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UNIVERSITY OF CALIFORNIA,
IRVINE

Synthesis of Nodulisporic Acid Natural Products

DISSERTATION

submitted in partial satisfaction of the requirements
for the degree of

DOCTOR OF PHILOSOPHY

in Chemistry

by

Nicole Anne Godfrey

Dissertation Committee:
Assistant Professor Sergey V. Pronin, Chair
Professor Christopher D. Vanderwal
Distinguished Professor Larry E. Overman

2019

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DEDICATION

To

my parents, sister, family, and friends

for their encouragement and support.

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CURRICULUM VITAE

Nicole Anne Godfrey

Education

2014 – 2019 Ph.D. Chemistry, University of California Irvine; GPA 4.00

2010 – 2014 B.S. Chemistry, University of California Riverside; GPA 3.99

Research Experience

January 2015 – June 2019 Graduate Research Assistant, University of California Irvine, Department of Chemistry, Lab of Dr. Sergey V. Pronin

September 2012 – June 2014 Undergraduate Research Assistant, University of California Riverside, Department of Chemistry Lab of Dr. Michael C. Pirrung

June 2012 – August 2012 Intern, Celgene Corporation, Medicinal Chemistry

March 2011 – June 2012 Undergraduate Research Assistant, University of California Riverside, Lab of Dr. Gregory J. O. Beran

Publications and Posters

“A Catalytic Intermolecular Formal Ene Reaction Between Ketone-Derived Silyl Enol Ethers and Alkynes” Holmbo, S. D.*; Godfrey, N. G.*; Hirner, J. J.; Pronin, S. V. *J. Am. Chem. Soc.* **2016**, *138*, 12316–12319. (*Authors contributed equally)

“A Concise Approach Toward the Nodulisporic Acids” Godfrey, N. A.; Schatz, D. J.; Holmbo, S. D. Pronin, S. V. Presented at 2018 ACS DOC Graduate Research Symposium, July 26th 2018.

“Twelve-Step Asymmetric Synthesis of (–)-Nodulisporic Acid C” Godfrey, N. A.*; Schatz, D. J.*; Pronin, S. V. *J. Am. Chem. Soc.* **2018**, *140*, 12770–12774. (*Authors contributed equally)

Fellowships and Awards

March 2015 NSF Graduate Research Fellowship

September 2014 UC Irvine Provost Ph.D. Fellowship

June 2011 – June 2014 UC Riverside Chancellor’s Honor List

September 2010 UC Riverside Leonard Regent’s Scholarship

April 2014 ACS Division of Organic Chemistry Undergraduate Award in Organic Chemistry

June 2013 Nathaniel T. Coleman Endowed Scholarship

June 2013 Chemistry Alumni Scholarship

June 2013 UC Riverside University Honors Fellowship

June 2011, June 2012 Dr. Janet M. Boyce Memorial Endowed Fund for Women Majoring in the Sciences

June 2012 UC Riverside Award for Academic Excellence in Chemistry

June 2012 Science Circle of Awards in Excellence

June 2012 Moore-Gandolfo Memorial Scholarship in Chemistry

June 2011 UC Riverside Dean’s Summer Research Fellowship

ABSTRACT OF THE DISSERTATION

Synthesis of Nodulisporic Acid Natural Products

By

Nicole Anne Godfrey

Doctor of Philosophy in Chemistry

University of California, Irvine, 2019

Professor Sergey V. Pronin, Chair

The nodulisporic acids comprise a subclass of the paxilline indole diterpene family and express potent insecticidal activity. These natural products have been the targets of synthetic studies since their isolation due to their complex, polycyclic structures. Efficient assembly of these targets has necessitated the development of new chemical transformations to forge bonds otherwise incompatible with retrosynthetic disconnections. This thesis will describe the development of such chemical transformations, culminating in the synthesis of nodulisporic acid C in 12 steps longest linear sequence (LLS) from commercial material as well as the synthesis of an advanced intermediate *en route* to nodulisporic acid A. A convergent approach utilizing a late stage ketone α -arylation to unite the complex terpene and indenopyran fragments allowed for the brevity of the synthesis. Construction of the indenopyran was accomplished through a diastereo- and regioselective enyne cycloisomerization which afforded the desired stereochemistry and connectivity present in nodulisporic acids A and C. The strategy for the terpene fragment relied on a hydrogen atom transfer (HAT) initiated polycyclization of an α -disubstituted ketone. The synthesis of this intermediate required the selective functionalization of a ketone at the

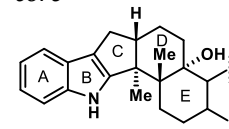
more substituted position to afford a 1,1-disubstituted alkene in an intermolecular fashion. The development of this transformation utilizing a formal ene reaction between an enoxy silane and a terminal alkyne in the presence of catalytic indium(III) bromide is also described herein. Importantly, this reaction is selective for the formation of quaternary centers even in the presence of other enolizable positions. The development of these new chemical transformations has allowed for efficient access to the most complex structural features of the nodulisporic acid family.

Chapter 1: Introduction

1.1 The Paxilline Indole Diterpenes

The paxilline indole diterpenes are a family of natural products with a complex terpene tricyclic core (CDE, Figure 1.1) and an indole containing western fragment that bears differing levels of complexity. The biological activity of these natural products is varied and includes insecticidal activity,¹ inhibition of potassium channels,² inhibition of mitosis,³ alteration of cellular lipid balance,⁴ and antimicrobial⁵ and antiviral⁶ activities. Synthetic chemists have been intrigued not only by this wide array of activity but also by the challenging scaffolds presented by even the simplest members of the family. Among the most complex members are those which contain elaborate substitution on the indole ring.

Figure 1.1: Paxilline core

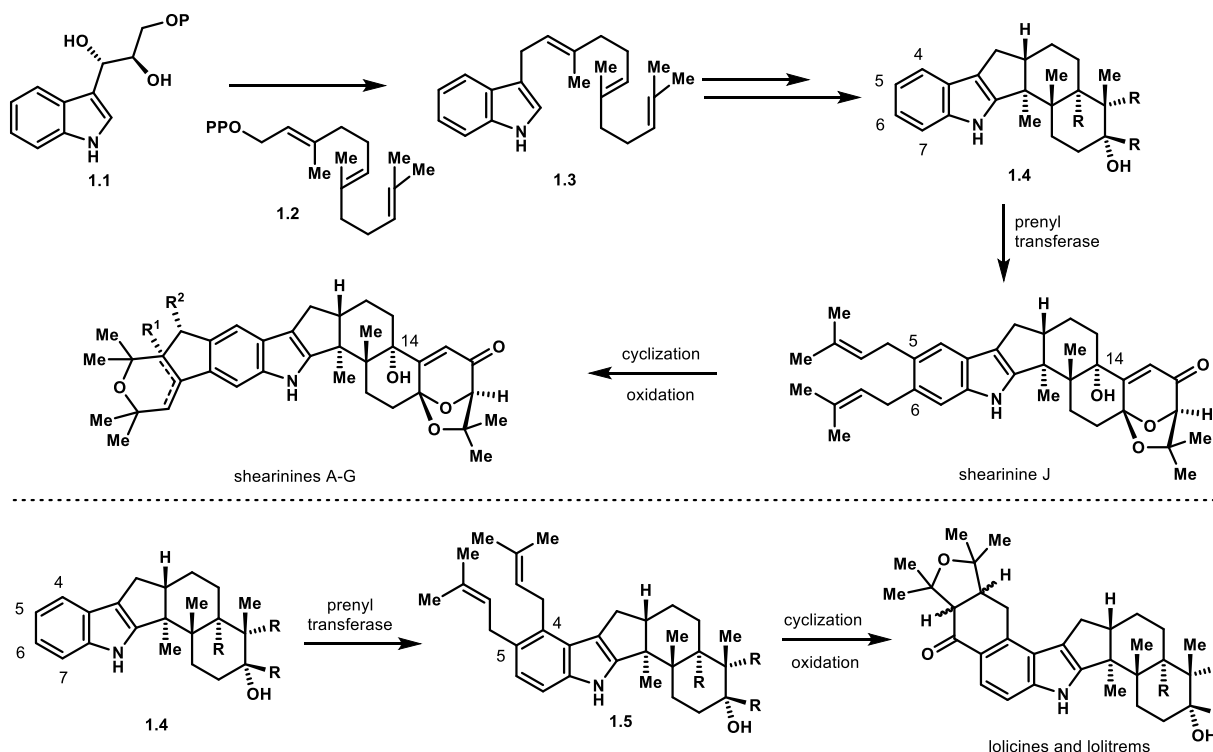


1.2 A Common Biosynthetic Origin

While it was readily accepted that the terpene fragment of the paxilline indole diterpenes arose through classical polyisoprenoid cyclizations to afford the tricyclic core, the source of the indole remained speculative until studies on nodulisporic acid A definitively revealed the source as indole-3-glycerol phosphate (**1.1**, Figure 1.2),⁷ not tryptophan as previously reported.⁸ Indole alkylation with geranylgeranylphosphate **1.2** and subsequent polycyclization and oxidation affords the eastern fragment (**1.4**). For members of the family containing highly substituted indoles, modification of the indole ring occurs after the terpene fragment has been elaborated. Prenylation followed by various selective cyclizations and oxidations gives rise to the diverse family of substituted paxilline indole diterpenes.^{7,9} For the nodulisporic acids,¹⁰ sheariniens,¹¹ and janthitrems,¹² prenylation at C5 and C6 followed by cyclization affords the (6.5.6) indenopyran ring

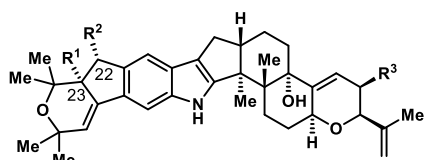
system (ie. shearinines A-G, Figure 1.2). The lolicines and lolitrems¹³ bear a tetrahydronaphthofuranone arising through prenylation at C4 and C5 followed by an alternate cyclization to afford a (5.6.6) ring system (Figure 1.2).

Figure 1.2: General biosynthetic pathway

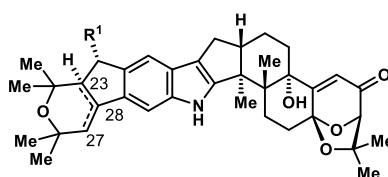


While these natural products all share similar structural features that could be targeted by a general synthetic approach, the nodulisporic acids are unique in their bioactivity. They are the only members of these five subgroups that are not tremorgenic in mammals. This lack of adverse reactivity stems from the absence of the C14 tertiary alcohol present in the other members (see 1.5, Figure 1.2).¹⁴ Due to this and other promising bioactivity, the nodulisporic acids have been the focus in much of the synthetic literature.

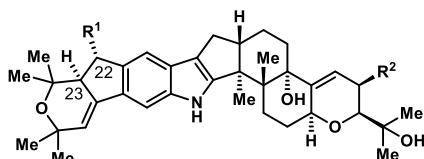
Figure 1.3: Indole substituted paxilline indole diterpenes



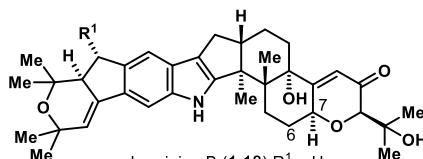
janthitrem B (1.6) R¹ = H, R² = R³ = OH
 janthitrem C* (1.7) R¹ = R² = H, R³ = OH
 JBIR-137 (1.8) R¹ = R² = $\Delta^{22,23}$, R³ = OH
 *stereochemistry at C23 undefined



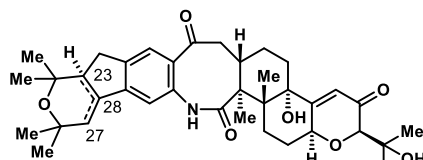
shearinine A (1.13) R¹ = H, $\Delta^{27,28}$
 shearinine D (1.14) R¹ = OH, $\Delta^{27,28}$
 shearinine E (1.15) R¹ = OMe, $\Delta^{27,28}$
 shearinine F (1.16) R¹ = OMe, $\Delta^{23,28}$
 shearinine G (1.17) R¹ = oxo, $\Delta^{23,28}$



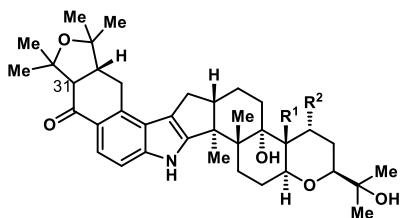
janthitrem A (1.9) C₃₇H₄₇NO₆ - structure unknown
 janthitrem E* (1.10) R¹ = R² = OH
 janthitrem F* (1.11) R¹ = R² = OAc
 janthitrem G* (1.12) R¹ = H, R² = OAc
 *stereochemistry at C22 and C23 undefined



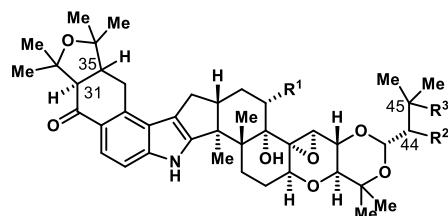
shearinine B (1.18) R¹ = H
 shearinine L (1.19) R¹ = H, $\Delta^{6,7}$
 shearinine M (1.20) R¹ = OH, $\Delta^{6,7}$



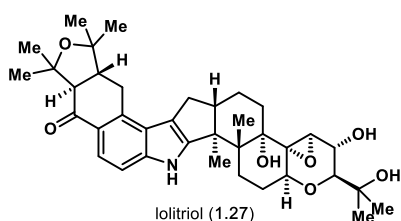
shearinine C and I (1.29) $\Delta^{27,28}$
 shearinine H (1.30) $\Delta^{23,28}$



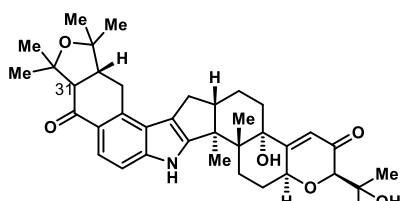
lolicine A (1.23) R¹ = Me, R² = OH
 lolicine A 11-O-propionate (1.24) R¹ = Me, R² = OC(O)Et
 lolicine B (1.25) R¹ = CHO, R² = OH
 lolicine B 11-O-propionate (1.26) R¹ = CHO, R² = OC(O)Et
 *Stereochemistry at C31 undefined



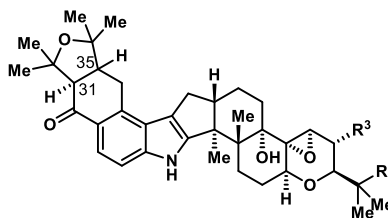
lolitrem A* (1.31) *trans*^{31,35}, R¹ = H, R² = R³ = epoxide
 lolitrem B (1.32) *trans*^{31,35}, R¹ = H, R² = R³ = $\Delta^{44,45}$
 lolitrem C (1.33) *trans*^{31,35}, R¹ = R² = R³ = H
 lolitrem F (1.34) *cis*^{31,35}, R¹ = H, R² = R³ = $\Delta^{44,45}$
 lolitrem H** (1.35) R¹ = OH, R² = R³ = $\Delta^{44,45}$
 *stereochemistry at C44 undefined
 **stereochemistry at C31 and C35 undefined



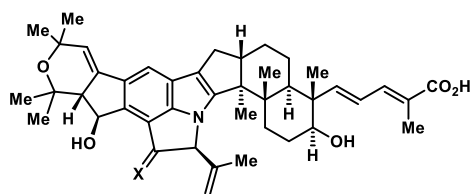
lolitriol (1.27)



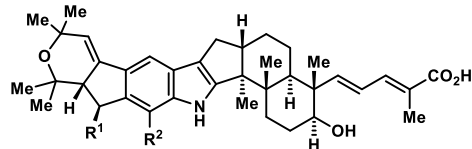
lolilline* (1.28)
 *stereochemistry at C31 undefined



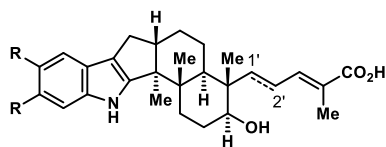
lolitrem E (1.36) *trans*^{31,35}, R¹ = OH, R² = OCH₂CH=CMe₂
 lolitrem N (1.37) *cis*^{31,35}, R¹ = R² = OH
 lolitrem M (1.38) *trans*^{31,35}, R¹ = H, R² = OH
 lolitrem N 10-O-propionate (1.39) *cis*^{31,35}, R¹ = OH, R² = OC(O)Et
 31-epi-lolitrem N (1.40) *trans*^{31,35}, R¹ = R² = OH



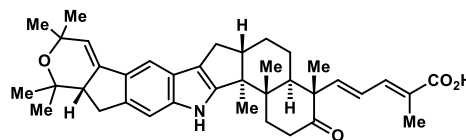
nodulisporic acid A (1.41) X = O
nodulisporic acid B (1.42) X = H₂



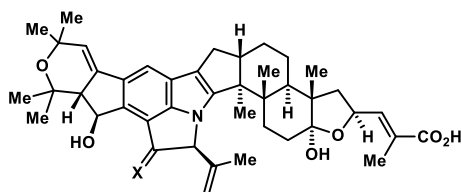
nodulisporic acid C (1.43) R¹ = OH; R² = CH₂=CHCMe₂
nodulisporic acid D (1.44) R¹ = R² = H



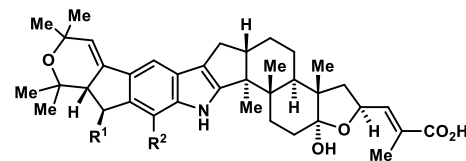
nodulisporic acid E (1.45) R = CH₂=CHCMe₂, Δ^{1',2'}
nodulisporic acid F (1.46) R = H



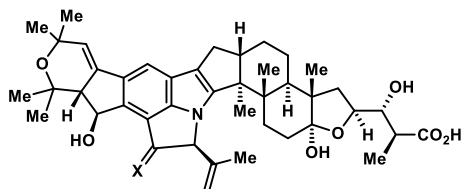
nodulisporic acid D₃ (1.47)



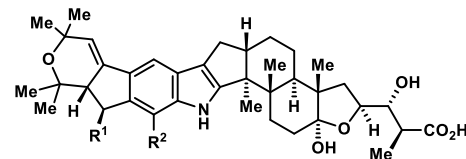
nodulisporic acid A₁ (1.48) X = O
nodulisporic acid B₁ (1.49) X = H₂



nodulisporic acid C₁ (1.50) R¹ = OH; R² = CH₂=CHCMe₂
nodulisporic acid D₁ (1.51) R¹ = R² = H



nodulisporic acid A₂ (1.52) X = O
nodulisporic acid B₂ (1.53) X = H₂



nodulisporic acid C₂ (1.54) R¹ = OH; R² = CH₂=CHCMe₂
nodulisporic acid D₂ (1.55) R¹ = R² = H

1.3 The Nodulisporic Acids

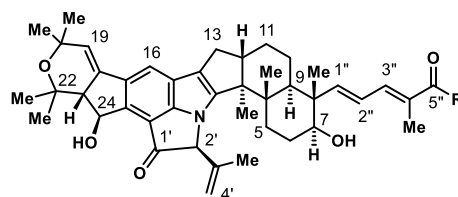
The nodulisporic acids (A–F, Figure 1.3) comprise a subclass of the paxilline indole diterpene family expressing potent activity against glutamate-gated chloride ion channels in invertebrates at levels comparable to ivermectin. This results in the disruption of neuronal ion channels and the eventual death of the insect. Unlike ivermectin, which also targets mammalian glycine- and GABA-gated chloride ion channels, the nodulisporic acids exhibit exclusive activity in invertebrates with no observed detrimental effects in mammals. This impressive safety profile makes the nodulisporic acids promising targets

for the development of medications to prevent transmission of vector-borne diseases such as malaria and Zika virus or for the treatment of fleas and ticks on domestic animals.

The nodulisporic acid subtypes (NsA A–F, A₁–D₁, A₂–D₂, and D₃) contain differing levels of oxidation on the chain off of C8 (see Table 1.1 for numbering). NsA A–F contain a dienoid acid chain (**1.41**–**1.46**, Figure 1.3). NsA A₁–D₁ contain additional oxidation at C7 which has cyclized to form a tetrahydrofuran ring (**1.48**–**1.51**). NsA A₂–D₂ contain the tetrahydrofuran ring with added oxidation of the enoic acid to afford a β -hydroxy carboxylic acid (**1.52**–**1.55**). NsA D₃ contains the unfunctionalized dienoid acid chain with the alcohol at C7 oxidized to the ketone (**1.47**).

The most potent member of the nodulisporic acids, NsA A, is also the most structurally complex. It contains the tricyclic terpene core of the other members, the indenopyran of NsA B and C, the additional highly strained five membered ring of NsA B, as well as added oxidation on the strained ring. Isolated in 1997 by Ondeyka and co-workers,¹⁵ NsA A has been the target of both structure-activity relationship (SAR) probes as well as synthetic explorations. A series of analogs (Table 1.1) were synthesized from the parent NsA A which had up to two orders of magnitude increase in activity in the flea feeding assay (Entries 8 and 12), with mono- and disubstituted amides affording the largest increases in potency. However, further exploration of chemical modifications to NsA A

Table 1.1: Nodulisporic acid A and nodulisporamide activity in flea assay



Entry	R	LD ₉₀ (ppm)
1	OH	1
2	OCH ₂ CH ₂ OCH ₂ CH ₂ OH	0.1
3	NHCH ₂ CH ₂ OH	0.5
4	NH ₂	0.1
5	NHMe	0.1
6	NH- <i>n</i> -Hexyl	0.5
7	NHCH ₂ Ph(4-Cl)	0.1
8	NHC(Me) ₂ C(O)NMe ₂	0.01
9	NMe ₂	0.1
10	N(Et) <i>n</i> Pr	0.1
11	<i>N</i> -1-[(4-CO ₂ Et)Piperazinyl]	0.1
12	<i>N</i> -1-[(4-SO ₂ Me)Piperazinyl]	0.01

revealed that much of the molecule was non-permissive in that any modification decreased the activity.¹ This includes altering the oxidation states at C24, C1', and C7 as well as modifications of the dienoic acid chain. Importantly, elimination of the acid labile secondary alcohol on the indenopyran decreased activity by an order of magnitude. Preservation of this alcohol provided many challenges during attempts to synthesize the western half of NsA A, B, and C (*vide infra*).

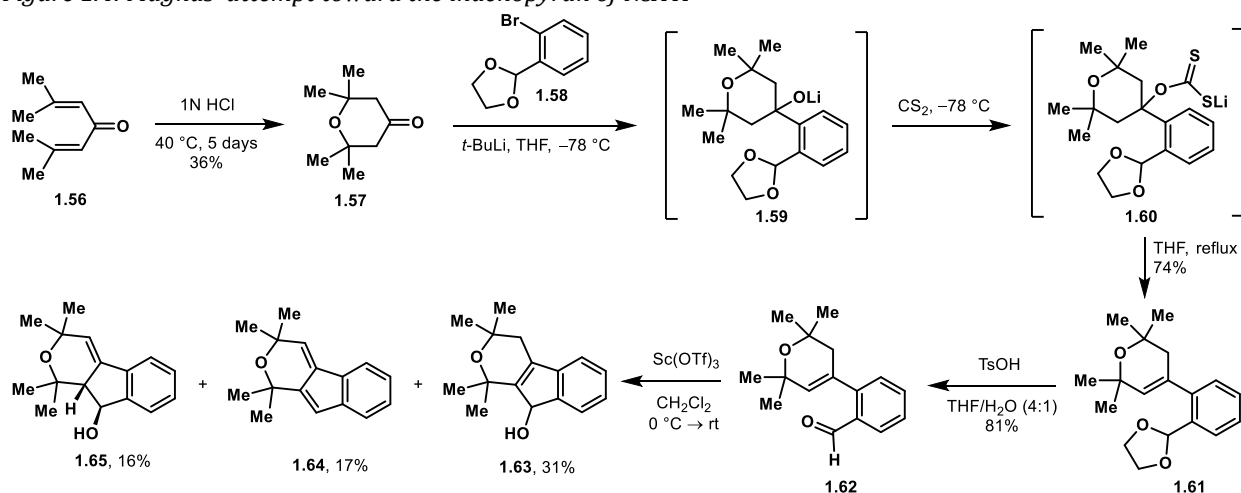
1.4 Previous Synthetic Work

1.4.1 Progress Toward and Completed Syntheses of the Nodulisporic Acids

While there has been a significant amount of synthetic work toward the terpene fragment of the paxilline indole diterpenes with many completed syntheses,¹⁶ there have been fewer successful reports toward the western fragments of the nodulisporic acids, shearinines, janthitrems, lolicines, and lolitrems. The complex substituted indoles have attracted synthetic chemists since the early discovery of the nodulisporic acids, with the first report from Magnus¹⁷ working toward the indenopyran of NsA A.

Starting with phorone, treatment with HCl afforded γ -lactone **1.57** (Figure 1.4). Addition of the aryllithium derived from **1.58** followed by trapping with carbon disulfide and heating to reflux afforded dihydropyran **1.61**. Treatment with a variety of Lewis acids to close the final ring yielded several products, with the best conditions affording 16% of the desired secondary alcohol **1.65**, 17% of diene **1.64**, and 31% of isomerized dihydropyran **1.63**. Optimization attempts revealed methods for the selective formation of **1.64** or **1.63**; however, selective formation of the desired product remained elusive. This was the first report to highlight one of the main challenges in the synthesis of NsA A, which is the lability of the benzylic alcohol.

Figure 1.4: Magnus' attempt toward the indenopyran of NsA A



Following Magnus' initial report, the field was dominated by Smith for the next decade and a half, culminating in several generations of strategies and the successful syntheses of NsA B, C,¹⁸ D,¹⁹ and F.²⁰ Smith's first generation route toward the indenopyran of NsA A utilized an enantioselective metalloenamine addition into aldehyde **1.68** (Figure 1.5) to set the stereochemistry of the secondary alcohol. Protection and vinyl triflate formation followed by the Shibasaki–Mori protocol for tandem transmetallation and cyclization closed the final ring to form **1.74** in 11 steps from commercial material.²¹

Figure 1.5: Smith's first generation route to the indenopyran

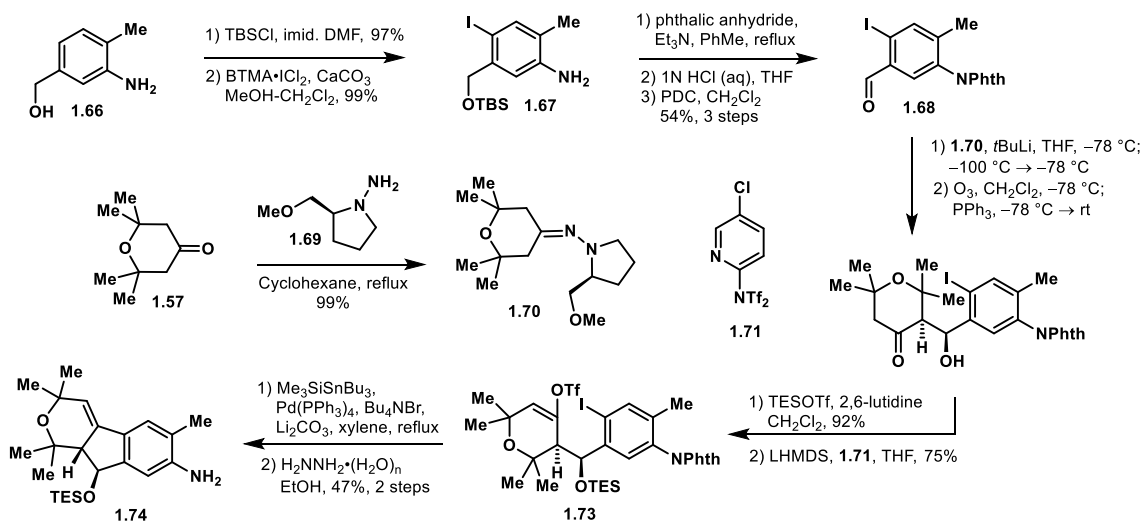
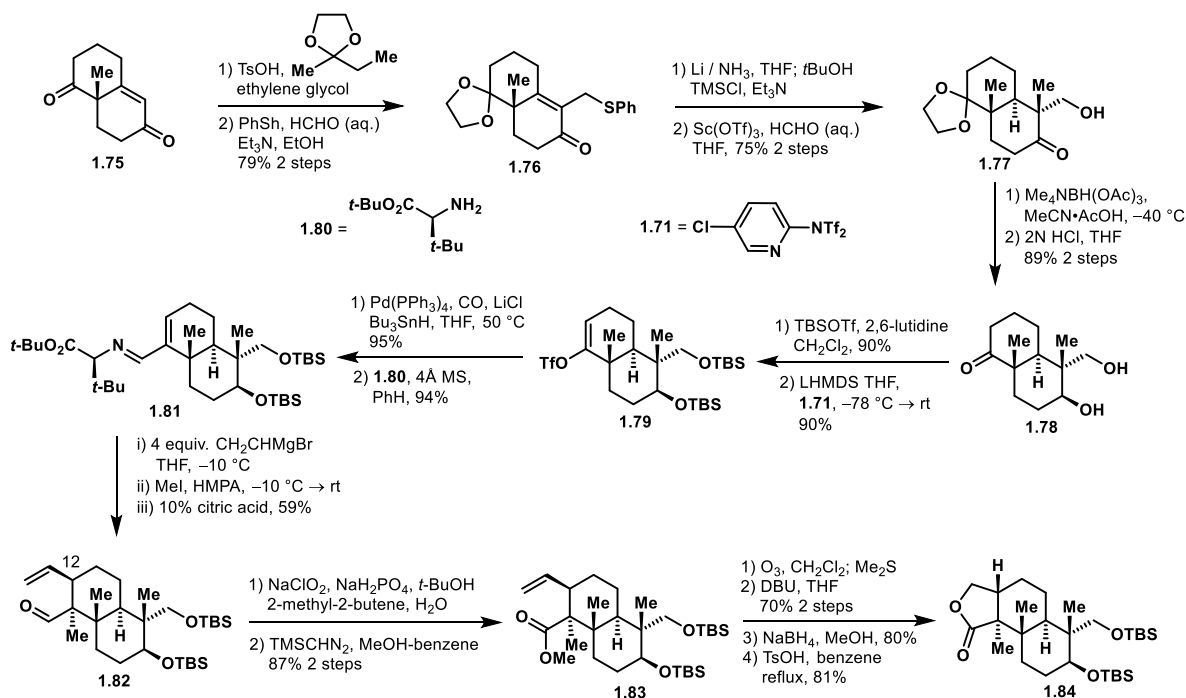
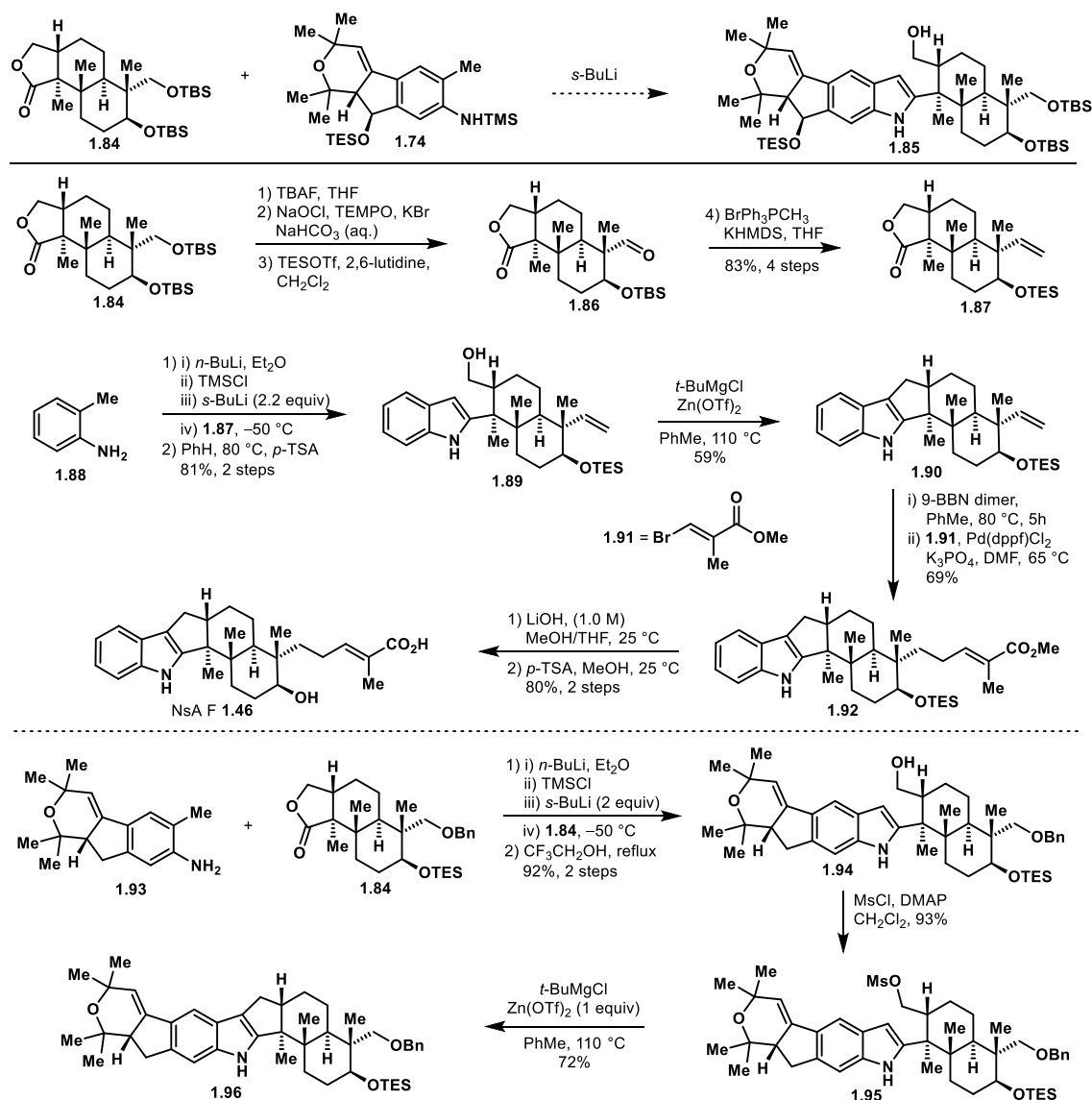


Figure 1.6: Smith's second generation approach toward the terpene fragment



Smith's first generation route toward the terpene fragment started with Wieland-Miesher ketone and took a total of 23 steps to the elaborated fragment. In the same report, Smith detailed his second generation approach which aimed to solve the step count and efficiency problems of the first. Starting again with Wieland-Miesher ketone, ketylation and Kirk-Petrow (phenylthio)methylation afforded enone **1.76**. Reduction with Li/NH₃ followed by alkylation with aqueous formaldehyde, ketone reduction, and ketal hydrolysis afforded diol **1.78**. Alcohol protection, vinyl triflate formation, palladium carbonylative coupling, and condensation with **1.80** afforded the substrate for Smith's key step. Koga three component conjugate addition-alkylation and hydrolysis delivered aldehyde **1.82** in 59% yield with the undesired stereochemistry at carbon 12. The sequence was concluded with oxidation and methylation of aldehyde **1.82** followed by ozonolysis, epimerization, reduction, and lactone formation to deliver **1.84** in a total of 17 steps from Wieland-Miesher ketone.²²

Figure 1.7: Smith's first generation coupling strategy and application to NsA F and the core of NsA D



In his first generation coupling approach, Smith envisioned uniting the two fragments utilizing a tactic from his synthesis of penitrem D²³ (Figure 1.7). Double deprotonation of the benzylic methyl and the TMS protected aniline of indenopyran **1.74** followed by addition of lactone **1.84** would lead to acylation and hetero-Peterson olefination to form indole **1.85**. Indole alkylation of the resulting primary alcohol would close the final five membered ring. Unfortunately, attempted application of this strategy

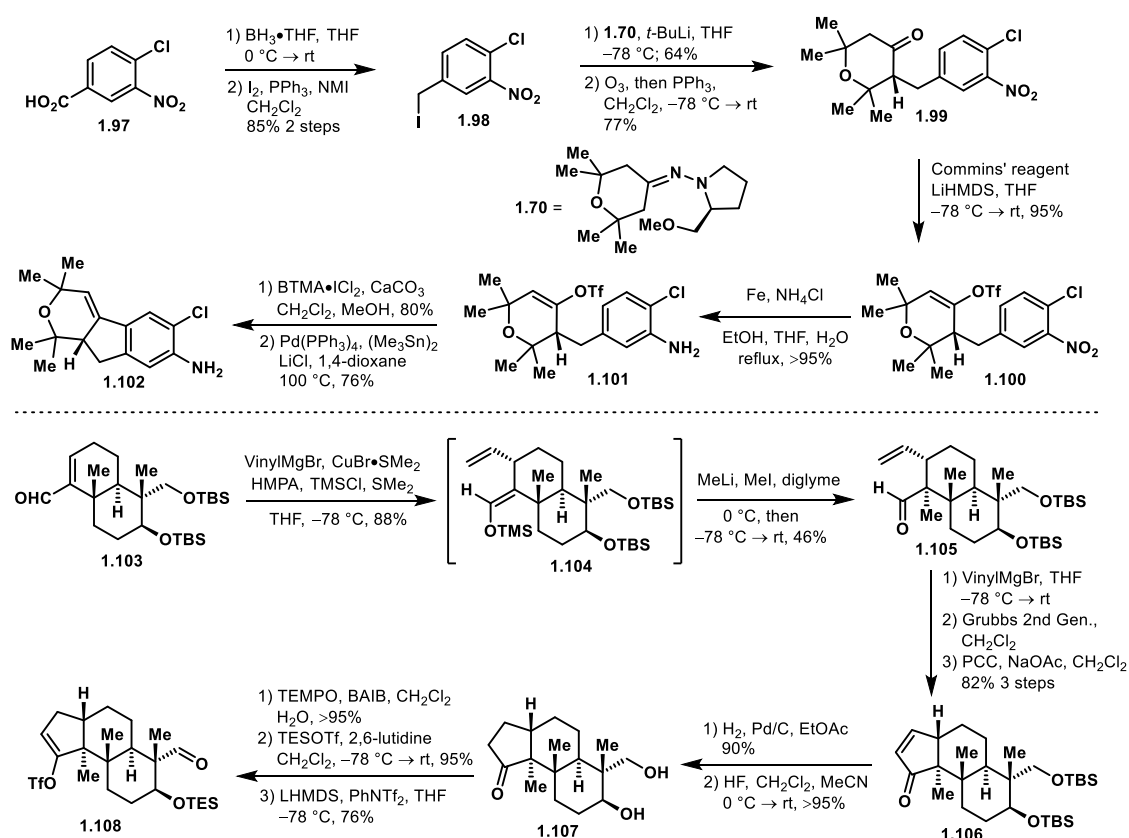
under various conditions resulted in elimination of the benzylic alcohol following deprotonation of the aniline. Attempts to work around this problem ultimately failed and the indole could only be forged with elimination of the benzylic alcohol.²⁴

While this strategy was unable to produce NsA A or B, Smith was successful in using this approach to synthesize NsA F,²⁵ which lacks any additional substitution on the indole, and the core of NsA D,²⁶ which lacks the secondary benzylic alcohol. Starting with lactone **1.84**, deprotection and oxidation of the primary alcohol followed by TES-protection of the secondary alcohol afforded aldehyde **1.86** (Figure 1.7). The coupling partner was completed with a Wittig olefination. Formation of indole **1.89** with 2-methylaniline proceeded in high yield using the acylation and hetero-Peterson olefination strategy. Closure of the remaining five-membered ring followed by installation of the enoic acid side chain delivered NsA F **1.46**. The core of NsA D was similarly constructed from indenopyran **1.93** which was synthesized in the same way as **1.74** (Figure 1.5) with an enantioselective alkylation replacing the addition into aldehyde **1.68**. Coupling with lactone **1.84** and closure of the five-membered ring afforded the heptacyclic core of NsA D **1.96** (Figure 1.7).

Smith recognized that this strategy could not be applied to the entire family of nodulisporic acids due to the elimination of the benzylic alcohol and set out to redesign the coupling strategy. Keeping with a convergent approach featuring a late stage indole formation, Smith's second generation approach sought to bring together two elaborated fragments in a Barluenga indolization.¹⁹ To accommodate this approach, Smith modified his synthesis of the indenopyran slightly to substitute the arylmethyl for arylchloride **1.102** (Figure 1.8); however the overall Ender's alkylation strategy remained the same. The route to the tricyclic terpene fragment was also altered so that the five membered ring on

the terpene core was formed before the fragment coupling step. To achieve this, enal **1.103** from the previous synthesis of NsA F²⁵ was treated with vinylmagnesium bromide in the presence of copper(I) iodide followed by trapping of the enolate with TMSCl (Figure 1.8). Methylation of enoxysilane **1.104** afforded aldehyde **1.105**. Importantly, this new conjugate addition–alkylation sequence afforded the desired stereochemistry at both centers. Vinylmagnesium bromide addition into the aldehyde followed by Grubbs ring-closing metathesis and oxidation of the secondary alcohol afforded enone **1.106**. A series of redox and functional group manipulations delivered vinyl triflate **1.108**.

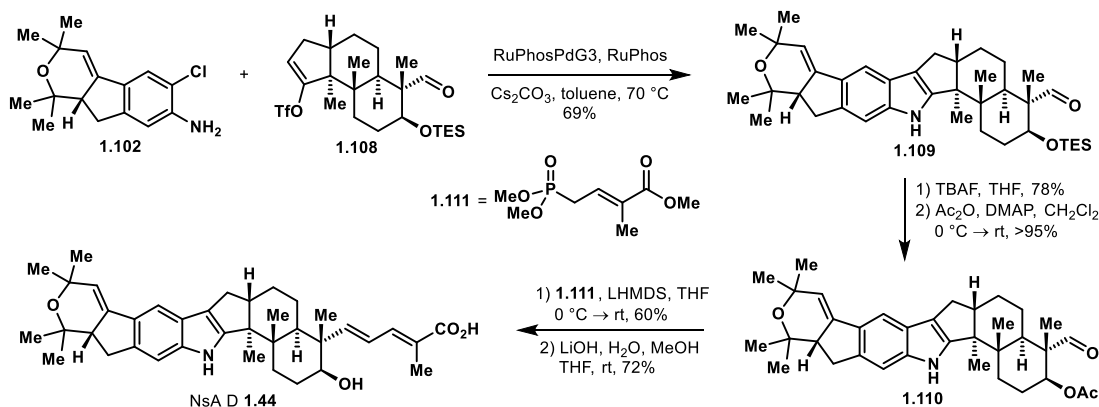
Figure 1.8: Smith's revised fragment syntheses



With chloroaniline **1.102** and vinyltriflate **1.108** in hand, Smith turned his efforts toward the fragment coupling (Figure 1.9). Treatment of these fragments with Buchwald's 3rd generation RuPhosPd precatalyst effected a Buchwald-Hartwig coupling with the

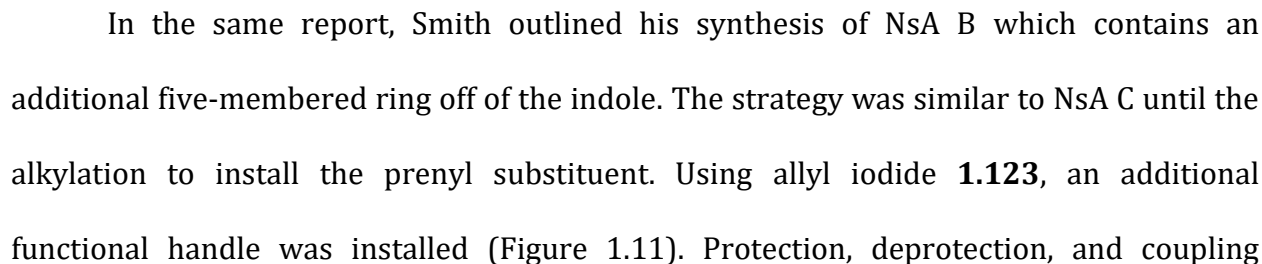
aniline, followed by intramolecular Heck coupling with the aryl chloride to afford indole **1.109** in good yield. The TES protecting group was replaced with an acyl group to permit HWE olefination. Global deprotection delivered NsA D in 24 LLS from Wieland–Miesher ketone.¹⁹

Figure 1.9: End stage synthesis of NsA D



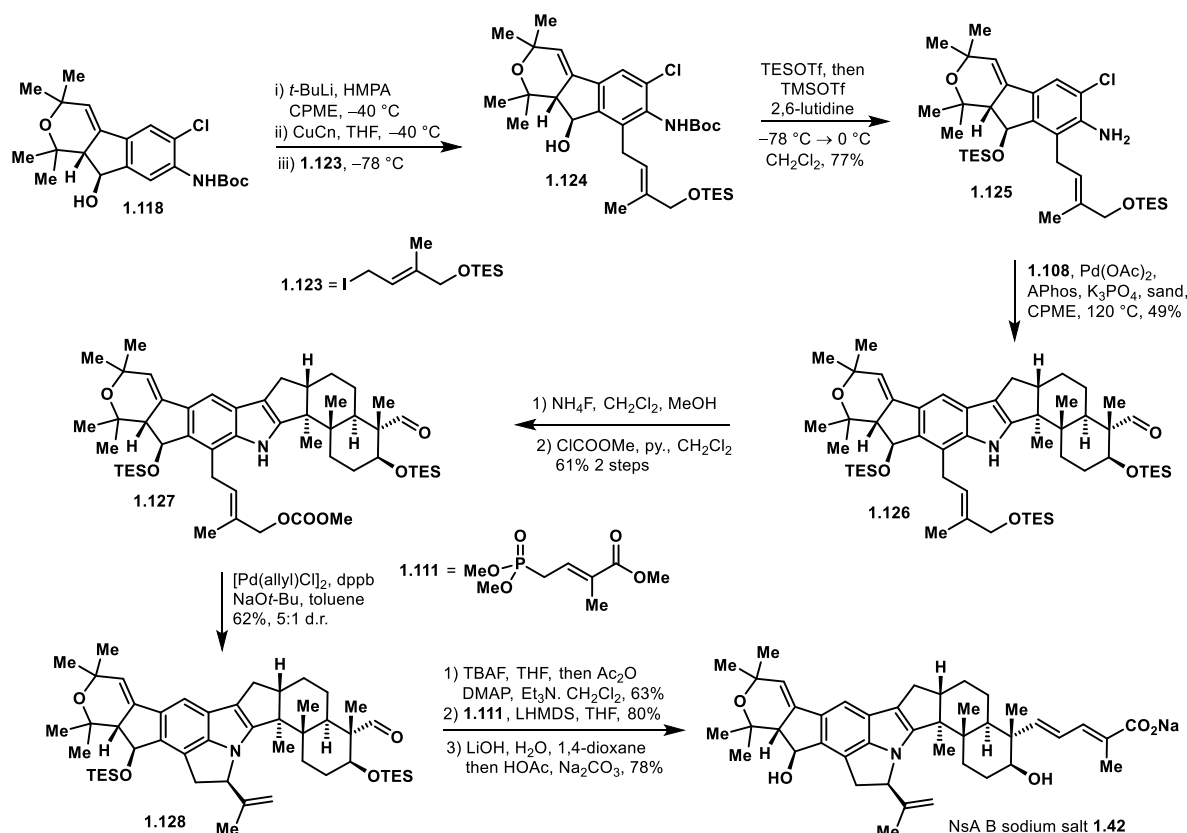
With a successful synthesis of NsA D in hand, Smith turned his attention toward more complex members of the family. NsA C is similar in structure to NsA D with the additional benzylic alcohol and a prenyl substituent off of the aromatic ring. The strategy for this natural product was much the same as for the previous synthesis (Figure 1.10). Formation of the indenopyran again utilized an enantioselective addition into aldehyde **1.114**. Instead of using the tandem stannylation–Stille coupling strategy, Smith utilized a Nozaki–Hiyama–Kishi reaction to eliminate the need for toxic tin reagents without affecting the step count. Protection of the secondary alcohol and elimination of the tertiary alcohol formed the desired alkene (**1.117**), and subsequent deprotection afforded the substrate for Smith’s next key step. A chemoselective trianion alkylation reaction installed the prenyl substituent in the desired position (**1.120**). Concomitant TES-protection and Boc-deprotection delivered the substrate for the coupling reaction. Subjecting chloroaniline

Figure 1.10: Smith's synthesis of NsA C



proceeded as in NsA C to afford indole **1.126**. Selective deprotection of the primary alcohol followed by carbamate formation furnished the substrate for Tsuji–Trost allylation to form the five membered ring. Allylation proceeded in good yield with 5:1 d.r. and subsequent protecting group exchange followed by HWE olefination and global deprotection delivered NsA B **1.42**.¹⁸

Figure 1.11: Smith's synthesis of NsA B

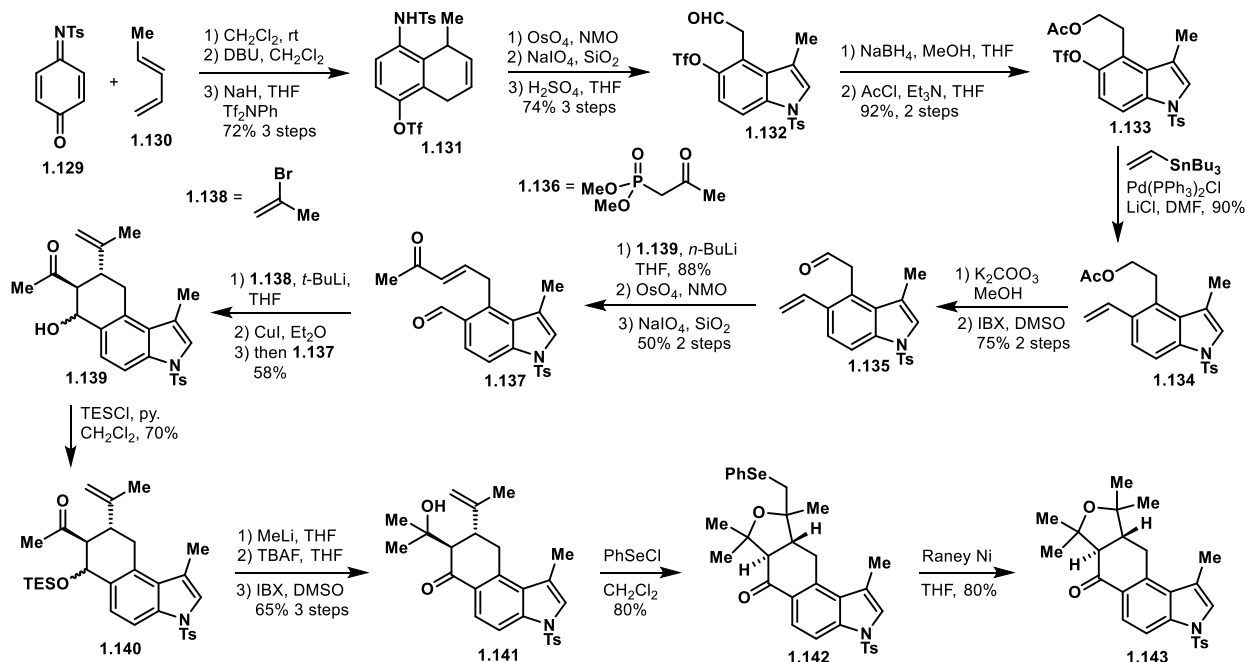


1.4.2 Progress Toward the Lolicines and Lolitrems

While the lolicines and lolitrems bear differing western halves compared to the nodulisporic acids, shearinines, and janthitrems, all result from the cyclization and oxidation of two prenyl substituents off of the indole ring. While the nodulisporic acids have received the most attention in the literature due to their promising bioactivity, a comparison of synthetic routes is still informative.

The sole report comes from Kerr²⁷ in 2006 detailing a synthesis of the western half of the lolicines and lolitrems (Figure 1.12). A Diels–Alder cycloaddition followed by aromatization and triflation afforded **1.131**, the substrate for indole formation. Dihydroxylation followed by oxidative cleavage and condensation with the aniline produced indole **1.132** in good yield over three steps. Reduction of the newly formed aldehyde and acylation delivered the substrate for Stille coupling to form indole **1.134**. Saponification and oxidation afforded aldehyde **1.135** which was then subjected to HWE olefination, dihydroxylation, and oxidative cleavage. A tandem conjugate addition–aldol sequence closed the six-membered ring and set the *trans* stereochemistry present in the natural products (**1.139**). Oxidation of the newly formed alcohol and closure of the final ring proceeded in four steps, with a Raney nickel reduction delivering the fully elaborated western half of the lolicines and lolitrems (**1.143**) in 21 steps.

Figure 1.12: Kerr's synthesis of the western half of the lolicines and lolitrems



1.5 Summary

The paxilline indole diterpenes are a class of natural products with complex structures and varied biological activities. The nodulisporic acid, shearinine, janthitrem, lolicine, and lolitrem subsets share a common biosynthetic pathway wherein the cyclization and oxidation of two prenyl substituents off of the indole forms the complex western halves. Because of these and additional similarities in the terpene halves, it is reasonable to imagine a common synthetic route that could diverge to create each unique substitution pattern. Thus far, most of the literature revolves around the nodulisporic acids due to their promising insecticidal activity.

While Smith and Kerr were successful in synthesizing the complex western halves of the nodulisporic acids and the lolicines and lolitrems, respectively, with Smith's work culminating in successful syntheses of NsA B, C, D, and F, there remains room for improvement. These syntheses built up the western halves in a stepwise manner, leading to high step counts and low efficiency. Smith's strategy has evolved only marginally since his initial report in 2001, with efforts focusing on the fragment coupling strategy instead. Neither Magnus, Smith, nor Kerr took advantage of a biosynthetically inspired polycyclization to increase the efficiency of their syntheses and relied instead on known chemistry to build the western fragments.

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Chapter 2: Nodulisporic Acid C

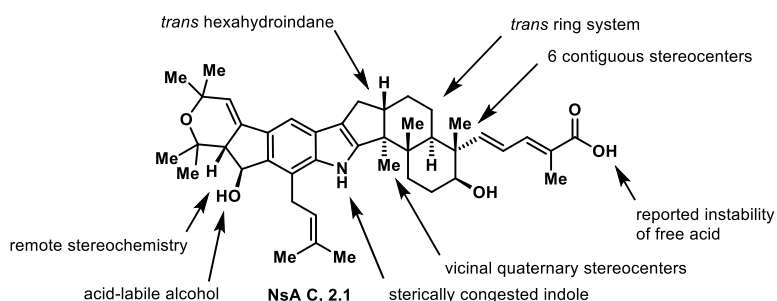
2.1 Synthetic Planning

2.1.1 Synthetic Challenges

NsA C (**2.1**, Figure 2.1) presents many synthetic challenges that were highlighted in the work of Magnus and Smith (*vide supra*). These challenges include, on the indenopyran half, remote stereochemistry, an acid labile alcohol, and a strained indole. On the terpene fragment, an all *trans* ring system

contains a *trans* hexahydroindane and six contiguous stereocenters including vicinal quaternary stereocenters.

Figure 2.1: NsA C synthetic challenges



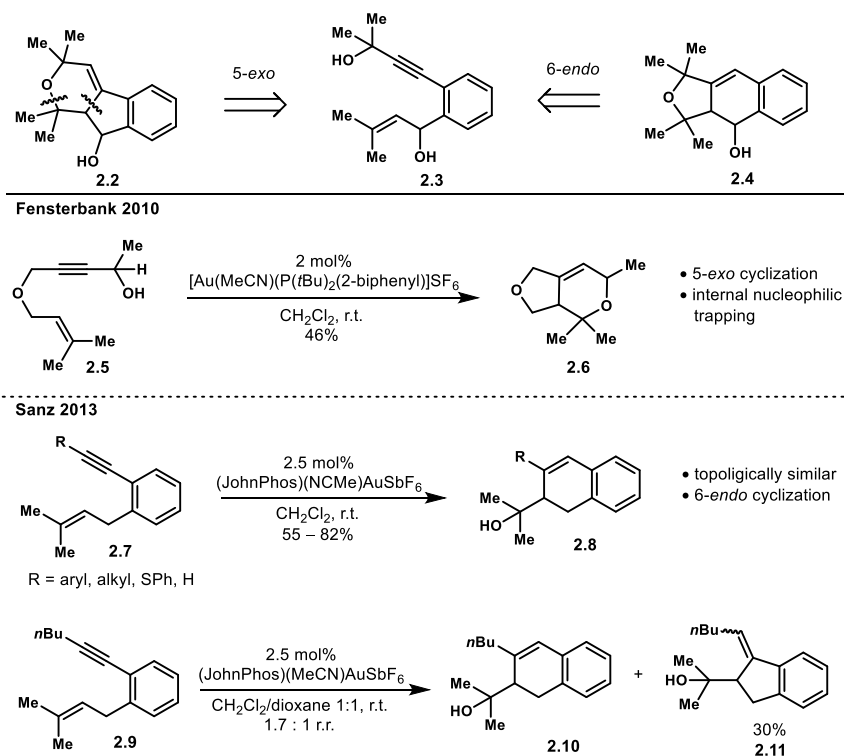
2.1.2 Indenopyran Formation

While replicating the prenyl cyclizations and oxidations that nature achieves exactly was outside of our ability, we believed we could design a system that would bias a polycyclization toward formation of the desired ring system with the oxidation pre-installed. We imagined a regio- and diastereoselective enyne cycloisomerization could allow us to build the desired indenopyran.

Enyne cycloisomerizations are well known with a variety of possible regio- and stereochemical outcomes. To forge the desired bonds, we imagined building an internal aryl-substituted alkyne with an allylic alcohol pendent on the aromatic ring (**2.3**, Figure 2.2). A 1,6-enyne cycloisomerization could then afford the entire tricyclic indenopyran framework with the benzylic alcohol in place (**2.2**). 1,6-Enyne cycloisomerizations of this type can proceed in a 5-*exo* or 6-*endo* fashion and terminate with regeneration of the alkene or

nucleophilic trapping, either internal or external.¹ We found two relevant reports in the literature exploring similar cyclizations (Figure 2.2). The first report from Fensterbank² showed a 5-*exo* cyclization onto an internal alkyne with nucleophilic trapping from a pendant alcohol to form a fused bicycle (**2.6**, Figure 2.2). While this reactivity suggested that our desired regiochemistry was possible, a topologically more similar example from Sanz³ suggested the 6-*endo* cyclization could be favored. In this example, the regiochemistry was somewhat dependent on the choice of solvent, with dichloromethane affording exclusively the 6-*endo* product and a 1:1 mixture of dichloromethane and 1,4-dioxane producing a 1.7:1 mixture of 6-*endo* and 5-*exo* cyclization products.

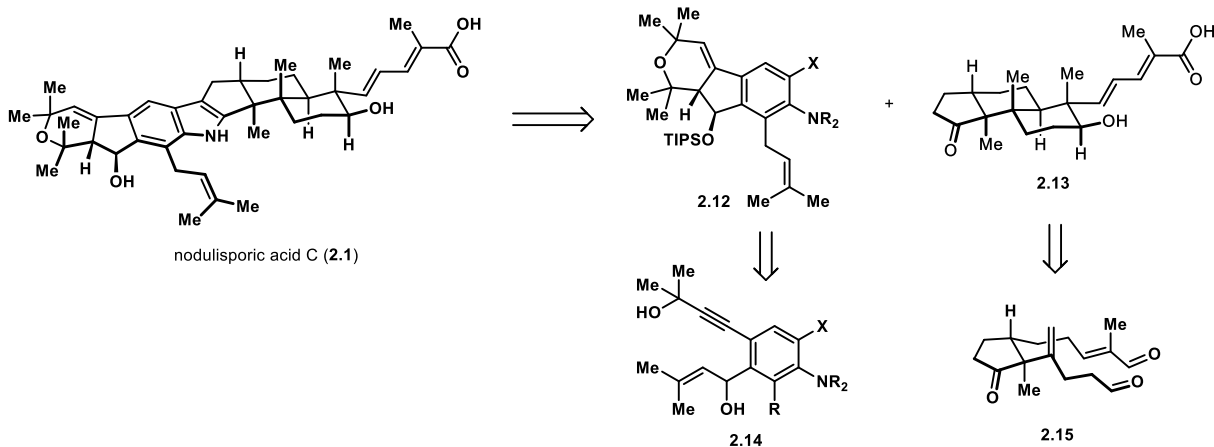
Figure 2.2: Proposed enyne cycloisomerization and related examples



2.1.3 Retrosynthesis

We imagined that if we could synthesize a fully elaborated indenopyran fragment, we could then bring it together with the terpene half of NsA C through a late stage indole formation (Figure 2.3). This convergent approach would increase the efficiency of the synthesis and allow us to generate larger amounts of material quickly. In addition to the enyne cycloisomerization, the development of another polycyclization to build the terpene fragment would afford an increase in efficiency compared to previous syntheses.

Figure 2.3: Retrosynthetic analysis of NsA C

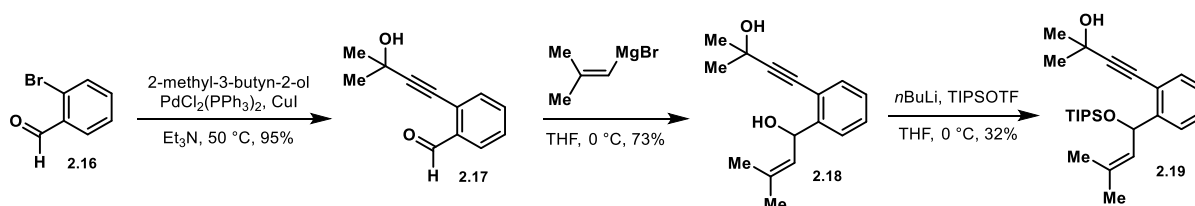


2.2 Synthesis of Nodulisporic Acid C

2.2.1 Development of a 1,6-Enyne Cycloisomerization

In order to explore the regio- and stereochemical outcome of the desired 1,6-enyne cycloisomerization, we designed a model system with the same topology at the reactive centers as our desired system. Starting with 2-bromobenzaldehyde, Sonogashira coupling⁴ followed by 2-methyl-1-propenylmagnesium bromide addition into the aldehyde⁵ afforded alcohol **2.18**. TIPS-protection then delivered the model enyne **2.19** to test the cycloisomerization (Figure 2.4).

