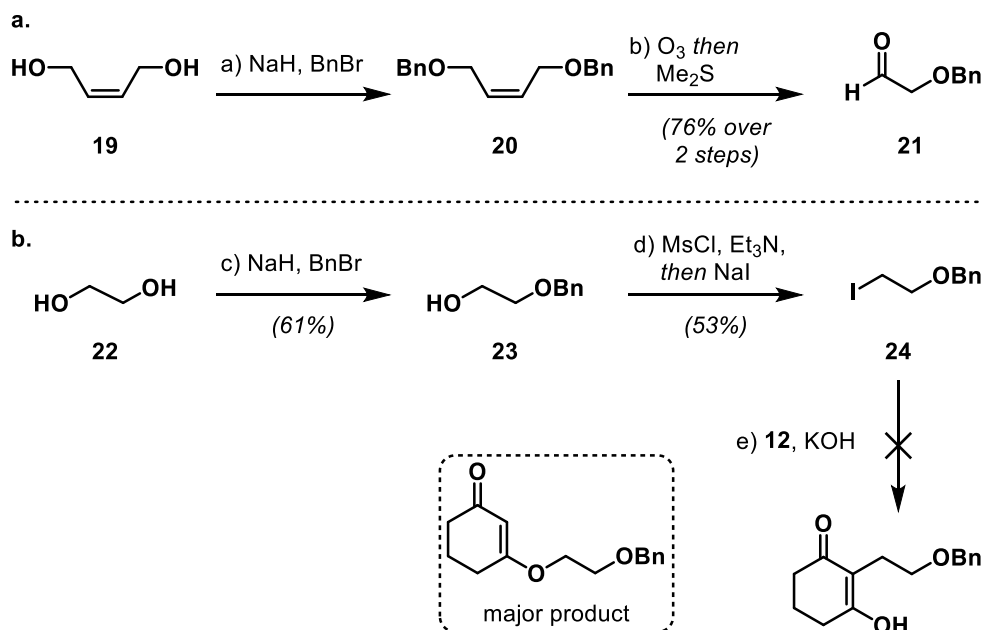
Intending to rapidly forge the tricyclic framework of **1**, the forward synthesis of strychnochromine begins with a reductive Knoevenagel condensation of 1,3-cyclohexanedione (**13**) with **X**, and one-pot formation of the vinylogous ester following a solvent swap in excellent yield (Scheme 1.3).²¹ Reduction and acidic treatment of **14** readily affords α -functionalized enone **15** in a 71% yield. Deprotonation with LiHMDS and subsequent addition of methyl cyanofornate (Mander's Reagent) establishes the desired 1,3-dicarbonyl motif in preparation for the first key step of the synthesis. Slow addition of hydroxylamine **12** into a mixture of **11** and FeCl₃ affects an overall redox-neutral α -amination reaction.²² A potential mechanism of this reaction is discussed in detail further on. In order to achieve the desired carbopalladation reactivity and regioselectivity *via* Heck reaction from intermediate **10**, the enone must first be reduced with Luche conditions and protected as the silyl ether to ensure the carbopalladation proceeds with the desired



Scheme 1.3 Key α -amination step and first cyclization towards polycyclic framework. a) Hantzsch ester (1.0 equiv), and dl-proline (0.1 equiv), 1-benoxylaldehyde (1.0 equiv), CH₂Cl₂ (0.25 M), 23 °C, 12 h; then K₂CO₃ (1.2 equiv), Me₂SO₄ (1.1 equiv), acetone (0.5 M), reflux, 3 h, 86%; b) DIBAL-H (1.5 equiv), toluene (0.25 M), 0 °C, 1 h, 71%; c) LiHMDS (1.3 equiv), NCCO₂Me (1.2 equiv), THF (0.2 M), -78 to 0 °C, 3 h, 83%; d) FeCl₃ (0.1 equiv), **12** (1.2 equiv), dioxane (0.25 M), 50 °C, 3 h, 78%; e) CeCl₃·7H₂O (2.0 equiv), NaBH₄ (8.0 equiv), MeOH/CH₂Cl₂ = 10:1 (0.05 M), 0 °C, 15 min; f) Imidazole (5.0 equiv), DMAP (0.25 equiv), TES-Cl (5.0 equiv), DMF (0.2 M), 0 to 23 °C, 16 h, 69% over 2 steps; g) Pd(OAc)₂ (0.4 eq), Ph₃P (2.0 equiv), K₂CO₃ (2.0 equiv), toluene (0.1 M), 90 °C, 1 h, then LiAlH₄ (2.0 equiv), 0 °C, 30 min, 90%; **R** = CH₂CH₂OBn

regioselectivity. Fortunately, the Heck and ester reduction sequence can be telescoped into a single-pot to directly afford **18** in excellent overall yield.

The forward synthesis as laid out in Scheme 1.3 and described by Dr. Fangjie Yin is remarkably robust, beginning at >200 mmol scale.²⁰ Despite this scalability, some practical considerations limited both the ease, and timeliness of material pushing. In the first step, column chromatography of the reductive Knoevenagel product is substantively hindered by presence of stoichiometric quantities of Hantzsch pyridine byproduct. In an attempt to simplify the largest purification of the synthesis, we sought to eliminate the need for redox manipulation in the reductive Knoevenagel condensation by switching to an alkyl electrophile. Anticipating that competitive *O*- vs. *C*- alkylation may be an issue, we hoped the application of a relatively soft alkyl iodide electrophile may provide some selectivity, however upon treatment of **13** with base in

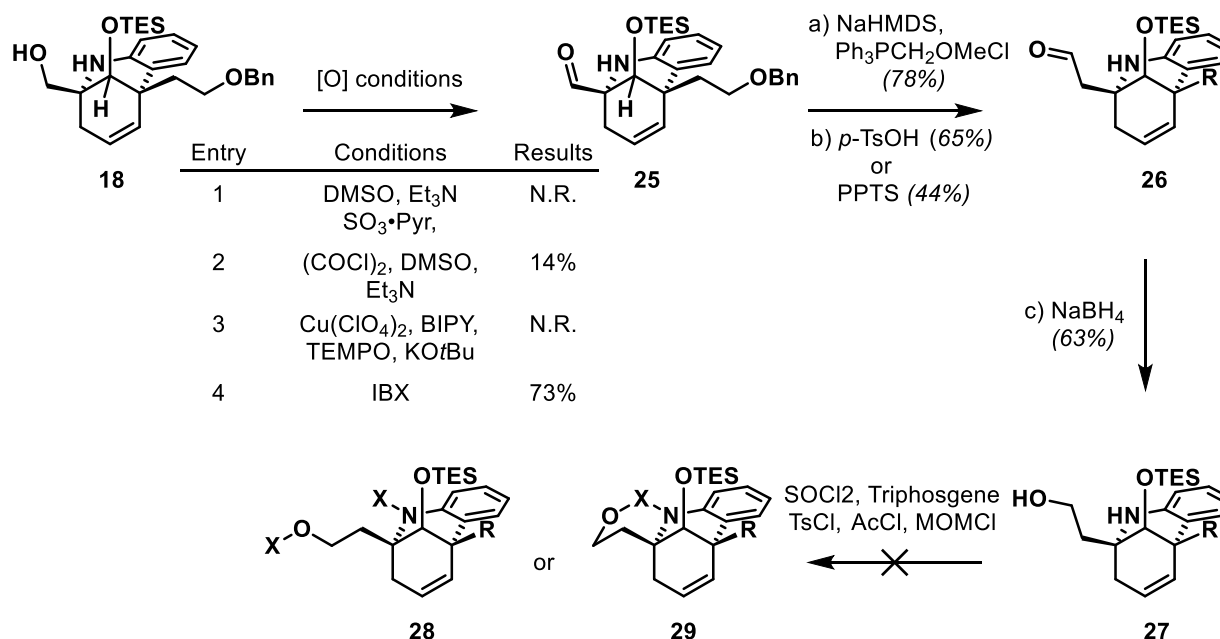


Scheme 1.4 **a**) Benzyloxyaldehyde synthesis a) NaH (3.5 eq), BnBr (2.0 eq), THF (0.25 M), 0 °C, 12 h; b) O₃, CH₂Cl₂:MeOH = 3:1 (0.3 M), Me₂S (4.0 eq) -78 °C to 23 °C, 16 h, 76% over 2 steps. **b**) Attempted halide alkylation c) NaH (1.0 eq), BnBr (1.0 eq), THF (0.25 M), 0 °C, 12 h, 61%; d) MsCl (2.0 eq), Et₃N (2.0 eq) CH₂Cl₂ (0.5 M), 0 °C, 30 minutes *then* NaI (10.0 eq), CH₂Cl₂:acetone = 1:3 (0.1 M), 23 °C, 12 h, 53% e) **12** (1,3-cyclohexanedione) (1.0 eq), **24** (1.0 eq), KOH (1.0 eq), EtOH:H₂O = 7:1 (0.15 M)

the presence of **13**, only the *O*-alkylated vinylogous ester product was observed (scheme 1.3).^{23–26}

These efforts were then abandoned in favor of the previously developed reductive Knoevenagel to prioritize the late-stage chemistry.

Having secured and optimized a reliable route to **18**, we next endeavored to model the efficacy of the final homologation sequence on this tricyclic framework. Moreover, the optionality this homologated framework would exhibit contrasted with the rigidity of **23** presented this as an alluring alternative. With a preliminary screen of oxidative conditions, we ultimately found that IBX was an efficient oxidant in this capacity, though we maintained reservations about its implementation late-stage in the presence of a 3° amine (Scheme 1.5). From aldehyde **25**, Wittig homologation afforded the corresponding enol-ether which could be facilely hydrolyzed with acidic treatment, and subsequently reduced in moderate yields. Noteworthy in the transposition of this model study to the final route is the slightly increased temperature for the Wittig reaction as a result of the increased steric encumbrance of the latter material (Scheme 1.7). Unfortunately,



Scheme 1.5 Homologation model studies and protection attempts. a) NaHMDS (2.0 eq), Ph₃PCH₂OMeCl (2.5 eq), THF (0.1 M), -78 °C to 0 °C, 78%; b) PPTS/*p*-TsOH (0.5 eq), CH₂Cl₂ (0.5 M), 23 °C, 1.5 h, 44%/65%. c) NaBH₄ (1.5 eq), CH₂Cl₂:MeOH = 1:1 (0.1 M), 0 °C, 63%. **R** = CH₂CH₂OBn

despite the success of this model homologation sequence, all attempts to protect the amino alcohol moiety in a cyclic fashion were unsuccessful, and attempted bis-protection failed to functionalize the anilinic nitrogen, thus our efforts were consolidated to focus on the non-homologated variant.

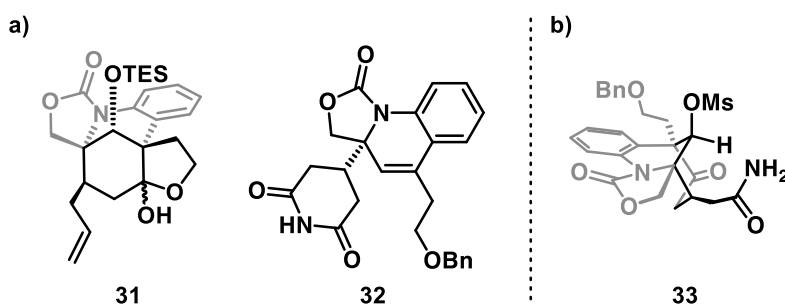


Figure 1.1 a) Representative lactol & fragmentation structures. b) Possible conformation of the stereoelectronically inhibited S_N2 reaction

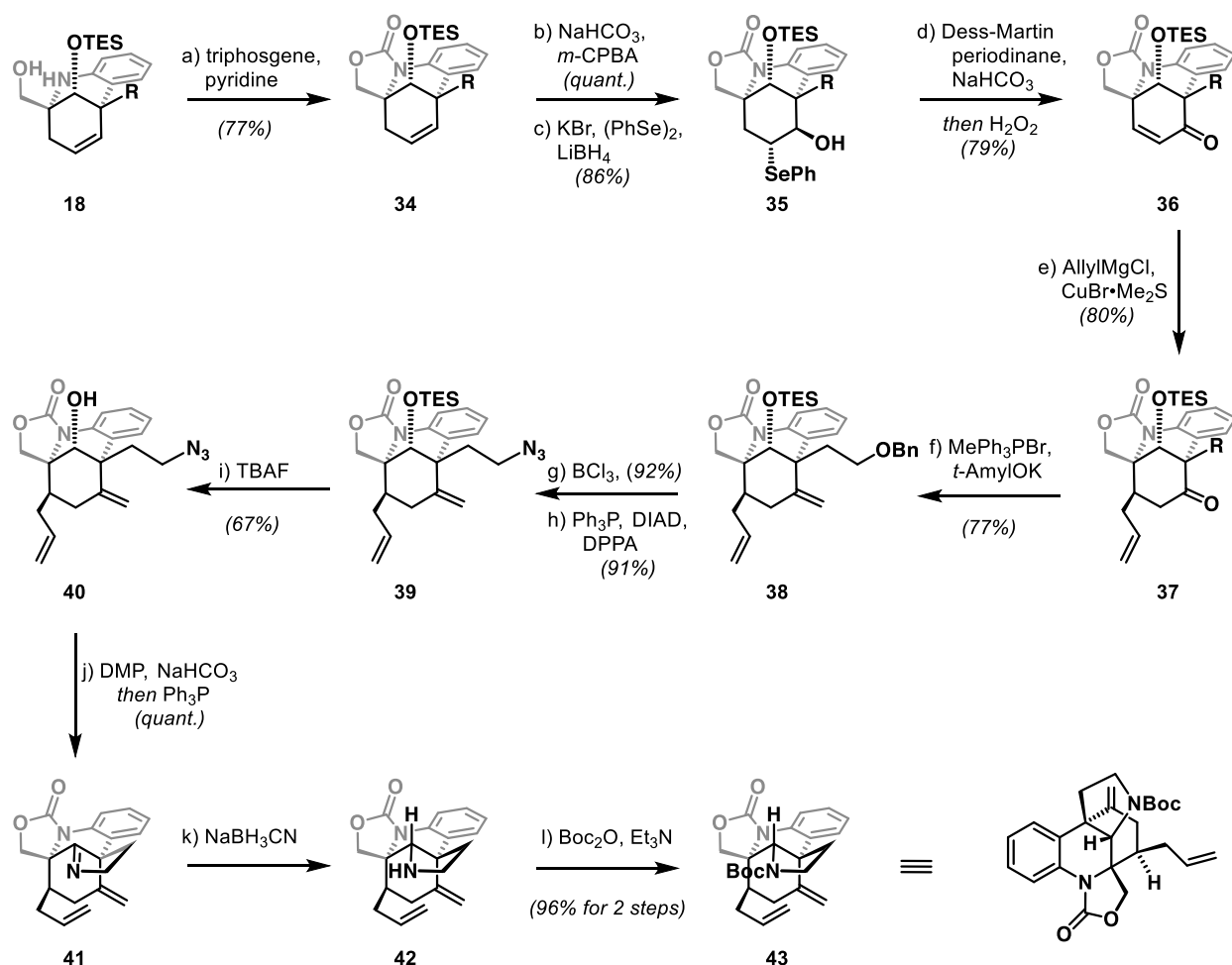
1.2.2 Completion of the Total Synthesis

Continuing the forward synthesis, **18** was first protected with triphosgene, affording the cyclic carbamate **34**. Protection prevents any undesirable side reactions from either the imminent epoxidation, or subsequent oxidative conditions. Notably, epoxidation of **34** is sensitive to trace quantities of benzoic acid in the *m*CPBA. We first circumvented this issue by pre-washing the allotted *m*CPBA as a solution in CH_2Cl_2 with pH 7.4 phosphate buffer, drying over Na_2SO_4 , filtration, and direct application of the solution to the substrate to avoid concentration of the potentially explosive peroxyacid which affords the epoxide in quantitative yield as a single diastereomer and in excellent purity upon work-up. We later buffered the reaction mixture with NaHCO_3 to identical effect. Application of Sharpless's elegant sequence to convert epoxides into α,β -unsaturated ketones *via* selenation, oxidation, and elimination proceeds smoothly in a regiospecific fashion.²⁷ This newly minted enone is then immediately subjected to conjugate addition of an allyl-cuprate, and subsequent masking of the resultant ketone as an exocyclic olefin braces the molecule for Lewis acidic benzyl ether deprotection (Scheme 1.6). This olefination

based masking strategy is necessitated by highly favorable lactol formation of the aforementioned ketone and pendant alcohol upon deprotection, as well as retro-aldol fragmentations under basic conditions (Figure 1.1).²⁰

Having successfully deterred the undesired reactivity, the stage is set for pyrrolidine ring formation. Mitsunobu reaction of the primary alcohol with DPPA affords azide **39** in great yield, and following TBAF deprotection, a one-pot oxidation-Staudinger/Aza-Wittig sequence affords imine **41** (Scheme 1.6). The suprafacial attack of the intermediate iminophosphorane is key to the success of this transformation, as all previous S_N2 type cyclization attempts failed. We presume these failures are due to the coplanar arrangement of the s* orbital of the electrophile with the carbon framework itself, stereoelectronically precluding effective substitution (Figure 1.1).²⁸ Additionally, formation of the thermodynamically favorable triphenylphosphine oxide likely further aids in the efficiency of this process. Imine **41** can then be diastereoselectively reduced and protected (in anticipation of the oxidative cleavage of our masked olefin) in excellent yield over 2 steps, affording Boc-carbamate **42**.

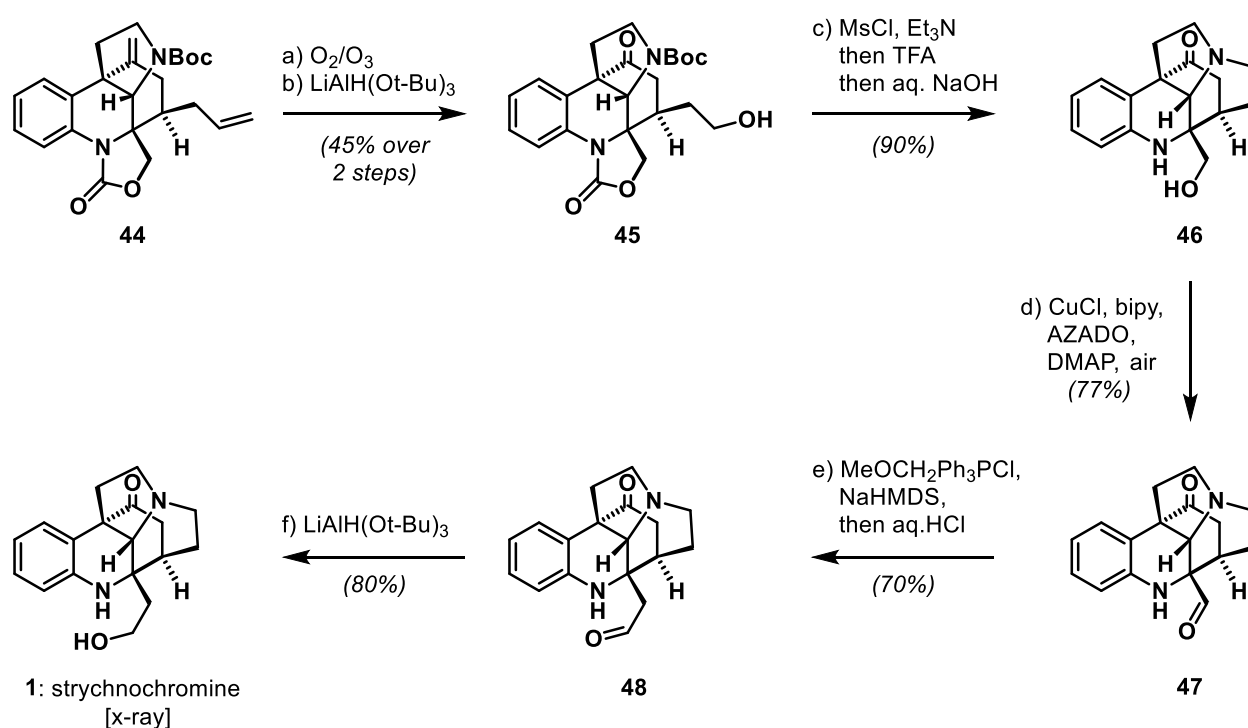
Working towards the final ring-closing event, oxidative cleavage was first attempted with Lemieux-Johnson conditions, however this resulted in only trace quantities of the doubly-cleaved material (Scheme 1.7). We hypothesized that the smaller and more reactive ozone would prove superior, and it ultimately was, albeit with extensive optimization. Critically, use of the relatively unusual DMF solvent proved necessary to limit the formation of undesired byproducts and improve yield.^{20,29–31} Exploiting the steric hindrance of neopentyl ketone allows us to use a bulky reducing agent in the form of LiAlH(OtBu)₃ to selectively reduce the aldehyde to the primary



Scheme 1.6 Intermediate FGI and Staudinger/aza-Wittig cyclization. a) triphosgene (0.4 eq), pyridine (4.0 equiv), CH_2Cl_2 (0.1 M), 0 °C, 5 min, 77%; b) *m*-CPBA (5.0 equiv), NaHCO_3 (10.0 equiv), CH_2Cl_2 (0.1 M), 0 to 23 °C, 5 min, quantitative; c) KBr (10.0 equiv), $(\text{PhSe})_2$ (1.2 equiv), LiBH_4 (2 M in THF, 2.8 equiv), THF (0.2 M), 23 to 60 °C, 2 h, 86%; d) DMP (2.0 equiv), NaHCO_3 (5.0 equiv), DCE (0.1 M), 23 °C, 2 h, then H_2O_2 (35% in H_2O , 2.0 equiv), 80 °C, 1 h, 79%; e) allylmagnesium chloride (2 M in THF, 4.0 equiv), $\text{CuBr}\cdot\text{Me}_2\text{S}$ (2.0 equiv), THF (0.2 M), -78 to -45 °C, 2 h, 80%; f) methyltriphenylphosphonium bromide (3.0 equiv), potassium *t*-pentoxide (1.7 M in Toluene, 2.5 equiv), toluene (0.2 M), 80 °C, 1 h, 77%; g) BCl_3 (1.0 M in CH_2Cl_2 , 3.0 equiv), CH_2Cl_2 (0.1 M), 0 °C, 10 min, 92%; h) Ph_3P (2.0 equiv), DIAD (2.0 equiv), DPPA (2.0 equiv), THF (0.3 M), 23 °C, 16 h, 91%; i) TBAF (1.0 M in THF, 2.0 equiv), THF (0.1 M), 0 °C, 30 min, 67%; j) NaHCO_3 (5.0 equiv), Dess-Martin periodinane (2.0 equiv), DCE (0.1 M), 23 °C, 1 h, then Ph_3P (5.0 equiv), 80 °C, 1 h, quantitative; k) NaBH_3CN (1.0 M in THF, 3.0 equiv), $\text{MeOH/TFA} = 10:1$ (0.1 M), 0 to 23 °C, 16 h; l) Et_3N (3.0 equiv), Boc_2O (3.0 equiv), CH_2Cl_2 (0.1 M), 0 to 23 °C, 1 h, 96%. **R** = $\text{CH}_2\text{CH}_2\text{OBn}$

alcohol in a modest yield over 2 steps. From , application of a beautiful and simplistic one-pot sequence developed by Dr. Fangjie Yin completes the pentacyclic core of the natural product. Specifically, operations include primary alcohol mesylation, Boc-pyrrolidine deprotection, and treatment of aqueous base, concomitantly hydrolyzing the carbamate, and deprotonating the amine salt allowing for 6-*exo*-tet cyclization.²⁰ We had simultaneously pursued the final piperidine ring closure *via* an anti-Markovnikov hydroamination reaction, however the analogous vinyl conjugate

addition into enone **36** never proceeded above 50% conversion.³² Thus, this remarkably efficient one-pot procedure both completes the densely caged framework of strychnochromine, and simultaneously primes us for an analogous homologation sequence to that previously discussed (scheme 1.7). The two major differences which arose in the transition of our model study to the real system are: 1) Iwabuchi-Stahl type oxidation proved most effective, as on the fully elaborated system IBX was poorly tolerated, and; 2) the same bulky reducing agent was employed to ensure similar selectivity to that observed in the preceding reduction (Scheme 1.7).^{33,34} Upon purification, we successfully verified the structure of **1** by both NMR and SXRD.



Scheme 1.7 Strychnochromine endgame. a) O₃ (30% in O₂), DMF (0.05 M), -60 °C, 30 min, then Me₂S (10.0 equiv), -60 to 23 °C, 16 h, 45%; b) LiAlH(Ot-Bu)₃ (1.0 M in THF, 2.0 equiv), THF (0.05 M), -78 °C, 2 h, quantitative; c) Et₃N (3.0 equiv), MsCl (3.0 equiv), CH₂Cl₂ (0.1 M), 0 to 23 °C, 30 min, then TFA (14.7 equiv), 23 °C, 2 h, then NaOH (3.0 M in H₂O, 100 equiv), 23 °C, 20 h, 90%; d) AZADO (5 mol%), 2,2'-bipyridyl (5 mol%), DMAP (10 mol%), CH₃CN (0.1 M), open to air, 23 °C, 3 h, 77%; e) MeOCH₂Ph₃PCl (4.0 equiv), NaHMDS (1.0 M in THF, 3.0 equiv), THF (0.1 M), 0 °C, 10 min, 70%; f) LiAlH(Ot-Bu)₃ (1.0 M in THF, 3.0 equiv), THF (0.03 M), -78 to -40 °C, 2 h, 80%.

1.2.3 Conclusion & Opportunities

The amalgamation of these reactions constitutes the first reported total synthesis of strychnochromine (**1**) in 25 steps, with an overall yield of 0.74% and an average yield of 82%. We believe the route to have demonstrated a considerable degree of both robustness and scalability, and yet believe potential improvements are possible as well. Realizing that all the chemistry in the synthesis proceeds either stereospecifically or diastereoselectively, the installation of the first fully substituted carbon dictates the chirality of the molecule forevermore. Hence the simple transfiguration of the racemic α -amination reaction into an enantioselective transformation would render the totality of the synthesis asymmetric. The opportunity to both accomplish an asymmetric synthesis and contribute to the field of enantioselective catalysis inspired us to pursue this course of study.

1.3 Divergent Asymmetric Access to Alkaloid Scaffolds

1.3.1 Introduction to Asymmetric α -Amination Reactions

The ubiquity of α -amino acids in subfields of both chemical biology and organic synthesis has imparted immense value to methodologies which can both efficiently utilize these build blocks, as well as provide access to new or unnatural amino acids.^{35–39} Furthermore, the self-evident prevalence of chiral α -amino acid motifs in bioactive natural products incentivizes the development of a multitude of techniques to achieve their synthesis. The importance of new amination technologies is further highlighted by the sheer number of reviews focused on asymmetric amination and aza-quaternary center (α -tertiary amines) formation.^{34–36,39–57} Due to the enormity of the α -amination field generally, this discussion will be limited three to areas of catalytic asymmetric reactions which predominate the literature. These three interrelated areas are:

1) organocatalytic reactions; 2) hydrogen bond donor catalysis; and 3) Lewis acid catalyzed transformations.

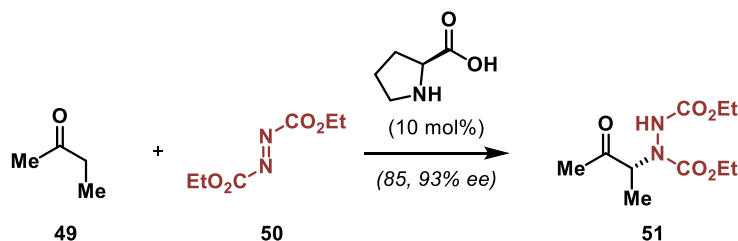
1.3.2 *Organocatalyzed Nitrosoaldol Reactions*

While the roots of organocatalysis run old and deep, with its popularization at the dawn of the 2nd millennium there emerged a contemporary boom in the prevalence of enantioselective carbonyl α -functionalization reactions.^{49,50,57,59–62} The first examples to affect an α -amination of aldehydes and ketones were nearly simultaneous reports by Benjamin List and Karl Jørgensen, respectively in 2002 (Scheme 1.8).^{63,64} This reaction used simple L-proline as the catalyst to transiently form a chiral enamine, which subsequently attacks an azodicarboxylate electrophile to afford the α -aminated product, typically in excellent (>90%) enantiomeric excess. The use of azodicarboxylate electrophiles is especially convenient due to their high electrophilicity and commercial availability and this convenience has likely influenced both their traditional and modern application. However, their synthetic utility is limited by the necessity to reduce the α -hydrazino moiety to liberate the desired free amine.^{40,47,48,56,65} As a result, alternative electrophilic nitrogen sources were and are highly desirable.³⁹

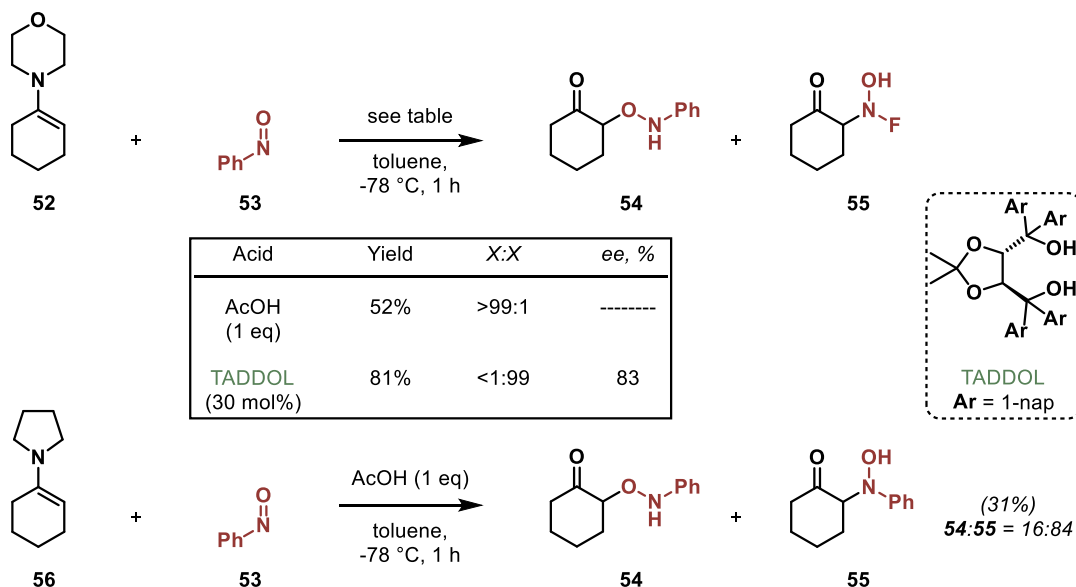
While it may initially appear feasible to simply swap the electrophile for one more synthetically direct such as nitrosobenzene, where the aryl group could serve as a point of diversity, affording arylamines upon reduction, but this substitution is in fact more nuanced.^{66,67} When considering nitrosoaldol reactivity, subtle steric interactions can impart significant impacts on the selectivity. α -Branched aldehydes exhibit different selectivity than their unbranched counterparts. The same is true for cyclic and acyclic ketones, with most typically preferring *O*-selective nitroso aldol products.^{68,69} Similarly, Yamamoto has found that the successful translation of enamine reactivity to α -amination in a stoichiometric capacity requires careful choice of the enamine

intermediate alongside the addition of a Brønsted acid to activate the nitrosoarene for attack at nitrogen (Scheme 1.8).

a) Jørgenson, 2002



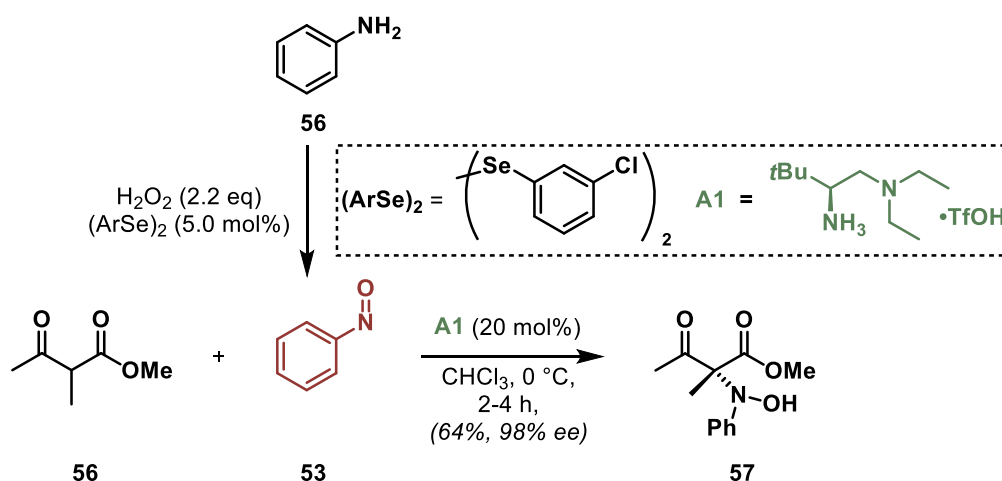
b) Yamamoto, 2005



Scheme 1.8 Organocatalytic α -amination precedent. a) O-selective nitrosoaldol demonstrated by Lewis. b) Brønsted acid induced N-selective nitrosoaldol

Chiral primary amine catalyzed nitrosoaldol reactions have since been made more synthetically viable in large part due to the work of Prof. Sanzhang Luo. Perhaps the most significant practical limitation of nitrosoaldol chemistry is the inherent instability of the intermediate nitroso species, particularly if they must be independently synthesized. To circumvent this issue the Luo group utilized tandem oxidation and chiral primary amine catalysis to effect N-selective nitrosoaldol reaction.^{70,71} Protected hydroxylamines can be oxidized *in situ* under aerobic copper conditions, whereas electron-deficient anilines must first be oxidized separately by a selenium catalyst with stoichiometric hydrogen peroxide to freshly prepare a solution of the

desired nitrosoarene (Scheme 1.9). While this certainly represents a notable improvement in ease of nitrosoarene synthesis, this method is limited largely to acyclic β -ketoesters, often with low yields, appreciable amounts of *O*-selective product, and still necessitates subsequent reduction of the hydroxylamine.



Scheme 1.9 Sanzhang Luo's joint chiral primary amine and selenium catalysed nitrosoaldol system

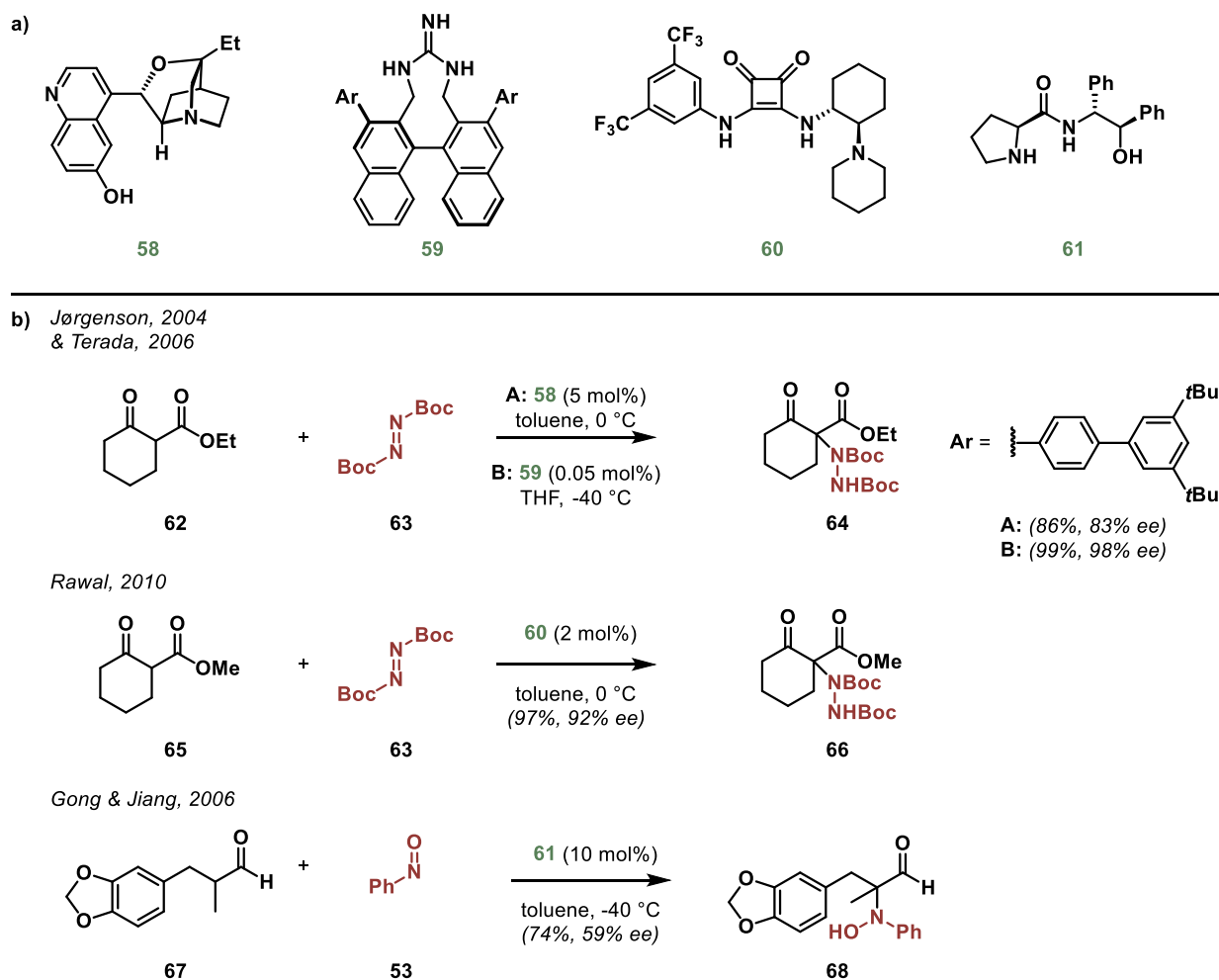
Despite Luo's advancements in application, the apparent discrepancy in nitrosoarene reactivity and activation observed by Yamamoto enraptured the chemistry community. The initially proposed origin of selectivity was the existence of minute energy differences in the various hydrogen bond clusters formed, where lower pK_a Brønsted acids prefer to protonate the more basic nitrogen, ultimately enhancing *O*-selectivity. Kinetic studies by Donna Blackmond also indicated the importance of hydrogen bonding in the reactivity of these intermediates, though a more in-depth mechanistic discussion will commence later in this chapter.^{66,67} Thus the pursuit of effective hydrogen bond catalysts for a more general amination reaction had begun.

1.3.3 *Hydrogen-Bond Catalysis & Nitrosoaldol Reactions*

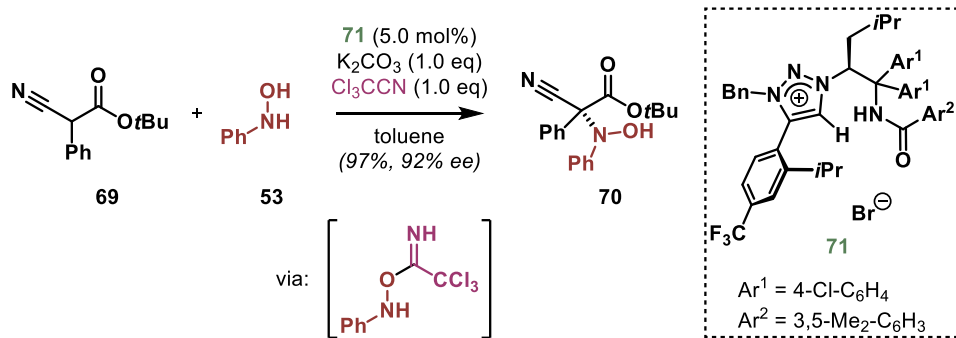
The union of hydrogen-bond catalysis proved fruitful in fostering a number of catalytic systems capable of enantioselective α -amination reactivity (Scheme 1.10).^{46,72–74} Shortly after his initial publication, Jørgensen disclosed a method which employed β -isocupreidine (**58**) as a catalyst to achieve both high yields and enantioselectivities in this reaction.⁷² The operative catalytic mechanism is not fully elucidated, however it is also possible the alkaloid acts as a chiral ammonium counterion.⁷⁵ Prof. Masahiro Terada then reported the application of a chiral binaphthyl-guanidine hydrogen bond catalyst to vastly improved efficacy, capable of achieving α -hydrazination with just 0.05 mol% catalyst at cryogenic temperatures, in excellent yields and enantioselectivities.⁷³ The advent of Rawal's squaramide derived catalysts debuted a new class of effective and comparatively easy to synthesize chiral hydrogen bond catalysts. These chiral squaramides quickly found purchase in the area of α -amination, affording (**64**) in an excellent 92% enantiomeric excess.^{76,77} Each of these examples represent significant advancements, yet all are limited to azodicarboxylate moieties as the electrophilic nitrogen source (Scheme 1.10).

In this vein the first report of an asymmetric *N*-selective nitrosoaldol reaction of an aldehyde utilized a chiral prolinamide. In contrast, the majority of reports of attempted nitrosoaldol reactions using classic hydrogen-bond catalysts (ex. thioureas) result in *O*-selective nitrosoaldol (Scheme 1.10).^{78,79} Again, the expansion of these technologies to more diversely substituted nitrogen electrophiles would provide greater synthetic utility. In this capacity, the advancement with the greatest synthetic potential is Takashi Ooi's recently reported hydroxylamine activation method for α -amination combined with a niche triazolium hydrogen bond catalyst. This catalytic system avoids promiscuous nitroso intermediates altogether, instead opting to activate the *N*—*O*

σ -bond, with essentially a trichloroacetimidate now acting as the nucleofuge (Scheme 1.11). The substrate scope of this reaction is perhaps the most general of the reaction conditions examined thus far, allowing for successful pairing of a breadth of nucleophiles from 2-oxindoles to substituted α -cyanoesters, with a range of both alkyl- and arylhydroxylamines in an enantioselective fashion (Scheme 1.11). This method can also be applied in an intramolecular sense to form spirocyclic heterocycles. The major limitation of this methodology is the lengthy synthesis of the catalyst, which requires at least 6 steps.^{80,81}



Scheme 1.10 a) Select hydrogen bond catalysts. b) Select notable examples of asymmetric *H*-bond catalyzed α -amination



Scheme 1.11 Takashi Ooi's trichloroacetimidate activation of hydroxylamines

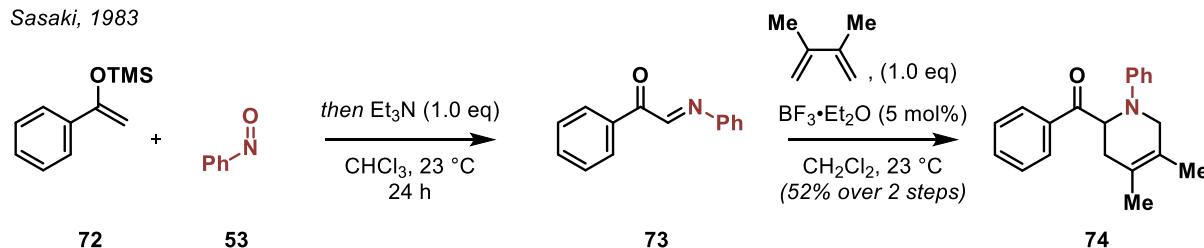
1.3.4 Lewis-Acid Catalyzed Nitrosoaldol Reactions

Fortunately for the synthetic community, the promise of more easily adopted α -amination methods found some respite in Lewis acid catalysis, though its metamorphosis from inception to more practical and greener alternatives is both gradual and ongoing. While some asymmetric α -hydrazinations were reported previously using copper catalysts in the presence of chiral bisoxazoline (BOX) ligands, the first instances of effective nitrosoaldol from common explicit carbonyl nucleophiles was reported by Sasaki in 1983, in which silyl enol ethers demonstrated mild reactivity with nitrosobenzene to generate α -iminoketones upon treatment with triethylamine as a base (Scheme 1.12).^{82–84}

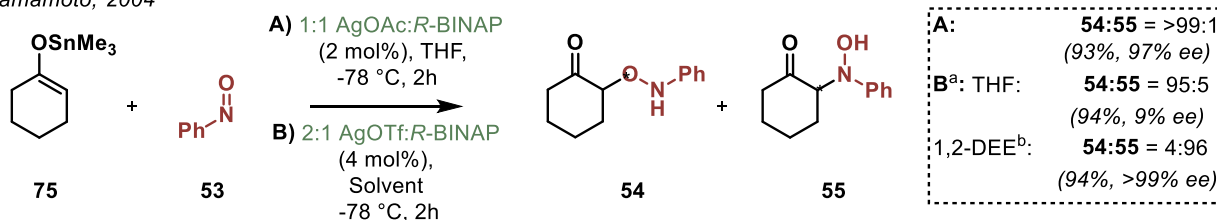
Nearly two decades down the road, Yamamoto capitalized on the enhanced power of tin enolates to accomplish an effectual nitrosoaldol reaction, likely much to the chagrin of the modern “green” chemist.^{85,86} These tin enolates displayed a marked increase in reactivity with nitrosobenzene over their silyl analogs, and ultimately allowed for the addition of a BINAP derived chiral Ag(I) Lewis acid complex to induce asymmetry. Intriguingly, the nitrosoarene’s ambident reactivity can be profoundly influenced *via* either the metal to ligand ratio chosen, or the solvent (Scheme 1.12). While the impact of Ag-complex stoichiometry is well defined (1:1 ligand:Ag(I) affords *O*-selective products, and 2:1 affords *N*-selection), the rationale remains somewhat elusive,

and the solvent effects appear to defy first-principles based inductive reasoning altogether. For example, both DMF and Et₂O exhibit *N*-selectivity, while THF favors formation of the *O*-adduct (Scheme 1.12).^{85,86} The rather specific and arguably peculiar reactive partners involved in this nascent technology resulted in its sluggish adoption amongst synthetic chemists, with no reports of its application in total synthesis, to the best of our knowledge, as of today (April 24, 2024).

Sasaki, 1983



Yamamoto, 2004



Scheme 1.12 Seminal precedents from Sasaki & Yamamoto for nitrosoaldol reactivity. a) percent ee refers to *N*-adduct. b) 1,2-DEE = 1,2-Diethoxyethane

Similarly to the upgrade in utility the chiral primary amine catalyzed nitrosoaldol reaction acquired, Lewis acid catalyzed nitrosoaldols experienced an analogous practical enhancement with the incorporation of *in-situ* oxidation to form the nitrosoarene intermediates. One of the first major examples of this chemistry to perform an *N*-selective nitrosoaldol was that of Prof. Javier Read de Alaniz, who used a Cu(I)/Cu(II) system to effect this transformation with air as the terminal oxidant.⁸⁷ Note the use of alcoholic solvent in this reaction, as it is essential to achieve the desired *N*/*O*- selectivity (Scheme 1.13). This work was later expanded to a number of reactions with *C*-nitroso intermediates, including a diastereoselective nitroso-ene reaction of silylenol ethers using a camphorsultam derived hydroxamic acid (EleNOR).^{87–91}

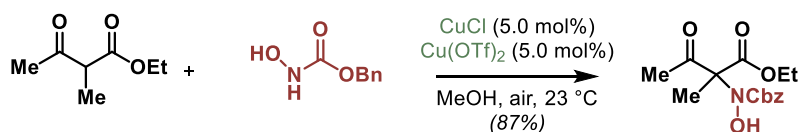
The first asymmetric Lewis acid catalyzed nitrosoaldol reaction with *in situ* oxidation used MnO₂ as a relatively mild and selective oxidant, with asymmetric induction arising due to chelation of the magnesium Lewis with *N,N'*-dioxide ligand L1, and the substrate (scheme 1.13).⁹² The researchers suggest the deliberate use of magnesium is critical here due to a substantive difference in the oxo- vs aza-philicity of the Lewis acid, but in the context of all the other findings, the observed selectivity likely results from a combination of both solvent and steric factors. Alternatively, the majority of the substrate scope in this context contains additional π -systems, which could theoretically facilitate preorganization of the *N*-selective transition state via π -stacking interactions and bias the reaction outcome. Nevertheless, in his first independent publication, Baidya reported one of the first instances of *in situ* N—O bond cleavage of in an α -amination reaction using bulky silyl enol ethers such as **84**. Due to the reluctance of the more traditional TMS- or TBS-enol ethers to perform a similar bond cleavage, it is hypothesized that a 6-membered cyclic rearrangement delivers the product, albeit racemically, upon aqueous workup without further need for reduction (Scheme 1.13).⁹³ The scope of this reaction was later broadened to include electron deficient anilines as the electrophilic nitrogen source using Oxone™ as the oxidant.⁹⁴

Contemporary with this report was Srivastava's application of an Fe(II)/Fe(III) dual-purpose catalytic system with Fe(II) as the oxidant, and Fe(III) as the Lewis acid in the first instance of concomitant nitrosoaldol reactivity and N—O bond cleavage in α -amination chemistry (Scheme 1.13).⁹⁵ Intriguingly, the lack of a terminal oxidant indicates that Fe(III) may be in-part responsible for the reduction, though potential mechanisms will be examined in greater detail in section 1.3.5. The modest, reported scope consists largely of acyclic β -ketoesters, though is demonstrably robust as it operated with great efficacy in the route towards strychnochromine

(1) above (Scheme 1.3). The same paper indicates the reaction proceeds smoothly, though at a diminished pace, with copper catalysts, and this result was the seed which blossomed into a study published concurrently with our own research efforts detailed below.⁹⁶ The invocation of a Cu(II) catalyst naturally allowed for the addition of a BOX ligand, betwixt which the synergy has been well documented.^{97–100} However, this condition set is lamentably finicky, with a remarkably narrow substrate scope exhibiting an expansive range of enantiomeric excess (from 10-93% *ee*) across minute structural changes (Scheme 1.13).

The rapid progress in α -amination across myriad subdisciplines of organic chemistry was accompanied by parallel growth in the number of mechanistic conjectures. The significant impact of miniscule changes on reaction outcomes suggests an intricate and precariously balanced reaction landscape, obfuscating the root causes. This is especially true when one considers the instability of the starting hydroxylamines, as well as the propensity for dimerization, disproportionation, and tautomerization side reactions of the various nitrosoarene intermediates.¹⁰¹ In an attempt to amalgamate this assortment of results into a single coherent theory, former American Chemical Society President Prof. Donna Nelson invokes hard-soft acid base theory.¹⁰² Seminal theoretical works posit that protonation of nitrosoarenes is more energetically favored at the oxygen atom, as opposed to the nitrogen as argued by Yamamoto.^{102–104}

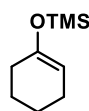
Read de Alaniz, 2012, 2015



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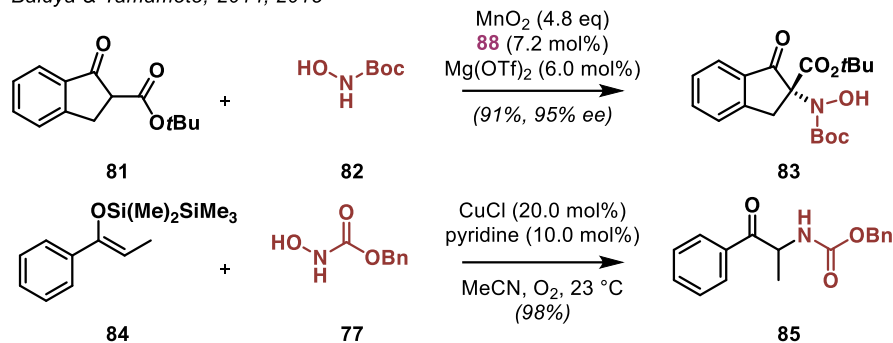


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EleNOR

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Baidya & Yamamoto, 2014, 2015



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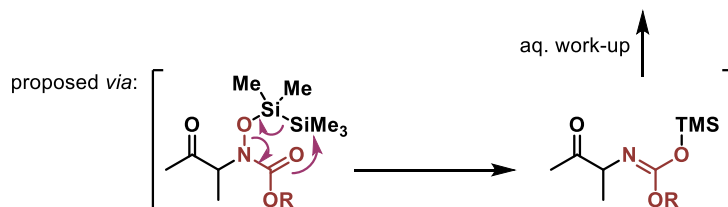
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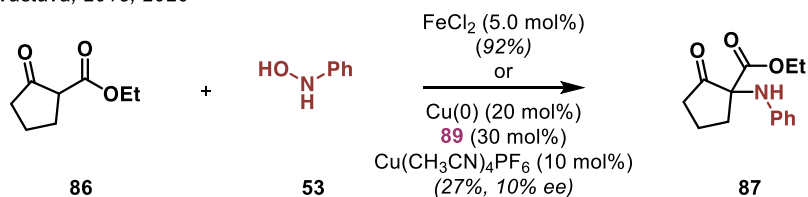
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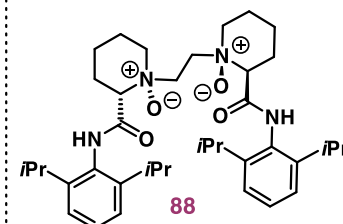
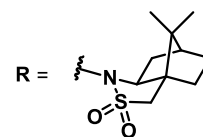
Srivastava, 2015, 2020



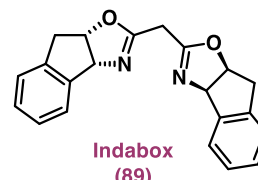
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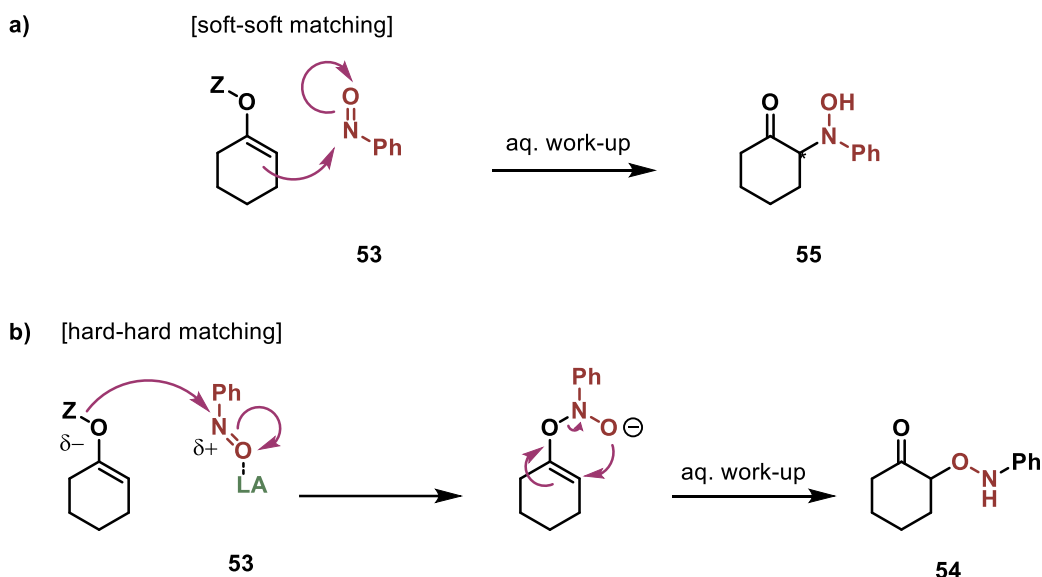


Indabox
(89)

Scheme 1.13 Key examples of Lewis acid catalyzed reactions with *in situ* oxidation

Furthermore, Nelson claims that despite nitrosoarenes' ambidentate ligand behavior with Lewis acids, the net effect of their coordination is calculated to result in an increase of the partial positive character on the nitrogen. Since both modes of activation serve to increase the electrophilicity at nitrogen, how is the *O*-adduct explained? This observation can be rationalized if the strength of activation is correlated to hardness/softness of the nitrogen electrophile, which

then reacts preferentially with the electronically matched portion of the nucleophile. This paradigm necessitates the formation of an O—N bond in the case of the hard oxygen anion of the enolate serving as the nucleophile, upon which a [2,3]-sigmatropic rearrangement will then give α -aminooxylation product **54** (Scheme 1.14). This mechanism however does not preclude the demonstrably important role of the steric interactions. As the steric bulk of either the nucleophile and/or the solvent increases, so does the likelihood of ultimate O-adduct formation due to the decreased accessibility of the N-electrophilic center with the softer, more encumbered C-nucleophile.¹⁰²



Scheme 1.14 Potential mechanisms of nitrosoaldol reactions **a)** Prosoposed *N*-selective nitrosoaldol mechanism. **b)** Proposed *O*-selective mechanism incorporating a [2,3]-sigmatropic rearrangement.

Despite the multitudinous reactivities available to nitrosoarenes and related species, a plethora of interesting and creative reactions have been developed in this space which do not fit cleanly into the categorizations set forth here. Alternatively, one can view the unique capabilities and promiscuity of these reactive intermediates as testimony to their extraordinary synthetic potential once tamed. Some areas of academic interest beyond the bounds of this discussion span

from frustrated Lewis pairs, to chiral phosphoric acid catalysis, and the implementation of new electrophilic amination reagents.^{78,91,105–116}

Because of this complexity and the disproportionate impact of seemingly subtle steric and electronic factors, nitroso chemistry could greatly benefit from the application of artificial intelligence/machine learning technology to efficiently predict reaction outcome. Indeed, the existing literature could be a viable data pool as both *O*- and *N*- selective reactions are widely reported, and the successful conditions for one are inherently a negative result in the case of the other, analogous to the 5-*exo* vs. 6-*endo* cyclization analysis recently published.¹¹⁷ Until such technology exists, I remain optimistic that the illuminating abilities of computation will continue deconvoluting the mysteries of nitroso-reactivity to empower the rationale design of new nitroso-centric chemistries. For now, we must make use of this prior knowledge in an endeavor to accomplish an asymmetric amination *en route* to strychnochromine (**1**) (Scheme 1.2).

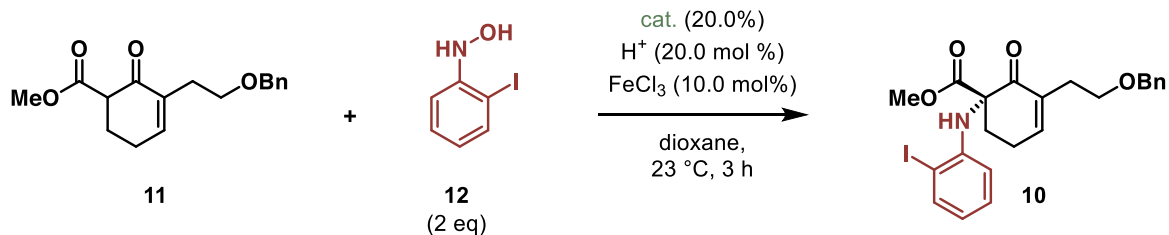
1.3.5 Initial Hit Discovery and Optimization

The observant scholar will notice that the University of Chicago was a hotbed of not only α -amination chemistry, but chiral hydrogen bond and Lewis acid catalysis more. In addition to Profs. Yamamoto and Rawal, our own group has found success in this domain harnessing the power of nitrones.^{118,119} The confluence of the methodological challenges, literature gaps, UChicago scholarly tradition, and goal of minimizing asymmetric step-count towards strychnochromine (**1**) inspired us to pursue this research endeavor (Schemes 1.2 & 1.3).

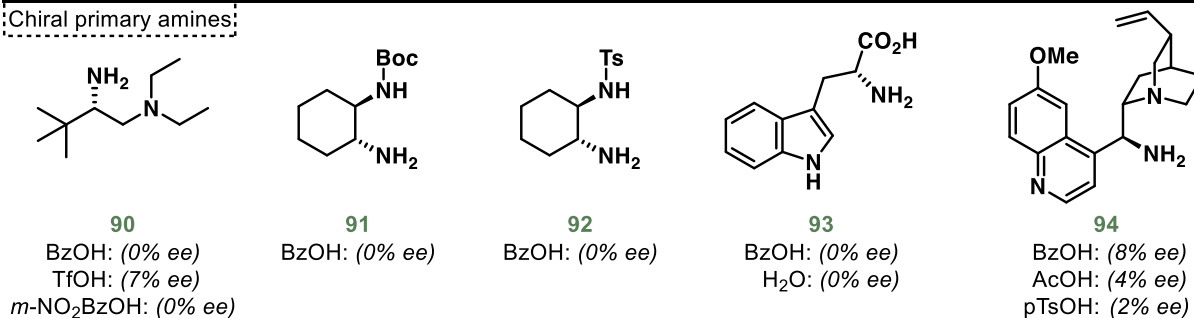
We first began by attempting to combine the racemically efficacious Fe(III) catalytic system with organocatalysis by simple addition of a chiral primary amine and an acid, hoping to form a chiral enamine intermediate, and ultimately yield **10** enantioselectively. After screening a number of catalysts which were successful in our nitrone chemistry, we only observed minorly

enantioenriched product (Table 1.1).^{118–120} We did observe some dependence upon the pK_a of the acid used, which is consistent with enamine catalysis due to its effect on the condensation/hydrolysis equilibrium; however, we tentatively concluded the background reaction proceeds more rapidly than condensation and subsequent nucleophilic attack of the enamine.

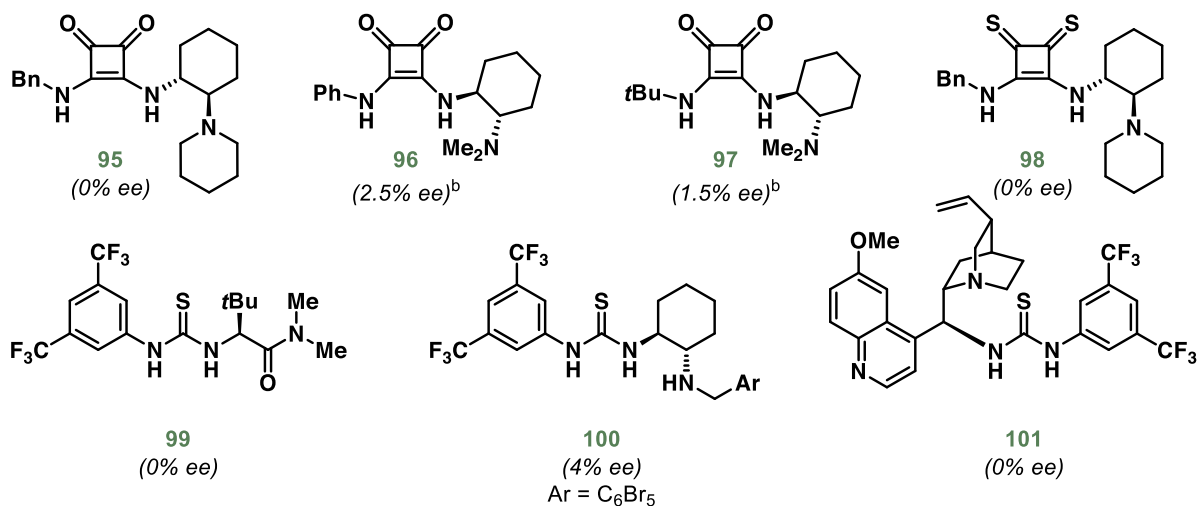
Optimistic that catalytic activation of the intermediate nitrosobenzene in a chiral environment could enable our desired transformation, we then screened a number of hydrogen bond donor catalysts, again with little overall success. Notably, while we never isolated any of the *O*-selective nitrosoaldol product as was previously discussed, these reactions were overall relatively low-yielding (<15%) and quite messy. However, given the presence of a barely scalemic mixture across both modes of activation, we hypothesized that a bifunctional catalyst may provide a synergistic effect, but this endeavor was also ultimately fruitless (Table 1.1).



Chiral primary amines:



Hydrogen-bond catalysts^a



Bifunctional catalysts

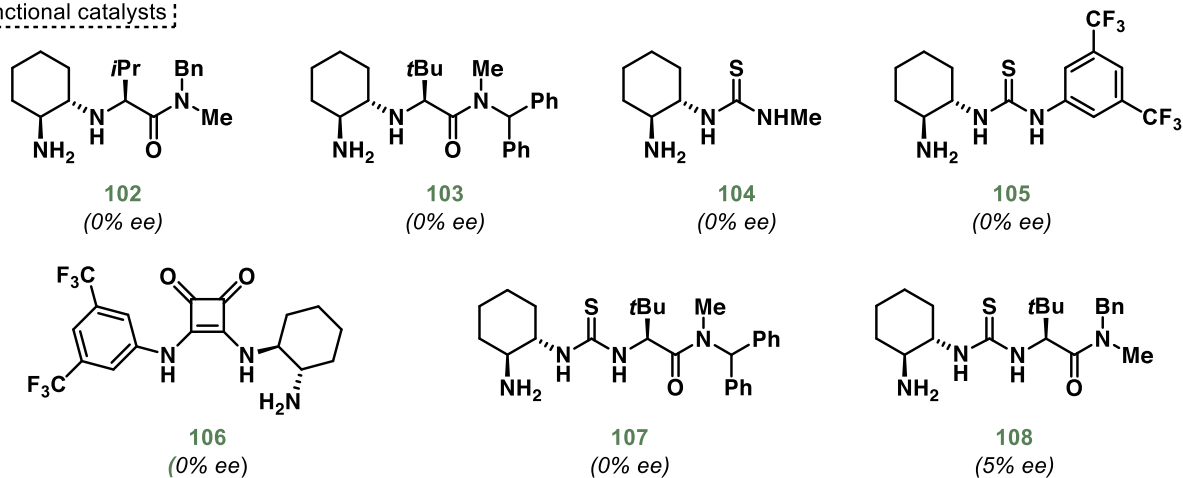
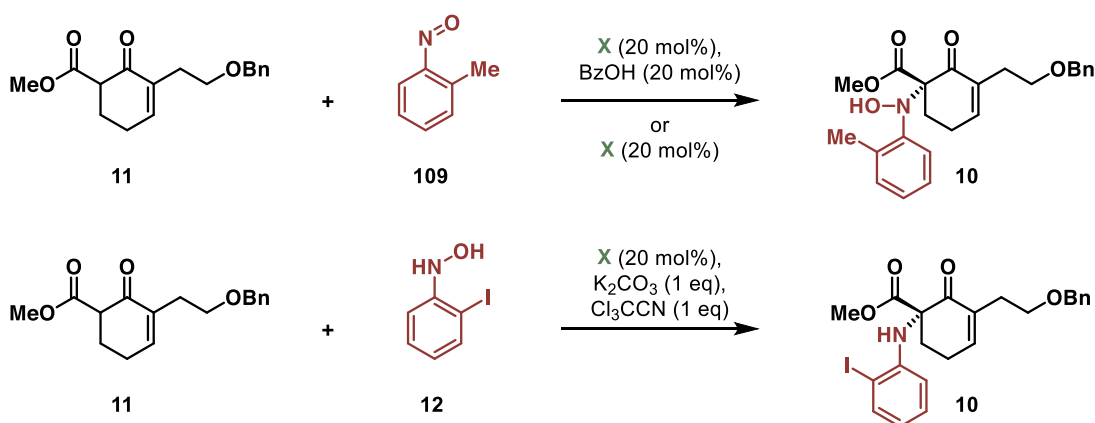


Table 1.1 Initial screens under iron catalyzed conditions. ^a H^+ source omitted. ^b reaction run at 50 °C

Given the resoundingly poor enantioselectivities, we felt assured in our assumption that the background reaction catalyzed by Fe(II/III) was simply too effective. We hypothesized that a slower reaction such as a simple chiral enamine nucleophilic attack alone would be sufficient, even if a separate reduction step must be added to cleave the N—O bond. To test this conjecture, we used readily available *o*-nitrosotoluene as an analog to the *o*-iodonitrosobenzene we were previously generating *in situ* in combination with the Luo diamine, however no reaction was observed except for nitrosoarene dimerization and decomposition (Scheme 1.15). Hoping to avoid these non-productive side reactions we then took inspiration from Takashi Ooi and first activated the hydroxylamine with trichloroacetonitrile to form the corresponding acetimidate, which could potentially be used in tandem with a chiral enamine, but this too was unsuccessful (Scheme 1.15).



Scheme 1.15 Failed attempts to modified literature conditions to the strychnochromine system.

Revisiting the literature, Srivastava noted that copper also served as a competent catalyst in the α -amination chemistry.⁹⁵ We then began an abbreviated screen with copper catalysts and to our delight we immediately observed improved enantioinduction in the course of this reaction (Table 1.2). However, because across the board our highest *ee* values were obtained using amines bearing a pendant 3° amine moiety, we believed the modest improvement in enantioselectivity to be more consistent with ligation of the 3° amine. Intriguingly, addition of benzoic acid to the

reaction involving the quinine-derived amine **94** resulted in increased *ee*. While we have no evidence upon which to discredit a chiral enamine mechanism, we propose the following alternative rationalization: the addition of acid slows the reduction of the hydroxylamine, decreasing the overall concentration of the nitrosoarene intermediate and slowing the relative rate of the background reaction.¹²¹

Having realized our source of chirality is likely a classical metal-ligand based interaction, an idea corroborated by the concomitant publication of Srivastava's copper-catalyzed amination, we were prompted to revisit a more classical Cu-Box type system. Cu-Box systems have a long history of success in α -amination, and fortunately we observed 32% *ee* in our first trial (Table 1.2).^{83,96,100,122} As previously mentioned, Srivastava's publication features an exceptionally limited scope, and minimal data, lacking any supplementary information entirely upon which to guide our asymmetric synthesis of **10**.^{1,96} Recognizing that the multiple binding modes of the triflate counterion could potentially impact the selectivity, we then screened a number of copper catalysts with varied counterions and oxidation states (Table 1.3). This screen elucidated CuBr₂ as the optimal balance between high enantioselectivity and reaction yield.

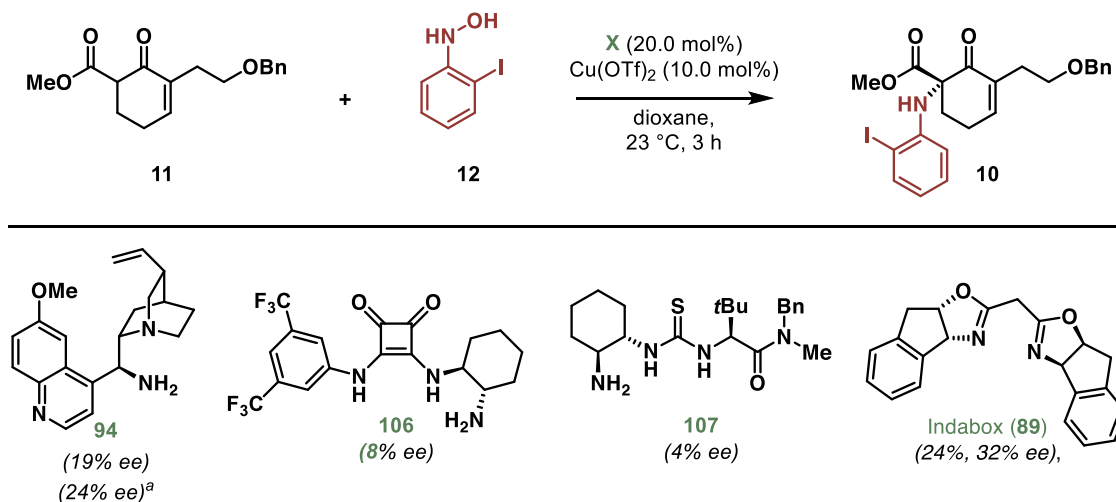
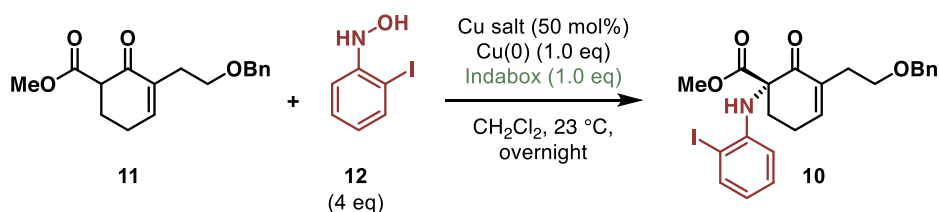


Table 1.2 Promising results from initial copper catalyzed screen. ^a up to this % *ee* obtained with 20.0 mol% BzOH additive.

¹ The published corrigendum to this paper contains both an apology and an empty SI file which simply states "no data was used for the research described in the article."

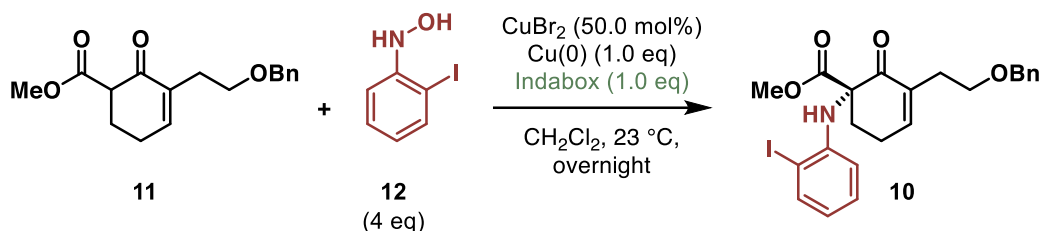


Entry	Catalyst	% Yield	% ee
1	Cu(OTf) ₂	56	30
2	CuBr ₂	63	64
3	CuCl ₂	40	N.D.
4	Cu(BF ₄) ₂	36	N.D.
5	Cu(AcAc) ₂	25	N.D.
6	CuCN	43	N.D.
7	CuCl	44	66
8	CuBr	18	68
9	CuI	28	71
10	Cu(MeCN) ₄ PF ₆	37	39

Table 1.3 Copper source screen

Unfortunately, we experienced some issues with the reproducibility of the reaction, which prompted us to re-examine our condition set. Slow addition of the hydroxylamine was important for both the Fe(II/III) and Cu(I/II) catalyzed systems. Intriguingly, air is evidently the best atmosphere for this reaction as the entry set up under completely anaerobic conditions (glovebox) resulted in no conversion at all. Conversely, reactions under O₂ atmosphere featured both a diminished yield and an increase in the observed azoxybenzene byproducts. Presumably, the higher concentration of oxygen increases the rate of hydroxylamine oxidation, subsequently increasing the concentration of the intermediate nitrosoarene, and therefore the rates of the dimerization and decomposition pathways (Table 1.4). The omission of elemental copper yielded only trace quantities of **X**, and anecdotally we observed that its presence did make the reaction more reliable, presumably assisting in keeping the copper on cycle. The increase in yield we observed when running the reaction under aerobic but anhydrous conditions seemed counterintuitive, as the reaction is proposed to generate H₂O, though the redox chemistry of

hydroxylamines is incredibly complex and difficult to study, particularly with various metal catalysts (Figure 1.2).^{123–127}



Entry	Catalyst	% Yield	% ee
1	anaerobic	-----	-----
2	No Cu(0)	trace	-----
3	anhydrous	75	67
4	open to air	26	63
5	O ₂ atmosphere	13	65
6	2-Me-but-2-ene ^a	82	75 ^b

Table 1.4 Copper condition screen. ^a2.0 eq ^breaction performed with **X** as ligand

This reaction is proposed to proceed through aerobic oxidation of the hydroxylamine to the nitrosoarene species, which serves as an electrophile further activated by the Lewis acidic metal catalyst in a nitroso-aldol reaction (Figure 1.2). The resultant alkylarylhydroxylamine can move downstream to **10** in a number of ways, including disproportionation with another equivalent of hydroxylamine, or direct reduction by the metal.^{52,128–136} Inspired by some metal-oxo work done by University of Chicago Prof. John Anderson's group, we wanted to test for the presence of hydrogen peroxide in the reaction system.¹³⁷ The existence of Cu-oxo systems is debated, and typically requires low-coordinate geometry; but given the potential for various fleeting and redox active Cu-bound species we decided to add 2-Methyl-2-butene as an oxidant scavenger. While not a selective trap for H₂O₂, this was reliably successful in improving the yield of the reaction (Table 1.4).¹³⁸ Unfortunately, this additive also decreased the enantioselectivity, and was ultimately left out of the optimized conditions. With all of this data we decided to move forward with CuBr₂ as

the optimal catalyst, and additionally found we were able to decrease the loading to 20.0 mol%, and 50.0 mol% of the Cu(II) salt and Cu(0) respectively without any deleterious effects on the yield or enantioselectivity. Finally, it is worth noting that when scaling this reaction up, high ligand purity and vigorous stirring is essential to maintaining adequate yields.

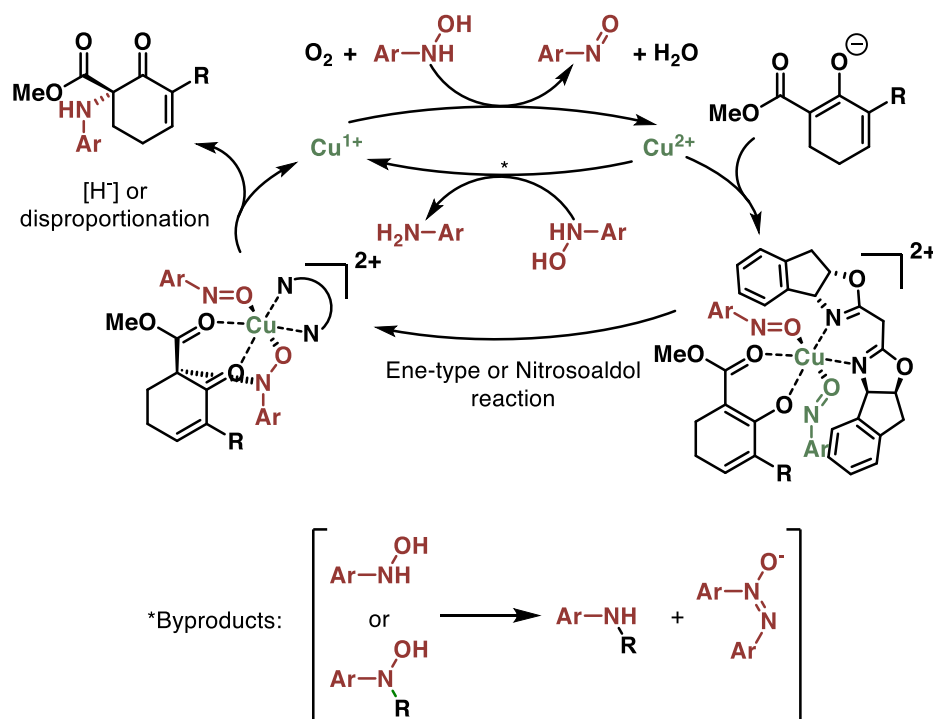


Figure 1.2 Proposed mechanism of the asymmetric copper catalyzed nitrosoaldol reaction

While these improvements are notable, in order to classify our total synthesis as asymmetric we still needed to improve the enantioselectivity of the reaction. To do this, we then undertook the task of ligand screening (Table 1.5). From the parent Indabox ligand we can easily make a number of derivatives by deprotonating with either NaH, or *n*BuLi. If NaH is used, the quality of the reagent is significant, and the presence of noticeable quantities of NaOH will decrease the yield.^{139,140} The first analog we tested was version **110**, which gave an immediate boost up to 65% *ee*. As we increased the bulk of the alkyl substituents we observed consistent yields, but the enantioselectivity seemed to peak at 78% *ee*. The addition of a dibenzyl moiety

(**117**) actually decreased the enantioselectivity. This can potentially be rationalized by the additional π -systems causing slippage of the nitrosoarene ligand due to competitive π -stacking. Hoping to improve upon the *n*-pentyl ligand, we hypothesized its selectivity was attributable to the folding of the alkyl chain, which impacts the bite angle of the ligand through steric repulsion.^{99,100} We then tested this by synthesizing branched ligands to mixed results. The cycloalkane systems proved most efficacious by far, but we are currently uncertain as to the origin of the different enantioinduction between methylcyclobutyl ligand **120** and the isobutyl substituted **118**. Finally, a screen of classic box ligands, analogous PyBOX ligands, and semicorrin ligands showed modest selectivity for the opposite enantiomer, no selectivity, and poor selectivity respectively (Table 1.5).

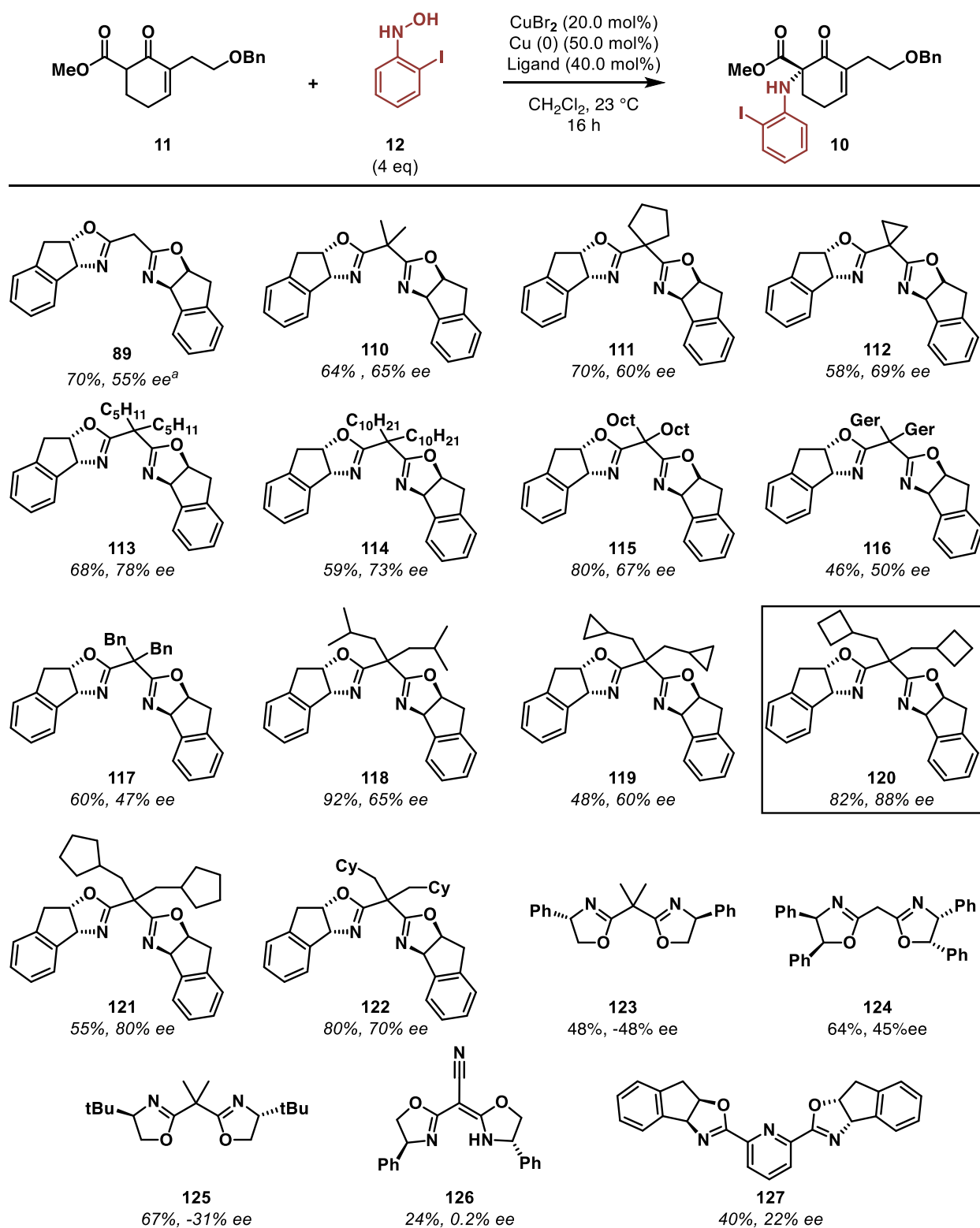


Table 1.5 Ligand Screen. ^aAverage across >5 trials

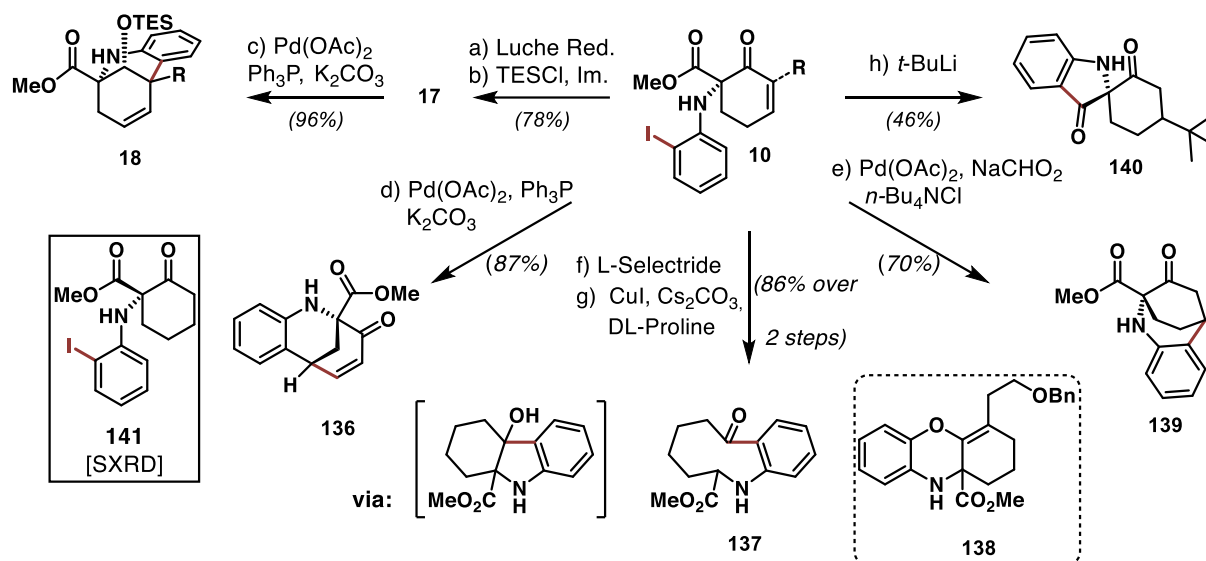
With ligand **120** providing our desired substrate in 82% yield and 88% *ee*, we then sought to briefly explore the substrate scope. A small number of substrates were subjected to the reaction conditions, though accurate yield determination was unsuccessful due to generally poor conversion, and the persistent contamination of hydroxylamine byproducts (Figure 1.6).

inally, having successfully developed α -amination conditions adequate to enable a formal asymmetric synthesis of strychnochromine, then needed to determine the absolute stereochemistry. To our disappointment, Mosher's ester analysis was inconclusive, so we turned our sights towards crystallography instead. We decided to push the asymmetric material through the Heck reaction, reduction, protection sequence, towards the analogous epoxide of **34**, which was readily crystallizable as the racemic mixture, however the enantioenriched scalemic mixture failed to crystallize.^{141,142} While this was surprising, we were thankfully able to prove that the alternate enantiomer of our ligand produces an equal but opposite enantiomeric excess (85% *ee*) providing access to enantiomers of **1**. Undeterred by our inability to identify the absolute stereochemistry, we then sought to realize the potential of the various functional groups of the scaffold points of diversification.

1.3.6 Divergent Scaffold Synthesis

We first subjected enone **10** to Heck reaction conditions, expecting to form the bicyclic system with opposite regioselectivity to that of the reduced case, but we instead observed serendipitous γ -functionalization (Figure 1.7). This is likely due to the strain induced by the would-be β -hydrogen eliminated product, so in order to access this product preferentially we subjected the unsubstituted enone instead to reductive Heck conditions, with sodium formate as the reductant, which smoothly afforded **139** in 70% yield.

Having successfully engaged the olefin in a chemoselective fashion, we then hoped to selectively engage the two carbonyls. Direct treatment of the aryl iodide with *t*BuLi affects a lithium-iodide exchange, which preferentially cyclizes into the proximal ester, affording the spirocyclic 3-oxindole structure evident in some biological dyes (Figure 1.7).^{143,144} Finally, we hoped to engage the ketone selectively under Ullman coupling conditions to afford the interesting benzomorpholine scaffold of **138**.¹⁴⁵ This was unsuccessful under a small number of conditions as the enone, however following conjugate reduction, we subjected the resulting β -ketoester **X** to Ullman coupling conditions. Instead of our desired **138**, we believe to have observed a Cu-initiated Dowd-Beckwith rearrangement to give the macrocyclic indole **137** as a single diastereomer.¹⁴⁶ Importantly, the intermediate **141** was a crystalline solid, and the both necessary and convenient iodide aided in determination of the absolute stereochemistry. With this information, we were able to determine that we did indeed need the enantiomeric form of **120**. We hope that the conjunction of this diverse synthetic utility and well-informed stereochemical outcome will allow facile asymmetric access to complex alkaloid scaffolds for further synthetic studies, or biological evaluation.



Scheme 1.16 Diverse scaffold synthesis from common motif. a) CeCl₃·7H₂O (2.0 eq), NaBH₄ (8.0 eq), CH₂Cl₂:MeOH = 1:10 (0.1 M), 0 °C, 78%; b) TESCl (5.0 eq), Imidazole (5.0 eq), DMAP (25.0 mol%), DMF (0.1 M) 0 °C to 23 °C, 16 h, quant.; c) Pd(OAc)₂ (40.0 mol%), Ph₃P (2.0 eq), K₂CO₃ (2.0 eq), toluene (0.1 M), 90 °C, 3 h, 96%; d) Pd(OAc)₂ (40.0 mol%), Ph₃P (2.0 eq), K₂CO₃ (2.0 eq), DMF (0.1M), 110 °C, 1.5 h 87%; e) Pd(OAc)₂, (40.0 mol%), *n*-Bu₄NCl (2.0 eq), NaCHO₂ (2.0 eq), DMF (0.1 M), 80 °C, 1.5 h 70%. f) L-Selectride (1.25 eq), THF, -78 °C, 2 h; g) CuI (50.0 mol%), CsCO₃ (1.0 eq), DL-proline (50.0 mol%), DMF (0.1 M), 86%; h) *t*BuLi (2.2eq), Et₂O (0.1 M), -45 °C, 2 h (46%).

1.3.7 Conclusion

Throughout the course of these studies, we were able to further develop a Cu-catalyzed asymmetric α -amination methodology which directly delivers arylamines to β -ketoenones in high enantioselectivities and good yields. We initially aspired to use a chiral enamine functionality or a hydrogen bond catalyst, however both of these strategies proved ineffective. We ultimately found success using a bifunctional copper catalyst system to both oxidize the arylhydroxylamine to the nitrosoarene *in situ*, and act as a Lewis acid in the presence of a chiral ligand to afford the α -amination product enantioselectively. The major limitations of this work include the necessity of excess hydroxylamine, and high copper loadings. The hydroxylamines themselves can suffer from thermal instability, with this symptom worsening with increasing electron richness of the aromatic ring. Additionally, to perform the reaction on large scale, vigorous stirring and scrupulously pure ligand is essential (recrystallization is necessary, FCC is insufficient despite pure NMRs). Mechanistically, we hope that our experiment adding a potential scavenger is

informative to any scholars looking to investigate this further, as a better elucidated mechanism of the hydroxylamine-metal interactions may allow for rational optimization/reaction design, and potentially the expansion of the substrate scope. Despite these limitations, we find the scaffold access enabled by this framework to be of particular interest, as the substrates are easily synthesized yet densely functionalized, essentially providing a vast synthetic playground.

1.4 Outlook & Conclusion

Overall, we successfully completed the first asymmetric formal synthesis of strychnochromine (**1**) in equivalent step count and yield to the racemic route (25 steps, 0.74% overall yield, >82% avg. yield). The copper catalyzed asymmetric α -amination reaction provides ready access to 5 unique and synthetically challenging molecular architectures and notably provides the arylamines directly without the need for a subsequent reduction step. Moreover, we had hoped our synthetic efforts would allow access to materials for further biological studies, and to our delight we have received preliminary results from a screen of our synthetic intermediates indicating that this alkaloid backbone exhibits mild bioactivity in an unpublished screen against natriuretic peptide receptor 1. We are optimistic that similar synthetic strategies will be successfully applied to related bioactive natural products in the future.

1.5 References

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1.6 *Experimental Section*

1.6.1 *Syntheses of Selected Intermediates*

General Procedures: All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Dry tetrahydrofuran (THF), toluene, diethyl ether (Et₂O), dichloromethane (CH₂Cl₂), and acetonitrile (CH₃CN) were obtained by passing commercially available pre-dried, oxygen-free formulations through activated alumina columns. Yields refer to chromatographically and spectroscopically (¹H and ¹³C NMR) homogeneous materials, unless otherwise stated. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Reactions were magnetically stirred and monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent, and an ethanolic solution of phosphomolybdic acid and cerium sulfate or a solution of KMnO₄ in aq. NaHCO₃ and heat as developing agents. SiliCycle silica gel (60, academic grade, particle size 0.040–0.063 mm) was used for flash column chromatography. Preparative thinlayer chromatography separations were carried out on 0.50 mm E. Merck silica gel plates (60F254). NMR spectra were recorded on Bruker 400 and 500 MHz instruments and calibrated using residual undeuterated solvent as an internal reference. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, br = broad, app = apparent. IR spectra were recorded on a Perkin-Elmer 1000 series FT-IR spectrometer. High- resolution mass spectra (HRMS) were recorded on Agilent 6244 Tof-MS using ESI (Electrospray Ionization) at the University of Chicago Mass Spectroscopy Core Facility. All ee values were determined by HPLC on Daicel Chiralcel or Chiralpak columns. For procedures and characterization of strychnochromine synthetic intermediates **1**- see reference 1.²⁰ Chiral H-bonding catalysts were either synthesized by Snyder group alumni Drs. Vlad Lisnyak &

Tessa Lynch-colameta, or borrowed from the lab of Prof. Viresh Rawal, for which they are graciously thanked.

Iodoalkane 24. A solution of alcohol (500.0 mg, 3.29 mmol, 1.0 eq) in CH_2Cl_2 (6 mL) was cooled to 0 °C. MsCl (0.753 g, 6.57 mmol, 2.0 eq) was added followed by Et_3N (665.0 mg, 0.916 mL, 6.57 mmol, 2.0 eq) dropwise. The reaction mixture was stirred at 23 °C for 20 minutes, then acetone (25 mL) added, followed by NaI (4.92 g, 32.8 mmol, 10.0 eq). Reaction stirred at 23 °C overnight, diluted with Et_2O (15 mL), quenched with NaHCO_3 (2 x 15 mL), then phases separated. Aqueous phase extracted twice with Et_2O (2 x 20 mL), organic phases combined, dried over Na_2SO_4 , filtered, and evaporated. Purified by FCC (5% Hex: Et_2O) to afford a clear oil (456 mg, 53% yield). ^1H NMR (500 MHz, CDCl_3) δ 7.36 (d, J = 4.4 Hz, 4H), 7.31 (dt, J = 5.6, 4.1 Hz, 1H), 4.58 (s, 2H), 3.74 (t, J = 6.8 Hz, 2H), 3.29 (d, J = 6.7 Hz, 2H).

Aldehyde 25. To a round bottom flask under argon was added IBX (90.0 mgs, 0.323 mmol, 3 eq), and DMSO (0.1 M). The mixture was stirred for 2-5 minutes to dissolve. Then, alcohol **18** (50.0 mgs, 0.108 mmol, 1 eq) was added and the reaction was stirred for 1 hour, then quenched with sat. aq. NaHCO_3 (5 mL) and sat. aq. $\text{Na}_2\text{S}_2\text{O}_3$ (5 mL), diluted with EtOAc (10 mL), and the phases separated. The combined organic layer was washed with H_2O (3 x 10 mL), then brine (1 x 10 mL), dried over Na_2SO_4 , filtered, and evaporated. Purified by FCC (Hex: EtOAc 7:1). Aldehyde **25** obtained as a yellow oil (36.4 mgs, 73%). ^1H NMR (500 MHz, CDCl_3) δ 9.77 (d, J = 0.8 Hz, 1H), 7.42 – 7.35 (m, 4H), 7.34 – 7.28 (m, 1H), 7.07 (dd, J = 7.6, 1.4 Hz, 1H), 6.99 (td, J = 7.5, 1.4 Hz, 1H), 6.66 – 6.59 (m, 2H), 5.66 (ddd, J = 9.6, 4.9, 2.0 Hz, 1H), 5.47 (dd, J = 9.6, 2.6 Hz, 1H), 5.01

(s, 1H), 4.62 (d, $J = 12.0$ Hz, 1H), 4.53 (d, $J = 11.9$ Hz, 1H), 4.45 (s, 1H), 3.79 – 3.53 (m, 2H), 2.64 (dt, $J = 17.1, 2.4$ Hz, 1H), 2.50 – 2.36 (m, 1H), 2.26 – 2.17 (m, 1H), 2.02 (ddd, $J = 17.1, 5.0, 0.9$ Hz, 1H), 0.71 (t, $J = 8.0$ Hz, 9H), 0.45 – 0.34 (m, 6H).

Aldehyde 26. Phosphonium salt (67.4 mgs, .196 mmol, 2.5 eq), was added to a flame dried flask, then evacuated and backfilled thrice with argon. THF (2 mL, 0.1 M) added and suspension cooled to -78 °C. NaHMDS (157 mL, .157 mmol, 2.0 eq) added dropwise, and stirred for 1 hour at -78 °C. Aldehyde (36.4 mgs, 0.0785 mmol, 1.0 eq) dissolved in 1 mL THF and added dropwise at -78 °C, then allowed to slowly warm to 23 °C. After 2.5 hours, the reaction was quenched with sat. aq. NH_4Cl (5 mL), diluted with EtOAc (5 mL), then the phases were separated. The aqueous phase was extracted with EtOAc (3 x 10 mL). The combined organic phase was dried over Na_2SO_4 , filtered, and concentrated in vacuo. This crude material was then used directly in the next step. The intermediate enol ether (23.0 mgs, 0.0481 mmol, 1.0 eq) dissolved in CHCl_3 (0.05 M), and PPTS (6.0 mgs, 0.0241 mmol, 0.5 eq) was added. The reaction was stirred for 18 hours, then quenched with NaHCO_3 (5 mL), then the phases were separated. Aqueous phase extracted twice with CH_2Cl_2 (2 x 5 mL) and the organic phases combined. The combined organic layer was dried over Na_2SO_4 , filtered, and evaporated *in vacuo*. The crude material was then purified by flash column chromatography (silica gel, Hex:EtOAc = 3:1) to afford the desired aldehyde as a yellow oil (10.3 mg, 44% yield). ^1H NMR (500 MHz, CDCl_3) δ 9.96 (s, 1H), 7.40 – 7.34 (m, 5H), 7.30 (ddd, $J = 5.5, 3.6, 2.4$ Hz, 1H), 7.04 (dd, $J = 7.8, 1.4$ Hz, 1H), 6.92 (ddd, $J = 7.9, 7.3, 1.4$ Hz, 1H), 6.55 (td, $J = 7.5, 1.2$ Hz, 1H), 6.40 (dd, $J = 7.9, 1.2$ Hz, 1H), 5.58 (ddd, $J = 9.8, 5.1, 2.0$ Hz, 1H), 5.35 (dd, $J = 9.6, 2.5$ Hz, 1H), 4.61 (dd, $J = 12.0, 1.4$ Hz, 1H), 4.54 (s, 1H), 4.51 (d, $J = 11.9$ Hz, 1H), 3.95 (s, 1H), 3.72 – 3.54 (m, 2H), 3.45 (s, 1H), 3.33 (s, 1H), 2.84 (qd, $J = 16.8, 1.6$ Hz, 2H),

2.53 (ddd, $J = 17.4, 5.1, 0.9$ Hz, 1H), 2.39 (td, $J = 9.3, 4.8$ Hz, 1H), 2.33 (dt, $J = 17.4, 2.5$ Hz, 1H), 2.20 (ddd, $J = 13.5, 9.7, 6.0$ Hz, 2H), 0.80 – 0.75 (m, 9H), 0.54 – 0.49 (m, 6H).

Alcohol 27. Aldehyde **26** (653 mgs, 1.37 mmol, 1 eq) was dissolved in CH_2Cl_2 :MeOH (13.5 mL, 1:1, 0.1 M), placed under an argon atmosphere, and then cooled to 0 °C. While stirring, NaBH_4 (78.0 mgs, 2.05 mmol, 1.5 eq) was added in a single portion, and the reaction mixture was stirred for 30 minutes. Then, the reaction was quenched with sat. aq. NH_4Cl (15 mL), and the phases were separated. The aqueous layer was then extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layer was dried over Na_2SO_4 , filtered, and evaporated *in vacuo*. The crude material was then purified by flash column chromatography (silica gel, Hex:EtOAc = 3:1), and the desired alcohol was afforded as a yellow oil (416 mg, 63%). ^1H NMR (500 MHz, CDCl_3) δ 7.42 – 7.33 (m, 4H), 7.32 – 7.27 (m, 1H), 7.03 (dd, $J = 7.7, 1.5$ Hz, 1H), 6.89 (td, $J = 7.6, 1.4$ Hz, 1H), 6.51 (td, $J = 7.4, 1.3$ Hz, 1H), 6.36 (dd, $J = 7.9, 1.2$ Hz, 1H), 5.63 (ddd, $J = 9.7, 5.2, 2.0$ Hz, 1H), 5.37 (dd, $J = 9.7, 2.6$ Hz, 1H), 5.02 (s, 1H), 4.61 (d, $J = 11.9$ Hz, 1H), 4.51 (d, $J = 11.9$ Hz, 1H), 4.05 – 3.94 (m, 2H), 3.77 (s, 1H), 3.72 – 3.57 (m, 2H), 2.47 (dd, $J = 17.3, 5.2$ Hz, 1H), 2.39 (ddd, $J = 13.3, 9.8, 5.0$ Hz, 1H), 2.27 – 2.11 (m, 3H), 1.65 (dt, $J = 14.3, 4.0$ Hz, 1H), 0.78 (t, $J = 7.9$ Hz, 9H), 0.53 – 0.46 (m, 6H).

Hydroxylamine 12. Ammonium chloride (6.48 g, 120.0 mmol, 1.2 eq) was placed in a round bottom flask with a stir bar, and dissolved in H_2O (150 mL). After it was fully dissolved, the reaction flask was placed in a 0 °C ice bath, and a solution of 1-iodo-2-nitrobenzene (25.0 g, 100 mmol, 1.0 eq) in EtOH (75 mL) was added. The resulting mixture was stirred vigorously, while Zn powder (13.1 g, 200 mmol, 2.0 eq) was added slowly in 6 portions. The reaction was

allowed to warm to 23 °C, and stirred for 3 hours. Then, the mixture was filtered through a pad of celite, and the volatile organics were removed *in vacuo*. The mixture was then diluted with EtOAc (100 mL), and the phases were separated. The aqueous phase was extracted with EtOAc (3 x 50 mL), then the combined organic phase was washed with brine (1 x 100 mL). The combined organic layer was dried over Na₂SO₄, filtered, and evaporated *in vacuo*. The crude material was then purified by flash column chromatography (silica gel, Hex:EtOAc = 3:1). This afforded the desired hydroxylamine as a yellow solid (17.1 g, 72.6 mmol, 72% yield). **NOTE:** whenever concentrating a solution of this material, it is critical to keep the water bath below 23 °C, otherwise significant decomposition is observed. ¹H NMR (500 MHz, CDCl₃) δ 7.68 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.33 (ddd, *J* = 8.5, 7.3, 1.4 Hz, 1H), 7.25 (dd, *J* = 8.1, 1.6 Hz, 1H), 6.87 (s, 1H), 6.72 (td, *J* = 7.6, 1.7 Hz, 1H), 5.44 – 5.24 (broad, 1H).

