Total Synthesis of Imidazole-Containing β-Carboline Alkaloids and Pyrrole-Imidazole Alkaloids

by

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Abstract

Total Synthesis of Imidazole-Containing β-Carboline Alkaloids and Pyrrole-Imidazole Alkaloids

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The first part in this dissertation focuses on the development of an enantioselective total synthesis of villagorgin A, from another natural product haploscleridamine. Haploscleridamine was targeted first as it was thought that a successful approach to this family member would permit access to the other congeners through minor modifications, including conversion to villagorgin A. Moreover, villagorgin A has just one additional carbon atom compared to haploscleridamine, the introduction of which can be envisioned through a Pictet-Spengler reaction with formaldehyde. On completion of the haploscleridamine synthesis, attention was turned to the brominated congener, lissoclin C. Lissoclin C can be accessed from the same intermediate 3-piperidinone used en route to haploscleridamine by reaction with a different hydrazone derivative.

The second part of this dissertation illustrates an approach, which relied on ring closing metathesis (RCM) to afford the key intermediate piperidinone which in turn was constructed from a protected histidine derivative. The RCM precursor was accessed by N-allylation and Grignard chemistry. Reduction followed by the installation of the indole moiety, put the finishing touches on the core framework. Deprotection then gave haploscleridamine. A subsequent hexafluroisopropanol-mediated Pictet-Spengler reaction provided villagorgin A.

The third part of this dissertation describes the development of a synthetic route to assess the stereochemical purity of both haploscleridamine and villagorgin A. First the same synthetic sequence was conducted but with racemic histidine. Samples of racemic and non-racemic haploscleridamine and villagorgin A were assessed by HPLC using chiral column, they essentially gave indistinguishable results; each showed essentially a 1:1 mixture of both enantiomers. These results implied that our nominally asymmetric syntheses had delivered almost racemic products. An approach includes to minimize epimerization was developed avoiding the use of DIBAL-H in the reduction step. Repetition of the prior sequence delivered scalemic haploscleridamine and villagorgin A in 30% ee.

The fourth part of this dissertation addresses the total synthesis of a pyrrole-imidazole alkaloids named ageliferin. It describes a method to construct the complete framework of ageliferin via a stereoselective intramolecular Diels Alder reaction and

a detailed discussion of the problems that arise during the attempted installation of 2-amino group on the imidazole ring. Two different approaches were pursued for incorporation of the C2 amine to complete total synthesis of ageliferin either via C2 amination pre-Diels-Alder or C2 amination post Diels-Alder.

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List of abbreviations

BOC	tert-Butoxycarbonyl
Cbz	Benzyloxycarbonyl
CDI	1-1'-Carbonyldiimidazole
CSA	(1R)-(−)-10-Camphorsulfonic acid
DCC	N, N′-Dicyclohexylcarbodiimide
DIBAL-H	Diisobutylaluminum hydride
DIEA	N, N-Diisopropylethylamine
DME	Dimethoxyethane
DMF	Dimethylformamide
DMP	Dess-Martin periodinane
EDCI	N-(3-Dimethylaminopropyl)-N′-ethylcarbodiimide hydrochloride
ESI-MS	Electrospray Ionization Mass Spectrometry
HFIP	1,1,1,3,3,3-Hexafluoro-2-propanol
HOBT	1-Hydroxybenzotriazole

KHMDS	Potassium bis(trimethylsilyl)amide
LDA	Lithium diisopropylamide
NBS	N-Bromosuccinimide
TBAF	Tetrabutylammonium fluoride
TFA	Trifluoroacetic acid
TFE	2,2,2-Trifluoroethanol
THF	Tetrahydrofuran
TMS	Trimethylsilyl
$TrisN_3$	2,4,6-Triisopropylbenzenesulfonyl azide
TsN_3	*p*-toluene sulfonic azide

CHAPTER 1

INTRODUCTION

1.1 Natural Products and their Importance as Drugs

Natural products and related congeners have historically been an incredible source of therapeutic agents.[1] It has long been recognized that natural product structures have the characteristics of high chemical diversity, biochemical specificity and structural novelty that make them favorable as lead structures for drug discovery. During the last few decades, marine sources have proven to be among a most promising source of natural products for drug discovery.[2] Traditionally plants and terrestrial microorganisms have been the most important focus in the search for new drug candidates from nature. However, in current years marine organisms such as sponges, tunicates, shell-less molluscs and others are progressively attracting more attention due to their production of structurally unique and pharmacologically active compounds. Today, many new chemotherapeutic agents are synthetically derived, based on "rational" drug design. The study of natural products has advantages over de novo drug design is that it often leads to materials having new structural features with novel biological activity. Nature remains one of the most important sources of pharmacologically active compounds in the search for drugs against life-threatening diseases such as microbial infections, diseases of the heart and the circulatory system, cancer, and others. However, the process of isolating organic molecules from their

natural sources can be expensive in terms of committed time, material expense and availability (access due to adverse political issues or disappearing ecosystem of the source organism). These issues can make it hard to explore their complete biological profile due to inadequate material supply. On the other hand, this difficulty offers a chance to researchers to develop a synthetic approach to these molecules thereby, facilitating exploration of their molecular properties and often permitting confirmation of their structural identities and driving innovation in synthesis.

1.2 Imidazole-Containing β-Carboline Alkaloids

Indole alkaloids derived from marine sources show unique promise in the development of new drug leads.[3] They are recognizable by their tricyclic, pyridine-fused indole framework (where the rings are labelled as A, B and C), and categorized according to the degree of saturation (unsaturated β-carbolines, C ring partially saturated: 3,4-dihydro and C ring fully saturated: 1,2,3,4-tetrahydro) and the position of the N-atom in the C-ring as α-, β-, γ- or δ-carbolines.[4] (**Figure- 1.1**) These alkaloids show a variety of biological activities including cytotoxicity, antiviral, antiparasitic, anti-inflammatory, serotonin antagonism, Ca-releasing, calmodulin antagonism, and other pharmacological activities. Imidazole-containing alkaloids, most notably the oroidin family,[5] are a large collection of sponge-derived secondary metabolites, similarly indole-containing alkaloids abound, but alkaloids containing both

frameworks are less common. Although β-carbolines are common structural elements, imidazole-containing β-carbolines are not and those containing the lower oxidation state tetrahydro-β-carboline framework are rarer still. During the last few years, our lab has been interested in the synthesis of indole alkaloids containing an imidazole moiety isolated from different natural sources including, haploscleridamine, villagorgin A, villagorgin B and lissoclin C.

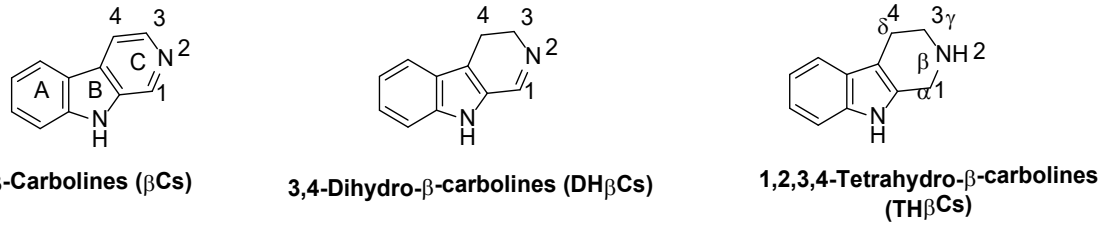


Figure 1. 1: The Basic Structural Units of βC, DHβC, THβC

1.3 Example and Pharmacological Importance of β-Carboline Imidazole Alkaloids

Imidazole containing β-carboline alkaloids are a family of natural and synthetic indole-containing heterocyclic compounds, and they are broadly distributed in nature.[6] These alkaloids have been of interest, because of their diverse biological activities. Their pharmacological activity makes them attractive as sedative, anxiolytic, hypnotic, anticonvulsant, antitumor, antiviral, antiparasitic or antimicrobial drug candidates.[7, 8] Haploscleridamine (**1**) is a novel tryptamine-derived alkaloid[9] isolated from a marine sponge of the order *Haplisclerida* collected in Palau and described in 2002 by Faulkner and coworkers.[10] This novel β-tetrahydrocarboline was shown to inhibit cathepsin K (IC_{50} = 26 μM), a cysteine protease, involved in osteoporosis and thus this natural product may serve as a lead compound in the development of treatments for this disease. The brominated analog, lissoclin C (**2**) was one of five alkaloids isolated from a tropical ascidian, *Lissoclinum* sp., and while the crude extract was active against *Candida albicans*, the purified alkaloid was inactive against the same organism in a disk diffusion assay.[11] Further related compounds include two diastereomeric carboxyl-containing derivatives, hyrtiorecticulin A (**3**) and B (**4**) have been isolated from the marine sponge *Hyrtios reticulatus.*[12] Both of these natural products inhibited the E1-catalyzed ubiquitin-activation reaction with IC_{50} values of 2.4 and 35 μM respectively.[12] Related, but more highly functionalized, examples have been described, in particular villagorgin A (**5**) which has an additional carbon atom and ring compared to haploscleridamine (**1**),[13] formally requiring a Pictet-Spengler reaction from **1** for its synthesis. Villagorgin A (**5**) and the related and more highly

oxidized congener villagorgin B (**6**) were described as exhibiting acetylcholine antagonist activity and inhibiting human platelet aggregation, however their potency in these assays was not reported.[13] Other, more highly oxidized β-carbolines containing imidazole moieties have been isolated from marine sources, for example hainanerectamine C (**7**),[14] gesashidine (**8**)[15] and dragmacidonamines A (**10**) and B (**9**)[16] (**Figure 1.2**).

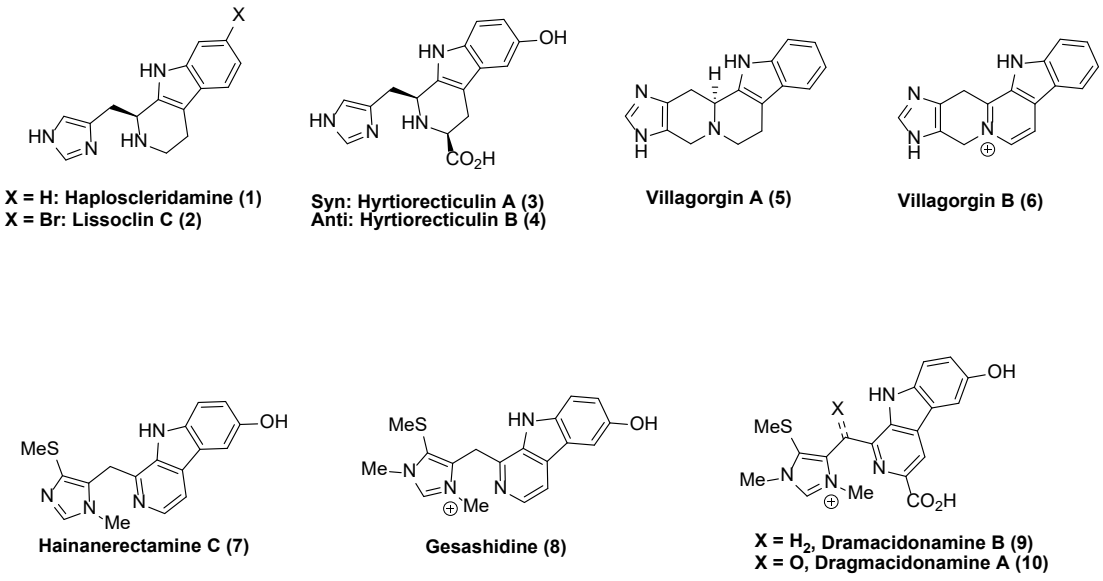
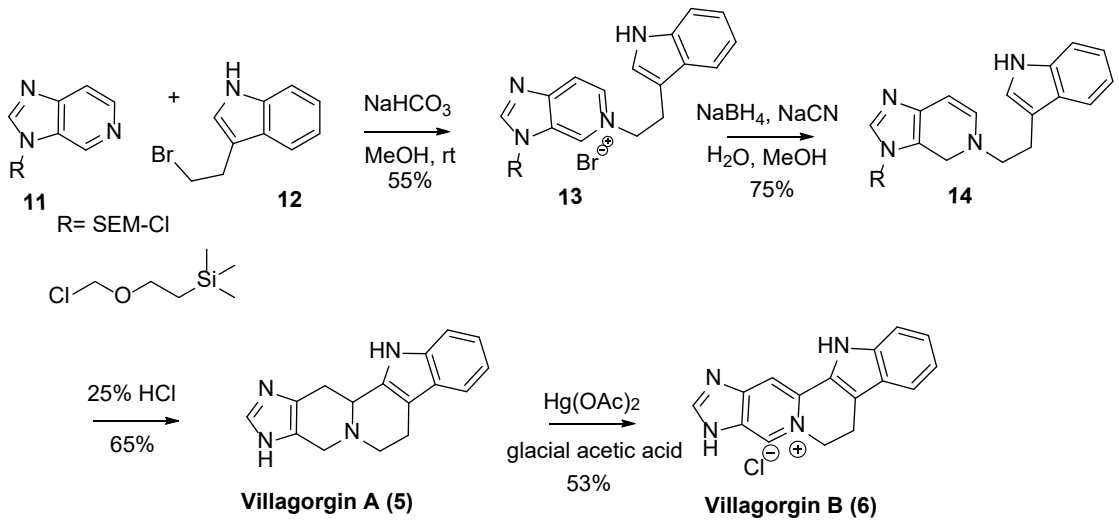


Figure 1.2: Selected Indole-Imidazole Alkaloids

1.4 Reported Synthesis of Villagorgin A

The interesting biological activities of villagorgin A (**5**) and villagorgin B (**6**) alkaloids make them attractive synthetic targets. However, since their isolation in 1993, villagorgin A and villagorgin B have not attracted substantial synthetic attention. Kuehne and coworkers have been the only group so far to publish a synthetic approach to these two natural products, leading to racemic material. According to their synthetic route, illustrated in (**Scheme 1.1**) a reduction and a Pictet-Spengler-like cyclization of an indolylethylimidazopyridium salt (**13**). Subsequent oxidation of villagorgin A (**5**) with mercuric acetate gave villagorgin B (**6**).[17]

Scheme 1.1 Synthesis of Racemic Villagorgin A



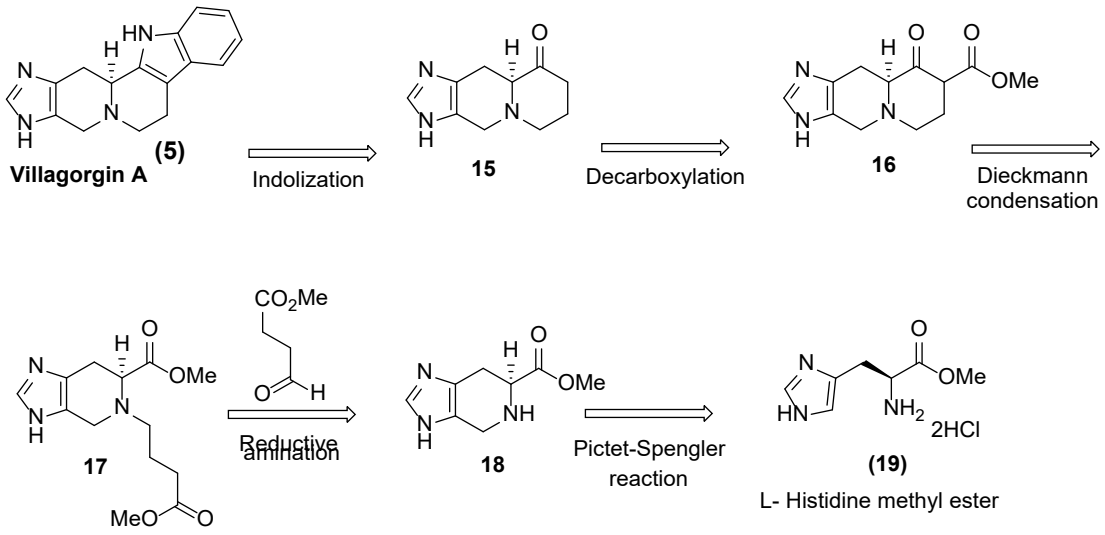
1.5 Preliminary Approaches and Results En Route to Synthesis Villagorgin A

In total, three different routes to gain access to villagorgin were investigated in our group. It was proposed initially to assemble the key intermediate either through two different Dieckmann cyclizations[18, 19] of a diester or through ring-closing metathesis of the appropriate diene (**Scheme 1.2, 1.3 and 1.4**).

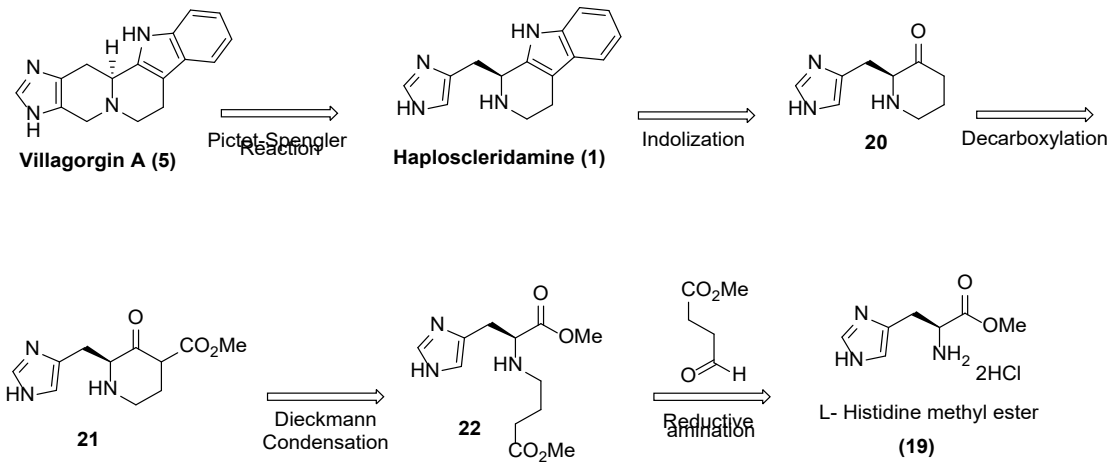
Two different retrosynthetic routes involving the Dieckmann condensation were proposed that differ in the timing of the Pictet-Spengler reaction (Scheme 1.2 and 1.3). In route I, the retrosynthetic approach employs a Pictet-Spengler reaction early in the sequence followed by Fischer indole synthesis. Alternatively in route II, a potentially versatile and attractive route for the synthesis of imidazolyl β-carboline ring systems using the L-histidine methyl ester (**19**), as starting material was

designed. Koda *et al.* explored the synthesis of villagorgin A (**5**) via a Dieckmann condensation reaction followed by decarboxylation to assemble the key intermediate **20** which was then to be used in Fischer indole synthesis to provide haploscleridamine (**1**). Subsequently, a Pictet-Spengler reaction[19] of haploscleridamine (**1**) will be employed in the later stages of the synthesis to deliver villagorgin A.

Scheme 1.2 Retrosynthetic Analysis (Route I) for Villagorgin A



Scheme 1.3 Retrosynthetic Analysis (Route II) for Villagorgin A

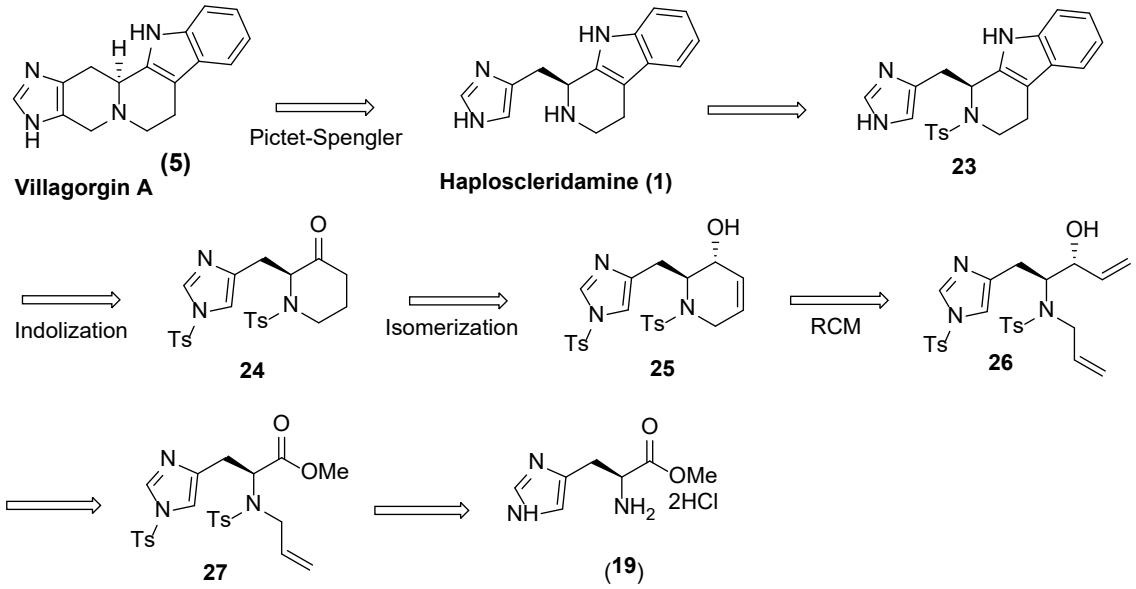


These Dieckmann routes were synthetically appealing because they potentially give access to non-racemic haploscleridamine (**1**) and villagorgin A (**5**). Unfortunately, while access to derivatives related to **17** and **22** was accomplished, the Dieckmann reactions themselves were unsuccessful. In addition, this condensation is a potentially risky step in this approach, due to the presence of acidic α-carbonyl protons in the substrate which means that it can potentially undergo racemization under basic conditions typically employed for Dieckmann reaction.

In order to avoid this potential for racemization, Koda *et al.* investigated a third approach towards villagorgin A (**5**); a second-generation approach involving ring closing metathesis (RCM). Starting from L-histidine after several steps, including a key ring closing metathesis of diene **26**, the key piperidinone **24** was obtained (**Scheme 1.4**).

Koda *et al.* attempted several variants of the classical Fischer-indole synthesis to construct indole **23**. For example, attempts to perform the reaction under acidic conditions such as PPA, conc. HCl, and $ZnCl_2$ were not successful.[20] By this time, Koda *et al.* had become aware of an alternative indole synthesis developed by the Buchwald lab which involved a hydrazone transfer reaction in the presence of *p*-$TsOH \cdot H_2O$[21, 22] Only partial success was observed when initial experiments were conducted with *p*-$TsOH \cdot H_2O$, phenyl hydrazine and ketone **24** resulting in a low yields of compound **23**. Numerous byproducts were formed including unreacted starting materials (hydrazone and mono-tosyl protected ketone), which led to difficulties in purification by column chromatography. These difficulties not withstanding if optimized a potential solution to completing the synthesis was now in hand.

Scheme 1.4 Second Generation Retrosynthesis of Villagorgin A



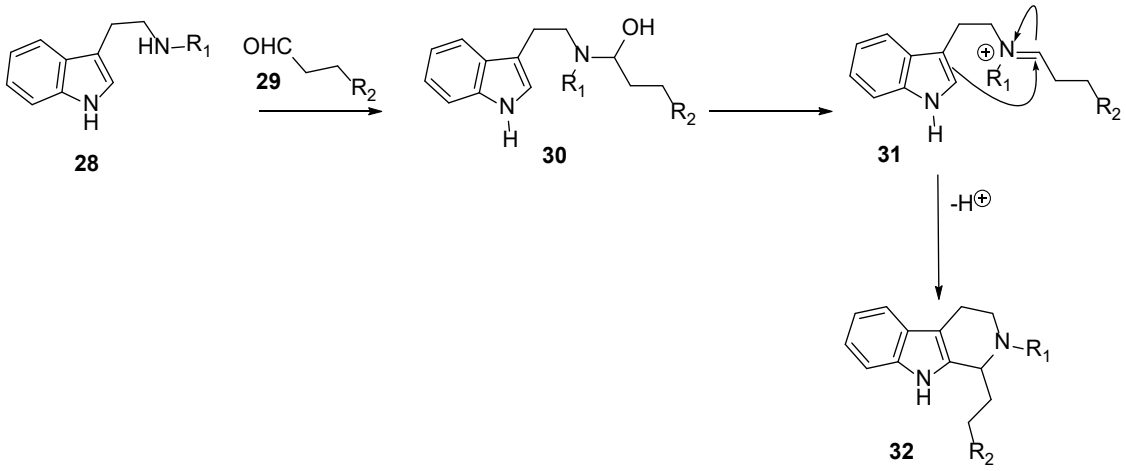
1.6 Key Reactions for Completion of Tetrahydro-β-carboline Ring

1.6.1 Pictet-Spengler Reaction

The Pictet-Spengler reaction is one of the most efficient synthetic methods for the construction of privileged pharmacophores such as tetrahydroisoquinolines (THIQs), tetrahydro-β-carbolines (THBCs), and poly heterocyclic moieties.[23] The Pictet-Spengler reaction has been employed in tandem reactions sequenced with the reactions including ring-closing metathesis, isomerization, Michael addition, and gold- or Brønsted acid-catalyzed N-acyliminium cyclization.[24] Moreover the Pictet-Spengler reaction

has also been successfully employed in solid-phase synthesis, delivering products with various structures, for example peptidomimetics, synthetic heterocycles, and natural compounds. Finally, the enzymatic version of Pictet-Spengler has been reported in biosynthesis, biotransformations, and bioconjugations.[23] The mechanism of the Pictet-Spengler reaction proceeds by initial formation from indolylethylamine **28** and a carbonyl compound **29** through an intermediate carbinolamine **30**, which upon loss of water forms an iminium ion **31**. The iminium ion **31**, undergoes nucleophilic attack by the indole to construct an annulated tetrahydro-β-carboline moiety **32** (**Scheme 1.5**).[25]

Scheme 1.5 Pictet-Spengler Mechanism

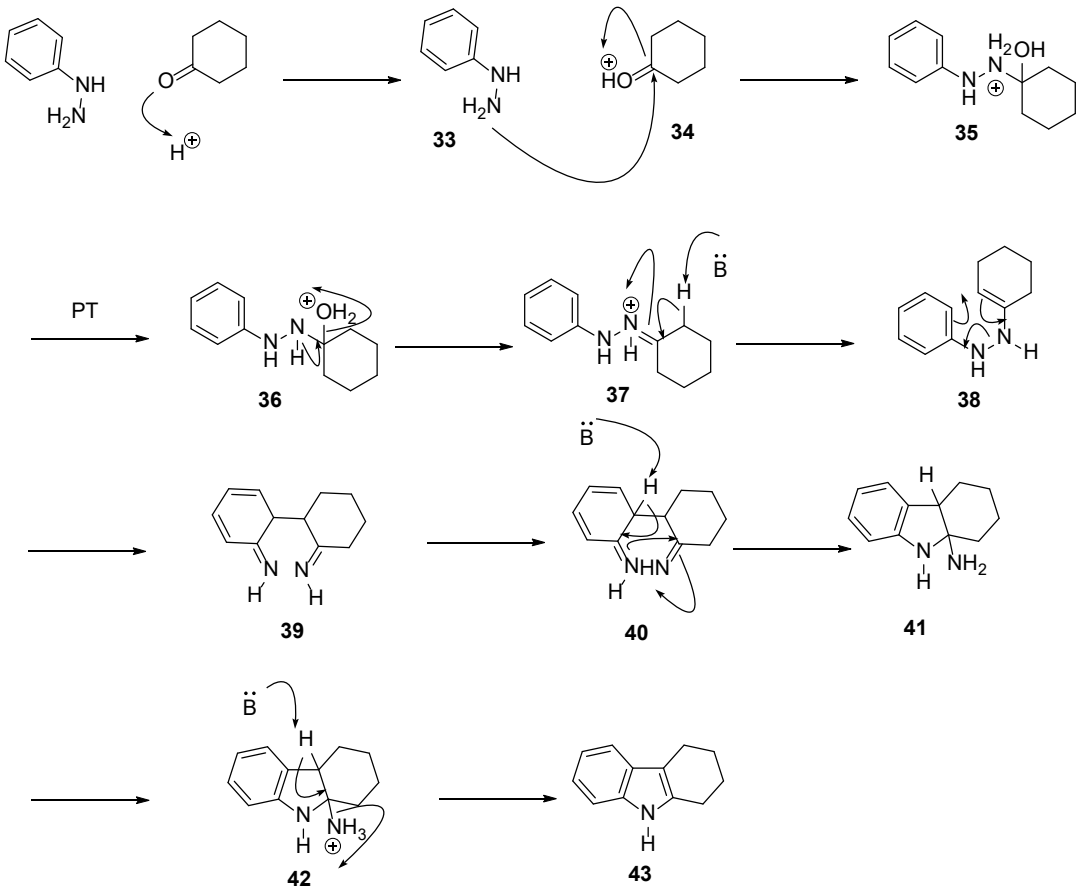


1.6.2 Fischer Indole Synthesis

More than a century ago Emil Fischer discovered that the indole nucleus can be prepared by the reaction of aryl hydrazines and enolizable ketones, which rearranged upon heating in acid with loss of ammonia.[26] Since this invention the reaction has been the subject of much investigational work and is now among the most versatile methods for the preparation of indoles. Mechanistically, the process involves reaction of a hydrazine **33** with an aldehyde or ketone **34** initially form to a hydrazone **35** which tautomerizes to ene-hydrazine **37**. A subsequent [3,3]-sigmatropic rearrangement then produces an imine **39**. The resulting imine forms a cyclic aminoacetal (or aminal), which

under acid catalysis eliminates NH_3, affording the aromatized indole **42** (**Scheme 1.6**).[26]

Scheme 1.6 Fischer-Indole Mechanism

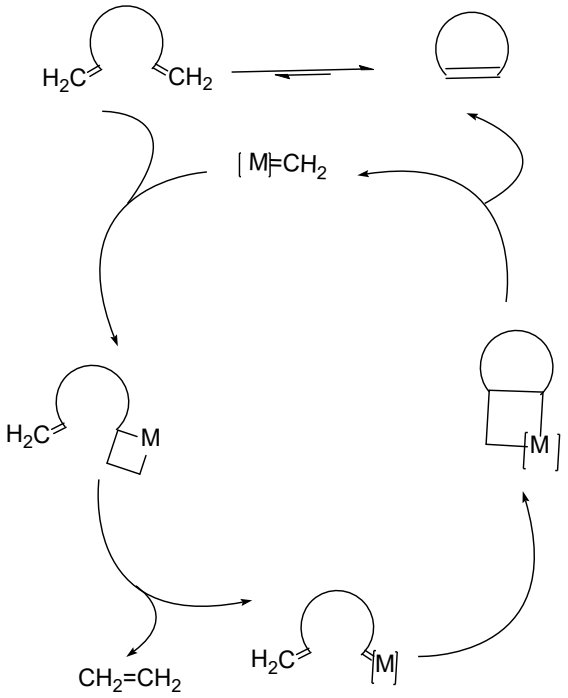


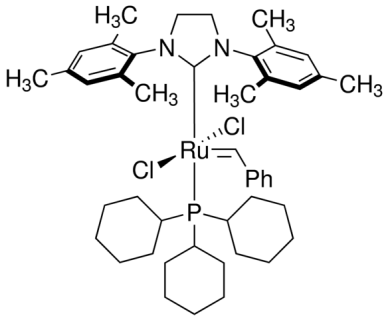
1.6.3 Olefin Ring-Closing Metathesis Reactions

Olefin metathesis has drawn a great deal of attention over an extended period.[27] Ring-closing metathesis (RCM) of alkenes in particular permits the synthesis of rings ranging in size from small rings to macrocycles. Effective metathesis reactions involving metal carbenes has been accomplished by the development of stable and easy to handle catalysts. The construction of macrocycles by ring-closing metathesis (RCM) is often used as the crucial step in the total synthesis of natural products having large rings. This reaction is appealing because of its high functional group compatibility and the possibility for further transformations.[28] A broad range of catalysts have been shown to induce metathesis. The extremely active and broadly used catalysts are Mo- or Ru-based complexes. The Ru-based catalysts in particular are much more stable and show a higher functional-group tolerance than Mo-based catalysts.[29] Mo-based complexes suffer from high oxygen and moisture sensitivity. In particular, the advancement of ruthenium alkylidene complexes bearing *N*-heterocyclic carbene ligands (NHC) (*i.e.* Classical Grubbs' II and Hoveyda–Grubbs' II catalysts) has largely expanded the scope and the efficiency of this reaction. Furthermore, many metathesis catalysts have now become commercially available, thus rendering RCM more widely applicable.[30]According to the mechanism, the reaction proceeds via a sequence of [2+2] cycloaddition and retro-cycloaddition reactions; the construction of unsaturated cyclic systems is

mainly driven by entropy gained by release of ethylene or other volatile side products (**Scheme 1.7**).[31]

Scheme 1.7 Ring Closing Metathesis





Grubbs' second generation catalyst

CHAPTER-2

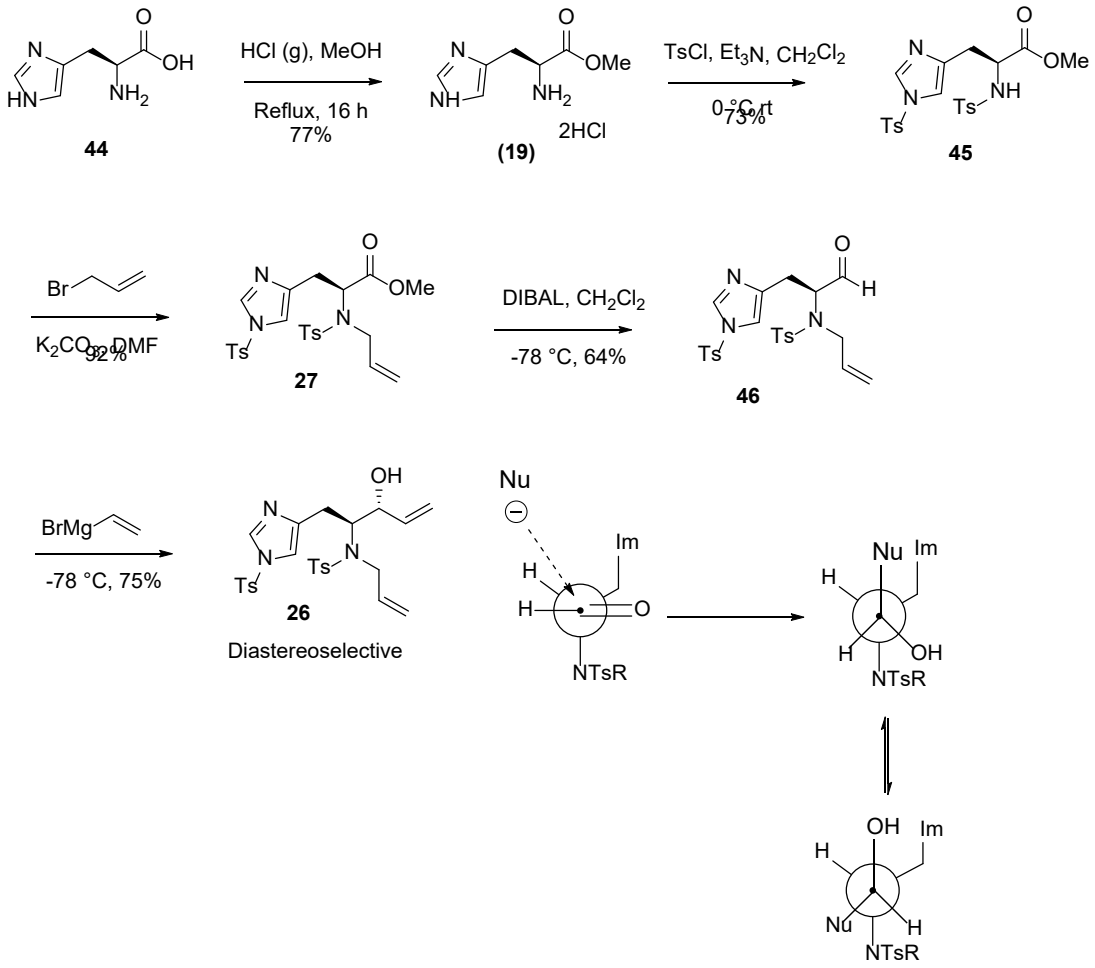
2.1 Total Synthesis of Haploscleridamine

The synthesis commenced from L-histidine, through a sequence of steps including bis N-tosylation, allylation and diastereoselective formation of alcohol **26** from aldehyde **46** by Grignard addition (the structure confirmed by X-ray crystallography). The sequence was developed up to this point by Koda and Meng, but the present studies have cleaned up details of several of these transformations including assignment the stereochemistry of compound **26.** In addition, the next five steps, which were investigated previously, have now been significantly optimized.

Histidine methyl ester (**19**) was prepared in 77% yield from the corresponding acid by heating it in saturated HCl/MeOH for 16 hours. Histidine methyl ester (**19**) was protected with a tosyl group both on the imidazole nitrogen and the amino nitrogen to furnish bis sulfonamide **45** in 73% yield.[32] The tosyl protected intermediate was then N-allylated using allyl bromide in presence of K_2CO_3 to afford **27** in 92% yield. With the tosyl protected methyl ester **27** in hand, the next step was selective reduction of the methyl ester group. The ester group was reduced selectively to the aldehyde by using DIBAL-H at -78 °C and dichloromethane as solvent. The identity of the product obtained **46** was confirmed through ^{1}H NMR spectroscopy analysis as a distinct aldehyde peak at **δ** 9.68 and was observed along with the disappearance of the methyl ester peak at **δ** 3.5 and confirmed through X-ray crystallography. Aldehyde **46**, on

treatment with vinyl magnesium bromide Grignard reagent, afforded allylic alcohol **26** as a single diastereomer with an overall yield of 75%. The relative stereochemistry of this adduct was determined by X-ray crystallography and is consistent with the modified Felkin-Ahn model with the polar group anti to the incoming nucleophile (**Scheme 2.1**).[33] Examination of the ^{1}H NMR spectrum of the presence of a small amount of ester **27** and the corresponding alcohol carried through from the previous step.

Scheme 2.1 Synthesis of Haploscleridamine



44 **(19)** **45** **27** **46** **26**

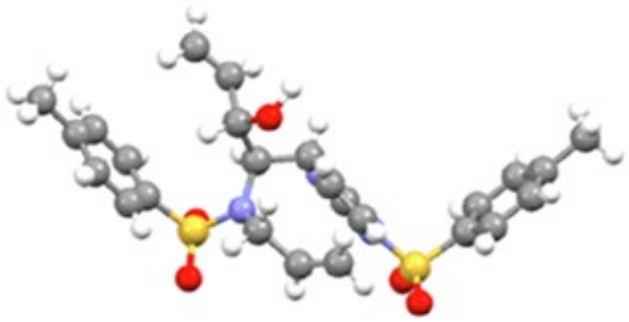


Figure 2. 1: X-ray structure of 26

Initially Koda *et al.* attempted oxidation of allylic alcohol **26** with IBX affording the corresponding ketone **47** in 65% yields (**Scheme 2.3**).[34] The first efforts to perform the RCM reaction were done using the first-generation Grubbs' catalyst in CH_2Cl_2 to prepare a 0.1 M solution with 1.1 equivalents of *p*-TsOH·H_2O. Earlier work from our lab had shown it was necessary to protonate the basic imidazole nitrogen to obtain good yields in RCM reaction. The RCM occurred to give the cyclic product **48** in 20% yield. Motivated by this promising result, the reaction was attempted, using the 0.1 M solution of the starting material but was initially heated at reflux with 1.1 equivalents of *p*-TsOH·H_2O in CH_2Cl_2 for 30 minutes and then second-generation Grubbs' catalyst was added instead of first-generation Grubbs' catalyst. Purification of the crude material by column chromatography provided the pure enone **48** in 35% yield. As the overall yield of RCM reaction was low, it was decided to perform the RCM reaction from substate allylic alcohol **26** instead of allylic ketone **47** which was more

successful, affording the cyclohexene derivatives **25** in 80% yield. The ring closing metathesis has now been optimized in CH_2Cl_2 to use 5 mol% of Grubbs' 2nd generation catalyst affords cyclohexenol **25** in high yield after 3 hours at reflux. Note the use of *p*-TsOH·H_2O was unnecessary, and the loading of the metathesis catalyst was substantially reduced. Previously, oxidation of cyclic alcohol to the corresponding enone was attempted in ethyl acetate in presence of IBX but it was observed that the reaction was slow if ethyl acetate was used as the solvent. After that acetone was used as a solvent in which better rates and yields were obtained. A possible explanation for this observation is that IBX has higher solubility in acetone than in ethyl acetate. Meanwhile, the workup of this reaction is very easy: a vacuum filtration through a Celite pad and followed by washing with CH_2Cl_2 and concentration of the filtrate afforded the pure product **48** in excellent yield. Formation of piperidinone **24** was completed by catalytic reduction using 10% Pd-C (ethyl acetate: ethanol; 1:3) and was accomplished in 85% yield (**Scheme 2.3**).

As noted earlier, Koda *et al.* attempted several variants of the classical Fischer-indole synthesis to construct indole **23**. The piperidone ring was subjected to the Fischer indole synthesis using phenylhydrazine in absolute ethanol with few drops of acetic acid. After formation of the phenylhydrazone, it was treated with PPA and heated to 160 °C for 45 minutes. But further cyclization of the hydrazone to the indole ring did not appear to take place. Other

catalysts such as HCl/EtOH, $ZnCl_2$/AcOH and AcOH/HCl gave poor result for the formation of hydrazone. After several attempts to install the indole group by traditional approach with *p*-TsOH·H_2O, phenyl hydrazine and ketone provided low yield with numerous byproducts. Employment of the benzophenone hydrazone derivative resulted in formation of the desired indole via a hydrazine transfer Fischer-indole process described by Buchwald.[35]

The first attempts to perform this reaction were done using with 4.0 equivalents of *p*-TsOH·H_2O, 3.0 equivalents of hydrazine, and 1.0 equivalents of piperidinone at reflux for 24 hours. The reaction occurred to give the traces product. Continuation for another 48 hours did improve the reaction yields from traces to 20%. Furthermore, when similar reaction conditions were used under microwave irradiation, resulted in little improvement to the desired product yields. Motivated by this promising result, the reaction was attempted, using 2.5 equivalents of *p*-TsOH·H_2O, 1.0 equivalent of hydrazine, and 1.5 equivalents of piperidone at reflux condition for 72 hours. After work up with aqueous $NaHCO_3$ and extracting with dichloromethane the ^{1}H-NMR spectrum of the crude product showed the desired product. Purification of the crude material by column chromatography provided the pure indole in 65% yield (**Table 1.1**).

These conditions resulted in the formation of mono tosylated product **23** and thus completion of the synthesis required tosyl deprotection which was accomplished by

reductive cleavage using Mg/MeOH under sonication at 48 °C (**Scheme 2.3**).[36] The spectroscopic data of synthetic haploscleridamine [α] = -7.6 (c = 0.47, MeOH) was identical in all respects to that reported for the isolated material.[37]

Scheme 2.2 Fischer-Indole synthesis

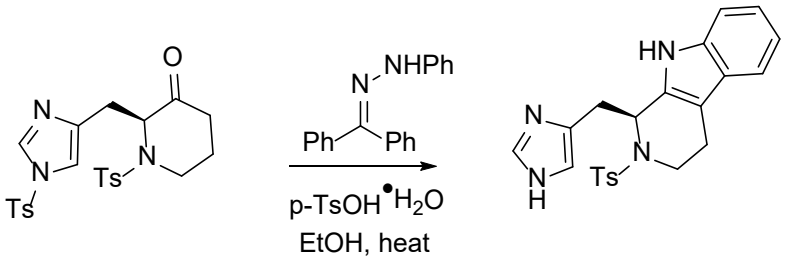
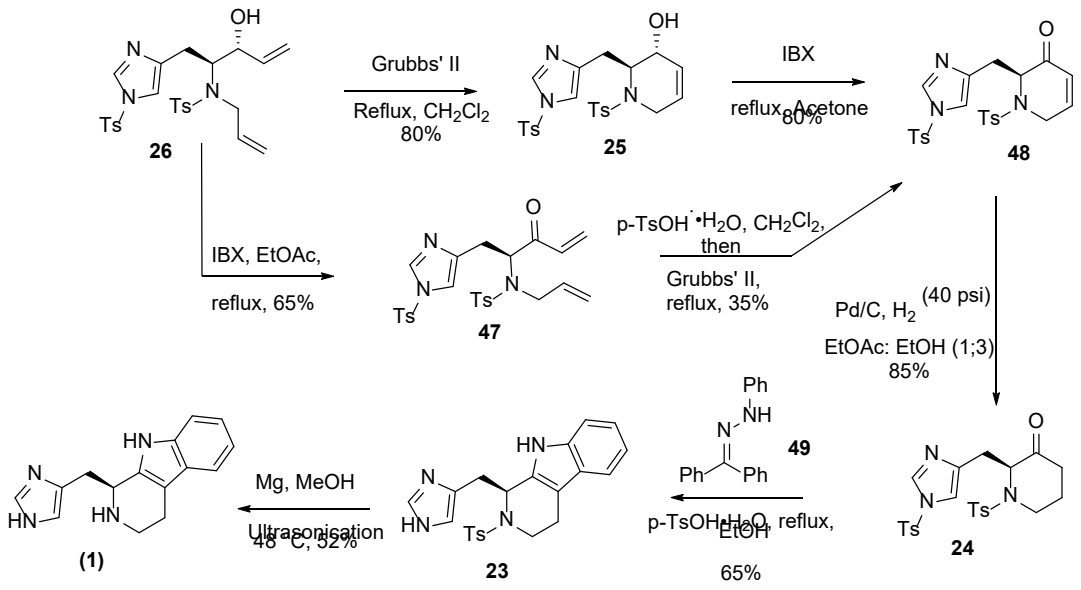


Table 1. 1: Reaction Condition for Fischer-Indole Synthesis

Entry	TsOH (equiv)	Hydrazone (equiv)	Ketone (equiv)	Conditions	Time/ h	Yield/%
1	4	3	1	reflux	24	Traces
2	4	3	1	reflux	48	Traces
3	5	4	1	reflux	96	20
4	5	4	1	microwave 90 °C	1	41
5	2.5	1	1.5	microwave 90 °C	1	21
6	2.5	1	1.5	reflux	24	21

7	2.5	1	1.5	reflux	72	65

Scheme 2.3 Synthesis of Haploscleridamine



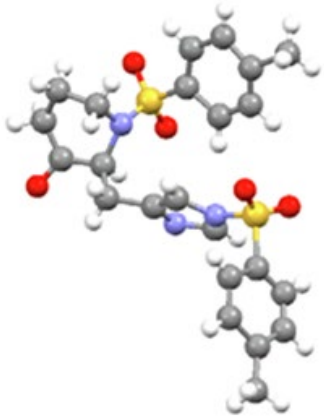


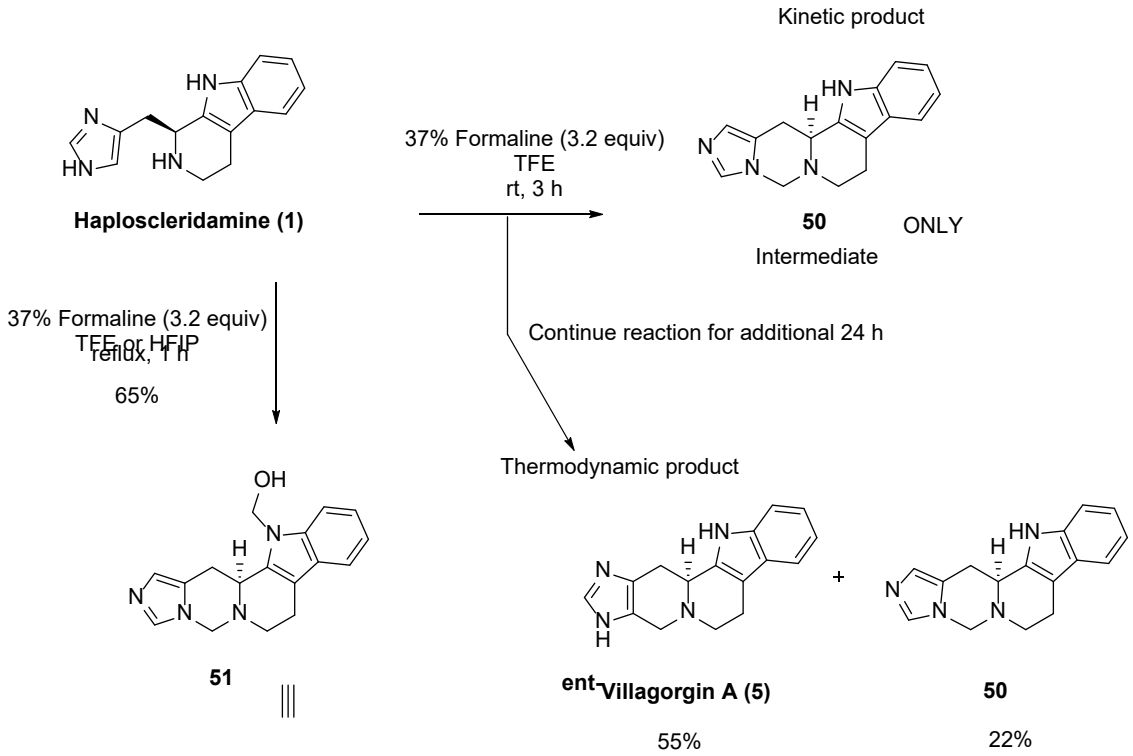
Figure 2.2: X-ray structure of 24

2.2 Synthesis of Villagorgin A

Haploscleridamine (**1**) was targeted first as it was thought that a successful approach to this family member would permit access to the other congeners through minor modifications, including conversion to villagorgin A (**5**). Villagorgin A (**5**) has just one additional carbon atom and an additional ring compared to haploscleridamine (**1**) the introduction of which can be envisioned through a Pictet-Spengler reaction from **1** and formaldehyde. Initial attempts to perform this transformation under classical conditions were unsuccessful until a recent report describing the trifluoroethanol-mediated Pictet-Spengler reaction appeared.[38] Interestingly, it was observed under these conditions that after 3 hours adduct isovillagorgin (**50**) [α] = -

5.3 (c = 0.28, MeOH), formed. However, continuation of the reaction for an additional 24 hours, resulted in formation of a mixture of compound **5** and **50** favoring the former. These observations suggest that **50** is in fact the kinetic product which converts to the more stable villagorgin A (**5**) [α] = - 4.3 (c = 0.17, MeOH) over time. Conducting the Pictet-Spengler reaction under the same reaction conditions with another fluorinated solvent hexafluoro-2-propanol showed similar results. Unexpectedly and interestingly, employing TFE at reflux in the Pictet-Spengler reaction, resulted in the formation of the hydroxymethylated β-carboline **51** [α] = - 5.2 (c = 0.31, MeOH), the structure of which was confirmed by X-ray (**Scheme 2.4**). The spectroscopic data of synthetic villagorgin A match with that reported for natural material.

Scheme 2.4 Synthesis of Villagorgin A



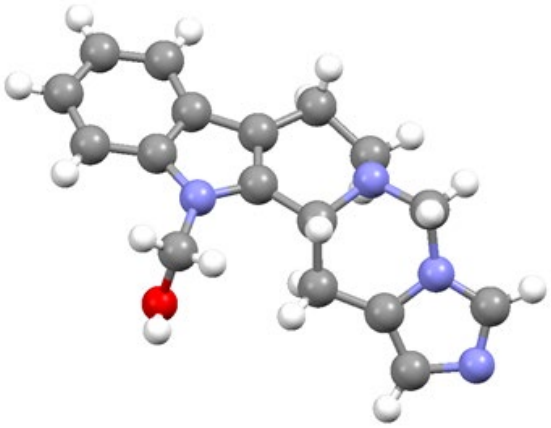
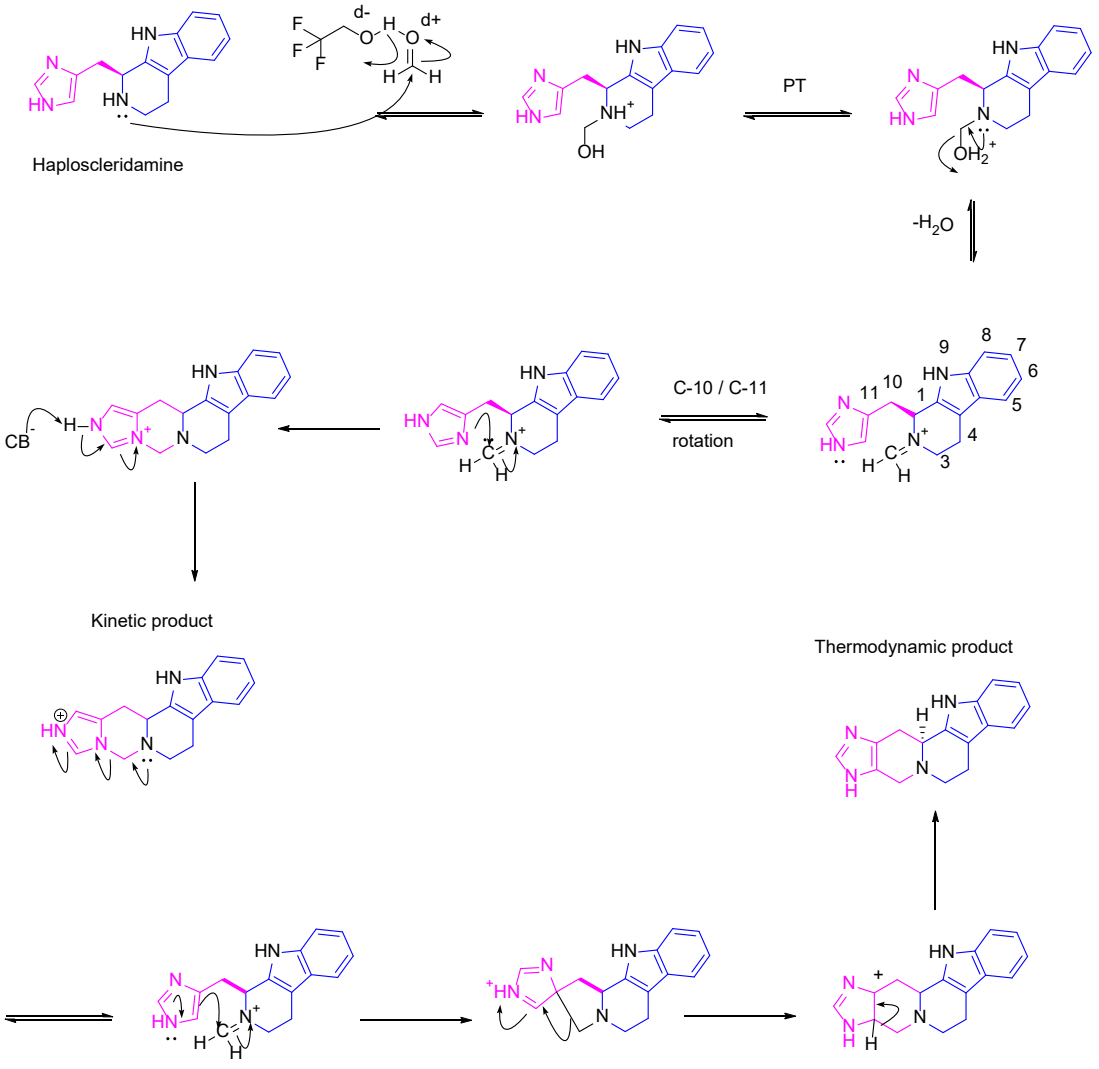


Figure 2.3: X-ray structure of 51

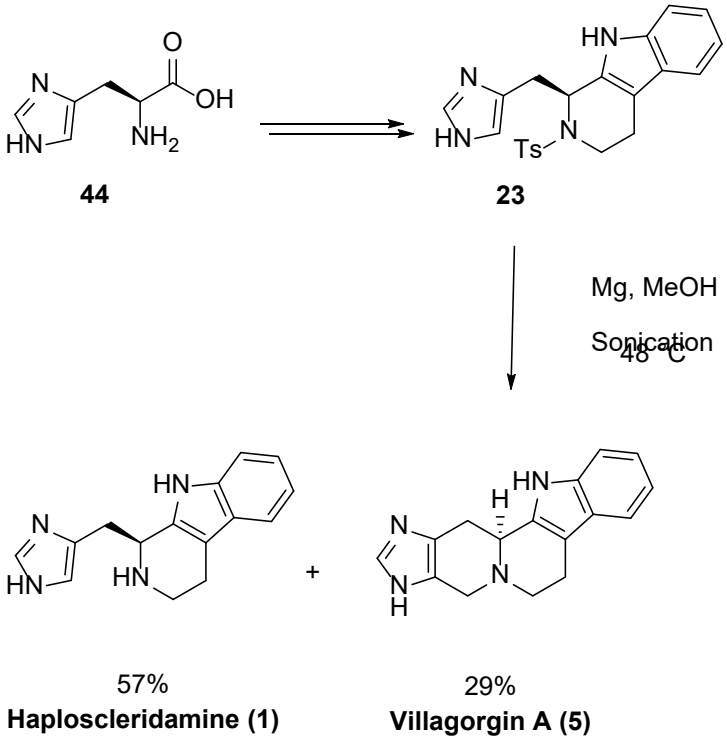
Scheme 2.4 A Synthesis of Villagorgin A


Haploscleridamine
PT
-H2O
C-10 / C-11
rotation
Kinetic product
Thermodynamic product

2.3 Synthesis of Villagorgin A in Situ

After obtaining synthetic villagorgin A, we recognized that a second product was formed in the reductive detosylation, which was determined to be villagorgin A **(5)** [α] = - 6.8 (c = 0.25, MeOH). Presumably, some formaldehyde is produced from methanol which in turn then reacts with formed haploscleridamine (**1**).

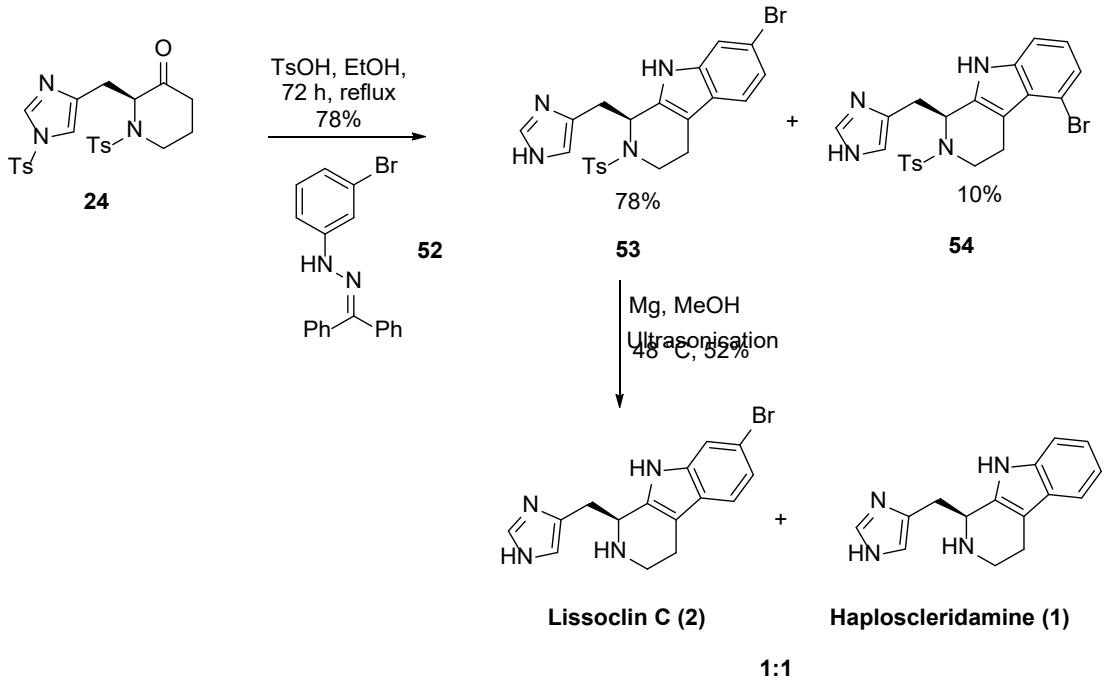
Scheme 2.5 Synthesis of Villagorgin A



2.4 Synthesis of Lissoclin C

With a synthesis of haploscleridamine (**1**) completed, thought turned to the brominated congener, lissoclin C (**2**) which should be obtainable through use of the appropriate hydrazone derivative with piperidinone **24**. Specifically employing the *m*-bromophenyl benzophenone hydrazone derivative **52** resulted in formation of the desired bromo indole **53** in 78% yield and a small amount of the regioisomer **54**.[35] Completion of the synthesis required the removal of the N-Ts group. Reductive detosylation would then deliver the natural product **2**. However reductive cleavage of the tosyl group using Mg in MeOH which was successfully used en route to haploscleridamine (**1**) resulted in competitive debromination along with formation of the desired product **2** as an inseparable mixture. Experiments were conducted using different equivalents of Mg turnings and shorter reaction times, but this still results in variable mixtures of brominated and de-brominated products which proved difficult to purify chromatographically. Attempts to remove the Ts group under other conditions, including using Red-Al[39] or Na naphthalide[40] were either unsuccessful or resulted in reductive debromination (**Scheme 1.13**).

Scheme 2.6 Synthesis of Lissoclin C



CHAPTER 3

3.1 Synthetic Route to Assess the Stereochemical Purity of Haploscleridamine and Villagorgin A

β-Carboline (βC) alkaloids occur all over nature and show various biological activities.[41] Chrisey and Brossi, Reddy and Cook, Yan *et al*., described the optical rotation value achieved for C-1 substituted tetrahydro-β-carboline alkaloids or closely related compounds was very close to 0 °.[41-44] The low optical rotation of a tetrahydro β-carboline suggested that they might experience racemization when subjected to the acid/base conditions employed during the standard isolation procedure.

The stereochemical center in the natural products described in this dissertation is prone to racemization, a feature that was noted in the isolation papers.[11] Searle *et al*. reported in their isolation paper that the optical activity of the lissoclin C (**2**) was almost zero. Both the specific rotation and circular dichroism spectrum (CD) of the TFA salt of lissoclin C (**2**) were near to 0 °, indicating the compound was nearly racemic. Searle *et al*. postulate a possible explanation for loss of optical activity for lissoclin C (**2**) would involve protonation of the piperidine ring followed by reversible ring opening to an

achiral intermediate, stabilized by the electron donating 7-bromo substituent (**Figure 3.1**).

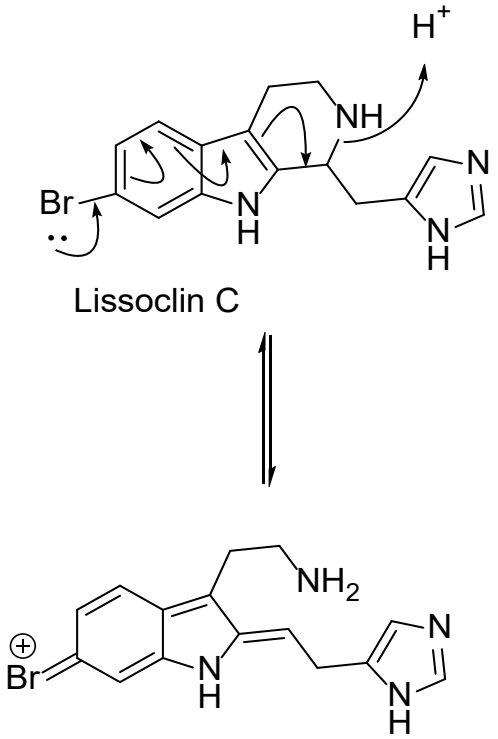
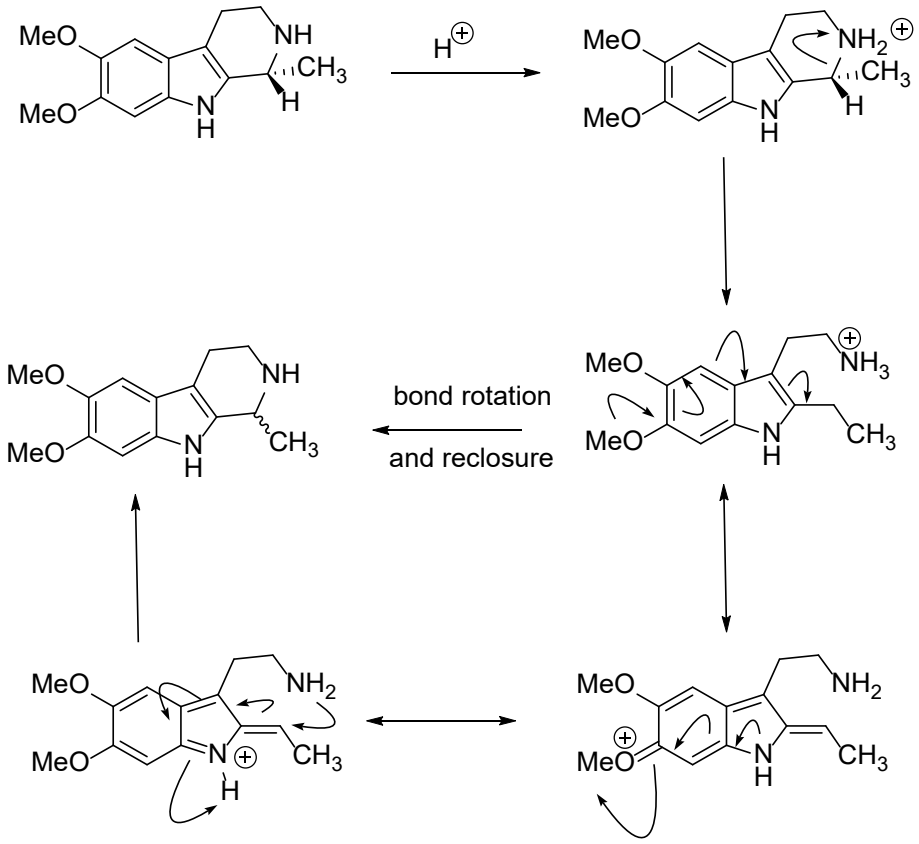


Figure 3. 1: Possible Mechanism for Loss of Optical Activity (Lissoclin C)

These molecules are chiral by nature but appear to have lost their optical activity during isolation and purification.[42] Another example of racemization of a C-1 substituted tetrahydro-β-carboline alkaloid (-)-tetrahydroharmine was reported by Brossi (**Scheme 3.1**).[42]

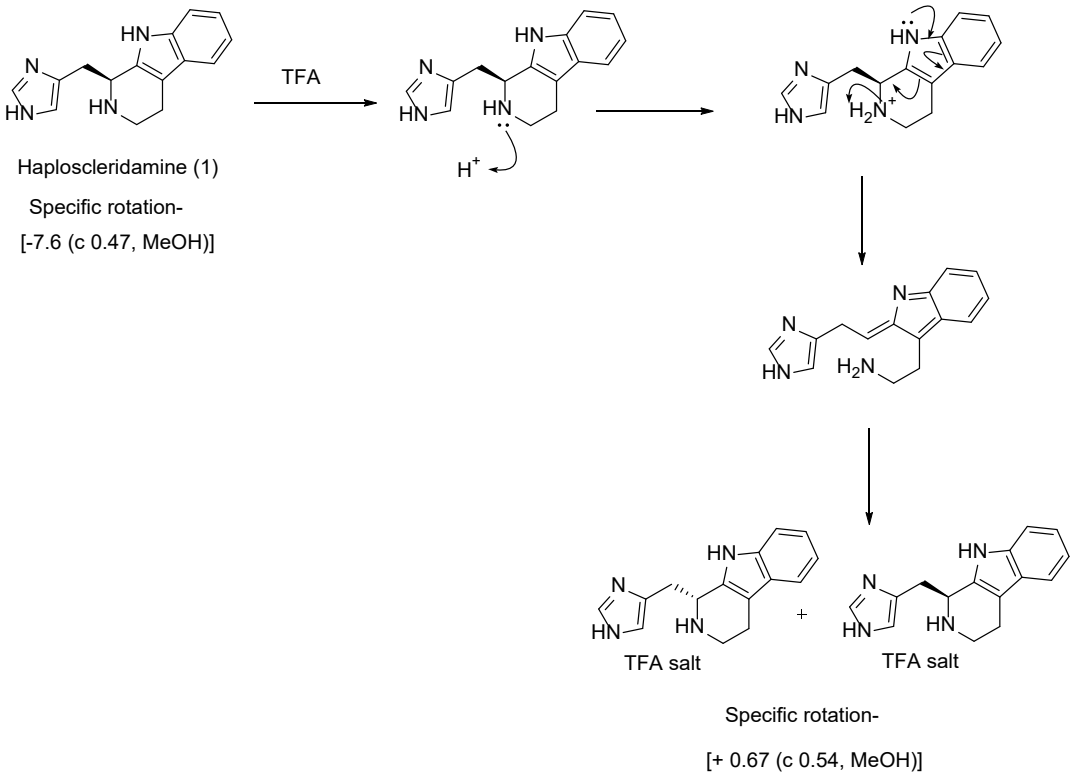
Scheme 3.1 Mechanism for Loss of Optical Activity



The spectral properties of the synthetic alkaloid were identical to the natural product except for the optical rotation. The specific rotation of haploscleridamine (**1**) was found to be [α] = -7.6 (c 0.47, MeOH), while that reported for the natural product was [α] = -3.4° (c 0.78, MeOH).[37] It was believed that the 1,2,3,4-tetrahydro-β-carboline

had undergone partial racemization during the acid/base mediated isolation procedure.[11] To test this hypothesis, optically enriched haploscleridamine (**1**) was exposed to trifluoroacetic acid in dichloromethane at room temperature, as illustrated in (**Scheme 3.2**). The proton NMR spectrum and R_f of the alkaloid which resulted were unchanged, however, the optical rotation of this material was now [α] = + 0.67 (c 0.54, MeOH). Based on this experiment, it is believed that the mechanism of racemization of **1** occurred in a similar fashion to lissoclin C and as illustrated in (**Scheme 3.2**).

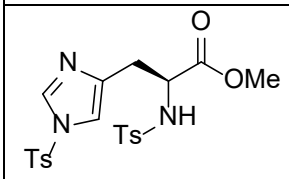
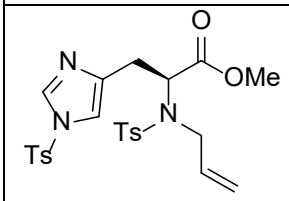
Scheme 3.2 Postulated Mechanism for Racemization

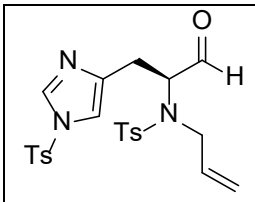
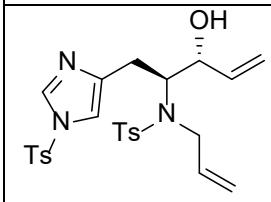
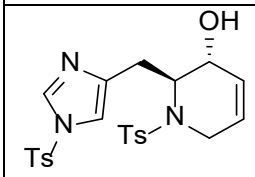
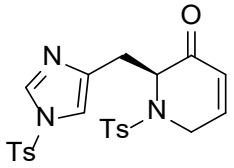
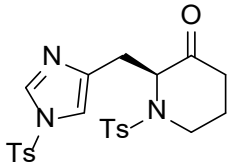
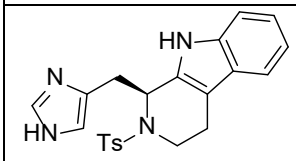


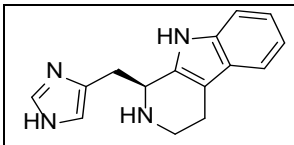
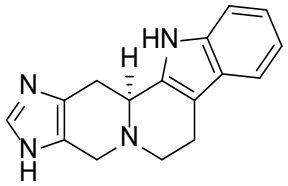
Although in the present study we have reported syntheses starting from *S*-histidine and we have obtained synthetic materials with higher rotation values, we did not know the enantiomer composition. In order to address this, we performed the same synthetic sequence with racemic histidine to provide racemic samples for HPLC analysis.

After preparation of racemic intermediated and natural products, we compared the enantiomeric purity with the non-racemic compounds by HPLC column shown below in (**Table 3.1**). When both racemic and non-racemic haploscleridamine (**1**) and villagorgin A (**5**) were assessed using column, they essentially gave identical results; each showed essentially a 1:1 mixture of both enantiomers. These results suggested that our asymmetric syntheses had delivered close to racemic products. While this was certainly a possibility, the fact that the optical rotations were > 0 for the synthetic natural products suggested that while they may have been scalemic, they were not racemic (**Table 3.1**).

Table 3. 1: Enantiomeric excess purity

Structure	Method	% ee
	ChiralPak IC (15 cm x 3.1 mm, 2.7 um FPP) 100% Ethanol, flow rate 0.8 mL/min, column temperature ambient, λ = 254 nm	>99
	MaltoShell (10 cm x 4.6 mm, 2.7 um FPP) 15-25-60 Methanol, Ethanol, Heptane flow rate 0.8 mL/min, column temperature ambient, λ = 254 nm	>99

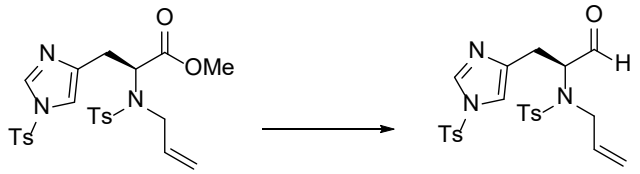
	ChiralPak IC (15 cm x 3.1 mm, 2.7 um FPP) 100% Ethanol, flow rate 0.8 mL/min, column temperature ambient, λ = 254 nm	2.6
	MaltoShell (10 cm x 4.6 mm, 2.7 um SPP) 5:10:85 MeOH: IPA Heptane, flow rate 1 mL/min, λ = 254 nm	2.0
	MaltoShell (10 cm x 4.6 mm, 2.7 um FPP) 15-25-60 Methanol, Ethanol, Heptane flow rate 0.8 mL/min, column temperature ambient, λ = 254 nm	17.0
	MaltoShell (10 cm x 4.6 mm, 2.7 um FPP) 15-25-60 Methanol, Ethanol, Heptane flow rate 0.8 mL/min, column temperature ambient, λ = 254 nm	2.8
	MaltoShell (10 cm x 4.6 mm, 2.7 um FPP) 15-25-60 Methanol, Ethanol, Heptane flow rate 0.8 mL/min, column temperature ambient, λ = 254 nm	10.8
	NicoShell 2.7 µm SPP, 3 mm ID x 150 mm L, 100% methanol 0.1% ammonium trifluoroacetate, 0.4 mL/min, detection UV 254 nm, temperature 25 ˚C.	3.0

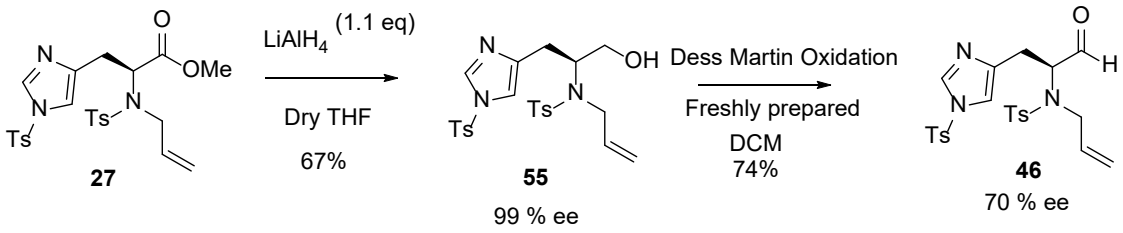
	NicoShell 2.7 µm SPP, 3 mm ID x 150 mm L, 100% methanol 0.1% ammonium trifluoroacetate, 0.4 mL/min, detection UV 254 nm, temperature 25 ˚C.	2.8
	NicoShell 2.7 µm SPP, 3 mm ID x 150 mm L, 100% methanol 0.1% ammonium trifluoroacetate, 0.4 mL/min, detection UV 254 nm, temperature 25 ˚C.	2.8

From the enantiomeric excess purity table, it came into our attention that lability of the stereogenic center of α-amino aldehydes, which is prone to epimerization in the presence of acid or base.[45] We anticipated that there might be a problem with our approach due to having chances of racemization during basic workup process in the reduction step. After encountering difficulties with this initial approach, we considered an alternative sequence where the α-amino methyl ester **27,** was fully reduced to the corresponding alcohol **55** and then selectively re-oxidized to the desired α-amino aldehyde **46** (**Scheme 3.3**). In order to avoid basic conditions and prolonged workup, which could cause loss of chiral integrity of the resulting amino aldehyde, we used $LiAlH_4$ as the reducing agent leading to formation of alcohol and quenching the aluminum complexation using ethyl acetate instead of the commonly used NaOH solution.

Reduction with $LiAlH_4$ provided alcohol **53** intermediate with 99% ee in moderate yield. The ester **27** in freshly distilled THF was added dropwise to a cooled suspension of $LiAlH_4$ in dry THF, and the mixture was stirred at 0 °C. After stirring for 3 h at this temperature the reaction was quenched while still at 0 °C with ethyl acetate (excess). After warming to room temperature, the resulting mixture was stirred for another 2 h. Then, the residue was filtered and rinsed with ethyl acetate and the filtrate was concentrated. The crude product was purified by flash chromatography to provide the pure alcohol **55** compound in 67% yield.[46] Oxidation of the alcohol with the Dess–Martin periodinane provides exceptional results, furnishing the desired aldehydes **46** with 70% ee and in 74% yield (**scheme 3.3**) (**Table 3.2**).[47]

Scheme 3.3 Conversion of Ester to Aldehyde via Alcohol





After optimization we repeated whole sequence starting from aldehyde to the final compounds haploscleridamine (**1**) and villgorgin A (**5**). Aldehyde derivative **46** which was then treated with vinylmagnesium bromide to afford the expected allylic alcohol **26** as a single diastereomer. Ring closing metathesis, using only 5 mol% of Grubbs' 2nd generation catalyst afforded the corresponding cyclized product **25** in 80% yield on a gram scale. Oxidation of the alcohol with IBX to enone **48** and catalytic hydrogen of the double bond afforded the key heterocycle **24**. Employment of the benzophenone hydrazone derivative resulted in formation of the desired indole **23** via a hydrazine transfer Fischer-indole process described by Buchwald.[35] Haploscleridamine (**1**) [α] = - 13.7 (c = 0.28, MeOH) was obtained upon removal of the N-tosyl group by reduction

with magnesium in methanol. The same observation was noted as before, a second product was also formed in the reductive detosylation, namely villagorgin A (**5**) [α] = - 13.5 (c = 0.31, MeOH) (**Scheme 3.4**).

Scheme 3.4 Revised Synthesis Route of Haploscleridamine

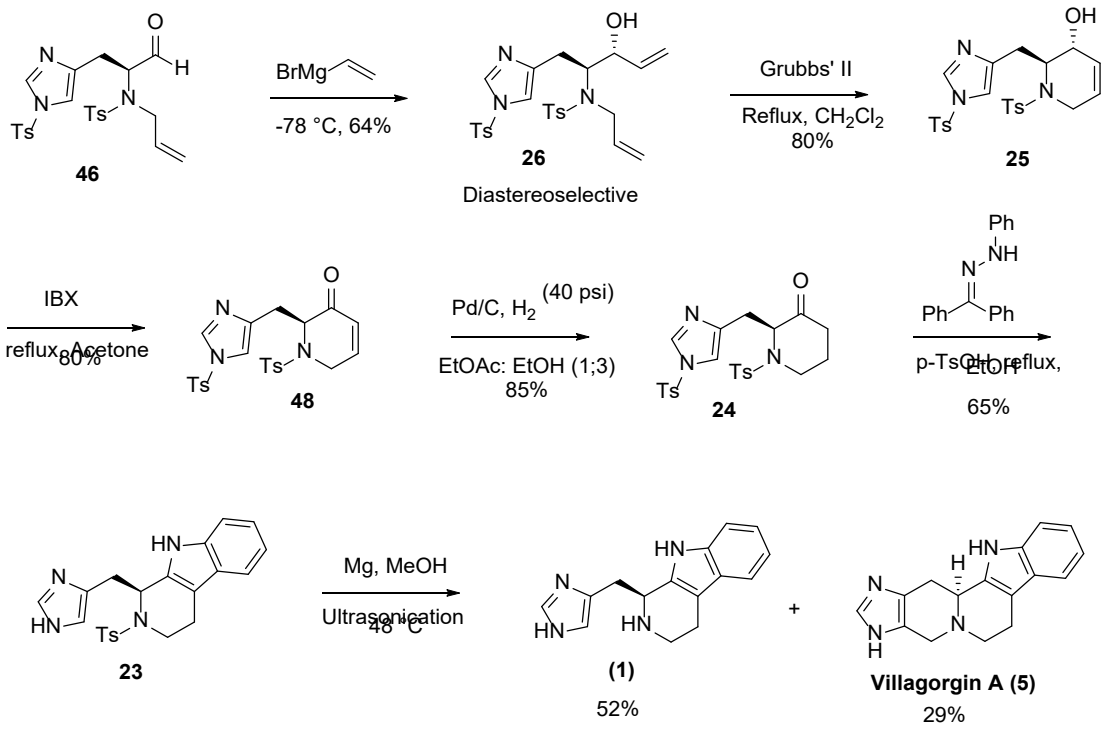
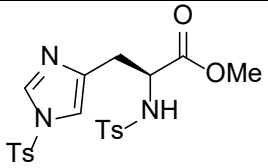
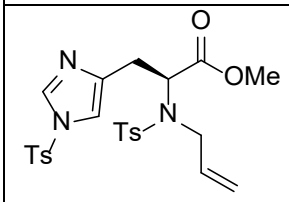
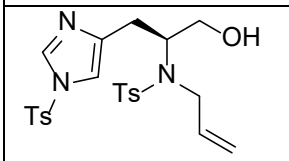
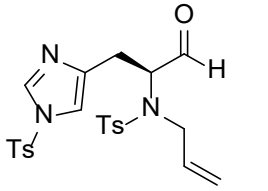
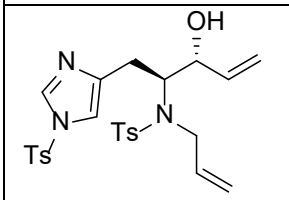
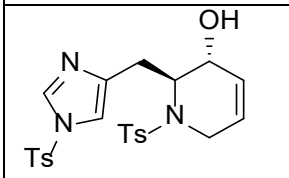
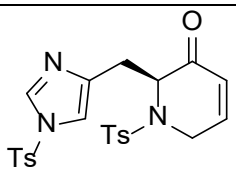
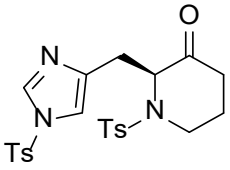
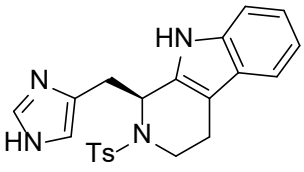
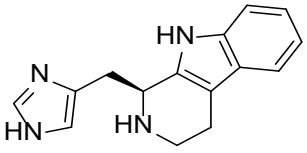
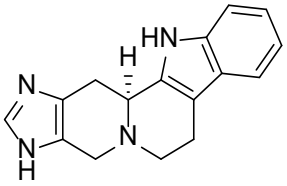


Table 3.2: Enantiomeric Excess Purity

Structure	Method	% EE
	ChiralPak IC column 3 µm, 3 mm ID x 150 mm L, 100% ethanol, 0.4 mL/min, detection UV 254 nm, temperature 25 ˚C.	>99
	MaltoShell 2.7 µm SPP, 4.6 mm ID x 100 mm L, 20%-15%-65% ethanol-methanol-heptane, 1 mL/min, detection UV 254 nm, temperature 25 ˚C.	>99
	MaltoShell 2.7 µm SPP, 4.6 mm ID x 100 mm L, 20%-15%-65% ethanol-methanol-heptane, 1 mL/min, detection UV 254 nm, temperature 25 ˚C.	>99
	ChiralPak IC 3 µm, 3 mm ID x 150 mm L, 100% ethanol, 0.4 mL/min, detection UV 254 nm, temperature 25 ˚C.	70
	MaltoShell 2.7 µm SPP, 4.6 mm ID x 100 mm L, 5%-5%-90% ethanol-methanol-heptane, 1 mL/min, detection UV 254 nm, temperature 25 ˚C.	75
	MaltoShell 2.7 µm SPP, 4.6 mm ID x 100 mm L, 10%-10%-80% ethanol-methanol-heptane, 1 mL/min, detection UV 254 nm, temperature 25 ˚C.	50

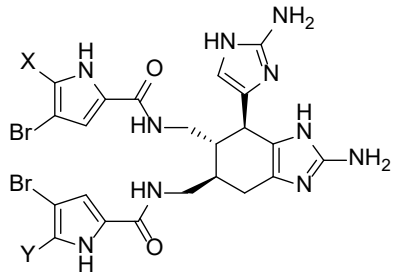
	MaltoShell 2.7 µm SPP, 4.6 mm ID x 100 mm L, 15%-10%-75% ethanol-methanol-heptane, 1 mL/min, Detection UV 254 nm, temperature 25 ˚C.	50
	MaltoShell 2.7 µm SPP, 4.6 mm ID x 100 mm L, 15%-15%-70% ethanol-methanol-heptane, 1 mL/min, detection UV 254 nm, temperature 25 ˚C.	35
	NicoShell 2.7 µm SPP, 3 mm ID x 150 mm L, 100% methanol 0.1% ammonium trifluoroacetate, 0.4 mL/min, detection UV 254 nm, temperature 25 ˚C.	30
	NicoShell 2.7 µm SPP, 3 mm ID x 150 mm L, 100% methanol 0.1% ammonium trifluoroacetate, 0.4 mL/min, detection UV 254 nm, temperature 25 ˚C.	30
	on NicoShell 2.7 µm SPP, 3 mm ID x 150 mm L, 100% methanol 0.1% ammonium trifluoroacetate, 0.4 mL/min, detection UV 254 nm, temperature 25 ˚C.	30

In summary, we have completed the first asymmetric total synthesis of the β-carboline alkaloid, haploscleridamine (**1**) and villagorgin A (**5**). Critical to the success of this synthesis campaign was a ring-closing metathesis reaction of an imidazole derivative to facilitate construction of the key piperidinone. Subsequent application of the Buchwald modification of the classical Fischer indole synthesis provides the β-carboline framework. Reductive removal of an N-tosyl group was accomplished by dissolving metal reduction. The optical rotation of the synthetic

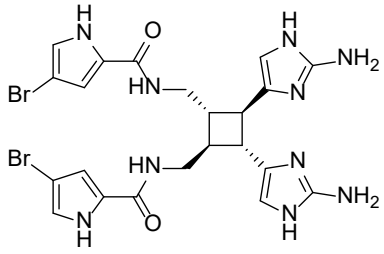
material was in the same direction as the natural material indicating that the chiral center possesses an S-configuration. In collaboration with the Dr. Armstrong lab, we have been estimating the enantiomeric purity of intermediates en route to these natural products. Successfully completed the synthesis of the racemic series and in doing so we have discovered that our synthetic materials are scalemic (R/S mixtures but not racemates). As a result, we have established where the partial racemization occurs (N-protected α amino ester to aldehyde) and redesigned our synthesis to partially overcome this racemization issue. Revised synthesis completed and final natural products haploscleridamine (**1**) and villagorgin A (**5**) obtained with 30% enantiomer excess purity.

CHAPTER 4

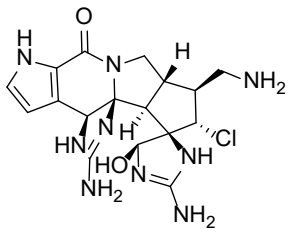
Pyrrole imidazole alkaloids' biological role started to be explored in the late '90s, when it was realized that sponges' structural defenses alone (spongin fibers and needle like spicules) were ineffective feeding deterrents towards predatory reef fish.[48] The first report in this respect dates back to 1996, when an ecoassay guided isolation, performed on the extracts of sponges of the genus *Agelas*, allowed the identification of 4,5-dibromopyrrole-2-carboxylic acid and oroidin as the major components responsible for the observed chemical feeding deterrence.[49] These alkaloids are fascinating due to their biogenetic relationships leading to a large, structurally diverse family based on a common key metabolite, oroidin.[48] The oroidin alkaloids, are a class of sponge-derived metabolites now numbering some 250 plus members which are known as pyrrole-imidazole alkaloids.[50] Oroidin functions as basis of structural diversity on the skeletal level by undergoing cyclization, dimerization, or reaction with other metabolites. Example of dimers includes ageliferin (**56a**) sceptrin (**57**), styloguanidine (**58**), nakamuric acid (**59**), palau'amine (**60**), axinellamine A (**61**) (**Figure 4.1**). This dissertation mainly focuses on total synthesis of ageliferin. Ageliferin has antibacterial properties and can cause biofilms to dissolve.[51]



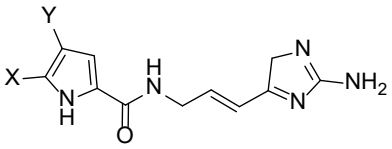
X = Y = H, (–)-ageliferin (**56a**)
X = H, Y = Br, bromoageliferin (56b)
X = Y = Br, : dibromoageliferin (57c)
(1990, revised absolute configuration 2014)



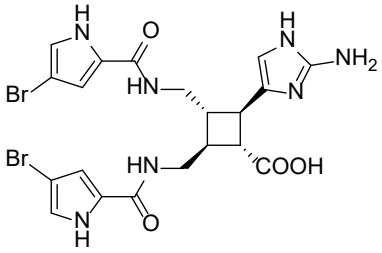
(–)-sceptrin (**57**)
(1981, revised absolute configuration 2014)



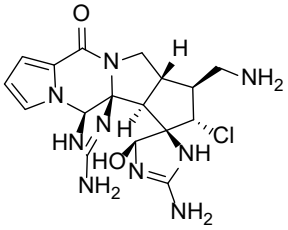
(–)-styloguanidine (**58**)
(1995, revised relative configuration 2007)



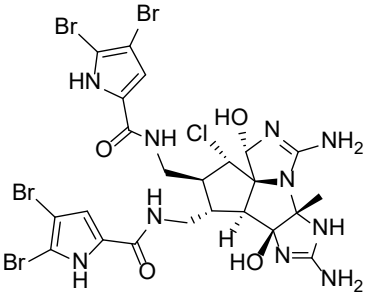
X = Y= Br: Oroidin
X = H; Y= Br: Hymenidin
X = Y = H: Clathrodin



(–)-nakamuric acid (**59**)
(1999, revised absolute configuration 2014)



(–)-palau'amine (**60**)
(1993, revised relative configuration 2007)



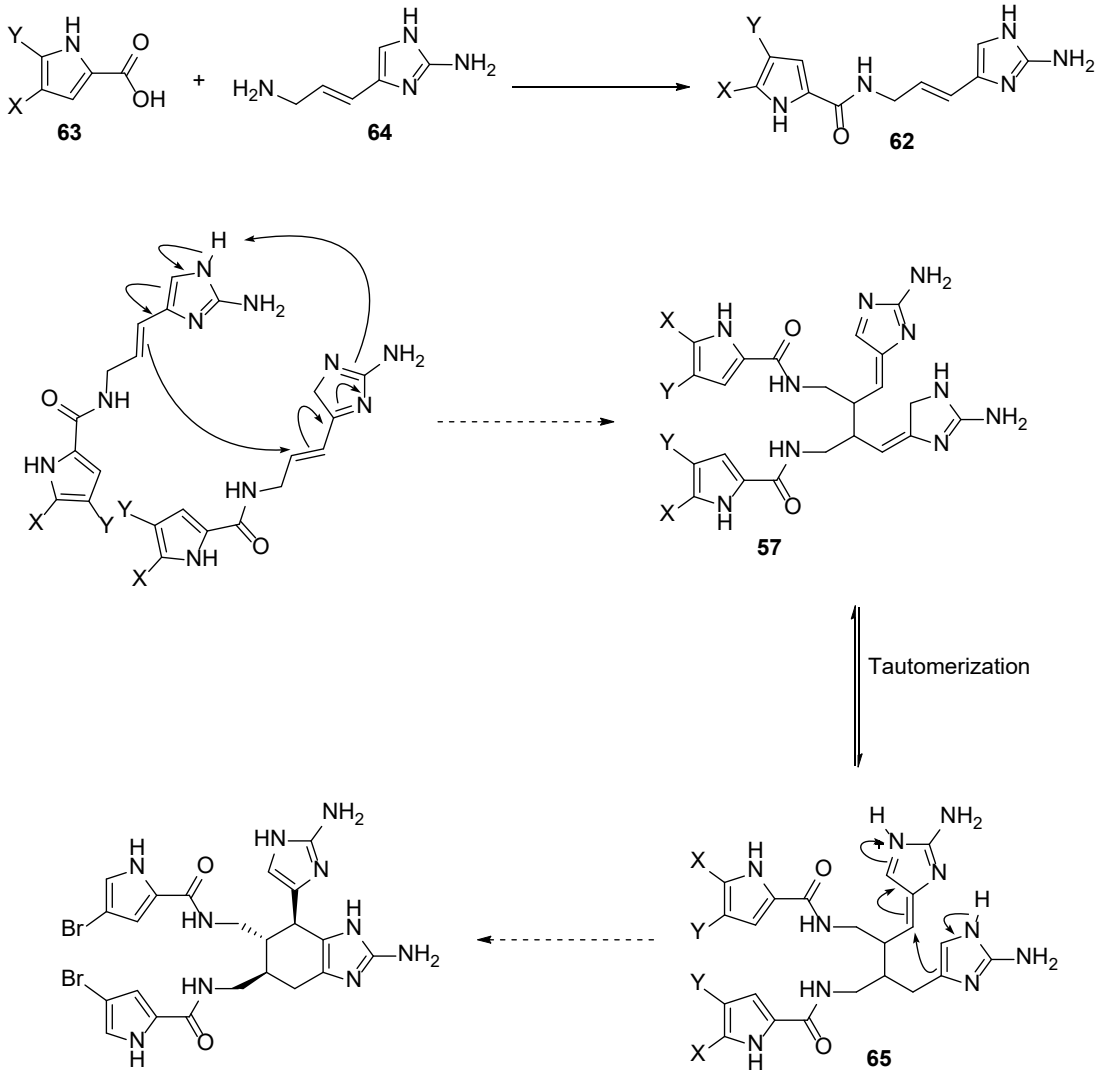
(–)-axinellamine A (**61**)
(1999)

Figure 4. 1: Examples of Dimeric Pyrrole Imidazole Alkaloids

4.1 Reported biosynthesis of ageliferin

Ageliferin (**56a**), bromoageliferin (**56b**), and dibromoageliferin (**56c**) were isolated from a sponge of the *Agelas* species harvested off the coast of Okinawa, Japan[51] in 1990 by Kobayashi and co-workers, and Rinehart and co-workers more or less simultaneously from a sponge taken from the Caribbean in 1991.[52] A biosynthesis of ageliferins was proposed by Al-Mourabit in 2001.[53] The motivation behind this approach was the leading biosynthetic hypothesis that the oroidin dimers arose from enzyme-catalyzed Diels-Alder dimerization of hymenidin **62**.[53, 54] In principle, two bromopyrrole imidazole natural products **62** (hymenidin and oroidin) arising from the coupling of **63** and **64** (**Scheme 4.1**) which can dimerize to produce sceptrin (**57**), or a species which tautomerizes to intermediate **65** and this can then undergo a similar cyclization to give the ageliferins (**56a**) (**Scheme 4.1**).

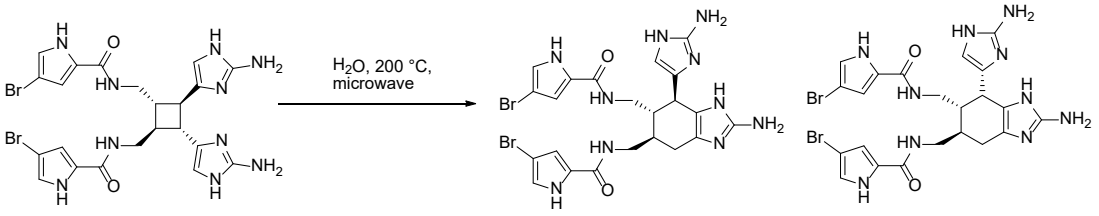
Scheme 4.1 Proposed Biosynthesis of Ageliferin



4.2 Baran's Approach Towards Ageliferin from Sceptrin

The isolation reports show that sceptrin was present in greater abundance than any other dimeric oroidin derivative, suggesting a hypothesis that sceptrin serves as a the building block for ageliferin and potentially other congeners.[55] Baran *et al*. have shown that sceptrin undergoes a net 1,3-sigmatropic rearrangement followed by a double bond isomerization under thermal conditions to form ageliferin. Specifically, sceptrin bis-hydrochloride after treatment with water at 200 °C under microwave irradiation afforded ageliferin in a modest yield.[55] This study revealed that another isomeric compound was isolated in these conditions. ^{1}H-NMR suggests that this additional product was an epimer of ageliferin; the ^{1}H-NMR data of *epi*-ageliferin (**56a**) were identical to nagelamide E (**66**) (**Scheme 4.2**).[56]

Scheme 4.2 Synthesis of Ageliferin from Sceptrin

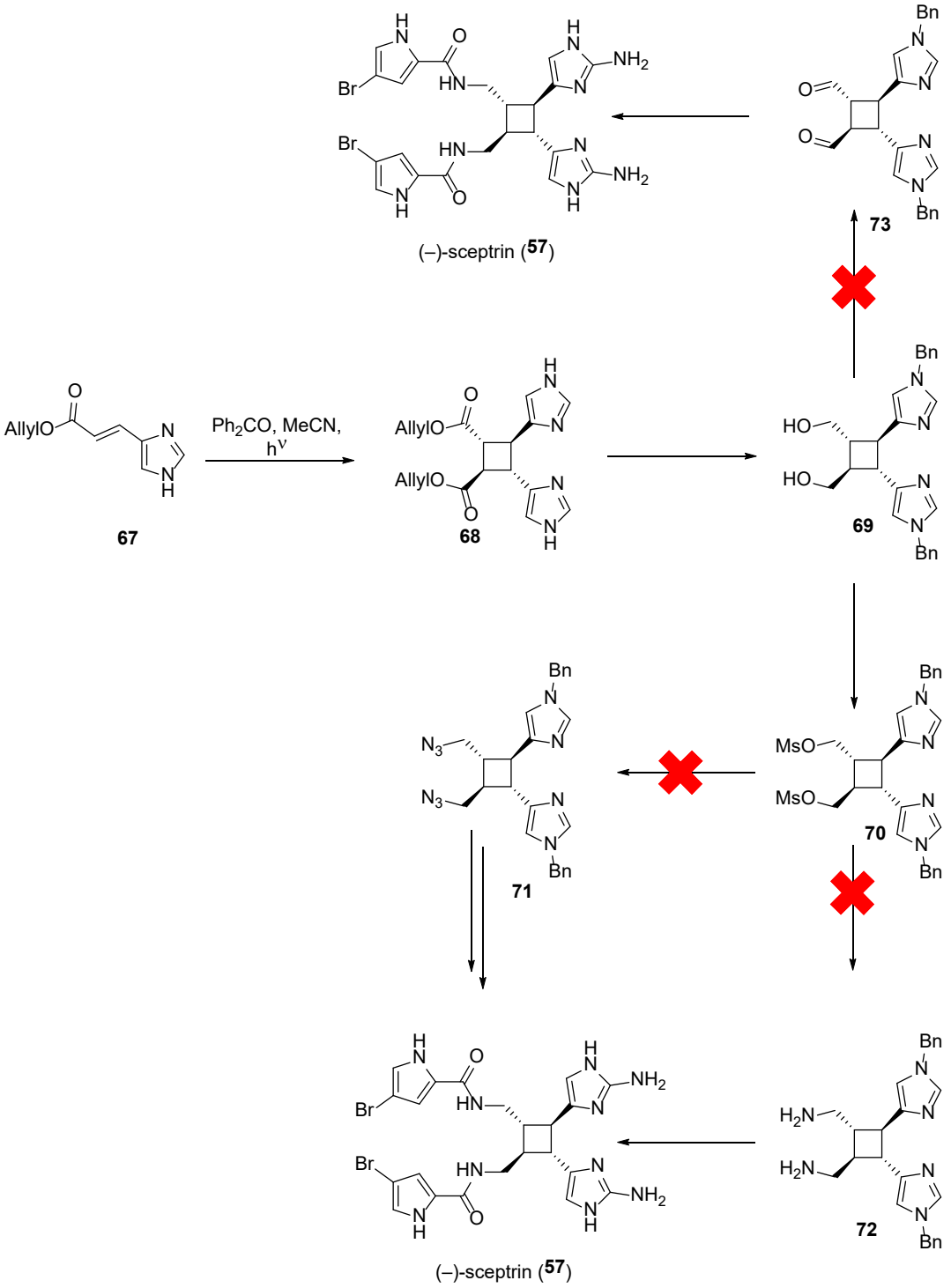


(–)-sceptrin (**57**) (–)-ageliferin (**56a**) Nagelamide E (**66**)

4.2 A Baran's Approach Towards Sceptrin

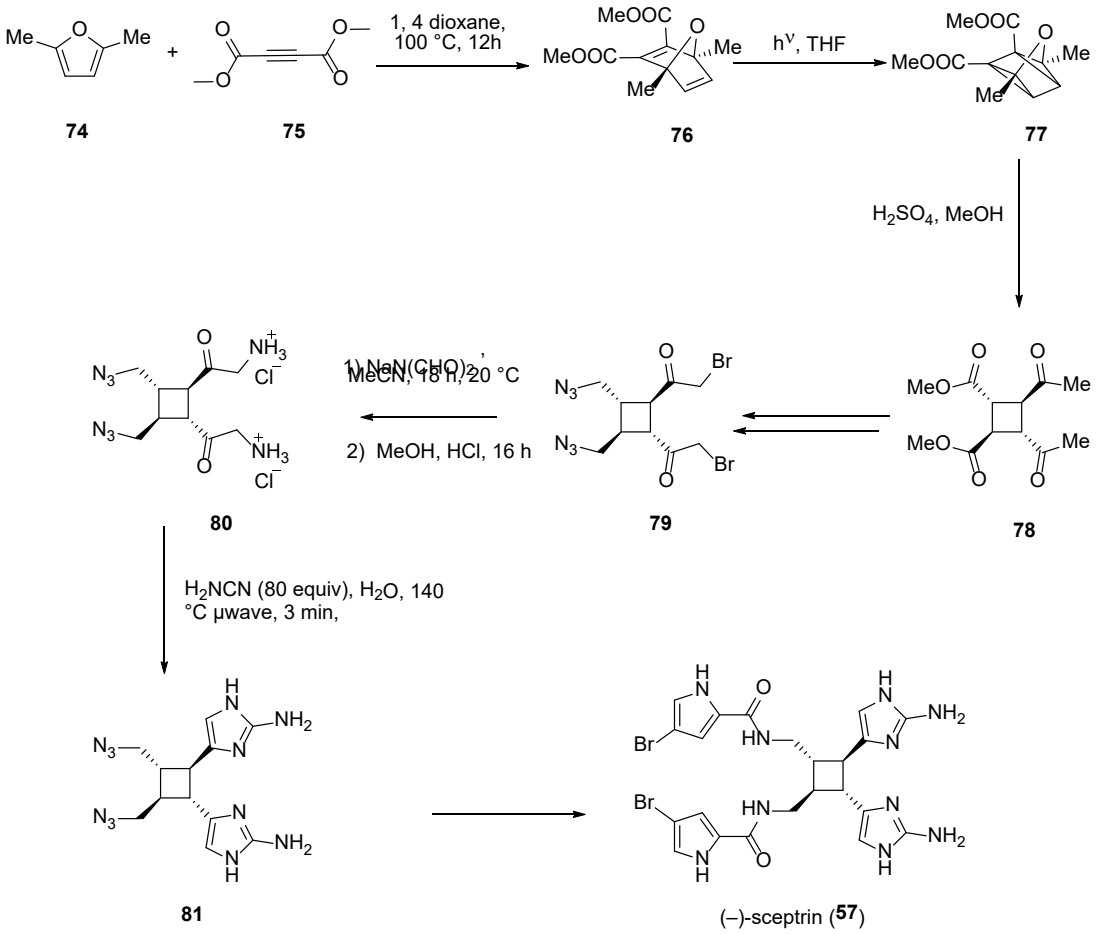
Baran's first generation approach was to produce the complete framework followed by C2-functionalization of the imidazole rings.[55] Starting with urocanic acid (**67**), esterification (**Scheme 4.3**) followed by benzophenone-sensitized photodimerization proceeded in good yield to give all-*trans*cyclobutane **68**. It was observed that the allyl ester was the most suitable substrate towards photodimerization. Other esters, such as the methyl ester, resulted in the production of a mixture of isomers. Benzyl protection followed by DIBAL-mediated ester reduction provided the diol **69** in excellent yield. Mesylation of the diol proceeded in quantitative yield but all the attempts to react the mesylate with either azide or amines were not fruitful. An attempt was also made to oxidize the diols to dialdehyde **73** in order to test reductive amination but no success. Furthermore, the bis-TBS ethers were used to functionalize the C-2 positions of the imidazole and this attempt also proved to be unsuccessful (**Scheme 4.3**).

Scheme 4.3 Approaches Towards Synthesis of Sceptrin



After failure of this first-generation approach, Baran *et al*. followed an alternate approach that included attempts towards the de novo synthesis of imidazole rings.[57] This time, the approach to synthesize sceptrin consisted of three different pathways. In pathway A, the 2-aminoimidazole **81** would be accessed from bromoketone **79**, followed by reduction of the azides in intermediate **81**. Attachment of the bromopyrrole amides will complete the synthesis. However, all the attempts to reduce the azido group and convert the resulting amine to bromopyrrole carboxamide resulted in the isolation of very trace amount of desired product (**Scheme 4.4**).

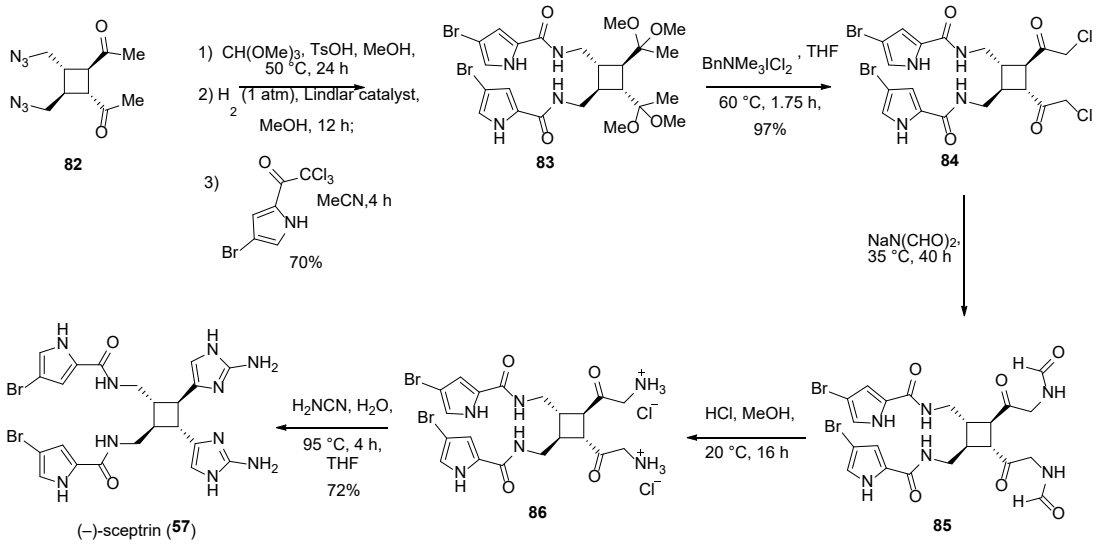
Scheme 4.4 An Alternative Approach to Synthesis Sceptrin



Although not to a surprise, handling of 2-aminoimidazole was challenging due to the high polarity. The group has decided to install the imidazole ring at the end of the

sequence. Specifically, protection of the methyl ketone as a ketal followed by azide reduction with Lindlar catalyst and acylation with bromopyrrole gave **83**. Functionalization of the α-methyl group of **83** was not so easy because of the presence of other groups towards competitive halogenation. After several attempts the group was able to successfully install the α-chloro functionality **84** by using benzyl trimethylammonium dichloriodate.[58] Finally, the previous approach to install the 2-aminoimidazole was used to complete the total synthesis of sceptrin (**Scheme 4.5**).

Scheme 4.5 A final Approach to Synthesis Sceptrin

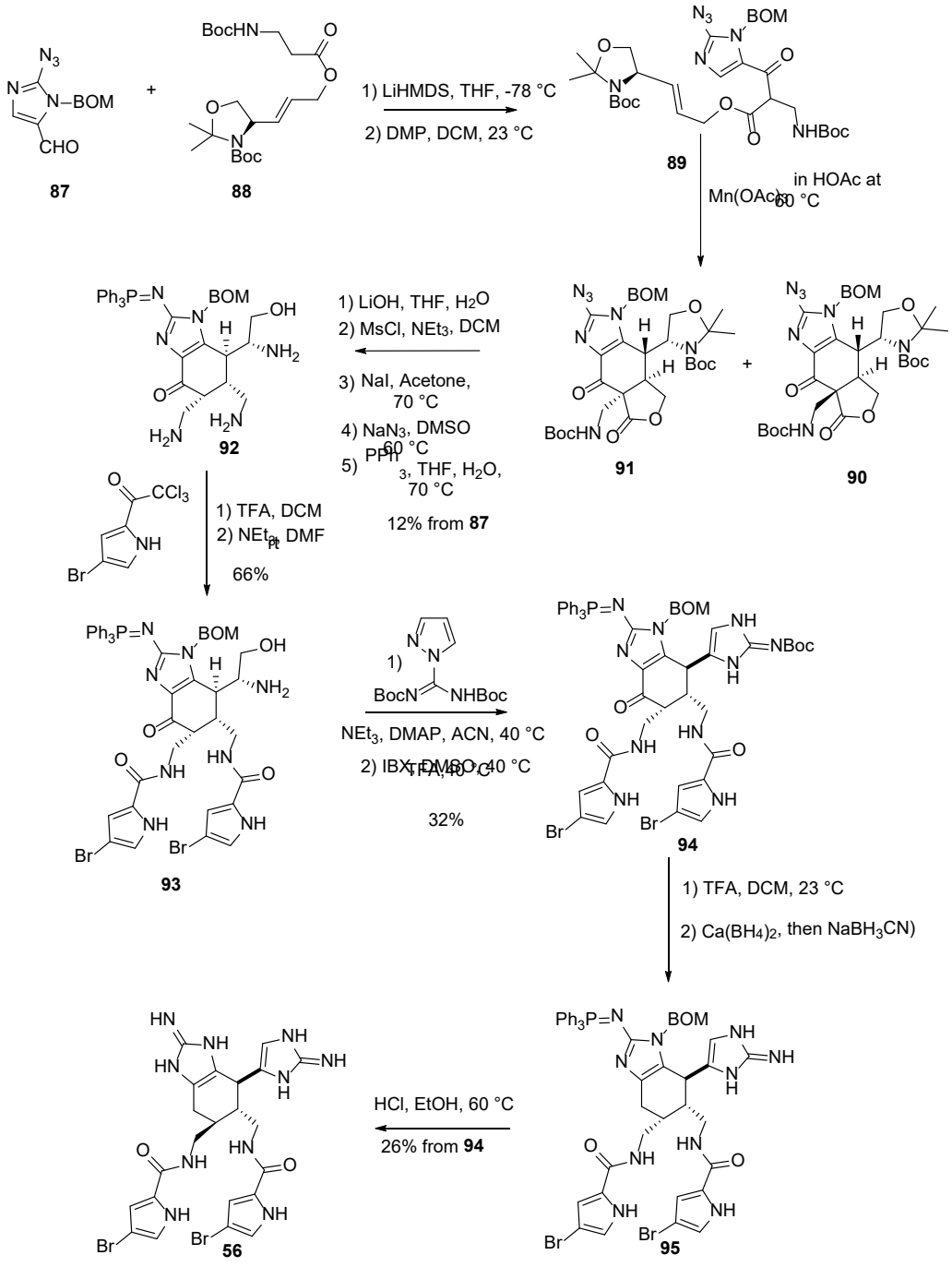


4.3 Chen's Approach Towards Ageliferin

In contrast to Baran's approach to synthesize [2+2] dimer, sceptrin, Chen has adopted a complementary [4+2] approach to access ageliferin.[59] This approach is based on the hypothesis that a single electron transfer (SET) reaction is used to convert hymenidin to ageliferin. This group has completed the synthesis of *ent*-ageliferin by utilizing an oxidative radical tandem cyclization reaction.

Specifically, after synthesizing 2-azido-4-formyl imidazole **89** in 3 steps starting from BOM-protected imidazole **87** and the allylic ester **88** starting from the allylic alcohol. β-Keto ester **89** was synthesized from **87** and **88** by aldol condensation followed by Dess-Martin oxidation. $Mn(OAc)_3$ treatment of **89** in acetic acid provided a mixture of **90** and **91**. This mixture, after treatment with LiOH produced a single diastereomer **92** because of the rapid epimerization at C9. Mesylation followed by azidation and reduction of the alcohol provided the diamine. Acylation of this diamine with the pyrrole trichloroketone gave the acylated product **93** in good yield. Guanylation followed by oxidation and ring closing provided the imidazole **95**. BOM deprotection and hydrolysis of N-PPh_3 provided ent-ageliferin (**Scheme 4.6**).

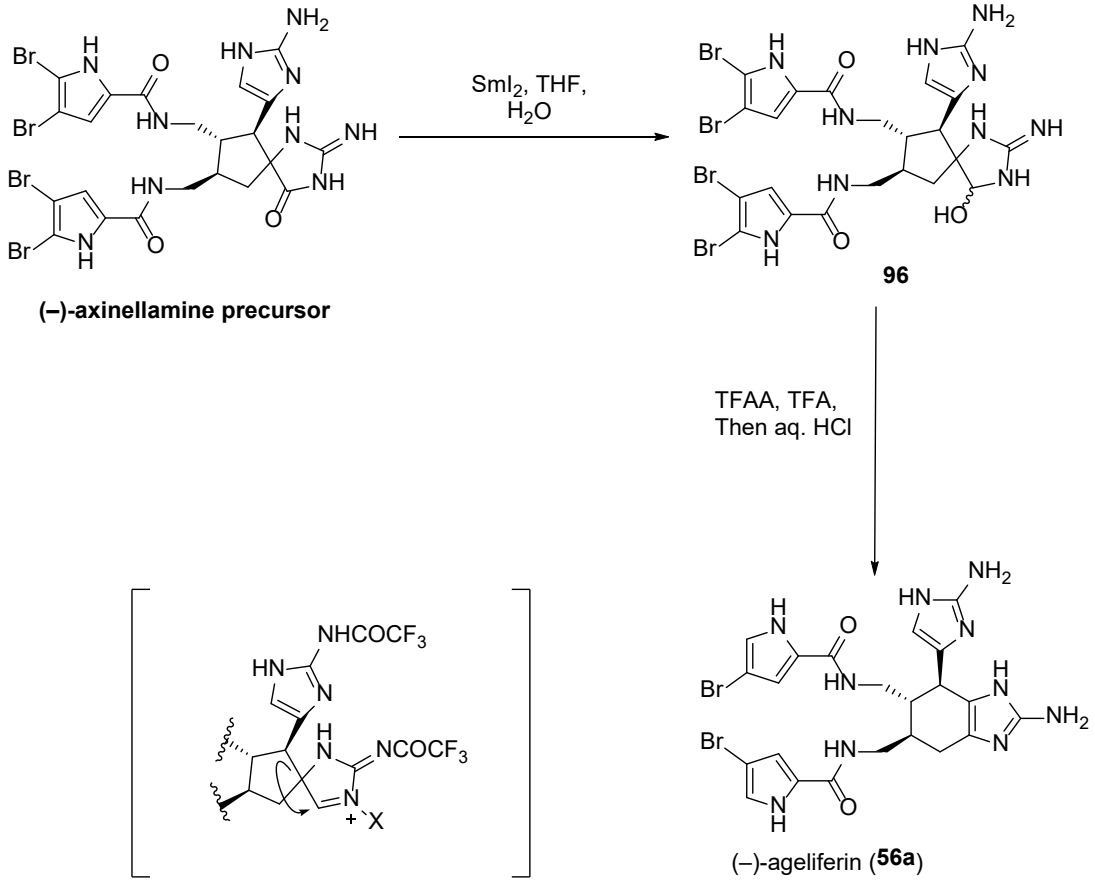
Scheme 4.6 Approach to Synthesis ent-ageliferin



4.4 Harran's Method for Total Synthesis of Ageliferin

Harran and his team synthesized ageliferin via an acyl *N*-amidinyliminium ion rearrangement.[60] As previously discussed, the tetrahydrobenzimidazole motif in ageliferin is considered to be a precursor to smaller ring oroidin spirocycles such as palau'amine, konbu'acidin, axinellamines and massadine.[55] Such an approach was adopted by several groups to covert ageliferin like frameworks to precursors of axinellamine.[61-63] Harran on the other hand pursued a reverse outcome where the group has found a way to rearrange axinellamine precursors into ageliferin (**61→56a**). Specifically, **61**, when treated with excess SmI_2, resulted into rapid debromination at C6' and C6'' resulted followed by the reduction of the carbonyl to the corresponding hemiaminal as a samarium salt. The hemiaminal **96** was freed from its samarium salt by subjecting this to preparative HPLC conditions. The HPLC-purified material was exposed to TFAA in TFA to initiate the ring-expanding rearrangement. Finally, racemic natural product was isolated by hydrolytic work up of the trifluoro acylated product **56a (Scheme 4.7**).

Scheme 4.7 Approach to Synthesis *ent*-Ageliferin

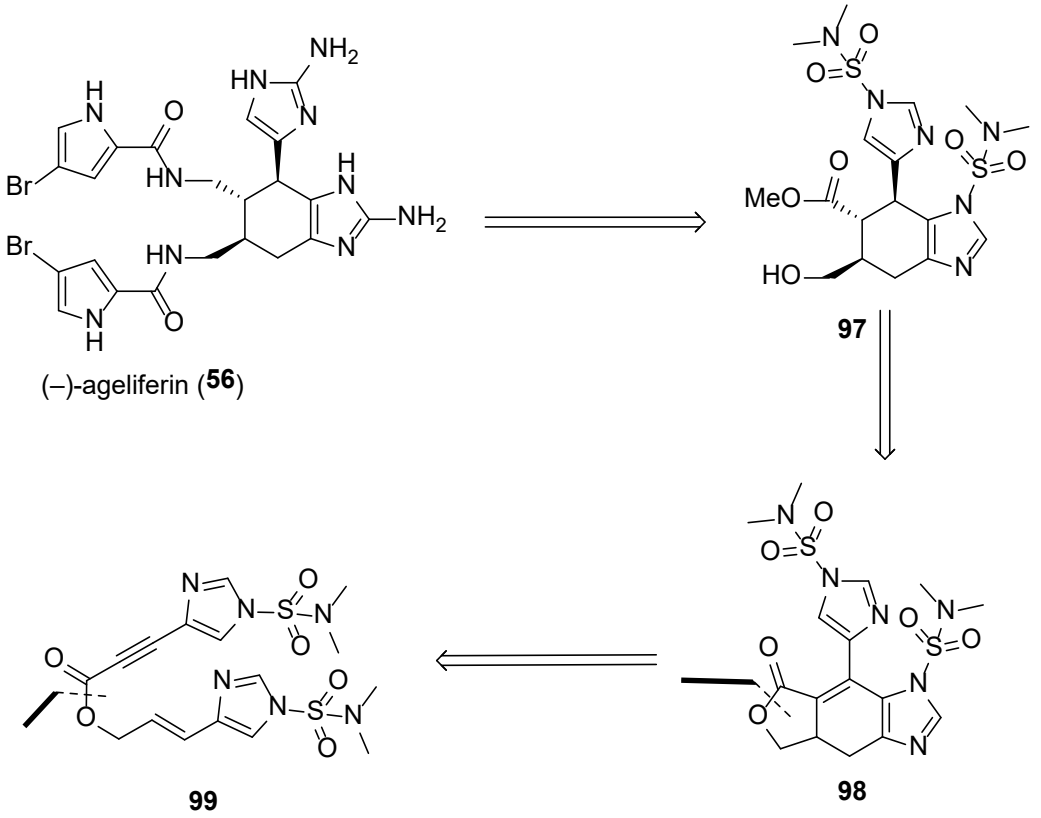


4.5 Our Approach Towards Synthesis of Ageliferin

4.5 A First-Generation Approach

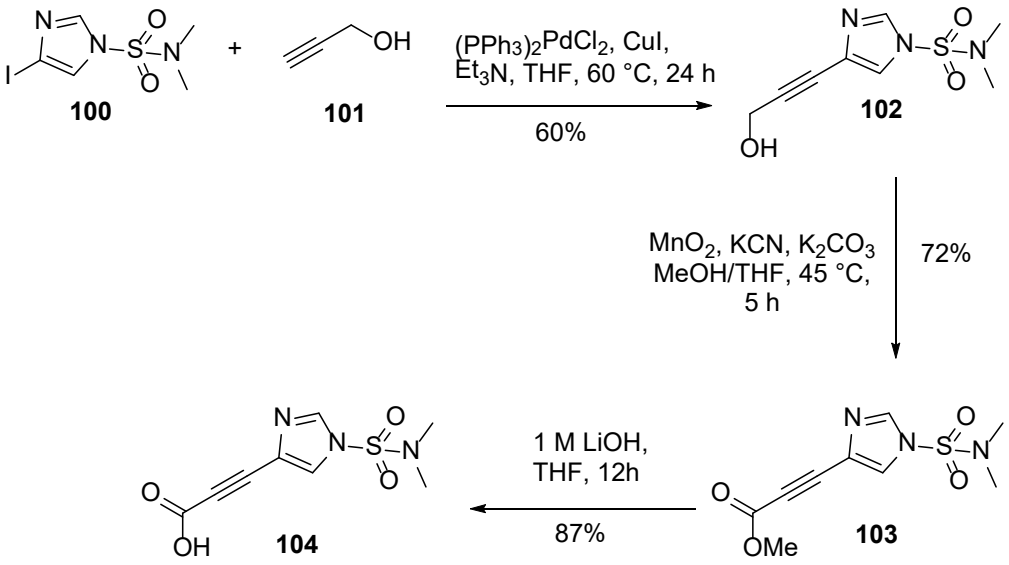
The first-generation approach towards the synthesis of ageliferin (**56a**) was adapted from synthetic attempts toward other oroidin alkaloids. Explicitly, construction of the amide bonds containing the pyrrole rings through a series of Mitsunobu reactions via a diol, C2 amination and deprotection of a hydroxy ester intermediate **97** (**Scheme 4.8**). Intermediate **97** could be obtained from the cycloadduct **98** via reduction of the double bond followed by methanolysis to open the lactone ring. Propriolate **99** would serve as a precursor in a Diels-Alder reaction to produce the cycloadduct **98**.

Scheme 4.8 First-Generation Approach to Synthesis Ageliferin



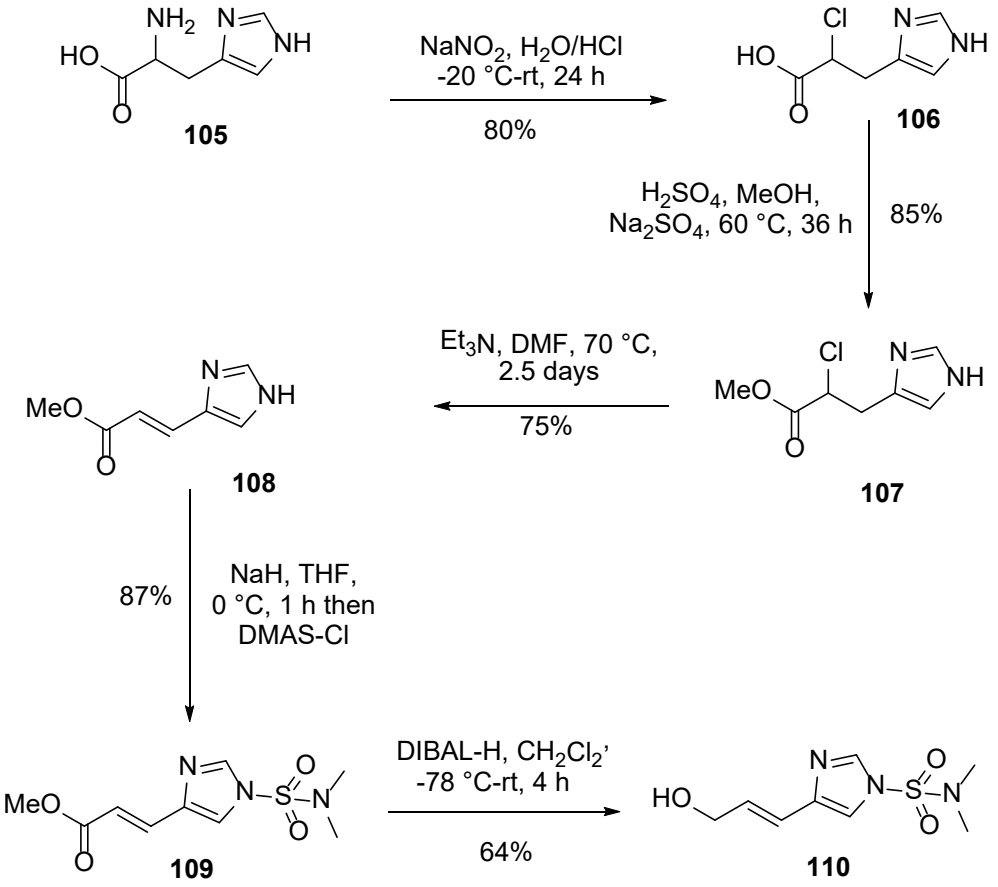
To begin with, Dr. Lima in our group has started to synthesize the key propriolate intermediate that was required for the intramolecular DA reaction. Sonogashira reaction was tried first with the THP protected propargylic alcohol and later the THP protection and deprotection was omitted by developing a direct Sonogashira reaction with un-protected alcohol.[64, 65] Several attempts were made to oxidize the alcohol **102** to either the corresponding acid or the aldehyde but to no avail. Finally, a tandem oxidative esterification using MnO_2 and catalytic KCN in methanol was successful (**Scheme 4.9**).[66]

Scheme 4.9 Synthesize the Key Propriolate Intermediate



The other coupling partner (allylic alcohol **110)** is a common building block in our lab and a method to prepare it in five steps starting from histidine (**105**) has already been developed (**Scheme 4.10**) or it can be prepared from urocanic acid.[67]

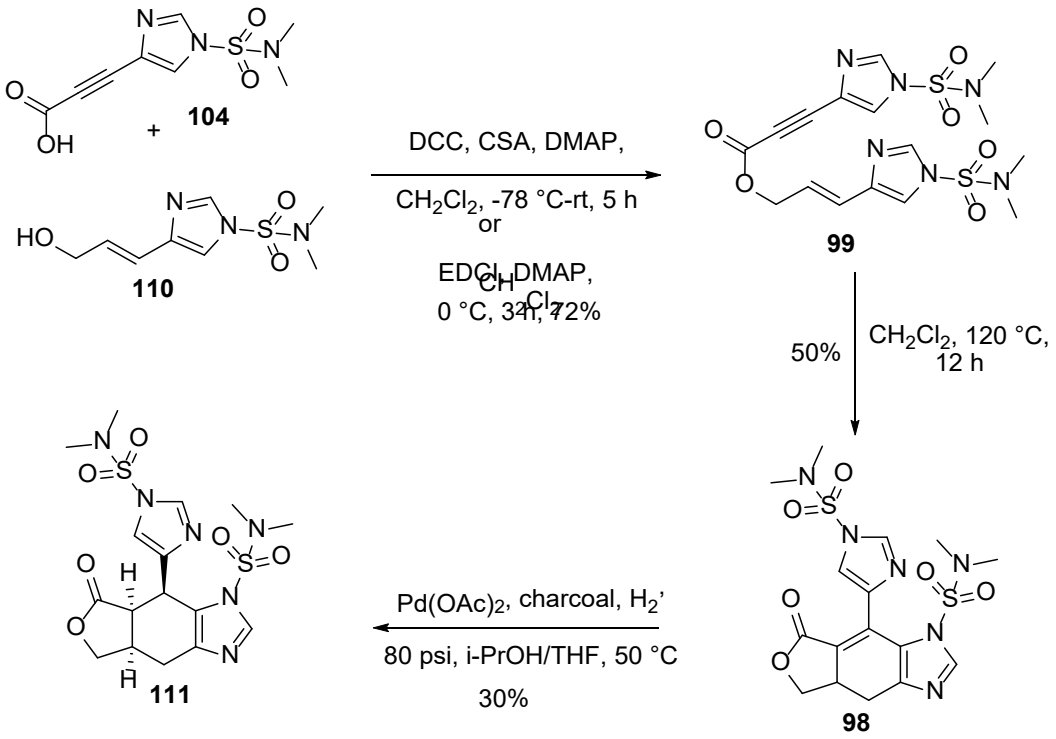
Scheme 4.10 Synthesize the Another Key Propriolate Intermediate



After successfully synthesizing the acid and the allylic alcohol, these two coupling partners were joined together using DCC first. But the ester isolated from this DCC coupling was not a suitable substrate for the DA reaction. Potentially because of the presence of byproducts from the DCC coupling. Later it was found out that when the coupling was performed using EDCI·HCl, the product thus formed was suitable to produce the DA product in good overall yield.[64] After struggling in reducing

the double bond using standard reduction conditions (Pd/C, H_2), it was found that the reduction can be achieved using $Pd(OAc)_2$, and charcoal as a catalyst for the hydrogenation.[68] Although all cis lactone was successfully synthesized, it was later found out that the lactone of **111** can be treated with NaOMe/MeOH to open the ring and provide desired all trans isomer. It has been demonstrated in our lab before those similar systems undergo an epimerization to relieve steric strain upon opening of the lactone resulting in the desired trans stereochemistry. As will become apparent due to competitive intramolecular cyclization and multiple steps, this approach was abandoned (**Scheme 4.11**).

Scheme 4.11 Synthesis the Key Intermediate Lactone

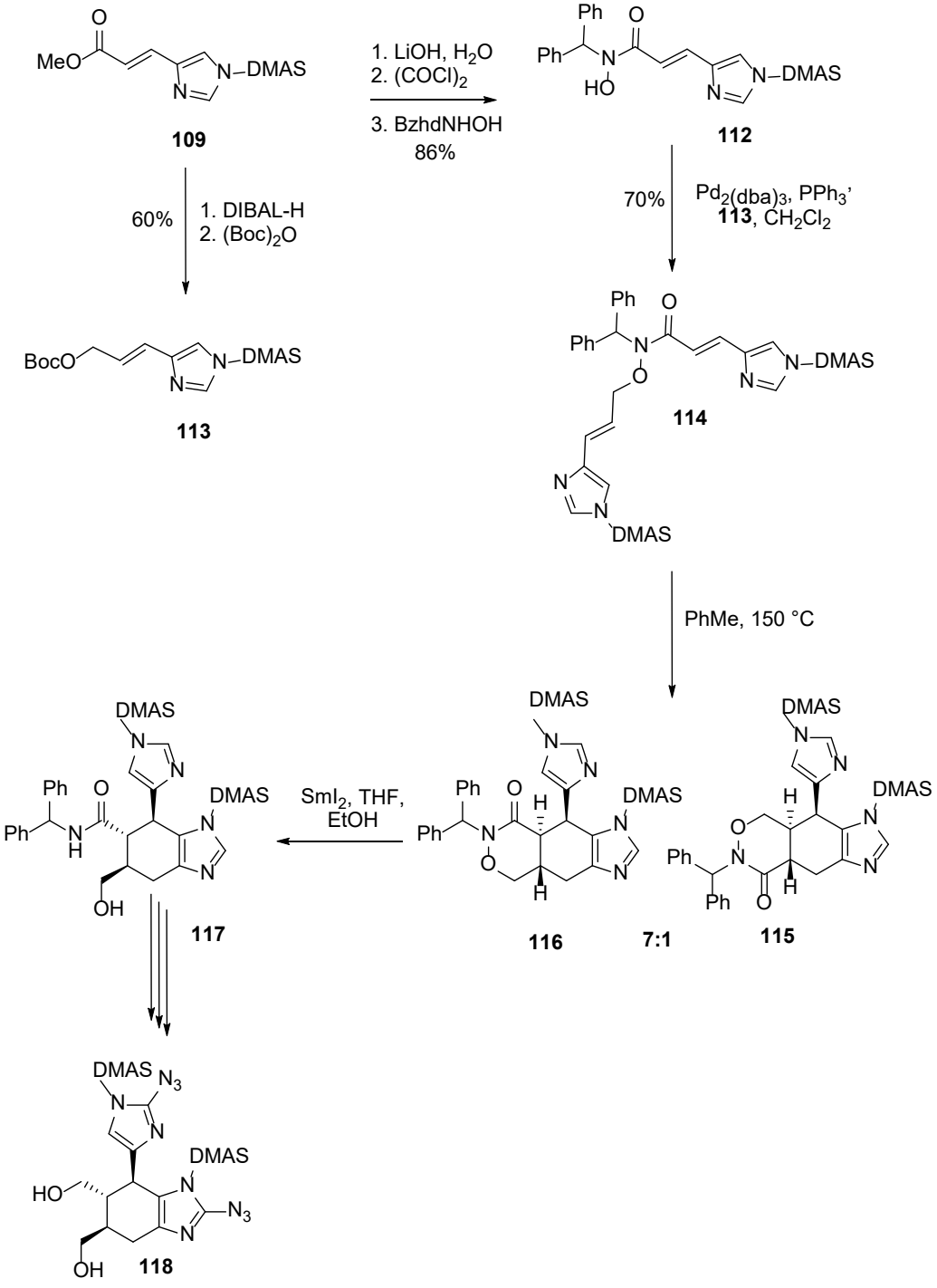


4.5 B Approach Via hydroxamate linkage

Although failure of this approach was disappointing, a lot was learned from these reactions. A revised approach involved the utilization of a hydroxamate **112**, that would serve as a substrate in DA reaction. Hydroxamate **114** was evolved while pursuing the total synthesis of axinellamine and massadine in our lab (**Scheme 4.12**).[61] For the synthesis of required substrate **109**, the same sequence was followed starting

from the uraconic acid via esterification followed by protection of the imidazole nitrogen provided the ester **109**. Other protecting groups including benzyl and SEM were also tried successfully but for simplicity, only DMAS group is shown here. Ester hydrolysis, conversion of the carboxylic acid thus formed to the acyl chloride and finally coupling with benzhydryl hydroxylamine afforded **112**. The allylic carbonate **113** was synthesized by ester reduction using DIBAL-H followed by BOC protection. Here too, other protecting groups were successfully tried. Reaction of **112** and **113** in the presence of Pd_2dba_3 provided the required pseudo dimer **114** in generally good yield. Subjection of the dimer **114** to intramolecular DA reaction in toluene at 150 °C (sealed tube) led to a smooth cycloaddition providing a mixture of the normal and inverse electron demand product **116** and **115** respectively favoring the normal addition product. N-O bond reduction using SmI_2 in THF and EtOH provided the hydroxy amide **117**. Elaboration of this compound to diol bis azide was successfully achieved but further reactions on the diol to convert this to the corresponding acyl pyrrole were complicated due to competitive intramolecular cyclization reactions causing this approach to put on hold (**Scheme 4.12**).

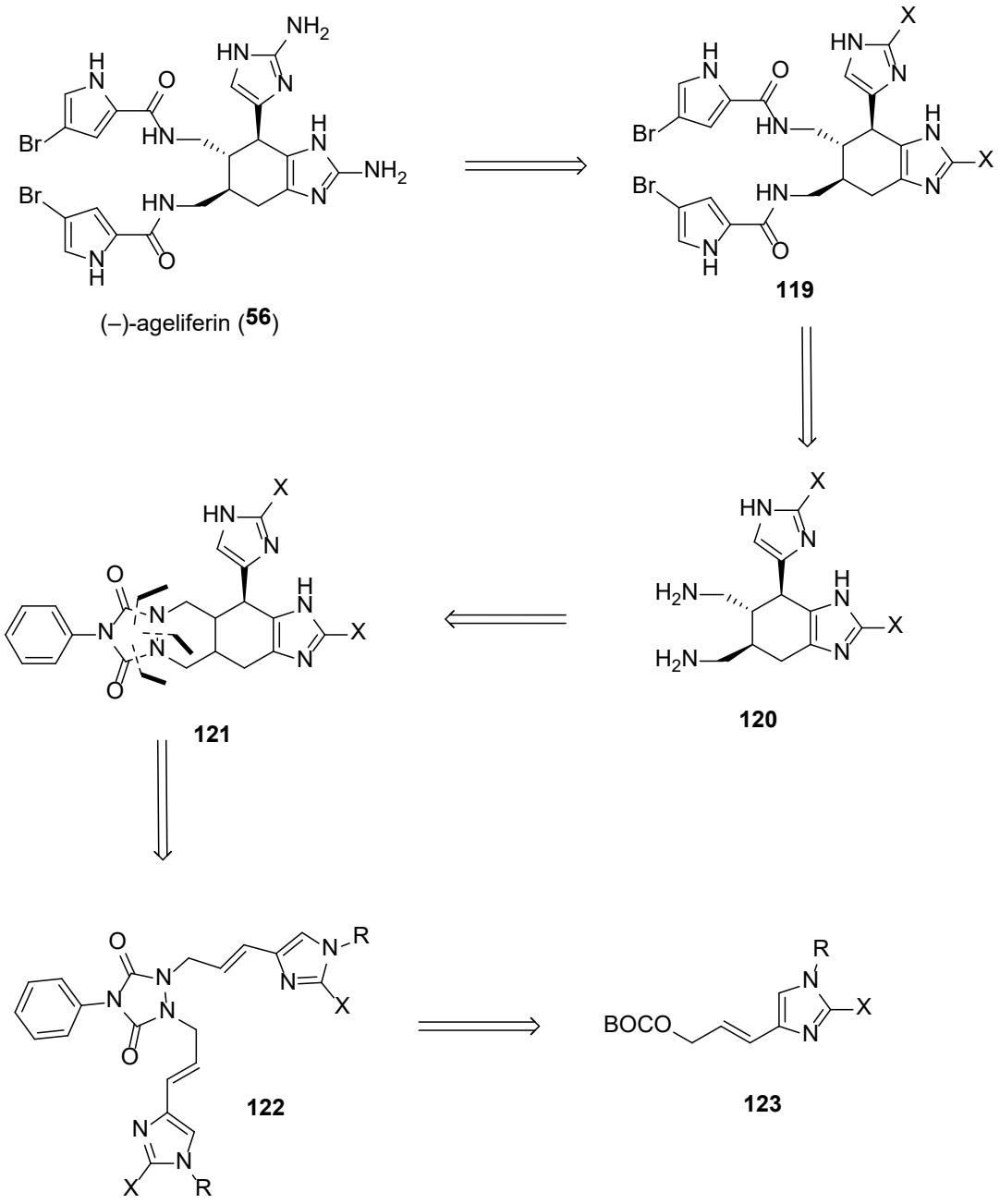
Scheme 4.12 Synthesis the Key Intermediate via Hydroxamate Linkage



4.6 Current Pre-DA Approach (Results and Discussions)

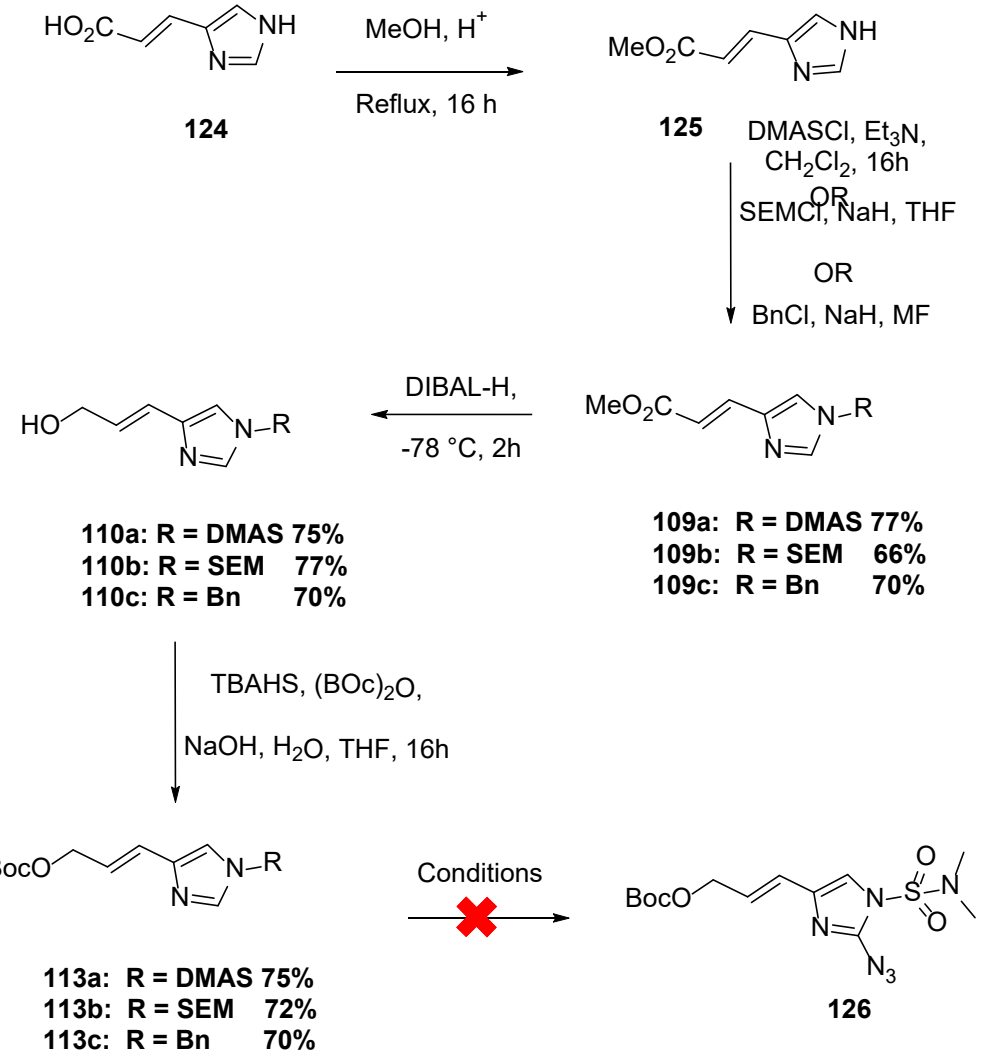
After successful assembly of tetrahydrobenzimidazole with the desired stereochemistry, our focus was on elaboration of this key intermediate to complete the total synthesis. Learning lessons from previous generations' approaches, we proposed a similar DA approach however with an N-N connection where nitrogens would come from a urazole moiety (**Scheme-4.13**, **119**). In principle, the 2-amino group can be installed from the corresponding 2-functionalized intermediate. The required 2-functionalized intermediate could be accessed via N-acylation of the diamine **120**. The diamine **120** could be synthesized from the corresponding tetrahydrobenzimidazole **121**. The THB **121** could be obtained by performing a DA reaction on urazole dimer **122**. The dimer **122** could be constructed by a Tsuji-Trost reaction with a BOC activated allylic alcohol. The alcohol can be accessed via a known synthetic route from the urocanic acid **123** (**Scheme 4.13**).

Scheme 4.13 Proposed Retrosynthetic Scheme of Ageliferin



With the above retrosynthetic scheme in mind, we started a campaign toward the synthesis of a key intermediate **126** where we wanted to have the C-2 position of the imidazole ring already functionalized in such a way that the pre-existing functionality could later be converted into desired amine. Specifically, we started with a commercially available acid **124** and performed a sequential esterification, DMAS, SEM, Bn protection, reduction and finally, BOC protection to afford DMAS, SEM, Bn protected -OBOC intermediates[65] **113a, 113b, 113c** that were ready to be C-2 functionalized. Our lab has already completed the total synthesis of a number of oroidin alkaloids that contain 2-aminoimidazoles by C-2 azidation followed by reduction.[69, 70] We started our investigation following this well stablished approach.[70] Installation of C-2 azide proved to be complicated using the -OBOC precursor. A complex reaction mixture resulted when this substrate was treated with n-BuLi and TsN_3, probably because of the instability of -OBOC group in these conditions (**Scheme 4.14**).

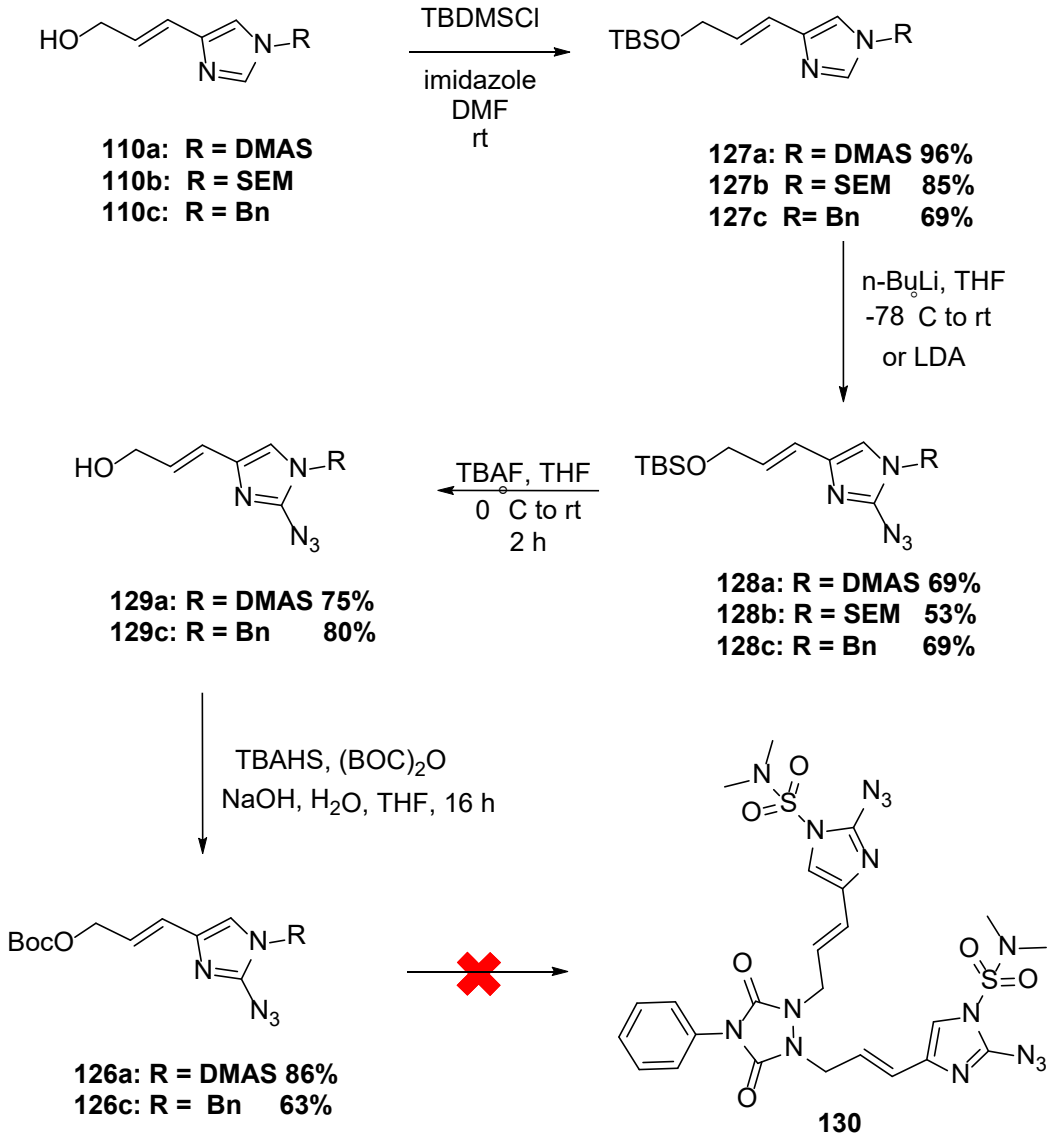
Scheme 4.14 Synthesis the Key Intermediate



Later, it was decided to attempt azidation earlier in the sequence. In particular, -OTBS intermediates were prepared **127a, 127b, 127c** and then treated with 1.1 equiv.

of n-BuLi at -78 °C followed by the addition of TsN_3 and this reaction provided the C-2 azidated intermediate with moderate yields. For yield optimization, LDA was also used as an alternative to n-BuLi, but the results were almost identical. The C-2 azides **128a, 128c** intermediates were then subjected to TBAF assisted TBS deprotection followed by Boc protection to produce the -OBOC intermediates with good overall yield **126a, 126c.** The next step was to install the two carboxamide nitrogen source "urazole." Following the methods developed in our group, $Pd_2(dba)_3$ was used to facilitate the Tsuji-Trost reaction using the azide intermediate but unfortunately[71] these standard reaction conditions did not afford the desired product. Most likely, azide was interfering through Pd-catalyzed side reactions (**Scheme 4.15**).[72]

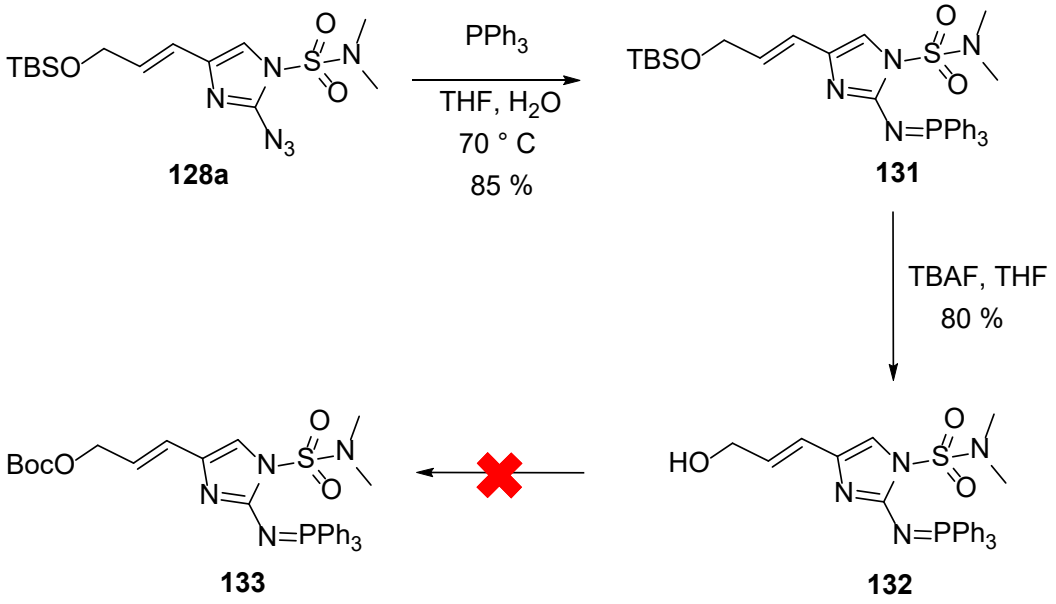
Scheme 4.15 Synthesis the DA Precursor



Inspired by Chen's approach towards ageliferin total synthesis, we sought to protect the azide from taking part in potential Pd-catalyzed side reactions.[59]

Subsequently, the azide **128a** was taken and was subjected to Staudinger reaction conditions in order to generate the iminophosphorane intermediate. The -OTBS derivative **128a** was treated with triphenylphosphine in THF and water at 70 °C. The desired iminophosphorane was isolated in excellent yield. This intermediate was treated with TBAF in THF to produce the corresponding allylic alcohol **132**. Unfortunately, BOC protection in aqueous medium did not produce the desired product because of decomposition of the starting material. Other conditions were also attempted by using triethylamine as a base in DCM but resulted in no success (**Scheme 4.16**).