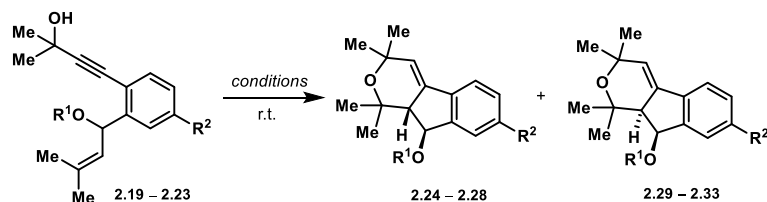
Figure 2.4: Synthesis of a model system



With a model system in hand, we began investigating our first key step of the synthesis. We explored several gold and indium complexes and no product was observed in the reaction with indium(III) bromide or iodide, or with gold(I) or gold(III) chlorides. Gold(I) complexes with phosphine ligands and various silver(I) salts were also unreactive; however, using a more reactive gold(I) NHC complex with silver(I) halide scavengers produced better results (Table 2.1). Using silver(I) triflate we obtained the desired indenopyran in 1:1 d.r. (Entry 2), and switching to

Table 2.1: Enyne cycloisomerization exploration

silver(I) hexafluoroantimonate increased the d.r. to 2.5:1 favoring the desired diastereomer (**2.24**, Entry 3) as determined by NOE studies. Silver(I) tetrafluoroborate gave a similar result with 2:1 d.r. (Entry 4). One of the major undesired side products we observed in this reaction was the elimination of



Entry	R ¹	R ²	Pre-catalyst	Additive	Solvent	d.r.
1	TIPS	H	10% Ph ₃ PAuCl	10% AgSbF ₆	DCE	—
2	TIPS	H	10% IPrAuCl	10% AgOTf	DCE	1:1
3	TIPS	H	15% IPrAuCl	10% AgSbF ₆	DCE	2.5:1
4	TIPS	H	15% IPrAuCl	10% AgBF ₄	DCE	2:1
5	TIPS	H	15% IPrAuCl	—	DCE	—
6	TIPS	H	10% IPrAuCl	10% AgSbF ₆ 20% 2,6-di- <i>tert</i> -butylpyridine	DCE	1:1
7	TIPS	H	15% JackiPhosAuCl	10% AgSbF ₆	DCE	—
8	TIPS	H	15% IPrAuCl	10% AgSbF ₆	DCE, wet	1:1
9	TIPS	H	15% IPrAuCl	10% AgSbF ₆	Trifluorotoluene	1:1
10	TIPS	H	15% IPrAuCl	10% AgSbF ₆	DCM	1:1
11	H	H	15% IPrAuCl	10% AgSbF ₆	DCE	—
12	Bn	H	15% IPrAuCl	10% AgSbF ₆	DCE	1:1
13	Ac	H	15% IPrAuCl	10% AgSbF ₆	DCE	—
14	TIPS	NO ₂	15% IPrAuCl	10% AgSbF ₆	DCE	1:1

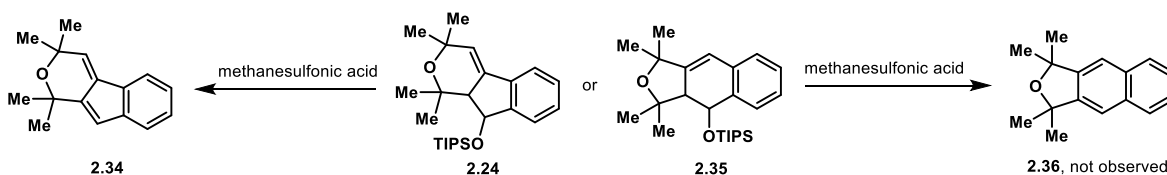
the benzylic silyl ether, which is known to be very acid sensitive.⁶ In an attempt to reduce the amount of elimination, 2,6-di-*tert*-butylpyridine was added to the reaction; however, this

decreased the d.r. to 1:1 (Entry 6). Various other solvents were also explored and while several halogenated solvents afforded the desired product, albeit with lower d.r. (Entries 8–10), non-halogenated solvents such as toluene and THF completely shut down the reactivity at room temperature. We also explored protecting groups other than TIPS, with smaller silyl protecting groups proving to be too labile and the acyl group shutting down reactivity (Entry 13). The unprotected alcohol was also incompatible with this reaction (Entry 11). The benzyl ether fared better, albeit with a lower d.r. (Entry 12). Adding a nitro substituent on the aromatic ring also decreased the d.r. to 1:1 (Entry 14); however, this substrate proved to be more robust and we observed less of the elimination product. This result along with the result from adding di-*tert*-butylpyridine suggested the higher d.r. observed in the other cases may have been due to decomposition of one diastereomer at a faster rate than the other. This was confirmed by resubjecting a 1:1 mixture of product diastereomers to the reaction conditions. After several hours, the product was re-isolated and a 3:1 d.r. was observed by ^1H NMR with a loss in yield.

Despite the issues with diastereoselectivity, in every case where product was formed we observed a single regioisomer. Based solely on NMR data we were unable to conclusively prove that the isolated product was the desired indenopyran. We therefore set out to prove the structure following further transformations. Knowing that the benzylic alcohol was prone to acid mediated elimination, we proposed that treatment of the product with acid would yield a diene. If we had formed indenopyran **2.24**, elimination to the unsymmetrical diene **2.34** would be clear (Figure 2.5). If instead we formed the undesired 6-*endo* product **2.35**, diene **2.36** would be symmetrical. Examination of ^1H and ^{13}C NMR would then identify the product. Treatment of our enyne cycloisomerization product with methanesulfonic acid

afforded the desired diene (**2.34**, Figure 2.5). ^1H and ^{13}C NMR both confirmed that the product formed was not symmetrical, thus proving the structure of our enyne cycloisomerization to be the desired indenopyran derived from the 5-*exo* cyclization.

Figure 2.5: Structure confirmation of the enyne cycloisomerization product



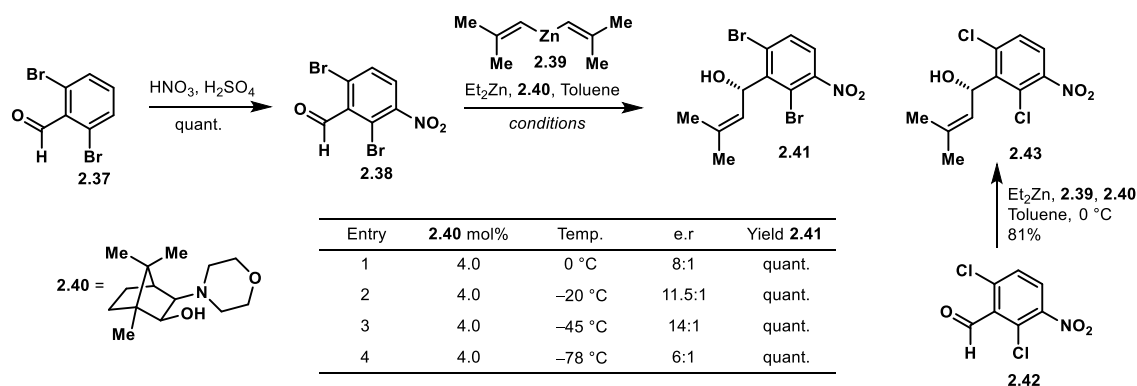
The experiments on the model system showed that it was possible to achieve the desired 5-*exo* cyclization on our system. Consequently, we decided to move forward with this strategy for the nodulisporic acids. We hoped that with additional substitution or further catalyst screenings we would be able to achieve a higher diastereoselectivity.

2.2.2 Synthesis of the Indenopyran Fragment

At the outset of the project we had various ideas concerning formation of the indole in the late stage fragment coupling. Not knowing which plan would ultimately prove successful, we targeted two different substitution patterns for the indenopyran fragment, one with a functional handle for the coupling in the form of an aryl chloride and one without. The non-chlorinated route began with commercially available 2,6-dibromobenzaldehyde. Nitration with fuming nitric acid and sulfuric acid afforded **2.38** in quantitative yield (Figure 2.6). The first stereocenter was then set using the Walsh procedure.⁷ After brief optimization we found that the highest e.r.⁸ could be obtained at $-45\text{ }^{\circ}\text{C}$ in the presence of 4 mol% of chiral aminoalcohol **2.40**. It is notable that the e.r. eroded dramatically at $-78\text{ }^{\circ}\text{C}$. We believe this may be due to decreased solubility of the aminoalcohol catalyst at lower temperatures, allowing the racemic background reaction to become more prevalent. The dichloro variant

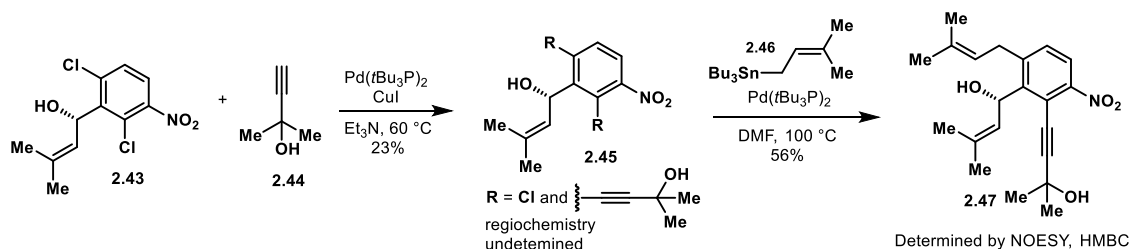
was also prepared in a similar manner starting from commercially available 2,6-dichloro-5-nitrobenzaldehyde following the same procedure. The isopropenyl zinc⁹ and the aminoalcohol¹⁰ reagents were prepared according to known procedures.

Figure 2.6: Synthesis of alcohols **2.41** and **2.43**



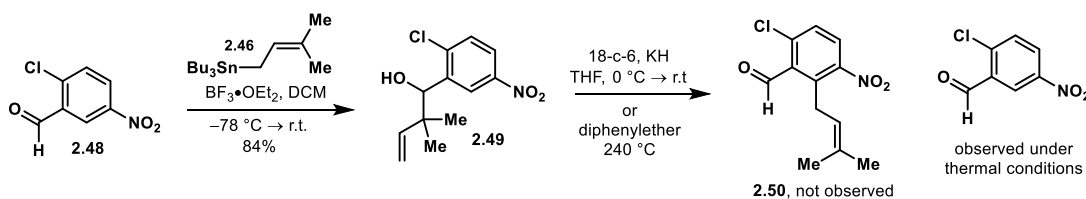
With the benzylic alcohol in hand, we began exploring conditions to achieve a selective Sonogashira¹¹ monocoupling in the presence of two activated halides. Beginning with dichloroarene **2.43**, subjection to palladium(0) and copper(I) iodide in the presence of one equivalent of alkyne **2.44** afforded a single regioisomer, albeit in low yield (Figure 2.7). 2D NMR experiments were unable to clarify which regioisomer was formed at this stage; however, after subjection to Stille coupling conditions with **2.46** to install the prenyl substituent, both NOESY and HMBC conclusively showed the undesired regiochemistry through interactions between the prenyl methylene and the aromatic ring. Attempts at inducing the desired selectivity during the Sonogashira coupling using bulky ligands, including XantPhos, *t*-BuXPhos, and XPhos all failed to produce any Sonogashira coupling products. We imagined that changing the order of operations could afford the desired selectivity. Unfortunately, attempts at performing a Sonogashira coupling on 2,6-dichloro-5-nitrobenzaldehyde also failed, and Stille coupling on **2.43** proved to be unselective.

Figure 2.7: Attempted selective Sonogashira coupling



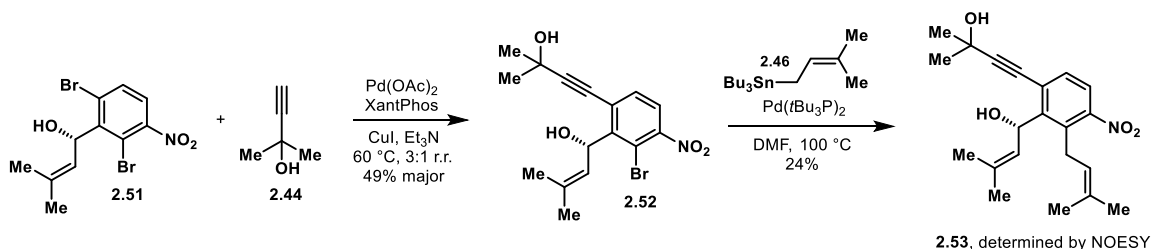
As an alternative method for the selective installation of the prenyl substituent, we imagined an oxy-Cope rearrangement of alcohol **2.49** which would deliver the prenyl to the only available position on the aromatic ring. Alcohol **2.49** was synthesized from 2-chloro-5-nitrobenzaldehyde via a reverse prenylation (Figure 2.8). Unfortunately, under anionic conditions we observed only decomposition, and under thermal conditions we observed the product of an apparent retro-ene reaction to deliver the starting aldehyde.

Figure 2.8: Attempted oxy-Cope rearrangement



We were concurrently working to explore the selectivity during Sonogashira coupling with the dibromo-substituted system. Subjection to XantPhos and palladium(II) acetate in the presence of copper(I) iodide provided a 3:1 mixture of monocoupling products favoring the desired as well as recovered starting material (Figure 2.9). The major product was isolated in 49% yield, and subsequent Stille coupling afforded enough material to confirm the desired regioisomer was the major product via NOESY analysis and comparison with **2.47** (Figure 2.7).

Figure 2.9: Attempted Sonogashira coupling



Attempts to optimize the Sonogashira coupling were largely ineffective. Varying the amount of copper had little effect on either the regioisomeric ratio (r.r.) or the yield (Entry 1, Table 2.2). Deviation from triethylamine as solvent produced no recognizable products (Entry 2). Removal of copper saw a slight increase in r.r. but a large decrease in yield (Entry 3). Removal of the ligand saw a decrease in both yield and r.r. (Entry 4). Using dppf or triphenylphosphine ligands increased the amount of the double Sonogashira coupling product observed and

Table 2: Sonogashira coupling optimization

also decreased the r.r. (Entries 5 and 6).

Despite the low r.r. and some intermittent reproducibility issues, we decided to move forward in the synthesis.

Entry	Pd source	Ligand	Additives	Conditions	Result
1	Pd(OAc) ₂ (4 mol%)	XantPhos (4 mol%)	CuI (0.5–4%)	Et ₃ N, 60 °C	3:1 r.r. 30–49% yield
2	Pd(OAc) ₂ (4 mol%)	XantPhos (4 mol%)	CsCO ₃ (2 equiv)	MeCN, 40 → 60 °C	decomposition
3	Pd(OAc) ₂ (4 mol%)	XantPhos (4 mol%)	—	Et ₃ N, 60 °C	4:1 r.r. 23% yield
4	Pd(OAc) ₂ (4 mol%)	—	—	Et ₃ N, 60 °C	2:1 r.r. 11% yield, 60% SM
5	PdCl ₂ (dppf)•DCM (4 mol%)	—	—	Et ₃ N, 60 °C	double coupling
6	PdCl ₂ (PPh ₃) ₂ (2 mol%)	—	CuI (4 mol%)	Et ₃ N, 60 °C	double coupling

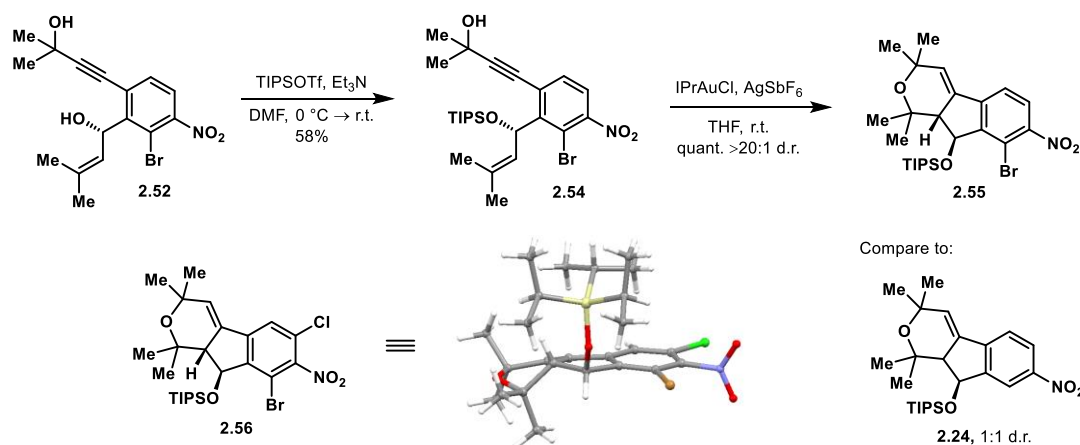
Knowing that the Stille coupling did not work well on diol **2.52**, we decided to attempt the enyne cycloisomerization first, hypothesizing that the aryl bromide would be more sterically accessible after the cyclization. Based on our explorations with the model system

we expected one of the major side products of the cycloisomerization to be elimination of the benzylic alcohol. While the model system worked best in DCE, we decided to explore more Lewis basic solvents which might help to prevent elimination in the event that any acids were generated during the reaction. We reasoned that the added electron withdrawing nitro group on the aromatic ring would cause the alkyne to be more electrophilic and could balance any decrease in the Lewis acidity of the gold catalyst caused by the more coordinating solvents. Alternatively, this could cause the alkyne to coordinate more weakly to the gold catalyst, decreasing the reactivity. However, we believed the right solvent or combination of solvents would reduce the undesired elimination while retaining the desired reactivity.

Protection of the secondary alcohol afforded silyl ether **2.54** in 58% yield with most of the mass balance corresponding to the elimination product (Figure 2.10). We next attempted the enyne cycloisomerization. Gratifyingly, using the same NHC gold catalyst with silver hexafluoroantimonate in THF, the reaction afforded a single diastereomer in quantitative yield. The product was confirmed to have the desired *trans* stereochemistry through X-ray crystallography of related enyne cycloisomerization product **2.56**. The drastic change in diastereoselectivity between this substrate and the model system was surprising, considering the only difference between a 1:1 d.r. and a single diastereomer was the bromide *ortho* to the nitro group. We believe that allylic strain between the benzylic silyl ether and the aryl bromide forces the silyl group to rotate toward the reaction center. This rotation imparts additional negative steric interactions in the transition state, causing one diastereomer to be favored over the other. The effect of the bromide is also supported by comparing the ¹H NMRs of the enyne starting materials. With additional substitution, the

peaks in the NMRs for **2.54** show evidence of restricted rotation, with some peaks greatly broadened. Running high temperature NMR experiments can sharpen the peaks slightly. The NMR of the unsubstituted enyne shows no evidence of restricted rotation.

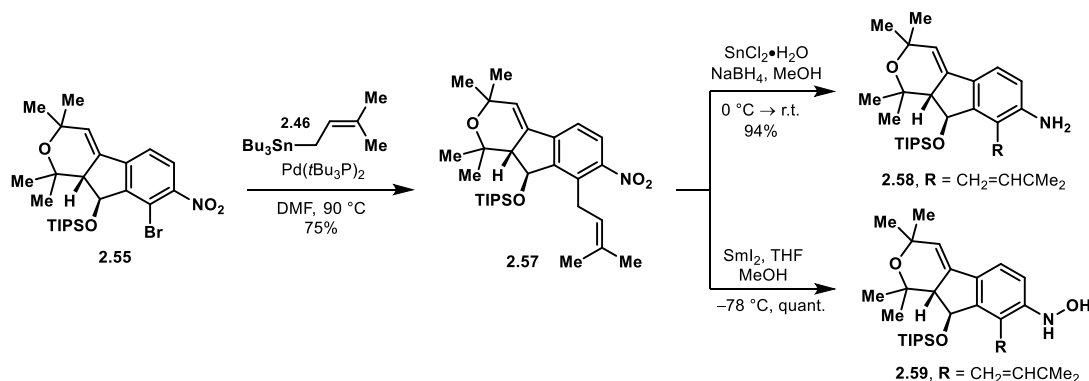
Figure 2.10: Indenopyran formation



Elaboration of **2.55** to a suitable coupling partner began with a Stille coupling to afford prenylated arene **2.57** in 75% yield (Figure 2.11), a vast improvement over the same reaction on diol **2.52** (Figure 2.9). This improvement is likely due to the steric encumbrance of the benzylic alcohol substituent off of the aromatic ring. Once tied back in the indenopyran, even bearing the bulky TIPS group, the arylbromide is more available for oxidative addition.

The nitro group on the aromatic ring could then be either fully reduced in the presence of tin(II) chloride or partially reduced in the presence of samarium(II) iodide to afford aniline **2.58** in 88% yield or hydroxylamine **2.59** in quantitative yield, respectively. We imagined that these two oxidation states would allow us to target a variety of coupling strategies to forge the final indole ring.

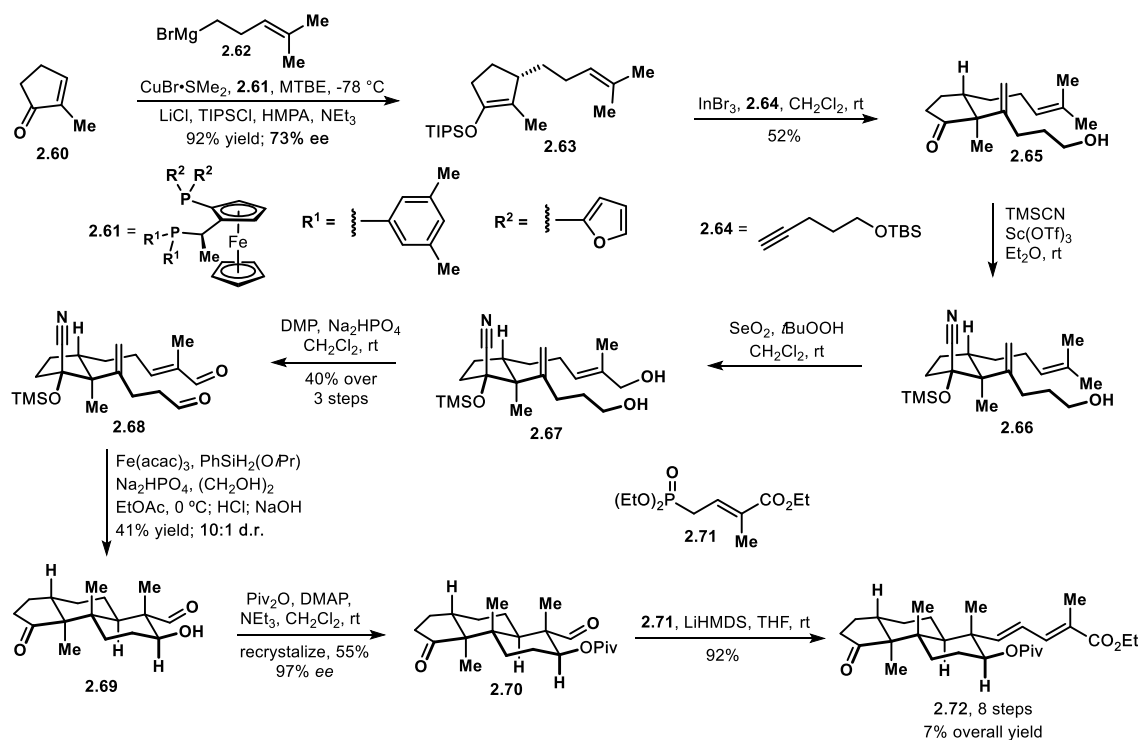
Figure 2.11: Elaboration to aniline **2.58** and hydroxylamine **2.59**



2.2.3 Synthesis of the Terpene Fragment

Synthesis of the terpene fragment of the nodulisporic acids was concurrently being performed by Devon Schatz. The synthesis began with an asymmetric conjugate addition to 2-methyl-2-cyclopentene-1-one.¹² After extensive screening, JosiPhos derivative SL-J015-1 was identified as a suitable ligand for the addition, affording a 73% *ee* with trapping of the enolate as the TIPS enoxysilane (Figure 2.12). Subsequent alkenylation with alkyne **2.64** in the presence of indium(III) bromide afforded ketone **2.65** after acidic workup. Cyanohydrin formation followed by Sharpless allylic oxidation¹³ and double oxidation of diol **2.67** delivered the substrate for the key step in the synthesis of the terpene fragment. Building on work done previously in our lab,¹⁴ chemoselective iron-mediated hydrogen atom transfer (HAT) to the 1,1-disubstituted alkene followed by conjugate addition, reduction to the enolate, and aldol reaction to close the final ring afforded tricyclic ketone **2.69** in high d.r. and 41% yield. The 10:1 d.r. observed for this system was shown to be dependent on the presence of the cyanohydrin, with the free ketone slightly favoring the *cis*-decalin system.

Figure 2.12: Synthesis of the terpene fragment by Devon Schatz

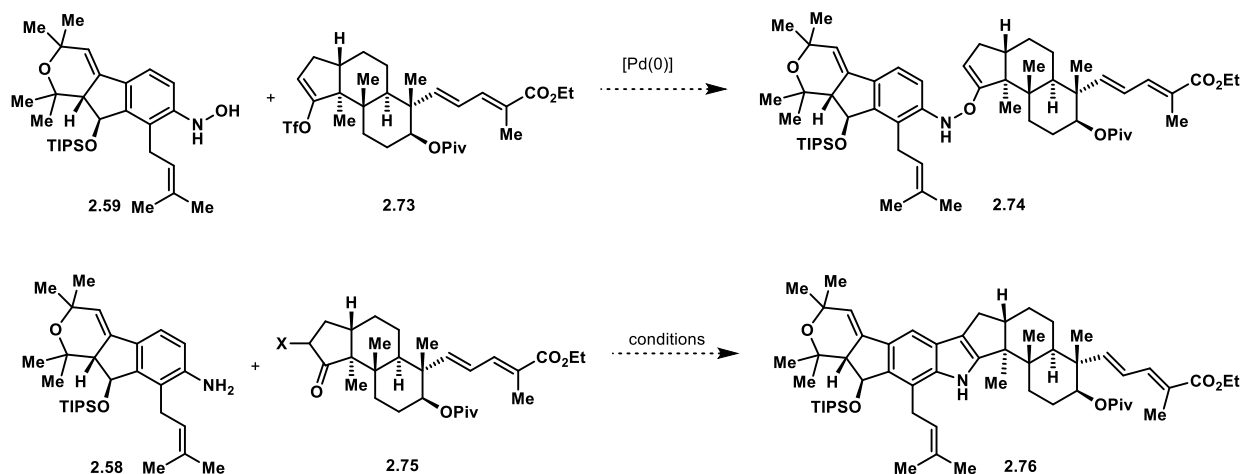


After protection as the pivalate, recrystallization from hexanes afforded **2.70** in 97% *ee* and 55% yield. The final HWE olefination provided access to the terpene core of the nodulisporic acids in only eight steps from commercial material.

2.2.4 First Generation Fragment Coupling Strategies

With both the indenopyran and terpene fragments in hand, we turned our sights on strategies to bring them together. From hydroxylamine **2.59** we imagined a C-O coupling to furnish **2.74** would provide a suitable substrate for a [3,3] sigmatropic rearrangement to afford the aminoketone (Figure 2.13). Condensation would then deliver the indole. Alternatively, starting with aniline **2.58**, we imagined several possible indolization strategies discussed below.

Figure 2.13: First generation fragment coupling strategies



We began by exploring the coupling of hydroxylamine **2.59** and triflate **2.73**, derived from ketone **2.72**. Based on ongoing studies being performed by Devon Schatz on a similar system (*vide infra*), we decided to start with Buchwald's RuPhosPd third generation precatalyst. The initial reactions using cesium carbonate as the base proved to be unproductive even at high temperatures (Table 2.3, Entries 1 and 2). Reasoning that a stronger base was required, we attempted the same reaction with sodium hydride (Entry 3); however, these conditions reduced hydroxylamine **2.59** to the corresponding aniline. The same reaction with KHMDS afforded ketone **2.72** from triflate **2.73** (Entry 4). This result

Table 2.3: Attempted hydroxylamine coupling

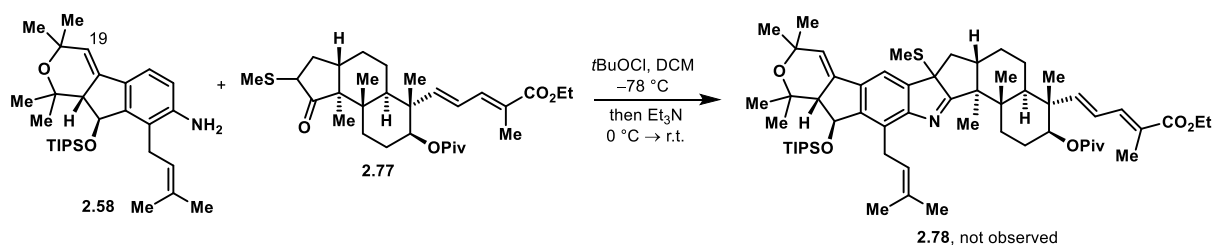
Entry	2.59 (equiv)	2.73 (equiv)	Conditions	Result
1	1	1	RuPhodPdG3, RuPhos Cs ₂ CO ₃ , toluene, 70 °C	no reaction
2	1	1	RuPhodPdG3, RuPhos Cs ₂ CO ₃ , toluene, 100 °C	no reaction
3	2	1	RuPhodPdG3, RuPhos NaH, toluene, 70 °C	2.73 reduction to aniline
4	2	1	RuPhodPdG3, RuPhos KHMDS, toluene, 70 °C	2.73 conversion to ketone
5	0	1	RuPhodPdG3, RuPhos KHMDS, toluene, 70 °C	decomposition
6	2	1	RuPhos, KHMDS, toluene, 70 °C	2.73 conversion to ketone
7	2	1	KHMDS, toluene, 70 °C	2.73 conversion to ketone

seemed promising as it suggested the desired C-O coupling may have occurred, but was followed by cleavage of the N-O bond. To explore this further, three control experiments were run, one in the absence of hydroxylamine **2.59** (Entry 5), one in the absence of a palladium

source (Entry 6), and one in the absence of both palladium and the ligand (Entry 6). These experiments revealed that the reduction occurred in the absence of any coupling reagents, and that only the hydroxylamine and a base needed to be present. This suggested nucleophilic removal of the triflate via the deprotonated hydroxylamine and protonation of the resulting enolate to regenerate ketone **2.72**. While Devon worked on synthesizing the vinyl bromide derivative of ketone **2.72** to overcome this issue,¹⁵ we began to explore other indole formation strategies.

We continued our efforts by attempting a Gassman¹⁶ indole synthesis to form the methylthio-3H-indole. A subsequent reduction would form the desired indole. Methylthioketone **2.77** was synthesized by Devon Schatz from ketone **2.72** in one step with LDA and dimethyldisulfide. Subjection of aniline **2.58** and methylthioketone **2.77** to *tert*-butyl hypochlorite afforded none of the desired product (Figure 2.14). Attempting a model reaction with ethyl (methylthio)acetate in place of ketone **2.77** resulted only in chlorination of the electron rich styrene of the indenopyran at C19.

Figure 2.14: Attempted Gassman indole synthesis

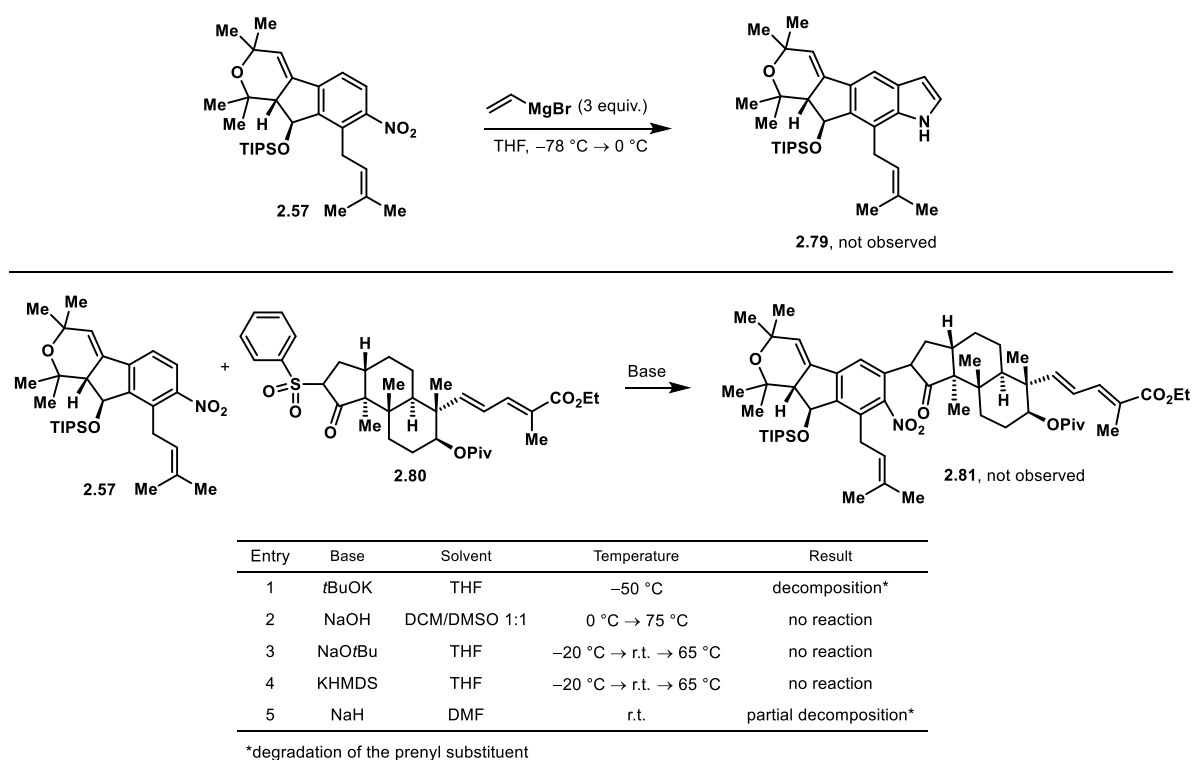


Failure of the Gassman synthesis to provide the desired indole lead us to explore the reactivity of nitroarene **2.57** (Figure 2.15). We imagined we could take advantage of two modes of reactivity. The nitro group could lend itself to a Bartoli¹⁷ indole synthesis, though the unfavorable steric interactions with the prenyl substituent were expected to be

challenging to overcome. The position *ortho* to the nitro group is also highly activated toward nucleophilic attack by an enolate equivalent. Leveraging a vicarious nucleophilic substitution (VNS)¹⁸ strategy, we imagined forging the desired C-C bond followed by nitro reduction and condensation to afford the indole.

To test the Bartoli indole synthesis we began with nitroarene **2.57** and attempted the reaction with vinylmagnesium bromide for a proof of concept. Unfortunately, we observed none of the desired reactivity and isolated only the starting material under a variety of conditions (Figure 2.15).

Figure 2.15: Attempted Bartoli and VNS indolizations



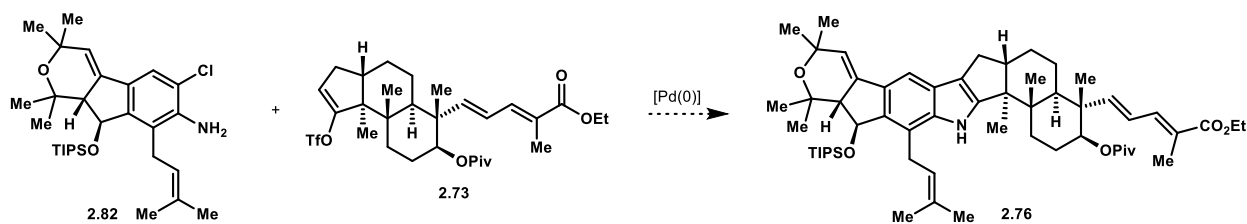
We attempted the VNS reaction using sulfone **2.80**, which was synthesized by Devon Schatz in two steps from ketone **2.72**. We imagined that an initial nucleophilic attack would proceed at the desired *ortho* position. The sulfone would then undergo elimination and rearomatization to afford arylketone **2.81**. Unfortunately, under a variety of conditions

(Figure 2.15), we did not observe the desired bond formation. We did observe products related to the degradation of the prenyl substituent, presumably through initial deprotonation of the benzylic methylene followed by deleterious reactivity.

2.2.5 Synthesis of the Chlorinated Indenopyran

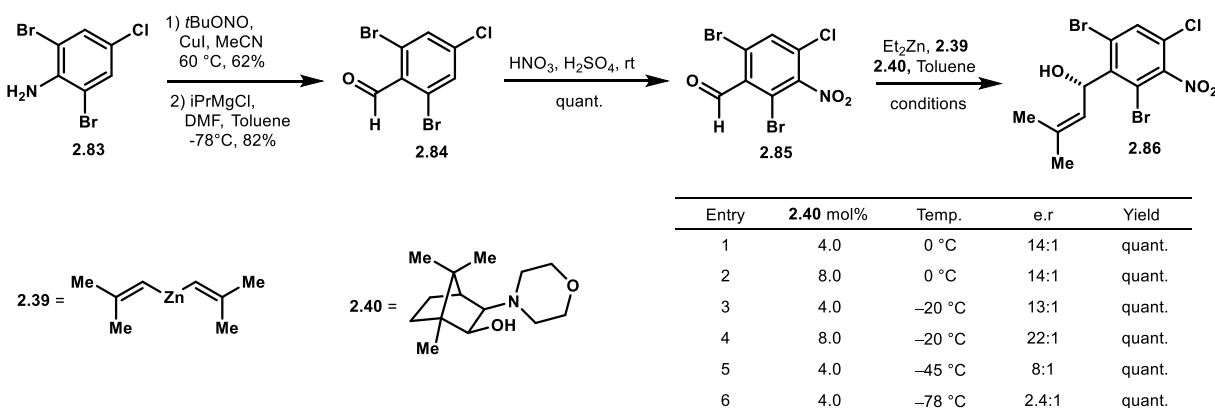
Based on our work thus far we decided to pursue an alternate coupling strategy. We became interested in Smith's approach toward NsA D¹⁹ (at this stage, Smith's synthesis of NsA C²⁰ had not been published), specifically the Barluenga²¹ indole synthesis. We imagined a palladium coupling cascade could deliver the desired indole from a chloroaniline and a vinyl triflate despite the added steric bulk of the prenyl substituent (Figure 2.16). To this end, we required a chlorinated version of the indenopyran.

Figure 2.16: Barluenga indolization strategy



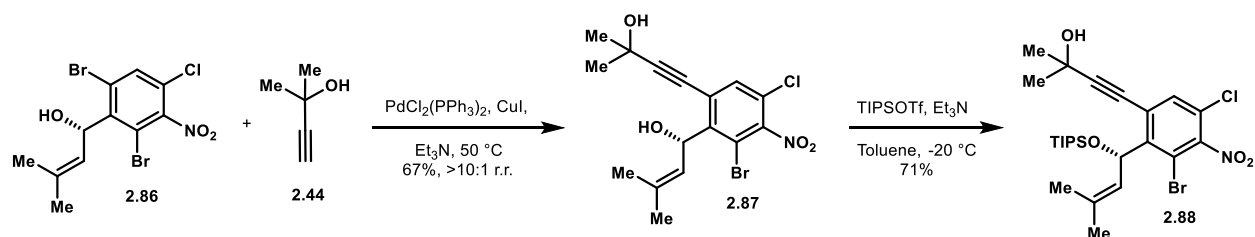
We began our synthesis with commercially available aniline **2.83** (Figure 2.17). Sandmeyer iodination²² followed by formylation afforded aldehyde **2.84**, and nitration with fuming nitric acid and sulfuric acid delivered aldehyde **2.85**. Using the Walsh procedure,⁶ isopropenylzinc addition into the aldehyde proceeded in quantitative yield, and after brief optimization we were able to achieve 22:1 e.r.⁶ at -20 °C with 8 mol% of aminoalcohol **2.40**. Here we again saw a decrease in e.r. at colder temperatures, presumably due to decreased solubility of the aminoalcohol catalyst.

Figure 2.17: Synthesis of alcohol **2.86**



We expected to have difficulty with the Sonogashira coupling based on our work with the non-chlorinated system. Additionally, in this new substrate two activated aryl bromides and an activated aryl chloride could all potentially participate in the reaction. Previously, we were only able to obtain a 3:1 r.r. with our optimized conditions. Fortunately, treatment of alcohol **2.86** with bis(triphenylphosphine)palladium(II) chloride and copper(I) iodide in the presence of alkyne **2.44** afforded only the desired regioisomer in 67% yield. The reason for this dramatic change in reactivity between the chlorinated and non-chlorinated substrates is unclear at this time. It is possible that the added substitution *ortho* to the nitro group forces it out of plane and thus out of conjugation with the aromatic ring, as seen in the X-ray crystal structure of indenopyran **2.89** (Figure 2.19). This would make the aryl bromides less reactive toward oxidative addition, allowing other factors to play a larger role in determining the regiochemistry. In this case, the more sterically available bromide with only one *ortho* substituent reacted faster to afford the desired regioisomer. Moving forward, silyl protection afforded silyl ether **2.88** in good yield.

Figure 2.18: Synthesis of silyl ether **2.88**

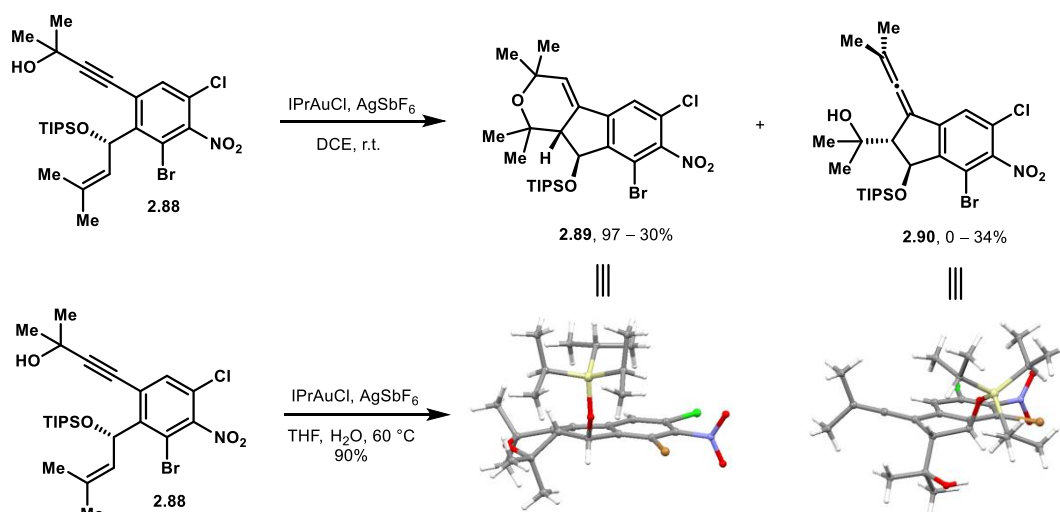


With silyl ether **2.88** in hand, we turned our attention toward the enyne cycloisomerization (Figure 2.19). The same conditions we found to work with the model system delivered the desired product in 97% yield as a single diastereomer with no evidence of the undesired 6-*endo* cyclization. Satisfied with this result, we immediately attempted to scale up the reaction. On larger scales we began to observe issues with reproducibility and decreased conversion. We also observed the formation of a second product, previously unseen in both our model system and the non-chlorinated route. Isolation of this product and resubjection to the reaction conditions afforded exclusively indenopyran **2.89**. Based on this information and characterization data, we hypothesized that the new product was allene **2.90**, which we propose arises through the elimination of an alkenylgold species instead of the desired protodemetalation. The allene structure was ultimately confirmed by X-ray crystallography.

Based on our observations during scale-up and the new formation of allene **2.90**, we hypothesized that the irreproducibility issues may stem from a difference in moisture content in the reaction. If exogenous water were to interact with gold(I) in the reaction, a Brønsted acid would be formed and could help catalyze the conversion of allene **2.90** to indenopyran **2.89**. This theory was partially confirmed by subjecting allene **2.90** to mild acid in the absence of any Lewis acid to afford indenopyran **2.89** in quantitative yield. With the

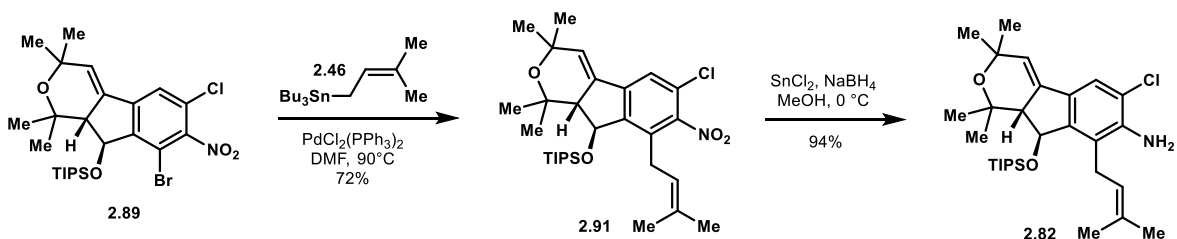
addition of 20 mol% of water to the enyne cycloisomerization, the allene was no longer observed by TLC. We ultimately found that a combination of THF and 20 mol% water provided the highest yield.

Figure 2.19: Attempted enyne cycloisomerization of silyl ether **2.88**



To complete the synthesis of the chlorinated indenopyran fragment, a Stille coupling was performed to install the prenyl substituent. Reduction of the nitro group with tin(II) chloride and sodium borohydride proceeded well and afforded the aniline in nine steps from commercial material.

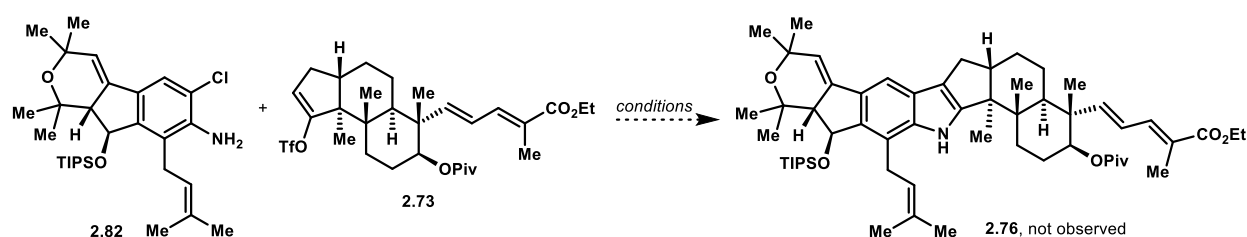
Figure 2.20: Completion of the chlorinated indenopyran fragment



With our new coupling fragment in hand, we turned our attention toward the proposed palladium-coupling cascade. Initial reaction attempts with several Buchwald

precatalysts were largely unsuccessful, with reduction of triflate **2.73** as the only observable product (Table 2.4). This reduction suggested a successful oxidative addition into the vinyl triflate bond, followed by deleterious reactivity. We hypothesized that the increased steric bulk of the prenyl substituent prevented the desired Buchwald coupling. We tested this theory with a model system of aniline **2.82**. Under similar conditions, 2-chloroaniline was successfully coupled with triflate **2.73** to form an indole. However, when we attempted the same coupling with 2-chloro-6-methylaniline, we did not observe any of the desired product. Further optimizations performed by Devon Schatz were unable to overcome this challenge.

Table 2.4: Attempted palladium-coupling cascade



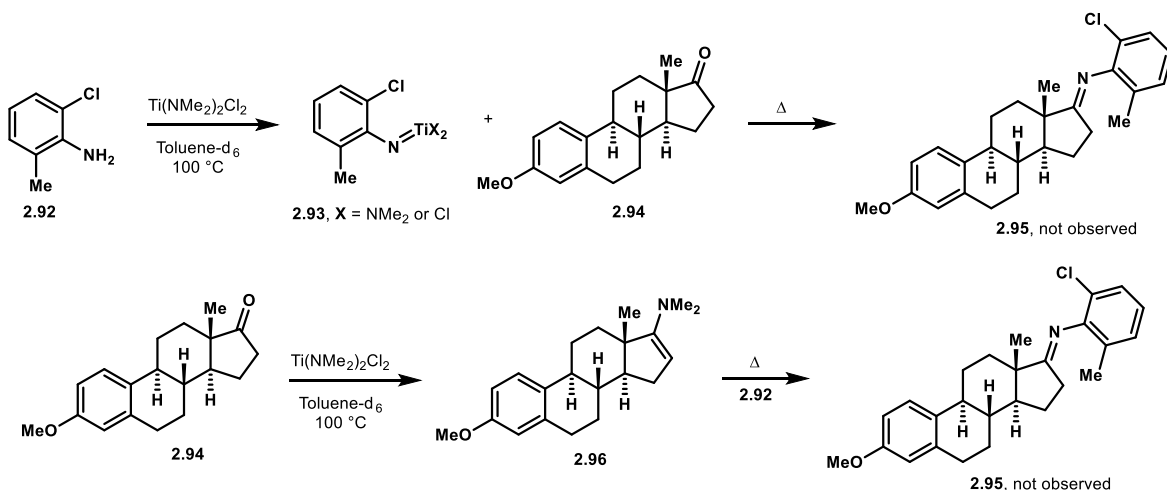
Entry	Pd source	Ligand	Conditions	Result
1	RuPhosPdG3	RuPhos	Cs ₂ CO ₃ , Toluene, 70 °C	reduction of triflate
2	RuPhosPdG3	RuPhos	Cs ₂ CO ₃ , Toluene, 110 °C	reduction of triflate
3	XPhosPdG3	XPhos	Cs ₂ CO ₃ , Toluene, 70 °C	no reaction
4	XPhosPdG3	XPhos	Cs ₂ CO ₃ , Toluene, 110 °C	reduction of triflate
5	Pd ₂ (dba) ₃	SPhos	Cs ₂ CO ₃ , Toluene, 70 °C	no reaction
6	Pd ₂ (dba) ₃	SPhos	Cs ₂ CO ₃ , Toluene, 110 °C	reduction of triflate

2.2.6 Second Generation Fragment Coupling Strategies

We proposed that forming the imine via amine condensation would allow us to forge the final bond of the indole using Smith's Heck coupling strategy. Unfortunately, the resistance of ketones of this type to simple condensations has been well documented.¹³ To this end, we attempted to form a titanium-imido complex²³ from 2-chloro-6-methylaniline and a titanium(IV) complex (Figure 2.21). We hoped that the driving force of titanium oxide formation would be enough to achieve the challenging condensation. Upon mixing 2-chloro-

6-methylaniline and bis(dimethylamino)titanium(IV) chloride in an NMR tube equipped with a J. Young valve in deuterated toluene at room temperature under nitrogen, a 1:1 mixture of the aniline and a new species was observed by ^1H NMR. With heating to 100 °C, the aniline was fully consumed. Upon addition of estrone derivative **2.94** and heating to 100 °C, ^1H NMR showed full consumption of the ketone; however, after aqueous work up only the starting ketone and aniline were observed. Based on Smith's work¹⁸ we knew the imine would be hydrolytically stable and we hypothesized that the ketone was being converted into something other than the desired product.

Figure 2.21: Attempted imine formation



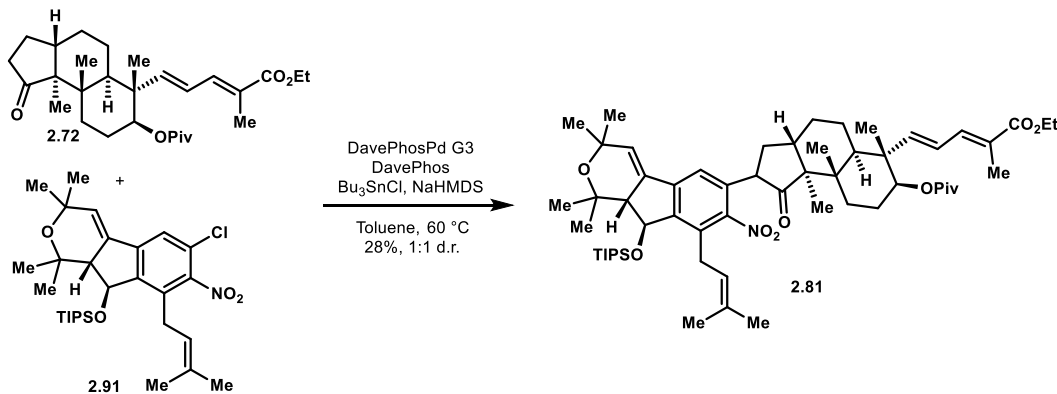
In order to explore the reaction further, we attempted the same transformation without addition of the aniline and observed full conversion at 100 °C to enamine **2.96**. Instead of the aniline condensing on the ketone, the dimethylamine ligand on the titanium(IV) was reacting. This enamine proved to be very hydrolytically unstable and all attempts at isolation returned only the starting ketone. We hypothesized that we could use this instability to drive conversion to the more stable imine; however, subsequent addition of 2-chloro-6-methylaniline had no effect and we again isolated only the ketone. Using

titanium(IV) chloride instead of the bis(dimethylamine) complex to avoid enamine formation returned only the two starting materials.

After two unsuccessful strategies to forge the C-N bond, we decided to attempt formation of the C-C bond first. We imagined that moving the reaction center further from the steric bulk of the prenyl group would allow us to forge the desired bonds. To this end, we attempted to utilize nitroarene **2.91** in a ketone arylation with **2.72**. This strategy would also remove one step from each fragment synthesis.

After an initial catalyst screening, Devon Schatz discovered a tin enolate coupling strategy that was able to forge the desired bond. Treatment of ketone **2.72** with sodium hexamethyldisilazide in the presence of tributyltin chloride followed by addition DavePhosPd G3, additional DavePhos ligand, and nitroarene **2.91** afforded the desired product in 28% yield as a 1:1 mixture of diastereomers (Figure 2.22). We were unconcerned with the d.r. as this stereocenter would be removed after indole formation. This initial result allowed us to move forward and test our indole formation strategy.

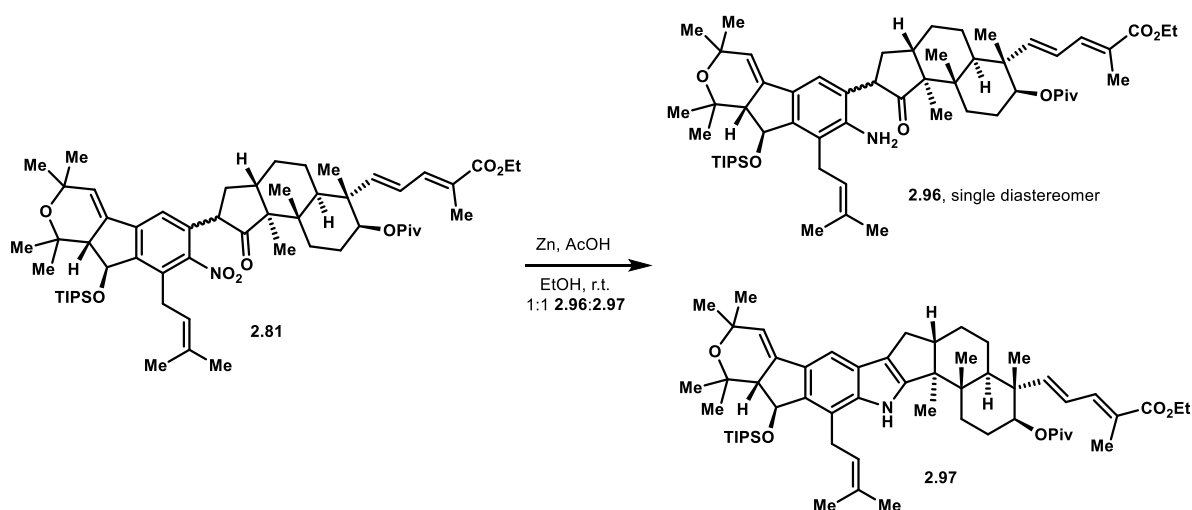
Figure 2.22: Ketone arylation for fragment coupling



Based on our previous work toward NsA C and related natural products¹³ we knew that performing condensations onto ketone **2.72** failed due to the steric encumbrance

around the ketone. We hoped that performing the reaction in an intramolecular fashion would help overcome some of these challenges. Our first task was to reduce the nitro group in the presence of a variety of sensitive functional groups. Attempted reductions in the presence of weak acids with of tin(II) chloride, aluminum metal, indium metal, iron(III) chloride with zinc metal, and aluminum metal with nickel(II) chloride did not effect the desired reduction. Fortunately, reduction of the 1:1 mixture of diastereomers with zinc metal in the presence of acetic acid in ethanol fully reduced the nitro group to afford two different products. By ^1H NMR we observed a 1:1 mixture of aminoketone **2.96** and indole **2.97**. Resubjection to the reduction conditions had no effect on the ratio and attempted condensation with any acids stronger than acetic acid eliminated the secondary TIPS-ether.

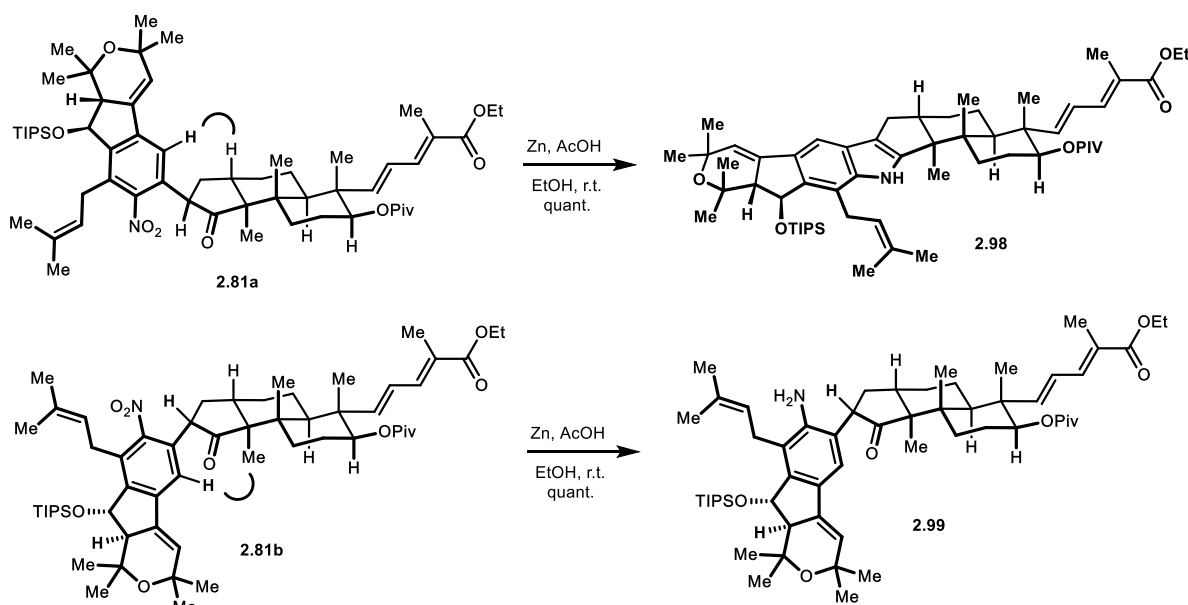
Figure 2.23: Reduction of nitroketone **2.81**



After further scrutiny of the crude reaction mixture, we observed that the aminoketone was present as a single diastereomer. This, combined with the correlation between the 1:1 mixture of indole to aminoketone and the 1:1 d.r. of the starting material made us believe that one of the diastereomers condensed *in situ* after reduction to form the

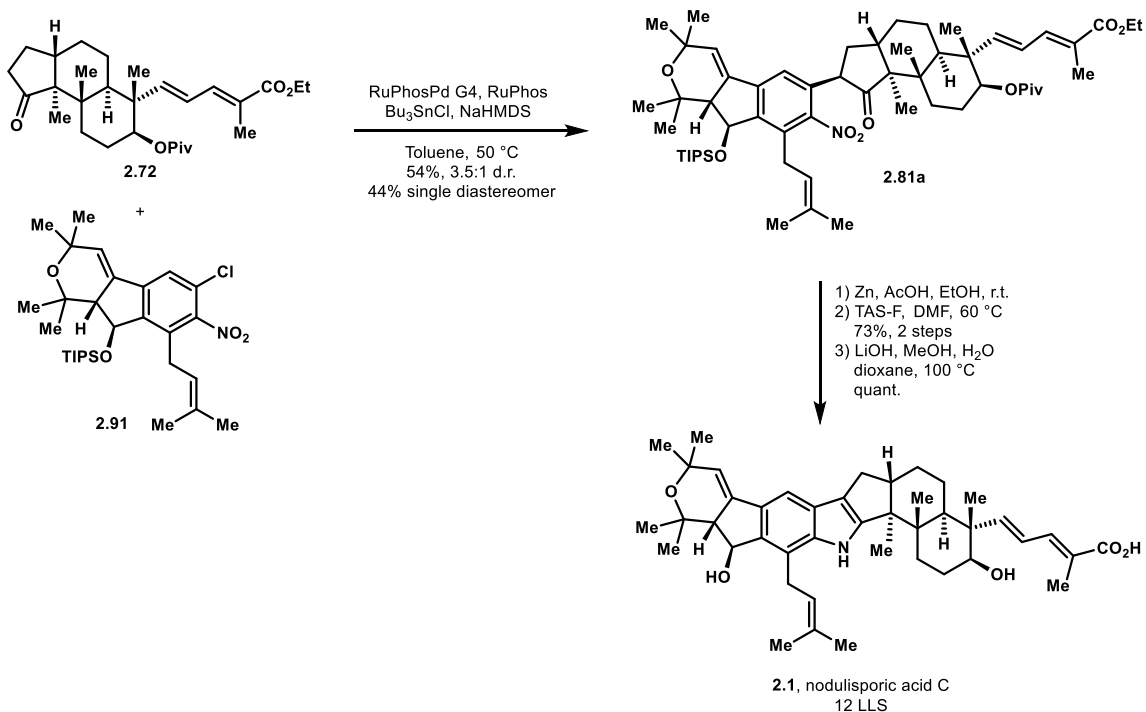
indole while the other remained as the aminoketone. We confirmed this hypothesis by separating the diastereomeric nitroketones and subjecting them separately to the reduction conditions (Figure 2.24). One diastereomer condensed to form the indole following reduction and the other remained as the aminoketone. NOESY analysis of nitroketones **2.81a** and **2.81b** comparing interactions of the aromatic proton with the terpene fragment allowed us to determine the stereochemistry. The diastereomer which cyclized to form the indole had the arene *trans* to the α -methyl of the cyclopentanone, supported by an interaction between the aromatic and methine protons shown (**2.81a**, Figure 2.24). The diastereomer which remained as the aminoketone had the arene *cis* to the α -methyl, evidenced by an interaction between the aromatic proton and the α -methyl (**2.81b**, Figure 2.24). We believe that this α -methyl discourages attack on the carbonyl from the bottom face, resulting in aminoketone **2.99** failing to condense to form the indole. Importantly, the facile indole formation through condensation of reduced **2.81a** is in stark contrast to previous reports describing the difficulty of cyclodehydration of similar systems.²⁴

Figure 2.24: Reduction of arylketones **2.81a** and **2.81b**



We were unable to find conditions to isomerize **2.81b** or to condense **2.99** without elimination of the TIPS-ether; however, after further optimization Devon Schatz was able to increase the d.r. to 3.5:1 favoring **2.81a**, with a 44% yield of the desired diastereomer (Figure 2.25). Subsequent reduction with zinc and acetic acid proceeded smoothly. Deprotection attempts with TBAF or CsF were either ineffective or caused elimination of the secondary alcohol. Fortunately, treatment with TAS-F cleaved the silyl group cleanly, affording a 73% yield of the free alcohol over two steps. The final saponification required high temperatures to cleave the pivalate. Nonetheless, treatment with lithium hydroxide in methanol, water, and dioxane delivered NsA C in 12 longest linear steps from commercial starting materials.²⁵

Figure 2.25: Synthesis of NsA C



Previous reports had noted the instability of NsA C as the free acid;¹⁹ however, with careful treatment and avoidance of chlorinated solvents (ie. CDCl₃) which could decompose

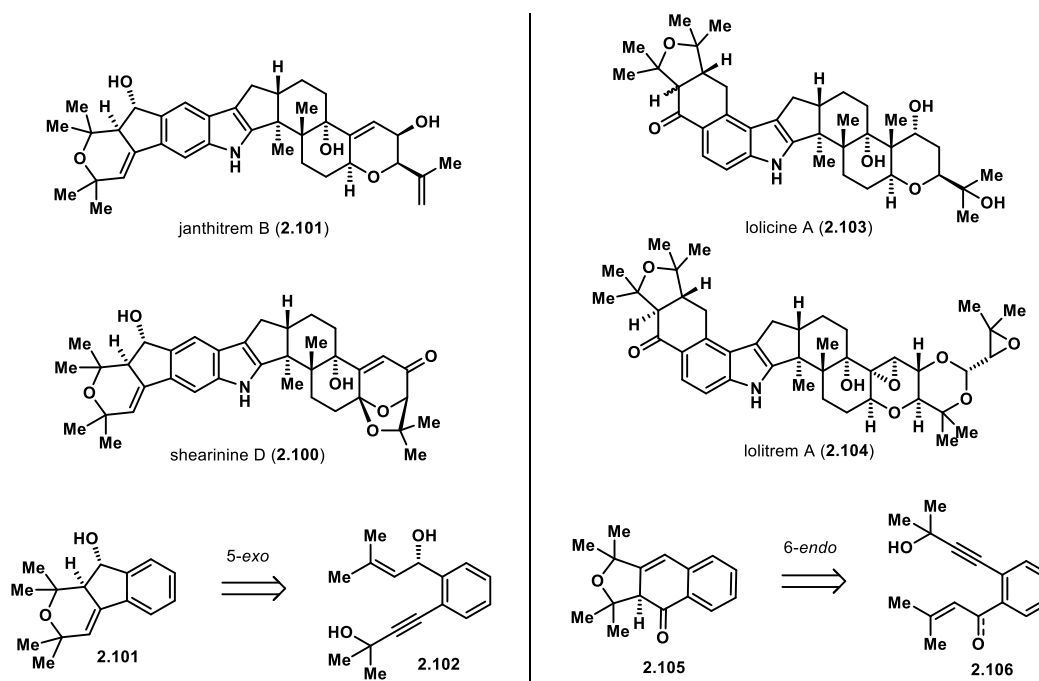
slowly to form small amounts of strong acids we were able to isolate and characterize the free acid,²⁶ which matched well with the reported spectra in the original isolation paper.²⁷

2.3 Summary

The successful development of a regio- and diastereoselective enyne cycloisomerization to forge an indenopyran allowed us to synthesize the western half of NsA C in only eight steps from commercial material. The terpene fragment was likewise synthesized in only eight steps utilizing a diastereoselective HAT-initiated polycyclization. We were also able to develop a ketone arylation with two highly substituted coupling partners to bring the two fragments together. Reduction with concomitant indole formation followed by deprotection delivered NsA C in only 12 LLS from commercial material.