1.6.2 Syntheses of Chiral Amines

Luo Diamine 90. To a solution of *N*-Boc-tert-Leucine (5.00 g, 21.6 mmol, 1.0 eq) at 0 °C in anhydrous CH₂Cl₂ (35 mL) was added DCC (4.906 g, 23.8 mmol, 1.1 eq) in anhydrous CH₂Cl₂ (20 mL) and stirred for 30 minutes. Then, Et₂NH (1.58 g, 21.6 mmol, 1.0 eq) in anhydrous CH₂Cl₂ (10 mL), was added over 1 hour. The mixture was then stirred at 23 °C for 12 hours, after which the white precipitate was filtered through a pad of celite and washed with CH₂Cl₂ (2 x 20 mL). The organic phase was then washed with 2% aq. HCl (10 mL), then 4% aq. NaHCO₃ (2 x 25 mL), then brine (2 x 20 mL). The combined organic layer was dried over Na₂SO₄, filtered, and evaporated *in vacuo*. The crude material was then purified by flash column chromatography (silica gel, Hex:EtOAc = 2:1) to afford the intermediate amide as a yellow oil (3.7 g, 12.9 mmol, 60% yield). ¹H NMR (400 MHz, CDCl₃) δ 5.28 (d, *J* = 8.3 Hz, 1H), 4.45 (d, *J* = 9.9 Hz, 1H), 3.69 (ddq,

$J = 44.9, 14.4, 7.1$ Hz, 2H), 3.24 (dq, $J = 14.5, 7.1$ Hz, 1H), 3.01 (dq, $J = 14.0, 7.1$ Hz, 1H), 1.42 (s, 9H), 1.20 (t, $J = 7.1$ Hz, 3H), 1.11 (t, $J = 7.1$ Hz, 3H), 0.97 (s, 9H).

To the above amide (3.7 g, 12.9 mmol, 1.0 eq) was then added anhydrous MeOH (40 mL), followed by acetyl chloride (5.0 mL) slowly. Once the addition was complete, the reaction was fitted with a reflux condenser and heated to reflux for 1 hour, then cooled to 23 °C. The volatile organics were evaporated, CH₂Cl₂ (50 mL), then H₂O (20 mL) and the pH was adjusted to pH 12 with solid K₂CO₃. The phases were then separated with a separatory funnel, and the aqueous phase was extracted with CH₂Cl₂ (3 x 20 mL). The combined organic layer was dried over Na₂SO₄, filtered, and evaporated *in vacuo*. The crude material was then purified by flash column chromatography (silica gel, 5% MeOH in CH₂Cl₂ → 10% MeOH in CH₂Cl₂) to afford the desired amine as an oil (2.4 g, 12.9 mmol, quantitative). ¹H NMR (400 MHz, CDCl₃) δ 3.69 (dtd, $J = 14.3, 7.1, 1.1$ Hz, 1H), 3.58 (dq, $J = 14.2, 7.2, 1.1$ Hz, 1H), 3.39 (s, 1H), 3.19 (dq, $J = 14.4, 7.1$ Hz, 1H), 3.07 (dq, $J = 14.0, 7.1$ Hz, 1H), 1.19 (t, $J = 7.2$ Hz, 3H), 1.12 (t, $J = 7.1$ Hz, 3H), 0.98 (s, 9H).

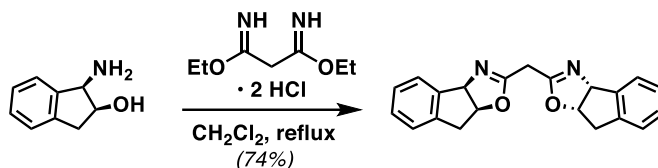
The above amide (2.4 g, 12.9 mmol, 1.0 eq) was dissolved in anhydrous THF (25 mL, 0.5 M) and cooled to 0 °C, then solid LiAlH₄ (391 mg, 10.3 mmol, 0.8 eq) was added portionwise, and the mixture was heated to refluxed for 4 hours. After cooling to 23 °C, the reaction was quenched with solid Na₂SO₄ • 10 H₂O (3.0 g). The mixture was then filtered through celite, and washed with THF several times. The combined organic layer was dried over Na₂SO₄, filtered, and evaporated *in vacuo*. The desired amine was then purified by vacuum distillation to afford the desired amine as a yellow oil (1.98 g, 11.5 mmol, 89% yield). ¹H NMR (400 MHz, CDCl₃) δ 2.67 – 2.33 (m, 6H), 2.10 (dd, $J = 12.5, 10.9$ Hz, 1H), 1.64 (s, 2H), 1.08 – 0.94 (m, 6H), 0.88 (s, 9H).

Quinine derived amine 94. To a flame-dried 100 mL round bottom flask was added a condenser and stir bar. The apparatus was then evacuated and backfilled with N₂ thrice. The cinchona alkaloid (1.0 g, 3.08 mmol, 1.0 eq), Ph₃P (0.968 g, 3.696 mmol, 1.2 eq) and anhydrous THF (15 mL) was added, and stirred until completely dissolved. The solution was then cooled to 0 °C, stirred for 5 minutes, then diisopropyl azodicarboxylate (0.728 mL, 3.696 mmol, 1.2 eq) was added slowly over 5 minutes, and the solution changed from colorless to a pale orange/yellow color. After 5 minutes of stirring, DPPA (0.8 mL, 3.696, 1.2 eq) was added dropwise and the reaction stirred for 15 minutes at 0 °C, after which it was removed from the bath and stirred at 23 °C for 4 hours. The reaction mixture was then moved to a 45 °C bath and stirred for 2 hours. Then, another portion of Ph₃P (0.968 g, 3.696 mmol, 1.2 eq) was added and the reaction was stirred overnight. The reaction was then let cool to 23 °C, transferred to a larger flask, rinsed with CH₂Cl₂ and the volatile organics were evaporated *in vacuo*. Then, a stir bar was added and CH₂Cl₂ (80 mL) was added, followed by the slow addition of 2M HCl (80 mL), while stirring vigorously over 10 minutes. The phases were then separated, the aqueous phase was washed with CH₂Cl₂ (2 x 25 mL), then basified to pH 12 with 6 M NaOH. The aqueous layer was then extracted with CH₂Cl₂ (4 x 80 mL), dried over Na₂SO₄, filtered, and evaporated. The crude material was then purified by flash column chromatography (silica gel, EtOAc:MeOH = 8:1 → 4:1 → CH₂Cl₂:MeOH = 4:1) to afford the desired amine (0.714 g, 2.209 mmol, 72% yield). ¹H NMR (400 MHz, CDCl₃) δ 8.75 (d, J = 4.6 Hz, 1H), 8.04 (d, J = 9.2 Hz, 1H), 7.46 (d, J = 4.3 Hz, 1H), 7.39 (dd, J = 9.2, 2.7 Hz, 1H), 5.80 (ddd, J = 17.5, 10.3, 7.5 Hz, 1H), 5.08 – 4.87 (m, 2H), 4.60 (d, J = 10.1 Hz, 1H), 3.97 (s, 3H), 3.37 – 3.03 (m, 3H), 2.91 – 2.74 (m, 2H), 2.30 (s, 1H), 1.93 (s, 4H), 1.69 – 1.38 (m, 4H), 0.83 – 0.73 (m, 1H).

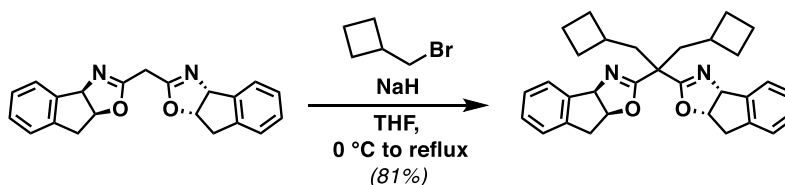
1.6.3 Syntheses of Selected Ligands

PyBOX ligand 127. 2,6-Pyridinedicarboxylic acid (500.0 mg, 2.99 mmol, 1.0 eq) was added to a round bottom flask with a stir bar, followed by CH_2Cl_2 (20 mL). Then, **EDC** (1.3 g, 6.73 mmol, 2.25 eq) was added followed by **HOBt** (910.0 mg, 6.73 mmol, 2.25 eq). This mixture was stirred for 20 minutes, then (1R,2S)-(+)-cis-1-Amino-2-indanol (893.0 mg, 5.98 mmol, 2.0 eq) was added and the reaction allowed to stir overnight at 23 °C. The next morning, the reaction was quenched with sat. aq. NaHCO_3 (20 mL). The phases were separated, the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL), then the combined organic layer was dried over Na_2SO_4 , filtered, and evaporated *in vacuo*. The crude material was then purified by flash column chromatography to afford the intermediate diamine as a tan amorphous solid (1.25 g, 2.89 mmol, 97% yield). To this material (800. mgs, 1.86 mmol, 1.0 eq) was then added in $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (6 mL, 15 % w/v, 24.6 eq) and heated to 120 °C for 6h. The mixture became homogenous at 75 °C. After the 6 h period the solution was allowed to cool to 23 °C, diluted with CH_2Cl_2 (20 mL) and poured into ice-cold 2N NaOH (50 mL). The phases were separated, the CH_2Cl_2 was diluted with Et_2O (50 mL), and the resulting suspension was filtered through a silica pad, and washed with $\text{CH}_2\text{Cl}_2:\text{Et}_2\text{O} = 1:1$ (20 mL). The volatile organics were removed *in vacuo* and the crude solid was purified via recrystallization ($\text{CHCl}_3:\text{MeOH} = 1:1$) to afford the desired PyBOX ligand as a white solid (103 mgs, 0.261 mmol, 14% yield). ^1H NMR (400 MHz, CDCl_3) δ 8.02 (d, $J = 7.9$ Hz, 2H), 7.71 (t, $J = 7.9$ Hz, 1H), 7.47 (d, $J = 5.2$ Hz, 2H), 7.18 (d, $J = 2.7$ Hz, 5H), 5.71 (d, $J = 8.0$ Hz, 2H), 5.53 (ddd, $J = 8.2, 5.0, 3.5$ Hz, 2H), 3.45 – 3.38 (m, 4H).

General Procedures for IndaBOX synthesis.



IndaBOX 89. Prepared according to a modified literature procedure.¹¹ (1S,2R)-(-)-cis-1-Amino-2-indanol (1.08 g, 7.24 mmol, 2.1 equiv) and diethyl malonimidate dihydrochloride (0.80 g, 3.46 mmol, 1.0 equiv) were taken up in CH_2Cl_2 (80 mL), and the resulting suspension was refluxed for 16 h. Upon completion, the reaction contents were poured into water (160 mL) and extracted with CH_2Cl_2 (4×40 mL). The combined organic layers were dried (MgSO_4), filtered and concentrated. The resultant crude product was recrystallized from EtOH (100 mL), then dried overnight in a vacuum desiccator to give the parent ligand as a white crystalline solid. Spectral data matched those previously reported.



Bis(methylcyclobutyl)-IndaBOX 120. Prepared according to a literature procedure.¹² Parent ligand **89** (2.0 g, 6.05 mmol, 1.0 equiv) was dissolved in THF (50 mL) and cooled to 0 °C. NaH (60% dispersion in mineral oil, 0.726 g, 18.15 mmol, 3.0 equiv) added portionwise. Mixture stirred for 10 minutes at 0 °C then, alkylbromide (1.98 g, 1.57 mL, 12.31 mmol, 2.2 equiv) was added dropwise. Following the addition, the reaction was allowed to warm to room temperature, then brought to reflux and stirred overnight. The next day, the reaction was cooled to room temperature and quenched with saturated aqueous NH_4Cl (50 mL), the phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3×50 mL). The combined organic solution

was washed with brine, dried over Na₂SO₄, filtered, and evaporated. The crude material was recrystallized from hot ethyl acetate. *Note:* in some instances when the crude material did not recrystallize it was first purified by flash column chromatography (silica gel, hexane/acetone, 1:10→1:1) before being recrystallized. In our hands, despite spectroscopically clean material after column chromatography, recrystallization was necessary to provide both a colorless white solid and reliable enantioselectivities (2.3 g , 81% yield).

120: $R_f = 0.4$ (silica gel, EtOAc/hexanes/Et₃N, 1:3:1 drop);

IR (film) ν_{max} 2954, 2862, 1652, 1646, 1189, 1002, 750 cm⁻¹;

¹H NMR (500 MHz, CDCl₃) δ 7.52 – 7.48 (m, 2H), 7.28 – 7.24 (m, 5H), 7.24 – 7.19 (m, 2H), 5.47 (d, $J = 7.7$, 2H), 5.13 (ddd, $J = 8.0, 6.8, 1.5$ Hz, 2H), 3.28 – 3.18 (dd, 2H), 2.86 – 2.76 (d, 2H), 2.14 – 2.02 (m, 4H), 2.02 – 1.95 (m, 2H), 1.82 (t, $J = 5.8$ Hz, 2H), 1.65 – 1.51 (m, 9H), 1.46 (q, $J = 9.0, 8.4$ Hz, 2H);

¹³C NMR (125 MHz, CDCl₃) δ 168.25, 141.98, 139.90, 128.43, 127.49, 125.74, 125.02, 101.33, 82.83, 76.49, 44.87, 39.52, 38.61, 31.94, 29.42, 29.38, 19.16;

HRMS (ESI) calcd for C₃₁H₃₄N₂O₂⁺ [M + Na⁺] 489.2512, found 489.2511.

Dimethyl IndaBOX 110. Synthesized following the general procedure for ligand synthesis. (70.0 mgs, 33% yield) ¹H NMR (400 MHz, CDCl₃) δ 7.56 – 7.50 (m, 2H), 7.29 – 7.21 (m, 6H), 5.55 (d, $J = 7.9$ Hz, 2H), 5.30 (t, $J = 7.2$ Hz, 2H), 3.72 (q, $J = 7.0$ Hz, 2H), 3.32 (dd, $J = 18.0, 7.0$ Hz, 2H), 3.01 – 2.92 (m, 2H), 1.44 (s, 6H).

Spirocyclopentyl IndaBOX 111. Synthesized following the general procedure for ligand synthesis. (145 mgs, 50% yield) ¹H NMR (400 MHz, CDCl₃) δ 7.49 (s, 2H), 7.26 – 7.15 (m, 6H),

5.52 (d, $J = 7.8$ Hz, 2H), 5.26 (t, $J = 7.4$ Hz, 2H), 3.30 (dd, $J = 17.8, 7.0$ Hz, 2H), 2.96 (d, $J = 18.6$ Hz, 2H), 2.25 – 1.99 (m, 4H), 0.89 – 0.80 (m, 4H).

Spirocyclopropyl IndaBOX 112. Synthesized following the general procedure for ligand synthesis. (213 mgs, 39% yield). matched previously reported spectrum.¹⁴⁰ ^1H NMR (400 MHz, CDCl_3) δ 7.48 – 7.41 (m, 1H), 7.26 – 7.18 (m, 3H), 5.52 (d, $J = 7.9$ Hz, 1H), 5.32 (ddd, $J = 8.0, 7.0, 2.0$ Hz, 1H), 3.38 (dd, $J = 17.9, 7.0$ Hz, 1H), 3.19 (dd, $J = 17.9, 1.9$ Hz, 1H), 1.37 – 1.24 (m, 2H).

Bis(*n*-pentyl) IndaBOX 113. Synthesized following the general procedure for ligand synthesis. (234 mgs, 83% yield) ^1H NMR (400 MHz, CDCl_3) δ 7.49 (p, $J = 4.9, 4.4$ Hz, 2H), 7.26 – 7.19 (m, 6H), 5.54 (d, $J = 7.7$ Hz, 2H), 5.22 (ddd, $J = 7.9, 6.8, 1.5$ Hz, 2H), 3.29 (dd, $J = 17.9, 6.7$ Hz, 2H), 2.96 (d, $J = 17.9$ Hz, 2H), 1.93 – 1.74 (m, 4H), 1.10 – 1.02 (m, 6H), 0.96 – 0.80 (m, 6H), 0.71 – 0.65 (m, 6H).

Bis(*n*-decanyl) IndaBOX 114. Synthesized following the general procedure for ligand synthesis. (225 mgs, 49% yield). ^1H NMR (400 MHz, CDCl_3) δ 7.56 – 7.45 (m, 2H), 7.23 (dt, $J = 7.4, 4.3$ Hz, 6H), 5.54 (d, $J = 7.6$ Hz, 2H), 5.22 (ddd, $J = 7.9, 6.7, 1.5$ Hz, 2H), 3.29 (dd, $J = 17.9, 6.7$ Hz, 2H), 3.00 – 2.88 (m, 2H), 1.92 – 1.74 (m, 4H), 1.34 – 0.96 (m, 28H), 0.88 (t, $J = 7.0$ Hz, 7H), 0.69 (q, $J = 11.7, 8.9$ Hz, 3H).

Bis(*n*-octyl) IndaBOX 115. Synthesized following the general procedure for ligand synthesis. (189 mgs, 36% yield). ^1H NMR (400 MHz, CDCl_3) δ 7.50 (p, $J = 4.9$ Hz, 2H), 7.26 –

7.20 (m, 6H), 5.54 (d, $J = 7.6$ Hz, 2H), 5.22 (ddd, $J = 7.9, 6.8, 1.5$ Hz, 2H), 3.29 (dd, $J = 17.9, 6.8$ Hz, 2H), 2.95 (d, $J = 17.9$ Hz, 2H), 1.93 – 1.73 (m, 4H), 1.28 – 0.92 (m, 18H), 0.86 (t, $J = 7.1$ Hz, 6H), 0.71 (d, $J = 7.3$ Hz, 2H).

Bis(geranyl) IndaBOX 116. Synthesized following the general procedure for ligand synthesis. (371 mgs, 68% yield). ^1H NMR (400 MHz, CDCl_3) δ 7.53 – 7.46 (m, 2H), 7.23 (h, $J = 4.2, 3.8$ Hz, 6H), 5.56 (d, $J = 7.8$ Hz, 2H), 5.24 (ddt, $J = 8.3, 6.8, 1.5$ Hz, 2H), 4.92 (dddd, $J = 8.5, 5.8, 2.8, 1.4$ Hz, 2H), 4.61 – 4.51 (m, 2H), 3.30 (dd, $J = 17.9, 6.7$ Hz, 2H), 3.09 – 2.94 (m, 2H), 2.54 (d, $J = 7.3$ Hz, 4H), 1.77 – 1.48 (m, 21H), 1.42 – 1.32 (m, 6H).

Bis(Benzyl) IndaBOX 117. Synthesized following the general procedure for ligand synthesis. (240 mgs., 62%). ^1H NMR (400 MHz, CDCl_3) δ 7.48 (d, $J = 7.4$ Hz, 2H), 7.37 – 7.27 (m, 6H), 7.03 – 6.96 (m, 2H), 6.81 (dd, $J = 8.5, 6.9$ Hz, 4H), 6.77 – 6.71 (m, 4H), 5.61 (d, $J = 7.8$ Hz, 2H), 5.32 (t, $J = 7.3$ Hz, 2H), 3.35 (dd, $J = 18.1, 6.7$ Hz, 2H), 3.25 (d, $J = 14.3$ Hz, 2H), 3.07 (dd, $J = 16.3, 10.1$ Hz, 4H).

Bis(iso-butyl) IndaBOX 118. Synthesized following the general procedure for ligand synthesis. (263.5 mgs, 65% yield). ^1H NMR (400 MHz, CDCl_3) δ 7.48 – 7.38 (m, 2H), 7.21 – 7.11 (m, 6H), 5.44 (d, $J = 7.7$ Hz, 2H), 5.06 (ddd, $J = 7.9, 6.7, 1.4$ Hz, 2H), 3.12 (dd, $J = 17.9, 6.7$ Hz, 2H), 2.69 (d, $J = 17.9$ Hz, 2H), 1.97 – 1.77 (m, 4H), 1.49 – 1.33 (m, 2H), 0.71 (d, $J = 6.6$ Hz, 6H), 0.54 (d, $J = 6.7$ Hz, 6H).

Bis(methylcyclopropyl) IndaBOX 119. Synthesized following the general procedure for ligand synthesis. (76.5 mgs, 58% yield). ^1H NMR (400 MHz, CDCl_3) δ 7.53 – 7.45 (m, 2H), 7.24 (dd, J = 4.0, 2.3 Hz, 6H), 5.60 – 5.50 (m, 2H), 5.22 (ddd, J = 7.8, 6.7, 1.4 Hz, 2H), 3.30 (dd, J = 17.9, 6.7 Hz, 2H), 3.03 (dd, J = 17.8, 1.3 Hz, 2H), 2.09 (dd, J = 14.3, 6.1 Hz, 2H), 1.84 (dd, J = 14.3, 7.4 Hz, 2H), 0.39 (dt, J = 10.4, 5.8, 2.5 Hz, 2H), 0.18 (tt, J = 9.7, 4.2 Hz, 2H), -0.11 (dq, J = 9.5, 5.0 Hz, 2H), -0.16 – -0.27 (m, 2H), -0.32 (ddd, J = 10.5, 9.3, 5.0 Hz, 2H).

Bis(methylcyclopentyl) IndaBOX 121. Synthesized following the general procedure for ligand synthesis. (235 mgs, 63% yield). ^1H NMR (400 MHz, CDCl_3) δ 7.53 – 7.42 (m, 2H), 7.26 – 7.20 (m, 6H), 5.56 – 5.49 (m, 2H), 5.30 – 5.22 (m, 1H), 5.20 – 5.12 (m, 1H), 3.42 – 3.19 (m, 3H), 2.93 (dd, J = 41.8, 17.9 Hz, 2H), 2.07 (dd, J = 6.4, 2.7 Hz, 2H), 1.69 – 1.40 (m, 10H), 1.35 – 1.27 (m, 3H), 1.02 – 0.71 (m, 7H).

Bis(methylcyclohexyl) IndaBOX 122. Synthesized following the general procedure for ligand synthesis (343 mgs, 73). ^1H NMR (400 MHz, CDCl_3) δ 7.54 – 7.47 (m, 2H), 7.26 – 7.19 (m, 6H), 5.57 (d, J = 7.7 Hz, 2H), 5.20 (ddd, J = 7.8, 6.7, 1.2 Hz, 2H), 3.28 (dd, J = 18.0, 6.6 Hz, 2H), 3.09 – 2.97 (m, 2H), 1.84 (qd, J = 14.5, 5.7 Hz, 4H), 1.53 – 1.32 (m, 6H), 1.19 – 1.03 (m, 4H), 1.02 – 0.74 (m, 8H), 0.70 – 0.52 (m, 4H).

General Procedure for α -Esterification

methyl 2-oxocyclohex-3-ene-1-carboxylate 128. To a flame dried flask with a stir bar was added a solution of 2-Cyclohexen-1-one (962 mgs, 0.97 mL, 10.0 mmol) in anhydrous THF (20.0 mL). The solution was then cooled to -78 °C, then LiHMDS (13 mL, 1.0 M in THF, 13.0

mmol, 1.3 eq) was added slowly, and stirred at the same temperature for 1 hour. Then, methyl cyanoformate (Mander's reagent, 1.02 mgs, 952 μ L, 12.0 mmol, 1.2 eq) was added dropwise. The reaction was allowed to slowly warm to 0 °C, before being quenched with sat. aq. NaHCO₃ (20 mL). The phases were separated and the aqueous phase was extracted with Et₂O (3 x 20 mL). The combined organic layer was dried over Na₂SO₄, filtered, and evaporated *in vacuo*. The crude material was then purified by flash column chromatography (silica gel, Hex:EtOAc = 1:6 → 1:2) to give the β -ketoester as a light yellow oil (1.198, 78% yield). ¹H NMR (400 MHz, CDCl₃) δ 7.01 – 6.88 (m, 1H), 6.03 – 5.92 (m, 1H), 3.66 (dd, *J* = 3.5, 1.6 Hz, 3H), 3.38 – 3.30 (m, 1H), 2.41 – 2.10 (m, 4H). **Amination Product:** (62% yield, ~70% *ee*), ¹H NMR (400 MHz, CDCl₃) δ 7.71 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.16 – 7.11 (m, 1H), 7.06 – 6.98 (m, 1H), 6.66 (dd, *J* = 8.2, 1.4 Hz, 1H), 6.48 (td, *J* = 7.6, 1.4 Hz, 1H), 6.17 (ddd, *J* = 10.2, 2.9, 1.4 Hz, 1H), 6.02 (br, 1H, N—H), 3.64 (s, 3H), 3.16 – 3.08 (m, 1H), 2.97 (dddd, *J* = 21.0, 10.8, 5.5, 2.8 Hz, 1H), 2.49 (dt, *J* = 20.5, 5.7 Hz, 1H), 2.11 (ddd, *J* = 14.1, 10.2, 5.9 Hz, 1H).

methyl 3-methyl-2-oxocyclopent-3-ene-1-carboxylate 129. Synthesized following the general procedure for α -Esterification (162 mgs, 63% yield). **Major Tautomer:** ¹H NMR (400 MHz, CDCl₃) δ 7.39 (tp, *J* = 3.3, 1.5 Hz, 1H), 3.76 (s, 3H), 3.43 (dd, *J* = 6.9, 2.6 Hz, 1H), 2.95 (ddq, *J* = 18.8, 4.9, 2.4 Hz, 1H), 2.78 (dddd, *J* = 18.8, 7.0, 2.8, 2.1 Hz, 1H), 1.79 (td, *J* = 2.2, 1.4 Hz, 3H). **Amination Product:** (28 mgs, 76% yield) ¹H NMR (400 MHz, CDCl₃) δ 7.72 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.53 (q, *J* = 2.4 Hz, 1H), 7.17 – 7.07 (m, 1H), 6.51 (td, *J* = 7.6, 1.4 Hz, 1H), 6.26 (dd, *J* = 8.1, 1.3 Hz, 1H), 5.39 (s, 1H), 3.66 (s, 3H), 3.57 (dq, *J* = 18.2, 2.3 Hz, 1H), 2.81 (dt, *J* = 18.1, 2.5 Hz, 1H), 1.90 (d, *J* = 2.0 Hz, 3H).

methyl 4-methyl-2-oxocyclopent-3-ene-1-carboxylate 130. Synthesized following the general procedure for α -Esterification (144 mgs, 56% yield). **Major Tautomer:** ^1H NMR (400 MHz, CDCl_3) δ 5.91 (dd, $J = 3.1, 1.6$ Hz, 1H), 3.76 (d, $J = 1.5$ Hz, 3H), 3.50 – 3.42 (m, 1H), 3.06 – 2.95 (m, 1H), 2.82 – 2.70 (m, 1H), 2.18 (d, $J = 1.3$ Hz, 3H). **Amination Product:** (20 mgs, 54% yield) ^1H NMR (400 MHz, CDCl_3) δ 7.72 (dd, $J = 7.9, 1.5$ Hz, 1H), 7.13 (t, $J = 7.7$ Hz, 1H), 6.51 (t, $J = 7.4$ Hz, 1H), 6.31 – 6.24 (m, 1H), 6.06 (s, 1H), 5.39 (s, 1H), 3.66 (s, 3H), 3.55 (s, 1H), 2.82 (d, $J = 17.7$ Hz, 1H), 2.26 (d, $J = 1.2$ Hz, 3H).

methyl 2-oxocyclohept-3-ene-1-carboxylate 131. Synthesized following the general procedure for α -Esterification (200.0 mgs, 44% yield). **Major Tautomer:** ^1H NMR (400 MHz, CDCl_3) δ 12.57 (s, 1H), 6.27 (dt, $J = 12.4, 4.8$ Hz, 1H), 5.95 (dt, $J = 12.4, 2.0$ Hz, 1H), 3.78 (s, 3H), 2.48 – 2.43 (m, 2H), 2.39 – 2.32 (m, 2H), 1.91 – 1.82 (m, 3H). **Minor Tautomer:** ^1H NMR (400 MHz, CDCl_3) δ 6.63 (ddd, $J = 12.1, 6.0, 4.7$ Hz, 1H), 6.07 (ddd, $J = 12.2, 2.2, 1.4$ Hz, 1H), 3.70 – 3.63 (m, 1H), 2.56 – 2.47 (m, 2H), 2.29 – 1.94 (m, 4H). **Amination Product:** (17 mgs, 22% yield) ^1H NMR (400 MHz, CDCl_3) δ 8.39 (s, 1H), 7.65 (dd, $J = 7.8, 1.4$ Hz, 1H), 7.32 – 7.26 (m, 1H), 7.24 – 7.16 (m, 1H), 6.69 (td, $J = 7.6, 1.7$ Hz, 1H), 6.43 (dt, $J = 12.5, 4.8$ Hz, 1H), 6.01 (dt, $J = 12.5, 1.9$ Hz, 1H), 3.82 (s, 3H), 2.54 (ddd, $J = 14.8, 8.3, 2.8$ Hz, 1H), 2.48 (ddt, $J = 6.0, 3.9, 1.9$ Hz, 1H), 2.27 – 2.13 (m, 1H), 2.04 (dtt, $J = 15.0, 7.6, 3.4$ Hz, 1H), 1.86 (dddd, $J = 14.4, 11.0, 7.0, 3.6$ Hz, 1H).

methyl 1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate 132. Synthesized following the general procedure for α -Esterification (300.0 mgs, 54% yield). **Major Tautomer:** ^1H NMR (400 MHz, CDCl_3) δ 12.40 (s, 1H), 7.80 (dd, $J = 7.5, 1.7$ Hz, 1H), 7.37 – 7.27 (m, 2H), 7.20 – 7.14

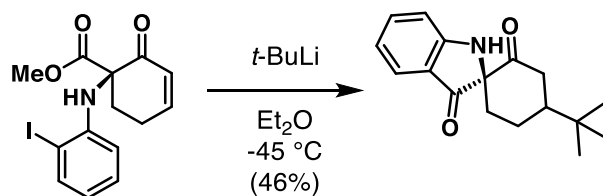
(m, 1H), 3.83 (s, 3H), 2.82 (dd, $J = 8.9, 6.6$ Hz, 2H), 2.57 (dd, $J = 8.9, 6.7$ Hz, 2H). **Minor Tautomer:** ^1H NMR (400 MHz, CDCl_3) δ 8.05 (dd, 1H), 7.50 (td, $J = 7.5, 1.4$ Hz, 1H), 7.31 (dd, $J = 3.3, 1.8$ Hz, 1H), 7.24 (m, 1H), 3.63 (dd, $J = 10.3, 4.7$ Hz, 1H), 3.03 (qt, $J = 17.0, 5.1$ Hz, 2H), 2.50 (ddd, $J = 15.3, 9.4, 4.5$ Hz, 2H), 2.37 (dq, $J = 13.5, 4.9$ Hz, 1H). **Amination Product:** ^1H NMR (400 MHz, CDCl_3) δ 8.06 (dd, $J = 7.8, 1.4$ Hz, 1H), 7.72 (dd, $J = 7.8, 1.5$ Hz, 1H), 7.57 – 7.51 (m, 1H), 7.35 (t, $J = 7.6$ Hz, 1H), 7.27 (d, $J = 3.4$ Hz, 1H), 7.17 – 7.10 (m, 1H), 6.74 (dd, $J = 8.2, 1.4$ Hz, 1H), 6.49 (td, $J = 7.6, 1.4$ Hz, 1H), 6.06 (s, 1H), 3.60 (s, 2H), 3.50 (ddd, $J = 17.2, 11.5, 5.2$ Hz, 1H), 3.15 (ddd, $J = 14.0, 5.2, 3.1$ Hz, 1H), 3.03 (ddd, $J = 17.8, 5.6, 3.1$ Hz, 1H), 2.33 (ddd, $J = 14.0, 11.5, 5.5$ Hz, 1H). [Note: some azoxybenzene impurity present]

methyl 2-oxo-1,2,3,4-tetrahydronaphthalene-1-carboxylate 133. To a flame dried flask containing freshly made LDA (0.5 M, 3.09 mmol) with a stir bar was added a solution of β -tetralone (398 mgs, 2.72 mmol, 1.0 eq) in anhydrous THF (1.5 mL) dropwise, and the reaction was allowed to warm 23 °C and stirred for 1 hour. Then the reaction was cooled back down to -78 °C, anhydrous HMPA (257 μL , 3.09 mmol, 1.135 eq) was added, and allowed to stir for 10 minutes followed by the addition of Mander's reagent (263 μL , 3.09 mmol, 1.135 eq). The reaction was then stirred at this temperature for 2 hours before being quenched with sat. aq. NaHCO_3 (10 mL). The phases were separated and the aqueous phase was extracted with Et_2O (3 x 25 mL). The combined organic layer was dried over Na_2SO_4 , filtered, and evaporated *in vacuo*. The crude material was then purified by flash column chromatography (silica gel, Hex:EtOAc = 5:1) to afford the desired β -ketoester as a yellow oil (206 mgs, 37% yield). ^1H NMR (400 MHz, CDCl_3) δ 13.30 (s, 1H), 7.72 – 7.65 (m, 1H), 7.19 (td, $J = 7.6, 1.7$ Hz, 1H), 7.16 – 7.10 (m, 1H), 7.07 (td, $J = 7.3, 1.3$ Hz, 1H), 3.92 (s, 3H), 2.86 – 2.79 (m, 2H), 2.54 (dd, $J = 8.4, 6.6$ Hz, 2H).

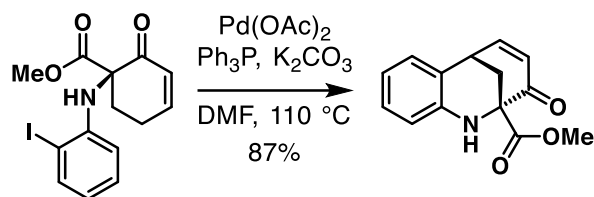
methyl 1-oxo-2,3-dihydro-1H-indene-2-carboxylate 134. Synthesized following the general procedure for α -Esterification (257 mgs, 49% yield). ^1H NMR (400 MHz, CDCl_3) δ 7.81 – 7.74 (m, 1H). **Mixture of tautomers:** ^1H NMR (400 MHz, CDCl_3) δ 7.81 – 7.74 (m, 2H), 7.61 (dtd, J = 16.6, 7.4, 1.3 Hz, 2H), 7.49 (ddt, J = 9.8, 7.7, 1.0 Hz, 2H), 7.45 – 7.29 (m, 4H), 3.81 (d, J = 10.9 Hz, 5H), 3.74 (dd, J = 8.3, 4.1 Hz, 1H), 3.57 (dd, J = 17.3, 4.1 Hz, 1H), 3.38 (dd, J = 17.2, 8.3 Hz, 1H), 3.24 – 3.12 (m, 2H), 3.04 (ddd, J = 16.1, 8.2, 3.5 Hz, 1H), 2.88 (ddd, J = 14.2, 8.2, 7.5 Hz, 1H), 2.77 (ddd, J = 14.3, 7.6, 3.5 Hz, 1H), 2.72 – 2.66 (m, 1H).

methyl 2-methyl-3-oxo-3-phenylpropanoate 135. Propiophenone (530 μL , 4.0 mmol, 1.0 eq) was dissolved in Toluene:dimethylcarbonate (5:1, 0.08M, 48 mL) at 23 $^\circ\text{C}$, then cooled to 0 $^\circ\text{C}$. NaH (60% in mineral oil, 1.6 g, 40.0 mmol 10.0 eq) was added in 5 portions, then the suspension was stirred at 0 $^\circ\text{C}$ for 10 minues, then heated to reflux overnight. After 16 h, the reaction was cooled to 0 $^\circ\text{C}$, acidified slowly with 1 M HCl, and the phases were separated. The aqueous phase was extracted with EtOAc (3 x 25 mL). The combined organic layer was dried over Na_2SO_4 , filtered, and evaporated *in vacuo*. The crude material was then purified by flash column chromatography (silica gel, Hex:EtOAc = 3:1) to afford the desired β -ketoester as a colorless oil (713 mgs, 93% yield). ^1H NMR (500 MHz, CDCl_3) δ 8.02 – 7.95 (m, 2H), 7.62 – 7.56 (m, 1H), 7.52 – 7.46 (m, 2H), 4.41 (q, J = 7.1 Hz, 1H), 3.69 (s, 3H), 1.50 (d, J = 7.1 Hz, 3H).

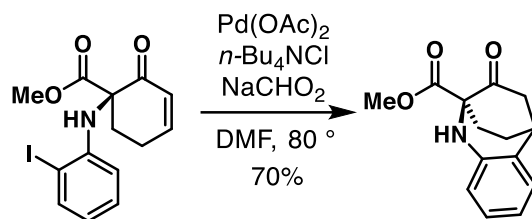
1.6.4 Divergent Scaffold Syntheses & Procedures



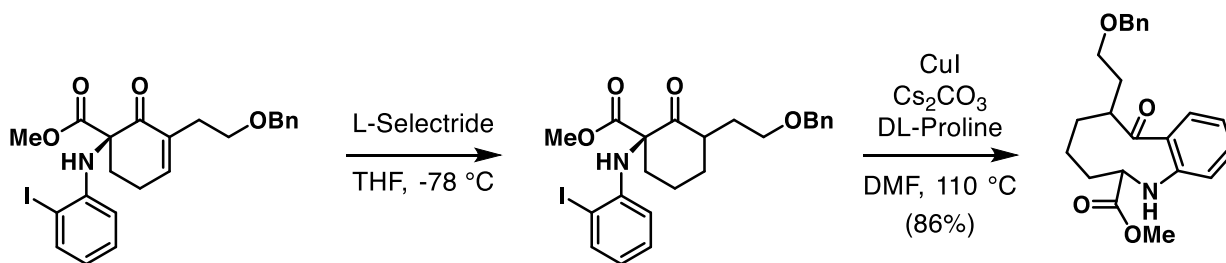
Spirocycle 140. To a flame-dried round bottom flask was added solution of α -aminated β -ketoester (37.1 mg, 0.10 mmol, 1.0 equiv) in Et_2O (1.0 mL) at $23\text{ }^\circ\text{C}$. The solution was then cooled to $-45\text{ }^\circ\text{C}$ and $t\text{-BuLi}$ (0.37 mL, 1.7 M in pentane, 0.22 mmol, 2.2 equiv) was added dropwise. The reaction was then stirred at this temperature for 2 h. Upon completion, the reaction contents were quenched by the addition of saturated aqueous NH_4Cl (3 mL) and warmed to $23\text{ }^\circ\text{C}$. The phases were poured into a separatory funnel and separated, and the aqueous phase extracted with Et_2O ($3 \times 5\text{ mL}$). The combined organic layers were then washed with brine (10 mL), dried (Na_2SO_4), filtered, and evaporated. The resultant crude material was purified by flash column chromatography (silica gel, $\text{EtOAc}/\text{hexane} = 3:1$) to give spirocycle **140** (12.5 mg, 0.046 mmol, 46% yield) as a yellow oil. **120**: $R_f = 0.37$ (silica gel, $\text{EtOAc}/\text{hexanes}$, 3:7); IR (film) ν_{max} 3356, 2961, 2855, 1691, 1618, 1485, 1470, 752 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.53 (d, $J = 7.8\text{ Hz}$, 1 H), 7.47 (t, $J = 7.7\text{ Hz}$, 1 H), 6.98 (d, $J = 8.1\text{ Hz}$, 1 H), 6.88 (t, $J = 7.3\text{ Hz}$, 1 H), 2.98 (t, $J = 12.7\text{ Hz}$, 1 H), 2.55 (dd, $J = 12.2, 2.8\text{ Hz}$, 1 H), 2.51–2.39 (m, 1 H), 2.28 (d, $J = 13.5\text{ Hz}$, 1 H), 1.91 (td, $J = 13.5, 4.3\text{ Hz}$, 1 H), 1.76 (d, $J = 14.0\text{ Hz}$, 1 H), 1.61 (t, $J = 13.0\text{ Hz}$, 2 H), 0.98 (d, $J = 1.7\text{ Hz}$, 10 H); ^{13}C NMR (101 MHz, CDCl_3) δ 205.17, 196.93, 161.60, 137.42, 124.89, 120.54, 120.42, 114.00, 50.54, 40.09, 38.05, 33.14, 29.71, 27.35, 21.06; HRMS (ESI) calcd for $\text{C}_{17}\text{H}_{22}\text{NO}_2^+ [\text{M} + \text{Na}^+]$ 272.1645, found 272.1590.



Bicyclic enone 136. To a flame-dried flask at $23\text{ }^\circ\text{C}$ containing $\text{Pd}(\text{OAc})_2$ (9.0 mg, 0.040 mmol, 0.4 equiv), Ph_3P (20.9 mg, 0.080 mmol, 0.8 equiv) and K_2CO_3 (27.6 mg, 0.20 mmol, 2.0 equiv) under an argon atmosphere was added a solution of α -aminated β -ketoester (37.1 mg, 0.10 mmol, 1.0 equiv) in DMF (1.0 mL).⁴ The resultant mixture was then warmed to $110\text{ }^\circ\text{C}$ and stirred at that temperature for 1.5 h. Upon completion, the reaction contents were then cooled to $23\text{ }^\circ\text{C}$ and quenched with saturated aqueous NaHCO_3 (10 mL). The mixture was poured into a separatory funnel and the layers were separated. The aqueous layer was extracted with EtOAc ($3 \times 10\text{ mL}$), and the combined organic layers were dried (Na_2SO_4), filtered, and evaporated. The resultant crude material was purified by flash column chromatography (silica gel, EtOAc /hexanes, 1:3) to give bicyclic enone **136** (21.2 mg, 0.087 mmol, 87% yield) as a yellow oil. **136**: $R_f = 0.29$ (silica gel, EtOAc /hexanes, 1:3); IR (film) ν_{max} 3382, 2922, 2850, 2360, 1743, 1674, 1489, 749 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.20–7.03 (m, 3 H), 6.75–6.66 (m, 2 H), 6.14 (d, $J = 9.9\text{ Hz}$, 1H), 5.31 (d, $J = 12.4\text{ Hz}$, 1 H), 3.89 (s, 3 H), 3.66 (dt, $J = 6.5, 3.1\text{ Hz}$, 1 H), 2.78–2.70 (m, 1 H), 1.96 (dt, $J = 12.7, 2.3\text{ Hz}$, 1 H); ^{13}C NMR (101 MHz, CDCl_3) δ 190.25, 170.92, 151.25, 139.95, 128.79, 127.55, 126.74, 117.79, 117.38, 114.68, 63.58, 53.08, 34.31, 28.76;



Bicyclic β -ketoester 139. To a flame-dried flask at 23 °C containing Pd(OAc)₂ (9.0 mg, 0.040 mmol, 0.4 equiv), *n*-Bu₄NCl (55.6 mg, 0.20 mmol, 2.0 equiv), sodium formate (813.6 mg, 0.20 mmol, 2.0 equiv) and α -aminated β -ketoester (37.1 mg, 0.10 mmol, 1.0 equiv) was added anhydrous DMF (1.0 mL). The resultant mixture was then warmed to 80 °C and stirred at that temperature for 1 h. Upon completion, the reaction contents were then cooled to 23 °C and quenched with saturated aqueous NaHCO₃ (10 mL). The mixture was poured into a separatory funnel and the layers were separated. The aqueous layer was extracted with Et₂O (3 $\times$ 10 mL), and the combined organic layers were dried (Na₂SO₄), filtered, and evaporated. The resultant crude material was purified by flash column chromatography (silica gel, EtOAc/hexanes = 1:3) to give bicyclic β -ketoester **139** (17.1 mg, 0.07 mmol, 70% yield) as a yellow oil. **139**: R_f = 0.34 (silica gel, EtOAc/hexanes, 3:1); IR (film) $\nu_{\max}$ 3372, 3052, 3014, 2954, 2925, 2852, 1742, 1722, 1604, 1583, 1480, 1441, 1272, 750 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 6.97 (td, J = 7.7, 1.6 Hz, 1 H), 6.86 (dd, J = 7.7, 1.6 Hz, 1 H), 6.62–6.53 (m, 2 H), 5.25–5.20 (m, 1 H), 3.79 (s, 3 H), 2.99 (tt, J = 5.0, 2.5 Hz, 1 H), 2.91–2.81 (m, 2 H), 2.65 (ddd, J = 14.5, 10.5, 5.4 Hz, 1 H), 2.39 (ddd, J = 14.7, 9.6, 5.6 Hz, 1 H), 2.17 (dddt, J = 13.8, 9.5, 4.6, 2.0 Hz, 1 H), 2.05 (ddt, J = 13.8, 10.6, 5.4 Hz, 1 H); ¹³C NMR (101 MHz, CDCl₃) δ 190.25, 170.92, 151.25, 139.95, 128.79, 127.55, 126.74, 117.79, 117.38, 114.68, 63.58, 53.08, 34.31, 28.76; HRMS (ESI) calcd for C₁₄H₁₆NO₃⁺ [M + H ⁺] 246.1125, found 246.1124.



Macrocycle 137. To a flame-dried round bottom flask at 23 °C was added a solution of **XX** (23.5 mg, 0.063 mmol, 1.0 equiv) in anhydrous THF (0.67 mL). The resultant solution was then cooled to -78 °C and L-Selectride (0.084 mL, 1.0 M in THF, 0.084 mmol, 1.25 equiv) was added dropwise. The reaction contents were then stirred at this temperature for 2 h before being quenched with saturated aqueous NH₄Cl (1 mL) and being warmed to 23 °C. The contents were poured into a separatory funnel, the phases were separated, and the aqueous phase extracted with EtOAc (3 × 5 mL). The combined organic layers were then washed with brine (5 mL), dried (Na₂SO₄), filtered, and evaporated. The resultant crude material was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:5) to give the desired conjugate reduction product **141** (232 mg, 93% yield) as a white crystalline solid. ¹H NMR (400 MHz, CDCl₃) δ 7.68 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.56 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.49 – 7.44 (m, 1H), 7.36 – 7.29 (m, 4H), 7.11 (td, *J* = 7.8, 7.1, 1.5 Hz, 1H), 6.63 (dd, *J* = 8.2, 1.4 Hz, 1H), 6.44 (td, *J* = 7.5, 1.4 Hz, 1H), 6.27 (s, 1H), 4.80 (s, 1H), 4.51 – 4.40 (m, 2H), 3.58 (s, 3H), 3.45 (q, *J* = 7.3 Hz, 4H), 2.74 (ddt, *J* = 13.0, 7.7, 5.2 Hz, 1H), 2.28 – 2.03 (m, 4H), 1.79 (ddd, *J* = 14.3, 5.3, 3.3 Hz, 1H), 1.64 – 1.54 (m, 1H).

Pressing forward, to a round bottom flask charged with **141** (10.0 mg, 0.027 mmol, 1.0 equiv) was added CuI (2.5 mg, 0.013 mmol, 0.5 equiv), Cs₂CO₃ (8.8 mg, 0.027 mmol, 1.0 equiv), and DL-Proline (1.5 mg, 0.013 mmol, 0.5 equiv). The flask was then evacuated under reduced pressure, and backfilled with argon. The solids were then dissolved in DMSO (0.5 mL) and heated at 50 °C for 12 h. Upon completion, the reaction mixture was cooled to 23 °C, quenched with

saturated NH_4Cl (10 mL), and extracted with CHCl_3 (3×10 mL). The combined organic layers were then washed with 5% aqueous LiCl (3×10 mL), dried (Na_2SO_4), filtered, and evaporated to give macrocycle **137** (19.1 mgs, 50% yield) as a yellow oil: ^1H NMR (400 MHz, CDCl_3) δ 7.66 (dd, $J = 8.1, 1.5$ Hz, 1H), 7.37 – 7.26 (m, 5H), 7.17 (ddd, $J = 8.4, 7.4, 1.5$ Hz, 1H), 6.47 (ddd, $J = 7.0, 3.8, 2.3$ Hz, 2H), 4.59 (s, 1H), 4.48 (d, $J = 1.5$ Hz, 2H), 4.07 (t, $J = 6.5$ Hz, 1H), 3.72 (s, 3H), 3.56 – 3.46 (m, 2H), 2.58 (dq, $J = 9.5, 5.6, 5.0$ Hz, 1H), 2.03 – 1.64 (m, 6H), 1.51 (pd, $J = 8.4, 7.7, 4.5$ Hz, 4H).

1.6.5 SXR data of Select Intermediates

Crystallographic Experimental Section

Crystal growth of C₃₁H₃₄N₂O₂: Russell Kielawa (prof. Scott Snyder's group).

Data collected/reported: Sophie Whitmeyer /Alexander S. Filatov, March / 2022 (X-ray Laboratory, Searle B013, Department of Chemistry, the University of Chicago, Chicago, IL).

General information: The diffraction data were measured at 100 K on a Bruker D8 VENTURE diffractometer equipped with a microfocus Mo-target X-ray tube ($\lambda = 0.71073 \text{ \AA}$) and PHOTON 100 CMOS detector. Data were collected using ω scans to survey a hemisphere of reciprocal space. Data reduction and integration were performed with the Bruker APEX4 software package (Bruker AXS, version 2021.4-0, 2021). Data were scaled and corrected for absorption effects using the multi-scan procedure as implemented in SADABS (Bruker AXS, version 2014/5, Krause, Herbst-Irmer, Sheldrick & Stalke, *J. Appl. Cryst.* **2015**, 48, 3-10). The structure was solved by SHELXT (Version 2018/2: Sheldrick, G. M. *Acta Crystallogr.* **2015**, A71, 3-8) and refined by a full-matrix least-squares procedure using OLEX2 (O. V. Dolomanov, L. J. Bourhis, R. J. Gildea, J. A. K. Howard and H. Puschmann. *J. Appl. Crystallogr.* **2009**, 42, 339-341) (XL refinement program version 2018/3, Sheldrick, G. M. *Acta Crystallogr.* **2015**, C71, 3-8). Crystallographic data and details of the data collection and structure refinement are listed in Table 1.

Specific details for structure refinement: All atoms were refined with anisotropic thermal parameters. All hydrogen atoms were included in idealized positions for structure factor calculations. All structures are drawn with thermal ellipsoids at 50% probability.

Table 1 Crystal data and structure refinement for 1129_RK_Snyder1.

Identification code	1129_RK_Snyder1
Empirical formula	C ₃₁ H ₃₄ N ₂ O ₂
Formula weight	466.60
Temperature/K	100(2)
Crystal system	orthorhombic
Space group	P2 ₁ 2 ₁ 2 ₁
a/Å	8.8356(7)
b/Å	13.4970(11)
c/Å	20.7250(18)
α/°	90
β/°	90
γ/°	90
Volume/Å ³	2471.5(4)
Z	4
ρ _{calc} /g/cm ³	1.254
μ/mm ⁻¹	0.078
F(000)	1000.0
Crystal size/mm ³	0.403 × 0.34 × 0.22
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	4.956 to 62.428
Index ranges	-12 ≤ h ≤ 12, -19 ≤ k ≤ 19, -30 ≤ l ≤ 30
Reflections collected	67725
Independent reflections	8007 [R _{int} = 0.0378, R _{sigma} = 0.0203]
Data/restraints/parameters	8007/0/316
Goodness-of-fit on F ²	1.046
Final R indexes [I ≥ 2σ (I)]	R ₁ = 0.0377, wR ₂ = 0.0938
Final R indexes [all data]	R ₁ = 0.0424, wR ₂ = 0.0968
Largest diff. peak/hole / e Å ⁻³	0.36/-0.17

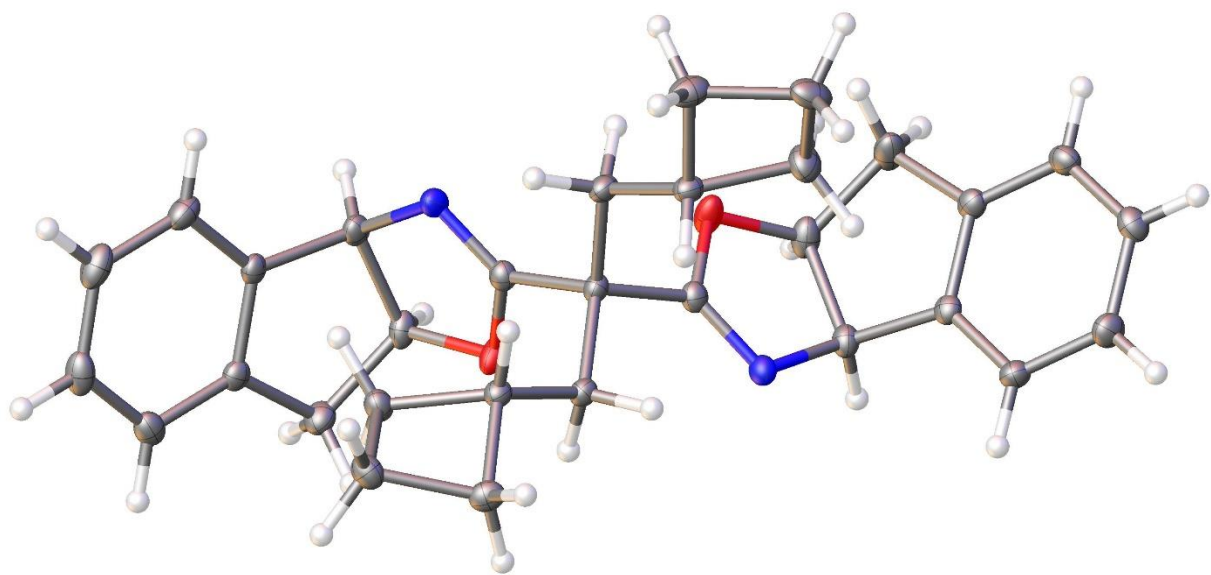
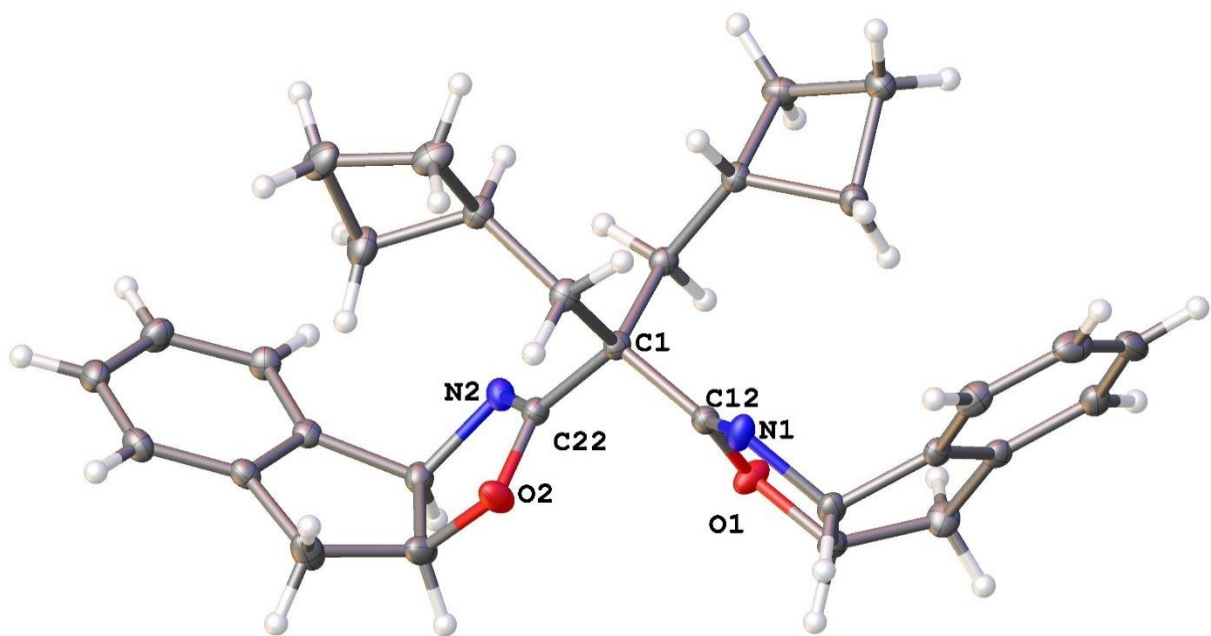
$$R_{\text{int}} = \sum |F_o^2 - \langle F_o^2 \rangle| / \sum |F_o^2|$$

$$R_1 = \sum ||F_o| - |F_c|| / \sum |F_o|$$

$$wR_2 = [\sum [w (F_o^2 - F_c^2)^2] / \sum [w (F_o^2)^2]]^{1/2}$$

$$\text{Goodness-of-fit} = [\sum [w (F_o^2 - F_c^2)^2] / (n-p)]^{1/2}$$

n: number of independent reflections; p: number of refined parameters



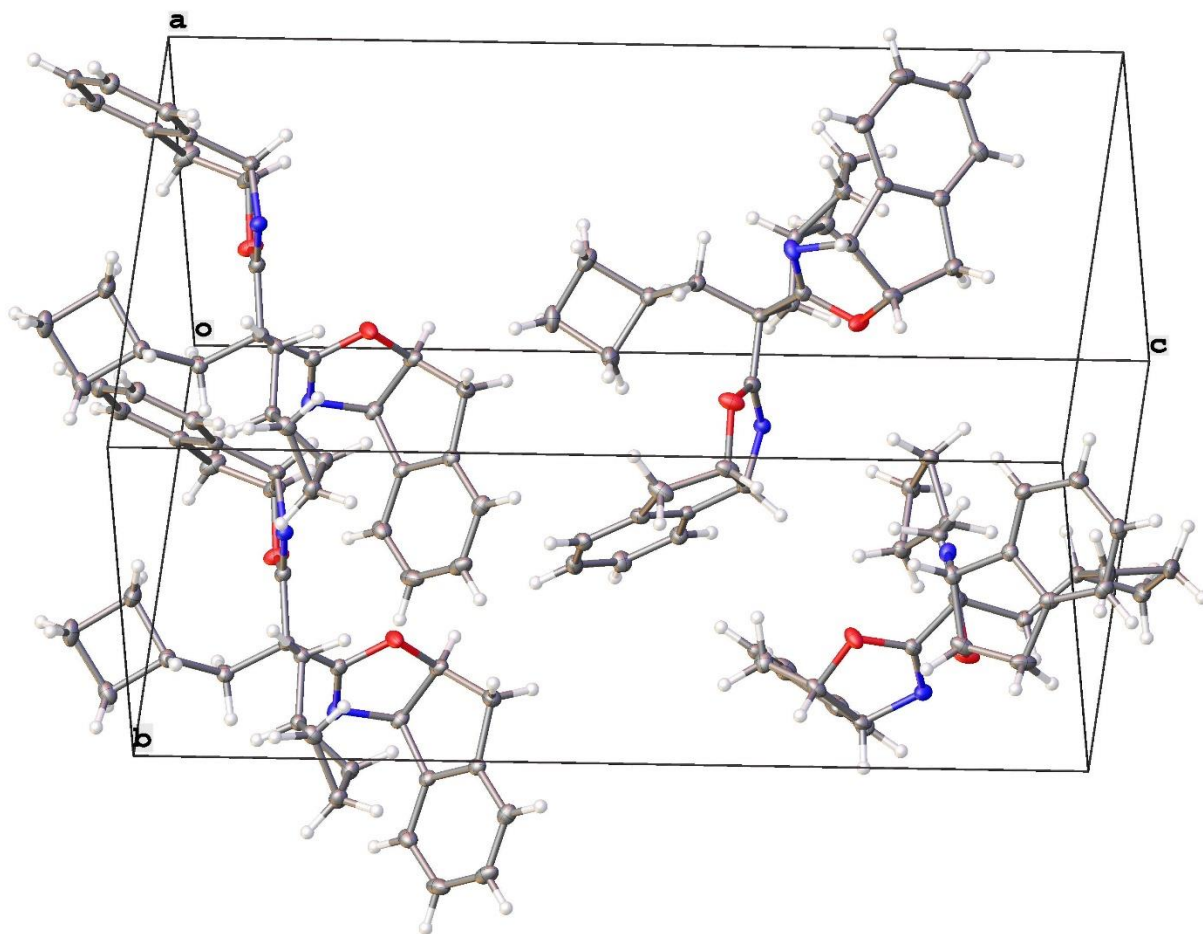


Table 2 Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($\text{\AA}^2 \times 10^3$) for 1129_RK_Snyder1. U_{eq} is defined as 1/3 of the trace of the orthogonalised U_{ij} tensor.

Atom	x	y	z	$U(\text{eq})$
O1	6780.2(12)	4267.4(8)	7413.7(5)	20.2(2)
O2	5718.4(12)	5442.5(8)	6129.0(6)	21.4(2)
N1	8802.2(14)	4039.9(10)	6757.8(6)	17.8(2)
N2	3666.6(14)	4480.2(9)	6332.1(5)	15.9(2)
C1	6217.3(15)	3707.4(10)	6332.0(6)	13.5(2)
C2	7023.7(16)	3546.7(11)	5678.4(6)	16.0(2)
C3	6055.0(16)	3172.9(11)	5124.6(7)	16.4(2)
C4	6912.2(19)	2953.4(13)	4487.8(7)	22.7(3)
C5	5557(2)	3379.5(13)	4113.2(7)	24.9(3)
C6	5029.6(19)	3893.3(13)	4740.6(7)	23.6(3)
C7	5371.0(15)	2776.9(10)	6577.0(7)	14.2(2)
C8	6259.2(15)	1819.3(10)	6578.2(6)	14.4(2)
C9	5410.4(17)	884.6(10)	6806.5(7)	18.2(3)
C10	6932.7(18)	486.4(11)	7061.6(7)	19.5(3)
C11	7467.1(17)	1577.2(11)	7101.5(7)	17.5(3)
C12	7381.2(16)	4014.2(10)	6829.0(6)	14.8(2)
C13	9438.8(16)	4320.1(11)	7394.0(7)	16.6(2)
C14	8041.4(17)	4546.7(11)	7823.7(7)	17.6(3)
C15	8126.6(17)	3882.4(12)	8419.5(7)	19.7(3)
C16	9403.7(15)	3174.2(10)	8276.4(6)	15.0(2)
C17	10178.9(15)	3445.3(10)	7719.9(7)	14.5(2)
C18	11434.1(16)	2913.5(12)	7512.3(7)	20.2(3)
C19	11879.7(18)	2091.2(12)	7870.6(8)	24.1(3)
C20	11081.9(18)	1802.2(11)	8417.9(8)	22.8(3)
C21	9845.4(17)	2348.5(11)	8629.0(7)	18.7(3)
C22	5089.1(16)	4544.1(10)	6272.0(6)	14.8(2)
C23	3061.1(16)	5481.3(11)	6203.4(7)	16.7(2)
C24	4471.5(17)	6145.4(11)	6096.2(8)	20.8(3)
C25	4343.9(19)	6612.7(12)	5425.2(8)	24.2(3)
C26	2927.1(16)	6166.2(10)	5141.0(7)	16.2(2)
C27	2211.8(15)	5540.0(10)	5574.9(6)	14.3(2)
C28	858.4(16)	5069.0(11)	5420.6(7)	17.0(3)
C29	226.0(18)	5253.8(12)	4816.7(7)	20.3(3)
C30	940.2(18)	5885.9(11)	4380.6(7)	19.2(3)
C31	2298.0(17)	6341.1(11)	4537.1(7)	18.3(3)

Table 3 Anisotropic Displacement Parameters ($\text{\AA}^2 \times 10^3$) for 1129_RK_Snyder1. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+\dots]$.

Atom	U ₁₁	U ₂₂	U ₃₃	U ₂₃	U ₁₃	U ₁₂
O1	13.0(5)	27.9(6)	19.8(5)	-9.1(4)	-3.7(4)	3.3(4)
O2	15.2(5)	14.6(5)	34.5(6)	1.9(4)	-7.0(4)	-1.9(4)
N1	14.4(5)	23.5(6)	15.5(5)	3.7(4)	-3.0(4)	-4.1(5)
N2	15.0(5)	17.2(5)	15.6(5)	1.4(4)	-0.1(4)	2.6(4)
C1	10.9(5)	15.1(6)	14.5(5)	-0.5(4)	-1.3(4)	0.7(5)
C2	12.2(6)	19.9(6)	15.9(5)	0.1(5)	0.9(5)	-0.8(5)
C3	14.4(6)	19.8(6)	15.0(5)	0.1(5)	1.2(5)	-1.5(5)
C4	20.7(7)	28.1(7)	19.3(6)	-5.5(6)	4.6(5)	-4.4(6)
C5	30.8(8)	29.5(8)	14.3(6)	1.5(5)	0.8(6)	-9.0(7)
C6	24.7(7)	29.6(8)	16.5(6)	0.6(6)	-2.8(5)	3.1(6)
C7	12.0(5)	15.0(6)	15.5(5)	-0.6(4)	-0.3(4)	-0.8(4)
C8	13.2(5)	16.3(6)	13.6(5)	-0.1(4)	0.3(4)	0.1(5)
C9	18.3(6)	15.2(6)	21.0(6)	-2.2(5)	2.1(5)	-2.5(5)
C10	24.3(7)	15.9(6)	18.3(6)	1.0(5)	-1.7(5)	0.6(6)
C11	18.1(6)	17.4(6)	17.0(6)	2.2(5)	-2.9(5)	-0.9(5)
C12	15.0(6)	13.4(6)	16.0(5)	0.6(4)	-2.0(5)	0.1(5)
C13	13.7(6)	17.7(6)	18.3(6)	1.7(5)	-4.1(5)	-3.1(5)
C14	16.2(6)	16.2(6)	20.4(6)	-3.7(5)	-6.2(5)	2.0(5)
C15	16.8(6)	23.6(7)	18.7(6)	-1.3(5)	1.4(5)	3.7(5)
C16	12.8(5)	15.3(6)	16.9(6)	-1.6(4)	-2.6(5)	-1.7(5)
C17	11.5(5)	15.5(6)	16.4(6)	-0.6(4)	-3.6(4)	-0.9(5)
C18	13.4(6)	26.5(7)	20.7(6)	-4.5(5)	0.3(5)	0.3(5)
C19	17.7(7)	22.3(7)	32.3(8)	-9.2(6)	-4.7(6)	5.1(6)
C20	23.8(7)	13.8(6)	30.7(7)	-1.0(6)	-9.9(6)	1.8(5)
C21	19.9(6)	16.6(6)	19.7(6)	1.6(5)	-4.5(5)	-4.4(5)
C22	15.4(6)	14.4(6)	14.7(5)	-0.6(4)	-2.6(4)	0.4(5)
C23	16.1(6)	17.4(6)	16.6(5)	-0.4(5)	-2.0(5)	3.2(5)
C24	19.6(6)	14.8(6)	28.0(7)	-2.1(5)	-7.9(6)	1.0(5)
C25	18.7(7)	19.3(7)	34.6(8)	7.7(6)	-7.3(6)	-5.1(6)
C26	14.9(6)	13.0(6)	20.7(6)	1.7(5)	-0.1(5)	0.9(5)
C27	13.3(6)	14.2(6)	15.2(5)	-1.2(4)	0.6(4)	2.9(5)
C28	14.5(6)	18.6(6)	17.8(6)	1.4(5)	1.3(5)	-1.6(5)
C29	18.0(7)	22.3(7)	20.7(6)	-0.8(5)	-3.5(5)	-3.5(5)
C30	23.4(7)	18.5(6)	15.5(6)	-0.1(5)	-1.8(5)	1.7(5)
C31	19.6(7)	16.0(6)	19.4(6)	3.9(5)	1.9(5)	1.4(5)

Table 4 Bond Lengths for 1129_RK_Snyder1.

Atom	Atom	Length/Å	Atom	Atom	Length/Å
O1	C12	1.3663(16)	C10	C11	1.548(2)
O1	C14	1.4512(17)	C13	C14	1.553(2)
O2	C22	1.3664(17)	C13	C17	1.5094(19)
O2	C24	1.4554(18)	C14	C15	1.528(2)
N1	C12	1.2647(18)	C15	C16	1.508(2)
N1	C13	1.4826(18)	C16	C17	1.3903(19)
N2	C22	1.2659(18)	C16	C21	1.389(2)
N2	C23	1.4775(18)	C17	C18	1.389(2)
C1	C2	1.5458(18)	C18	C19	1.392(2)
C1	C7	1.5473(18)	C19	C20	1.391(2)
C1	C12	1.5133(18)	C20	C21	1.389(2)
C1	C22	1.5115(19)	C23	C24	1.551(2)
C2	C3	1.5181(19)	C23	C27	1.5053(19)
C3	C4	1.550(2)	C24	C25	1.531(2)
C3	C6	1.549(2)	C25	C26	1.509(2)
C4	C5	1.538(2)	C26	C27	1.3866(19)
C5	C6	1.546(2)	C26	C31	1.390(2)
C7	C8	1.5120(18)	C27	C28	1.3915(19)
C8	C9	1.5421(19)	C28	C29	1.393(2)
C8	C11	1.5563(19)	C29	C30	1.394(2)
C9	C10	1.542(2)	C30	C31	1.386(2)

Table 5 Bond Angles for 1129_RK_Snyder1.

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
C12	O1	C14	106.61(11)	C15	C14	C13	107.99(11)
C22	O2	C24	106.29(11)	C16	C15	C14	104.47(12)
C12	N1	C13	106.25(12)	C17	C16	C15	111.40(12)
C22	N2	C23	106.22(12)	C21	C16	C15	127.98(13)
C2	C1	C7	113.36(11)	C21	C16	C17	120.61(13)
C12	C1	C2	108.77(11)	C16	C17	C13	111.32(12)
C12	C1	C7	109.09(11)	C18	C17	C13	127.68(13)
C22	C1	C2	109.68(11)	C18	C17	C16	120.95(13)
C22	C1	C7	108.34(11)	C17	C18	C19	118.19(14)
C22	C1	C12	107.44(11)	C20	C19	C18	121.00(14)
C3	C2	C1	116.70(11)	C21	C20	C19	120.43(14)
C2	C3	C4	115.58(12)	C16	C21	C20	118.78(14)
C2	C3	C6	120.64(13)	O2	C22	C1	114.36(11)

Table 5 Bond Angles for 1129_RK_Snyder1.

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
C6	C3	C4	88.18(11)	N2	C22	O2	119.06(13)
C5	C4	C3	88.74(12)	N2	C22	C1	126.57(13)
C4	C5	C6	88.74(11)	N2	C23	C24	105.27(11)
C5	C6	C3	88.52(12)	N2	C23	C27	112.64(11)
C8	C7	C1	116.33(11)	C27	C23	C24	104.25(11)
C7	C8	C9	116.58(11)	O2	C24	C23	102.99(11)
C7	C8	C11	122.45(11)	O2	C24	C25	111.51(13)
C9	C8	C11	87.01(10)	C25	C24	C23	108.00(12)
C10	C9	C8	88.06(11)	C26	C25	C24	104.54(12)
C9	C10	C11	87.30(11)	C27	C26	C25	111.61(12)
C10	C11	C8	87.33(10)	C27	C26	C31	120.36(13)
O1	C12	C1	114.08(11)	C31	C26	C25	127.99(13)
N1	C12	O1	118.85(12)	C26	C27	C23	111.47(12)
N1	C12	C1	127.06(13)	C26	C27	C28	121.41(13)
N1	C13	C14	104.99(11)	C28	C27	C23	127.10(13)
N1	C13	C17	111.27(12)	C27	C28	C29	117.99(13)
C17	C13	C14	104.00(11)	C28	C29	C30	120.70(14)
O1	C14	C13	102.92(10)	C31	C30	C29	120.75(13)
O1	C14	C15	111.02(12)	C30	C31	C26	118.79(13)

Table 6 Torsion Angles for 1129_RK_Snyder1.

A	B	C	D	Angle/°	A	B	C	D	Angle/°
O1	C14	C15	C16	103.11(13)	C14	O1	C12	N1	1.65(18)
O2	C24	C25	C26	109.04(14)	C14	O1	C12	C1	-179.49(11)
N1	C13	C14	O1	6.09(14)	C14	C13	C17	C16	-1.38(15)
N1	C13	C14	C15	123.56(12)	C14	C13	C17	C18	176.27(14)
N1	C13	C17	C16	-113.91(13)	C14	C15	C16	C17	8.46(16)
N1	C13	C17	C18	63.75(18)	C14	C15	C16	C21	-172.31(14)
N2	C23	C24	O2	3.91(14)	C15	C16	C17	C13	-4.52(16)
N2	C23	C24	C25	121.99(12)	C15	C16	C17	C18	177.65(13)
N2	C23	C27	C26	-115.41(13)	C15	C16	C21	C20	-178.75(14)
N2	C23	C27	C28	66.18(18)	C16	C17	C18	C19	1.1(2)
C1	C2	C3	C4	-176.18(12)	C17	C13	C14	O1	-110.91(12)
C1	C2	C3	C6	79.77(17)	C17	C13	C14	C15	6.57(15)
C1	C7	C8	C9	-178.59(11)	C17	C16	C21	C20	0.4(2)
C1	C7	C8	C11	76.99(16)	C17	C18	C19	C20	0.7(2)
C2	C1	C7	C8	49.58(15)	C18	C19	C20	C21	-1.9(2)

Table 6 Torsion Angles for 1129_RK_Snyder1.

A	B	C	D	Angle/°	A	B	C	D	Angle/°
C2	C1	C12	O1	174.22(11)	C19	C20	C21	C16	1.3(2)
C2	C1	C12	N1	-7.0(2)	C21	C16	C17	C13	176.19(12)
C2	C1	C22	O2	-62.80(14)	C21	C16	C17	C18	-1.6(2)
C2	C1	C22	N2	116.18(15)	C22	O2	C24	C23	-3.18(14)
C2	C3	C4	C5	-141.48(13)	C22	O2	C24	C25	-118.76(13)
C2	C3	C6	C5	136.92(13)	C22	N2	C23	C24	-3.28(15)
C3	C4	C5	C6	18.14(12)	C22	N2	C23	C27	109.69(13)
C4	C3	C6	C5	18.02(12)	C22	C1	C2	C3	-66.38(15)
C4	C5	C6	C3	-18.16(12)	C22	C1	C7	C8	171.56(11)
C6	C3	C4	C5	-18.11(12)	C22	C1	C12	O1	55.56(15)
C7	C1	C2	C3	54.85(16)	C22	C1	C12	N1	-125.68(15)
C7	C1	C12	O1	-61.68(15)	C23	N2	C22	O2	1.37(17)
C7	C1	C12	N1	117.08(16)	C23	N2	C22	C1	-177.57(12)
C7	C1	C22	O2	172.99(11)	C23	C24	C25	C26	-3.42(16)
C7	C1	C22	N2	-8.03(19)	C23	C27	C28	C29	177.50(14)
C7	C8	C9	C10	-149.03(12)	C24	O2	C22	N2	1.33(17)
C7	C8	C11	C10	143.71(13)	C24	O2	C22	C1	-179.61(11)
C8	C9	C10	C11	24.08(10)	C24	C23	C27	C26	-1.81(16)
C9	C8	C11	C10	23.86(10)	C24	C23	C27	C28	179.78(13)
C9	C10	C11	C8	-23.86(10)	C24	C25	C26	C27	2.40(17)
C11	C8	C9	C10	-23.95(10)	C24	C25	C26	C31	-179.87(14)
C12	O1	C14	C13	-4.76(14)	C25	C26	C27	C23	-0.36(17)
C12	O1	C14	C15	-120.07(13)	C25	C26	C27	C28	178.15(13)
C12	N1	C13	C14	-5.35(15)	C25	C26	C31	C30	-176.98(15)
C12	N1	C13	C17	106.55(14)	C26	C27	C28	C29	-0.8(2)
C12	C1	C2	C3	176.38(12)	C27	C23	C24	O2	-114.85(12)
C12	C1	C7	C8	-71.77(14)	C27	C23	C24	C25	3.23(16)
C12	C1	C22	O2	55.26(14)	C27	C26	C31	C30	0.6(2)
C12	C1	C22	N2	-125.76(15)	C27	C28	C29	C30	0.5(2)
C13	N1	C12	O1	2.57(18)	C28	C29	C30	C31	0.3(2)
C13	N1	C12	C1	-176.14(13)	C29	C30	C31	C26	-0.8(2)
C13	C14	C15	C16	-9.00(15)	C31	C26	C27	C23	-178.30(13)
C13	C17	C18	C19	-176.37(14)	C31	C26	C27	C28	0.2(2)

Crystallographic Experimental Section

Crystal growth of C₁₄H₁₆INO₃: Russell Kielawa (prof. Scott Snyder's group).

Data collected/reported: Sophie Whitmeyer /Alexander S. Filatov, March / 2023 (X-ray Laboratory, Searle B013, Department of Chemistry, the University of Chicago, Chicago, Il).

General information: The diffraction data were measured at 100 K on a Bruker D8 VENTURE diffractometer equipped with a microfocus Mo-target X-ray tube ($\lambda = 0.71073 \text{ \AA}$) and PHOTON 100 CMOS detector. Data were collected using ω scans to survey a hemisphere of reciprocal space. Data reduction and integration were performed with the Bruker APEX4 software package (Bruker AXS, version 2021.4-0, 2021). Data were scaled and corrected for absorption effects using the multi-scan procedure as implemented in SADABS (Bruker AXS, version 2016/2, Krause, Herbst-Irmer, Sheldrick & Stalke, *J. Appl. Cryst.* **2015**, *48*, 3-10). The structure was solved by SHELXT (Version 2018/2: Sheldrick, G. M. *Acta Crystallogr.* **2015**, *A71*, 3-8) and refined by a full-matrix least-squares procedure using OLEX2 (O. V. Dolomanov, L. J. Bourhis, R. J. Gildea, J. A. K. Howard and H. Puschmann. *J. Appl. Crystallogr.* **2009**, *42*, 339-341) (XL refinement program version 2018/3, Sheldrick, G. M. *Acta Crystallogr.* **2015**, *C71*, 3-8). Crystallographic data and details of the data collection and structure refinement are listed in Table 1.

Specific details for structure refinement: All atoms were refined with anisotropic thermal parameters. All hydrogen atoms were included in idealized positions for structure factor calculations except that of NH group which was identified in the difference Fourier map and refined independently. The absolute structure is reliably identified. All structures are drawn with thermal ellipsoids at 50% probability.

Table 1 Crystal data and structure refinement for 1264_rkielawa_snyder.

Identification code	1264_rkielawa_snyder
Empirical formula	C ₁₄ H ₁₆ INO ₃
Formula weight	373.18
Temperature/K	100(2)
Crystal system	orthorhombic
Space group	P2 ₁ 2 ₁ 2 ₁
a/Å	7.8894(5)
b/Å	11.3478(7)
c/Å	15.5723(9)
α/°	90
β/°	90
γ/°	90
Volume/Å ³	1394.15(15)
Z	4
ρ _{calc} /g/cm ³	1.778
μ/mm ⁻¹	2.300
F(000)	736.0
Crystal size/mm ³	0.3 × 0.214 × 0.15
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	4.442 to 74.308
Index ranges	-13 ≤ h ≤ 13, -19 ≤ k ≤ 19, -26 ≤ l ≤ 26
Reflections collected	233214
Independent reflections	7177 [R _{int} = 0.0391, R _{sigma} = 0.0124]
Data/restraints/parameters	7177/0/177
Goodness-of-fit on F ²	1.101
Final R indexes [I ≥ 2σ (I)]	R ₁ = 0.0156, wR ₂ = 0.0334
Final R indexes [all data]	R ₁ = 0.0177, wR ₂ = 0.0339
Largest diff. peak/hole / e Å ⁻³	0.69/-0.25
Flack parameter	0.006(10)
Hoof parameter	0.003(3)

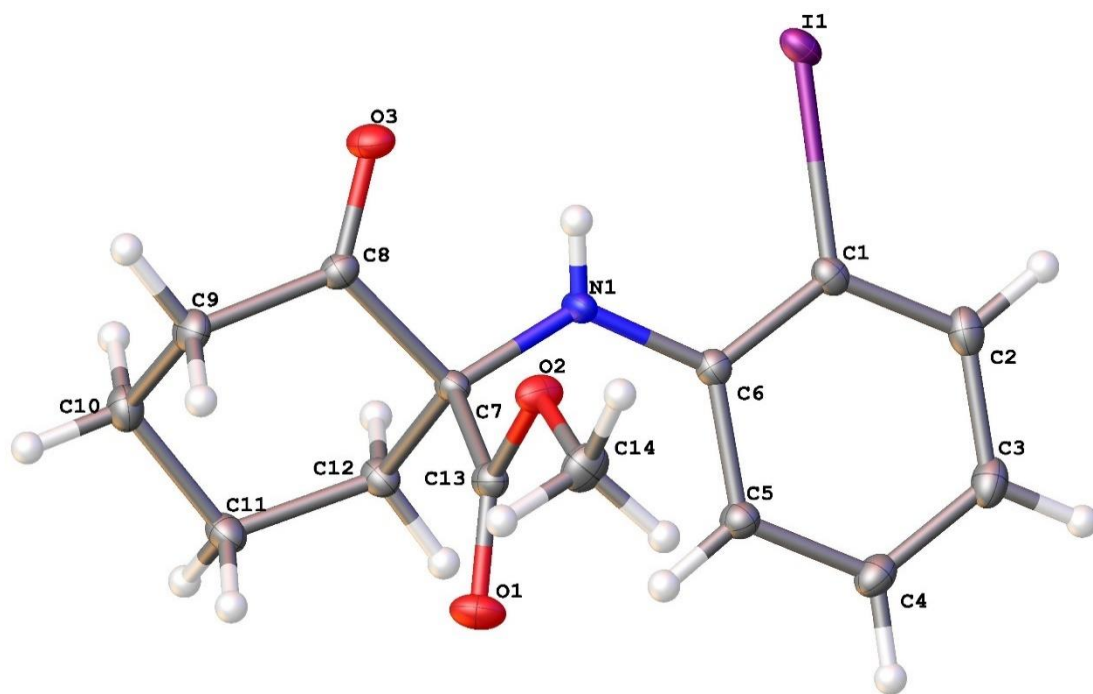
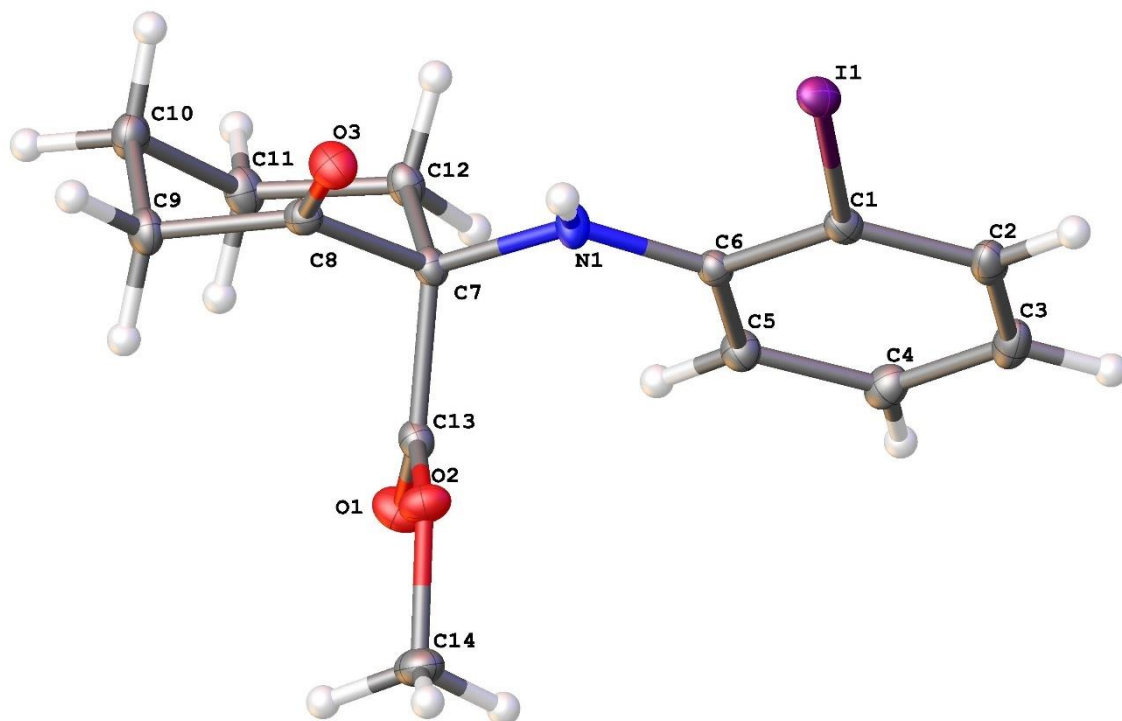
$$R_{\text{int}} = \sum |F_o^2 - \langle F_o^2 \rangle| / \sum |F_o^2|$$

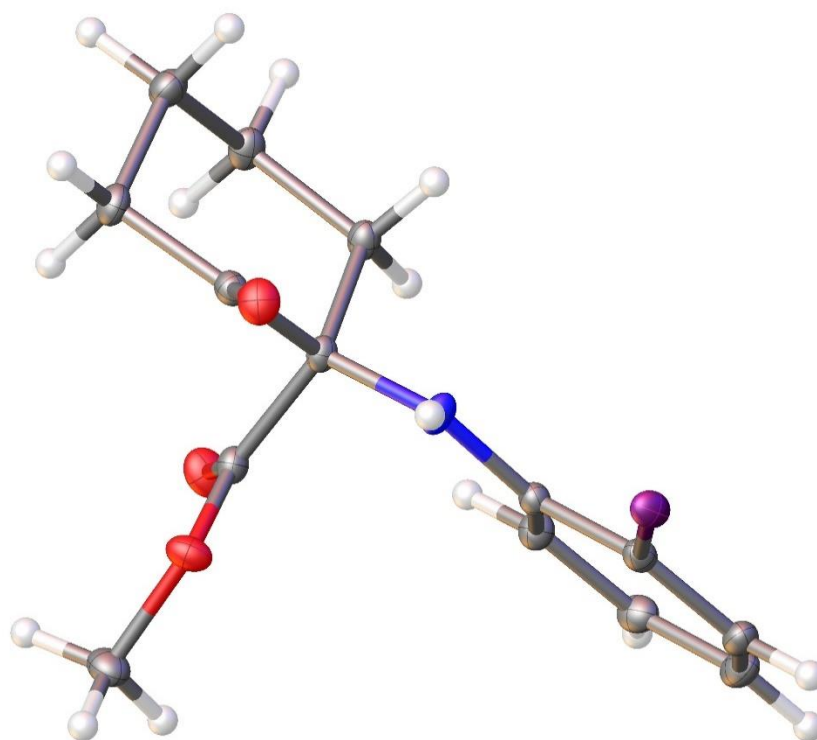
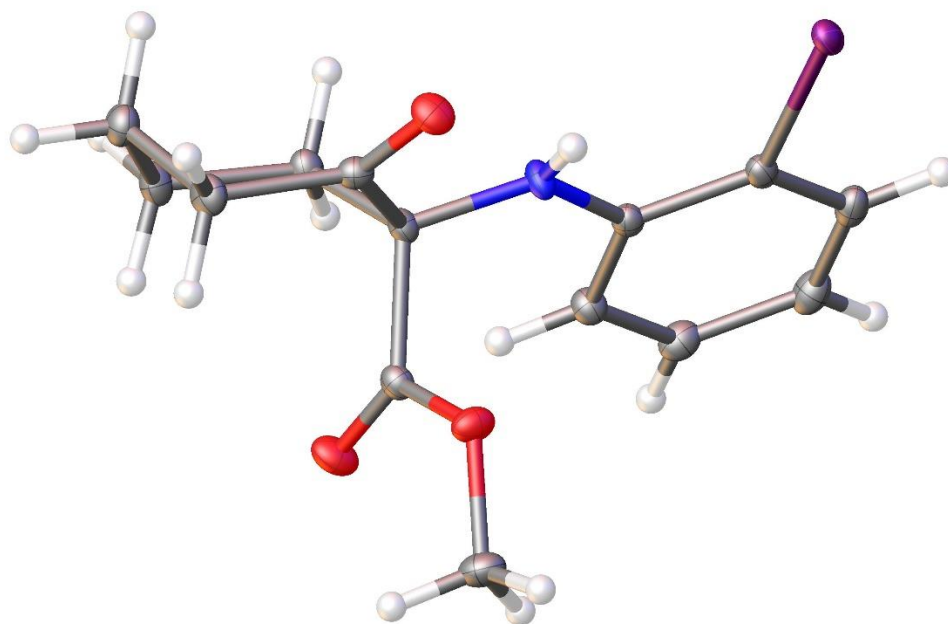
$$R_1 = \sum ||F_o| - |F_c|| / \sum |F_o|$$

$$wR_2 = [\sum [w (F_o^2 - F_c^2)^2] / \sum [w (F_o^2)^2]]^{1/2}$$

$$\text{Goodness-of-fit} = [\sum [w (F_o^2 - F_c^2)^2] / (n-p)]^{1/2}$$

n: number of independent reflections; p: number of refined parameters





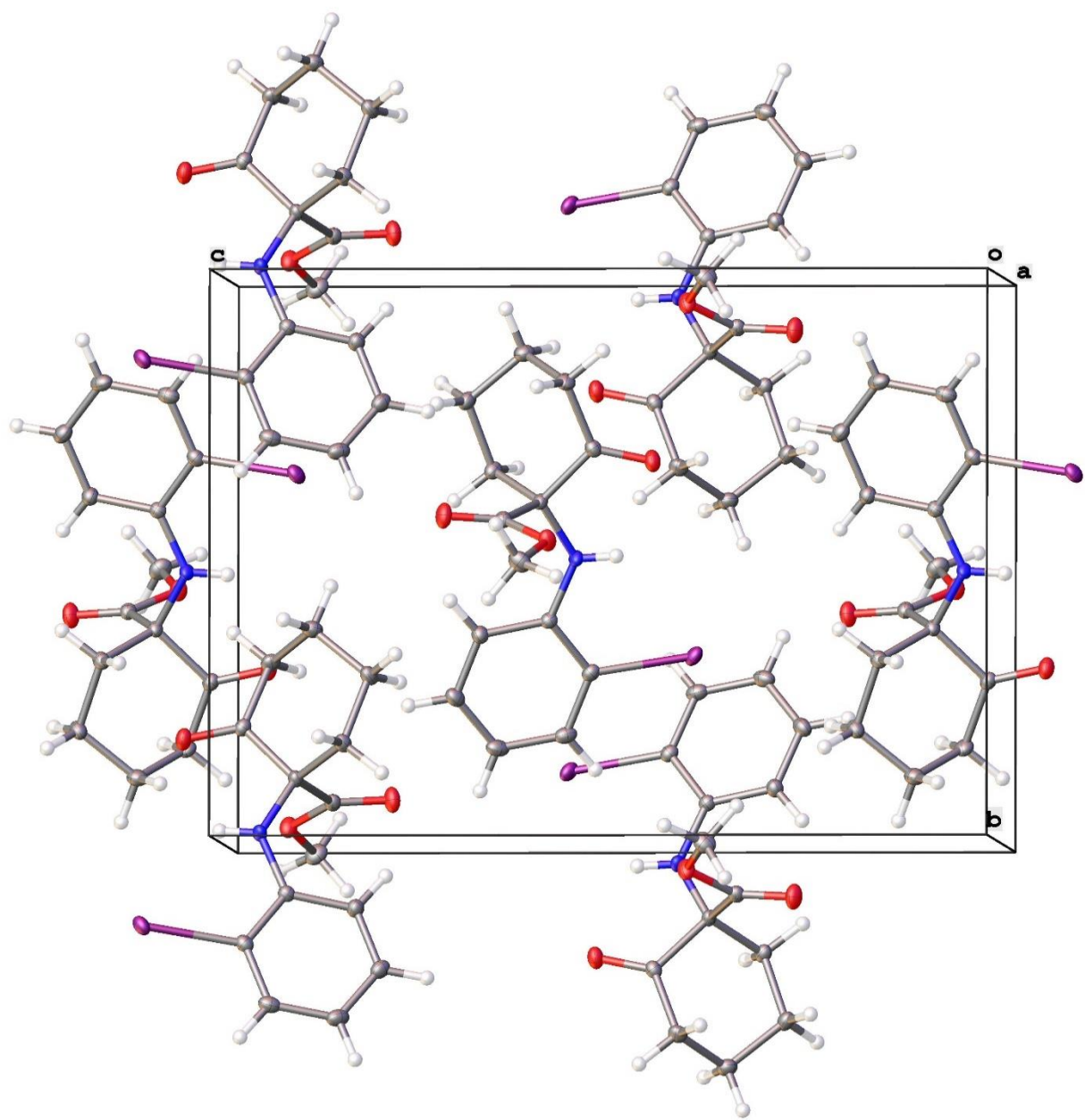


Table 2 Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($\text{\AA}^2 \times 10^3$) for 1264_rkielawa_snyder. U_{eq} is defined as 1/3 of the trace of the orthogonalised U_{ij} tensor.

Atom	x	y	z	U_{eq}
I1	9119.7(2)	6559.5(2)	4103.1(2)	14.93(2)
O1	4756.4(14)	4210.6(11)	7161.7(7)	19.6(2)
O2	4052.5(14)	4671.1(9)	5803.5(6)	16.31(17)
O3	6561.2(14)	3193.3(9)	4546.1(7)	17.41(19)
N1	7587.8(16)	4883.6(10)	5565.0(7)	13.54(18)
C1	8660.1(16)	6866.0(12)	5412.9(9)	12.9(2)
C2	9096.2(19)	7954.8(11)	5751.1(9)	16.4(2)
C3	8856.9(17)	8186.3(12)	6619.6(10)	17.8(2)
C4	8183.9(18)	7309.6(12)	7139.3(9)	16.5(2)
C5	7738.4(17)	6219.0(12)	6803.6(9)	14.2(2)
C6	7963.0(14)	5965.1(10)	5925.5(9)	11.65(18)
C7	6801.1(15)	3901.2(11)	5996.1(8)	11.50(19)
C8	6349.9(16)	2978.8(12)	5300.3(8)	12.5(2)
C9	5720.8(18)	1819.6(11)	5633.6(9)	15.8(2)
C10	7078.9(18)	1270.3(12)	6218.0(10)	17.0(2)
C11	7440.1(19)	2098.1(12)	6962.7(9)	15.8(2)
C12	8009.5(16)	3311.0(12)	6648.1(8)	14.0(2)
C13	5102.0(16)	4269.0(12)	6410.7(8)	12.5(2)
C14	2427.4(19)	5097.0(13)	6097.3(10)	19.3(2)

Table 3 Anisotropic Displacement Parameters ($\text{\AA}^2 \times 10^3$) for 1264_rkielawa_snyder. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+\dots]$.

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
I1	15.30(3)	15.86(3)	13.63(3)	4.80(3)	3.09(3)	0.96(3)
O1	18.3(5)	28.5(5)	11.9(4)	1.4(4)	2.7(3)	-0.7(4)
O2	15.7(4)	20.0(4)	13.2(4)	-0.7(3)	-1.3(4)	5.3(4)
O3	19.7(5)	21.5(5)	11.0(4)	-1.5(3)	0.1(3)	-2.0(4)
N1	18.9(5)	12.1(4)	9.6(4)	0.5(3)	2.1(4)	-4.2(4)
C1	11.4(4)	13.4(5)	14.0(5)	2.3(4)	-0.1(4)	0.6(4)
C2	14.6(5)	12.4(5)	22.1(6)	2.6(4)	-2.5(5)	-0.5(4)
C3	18.4(6)	12.7(5)	22.2(6)	-1.8(4)	-5.7(5)	-0.2(4)
C4	17.6(5)	16.0(6)	16.0(5)	-3.5(4)	-3.3(4)	1.4(4)
C5	15.0(5)	14.8(5)	12.9(5)	-0.5(4)	-0.3(4)	-1.3(4)
C6	10.3(4)	12.0(4)	12.6(4)	0.6(4)	-0.6(4)	-0.5(3)
C7	12.6(4)	12.1(5)	9.8(5)	0.8(4)	0.1(4)	-2.3(4)
C8	11.2(4)	14.0(5)	12.5(5)	-1.8(4)	-0.5(4)	0.0(4)
C9	17.1(5)	13.7(5)	16.5(5)	-1.7(4)	-1.3(4)	-4.1(4)

Table 3 Anisotropic Displacement Parameters ($\text{\AA}^2 \times 10^3$) for 1264_rkielawa_snyder. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+\dots]$.

Atom	U ₁₁	U ₂₂	U ₃₃	U ₂₃	U ₁₃	U ₁₂
C10	18.7(6)	12.8(5)	19.5(6)	1.2(4)	-0.9(5)	-1.4(4)
C11	17.9(5)	15.8(5)	13.8(5)	3.2(4)	-2.1(4)	-2.9(4)
C12	13.9(5)	14.6(5)	13.4(5)	1.5(4)	-2.2(4)	-2.5(4)
C13	12.7(5)	12.7(5)	12.2(5)	-0.2(4)	0.2(4)	-2.3(4)
C14	15.0(5)	20.1(6)	22.8(6)	-4.2(5)	1.2(5)	3.2(5)

Table 4 Bond Lengths for 1264_rkielawa_snyder.

Atom	Atom	Length/ $\text{\AA}$	Atom	Atom	Length/ $\text{\AA}$
I1	C1	2.1006(14)	C3	C4	1.388(2)
O1	C13	1.2028(16)	C4	C5	1.3886(19)
O2	C13	1.3370(16)	C5	C6	1.4086(19)
O2	C14	1.4445(18)	C7	C8	1.5481(18)
O3	C8	1.2110(16)	C7	C12	1.5454(17)
N1	C6	1.3817(16)	C7	C13	1.5452(18)
N1	C7	1.4417(16)	C8	C9	1.4987(19)
C1	C2	1.3865(18)	C9	C10	1.538(2)
C1	C6	1.4089(18)	C10	C11	1.519(2)
C2	C3	1.391(2)	C11	C12	1.5284(18)

Table 5 Bond Angles for 1264_rkielawa_snyder.

Atom	Atom	Atom	Angle/ $^\circ$	Atom	Atom	Atom	Angle/ $^\circ$
C13	O2	C14	116.10(11)	N1	C7	C13	111.05(10)
C6	N1	C7	126.15(11)	C12	C7	C8	107.98(10)
C2	C1	I1	118.26(10)	C13	C7	C8	106.00(10)
C2	C1	C6	121.89(13)	C13	C7	C12	112.19(10)
C6	C1	I1	119.83(10)	O3	C8	C7	120.75(12)
C1	C2	C3	120.28(12)	O3	C8	C9	123.91(12)
C4	C3	C2	118.92(12)	C9	C8	C7	115.29(11)
C3	C4	C5	121.07(13)	C8	C9	C10	109.27(11)
C4	C5	C6	121.05(12)	C11	C10	C9	109.38(11)
N1	C6	C1	119.86(12)	C10	C11	C12	111.54(11)
N1	C6	C5	123.31(11)	C11	C12	C7	114.81(10)
C5	C6	C1	116.79(11)	O1	C13	O2	124.47(13)
N1	C7	C8	107.21(10)	O1	C13	C7	126.02(12)
N1	C7	C12	112.05(10)	O2	C13	C7	109.51(11)

Table 6 Torsion Angles for 1264_rkielawa_snyder.

A	B	C	D	Angle/°	A	B	C	D	Angle/°
I1	C1	C2	C3	-178.29(10)	C6	C1	C2	C3	0.2(2)
I1	C1	C6	N1	0.12(16)	C7	N1	C6	C1	-176.89(12)
I1	C1	C6	C5	178.05(9)	C7	N1	C6	C5	5.3(2)
O3	C8	C9	C10	118.64(15)	C7	C8	C9	C10	-58.87(15)
N1	C7	C8	O3	-5.19(17)	C8	C7	C12	C11	-47.66(14)
N1	C7	C8	C9	172.40(11)	C8	C7	C13	O1	123.51(15)
N1	C7	C12	C11	-165.50(11)	C8	C7	C13	O2	-56.61(13)
N1	C7	C13	O1	-120.38(15)	C8	C9	C10	C11	59.66(15)
N1	C7	C13	O2	59.50(14)	C9	C10	C11	C12	-57.48(15)
C1	C2	C3	C4	0.3(2)	C10	C11	C12	C7	53.41(16)
C2	C1	C6	N1	-178.35(12)	C12	C7	C8	O3	-126.10(13)
C2	C1	C6	C5	-0.42(18)	C12	C7	C8	C9	51.49(14)
C2	C3	C4	C5	-0.5(2)	C12	C7	C13	O1	5.88(19)
C3	C4	C5	C6	0.3(2)	C12	C7	C13	O2	-174.24(10)
C4	C5	C6	N1	178.01(12)	C13	C7	C8	O3	113.49(13)
C4	C5	C6	C1	0.16(19)	C13	C7	C8	C9	-68.92(14)
C6	N1	C7	C8	170.05(12)	C13	C7	C12	C11	68.78(14)
C6	N1	C7	C12	-71.65(16)	C14	O2	C13	O1	2.4(2)
C6	N1	C7	C13	54.69(17)	C14	O2	C13	C7	-177.52(11)

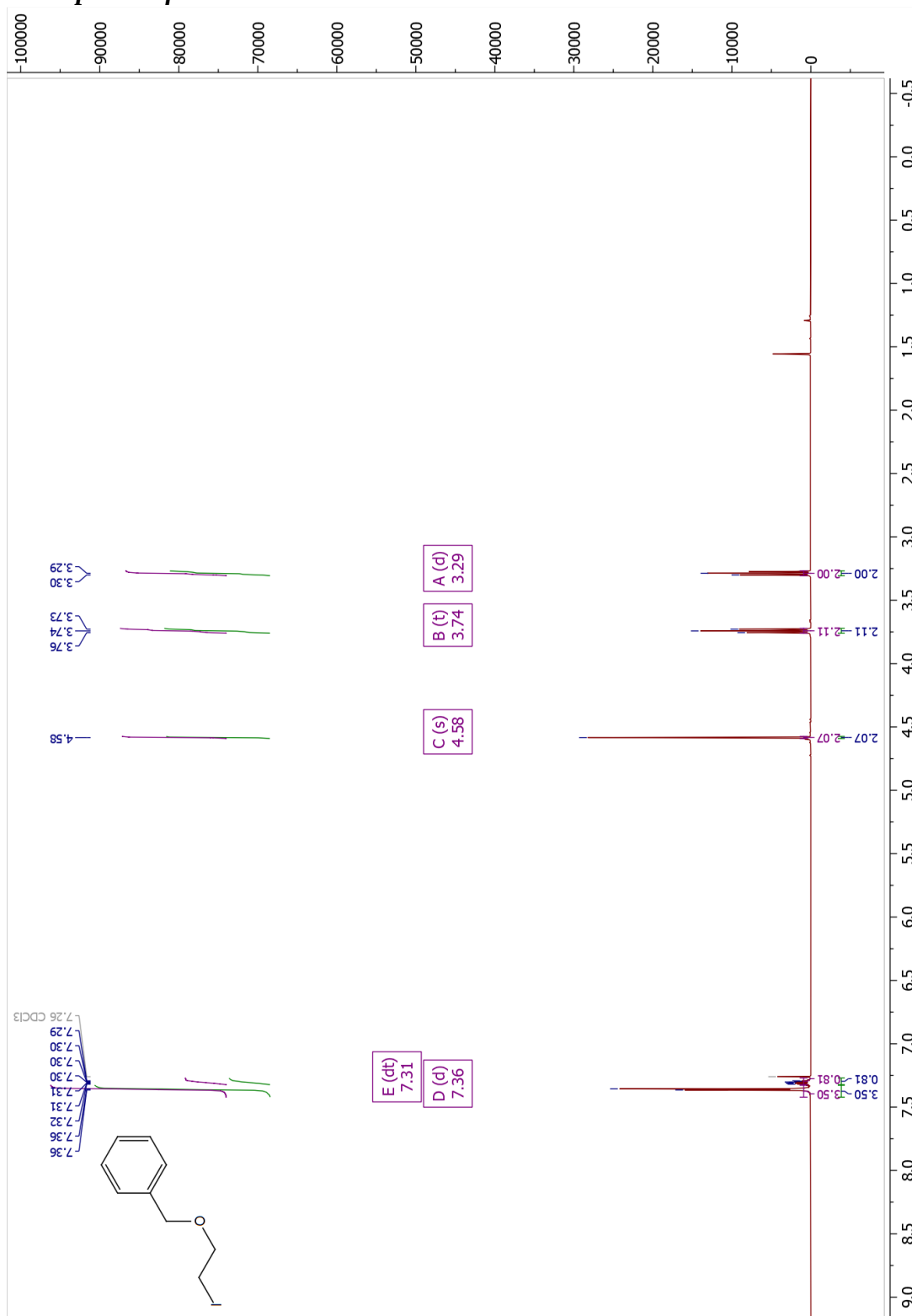
Table 7 Hydrogen Atom Coordinates ($\text{\AA} \times 10^4$) and Isotropic Displacement Parameters ($\text{\AA}^2 \times 10^3$) for 1264_rkielawa_snyder.