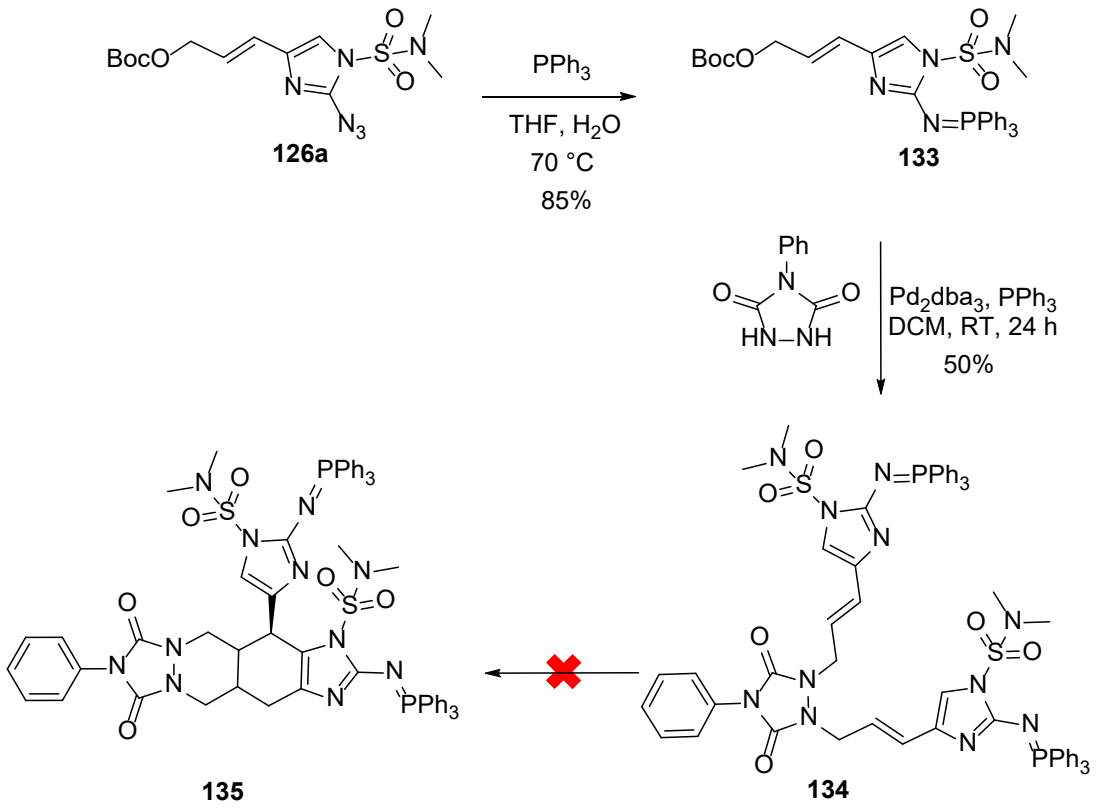
Scheme 4.16 Preparation of Iminophosphorane Intermediate



However, to our delight, a slight change in reaction sequence provided us the desired BOC protected iminophophorane **133** in good overall yield (X-ray, Figure 4.2). Specifically, TBS deprotection and BOC protection reactions were performed prior to Staudinger reaction (**scheme 4.15**). After the successful synthesis of iminophosphorane, we were excited to see that this intermediate works well under Tsuji-Trost condition and it provided the dimeric imidazole **134** in good yield. This dimer was all set for the DA reaction but surprisingly, standard DA reaction conditions produced a complex mixture with no desired product **135** formation. While this

outcome was disappointing, it illustrated the point that DA reaction might be problematic if there is overcrowding around the imidazole ring (**Scheme 4.16 A**).

Scheme 4.16 A Successful Approach to Prepare Dimeric Imidazole



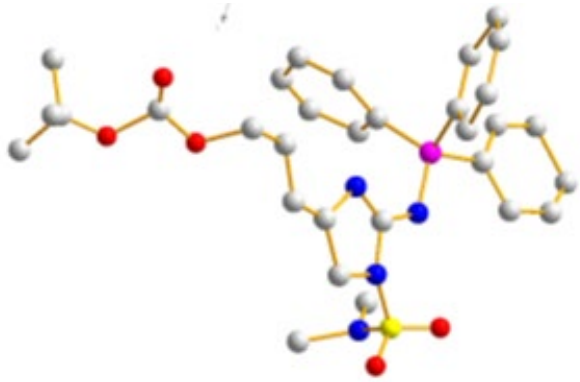
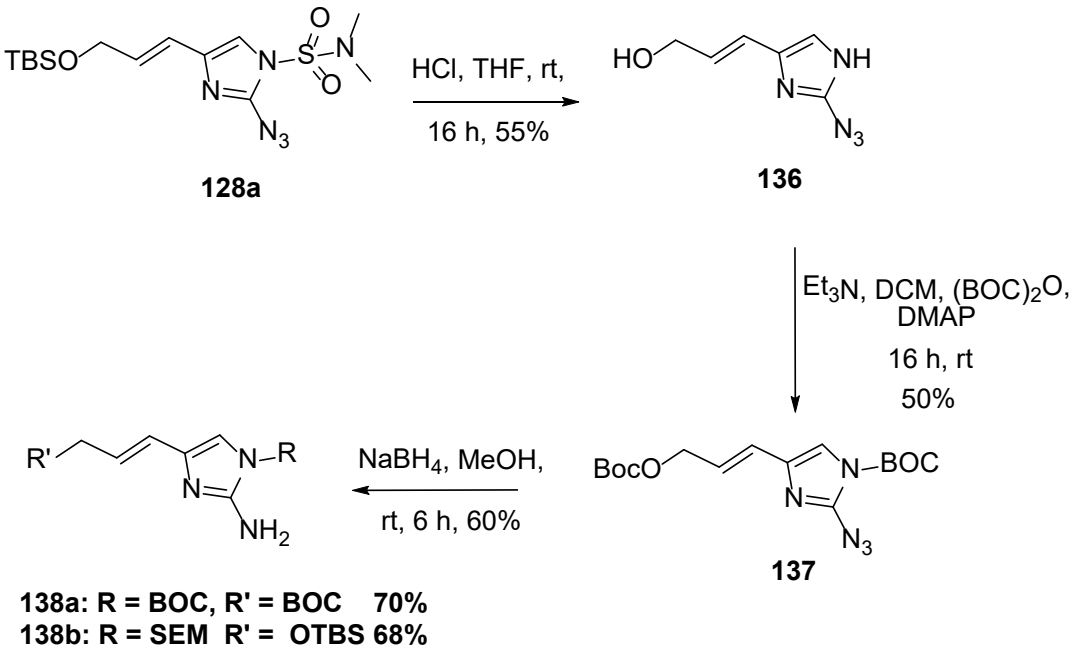


Figure 4.2 X-ray structure of 133

Although the DA reaction outcome was disappointing, the progress in constructing fully functionalized intermediates via this approach was really encouraging. As a result, hydrolysis of iminophosphorane was proposed prior to performing the DA reaction. The only caution with this sequence is that it might be difficult to deprotect the DMAS group if the hydrolysis is performed to convert the iminophosphorane to the amine. An early plan was to simply replicate the sequence to produce BOC-iminophosphorane **133**. To execute this plan quickly, we started with the DMAS-azide **128a** and converted this to bis-BOC amine **138a** in 4 simple steps. First, DMAS-TBS-azide **128a** was treated with HCl in THF for dual deprotection. Unfortunately, this substituted product **136** was unstable in MeOH solution and when it was left in the NMR tube to record the ^{13}C-NMR, the compound decomposed. So, in scale up batch crude product was used directly without purification. The allylic alcohol **136** was then subjected to biphasic BOC protection conditions to produce the bis-Boc azide **137**.

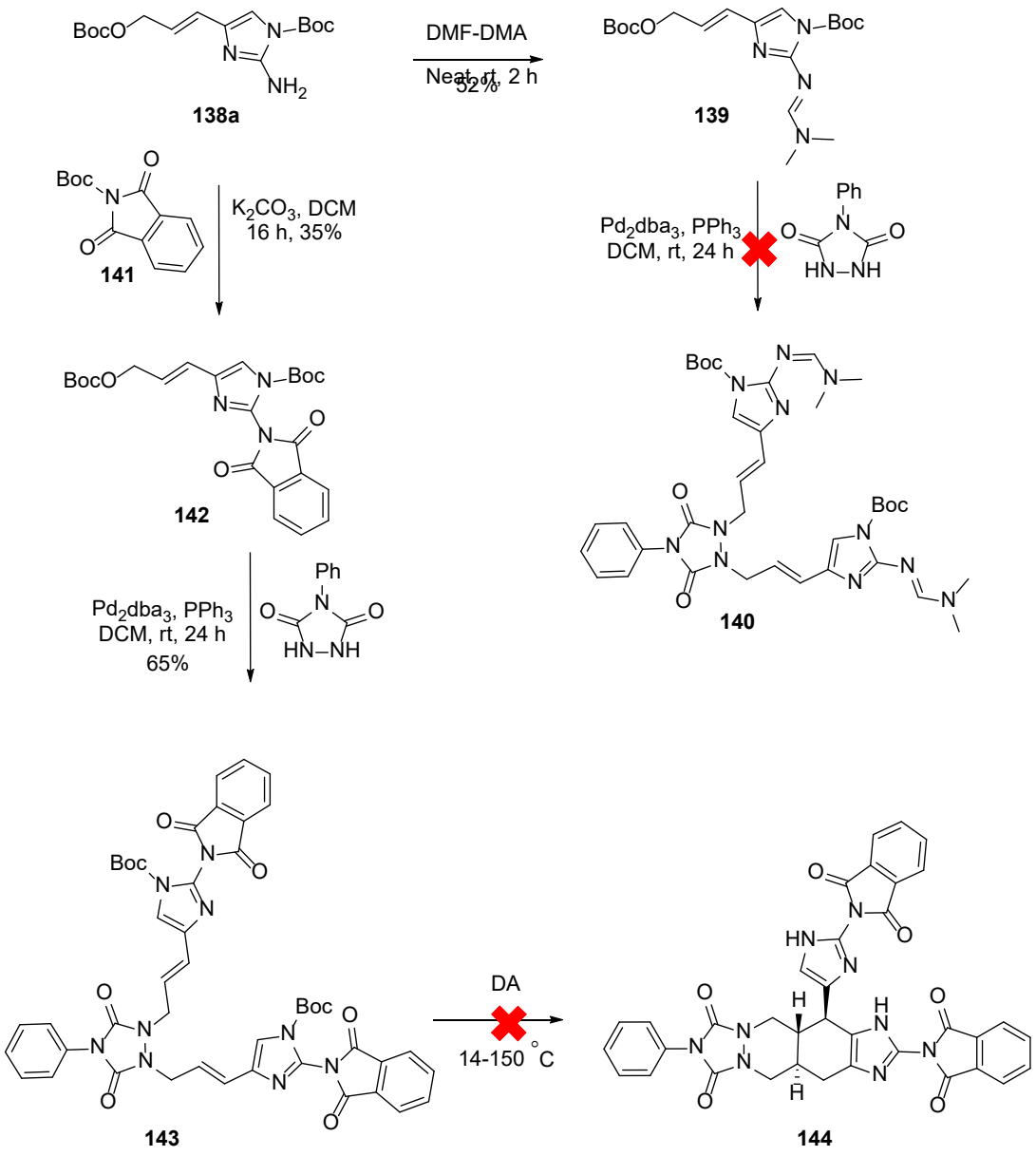
The azide **137** was subsequently reduced to the corresponding amine using $NaBH_4$. Having the bis-BOC amine in hand, our plan was to protect the amine to minimize amino palladation and catalyst poisoning.[73, 74] Just out of curiosity, the amino intermediate was subjected to Tsuji-Trost reaction conditions, but to no avail (**Scheme 4.17**).

Scheme 4.17 Approach to Prepare 2-Amino Imidazole



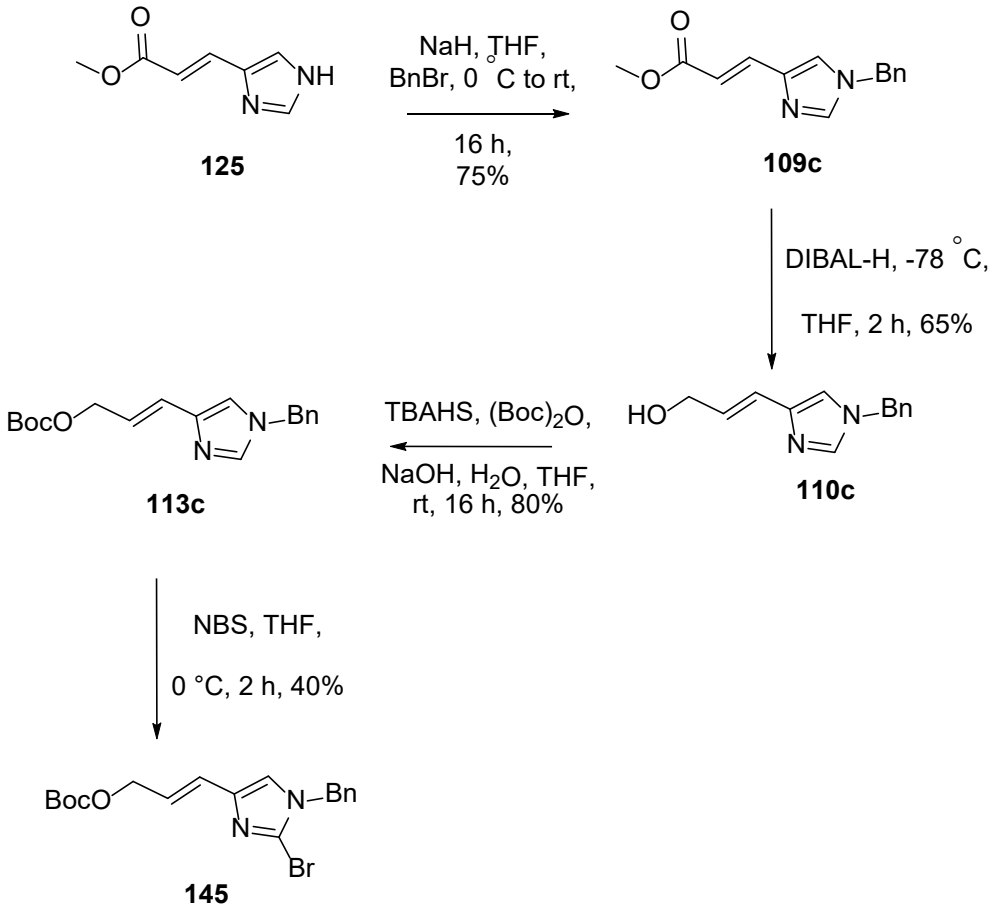
It was not surprising that amine can poison palladium, but the reaction still was attempted and amine **138a** did not undergo dimerization under standard Tsuji-Trost reaction conditions. As a result, the amine **138a** was treated with DMF-DMA and BOC-phthalimide to afford the imino **139**[75] and the pthalimido **140**[62] protected compounds respectively. It was quite encouraging to see that phthaloyl intermediate **142** produced the dimer **143** under standard Tsuji-Trost conditions. On the other hand, the amidine **139** did not undergo dimerization. The N-phthalimide **143** dimer was subjected to DA conditions, however the reaction conditions did not afford the desired product, but decomposition was observed (**Scheme 4.18**). Our assumption here is that either NBOC groups are thermally labile resulting in decomposition or crowding in the transition state due to the presence of bulky protecting groups retards the cycloaddition and decomposition occurs at the elevated reaction temperatures.

Scheme 4.18 Protection of 2-Aminoimidazole



As azide as an amine precursor was proved to be an inappropriate substrate in the steps following its introduction investigation of other amine precursors were warranted. Based on literature, there are multiple options available to pursue this approach, such as; halogens (Br, Cl and I),[76-78] sulfoxides/ sulfones,[79] and diazonium salts etc.[80, 81] To begin with, the 2-bromo analog was thought to be the suitable substrate as a precursor to potential cross-coupling reactions. For this reaction, DMAS protecting group proved to be unfruitful. Specifically, when DMAS protected OTBS intermediate **127** was treated with n-BuLi followed by NBS, a complex reaction mixture was formed. After encountering problems associated with DMAS protecting groups, our focus shifted to benzyl protection. With the benzyl protecting group, to make the approach step economical, C-2 bromination was investigated with OBOC intermediate **113a**. Starting with the ester **125** which then treating with BnBr followed by DIBAL-H reduction produced the allylic alcohol **110c**. Bi-phasic BOC protection using a phase transfer catalyst produced the -OBOC intermediate **113c** in excellent yield. Bromination was investigated using n-BuLi/ NBS combination resulting complex reaction mixture. Later, it was found that when **113c** was treated with NBS in THF at lower temperature, the 2-brominated product **145** was formed in moderate yield (**Scheme 4.19**).

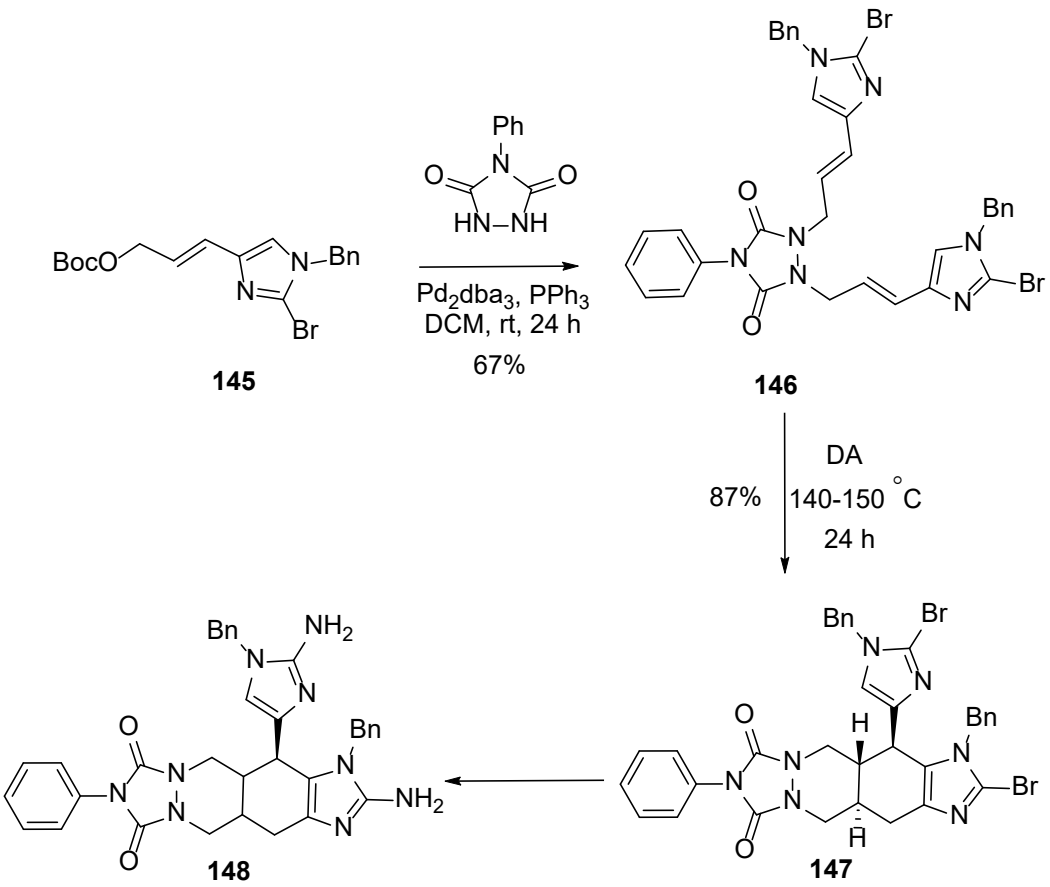
Scheme 4.19 Preparation of C2-Halo Imidazole Derivative



Although the yield for bromination was modest, sufficiently product was in hand to carry it forward to test the hypothesis. Intermediate **145** was converted to the imidazole dimer via Tsuji-Trost reaction to produce **146**. Intermediate **146** was then taken in toluene and the dimer was heated to 140-150 °C for 24 h. We were delighted to observe not only the DA reaction took place with an excellent yield but also the reaction was

stereoselective and only the all-trans isomer was isolated. No evidence of the cis isomer was observed in the ^{1}HNMR spectrum of the crude reaction mixture. Electrostatically driven noncovalent interaction between a region of positive electrostatic potential on the outer side of the halogen X in a molecule R-X and a negative site of the pi-electrons of an unsaturated system[82] and that interaction might be stabilizing the transition state and produced only all trans isomer. Several attempts were made to convert the bromo-benzimidazole **147** to the amino product **148**. For example, **147** was treated with ammonia for the direct conversion under thermal conditions,[83] but the desired product was not observed. As an alternative, **147** was also treated with benzophenone imine under Pd-catalyzed reaction conditions to produce the imine as an amine precursor.[84] The rection with benzophenone imine also did not afford the desired product. **147** being an advanced intermediate, we thought this reaction has a potential and can act as a key reaction to complete the total synthesis (**Scheme 4.20**).

Scheme 4.20 Construction of C2-Functionalized THB



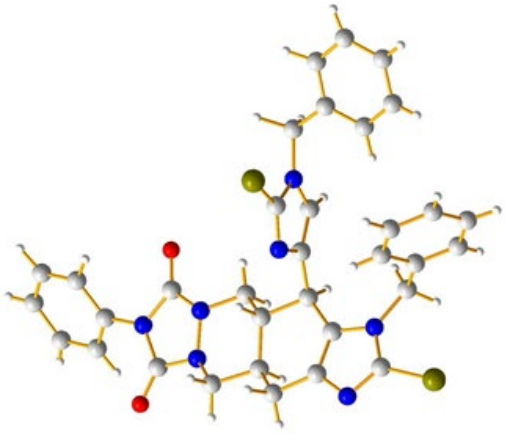
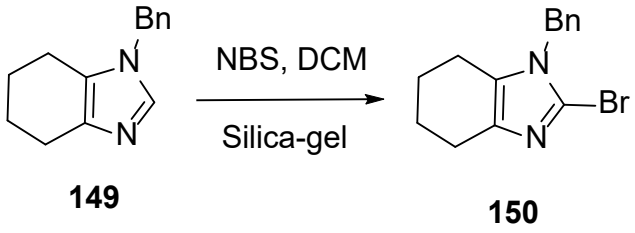


Figure 4.3: X-ray structure of 147

As mentioned above about the bromotetrahydrobenzimidazole being a key intermediate, it was worth spending some time to understand the conversion of bromo to amine in detail. To do so, we thought to study some of these reactions on simpler substrates. To investigate this plan, we synthesized a simple benzyl protected tetrahydrobenzimidazole **149** and brominated this using NBS in DCM and silica gel.[85] The product **150** was crystalline, and the structure was confirmed by the crystal structure as well.

Scheme 4.21 C2 Bromination on Tetrahydrobenzimidazole



149 **150**

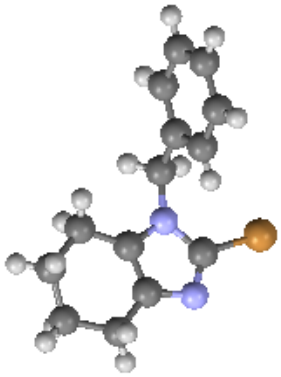
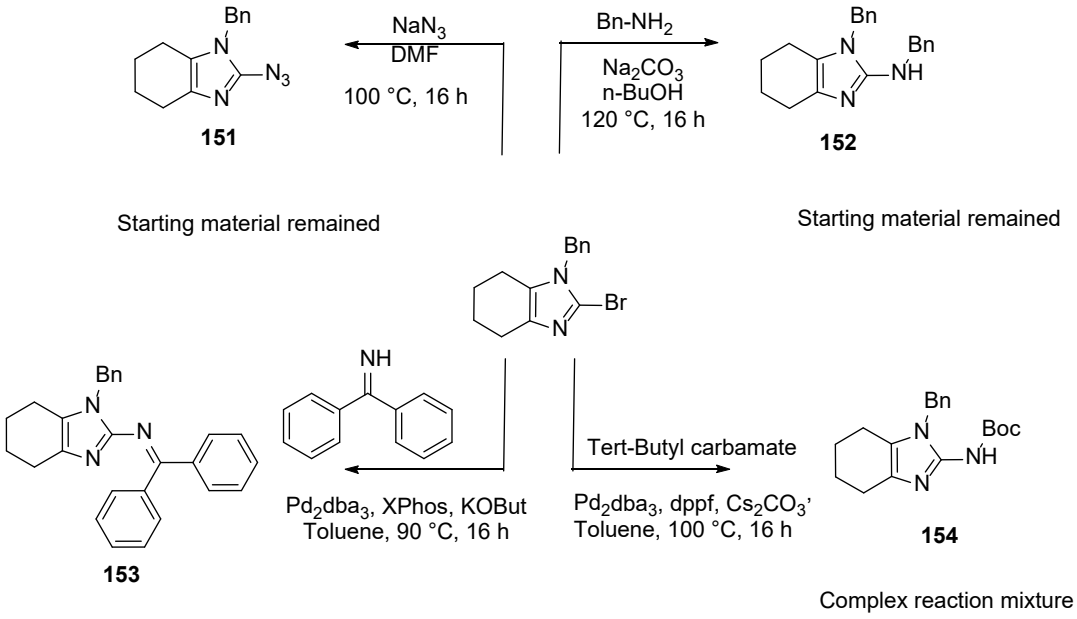


Figure 4.4: X-ray structure of 150

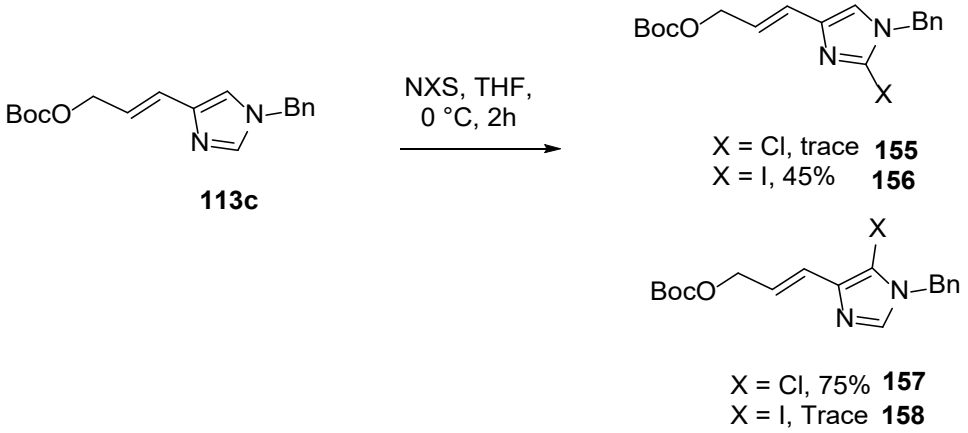
Reactions of **150** with NaN_3 in DMF at 100 °C[86] and Bn-NH_2/ Na_2CO_3 in n-BuOH at 120 °C[87] both resulted in no reaction and only starting bromo was recovered. Pd-catalyzed reactions with benzophenone imine[84] and tert-butyl carbamate also resulted in recovery of starting material and a complex reaction mixture respectively (**Scheme 4.22**).

Scheme 4.22 C2 Amination on Model Substrate



As the bromo precursor did not produce the desired amino product, and we interpreted these observations to suggest that the C2-position was not electrophilic enough. There are related examples of nucleophilic displacement for 2-chloroimidazole,[88] and thus our next target was the 2-chloro analog. As stated above, halogenation performed on the -OBOC intermediate was lower yielding of C2 substitution because of the formation of both isomers i.e., C2 and C5 (**Scheme 4.23**).

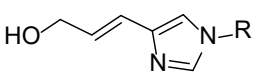
Scheme 4.23 Preparation of C2-Halo Imidazole Derivative



As the halogenation reaction was low yielding because of the formation of the mixture of regioisomers, it was tested on the -OTBS intermediate **127a, 127c**. To our delight, this reaction was regioselective and exclusive production of 2-halo isomer was observed. As there were successful attempts made towards the synthesis of 2-azido intermediate via lithiation of C-2 position (**Scheme 4.15**). Identical attempt was made to generate the anion using n-BuLi in THF and the anion thus formed was quenched with hexachloroethane to produce the 2-chloro product. Although no attempts were made to isolate it, ^{1}H-NMR spectrum of the crude reaction mixture indicated the formation of C-5 regioisomer as a minor product (**Scheme 4.24**). We were delighted with this outcome and quickly wanted to take this chloro derivative to the DA step.

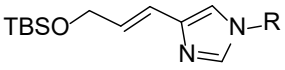
We also took this opportunity to elaborate the benzyl protected O-TBS intermediate with other 2-amino surrogates including formation of C2 S-Ph **159** and C2 S-Me **161** derivatives. These intermediates might provide the amine upon treatment of the corresponding sulfones with ammonia. Also, as we found OTBS group to be more suitable and appropriate in producing the desired regioisomers under these reaction conditions, halogenation was also investigated on this substate. As expected, yields for the formation of 2-halogenated products were improved substantially. Clearly, the OTBS intermediate was found out to be the best substrate to carry out lithiation followed by electrophilic trapping at the 2-position (**Scheme 4.24**). 2-Chloro, iodo, S-Ph and S-Me intermediates were synthesized following this protocol and all these products were isolated in moderate to good yields. All these five 2-functionalized intermediates **159** to **163** were taken forward to OBOC stage following the same protocol, i.e., TBAF mediated TBS deprotection followed by BOC protection (**Scheme 4.24**).

Scheme 4.24 Preparation of C2-Functionalized Imidazole Derivative



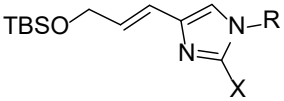
110a: R = DMAS
110c: R = Bn

TBDMSCl
imidazole
DMF
rt



127a: R = DMAS 96%
127c: R = Bn 80%

n-BuLi, THF



159: R = Bn, X = SPh 60%

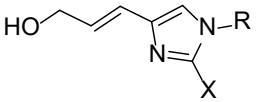
160: R = DMAS, X = SPh 45%

161: R = Bn, X = SMe 60%

162: R = Bn, X = I 75%

163: R = Bn, X = Cl 75%

TBAF, THF



164: R = Bn, X = SPh 63%

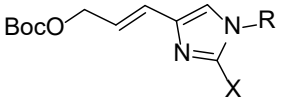
165: R = DMAS, X = SPh 54%

166: R = Bn, X = SMe 50%

167: R = Bn, X = I 63%

168: R = Bn, X = Cl 77%

Et_3N, DCM, $(BOC)_2O$,
DMAP
2 h, rt



164a: R = Bn, X = SPh 65%

165a: R = DMAS, X = SPh 81%

166a: R = Bn, X = SMe 75%

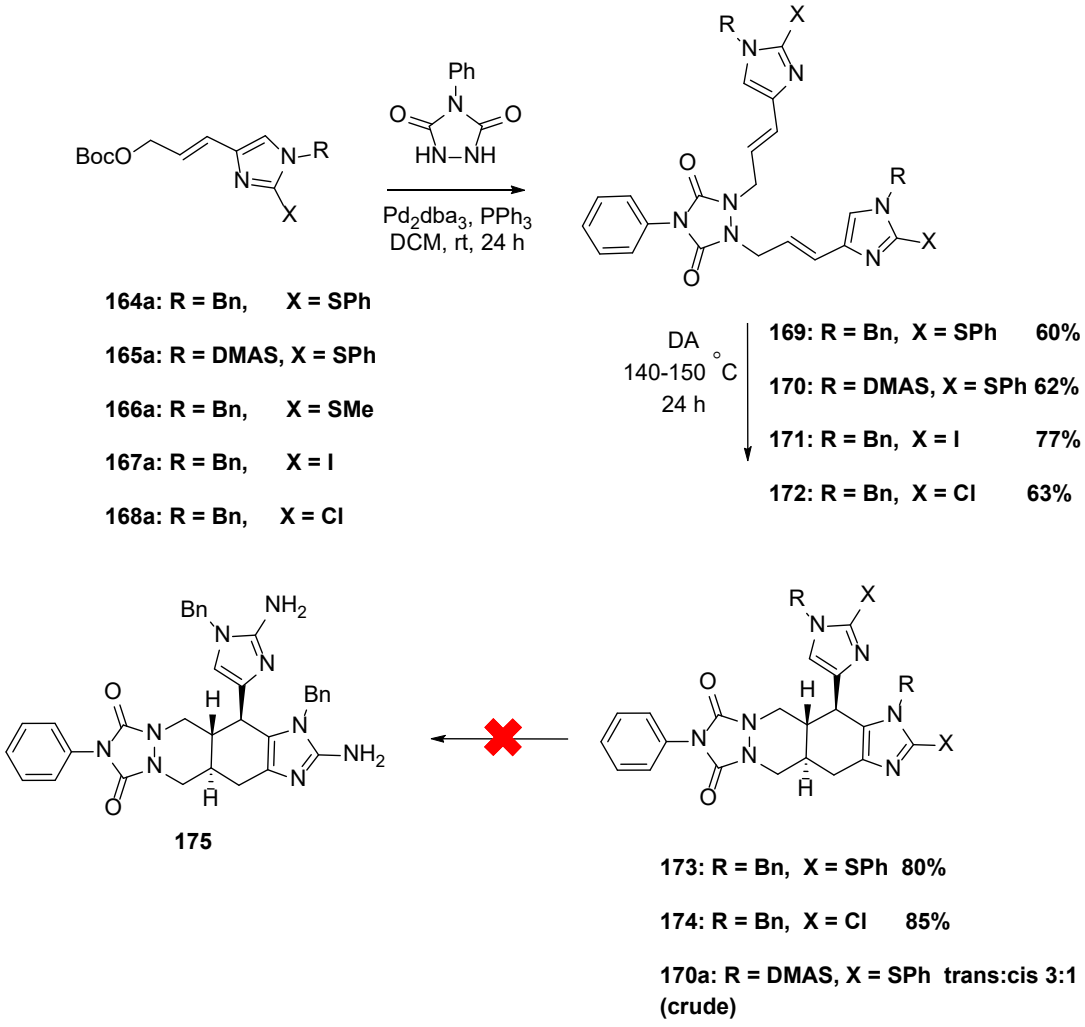
167a: R = Bn, X = I 68%

168a: R = Bn, X = Cl 80%

Learning from our previous approaches regarding the uncertainties of different substrates towards Tsuji-Trost and DA reactions, it was decided to take all these five intermediates through the next steps in parallel. Four out of five OBOC intermediates underwent Tsuji-Trost reaction to produce the dimeric compound in good yields. Interestingly, S-Me **166a** compound did not produce the desired product, a complex reaction mixture was formed. We assume in this case that the sulfur is poisoning the catalyst and thus the reaction did not procced. Out of these four dimers, two (S-Ph **169,** -Cl, **172**) underwent DA reactions to produce an exclusive trans tetrahydrobenzimidazole. However, DMAS protected dimer **170** did not show stereoselectivity, it produced mixture of trans and cis adduct (3:1 ratio) confirmed from TLC and the ^{1}H NMR of the crude reaction mixture. The probable reason for this stereochemistry might be attributed to the overcrowded DMAS group which prohibited the π-π stacking of both phenyl ring. Surprisingly, the iodo dimer did not undergo DA reaction; possibly, because of steric factors (**Scheme 4.24 A**). All the attempts to date, to advance these well-known amine precursors did not afford the desired products. For example, thiophenyl tetrahydrobenzimidazole was treated with mCPBA to produce a mixture of sulfoxide and sulfone in situ, and to this ammonia in dioxane was added. The progress of reaction was monitored by TLC at various temperatures, however only starting sulfoxide and sulfone remained. The 2-chloro and 2-bromo tetrahydrobenzimidazoles were treated with ammonia in 1,4-dioxane and the mixture was heated in a sealed tube for several hours up to 110 °C, but only the starting

halo compounds were observed on TLC, no new spot formation was observed. In our experience, formation of 2-aminoimidazoles results in a dramatic increase in polarity.

Scheme 4.24 A Preparation of C2-Functionalized Diels-Alder Adduct



164a: R = Bn, X = SPh

165a: R = DMAS, X = SPh

166a: R = Bn, X = SMe

167a: R = Bn, X = I

168a: R = Bn, X = Cl

169: R = Bn, X = SPh 60%

170: R = DMAS, X = SPh 62%

171: R = Bn, X = I 77%

172: R = Bn, X = Cl 63%

175

173: R = Bn, X = SPh 80%

174: R = Bn, X = Cl 85%

170a: R = DMAS, X = SPh trans:cis 3:1 (crude)

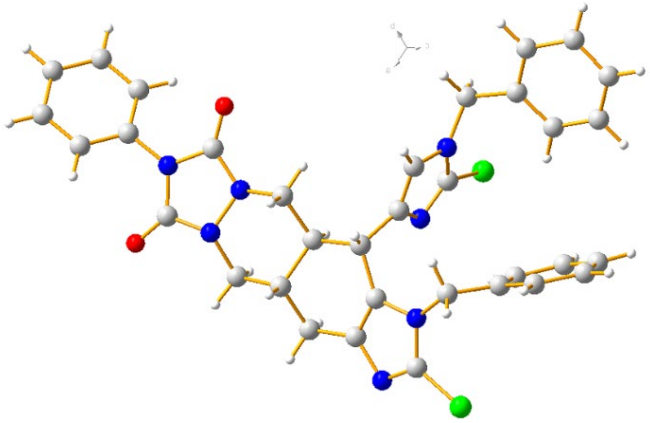


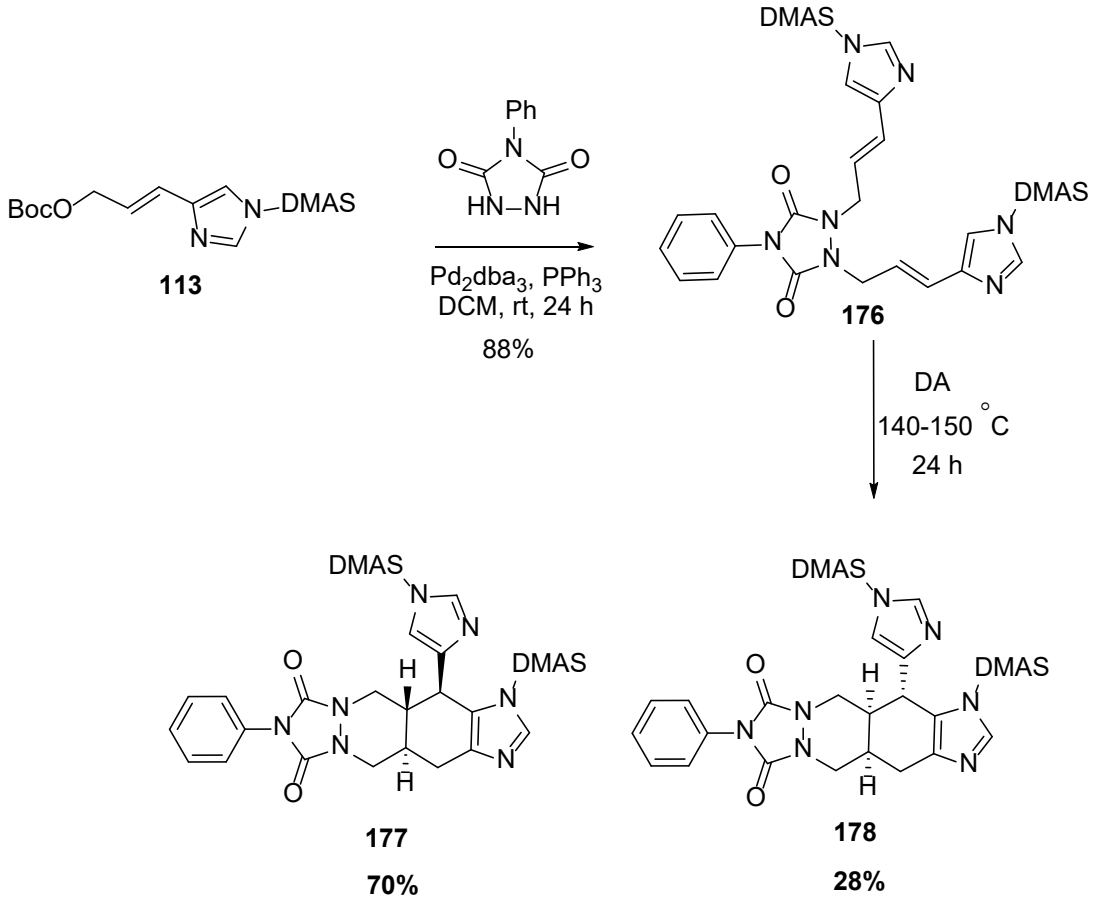
Figure 4.5: X-ray structure of 174

4.7 Current Post-DA Approach (Results and discussions)

In all these pre-DA C2 functionalization reactions, our goal was to minimize the complexity associated with bis functionalization in the latter stages of the synthesis. However, further elaboration of all the amine precursors was found to be challenging and as noted above has yet to be realized. To circumvent this issue, we thought about taking C2 unfunctionalized product to the DA step. This DA product would then be functionalized using lithiation followed by quenching of the anion with different amine electrophiles. The assembly of all trans DA adduct was quick and simple starting with the OBOC imidazole **113a** following the same reaction sequence. To begin with, we chose the DMAS protected imidazole keeping in mind that electron withdrawing group would help stabilizing the anion generated after n-BuLi treatment eventually producing the C2 functionalized imidazole. The OBOC intermediate was

subjected to Tsuji-Trost conditions and the dimer **176** was produced in good yield. The dimer **176** then underwent intramolecular DA reaction to form mixture of cis and trans tetrahydrobenzimidazoles **178** and **177** respectively. It was interesting to see that a significant amount of the cis isomer was also isolated in this case where the imidazole lacked the substituent. Moreover, from the X-ray structure it was clear that the cis adduct is sterically hindered because of non-bonded H-H interaction. On the other hand, the trans substrate lacked such interaction resulting in the formation via an endo transition state. The other hypothesis, DMAS being a bulkier group minimizes the secondary orbital interactions between non-bonding C2 substituents and the non-bonding diene cannot be ruled out (**Scheme 4.25**).

Scheme 4.25 Preparation of Unfunctionalized Diels-Alder Adduct



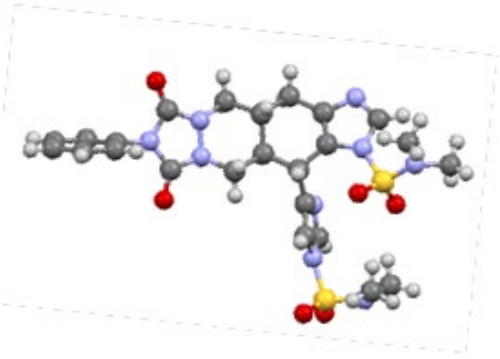


Figure 4.6: X-ray structure of 177

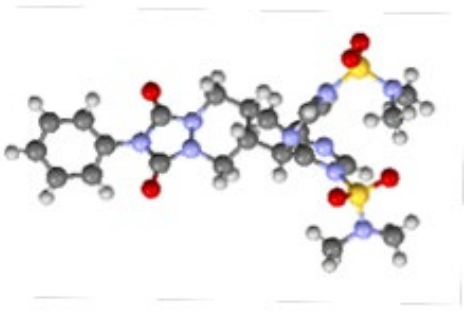
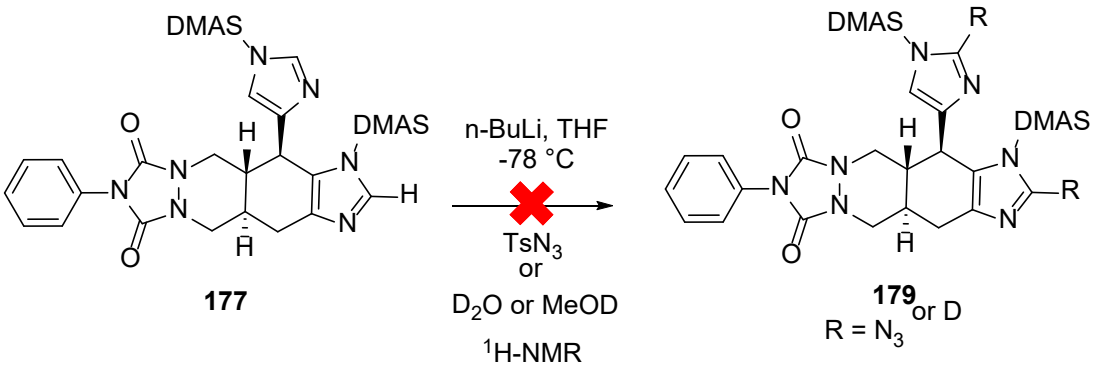


Figure 4.7: X-ray structure of 178

After many attempts on the monomers described above, we knew that halogenation or sulfenylation would not provide us a solution because of the prior hurdles encountered while converting these amine precursors to the corresponding amine. However, if we could elaborate this intermediate to the corresponding C-2 azide, there is a chance that we could reduce the azide to desired amine. The major diastereomer was subjected to n-BuLi or LDA to form the bis anion followed by quenching the anion with TsN_3. In both these reactions, no desired product was isolated. It is not clear what is happening because efforts to establish whether metalation occurred or not were unsuccessful (no deuterium incorporation with BuLi then (D_2O or MeOD). This suggests some short of reversible addition to the organolithium. Following the prior conditions, we were only able to recover the starting material whereas the later condition resulted in a complex reaction mixture (**Scheme 4.26**).

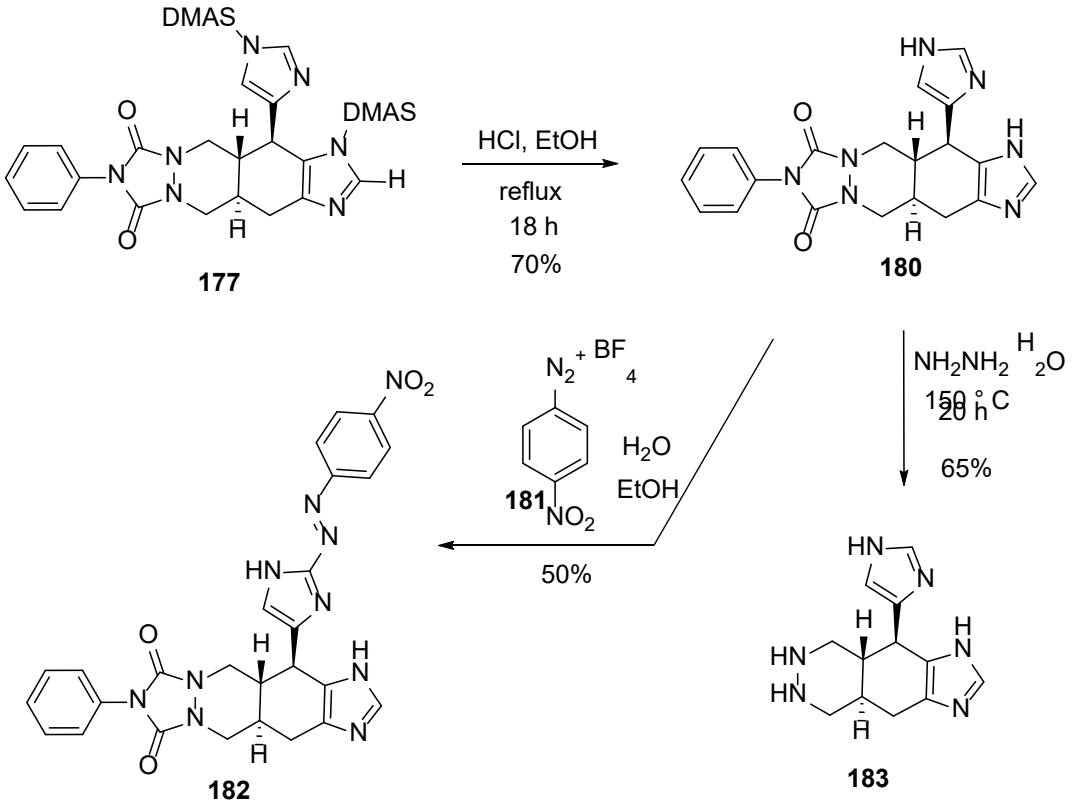
Scheme 4.26 Preparation of C2-functionalized Diels-Alder Adduct



With all the above methods applied towards C-2 amination on the dimer, there was a clue towards a potential problem. One possibility being the presence of urazole ring that inhibits the formation of anion after BuLi treatment probably by Li chelation with urazole carbonyls. To avoid this potential problem, it was planned to deprotect the imidazole nitrogen before C-2 functionalization. Also, in parallel we planned to remove the urazole ring prior further elaboration of intermediate **177**. First, the DMAS protected intermediate **177** was treated with HCl in EtOH to remove the DMAS group and provide the unprotected imidazole **180**. This was further treated with excess of hydrazine hydrate at elevated temperature 150 °C to produce the very advanced intermediate **183**.[89] The unprotected tetrahydrobenzimidazole **180** was also subjected towards diazotization reaction and was treated with p-nitrophenyl diazonium salt to produce a brown colored non-polar spot-on TLC. The compound **181** can be prepared

by the treatment of primary amine and sodium nitrite in 40% fluoroboric acid.[90] We were delighted to see this result and after isolation of the non-polar spot, it was clear by ^{1}H-NMR that there were only one p-substituted phenyl ring protons were present. In order to get bis azo derivative we increased the equivalents (4 to 8) of diazonium salts but did not convert mono to di-azo derivative. Unfortunately, this mono substituted product **182** was unstable in MeOH solution and when it was left in the NMR tube to record the ^{13}C-NMR, the compound decomposed. Although, we were unable to record and analyze the ^{13}C-NMR of this intermediate, closer analysis of the ^{1}H-NMR suggests that diazotization occurred on the unfused imidazole ring. We are trying to repeat the reaction and the NMR studies would be performed in different solvent to check the stability of **182** (**Scheme 4.27**).

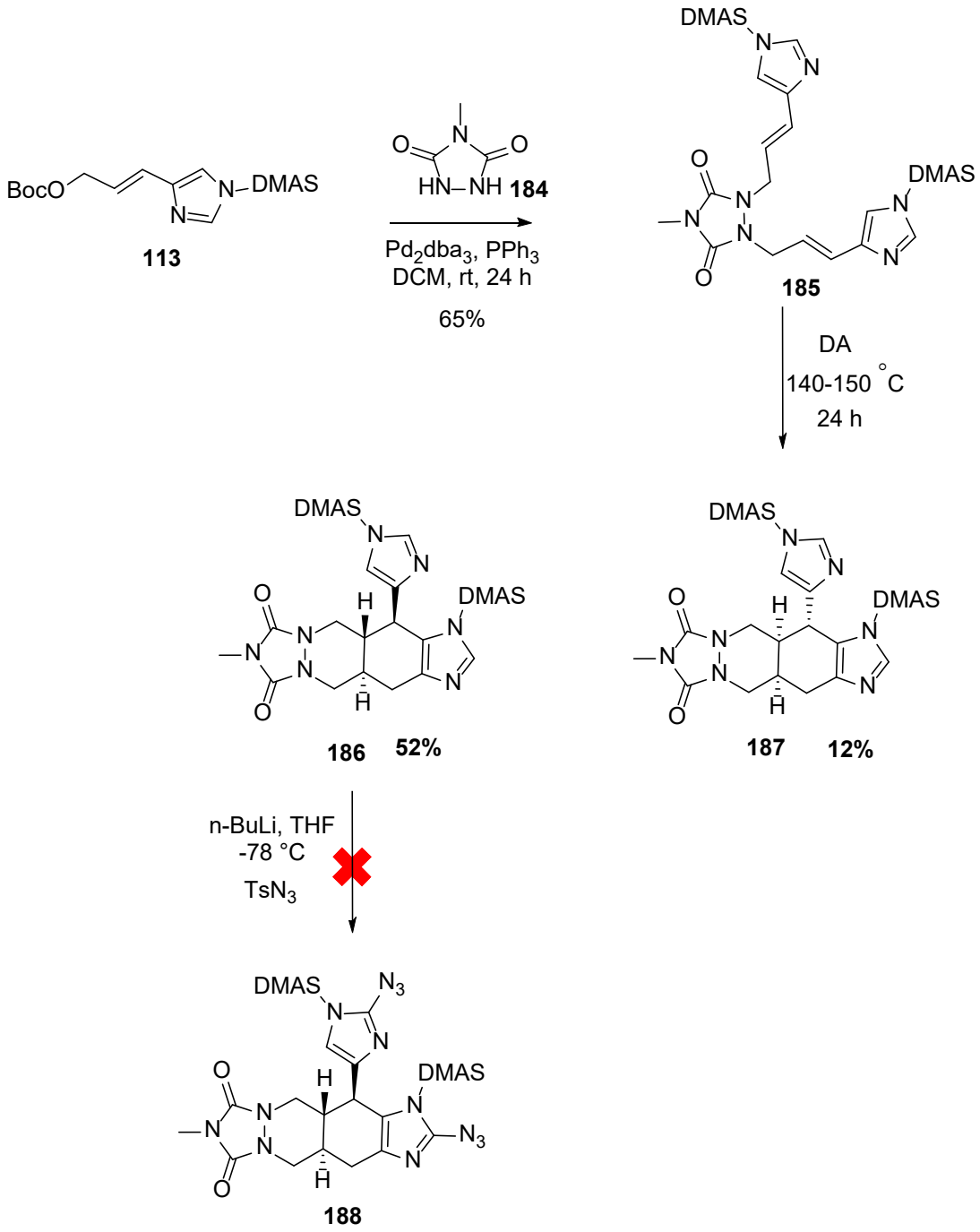
Scheme 4.27 Preparation of C2-functionalized Diels-Alder Adduct



From the above observation it was initially thought that the presence of N-phenyl urazole ring the phenyl ring may act as a competitive site to generate anions that inhibits the formation of C2 lithiation on imidazole ring after n-BuLi treatment. To avoid this problem, it was planned to prepare N-methyl urazole

instead of N-phenyl urazole. N-methyl urazole **184** can be prepared by the treatment of ethyl carbazate and CDI in methylamine for 4 h. After recrystalization from i-PrOH, the intermediate ethyl 2-(methylcarbamoyl) hydrazine1-carboxylate was treated with K_2CO_3, MeOH/H_2O at 60 ˚C to obtain N-methyl urazole **184** in excellent yield.[91] The DMAS-protected urazole derivatives **185** prepared via the Tsuji-Trost reaction delivers the mixture of trans and cis cycloadduct **186**, **187** respectively in moderate yield, but we were still unable to azidate it through a standard protocol (n-BuLi then TsN_3) (**Scheme 4.28**).

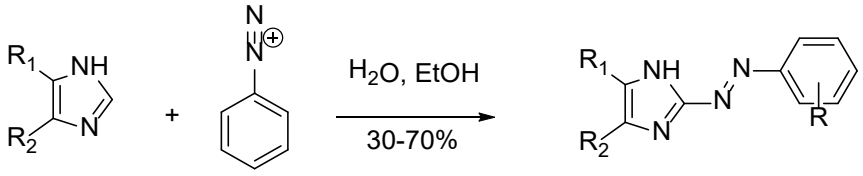
Scheme 4.28 Preparation of Diels-Alder Adduct

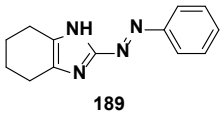


4.8 Synthesis of 2-azoimidazoles:

The diazotization reaction on unprotected tetrahydrobenzimidazole **180** was successful when that treated with p-nitrophenyl diazonium salt. We were delighted to see this result and investigated other diazotization reactions on substituted imidazole with three different types of diazonium salts. The benzimidazole was subjected towards diazotization reaction and was treated with phenyl diazonium salt to produce **189** as a brown colored precipitation. The pure compound was obtained by filtration followed by column chromatography. The model structure benzimidazole was also treated with p-methoxy phenyl diazonium salt and para nitro diazonium salt resulted **190** and **191** in 40-50% yields. After model reactions our attention turned to other substrates. Investigated diazotization reaction on 4-methyl imidazole. Interestingly, it delivered bis-diazo compounds. Because of methyl group in imidazole ring increases the electron density and that might be the probable reason behind that bis adduct formation. Only with p-nitro diazonium salt resulted 5-substituted diazo compound **194**. Reaction with bi-phenyl imidazole resulted p-methoxy and p-nitro diazonium salts were successful but we were still unable to substitute azo with phenyl diazonium salt through a standard protocol.

Scheme 4.29 2-diazotization on imidazole by azo chemistry





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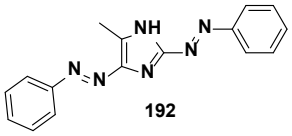

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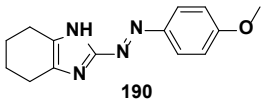

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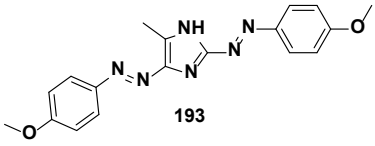

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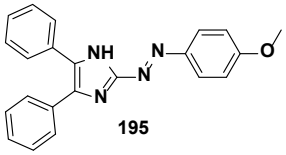

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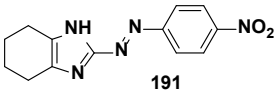
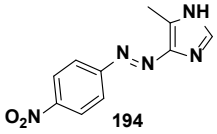
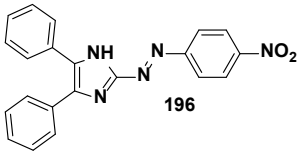


191



194



196

In summary, two different approaches were pursued for incorporation of the C2 amine to complete total synthesis of ageliferin either via C2 amination pre-Diels-Alder or C2 amination post Diels-Alder. The pre-Diels-Alder approach has been explored which offers the chance of using Pd-catalyzed cross-coupling at C2 via the 2-halo derivative. Halogenated C2-derivatives were converted into the urazole derivative via Tsuji-Trost reaction. When these dienes were subjected to a Diels-Alder reaction, a single, all trans stereoisomer was observed in excellent yield. Other approaches have evaluated include incorporation of the C2-amine prior to cycloaddition. The 2-azido derivative was prepared via C2-metallation, followed by reduction to the corresponding amine with $NaBH_4$, but the Tsuji-Trost chemistry did not work. Three different coupling reaction were explored with protected amine derivatives, the first one was with DMF-DMA and resulted in good yield, but the Tsuji-Trost reaction did not proceed. Two other coupling reactions with phthaloyl and triphenyl phosphine derivative were attempted but the Diels-Alder reaction did not proceed. The post-Diels-Alder approach has been investigated which relies on the DMAS-protected urazole derivatives via Tsuji-Trost reaction delivers the mixture of trans and cis cycloadduct in good yield but reactions to azidate using standard protocols (n-BuLi then TsN_3) were unsuccessful. It is not clear what is happening because efforts to establish whether metalation occurred were unsuccessful (no deuterium incorporation with BuLi then D_2O or MeOD). Given this lack of success, we chose to pursue different strategies for incorporation of C2 amine. N-protective DMAS group could

be removed and from the urazole framework and, on this substrate, evaluated the addition of diazonium salts. We only observed mono addition on. Currently, we are trying to take this vital intermediate to the proceeding steps. Specifically, the phthalazine **183** would be treated with brominating reagent. Based on our previous experience with C2 bromination, the preferred method would be to treat **183** with NBS in THF. However, keeping in mind the polarity of this substrate, there could be potential solubility issues associated with this. The choice of the reagent and solvent totally depends on the solubility of the substrate. We will also try Br_2 in AcOH to overcome the solubility issue. Another approach will include N-N bond reduction of phthalazine 183 followed by acylation with bromo pyrrole intermediate and at the end C2 amination.

EXPERIMENTAL DETAILS

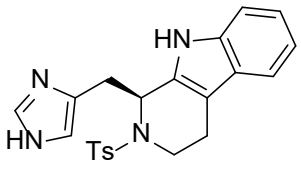
All reagents were purchased from commercial suppliers and used without purification unless otherwise specified. All reactions involving moisture sensitive reagents were conducted in flame-dried glassware under a dry nitrogen atmosphere. All solvents used in moisture sensitive reactions were purified by Innovative Technology's Pure Solve solvent purification system. NMR spectra were recorded on JEOL ECX 300 MHz and Eclipse+ 500 MHz spectrometers. ^{1}H NMR spectra were recorded in $CDCl_3$ (unless otherwise indicated) at a spectrometer frequency of 300.5 MHz or 500.1 MHz using residual $CHCl_3$ (δ = 7.26 ppm) as an internal reference. For spectra recorded in other solvents, residual MeOH (δ = 3.31 ppm) or DMSO (δ = 2.50 ppm) were used as internal references. ^{13}C NMR spectra were recorded in $CDCl_3$ (unless otherwise indicated) at a spectrometer frequency of 75.6 MHz or 125.8 MHz using residual $CHCl_3$ (δ = 77.2 ppm) as an internal reference. For spectra recorded in other solvents, residual MeOH (δ = 39.5 ppm) or DMSO (δ = 49.0 ppm) were used as internal references. Melting points were recorded on a Laboratory Devices Inc. Mel Temp apparatus and are uncorrected. Infrared (IR) spectra were obtained on a Bruker ALPHA FT-IR spectrometer using neat samples (ATR spectroscopy); all absorptions are reported in cm^{-1}.130 High resolution mass spectra (HRMS) were performed by the Shimadzu Center for Advanced Analytical Chemistry by electrospray ionization (ESI) and time-of-flight detection (TOF) unless otherwise indicated. All mass spectral data are reported as m/z (relative intensity). Analytical thin layer chromatography (TLC)

was performed on Sorbent Technologies Silica G TLC aluminum backed plates (200 μm thickness). Liquid chromatography was performed using Sorbent Technologies Standard Grade Silica Gel (230 x 400 mesh). In polarimeter the degree of rotation α is dependent on the concentration of the compound (c), the path length of the sample cell (l), and the wavelength of light that is used. The yellow light of a sodium lamp (the 'D' line of Na, wavelength = 589 nm) is used as a light source. Methanol is used as a solvent.

Chromatographic Conditions: The liquid chromatography system used was the Agilent Technologies 1200 series set from Agilent (Santa Clara. CA, USA) including a quaternary pump, mobile phase degasser, 96 vial sample injector, and diode array UV detector. A personal computer drove the chromatographic system and handled data with the ChemStation for LC 3D systems Rev. 03.02 software (Agilent). Acetonitrile solutions of all samples were made at a concentration of 2 mg/mL. One microliter of each individual solution was injected for each analysis.

The AZYP Columns used for separations were NicoShell column (3 mm i.d. x 150 mm) and MaltoShell (4.6 mm i.d. x 100 mm) the AZYP columns were packed with superficially porous (SPP) 2.7 μm particles provided by AZYP, LLC (Arlington, TX, USA). The Chiralpack IC -3 column (3 mm i.d. x 150 mm) was packed with 3 μm fully porous particles and provided by Daicel (Chiral Technologies, West Chester, PA, USA).

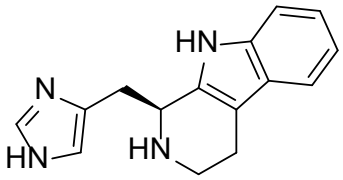
S-1-((1H-Imidazol-5-yl) methyl) -2-tosyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b] indole (23) Microwave Method:



A suspension of piperidinone **24** (50 mg, 0.10 mmol), benzophenone phenylhydrazone (109 mg, 0.40 mmol) and p-TsOH·H_2O (97 mg, 0.51 mmol) in EtOH (1.5 mL) was heated under microwave irradiation at 90 °C for 1 h (pre-stir = 5 min, pressure = 1 bar, vial type 10-20 mL, 90 s ramp). The reaction mixture was cooled to room temperature, diluted with CH_2Cl_2 (20 mL) and washed with saturated aqueous sodium bicarbonate solution (3 x 25 mL) followed by water (10 mL) and brine (10 mL). The organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by column chromatography (MeOH/EtOAc = 1:9) to afford compound **23** (19 mg, 46%) as an off-white solid. **Thermal Method**: A suspension of enone (134 mg, 0.275 mmol), benzophenone phenylhydrazone (50 mg, 0.18 mmol) and p-TsOH·H_2O (86 mg, 0.45 mmol) was in EtOH (2.0 mL) heated to reflux for 72 h. The reaction mixture was cooled to room temperature, diluted with CH_2Cl_2 (20 mL) and washed with saturated aqueous sodium bicarbonate solution (3 x 25 mL) followed by water (20 mL) and brine (20 mL). The organic part was dried over Na_2SO_4 and concentrated under reduced pressure. The crude was purified by column chromatography (MeOH/EtOAc = 2:8) to

afford desired compound 20 (48 mg, 65%) as an off-white solid. m.p. = 138-142 °C. [α] = -10.1 (c 0.62, MeOH); ^{1}H NMR (500 MHz, Chloroform-*d*) δ 9.70 (s, 1H), 7.18 (d, *J* = 8.3 Hz, 2H), 6.95 – 6.83 (m, 3H), 6.68 (dd, *J* = 18.4, 8.3 Hz, 3H), 6.61 (t, *J* = 7.8 Hz, 1H), 6.46 (bs, 1H), 5.03– 4.97 (m, 1H), 3.76 (dd, *J* = 14.4, 5.2 Hz, 1H), 2.98 (ddd, *J* = 14.4, 12.3, 5.2 Hz, 1H), 2.84 (m, 2H), 2.13 (dd, *J* = 15.4, 3.5 Hz, 2H), 2.04-2.03 (m, 1H), 1.95 (s, 3H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ 143.5, 137.9, 136.1, 135.2, 129.7, 126.7, 126.6, 121.8, 119.2, 118.1, 111.5, 107.4, 53.6, 40.4, 21.5, 20.2; FT-IR (neat, cm^{-1}): 3376, 3055, 2921, 2850, 1739, 1492, 1325, 1150, 1090, 919, 812. HR-MS (m/z): calc for $[M+Na]^{+}$ $C_{22}H_{22}N_4O_2S$, 429.1356, found: 429.1351

S-1-((1H-Imidazol-5-yl)methyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (Haploscleridamine) (1):



Mg (turnings) was added (29 mg, 1.23 mmol) to a solution of indole **23** (50 mg, 0.123 mmol) in dry MeOH (2 mL), and the mixture was sonicated at 48 °C until all magnesium turnings were consumed. MeOH was evaporated, sat. aqueous solution of NH_4Cl (10 mL) was added and the resulting mixture extracted with CH_2Cl_2 (3x10 mL). The combined extracts were dried over

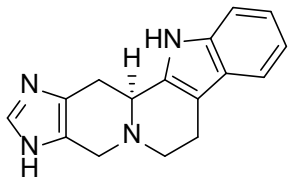
anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography (ammoniacal MeOH/DCM = 1:49) to provide haploscleridamine (**1**) (16 mg, 52%) as a colorless solid. m.p. = 158-162 °C; [α] = -7.6 (c = 0.47, MeOH). ^{1}H NMR (500 MHz, Methanol- d_4): δ 7.91 (bs, 1H), 7.47 (dt, *J* = 8.0, 1.0 Hz, 1H), 7.36 (dt, *J* = 8.0, 1.0 Hz, 1H), 7.15 (ddd, *J* = 8.0, 7.1, 1.0 Hz, 1H), 7.02 (bs, 1H), 7.04 (ddd, *J* = 8.0, 7.1, 1.0 Hz, 1H), 4.97 (dd, *J* = 8.7, 2.3 Hz,1H), 3.71 (td, *J* = 9.7, 4.5 Hz, 1H), 3.56 (dd, *J* = 10.0, 4.3 Hz, 1H), 3.44 (m, 1H), 3.24 (dd, *J* = 15.6, 9.2 Hz, 1H), 3.08 (m, 2H). ^{13}C NMR (126 MHz Methanol-d_4) δ 138.4, 136.8, 132.8, 129.3, 127.4, 123.7, 120.7, 119.3, 117.9, 112.5, 108.0, 54.7, 43.0, 30.1, 19.6. FT-IR (neat, cm^{-1}): 3130, 3112, 2957, 2925, 2850, 2800, 1633, 1434, 1304, 1195, 1084, 1007,742, 620. HR-MS (m/z): calc for $[M+Na]^+$ $C_{15}H_{17}N_4$ 276.1345, found $[M+H]^+$ 253.1526.

(S)-1-((1H-Imidazol-5-yl) methyl) -2,3,4,9-tetrahydro-1H-pyrido[3,4-b] indole (Haploscleridamine) TFA salt: To a stirred solution of (5 mg, 0.019 mmol) of synthetic haploscleridamine in dichloromethane (5 mL) was added trifluoroacetic acid (2 mL) at 0 °C. The resulting reaction mixture was stirred for 0.5 h at the same temperature; concentration under reduced pressure afforded TFA salt (5.3 mg, 98%) as an off-white solid. [α] = +0.67 (c = 0.56, MeOH), ^{1}H NMR (500 MHz, Methanol-d_4): δ 8.92 (d, *J* = 1.3 Hz, 1H), 7.50 (dt, *J* = 8.0, 1.0 Hz, 1H), 7.37 (dt, *J* = 8.2, 1.0 Hz,

1H), 7.34 (d, *J* = 1.3 Hz, 1H), 7.18 (ddd, *J* = 8.3, 7.1, 1.2 Hz, 1H), 7.08 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 5.09 (dd, *J* = 8.9, 5.0 Hz, 1H), 3.77 – 3.69 (m, 2H), 3.53 – 3.41 (m, 2H), 3.17 – 3.08 (m, 2H); ^{13}C NMR (126 MHz, Methanol-d_4): δ 138.4, 136.1, 128.6, 128.2, 127.3, 124.0, 120.9, 119.6, 119.3, 112.5, 108.38, 53.5, 42.8, 28.4, 19.4

Haploscleridamine (free base): To a solution of **1** TFA (5.3 mg, 0.018 mmol) in dichloromethane (5 mL) was added water (5 mL). Solid sodium bicarbonate was added until the solution reached a pH of 7. The resulting solution was extracted with dichloromethane (3 x 5mL). The combined organic extracts were dried and then evaporated under reduced pressure to afford an off-white solid (4.2 mg, 94%). [α] = -6.2 (c = 0.54, MeOH). ^{1}H NMR (500 MHz, Methanol-d_4): δ 7.67 (d, *J* = 1.1 Hz, 1H), 7.41 (ddd, *J* = 7.8, 1.0, 1.0 Hz, 1H), 7.32 (ddd, *J* = 8.1, 1.0, 1.0 Hz, 1H), 7.07 (dt, *J* = 7.6, 1.0 Hz, 1H), 6.98 (dt, *J* = 7.8, 1.0 Hz, 1H), 6.87 (bs, 1H), 4.37 (dd, *J* = 7.5, 2.8 Hz, 1H), 3.28-3.33 (m, 2H), 2.99-3.01 (m, 2H), 2.83-2.71 (m, 2H); ^{13}C NMR (126 MHz, Methanol-d_4): δ 137.7, 136.4, 136.0, 134.9, 128.5, 122.1, 119.8, 119.7, 118.6, 111.9, 109.0, 53.9, 43.1, 33.0, 22.8

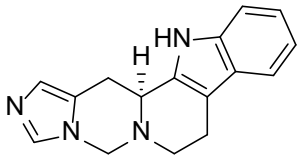
Villagorgin A (5)



A solution of haploscleridamine (**1**) (12.7 mg, 0.05 mmol) and 37% aqueous formaldehyde (1.7 μL, 0.16 mmol) in 2,2,2-trifluoroethanol (0.5 mL) was stirred during 3 h at room temperature. TLC showed total consumption of starting material and one non-polar spot found compared to starting material. The reaction was continued for another 12 h, a new more polar spot was observed. After an additional 12 h there was no apparent change by TLC had occurred and thus the reaction mixture was concentrated under reduced pressure. The crude material was purified by column chromatography (ammoniacal MeOH:CH_2Cl_2 = 1:19) to afford the less polar product **50** (3.0 mg, 22%) and using (ammoniacal MeOH:CH_2Cl_2 = 1:9) to afford the desired compound **5** (7.2 mg, 55%) as colorless solid): m.p. = 145-150 °C, [α] = -6.8 (c = 0.25, MeOH), ^{1}H NMR (500 MHz, Methanol-d_4): δ 7.60 (d, *J* = 2.7 Hz, 1H), 7.44 – 7.40 (m, 1H), 7.31 (dd, *J* = 7.0, 3.9 Hz, 1H), 7.09 – 7.04 (m, 1H), 7.01 – 6.96 (m, 1H), 4.00 (dd, *J* = 14.1, 3.3 Hz, 1H), 3.84 (m, 1H), 3.62 (m, 1H), 3.37 (m, 1H), 3.34 (m, 1H), 3.05 (m, 1H), 2.89 (ddd, *J* = 3.8, 8.4, 15 Hz, 1H), 2.79 (m, 1H), 2.73 (m, 1H). ^{13}C NMR (126 MHz, Methanol-d_4): δ 138.4, 135.6, 134.8, 129.8, 128.0, 122.3, 119.9, 118.8, 112.0, 108.4, 73.8, 58.5, 54.0, 53.3, 29.2, 22.3. FT-IR (neat, cm^{-1}): 3096, 2957, 1717, 1616, 1526, 1440,

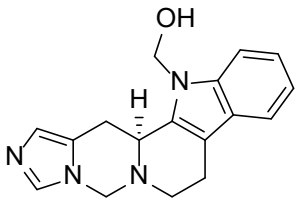
1349, 1288, 1268, 1193, 1134, 1072, 978, 924, 822, 777, 718. HR-MS (*m/z*): Calcd. for $[M+H]^+$ $C_{16}H_{17}N_4$ 265.1448, found 265.1444.

Isovillagorgin A (50)



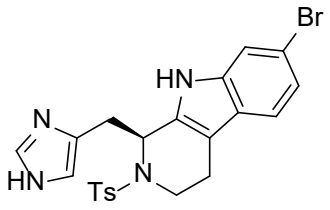
m.p. = 148-152 °C, [α] = -5.3 (c = 0.28, MeOH), ^{1}H NMR (500 MHz, Methanol-d_4): δ 7.64 (s, 1H), 7.42 (dd, *J* = 8.9, 1.8 Hz, 1H), 7.30 (dd, *J* = 8.1, 3.7 Hz, 1H), 7.09 – 7.04 (m, 1H), 7.02 – 6.96 (m, 1H), 6.80 (s, 1H), 5.24 (dd, *J* = 9.7, 7.3 Hz, 1H), 4.72 (d, *J* = 9.8 Hz, 1H), 4.04 – 3.98 (m, 1H), 3.48 (dt, *J* = 16.0, 4.7 Hz, 1H), 3.27 (d, *J* = 6.3 Hz, 1H), 2.97 – 2.79 (m, 4H). ^{13}C NMR (126 MHz, Methanol-d_4): δ 138.3, 134.7, 128.0, 124.5, 122.4, 120.0, 118.8, 112.0, 108.0, 67.1, 55.9, 50.1, 49.1, 49.0, 26.9, 22.3. FT-IR (neat, cm^{-1}): 2918, 2849, 1561, 1498, 1452, 1322, 1292, 1271, 1162, 1098, 1050, 1009, 941, 801, 739, 657, HR-MS (*m/z*): Calcd. for $[M+H]^+$ $C_{16}H_{17}N_4$ 265.1448, found 265.1448.

Hydroxymethylated β-carboline (51)



A solution of haploscleridamine (**1**) (10 mg, 0.03 mmol) and 37% aqueous formaldehyde (1.5 μL, 0.14 mmol) in 2,2,2-trifluoroethanol (0.5 mL) was heated at reflux 1 h. The reaction mixture was concentrated under reduced pressure. The resulting crude product was purified by column chromatography (ammoniacal MeOH:CH_2Cl_2 = 1:19) to afford (7.5 mg, 65%), the structure of which was confirmed by X-ray. m.p. = 150-155 °C, [α] = - 5.2 (c = 0.31, MeOH), ^{1}H NMR (500 MHz, Methanol-d_4): δ 7.61 (d, J = 3.6 Hz, 1H), 7.46 (ddd, J = 19.3, 7.8, 3.6 Hz, 2H), 7.19 – 7.04 (m, 2H), 6.76 (d, J = 2.8 Hz, 1H), 5.64 – 5.54 (m, 2H), 5.48 (d, J = 4.5 Hz, 1H), 5.33 – 5.18 (m, 2H), 4.62 – 4.54 (m, 1H), 3.46 (dt, J = 16.6, 4.5 Hz, 1H), 3.22 (dd, J = 9.9, 5.0 Hz, 1H), 3.12 – 2.92 (m, 3H), 2.83 (dd, J = 15.3, 2.8 Hz, 1H). ^{13}C NMR (125.8 MHz, Methanol-d_4): δ 138.6, 137.0, 135.2, 130.6, 127.3, 121.6, 119.5, 117.7, 117.6, 109.2, 107.5, 66.0, 65.5, 50.2, 44.1, 29.4, 21.4. FT-IR (neat, cm^{-1}): 3584, 3096, 2957, 1717, 1616, 1526, 1440, 1349, 1330, 1288, 1268, 1193, 1134, 1072, 978, 924, 822, 777, 718. HR-MS (*m/z*): Calcd. for $[M+H]^+$ $C_{17}H_{19}N_4O$ 295.1502, found 295.1490.

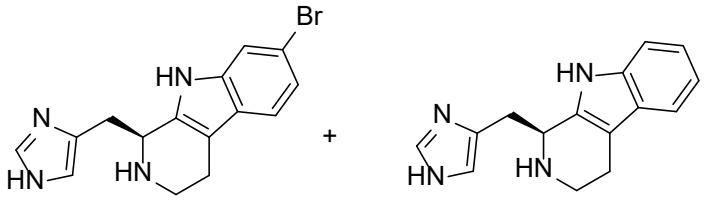
S-1-((1H-Imidazol-5-yl) methyl)-7-bromo-2-tosyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b] indole (53):



A suspension of piperidinone **24** (104 mg, 0.21 mmol), benzophenone hydrazone **52** (50 mg, 0.142 mmol) and PTSA (67 mg, 0.355 mmol) was in EtOH (6 mL) heated to reflux for 72 h. The reaction mixture was cooled to room temperature, diluted with dichloromethane (20 mL) and washed with saturated sodium bicarbonate solution (3 x 25 mL) followed by water (20 mL) and brine (20 mL). The organic part was dried over sodium sulfate and concentrated under reduced pressure. The crude was purified by column chromatography (MeOH: EtOAc = 1:49) to afford desired compound **53** (50 mg, 72%). m.p. = 144-148 °C, [α] = -9.9 (c = 0.15, MeOH). ^{1}H NMR (500 MHz, Chloroform-*d*): δ 10.52 (d, *J* = 8.8 Hz, 1H), 7.68 (s, 1H), 7.58 (dd, *J* = 8.3, 1.5 Hz, 2H), 7.42 (d, *J* = 1.7 Hz, 1H), 7.16 (d, *J* = 8.4 Hz, 1H), 7.09 (dd, *J* = 8.4, 1.7 Hz, 3H), 6.87 (s, 1H), 5.36 (t, *J* = 6.3 Hz, 1H), 4.16 (dd, *J* = 14.4, 5.4 Hz, 1H), 3.41 – 3.34 (m, 1H), 3.23 (d, *J* = 6.3 Hz, 2H), 2.50 (dd, *J* = 15.5, 3.6 Hz, 1H), 2.40 – 2.30 (m, 1H), 2.28 (s, 3H). ^{13}C NMR (126 MHz, Chloroform-*d*): δ 143.5, 138.0, 136.8, 134.8, 134.2, 129.7, 126.7, 125.4, 122.2, 119.2, 115.0, 114.3, 107.3, 53.3, 40.5, 34.8, 29.8, 21.5, 20.2. FT-IR (neat, cm^{-1}): 3361, 2922, 2852, 1618, 1596, 1560, 1465, 1459, 1450, 1438, 1377, 1326, 1302, 1151, 1090, 910,

799, 717, 654, 584. HR-MS (*m/z*): calcd. for $[M+H]^+$ $C_{22}H_{22}BrN_4O_2S$ 487.0505, found 487.0606.

(S)-1-((1H-imidazol-5-yl)methyl)-7-bromo-2-tosyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (2):

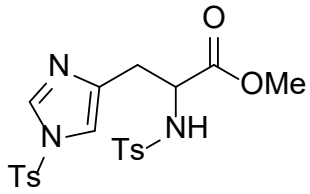


Lissoclin C (2) **Haploscleridamine (1)**

Mg (turnings) was added (4.5 mg, 0.195 mmol) to a solution of indole (19 mg, 0.039 mmol) in dry MeOH (2 mL), and the mixture was sonicated at 48 °C until all magnesium turnings were consumed. The TLC of the reaction mixture was checked and that exactly matched with haploscleridamine. MeOH was evaporated, saturated ammonium chloride (15 mL) was added and extracted with dichloromethane (2x 30 mL). The combined extracts were dried over anhydrous Na_2SO_4, concentrated under reduced pressure. The crude product was purified by column chromatography (Ammoniacal MeOH: DCM = 1: 9) to provide a 1:1 mixture of haploscleridamine and lissoclin C (11.5 mg, 52%) as colorless solid. Protons and carbons which correspond to Lissoclin C are **highlighted.** ^{1}H NMR (500

MHz, Methanol-d_4) δ ^{1}H NMR (500 MHz, Methanol-d_4) δ 7.83 (s, 1H), 7.82 (s, 1H), 7.50 (dd, J = 7.9, 1.1 Hz, 1H), 7.38 (q, J = 0.9 Hz, 1H), 7.37 (s, 1H), 7.20 (d, J = 0.8 Hz, 1H), 7.19 (dd, J = 3.2, 1.4 Hz, 1H), 7.18 – 7.17 (m, 1H), 7.16 (d, J = 1.0 Hz, 1H), 7.09 – 7.05 (m, 1H), 7.05 – 7.01 (m, 1H), 4.98 (dd, J = 9.3, 4.0 Hz, 1H), 4.98 (dd, J = 9.3, 4.0 Hz, 1H), 3.78 – 3.70 (m, 3H), 3.56 (ddd, J = 15.1, 10.0, 4.4 Hz, 4H), 3.51 – 3.40 (m, 5H), 3.25 (ddd, J = 15.6, 9.1, 4.4 Hz, 4H), 3.15 – 3.04 (m, 4H). ^{13}C NMR (126 MHz, Methanol-d_4) δ *139.3*, 138.3, 136.8, 132.7, *130.8*, 129.2, 127.3, *126.1*, *124.5*, *123.9*, 123.7, *120.8*, 120.7, 119.2, 117.7,*117.0, 115.4*, *114.6*, 112.5, *112.0*, *108.5*, 107.9, 54.6, *54.5*, 42.9, *42.7*, 30.0, *29.9*, *21.7*, 19.5. HR-MS (m/z): calcd. for $[M+H]^+$ $C_{15}H_{16}N_4$, 253.1356, and $[M+H]^+$ $C_{15}H_{15}BrN_4$, 331.0432

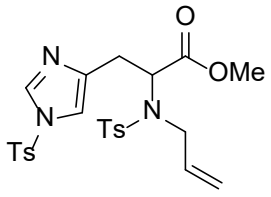
(±)-2-(Toluene-4-sulfonylamino)-3-[1-(toluene-4-sulfonyl)-1*H*-imidazol-4-ylpropionic acid methyl ester (**45**):



Histidine methyl ester hydrochloride (±)-**19** (8.0 g, 28.7 mmol) was dissolved in dichloromethane (50 mL), triethylamine (15 mL) and tosyl chloride (11 g, 57.5 mmol) were slowly added with vigorous stirring and cooled in an

ice bath. The reaction mixture was stirred at 0 °C for 30 min and then room temperature for 2 h, additional dichloromethane (50 mL) was added to the reaction mixture and the solution was washed with water and brine (3 x 25 mL) and dried over anhydrous Na_2SO_4 The extract was concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, EtOAc/hexane = 50:50) to furnish desired compound **(±)-45** (12.0 g, 88%) as a colorless crystalline solid. m.p. = 183-185 ℃, ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.82 (d, *J* = 1.3 Hz, 1H), 7.77 (d, *J* = 8.4 Hz, 2H), 7.65 (d, *J* = 8.3 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.24 (d, *J* = 8.0 Hz, 2H), 7.02 (d, *J* = 1.1 Hz, 1H), 5.74 (d, *J* = 8.7 Hz, 1H), 4.19 (dt, *J* = 8.7, 5.6 Hz, 1H), 3.46 (s, 3H), 2.91 (d, *J* = 6.3 Hz, 2H), 2.41 (d, *J* = 11.0 Hz, 6H), ^{13}C NMR (126 MHz, Chloroform-*d*) δ 171.2, 146.5, 143.7, 139.3, 137.0, 136.4, 134.9, 130.6, 129.7, 127.4, 127.2, 115.2, 55.0, 52.6, 31.4, 21.8, 21.6. FT-IR (neat, cm^{-1}): 3478, 3011, 2584, 2310, 2180, 2071, 1920, 1796, 1747, 1632, 1594, 1458, 969, 913, 845, 813, 781, 657, 560, 477. HR-MS (m/z): calcd. for $[M+H]^+$ $C_{21}H_{23}N_3O_6S_2$ 478.1101, found 478.1087.

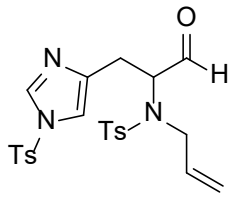
(±)-2-[Allyl-(toluene-4-sulfonyl)-amino]-3-[1-(toluene-4-sulfonyl)-1*H*-imidazol-4-yl]-propionic acid methyl ester (27):



Tosyl protected histidine (±)-**45** (13.0 g, 27.5 mmol) was dissolved in DMF (70 mL) and K_2CO_3 (5.6 g, 41.0 mmol) was added and stirred for 1h. Then allyl bromide (3 mL, 30.3 mmol) was added, and the reaction mixture was stirred at room temperature for 16h. The reaction mixture was cooled in ice-cold water, the resulting precipitated solid was isolated by vacuum filtration and washed thoroughly with hexanes. The crude compound was purified through flash chromatography (silica gel, EtOAc/hexane = 40:60) to afford (±)-**27** (12.7 g, 84 %) as white solid m.p. = 116-120 ℃, ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.83 (t, *J* = 1.2 Hz, 1H), 7.81 – 7.74 (m, 2H), 7.61 (d, *J* = 8.0 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.27 – 7.21 (m, 2H), 7.06 – 7.02 (m, 1H), 5.58 (ddt, *J* = 16.6, 10.0, 6.3 Hz, 1H), 5.13 – 4.92 (m, 2H), 4.80 (dd, *J* = 9.0, 5.9 Hz, 1H), 3.93 – 3.62 (m, 2H), 3.51 (d, *J* = 0.9 Hz, 3H), 3.24 – 3.12 (m, 1H), 3.01 – 2.82 (m, 3H), 2.41 (s, 6H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 170.8, 146.3, 143.6, 140.4, 137.2, 136.2, 135.1, 134.5, 130.5, 129.5, 127.5, 127.3, 118.1, 115.2, 59.0, 52.2, 48.9, 29.2, 21.8, 21.6. FT-IR (neat, cm^{-1}): 3110, 3118, 2936, 1723, 1640, 1590, 1485, 1480, 1430, 1300, 1285, 1200, 1195, 1161, 1081,

990, 878, 790, 757, 730, 670, 580, 541, 450. HR-MS (m/z): calcd. for $[M+H]^+$ $C_{24}H_{27}N_3O_6S_2$ 518.1414, found 518.1406.

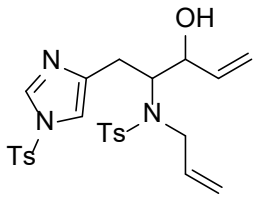
(±)-*N*-Allyl-*N*-1-formyl-2-[1-(toluene-4-sulfonyl)-1*H*-imidazol-4-yl]-ethyl-4-methyl-benzenesulfonamide (**46**):



The ester (±)-**27** (5.0 g, 9.7 mmol) was dissolved in dry CH_2Cl_2 (50 mL) and cooled to -78 °C. A precooled (-78 °C) solution of DIBAL-H (19.3 mL) was slowly added to the reaction mixture. After stirring for 2 h at this temperature the reaction was quenched while still at -78 °C with water (0.77 mL), 15% NaOH (0.77 mL) and then water (2 mL). After warming to room temperature and the resulting mixture was stirred for 30min the residue was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic solutions were washed with brine and dried over anhydrous Na_2SO_4. The concentrated residue was purified by flash chromatography (silica gel, EtOAc/hexane = 40:60) to furnish the aldehyde (±)-**46** as a colorless solid (3.0 g, 64%). m.p. = 106-110 °C, ^{1}H NMR (500 MHz, Chloroform-*d*) δ 9.65 (s, 1H), 7.75 – 7.73 (m, 2H), 7.61 – 7.58 (m, 2H), 7.35 – 7.32 (m, 2H), 7.28 – 7.23 (m, 2H), 6.69 (s, 1H), 5.71 – 5.61 (m, 1H), 5.15 (d, *J* = 1.3 Hz, 1H), 5.12 (dq, *J* = 6.9, 1.2 Hz, 1H), 4.47

(dd, *J* = 9.3, 5.1 Hz, 1H), 3.89 – 3.83 (m, 1H), 3.63 (ddt, *J* = 15.5, 6.7, 1.3 Hz, 1H), 3.19 (ddd, *J* = 15.4, 5.1, 1.1 Hz, 1H), 2.69 (dd, *J* = 15.4, 9.2 Hz, 1H), 2.43 (d, *J* = 17.5 Hz, 6H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 198.8, 146.4, 144.0, 140.4, 137.5, 136.2, 135.0, 133.3, 130.5, 129.9, 127.3, 127.2, 120.5, 114.9, 65.6, 49.9, 26.0, 21.8, 21.7. FT-IR (neat, cm^{-1}): 3150, 3120, 2934, 2833, 1907, 1721, 1586, 1470, 1246, 1207, 1144, 930, 773, 615, 510. HR-MS (m/z): calcd. for $[M+H]^+$ $C_{23}H_{25}N_3O_5S_2$ 488.1308, found 488.1314.

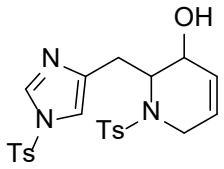
(±)-*N*-Allyl-*N*-{2-hydroxy-1-[1-(toluene-4-sulfonyl)-1*H*-imidazol-4-yl-methyl]-but-3-enyl}-4-methyl-benzenesulfonamide (**26**):



A solution of aldehyde (±)-**46** (6.3 g, 13 mmol) in THF (50 mL) was added to a solution of vinyl magnesium bromide (1.3 M in THF, 11 mL) at -78 °C, and the mixture was stirred for 2 h. After stirring for an additional 1h at 25 °C, a saturated solution of NH_4Cl (30 mL) was added to the mixture which was then extracted with ethyl acetate (3 x 25 mL). The organic phase was washed with brine, dried over anhydrous Na_2SO_4, and then evaporated to give an oil. The crude product was purified by flash chromatography (silica gel, EtOAc/hexane = 50:50), to give the desired alcohol (±)-**26** (5.0 g, 76%). m.p. = 132-136 °C, ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.77 (s, 1H), 7.76 (d, *J* = 2.3 Hz, 2H), 7.56 – 7.53 (m, 2H), 7.36 – 7.33 (m, 2H), 7.22

– 7.19 (m, 2H), 6.85 (d, *J* = 1.3 Hz, 1H), 5.83 – 5.69 (m, 2H), 5.22 – 5.12 (m, 3H), 5.03 (ddt, *J* = 16.2, 10.5, 1.5 Hz, 2H), 4.28 (tt, *J* = 5.7, 1.7 Hz, 1H), 4.04 (ddd, *J* = 8.3, 5.3, 4.1 Hz, 1H), 3.93 – 3.81 (m, 3H), 2.85 (ddd, *J* = 15.4, 5.4, 1.1 Hz, 1H), 2.77 (dd, *J* = 15.3, 8.4 Hz, 1H), 2.49 – 2.45 (m, 1H), 2.42 (d, *J* = 3.2 Hz, 6H), 2.37 (d, *J* = 12.3 Hz, 1H). ^{13}C NMR (126 MHz, Chloroform- *d*) δ 146.5, 143.5, 141.2, 138.2, 137.8, 136.0, 135.8, 134.9, 130.5, 129.6, 127.4, 127.2, 117.7, 116.0, 114.9, 74.8, 62.5, 48.5, 26.6, 21.8, 21.6. FT-IR (neat, cm^{-1}): 3100, 1729, 1621, 1510, 1230, 1134, 1070, 984, 915, 824, 741, 644, 582, 468, 435, 410. HR-MS (m/z): calcd. for $[M+H]^+$ $C_{25}H_{29}N_3O_5S_2$ 515.1621, found, 515.1605.

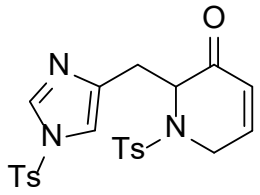
(±)-1-(Toluene-4-sulfonyl)-3-[1-(toluene-4-sulfonyl)-1H-imidazol-4-yl-methyl]-1,2,3,4-tetrahydropyridin-4-ol (**25**):



The allylic alcohol (±)-**26** (3.0 g, 5.8 mmol) was taken up in dry CH_2Cl_2 (40 mL). The Grubbs' second-generation catalyst (0.246 g, 0.29 mmol, 5 mol%) was added, followed by heating the mixture at reflux for 3 h. The mixture was stirred at room temperature for 6 h, at which time TLC analysis indicated the completion of the reaction. The solvent was concentrated. The crude product was purified by chromatography EtOAc/hexanes = 75:25) to give the title compound (±)-

25 as a colorless solid (1.8 g, 65%). m.p. = 146-148 °C, ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.85 (d, *J* = 1.3 Hz, 1H), 7.80 (d, *J* = 8.4 Hz, 2H), 7.64 (d, *J* = 8.3 Hz, 2H), 7.37 – 7.33 (m, 2H), 7.24 (d, *J* = 7.9 Hz, 2H), 7.03 (d, *J* = 1.1 Hz, 1H), 5.90 (dd, *J* = 3.8, 1.4 Hz, 1H), 4.36 (t, *J* = 7.5 Hz, 1H), 4.11 (dd, *J* = 18.7, 2.8 Hz, 1H), 3.97 – 3.93 (m, 1H), 3.61 – 3.55 (m, 1H), 2.56 – 2.45 (m, 3H), 2.41 (d, *J* = 10.1 Hz, 6H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 146.4, 143.7, 140.9, 136.8, 136.2, 134.9, 130.6, 129.8, 127.5, 127.3, 127.1, 125.8, 114.4, 64.9, 58.6, 40.6, 27.8, 21.8, 21.6. FT-IR (neat, cm^{-1}): 3727, 3117, 1726, 1572, 1366, 1143, 1060, 910, 820, 770, 530. HR-MS (m/z): calcd. for $[M+H]^{+}$ $C_{23}H_{26}N_3O_5S_2$ 488.1308, found 488.1312.

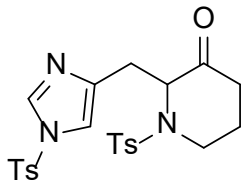
(±)-1-tosyl-2-[(1-tosyl-1H-imidazol-4-yl) methyl]-1,6-dihydropyridin-3(2H)-one (48):



To a stirred solution of cyclic alcohol **(**±)-**25** (1.8 g, 3.70 mmol) in acetone (50 mL) was added IBX (1.1 g, 4.07 mmol) at 0 °C. The resulting reaction mixture was heated to reflux for 6h. The reaction mixture was cooled to room temperature, and resulting slurry was filtered and washed with ethyl acetate. The filtrated was concentrated under reduced pressure. Crude product was purified by column chromatography (EtOAc/Hexanes = 4:1) to afford desired compound (±)-**48**

(1.4 g, 82%) as an off-white solid. m.p. = 105-108 °C, ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.86 (d, *J* = 1.3 Hz, 1H), 7.79 (d, *J* = 8.5 Hz, 2H), 7.51 (d, *J* = 8.3 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.21 (d, *J* = 7.9 Hz, 3H), 6.68 (ddd, *J* = 10.4, 4.9, 1.9 Hz, 1H), 5.76 (dt, *J* = 10.4, 2.3 Hz, 1H), 4.64 (t, *J* = 7.5 Hz, 1H), 4.40 (ddd, *J* = 21.0, 4.9, 1.6 Hz, 1H), 4.00 (dt, *J* = 21.1, 2.1 Hz, 1H), 2.90 (d, *J* = 7.5 Hz, 2H), 2.39 (d, *J* = 16.2 Hz, 6H). ^{13}C NMR (126 MHz, Chloroform- *d*) δ 193.4, 146.4, 144.3, 144.1, 139.4, 136.3, 136.1, 134.9, 130.5, 130.0, 127.4, 127.0, 126.7, 115.4, 61.1, 41.2, 29.2, 21.8, 21.6. FT-IR (neat, cm^{-1}): 3427, 3129, 2940, 1686, 1490, 1464, 1387, 1163, 1154, 1100, 757, 698, 550, 520. HR-MS (m/z): calcd. for $[M+H]^{+}$ $C_{23}H_{24}N_3O_5S_2$ 486.1152, found 486.1170.

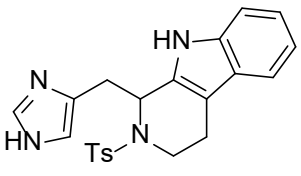
(±)-1-(Toluene-4-sulfonyl)-3-[1-(toluene-4-sulfonyl)-1*H*-imidazol-4-ylmethyl]-piperidin-4-one 24:



The enone (±)-**48** (1.0 g, 2.04 mmol) and 10% Pd/C (200 mg) were placed in a 1:3 mixture of ethyl acetate and ethanol (10 mL) and under H_2 (40 psi). Then, the catalyst was filtered and rinsed with ethyl acetate and the filtrate was concentrated. The crude product was purified by flash chromatography

(EtOAc/hexanes = 80:20) to provide the pure title compound (±)-**24** (0.85 g, 85%) as a yellow solid. m.p. = 125-130 ℃, ^{1}H NMR (500 MHz, Chloroform- *d*) δ 7.81 (d, *J* = 1.2 Hz, 1H), 7.78 (d, *J* = 8.4 Hz, 2H), 7.56 (d, *J* = 8.3 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.23 (s, 2H), 7.07 (s, 1H), 4.52 (t, *J* = 7.1 Hz, 1H), 3.80 – 3.73 (m, 1H), 3.27 – 3.19 (m, 1H), 2.45 (d, *J* = 16.3 Hz, 1H), 2.39 – 2.36 (m, 1H), 2.23 (dt, *J* = 16.1, 5.4 Hz, 1H), 1.78 – 1.67 (m, 2H). ^{13}C NMR (126 MHz, Chloroform- *d*) δ 206.2, 146.3, 143.9, 139.4, 137.2, 136.2, 135.0, 130.5, 130.0, 127.4, 127.0, 115.5, 63.7, 40.3, 36.5, 30.1, 23.2, 21.8, 21.6. FT-IR (neat, cm^{-1}): 3422, 3119, 2930, 1738, 1620, 1510, 1360, 1260, 1210, 1100, 1010, 720, 680, 550, 530, 510. HR-MS (m/z): calcd. for $[M+H]^{+}$ $C_{23}H_{26}N_3O_5S_2$, 488.1308, found 488.1322

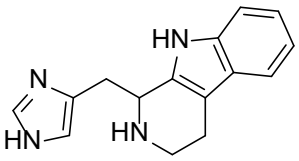
(±)-Synthesis of -1-((1H-imidazol-5-yl) methyl)-2-tosyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b] indole 23:



A suspension of enone (±)-**24** (67 mg, 0.14 mmol), benzophenone phenylhydrazone (25 mg, 0.09 mmol) and p-TsOH·H_2O (45 mg, 0.23 mmol) was in EtOH (3 mL) heated to reflux for 72 h. The reaction mixture was cooled to room temperature, diluted with CH_2Cl_2 (20 mL) and washed with saturated sodium bicarbonate solution (3 x 25 mL) followed by water (20 mL) and brine (20 mL). The

organic part was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude was purified by column chromatography (MeOH/EtOAc = 1:49) to afford desired compound (±)-**23** (25 mg, 70%) as an off-white solid. m.p. = 136-140 °C, ^{1}H NMR (500 MHz, Chloroform- *d*) δ 10.05 (d, *J* = 9.9 Hz, 1H), 7.65 (s, 1H), 7.56 (d, *J* = 7.4 Hz, 2H), 7.33 – 7.26 (m, 2H), 7.09 (t, *J* = 7.6 Hz, 1H), 7.04 (d, *J* = 7.9 Hz, 2H), 7.03 – 6.99 (m, 1H), 6.85 (s, 1H), 5.41 (t, *J* = 6.0 Hz, 1H), 4.15 (dd, *J* = 13.8, 4.7 Hz, 1H), 3.42 – 3.33 (m, 1H), 3.23 (dd, *J* = 15.1, 5.7 Hz, 2H), 2.55 – 2.50 (m, 1H), 2.39 (dd, *J* = 10.9, 5.2 Hz, 1H), 2.24 (s, 3H). ^{13}C NMR (126 MHz, Chloroform- *d*) δ 143.4, 138.0, 136.1, 133.2, 129.7, 126.7, 121.8, 119.1, 118.0, 111.4, 107.3, 53.6, 40.4, 21.4, 20.2. FT-IR (neat, cm^{-1}): 3366, 3045, 2898, 2840, 1730, 1492, 1315, 1135, 1080, 900, 820. HR-MS (m/z): calcd. for $[M+H]^+$ $C_{22}H_{23}N_4O_2S$, 407.1536, found 407.1543.

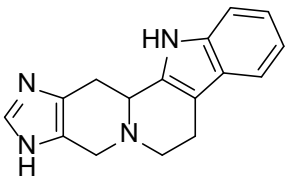
(±)-Synthesis of 1-((1H-imidazol-5-yl) methyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-*b*] indole (Haploscleridamine) 1:



Mg (turnings) was added (12 mg, 0.49 mmol) to a solution of indole (±)- **23** (20 mg, 0.049 mmol) in dry MeOH (2 mL), and the mixture was sonicated at 48 °C until all magnesium turnings were consumed. MeOH was evaporated, acidified with concentrated HCl, and extracted with ethyl acetate (2 x 20 mL) to remove side products. The aqueous solution was basified with $NaHCO_3$ until

the pH value was adjusted to 7-8, extracted with ethyl acetate (2 x 30 mL). The combined extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography (ammoniacal MeOH/DCM = 1:9) to provide haploscleridamine (±)**-1** (7 mg, 59%) as a colorless solid. M.p. = 155-160 °C, ^{1}H NMR (500 MHz, Methanol-d_4) δ 7.70 (d, J = 1.0 Hz, 1H), 7.45 (s, 1H), 7.33 (d, J = 8.1 Hz, 1H), 7.13 – 7.10 (m, 1H), 7.04 – 7.00 (m, 1H), 6.95 (s, 1H), 4.77 (dd, J = 8.6, 3.5 Hz, 1H), 3.59 (dt, J = 12.5, 4.9 Hz, 1H), 3.45 (d, J = 4.3 Hz, 1H), 3.42 (d, J = 4.1 Hz, 1H), 3.11 (dd, J = 15.4, 9.2 Hz, 1H), 3.01 – 2.94 (m, 2H). ^{13}C NMR (126 MHz, Methanol-d_4) δ 140.2, 138.3, 137.1, 135.3, 131.6, 123.4, 120.5, 119.2, 112.4, 108.2, 55.0, 43.0, 31.5, 20.6. FT-IR (neat, cm^{-1}): 3135, 3110, 2950, 2920, 2830, 2795, 1630, 1429, 1300, 1185, 1064, 1000, 748, 600 HR-MS (m/z): calcd. for $[M+H]^+$ $C_{15}H_{17}N_4$ 253.1448, found 253.1441.

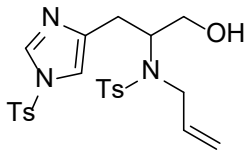
Villagorgin A (±)-5:



Mg (turnings) was added (9.4 mg, 0.39 mmol) to a solution of indole (±)- **23** (20 mg, 0.049 mmol) in dry MeOH (2 mL), and the mixture was sonicated at 48 °C until all magnesium turnings were consumed. MeOH was evaporated, saturated ammonium chloride (15 mL) was added and extracted with

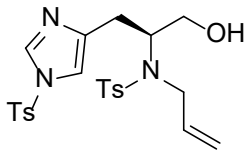
dichloromethane (2x 30 mL). The combined extracts were dried over anhydrous Na_2SO_4, concentrated under reduced pressure. During reaction, a non-polar spot formed villagorgin A (±)**-5** along with haploscleridamine (±)**-1**. The crude product was purified by column chromatography (Ammoniacal MeOH: DCM = 1: 19) to provide as colorless solid Villagorgin A **(±)-5** (3.7 mg 29%) and by using (Ammoniacal MeOH: DCM = 1: 9) provided haploscleridamine (±)**-1** (7 mg, 57%) as a colorless solid. m.p. = 145-152 ℃, ^{1}H NMR (500 MHz, Methanol-d_4) δ 7.57 (s, 1H), 7.40 (d, *J* = 7.8 Hz, 1H), 7.30 (d, *J* = 8.4 Hz, 1H), 7.05 (t, *J* = 7.4 Hz, 1H), 6.97 (t, *J* = 7.4 Hz, 1H), 3.99 (d, *J* = 13.7 Hz, 1H), 3.85 (d, *J* = 14.4 Hz, 1H), 3.65 – 3.62 (m, 1H), 3.36 (d, *J* = 3.7 Hz, 1H), 3.32 (d, *J* = 1.7 Hz, 1H), 2.99 (tdd, *J* = 11.6, 4.9, 2.4 Hz, 1H), 2.88 (td, *J* = 11.3, 3.7 Hz, 1H), 2.83 – 2.77 (m, 1H), 2.75 – 2.68 (m, 1H). ^{13}C NMR (126 MHz, Methanol-d_4) δ 138.4, 135.6, 134.8, 129.8, 128.0, 122.3, 119.9, 118.8, 112.0, 108.4, 73.8, 58.5, 54.0, 53.3, 29.2, 22.3. FT-IR (neat, cm^{-1}): 3094, 2957, 1714, 1616, 1525, 1440, 1345, 1285, 1262, 1193, 1100, 1072, 950, 924, 822, 750, 713. HR-MS (m/z): calcd. for $[M+H]^+$ $C_{16}H_{17}N_4$ 265.1448, found 265.1422.

(±)-N-allyl-N-(1-hydroxy-3-(1-tosyl-1H-imidazol-4-yl) propan-2-yl)-4-methylbenzenesulfonamide (**55**):



The ester **(±)-27** (200 mg, 0.38 mmol) in freshly distilled THF (15mL) was added dropwise to a cooled suspension of $LiAlH_4$ (0.014 g, 0.38 mmol) in dry THF (10 mL), and the mixture was stirred at 0 °C. After stirring for 3 h at this temperature the reaction was quenched while still at 0 °C with ethyl acetate (excess). After warming to room temperature, the resulting mixture was stirred for another 2 h. Then, the residue was filtered and rinsed with ethyl acetate and the filtrate was concentrated. The crude product was purified by flash chromatography (Silica gel, EtOAc/hexanes: 60/40) to provide the pure title compound **(±)-55** (125 mg, 67%) as a white solid. m.p. 97-99 °C. [α] = 3.5 (c = 1.0, MeOH). ^{1}H NMR (500 MHz, Chloroform- *d*): δ 7.83 – 7.76 (m, 3H), 7.60 (s, 2H), 7.35 (d, *J* = 8.1 Hz, 2H), 7.23 (d, *J* = 8.1 Hz, 2H), 6.96 (d, *J* = 1.3 Hz, 1H), 5.81 (ddt, *J* = 16.6, 10.2, 6.2 Hz, 1H), 5.22 – 5.17 (m, 1H), 5.10 – 5.06 (m, 1H), 4.08 – 4.03 (m, 1H), 3.98 – 3.82 (m, 3H), 3.57 (qd, *J* = 12.1, 5.7 Hz, 2H), 2.85 – 2.76 (m, 1H), 2.65 (dd, *J* = 14.7, 6.9 Hz, 1H), 2.42 (s, 3H), 2.41 (s, 3H). ^{13}C NMR (126 MHz, Chloroform- *d*): δ 146.5, 143.5, 141.0, 137.8, 136.2, 136.0, 134.9, 130.6, 129.7, 127.4, 127.1, 117.7, 114.6, 63.3, 59.9, 47.6, 28.8, 21.8, 21.6. FT-IR (neat, cm^{-1}): 3143, 3024, 2918, 2846, 1590, 1493, 1379, 1170, 1052, 979, 863, 588, 530. HR-MS (*m/z*): calcd. for $[M+H]^+$ $C_{23}H_{27}N_3O_5$, 490.1487 found 490.1464.

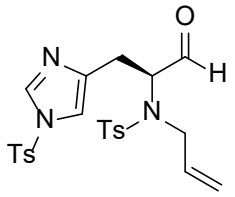
S-N-allyl-N-(1-hydroxy-3-(1-tosyl-1H-imidazol-4-yl) propan-2-yl)-4-methylbenzenesulfonamide (**55**):



The ester **27** (300 mg, 0.58 mmol) in freshly distilled THF (15mL) was added dropwise to a cooled suspension of $LiAlH_4$ (0.021 g, 0.58 mmol) in dry THF (10 mL), and the mixture was stirred at 0 °C. After stirring for 3 h at this temperature the reaction was quenched while still at 0 °C with ethyl acetate (excess). After warming to room temperature, the resulting mixture was stirred for another 2 h. Then, the residue was filtered and rinsed with ethyl acetate and the filtrate was concentrated. The crude product was purified by flash chromatography (Silica gel, EtOAc/hexanes: 60/40) to provide the pure title compound **55** (200 mg, 67%) as a white solid. m.p. 96-98 °C. [α] = -51.8 (c = 0.80, MeOH). ^{1}H NMR (500 MHz, Chloroform- *d*): δ 7.78 (d, *J* = 8.1 Hz, 3H), 7.60 (d, *J* = 8.1 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.22 (d, *J* = 8.0 Hz, 2H), 6.94 (s, 1H), 5.81 (ddt, *J* = 16.6, 10.1, 6.2 Hz, 1H), 5.31 – 5.15 (m, 1H), 5.07 (d, *J* = 10.2 Hz, 1H), 4.10 – 4.01 (m, 1H), 3.98 – 3.82 (m, 2H), 3.57 (qd, *J* = 12.1, 5.6 Hz, 2H), 2.79 (dd, *J* = 14.6, 8.0 Hz, 1H), 2.64 (dd, *J* = 14.6, 6.8 Hz, 1H), 2.41 (d, *J* = 6.7 Hz, 6H).; ^{13}C NMR (126 MHz, Chloroform- *d*): δ 146.5, 143.5,

141.1, 137.8, 136.2, 136.0, 134.9, 130.6, 129.8, 127.4, 127.1, 117.7, 114.7, 63.3, 59.9, 47.6, 28.8, 21.8, 21.6; FT-IR (neat, cm^{-1}): 3163, 3124, 2928, 2875, 1646, 1593, 1493, 1379, 1170, 1152, 1076, 979,863, 588, 539. HR-MS (*m/z*): calcd. for $[M+H]^+$ $C_{23}H_{27}N_3O_5$, 490.1487 found 490.1464.

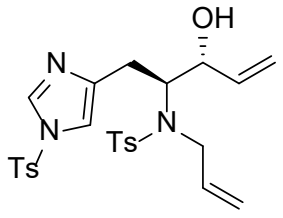
S-N-allyl-4-methyl-N-(1-oxo-3-(1-tosyl-1H-imidazol-4-yl)propan-2-yl) benzenesulfonamide (**46**):



The alcohol **55** (85 mg, 0.17 mmol) was dissolved in 12 mL of H_2O-saturated CH_2CI_2. (Using a separatory funnel, the CH_2CI_2 was shaken with several milliliters of H_2O and then separated from the water layer). DMP was added (94 mg, 0.22 mmol), the clear solution turned cloudy toward the end of wet CH_2Cl_2 addition, which required 30 min. The resultant cloudy reaction mixture was vigorously stirred for 16 h. The mixture was diluted with ether, then concentrated until a few mL of solvent by rotary evaporator. The residue was taken in 30 mL of ether and then washed with 15 mL of 1:1 10% $Na_2S_2O_3$: saturated aqueous $NaHCO_3$, followed by 10 mL of H_2O and 10 mL of brine. The aqueous washings were back extracted with 20 mL of Et_2O, and this organic layer was washed with H_2O and brine. The combined organic part was dried with Na_2SO_4 and concentrated. (Silica gel, EtOAc/hexane = 40:60) to furnish the aldehyde **46** as a colorless solid (62 mg, 74%) as a crystalline solid. m.p. 108-110 °C. [α] = -30.4 (c = 0.92, MeOH). ^1H NMR (500 MHz,

Chloroform- *d*): δ= 9.65 (s, 1H), 7.76 – 7.72 (m, 3H), 7.60 (d, *J* = 8.3 Hz, 2H), 7.36 – 7.32 (m, 2H), 7.28 – 7.26 (m, 2H), 5.72 – 5.62 (m, 1H), 5.16 (s, 1H), 5.13 (dd, *J* = 7.3, 1.2 Hz, 1H), 4.47 (dd, *J* = 9.2, 5.1 Hz, 1H), 3.86 (dd, *J* = 15.5, 6.7 Hz, 1H), 3.68 – 3.60 (m, 1H), 3.19 (dd, *J* = 16.5, 5.1 Hz, 1H), 2.70 (dd, *J* = 15.4, 9.2 Hz, 1H), 2.46 (s, 3H), 2.42 (s, 4H). ^{13}C NMR (126 MHz, Chloroform- *d*): δ 198.8, 146.4, 144.1, 140.3, 137.5, 136.2, 135.0, 133.3, 130.5, 129.9, 127.3, 127.2, 120.5, 114.9, 65.5, 49.9, 25.9, 21.8, 21.7. FT-IR (KBr, cm^{-1}): 3157, 3126, 2924, 2863, 1909, 1731, 1596, 1478, 1256, 1217, 1154, 940, 793, 625, 520. HR-MS (*m/z*): calcd. for $[M+H]^+$ $C_{23}H_{26}N_3O_5S_2$ 488.1314, found 488.1308

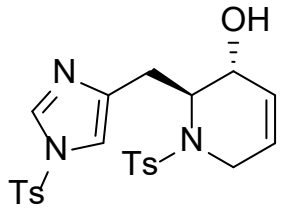
N-Allyl-N-{2-hydroxy-1-[1-(toluene-4-sulfonyl)-1H-imidazol-4-yl-methyl]-but-3-enyl}-4-methyl-benzenesulfonamide (26):



A solution of **46** (200 mg, 4.12 mmol) in THF (5.0 mL) was added to a solution of vinyl magnesium bromide (1.3 M in THF, 5.3 mL) at -78 °C, and the mixture was stirred for 2 h. After stirring for an additional 1 h at 25 °C, a saturated aqueous solution of NH_4Cl (25 mL) was added to the mixture which was then extracted with EtOAc. The organic phase was washed with brine, dried over anhydrous Na_2SO_4, and then evaporated to give an oil. The crude product was purified

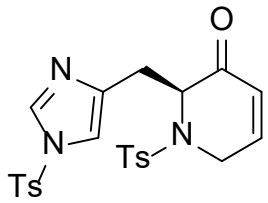
by flash chromatography (silica gel, EtOAc/hexane 50/50), to give the desired alcohol **26** (0.33 g, 75%): [α] = -27.6 (c = 0.45, MeOH). ^{1}H NMR (500 MHz, Chloroform- *d*) δ 7.81 – 7.69 (m, 3H), 7.56 (d, *J* = 8.1 Hz, 2H), 7.35 (d, *J* = 8.2 Hz, 2H), 7.20 (s, 1H), 6.83 (s, 1H), 5.87 – 5.69 (m, 2H), 5.18 (t, *J* = 15.9 Hz, 2H), 5.05 (t, *J* = 9.8 Hz, 2H), 4.30 (s, 1H), 4.10 – 3.98 (m, 1H), 3.94 – 3.83 (m, 2H), 2.86 – 2.69 (m, 2H), 2.43 (d, *J* = 2.1 Hz, 6H). ^{13}C NMR (126 MHz, Chloroform- *d*) δ 146.4, 143.5, 141.4, 138.2, 137.8, 136.1, 135.9, 135.0, 130.5, 129.6, 127.3, 127.2, 117.7, 116.0, 114.8, 74.9, 62.5, 48.5, 26.6, 21.8, 21.6; FT-IR (neat, cm^{-1}): 3112, 1749, 1641, 1515, 1240, 1174, 1090, 994, 925, 824, 771, 674, 592, 478, 455, 417. HR-MS (m/z): calcd. for $[M+H]^{+}$ $C_{25}H_{30}N_3O_5S_2$ 516.1627, found 516.1621

(3S,4R)-1-(Toluene-4-sulfonyl)-3-[1-(toluene-4-sulfonyl)-1H-imidazol-4-yl-methyl]-1,2,3,4- tetrahydropyridin-4-ol (**25**)**:**



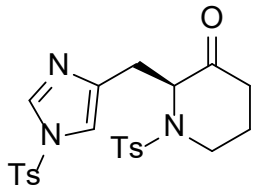
The allylic alcohol **26** (4.6 g, 8.93 mmol), was dissolved in dry CH_2Cl_2 (60 mL). The Grubbs' second-generation catalyst (0.38 g, 0.45 mmol, 5 mol%) was added, followed by heating the mixture at reflux for 3 h. The mixture was stirred at room temperature for 6 h, at which time TLC analysis indicated the completion of the reaction. The solvent was concentrated. The crude product was purified by chromatography (EtOAc/hexanes = 75:25) to give the title compound **25** as a colorless solid (3.4 g, 80%): m.p. 147-149 °C, [α] = - 27.9 (c = 0.27, MeOH). ^{1}H NMR (500 MHz, Chloroform- *d*) δ 7.84 – 7.75 (m, 3H), 7.66 – 7.59 (m, 2H), 7.31 (d, *J* = 8.2 Hz, 2H), 7.21 (d, *J* = 8.0 Hz, 2H), 7.00 (d, *J* = 1.3 Hz, 1H), 5.92 – 5.83 (m, 2H), 4.36 (ddd, *J* = 8.4, 6.6, 1.7 Hz, 1H), 4.12 – 4.06 (m, 1H), 3.97 – 3.89 (m, 1H), 3.59 – 3.51 (m, 1H), 2.45 (dd, *J* = 17.6, 7.6 Hz, 2H), 2.38 (d, *J* = 9.0 Hz, 6H). ^{13}C NMR (126 MHz, Chloroform- *d*) δ 146.4, 143.6, 140.9, 136.8. 136.2, 134.9, 130.5, 129.8, 127.4, 127.3, 126.9, 125.7, 114.4, 64.9, 58.5, 40.6, 27.7, 21.8, 21.6; FT-IR (neat, cm^{-1}): 3747, 3115, 1796, 1592, 1388, 1173, 1080, 930, 840, 770, 550. HR-MS (m/z): calcd. for $[M+H]^+$ $C_{23}H_{26}N_3O_5S_2$ 488.1314, found 488.1308.

S-1-Tosyl-2-((1-tosyl-1H-imidazol-4-yl) methyl)-1,6-dihydropyridin-3(2H) -one (48):



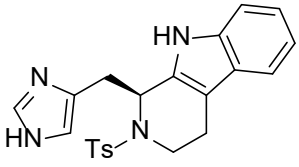
To a stirred solution of **25** (3.6 g, 7.38 mmol) in acetone (60 ml) was added IBX (2.27 g, 8.11 mmol) at 0 °C. The resulting reaction mixture was heated to reflux for 6 h. The reaction mixture was cooled to room temperature, and resulting slurry was filtered and washed with ethyl acetate. The filtrated was concentrated under reduced pressure. Crude product was purified by column chromatography (EtOAc/Hexanes = 4:1) to afford compound **48** (2.9 g, 81%) as off-white solid. m.p. = 103-105 °C. [α] = -30.8 (c = 0.37, MeOH). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.86 (d, *J* = 1.3 Hz, 1H), 7.79 (d, *J* = 8.5 Hz, 2H), 7.51 (d, *J* = 8.3 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.21 (d, *J* = 7.9 Hz, 3H), 6.68 (ddd, *J* = 10.4, 4.9, 1.9 Hz, 1H), 5.76 (dt, *J* = 10.4, 2.3 Hz, 1H), 4.64 (t, *J* = 7.5 Hz, 1H), 4.40 (ddd, *J* = 21.0, 4.9, 1.6 Hz, 1H), 4.00 (dt, *J* = 21.1, 2.1 Hz, 1H), 2.90 (d, *J* = 7.5 Hz, 2H), 2.39 (d, *J* = 16.2 Hz, 6H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 193.4, 146.3, 144.3, 144.1, 139.3, 136.3, 136.1, 134.9, 130.5, 130.3, 130.0, 127.4, 127.2, 127.0, 126.7, 115.4, 61.1, 41.3, 29.2, 21.8, 21.6. FT-IR (neat, cm^{-1}): 3427, 3129, 2940, 1686, 1490, 1464, 1387, 1163, 1154, 1100, 757, 698, 550, 520. HR-MS (m/z): calcd. for $[M+H]^+$ $C_{23}H_{24}N_3O_5S_2$ 486.1157, found 486.1152.

S-1-(Toluene-4-sulfonyl)-3-[1-(toluene-4-sulfonyl)-1H-imidazol-4-ylmethyl]-piperidin-4-one (**24**)**:**



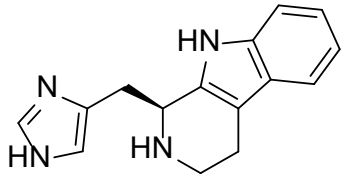
The enone **48** (800 mg, 1.63 mmol) and 10% Pd/C (160 mg) were placed in a 1:3 mixture of ethyl acetate and ethanol (10 mL) and under H_2 (40 psi). Then, the catalyst was filtered and rinsed with ethyl acetate and the filtrate was concentrated. The crude product was purified by flash chromatography (EtOAc/hexanes: 80/20) to provide the pure title compound **24** (680 mg, 85%) as a yellow solid. [α] = - 13.8 (c = 0.93, MeOH). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.76 (s, 1H), 7.74 (d, 2H, *J* = 8.3 Hz), 7.53 (d, 2H, *J* = 8.3 Hz), 7.30 (d, 2H,), 7.2 (d, 2H, *J* = 8.3 Hz), 7.03 (s, 1H), 4.49 (t, 1H, *J* = 7.3 Hz), 3.73 (ddd, 1H, *J* = 19.3, 9.6, 4.6, Hz), 3.20 (ddd, 1H, *J* = 19.3, 9.6, 5.0 Hz), 2.95 (d, 2H, *J* = 7.3 Hz), 2.42 (dd, 2H, *J* = 14.7, 6.9 Hz), 2.43 (s, 6H), 2.20 (ddd, 1H, *J* = 21.5, 11.0, 5.5, Hz), 1.64-1.74 (m, 2H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ 206.2, 146.3, 143.9, 139.5, 137.2, 136.2, 135.0, 130.5, 130.0, 127.3, 127.0, 115.5, 63.7, 40.3, 36.5, 30.1, 23.2, 21.8, 21.6; FT-IR (neat, cm^{-1}): 3422, 3119, 2930, 1738, 1620, 1510, 1360, 1260, 1210, 1100, 1010, 720, 680, 550, 530, 510. HR-MS (m/z): calcd. for $[M+H]^+$ $C_{23}H_{26}N_3O_5S_2$ 488.1314, found 488.1308.

S-1-((1H-Imidazol-5-yl) methyl) -2-tosyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b] indole (23):



A suspension of enone (67 mg, 0.13 mmol), benzophenone phenylhydrazone (25 mg, 0.09 mmol) and p-TsOH·H_2O (43 mg, 0.23 mmol) was in EtOH (2.0 mL) heated to reflux for 72 h. The reaction mixture was cooled to room temperature, diluted with CH_2Cl_2 (15 mL) and washed with saturated aqueous sodium bicarbonate solution (3 x 25 mL) followed by water (15 mL) and brine (15 mL). The organic part was dried over sodium sulfate and concentrated under reduced pressure. The crude was purified by column chromatography (MeOH/EtOAc = 2:8) to afford desired compound 20 (24 mg, 65%) as an off-white solid. m.p. = 138-142 °C. [α] = -14.9 (c = 0.43, MeOH); ^{1}H NMR (500 MHz, Chloroform-*d*) δ 9.70 (s, 1H), 7.18 (d, *J* = 8.3 Hz, 2H), 6.95 – 6.83 (m, 3H), 6.68 (dd, *J* = 18.4, 8.3 Hz, 3H), 6.61 (t, *J* = 7.8 Hz, 1H), 6.46 (bs, 1H), 5.03– 4.97 (m, 1H), 3.76 (dd, *J* = 14.4, 5.2 Hz, 1H), 2.98 (ddd, *J* = 14.4, 12.3, 5.2 Hz, 1H), 2.84 (m, 2H), 2.13 (dd, *J* = 15.4, 3.5 Hz, 2H), 2.04-2.03 (m, 1H), 1.95 (s, 3H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ 143.5, 137.9, 136.1, 135.2, 129.7, 126.7, 126.6, 121.8, 119.2, 118.1, 111.5, 107.4, 53.6, 40.4, 21.5, 20.2; FT-IR (neat, cm^{-1}): 3376, 3055, 2921, 2850, 1739, 1492, 1325, 1150, 1090, 919, 812. HR-MS (m/z): calc for $[M+Na]^+$ $C_{22}H_{22}N_4O_2S$, 429.1356, found: 429.1351

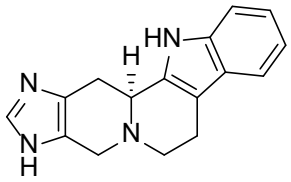
S-1-((1H-Imidazol-5-yl)methyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (Haploscleridamine) (1):



Mg (turnings) was added (14.6 mg, 0.61 mmol) to a solution of indole (±)- **23** (25 mg, 0.061 mmol) in dry MeOH (2 mL), and the mixture was sonicated at 48 °C until all magnesium turnings were consumed. MeOH was evaporated, saturated ammonium chloride (15 mL) was added and extracted with dichloromethane (2x 30 mL). The combined extracts were dried over anhydrous Na_2SO_4, concentrated under reduced pressure. During reaction, a non-polar spot formed villagorgin A **5** along with haploscleridamine **1**. The crude product was purified by column chromatography (ammoniacal MeOH: DCM = 1: 19) to provide as colorless solid Villagorgin A **(±)-5** (3.8 mg 23%) and by using (Ammoniacal MeOH: DCM = 1: 9) provided haploscleridamine (±)**-1** (8 mg, 52%) as a colorless solid.; [α] = -13.7 (c = 0.28, MeOH). ^{1}H NMR (Methanol-d_4): δ = 7.65 (bs, 1H), 7.39 (d, J = 7.8 Hz, 1H), 7.30 (d, J = 7.8 Hz, 1H), 7.00 (dt, J= 8.0, 1.0 Hz, 1H), 6.98 (dt, J = 7.8, 1.0 Hz, 1H), 6.87 (bs, 1H), 4.48 (dd, J = 9.1, 4.1 Hz, 1H), 3.37 (td J = 9.1, 4.1 Hz, 1H), 3.32 (td, J = 9.1, 4.1 Hz, 1H), 3.05 (ddd, J = 13.9, 9.1, 5.2 Hz, 1H), 3.00 (dd, J = 13.9, 9.0 Hz, 1H), 2.87-2.74 (m, 2H). ^{13}C NMR (Methanol-d_4) δ 137.9, 136.6, 135.5, 134.3, 128.2, 122.5, 120.0, 118.8, 117.8, 112.0, 108.7, 54.3, 43.0, 32.2, 21.9.

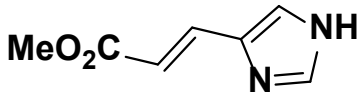
FT-IR (neat, cm^{-1}): 3151, 2923, 2846, 1735, 1619, 1450, 1372, 1228, 1100, 739. HR-MS (m/z): calc for $[M-H]^+$ $C_{15}H_{16}N_4$, 251.1302, found: 251.1307

Villagorgin A (5)



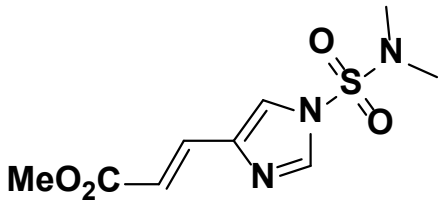
m.p. = 145-150 °C, [α] = -13.5 (c = 0.31, MeOH), ^{1}H NMR (500 MHz, Methanol-d_4): δ 7.60 (d, *J* = 2.7 Hz, 1H), 7.44 – 7.40 (m, 1H), 7.31 (dd, *J* = 7.0, 3.9 Hz, 1H), 7.09 – 7.04 (m, 1H), 7.01 – 6.96 (m, 1H), 4.00 (dd, *J* = 14.1, 3.3 Hz, 1H), 3.84 (m, 1H), 3.62 (m, 1H), 3.37 (m, 1H), 3.34 (m, 1H), 3.05 (m, 1H), 2.89 (ddd, *J* = 3.8, 8.4, 15 Hz, 1H), 2.79 (m, 1H), 2.73 (m, 1H). ^{13}C NMR (126 MHz, Methanol-d_4): δ 138.4, 135.6, 134.8, 129.8, 128.0, 122.3, 119.9, 118.8, 112.0, 108.4, 73.8, 58.5, 54.0, 53.3, 29.2, 22.3. FT-IR (neat, cm^{-1}): 3096, 2957, 1717, 1616, 1526, 1440, 1349, 1288, 1268, 1193, 1134, 1072, 978, 924, 822, 777, 718. HR-MS (*m/z*): Calcd. for $[M+H]^+$ $C_{16}H_{17}N_4$ 265.1448, found 265.1444.

Synthesis of methyl (E)-3-(1H-imidazol-4-yl) acrylate (125):



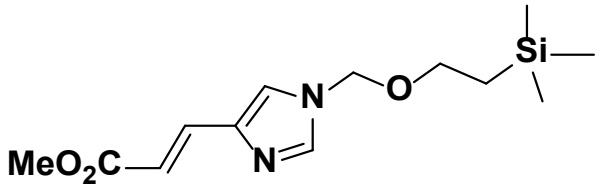
4-imidazole acrylic acid (15.0 g, 108.69 mmol) was dissolved in methanol (150 mL), sulfuric acid (8.4 mL, 152.05 mmol) and sodium sulfate (2.1 g, 15.27 mmol) were slowly added with vigorous stirring and cooled in an ice bath. The reaction mixture was stirred at room temperature for 5 h then heated to reflux for 20 hours. To a solution of the sulfate salt in dichloromethane (100 mL) was added water (30 mL). Solid sodium bicarbonate was added until the solution reached a pH of 7. The resulting solution was extracted with dichloromethane (3 x 100 mL). The combined organic extracts were dried with Na_2SO_4 and then evaporated under reduced pressure to afford an off-white solid. The residue was purified by flash chromatography (silica gel, EtOAc/hexane = 70:30) to furnish **125** (16.0 g, 86%) as a colorless crystalline solid: m.p. = 92-94 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.23 (d, J = 1.2 Hz, 1H), 8.06 – 7.98 (m, 1H), 7.54 (d, J = 16.2 Hz, 1H), 6.88 (d, J = 16.2 Hz, 1H), 3.70 (s, 3H). ^{13}C NMR (500 MHz, DMSO-d_6) δ 166.5, 136.9, 130.1, 129.1, 122.3, 120.5, 52.4. FT-IR (neat, cm^{-1}): 3133, 2170, 2137, 1946, 1707, 1646, 1542, 1507, 1429, 1326, 1297, 1259, 1211, 1095, 983, 969, 854, 739, 684, 616, 512. HR-MS (*m/z*): calcd. for $[M+H]^+$ $C_7H_9N_2O_2$ 153.0625, found 153.0610.

Synthesis of methyl (E)-3-(1-(N, N-dimethylsulfamoyl)-1H-imidazol-4-yl) acrylate (109a):



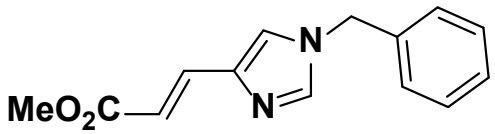
Methyl ester **125** (1.0 g, 6.57 mmol) was dissolved in dichloromethane (30 mL), triethylamine (2.2 mL, 15.9 mmol) and DMASCl (0.8 mL, 7.08 mmol) were slowly added with vigorous stirring and cooled in an ice bath. The reaction mixture was stirred at 0 °C for 30 min and then room temperature for 2 h, additional dichloromethane (30 mL) was added to the reaction mixture and the solution was washed with water and brine (3 x 20 mL) and dried with Na_2SO_4. The extract was concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, EtOAc/hexane = 50:50) to furnish **109a** (0.9 g, 70 %) as a colorless crystalline solid: m.p. = 98-100 °C. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.87 (t, *J* = 1.0 Hz, 1H), 7.49 (dd, *J* = 15.6, 0.6 Hz, 1H), 7.36 (d, *J* = 1.2 Hz, 1H), 6.65 (d, *J* = 15.6 Hz, 1H), 3.77 (s, 3H), 2.87 (s, 6H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 167.4, 139.4, 137.6, 134.5, 119.3, 118.7, 51.8, 38.3. FT-IR (neat, cm^{-1}): 3128, 2951, 1711, 1640, 1531, 1481, 1462, 1416, 1386, 1337, 1261, 1189, 1078, 963, 929, 793, 724, 689, 582, 512. HR-MS (*m/z*): calcd. for $[M+H]^+$ $C_9H_{14}N_3O_4S$ 260.2830, found 260.2824.

Synthesis of methyl (E)-3-(1-((2-(trimethylsilyl) ethoxy) methyl)-1H-imidazol-4-yl) acrylate (109b):



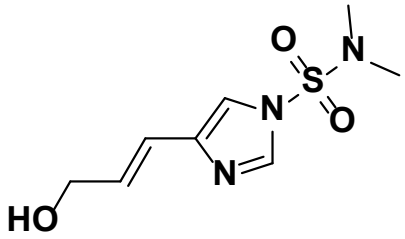
Methyl ester **125** (0.5 g, 2.66 mmol) was dissolved in THF (20 mL), 60% sodium hydride (0.05 g, 3.72 mmol) and SEMCl (0.5 mL, 3.0 mmol) were slowly added with vigorous stirring and cooled in an ice bath. The reaction mixture was stirred at 0 °C for 30 min and then room temperature for 18 h, additional ice water (15 mL) was added, and additional ethyl acetate (2x 20 mL) was added to the reaction mixture and the solution was washed with water and brine (3 x 10 mL) and dried over anhydrous Na_2SO_4. The extract was concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, EtOAc/hexane = 50:50) to furnish **109b** (0.5 g, 66 %) as a colorless crystalline solid: m.p. = 70-72 °C. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.46 (d, *J* = 1.2 Hz, 1H), 7.38 (d, *J* = 15.6 Hz, 1H), 7.09 (d, *J* = 1.3 Hz, 1H), 6.40 (d, *J* = 15.6 Hz, 1H), 5.12 (d, *J* = 20.5 Hz, 3H), 3.58 (s, 3H), 3.39 – 3.23 (m, 2H), 0.78 – 0.67 (m, 2H), -0.08 – -0.33 (m, 9H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 167.8, 139.0, 138.6, 138.6, 137.0, 121.6, 121.37, 116.0, 76.0, 66.5, 66.0, 60.2, 53.5, 51.3, 20.9, 17.9, 17.6, 14.1, 14.0, -1.5. FT-IR (neat, cm^{-1}): 3109, 2955, 2929, 1701, 1639, 1499, 1450, 1359, 1293, 1225, 1158, 1138, 1046, 1019, 985, 921, 831, 706, 680, 518, 411. HR-MS (*m/z*): calcd. for $[M+H]^+$ $C_{13}H_{23}N_2O_3Si$ 283.1548, found 283.1542.

Synthesis of methyl (E)-3-(1-benzyl-1H-imidazol-4-yl) acrylate (109c):



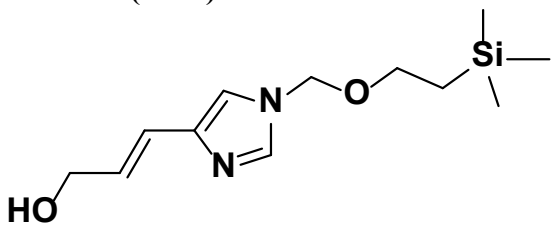
Methyl ester **125** (1.0 g, 6.64 mmol) was dissolved in DMF (20 mL), 60% sodium hydride (0.23 g, 9.82 mmol) and benzyl chloride (1.6 mL, 13.12 mmol) were slowly added with vigorous stirring and cooled in an ice bath. The reaction mixture was stirred at 0 °C for 30 min and then room temperature for 18 h, additional ice water was added and stirred the reaction mixture solution for 1 hour. A solid precipitation formed and was filtered through a sintered glass funnel. The solids were washed with cold water and dried under vacuum pump. The residue was purified by flash chromatography (silica gel, EtOAc/hexane = 50:50) to furnish **109c** (0.9 g, 70%) as a colorless crystalline solid: m.p. = 118-120 °C. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.58 (s, 1H), 7.52 (d, *J* = 15.7 Hz, 1H), 7.36 (d, *J* = 7.2 Hz, 3H), 7.16 (d, *J* = 8.9 Hz, 2H), 7.07 (s, 1H), 6.55 (d, *J* = 15.6 Hz, 1H), 5.10 (s, 2H), 3.75 (s, 3H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ168.1, 138.8, 138.6, 136.1, 135.4, 129.3, 128.7, 128.6, 128.1, 127.5, 121.8, 116.0, 51.6, 51.2. FT-IR (neat, cm^{-1}): 3131, 3097, 3023, 2922, 1698, 1631, 1437, 1297, 1194, 1159, 1039, 979, 858, 792, 773, 743, 694, 669, 621, 577, 519, 471. HR-MS (*m/z*): calcd. for [M+H]$^{+}$ $C_{14}H_{15}N_2O_2$ 243.2821, found 243.2811.

Synthesis of (E)-4-(3-hydroxyprop-1-en-1-yl)-N,N-dimethyl-1H-imidazole-1-sulfonamide (110a):



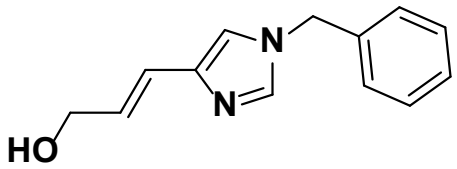
Compound **109a** (8.7 g, 33.81 mmol) was dissolved in CH_2Cl_2 (300 mL) under argon. The mixture was cooled to -78 °C then DIBAL-H (1M in hexanes, 101.6 mL, 101.62 mmol) was added dropwise. The reaction mixture was stirred for 2 hours at the same temperature and then water (4mL), followed by NaOH (4 mL, 2N) and water (10 mL) were added. The reaction mixture was stirred at room temperature for 30 min. The mixture was filtered through Celite and washed with (1: 2) methanol CH_2Cl_2 mixture (150 mL) and dried with Na_2SO_4 (anhydrous). The extract was concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, EtOAc/hexane = 80:20) to furnish **110a** (6 g, 77%) as a colorless crystalline solid: : m.p. = 112-114 °C, ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.83 – 7.82 (d, 1H), 7.11 (s, 1H), 6.61 (s, 1H), 6.46 (s, 1H), 4.27 (s, 2H), 2.84 (s, 7H), 2.18 (s, 1H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 141.1, 137.0, 130.8, 120.6, 114.2, 63.1, 38.3. FT-IR (neat, cm^{-1}): 3344, 3131, 2918, 1737, 1478, 1419, 1382, 1333, 1265, 1167,1083,1007, 962, 907, 805, 752, 730, 597, 513. HR-MS (*m/z*): calcd. for $[M+H]^+$ $C_8H_{14}N_3O_3S$ 232.1520, found 232.1514.

Synthesis of (E)-3-(1-((2-(trimethylsilyl) ethoxy) methyl)-1H-imidazol-4-yl) prop-2-en-1-ol (110b):



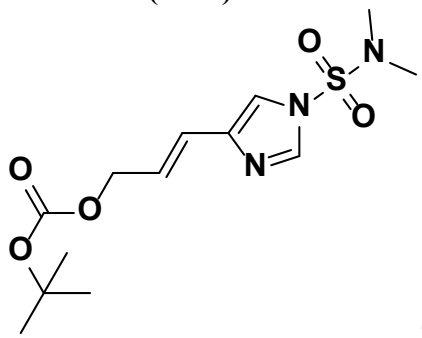
Compound **109b** (0.5 g, 1.83 mmol) was dissolved in CH_2Cl_2 (50 mL) under argon. The mixture was cooled to -78 °C and DIBAL-H (1M in hexanes, 3.5 mL, and 3.56 mmol) was added dropwise. The reaction mixture was stirred for 2 hours at the same temperature and then water (0.15 mL), followed by NaOH (0.15 mL, 2N) and water (0.36 mL) were added. The reaction mixture was stirred at room temperature for 30 min. The mixture was filtered through Celite and washed with methanol CH_2Cl_2 mixture (50 mL) and dried with Na_2SO_4. The extract was concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, EtOAc/hexane = 80:20) to furnish **110b** (0.35g ,77 %) as a yellow sticky liquid. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.50 (d, *J* = 1.3 Hz, 1H), 6.90 (d, *J* = 1.4 Hz, 1H), 6.46 (d, *J* = 2.1 Hz, 2H), 5.16 (s, 2H), 4.40 – 4.12 (m, 2H), 3.48 – 3.31 (m, 2H), 0.93 – 0.81 (m, 2H), -0.07 (s, 19H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 140.6, 137.6, 128.6, 121.9, 116.3, 76.0, 66.5, 63.1, 17.7, -1.3. FT-IR (neat, cm^{-1}): 2952, 1672, 1632, 1357, 1247, 969, 832, 692. HR-MS (*m/z*): calcd. for $[M+H]^+$ $C_{12}H_{23}N_2O_2Si$ 255.1539, found 255.1551.

Synthesis of (E)-3-(1-benzyl-1H-imidazol-4-yl)prop-2-en-1-ol (110c):



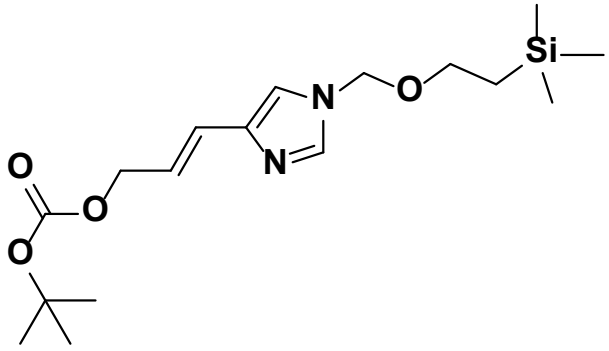
Compound **109c** (3.0 g, 12.39 mmol) was dissolved in CH_2Cl_2 (50 mL) under argon. The mixture was cooled to -78 °C. DIBAL-H (1M in hexanes, 24.8 mL, and 24.80 mmol) was added dropwise. The reaction mixture was stirred for 2 hours at same temperature and then water (1 mL), followed by NaOH (1 mL, 2N) and water (2.4 mL) were added. The reaction mixture was stirred at room temperature for 30 min. The mixture was filtered through Celite and the pad was washed with methanol CH_2Cl_2 mixture (2x50 mL) and dried with Na_2SO_4. The extract was concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, EtOAc/hexane = 80:20) to furnish **110c** (1.8 g , 70%) as a colorless crystalline solid: m.p. = 68-70 °C. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.46 (s, 1H), 7.35 – 7.28 (m, 3H), 7.12 (dd, *J* = 7.8, 1.5 Hz, 2H), 6.78 (s, 1H), 6.45 (s, 2H), 5.02 (s, 2H), 4.23 (s, 2H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 140.4, 138.2, 137.6, 136.0, 130.8, 129.1, 128.4, 128.1, 128.0, 127.4, 127.1, 126.7, 122.4, 116.9, 63.3, 62.9, 51.0. FT-IR (neat, cm^{-1}): 3113, 2845, 1729, 1666, 1629, 1538, 1495, 1453, 1354, 1312, 1117, 1089, 1043, 968, 706, 632, 451, 434. HR-MS (*m/z*): calcd. for $[M+H]^+$ $C_{13}H_{15}N_2O$ 215.2710, found 215.2706.

Synthesis of (E)-tert-butyl (3-(1-(N,N-dimethylsulfamoyl)-1H-imidazol-4-yl)allyl) carbonate (113a):



Compound **110a** (1.0 g, 4.67 mmol) was dissolved in tetrahydrofuran (20 mL), 5% aqueous NaOH (20 mL) and $(BOC)_2O$ (4.0 mL, 18.6 mmol) and tetrabutyl ammonium hydrogen sulfate (0.047 g, 0.14 mmol) were slowly added with vigorous stirring of the solution. The reaction mixture was stirred at room temperature for 18 h, ethyl acetate (20 mL) was added to the reaction mixture and the solution was washed with water and brine (3 x 10 mL) and dried over anhydrous Na_2SO_4. The extract was concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, EtOAc/hexane = 20:80) to furnish **113a** (1.2 g, 86%) as a colorless crystalline solid: m.p. = 100-102 °C. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.84 (d, *J* = 1.1 Hz, 1H), 7.13 (d, *J* = 1.2 Hz, 1H), 6.53 – 6.49 (m, 2H), 4.70 (d, *J* = 4.5 Hz, 2H), 2.85 (s, 6H), 1.48 (s, 9H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 153.4, 140.6, 137.0, 124.9, 123.8, 114.8, 82.3, 66.9, 38.3, 27.8. FT-IR (neat, cm-^{1}) : 3129, 2981, 1734, 1488, 1418, 1384, 1367, 1275, 1203, 1173, 1119, 1084, 1069, 1007, 974, 850, 793, 743, 613, 595, 531, 512, 407. HR-MS (*m/z*): calcd. for $[M+H]^+$ $C_{13}H_{22}N_3O_5S$ 332.3940, found 332.3938.

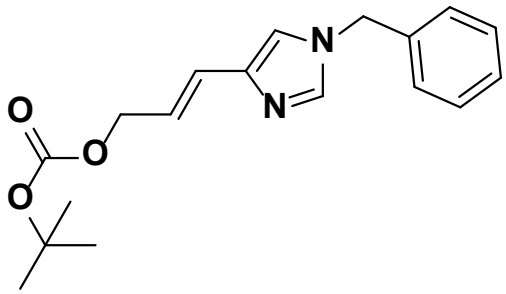
Synthesis of (*E*)-*tert*-butyl (3-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-4-yl)allyl) carbonate (113b):



Compound **110b** (0.5 g, 1.96 mmol) was dissolved in DCM (25 mL), triethyl amine (0.3 mL, 2.33 mmol) and $(BOC)_2O$ (0.85 mL, 3.2 mmol) and DMAP (0.023 g, 0.19 mmol) were slowly added with vigorous stirring to the solution. The reaction mixture was stirred at room temperature for 18 h, ethyl acetate (20 mL) was added to the reaction mixture and the solution was washed with water and brine (3 x 10 mL) and dried with Na_2SO_4. The extract was concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, EtOAc/hexane = 20:80) to furnish **113b** (0.5 g, 72%) as a yellow sticky liquid. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.46 (s, 1H), 6.91 (d, *J* = 1.3 Hz, 1H), 6.47 (d, *J* = 10.2 Hz, 1H), 6.39 – 6.29 (m, 1H), 5.14 (s, 2H), 4.62 (d, *J* = 12.8 Hz, 2H), 3.42 – 3.36 (m, 2H), 1.40 (s, 10H), 0.86 – 0.79 (m, 3H), -0.10 (s, 10H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 153.4, 140.1, 137.7, 125.8, 125.7, 121.7, 117.1, 81.1, 76.0, 67.4, 66.4, 53.5, 27.8, 17.7, -1.4. FT-IR (neat, cm^{-1}): 2951, 1736, 1498, 1457, 1367, 1273, 1248, 1156, 1090, 968,

916, 856, 760, 694, 462. HR-MS (*m/z*): calcd. for $[M+H]^+$ $C_{17}H_{31}N_2O_4Si$ 355.2254, found 355.2259.

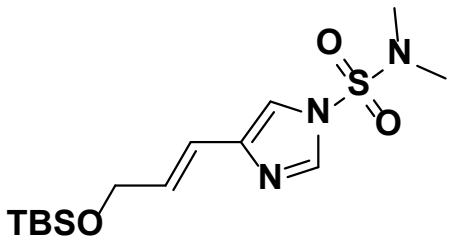
Synthesis of (E)-3-(1-benzyl-1H-imidazol-4-yl)allyl tert-butyl carbonate (113c):



Compound **110c** (4.5 g, 20.93 mmol) was dissolved in tetrahydrofuran (30 mL), 5% aqueous NaOH (30 mL) and $(BOC)_2O$ (18.3 mL, 83.72 mmol) and tetra butyl ammonium hydrogen sulfate (0.16 g, 0.49 mmol) were slowly added with vigorous stirring to the solution. The reaction mixture was stirred at room temperature for 18 h, additional ethyl acetate (40 mL) was added to the reaction mixture and the solution was washed with water and brine (3 x 20 mL) and dried with Na_2SO_4. The extract was concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, EtOAc/hexane = 20:80) to furnish **113c** (3.8 g, 86 %) as a yellow crystalline solid: m.p. = 70-72 °C. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.49 – 7.46 (m, 1H), 7.35 – 7.29 (m, 3H), 7.14 – 7.11 (m, 2H), 6.82 (d, *J* = 1.3 Hz, 1H), 6.53 – 6.47 (m, 1H), 6.37 (dt, *J* = 15.7, 6.4 Hz, 1H), 5.04 (s, 2H), 4.65 (dd, *J* = 6.4, 1.2 Hz, 2H), 1.46 (dd, *J* = 29.5, 0.6 Hz, 11H). ^{13}C NMR (126 MHz,

Chloroform-*d*) δ 139.9, 137.8, 135.9, 129.1, 128.5, 127.4, 126.1, 121.5, 117.7, 82.1, 67.5, 51.0, 27.8. FT-IR (neat, cm^{-1}): 1734, 1721, 1496, 1393, 1367, 1248, 1148, 1110, 1042, 1030, 977, 961, 941, 856, 776, 690, 632, 531, 503, 456, 417. HR-MS (*m/z*): calcd. for $[M+H]^+$ $C_{18}H_{23}N_2O_3$ 315.1614, found 315.1613

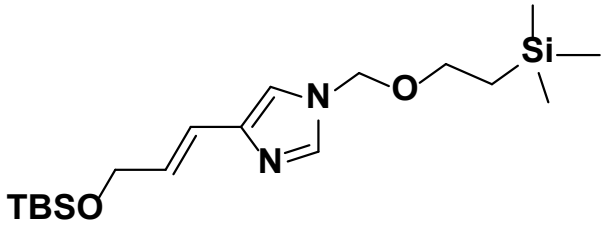
Synthesis of (E)-4-(3-((tert-butyldimethylsilyl)oxy)prop-1-en-1-yl)-N,N-dimethyl-1H-imidazole-1-sulfonamide (127a):



Compound **110a** (0.25 g, 1.04 mmol) was dissolved in DMF (20 mL). TBSCl (0.4 g, 1.6 mmol) and imidazole (0.245 g, 3.54 mmol) were added to the solution followed by stirring the reaction mixture at room temperature for 24 hours. Reaction progress was monitored by TLC. Ethyl acetate (50 mL) was added to the reaction mixture and the solution was washed with water and brine (3 x 30 mL) and dried over anhydrous Na_2SO_4. The extract was concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, EtOAc/hexane = 40:60) to furnish **127a** (0.3 g, 96%) as a white crystalline solid: m.p. = 76-78 °C. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.86 (d, *J* = 1.0 Hz, 1H), 7.10 (d, *J* = 1.3 Hz, 1H), 6.57 (dt, *J* = 15.6, 4.2 Hz, 1H), 6.47 (dt, *J* = 15.6, 1.9 Hz, 1H), 4.34 (dd, *J* = 4.2, 1.8 Hz, 2H), 2.86 (s, 6H), 0.92 (s, 9H), 0.09 (s, 6H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 141.3, 136.8,

131.6, 118.7, 113.8, 63.2, 38.3, 26.0, 18.5, -5.1. FT-IR (neat, cm^{-1}): 3132, 2929, 2884, 2842, 1482, 1464, 1419, 1376, 1265, 1246, 1234, 1078, 1045, 967, 856, 811, 771, 731, 688, 587, 514. HR-MS (*m/z*): calcd. for $[M+H]^+$ $C_{14}H_{28}N_3O_3SSi$ 346.5320, found 346.5318.

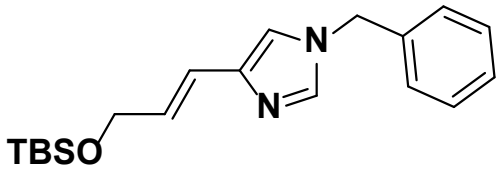
Synthesis of (E)-4-(3-((tert-butyldimethylsilyl)oxy)prop-1-en-1-yl)-1-((2-trimethylsilyl)ethoxy)methyl)-1H-imidazole (127b):



Compound **110b** (0.2 g, 0.83 mmol) was dissolved in DMF (15 mL). TBSCl (0.18 g, 1.25 mmol), imidazole (0.12 g, 1.80 mmol), followed by stirring the reaction mixture at room temperature for 24 hours. The reaction progress was monitored by TLC. Ethyl acetate (20 mL) was added to the reaction mixture and the solution was washed with water (15 mL) and brine (3 x 10 mL) and dried over anhydrous Na_2SO_4. The extract was concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, EtOAc/hexane = 40:60) to furnish **127b** (0.25 g, 85%) as a yellow sticky liquid. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.45 (d, *J* = 1.4 Hz, 1H), 6.86 (d, *J* = 1.3 Hz, 1H), 6.52 – 6.26 (m, 2H), 5.13 (s, 2H), 4.25 (dd, *J* = 4.5, 1.5 Hz, 2H), 3.44 – 3.26 (m, 2H), 0.85 (s, 8H), 0.84 – 0.79 (m, 3H),

0.05 (s, 6H), -0.10 (s, 9H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 140.9, 137.9, 137.4, 136.7, 128.1, 120.8, 116.2, 116.0, 92.0, 75.9, 72.0, 66.3, 66.0, 63.6, 29.7, 27.8, 26.0, 25.8, 18.5, 18.0, 17.7, -1.4, -3.4, -4.9, -5.1, -5.4. FT-IR (neat, cm^{-1}) : 2951, 2855, 1686, 1499, 1461, 1359, 1248, 1094, 967, 938, 835, 776, 693, 625. HR-MS (*m/z*): calcd. for $[M+H]^+$ $C_{18}H_{37}N_2O_2Si_2$ 369.2409, found 369.2404.