These two key polycyclizations are expected to provide access to similar paxilline indole diterpene natural products bearing substitution derived from the cyclization of prenyl substituents. The janthitrems and shearinines have an inverted orientation of the indenopyran compared to the nodulisporic acids (**2.101**, Figure 2.26) but could potentially be constructed using the same cyclization with altered positions of the alkyne and the benzyl alcohol. The western half of the lolicines and lolitrems (**2.105**, Figure 2.26) could potentially be formed through the alternative *6-endo* cyclization from a similar system.

Figure 2.26: Enyne cycloisomerization toward the janthitrems, shearinines, lolicines, and lolitrems



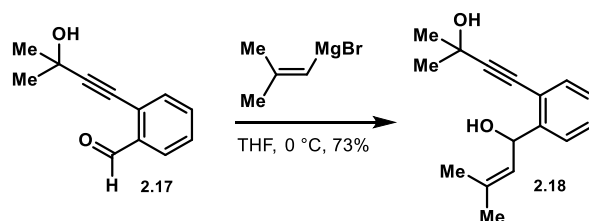
2.4 Experimental Section

2.4.1 General Experimental Details

All reactions were carried out in flame-dried glassware under positive pressure of dry nitrogen unless otherwise noted. Reaction solvents including tetrahydrofuran (THF, Fisher, HPLC Grade), dichloromethane (DCM, Fisher, HPLC Grade), and toluene (Fisher, HPLC Grade) were dried by percolation through a column packed with neutral alumina and a column packed with a supported copper catalyst for scavenging oxygen (Q5) under positive pressure of argon. Anhydrous 1,2-dichloroethane (Fisher, ACS Grade) and anhydrous triethylamine (Oakwood Chemical) were distilled from calcium hydride (10% w/v) under positive pressure of nitrogen. Anhydrous hexamethylphosphoramide (HMPA, Oakwood Chemical) was distilled from calcium hydride (10% w/v) under vacuum (*ca.* 0.1 torr).

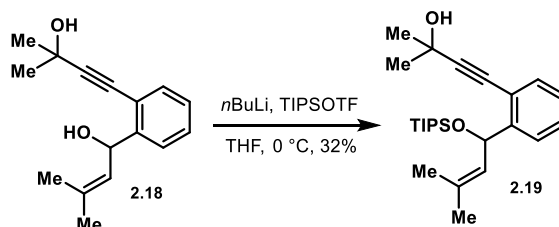
Solvents for extraction, thin layer chromatography (TLC), and flash column chromatography were purchased from Fischer (ACS Grade) and VWR (ACS Grade) and used without further purification. Chloroform- d and benzene- d_6 for ^1H and ^{13}C NMR analysis were purchased from Cambridge Isotope Laboratories and used without further purification. Commercially available reagents were used without further purification unless otherwise noted. Reactions were monitored by thin layer chromatography (TLC) using precoated silica gel plates (EMD Chemicals, Silica gel 60 F₂₅₄). Flash column chromatography was performed over silica gel (Acros Organics, 60 Å, particle size 0.04-0.063 mm). ^1H NMR and ^{13}C NMR spectra were recorded on Bruker DRX-500 (BBO probe), Bruker DRX-500 (TCI cryoprobe), Bruker AVANCE600 (TBI probe), and Bruker AVANCE600 (BBFO cryoprobe) spectrometers using residual solvent peaks as internal standards (CHCl_3 @ 7.26 ppm ^1H NMR, 77.00 ppm ^{13}C NMR; C_6H_6 @ 7.16 ppm ^1H NMR, 128.00 ppm ^{13}C NMR). High-resolution mass spectra (HRMS) were recorded on Waters LCT Premier TOF spectrometer with ESI and CI sources.

2.4.2 Experimental Procedures



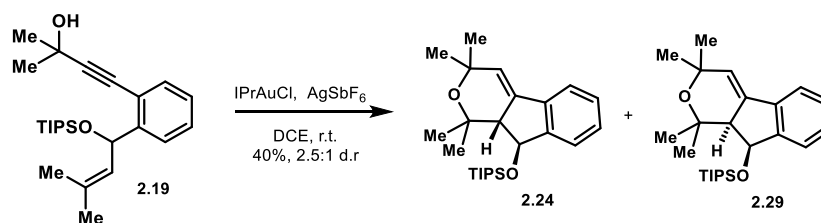
Diol 2.18. Aldehyde **2.17**²⁸ (1.787 g, 9.50 mmol) was dissolved in THF (24 mL) and cooled to 0 °C. A solution of 2-methyl-1-propenylmagnesium bromide (47.5 mL of a 0.50 M solution in THF, 24 mmol) was added dropwise over the course of 1 h. The reaction was allowed to warm to room temperature, then stirred for 1.5 h. The reaction was quenched with saturated ammonium chloride and extracted with diethyl ether. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, and condensed under

reduced pressure. Purification by flash chromatography (gradient elution: 25% to 50% ethyl acetate in hexanes) afforded 1.69 g (73% yield) of diol **2.18** as a yellow oil. $R_f = 0.2$ (20% CH_2Cl_2 in hexanes); ^1H NMR (500 MHz, C_6D_6) δ 7.56 (dd, $J = 7.8, 0.7$ Hz, 1H), 7.41 (dd, $J = 7.7$ Hz, 1.3 Hz, 1H), 7.08 (td, $J = 7.6, 1.3$ Hz, 1H), 6.91 (td, $J = 7.5, 1.3$ Hz, 1H), 5.94 (d, $J = 8.6$ Hz, 1H), 5.53 (m, 1H), 1.99 (br s, 1H), 1.87 (br s, 1H), 1.73 (d, $J = 1.3$ Hz, 3H), 1.55 (d, $J = 1.2$ Hz, 3H), 1.47 (s, 6H); ^{13}C NMR (125 MHz, C_6D_6) δ 147.2, 135.1, 132.77, 129.0, 128.5, 127.2, 126.8, 121.1, 99.4, 80.8, 69.4, 65.4, 31.6, 25.8, 18.7; HRMS (ES+) calculated for $\text{C}_{16}\text{H}_{20}\text{O}_2\text{Na}$ $[\text{M}+\text{Na}]^+$: 267.1361, found: 267.1352.



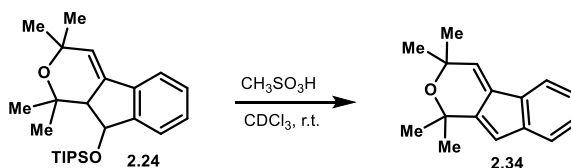
Silyl ether 2.19. Diol **2.18** (0.219 g, 0.90 mmol) was dissolved in THF (4 mL) and cooled to 0 °C. $n\text{BuLi}$ (0.40 mL of a 2.27 M solution in hexanes, 0.90 mmol) was added over 10 min and the reaction was stirred at 0 °C for 30 min. TIPSOTf (0.241 mL, 0.90 mmol) was added and the reaction was allowed to warm to room temperature. After 6 h the reaction was diluted with water and extracted with ether. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, and condensed under reduced pressure. Purification by flash chromatography (gradient elution: 5% to 10% ethyl acetate in hexanes) afforded 0.120 g (32% yield) of silyl ether **2.19** as a yellow oil. $R_f = 0.5$ (20% CH_2Cl_2 in hexanes); ^1H NMR (500 MHz, C_6D_6) δ 7.76 (dt, $J = 7.9, 1.7$ Hz, 1H), 7.39 (dd, $J = 7.8, 1.1$ Hz, 1H), 7.12 (td, $J = 7.6, 1.3$ Hz, 1H), 6.88 (td, $J = 7.5, 1.2$ Hz, 1H), 6.23 (d, $J = 8.8$ Hz, 1H), 5.61 (dt, $J = 8.7, 1.3$ Hz, 1H), 1.90 (d, $J = 1.2$ Hz, 3H), 1.54 (d, $J = 1.2$ Hz, 3H), 1.51 (s, 6H), 1.22 (m, 3H), 1.16 (m, 18H);

^{13}C NMR (125 MHz, C_6D_6) δ 148.1, 132.6, 131.4, 130.5, 129.2, 127.4, 126.9, 120.0, 98.4, 81.4, 70.0, 65.5, 31.7, 31.6, 25.8, 19.6, 18.3, 18.3, 12.7; GC/MS (EI): m/z (%) 400.39 (0.5, M^+), 367.37 (9), 357.35 (87, $[\text{M}-\text{C}_3\text{H}_7]^+$), 339.34 (21), 301.30 (11), 259.22 (17), 209.31 (63), 194.29 (100), 179.26 (94), 131.26 (45), 103.22 (54).

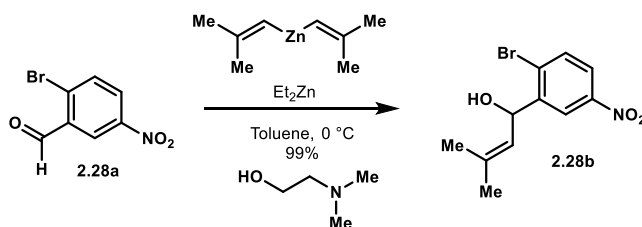


Indenopyran 2.24. In a glovebox under pressure of nitrogen, a one-dram vial was charged with AgSbF₆ (0.9 mg, 0.0025 mmol) and IPrAuCl (2.4 mg, 0.0038 mmol). The vial was sealed with a screw cap containing a teflon-lined septum and removed from the glovebox. Under a positive pressure of nitrogen, DCE (0.2 mL) was added to the vial and the contents were stirred for 15 min. After allowing the precipitate to settle, the solution layer was transferred to another one-dram vial containing silyl ether **2.19** (10 mg, 0.025 mmol) dissolved in DCE (0.3 mL). This reaction was stirred at room temperature for 1.5 h. The reaction was diluted with hexanes, washed with water and brine, dried over anhydrous sodium sulfate, and condensed under reduced pressure. Purification by flash chromatography (gradient elution: 1% to 10% ethyl acetate in hexanes) afforded 4 mg (40% yield) of indenopyran **2.24** as a 2.5:1 mixture of diastereomers. The diastereoselectivity was later confirmed to be due to decomposition of the undesired diastereomer. R_f = 0.7 (10% CH_2Cl_2 in hexanes); ^1H NMR (500 MHz, C_6D_6) δ 7.57 (d, J = 7.5 Hz, 1H), 7.44 (d, J = 7.5 Hz, 0.4H), 7.38 (d, J = 7.4 Hz, 0.4H), 7.35 (d, J = 7.5 Hz, 1H), 7.19-7.12 (m, 2.4H), 7.07 (t, J = 7.5 Hz, 0.4H), 6.01 (d, J = 2.8 Hz, 0.4H), 5.91 (d, J = 2.9 Hz, 1H), 5.42 (d, J = 6.8 Hz, 0.4H), 5.29 (d, J = 5.1 Hz, 1H), 3.08 (dd, J = 5.0, 3.0

Hz, 1H), 2.70 (dd, $J = 6.8, 3.0$ Hz, 0.4 H), 1.66 (s, 3H), 1.64 (s, 1.2H), 1.63 (s, 1.2H), 1.44 (s, 1.2 H), 1.40 (s, 1.2H), 1.38 (s, 3H), 1.31 (s, 3H), 1.22-1.18 (m, 4.2H), 1.14 (m, 25.2H), 1.06 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 146.9, 146.4, 140.0, 139.2, 137.2, 136.1, 128.9, 128.7, 128.6, 128.4, 126.0, 125.7, 123.6, 123.3, 121.4, 78.4, 74.9, 73.9, 72.6, 72.2, 59.8, 53.4, 32.5, 32.0, 30.9, 30.6, 30.0, 29.5, 25.7, 23.3, 18.71, 18.69, 18.6, 18.4, 14.4, 14.2; HRMS (ES+) calculated for $\text{C}_{25}\text{H}_{40}\text{O}_2\text{SiNa}$ $[\text{M}+\text{Na}]^+$: 423.2695, found: 423.2707.

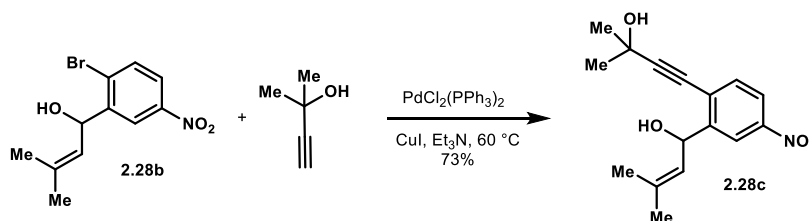


Diene 2.34. Indenopyran **2.24** (4 mg, 0.4 mmol) was dissolved in CDCl_3 and added to an NMR tube. Three drops of methane sulfonic acid were added. After ten min, ^1H NMR showed no remaining starting material. The reaction was quenched with trimethylamine, washed with water, dried over anhydrous sodium sulfate, and condensed under reduced pressure. Crude ^1H NMR and ^{13}C NMR are provided. ^1H NMR (500 MHz; CDCl_3): δ 7.53 (d, $J = 7.3$ Hz, 1H), 7.24-7.20 (m, 2H), 7.13 (td, $J = 7.0$ Hz, 1.5 Hz, 1H), 6.72 (d, $J = 1.8$ Hz, 1H), 6.39 (d, $J = 1.5$ Hz, 1H), 1.55 (s, 6H), 1.48 (s, 6H). ^{13}C NMR (125 MHz; CDCl_3): δ 143.5, 142.8, 134.0, 133.9, 127.9, 124.3, 124.0, 120.6, 120.5, 119.8, 73.2, 72.8, 31.5, 30.6.



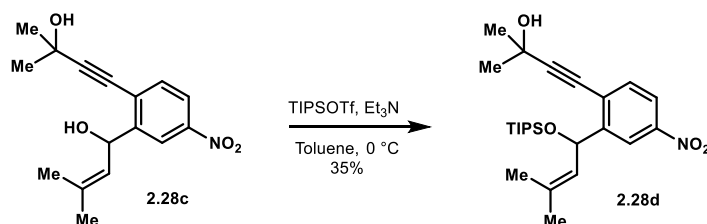
Alcohol 2.28b. A flame-dried Schlenk under N_2 was charged with bis(2-methylprop-1-en-1-yl)zinc²⁹ (0.19 g, 1.1 mmol), N,N-dimethylaminoethanol (15 μL , 0.15 mmol), and toluene (5 mL), and cooled to 0 $^\circ\text{C}$. Diethyl zinc (32 μL , 3.1 mmol) was added slowly and the reaction

stirred for 10 min. A solution of **2.28a** (prepared in one step from 2-bromobenzaldehyde³⁰ as a 12:1 mixture of regioisomers) (0.23 g, 1.0 mmol) in toluene (4 mL) was added dropwise. The reaction was then quenched with sat. aq. NH₄Cl and extracted twice with toluene. The combined organic layers were washed with brine and dried over anhydrous sodium sulfate. Concentration under reduced pressure afforded 0.264 g of (99% yield) alcohol **2.28b** as a dark yellow oil and a 12:1 mixture of regioisomers. *R*_f = 0.4 (20% ethyl acetate in hexanes); ¹H NMR (500 MHz, CDCl₃) δ 8.51 (d, *J* = 2.8 Hz, 1H), 7.96 (dd, *J* = 8.7, 2.8 Hz, 1H), 7.68 (d, *J* = 8.7 Hz, 1H), 5.73 (d, *J* = 9.1 Hz, 1H), 5.20-5.17 (m, 1H), 2.09 (brs, 1H), 1.91 (d, *J* = 1.3 Hz, 3H), 1.76 (d, *J* = 1.2 Hz, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 147.8, 145.5, 139.1, 133.8, 129.1, 125.0, 123.2, 122.8, 69.8, 25.9, 18.9; HRMS (CI) calculated for C₁₁H₁₂BrNO₃ [M]⁺: 286.9981, found: 286.9986.

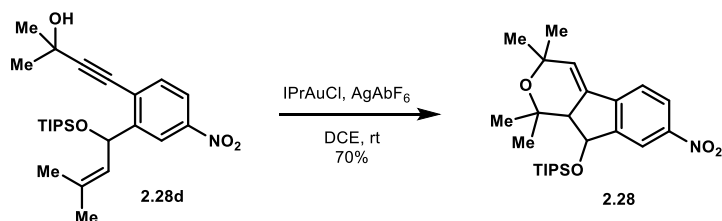


Diol 2.28c. A flame-dried Schlenk under N₂ was charged with PdCl₂(PPh₃)₂ (18 mg, 0.025 mmol) and CuI (2.4 mg, 0.012 mmol). A solution of alcohol **2.28b** (0.14 g, 0.5 mmol) in triethylamine (2 mL) was degassed with argon and added to the Schlenk. 2-Methyl-3-buten-2-ol (0.1 mL, 1.0 mmol) was added to the Schlenk and the reaction was heated to 60 °C for 30 min, then another portion of PdCl₂(PPh₃)₂ (18 mg, 0.025 mmol) and CuI (2.4 mg, 0.012 mmol) was added and heated an additional 1.5 h. The reaction was cooled to room temperature, diluted in ethyl acetate, and filtered through Celite. Concentration under reduced pressure followed by purification by flash chromatography (gradient elution 25 to

35% EtOAc in hexanes with 5% increments) afforded 0.109 g (73% yield) of diol **2.28c** as a yellow solid. $R_f = 0.3$ (40% ethyl acetate in hexanes); ^1H NMR (500 MHz, CDCl_3) δ 8.41 (d, $J = 2.4$ Hz, 1H), 8.03 (dd, $J = 8.5, 2.4$ Hz, 1H), 7.51 (d, $J = 8.5$ Hz, 1H), 5.84 (dd, $J = 8.7, 2.5$ Hz, 1H), 5.36 (m, 1H), 2.37 (brs, 1H), 2.32 (brs, 1H), 1.86 (d, $J = 1.4$ Hz, 3H), 1.76 (d, $J = 1.4$ Hz, 3H), 1.62 (s, 6H); ^{13}C NMR (126 MHz, CDCl_3) δ 148.0, 147.7, 138.2, 133.6, 127.1, 136.2, 122.0, 121.6, 103.5, 79.0, 68.6, 65.8, 31.4, 31.3, 25.9, 18.9; HRMS (ES+) calculated for $\text{C}_{16}\text{H}_{19}\text{NO}_4\text{Na}$ $[\text{M}+\text{Na}]^+$: 312.1212, found: 312.1219.

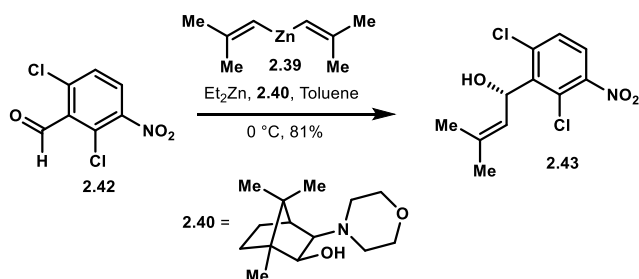


Silyl ether 2.28d. A round-bottom flask under N_2 was charged with diol **2.28c** (0.109 g, 0.38 mmol), Et_3N (0.21 mL, 1.52 mmol), and toluene (1.9 mL) and cooled to 0 °C. TIPSOTf (0.20 mL, 0.76 mmol) was added dropwise and the reaction stirred at 0 °C for 45 min. The reaction was quenched sat. aq. NaHCO_3 and partitioned in EtOAc, then washed with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. Purification on Et_3N -deactivated silica gel (gradient elution 10 to 15% EtOAc in hexanes) afforded 60 mg (35% yield) of silyl ether **2.28d**. $R_f = 0.3$ (20% ethyl acetate in hexanes); ^1H NMR (500 MHz, C_6D_6) δ 8.84 (d, $J = 2.4$ Hz, 1H), 7.70 (dd, $J = 8.5, 2.4$ Hz, 1H), 7.13 (d, $J = 8.5$ Hz, 1H), 6.21 (d, $J = 8.9$ Hz, 1H), 5.49-5.46 (m, 1H), 1.94 (d, $J = 1.2$ Hz, 3H), 1.73 (brs, 1H), 1.62 (d, $J = 1.1$ Hz, 3H), 1.54 (s, 6H), 1.25-1.18 (m, 21H); ^{13}C NMR (151 MHz, C_6D_6) δ 149.8, 148.3, 133.4, 133.1, 129.2, 125.7, 122.5, 121.6, 102.9, 79.6, 69.4, 65.4, 31.4, 31.2, 25.7, 19.6, 18.2, 18.1, 12.6; HRMS (CI) calculated for $\text{C}_{25}\text{H}_{39}\text{NO}_4\text{Si}$ $[\text{M}]^+$: 445.2648, found: 445.2647.

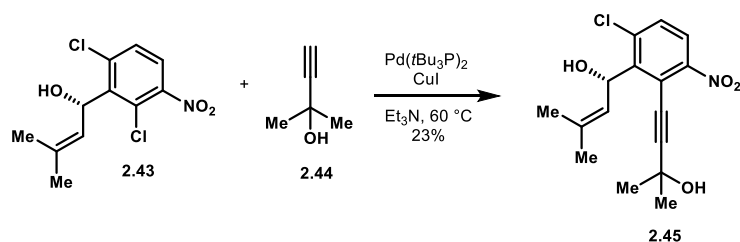


Indenopyran 2.28. In a glovebox under pressure of nitrogen, a one-dram vial was charged with AgSbF₆ (1.6 mg, 0.0044 mmol) and IPrAuCl (4.0 mg, 0.0066 mmol). The vial was sealed with a screw cap containing a teflon-lined septum and removed from the glovebox. Under a positive pressure of nitrogen, DCE (0.2 mL) was added to the vial and the contents were stirred for 15 min. After allowing the precipitate to settle, 0.1 mL of this solution was transferred to another one-dram vial containing silyl ether **2.28d** (10 mg, 0.022 mmol) dissolved in DCE (0.1 mL). This reaction was stirred at room temperature for 1 h. The reaction was diluted with hexanes, filtered through Celite, and condensed under reduced pressure. Purification by flash chromatography (gradient elution: 10 to 15% DCM in hexanes) afforded 7 mg (70% yield) of indenopyran **2.28** as a 1.2:1 mixture of diastereomers. *R*_f = 0.4 (30% DCM in hexanes); ¹H NMR (500 MHz, CDCl₃) δ 8.33 (d, *J* = 2.1 Hz, 1.2H), 8.32 (d, *J* = 2.1 Hz, 1H), 8.21-8.17 (m, 2.2H), 7.60 (d, *J* = 8.4 Hz, 1.2H), 7.54 (d, *J* = 8.4 Hz, 1H), 6.36 (d, *J* = 3.0 Hz, 1.2H), 6.27 (d, *J* = 3.0 Hz, 1H), 5.64 (d, *J* = 7.0 Hz, 1.2H), 5.22 (d, *J* = 5.3 Hz, 1H), 2.90 (dd, *J* = 5.3, 3.0 Hz, 1H), 2.84 (dd, *J* = 7.0, 3.0 Hz, 1.2 H), 1.52 (s, 3.6H), 1.49 (s, 3H), 1.43 (s, 3.6H), 1.39 (s, 3.6 H), 1.36 (s, 3H), 1.35 (s, 3H), 1.31 (s, 3.6H), 1.24 (m, 3.6H), 1.16 (m, 12H), 1.11 (m, 23.4H), 1.05 (s, 3H), 0.94 (d, *J* = 7.0 Hz, 10.8H); ¹³C NMR (151 MHz, CDCl₃) δ 148.05, 147.6, 147.4, 147.3, 146.0, 144.7, 135.4, 134.3, 128.9, 128.3, 124.5, 124.2, 121.6, 121.4, 121.3, 120.9, 77.3, 75.1, 74.9, 74.1, 72.9, 72.6, 59.6, 53.0, 31.9, 31.4, 30.3,

30.1, 29.5, 29.0, 25.0, 23.2, 18.6, 18.4, 18.2, 17.8, 14.1, 13.9; HRMS (ES+) calculated for $C_{25}H_{39}NO_4SiNa$ $[M+Na]^+$: 468.2546, found: 468.2540.

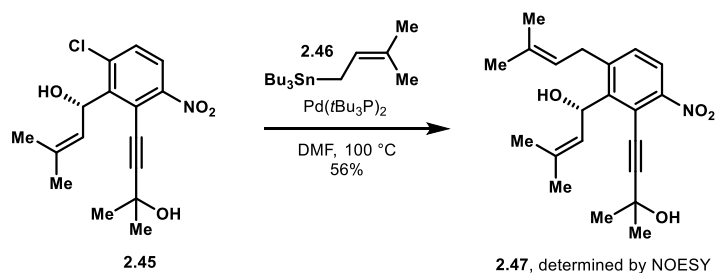


Alcohol 2.43. A flame-dried Schlenk under N_2 was charged with bis(2-methylprop-1-en-1-yl)zinc²⁶ **2.39** (58 mg, 0.33 mmol), aminoalcohol **2.40**³¹ (0.7 mg, 0.003 mmol), and toluene (1.5 mL) and cooled to 0 °C. Diethyl zinc (95 μ L, 0.93 mmol) was added slowly and the reaction stirred for 10 min. A solution of nitroaldehyde **2.42** (66 mg, 0.3 mmol) in toluene (1.2 mL) was added dropwise. The reaction was then quenched with sat. aq. NH_4Cl and extracted twice with toluene. The combined organic layers were washed with brine and dried over anhydrous sodium sulfate. Concentration under reduced pressure afforded 67 mg alcohol **2.43** (0.24 mmol, 81% yield) as a dark yellow oil. 1H NMR (500 MHz; $CDCl_3$) δ 7.57 (d, J = 8.7 Hz, 1H), 7.44 (d, J = 8.7 Hz, 1H), 6.21 (t, J = 7.3 Hz, 1H), 5.80-5.77 (m, 1H), 2.61 (d, J = 7.0 Hz, 1H), 1.86 (d, J = 1.3 Hz, 3H), 1.79 (d, J = 1.3 Hz, 3H).



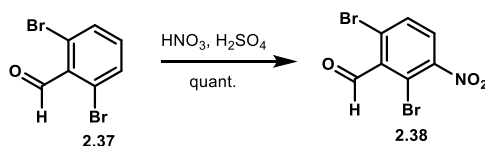
Alcohol 2.45. Bis(Tri-*tert*-butylphosphine)palladium(0) (2 mg, 0.004 mmol) and copper(I) iodide (0.8 mg, 0.004 mmol) were added to a flame-dried Schlenk in a glovebox. The Schlenk was transferred to a manifold and placed under nitrogen, then a degassed solution of alcohol

2.45 in triethylamine (28 mg, 0.1 mmol in 0.4 mL) was added, followed by 2-methyl-3-butyl-2-ol **2.44** (11 μ L, 0.11 mmol) and heated to 60 °C for 2.5 h. The reaction was then cooled to room temperature, diluted with ethyl acetate, filtered through Celite, and concentrated under reduced pressure. Purification by flash chromatography (gradient elution 10 to 30% EtOAc in hexanes in 10% increments) afforded 7.6 mg (0.023 mmol, 23% yield). ^1H NMR (500 MHz, CDCl_3) δ 7.75 (d, J = 8.8 Hz, 1H), 7.44 (d, J = 8.8 Hz, 1H), 6.15 (t, J = 8.7 Hz, 1H), 5.82-5.80 (m, 1H), 3.14 (d, J = 9.1 Hz, 1H), 2.45 (s, 1H), 1.87 (d, J = 1.2 Hz, 3H), 1.77 (d, J = 0.9 Hz, 3H), 1.64 (s, 6H); ^{13}C NMR (126 MHz; CDCl_3) δ 150.9, 145.3, 139.6, 138.0, 130.7, 123.8, 123.5, 117.5, 108.7, 84.1, 75.3, 69.2, 31.2, 30.85, 30.79, 26.1.

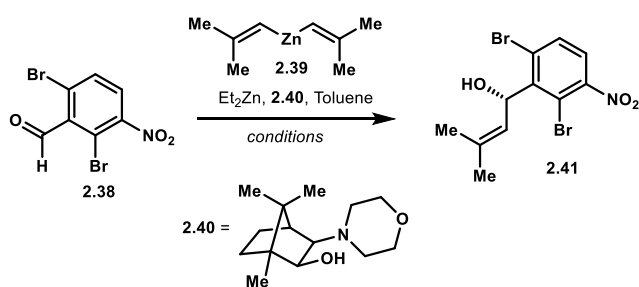


Diol 2.47. Diol **2.45** (6.5 mg, 0.02 mmol), tributyl(3-methyl-2-butenyl)tin **2.46** (20 μ L, 0.06 mmol), bis(tri-*tert*-butylphosphine)palladium(0) (1 mg, 0.002 mmol) and DMF (0.1 mL) were combined in a flame-dried Schlenk under N_2 and heated to 100 °C for 2h. The reaction was then cooled to room temperature, diluted with EtOAc, filtered through Celite, and concentrated under reduced pressure. Purification by flash chromatography (gradient elution 5 to 35% in 10% increments) afforded 4 mg diol **2.47** (0.011 mmol, 56% yield). ^1H NMR (500 MHz; C_6H_6) δ 7.31 (d, J = 8.4 Hz, 1H), 6.75 (d, J = 8.4 Hz, 1H), 6.14 (t, J = 7.0 Hz, 1H), 6.16-6.13 (m, 1H), 5.15-5.11 (m, 1H), 3.52-3.42 (m, 2H), 2.61 (d, J = 6.3 Hz, 1H), 1.97 (s, 1H), 1.71 (d, J = 1.1 Hz, 3H), 1.62 (d, J = 1.1 Hz, 3H), 1.57 (s, 3H), 1.53-1.50 (m, 3H), 1.43 (s, 3H),

1.42 (s, 3H); ^{13}C NMR (126 MHz; C_6D_6) δ 151.2, 146.4, 145.7, 137.2, 133.4, 130.6, 126.6, 122.7, 116.0, 107.4, 76.4, 69.0, 65.6, 32.3, 31.1, 30.9, 25.86, 25.72.

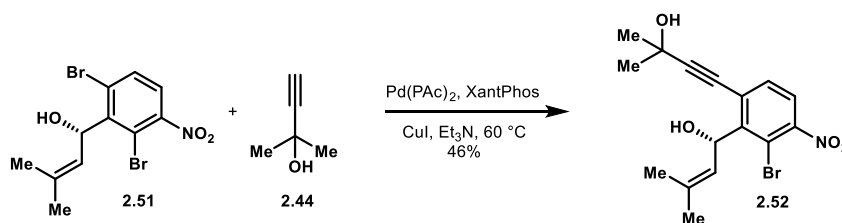


Nitroaldehyde 2.38. 2,6-Dibromobenzaldehyde (6.4 g, 24.2 mmol) was dissolved in H_2SO_4 (24 mL) and HNO_3 (3.6 mL) at 0°C for 5 min. Ice was added and then the reaction was poured into H_2O and extracted three times with dichloromethane. The combined organic layers were washed once with H_2O and twice with sat. aq. NaHCO_3 , then dried over anhydrous sodium sulfate. Concentration under reduced pressure afforded 7.4 g (99% yield) of nitroaldehyde **2.38** as a light yellow solid. $R_f = 0.4$ (10% ethyl acetate in hexanes); ^1H NMR (500 MHz, CDCl_3) δ 10.18 (s, 1H), 7.80 (d, $J = 8.6$, 1H), 7.71 (d, $J = 8.6$, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ 189.7, 150.7, 134.2, 127.8, 127.1, 115.9; HRMS (CI) calculated for $\text{C}_7\text{H}_3\text{Br}_2\text{NO}_3$ $[\text{M}]^+$: 308.8464, found: 308.8459.



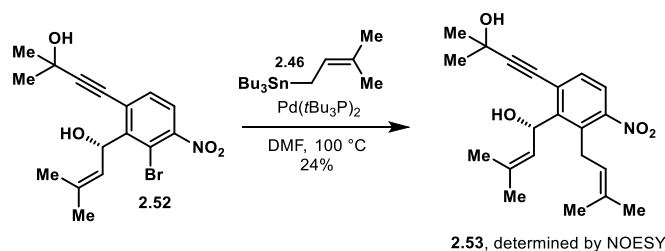
Alcohol 2.41. A flame-dried Schlenk under N_2 was charged with bis(2-methylprop-1-en-1-yl)zinc²⁶ **2.39** (1.16 g, 6.6 mmol), aminoalcohol **2.40**²⁸ (57 mg, 0.24 mmol), and toluene (30 mL) and cooled to 0°C . Diethyl zinc (1.9 mL, 18.6 mmol) was added slowly and the reaction stirred for 10 min. A solution of nitroaldehyde **2.38** (1.85 g, 6.0 mmol) in toluene (24 mL) was added via syringe pump over 20 min. The reaction was then quenched with sat. aq.

NH₄Cl and extracted twice with toluene. The combined organic layers were washed with brine and dried over anhydrous sodium sulfate. Concentration under reduced pressure afforded 2.2 g alcohol **2.41** (quant. yield) as a dark yellow oil. 84% *ee* by Mosher ester analysis comparing integration values for the vinyl CH for the diastereomeric esters. *R*_f = 0.25 (10% ethyl acetate in hexanes); ¹H NMR (500 MHz, CDCl₃) δ 7.69 (d, *J* = 8.5 Hz, 1H), 7.38 (d, *J* = 8.5 Hz, 1H), 6.19 (t, *J* = 8.3 Hz, 1H), 5.78 (d, *J* = 8.4 Hz, 1H), 2.75 (d, *J* = 8.2 Hz, 1H), 1.88 (s, 3H), 1.79 (s, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 151.7, 143.5, 140.7, 134.2, 127.1, 123.7, 122.7, 115.4, 72.9, 26.1, 19.0; [α]_D²² +101.0 (c 1.0, CHCl₃); HRMS (FI+) calculated for C₁₁H₁₁Br₂NO₃ [M]⁺: 364.9086, found: 364.9091.

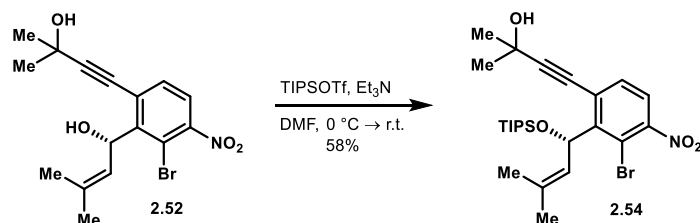


Diol 2.52. A flame-dried Schlenk under N₂ was charged with Pd(OAc)₂ (27 mg, 0.12 mmol), XantPhos (69 mg, 0.12 mmol), CuI (5.7 mg, 0.03 mmol) and DCM (0.5 mL) and stirred for 10 min. The solvent was evaporated and replaced with a solution of alcohol **2.51** (1.10 g, 3.0 mmol) in triethylamine (12 mL) that had been degassed with argon. 2-Methyl-3-butyn-2-ol **2.44** (0.31 mL, 3.24 mmol) was added to the Schlenk and the reaction as heated to 60 °C for 2 h. The reaction was cooled to room temperature, diluted in ethyl acetate, and filtered through Celite. Concentration under reduced pressure followed by purification by flash chromatography (gradient elution 25 to 35% EtOAc in hexanes in 5% increments) afforded 0.353 g (35% yield) of diol **2.52** as a yellow solid. *R*_f = 0.45 (50% ethyl acetate in hexanes); ¹H NMR (500 MHz, CDCl₃) δ 7.50 (d, *J* = 8.3 Hz, 1H), 7.47 (d, *J* = 8.3 Hz, 1H), 6.11 (d, *J* = 8.6 Hz,

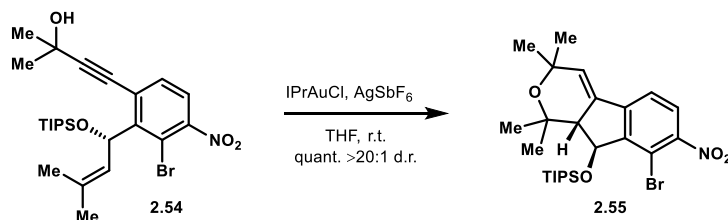
1H), 5.75 (dt, $J = 8.5, 1.2$ Hz, 1H), 3.09 (brs, 1H), 2.25 (brs, 1H), 1.89 (d, $J = 0.9$ Hz, 3H), 1.78 (s, 3H), 1.64 (s, 6H); ^{13}C NMR (126 MHz, CDCl_3) δ 151.2, 147.2, 139.5, 133.6, 126.1, 123.6, 122.8, 114.3, 104.2, 79.1, 71.4, 65.8, 31.13, 31.08, 26.1, 18.9; $[\alpha]_{\text{D}}^{22} +94.4$ (c 1.0, CHCl_3); HRMS (ES+) calculated for $\text{C}_{16}\text{H}_{18}\text{BrNO}_4\text{Na}$ $[\text{M}+\text{Na}]^+$: 390.0317, found: 390.0314.



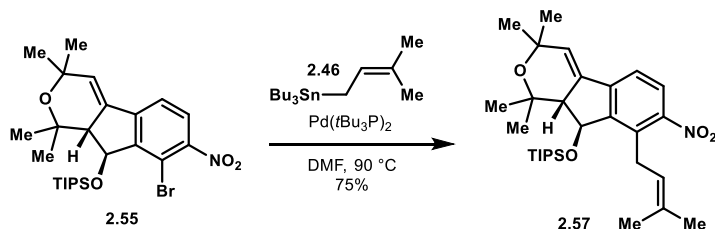
Diol 2.53. Diol **2.52** (26 mg, 0.071 mmol), tributyl(3-methyl-2-butenyl)tin **2.46** (70 μL , 0.21 mmol), bis(tri-*tert*-butylphosphine)palladium(0) (3.6 mg, 0.007 mmol) and DMF (0.66 mL) were combined in a flame-dried Schlenk under N_2 and heated to 100 $^\circ\text{C}$ for 1h. The reaction was quenched with aqueous KF, cooled to room temperature, diluted with EtOAc, and washed three times with water, once with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. Purification by flash chromatography (gradient elution 30 to 40% EtOAc in hexanes in 5% increments) afforded 6 mg impure diol **2.53** (0.017 mmol, 23% yield). ^1H NMR (500 MHz; CDCl_3) δ 7.49 (d, $J = 8.3$ Hz, 1H), 7.40 (d, $J = 8.3$ Hz, 1H), 5.89 (t, $J = 7.7$ Hz, 1H), 5.72-5.69 (m, $J = 1.4$ Hz, 1H), 5.04-5.01 (m, $J = 1.5$ Hz, 1H), 3.60 (qd, $J = 14.7, 6.0$ Hz, 2H), 2.90 (d, $J = 7.1$ Hz, 1H), 2.28 (s, 1H), 1.80 (d, $J = 1.0$ Hz, 3H), 1.75 (s, 3H), 1.70 (d, $J = 0.9$ Hz, 3H), 1.68 (d, $J = 1.4$ Hz, 3H), 1.63 (s, 6H); ^{13}C NMR (151 MHz; CDCl_3) δ 151.4, 146.9, 138.7, 133.9, 133.8, 132.2, 125.6, 122.6, 121.3, 102.9, 80.5, 68.4, 65.9, 31.25, 31.22, 28.0, 27.5, 27.0, 26.1, 25.7.



Silyl ether 2.54. A round-bottom flask under N₂ was charged with diol **2.52** (0.388 g, 1.05 mmol), Et₃N (0.44 mL, 3.15 mmol), and DMF (1 mL) and cooled to 0 °C. TIPSOTf (0.36 mL, 1.36 mmol) was added dropwise and the reaction stirred at 0 °C for 30 min, then warmed to r.t. for 1.5 h. The reaction was diluted in EtOAc and washed once with sat. aq. NaHCO₃, three times with H₂O, and once and brine. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. Purification on Et₃N-deactivated silica gel (gradient elution 10 to 15% EtOAc in hexanes) afforded 0.308 g (58% yield) of protected alcohol **2.54** as a yellow solid. NMR spectra show peak broadening due to restricted rotation of the TIPS-ether, resulting in several peaks missing in the ¹³C NMR. R_f = 0.5 (30% ethyl acetate in hexanes); ¹H NMR (500 MHz, CDCl₃) δ 7.47 (d, *J* = 7.9 Hz, 1H), 7.38 (brs, 1H), 6.19 (brs, 1H), 6.10 (d, *J* = 8.0 Hz), 2.02 (brs, 1H), 1.75 (brs, 3H), 1.72 (s, 3H), 1.63 (s, 6H), 1.16-1.08 (m, 3H), 1.04 (d, *J* = 7.4 Hz, 9H), 0.98 (d, *J* = 7.4 Hz, 9H); ¹³C NMR (126 MHz, CDCl₃) δ 134.7, 134.3, 132.8, 126.1, 122.1, 113.9, 102.2, 71.9, 65.9, 31.1, 26.2, 18.05, 18.03, 12.4; [α]_D²² -3.7 (c 1.0, CHCl₃); HRMS (ES⁺) calculated for C₂₅H₃₈BrNO₄SiNa [M+Na]⁺: 548.1635, found: 548.1643.

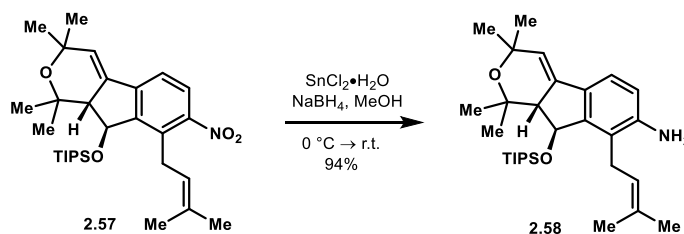


Indenopyran 2.55. IPrAuCl (21 mg, 0.034 mmol) and AgSbF₆ (10 mg, 0.028 mmol) were combined in a dram vial under N₂ and dissolved in THF (0.6 mL) and stirred for 10 min at rt, then the precipitate was allowed to settle. The supernatant was added to the round-bottom flask containing silyl ether **2.54** (0.292 g, 0.56 mmol) in THF and the reaction stirred at r.t. for 1 h. The reaction was diluted in hexanes and filtered through Celite, then concentrated under reduced pressure to afford 0.292 g (quant. yield) of indenopyran **2.55** as a yellow solid and a single diastereomer. R_f = 0.55 (10% ethyl acetate in hexanes); ¹H NMR (500 MHz, CDCl₃) δ 7.77 (d, *J* = 8.2 Hz, 1H), 7.49 (d, *J* = 8.2 Hz, 1H), 6.27 (d, *J* = 2.8 Hz, 1H), 5.24 (d, *J* = 3.0 Hz, 1H), 2.84 (t, *J* = 2.9 Hz, 1H), 1.52 (s, 3H), 1.36 (s, 3H), 1.32 (s, 3H), 1.16-1.08 (m, 3H), 1.01 (d, *J* = 7.4 Hz, 9H), 0.95 (d, *J* = 7.4 Hz, 9H), 0.88 (s, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 150.1, 147.7, 144.5, 135.6, 129.6, 126.7, 119.5, 115.0, 78.9, 74.7, 73.0, 57.9, 31.1, 29.8, 29.7, 22.0, 18.5, 18.5, 13.9; [α]_D²² -43.2 (c 1.0, CHCl₃); HRMS (ES⁺) calculated for C₂₅H₃₈BrNO₄SiNa [M+Na]⁺: 548.1635, found: 548.1647.



Indenopyran 2.57. Bis(tri-*tert*-butylphosphine)palladium(0) (8.2 mg, 0.16 mmol) was added to a flame-dried Schlenk flask in the glovebox. The flask was removed from the glovebox and placed under nitrogen on a manifold. A solution of indenopyran **2.56** (0.162 g, 0.31 mmol) in DMF (3.1 mL) was added, followed by tributyl(3-methyl-2-butenyl)tin **2.46** (0.31 mL, 0.93 mmol) and the reaction was heated to 90 °C for 45 min. The reaction was cooled to room temperature, quenched with aqueous KF (1.0 M) and stirred for 10 min. The

reaction was then partitioned with EtOAc and washed three times with water, once with brine, and dried over anhydrous sodium sulfate. Purification by flash chromatography (gradient elution 15 to 20% DCM in hexanes) afforded 0.119 g (0.23 mmol, 75% yield) of indenopyran **2.57** as a light yellow oil. R_f = 0.5 (5% EtOAc in hexanes); ^1H NMR (500 MHz; CDCl_3) δ 7.82 (d, J = 8.3 Hz, 1H), 7.38 (d, J = 8.4 Hz, 1H), 6.21 (d, J = 2.8 Hz, 1H), 5.27 (d, J = 3.1 Hz, 1H), 5.01-4.98 (m, 1H), 3.95 (dd, J = 14.9, 7.0 Hz, 1H), 3.81 (dd, J = 15.0, 6.2 Hz, 1H), 2.81 (t, J = 2.9 Hz, 1H), 1.74 (s, 3H), 1.65 (s, 3H), 1.50 (s, 3H), 1.35 (s, 3H), 1.32 (s, 3H), 1.02-0.96 (m, 12H), 0.90 (d, J = 6.9 Hz, 9H), 0.86 (s, 3H); ^{13}C NMR (126 MHz; CDCl_3) δ 149.9, 146.5, 143.8, 136.5, 135.9, 134.0, 127.9, 126.4, 120.8, 118.3, 77.2, 74.7, 73.0, 57.6, 31.2, 29.9, 29.7, 27.7, 25.7, 21.8, 18.32, 18.22, 18.14, 14.0; $[\alpha]_D^{22}$ -54.9 (c 1.0, CHCl_3); HRMS (ES+) calculated for $\text{C}_{30}\text{H}_{47}\text{NO}_4\text{SiNa}$ $[\text{M}+\text{Na}]^+$: 536.3172, found: 536.3188.



Aniline 2.58. Indenopyran **2.57** (0.119 g, 0.23 mmol), $\text{SnCl}_2 \cdot \text{H}_2\text{O}$ (0.311 g, 1.38 mmol) and MeOH (2.3 mL) were combined in a round bottom flask and cooled to 0 °C. NaBH_4 (35 mg, 0.92 mmol) was added and the flask was capped with a rubber septum and placed under N_2 . The reaction was allowed to warm to room temperature over 1 hr, then quenched with saturated aqueous ammonium chloride and partitioned with EtOAc. The aqueous layer was extracted twice with EtOAc, and the combined organic layers were washed with water and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to afford 0.094 g (0.23 mmol, 94% yield) of aniline **2.58**. R_f = 0.45 (10% EtOAc in hexanes); ^1H

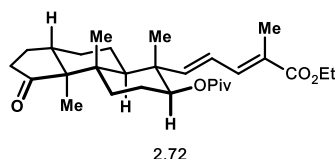
Reaction scheme showing the conversion of compound 2.57 to compound 2.59. The reaction conditions are SmI_2 , THF, MeOH, -78°C , quant.

Compound 2.57 (left) is a tricyclic molecule with a TIPSO group, a nitro group (NO_2), and a methylallyl group.

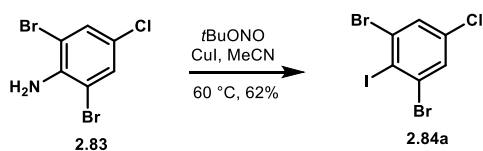
Compound 2.59 (right) is the product, which is identical to 2.57 but with the nitro group reduced to a hydroxylamine group (NHOH).

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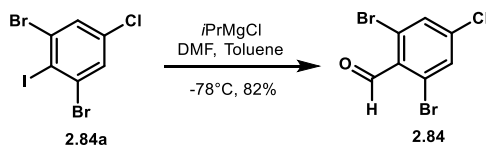
$[\alpha]_D^{22}$ -18.2 (c 0.80, CHCl₃); HRMS (ES⁺) calculated for C₃₀H₄₉NO₃SiNa [M+Na]⁺: 522.3380, found: 522.3378.



Ketone **2.72** was prepared by Devon Schatz according to the literature.²²

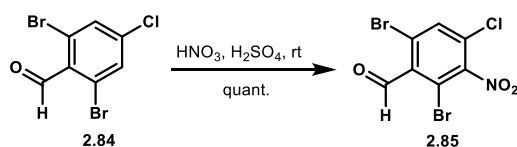


Aryl iodide 2.84a. A flame-dried Schlenk under N₂ was charged with 4-chloro-2,6-dibromoaniline (6.85 g, 24 mmol), *t*BuONO (4.3 mL, 36 mmol), CuI (9.14 g, 48 mmol), and MeCN (96 mL) and heated to 60 °C for 16h. The reaction was then cooled to room temperature, diluted in 1:1 hexanes/ethyl acetate, and filtered through Celite. Concentration under reduced pressure followed by purification by flash chromatography (gradient elution: 2% to 4% EtOAc in hexanes) afforded 6.2 g (65% yield) of aryl iodide 2.84a as red crystals. ¹H and ¹³C MNR data match that provided in the literature.³²

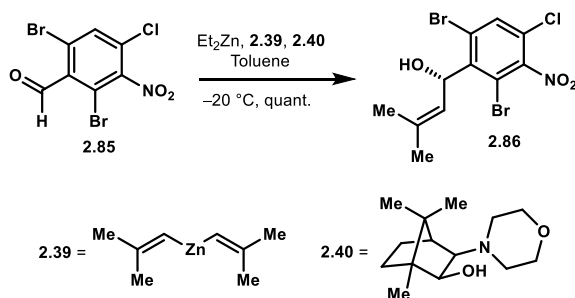


Aryl aldehyde 2.84. A flame-dried Schlenk under N₂ was charged with aryl iodide **2.84a** (5.15 g, 13 mmol) and toluene (30 mL), then cooled to -78 °C. *i*PrMgCl (7.9 mL, 1.82 M in THF) was added slowly and the reaction stirred for 1.5 h. DMF (2.0 mL, 26 mmol) was added,

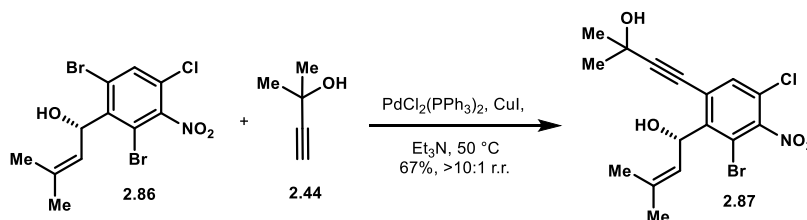
stirred for 5 min, then warmed slowly to room temperature over 1.5 h. The reaction was quenched with sat. aq. NH_4Cl and extracted three times with toluene. The combined organic layers were washed with H_2O and brine and dried over anhydrous sodium sulfate, then concentrated under reduced pressure. The crude was dissolved in 20% DCM in hexanes and filtered through silica to afford 3.2 g (82% yield) of aryl aldehyde **2.84** as a yellow solid. R_f = 0.25 (20% DCM in hexanes); ^1H NMR (500 MHz, CDCl_3) δ 10.21 (s, 1H), 7.68 (s, 2H); ^{13}C NMR (151 MHz, CDCl_3) δ 190.2, 139.6, 133.7, 131.2, 125.4; HRMS (FI+) calculated for $\text{C}_7\text{H}_3\text{Br}_2\text{ClO}$ $[\text{M}]^+$: 297.8217, found: 297.8212.



Nitroaldehyde 2.85. Aryl aldehyde **2.84** (3.2 g, 10.7 mmol) was dissolved in H_2SO_4 (10 mL) and HNO_3 (1.7 mL) at room temperature for 5 min. Ice was added and the reaction poured into H_2O and extracted three times with dichloromethane. The combined organic layers were washed once with H_2O and twice with sat. aq. NaHCO_3 , then dried over anhydrous sodium sulfate. Concentration under reduced pressure afforded 3.7 g (quant. yield) of nitroaldehyde **2.85** as a light yellow solid. R_f = 0.3 (10% ethyl acetate in hexanes); ^1H NMR (500 MHz, CDCl_3) δ 10.15 (s, 1H), 7.88 (s, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ 188.6, 137.0, 135.0, 133.0, 130.3, 126.1, 116.3; HRMS (CI) calculated for $\text{C}_7\text{HBr}_2\text{ClNO}_3$ $[\text{M}-\text{H}]^+$: 341.7990, found: 341.7997.

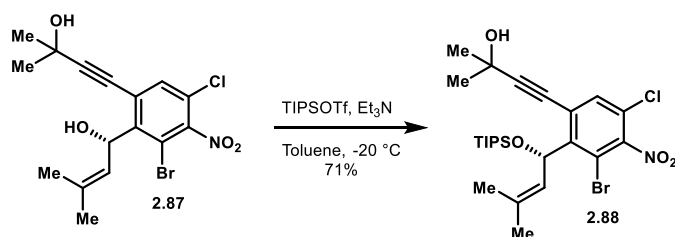


Alcohol 2.86. A flame-dried Schlenk under N₂ was charged with bis(2-methylprop-1-en-1-yl)zinc²⁶ **2.39** (0.96 g, 5.5 mmol), aminoalcohol **2.40**²⁸ (48 mg, 0.2 mmol), and toluene (25 mL), and cooled to -20 °C. Diethyl zinc (1.6 mL, 15.5 mmol) was added slowly and the reaction stirred for 10 min. A solution of nitroaldehyde **2.85** (1.72 g, 5 mmol) in toluene (20 mL) was added via syringe pump over 20 min. The reaction was then quenched with sat. aq. NH₄Cl and extracted twice with toluene. The combined organic layers were washed with brine and dried over anhydrous sodium sulfate. Concentration under reduced pressure afforded 2.0 g alcohol **2.86** (quant. yield) as a dark yellow oil. 89% *ee* by Mosher ester analysis comparing integration values for the vinyl CH for the diastereomeric esters. R_f = 0.5 (20% ethyl acetate in hexanes); ¹H NMR (500 MHz, CDCl₃) δ 7.76 (s, 1H), 6.09 (t, J = 8.0 Hz, 1H), 5.75-5.72 (m, 1H), 2.56 (d, J = 7.6 Hz, 1H), 1.87 (d, J = 1.3 Hz, 3H), 1.79 (d, J = 1.1 Hz, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 150.5, 141.7, 140.8, 134.5, 125.12, 125.07, 122.3, 115.4, 72.5, 26.1, 19.0; [α]_D²² +87.2 (c 1.0, CHCl₃); 89% *ee*; HRMS (FI+) calculated for C₁₁H₁₀Br₂ClNO₃ [M]⁺: 398.8695, found: 398.8681.



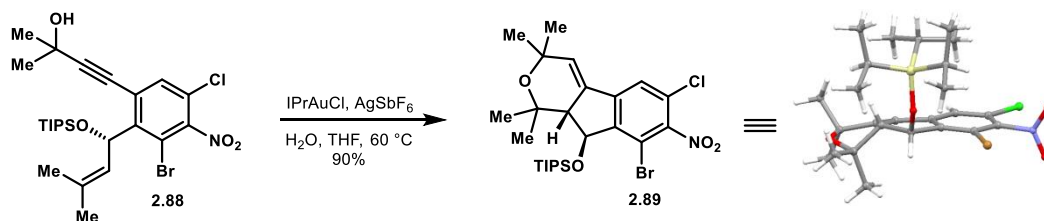
Diol 2.87. A flame-dried Schlenk under N₂ was charged with PdCl₂(PPh₃)₂ (56 mg, 0.08 mmol) and CuI (8 mg, 0.04 mmol). A solution of alcohol **2.86** (0.80 g, 2.0 mmol) in triethylamine (8 mL) was degassed with argon and added to the Schlenk. 2-Methyl-3-butyn-2-ol (0.21 mL, 2.2 mmol) was added to the Schlenk and the reaction was heated to 60 °C for 2 h. The reaction was cooled to room temperature, diluted in ethyl acetate, and filtered

through Celite. Concentration under reduced pressure followed by purification by flash chromatography (gradient elution: 30 to 40% EtOAc in hexanes) afforded 0.542 g diol **2.87** (67% yield) as a yellow solid. R_f = 0.5 (50% ethyl acetate in hexanes); ^1H NMR (500 MHz, CDCl_3) δ 7.55 (s, 1H), 5.99 (t, J = 8.6 Hz, 1H), 5.74-5.70 (m, 1H), 2.92 (d, J = 8.6 Hz, 1H), 2.23 (s, 1H), 1.86 (d, J = 1.3 Hz, 3H), 1.77 (d, J = 1.3 Hz, 3H), 1.64 (s, 6H); ^{13}C NMR (126 MHz, CDCl_3) δ 150.1, 145.2, 139.6, 134.3, 125.2, 124.4, 123.2, 114.5, 104.3, 78.1, 71.1, 65.7, 31.04, 31.00, 26.1, 18.9; $[\alpha]_D^{22}$ +90.1 (c 1.0, CHCl_3); 89% *ee*; HRMS (ES+) calculated for $\text{C}_{16}\text{H}_{17}\text{BrClNO}_4\text{Na}$ $[\text{M}+\text{Na}]^+$: 425.9906, found: 425.9914.

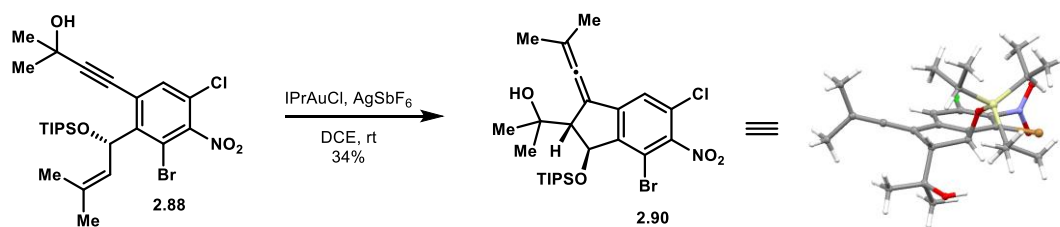


Silyl ether 2.88. A round-bottom flask under N_2 was charged with diol **2.87** (1.23 g, 3.05 mmol), Et_3N (2.55 mL, 18.3 mmol), and toluene (15 mL) and cooled to $-10\text{ }^\circ\text{C}$. TIPSOTf (1.64 mL, 6.1 mmol) was added dropwise and the reaction stirred at $-10\text{ }^\circ\text{C}$ for 3 h. The reaction was quenched with dry MeOH (1.5 mL) and warmed to room temperature for 10 min. The reaction was diluted in toluene and washed with sat. aq. NaHCO_3 and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. Purification on Et_3N -deactivated silica gel (gradient elution: 5% to 15% EtOAc in hexanes with 2.5% increments) afforded 1.20 g (71% yield) of silyl ether **2.88**. ^1H and ^{13}C NMR both show peak broadening due to restricted rotation of the TIPS-ether. R_f = 0.45 (10% ethyl acetate in hexanes); ^1H NMR (500 MHz, CDCl_3) δ 7.52 (s, 1H), 6.23-5.91 (m, 2H), 2.05 (s, 1H), 1.74 (s, 3H), 1.72 (s, 3H), 1.62 (d, J = 2.6 Hz, 6H), 1.15-1.08 (m, 3H), 1.03 (d, J = 7.6 Hz, 9H), 0.98 (d, J = 7.5 Hz, 9H); ^{13}C NMR

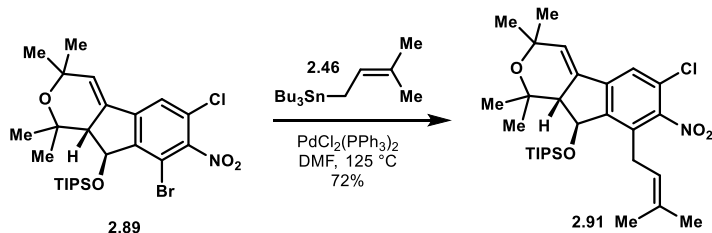
(126 MHz, CDCl₃) δ 151.6, 145.4, 135.2, 134.6, 133.2, 125.8, 123.8, 114.2, 102.4, 78.6, 71.5, 65.8, 31.1 (2C), 26.2, 19.4, 18.04, 17.99, 12.3; $[\alpha]_D^{22}$ -0.58 (c 1.0, CHCl₃); 89% *ee*, HRMS (ES+) calculated for C₂₅H₃₇BrClNO₄SiNa [M+Na]⁺: 582.1242, found: 582.1234.