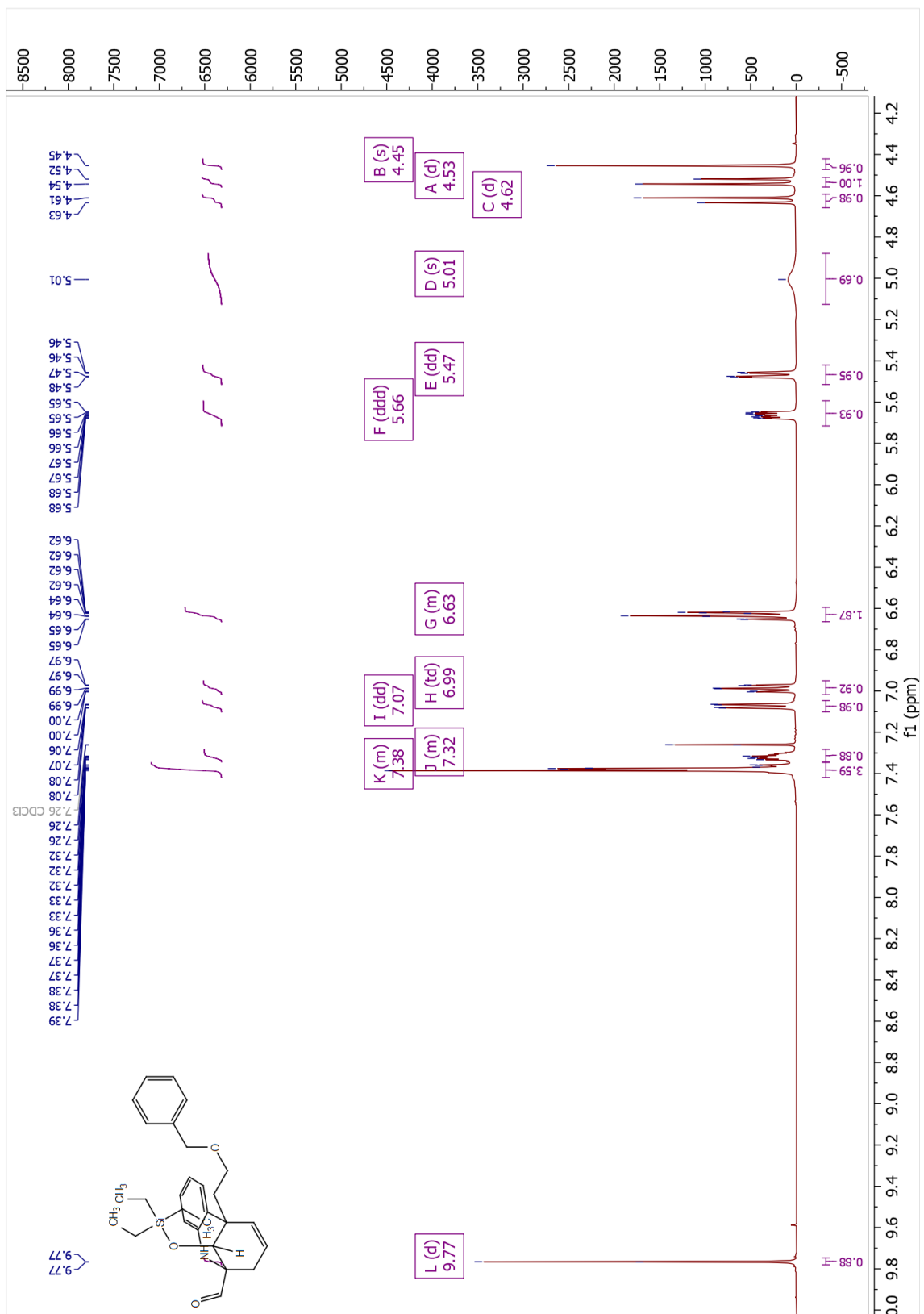
Atom	x	y	z	U(eq)
H1	7500(30)	4840(20)	5047(15)	26(6)
H2	9560.38	8545.1	5388.02	20
H3	9149.22	8932.4	6853.36	21
H4	8025.4	7458.05	7734.26	20
H5	7274.83	5634.81	7172.1	17
H9A	5476.16	1283.51	5147.6	19
H9B	4659.61	1938.54	5961.65	19
H10A	6674.97	502.29	6439.44	20
H10B	8130.6	1133	5885.95	20
H11A	8336.64	1753.63	7329.96	19
H11B	6404.15	2185.21	7315.83	19
H12A	9141.17	3231.5	6379.63	17
H12B	8131.56	3837.52	7151.23	17

Table 7 Hydrogen Atom Coordinates ($\text{\AA}\times 10^4$) and Isotropic Displacement Parameters ($\text{\AA}^2\times 10^3$) for 1264_rkielawa_snyder.

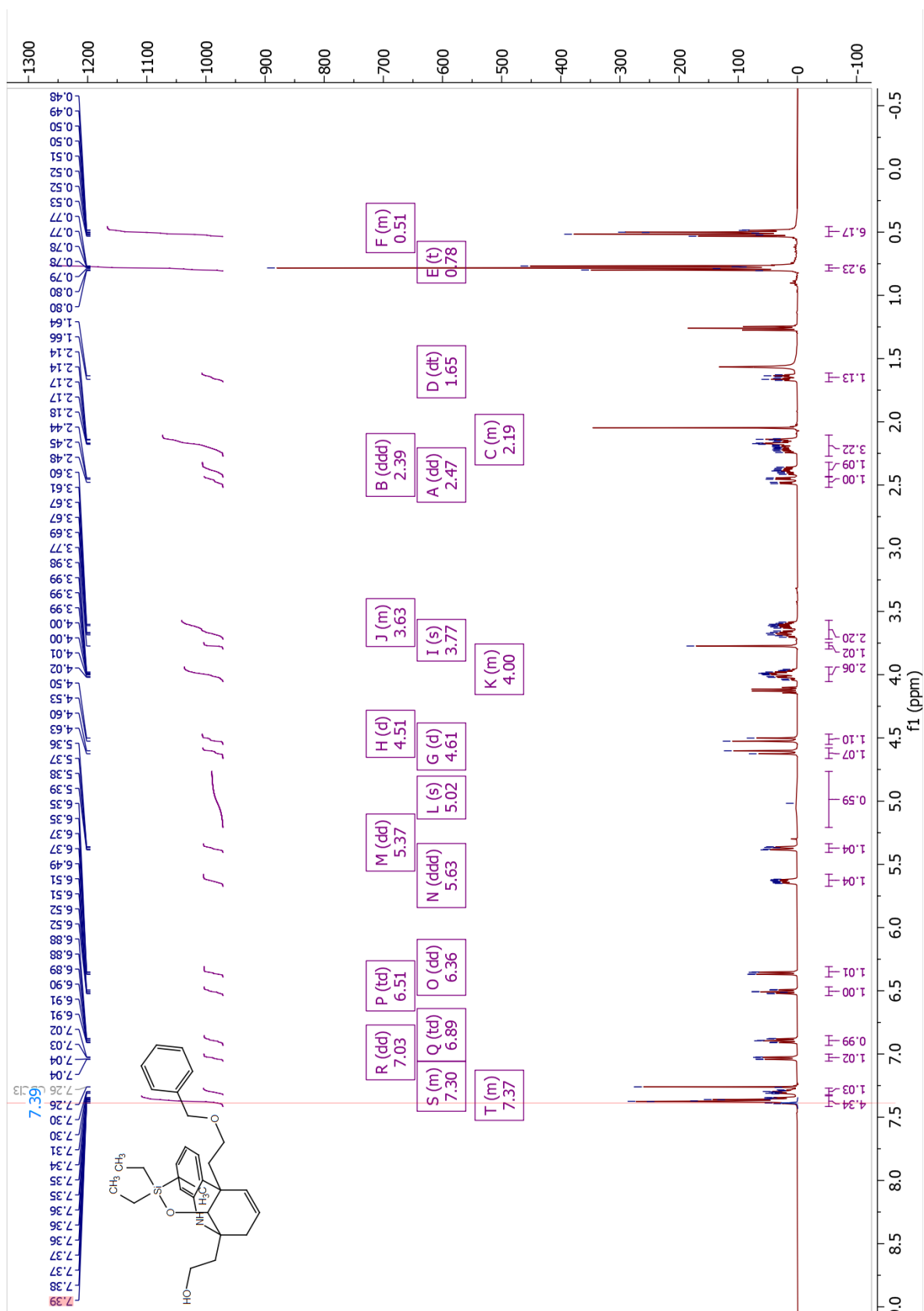
Atom	x	y	z	U(eq)
H14A	1767.82	5379.77	5605.5	29
H14B	2598.84	5744.59	6504.5	29
H14C	1813.1	4455.46	6381.34	29

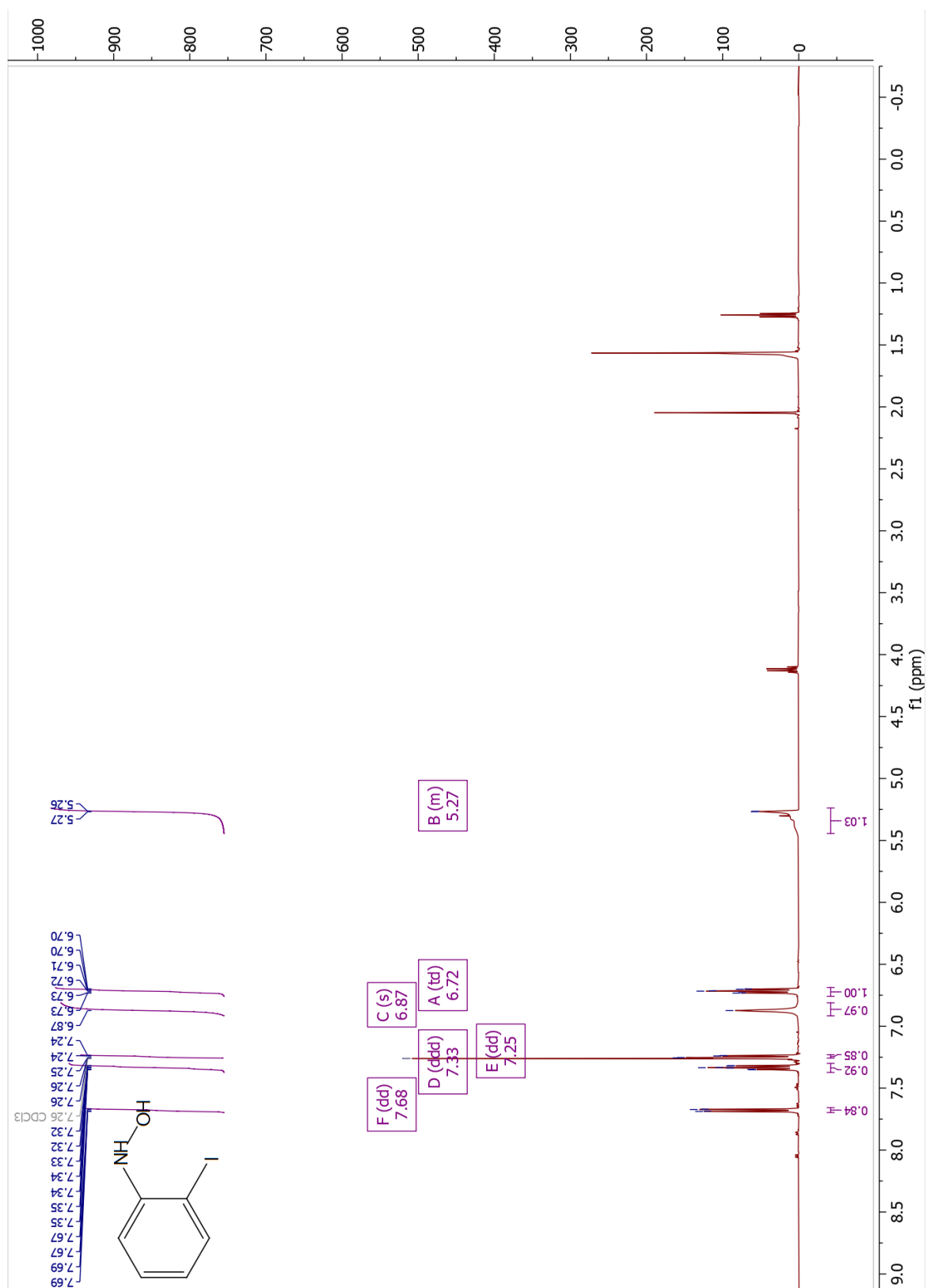
1.6.6 NMR Spectra of Selected Intermediates