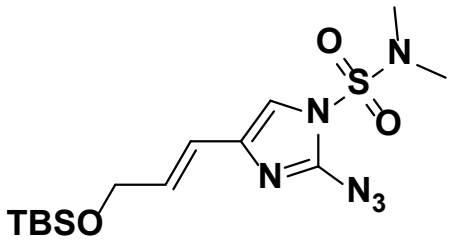
Synthesis of (E)-1-benzyl-4-(3-((tert-butyldimethylsilyl) oxy) prop-1-en-1-yl)-1H-imidazole (127c):



Compound **110c** (0.25 g, 0.76 mmol) was dissolved in THF (20 mL). TBSCl (0.17 g, 1.14 mmol) followed by imidazole (0.13 g, 1.90 mmol) were added to the solution. The reaction mixture was stirred at room temperature for 24 hours and monitored by TLC analysis. Ethyl acetate (30 mL) was added to the reaction mixture and the solution was washed with water (20 mL) and brine (3 x 10 mL) and dried with Na_2SO_4. The extract was concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, EtOAc/hexane = 40:60) to furnish **127c** (0.20 g, 80%) as a brown sticky liquid. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.45 (s, 1H), 7.34 – 7.25 (m, 3H), 7.15 – 7.07 (m, 2H), 6.77 (s, 1H),

6.61 – 6.31 (m, 2H), 5.02 (s, 2H), 4.29 (dd, J = 4.6, 1.5 Hz, 2H), 0.90 (s, 9H), 0.06 (s, 6H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 140.8, 137.5, 136.1, 129.0, 128.3, 127.8, 127.3, 120.5, 117.1, 64.6, 52.0, 27.0, 19.0, -5.1. FT-IR (neat, cm^{-1}) : 2950, 2927, 2895, 2853, 1535, 1493, 1471, 1454, 1397, 1301, 1274, 1145, 1065, 986, 761, 715, 691, 733, 660, 615, 457, 421. HR-MS (*m/z*): calcd. for $[M+H]^+$ $C_{19}H_{29}N_2OSi$ 329.2044, found 329.2029.

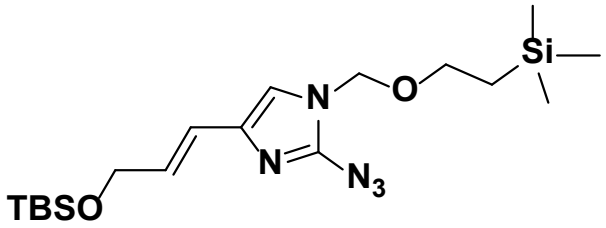
Synthesis of (E)-2-azido-4-(3-((tert-butyldimethylsilyl) oxy) prop-1-en-1-yl)-N, N-dimethyl-1H-imidazole-1-sulfonamide (128a):



Compound **127a** (0.34 g, 0.98 mmol) was dissolved in anhydrous THF (15 mL) and cooled to -78 °C. Then n-BuLi (0.67 mL, 1.67 mmol) was added dropwise to the cooled solution. The resulting solution was stirred for 40 min. Degassed tosyl azide (0.37 g, 1.96 mmol) in THF (10 mL) was added to the solution and then cold bath was removed. The reaction mixture was stirred for 2 hours and then quenched with saturated ammonium chloride (5 mL)). The mixture was extracted with ethyl acetate (3x 20 mL) then the combined organic extracts were washed with water (15 mL), followed by brine solution (10 mL) and dried over anhydrous Na_2SO_4. The extract was concentrated under reduced pressure. The residue was purified by flash

chromatography (silica gel, EtOAc/hexane = 90:10) to furnish **128a** (0.26 g, 69 %) as a red solid: m.p. = 80-82 °C. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 6.96 (s, 1H), 6.45 (dt, *J* = 15.4, 4.3 Hz, 1H), 6.34 (dt, *J* = 15.4, 1.7 Hz, 1H), 2.95 (s, 6H), 0.92 (s, 9H), 0.08 (s, 5H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 140.5, 137.1, 130.9, 118.8, 115.7, 63.2, 38.5, 26.0, 25.7, 18.5, -5.2. FT-IR (neat, cm^{-1}): 2929, 2855, 2158, 1617, 1521, 1459, 1419, 1373, 1308, 1210, 1117, 994, 957, 834, 775, 719, 687, 667, 638, 617, 588. 516, 417. HR-MS (*m/z*): calcd. for [M+H] $^{+}$ $C_{14}H_{27}N_6O_3SSi$ 387.1355, found 387.1350.

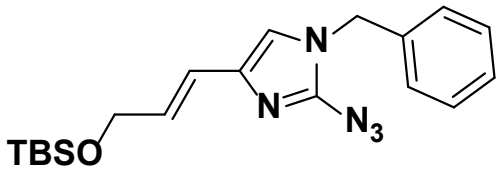
Synthesis of (E)-2-azido-4-(3-((tert-butyldimethylsilyl) oxy)prop-1-en-1-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazole (128b):



Compound **127b** (0.2 g, 0.54 mmol) was dissolved in anhydrous THF (20 mL) and cooled to -78 °C. Then n-BuLi (0.36 mL, 0.92 mmol) was added dropwise to the cooled solution. The solution was stirred for 40 min. Degassed tosyl azide (0.19 g, 1.0 mmol) in THF (10 mL) was added to the solution and the cold bath was removed. The reaction mixture was stirred for 2 hours and then quenched with saturated ammonium chloride (5 mL). The mixture was extracted with

ethyl acetate (3x 15 mL), washed with water (10 mL), followed by brine solution (10 mL) and dried with Na_2SO_4. The combined organic solutions were concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, EtOAc/hexane = 90:10) to furnish **128b** (0.10 g, 53%): as a yellow sticky liquid. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 6.73 (s, 1H), 6.38 (d, *J* = 4.4 Hz, 2H), 5.02 (s, 2H), 4.32 (d, *J* = 2.5 Hz, 2H), 3.54 – 3.43 (m, 2H), 0.92 (s, 9H), 0.88 (d, *J* = 8.1 Hz, 2H), 0.08 (s, 6H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 141.1, 138.3, 128.5, 120.2, 115.4, 73.6, 66.5, 63.5, 26.1, 18.5, 17.7, -1.3, -5.1. FT-IR (neat, cm^{-1}) : 2952, 2856, 2147, 1669, 1508, 1471, 1360, 1248, 1085, 938, 831, 775, 692, 665. HR-MS (*m/z*): calcd. for $[M+H]^+$ $C_{18}H_{36}N_5O_2Si_2$ 409.6822, found 409.6818.

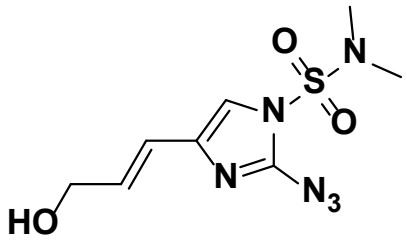
Synthesis of (E)-2-azido-1-benzyl-4-(3-((tert-butyldimethylsilyl) oxy)prop-1-en-1-yl)-1H-imidazole (128c):



Compound **127c** (0.3 g, 0.91 mmol) was dissolved in anhydrous THF (20 mL) and cooled to -78 °C. Then n-BuLi (0.62 mL, 1.55 mmol) was added dropwise to the cooled solution. The solution was stirred for 40 min. Degassed tosyl azide (0.35 g, 1.8 mmol) in THF (10 mL) was added to the solution and then the cold bath was removed. The reaction mixture was stirred for 2 hours and

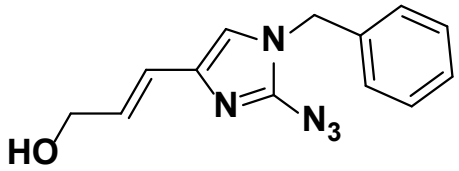
then quenched with saturated ammonium chloride (5 mL). The mixture was extracted with ethyl acetate (3x 15 mL), washed with water (10 mL), followed by brine solution (10 mL) and dried over anhydrous Na_2SO_4. The combined organic solutions were concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, EtOAc/hexane = 90:10) to furnish **128c** (0.23 g, 69%) as a brown sticky liquid. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.34 – 7.26 (m, 3H), 7.17 – 7.10 (m, 2H), 6.58 (s, 1H), 6.37 (d, *J* = 4.0 Hz, 2H), 4.81 (s, 2H), 4.30 (d, *J* = 3.0 Hz, 2H), 0.91 (s, 9H), 0.09 (s, 6H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 140.6, 138.1, 136.0, 129.0, 128.2, 128.0, 127.9, 127.6, 127.4, 120.5, 115.7, 63.5, 48.7, 26.1, 18.5, -5.1. FT-IR (neat, cm^{-1}) : 2929, 2854, 2200, 2185, 2132, 2011, 1992, 1976, 1497, 1471, 1358, 1251, 1174, 1101, 1061, 960, 835, 775, 667. HR-MS (*m/z*): calcd. for $[M+H]^+$ $C_{19}H_{28}N_5OSi$ 370.1420, found 370.1414.

Synthesis of (E)-2-azido-4-(3-hydroxyprop-1-en-1-yl)-N,N-dimethyl-1H-imidazole-1-sulfonamide (129a):



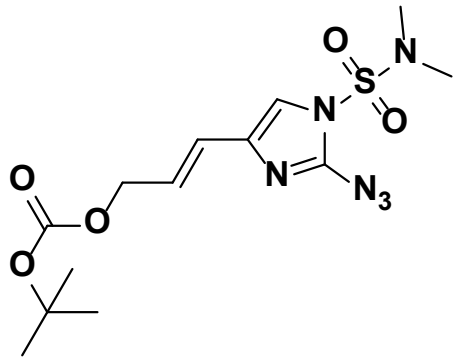
To a solution of the compound **128a** (2.3 g, 5.94 mmol) obtained above in THF (15 mL) was added TBAF (1.0 M, 8.9 mL, 8.9 mmol) at 0 °C. The reaction was stirred at room temperature for 2 h and monitored by TLC analysis. The solvent was then removed by rotary evaporation and then ethyl acetate (2x20 mL) was added, washed successively with water (15 mL) and brine (10 mL), dried over sodium sulfate, filtered, concentrated, and purified by flash column chromatography over silica gel, EtOAc/hexane = 70:30) to give **129a** (1.2 g, 75%) as a yellow sticky liquid. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 6.95 (s, 1H), 6.47 (dt, *J* = 15.6, 5.3 Hz, 1H), 6.32 (dt, *J* = 15.6, 1.5 Hz, 1H), 4.26 (dd, *J* = 5.3, 1.5 Hz, 2H), 3.43 (s, 1H), 2.93 (s, 6H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 160.9, 140.7, 136.7, 130.4 120.2, 116.1, 62.9, 38.5. FT-IR (neat, cm^{-1}): 3154, 2924, 2152, 1730, 1565, 1520, 1456, 1420, 1390, 1250, 1173, 1127, 1073, 962, 853, 723, 640, 617, 572, 514. HR-MS (*m/z*): calcd. for [M+H] $^{+}$ $C_8H_{13}N_6O_3S$ 273.1014, found 273.1013.

Synthesis of (E)-3-(2-azido-1-benzyl-1H-imidazol-4-yl)prop-2-en-1-ol (129c):



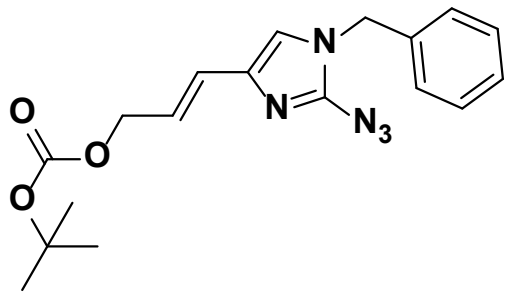
To a solution of the compound **128c** (0.2 g, 0.54 mmol) obtained above in THF (5 mL) was added TBAF (1.0 M, 0.8 mL, 0.8 mmol) at 0 °C. The reaction was stirred at room temperature for 2 h and monitored by TLC analysis. The solvent was then removed by rotary evaporation and the residue was diluted with ethyl acetate (2x30 mL), washed successively with water (5 mL) and brine (5mL), dried over sodium sulfate, filtered, concentrated, and purified by flash column chromatography over silica gel, EtOAc/hexane = 70:30) to give **129c** (0.11 g, 80%) as a brown sticky liquid. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.36 – 7.28 (m, 3H), 7.16 – 7.12 (m, 2H), 6.61 (s, 1H), 6.53 – 6.27 (m, 2H), 4.85 (s, 2H), 4.26 (d, *J* = 6.4 Hz, 2H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 141.0, 137.7, 135.8, 129.0, 128.3, 127.5, 127.4, 122.3, 116.1, 63.6, 48.8. FT-IR (neat, cm^{-1}): 3323, 2960, 2874, 2132, 1654, 1478, 1380, 1272, 1090, 969, 882, 711. HR-MS (*m/z*): calcd. for $[M+H]^+$ $C_{13}H_{14}N_5O$ 256.1109, found 256.1106.

Synthesis of (E)-3-(2-azido-1-(N, N-dimethylsulfamoyl)-1H-imidazol-4-yl) allyl tert-butyl carbonate (126a):



Compound **129a** (1.9 g, 6.9 mmol) was dissolved in tetrahydrofuran (15 mL), 5% aqueous NaOH (15 mL) and $(BOC)_2O$ (4.5 mL, 20.9 mmol) and tetrabutyl ammonium hydrogen sulfate (0.054 g, 0.16 mmol) were slowly added with vigorous stirring of the solution. The reaction mixture was stirred at room temperature for 18 h, ethyl acetate (20 mL) was added to the reaction mixture and the solution was washed with water and brine (3 x 15 mL) and dried with Na_2SO_4. The extract was concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, EtOAc/hexane = 20:80) to furnish **126a** (1.2 g, 86%) as a colorless crystalline solid: m.p. = 90-92 °C. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.00 (s, 1H), 6.49 – 6.43 (m, 1H), 6.43 – 6.37 (m, 1H), 4.69 (d, *J* = 5.2 Hz, 2H), 2.96 (s, 6H), 1.49 (s, 9H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 153.4, 140.8, 136.3, 124.6, 123.4, 116.7, 82.3, 66.8, 38.5, 38.5, 29.8, 28.1, 27.8. FT-IR (neat, cm^{-1}) : 2920, 2851, 2157, 1986, 1732, 1526, 1456, 1379, 1276, 1254, 1155, 1114, 1073, 975, 853, 793, 731, 648, 579, 509, 471. HR-MS (*m/z*): calcd. for $[M+H]^+$ $C_{13}H_{21}N_6O_5S$ 373.1206, found 373.1204.

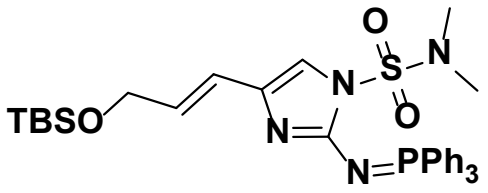
Synthesis of (E)-3-(2-azido-1-benzyl-1H-imidazol-4-yl)allyl tert-butyl carbonate (126c):



Compound **129c** (0.1 g, 0.40 mmol) was dissolved in tetrahydrofuran (5 mL), 5% aqueous NaOH (5 mL) and $(BOC)_2O$ (0.2 mL, 0.8 mmol) and tetrabutyl ammonium hydrogen sulfate (0.004 g, 0.012 mmol) were slowly added with vigorous stirring of the solution. The reaction mixture was stirred at room temperature for 18 h, additional ethyl acetate (20 mL) was added to the reaction mixture and the solution was washed with water (2 x 10 mL) and brine (10 mL) and dried with Na_2SO_4. The combined organic solutions were concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, EtOAc/hexane = 20:80) to furnish **126c** (0.09 g, 63 %) as a brown sticky liquid. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.31 (dd, *J* = 12.3, 6.7 Hz, 3H), 7.14 – 7.10 (m, 2H), 6.62 (s, 1H), 6.43 – 6.30 (m, 2H), 4.83 (s, 2H), 4.65 (d, *J* = 5.1 Hz, 2H), 1.46 (s, 9H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 153.5, 141.1, 137.3, 135.7, 129.0, 128.3, 127.3, 125.4, 121.6, 116.7, 82.0, 67.4, 53.5, 48.8, 27.9. FT-IR (neat, cm^{-1}) : 2929, 2134, 1734, 1664,

1543, 1503, 1473, 1454, 1368, 1273, 1253, 1158, 1109, 965, 857, 793, 709, 651. HR-MS (*m/z*): calcd. for $[M+H]^+$ $C_{18}H_{22}N_5O_3$ 356.1123, found 356.1115.

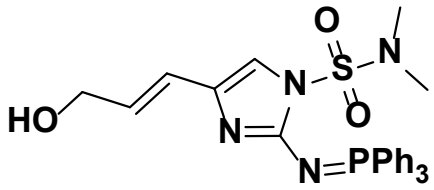
Synthesis of (E)-4-(3-((tert-butyldimethylsilyl) oxy) prop-1-en-1-yl)-N, N-dimethyl-2-((triphenyl-l5-phosphaneylidene)amino)-1H-imidazole-1-sulfonamide (131):



To a solution of compound **128a** (0.05 g, 0.1 mmol,) in tetrahydrofuran (1 mL) was added triphenylphosphine (0.084 g, 0.3 mmol, 2.5 equiv) at 23 °C. Then water (0.25 mL) was added to the solution. Heated up to 60 °C for one hour. Cooled to room temperature, the volatiles were removed by rotary evaporation to afford crude compound, extracted with ethyl acetate (3x 10 mL), washed with water (10 mL), followed by brine solution (10 mL) and dried with Na_2SO_4. The combined organic solutions were concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, EtOAc/hexane = 70:30) to furnish **131** (0.065 g, 85 %) as a blue sticky liquid. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.84 (dd, *J* = 12.4, 7.7 Hz, 6H), 7.61 – 7.49 (m, 3H), 7.44 (ddt, *J* = 10.1, 7.1, 2.4 Hz, 6H), 6.77 (d, *J* = 2.5 Hz, 1H), 6.25 – 6.02 (m, 2H), 4.21 (d, *J* = 4.1 Hz, 2H), 2.89

(s, 6H), 0.89 (s, 11H), 0.04 (s, 6H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 151.7, 135.1, 133.4, 133.3, 132.1, 129.4, 128.5, 128.4, 127.4, 121.7, 113.2, 64.0, 39.0, 26.1, 18.5, -4.9. FT-IR (neat, cm^{-1}): 3058, 2927, 2854, 1556, 1530, 1483, 1470, 1436, 1342, 1294, 1250, 1162, 1111, 1076, 1009, 996, 963, 834, 776, 718, 691, 593, 522, 417, 406. HR-MS (*m/z*): calcd. for [M+H] $^{+}$ $C_{32}H_{42}N_4O_3PSSi$ 621.1240, found 621.1239.

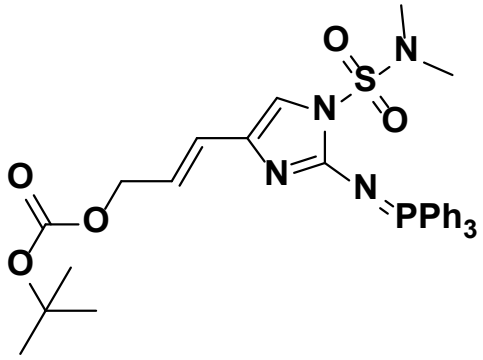
Synthesis of (E)-4-(3-hydroxyprop-1-en-1-yl)-N, N-dimethyl-2-((triphenyl-l5-phosphaneylidene) amino)-1H-imidazole-1-sulfonamide (132):



To a solution of the compound **131** (0.05 g, 0.08 mmol) obtained above in THF (1.5 mL) was added TBAF (1.0 M, 0.13 mL, 0.1 mmol) at 0 °C. The reaction was stirred at room temperature for 2 h and monitored by TLC analysis. The combined organic solutions were concentrated under reduced pressure. and the residue was diluted with ethyl acetate (2x10 mL), washed successively with water (5 mL) and brine (5mL), dried over Na_2SO_4, filtered, concentrated, and purified by flash column chromatography over silica gel, EtOAc/hexane = 70:30) to give **132** (0.035 g, 80%) as a blue sticky liquid. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.83 (dd, *J* = 12.1, 7.7 Hz, 6H), 7.54 (t, *J* = 7.0 Hz, 3H), 7.49 – 7.41 (m, 6H), 6.82 – 6.77 (m,

1H), 6.14 (s, 2H), 4.15 (s, 2H), 2.89 (s, 6H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 133.4, 133.3, 132.2, 129.3, 128.6, 128.5, 126.7, 123.5, 113.7, 63.9, 53.5, 39.0, 29.8. FT-IR (neat, cm^{-1}): 2922, 1527, 1483, 1436, 1342, 1292, 1157, 1111, 1009, 963, 718, 691, 591, 520, 455. HR-MS (*m/z*): calcd. for $[M+H]^+$ $C_{26}H_{28}N_4O_3PS$ 507.1532, found 507.1529.

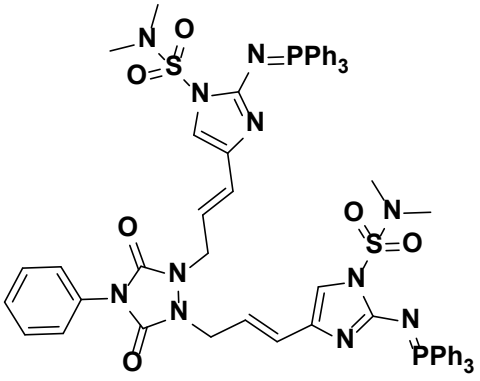
Synthesis of (E)-tert-butyl (3-(1-(N, N-dimethylsulfamoyl)-2-((triphenyl-l5-phosphaneylidene) amino)-1H-imidazol-4-yl) allyl) carbonate (133):



To a solution of compound **126a** (0.7 g, 1.87 mmol,) in tetrahydrofuran (22 mL) was added triphenylphosphine (1.2 g, 4.7 mmol) at 23 °C. Then water (5.4 mL) was added to the solution. Heated up to 60 °C for one hour. Cooled to room temperature, the volatiles were removed by rotary evaporation to afford crude compound, extracted with ethyl acetate (3x 25 mL), washed with water (15 mL), followed by brine solution (15 mL) and dried over anhydrous Na_2SO_4. The extract was concentrated under reduced pressure. The residue was purified by flash

chromatography (silica gel, EtOAc/hexane = 70:30) to furnish **133** (1.1 g, 85%) as a yellow solid: m.p. = 158-160 °C. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.83 (ddt, *J* = 12.4, 7.0, 1.4 Hz, 6H), 7.58 – 7.50 (m, 3H), 7.45 (tdd, *J* = 8.3, 3.0, 1.4 Hz, 7H), 6.81 (d, *J* = 2.5 Hz, 1H), 6.21 (dt, *J* = 15.2, 1.3 Hz, 1H), 6.04 (dt, *J* = 15.2, 6.7 Hz, 1H), 4.58 (s, 2H), 2.89 (s, 6H), 1.47 (s, 9H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 153.5, 151.8, 134.5, 133.4, 133.3, 132.2, 132.2, 129.3, 128.6, 128.5, 128.5, 126.6, 120.7, 114.4, 82.0, 67.9, 53.5, 39.0, 29.8, 27.9, 22.7, 14.2. FT-IR (neat, cm^{-1}): 2924, 2162, 2048, 1737, 1559, 1535, 1437, 1370, 1347, 1271, 1173, 1111, 1078, 997, 959, 854, 814, 751, 692, 644, 595, 518, 454. HR-MS (*m/z*): calcd. for [M+H] $^{+}$ $C_{31}H_{36}N_4O_5PS$ 607.2152, found 607.2138

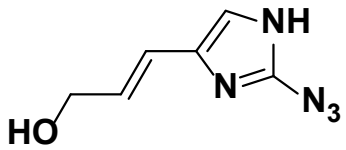
Synthesis of 4-((E)-3-(2-((E)-3-(1-(N, N-dimethylsulfamoyl)-2-((triphenyl-l5-phosphaneylidene) amino)-1H-imidazol-4-yl) allyl)-3,5-dioxo-4-phenyl-1,2,4-triazolidin-1-yl) prop-1-en-1-yl)-N, N-dimethyl-2-((triphenyl-l5-phosphaneylidene) amino)-1H-imidazole-1-sulfonamide (134):



Compound **133** (0.7 g, 1.15 mmol) was taken in DCM (10 mL), then N-phenyl urazole (0.11 g, 0.6 mmol) PPh_3 (0.016 g, 0.06 mmol), Pd_2dba_3 (0.017g, 0.02 mmol) were added and the mixture flushed with nitrogen gas three times. The reaction mixture was stirred at room temperature under nitrogen for 24 hours. The reaction progress was monitored by TLC analysis. On completion ethyl acetate (30 mL) was added to the reaction mixture and the solution was washed with water and brine (3 x 10 mL) and dried with Na_2SO_4. The extract was concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, EtOAc/hexane = 60:40) to furnish **134** (0.65 g, 50%) as a yellow crystalline solid: m.p. = 138-140 °C. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.80 (ddt, *J* = 12.4, 6.9, 1.4 Hz, 12H), 7.52 – 7.45 (m, 11H), 7.43 – 7.38 (m, 12H), 6.77 (d, *J* = 2.5 Hz, 2H), 6.17 (d, *J* = 15.2 Hz, 2H), 5.87 (dt, *J* = 14.7, 6.9 Hz, 2H), 4.26 – 4.18 (m, 4H), 2.91 (s, 12H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 153.3, 151.9, 134.1, 133.4, 133.3, 132.2, 129.2, 129.1, 128.6, 128.5, 128.0, 127.2, 125.4, 119.3, 114.2, 53.5, 47.5, 39.0. FT-IR (neat, cm^{-1}) : 1772,

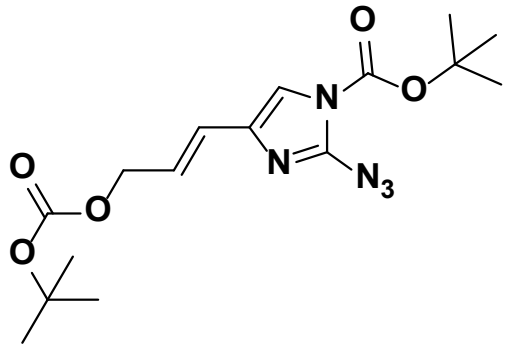
1710, 1523, 1356, 1336, 1158, 1065, 971, 773, 522, 468, 456, 444, 435, 425, 415, 404. HR-MS (*m/z*): calcd. for $[M+H]^+$ $C_{60}H_{58}N_{11}O_6P_2S_2$ 1154.3516, found 1154.3520.

Synthesis of (E)-3-(2-azido-1H-imidazol-4-yl) prop-2-en-1-ol (136):



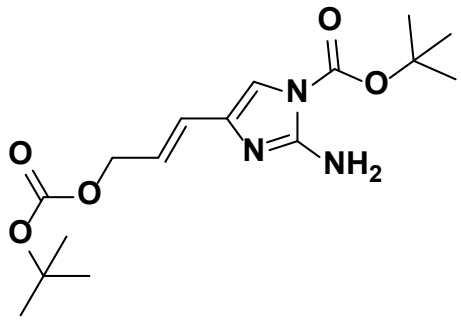
To a solution of the compound **128** (0.3 g, 0.77 mmol) obtained above in THF (30 mL) was added HCl (3 mL) at 0 °C. After stirring for 16 hours. To a solution of HCl salt in ethyl acetate (20 mL) was added water (20 mL). Solid sodium bicarbonate was added until the solution reached a pH of 7. The resulting solution was extracted with ethyl acetate (3 x 30mL). The combined organic extracts were dried with Na_2SO_4 and then evaporated under reduced pressure to afford the crude compound. The residue was purified by flash chromatography (silica gel, EtOAc) to furnish **136** (0.07 g, 55%) as a brown sticky liquid. ^{1}H NMR (500 MHz, Methanol-d_4) δ 6.79 (s, 1H), 6.38 (d, J = 15.9 Hz, 1H), 6.27 – 5.91 (m, 1H), 4.15 (s, 2H). FT-IR (neat, cm^{-1}): 3121, 1695, 1640, 1605, 1516, 1435, 1343, 1319, 1294, 1218, 1197, 1104, 1023, 973, 927, 911, 856, 753, 721, 680, 640, 569, 528, 495, 475, 451. HR-MS (*m/z*): calcd. for $[M+H]^+$ $C_6H_8N_5O$ 165.1318, found 165.1300.

Synthesis of tert-butyl (E)-2-azido-4-(3-((tert-butoxycarbonyl) oxy) prop-1-en-1-yl)-1H-imidazole-1-carboxylate (137):



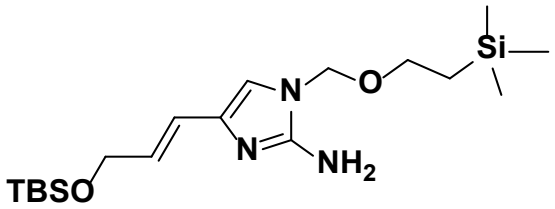
Compound **136** (0.18 g, 1.0 mmol) was dissolved in DCM (5 mL), triethyl amine (0.12 mL, 1.3 mmol) and $(BOC)_2O$ (0.3 mL, 1.3 mmol) and DMAP (0.008 g, 0.06 mmol) were slowly added with vigorous stirring solution. The reaction mixture was stirred at room temperature for 16 h. Ethyl acetate (20 mL) was added to the reaction mixture and the solution was washed with water and brine (3 x 10 mL) and dried with Na_2SO_4. The extract was concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, EtOAc/hexane = 80:20) to furnish **137** (0.2 g, 50 %) as a blue crystalline solid: m.p. = 108-110°C. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.03 (s, 1H), 6.48 – 6.36 (m, 2H), 4.68 (d, *J* = 5.7 Hz, 2H), 1.58 (s, 9H), 1.48 (s, 9H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 153.4, 146.1, 142.9, 136.6, 124.6, 123.7, 114.4, 86.1, 82.3, 66.9, 27.9. FT-IR (neat, cm^{-1}): 2980, 2143, 1737, 1520, 1457, 1394, 1368, 1274, 1250, 1147, 1100, 967, 844, 791, 767, 529, 493, 479, 464, 432, 418. HR-MS (*m/z*): calcd. for $[M+H]^+$ $C_{16}H_{24}N_5O_5$ 366.1220, found 366.1214.

Synthesis of tert-butyl (E)-2-amino-4-(3-((tert-butoxycarbonyl) oxy) prop-1-en-1-yl)-1H-imidazole-1-carboxylate (138a):



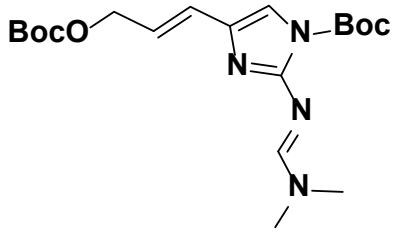
Compound **137** (1.8 g, 4.93 mmol) was dissolved in methanol (15 mL), sodium borohydride (0.7 g, 19.7 mmol) was slowly added with vigorous stirring solution. The reaction mixture was stirred at room temperature for 18 h. DCM (20 mL) was added to the reaction mixture and the solution was washed with water and brine (3 x 10 mL) and dried with Na_2SO_4. The extract was concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, EtOAc/hexane = 80:20) to furnish **138a** (0.9 g, 60%) as a yellow crystalline solid: m.p. = 102-104 °C. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 6.73 (s, 1H), 6.37 – 6.25 (m, 2H), 5.86 (s, 2H), 4.66 (d, *J* = 5.4 Hz, 2H), 1.58 (s, 9H), 1.47 (s, 9H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 153.4, 150.4, 149.2, 135.1, 124.5, 123.3, 109.7, 85.5, 82.2, 67.2, 28.0. FT-IR (neat, cm^{-1}): 3717, 2925, 2216, 2158, 2143, 2023, 1969, 1734, 1627, 1456, 1368, 1276, 1251, 1148, 846, 772, 564, 458, 427. HR-MS (*m/z*): calcd. for [M+H] $^+$ $C_{16}H_{26}N_3O_5$ 340.3815, found 340.3810

Synthesis of (E)-4-(3-((tert-butyldimethylsilyl) oxy) prop-1-en-1-yl)-1-((2-(trimethylsilyl) ethoxy) methyl)-1H-imidazol-2-amine (138b):



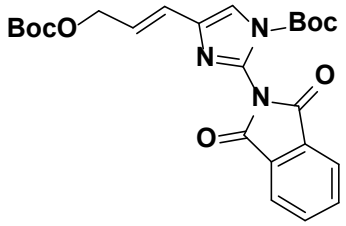
Compound **128b** (0.3 g, 0.73 mmol) was taken in MeOH (15 mL), $NaBH_4$ (0.10 g, 2.93 mmol) was added portion-wise to the reaction mixture. The reaction mixture was stirred at room temperature for 24 hours. The reaction progress was monitored by TLC analysis, then ethyl acetate (20 mL) was added to the reaction mixture and the solution was washed with water (15 mL) and brine (3 x 10 mL) and dried with Na_2SO_4. The extract was concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, EtOAc/hexane = 60:40) to furnish **138b** (0.19 g, 68 %) as a brown liquid. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 6.45 (s, 1H), 6.35 – 6.19 (m, 2H), 5.03 (s, 2H), 4.62 (d, *J* = 16.3 Hz, 2H), 4.33 – 4.23 (m, 2H), 3.51 (d, *J* = 7.5 Hz, 2H), 1.24 (s, 2H), 0.90 (s, 9H), 0.07 (s, 7H), -0.02 (s, 9H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 148.8, 134.3, 126.9, 120.3, 113.1, 74.7, 66.2, 63.7, 29.8, 26.1, 18.5, 17.8, -1.3, -5.1. FT-IR (neat, cm^{-1}) : 2927, 2856, 1978, 1670, 1470, 1360, 1248, 1072, 937, 833, 775, 691. HR-MS (*m/z*): calcd. for $[M+H]^+$ $C_{18}H_{38}N_3O_2Si_2$ 384.6810, found 384.6800.

Synthesis of tert-butyl 4-((E)-3-((tert-butoxycarbonyl) oxy) prop-1-en-1-yl)-2-(((E)-(dimethylamino) methylene) amino)-1H-imidazole-1-carboxylate (139):



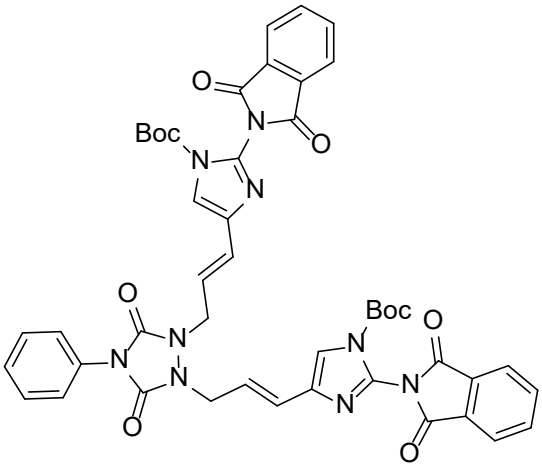
The amine **138a** (0.025 g, 0.07 mmol) was taken in DMF.DMA (5 mL). The reaction mixture was stirred at room temperature for 2 h, additional dichloromethane (10 mL) was added to the reaction mixture and the solution was washed with water (5 mL) and brine (5 mL) and dried over anhydrous Na_2SO_4. The extract was concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, EtOAc/hexane = 30:70) to furnish **139** (0.015 g, 53%) as a brown sticky liquid. ^{1}H NMR (500 MHz, Methanol-d_4) δ 8.14 (s, 1H), 7.14 (s, 1H), 6.39 (d, J = 16.9 Hz, 1H), 6.27 (dt, J = 15.7, 6.3 Hz, 1H), 4.62 (dd, J = 6.3, 1.3 Hz, 2H), 3.12 (s, 3H), 3.06 (s, 3H), 1.58 (s, 9H), 1.45 (s, 9H). ^{13}C NMR (126 MHz, Methanol-d_4) δ 157.0, 123.7, 122.6, 113.0, 85.4, 80.6, 66.9, 41.3, 33.6, 26.8, 26.7. FT-IR (neat, cm^{-1}): 2978, 1740, 1618, 1422, 1367, 1274, 1250, 1145, 962, 848, 767. HR-MS (*m/z*): calcd. for $[M+H]^+$ $C_{19}H_{31}N_4O_5$ 395.1422, found 395.1420.

Synthesis of tert-butyl (E)-4-(3-((tert-butoxycarbonyl) oxy) prop-1-en-1-yl)-2-(1,3-dioxoisoindolin-2-yl)-1H-imidazole-1-carboxylate (142):



The amine **138a** (0.1 g, 0.29 mmol) was dissolved in dichloromethane (10 mL), K_2CO_3 (0.12 gm, 0.88 mmol) and modified Nefkens' reagent (N-BOC pthalimide) (0.14 g, 0.58 mmol) were simultaneously added to the solution. The reaction mixture was stirred at room temperature for 24 h, DCM (20 mL) was added to the reaction mixture and the solution was washed with 10% $NaHCO_3$ (5 mL), water and brine (5 mL) and dried with Na_2SO_4. The extract was concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, EtOAc/hexane = 50:50) to furnish **142** (0.05 g, 36 %) as a colorless sticky liquid. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.97 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.82 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.42 (s, 1H), 6.51 (t, *J* = 1.6 Hz, 2H), 4.70 (d, *J* = 4.5 Hz, 2H), 1.49 (s, 12H), 1.39 (s, 10H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 166.0, 145.9, 137.9, 135.0, 132.0, 126.9, 125.2, 124.3, 123.6, 117.1, 86.7, 82.3, 66.9, 52.5, 27.9, 27.8, 27.6. FT-IR (neat, cm^{-1}): 2923, 2853, 1733, 1540, 1458, 1368, 1251, 1147, 1097, 965, 883, 840, 766, 716, 602, 528. HR-MS (*m/z*): calcd. for $[M+H]^+$ $C_{24}H_{28}N_3O_7$ 470.1921, found 470.1919.

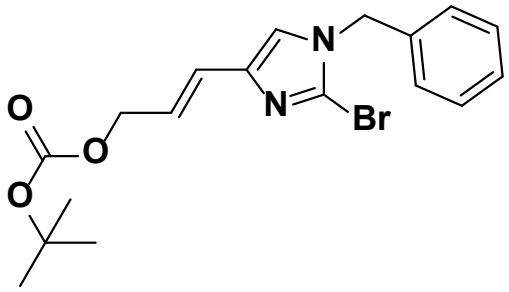
Synthesis of di-tert-butyl 4,4'-((1E,1'E) -(3,5-dioxo-4-phenyl-1,2,4-triazolidine-1,2-diyl) bis(prop-1-ene-3,1-diyl)) bis(2-(1,3-dioxoisoindolin-2-yl)-1H-imidazole-1-carboxylate) (143):



Compound **142** (0.05 g, 0.10 mmol) was charged in a dried glass round bottomed flask equipped with a magnetic stir bar in DCM (10 mL) and then N-phenylurazole (0.01 g, 0.056 mmol), PPh_3 (0.0014 g, 0.005mmol), Pd_2dba_3 (0.0015g, 0.001 mmol), were added and the mixture was flushed with nitrogen three times. The reaction mixture was stirred at room temperature under nitrogen gas for 24 hours. The reaction progress was monitored by TLC. Ethyl acetate (30 mL) was added to the reaction mixture and the solution was washed with water and brine (3 x 10 mL) and dried with Na_2SO_4. The extract was concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, EtOAc/hexane = 60:40) to furnish **143** (0.06 g, 63%) as a yellow sticky liquid. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.97 (dd, *J* = 5.5, 3.0 Hz, 5H), 7.81 (dd, *J* = 5.5, 3.1 Hz, 5H), 7.54 – 7.51 (m, 2H), 7.42 (d, *J* = 1.7 Hz, 1H), 7.40 – 7.29 (m, 2H), 6.54 (d, *J* = 15.7 Hz, 2H), 6.45 (dt, *J* = 15.6, 6.4 Hz, 2H), 4.42 (d, *J* = 6.4 Hz, 4H), 1.37 (s, 18H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 166.0, 153.3, 137.4, 135.0, 132.7, 131.9, 129.8, 129.1, 125.6, 125.3,

124.4, 123.8, 123.3, 119.0, 117.6, 86.7, 47.4, 29.8, 27.6. FT-IR (neat, cm^{-1}): 2952, 2851, 1795, 1759, 1731, 1537, 1309, 1253, 1145, 1096, 965, 814, 765, 646, 528, 505, 457. HR-MS (*m/z*): calcd. for $[M+H]^+$ $C_{46}H_{42}N_9O_{10}$ 880.3049, found 880.3041.

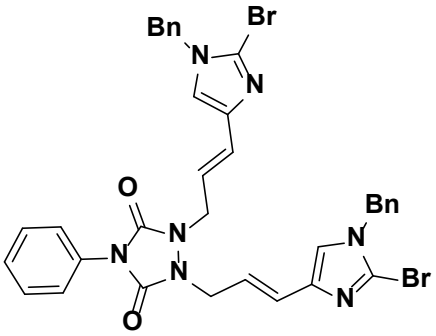
Synthesis of (E)-3-(1-benzyl-2-bromo-1H-imidazol-4-yl) allyl tert-butyl carbonate (145):



Compound **113** (1.0 g, 3.18 mmol) was dissolved in tetrahydrofuran (20 mL), N-bromosuccinimide (0.67 g, 3.80 mmol) was slowly added with vigorous stirring and ice-cooled solution. The reaction mixture was stirred at same temperature for 2 h, ethyl acetate (30 mL) was added to the reaction mixture and the solution was washed with water and brine (3 x 10 mL) and dried with Na_2SO_4. The extract was concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, EtOAc/hexane = 20:80) to furnish **145** (0.4 g, 41 %) as a colorless crystalline solid: m.p. = 106-108 °C. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.37 – 7.32 (m, 3H), 7.16 – 7.13 (m, 2H), 6.87 (s, 1H), 6.48 – 6.37 (m, 2H), 5.07 (s, 2H), 4.64 (d, *J* = 5.1 Hz, 2H), 1.46 (s, 9H).^{13}C NMR (126 MHz, Chloroform-*d*) δ

153.4, 139.8, 135.0, 129.2, 128.6, 127.4, 124.0, 123.2, 120.6, 120.0, 82.2, 67.1, 51.6, 27.9, 27.8. FT-IR (neat cm^{-1}): 2981, 1735, 1545, 1439, 1395, 1366, 1278, 1250, 1203, 1149, 1117, 1073, 1031, 965, 945, 858, 839, 791, 764, 744, 726, 691, 536, 513, 462, 451. HR-MS (*m/z*): calcd. for $[M+H]^+$ $C_{18}H_{22}BrN_2O_3$ 393.1420, found 393.1414.

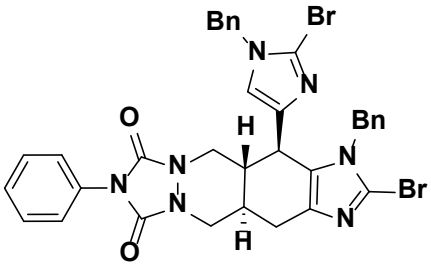
Synthesis of 1,2-bis((E)-3-(1-Benzyl-2-bromo-1H-imidazol-4-yl) allyl)-4-phenyl-1,2,4-triazolidine-3,5-dione (146):



Compound **145** (0.22 g, 0.56 mmol) was dissolved in DCM (10 mL). Then N-phenyl urazole (0.05 g, 0.28 mmol), PPh_3 (0.007 g, 0.03mmol), Pd_2dba_3 (0.007g, 0.008 mmol), were added to the solution and the mixture was purged with nitrogen gas three times. The reaction mixture was stirred at room temperature under nitrogen gas for 24 hours. The reaction progress was monitored by TLC. Ethyl acetate (30 mL) was added to the reaction mixture and the solution was washed with water and brine (3 x 10 mL) and dried with Na_2SO_4. The extract was concentrated

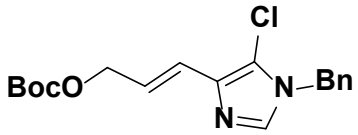
under reduced pressure. The residue was purified by flash chromatography (silica gel, EtOAc/hexane = 60:40) to furnish **146** (0.14 g, 69%) as a yellow crystalline solid: m.p. = 88-90 °C. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.65 (d, *J* = 8.0 Hz, 1H), 7.50 (d, *J* = 7.8 Hz, 2H), 7.46 – 7.40 (m, 3H), 7.37 – 7.31 (m, 7H), 7.15 (d, *J* = 7.4 Hz, 3H), 6.87 (s, 2H), 6.42 (d, *J* = 15.6 Hz, 2H), 6.31 (dd, *J* = 14.9, 7.3 Hz, 2H), 5.04 (s, 4H), 4.35 (d, *J* = 6.5 Hz, 4H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 153.2, 139.8, 135.1, 132.1, 131.6, 129.2, 129.0, 128.6, 128.6, 128.0, 127.4, 125.9, 125.5, 121.1, 120.9, 120.4, 51.5, 47.3. FT-IR (neat, cm^{-1}): 1768, 1704, 1498, 1453, 1416, 1354, 1273, 1146, 1093, 1027, 963, 764, 706, 691, 647, 539, 506, 457. HR-MS (*m/z*): calcd. for $[M+H]^{+}$ $C_{34}H_{30}N_7O_2Br_2$ 726.0822, found 726.0916.

Synthesis of (4aR,11aS,12S)-1-Benzyl-12-(1-benzyl-2-bromo-1H-imidazol-4-yl)-2-bromo-8-phenyl-4,4a,5,11,11a,12-hexahydro-1H,7H-imidazo[4,5-g] [1,2,4] triazolo[1,2-b] phthalazine-7,9(8H)-dione (147):



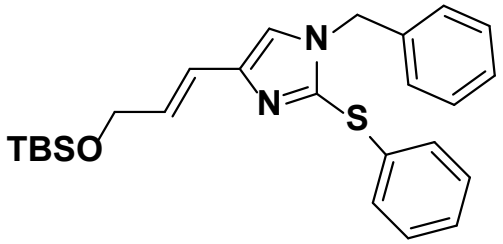
The compound **146** (0.15 g, 0.20 mmol) was dissolved in toluene (10 mL) in sealed tube and heated to 130 to 140 °C for 24 hours. After 24 h the reaction mixture was cooled to room temperature and then evaporated to dryness under reduced pressure. The residue was purified by flash chromatography (silica gel, EtOAc) to furnish **147** (0.13 g, 86%) as a colorless crystalline solid: m.p. = 160-162 °C. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.47 – 7.44 (m, 4H), 7.44 – 7.40 (m, 3H), 7.38 – 7.33 (m, 2H), 7.26 – 7.19 (m, 5H), 7.16 (dq, *J* = 6.6, 2.8, 2.4 Hz, 2H), 6.61 – 6.52 (m, 3H), 5.04 (dt, *J* = 15.1, 3.7 Hz, 2H), 4.75 (dd, *J* = 15.1, 3.5 Hz, 1H), 4.38 (dd, *J* = 16.7, 11.5 Hz, 1H), 4.25 (dd, *J* = 12.1, 4.3 Hz, 1H), 4.00 (dt, *J* = 11.9, 4.9 Hz, 1H), 3.37 (d, *J* = 9.8 Hz, 1H), 2.99 (t, *J* = 11.6 Hz, 2H), 2.81 (td, *J* = 11.6, 3.6 Hz, 1H), 2.22 (dq, *J* = 15.9, 6.1, 4.8 Hz, 2H), 2.14 – 2.04 (m, 2H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 151.9, 139.4, 134.9, 131.2, 129.4, 129.4, 129.3, 129.0, 128.8, 128.3, 127.9, 125.6, 120.9, 120.8, 51.7, 49.3, 47.9, 46.5, 42.6, 37.0, 35.8. FT-IR (neat, cm^{-1}): 1708, 1496, 1452, 1419, 1363, 1290, 1204, 1133, 1028, 788, 764, 712, 690, 645, 559, 506, 420. HR-MS (*m/z*): calcd. for $[M+H]^+$ $C_{34}H_{30}Br_2N_7O_2$ 726.0922, found 726.0916.

Synthesis of (E)-3-(1-Benzyl-5-chloro-1H-imidazol-4-yl) allyl tert-butyl carbonate 157:



Compound **113A** (0.25 g, 0.80 mmol) was dissolved in tetrahydrofuran (10 mL) and cooled in an ice-bath, N-chlorosuccinimide (0.11 g, 0.88 mmol) were slowly added with vigorous stirring. The reaction mixture was stirred at same temperature for 2 h, ethyl acetate (20 mL) was added to the reaction mixture and the solution was washed with water and brine (3 x 10 mL) and dried with Na_2SO_4. The extract was concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, EtOAc/hexane = 20:80) to furnish **157** (0.21 g, 75%) as a yellow sticky liquid. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.45 (s, 1H), 7.34 -7.29 (m, 3H), 7.11 (d, *J* = 8.3 Hz, 2H), 6.56 – 6.44 (m, 2H), 5.05 (s, 2H), 4.68 (d, *J* = 5.2 Hz, 2H), 1.46 (s, 9H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 153.3, 136.5, 134.5, 133.0, 129.5, 129.2, 128.7, 128.6, 128.0, 127.5, 124.7, 121.1, 116.4, 82.3, 67.1, 49.3, 27.8. FT-IR (neat, cm^{-1}): 1737, 1533, 1496, 1455, 1368, 1274, 1252, 1155, 1121, 917, 854, 727, 659, 551, 526, 461. HR-MS (*m/z*): calcd. for [M+H] $^+$ $C_{18}H_{22}ClN_2O_3$ 349.8320, found 349.8318.

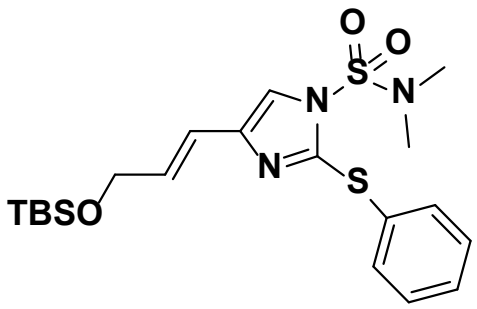
Synthesis of (E)-1-benzyl-4-(3-((tert-butyl dimethylsilyl) oxy) prop-1-en-1-yl)-2-(phenylthio)-1H-imidazole (159):



Compound **127B** (0.25 g, 0.75 mmol) was dissolved in anhydrous THF (15 mL) and cooled to -78 °C. Then n-BuLi (2.5 M, 0.3 mL, 0.83 mmol) was added dropwise to the cooled solution. The solution was stirred for 40 min. Then degassed solution of diphenyl disulfide (0.4 g, 1.65 mmol) in THF (10 mL) was added to the solution and removed the cold bath. The reaction mixture was stirred for 2 hours and then the reaction mixture was quenched with saturated ammonium chloride (5 mL). The resulting mixture was extracted with ethyl acetate (3x 15 mL), washed with water (10 mL), followed by brine solution (10 mL) and dried with Na_2SO_4. The extract was concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, EtOAc/hexane = 90:10) to furnish **159** (0.2 g, 61%) as a yellow sticky liquid. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.23 – 7.20 (m, 4H), 7.18 (d, *J* = 4.9 Hz, 2H), 7.14 – 7.09 (m, 2H), 6.98 (dd, *J* = 6.3, 1.7 Hz, 2H), 6.92 (s, 1H), 6.48 (t, *J* = 2.4 Hz, 2H), 5.08 (s, 2H), 4.31 (d, *J* = 1.5 Hz, 2H), 0.92 (s, 9H), 0.08 (s, 6H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 141.5, 138.0, 136.0, 135.0, 129.31, 129.2, 129.1, 128.9, 128.9, 128.7, 128.2, 128.0, 127.9, 127.6, 127.5, 126.7, 120.7, 119.9, 63.6, 50.8, 32.3, 26.1, 18.5, -5.1, -5.2, -5.3. FT-IR (neat, cm^{-1}): 2927,

2854, 1725, 1581, 1496, 1440, 1421, 1388, 1359, 1300, 1250, 1104, 1024, 1005, 964, 834, 775, 732, 689, 463. HR-MS (*m/z*): calcd. for $[M+H]^+$ $C_{25}H_{33}N_2OSSi$ 437.2072, found 437.2069

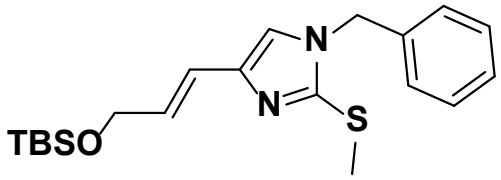
Synthesis of (E)-4-(3-((tert-butyl dimethylsilyl) oxy) prop-1-en-1-yl)-N, N-dimethyl-2-(phenylthio)-1H-imidazole-1-sulfonamide (160):



Compound **127** (0.25 g, 0.72 mmol) was dissolved in anhydrous THF (15 mL) and cooled to -78 °C. Then n-BuLi (2.5 M, 0.3 mL, 0.8 mmol) was added dropwise to the cooled solution. The solution was stirred for 40 min and a degassed solution of diphenyl disulfide (0.3 g, 1.58 mmol) in THF (10 mL) was added to the solution and the cold bath was removed. The reaction mixture was stirred for 2 hours and then the reaction mixture was quenched with saturated ammonium chloride (5 mL). Extracted with ethyl acetate (3x 15 mL), washed with water (10 mL), followed by brine solution (10 mL) and dried with Na_2SO_4. The extract was concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, EtOAc/hexane = 90:10) to furnish **160** (0.15 g, 45%) as a white sticky liquid**.** ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.45 – 7.42 (m, 2H), 7.34 –

7.28 (m, 3H), 6.49 – 6.28 (m, 2H), 4.28 (dd, *J* = 4.0, 1.4 Hz, 2H), 2.93 (s, 6H), 0.91 (s, 9H), 0.06 (s, 6H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 140.8, 140.1, 131.9, 131.2, 131.1, 129.2, 128.9, 118.9, 118.9, 63.3, 38.6, 26.2, 26.0, 26.0, 25.8, 18.5, -5.2. FT-IR (neat, cm^{-1}): 2927, 2854, 1643, 1553, 1471, 1439, 1389, 130, 1252, 1102, 1024, 966, 836, 778, 726, 689, 603, 518. HR-MS (*m/z*): calcd. for $[M+H]^+$ $C_{20}H_{32}N_3O_3S_2Si$ 454.1635, found 454.1630

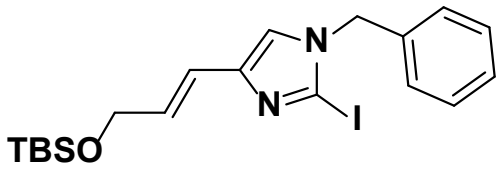
Synthesis of (E)-1-Benzyl-4-(3-((tert-butyl dimethyl silyl) oxy) prop-1-en-1-yl)-2-(methyl thio)-1H-imidazole (161):



Compound **127B** (0.25 g, 0.76 mmol) was dissolved in anhydrous THF (15 mL) and cooled to -78 °C. Then n-BuLi (2.5 M, 0.3 mL, 0.84 mmol) was added dropwise to the cooled solution. The solution was stirred for 40 min and then a degassed solution of dimethyl disulfide (0.15 g, 1.6 mmol) in THF (10 mL) was added to the solution and the cold bath was removed. The reaction mixture was stirred for 2 hours and then the reaction mixture was quenched with saturated ammonium chloride (5 mL). Extracted with ethyl acetate (3x 15 mL), washed with water (10 mL), followed by brine solution (10 mL) and dried with anhydrous Na_2SO_4.

The extract was concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, EtOAc/hexane = 90:10) to furnish **161** (0.2 g, 60%) as a yellow sticky liquid. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.34 – 7.24 (m, 3H), 7.15 – 7.10 (m, 2H), 6.81 (s, 1H), 6.44 – 6.37 (m, 2H), 5.05 (s, 2H), 4.30 (d, *J* = 2.9 Hz, 2H), 2.54 (s, 3H), 0.91 (s, 9H), 0.07 (s, 6H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 143.4, 140.6, 136.3, 129.0, 128.1, 127.7, 127.3, 120.80, 118.6, 63.7, 50.1, 29.8, 26.1, 18.55, 16.9, -5.1. FT-IR (neat, cm^{-1}): 2927, 2854, 1723, 1563, 1497, 1454, 1348, 1251, 1103, 1005, 965, 835, 777, 697. HR-MS (*m/z*): calcd. for $[M+H]^{+}$ $C_{20}H_{31}N_2OSSi$ 375.1831, found 375.1829.

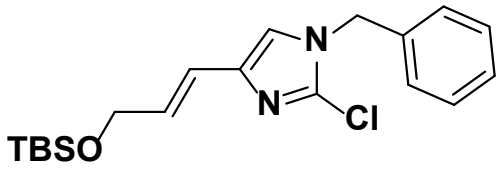
Synthesis of (E)-1-Benzyl-4-(3-((tert-butyl dimethyl silyl) oxy) prop-1-en-1-yl)-2-iodo-1H-imidazole (162):



Compound **127B** (0.1 g, 0.30 mmol) was dissolved in anhydrous THF (10 mL) and cooled to -78 °C. Then n-BuLi (2.5 M, 0.13 mL, 0.33 mmol) was added dropwise to the cooled solution. The solution was stirred for 40 min and then a degassed solution of N-iodosuccenamide (0.15 g, 0.67 mmol) in THF (10 mL) was added to the solution. The cold bath was removed, and the reaction mixture

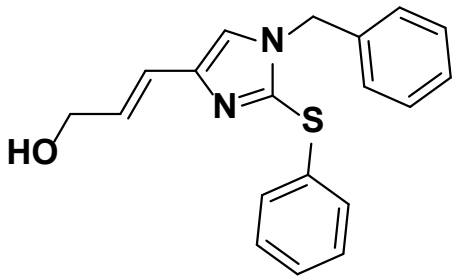
was stirred for 2 hours. The reaction mixture was quenched with ammonium chloride (saturated) (5 mL). Extracted with ethyl acetate (3x 15 mL), washed with water (10 mL), followed by brine solution (10 mL) and dried with Na_2SO_4. The extract was concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, EtOAc/hexane = 90:10) to furnish **162** as a yellow sticky liquid (0.165 g, 75%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.39 – 7.28 (m, 3H), 7.17 – 7.04 (m, 2H), 6.88 (s, 1H), 6.38 (d, *J* = 4.4 Hz, 2H), 5.03 (s, 2H), 4.29 (d, *J* = 3.2 Hz, 2H), 0.89 (s, 9H), 0.06 (s, 6H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 144.1, 135.6, 129.08, 128.7, 128.4, 127.3, 120.3, 119.9, 91.4, 63.4, 53.2, 29.8, 26.1, 18.5, -5.2, -5.2. FT-IR (neat, cm^{-1}): 2925, 2853, 2185, 2046, 2015, 1721, 1496, 1454, 1419, 1359, 1296, 1250, 1108, 1065, 1005, 961, 834, 774, 706, 662, 631, 488. HR-MS (*m/z*): calcd. for $[M+H]^+$ $C_{19}H_{28}IN_2OSi$ 455.0998, found 455.0992

Synthesis of (E)-1-Benzyl-4-(3-((tert-Butyldimethyl silyl) oxy) prop-1-en-1-yl)-2-chloro-1H-imidazole (163):



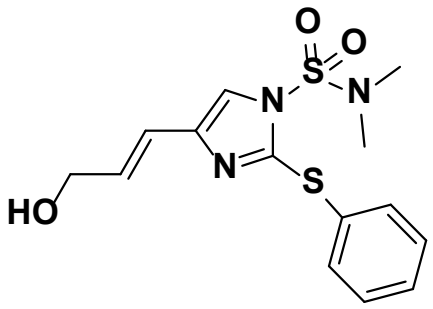
Compound **127B** (0.2 g, 0.60 mmol) was dissolved in anhydrous THF (15 mL) and cooled to -78 °C. Then n-BuLi (2.5 M, 0.26 mL, 0.67 mmol) was added dropwise to the cooled solution. The solution was stirred for 40 min then a degassed solution of hexachloroethane (0.3 g, 1.34 mmol) in THF (10 mL) was added to the solution and the cold bath was removed. The reaction mixture was stirred for 2 hours and then the reaction mixture was quenched with ammonium chloride (saturated) (5 mL). Extracted with ethyl acetate (3x 15 mL), washed with water (10 mL), followed by brine solution (10 mL) and dried with Na_2SO_4. The extract was concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, EtOAc/hexane = 90:10) to furnish **163** (0.165 g, 75%) as a yellow sticky liquid. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.38 – 7.23 (m, 4H), 7.24 – 7.03 (m, 2H), 6.75 (s, 1H), 6.48 – 6.24 (m, 2H), 5.03 (s, 2H), 4.28 (d, *J* = 3.1 Hz, 2H), 0.90 (s, 9H), 0.06 (s, 7H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 139.5, 135.4, 132.5, 129.1, 129.0, 128.6, 128.4, 128.3, 127.4, 127.3, 119.9, 117.9, 63.4, 50.3, 26.0, 18.5, -5.2. FT-IR (neat, cm^{-1}): 3272, 2927, 2855, 1715, 1541, 1496, 1469, 1441, 1406, 1358, 1251, 1074, 833, 773, 696, 668. HR-MS (*m/z*): calcd. for $[M+H]^+$ $C_{19}H_{28}N_2ClOSi$ 362.1632, found 362.1630.

Synthesis of (E)-3-(1-benzyl-2-(phenyl thio)-1H-imidazol-4-yl) prop-2-en-1-ol (164):



To a solution of the compound **159** (0.15 g, 0.35 mmol) obtained above in THF (15 mL) was added TBAF (1.0 M, 0.52 mL, 0.52 mmol) at 0 °C. The cold bath was removed, and the reaction was stirred at room temperature for 2 h. The solvent was then removed by rotary evaporation and the residue was diluted with ethyl acetate (2x30 mL), washed successively with water (5 mL) and brine (5mL), dried over Na_2SO_4, filtered, concentrated, and purified by flash column chromatography over silica gel, EtOAc/hexane = 70:30) to give **164** (0.07 g, 63 %) as a white sticky liquid. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.23 (d, *J* = 4.5 Hz, 3H), 7.18 (d, *J* = 8.3 Hz, 2H), 7.13 (d, *J* = 1.4 Hz, 3H), 6.98 (dd, *J* = 5.3, 2.2 Hz, 2H), 6.92 (s, 1H), 6.55 – 6.40 (m, 2H), 5.08 (s, 2H), 4.24 (d, *J* = 4.0 Hz, 2H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 141.1, 138.2, 135.9, 134.7, 129.3, 128.9, 128.9, 128.24, 128.2, 127.6, 126.8, 121.9, 120.2, 63.2, 50.8. FT-IR (neat, cm^{-1}): 3249, 2848, 1495, 1477, 1440, 1420, 1354, 1301, 1148, 1985, 1023, 1000, 966, 739, 713, 689, 515. HR-MS (*m/z*): calcd. for $[M+H]^+$ $C_{19}H_{19}N_2OS$ 323.1195, found 323.1190.

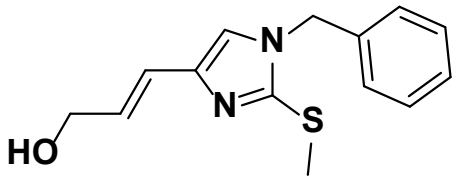
Synthesis of (E)-4-(3-hydroxyprop-1-en-1-yl)-N, N-dimethyl-2-(phenylthio)-1H-imidazole-1-sulfonamide (165):



To a solution of the compound **160** (0.15 g, 0.33 mmol) obtained above in THF (15 mL) was added TBAF (1.0 M, 0.5 mL, 0.5 mmol) at 0 °C. The cold bath was removed, and the reaction was stirred at room temperature for 2 h. The solvent was then removed by rotary evaporation and the residue was diluted with ethyl acetate (2x30 mL), washed successively with water (5 mL) and brine (5mL), dried with anhydrous Na_2SO_4, filtered, concentrated, and purified by flash column chromatography over silica gel, EtOAc/hexane = 70:30) to give **165** (0.06 g, 54 %) as a yellow sticky liquid. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.47 – 7.44 (m, 2H), 7.35 – 7.28 (m, 3H), 7.27 (s, 1H), 6.46 (dt, *J* = 15.7, 5.3 Hz, 1H), 6.36 (dt, *J* = 15.6, 1.5 Hz, 1H), 4.23 (dd, *J* = 5.3, 1.5 Hz, 2H), 2.94 (s, 6H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 141.4, 139.7, 131.6, 131.5, 130.5, 129.3, 128.3, 120.5, 119.1, 63.2, 38.6. FT-IR (neat, cm^{-1}): 3311, 1477, 1438, 1386, 1318, 1274,

1236, 1173, 1108, 1051, 969, 728, 703, 689, 623, 601, 519. HR-MS (*m/z*): calcd. for $[M+H]^+$ $C_{14}H_{17}N_3O_3S_2$ 340.1680, found 340.1674

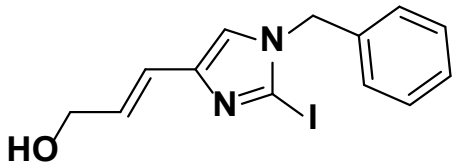
Synthesis (E)-3-(1-Benzyl-2-(methylthio)-1H-imidazol-4-yl) prop-2-en-1-ol (166):



To a solution of the compound **161** (0.15 g, 0.40 mmol) obtained above in THF (15 mL) was added TBAF (1.0 M, 0.6 mL, 0.60 mmol) at 0 °C. The cold bath was removed, and the reaction was stirred at room temperature for 2 h. The solvent was then removed by rotary evaporation and the residue was diluted with ethyl acetate (2x30 mL), washed successively with water (5 mL) and brine (5mL), with anhydrous Na_2SO_4, filtered, concentrated, and purified by flash column chromatography over silica gel, EtOAc/hexane = 70:30) to give **166** (0.05 g, 50 %) as yellow sticky liquid. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.36 – 7.26 (m, 3H), 7.16 – 7.06 (m, 2H), 6.83 (s, 1H), 6.50 – 6.36 (m, 2H), 5.05 (s, 2H), 4.25 (dd, *J* = 5.2, 0.9 Hz, 2H), 2.55 (s, 3H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 143.8, 140.1, 136.2, 129.0, 128.2, 127.5, 127.3, 122.5, 119.0, 63.6, 50.2, 16.8. FT-IR (neat, cm^{-1}): 3257, 2925, 1722, 1665, 1624, 1560, 1496, 1436, 1352, 1312, 1153, 1077, 1000, 964, 809,

711, 646, 454. HR-MS (*m/z*): calcd. for $[M+H]^+$ $C_{14}H_{17}N_2OS$ 261.1040, found 261.1035

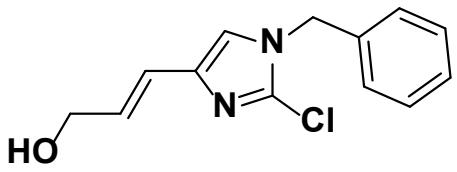
Synthesis of (E)-3-(1-Benzyl-2-iodo-1H-imidazol-4-yl) prop-2-en-1-ol (167):



To a solution of the compound **162** (0.15 g, 0.33 mmol) obtained above in THF (15 mL) was added TBAF (1.0 M, 0.5 mL, 0.49 mmol) at 0 °C. The cold bath was removed, and the reaction was stirred at room temperature for 2 h. The solvent was then removed by rotary evaporation and the residue was diluted with ethyl acetate (2x30 mL), washed successively with water (5 mL) and brine (5mL), dried over sodium sulfate, filtered, concentrated, and purified by flash column chromatography over silica gel, EtOAc/hexane = 70:30) to give **167** (0.07 g, 63%): m.p. = 118-120 °C. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.36 – 7.29 (m, 3H), 7.12 (dd, *J* = 8.0, 1.6 Hz, 2H), 6.89 (s, 1H), 6.50 – 6.34 (m, 2H), 5.02 (s, 2H), 4.24 (dd, *J* = 5.4, 1.4 Hz, 2H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 143.7, 135.5, 129.1, 129.1, 128.4, 128.4, 127.3, 121.5, 120.7, 91.7, 63.3, 53.3. FT-IR (neat, cm^{-1}): 3329, 3118, 2927, 2870, 1658, 1603, 1497, 1446, 1419, 1388, 1298, 1194, 1145, 1081, 1005, 968,

834, 776, 692, 644, 527, 460. HR-MS (*m/z*): calcd. for $[M+H]^+$ $C_{13}H_{14}IN_2O$ 341.0118, found 341.0114.

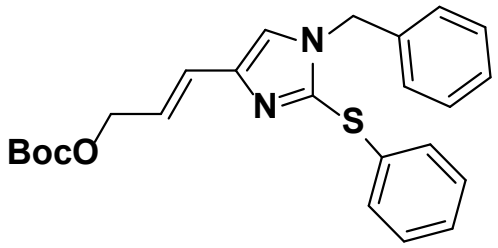
Synthesis of (E)-3-(1-Benzyl-2-chloro-1H-imidazol-4-yl) prop-2-en-1-ol (168):



To a solution of the compound **163** (0.23 g, 0.67 mmol) obtained above in THF (5 mL) was added TBAF (1.0 M, 1.0 mL, 1 mmol) at 0 °C. The cold bath was removed, and the reaction was stirred at room temperature for 2 h. The solvent was then removed by rotary evaporation and the residue was diluted with ethyl acetate (2x30 mL), washed successively with water (5 mL) and brine (5mL), dried over sodium sulfate, filtered, concentrated, and purified by flash column chromatography over silica gel, EtOAc/hexane = 70:30) to give **168** (0.11 g, 77%) as a yellow sticky liquid. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.34 – 7.25 (m, 3H), 7.13 – 7.09 (m, 2H), 6.74 (s, 1H), 6.44 – 6.30 (m, 2H), 4.98 (s, 2H), 4.20 (dd, *J* = 5.1, 1.4 Hz, 2H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 139.1, 135.3, 132.5, 129.1, 129.1, 128.7, 128.4, 127.4, 121.1, 118.3, 62.9, 50.3, 50.1. FT-IR (neat, cm^{-1}): 3345, 3132, 2873, 1674, 1633, 1543, 1496, 1468, 1441, 1361, 1308, 1147, 1110, 1084, 993, 947,

837, 693, 651, 498, 466, 452. HR-MS (*m/z*): calcd. for $[M+H]^+$ $C_{13}H_{14}N_2OCl$ 249.0789, found 249.0771.

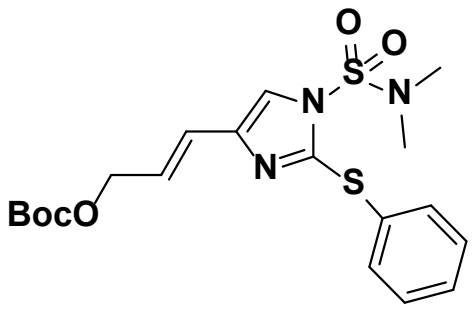
Synthesis of (E)-3-(1-Benzyl-2-(phenylthio)-1H-imidazol-4-yl) allyl tert-butyl carbonate (164a):



Compound **164** 0.07 g, 0.22 mmol) was dissolved in DCM (10 mL), triethylamine (0.036 mL, 0.26 mmol) and $(BOC)_2O$ (0.09 mL, 0.43 mmol) and DMAP (0.002 g, 0.021mmol) were added slowly with vigorous stirring solution. The reaction mixture was stirred at room temperature for 18 h. Ethyl acetate (10 mL) was added to the reaction mixture and the solution was washed with water and brine (3 x 5 mL) and dried with Na_2SO_4. The extract was concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, EtOAc/hexane = 20:80) to furnish **164a** (0.06 g, 65%) as a brown sticky liquid. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.27 – 7.24 (m, 3H), 7.21 (d, *J* = 7.2 Hz, 2H), 7.18 – 7.14 (m, 3H), 7.02 – 6.98 (m, 2H), 6.95 (s, 1H), 6.54 – 6.41 (m, 2H), 5.11 (s, 2H), 4.67 (d, *J* = 5.3 Hz, 2H), 1.48 (s, 9H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 153.5, 140.5, 138.6, 135.8, 134.6, 129.3, 128.9, 128.3, 128.2, 127.6, 126.8, 125.6, 122.4,

120.8, 82.1, 67.4, 50.8, 27.9. FT-IR (neat, cm^{-1}): 2977, 1735, 1581, 1496, 1477, 1440, 1392, 1367, 1273, 1252, 1156, 1109, 966, 858, 792, 690, 464. HR-MS (*m/z*): calcd. for $[M+H]^+$ $C_{24}H_{27}N_2O_3S$ 423.1724, found 423.1722.

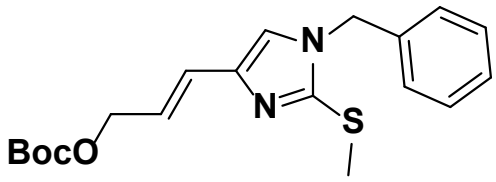
Synthesis of (E)-tert-butyl (3-(1-(N, N-dimethylsulfamoyl)-2-(phenylthio)-1H-imidazol-4-yl) allyl) carbonate (165a):



Compound **165** (0.05 g, 0.14 mmol) was dissolved in DCM (10 mL), triethylamine (0.02 mL, 0.22 mmol) and $(BOC)_2O$ (0.09 mL, 0.42 mmol) and DMAP (0.002 g, 0.021mmol) were added slowly with vigorous stirring solution. The reaction mixture was stirred at room temperature for 18 h. Ethyl acetate (10 mL) was added to the reaction mixture and the solution was washed with water and brine (3 x 5 mL) and dried with Na_2SO_4. The extract was concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, EtOAc/hexane = 20:80) to furnish **165a** (0.05g, 81%) as a brown liquid. ^1H NMR (500 MHz, Chloroform-*d*) δ 7.47 (dd, *J* = 6.5, 1.8 Hz, 2H), 7.36 – 7.30 (m, 3H), 7.28 (s,

1H), 6.40 – 6.38 (m, 2H), 4.64 (s, 2H), 2.95 (s, 6H), 1.47 (s, 9H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 153.4, 141.8, 139.2, 131.8, 131.2, 129.3, 128.4, 124.6, 123.6, 119.61, 82.3, 67.0, 38.6, 29.8, 27.8, 14.2. FT-IR (neat, cm^{-1}): 2925, 1736, 1581, 1439, 1389, 1332, 1273, 1251, 1157, 1101, 967, 857, 745, 725,602, 517,470. HR-MS (*m/z*): calcd. for $[M+H]^+$ $C_{19}H_{26}N_3O_5S_2$ 440.1300, found 440.1299.

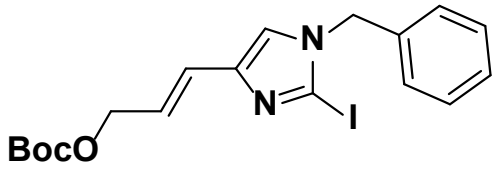
Synthesis of (E)-3-(1-Benzyl-2-(methylthio)-1H-imidazol-4-yl) allyl tert-butyl carbonate (166a):



Compound **166 (**0.03 g, 0.12 mmol) was dissolved in DCM (10 mL), triethylamine (0.019 mL, 0.138 mmol) and $(BOC)_2O$ (0.095 g, 0.43 mmol) and DMAP (0.002 g, 0.011mmol) were added slowly with vigorous stirring solution. The reaction mixture was stirred at room temperature for 18 h. Ethyl acetate (10 mL) was added to the reaction mixture and the solution was washed with water and brine (3 x 5 mL) and dried with Na_2SO_4. The extract was concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, EtOAc/hexane = 20:80) to furnish **166a** (0.035 g, 81%) as a brown crystalline liquid. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.33 – 7.27 (m, 3H), 7.13 – 7.09 (m, 2H), 6.84

(s, 1H), 6.49 – 6.34 (m, 2H), 5.03 (s, 2H), 4.64 (dd, J = 6.3, 1.1 Hz, 2H), 2.54 (s, 3H), 1.45 (d, J = 5.9 Hz, 9H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 153.5, 146.8, 144.0, 139.6, 136.1, 129.0, 128.2, 127.3, 125.8, 121.3, 119.6, 85.2, 82.0, 67.5, 50.0, 27.8, 27.4, 16.5. FT-IR (neat, cm^{-1}): 2981, 1802, 1753, 1457, 1395, 1371, 1306, 1255, 1211, 1160, 1114, 1066, 951, 844, 775, 664, 521. HR-MS (*m/z*): calcd. for $[M+H]^+$ $C_{19}H_{25}N_2O_3S$ 361.1568, found 361.1563.

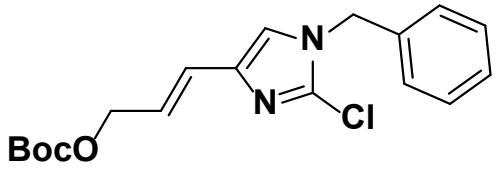
Synthesis of (E)-3-(1-Benzyl-2-iodo-1H-imidazol-4-yl) allyl tert-butyl carbonate (167a):



Compound **167** (0.07 g, 0.20 mmol) was dissolved in DCM (10 mL), triethylamine (0.024 mL, 0.25 mmol) and $(BOC)_2O$ (0.067 g, 0.30 mmol) and DMAP (0.002 g, 0.025 mmol) were added slowly with vigorous stirring. The reaction mixture was stirred at room temperature for 18 h. Ethyl acetate (10 mL) was added to the reaction mixture and the solution was washed with water and brine (3 x 5 mL) and dried with Na_2SO_4. The extract was concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, EtOAc/hexane = 20:80) to furnish **167a** (0.6 g, 68%) as a brown crystalline solid: m.p. = 110-112 °C. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.40 – 7.27 (m, 3H), 7.18 – 7.05 (m, 2H), 6.91

(s, 1H), 6.43 – 6.35 (m, 2H), 5.03 (s, 2H), 4.64 (d, J = 5.2 Hz, 2H), 1.45 (s, 9H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 153.4, 143.2, 135.4, 129.1, 128.4, 127.3, 124.9, 122.3, 121.3, 91.9, 82.1, 67.2, 53.3, 27.8. FT-IR (neat, cm^{-1}): 2927, 1735, 1493, 1447, 1392, 1364, 1275, 1197, 1116, 998, 963, 857, 839, 760, 690, 596, 532, 483, 455, 431, 419. HR-MS (*m/z*): calcd. for $[M+H]^+$ $C_{18}H_{22}IN_2O_3$ 441.0669, found 441.0662.

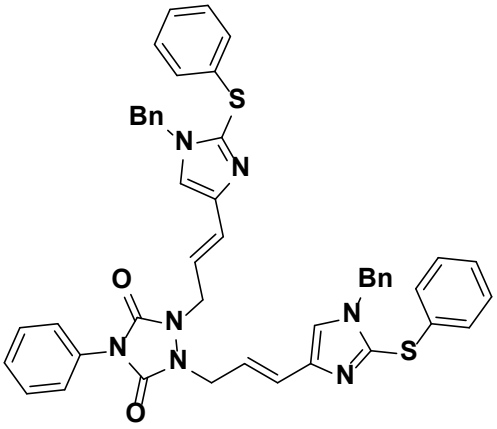
Synthesis (E)-3-(1-benzyl-2-chloro-1H-imidazol-4-yl) allyl tert-butyl carbonate (168a):



Compound **168** (0.56 g, 2.25 mmol) was dissolved in DCM (25 mL), triethyl amine (0.26 mL, 2.5 mmol) and $(BOC)_2O$ (0.64 mL, 2.9 mmol) and DMAP (0.028 g, 0.23 mmol) were added slowly added with vigorous stirring. The reaction mixture was stirred at room temperature for 18 h. Ethyl acetate (20 mL) was added to the reaction mixture and the solution was washed with water and brine (3 x 10 mL) and dried with Na_2SO_4. The extract was concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, EtOAc/hexane = 20:80) to furnish **168a** (0.5 g, 80%) as a brown crystalline solid: m.p. 108- 110°C. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.38 – 7.30 (m, 3H), 7.17 – 7.13 (m, 2H), 6.80 (s, 1H), 6.44 – 6.33 (m, 2H), 5.05 (s, 2H), 4.65 (d, J = 4.9 Hz, 2H), 1.47 (s, 9H). ^{13}C NMR

(126 MHz, Chloroform-*d*) δ 153.4, 138.6, 135.2, 132.9, 129.2, 128.5, 127.4, 124.9, 122.3, 118.9, 82.1, 67.2, 50.4, 27.9. FT-IR (neat, cm^{-1}): 2984, 1735, 1671, 1546, 1406, 1367, 1250, 1149, 1108, 1031, 1001, 969, 945, 839, 793, 743, 691, 648, 528, 467, 452, 434. HR-MS (*m/z*): calcd. for $[M+H]^+$ $C_{18}H_{22}N_2O_3Cl$ 349.1313, found 349.1309.

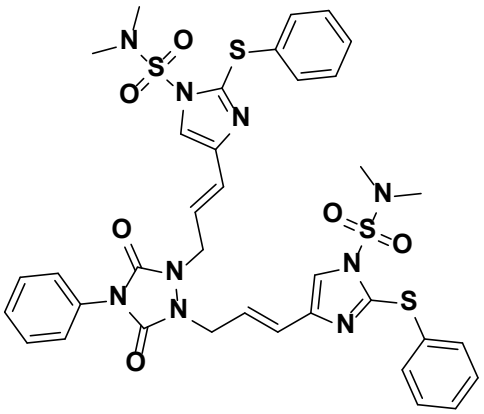
Synthesis of 1,2-bis((E)-3-(1-benzyl-2-(phenylthio)-1H-imidazol-4-yl) allyl)-4-phenyl-1,2,4-triazolidine-3,5-dione (169):



Compound **164a** (0.047 g, 0.11 mmol) was dissolved in DCM (10 mL). N-phenyl urazole (0.01 g, 0.056 mmol) PPh_3 (0.0014 g, 0.0056 mmol), Pd_2dba_3 (0.0015 g, 0.0016 mmol), were added and the reaction mixture was purged with nitrogen gas three times. The reaction mixture was stirred at room temperature under nitrogen gas for 24 hours. The reaction progress was monitored by TLC analysis. Ethyl acetate (20 mL) was added to the reaction mixture and the solution was

washed with water and brine (3 x 10 mL) and dried with Na_2SO_4. The extract was concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, EtOAc/hexane = 80:20) to furnish **169** (0.026 g, 60%) as a yellow sticky liquid. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.54 – 7.48 (m, 2H), 7.43 (t, *J* = 7.9 Hz, 2H), 7.35 – 7.29 (m, 1H), 7.26 – 7.19 (m, 11H), 7.17 – 7.12 (m, 6H), 7.00 (dd, *J* = 5.1, 2.3 Hz, 3H), 6.98 (s, 2H), 6.52 (d, *J* = 15.7 Hz, 2H), 6.38 (dt, *J* = 15.7, 6.7 Hz, 2H), 5.08 (s, 4H), 4.45 – 4.27 (m, 4H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 153.2, 140.0, 138.7, 135.7, 134.4, 131.7, 129.4, 129.1, 129.0, 128.3, 128.3, 127.9, 127.6, 126.9, 126.5, 125.5, 121.1, 50.9, 47.4. FT-IR (neat, cm^{-1}): 2924, 1768, 1700, 1581, 1477, 1417, 1351, 1077, 1023, 964, 811, 721, 688, 653, 606, 524, 469. HR-MS (*m/z*): calcd. for $[M+H]^+$ $C_{46}H_{40}N_7O_2S_2$ 786.2631, found 786.2631

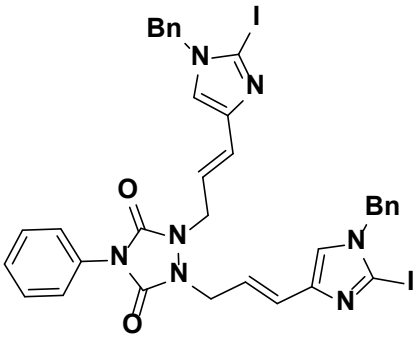
Synthesis of 4-((E)-3-(2-((E)-3-(1-(N, N-dimethylsulfamoyl)-2-(phenylthio)-1H-imidazol-4-yl) allyl)-3,5-dioxo-4-phenyl-1,2,4-triazolidin-1-yl) prop-1-en-1-yl)-N, N-dimethyl-2-(phenylthio)-1H-imidazole-1-sulfonamide (170):



Compound **165a** (0.025 g, 0.056 mmol) charge in a dried glass reaction round bottomed flask equipped with a magnetic stir bar in DCM (10 mL). N-phenyl urazole (0.005 g, 0.028 mmol) PPh_3 (0.0007 g, 0.0028 mmol), Pd_2dba_3 (0.0007 g, 0.0008 mmol), were added and the reaction mixture was purged with nitrogen gas three times. The reaction mixture was stirred at room temperature under nitrogen gas for 24 hours. The reaction progress was monitored by TLC. Ethyl acetate (20 mL) was added to the reaction mixture and the solution was washed with water and brine (3 x 10 mL) and dried with Na_2SO_4. The extract was concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, EtOAc/hexane = 80:20) to furnish **170** (0.028 g, 62 %) as a yellow sticky liquid. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.68 – 7.64 (m, 2H), 7.46 (d, *J* = 14.1 Hz, 9H), 7.30 (s, 6H), 6.41 (d, *J* = 15.6 Hz, 2H), 6.36 – 6.26 (m, 2H), 4.33 (dd, *J* = 6.6, 1.2 Hz, 4H), 2.95 (s, 12H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 153.4, 138.7, 135.1, 132.2, 132.1, 132.1, 131.4, 130.6, 129.4, 129.2, 128.6, 128.6, 128.3, 128.2, 125.5, 125.2, 123.1, 120.1, 47.4, 38.6, 29.8. FT-IR (neat, cm^{-1}): 2923, 2853,

1770, 1707, 1581, 1502, 1478, 1416, 1387, 1276, 1173, 1108, 1049, 1024, 965, 909, 768, 721, 647, 568, 539, 514. HR-MS (*m/z*): calcd. for $[M+H]^+$ $C_{36}H_{38}N_9O_6S_4$ 820.1800, found 820.1797.

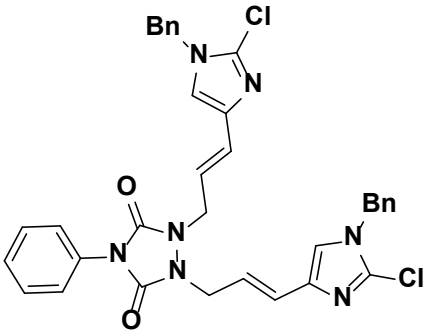
Synthesis of 1,2-bis((E)-3-(1-Benzyl-2-iodo-1H-imidazol-4-yl)allyl)-4-phenyl-1,2,4-triazolidine-3,5-dione (171):



Compound **167a** (0.04 g, 0.11 mmol) was dissolved in DCM (10 mL). N-phenyl urazole (0.01 g, 0.056 mmol) PPh_3 (0.0014 g, 0.0056 mmol), Pd_2dba_3 (0.0015 g, 0.0016 mmol), were added and the reaction mixture was purged with nitrogen gas three times. The reaction mixture was stirred at room temperature under nitrogen gas for 24 hours. The reaction progress was monitored by TLC. Ethyl acetate (20 mL) was added to the reaction mixture and the solution was washed with water and brine (3 x 10 mL) and dried with Na_2SO_4. The extract was concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, EtOAc/hexane = 80:20) to furnish **171** (0.35 g, 77%) as a yellow crystalline solid:

m.p. = 170-172 °C. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.52 – 7.48 (m, 2H), 7.43 (d, *J* = 7.6 Hz, 2H), 7.37 – 7.30 (m, 7H), 7.16 – 7.11 (m, 4H), 6.92 (s, 2H), 6.42 (d, *J* = 16.8 Hz, 2H), 6.35 – 6.26 (m, 2H), 5.02 (s, 4H), 4.35 (d, *J* = 7.8 Hz, 4H).^{13}C NMR (126 MHz, Chloroform-*d*) δ 153.2, 142.7, 135.3, 132.2, 132.1, 131.6, 129.1, 129.0, 128.6, 128.5, 127.9, 127.4, 126.1, 125.5, 121.6, 120.9, 92.1, 53.3, 47.3. FT-IR (neat, cm^{-1}): 1763, 1693, 1600, 1497, 1440, 1417, 1379, 1291, 1147, 1119, 1029, 963, 828, 719, 619, 539, 483. HR-MS (*m/z*): calcd. for $[M+H]^+$ $C_{34}H_{30}I_2N_7O_2$ 822.0510, found 822.0503.

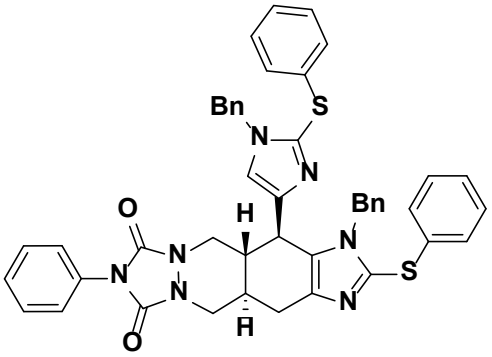
Synthesis of 1,2-bis((E)-3-(1-Benzyl-2-chloro-1H-imidazol-4-yl) allyl)-4-phenyl-1,2,4-triazolidine-3,5-dione (172):



Compound **168a** (0.32 g, 0.90 mmol) was dissolved in DCM (15 mL). N-phenyl urazole (0.08 g, 0.45 mmol) PPh_3 (0.012 g, 0.045mmol), Pd_2dba_3 (0.012g, 0.013 mmol), were added and the reaction mixture was purged with nitrogen gas three times. The reaction mixture was stirred at room temperature under nitrogen gas for 24 hours. The reaction progress was monitored by TLC. Ethyl acetate

(30 mL) was added to the reaction mixture and the solution was washed with water and brine (3 x 10 mL) and dried with Na_2SO_4. The extract was concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, EtOAc/hexane = 80:20) to furnish **172** (0.18 g, 63%) as a yellow crystalline solid: m.p. = 66-68 °C. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.49 (s, 2H), 7.43 (s, 2H), 7.38 – 7.29 (m, 7H), 7.15 (d, *J* = 8.2 Hz, 4H), 6.80 (s, 2H), 6.41 (d, *J* = 16.7 Hz, 2H), 6.29 (dt, *J* = 15.6, 6.6 Hz, 2H), 5.03 (s, 4H), 4.34 (dd, *J* = 6.7, 1.1 Hz, 4H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 153.2, 138.2, 135.1, 133.0, 131.6, 129.2, 129.1, 128.6, 127.9, 127.4, 126.1, 125.5, 120.8, 119.3, 53.5, 50.4, 47.3. FT-IR (neat, cm^{-1}): 1700, 1457, 1416, 1352, 1309, 1269, 1203, 1139, 1083, 993, 763, 686, 541, 505, 484. HR-MS (*m/z*): calcd. for $[M+H]^+$ $C_{34}H_{30}N_7O_2Cl_2$ 638.1833, found 638.1828.

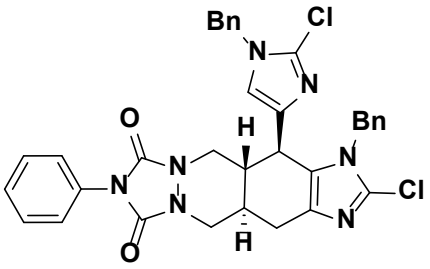
Synthesis of (4aR,11aS,12S)-1-Benzyl-12-(1-benzyl-2-(phenylthio)-1H-imidazol-4-yl)-8-phenyl-2-(phenylthio)-4,4a,5,11,11a,12-hexahydro-1H,7H-imidazo[4,5-g][1,2,4]triazolo[1,2-b]phthalazine-7,9(8H)-dione (173):



The compound **169** (0.025 g, 0.031 mmol) was dissolved in toluene (5 mL) in sealed tube and heated to 130 to 140 °C for 24 hours. After 24 h cooled the reaction mixture to room temperature and then evaporated under reduced pressure. The residue was purified by flash chromatography (silica gel, EtOAc) to furnish **173** (0.02 g, 80%) as a colorless crystalline solid: m.p. = 210-212 °C. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.47 – 7.43 (m, 4H), 7.29 (d, *J* = 7.3 Hz, 2H), 7.21 – 7.12 (m, 11H), 7.03 (d, *J* = 7.5 Hz, 2H), 6.96 – 6.92 (m, 2H), 6.54 (s, 1H), 6.32 (d, *J* = 7.5 Hz, 2H), 5.28 (dd, *J* = 18.2, 15.5 Hz, 2H), 4.81 (d, *J* = 14.8 Hz, 1H), 4.28 (dd, *J* = 12.1, 4.6 Hz, 1H), 4.10 (d, *J* = 16.4 Hz, 1H), 4.01 (dd, *J* = 12.0, 4.4 Hz, 1H), 3.35 – 3.29 (m, 2H), 3.06 – 2.96 (m, 2H), 2.81 (t, *J* = 11.7 Hz, 1H), 2.71 – 2.62 (m, 1H), 2.35 – 2.24 (m, 1H), 2.09 (ddd, *J* = 15.5, 10.5, 4.6 Hz, 1H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 152.0, 139.5, 135.7, 134.2, 131.3, 129.6, 129.4, 129.3, 129.2, 128.8, 128.6, 128.6, 128.4, 128.3, 128.1, 127.5, 127.3, 125.7, 125.6, 121.3, 51.0, 48.2, 46.8, 43.0, 37.4, 36.1, 29.8. FT-IR (neat, cm^{-1}): 2920, 2852, 1776, 1715, 1551, 1483,

1434, 1361, 1310, 1223, 1128, 1100, 1028, 947, 876, 789, 742, 714, 689, 662, 552, 483, 454. HR-MS (*m/z*): calcd. for $[M+H]^+$ $C_{46}H_{40}N_7O_2S_2$ 786.2668, found 786.2662.

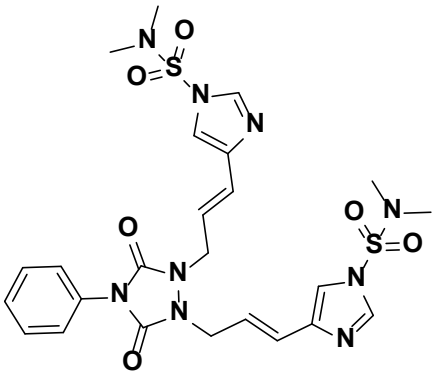
Synthesis of (4aR,11aS,12S)-1-Benzyl-12-(1-benzyl-2-chloro-1H-imidazol-4-yl)-2-chloro-8-phenyl-4,4a,5,11,11a,12-hexahydro-1H,7H-imidazo[4,5-g][1,2,4]triazolo[1,2-b]phthalazine-7,9(8H)-dione (174):



The compound **172** (0.2 g, 0.31 mmoL) was dissolved in toluene (10 mL) in sealed tube and heated to 130 to 140 °C for 24 hours. After 24 h cooled the reaction mixture to room temperature and then evaporated under reduced pressure. The residue was purified by flash chromatography (silica gel, EtOAc) to furnish **174** (0.17 g, 85%) as a colorless crystalline solid: m.p. = 228-230 °C. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.47 – 7.43 (m, 6H), 7.43 – 7.37 (m, 4H), 7.35 (d, *J* = 9.2 Hz, 2H), 7.23 – 7.14 (m, 6H), 6.58 (d, *J* = 6.3 Hz, 2H), 6.44 (s, 1H), 5.00 (t, *J* = 15.9 Hz, 2H), 4.73 (d, *J* = 15.1 Hz, 1H), 4.35 (d, *J* = 16.8 Hz, 1H), 4.24 (dd, *J* = 12.1, 4.5 Hz, 1H), 4.01 (dd, *J* = 12.0, 4.4 Hz, 1H), 3.35 – 3.30 (m, 1H), 3.02 – 2.95 (m, 1H), 2.85 – 2.79 (m, 2H), 2.59 – 2.51 (m, 1H), 2.23 – 2.15 (m, 1H), 2.06 (ddd, *J* = 16.3, 11.3, 4.9 Hz, 1H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 152.0, 152.0,

138.5, 135.5, 135.1, 135.0, 132.8, 131.3, 129.4, 129.3, 129.2, 128.9, 128.6, 128.3, 127.9, 127.6, 126.2, 125.6, 125.6, 119.3, 50.5, 48.1, 47.7, 46.7, 42.7, 37.1, 36.1, 27.6. FT-IR (neat, cm^{-1}): 1772, 1709, 1415, 1363, 1290, 1209, 1132, 1065, 1027, 838, 691, 644, 540, 505, 455, 421. HR-MS (*m/z*): calcd. for $[M+H]^+$ $C_{34}H_{30}N_7O_2Cl_2$ 638.1833, found 638.1828.

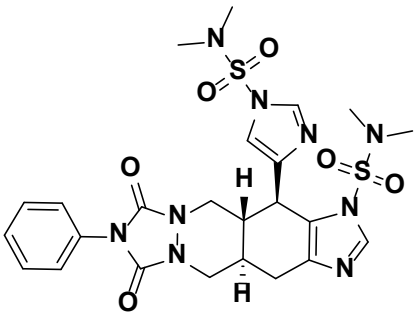
Synthesis of 4-((E)-3-(2-((E)-3-(1-(N, N-dimethylsulfamoyl)-1H-imidazol-4-yl) allyl)-3,5-dioxo-4-phenyl-1,2,4-triazolidin-1-yl) prop-1-en-1-yl)-N, N-dimethyl-1H-imidazole-1-sulfonamide (176):



Compound **113a** (1.0 g, 3.2 mmol) was charged in a dried glass reaction round bottomed flask equipped with a magnetic stir bar with THF (15 mL). N-phenyl urazole (0.3 g, 1.66 mmol) PPh_3 (0.033g, 0.12 mmol), Pd_2dba_3 (0.073 g, 0.08 mmol), were added and the reaction mixture was purged with nitrogen gas three times. The reaction mixture was stirred at 80 °C under nitrogen gas for 24 hours. The reaction progress was monitored by TLC. Ethyl acetate (20 mL) was added to the

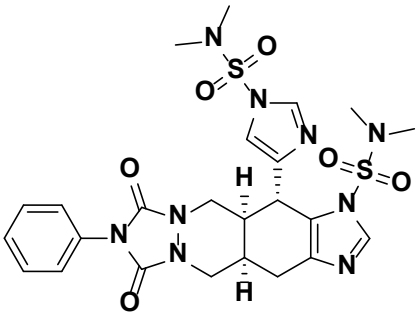
reaction mixture and the solution was washed with water and brine (3 x 10 mL) and dried with Na_2SO_4. The extract was concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, EtOAc/hexane = 60:40) to furnish **176** (0.85 g, 88%) as a yellow crystalline solid: m.p. = 190-192 °C. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.91 – 7.80 (m, 2H), 7.54 – 7.48 (m, 2H), 7.46 – 7.38 (m, 2H), 7.33 (tt, *J* = 7.5, 2.9 Hz, 1H), 7.21 – 7.13 (m, 2H), 6.62 – 6.39 (m, 4H), 4.41 (d, *J* = 6.4 Hz, 4H), 2.86 (dd, *J* = 5.2, 2.2 Hz, 12H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 153.4, 140.0, 137.0, 131.5, 129.1, 128.2, 125.4, 123.5, 115.2, 47.5, 38.3. FT-IR (neat, cm^{-1}): 3102, 1760, 1688, 1487, 1450, 1419, 1384, 1336, 1200, 1165, 1007, 764, 731, 640, 595, 508, 458. HR-MS (*m/z*): calcd. for $[M+H]^+$ $C_{24}H_{29}N_9O_6S_2$ 604.1755, found 604.1694.

Synthesis of (4aR,11aS,12S)-12-(1-(N, N-dimethylsulfamoyl)-1H-imidazol-4-yl)-N,N-dimethyl-7,9-dioxo-8-phenyl-4,4a,5,8,9,11,11a,12-octahydro-1H,7H-imidazo[4,5-g][1,2,4]triazolo[1,2-b]phthalazine-1-sulfonamide (177):



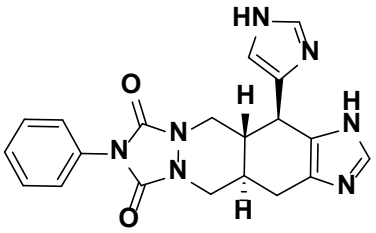
The compound **176** (2.5 g, 4.1 mmol) was dissolved in toluene (10 mL) in sealed tube and heated to 130 to 140 °C for 24 hours. After 24 h cooled the reaction mixture to room temperature and then evaporated under reduced pressure. The residue was purified by flash chromatography (silica gel, MeOH/EtOAc = 20:80) to furnish **177** (1.7 g, 70%) as a colorless crystalline solid: m.p. = 202-204 °C. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.84 (d, *J* = 1.4 Hz, 1H), 7.75 (s, 1H), 7.49 – 7.41 (m, 5H), 7.40 – 7.32 (m, 1H), 7.14 (d, *J* = 1.4 Hz, 1H), 4.31 (dd, *J* = 12.1, 4.5 Hz, 1H), 4.21 (dd, *J* = 12.0, 4.4 Hz, 1H), 3.93 (d, *J* = 8.0 Hz, 1H), 3.05 – 2.99 (m, 2H), 2.92 – 2.90 (m, 1H), 2.88 (s, 7H), 2.81 (s, 6H), 2.63 (ddd, *J* = 15.9, 11.1, 2.7 Hz, 1H), 2.23 (tdd, *J* = 11.3, 9.4, 4.4 Hz, 1H), 2.11 (dtd, *J* = 15.8, 11.1, 4.5 Hz, 1H), 1.25 (d, *J* = 3.1 Hz, 1H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 152.1, 151.8, 142.5, 138.7, 137.2, 136.6, 131.2, 129.3, 128.3, 125.6, 125.4, 116.3, 48.1, 46.8, 43.6, 38.2, 38.0, 36.6, 35.8, 27.9. FT-IR (neat, cm^{-1}): 2910, 2118, 1767, 1708, 1456, 1419, 1385, 1279, 1172, 1082, 1004, 961, 826, 777, 690, 646, 596, 513, 446. HR-MS (*m/z*): calcd. for $[M+H]^{+}$ $C_{24}H_{30}N_9O_6S_2$ 604.1755, found 604.1735.

Synthesis of (4aR,11aR,12R)-12-(1-(N, N-dimethylsulfamoyl)-1H-imidazol-4-yl)-N,N-dimethyl-7,9-dioxo-8-phenyl-4,4a,5,8,9,11,11a,12-octahydro-1H,7H-imidazo[4,5-g] [1,2,4]triazolo[1,2-b]phthalazine-1-sulfonamide (178):



Compound **178** (28%) m.p. = 206-208 °C. ^{1}H NMR (301 MHz, Chloroform-*d*) δ 7.93 – 7.85 (m, 1H), 7.86 (dt, *J* = 3.3, 1.5 Hz, 1H), 7.52 – 7.37 (m, 3H), 7.42 – 7.32 (m, 1H), 7.27 (dd, *J* = 3.4, 1.6 Hz, 1H), 6.69 (d, *J* = 3.2 Hz, 1H), 5.34 – 5.26 (m, 0H), 4.23 (s, 1H), 4.13 (dt, *J* = 10.3, 2.9 Hz, 1H), 4.02 (d, *J* = 12.1 Hz, 1H), 3.38 (dd, *J* = 12.4, 3.8 Hz, 1H), 3.26 – 3.15 (m, 1H), 2.96 (dd, *J* = 8.7, 3.2 Hz, 1H), 2.85 – 2.74 (m, 9H), 2.61 (s, 1H), 2.06 – 2.02 (m, 1H), 1.68 (s, 3H), 1.30 – 1.22 (m, 1H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 152.8, 151.9, 142.9, 138.6, 137.8, 137.1, 128.8, 127.4, 126.0, 122.4, 115.7, 43.1, 40.0, 37.6, 36.9, 34.7, 34.4, 22.5. FT-IR (neat, cm^{-1}): 2909, 2110, 1707, 1456, 1419, 1385, 1279, 1172, 1082, 1004, 961, 826, 786, 690, 646, 596, 562, 513, 444. HR-MS (*m/z*): calcd. for $[M+H]^+$ $C_{24}H_{30}N_9O_6S_2$ 604.1745, found 604.1730

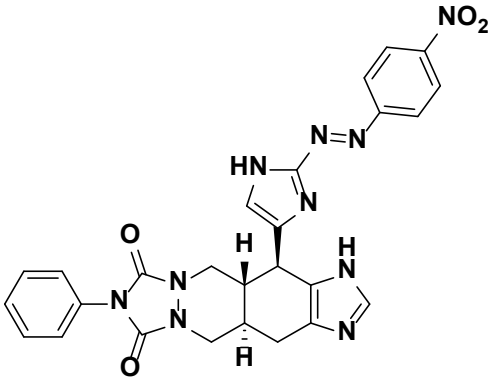
Synthesis of (4aR,11aS,12R)-12-(1H-imidazol-4-yl)-8-phenyl-4,4a,5,11,11a,12-hexahydro-1H,7H-imidazo[4,5-g][1,2,4]triazolo[1,2-b]phthalazine-7,9(8H)-dione (180):



DMAS protected Diels-Alder adduct **177** (0.5 g, 1.6 mmol) was dissolved in EtOH (10 mL) and HCl (5 mL) was added and heated to reflux the solution for overnight. To a solution of HCl salt in dichloromethane (60 mL) was added water (30 mL). Solid sodium bicarbonate was added until the solution reached a pH of 7. The resulting solution was extracted with dichloromethane (3 x 50 mL). The combined organic extracts were dried with Na_2SO_4 and then evaporated under reduced pressure to afford an off-white solid. The residue was purified by flash chromatography (silica gel, EtOAc/hexane = 70:30) to furnish **180** (0.45 g, 70%) as a colorless crystalline solid: m.p. = 240-242 °C. ^{1}H NMR (500 MHz, Methanol-d_4) δ 7.71 – 7.67 (m, 1H), 7.52 (s, 1H), 7.48 – 7.42 (m, 4H), 7.42 – 7.35 (m, 1H), 7.08 (d, J = 0.9 Hz, 1H), 4.25 (dd, J = 12.0, 4.3 Hz, 1H), 3.93 (dd, J = 12.1, 4.2 Hz, 1H), 3.87 (d, J = 9.4 Hz, 1H), 3.10 (dt, J = 17.6, 11.7 Hz, 2H), 2.90 (dd, J = 15.4, 4.4 Hz, 1H),

2.54 (ddd, *J* = 15.5, 10.5, 2.3 Hz, 1H), 2.22 (ddtd, *J* = 22.1, 15.6, 11.2, 4.8 Hz, 3H). ^{13}C NMR (126 MHz, Methanol-d_4) δ 152.2, 137.4, 135.7, 134.3, 128.7, 128.1, 125.9, 116.8, 46.5, 42.3, 36.3, 35.9, 25.4. FT-IR (neat, cm^{-1}): 3124, 2854, 1769, 1494, 1419, 1365, 1285, 1215, 1026, 818, 764, 735, 711, 689, 647, 547, 504. HR-MS (*m/z*): calcd. for $[M+H]^+$ $C_{20}H_{20}N_7O_2$ 390.1580, found 390.1578.

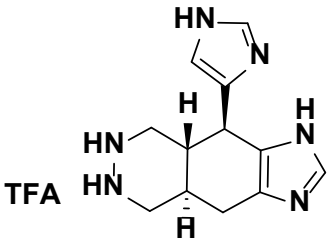
Synthesis of (4aR,11aS,12R)-12-(2-((E)-(4-nitrophenyl) diazenyl)-1H-imidazol-4-yl)-8-phenyl-4,4a,5,11,11a,12-hexahydro-1H,7H-imidazo[4,5-g] [1,2,4] triazolo[1,2-b] phthalazine-7,9(8H)-dione (182):



Compound **180** (0.04 g, 0.1 mmol) was dissolved in EtOH (10 mL) and then was added to the cooled solution of para nitro tetrafluoro diazonium salt (0.1 g, 0.4 mmol) in water (15 mL). The reaction mixture was stirred at room temperature for 18 hours. Solution turned into red solid precipitation. Filtered the solid compound through sintered glass funnel and washed with cold water to afford a red solid compound **182**: m.p. = 210-212 °C. ^{1}H NMR (500 MHz, Methanol-d_4) δ 8.35 (d, *J* = 9.1 Hz, 2H), 8.02 (d, *J* = 9.0 Hz, 2H), 7.72 (s, 1H), 7.47 – 7.43 (m, 4H), 7.39 (t, *J* = 6.8 Hz, 1H), 7.17 (s,

1H), 4.28 (dd, *J* = 11.9, 4.0 Hz, 1H), 3.94 (dd, *J* = 12.0, 4.0 Hz, 1H), 3.12 (q, *J* = 11.2 Hz, 2H), 3.07 – 3.02 (m, 1H), 2.74 – 2.65 (m, 1H), 2.35 – 2.25 (m, 2H). FT-IR (neat, cm^{-1}): 3148, 1768, 1700, 1590, 1518, 1502, 1426, 1340, 1105, 1061, 911, 852, 752, 690, 585, 446. HR-MS (*m/z*): calcd. for $[M+H]^+$ $C_{26}H_{23}N_{10}O_4$ 539.5328, found 539.53.14.

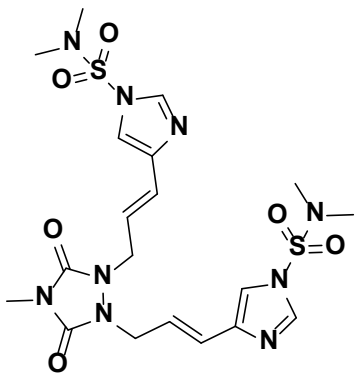
Synthesis of (4aR,8aS,9R)-9-(1H-imidazol-4-yl)-4,4a,5,6,7,8,8a,9-octahydro-1H-imidazo[4,5-g] phthalazine (183):



To a stirred solution of compound **180** (0.3 g, 0.76 mmol) in hydrazine hydrate (30 mL, 10 vol) was stirred at 150 °C for 20 h. When TLC showed complete consumption of the starting material, the reaction mixture evaporated to dry under reduced pressure. The residue was purified by flash chromatography (silica gel, MeOH/EtOAc = 20:80) to furnish **183** (0.125 g, 65%). Then compound was dissolved in DCM (10 mL) then cooled the reaction mixture to 0 °C, TFA (1 mL) was added, and the reaction mixture was stirred at same temperature for 1 hour. Removed the residual solvent under reduced pressure to afford **183** TFA salt (0.125 g, quant) as sticky brown liquid. ^{1}H NMR (500 MHz, Methanol-d_4) δ 8.92 (d, *J* = 1.2 Hz, 1H), 8.78 (s, 1H), 7.65 (d, *J* =

1.3 Hz, 1H), 4.26 (d, J = 9.7 Hz, 1H), 3.66 – 3.61 (m, 1H), 3.54 (dd, J = 13.1, 3.9 Hz, 1H), 3.20 (dd, J = 13.4, 3.9 Hz, 1H), 3.08 – 2.91 (m, 4H), 2.61 (dt, J = 8.3, 1.8 Hz, 2H), 2.59 – 2.52 (m, 1H), 2.38 – 2.33 (m, 1H), 2.33 – 2.25 (m, 1H), 2.21 (qd, J = 11.1, 4.2 Hz, 1H). ^{13}C NMR (126 MHz, Methanol-d_4) δ 135.6, 133.9, 130.0, 127.7, 125.6, 119.1, 49.0, 40.1, 33.8, 32.9, 23.1. FT-IR (neat, cm^{-1}): 3120, 2864, 1769, 1494, 1419, 1365, 1285, 1215, 1026, 818, 760, 730, 700, 680, 640, 540, 510. HR-MS (*m/z*): calcd. for $[M+H]^+$ $C_{12}H_{17}N_6$ 245.1599, found 245.1588.

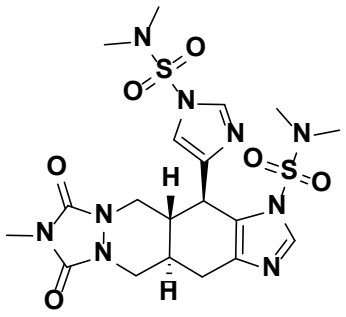
Synthesis of 4-((E)-3-(2-((E)-3-(1-(N, N-dimethylsulfamoyl)-1H-imidazol-4-yl) allyl)-4-methyl-3,5-dioxo-1,2,4-triazolidin-1-yl) prop-1-en-1-yl)-N, N-dimethyl-1H-imidazole-1-sulfonamide (185):



Compound **113** (0.14 g, 0.43 mmol) was dissolved in DCM (15 mL). Then N-phenyl urazole (0.025 g, 0.22 mmol) PPh_3 (0.05 g, 0.021 mmol), Pd_2dba_3 (0.005 g, 0.006 mmol), were added to the reaction mixture and the reaction

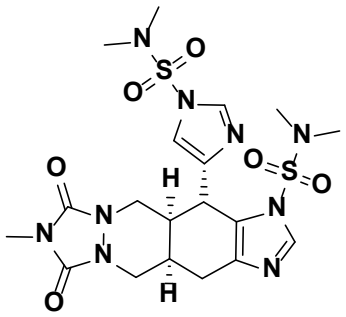
mixture was purged with nitrogen gas three times. The reaction mixture was stirred at room temperature under nitrogen gas for 24 hours. The reaction progress was monitored by TLC. Ethyl acetate (20 mL) was added to the reaction mixture and the solution was washed with water and brine (3 x 10 mL) and dried with Na_2SO_4. The extract was concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, EtOAc) to furnish **185** (0.15 g, 64%) as a yellow crystalline solid: m.p. = 158-160 °C. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.81 (d, *J* = 1.4 Hz, 2H), 7.12 (d, *J* = 1.2 Hz, 2H), 6.46 (d, *J* = 15.7 Hz, 2H), 6.35 (dt, *J* = 15.7, 6.5 Hz, 2H), 4.30 (dd, *J* = 6.5, 1.2 Hz, 4H), 3.05 (s, 3H), 2.85 (s, 12H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 155.1, 140.2, 137.1, 125.2, 123.5, 115.1, 53.5, 47.4, 45.9, 38.3, 25.7, 8.7. FT-IR (neat, cm^{-1}): 1758, 1693, 1466, 1419, 1381, 1191, 1161, 1008, 957, 892, 761, 721, 594, 530, 514, 471. HR-MS (*m/z*): calcd. for $[M+H]^+$ $C_{19}H_{28}N_9O_6S_2$ 542.1672, found 542.1667.

Synthesis of (4aR,11aS,12S)-12-(1-(N, N-dimethylsulfamoyl)-1H-imidazol-4-yl)-N, N,8-trimethyl-7,9-dioxo-4,4a,5,8,9,11,11a,12-octahydro-1H,7H-imidazo [4,5-g] [1,2,4] triazolo[1,2-b] phthalazine-1-sulfonamide (186):



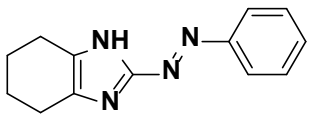
The compound **185** (0.15 g, 0.28 mmol) was dissolved in toluene (10 mL) in sealed tube and heated to 130 to 140 °C for 24 hours. After 24 h cooled the reaction mixture to room temperature and then evaporated to dry completely under reduced pressure. The residue was purified by flash chromatography (silica gel, MeOH/EtOAc = 60:40) to furnish **186** (0.08 g, 53.6%) as a yellow crystalline solid: m.p. = 188-200 °C. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.81 (d, *J* = 1.4 Hz, 1H), 7.71 (s, 1H), 7.10 (d, *J* = 1.3 Hz, 1H), 4.19 (dd, *J* = 12.0, 4.5 Hz, 1H), 4.13 – 4.07 (m, 2H), 3.87 (dd, *J* = 8.5, 2.1 Hz, 1H), 3.45 (s, 1H), 3.04 (s, 3H), 2.94 – 2.89 (m, 2H), 2.86 (s, 6H), 2.80 (s, 6H), 2.61 – 2.52 (m, 1H), 2.18 – 2.09 (m, 1H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 153.54, 153.2, 142.5, 138.8, 137.1, 136.6, 125.4, 116.2, 60.5, 50.8, 47.9, 46.7, 43.7, 38.2, 38.0, 36.6, 35.9, 27.9, 25.2, 21.1, 14.3. FT-IR (neat, cm^{-1}): 2925, 1762, 1697, 1469, 1418, 1272, 1208, 1158, 1073, 1009, 963, 831, 815, 771, 586, 514, 406. HR-MS (*m/z*): calcd. for $[M+H]^+$ $C_{19}H_{28}N_9O_6S_2$ 542.1598, found 542.1588.

Synthesis of (4aR,11aR,12R)-12-(1-(N, N-dimethylsulfamoyl)-1H-imidazol-4-yl)-N, N,8-trimethyl-7,9-dioxo-4,4a,5,8,9,11,11a,12-octahydro-1H,7H-imidazo[4,5-g] [1,2,4] triazolo[1,2-b] phthalazine-1-sulfonamide (187):



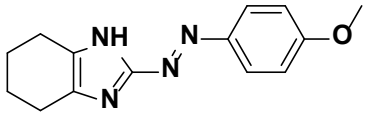
Compound **187** (0.02 g, 13 %) as a colorless crystalline solid: m.p. = 130-132 °C. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.86 (s, 1H), 7.83 (s, 1H), 6.65 (s, 1H), 4.18 (s, 1H), 4.01 (d, *J* = 8.2 Hz, 1H), 3.90 (d, *J* = 11.8 Hz, 1H), 3.25 (dd, *J* = 12.3, 2.9 Hz, 1H), 3.06 (s, 3H), 2.86 (d, *J* = 4.3 Hz, 2H), 2.81 (s, 1H), 2.79 (s, 6H), 2.78 (s, 6H), 2.66 (d, *J* = 9.3 Hz, 1H), 2.53 (d, *J* = 10.4 Hz, 1H), 2.34 (s, 1H). ^{13}C NMR (126 MHz, Methanol-d_4) δ 153.7, 153.5, 142.1, 138.5, 137.7, 137.0, 125.3, 117.0, 48.1, 48.0, 47.8, 47.7, 47.5, 47.3, 47.1, 46.0, 43.4, 37.2, 36.9, 36.0, 35.2, 27.0, 24.0. FT-IR (neat, cm^{-1}): 2922, 1762, 1690, 1466, 1418, 1386, 1265, 1171, 1078, 1007, 960, 849, 772, 723, 591, 512. HR-MS (*m/z*): calcd. for $[M+H]^+$ $C_{19}H_{28}N_9O_6S_2$ 542.1703, found 542.1687.

Synthesis of (E)-2-(phenyldiazenyl)-4,5,6,7-tetrahydro-1H-benzo[d]imidazole (189):



Benzimidazole (0.05 g, 0.40 mmol) was dissolved in EtOH (2.5 mL) and then was added to the cooled solution of phenyl tetrafluoro diazonium salt (0.1 g, 0.40 mmol) in water (25 mL). The reaction mixture was stirred at room temperature for 18 hours. Solution turned into red solid precipitation. Filtered the solid compound through sintered glass funnel and washed with cold water to afford a red solid compound **189** (0.07 g, 78%) as a yellow crystalline solid: m.p. = 158-160 °C. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.85 (dd, *J* = 7.0, 1.7 Hz, 2H), 7.45 – 7.39 (m, 3H), 2.68 (s, 4H), 1.86 (s, 4H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 153.3, 152.4, 133.1, 131.0, 129.2, 122.9, 23.5, 23.0. FT-IR (neat, cm^{-1}): 2932, 2847, 1575, 1478, 1421, 1321, 1279, 1218, 1187, 1135, 1058, 1032, 922, 902, 838, 813, 761, 702, 683, 564, 513, 484. HR-MS (*m/z*): calcd. for $[M+H]^+$ C_{13} $H_{15}N_4$ 227.1274, found 227.1269

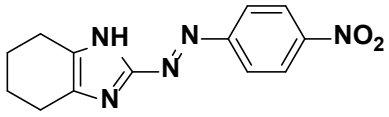
Synthesis of (E)-2-((4-methoxyphenyl) diazenyl)-4,5,6,7-tetrahydro-1H-benzo[d]imidazole (190):



Benzimidazole (0.2 g, 1.64 mmol) was dissolved in EtOH (5 mL) and then was added to the cooled solution of para methoxy tetrafluoro diazonium salt (0.36 g, 1.64 mmol) in water (50 mL). The reaction mixture was stirred at room temperature for 18 hours. Solution turned into red solid precipitation. Filtered the solid compound

through sintered glass funnel and washed with cold water to afford a red solid compound **190** (0.2 g, 48%) as a brown crystalline solid: m.p. = 180-182 °C. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.84 (d, *J* = 9.0 Hz, 2H), 6.95 (d, *J* = 9.1 Hz, 2H), 2.67 (s, 4H), 1.86 (s, 4H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 162.2, 153.2, 146.7, 124.9, 114.4, 55.7, 23.0, 23.0. FT-IR (neat, cm^{-1}): 2924, 2836, 1580, 1498, 1426, 1324, 1305, 1247, 1192, 1143, 1101, 957, 914, 837, 766, 813, 703, 639, 683, 577, 473, 420. HR-MS (*m/z*): calcd. for $[M+H]^+$ $C_{14}H_{17}N_4O$ 257.1376, found 257.1372

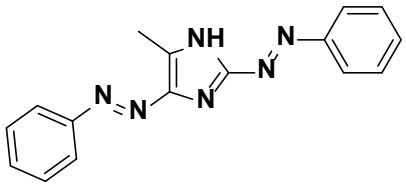
Synthesis of (E)-2-((4-nitrophenyl) diazenyl)-4,5,6,7-tetrahydro-1H-benzo[d]imidazole (191):



Benzimidazole (0.05 g, 0.46 mmol) was dissolved in EtOH (2.5 mL) and then was added to the cooled solution of para nitro tetrafluoro diazonium salt (0.1 g, 0.46 mmol) in water (25 mL). The reaction mixture was stirred at room temperature for 18 hours. Solution turned into red solid precipitation. Filtered the solid compound through sintered glass funnel and washed with cold water to afford a red solid compound **191** (0.75 g, 60%) as a brown crystalline solid: m.p. = 178-180 °C. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.32 (d, *J* = 8.7 Hz, 2H), 7.95 (d, *J* = 8.6 Hz, 2H), 2.75 (s, 4H), 1.88 (s, 4H). FT-IR (neat, cm^{-1}): 2931, 1605,1420, 1317, 1183, 1128, 1102, 907,

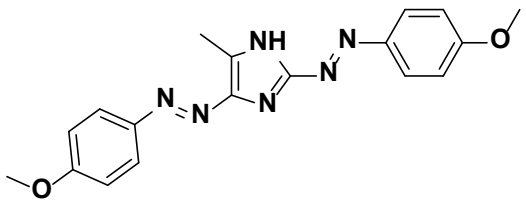
856, 804, 711, 666, 559, 454, 439, 424. HR-MS (*m/z*): calcd. for $[M+H]^+$ C_{13} $H_{14}N_5O2$ 272.1119, found 272.1115

Synthesis of 5-methyl-2,4-bis((E)-phenyldiazenyl)-1H-imidazole (192):



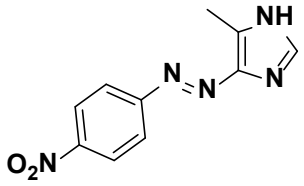
4-methyl imidazole (0.1 g, 1.21 mmol) was dissolved in EtOH (2.5 mL) and then was added to the cooled solution of phenyl tetrafluoro diazonium salt (0.2 g, 1.21 mmol) in water (25 mL). The reaction mixture was stirred at room temperature for 18 hours. Solution turned into red solid precipitation. Filtered the solid compound through sintered glass funnel and washed with cold water. The residue was purified by flash chromatography (silica gel, EtOAc/Hexanes = 20:80) to furnish **192** (0.15 g, 43%) as a yellow crystalline solid: m.p. = 180-182 °C. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.98 – 7.93 (m, 2H), 7.92 – 7.86 (m, 2H), 7.51 – 7.47 (m, 5H), 7.45 – 7.40 (m, 1H), 2.75 (s, 3H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 153.0, 152.8, 152.4, 132.7, 131.0, 129.4, 129.3, 123.7, 122.8. FT-IR (neat, cm^{-1}): 2916, 1677, 1567, 1494, 1426, 1389, 1320, 1289, 1236, 1194, 1155, 1136, 1017, 947, 920, 903, 765, 678, 621, 558, 517, 443. HR-MS (*m/z*): calcd. for $[M+H]^+$ C_{16} $H_{15}N_6$ 291.1337 found 291.1332

Synthesis of 2,4-bis((E)-(4-methoxyphenyl) diazenyl)-5-methyl-1H-imidazole (193):



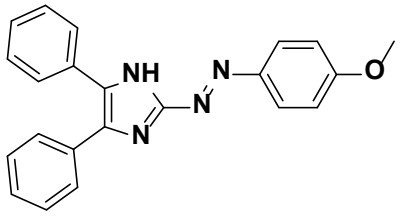
4-methyl imidazole (0.1 g, 1.21 mmol) was dissolved in EtOH (2.5 mL) and then was added to the cooled solution of para methoxy tetrafluoro diazonium salt (0.27 g, 1.21 mmol) in water (25 mL). The reaction mixture was stirred at room temperature for 18 hours. Solution turned into red solid precipitation. Filtered the solid compound through sintered glass funnel and washed with cold water. The residue was purified by flash chromatography (silica gel, EtOAc/Hexanes = 50:50) to furnish **193** (0.16 g, 38%) as a yellow crystalline solid: m.p. = 162-164 °C. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.97 (d, *J* = 7.0 Hz, 2H), 7.87 (d, *J* = 9.0 Hz, 2H), 7.01 (d, *J* = 2.2 Hz, 1H), 7.00 (d, *J* = 2.3 Hz, 2H), 6.98 (d, *J* = 2.1 Hz, 1H), 3.89 (d, *J* = 5.5 Hz, 6H), 2.71 (s, 3H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 163.5, 162.0, 147.4, 147.0, 125.9, 124.5, 114.7, 114.5, 55.8, 55.7, 29.8. FT-IR (neat, cm^{-1}): 2917, 2849, 1595, 1578, 1497, 1438, 1388, 1321, 1296, 1242, 1155, 1177, 1025, 832, 560, 527, 504, 470, 454, 419, 405. HR-MS (*m/z*): calcd. for $[M+H]^+$ C_{18} $H_{19}N_6O_2$ 351.1538 found 351.1532

Synthesis of (E)-5-methyl-4-((4-nitrophenyl) diazenyl)-1H-imidazole (194):



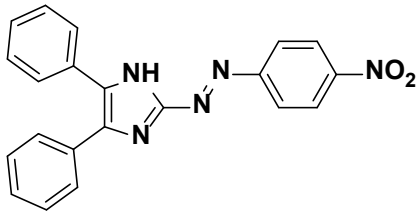
4-methyl imidazole (0.1 g, 1.21 mmol) was dissolved in EtOH (2.5 mL) and then was added to the cooled solution of para nitro tetrafluoro diazonium salt (0.29 g, 1.21 mmol) in water (25 mL). The reaction mixture was stirred at room temperature for 18 hours. Solution turned into red solid precipitation. Filtered the solid compound through sintered glass funnel and washed with cold water. The residue was purified by flash chromatography (silica gel, EtOAc/Hexanes = 60:40) to furnish **194** (0.16 g, 38%) as a yellow crystalline solid: m.p. = 168-170 °C. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.79 (s, 1H), 8.44 (d, *J* = 9.9 Hz, 2H), 8.00 (d, *J* = 9.1 Hz, 2H), 2.75 (s, 3H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 161.4, 147.5, 142.8, 140.8, 125.8, 125.1, 125.0, 123.4, 120.5, 27.5. FT-IR (neat, cm^{-1}): 2918, 2850, 1731, 1588, 1515, 1461, 1377, 1338, 1181, 1156, 1104, 1014, 906, 859, 813, 754, 682, 470, 460. HR-MS (*m/z*): calcd. for $[M+H]^+$ C_{18} $H_{19}N_6O_2$ 232.0818 found 232.0814

Synthesis of (E)-2-((4-methoxyphenyl) diazenyl)-4,5-diphenyl-1H-imidazole (195):

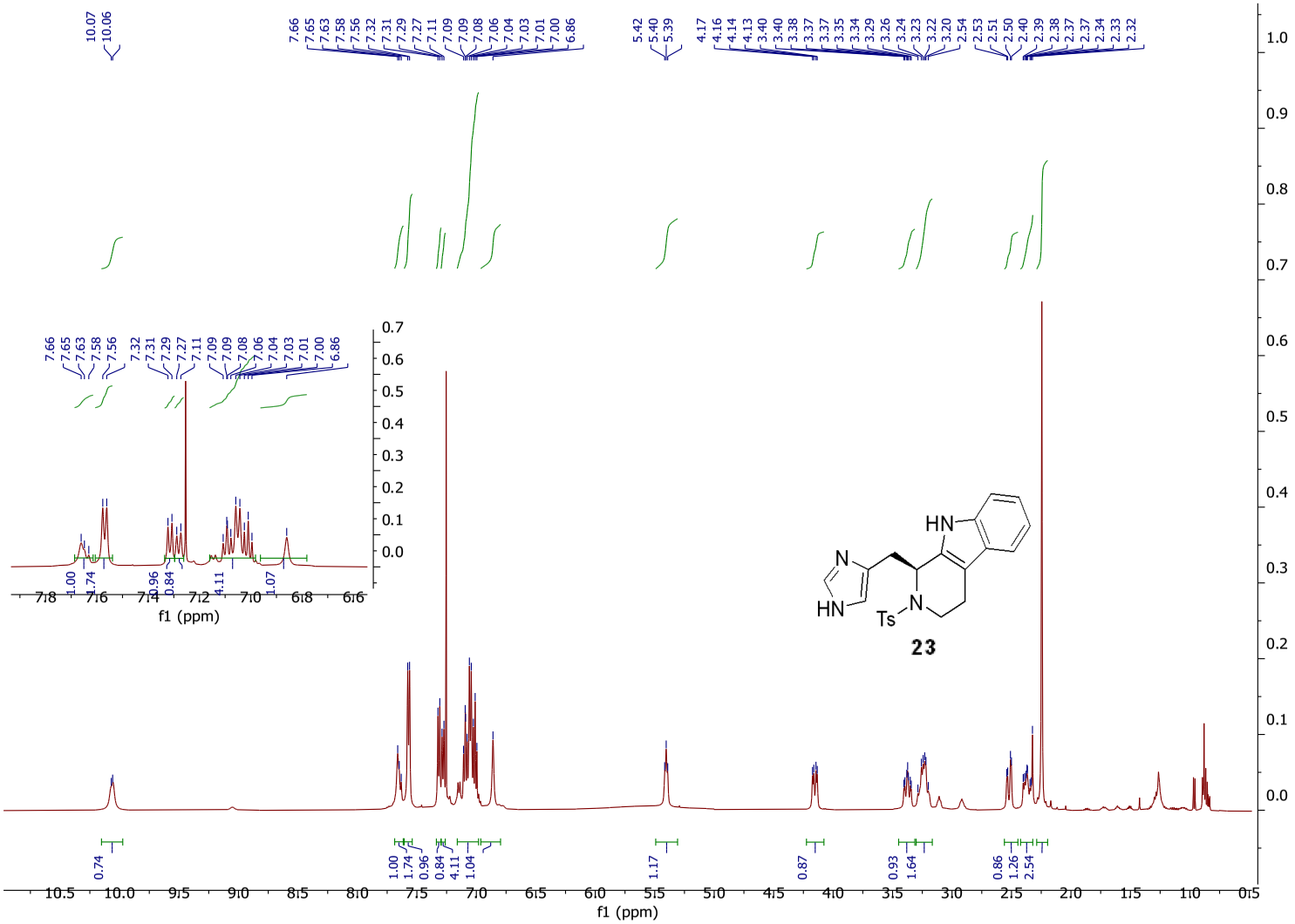


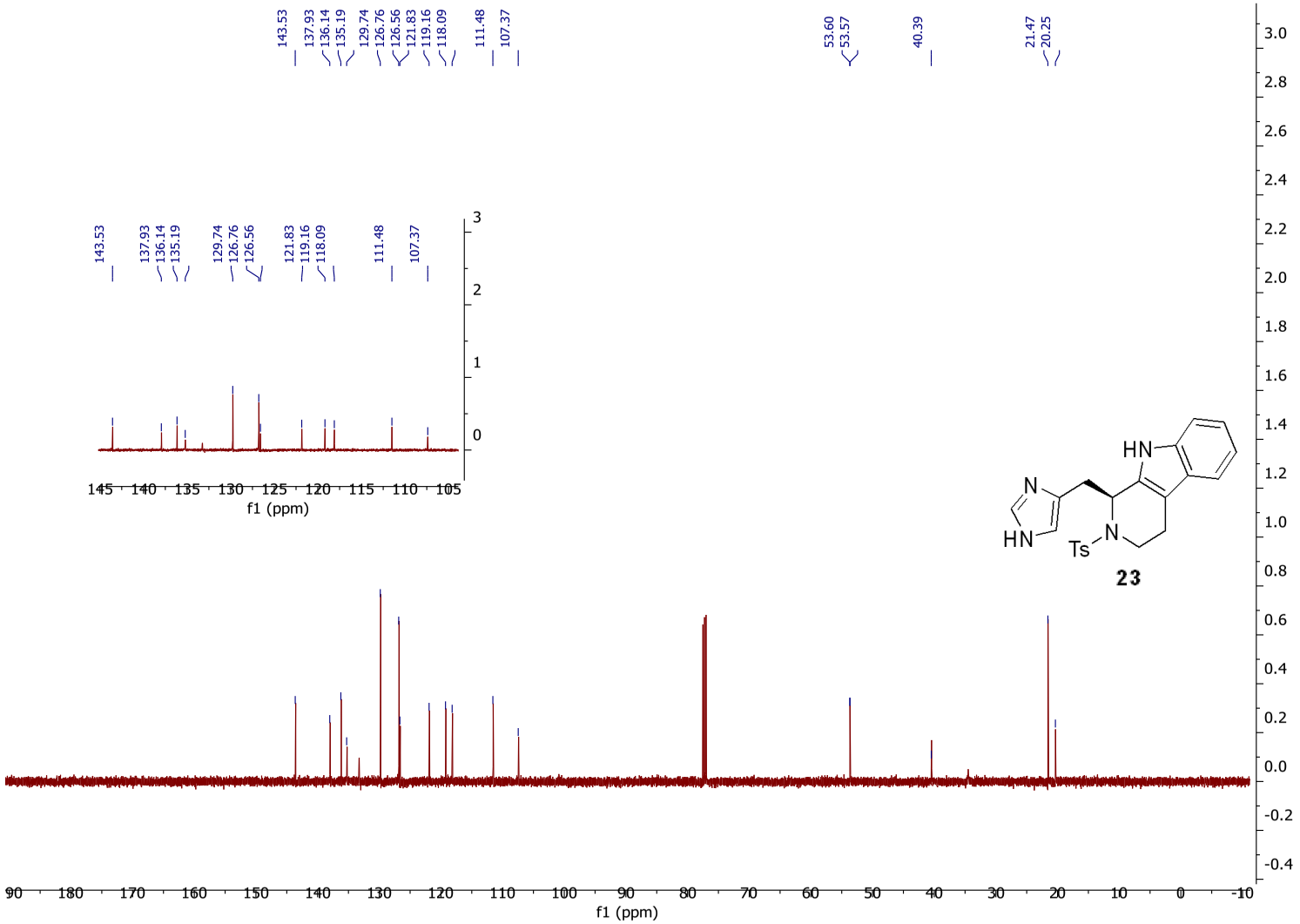
Bi-phenyl imidazole (0.1 g, 0.45 mmol) was dissolved in EtOH (2.5 mL) and then was added to the cooled solution of para methoxy tetrafluoro diazonium salt (0.1 g, 0.45 mmol) in water (25 mL). The reaction mixture was stirred at room temperature for 18 hours. Solution turned into red solid precipitation. Filtered the solid compound through sintered glass funnel and washed with cold water. The residue was purified by flash chromatography (silica gel, EtOAc/Hexanes = 40:60) to furnish **195** (0.06 g, 37%) as a yellow crystalline solid: m.p. = 160-162 °C. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.94 (d, *J* = 9.0 Hz, 2H), 7.62 (s, 5H), 7.35 (d, *J* = 8.0 Hz, 5H), 6.99 (d, *J* = 9.0 Hz, 2H), 3.88 (s, 3H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 162.9, 153.8, 146.7, 128.7, 128.0, 125.3, 114.6, 55.7. FT-IR (neat, cm^{-1}): 2953, 1730, 1676, 1595, 1458, 1376, 1253, 1180, 1081, 1018, 967, 839, 720, 610, 550. HR-MS (*m/z*): calcd. for $[M+H]^+$ $C_{22}H_{19}N_4O$ 354.1515 found 354.1509

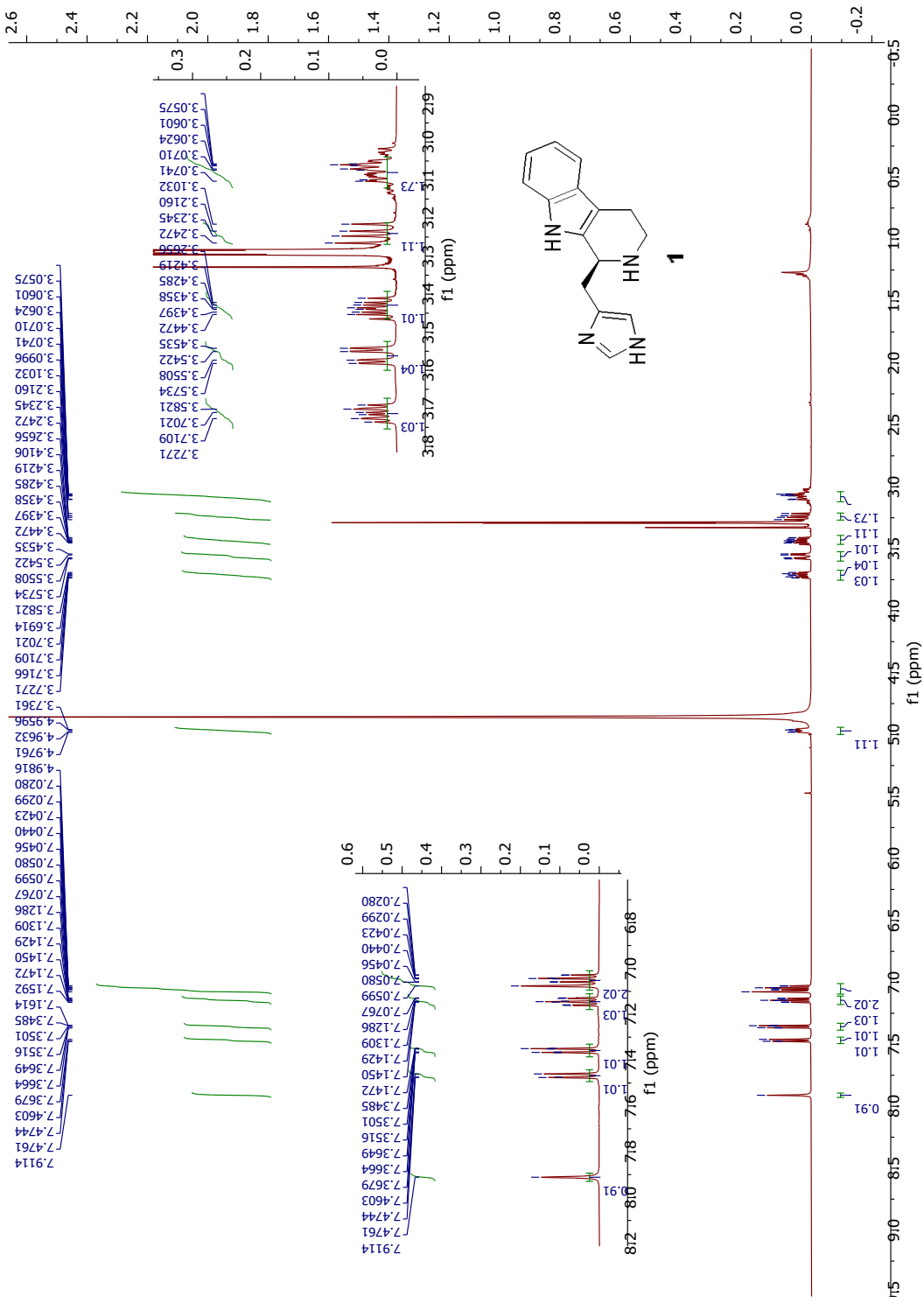
Synthesis of (E)-2-((4-nitrophenyl) diazenyl)-4,5-diphenyl-1H-imidazole (196):

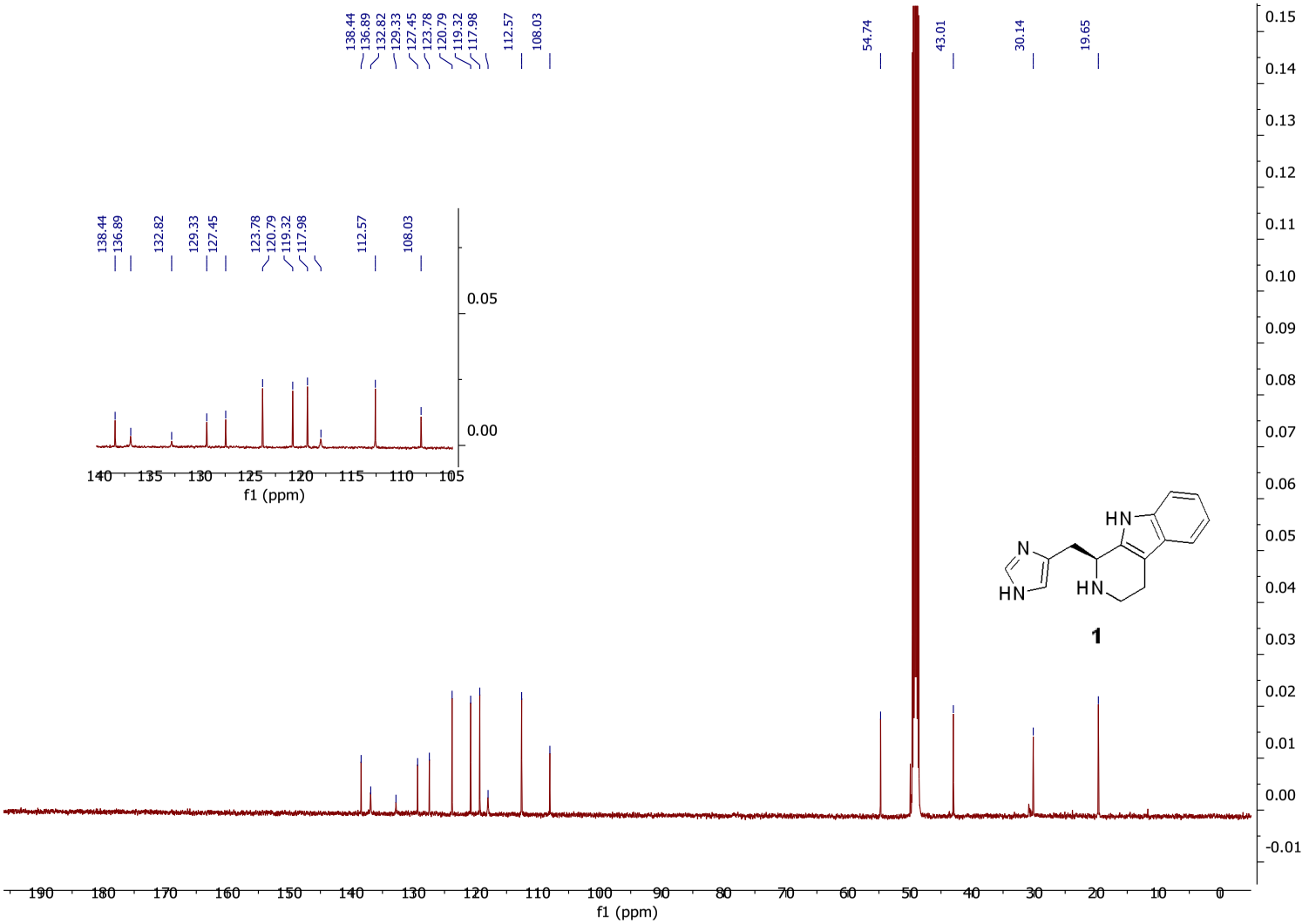


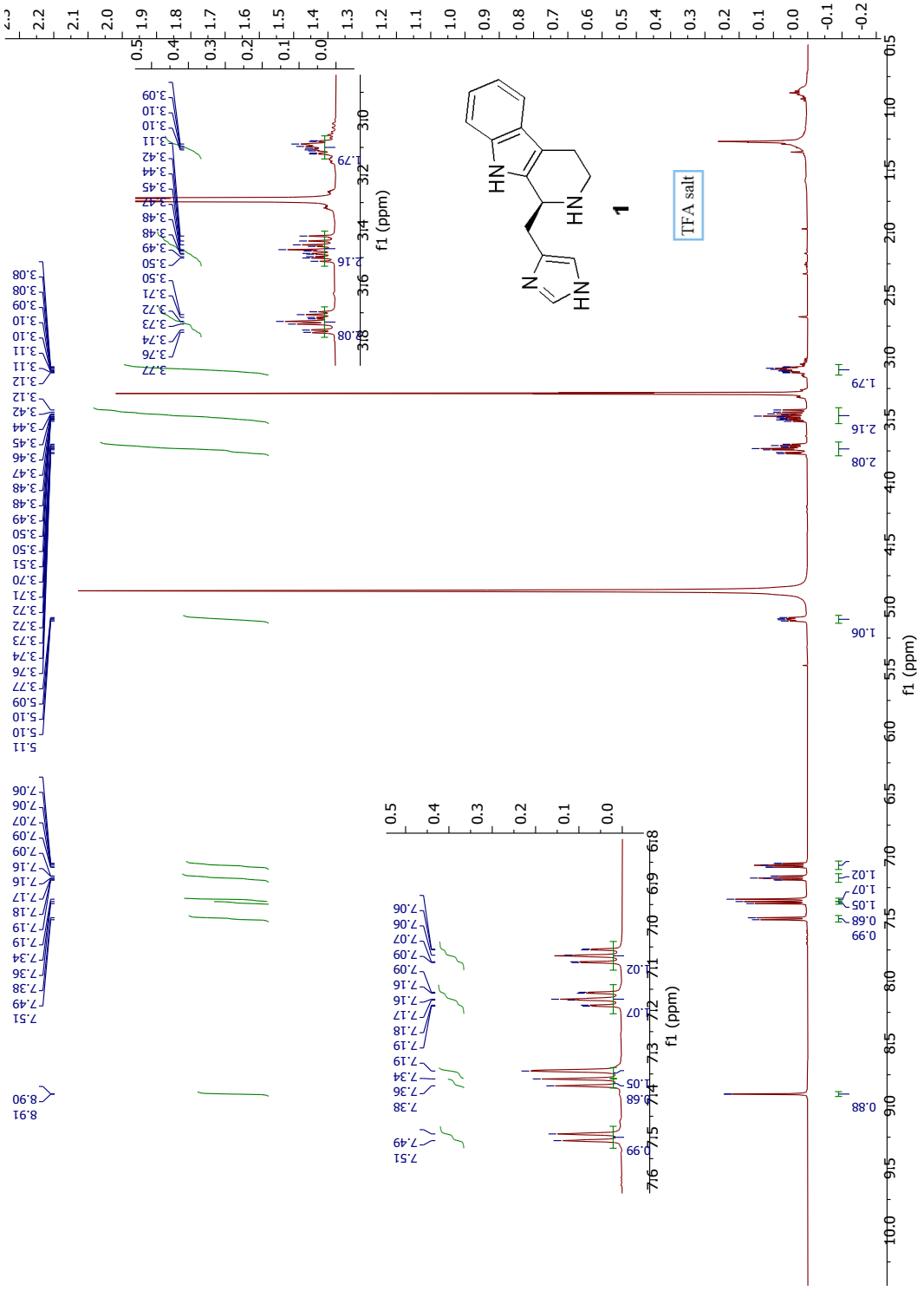
Bi-phenyl imidazole (0.1 g, 0.45 mmol) was dissolved in EtOH (2.5 mL) and then was added to the cooled solution of para nitro tetrafluoro diazonium salt (0.1 g, 0.45 mmol) in water (25 mL). The reaction mixture was stirred at room temperature for 18 hours. Solution turned into red solid precipitation. Filtered the solid compound through sintered glass funnel and washed with cold water. The residue was purified by flash chromatography (silica gel, EtOAc/Hexanes = 60:40) to furnish **196** (0.05 g, 30%) as a yellow crystalline solid: m.p. = 178-180 °C. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.27 (d, *J* = 9.0 Hz, 2H), 7.91 (d, *J* = 8.9 Hz, 2H), 7.61 (s, 4H), 7.35 (s, 6H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 155.4, 153.7, 148.7, 128.2, 124.9, 123.5. FT-IR (neat, cm^{-1}): 2922, 1603, 1585, 1513, 1466, 1431, 1395, 1219, 1140, 1097, 856, 793, 763, 724, 609, 539, 488, 460. HR-MS (*m/z*): calcd. for $[M+H]^+$ $C_{21}H_{16}N_5O_2$ 370.1280 found 370.1273

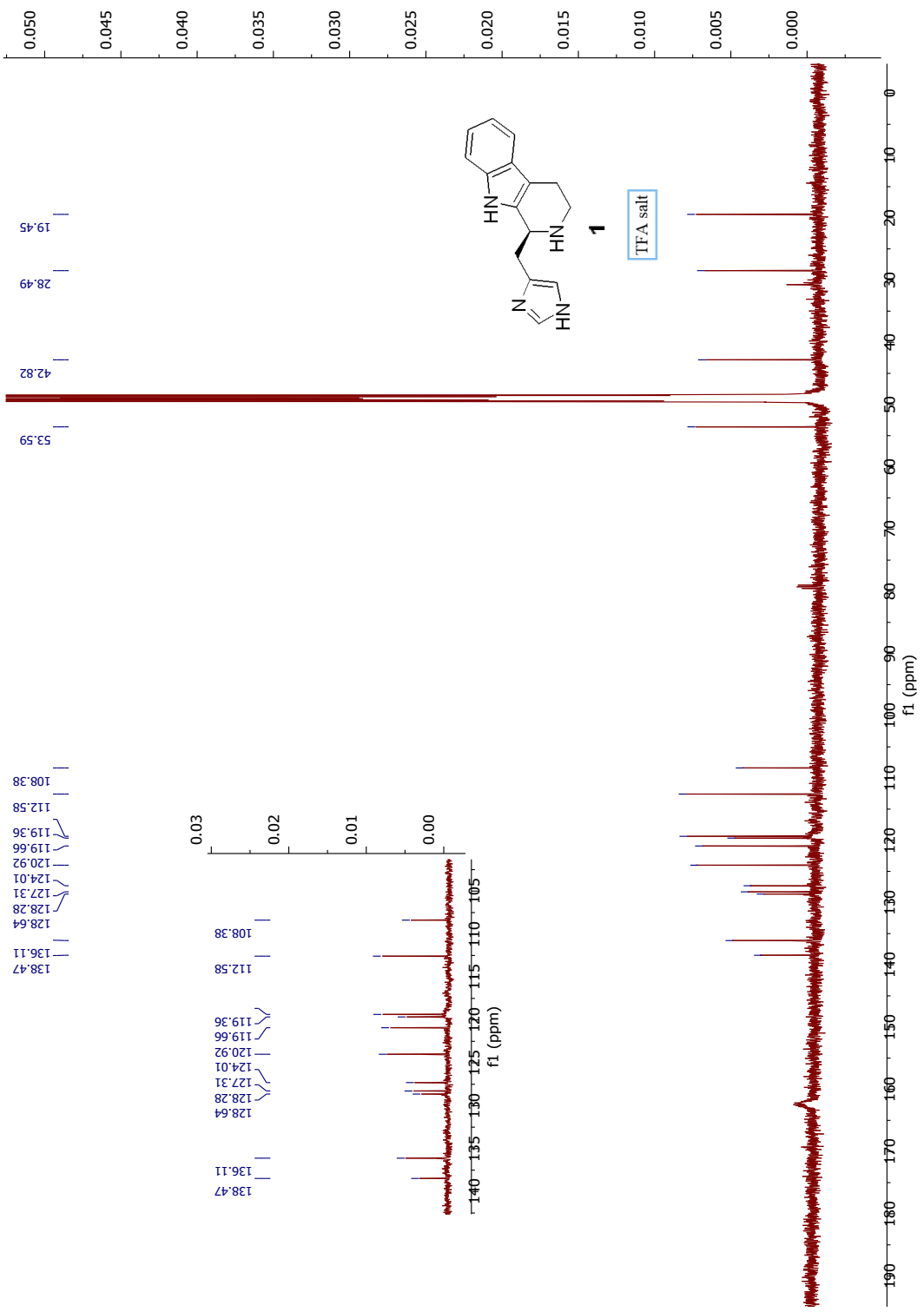

10.07
10.06
7.66
7.65
7.63
7.58
7.56
7.32
7.31
7.29
7.27
7.11
7.09
7.09
7.08
7.06
7.04
7.03
7.01
7.00
6.86
5.42
5.40
5.39
4.17
4.16
4.14
4.13
3.40
3.40
3.38
3.37
3.37
3.35
3.34
3.29
3.26
3.24
3.23
3.22
3.20
2.54
2.53
2.51
2.50
2.40
2.39
2.38
2.37
2.37
2.34
2.33
2.32
f1 (ppm)
HN
N
HN
N
Ts
23