Indenopyran 2.89. H₂O (8 μ L) and THF (0.5 mL) were combined under N₂ and 0.1 mL of this solution was added to a round-bottom flask containing silyl ether **2.88** (0.270 g, 0.48 mmol) in THF (3 mL). IPrAuCl (36 mg, 0.058 mmol) and AgSbF₆ (16 mg, 0.048 mmol) were combined in a dram vial under N₂ and dissolved in THF (1.5 mL) and stirred for 10 min at r.t., then the precipitate was allowed to settle. The supernatant was added to the round-bottom flask containing silyl ether **2.88** in THF and the reaction was heated to 60 °C for 3.5 h. The reaction was diluted in hexanes and filtered through Celite, then concentrated under reduced pressure. Purification by flash chromatography (elution 5% EtOAc in hexanes) afforded 0.241 g (0.43 mmol, 90% yield) of indenopyran **2.89** as a yellow solid and a single diastereomer. *R*_f = 0.45 (5% ethyl acetate in hexanes); ¹H NMR (600 MHz, CDCl₃) δ 7.53 (s, 1H), 6.24 (d, *J* = 2.8 Hz, 1H), 5.17 (d, *J* = 3.1 Hz, 1H), 2.83 (d, *J* = 3.0 Hz, 1H), 1.50 (s, 3H), 1.35 (s, 3H), 1.32 (s, 3H), 1.15-1.09 (m, 3H), 1.02 (d, *J* = 7.4 Hz, 9H), 0.96 (d, *J* = 7.4 Hz, 9H), 0.89 (s, 3H); ¹³C NMR (151 MHz, CDCl₃) δ 149.9, 145.3, 142.7, 134.8, 129.7, 127.1, 121.0, 114.0, 78.5, 74.6, 73.0, 58.0, 31.1, 29.7 (2C), 22.0, 18.5, 18.3, 13.9; $[\alpha]_D^{22}$ -6.5 (c 1.0, CHCl₃); 89% *ee*; HRMS (ES+) calculated for C₂₅H₃₇BrClNO₄SiNa [M+Na]⁺: 580.1242, found: 580.1251.

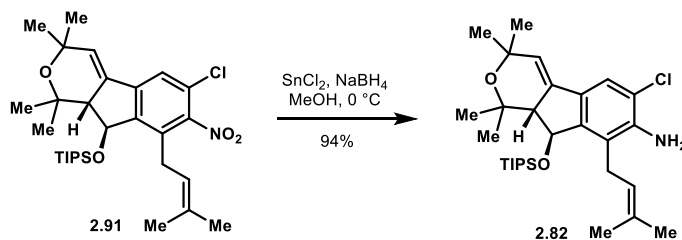


Allene 2.90. A round-bottom flask containing silyl ether **2.88** (0.187 g) in DCE (1.8 mL). IPrAuCl (12 mg, 0.020 mmol) and AgSbF₆ (5 mg, 0.016 mmol) were combined in a dram vial under N₂ and dissolved in DCE (1.5 mL) and stirred for 10 min at rt, then the precipitate was allowed to settle. The supernatant was added to the round-bottom flask containing silyl ether **2.88** in DCE and the reaction was stirred at r.t. for 16 h. The reaction was diluted in hexanes and filtered through Celite, then concentrated under reduced pressure. Purification by flash chromatography (gradient elution: 2.5% to 7% EtOAc in hexanes in 2.5% increments) afforded 63 mg g of allene **2.90** (34% yield) as a yellow solid and a single diastereomer as well as 68 mg dihydropyran **2.89** (see above). R_f = 0.6 (10% ethyl acetate in hexanes); ¹H NMR (600 MHz, CDCl₃) δ 7.26 (s, 1H), 5.37 (s, 1H), 2.90 (s, 1H), 1.87 (s, 3H), 1.84 (s, 3H), 1.53 (s, 1H), 1.21-1.13 (m, 6H), 1.07-1.05 (m, 18H), 0.99 (s, 3H); ¹³C NMR (151 MHz, CDCl₃) δ 200.5, 148.7, 145.0, 144.4, 126.7, 122.8, 112.2, 103.6, 102.4, 72.3, 63.2, 28.9, 26.5, 20.7, 20.3, 18.4, 17.8, 13.2; HRMS (ES⁺) calculated for C₂₅H₃₇BrClNO₄SiNa [M+Na]⁺: 582.1242, found: 582.1208.



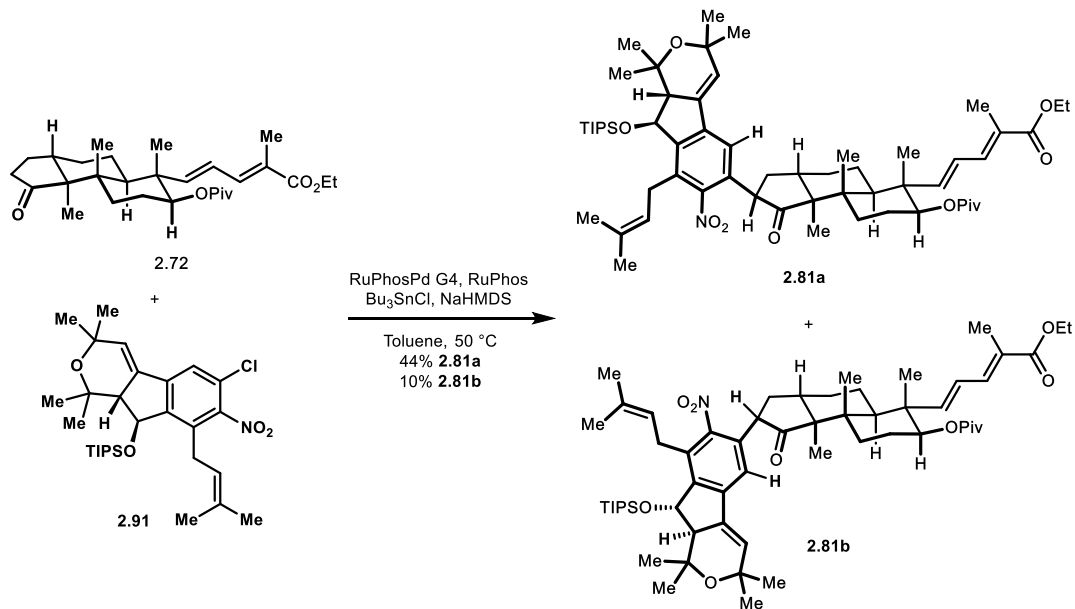
Nitrochloroarene 2.91. A flame-dried Schlenk under N₂ was charged with indenopyran **2.89** (0.452 g, 0.81 mmol), PdCl₂(PPh₃)₂ (56 mg, 0.08 mmol), tributyl(3-methyl-2-

butenyl)tin (0.54 mL, 1.62 mmol), and DMF (4 mL) and heated to 125 °C for 2 h. The reaction was quenched with 1N aq. KF (1.6 mL) and extracted three times with ethyl acetate. The combined organic layers were washed with water and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. Purification by flash chromatography (gradient elution 15 to 12% DCM in hexanes) afforded 0.318 g (72% yield) of nitrochloroarene **2.91** as a yellow oil. R_f = 0.5 (5% ethyl acetate in hexanes); ^1H NMR (500 MHz, CDCl_3) δ 7.42 (s, 1H), 6.16 (d, J = 2.8 Hz, 1H), 5.20 (d, J = 3.1 Hz, 1H), 4.99-4.96 (m, 1H), 3.87 (dd, J = 15.3, 7.0 Hz, 1H), 3.27 (dd, J = 15.3, 6.3 Hz, 1H), 2.79 (t, J = 2.9 Hz, 1H), 1.70 (s, 3H), 1.66 (s, 3H), 1.48 (s, 3H), 1.34 (s, 3H), 1.31 (s, 3H), 1.05-0.97 (m, 12H), 0.92 (d, J = 6.8 Hz, 9H), 0.85 (s, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 149.8, 144.1, 141.9, 135.2, 134.8, 134.5, 127.9, 126.4, 119.85, 119.80, 773.0, 74.7, 73.0, 57.6, 31.2, 29.8, 29.6, 27.3, 25.7, 21.8, 18.3, 18.2, 18.1, 14.0; $[\alpha]_D^{22}$ -32.6 (c 1.0, CHCl_3); 89% *ee*; HRMS (ES+) calculated for $\text{C}_{30}\text{H}_{46}\text{ClNO}_4\text{SiNa}$ $[\text{M}+\text{Na}]^+$: 570.2783, found: 570.2784.



Aniline 2.82. Nitroarene **2.91** (0.12 g, 0.23 mmol), $\text{SnCl}_2 \cdot \text{H}_2\text{O}$ (0.31 g, 1.38 mmol), and MeOH (2.3 mL) were combined in a round bottom flask and cooled to 0 °C. NaBH_4 (35 mg, 0.92 mmol) was added portionwise and the reaction was allowed to warm to r.t. over 1 h. The reaction was quenched with aqueous ammonium hydroxide and partitioned with EtOAc. The aqueous layer was extracted twice with a 1:1 EtOAc:hexanes mixture and the combined organic layers were washed with water and brine, dried over anhydrous sodium sulfate, and

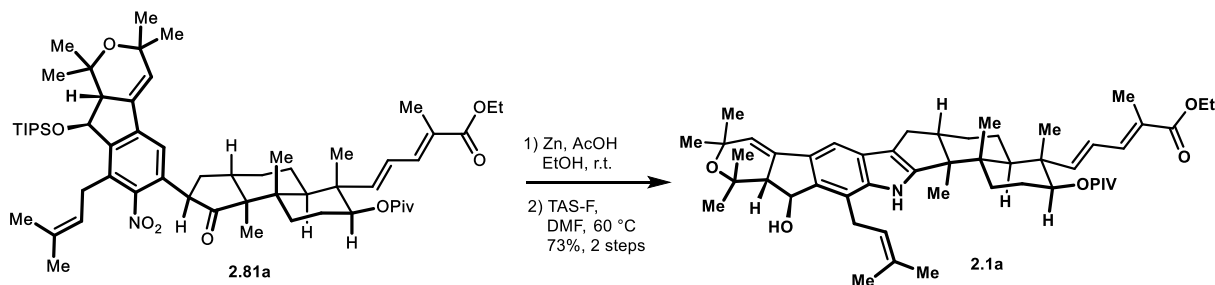
concentrated under reduces pressure to afford 0.104 g (0.22 mmol, 94% yield) of aniline **2.82** as a yellow oil. $R_f = 0.5$ in 5% EtOAc; ^1H NMR (500 MHz; CDCl_3) δ 7.29 (s, 1H), 5.81 (d, $J = 2.7$ Hz, 1H), 5.15 (d, $J = 3.2$ Hz, 1H), 5.02 (t, $J = 6.1$ Hz, 1H), 4.19 (s, 2H), 3.74 (dd, $J = 16.2$, 5.1 Hz, 1H), 3.29 (dd, $J = 16.0$, 7.1 Hz, 1H), 2.71 (t, $J = 2.8$ Hz, 1H), 1.80 (s, 3H), 1.72 (s, 3H), 1.47 (s, 3H), 1.32 (s, 3H), 1.28 (s, 3H), 0.99-0.96 (m, 13H), 0.90-0.88 (m, 12H); ^{13}C NMR (126 MHz; CDCl_3) δ 143.9, 142.3, 136.3, 134.6, 130.5, 124.8, 121.6, 121.3, 120.7, 118.9, 74.7, 72.9, 57.8, 31.7, 30.3, 29.86, 29.75, 27.4, 25.7, 22.1, 18.38, 18.18, 14.1; $[\alpha]_D^{22} -14.5$ (c 1.0, CHCl_3); 89% *ee*; HRMS (ES⁺) calculated for $\text{C}_{30}\text{H}_{46}\text{ClNO}_4\text{SiNa}$ $[\text{M}+\text{Na}]^+$: 518.3221, found: 518.3243.



Arylketones 2.81a and 2.81b. Synthesized by Devon Schatz. Ketone **2.72** (72.0 mg, 0.15 mmol) and chloroarene **2.91** (92.1 mg, 0.17 mmol) were azeotropically dried with benzene in separate dram vials before being transferred into a glovebox. To the dram vial containing chloroarene **2.91** was added RuPhosPd G4 (32.3 mg, 0.038 mmol) and RuPhos (17.7 mg, 0.038 mmol). To the dram vial containing ketone **2.72** was added Bu_3SnCl (3.04 mL, 0.05 M in toluene), which was then placed in a freezer cooled to -25 °C for 1 h. A 0.05 M solution of

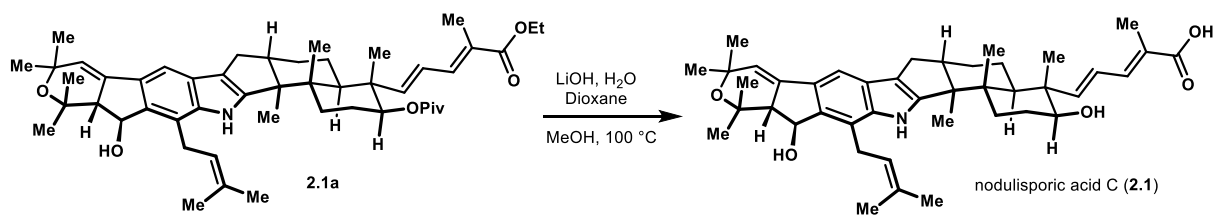
NaHMDS in toluene was also prepared and placed in the freezer for 1 h. NaHMDS (3.35 mL, 0.05 M) was then added to the ketone solution and placed back in the freezer for 30 min, then allowed to warm to r.t. over an additional 30 min. The tin enolate solution was next added to the vial containing arylchloride, precatalyst and ligand, cooled back down to -25 °C for 1 h and then added NaHMDS (0.76 mL, 0.05 M). The reaction was warmed back up to r.t. then heated to 50 °C in a sand bath for 17 h. The reaction mixture was removed from the glovebox, quenched with a saturated aqueous solution of NH₄Cl and extracted with ethyl acetate three times (30 mL combined). The combined organic layers were washed with water (20 mL), brine (20 mL), dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Purification by flash chromatography (gradient elution: 100% hexanes to 8% ethyl acetate in hexanes) yielded a mixture of diastereomers and starting ketone **2.72**. Further purification by preparatory TLC (15% ethyl acetate in hexanes) allowed for separation of diastereomers, yielding undesired arylketone **2.81b** (16.0 mg, 10% yield) and desired arylketone **2.81a** (72.5 mg, 44% yield) and as pale-yellow amorphous solids along with starting ketone **2.72** (19.8 mg, 28% recovery). Characterization of **2.81a**: R_f = 0.52 (20% ethyl acetate in hexanes); ¹H NMR (500 MHz, CD₃OD) δ 7.27 (s, 1H), 7.16 (d, 1H, J = 11.4 Hz), 6.37-6.32 (m, 2H), 5.89 (d, 1H, J = 15.3 Hz), 5.28 (d, 1H, J = 3.1 Hz), 4.94-4.92 (m, 1H), 4.67 (dd, 1H, J = 11.4, 4.6 Hz), 4.19 (q, 2H, J = 7.0 Hz), 3.88 (dd, 1H, J = 15.4, 7.0 Hz), 3.73 (dd, 1H, J = 10.5, 2.0 Hz), 3.35 (dd, 1H, J = 15.6, 6.8 Hz), 2.81 (t, 1H, J = 2.8 Hz), 2.70-2.62 (m, 1H), 2.27-2.20 (m, 1H), 2.18-2.16 (m, 1H), 2.06 (ddd, 1H, J = 13.5, 7.2, 2.1 Hz), 1.90 (d, 3H, J = 1.2 Hz), 1.83 – 1.74 (m, 4H), 1.70 (s, 3H), 1.64 (s, 3H), 1.57-1.44 (m, 7H), 1.34 (s, 3H), 1.33 (s, 3H), 1.30 (t, 3H, J = 7.1 Hz), 1.21 (s, 3H), 1.18 (s, 3H), 1.17 (s, 3H), 1.10 (s, 9H), 1.02-0.99 (m, 12H), 0.93 (d, 9H, J = 6.1 Hz), 0.86 (s, 3H); ¹³C

NMR (125 MHz, CD₃OD) δ 217.9, 179.2, 170.0, 154.0, 153.3, 145.0, 142.7, 139.7, 137.0, 136.3, 135.1, 134.0, 127.9, 126.7, 126.1, 121.5, 118.3, 78.8, 78.4, 76.0, 74.4, 61.8, 59.0, 58.0, 47.8, 46.9, 46.5, 40.44, 40.43, 39.9, 33.0, 31.4, 31.3, 30.1, 30.0, 28.4, 27.5, 26.7, 25.7, 24.6, 24.3, 22.1, 18.7, 18.6, 18.2, 18.1, 15.1, 14.6, 12.9, 12.7, 12.3; $[\alpha]_D^{22}$ -115.4 (c 1.0, CHCl₃); HRMS (ES+) calculated for C₅₉H₈₉O₉SiNa [M+Na]⁺: 1006.6204, found: 1006.6236. Characterization for **2.81b**: R_f = 0.48 (20% ethyl acetate in hexanes); ¹H NMR (500 MHz, CD₃OD) δ 7.18 (s, 1 H), 7.16 (d, 1 H, J = 11.2 Hz), 6.35 (dd, 1 H, J = 15.4, 11.2 Hz), 6.29 (d, 1 H, J = 2.6 Hz), 5.89 (d, 1 H, J = 15.4 Hz), 5.28 (d, 1 H, J = 3.0 Hz), 5.03-5.00 (m, 1 H), 4.69 (dd, 1 H, J = 11.0, 4.8 Hz), 4.19 (q, 2 H, J = 7.1 Hz), 3.91 (dd, 1 H, J = 15.3, 7.5 Hz), 3.35 (dd, 1 H, J = 10.7, 8.1 Hz), 3.19 (dd, 1 H, J = 15.2, 5.7 Hz), 2.80 (t, 1 H, J = 2.8 Hz), 2.42-2.36 (m, 1 H), 2.25 (ddd, 1 H, J = 12.1, 8.1, 5.2 Hz), 2.21-2.18 (m, 1 H), 1.90 (d, 3 H, J = 1.2 Hz), 1.84-1.81 (m, 2 H), 1.79-1.75 (m, 1 H), 1.73 (s, 3 H), 1.71-1.68 (m, 2 H), 1.66 (s, 3 H), 1.51-1.46 (m, 6 H), 1.33 (s, 3 H), 1.32 (s, 3 H), 1.29 (t, 3 H, J = 7.1 Hz), 1.31-1.28 (m, 1 H), 1.20 (s, 3 H), 1.18 (s, 3 H), 1.15 (s, 3 H), 1.10 (s, 9 H), 1.02-0.97 (m, 12 H), 0.92 (d, 9 H, J = 6.7 Hz), 0.86 (s, 3 H); ¹³C NMR (125 MHz, CD₃OD) δ 219.5, 179.2, 170.0, 154.0, 153.2, 145.4, 142.8, 139.7, 136.9, 135.0, 134.8, 133.8, 128.1, 126.8, 126.1, 121.8, 118.9, 78.7, 78.3, 76.0, 74.4, 61.8, 58.9, 58.3, 54.1, 47.0, 46.6, 40.5, 40.2, 39.9, 35.1, 31.6, 31.4, 30.01, 29.99, 28.3, 27.6, 25.8, 25.7, 24.9, 24.3, 22.1, 19.1, 18.7, 18.5, 18.2, 15.2, 14.6, 12.8, 12.7, 10.9; $[\alpha]_D^{22}$ -52.1 (c 1.0, CHCl₃); HRMS (ES+) calculated for C₅₉H₈₉O₉SiNa [M+Na]⁺: 1006.6204, found: 1006.6193.



Nodulisporic acid C diester 2.1a. A 1 dram vial was charged with **2.81a** (19 mg, 0.019 mmol), Zn dust (62 mg, 0.95 mmol), AcOH (54 μ L, 0.95 mmol), and EtOH (1.9 mL) and stirred vigorously at room temperature for 45 min. The reaction was diluted in ethyl acetate and filtered through Celite, then concentrated under reduced pressure. The crude material was added to an oven-dried 1 dram vial, then transferred into a glovebox. The vial was charged with TAS-F and DMF, sealed with a screw cap containing a septum, and heated to 60 °C in the hood under N₂ for 1h. The reaction was quenched with sat. aq. NH₄Cl and extracted twice with ethyl acetate. The combined organic layers were washed twice with H₂O and once with brine, then dried over anhydrous sodium sulfate and concentrated under reduced pressure. Purification on pH 7 silica (gradient elution: 10% to 15% EtOAc in hexanes) afforded 10.5 mg (73 % yield, 2 steps) of nodulisporic acid C diester **2.1a** as a yellow solid. R_f = 0.25 (20% ethyl acetate in hexanes); ¹H NMR (600 MHz, CDCl₃) δ 7.83 (s, 1H), 7.40 (s, 1H), 7.16 (d, J = 11.1 Hz, 1H), 6.28 (dd, J = 15.4, 11.2 Hz, 1H), 5.96 (d, J = 2.85 Hz, 1H), 5.80 (d, J = 15.3 Hz, 1H), 5.42-5.39 (m, 1H), 5.08 (dd, J = 8.8, 5.0 Hz, 1H), 4.67 (dd, J = 9.9, 6.4 Hz, 1H), 4.20 (q, J = 7.1 Hz, 2H), 3.84-3.75 (m, 2H), 2.75-2.70 (m, 1H), 2.68 (dd, J = 4.8, 2.9 Hz, 1H), 2.64 (dd, J = 13.3, 6.4 Hz, 1H), 2.31 (dd, J = 13.3, 10.6 Hz, 1H), 2.09-2.04 (m, 1H), 1.92 (d, J = 1.2 Hz, 3H), 1.90-1.86 (m, 5H), 1.80-1.77 (m, 1H), 1.76 (d, J = 1.0 Hz, 3H), 1.73-1.71 (m, 1H), 1.61-1.54 (m, 1H), 1.51-1.49 (m, 5H), 1.46-1.40 (m, 1H), 1.34 (s, 3H), 1.32-1.30 (m, 6H), 1.17 (s, 3H), 1.16 (s, 3H), 1.12 (s, 9H), 1.08 (s, 3H), 1.02 (s, 3H); ¹³C NMR (151 MHz, CDCl₃) δ 177.8, 168.7, 152.0, 151.3, 141.2, 138.2, 136.1, 135.4, 133.0, 131.9, 126.8, 126.0, 125.2, 123.4, 121.8, 120.4, 118.6, 107.6, 77.2, 76.6, 74.0, 72.7, 60.7, 60.4, 53.2, 49.0, 45.8, 45.1, 39.1, 39.0, 33.2, 33.1, 30.1, 30.0, 27.6, 27.30, 27.26, 25.8, 25.2, 24.5, 23.6, 22.9, 19.4, 18.2, 14.6, 14.5,

12.8, 12.3; $[\alpha]_D^{22}$ -19.8 (c 0.5, CHCl₃); HRMS (ES+) calculated for C₅₀H₆₉NO₆Na [M+Na]⁺: 802.5023, found: 802.5002.



Nodulisporic acid C 2.1. A 1 dram vial was charged with **2.1a** (6 mg, 0.008 mmol) and LiOH·H₂O (17 mg, 0.40 mmol) and flushed with argon. H₂O (50 μL) that had been degassed with argon was added, followed by dioxane (0.1 mL) and MeOH (50 μL). The dram vial was again flushed with argon and sealed with a teflon-lined screw cap. The reaction was heated to 100 °C for 30h, then cooled to r.t.. The solvents were evaporated under reduced pressure and the crude was dissolved in a mixture of AcOH (0.14 mL) and EtOAc (2 mL) and sonicated until homogeneous. The volatiles were evaporated under reduced pressure, re-dissolved in EtOAc, and transferred to a round bottom flask with filtering through Celite. The solvent was again evaporated under reduced pressure to afford 5.5 mg (*ca.* 100% yield) of a yellow solid. The crude was dissolved in acetone-d₆ and transferred to an NMR tube. After collection of spectral data, 10 μL of D₂O was added and new spectra were collected. 10 μL of a saturated solution of NaHCO₃ in D₂O was added and shaken thoroughly, then new spectra of the sodium salt of nodulisporic acid C were collected. During the course of our investigations we were unable to obtain an adequate spectrum of the sodium salt in the absence of water due to substantial peak broadening. Upon addition of D₂O, rapid exchange of the indole NH with deuterium was observed. This and the D₂O/(CD₃)₂CO mixture could also account for the differences in chemical shift of the sodium salt compared to the reported spectra. However, we found that the free acid of nodulisporic acid C matched the reported spectra well and as

such was used for comparison. Characterization of NsA C free acid: $R_f = 0.5$ (10% methanol in DCM); ^1H NMR (600 MHz, $(\text{CD}_3)_2\text{CO}$) δ 9.04 (s, 1H), 7.32 (s, 1H), 7.22 (d, $J = 11.0$ Hz, 1H), 6.38 (dd, $J = 15.4, 11.3$ Hz, 1H), 5.99-5.97 (m, 2H), 5.31-5.30 (m, 1H), 5.03 (d, $J = 4.9$ Hz, 1H), 4.03 (dd, $J = 15.3, 8.0$ Hz, 1H), 3.71 (dd, $J = 15.1, 5.4$ Hz, 1H), 3.49 (dd, $J = 10.7, 4.4$ Hz, 1H), 2.78-2.73 (m, 1H), 2.69 (dd, $J = 4.8, 3.0$ Hz, 1H), 2.63 (dd, $J = 12.9, 6.4$ Hz, 1H), 2.30 (dd, $J = 12.3, 11.7$ Hz, 1H), 1.92 (s, 3H), 1.91-1.85 (m, 2H), 1.84 (s, 3H), 1.81-1.78 (m, 1H), 1.78-1.75 (m, 1H), 1.73-1.69 (m, 1H), 1.68 (s, 3H), 1.65-1.57 (m, 2H), 1.54-1.45 (m, 2H), 1.41 (s, 3H), 1.28 (s, 3H), 1.26 (s, 3H), 1.16 (s, 3H), 1.09 (s, 3H), 1.07 (s, 3H), 1.02 (s, 3H); ^{13}C NMR (126 MHz, $(\text{CD}_3)_2\text{CO}$) δ 170.5, 154.8, 153.1, 142.2, 139.6, 137.7, 137.3, 132.2, 131.7, 127.4, 125.8, 124.4, 123.4, 119.8, 118.9, 107.6, 77.0, 76.5, 74.3, 72.7, 60.7, 54.4, 49.8, 47.9, 45.1, 39.8, 33.5, 32.4, 30.44, 30.43, 29.8, 28.0, 27.7, 26.6, 25.8, 25.5, 23.2, 19.4, 18.2, 14.8, 12.9, 11.8; $[\alpha]_D^{22} - 18.9$ (c 0.4, MeOH); HRMS (ES+) calculated for $\text{C}_{43}\text{H}_{57}\text{NO}_5\text{Na}$ $[\text{M}+\text{Na}]^+$: 690.4135, found: 690.4130. Characterization of NsA C sodium salt: ^1H NMR (600 MHz, $(\text{CD}_3)_2\text{CO}$) δ 9.04 (s, 1H), 7.30 (s, 1H), 7.16 (d, $J = 11.2$ Hz, 1H), 6.34 (dd, $J = 15.4, 11.2$ Hz, 1H), 5.95 (d, $J = 2.9$ Hz, 1H), 5.90 (d, $J = 15.3$ Hz, 1H), 5.30 (t, $J = 6.9$ Hz, 1H), 5.01 (d, $J = 5.1$ Hz, 1H), 4.01 (dd, $J = 15.0, 7.8$ Hz, 1H), 3.71 (dd, $J = 15.0, 5.6$ Hz, 1H), 3.46 (dd, $J = 11.1, 4.6$ Hz, 1H), 2.76-2.71 (m, 1H), 2.69 (dd, $J = 4.9, 3.0$ Hz, 1H), 2.61 (dd, $J = 13.1, 6.4$ Hz, 1H), 2.27 (dd, $J = 13.0, 10.8$ Hz, 1H), 1.89 (s, 3H), 1.87-1.85 (m, 2H), 1.82 (s, 3H), 1.81-1.77 (m, 1H), 1.77-1.74 (m, 1H), 1.71-1.67 (m, 1H), 1.66 (s, 3H), 1.63-1.55 (m, 2H), 1.54-1.49 (m, 1H), 1.48-1.42 (m, 1H), 1.40 (s, 3H), 1.27 (s, 3H), 1.26 (s, 3H), 1.14 (s, 3H), 1.07 (s, 3H), 1.05 (s, 3H), 1.00 (s, 3H); ^{13}C NMR (126 MHz, $(\text{CD}_3)_2\text{CO}$) δ 153.6, 153.0, 142.0, 138.4, 137.5, 137.2, 132.1, 131.7, 127.3, 126.0, 124.3, 123.3, 119.7, 118.7, 107.5, 76.9, 74.4, 72.8, 60.5, 54.3, 49.8, 47.7, 45.0, 39.7, 33.4, 32.3, 30.3,

30.3, 27.9, 27.5, 26.5, 26.0, 25.8, 25.3, 23.1, 19.3, 18.1, 14.8, 13.3, 11.8; $[\alpha]_{\text{D}}^{22}$ -25.5 (c 0.4, MeOH).

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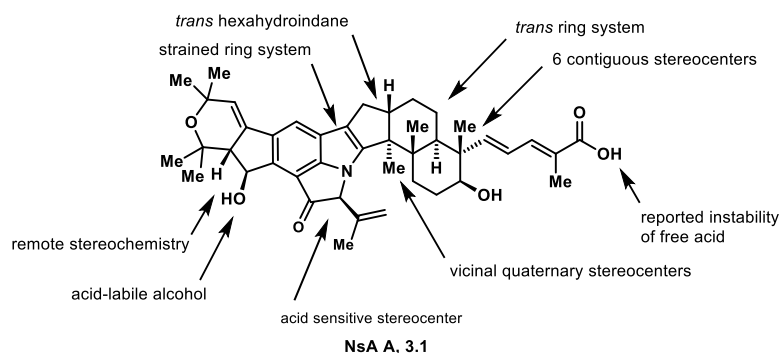
Chapter 3: Nodulisporic Acid A

3.1 Synthetic Planning

3.1.1 Synthetic Challenges

From a bioactivity perspective, NsA A (**3.1**, Figure 1) is the most important member of the nodulisporic acid family, with the highest natural potency and several known derivatives with improved

activity.¹ NsA A has all of the same structural challenges as NsA C, with an additional highly strained five-membered ring bearing an acid and base

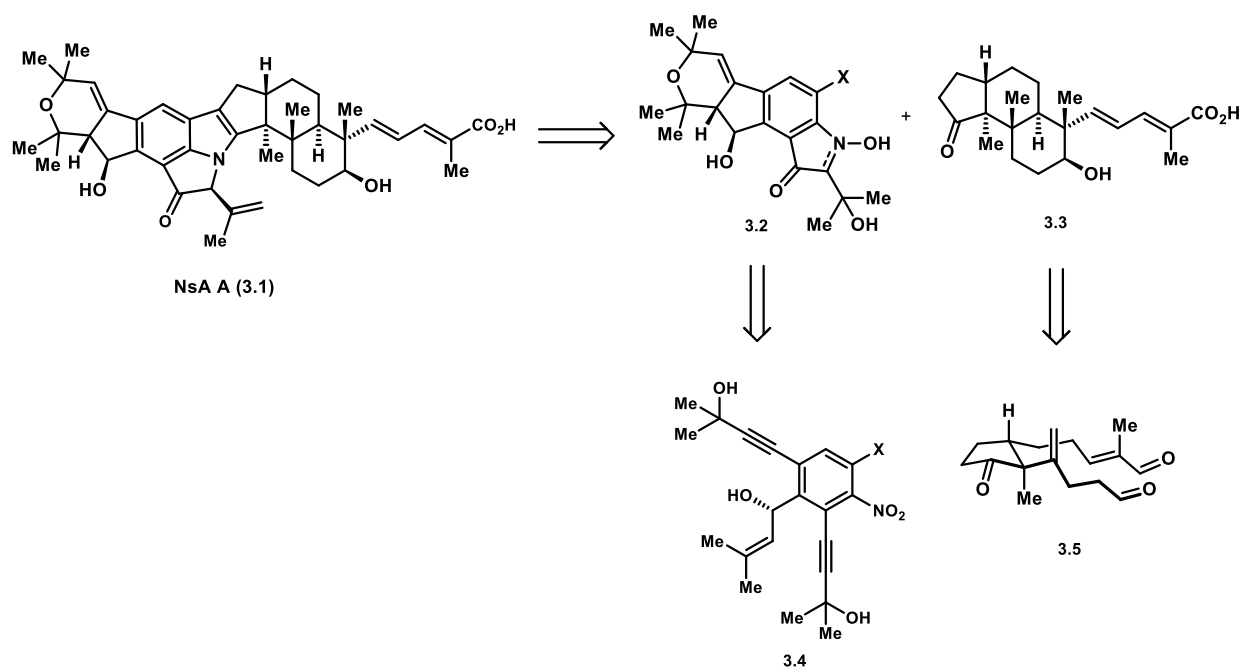


sensitive stereocenter. To date, a total synthesis of NsA A has not been reported; however, we imagined that the synthetic insights we gained during our synthesis of NsA C would allow us to utilize a similar strategy toward NsA A.

3.1.2 Retrosynthesis

We imagined a similar highly convergent strategy based on formation of the indole from two elaborated fragments. The terpene fragment would remain the same, while the indenopyran (**3.2**, Figure 3.2) would bear the additional five-membered ring installed prior to the fragment coupling. To construct the indenopyran fragment we proposed a dual alkyne cyclization to build three rings in a single step from diyne **3.4**. The enyne cycloisomerization to build the first two rings had already been proven in our synthesis of NsA C, and we believed that a similar Lewis acid catalyzed nitro-alkyne cyclization would afford the desired five-membered ring.

Figure 3.2: Retrosynthetic analysis of NsA A



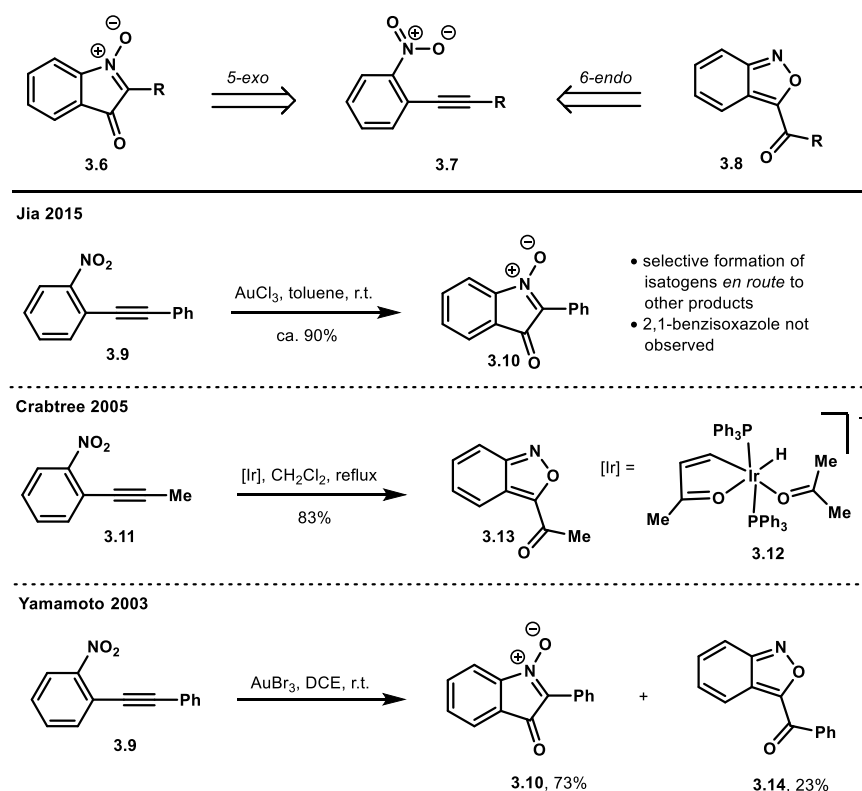
There is an inherent potential selectivity issue in the use of diyne **3.4** in our proposed dual cyclization. The two identical alkynes would both presumably be activated by a Lewis acid catalyst. If the alkyne *para* to the nitro group were activated first, the only possible reaction would be the desired enyne cycloisomerization. However, if the alkyne *ortho* to the nitro group were activated, either the alkene or the nitro group could attack, the former leading to an undesired and synthetically unusable product. We hoped that the sterically more accessible alkyne would react first, followed by the more hindered alkyne with double *ortho* substitution. Furthermore, we reasoned that if the more hindered alkyne were activated before the enyne cycloisomerization had been fully completed, the nitro group would be more nucleophilic and the desired cyclization would be kinetically favored.

3.1.3 Isatogen Formation

Nitro-alkyne cyclizations to form isatogens are well known;² however, these cyclizations can also form a 2,1-benzisoxazole (**3.8**, Figure 3.3) after a regioisomeric attack

on the alkyne and often produce a mixture of the two products.³ A report from Jia⁴ demonstrated selective formation of an isotogen *en route* to indoline-3-ones (Figure 3.3). Crabtree⁵ showed that an iridium hydride complex could selectively form the 2,1-benzisoxazole through a similar mechanism. Yamamoto⁶ reported a mixture of the two possible products using the same system as Jia under slightly different conditions. These reports indicated that while formation of the desired isotogen was possible, formation of a mixture of products or the undesired 2,1-benzisoxazole was also possible. In order to test this reaction, we designed a model system with a similar topography to our desired cyclization, here focusing only on the nitroalkyne cyclization rather than the dual cyclization for simplicity.

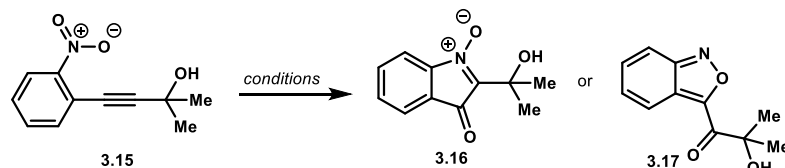
Figure 3.3: Proposed nitro-alkyne cyclization and relevant examples



3.2 Progress Toward the Synthesis of Nodulisporic Acid A

3.2.1 Development of a Nitro-Alkyne Cyclization

We chose to test the nitro-alkyne cyclization with arene **3.15** (Table 3.1), which we synthesized in one step from 2-bromonitrobenzene through a Sonogashira coupling. With our dual cyclization in mind, we initially tested the reaction with the IPrAuCl/AgSbF₆ system we used for the enyne cycloisomerization, hoping that this catalyst could effect both transformations. Unfortunately, even at –35 °C these conditions resulted in decomposition of our substrate (Table 3.1, Entry 1). Hoping to decrease the activity of the catalyst, we attempted the same transformation in the absence of any halide scavenger but observed no reaction, even with elevated temperatures (Entry 2). Switching to a phosphine ligand afforded decomposition at room temperature (Entry 3) and no reaction at lower temperatures (Entry 4). Using a different halide scavenger had no effect on the reactivity (Entry 5). At this point we decided to try conditions known in the literature to activate the alkyne to determine if the cyclization would produce our desired isatogen, irrespective of the conditions that might effect the indenopyran formation. Fortunately, in the presence of gold(III) chloride in toluene the cyclization afforded 58% of the desired isatogen with no observable formation of the 2,1-benzisoxazole (Entry 6).



Entry	Conditions	Result
1	10 mol% IPrAuCl, 20 mol% AgSbF ₆ , DCM, –35 °C	decomposition
2	10 mol% IPrAuCl, DCM –35 °C → 40 °C	no reaction
3	10 mol% AuCl(PPh ₃), 20 mol% AgSbF ₆ , DCM, 0 °C → r.t.	decomposition
4	10 mol% AuCl(PPh ₃), 20 mol% AgSbF ₆ , DCM, –35 °C → –10 °C	no reaction
5	10 mol% AuCl(PPh ₃), 20 mol% AgBF ₄ , DCM, –35 °C → –10 °C	decomposition
6	10 mol% AuCl, toluene, 0 °C	58% 3.16 , 3.17 not observed
7	20 mol% AcOH, MeCN, 82 °C	57% 3.16 , 3.17 not observed

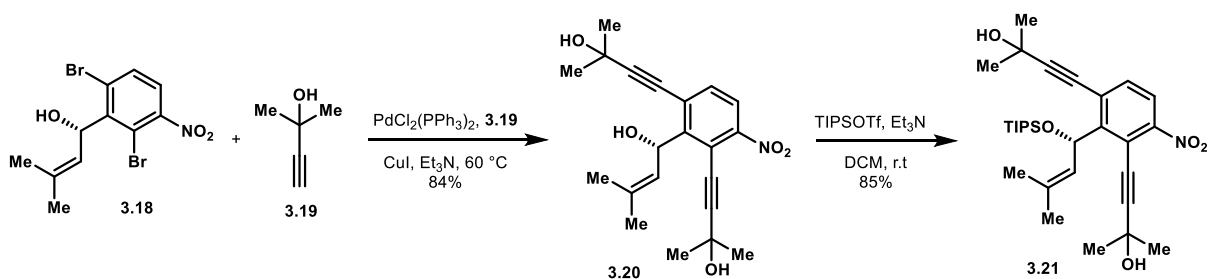
(Entry 5). At this point we decided to try conditions known in the literature to activate the alkyne to determine if the cyclization would produce our desired isatogen, irrespective of the conditions that might effect the indenopyran formation. Fortunately, in the presence of gold(III) chloride in toluene the cyclization afforded 58% of the desired isatogen with no observable formation of the 2,1-benzisoxazole (Entry 6).

During these studies we also observed trace amounts of isotogen formation from samples of **3.15** dissolved in solution for extended periods of time. We hypothesized that trace amounts of acid could be slowly catalyzing the reaction and therefore set out to probe the feasibility of this reaction in the presence of Brønsted acids. Under various conditions, we observed none of the desired reactivity, with the lone exception of acetic acid in acetonitrile at reflux (Entry 7). Under these conditions, we were able to replicate the yield of the gold(III) chloride reaction with a much cheaper and easier to handle reagent and were excited to test this cyclization on our fully elaborated system.

3.2.2 Synthesis of the Indenopyran Fragment

In the same way that we targeted chlorinated and non-chlorinated substrates for the synthesis of NsA C, we targeted both variants of the indenopyran for NsA A to afford the largest number of options for the fragment coupling strategy. The non-chlorinated indenopyran synthesis began with alcohol **3.18** (Figure 3.4) from our synthesis of NsA C.⁷ Sonogashira coupling installed both alkynes in a single reaction to provide diyne **3.20**, and silyl protection afforded the substrate to test our enyne cycloisomerization.

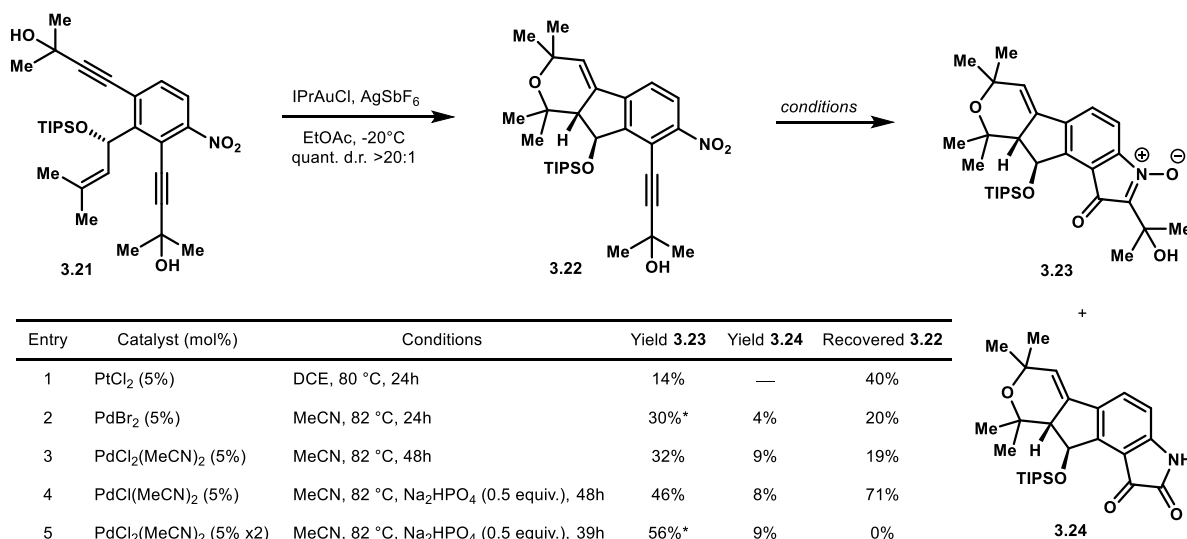
Figure 3.4: Synthesis of the enyne cycloisomerization precursor



We decided that it would be better to perform only the enyne cycloisomerization first. This would allow us to examine each reaction individually, and once we better understood the nitro-alkyne reactivity we could attempt the dual cyclization. Subjection of enyne **3.21**

to IPrAuCl and AgSbF₆ in halogenated solvents decomposed the starting material, even at – 35 °C. We reasoned that a more Lewis basic solvent could decrease the Lewis acidity of the IPrAuCl/AgSbF₆ system and ultimately found that running the reaction in ethyl acetate led to quantitative formation of the desired indenopyran (**3.22**, Table 3.2).

Table 3.2: Optimization of the nitro-alkyne cyclization



Catalysts affording no product: AuCl₃, PdCl₂(PPh₃)₂, CuBr • SMe₂, IPrAuCl/AgSbF₆, RhCl(PPh₃)₃/AgSbF₆, (MeCN)₄Pd(BF₄)₂, AgBF₄, AgNO₃, CuOTf • C₆H₆, PdI₂, ZnBr₂, InBr₃, Pd(OAc)₂, Hg(OTf)₂, NiBr₂, GaCl₃, HCl, AcOH, TFA, chloroacetic acid, trichloroacetic acid

*Isolated yields

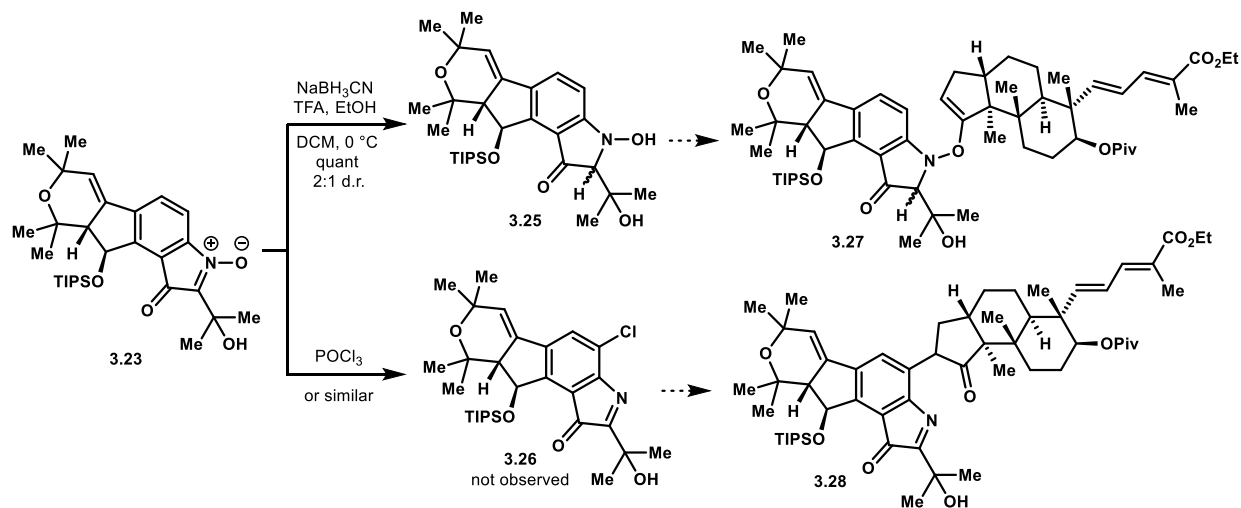
With the indenopyran in hand, we turned our sights to the nitro-alkyne cyclization. Unfortunately the conditions from our model system experiment did not produce any of the desired isatogen **3.23** (Table 3.2). Gold(III) chloride was unreactive while several Brønsted acids including acetic acid in acetonitrile served only to eliminate the benzylic silyl ether. We had initial success with platinum(II) chloride affording 14% yield of our desired isatogen (**3.23**) and 40% remaining nitroalkyne **3.22** (Entry 1). We achieved higher yields with palladium(II) halides, with bis(acetonitrile)palladium(II) chloride in acetonitrile affording a 32% yield of the desired product (Entry 3); however, we also isolated isatin **3.24** as an unexpected side product in the reaction. Isatin **3.24** likely arises through initial retro-aldol

of the isatogen followed by reduction to the isatin. Similar reductions have been observed in related isatogens formed from the corresponding 2-nitrophenyl haloacetylenes upon treatment with various palladium(II) species.⁸ Switching the solvent from acetonitrile to DMF or DMA produced less of the undesired isatin and better mass recovery but with very low yields of the isatogen. We discovered that addition of anhydrous dibasic sodium phosphate increased the yield to 46% while keeping the yield of the isatin low (Entry 4). Increased catalyst loadings did not increase the yield of **3.23**, though we found that addition of a second portion of catalyst halfway through the reaction increased the yield to 56% with full consumption of the starting material (Entry 5).⁹ Unfortunately, these conditions were unable to effect the desired enyne cycloisomerization to build the indenopyran from diyne **3.21**. We decided to move forward with the synthesis while performing two separate cyclizations with the hope of discovering conditions to perform the proposed dual cyclization at a later time.

We imagined two possible approaches to a coupling partner for the indenopyran fragment. In the first, a reduction afforded hydroxylamine **3.25** (Figure 3.5), which we imagined could be used in a Chan-Lam type coupling¹⁰ followed by a [3,3] sigmatropic rearrangement to afford an aminoketone or indole after condensation. We also imagined a ketone arylation strategy where we would need a functional handle *ortho* to the nitrone. In this case, we thought an aryl chloride could be installed with concomitant reduction of the nitrone to provide chloroarene **3.26**.¹¹ Unfortunately, in the presence of POCl₃ or tosylchloride and triethylbenzylammonium chloride we observed none of the desired product. Rather than continue chlorination attempts on this system, we utilized our model

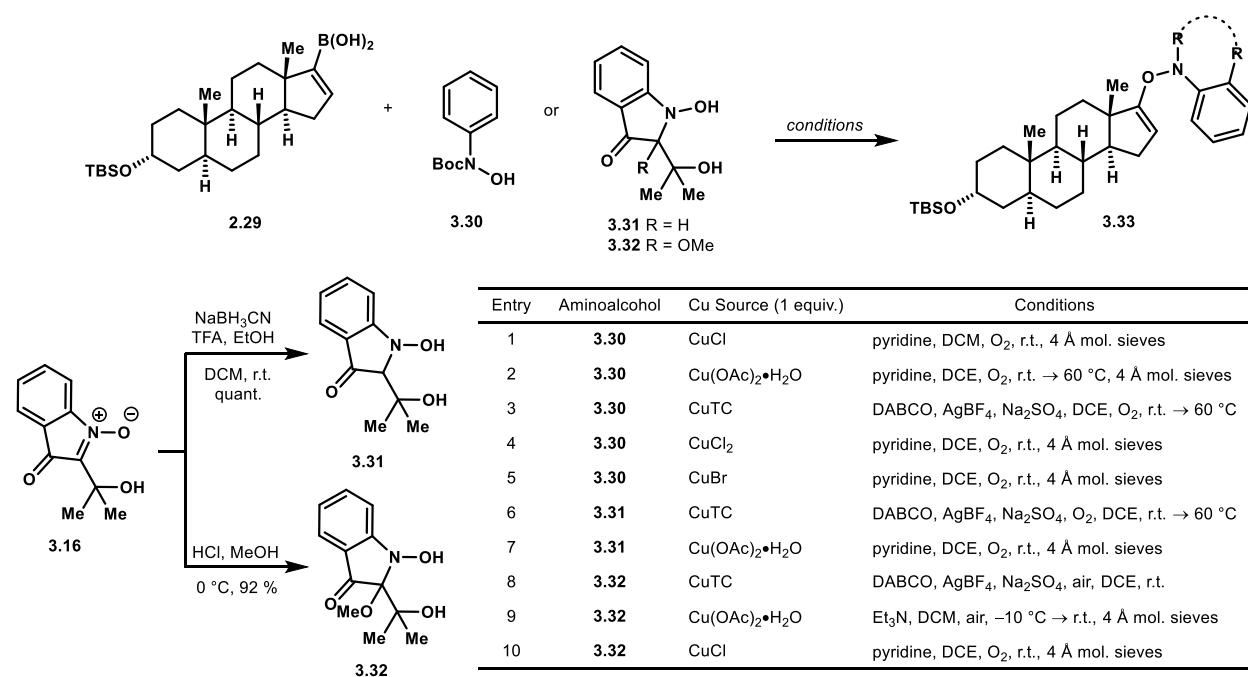
system from the nitro-alkyne reaction to explore further options. Unfortunately, under a variety of conditions we were unable to observe incorporation of the chlorine.¹²

Figure 3.5: Elaboration to possible coupling fragments



We began our explorations of the fragment union with the Chan-Lam coupling, using model systems for ease of analysis. *N*-*tert*-boc-*N*-phenylhydroxylamine was prepared according to known procedures.¹³ Aminoalcohol **3.31** was prepared from isatogen **3.16** via reduction with sodium cyanoborohydride (Figure 3.6). Aminoalcohol **3.32** was similarly prepared from isatogen **3.16** upon treatment with acidic methanol. Unfortunately, under a variety of conditions with various copper sources we never observed the desired C-O coupling product (Figure 3.6). Vinylboronic acid **3.29** proved to be unreactive under these conditions, with all reaction conditions decomposing the aminoalcohol starting materials. Based on these results and those of our attempted palladium C-O coupling reactions using vinyltriflates during our synthesis of NsA C,¹⁴ we decided to attempt a different strategy for the fragment coupling.

Figure 3.6: Attempted Chan-Lam coupling and synthesis of hydroxylamines **3.31** and **3.32**



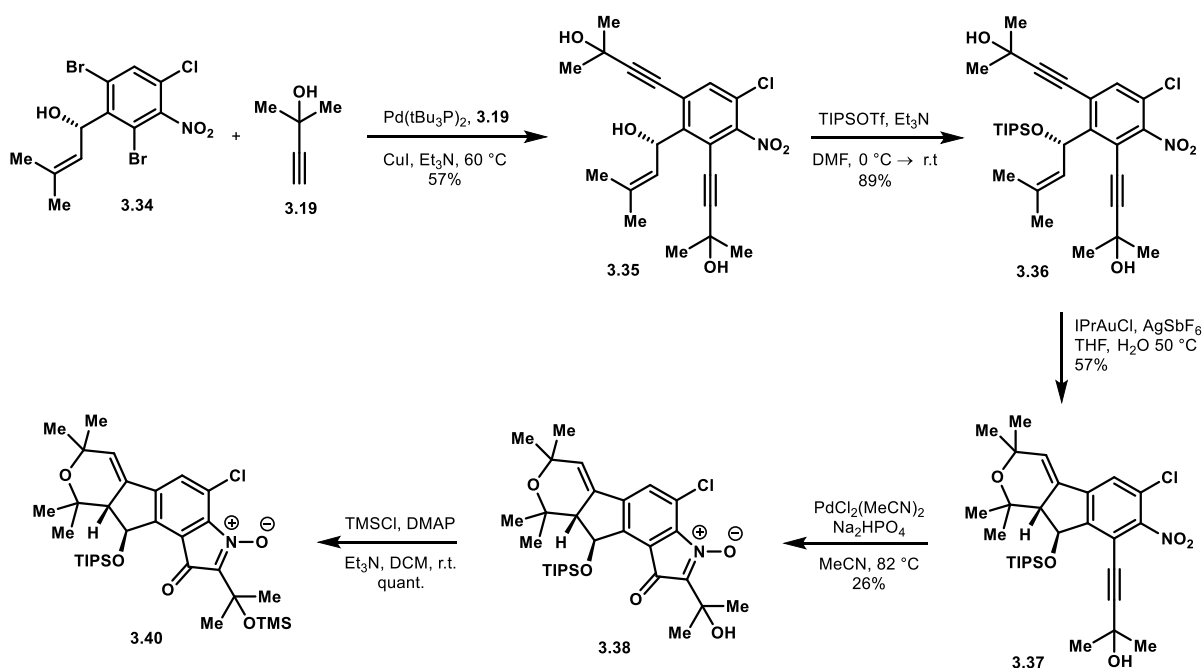
3.2.3 Synthesis of the Chlorinated Indenopyran Fragment

After several unsuccessful fragment coupling attempts, we focused our attention on the ketone arylation strategy used to construct NsA C. For this, we required an aryl chloride installed on the aromatic ring. After our initial unsuccessful attempts to add the chlorine following isotogen formation, we decided to build the fragment with the chlorine already installed.

Alcohol **3.34** from our synthesis of NsA C proved to be significantly less reactive than its non-chlorinated counterpart and necessitated the use of a much more active palladium catalyst to effect the Sonogashira coupling. Subjection to coupling conditions with bis(tri-tert-butylphosphine)palladium(0) afforded diyne **3.35** (Figure 3.7). Silyl protection then afforded the substrate for the enyne cycloisomerization (**3.36**). As seen in our synthesis of NsA C, the chlorine substituent deactivated the alkyne toward the reaction and we had to use more forcing conditions. Nonetheless, heating to 50 °C in THF with 20 mol% of added water

delivered indenopyran **3.37**. Isatogen formation was attempted under the same conditions we found to work best on the non-chlorinated system except with an increase in catalyst loading from 5 to 10 mol%. Unfortunately, we observed a nearly 1:1 ratio of the desired product (**3.38**) to the undesired isatin. Attempts to perform the nitro-alkyne cyclization with the tertiary alcohol protected in the form of a TMS silyl ether greatly decreased the solubility of the material, affording none of the desired isatogen, and use of a methyl protecting group increased solubility but still delivered no product. Three portion-wise additions of the catalyst afforded a 26% yield of isatogen **3.38**, and despite the poor yield, this allowed us to move forward with the synthesis. The coupling fragment **3.40** was completed with a quantitative TMS protection of the tertiary alcohol.

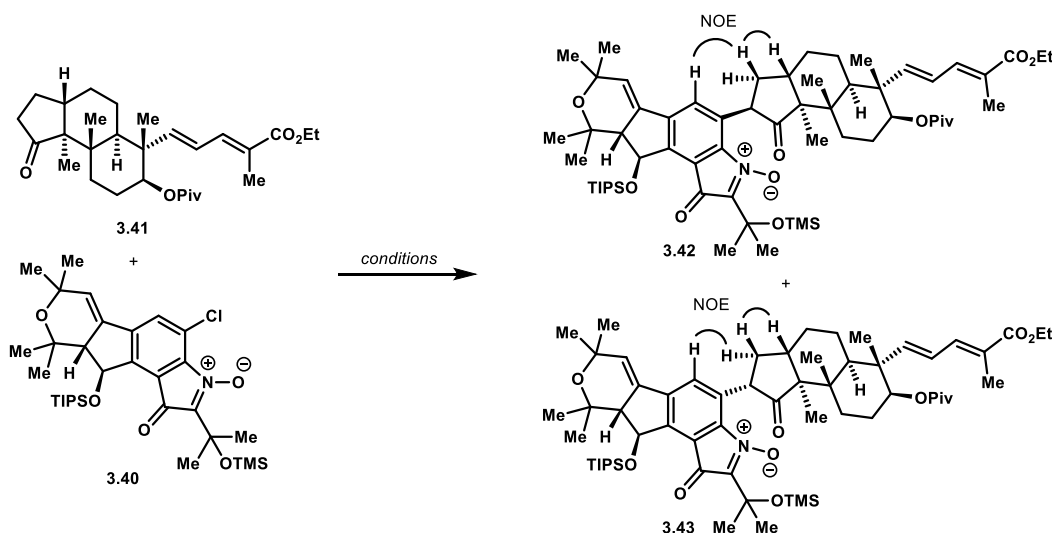
Figure 3.7: Synthesis of the chlorinated indenopyran



With our new coupling fragment in hand, we turned our attention toward the ketone arylation using the same tricyclic ketone from our synthesis of NsA C. The optimized NsA C conditions afforded only traces of the desired coupling products (Entry 1, Table 3.3), but

increasing the catalyst loading to 50 mol% afforded a combined 29% yield of the two diastereomers (**3.42** and **3.43**, Table 3.3) in 1:1 d.r. Isolation of each diastereomer and characterization allowed us to tentatively assign the stereochemistry as shown based on NOESY correlations between the aromatic proton and the terpene fragment (illustrated on **3.42** and **3.43**, Table 3.3).¹⁵ Until we found the right reduction conditions it was impossible to know if condensation of one diastereomer would be preferred over the other during indole formation, as was the case for NsA C; however, we continued the optimization under the assumption that **3.42** would allow for easier formation of the indole, drawing a parallel from the stereochemistry of the NsA C arylation products.