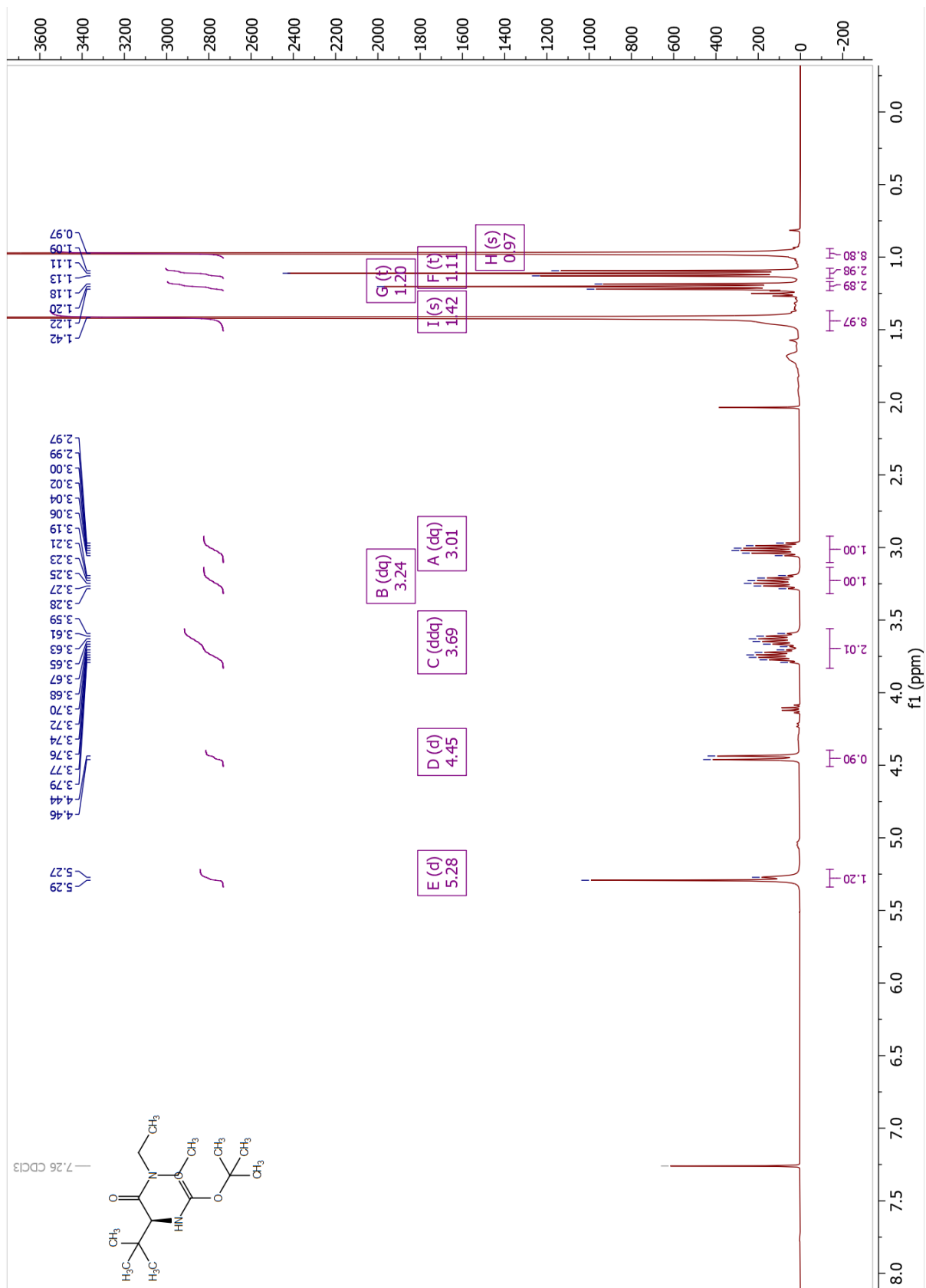


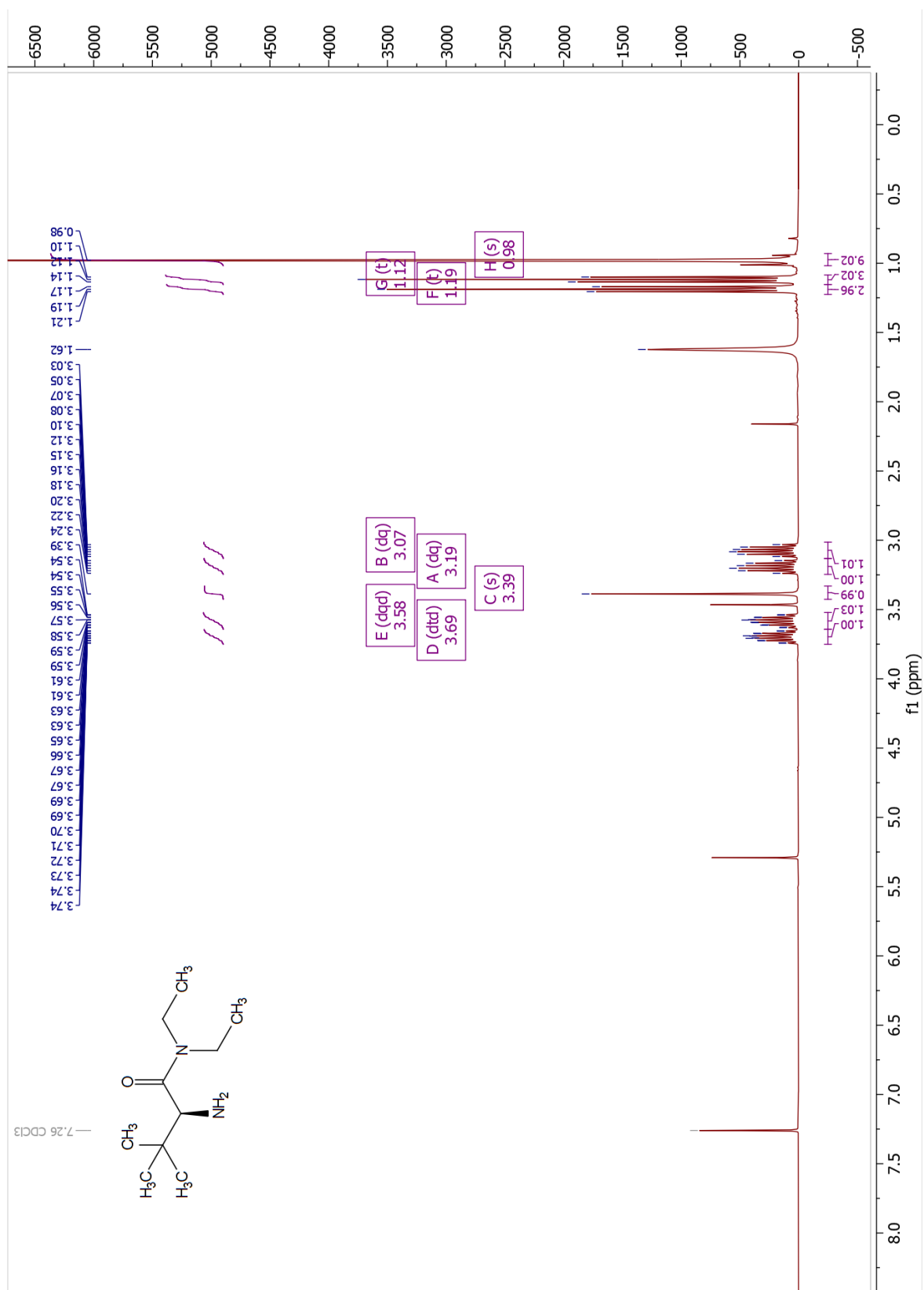


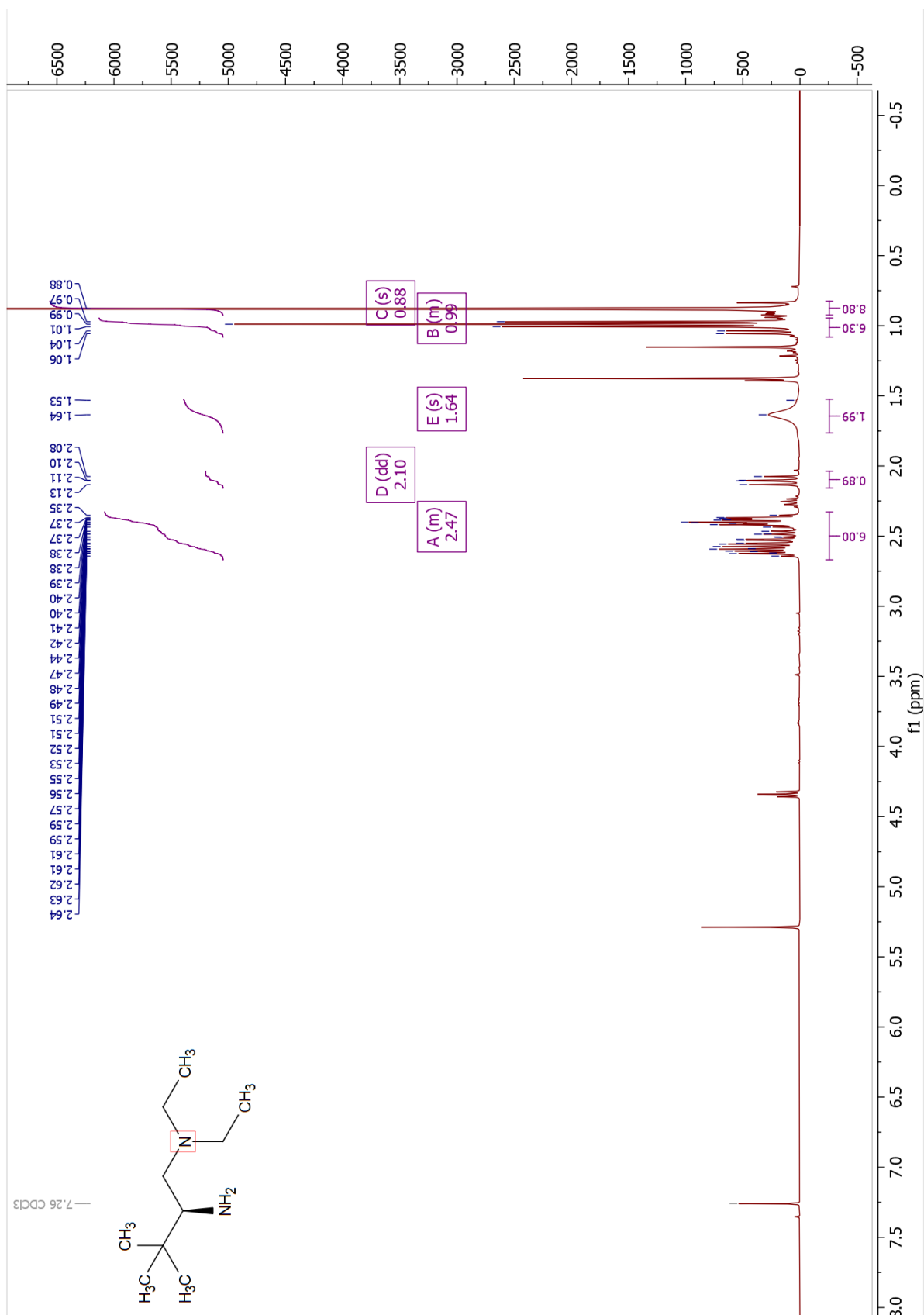


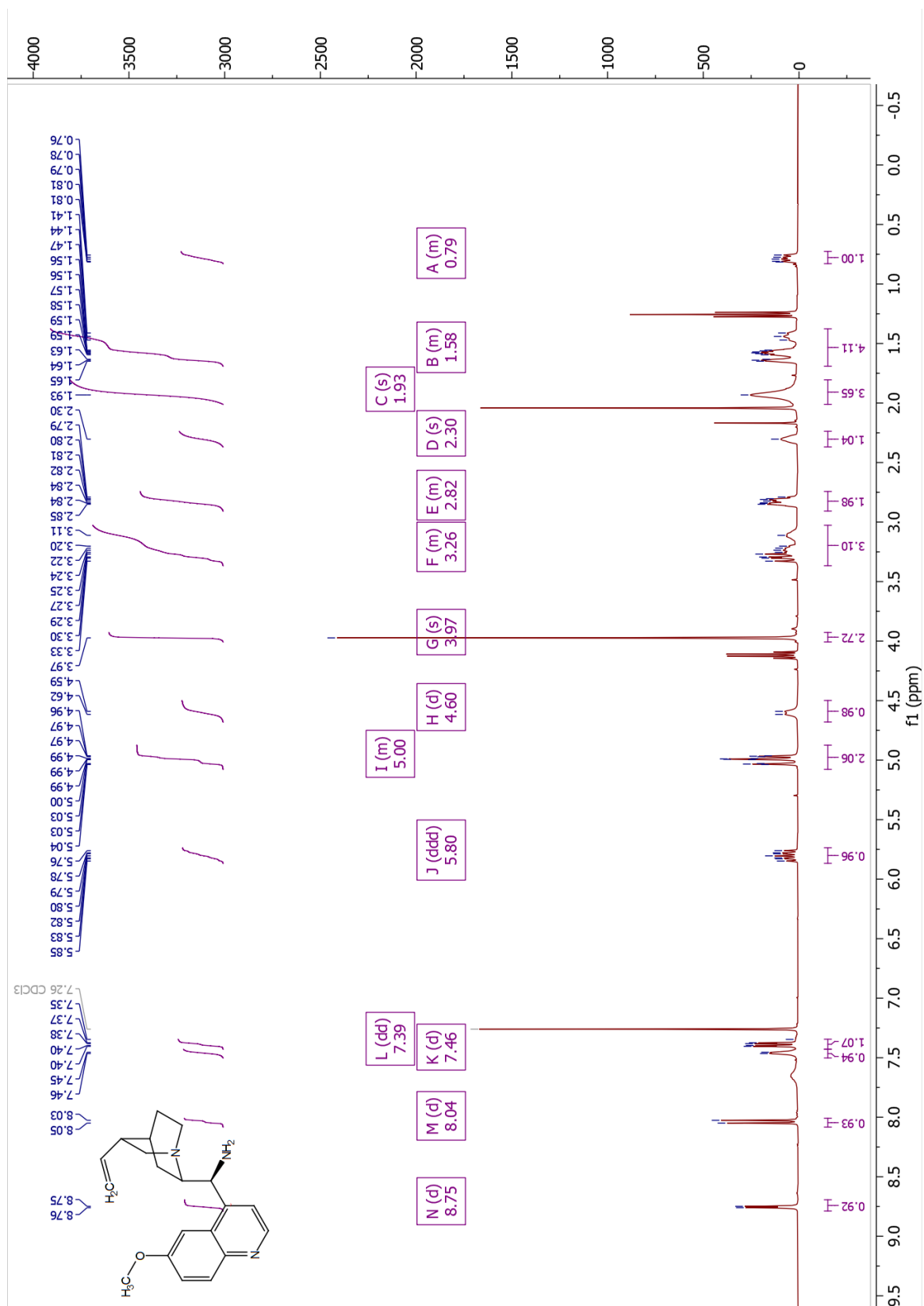


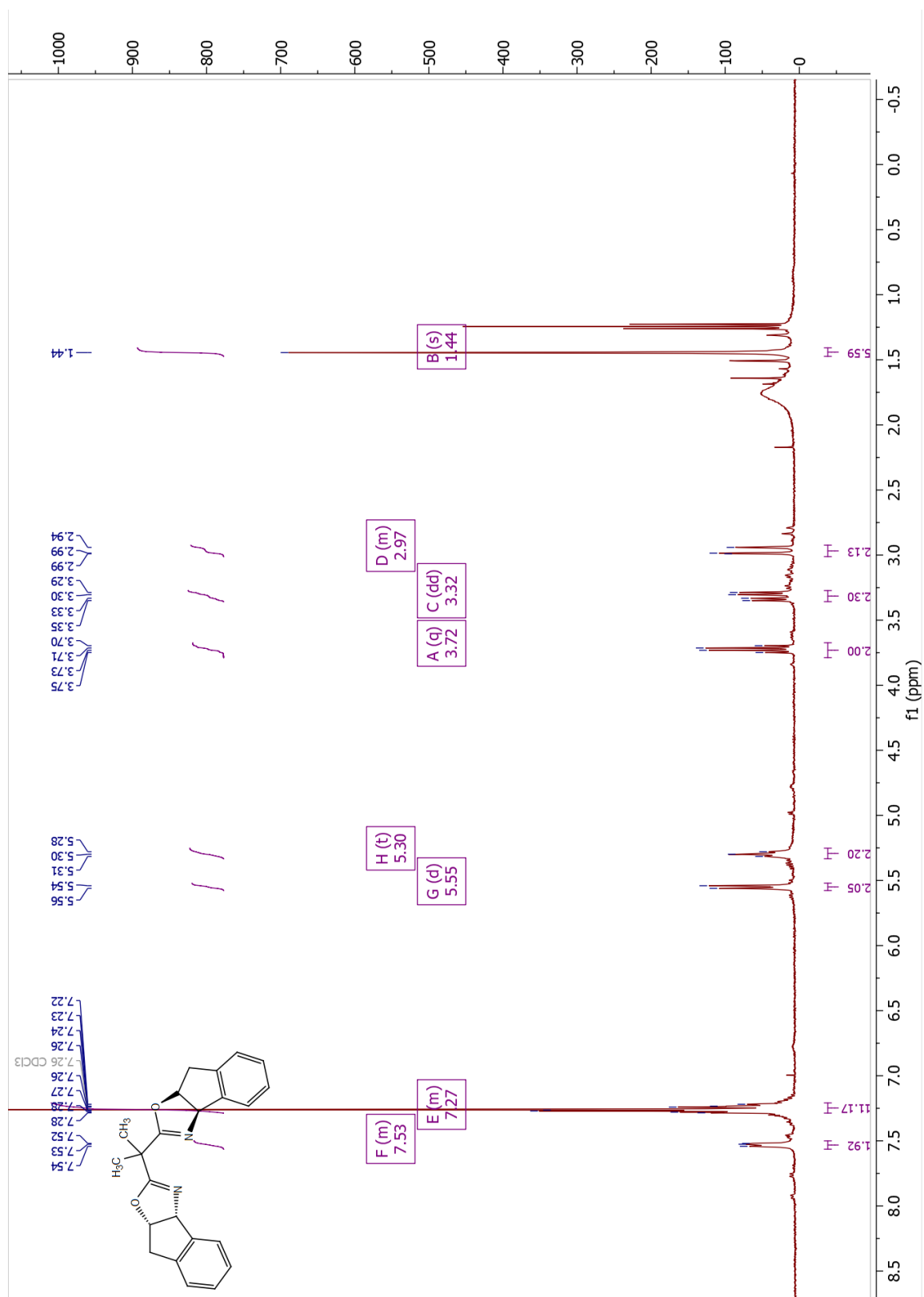


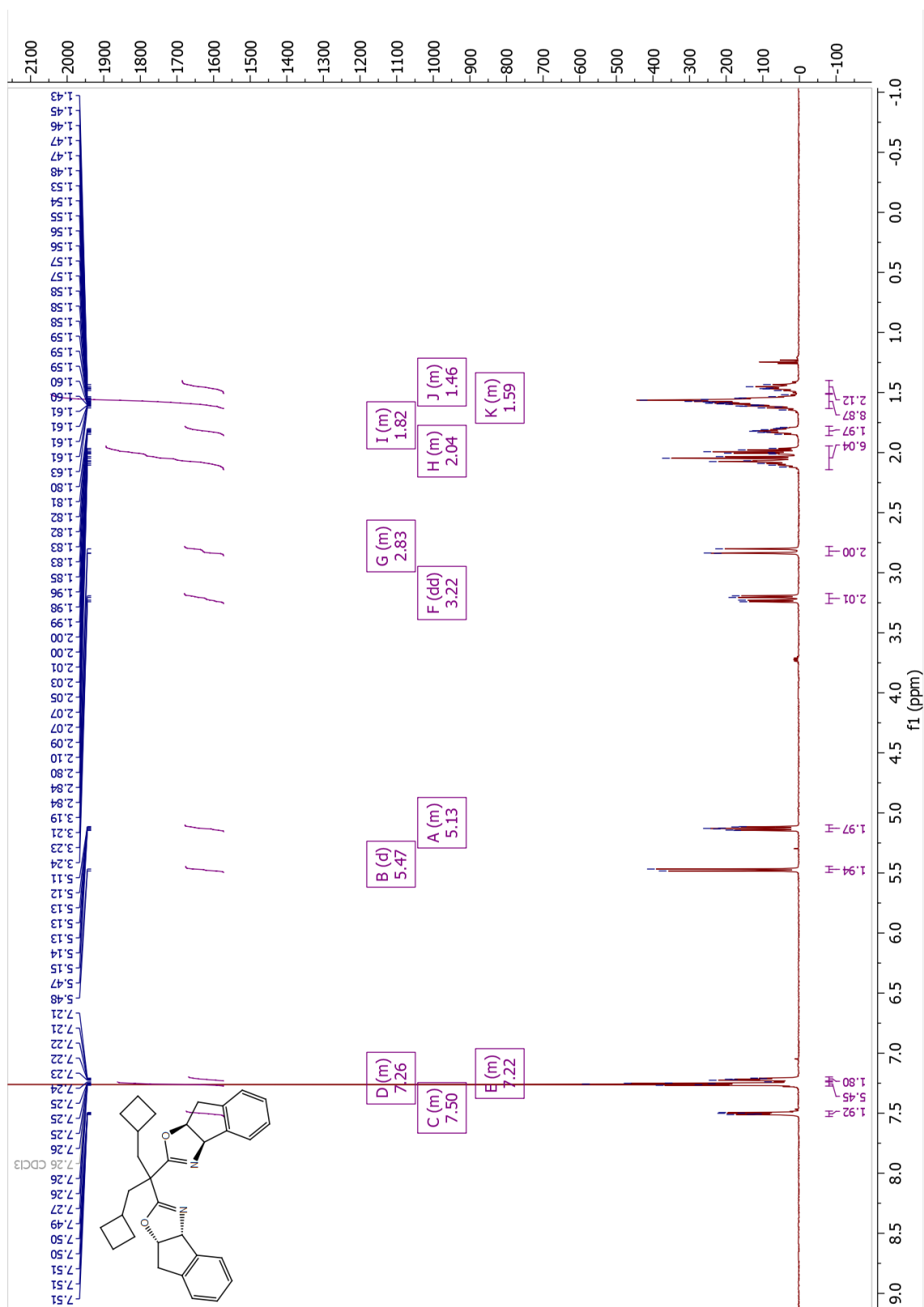


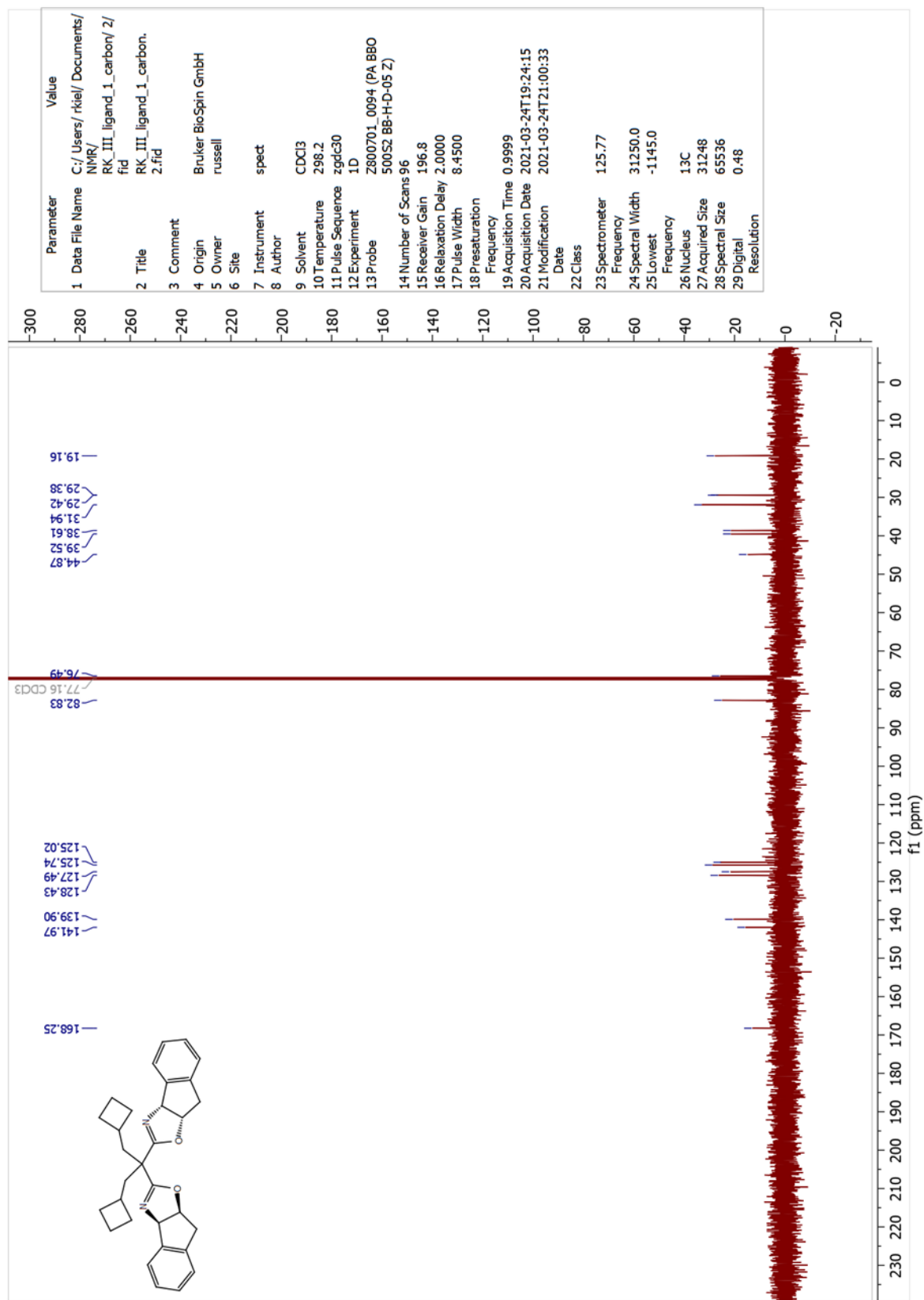


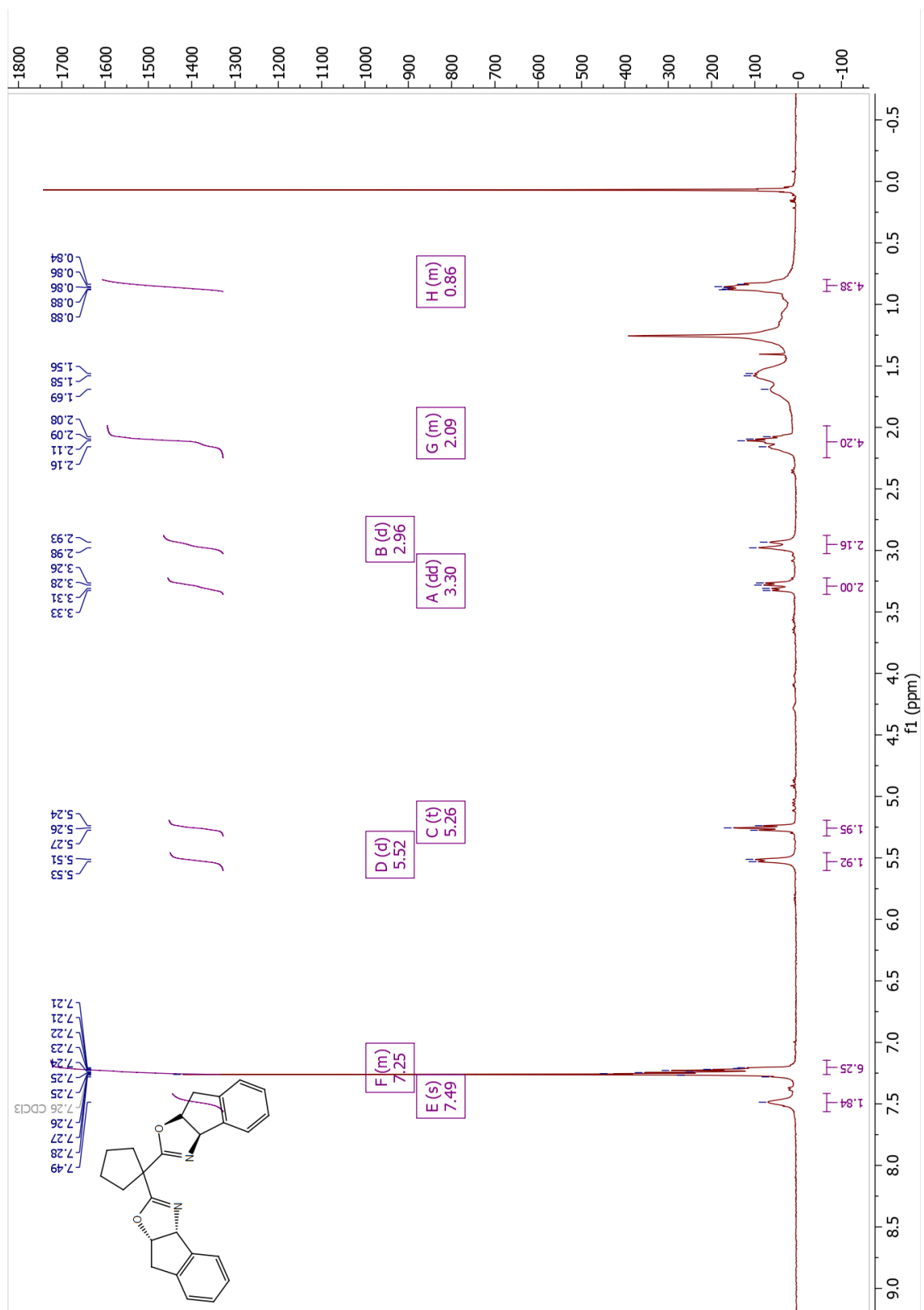


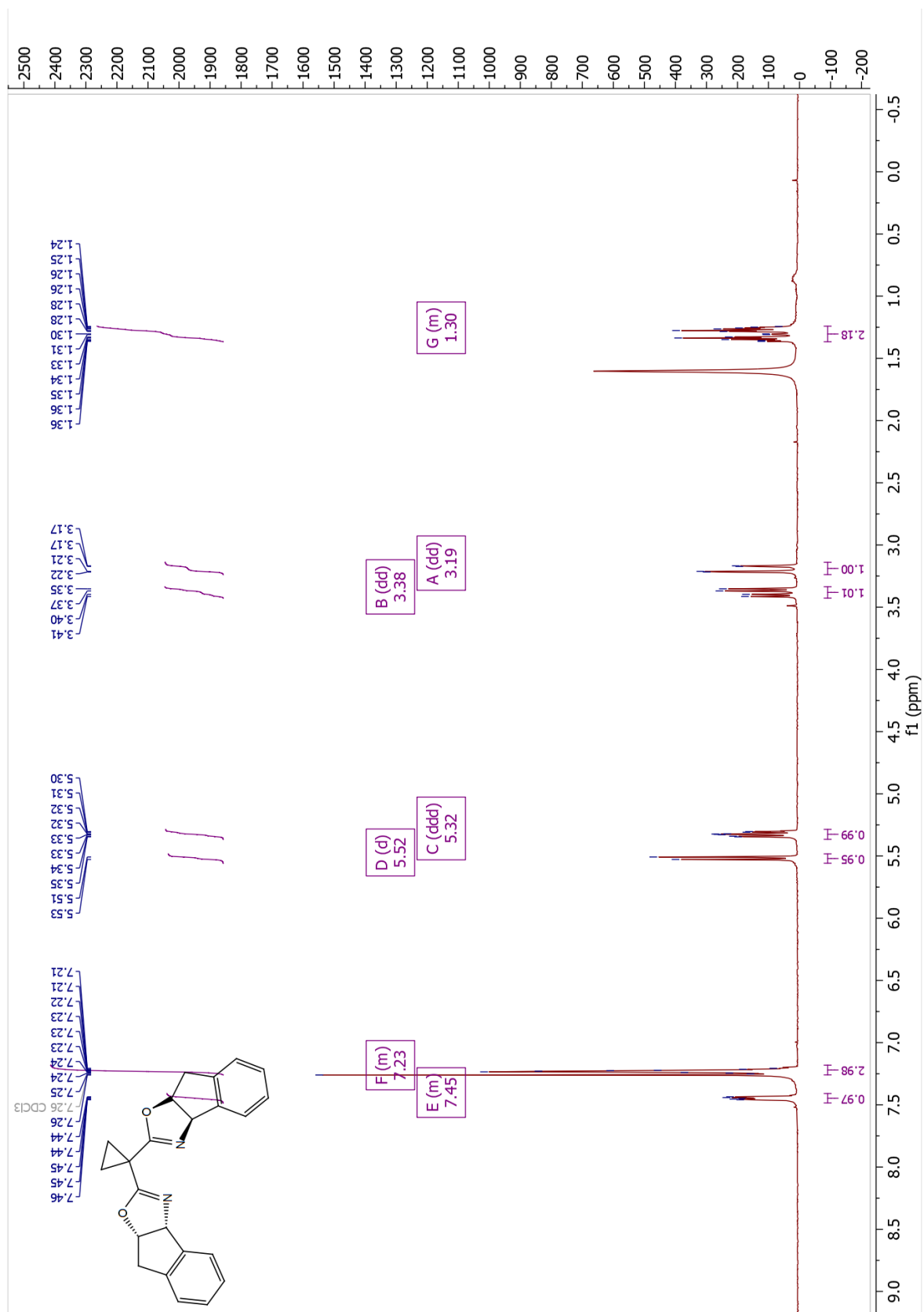


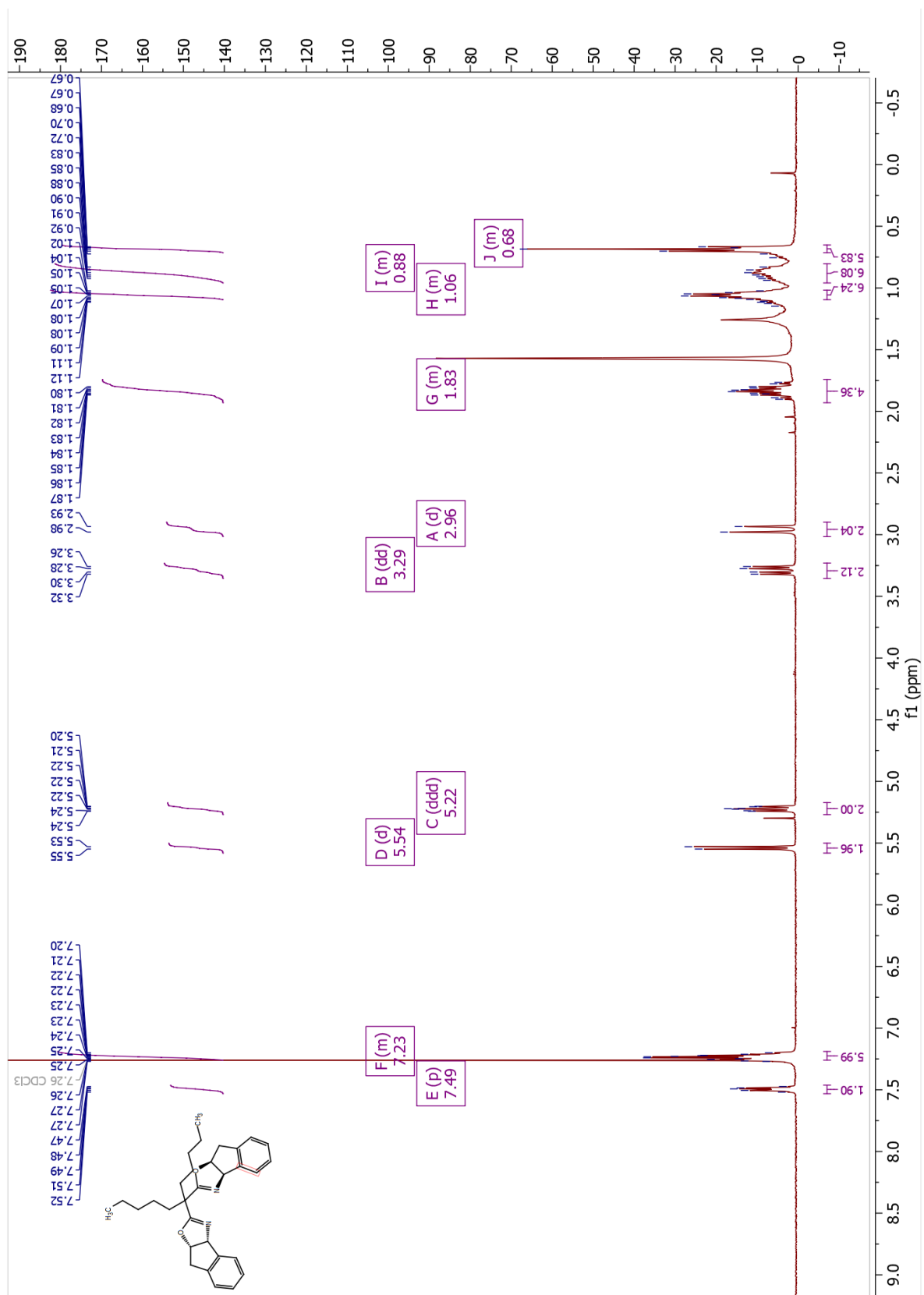


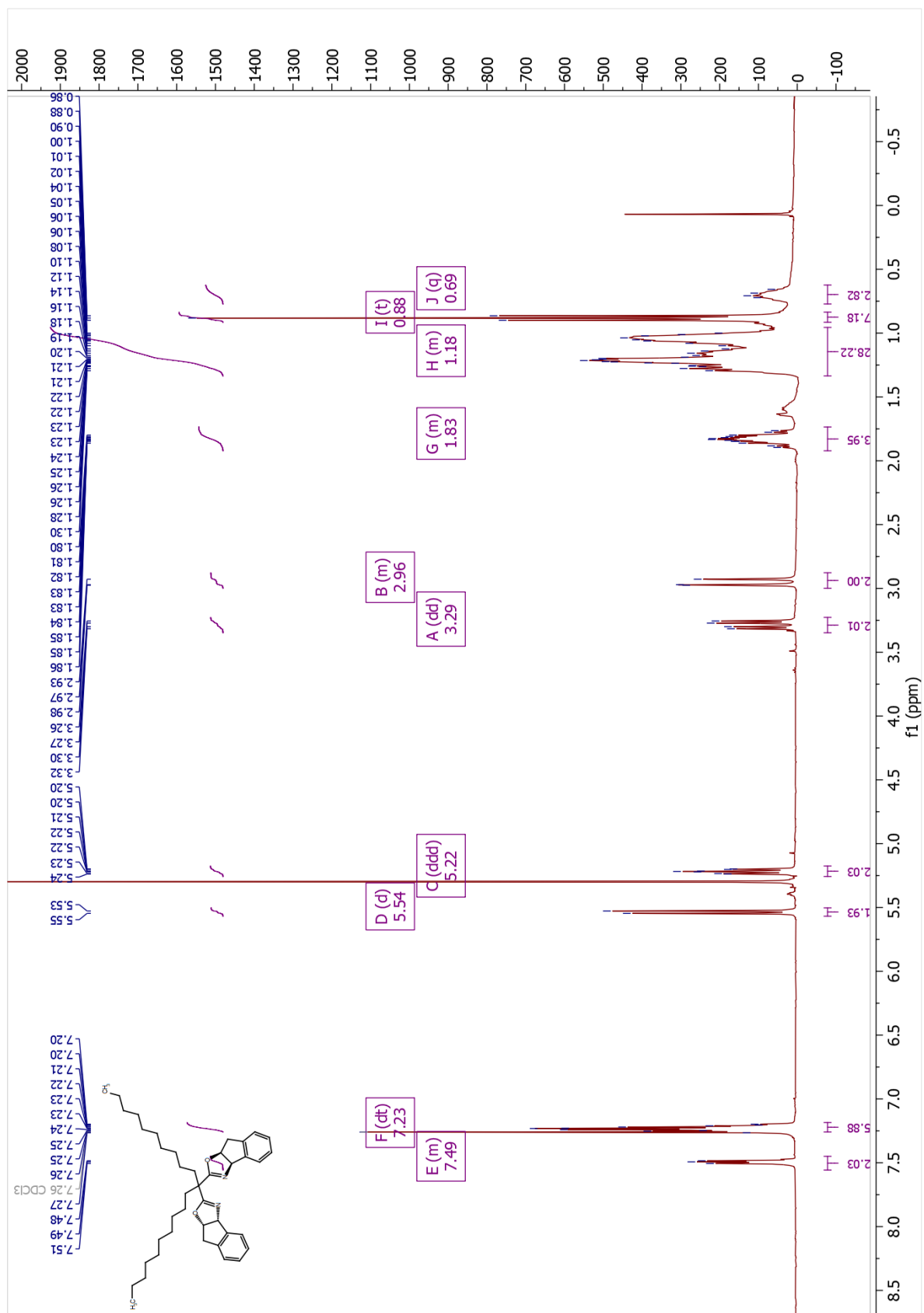


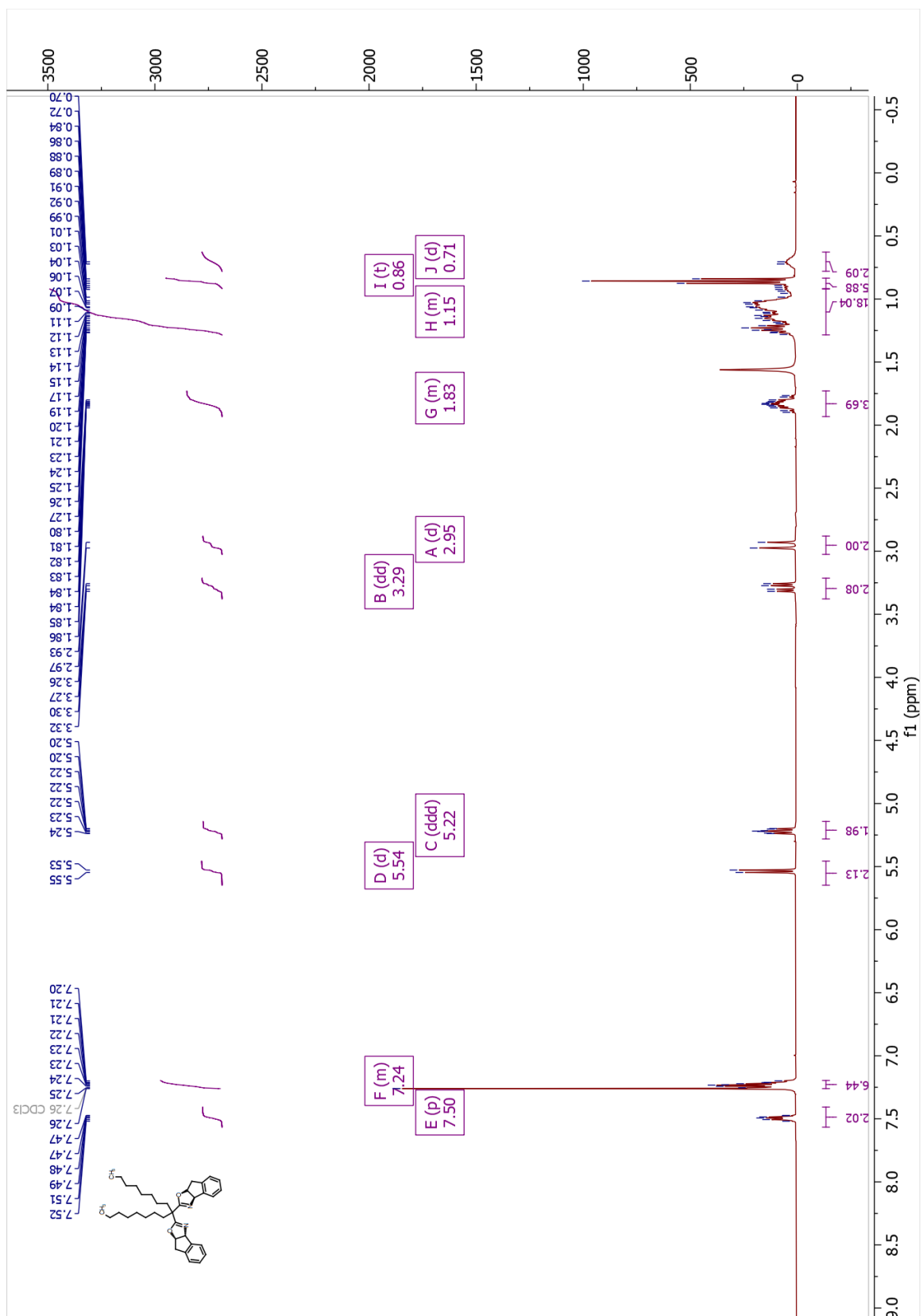


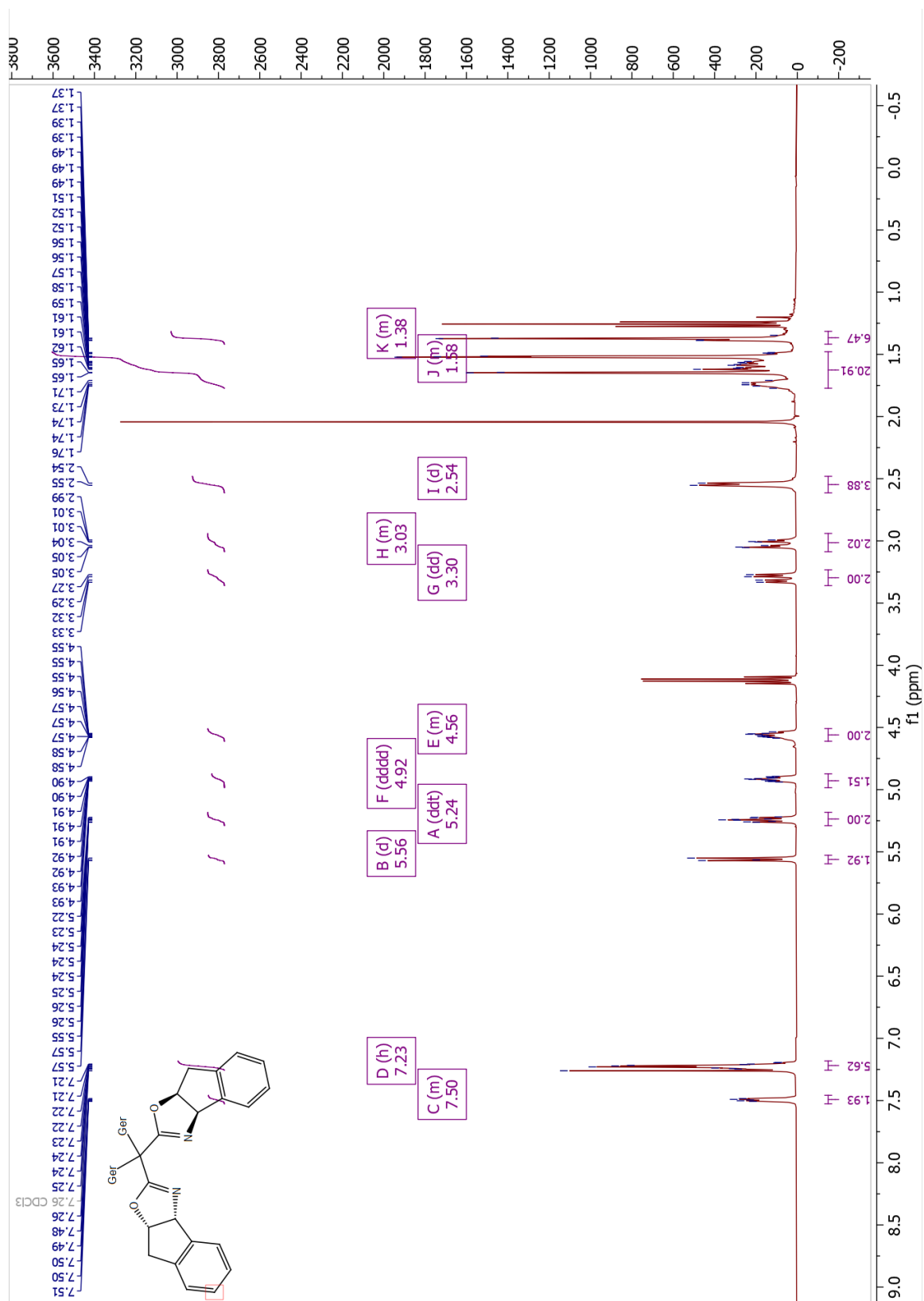


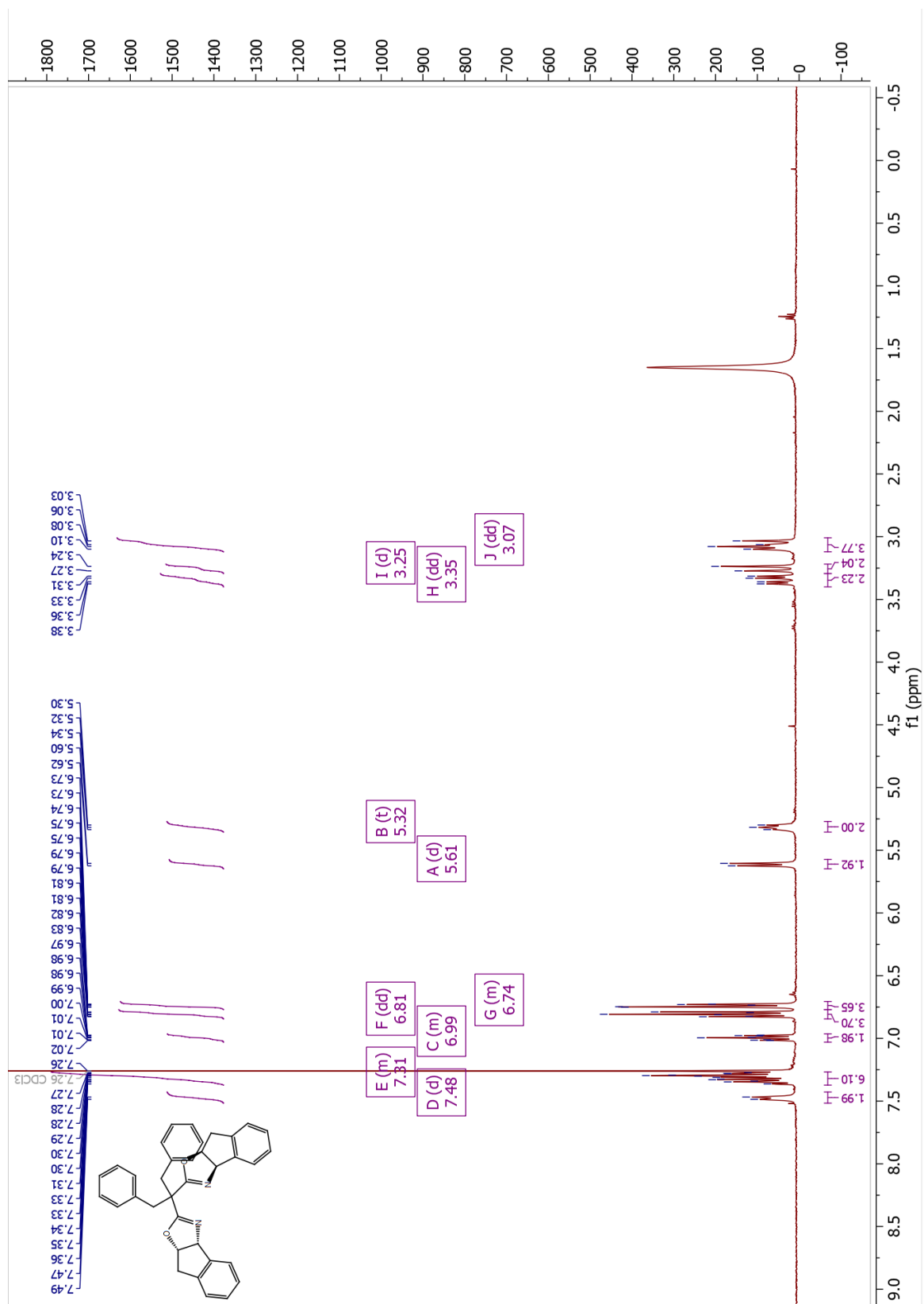


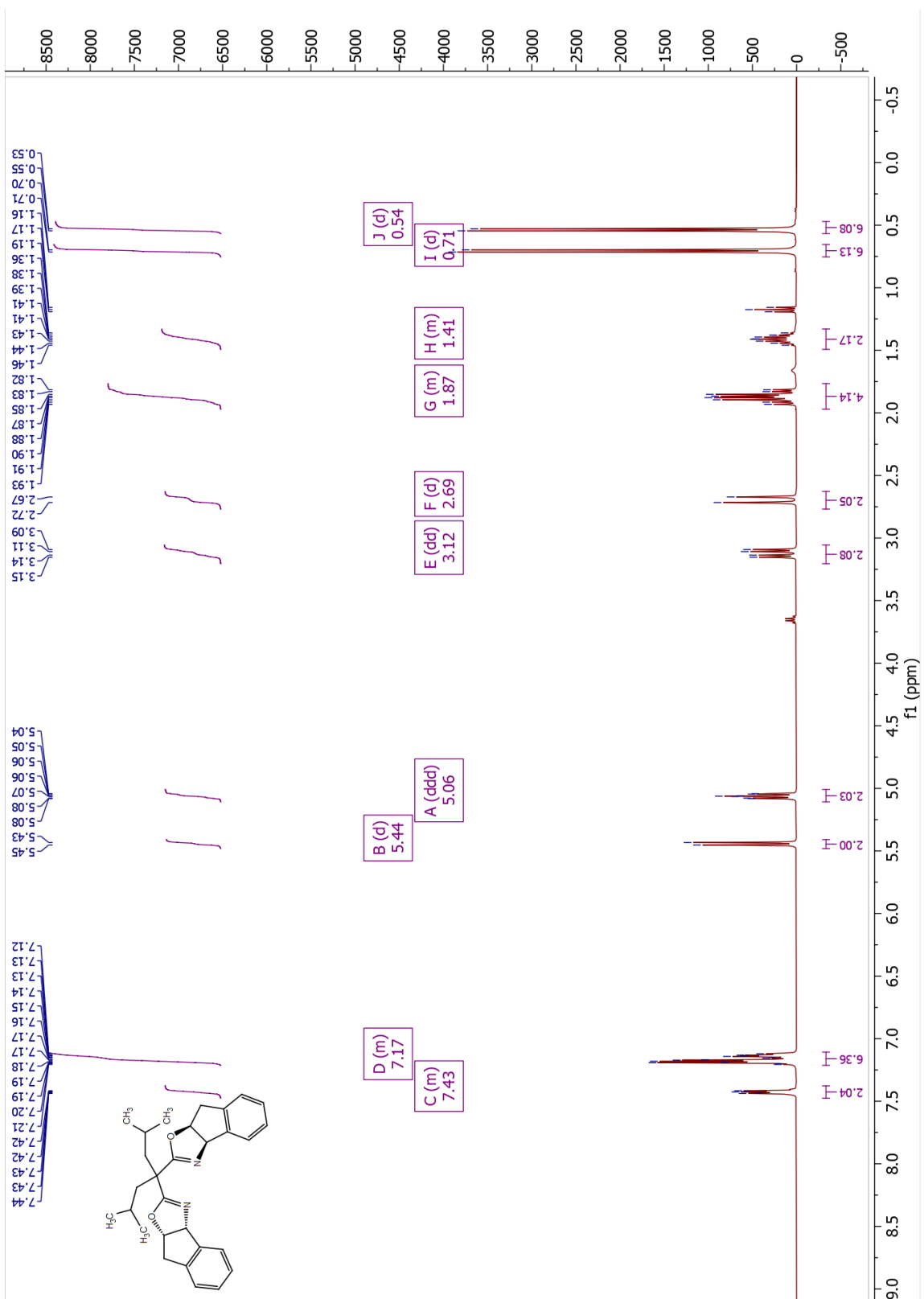


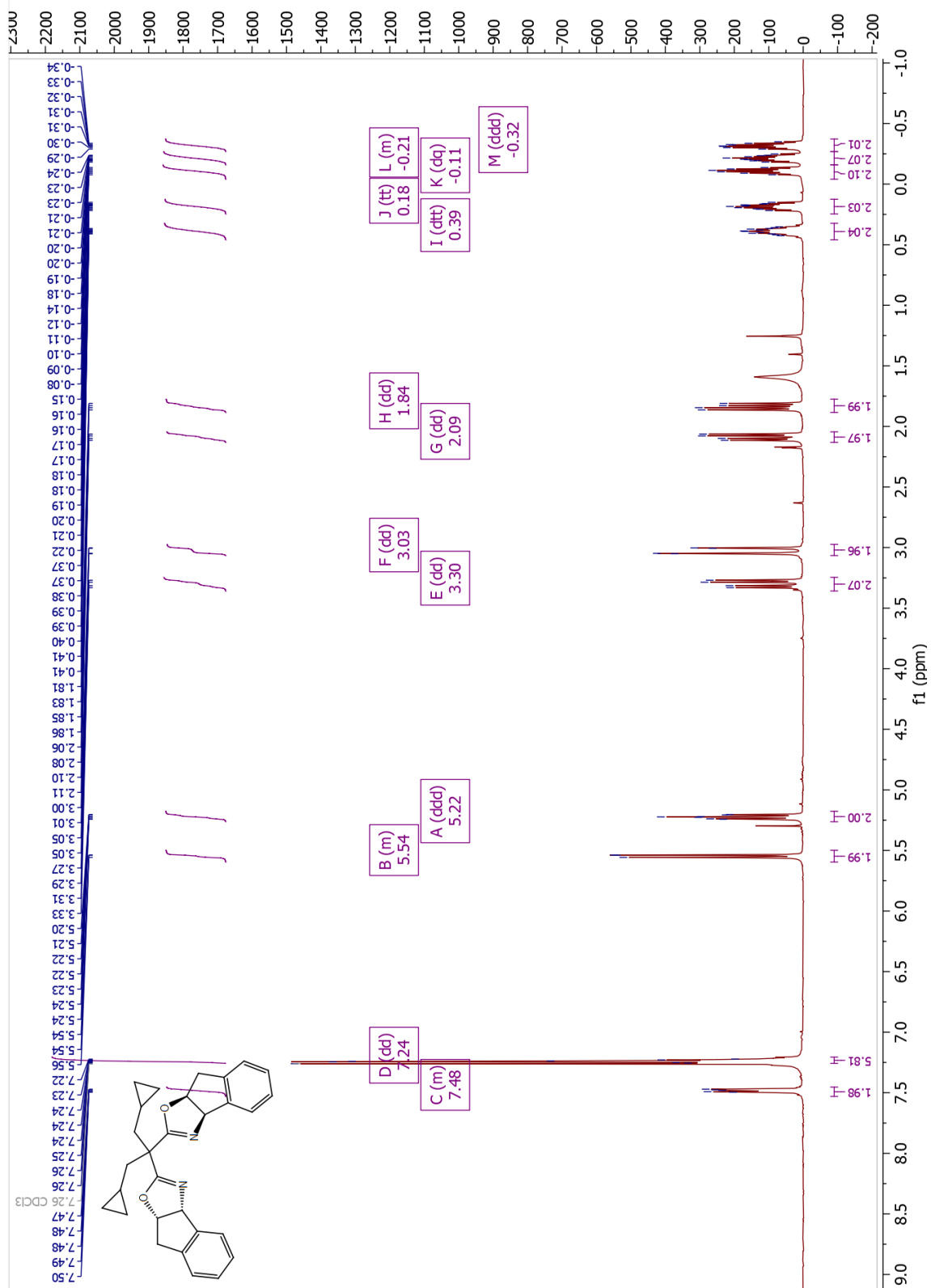


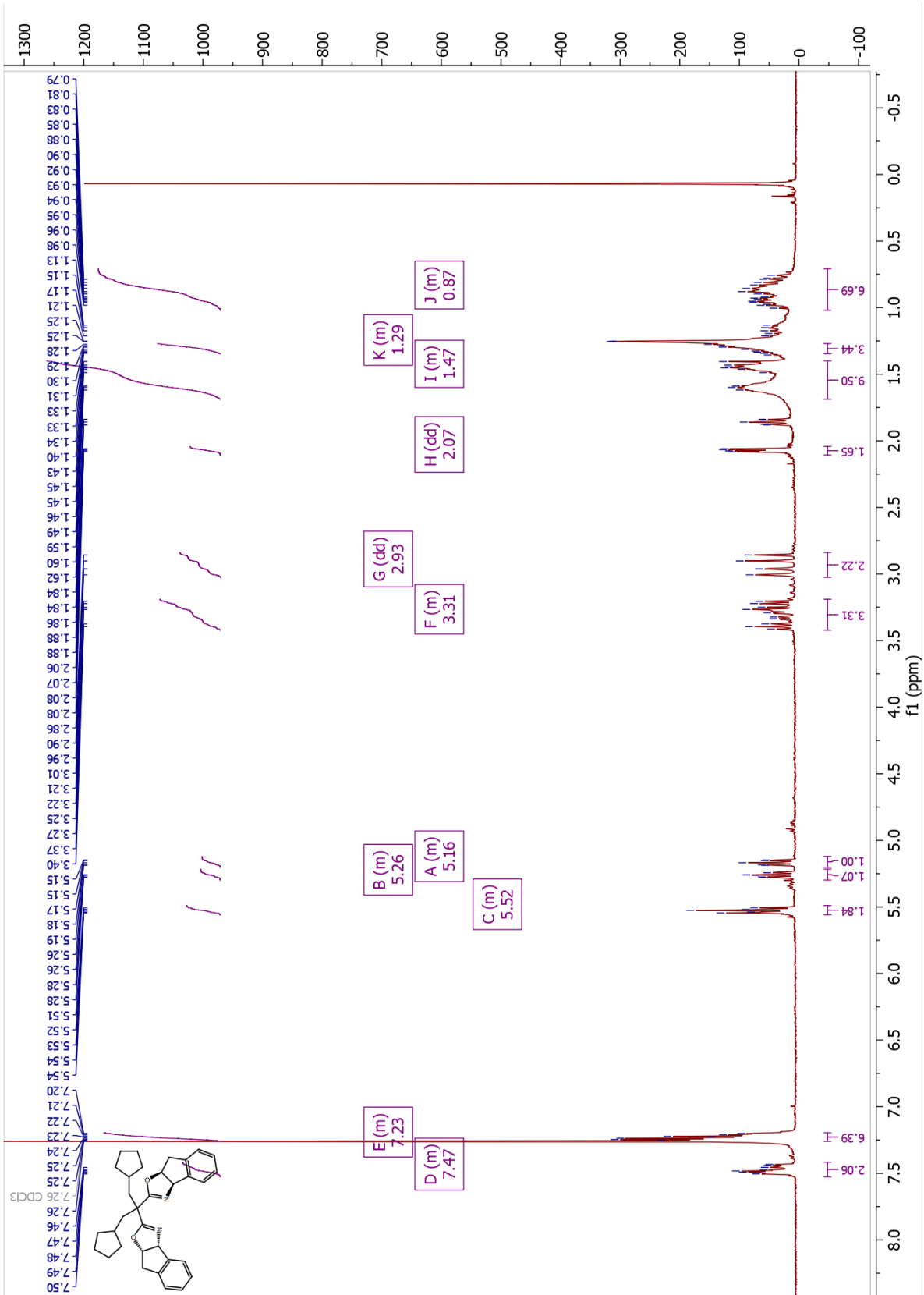


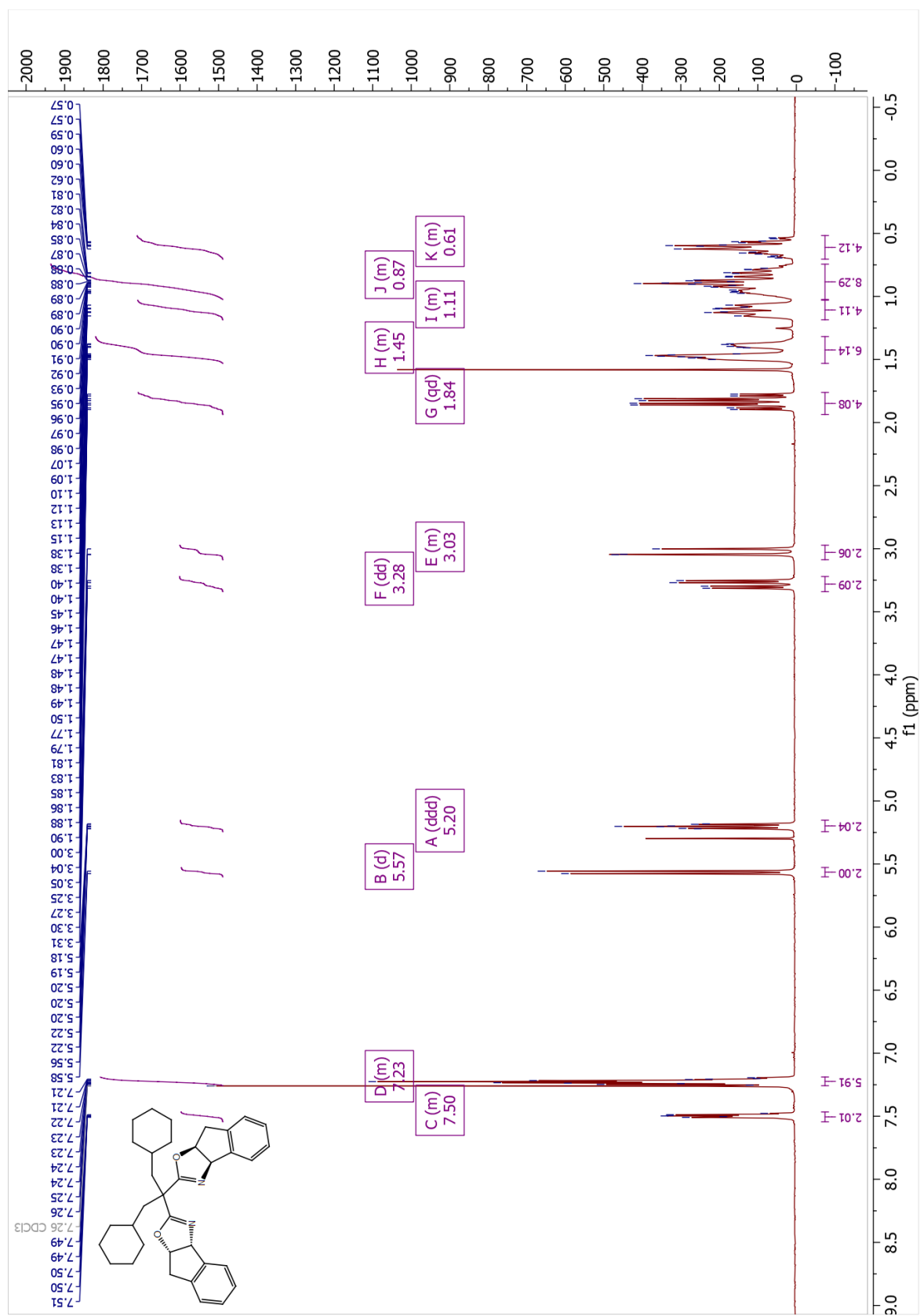


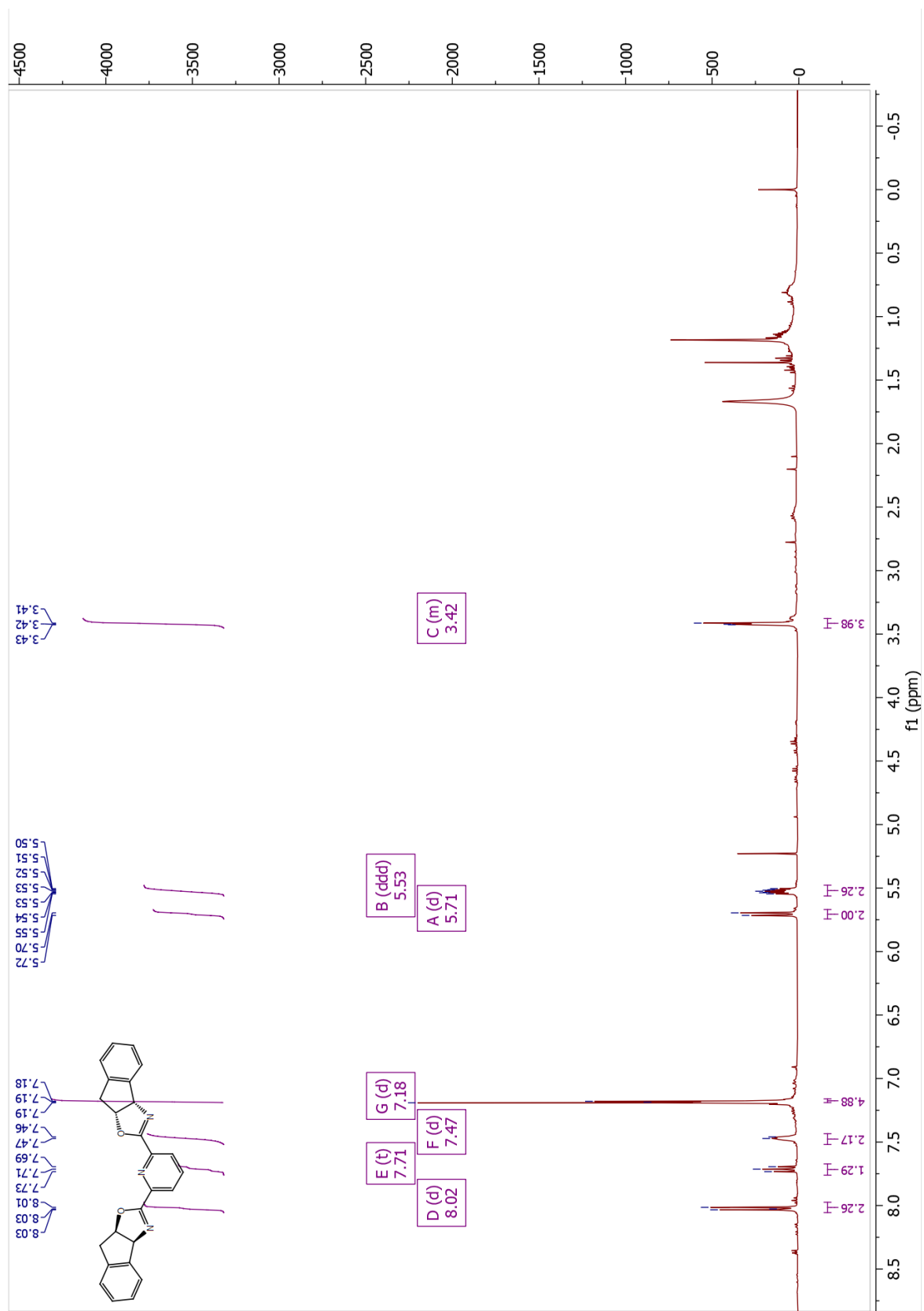


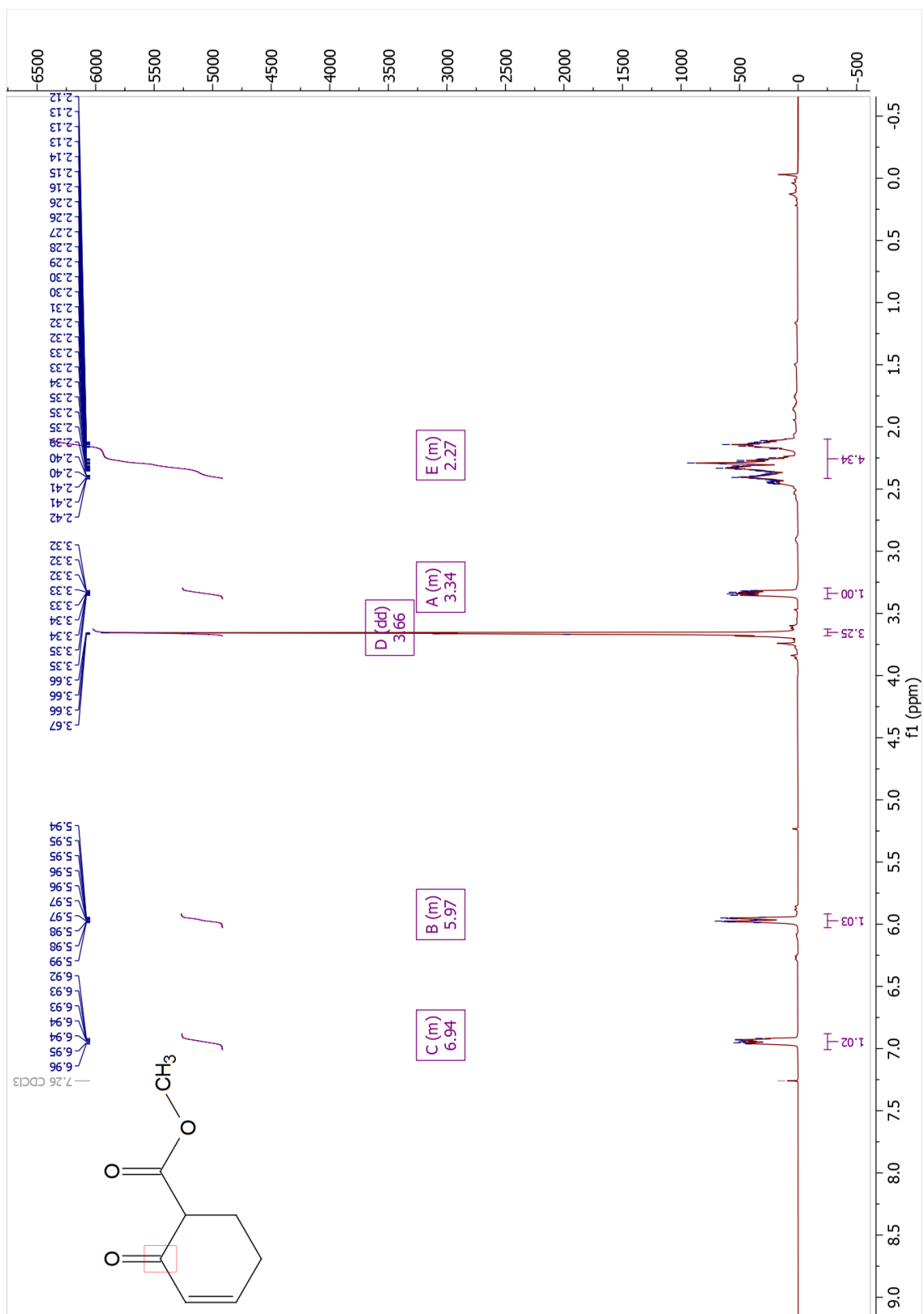


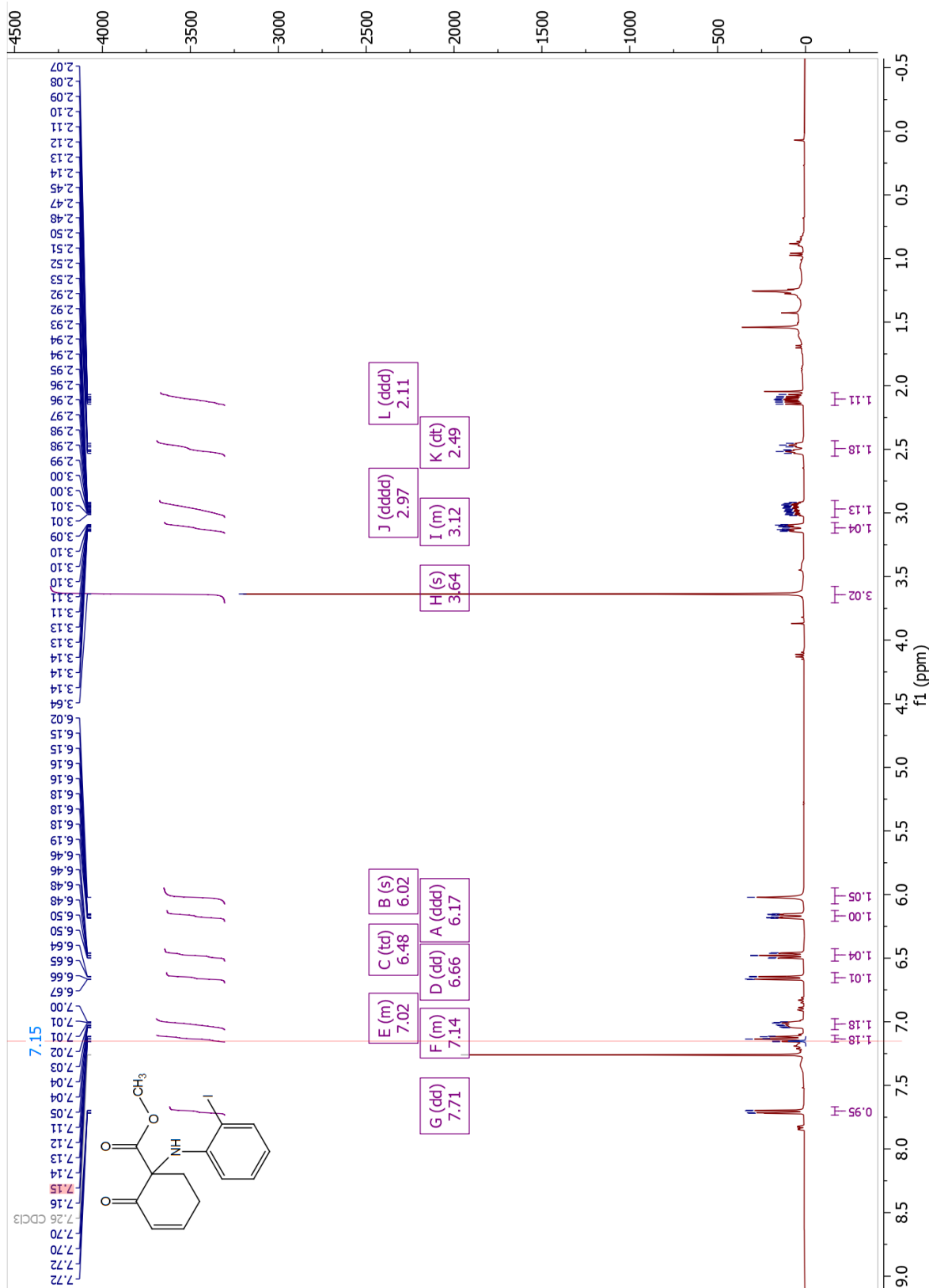


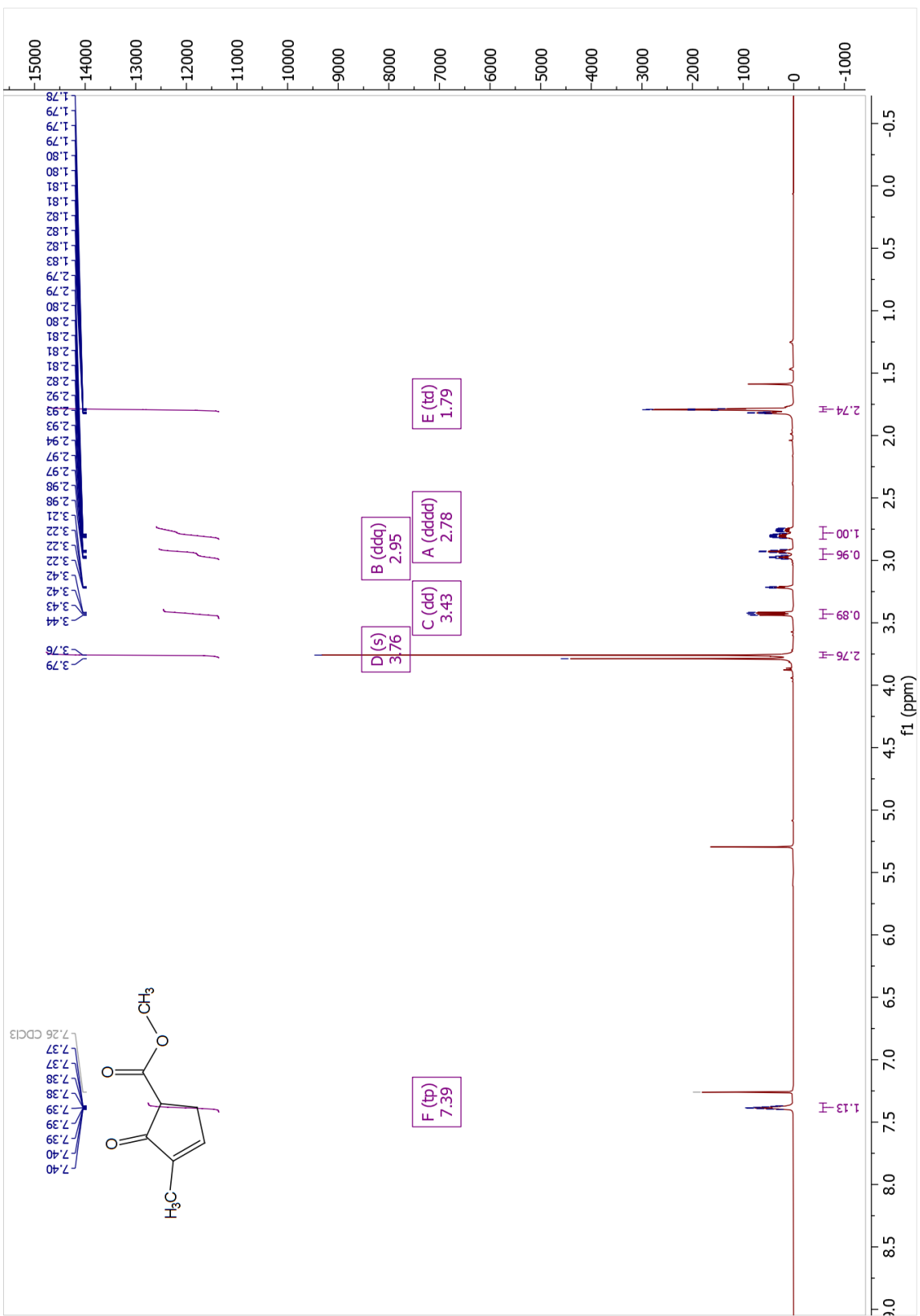


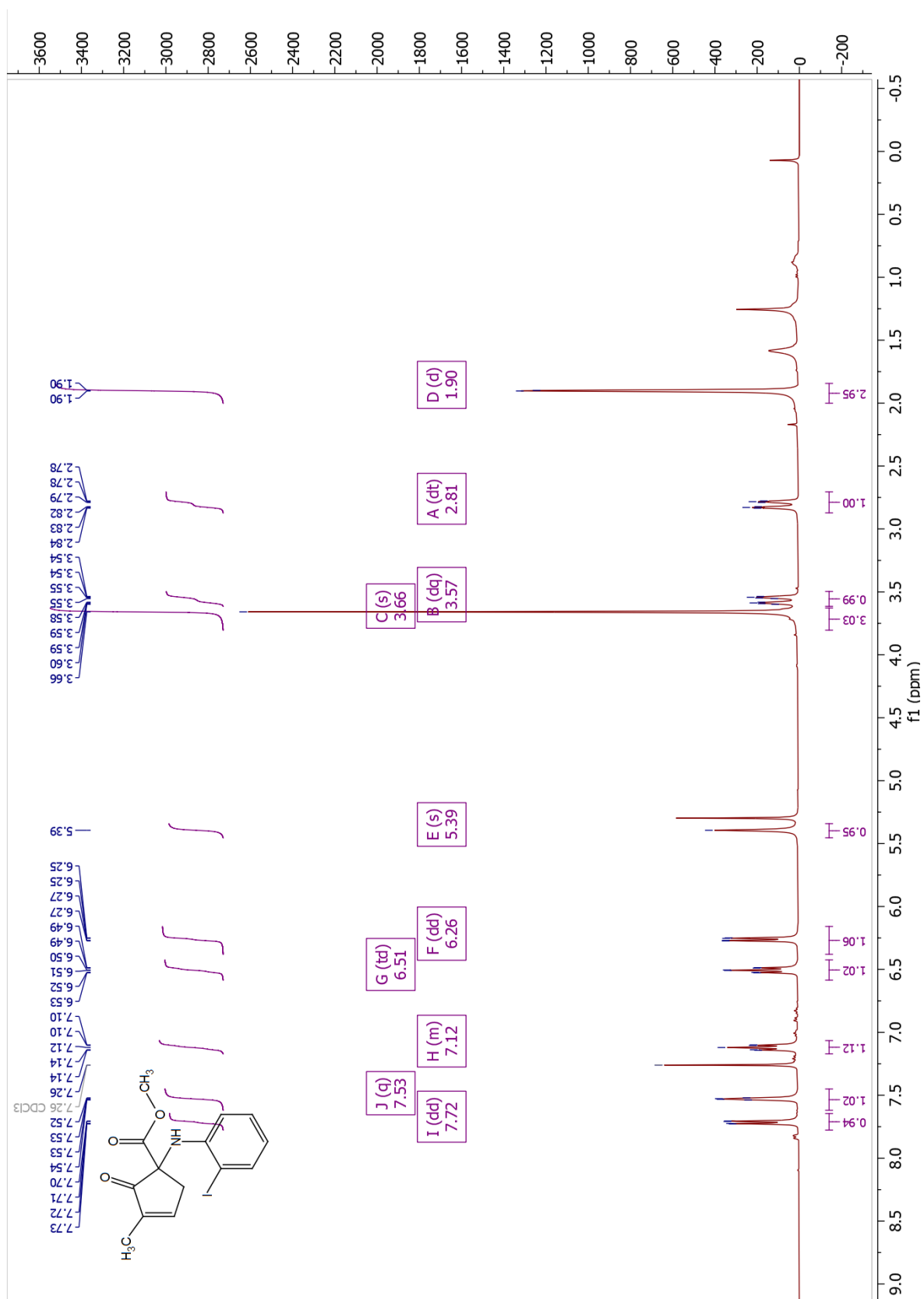


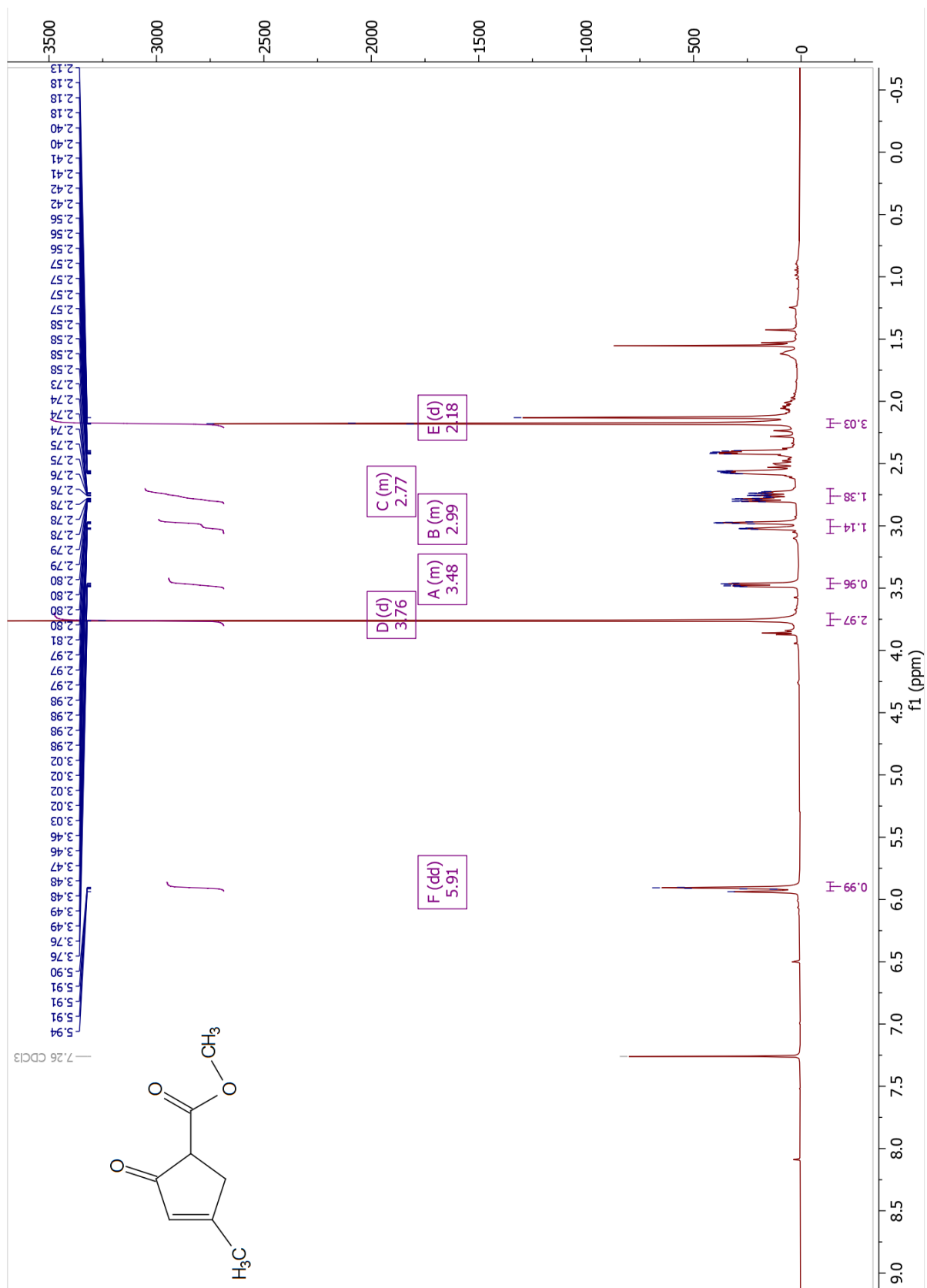


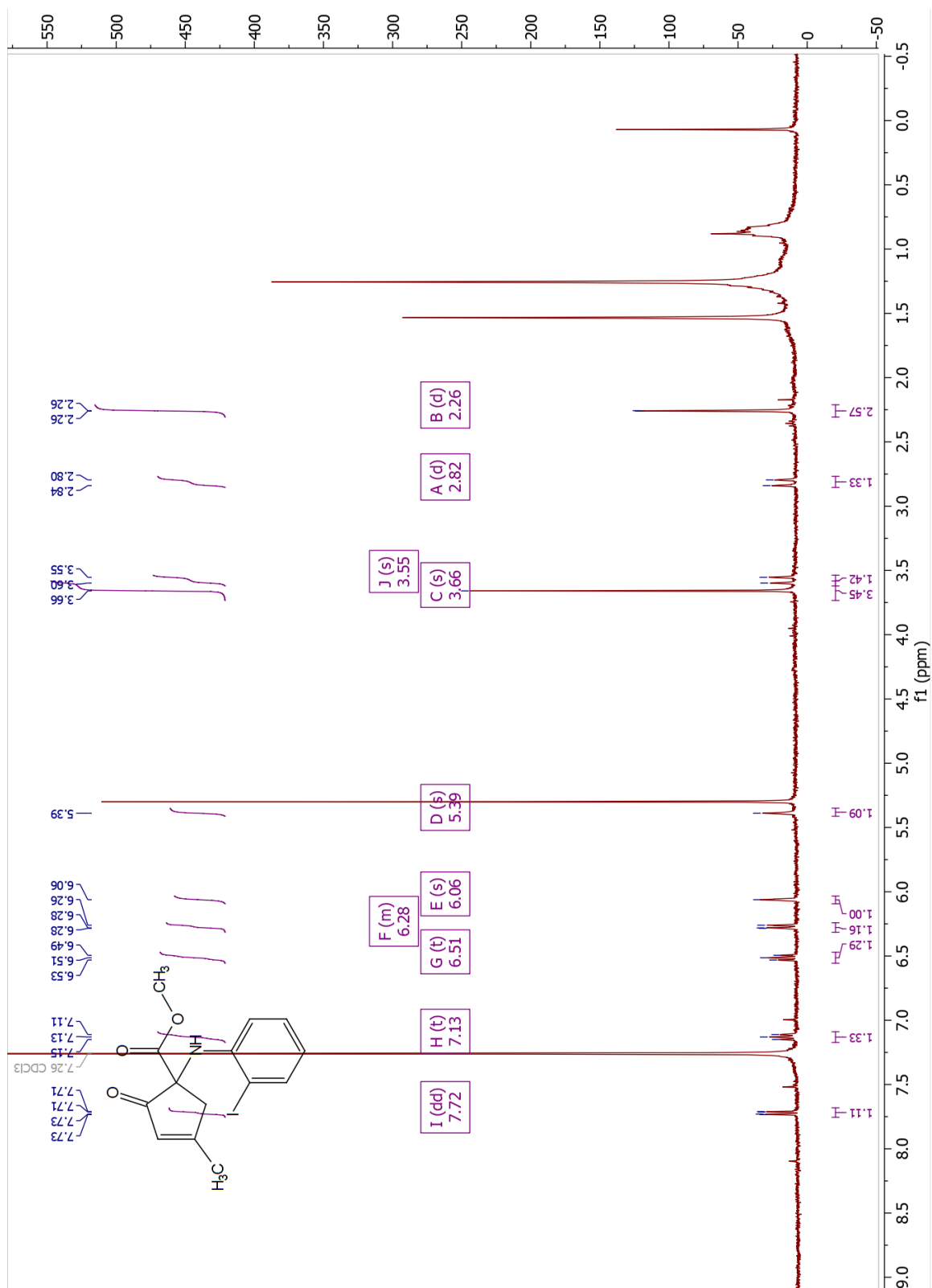


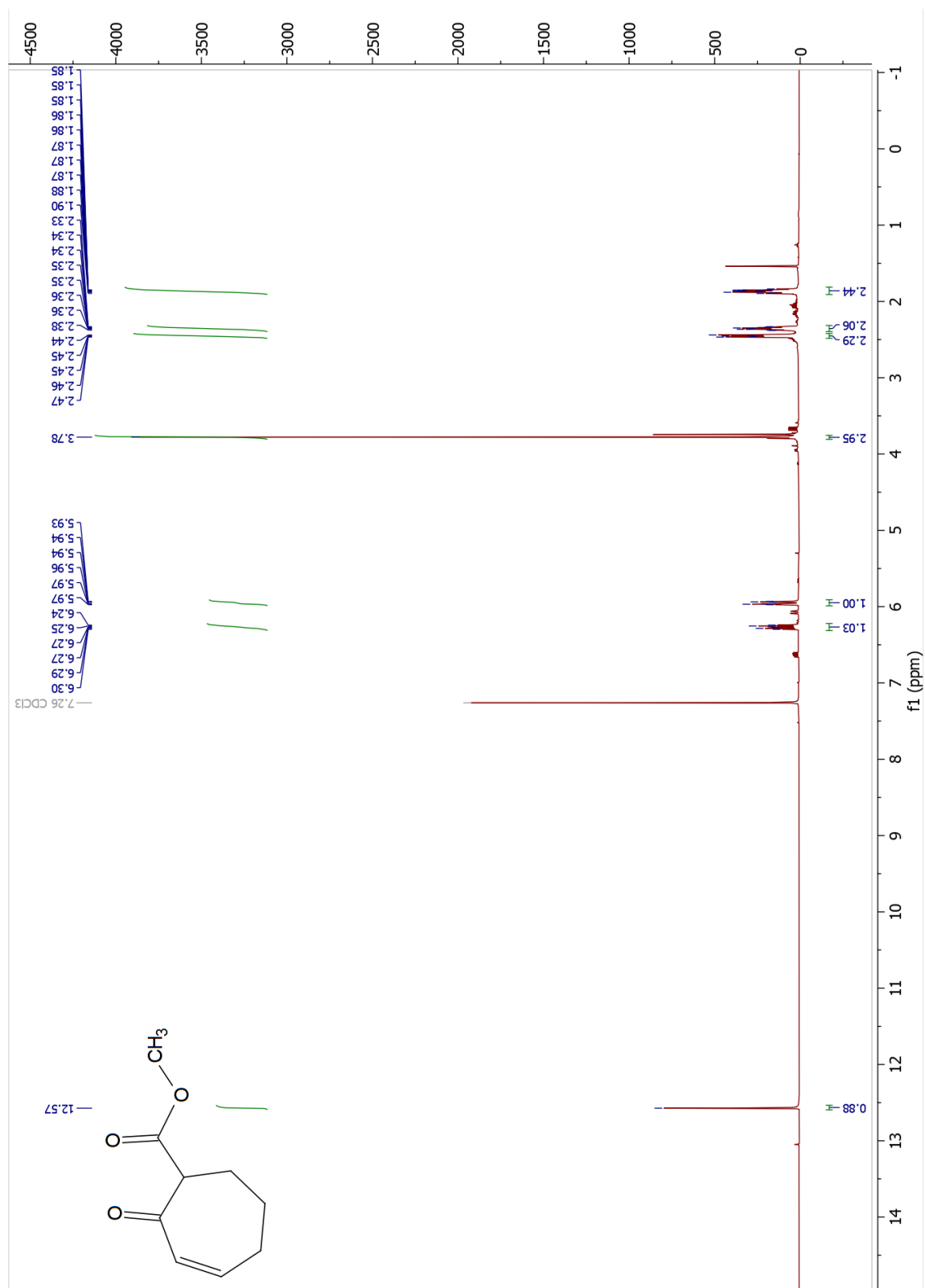


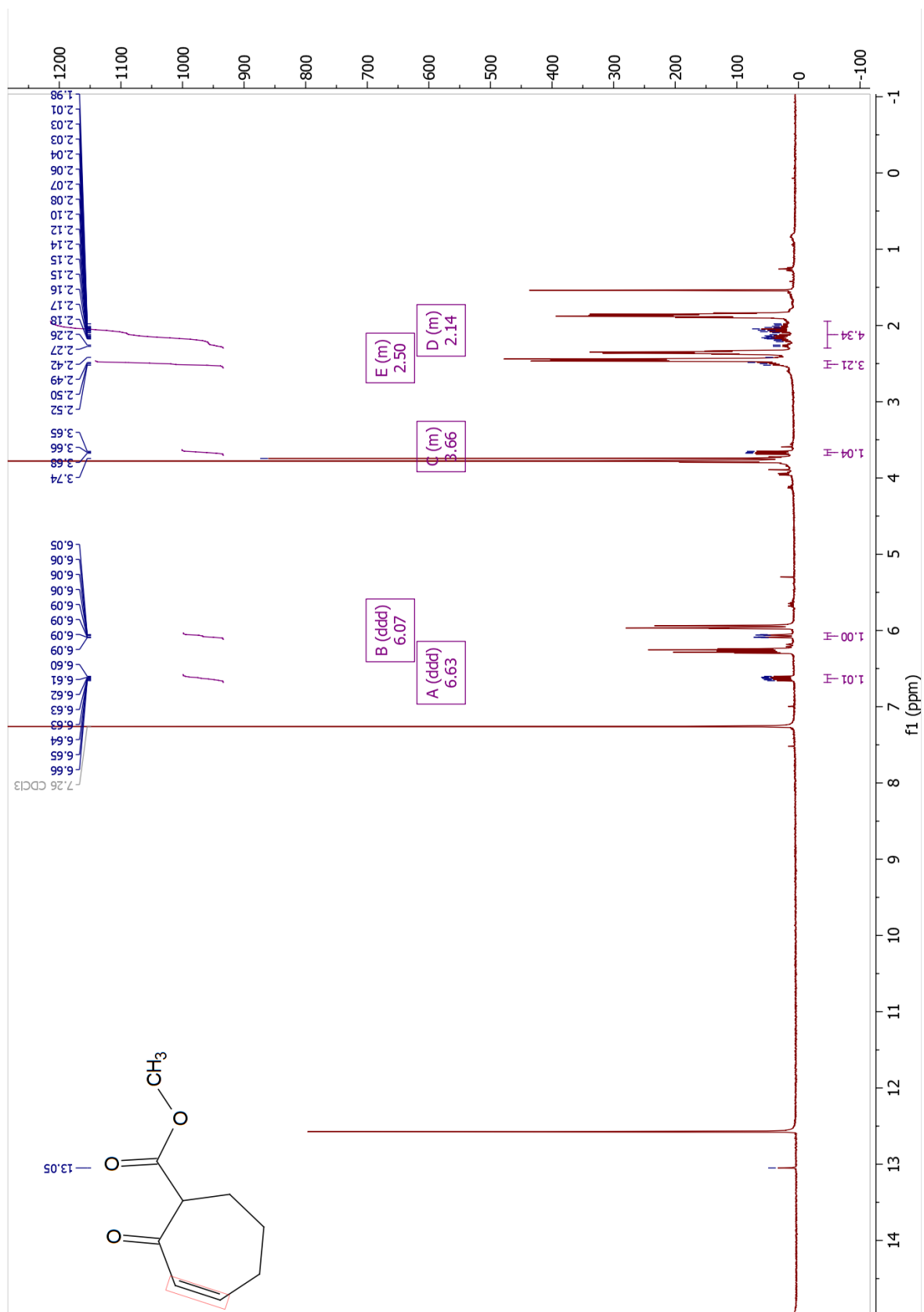


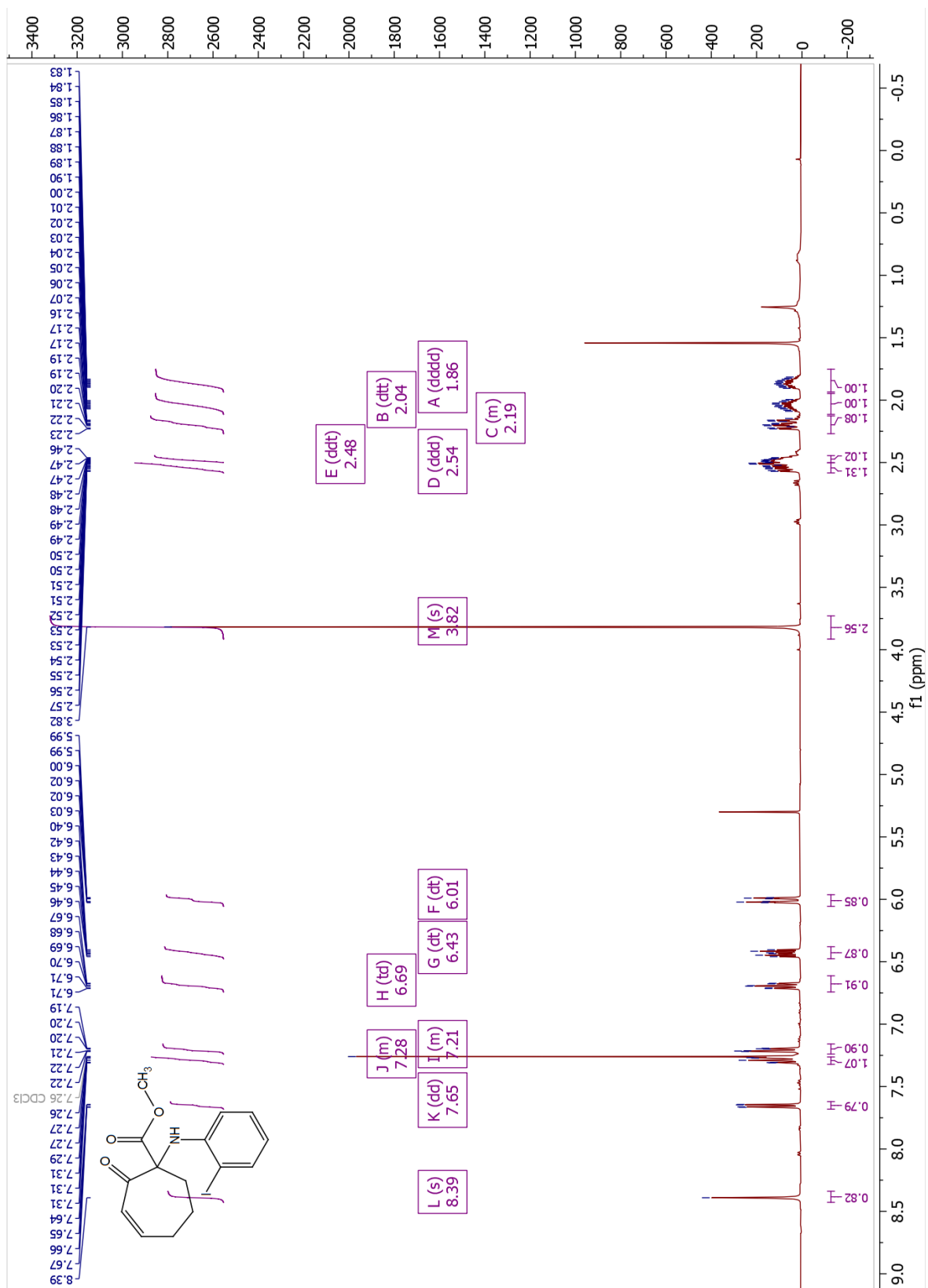


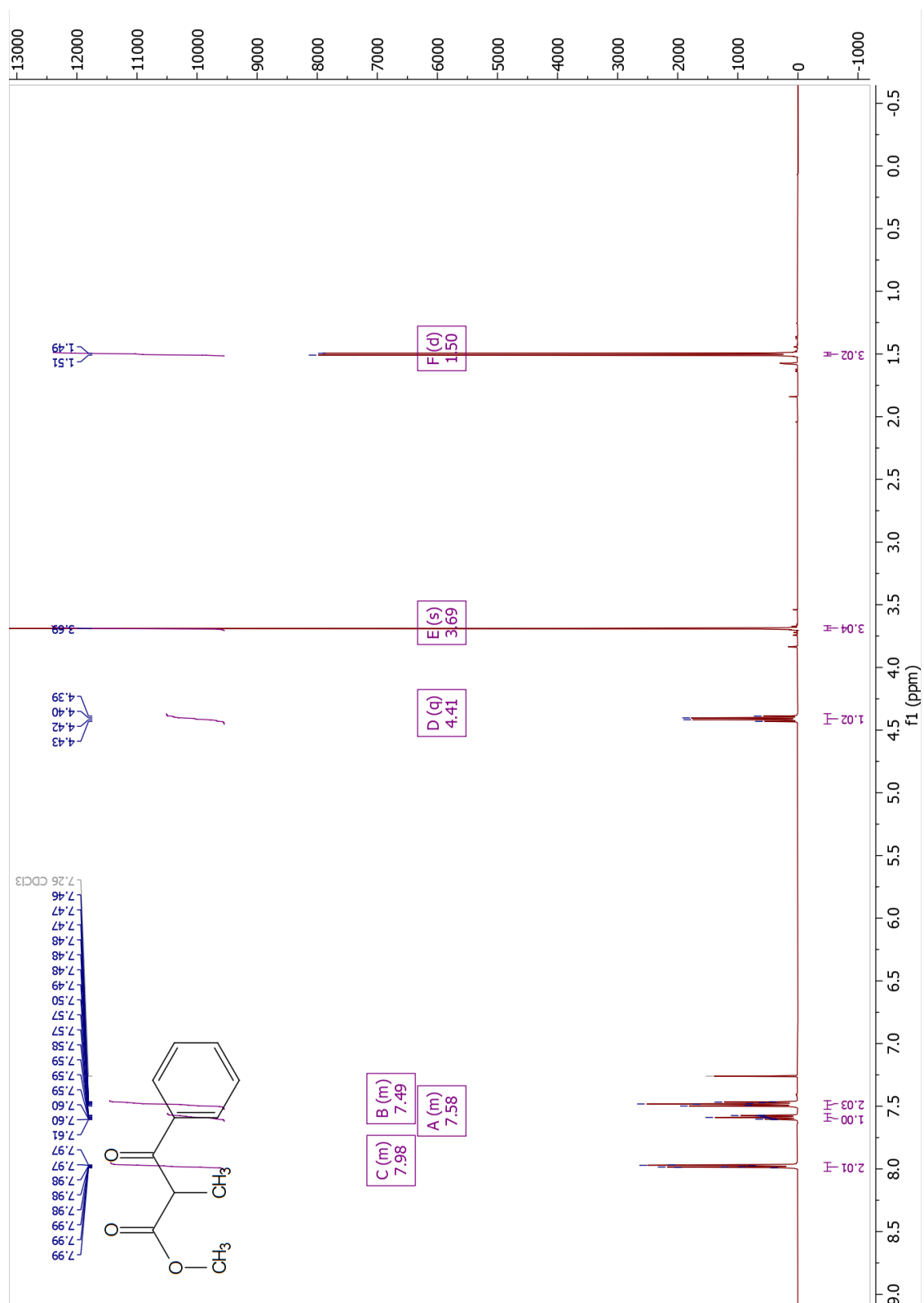


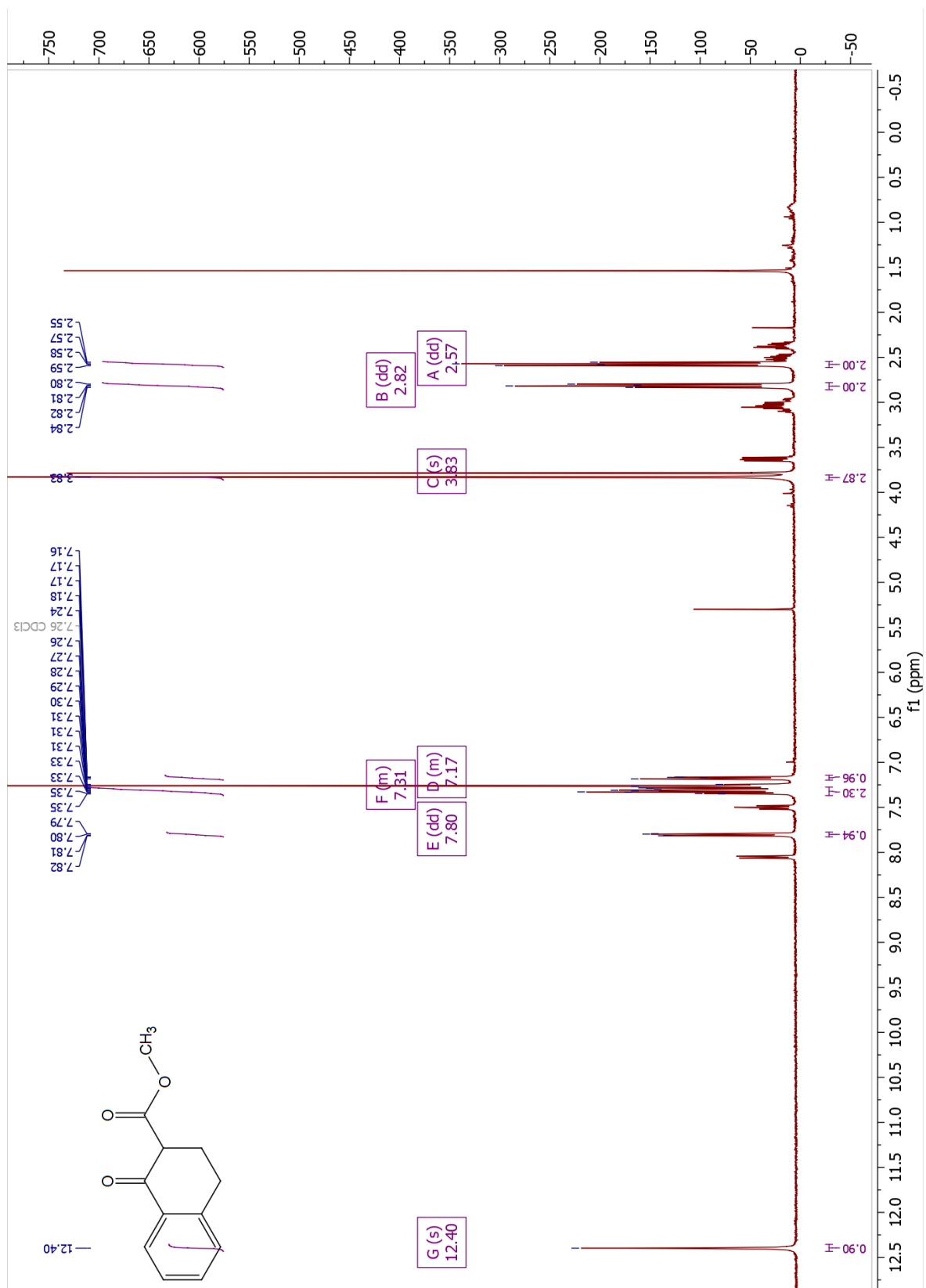


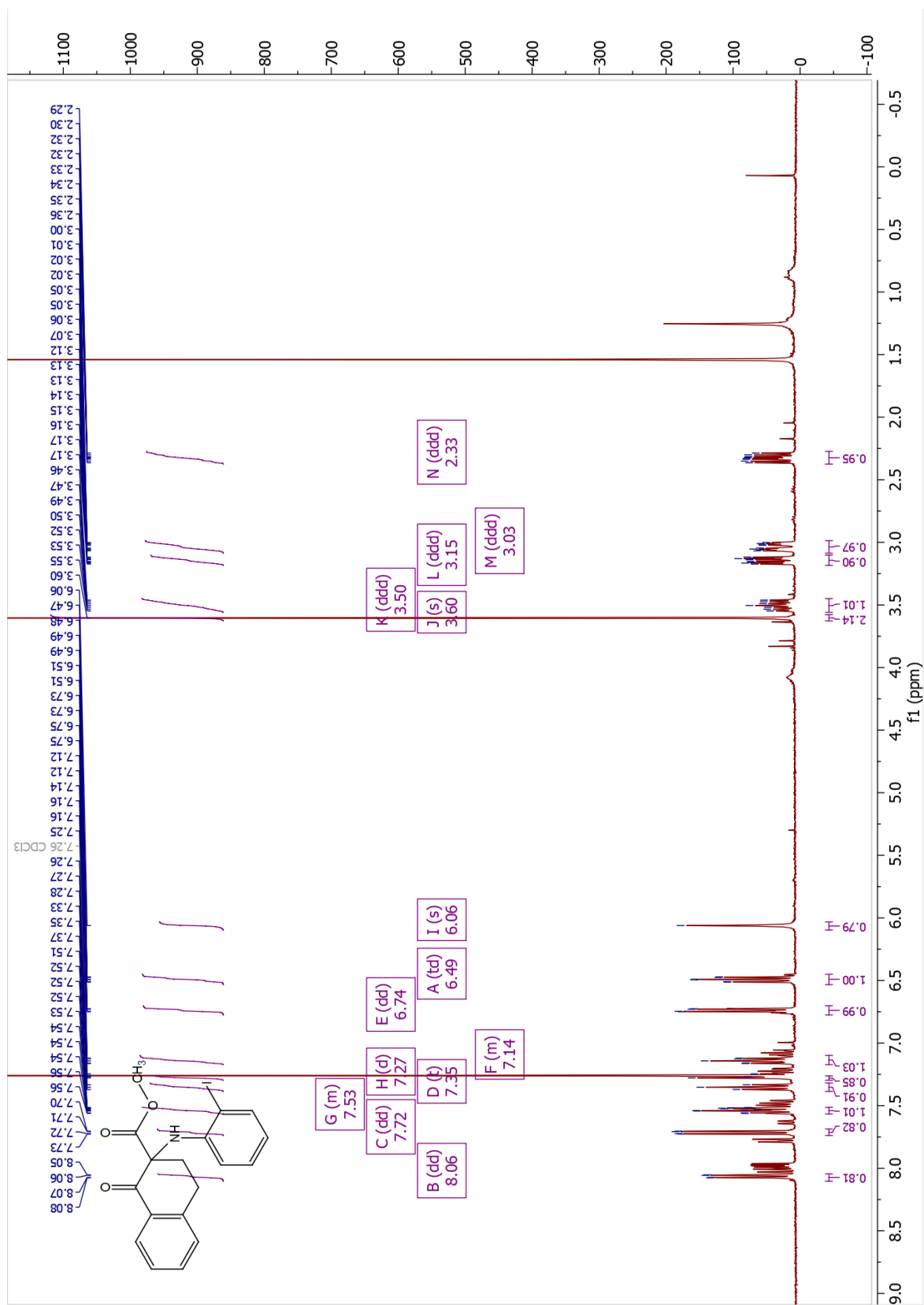


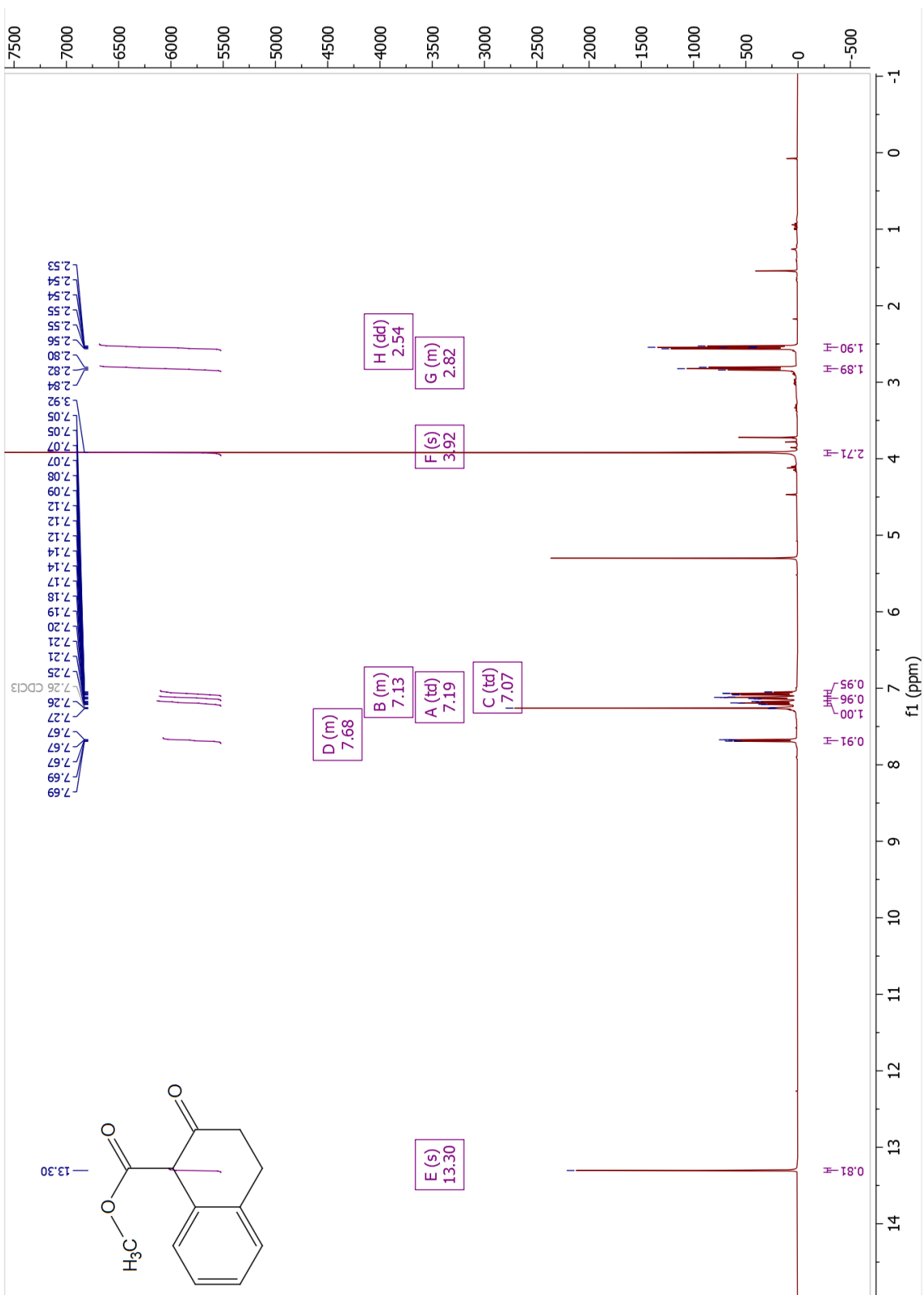


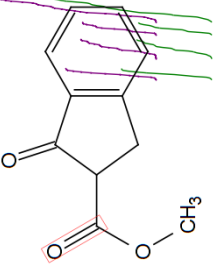


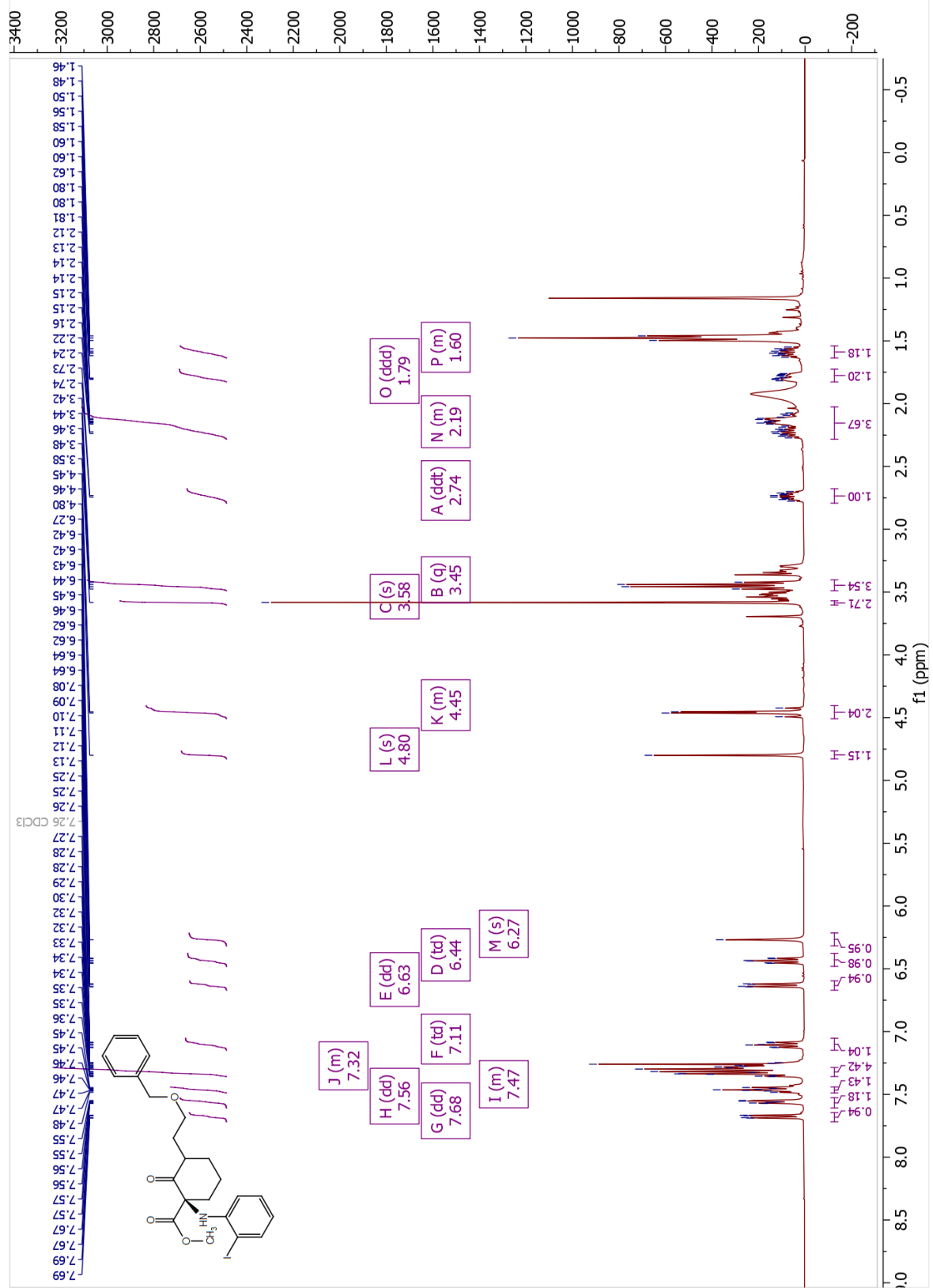


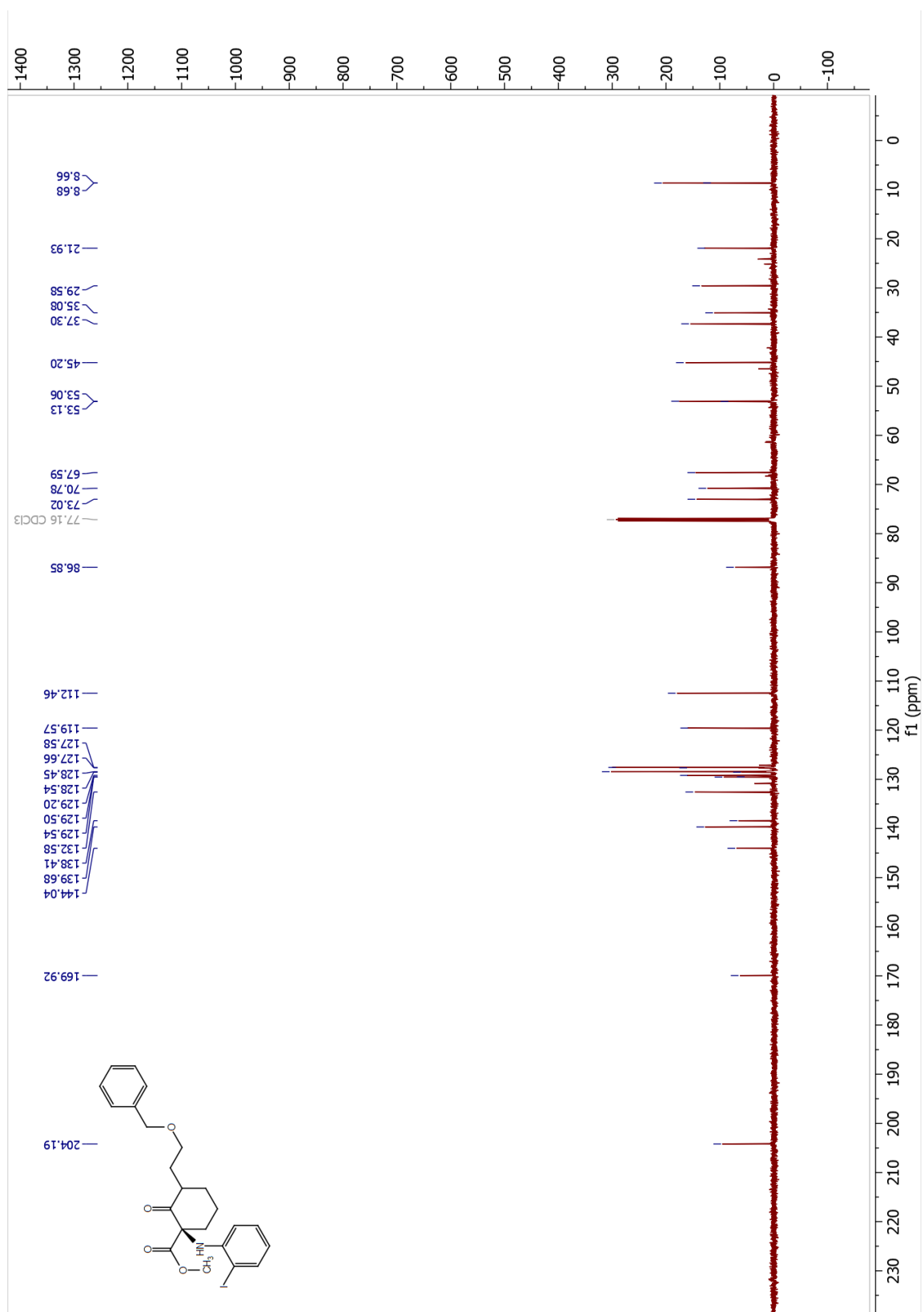


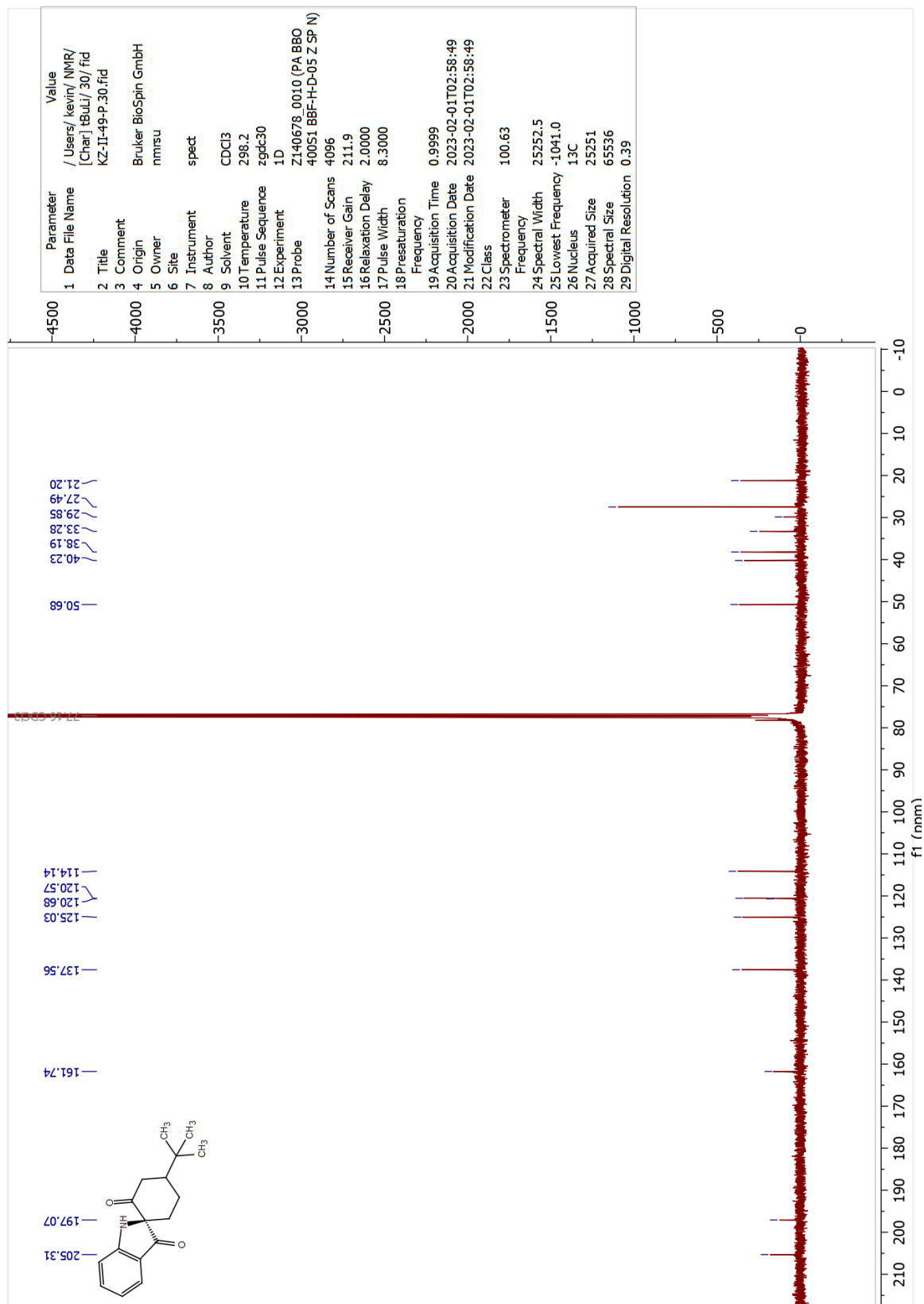


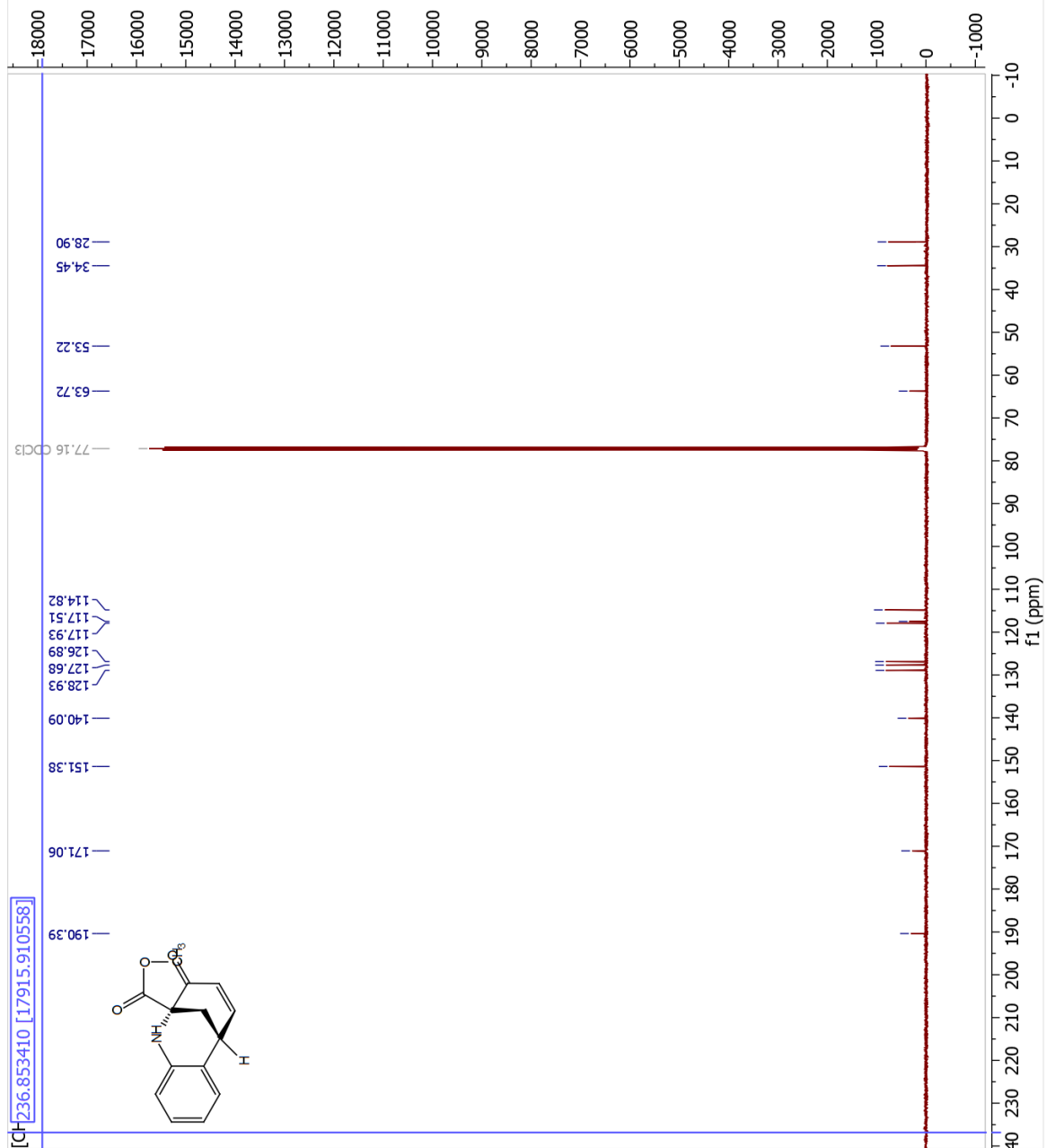




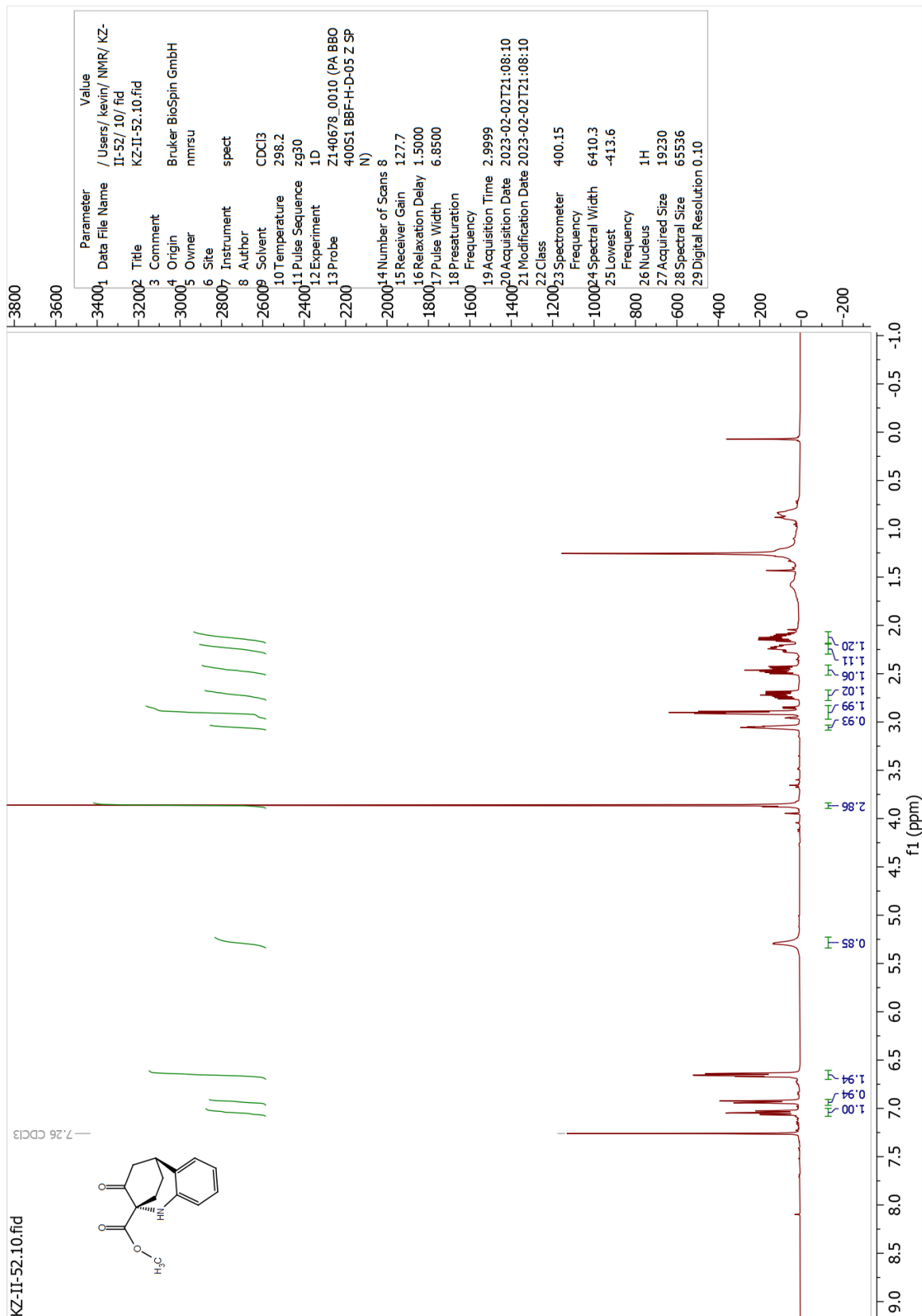




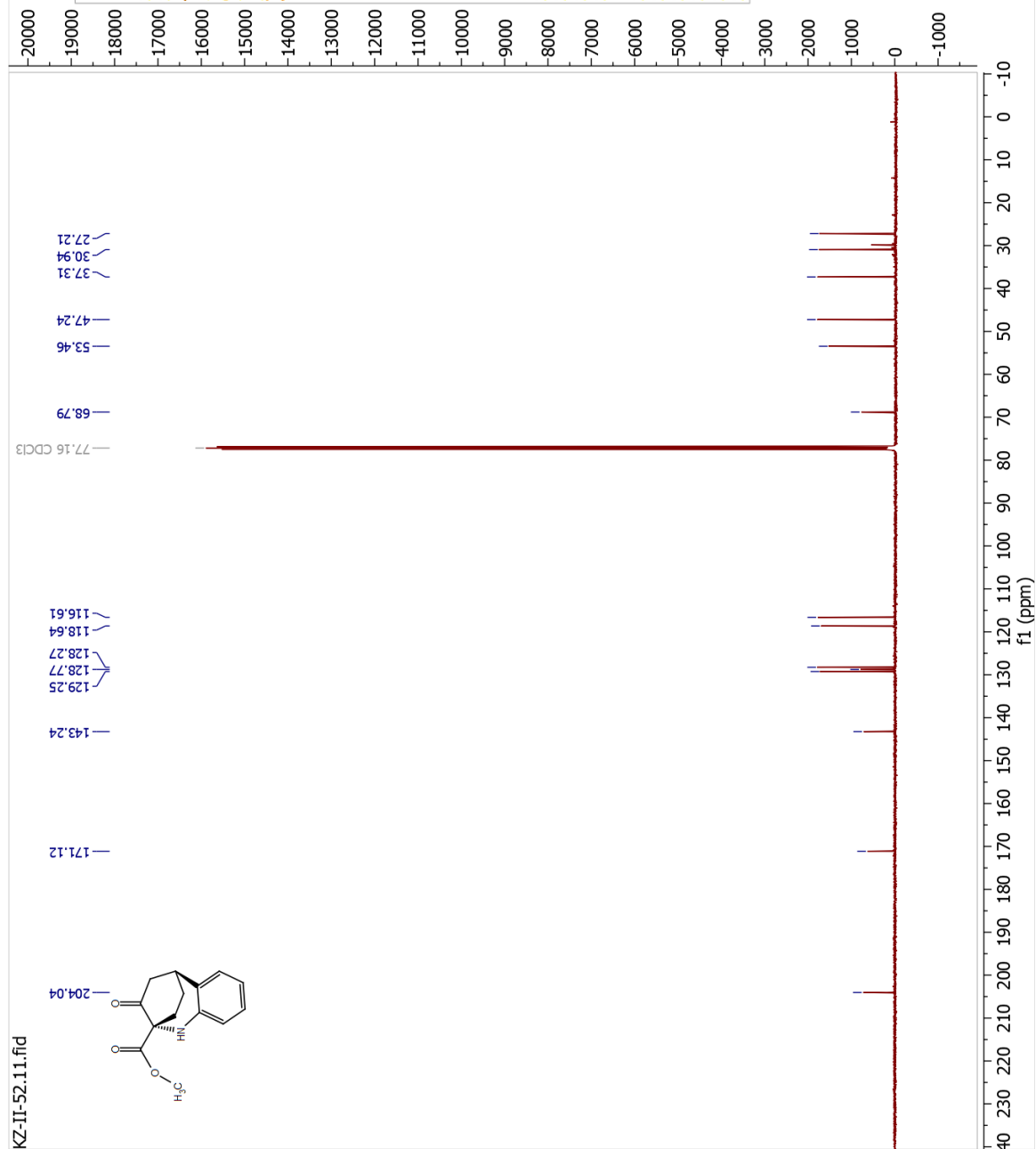
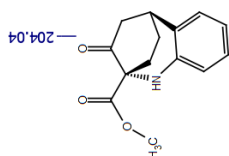




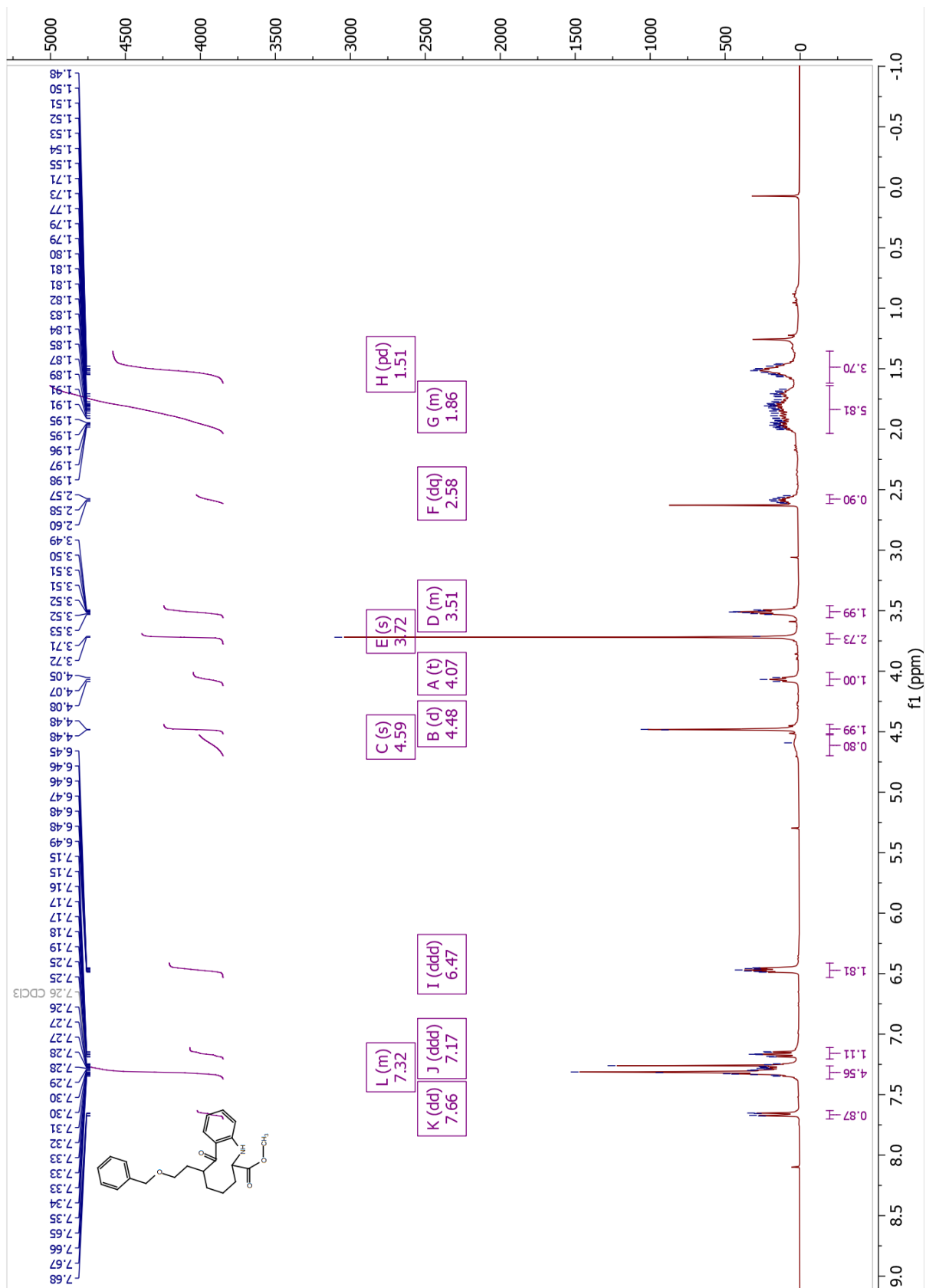
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7 Instrument	spect
8 Author	
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11 Pulse Sequence	zgdc30
12 Experiment	1D
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18 Presaturation	
Frequency	0.9999
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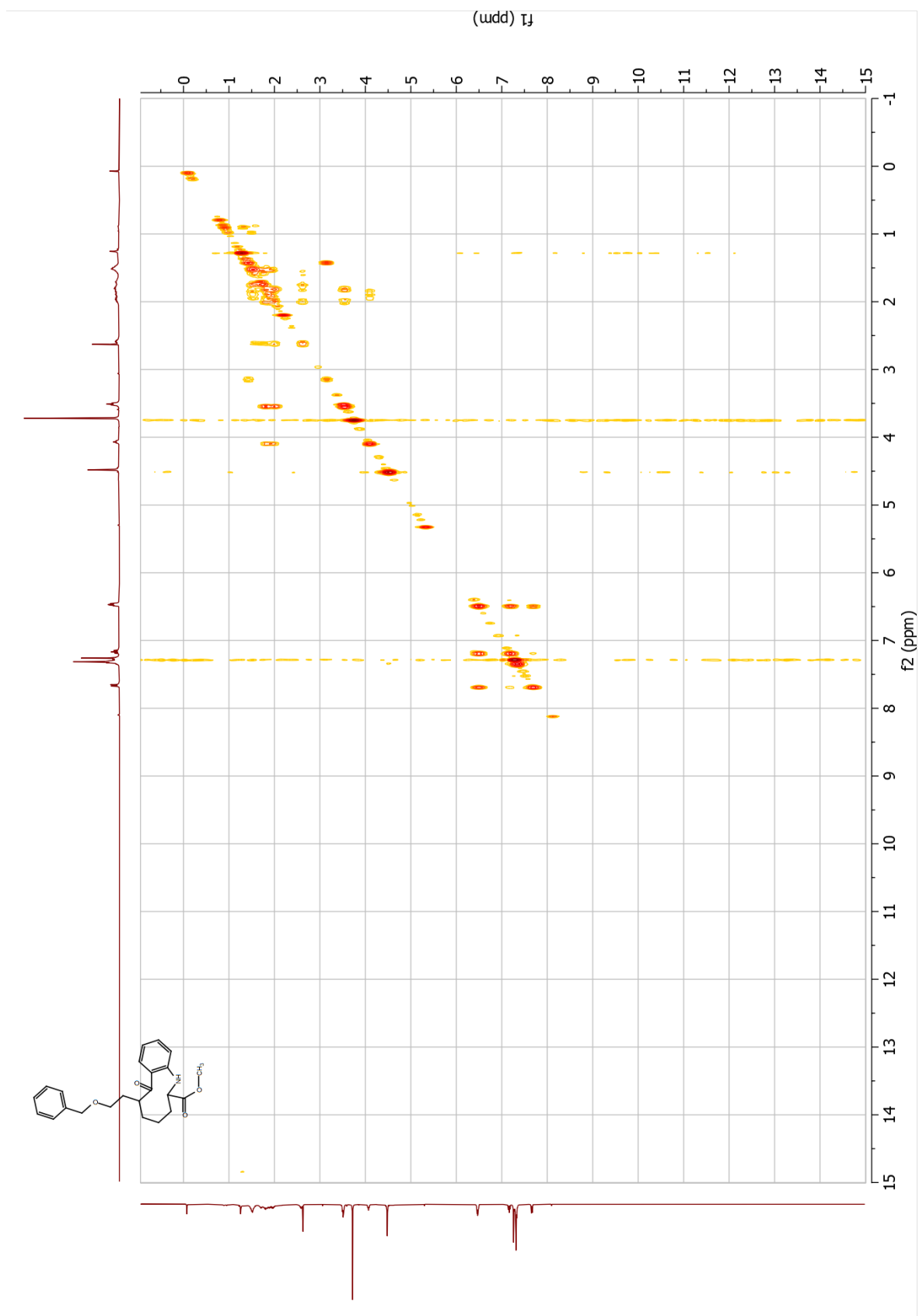


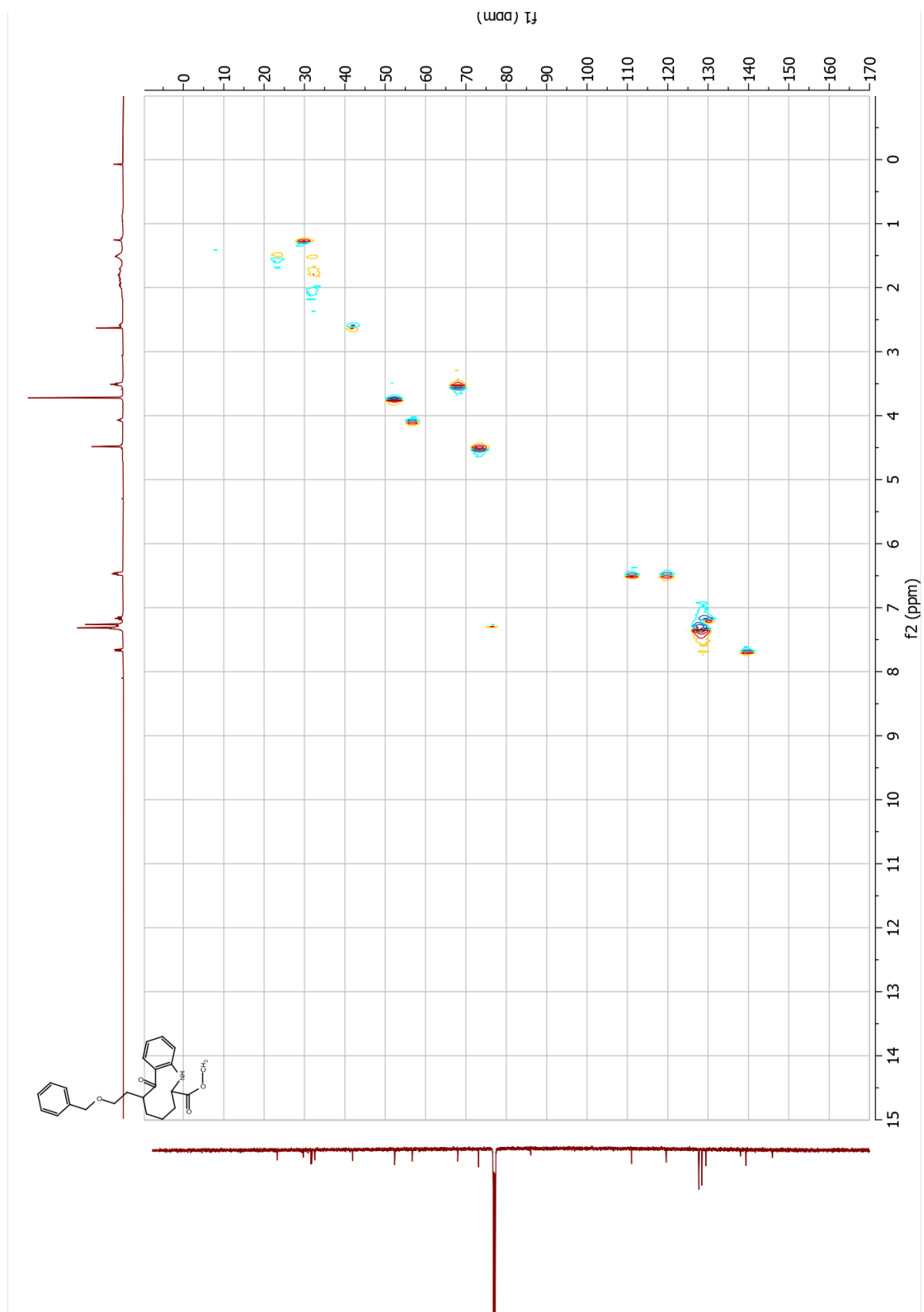
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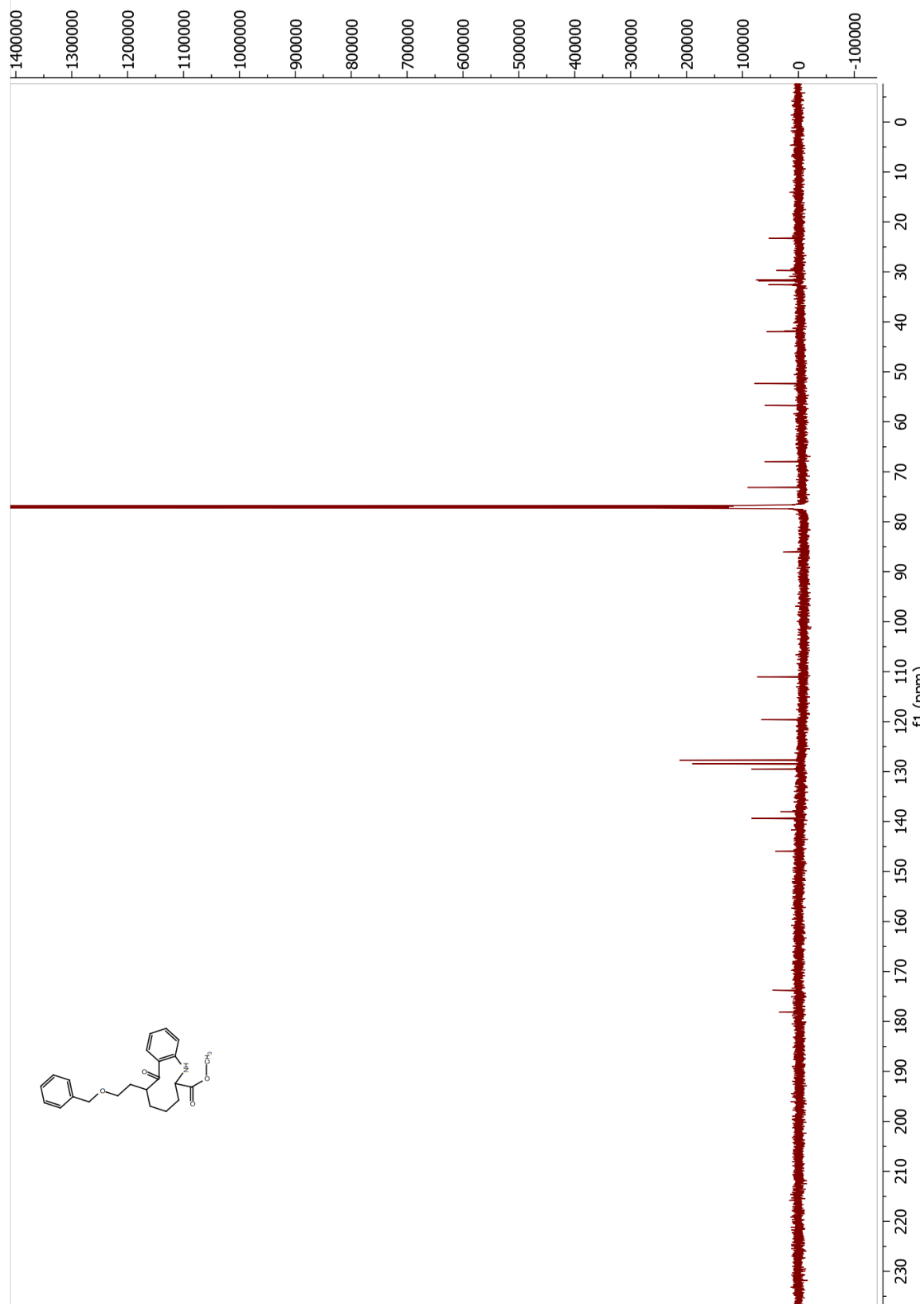


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28 Spectral Size	65536
29 Digital Resolution	0.39









1.6.7 HPLC Traces of Selected Intermediates

Racemic HPLC trace

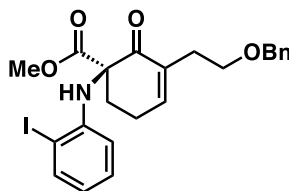
OJ-H, 1 mL/min, 90:10 Hexane:Isopropanol



Analysis Report

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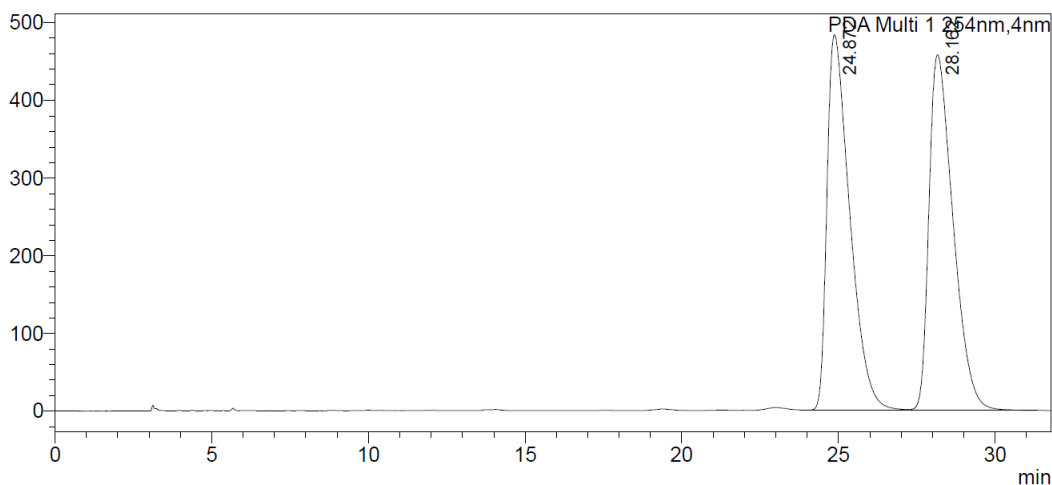
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Method Filename : Default Method.lcm
Batch Filename :
Vial # : -1
Injection Volume : 20 uL
Date Acquired : 7/28/2020 10:04:52 AM
Date Processed : 7/28/2020 10:36:43 AM



Sample Type : Unknown
Acquired by : Snyder Group
Processed by : Snyder Group

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mAU



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PDA Ch1 254nm

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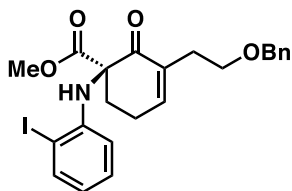
Asymmetric HPLC trace

OJ-H, 1 mL/min, 90:10 Hexane:Isopropanol



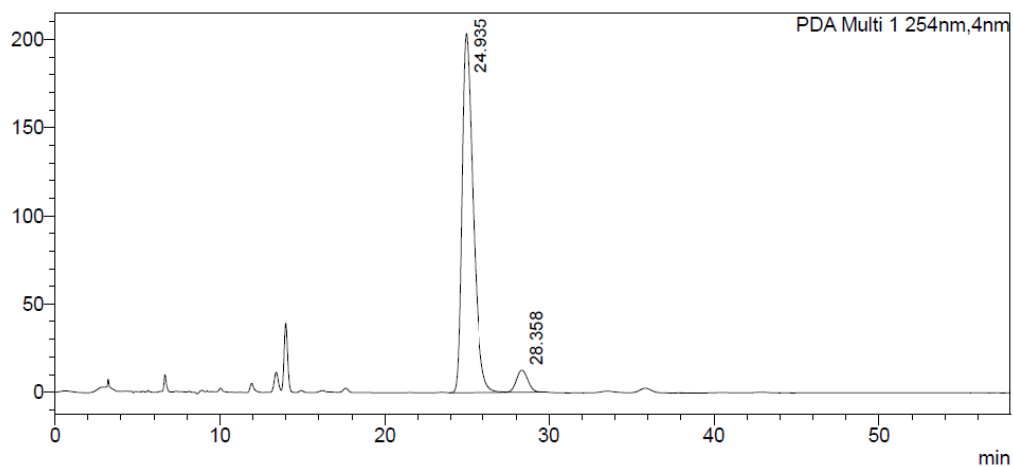
Analysis Report

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Chapter 2:

A Lewis Acid Template Approach to Akuammiline Alkaloids

2.1 Preamble

2.1.1 Introduction to the Methanoquinolizidine Framework

Moving away from the infamous *strychnos* alkaloids and looking more broadly at strained, densely-functionalized natural products, the akuammiline family of alkaloids have garnered an almost unfathomable level of attention from the synthetic organic community.¹⁻⁶ Biosynthetically related to the *strychnos* family, the unifying feature of the akuamma class of indole alkaloids is the cage-like polycyclic methanoquinolizidine core. This structural motif is a transposition of the ring joined at C2 to the C7 position of the indole in the *strychnos* and akuammaline cases respectively. This modification simultaneously imposes both a beautiful architecture and substantial synthetic challenge (Figure 2.1). The difficulty of their synthesis becomes apparent when contrasted to the structure of adamantane. Whereas the conjoined ring system of adamantane allows for all the rings to sit in the chair conformation, thereby minimizing the overall strain, the migration of the ring junction to the bridging nitrogen atom instead enforces two of the rings to occupy a boat conformation (Figure 2.2).⁴ The overall strain of the polycyclic system is likely further exacerbated by ring puckering due to the presence of the nitrogen, amplifying the effect of the multiple 1,3-diaxial interactions.

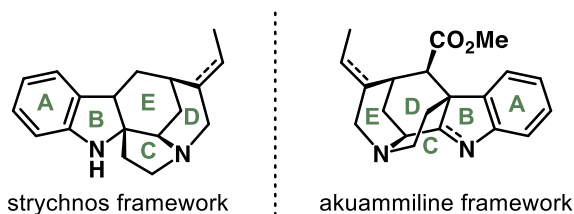


Figure 2.1 Representative strychnos and akuammiline alkaloid frameworks

Despite the significant attention these alkaloids have received, only a small number of all the isolated congeners have succumbed to total synthesis.¹ In their informative review of the

seminal works in this area, Gaich *et. al.* argue the D-ring formation is the crucial step the syntheses of these alkaloids.⁴ While undoubtedly essential to the overall architecture, we propose that the successful syntheses of these molecules actually hinge on the timely synthesis of the E-ring (Figure 2.1). To explore the validity of this statement, we will analyze a number of representative syntheses, broadly categorizing the strategies and patterns which have ultimately lead to synthetic victory.

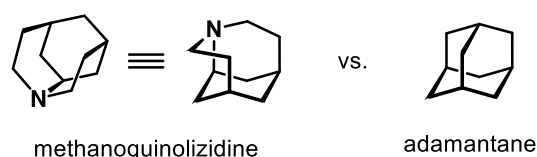
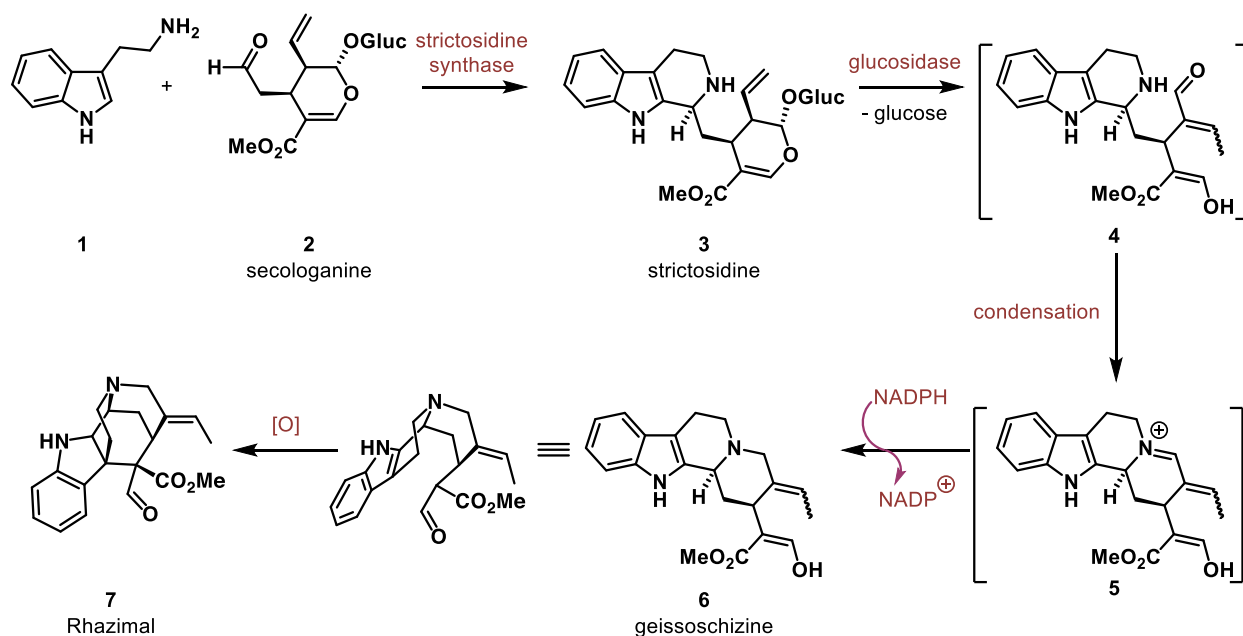


Figure 2.2 Methanoquinolizidine core structure comparison

The biosynthesis begins with an enzyme catalyzed Pictet-Spengler reaction of tryptamine (**1**) and secologanine (**2**) to forge strictosidine (**3**). This intermediate is then deglycosylated and hydrolyzed by strictosidine β -glucosidase to liberate the transient aldehyde (**4**) which quickly undergoes condensation and reduction to form E-ring of the finale framework.^{4,7} Notably, this step determines the stereochemistry of the ethylidene moiety, with the majority of the natural products exhibiting what is ultimately the *E*-isomer. In support of Prof. Gaich's supposition, Nature does indeed form the bridging D-ring last *via* an oxidative and dearomative coupling to afford rhazimal (**7**) which is the progenitor of a number of family members *via* a variety of reduction/oxidation processes, deformylations, or other rearrangements (Scheme 2.1).

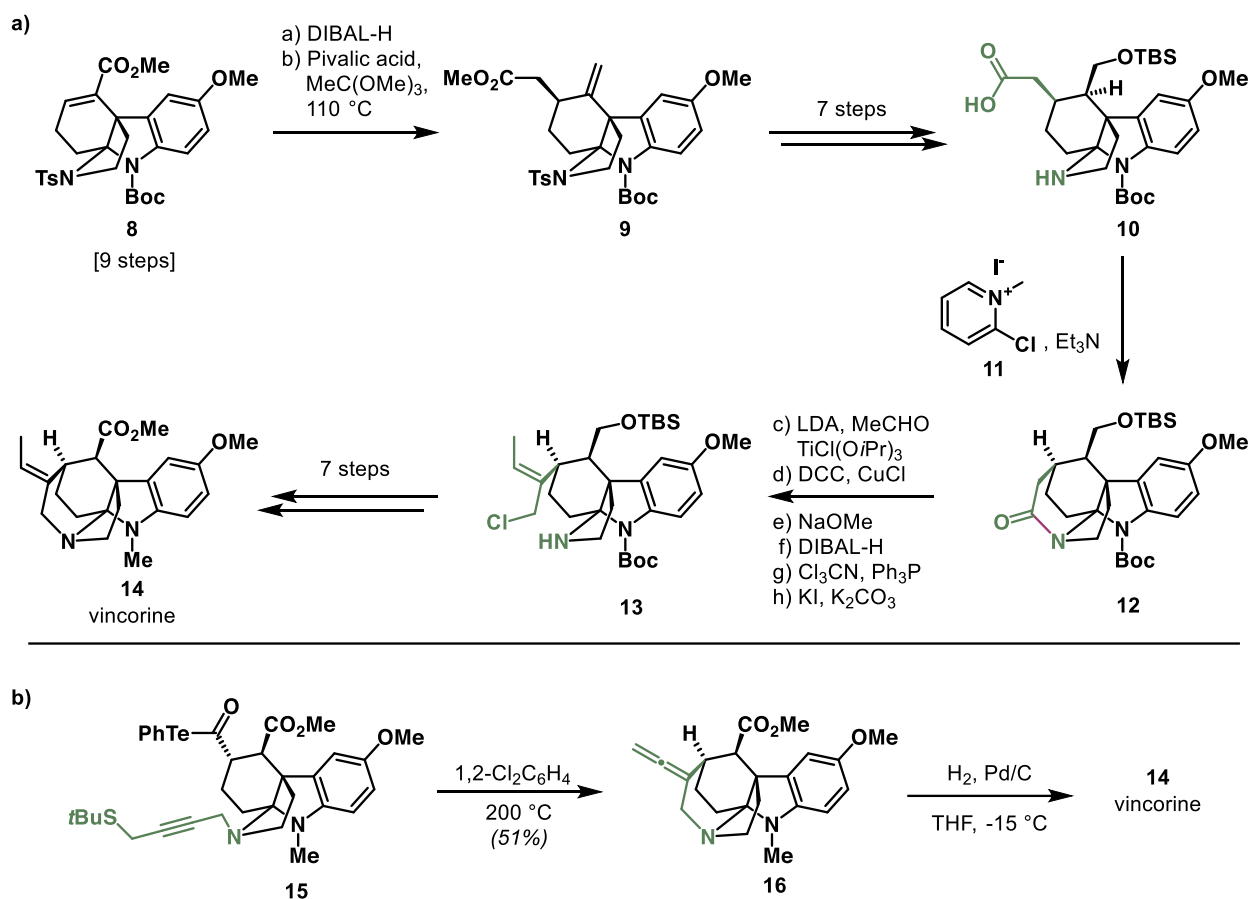


Scheme 2.1 Proposed biosynthesis of akuammiline alkaloids

2.1.2 Synthetic Strategies for Methanoquinolizidine Formation

Perhaps more illustrative of the challenging akuammiline E-ring formation is the first ever reported akuammiline alkaloid synthesis, a 31 step synthesis of vincorine by Prof. Yong Qin.^{5,8} Beginning from α,β -unsaturated ester (**8**) (synthesized in 9 steps from a known *N*-Tosyl-tetrahydro- β -carboline) treatment with DIBAL-H affords the allylic alcohol, which then undergoes a Johnson-Claisen rearrangement to transpose the functional handle to a more accessible position. This rearrangement was necessitated by the failure of a number of classic approaches to functionalize the enoate ester using Heck or related chemistries. This newly formed ester is then hydrolyzed, and treated with Mukaiyama's reagent (**11**), yielding amide **12** and forging the E-ring.^{9,10} However, from here installation of the ethylidene moiety using unique *syn*-elimination conditions then allowed for a number of functional group interconversions as well as a subsequent ring cleavage, and reformation event *via* intramolecular S_N2 of intermediate **13** (Scheme 2.2). Installation of the left-hand ring and the necessary peripheral functionality

necessitated an additional 21 steps from **8**. This approach also proved fruitful in a recently published synthesis of strictamine.¹¹



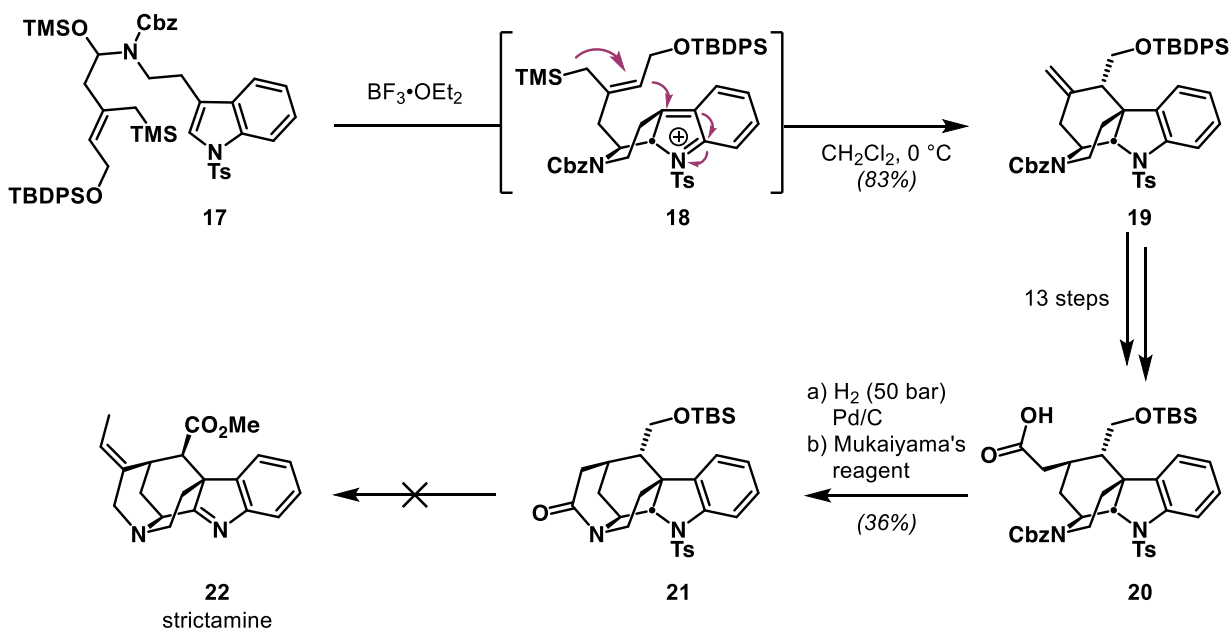
Scheme 2.2 a) Yong Qin's total synthesis of vincorine with emphasis on E-ring formation; b) MacMillan's 9-step enantioselective total synthesis of vincorine.

Just 4 years after the inaugural synthesis, the MacMillan group reported an elegant and efficient asymmetric total synthesis of the same natural product.¹² Their approach towards *E*-ring construction by forging a carbon-carbon bond as opposed to the carbon-nitrogen bond in the Qin synthesis ultimately has the added benefit of avoiding the molecular gymnastics of their predecessors. The MacMillan group instead utilized a thermally promoted alkyne radical cyclization initiated with an acyl telluride at 200 °C. Notably, the telluride was necessary to eliminate the thiopyridine recoupled byproduct formed under a variety of more classic conditions. The high temperature was also necessary to achieve reasonable yields of the highly

strained core despite full conversion under more mild conditions. The resultant allene could then be selectively hydrogenated to afford the natural product in just 9 steps (Scheme 2.2).

While vincorine exhibits a slightly altered framework, it is an illustrative example of the synthetic challenge posed by the E-ring as additionally evidenced by the requisite forcing conditions to achieve the final cyclization. Moreover, Qin's original strategy was later successfully deployed to build the methanoquinolizidine motif in Blakey's synthetic studies toward strictamine despite their inability to access the natural product itself (Scheme 2.3).¹³ This particular example also highlights a distinct mechanism which affords the D-ring in high yield, although the E-ring manipulations were ultimately the Achilles' heel of the synthesis. Despite these notable instances, there is a general dearth of late-stage E-ring formation strategies evident in the literature; whereas contrary to the solitude of these examples, many syntheses easily accomplish E-ring cyclization in the absence of the rest of the framework.

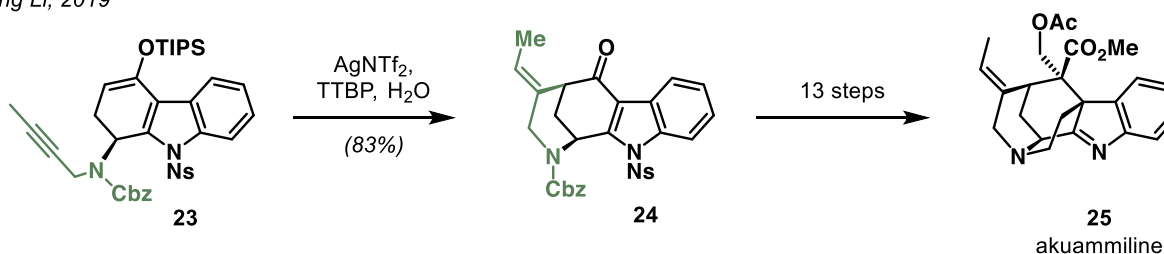
Blakey, 2016



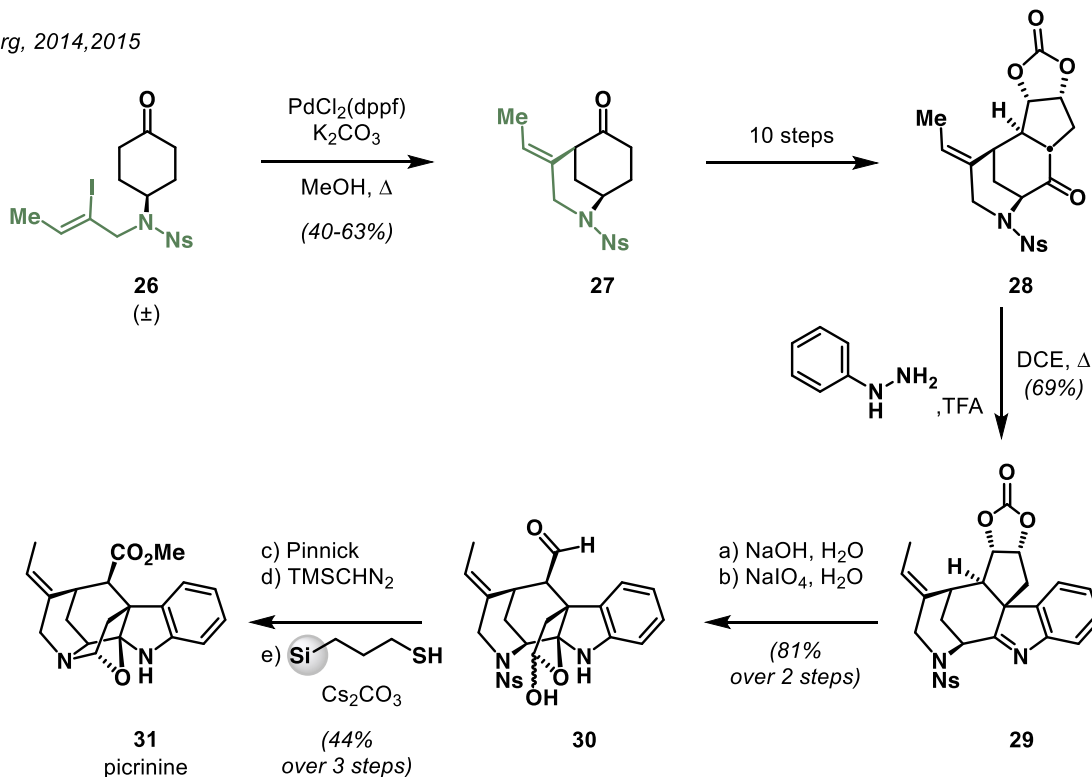
Scheme 2.3 Blakey's iminium cascade and lactamization approach to the pentacyclic core structure

One such effective maneuver to affect early-stage E-ring formation is the metal-mediated alkyne cyclization utilized by both the Garg and Li groups, though the Li synthesis effects this transformation with the indole already installed (Scheme 2.4).^{14–17} This approach is also mechanistic simplification over the palladium enolate coupling which exhibited a variable and moderate yield (Scheme 2.4). Both of these approaches are relatively versatile, and Garg has synthesized a number of akuammiline alkaloids utilizing this powerful Fischer indolization approach.^{6,14,18–20} This synthesis is also notable for the late-stage formation of the bis(*N,O*)-acetal

a) Ang Li, 2019



b) Garg, 2014,2015



Scheme 2.4 a) Garg and Li's early-stage alkyne cyclization approach; b) Garg's synthesis of picrinine featuring a late-stage Fischer indolization

moiety of **31**, which to date is the only conceptual strategy which has been successfully employed, with the exception of our own groups studies (Scheme 2.4).^{18,19,21,22}

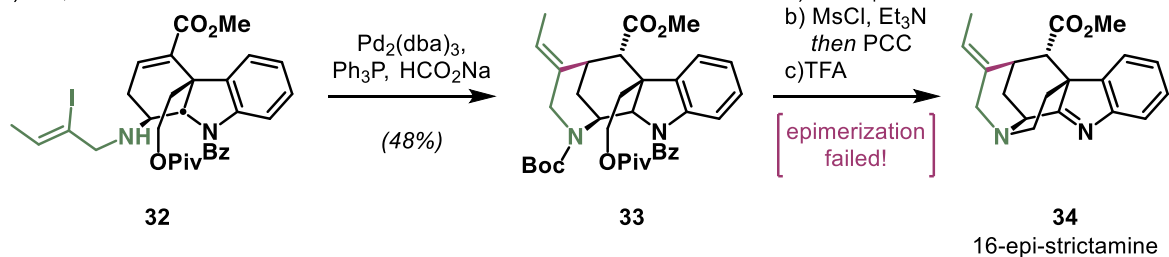
The engagement of an α,β -unsaturated synthon in metal-mediated transformations is undeniably a popular tactic amongst chemists in attempts to form the E-ring, however the astute reader may recall that this approach failed Prof. Yong Qin in his synthesis of vincorine.⁸ In a twist of fate, Qin's group would later find moderate success in the analogous reaction lacking the C-ring; however, this reaction resulted in the undesired stereochemistry of ester α -carbon (**33**, Scheme 2.5).²³ Following the subsequent C-ring cyclization, **34** proved resistant to epimerization. We assume the inability to epimerize stems from the egregious steric hindrance imposed by the rest of the methanoquinolizidine framework.

Perhaps the most notorious successful example of a late-stage E-ring formation is Prof. Jieping Zhu's nickel-mediated cyclization towards strictamine (**27**, Scheme 2.5a).^{24,25} These conditions are well precedented for alkaloid synthesis in other formats, but their implementation here has yielded mixed results as evidenced by the low overall yield, and equimolar ratio of products, and is undeniably a precedent of great importance. To our knowledge this is the only example of methanoquinolizidine E-ring closure in the presence of the rest of the framework, and are the conditions referenced at the crux of 6 formal syntheses, including one from our own group.²⁶⁻³¹ This reaction appears to demonstrate remarkable sensitivity to the steric environment, generally finding greater success in the absence of the N4-C5 bond, as demonstrated by a more recent synthesis of Picrinine by the groups of Wang & Zhai (**31**, Scheme 2.5c).^{23,32}

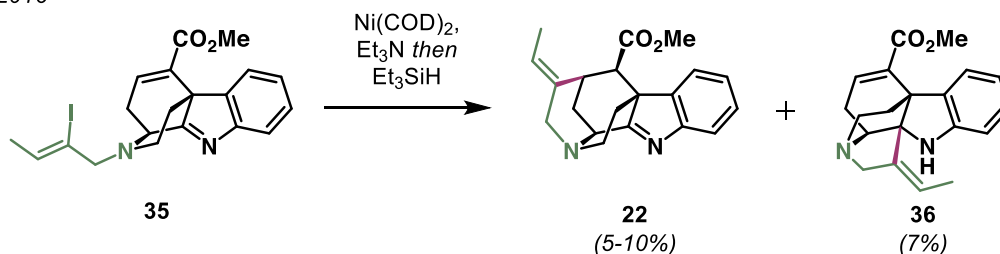
We believe that the difficulty of this reaction in the presence of the tetracyclic ABCD-scaffold originates from the high energy barrier of the double boat conformation (Scheme 2.5d). Without the full pentacyclic framework it is likely the C-ring predominantly occupies the chair

conformation. This conformer could then preclude the necessary reactive geometry of the E-ring sidechain, preventing productive cyclization and potentially rationalizing the substantial amount of dehalogenation and indolenine addition products observed. In order to pre-pay a portion of the energetic costs associated with such a process, we developed a synthetic hypothesis in which the installation of an additional ring (in this case, the bis(hemiaminal) moiety) would lock the C-ring into the boat conformation, facilitating the ultimate cyclization. This strategy has the added allure of access to the more functionally intriguing and arguably more challenging natural products.

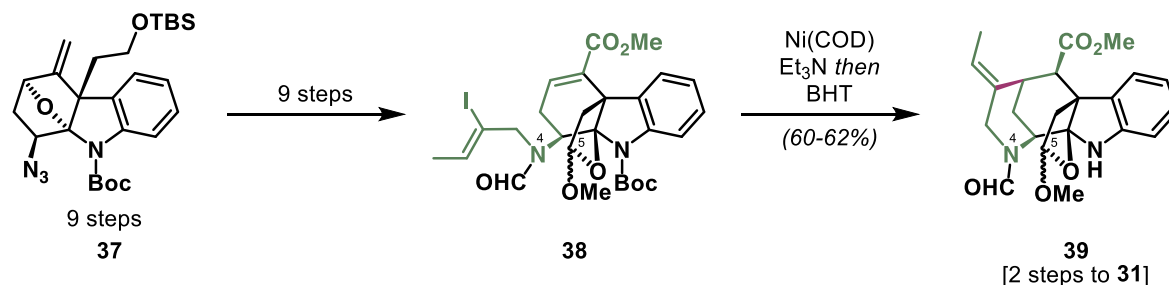
a) Qin, 2019



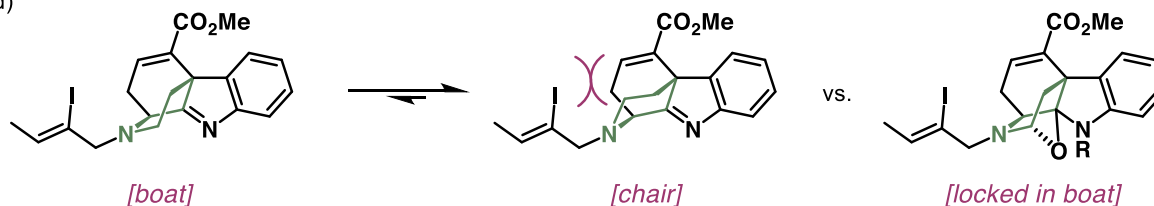
b) Zhu, 2016



c) Wang & Zhai, 2021



d)



Scheme 2.5 a) Qin's Pd-Heck resulting in an un-epimerizable ester; b) Zhu's synthesis of strictamine; c) Wang & Zhai's synthesis of picrinine using reductive Ni-mediated conditions; d) Conformational analysis of Ni-mediated cyclization

2.2 Snyder Group Synthetic Strategy Towards Caged Alkaloids

In addition to the attention akuammiline alkaloids have garnered from the synthetic community, our own group has pursued syntheses of a number of structurally related alkaloids.^{27,33–35} The modular strategy we have devised begins with the formation of a tetrahydro- β -carboline, of which there are plentiful options.^{36,37} From here, the asymmetric introduction of the propargyl sidechain sets the stage for the key 6-*endo*-dig cyclization to rapidly form the tetracyclic ABCD framework. Here is where the syntheses diverge, as the final ring closing events and functional group interconversions are target specific. Although our synthesis of scholarisine A takes a different approach, this general concept has proven useful in three other instances, resulting in the successful total synthesis of 2 alkaloids, and the aforementioned formal synthesis of strictamine (Figure 2.3). The latter is the most direct interpretation of this strategy, and also highlights the challenging nature of the final E-ring cyclization.