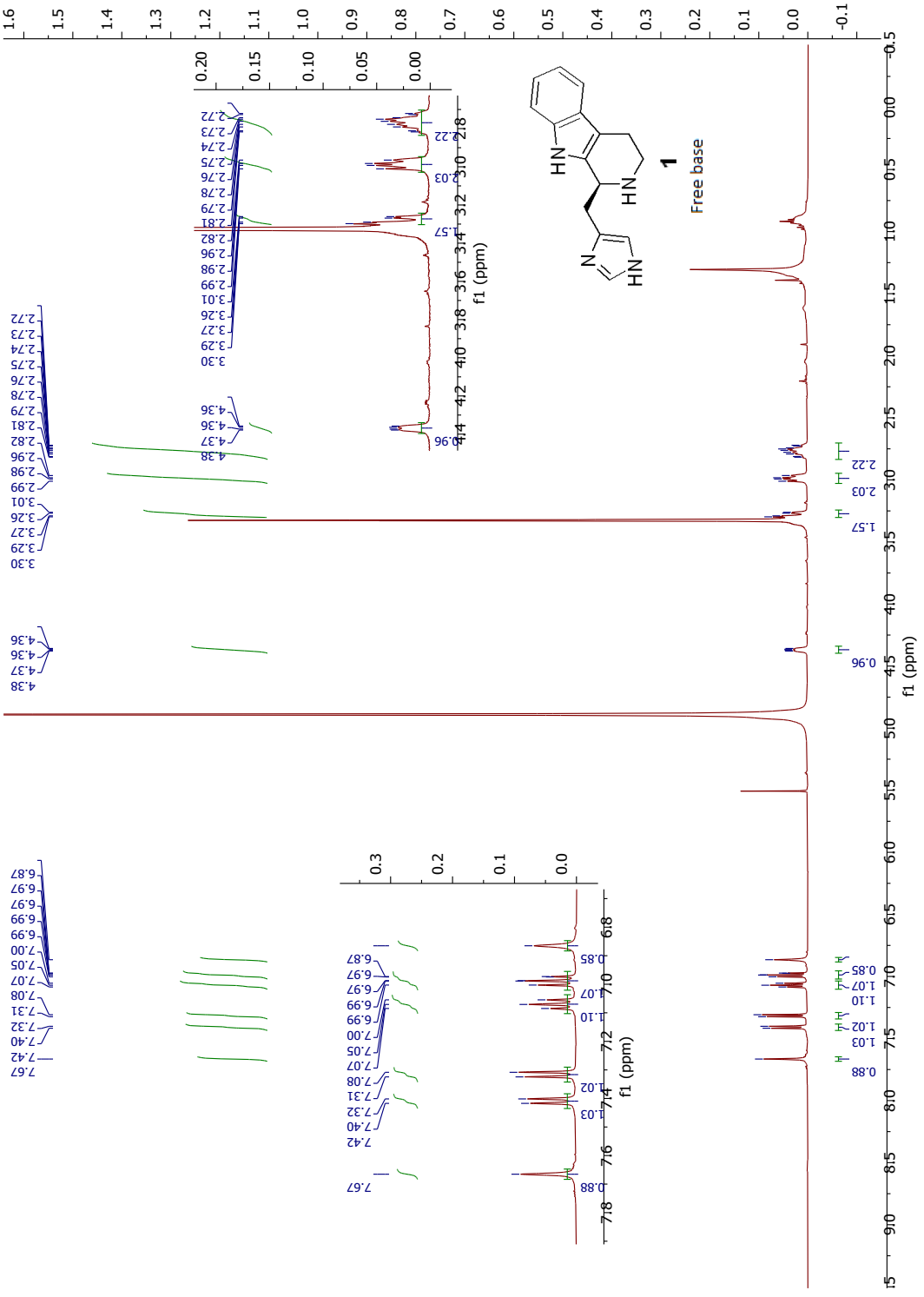

143.53
137.93
136.14
135.19
129.74
126.76
126.56
121.83
119.16
118.09
111.48
107.37
53.60
53.57
40.39
21.47
20.25
f1 (ppm)
HN
N
HN
N
Ts
23

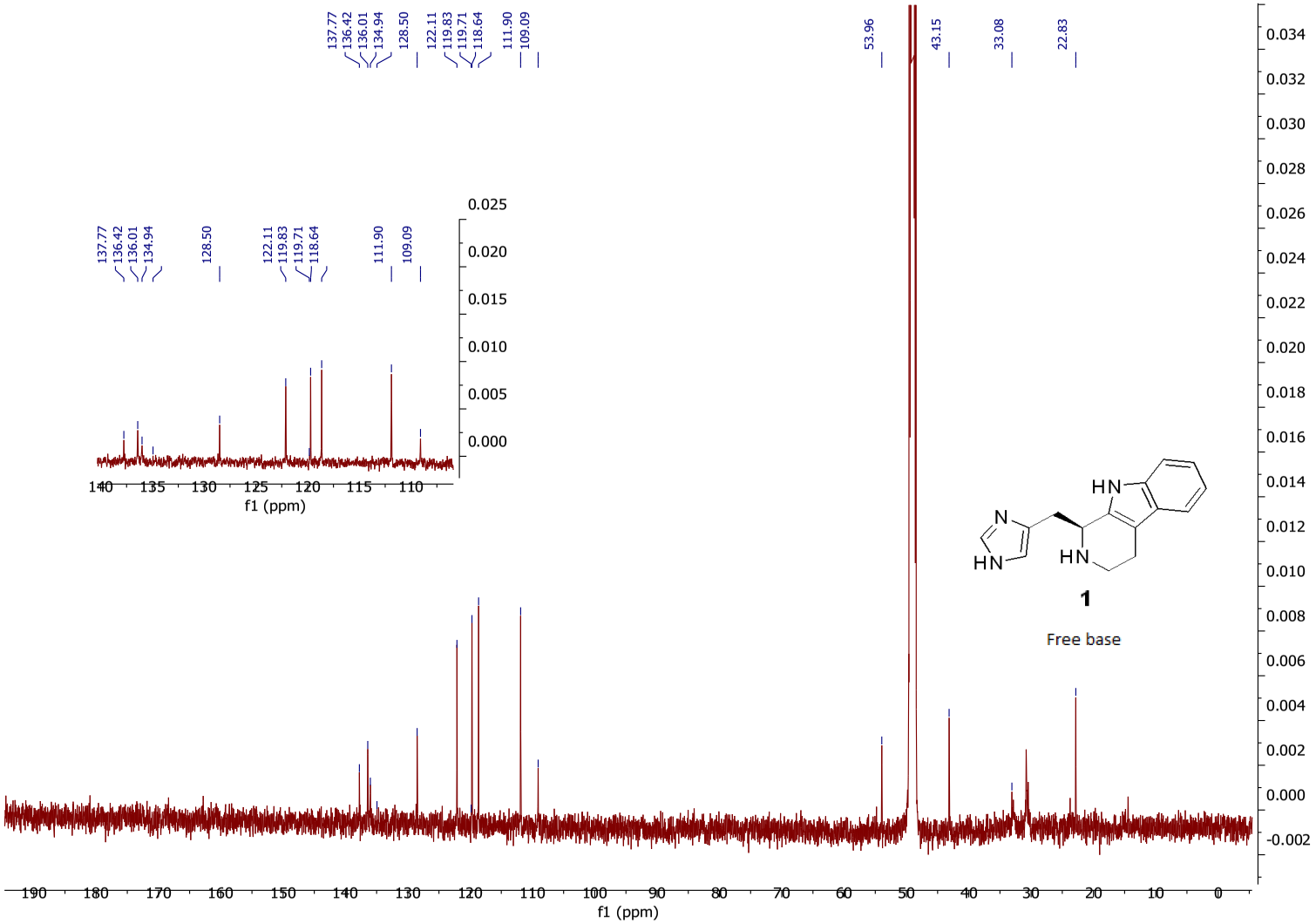

1
f1 (ppm)

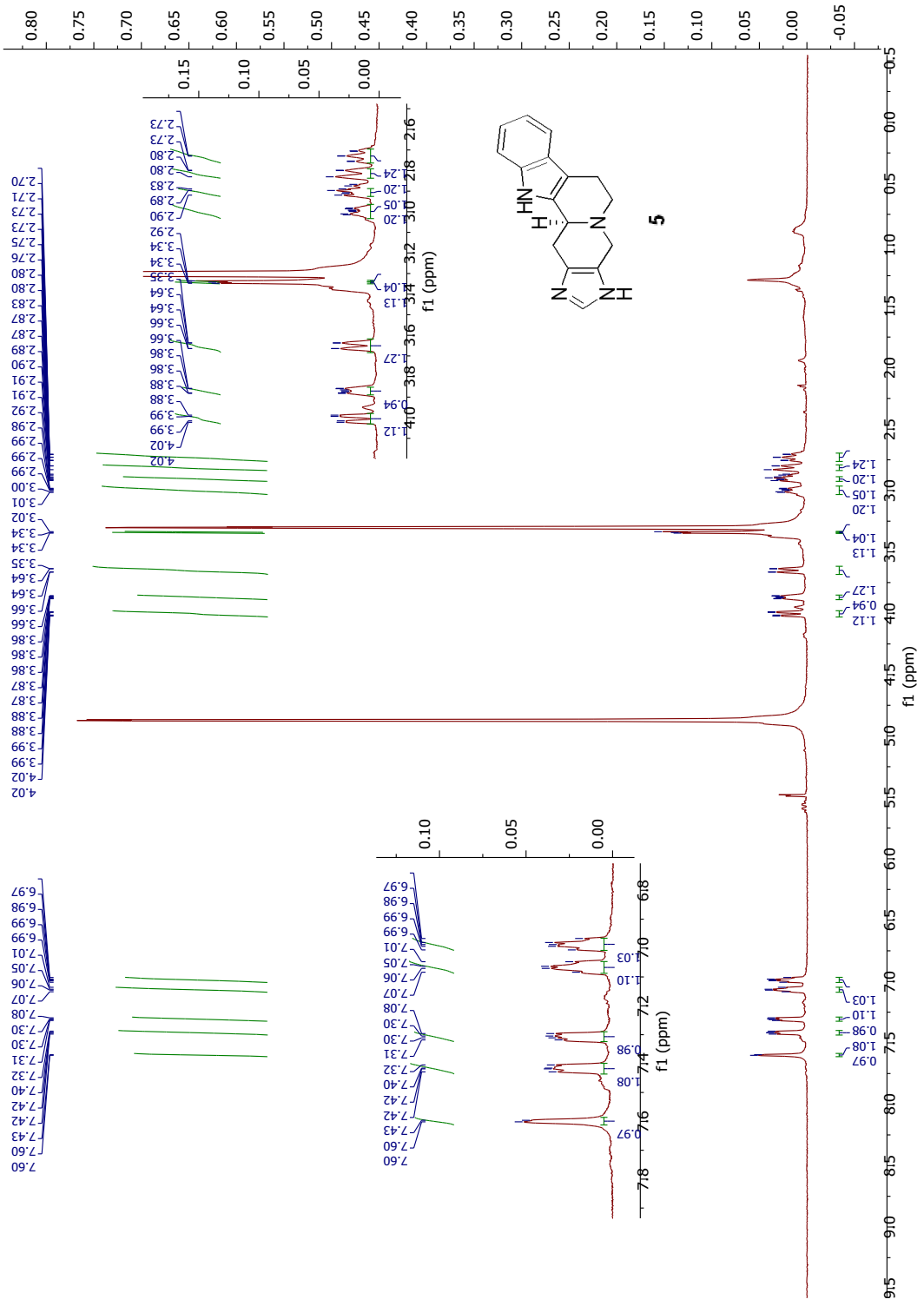

138.44
136.89
132.82
129.33
127.45
123.78
120.79
119.32
117.98
112.57
108.03
54.74
43.01
30.14
19.65
0.15
0.14
0.13
0.12
0.11
0.10
0.09
0.08
0.07
0.06
0.05
0.04
0.03
0.02
0.01
0.00
-0.01
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)
0.05
0.00
140 135 130 125 120 115 110 105
f1 (ppm)
HN
N
HN
HN
1

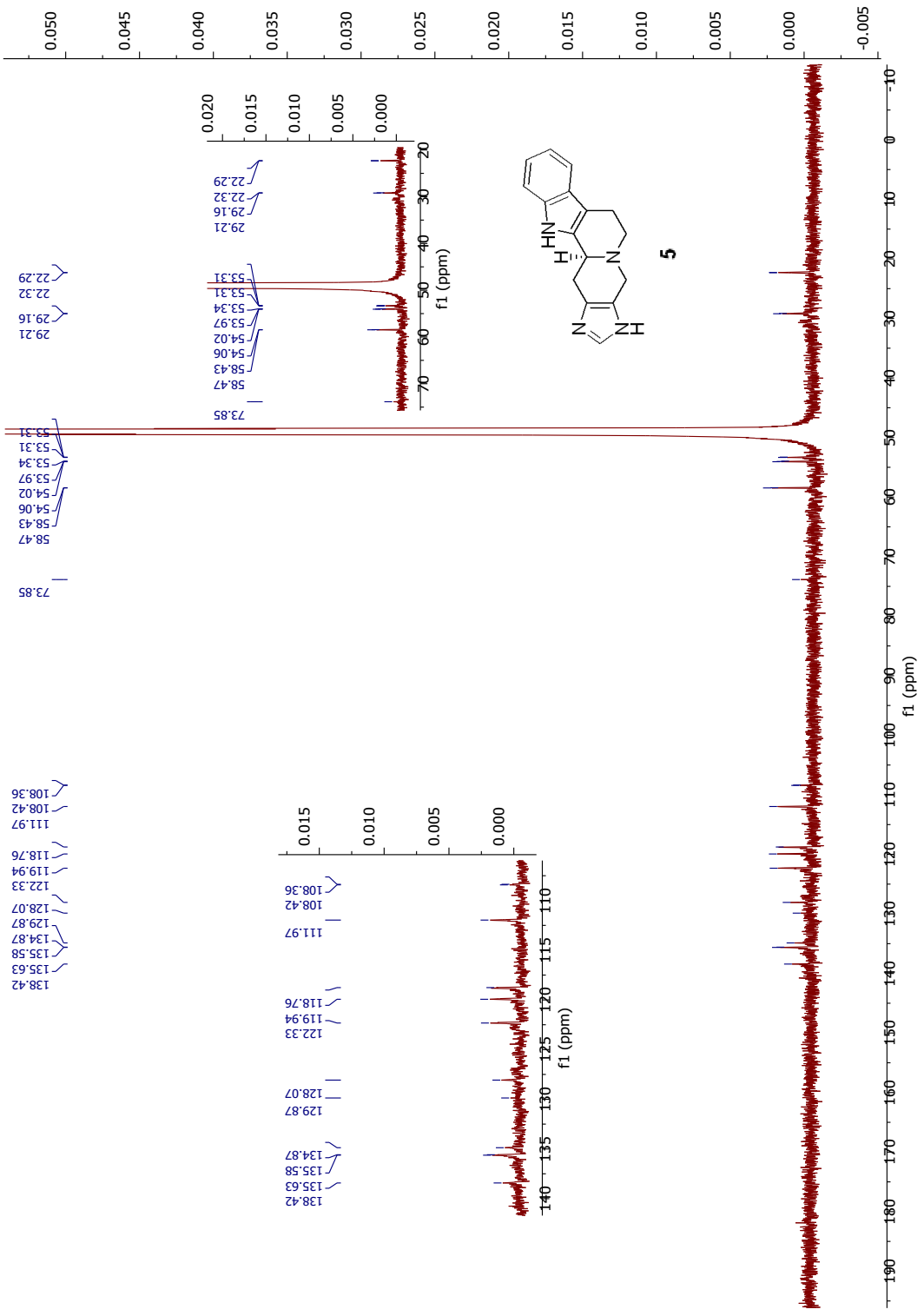

HN
HN
NH
N
1
TFA salt
f1 (ppm)

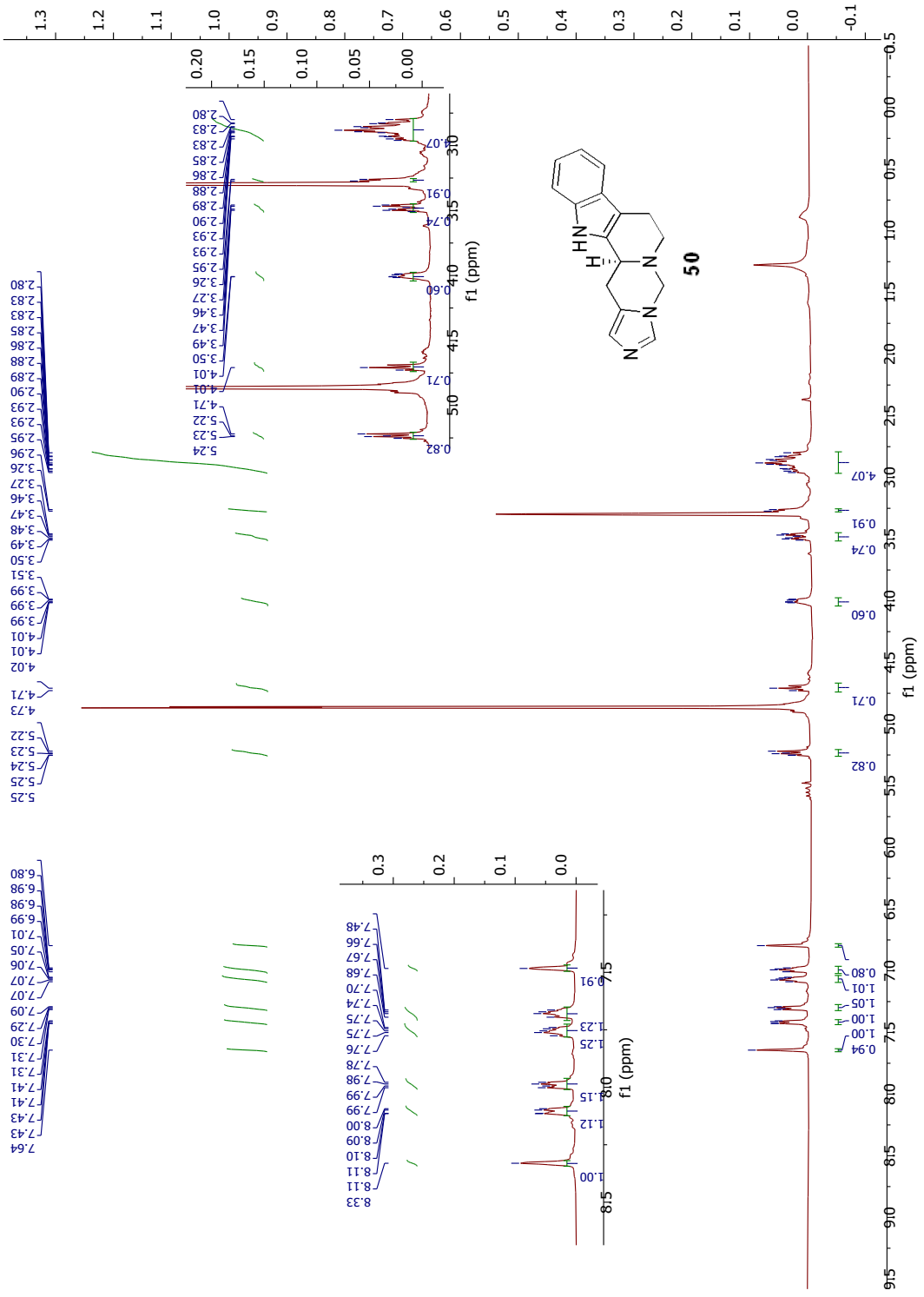

1
TFA salt
f1 (ppm)

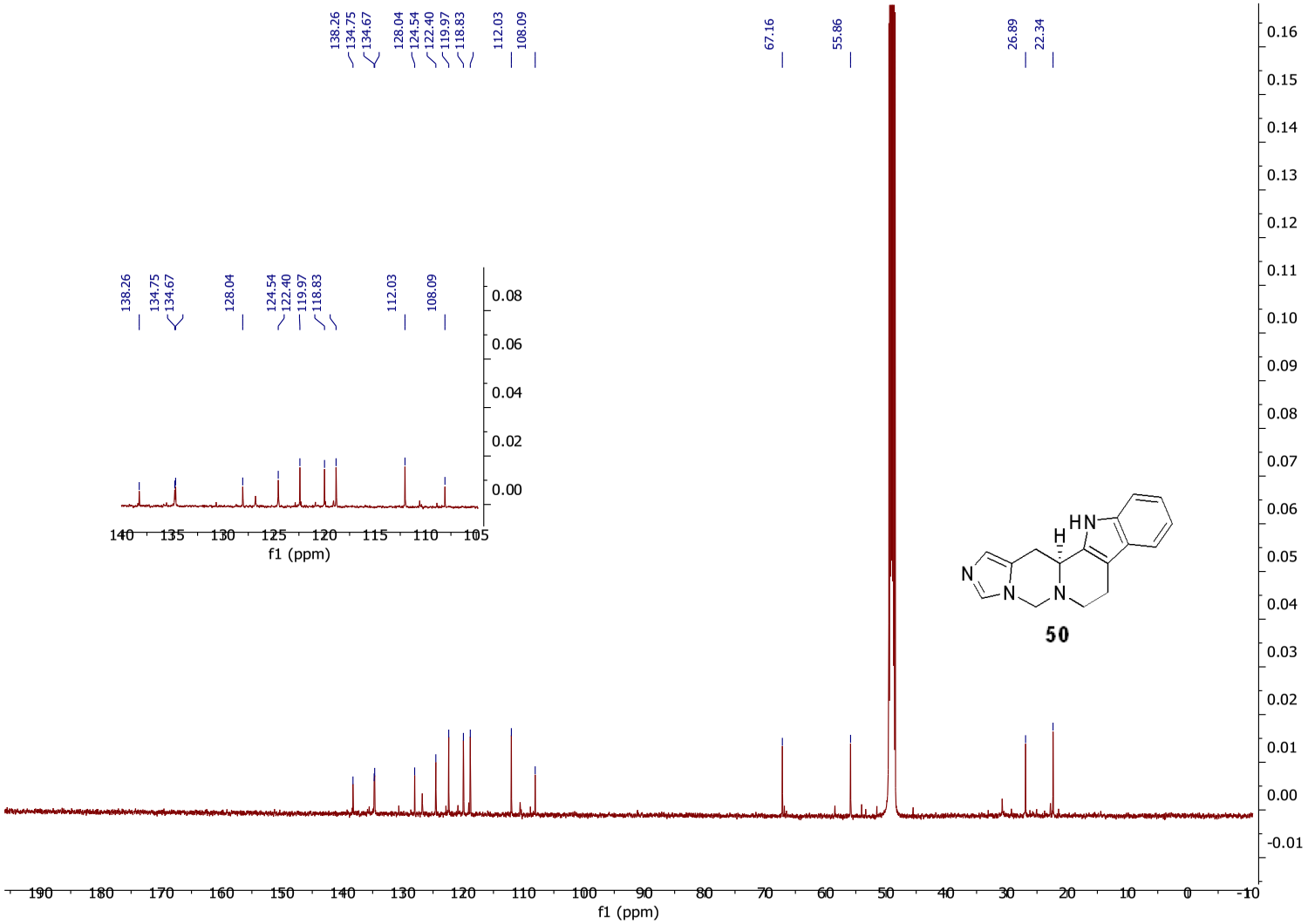

1
Free base
f1 (ppm)

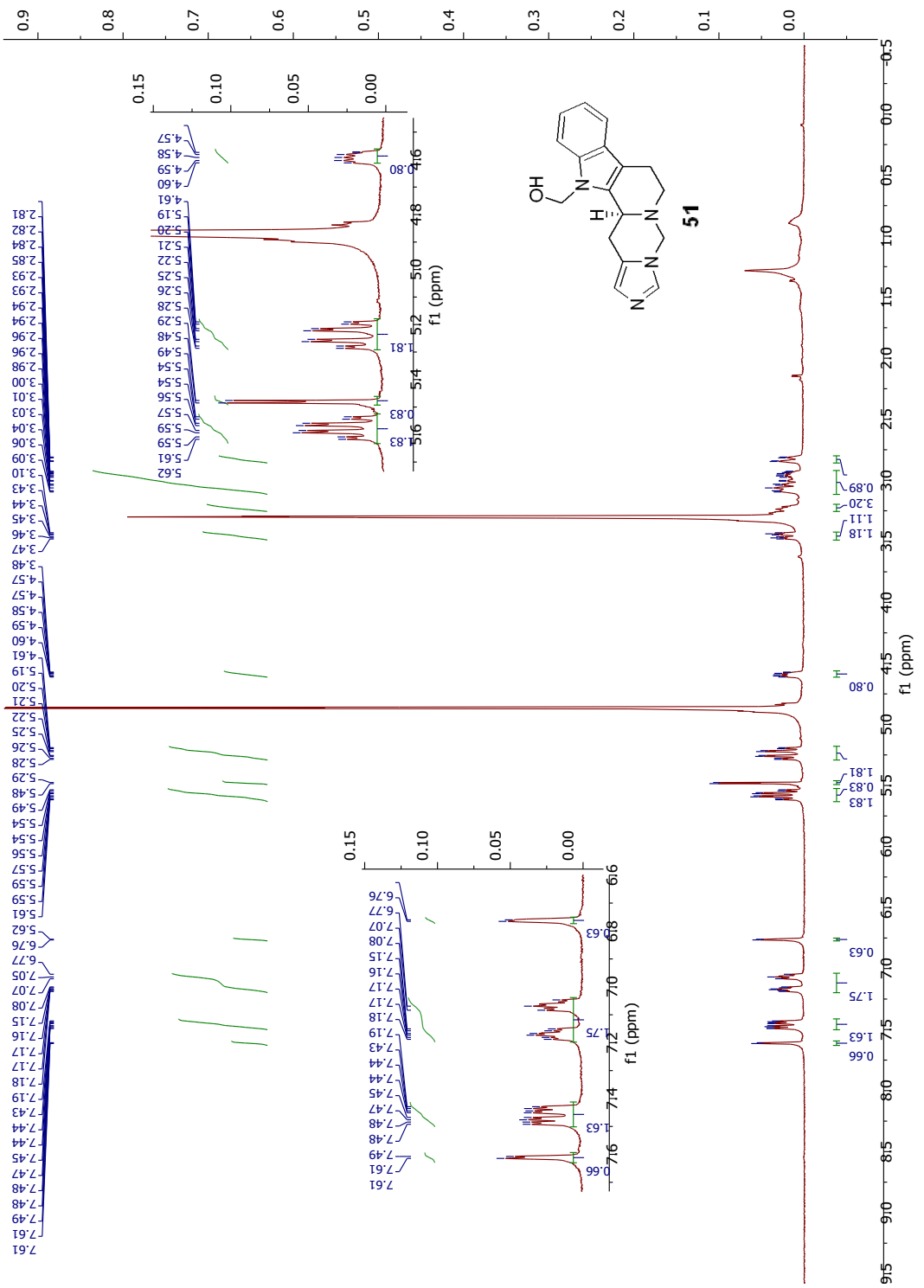

137.77
136.42
136.01
134.94
128.50
122.11
119.83
119.71
118.64
111.90
109.09
53.96
43.15
33.08
22.83
f1 (ppm)
HN
N
HN
HN
1
Free base

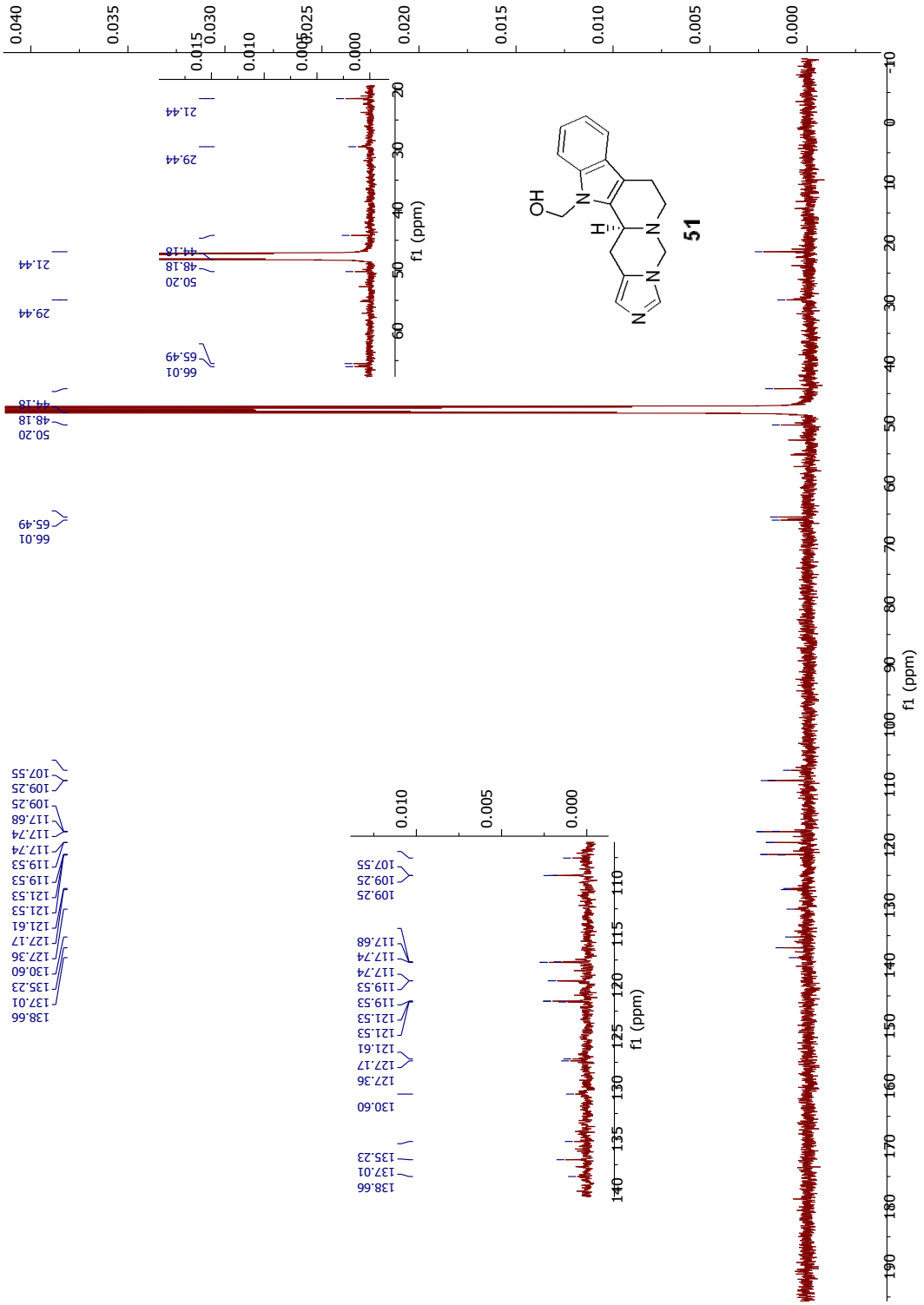

5
f1 (ppm)

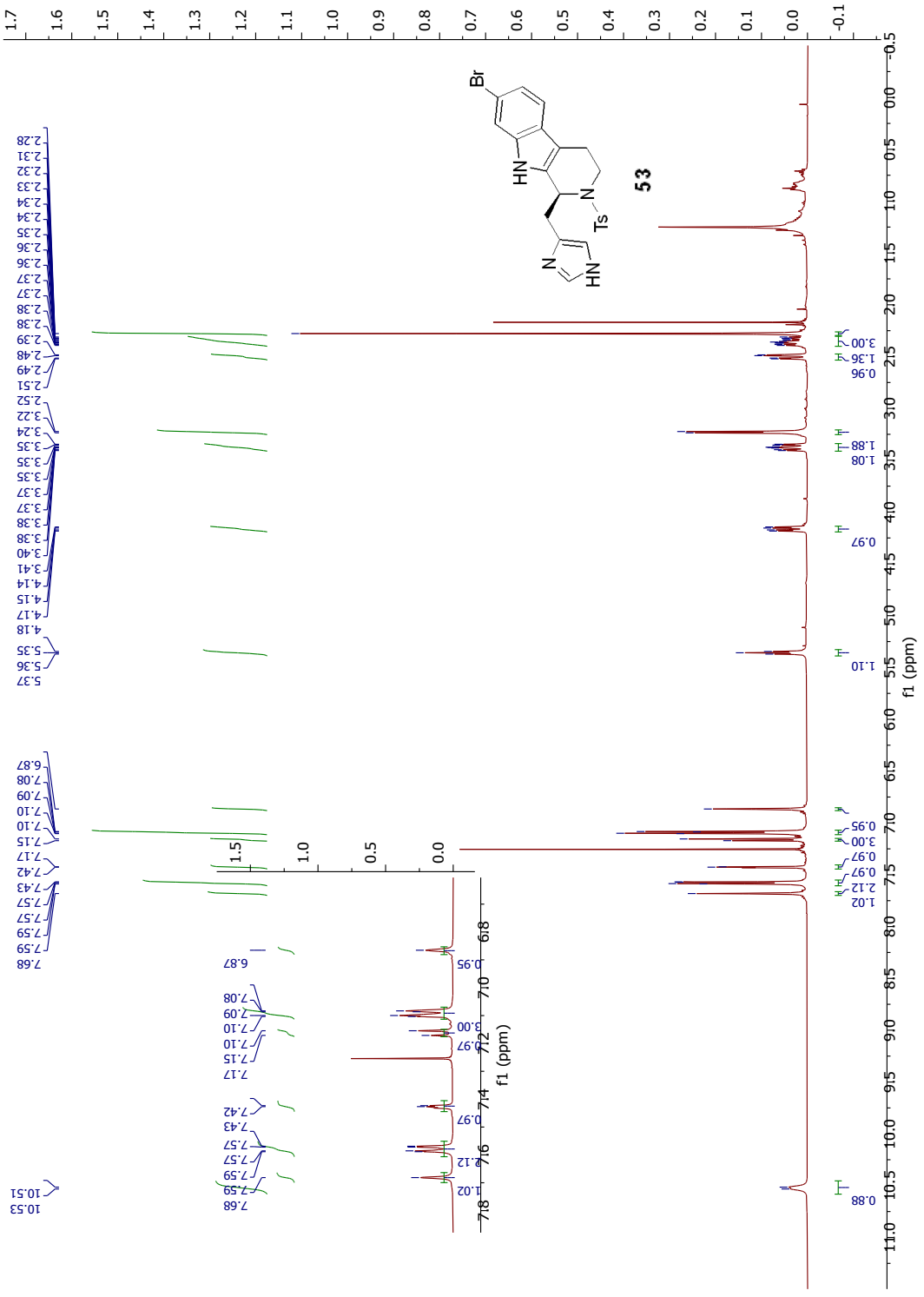

5
f1 (ppm)

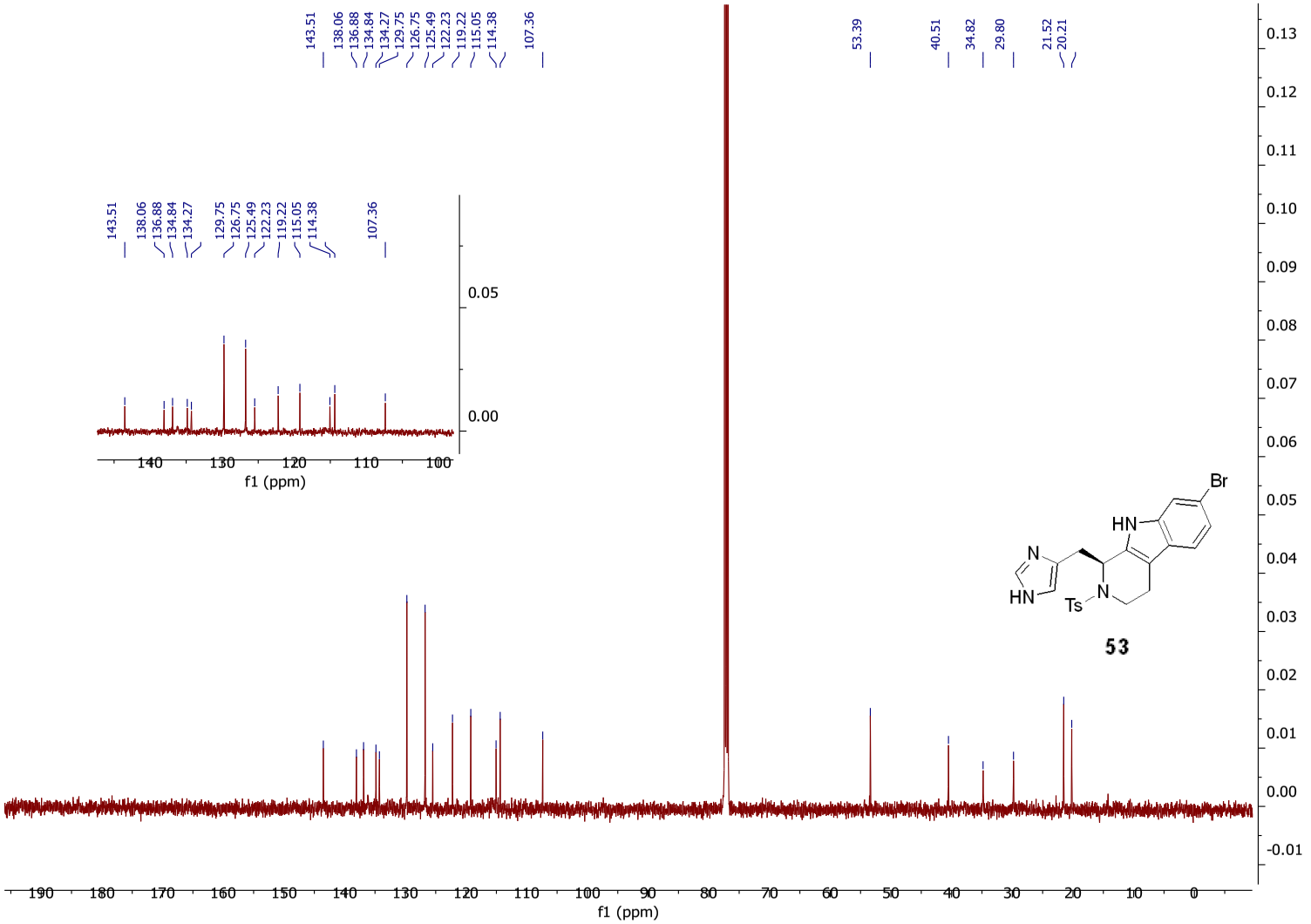

50
f1 (ppm)

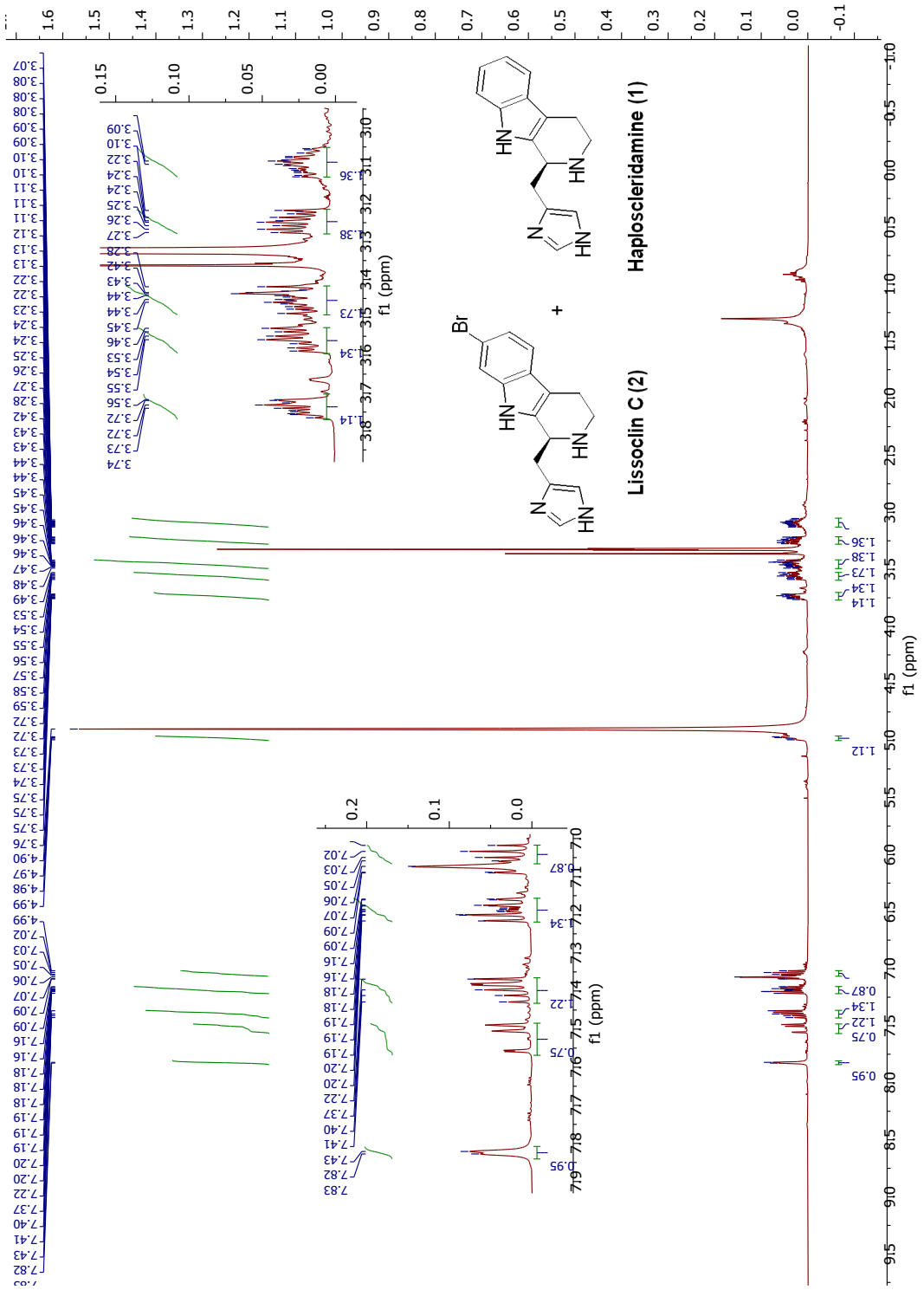

138.26
134.75
134.67
128.04
124.54
122.40
119.97
118.83
112.03
108.09
67.16
55.86
26.89
22.34
f1 (ppm)
HN
H
N
N
N
50

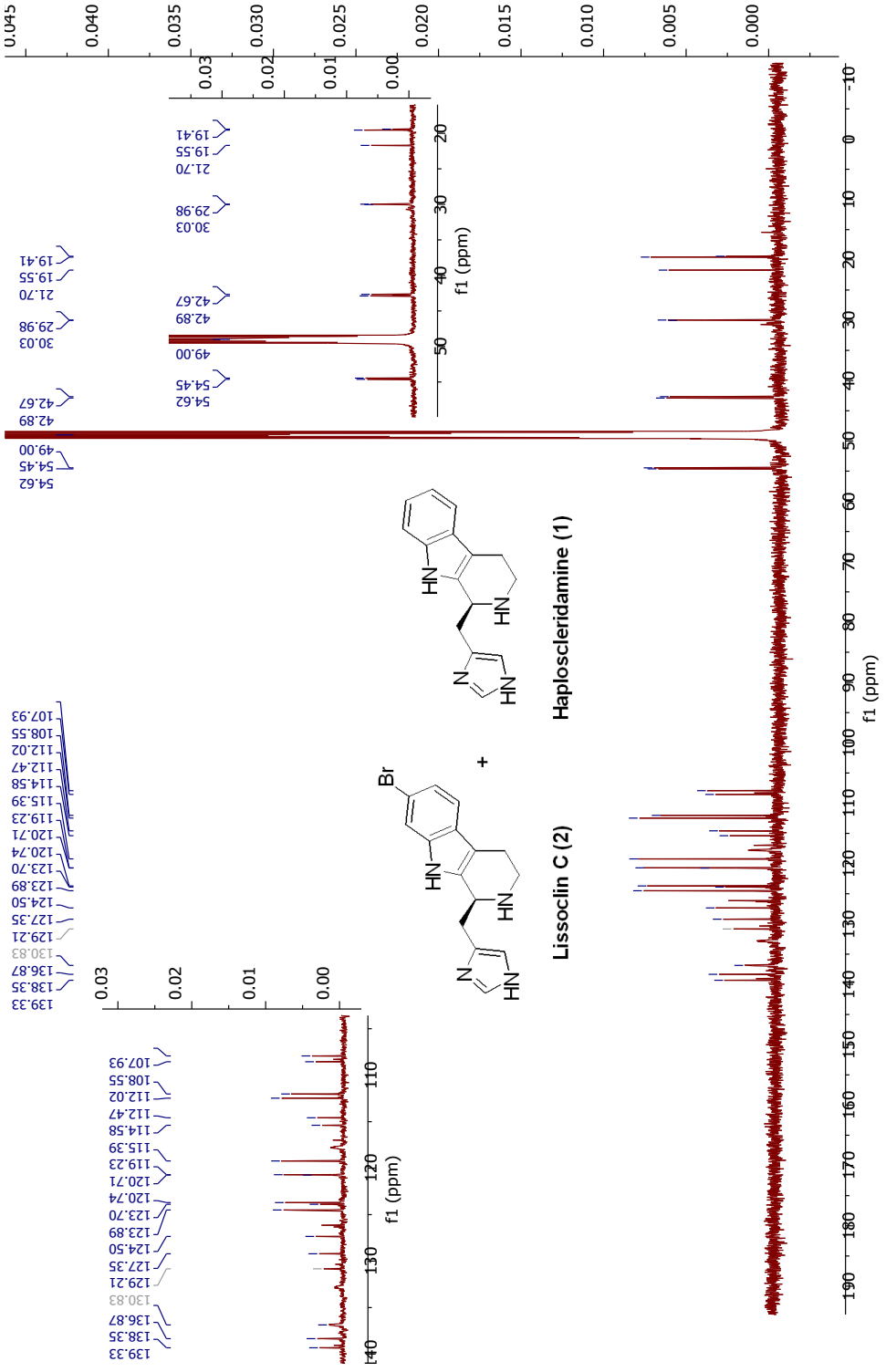

OH
N
H
N
N
N
51
f1 (ppm)

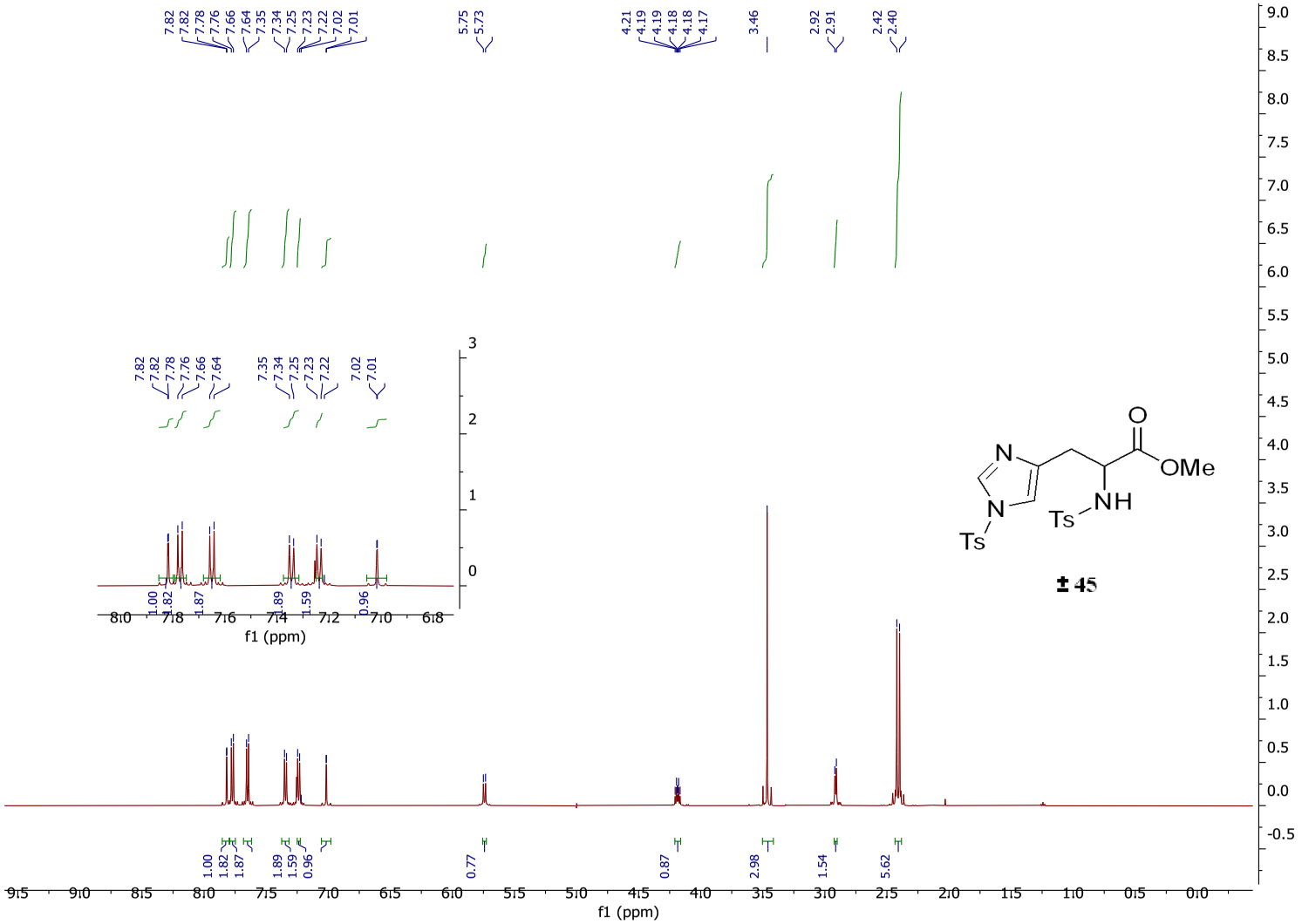

51
f1 (ppm)


Br
HN
N
Ts
N
HN
53
f1 (ppm)

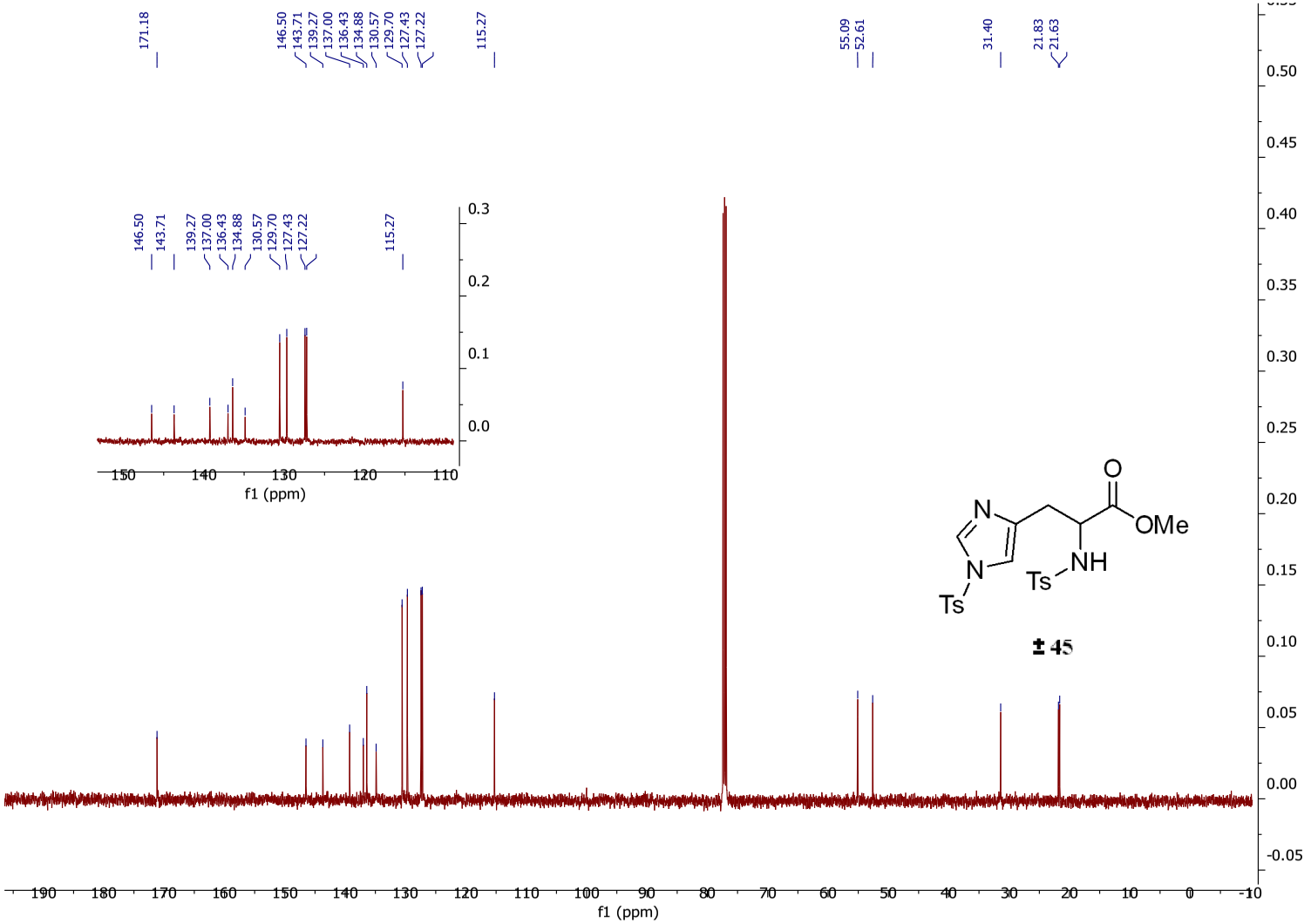

143.51
138.06
136.88
134.84
134.27
129.75
126.75
125.49
122.23
119.22
115.05
114.38
107.36
53.39
40.51
34.82
29.80
21.52
20.21
f1 (ppm)
Br
HN
N
HN
Ts
N
53

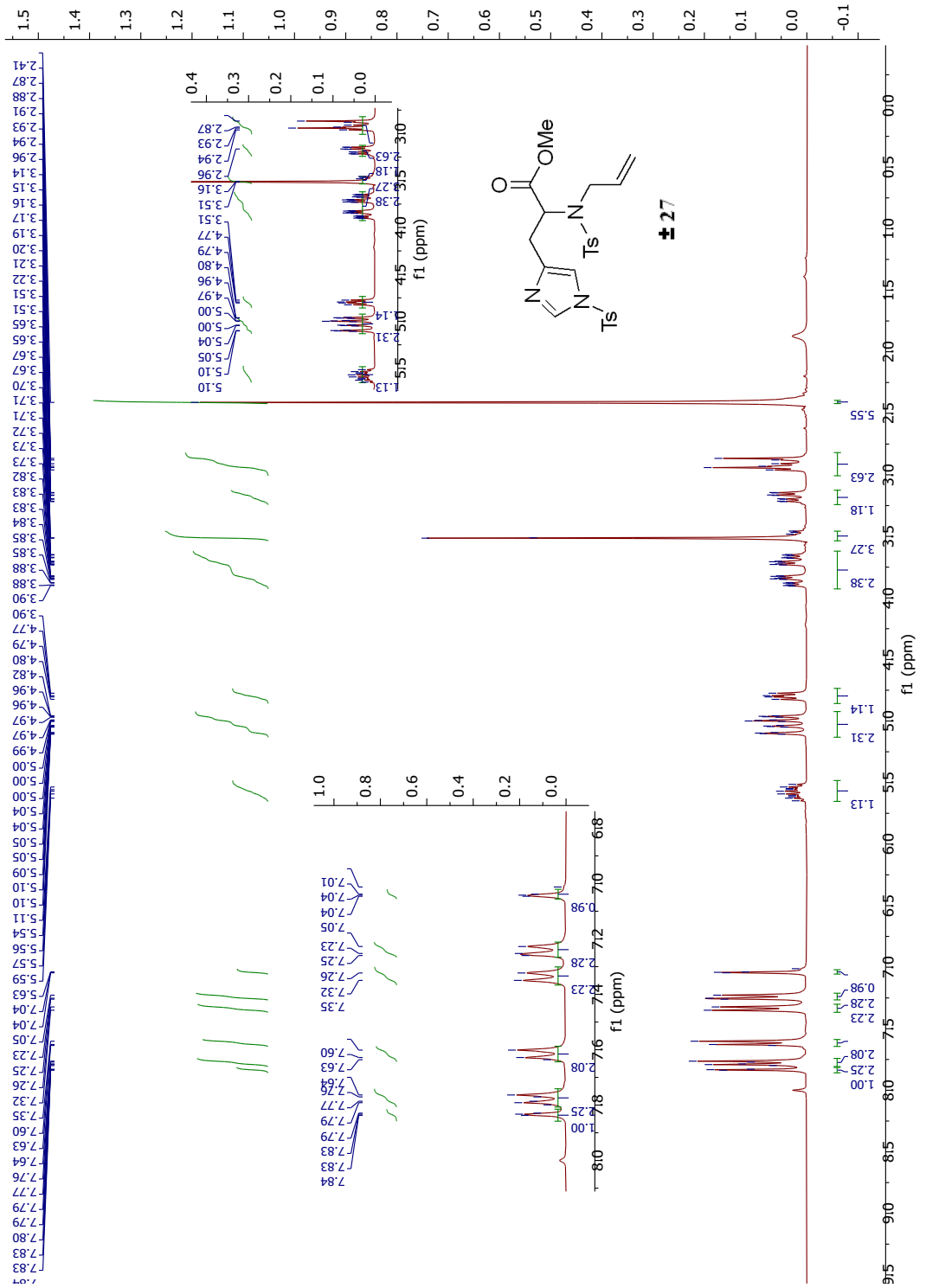

Haplosclerididamine (1)
Lissoclin C (2)
f1 (ppm)

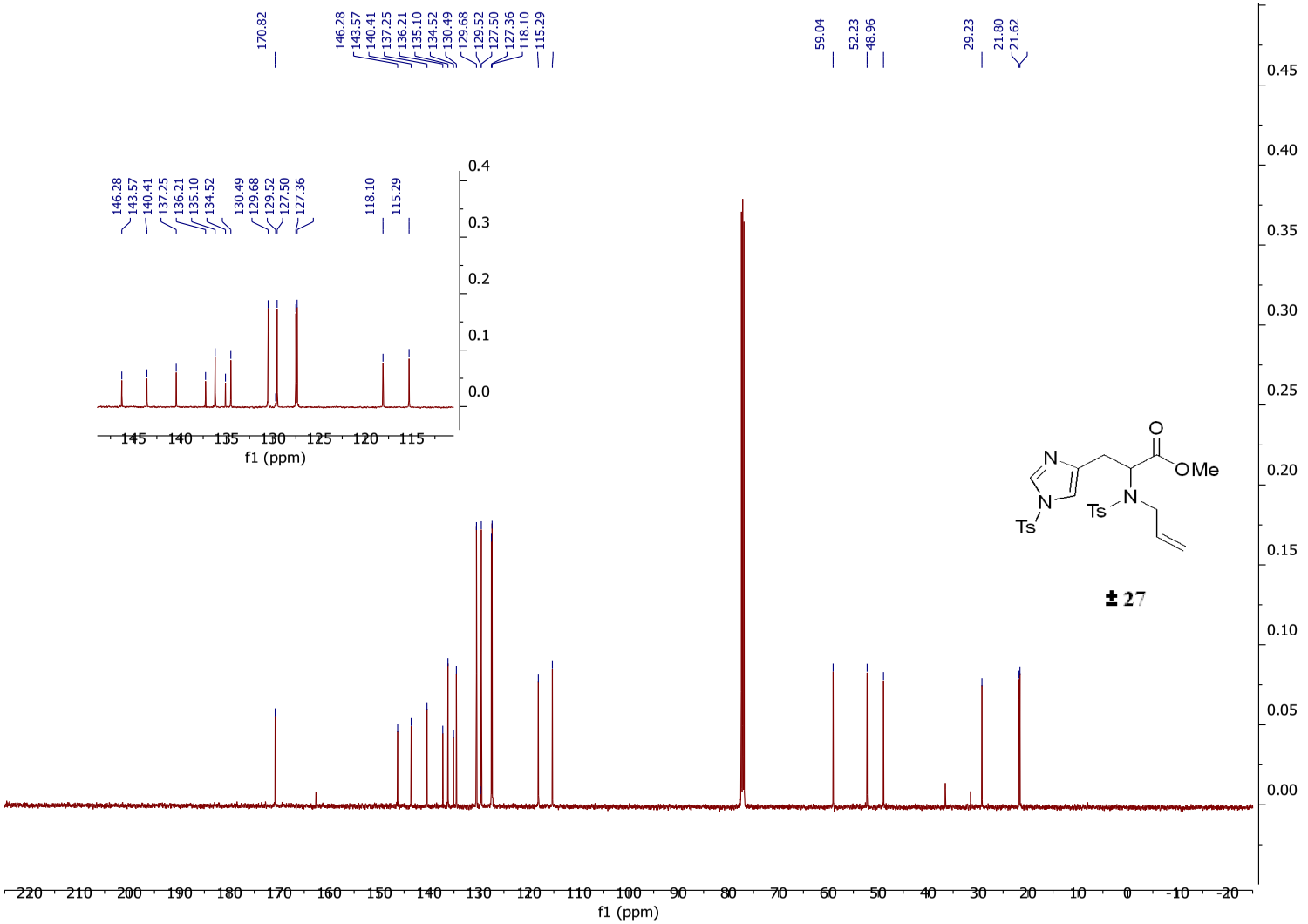

Haploscleridamine (1)
Lissoclin C (2)
+
Br
HN
NH
N
HN
f1 (ppm)


7.82
7.82
7.78
7.76
7.66
7.64
7.35
7.34
7.25
7.23
7.22
7.02
7.01
5.75
5.73
4.21
4.19
4.19
4.18
4.18
4.17
3.46
2.92
2.91
2.42
2.40
f1 (ppm)
1.00
1.82
1.87
1.89
1.59
0.96
0.77
0.87
2.98
1.54
5.62
N
O
OMe
NH
Ts
Ts

± 45


171.18
146.50
143.71
139.27
137.00
136.43
134.88
130.57
129.70
127.43
127.22
115.27
55.09
52.61
31.40
21.83
21.63
f1 (ppm)
N
N
Ts
NH
Ts
O
OMe
± 45


OMe
O
N
Ts
N
Ts
± 27
f1 (ppm)


170.82
146.28
143.57
140.41
137.25
136.21
135.10
134.52
130.49
129.68
129.52
127.50
127.36
118.10
115.29
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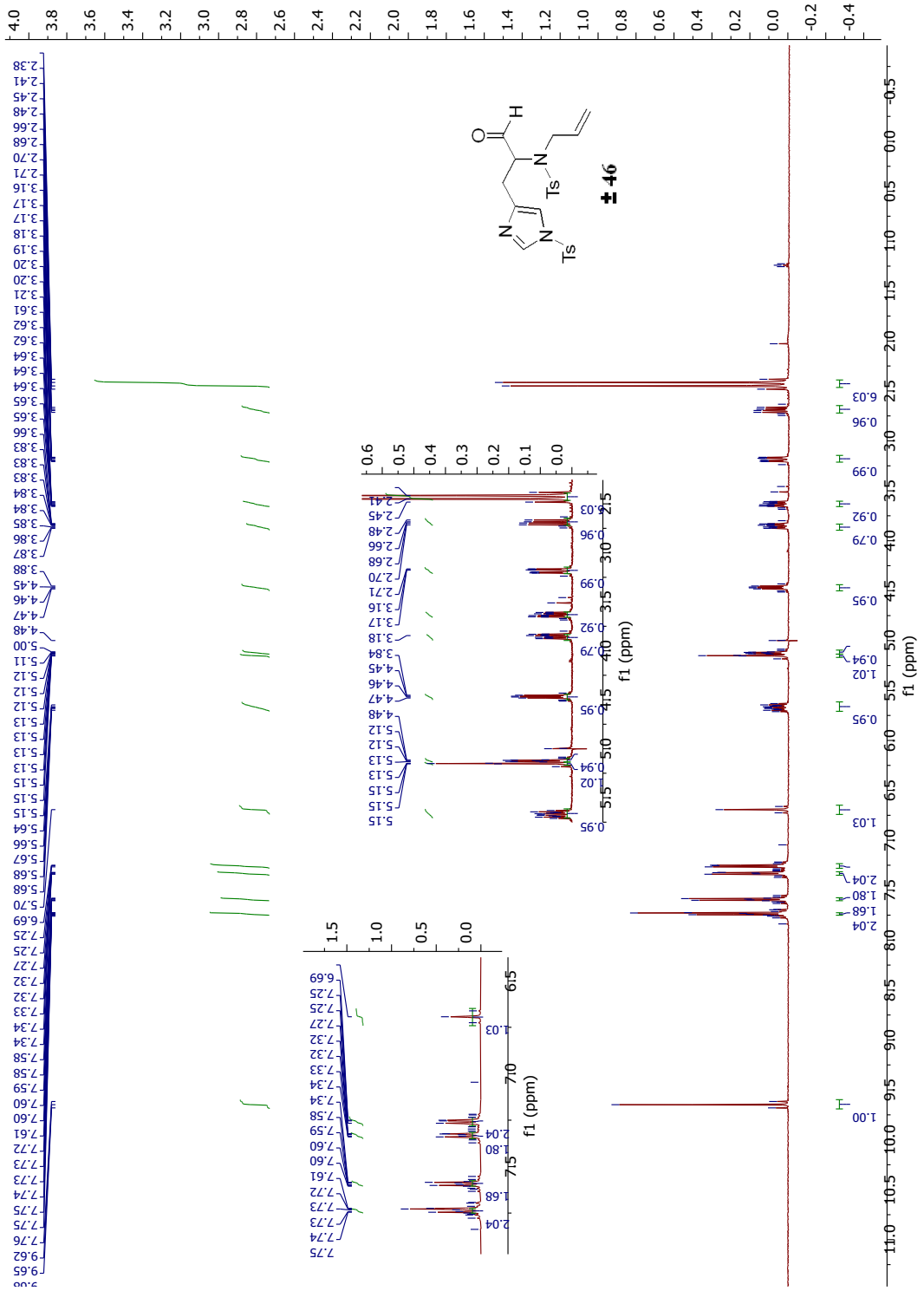
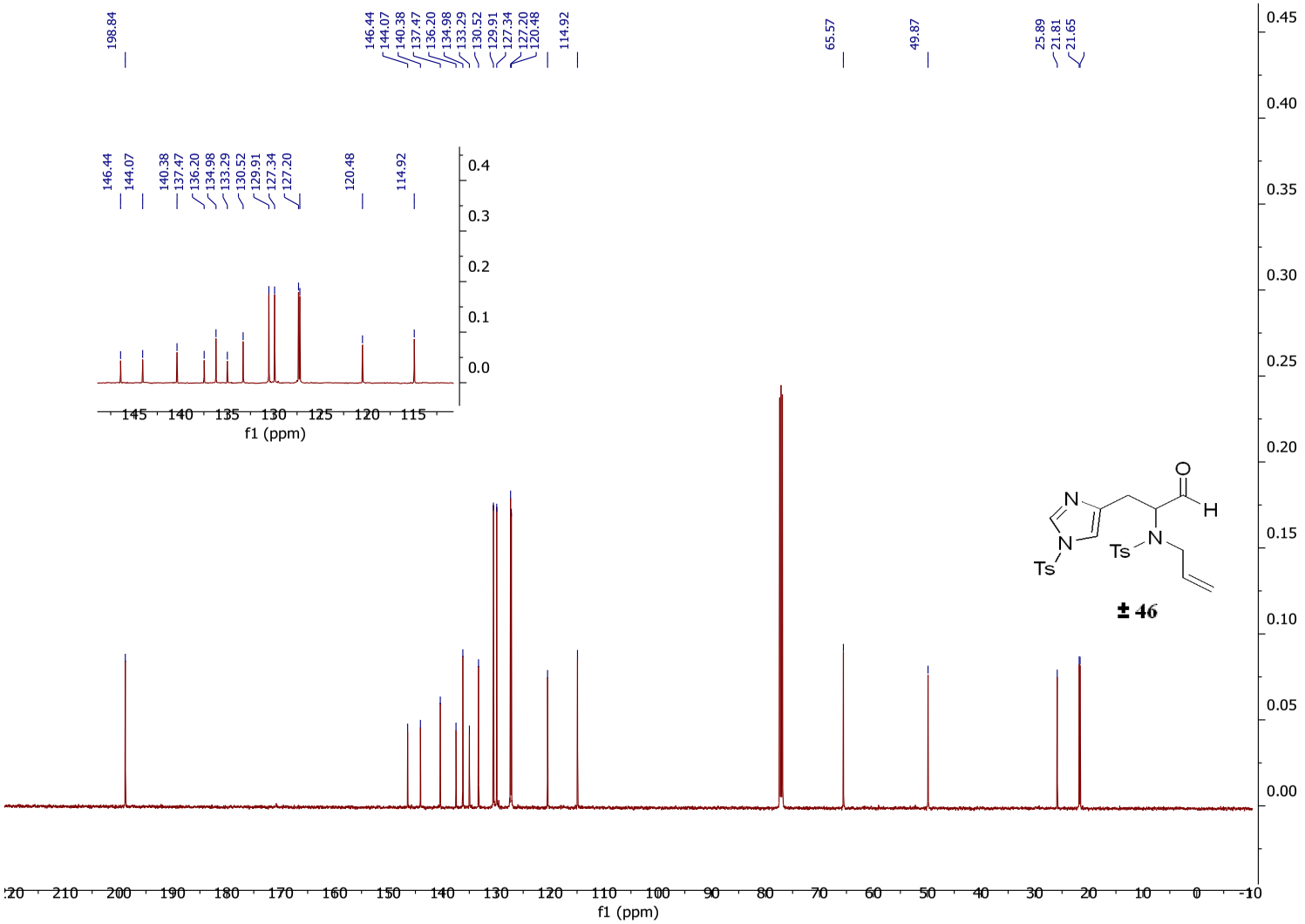
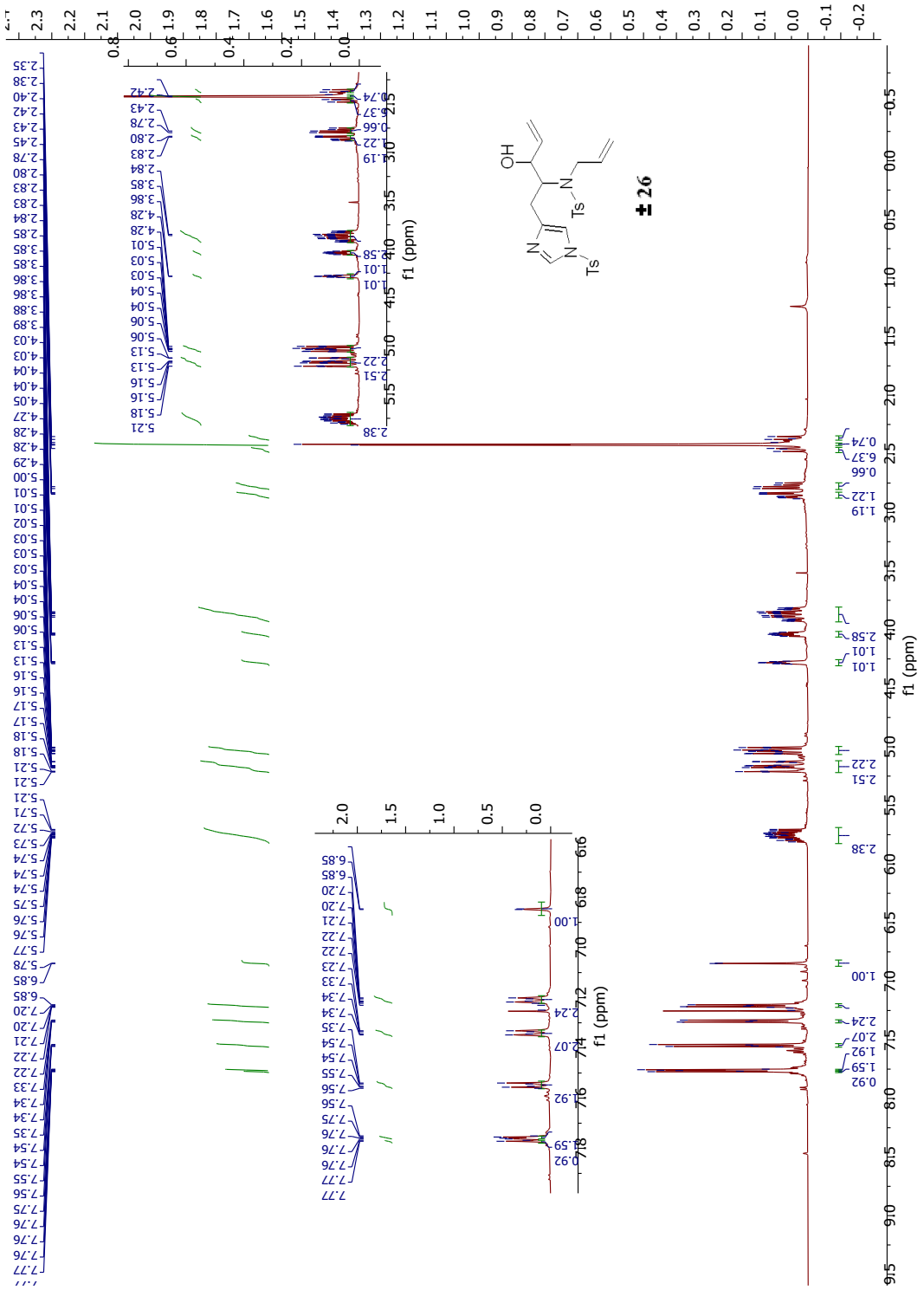
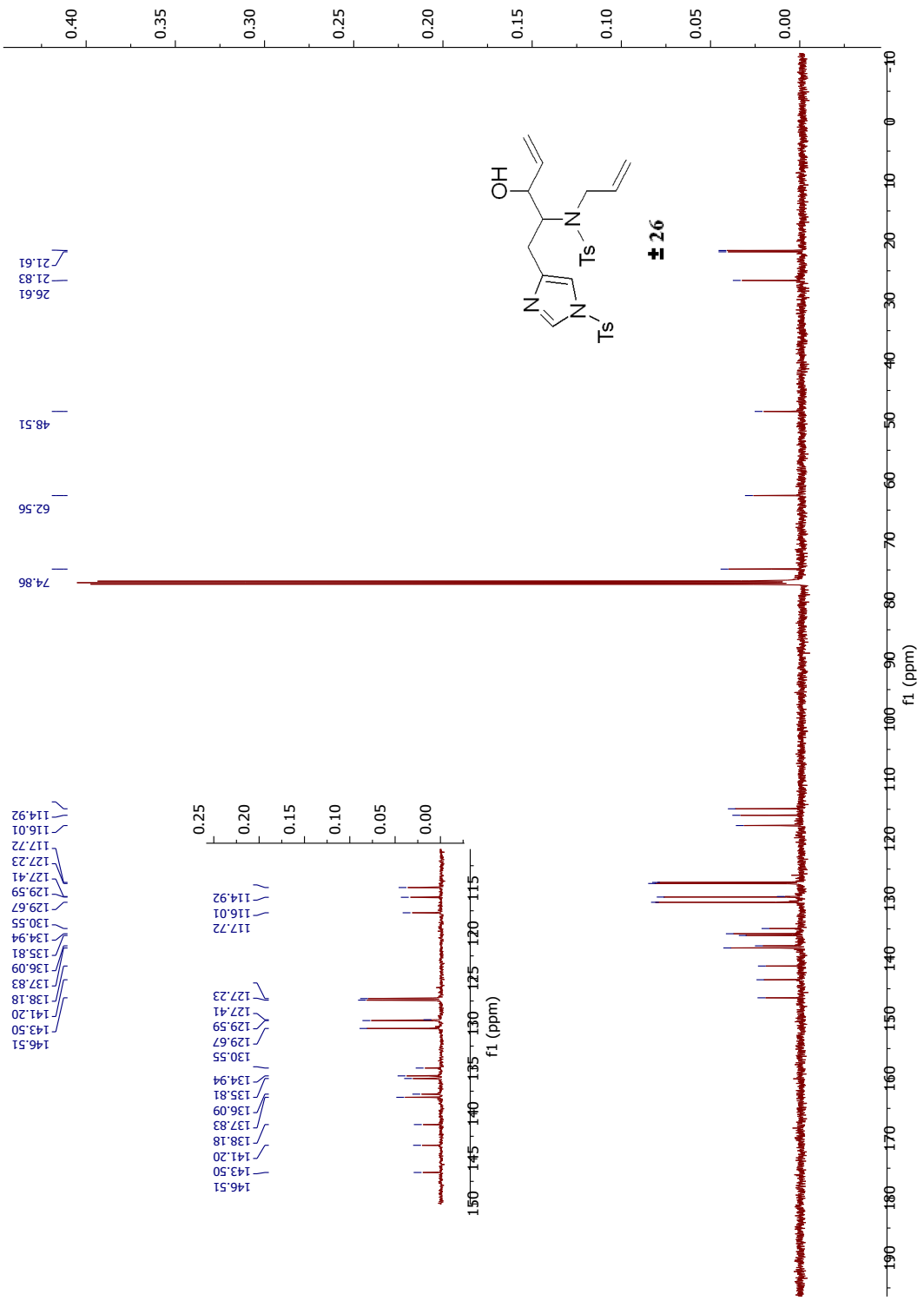
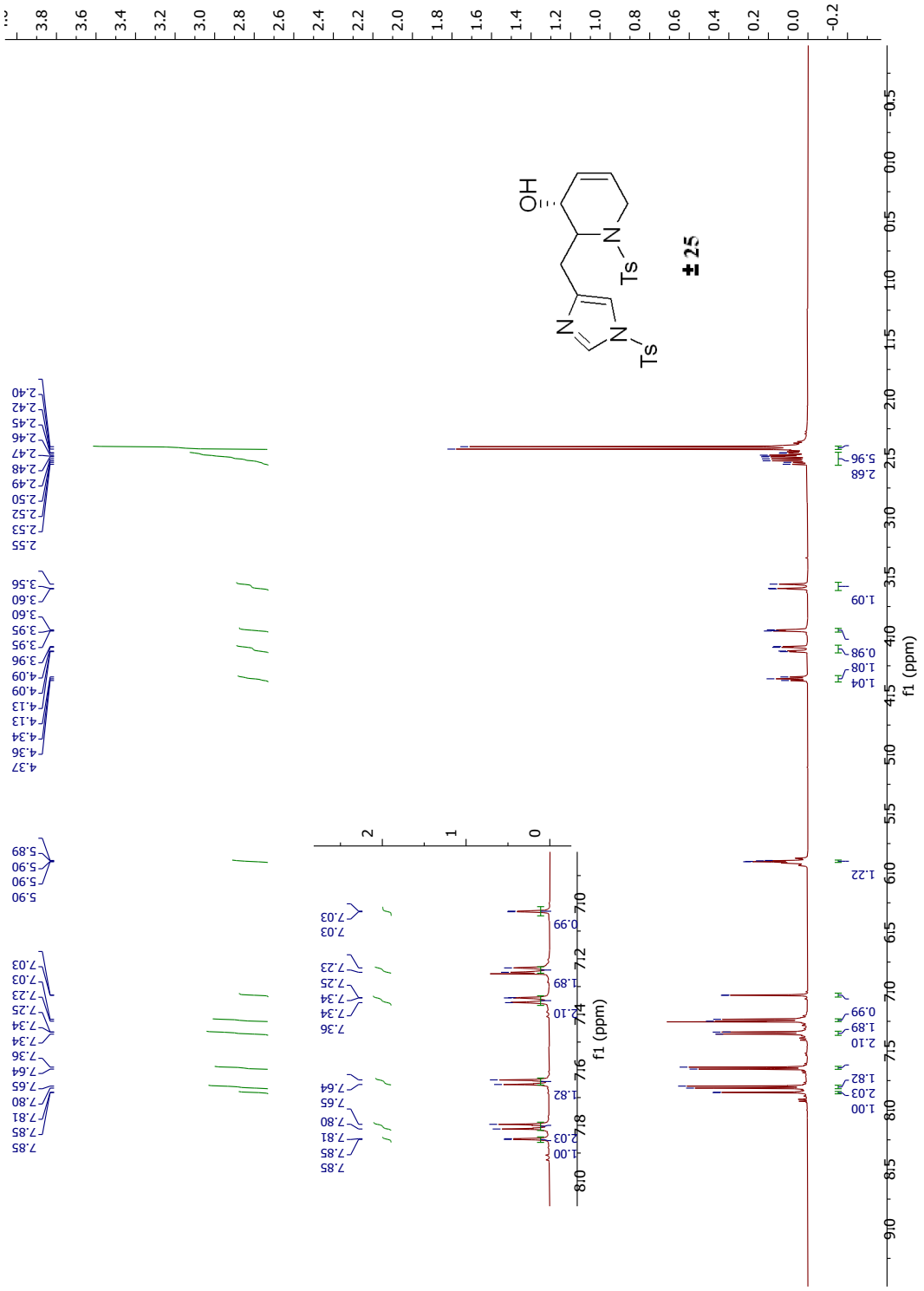
52.23
48.96
29.23
21.80
21.62
f1 (ppm)
OMe
Ts
Ts
± 27

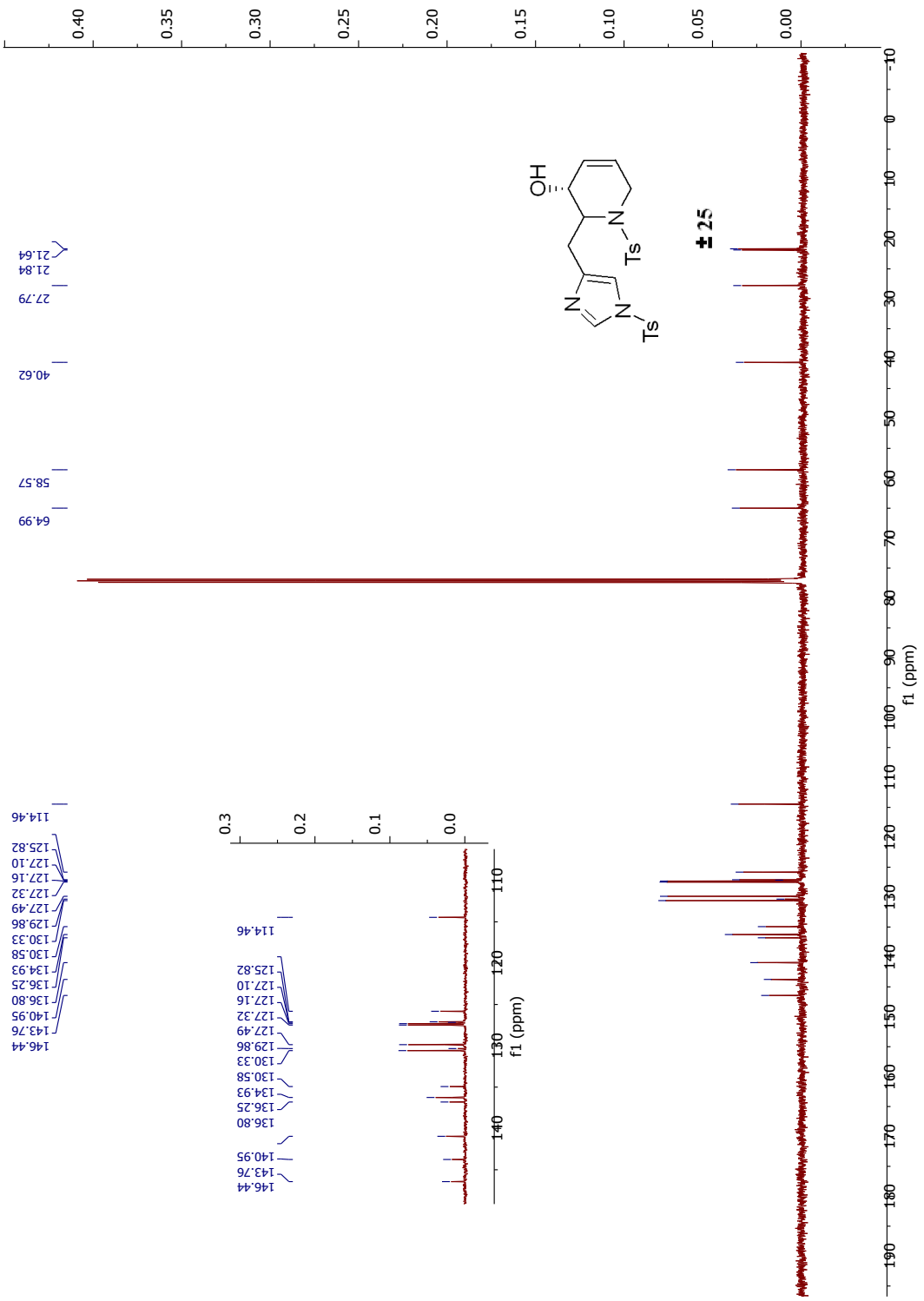

f1 (ppm)
± 46

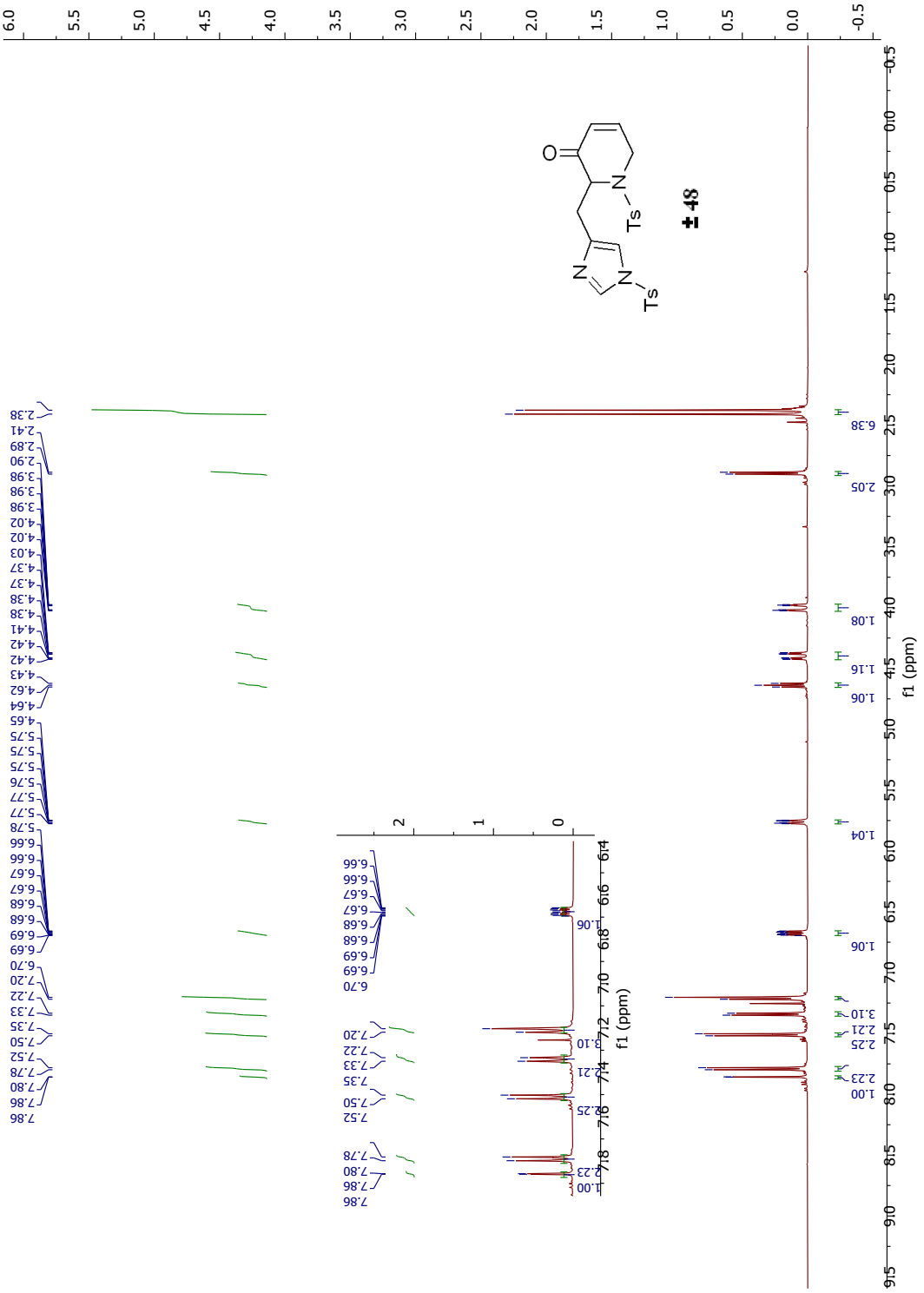

198.84
146.44
144.07
140.38
137.47
136.20
134.98
133.29
130.52
129.91
127.34
127.20
120.48
114.92
65.57
49.87
25.89
21.81
21.65
f1 (ppm)
± 46

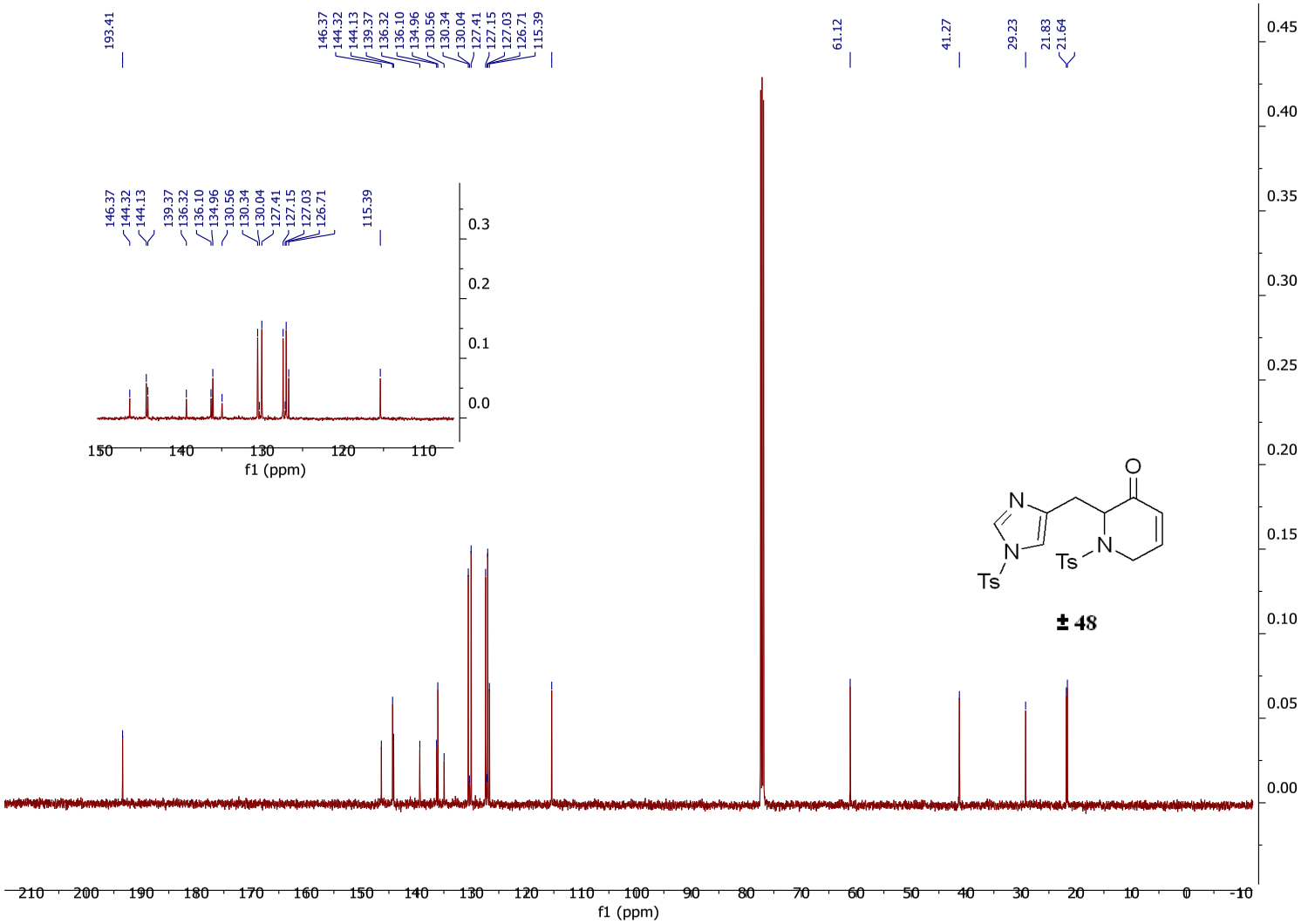

OH
N
Ts
N
Ts
± 26
f1 (ppm)

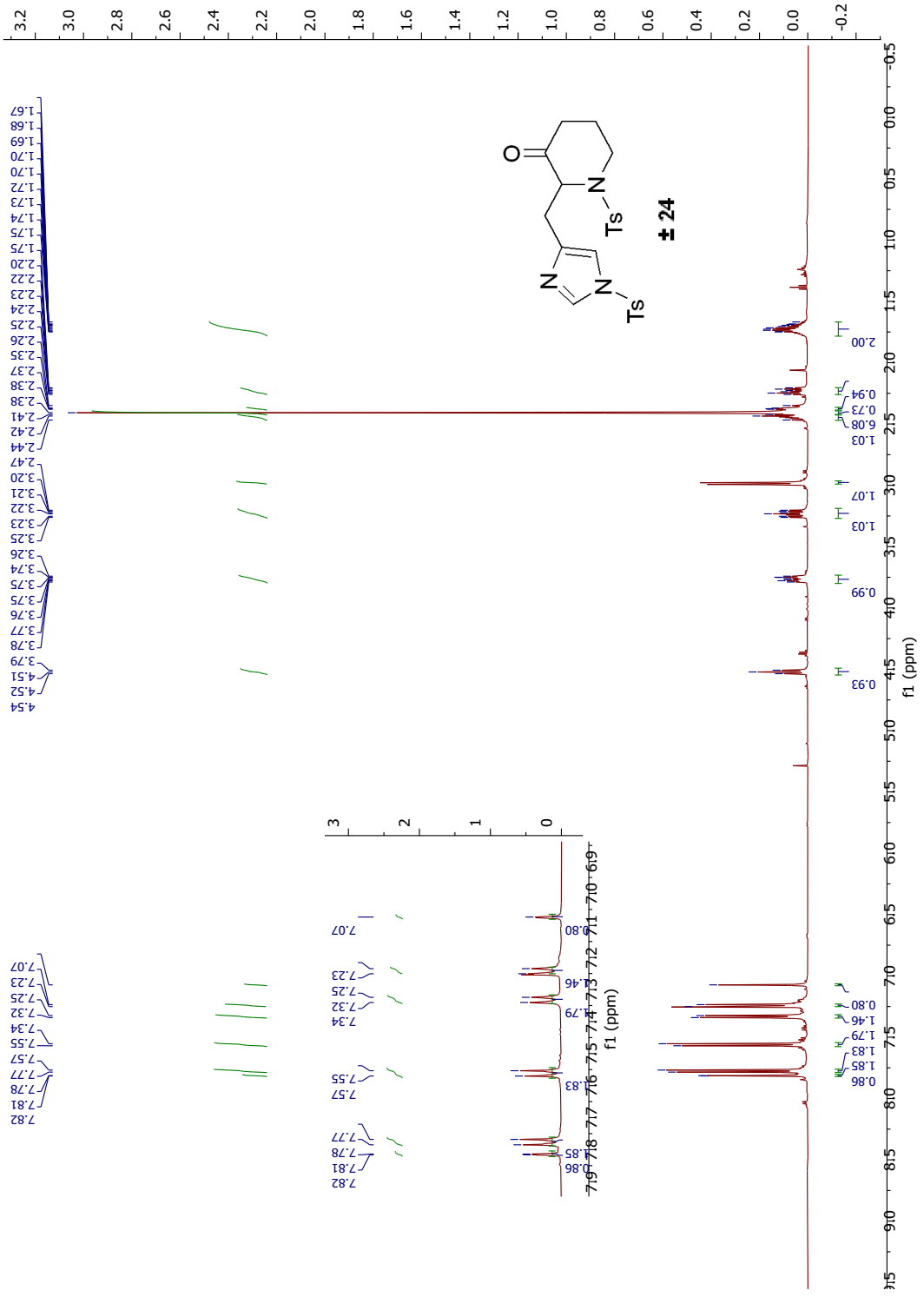

OH
N
Ts
N
N
Ts
± 26
f1 (ppm)
f1 (ppm)
74.86
62.56
48.51
26.61
21.83
21.61
146.51
143.50
141.20
138.18
137.83
136.09
135.81
134.94
130.55
129.67
129.59
127.41
127.23
117.72
116.01
114.92

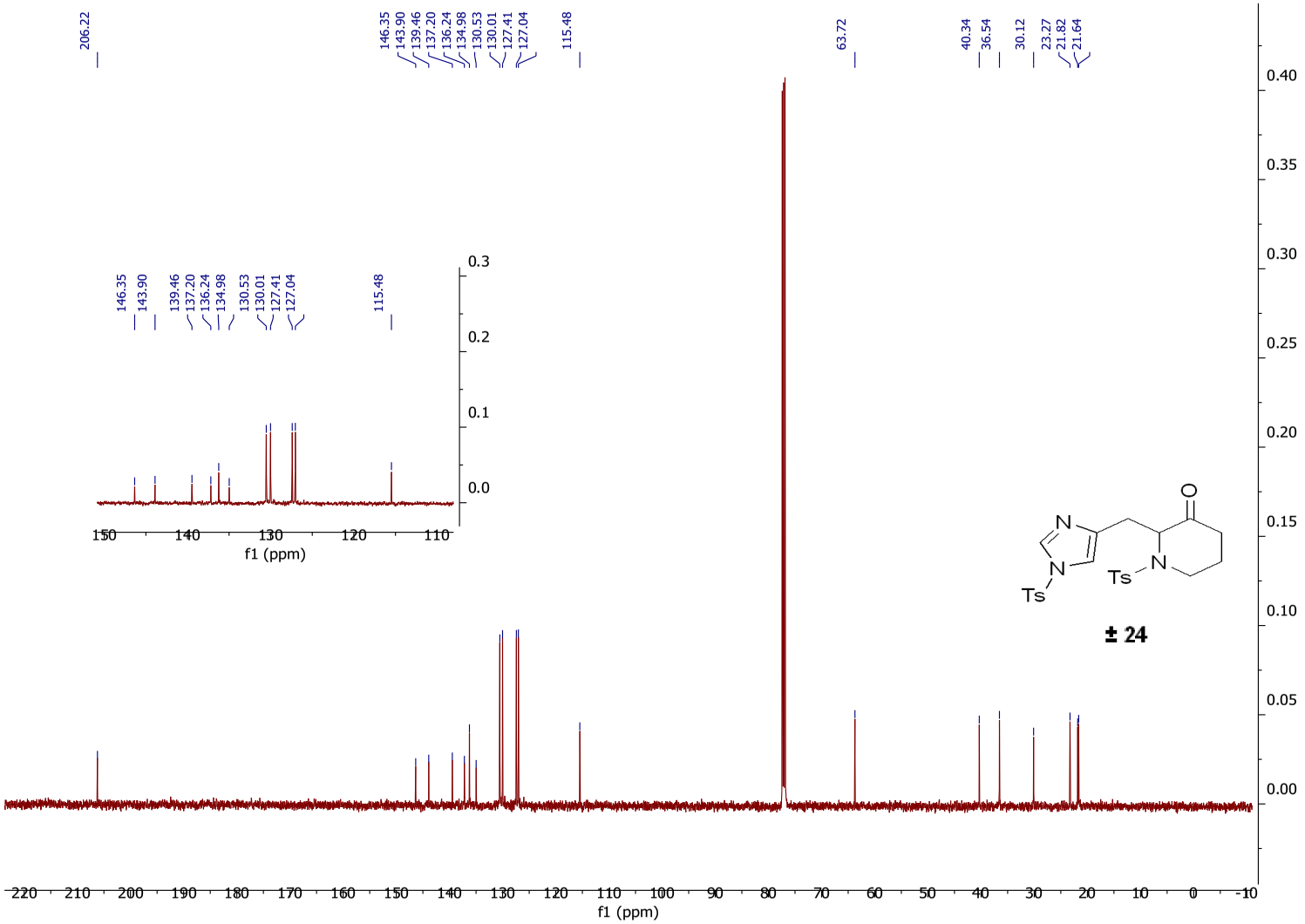

OH
N
Ts
N
Ts
f1 (ppm)

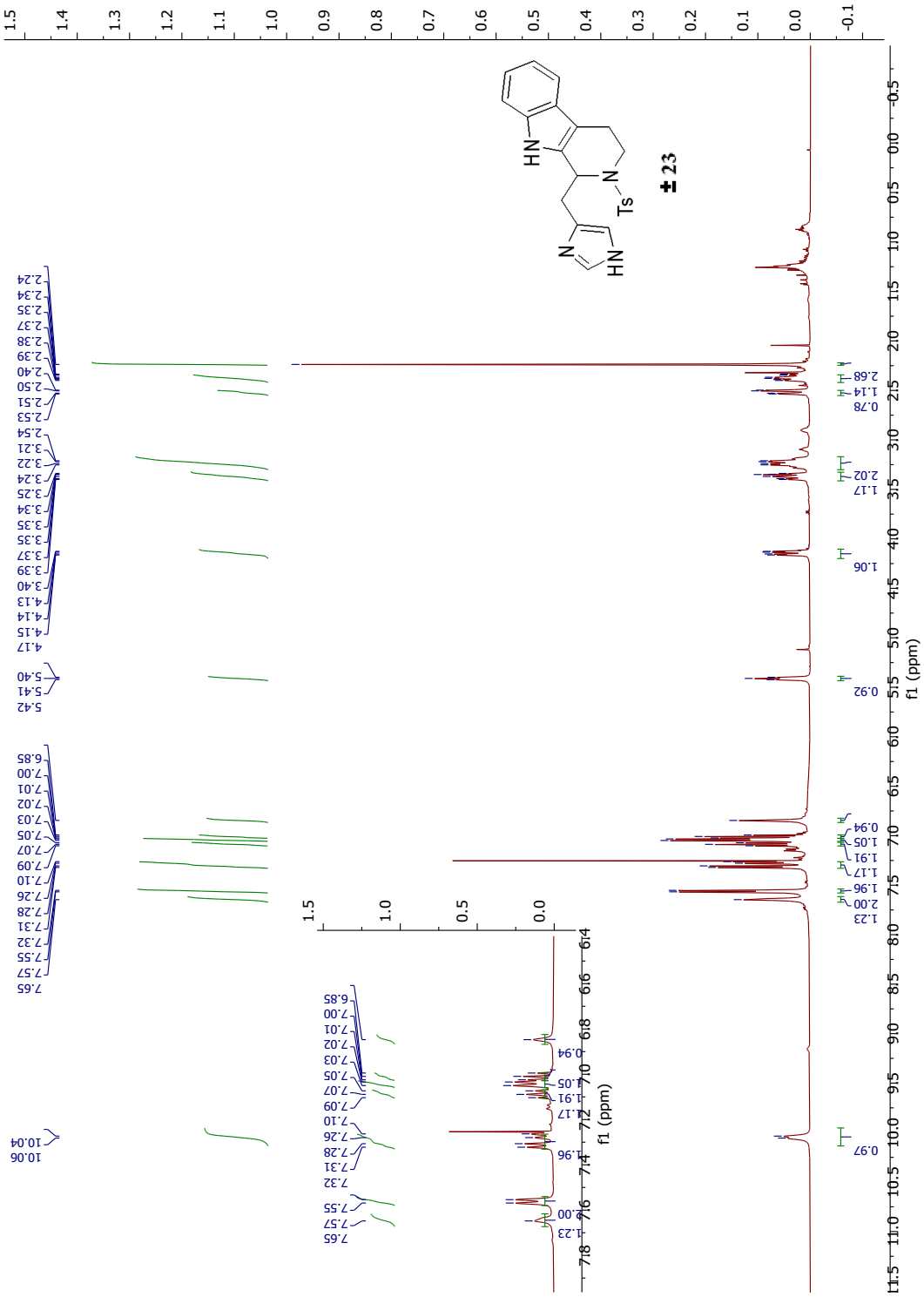

OH
N
Ts
N
N
Ts
± 25
f1 (ppm)
114.46
125.82
127.10
127.16
127.32
127.49
129.86
130.33
130.58
134.93
136.25
136.80
140.95
143.76
146.44
64.99
58.57
40.62
27.79
21.84
21.64

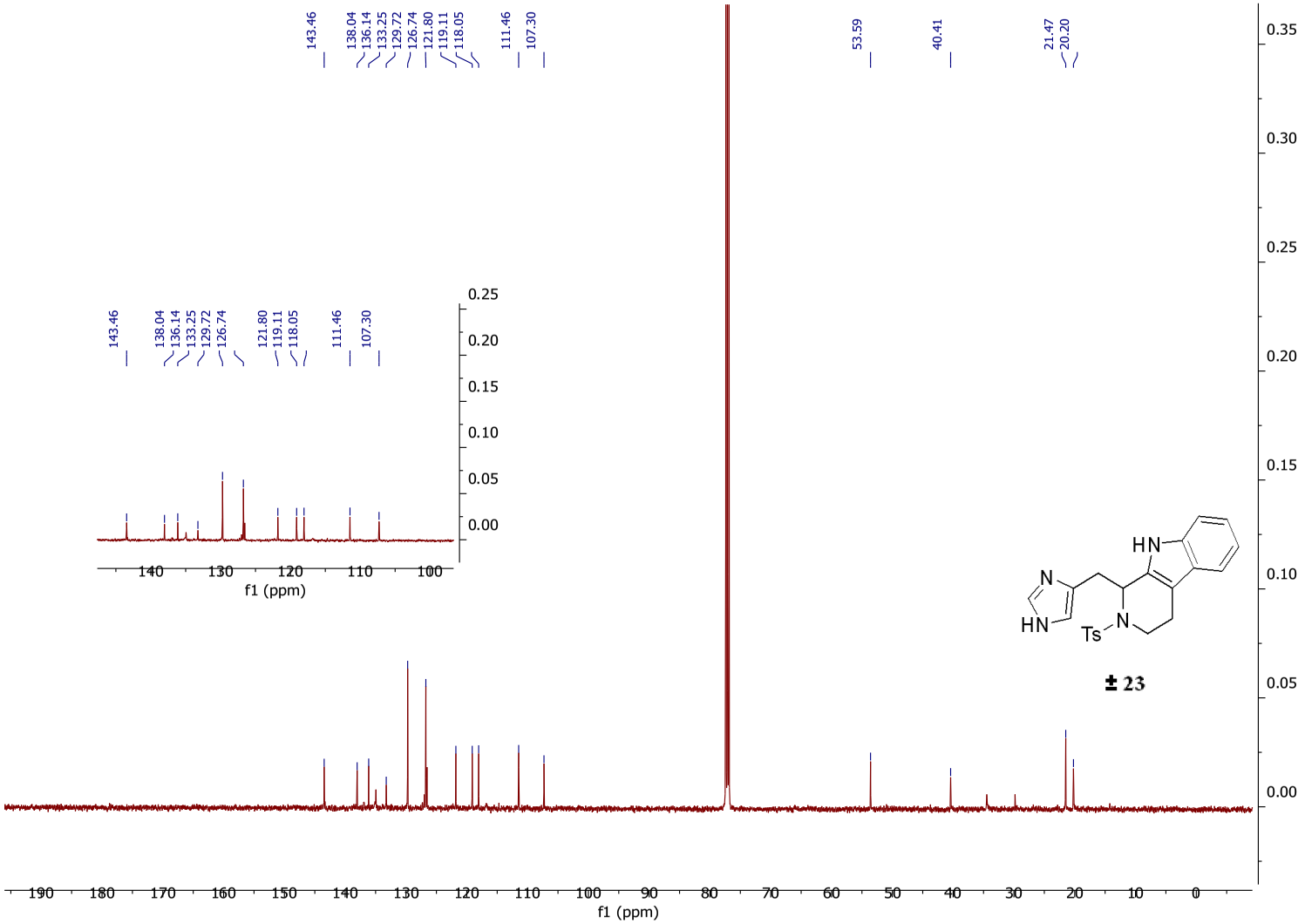

O
N
Ts
N
N
Ts
± 48
f1 (ppm)

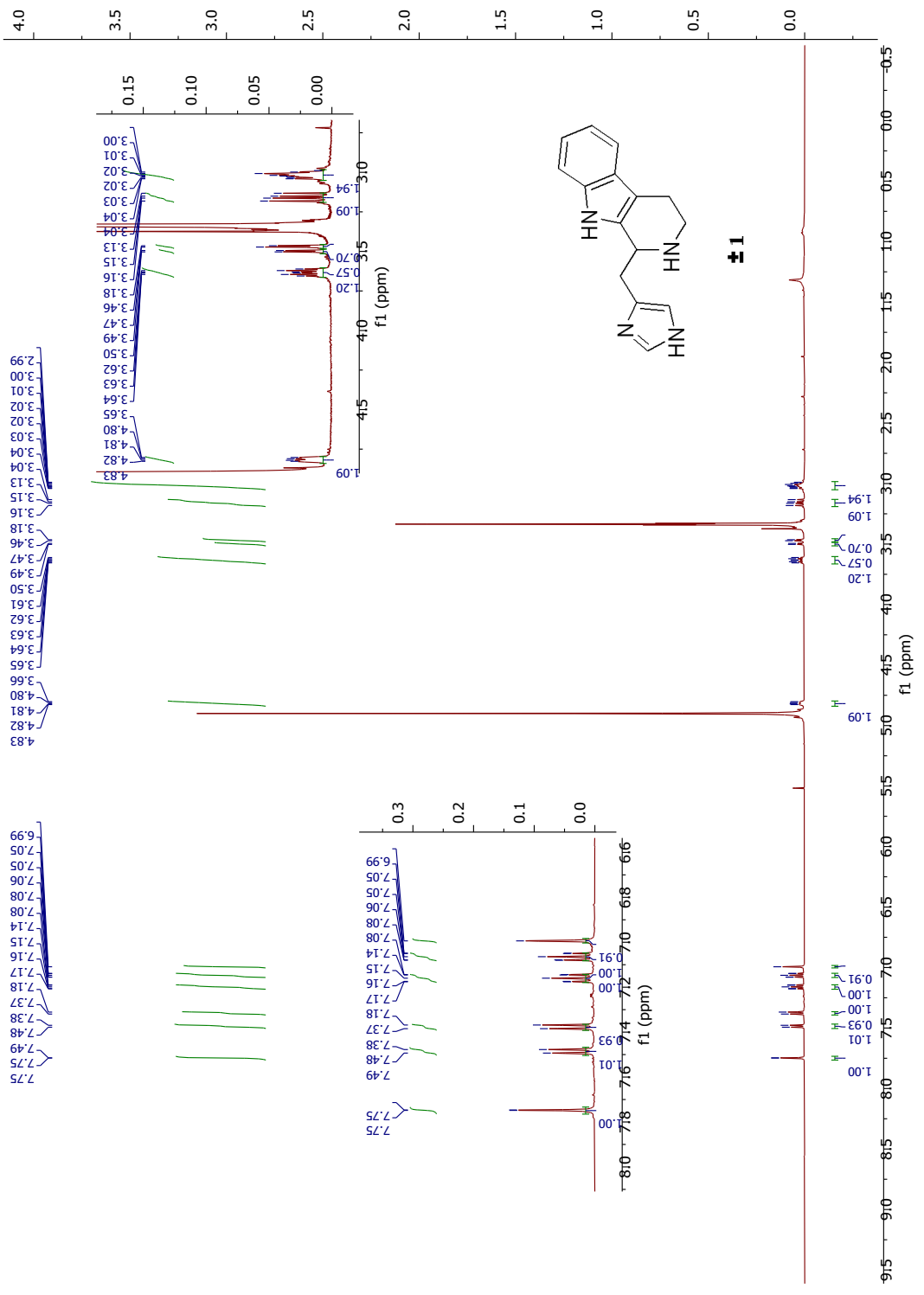

193.41
146.37
144.32
144.13
139.37
136.32
136.10
134.96
130.56
130.34
130.04
127.41
127.15
127.03
126.71
115.39
61.12
41.27
29.23
21.83
21.64
f1 (ppm)
O
N
N
Ts
Ts
N
± 48

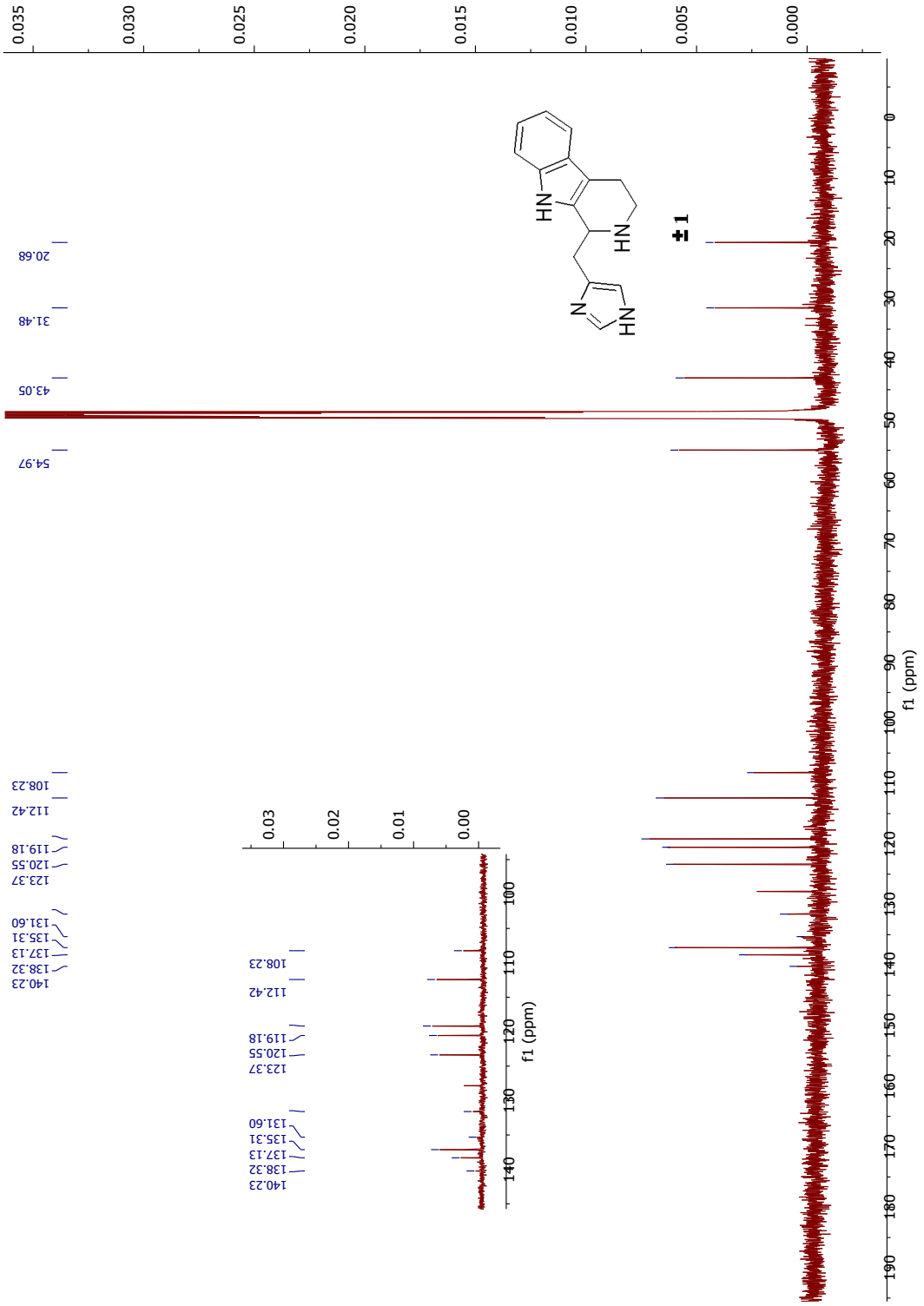

O
N
Ts
N
N
Ts
± 24
f1 (ppm)

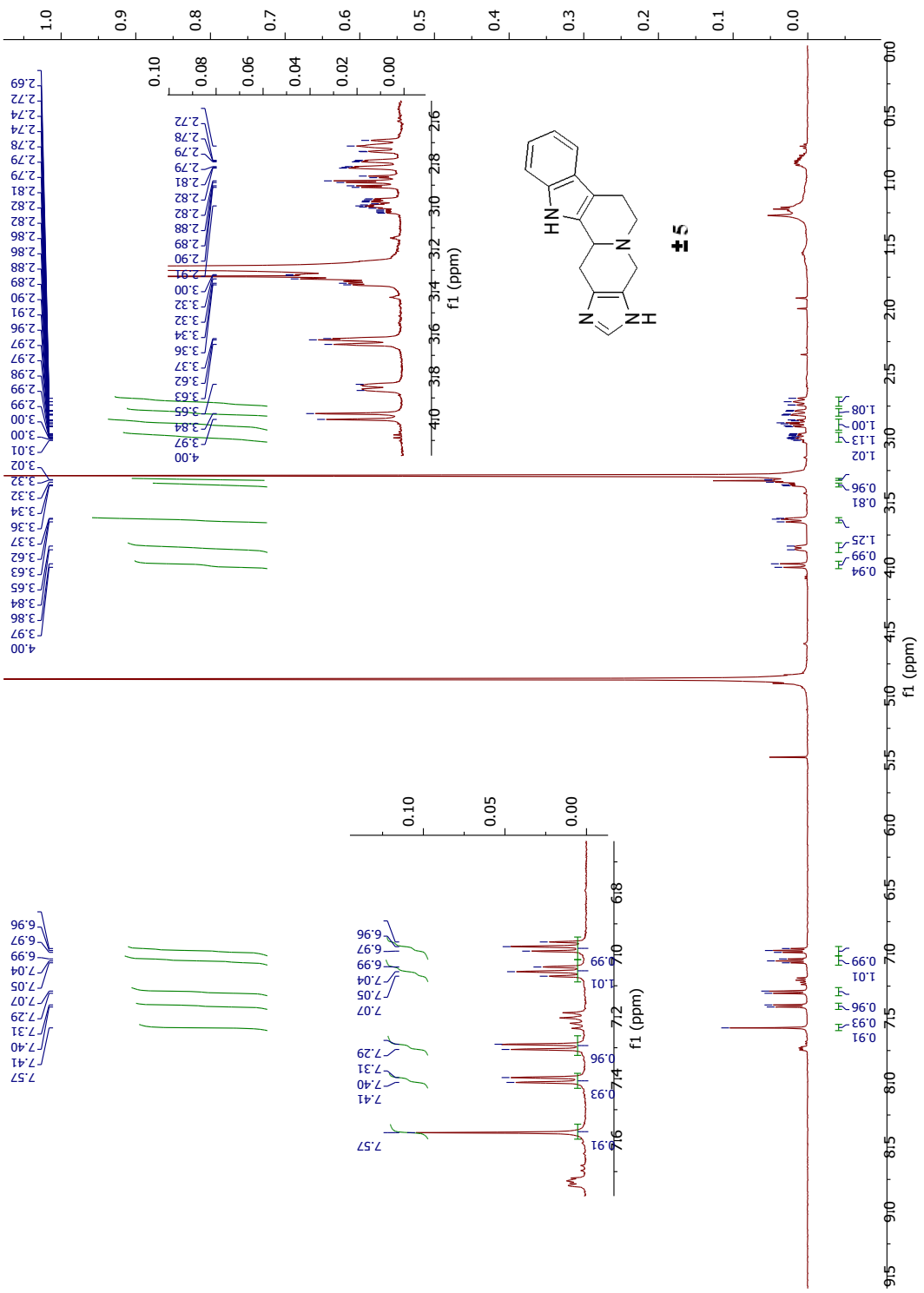

206.22
146.35
143.90
139.46
137.20
136.24
134.98
130.53
130.01
127.41
127.04
115.48
63.72
40.34
36.54
30.12
23.27
21.82
21.64
f1 (ppm)
Ts
Ts
± 24

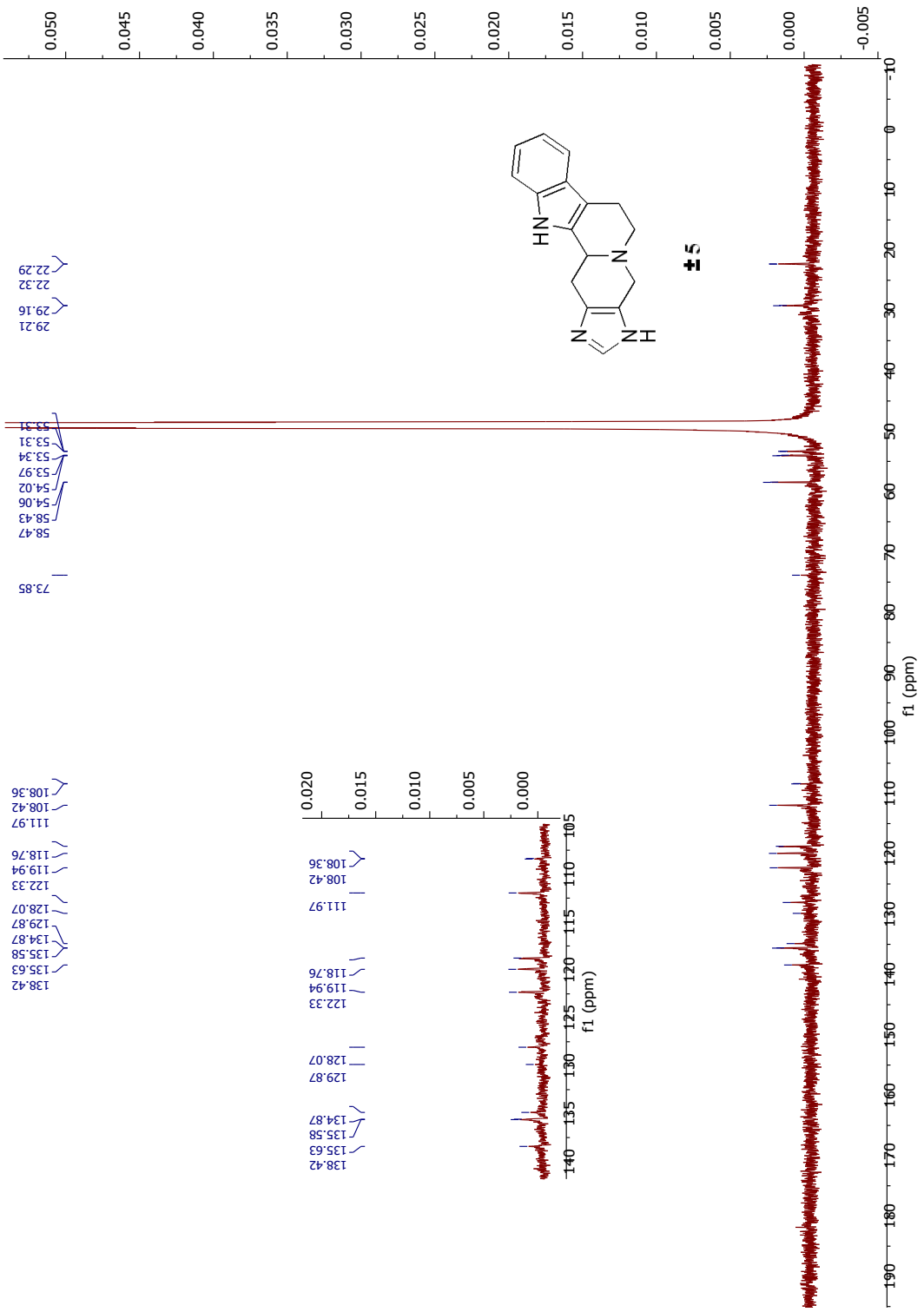

HN
N
Ts
N
HN
± 23
f1 (ppm)

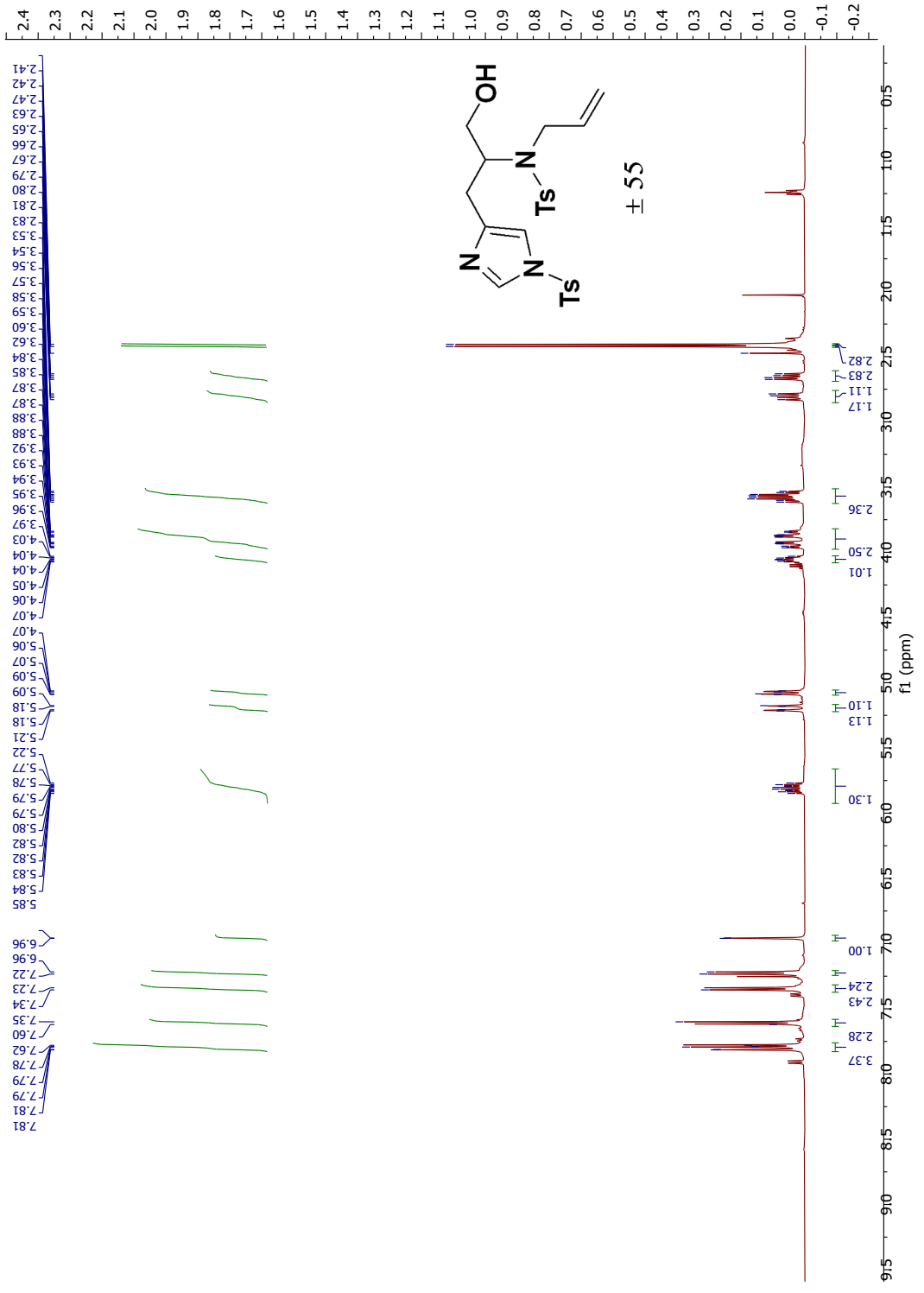

143.46
138.04
136.14
133.25
129.72
126.74
121.80
119.11
118.05
111.46
107.30
53.59
40.41
21.47
20.20
f1 (ppm)
HN
N
HN
Ts
N
± 23

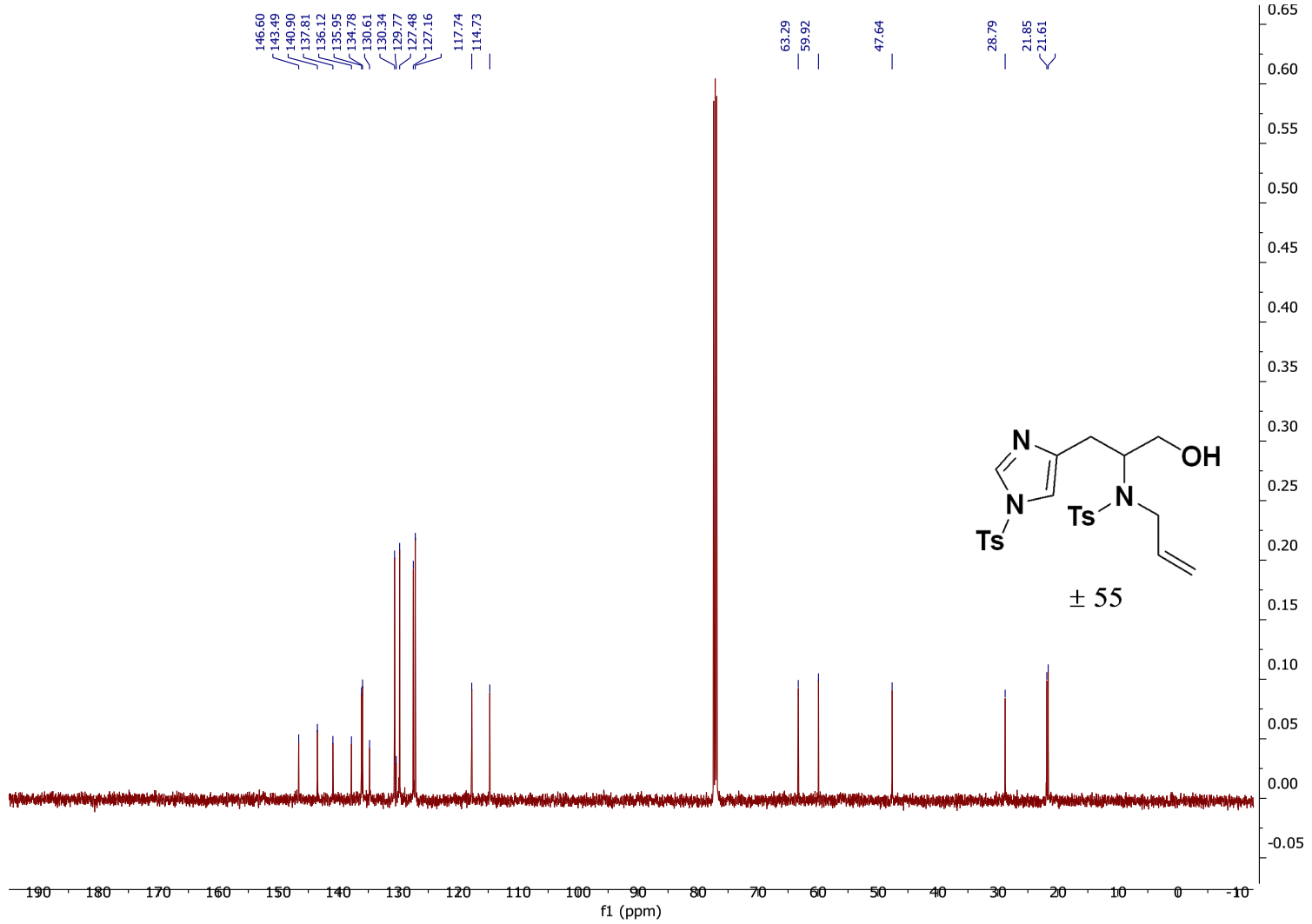

±1
f1 (ppm)

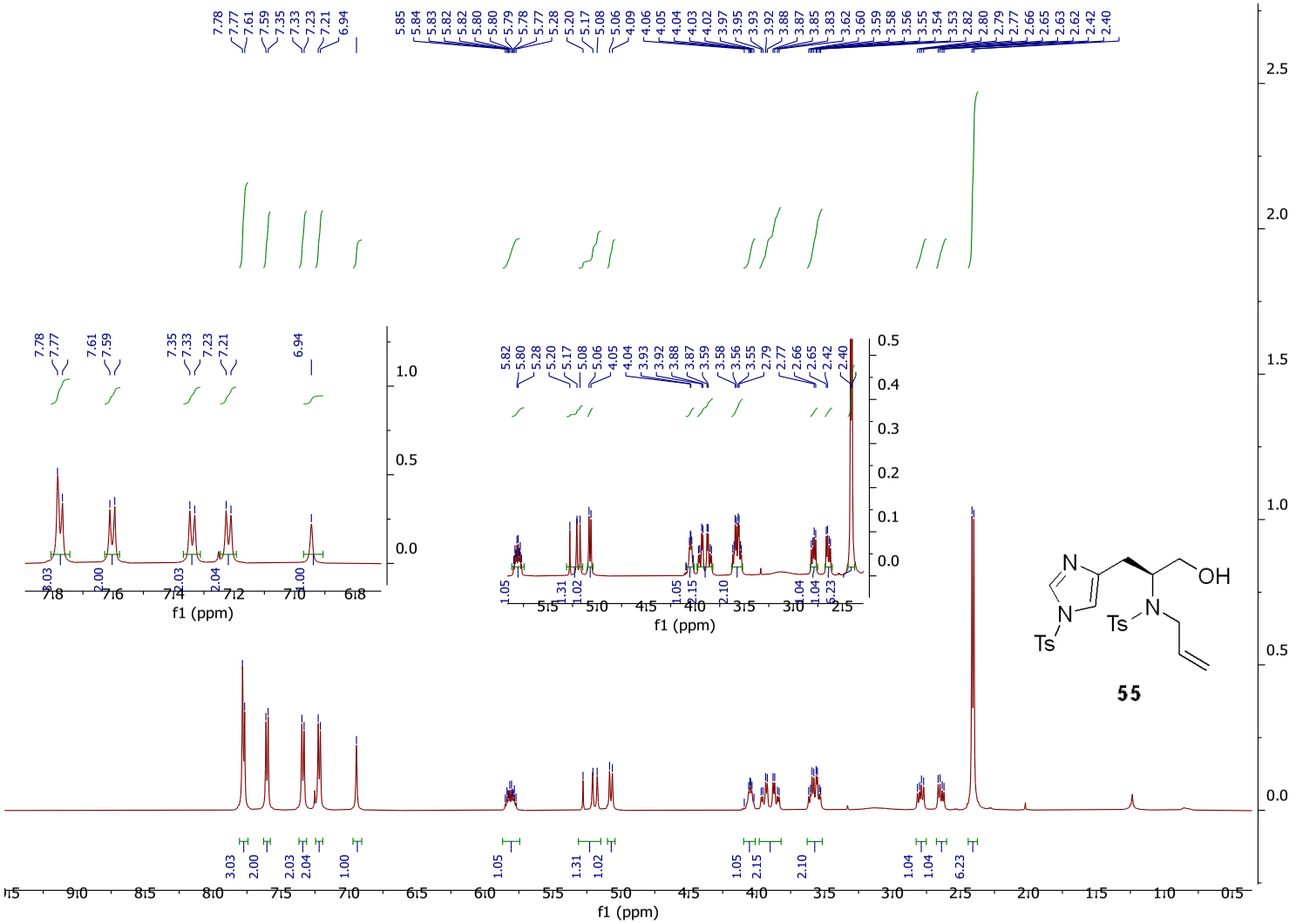

±1
f1 (ppm)
20.68
31.48
43.05
54.97
108.23
112.42
119.18
120.55
123.37
131.60
135.31
137.13
138.32
140.23

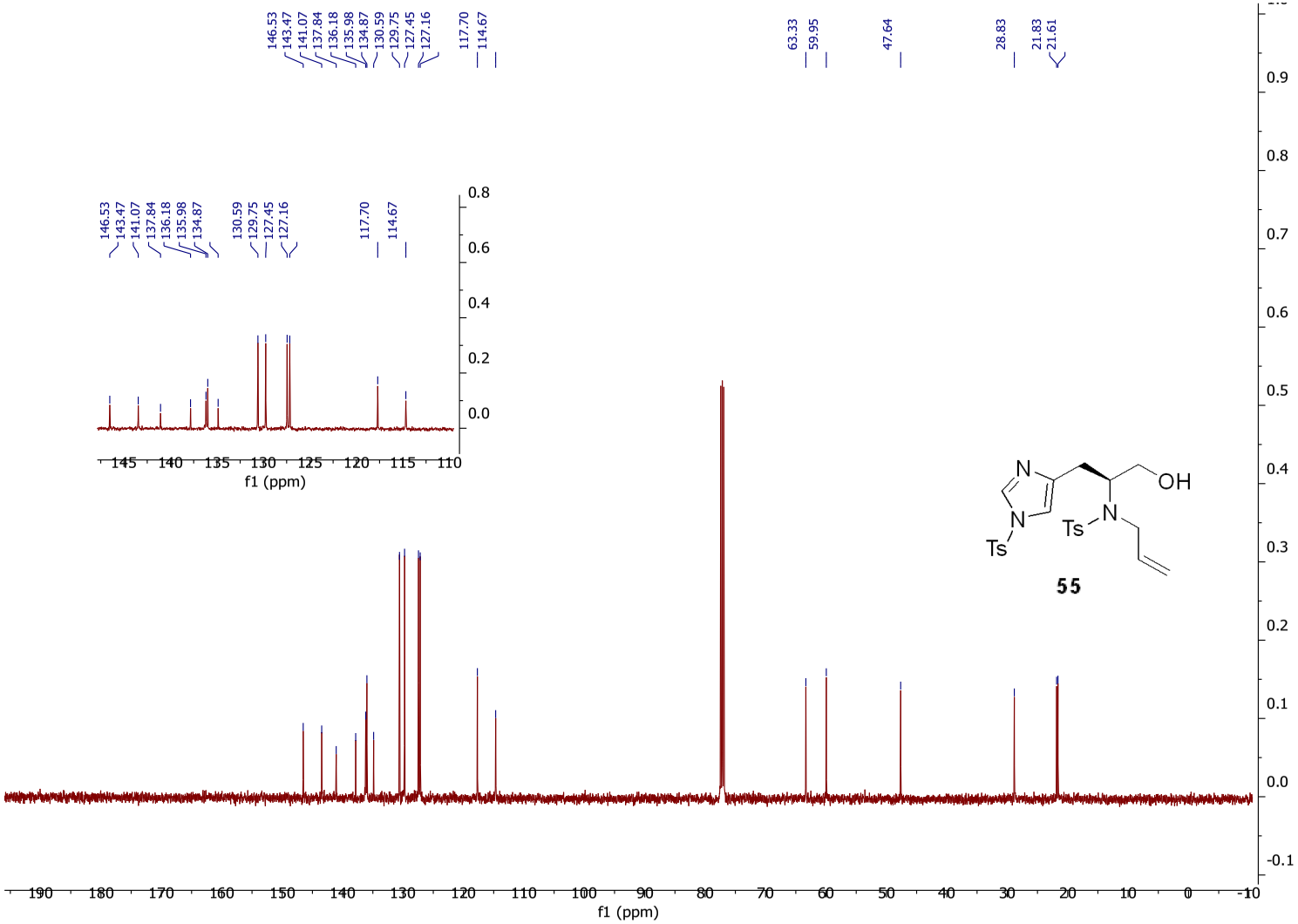

f1 (ppm)
+5

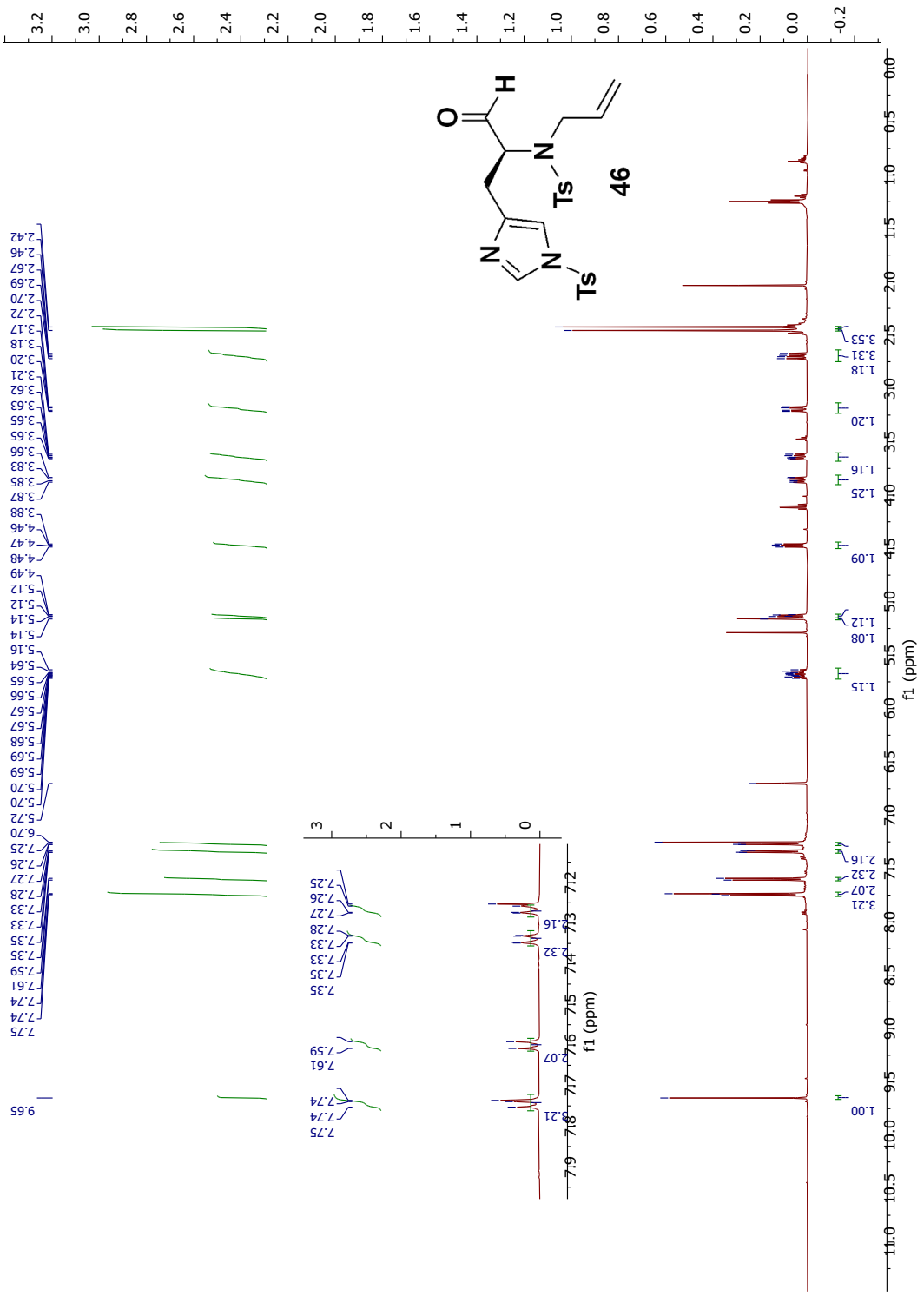

+5
f1 (ppm)
138.42
135.63
135.58
134.87
129.87
128.07
122.33
119.94
118.76
111.97
108.42
108.36
73.85
58.47
58.43
54.06
54.02
53.97
53.34
53.31
29.21
29.16
22.32
22.29

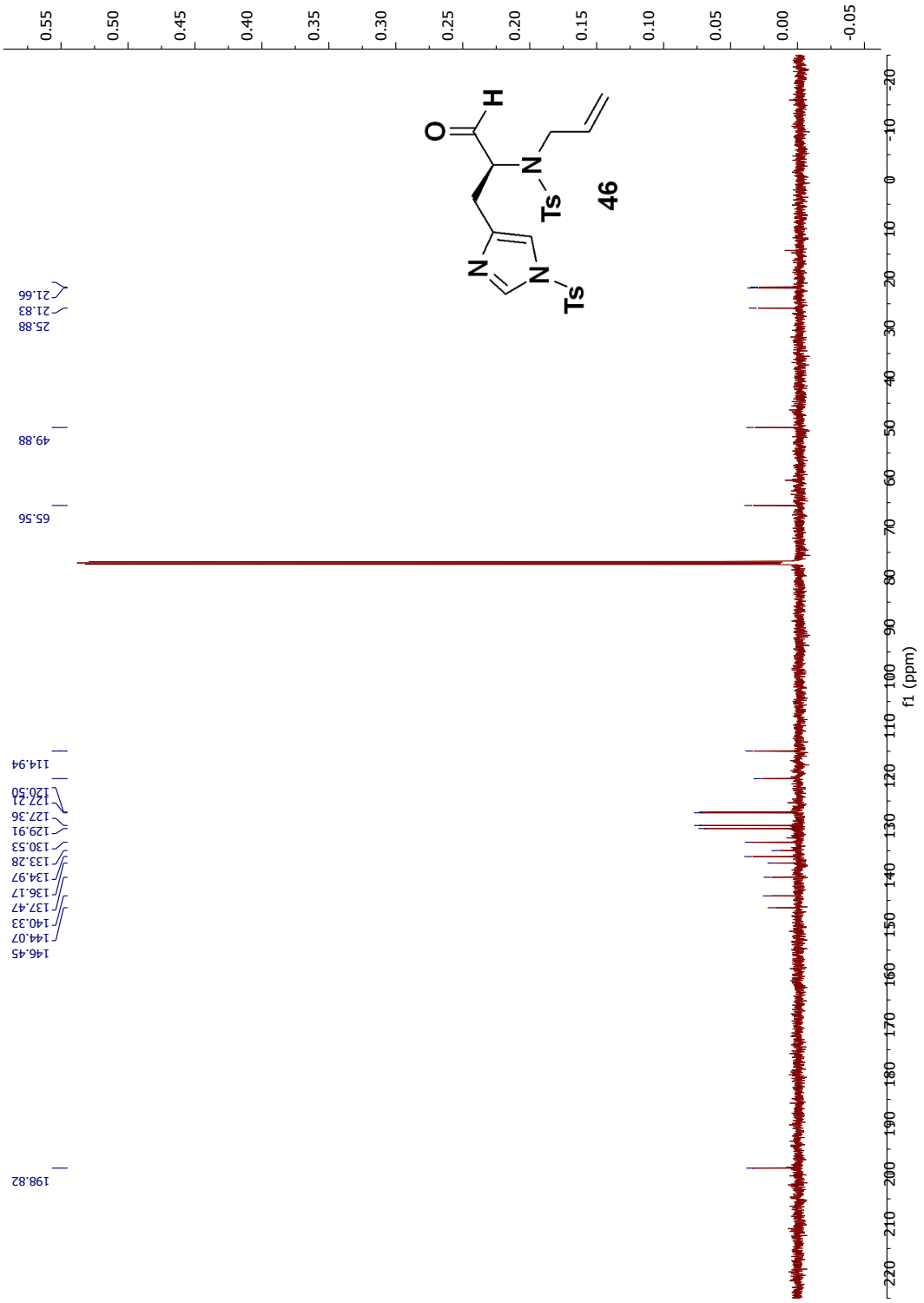

OH
N
Ts
N
Ts
± 55
f1 (ppm)

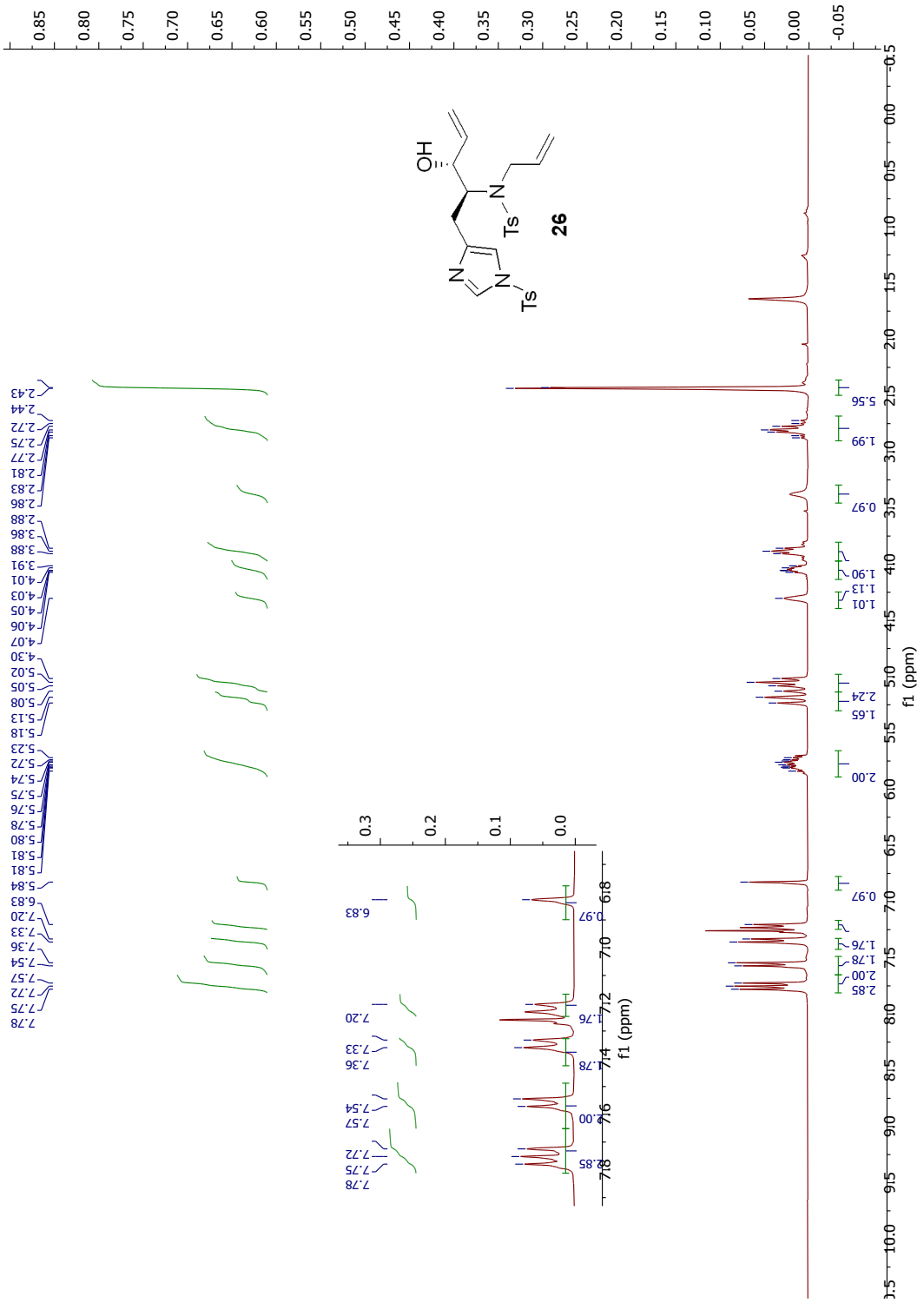

146.60
143.49
140.90
137.81
136.12
135.95
134.78
130.61
130.34
129.77
127.48
127.16
117.74
114.73
63.29
59.92
47.64
28.79
21.85
21.61
N
N
Ts
Ts
N
OH
± 55
f1 (ppm)