Table 3.3: Optimization of the ketone arylation



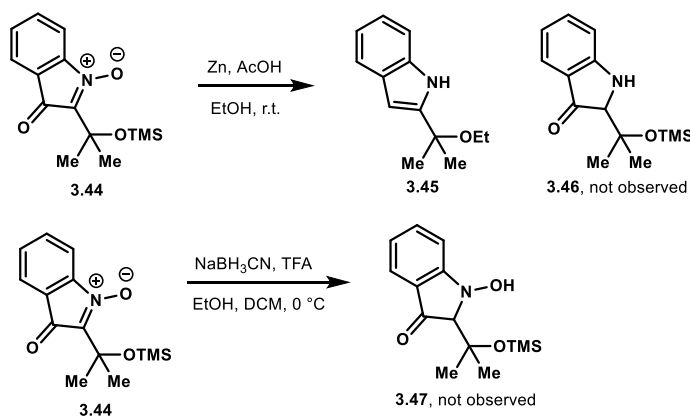
Entry	Pd Source (equiv)	Ligand (equiv)	Conditions	Yield 3.42	Yield 3.43
1	RuPhosPdG4 (0.25)	RuPhos (0.25)	Bu ₃ SnCl, NaHMDS, Toluene, 50 °C, 16h	trace	trace
2	RuPhosPdG4 (0.50)	RuPhos (0.50)	Bu ₃ SnCl, NaHMDS, Toluene, 50 °C, 16h	15%	14%
3	RuPhosPdG4 (0.50)	RuPhos (0.50)	Bu ₃ SnCl, NaHMDS, Toluene, 50 °C, 26h	15%	22%
4	RuPhosPdG4 (1.0)	RuPhos (1.0)	Bu ₃ SnCl, NaHMDS, Toluene, 50 °C, 16h	—	6%
5	RuPhosPdG4 (0.25)	RuPhos (0.25)	Bu ₃ SnCl, NaHMDS, Toluene, 70 °C, 16h	—	19%
6	RuPhosPdG4 (0.50)	RuPhos (0.50)	Bu ₃ SnCl, NaHMDS, Toluene, 70 °C, 16h	—	21%
7	RuPhosPdG4 (0.50)	RuPhos (0.50)	Bu ₃ SnCl, NaHMDS, THF, 50 °C, 16h	—	—
8 ^a	RuPhosPdG4 (0.50)	RuPhos (0.50)	Bu ₃ SnCl, NaHMDS, Toluene, 50 °C, 16h	22%	16%
9 ^a	RuPhosPdG4 (0.50)	RuPhos (0.50)	Bu ₃ SnCl, NaHMDS, Toluene, 50 °C, 25h	16%	23%
10 ^a	XPhosPdG3 (0.50)	XPhos (0.50)	Bu ₃ SnCl, NaHMDS, Toluene, 50 °C, 16h	20%	15%
11 ^a	CPhosPdG4 (0.50)	CPhos (0.50)	Bu ₃ SnCl, NaHMDS, Toluene, 50 °C, 16h	26%	12%
12 ^{a,b}	RuPhosPdG4 (0.50)	RuPhos (0.50)	Bu ₃ SnCl, NaHMDS, Toluene, 50 °C, 16h	28%	13%

Reactions were run on 0.005 mmol scale. a) 1.3 equiv. **3.40** used instead of 1.1 b) 0.015 mmol scale

Allowing the reaction run to longer increased the yield of **3.43** while the yield of **3.42** remained the same (Entry 3). The use of stoichiometric palladium shut down the reaction (Entry 4) and higher temperatures afforded only **3.43** (Entries 5 and 6). Switching the solvent from toluene to THF also shut down reactivity (Entry 7). Increasing the ratio of isatogen **3.40** to ketone **3.41** increased the yield and also favored **3.42** in a 1.4:1 ratio (Entry 8), but increasing the reaction time only inverted the d.r. (Entry 9). Using other Buchwald ligands, XPhos afforded nearly the same results as RuPhos (Entry 10). CPhos increased the yield of **3.43** slightly to 26% while increasing the d.r. to 2.2:1 (Entry 11), although increasing the scale of the reaction with RuPhos achieved the same increase in d.r. (Entry 12).

Methods to reduce the nitron to the amine in a single step were first explored on a model system with isatogen **3.44** (Figure 3.8). Treatment with zinc and acetic acid in ethanol afforded none of the desired reduced product and instead delivered indole **3.45**, presumably through over-reduction of the ketonitrone and elimination to form the indole. Attempts to reduce nitron **3.44** to the hydroxylamine also failed in the presence of the TMS protected alcohol despite earlier success in reducing the free alcohol (**3.31**, Figure 3.6). Explorations of alternate reduction conditions are currently underway.

Figure 3.8: Attempted nitron reduction



3.3 Summary

Two highly elaborated indenopyran fragments *en route* to NsA A were successfully synthesized from simple starting materials, despite reactivity issues associated with the additional chlorine substitution. These syntheses were accomplished through the development of two regioselective, Lewis acid catalyzed alkyne cyclizations to stitch together the carbon framework from simple polysubstituted arenes. The chlorinated indenopyran was then coupled with the terpene fragment of NsA A using a challenging ketone arylation strategy to afford an advanced intermediate toward NsA A. Future work will involve elaboration to the final natural product through a nitron reduction and condensation to form the indole, followed by elimination of the tertiary alcohol and two deprotections. Further optimization will also be performed to effect both alkyne cyclizations in a single step.

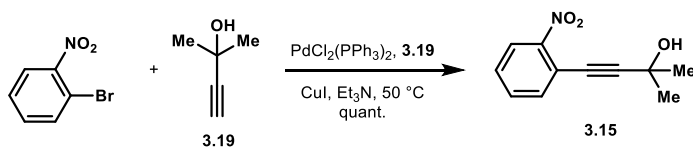
3.4 Experimental Section

3.4.1 General Experimental Details

All reactions were carried out in flame-dried glassware under positive pressure of dry nitrogen unless otherwise noted. Reaction solvents including tetrahydrofuran (THF, Fisher, HPLC Grade), dichloromethane (DCM, Fisher, HPLC Grade), and toluene (Fisher, HPLC Grade) were dried by percolation through a column packed with neutral alumina and a column packed with a supported copper catalyst for scavenging oxygen (Q5) under positive pressure of argon. Anhydrous 1,2-dichloroethane (Fisher, ACS Grade), anhydrous triethylamine (Oakwood Chemical) and anhydrous dimethylformamide (Fisher, ACS Grade) were distilled from calcium hydride (10% w/v) under positive pressure of nitrogen. Solvents for extraction, thin layer chromatography (TLC), and flash column chromatography were

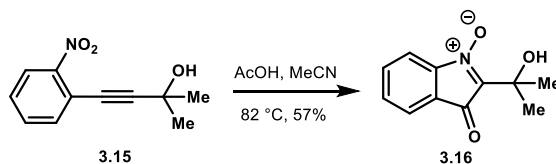
purchased from Fischer (ACS Grade) and VWR (ACS Grade) and used without further purification. Chloroform-d and benzene-d₆ for ¹H and ¹³C NMR analysis were purchased from Cambridge Isotope Laboratories and used without further purification. Commercially available reagents were used without further purification unless otherwise noted. Reactions were monitored by thin layer chromatography (TLC) using precoated silica gel plates (EMD Chemicals, Silica gel 60 F₂₅₄). Flash column chromatography was performed over silica gel (Acros Organics, 60 Å, particle size 0.04-0.063 mm). ¹H NMR and ¹³C NMR spectra were recorded on Bruker DRX-500 (BBO probe), Bruker DRX-500 (TCI cryoprobe), Bruker AVANCE600 (TBI probe), and Bruker AVANCE600 (BBFO cryoprobe) spectrometers using residual solvent peaks as internal standards (CHCl₃ @ 7.26 ppm ¹H NMR, 77.00 ppm ¹³C NMR; C₆H₆ @ 7.16 ppm ¹H NMR, 128.00 ppm ¹³C NMR). High-resolution mass spectra (HRMS) were recorded on Waters LCT Premier TOF spectrometer with ESI and CI sources.

3.4.2 Experimental Details

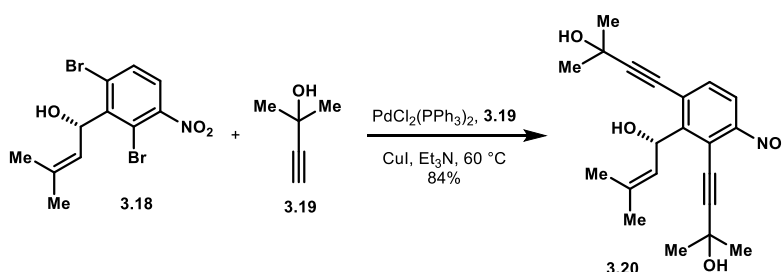


Alkyne 3.15. 2-Bromonitrobenzene (0.808 g, 4.0 mmol), PdCl₂(PPh₃)₂ (56 mg, 0.08 mmol), and CuI (8 mg, 0.04 mmol) were combined in a flame-dried Schlenk flask and the atmosphere was exchanged with N₂. Triethylamine (16 mL) and 2-methyl-3-butyn-2-ol **3.19** (0.46 mL, 4.8 mmol) were added and the reaction was heated to 50 °C for 1h. The reaction was cooled to room temperature and diluted in EtOAc, then filtered through Celite and concentrated under reduced pressure. Purification by flash chromatography (elution 20% EtOAc in hexanes) afforded 0.82 g (quant. yield) of alkyne **3.15** as a yellow solid. R_f = 0.3 (30% EtOAc in hexanes); ¹H NMR (500 MHz; CDCl₃) δ 8.03 (dd, *J* = 8.3, 1.2 Hz, 1H), 7.61-7.54 (m, 2H), 7.45

(ddd, $J = 8.3, 7.3, 1.6$ Hz, 1H), 2.10 (s, 1H), 1.65 (s, 6H); ^{13}C NMR (126 MHz; CDCl_3) δ 150.1, 134.7, 132.9, 128.9, 124.7, 118.3, 101.7, 77.8, 66.0, 31.2; HRMS (ES+) calculated for $\text{C}_{11}\text{H}_{11}\text{NO}_3\text{Na}$ $[\text{M}+\text{Na}]^+$: 228.0637, found: 228.0641.

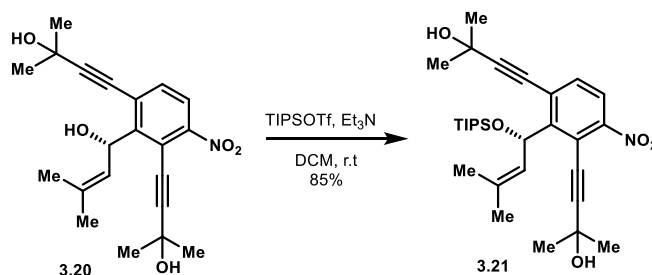


Nitron 3.16. Alkyne **3.15** (62 mg, 0.30 mmol), acetic acid (3 μL , 0.06 mmol), and acetonitrile (3.0 mL) were combined in a dram vial, sealed, and heated to 82 $^{\circ}\text{C}$ for 4 h. The reaction was cooled to room temperature, quenched with saturated aqueous NaHCO_3 , and extracted twice with EtOAc. The combined organic layers were washed with water and brine and dried over anhydrous sodium sulfate. Concentration under reduced pressure and purification by flash chromatography (elution 10% EtOAc in hexanes) afforded 35 mg (0.17 mmol, 57% yield) of nitron **3.16** as a yellow solid. $R_f = 0.5$ (30% EtOAc in hexanes); ^1H NMR (500 MHz; CDCl_3) δ 7.66 (td, $J = 7.4, 1.6$ Hz, 1H), 7.61-7.53 (m, 3H), 5.27 (s, 1H), 1.64 (s, 6H); ^{13}C NMR (126 MHz; CDCl_3) δ 185.2, 147.1, 140.9, 134.8, 131.7, 122.8, 122.0, 114.1, 70.2, 26.9; HRMS (ES+) calculated for $\text{C}_{11}\text{H}_{11}\text{NO}_3\text{Na}$ $[\text{M}+\text{Na}]^+$: 228.0637, found: 228.0626.



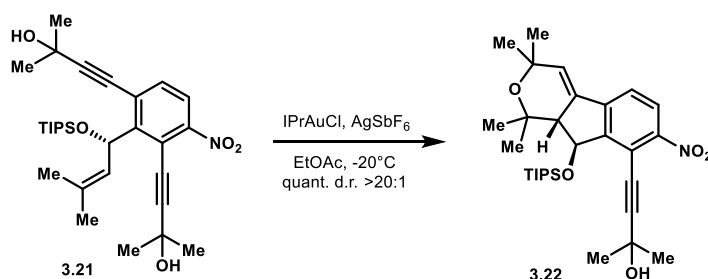
Triol 3.20. A flame-dried Schlenk under N_2 was charged with $\text{PdCl}_2(\text{PPh}_3)_2$ (105 mg, 0.15 mmol) and CuI (13 mg, 0.07 mmol). A solution of alcohol **3.18** (1.35 g, 3.70 mmol) in triethylamine (15 mL) was degassed with argon and added to the Schlenk. 2-Methyl-3-

butyn-2-ol (1.1 mL, 11.1 mmol) was added to the Schlenk and the reaction was heated to 60 °C for 4 h. The reaction was cooled to room temperature, diluted in ethyl acetate, and filtered through Celite. Concentration under reduced pressure followed by purification by flash chromatography (gradient elution: 1-5% MeOH in DCM in 1% increments) afforded 1.15 g (3.11 mmol, 84% yield) of triol **3.20** as a light brown solid. R_f = 0.35 (7% MeOH in DCM); ^1H NMR (500 MHz; CDCl_3) δ 7.70 (d, J = 8.5 Hz, 1H), 7.40 (d, J = 8.5 Hz, 1H), 6.19 (d, J = 8.2 Hz, 1H), 5.97-5.95 (m, 1H), 1.74 (d, J = 1.1 Hz, 3H), 1.68 (s, 3H), 1.64-1.62 (m, 12H); ^{13}C NMR (151 MHz; CDCl_3) δ 150.8, 149.5, 137.6, 133.4, 126.7, 124.6, 122.9, 116.3, 107.1, 103.6, 79.4, 75.2, 69.3, 65.9, 65.5, 31.1, 31.0, 30.9, 30.8, 26.0, 18.8; $[\alpha]_D^{22}$ +75.5 (c 1.0, CHCl_3); HRMS (ES+) calculated for $\text{C}_{21}\text{H}_{25}\text{NO}_5\text{Na}$ $[\text{M}+\text{Na}]^+$: 394.1631, found: 394.1629.



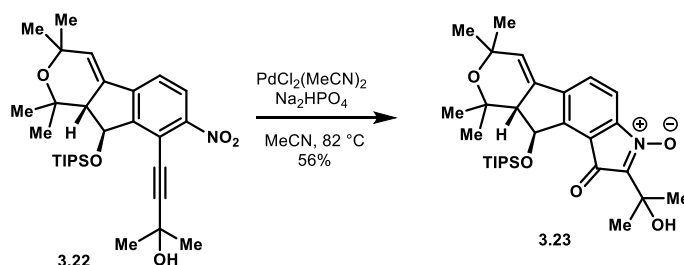
Silyl ether 3.21. Triol **3.20** (1.50 g, 4.04 mmol), Et_3N (1.1 mL, 8.08 mmol), and DCM (8.0 mL) were combined in a flame-dried round bottom flask under nitrogen. The flask was then cooled to 0 °C and TIPSOTf (1.3 mL, 4.85 mmol) was added dropwise. The reaction was warmed to room temperature and stirred for 2 h. The reaction was quenched with saturated aqueous ammonium chloride after the addition of excess Et_3N and extracted three times with EtOAc. The combined organic layers were washed with water and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. Purification by flash chromatography (gradient elution 10-20% EtOAc in hexanes) afforded 1.80 g (3.41 mmol, 85% yield) of silyl ether **3.21** as a yellow oil. Spectral data was collected at 50 °C in an

attempt to reduce peak broadening. Many ^{13}C peaks are missing due to broadness. $R_f = 0.43$ (30% EtOAc in hexanes); ^1H NMR (600 MHz; CDCl_3) δ 7.65 (br s, 1H), 7.44 (br d, $J = 8.5$ Hz, 1H), 6.16 (br s, 2H), 2.01 (br s, 1H), 1.96 (br s, 1H), 1.76 (s, 3H), 1.73 (s, 3H), 1.64 (s, 3H), 1.64 (s, 3H), 1.62 (s, 6H), 1.19-1.12 (m, 3H), 1.05 (d, $J = 7.4$ Hz, 9H), 0.98 (d, $J = 7.4$ Hz, 9H); ^{13}C NMR (151 MHz; CDCl_3) δ 150.2, 127.3, 122.4, 70.4, 65.9, 31.2, 30.9, 26.1, 18.08, 18.05, 12.5; $[\alpha]_D^{22} -14.0$ (c 1.0, CHCl_3); HRMS (ES+) calculated for $\text{C}_{30}\text{H}_{45}\text{NO}_5\text{SiNa}$ $[\text{M}+\text{Na}]^+$: 550.2964, found: 550.2963.



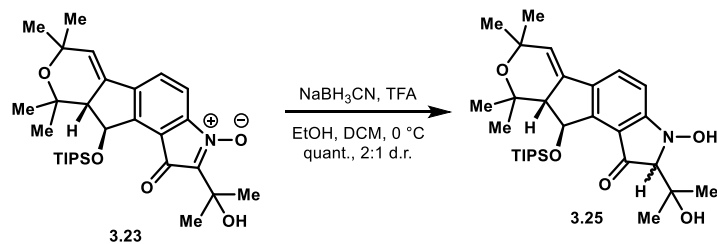
Indenopyran 3.22. IPrAuCl (99 mg, 0.16 mmol) and AgSbF₆ (41 mg, 0.12 mmol) were combined in a flame-dried Schlenk flask in the glovebox. The flask was capped, removed from the glovebox, and placed under N₂ on a manifold. To the flask was added dry EtOAc (6.0 mL) and the resulting slurry was stirred for 10 min at r.t., then the precipitate was allowed to settle. The supernatant was added to new flame-dried Schlenk flask containing silyl ether **3.21** in dry EtOAc (6.0 mL) at -20°C . The reaction was stirred for 4 h with gradual warming to -5°C , then diluted in EtOAc, washed with water and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to afford 0.640g (quant. yield) of indenopyran **2.89** as a yellow solid and a single diastereomer. $R_f = 0.75$ (30% EtOAc in hexanes); ^1H NMR (500 MHz; CDCl_3) δ 7.98 (d, $J = 8.4$ Hz, 1H), 7.48 (d, $J = 8.4$ Hz, 1H), 6.26 (d, $J = 2.8$ Hz, 1H), 5.28 (d, $J = 2.8$ Hz, 1H), 2.81 (t, $J = 2.7$ Hz, 1H), 2.13 (s, 1H), 1.64 (s, 6H), 1.52 (s, 3H), 1.36 (s, 3H), 1.32 (s, 3H), 1.10-1.03 (m, 3H), 0.99 (d, $J = 7.2$ Hz, 9H), 0.94 (d, $J = 7.2$ Hz,

9H), 0.86 (s, 3H); ^{13}C NMR (126 MHz; CDCl_3) δ 150.8, 149.1, 144.2, 135.8, 129.2, 126.0, 119.8, 117.2, 106.6, 77.3, 76.0, 74.7, 73.0, 66.1, 57.9, 31.2, 31.0, 29.8, 29.6, 21.9, 18.5, 18.3, 13.8; $[\alpha]_{\text{D}}^{22}$ -1.28 (c 1.0, CHCl_3); HRMS (ES+) calculated for $\text{C}_{30}\text{H}_{45}\text{NO}_5\text{SiNa}$ $[\text{M}+\text{Na}]^+$: 550.2964, found: 550.2939.

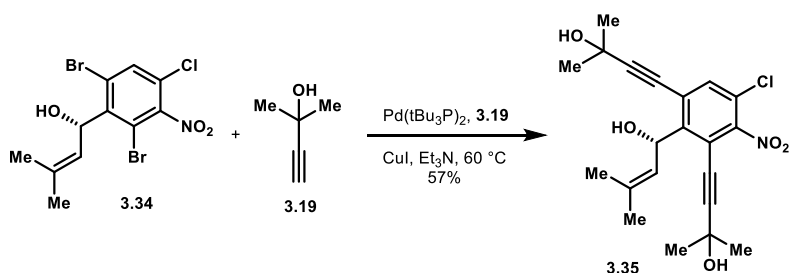


Isatogen 3.32. Na_2HPO_4 (35 mg, 0.25 mmol) was added to a Schlenk flask and flame-dried under reduced pressure, then the atmosphere was replaced with N_2 . Under a flow of N_2 , indenopyran **3.22** (0.264 g, 0.5 mmol) and $\text{PdCl}_2(\text{MeCN})_2$ (6.5 mg, 0.025 mmol) were added, followed by acetonitrile (5 mL). The Schlenk was capped with a yellow cap and sealed with parafilm. The reaction was heated to $82\text{ }^\circ\text{C}$ for 39 h with repeated additions of 6.5 mg of $\text{PdCl}_2(\text{MeCN})_2$ after 16 h and then an additional 9h for a total of 19.5 mg (0.75 mmol) of $\text{PdCl}_2(\text{MeCN})_2$ added. The reaction was cooled to r.t., diluted in EtOAc, and washed with water and brine, then dried over anhydrous sodium sulfate and concentrated under reduced pressure. Purification by flash chromatography (elution 7% EtOAc in hexanes) afforded 0.148 g (0.28 mmol, 56% yield) of isatogen **3.23** as a red oil. R_f = 0.45 (20% EtOAc in hexanes); ^1H NMR (600 MHz; CDCl_3) δ 7.70 (d, J = 8.0 Hz, 1H), 7.60 (d, J = 8.0 Hz, 1H), 6.21 (d, J = 2.9 Hz, 1H), 5.44 (d, J = 3.1 Hz, 1H), 2.86 (t, J = 2.9 Hz, 1H), 1.64 (s, 3H), 1.63 (s, 3H), 1.53 (s, 3H), 1.36 (s, 3H), 1.32 (s, 3H), 1.17-1.10 (m, 3H), 1.02 (d, J = 7.4 Hz, 9H), 0.97 (d, J = 7.4 Hz, 9H), 0.90 (s, 3H); ^{13}C NMR (151 MHz; CDCl_3) δ 184.4, 147.3, 144.7, 142.9, 140.2, 135.6, 127.4, 125.2, 119.8, 114.9, 75.0, 74.6, 72.8, 70.4, 59.3, 31.2, 30.0, 29.8, 27.2, 26.9, 22.2, 18.6, 18.5,

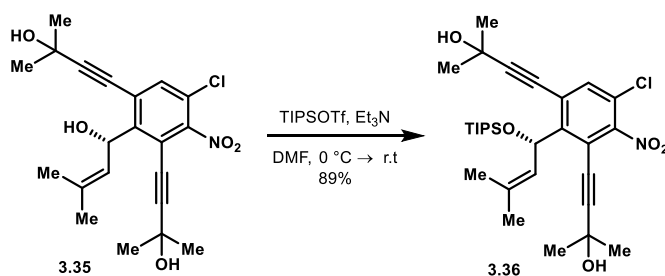
13.5; $[\alpha]_D^{22}$ -28.0 (c 1.0, CHCl₃); HRMS (ES+) calculated for C₃₀H₄₅NO₅SiNa [M+Na]⁺: 550.2964, found: 550.2964.



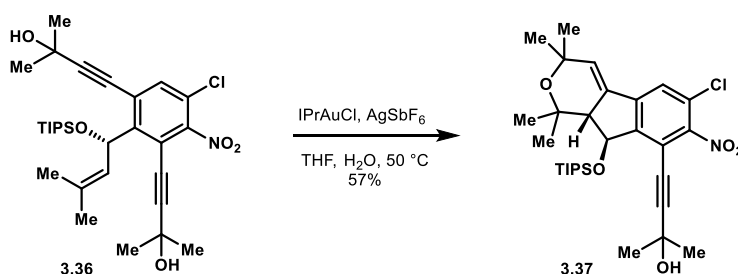
Aminoalcohol 3.25. Isatogen **3.23** (33 mg, 0.062 mmol) was added to a flame dried round bottom flask and the atmosphere exchanged with N₂. DCM (0.5 mL) was added and the solution was cooled to 0 °C. Trifluoroacetic acid (6 µL, 0.074 mmol) was added, followed by a solution of NaBH₃CN (3.9 mg, 0.062 mmol) in DCM (0.1 mL) and EtOH (0.12 mL). The reaction was stirred for 15 min, then quenched with saturated aqueous NaHCO₃. The reaction was diluted in DCM and washed with water, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to afford 33 mg (0.062 mmol, quant. yield) of aminoalcohol **3.25** as a yellow oil and a 4:1 mixture of diastereomers. ¹H NMR (500 MHz; CDCl₃) δ 7.72 (d, *J* = 8.5 Hz, 1.25H), 7.37 (d, *J* = 8.4 Hz, 1.25H), 6.35 (s, 1.25H), 6.00 (d, *J* = 2.7 Hz, 0.25H), 5.99 (d, *J* = 2.7 Hz, 1H), 5.49 (d, *J* = 2.9 Hz, 0.25H), 5.43 (d, *J* = 3.0 Hz, 1H), 3.72 (s, 1.25H), 3.40 (s, 1H), 2.82-2.80 (m, 1.25H), 1.58 (s, 3.75H), 1.51 (s, 3.75H), 1.42 (s, 0.75H), 1.40 (s, 3H), 1.35 (s, 3H), 1.35 (s, 3H), 1.30 (s, 3.75H), 1.29 (s, 0.75H), 1.25 (s, 0.75H), 1.10-1.01 (m, 3.75H), 1.00 (d, *J* = 7.0 Hz, 11.25H), 0.94 (d, *J* = 7.4 Hz, 2.25H), 0.91 (d, *J* = 7.2 Hz, 9H), 0.87 (s, 3H); ¹³C NMR (126 MHz; CDCl₃) δ 196.9, 196.5, 165.68, 165.66, 164.8, 143.4, 143.0, 136.4, 136.3, 136.2, 136.1, 129.0, 128.7, 123.4, 123.3, 121.2, 120.9, 117.8, 117.3, 81.9, 81.2, 76.1, 76.0, 74.8, 74.7, 73.4, 73.3, 72.9 (2C), 59.04, 58.9, 31.5, 30.13, 30.09, 29.9, 29.8, 26.9, 25.9, 25.5, 22.3, 22.2, 18.58, 18.55, 18.4, 17.8, 13.9, 13.6.



Triol 3.35. Bis(Tri-*tert*-butylphosphine)palladium(0) (0.16 g, 0.32 mmol) and copper(I) iodide (61 mg, 0.32 mmol) were added to a flame-dried Schlenk in a glovebox. The Schlenk was removed from the glovebox, connected to a manifold, and placed under nitrogen. A degassed solution of alcohol **3.34** in triethylamine (2.55 g, 6.38 mmol in 25.0 mL) and 2-methyl-3-butyn-2-ol **3.19** (2.5 mL, 0.11 mmol) was added to the Schlenk and the reaction was heated to 50°C for 5 h. The reaction was then cooled to r.t., diluted with ethyl acetate, filtered through Celite, and concentrated under reduced pressure. Purification by flash chromatography (gradient elution 25-50% EtOAc in hexanes in 5% increments) afforded 1.47 g (3.62 mmol, 57% yield). $R_f = 0.31$ (60% EtOAc in hexanes); ^1H NMR (600 MHz; CDCl_3) δ 7.42 (s, 1H), 6.07 (d, $J = 7.7$ Hz, 1H), 5.92 (d, $J = 8.0$ Hz, 1H), 1.72 (s, 3H), 1.67 (s, 3H), 1.61 (s, 6H), 1.57 (s, 3H), 1.56 (s, 3H); ^{13}C NMR (151 MHz; CDCl_3) δ 151.4, 147.4, 137.6, 134.1, 124.8, 124.1, 123.4, 116.5, 106.6, 102.8, 78.2, 73.3, 69.1, 65.6, 65.5, 31.2, 31.0, 30.8, 30.6, 25.9, 18.9; $[\alpha]_D^{22}$ 74.4 (c 1.0, CHCl_3); HRMS (ES+) calculated for $\text{C}_{21}\text{H}_{24}\text{ClNO}_5\text{Na}$ $[\text{M}+\text{Na}]^+$: 428.1241, found: 428.1252.

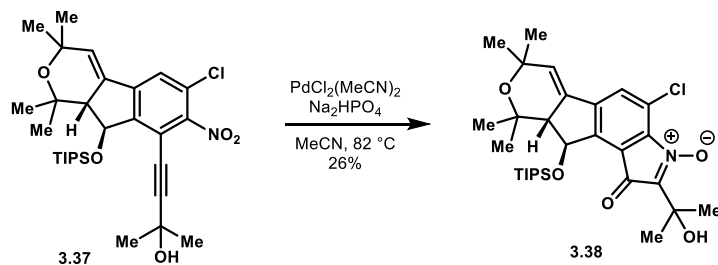


Silyl ether 3.36. Triol **3.35** (0.106 g, 0.26 mmol), Et₃N (0.08 mL, 0.54 mmol), and DMF (0.54 mL) were combined in a flame-dried round bottom flask under nitrogen. The flask was then cooled to 0 °C and TIPSOTf (0.08 mL, 0.31 mmol) was added dropwise. The reaction was warmed to r.t. and stirred for 2 h. The reaction was quenched with saturated aqueous ammonium chloride and extracted three times with DCM. The combined organic layers were washed with water and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. Purification by flash chromatography on Et₃N-treated silica (gradient elution 10-15% EtOAc in hexanes) afforded 0.130 g (0.23 mmol, 89% yield) of silyl ether **3.21** as a yellow oil. Spectral data was collected at 50 °C to reduce peak broadening. R_f = 0.3 (20% EtOAc in hexanes); ¹H NMR (600 MHz; CDCl₃) δ 7.46 (s, 1H), 6.07 (dt, *J* = 8.1, 1.2 Hz, 1H), 6.02 (d, *J* = 8.2 Hz, 1H), 1.92 (d, *J* = 8.2 Hz, 2H), 1.75 (d, *J* = 1.1 Hz, 3H), 1.73 (d, *J* = 0.9 Hz, 3H), 1.63 (d, *J* = 2.3 Hz, 6H), 1.57 (s, 6H), 1.16-1.06 (m, 3H), 1.05 (d, *J* = 7.3 Hz, 9H), 0.99 (d, *J* = 7.3 Hz, 9H); ¹³C NMR (151 MHz; CDCl₃) δ 152.0, 148.1, 135.0, 134.0, 126.9, 124.8, 123.0, 116.5, 106.3, 101.8, 79.4, 74.3, 70.2, 65.9, 65.8, 31.2, 30.8, 26.0, 19.2, 18.1, 18.0, 12.4; [α]_D²² – 3.82 (c 1.0, CHCl₃); HRMS (ES⁺) calculated for C₃₀H₄₄ClNO₅SiNa [M+Na]⁺: 584.2575, found: 584.2570.



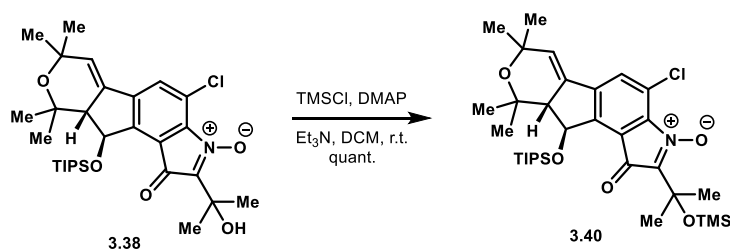
Indenopyran 3.37. H₂O (9 μL) and THF (0.9 mL) were combined under N₂ and 0.3 mL of this solution was added to a round-bottom flask containing silyl ether **3.36** (0.450 g, 0.80 mmol) in THF (5.0 mL). IPrAuCl (60 mg, 0.096 mmol) and AgSbF₆ (27 mg, 0.08 mmol) were

combined in a dram vial under N₂ and dissolved in THF (3.0 mL) and stirred for 10 min at r.t. This slurry was added to the round-bottom flask containing silyl ether **3.36** in THF and the reaction was heated to 50 °C for 26 h. The reaction was diluted in EtOAc and filtered through Celite, then concentrated under reduced pressure. Purification by flash chromatography (gradient elution 5-7% EtOAc in hexanes) afforded 0.0257 g (0.46 mmol, 57% yield) of indenopyran **2.89** as a yellow solid and a single diastereomer. Note: One ¹³C NMR peak is under the CDCl₃ peak. R_f = 0.45 (20% EtOAc in hexanes); ¹H NMR (500 MHz; CDCl₃) δ 7.50 (s, 1H), 6.20 (d, *J* = 2.8 Hz, 1H), 5.21 (d, *J* = 3.0 Hz, 1H), 2.79 (t, *J* = 2.8 Hz, 1H), 1.96 (s, 1H), 1.58 (s, 6H), 1.51 (s, 3H), 1.35 (s, 3H), 1.32 (s, 3H), 1.16-1.09 (m, 3H), 1.02 (d, *J* = 7.3 Hz, 9H), 0.98 (d, *J* = 7.3 Hz, 9H), 0.88 (s, 3H); ¹³C NMR (151 MHz; CDCl₃) δ 152.1, 146.2, 142.0, 135.0, 128.9, 126.0, 121.6, 116.2, 106.2, 74.6, 73.8, 73.0, 65.9, 58.1, 31.1, 31.0, 30.8, 29.8 (2C), 22.0, 18.6, 18.4, 13.8; [α]_D²² 22.5 (c 1.0, CHCl₃); HRMS (ES⁺) calculated for C₃₀H₄₄ClNO₅SiNa [M+Na]⁺: 584.2575, found: 584.2550.



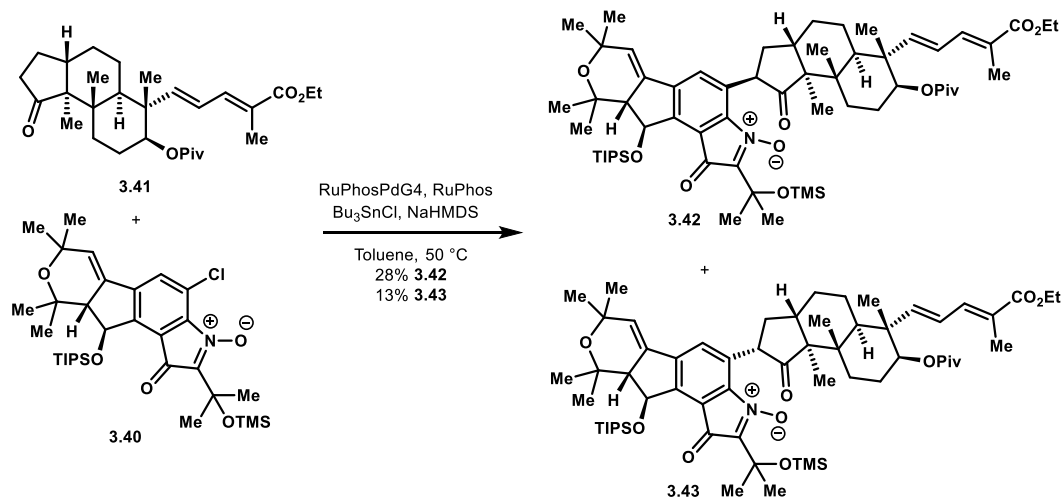
Isatogen 3.38. Anhydrous Na₂HPO₄ (8 mg, 0.055 mmol), indenopyran **3.37** (60 mg, 0.11 mmol), and PdCl₂(MeCN)₂ (3.0 mg, 0.011 mmol) were added to a dram vial and the atmosphere was replaced with N₂. Acetonitrile (1.1 mL) was added and dram vial was sealed. The reaction was heated to 82 °C for 30 h with repeated additions of PdCl₂(MeCN)₂ after 6 h and then an additional 16 h for a total of 9 mg (0.033 mmol) of PdCl₂(MeCN)₂ added. The reaction was cooled to room temperature, diluted in EtOAc, and washed with water and

brine, then dried over anhydrous sodium sulfate and concentrated under reduced pressure. Purification by flash chromatography (gradient elution 2.5-5% EtOAc in hexanes) afforded 16 mg (0.028 mmol, 26% yield) of isatogen **3.38** as a red oil. R_f = 0.6 (20% EtOAc in hexanes); ^1H NMR (500 MHz; CDCl_3) δ 7.61 (s, 1H), 6.26 (d, J = 2.9 Hz, 1H), 5.43 (d, J = 3.0 Hz, 1H), 5.25 (s, 1H), 2.85 (t, J = 2.9 Hz, 1H), 1.62 (s, 6H), 1.52 (s, 3H), 1.36 (s, 3H), 1.32 (s, 3H), 1.17-1.09 (m, 3H), 1.02 (d, J = 7.4 Hz, 9H), 0.97 (d, J = 7.4 Hz, 9H), 0.88 (s, 3H); ^{13}C NMR (126 MHz; CDCl_3) δ 183.3, 145.8, 141.7, 141.3, 139.8, 134.8, 129.1, 128.0, 123.3, 122.0, 77.4, 74.61, 74.56, 72.8, 70.3, 59.3, 31.1, 29.9, 29.7, 26.9, 26.7, 22.1, 18.6, 18.5, 13.4; $[\alpha]_D^{22}$ -40.2 (c 1.0, CHCl_3); HRMS (ES+) calculated for $\text{C}_{30}\text{H}_{44}\text{ClNO}_5\text{SiNa}$ $[\text{M}+\text{Na}]^+$: 584.2575, found: 584.2560.



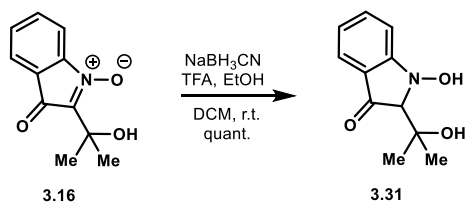
Isatogen 3.40. Isatogen **3.38** (21 mg, 0.37 mmol) and DMAP (1 mg, 0.007 mmol) were added to a dram vial and the atmosphere was replaced with N_2 . Et_3N (15 μL , 0.11 mmol) and DCM (0.37 mL) were added, followed by TMSCl (9 μL , 0.074 mmol). The reaction was stirred for 30 min, then quenched with saturated aqueous NH_4Cl and partitioned with EtOAc. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to afford 22 mg (0.37 mmol, quant. yield) of isatogen **3.40** as a red oil. R_f = 0.5 (10% EtOAc in hexanes); ^1H NMR (600 MHz; CDCl_3) δ 7.59 (s, 1H), 6.22 (d, J = 2.9 Hz, 1H), 5.45 (d, J = 3.0 Hz, 1H), 2.85 (t, J = 2.9 Hz, 1H), 1.72 (s, 3H), 1.71 (s, 3H), 1.52 (s, 3H), 1.35 (s, 3H), 1.31 (s, 3H), 1.19-1.11 (m, 3H), 1.03 (d, J = 7.4 Hz, 9H), 0.97 (d, J = 7.4 Hz, 9H), 0.88 (s, 3H), 0.14 (s, 9H); ^{13}C NMR (151 MHz; CDCl_3) δ 183.6, 145.4, 140.8,

140.4, 139.7, 134.9, 128.5, 127.7, 123.2, 122.3, 74.62, 74.59, 72.8, 72.6, 59.4, 31.1, 29.9, 29.8, 28.2, 28.1, 22.1, 18.6, 18.5, 13.4, 2.1; $[\alpha]_D^{22}$ -23.9 (c 1.0, CHCl₃); HRMS (ES+) calculated for C₃₃H₅₂ClNO₅Si₂Na [M+Na]⁺: 656.2971, found: 656.2963.

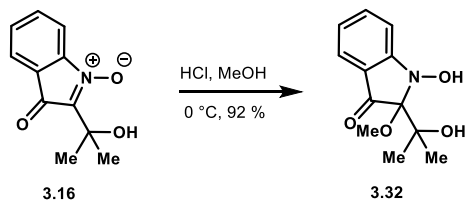


Arylketones 3.42 and 3.43. Ketone **3.41** (7 mg, 0.015 mmol) and isatogen **3.40** (13 mg, 0.022 mmol) were azeotropically dried with benzene in separate dram vials before being transferred into a glovebox. To the dram vial containing isatogen **3.40** was added RuPhosPd G4 (6.4mg, 0.0075 mmol) and RuPhos (3.5 mg, 0.0075 mmol). To the dram vial containing ketone **3.41** was added Bu₃SnCl (0.3 mL, 0.05 M in toluene), which was then placed in a freezer cooled to -25 °C for 20 min. A 0.05 M solution of NaHMDS in toluene was also prepared and placed in the freezer for 20 min. NaHMDS (0.32 mL, 0.05 M) was then added to the ketone solution and placed back in the freezer for 20 min, then allowed to warm to r.t. over an additional 20 min. The tin enolate solution was next added to the vial containing isatogen **3.40**, precatalyst and ligand, cooled back down to -25 °C for 20 min and then added NaHMDS (0.15 mL, 0.05 M). The reaction was warmed back up to r.t., then heated to 50 °C for 16 h. The reaction mixture was removed from the glovebox, quenched with saturated aqueous ammonium chloride and extracted with ethyl acetate three times. The combined

organic layers were washed with water, brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. ^1H NMR with added mesitylene as an internal standard shows 28% yield of **3.42** and 13% yield of **3.43**. Purification by preparatory TLC (15% ethyl acetate in hexanes) allowed for separation of diastereomers, yielding arylketone **3.42** (2.5 mg, 16% yield) and arylketone **3.43** (1 mg, 6.4% yield). Stereochemistry was tentatively assigned based on 2D NMR experiments. Characterization of **3.42**: ^1H NMR (600 MHz; CDCl_3) δ 7.24 (s, 1H), 7.15 (d, J = 11.3 Hz, 1H), 6.26 (dd, J = 15.3, 11.2 Hz, 1H), 6.03 (d, J = 2.4 Hz, 1H), 5.79 (d, J = 15.3 Hz, 1H), 5.44 (d, J = 3.1 Hz, 1H), 4.67-4.64 (m, 1H), 4.20 (q, J = 6.5 Hz, 2H), 2.83 (t, J = 2.9 Hz, 1H), 2.38-2.32 (m, 1H), 2.27-2.25 (m, 1H), 1.91-1.90 (m, 3H), 1.90-1.86 (m, 1H), 1.77-1.71 (m, 3H), 1.70 (s, 3H), 1.68 (s, 3H), 1.62-1.60 (m, 1H), 1.55 (s, 3H), 1.52 (s, 3H), 1.49-1.42 (m, 3H), 1.36 (s, 3H), 1.32-1.30 (m, 6H), 1.27-1.25 (m, 3H), 1.22 (s, 3H), 1.18 (s, 3H), 1.15-1.13 (m, 3H), 1.10 (s, 9H), 1.02 (d, J = 7.4 Hz, 9H), 0.97 (d, J = 7.4 Hz, 9H), 0.89 (s, 3H), 0.12 (s, 9H); HRMS (ES+) calculated for $\text{C}_{62}\text{H}_{95}\text{NO}_{10}\text{Si}_2\text{Na}$ $[\text{M}+\text{Na}]^+$: 1092.6393, found: 1093.6444. Characterization of **3.43**: ^1H NMR (500 MHz; CDCl_3) δ 7.20 (s, 1H), 7.15 (d, J = 11.4 Hz, 1H), 6.27 (dd, J = 15.3, 11.2 Hz, 1H), 6.13 (d, J = 2.8 Hz, 1H), 5.79 (d, J = 15.3 Hz, 1H), 5.44 (d, J = 3.0 Hz, 1H), 5.03 (dd, J = 10.8, 8.0 Hz, 1H), 4.69-4.65 (m, 1H), 4.20 (q, J = 7.1 Hz, 2H), 2.82 (t, J = 2.8 Hz, 1H), 2.50-2.43 (m, 2H), 2.24-2.22 (m, 1H), 1.92 (s, 3H), 1.85-1.72 (m, 4H), 1.70 (s, 3H), 1.68 (s, 3H), 1.65-1.62 (m, 2H), 1.54 (s, 3H), 1.52 (s, 3H), 1.45-1.40 (m, 2H), 1.35 (s, 3H), 1.32-1.29 (m, 6H), 1.29-1.22 (m, 2H), 1.17 (s, 3H), 1.16 (s, 3H), 1.15-1.11 (m, 3H), 1.11 (s, 9H), 1.02 (d, J = 7.4 Hz, 9H), 0.97 (d, J = 7.4 Hz, 9H), 0.88 (s, 3H), 0.12 (s, 9H); HRMS (ES+) calculated for $\text{C}_{62}\text{H}_{95}\text{NO}_{10}\text{Si}_2\text{Na}$ $[\text{M}+\text{Na}]^+$: 1092.6393, found: 1093.6400.

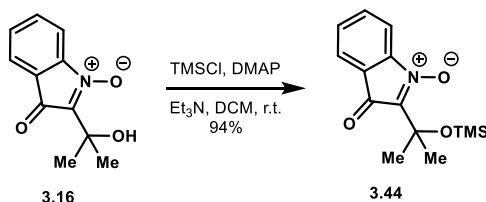


Aminoalcohol 3.31. Isatogen **3.16** (92 mg, 0.45 mmol) was added to a flame dried round bottom flask and the atmosphere exchanged with N₂. DCM (4.0 mL) was added and the solution was cooled to 0 °C. Trifluoroacetic acid (0.070 mL, 0.90 mmol) was added, followed by a solution of NaBH₃CN (28 mg, 0.45 mmol) in DCM (0.0.5 mL) and EtOH (0.5 mL). The reaction was stirred for 20 min, then quenched with saturated aqueous NaHCO₃. The reaction was diluted in DCM and washed with water, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to afford 93 mg (0.45 mmol, quant. yield) of aminoalcohol **3.25** as a yellow oil. ¹H NMR (500 MHz; CDCl₃) δ 7.66-7.62 (m, 2H), 7.37 (d, *J* = 8.5 Hz, 1H), 7.15 (t, *J* = 7.5 Hz, 1H), 6.56 (br s, 1H), 3.75 (s, 1H), 3.52 (br s, 1H), 1.41 (s, 3H), 1.33 (s, 3H); ¹³C NMR (126 MHz; CDCl₃) δ 198.7, 163.5, 137.3, 124.02, 123.96, 123.6, 116.5, 81.5, 73.3, 27.0, 25.8.



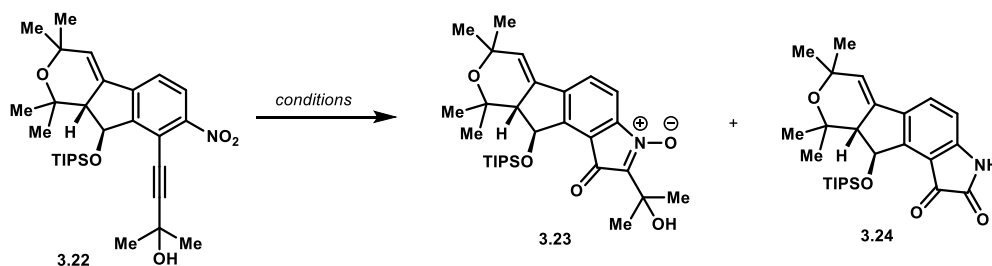
Hydroxylamine 3.32. Isatogen **3.16** (43 mg, 0.21 mmol) was dissolved in MeOH (2.0 mL) in a dram vial and cooled to 0 °C. HCl (0.18 mL, 2.1 mmol, conc.) was added and the reaction stirred for 1h, then quenched with saturated aqueous NaHCO₃ and extracted three times with DCM. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford 46 mg (0.19 mmol, 92% yield) of hydroxylamine **3.32** as a yellow oil. Note: subjection to acidic conditions in the absence of

methanol will revert hydroxylamine **3.32** to isatogen **3.16**. ^1H NMR (500 MHz; CDCl_3) δ 7.81 (s, 1H), 7.61 (t, J = 8.1 Hz, 1H), 7.56 (d, J = 7.7 Hz, 1H), 7.25 (d, J = 8.2 Hz, 1H), 6.97 (t, J = 7.4 Hz, 1H), 3.83 (s, 1H), 3.23 (s, 3H), 1.44 (s, 3H), 1.11 (s, 3H).



Isatogen 3.44. Isatogen **3.16** (96 mg, 0.47 mmol) and DMAP (11 mg, 0.094 mmol) were added to a dram vial and the atmosphere was replaced with N_2 . Et_3N (0.20 mL, 1.41 mmol) and DCM (4.7 mL) were added, followed by TMSCl (0.12 mL, 0.94 mmol). The reaction was stirred for 1 h, then quenched with saturated aqueous NH_4Cl and partitioned with EtOAc . The organic layer was washed with water and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to afford 0.123 g (0.44 mmol, 94% yield) of isatogen **3.44** as a yellow oil. R_f = 0.53 (20% EtOAc in hexanes); ^1H NMR (500 MHz; CDCl_3) δ 7.66-7.60 (m, 2H), 7.57-7.52 (m, 2H), 1.75 (s, 6H), 0.12 (s, 9H); ^{13}C NMR (126 MHz; CDCl_3) δ 186.0, 147.2, 134.4, 131.5, 123.0, 121.3, 114.1, 72.1, 28.4 (2C), 2.0; IR (thin film in DCM): 3440, 3054, 2985, 1711, 1520, 1356 cm^{-1} .

3.4.3 Tables of Conditions

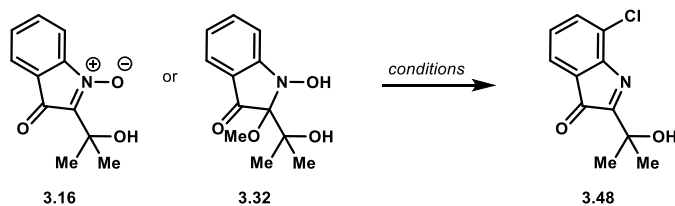


Entry	Catalyst	Additive	Solvent	Conditions	Result (NMR yields)
1	AuCl_3 (10 mol%)		Toluene	0 – 50 $^\circ\text{C}$	no reaction

2	AuCl ₃ (10 mol%)	2,6-di- <i>tert</i> -butylpyridine (5 mol%)	Toluene	r.t. – 70 °C	no reaction
3	AuCl ₃ (10 mol%)		Toluene	70 – 100 °C	elimination
4	TMSCl+MeOH (5 mol%)		MeCN	0 – 35 °C	desilylation
5	TMSCl+MeOH (5 mol%)		DCM	0 – 35 °C	no reaction
6	PdCl ₂ (PPh ₃) ₂ (5 mol%)		DCM	35 °C	no reaction
7	CuBr·SMe ₂ (25 mol%)		THF	65 °C	no reaction
8	CuBr·SMe ₂ (25 mol%)		Dioxane	60 – 90 °C	no reaction
9	CuOTf C ₆ H ₆ (5 mol%)		THF	r.t. – 60 °C	no reaction
10	RhCl(PPh ₃) ₃ (12 mol%)	AgSbF ₆ (10 mol%)	DCE	r.t. – 80 °C	no reaction
11	(MeCN) ₄ Pd(BF ₄) ₂ (5 mol%)		MeCN	r.t. – 40 °C	decomposition
12	(MeCN) ₄ Pd(BF ₄) ₂ (5 mol%)		DMF	r.t. – 80 °C	no reaction
13	(MeCN) ₄ Pd(BF ₄) ₂ (5 mol%)		Toluene	r.t. – 80 °C	no reaction
14	Pd(TFA) ₂		MeCN	r.t. – 80 °C	decomposition
15	Pd(OAc) ₂		MeCN	r.t. – 80 °C	no reaction
16	PtCl ₂ (5 mol%)		DCE	r.t. – 80 °C, 24h	14% 3.23 , 40% 3.22
17	AgBF ₄ (5 mol%)		Toluene	r.t. – 110 °C	minor decomposition
18	AgNO ₃ (5 mol%)		MeCN	r.t. – 80 °C	minor decomposition
19	ZnBr ₂ (5 mol%)		MeCN	r.t. – 80 °C	no reaction
20	ZnBr ₂ (5 mol%)		Toluene	r.t. – 100 °C	no reaction
21	InBr ₃ (5 mol%)		MeCN	r.t.	decomposition
22	InBr ₃ (5 mol%)		DCE	r.t. – 50 °C	decomposition
23	Hg(OTf) ₂ (5 mol%)		MeCN	r.t.	desilylation
24	Hg(OTf) ₂ (5 mol%)		THF	0 – 50 °C	no reaction
25	Hg(OTf) ₂ (5 mol%)		DCE	r.t.	desilylation
26	NiBr ₂		MeCN	r.t. – 80 °C	no reaction
27	GaCl ₃ (10 mol%)		MeCN	r.t.	desilylation
28	GaCl ₃ (10 mol%)		THF	0 – 50 °C	no reaction
29	GaCl ₃ (10 mol%)		DCE	r.t.	desilylation
30	PtCl ₂ (5 mol%)		Toluene	60 – 110 °C	decomposition

31	PtCl ₂ (5 mol%)	2,6-di- <i>tert</i> -butylpyridine (5 mol%)	Toluene	60 – 110 °C	decomposition
32	PtCl ₂ (5 mol%)		MeCN	r.t. -80 °C	no reaction
33	PdI ₂ (5 mol%)		MeCN	r.t. – 80 °C	no reaction
34	PdBr ₂ (5 mol%)		MeCN	r.t. – 80 °C, 16h	30% 3.23 , 15% 3.22
35	PdBr ₂ (5 mol%)		DMF	90 – 110 °C	no reaction
36	PdCl ₂ (MeCN) ₂ (5 mol%)		EtOAc	40 – 70 °C	no reaction
37	PdCl ₂ (MeCN) ₂ (5 mol%)		Toluene	40 – 70 °C	no reaction
38	PdCl ₂ (MeCN) ₂ (5 mol%)		DCE	40 – 70 °C	no reaction
39	PdCl ₂ (MeCN) ₂ (5 mol%)		DMSO	r.t. – 90 °C	minor decomposition
40	PdCl ₂ (MeCN) ₂ (5 mol%)		DMF	r.t. – 80 °C, 24h	11% 3.23 , 8% 3.22
41	PdCl ₂ (MeCN) ₂ (10 mol%)		MeCN	50 – 60 °C, 48 h	23% 3.23 , 9% 3.24 , 9% 3.22
42	PdCl ₂ (MeCN) ₂ (1 mol%)		MeCN	82 °C, 48h	16% 3.23 , 74% 3.22
43	PdCl ₂ (MeCN) ₂ (5 mol%)		MeCN	100 °C, 48h	8% 3.23 , 67% 3.22
44	PdCl ₂ (MeCN) ₂ (1 mol% x3)		MeCN	82 °C, 30h	20% 3.23 , 11% 3.24 , 42% 3.22
45	PdCl ₂ (MeCN) ₂ (2 mol% x3)		MeCN	82 °C, 30h	34% 3.23 , 13% 3.24 , 10% 3.22
46	PdCl ₂ (MeCN) ₂ (0.5 mol% x3)		MeCN	82 °C, 40h	25% 3.23 , 3% 3.24 , 54% 3.22
47	PdCl ₂ (MeCN) ₂ (10 mol%)	4A mol. Sieves	MeCN	82 °C, 48h	26% 3.23 , 3% 3.24 , 50% 3.22
48	PdCl ₂ (MeCN) ₂ (15 mol%)	4A mol. Sieves	MeCN	82 °C, 48h	25% 3.23 , 4% 3.24 , 42% 3.22
49	PdCl ₂ (MeCN) ₂ (10 mol%)	4A mol. Sieves (crushed)	MeCN	82 °C, 70h	28% 3.23 , 8% 3.24 , 36% 3.24
50	PdCl ₂ (MeCN) ₂ (5 mol% x2)	4A mol. Sieves	MeCN	82 °C, 48h	43% 3.23 , 5% 3.24 , 21% 3.22
51	PdCl ₂ (MeCN) ₂ (5 mol% x2)	4A mol. Sieves	MeCN	82 °C, 26h	47% 3.23 , 10% 3.24
52	PdCl ₂ (MeCN) ₂ (5 mol%)	Na ₂ HPO ₄ (15 mol%)	MeCN	82 °C, 22h	38% 3.23 , 11% 3.22
53	PdCl ₂ (MeCN) ₂ (5 mol%)	Na ₂ HPO ₄ (50 mol%)	MeCN	82 °C, 22h	24% 3.23 , 3% 3.24 , 59% 3.22
54	PdCl ₂ (MeCN) ₂ (5 mol%)	Na ₂ HPO ₄ (50 mol%)	MeCN	82 °C, 46h	32% 3.23 , 6% 3.24 , 47% 3.22
55	PdCl ₂ (MeCN) ₂ (5 mol%)	Na ₂ HPO ₄ (50 mol%, dried)	MeCN	82 °C, 23h	45% 3.23 , 12% 3.24

56	$\text{PdCl}_2(\text{MeCN})_2$ (2.5 mol%)	Na_2HPO_4 (50 mol%, dried)	MeCN	82 °C, 28h	36% 3.23 , 5% 3.25 , 48% 3.22
57	$\text{PdCl}_2(\text{MeCN})_2$ (5 mol% x3)	Na_2HPO_4 (50 mol%, dried)	MeCN	82 °C, 39h	56% 3.23 , 9% 3.25



Entry	SM	Activator	Chloride source	Conditions	Result
1	3.16	POCl_3	Et_3BnNCl	DCE, r.t. – 50 °C	partial decomposition
2	3.16	MsCl	Et_3BnNCl	DCE, r.t. – 50 °C	partial decomposition
3	3.16	$(\text{COCl})_2$	Et_3BnNCl	DCE, r.t.	partial decomposition
4	3.16	POCl_3	Bu_4NCl	DCE, r.t. – 50 °C	partial decomposition
5	3.16	CCl_4 , PPh_3		DCM, 0 °C - r.t.	decomposition
6	3.32	POCl_3		neat, r.t.	decomposition
7	3.32	POCl_3		DCE, r.t. – 50 °C	decomposition
8	3.32	SOCl_2		neat, r.t.	decomposition
9	3.32	SOCl_2	Et_3BnNCl	neat, r.t.	decomposition
10	3.32	CCl_4 , PPh_3		DCM, 0 °C - r.t.	formation of 3.16
11	3.32	TsCl		DCE, Et_3N , r.t.	formation of 3.16
12	3.32	MsCl		DCE, Et_3N , r.t.	formation of 3.16
13	3.32	TsCl	Et_3BnNCl	DCE, Et_3N , r.t.	formation of 3.16

3.5 References and Notes

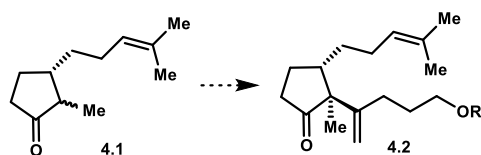
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- ¹ Meinke, P. T.; Smith, M. M.; Shoop, W. L. *Curr. Top. Med. Chem.* **2002**, *2*, 655–674 and references therein.
- ² For relevant examples, see: (a) Asao, N.; Sato, K.; Yamamoto, Y. *Tetrahedron Lett.* **2003**, *44*, 5675–5677. (b) Ramana, C. V.; Patel, P.; Vanka, K.; Miao, B. C.; Degterev, A. *Eur. J. Org. Chem.* **2010**, 5955–5966. (c) Kumar, C. V. S.; Ramana, C. V. *Org. Lett.* **2014**, *16*, 4766–4769. (d) Liu, R.-R.; Ye, S.-C.; Lu, C.-J.; Zhuang, G.-L.; Gao, J.-R.; Jia, Y.-X. *Angew. Chem. Int. Ed.* **2015**, *54*, 11205–11208.
- ³ See reference 2a-c as well as: (a) Li, X. W.; Incarvito, C. D.; Vogel, T.; Crabtree, R. H. *Organometallics* **2005**, *24*, 3066–3073. (b) Jadhav, A. M.; Bhunia, S.; Liao, H. Y.; Liu, R. S. *J. Am. Chem. Soc.* **2011**, *133*, 1769–1771.
- ⁴ See reference 2d.
- ⁵ See reference 3a.
- ⁶ See reference 2a.
- ⁷ See Chapter 2, Section 2.2.2.
- ⁸ (a) Söderberg, B.; Gorugantula, S. P.; Howerton, C. R.; Petersen, J. L.; Dantale, S. W. *Tetrahedron* **2009**, *65*, 7357–7363. (b) Maduli, E. J. M.; Edeson, S. J.; Swanson, S.; Procopiou, P. A.; Harrity J. P. A. *Org. Lett.* **2015**, *17*, 390–392.
- ⁹ For a complete list of conditions tried see Section 4.4.3.
- ¹⁰ De, P.; Nonappa; Pandurangan, K.; Maitra, U.; Wailes, S. *Org. Lett.* **2007**, *9*, 2767–2770.
- ¹¹ Ayyangar, N. R.; Kalkote, U. R.; Nikrad, P. V. *Tetrahedron Lett.* **1982**, *23*, 1099–1102.
- ¹² For a complete list of conditions tried see Section 4.4.3.
- ¹³ Wang, Y.; Liu, L.; Zhang, L. *Chem. Sci.* **2013**, *4*, 739–746.
- ¹⁴ See Chapter 2 Section 2.2.4.
- ¹⁵ Assignment of protons is speculative based on relevant ¹³C chemical shifts observed in the HMQC spectrum and several parallels drawn between these arylation products and those from our synthesis of NsA C discussed previously.