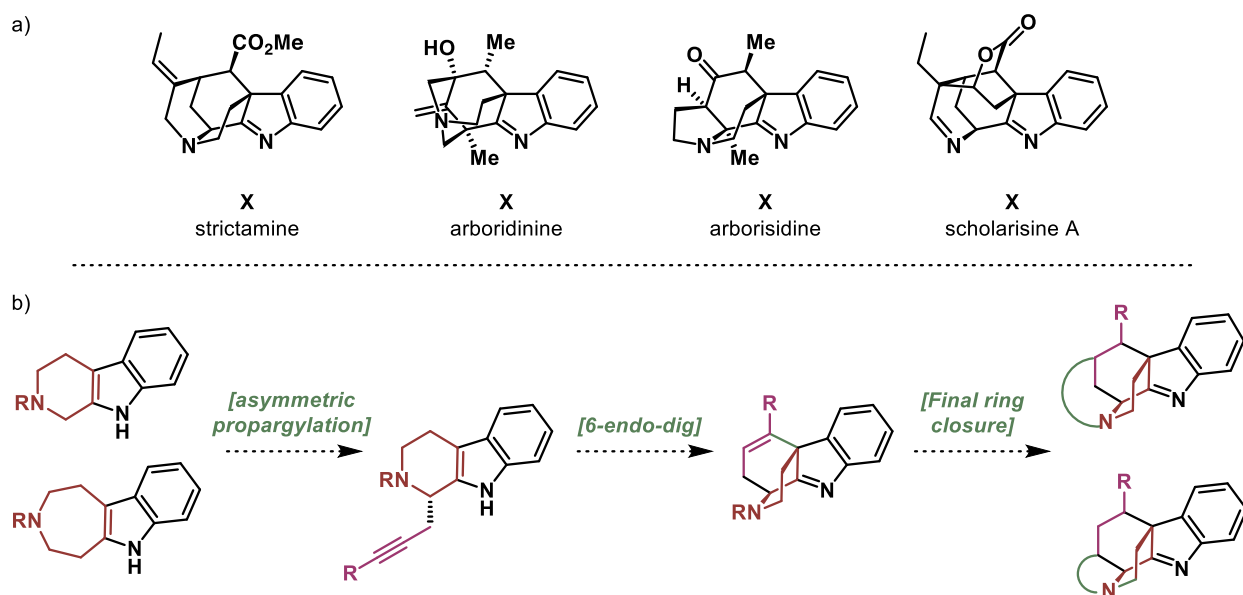
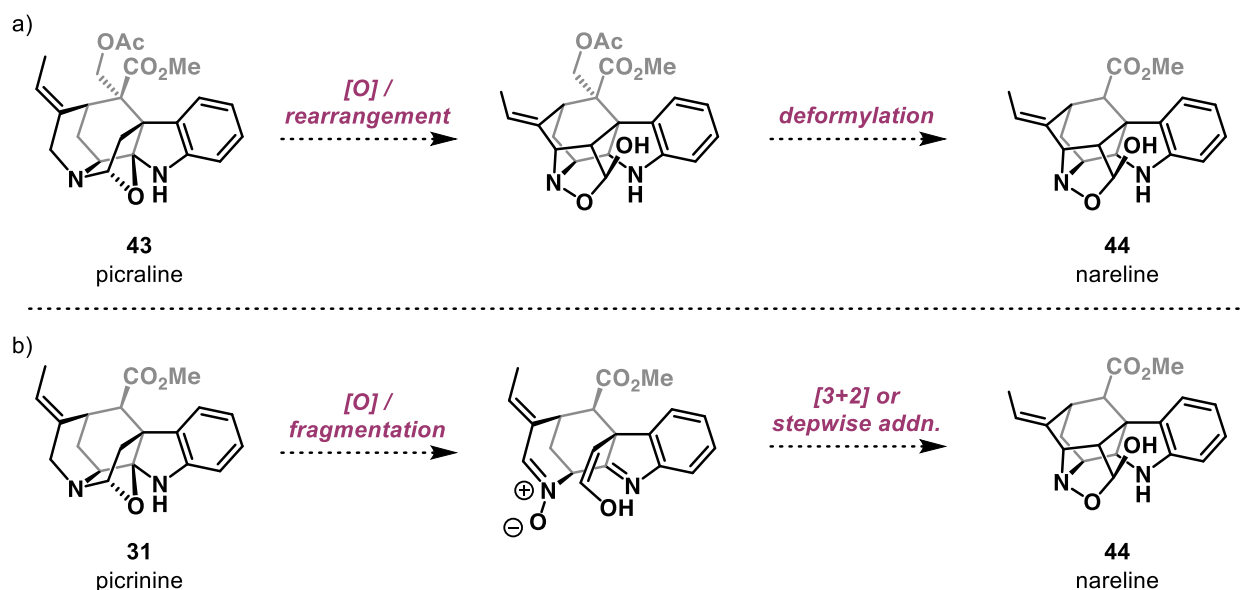


Figure 2.3 a) Snyder groups akuamma type synthetic studies; b) unified approach towards the akuamma alkaloid core

2.3 Snyder Group Progress Towards Picrinine

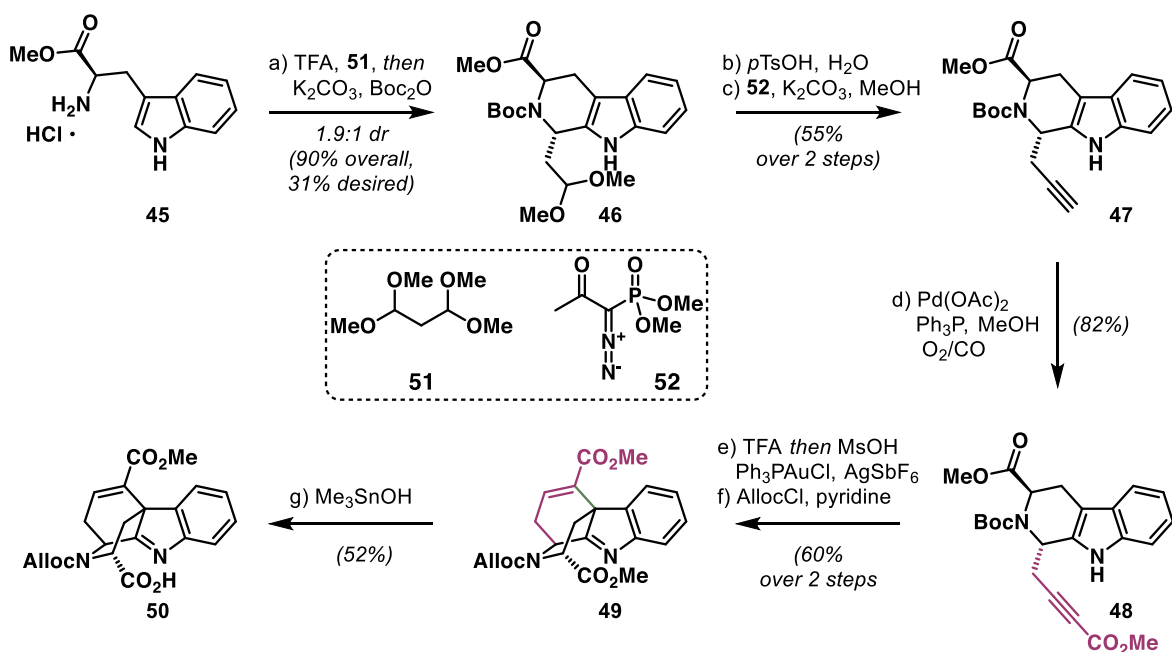
Our group's most recent efforts towards this family began with an intention to synthesize nareline (**44**), an alkaloid featuring a unique hydroxylamine ring system (hydroxyisoxazolidine) which is proposed to be an oxidized and rearranged derivative of the picraline framework.³⁸ Thus, picrinine became the retrosynthetic target, as the construction of the methanoquinolizidine core would be necessary in order to test various intramolecular cyclizations towards the nareline scaffold (Scheme 2.6).²²



Scheme 2.6 a) Proposed biosynthesis of nareline; b) initially proposed route towards nareline

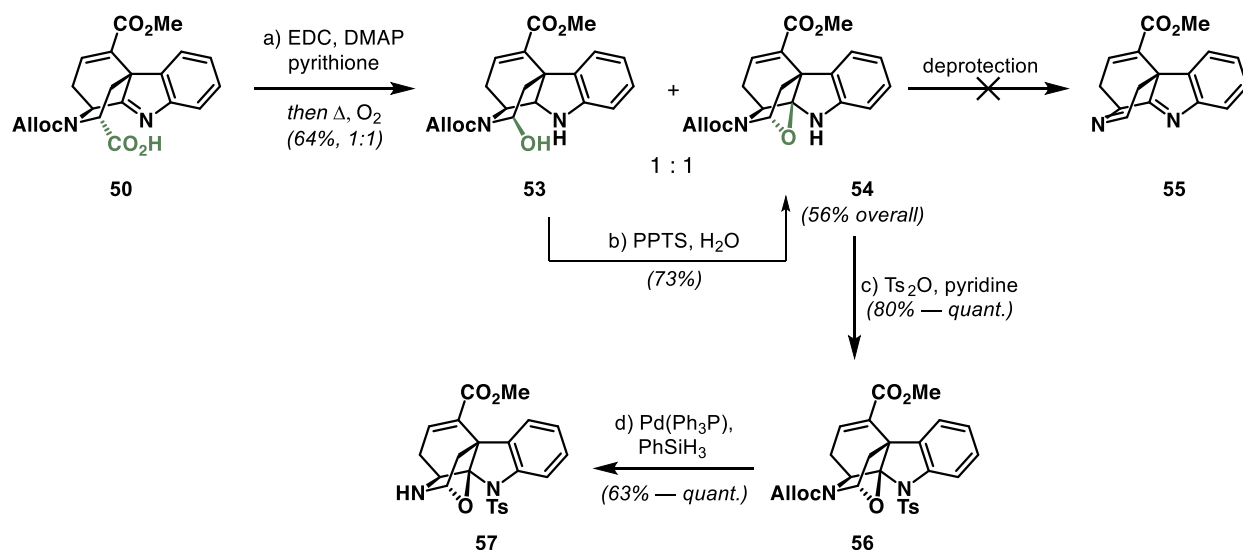
The initial route laid out in scheme 2.7 was designed by my friend and mentor Dr. Charles Cole, and herein we will detail the optimization of the route, and its evolution since the submission of his dissertation.²² The synthesis commences with a one-pot Pictet-Spengler and Boc protection sequence from D-tryptophan methyl ester hydrochloride to give a mixture of tetrahydro- β -carbolines, of which our desired *trans*-isomer is the minor product. Unfortunately, the dominant *cis*-isomer is incompetent in the synthesis as we have previously demonstrated its

inability to perform 6-*endo*-dig cyclization.²² We intended to address this problem, and indeed will, but at this point prioritized late-stage route scouting in the short term due to the affordability of the starting materials. With **46** in hand, we can readily hydrolyze the acetal, and homologate the pendant aldehyde using Ohira-Bestmann reagent. This terminal alkyne can then undergo a Pd-catalyzed carbonylation in the absence of the usual copper salt to afford ynoate-ester **48**.^{39,40} This Boc-protected precursor to the Au(I)-catalyzed cyclization must first be deprotected to avoid the anchimeric interference we previously observed with carbamate type protecting groups.^{41,42} Instead, the free amine is transiently protected as the mesylate salt, allowing the cyclization to proceed smoothly. This first phase of the synthesis concludes with a selective methyl ester hydrolysis using Me₃SnOH to hydrolyze the α -amino ester preferentially (Scheme 2.7).



Scheme 2.7 Initially developed synthetic route (a) **51** (1.5 eq), TFA:MeOH = 1:5 (0.6 M), 80 °C, then Boc₂O (1.2 eq) K₂CO₃ (4 eq), THF:H₂O = 1:1 (0.5 M), 90%, 1.9 dr; (b) pTsOH (0.5 eq), acetone:H₂O = 10:1 (0.1 M), 60 °C, 1 h; (c) **52** (1.5 equiv.), K₂CO₃ (2.0 equiv.), MeOH, 0 °C to 23 °C, 16 h, 59% over 2 steps; (d) Pd(OAc)₂ (0.3 equiv.), Ph₃P (0.6 equiv.), CO/O₂, DMF, MeOH, 23 °C, 16 h, 66%; (e) TFA, CH₂Cl₂, then Ph₃PAuCl (0.05 equiv.), AgSbF₆ (1.0 equiv.), MsOH (2.0 equiv.), 1,2-DCE, 23 °C, 18 h, then pyridine (10.0 equiv.), AllocCl (2.0 equiv.), 23 °C, 24 h, 65%.

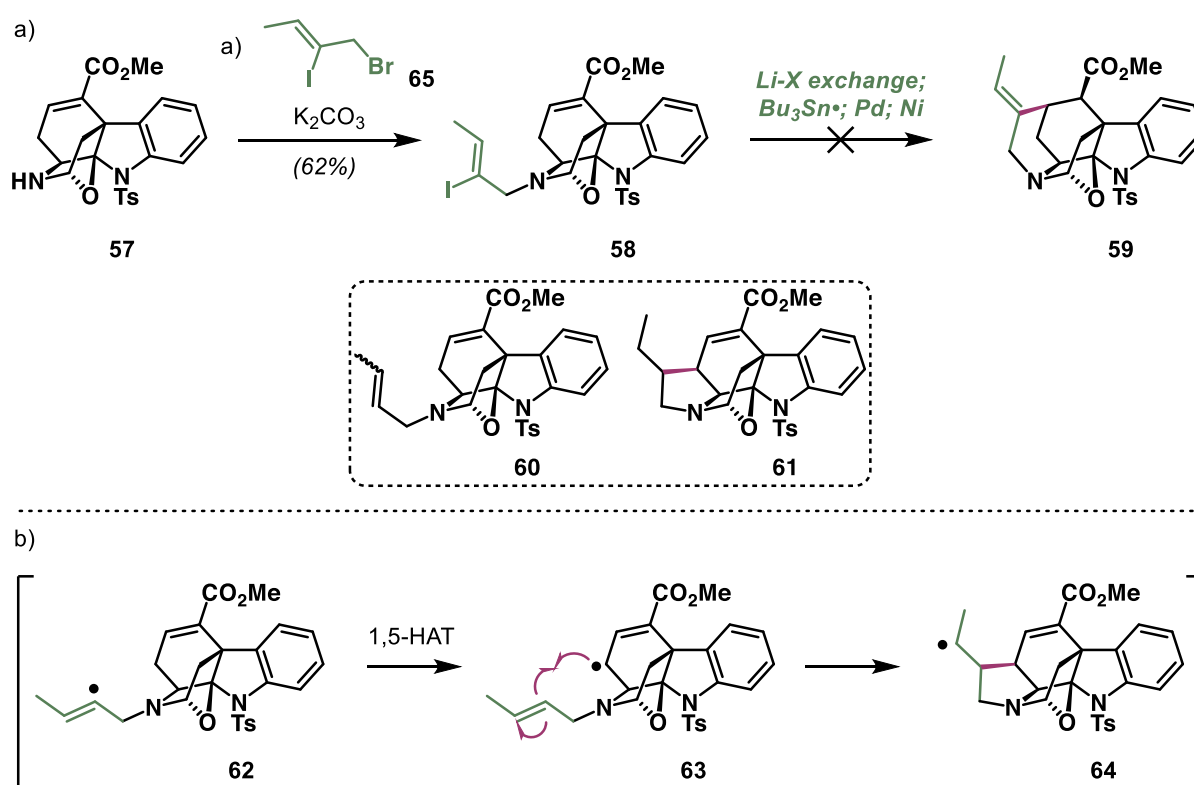
This newly forged carboxylic acid functionality is then used as the synthetic handle to establish the furoindole motif *via* clever application of an oxidative Barton decarboxylation.⁴³ The resultant hydroxyl group is installed as a mixture of epimers, with the α -epimer existing as the indolenine adduct (**54**), and locking the framework into the desired boat structure depicted in scheme 2.5d. The undesired epimer can be readily converted to the desired material upon treatment with mild acid in aqueous CH_2Cl_2 . Unfortunately, attempts to carry the free indoline-type nitrogen and deprotect the Alloc group only results in a formal dehydration to the bisimine functionality of **55**. At this point, the only electrophile found capable of protecting that relatively hindered and electronically complex indoline nitrogen was *p*-toluenesulfonic anhydride, resulting in sulfonamide **56**. Thankfully, with this second protecting group installed we can facilely deprotect the carbamate group. Of note, the yields of these steps are highly responsive to the quality of the reagents, although when run with strictly anhydrous solvents and high purity reagents, quantitative yields can be achieved (Scheme 2.8). This secondary amine is now available for divergent functionalization to test our synthetic hypothesis towards E-ring



Scheme 2.8 Furoindole formation and tosyl protection (a) EDC (1.5 equiv.), DMAP (1.5 equiv.), pyrithione (2.0 equiv.), PhMe, 23 °C, 16 h, then O_2 , 80 °C, 5 h, then t-BuSH (20.0 equiv.), 55%; (b) PPTS (3.0 equiv.), $\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$ (9:1), 23 °C, 24 h, 73%; (c) Ts_2O (1.5 equiv.), pyridine, CH_2Cl_2 , 0 °C to 23 °C, 2 h, 76%; (d) $\text{Pd}(\text{PPh}_3)_4$ (0.1 equiv.), PhSiH_3 (2.0 equiv.), CH_2Cl_2 , 0 °C, 15 min, 63%-quant.

formation.

With amine **57** in hand, we first sought to test our synthetic hypothesis by attempting cyclizations analogous to those which were previously in other akuammiline alkaloid syntheses.^{23,44,45} To our dismay, none of these conditions were effective in forming the E-ring, usually affording either the dehalogenated alkene, or simply recovered starting material (Scheme 2.9). In the case of radical conditions, an interesting cyclization product was observed which presumably arises from 1,5-HAT of the intermediate vinyl radical, followed by a rebound cyclization (scheme 2.9b). The general recalcitrance of this material to cooperate in the flask gave us the inkling that a more nuanced model was needed to understand the reactivity we were observing than the first order conformational analysis we previously suspected. However, it was at approximately this point when I joined the project, and will first detail the overall route



optimizations before delving further into the E-ring closure.

2.4 Initial Optimization Towards the Tetrahydro- β -Carboline

While the first phase of the route is both serviceable and scalable, the poor diastereoselectivity of the Pictet-Spengler greatly increased the purification time due to the difficult separation, and required excessive scale-up since over 50% of the material from the first step was unusable. While the actual mechanism of the Pictet-Spengler likely involves formation of a spirocyclic intermediate, and subsequent C-C bond migration, James Cook has found that a more intuitive analogous chair-transition state model can be used to reasonably predict reaction outcomes (Figure 2.4).⁴⁶ When examining our own system to rationalize the diastereomeric ratio, one of the first key factors is the addition of the methyl-ester moiety, which imposes an A^{1,3}-strain with the iminium hydrogen, generally disfavoring the *trans*-product. Conversely, the disfavorable interaction between the benzylic position and the indole N-H mimics A^{1,2}-strain, disfavoring the *cis*-disposed kinetic product. Finally, substitution of the iminium nitrogen generally also promotes formation of the *trans*-product due to an additional interaction imposed by the N-substituent and the R group. Given we need the methyl ester as a functional handle, the relatively small size of the methylene substituent on the side chain, and the lack of substitution on the iminium, our poor *trans*-selectivity was unfortunately not surprising.

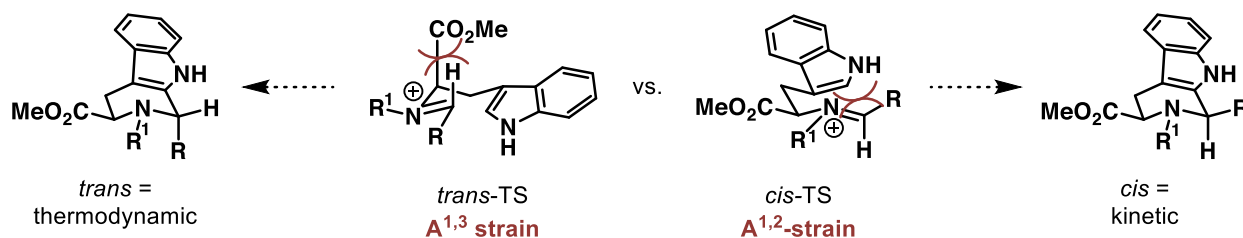
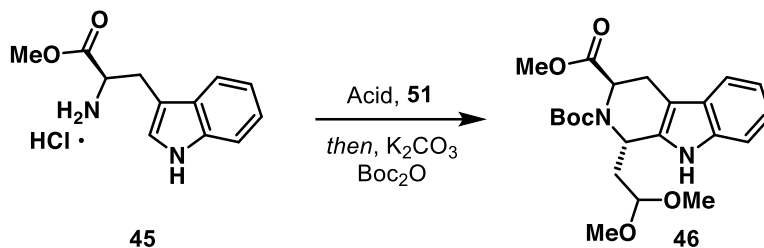


Figure 2.4. Simplified analysis of Pictet-Spengler products

Operating under the reasonable assumption that the *trans*-product is also the thermodynamically favored one, we then sought to alter the ratio of products by screening several acids, as well as temperatures of the reaction (Table 2.1). By running the reaction at 100 °C with otherwise identical conditions, we did observe an improved 1:1 ratio of products, but the decreased overall yield made this an untenable solution. This does however hint that our desired product was indeed the thermodynamic one, as increasing the temperature worked in our favor, potentially by facilitating the isomerization pathway. Disappointingly, attempts to use stronger acids resulted predominantly in decomposition, while their weaker counterparts typically effected no reaction (Table 2.1).

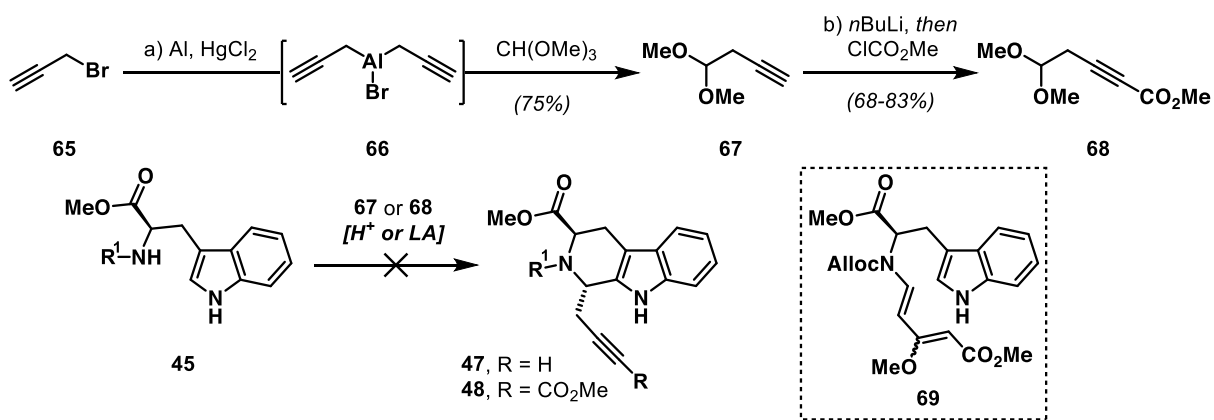


Acid	Results
TFA ^a	47%, 1:1 <i>dr</i>
MsOH	decomp
<i>p</i> -TSA	<30%, 1:1.4 <i>dr</i>
Cl ₂ HCCO ₂ H	N.R.

Table 2.1 Pictet-Spengler acid screen. ^aReaction run at 100 °C in a sealed tube

Resigned that the Pictet-Spengler paradigm will have limited selectivity, we instead opted to use the homopropargyl acetal **67** as our electrophile, shortening the synthetic sequence. The acetal can be prepared by preparation of the intermediate organoaluminum species.^{47,48} **67** is formed by activation of elemental aluminum activated by catalytic mercury(II) chloride followed by addition of propargyl bromide, and subsequent trapping with trimethyl orthoformate.

Interestingly, this transformation is proposed to proceed through activation of the orthoformate through Lewis acid coordination, and concomitant delivery of the nucleophile. Unfortunately, all attempts to forge the tetrahydro- β -carboline **47** were unsuccessful, often resulting in polymerization of the acetal. The addition of MeOH cosolvent did assist in stabilizing the acetal and limiting the polymerization, but no desired product was formed. We then synthesized the corresponding ynoate ester via deprotonation and capping with methyl chloroformate. Notably, it is necessary to maintain the reaction at -78 °C to prevent isomeric allene formation. This alternate acetal was also unsuccessful, only ever resulting in the non-cyclized conjugated vinylogous ester **69** (Scheme 2.10). We ultimately tried a number of other strategies, including using a carboxylic acid functionality, chiral phosphoric acids, IDPi, and tethering the carboxylic acid and amine moiety all to no avail.^{49,50}

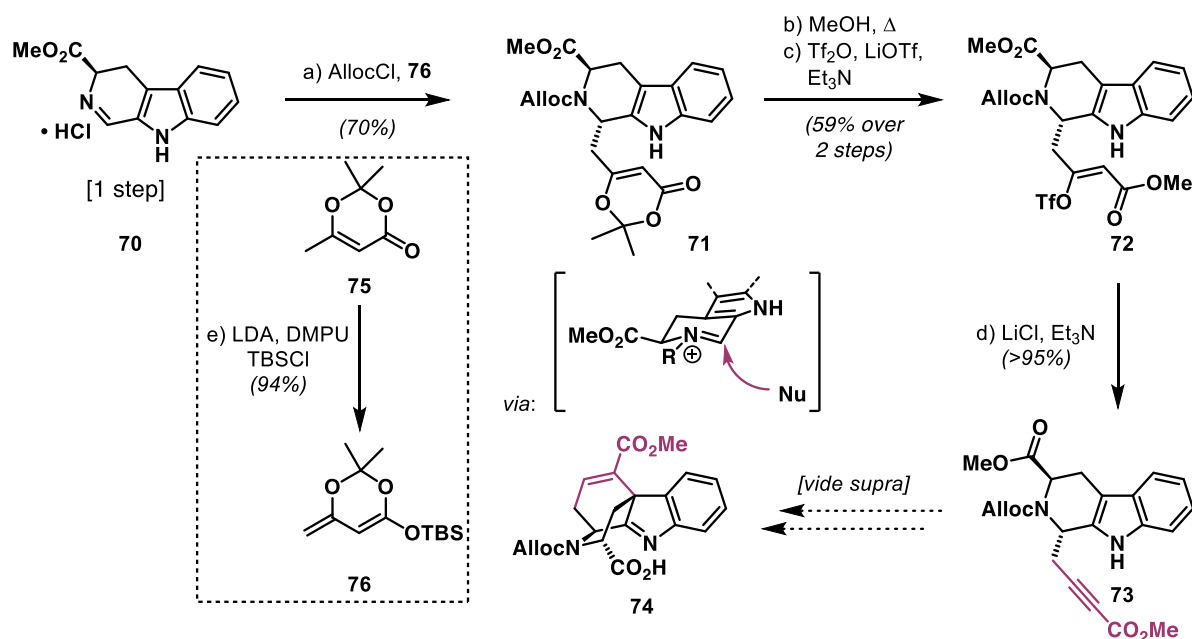


Scheme 2.10 Homologated alkyne acetal Pictet-Spengler attempts. a) Al (2.3 eq), HgCl₂ (0.01 eq), **65** (1.5 eq), CH(OMe)₃ (1.5 eq) Et₂O (0.4 M), -78 °C to reflux, 4 h, 75%; b) *n*BuLi (1.0 eq), ClCO₂Me (1.0 eq), Et₂O (0.1 M), -78 °C, 1.5 h, 68-83%.

By this point we had also further optimized the subsequent steps to improve the yield and reliability of the reaction in the wake of the poor diastereoselectivity. We ultimately found that switching the acid in the acetal hydrolysis step to the more mild PPTS limited Boc deprotection in comparison to *p*TsOH, and in a practical application of Le Chautelier's principle, increasing the amount of water in the reaction also facilitated acetal hydrolysis with the combination of

these changes making the reaction overall more reliable. Additionally, we had been observing epimerization in the homologation step to the *cis*-pictet Spengler isomer (presumably through a retro-aza-Michael reaction), but after screening a number of base and solvent conditions, the optimal solution was simply using strictly 1.0 equivalent of both Ohira-Bestmann reagent and K₂CO₃.⁵¹ The final optimization of this route was of a practical nature. At the suggestion of Dr. Phil Gemmel, we found that quenching of the Pd-carbonylation with saturated aqueous Na₂S₂O₃ precipitated the palladium, and greatly simplified purification of this material, as well as improving yields.⁵² Had we continued to optimize, this route would benefit from screening a number of bidentate ligands in the carbonylation step to assist in catalyst turnover, as we currently believe the multiple Lewis basic heteroatoms and π -systems are effectively chelating the Pd, both slowing the reaction and complicating purification.

Regardless of these improvements and with the failed alternate Pictet-Spengler approaches in mind, my colleague Justin Ngai was inspired to revisit the Bischler-Napieralski route which our group has utilized previously, but with a more functionalized nucleophile to avoid the redox manipulations which plagued previous iterations of this plan.²² To our delight, we found that formation of the iminium species and addition of silyl enol ether **76** affords the desired *trans*-isomer in good overall yield as a single diastereomer. Subsequent solvolysis, triflation, and elimination then intersect the previous route *via* the ynoate ester, and obviate the lethargic and expensive carbonylation (Scheme 2.11). The improved diastereoselectivity presumably arises due to the Fürst-Plattner rule: preferential axial attack of the nucleophile into the electrophilic iminium ion to form the intermediate chair conformer.

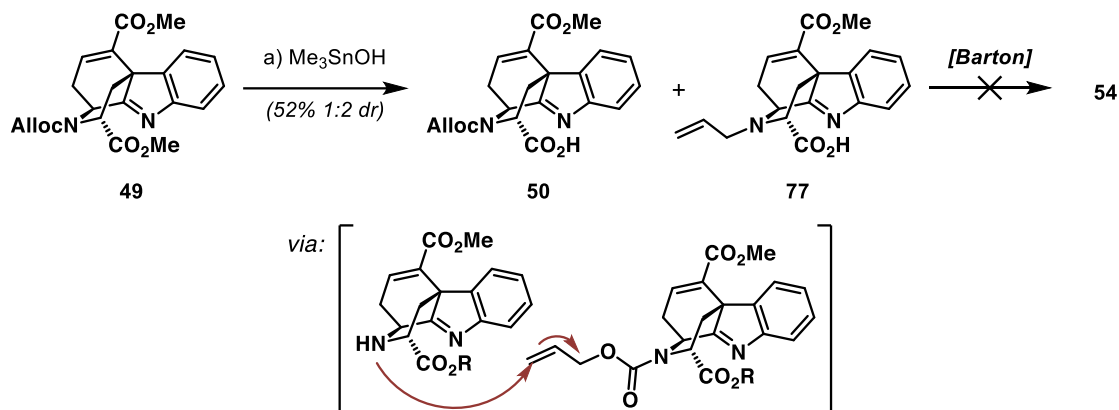


Scheme 2.11 Bischler-Napieralski synthetic route with improved diastereoselectivity. (a) **76** (1.5 eq), AllocCl (2.0 eq), CH₂Cl₂ (0.15 M) 0 °C to 23 °C, 12 h 70%; (b) MeOH:toluene = 1:9 (0.1 M), 90 °C, 12 h, sealed tube; (c) LiOTf (2.0 eq), Tf₂O (1.0 eq), Et₃N (1.5 eq), CH₂Cl₂ (0.075 M), -78 °C, 1 h, 59% over 2 steps; (e) LDA (1.25 eq), DMPU (1.5 eq), TBSCl (1.25 eq), THF (0.5 M), -78 °C, 1 h, then 23 °C, 2 h, 94%.

2.5 Synthesis of the Boat-Locked Conformer

Continuing on in our journey of optimization, we occasionally observed irregular yields in the oxidative Barton decarboxylation. Extensive screening of solvents, temperatures, and reaction times all had little to no effect on the overall yield of the product. This puzzling result prompted us to more closely examine the preceding hydrolysis reaction. The ¹H NMR of this substrate is convoluted by the zwitterionic nature of the carboxylic acid, which results in dramatic peak broadening. Thankfully, upon further investigation the ¹³C NMR revealed the loss of the allyloxy carbamate carbon. In separate experiments we verified that this allylamine substrate is incompetent in the Barton reaction, resulting only in decomposition. Comparison between different batches of material elucidated the solvent water content as the culprit, by what we assume to be an autocatalytic S_N2' type reaction originating from a trace amount of alloc-hydrolyzed material (**77**, Scheme 2.12).⁵³ Thankfully, this issue was easily solved by the addition of 4Å molecular sieves in the reaction. Intriguingly, in one particular instance we also observed

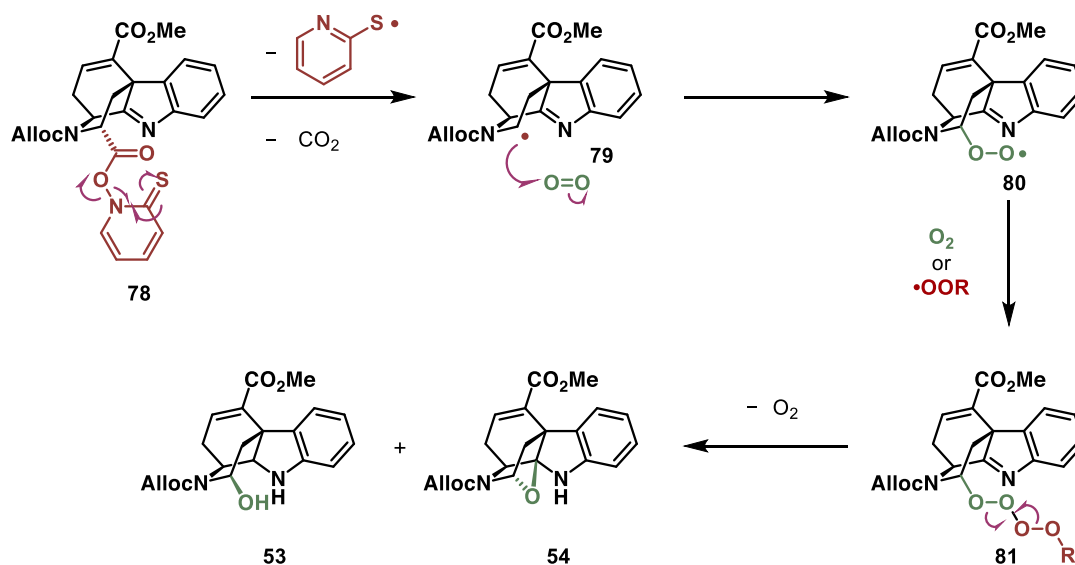
conversion of the starting material to the epimeric methyl ester, and the desired carboxylic acid product.⁵⁴



Scheme 2.12 Proposed mechanism for rearrangement under methyl ester hydrolysis conditions.

With the hydrolysis issues reliably solved, we then turned back to the Barton step. In the course of our previous reaction screening, we found that the addition of reducing agent at the end of the reaction bore no consequence on the yield. This is atypical, as generally a thiol or Ph_3P must be added to quench the endoperoxide radical and reduce the O-O bond formed as a result of oxygen trapping.⁴³ We feared that this apparent discrepancy implied that we instead formed the peroxy-bridged system. Fortunately, treatment of the cyclized barton product with a number of peroxide cleaving reagents resulted in no reaction, and HR-MS data further confirmed the desired structure.⁵⁵ This interesting observation is not completely without precedence, as in Baran & Nicolaou's CP molecule synthesis, they observed a similar result.⁵⁶ This likely occurs *via* a Russell type dimerization-disproportionation mechanism (Scheme 2.13).^{57,58} Moreover, we found that by using DIC instead of EDC as the coupling reagent led to a minor but important decrease in urea byproduct aggregation, lessening the frequency at which the O_2 needle clogged, and making the reaction more reliable as a whole. Lastly, we can also perform a reductive barton using Bu_3SnH to afford the strictamine type framework in an unoptimized 43% yield, though if

successful, this route would unfortunately lead to a synthesis longer than our previous formal synthesis.⁴²



Scheme 2.13 Proposed combination-disproportionation mechanism for oxidative Barton sequence.

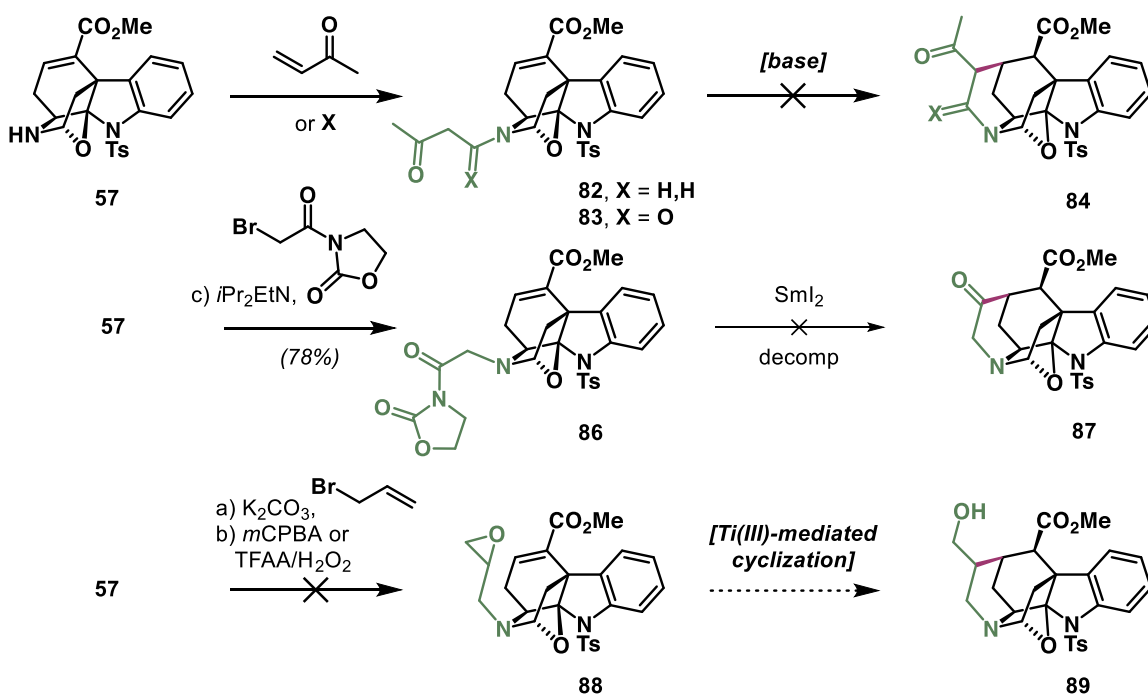
With access to the furoindole framework secured, deprotection of the alloc functionality liberates the secondary amine for diverse functionalization to probe E-ring cyclization strategies. Notably, only incredibly reactive electrophiles such as iodomethane or those activated by a neighboring π -system have been capable of *N*-alkylation thus far in our hands, and the use of strong bases (i.e. NaH) results in decomposition, likely due to the sensitive nature of the adjacent bis(hemiaminal) moiety. The minor improvement made in this capacity is the reduction of the reaction temperature to 50 °C, and the application of a micro-reflux condenser to improve the yield of the reaction on small scale with volatile electrophiles.

2.6 Synthetic Approaches Towards the Methanoquinolizidine Core

2.6.1 Attempted E-ring Cyclization Strategies & Invertomer Analysis

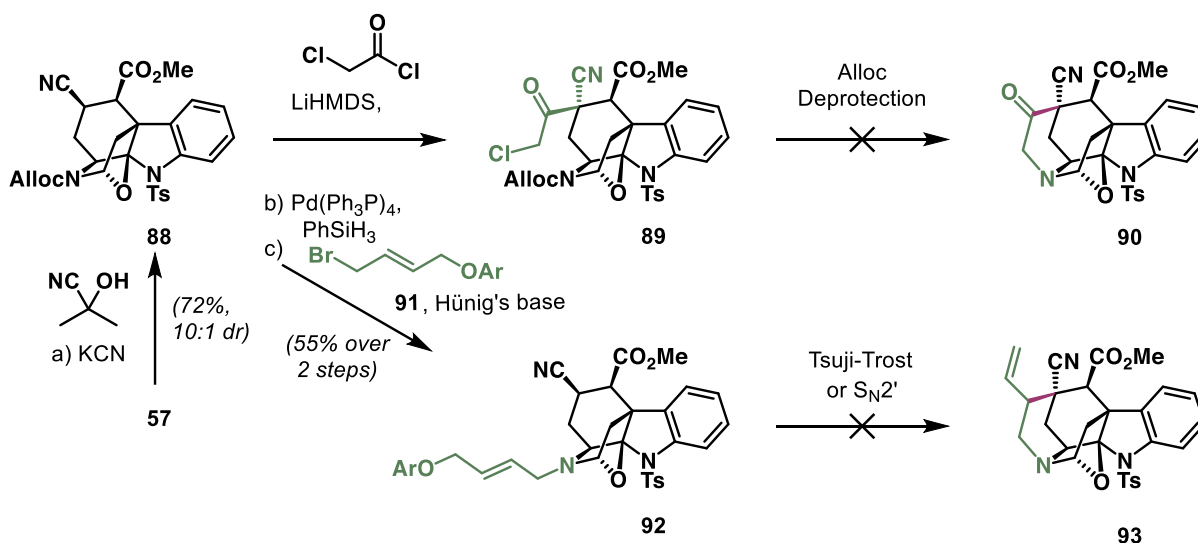
As mentioned previously, we tried a number of the reported successful E-ring closure methods on our furoindole system to no avail (Scheme 2.9). These failures prompted us to

expand our study into a broader set of reaction paradigms. Attempting a classic Michael addition only led to either recovered starting material, or retro-*aza*-Michael products (Scheme 2.13).²² Inspired by a contemporary alkaloid synthesis report, we sought to instead initiate the reaction at the enoate-ester and cyclize into the acyloxazolidinone of **85**, however treatment with SmI_2 only resulted in fragmentation of the sidechain.⁵⁹ Suspecting the greater steric encumbrance of our system compared to the literature example which lacks a corresponding C-ring, we hoped to implement a titanocene-mediated radical cyclization.⁶⁰ Unfortunately, we were unable to synthesize the requisite epoxide *via* an $\text{S}_{\text{N}}2$ reaction with epichlorohydrin, and attempts to oxidize the precursor allylamine all resulted in decomposition. Wary of the obvious potential for *N*-oxidation we also attempted acidic epoxidation conditions as well as pre-treatment of the substrate with acid, all unsuccessfully (Scheme 2.14).



Scheme 2.14 Additional furoindole E-ring cyclization attempts. (a) K_2CO_3 (5 eq), allyl bromide) (4 eq), MeCN (0.1 M), 50 °C 66%; (b) TFAA (6.0 eq), H_2O_2 (35% in H_2O , 5 eq), CH_2Cl_2 (0.1 M), 0 °C; (c) bromide (2.0 eq), Hünig's base (3.0 eq), MeCN (0.1 M), 50 °C, 78%.

In an attempt to implement Yong Qin's trick of transposing the reactive center slightly farther from the β -position, we began investigating the feasibility of various Michael-type additions to the α,β -unsaturated ester.^{8,23} Among a wide variety of attempted nucleophiles, only cyanide addition was successful affording **88** in a surprising 10:1 *dr* (Scheme 2.14).²² Despite the successful installation of this new reactive handle, we were unable to either hydrolyze or reduce it selectively. As a potential saving grace, we found we could deprotonate the α -position of the nitrile. The addition of chloroacetyl chloride into the resulting enolate afforded **89** in high yield, but concomitant deprotection and S_N2 only resulted in complex mixtures. Hoping to exploit the nucleophilicity of this position more directly, we then attempted a number of strategies including S_N2' attack, as well as Tsuji-Trost-type activation, all of which were unsuccessful (Scheme 2.15).^{61–63}



Scheme 2.15 Attempted E-ring cyclizations from the nitrile functional handle. (a) acetone cyanohydrin (4.0 equiv.), KCN (1.0 equiv.), DMSO, 30 °C, 16 h, 72%, 10:1 *dr*; (b) Pd(PPh₃)₄ (0.1 equiv.), PhSiH₃ (2.0 equiv.), CH₂Cl₂ 0 °C, 15 min, quant.; (c) allyl bromide (1.0 eq), Hünig's base (2.0 eq), MeCN (0.1 M), 60 °C, 55%.

In the wake of these additional failures, we sought to revise our synthetic hypothesis since evidently locking the system into the boat conformation was insufficient. The additional nuance we identified is the potential for distinct *N*-invertomers to be the cause of the undesired reactivity (Figure 2.5).⁶⁴ Hoping to apply our groups quaternary-guided synthetic strategy, we then explored quaternization of the tertiary amine *via* either oxidation or ammonium formation.^{65,66} We anticipated that the electrophile should approach from the more accessible southern face of the molecule, enforcing the desired sidechain geometry, but treatment with *m*CPBA only resulted in decomposition, and the substrate was completely unreactive towards salt formation. We even went as far as to subject **X** to neat refluxing methyl iodide, but still no reaction was observed following concentration (Figure 2.5). These results indicated to us the need for a sidechain that might both possess a reduced steric environment as well as fewer degrees of rotation, in hopes of minimizing the steric repulsions, and therefore decrease the energy-barrier of nitrogen inversion and increase the possibility of achieving the desired structural conformation. The most obvious choice of sidechain to implement was a terminal alkyne, and this idea enabled our further studies.

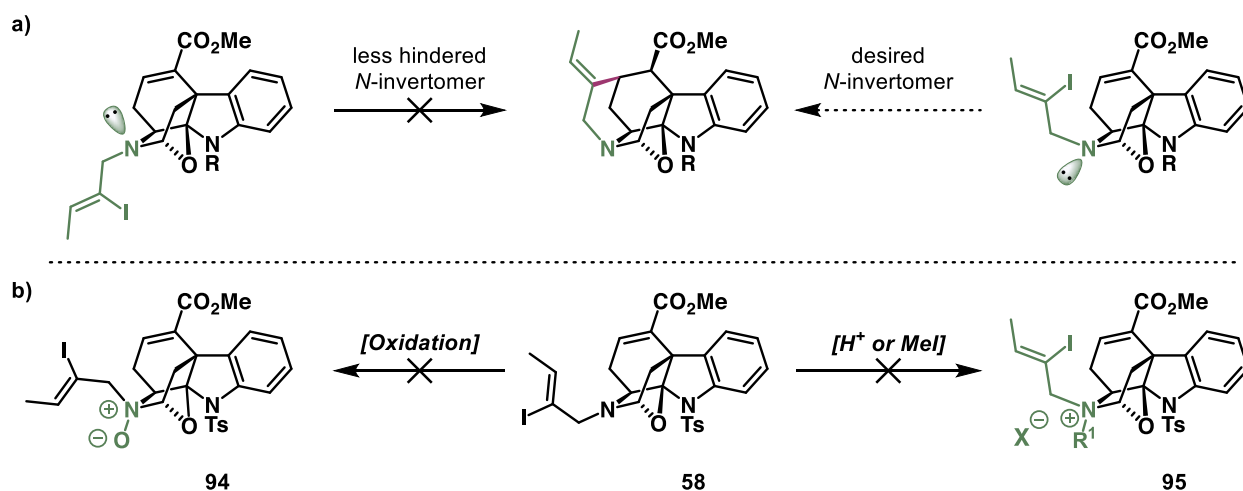
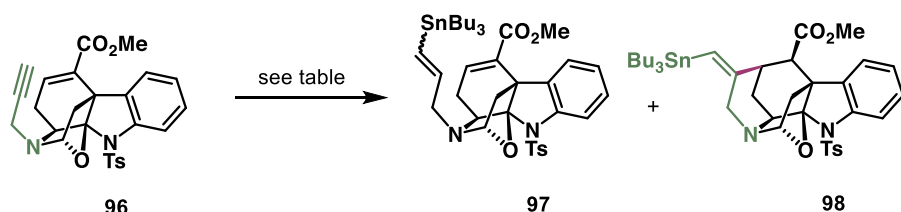


Figure 2.5 a) Nitrogen invertomer analysis. b) Failed amine oxidation and quaternization strategies. $R^1 = H, Me$

2.7 Alkyne Radical Cyclization & Lewis Acid Templating

We believed the most viable format in which to pursue the alkyne sidechain was a tin-mediated vinylic Giese addition. The corresponding propargylamine can be facily attained *via* alkylation of the secondary amine with propargyl bromide and K_2CO_3 as base in moderate yields (Scheme 2.16). Fortunately, slow addition of Bu_3SnH solution into a solution of propargylamine **96** resulted in a mixture of hydrostannylated **97** and the desired cyclized product as a single diastereomer (Table 2.2). This was a remarkable innovation since it was the first successful E-ring closure of this framework we had achieved, and the mass balance was quite high considering the notable strain introduced through such a transformation, though the product ratios were subpar. Expecting this reaction to have a relative high energy of activation we first tried increasing the temperature, but above 100 °C we only observed decomposition. We then tried to prevent premature vinyl-radical quenching by eliminating the $H^\bullet$ source entirely, however no reaction was observed. We were able to effect a slight improvement by decreasing the concentration of the reaction, thereby lowering the rate of intermolecular quenching, but this reaction was exceedingly sensitive and gave variable/irreplicable results (Table 2.2, entry 4).



Entry	Conditions ^a	Concentration (M)	Lewis Acid ^b	T (°C)	% Yield	X:X
1	Bu ₃ SnH	0.025	-----	85	82	3:1
2	Bu ₃ SnH	0.025	-----	110	decomp	N.A.
3	(Bu ₃ Sn) ₂	0.025	-----	85	N.R.	N.A.
4	Bu ₃ SnH	0.025	-----	85	50 ^c	2:1
5	[CpRhCO] ₂ , Bu ₃ SnH ^d	0.05	-----	23	decomp	N.A.
6	(Bu ₃ Sn) ₂ , Bu ₃ SnH	0.01	-----	85	68	1.4 : 1
7	Bu ₃ SnH ^e	0.01	ATPH	-78	decomp	N.A.
8	(Bu ₃ Sn) ₂ , Bu ₃ SnH	0.01	MgBr ₂ •OEt ₂ ^f	85	73	1: >20
9	(Bu ₃ Sn) ₂ , Bu ₃ SnH	0.01	LaCl ₃ , 4- <i>t</i> Bu-pyridine	85	76 (>85 BRSM)	1: >10

Table 2.2 Alkyne radical addition optimization. ^a AIBN (0.1 eq) used as initiator. ^b 20.0 mol% loading. ^c Highly variable yields and ratios. ^d AIBN omitted. ^e Et₃B used as initiator. ^f Above 7.0 mg scale, non-cyclized product is major.

Encouraged by this preliminary success, but in dire need of a replicable condition set, we screened alternate initiation procedures such as an interesting rhodium system but found no success. Delving into the literature, we found that Sn• additions into alkynes are an essentially thermoneutral process.⁶⁷ This is consistent with our results and the complete lack of reaction observed in the absence of an H• source, as our system is likely too congested for the resultant α-radical to be trapped with a trialkyltin species. Thus, without an effective radical trap (H•), the desired, but more strained, cyclized radical simply undergoes the reverse process, and resulting in exclusive recovery of starting material. Recognizing the need for a radical trap and hoping to exploit the observed equilibrium, we hypothesized that increasing the concentration of tin radicals in solution would push the equilibrium in our favor, and that slowly administering a H• source could effectively trap the cyclized α-radical. Gratifyingly, this proved true (Table 2.2,

entry 6). This was a significant development as it made the reaction reliable, although the product selectivity was still poor, again likely due to the generally high barrier of cyclization.

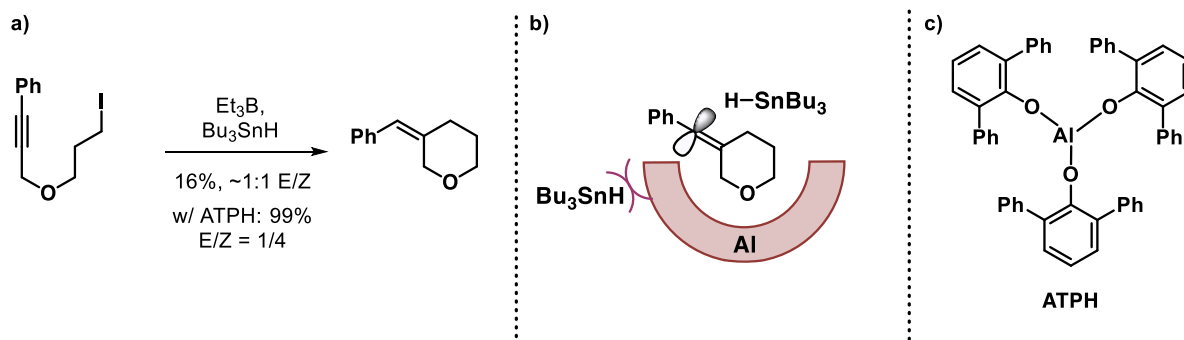


Figure 2.6 Maruoka precedent. **a)** Alkyne cyclization results; **b)** Rationalization for improved selectivity with template **c)** Structure of ATPH.

While we were pleased with the reliability of this reaction, we still needed to improve the ratio of cyclized to non-cyclized product. We ultimately found success based on a key precedent from Takashi Ooi and Keiji Maruoka. They observed substantial improvements in the yield of radical cyclizations of ethereal systems upon the addition of a bulky aluminum Lewis acid.⁶⁸ This is proposed to act through coordination of the ether linkage to the Lewis acid, and the steric environment of the bulky ligand forcing the reactive partners into close proximity, biasing the system towards the cyclized product (Figure 2.7). We hoped to replicate this template effect by coordination of a polydentate Lewis acid to the amine and/or furoindole moiety, thereby accelerating our desired cyclization *via* a Thorpe-Ingold-type effect at the heteroatom (Figure 2.7).⁶⁹

While the reported conditions resulted in decomposition of our starting material the first Lewis acid we tried ($\text{MgBr}_2 \cdot \text{OEt}_2$) afforded perfect selectivity for the cyclized product! The only downside of this exceptionally encouraging result, was the lack of scalability. Above 7 mg scale the non-cyclized product again dominated, likely due to the poor solubility of the salt in toluene, and the resultant heterogeneity of the mixture. Increasing the Lewis acid loading resulted in

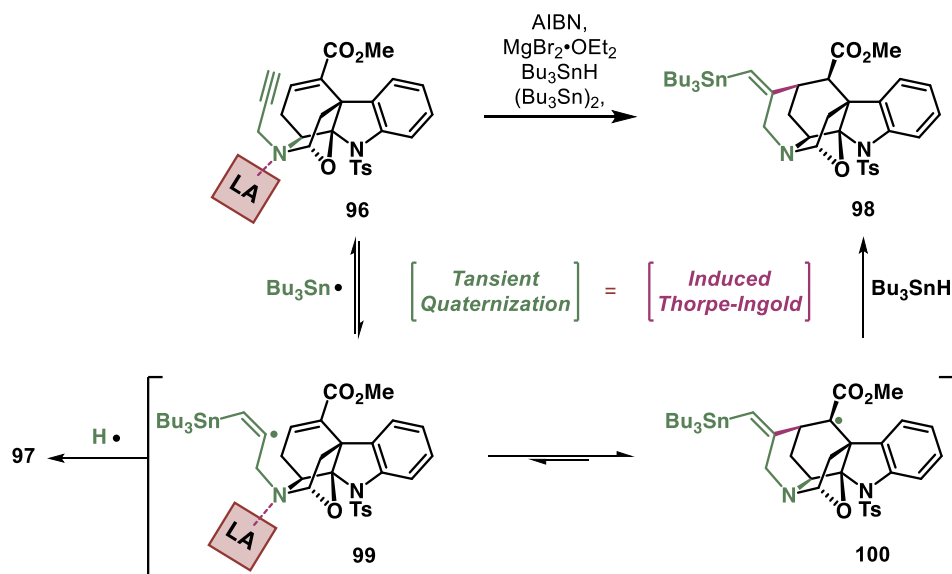


Figure 2.7 Proposed equilibrium mechanism of Sn cyclization

fracture of the furoindole motif. A brief solubility study determined that La(OTf)₃ was the most soluble in toluene at elevated temperatures, although LaCl₃ afforded the highest yields based on recovered starting material. The addition of a pyridine ligand serves to both solubilize the salt, and also buffer the system against any trace acid present, to protect the sensitive furoindole (Table 2.2). With this optimized condition set we can now scale up this reaction to nearly 100 mg scale. We of course cannot rule out the possibility of the Lewis Acid also acting to enhance the potency of the radical acceptor, but find it difficult to believe this to be the sole cause due to the recalcitrance of the enoate ester in other reactions. Realistically, it is possible these two (or more) interactions work in concert to facilitate the addition overall.^{70,71} We hope that future NOESY measurements in the presence of a Lewis acid will help elucidate potential mechanisms.¹

Because there are currently no other reports to our knowledge of E-ring closure with the rest of the methanoquinolizidine core in place, it is worth drawing a brief comparison to Zhu's chemistry.⁴⁴ An unusual facet of the nickel-mediated reaction as reported by Zhu is the resultant

¹ Prof. Guy Lloyd-Jones agreed that this was a good & reasonable idea.

stereochemistry of the ester. Classical organometallic logic dictates that if it were to proceed through a traditional two electron process (migratory insertion and reductive elimination), the ester should be *trans*-disposed with regard to the newly minted E-ring. The possibility exists for epimerization, but that seems unlikely in the context of Qin's studies, as it has yet to be achieved in a stepwise context.²³ Instead, we posit that following migratory insertion the subsequent Ni^{II} intermediate rapidly disproportionates due to the uncommonly hindered environment, and this resultant stabilized α -radical is selectively quenched from the more sterically accessible α -face.⁷²⁻⁷⁴ This conjecture is partially supported by our own developments, as our E-ring cyclization proceeds exclusively through a single-electron process, affording an invertible α -radical which is quenched exclusively from the rear face of the molecule.

Moreover, the Zhu chemistry has never been successfully replicated on the full methanoquinolizidine framework, either in our own hands, or in the literature (*vide supra*).^{22,27,41} Thus, our application of a Lewis acid templated alkyne radical cyclization marks the first reliable, robust, and high-yielding strategy developed to date. For this innovation we are grateful to have contributed to the substantial challenge of methanoquinolizidine formation.

Given the success of this overall reaction, in forging the E-ring in both high yield and as a single diastereomer, we hoped to expedite the total synthesis overall by using vinyl iodide **58**, or an internal alkyne. Unfortunately, any attempts to perform analogous ring closures of the internal alkyne on a lactone model system resulted in either recovered starting material or reduction to the alkene. The vinyl iodide again afforded the 1,5-HAT product **61** (Scheme 2.9). The addition of a propargylic alcohol as a directing group had no impact on the reaction with neither tin nor copper hydride. We expected that the additional steric interactions of the terminal substituent in our exceptionally rigid and congested system made the already thermoneutral reaction less

energetically favorable. Because silyl radical additions to alkynes are substantially more exergonic, we hoped that switching to a TMS_3SiH radical source would enable this cyclization, but even in the terminal alkyne case we only observed trace product, presumably due to the dramatic bulk of the silane (Figure 2.8).⁶⁷ Finally, we also attempted to use a bromo-capped alkyne under SmI_2 radical conditions, intending for the samarium to act as a tether for the enoate ester and bromine functionality, diastereoselectively delivering the vinyl bromide as a functional handle, but this was also unsuccessful (Figure 2.8).⁷⁵ Thus, we persisted investigating the endgame of the synthesis with vinylstannane **98**.

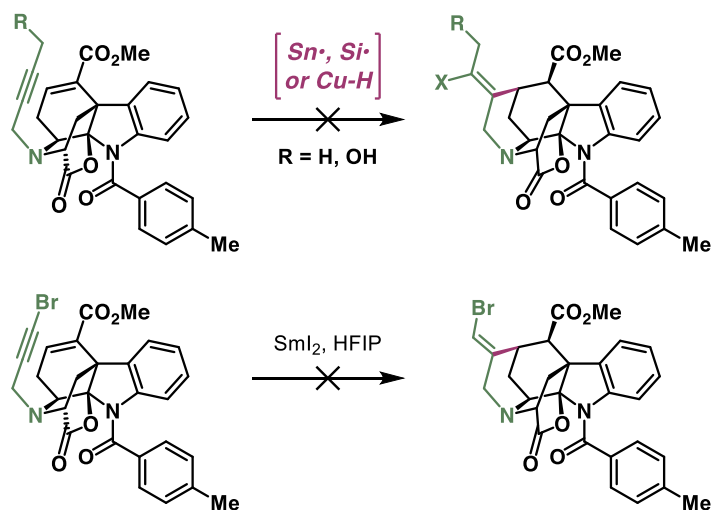
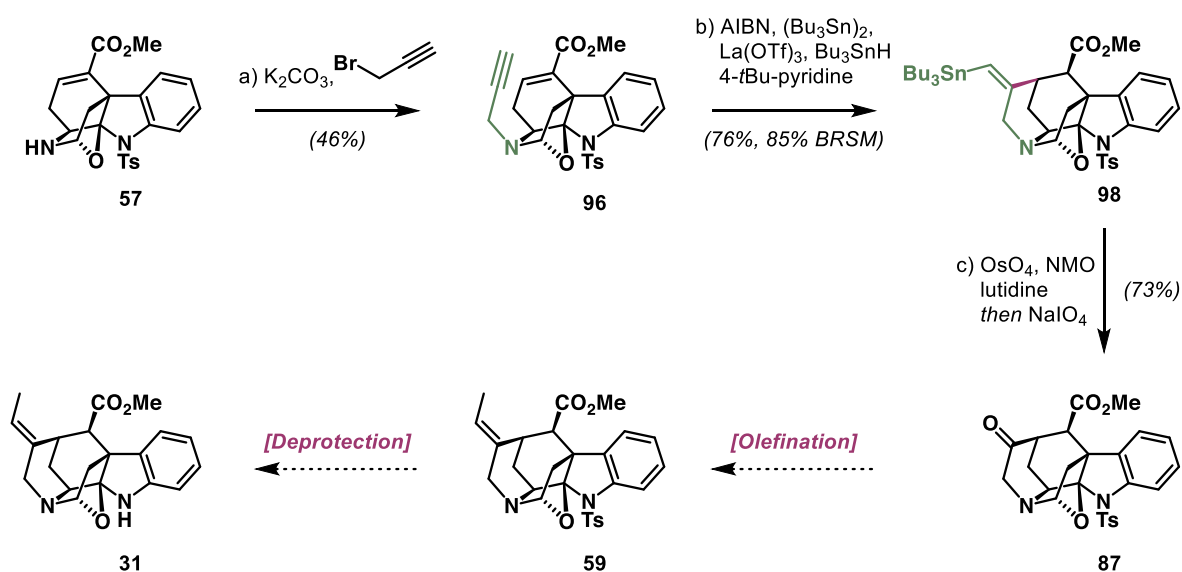


Figure 2.8 Alternative failed Lewis acid templated E-ring cyclization attempts.

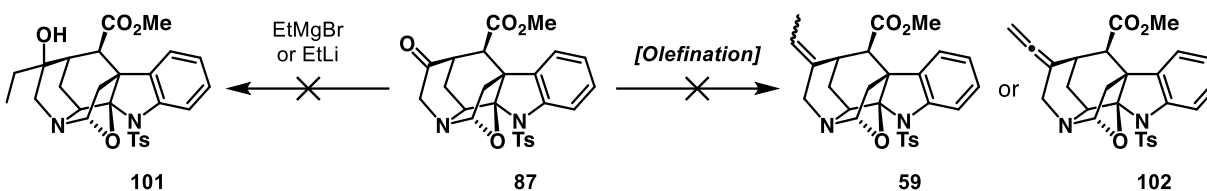
2.8 Olefin Isomerization & Endgame

The endgame we initially envisioned following the radical cyclization was oxidative cleavage of the olefin, installation of the ethylidene moiety *via* olefination, and finally a deprotection of the tosyl substituted indoline (Scheme 2.16). Intriguingly, we are able to directly cleave the vinylstannane to the ketone using a stepwise Lemieux-Johnson procedure. Here we

intentionally use NMO as the oxidant for the dihydroxylation as opposed to just excess NaIO_4 because when NaIO_4 was used as the sole oxidant, we observed approximately 20% conversion from the vinyl stannane into the vinyl iodide due to the slightly acidic conditions of dihydroxylation (confirmed by mass spectrometry). Unfortunately, despite extensive screening the ketone proved impervious to olefination in our hands (Scheme 2.17). All attempts were met with no reaction, or complete decomposition upon exposure to a gross excess of reagents. Identical results were obtained when trying to instead form the allene directly under Ti-based olefination conditions, despite the success of such a procedure on a very similar but less cage-like alkaloid framework.^{76,77} Similarly, both Grignard reagents and organolithiums proved futile in affording the tertiary alcohol, precluding any possibility of dehydration to the desired olefin (Scheme 2.17).

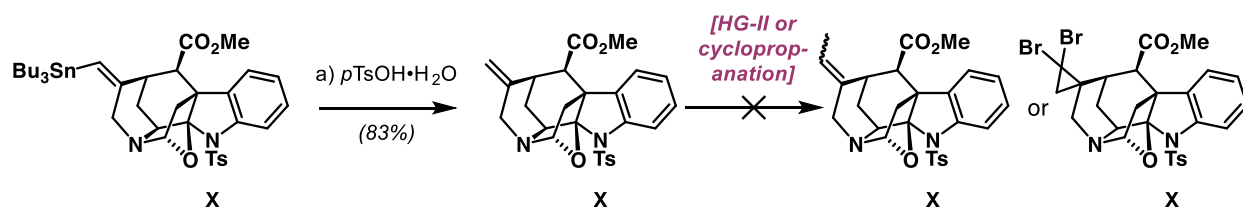


Scheme 2.16 Initially envisioned endgame. a) Propargyl bromide (5.0 eq), K_2CO_3 (7.0 eq), DMF (0.3 M), 50 °C, 2 h, 46%; b) AIBN (0.1 eq), $(\text{Bu}_3\text{Sn})_2$ (5.0 eq), Bu_3SnH (1.5 eq), $\text{La}(\text{OTf})_3$ (20.0 mol%), 4-*t*Bu-pyridine (60.0 mol%), slow addition toluene (0.01 M), 80 °C, 5 h, 76%, 85% BRSM; c) OsO_4 (10.0 mol%), NMO (2.0 eq), 2,6-lutidine (2.0 eq), acetone (0.1 M), 23 °C, 5 h, then NaIO_4 (4.0 eq), Acetone: H_2O = 1:1 (0.05 M), 1 h, 73%.



Scheme 2.17 Failed ketone functionalization attempts

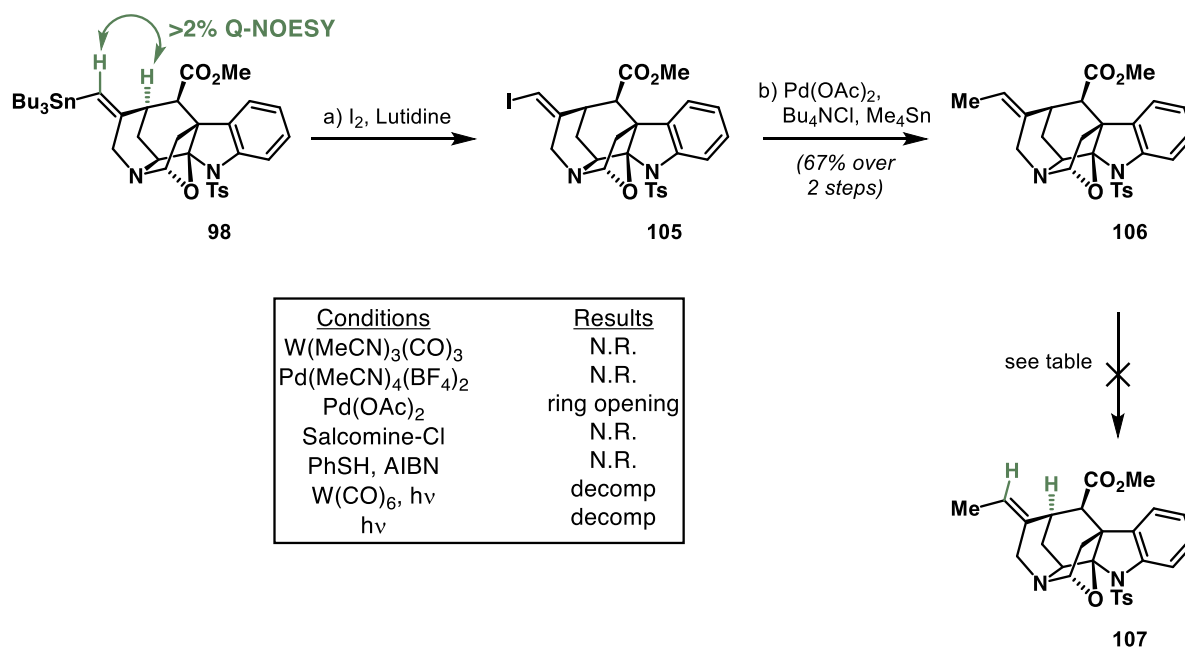
We instead sought to utilize the olefin following protodestannylation, to install the final carbon through either cyclopropanation, or olefin metathesis. Formation of the dibromocyclopropane would theoretically allow access to the allene upon a lithium-halogen exchanged induced rearrangement.^{78,79} We then hoped to be able to selectively hydrogenate the terminal olefin of the allene *a la* MacMillan's vincorine synthesis (Schemes 2.2 & 2.18).¹² Unfortunately both of these approaches led only to decomposition of the starting material.



Scheme 2.18 Failed terminal alkene functionalization attempts. a) *p*TsOH·H₂O (3.0 eq), CH₂Cl₂ (0.1 M), 23 °C, 1 h, 83%.

Thinking critically about how to best utilize the functionality we already have installed, we then envisioned a coupling reaction to install the final methyl. Unfortunately, direct coupling of the vinyl stannane under either palladium or copper catalyzed conditions was unsuccessful, but thankfully conversion of the vinylstannane to vinyl iodide **105** goes smoothly, and also allows for facile installation of the methyl under “ligandless” Jeffrey-type Stille coupling conditions (Scheme 2.19).^{80–82} With this methyl installed, we then proceeded to test isomerization, however both radical and mild organometallic conditions effected no reaction.^{83–86} More harsh organometallic conditions resulted in a Tsuji-Trost type ring-opened product, presumably to relieve strain, and photochemical conditions exclusively gave decomposition.^{87,88}

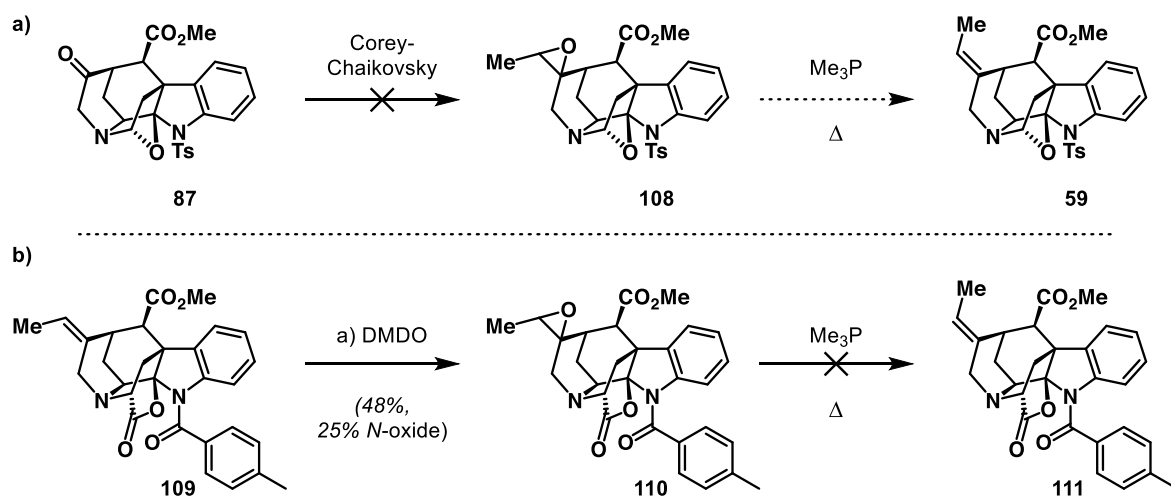
Examining why this isomerization was so difficult, we undertook a quantitative-NOE study, and discovered that the vinyl proton has a very high (>2%) correlation with the bridgehead proton, indicating they are extremely close in space. Thus, this isomerization would be contra-thermodynamic, and difficult to achieve.



Scheme 2.19 Final carbon installation and isomerization attempts. a) I₂ (2.0 eq), Lutidine (2.0 eq), CH₂Cl₂ (0.1 M), -78 °C, 2 h; b) Pd(OAc)₂ (10.0 mol%), Me₄Sn (5.0 eq), Bu₄NCl (2.3 eq), DMF (0.1 M), 80 °C, 10 min, 67% over 2 steps.

Nevertheless, we were undeterred by these failures and continued pressing forward towards the alkene isomer. Recognizing how unlikely the uphill isomerization would be, we changed tactics to a more stepwise yet stereospecific approach. We first tried installing the vinyl iodide diastereoselectively by exploring a variety of conditions and additives which are successful for vinylsilanes, however each only gave retention of stereochemistry, likely due either to tin's enhanced leaving group ability compared to silane, or the inability of the intermediate to fully rotate due to the steric encumbrance of our system.^{89–91} Instead, we hoped to invert the stereochemistry of the olefin through an epoxidation, deoxygenation sequence, invoking a Wittig-type intermediate. Despite previous unsuccessful attempts at epoxidation of

the uncyclized system, or *via* a Corey-Chaikovsky reaction of ketone **87**, we were ultimately able to successfully synthesize the epoxide with DMDO; however, subsequent reactions with Me₃P resulted in decomposition (Schemes 2.14 & 2.20).^{92,93} It may initially be surprising that DMDO was successful here given the propensity for forming the *N*-oxide, however it has been previously examined that the application of excess DMDO can result in cleavage of the *N*-oxide analogously to the Russell mechanism of oxygen disproportionation previously discussed, though we did see an appreciable amount of this side-product as well (25%).⁵⁸



Scheme 2.20 Epoxide inversion strategies **a)** Corey-Chaikovsky from the furoindole ketone. **b)** Lactone epoxidation route
a) DMDO (5.0 eq), CH₂Cl₂ (0.1 M), -78 °C, 1 h, 48%.

Given the failure of these stereospecific approaches, we instead targeted a mixture of alkene isomers through an intermediate aldehyde. Trying to capitalize on the oxidation already in place we attempted to hydrolyze vinyl iodide **105**, though unsurprisingly we observed decomposition under these strongly acidic conditions (Figure 2.9). However, inspired by our Stille coupling success, we hoped to install a more easily hydrolyzed functionality in the form of an amine or enol-ether *via* Buchwald-Hartwig coupling, but this approach also resulted in decomposition under coupling conditions.

Thinking more creatively about how to access the aldehyde, we then conducted oxygenation under radical conditions, but instead obtained vinylogous acid **114** (Figure 2.9). Attempts at selective oxidation were unsuccessful and control experiments indicated that the allylic oxidation occurred prior to the event which installs the terminal oxygen. Regardless of these interesting results obtained, we decided to move away from the aldehyde route as it would have imposed too many additional steps, in favor of a more direct route to the same intermediates: hydroboration.

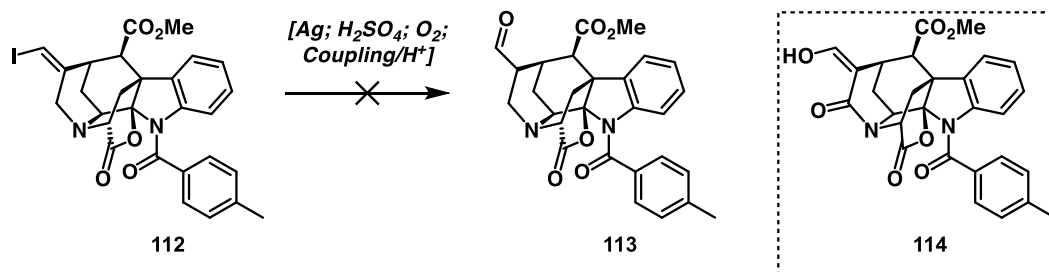
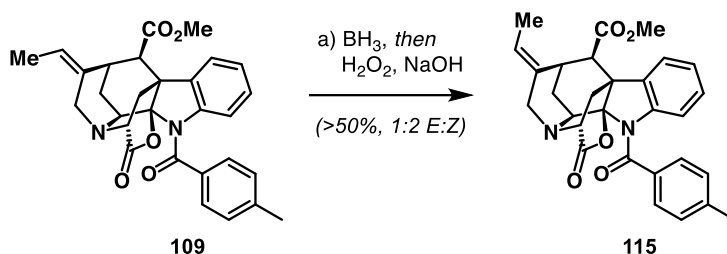


Figure 2.9 Unsuccessful attempts to convert vinyl iodide **113** into the aldehyde, and byproduct **114**

Finally, realizing that most of the unsuccessful conditions employed bulky reagents, we attempted to functionalize the undesired olefin **109** using BH_3 , hoping to get a mixture of alcohol isomers upon oxidation, and ideally a mixture of alkenes upon elimination. To our delight, treatment of the intermediate organoborane with oxidative basic conditions directly yielded a 2.5:1 mixture of isomers, favoring the undesired olefin (Scheme 2.21). This result was as surprising as it was difficult to reproduce. We are currently unsure as to why exactly the alkene was obtained directly as hydroxyl groups are canonically bad leaving groups, however one hypothesis is that the intermediate boronate is actually serving as the nucleofuge, but this has only been reported in systems with a strong aromatic driving force. Given that we lack such a driving force but do have a uniquely rigid and strained framework, it is possible that selectivity

originates from chemistry yet unbeknownst to us. However, as evidence for either of the two proposed explanations it is also worth noting that treatment of the alcohol obtained from the hydroboration/oxidation sequence with Burgess reagent resulted in exclusive formation of the undesired internal olefin isomer **109**.



Scheme 2.21 Promising hydroboration/oxidation sequence with observed *in situ* elimination. a) $\text{BH}_3 \cdot \text{THF}$ (1.0 M, 3.0 eq), THF (0.1 M), 23 °C, 2 h, then NaOH (3 M, 6.0 eq), H_2O_2 (33%, 3.0 eq), >50%, 2:1 *dr*.

Nevertheless, this preliminary result gave us the opportunity to attempt to separate the isomers; we have so far been unsuccessful in this task, and in fact observed gradual isomerization upon repeated exposure to acidic silica, further demonstrating how disfavored this ethylidene geometry is. In fact, in the most recent synthesis of picrinine, trace olefin isomerization to the unnatural isomer can be seen in the NMR following acid bis(hemiaminal) ring closure.³² Nevertheless, we hope to optimize this reaction to afford reliable product mixtures, as this should hopefully be easier on the furoindole structure as there is no fear of lactone hydrolysis. If this optimization proves difficult, a Zweifel-type olefination from the vinyl-iodide could be a promising alternative as the elimination can proceed stereospecifically based upon the conditions chosen (scheme 2.22).⁹⁴

Alternatively, longer isomerization sequences can be envisioned. Oxidation to the corresponding ketone **115**, and subsequent Barton iodination would generate the vinyl iodide. Upon treatment with Bu_3SnH , the resultant vinyl-radical can readily interconvert, and will

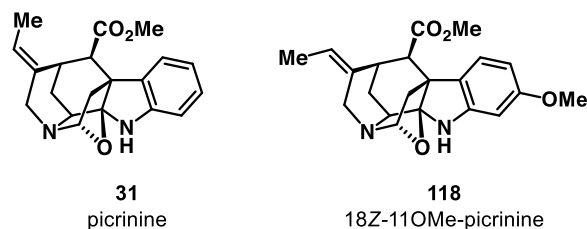


Figure 2.10 New natural product targets based on current results

2.9 Protecting Group Challenges & Innovation

2.9.1 *N*-Sulfonamide Protection & Deprotection

Tosyl protection is a common strategy for amine protection as the resultant sulfonamide is substantially deactivated compared to the starting materials, however the obvious trade-off for this stability is the difficulty of their removal. Tosylated amines are typically deprotected under relatively harsh dissolving metal reduction conditions, with SmI_2 among the most mild.⁹⁶ As such, we were concerned about the stability of the furoindole motif, and thus sought to investigate this as soon as possible once we achieved reliable access to the methanoquinolizidine core. Thus, we subjected **103** to a variety of conditions, which had been successful on all related molecules albeit none containing the bis(hemiaminal). All resulted in decomposition, and attempts to buffer the system by addition of either NH_4Cl or Et_3N were also unsuccessful (Figure 2.11).^{97,98}

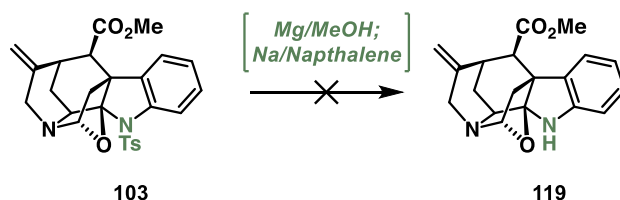
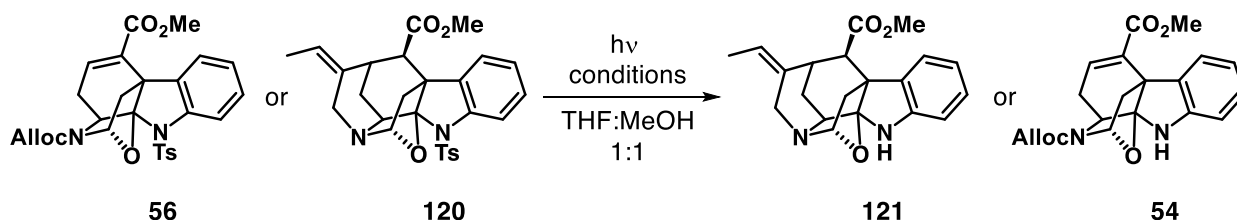


Figure 2.11 Failed reducing conditions for sulfonamide deprotection.

In light of these failures, we maintained a glimmer of hope that photochemical deprotection of the tosylated amine would be a viable path forward given its minor success in peptide applications.^{99–103} Indeed after much screening we were able to successfully deprotect the sulfonamide from **56**, however when we tested these conditions on the real system, we only observed decomposition (Table 2.3).



compound	glass	photosensitizer	additives	results
56	borosilicate	anisole	Na ₂ CO ₃ , Ascorbic Acid	48% (BRSM)
56	quartz	anisole	Na ₂ CO ₃ , Ascorbic Acid	decomp
120	borosilicate	anisole	Na ₂ CO ₃ , Ascorbic Acid	N.R.
120	borosilicate	1,2-dimethoxybenzene	Na ₂ CO ₃ , Hantzsch Ester	N.R.
120	borosilicate	1,2-dimethoxybenzene	Ascorbic Acid	N.R.
120	quartz	anisole	Na ₂ CO ₃ , Ascorbic Acid	decomp

Table 2.3 Photochemical tosyl deprotection condition screen

Considering the challenges associated with tosyl deprotection, we first sought to explore if any other protecting groups would be viable, keeping in mind the need for orthogonality to both Pd⁰, and tin radical conditions. Unfortunately, all common protecting groups were unsuccessful, often with recovery of starting material, or elimination to the two possible highly conjugated systems shown in Figure 2.12. Moreover, the failure of tosylchloride in spite of tosic anhydride's successful functionalization indicated that we needed a highly activated electrophile, prompting us to seek different classes of sulfonyl electrophiles. Sulfonyl fluorides, imidazolium salts, and highly electron withdrawn sulfonyl chlorides all gave no reaction with the

furoindole.^{104–107} Specifically, the failure of the tris(trifluormethyl)phenylsulfonyl chloride hinted that the problem was likely a combination of both steric and electronic factors, necessitating both an exceptionally active electrophile that is minimally encumbered.

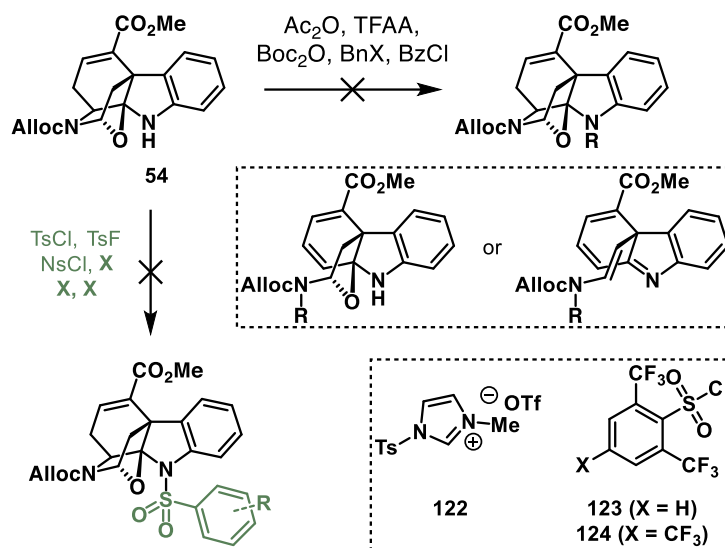
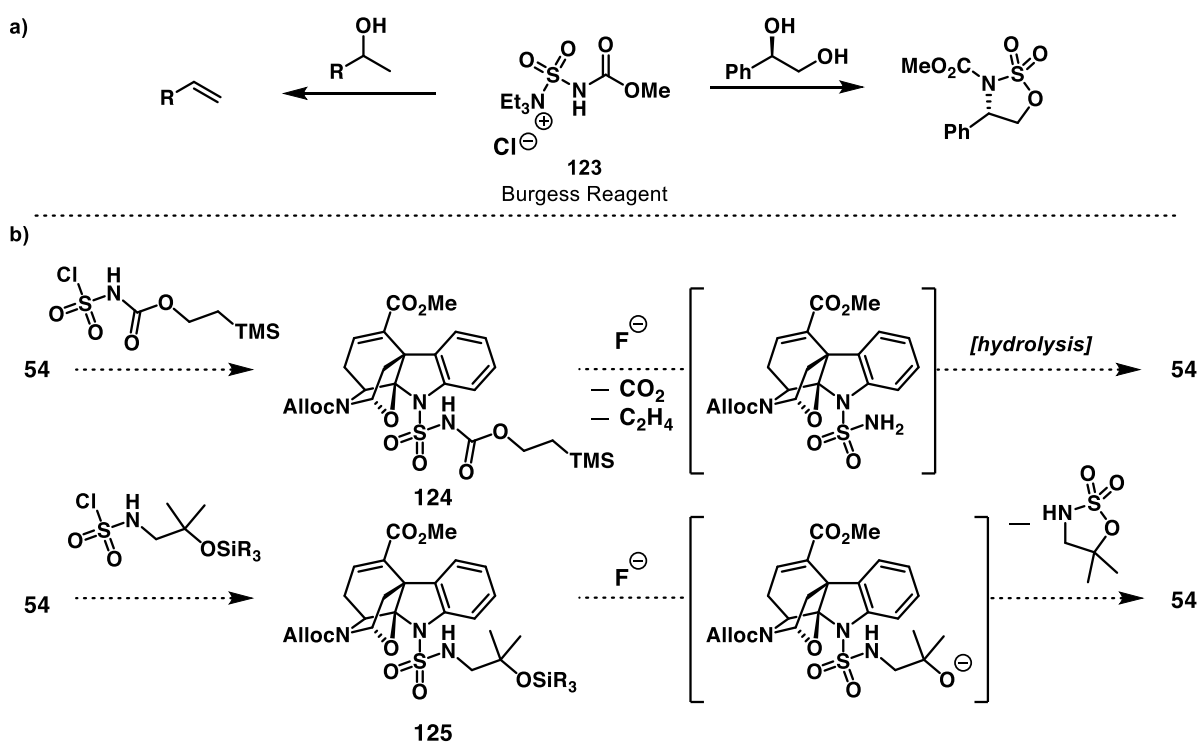


Figure 2.12 Alternate protecting groups attempted & byproducts observed.

2.9.2 Development of Sulfamoyl Chloride Protecting Groups & Urea Protection

Pulling inspiration from multiple sources (traceless protecting groups, phosphate prodrug hydrolysis, and the disseration of our very own Scott Snyder), we devised a novel protecting group concept which we hoped would allow for successful protection, as well as a facile deprotection under mild conditions at the final step. Snyder demonstrates Burgess-type reagents can do more than just dehydration, and despite the different electronics, the additional heteroatom could serve to distance the steric bulk from the reactive center.¹⁰⁸ The combination of the sulfamoyl chloride with TEOC-like traceless deprotection could easily liberate the indoline upon treatment with fluoride. Alternatively, the presence of a pendant silyl protected alcohol could allow for mild deprotection with fluoride, hoping the resultant alkoxide would

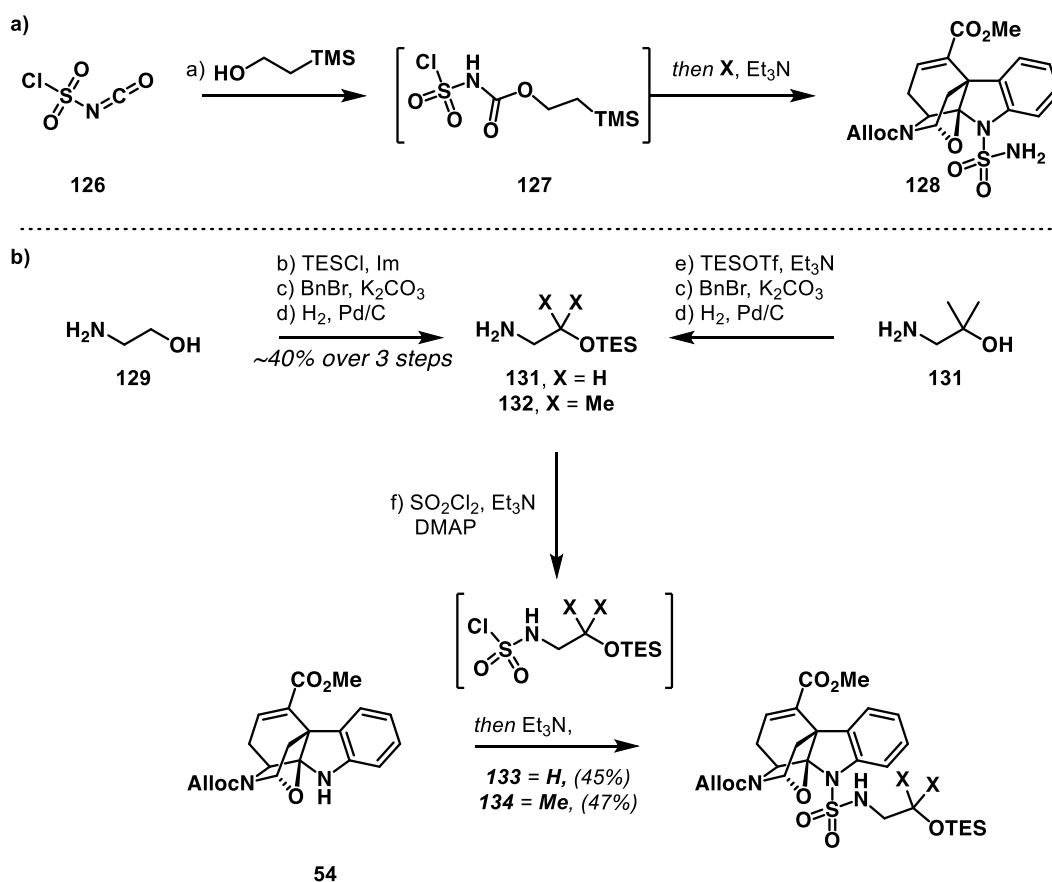
intramolecularly displace the natural product nitrogen, facilitated by Thorpe-Ingold acceleration (Scheme 2.23).



Scheme 2.23 Novel protecting group development **a)** Snyder precedent for divergent sulfamoyl electrophile reactivity **b)** Proposed protection and deprotection scheme.

To our delight, the trimethylsilyl ethanol derived sulfamoyl chloride can be easily made, and succeeded in protecting the furoindole motif, but upon scaling up, we saw predominantly formation of sulfamide **128**, presumably *via in situ* deprotection due to trace acid, despite co-solvent quantities of Et₃N (Scheme 2.24a). Turning instead to the pro-drug inspired variant, we first synthesized the desired amines. While both **131** and **132** can be obtained directly from selective silyl protection, the purity and high water content are incompatible with the sulfamoyl chloride formation. To circumvent this, we first benzylated the amine to reduce the polarity and dramatically simplify purification. Notably in both cases we could not selectively monobenzylate. Regardless, immediate debenzylation under hydrogenation conditions and azeotropic

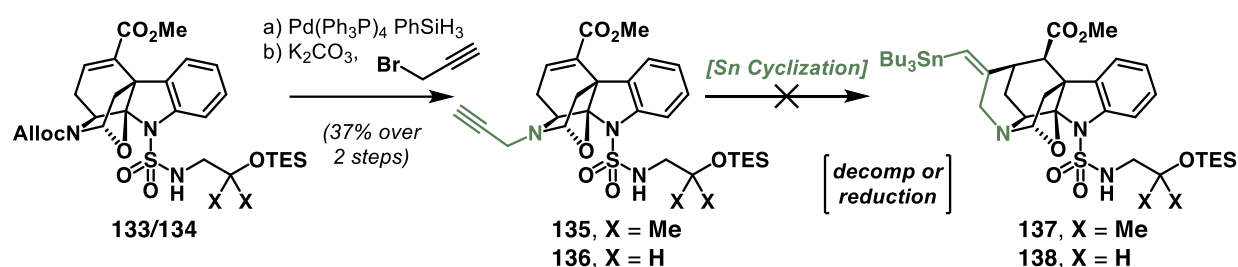
distillation of the water with anhydrous toluene afforded scrupulously pure and dry amines **131** and **132** (Scheme 2.23b). These can then be converted into the sulfamoyl chloride upon dropwise addition into a solution of SO_2Cl_2 .^{109,110} It is also important to include that the SO_2Cl_2 must be absolutely colorless for the success of this reaction. This can be achieved ideally by distillation, though simple degassing with argon to remove trace Cl_2 present is also sufficient. Finally, treatment of **54** with the crude sulfamoyl chloride and an excess of Et_3N yields the protected furoindole in moderate yields (Scheme 2.24b). These results were incredibly exciting, as this strategy seemed to somewhat generalizable, with the potential for diversity from the sulfamoyl



Scheme 2.24 Novel sulfamoyl chloride protections **a)** TMS-ethanol derived sulfamoyl chloride. **b)** Pro-drug inspired sulfamoyl chloride and subsequent furoindole protection. (a) 2-TMS-ethanol (1.0 eq), chlorosulfanyl isocyanate (1.0 eq), CH_2Cl_2 (0.5 M), -78°C , 1 h, then **54** (0.2 eq), Et_3N (5.0 eq), CH_2Cl_2 (0.2 M), 0°C , 2 h, 45-57%; (b) TESCl (1.2 eq), Im (2.0 eq), CH_2Cl_2 (0.1 M), 0°C to 23°C , 3 h; (c) BnBr (3.0 eq), K_2CO_3 (5.0 eq), CH_2Cl_2 (0.1 M), 45°C , 12 h; (d) Pd/C (15.0 mol%), H_2 (1 atm), $\text{EtOAc:MeOH} = 1:1$ (0.2 M), 48 h, 40% over 3 steps; (e) TESOTf (3.0 eq), Et_3N (5.0 eq), CH_2Cl_2 (0.1 M), -78°C to 23°C ; (f) SO_2Cl_2 (1.1 eq), Et_3N (1.5 eq), DMAP (10.0 mol%), -78°C to 23°C , 2 h, then **X** (0.2 eq), Et_3N (5.0 eq), CH_2Cl_2 (0.2 M), 0°C , 2 h, 45-47%

chloride, expanding the available methods of furoindole protection.

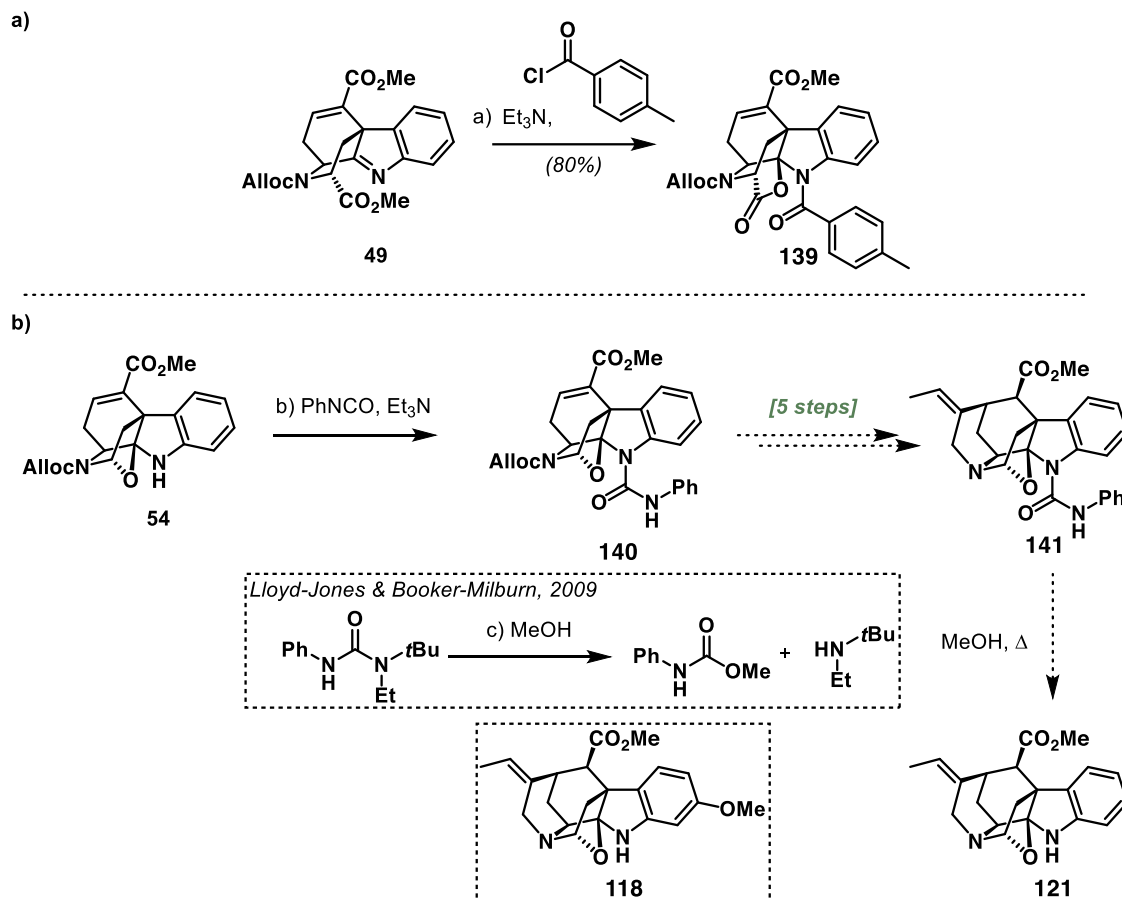
Aiming to test the viability of these new protecting groups, we pushed these compounds through the synthetic sequence. Unfortunately, **135** only afforded the corresponding alkyne reduction and no cyclized product. We hypothesize that this is due to the exceptional steric bulk of the tertiary silyl protected alcohol precluding Lewis-Acid coordination. We hoped the comparatively less capacious size of primary protected alcohol **136** would enable the desired cyclization, but this ultimately proved too labile, decomposing in the reaction (Scheme 2.25).



Scheme 2.25 Sulfamide protected tin cyclization attempts. (a) *vide supra*; (b) *vide supra*

Revitalized by the successful protection, we reevaluated our assumptions about what protections would be viable. Given that we are able to form lactone **139** upon treatment with acid chlorides, we knew benzoyl and similarly sized groups are viable; however, we also know that acid chlorides are incompetent electrophiles in our furoindole system, even with the addition of silver at elevated temperatures (Scheme 2.26). Combining this knowledge with the insights gained from our sulfamoyl chloride experiments we deduced that the steric environment is more important than we previously assumed. We then decided to again exploit the minimized steric environment of *sp*-hybridized carbons in the form of an isocyanate electrophile. Gratifyingly, treatment of furoindole **54** with excess phenyl isocyanate afforded the urea protected **140** in nearly quantitative yield. Current efforts are underway to examine the remaining late-stage chemistry in the urea format and we are optimistic that this can be facilyly deprotected in a late

stage under mild conditions such as simple treatment with methanol in hot toluene (scheme 2.26).^{111,112}



Scheme 2.26 a) Lactonization protection. a) toluoyl chloride (5.0 eq), Et₃N (10.0 eq), MeCN (0.5 M), 80 °C, 12 h, 80%; **b)** Urea protection and tentative endgame. (b) PhNCO (5.0 eq), Et₃N (10.0 eq), DCE (0.2 m), 60 °C, 3 h. c) MeOH (1.1 eq), toluene, 70 °C, >99%.

Overall, the complex steric and electronic factors of the furoindole system presented a number of trials and tribulations, but we were ultimately able to successfully elucidate the specific challenges and design a number of electrophiles capable of protecting the furoindole. While these novel groups were not enabling for the synthesis, we hope their discovery will find use in hindered amine protection elsewhere. Finally, we were able to identify a promising protection strategy in the form of a urea. We believe that this strategy has the potential to enable the total synthesis of bis(hemiaminal) containing alkaloids. Assuming our findings from this

revised endgame will translate well to the methoxy substituted equivalent, we believe this strategy has the potential to enable the total syntheses of the bis(hemiaminal) containing alkaloids **121** and **118**, thereby reducing the remaining synthetic challenge to the installation of the aryl-methoxy substituent.

2.10 6-OMe-Trp-OMe Synthesis Towards 18Z-(11-OMe)-picrinine

One can readily imagine two methods for introduction of the methoxy group: a late-stage borylation and coupling sequence; or the simple substitution of 6-OMe-Trp into our current synthetic route (Figure 2.13). The late-stage incorporation has several pros, including full confidence in the preceding steps, an additional sleek transformation, and the continued use of an inexpensive and abundant starting material. On the other hand, early-stage installation may be simpler, but begets a degree of uncertainty in the remainder of the route, as in many cases minor changes can have disproportionately large effects down the line.

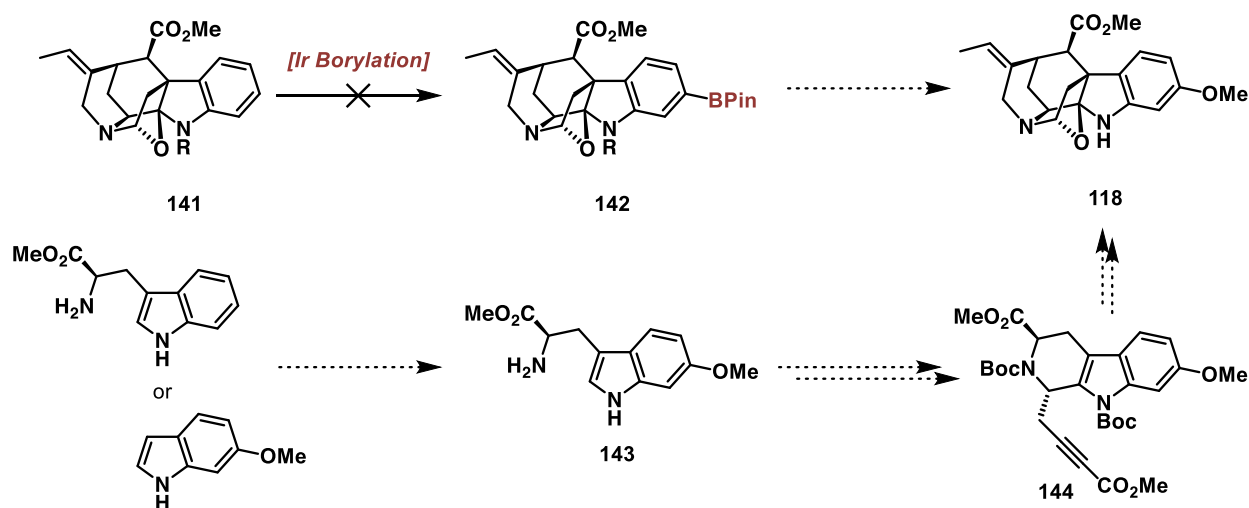
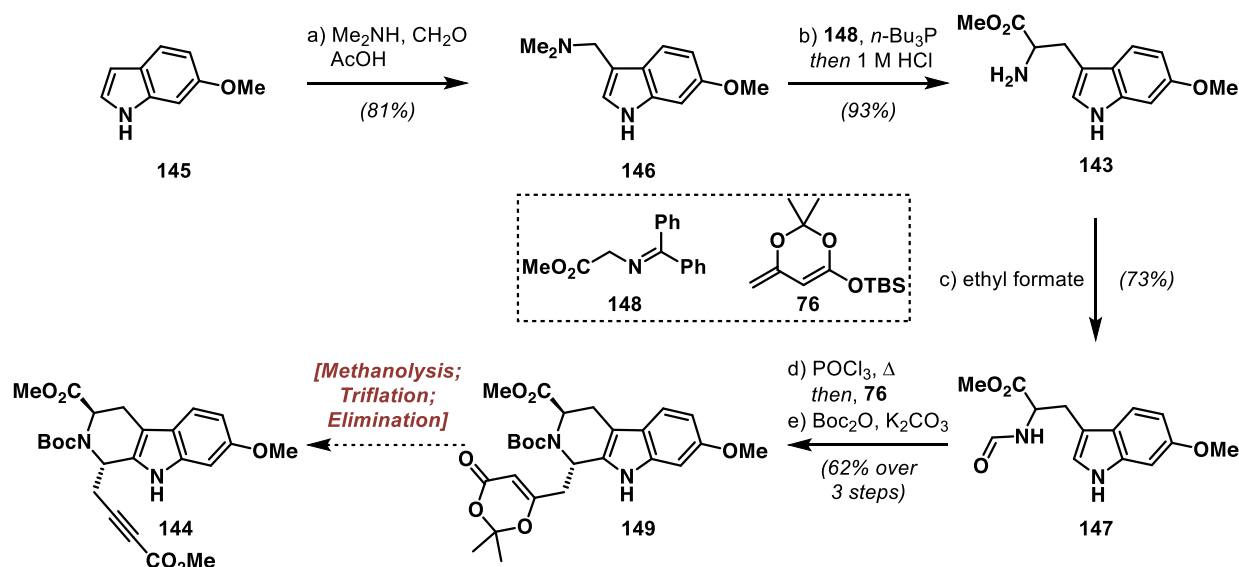


Figure 2.13 Possible approaches to incorporate the necessary methoxy substituent.