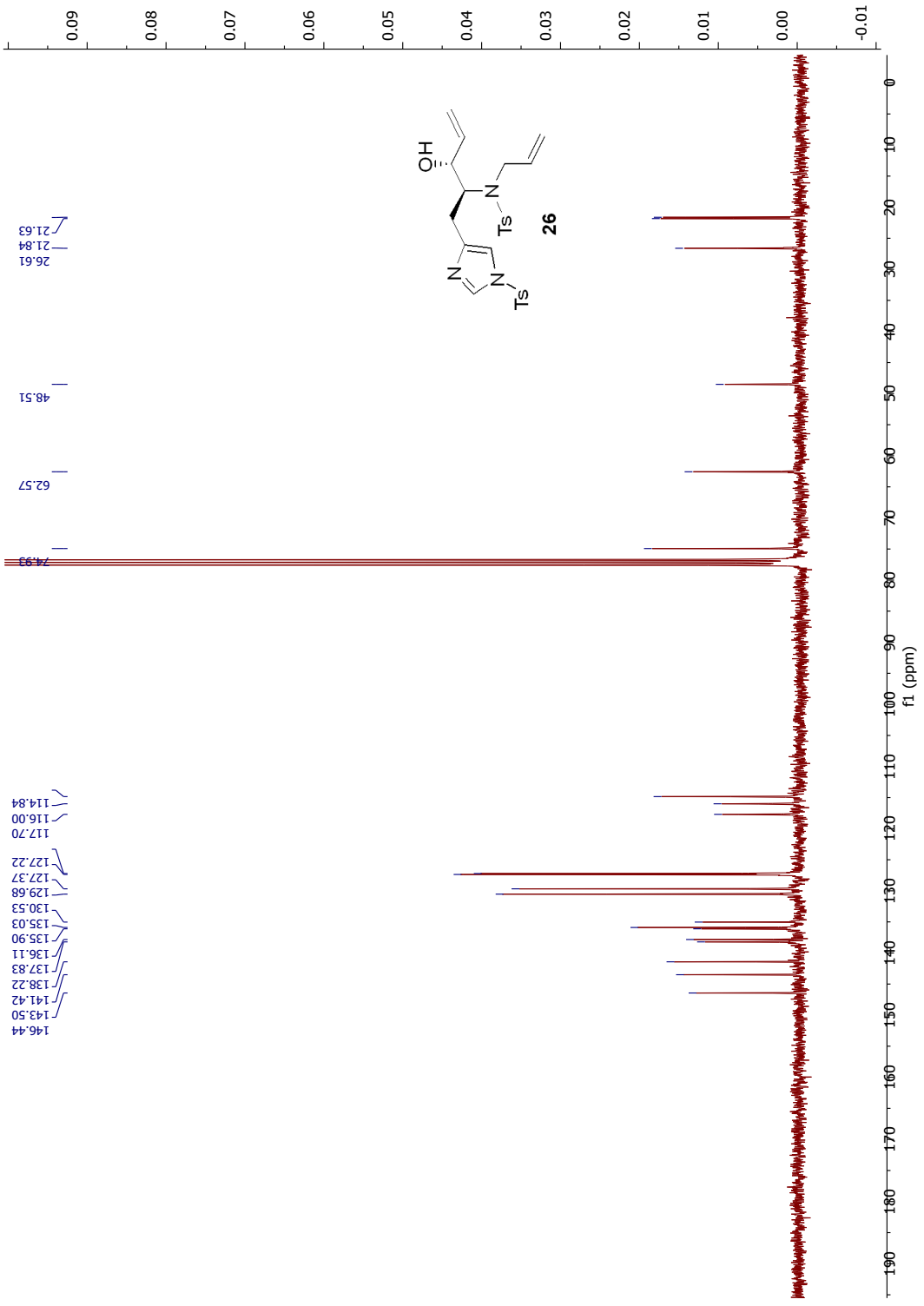

f1 (ppm)
55

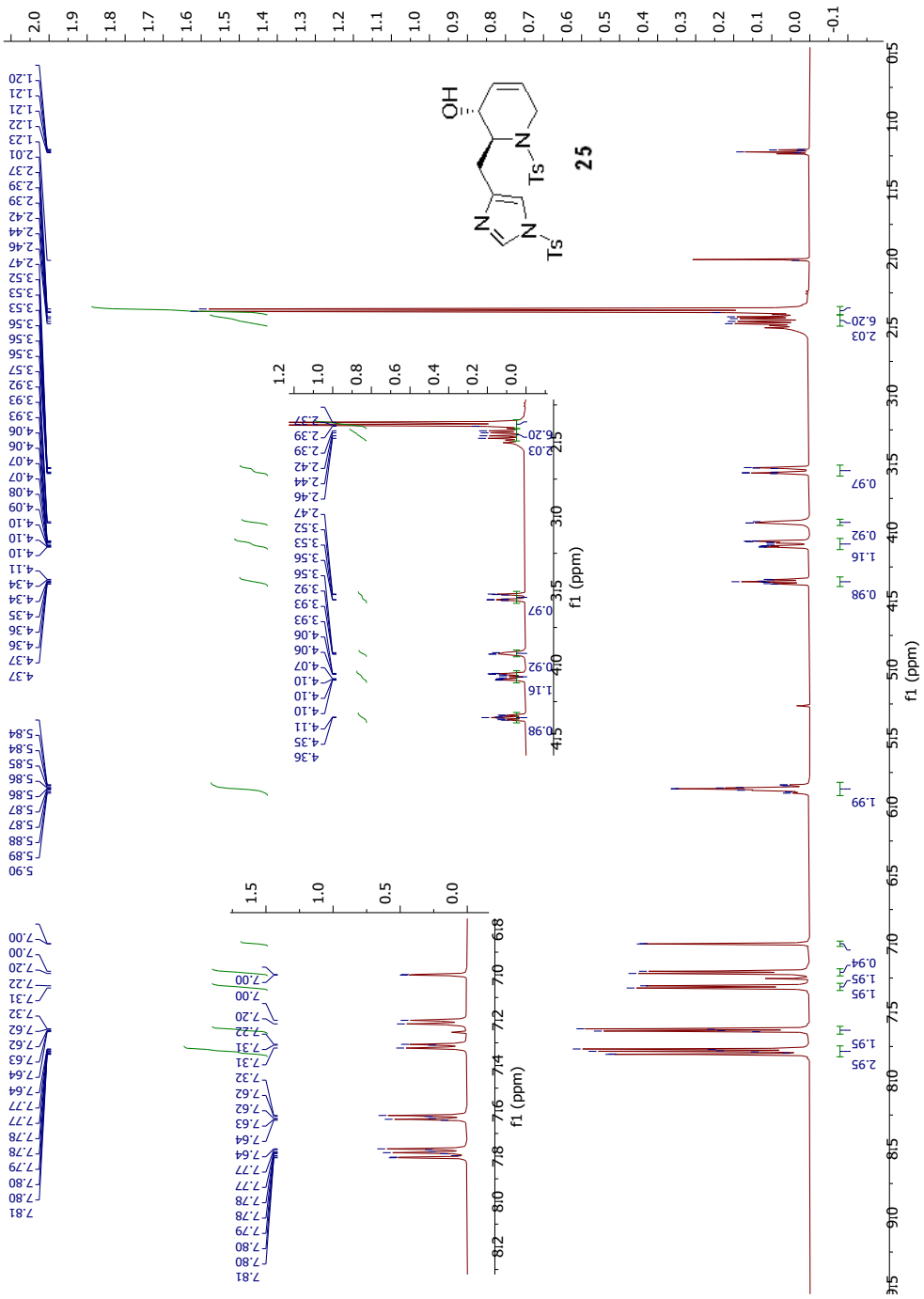

146.53
143.47
141.07
137.84
136.18
135.98
134.87
130.59
129.75
127.45
127.16
117.70
114.67
63.33
59.95
47.64
28.83
21.83
21.61
f1 (ppm)
OH
N
N
Ts
Ts
N
55

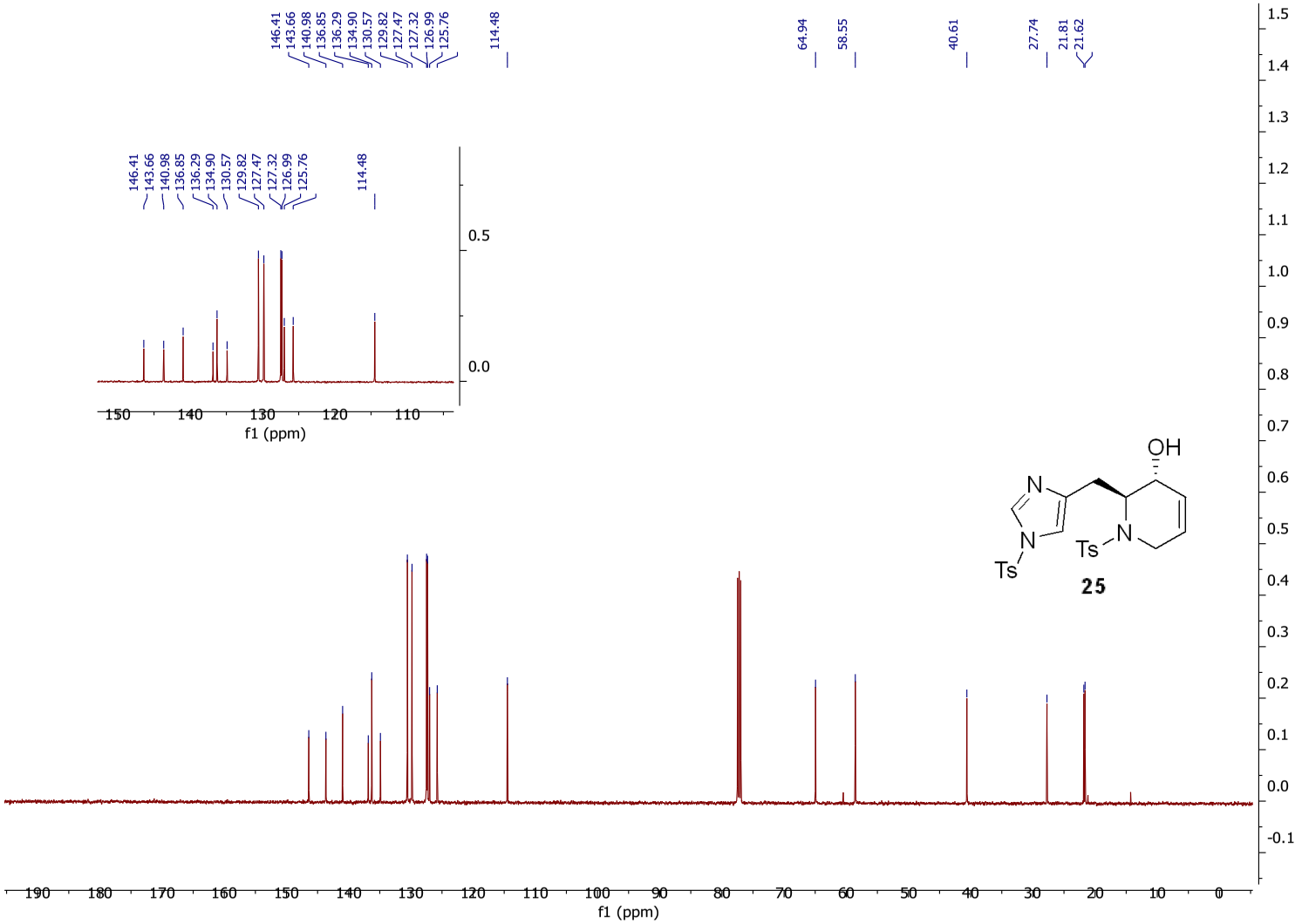

O
H
N
Ts
N
N
Ts
46
f1 (ppm)

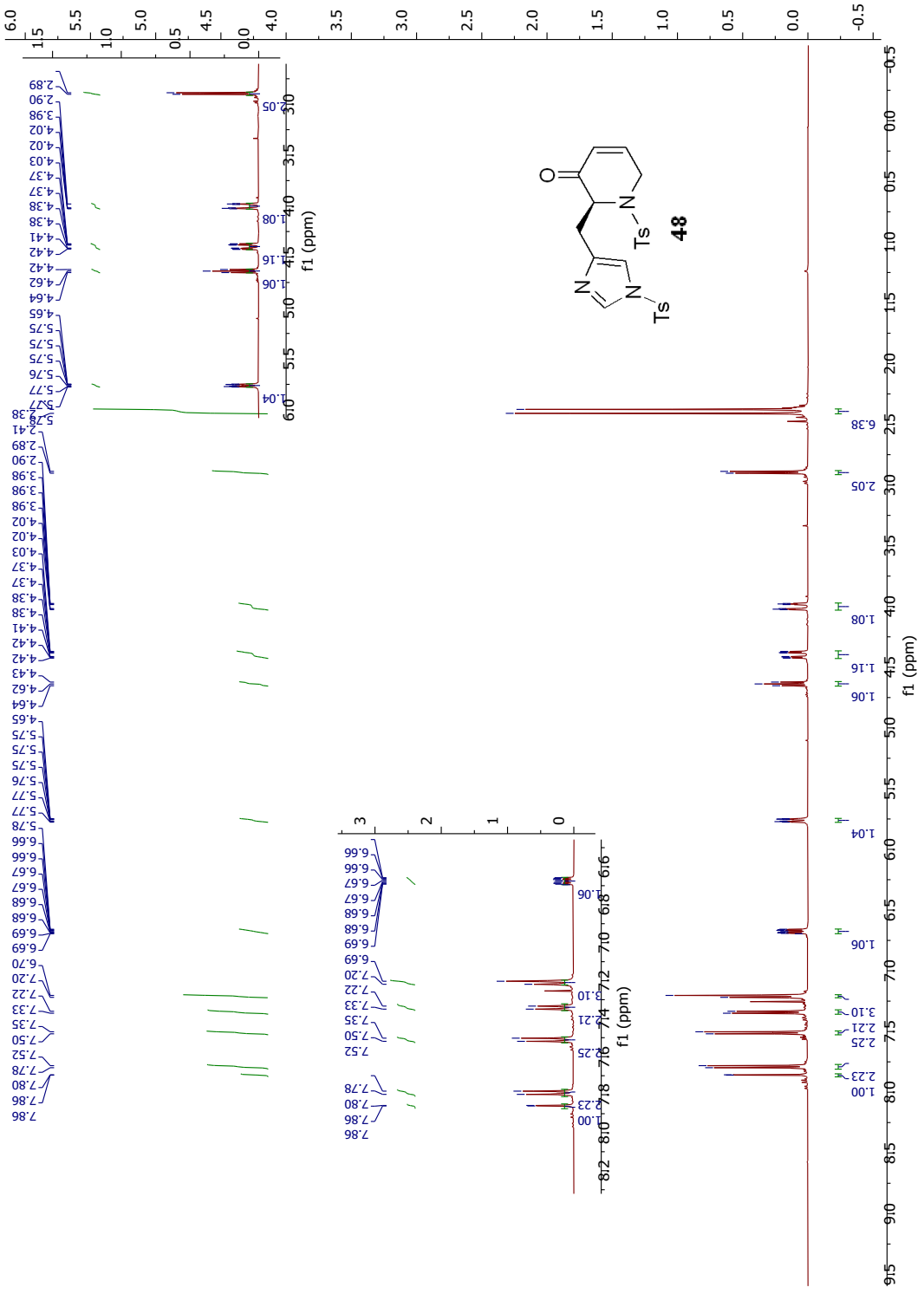

198.82
146.45
144.07
140.33
137.47
136.17
134.97
133.28
130.53
129.91
127.36
127.21
120.50
114.94
65.56
49.88
25.88
21.83
21.66
46
Ts
Ts
f1 (ppm)

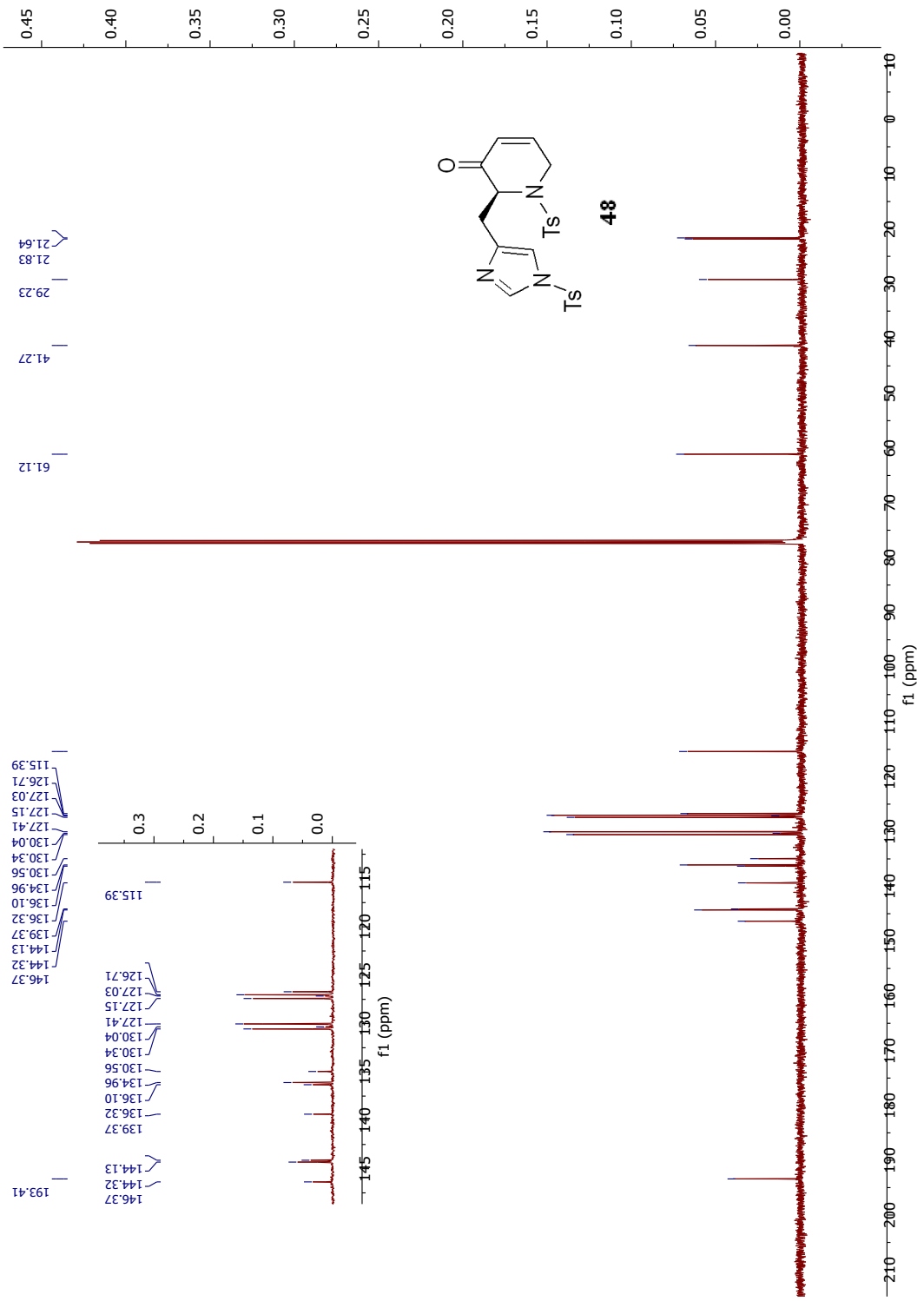

OH
Ts
Ts
26
f1 (ppm)

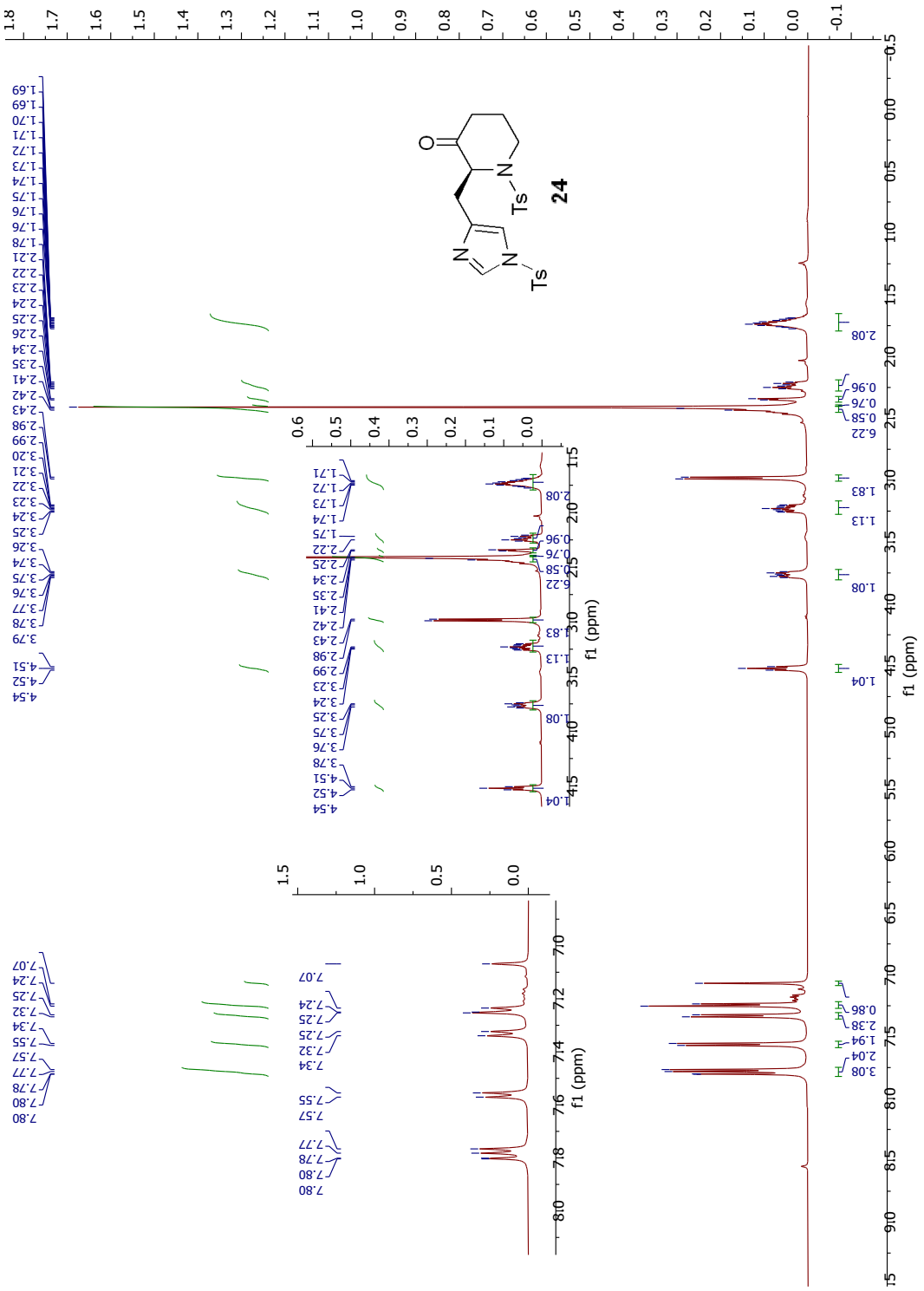

OH
N
Ts
N
N
Ts
26
21.63
21.84
26.61
48.51
62.57
74.93
114.84
116.00
117.70
127.22
127.37
129.68
130.53
135.03
135.90
136.11
137.83
138.22
141.42
143.50
146.44
f1 (ppm)

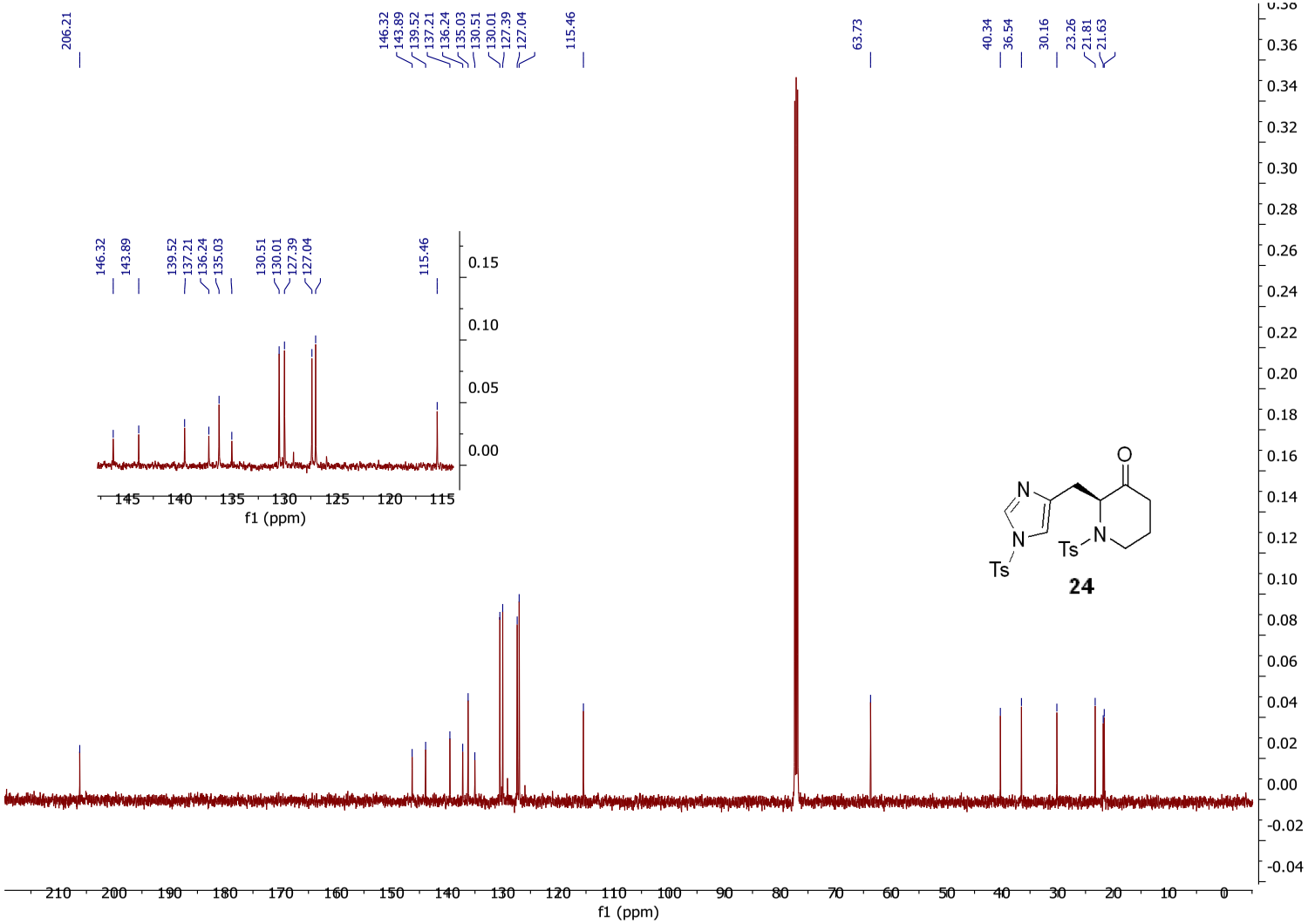

OH
N
N
Ts
Ts
25
f1 (ppm)

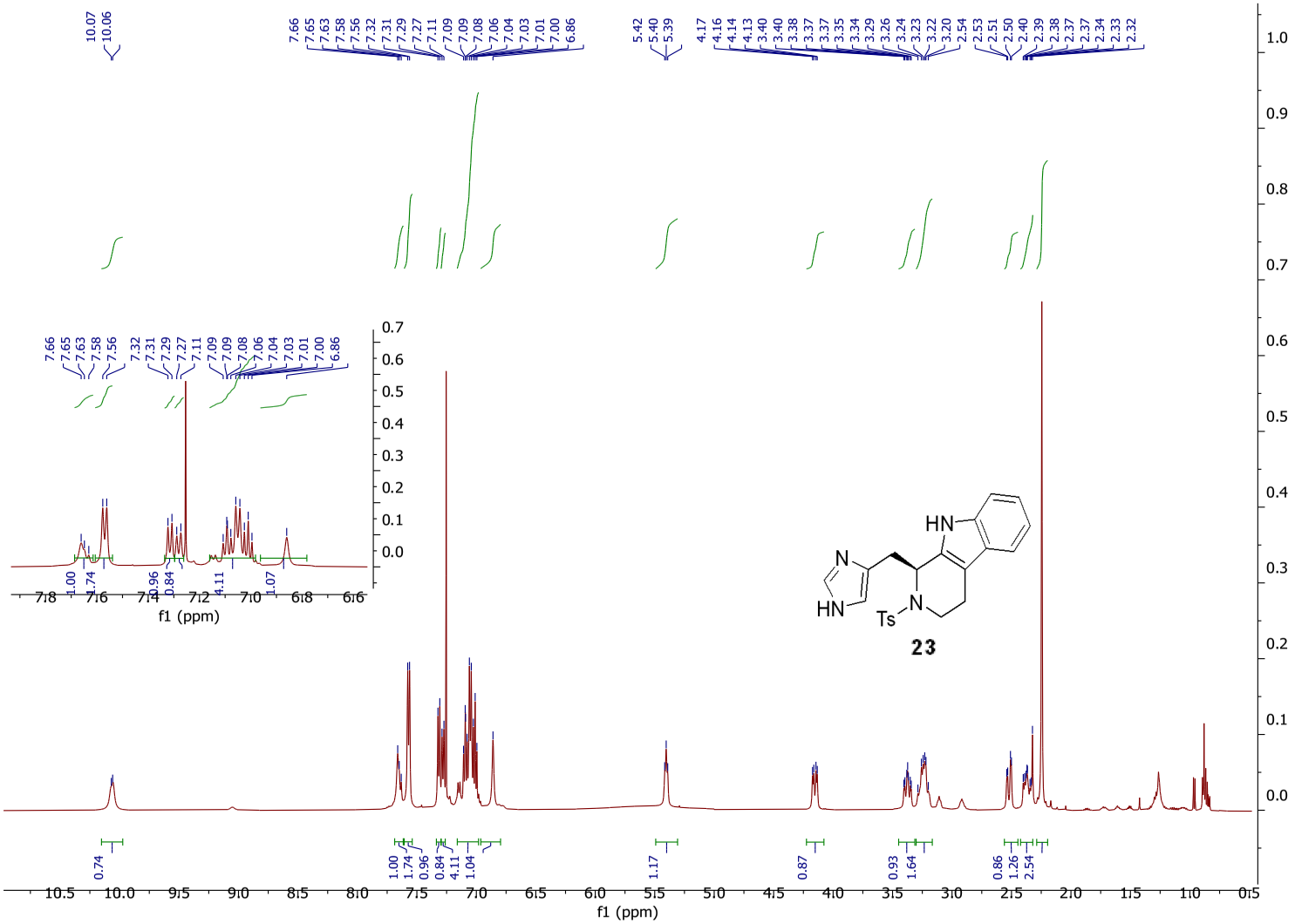

146.41
143.66
140.98
136.85
136.29
134.90
130.57
129.82
127.47
127.32
126.99
125.76
114.48
64.94
58.55
40.61
27.74
21.81
21.62
f1 (ppm)
OH
N
N
Ts
Ts
25

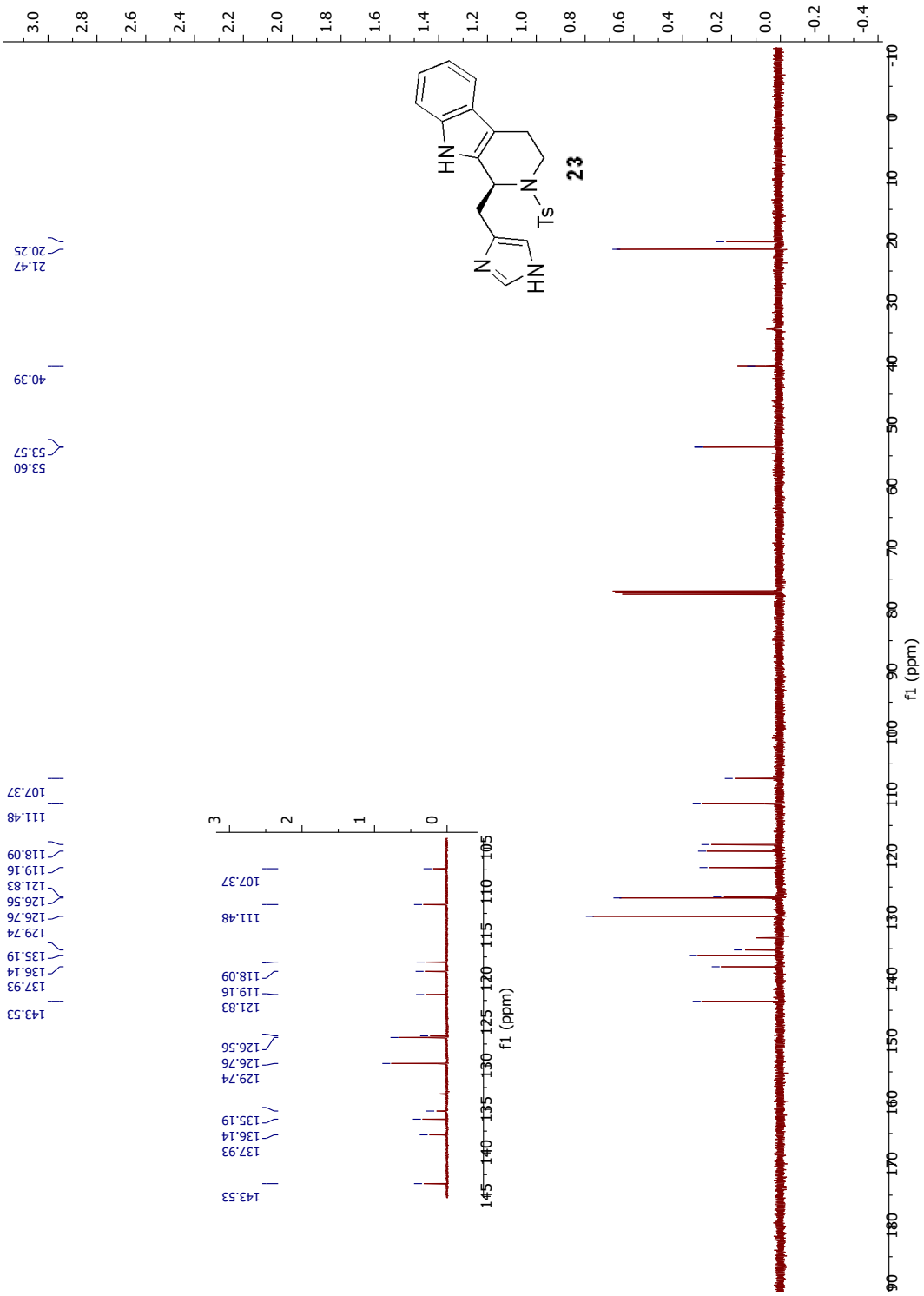

O
N
Ts
N
Ts
48
f1 (ppm)


48
f1 (ppm)
193.41
146.37
144.32
144.13
139.37
136.32
136.10
134.96
130.56
130.34
130.04
127.41
127.15
127.03
126.71
115.39
61.12
41.27
29.23
21.83
21.64


24
Ts
Ts
f1 (ppm)


206.21
146.32
143.89
139.52
137.21
136.24
135.03
130.51
130.01
127.39
127.04
115.46
63.73
40.34
36.54
30.16
23.26
21.81
21.63
f1 (ppm)
Ts
Ts
24


10.07
10.06
7.66
7.65
7.63
7.58
7.56
7.32
7.31
7.29
7.27
7.11
7.09
7.09
7.08
7.06
7.04
7.03
7.01
7.00
6.86
5.42
5.40
5.39
4.17
4.16
4.14
4.13
3.40
3.40
3.38
3.37
3.37
3.35
3.34
3.29
3.26
3.24
3.23
3.22
3.20
2.54
2.53
2.51
2.50
2.40
2.39
2.38
2.37
2.37
2.34
2.33
2.32
f1 (ppm)
HN
N
HN
N
Ts
23


23
Ts
HN
N
HN
f1 (ppm)
21.47
20.25
40.39
53.60
53.57
107.37
111.48
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119.16
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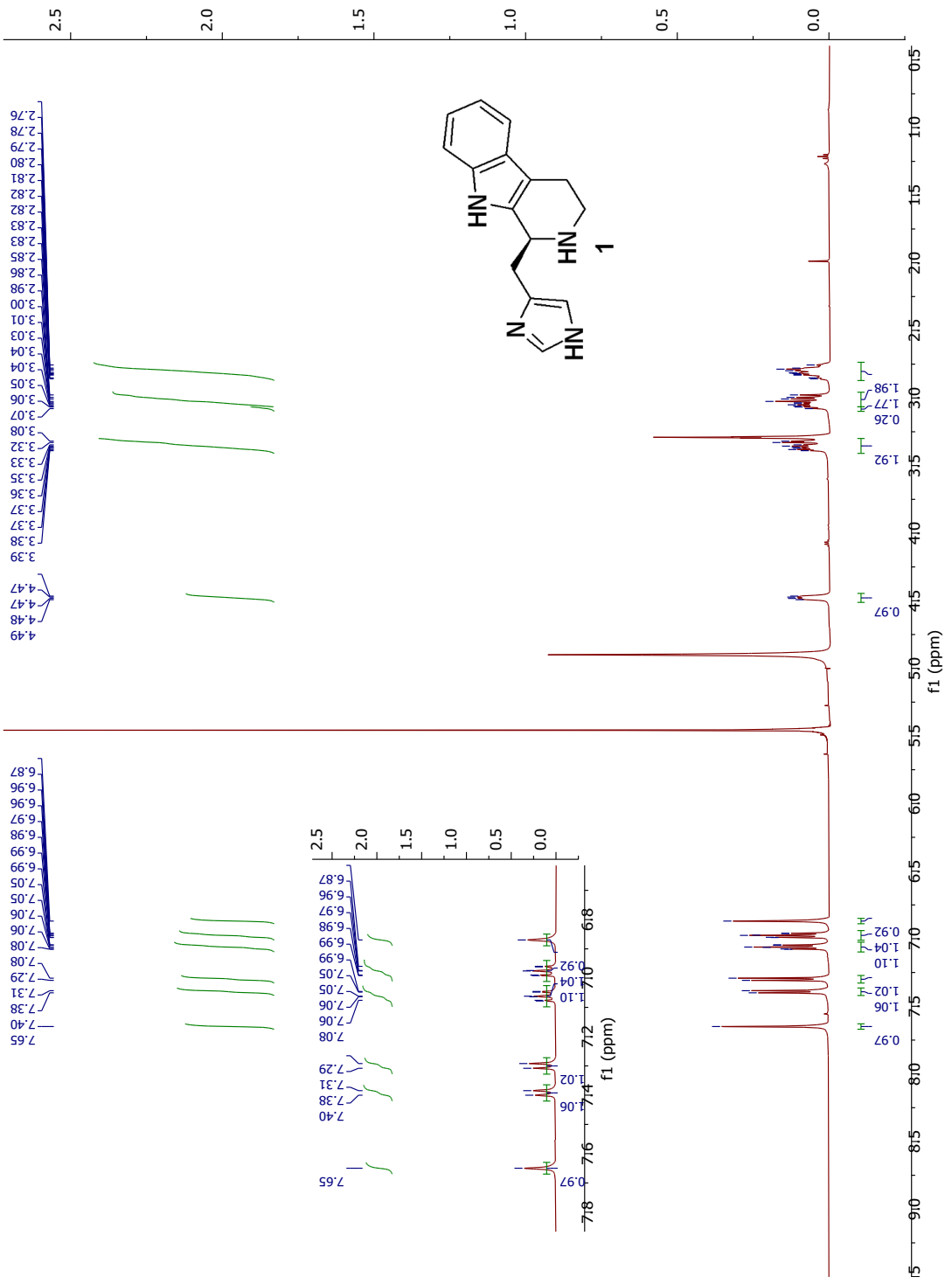
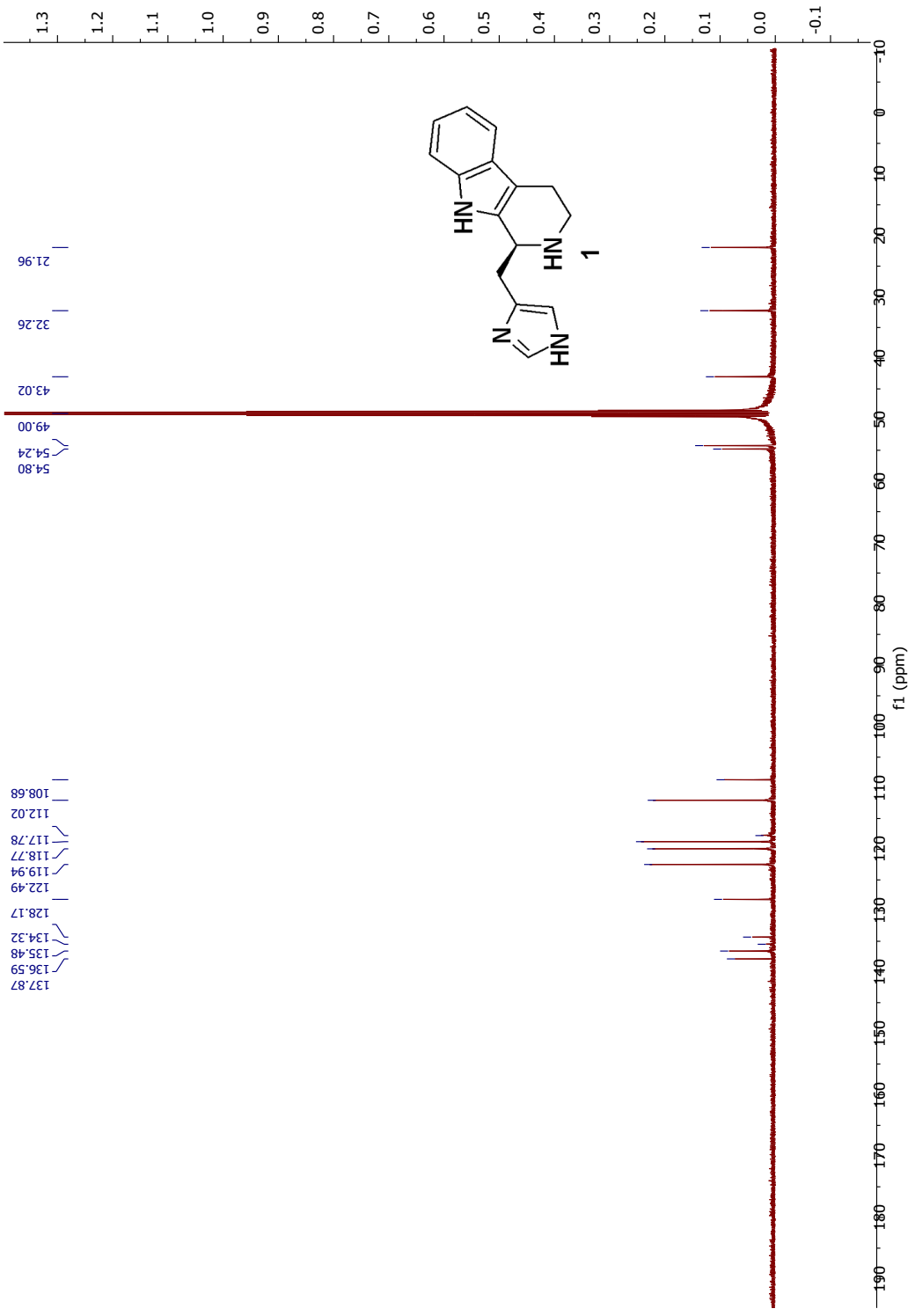
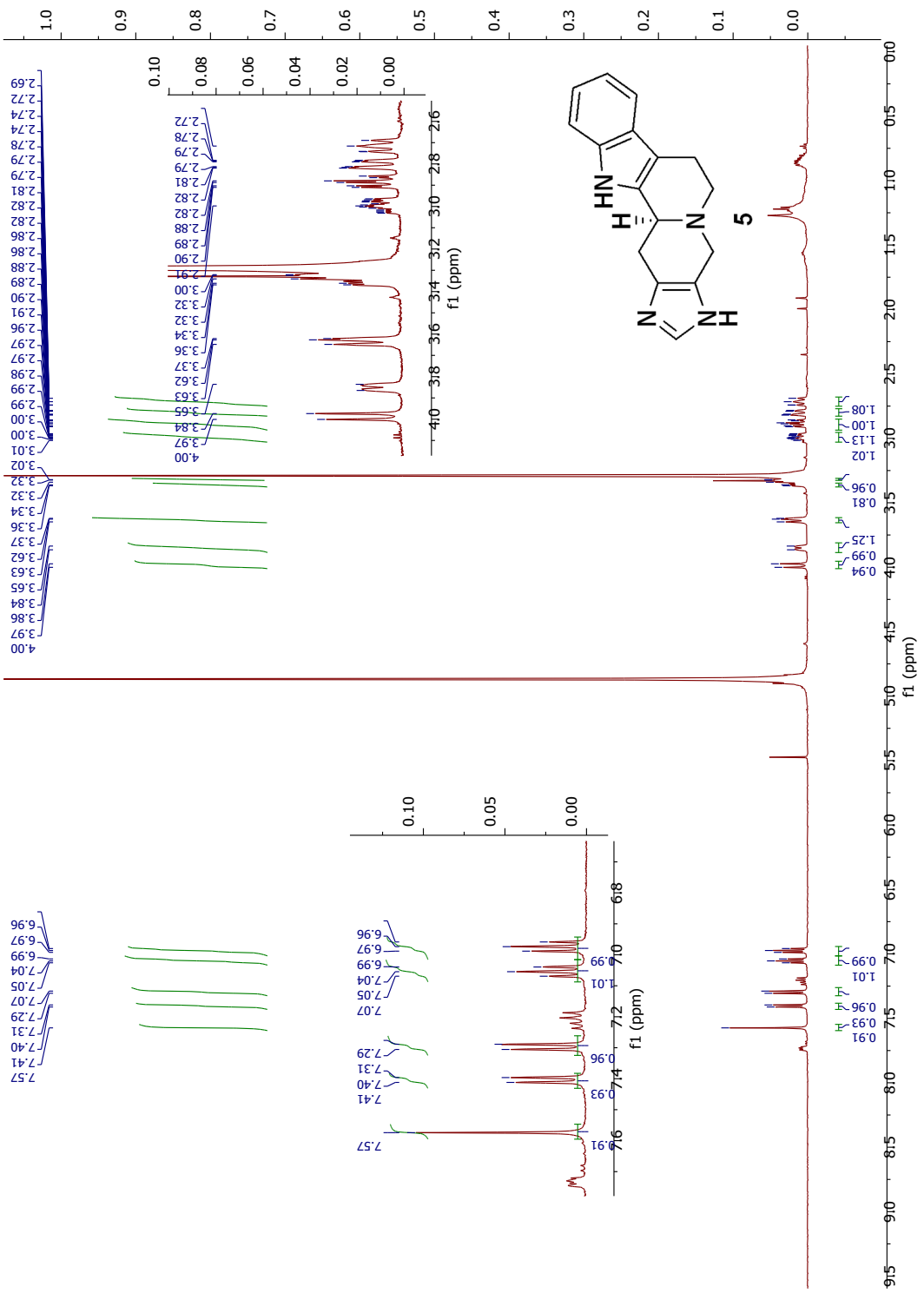
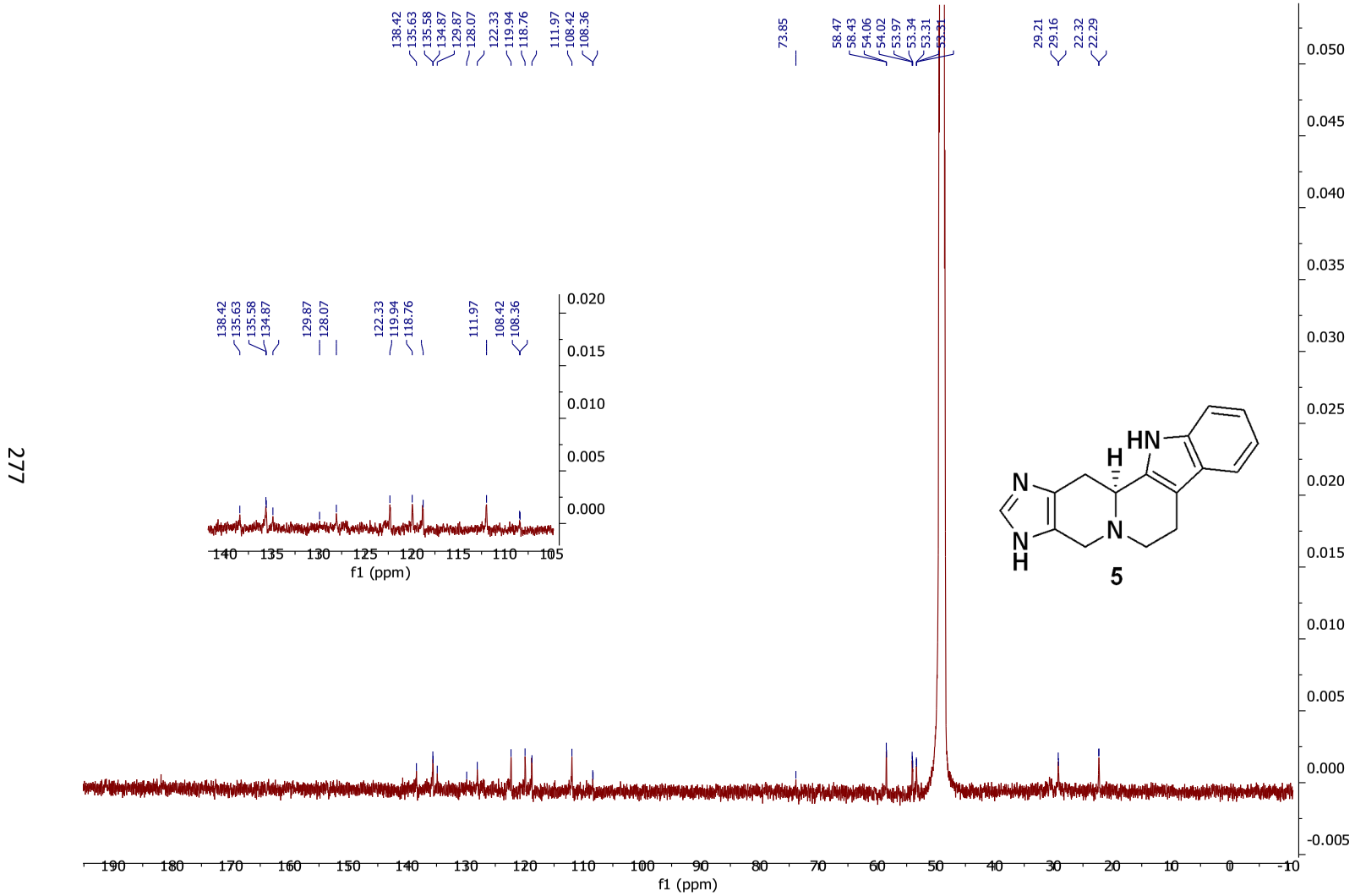
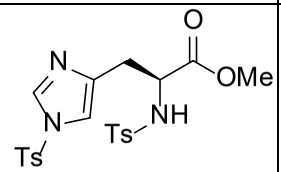
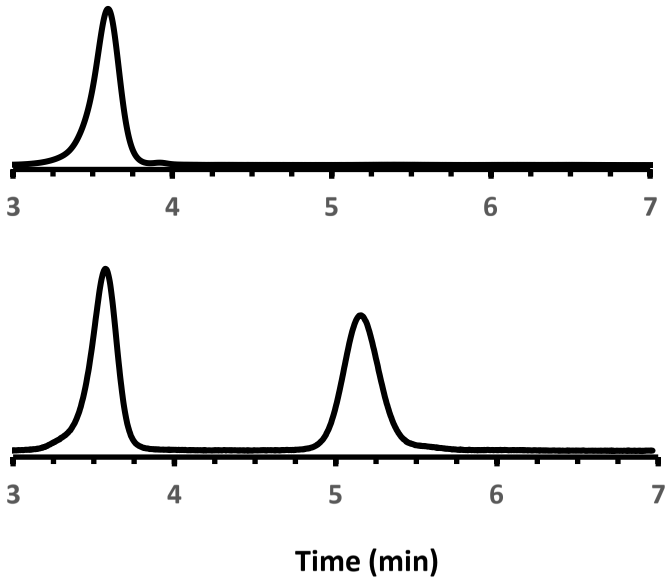
126.56
126.76
129.74
135.19
136.14
137.93
143.53

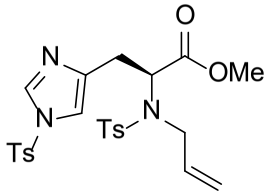
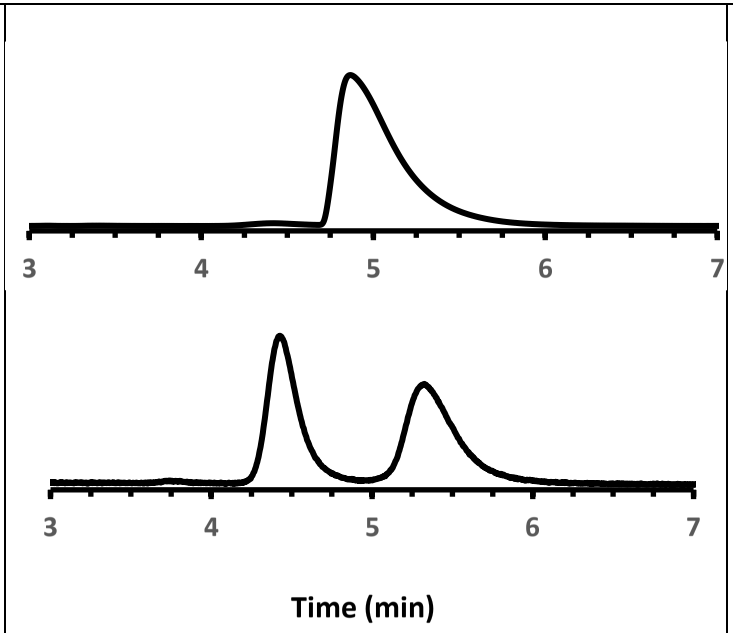

NH
HN
N
HN
1
f1 (ppm)

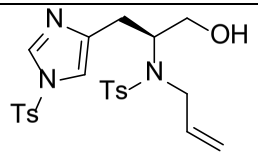
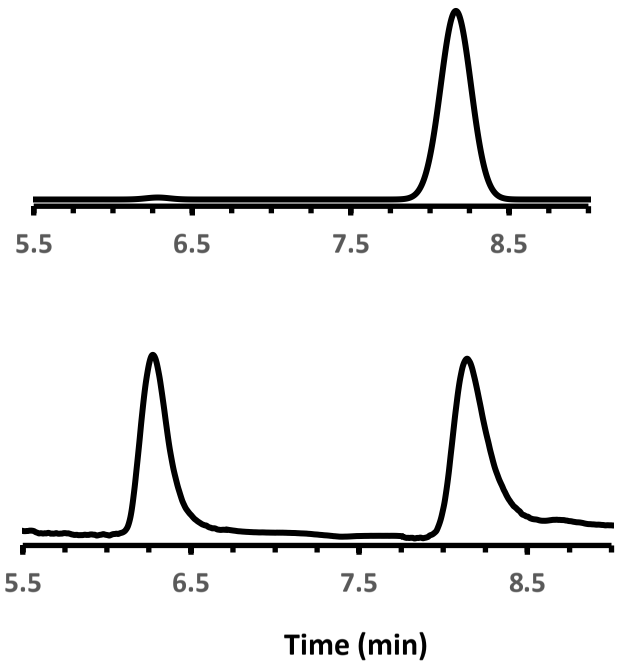

1.3
1.2
1.1
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
-0.1
HN
NH
N
HN
1
21.96
32.26
43.02
49.00
54.24
54.80
108.68
112.02
117.78
118.77
119.94
122.49
128.17
134.32
135.48
136.59
137.87
-10
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
f1 (ppm)

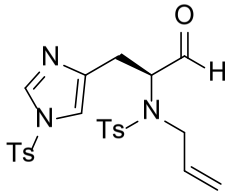
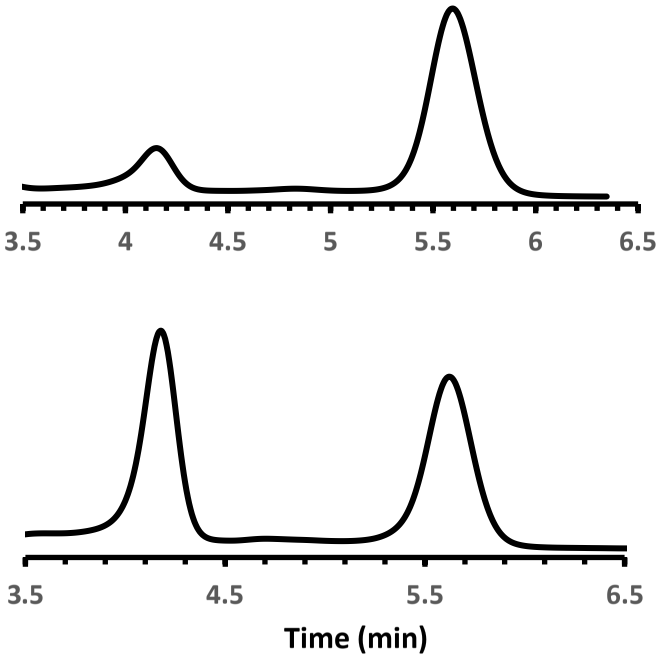

5
f1 (ppm)

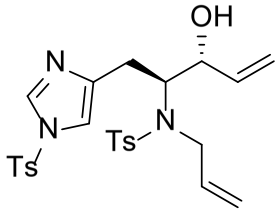
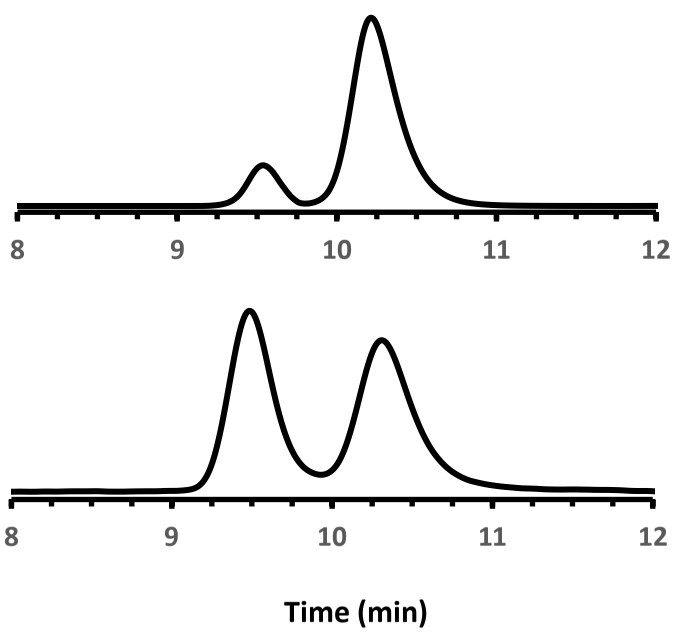

138.42
135.63
135.58
134.87
129.87
128.07
122.33
119.94
118.76
111.97
108.42
108.36
73.85
58.47
58.43
54.06
54.02
53.97
53.34
53.31
53.31
29.21
29.16
22.32
22.29
f1 (ppm)
HN
H
N
N
N
H
5

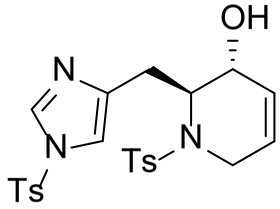
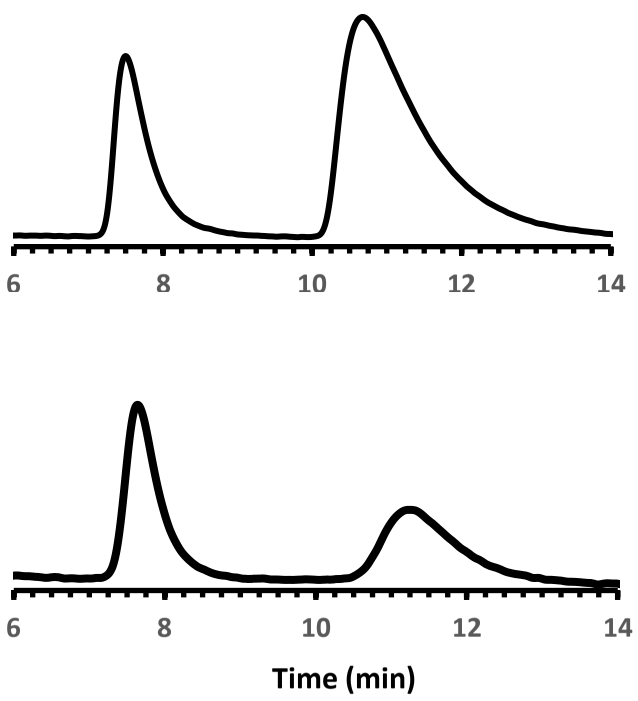
S. No.	Structure	Name (#)	Rac		%ee
1		S-2-(Toluene-4-sulfonylamino)-3-[1-(toluene-4-sulfonyl)-1*H*-imidazol-4-ylpropionic acid methyl ester (45)		ChiralPak IC column 3 µm, 3 mm ID x 150 mm L, 100% ethanol, 0.4 mL/min.	>99

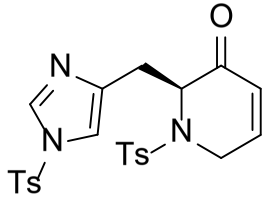
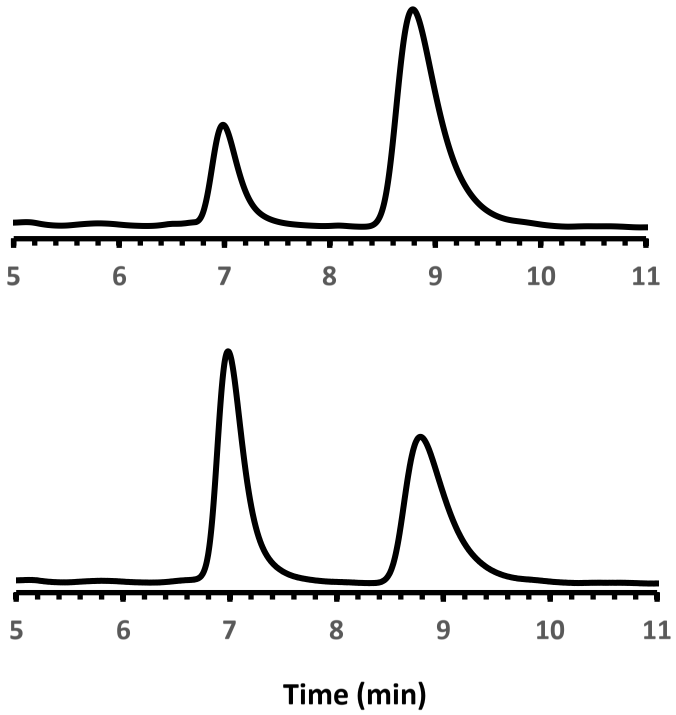
2		**S-2-[Allyl-(toluene-4-sulfonyl)-amino]-3-[1-(toluene-4-sulfonyl)-1*H*-imidazol-4-yl]-propionic acid methyl ester (27).**		**MaltoShell 2.7 µm SPP, 4.6 mm ID x 100 mm L, 20%-15%-65% ethanol-methanol-heptane.**	**>99**

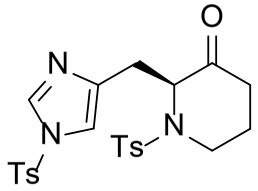
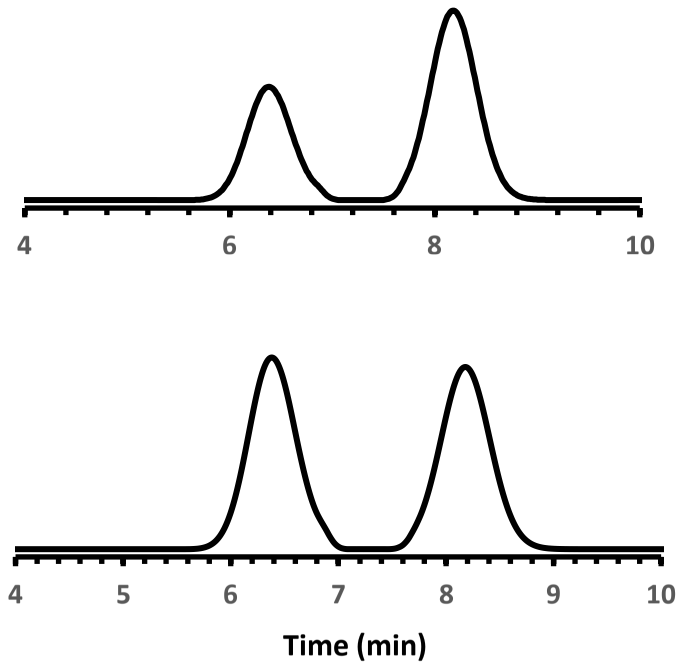
3		**S-N-allyl-N-(1-hydroxy-3-(1-tosyl-1H-imidazol-4-yl) propan-2-yl)-4-methylbenzenesulfonamide (55).**		**MaltoShell 2.7 µm SPP, 4.6 mm ID x 100 mm L, 20%-15%-65% ethanol-methanol-heptane**	**>99**

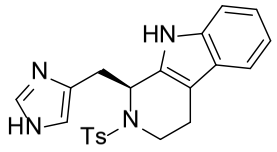
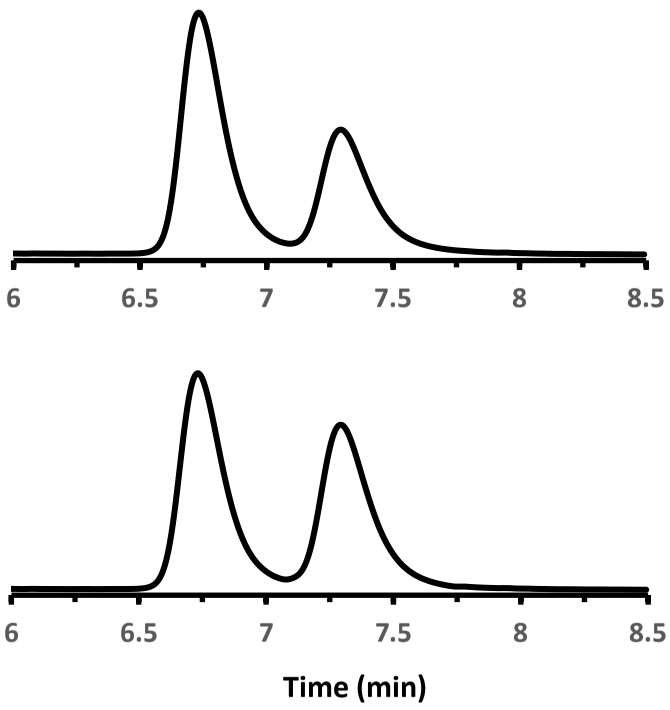
4		**S-N-allyl-4-methyl-N-(1-oxo-3-(1-tosyl-1H-imidazol-4-yl)propan-2-yl)benzenesulfonamide (46).**		**ChiralPak IC 3 µm, 3 mm ID x 150 mm L, 100% ethanol, 0.4 mL/min.**	**>70**

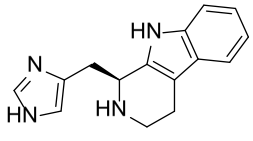
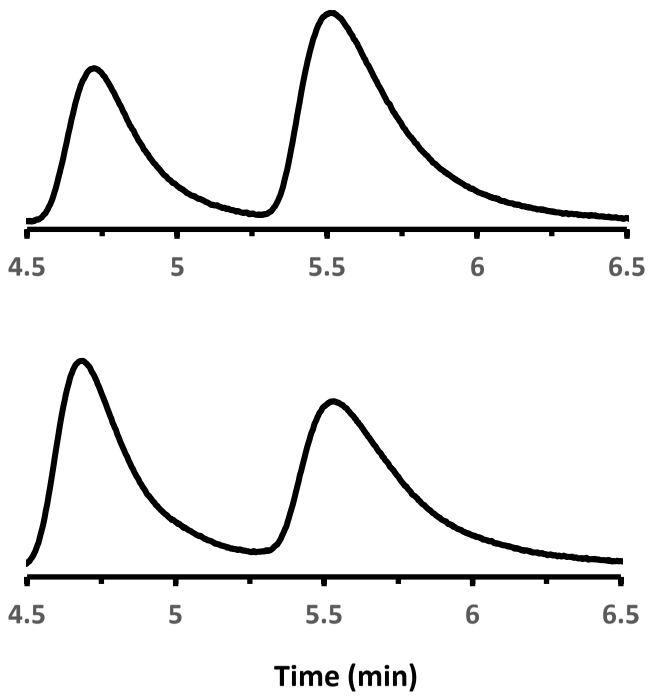
5		**N-Allyl-N-{2-hydroxy-1-[1-(toluene-4-sulfonyl)-1H-imidazol-4-yl-methyl]-but-3-enyl}-4-methyl-benzenesulfonamide (26).**		**MaltoShell 2.7 µm SPP, 4.6 mm ID x 100 mm L, 5%-5%-90% ethanol-methanol-heptane, 1 mL/min**	**>75**

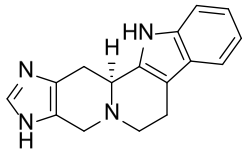
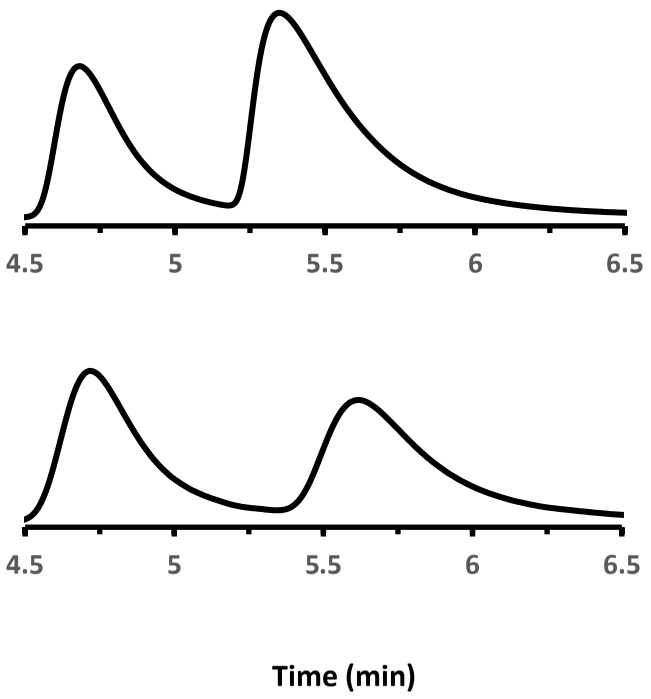
6		**(3S,4R)-1-(Toluene-4-sulfonyl)-3-[1-(toluene-4-sulfonyl)-1H-imidazol-4-yl-methyl]-1,2,3,4-tetrahydropyridin-4-ol (25):**		**MaltoShell 2.7 µm SPP, 4.6 mm ID x 100 mm L, 10%-10%-80% ethanol-methanol-heptane, 1 mL/min.**	**>50**

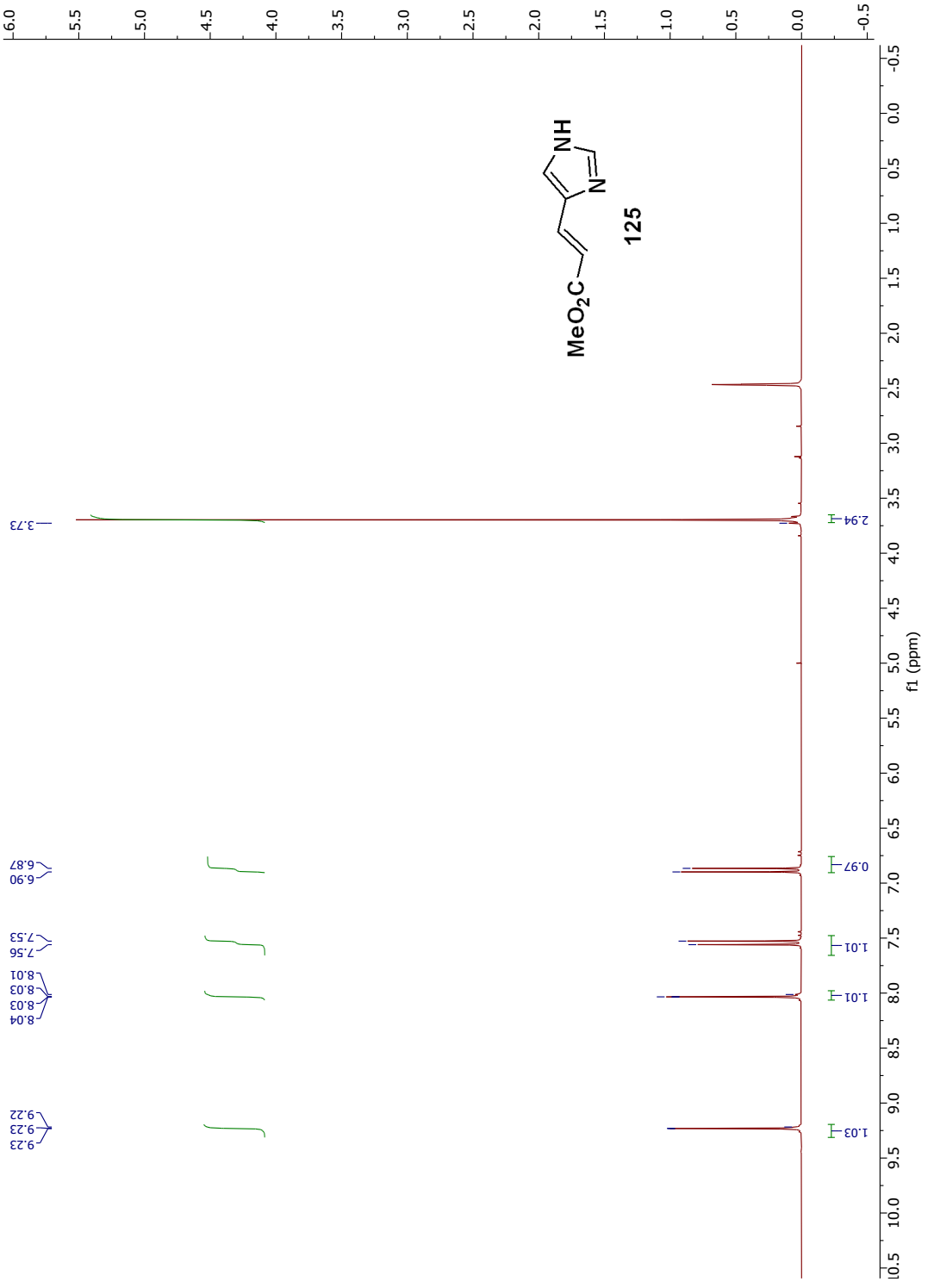
7		**S-1-Tosyl-2-((1-tosyl-1H-imidazol-4-yl) methyl)-1,6-dihydropyridin-3(2H) -one (48).**		**MaltoShell 2.7 µm SPP, 4.6 mm ID x 100 mm L, 15%-10%-75% ethanol-methanol-heptane, 1 mL/min.**	**>50**

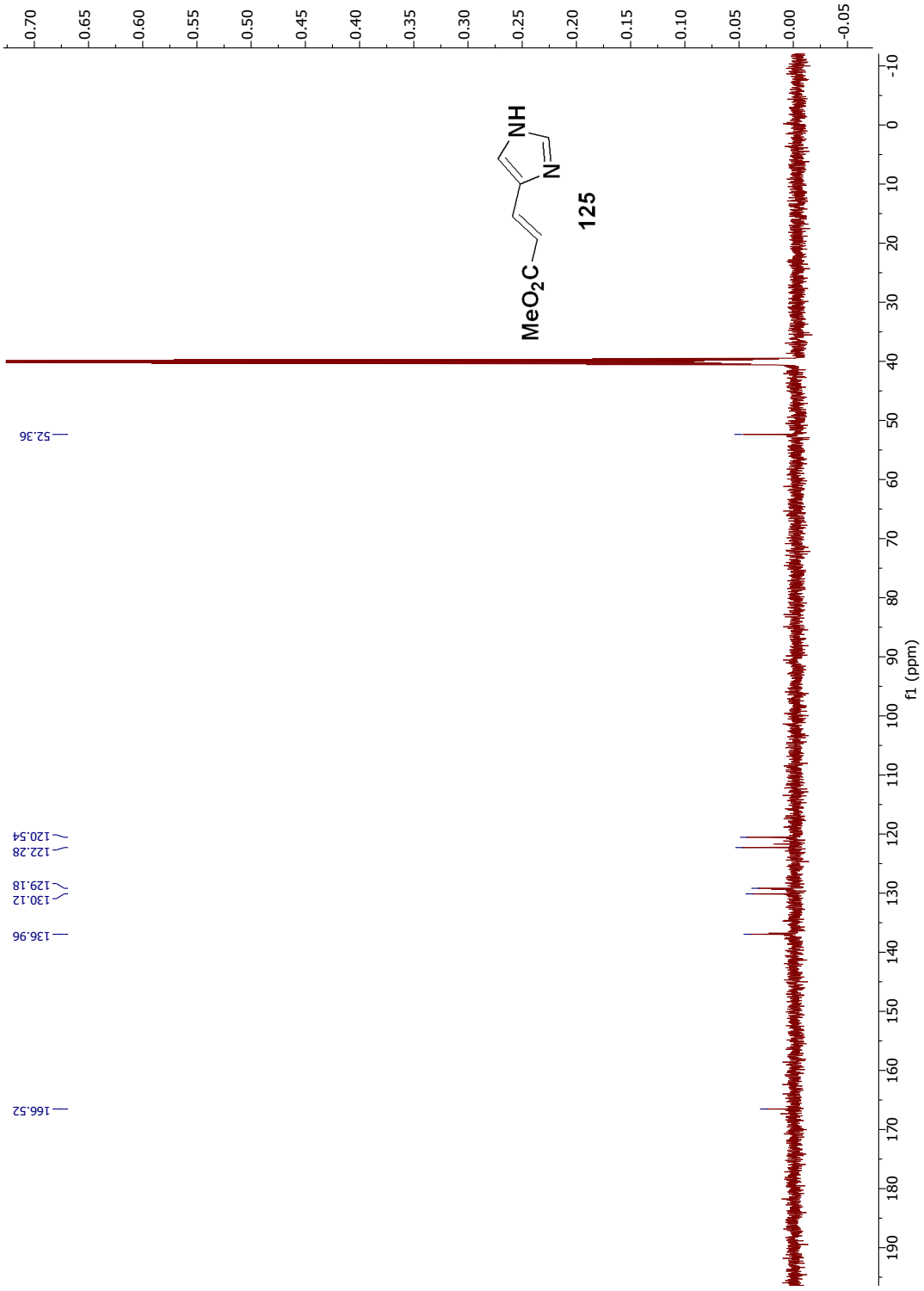
8		**S-1-(Toluene-4-sulfonyl)-3-[1-(toluene-4-sulfonyl)-1H-imidazol-4-ylmethyl]-piperidin-4-one (24).**		**MaltoShell 2.7 µm SPP, 4.6 mm ID x 100 mm L, 15%-15%-70% ethanol-methanol-heptane, 1 mL/min.**	**>35**

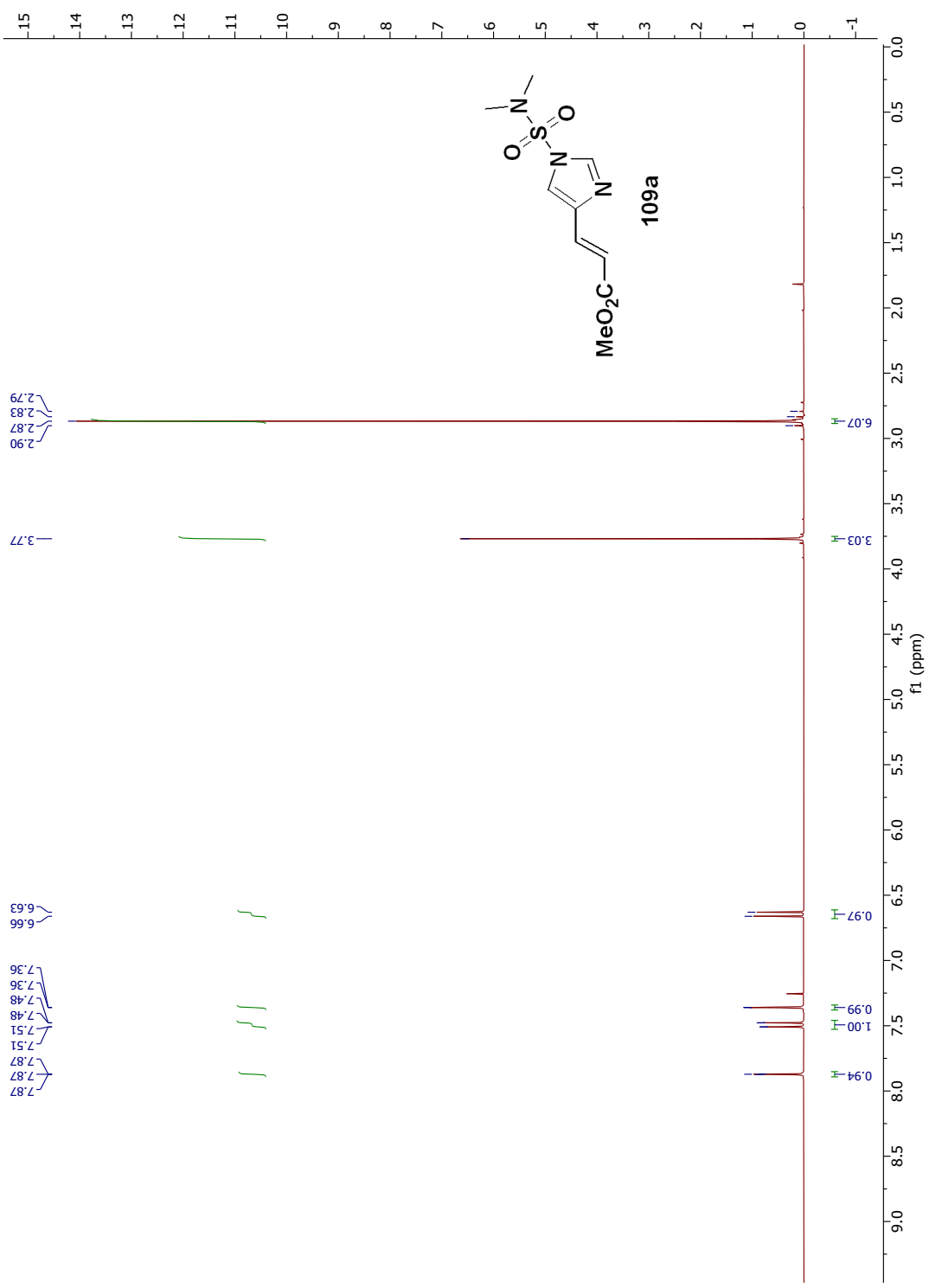
9		**S-1-((1H-Imidazol-5-yl) methyl) -2-tosyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b] indole (23).**		**NicoShell 2.7 µm SPP, 3 mm ID x 150 mm L, 100% methanol 0.1% ammonium trifluoroacetate, 0.4 mL/min.**	**>30**

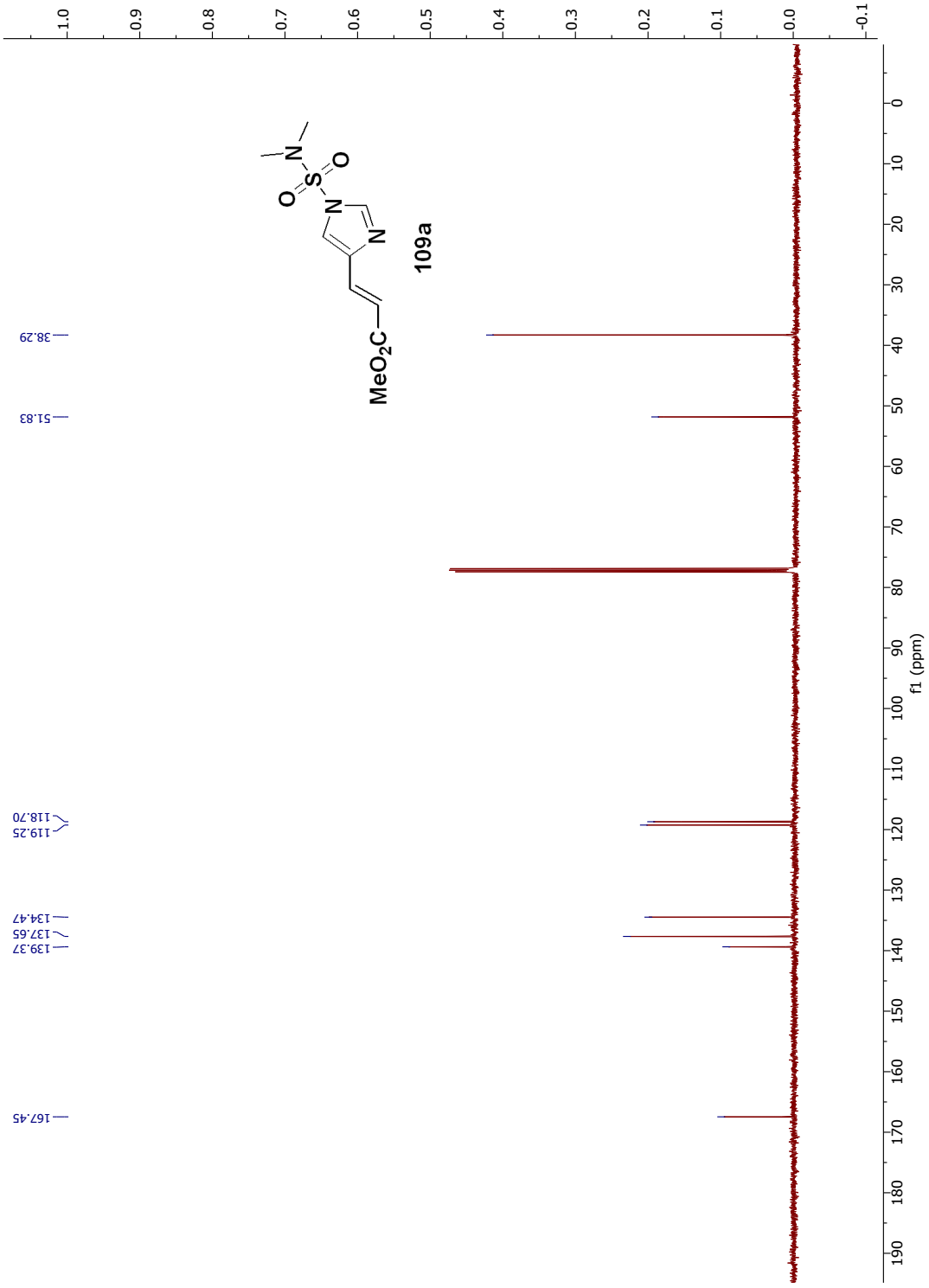
10		**S-1-((1H-Imidazol-5-yl)methyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (Halopscleridamine) (1).**		**NicoShell 2.7 µm SPP, 3 mm ID x 150 mm L, 100% methanol 0.1% ammonium trifluoroacetate, 0.4 mL/min.**	**>30**

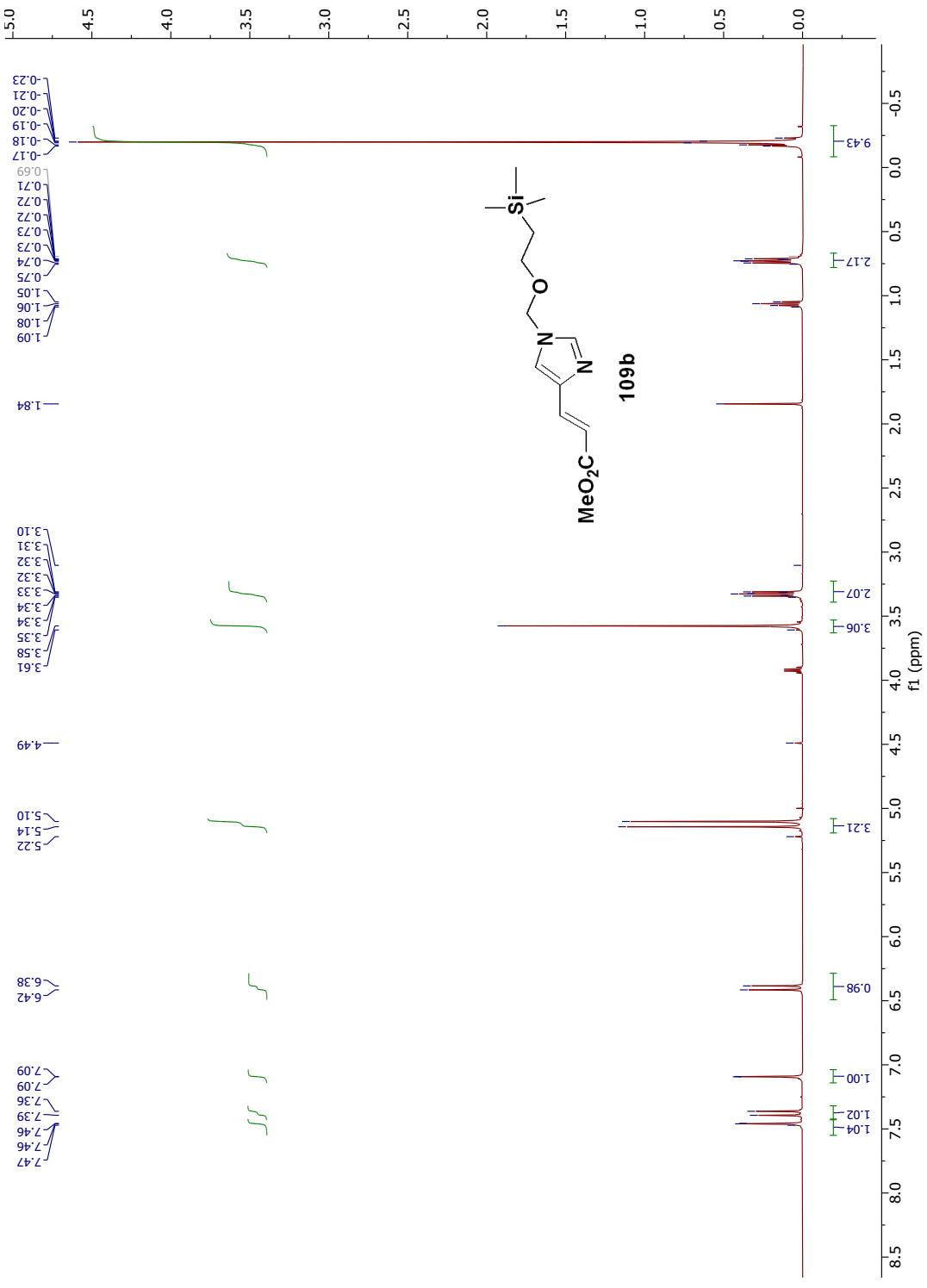
11		**Villagorgin A (5).**		**NicoShell 2.7 µm SPP, 3 mm ID x 150 mm L, 100% methanol 0.1% ammonium trifluoroacetate, 0.4 mL/min.**	**>30**

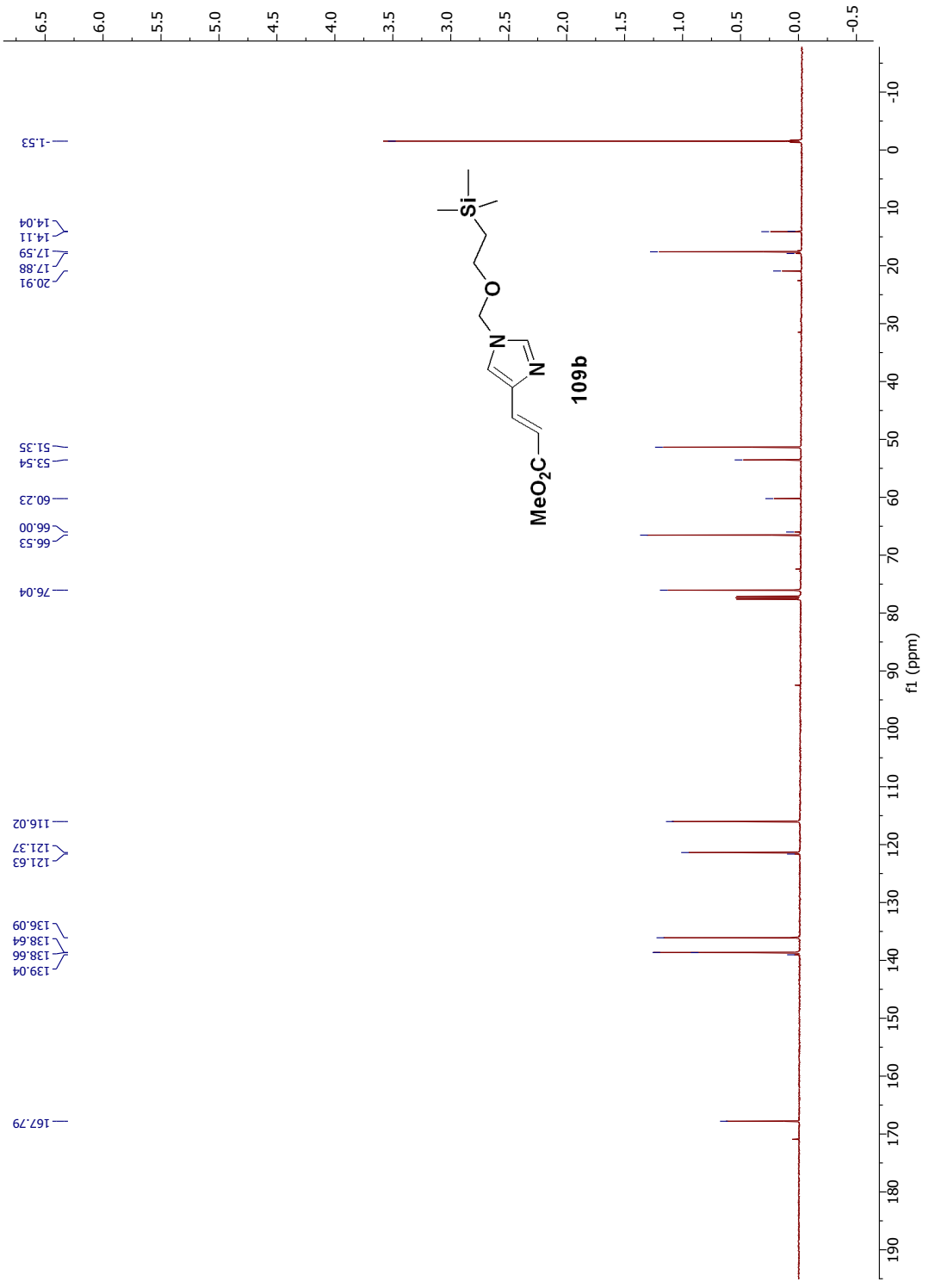

MeO2C
NH
N
125
9.23
9.23
9.22
8.04
8.03
8.03
8.01
7.56
7.53
6.90
6.87
3.73
1.03
1.01
1.01
1.01
0.97
2.94
f1 (ppm)

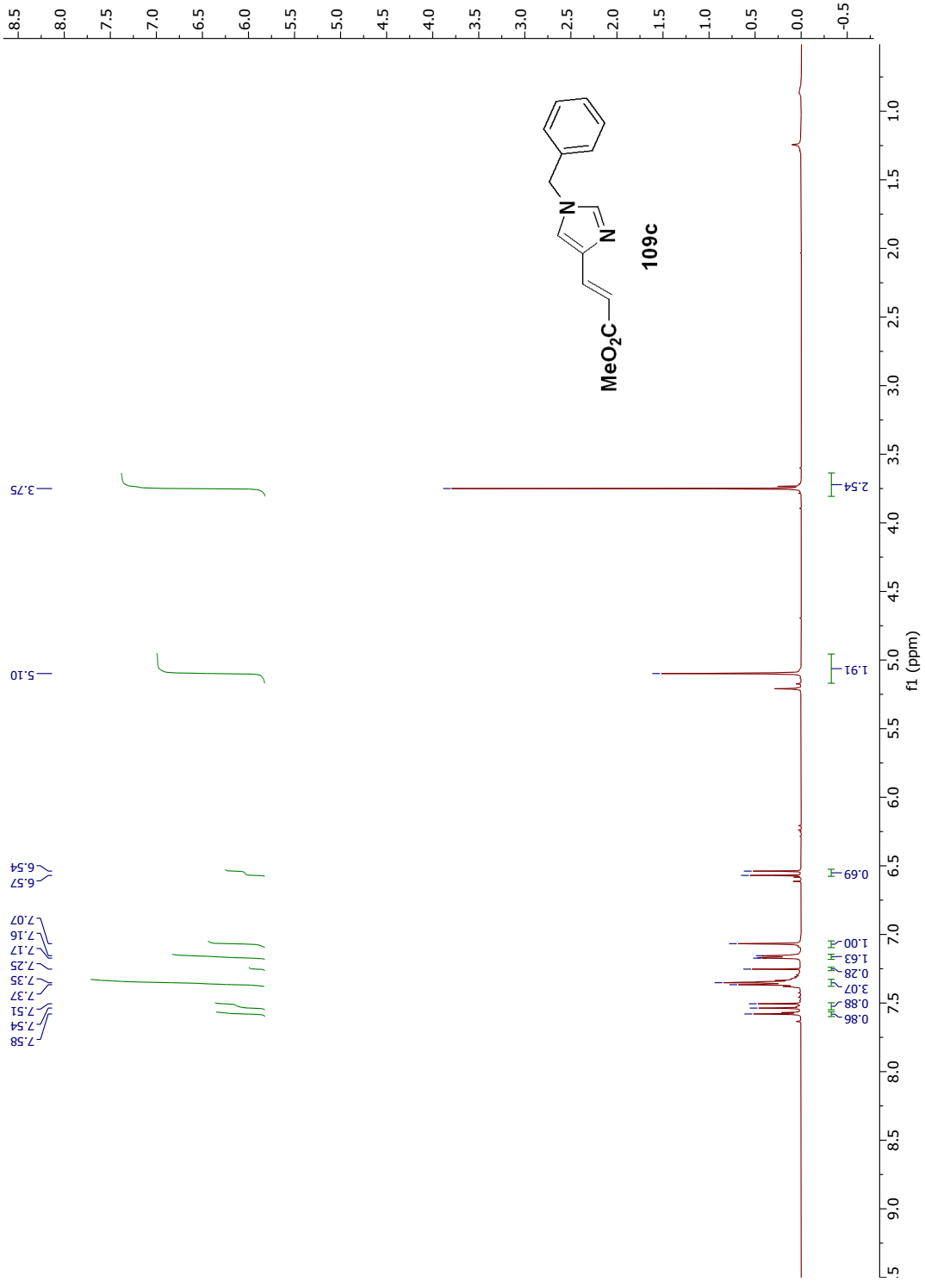

MeO2C
NH
N
125
52.36
120.54
122.28
129.18
130.12
136.96
166.52
f1 (ppm)

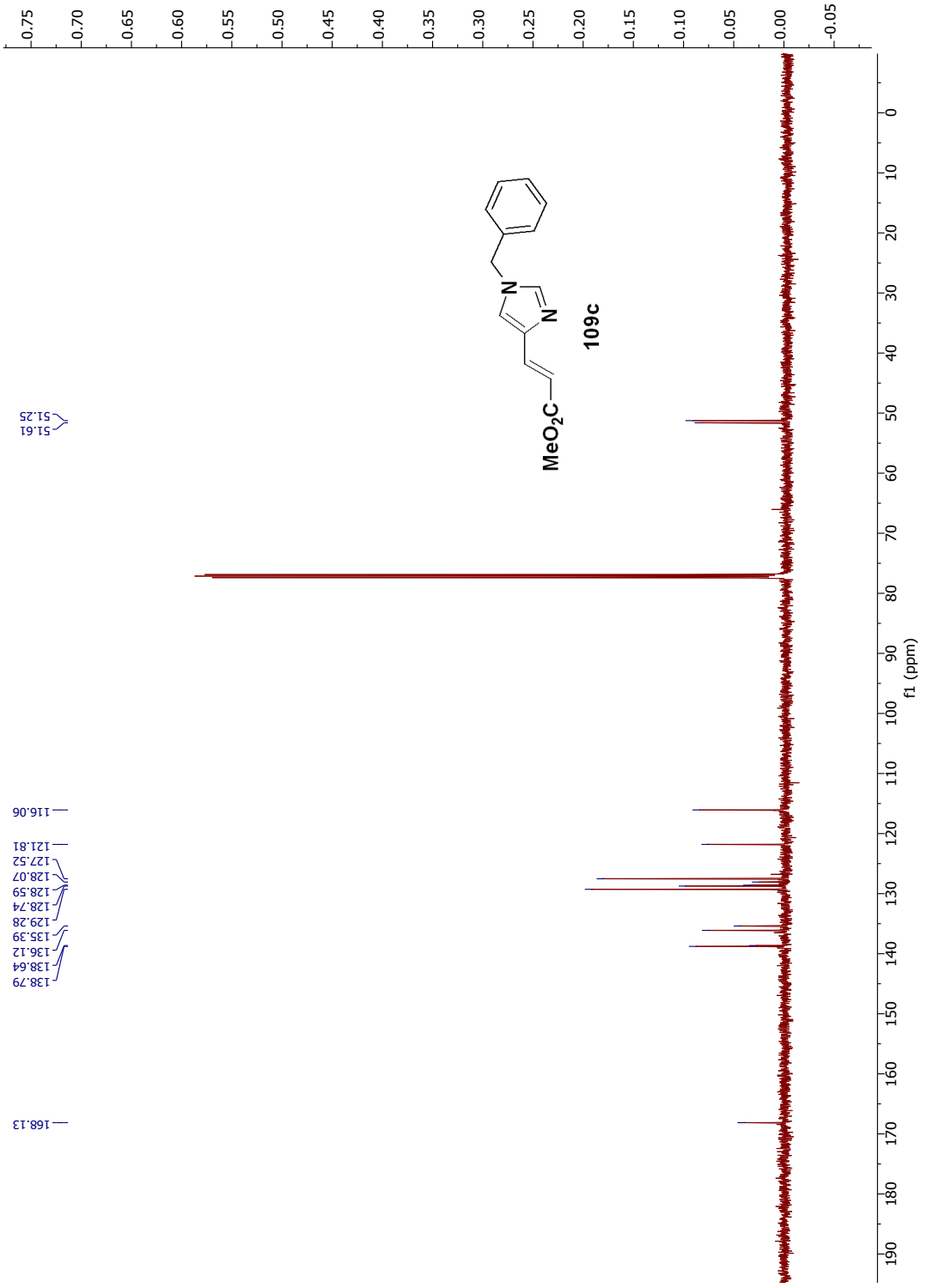

109a
f1 (ppm)

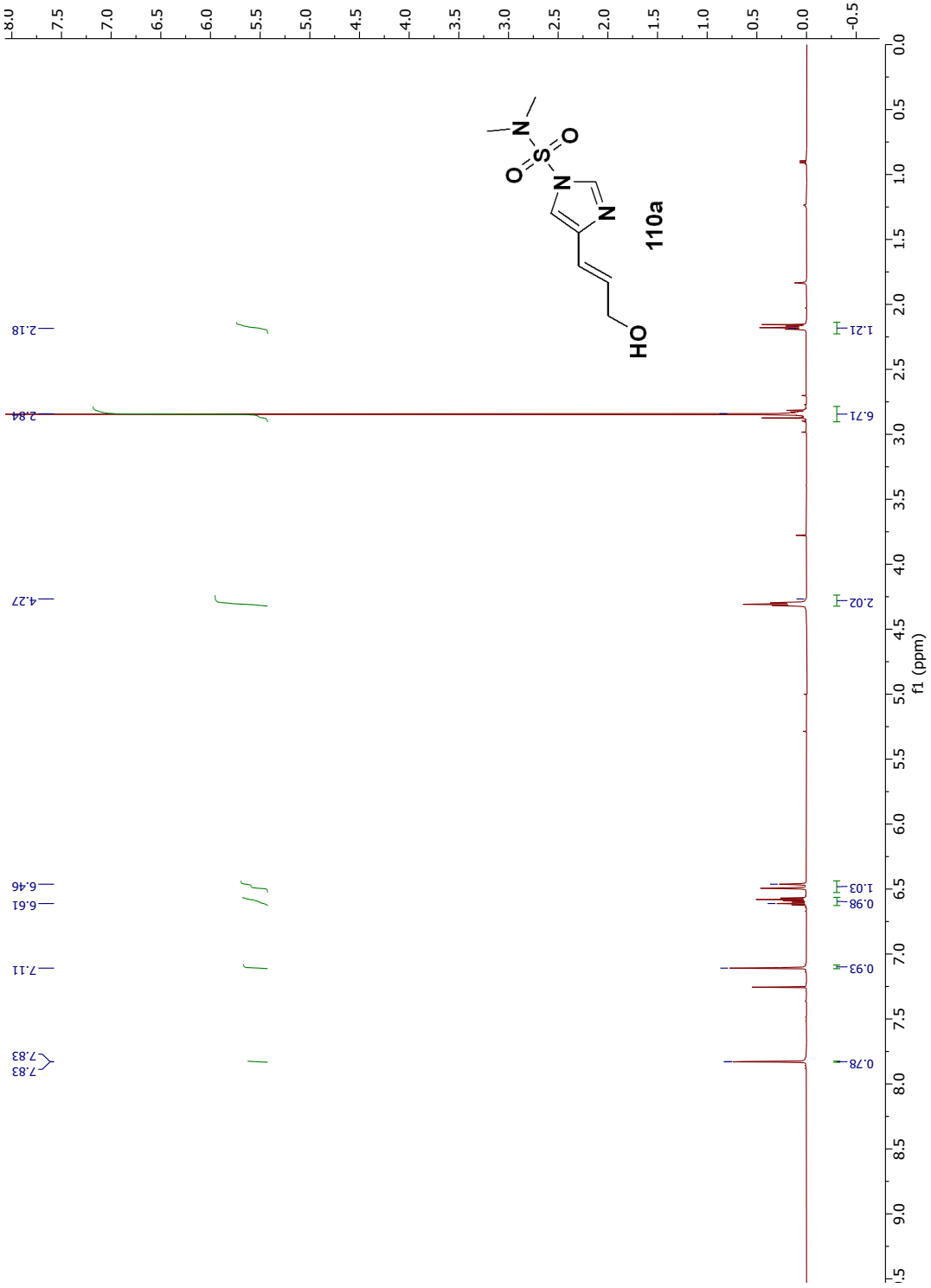

109a
MeO2C
38.29
51.83
119.25
118.70
139.37
137.65
134.47
167.45
f1 (ppm)

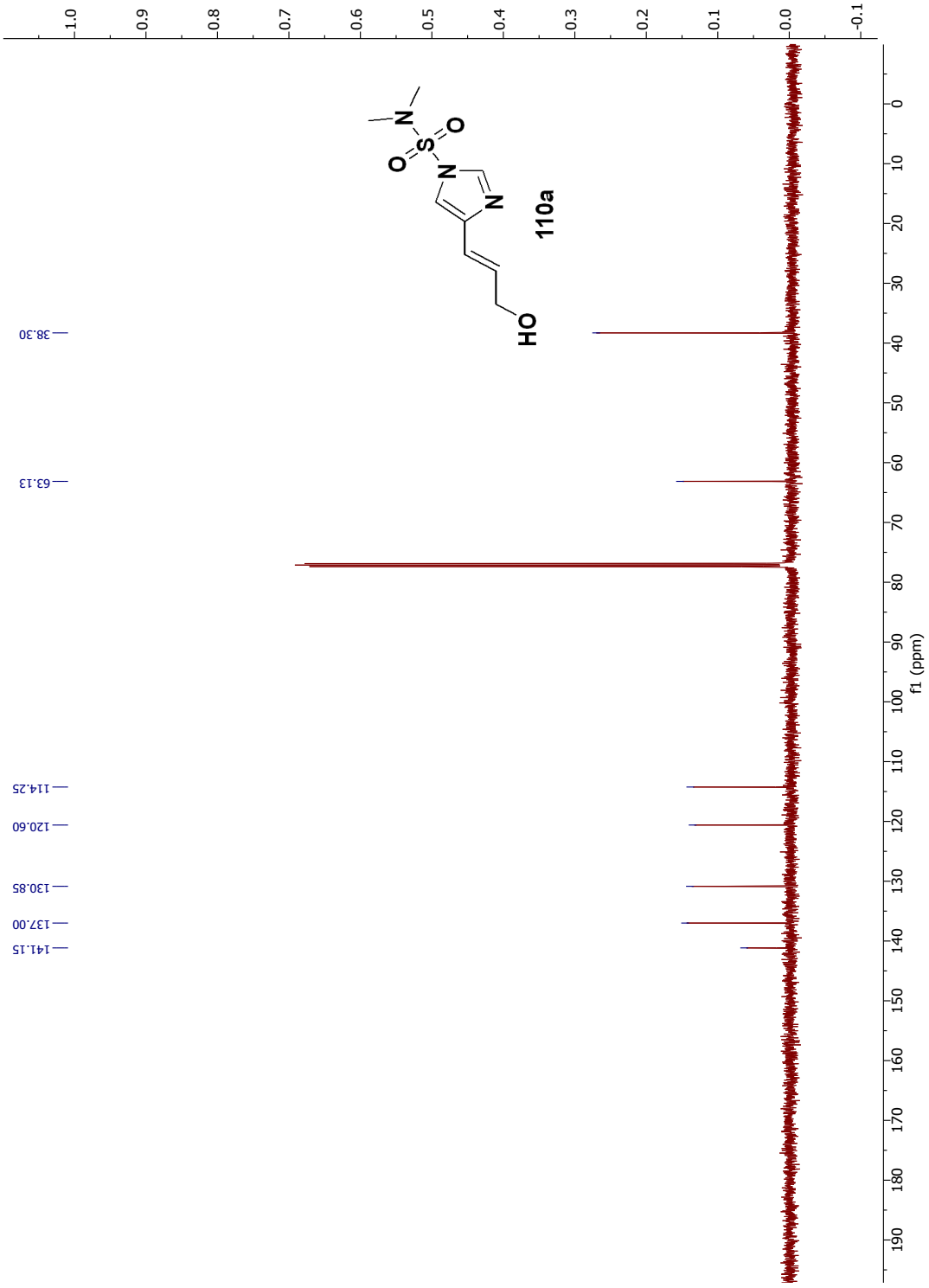

Si
O
N
N
MeO2C
109b
f1 (ppm)

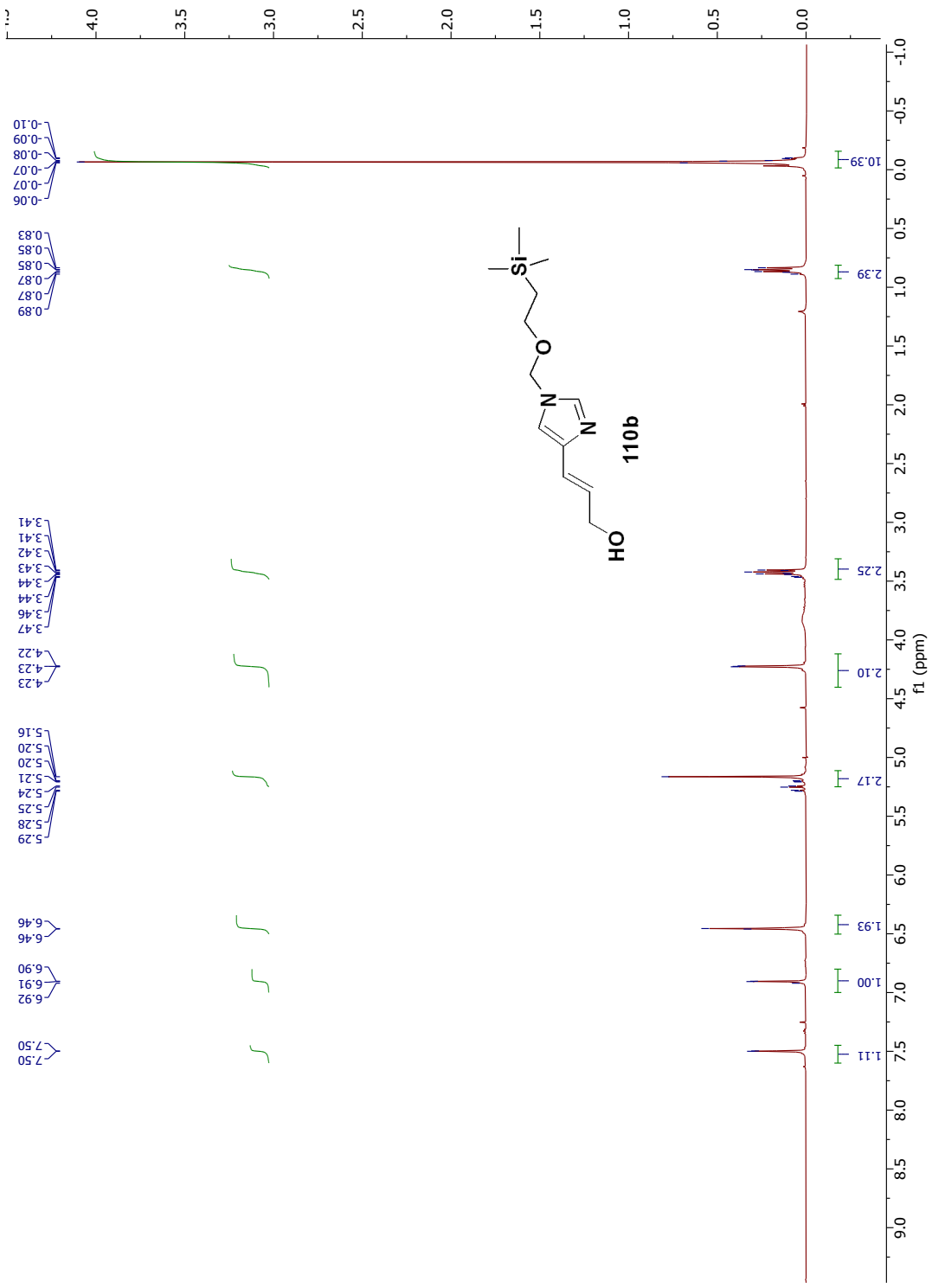

-1.53
14.04
14.11
17.59
17.88
20.91
51.35
53.54
60.23
66.00
66.53
76.04
116.02
121.37
121.63
136.09
138.64
138.66
139.04
167.79
109b
f1 (ppm)

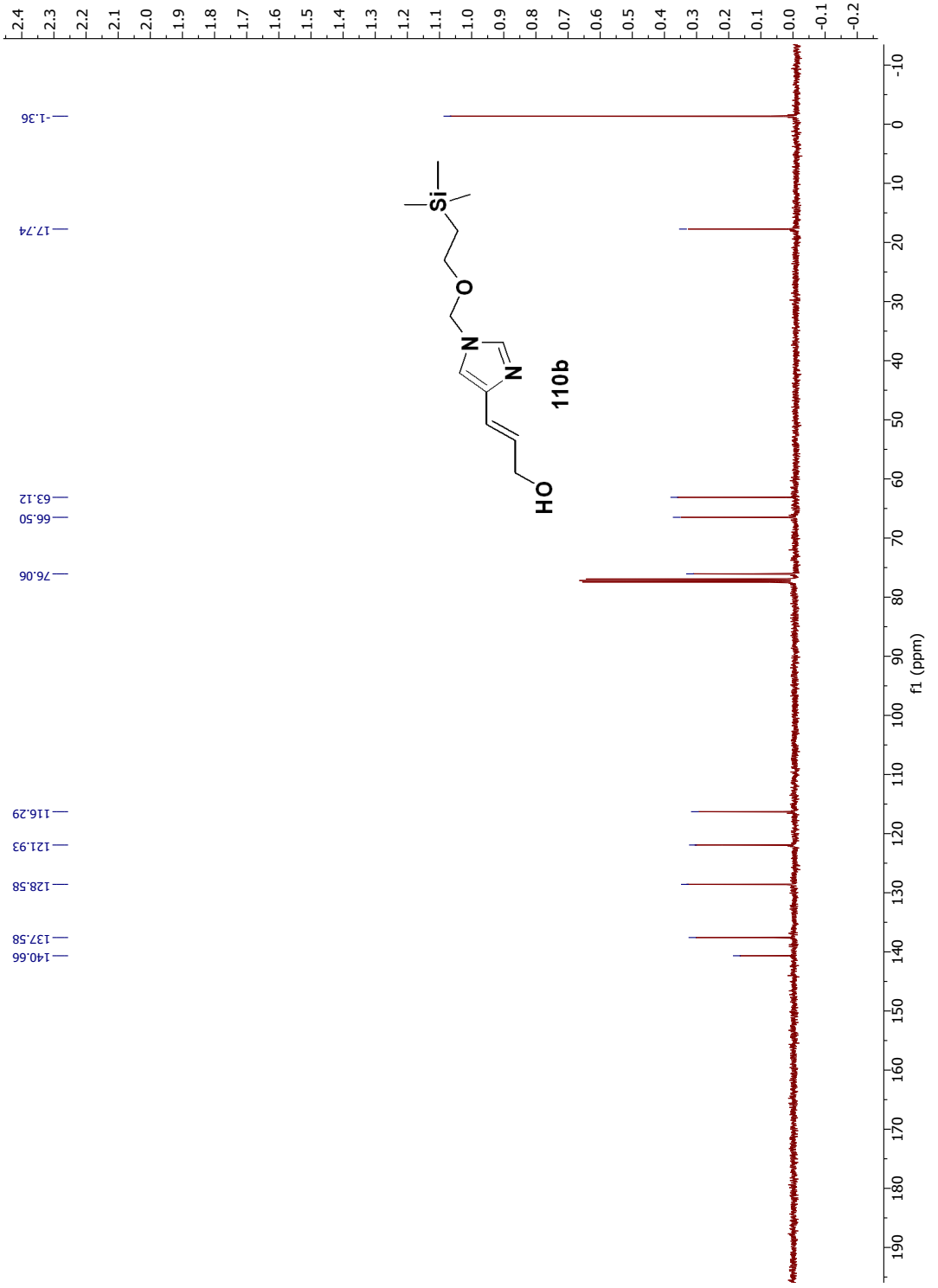

109c
MeO2C
f1 (ppm)

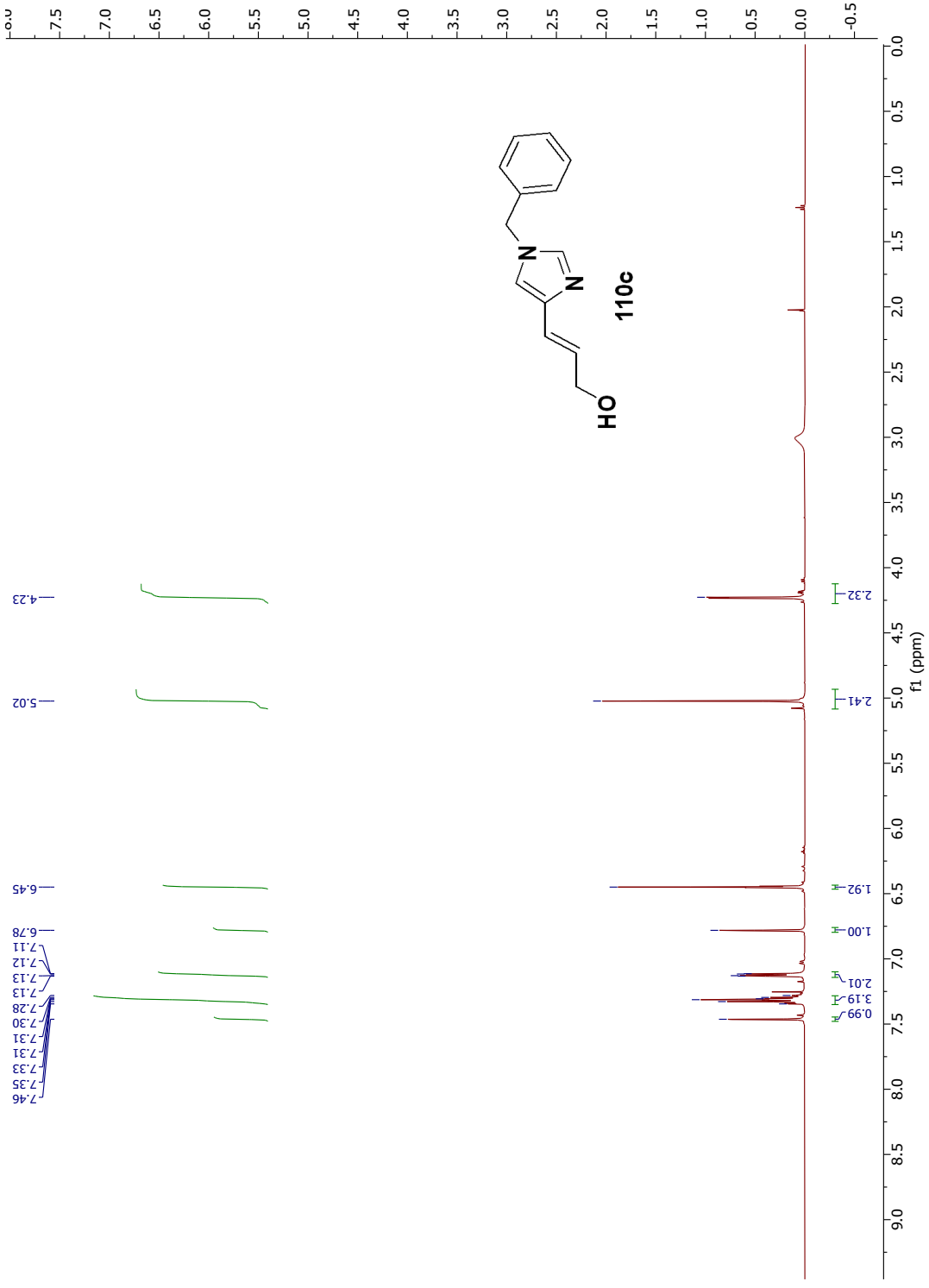

168.13
138.79
138.64
136.12
135.39
129.28
128.74
128.59
128.07
127.52
121.81
116.06
51.61
51.25
MeO2C
109c
f1 (ppm)

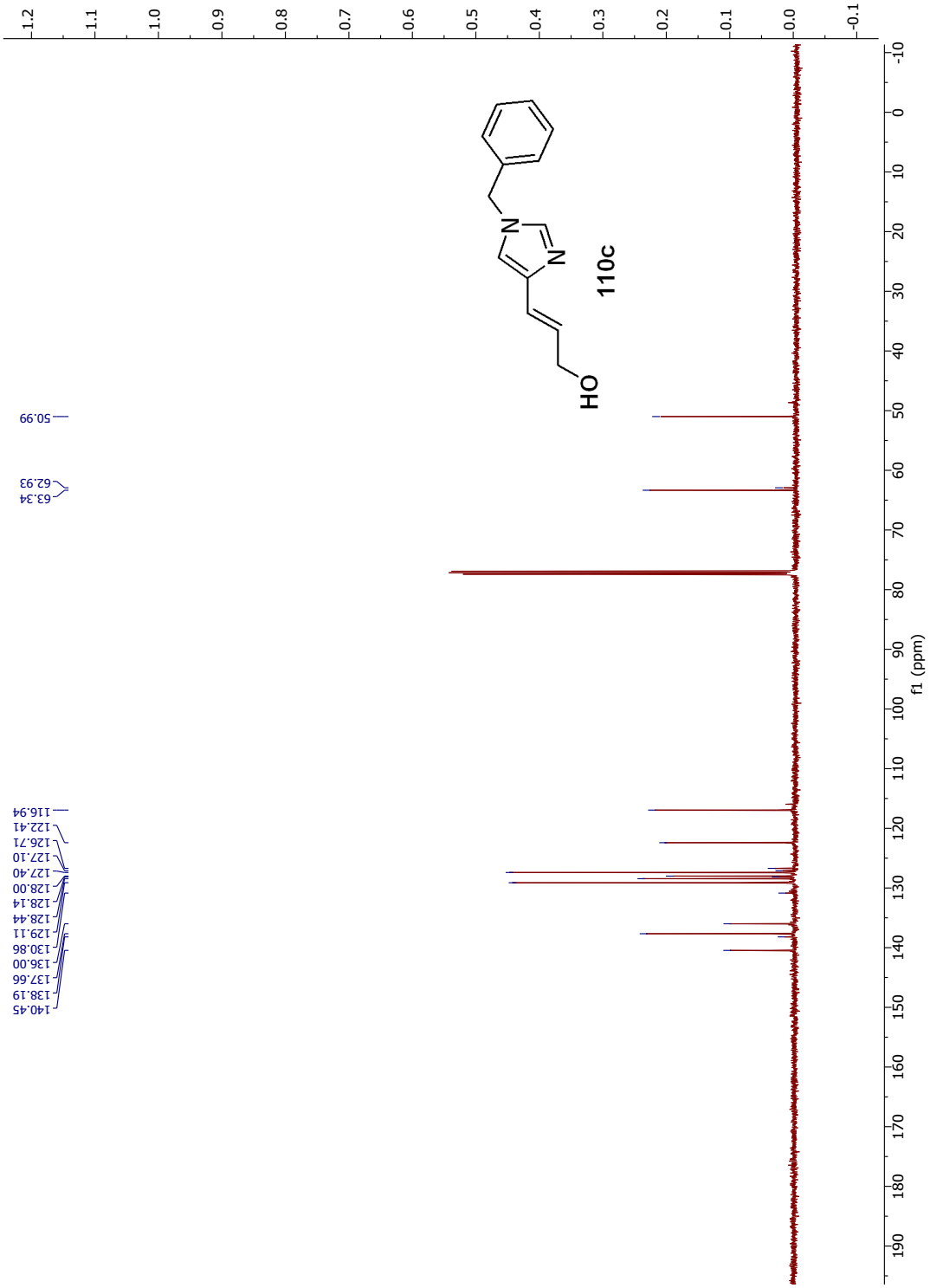

110a
HO
f1 (ppm)
7.83
7.83
7.11
6.61
6.46
4.27
2.84
2.18
0.78
0.93
0.98
1.03
2.02
6.71
1.21

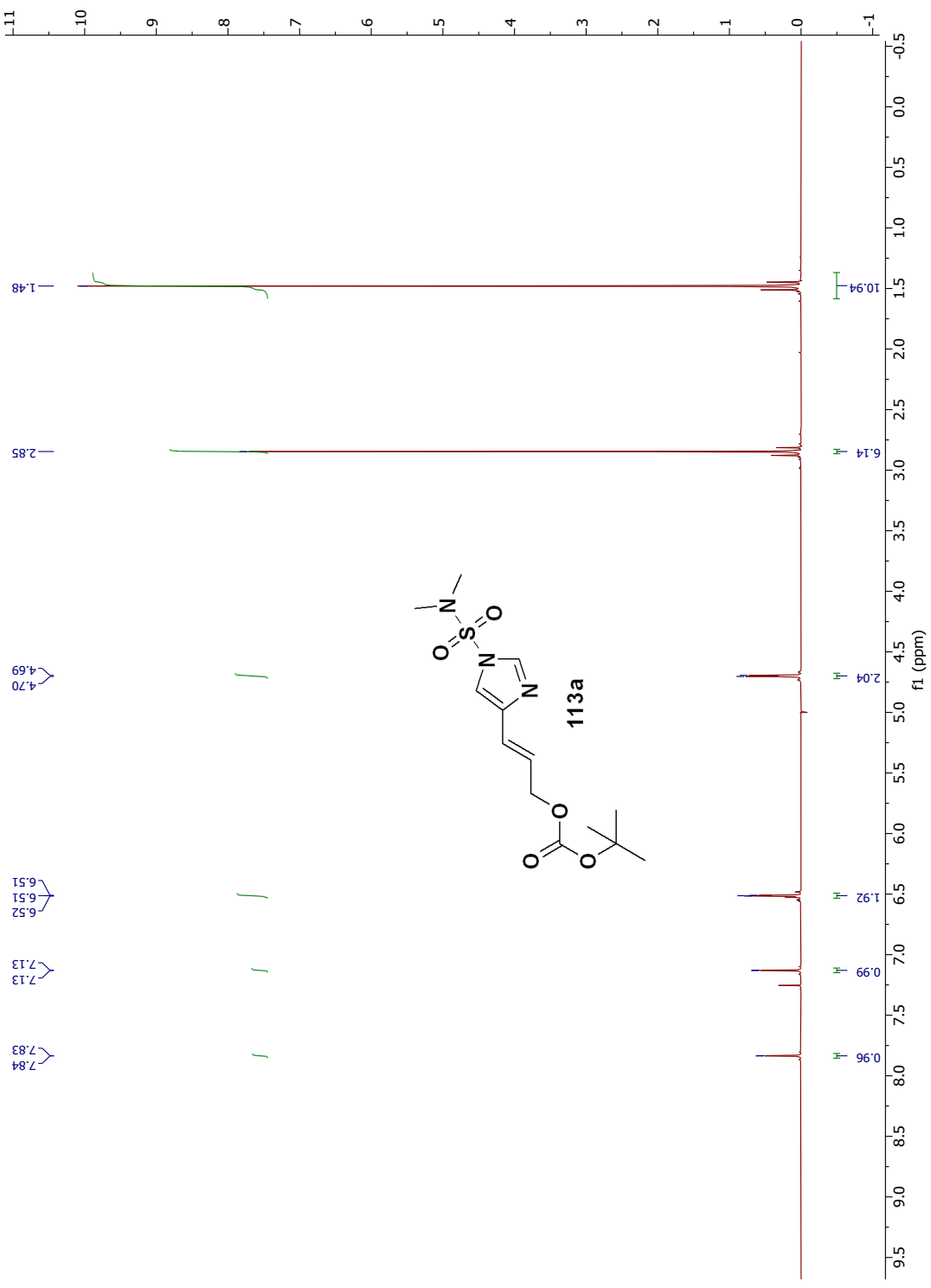

110a
HO
38.30
63.13
114.25
120.60
130.85
137.00
141.15
f1 (ppm)

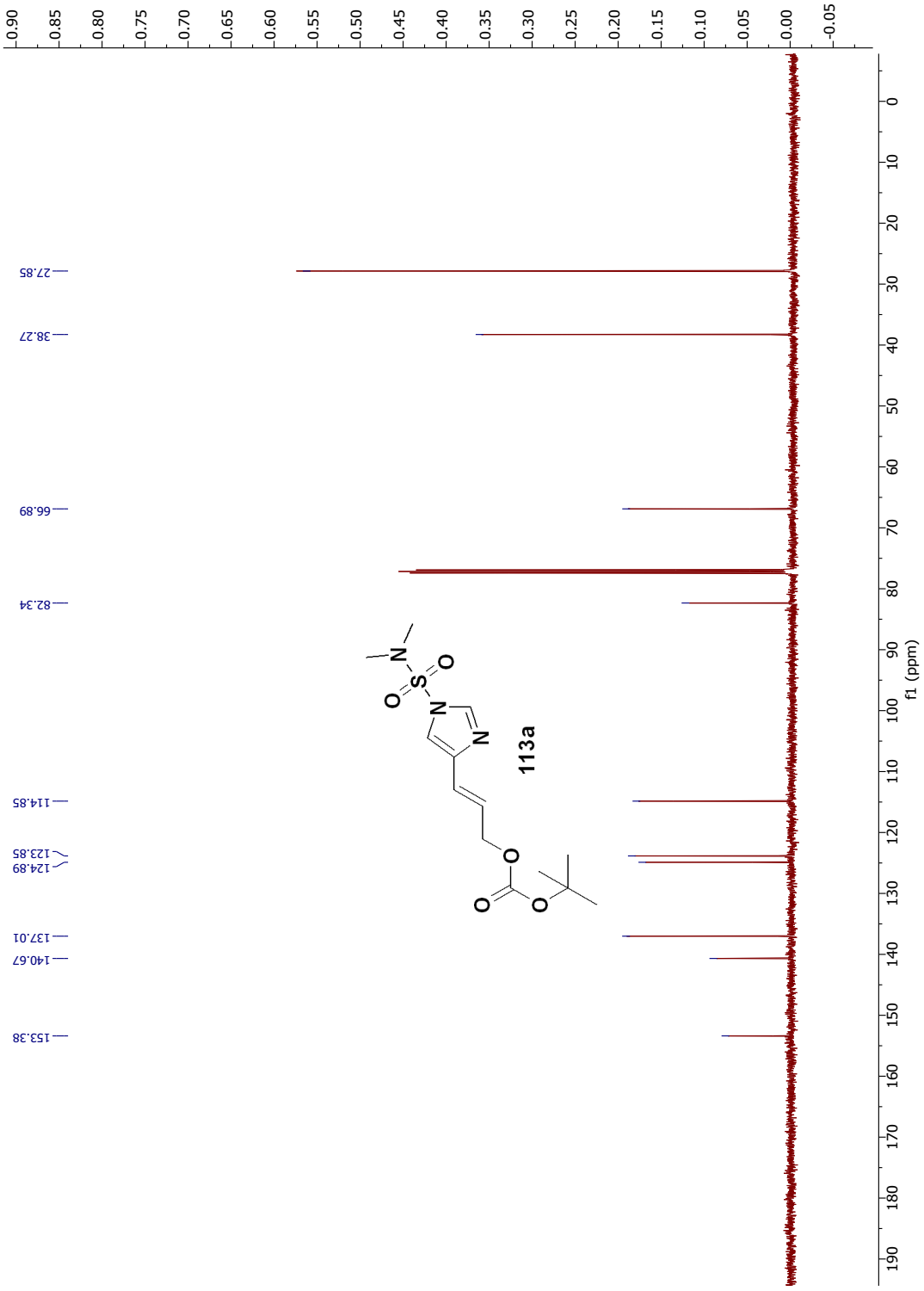

Si
O
N
N
HO
110b
f1 (ppm)

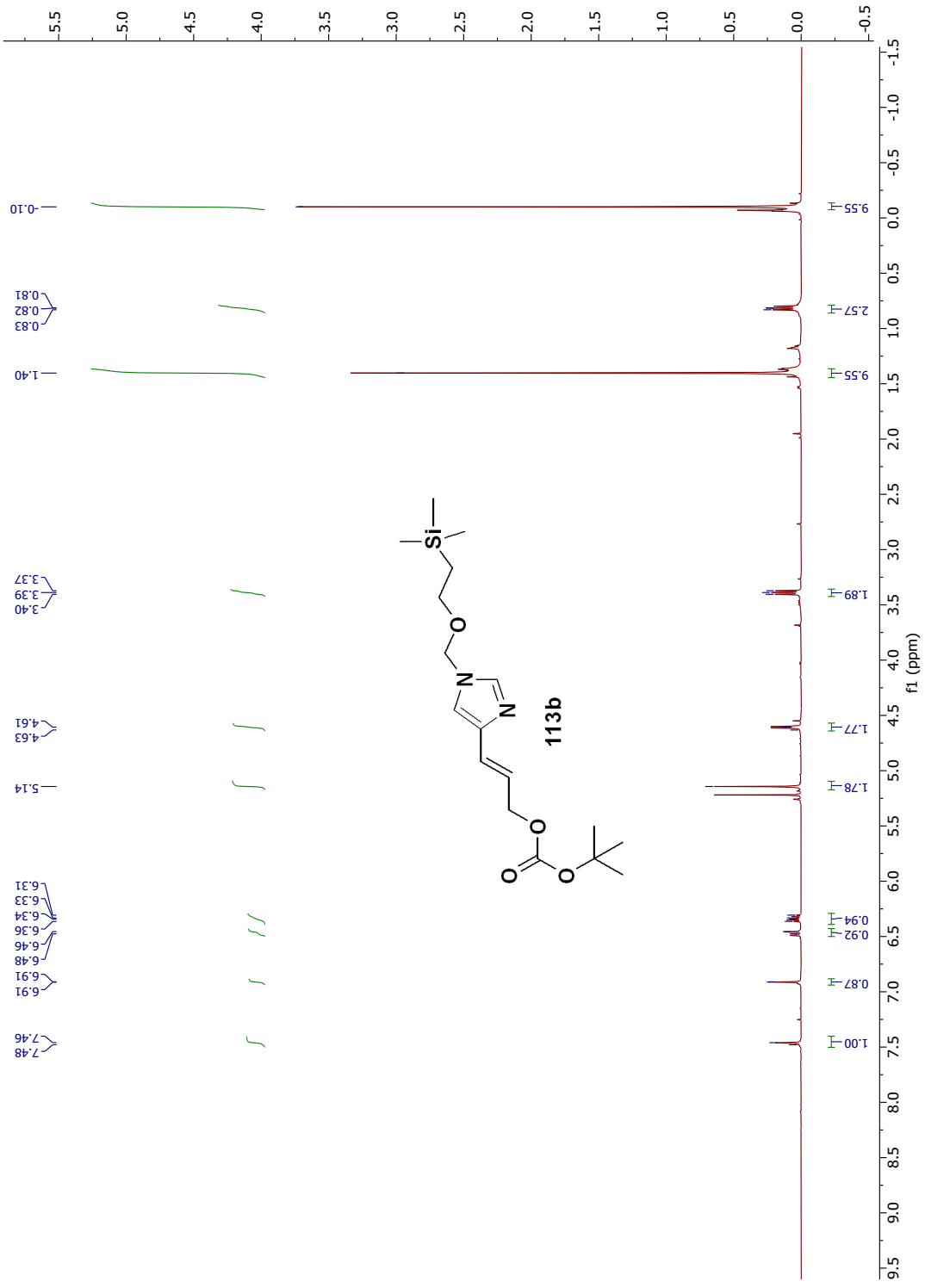

-1.36
17.74
63.12
66.50
76.06
116.29
121.93
128.58
137.58
140.66
110b
f1 (ppm)

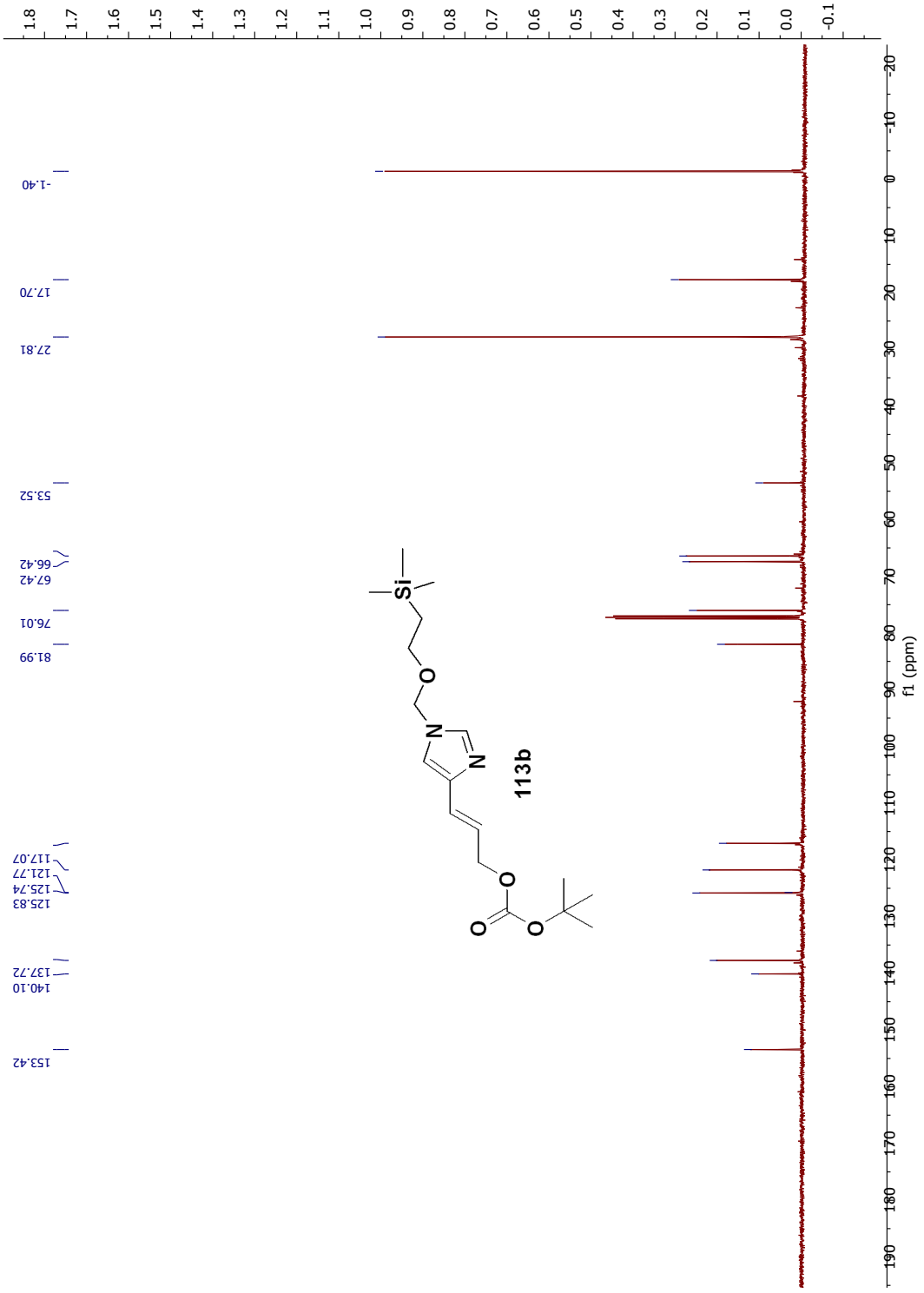

110c
HO
N
N
f1 (ppm)
2.32
2.41
1.92
1.00
2.01
3.19
0.99
4.23
5.02
6.45
6.78
7.11
7.12
7.13
7.13
7.28
7.30
7.31
7.31
7.33
7.35
7.46


110c
HO
N
N
50.99
62.93
63.34
116.94
122.41
126.71
127.10
127.40
128.00
128.14
128.44
129.11
130.86
136.00
137.66
138.19
140.45
f1 (ppm)


1.48
2.85
4.70
4.69
6.52
6.51
6.51
7.13
7.13
7.84
7.83
10.94
6.14
2.04
1.92
0.99
0.96
113a
f1 (ppm)


27.85
38.27
66.89
82.34
114.85
123.85
124.89
137.01
140.67
153.38
113a
f1 (ppm)


-0.10
0.81
0.82
0.83
1.40
3.37
3.39
3.40
4.61
4.63
5.14
6.31
6.33
6.34
6.36
6.46
6.48
6.91
6.91
7.46
7.48
-0.10
0.81
0.82
0.83
1.40
3.37
3.39
3.40
4.61
4.63
5.14
6.31
6.33
6.34
6.36
6.46
6.48
6.91
6.91
7.46
7.48
9.55
2.57
9.55
1.89
1.77
1.78
0.94
0.92
0.87
1.00
Si
O
N
N
O
O
O
113b
f1 (ppm)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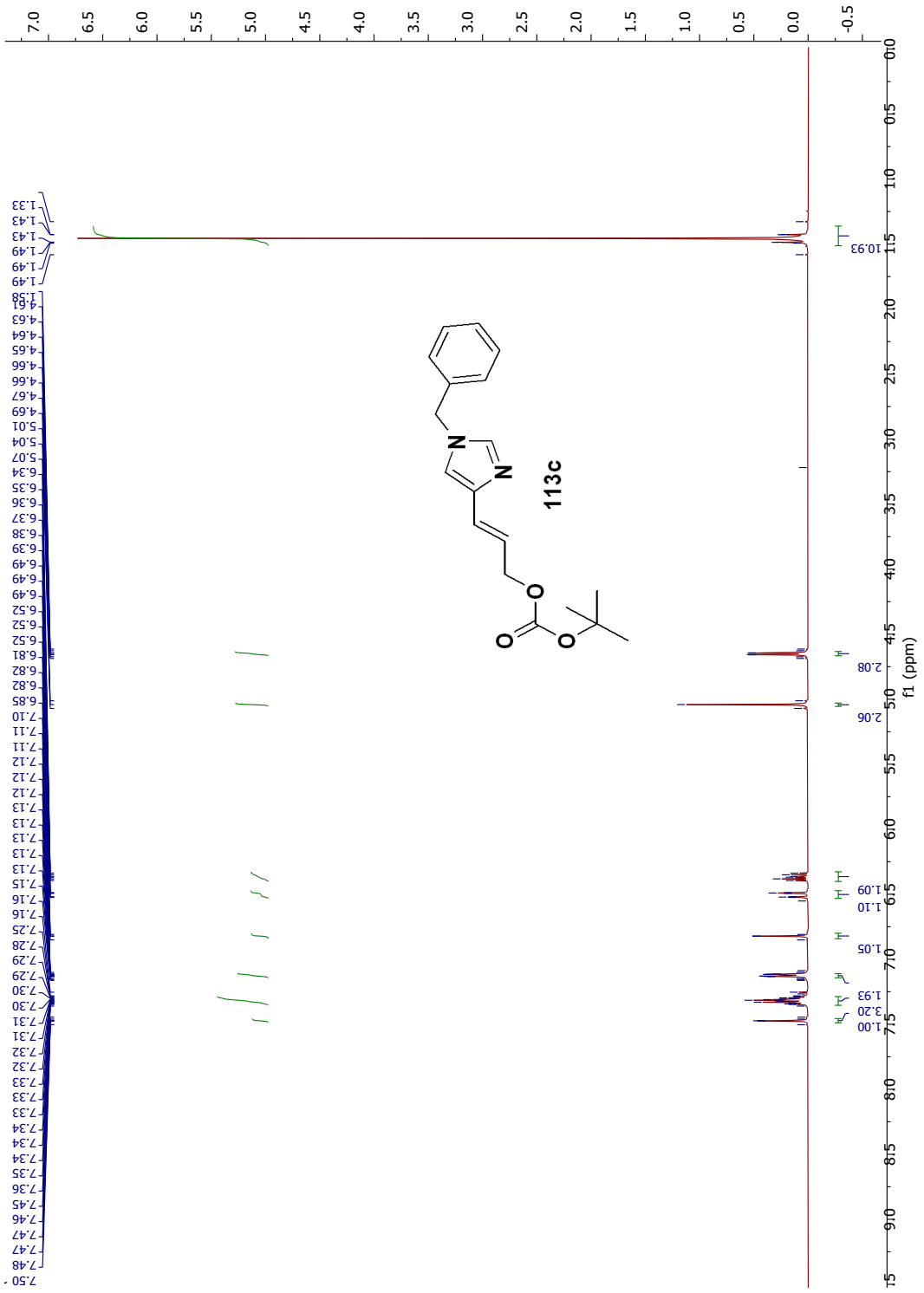
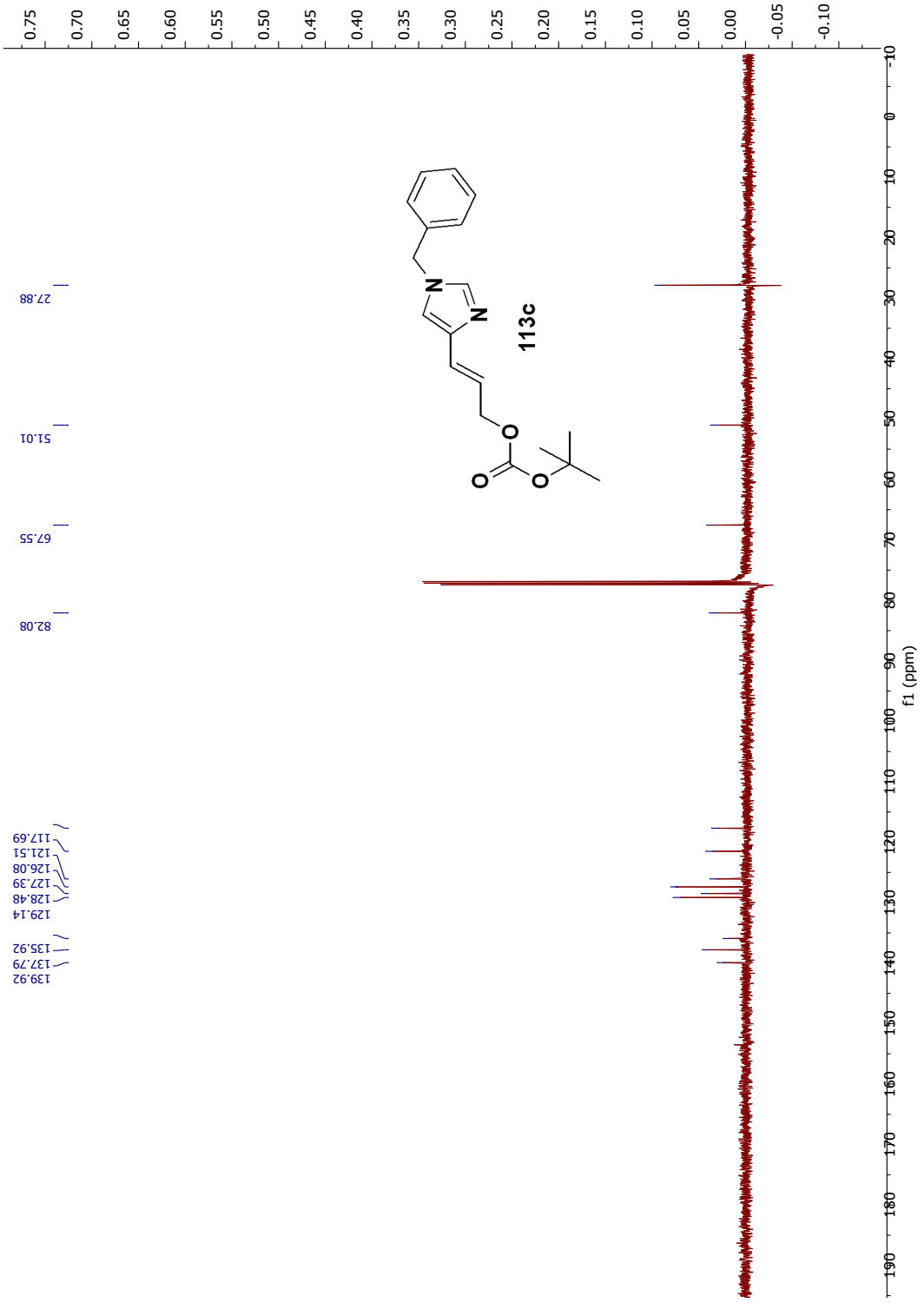
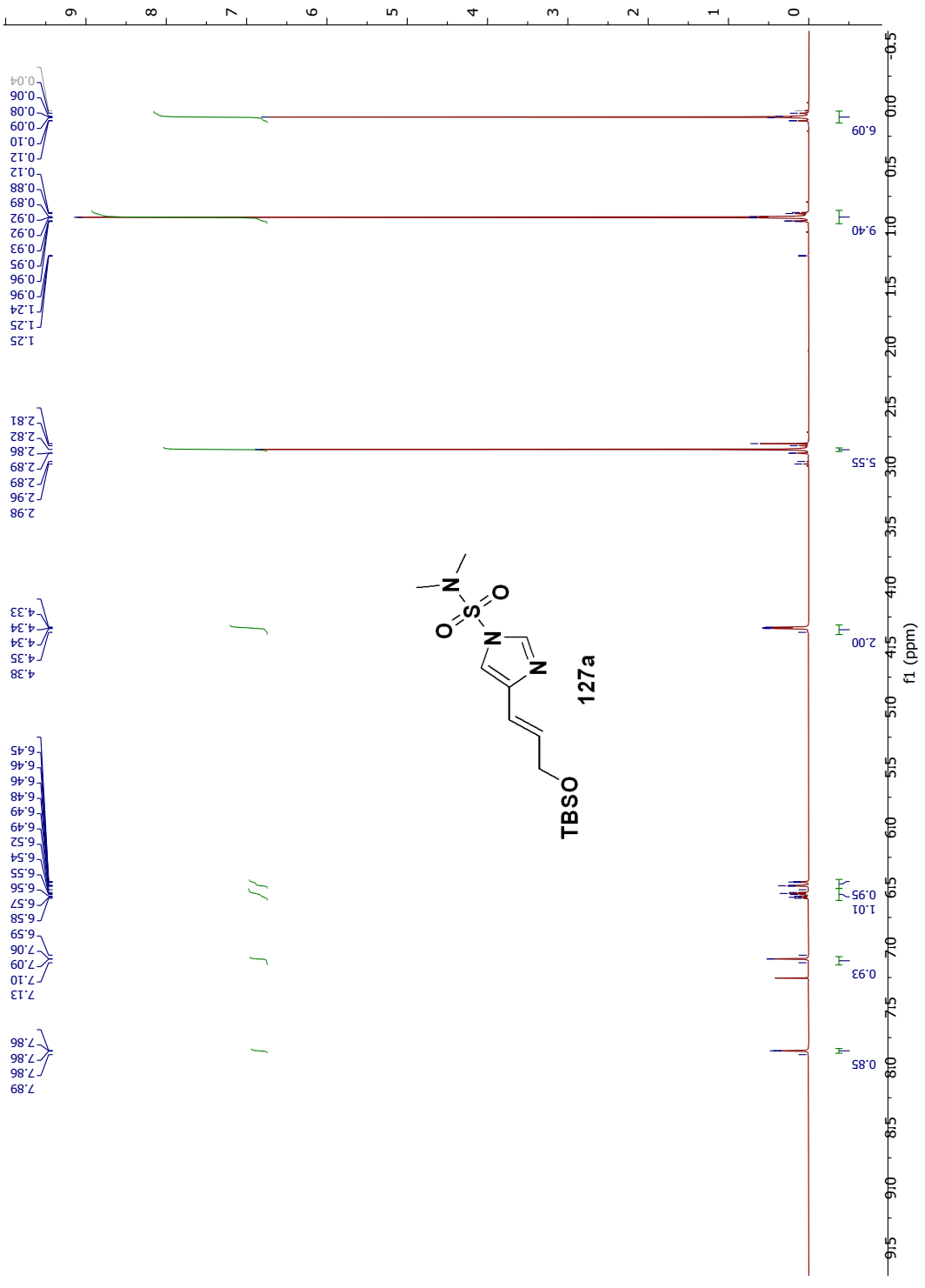
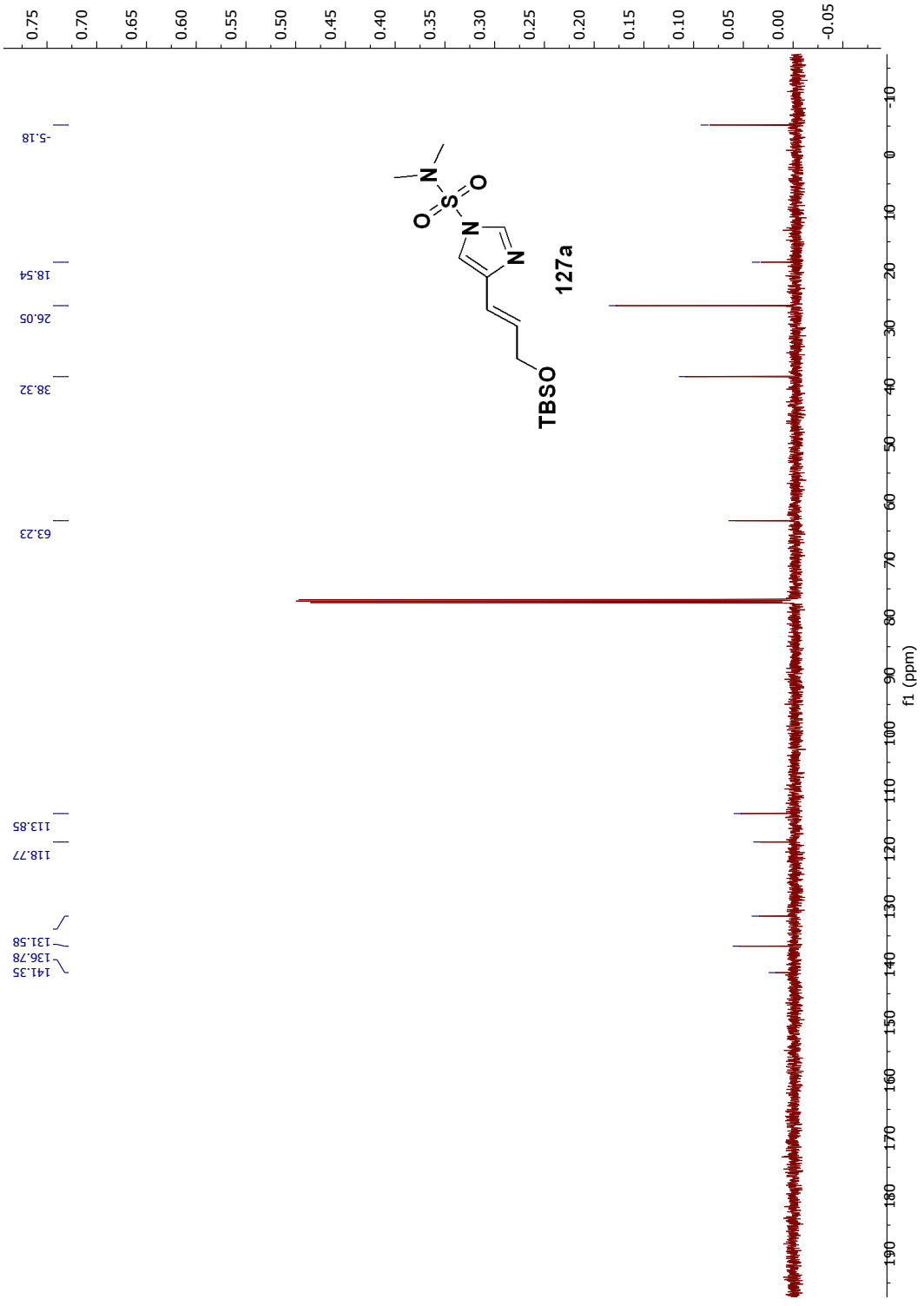
17.70
27.81
53.52
66.42
67.42
76.01
81.99
117.07
121.77
125.74
125.83
137.72
140.10
153.42
Si
O
N
N
O
O
O
113b
f1 (ppm)