Chapter 4: Development of a Formal Ene Reaction for the Alkenylation of Unsymmetrical Ketones

4.1 Introduction

During our explorations into the paxilline indole diterpenes¹ we became interested in methods to assemble β,γ -unsaturated ketones in an intermolecular fashion through a ketone alkenylation strategy (**4.1** $\rightarrow$ **4.2**, Figure 4.1). Such a transformation would allow for

Figure 4.1: Desired alkenylation strategy

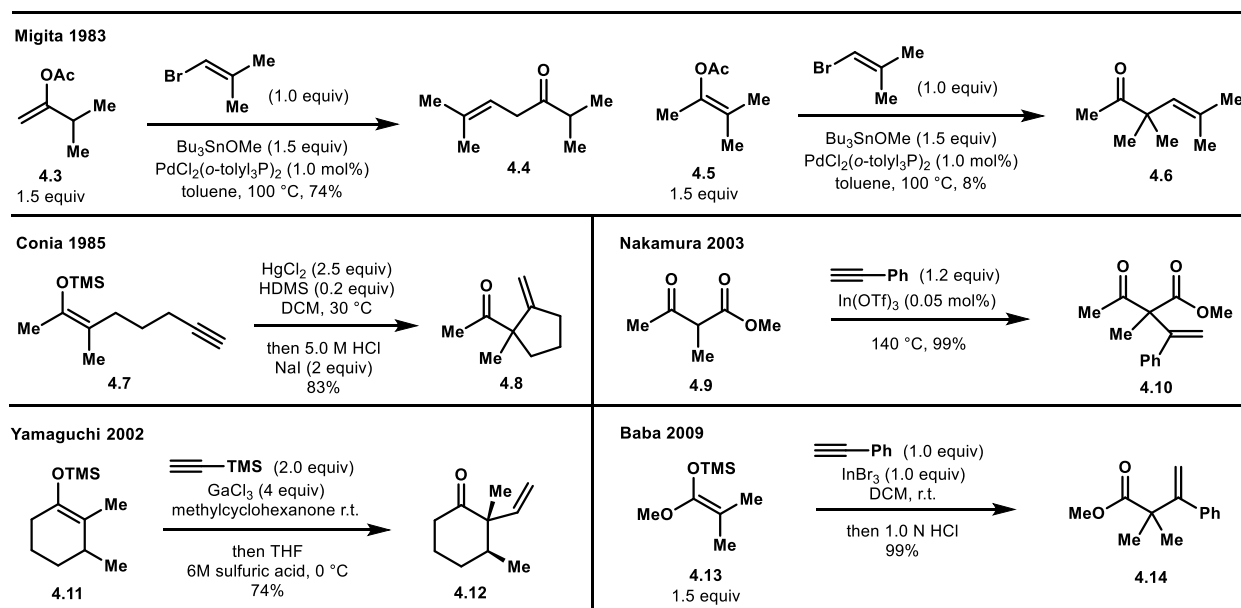


convenient access to complex structures containing orthogonal functionalization sites. The first report from Migita² detailed an intermolecular palladium(0) catalyzed cross coupling between *in situ*-generated tin enolates and vinyl bromides (Figure 4.2). Unfortunately, this method was unable to efficiently form quaternary centers. Subsequent works from other groups extended the scope of palladium(0) and nickel(0) alkenylations of this type, though the substrates were limited to aryl alkyl or alkenyl alkyl ketones bearing only one enolizable position due to issues concerning the selectivity of enolate formation.^{3,4}

In light of these limitations, we became interested in reactions involving the activation of alkynes toward attack by an enolate equivalent. Conia's⁵ pioneering report details an intramolecular cyclization of a terminal alkyne onto an enoxysilane (Figure 4.2) mediated by stoichiometric mercury(II) chloride. Subsequent reports of aluminum(III)-mediated⁶ and transition-metal-catalyzed⁷ alkenylations with enoxysilanes described similar intramolecular transformations; however, the corresponding intermolecular transformations had little precedent. Among those included Yamaguchi's⁸ intermolecular alkenylation of enoxysilanes which required the use of superstoichiometric gallium(III)

chloride and was limited in scope to TMS-acetylene (Figure 4.2). Nakamura⁹ reported the first catalytic intermolecular process of this type using 1,3-dicarbonyls to activate the α -position toward enolization; however, this method was not applicable unactivated ketones.

Figure 4.2: Relevant alkenylations



We became interested in the work of Baba¹⁰ wherein he used silyl ketene acetals and terminal alkynes in the presence of stoichiometric indium(III) bromide to effect an alkenylation to form quaternary centers. While Baba's initial report was limited to silyl ketene acetals, which have only a single enolizable position, we believed this reaction could be made to be more general. Based on this work, we developed an alkenylation of an enoxysilane derived from an unsymmetrical ketone. Treatment with substoichiometric indium(III) bromide selectively formed the β,γ -unsaturated ketone at the more substituted position to deliver an intermediate *en route* to the paxilline indole diterpenes (Figure 4.1).¹

Despite this initial success, we imagined if we could render this reaction catalytic we may be able to effect a formal ene reaction to regenerate the enoxysilane, which has never

been observed in a bimolecular setting. The regeneration of a useful functional handle could prove advantageous in this method's application in complex synthesis. This type of reaction poses many new challenges that previous works had not addressed. Enoxysilanes derived from unsymmetrical ketones will isomerize under acidic conditions¹¹ which can arise during processes catalyzed by metal salts,¹² leading to potential selectivity issues. Additionally, the product of our proposed formal ene reaction could itself be a substrate for this reaction. As such, the transformation would require the selective functionalization of the more substituted enoxysilane in the presence of the less substituted products, resulting in the formation of quaternary centers. This would be of particular use for building systems such as ketone **4.2** (Figure 4.1) *en route* to the paxilline indole diterpenes.

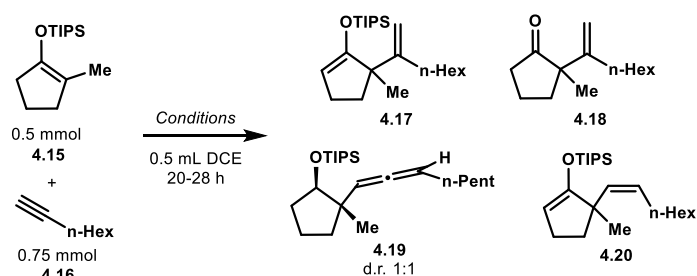
4.2 Development of the Alkenylation

4.2.1 Initial Reaction Explorations

We began our optimization attempts¹³ using metals that have been shown to participate in similar reactions. *Table 4.1: Alkenylation optimization*

Gold(I) complexes proved to be poor catalysts, with the best combination affording only small amounts of the desired product (Entry 1, Table 4.1).

Zinc(II) bromide was similarly unsuccessful (Entry 2). Nakamura's conditions⁹ afforded none of the desired product (Entry 3), but we had more success with indium(III) halides.



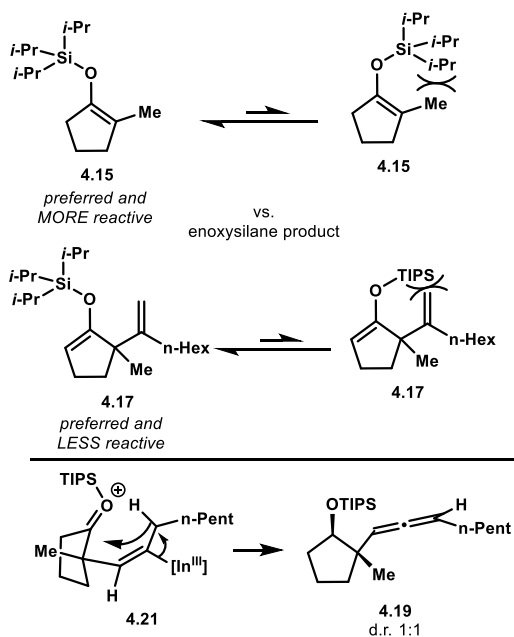
Entry	Conditions	4.17 (%)	4.18 (%)	4.19 (%)	4.20 (%)
1	5 mol% IPrAuCl, 5 mol% NaBARF, 65 °C	11	8	10	<1
2 ^a	10 mol% ZnBr ₂ , 65 °C	4	5	1	<1
3	5 mol% In(OTf) ₃ , 65 °C	<1	1	<1	<1
4	5 mol% InCl ₃ , 65 °C	5	9	<1	<1
5	5 mol% InBr₃, 65 °C	72	5	6	2
6	5 mol% InI ₃ , 65 °C	36	6	7	<1
7	5 mol% InBr ₃ , 5 mol% NaBARF, 65 °C	40	11	3	<1
8	5 mol% InBr₃, 50 °C	65	9	3	<1
9	5 mol% MeOH, 8 mol% TMSBr, 65 °C	<1	<1	<1	<1
10	5 mol% TfOH, 65 °C	<1	<1	<1	<1

(a) reaction run in the absence of solvent

While indium(III) chloride provided low yields (Entry 4), indium(III) bromide afforded 72% of the desired enoxysilane (Entry 5). Indium (III) iodide afforded lower yields and selectivity (Entry 6). Addition of halide scavengers with the intent of increasing the catalyst reactivity only decreased the yield (Entry 7). At lower temperatures, indium(III) bromide afforded less of the observed side products with only a minor loss in yield (Entry 8). Reactions attempted in the presence of anhydrous acid afforded no observable alkenylation products (Entries 9 and 10).

The selectivity of this reaction is of particular note. In all of these trials we observed none of the products of double alkenylation. Despite our product being an enoxysilane, the reaction is selective for the more substituted enoxysilane starting material. We speculatively attribute this selectivity to the conformational preferences of the siloxy group. In the enoxysilane starting materials and products, the silyl group is preferentially pointed away from most substituted position due to A(1,3) strain (Figure 4.3). In the starting materials, this means the silyl group is pointed away from the alkene, leaving it available to react (ie. **4.15**). The products, however, have the silyl group in the same direction as the alkene, blocking it from undergoing a second round of alkenylation (ie. **4.17**).

Figure 4.3: Selectivity and allene formation



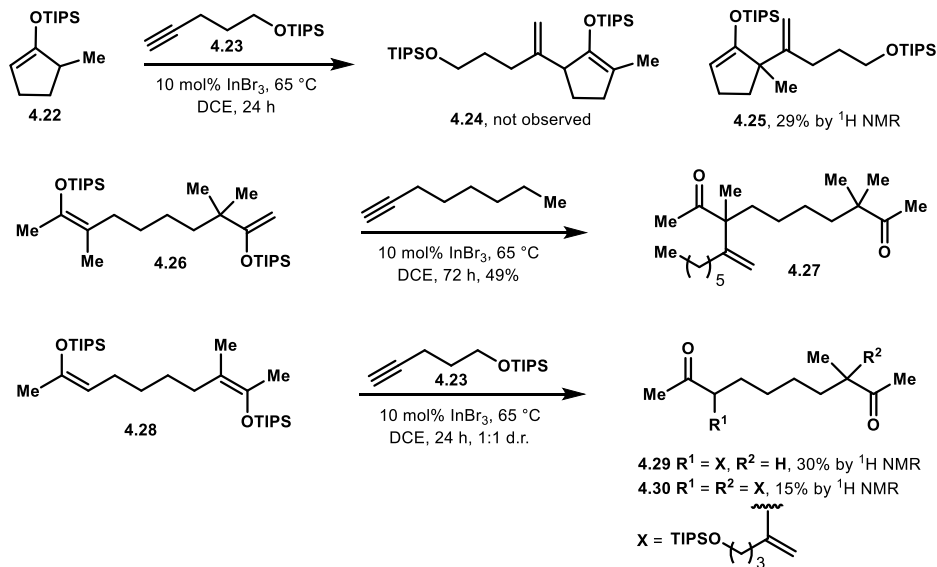
These reactions were also selective for the formation of 1,1-disubstituted alkenes, with only small amounts of regioisomer **4.20** (Table 4.1) observed. We did observe the

unexpected allene side product **4.19** in our reactions with gold(I) and indium(III) halides, which presumably arises through initial regioisomeric attack on the alkyne followed by hydride transfer into the siloxocarbenium (**4.21**, Figure 4.3). While the allene was inseparable from the enoxysilane products, lowering the temperature produced less of the undesired allene and the products could be isolated in >95% purity.

4.2.2 Selectivity of the Alkenylation

To further explore the selectivity of this transformation, we subjected enoxysilane **4.22** to our alkenylation conditions (Figure 4.4). Somewhat surprisingly, we did not observe the product of alkenylation at the least substituted position and instead observed *in situ* isomerization of the double bond followed by formation of **4.25**. The experiment confirmed that the enoxysilanes were undergoing isomerization *in situ*, and despite the presence of the less substituted substrate, our reaction was still selective for the formation of quaternary centers. This level of selectivity with unsymmetrical ketones was previously incredibly difficult to achieve.¹⁴

Figure 4.4: Explorations of selectivity

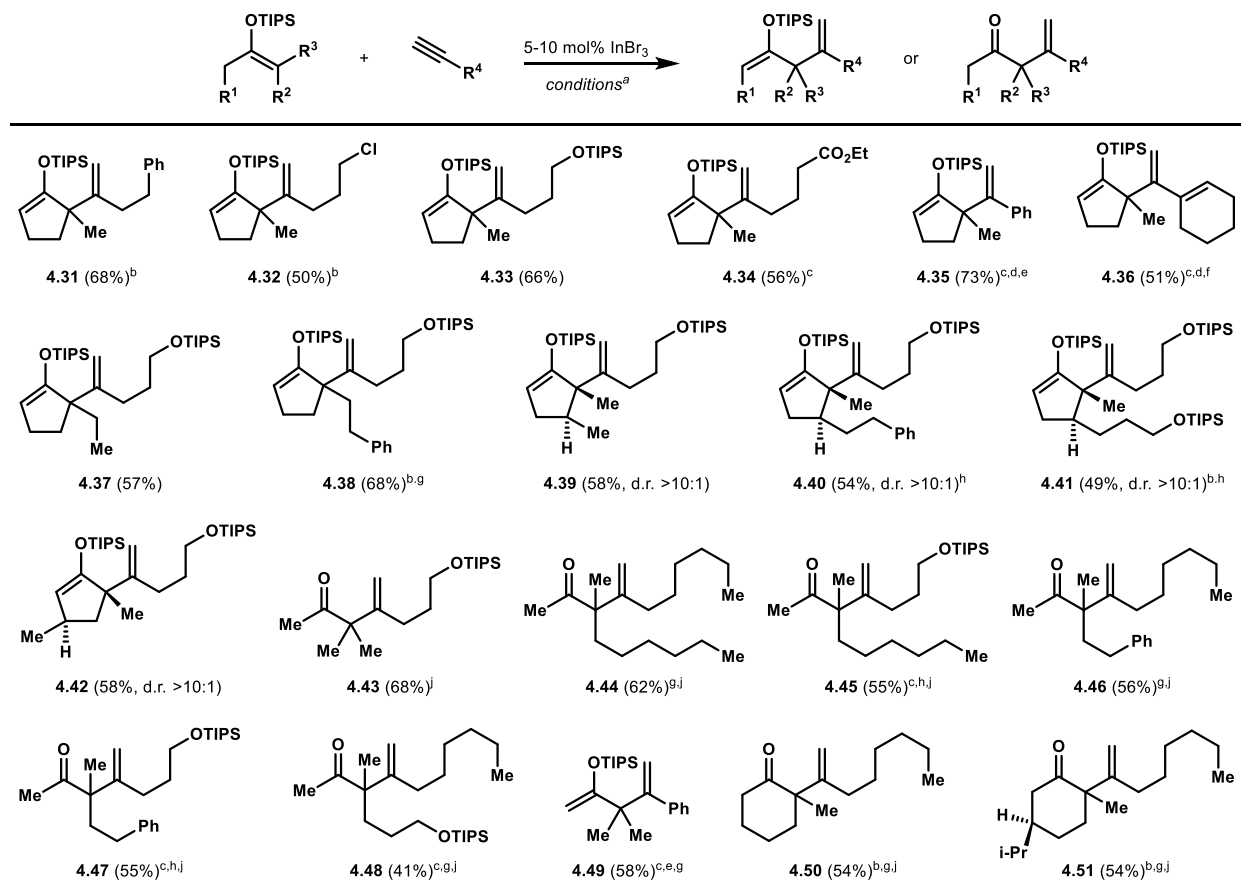


To test the limits of the observed selectivity we synthesized two diketones with multiple enolizable positions and subjected them to our alkenylation conditions following enoxysilane formation. Enoxysilane **4.26**¹⁵ reacted with 1-octyne exclusively at the most substituted position to afford diketone **4.27** after a mild acidic work up (Figure 4.4). This observation correlates with the observed lack of reactivity of the products of alkenylation, which are similar in structure to the unreactive site in **4.26**. Enoxysilane **4.28** gave somewhat different results and we observed two products of this reaction. The first arose though a single alkenylation event that corresponded to reaction at the disubstituted enoxysilane preferentially over the mono- and trisubstituted enoxysilanes (**4.29**). The second product corresponded to a double alkenylation event at the two most substituted positions (**4.30**). In both cases, the monosubstituted enoxysilane remained unreactive. This mixed selectivity suggests that the method may be applicable to a wider scope than the synthesis of quaternary centers and is consistent with our hypothesis regarding the reactivity of the enoxysilane products (Figure 4.3). Unfortunately, attempted reactions with various disubstituted enoxysilanes all suffered from the hydrolytic instability of the starting materials and we were unable to afford synthetically useful yields.

4.2.3 Scope of the Alkenylation¹⁶

This transformation was shown to be tolerant of a variety of functional groups including aromatic rings, alkyl chlorides, silyl ethers, and, surprisingly, Lewis basic esters (**4.31** – **4.34**, Table 4.2). The reaction also tolerated conjugated alkynes (**4.35** and **4.36**) and non-methyl substitution at the α -position (**4.37** and **4.38**). Substrates with additional substitution at the 3- or 4-position on the cyclopentanone ring afforded high d.r. with synthetically useful yields (**4.39** – **4.42**). We also explored the scope of acyclic substrates;

Table 4.2: Substrate scope



(a) 1 equiv. silyl enol ether, 1.5 equiv. alkyne, 10 mol% InBr₃, DCE (1 M in silyl enol ether), 65 °C, ca. 24 h; r.r. >10:1 (except **4.36**: r.r. 9:1); siloxydienes (except **4.35**, **4.36**, **4.49**) contained ca. 5% allene. (b) Heated to 50 °C. (c) Heated to 80 °C. (d) 5 mol% InBr₃. (e) neat (f) 5 M in silyl enol ether (g) Heated for ca. 72 h. (h) Heated for ca. 48 h. (i) NMR yield with respect to mesitylene internal standard. (j) After hydrolysis.

however, the enoxysilane products proved to be very hydrolytically unstable and were isolated as the ketones after a mild hydrolytic work-up (**4.43** – **4.48**) except when run in the absence of solvent (**4.49**). Explorations of cyclohexanone-derived enoxysilanes revealed these substrates produced more of the undesired allene side products. For purification purposes, these products were also isolated as the ketones after a hydrolytic work-up (**4.50** and **4.51**). Under these conditions, reactions with substrates containing pendant alkyl bromides or ketones failed, as well as those with additional substitution at the 3-position of the alkyne. Internal alkynes and TMS-acetylene also did not participate in the reaction. We attempted the catalytic alkenylation with homoprenyl substitution (Figure 4.1) at the 3

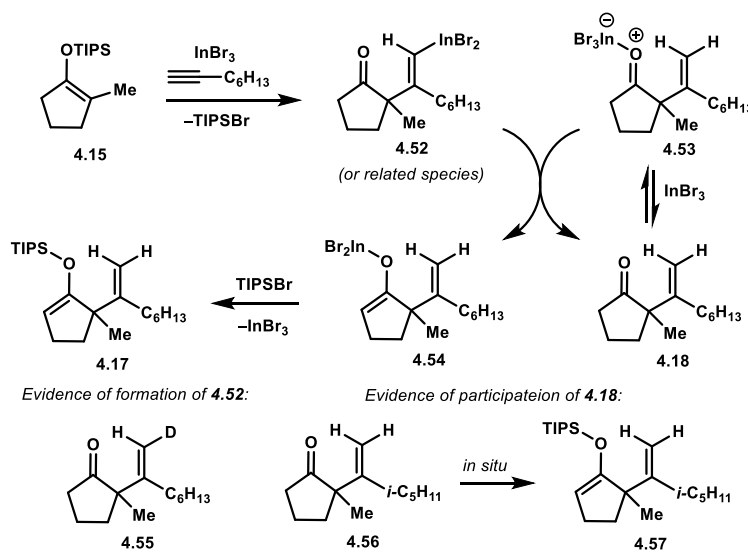
position of the cyclopentanone; however, our yields were lower than the corresponding stoichiometric reaction used in our synthesis of NsA C (*vide supra*), with a 15% catalyst loading affording only 40% of the product.

4.2.4 Mechanistic Studies

With a substrate scope in hand we next turned our attention toward mechanistic studies. After several deuterium labeling and quenching studies performed by Stephen Holmbo, we proposed the mechanism in Figure 4.5 beginning with attack of enoxysilane **4.15** on the activated indium-alkyne complex to form alkenylindium **4.52** with loss of TIPSBr. Anti-addition is supported by the observation of **4.55** after treatment with deuterated methanol and desilylation is supported by the observation of TIPSBr in various NMR experiments. Protodemetalation then affords ketone **4.18**, which can coordinate to indium to serve as the Brønsted acid for subsequent protodemetalations. We believe the indium-alkyne complex could serve as the

Figure 4.5: Proposed mechanism

initial proton source for this transformation, supported by observed deuterium scrambling when the reaction was run with the deuterated alkyne, as well as the observation of an induction period during the reaction. While the indium-alkyne complex is



serving as the proton source, the reaction is slow. After a sufficient concentration of **4.18** is created, the reaction proceeds more quickly. Additionally, NMR experiments have confirmed

that **4.18** is present at the same concentration throughout the reaction. Participation of ketone **4.18** is supported by the observation that ketone **4.56** undergoes *in situ* silylation when added to the reaction. After formation of indium enolate **4.54**, resilylation with TIPSBr affords enoxysilane **4.17**.

4.3 Summary

We successfully developed a catalytic formal ene reaction for the synthesis of β,γ -unsaturated ketones from ketone-derived enoxysilanes and terminal alkynes.¹⁷ This reaction is highly selective for the formation of quaternary centers and is able to regenerate the enoxysilane without undergoing a second alkenylation event. Complex substitution patterns as well as a variety of functional groups are tolerated, allowing efficient access to challenging scaffolds. There is no alternative to this transformation in the current literature, but future works will explore expanding the substrate scope and improving overall efficiency.

4.4 Experimental Section

4.4.1 General Experimental Details

All reactions were carried out in flame-dried glassware under positive pressure of dry nitrogen unless otherwise noted. Reaction solvents including tetrahydrofuran (THF, Fisher, HPLC Grade), dichloromethane (DCM, Fisher, HPLC Grade), and toluene (Fisher, HPLC Grade) were dried by percolation through a column packed with neutral alumina and a column packed with a supported copper catalyst for scavenging oxygen (Q5) under positive pressure of argon. Anhydrous 1,2-dichloroethane (Fisher, ACS Grade) and anhydrous triethylamine (Oakwood Chemical) were distilled from calcium hydride (10% w/v) under positive pressure of nitrogen. Anhydrous hexamethylphosphoramide (HMPA, Oakwood

Chemical) was distilled from calcium hydride (10% w/v) under vacuum (*ca.* 0.1 torr). Solvents for extraction, thin layer chromatography (TLC), and flash column chromatography were purchased from Fischer (ACS Grade) and VWR (ACS Grade) and used without further purification. Chloroform-*d* and benzene-*d*₆ for ¹H and ¹³C NMR analysis were purchased from Cambridge Isotope Laboratories and used without further purification. Commercially available reagents were used without further purification unless otherwise noted. Reactions were monitored by thin layer chromatography (TLC) using precoated silica gel plates (EMD Chemicals, Silica gel 60 F₂₅₄). Flash column chromatography was performed over silica gel (Acros Organics, 60 Å, particle size 0.04-0.063 mm). ¹H NMR and ¹³C NMR spectra were recorded on Bruker DRX-500 (BBO probe), Bruker DRX-500 (TCI cryoprobe), Bruker AVANCE600 (TBI probe), and Bruker AVANCE600 (BBFO cryoprobe) spectrometers using residual solvent peaks as internal standards (CHCl₃ @ 7.26 ppm ¹H NMR, 77.00 ppm ¹³C NMR; C₆H₆ @ 7.16 ppm ¹H NMR, 128.00 ppm ¹³C NMR). High-resolution mass spectra (HRMS) were recorded on Waters LCT Premier TOF spectrometer with ESI and CI sources.

4.4.2 General Procedure for the Alkenylation of Enoxysilanes

Reactions in solution. In a glovebox under pressure of nitrogen, a 5 mL Schlenk flask was charged with InBr₃ (0.05-0.10 equiv). The flask was sealed with a plastic cap, removed from the glovebox, and connected to a double bank vacuum manifold. The plastic cap was replaced with a rubber septum under continuous flow of nitrogen. Anhydrous 1,2-dichloroethane (1 M in substrate), the silyl enol ether (1.0 equiv), and alkyne (1.5 equiv) were added. Under flow of nitrogen, the septum was replaced with a yellow cap, which was secured with Parafilm. The nitrogen inlet for the Schlenk flask was closed and the reaction was heated to 50-80 °C for 23-72 h.

Reactions in the absence of solvent. A 4 mL vial was charged with the silyl enol ether (1.0 equiv) and alkyne (1.5 equiv). The reagents were degassed with a flow of nitrogen for 10 min and transferred to a glovebox. The reaction vial was charged with InBr₃ (0.05-0.10 equiv) and sealed with a Teflon-lined plastic screw-cap, which was secured with electrical tape. The vial was removed from the glovebox and heated to 50-80 °C for 24-72 h.

Isolation of 2-siloxy-1,4-dienes. The reaction was quenched with anhydrous Et₃N (0.5 mL), then anhydrous EtOH (1 mL) was added and the reaction was stirred for 20 min at room temperature. Purification by flash chromatography on Et₃N-treated silica gel yielded the desired 2-siloxy-1,4-dienes (*Note 1*).

Isolation of β,γ -unsaturated ketones. The reaction was quenched with anhydrous EtOH (1 mL) and stirred until TLC analysis indicated complete hydrolysis of siloxydienes (*Note 2*). The reaction was diluted with hexanes, washed with saturated aqueous NaHCO₃ and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. Purification by flash chromatography yielded the desired β,γ -unsaturated ketones (*Note 3*).

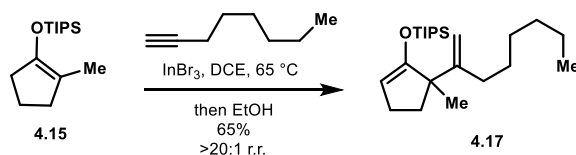
Note 1: All 2-siloxy-1,4-dienes derived from alkylacetylenes contained small admixture of corresponding allenes (*ca.* 5 mol%; see discussion in the manuscript), inseparable from the desired products. 2-Siloxy-1,4-dienes were obtained as mixtures of regioisomers with varying ratios (see entries below or Table 2 in the manuscript). The ratios were identified based on integration of alkenes in ¹H NMR spectra.

Note 2: In some cases, addition of small amounts of aqueous HCl was necessary.

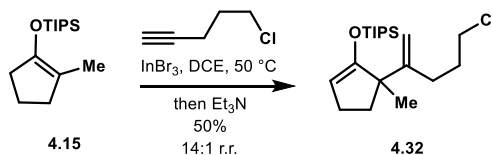
Note 3: β,γ -Unsaturated ketones were obtained as mixtures of regioisomers with varying ratios (see entries below or Table 2 in the manuscript). The ratios were identified based on integration of alkenes in ¹H NMR spectra.

4.4.3 Alkenylation Reactions

Compounds **4.27**, **4.31**, **4.33**, **4.37**, **4.38**, **4.40**, **4.50**, and **4.51** were prepared by Stephen Holmbo according to the literature.¹⁶ Diketone **4.49** was prepared by Sergey Pronin.

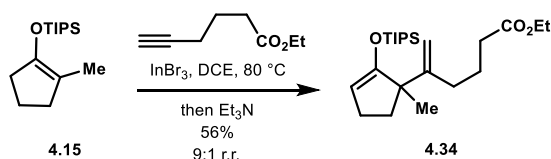


Enoxysilane 4.17. Prepared according to “General procedure for the alkenylation of silyl enol ethers” from enoxysilane **4.15**¹⁸ (ratio of tetra- and trisubstituted isomers $\geq 10:1$) and 1-octyne. The reaction was performed in solution on a 0.50 mmol scale with 0.1 equiv of InBr_3 . The reaction mixture was heated to 50°C for 23 h. The alkenylation proceeded in 65% yield (0.32 mmol, 0.12 g of enoxysilane **4.17** obtained, >20:1 r.r.). Runs with solvent front in hexanes; ^1H NMR (600 MHz, CDCl_3) δ 4.90 (d, $J = 1.2$ Hz, 1H), 4.77 (d, $J = 1.4$ Hz, 1H), 4.53 (t, $J = 2.3$ Hz, 1H), 2.20-2.17 (m, 2H), 2.03-2.00 (m, 2H), 1.98-1.93 (m, 1H), 1.61 (ddd, $J = 12.9$, 8.0, 6.2 Hz, 1H), 1.49-1.43 (m, 2H), 1.33-1.26 (m, 6H), 1.23 (s, 3H), 1.21-1.15 (m, 3H), 1.09-1.05 (m, 18H), 0.88 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 159.2, 154.4, 107.1, 99.4, 53.0, 36.4, 32.1, 31.8, 29.7, 28.7, 26.1, 24.0, 22.9, 18.22, 18.20, 14.3, 12.7; HRMS (CI) calculated for $\text{C}_{23}\text{H}_{44}\text{OSi}$ $[\text{M}]^+$: 364.3161, found: 364.3161.

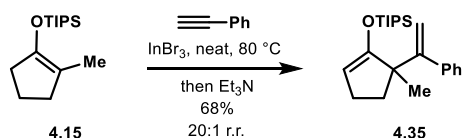


Enoxysilane 4.32. Prepared according to “General procedure for the alkenylation of silyl enol ethers” from enoxysilane **4.15**¹⁷ (ratio of tetra- and trisubstituted isomers $\geq 10:1$) and 5-chloro-1-pentyne. The reaction was performed in solution on a 0.50 mmol scale with 0.1 equiv of InBr_3 . The reaction mixture was heated to 50°C for 26 h. The alkenylation proceeded

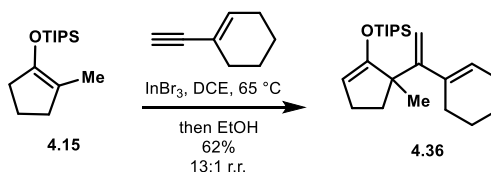
in 50% yield (0.25 mmol, 0.089 g of enoxysilane **4.32** obtained, 14:1 r.r.). R_f = 0.65 (hexanes); ^1H NMR (500 MHz, CDCl_3) δ 4.95 (d, 1H, J = 0.79 Hz, 1H), 4.78 (d, J = 0.97 Hz, 1H), 4.55 (t, J = 2.4 Hz, 1H), 3.55 (t, J = 6.6 Hz, 2H), 2.23-2.14 (m, 4H), 1.99-1.92 (m, 3H), 1.63 (ddd, J = 13.0, 8.0, 6.2, 2H), 1.24 (s, 3H), 1.23-1.15 (m, 3H), 1.11-1.03 (m, 18H); ^{13}C NMR (125 MHz, CDCl_3) δ 158.7, 152.5, 108.0, 99.7, 52.9, 45.2, 36.2, 31.7, 28.9, 25.9, 23.9, 18.11, 18.09, 12.6; HRMS (CI) calculated for $\text{C}_{20}\text{H}_{37}\text{ClOSi}$ $[\text{M}]^+$: 356.2302, found: 356.2309.



Enoxysilane 4.34. Prepared according to “General procedure for the alkenylation of silyl enol ethers” from enoxysilane **4.15**¹⁷ (ratio of tetra- and trisubstituted isomers $\geq 10:1$) and ethyl hex-5-ynoate.¹⁹ The reaction was performed in solution on a 0.25 mmol scale with 0.1 equiv of InBr_3 . The reaction mixture was heated to 80°C for 23 h. The alkenylation proceeded in 56% yield (0.14 mmol, 0.047 g of enoxysilane **4.34** obtained, 9:1 r.r.). R_f = 0.5 (5% EtOAc in hexanes); ^1H NMR (500 MHz, CDCl_3) δ 5.01 (d, J = 1.0 Hz, 1H), 4.86 (d, J = 1.0 Hz, 1H), 4.60 (t, J = 2.3 Hz, 1H), 4.18 (q, J = 7.1 Hz, 2H), 2.28-2.20 (m, 2H), 2.16-2.07 (m, 2H), 1.99 (ddd, J = 13.5, 7.5, 5.9 Hz, 1H), 1.91-1.85 (m, 2H), 1.68 (ddd, J = 13.0, 8.3, 5.9 Hz, 1H), 1.31 (t, J = 7.0 Hz, 3H), 1.30 (s, 3H), 1.28-1.20 (m, 3H), 1.13-1.11 (m, 18H); ^{13}C NMR (125 MHz, CDCl_3) δ 173.8, 158.9, 152.9, 107.8, 99.5, 60.2, 52.9, 36.2, 34.4, 31.0, 25.9, 24.0, 23.8, 18.10, 18.08, 14.3, 12.6; HRMS (ESI) calculated for $\text{C}_{23}\text{H}_{42}\text{O}_3\text{SiNa}$ $[\text{M}+\text{Na}]^+$: 417.2801, found: 417.2794.

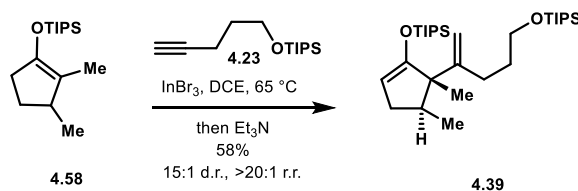


Enoxysilane 4.35. Prepared according to “General procedure for the alkenylation of silyl enol ethers” from silyl enol ether **4.15**¹⁷ (ratio of tetra- and trisubstituted isomers $\geq 10:1$) and phenylacetylene. The reaction was performed in the absence of solvent on a 0.50 mmol scale with 0.05 equiv of InBr_3 . The reaction mixture was heated to 80 °C for 26 h. The alkenylation proceeded in 73% yield (0.36 mmol, 0.13 g of enoxysilane **4.35** obtained, 20:1 r.r.). TLC: R_f = 0.75 (hexanes); ^1H NMR (500 MHz, CDCl_3) δ 7.29-7.22 (m, 5H), 5.22 (d, J = 1.7 Hz, 1H), 4.99 (d, J = 1.7 Hz, 1H), 4.57 (t, J = 2.3 Hz, 1H), 2.17-2.06 (m, 2H), 2.02-1.96 (m, 1H), 1.72-1.67 (m, 1H), 1.29 (s, 3H), 1.26-1.19 (m, 3H), 1.11-1.09 (m, 18H); ^{13}C NMR (125 MHz, CDCl_3) δ 158.4, 154.9, 143.5, 128.7, 127.5, 126.5, 114.1, 100.5, 52.7, 36.8, 25.8, 24.9, 18.27, 18.25, 12.7; HRMS (CI) calculated for $\text{C}_{23}\text{H}_{36}\text{OSi}$ $[\text{M}]^+$: 356.2535, found: 356.2522.

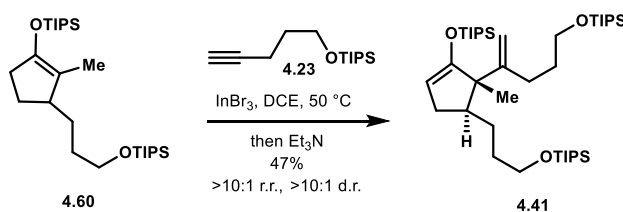


Enoxysilane 4.36. Prepared according to “General procedure for the alkenylation of silyl enol ethers” from silyl enol ether **4.15**¹⁷ (ratio of tetra- and trisubstituted isomers $\geq 10:1$) and 1-ethynylcyclohexene. The reaction was performed in solution (5 M in the silyl enol ether) on a 0.50 mmol scale with 0.05 equiv of InBr_3 . The reaction mixture was heated to 80 °C for 26 h. The alkenylation proceeded in 51% yield (0.26 mmol, 0.078 g of enoxysilane **4.36** obtained, 13:1 r.r.). R_f = 0.9 (hexanes); ^1H NMR (500 MHz, CDCl_3) δ 5.57-5.55 (m, 1H), 4.88 (d, J = 2.1 Hz, 1H), 4.83 (d, J = 2.1 Hz, 1H), 4.51 (t, J = 2.3 Hz, 1H), 2.22-2.15 (m, 3H), 2.14-2.08 (m, 1H), 2.06-2.00 (m, 3H), 1.68-1.58 (m, 3H), 1.57-1.52 (m, 2H), 1.23-1.15 (m, 6H), 1.10-1.04 (m, 18H); ^{13}C NMR (125 MHz, CDCl_3) δ 159.5, 156.9, 139.9, 123.9, 110.5, 99.3, 52.1, 37.3,

29.9, 25.8, 25.6, 25.0, 23.3, 22.3, 18.3, 18.2, 12.7; HRMS (CI) calculated for $C_{23}H_{40}OSi$ $[M]^+$: 360.2849, found: 360.2851.

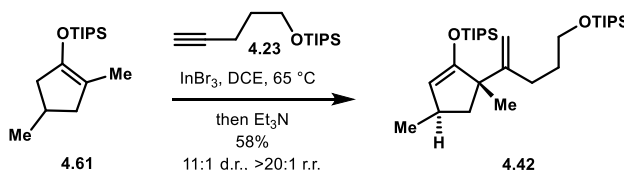


Enoxysilane 4.39. Prepared according to “General procedure for the alkenylation of silyl enol ethers” from silyl enol ether **4.58** (ratio of tetra- and trisubstituted isomers >10:1) and alkyne **4.23**. The reaction was performed in solution on a 0.50 mmol scale with 0.1 equiv of $InBr_3$. The reaction mixture was heated to 65 °C for 23 h. The isolated product was further purified by heating to 50 °C under vacuum (ca. 0.1 torr) to remove the remaining alkyne. The alkenylation proceeded in 58% yield (0.29 mmol, 0.15 g of enoxysilane **4.39** obtained, 15:1 d.r., >20:1 r.r.). R_f = 0.57 (hexanes); 1H NMR (500 MHz, $CDCl_3$) δ 4.88-4.87 (m, 2H), 4.49 (t, J = 2.2 Hz, 1H), 3.72-3.64 (m, 2H), 2.29 (ddd, J = 13.7, 7.9, 2.6 Hz, 1H), 2.27-2.20 (m, 1H), 2.18-2.11 (m, 1H), 2.07-2.00 (m, 1H), 1.81 (ddd, J = 13.8, 8.3, 1.7 Hz, 1H), 1.75-1.70 (m, 2H), 1.20-1.14 (m, 3H), 1.10-1.04 (m, 42H), 0.85 (d, J = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.9, 153.1, 108.5, 98.8, 63.6, 55.4, 38.6, 34.6, 23.5, 27.7, 18.08, 18.06, 16.5, 14.4, 12.6, 12.1; HRMS (CI) calculated for $C_{30}H_{60}O_2Si_2$ $[M]^+$: 508.4132, found: 508.4130.



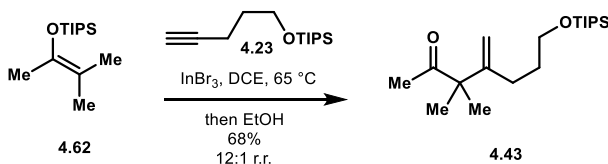
Enoxysilane 4.41. Prepared according to “General procedure for the alkenylation of silyl enol ethers” from enoxysilane **4.60** (ratio of tetra- and trisubstituted isomers >10:1) and

alkyne **4.23**. The reaction was performed in solution on a 0.50 mmol scale with 0.1 equiv of InBr_3 . The reaction mixture was heated to 50 °C for 48 h. The product was isolated by flash chromatography (elution 0.5 to 1% EtOAc in hexanes) and then heated to 50 °C under vacuum (ca. 0.1 torr) to remove remaining alkyne. The alkenylation proceeded in 48% yield (0.24 mmol, 0.17 g of enoxysilane **4.41** obtained). The minor isomer (ratio >10:1) could not be unambiguously assigned as diastereomer or regioisomer. R_f = 0.65 (hexanes); ^1H NMR (500 MHz, CDCl_3) δ 4.88 (s, 2H), 4.49 (t, J = 2.1 Hz, 1H), 3.73-3.61 (m, 4H), 2.32 (ddd, J = 14.1, 7.9, 2.8 Hz, 1H), 2.18-1.97 (m, 3H), 1.82 (ddd, J = 14.2, 9.1, 1.7 Hz, 1H), 1.75-1.68 (m, 2H), 1.55-1.51 (m, 1H), 1.49-1.32 (m, 2H), 1.26-1.15 (m, 4H), 1.11-0.96 (m, 63H); ^{13}C NMR (125 MHz, CDCl_3) δ 160.1, 153.2, 108.9, 98.6, 64.0, 63.9, 55.5, 43.9, 32.9, 32.7, 31.7, 28.0, 26.2, 18.2, 16.8, 12.7, 12.2; HRMS (ESI) calculated for $\text{C}_{41}\text{H}_{84}\text{O}_3\text{Si}_3\text{Na}$ $[\text{M}+\text{Na}]^+$: 731.5626, found: 731.5621.

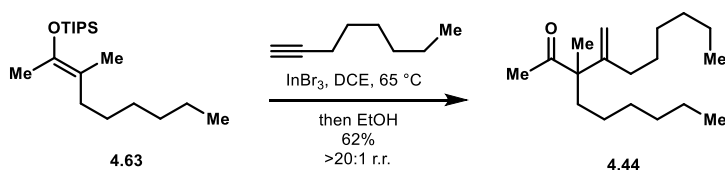


Enoxysilane 4.42. Prepared according to “General procedure for the alkenylation of silyl enol ethers” from enoxysilane **4.61** (ratio of tetra- and trisubstituted isomers >10:1) and alkyne **4.23**. The reaction was performed in solution on a 0.50 mmol scale with 0.1 equiv of InBr_3 . The reaction mixture was heated to 65 °C for 23 h. The alkenylation proceeded in 58% yield (0.29 mmol, 0.15 g of enoxysilane **4.42** obtained, 11:1 d.r., >20:1 r.r.). R_f = 0.65 (hexanes), ^1H NMR (500 MHz, CDCl_3) δ 4.96 (d, J = 1.0 Hz, 1H), 4.82 (d, J = 1.3 Hz, 1H), 4.55 (d, J = 1.9 Hz, 1H), 3.81-3.71 (m, 2H), 2.70-2.62 (m, 1H), 2.22 (dd, J = 13.0, 7.9, 1H), 2.19-2.08 (m, 2H), 1.85-1.74 (m, 2H), 1.31 (s, 3H), 1.27-1.20 (m, 4H), 1.18-1.10 (m, 39H), 1.05 (d, J =

6.8 Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 158.0, 153.6, 106.9, 106.5, 63.6, 53.8, 45.6, 33.6, 32.2, 27.8, 25.7, 23.2, 18.12, 18.09, 12.6, 12.0; HRMS (CI) calculated for $\text{C}_{30}\text{H}_{60}\text{O}_2\text{Si}_2$ $[\text{M}]^+$: 508.4132, found: 508.4178.

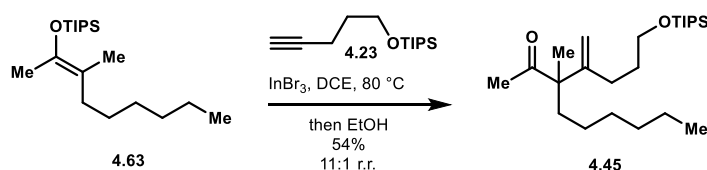


Ketone 4.43. Prepared according to “General procedure for the alkenylation of silyl enol ethers” from enoxysilane **4.62** (ratio of tetra- and disubstituted isomers 7:1) and alkyne **4.23**. The reaction was performed in solution on a 0.5 mmol scale with 0.1 equiv of InBr_3 . The reaction mixture was heated to 65°C for 23 h. The product was isolated by flash chromatography (elution hexanes to 1% EtOAc in hexanes). The alkenylation proceeded in 68% yield (0.34 mmol, 0.11 g of ketone **4.43** obtained, 12:1 r.r.). R_f = 0.3 (5% EtOAc in hexanes); ^1H NMR (500 MHz, C_6D_6) δ 4.94 (d, J = 0.56 Hz, 1H), 4.91 (t, J = 1.2 Hz, 1H), 3.56 (t, J = 6.2 Hz, 2H), 2.02-1.98 (m, 2H), 1.82 (s, 3H), 1.68-1.63 (m, 2H), 1.13 (s, 6H), 1.12-1.08 (m, 18H), 1.07-1.02 (m, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 209.2, 152.5, 109.6, 63.2, 54.5, 32.4, 28.8, 24.4, 23.6, 18.3, 12.4; HRMS (ESI) calculated for $\text{C}_{19}\text{H}_{38}\text{O}_2\text{SiNa}$ $[\text{M}+\text{Na}]^+$: 349.2539, found: 349.2526.

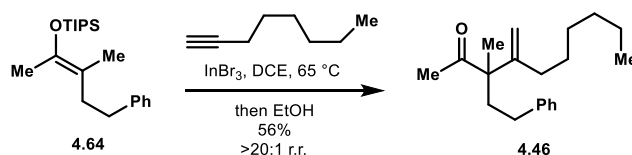


Ketone 4.44. Prepared according to “General procedure for the alkenylation of silyl enol ethers” from enoxysilane **4.63** (ratio of tetra- and disubstituted isomers 9:1) and 1-octyne. The reaction was performed in solution on a 0.25 mmol scale with 0.1 equiv of InBr_3 . The

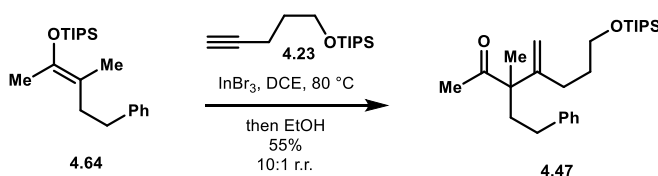
reaction mixture was heated to 65 °C for 68 h. The product was isolated by flash chromatography (elution with 20-40% DCM in hexanes). The alkenylation proceeded in 62% yield (0.16 mmol, 42 mg of ketone **4.44** obtained, >20:1 r.r.). R_f = 0.45 (30% CH₂Cl₂ in hexanes); ¹H NMR (500 MHz, CDCl₃) δ 5.04 (s, 1H), 5.03 (s, 1H), 2.01 (s, 3H), 1.85-1.73 (m, 2H), 1.70-1.60 (m, 2H), 1.46-1.39 (m, 2H), 1.33-1.21 (m, 12H), 1.18 (s, 3H), 1.11-0.99 (m, 2H), 0.91-0.82 (m, 6H); ¹³C NMR (125 MHz, CDCl₃) δ 212.4, 151.3, 110.8, 58.2, 34.9, 32.5, 32.04, 32.01, 30.3, 29.5, 28.5, 25.3, 24.3, 22.91, 22.98, 20.3, 14.3; HRMS (ESI) calculated for C₁₈H₃₄ONa [M+Na]⁺: 289.2507, found: 289.2498.



Ketone 4.45. Prepared according to “General procedure for the alkenylation of silyl enol ethers” from enoxysilane **4.63** (ratio of tetra- and disubstituted isomers 9:1) and alkyne **4.23**. The reaction was performed in solution on a 0.25 mmol scale with 0.1 equiv of InBr₃. The reaction mixture was heated to 80 °C for 48 h. The product was isolated by flash chromatography (elution with 20-50% DCM in hexanes), then heated to 50 °C under vacuum (ca. 0.1 torr) to remove remaining hydrolyzed starting material. The alkenylation proceeded in 54% yield (0.14 mmol, 53 mg of ketone **4.45** obtained, 11:1 r.r.). R_f = 0.3 (30% CH₂Cl₂ in hexanes); ¹H NMR (500 MHz, CDCl₃) δ 5.05 (s, 2H), 3.68 (t, J = 6.3 Hz, 2H), 2.01 (s, 3H), 1.98-1.84 (m, 2H), 1.74-1.62 (m, 4H), 1.31-1.22 (m, 6H), 1.19 (s, 3H), 1.13-0.98 (m, 21H), 0.87 (t, J = 6.8 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 212.1, 150.8, 110.7, 63.1, 58.1, 34.8, 31.9, 31.8, 30.1, 28.6, 25.2, 24.2, 22.8, 20.3, 18.2, 14.2, 12.1; HRMS (ESI) calculated for C₂₄H₄₈O₂SiNa [M+Na]⁺: 419.3321, found: 419.3313.

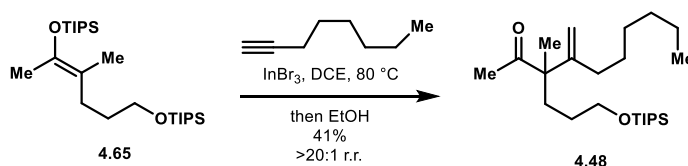


Ketone 4.46. Prepared according to “General procedure for the alkenylation of silyl enol ethers” from enoxysilane **4.64** (ratio of tetra- and disubstituted isomers 7:1) and 1-octyne. The reaction was performed in solution on a 0.25 mmol scale with 0.1 equiv of InBr_3 . The reaction mixture was heated to 65 °C for 68 h. The product was isolated by flash chromatography (elution with 20-50% DCM in hexanes). The alkenylation proceeded in 56% yield (0.14 mmol, 40 mg of ketone **4.46** obtained, >20:1 r.r.). $R_f = 0.25$ (30% CH_2Cl_2 in hexanes); ^1H NMR (600 MHz, CDCl_3) δ 7.29-7.26 (m, 2H), 7.20-7.16 (m, 3H), 5.11 (m, 2H), 2.45-2.35 (m, 2H), 2.07 (s, 3H), 2.02-1.93 (m, 2H), 1.93-1.87 (m, 1H), 1.84-1.79 (m, 1H), 1.50-1.45 (m, 2H), 1.33-1.26 (m, 9H), 0.88 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 211.7, 150.6, 142.6, 128.5, 128.4, 126.0, 111.2, 58.0, 36.8, 32.4, 31.9, 30.8, 29.4, 28.4, 25.2, 22.8, 20.2, 14.2; HRMS (ESI) calculated for $\text{C}_{20}\text{H}_{30}\text{ONa}$ $[\text{M}+\text{Na}]^+$: 309.2194, found: 309.2180.



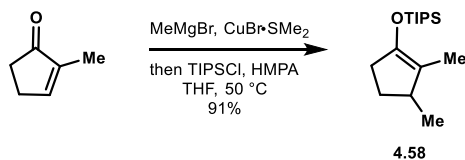
Ketone 4.47. Prepared according to “General procedure for the alkenylation of silyl enol ethers” from enoxysilane **4.64** (ratio of tetra- and disubstituted isomers 7:1) and alkyne **4.23**. The reaction was performed in solution on a 0.25 mmol scale with 0.1 equiv of InBr_3 . The reaction mixture was heated to 80 °C for 48 h. The product was isolated by flash chromatography (elution with 20-40% DCM in hexanes), then heated to 50 °C under vacuum (ca. 0.1 torr) to remove remaining hydrolyzed starting material. The alkenylation proceeded

in 55% yield (0.14 mmol, 57 mg of ketone **4.47** obtained, 10:1 r.r.). $R_f = 0.2$ (30% CH_2Cl_2 in hexanes); ^1H NMR (500 MHz, CDCl_3) δ 7.29-7.26 (m, 2H), 7.19-7.16 (m, 3H), 5.13 (s, 2H), 3.70 (t, $J = 6.3$ Hz, 2H), 2.46-2.35 (m, 2H), 2.07 (s, 3H), 2.04-1.89 (m, 4H), 1.78-1.69 (m, 2H), 1.32 (s, 3H), 1.12-1.01 (m, 21H); ^{13}C NMR (125 MHz, CDCl_3) δ 211.5, 150.3, 142.6, 128.5, 128.4, 125.9, 111.3, 63.1, 58.0, 36.9, 31.8, 30.8, 28.6, 25.2, 20.2, 18.2, 12.1; HRMS (ESI) calculated for $\text{C}_{26}\text{H}_{44}\text{O}_2\text{SiNa}$ $[\text{M}+\text{Na}]^+$: 439.3008, found: 439.2998.

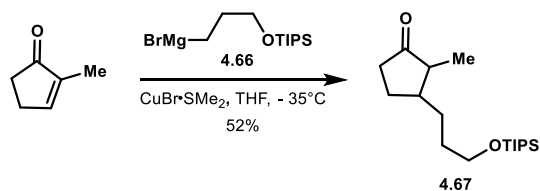


Ketone 4.48. Prepared according to “General procedure for the alkenylation of silyl enol ethers” from enoxysilane **4.65** (ratio of tetra- and disubstituted isomers 9:1) and 1-octyne. The reaction was performed in solution on a 0.25 mmol scale with 0.1 equiv of InBr_3 . The reaction mixture was heated to 80 °C for 72 h. The product was isolated by flash chromatography (elution with 20-40% DCM in hexanes). The alkenylation proceeded in 41% yield (0.10 mmol, 41 mg of ketone **4.48** obtained, >20:1 r.r.). $R_f = 0.3$ (30% CH_2Cl_2 in hexanes); ^1H NMR (500 MHz, CDCl_3) δ 5.07 (s, 1H), 5.05 (s, 1H), 3.67 (t, $J = 6.4$ Hz, 2H), 2.03 (s, 3H), 1.87-1.69 (m, 4H), 1.46-1.41 (m, 2H), 1.40-1.34 (m, 1H), 1.33-1.22 (m, 7H), 1.19 (s, 3H), 1.12-1.01 (m, 21H), 0.88 (t, $J = 6.9$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 212.2, 151.0, 110.8, 63.8, 57.7, 32.4, 31.9, 31.0, 29.4, 28.4, 27.9, 25.2, 22.8, 20.2, 18.2, 14.2, 12.1; HRMS (ESI) calculated for $\text{C}_{24}\text{H}_{48}\text{O}_2\text{SiNa}$ $[\text{M}+\text{Na}]^+$: 419.3321, found: 419.3306.

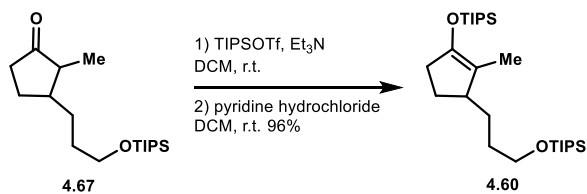
4.4.4 Preparation of Starting Materials



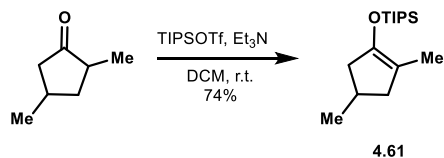
Enoxysilane 4.58. A solution of methylmagnesium bromide (1.74 mL of a 2.98 M solution in diethyl ether, 5.2 mmol) was added to a suspension of CuBr·SMe₂ (82 mg, 0.40 mmol) in THF (4 mL) at $-35\text{ }^{\circ}\text{C}$ over the course of 5 min. The resulting solution was stirred for 20 min and cooled to $-45\text{ }^{\circ}\text{C}$. 2-Methyl-2-cyclopenten-1-one (0.39 mL, 4.0 mmol) was added to the reaction mixture over the course of 30 min. The resulting solution was stirred for 40 min at $-45\text{ }^{\circ}\text{C}$ and treated with TIPSCl (1.96 mL, 9.2 mmol). The reaction mixture was warmed up to room temperature and treated with HMPA (3.2 mL, 18.4 mmol). The resulting suspension was heated to $50\text{ }^{\circ}\text{C}$ for 17 h and quenched with a 3:1 (v/v) mixture of saturated aqueous NH₄Cl and 28% (v/v) aqueous NH₃. The resulting solution was diluted with hexanes. The layers were separated, and the organic layer was washed with water, then brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. Purification by flash chromatography on Et₃N-treated silica gel (elution with 1% Et₃N in hexanes) afforded 0.98 g (91% yield) of enoxysilane **4.58** as a colorless oil. $R_f = 0.85$ (hexanes); ¹H NMR (500 MHz, CDCl₃) δ 2.47-2.43 (m, 1H), 2.32-2.26 (m, 2H), 2.05-1.99 (m, 1H), 1.53 (s, 3H), 1.34-1.27 (m, 1H), 1.15-1.08 (m, 3H), 1.08 (d, $J = 6.0\text{ Hz}$, 18H), 0.97 (d, $J = 6.8\text{ Hz}$, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 146.7, 117.0, 39.4, 32.9, 29.5, 20.2, 18.1, 13.0, 10.2; HRMS (CI) calculated for C₁₆H₃₂OSi [M]⁺: 268.2222, found: 268.2234.



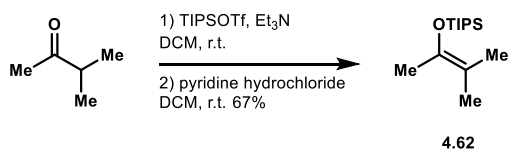
Ketone 4.67. A solution of Grignard **4.66** (23.6 mL of a 0.22 M solution in THF, 5.2 mmol, prepared from (3-bromopropoxy)triisopropylsilane²⁰) was added to a suspension of $\text{CuBr} \cdot \text{SMe}_2$ (82 mg, 0.40 mmol) in THF (1 mL) at -35°C over the course of 5 min. The resulting solution was stirred for 20 min and cooled to -45°C . 2-Methyl-2-cyclopenten-1-one (0.39 mL, 4.0 mmol) was added to the reaction mixture over the course of 30 min. The resulting solution was stirred for 15 min at -45°C and quenched with degassed saturated aqueous NH_3Cl . The resulting solution was diluted with diethyl ether, the layers were separated, and the organic layer was washed with water, then brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. Purification by flash chromatography on silica gel (gradient elution with 1-6% EtOAc in hexanes) and then heating to 50°C under vacuum (ca. 0.1 torr) to remove TIPS OH afforded 0.65 g (52% yield) of ketone **4.67** as a colorless oil (1.5:1 d.r., contaminated with 5% TIPS OH). $R_f = 0.4$ (5% EtOAc in hexanes); ^1H NMR (500 MHz, C_6D_6) δ 3.59 (t, $J = 6.2$ Hz, 2H), 3.55 (t, $J = 6.2$ Hz, 1.3H), 2.03-1.89 (m, 2.4H), 1.85-1.78 (m, 0.7H), 1.77-1.69 (m, 1.7H), 1.67-1.62 (m, 1H), 1.61-1.48 (m, 2.4H), 1.47-1.40 (m, 1H), 1.39-1.18 (m, 4.8H), 1.15-1.05 (m, 36.7H), 1.03 (dd, $J = 6.6, 0.83$ Hz, 3H), 0.88 (dd, $J = 7.47, 0.82$ Hz, 2H); ^{13}C NMR (125 MHz, C_6D_6) δ 218.7, 217.9, 63.74, 63.99, 50.3, 46.7, 44.6, 39.9, 37.1, 36.0, 31.6, 31.0, 30.8, 27.3, 25.8, 25.7, 18.33, 18.31, 13.0, 12.39, 12.37, 9.9; HRMS (CI) calculated for $\text{C}_{18}\text{H}_{40}\text{NO}_2\text{Si}$ $[\text{M}+\text{NH}_4]^+$: 330.2828, found: 330.2828.



Enoxysilane 4.60. TIPSOTf (0.62 mL, 2.3 mmol) was added to a solution of ketone **4.67** (0.65 g, 2.1 mmol) in DCM (6 mL). Triethylamine (0.52 mL, 3.7 mmol) was added over 2 minutes. The reaction was stirred at room temperature for 17 h, then diluted in hexanes, washed with saturated aqueous NaHCO₃ and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to yield a 1:1 mixture of trisubstituted to disubstituted siloxyalkenes. The crude material was dissolved in DCM (2 mL) and added to a Schlenk flask charged with pyridine hydrochloride (0.012 g, 0.1 mmol) and stirred at room temperature for 1 h. The reaction was quenched with 1 mL Et₃N, diluted with hexanes, washed with saturated aqueous NaHCO₃ and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. Purification through a neutral alumina plug (elution with 1% Et₃N in hexanes) then heating to 50 °C under vacuum (ca. 0.1 torr) to remove TIPSOH afforded 0.94 g (96% yield) of enoxysilane **4.60** as a colorless oil. *R*_f = 0.5 (hexanes); ¹H NMR (500 MHz, C₆D₆) δ 3.68 (t, *J* = 6.7 Hz, 2H), 2.50-2.44 (m, 1H), 2.36-2.24 (m, 2H), 1.99-1.92 (m, 1H), 1.77-1.62 (m, 5H), 1.58-1.50 (m, 1H), 1.49-1.40 (m, 1H), 1.32-1.22 (m, 1H), 1.16-1.08 (m, 42H); ¹³C NMR (125 MHz, C₆D₆) δ 147.4, 115.4, 64.1, 44.8, 33.4, 30.9, 30.7, 26.9, 18.4, 18.2, 13.3, 12.4, 10.7; HRMS (CI) calculated for C₂₇H₅₇O₂Si₂ [M+H]⁺: 469.3897, found: 469.3905.

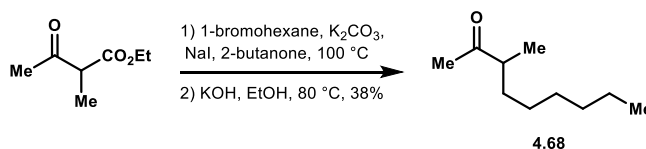


Enoxysilane 4.61. TIPSOTf (1.1 mL, 4 mmol) was added to a solution of 2,4-dimethylcyclopentanone (0.5 mL, 2.0 mmol) in DCM (12 mL). Triethylamine (1.0 mL, 7.2 mmol) was added over 2 minutes. The reaction was stirred at room temperature for 5 h, then diluted in hexanes, washed with saturated aqueous NaHCO₃ and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. Purification by flash chromatography of Et₃N-treated silica gel (elution 1% Et₃N in hexanes) afforded 0.79 g (74% yield) of enoxysilane **4.61** as a colorless oil. R_f = 0.85 (hexanes); ¹H NMR (500 MHz, CDCl₃) δ 2.50 (dd, J = 14.0, 9.0 Hz, 1H), 2.35 (dd, J = 14.6, 8.4 Hz 1H), 2.29-2.21 (m, 1H), 1.98-1.93 (m, 1H), 1.78-1.76 (m, 1H), 1.55 (s, 3H), 1.16-1.05 (m, 21H), 1.03 (d, J = 6.8 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 145.3, 111.4, 42.4, 42.1, 28.3, 22.5, 18.0, 12.9, 12.0; HRMS (CI) calculated for C₁₆H₃₂OSi [M]⁺: 268.2222, found: 268.2223.