We first chose to investigate the borylation route, however all attempts to borylate various intermediates were either unsuccessful, or gave undesired borylation selectivity.^{113–115} These lackluster results in tandem with our concerns about the solubility of late-stage

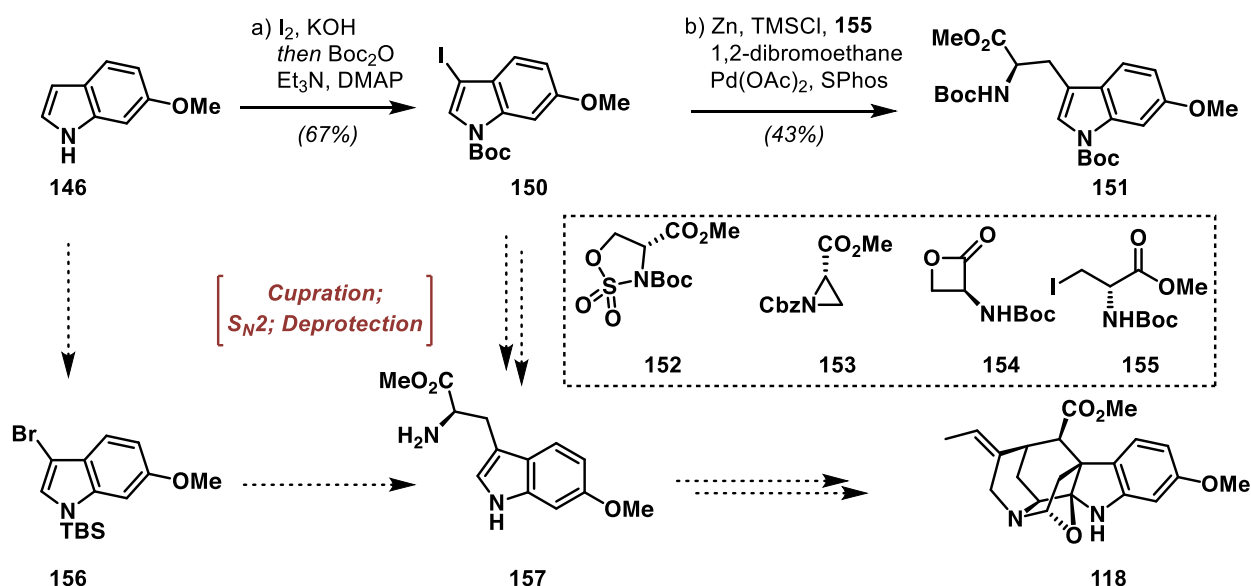
intermediates in the necessary nonpolar solvents, selectivity in the presence of the aromatic protecting group and the compatibility of both borylation and coupling conditions with late-stage intermediates resulted in this strategy being quickly abandoned (Figure 2.13), in favor of pursuing incorporation at the beginning of the route.

Following Baran's precedent, we were able to successfully replicate their synthesis of 6-OMe-Trp, however the lengthy sequence rife with protecting group manipulations and reported scalability issues deemed this option too inefficient.¹¹⁶ Instead, we are currently seeking to synthesize the same intermediate with more classical conditions, starting from 6-OMe-indole. We have already achieved this in a racemic sense using a Somei-Kametani reaction from gramine **146** (Scheme 2.27).^{117–119} This has subsequently enabled investigation of the early steps with the new compound **143**, and thus the first phase of the synthesis proceeds smoothly, though notably we are unable to protect the amine with AllocCl, and thus are moving forward with a Boc-carbamate instead.



Scheme 2.27 Racemic synthesis of 6-OMe-Trp-OMe. a) Me_2NH (4.0 eq), formalin (1.1 eq), AcOH (0.3 M), 23 °C, 12 h, 81%; b) **148** (1.0 eq), $n\text{-Bu}_3\text{P}$ (25.0 mol%), MeCN (0.1 M), 90 °C, 12 h, then aq. HCl (1.0 M, 3.0 eq), THF (0.16 M), 30 minutes (93%); c) ethyl formate (0.1 M), 60 °C, 16 h, 73%; d) POCl_3 (1.1 eq) CH_2Cl_2 (0.15 M), 45 °C, 2.5 h then **76** (1.5 eq), 23 °C, 16 h; e) Boc_2O (2.0 eq), K_2CO_3 (4.0 eq), THF:H₂O = 1:1, 16 h, 62% over 3 steps.

Still wishing to target a globally asymmetric synthesis, we have so far achieved a Negishi coupling towards **151** using chiral pool starting materials, however this reaction is poor yielding on scale up.¹²⁰ Hoping to avoid expensive reagents and low yields in the first step, we are currently investigating a number of electrophiles, including sulfamidates, lactones, and aziridines with plans to functionalize the indole *via* substitution chemistry.¹²¹ To this end, protection of the indole N-H bond may be required to prevent competitive *N*-alkylation. Similarly, the use of aryl-cuprates may enhance the nucleophilicity, but we have already observed challenges using *in situ* formed aryl-lithiums as these are excessively basic, preferring deprotonation to substitution chemistry. These efforts are currently ongoing in the lab, and we are especially optimistic about the scalability of the S_N2 approach if one of the electrophiles proves suitable (Scheme 2.28). We believe that these results, in combination with our advancements in the E-ring closure and protecting group areas will lead to the first synthesis of 18Z-(11-OMe)-picrinine.



Scheme 2.28 Potential asymmetric approaches to 6-OMe-Trp-OMe & **118**. a) I₂ (1.0 eq), KOH (2.5 eq), DMF (0.4 M), 23 °C, 2 h, then Boc₂O (1.5 eq), DMAP (10.0 mol%), Et₃N (2.5 eq), CH₂Cl₂ (0.25 M), 23 °C 16 h, 67%; b) Zn (10.0 eq), **155** (1.0 eq), Pd(OAc)₂ (10.0 mol%), TMSCl (70.0 mol%), 1,2-dibromoethane (80.0 mol%), SPhos (20.0 mol%), DMF (0.5 M), 40 °C, 4 h, 43%.

2.11 Biological Evaluation of Opioid Receptor Agonism

Finally, I would like to briefly discuss the potential of our route to provide synthetic access to biologically useful analogs. Prof. Andrew Riley's group has recently reported the synthesis of akuammiline analogs which exhibit both higher potency, and selectivity for the μ - & κ -opioid receptors than the natural products themselves.^{122,123} This improvement is believed to originate *via* Van der Waals interactions of the aromatic ring in the hydrophobic pocket (Figure 2.14). They are currently accessing these analogs from the natural products themselves; however, if successful, our route would be one which allows unique access to indoline substituted derivatives, and our protecting group strategies could enable a broader range of SAR studies in this pocket (Figure 2.15). Moreover, because we can access both isomers, this is a great opportunity to investigate if the alkene geometry is at all relevant to the biological function of the molecule, as this region of the molecule appears to be highly solvent exposed in the co-crystal structure (blue arrow, Figure 2.14). We are excited about the potential for this work to

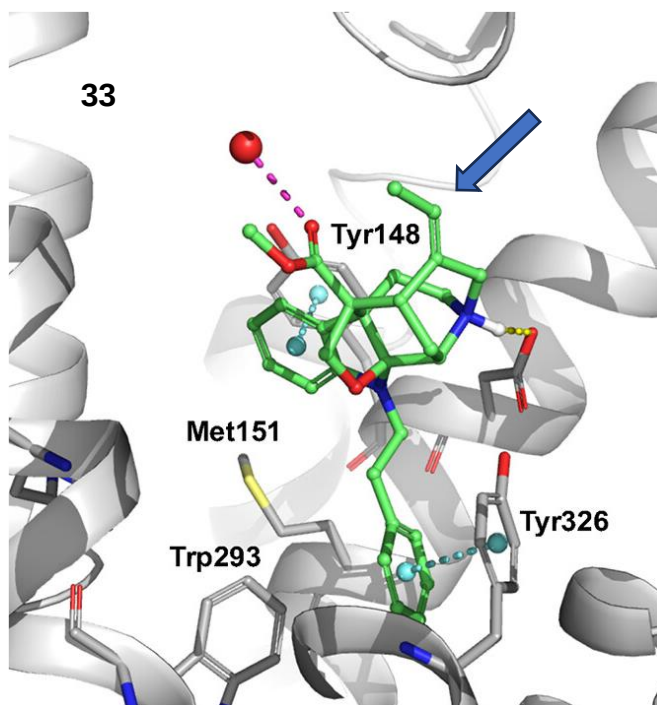


Figure 2.14 X-ray image taken from Riley *et. al.* 2023.

have a practical biological application.

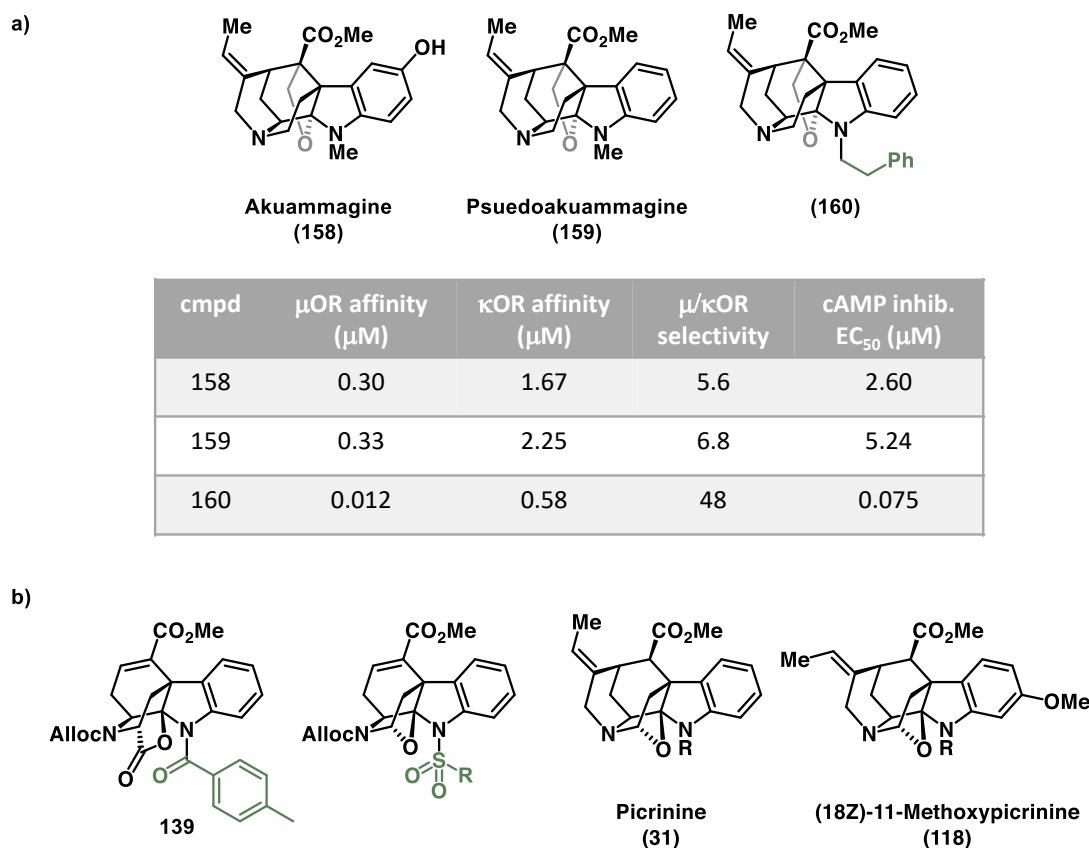


Figure 2.15 Biologically relevant structures and data. **a)** Riley group structures examined and corresponding biological data. **b)** Potential SAR diversification points accessible with our synthetic route.

2.12 Outlook and Future Considerations

Overall, the evolution of this total synthesis has been a whirlwind of both surprise challenges, and innovations. Thus far, major advancements in the field of alkaloid synthesis to which we have contributed are: only the second known procedure to close the E-ring of the methanoquinolizidine framework utilizing a unique Lewis acid template strategy to effect this transformation in high yields; identification of a lead towards accessing both alkene isomers of the akuammiline family; the development of a new class of sulfamoyl protecting groups for highly hindered or unreactive amines; and potential access to a useful divergent synthon for SAR studies in an opioid receptor agonist. Specifically, we hope this interesting application of a Lewis

acid will inspire other template guided synthetic endeavors in complex natural product synthesis. Still, further improvements can be made.

If the hydroboration and subsequent formation of the isomeric olefin proves unoptimizable, some promising alternatives include a Zweifel type olefination, or formation of a fully substituted vinyl-triflate or vinyl iodide, and subsequent reduction to the olefin should afford the desired alkene. Of course, we are working to asymmetrically synthesize 6-OMe-Trp-OMe and carry it through the rest of the synthesis. Currently, the step we foresee as most likely to be distinct from the non-substituted version is the Barton decarboxylation as the aromatic ring is now substantially more electron rich. Minor improvements could also be made *via* telescoping of the tin-mediated cyclization and iodination step. Finally, ultimate deprotection of the urea is still an open question, however we believe nucleophilic displacement should liberate the natural product under mild conditions. The combination of these final efforts should hopefully lead to the successful synthesis of 18Z-(11-OMe)-picrinine.

2.13 References

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2.14 *Experimental Section*

General Procedures

2.14.1 *Syntheses of Selected Intermediates*

General Procedures: All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Dry tetrahydrofuran (THF), toluene, diethyl ether (Et₂O), dichloromethane (CH₂Cl₂), and acetonitrile (CH₃CN) were obtained by passing commercially available pre-dried, oxygen-free formulations through activated alumina columns. Yields refer to chromatographically and spectroscopically (¹H and ¹³C NMR) homogeneous materials, unless otherwise stated. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Reactions were magnetically stirred and monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent, and an ethanolic solution of phosphomolybdic acid and cerium sulfate or a solution of KMnO₄ in aq. NaHCO₃ and heat as developing agents. SiliCycle silica gel (60, academic grade, particle size 0.040–0.063 mm) was used for flash column chromatography. Preparative thinlayer chromatography separations were carried out on 0.50 mm E. Merck silica gel plates (60F254). NMR spectra were recorded on Bruker 400 and 500 MHz instruments and calibrated using residual undeuterated solvent as an internal reference. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, br = broad, app = apparent. IR spectra were recorded on a Perkin-Elmer 1000 series FT-IR spectrometer. High-resolution mass spectra (HRMS) were recorded on Agilent 6244 Tof-MS using ESI (Electrospray Ionization) at the University of Chicago Mass Spectroscopy Core Facility. All ee values were determined by HPLC on Daicel Chiralcel or Chiralpak columns. For procedures and

characterization of compounds **46-58** synthetic intermediates see Charles Coles' thesis, University of Chicago, 2021.

Alkyne 47. To a flask containing acetal **46** (10.0 g, 23.9 mmol, 1.0 eq) was added Acetone:H₂O (4:1, 240 mL, 0.1 M), and PPTS (3.0 g, 11.95 mmol, 0.5 eq), and the resulting solution was refluxed at 80 °C for 4 hours. Upon completion, the reaction was quenched with sat. aq. NaHCO₃, placed into a separatory funnel, separated, and the aqueous phase was extracted with Et₂O (3 x 100 mL). The combined organic layer was then washed with brine (2 x 50 mL), dried over Na₂SO₄, filtered, and evaporated *in vacuo*. The crude material was then used directly in the next step. The crude residue was dissolved in MeOH (240 mL, 0.1 M), K₂CO₃ (3.30 g, 23.9 mmol, 1.0 eq) was added, and the mixture was cooled to 0 °C in an ice bath. Then Ohira-Bestmann reagent (4.59 g, 23.9 mmol, 1.0 eq) was added, and the mixture was allowed to warm to 23 °C overnight. After 16 h, the mixture was concentrated *in vacuo*. The crude residue was dissolved in EtOAc, and washed with H₂O (2 x 50 mL). The aqueous layer was extracted with EtOAc (2 x 50 mL), then the combined organic layer was washed with brine (2 x 50 mL), dried over Na₂SO₄, filtered, and evaporated *in vacuo*. The crude material was then purified by flash column chromatography (silica gel, Hex:EtOAc = 3:1) to afford the resultant alkyne **47** as a yellow solid (4.60 g, 12.5 mmol, 52% yield). ¹H NMR (400 MHz, CDCl₃) δ 8.23 (s, 1H), 7.58 – 7.48 (m, 1H), 7.37 (dt, *J* = 8.1, 1.0 Hz, 1H), 7.21 (ddd, *J* = 8.2, 7.1, 1.3 Hz, 1H), 7.14 (ddd, *J* = 8.1, 7.1, 1.1 Hz, 1H), 5.33 – 4.75 (m, 2H), 3.60 (s, 3H), 3.41 (d, *J* = 15.6 Hz, 1H), 3.19 (d, *J* = 16.6 Hz, 2H), 2.61 (s, 1H), 2.13 (s, 1H), 1.50 (s, 9H).

Carboxylic Acid 50. To a round bottom flask with stir bar was added 4 Å molecular sieves, then the flask was placed under vacuum and flame-dried thrice. Once cool, the flask was backfilled with argon, and Me₃SnOH (0.660 g, 3.60 mmol, 3.0 eq), followed by a solution of Ester **49** (0.500 g, 1.22 mmol, 1.0 eq) in 1,2-dichloroethane (7 mL, 0.175 M). The flask was then fitted with a reflux condenser, capped with a septum, and fitted with an argon balloon, and placed in a 90 °C oil bath for 12 hours. Then, an addition portion of Me₃SnOH (0.440 g, 2.40 mmol, 2.0 eq) was added and the mixture stirred for an additional 24 h. Upon completion, the reaction was filtered through a short pad of celite, washed with CH₂Cl₂ (15 mL) and concentrated *in vacuo*. The crude material was then purified by flash column chromatography (silica gel, Hex:Acetone = 1:1) to afford the desired acid **50** as a yellow foam (0.251 g, 0.633 mmol, 52%). ¹H NMR (400 MHz, CDCl₃) δ 7.48 (s, 1H), 7.14 (s, 1H), 6.90 (s, 1H), 6.76 (s, 1H), 6.00 – 5.86 (td, 1H), 5.30 (dd, *J* = 24.5, 13.8 Hz, 2H), 4.84 (s, 1H), 4.64 (s, 2H), 4.35 (s, 1H), 3.68 (s, 3H), 3.20 (s, 1H), 2.89 (s, 1H), 2.78 (d, *J* = 19.6 Hz, 1H), 2.52 (s, 1H).

Rearranged allylamine carboxylic acid 77: ¹H NMR (500 MHz, CDCl₃) δ 7.47 (s, 1H), 7.11 (s, 1H), 6.82 (d, *J* = 45.3 Hz, 2H), 5.82 (ddt, *J* = 16.8, 10.1, 6.6 Hz, 1H), 5.32 – 5.15 (m, 2H), 4.43 (s, 1H), 3.68 (s, 3H), 3.45 (s, 1H), 3.34 – 3.22 (m, 2H), 3.16 (s, 1H), 2.79 (s, 1H), 2.68 (d, *J* = 18.5 Hz, 1H), 2.56 (s, 1H), 2.41 (s, 1H). ¹³C NMR (101 MHz, CDCl₃) δ 165.46, 134.09, 128.69, 126.81, 119.67, 51.67, 31.78, 31.43, 31.07.

Furoindole 54. To a round bottom flask containing a stir bar and **carboxylic acid 50** (350. mgs, 0.883 mmol, 1.0 eq) was added DMAP (162 mgs, 1.32 mmol, 1.5 eq), and 2-mercaptopyridine *N*-oxide (a.k.a. pyrithione, 225 mgs, 1.77 mmol, 2.0 eq). Then toluene:CH₂Cl₂ (6:1, 31 mL, 0.0285 M) was added, then the flask was wrapped in aluminum foil. DIC (111 mgs, 138 µL,

0.883 mmol, 1.0 eq) was added, and the reaction as allowed to stir at 23 °C for 2 hours. After 2 hours, the reaction was fitted with a reflux condenser and the aluminum foil was removed. A long still needle was inserted down through the reflux condenser into the reaction mixture, and an O₂ balloon was connected to bubble oxygen into the reaction, and out the exhaust needle at the top of the reflux condenser. It was then placed in a pre-heated oil bath at 80 °C, and stirred at this temperature for 1 hour, with frequent monitoring to ensure the needle did not clog with urea byproduct precipitation. Upon completion, the reaction was cooled to 23 °C, and sat. aq. NH₄Cl (20 mL) was added. The layers were separated in a separatory funnel. The aqueous phase was extracted with EtOAc (3 x 15 mL). The combined organic layer was then dried over Na₂SO₄, filtered, and evaporated *in vacuo*. The crude material was then purified by flash column chromatography (silica gel, Hex: EtOAc = 10% → 30 %) to afford furoindole **50** as a white powdery solid (61.0 mgs, 19% yield), and epimer **49** (120. mgs, 37% yield) as a yellow powdery solid/oil. This material should be stored in the fridge.

Furoindole 54: ¹H NMR (500 MHz, CDCl₃) δ 7.61 – 7.53 (m, 1H), 7.11 (td, *J* = 7.7, 1.3 Hz, 1H), 6.85 (td, *J* = 7.6, 1.1 Hz, 1H), 6.73 (d, *J* = 7.7 Hz, 1H), 6.67 (ddd, *J* = 5.6, 2.3, 0.9 Hz, 1H), 5.93 (ddt, *J* = 16.3, 10.9, 5.8 Hz, 1H), 5.70 (d, *J* = 48.3 Hz, 1H), 5.35 – 5.28 (m, 1H), 5.24 (d, *J* = 10.4 Hz, 1H), 4.65 (d, *J* = 42.8 Hz, 3H), 4.05 (s, 1H), 3.73 (s, 3H), 3.11 (dd, *J* = 67.5, 20.4 Hz, 1H), 2.67 – 2.50 (m, 2H).

Epimer 53: ¹H NMR (500 MHz, CDCl₃) δ 7.99 – 7.95 (m, 1H), 7.65 (d, *J* = 7.3 Hz, 1H), 7.40 (td, *J* = 7.6, 1.3 Hz, 1H), 7.27 (dd, *J* = 7.6, 1.1 Hz, 1H), 6.87 (s, 1H), 5.98 (td, *J* = 12.9, 11.8, 6.3

Hz, 1H), 5.69 (d, $J = 5.3$ Hz, 1H), 5.51 – 5.33 (m, 2H), 5.28 (t, $J = 12.2$ Hz, 1H), 4.72 (d, $J = 5.6$ Hz, 2H), 3.83 (s, 3H), 3.44 (s, 1H), 3.40 (d, $J = 14.3$ Hz, 1H), 3.10 – 2.94 (m, 1H), 2.85 (ddd, $J = 19.7, 4.9, 2.5$ Hz, 1H), 1.48 (dd, $J = 14.4, 5.5$ Hz, 1H).

Propargylamine 96: To a solution of amine **57** (100.0 mg, 0.228 mmol, 1.0 eq) in MeCN (0.875 mL, 0.3 M) in a vial was added K_2CO_3 (221 mg, 1.60 mmol, 7.0 eq) followed by propargyl bromide (neat, distilled, 181 mgs, 115 μ L, 6.0 eq). The vial was capped, and the mixture was heated to 50 °C for 2-3 hours (monitored by TLC). Upon completion, the reaction was diluted with CH_2Cl_2 (5 mL) and sat. aq. $NaHCO_3$ (5 mL). The phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layer was then dried over Na_2SO_4 , filtered, and evaporated *in vacuo*. The crude material was then purified by flash column chromatography (silica gel, Hex:Acetone = 30%) to afford propargylamine **57** as a yellow powdery solid (50.3 mg, 46% yield). 1H NMR (500 MHz, $CDCl_3$) δ 8.06 – 8.01 (m, 2H), 7.58 (dd, $J = 7.7, 1.4$ Hz, 1H), 7.44 (d, $J = 8.2$ Hz, 1H), 7.27 (d, $J = 5.3$ Hz, 2H), 7.15 (td, $J = 7.9, 1.4$ Hz, 1H), 6.97 (td, $J = 7.6, 1.0$ Hz, 1H), 6.77 (dd, $J = 5.7, 2.3$ Hz, 1H), 4.85 (d, $J = 3.2$ Hz, 1H), 4.23 (q, $J = 1.8$ Hz, 1H), 3.76 (s, 1H), 3.69 (s, 3H), 3.56 (dd, $J = 2.5, 1.2$ Hz, 2H), 2.89 (ddd, $J = 20.2, 4.1, 2.4$ Hz, 1H), 2.73 (ddd, $J = 20.2, 5.4, 1.9$ Hz, 1H), 2.63 (s, 1H), 2.47 (d, $J = 11.9$ Hz, 1H), 2.38 (s, 3H), 2.36 (d, $J = 3.4$ Hz, 1H), 2.29 (t, $J = 2.5$ Hz, 1H).

Lactone propargylamine. Same procedure as above. 1H NMR (500 MHz, $CDCl_3$) δ 7.50 (d, $J = 7.5$ Hz, 1H), 7.47 (s, 1H), 7.21 (s, 2H), 6.97 (t, $J = 7.5$ Hz, 1H), 6.94 – 6.84 (m, 2H), 6.15 (d, $J = 8.1$ Hz, 1H), 4.46 (s, 1H), 3.72 (d, $J = 1.2$ Hz, 3H), 3.58 (d, $J = 4.9$ Hz, 1H), 3.57 (d, $J = 2.0$ Hz,

1H), 2.90 (dd, $J = 14.0, 5.1$ Hz, 1H), 2.69 – 2.62 (m, 1H), 2.57 – 2.49 (m, 1H), 2.45 (d, $J = 14.0$ Hz, 1H), 2.42 (s, 3H), 2.35 (d, $J = 2.7$ Hz, 1H).

Vinyl stannane 98: To an oven-dried microwave vial with a stir bar was added hexbutylditin (213 mg, 186 μ L, .367 mmol, 5.0 eq), LaCl_3 (2.7 mg, 0.011 mmol, 15.0 mol%), 4-*t*-Butylpyridine (4.8 μ L, 4.5 mg, 0.033 mmol, 0.45 eq), and AIBN (1.4 mg, 0.0088 mmol, 12.0 mol%). To this was added a solution of propargylamine **96** (35.0 mgs, 0.0734 mmol, 1.0 eq) in degassed toluene (5.48 mL, 0.0133 M). The mixture was then sealed with a microwave-vial septum cap, and degassed with argon for 5 minutes. The vial was then placed in an oil bath which has been pre-heated to 85 °C. A single drop of a Bu_3SnH solution (53 mg, 49 μ L, 0.184 mmol, 2.5 eq) in toluene (1.84 mL, 1.0 M) and the remainder of the solution was added *via* syringe pump over 5 hours. Upon completion of the reaction, the reaction mixture was concentrated *in vacuo*. The crude material was then purified by flash column chromatography (silica gel, 100% hexanes $\rightarrow$ 5% Et_2O in Hexanes $\rightarrow$ Hex: Et_2O = 1:1) to afford the desired vinyl stannane **98** as a yellow oil (23.5 mg, 42% yield, 78% BRSM) with unavoidable Sn contamination. ^1H NMR (500 MHz, CDCl_3) δ 8.06 – 7.97 (m, 1H), 7.55 (d, $J = 8.2$ Hz, 1H), 7.31 (dd, $J = 7.6, 1.4$ Hz, 1H), 7.26 (s, 5H), 7.16 (ddd, $J = 8.5, 7.5, 1.4$ Hz, 1H), 6.95 (td, $J = 7.6, 1.0$ Hz, 1H), 5.62 – 5.45 (m, 1H), 4.80 (d, $J = 2.3$ Hz, 1H), 4.61 (d, $J = 5.0$ Hz, 1H), 3.75 (dd, $J = 17.6, 2.6$ Hz, 1H), 3.66 (s, 3H), 3.28 (d, $J = 13.7$ Hz, 1H), 3.19 (d, $J = 3.7$ Hz, 1H), 3.06 (d, $J = 17.6$ Hz, 1H), 2.60 (d, $J = 3.8$ Hz, 1H), 2.37 (s, 3H), 2.28 (ddd, $J = 14.6, 5.1, 3.2$ Hz, 1H), 2.20 – 2.10 (m, 1H).

And the undesired non-cyclized vinyl stannane **97** ^1H NMR (500 MHz, CDCl_3) δ 8.00 (d, $J = 8.4$ Hz, 2H), 7.58 (dd, $J = 7.7, 1.4$ Hz, 1H), 7.42 (d, $J = 8.3$ Hz, 1H), 7.28 (d, $J = 8.1$ Hz, 2H), 7.13 (td, $J = 7.9, 1.4$ Hz, 1H), 6.96 (td, $J = 7.6, 1.1$ Hz, 1H), 6.78 – 6.73 (m, 1H), 5.94 – 5.83 (m, 1H), 5.27 (d, $J = 1.7$ Hz, 1H), 5.20 (d, $J = 10.2$ Hz, 1H), 4.72 (d, $J = 3.2$ Hz, 1H), 4.06 (d, $J = 4.0$ Hz, 1H), 3.74 (d, $J = 7.8$ Hz, 1H), 3.69 (s, 3H), 3.43 (dd, $J = 13.6, 6.6$ Hz, 1H), 3.39 – 3.33 (m, 1H), 2.87 – 2.79 (m, 1H), 2.66 – 2.57 (m, 1H), 2.44 – 2.33 (m, 4H), 2.17 (d, $J = 3.0$ Hz, 1H), 1.72 – 1.57 (m, 6H), 1.39 – 1.24 (m, 13H), 0.92 (t, $J = 7.3$ Hz, 8H).

Lactone vinylstannane. synthesized by the same procedure as the furoindole vinylstannane. ^1H NMR (500 MHz, CDCl_3) δ 7.55 (s, 2H), 7.34 – 7.29 (m, 1H), 7.26 (s, 4H), 7.02 – 6.90 (m, 2H), 6.36 (s, 1H), 5.59 (s, 1H), 4.77 (s, 1H), 3.96 – 3.87 (m, 1H), 3.68 (s, 3H), 3.58 – 3.50 (m, 2H), 3.40 (s, 1H), 3.04 (d, $J = 17.2$ Hz, 1H), 2.75 (d, $J = 4.2$ Hz, 1H), 2.42 (d, $J = 12.9$ Hz, 3H), 2.34 – 2.25 (m, 2H), 1.90 – 1.79 (m, 1H).

Vinyl Iodide 105. To a solution of vinyl stannane **98** (25.0 mg, 0.033 mmol, 1.0 eq) in CH_2Cl_2 (0.33 mL, 0.1 M) was added Lutidine (7.1 mg, 7.7 μL , 0.066 mmol, 2.0 eq). The solution was then cooled to -78°C , and a solution of I_2 in CH_2Cl_2 (0.35 M) was added dropwise until the strong purple/brown color persisted. The reaction was then stirred at -78°C for 1.5 h. Upon completion, the reaction was quenched with sat. aq. $\text{Na}_2\text{S}_2\text{O}_4$ (5 mL), and diluted with CH_2Cl_2 (5 mL). The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layer was then dried over Na_2SO_4 , filtered, and evaporated *in vacuo*. The crude residue was then co-evaporated with toluene to remove the lutidine, then pushed through a

silica plug (Hex:Acetone = 2:1) to give the desired vinyl iodide **105** ^1H NMR (500 MHz, CDCl_3) δ 8.06 – 7.96 (m, 2H), 7.55 (d, J = 8.3 Hz, 1H), 7.31 (dd, J = 7.6, 1.4 Hz, 1H), 7.28 (s, 2H), 7.20 – 7.15 (m, 1H), 6.97 (td, J = 7.6, 1.0 Hz, 1H), 5.90 (s, 1H), 4.86 (d, J = 2.4 Hz, 1H), 4.62 (d, J = 4.9 Hz, 1H), 3.71 (s, 3H), 3.46 (dd, J = 18.6, 2.8 Hz, 1H), 3.33 (d, J = 18.8 Hz, 1H), 3.28 (d, J = 3.6 Hz, 1H), 2.89 (d, J = 13.9 Hz, 1H), 2.59 (d, J = 3.7 Hz, 1H), 2.38 (s, 3H), 2.25 – 2.16 (m, 2H), 2.11 (d, J = 14.7 Hz, 1H). This material was used directly in the next step.

Lactone vinyl iodide 112. Synthesized using the same procedure from the furoindole iodination. ^1H NMR (500 MHz, CDCl_3) δ 7.54 (s, 2H), 7.38 – 7.32 (m, 1H), 7.25 (d, J = 1.8 Hz, 4H), 7.01 – 6.92 (m, 2H), 6.34 (s, 1H), 5.97 (s, 1H), 4.82 (s, 1H), 3.73 (s, 3H), 3.68 (d, J = 18.3 Hz, 1H), 3.60 (d, J = 4.4 Hz, 1H), 3.47 (d, J = 18.9 Hz, 2H), 3.18 (dd, J = 15.4, 4.6 Hz, 1H), 2.75 (d, J = 4.2 Hz, 1H), 2.44 (s, 3H), 2.38 (d, J = 15.5 Hz, 1H), 2.28 – 2.20 (m, 1H), 1.90 – 1.82 (m, 1H).

Trisubstituted alkene 106. To iodide **105** from the previous reaction was added $\text{Pd}(\text{OAc})_2$ (1.3 mg, 5.79 μmol , 10 mol%), $n\text{-Bu}_4\text{NCl}$ (37.0 mg, 0.133 mmol, 2.3 eq), and DMF (0.58 mL, 0.1 M). This solution was then degassed with argon for 5-10 minutes. Then, Me_4Sn (52.0 mg, 40 μL , 0.290 mmol, 5.0 eq) was added in a single portion, and the reaction mixture was placed in a pre-heated oil bath at 80 $^\circ\text{C}$. The reaction mixture almost immediately precipitates some palladium black, and the reaction is typically done in <5 minutes. Upon completion, the mixture is diluted with EtOAc (5 mL), and H_2O (5 mL), and transferred to a separatory funnel. The phases were then separated, and the aqueous layer was extracted with EtOAc (1 x 5 mL). The combined organic layer was then washed with H_2O (5 x 5 mL), brine (2 x 5 mL), dried over Na_2SO_4 ,

filtered, and evaporated *in vacuo*. The crude material was then purified by flash column chromatography (silica gel, Hex:Acetone 30%) to give the desired alkene **106** (11 mgs, 0.022 mmol, 67% yield over 2 steps) as a yellow oil. ¹H NMR (500 MHz, CDCl₃) δ 8.06 – 7.98 (m, 2H), 7.55 (d, *J* = 8.1 Hz, 1H), 7.30 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.26 (t, *J* = 4.1 Hz, 2H), 7.16 (ddd, *J* = 8.3, 7.5, 1.4 Hz, 1H), 6.95 (td, *J* = 7.6, 1.0 Hz, 1H), 5.19 – 5.08 (m, 1H), 4.81 (d, *J* = 2.5 Hz, 1H), 4.62 (d, *J* = 4.9 Hz, 1H), 3.68 (s, 3H), 3.57 – 3.46 (m, 1H), 3.31 (d, *J* = 18.1 Hz, 1H), 3.13 (d, *J* = 13.6 Hz, 1H), 3.04 (d, *J* = 3.5 Hz, 1H), 2.57 (d, *J* = 3.6 Hz, 1H), 2.37 (s, 3H), 2.24 (ddd, *J* = 14.5, 5.1, 3.2 Hz, 1H), 2.20 – 2.15 (m, 1H), 2.12 (dd, *J* = 14.5, 3.3 Hz, 1H), 1.59 – 1.52 (m, 3H).

Lactone trisubstituted alkene 109. Synthesized following the same procedure for the furoindole Stille coupling. ¹H NMR (500 MHz, CDCl₃) δ 7.54 (s, 2H), 7.36 – 7.28 (m, 1H), 7.25 (d, *J* = 5.3 Hz, 4H), 7.00 – 6.90 (m, 2H), 6.36 (s, 1H), 5.19 (q, *J* = 7.2 Hz, 1H), 3.69 (s, 4H), 3.55 (d, *J* = 4.4 Hz, 1H), 3.47 – 3.34 (m, 3H), 3.27 (s, 1H), 2.72 (d, *J* = 4.0 Hz, 1H), 2.43 (s, 3H), 2.33 (d, *J* = 15.2 Hz, 1H), 2.27 – 2.20 (m, 1H), 1.84 (dd, *J* = 14.5, 3.5 Hz, 1H), 1.62 (d, *J* = 6.9 Hz, 3H).

Lactone Alkene Isomer 115. To a solution of trisubstituted alkene **109** (4.0 mg, 0.0083 mmol, 1.0 eq) in anhydrous THF (83 μL, 0.1 M) at 0 °C was added a solution of BH₃•THF complex (2.1 mg, 25 μL, 1.0 M, 3.0 eq) dropwise. The reaction was stirred at 23 °C for 2-3 hours (monitored by TLC). Upon completion, the reaction was cooled to 0 °C and a freshly prepared solution of H₂O₂ (33% in H₂O, 2.3 μL, .025 mmol, 3.0 eq) in 3M NaOH (16.5 μL, 6.0 eq) was

added quickly in one portion. This mixture was then stirred for 12 minutes at 0 °C before the reaction mixture was poured into a separatory funnel containing sat. aq. Na₂S₂O₄ (5 mL) and CH₂Cl₂ (5 mL). After washing and phase separation, the aqueous layer was extracted with CH₂Cl₂ (3 x 3 mL). The combined organic layer was then washed with sat. aq. NaHCO₃ (2 x 5 mL), dried over Na₂SO₄, filtered, and evaporated *in vacuo*. The crude material was then purified by flash column chromatography (silica gel, Hex:Acetone = 2:1) then again via PLC (25% Et₂O in CH₂Cl₂) to afford the inseparable mixture of olefin isomers as a clear oil (3.9 mgs, 94% yield). Key peaks of desired olefin isomer: ¹H NMR (500 MHz, CDCl₃) δ 5.35 – 5.25 (m, 1H), 3.71 (s, 3H), 3.16 (d, *J* = 16.0 Hz, 1H), 2.94 (d, *J* = 16.1 Hz, 1H), 2.79 (d, *J* = 3.9 Hz, 1H), 2.02 – 1.95 (m, 1H), 1.68 (d, *J* = 7.0 Hz, 3H).

Oxazolidinone 86. To a solution of amine **57** (2.0 mg, 0.00456 mmol, 1.0 eq) in MeCN (0.1 mL, 0.05 M) in a vial was added Hünig's base (1.0 mg, 0.00912 mmol, 2.0 eq) followed by bromide **85** (3.0 mg, 0.0137 mmol, 3.0 eq). The vial was capped, and the mixture was heated to 50 °C for 2-3 hours (monitored by TLC). Upon completion, the reaction was diluted with CH₂Cl₂ (5 mL) and sat. aq. NaHCO₃ (5 mL). The phases were separated, and the aqueous layer was extracted with CH₂Cl₂ (3 x 5 mL). The combined organic layer was then dried over Na₂SO₄, filtered, and evaporated *in vacuo*. The crude material was then purified by flash column chromatography (silica gel, Hex:Acetone = 30%) to afford oxazolidinone **86** as a yellow powdery solid (1 mg, 78 % yield).

Allyl aryl ether 92. Same procedure as oxazolidinone alkylation. (7.8 mgs, 55% yield). ^1H NMR (400 MHz, CDCl_3) δ 8.20 (d, $J = 9.2$ Hz, 2H), 7.96 (d, $J = 8.3$ Hz, 2H), 7.47 (d, $J = 8.2$ Hz, 1H), 7.36 (d, $J = 7.5$ Hz, 1H), 7.28 (s, 2H), 7.18 (t, $J = 8.0$ Hz, 1H), 7.03 – 6.93 (m, 3H), 6.11 – 5.98 (m, 2H), 4.69 (dd, $J = 21.4, 4.0$ Hz, 2H), 4.05 (d, $J = 3.3$ Hz, 1H), 3.77 (s, 3H), 3.53 (dd, $J = 13.9, 5.0$ Hz, 1H), 3.45 – 3.33 (m, 2H), 3.09 (d, $J = 13.0$ Hz, 1H), 2.66 – 2.58 (m, 2H), 2.38 (s, 3H), 2.33 (dd, $J = 12.9, 3.7$ Hz, 1H), 2.18 (s, 1H).

Internal alkyne. synthesized following the same procedure as for propargylation. ^1H NMR (500 MHz, CDCl_3) δ 8.06 – 8.00 (m, 2H), 7.58 (dd, $J = 7.9, 1.4$ Hz, 1H), 7.43 (d, $J = 8.3$ Hz, 1H), 7.27 (d, $J = 2.2$ Hz, 2H), 7.14 (ddd, $J = 8.4, 7.5, 1.4$ Hz, 1H), 6.96 (td, $J = 7.6, 1.1$ Hz, 1H), 6.77 (ddd, $J = 5.5, 2.5, 0.9$ Hz, 1H), 4.84 (d, $J = 3.3$ Hz, 1H), 4.22 – 4.17 (m, 1H), 3.68 (s, 3H), 3.51 (q, $J = 2.4$ Hz, 2H), 2.88 (ddd, $J = 20.2, 4.1, 2.4$ Hz, 1H), 2.74 (ddd, $J = 20.2, 5.4, 1.9$ Hz, 1H), 2.48 (d, $J = 11.8$ Hz, 1H), 2.40 – 2.34 (m, 4H), 1.87 (t, $J = 2.4$ Hz, 3H).

Lactone internal alkyne. Synthesized following the general procedure for amine propargylation. ^1H NMR (500 MHz, CDCl_3) δ 7.50 (d, $J = 7.6$ Hz, 1H), 7.49 – 7.29 (m, 2H), 7.23 (d, $J = 20.6$ Hz, 3H), 6.96 (t, $J = 7.5$ Hz, 1H), 6.90 (dd, $J = 11.3, 5.6$ Hz, 1H), 6.14 (d, $J = 8.0$ Hz, 1H), 4.43 (s, 1H), 3.71 (s, 3H), 3.58 (d, $J = 4.9$ Hz, 1H), 3.50 (dd, $J = 4.5, 2.5$ Hz, 1H), 2.90 (dd, $J = 14.0, 5.1$ Hz, 1H), 2.68 – 2.59 (m, 1H), 2.56 – 2.49 (m, 1H), 2.43 (d, $J = 19.8$ Hz, 3H), 2.17 (s, 1H), 1.83 (s, 3H), 1.25 (s, 3H).

Ketone 87. To a solution of vinyl stannane **98** (11.0 mg, 0.014 mmol, 1.0 eq) in acetone (0.14 mL, 0.1 M) at 23 °C was added 2,6-Lutidine (3.0 mg, 3.3 μ L, 2.0 eq), followed by NMO (6.7 mg, 0.057 mmol, 4.0 eq), then OsO₄ (4% in H₂O, 17.5 μ L, 0.0029 mmol, 0.2 eq). This mixture was stirred for 4.5 hours, then H₂O (0.14 mL) was added followed by NaIO₄ (6.7 mg, 0.057 mmol, 4.0 eq), and stirred for an additional 30 minutes. Upon completion, the reaction mixture was poured into a separatory funnel containing sat. aq. Na₂S₂O₄ (5.0 mL) and CH₂Cl₂ (5.0 mL). The phases were separated, and the aqueous layer was extracted with CH₂Cl₂ (3 x 3 mL). The combined organic layer was then washed with brine (1 x 5 mL) dried over Na₂SO₄, filtered, and evaporated *in vacuo*. The crude material was then purified by flash column chromatography (silica gel, Hex: Acetone = 1:1) to give the desired ketone **87** as a light yellow oil. ¹H NMR (500 MHz, CDCl₃) δ 8.05 – 8.00 (m, 2H), 7.57 (d, *J* = 8.3 Hz, 1H), 7.31 – 7.27 (m, 3H), 7.23 – 7.18 (m, 1H), 6.98 (t, *J* = 7.5 Hz, 1H), 4.89 (d, *J* = 2.5 Hz, 1H), 4.77 (s, 1H), 3.73 (s, 3H), 3.59 (d, *J* = 18.8 Hz, 1H), 3.09 (d, *J* = 18.8 Hz, 1H), 2.98 (d, *J* = 3.8 Hz, 1H), 2.78 (d, *J* = 11.4 Hz, 1H), 2.76 (s, 1H), 2.39 (d, *J* = 6.3 Hz, 6H), 2.28 (dd, *J* = 14.8, 2.6 Hz, 1H). ¹³C NMR (126 MHz, CDCl₃) δ 214.02, 211.18, 172.08, 170.83, 144.89, 141.25, 140.84, 135.85, 135.65, 135.57, 134.54, 129.89, 129.73, 128.71, 128.56, 128.54, 128.52, 125.88, 125.05, 124.53, 124.32, 114.54, 114.23, 106.10, 105.70, 88.10, 87.49, 74.55, 53.04, 52.73, 52.59, 52.32, 51.29, 44.52, 40.48, 29.85, 23.51, 21.80.

Lactone Ketone. ¹H NMR (500 MHz, CDCl₃) δ 7.55 (s, 2H), 7.36 – 7.31 (m, 1H), 7.27 (q, *J* = 1.7 Hz, 2H), 7.01 – 6.94 (m, 2H), 6.34 (d, *J* = 6.9 Hz, 1H), 5.00 (d, *J* = 5.4 Hz, 1H), 3.84 (d, *J* = 18.0 Hz, 1H), 3.75 (s, 3H), 3.56 (d, *J* = 4.4 Hz, 1H), 3.21 (dt, *J* = 5.1, 2.9 Hz, 1H), 3.11 – 3.02 (m, 2H), 2.88 (d, *J* = 4.7 Hz, 1H), 2.43 (d, *J* = 16.7 Hz, 5H), 2.14 – 2.10 (m, 1H).

Cyclized furoindole disubstituted-alkene 103. To a round bottom flask containing vinyl stannane **98** (10.0 mg, 0.013 mmol, 1.0 eq) was added CH₂Cl₂ (0.13 mL, 0.1 M) followed silica gel (0.8 mg, 0.013 mmol, 1.0 eq), and then *p*-TsOH •H₂O (7.4 mg, 0.039 mmol, 3.0 eq). The reaction was allowed to stir at 23 °C for 3 hours. Upon completion, the reaction was quenched with sat. aq. NaHCO₃ (2.5 mL), and diluted with CH₂Cl₂ (3 mL). The phases were then separated, and the aqueous layer was extracted with CH₂Cl₂ (3 x 5 mL). The combined organic layer was then dried over Na₂SO₄, filtered, and evaporated *in vacuo*. The crude material was then purified by flash column chromatography (silica gel, Hex:Acetone = 30%) to afford the desired alkene as a clear oil (5.2 mg, 83% yield). ¹H NMR (500 MHz, CDCl₃) δ 8.01 (d, *J* = 8.4 Hz, 2H), 7.56 (d, *J* = 8.2 Hz, 1H), 7.33 (d, *J* = 7.5 Hz, 1H), 7.27 (d, *J* = 1.3 Hz, 2H), 7.19 – 7.14 (m, 1H), 6.99 – 6.93 (m, 1H), 4.91 (s, 1H), 4.83 (s, 1H), 4.68 (s, 1H), 4.63 (d, *J* = 4.9 Hz, 1H), 3.77 (d, *J* = 18.3 Hz, 1H), 3.70 (s, 3H), 3.31 (d, *J* = 40.7 Hz, 1H), 3.22 (d, *J* = 23.8 Hz, 1H), 3.16 (s, 1H), 2.63 (d, *J* = 3.8 Hz, 1H), 2.37 (s, 3H), 2.30 – 2.23 (m, 1H), 2.19 (dd, *J* = 13.8, 2.6 Hz, 1H), 2.14 (d, *J* = 14.3 Hz, 1H), 2.07 (d, *J* = 24.5 Hz, 1H).

Lactone Propargyl TBS-alcohol. Synthesized following general procedure for amine propargylation. (20 mg, 73% yield) ¹H NMR (500 MHz, CDCl₃) δ 7.50 (d, *J* = 7.5 Hz, 1H), 7.41 (d, *J* = 26.1 Hz, 2H), 7.21 (s, 2H), 6.95 (d, *J* = 7.5 Hz, 1H), 6.93 – 6.86 (m, 2H), 6.13 (d, *J* = 8.1 Hz, 1H), 4.40 – 4.30 (m, 3H), 3.75 – 3.65 (m, 3H), 3.61 – 3.52 (m, 3H), 2.89 (dd, *J* = 14.0, 5.0 Hz, 1H), 2.66 (dd, *J* = 20.0, 5.2 Hz, 1H), 2.55 – 2.49 (m, 1H), 2.46 – 2.37 (m, 3H), 0.91 (d, *J* = 1.8 Hz, 9H), 0.12 (s, 6H).

Lactone Propargyl alcohol. To the TBS-protected alcohol (10.0 mg, 0.016 mmol, 1.0 eq) dissolved in THF (0.16 mL, 0.1 M) and cooled to 0 °C was added TBAF (1.0 M in THF, 25 μ L, 0.025 mmol, 1.5 eq) and the reaction stirred for 30 minutes. Upon completion, the reaction was quenched with sat. aq. NH_4Cl (3 mL), diluted with CH_2Cl_2 (5 mL), and poured into a separatory funnel. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 5 mL). The combined organic layer was then dried over Na_2SO_4 , filtered, and evaporated *in vacuo*. The crude material was then purified by flash column chromatography (silica gel, Hex:Acetone = 2:1) to afford the desired alcohol as a yellow oil (4.6 mgs, 57% yield). ^1H NMR (500 MHz, CDCl_3) δ 7.51 (dd, J = 7.6, 1.2 Hz, 1H), 7.47 (s, 2H), 7.24 (d, J = 16.3 Hz, 3H), 6.97 (t, J = 7.5 Hz, 1H), 6.91 (t, J = 7.8 Hz, 1H), 6.88 (d, J = 4.1 Hz, 1H), 6.16 (d, J = 8.1 Hz, 1H), 4.57 (s, 1H), 4.28 (q, J = 16.2 Hz, 2H), 3.72 (s, 3H), 3.61 (q, J = 17.5 Hz, 2H), 3.53 (d, J = 4.7 Hz, 1H), 2.91 (dd, J = 14.0, 5.1 Hz, 1H), 2.61 – 2.48 (m, 2H), 2.43 (d, J = 14.6 Hz, 3H), 2.20 (s, 1H), 2.17 (d, J = 3.1 Hz, 1H).

Vinylogous acid 114. To a vial containing vinyl iodide **105** (2.0 mg, 0.0034 mmol, 1.0 eq) was added TEMPO (7.86 mg, 0.050 mmol, 15.0 eq) and a stock solution of AIBN in toluene (0.5 mg, 35 μ L, 0.0034 mmol, 1.0 eq). The reaction was then heated to 80 °C under an air atmosphere for 2 hours, and additional toluene added as needed to prevent drying out. Upon completion, the reaction was concentrated *in vacuo* and purified *via* PLC (Hex:Acetone = 2:1) to afford the vinylogous acid **114** (0.7 mg, 44% yield). ^1H NMR (600 MHz, CDCl_3) δ 9.46 (s, 1H), 7.56 (s, 2H), 7.21 (dd, J = 5.8, 3.2 Hz, 2H), 6.97 (dd, J = 5.9, 3.2 Hz, 2H), 6.33 (s, 2H), 5.12 (s, 1H), 4.84

(s, 1H), 4.11 (d, $J = 4.9$ Hz, 1H), 3.75 (dt, $J = 14.0, 5.7$ Hz, 2H), 3.64 (s, 3H), 3.60 (s, 1H), 3.35 (s, 1H), 2.84 (d, $J = 4.3$ Hz, 1H), 2.46 (s, 3H), 2.30 (dd, $J = 14.1, 3.8$ Hz, 1H), 2.25 (d, $J = 14.9$ Hz, 1H), 2.22 (t, $J = 7.6$ Hz, 1H), 2.16 – 2.10 (m, 1H). ^{13}C NMR (151 MHz, CDCl_3) δ 187.56, 170.41, 169.13, 167.93, 155.24, 143.65, 141.60, 135.79, 133.38, 131.41, 129.65, 129.51, 128.58, 128.27, 124.48, 124.46, 116.78, 104.01, 56.28, 55.24, 53.94, 52.11, 49.49, 31.20, 31.16, 29.72, 29.68, 26.61, 25.03, 22.71, 21.78.

Lactone Vinyl-BPin X. Synthesized utilizing the same procedure for stille coupling, but B_2Pin_2 was used in place of Me_4Sn . ^1H NMR (500 MHz, CDCl_3) δ 7.55 (s, 2H), 7.36 – 7.30 (m, 1H), 6.96 (td, $J = 6.8, 5.9, 4.1$ Hz, 2H), 6.35 (s, 1H), 5.10 (s, 1H), 4.78 (s, 1H), 4.12 (d, $J = 18.3$ Hz, 1H), 3.75 (dd, $J = 18.0, 2.2$ Hz, 1H), 3.71 (s, 3H), 3.63 – 3.57 (m, 1H), 3.42 – 3.31 (m, 2H), 2.79 (d, $J = 4.3$ Hz, 1H), 2.44 (s, 3H), 2.33 (d, $J = 15.3$ Hz, 1H), 2.29 – 2.23 (m, 1H), 1.84 (dd, $J = 14.5, 3.2$ Hz, 1H), 1.27 (d, $J = 5.2$ Hz, 12H). ^{11}B NMR (160 MHz, CDCl_3) δ 22.55.

Urea protected furoindole 140. To a solution of furoindole **54** (30.0 mgs, 0.0814 mmol, 1.0 eq) in 1,2-dichloroethane (0.81 mL, 0.1 M) at 23 °C, was added Et_3N (57.7 mgs, 80.0 μL , 0.57 mmol, 7.0 eq), followed by phenylisocyanate (48.4 mgs, 45 μL , 0.407 mmol, 5.0 eq). The reaction flask was then fitted with a micro-reflux condenser and placed into a pre-heated 60 °C oil bath. The reaction was allowed to stir at this temperature for 2-3 hours (monitored by TLC). Some precipitation was observed during this time. Upon completion, the reaction was quenched with sat. aq. NaHCO_3 (2.5 mL), and diluted with CH_2Cl_2 (3 mL). The phases were then separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic

layer was then dried over Na₂SO₄, filtered, and evaporated *in vacuo*. The crude material was then purified by flash column chromatography (silica gel, Hex:Acetone 10% → 30%) to afford the desired urea as a white microcrystalline or powdery solid (38.5 mgs, 97% yield). ¹H NMR (600 MHz, CDCl₃) δ 7.70 (d, *J* = 7.7 Hz, 1H), 7.55 (s, 1H), 7.50 (d, *J* = 19.0 Hz, 1H), 7.47 (s, 1H), 7.42 – 7.36 (m, 3H), 7.27 (s, 1H), 7.18 (t, *J* = 7.6 Hz, 1H), 7.08 (t, *J* = 7.6 Hz, 1H), 6.70 (d, *J* = 5.4 Hz, 1H), 6.05 – 5.81 (m, 2H), 5.34 (d, *J* = 15.6 Hz, 1H), 5.28 (d, *J* = 10.4 Hz, 1H), 4.65 (qd, *J* = 13.2, 5.4 Hz, 2H), 3.77 (s, 3H), 3.18 (d, *J* = 66.9 Hz, 1H), 2.68 (q, *J* = 12.3 Hz, 2H), 2.60 (d, *J* = 20.4 Hz, 1H). ¹³C NMR (151 MHz, CDCl₃) δ 166.11, 150.88, 138.00, 137.24, 132.41, 129.68, 129.60, 129.52, 129.39, 129.21, 129.15, 127.64, 124.63, 124.59, 124.03, 121.46, 120.14, 118.61, 113.38, 103.88, 84.94, 66.55, 60.56, 53.26, 51.93, 29.85, 14.35. ¹⁵N-H *via* HSQC = - 269.42 ppm.

2.14.2 Syntheses of Select Protection Intermediates

TMS-Ethanol Burgess-Type Reagent (SNOOT-Cl). To a solution of chlorosulfonyl isocyanate (7.09g, 4.34 mL, 50.0 mmol, 1.0 eq) in CH₂Cl₂ (12.5 mL, 4.0 M) at 0 °C was added a solution of TMS-ethanol (7.05 g, 8.55 mL, 52.5 mmol, 1.05 eq) in CH₂Cl₂ (12.5 mL, 4.0 M) slowly over 30 minutes using an addition funnel. Once complete, the reaction contents were concentrated on a rotary evaporator which had been previously evaporated and backfilled with argon. Upon concentration, the rotary evaporator was backfilled with argon, and white solids remained in the flask. This solid can be used directly, or can be dissolved in CH₂Cl₂ (50 mL, 1 M) to make a solution of the sulfamoyl chloride, which was used directly in the next step.

SNOOT-Furoindole 124. To a solution of furoindole **54** (50.0 mg, 0.135 mmol, 1.0 eq) in pyridine (1.4 mL, 0.1 M) at 23 °C was added sulfamoyl chloride solution (106 mgs, 0.4 mL, 0.407 mmol, 5.0 eq). The reaction was monitored by TLC (typically complete within 2 hours) and upon completion was quenched with sat. aq. NaHCO₃ (10 mL) and diluted with CH₂Cl₂ (10 mL). The phases were then separated, and the aqueous layer was extracted with CH₂Cl₂ (3 x 5 mL). The combined organic layer was then washed with brine (2 x 5 mL), dried over Na₂SO₄, filtered, and evaporated *in vacuo*. The remaining pyridine was removed azeotropically on the rotary evaporator with anhydrous toluene, then the crude material was then purified by flash column chromatography (silica gel, Hex:Et₂O = 1:1) to afford a mixture of the SNOOT protected **124**. ¹H NMR (600 MHz, CDCl₃) δ 7.87 (dt, *J* = 7.6, 0.9 Hz, 1H), 7.64 – 7.57 (m, 1H), 7.35 (td, *J* = 7.6, 1.3 Hz, 1H), 7.22 (td, *J* = 7.6, 1.2 Hz, 1H), 6.72 – 6.68 (m, 1H), 5.98 (ddt, *J* = 16.4, 11.0, 5.8 Hz, 1H), 5.79 (s, 1H), 5.36 (dd, *J* = 17.2, 1.5 Hz, 1H), 5.28 (dd, *J* = 10.4, 1.2 Hz, 1H), 4.94 (d, *J* = 3.8 Hz, 1H), 4.68 (s, 2H), 3.76 (s, 3H), 2.94 (dd, *J* = 14.2, 4.4 Hz, 1H), 2.74 (d, *J* = 19.7 Hz, 1H), 2.28 (dd, *J* = 14.2, 1.2 Hz, 1H), 1.54 (s, 4H), 1.26 (d, *J* = 7.0 Hz, 1H), -0.09 (s, 9H).

Furoindole Sulfamide NH₂ 128. ¹H NMR (400 MHz, CDCl₃) δ 7.73 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.53 (d, *J* = 8.2 Hz, 1H), 7.30 (ddd, *J* = 8.3, 7.5, 1.4 Hz, 1H), 7.12 (td, *J* = 7.5, 1.0 Hz, 1H), 6.75 – 6.69 (m, 1H), 5.93 (ddt, *J* = 16.4, 10.4, 5.8 Hz, 1H), 5.79 (s, 1H), 5.36 – 5.22 (m, 2H), 4.91 (d, *J* = 17.4 Hz, 2H), 4.60 (d, *J* = 6.2 Hz, 2H), 3.72 (s, 3H), 3.30 – 2.97 (m, 1H), 2.73 (d, *J* = 20.6 Hz, 1H), 2.63 (d, *J* = 12.2 Hz, 1H), 2.57 (dd, *J* = 12.2, 2.7 Hz, 1H).

Furoindole Sulfamide NMe₂. To a solution of sulfamide **X** (7.0 mgs, 0.0156 mmol, 1.0 eq) in MeCN (0.15 mL, 0.1 M) at 23 °C was added K₂CO₃ (11 mgs, 0.078 mmol, 5.0 eq), followed by iodomethane (8.9 mgs, 4μL, 0.063 mmol, 4.0 eq). The mixture was stirred at this temperature for 45 minutes, then was quenched with sat. aq. NaHCO₃ (3 mL), and diluted with EtOAc (3 mL). The reaction contents were poured into a separatory funnel, and the layers were extracted. The aqueous layer was extracted with EtOAc (3 x 3 mL). The combined organic layer was then washed with brine (1 x 5 mL), dried over Na₂SO₄, filtered, and evaporated *in vacuo* to provide sufficiently pure material as a clear oil. ¹H NMR (500 MHz, CDCl₃) δ 7.65 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.49 (d, *J* = 8.2 Hz, 1H), 7.22 (td, *J* = 7.9, 1.4 Hz, 1H), 7.03 (td, *J* = 7.6, 1.0 Hz, 1H), 6.68 (dd, *J* = 5.7, 2.3 Hz, 1H), 5.94 (ddt, *J* = 17.2, 10.4, 5.7 Hz, 1H), 5.78 (d, *J* = 33.3 Hz, 1H), 5.37 – 5.28 (m, 1H), 5.25 (d, *J* = 10.4 Hz, 1H), 4.78 (s, 1H), 4.61 (d, *J* = 6.1 Hz, 2H), 3.71 (s, 3H), 3.16 (s, 1H), 2.94 (s, 6H), 2.78 (dd, *J* = 19.6, 3.8 Hz, 1H), 2.67 – 2.53 (m, 2H).

oxa-quaternary dibenzylamine. To a solution of 1-Amino-2-methyl-2-propanol **131** (5.0 g, 56.1 mmol, 1.0 eq) in CH₂Cl₂ (250 mL, 0.225 M) was added Et₃N (32 mL, 23.2 g, 224 mmol, 4.0 eq) and the resultant solution was cooled to -78 °C. Then, TESOTf (29.65 g, 25.3 mL, 112.2 mmol, 2.0 eq) was added dropwise. The reaction mixture was then allowed to warm to 23 °C. Once warm, the reaction was quenched with sat. aq. NaHCO₃ (100 mL), and the mixture was poured into a separatory funnel. The phases were separated and the organic layer was washed with sat. aq. NH₄Cl (2 x 100 mL). The combined organic layer was then dried over Na₂SO₄, filtered, and evaporated *in vacuo*. This crude material was then dissolved in anhydrous MeCN (200 mL, 0.28 M) at 23 °C, and K₂CO₃ (31 g, 224 mmol, 4.0 eq) was added, followed by benzyl bromide (20.2 g, 14 mL, 118 mmol, 2.1 eq) and the resultant mixture was refluxed for 16 h. The

next day, the reaction mixture was concentrated to 1/4th volume, then diluted with Et₂O (200 mL) and deionized H₂O (200 mL). The phases were separated, the organic layer was then dried over Na₂SO₄, filtered, and evaporated *in vacuo*. The crude material was then purified by flash column chromatography (silica gel, Hex:Et₂O 2% → 5%) to give the protected dibenzylamine **X** (10.7 g, 50% yield) ¹H NMR (500 MHz, CDCl₃) δ 7.37 (d, *J* = 7.1 Hz, 4H), 7.29 (t, *J* = 7.5 Hz, 4H), 7.21 (t, *J* = 7.3 Hz, 2H), 3.67 (s, 4H), 2.40 (s, 2H), 1.13 (s, 6H), 0.90 (t, *J* = 7.9 Hz, 9H), 0.53 (q, *J* = 7.9 Hz, 6H).

Primary OTES dibenzylamine. prepared analogously to the one above, though TESCl and imidazole was used instead of TESOTf. ¹H NMR (400 MHz, CDCl₃) δ 7.38 (d, *J* = 6.9 Hz, 4H), 7.31 (t, *J* = 7.5 Hz, 4H), 7.25 – 7.19 (m, 2H), 3.69 (t, *J* = 6.7 Hz, 2H), 3.66 (s, 4H), 2.63 (t, *J* = 6.7 Hz, 2H), 0.92 (t, *J* = 7.9 Hz, 9H), 0.54 (q, *J* = 7.9 Hz, 6H).

Tertiary protected amine 132. To a solution of the dibenzylamine (3.0 g, 7.82 mmol, 1.0 eq) in anhydrous EtOAc (37.5 mL, 0.2M) under argon was added Pd/C (1.25 g, 1.17 mmol 15.0 mol%, 10 wt%). Then a hydrogen balloon was added and the reaction was stirred for up to 48 h. After which, the reaction was filtered through a pad of celite, and washed with EtOAc (25 mL), and concentrated *in vacuo* to give the desired amine **132** as a clear oil (1.25 g, 79% yield) ¹H NMR (500 MHz, CDCl₃) δ 2.52 (s, 2H), 1.49 (d, *J* = 4.7 Hz, 2H), 1.19 (d, *J* = 1.0 Hz, 6H), 0.95 (t, *J* = 7.9 Hz, 9H), 0.58 (q, *J* = 7.9 Hz, 6H).

Primary protected 131. (250mgs, 85% yield). ^1H NMR (500 MHz, CDCl_3) δ 3.62 (t, J = 5.3 Hz, 2H), 2.78 (t, J = 5.3 Hz, 2H), 1.46 (s, 2H), 0.96 (t, J = 8.0 Hz, 9H), 0.61 (q, J = 7.9 Hz, 6H).

General procedure for Sulfamoyl Chloride synthesis: To a flame dried flask was added high purity SO_2Cl_2 (74 mgs, 45 μL , 0.55 mmol, 1.1 eq) followed by anhydrous CH_2Cl_2 (1.25 mL, 0.4 M). This solution was then cooled to -78°C . Then, a solution of the desired amine (freshly azeotropically dried with anhydrous toluene, 100. mg, 0.5 mmol, 1.0 eq), Et_3N (75 mg, 111 μL , 0.075 mmol, 1.5 eq) and DMAP (6.0 mg, 0.05 mmol, 0.1 eq) in anhydrous CH_2Cl_2 (1.25 mL, 0.4 M) was added dropwise. Following the addition, the solution was warmed to 23°C and stirred at this temperature for 2 hours. During this time, the reaction mixture should stay clear, and ideally no precipitate should form. This crude solution can be used directly in the next step. Alternatively, after this time, the reaction was concentrated *in vacuo* on a rotary evaporator which had been previously placed under inert atmosphere. Upon concentration, the system was backfilled with argon, and the reaction flask immediately capped with a septum and argon balloon, affording the crude mixture as a white amorphous solid. Then, CH_2Cl_2 (0.5 mL, 1.0 M) was added, producing a light-yellow solution with white precipitate. The precipitate was taken up *via* needle & syringe, leaving behind the precipitate, and this solution was used in the next reaction.

NOTE: The SO_2Cl_2 must be crystal clear. This is preferably achieved via distillation, but sufficient degassing with argon can also yield sufficient results.

General procedure for furoindole sulfamoyl chloride protection: To a solution of furoindole **54** (30 mgs, 0.081 mmol, 1.0 eq) was in CH₂Cl₂ (0.81 mL, 0.1 M) at 0 °C was added Et₃N (205 mgs, 283 µL, 2.04 mmol, 25.0 eq) followed by the solution of sulfamoyl chloride (0.41 mL, 1.0M) dropwise. The solution was then allowed to warm to 23 °C and the reaction stirred for 2 hours. Upon completion, the reaction was quenched with sat. aq. NaHCO₃ (5 mL), and the mixture was poured into a separatory funnel. The phases were separated, and the aqueous layer was extracted with CH₂Cl₂ (3 x 5 mL). The combined organic layer was then washed with brine (1 x 5 mL), dried over Na₂SO₄, filtered, and evaporated *in vacuo*. The crude material was then purified by flash column chromatography (silica gel, Hex:Et₂O 35%) to give the desired sulfamide protected furoindole.

Oxa-quaternary sulfamide furoindole 134. (24 mgs, 0.038 mmol, 47%) ¹H NMR (400 MHz, CDCl₃) δ 7.66 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.43 (d, *J* = 8.1 Hz, 1H), 7.23 (ddd, *J* = 8.3, 7.4, 1.3 Hz, 1H), 7.05 (td, *J* = 7.6, 1.0 Hz, 1H), 6.69 (dd, *J* = 5.9, 2.3 Hz, 1H), 5.94 (ddt, *J* = 16.4, 11.0, 5.7 Hz, 1H), 5.77 (d, *J* = 40.8 Hz, 1H), 5.31 (d, *J* = 17.2 Hz, 1H), 5.25 (d, *J* = 10.4 Hz, 1H), 5.09 (d, *J* = 5.9 Hz, 1H), 4.87 (s, 1H), 4.71 – 4.54 (m, 2H), 3.71 (s, 3H), 3.04 (dd, *J* = 11.6, 6.1 Hz, 1H), 2.97 – 2.89 (m, 1H), 2.80 – 2.68 (m, 1H), 2.62 (d, *J* = 12.1 Hz, 1H), 2.56 (dd, *J* = 12.2, 2.7 Hz, 1H), 1.19 (s, 3H), 1.17 (s, 3H), 0.87 (t, *J* = 7.9 Hz, 6H), 0.51 (q, *J* = 7.9 Hz, 4H).

Primary sulfamide furoindole 133. (9.0 mgs, 55%) ¹H NMR (500 MHz, CDCl₃) δ 7.66 (d, *J* = 7.7 Hz, 1H), 7.43 (d, *J* = 8.2 Hz, 1H), 7.23 (t, *J* = 7.9 Hz, 1H), 7.05 (t, *J* = 7.6 Hz, 1H), 6.71 – 6.66 (m, 1H), 5.93 (ddt, *J* = 16.5, 11.0, 5.7 Hz, 1H), 5.77 (d, *J* = 50.9 Hz, 1H), 5.31 (d, *J* = 17.1

Hz, 1H), 5.25 (d, $J = 10.4$ Hz, 1H), 5.19 (s, 1H), 4.88 (s, 1H), 4.70 – 4.55 (m, 3H), 3.77 – 3.72 (m, 2H), 3.71 (d, $J = 1.3$ Hz, 3H), 3.60 (t, $J = 5.1$ Hz, 1H), 3.29 – 3.18 (m, 2H), 3.15 (q, $J = 5.7$ Hz, 2H), 2.74 (d, $J = 20.6$ Hz, 1H), 2.64 – 2.54 (m, 2H), 0.90 – 0.84 (m, 6H), 0.52 (q, $J = 7.9$ Hz, 4H).

Oxa-quaternary sulfamide furoindole free amine. Synthesized according to the general alloc deprotection procedure above (impure). ^1H NMR (500 MHz, CDCl_3) δ 7.64 (d, $J = 1.5$ Hz, 1H), 7.30 (d, $J = 8.3$ Hz, 1H), 7.22 (t, $J = 7.8$ Hz, 1H), 7.04 (t, $J = 7.3$ Hz, 1H), 6.82 – 6.76 (m, 1H), 5.01 – 4.93 (m, 2H), 3.73 (ddd, $J = 14.8, 12.0, 7.1$ Hz, 3H), 3.57 (d, $J = 6.2$ Hz, 3H), 3.54 – 3.44 (m, 2H), 3.27 (dd, $J = 55.8, 20.8$ Hz, 2H), 3.11 (dd, $J = 11.7, 5.3$ Hz, 1H), 3.02 – 2.93 (m, 2H), 1.25 (s, 6H), 1.21 (d, $J = 2.4$ Hz, 6H), 0.88 (t, $J = 7.9$ Hz, 10H), 0.52 (q, $J = 7.9$ Hz, 8H).

Oxa-quaternary sulfamide protected furoindole propargylamine 135. Synthesized according to the general furoindole propargylation procedure. (4.0 mgs, 43% over 2 steps). ^1H NMR (500 MHz, CDCl_3) δ 7.64 (d, $J = 7.8$ Hz, 1H), 7.44 (d, $J = 8.2$ Hz, 1H), 7.21 – 7.16 (m, 1H), 7.02 (q, $J = 7.4$ Hz, 1H), 6.76 – 6.67 (m, 1H), 4.89 (d, $J = 3.6$ Hz, 1H), 3.77 – 3.70 (m, 2H), 3.69 (d, $J = 1.3$ Hz, 3H), 3.50 (d, $J = 2.5$ Hz, 2H), 3.09 (dd, $J = 11.7, 6.6$ Hz, 1H), 2.94 (dd, $J = 11.7, 5.4$ Hz, 1H), 2.69 (q, $J = 3.4$ Hz, 2H), 2.53 (dd, $J = 11.9, 3.3$ Hz, 1H), 2.46 (dd, $J = 11.8, 3.3$ Hz, 1H), 2.17 (d, $J = 1.1$ Hz, 3H), 1.20 (s, 3H), 1.18 (s, 3H), 0.88 (t, $J = 7.9$ Hz, 9H), 0.52 (q, $J = 7.9$ Hz, 6H).

Primary sulfamide protected furoindole propargylamine 136. (13 mgs, 37% over 2 steps). ^1H NMR (500 MHz, CDCl_3) δ 7.65 (dd, $J = 7.7, 1.4$ Hz, 1H), 7.44 (d, $J = 8.2$ Hz, 1H), 7.21 (td, $J = 7.8, 1.5$ Hz, 1H), 7.06 – 7.00 (m, 1H), 6.73 (dd, $J = 4.7, 3.1$ Hz, 1H), 4.03 (t, $J = 3.2$ Hz, 1H), 3.69 (d, $J = 2.3$ Hz, 3H), 3.62 (dd, $J = 5.9, 4.4$ Hz, 2H), 3.51 (d, $J = 2.5$ Hz, 2H), 3.30 (ddt, $J = 9.7, 6.6, 4.8$ Hz, 1H), 3.21 (dq, $J = 12.7, 5.4$ Hz, 1H), 2.70 (q, $J = 3.4$ Hz, 2H), 2.53 (dd, $J = 11.9, 4.4$ Hz, 1H), 2.49 – 2.43 (m, 1H), 2.27 – 2.21 (m, 1H), 0.89 (t, $J = 7.9$ Hz, 9H), 0.55 – 0.49 (m, 6H).

2.14.3 Syntheses of Select Methoxy-substituted intermediates

6-OMe gramine 146. To a round bottom flask was added formalin (890 mgs, 0.82 mL, 11.0 mmol, 37 wt%, 1.1 eq), then it was diluted with glacial acetic acid (33 mL, 0.3 M). Aqueous dimethylamine (4.5 g, 5 mL, 40%, 40 mmol, 4.0 eq) was added, followed by 6-OMe-indole (1.47g, 10.0 mmol, 1.0 eq). The mixture turned a dark red. The reaction was then stirred until the indole was consumed on TLC (2-12 h) at which point it was diluted with 2M NaOH until the pH >10, then extracted with Et_2O (3 x 50 mL). The combined organic layer was then dried over Na_2SO_4 , filtered, and evaporated *in vacuo*, to give the desired gramine as a red oil in sufficient purity to be used in the next step. (1.66 g, 81% yield). ^1H NMR (500 MHz, CDCl_3) δ 7.96 (s, 1H), 7.57 (d, $J = 8.7$ Hz, 1H), 7.01 (d, $J = 2.1$ Hz, 1H), 6.85 (t, $J = 1.7$ Hz, 1H), 6.80 (dt, $J = 8.7, 1.8$ Hz, 1H), 3.84 (d, $J = 1.2$ Hz, 3H), 3.59 (s, 2H), 2.27 (d, $J = 1.1$ Hz, 6H).

Iminoester 148. Glycine methyl ester HCl salt (377 mgs, 3.00 mmol, 1.0 eq) was added to a round bottom flask, followed by benzophenone imine (0.5 mL, 3.00 mmol, 1.0 eq), CH_2Cl_2

(6.0 mL, 0.5 M), then Et₃N (0.42 mL, 3.00 mmol, 1.0 eq) dropwise. This mixture was stirred at 23 °C for 2 hours, then diluted with Et₂O (10 mL), filtered through celite, washed with Et₂O, poured into a separatory funnel. The organic layer was washed with H₂O (3 x 10 mL), then brine (3 x 10 mL), dried over MgSO₄, and evaporated to dryness to afford the desired imine as a light yellow oil, in sufficient purity to be used in the next step. (640 mgs, 84% yield). ¹H NMR (500 MHz, CDCl₃) δ 7.67 – 7.63 (m, 2H), 7.46 (d, *J* = 7.7 Hz, 2H), 7.43 – 7.37 (m, 2H), 7.34 (td, *J* = 7.5, 1.4 Hz, 2H), 7.20 – 7.14 (m, 2H), 4.22 (d, *J* = 1.3 Hz, 2H), 3.75 (d, *J* = 1.3 Hz, 3H).

(±)-6OMe-Trp-OMe 143. To a mixture of imine **148** (320. mgs, 1.26 mmol, 1.0 eq) and gramine **146** (258 mgs, 1.26 mmol, 1.0 eq) was added MeCN (12.6 mL, 0.1 M) then *n*-Bu₃P (63.7 mgs, 78 μL, 0.315 mmol, 25.0 mol%), and the mixture was refluxed for 24 hours. After this time, the mixture was evaporated *in vacuo* to concentration, dissolved in THF (7.6 mL, 0.165 M), and 1 M HCl (3.8 mL, 3.0 eq) was added. The resulting mixture was stirred for 30 minutes, then the volatile organics were evaporated *in vacuo*. The resulting residue was basified with sat. aq. NaHCO₃ to pH >8, and extracted with CH₂Cl₂ (3 x 10 mL). The combined organic layer was then washed with brine (2 x 5 mL), dried over Na₂SO₄, filtered, and evaporated *in vacuo*. The crude material was then purified by flash column chromatography (silica gel, CH₂Cl₂:MeOH = 2.5% → 5%) to afford the 6-OMe-Trp-OMe as a clear oil. ¹H NMR (500 MHz, CDCl₃) δ 8.07 (br, 1H), 7.46 (d, *J* = 8.6 Hz, 1H), 6.94 (d, *J* = 2.3 Hz, 1H), 6.84 (d, *J* = 2.2 Hz, 1H), 6.79 (dd, *J* = 8.7, 2.3 Hz, 1H), 3.83 (s, 3H), 3.71 (s, 3H), 3.24 (dd, *J* = 14.4, 4.7 Hz, 1H), 3.02 (dd, *J* = 14.4, 7.5 Hz, 1H), 2.04 (br, 2H).

(±)-Formylated-6OMe-Trp-OMe 147. To amine **147** (240.0 mgs, 0.97mmol, 1.0 eq) was added ethyl formate (10 mL, 0.1 M) and the solution refluxed for 16 h. Upon completion, the reaction mixture was concentrated *in vacuo* and the crude material was then purified by flash column chromatography (silica gel, Hex:EtOAc = 1:1) as a yellow oil (200 mgs, 73% yield). ¹H NMR (500 MHz, CDCl₃) δ 8.18 (d, *J* = 1.6 Hz, 1H), 7.98 (s, 1H), 7.39 (d, *J* = 8.7 Hz, 1H), 6.88 (d, *J* = 2.1 Hz, 1H), 6.84 (d, *J* = 2.2 Hz, 1H), 6.79 (dd, *J* = 8.7, 2.2 Hz, 1H), 6.12 (s, 1H), 5.01 (dt, *J* = 7.7, 5.2 Hz, 1H), 3.84 (s, 3H), 3.71 (s, 3H), 3.31 (d, *J* = 5.4 Hz, 2H).

6-OMe-tetrahydro-β-carboline. To a solution of *N*-formyl **147** (100.0 mgs, 0.362 mmol, 1.0 eq) was added anhydrous CH₂Cl₂ (2.5 mL, 0.15 M), followed by POCl₃ (61 mgs, 37 μL, 0.398 mmol, 1.1 eq). The resulting greenish mixture was refluxed for 2.5 hours, then concentrated *in vacuo*. The crude iminium salt was then redissolved in CH₂Cl₂ (2.5 mL, 0.15 M) and cooled to 0 °C in an ice bath. Then, silyl enol ether **76** (139 mgs, 0.543 mmol, 1.5 eq) was added, and the solution was allowed to warm to rt overnight (12 h). Upon completion, the reaction was quenched with sat. aq. NaHCO₃ (5 mL), and the reaction was poured into a separatory funnel. The phases were separated, and the combined organic layer was then dried over Na₂SO₄, filtered, and evaporated *in vacuo*. The crude material was then purified by flash column chromatography (silica gel, Hex:Acetone = 3:1 → 1:1) to give the desired product as a yellow amorphous solid (90.0 mgs, 62% yield). ¹H NMR (500 MHz, CDCl₃) δ 8.13 (s, 1H), 7.34 (d, *J* = 8.5 Hz, 1H), 6.81 (d, *J* = 2.3 Hz, 1H), 6.77 (dd, *J* = 8.6, 2.2 Hz, 1H), 5.35 (d, *J* = 144.4 Hz, 2H), 4.64 – 4.43 (m, 1H), 3.82 (s, 3H), 3.65 (s, 3H), 3.25 (dd, *J* = 15.8, 5.5 Hz, 1H), 3.02 (dd, *J* = 15.7, 5.2 Hz, 1H), 1.44 (s, 9H).

6-OMe-N-Boc-tetrahydro- β -carboline 149. To a round bottom flask containing β -carboline (30.0 mg, 0.075 mmol, 1.0 eq), and K_2CO_3 (41.5 mgs, 0.3 mmol, 4.0 eq). The solids were then dissolved in THF:H₂O (1:1, 0.75 mL, 0.1 M), and stirred at 23 °C. Then Boc_2O (49 mgs, 0.225 mmol, 3.0 eq) was added, and the mixture stirred for 24 h. Upon completion, the reaction was quenched with sat. aq. $NaHCO_3$ (5 mL), and poured into a separatory funnel. The phases were separated, and the combined organic layer was then dried over Na_2SO_4 , filtered, and evaporated *in vacuo*. The crude material was then purified by flash column chromatography (silica gel, Hex:Acetone = 3:1) to give the desired product as a yellow amorphous solid. ¹H NMR (500 MHz, $CDCl_3$) δ 8.13 (s, 1H), 7.34 (d, J = 8.5 Hz, 1H), 6.81 (d, J = 2.3 Hz, 1H), 6.77 (dd, J = 8.6, 2.2 Hz, 1H), 5.35 (d, J = 144.4 Hz, 2H), 4.64 – 4.43 (m, 1H), 3.82 (s, 3H), 3.65 (s, 3H), 3.25 (dd, J = 15.8, 5.5 Hz, 1H), 3.02 (dd, J = 15.7, 5.2 Hz, 1H), 1.44 (s, 9H).

3-Iodo-N-Boc-6-OMe indole 150. 6-Methoxyindole (1.47 g, 10.0 mmol, 1.0 eq), KOH (1.6 g, 25.0 mmol, 2.5 eq), and I_2 (2.54 g, 10.0 mmol, 1.0 eq) combined in a flask with DMF (25 mL, 0.4 M) and stirred for 2 hours. After this time, the reaction was quenched with sat. aq. $Na_2S_2O_4$ (25 mL), and diluted with EtOAc (10 mL). The reaction was then poured into a separatory funnel, and the layers separated. The aqueous phase was extracted with EtOAc (2 x 10 mL). The combined organic layer was then washed with brine (2 x 10 mL), dried over Na_2SO_4 , filtered, and evaporated *in vacuo*. This material was then used directly in the next step. To the crude residue was added CH_2Cl_2 (40 mL), followed by DMAP (112 mg, 10 mol%), Boc_2O (2.4 g), and Et_3N (2.5 mL). The reaction mixture was then allowed to stir for 12 h at 23 °C. Upon completion, the reaction was concentrated *in vacuo* and the crude residue was then purified by flash column chromatography (silica gel, Hex:Et₂O = 10%), to afford the desired indole as a

white solid (2.0 g, 54% yield). ^1H NMR (400 MHz, CDCl_3) δ 7.73 (s, 1H), 7.59 (s, 1H), 7.28 – 7.24 (m, 1H), 6.94 (dd, J = 8.7, 2.3 Hz, 1H), 3.88 (s, 3H), 1.66 (s, 9H).

3-Bromo-N-TBS-6-OMe indole 156. 6-Methoxyindole (515 mgs, 3.50 mmol, 1.0 eq) was dissolved in THF (10 mL, 0.34 M) and cooled to $-78\text{ }^\circ\text{C}$. Then $n\text{BuLi}$ (2.41 mL, 1.6 M in hexanes, 3.85 mmol, 2.1 eq) was added dropwise, then the reaction mixture was warmed to $-10\text{ }^\circ\text{C}$, and stirred for 15 minutes. After, the reaction mixture was cooled back down to $-50\text{ }^\circ\text{C}$, and a solution of TBSCl (606 mgs, 1.25 M, 4.03 mmol, 1.15 eq) was added slowly. Once the addition was complete, the reaction was stirred at $0\text{ }^\circ\text{C}$ for 3 hours. Then, the reaction was again cooled to $-78\text{ }^\circ\text{C}$ and NBS (627 mgs, 3.5 mmol) was added, and the mixture stirred in the dark for $-78\text{ }^\circ\text{C}$ for 2 hours, then allowed to warm to $23\text{ }^\circ\text{C}$. After warming, hexanes was added, and the reaction was filtered through a pad of celite. The filtrate was concentrated *in vacuo* then the crude material was purified by flash column chromatography (silica gel, hexanes). ^1H NMR (400 MHz, CDCl_3) δ 7.43 (d, J = 8.7 Hz, 1H), 7.05 (s, 1H), 6.98 (d, J = 2.1 Hz, 1H), 6.87 (dd, J = 8.7, 2.1 Hz, 1H), 3.85 (s, 3H), 0.95 (s, 9H), 0.59 (s, 6H). **Note:** similar compounds are noted to decompose rapidly above $0\text{ }^\circ\text{C}$ in the presence of any unprotected bromo-indole impurities, so high purity and sub-zero storage is essential.

2.14.4 Syntheses of Select Sidechains & Reagents

((4-bromobut-2-yn-1-yl)oxy)(tert-butyl)dimethylsilane. Procedure from Reisman *et. al. Org. Lett.* **2010**, 12, 780–783. (77% yield). ^1H NMR (400 MHz, CDCl_3) δ 4.37 (s, 2H), 3.94 (s, 2H), 0.91 (s, 9H), 0.12 (s, 6H)

Homopropargyl acetal 67. Synthesized via a modified literature procedure: *Org. Lett* **2007**,9, 1895-1898. To an oven dried 3-neck flask was added elemental aluminum (2.1g, 77.3 mmol, 2.3 eq), and HgCl₂ (115 mgs, 0.437 mmol, 0.013 eq). The flask was then fitted with a reflux condenser, and the remaining necks capped with septa. The whole system was evacuated and backfilled with argon thrice, and an argon balloon was attached. Then, Et₂O (25 mL) was added, followed by propargyl bromide (6.0 g, 80% in toluene, 5.4 mL, 50.4 mmol, 1.5 eq). The resulting solution was then refluxed for 1 hour. After this time, the reaction was cooled to -78 °C, and trimethyl orthoformate (3.65 mL, 33.6 mmol, 1.0 eq) in Et₂O (25 mL) was added dropwise, and the reaction allowed to stir at -78 °C. After 4 hours, H₂O (20 mL) and 3M NaOH (7 mL) were added slowly, then the reaction was allowed to slowly warm to 23 °C. The mixture was then poured directly into a separatory funnel, and the layers were separated. The organic layer was washed with brine (50 mL), then dried over MgSO₄, filtered, and evaporated *in vacuo* at less than 30 °C due to the volatility of the product. This directly afforded the desired homopropargyl acetal (4.3 g, 75%) as a 66 wt% solution in Et₂O/Toluene. ¹H NMR (400 MHz, CDCl₃) δ 4.54 (t, *J* = 5.6 Hz, 1H), 3.37 (s, 6H), 2.52 (dd, *J* = 5.6, 2.7 Hz, 2H), 2.02 (t, *J* = 2.7 Hz, 1H).

TMS-Homopropargyl acetal. To the homopropargyl acetal **67** (0.27 g, 2.37 mmol) in Et₂O (0.5 M) at -78 °C was added *n*BuLi (1.63 mL, 1.6 M in hexanes, 2.6 mmol, 1.1 eq). The mixture was stirred at -78 °C for 30 minutes, then, TMSCl (0.28 g, 2.6 mmol, 1.1 eq) was added, and allowed to stir for another 2 hours at -78 °C. Upon completion, the reaction was quenched with sat. aq. NH₄Cl (5 mL), and warmed to 23 °C, and poured into a separatory funnel. The phases were separated and the aqueous layer was extracted with Et₂O (2 x 5 mL). The combined organic layer was then dried over Na₂SO₄, filtered, and evaporated *in vacuo*. The crude material was then

purified by flash column chromatography (silica gel, Hex:Et₂O 10:1) to afford the desired alkyne as a clear oil. ¹H NMR (400 MHz, CDCl₃) δ 4.53 (t, *J* = 5.7 Hz, 1H), 3.38 (d, *J* = 2.3 Hz, 5H), 2.56 (d, *J* = 5.7 Hz, 2H), 0.15 (s, 7H).

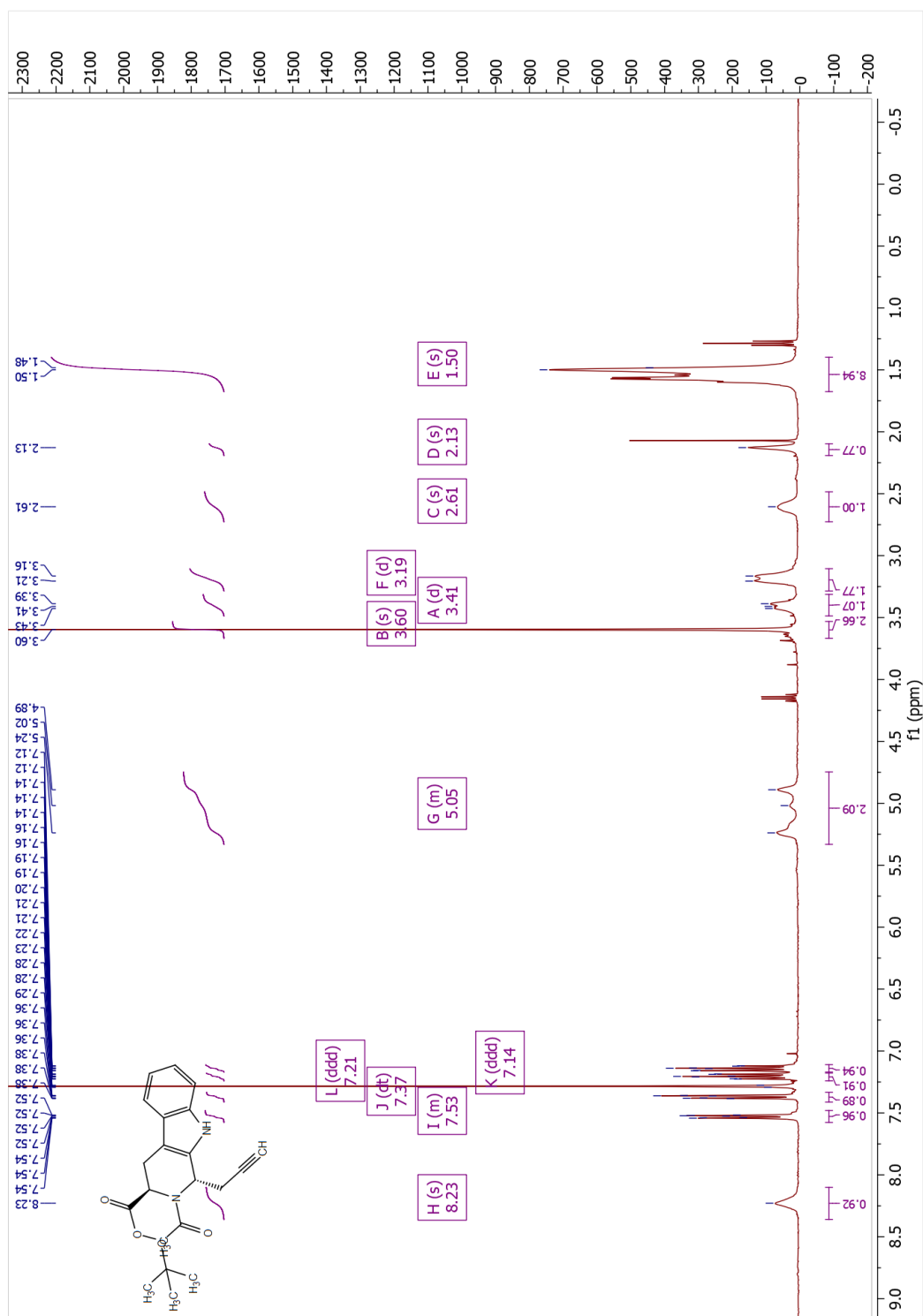
Homopropargyl ynoate ester 68. Synthesized using the same procedure as the TMS-homopropargyl acetal.

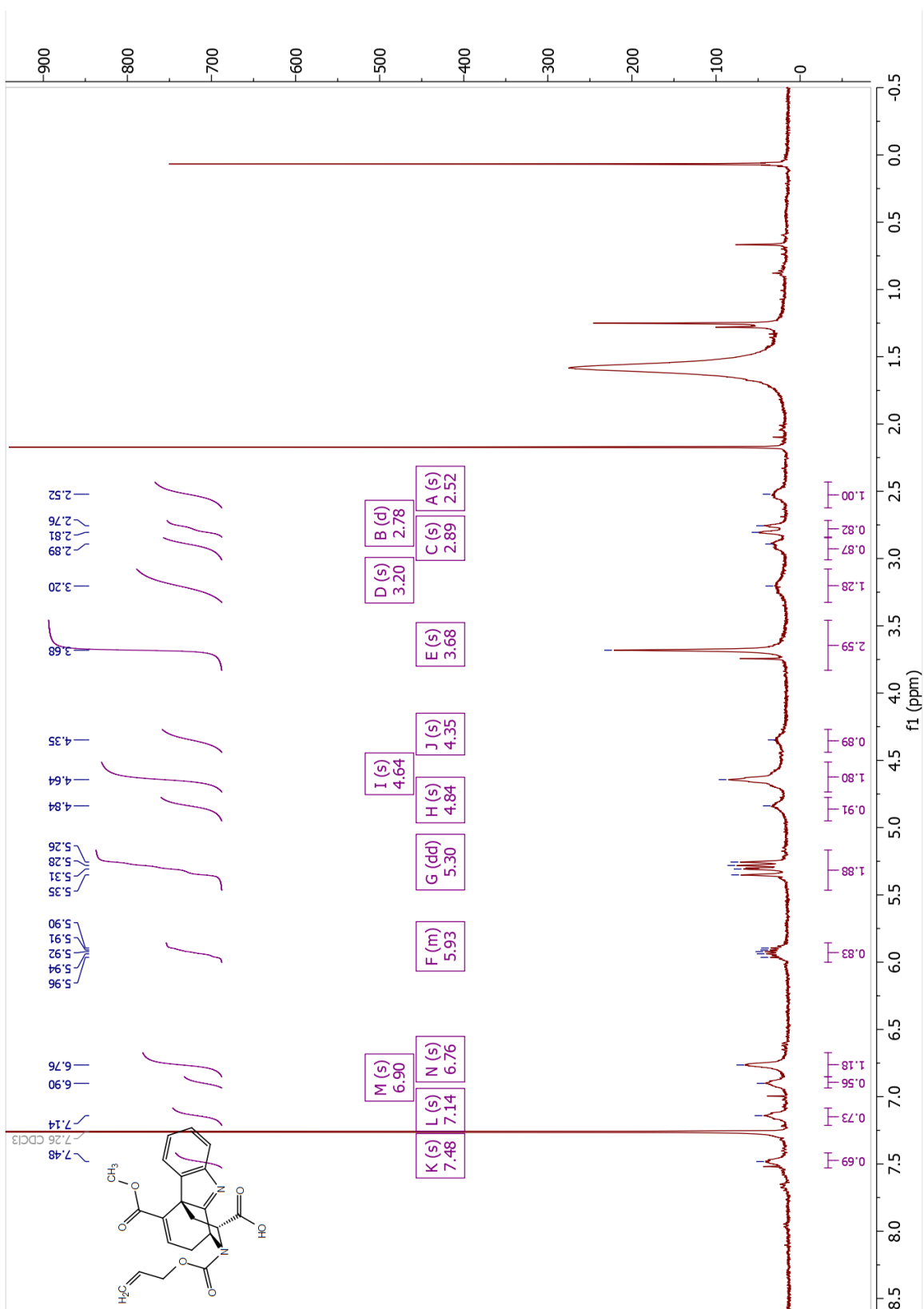
Bromo-oxazolidinone 85. To a solution of oxazolidinone (870.0 mgs, 10.0 mmol, 1.0 eq) in THF (15 mL, 0.67 M) was added NaH (60 wt% dispersion in mineral oil, 460.0 mg, 11.5 mmol, 1.15 eq) and the mixture was refluxed for 1 hour. Then, the mixture was cooled to 0 °C, and bromoacetyl bromide (2.02 g, 0.87 mL, 10.0 mmol, 1.0 eq) was added dropwise, and the mixture stirred for 4 hours at 0 °C. Upon completion, the reaction was quenched with sat. aq. NH₄Cl (10 mL), and warmed to 23 °C, and poured into a separatory funnel. The phases were separated and the aqueous layer was extracted with Et₂O (2 x 15 mL). The combined organic layer was then dried over Na₂SO₄, filtered, and evaporated *in vacuo*. The crude material was then purified by flash column chromatography (silica gel, Hex:Et₂O 5:1) to afford the desired oxazolidinone **86**. ¹H NMR (400 MHz, CDCl₃) δ 4.51 (s, 2H), 4.48 (dd, *J* = 8.6, 7.5 Hz, 2H), 4.08 (dd, *J* = 8.6, 7.5 Hz, 2H).

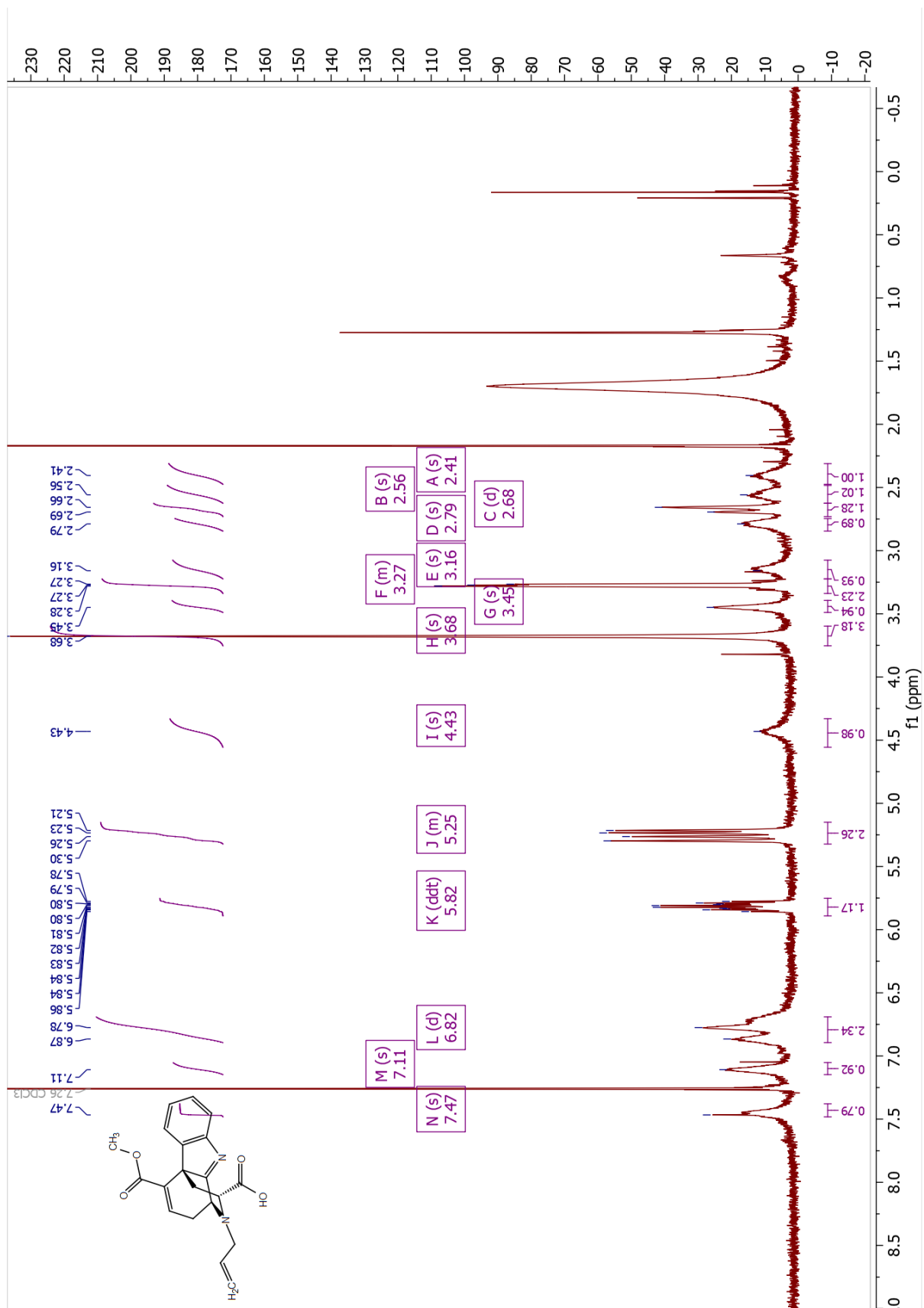
Silyl enol ether 76. To a solution of freshly made LDA (1.0 M, 12.5 mmol, 1.25 eq) in THF (12.5 mL) was added DMPU (1.92 g, 1.81 mL, 15 mmol, 1.5 eq), and stirred for 15 minutes at -78 °C. Then, dimethyl ketene acetone adduct (1.42 g, 10.0 mmol, 1.0 eq) in THF (10 mL) was

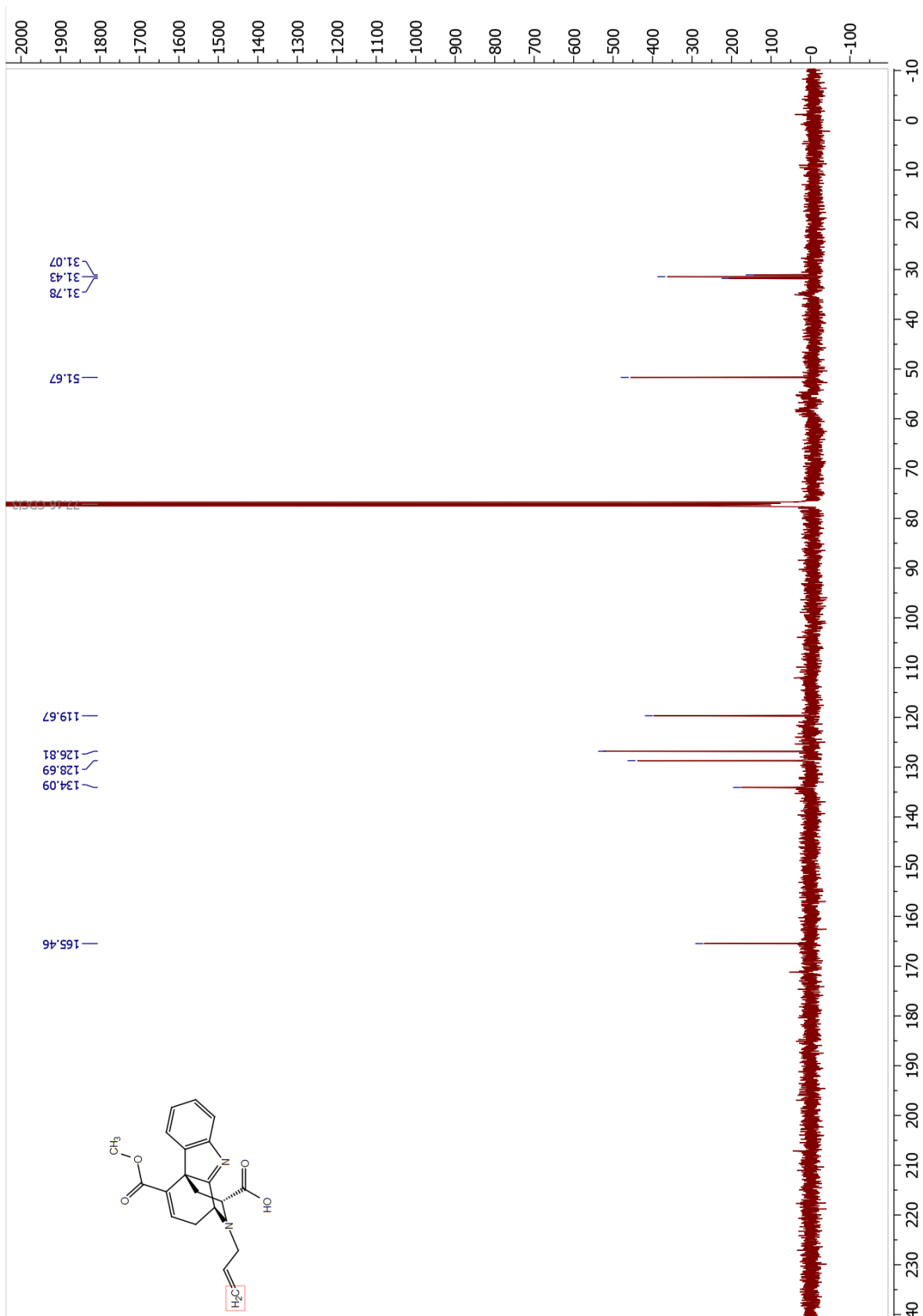
added dropwise, and the reaction stirred at -78 °C for 45 minutes, then for an additional 2 hours at 23 °C. Quenched with sat. aq. NaHCO₃ (10 mL), and the phases separated. The aqueous layer was extracted with hexanes (3 x 10 mL) and The combined organic layer was then washed with sat. aq. NaHCO₃ (2 x 10 mL), then brine (2 x 10 mL), dried over MgSO₄, filtered, and evaporated *in vacuo*. This crude mixture was then taken up in pentanes (20 mL), washed with sat. aq. NaHCO₃ (10 mL), dried over Na₂SO₄, filtered over celite, and evaporated *in vacuo* to give the silyl enol ether. ¹H NMR (500 MHz, CDCl₃) δ 4.66 (s, 1H), 4.06 (d, *J* = 0.8 Hz, 1H), 3.87 (d, *J* = 0.8 Hz, 1H), 1.54 (s, 6H), 0.94 (s, 9H), 0.21 (s, 6H).