113c
f1 (ppm)


113c
f1 (ppm)


TBSO
127a
f1 (ppm)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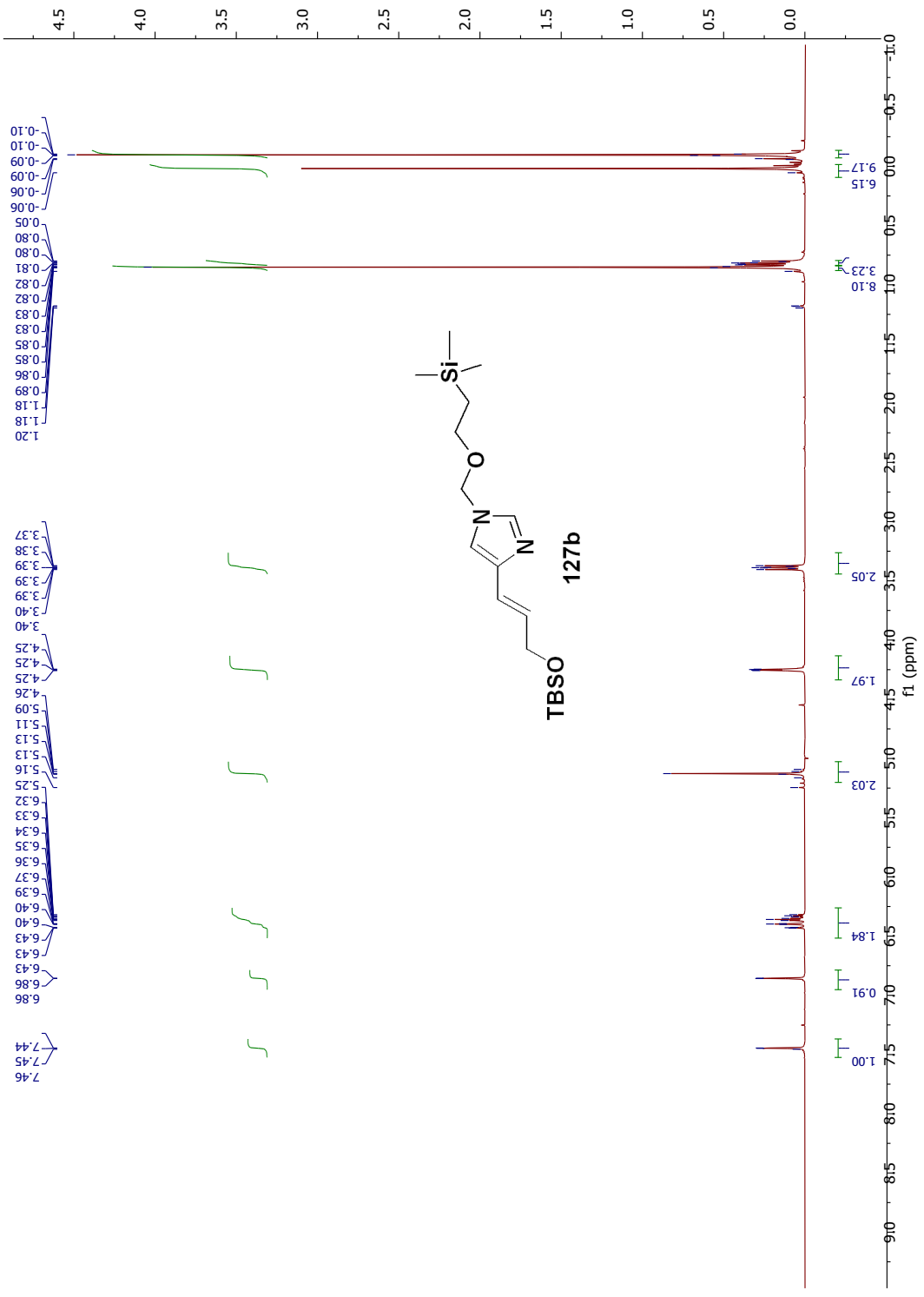
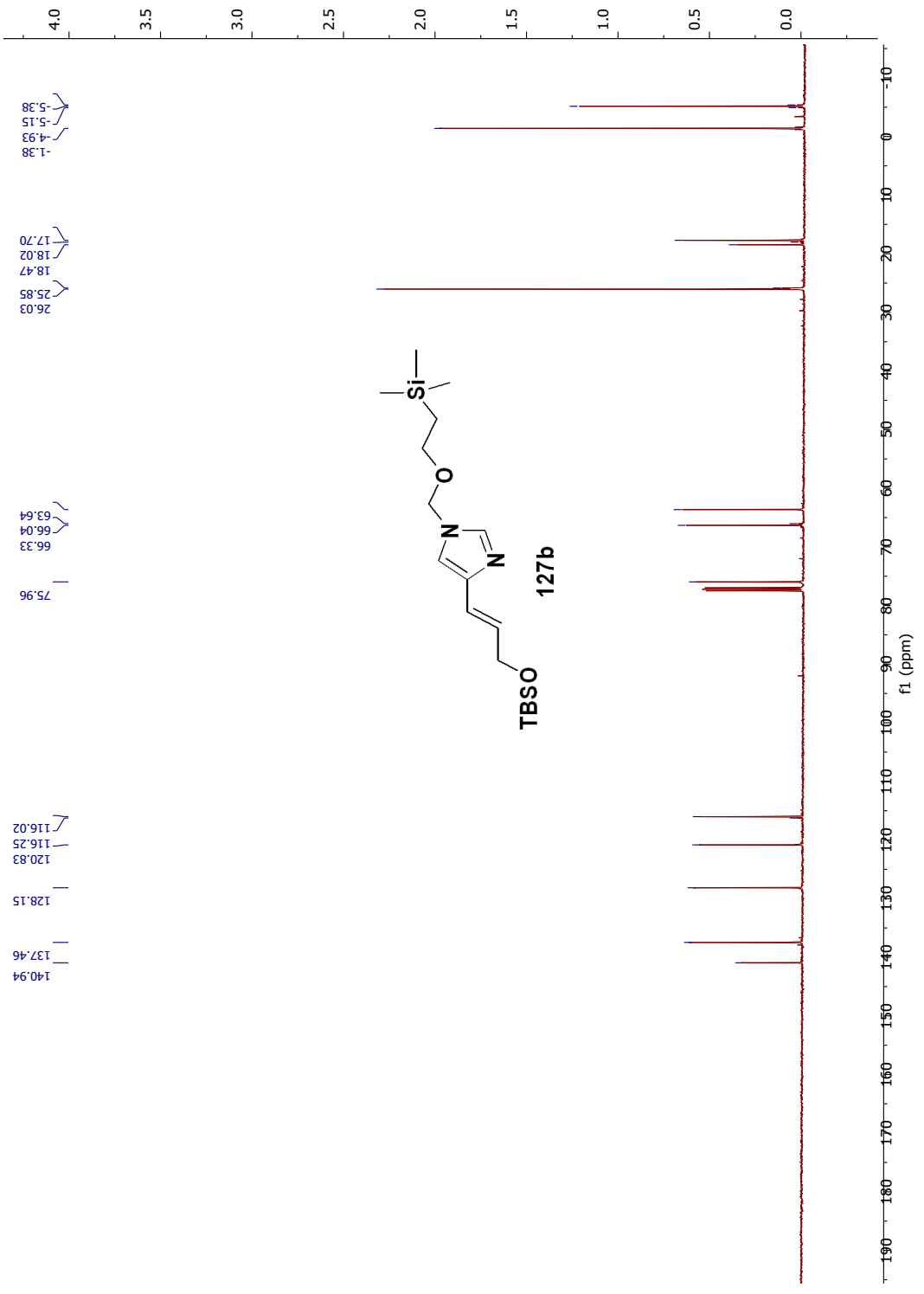
18.54
26.05
38.32
63.23
113.85
118.77
131.58
136.78
141.35
TBSO
127a
f1 (ppm)


TBSO
127b
f1 (ppm)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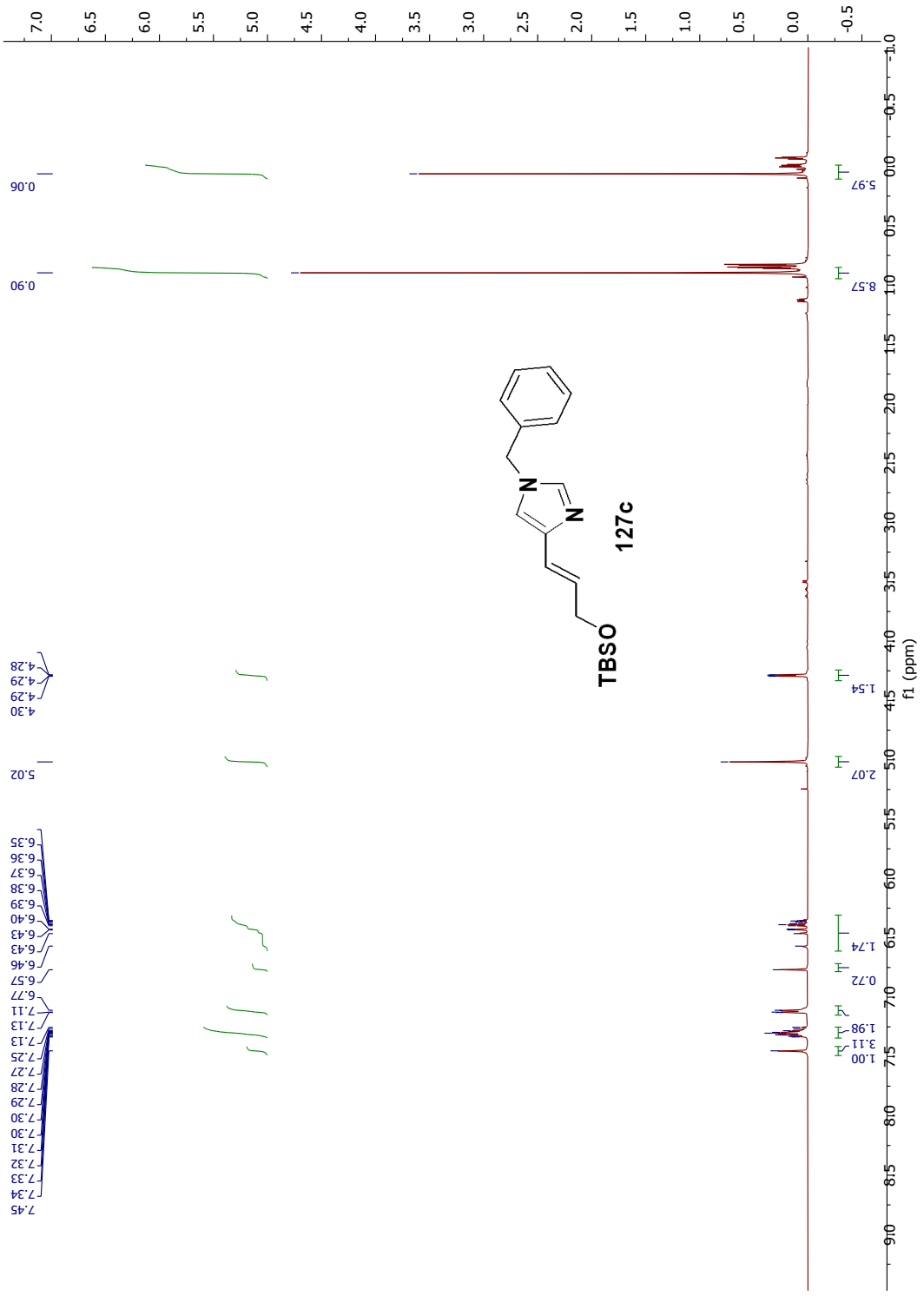
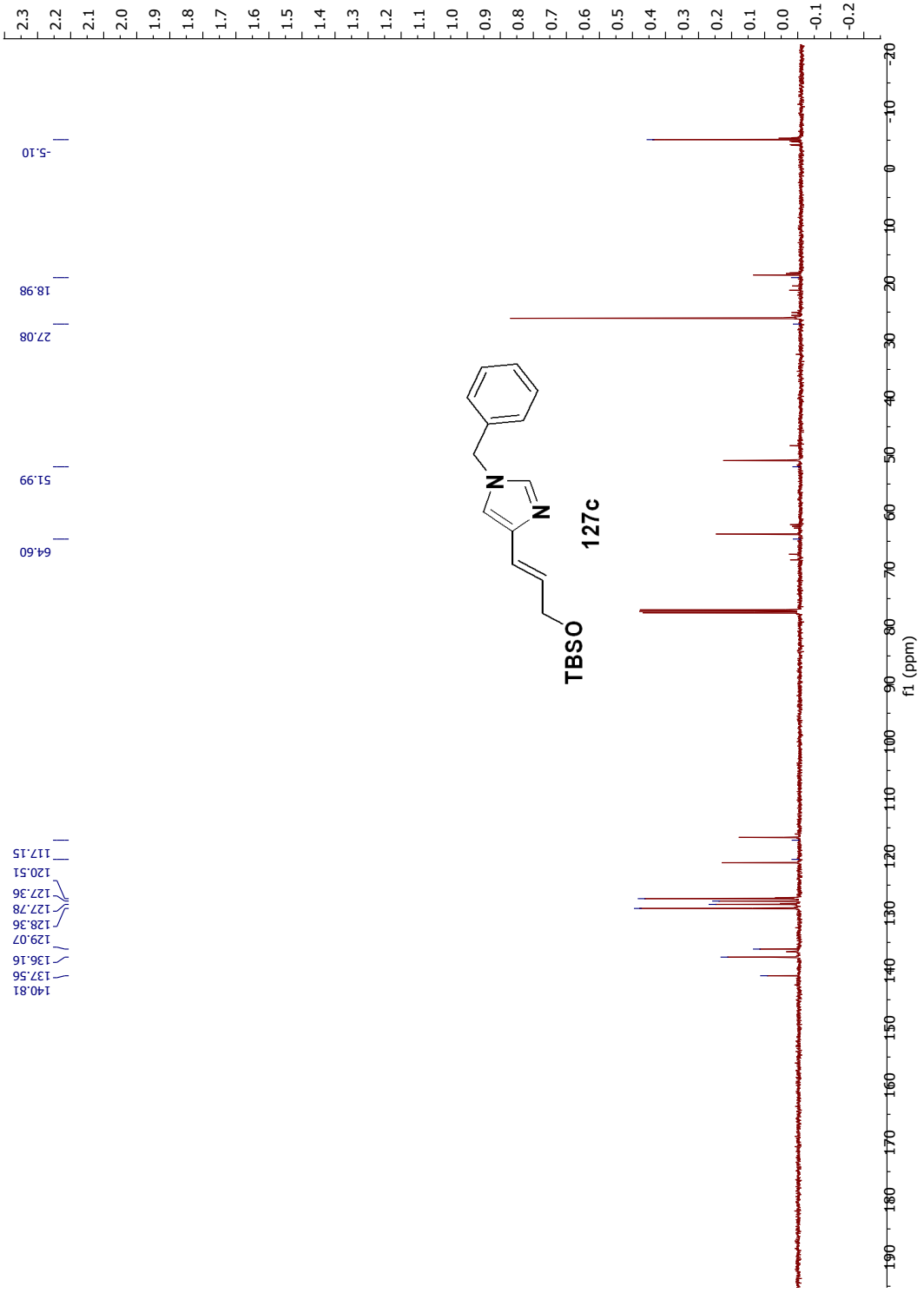
-4.93
-5.15
-5.38
17.70
18.02
18.47
25.85
26.03
63.64
66.04
66.33
75.96
116.02
116.25
120.83
128.15
137.46
140.94
TBSO
127b
f1 (ppm)


TBSO
127c
f1 (ppm)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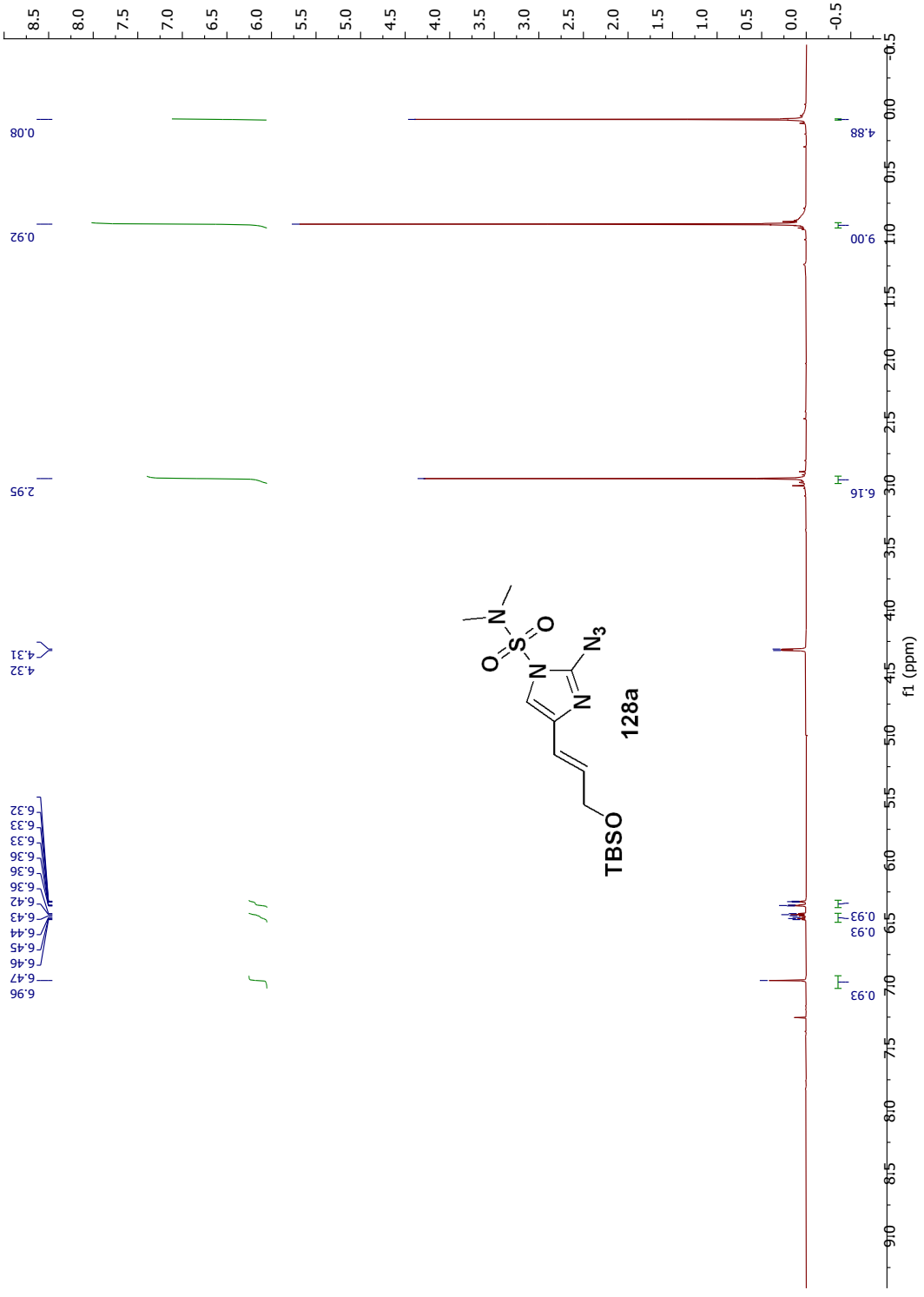
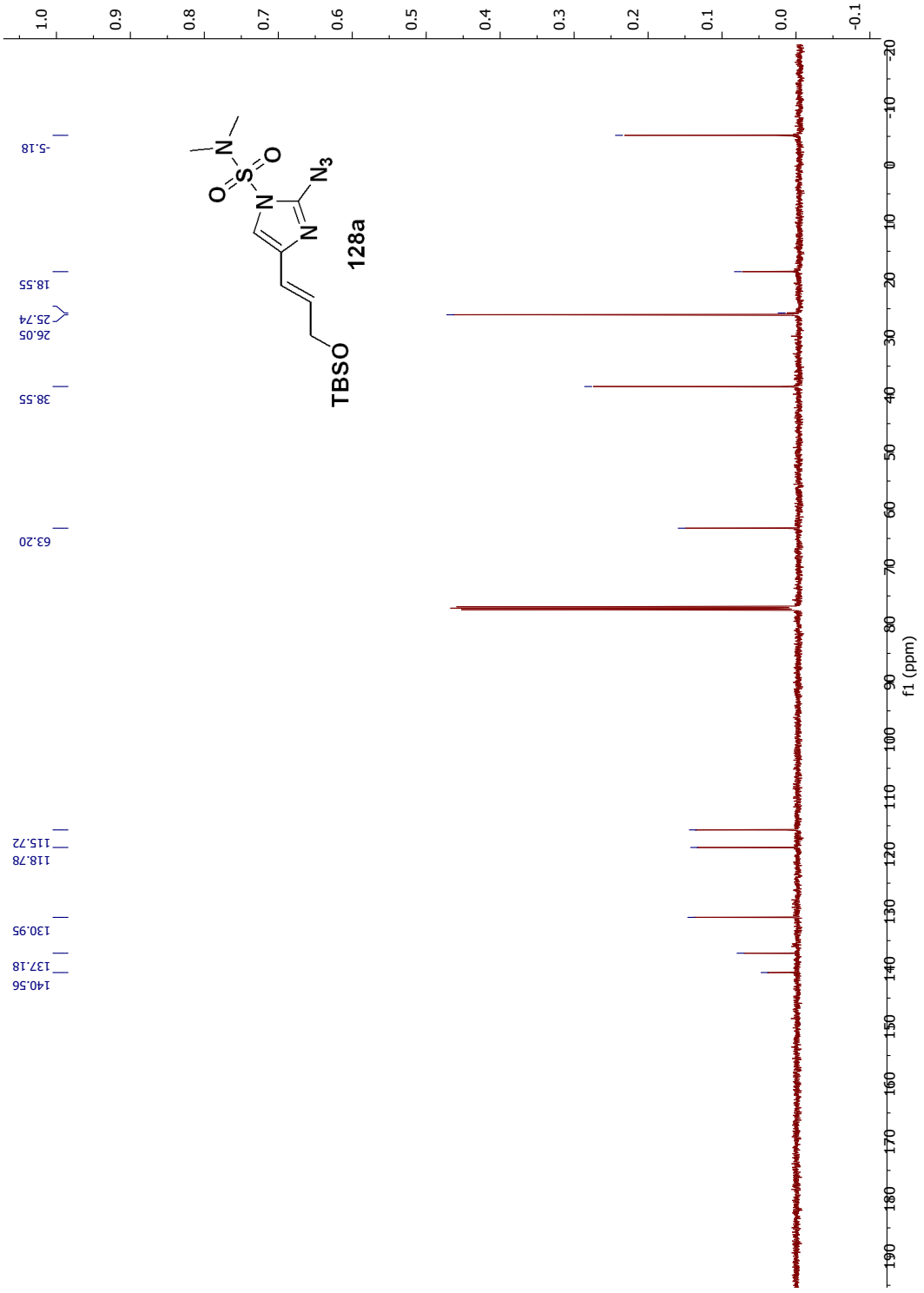
18.98
27.08
51.99
64.60
117.15
120.51
127.36
127.78
128.36
129.07
136.16
137.56
140.81
TBSO
N
N
127c
f1 (ppm)


TBSO
128a
f1 (ppm)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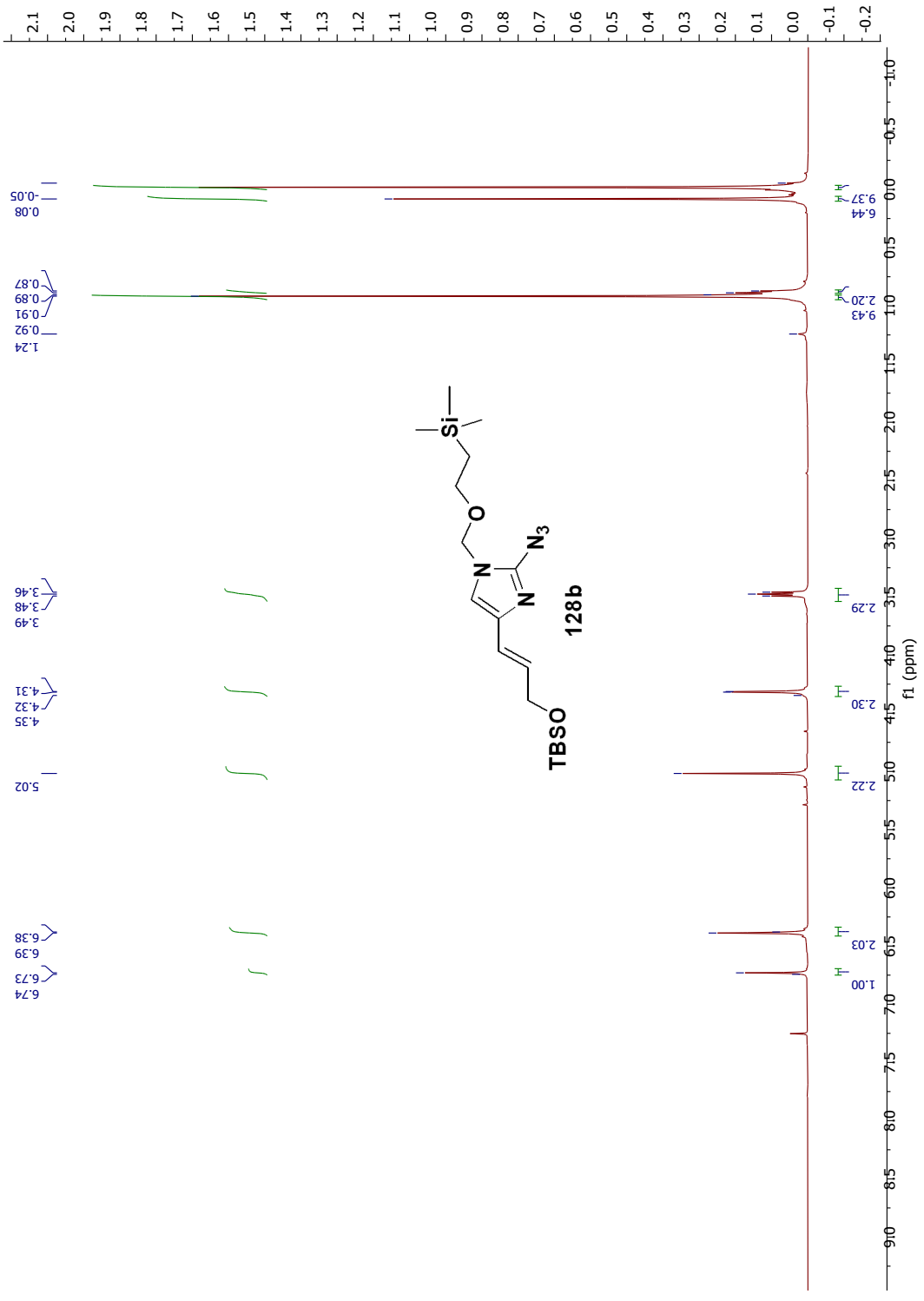
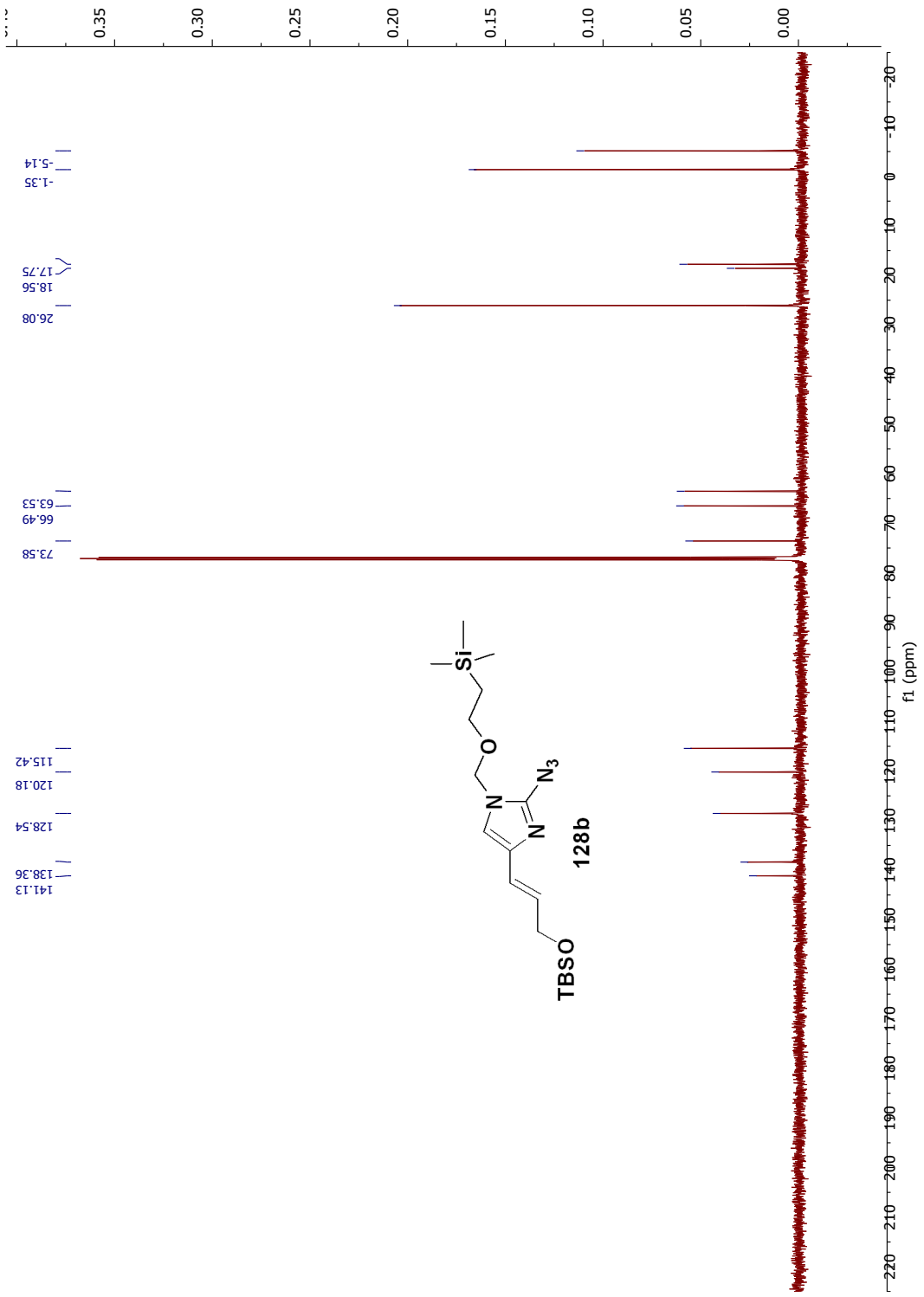
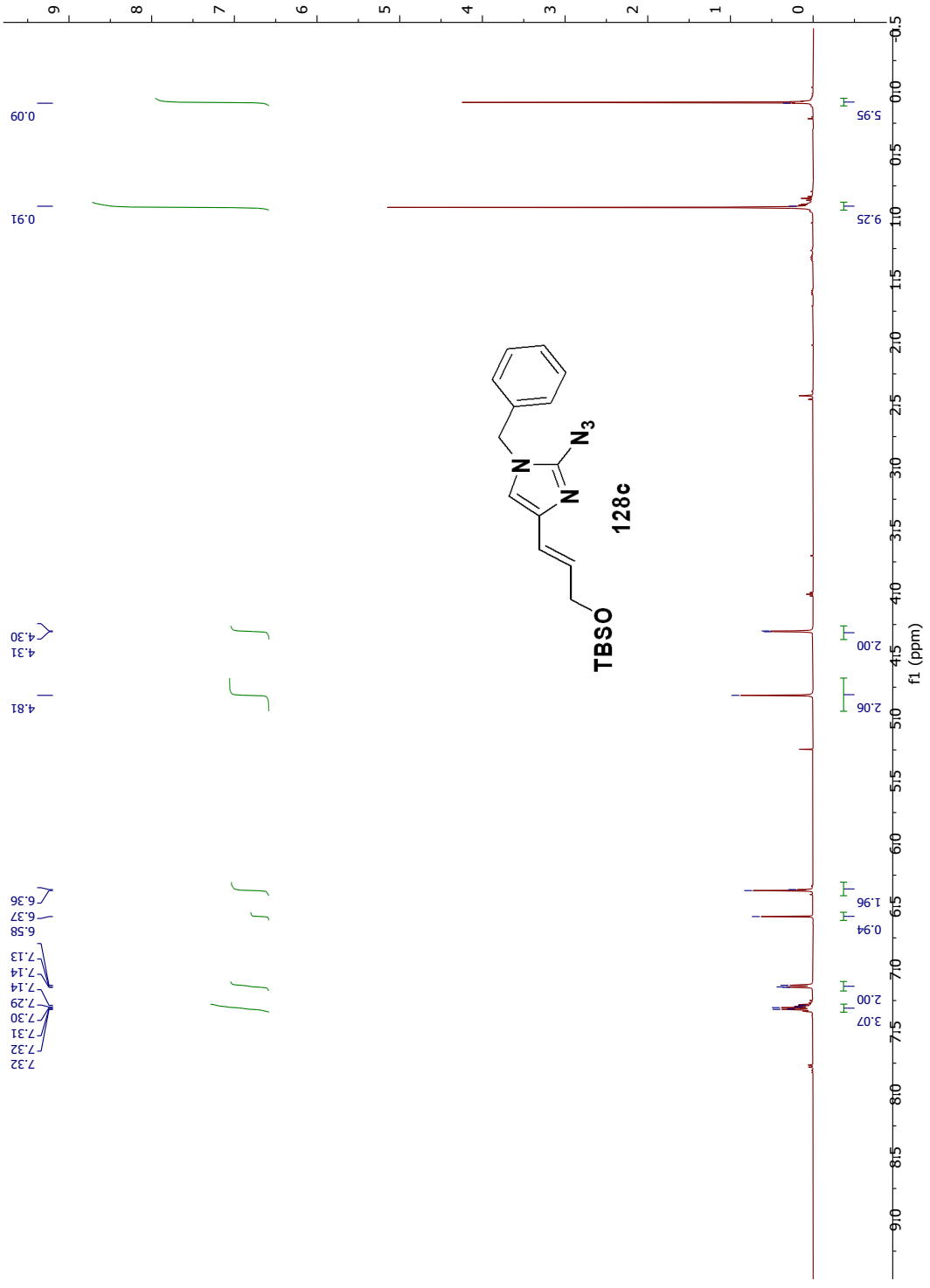
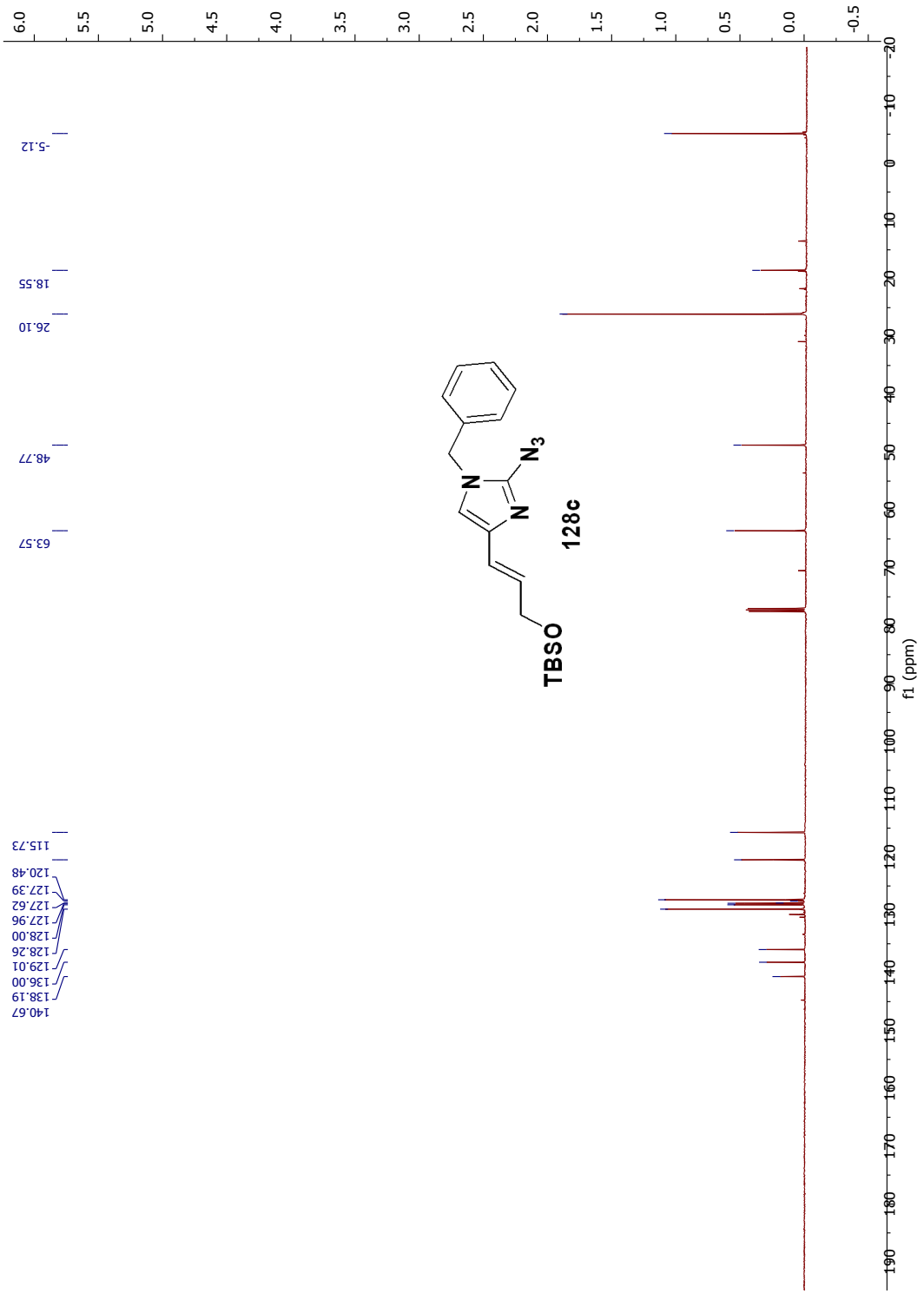
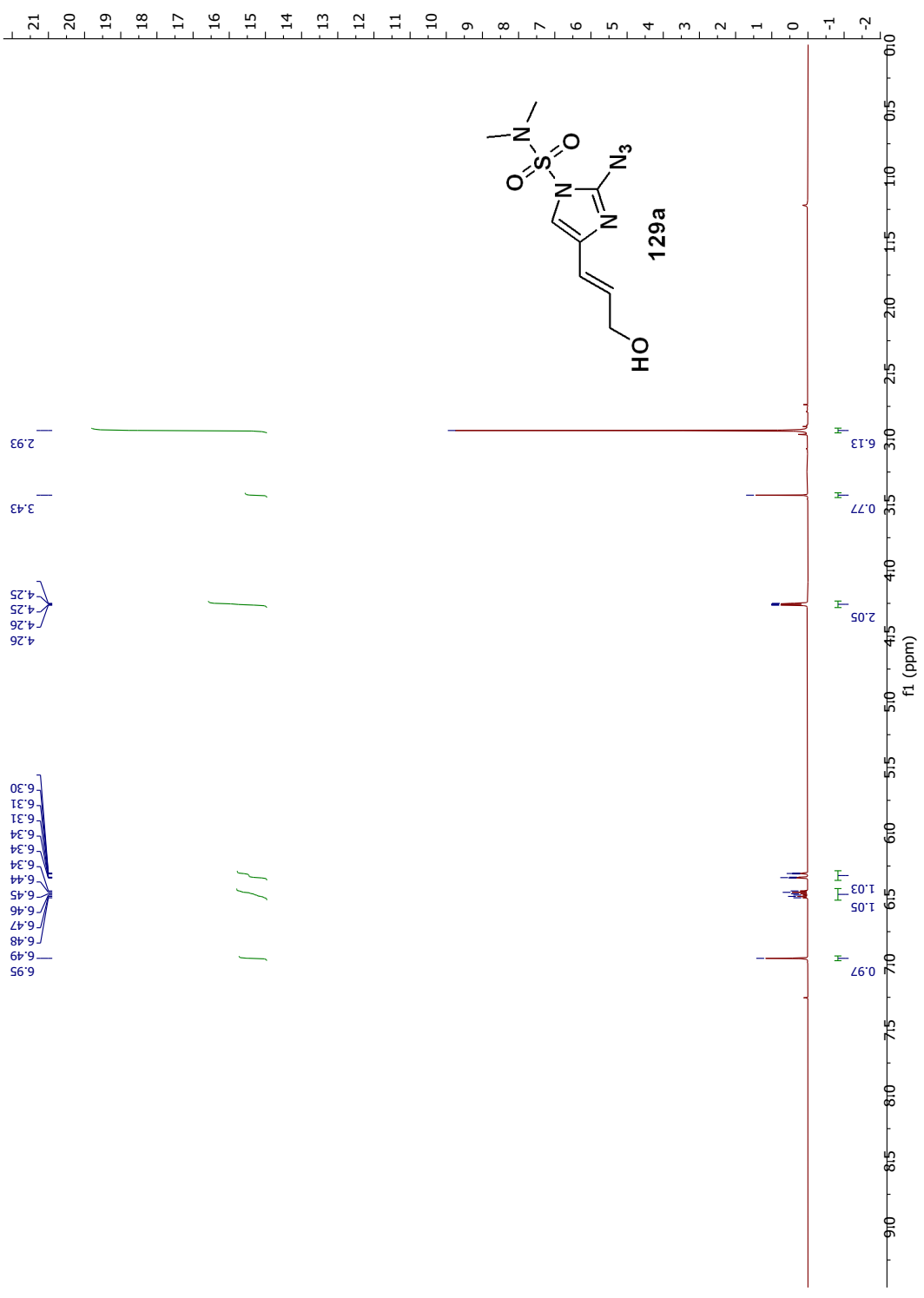
18.55
25.74
26.05
38.55
63.20
115.72
118.78
130.95
137.18
140.56
TBSO
128a
f1 (ppm)

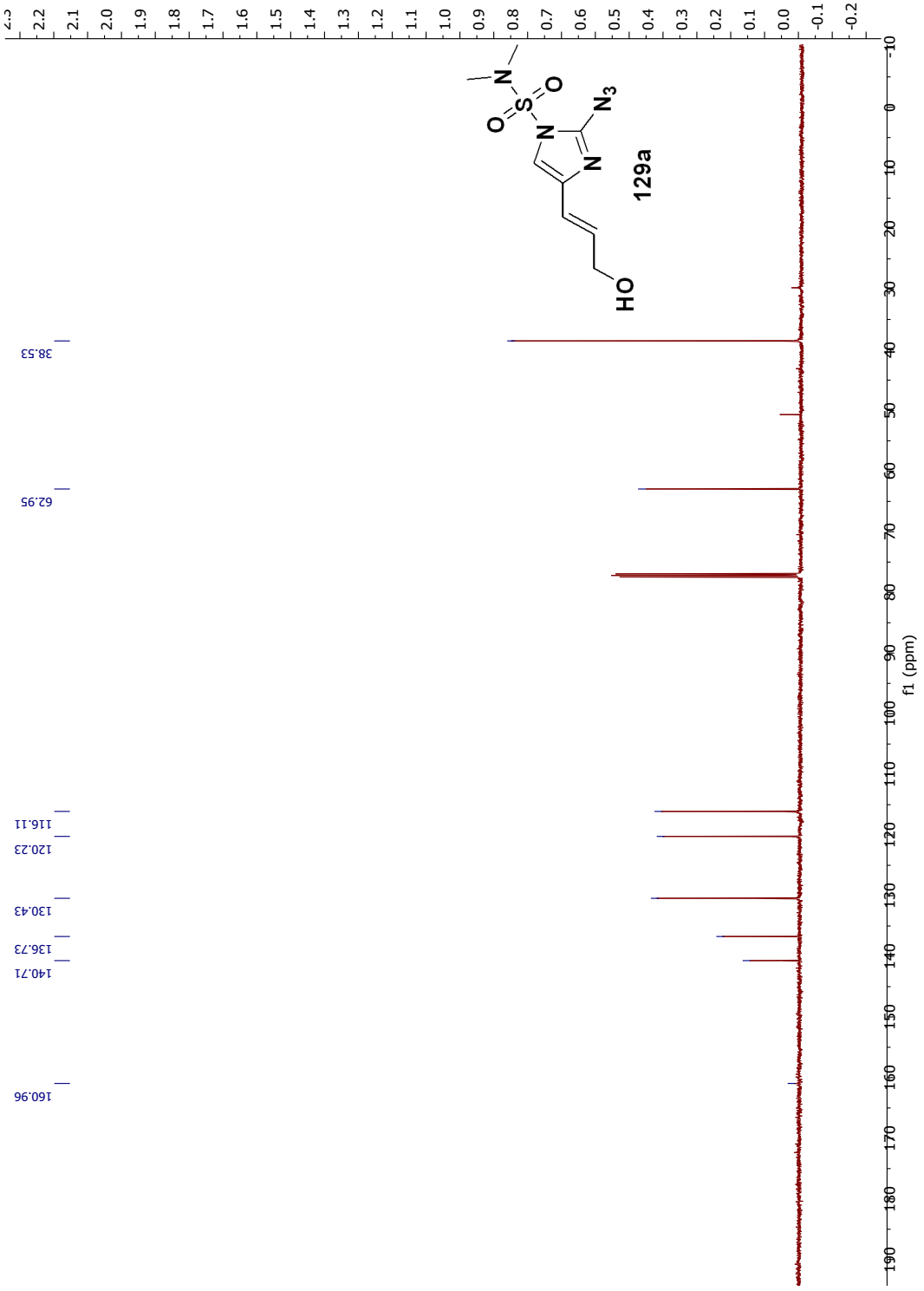

TBSO
128b
f1 (ppm)

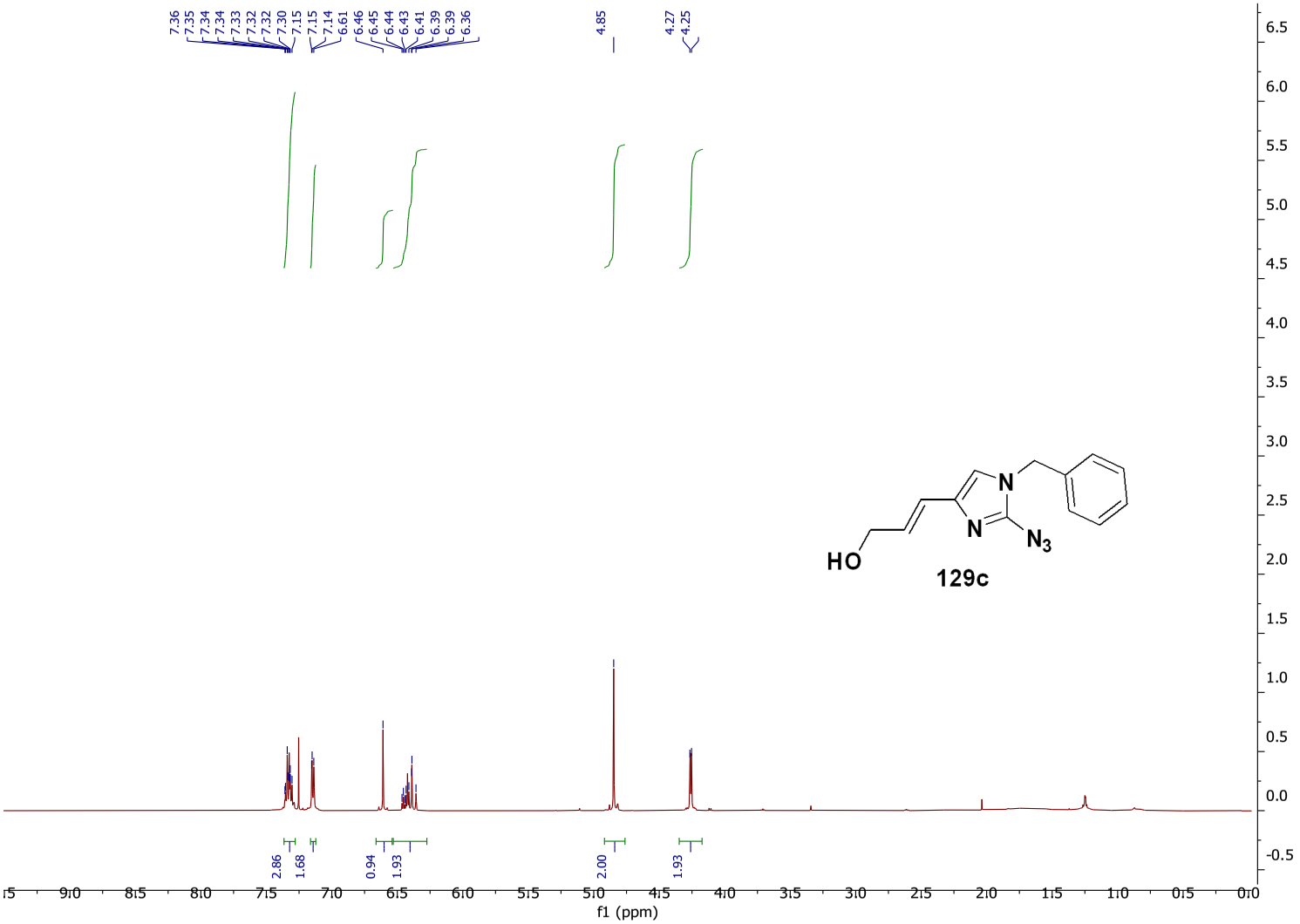

-5.14
-1.35
17.75
18.56
26.08
63.53
66.49
73.58
115.42
120.18
128.54
138.36
141.13
TBSO
128b
f1 (ppm)

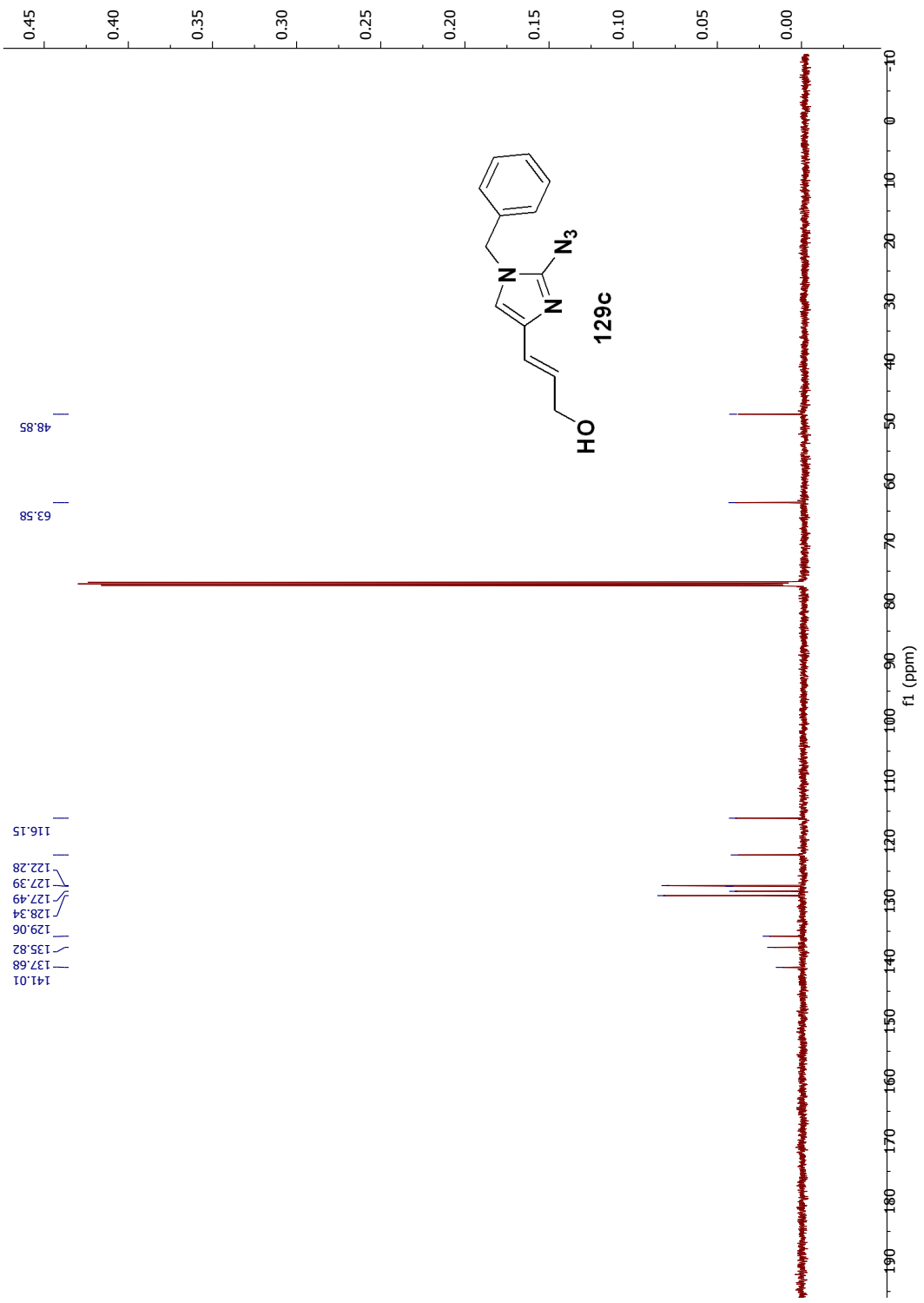

TBSO
N
N
N3
128c
f1 (ppm)

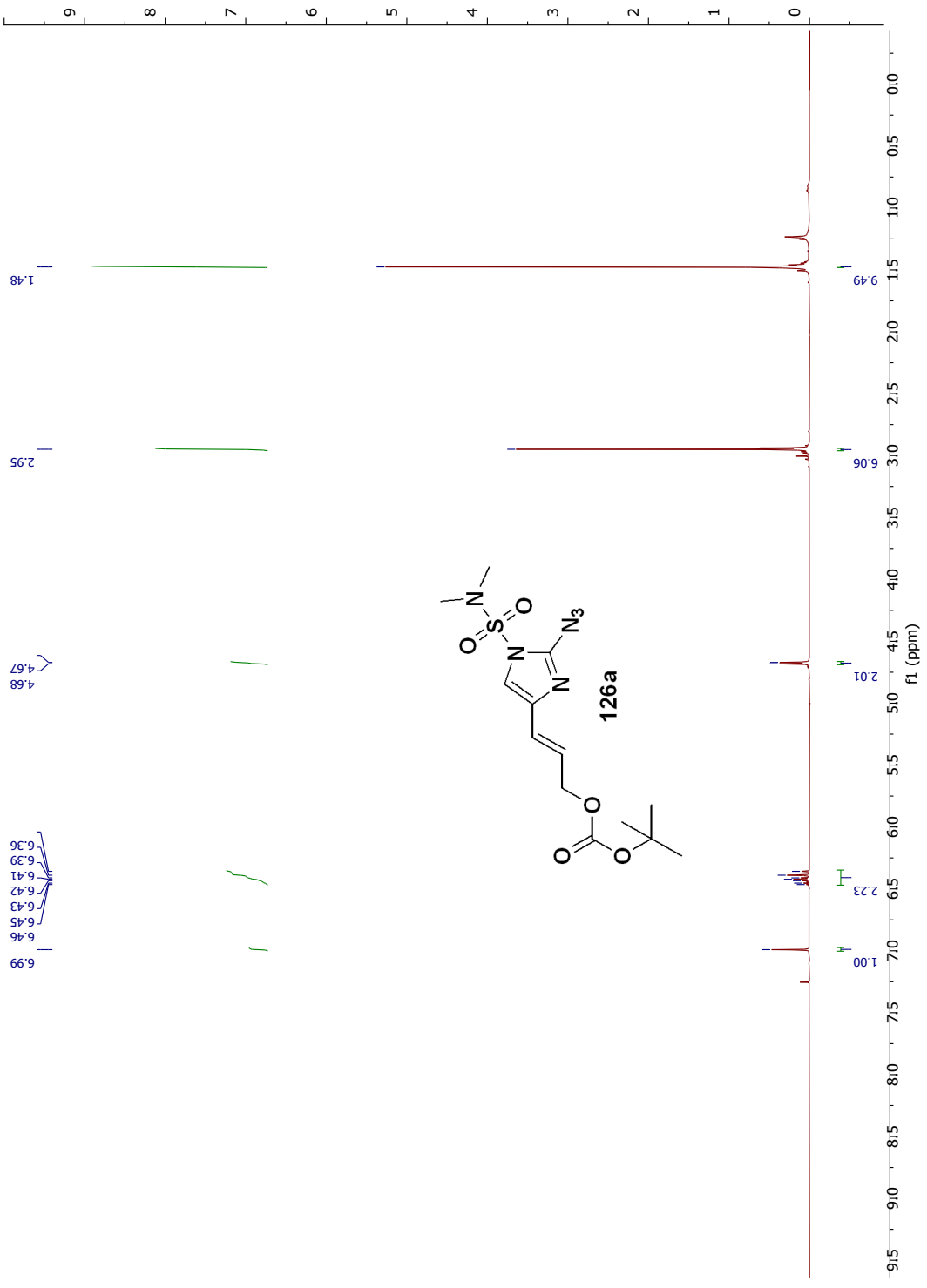

-5.12
18.55
26.10
48.77
63.57
115.73
120.48
127.39
127.62
127.96
128.00
128.26
129.01
136.00
138.19
140.67
TBSO
N
N
N3
128c
f1 (ppm)

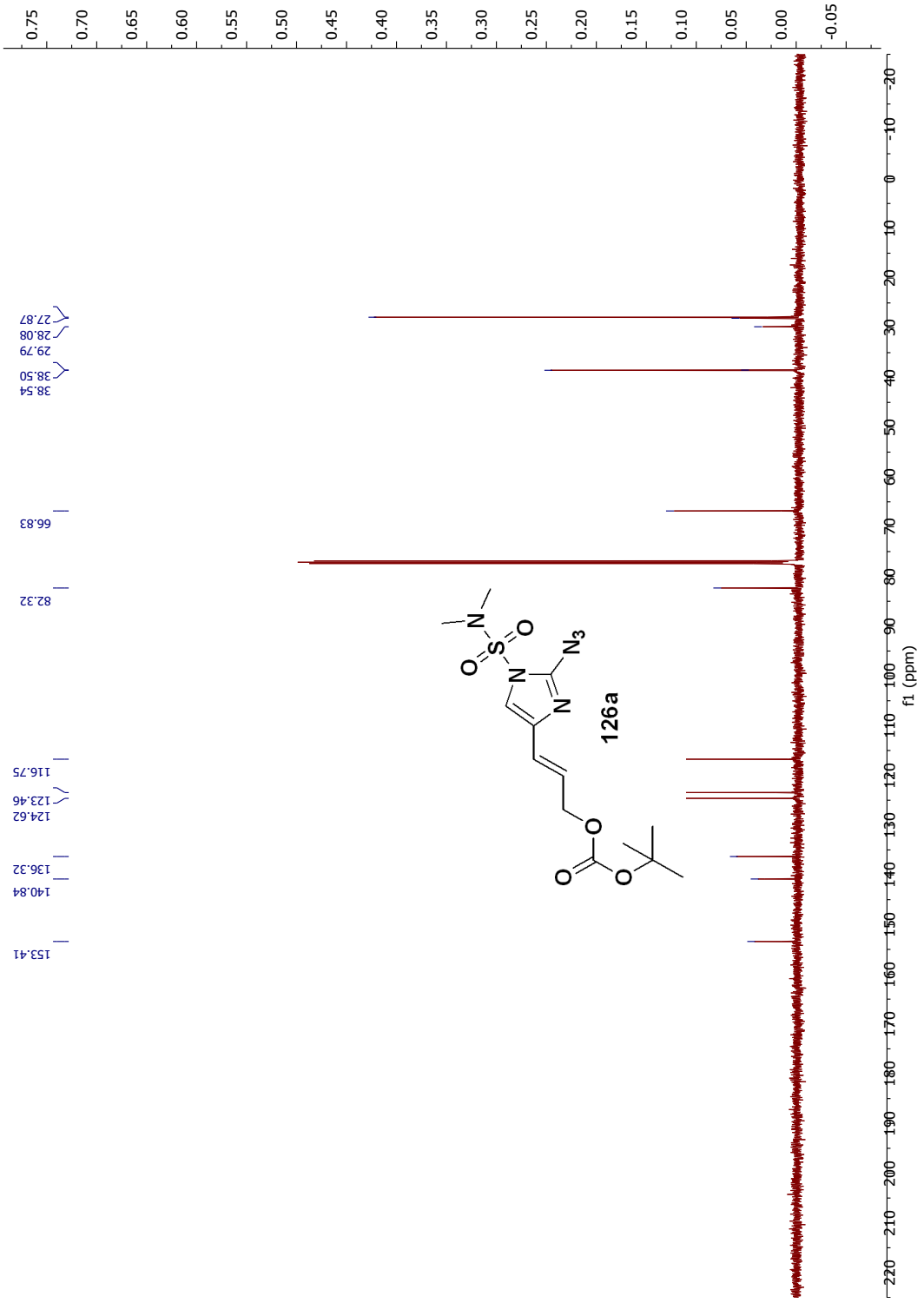

129a
HO
f1 (ppm)

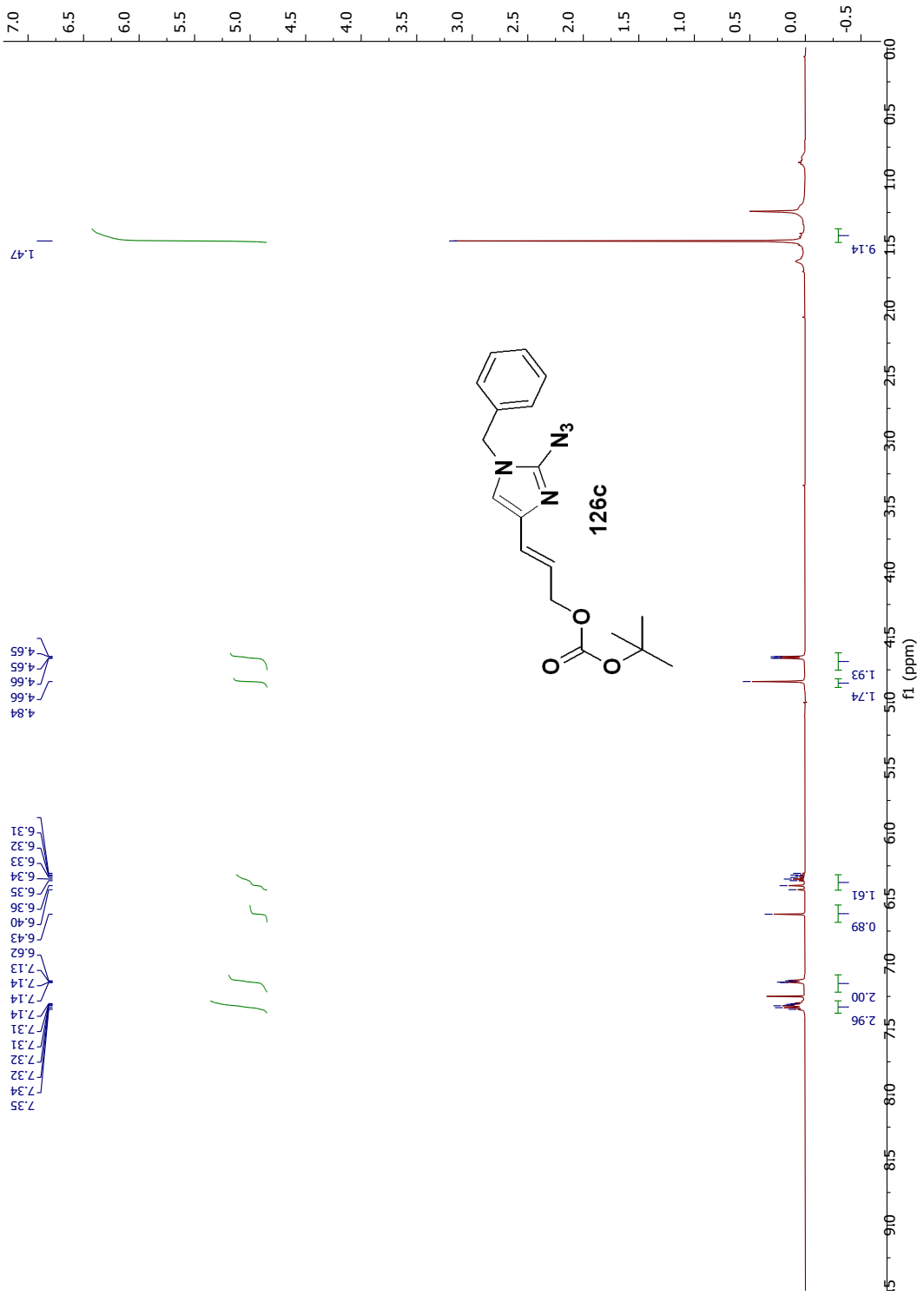

38.53
62.95
116.11
120.23
130.43
136.73
140.71
160.96
129a
HO
f1 (ppm)

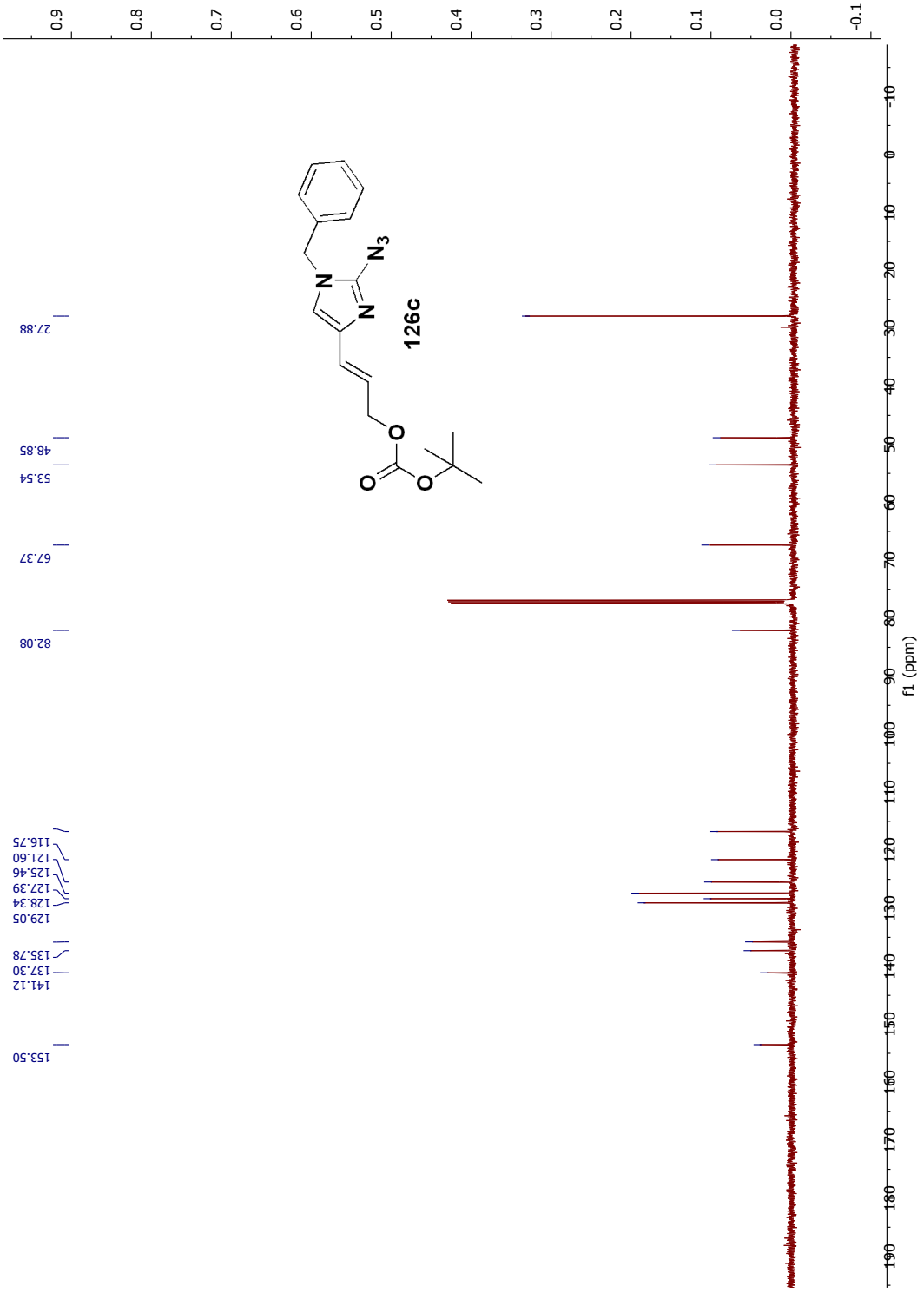

7.36
7.35
7.34
7.34
7.33
7.32
7.32
7.30
7.15
7.15
7.14
6.61
6.46
6.45
6.44
6.43
6.41
6.39
6.39
6.36
4.85
4.27
4.25
HO
N
N
N3
129c
2.86
1.68
0.94
1.93
2.00
1.93
f1 (ppm)

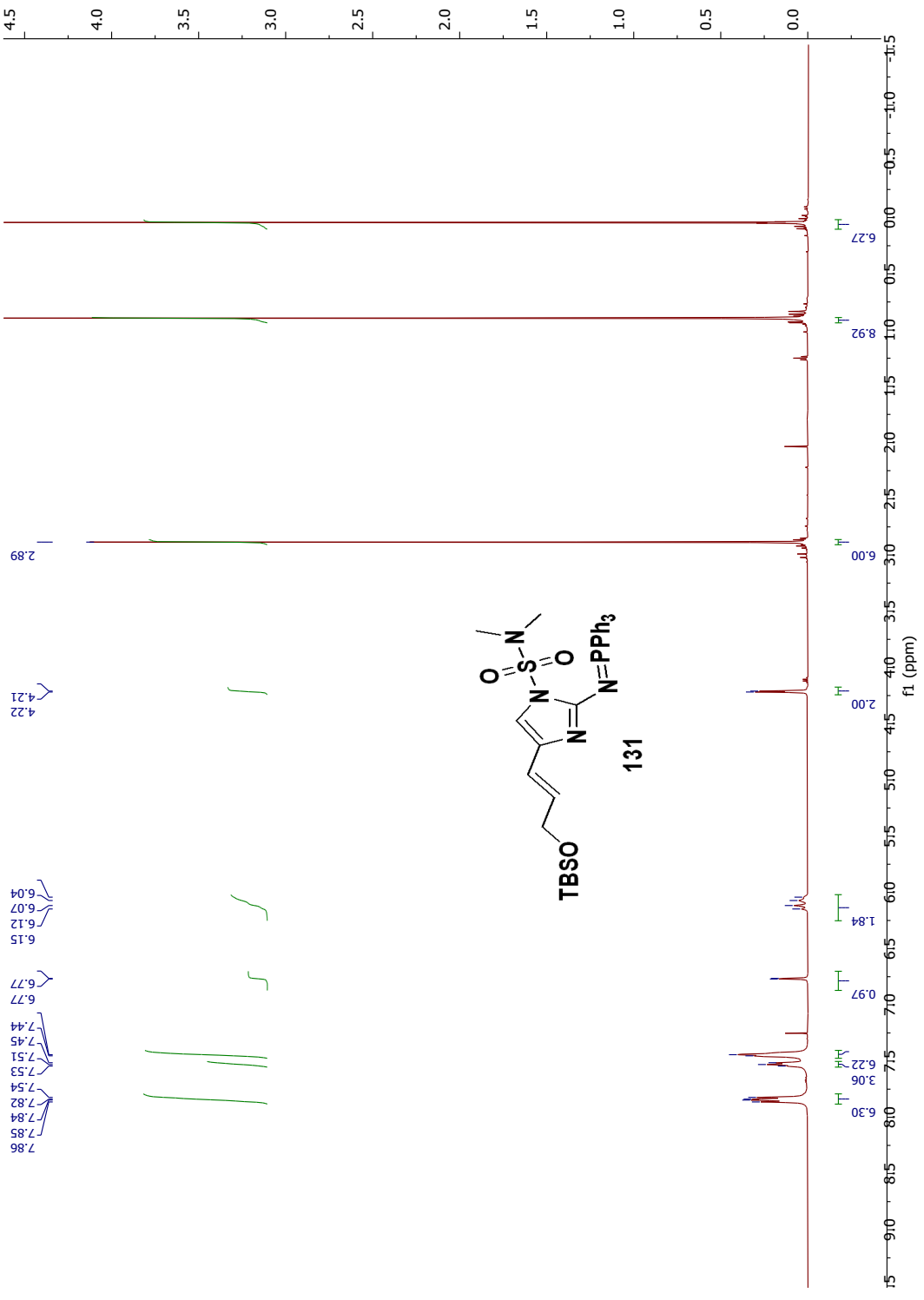

0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
48.85
63.58
116.15
122.28
127.39
127.49
128.34
129.06
135.82
137.68
141.01
N
N
N3
HO
129c
-10
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
f1 (ppm)

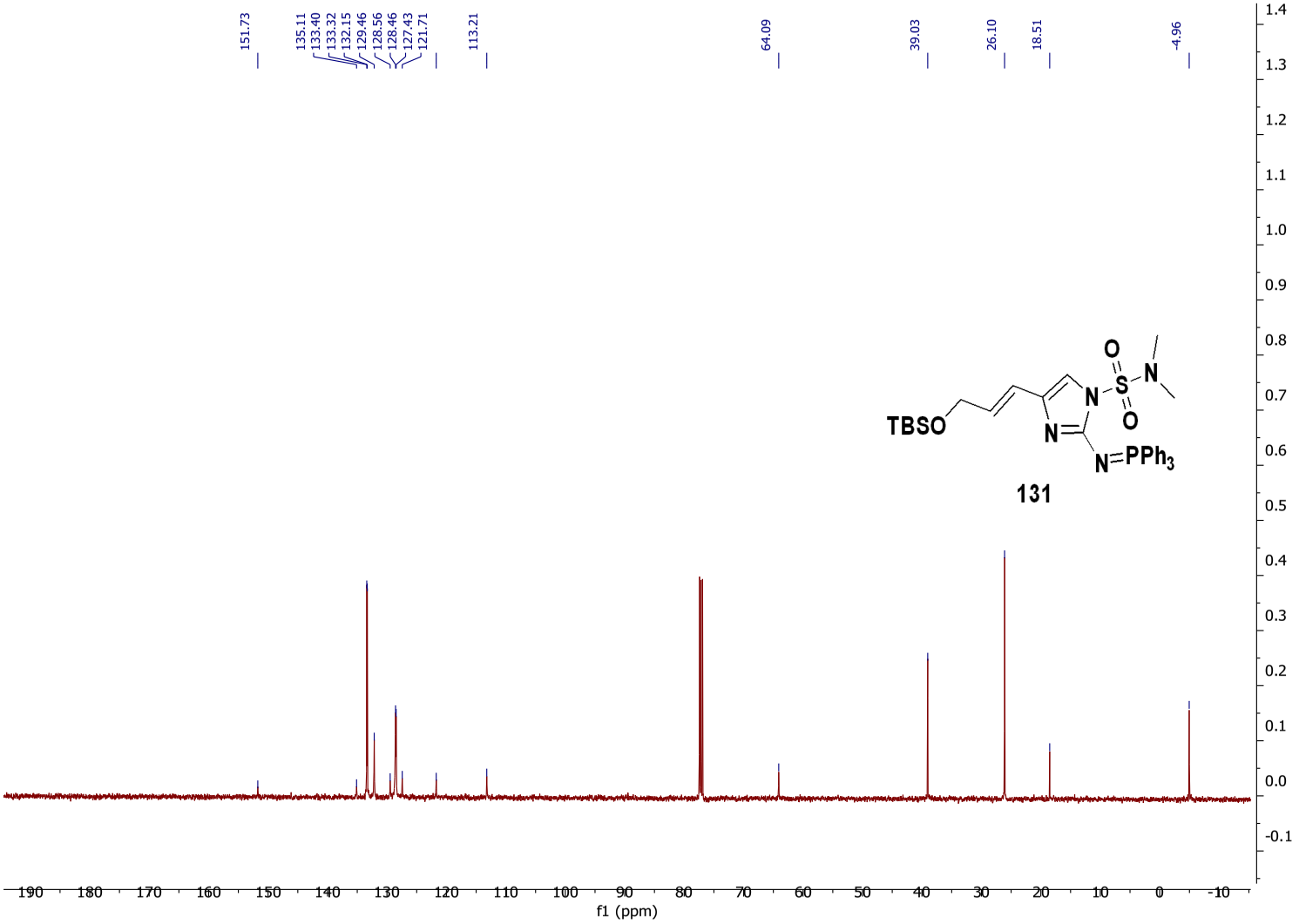

126a
f1 (ppm)
1.48
2.95
4.68
4.67
6.99
6.46
6.45
6.43
6.42
6.41
6.39
6.36
9.49
6.06
2.01
2.23
1.00

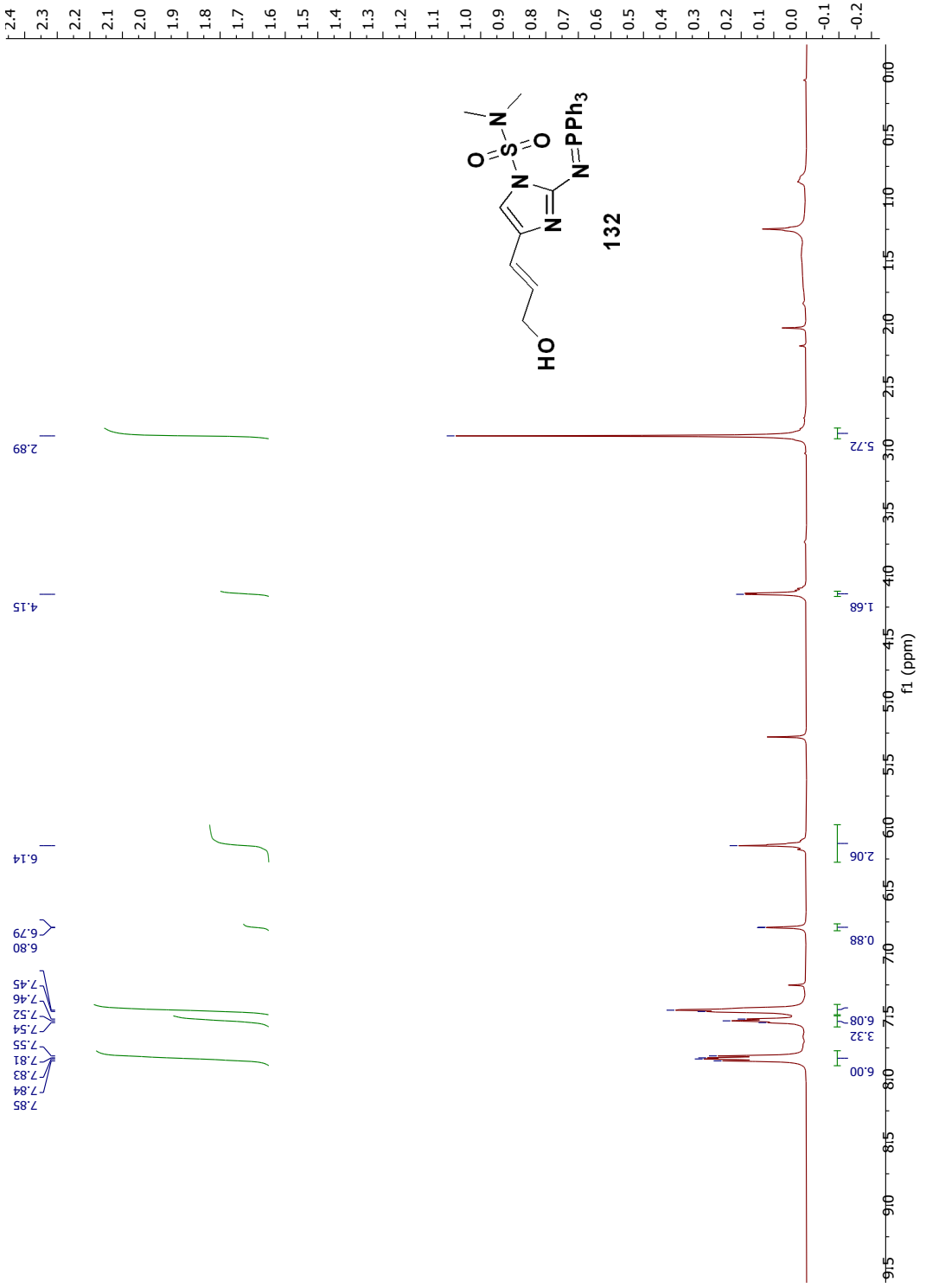

153.41
140.84
136.32
124.62
123.46
116.75
82.32
66.83
38.54
38.50
29.79
28.08
27.87
126a
f1 (ppm)

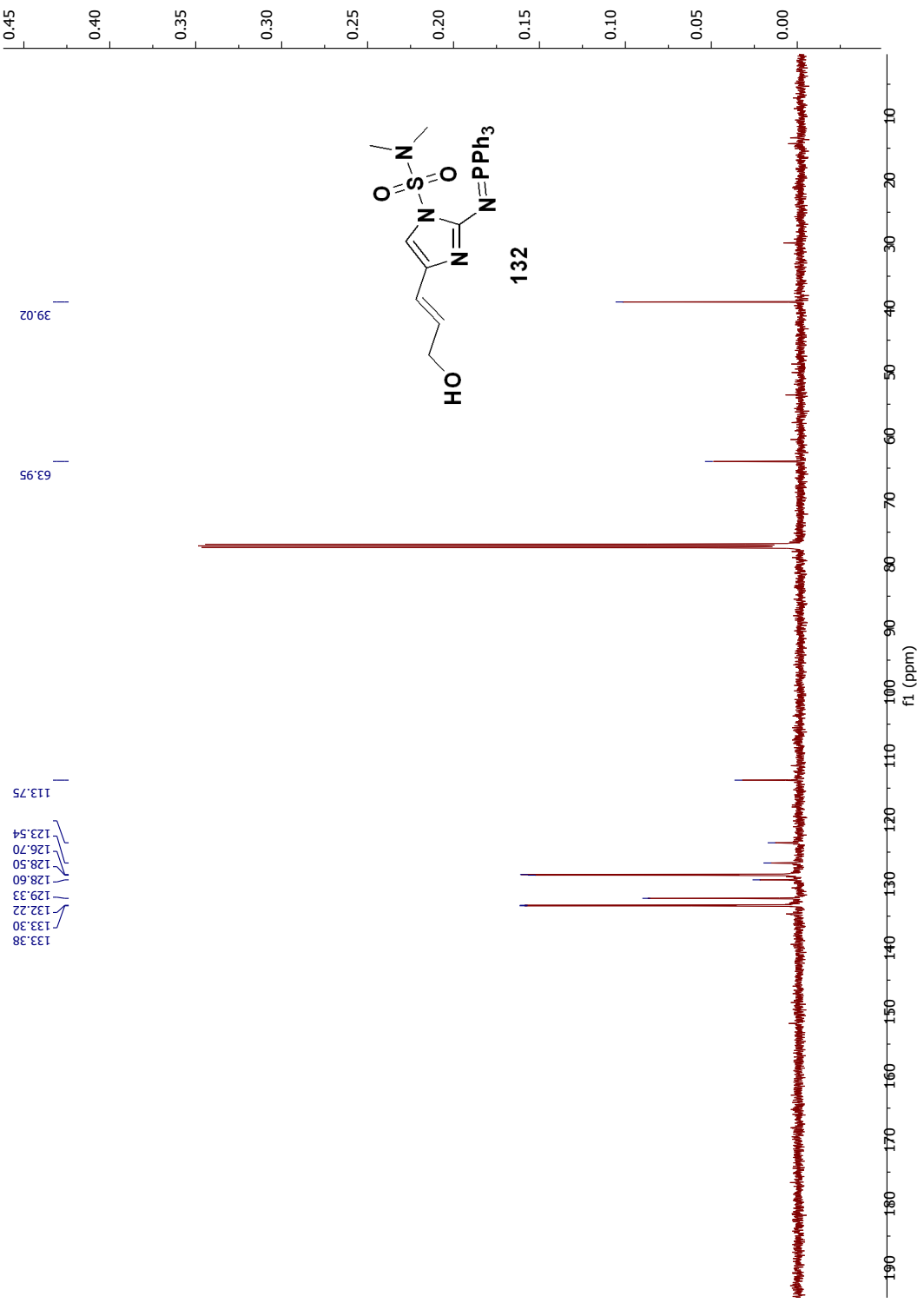

126c
f1 (ppm)

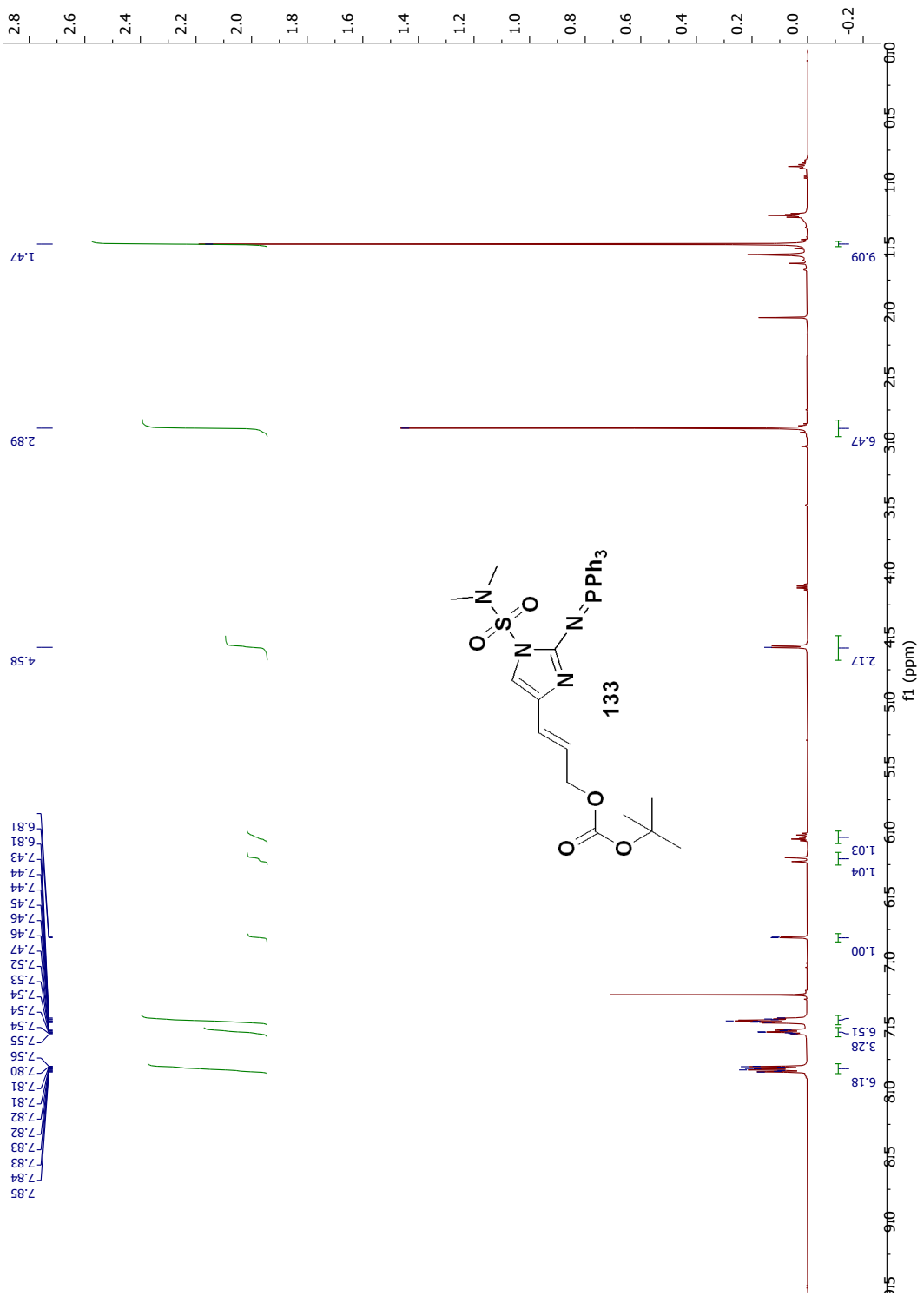

126c
N3
N
N
O
O
O
27.88
48.85
53.54
67.37
82.08
116.75
121.60
125.46
127.39
128.34
129.05
135.78
137.30
141.12
153.50
f1 (ppm)

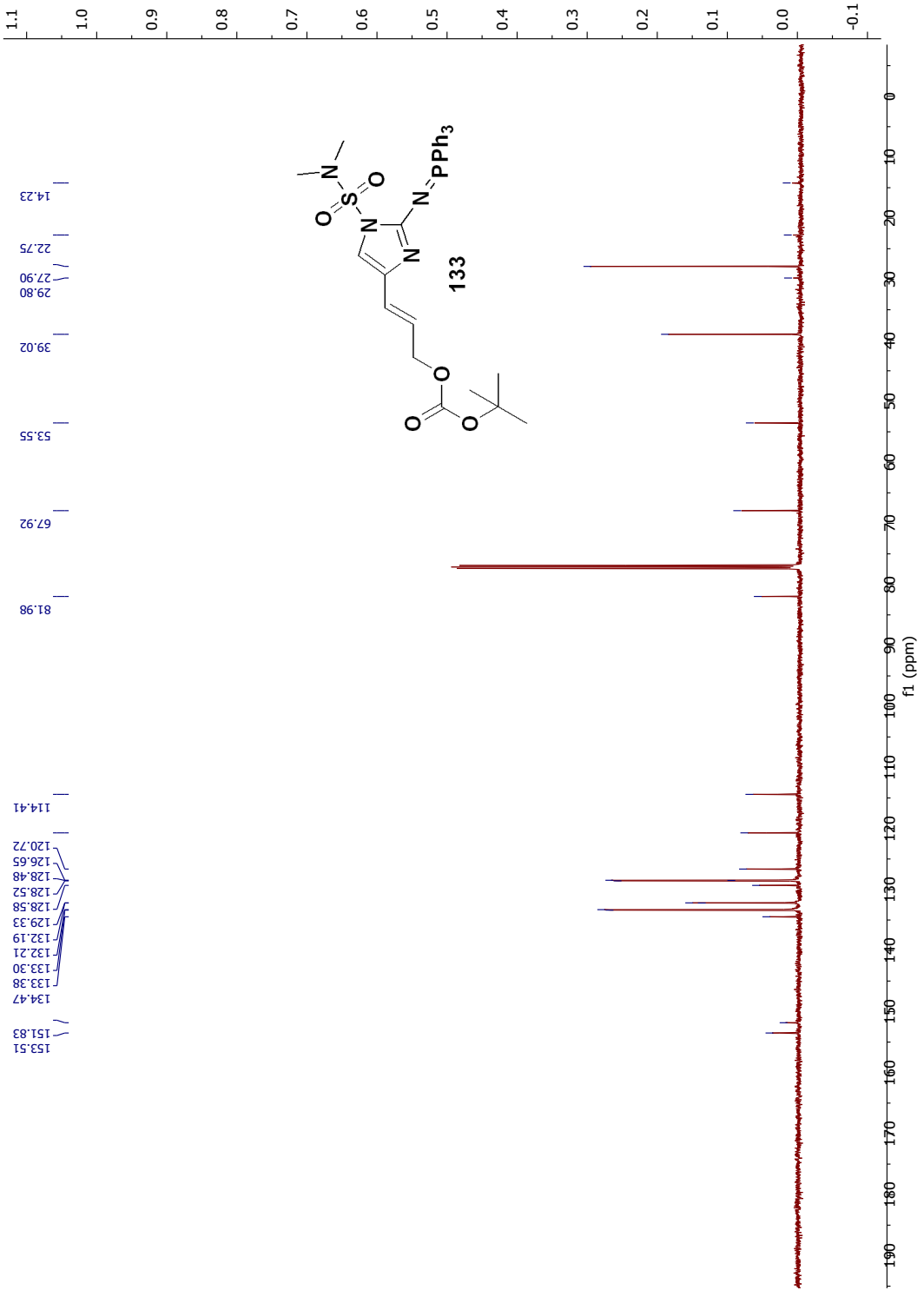

TBSO
131
f1 (ppm)


151.73
135.11
133.40
133.32
132.15
129.46
128.56
128.46
127.43
121.71
113.21
64.09
39.03
26.10
18.51
-4.96
TBSO
O
S
N
N
N
N=PPh3
131
f1 (ppm)


132
HO
f1 (ppm)


39.02
63.95
113.75
123.54
126.70
128.50
128.60
129.33
132.22
133.30
133.38
HO
N
S
O
N
N
N
PPh3
132
f1 (ppm)


133
f1 (ppm)


133
14.23
22.75
27.90
29.80
39.02
53.55
67.92
81.98
114.41
120.72
126.65
128.48
128.52
128.58
129.33
132.19
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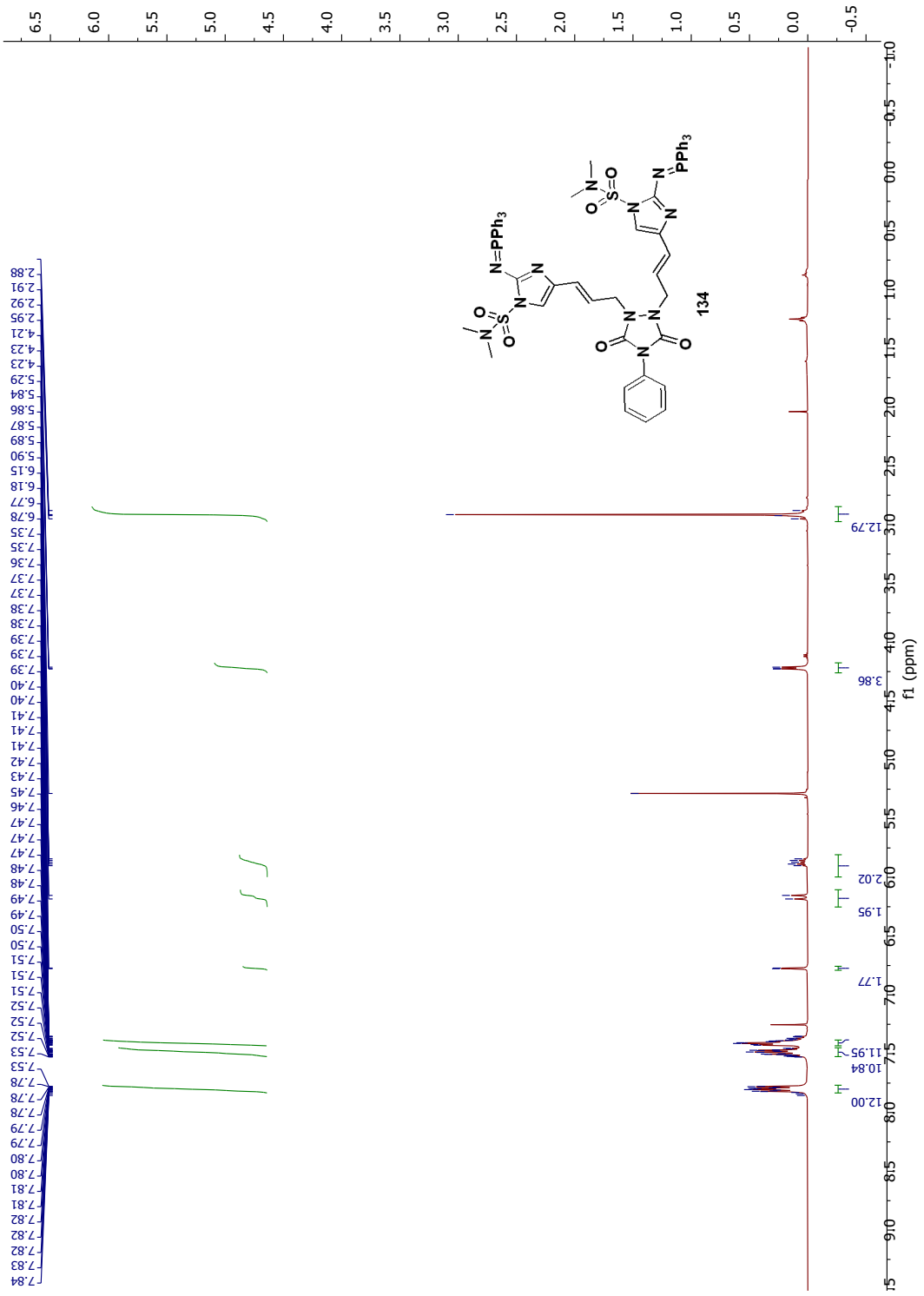
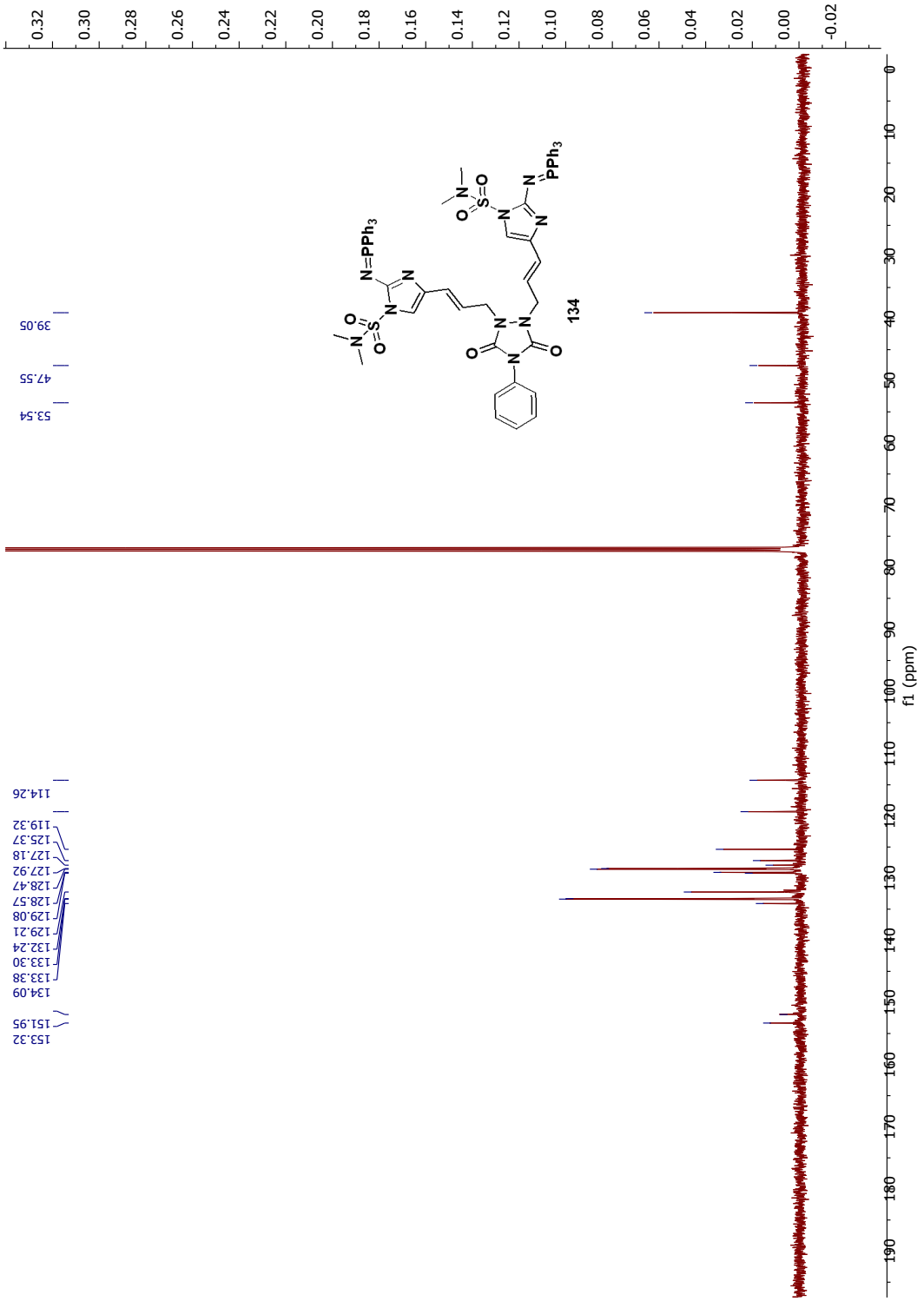
133.30
133.38
134.47
151.83
153.51
f1 (ppm)


134
12.79
3.86
2.02
1.95
1.77
11.95
10.84
12.00
f1 (ppm)


153.32
151.95
134.09
133.38
133.30
132.24
129.21
129.08
128.57
128.47
127.92
127.18
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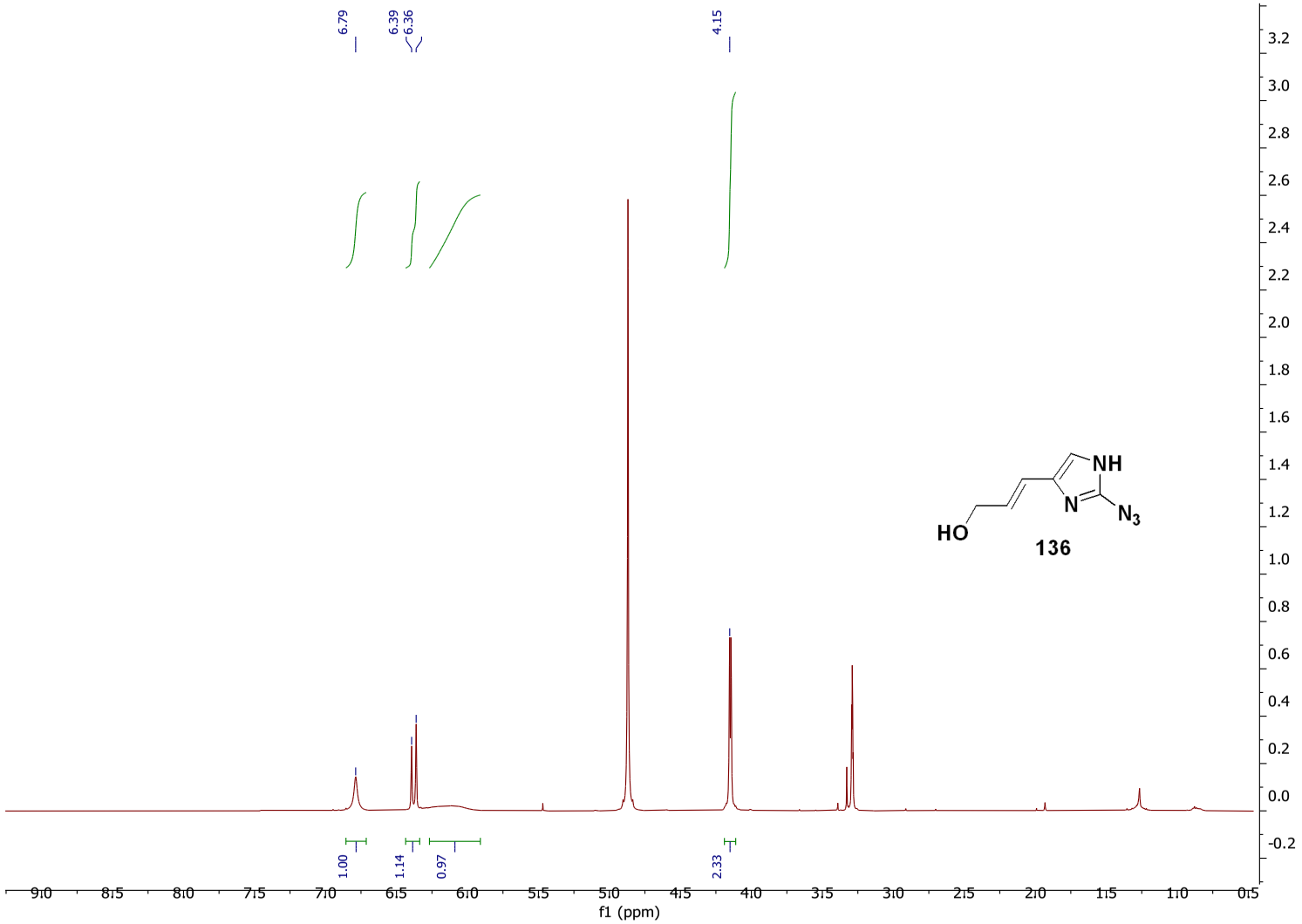
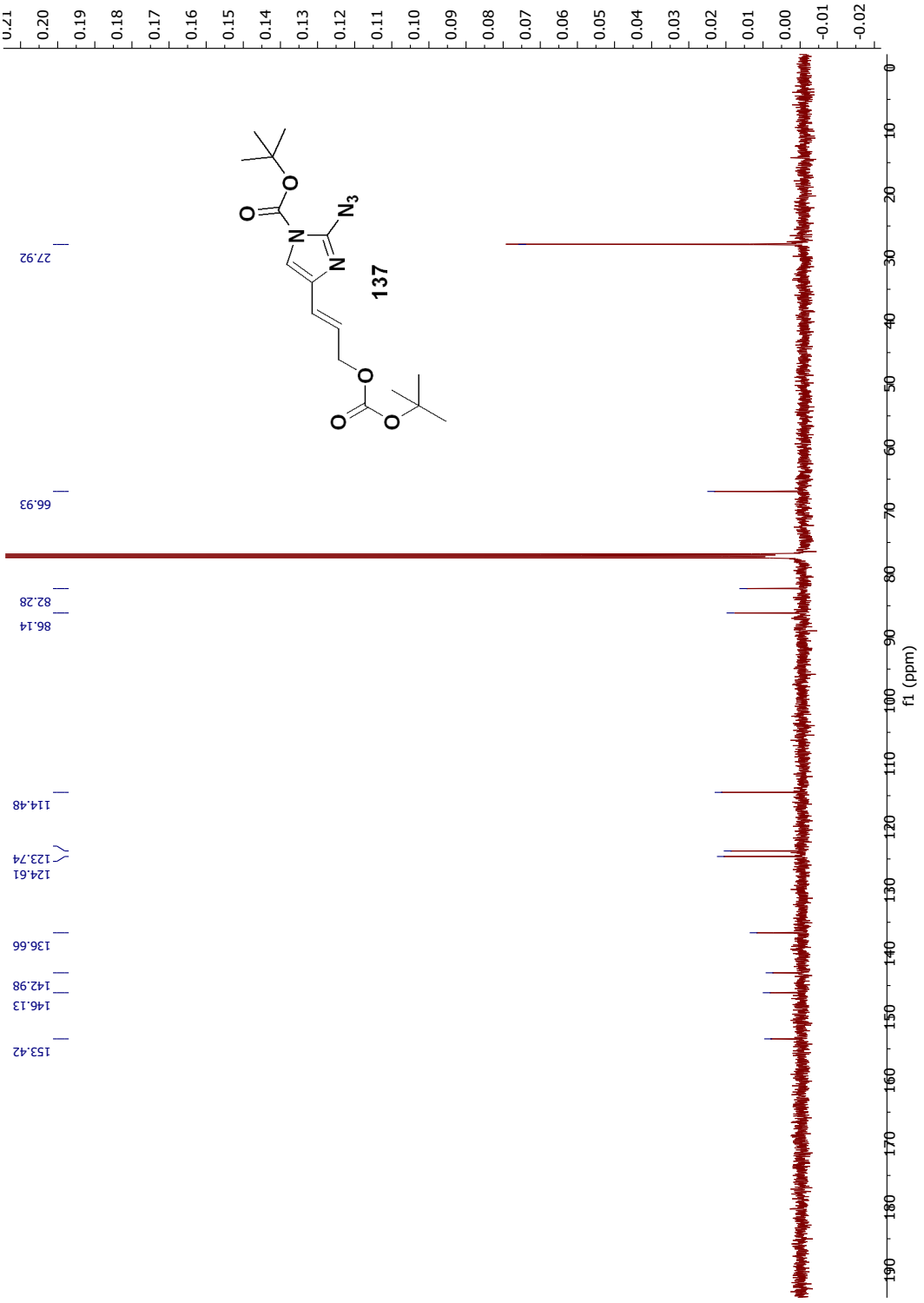
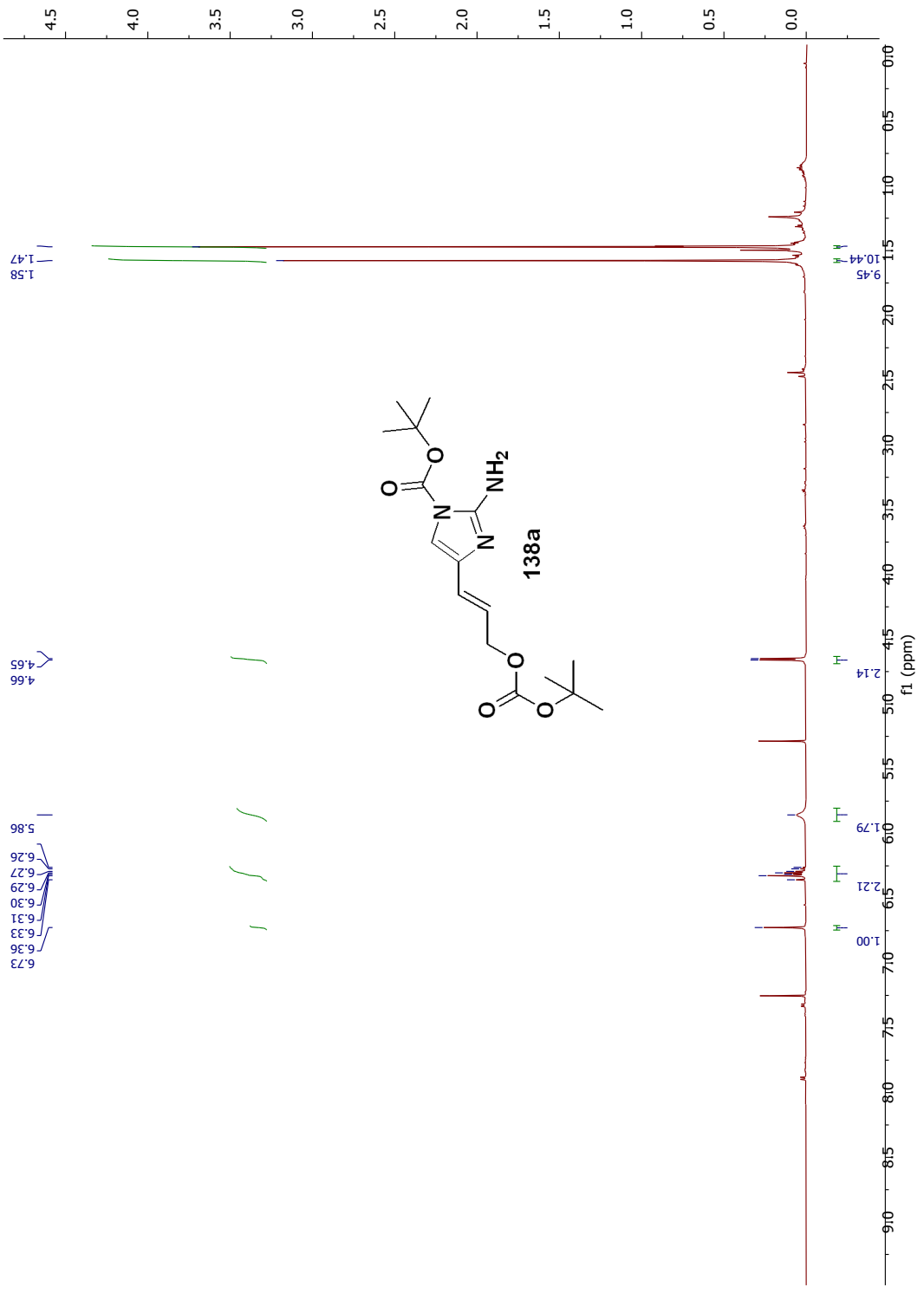
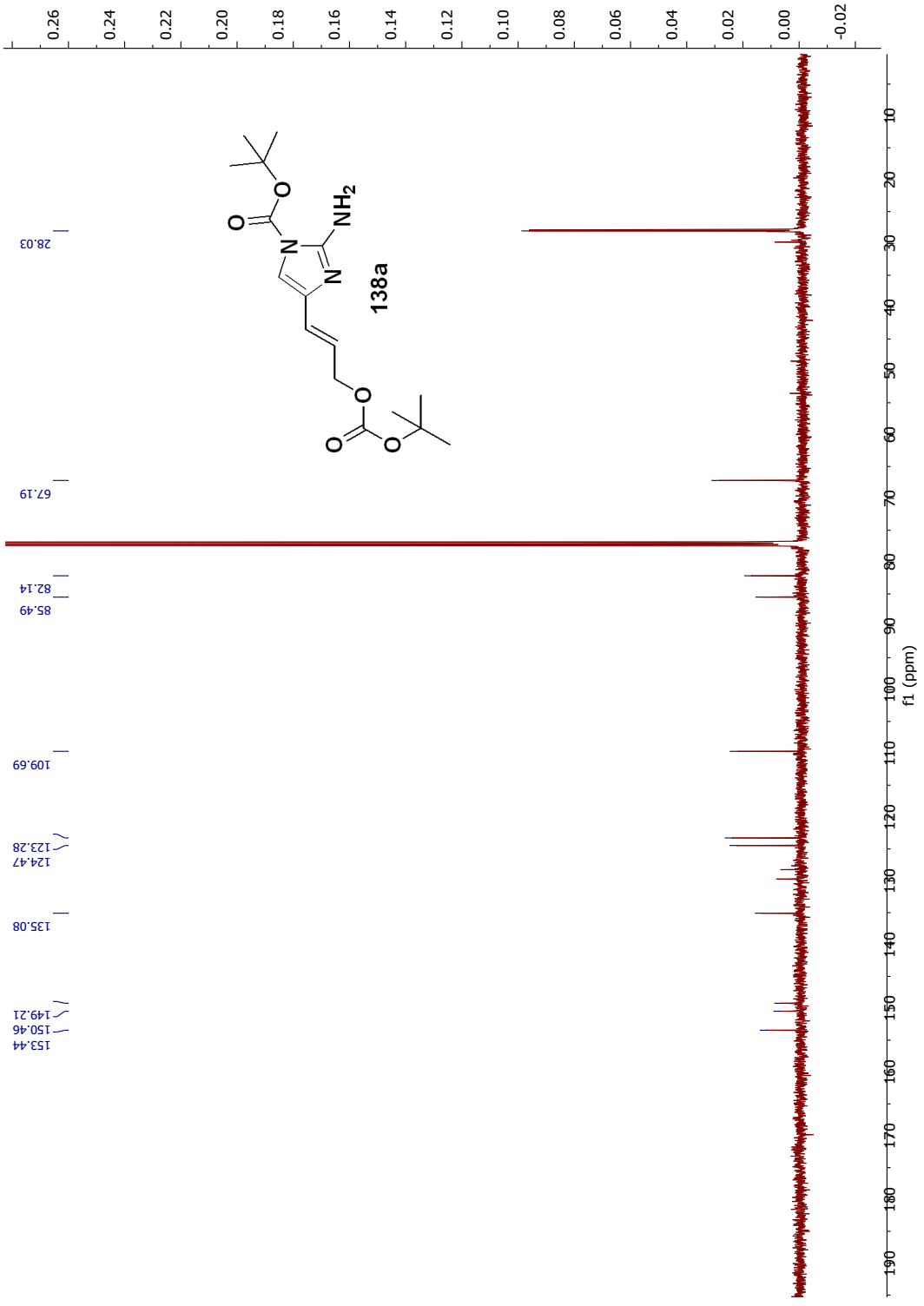
114.26
53.54
47.55
39.05
134
f1 (ppm)

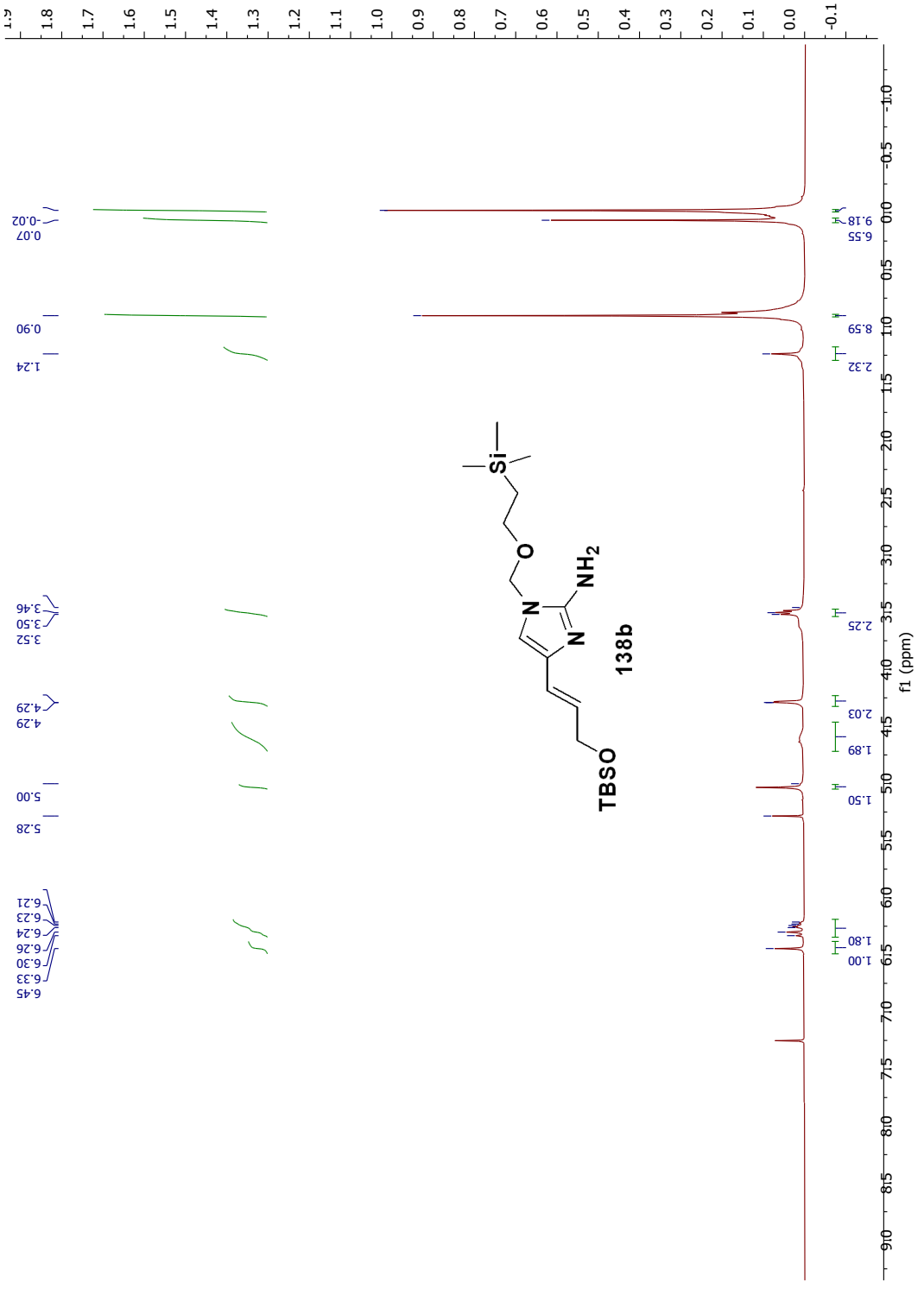

6.79
6.39
6.36
4.15
1.00
1.14
0.97
2.33
f1 (ppm)
NH
N
N3
HO
136

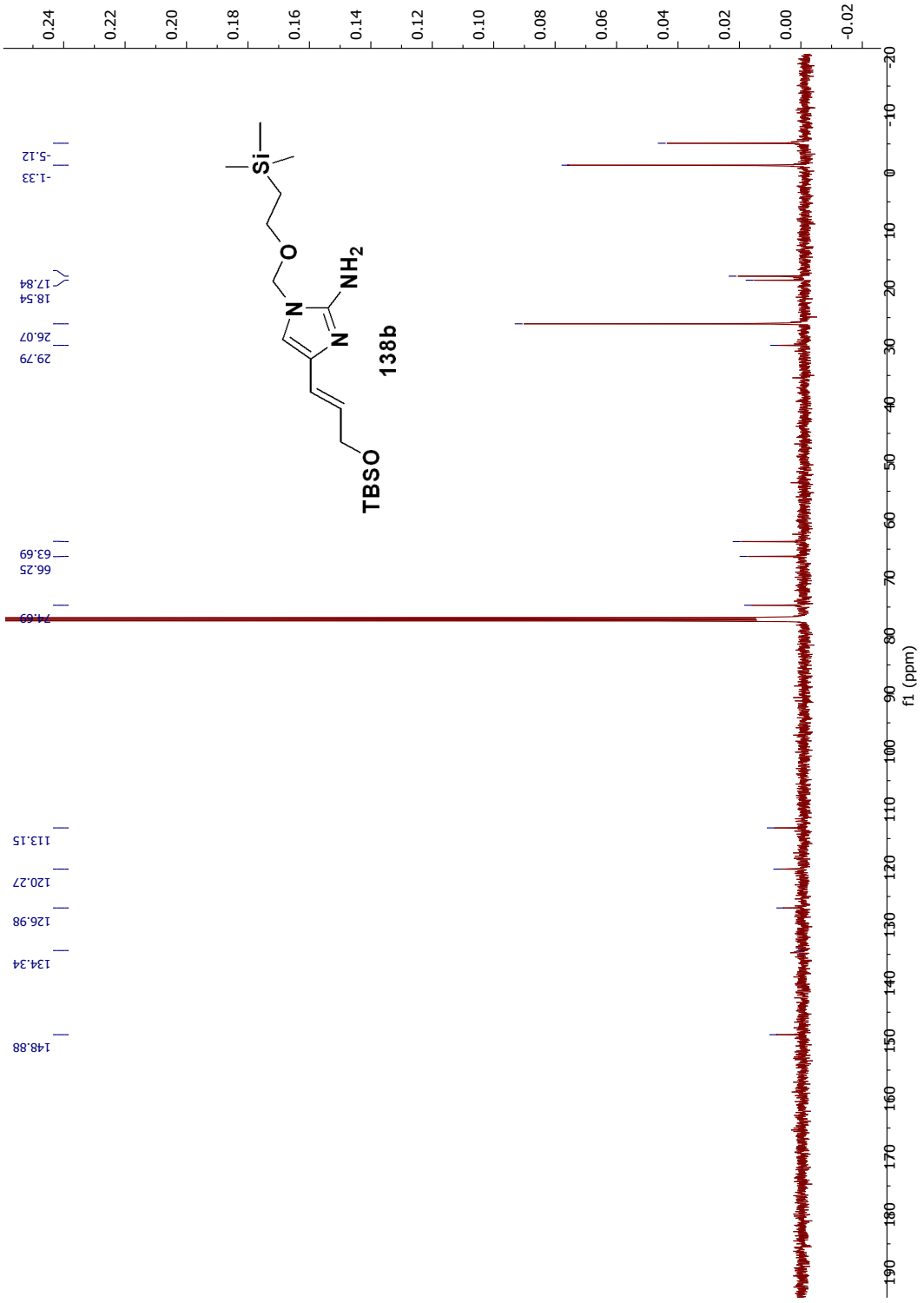
137
f1 (ppm)

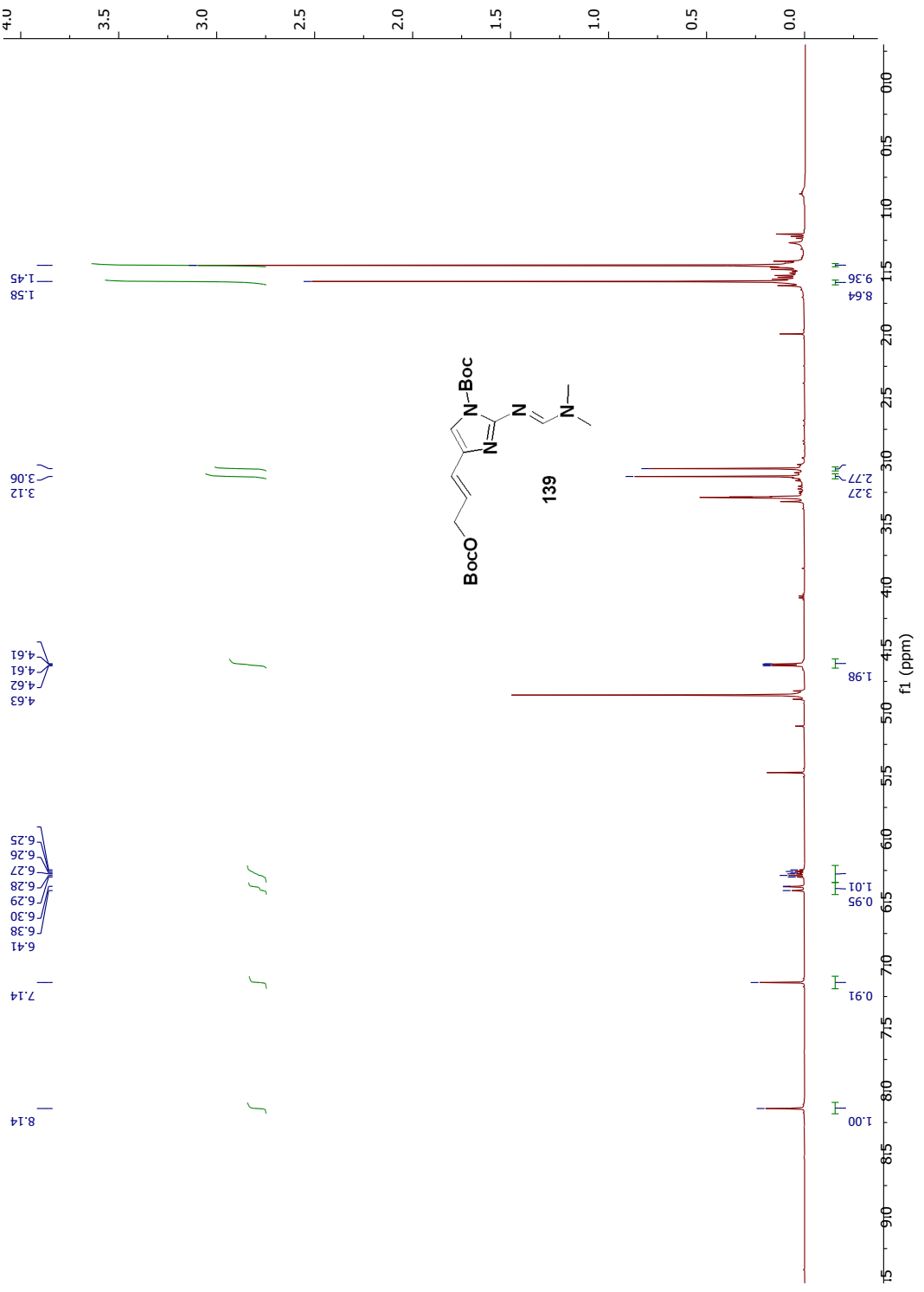

137
27.92
66.93
82.28
86.14
114.48
123.74
124.61
136.66
142.98
146.13
153.42
f1 (ppm)

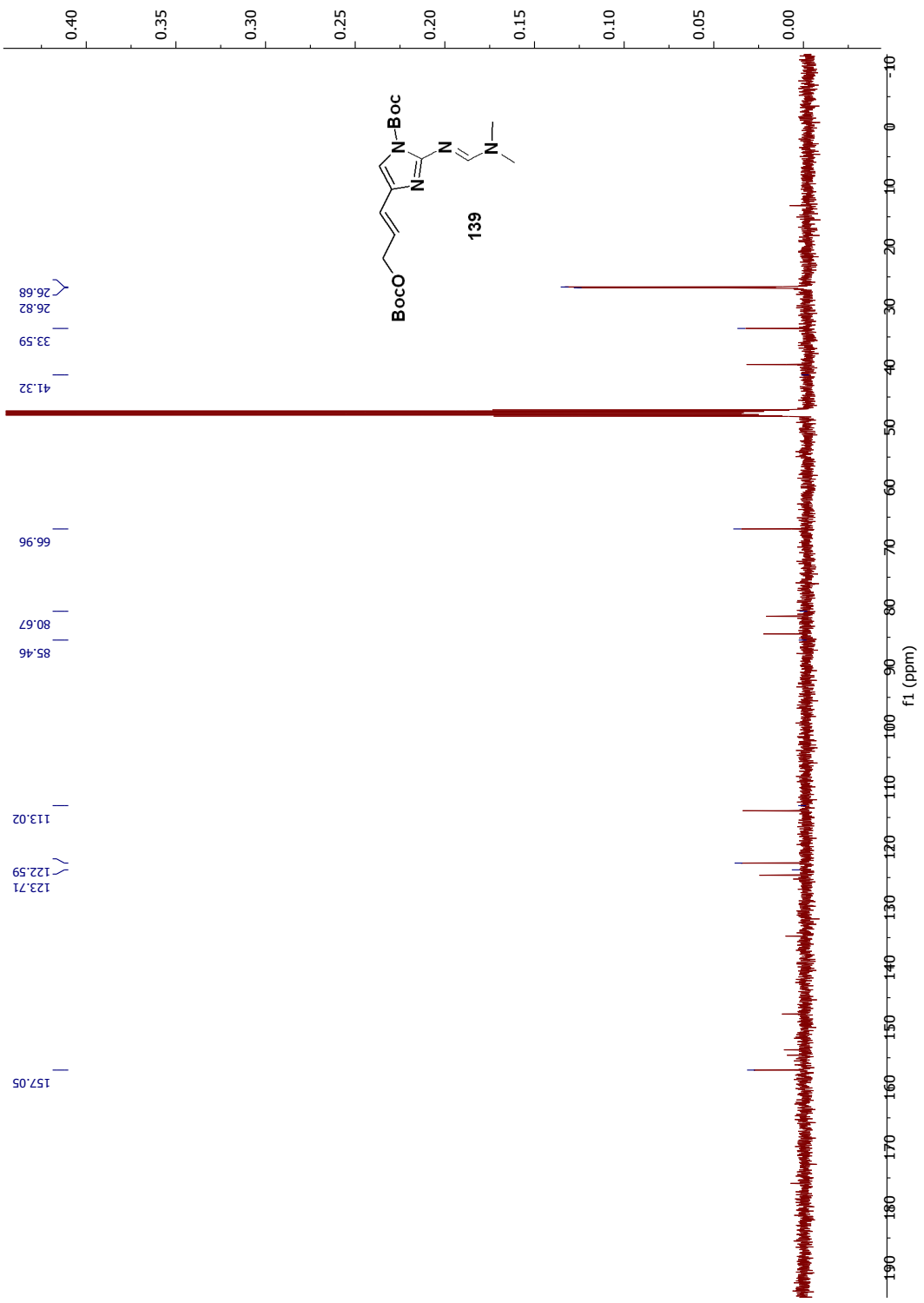

138a
NH2
f1 (ppm)

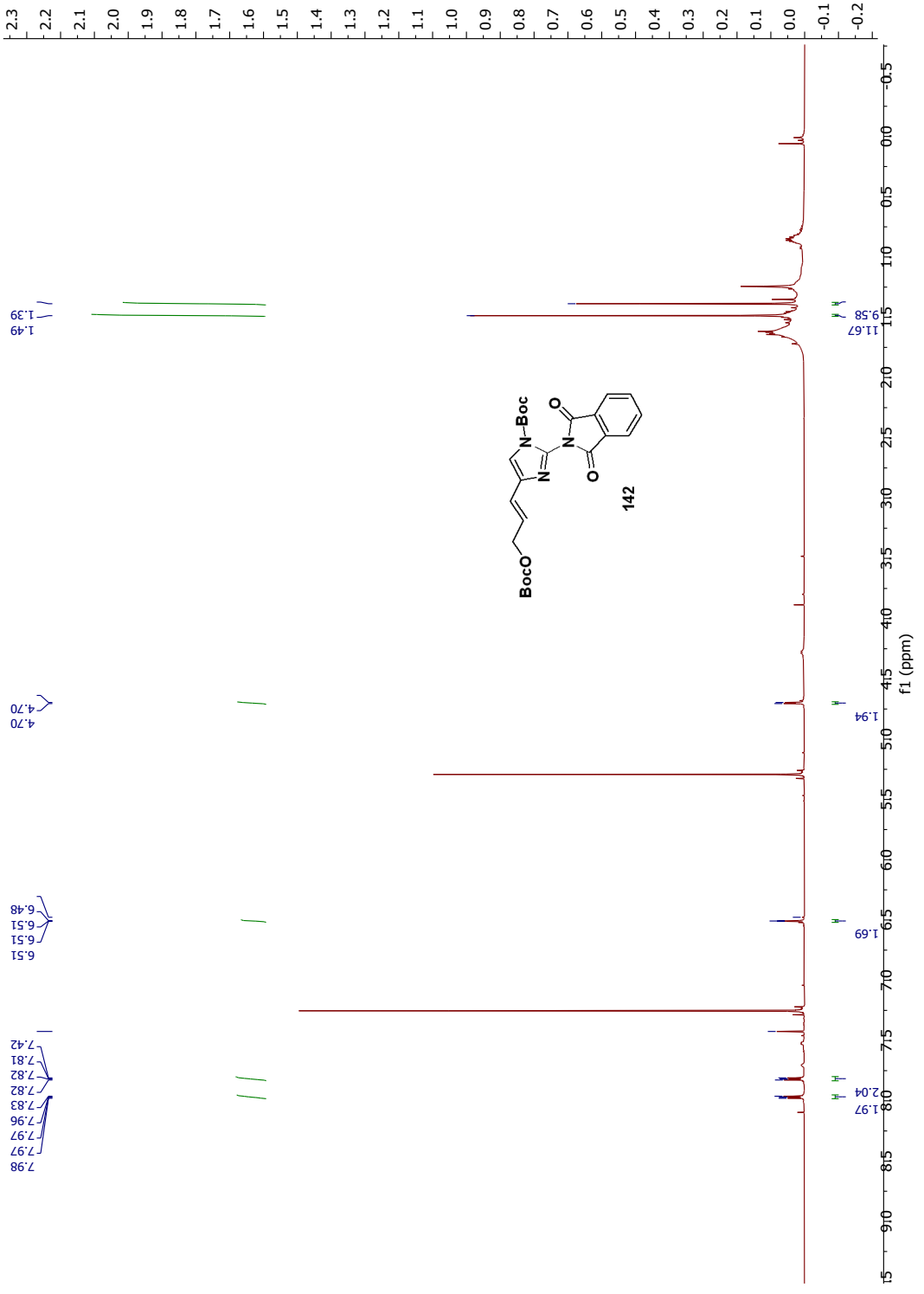

153.44
150.46
149.21
135.08
124.47
123.28
109.69
85.49
82.14
67.19
28.03
138a
f1 (ppm)

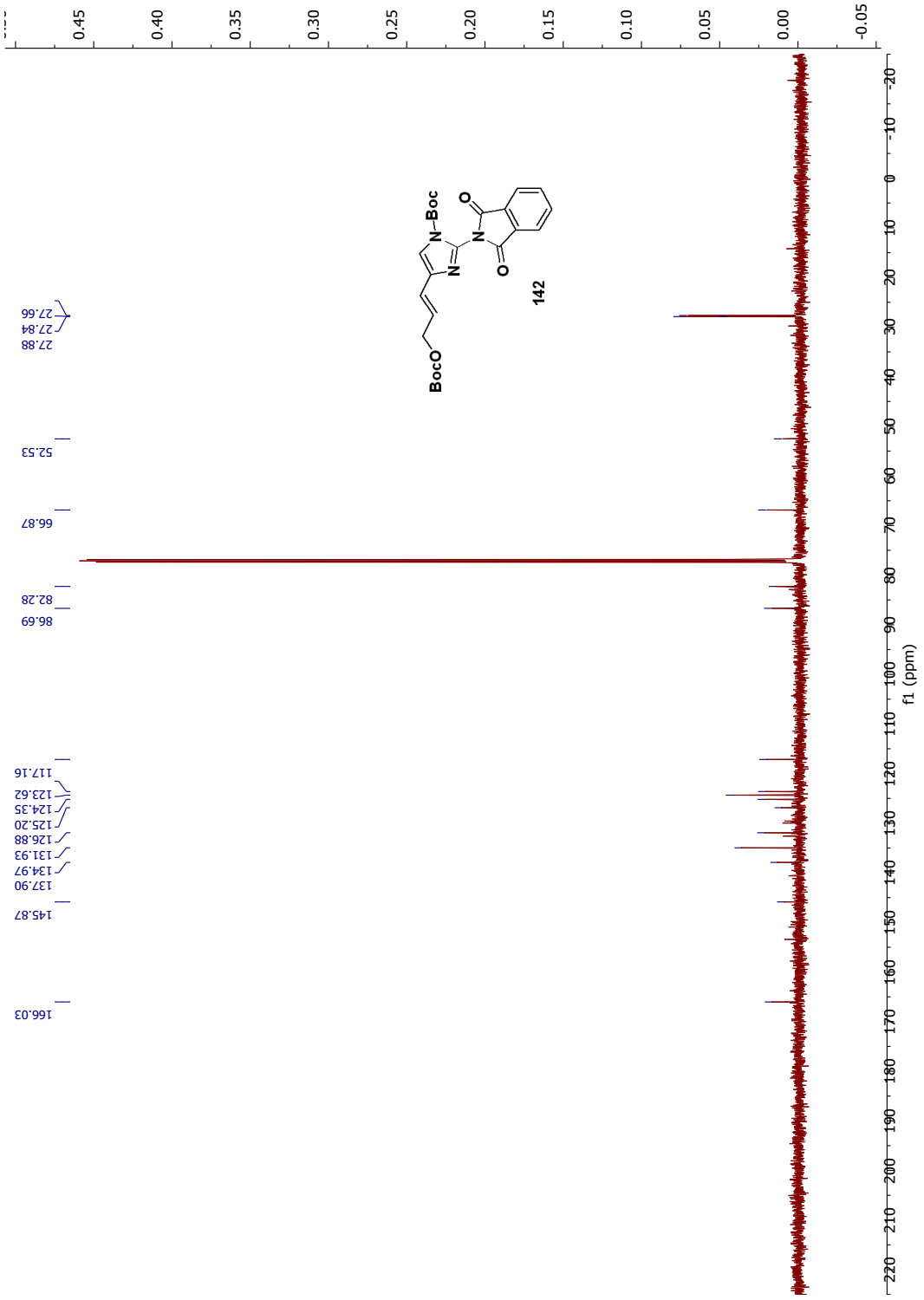

TBSO
138b
f1 (ppm)

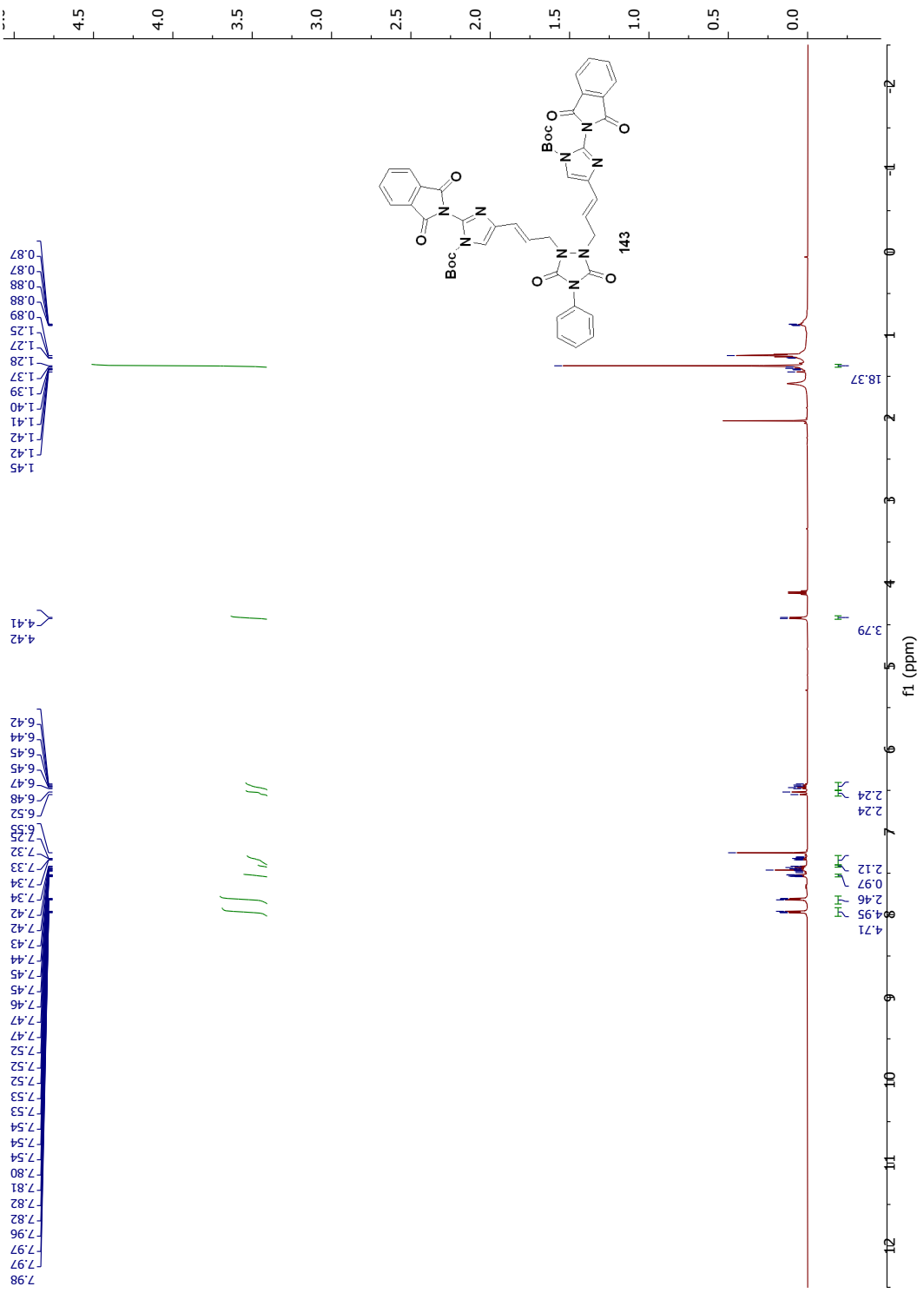

148.88
134.34
126.98
120.27
113.15
74.89
66.25
63.69
29.79
26.07
18.54
17.84
-1.33
-5.12
TBSO
138b
f1 (ppm)

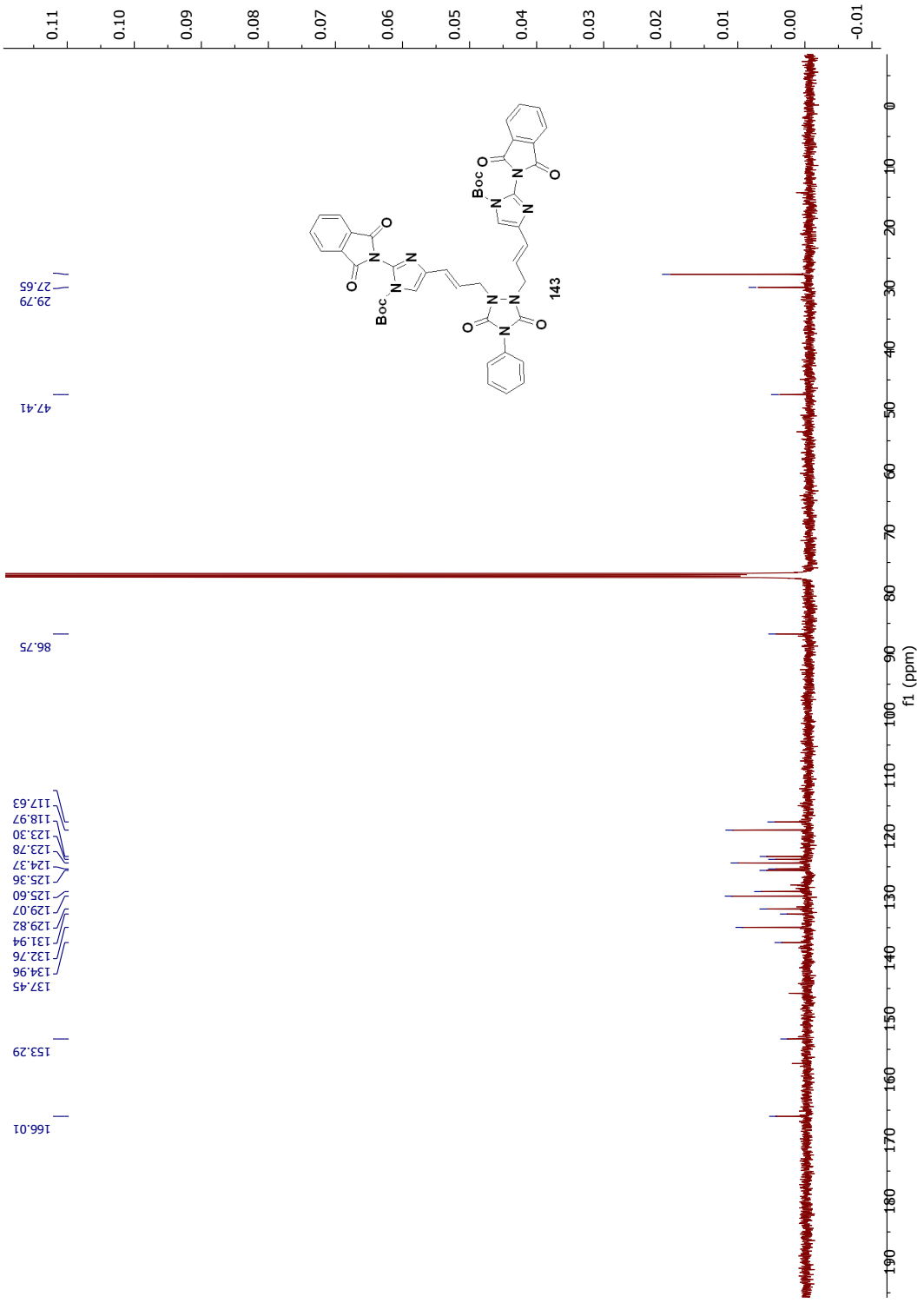

N–Boc
N
N
N
BocO
139
f1 (ppm)

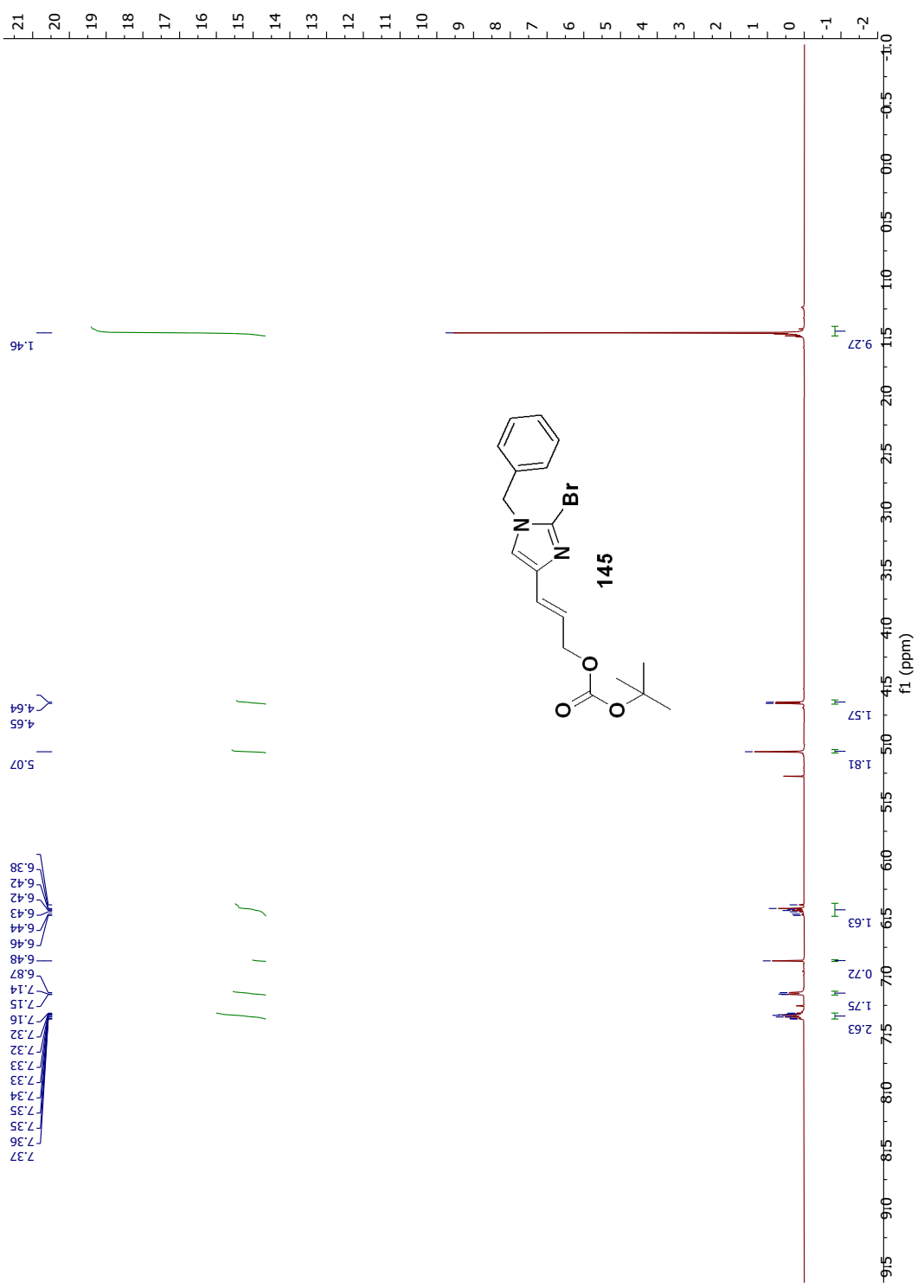

0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
N–Boc
N
N
N
BocO
139
26.68
26.82
33.59
41.32
66.96
80.67
85.46
113.02
122.59
123.71
157.05
f1 (ppm)