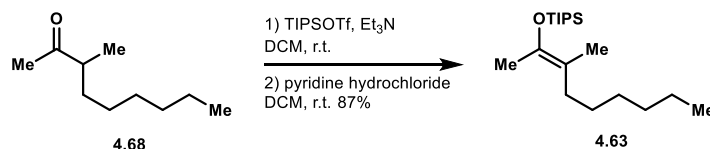
Enoxysilane 4.62. TIPSOTf (3.2 mL, 12 mmol) was added to a solution of 3-methyl-2-butanone (1.3 mL, 12 mmol) in DCM (36 mL). Triethylamine (2.2 mL, 16 mmol) was added over 2 minutes. The reaction was stirred at room temperature for 17 h, then diluted in hexanes, washed with saturated aqueous NaHCO₃ and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to yield exclusively the monosubstituted siloxyalkene. The crude material was dissolved in DCM (10 mL), added to a Schlenk flask charged with pyridine hydrochloride (0.139 g, 1.2 mmol), and stirred at room temperature for 1 h. The reaction was quenched with 1 mL of triethylamine, diluted with hexanes, washed with saturated aqueous NaHCO₃ and brine, dried over anhydrous sodium sulfate, and

concentrated under reduced pressure. Purification through a neutral alumina plug (elution with 1% Et₃N in hexanes) afforded 1.95 g (67% yield, 7:1 mixture of trisubstituted to disubstituted siloxyalkenes) of enoxysilane **4.62** as a colorless oil. R_f = 0.85 (hexanes); ¹H NMR (500 MHz, CDCl₃) δ 1.83 (s, 3H), 1.64 (s, 3H), 1.58 (s, 3H), 1.18-1.05 (m, 21H); ¹³C NMR (125 MHz, CDCl₃) δ 140.7, 108.5, 19.2, 18.6, 18.2, 17.8, 13.4; HRMS (CI) calculated for C₁₄H₃₁OSi [M+H]⁺: 243.2144, found: 243.2143.

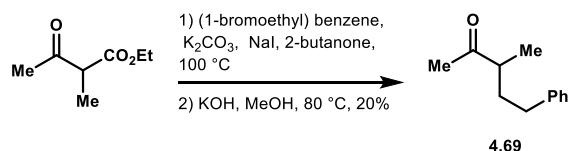


Ketone 4.68. Ethyl 2-methyl acetoacetate (4.2 mL, 30 mmol), 1-bromohexane (1.4 mL, 10 mmol), K₂CO₃ (8.3 g, 60 mmol), sodium iodide (3.0 g, 20 mmol), and 2-butanone (30 mL) were combined in a round bottom flask and the slurry was refluxed for 18 h. The reaction was cooled to room temperature, filtered through Celite, and concentrated to yield an orange oil. The crude material was dissolved in EtOH (30 mL) and potassium hydroxide (3.4 g, 60 mmol) was added. The reaction was refluxed for 1 h, cooled to room temperature, concentrated, dissolved in water, and acidified with 2 N HCl. This mixture was extracted with diethyl ether and the combined organic layers were washed with saturated aqueous NaHCO₃ and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. Purification by flash chromatography (gradient elution 2-3% Et₂O in hexanes) afforded 0.59 g (38% yield) of ketone **4.68** as a clear oil. R_f = 0.5 (10% EtOAc in hexanes); ¹H NMR (500 MHz, CDCl₃) δ 2.53-2.46 (m, 1H), 2.12 (s, 3H), 1.67-1.59 (m, 1H), 1.37-1.18 (m, 9H), 1.07 (d, J = 7.0, 3H), 0.87 (t, J = 7.0 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 213.1, 47.3, 33.0, 31.7, 29.4,

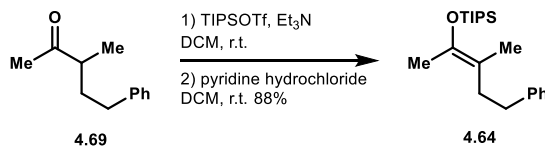
28.0, 27.2, 22.6, 16.2, 14.1; HRMS (CI) calculated for C₁₀H₂₄NO [M+NH₄]⁺: 174.1858, found: 174.1854.



Enoxysilane 4.63. TIPSOTf (1.1 mL, 4.2 mmol) was added to a solution of ketone **4.68** (0.59 g, 3.8 mmol) in DCM (12 mL). Triethylamine (0.95 mL, 6.8 mmol) was added over 2 minutes. The reaction was stirred at room temperature for 15 h, then diluted in hexanes, washed with saturated aqueous NaHCO₃ and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to yield exclusively the monosubstituted silyl enol ether. The crude material was dissolved in DCM (4 mL) and added to a Schlenk flask charged with pyridine hydrochloride (0.023 g, 0.2 mmol) and stirred at room temperature for 1 h. The reaction was quenched with 1 mL Et₃N, diluted with hexanes, washed with saturated aqueous NaHCO₃ and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. Purification through a neutral alumina plug (elution with 1% Et₃N in hexanes) then heating to 50 °C under vacuum (ca. 0.1 torr) to remove TIPSPHOH afforded 0.94 g (87% yield, 2:1 mixture of E and Z isomers, 9:1 trisubstituted to monosubstituted siloxyalkene) of enoxysilane **4.63** as a colorless oil. R_f = 0.9 (hexanes); ¹H NMR (500 MHz, C₆D₆) δ 2.32-2.28 (m, 1H), 2.00-1.97 (m, 2H), 1.84 (s, 3H), 1.82 (s, 3H), 1.80 (m, 1.5H), 1.61 (m, 1.5H), 1.55-1.48 (m, 1.5H), 1.45-1.38 (m, 3H), 1.38-1.24 (m, 7.5H), 1.21-1.08 (m, 31.5H), 0.94-0.88 (m, 4.5H); ¹³C NMR (125 MHz, C₆D₆) δ 141.5, 140.8, 115.8, 112.3, 33.7, 32.5, 32.3, 31.9, 30.1, 29.7, 28.9, 28.4, 23.18, 23.17, 18.8, 18.6, 18.44, 18.40, 17.0, 16.0, 14.4, 13.8, 13.7, 13.2; HRMS (CI) calculated for C₁₉H₄₀OSi [M]⁺: 312.2849, found: 312.2844.

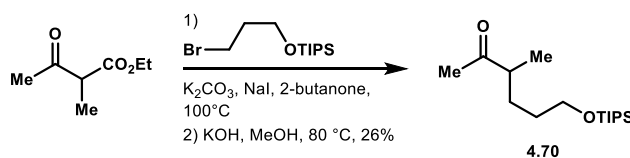


Ketone 4.69. Ethyl 2-methyl acetoacetate (8.5 mL, 60 mmol), (1-bromoethyl)benzene (2.7 mL, 20 mmol), K_2CO_3 (16.6 g, 120 mmol), sodium iodide (3.0 g, 20 mmol), and 2-butanone (60 mL) were combined in a round bottom flask and the slurry was refluxed for 18 h. The reaction was cooled to room temperature, filtered through Celite, and concentrated to yield an orange oil. The crude material was dissolved in MeOH (60 mL) and potassium hydroxide (6.7 g, 120 mmol) was added. The reaction was refluxed for 2 h, cooled to room temperature, concentrated, dissolved in water, and acidified with 2 N HCl. This mixture was extracted with diethyl ether and the combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. Purification by flash chromatography (gradient elution 2-3% Et_2O in hexanes) followed by vacuum distillation afforded 0.70 g (20% yield) of ketone **4.69** as a clear oil. R_f = 0.25 (5% $EtOAc$ in hexanes); 1H NMR (500 MHz, $CDCl_3$) δ 7.30-7.27 (m, 2H), 7.21-7.16 (m, 3H), 2.59 (ddd, J = 9.3, 6.7, 2.7 Hz, 2H), 2.56-2.50 (m, 1H), 2.13 (s, 3H), 2.01 (ddt, J = 13.7, 9.1, 6.9 Hz, 1H), 1.64 (ddt, J = 13.7, 9.0, 6.8 Hz, 1H), 1.14 (d, J = 7.0 Hz, 3H); δ 212.6, 141.8, 128.6, 128.5, 126.1, 46.6, 34.5, 33.5, 28.3, 16.5; HRMS (ESI) calculated for $C_{12}H_{16}ONa$ $[M+Na]^+$: 199.1099, found: 199.1100.



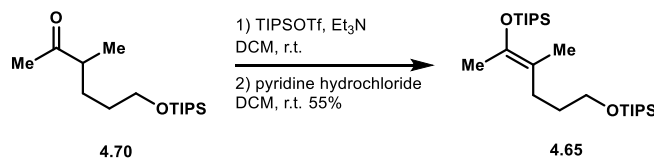
Enoxysilane 4.64. TIPSOTf (1.2 mL, 4.4 mmol) was added to a solution of ketone **4.69** (0.70 g, 4.0 mmol) in DCM (12 mL). Triethylamine (1.0 mL, 7.2 mmol) was added over 2 minutes.

The reaction was stirred at room temperature for 4 h, then diluted in hexanes, washed with saturated aqueous NaHCO_3 and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to yield exclusively the monosubstituted siloxyalkene. The crude material was dissolved in DCM (4 mL) and added to a Schlenk flask charged with pyridine hydrochloride (23 mg, 0.2 mmol) and stirred at room temperature for 1 h. The reaction was quenched with 1 mL Et_3N , diluted with hexanes, washed with saturated aqueous NaHCO_3 and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. Purification through a neutral alumina plug (elution with 1% Et_3N in hexanes) then heating to 50 °C under vacuum (ca. 0.1 torr) to remove TIPSPHOH afforded 1.17 g (88% yield, 1:1.7 mixture of E and Z isomers, 7:1 trisubstituted to monosubstituted siloxyalkene) of enoxysilane **4.64** as a colorless oil. $R_f = 0.65$ (hexanes); ^1H NMR (500 MHz, C_6D_6) δ 7.27-7.25 (m, 1.2H), 7.23-7.17 (m, 3.6H), 7.10-7.07 (m, 3.2H), 2.76 (dd, $J = 9.8, 6.6$ Hz, 1.2H), 2.63-2.55 (m, 3.2H), 2.23 (dd, $J = 8.3, 6.4$ Hz, 2H), 1.79 (s, 3H), 1.77 (s, 1.8H), 1.68 (s, 3H), 1.56 (s, 1.8H), 1.13-1.08 (m, 30.6H), 1.05-0.95 (m, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 143.3, 142.7, 142.3, 141.4, 128.9, 128.8, 128.62, 128.59, 126.04, 125.99, 111.7, 111.6, 36.0, 35.2, 34.8, 34.1, 19.5, 18.8, 18.43, 18.38, 17.1, 16.0, 13.74, 13.66; HRMS (CI) calculated for $\text{C}_{21}\text{H}_{37}\text{OSi}$ $[\text{M}+\text{H}]^+$: 333.2614, found: 333.2610.



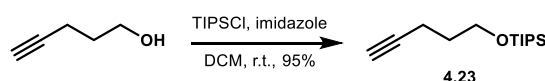
Ketone 4.70. Ethyl 2-methyl acetoacetate (3.9 mL, 27.3 mmol), (3-bromopropoxy)triisopropylsilane⁵ (2.7 g, 9.1 mmol), K_2CO_3 (7.6 g, 54.6 mmol), sodium iodide (2.7 g, 18.2 mmol), and 2-butanone (27 mL) were combined in a round bottom flask

and the slurry was refluxed for 24 h. The reaction was cooled to room temperature, filtered through Celite, and concentrated to yield an orange oil. The crude material was dissolved in MeOH (27 mL) and potassium hydroxide (3.1 g, 54.6 mmol) was added. The reaction was refluxed for 2 h, cooled to room temperature, concentrated, dissolved in water, and acidified with 2 N HCl. This mixture was extracted with diethyl ether and the combined organic layers were washed with saturated aqueous NaHCO₃ and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. Purification by flash chromatography (gradient elution 1-5% Et₂O in hexanes) afforded 0.71 g (26% yield) of ketone **4.70** as a clear oil. R_f = 0.3 (5% EtOAc in hexanes); ¹H NMR (500 MHz, CDCl₃) δ 3.67 (t, J = 6.2 Hz, 2H), 2.57-2.50 (m, 1H), 2.13 (s, 3H), 1.76-1.70 (m, 1H), 1.55-1.40 (m, 3H), 1.09 (d, J = 7.0 Hz, 3H), 1.08-1.03 (m, 21H); ¹³C NMR (125 MHz, CDCl₃) δ 213.0, 63.2, 47.1, 30.6, 29.3, 28.0, 18.2, 16.3, 12.1; HRMS (ESI) calculated for C₁₆H₃₄O₂SiNa [M+Na]⁺: 309.2226, found: 309.2216.



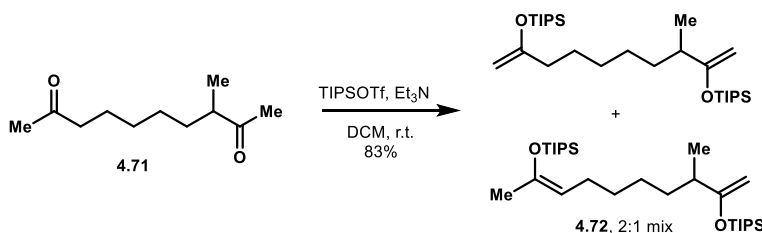
Enoxysilane 4.65. TIPSOTf (0.71 mL, 2.6 mmol) was added to a solution of ketone **4.70** (0.71 g, 2.4 mmol) in DCM (7 mL). Triethylamine (0.6 mL, 4.3 mmol) was added over 2 minutes. The reaction was stirred at room temperature for 3 h, then diluted in hexanes, washed with saturated aqueous NaHCO₃ and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to yield exclusively the monosubstituted silyl enol ether. The crude material was dissolved in DCM (2.5 mL) and added to a Schlenk flask charged with pyridine hydrochloride (0.028 g, 0.24 mmol) and stirred at room temperature for 16 h. The reaction was quenched with 1 mL Et₃N, diluted with hexanes, washed with

saturated aqueous NaHCO_3 and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. Purification on Et_3N -treated silica (elution with 1% Et_3N in hexanes) afforded 1.17 g (55% yield, 1:2 mixture of E and Z isomers, 8:1 trisubstituted to disubstituted siloxyalkene) of enoxysilane **4.65** as a colorless oil. $R_f = 0.55$ (hexanes); ^1H NMR (500 MHz, C_6D_6) δ 3.80 (t, $J = 6.86$ Hz, 1H), 3.64 (t, $J = 6.18$ Hz, 2H), 2.37-2.34 (m, 1H), 2.16-2.13 (m, 2H), 1.90 (s, 3H), 1.87-1.83 (m, 1H), 1.82 (s, 3H), 1.77 (s, 1.5H), 1.71-1.63 (m, 2H), 1.61 (s, 1.5H), 1.20-1.07 (m, 63H); ^{13}C NMR (125 MHz, C_6D_6) δ 141.8, 141.0, 112.2, 111.8, 64.4, 63.3, 32.3, 31.9, 30.0, 28.3, 18.8, 18.6, 18.44, 18.40, 18.38, 18.35, 17.0, 16.0, 13.8, 13.7, 12.5, 12.4; HRMS (CI) calculated for $\text{C}_{25}\text{H}_{55}\text{O}_2\text{Si}_2$ $[\text{M}+\text{H}]^+$: 443.3741, found: 443.3749.

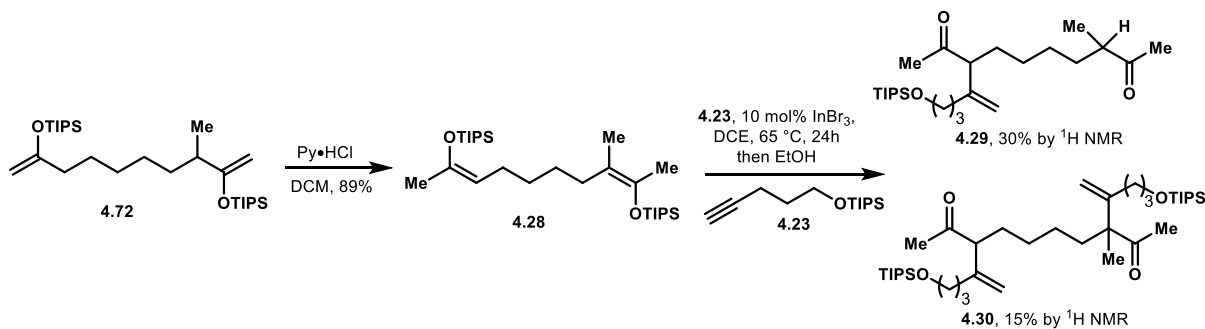


Alkyne 4.23. TIPSCl (4.5 mL, 15 mmol), 4-pentyn-1-ol (1.4 mL, 15 mmol), and imidazole (2.0 g, 30 mmol) were dissolved in DCM and stirred at room temperature for 2 h. The reaction was diluted in hexanes, washed with saturated aqueous NaHCO_3 and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. Purification by flash chromatography (elution with hexanes) afforded 3.4 g (95% yield) of alkyne **4.23** as a colorless oil. ^1H and ^{13}C NMR data match that provided in the literature.²¹

4.4.5 Alkenylation of a Diketone



Synthesis of enoxysilane 4.72. TIPSOTf (0.44 mL, 1.65 mmol) was added to a solution of diketone **4.71** (0.138 g, 0.75 mmol, synthesized by Sergey Pronin) in DCM (2.25 mL). Triethylamine (0.38 mL, 2.70 mmol) was added over 2 minutes. The reaction was stirred at room temperature for 2 h, then quenched with saturated aqueous NaHCO₃, diluted in hexanes, and washed with brine. Drying over anhydrous sodium sulfate and concentration under reduced pressure followed by purification on Et₃N- deactivated silica (elution 2% Et₃N in hexanes) afforded 0.306g (83% yield) of enoxysilane **4.72** as a 2:1 mixture of enoxysilanes favoring the least substituted product. ¹H NMR (500 MHz; C₆H₆) δ 4.46 (t, J = 7.0 Hz, 0.5H), 4.17 (s, 1H), 4.13 (s, 1H), 4.08 (s, 1.5H), 4.05 (s, 1.5H), 2.32-2.27 (m, 1H), 2.18-2.14 (m, 3.5H), 1.79-1.77 (m, 1.5H), 1.69-1.63 (m, 4H), 1.53-1.30 (m, 10H), 1.22-1.08 (m, 69H); ¹³C NMR (126 MHz; CDCl₃) δ 163.3, 163.2, 160.1, 146.9, 108.5, 89.2, 87.6, 41.31, 41.27, 37.2, 34.9, 34.8, 30.7, 29.8, 28.0, 27.9, 27.5, 26.1, 23.2, 19.5, 18.41, 18.35, 18.04, 17.99, 13.6, 13.2, 13.1.



Synthesis of Diketones 4.29 and 4.30. Enoxysilane **4.28** was dissolved in DCM (1.3 mL) and added to a Schlenk flask charged with pyridine hydrochloride (7 mg, 0.062 mmol) and stirred at room temperature for 2 h. The reaction was quenched with saturated aqueous NaHCO₃, diluted with hexanes, washed with saturated aqueous NaHCO₃ and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to afford 0.274 g (89% yield) of enoxysilane **4.28**. This mixture was alkenylated according to “General procedure

for the alkenylation of silyl enol ethers” with alkyne **4.23**. The reaction was performed in solution on a 0.25 mmol scale with 0.1 equiv of InBr₃. The reaction mixture was heated to 65 °C for 24 h. The reaction was quenched with 1 mL EtOH and 0.1 mL of aqueous HCl (1 M) and the resulting solution was stirred for 30 min. The alkenylation afforded two major products by NMR. Ketone **4.29** was made in 30% yield based on integration with mesitylene as an internal standard. Ketone **4.30** was made in 15% yield based on the same integration. Purification by flash chromatography (gradient elution 5 to 7% EtOAc in hexanes) afforded ketone **4.29** (34 mg, 0.080 mmol, 32% yield) and ketone **4.30** (56 mg) contaminated with large amounts of TIPSOH. Characterization of **4.29**: R_f = 0.4 (15% EtOAc in hexanes); ¹H-NMR (499 MHz; CDCl₃): δ 4.97 (s, 1H), 4.92 (s, 1H), 3.69 (t, J = 6.3 Hz, 2H), 3.05 (t, J = 7.3 Hz, 1H), 2.49-2.45 (m, 1H), 2.12 (d, J = 1.8 Hz, 3H), 2.10 (s, 3H), 2.02-1.96 (m, 1H), 1.80-1.73 (m, 1H), 1.71-1.65 (m, 3H), 1.63-1.60 (m, 1H), 1.52-1.45 (m, 1H), 1.31-1.21 (m, 5H), 1.09-1.03 (m, 24H); ¹³C NMR (126 MHz; CDCl₃) δ 213.0, 209.0, 147.0, 112.7, 62.9, 60.8, 47.2, 32.8, 31.2, 30.8, 29.5, 28.4, 27.8, 27.4, 18.2, 12.1. Characterization of **4.30**: R_f = 0.65 (15% EtOAc in hexanes); ¹H NMR (500 MHz; CDCl₃): δ 5.05 (s, 1H), 5.04 (s, 1H), 4.97 (s, 1H), 4.92 (s, 1H), 3.70-3.66 (m, 5H), 3.04 (t, J = 7.3 Hz, 1H), 2.09 (s, 3H), 2.01 (s, 3H), 1.92-1.85 (m, 2H), 1.71-1.63 (m, 4H), 1.51-1.48 (m, 1H), 1.45-1.40 (m, 2H), 1.18 (s, 3H), 1.09-1.03 (m, 48H + TIPSOH).

4.5 References and Notes

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¹⁵ Synthesized by Stephen Holmbo.

¹⁶ Stephen Holmbo synthesized compounds **4.27**, **4.31**, **4.33**, **4.37**, **4.38**, **4.40**, **4.50**, and **4.51**.

¹⁷ Holmbo, S. H.; Godfrey, N. A.; Hirner, J. J.; Pronin, S. V. *J. Am. Chem. Soc.* **2016**, *138*, 12316–12319.

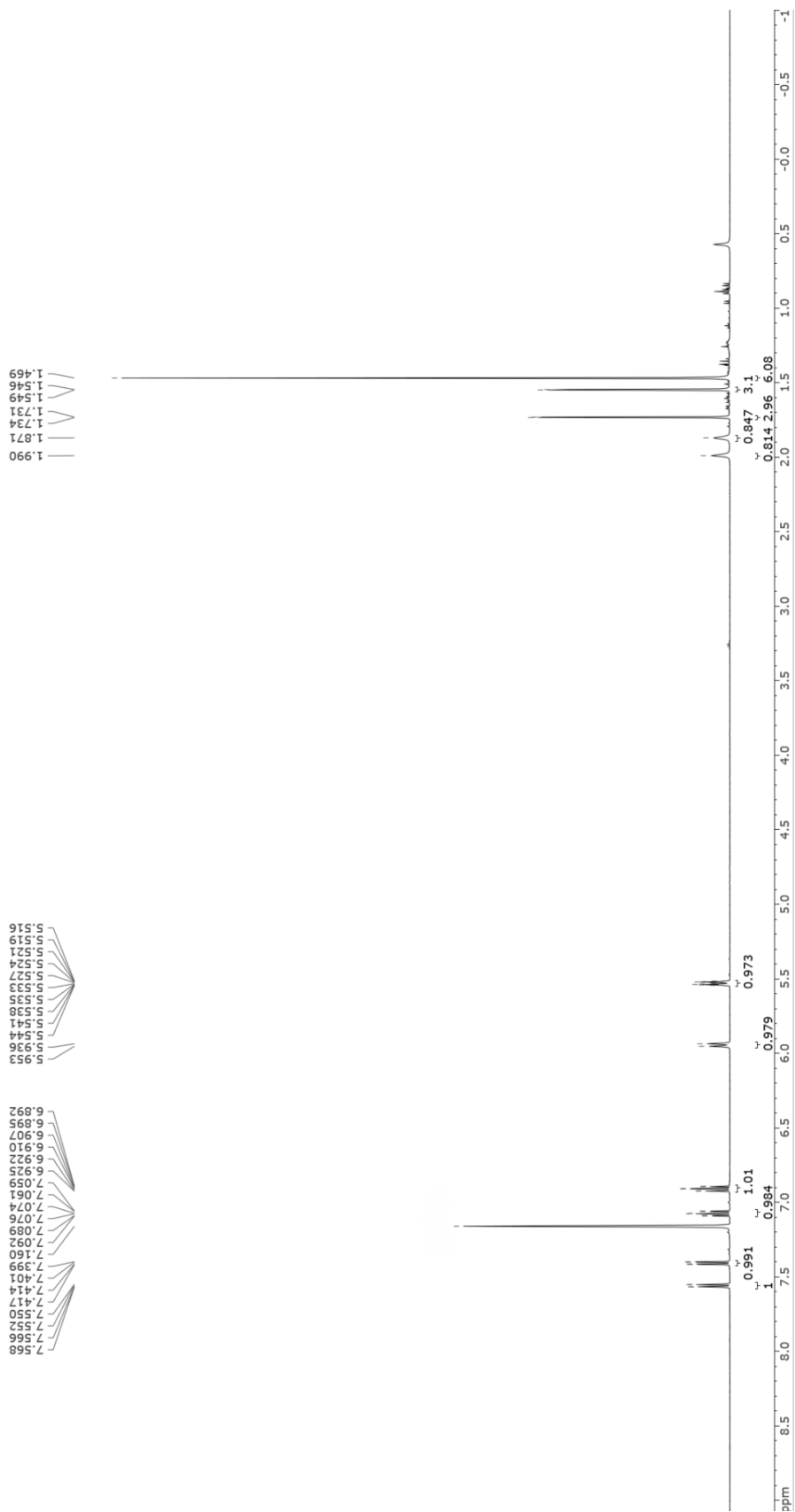
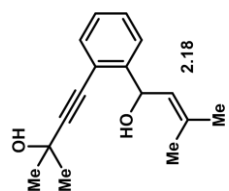
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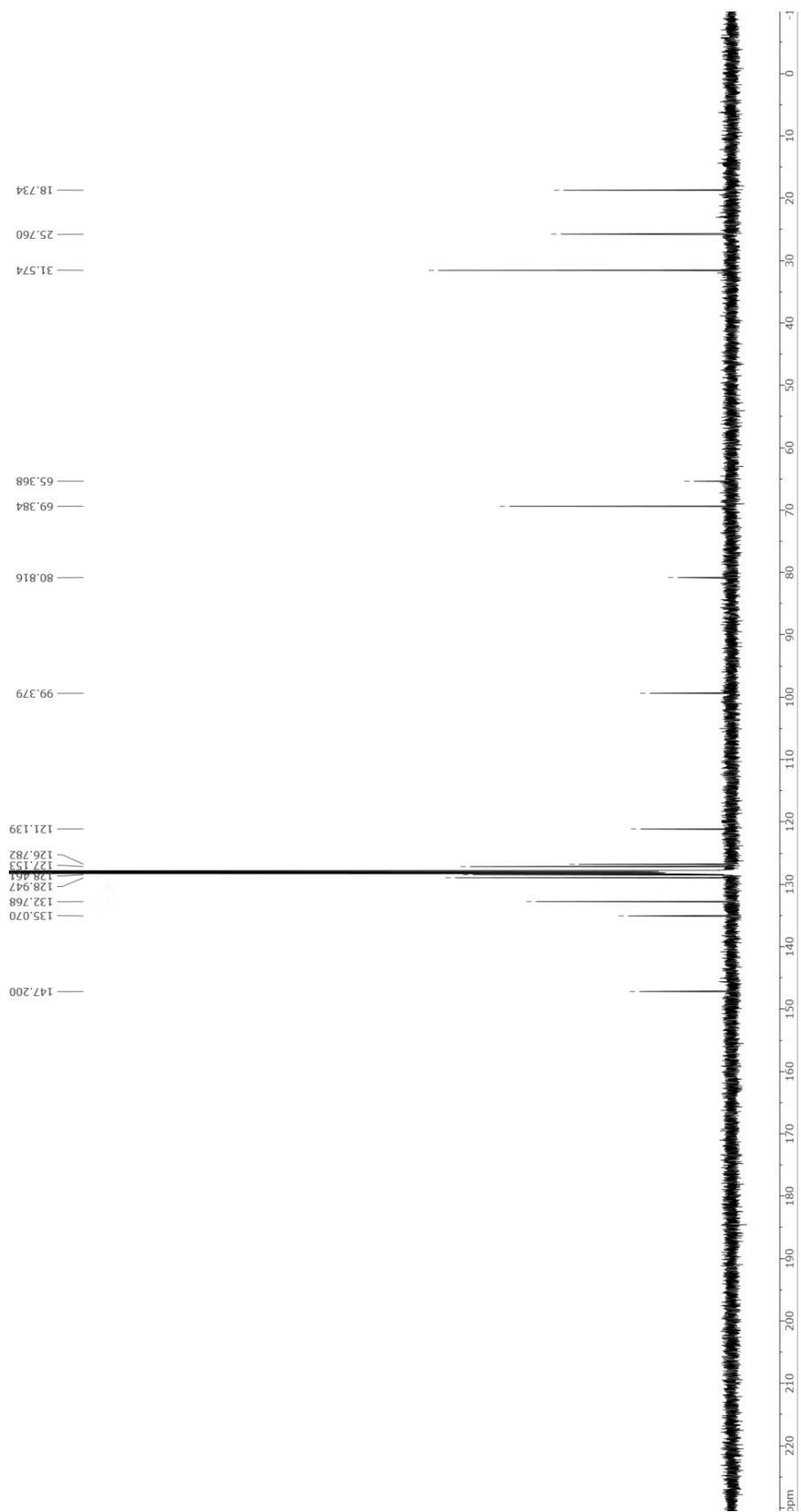
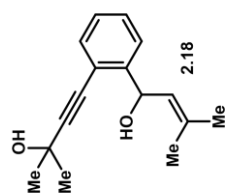
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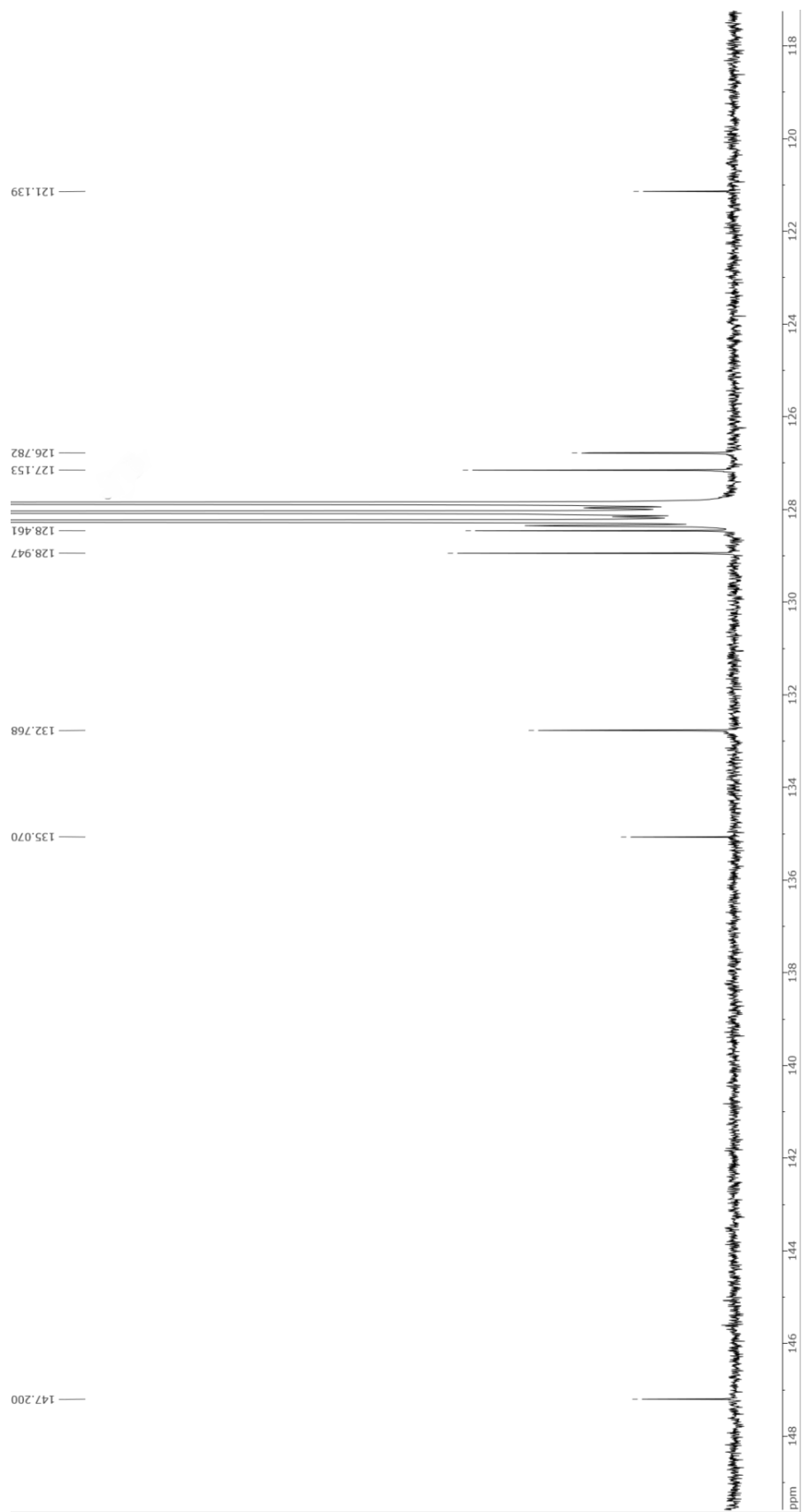
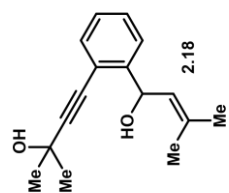
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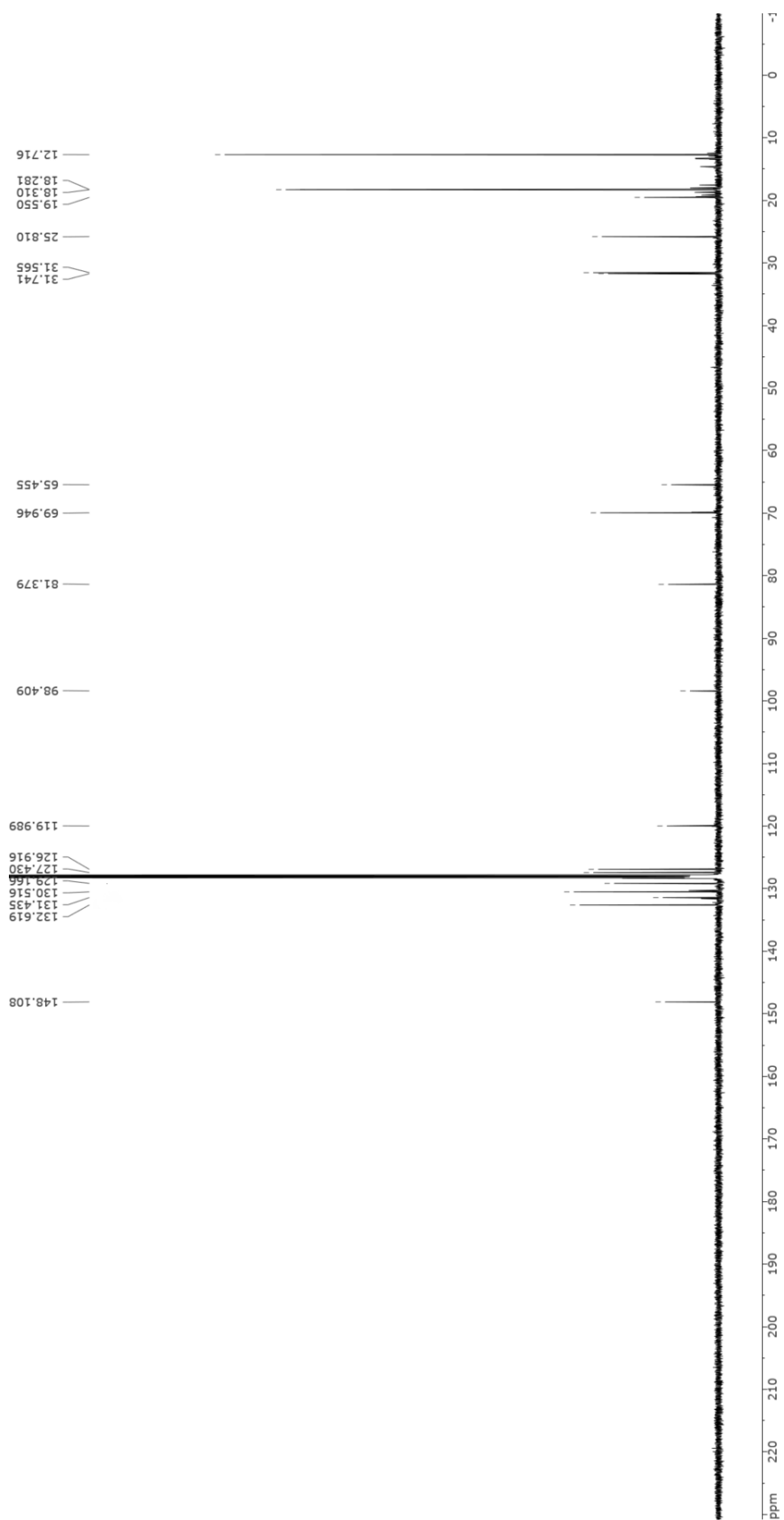
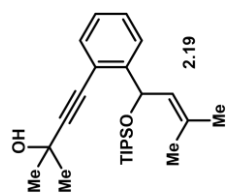
Appendix A: NMR Spectra for Chapter 2

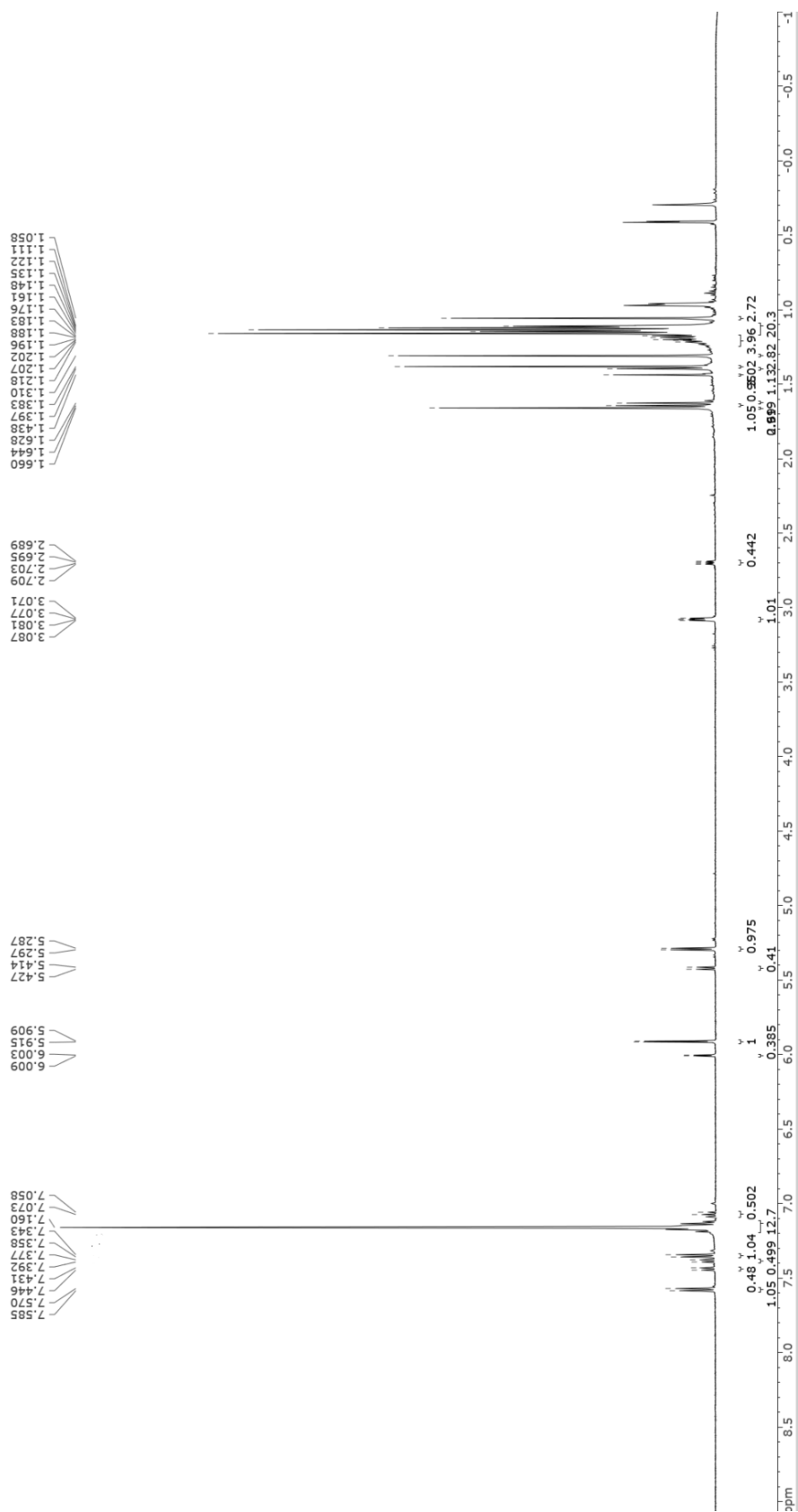
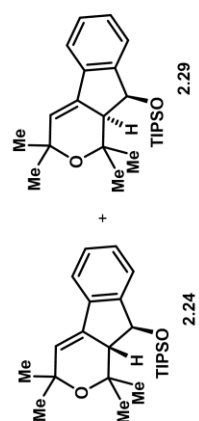


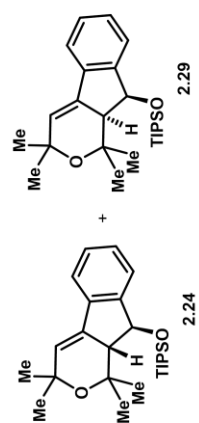


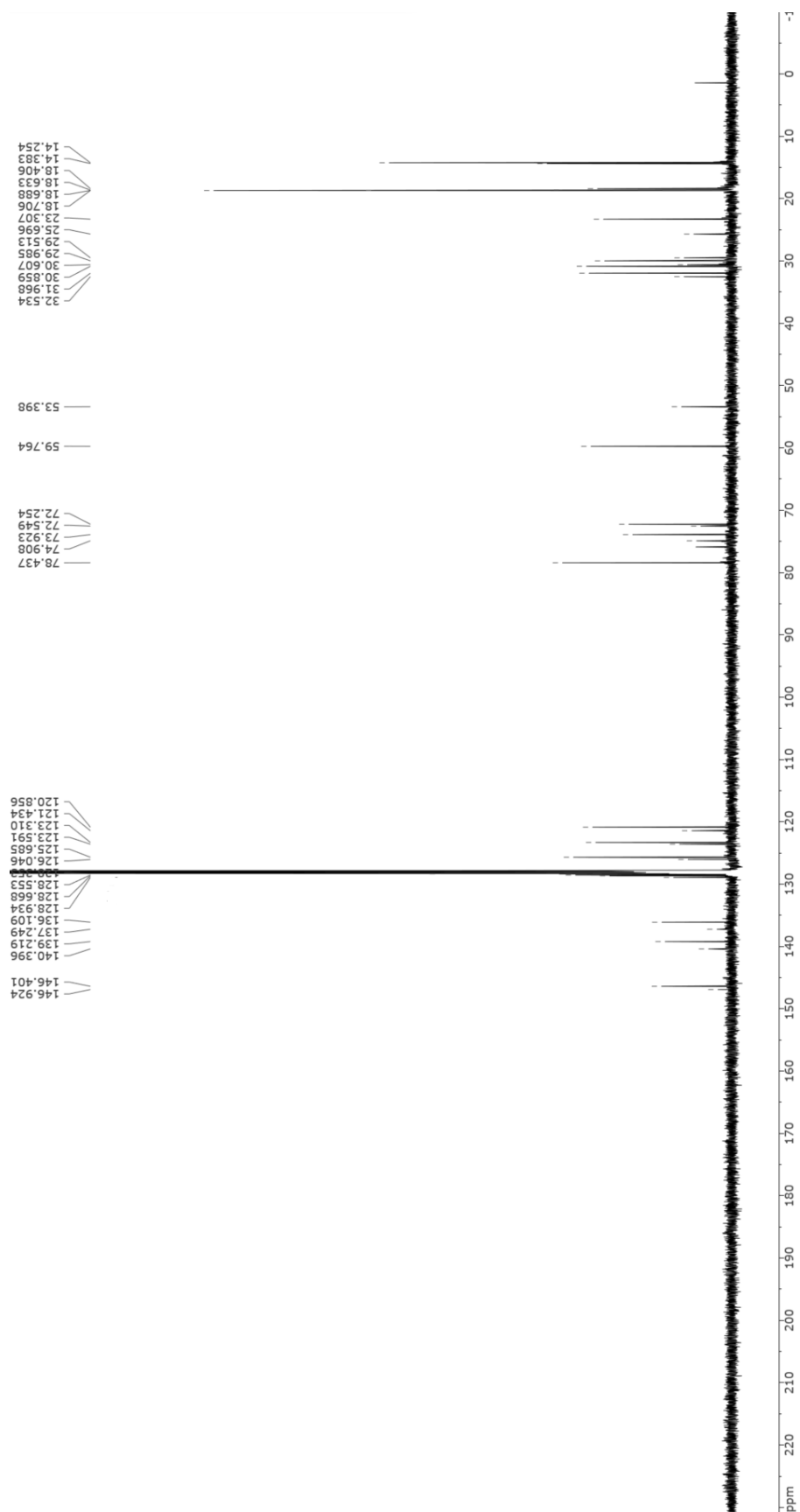
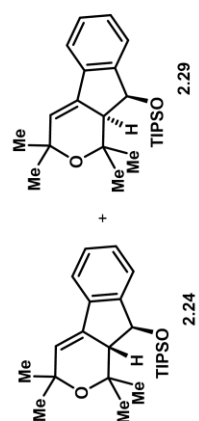


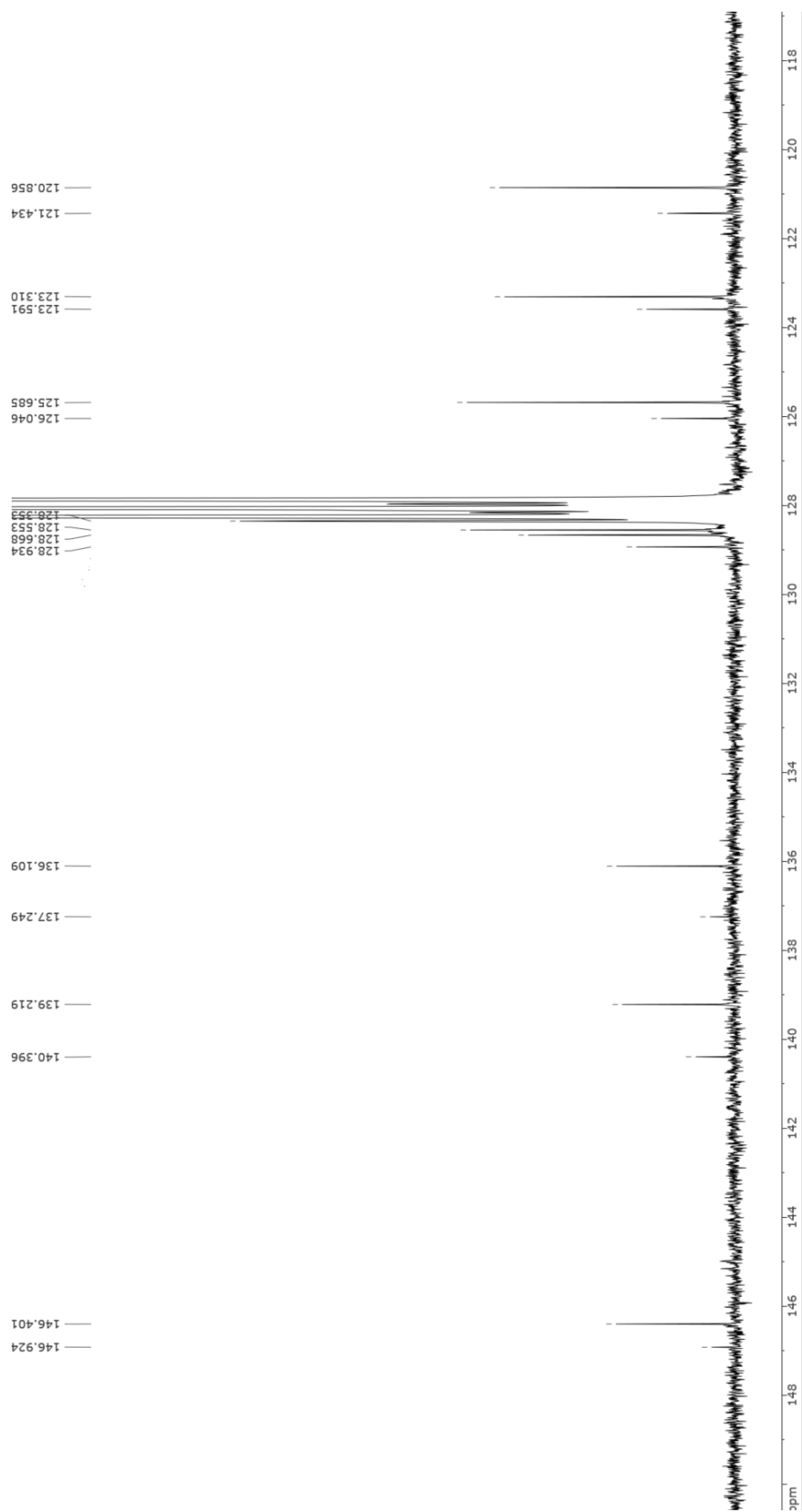
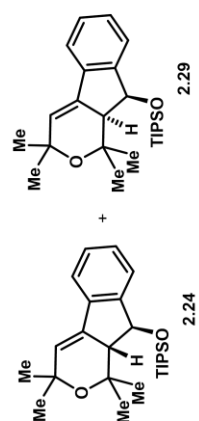


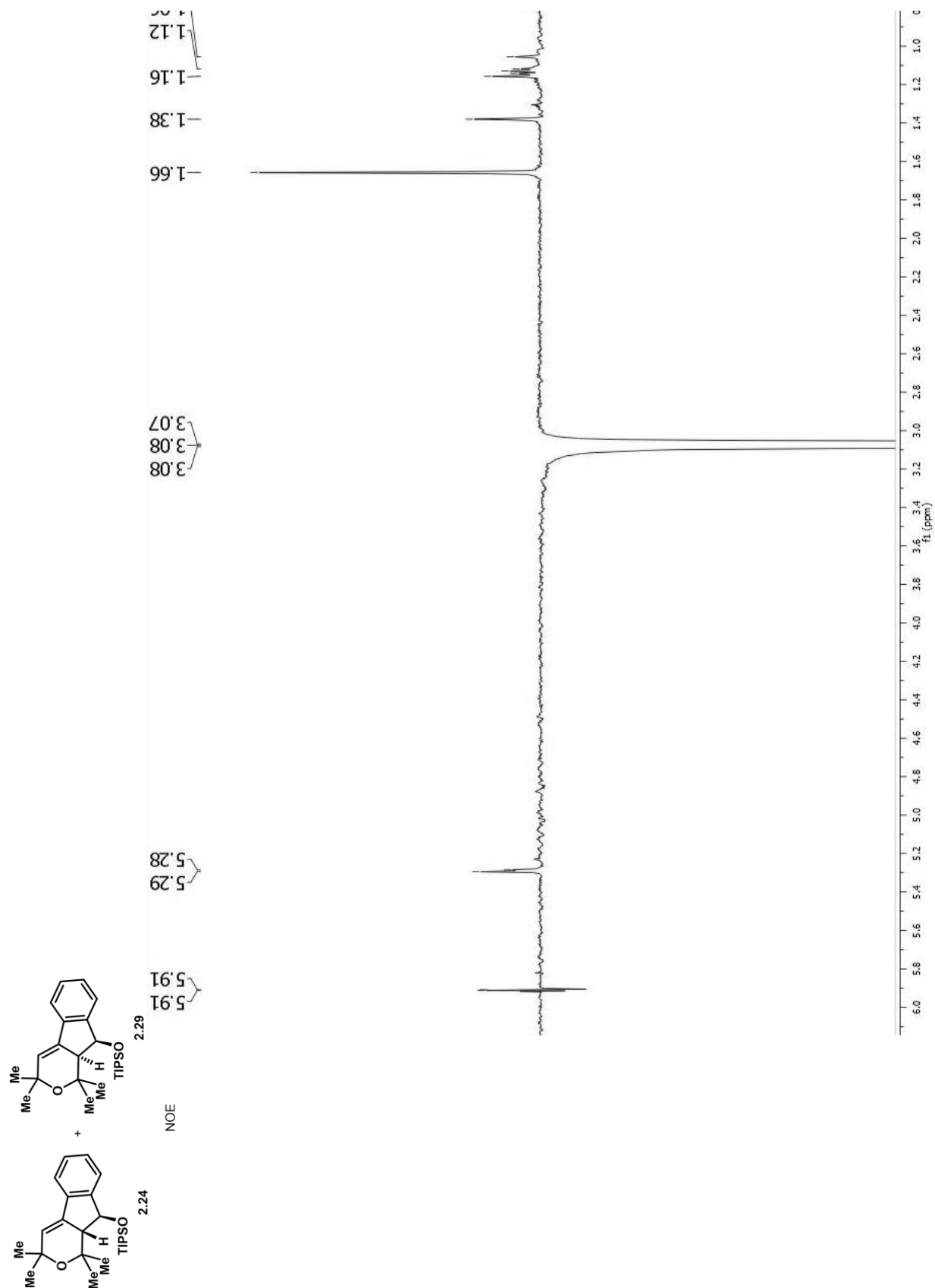


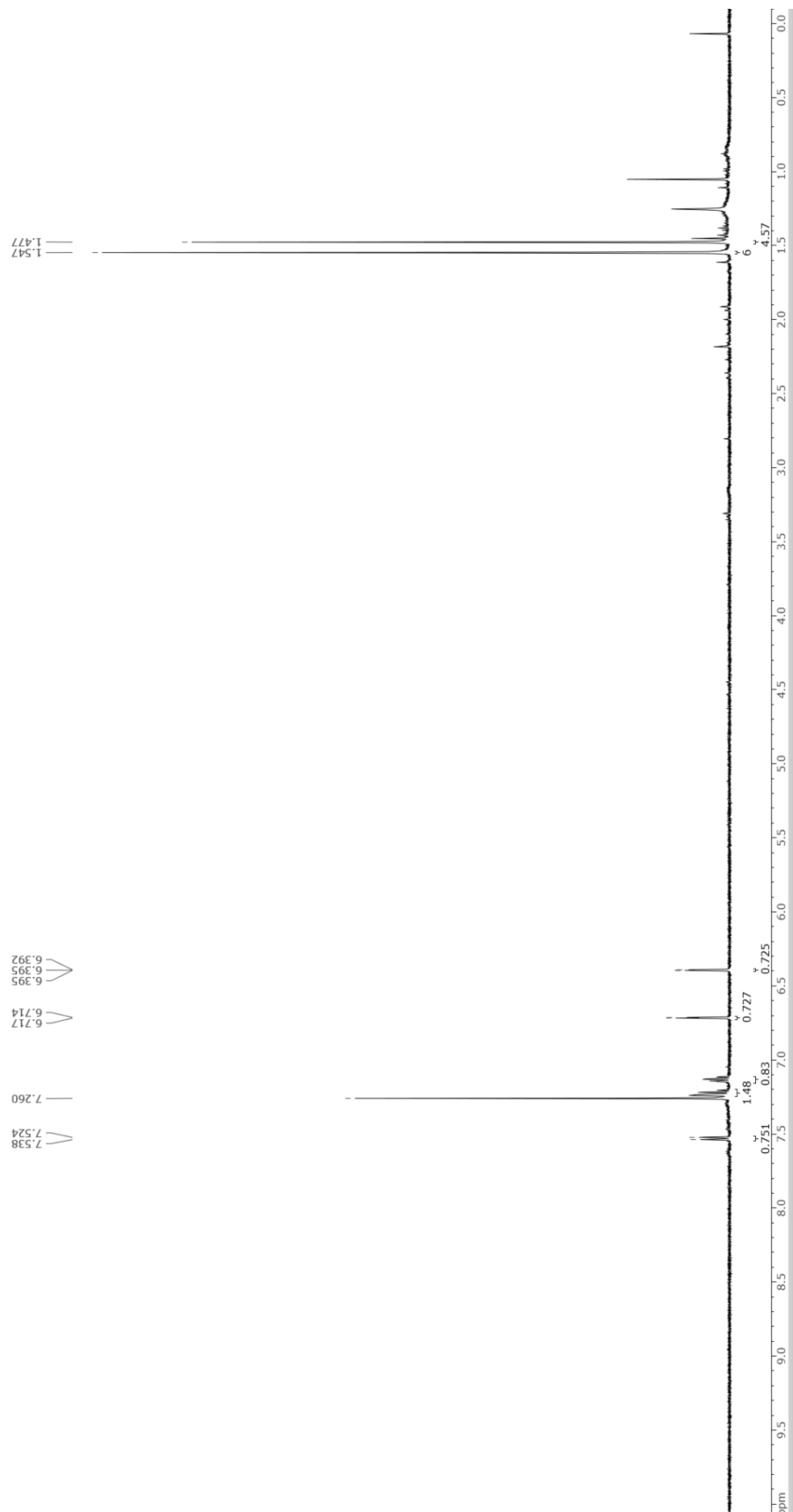
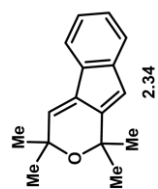


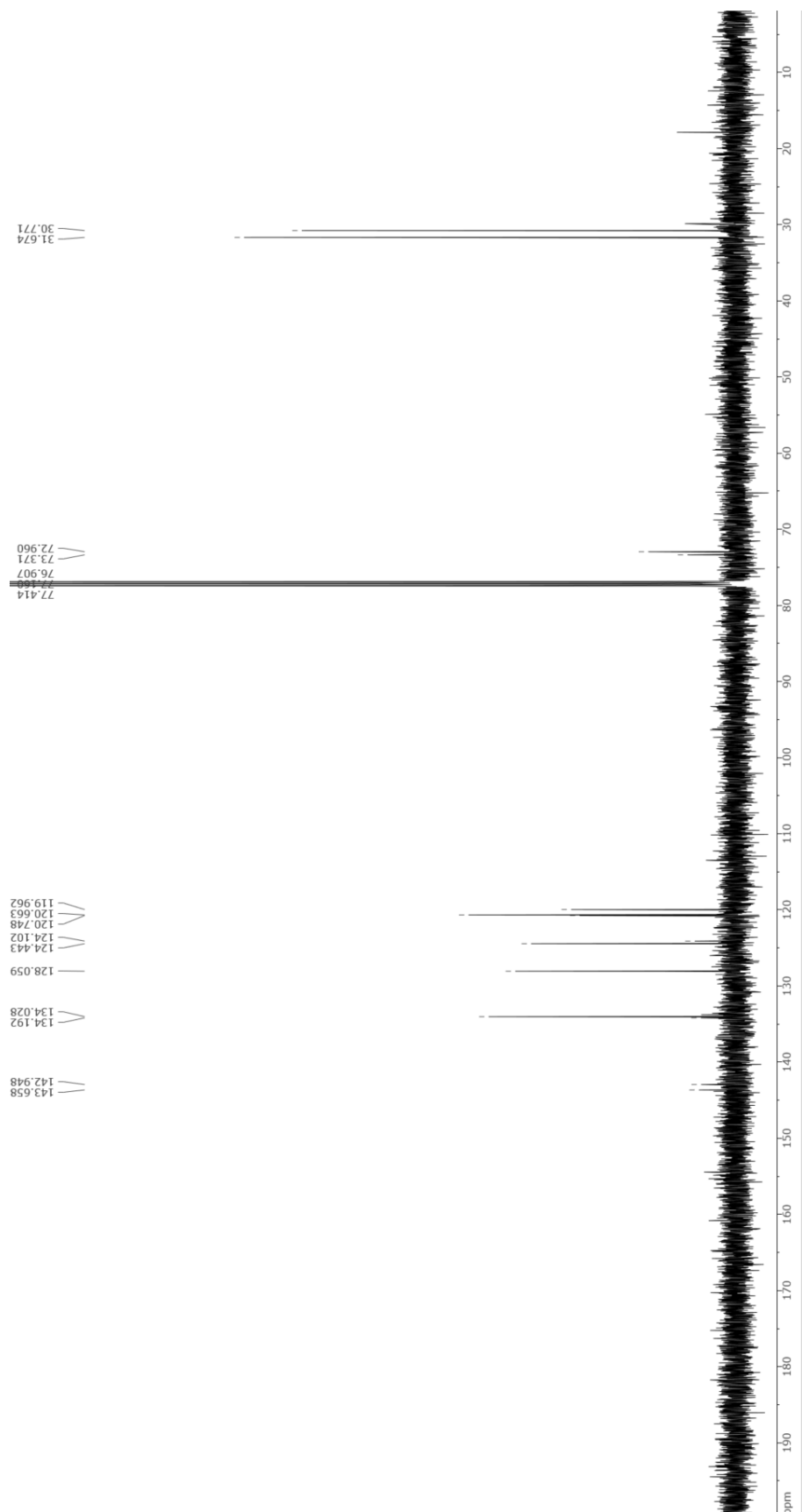
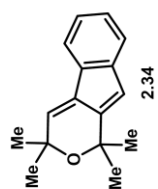