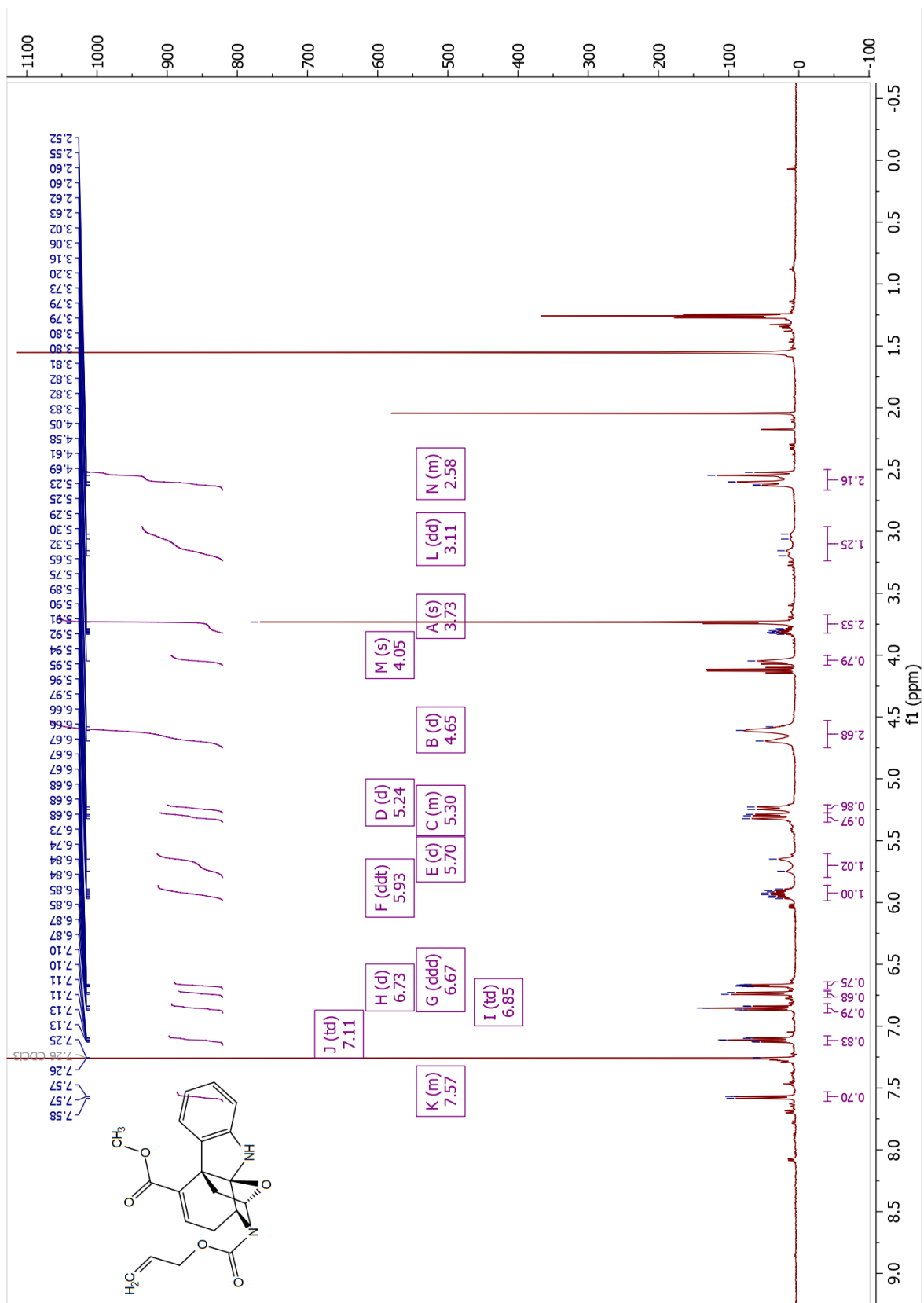
2.15 NMR Spectra of Selected Intermediates