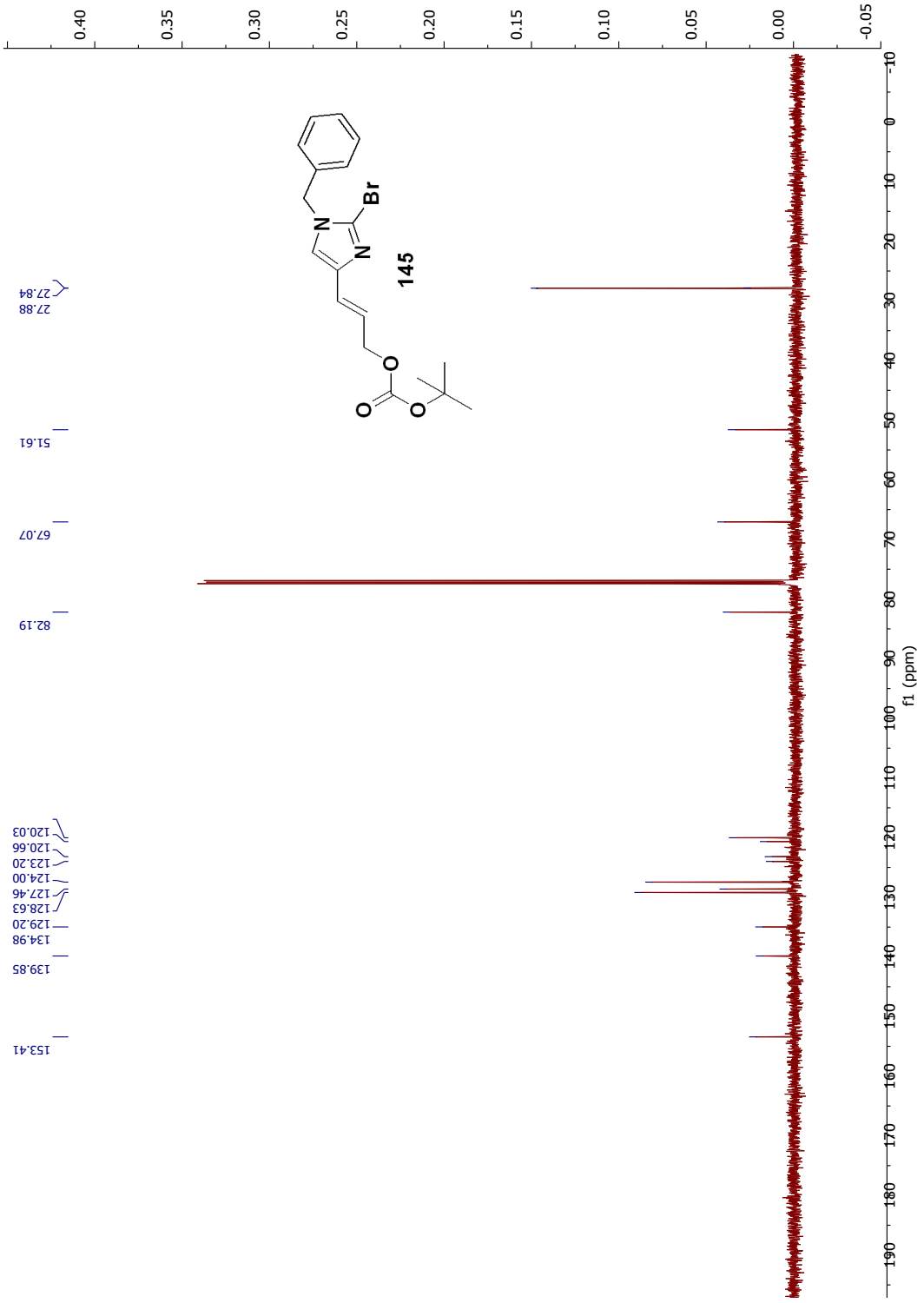

N–Boc
N
N
O
O
BocO
142
f1 (ppm)

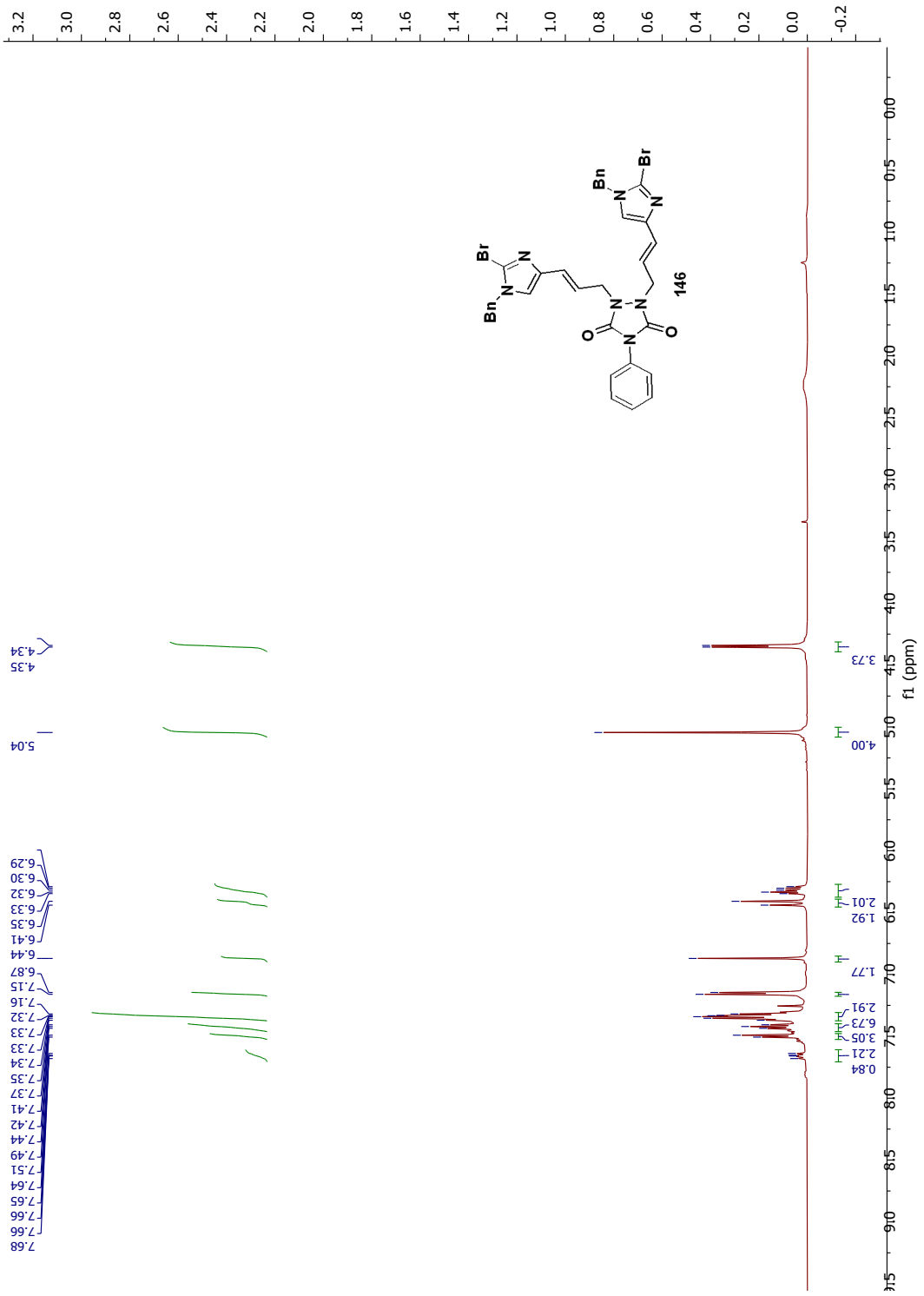

142
f1 (ppm)

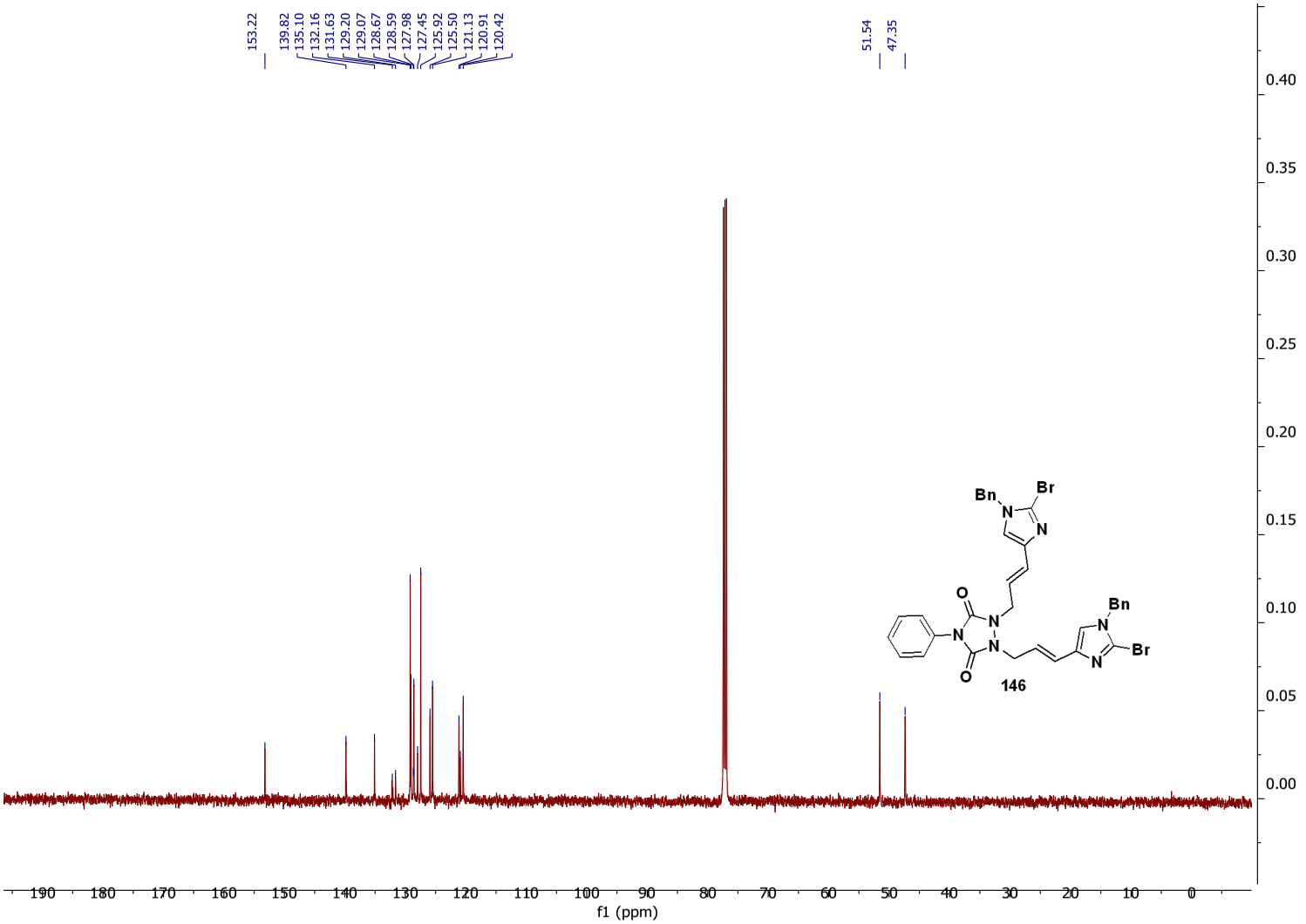

143
f1 (ppm)

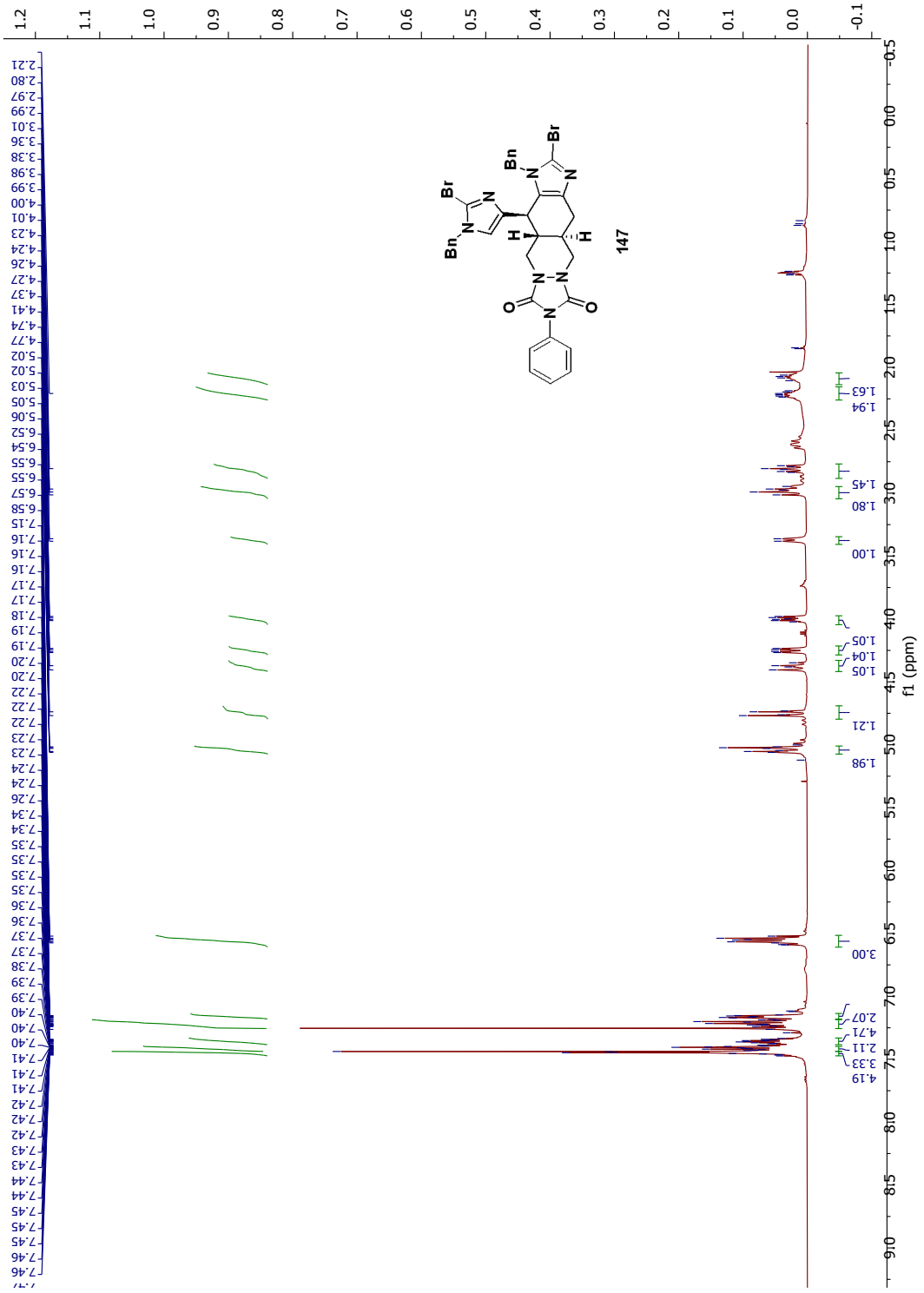

143
Boc
Boc
166.01
153.29
137.45
134.96
132.76
131.94
129.82
129.07
125.60
125.36
124.37
123.78
123.30
118.97
117.63
86.75
47.41
29.79
27.65
f1 (ppm)

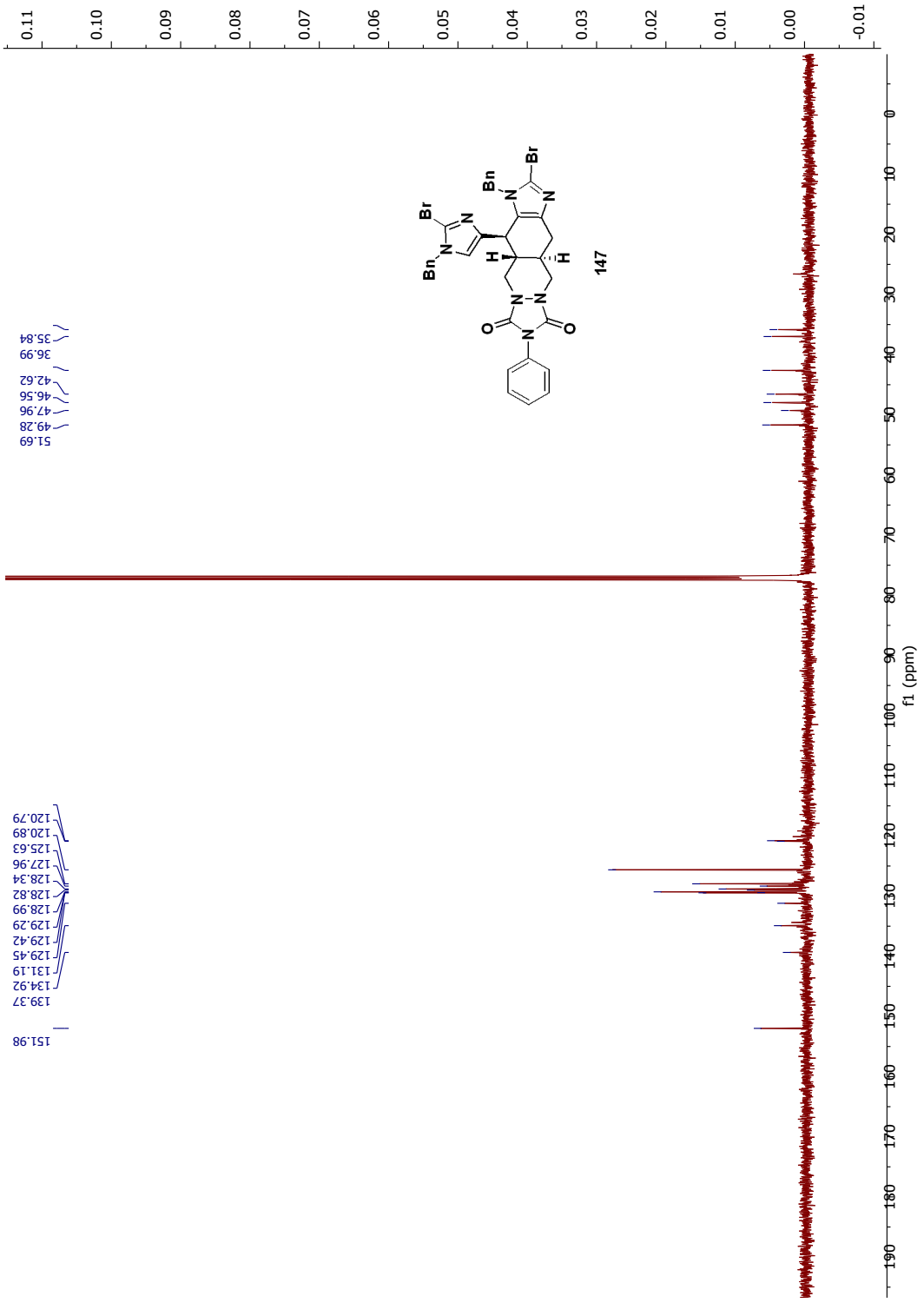

145
Br
N
N
O
O
O
f1 (ppm)

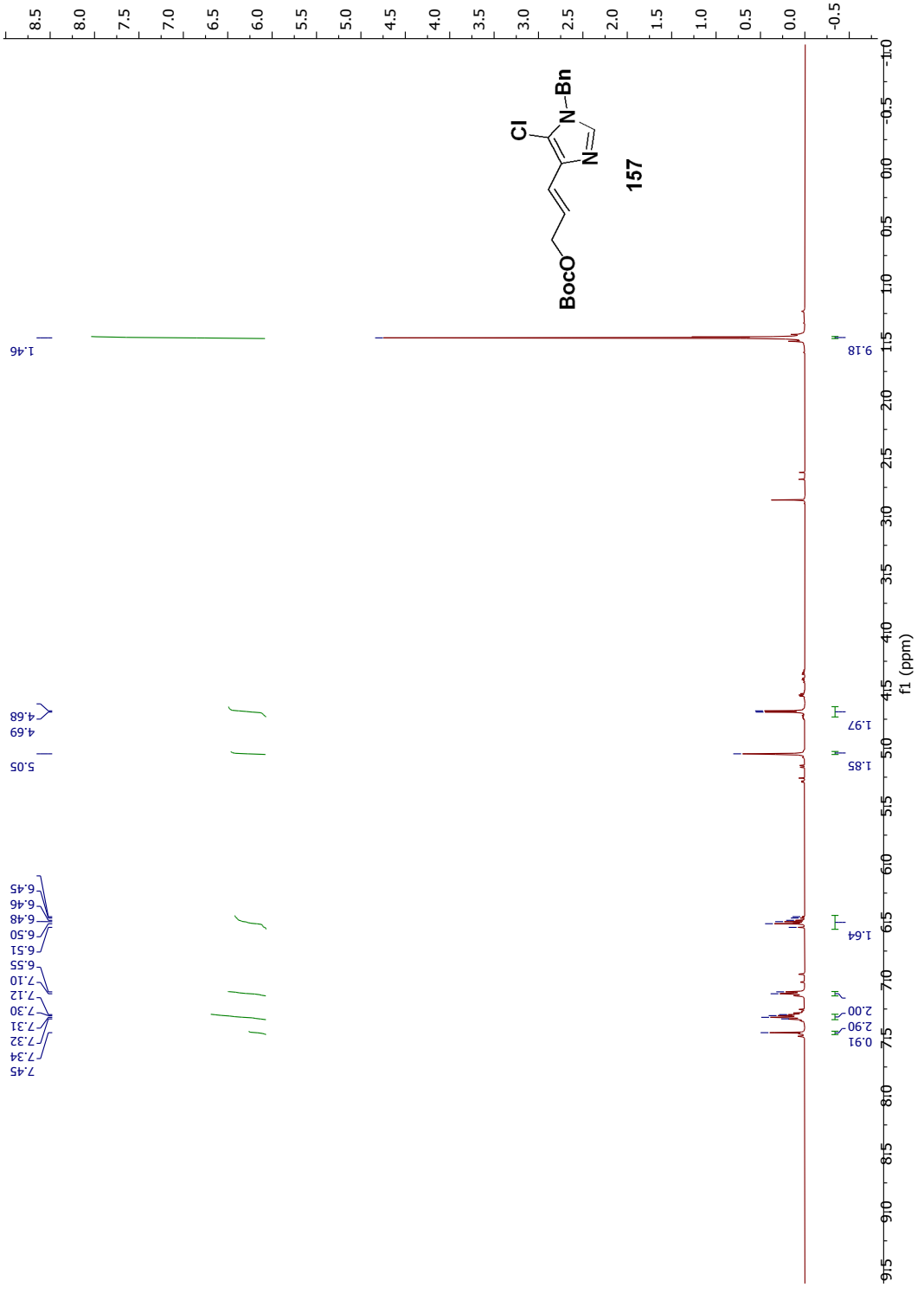

153.41
139.85
134.98
129.20
128.63
127.46
124.00
123.20
120.66
120.03
82.19
67.07
51.61
27.88
27.84
145
Br
N
N
O
O
O
f1 (ppm)

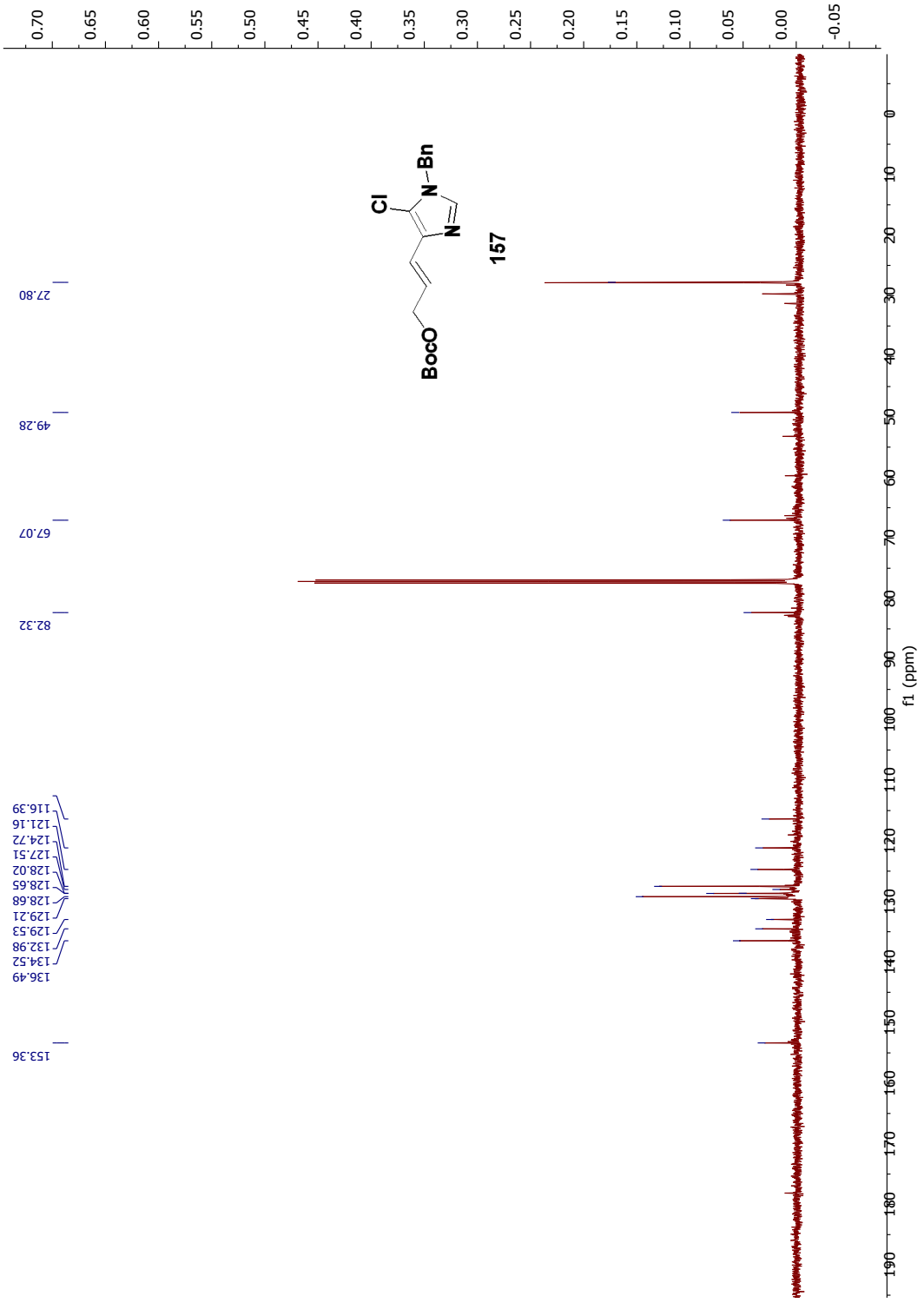

Br
Bn
N
N
O
O
146
f1 (ppm)

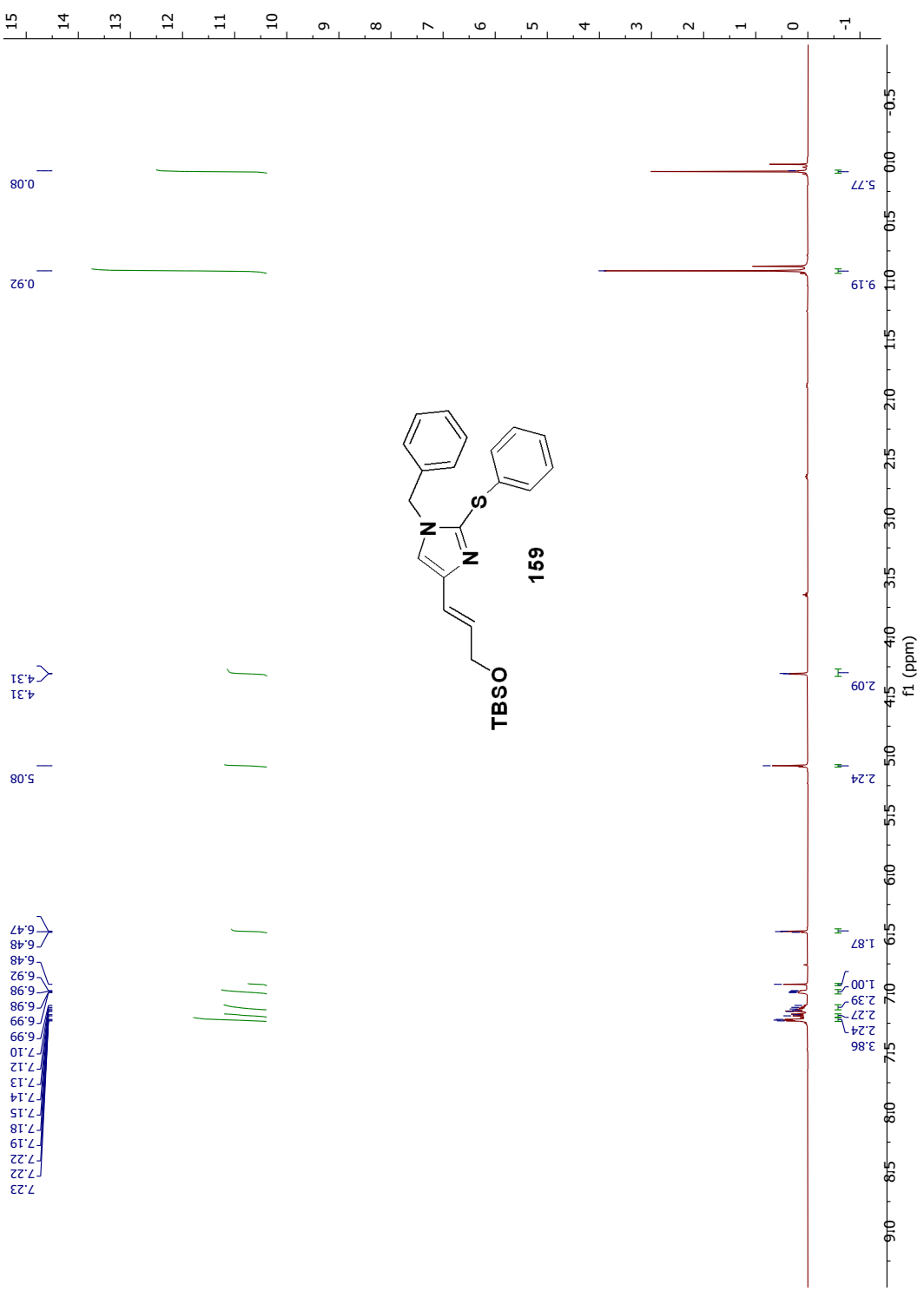

153.22
139.82
135.10
132.16
131.63
129.20
129.07
128.67
128.59
127.98
127.45
125.92
125.50
121.13
120.91
120.42
51.54
47.35
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)
Bn
Br
N
N
O
N
N
N
O
Bn
N
N
Br
146

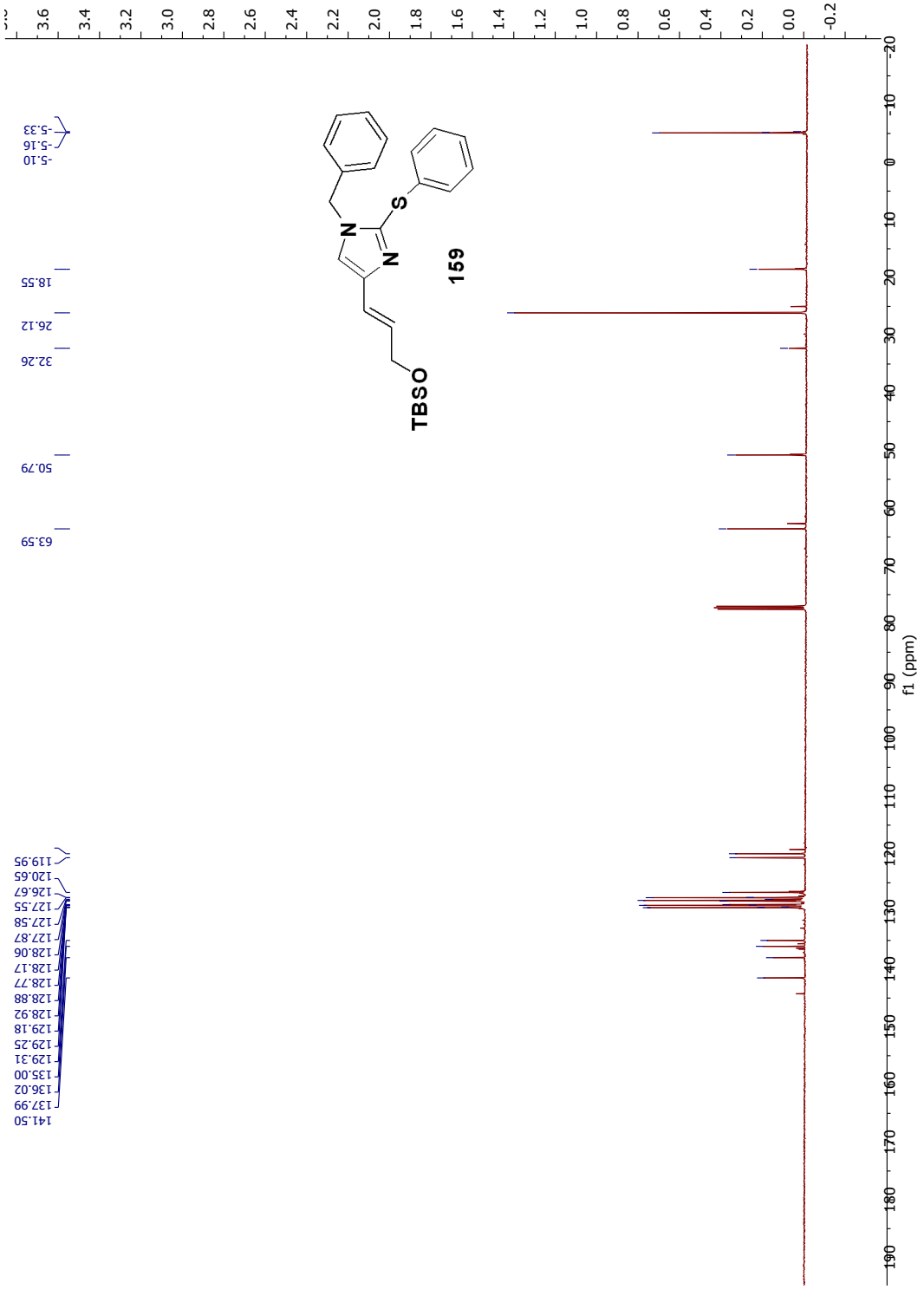

Br
Bn
N
N
H
H
O
O
147
f1 (ppm)

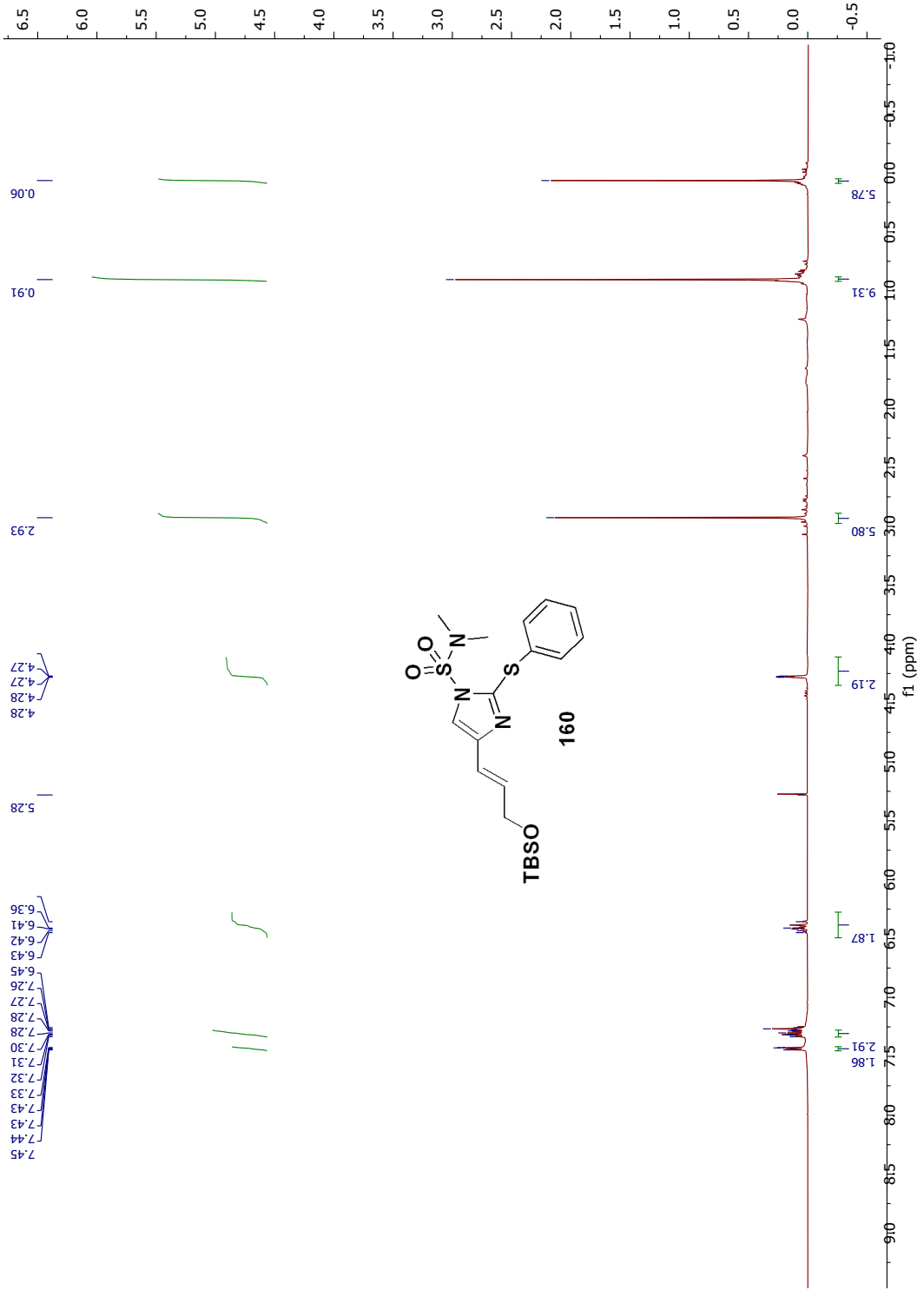

147
151.98
139.37
134.92
131.19
129.45
129.42
129.29
128.99
128.82
128.34
127.96
125.63
120.89
120.79
51.69
49.28
47.96
46.56
42.62
36.99
35.84
f1 (ppm)

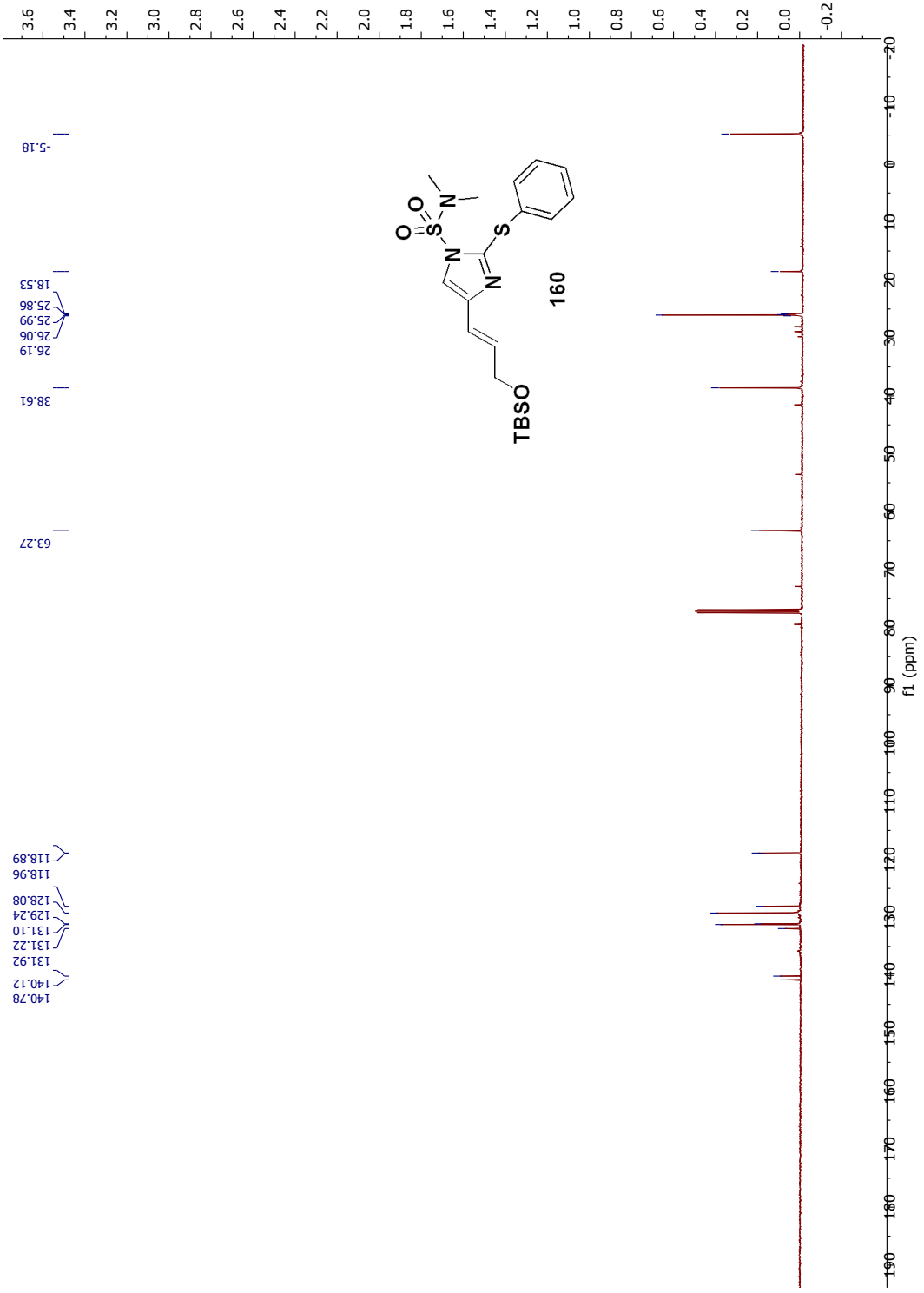

Cl
N–Bn
N
BocO
157
f1 (ppm)
1.46
5.05
4.69
4.68
7.45
7.34
7.32
7.31
7.30
7.12
7.10
6.55
6.51
6.50
6.48
6.46
6.45
9.18
1.97
1.85
1.64
2.00
2.90
0.91

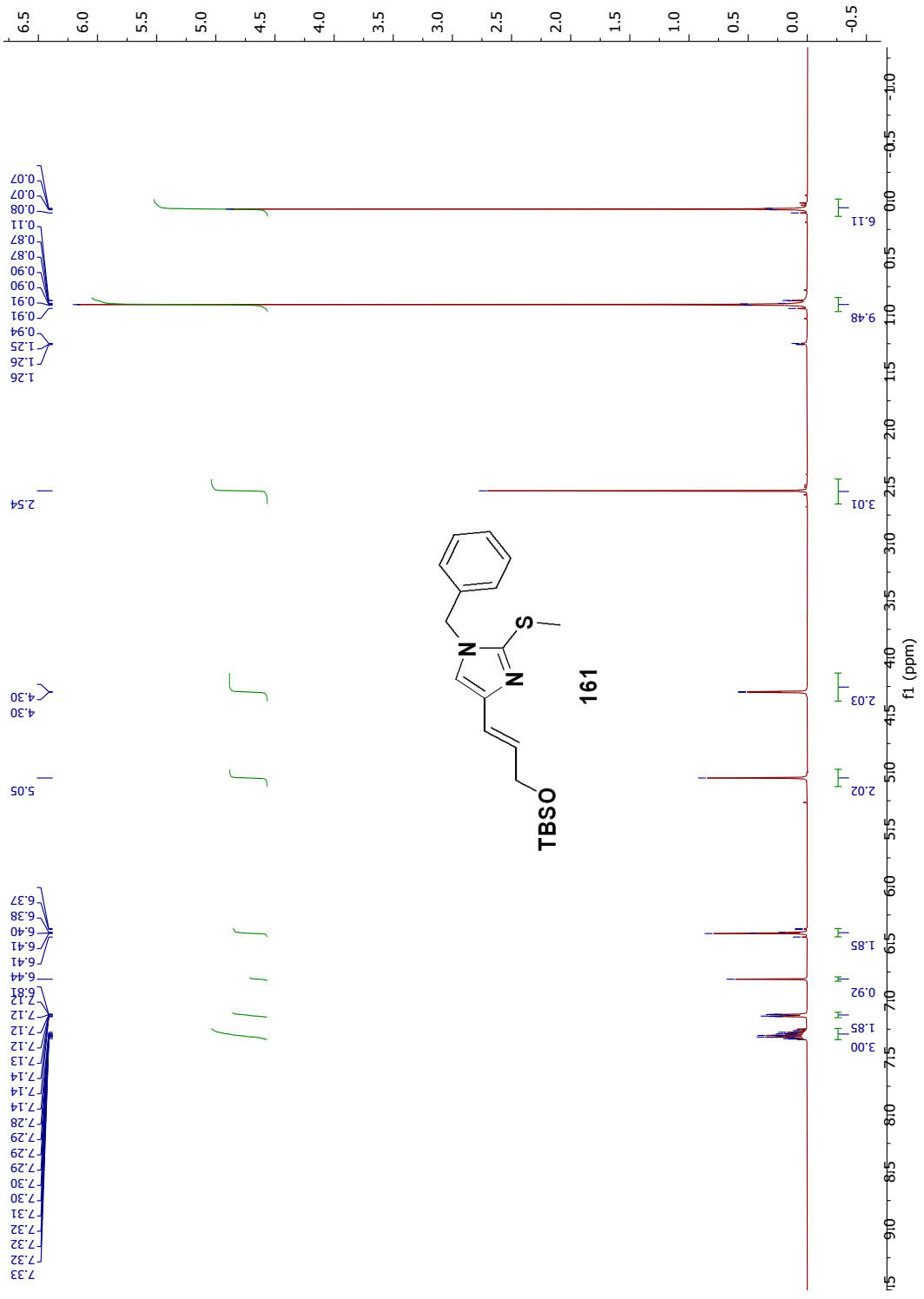

Cl
N
Bn
N
BocO
157
153.36
136.49
134.52
132.98
129.53
129.21
128.68
128.65
128.02
127.51
124.72
121.16
116.39
82.32
67.07
49.28
27.80
f1 (ppm)

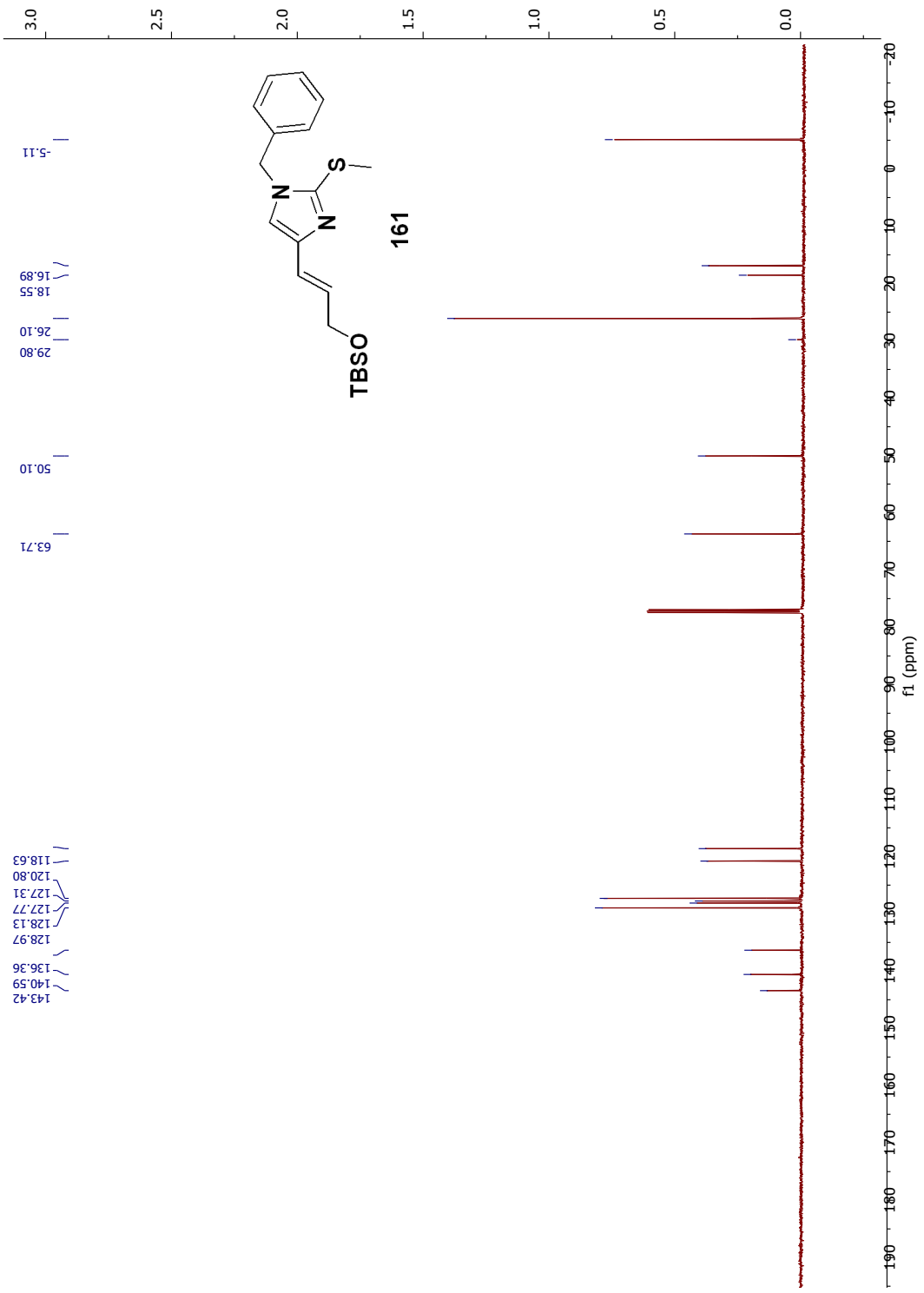

TBSO
N
N
S
159
f1 (ppm)

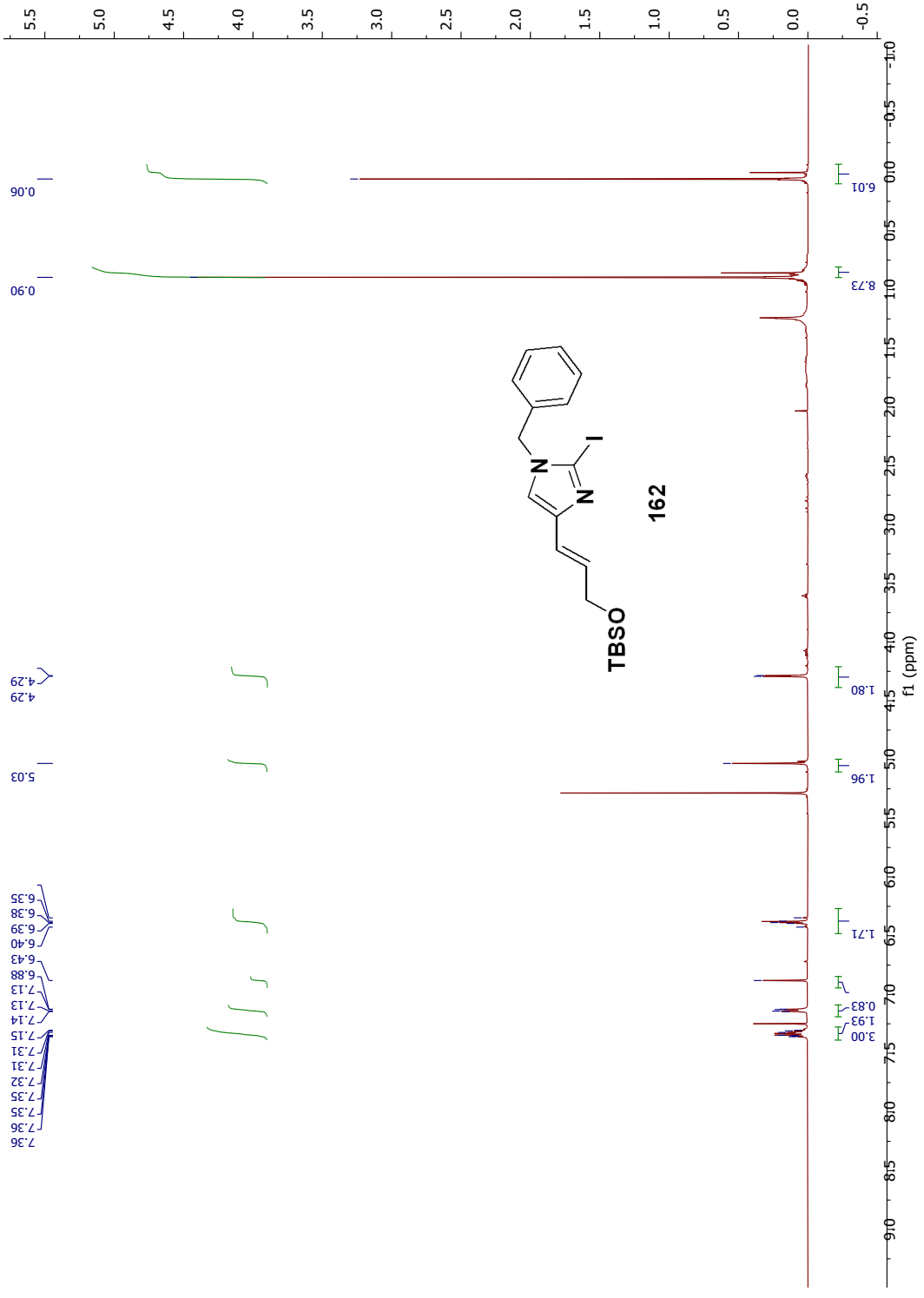

-5.33
-5.16
-5.10
18.55
26.12
32.26
50.79
63.59
119.95
120.65
126.67
127.55
127.58
127.87
128.06
128.17
128.77
128.88
128.92
129.18
129.25
129.31
135.00
136.02
137.99
141.50
TBSO
N
N
S
159
f1 (ppm)

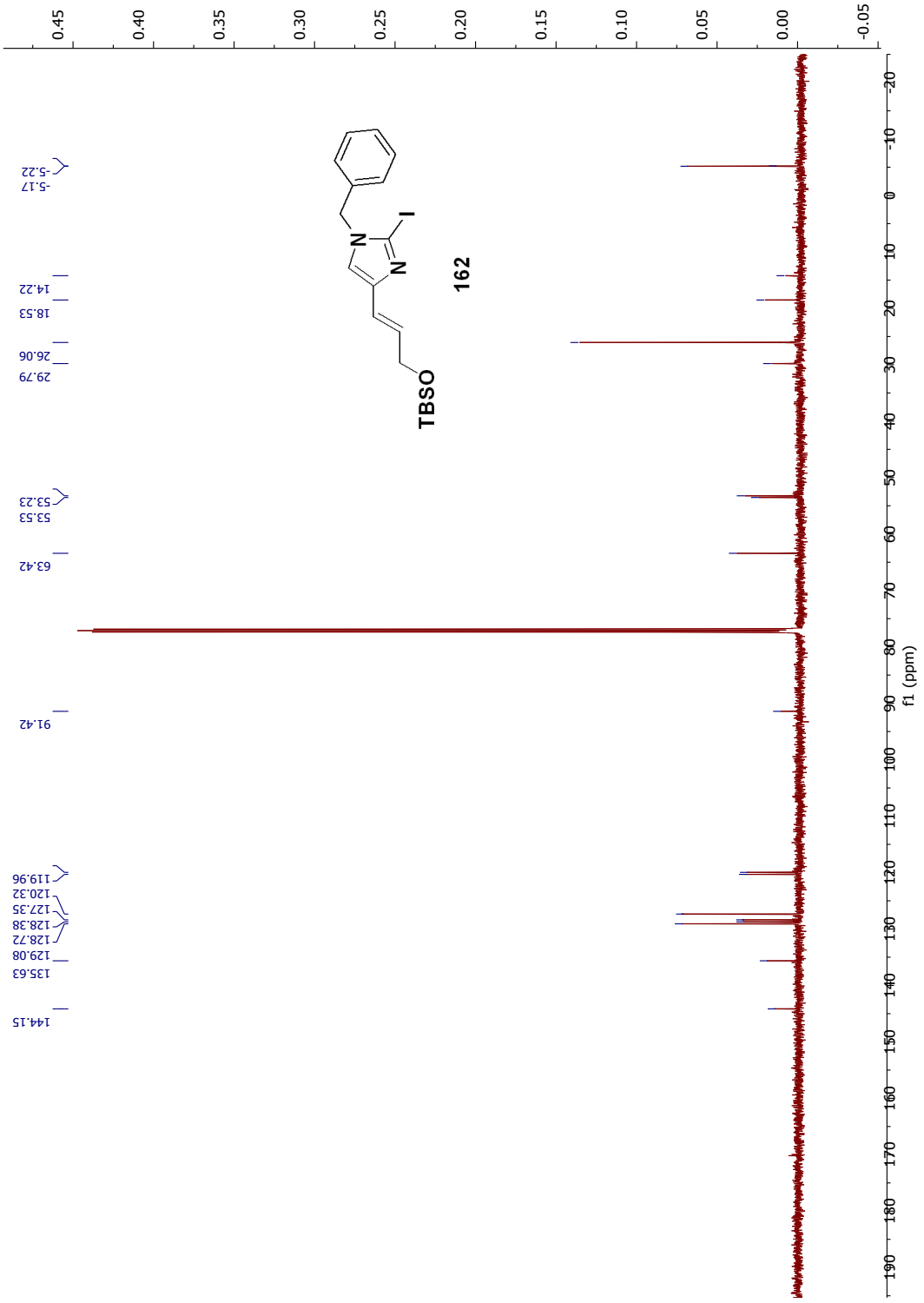

160
TBSO
f1 (ppm)


-5.18
18.53
25.86
25.99
26.06
26.19
38.61
63.27
118.89
118.96
128.08
129.24
131.10
131.22
131.92
140.12
140.78
TBSO
160
f1 (ppm)

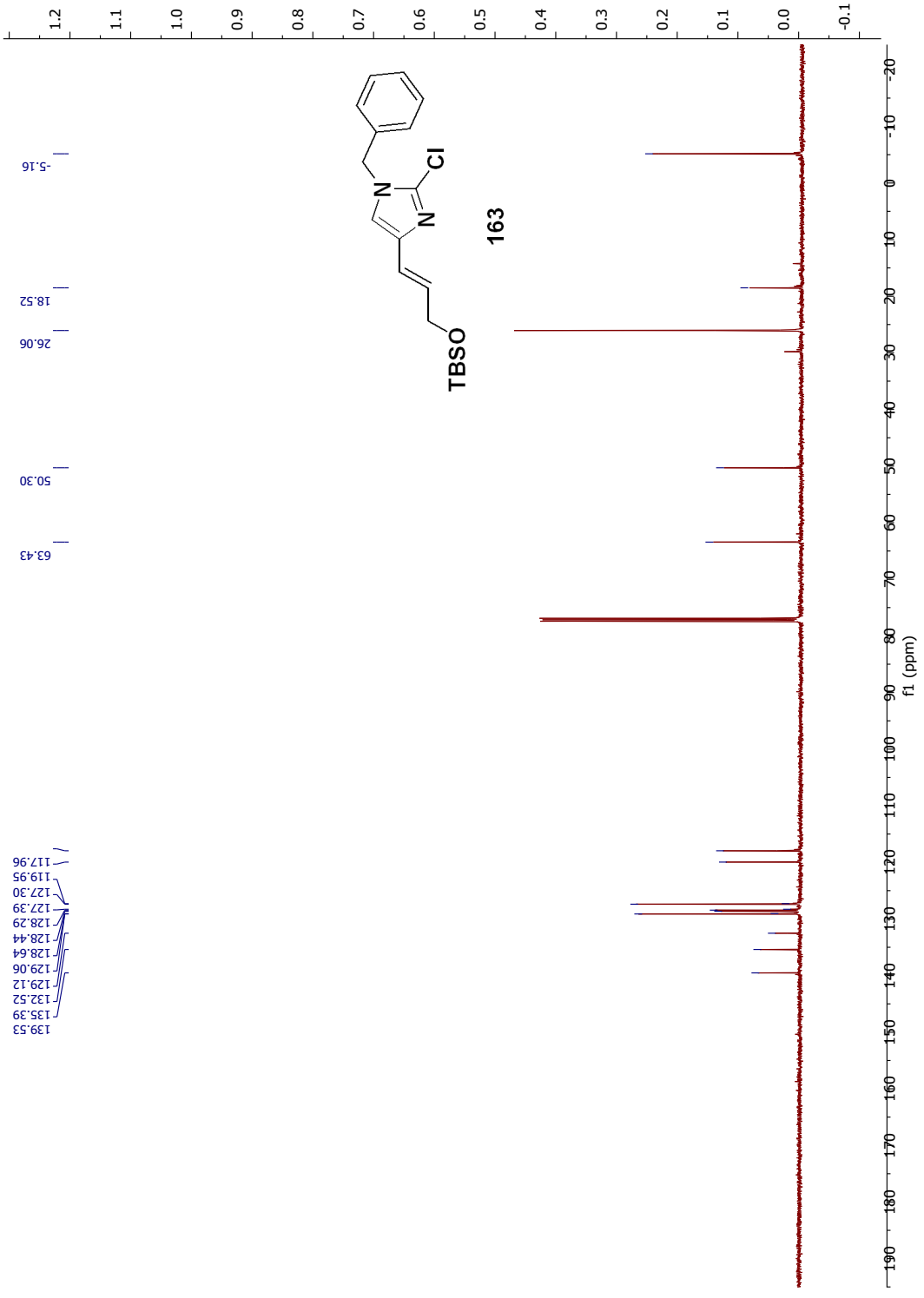

TBSO
N
N
S
161
f1 (ppm)

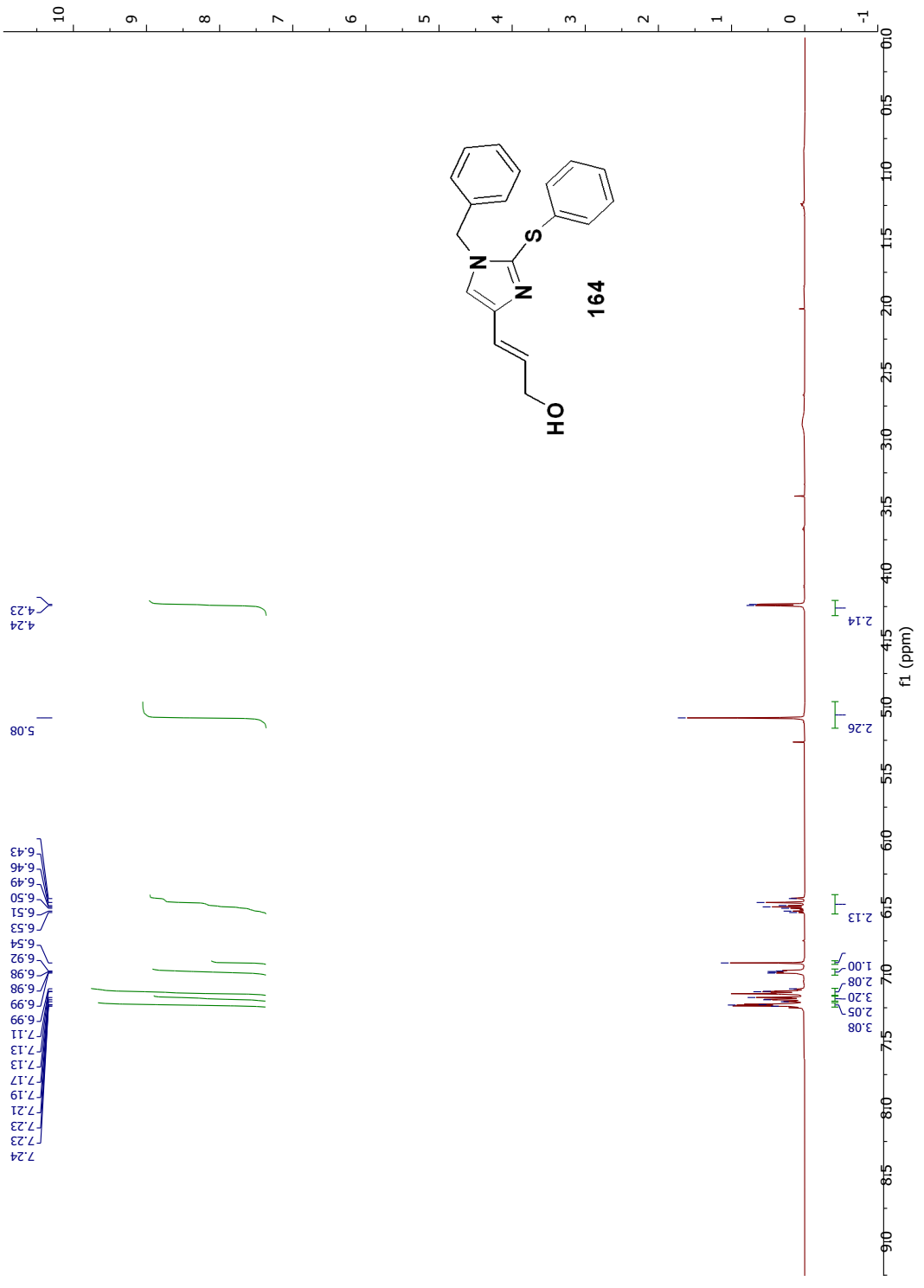

-5.11
16.89
18.55
26.10
29.80
50.10
63.71
118.63
120.80
127.31
127.77
128.13
128.97
136.36
140.59
143.42
TBSO
161
f1 (ppm)

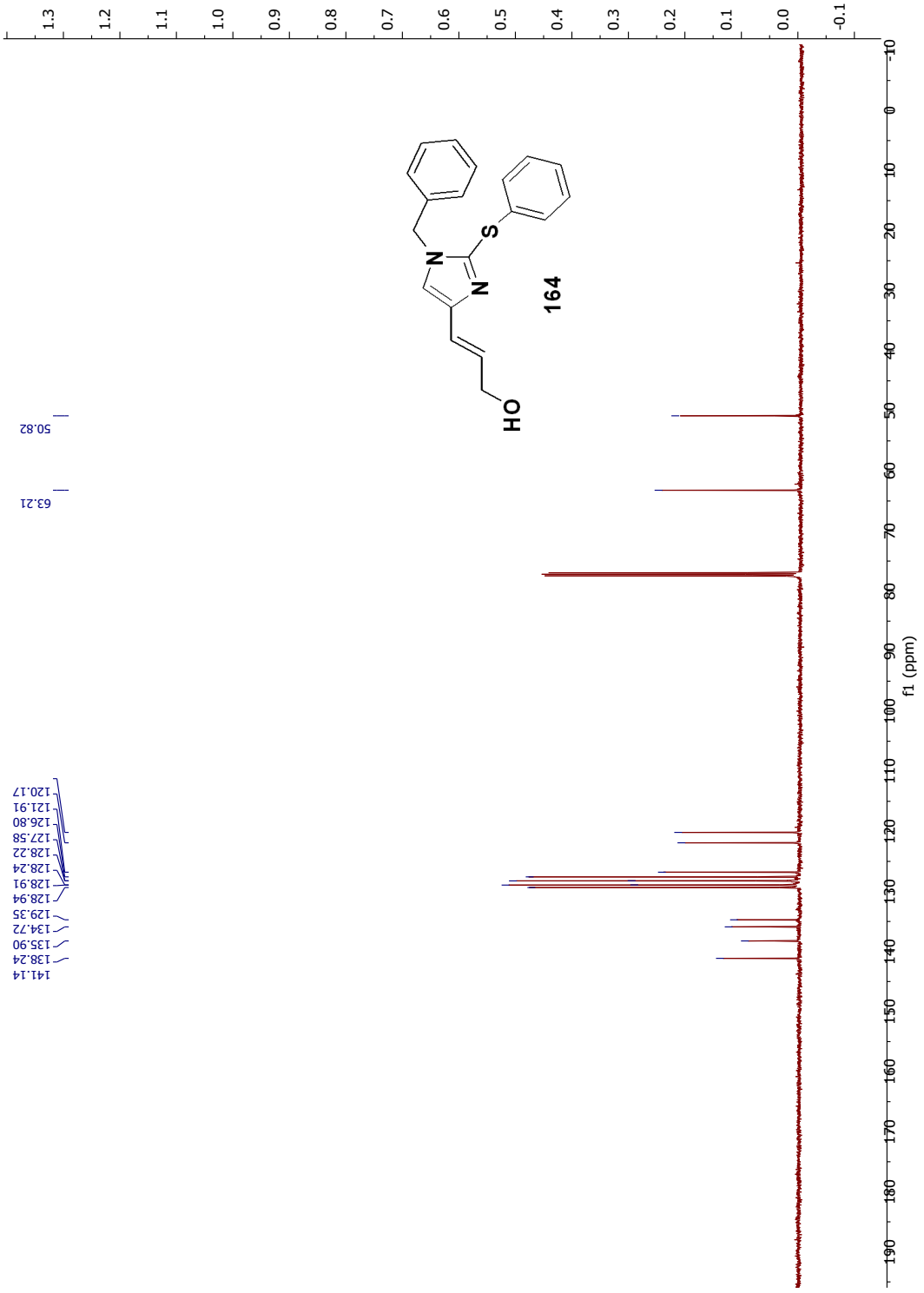

TBSO
N
N
I
162
f1 (ppm)

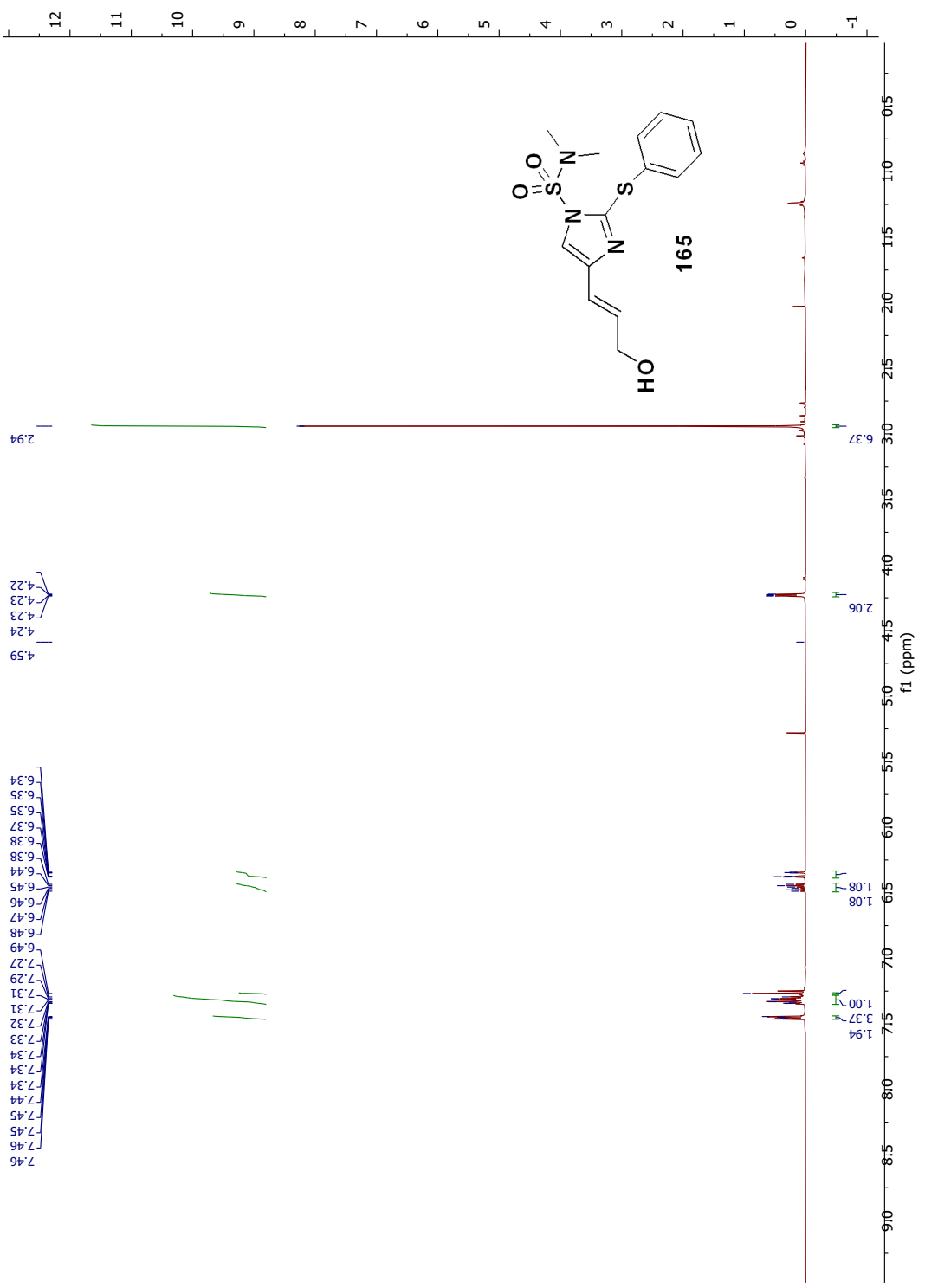

-5.22
-5.17
14.22
18.53
26.06
29.79
53.23
53.53
63.42
91.42
119.96
120.32
127.35
128.38
128.72
129.08
135.63
144.15
TBSO
N
N
I
162
f1 (ppm)

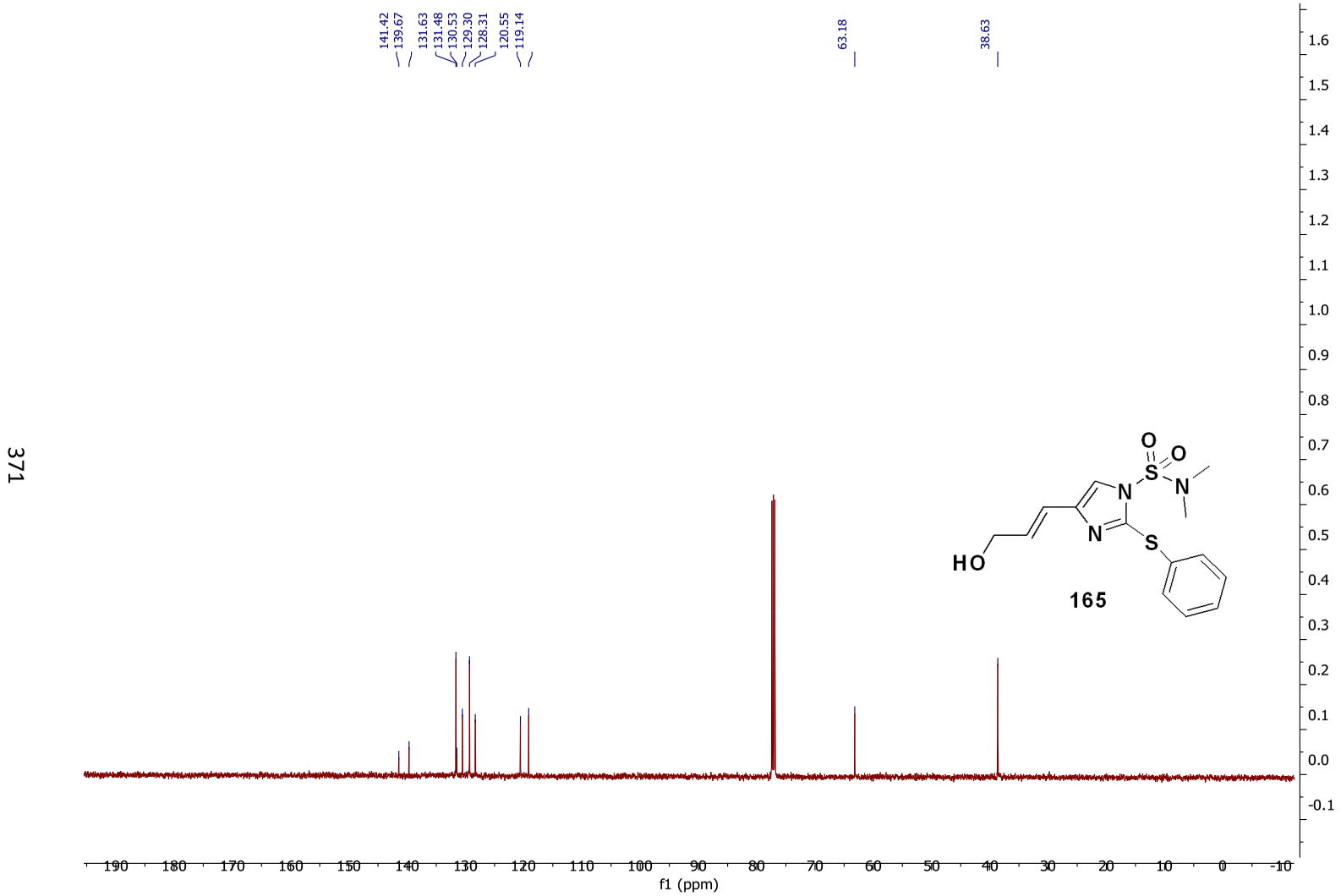
0.06
0.90
4.28
4.29
5.03
6.33
6.37
6.37
6.38
6.39
6.39
6.75
7.14
7.14
7.15
7.16
7.31
7.32
7.33
7.34
7.36
TBSO
N
N
Cl
163
f1 (ppm)

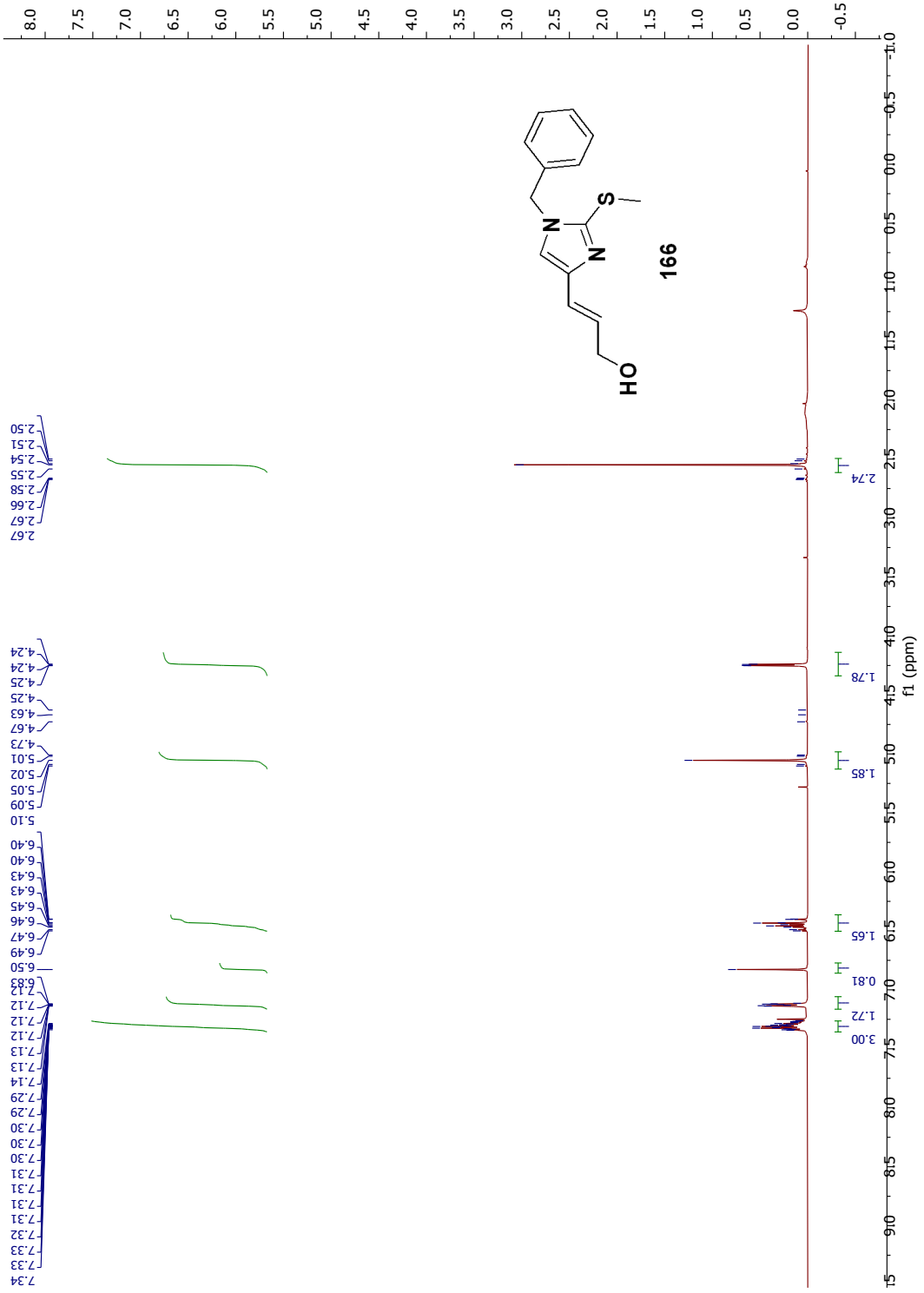

-5.16
18.52
26.06
50.30
63.43
117.96
119.95
127.30
127.39
128.29
128.44
128.64
129.06
129.12
132.52
135.39
139.53
Cl
N
N
TBSO
163
f1 (ppm)

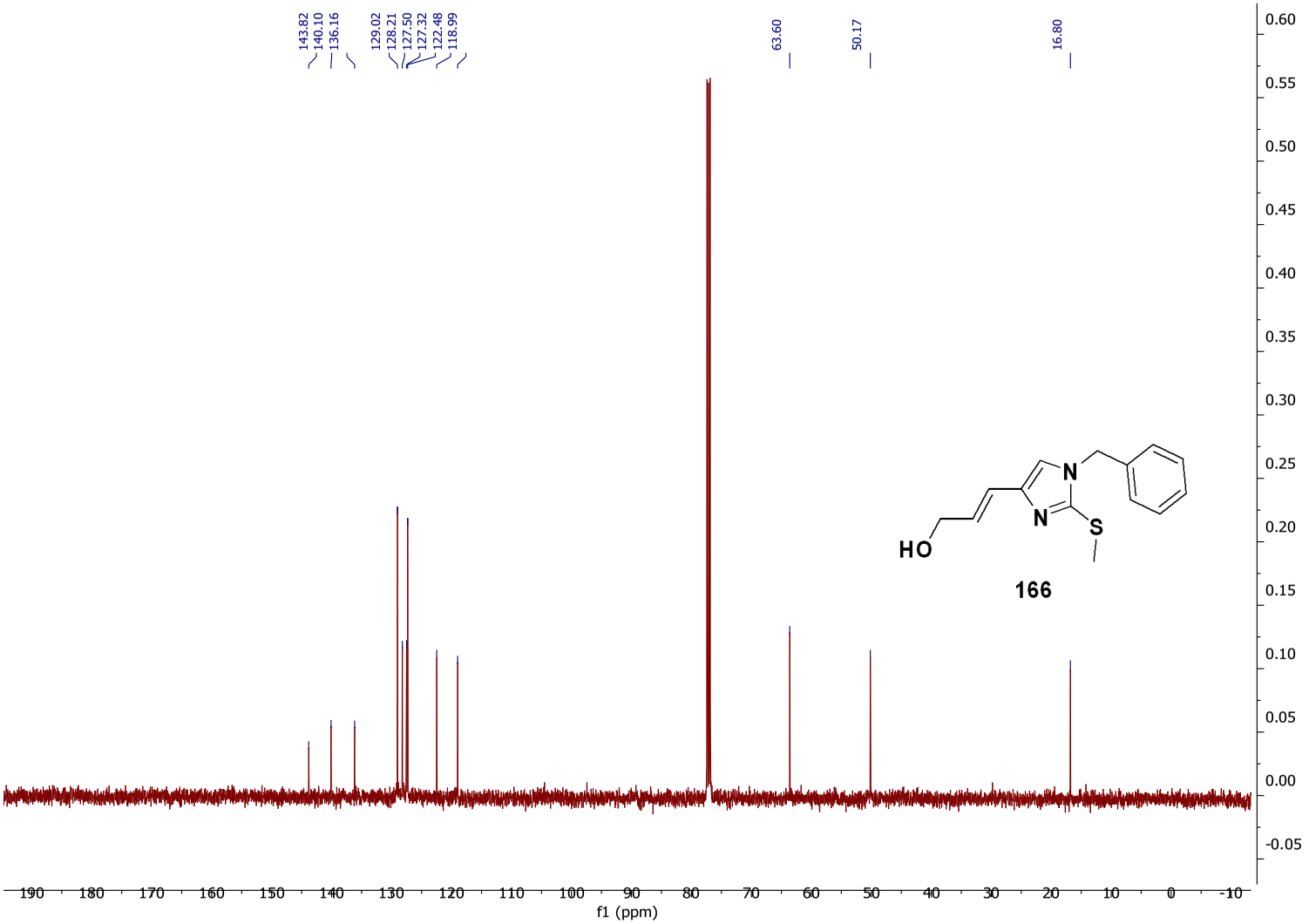

164
HO
N
N
S
f1 (ppm)
7.24
7.23
7.23
7.21
7.19
7.17
7.13
7.13
7.11
6.99
6.99
6.98
6.98
6.92
6.54
6.53
6.51
6.50
6.49
6.46
6.43
5.08
4.24
4.23
3.08
2.05
3.20
2.08
1.00
2.13
2.26
2.14

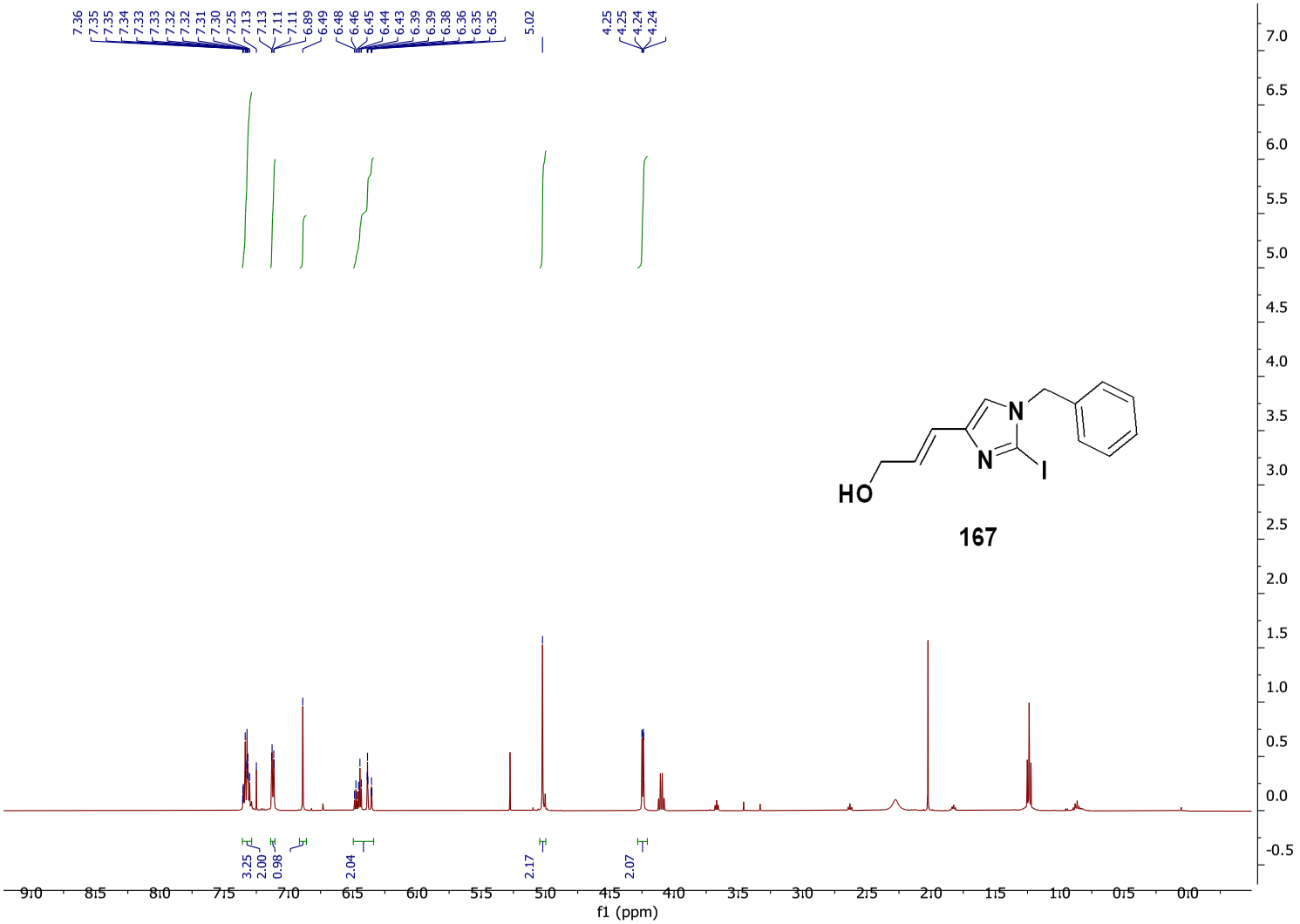

164
HO
N
N
S
50.82
63.21
120.17
121.91
126.80
127.58
128.22
128.24
128.91
128.94
129.35
134.72
135.90
138.24
141.14
f1 (ppm)


165
HO
f1 (ppm)

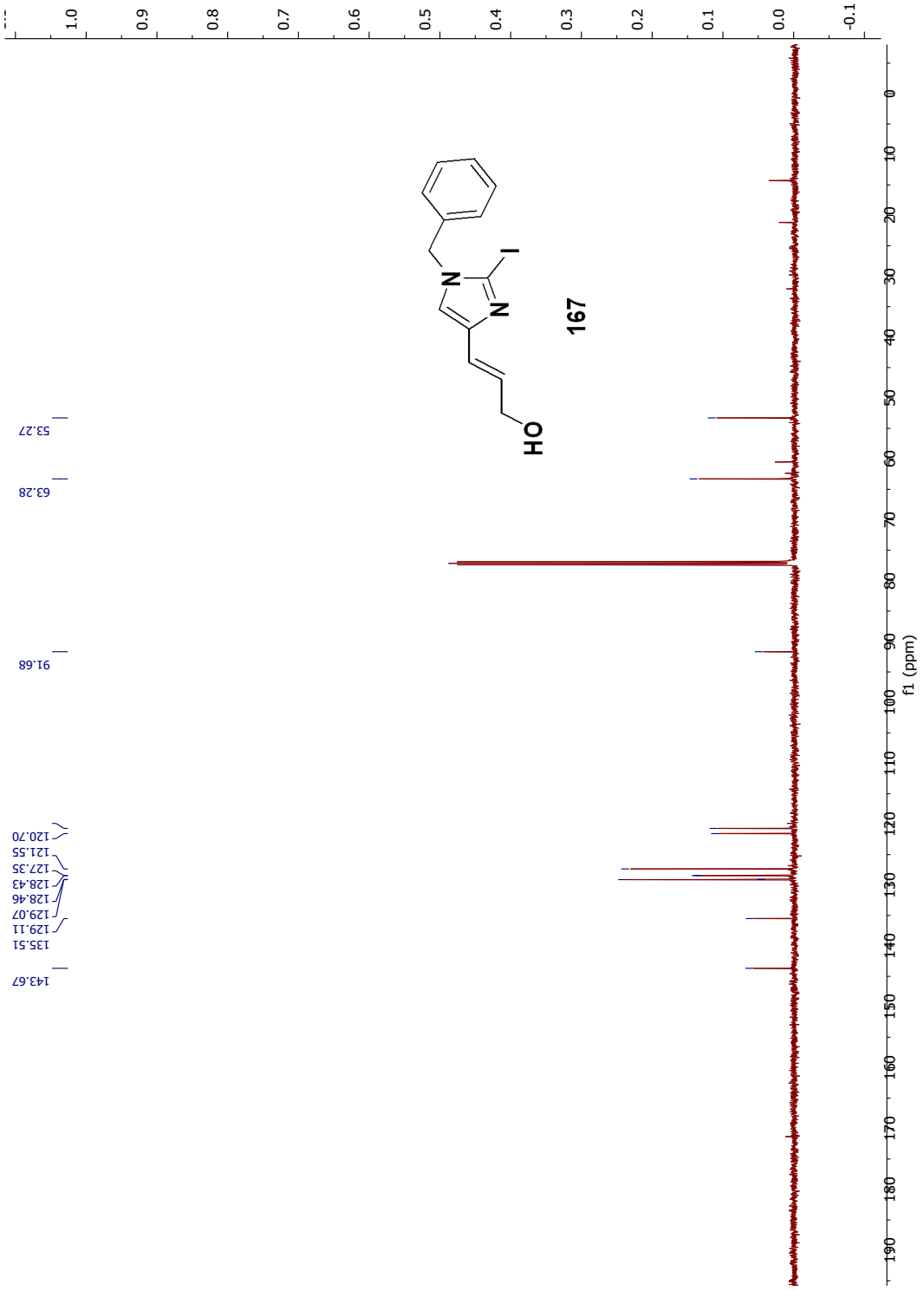

141.42
139.67
131.63
131.48
130.53
129.30
128.31
120.55
119.14
63.18
38.63
HO
O
O
S
N
N
N
S
165
f1 (ppm)

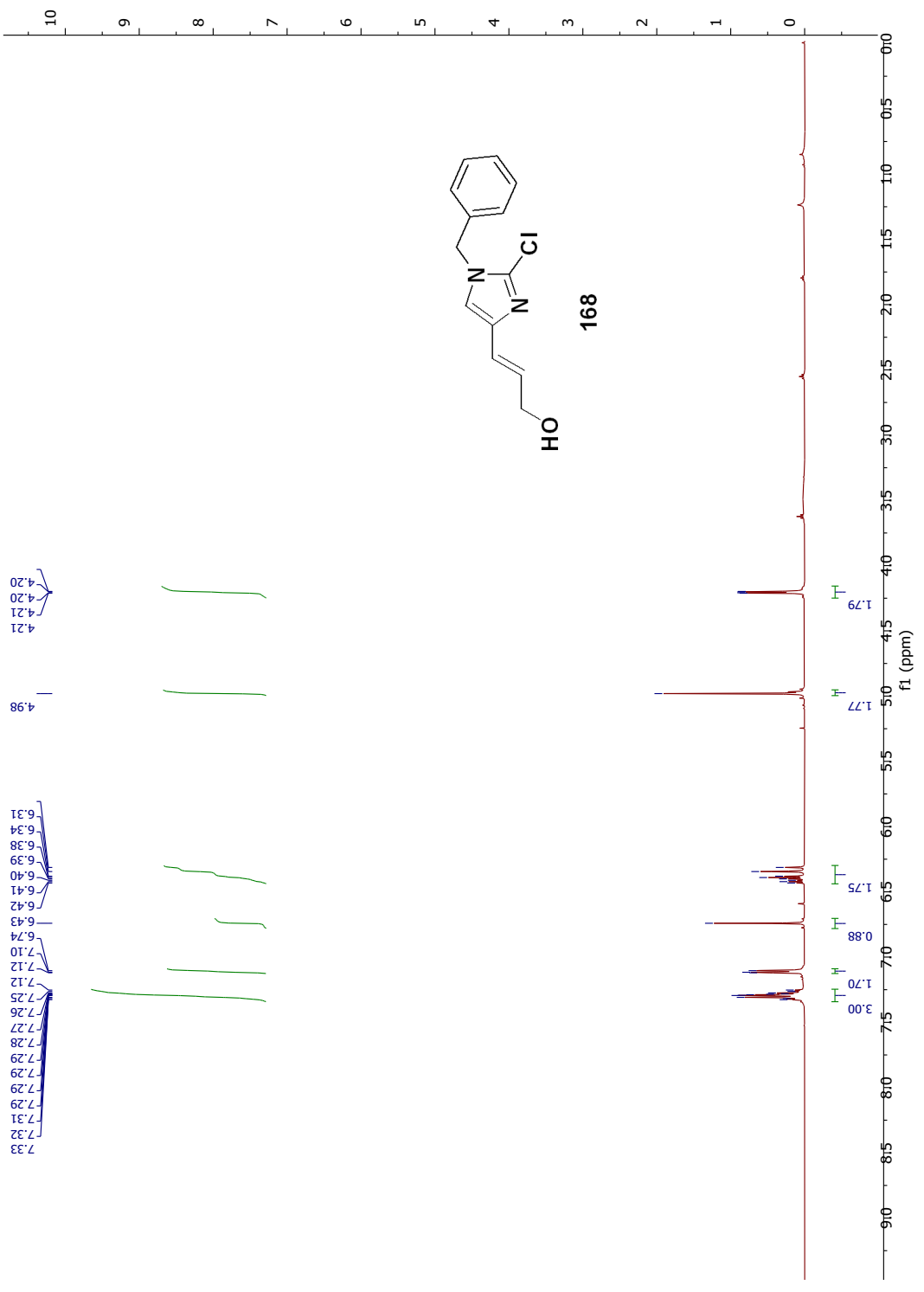

166
HO
N
N
S
f1 (ppm)

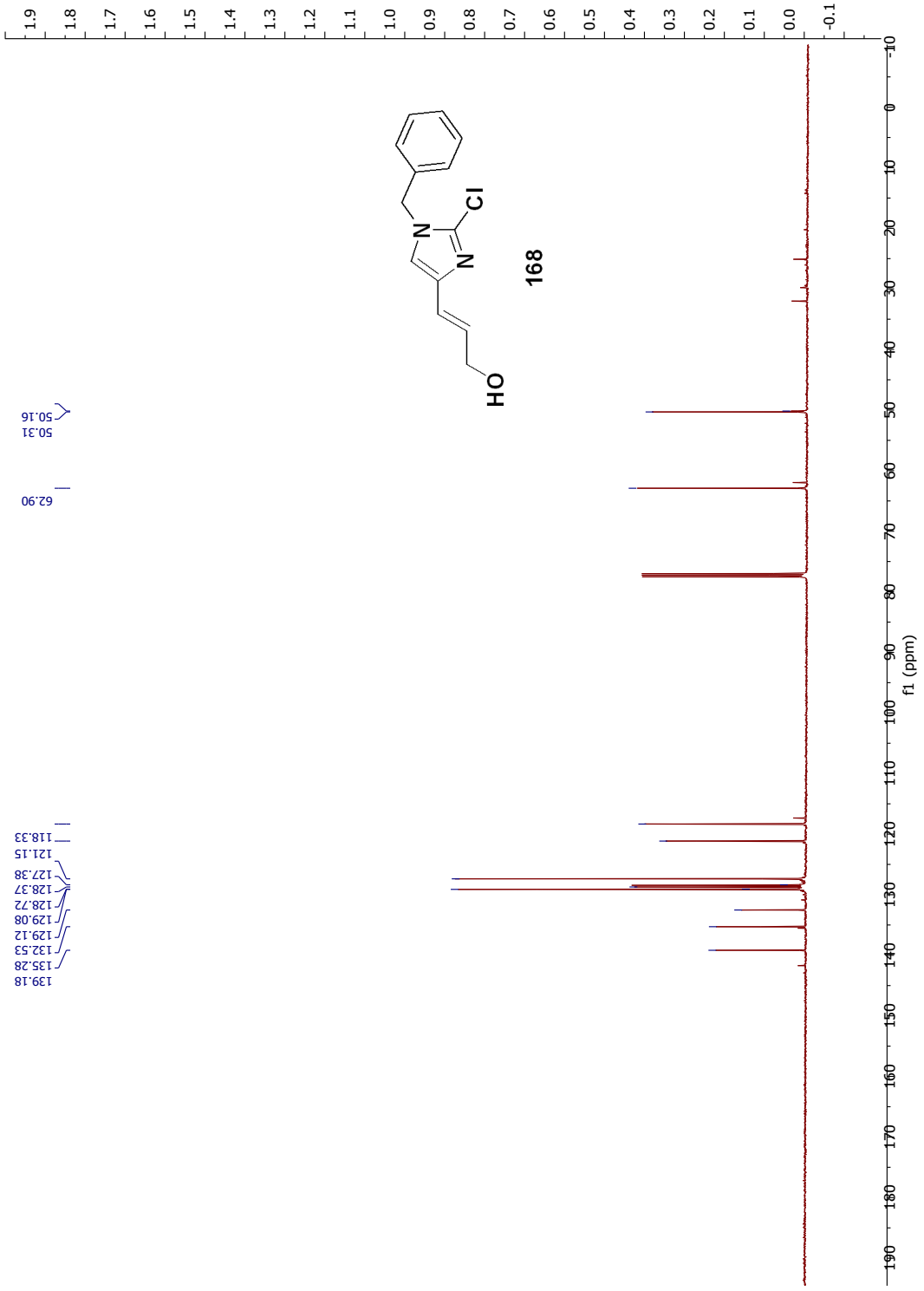

143.82
140.10
136.16
129.02
128.21
127.50
127.32
122.48
118.99
63.60
50.17
16.80
HO
N
N
S
166
f1 (ppm)

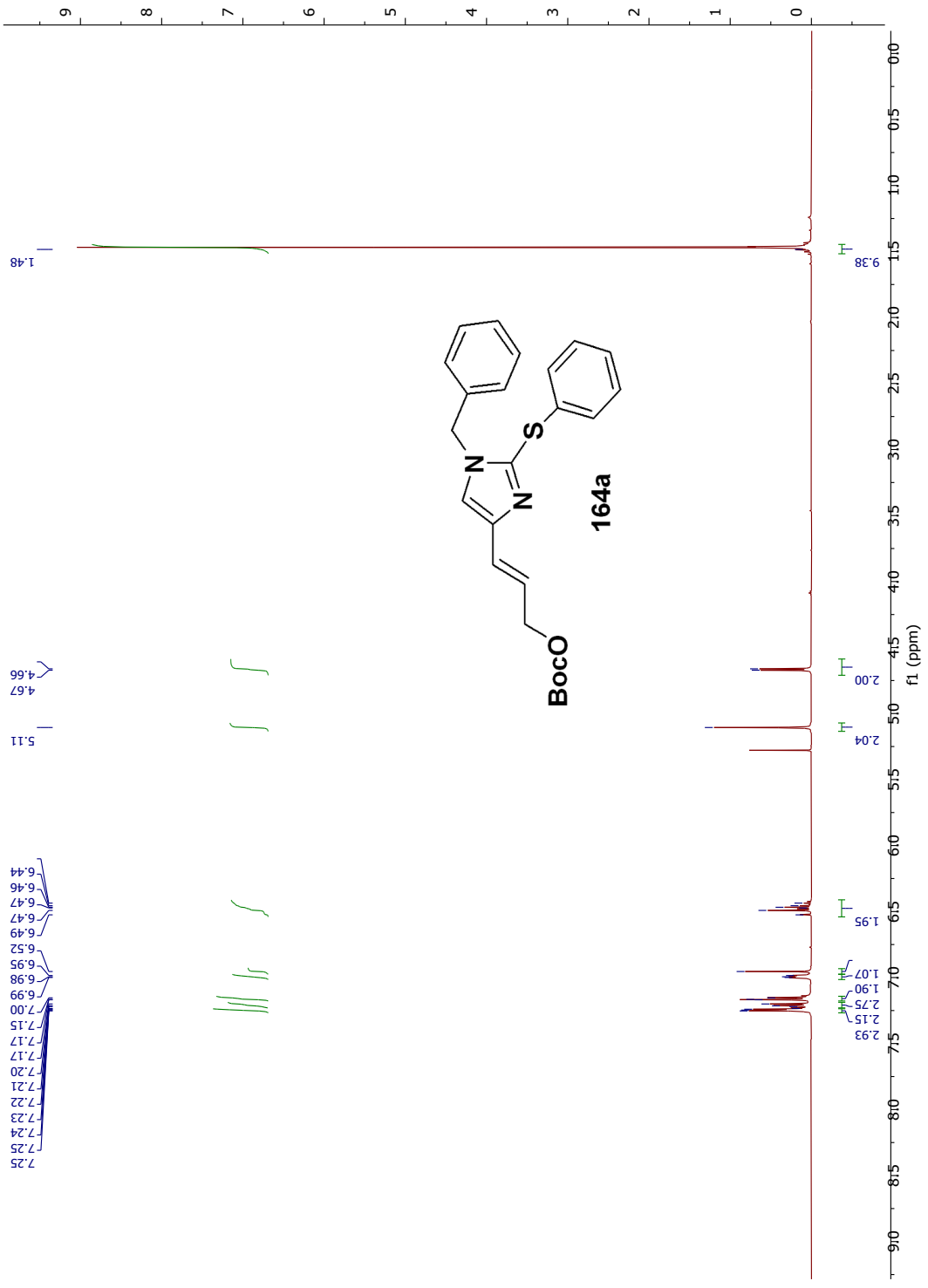

7.36
7.35
7.35
7.34
7.33
7.33
7.32
7.32
7.31
7.30
7.25
7.13
7.11
7.11
6.89
6.49
6.48
6.46
6.45
6.44
6.43
6.39
6.39
6.38
6.36
6.35
6.35
5.02
4.25
4.25
4.24
4.24
N
N
I
HO
3.25
2.00
0.98
2.04
2.17
2.07
f1 (ppm)

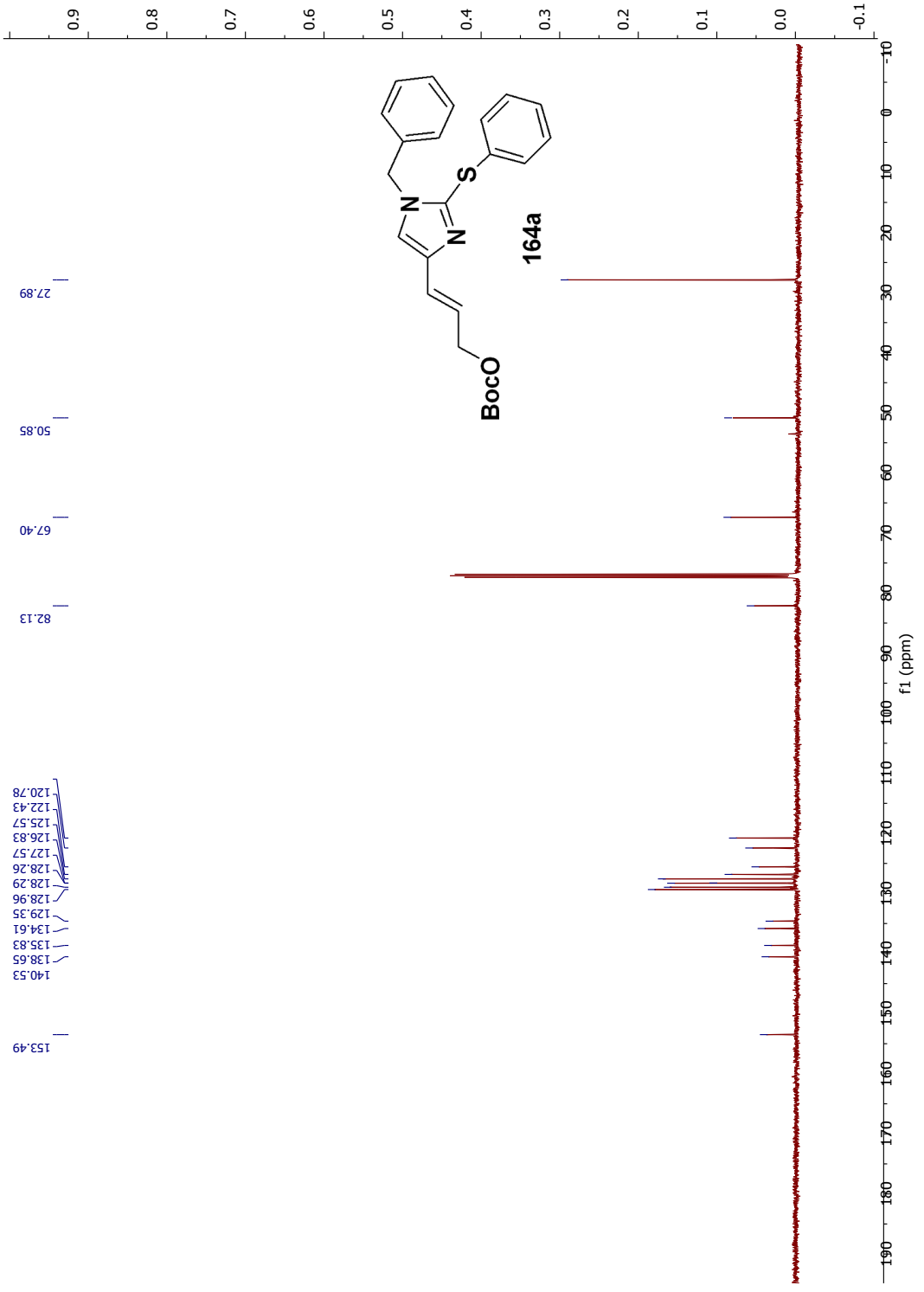
167

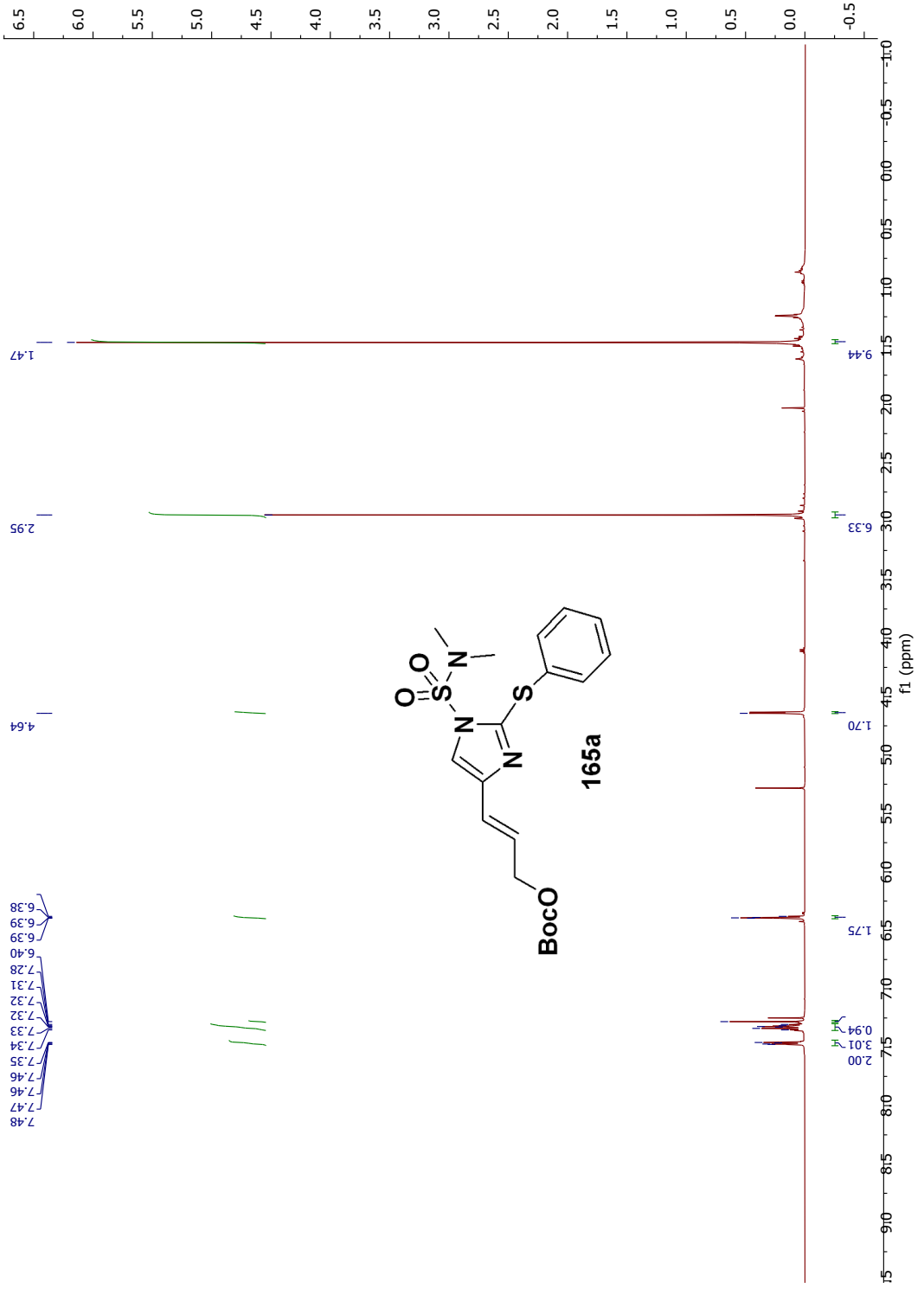

167
HO
I
N
N
53.27
63.28
91.68
120.70
121.55
127.35
128.43
128.46
129.07
129.11
135.51
143.67
f1 (ppm)

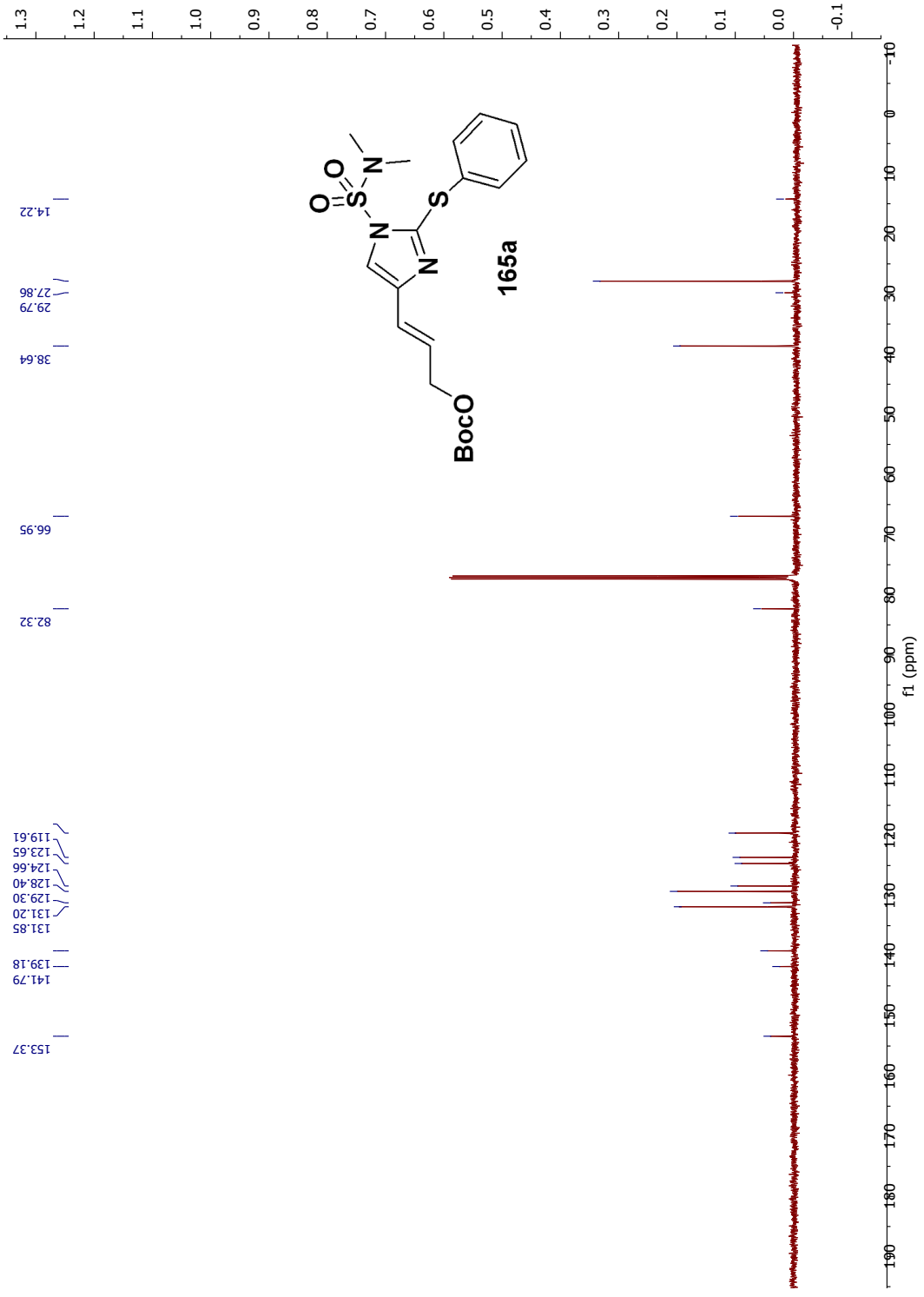

168
Cl
N
N
HO
f1 (ppm)
1.79
1.77
1.75
0.88
1.70
3.00
4.21
4.20
4.98
7.33
7.32
7.31
7.29
7.29
7.29
7.29
7.28
7.27
7.26
7.25
7.12
7.12
7.10
6.74
6.43
6.42
6.41
6.40
6.39
6.38
6.34
6.31

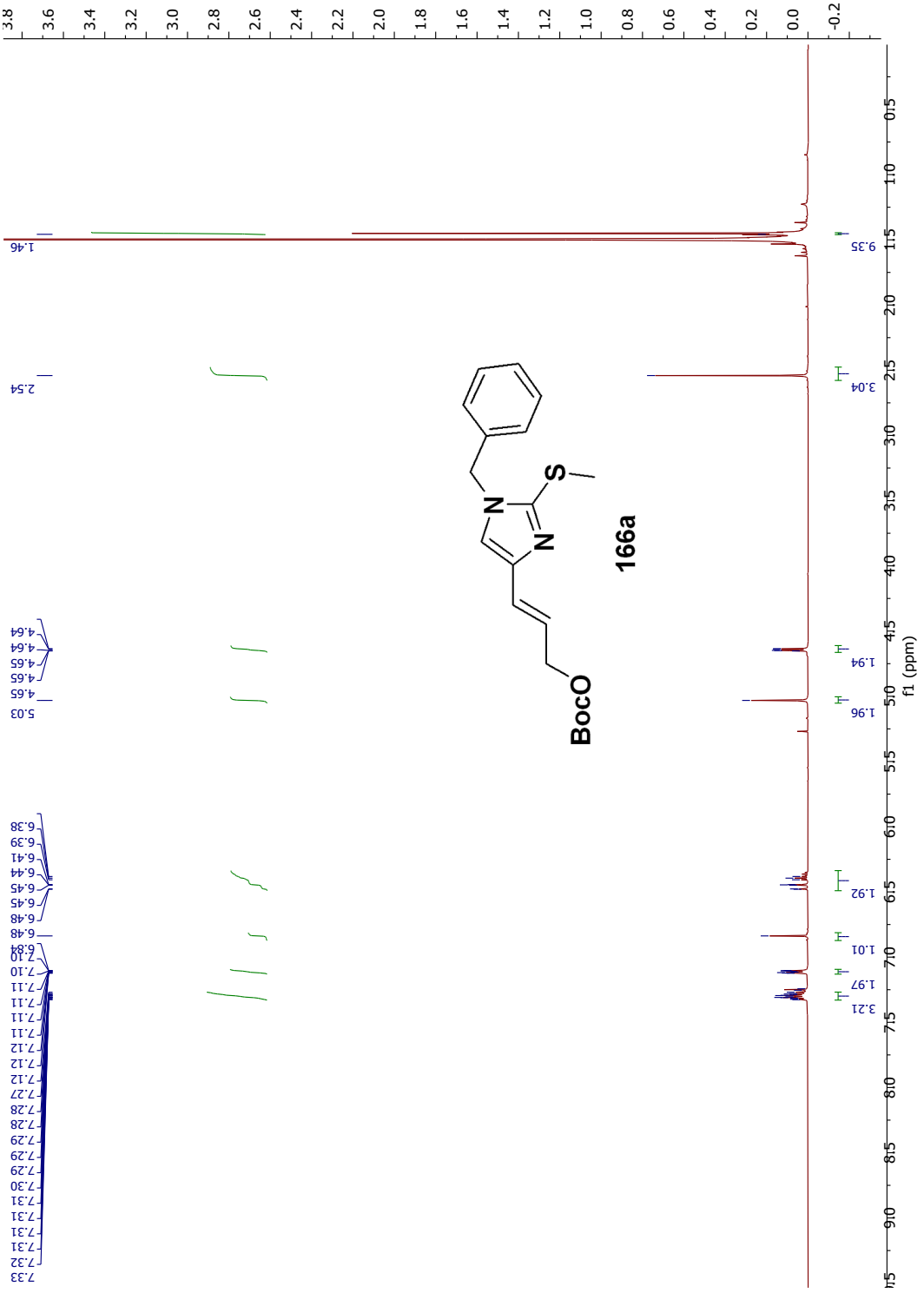

168
Cl
N
N
HO
50.31
50.16
62.90
139.18
135.28
132.53
129.12
129.08
128.72
128.37
127.38
121.15
118.33
f1 (ppm)

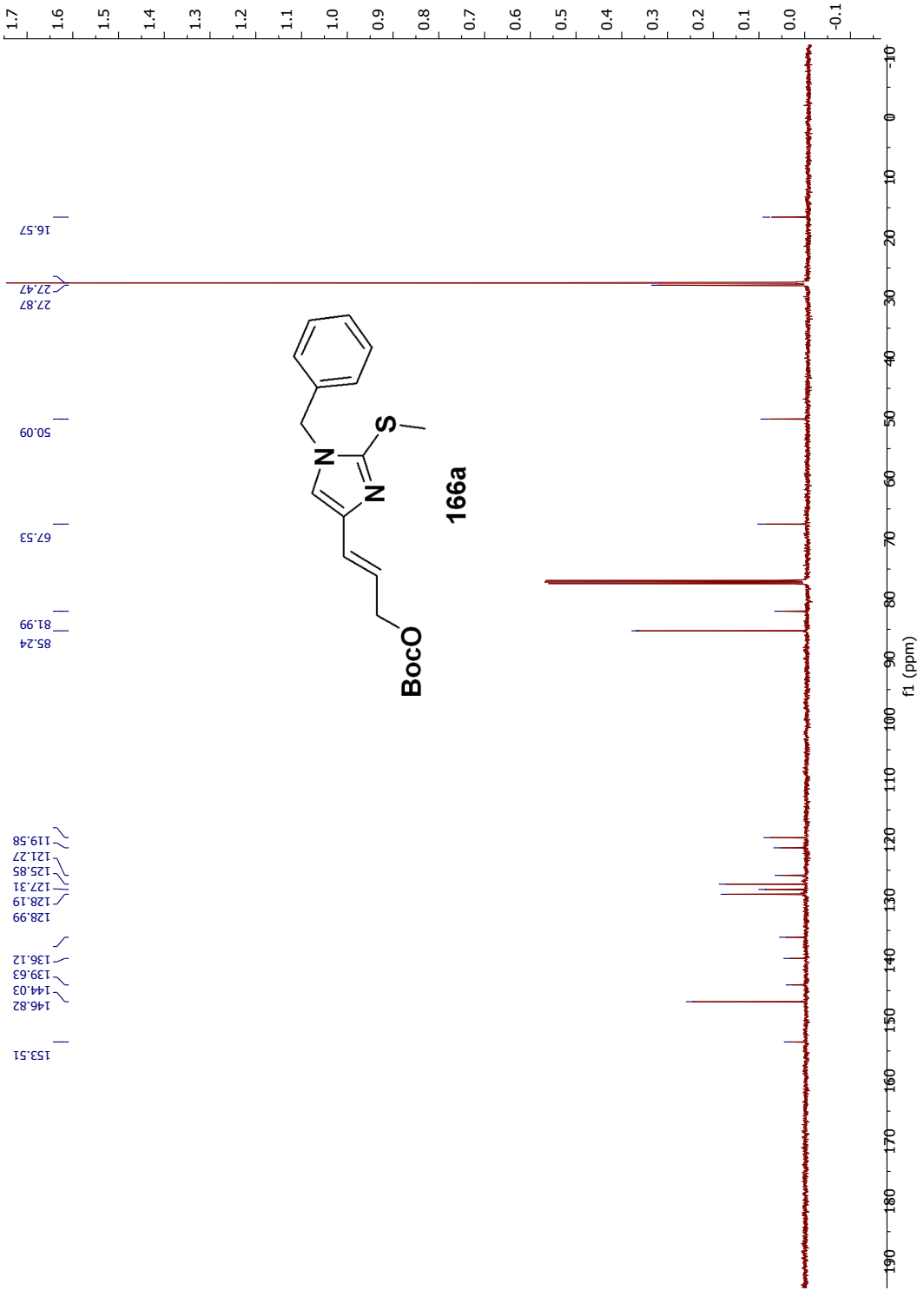

164a
BocO
N
N
S
f1 (ppm)

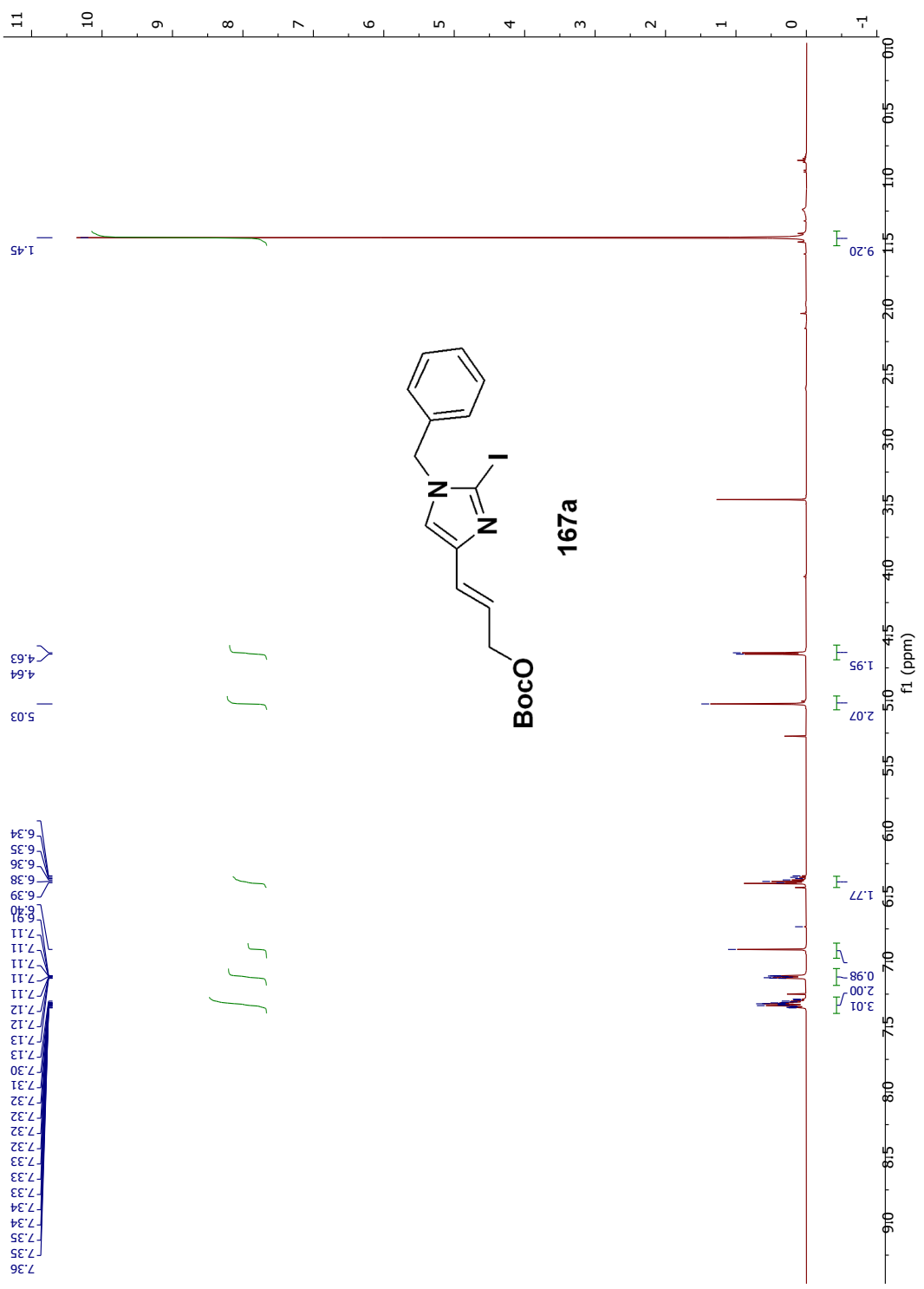

164a
BocO
N
N
S
f1 (ppm)
153.49
140.53
138.65
135.83
134.61
129.35
128.96
128.29
128.26
127.57
126.83
125.57
122.43
120.78
82.13
67.40
50.85
27.89

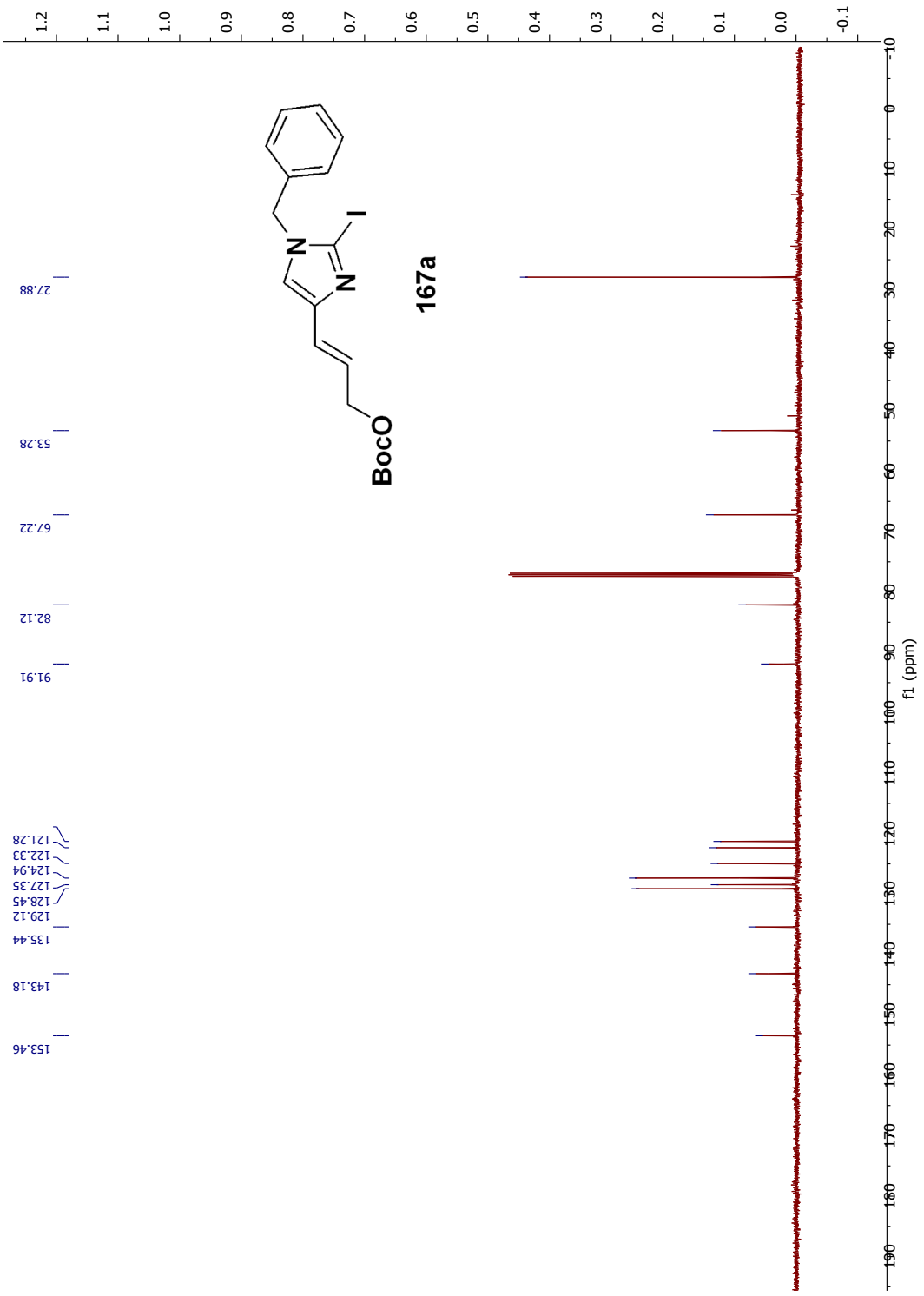

165a
BocO
f1 (ppm)

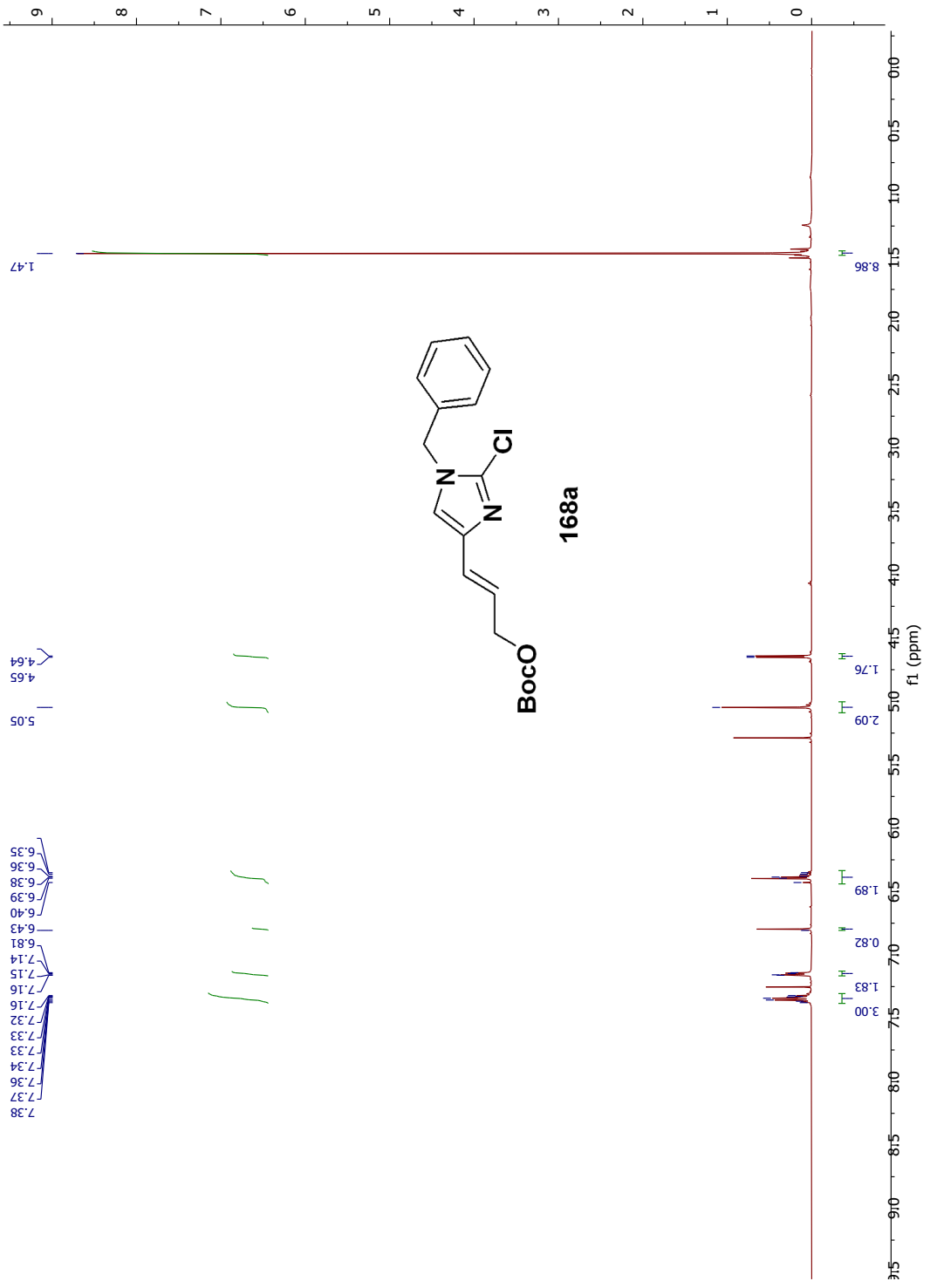

153.37
141.79
139.18
131.85
131.20
129.30
128.40
124.66
123.65
119.61
82.32
66.95
38.64
29.79
27.86
14.22
BocO
165a
f1 (ppm)

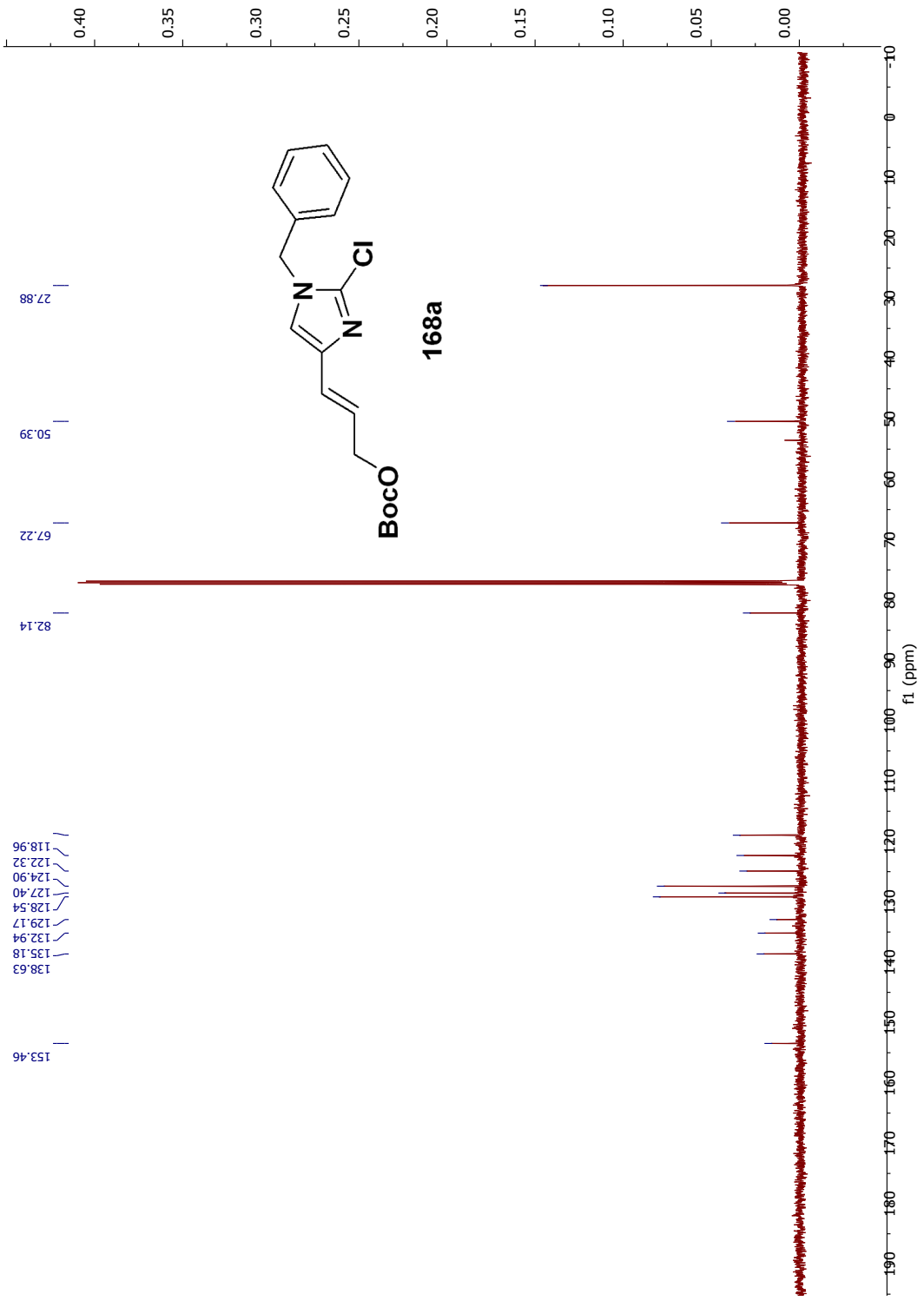

BocO
166a
f1 (ppm)

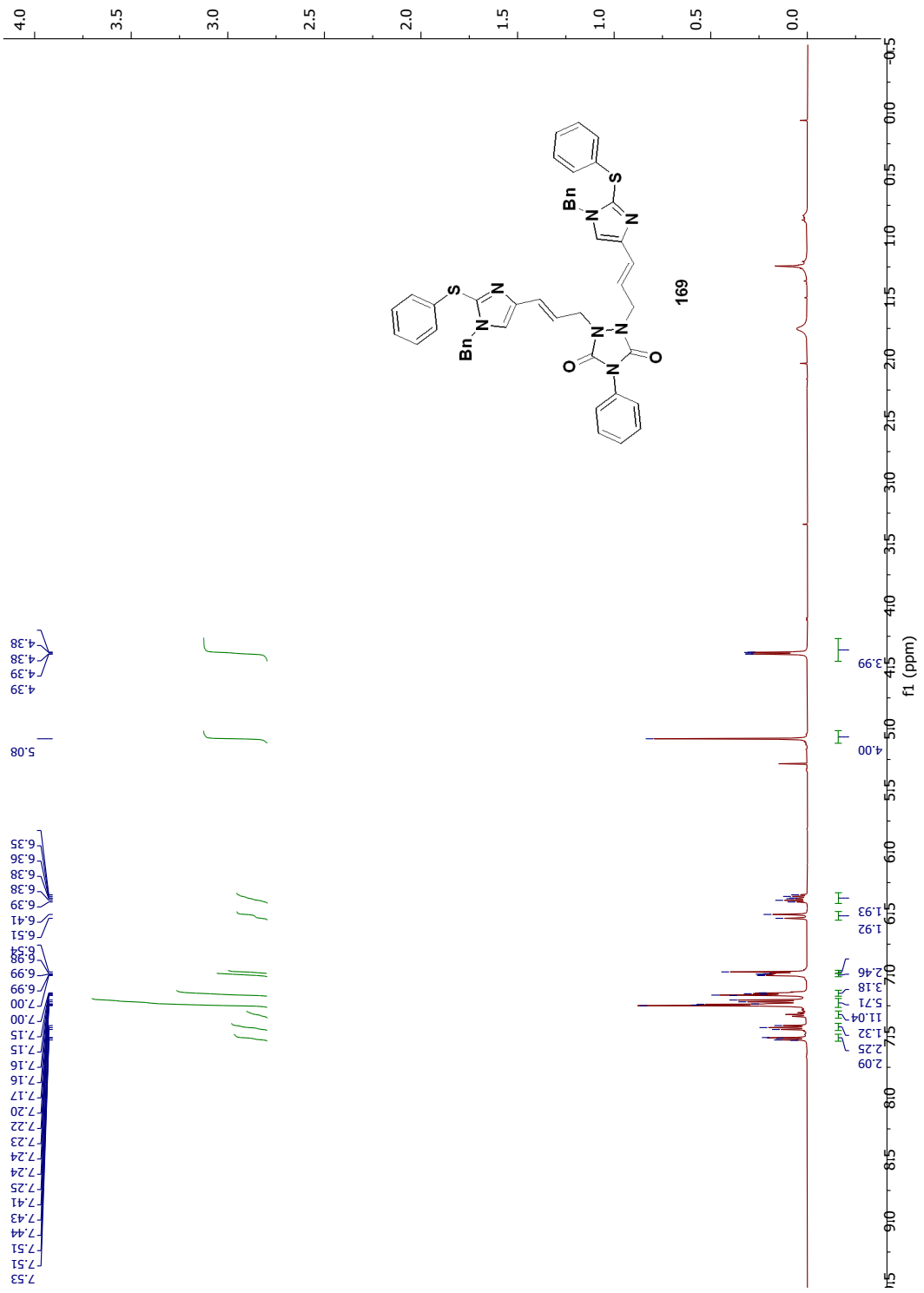

16.57
27.87
27.47
50.09
67.53
81.99
85.24
119.58
121.27
125.85
127.31
128.19
128.99
136.12
139.63
144.03
146.82
153.51
BocO
N
N
S
166a
f1 (ppm)

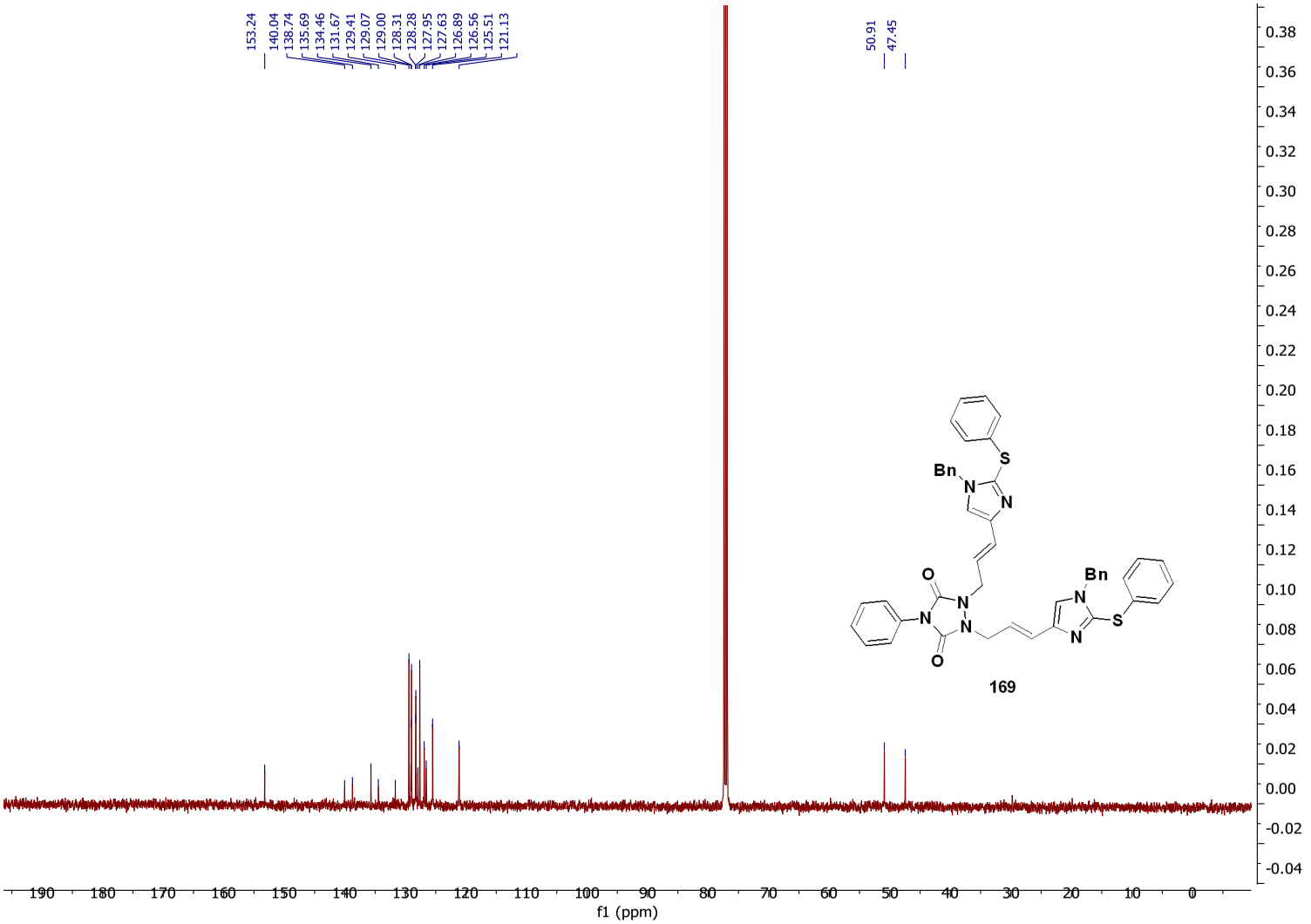

BocO
N
N
I
167a
f1 (ppm)


167a
BocO
N
N
I
153.46
143.18
135.44
129.12
128.45
127.35
124.94
122.33
121.28
91.91
82.12
67.22
53.28
27.88
f1 (ppm)

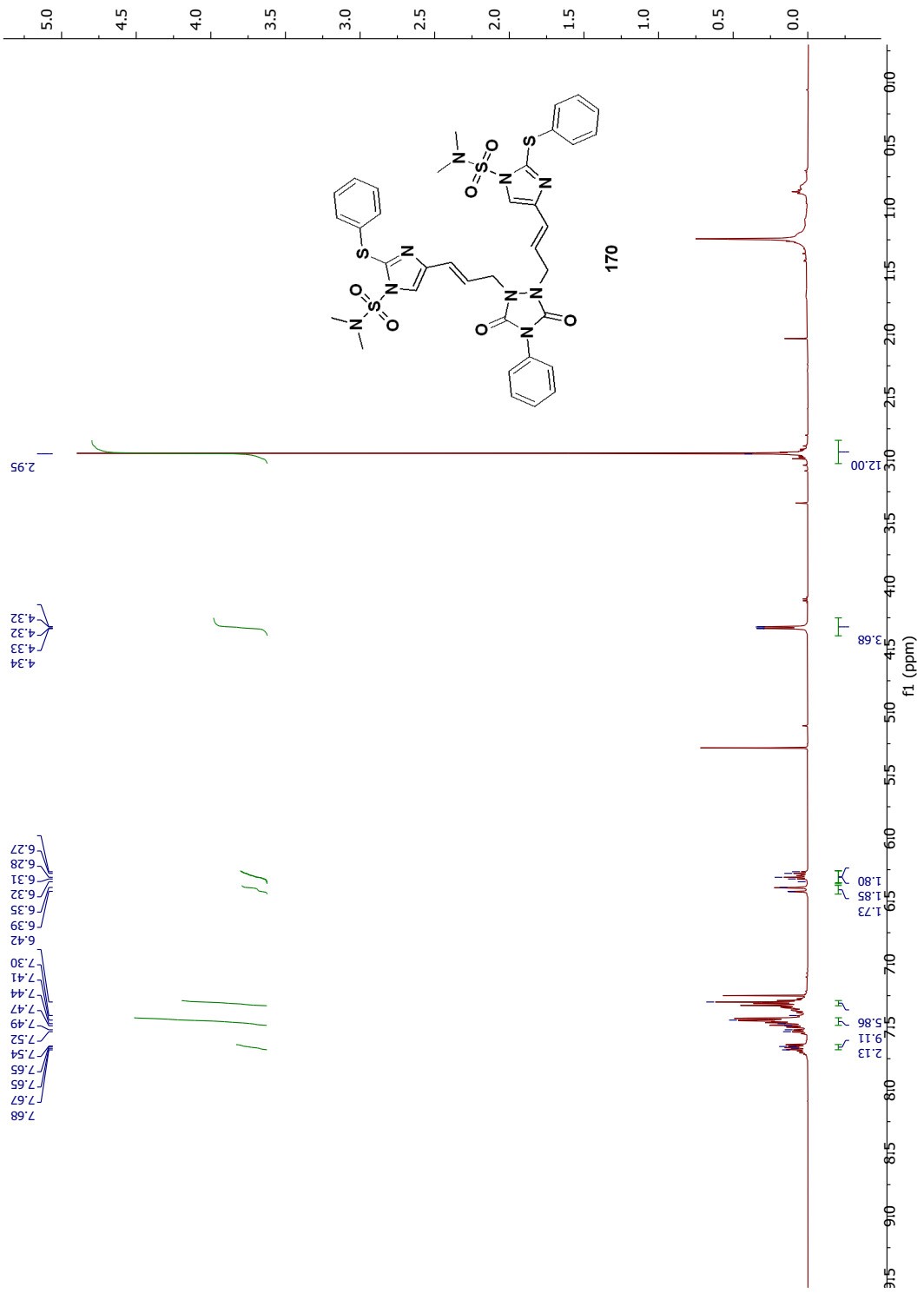

Cl
N
N
BocO
168a
f1 (ppm)

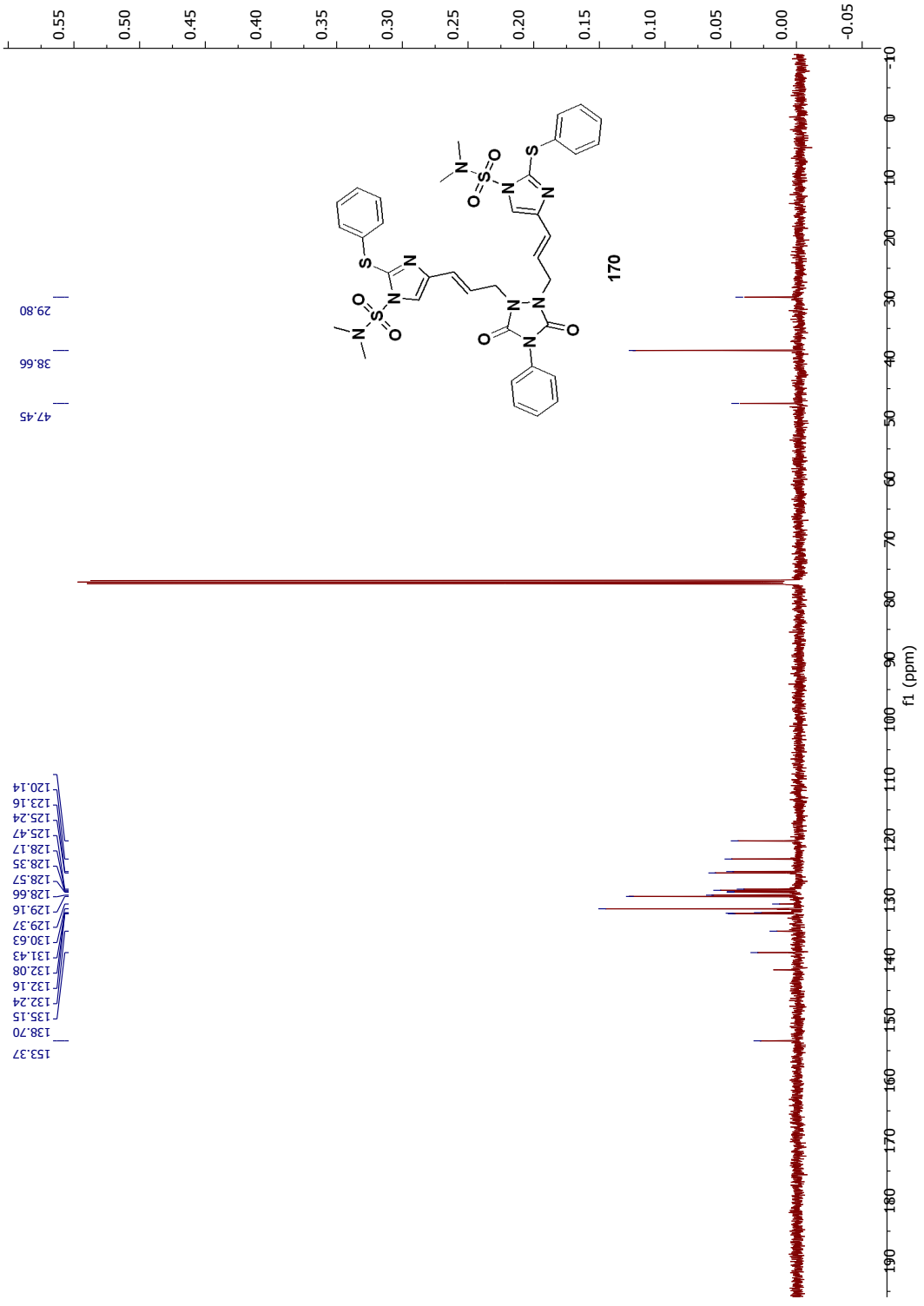

168a
Cl
N
N
BocO
27.88
50.39
67.22
82.14
118.96
122.32
124.90
127.40
128.54
129.17
132.94
135.18
138.63
153.46
f1 (ppm)