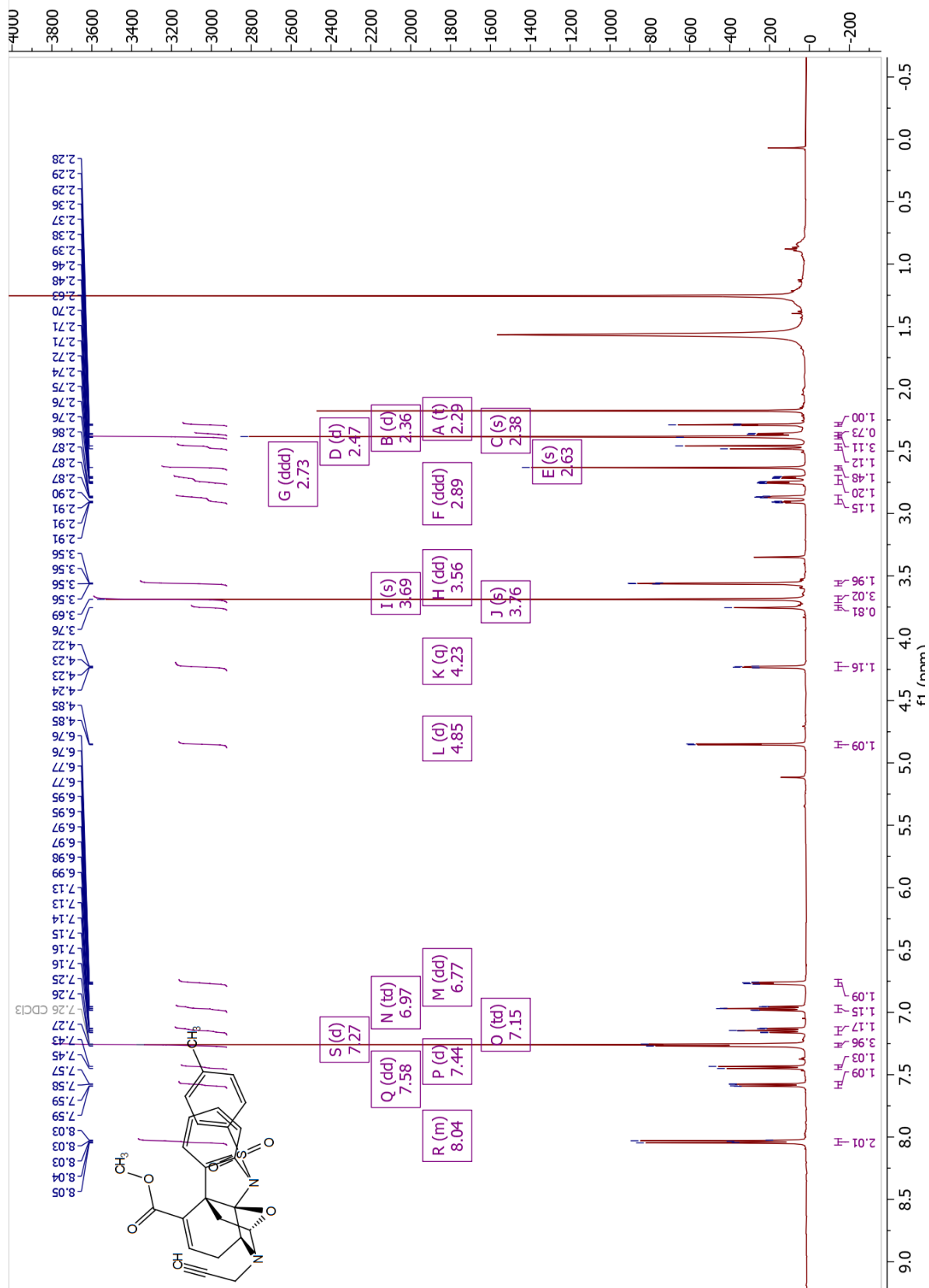


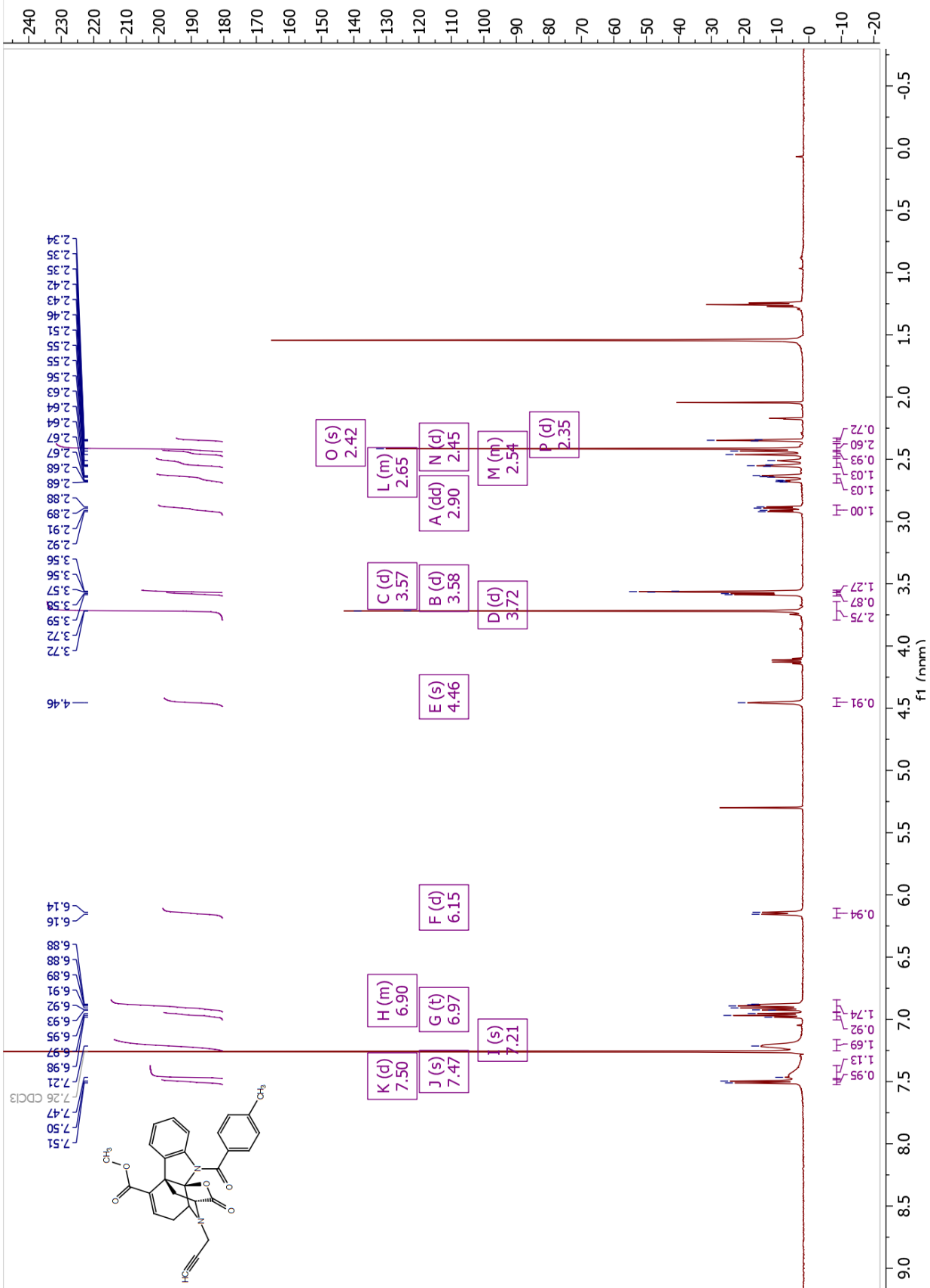


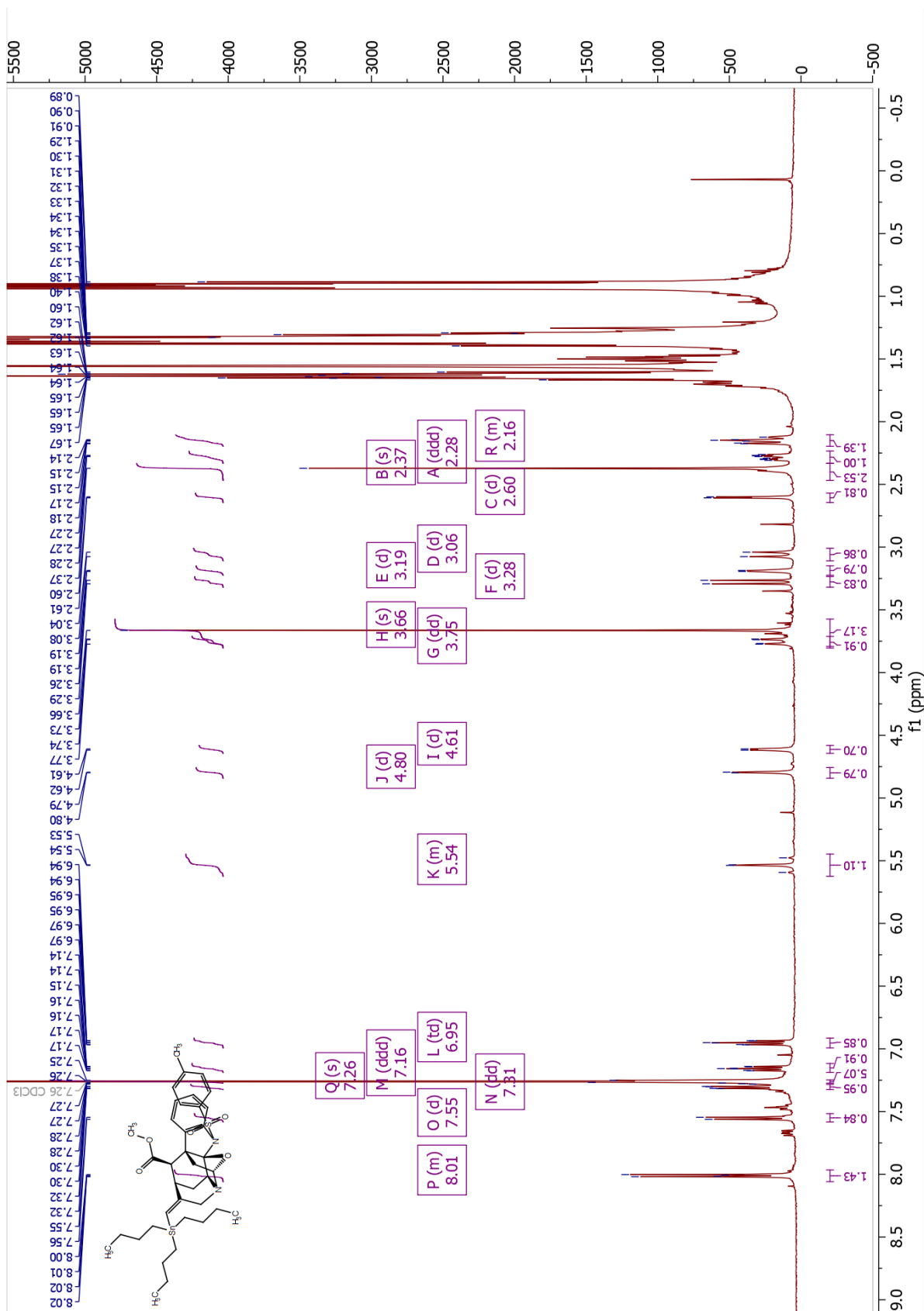


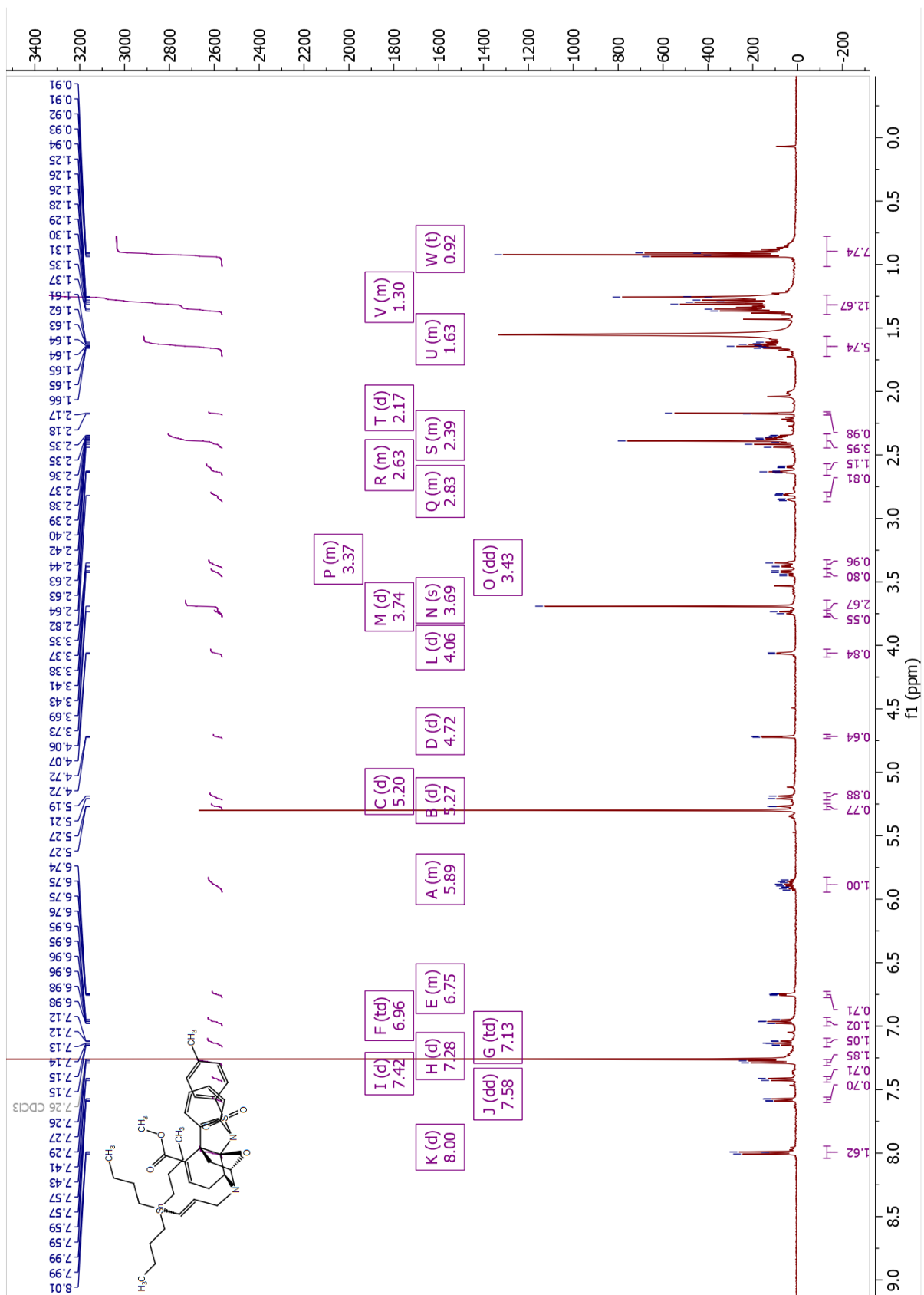


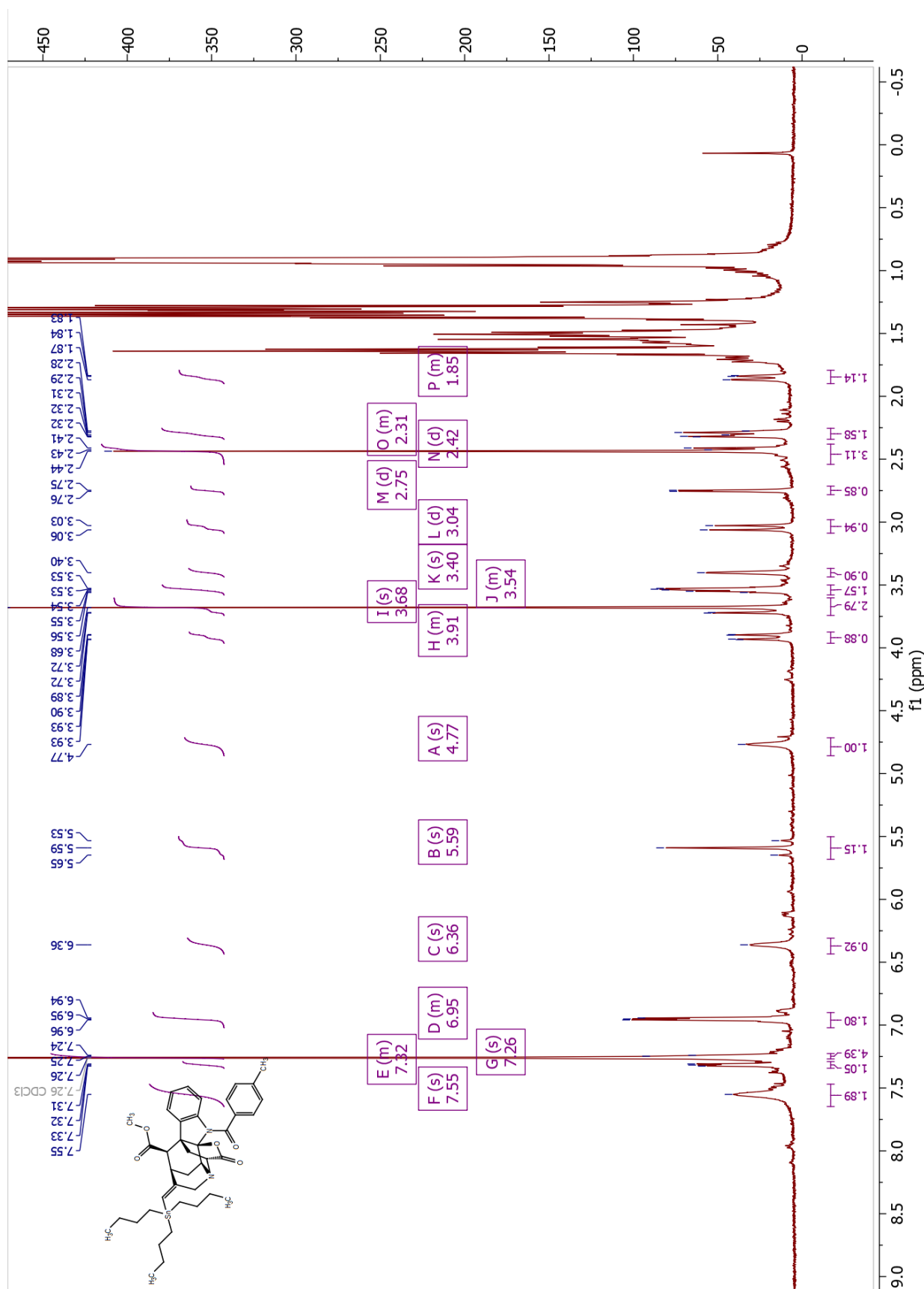


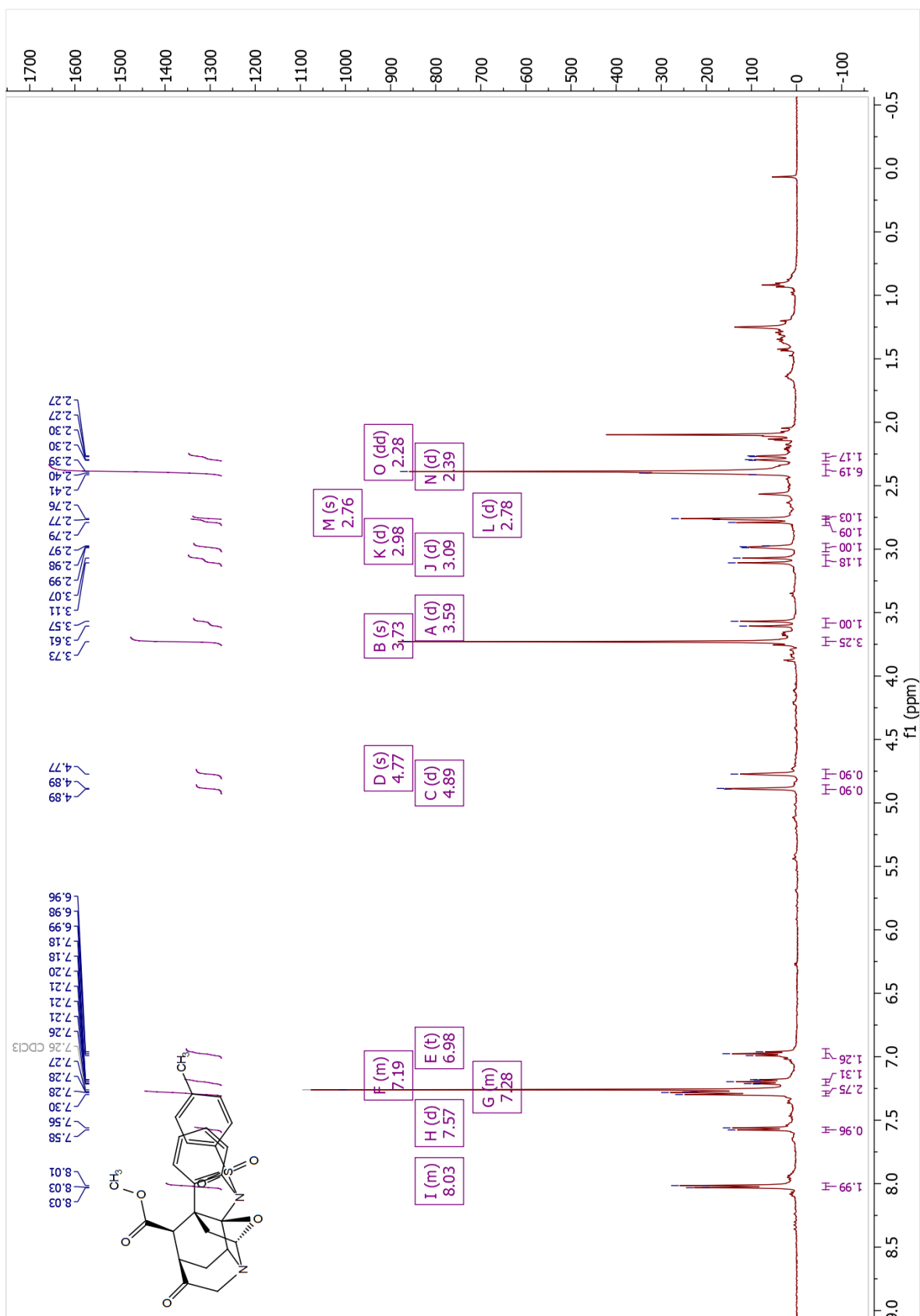


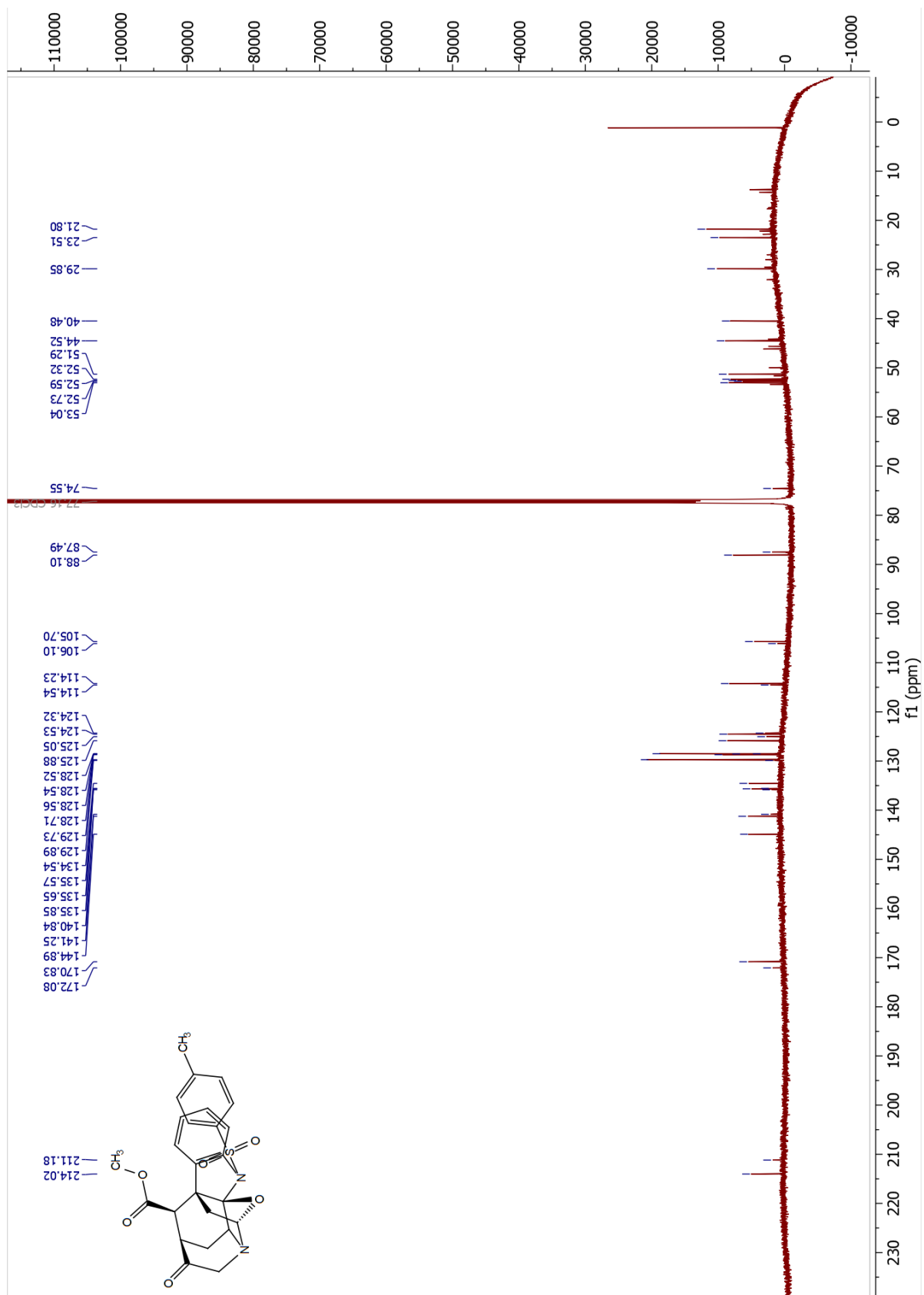




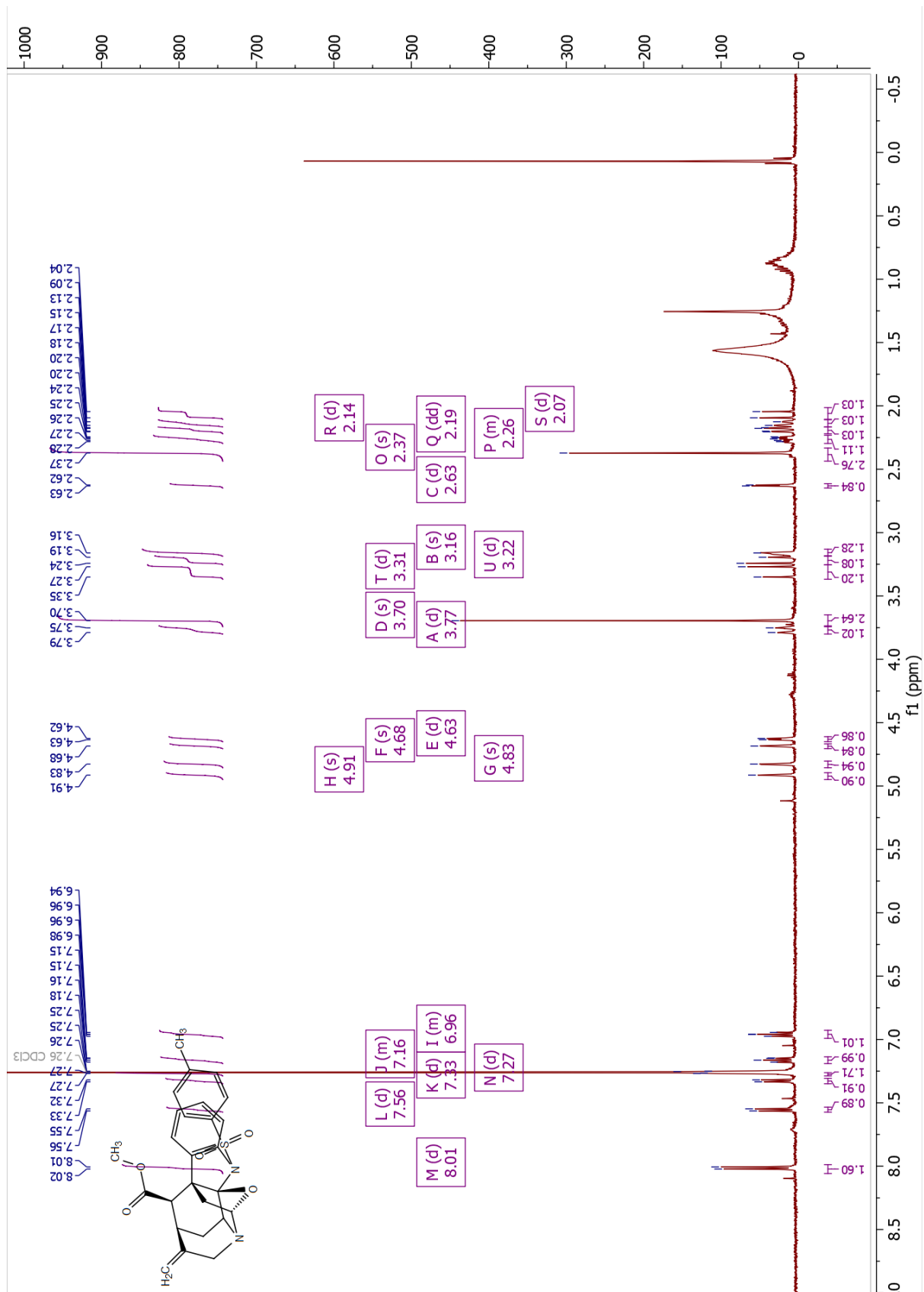


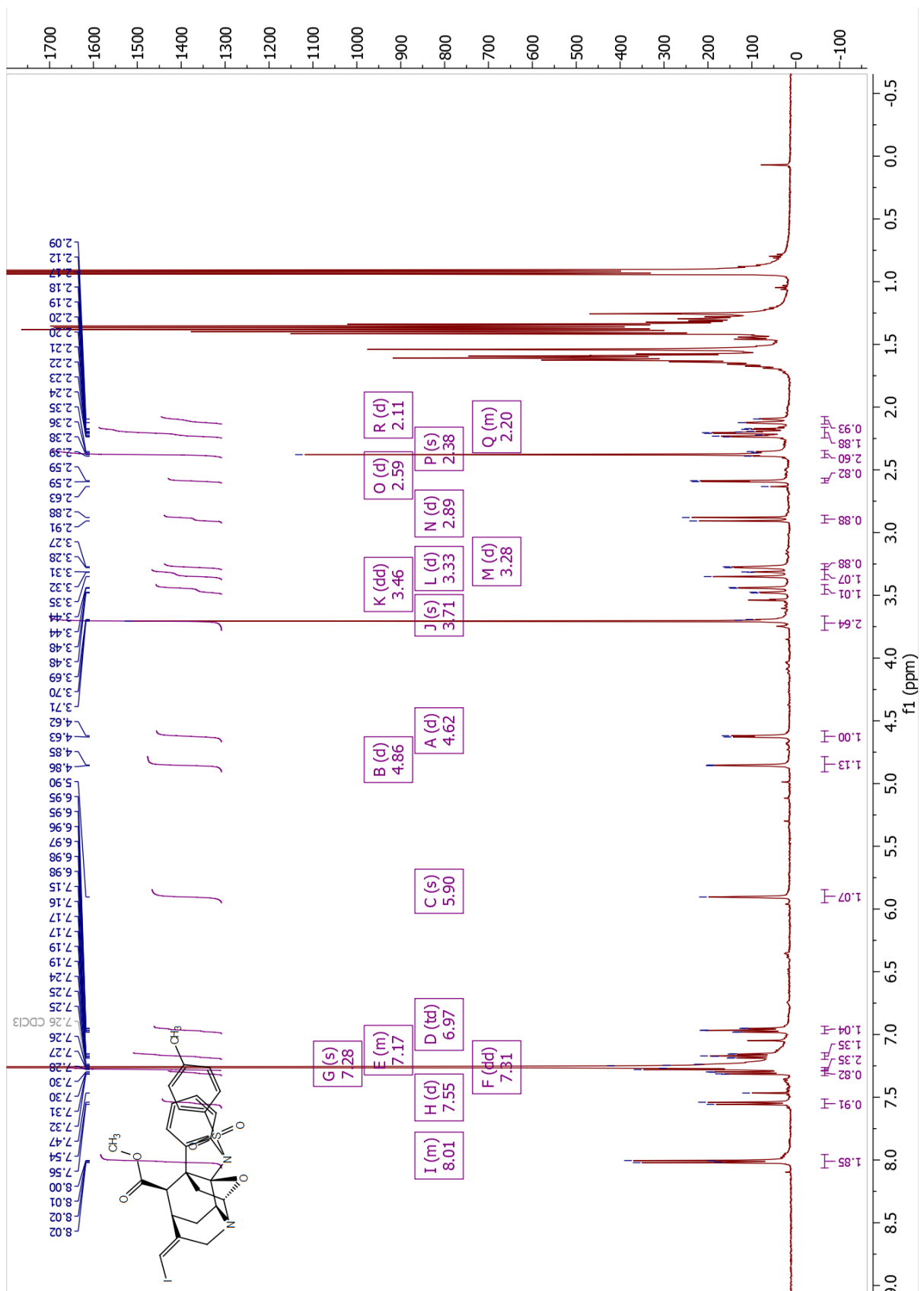


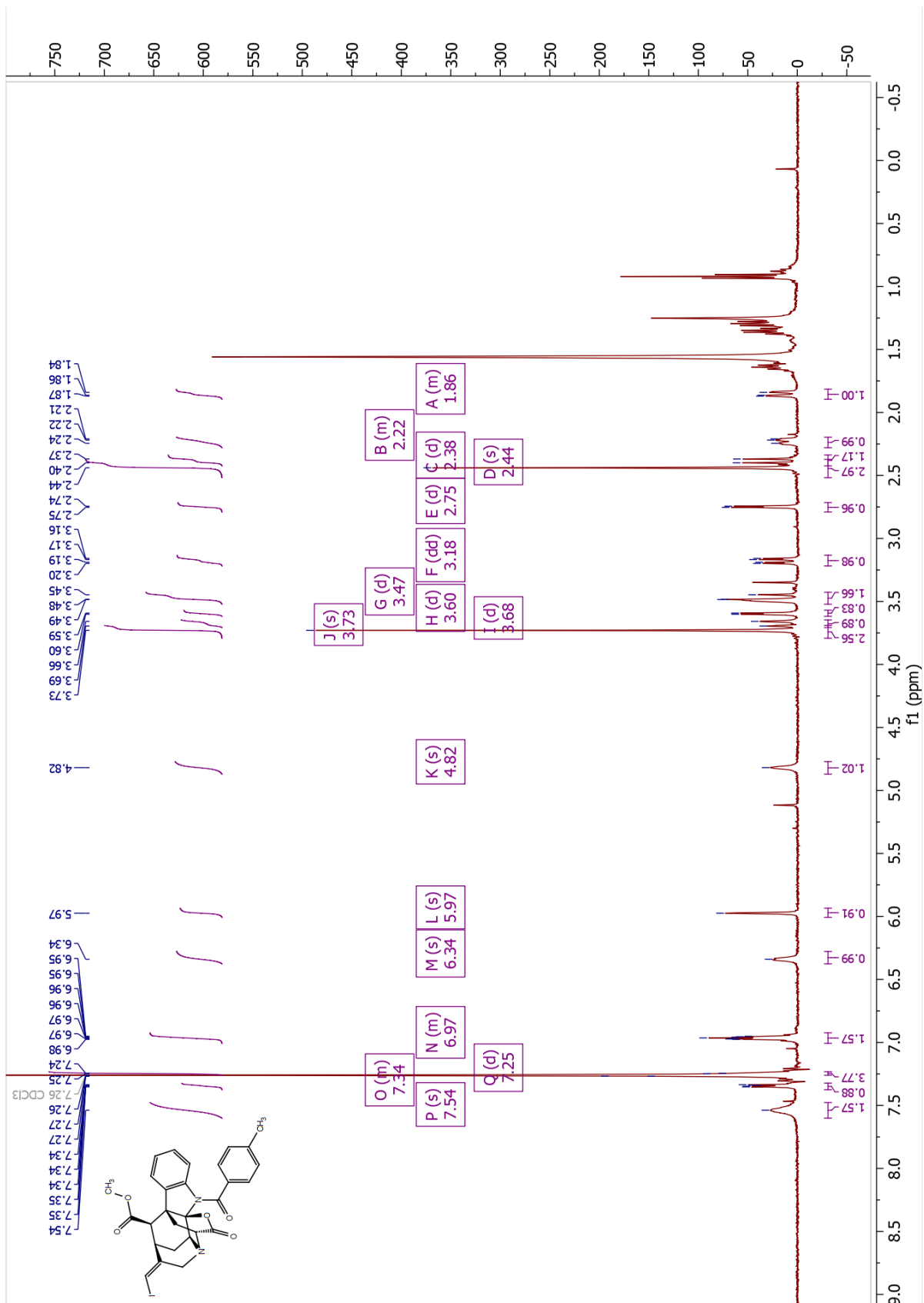


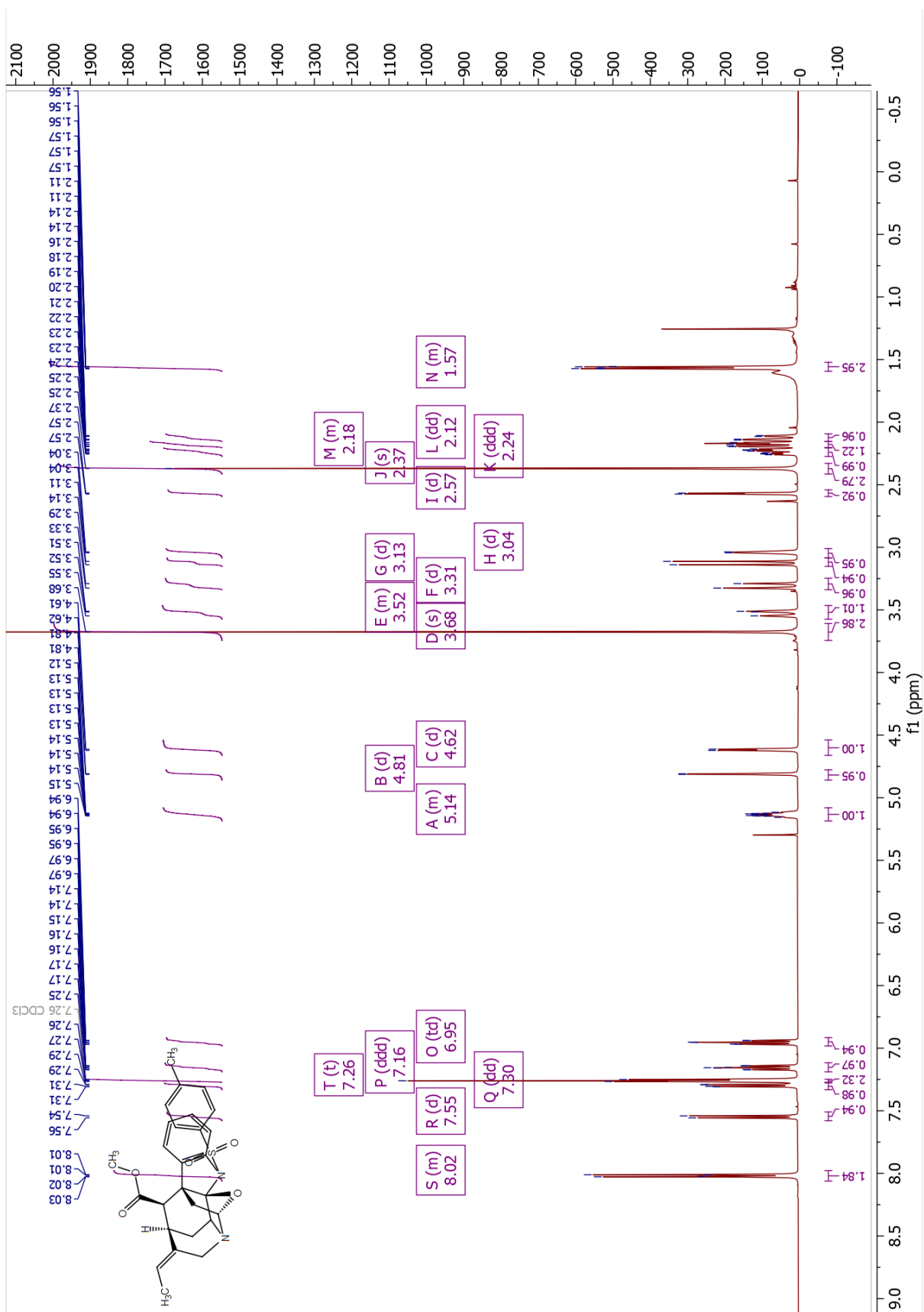


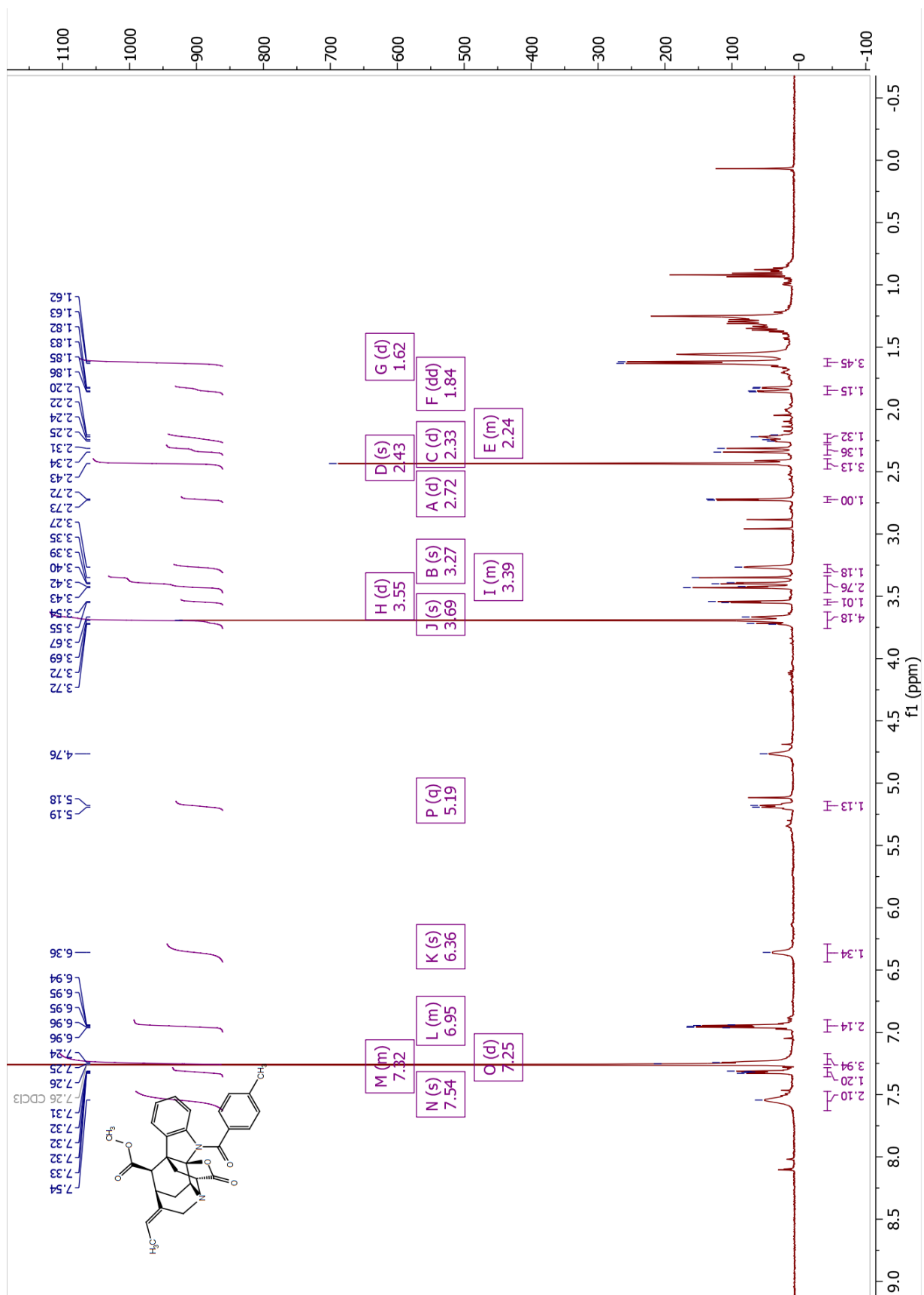


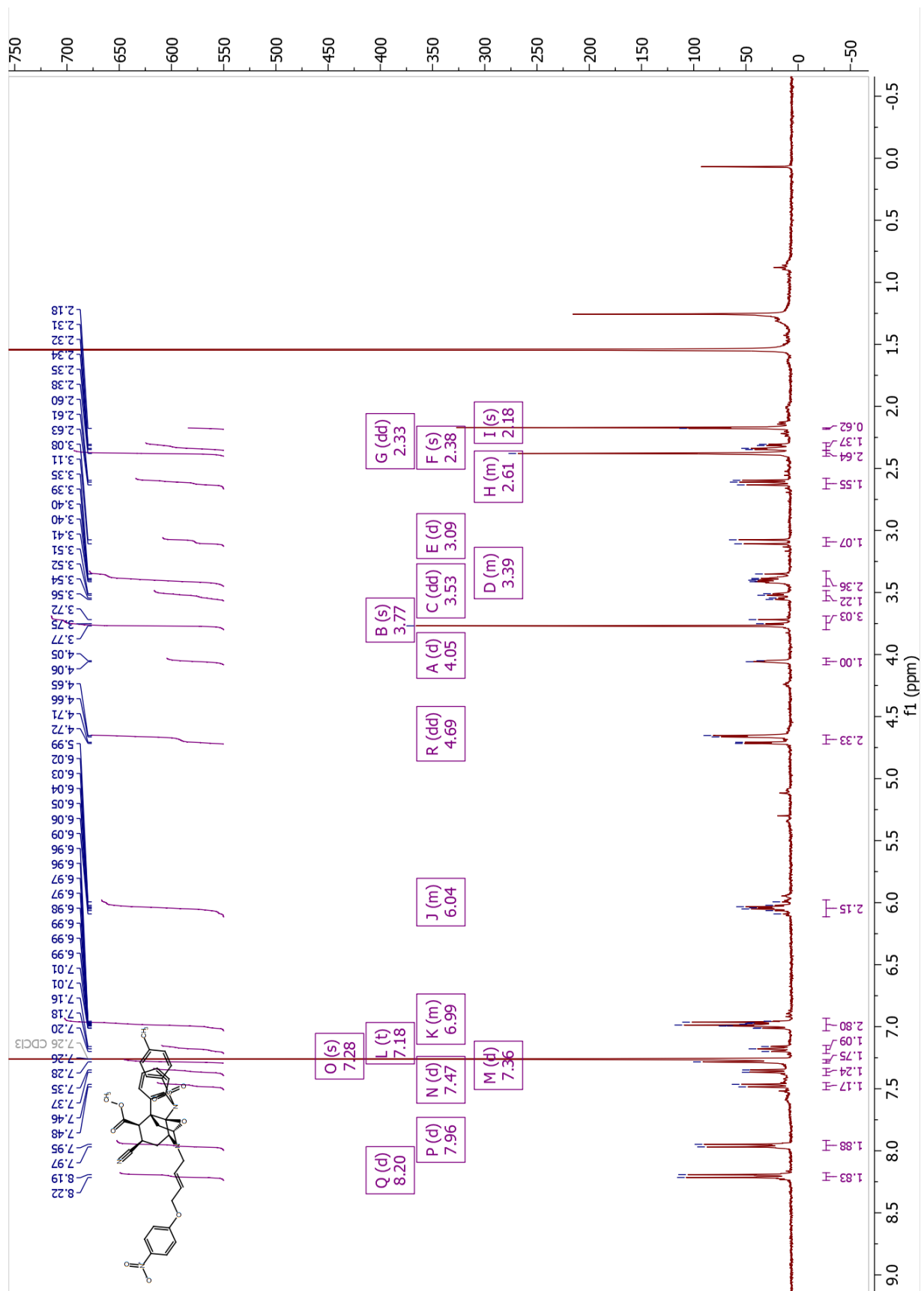


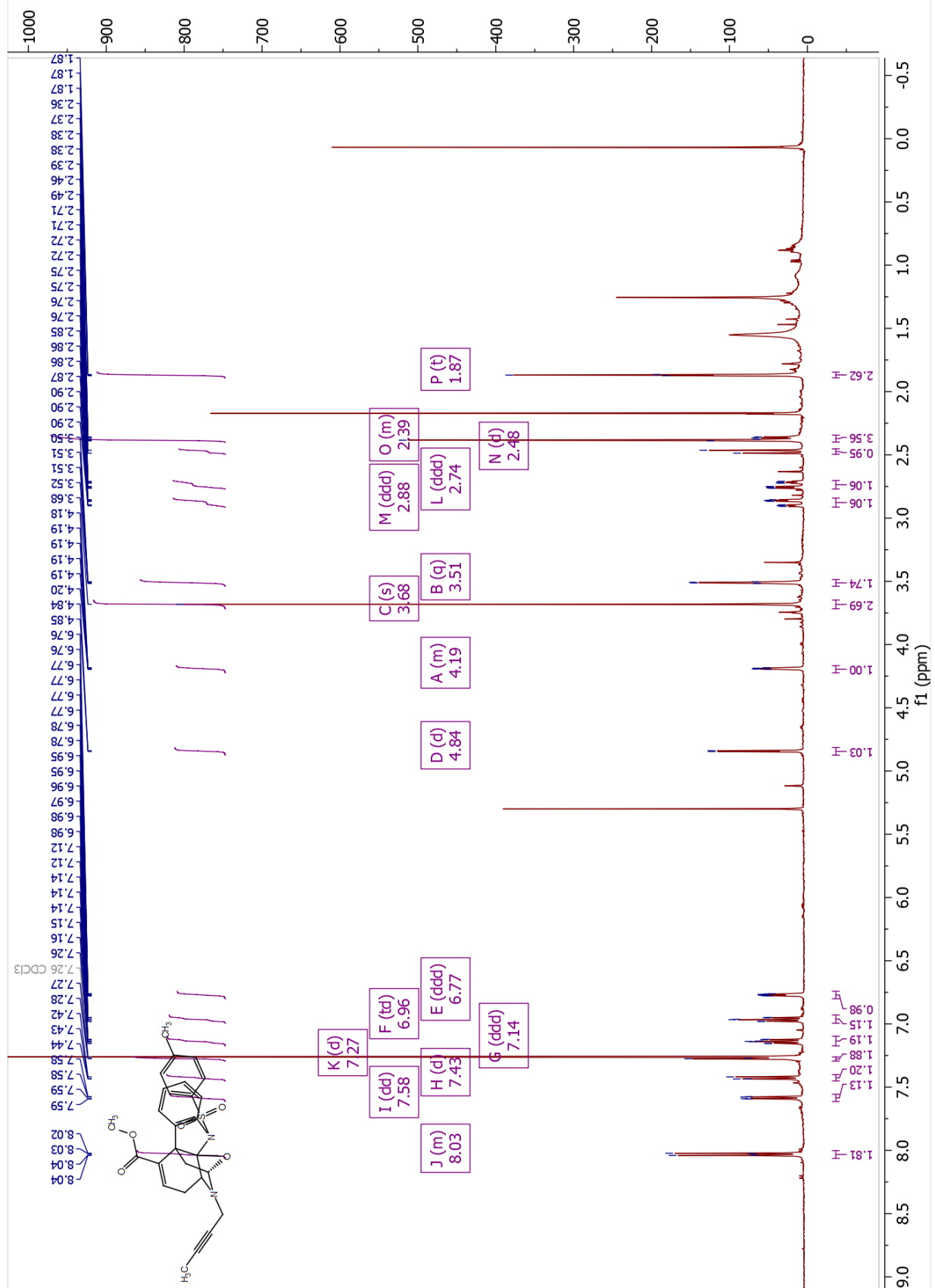




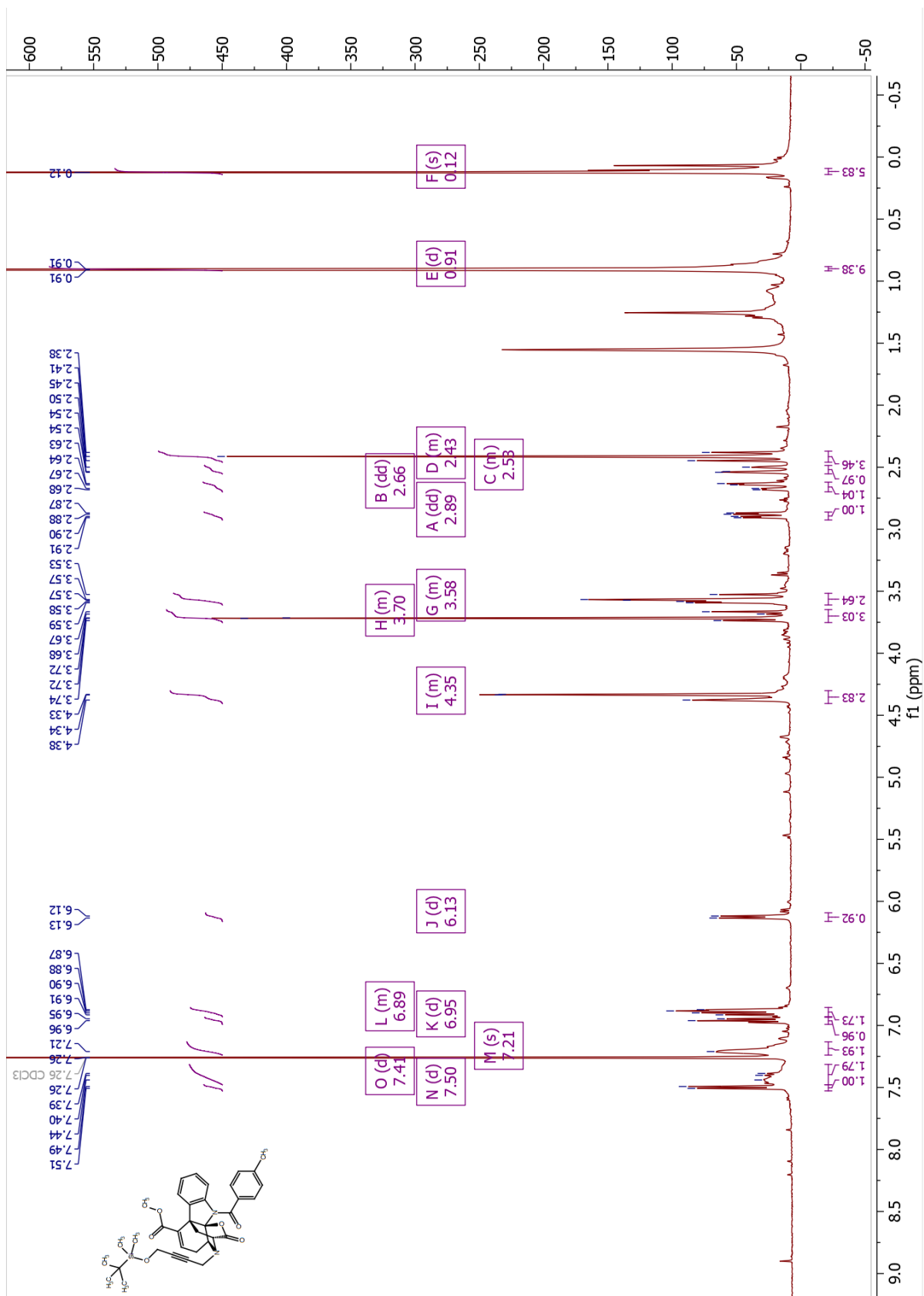




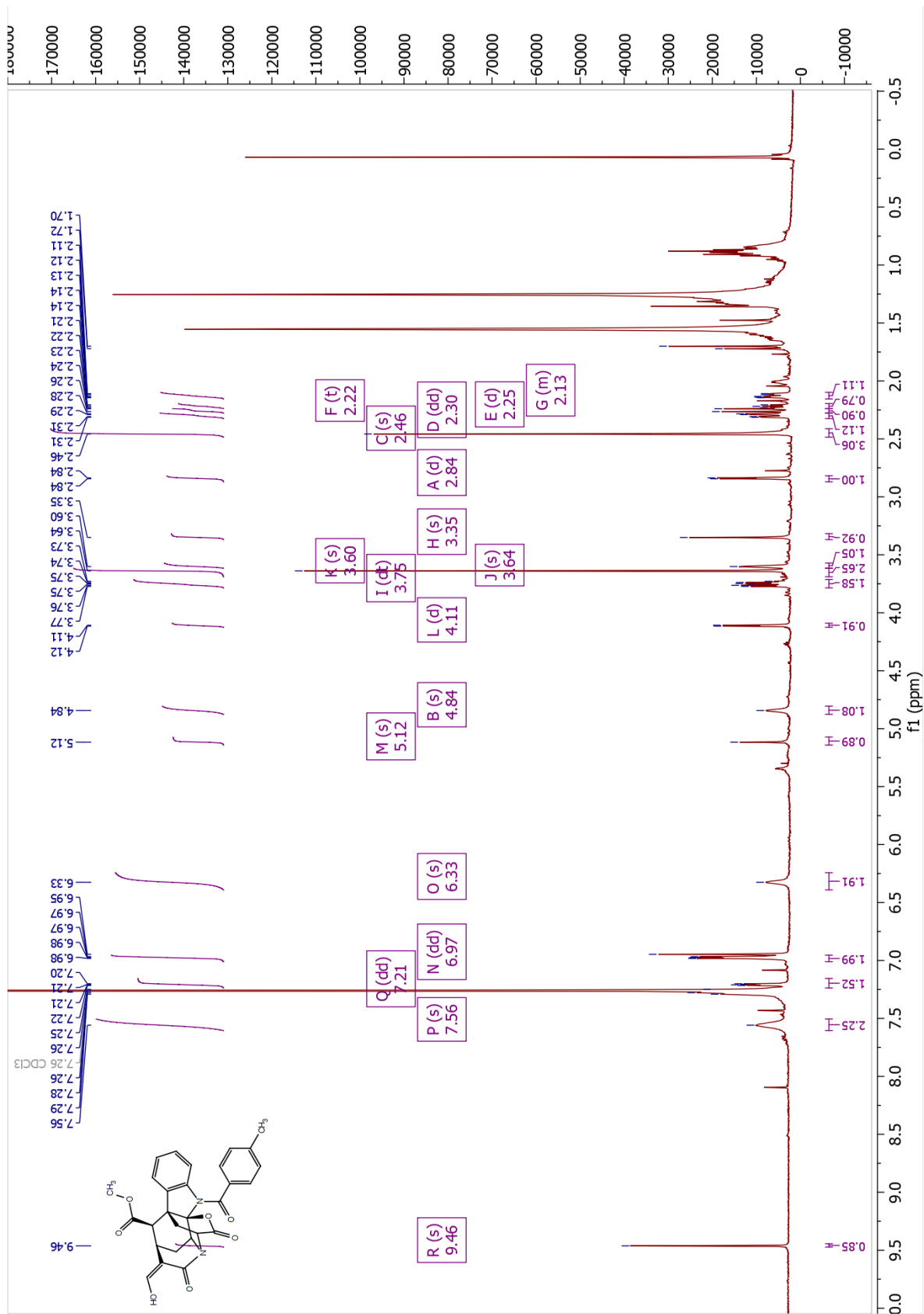


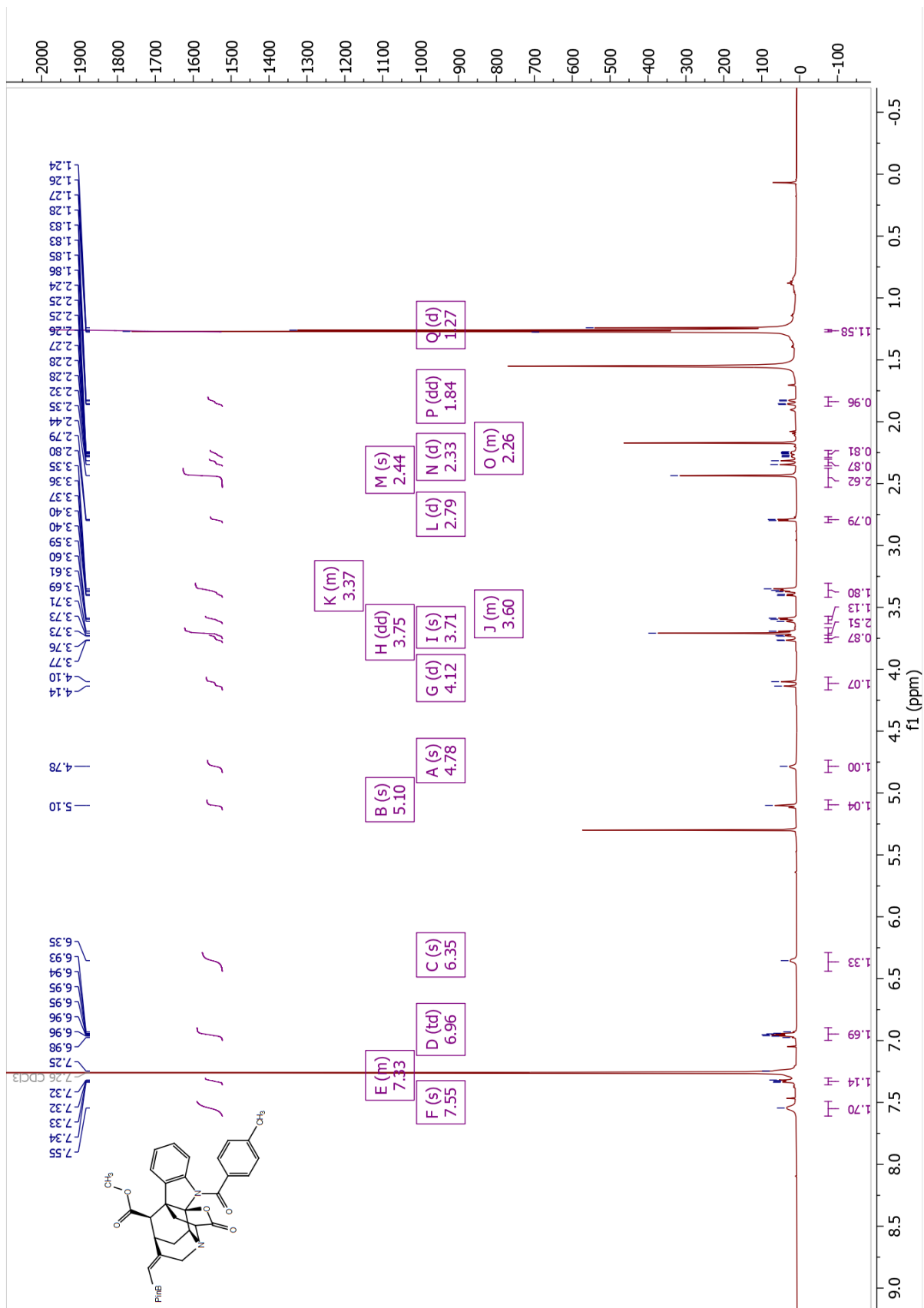


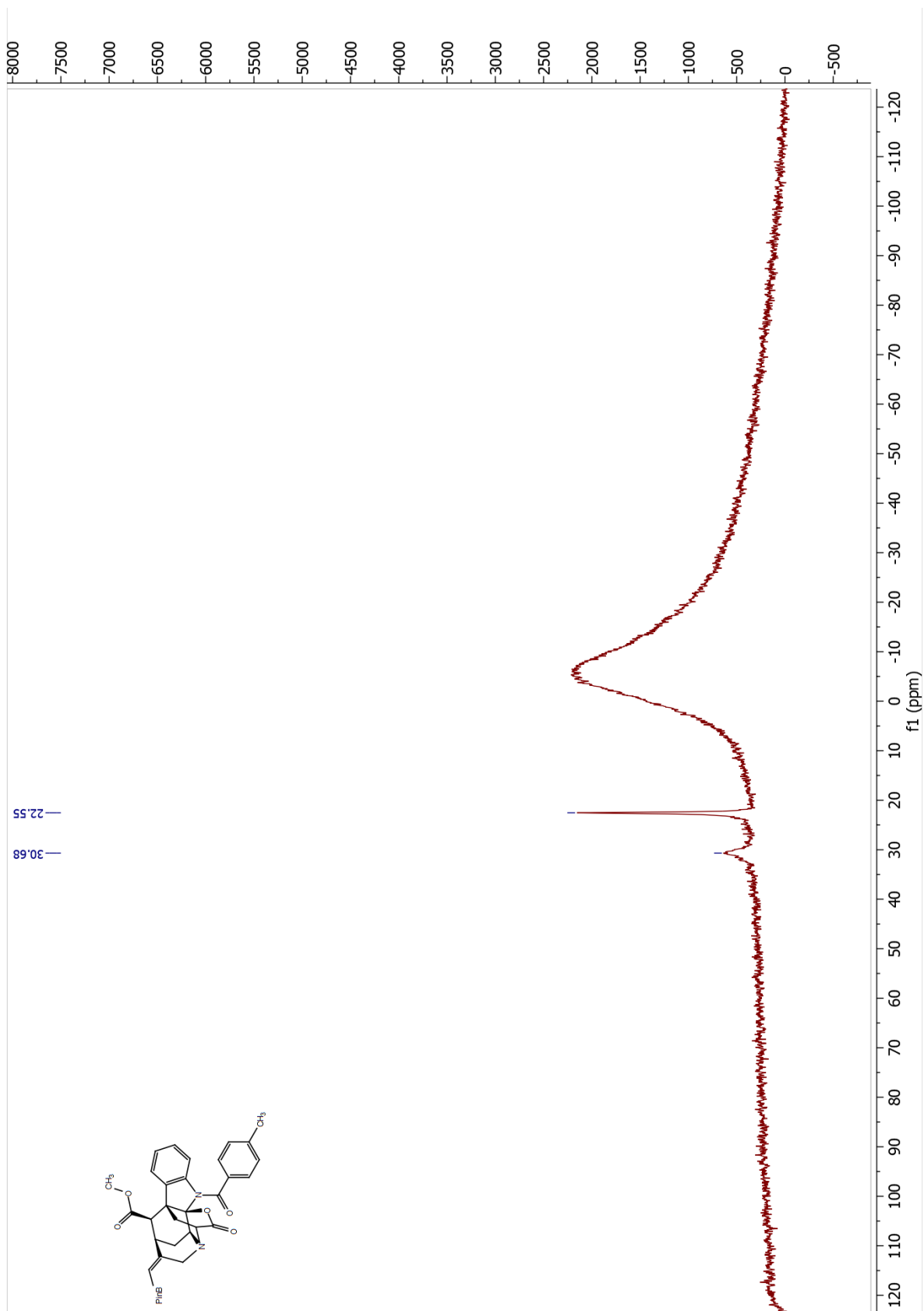


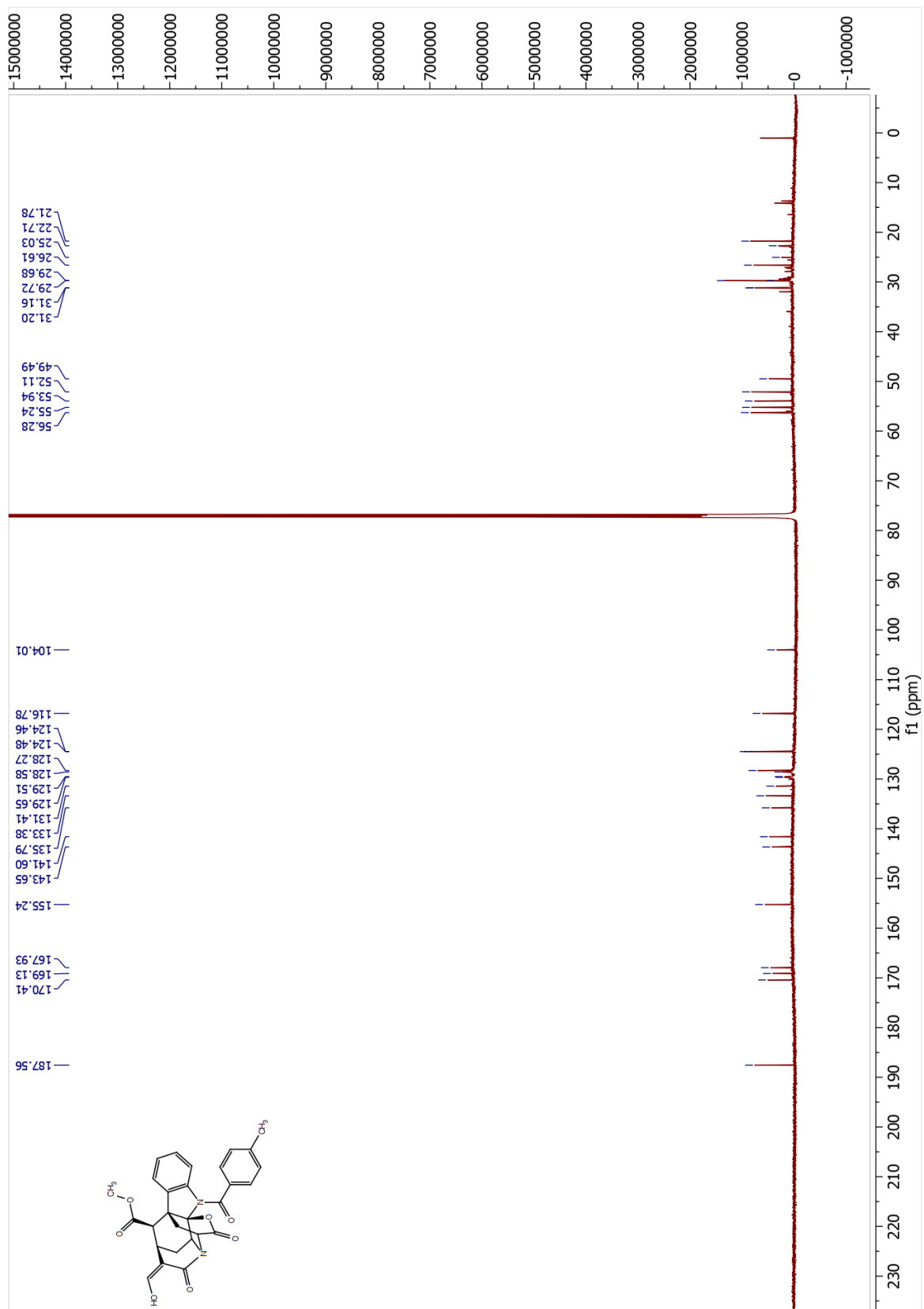


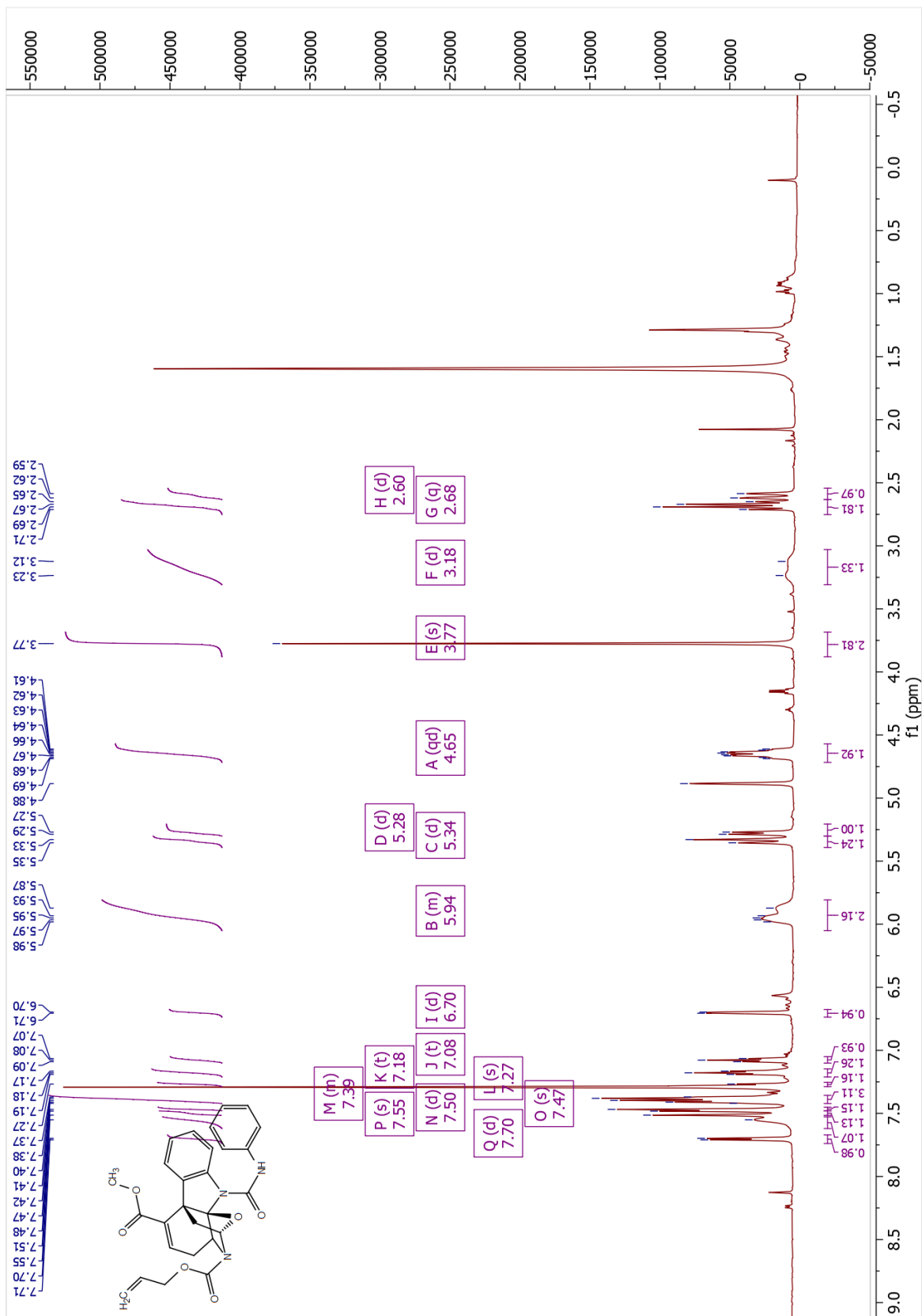


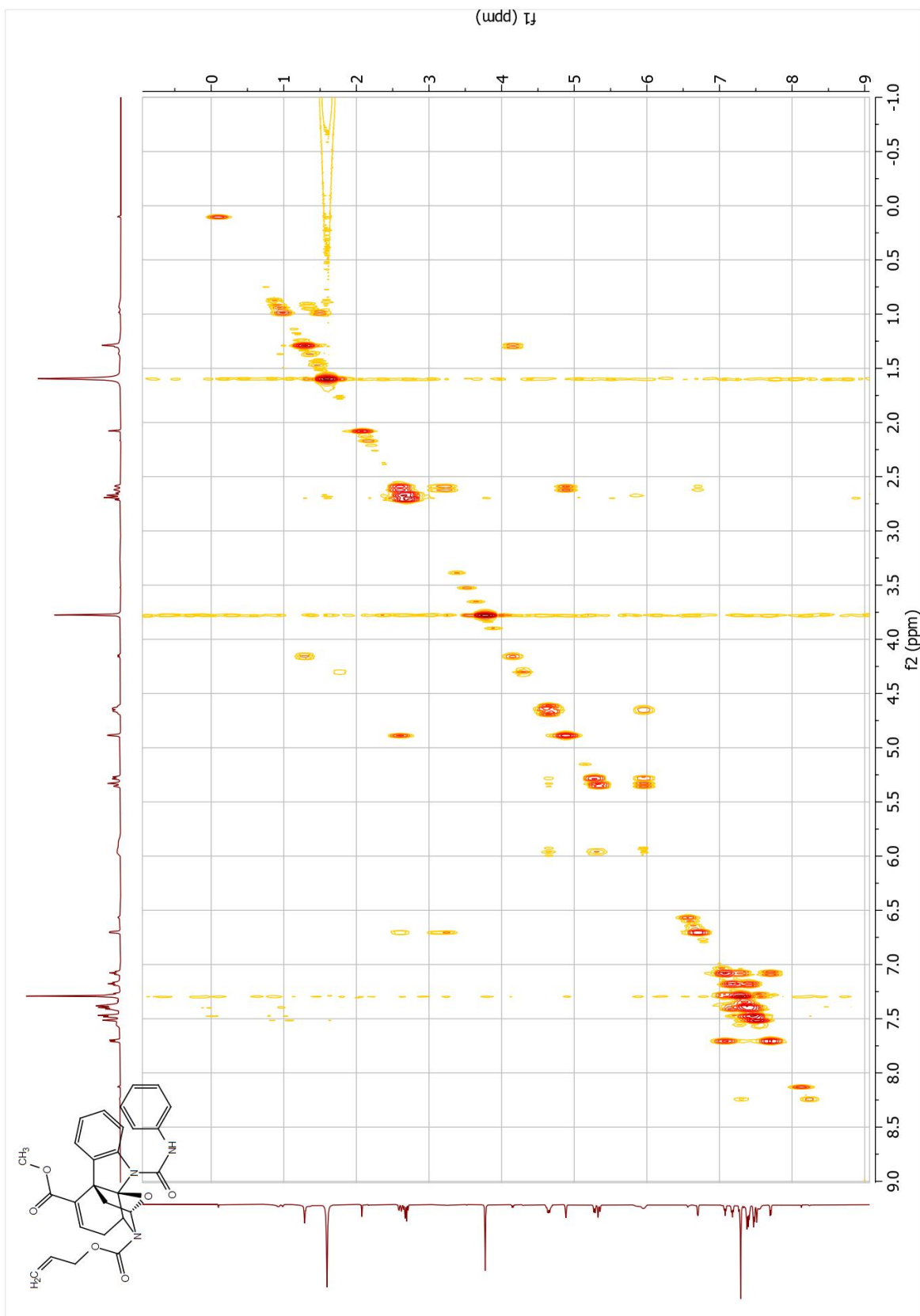


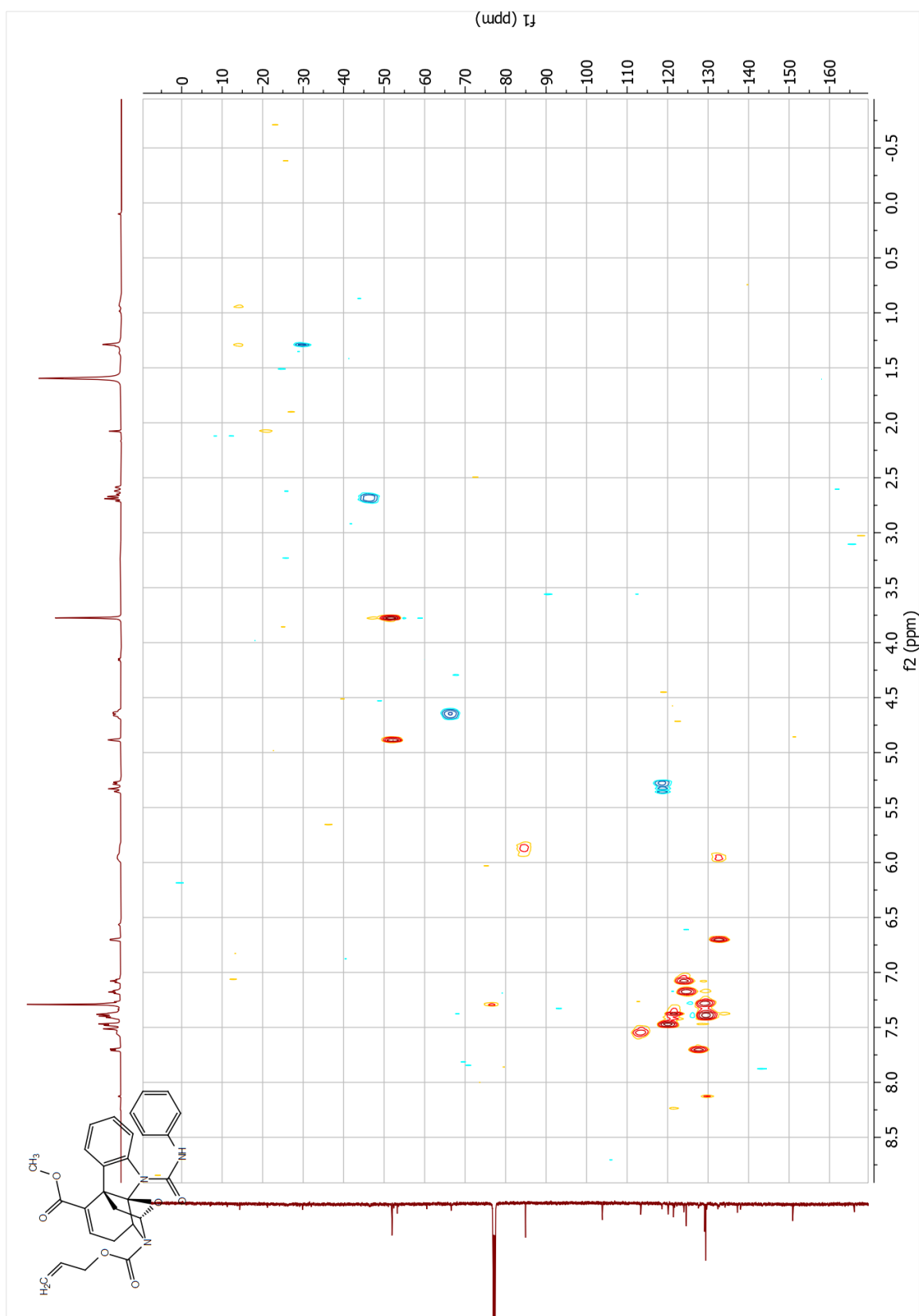


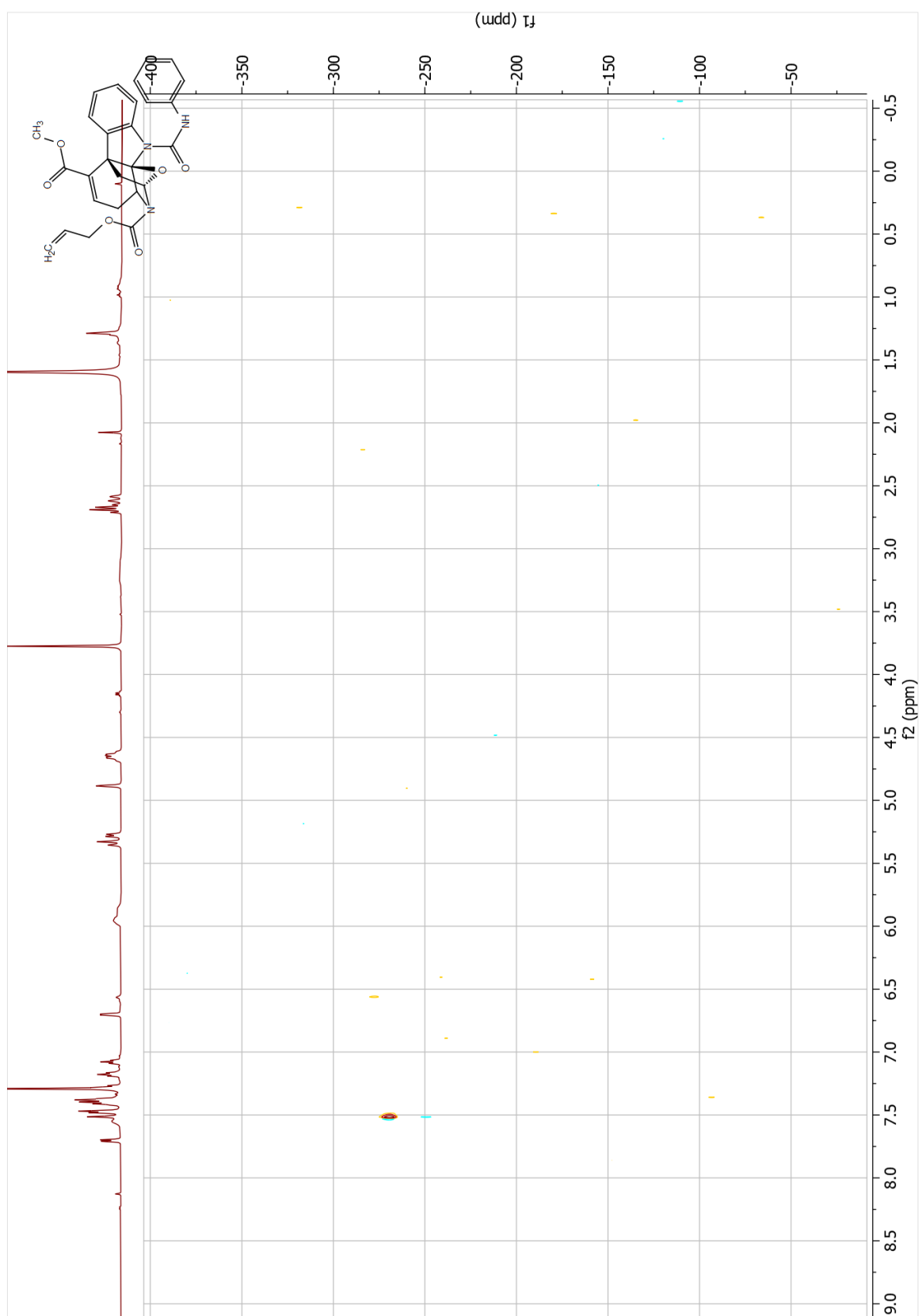


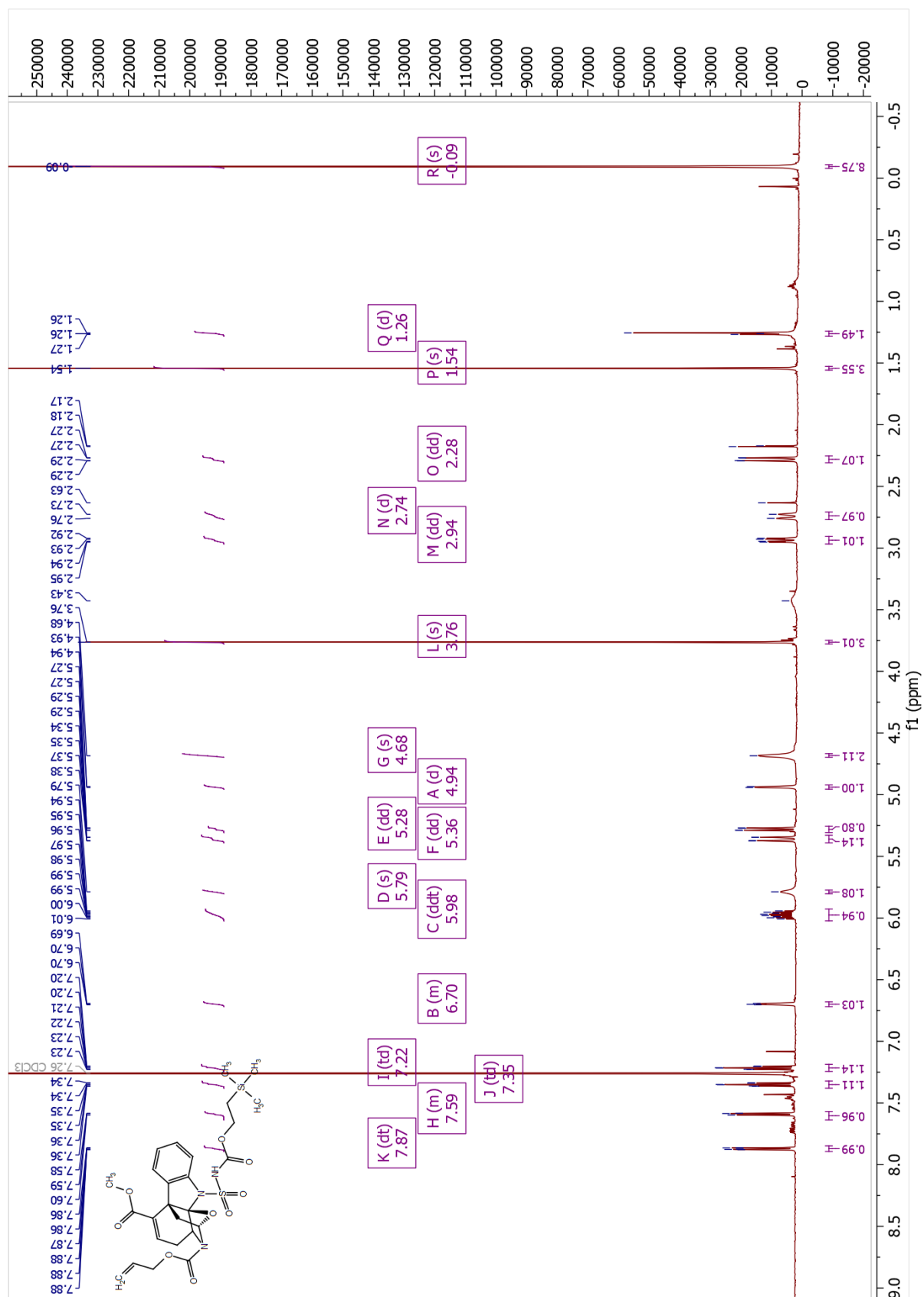


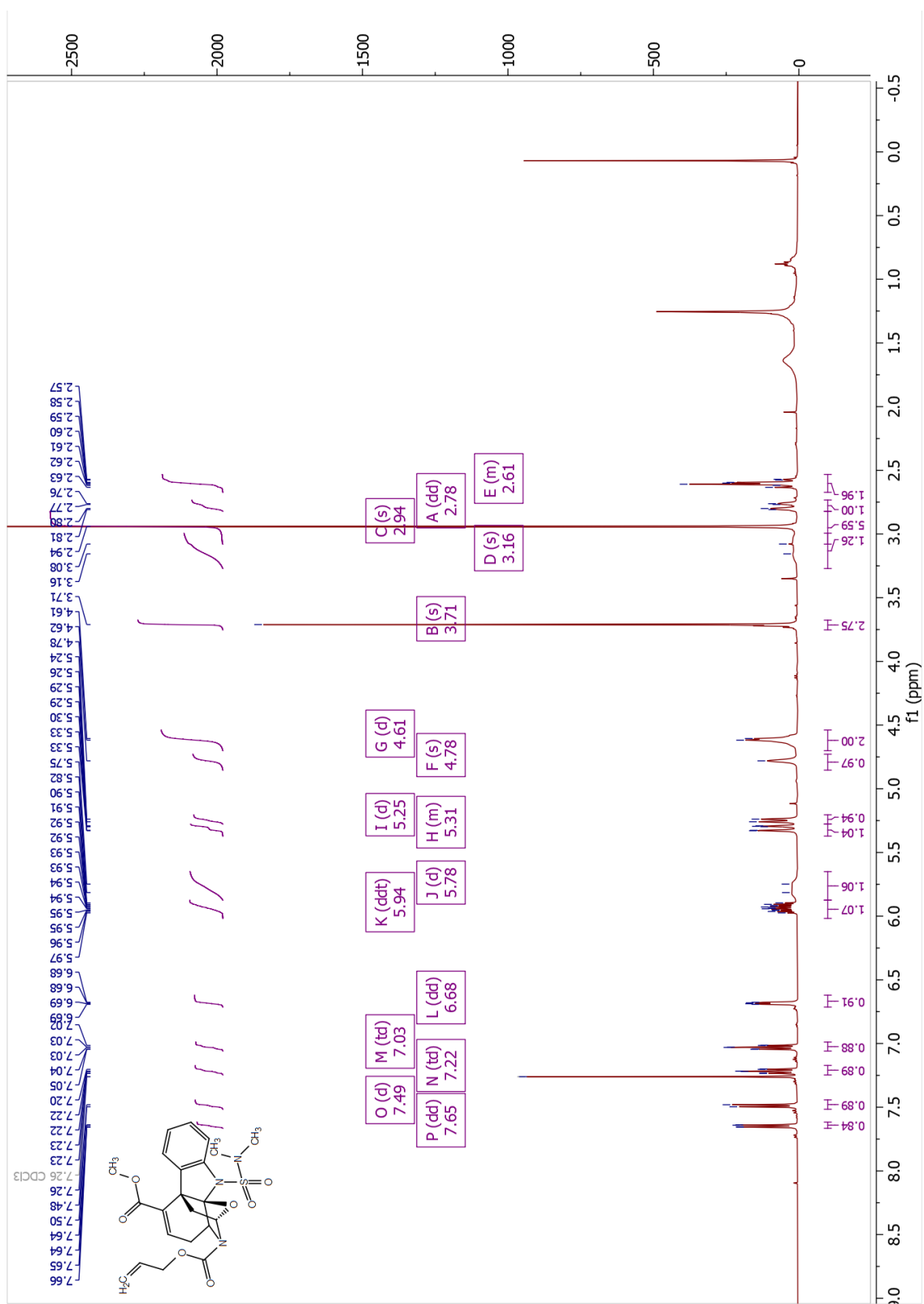


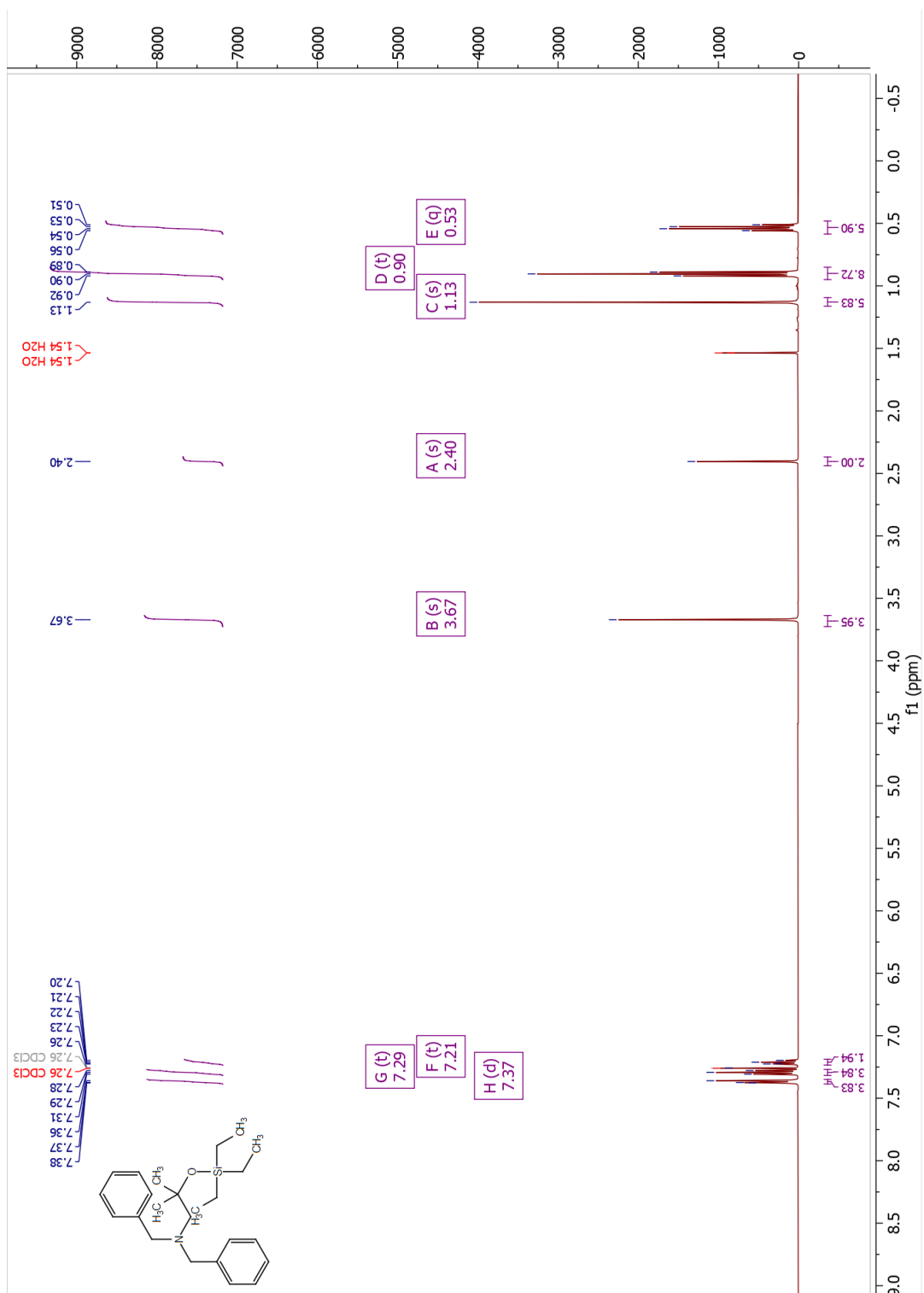




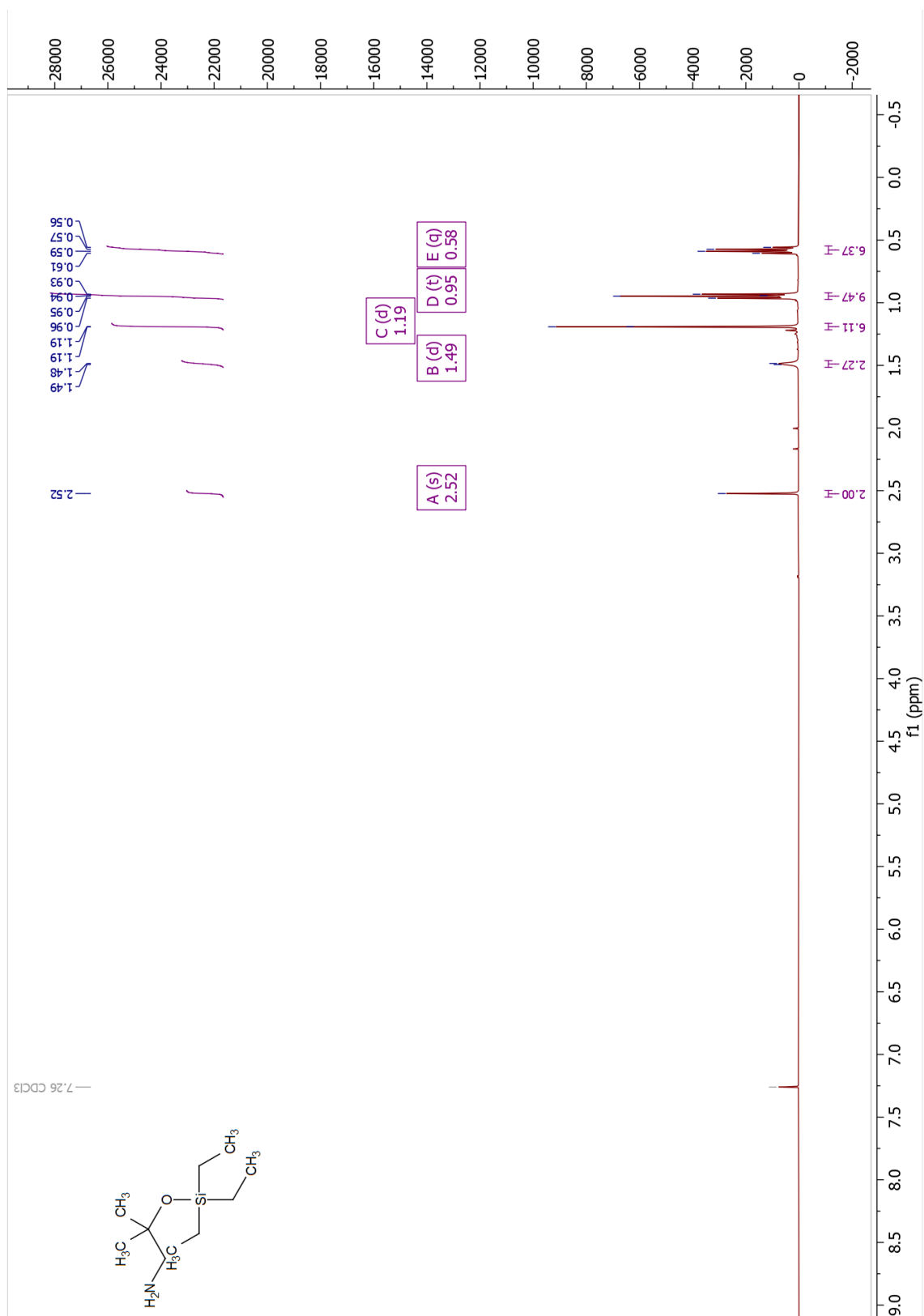


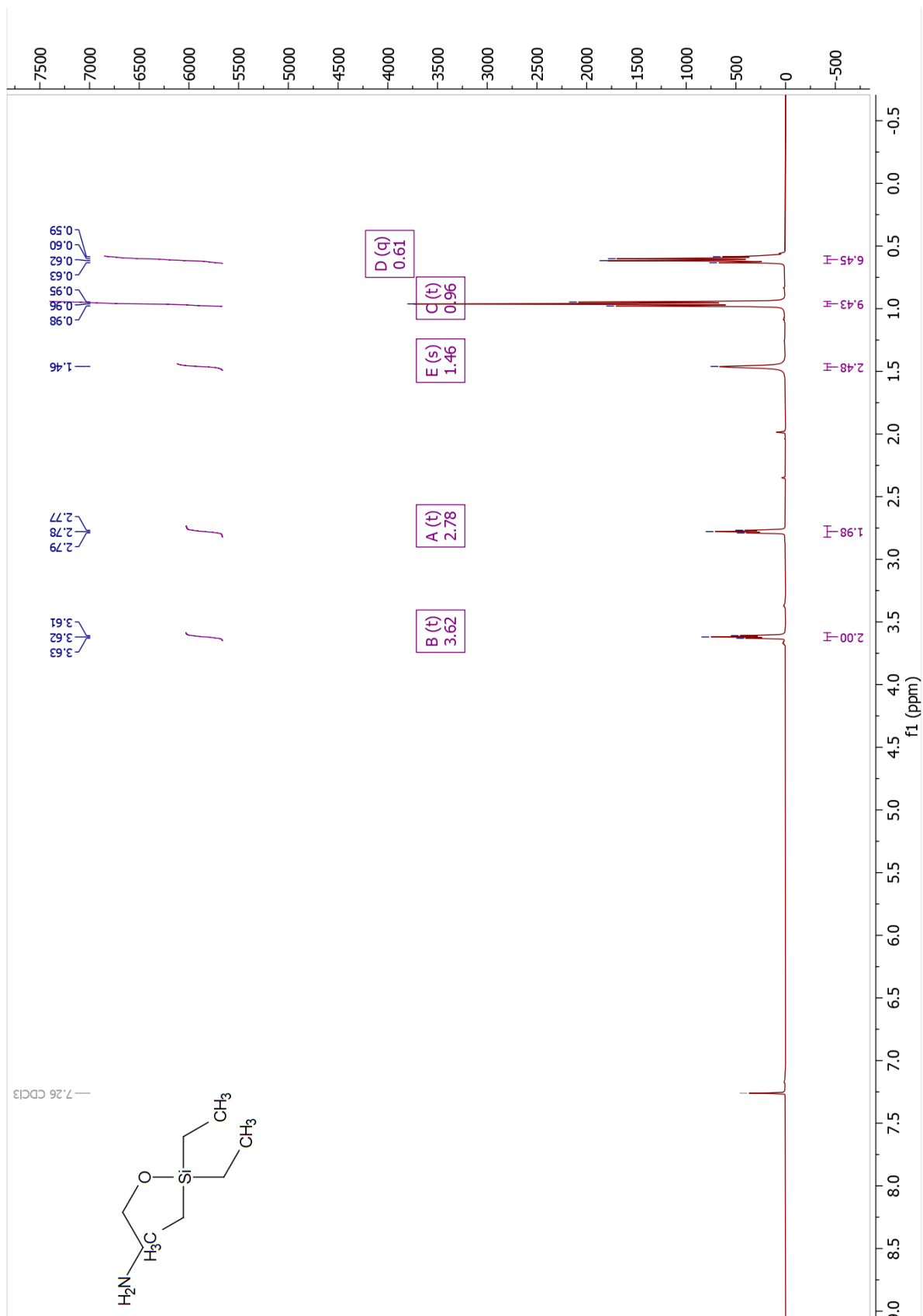


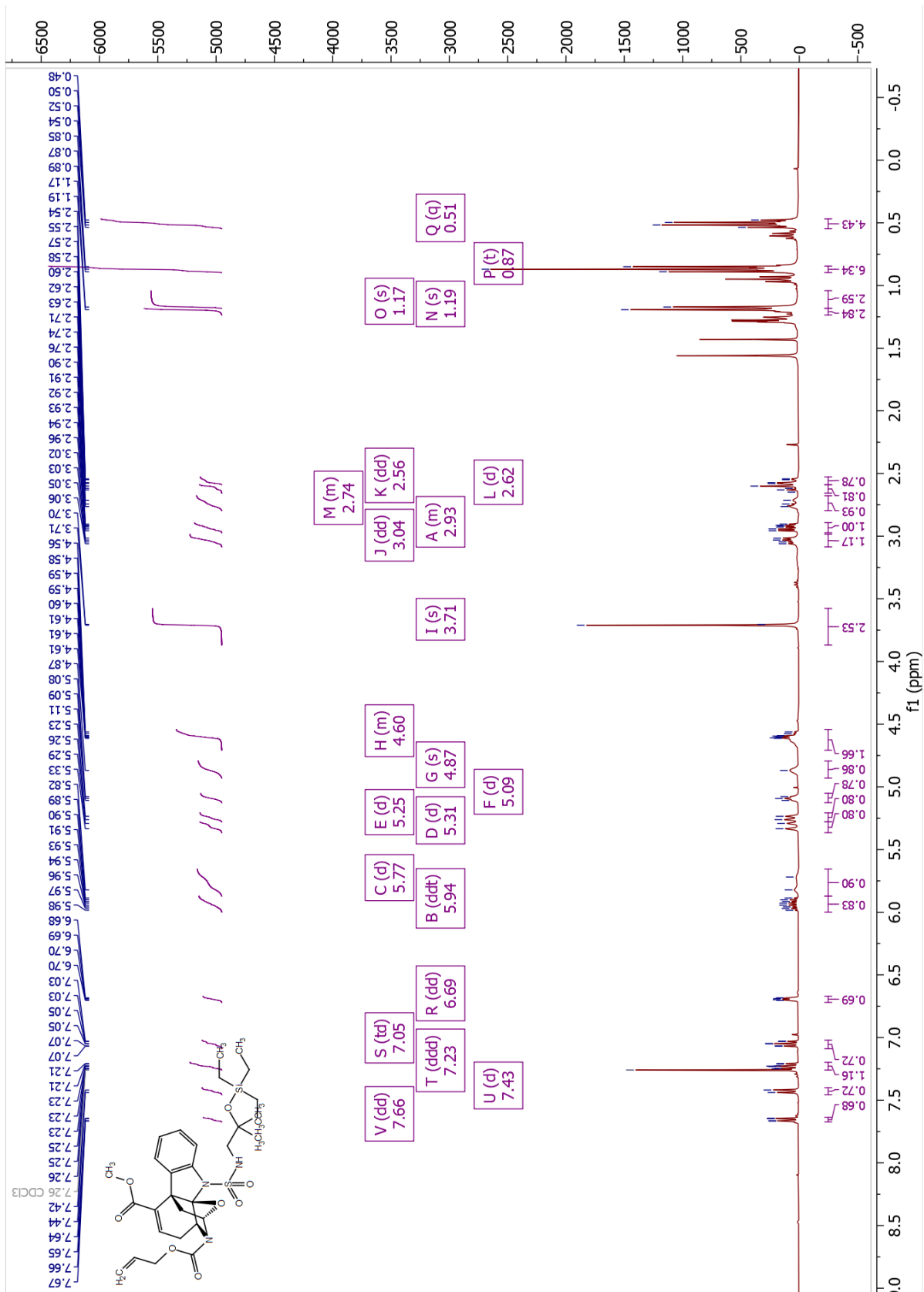


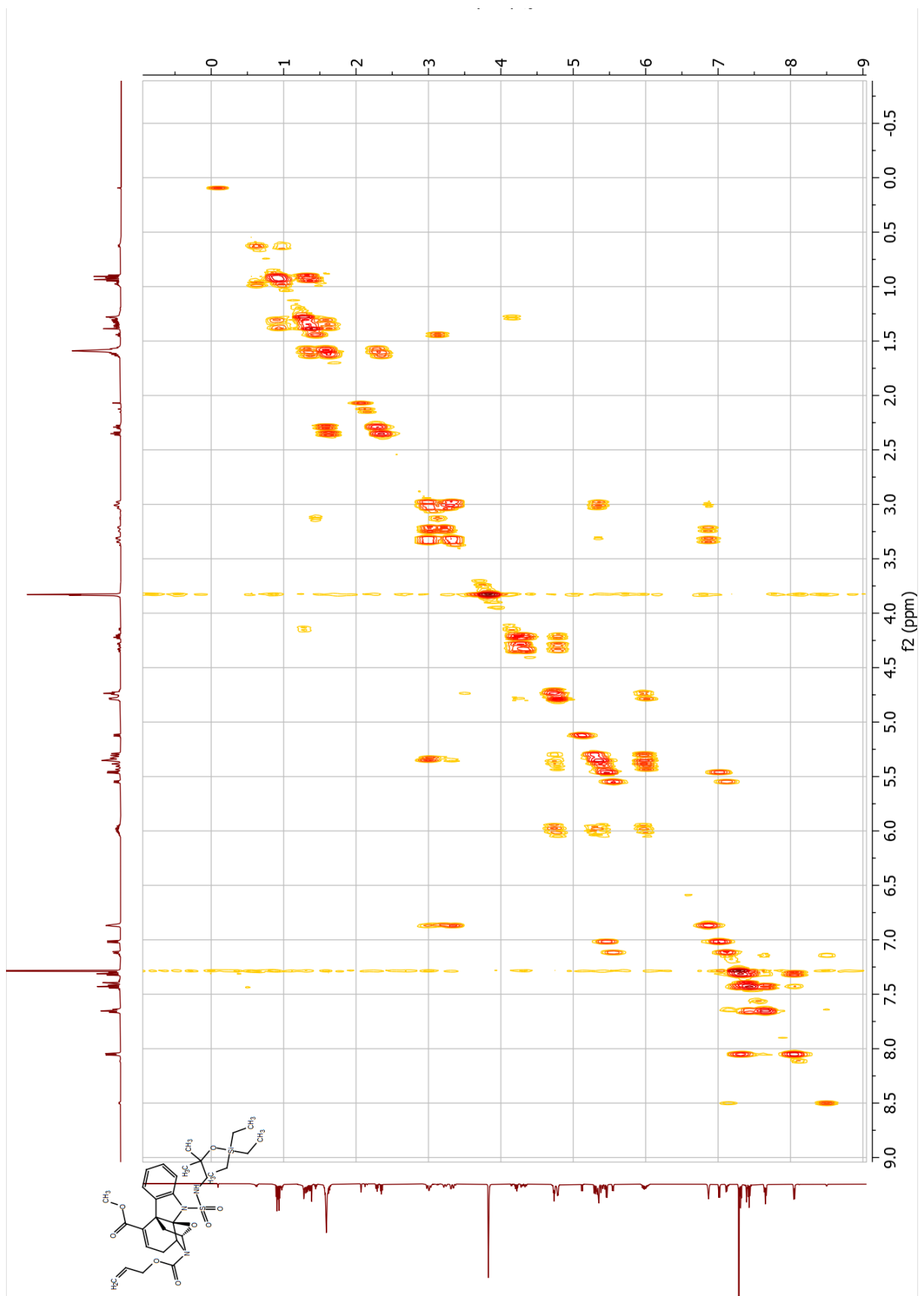


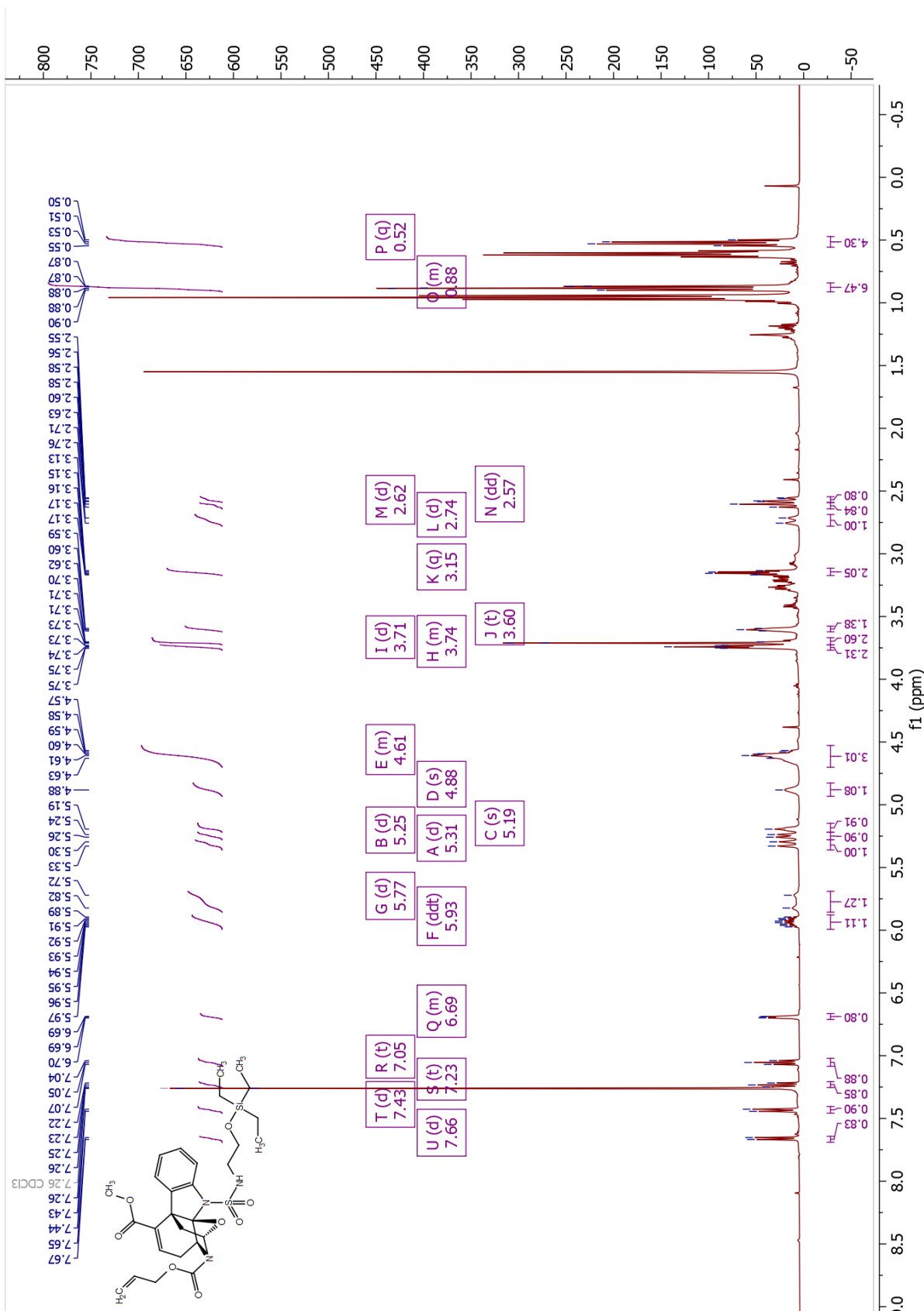


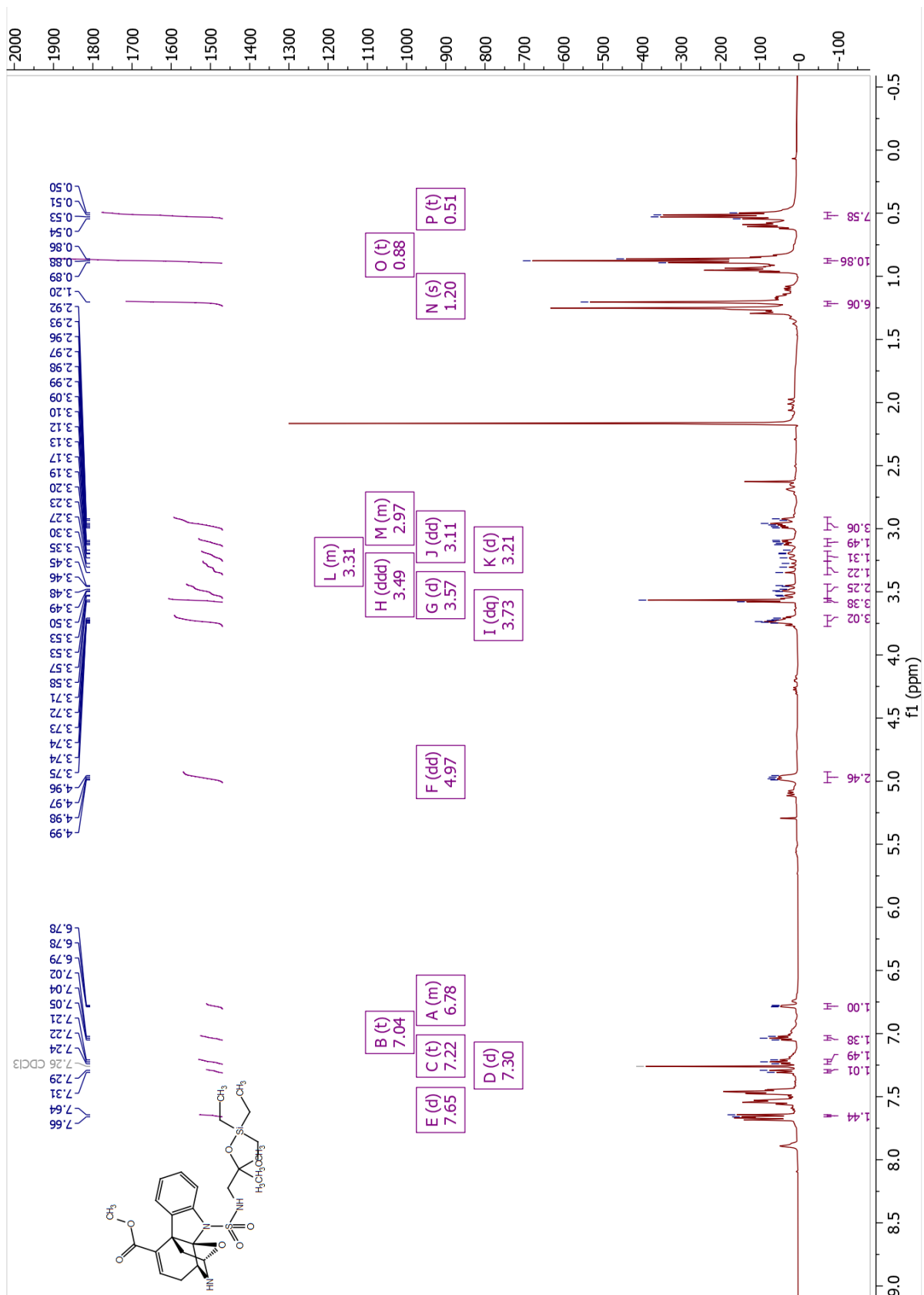


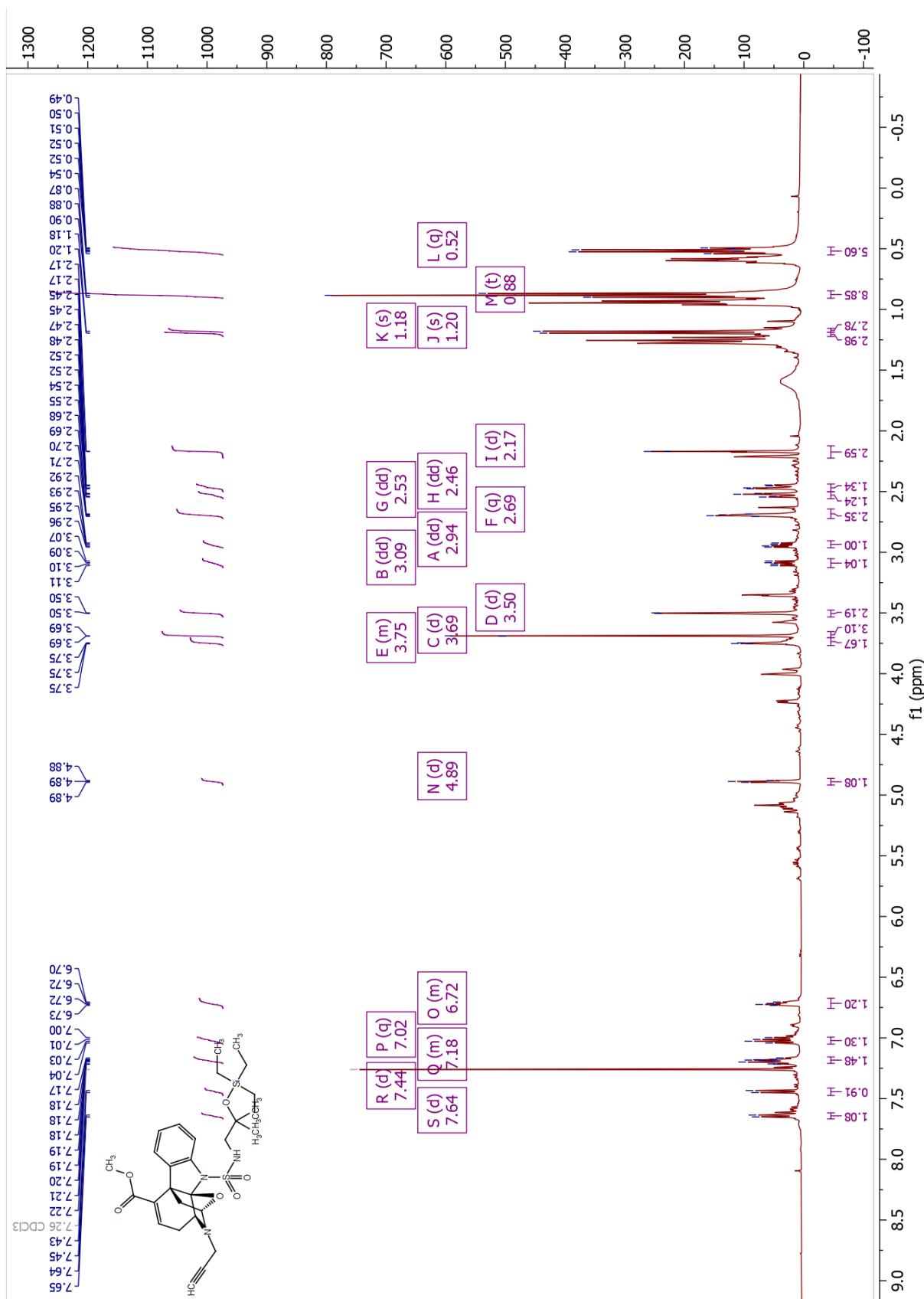


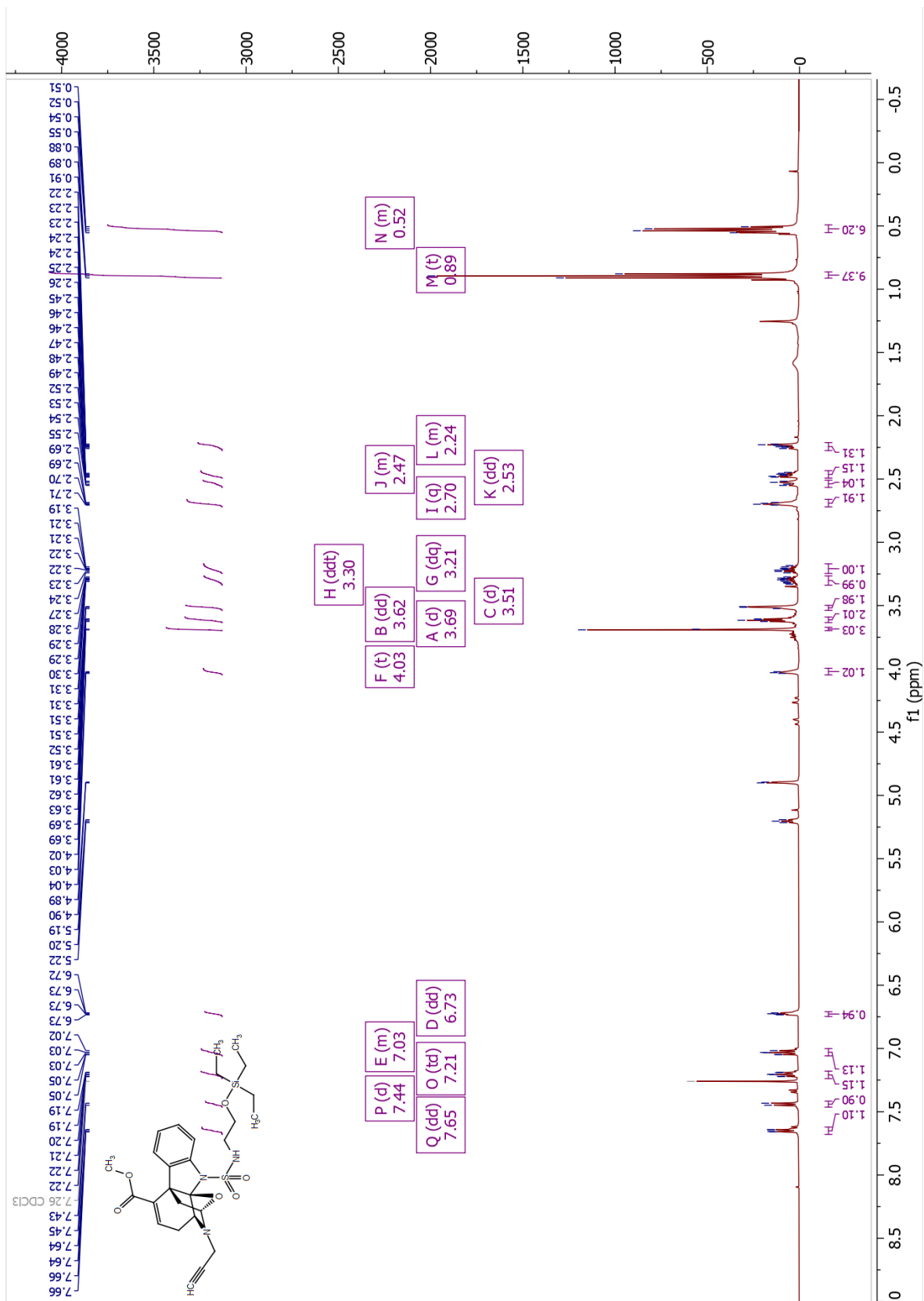


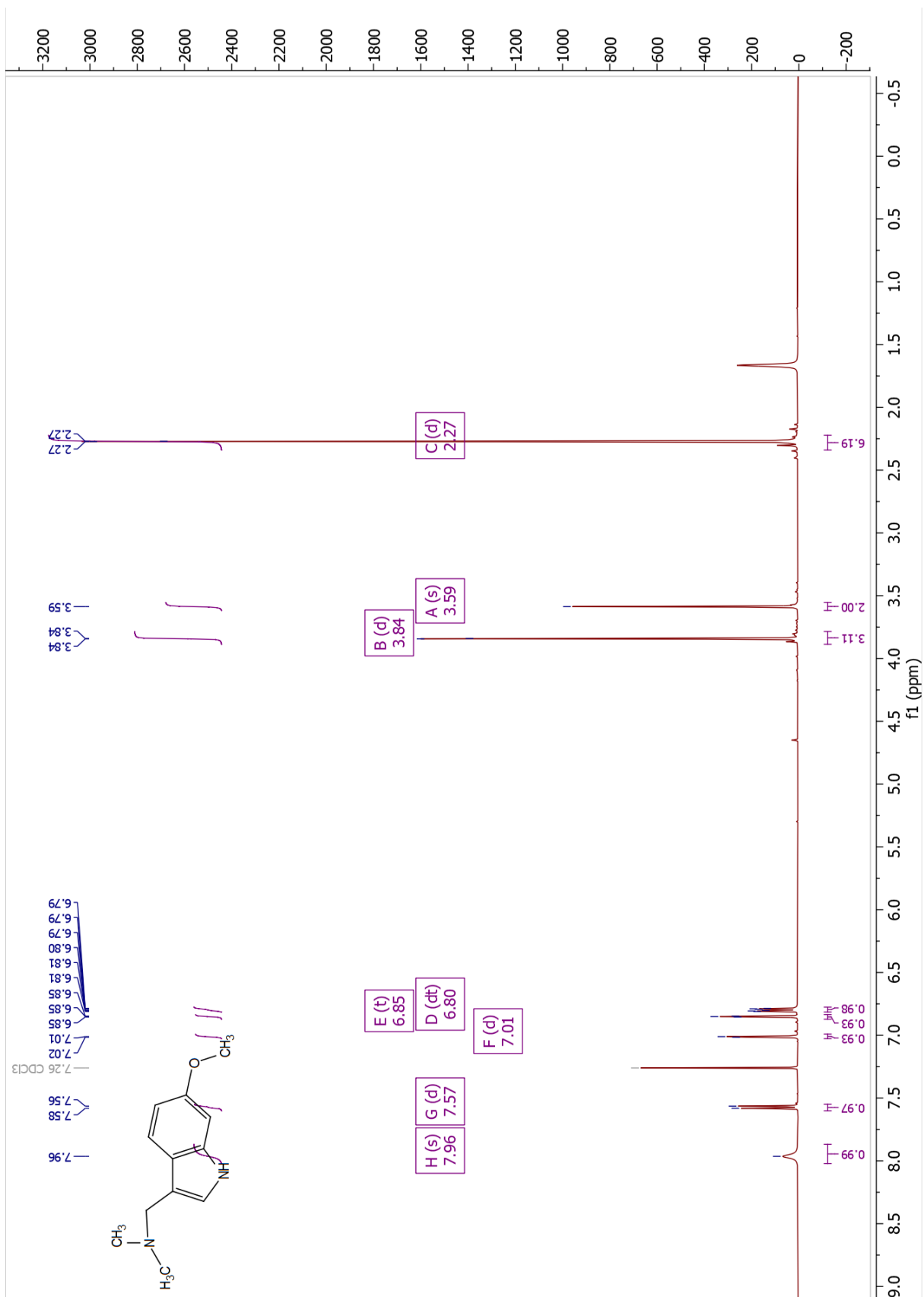


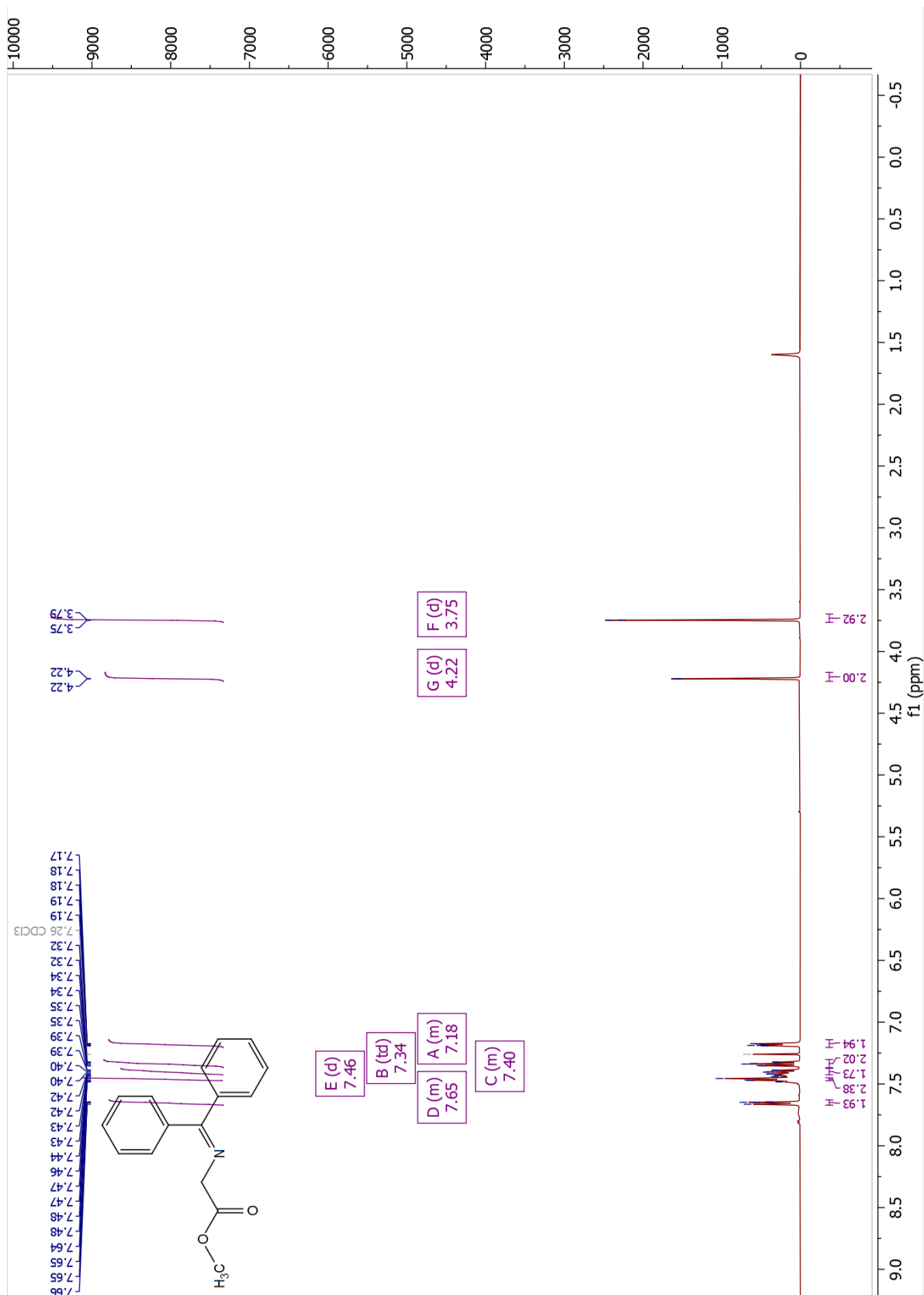


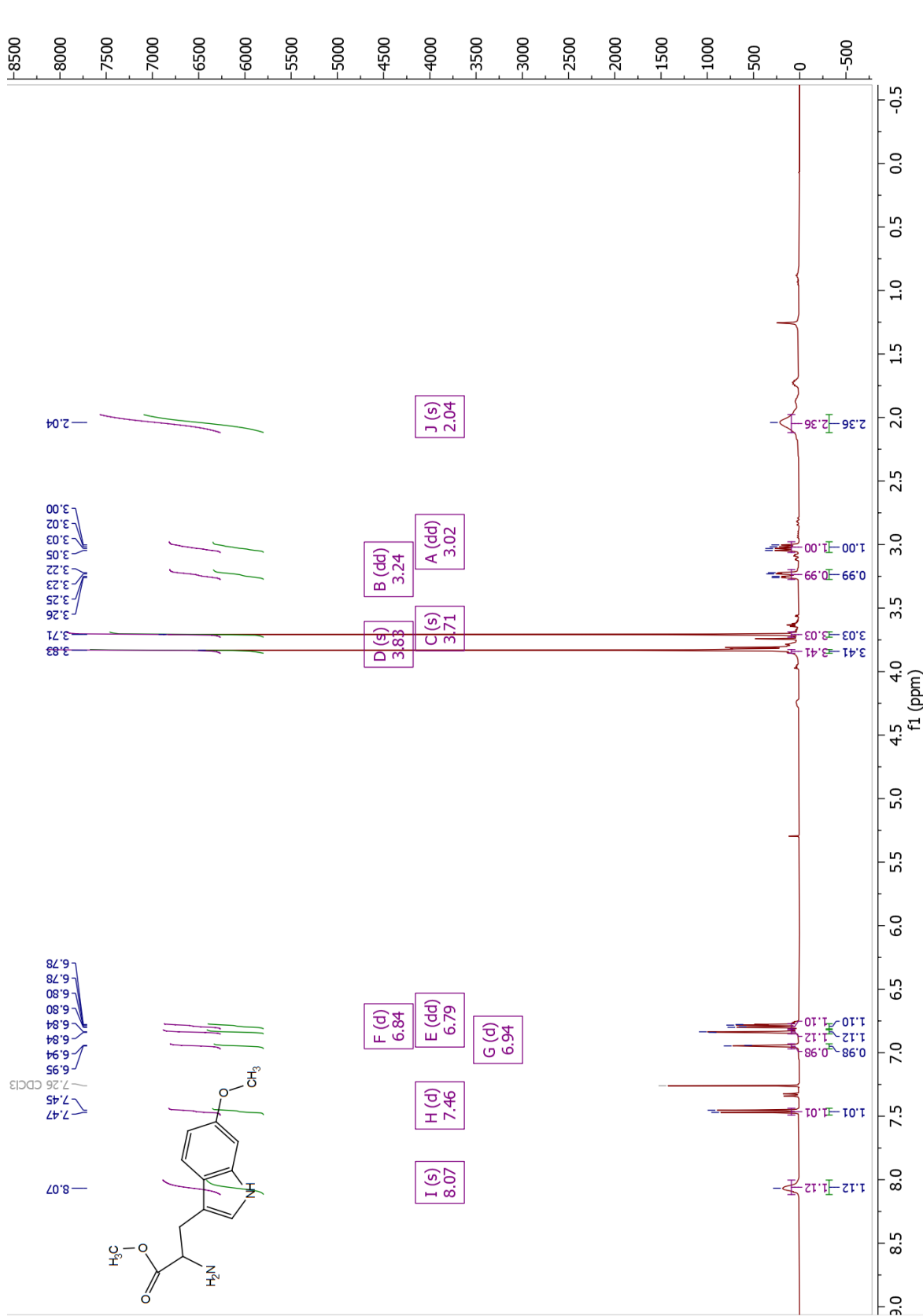


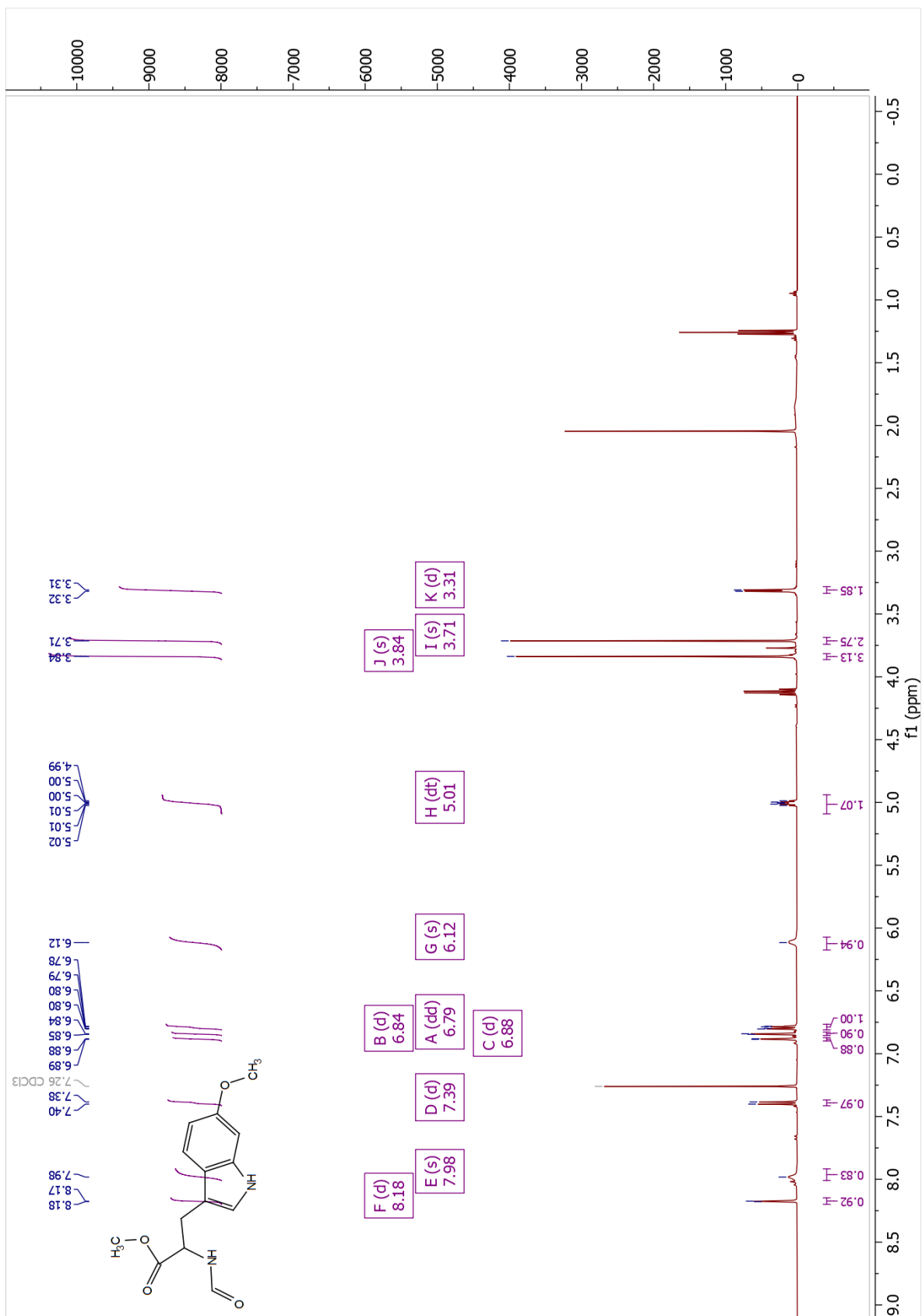


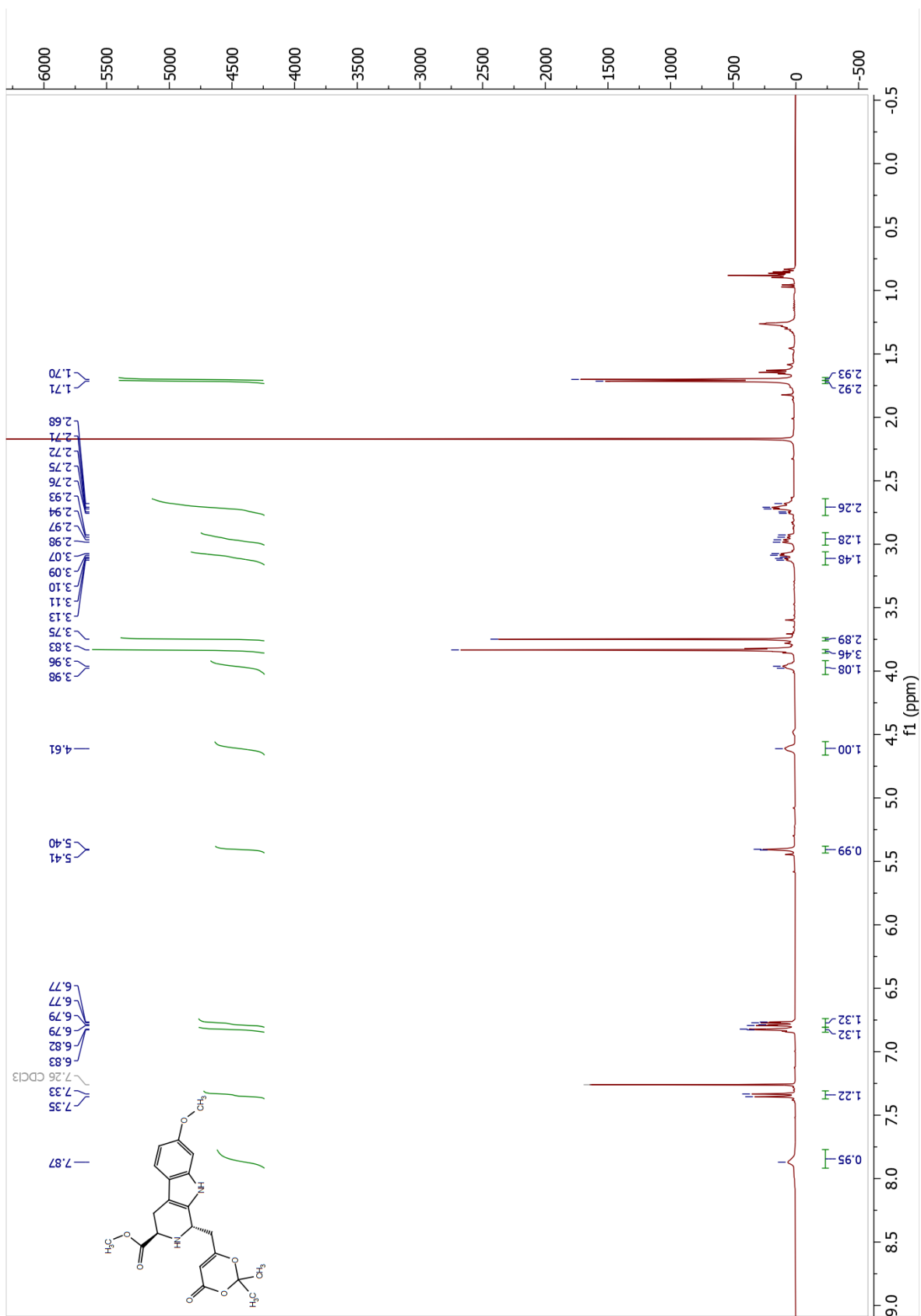


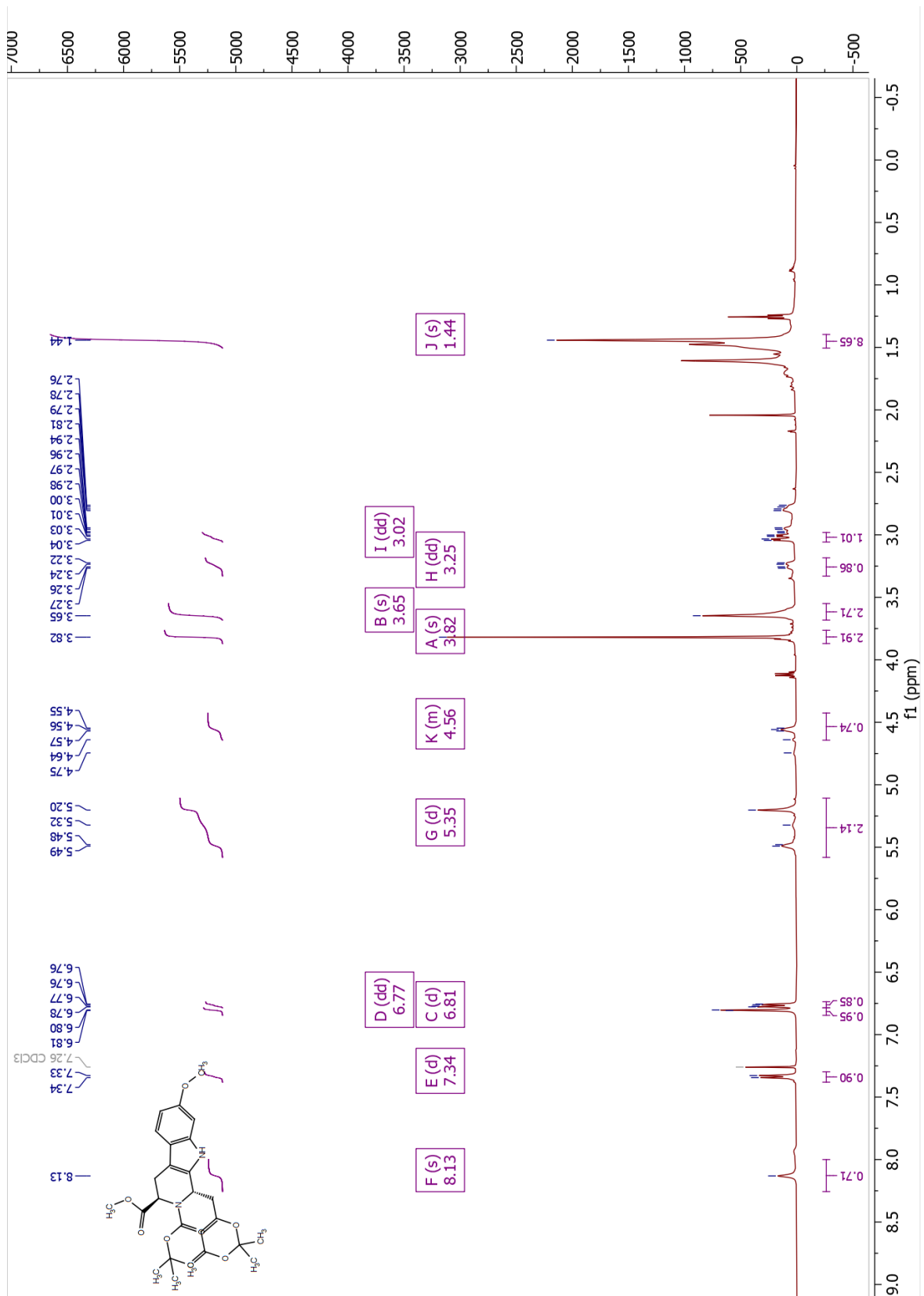


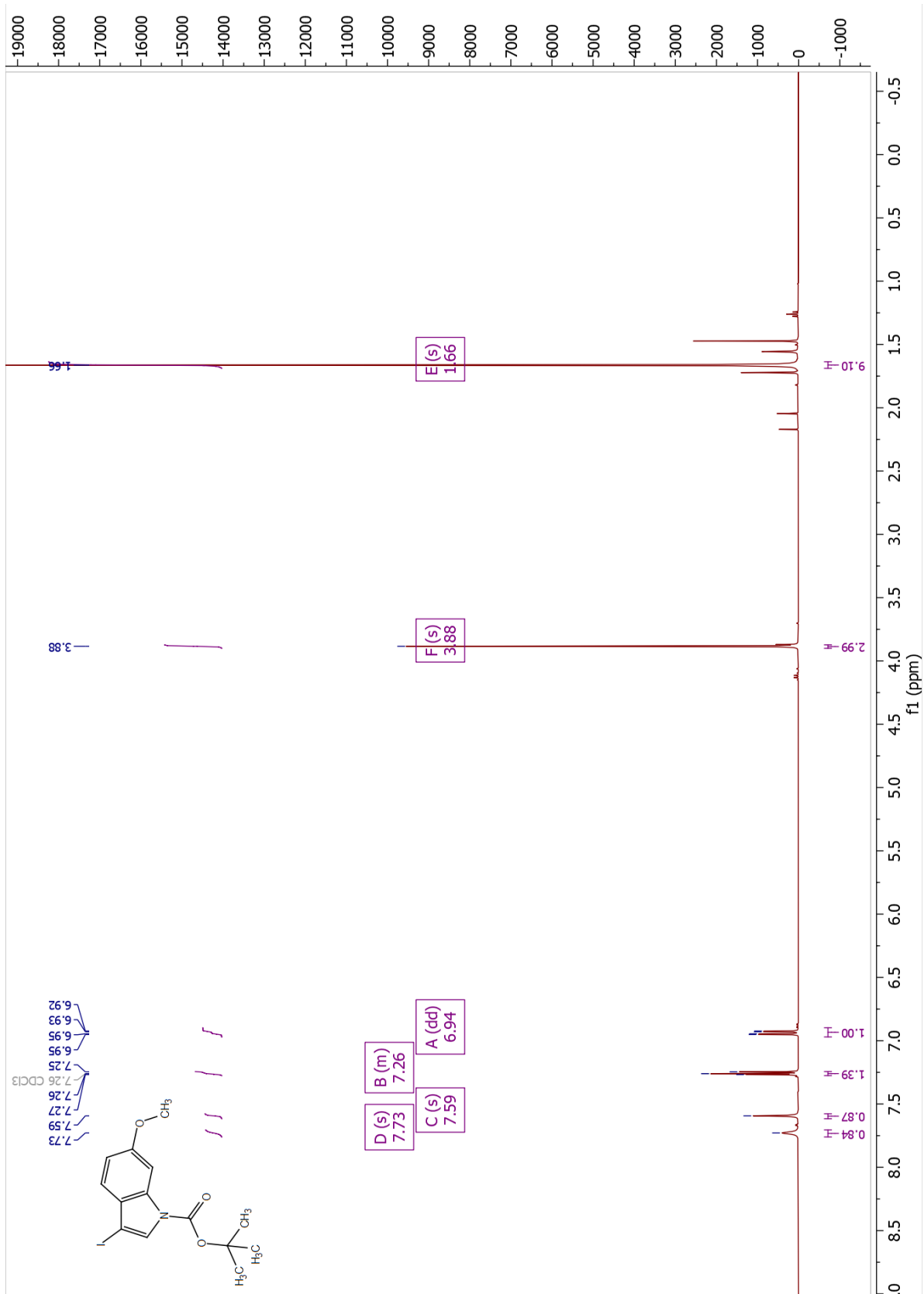


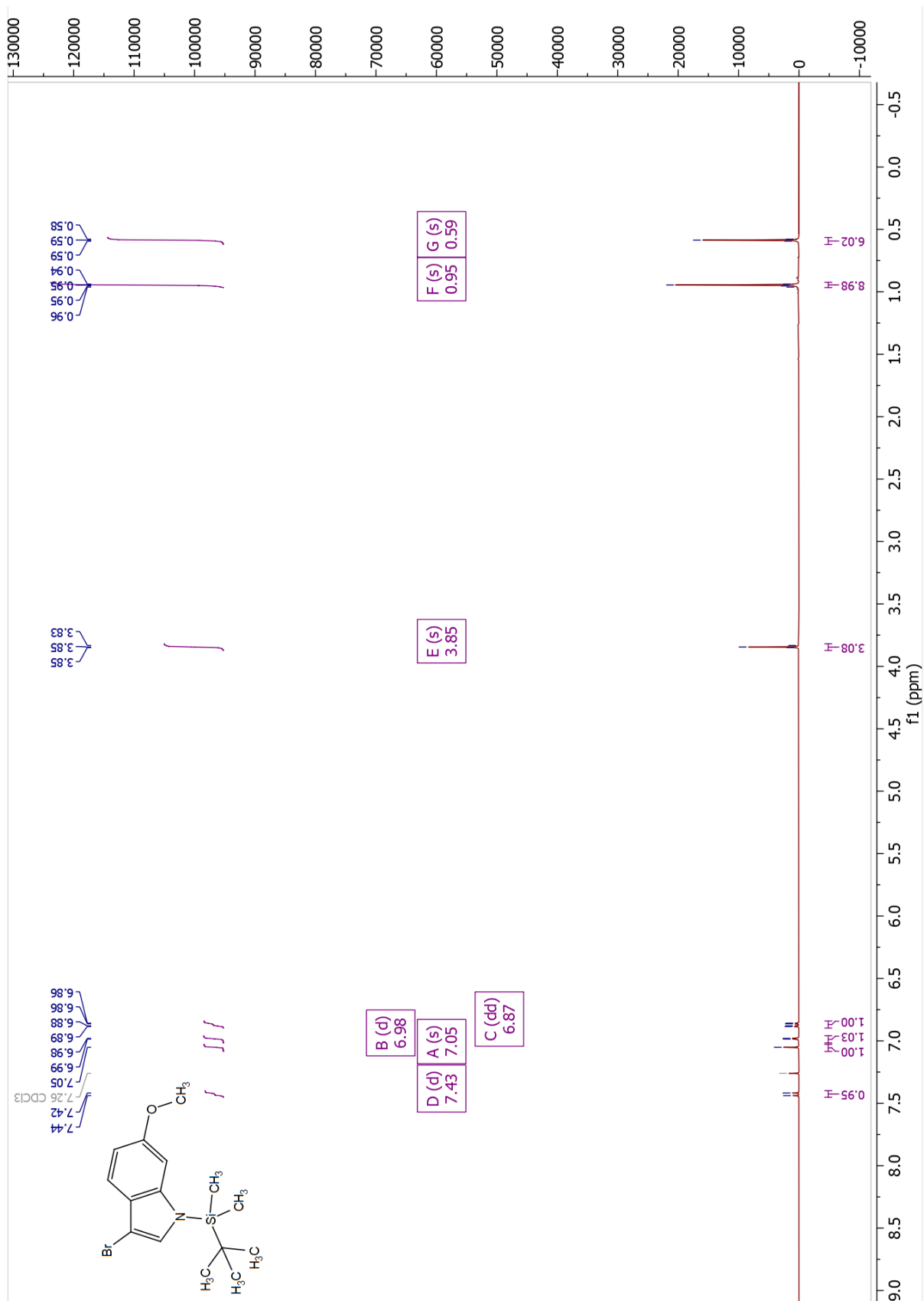


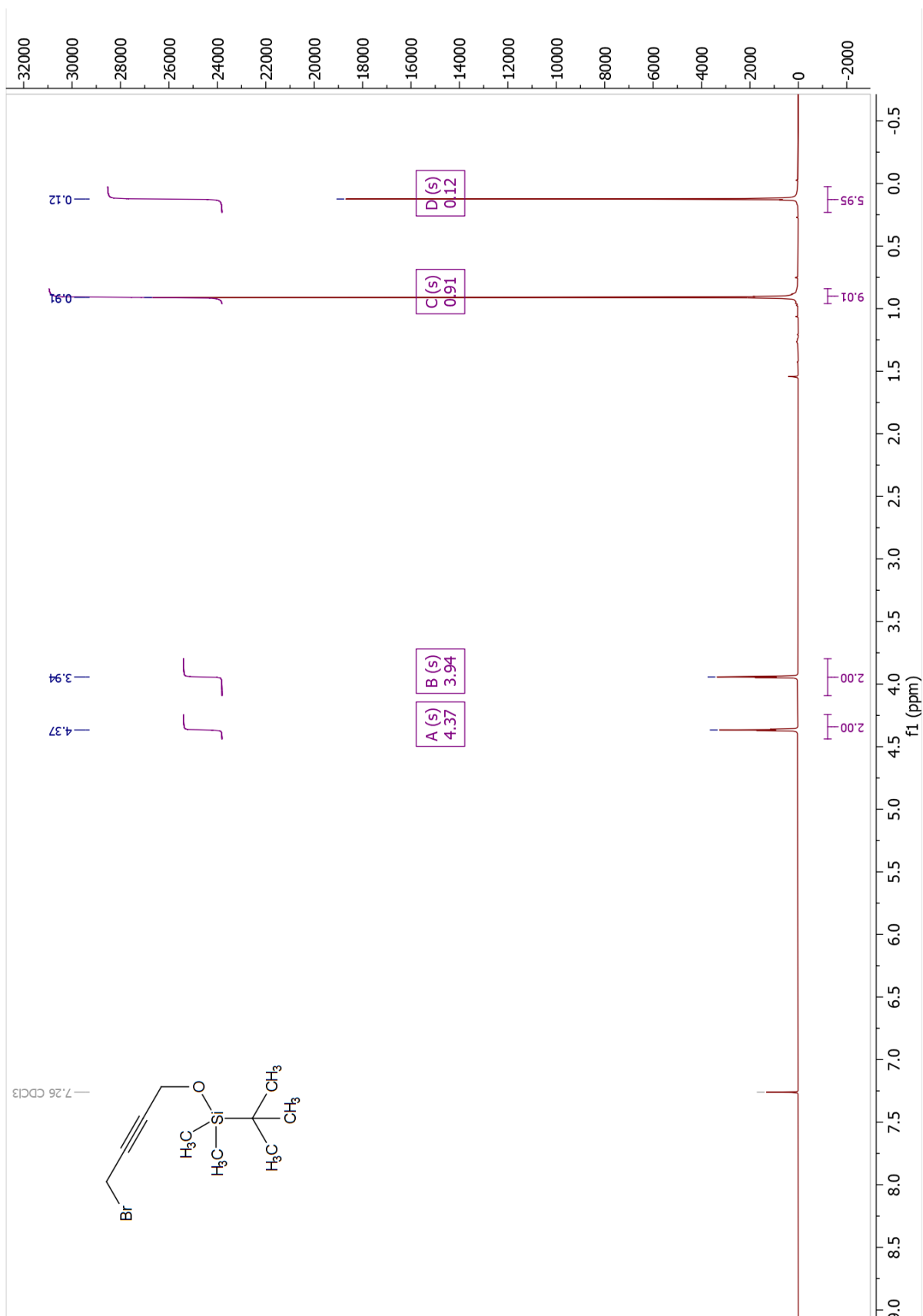


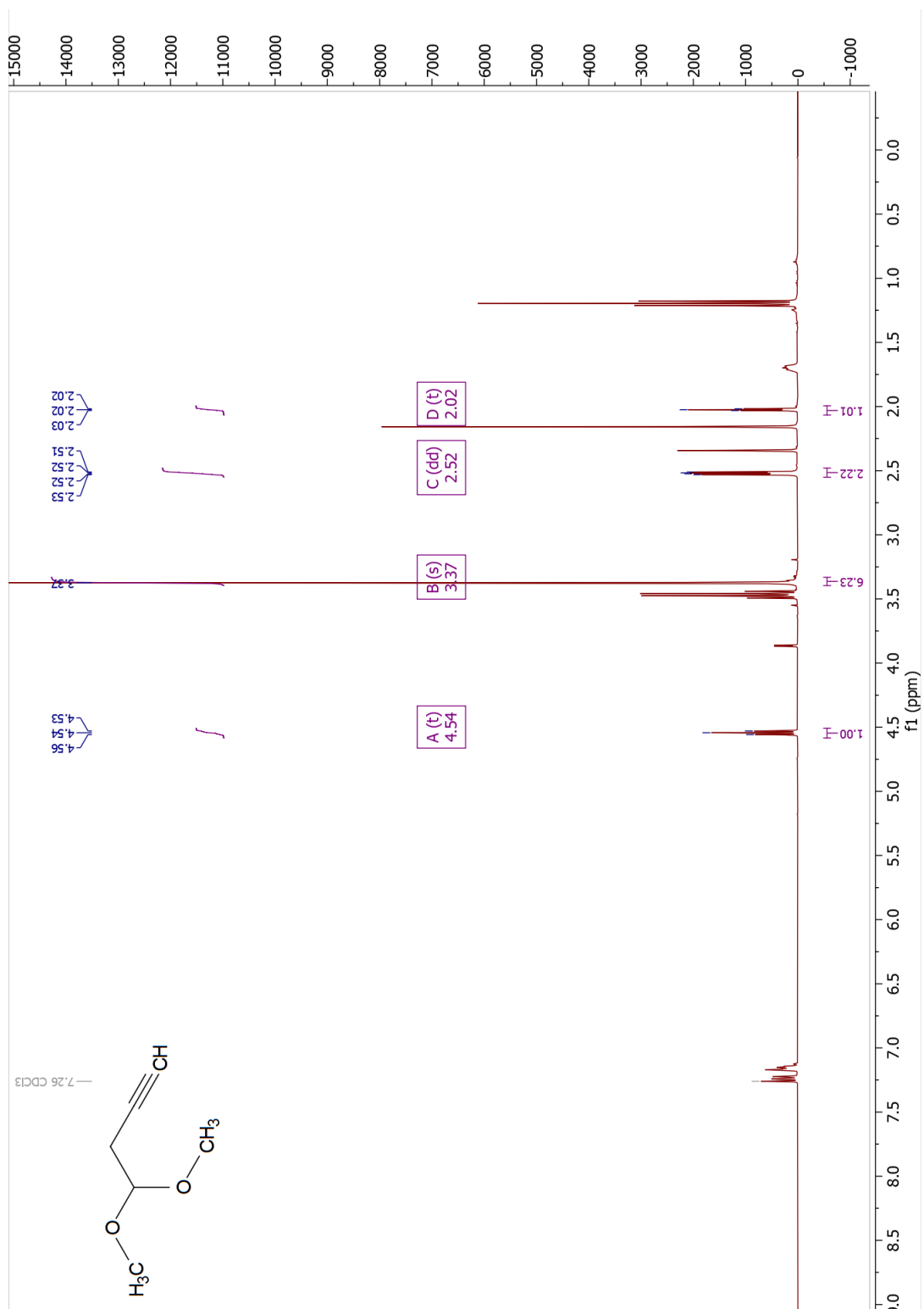


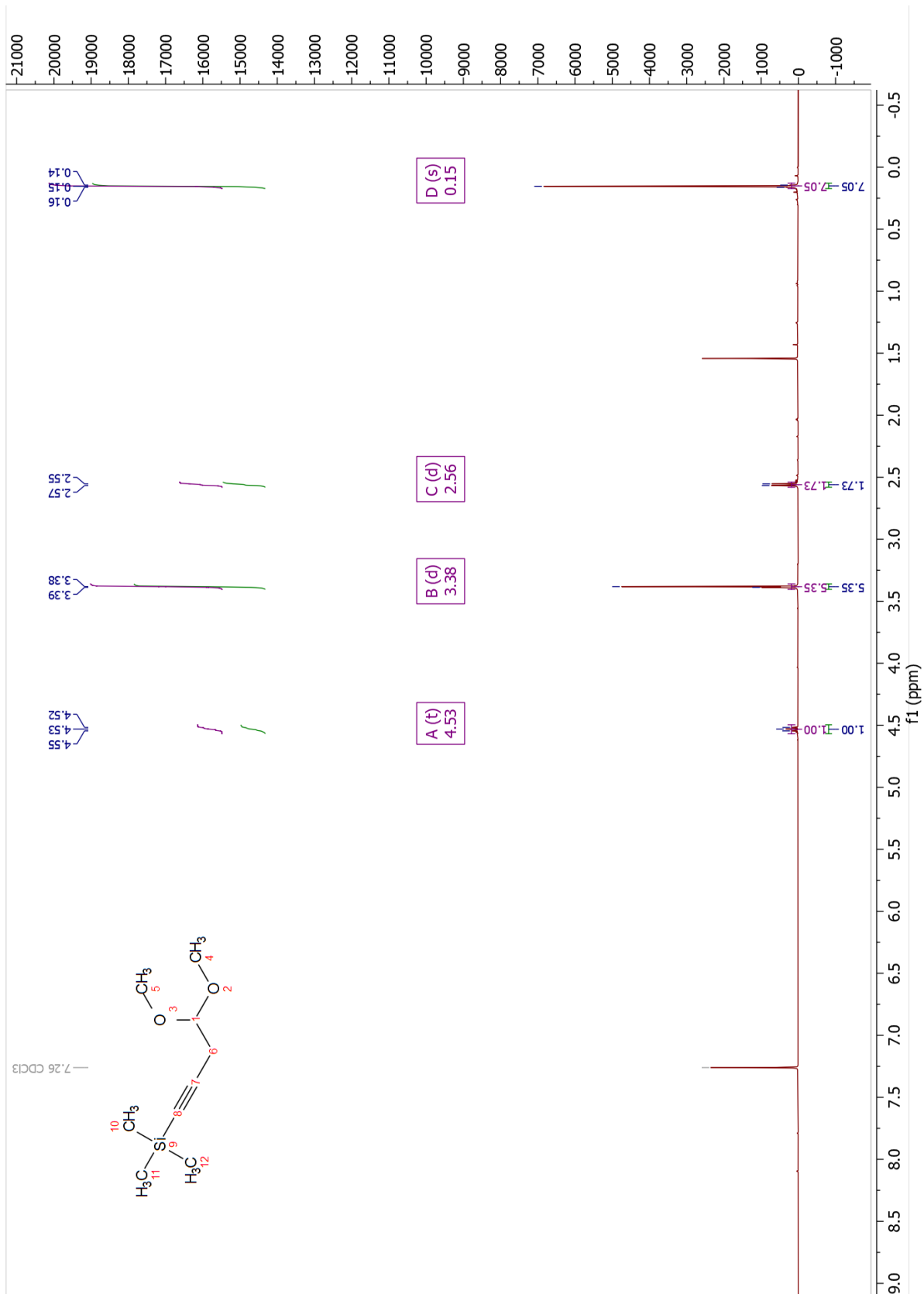


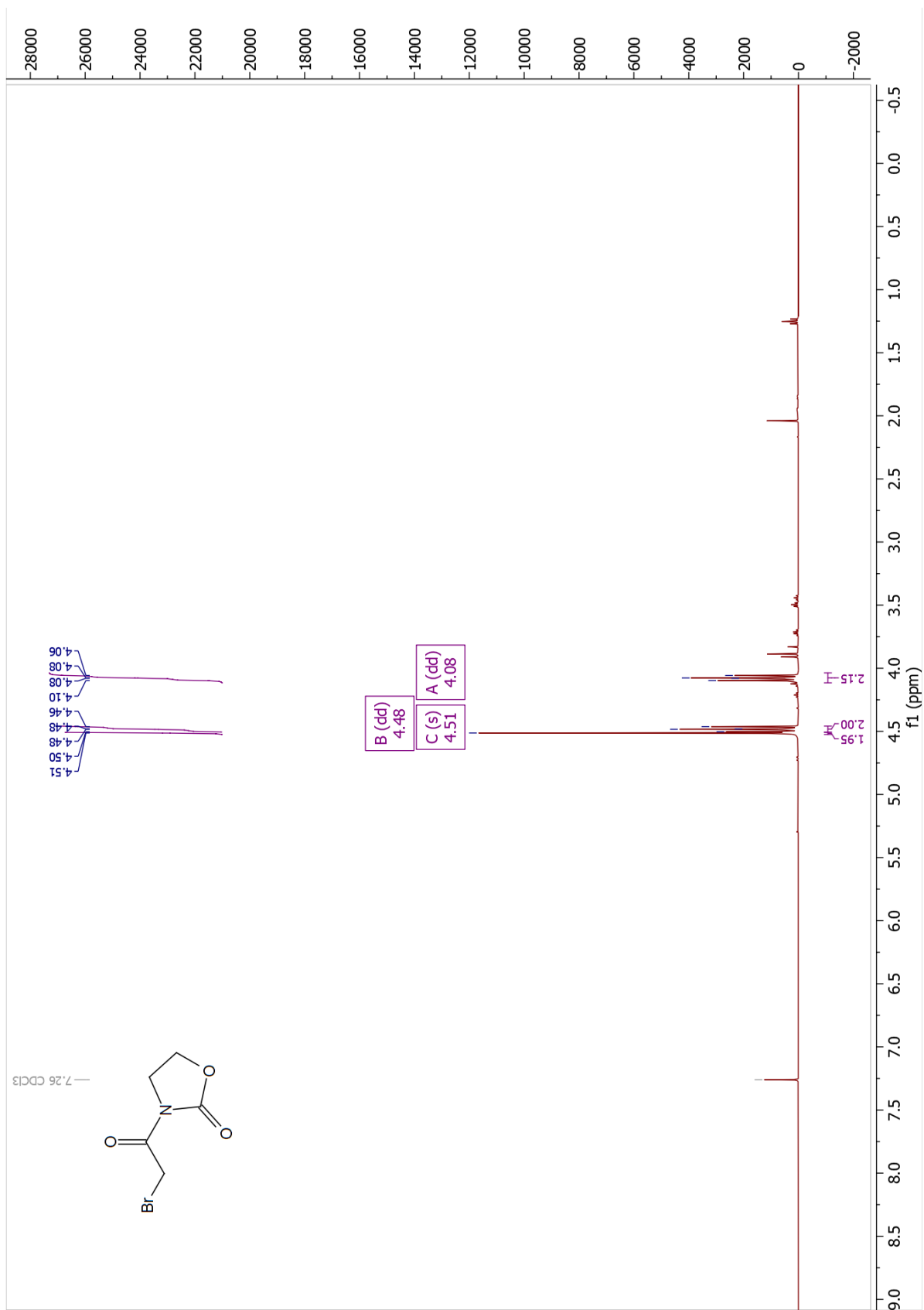


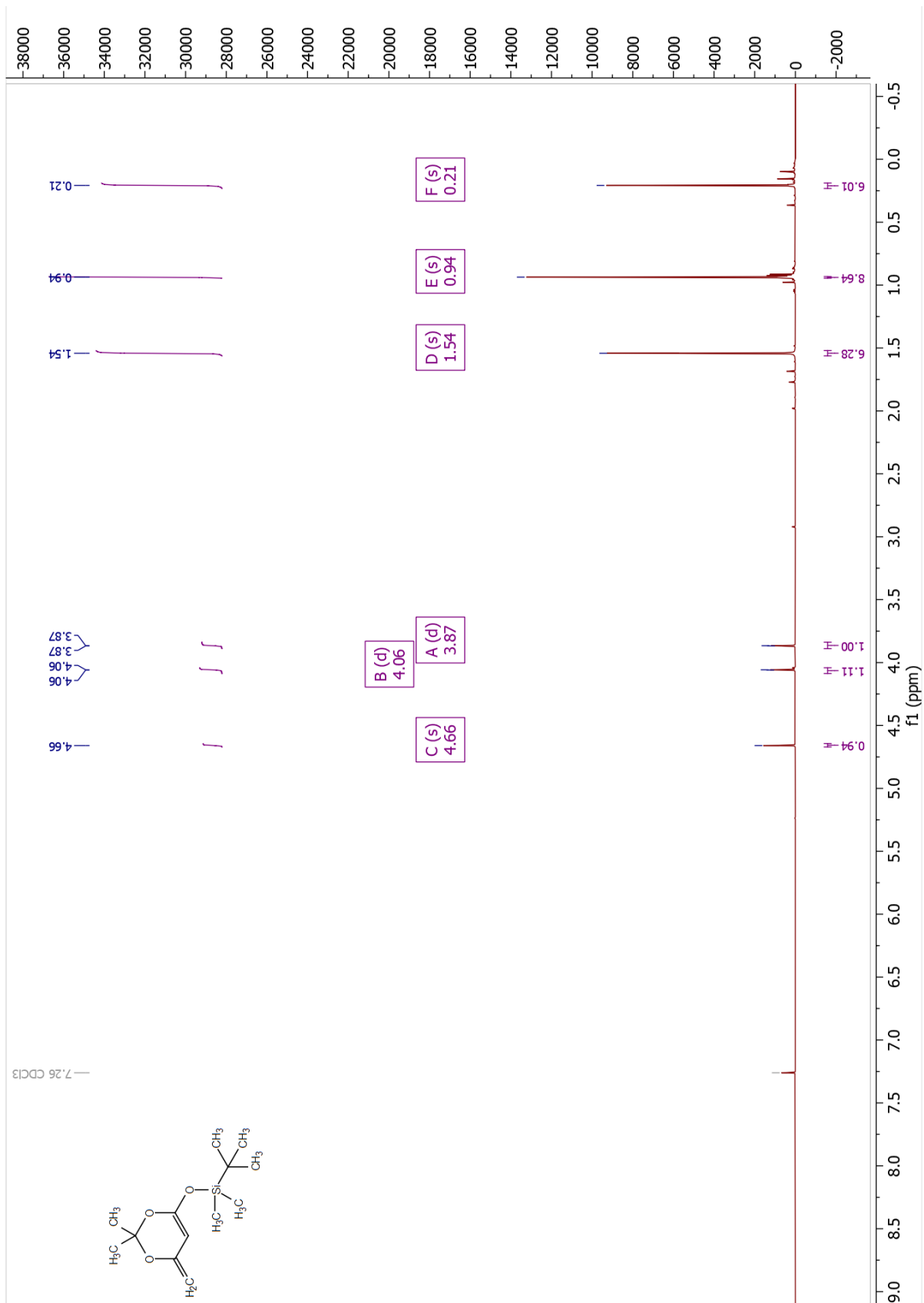




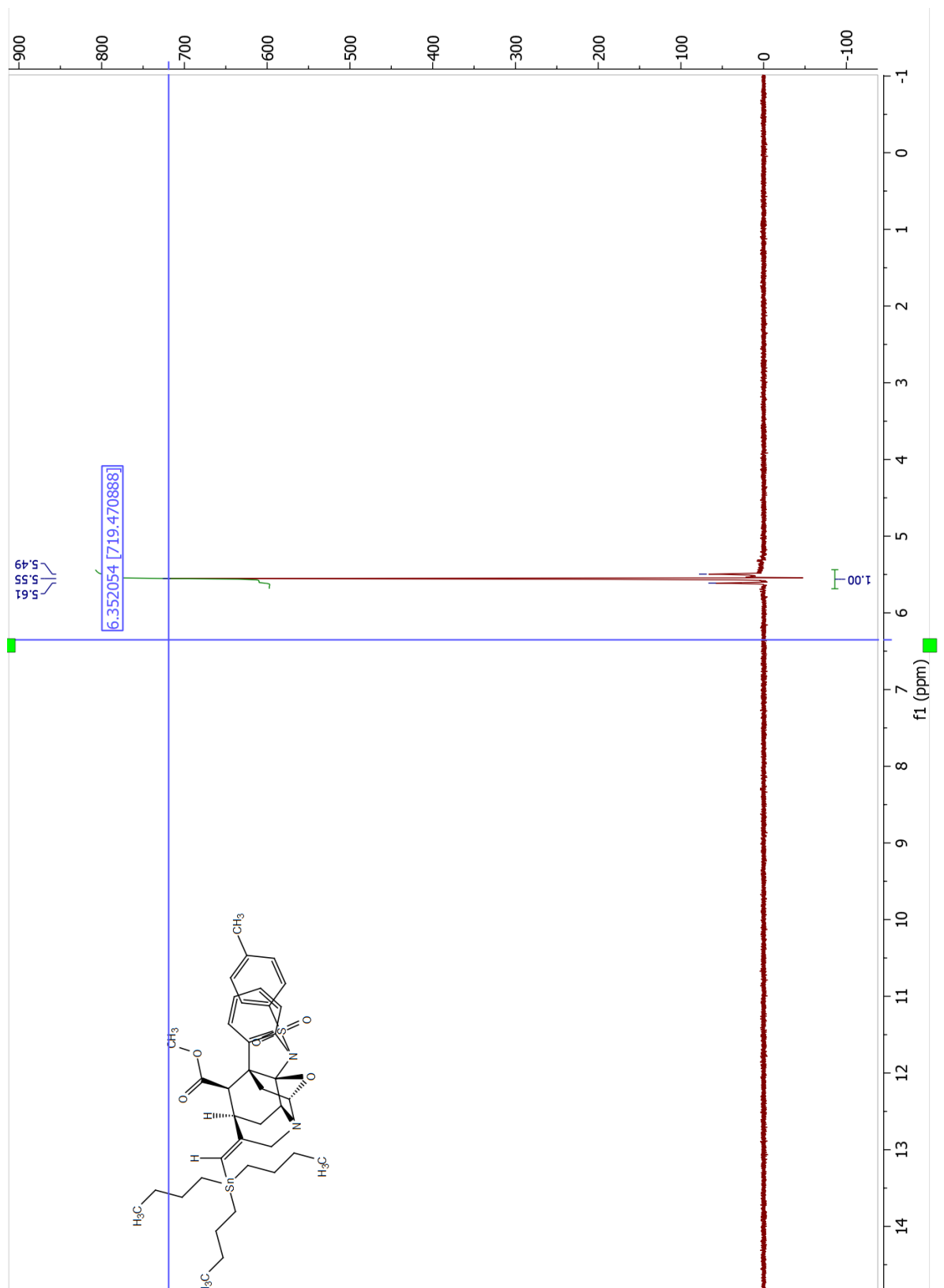


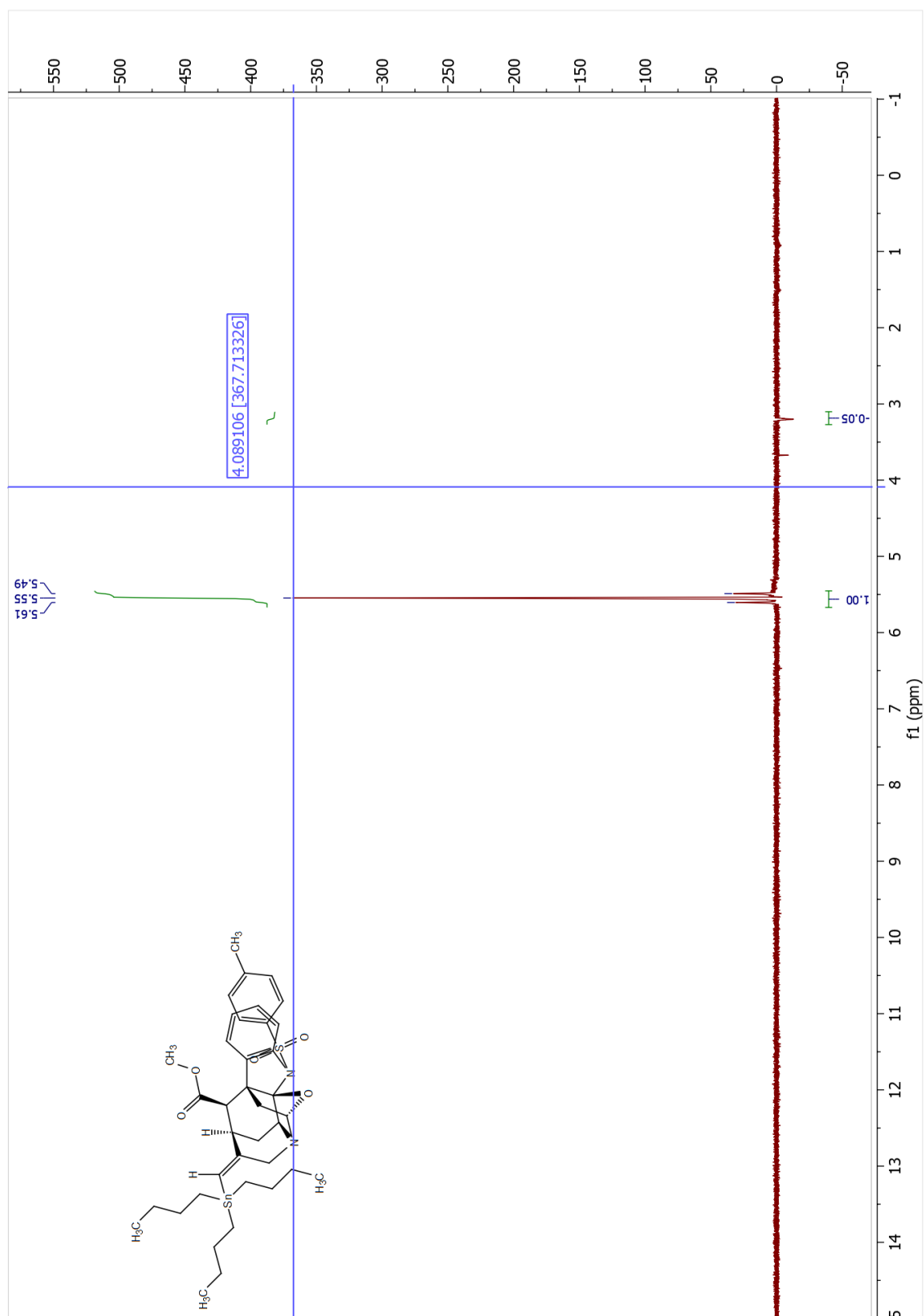




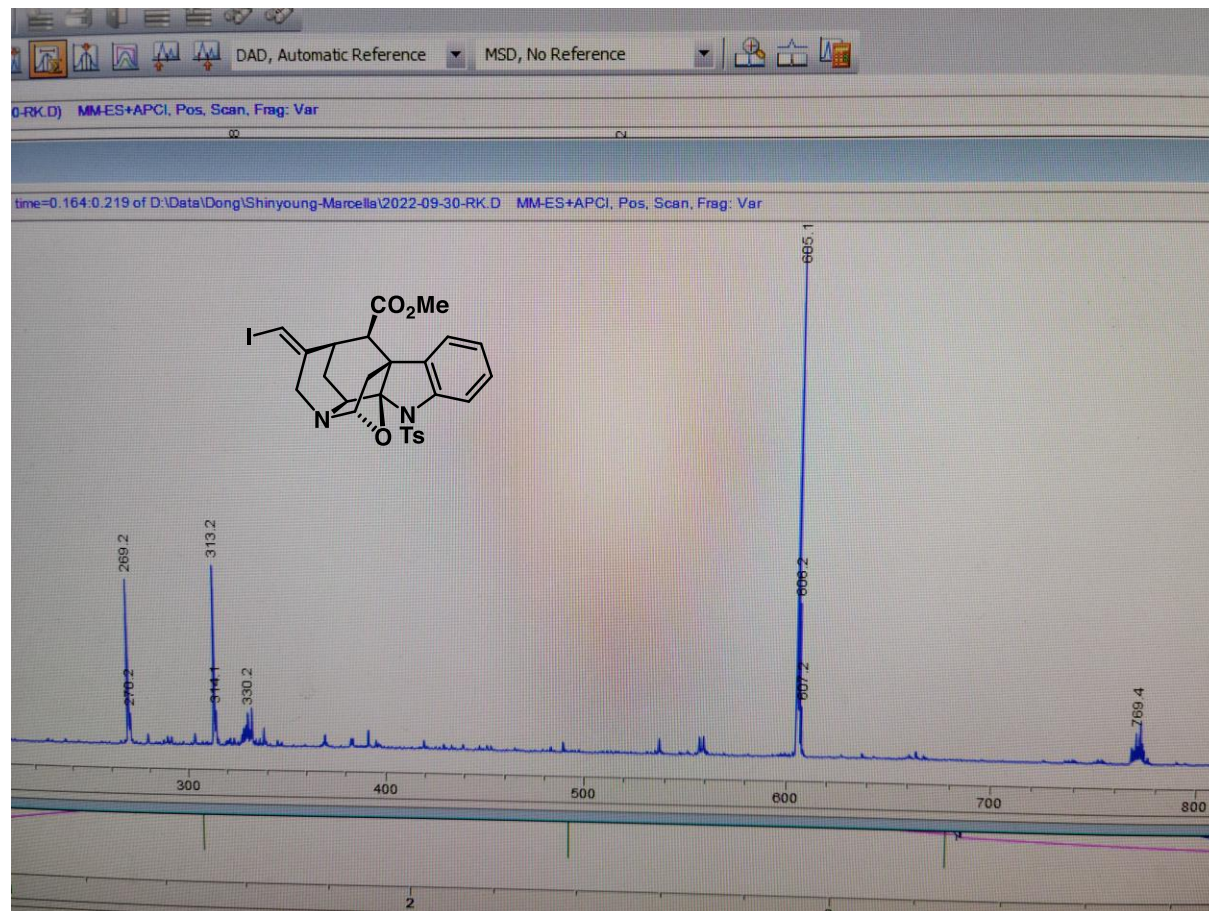


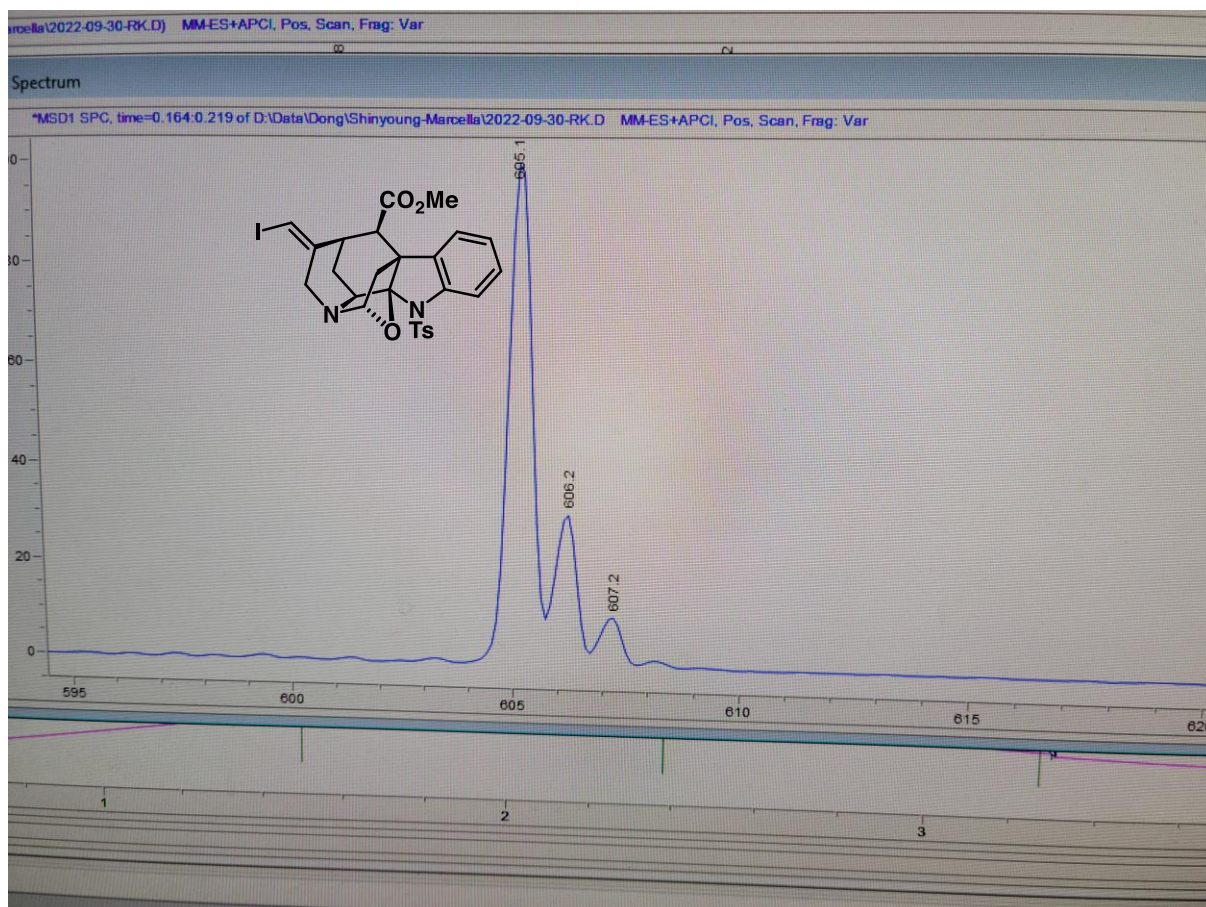
2.16 1D-NOE Spectra for Q-NOESY analysis



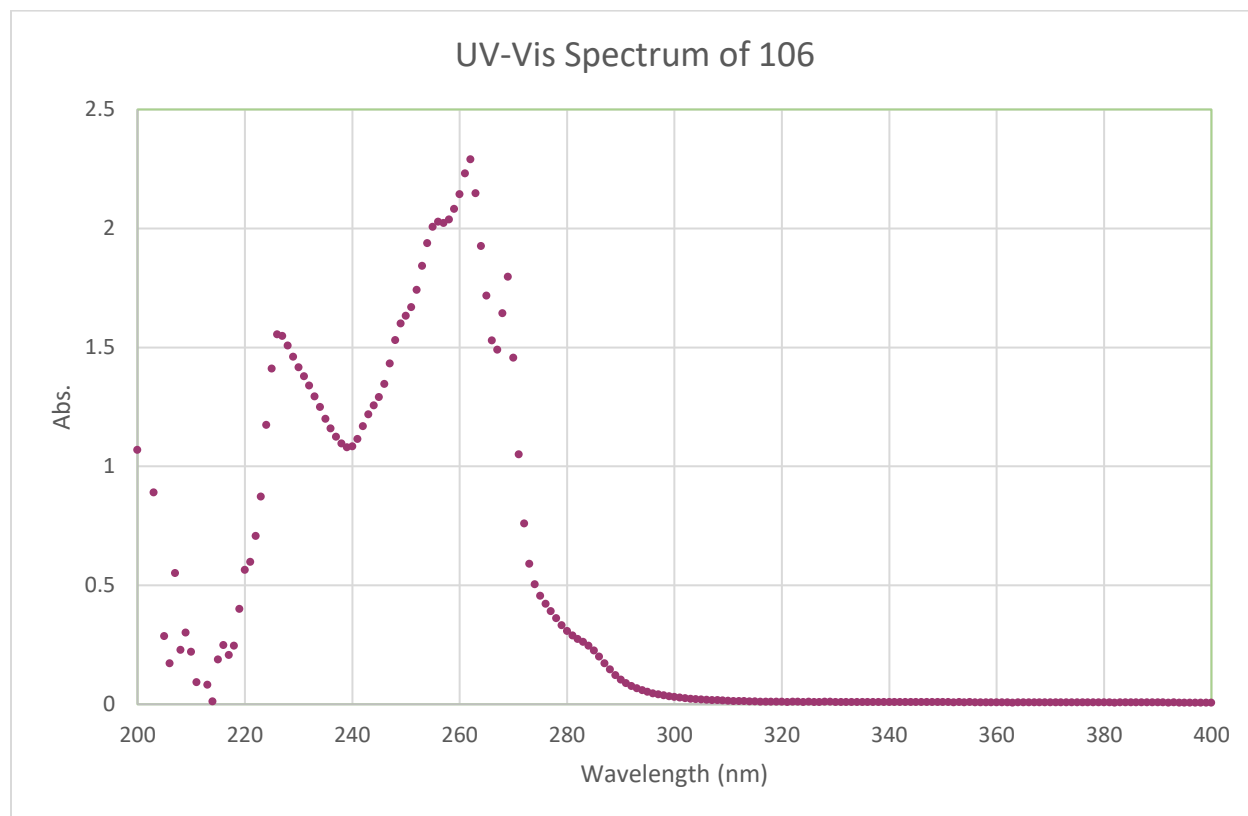


2.17 LC-MS Traces of Cyclized Vinyl Iodide





2.18 UV-Vis Data of Intermediate 106



Appendix A: Musings on Academia & the Human Experience

"I thought I was wrong once. I thought about it, and I was right!"

— Robert Kielawa

"We have a moral obligation to leave the world a better place than the world that we've found"

— Tim McIlrath

"It is well to remember that most arguments in favor of not trying a reaction are too flimsily based."

— R. B. Woodward

"The known is finite, the unknown infinite; intellectually we stand on an islet in the midst of an illimitable ocean of inexplicability. Our business in every generation is to reclaim a little more land, to add something to the extent and the solidity of our possessions."

— Thomas Henry Huxley

"Experience is the name so many people give to their mistakes."

— Oscar Wilde

"Intelligence without ambition is a bird without wings."

— Salvador Dali

"The riskiest thing we can do is just maintain the status quo."

— Bob Iger

"That you have been given a great intellect is not something to be proud of; it is a burden to bear...You must show yourself worthy of it, in will and action."

— Brent Weeks, *The Broken Eye*

"In death do triumph and failure humbly meet. We learn far less from victory than from defeat."

— Salman Rushdie, *Victory City*

“Strength does not make one capable of rule; it makes one capable of service.”

— Brandon Sanderson, *The Way of Kings*

“Cuius testiculos habes, habeas cardia et cerebellum.”

— Terry Pratchett, *Small Gods*

*“Marionettes dance afield beneath masterly hands - I stumble among them crossed by the strings
in tangled two-step and curse all these fools in their mad pirouette - I shall not live as they do
oh, no, leave me in my circles dance - these unbidden twitchings you see I swear on [Death's]
grave is artistry in motion.”*

— Steven Erikson, *Gardens of the Moon*

"The price of acquiescence is as nothing to the pain of refusal"

— Steven Erikson, *Deadhouse Gates*

“Maybe a long life does have to be filled with many unpleasant conditions if it's to seem long.”

— Joseph Heller, *Catch 22*

“He knew everything about literature except how to enjoy it”

— Joseph Heller, *Catch 22*

“Failure is a feeling long before it becomes an actual result”

— Michelle Obama, *Becoming*

*"Do you want to know the secret to surviving once you've gone down the rabbit hole?... Be a
rabbit."*

— Erin Morgenstern, *The Starless Sea*

"Open your eyes and see what you can with them before they close forever"

— Anthony Doerr, *All The Light We
Cannot See*

"All your life you wait and then it finally comes, and are you ready?"

— Anthony Doerr, *All The Light We
Cannot See*

"What is success? To laugh often and much; to win the respect of intelligent people and the affection of children; to earn the appreciation of honest critics and endure the betrayal of false friends; to appreciate the beauty; to find the best in others; to leave the world a bit better, whether by a healthy child, a garden patch or a redeemed social condition; to know even one life has breathed easier because you have lived. This is to have succeeded!"

— Ralph Waldo Emerson

"Ignorance is the ground of thought. Unproof is the ground of action... The only thing that makes life possible is permanent, intolerable uncertainty: not knowing what comes next."

— Ursula K LeGuin, *The Left Hand of
Darkness*

"When I was back in my apartment I took refuge in a hot shower. But even there I felt a vague unease, as if the hot water was not altogether real and reliable, and could not be counted on."

— Ursula K LeGuin, *The Left Hand of
Darkness*

"It is good to have an end to journey towards; but it is the journey that matters, in the end."

— Ursula K LeGuin, *The Left Hand of
Darkness*

"The snow of ignorance remains untrodden."

— Ursula K LeGuin, *The Left Hand of
Darkness*

"Sloth was literal death for us, while for them, it was the whole ambition of their lives."

— Ta-Nehisi Coates, *The Water Dancer*

"Besides, you're an apprentice in a proud trade, learning under the finest and most demanding masters it has to offer. Getting all the shit-work is excellent for your moral education."

— Scott Lynch, *Lies of Locke Lamora*

"Enlightenment! When it comes, it comes like a brick to the head"

— Scott Lynch, *Lies of Locke Lamora*

"The U.S.S.R. did so much bad"

— Julia Ruth Noel, *Picnic Tables*

"Don't blame a clown for acting like a clown. Ask yourself why you keep going to the circus."

— Unknown

"Innovation is progress in the face of tradition"

— Divad Sanders

"It felt like the world had divided into two different types of people, those who had felt pain and those who had yet to."

— Michelle Zauner, *Crying in H Mart*

"Reading is no longer a race that I might win, but a lifelong companion"

— Shannon Reed, *Why We Read*

"For the great things are not done by impulse, but by a series of small things brought together."

— Vincent van Gogh

"One day, there will be no more prey left anywhere, and London will have to stop moving"

— Philip Reeves, *Mortal Engines*

“The pleasure is deduced solely from the sense of identity – of repetition”

— Edgar Allen Poe

“Maturity is the capacity to endure uncertainty”

— John Huston Finley

“Supernatural is a word for anything that doesn’t fit your present understanding of the world”

— R.F. Kuang, The Poppy War

“Unless you want only ever to be a tiny modicum of existence that doesn’t understand it’s relation to the grander web of things, you will explore”

— R.F. Kuang, The Poppy War

“If we understood completely, then we would be gods.”

— R.F. Kuang, The Poppy War

“Was she now a goddess or a monster? Perhaps neither. Perhaps both.”

— R.F. Kuang, The Poppy War

“There she is, a human being, diving into the unknown, and she is wide awake.”

— Ottessa Moshfegh, My Year of Rest &
Relaxation

Appendix B: Auditory Accompaniments For Experimental Enthusiasm

Listed in chronological order by discovery:

Still Feel by Half Alive

Inhale by Duke Dumont, Ebenezer

Say So by Doja Cat

The Difference by Flume, Toro y Moi

Si Veo a Tu Mama by Bad Bunny

Something's Got To Give by Labrinth

Levitating by Dua Lipa

Too Sweet by Hozier

WAP (feat. Megan Thee Stallion) by Cardi B

Alive by NEEDTOBREATHE

Roses – Imanbek remix by SAINT JHN

Fuck Your Sunshine by Łaszewo

Grand Budapest by Wordsplayed, Weathrman

Heavy Hearted by The Jungle Giants

Green Light by Lorde

Oh My God by Adele

15 Minutes by Julian Lamadrid

Witchyman by Cain Culto

BREAK MY SOUL by Beyoncé

Two Sugars by Tai Verdes

Planet X by Calimossa

BLAME THE MOON by Cain culto

From Fire by Perta

Dance The Night by Dua Lipa

Sunflower by Post Malone, Swae Lee

You Wish by Flyana Boss

Triumph by Bishop Briggs

HOT TO GO! By Chappell Roan

Appendix C: Miscellaneous Experimental Tips, Tricks, & Techniques

1. Chemistry is hard enough and requires you to be at 100% to do it well. Therefore, you should prioritize doing whatever you need to do to keep you at 100%. Not burning out pays off in the long run, and the short run too.
2. When rotary evaporating something under inert atmosphere, evacuate and backfill the rotavap before putting on your flask.
3. You can pipette silica to fill Snyder/Pipette columns.
4. Always try to get better, even for something as trivial as fitting more spots on a TLC.
5. Even if you have a system for doing something or performing a given reaction, ask yourself if you can still do it better.
6. Karl-Fisher titration is your friend.
7. When writing your thesis SI, add some autocorrect shortcuts for key phrases like “dried over Na_2SO_4 ,” etc.
8. Label key reactions in the table of contents at the front of your notebook