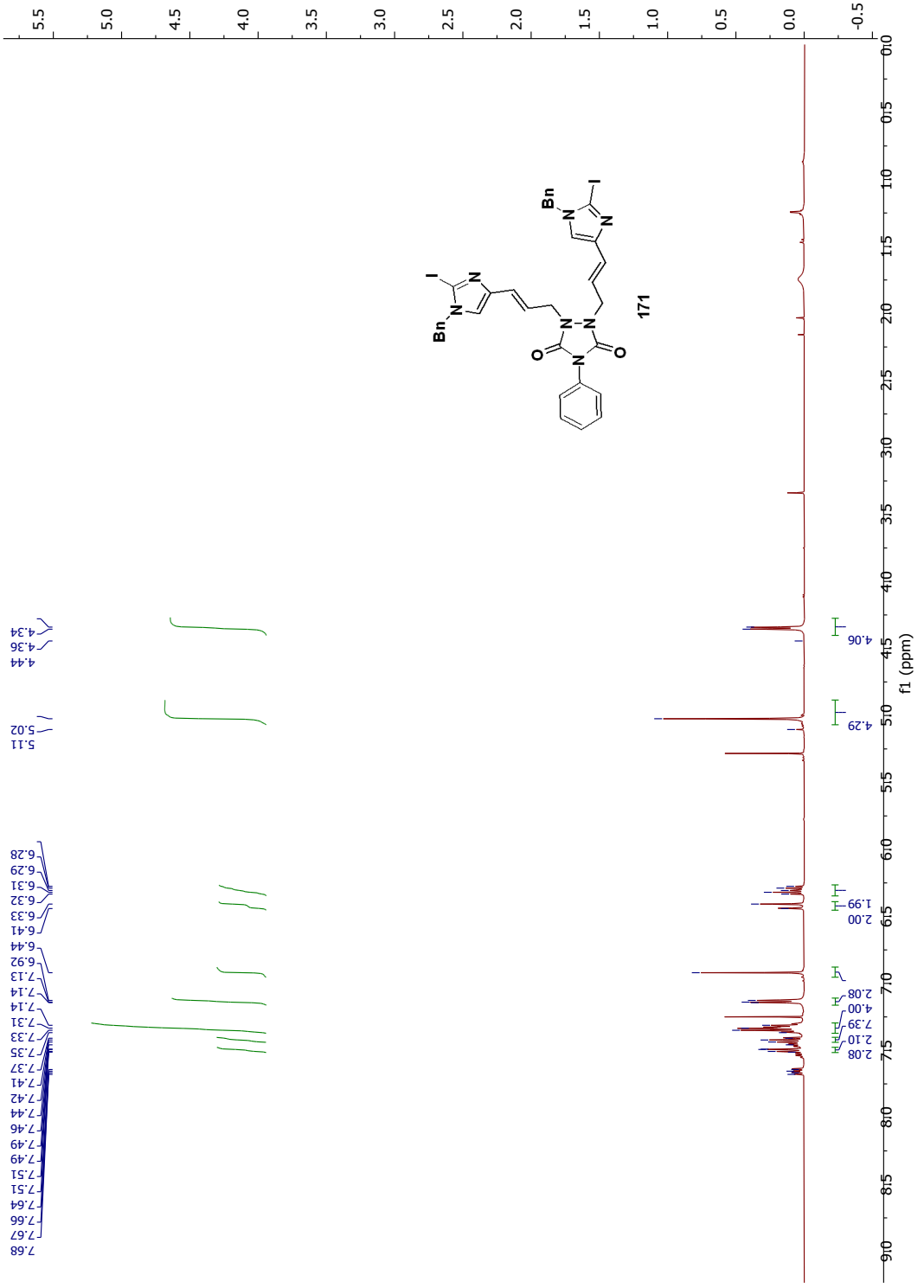

169
Bn
S
N
O
f1 (ppm)

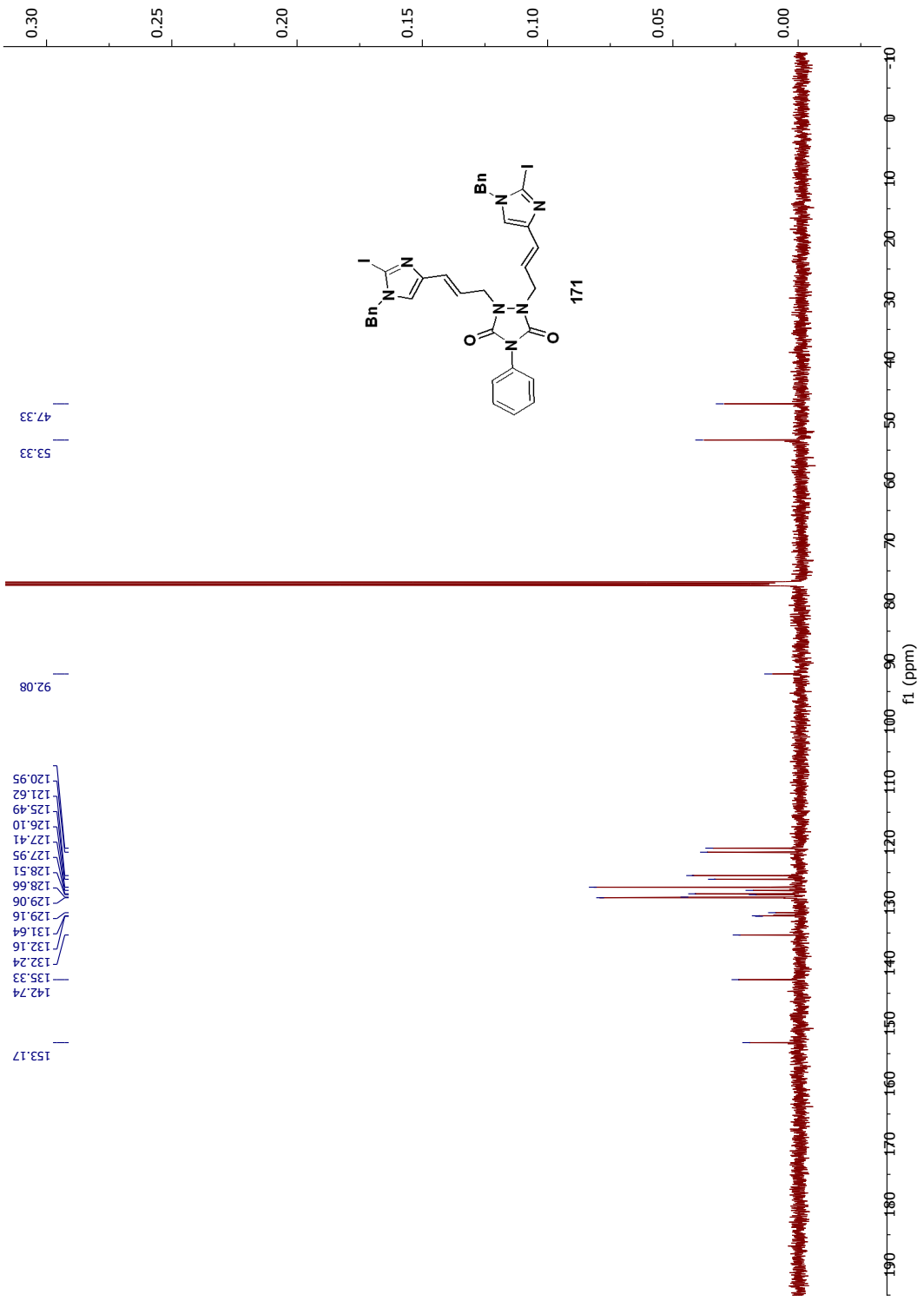

153.24
140.04
138.74
135.69
134.46
131.67
129.41
129.07
129.00
128.31
128.28
127.95
127.63
126.89
126.56
125.51
121.13
50.91
47.45
f1 (ppm)

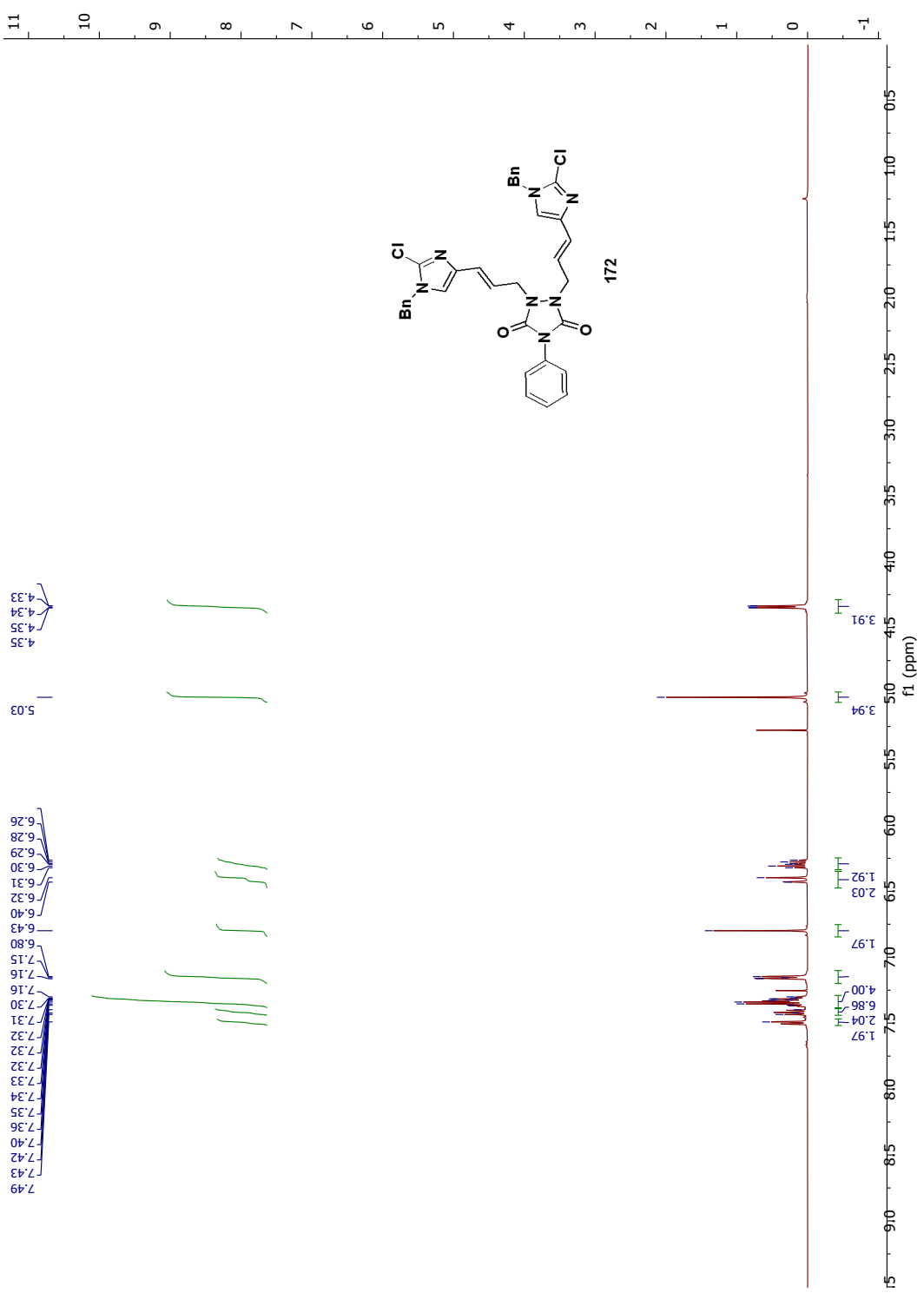
169

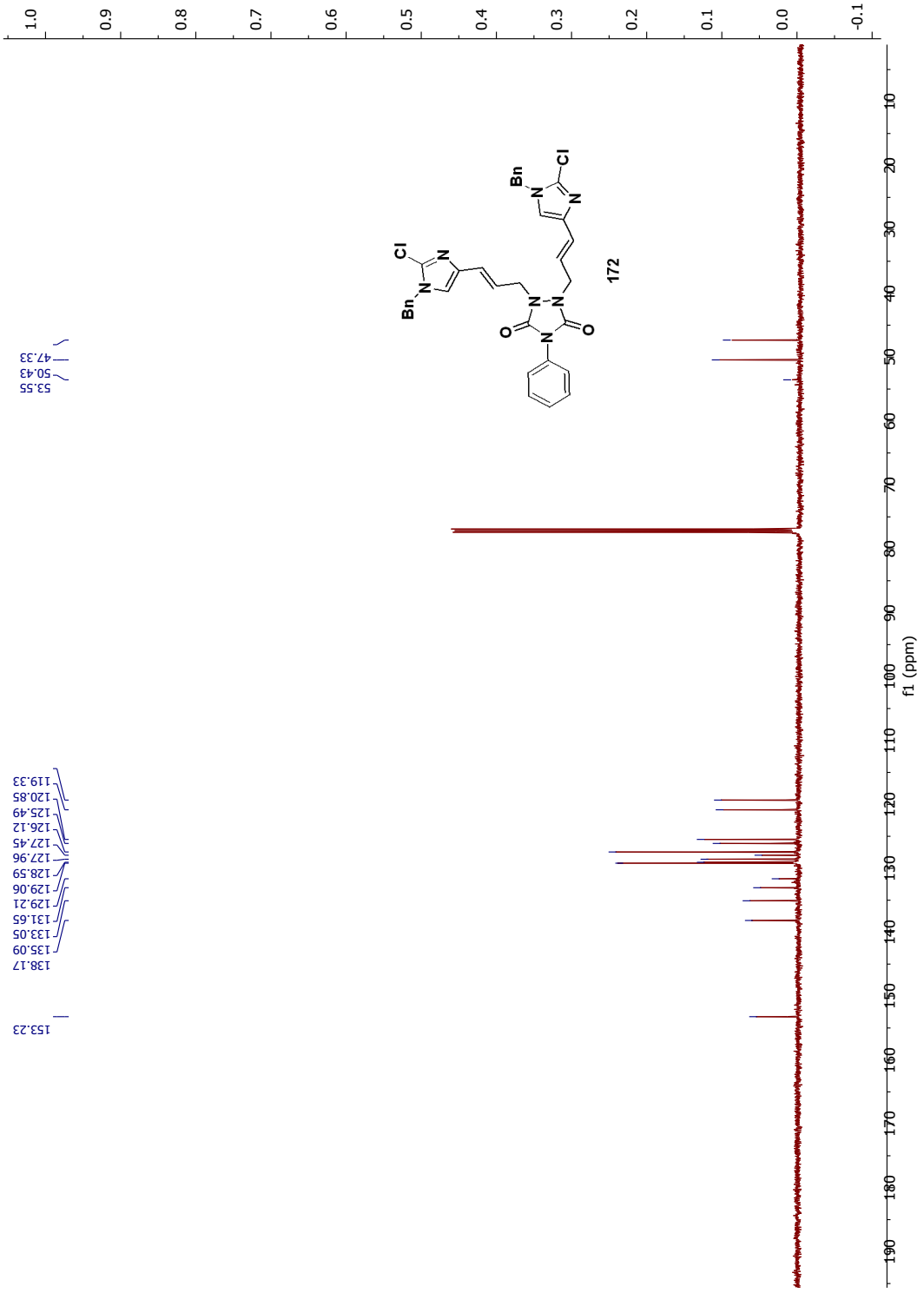

170
f1 (ppm)

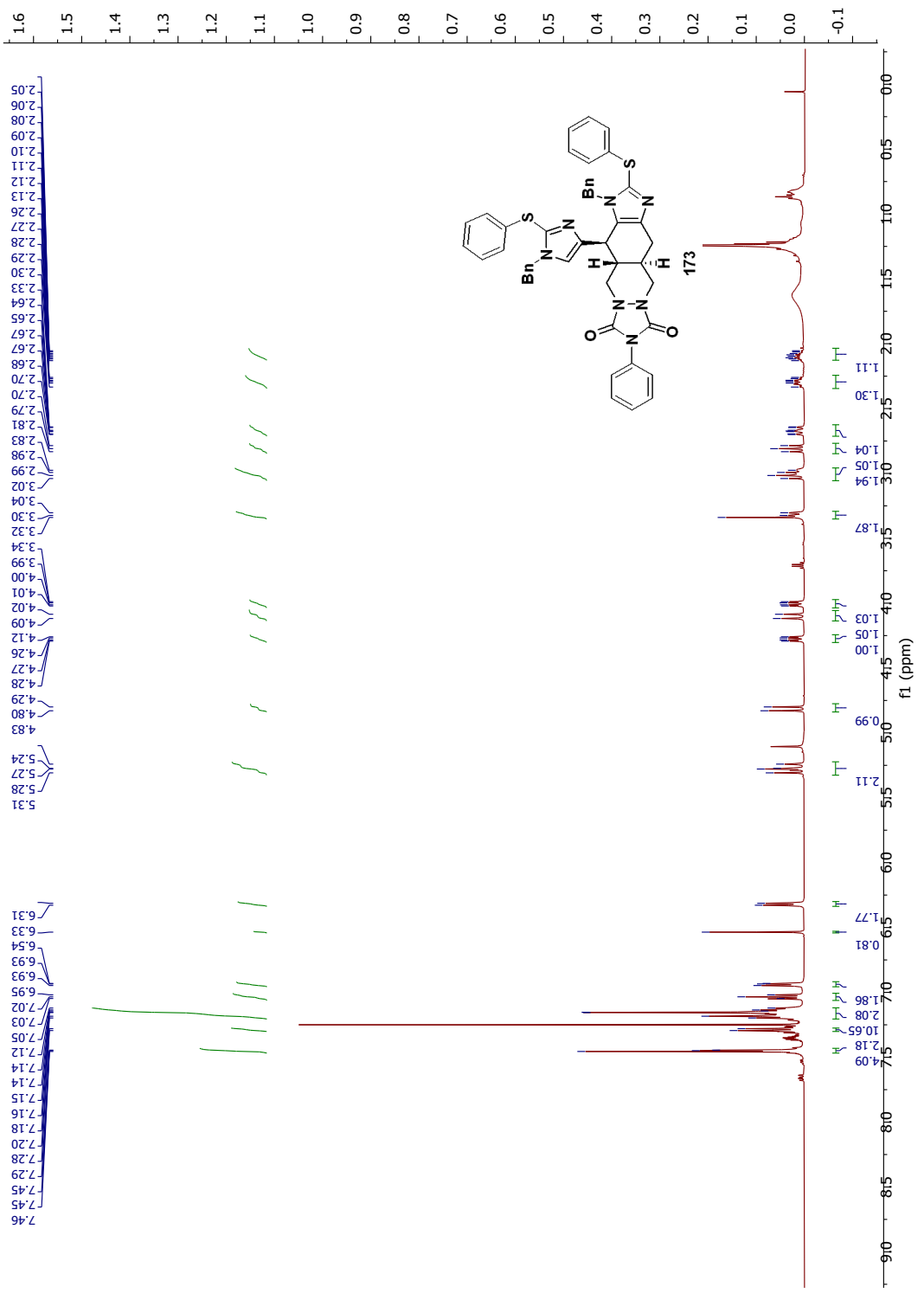

170
153.37
138.70
135.15
132.24
132.16
132.08
131.43
130.63
129.37
129.16
128.66
128.57
128.35
128.17
125.47
125.24
123.16
120.14
47.45
38.66
29.80
f1 (ppm)

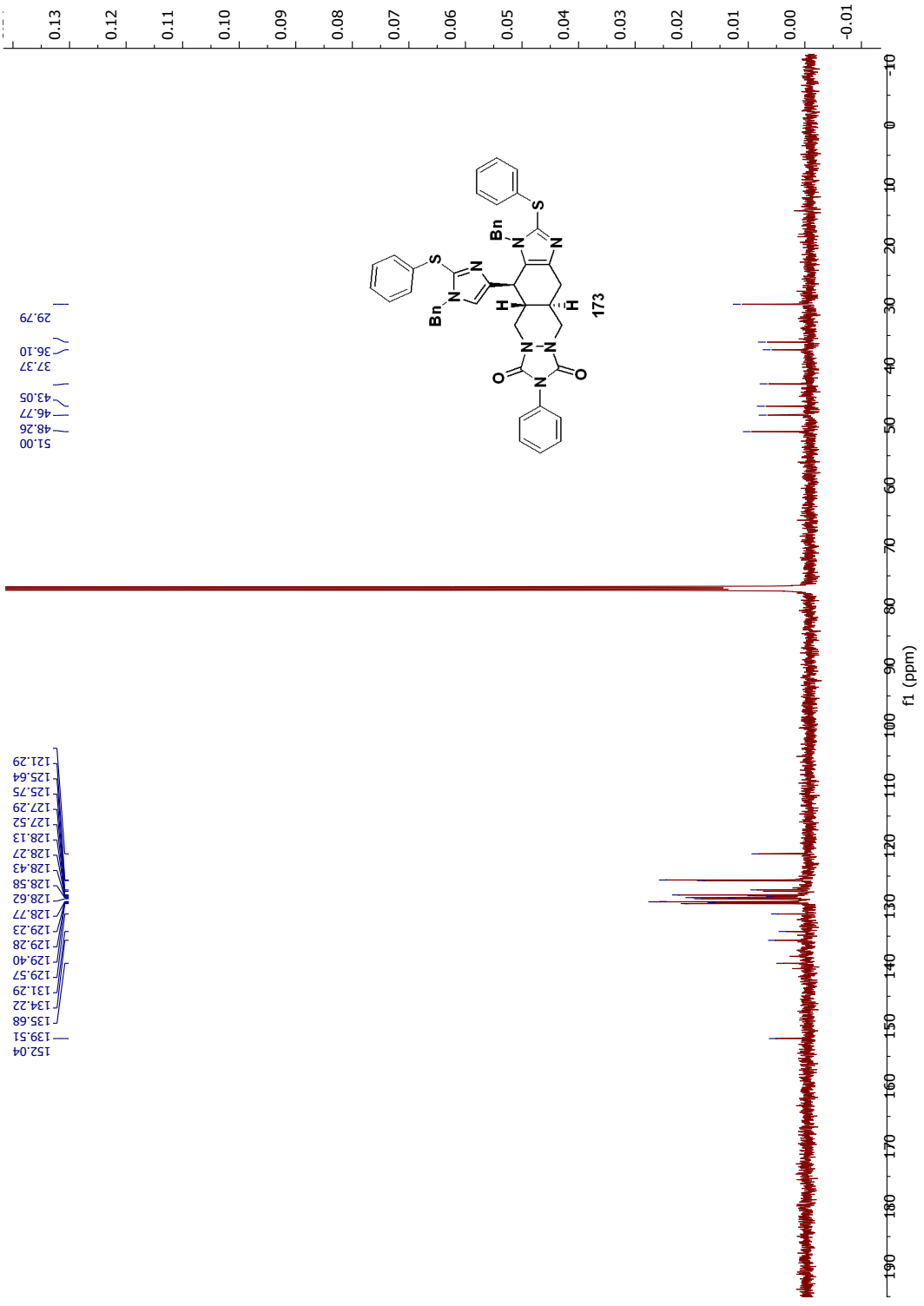

171
f1 (ppm)

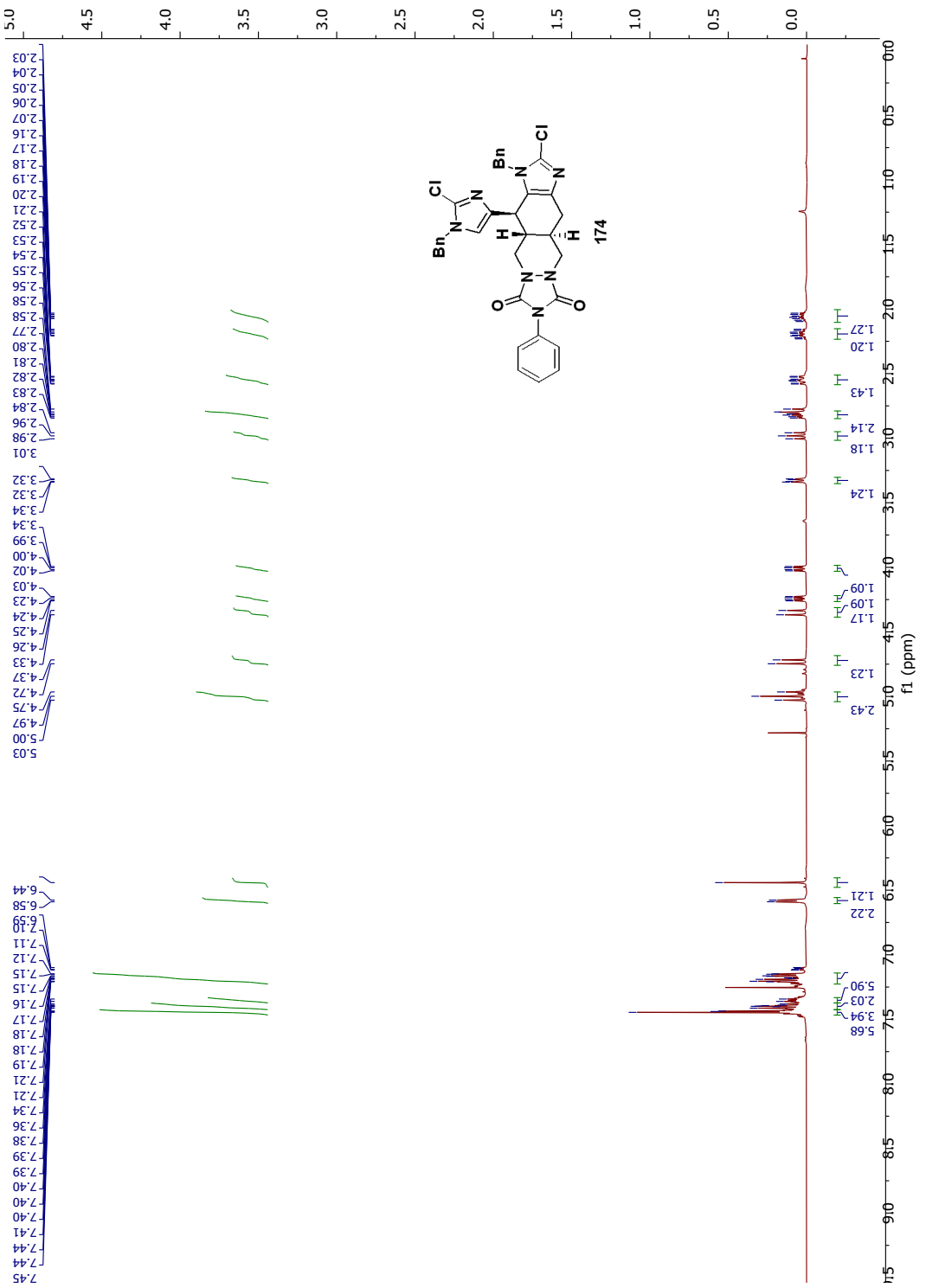

171
Bn
I
N
O
47.33
53.33
92.08
120.95
121.62
125.49
126.10
127.41
127.95
128.51
128.66
129.06
129.16
131.64
132.16
132.24
135.33
142.74
153.17
f1 (ppm)

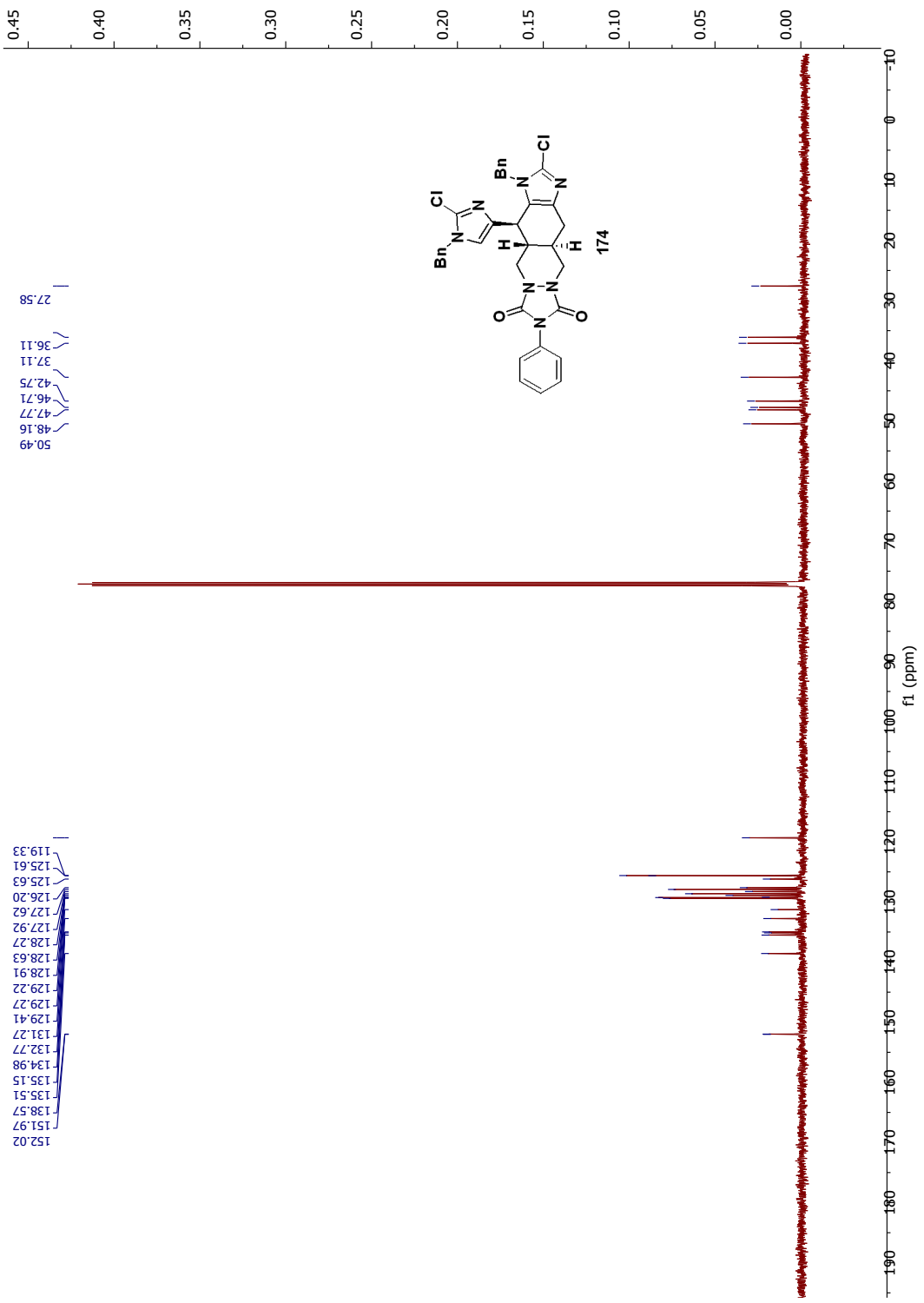

Cl
Bn
N
N
O
O
172
f1 (ppm)

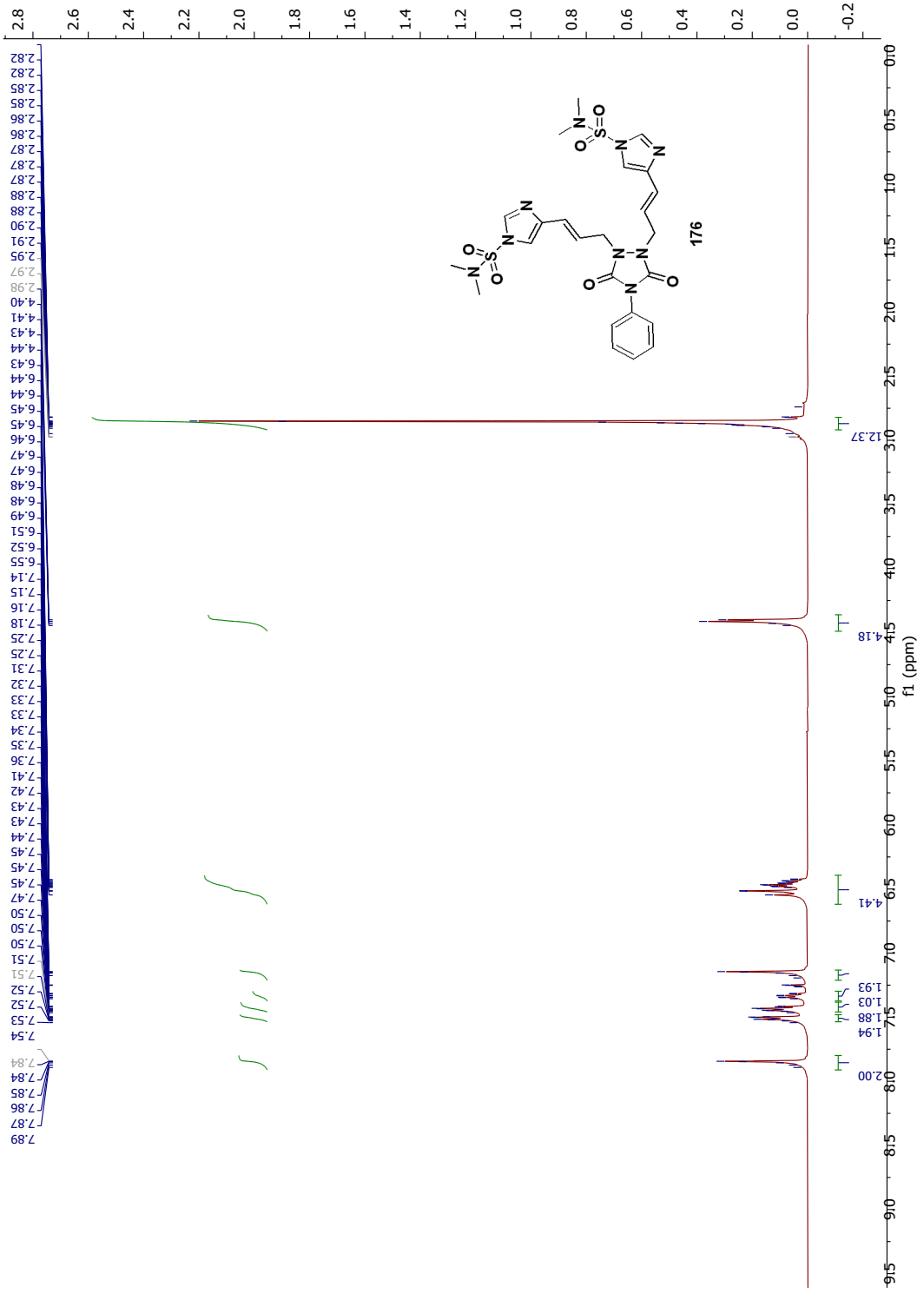

172
153.23
138.17
135.09
133.05
131.65
129.21
129.06
128.59
127.96
127.45
126.12
125.49
120.85
119.33
53.55
50.43
47.33
f1 (ppm)

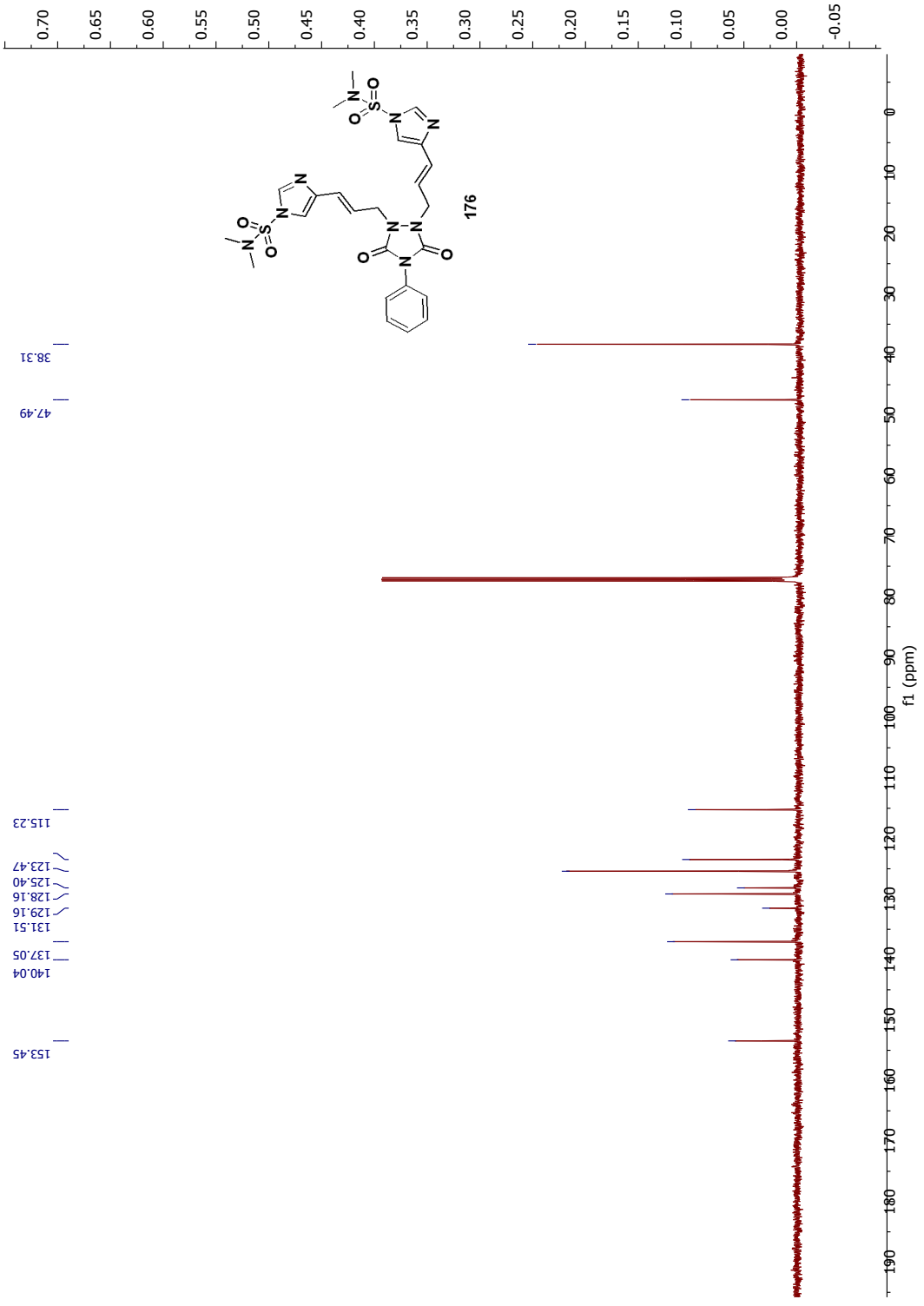

173
f1 (ppm)

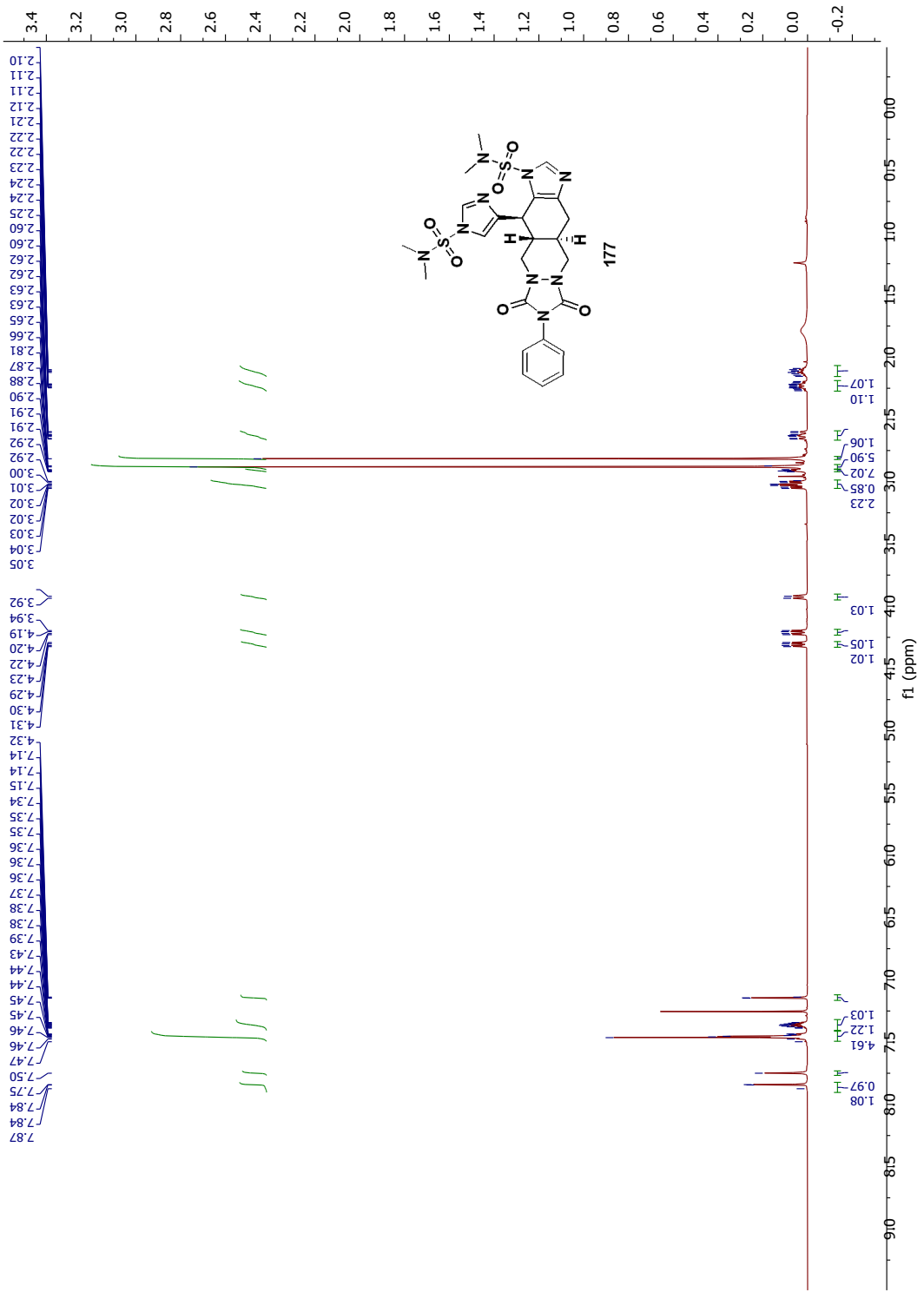

173
f1 (ppm)

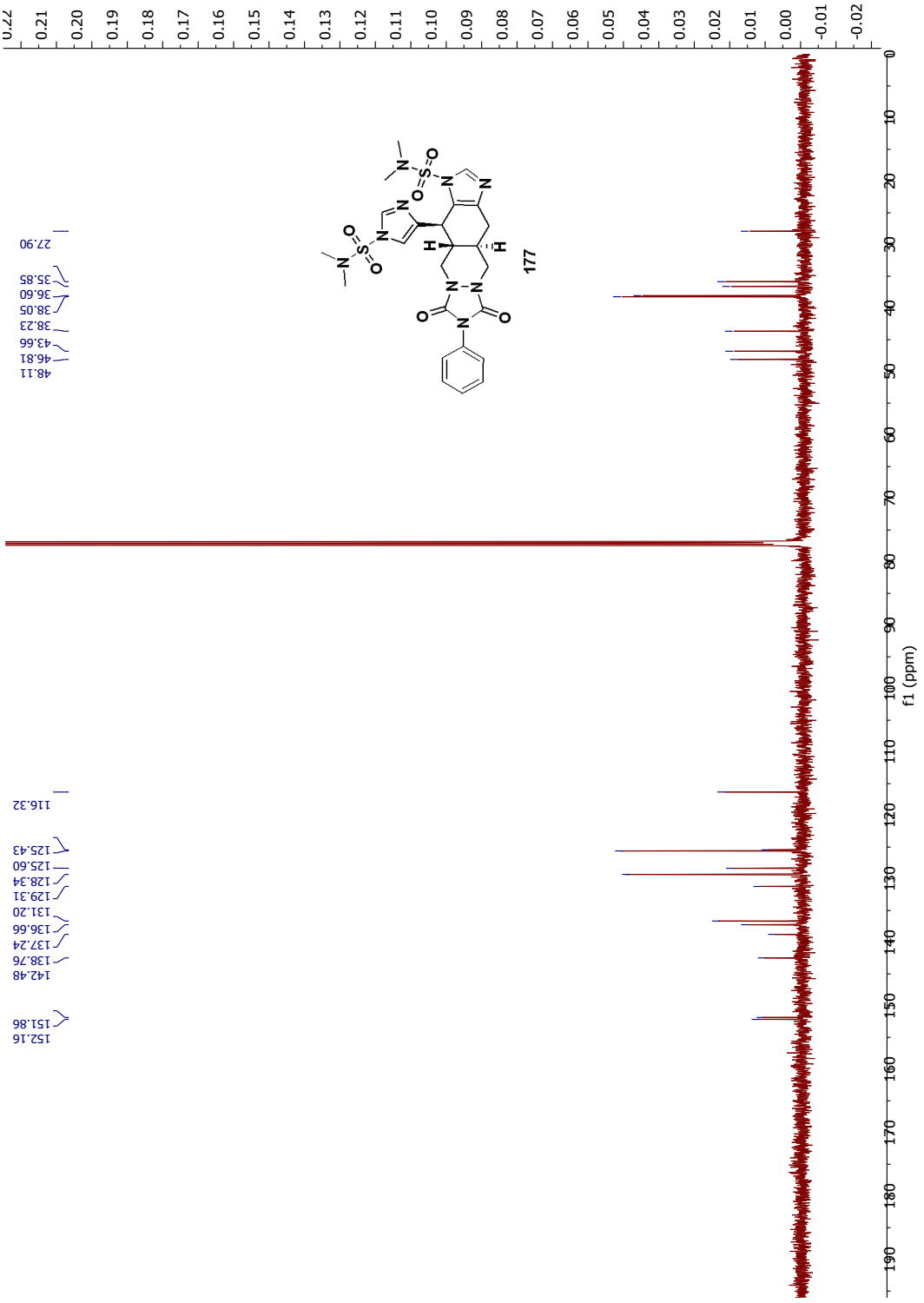

Cl
Bn
N
N
H
H
O
O
174
f1 (ppm)

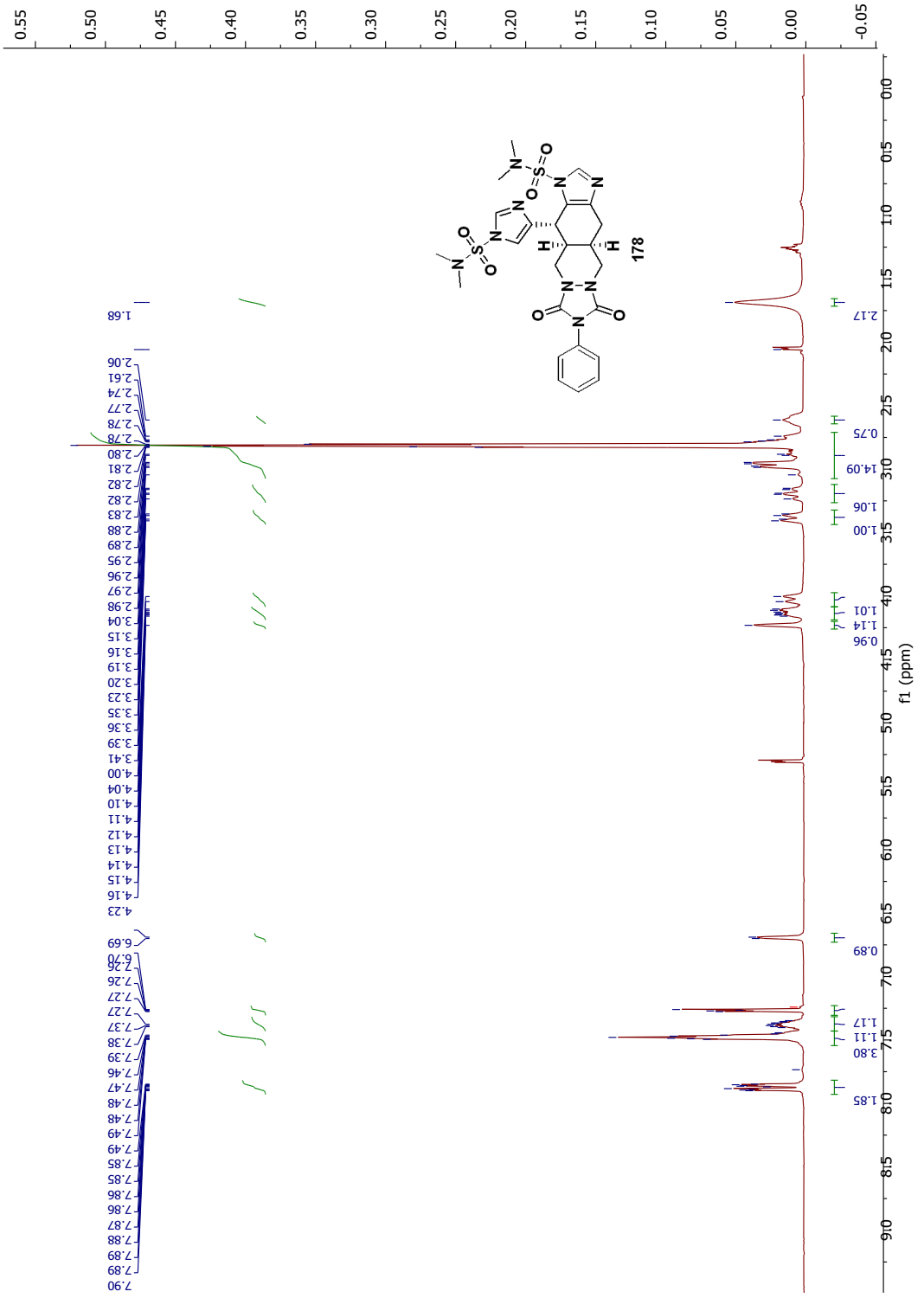

0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
Bn
Cl
Cl
Bn
H
H
174
O
O
27.58
36.11
37.11
42.75
46.71
47.77
48.16
50.49
119.33
125.61
125.63
126.20
127.62
127.92
128.27
128.63
128.91
129.22
129.27
129.41
131.27
132.77
134.98
135.15
135.51
138.57
151.97
152.02
-10
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
f1 (ppm)

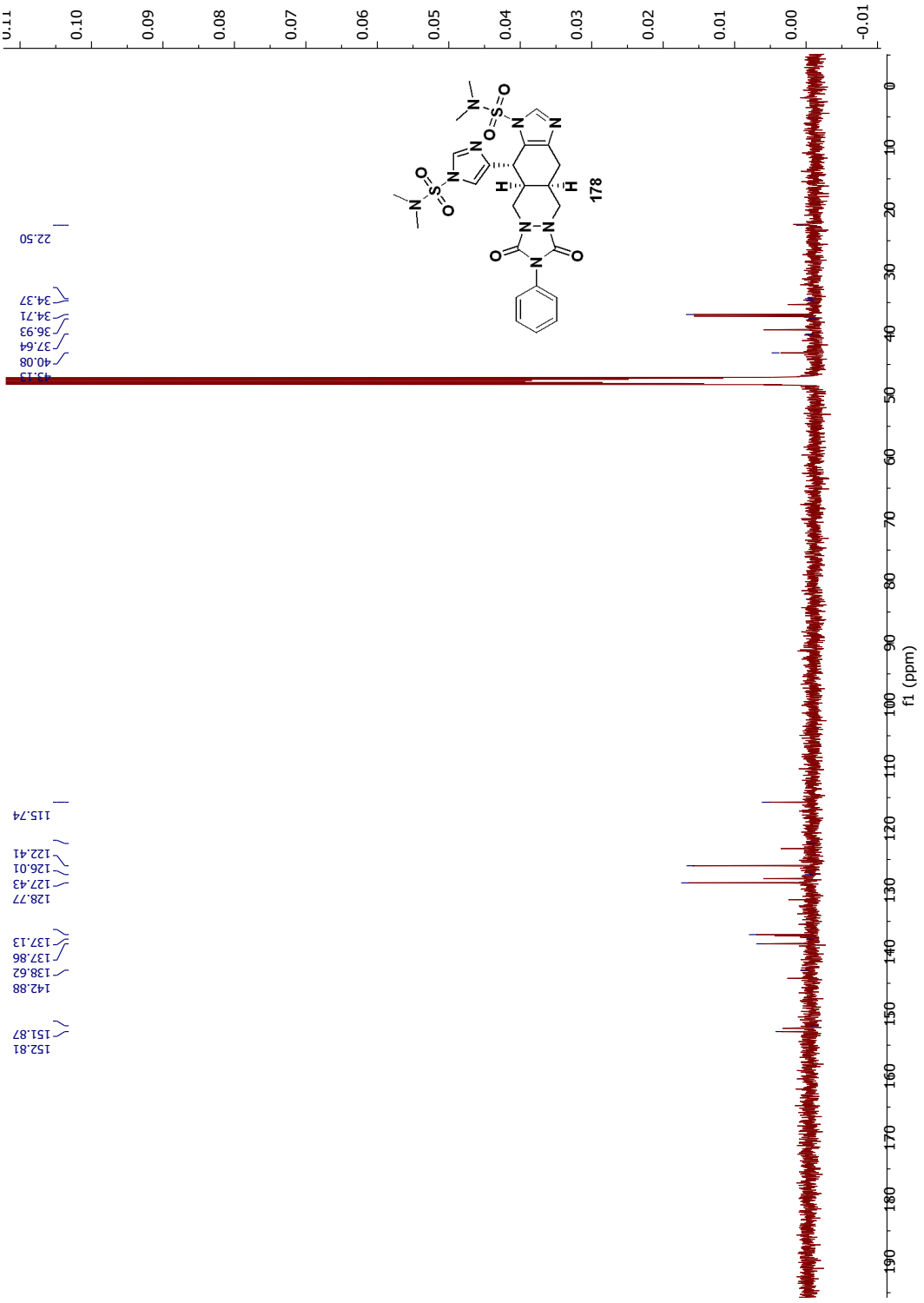

176
12.37
4.18
4.41
1.93
1.03
1.88
1.94
2.00
f1 (ppm)

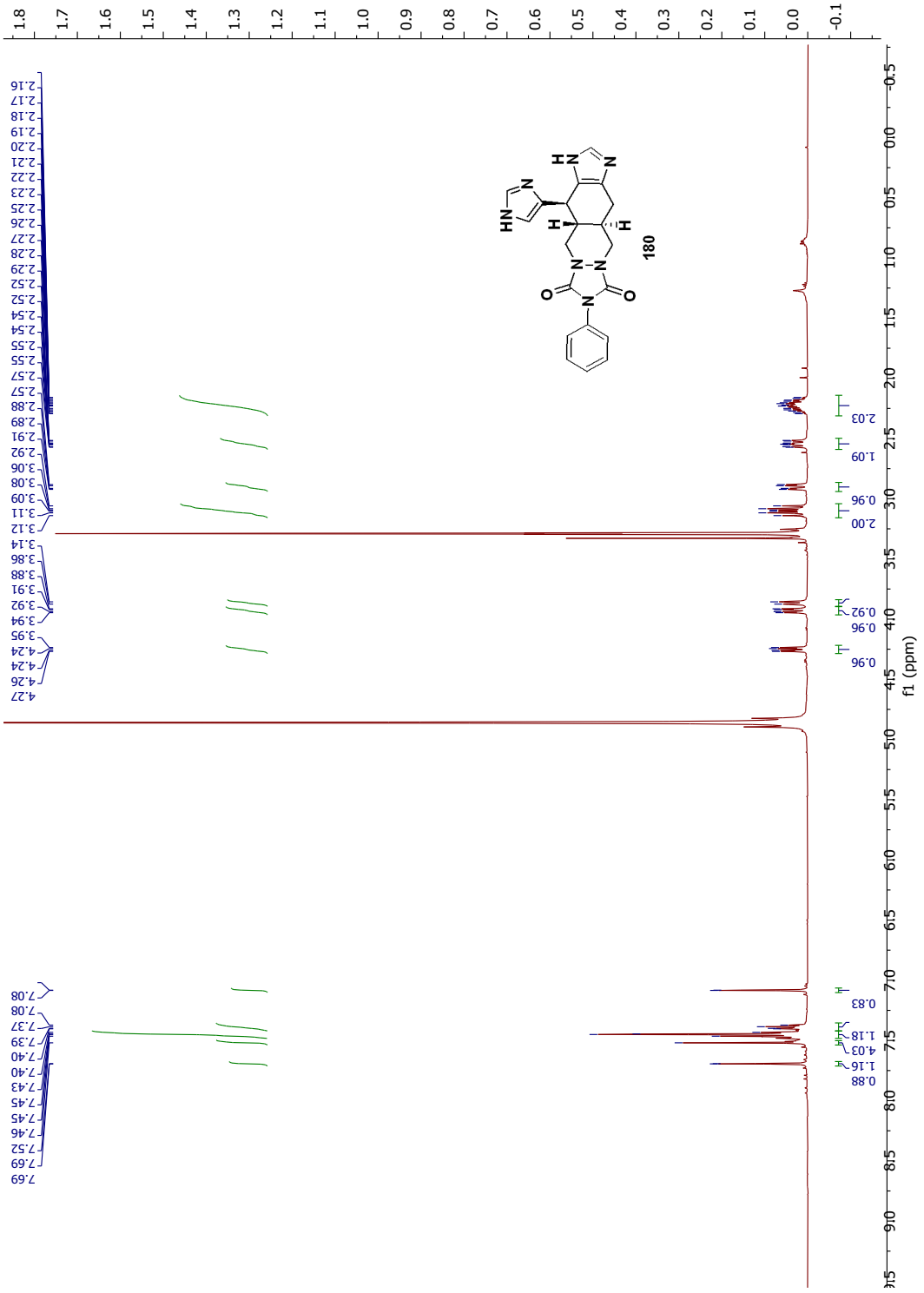

176
38.31
47.49
115.23
123.47
125.40
128.16
129.16
131.51
137.05
140.04
153.45
f1 (ppm)

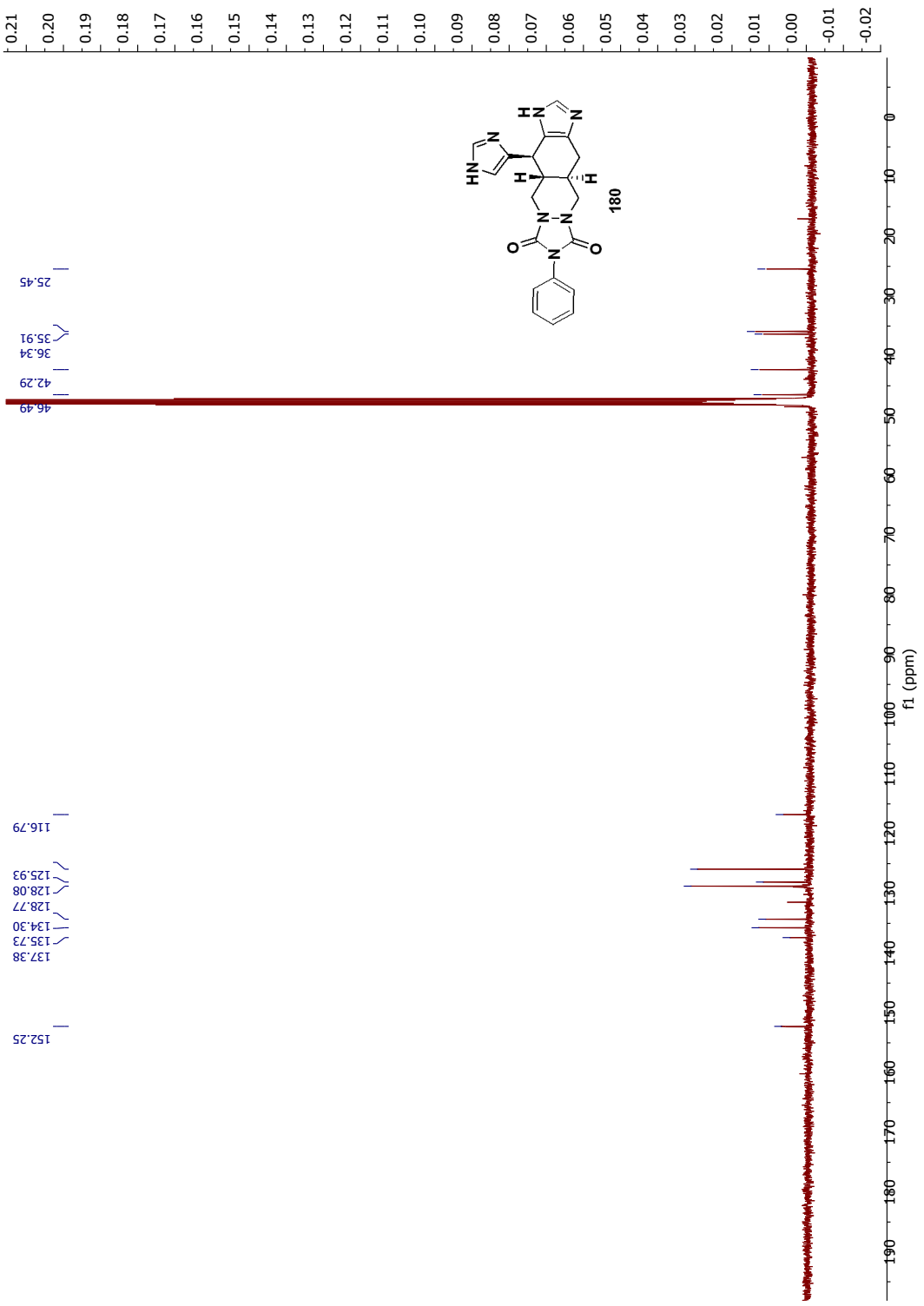

177
f1 (ppm)

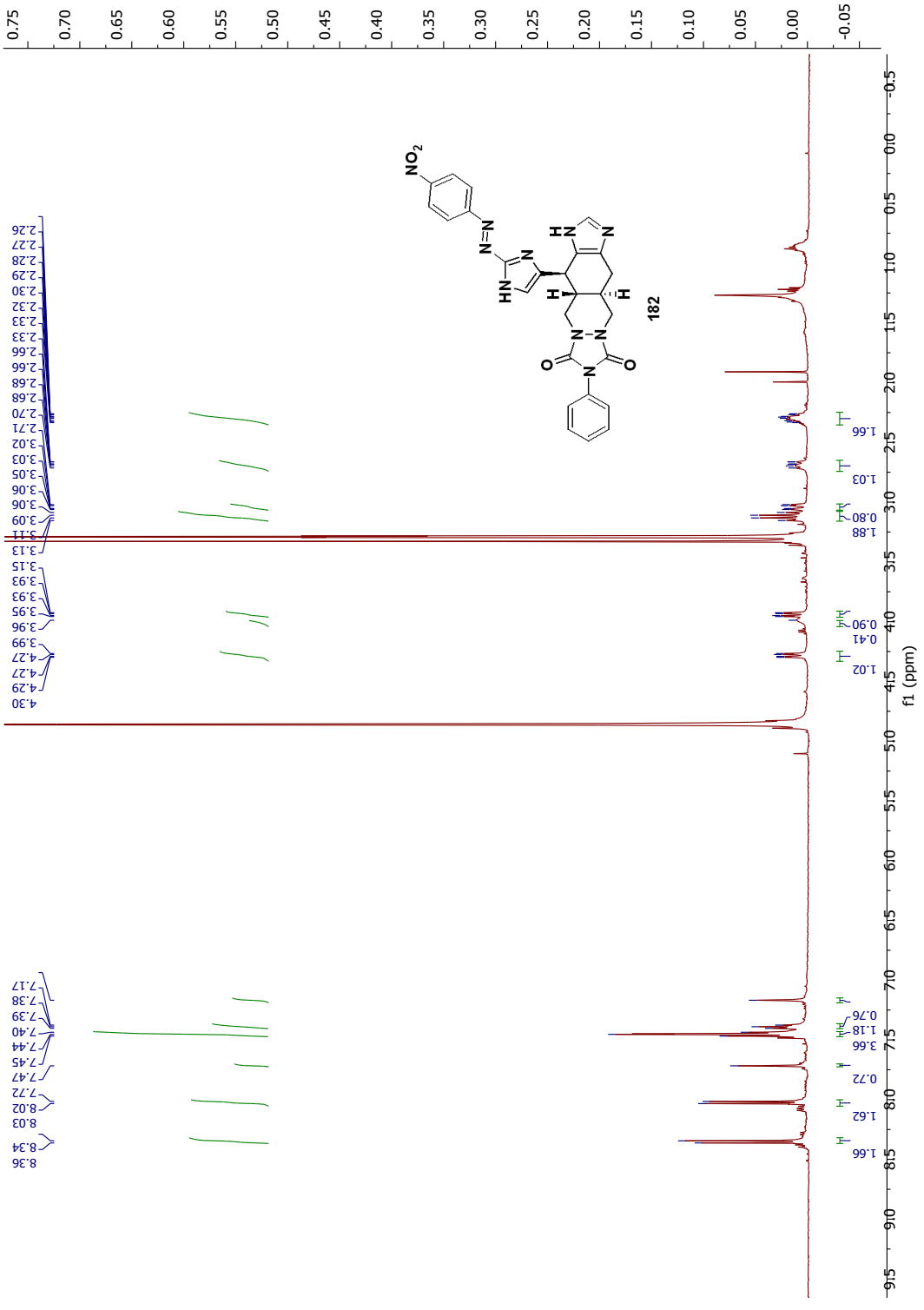

177
152.16
151.86
142.48
138.76
137.24
136.66
131.20
129.31
128.34
125.60
125.43
116.32
48.11
46.81
43.66
38.23
38.05
36.60
35.85
27.90
f1 (ppm)

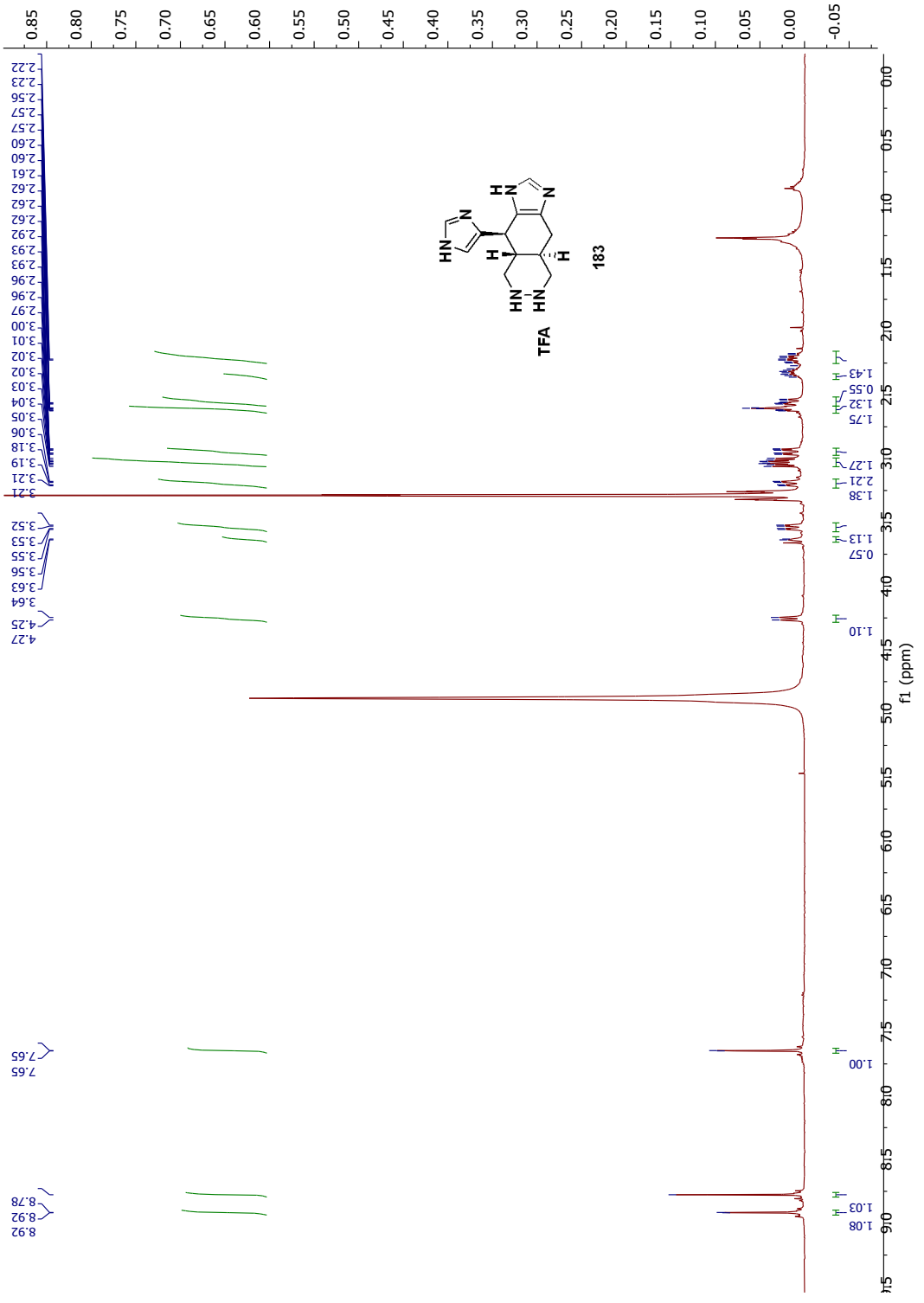

178
f1 (ppm)

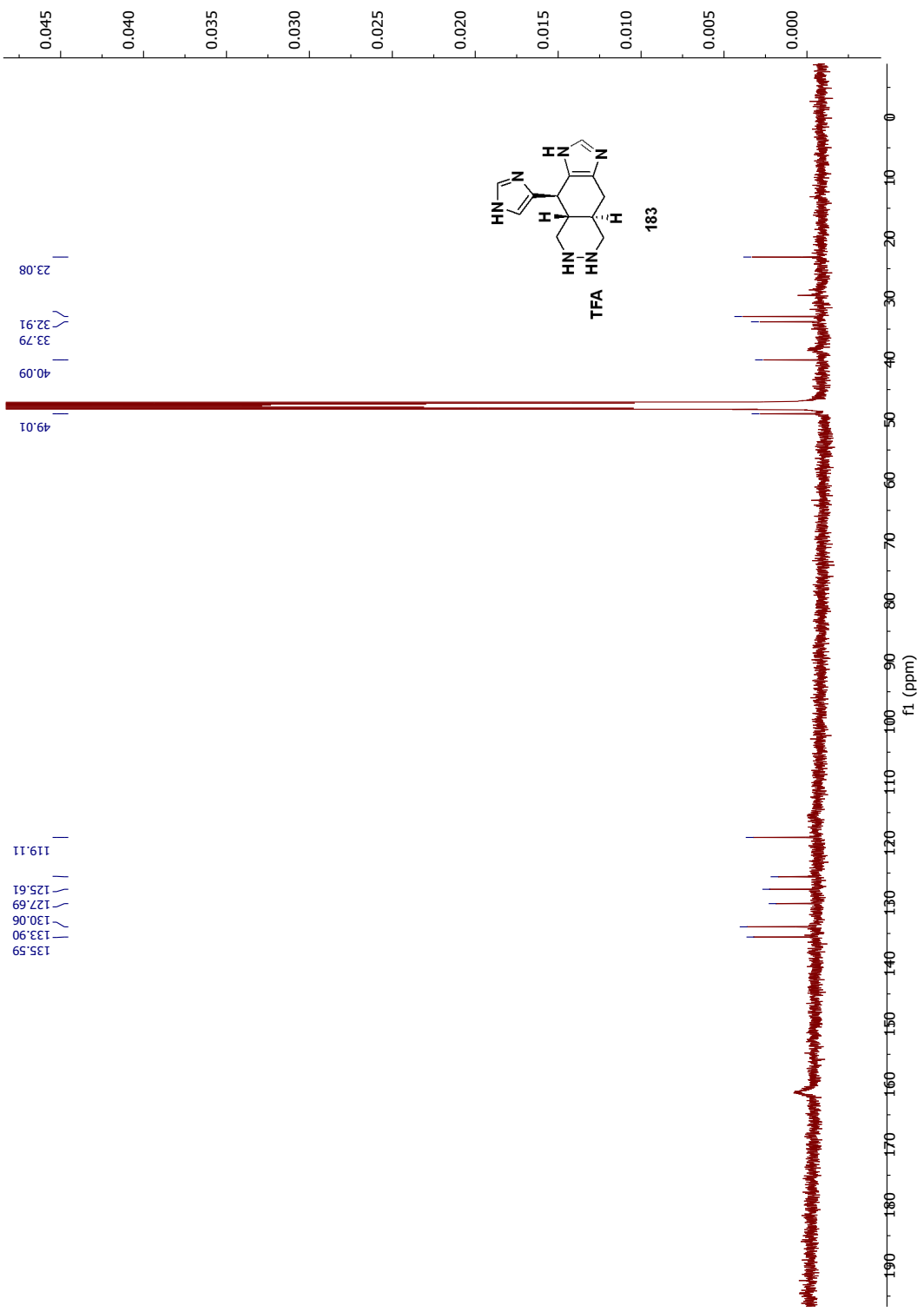

178
22.50
34.37
34.71
36.93
37.64
40.08
45.15
115.74
122.41
126.01
127.43
128.77
137.13
137.86
138.62
142.88
151.87
152.81
f1 (ppm)

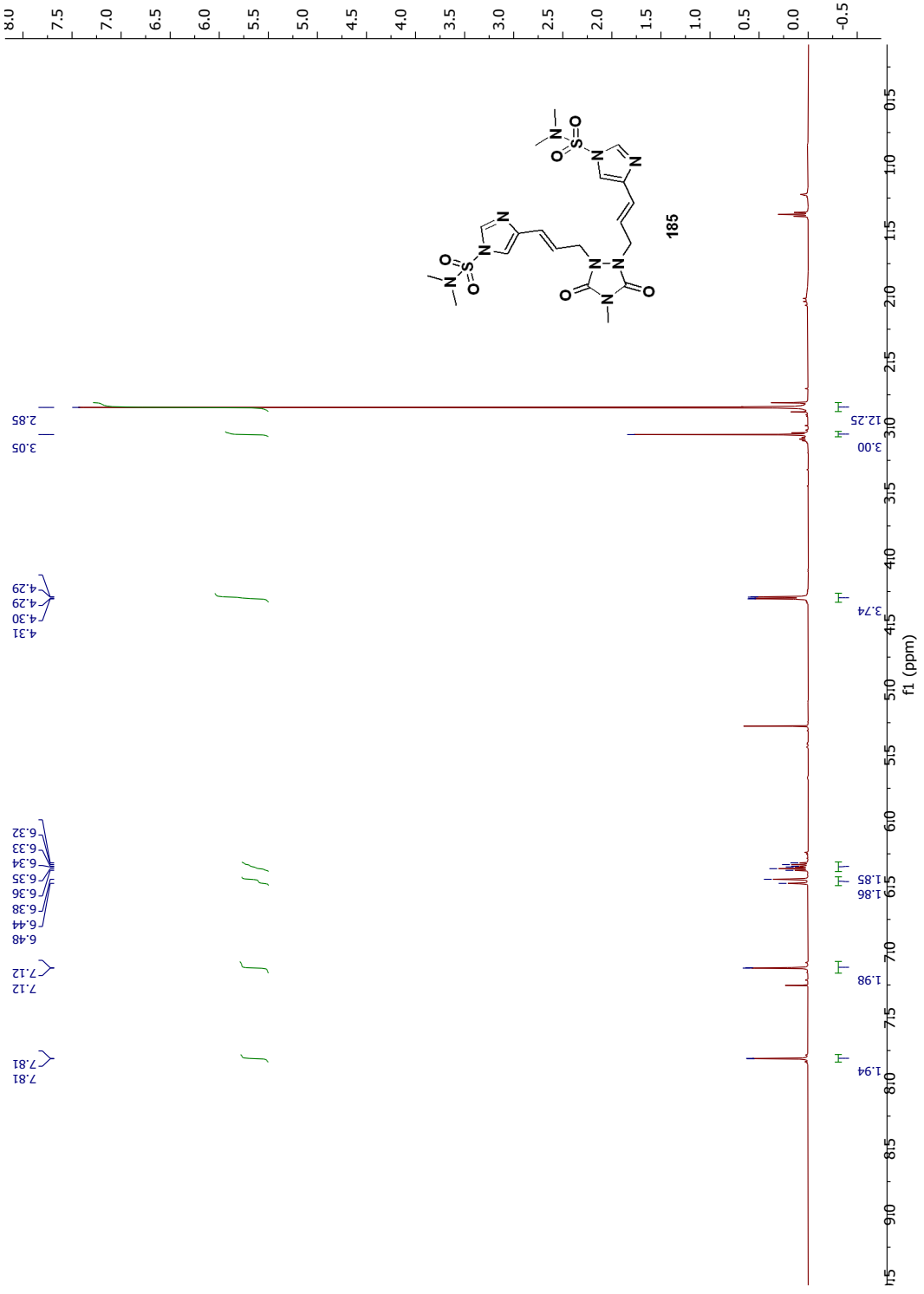

180
f1 (ppm)

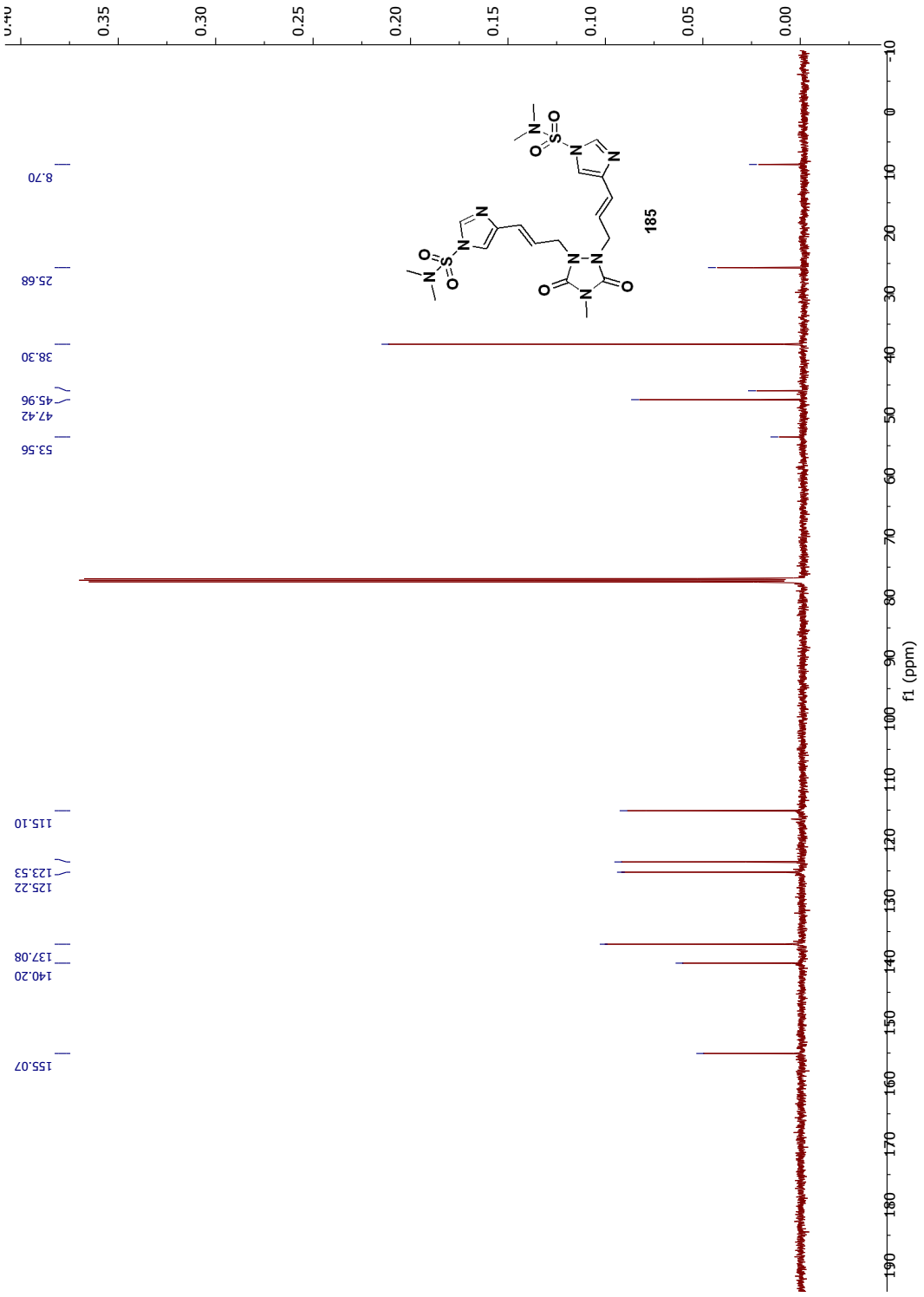

180
152.25
137.38
135.73
134.30
128.77
128.08
125.93
116.79
46.49
42.29
36.34
35.91
25.45
f1 (ppm)

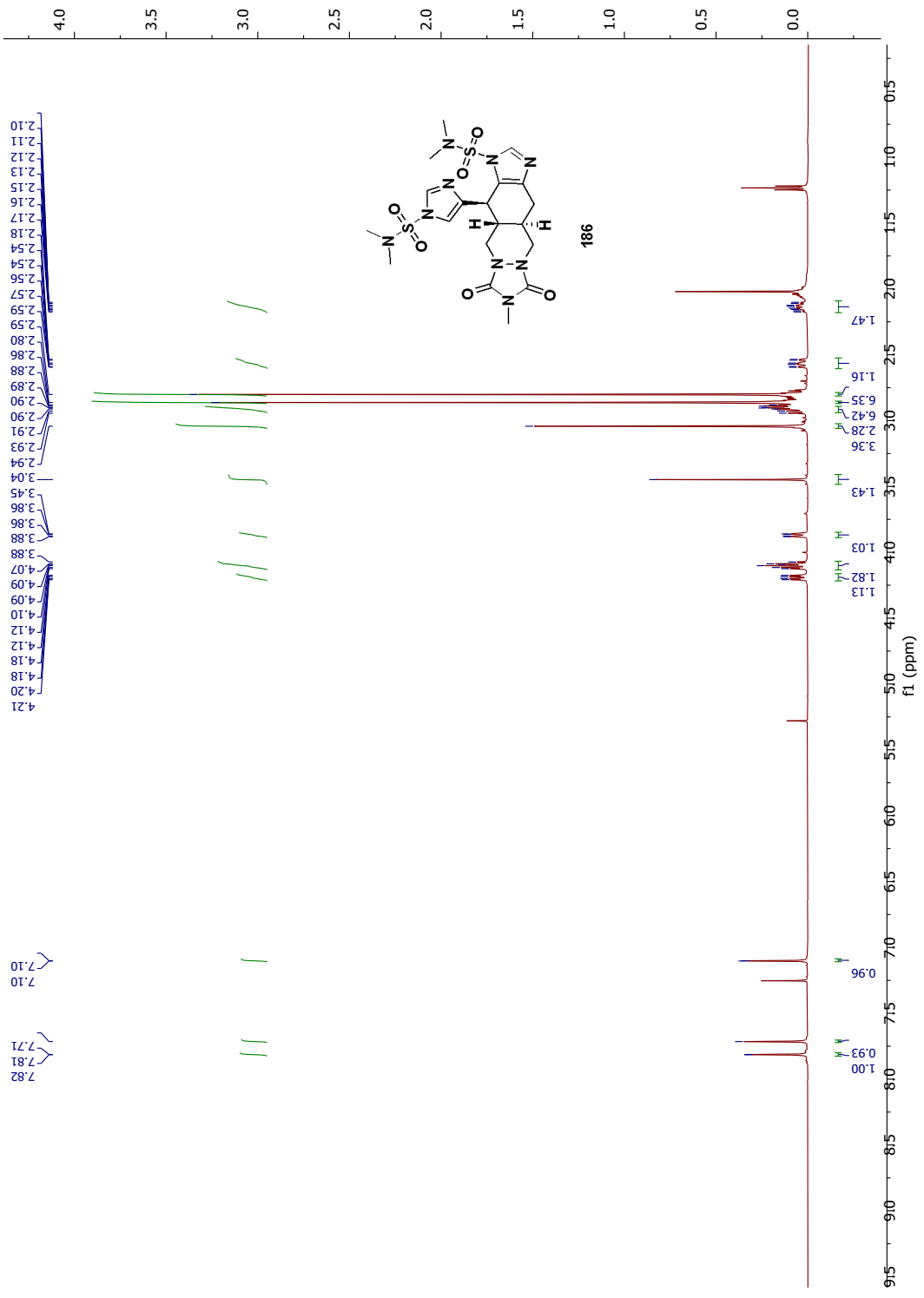

182
f1 (ppm)

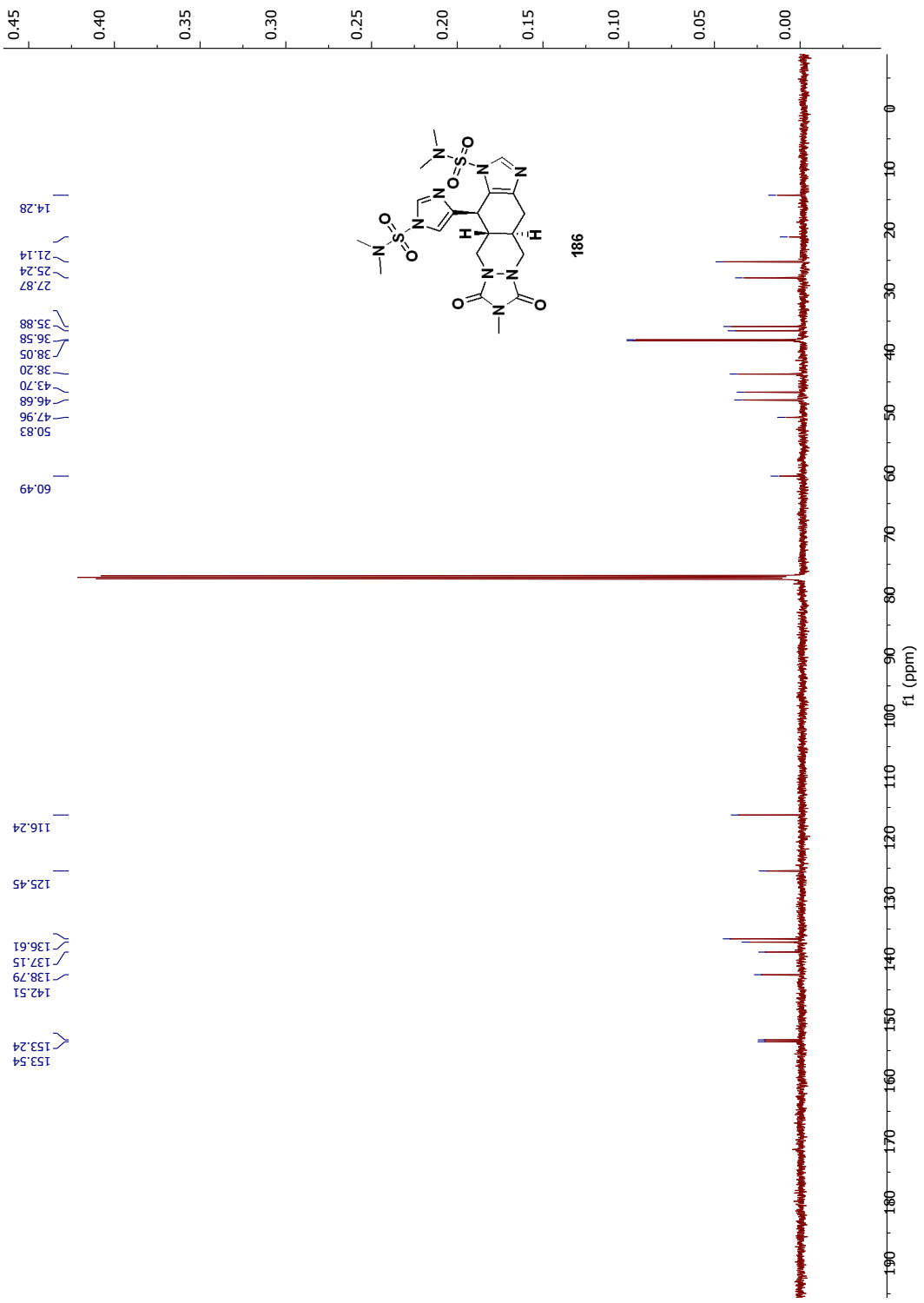

TFA
183
f1 (ppm)

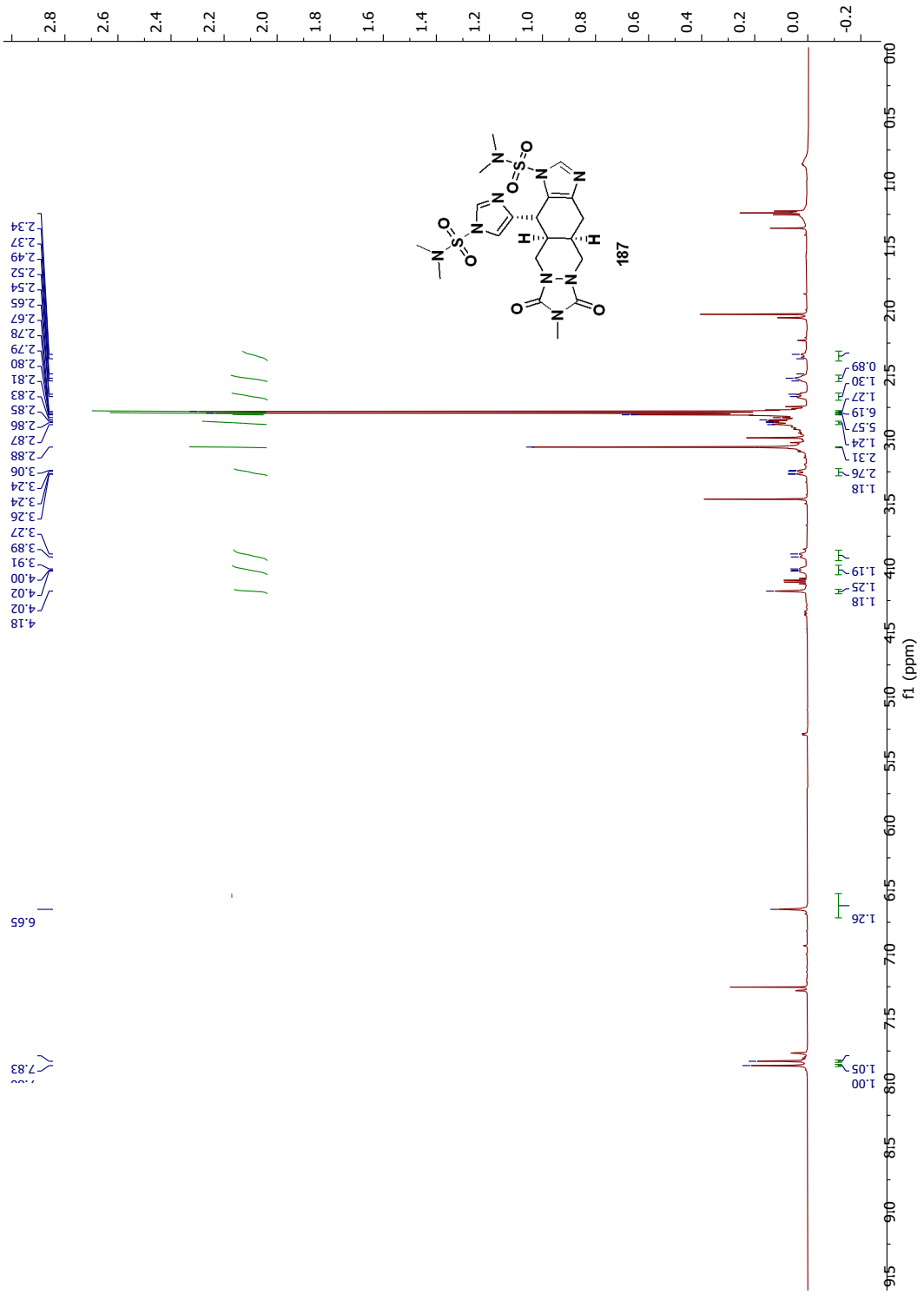

0.045
0.040
0.035
0.030
0.025
0.020
0.015
0.010
0.005
0.000
23.08
32.91
33.79
40.09
49.01
119.11
125.61
127.69
130.06
133.90
135.59
TFA
183
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
f1 (ppm)

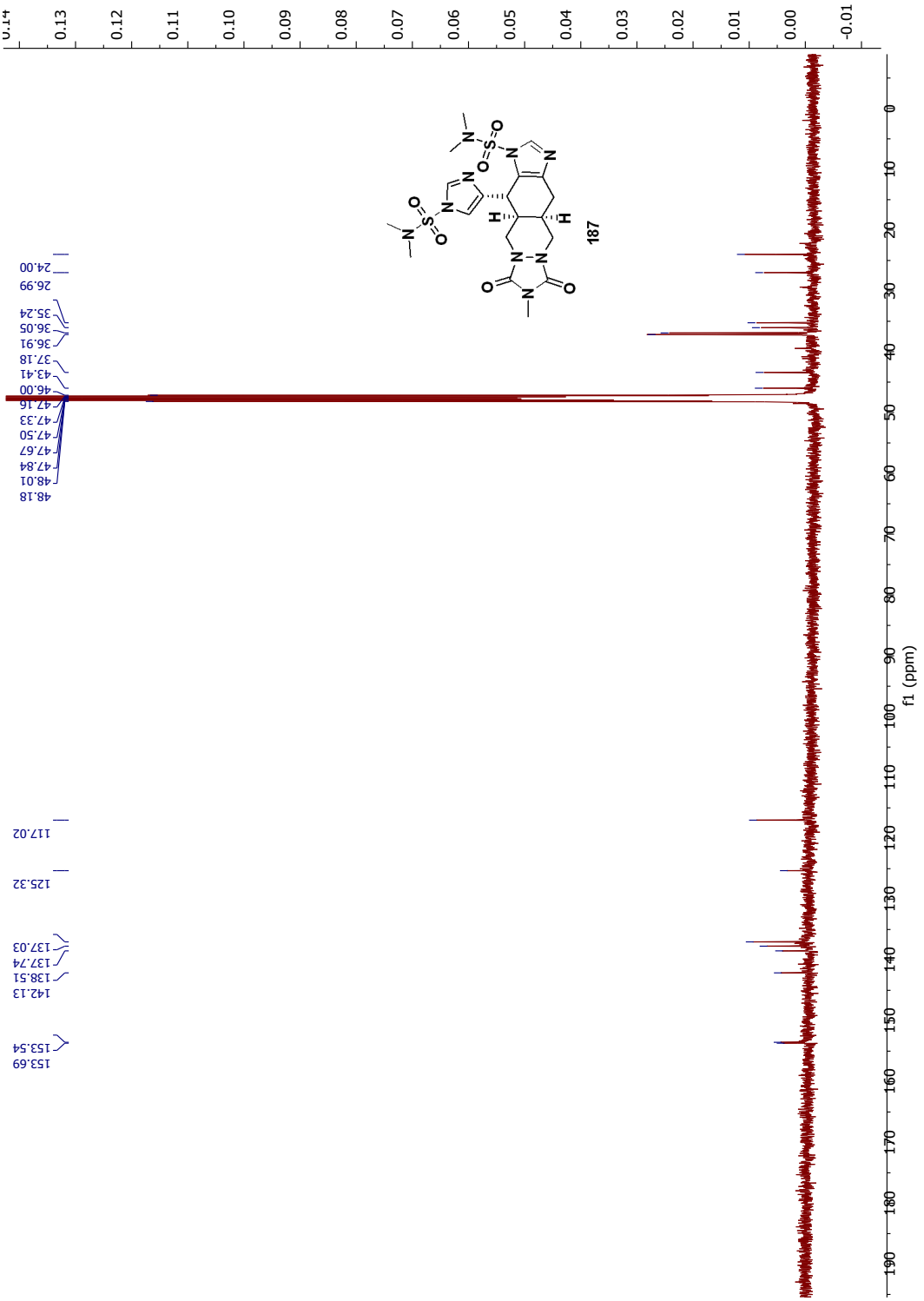

185
f1 (ppm)


185
8.70
25.68
38.30
45.96
47.42
53.56
115.10
123.53
125.22
137.08
140.20
155.07
f1 (ppm)

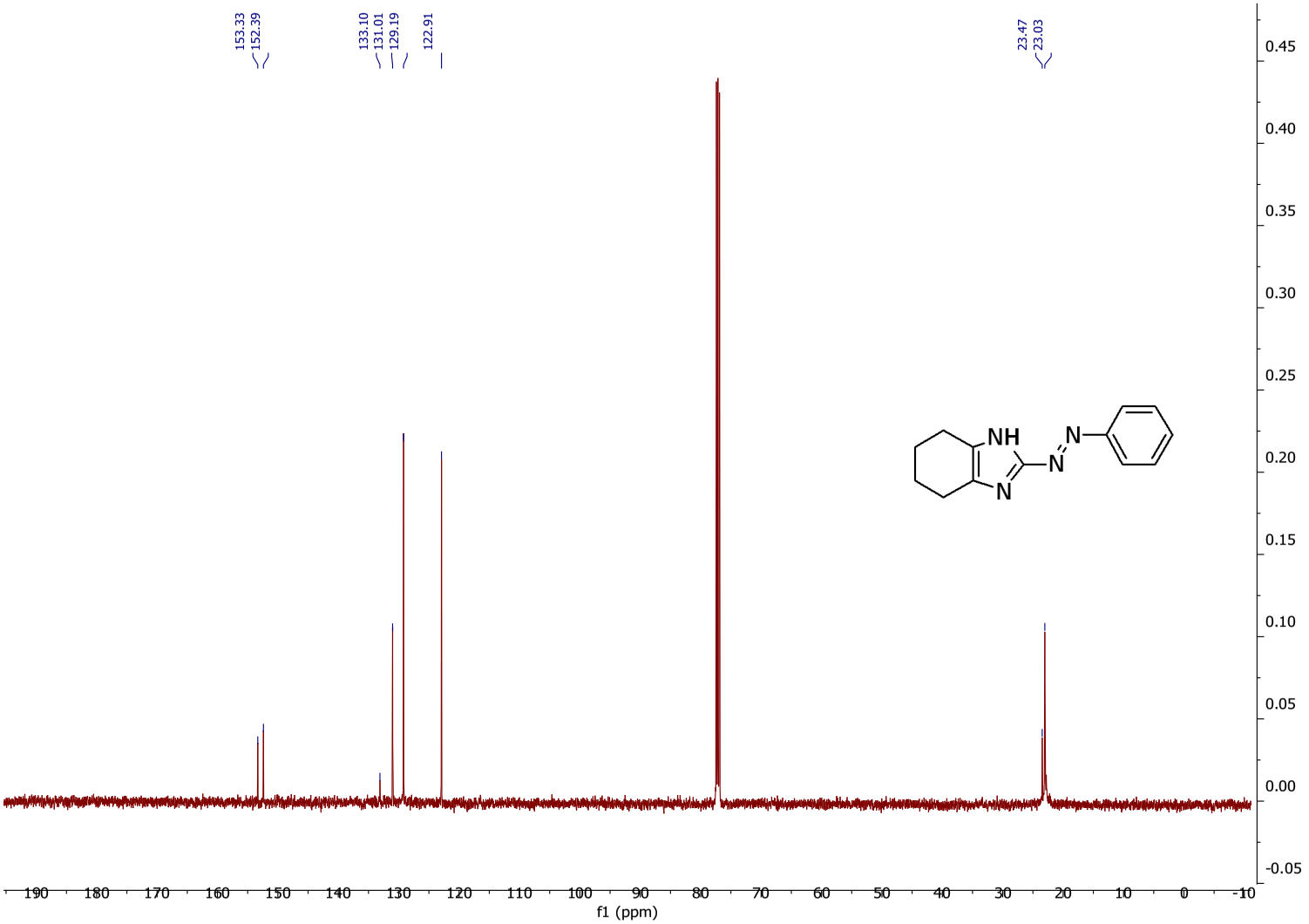

186
f1 (ppm)

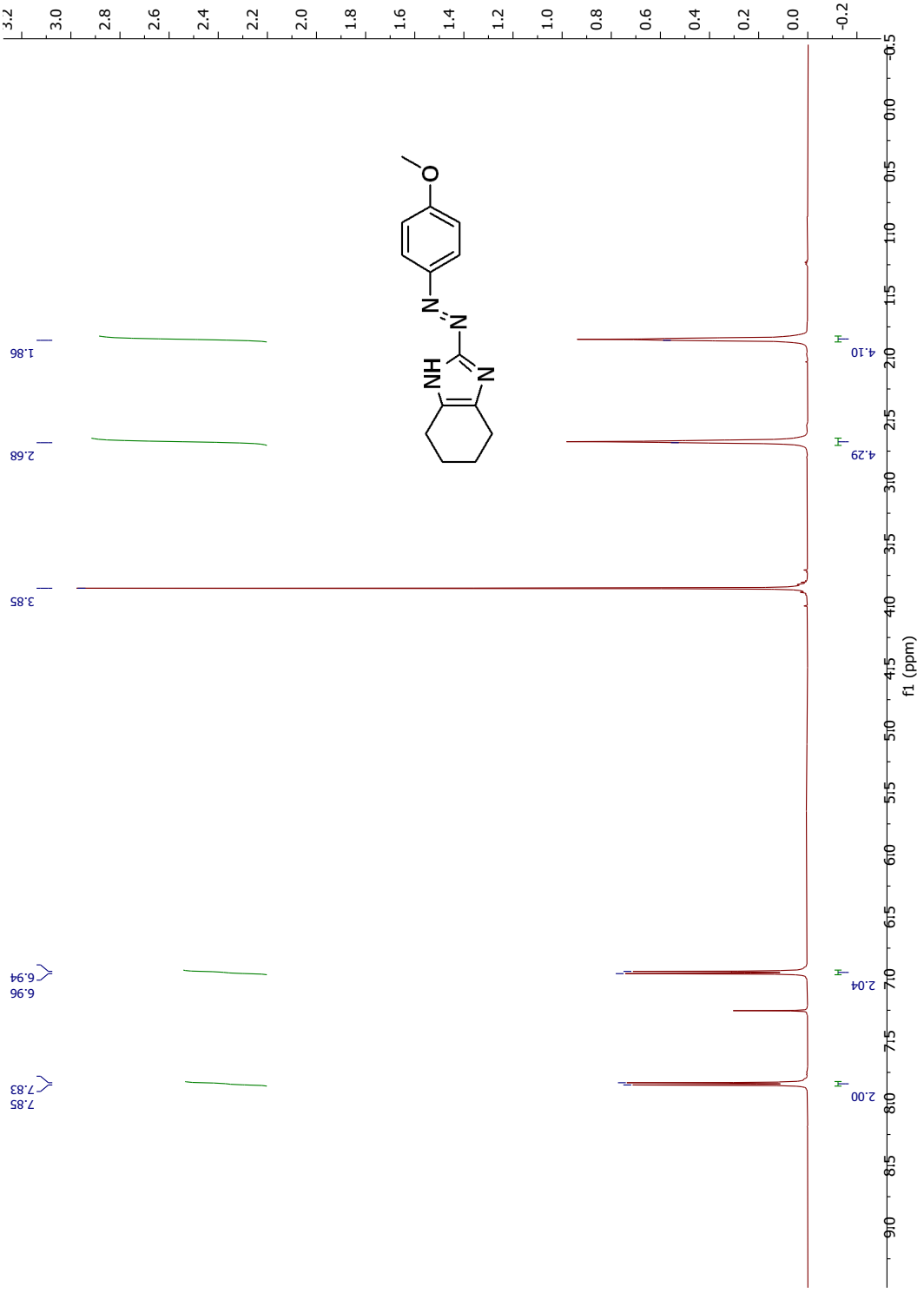

186
153.54
153.24
142.51
138.79
137.15
136.61
125.45
116.24
60.49
50.83
47.96
46.68
43.70
38.20
38.05
36.58
35.88
27.87
25.24
21.14
14.28
f1 (ppm)

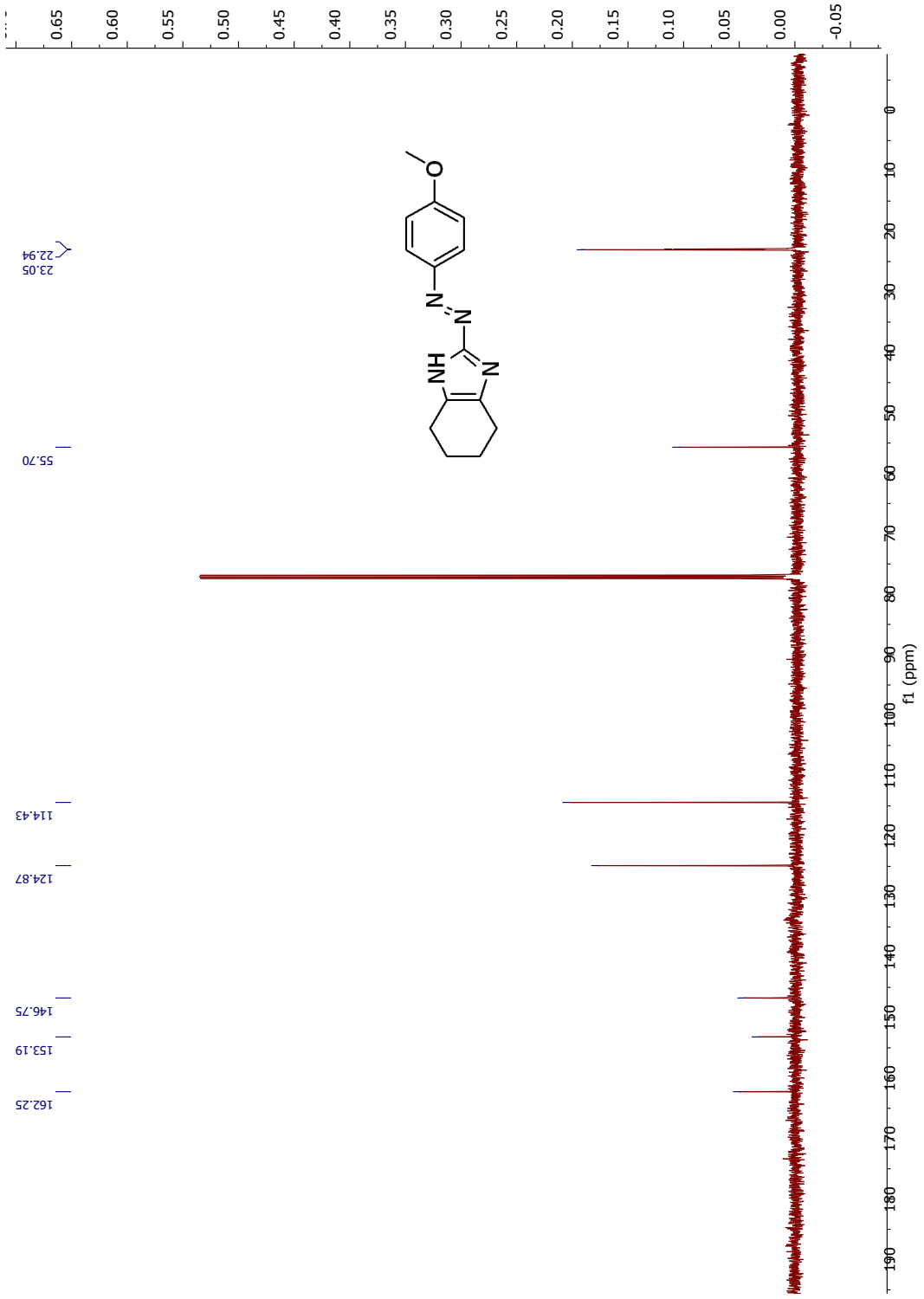

187
f1 (ppm)

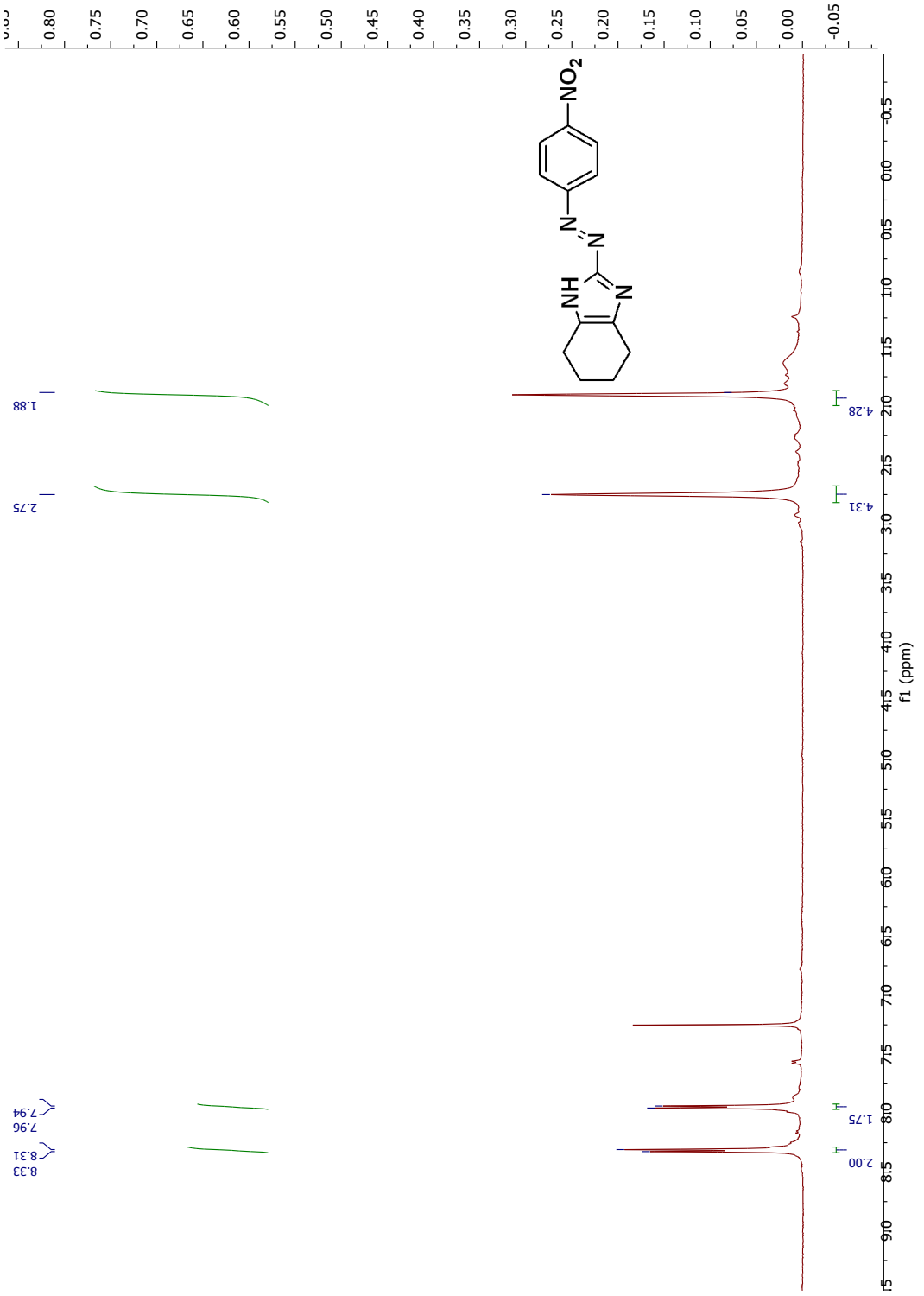

187
153.69
153.54
142.13
138.51
137.74
137.03
125.32
117.02
48.18
48.01
47.84
47.67
47.50
47.33
47.16
46.00
43.41
37.18
36.91
36.05
35.24
26.99
24.00
f1 (ppm)

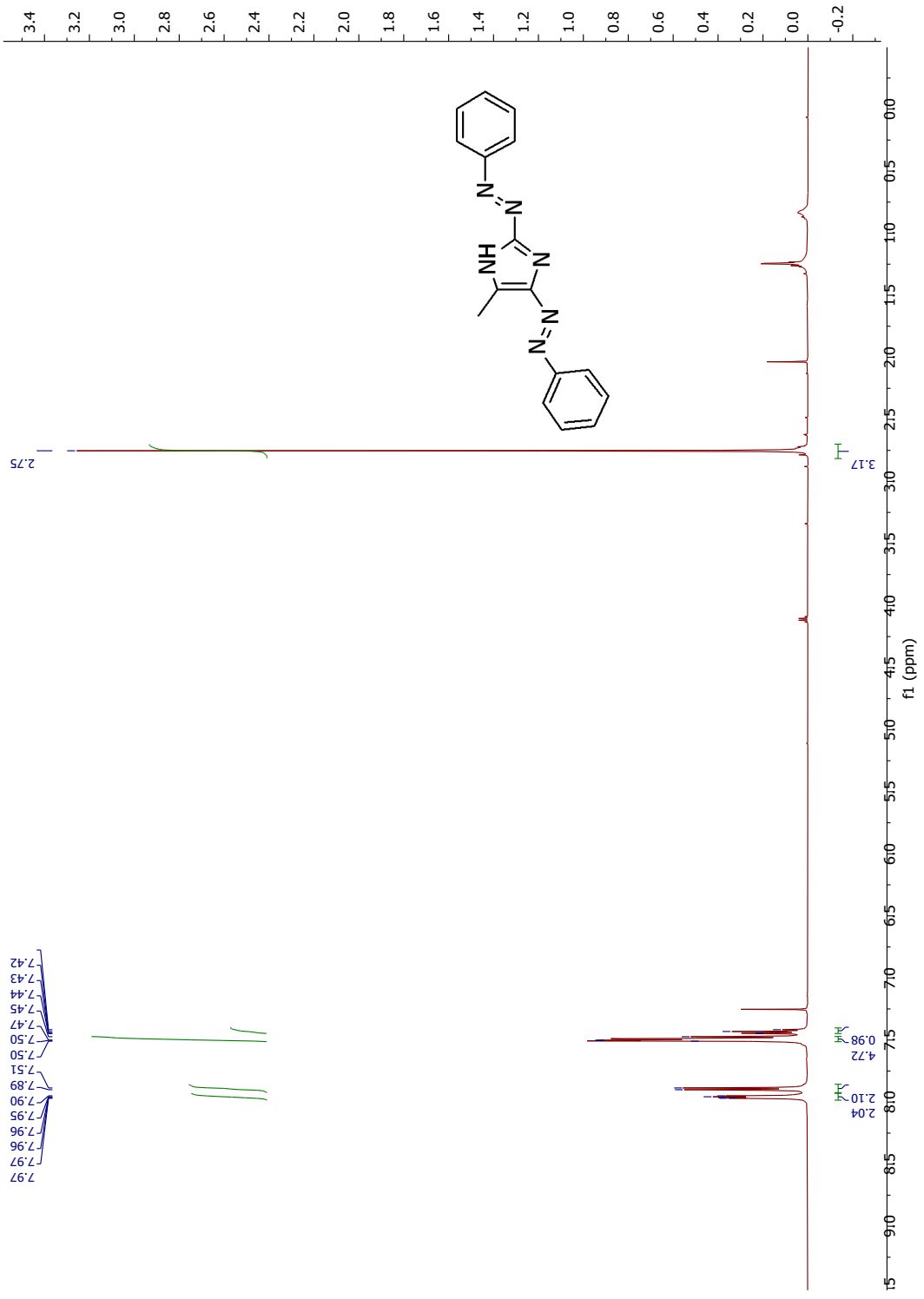
7.85
7.84
7.45
7.43
7.42
7.41
7.40
7.39
2.68
1.86
2.00
2.94
4.29
4.36
f1 (ppm)

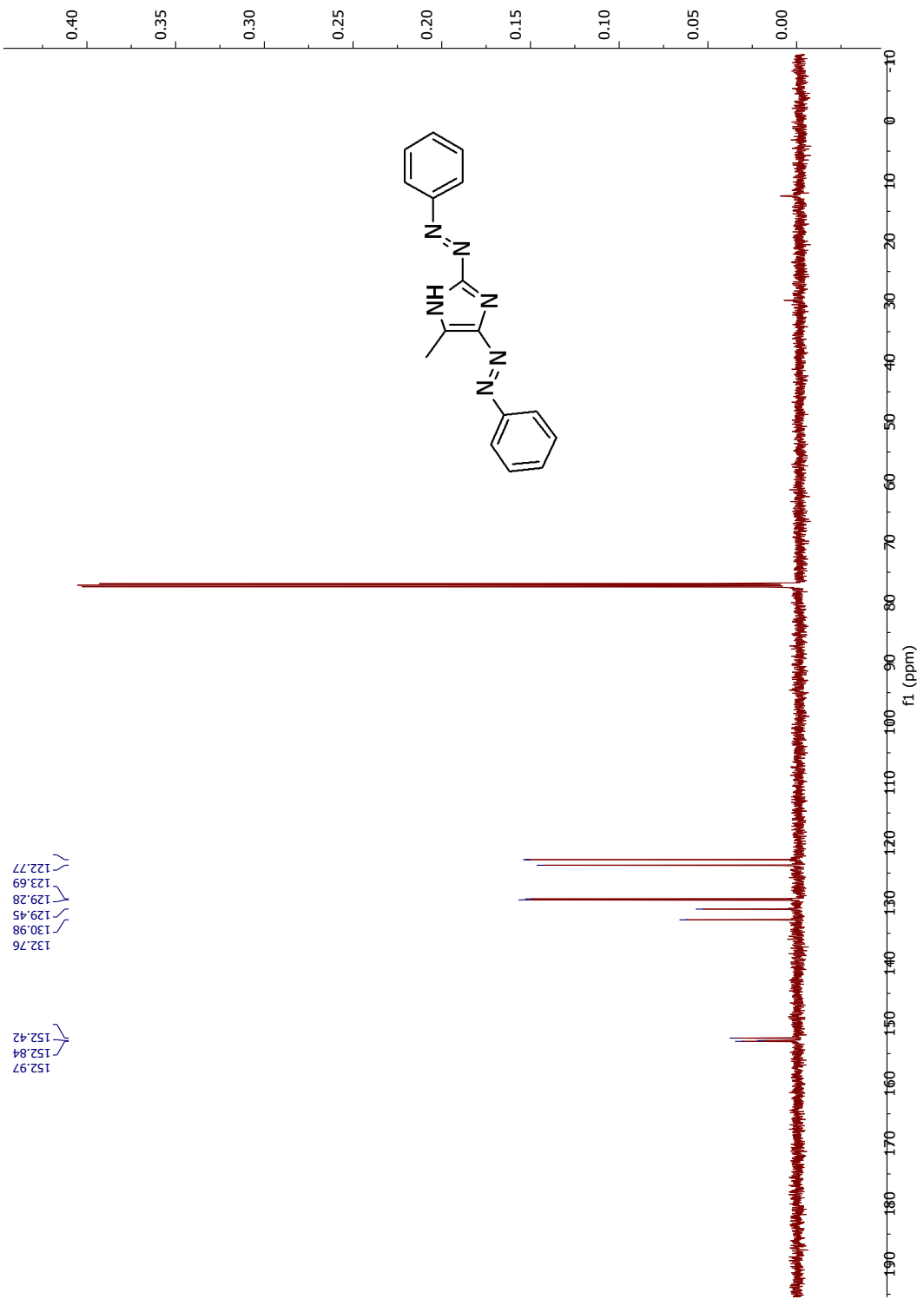

153.33
152.39
133.10
131.01
129.19
122.91
23.47
23.03
NH
N
N
N
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
-0.05
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

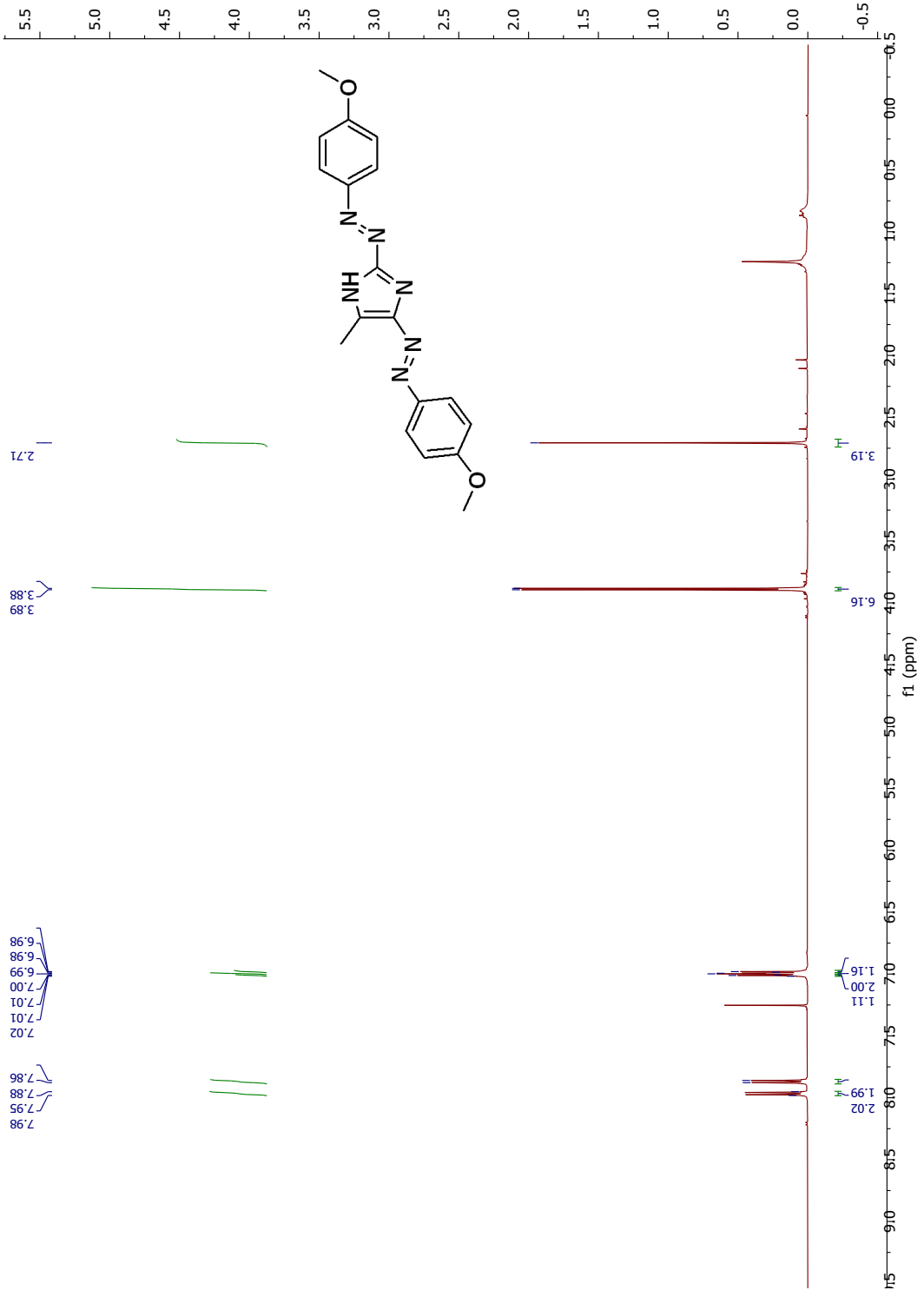

f1 (ppm)
7.85
7.83
6.96
6.94
3.85
2.68
1.86
2.00
2.04
4.29
4.10


0.65
0.60
0.55
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
-0.05
O
N
N
NH
N
23.05
22.94
55.70
114.43
124.87
146.75
153.19
162.25
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
f1 (ppm)


NO2
N
N
NH
N
8.33
8.31
7.96
7.94
2.75
1.88
2.00
1.75
4.31
4.28
f1 (ppm)


f1 (ppm)
2.75
3.17
2.04
2.10
0.98
4.72
7.97
7.97
7.96
7.96
7.95
7.90
7.89
7.51
7.50
7.50
7.47
7.45
7.44
7.43
7.42


0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
-10
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
f1 (ppm)
NH
N
N
N
N
152.97
152.84
152.42
132.76
130.98
129.45
129.28
123.69
122.77


f1 (ppm)
2.71
3.89
3.88
7.98
7.95
7.88
7.86
7.02
7.01
7.01
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6.98
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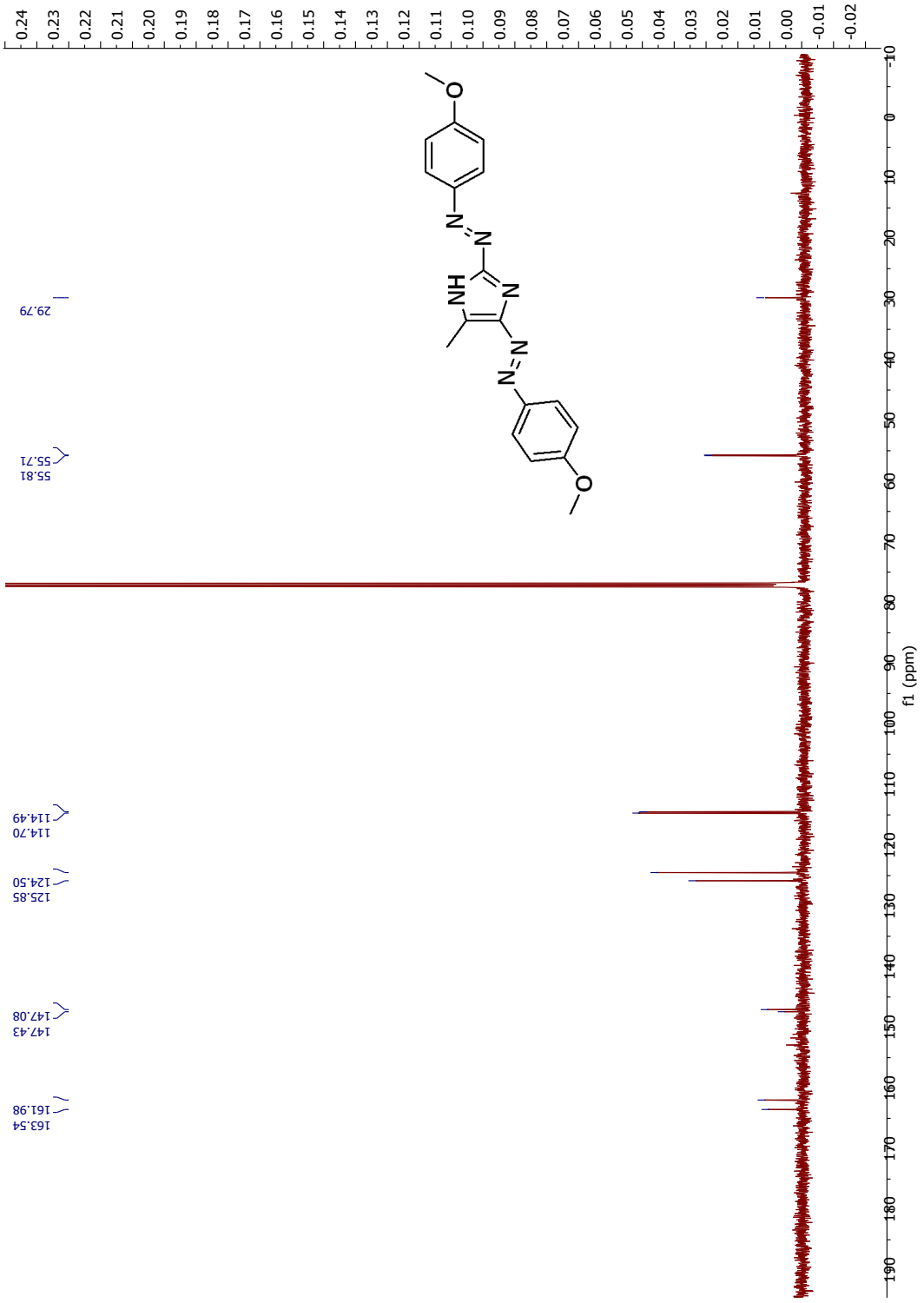
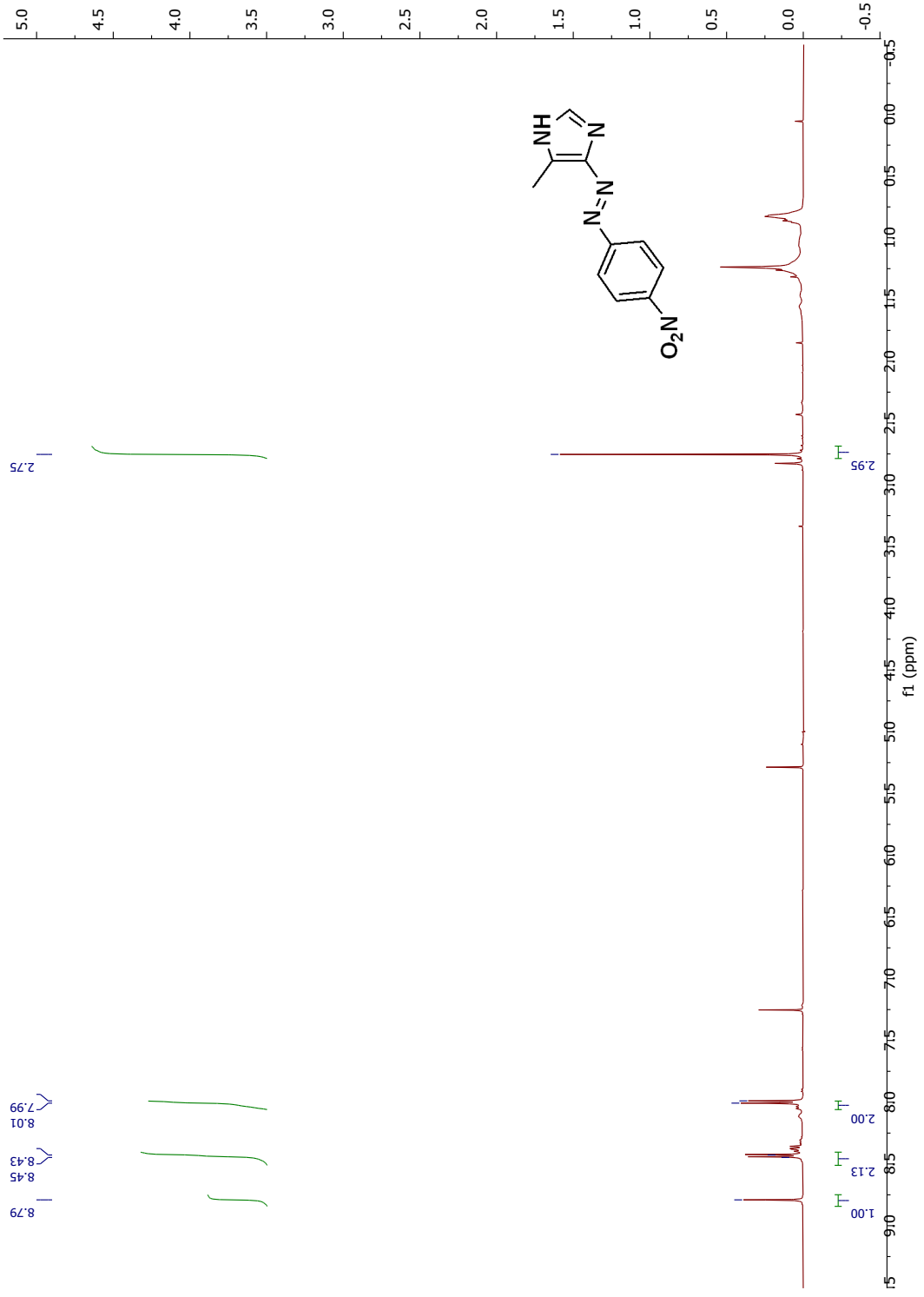
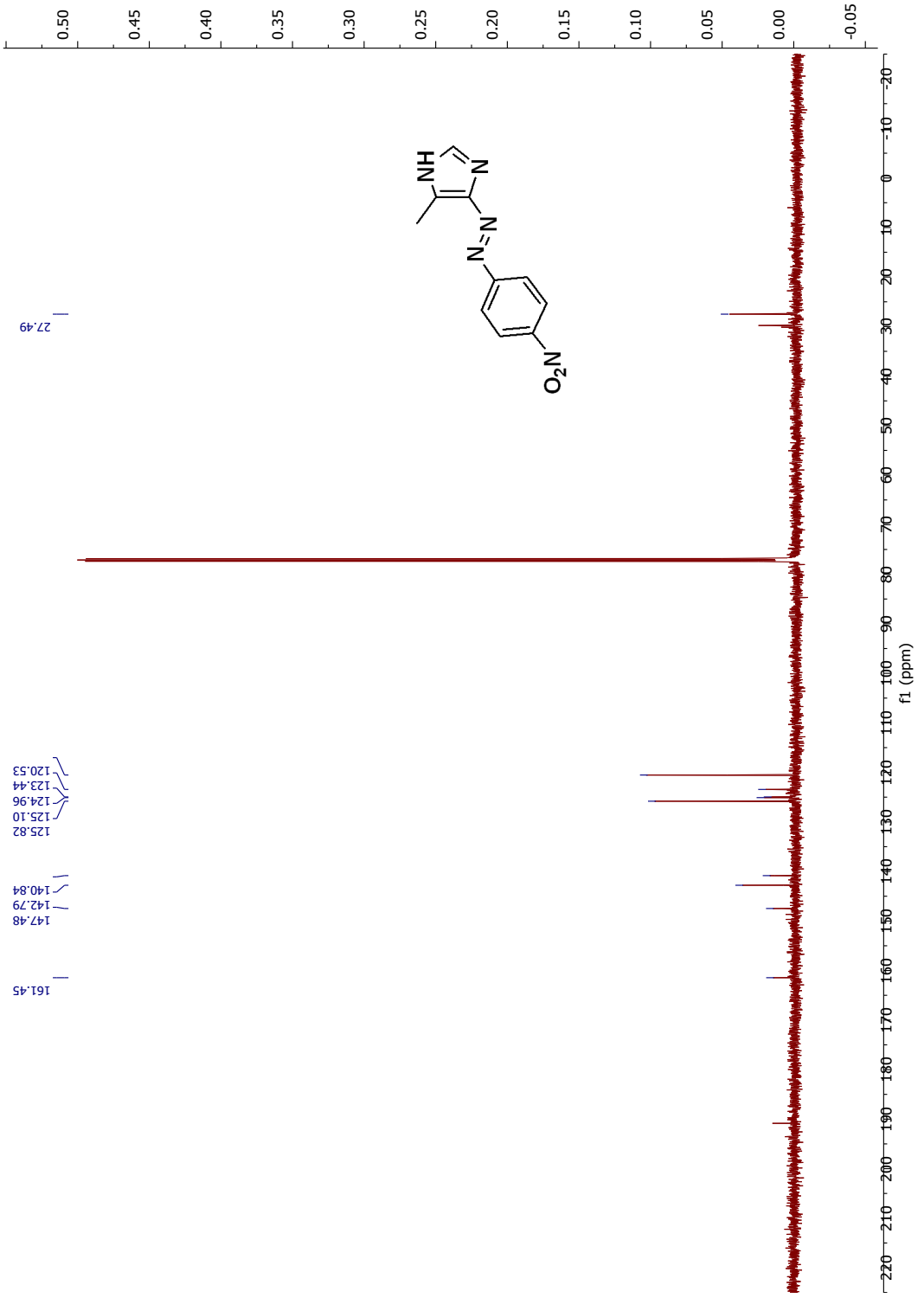
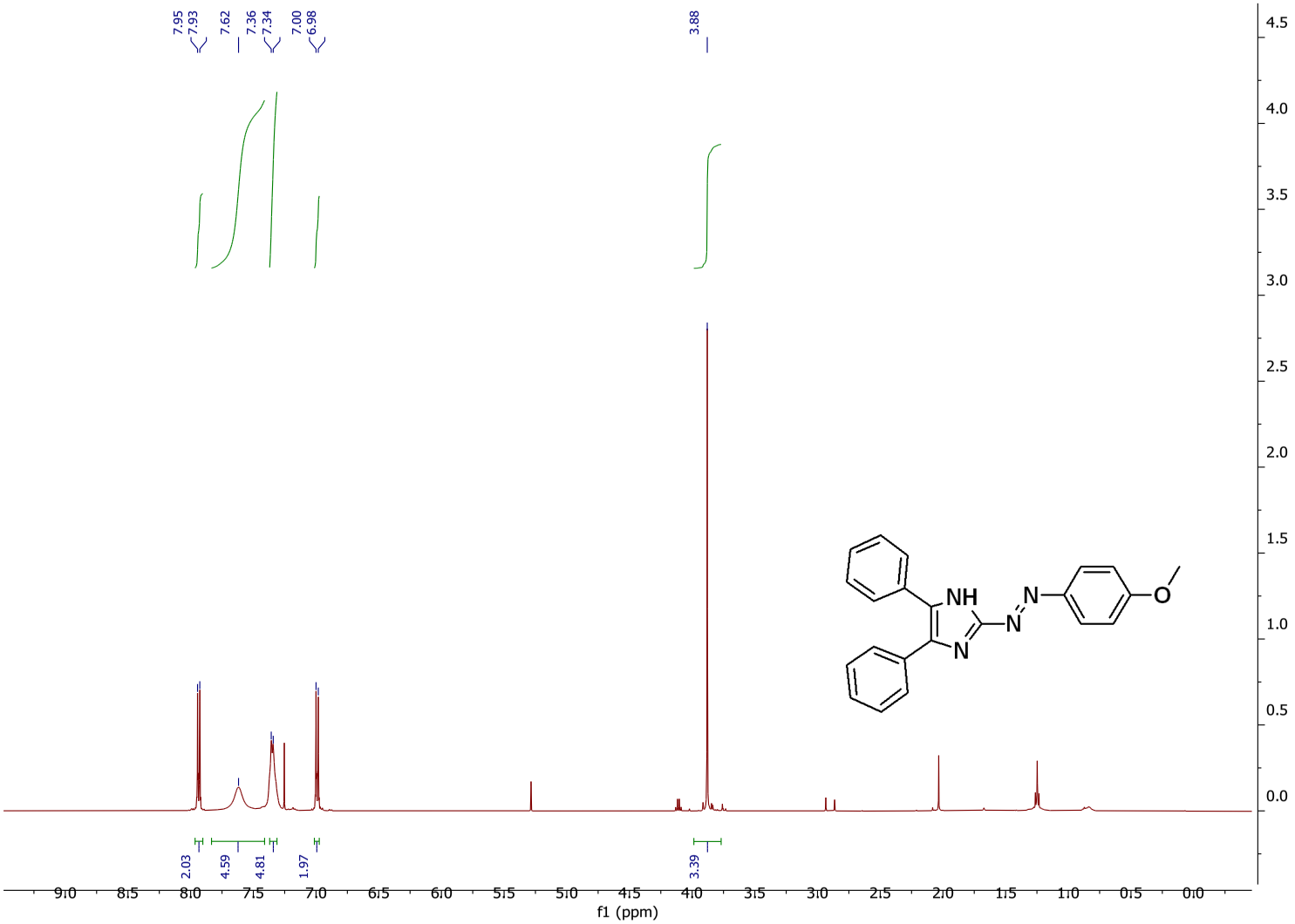
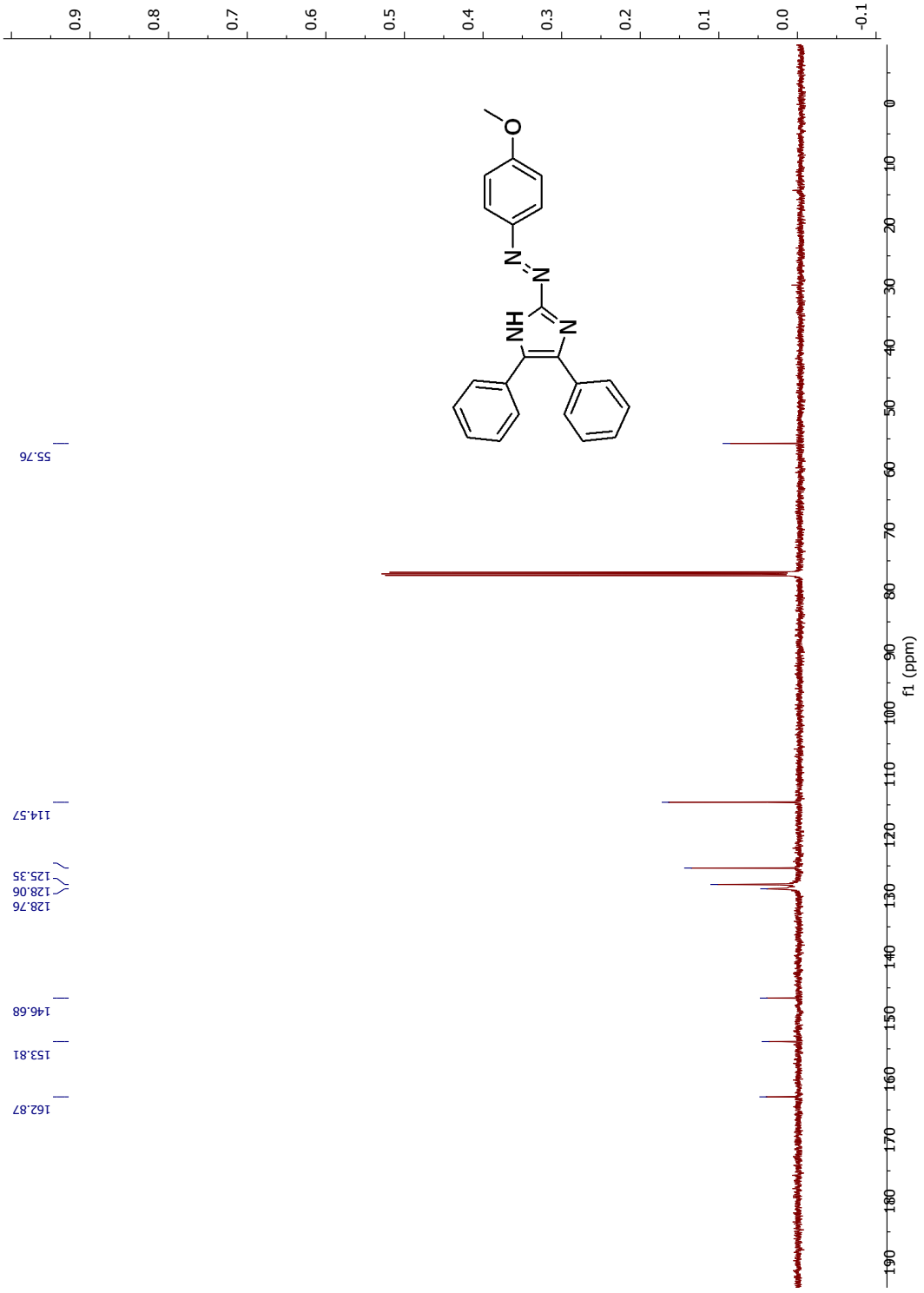
6.16
1.16
1.11
2.00
2.02
1.99

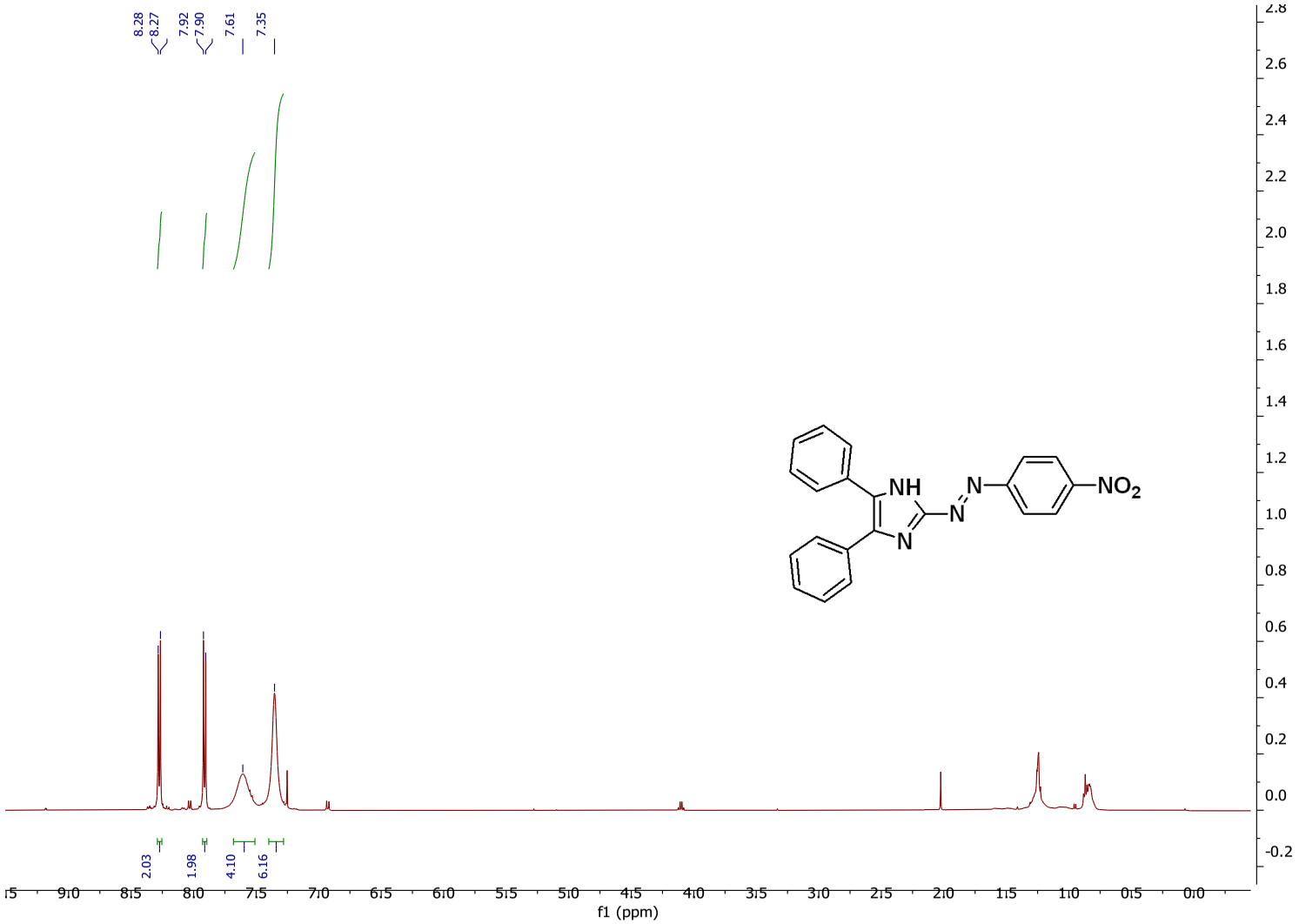

29.79
55.81
55.71
114.70
114.49
125.85
124.50
147.43
147.08
163.54
161.98
f1 (ppm)

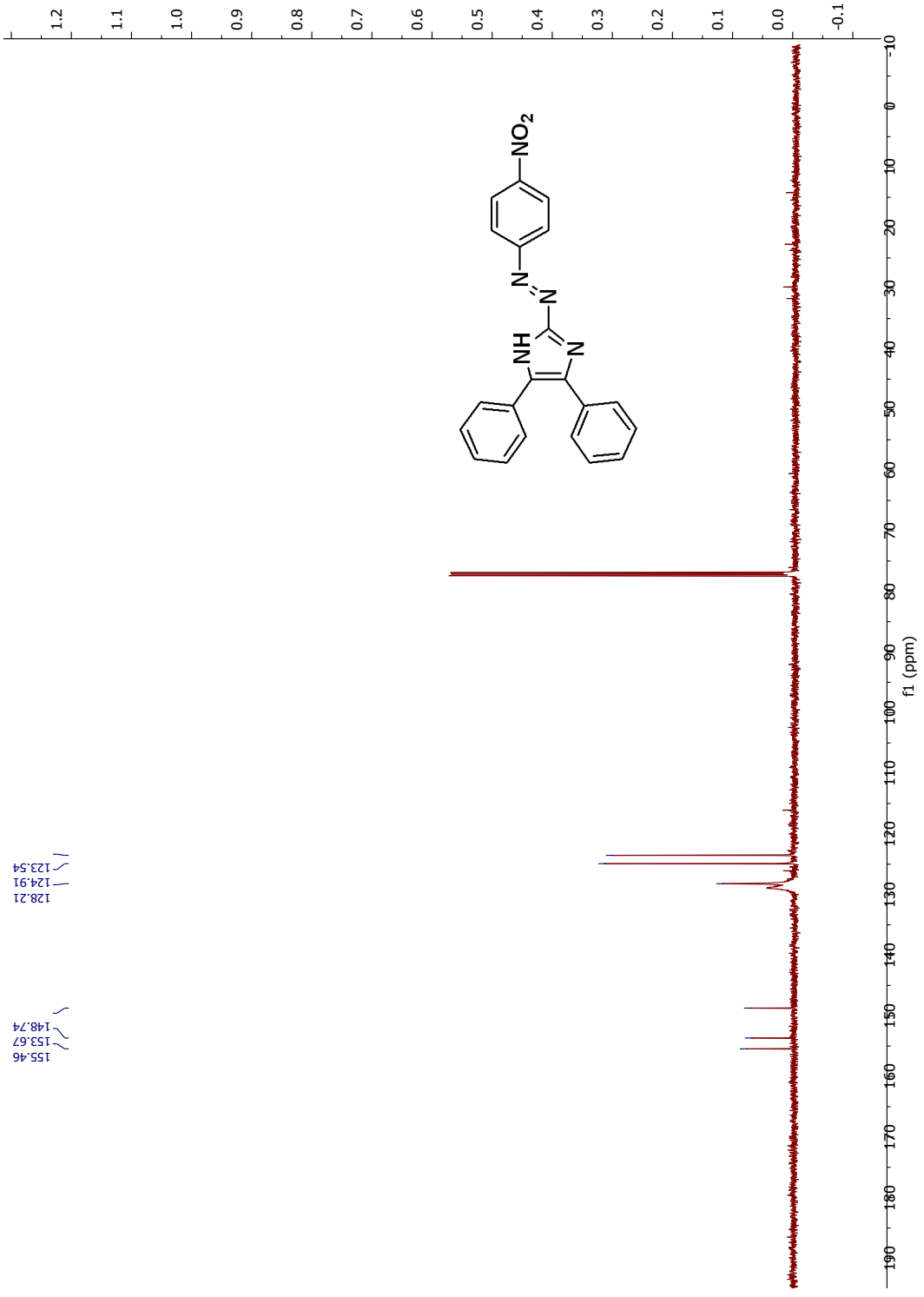

f1 (ppm)
2.75
8.79
8.45
8.43
8.01
7.99
2.95
2.00
2.13
1.00
NH
N
N
N
O2N


0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
-0.05
NH
N
N=N
O2N
27.49
120.53
123.44
124.96
125.10
125.82
140.84
142.79
147.48
161.45
f1 (ppm)


7.95
7.93
7.62
7.36
7.34
7.00
6.98
3.88
NH
N
N
N
O
2.03
4.59
4.81
1.97
3.39
f1 (ppm)


55.76
114.57
125.35
128.06
128.76
146.68
153.81
162.87
f1 (ppm)


8.28
8.27
7.92
7.90
7.61
7.35
NH
N
N
N
NO2
2.03
1.98
4.10
6.16
f1 (ppm)


155.46
153.67
148.74
128.21
124.91
123.54
f1 (ppm)

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BIOGRAPHICAL INFORMATION

Moumita Singha Roy is a native of India and was born and grew up in Nahata, a village in the state of West Bengal. She attended Calcutta University and she earned her Bachelor of Science degree from Calcutta University, W.B. India in 2006 and Master of Science degree from G.G.U. Chhattisgarh, India in 2008. She moved to Kolkata, India in April 2008 and joined the R&D team as project fellow in T.C.G. Lifesciences Limited. After serving at various positions in T.C.G. for more than 7 years, she moved to United states in Aug-2016 and joined The University of Texas at Arlington in the department of Chemistry and Biochemistry for perusing her Ph.D. studies in the field of medicinal chemistry with professor Dr. Carl John Lovely in Fall 2017. She received her Ph.D. degree from UTA in Dec-2021.