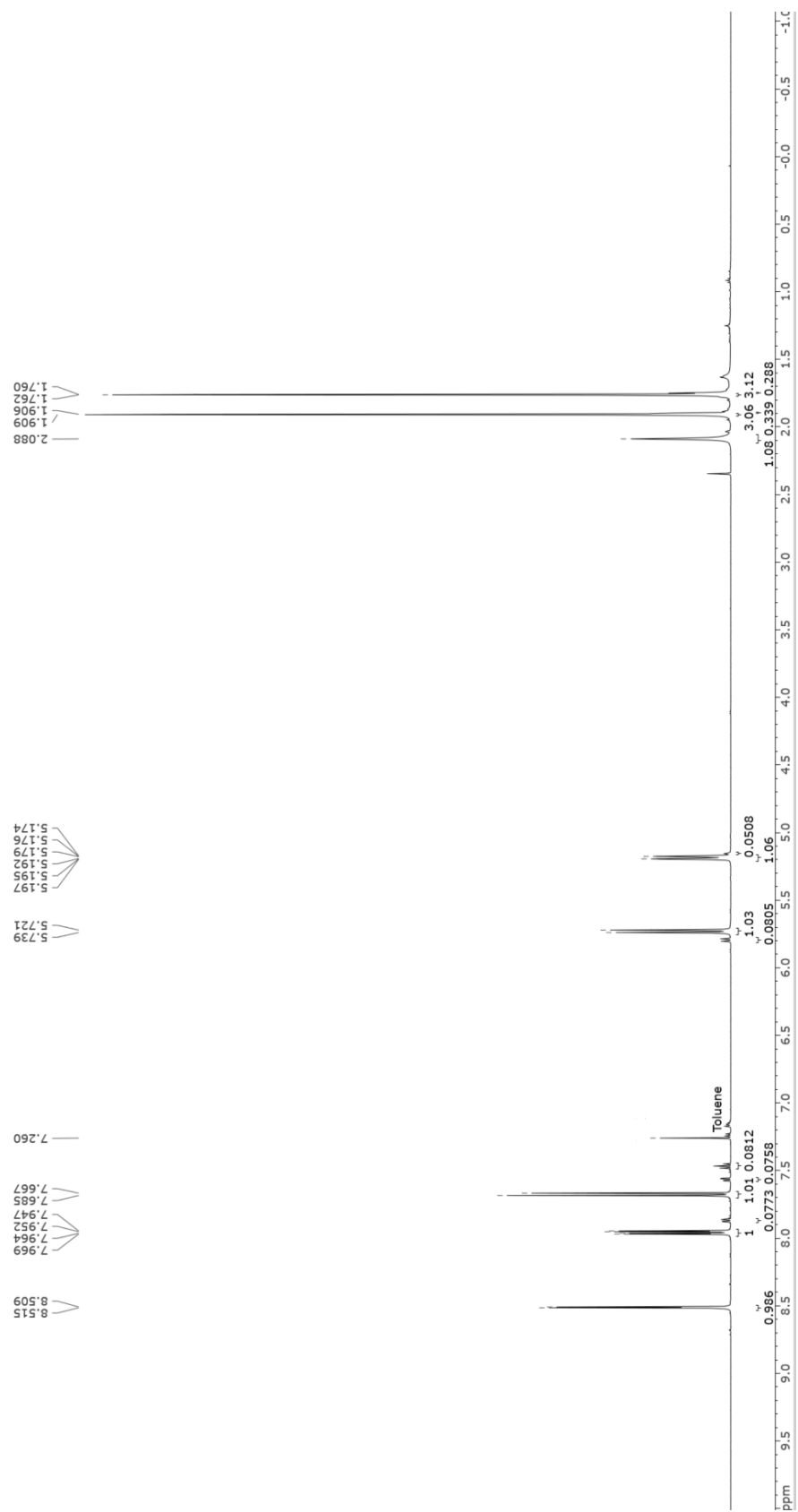
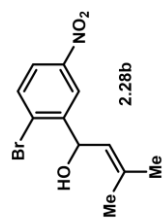


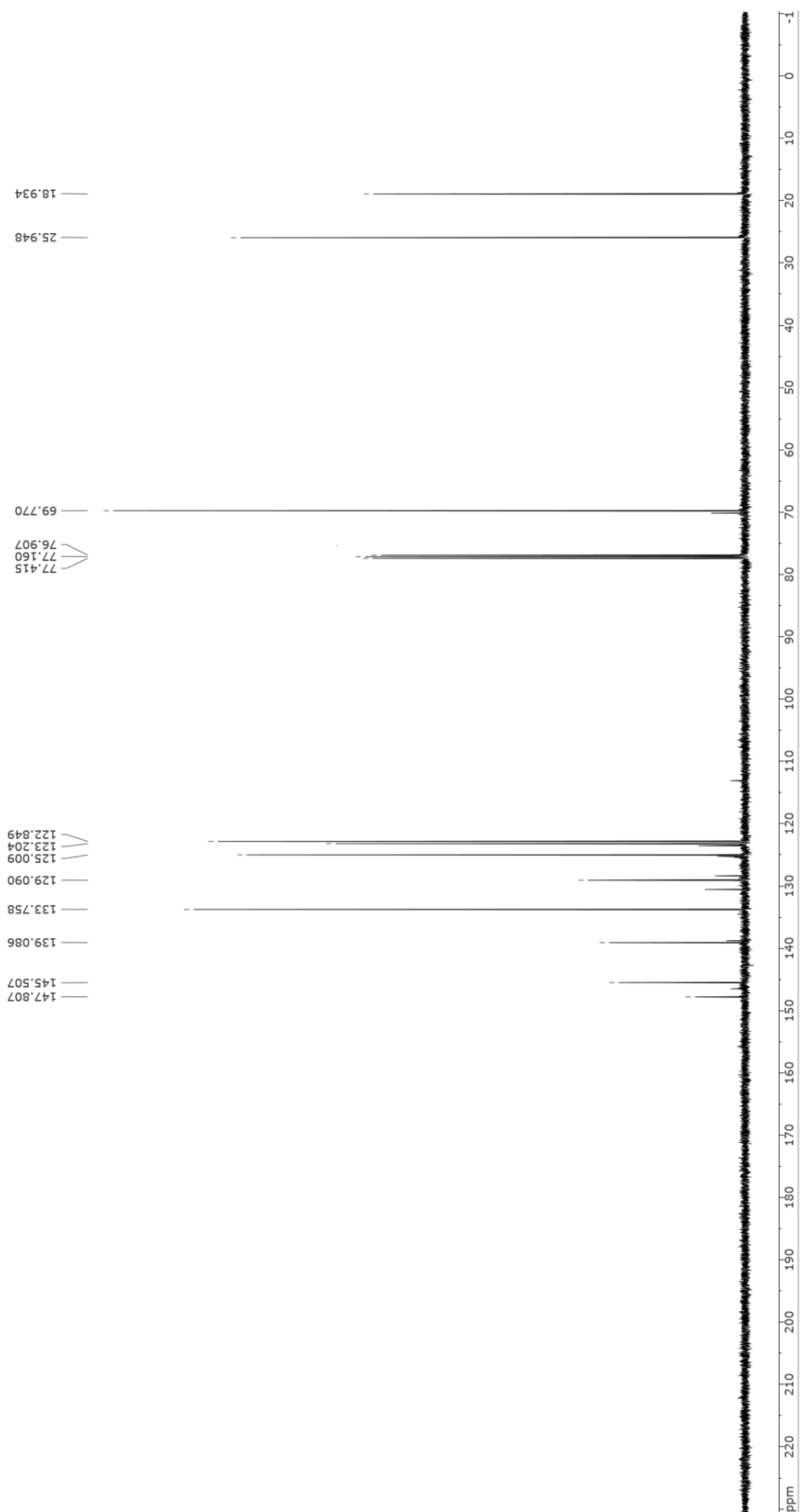
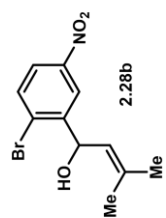


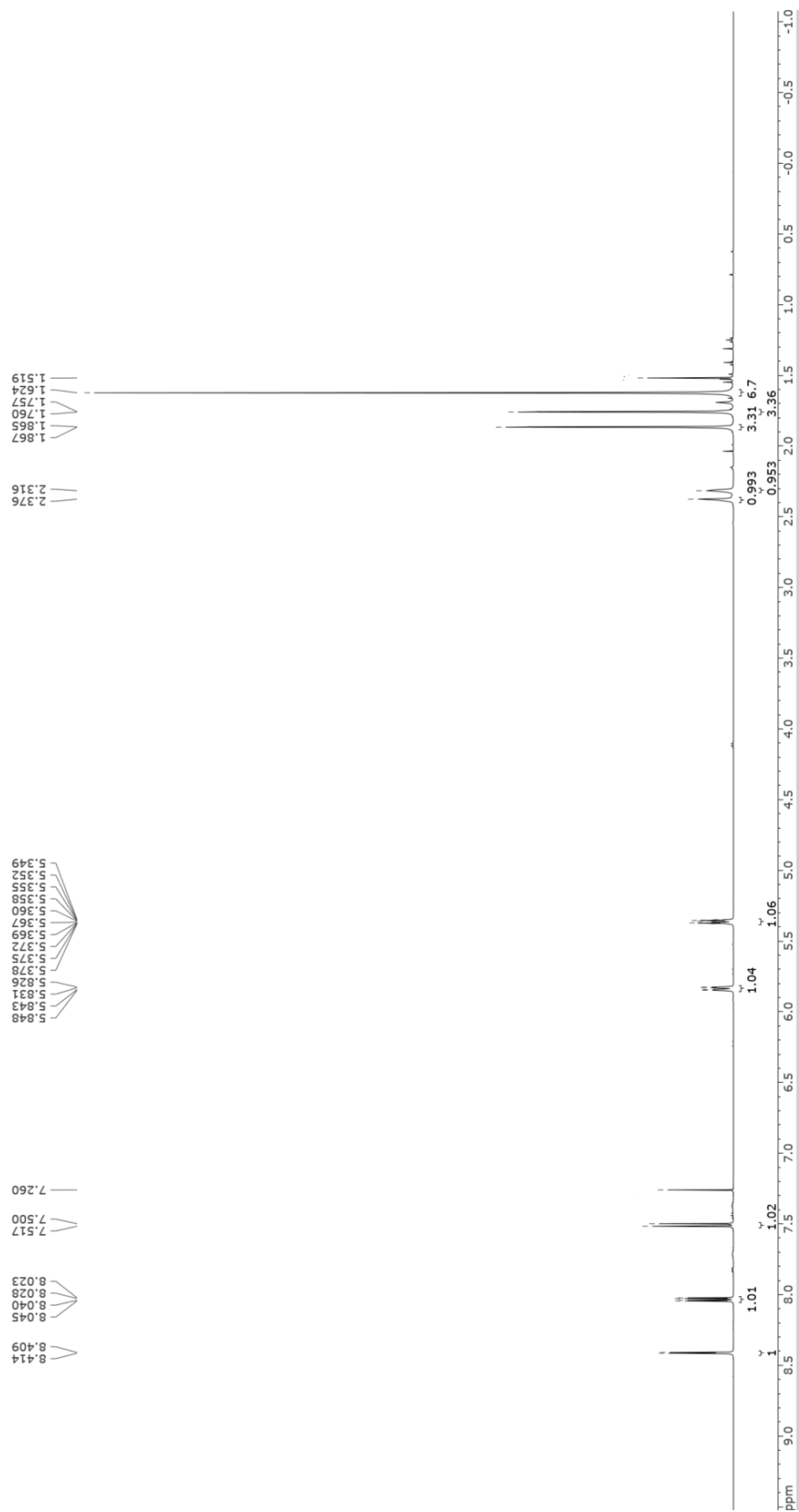
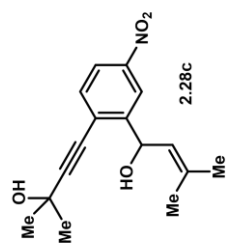


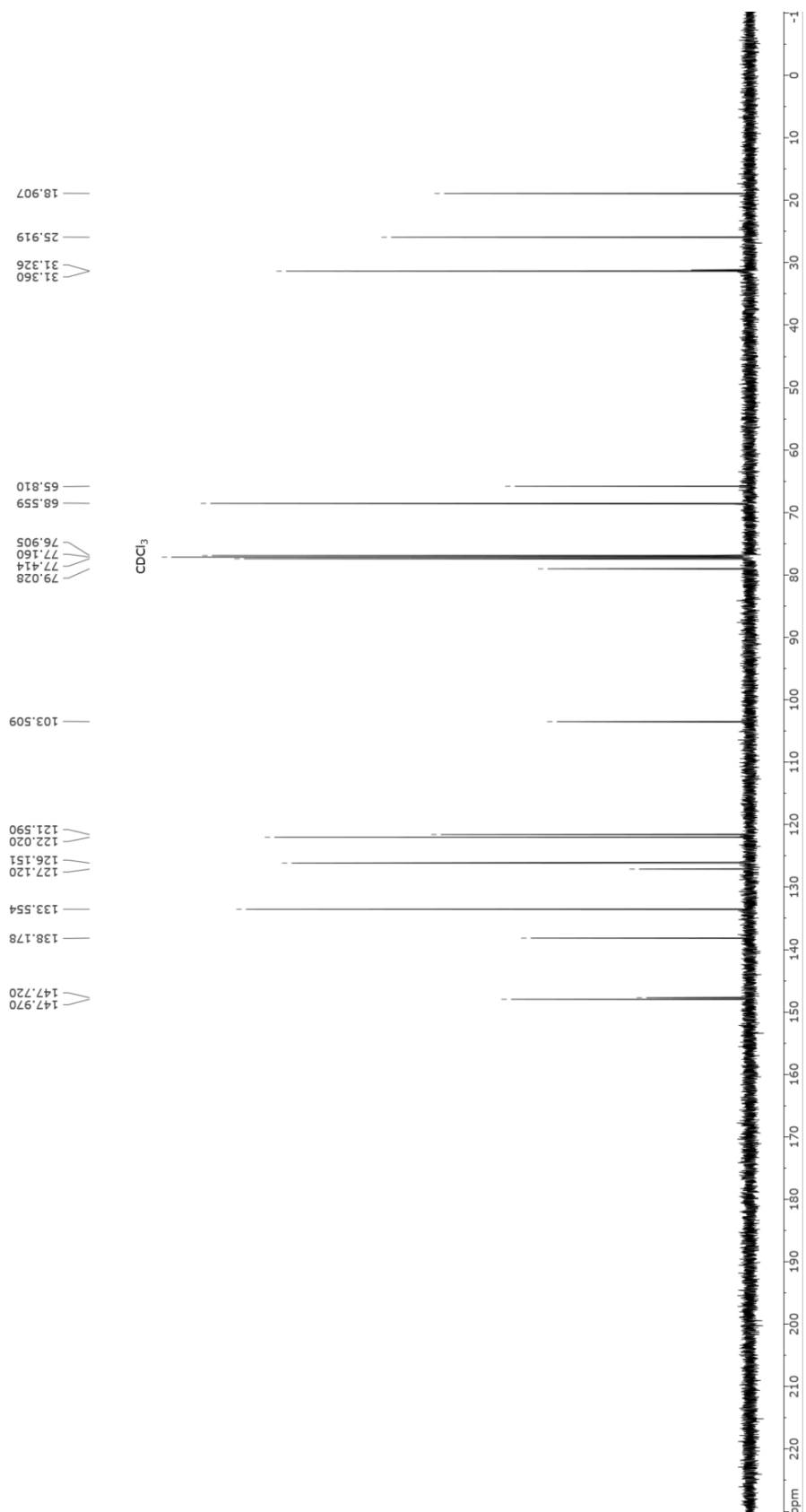
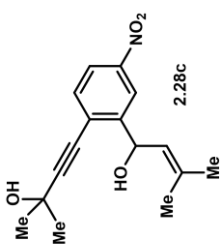


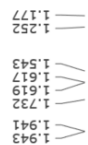


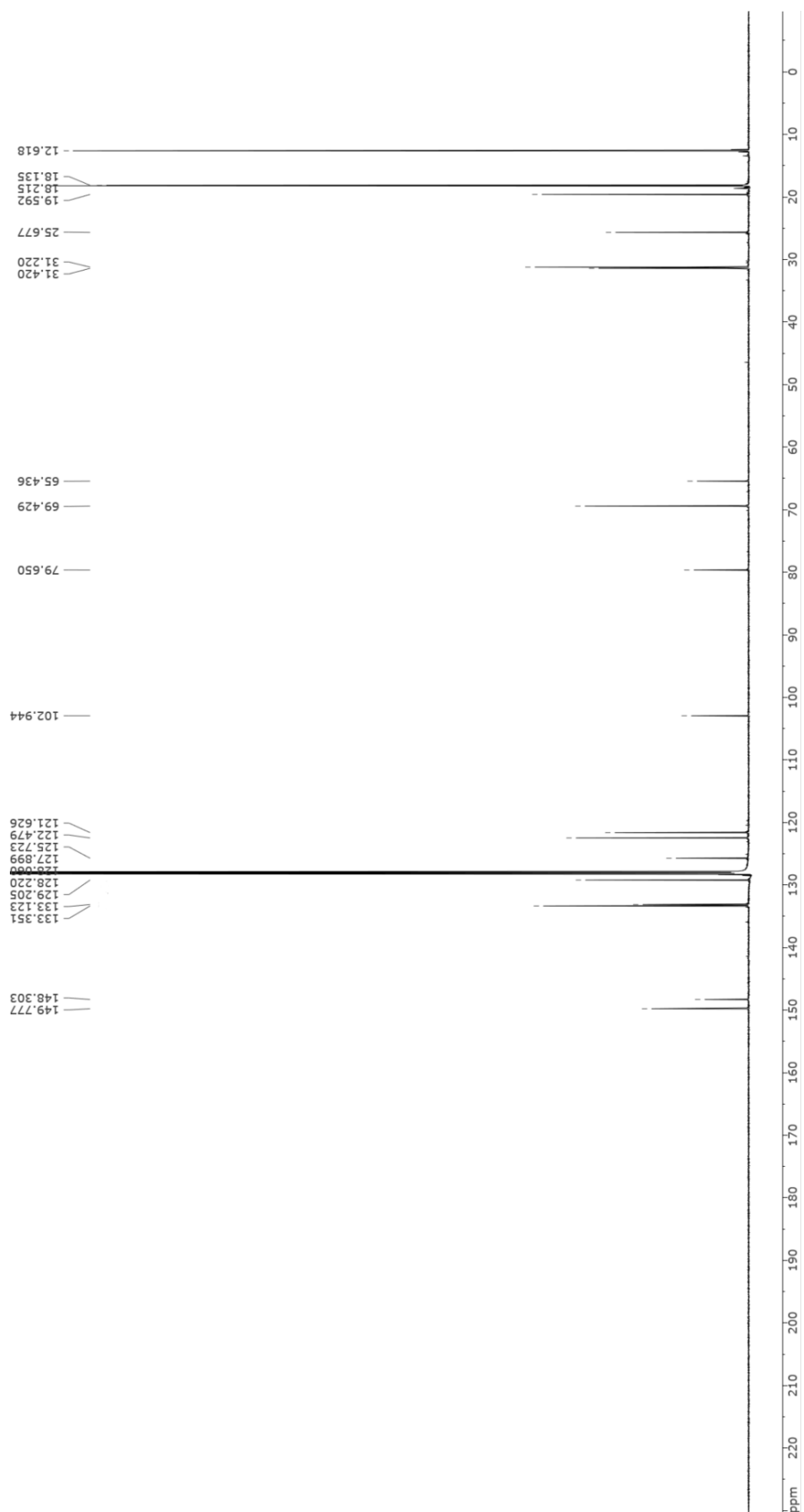
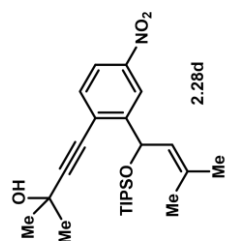


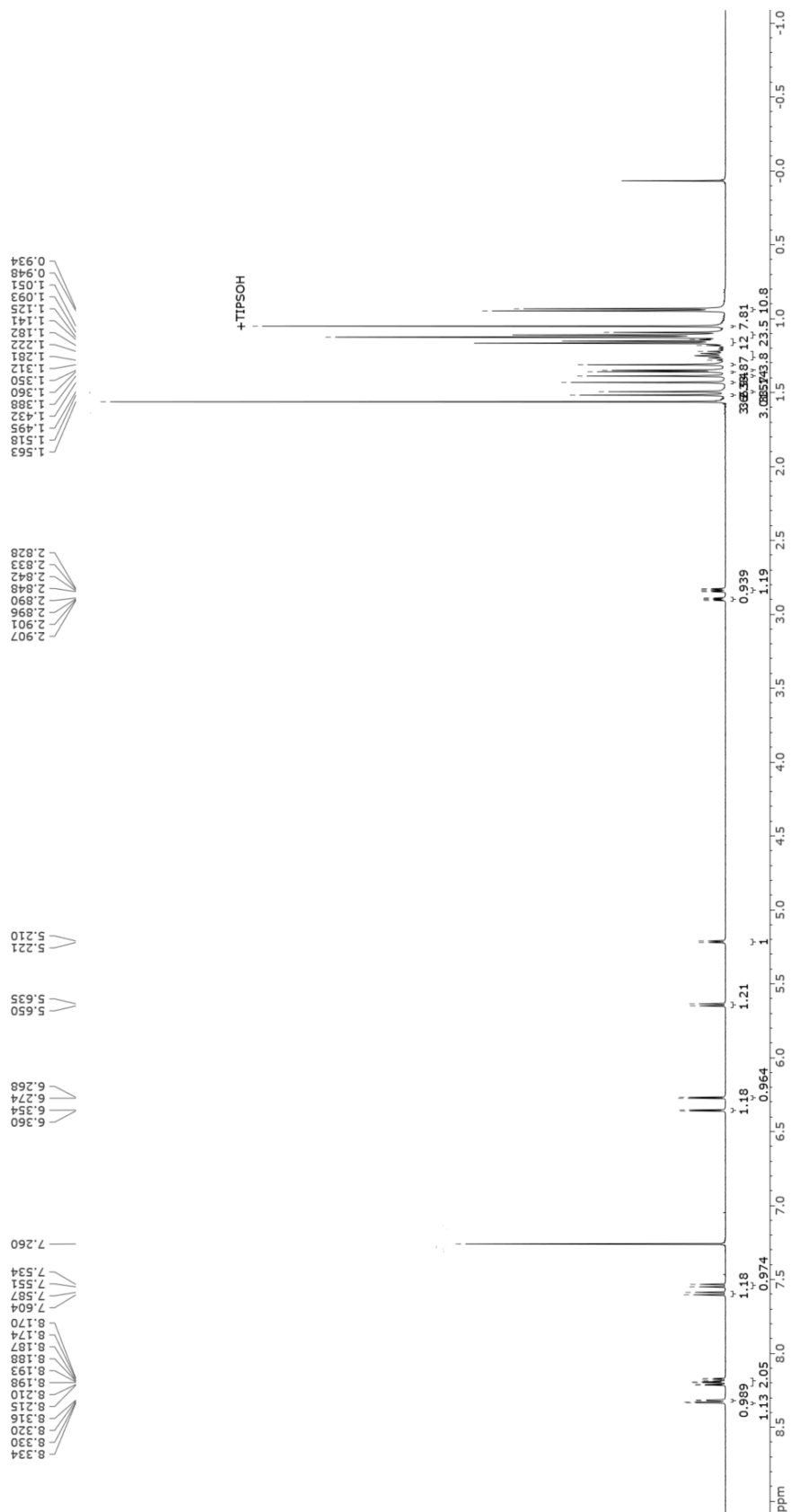
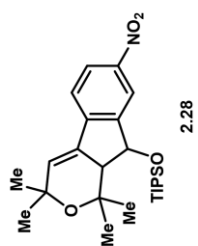


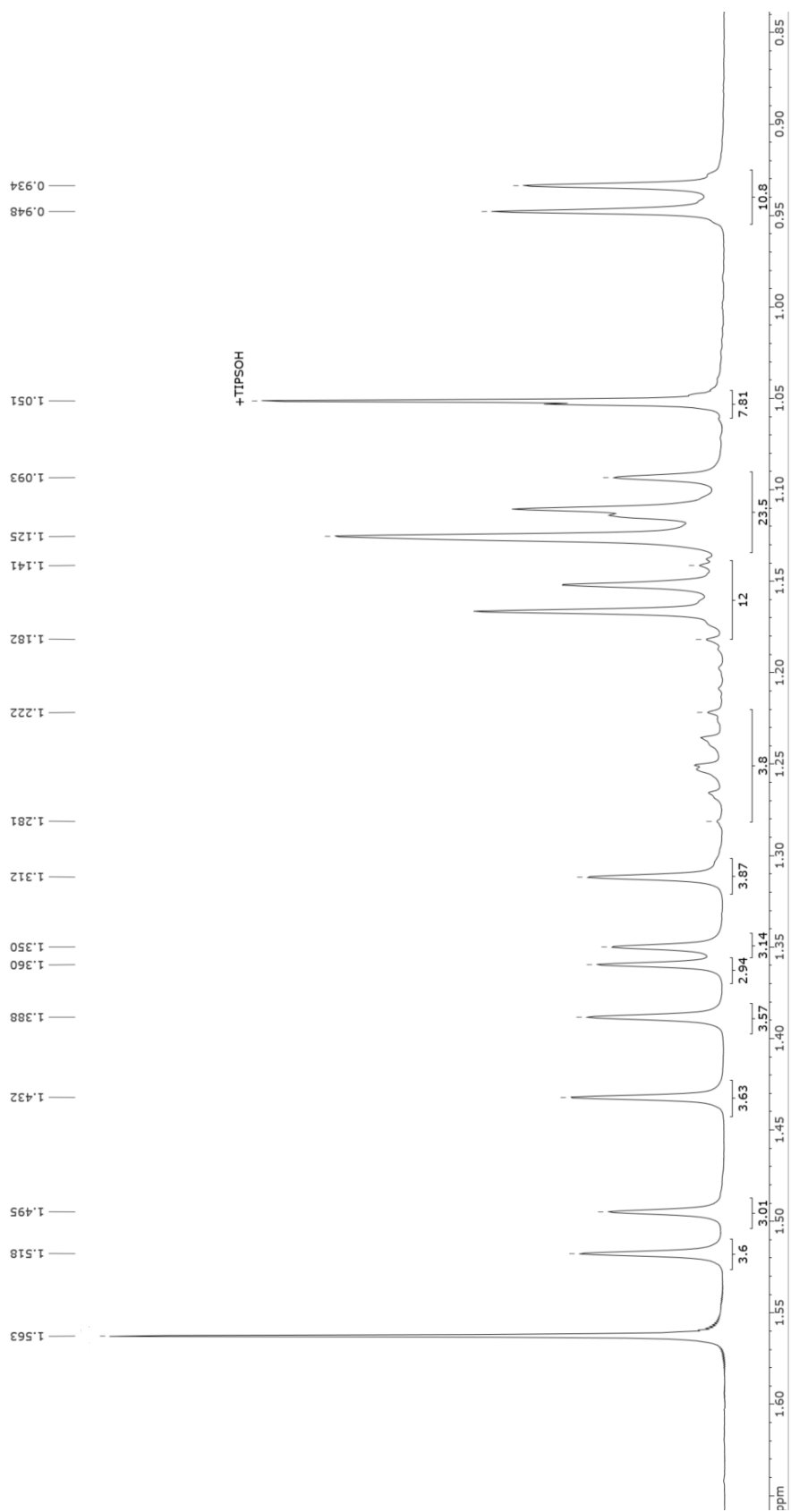
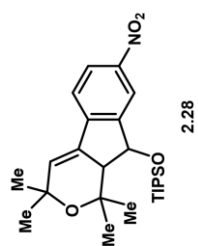


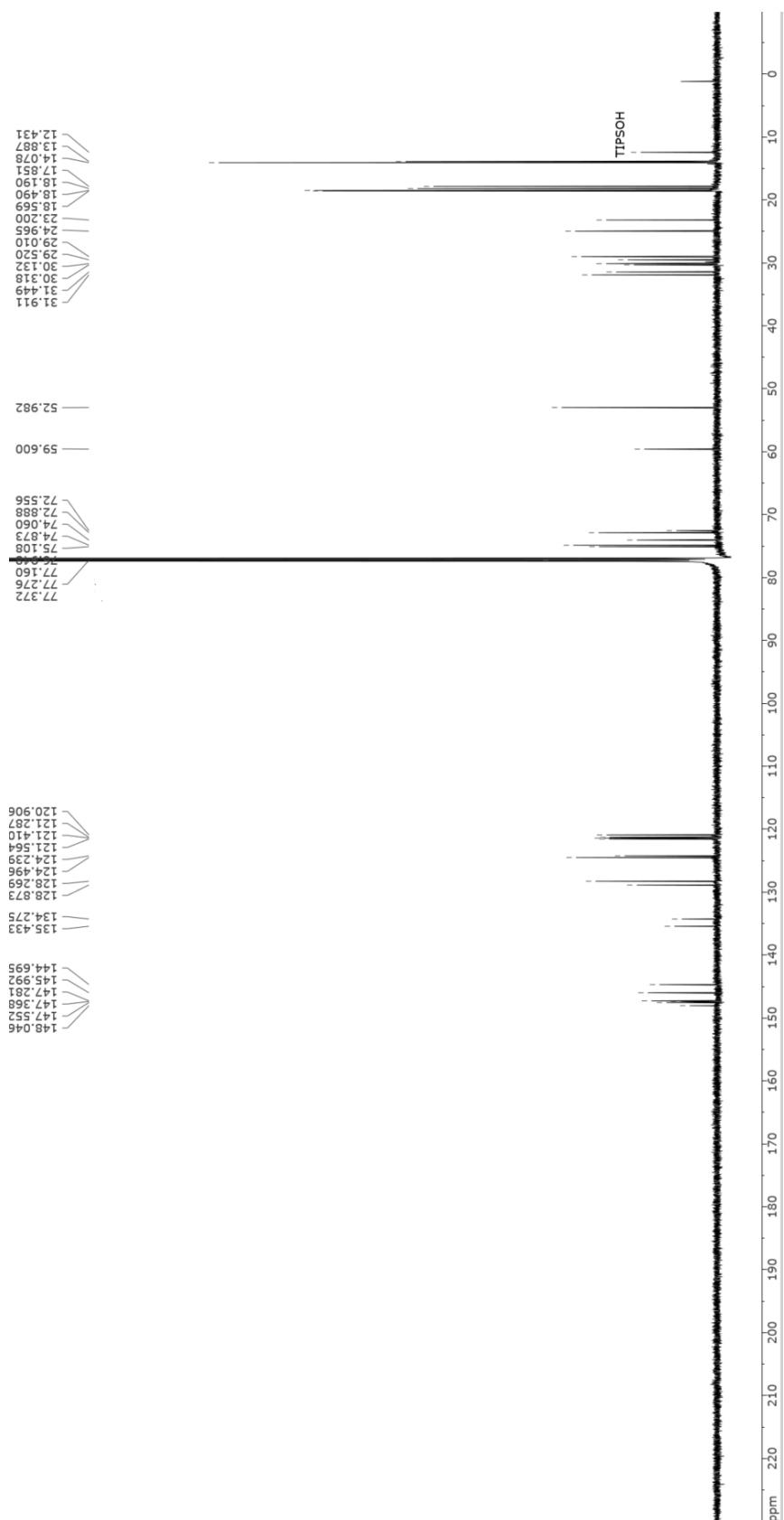
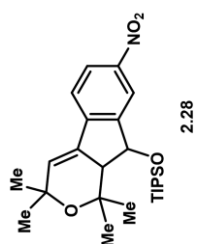




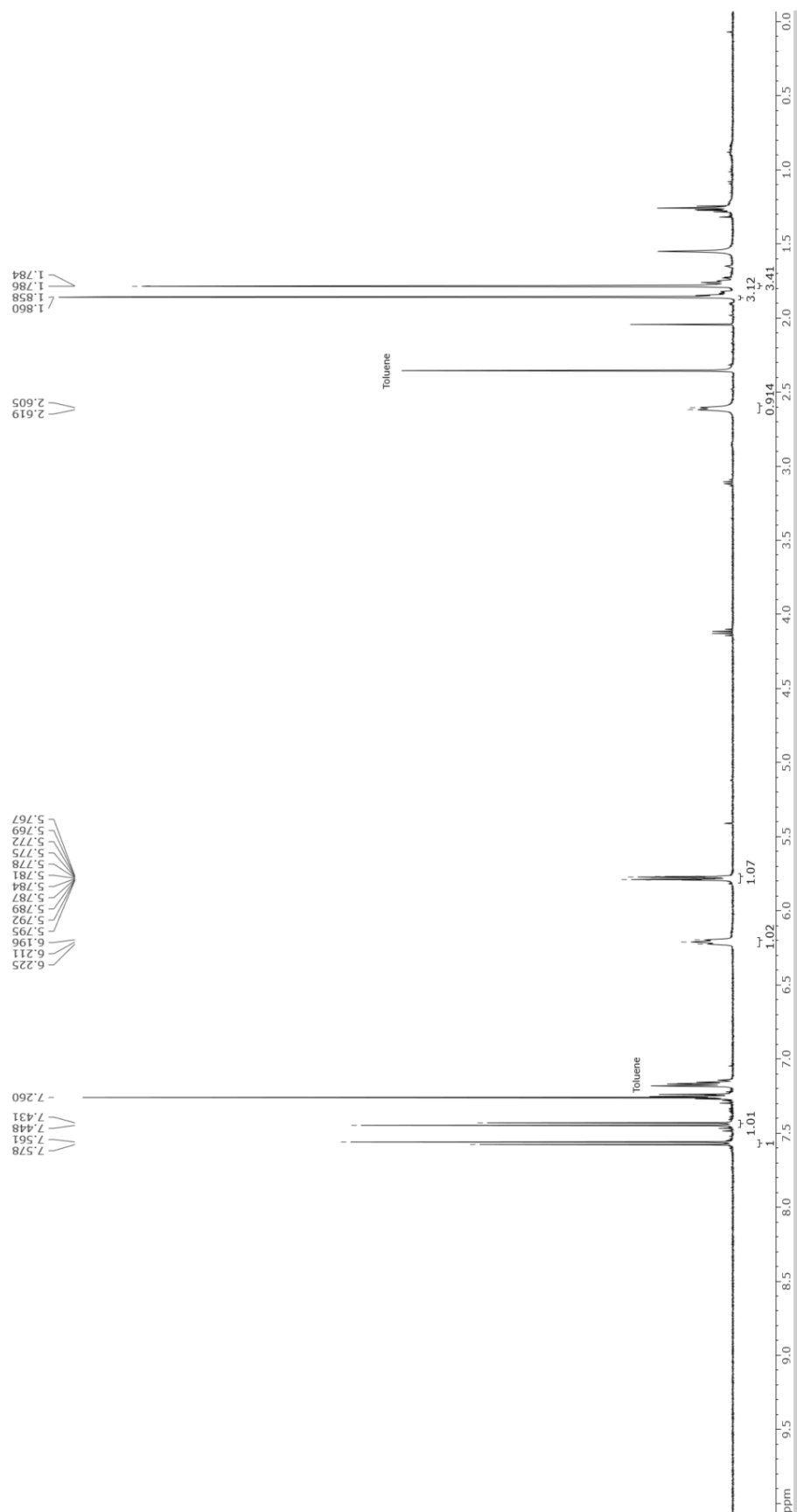
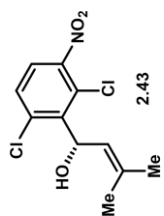


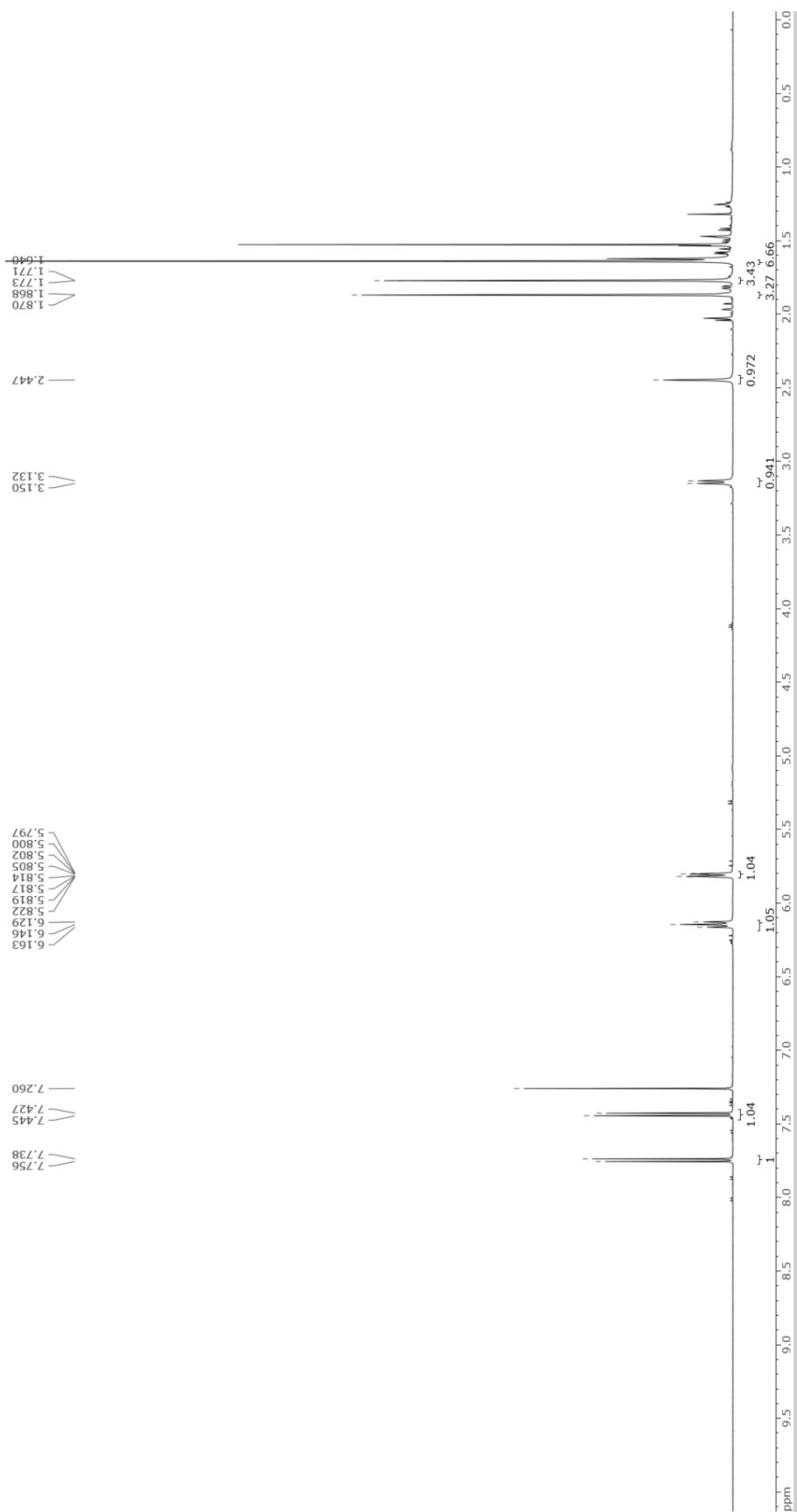
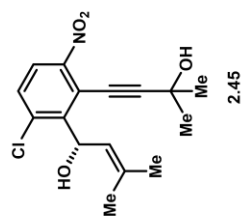


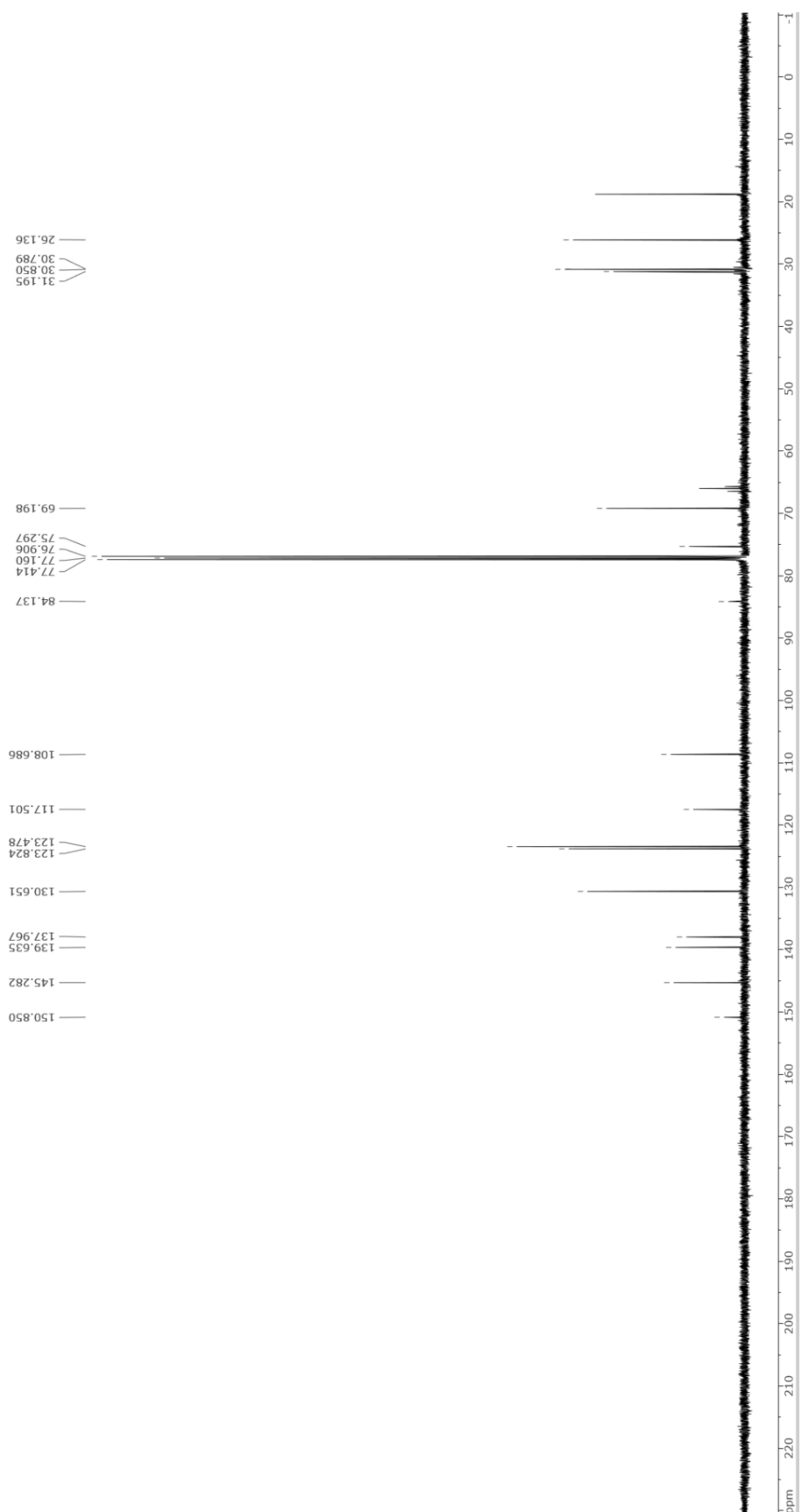
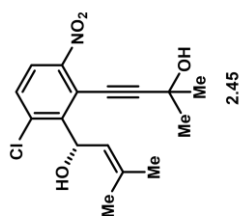


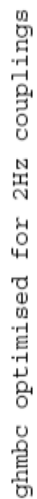
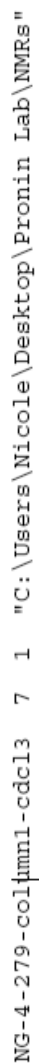


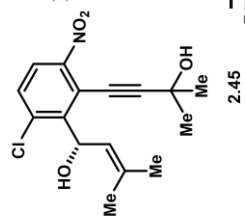




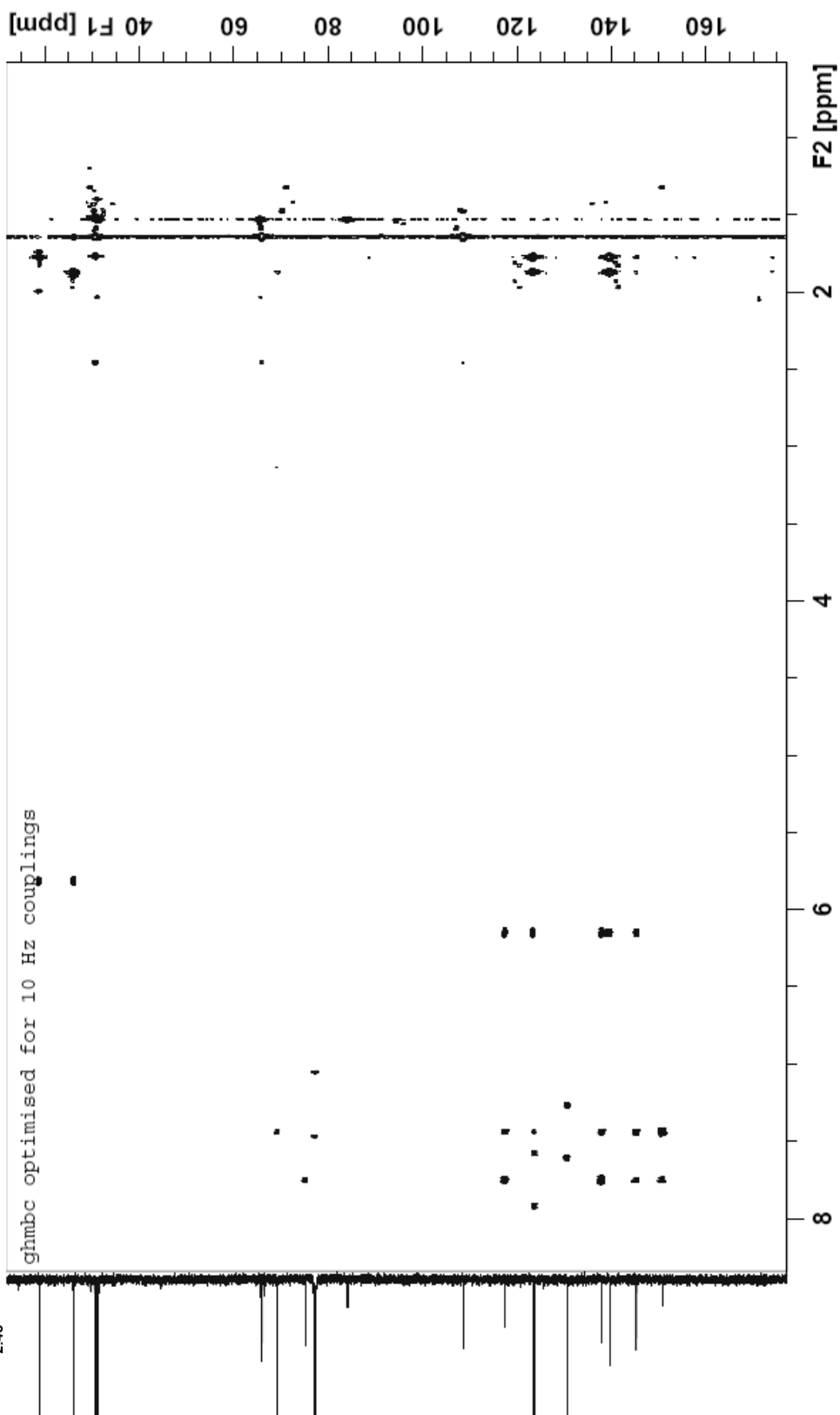


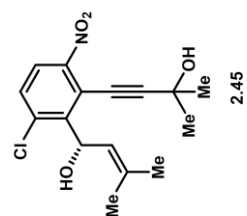




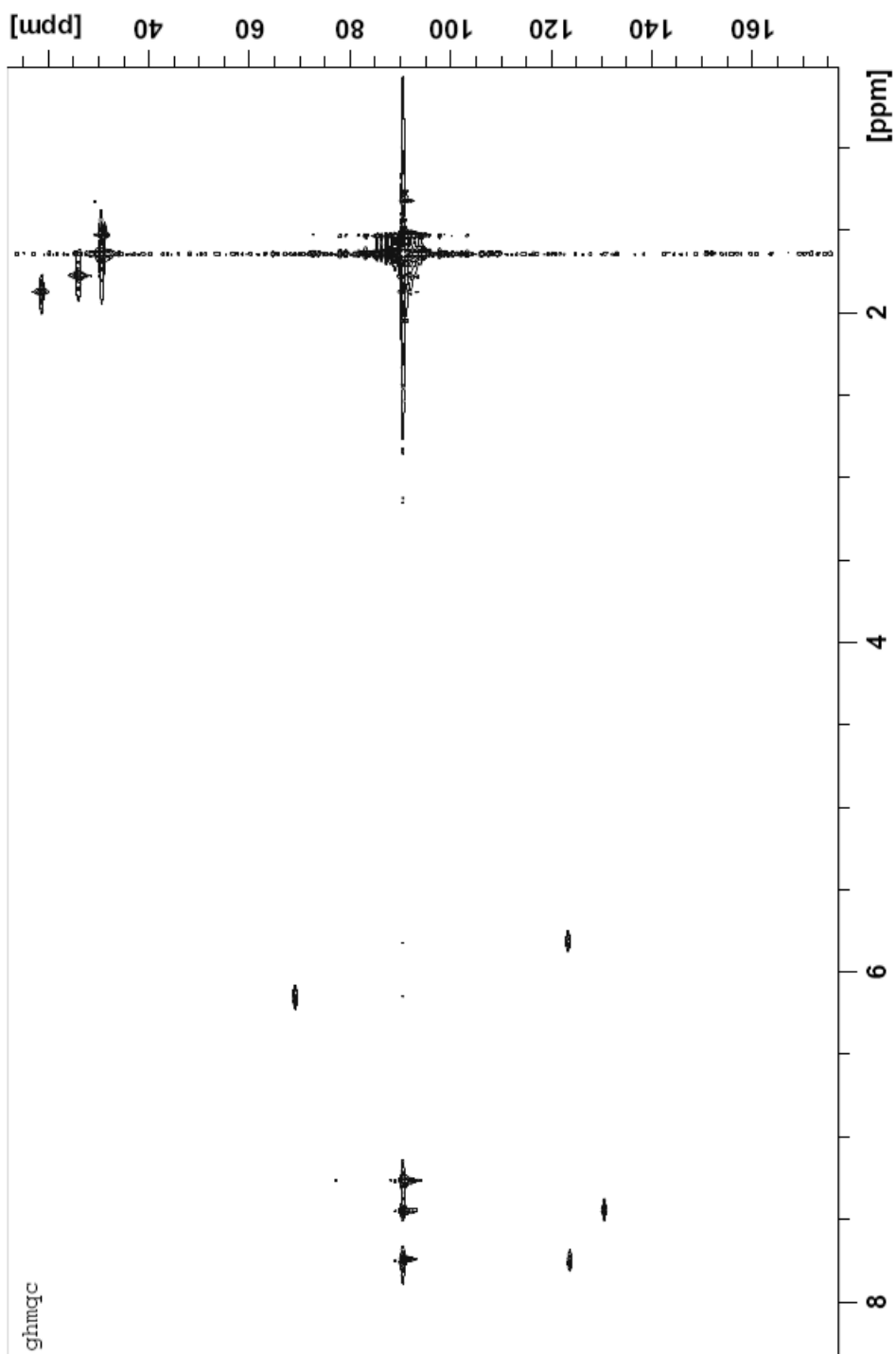


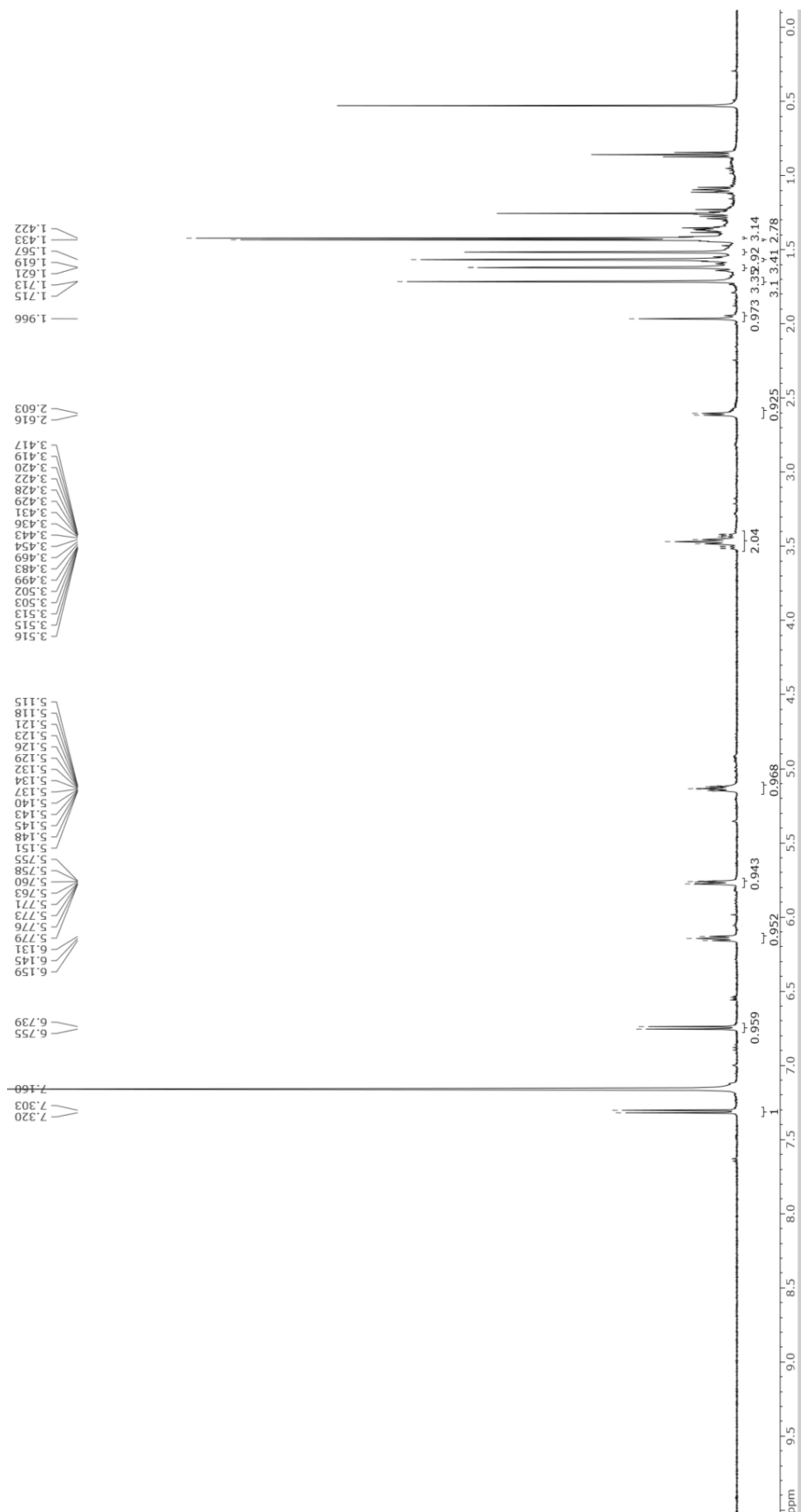
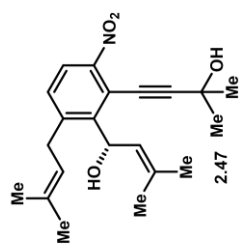
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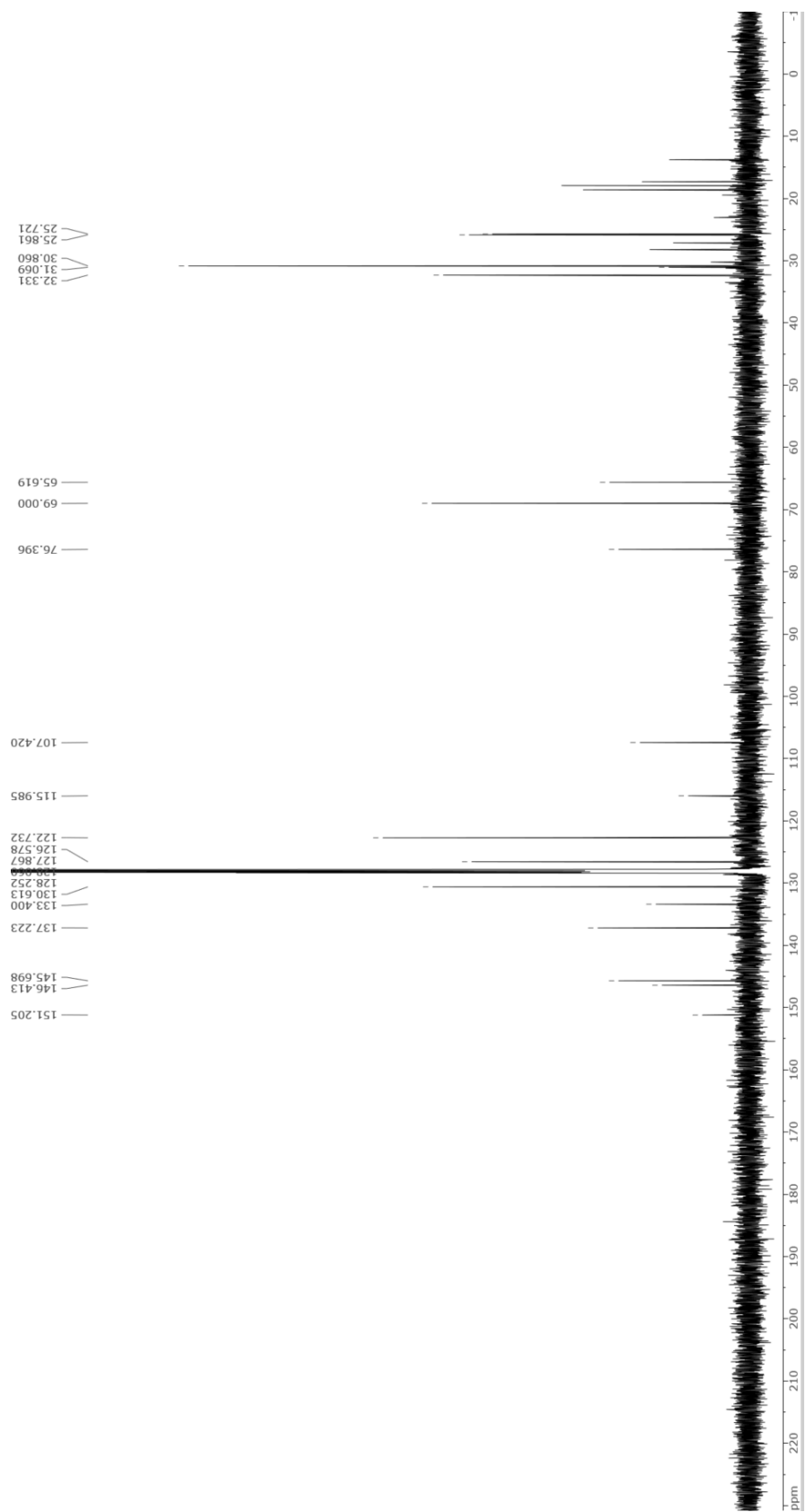
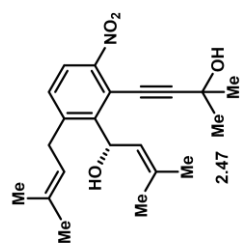


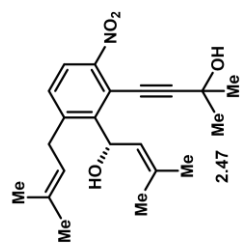


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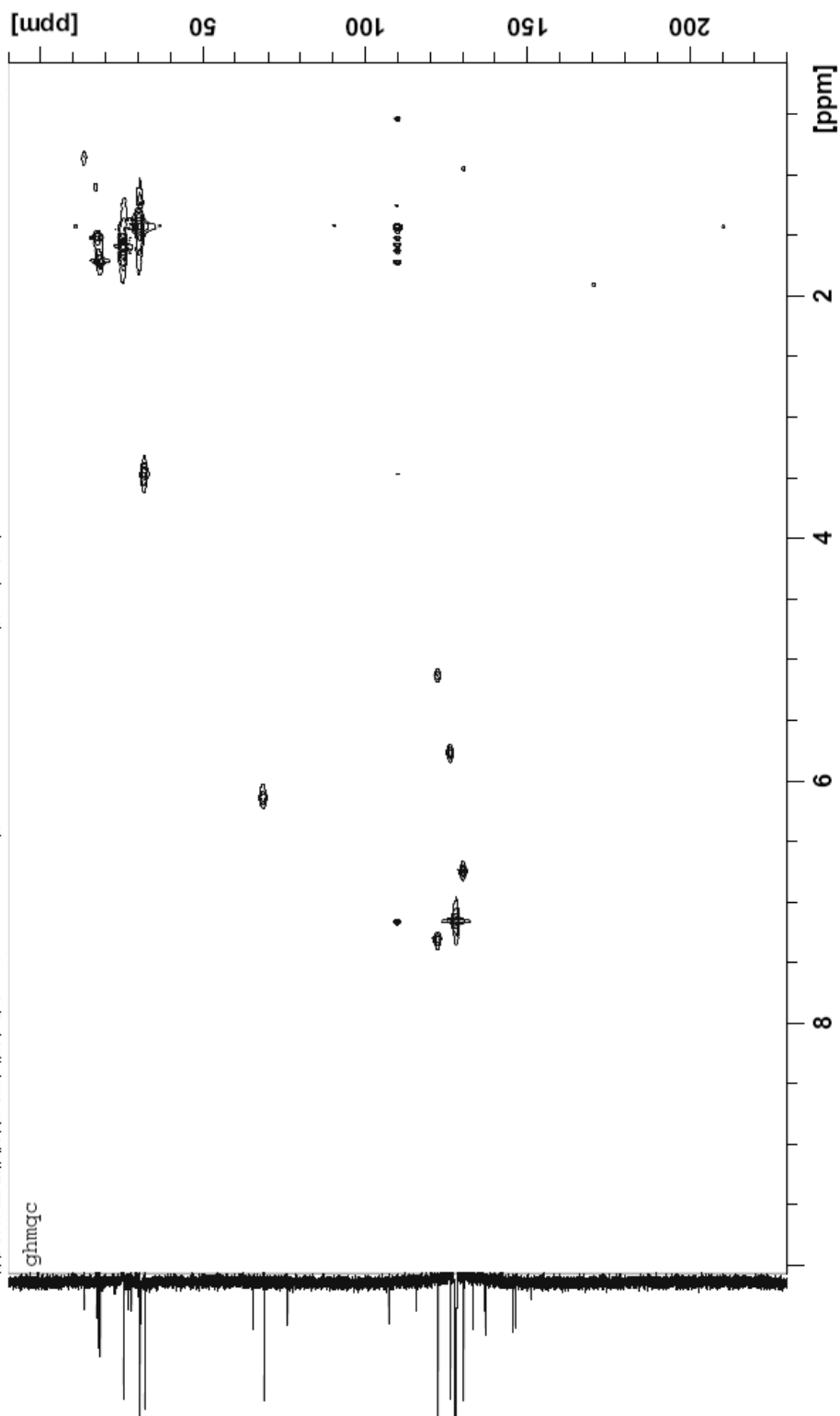


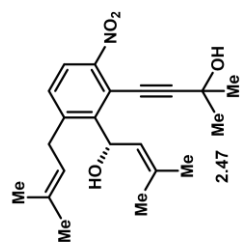




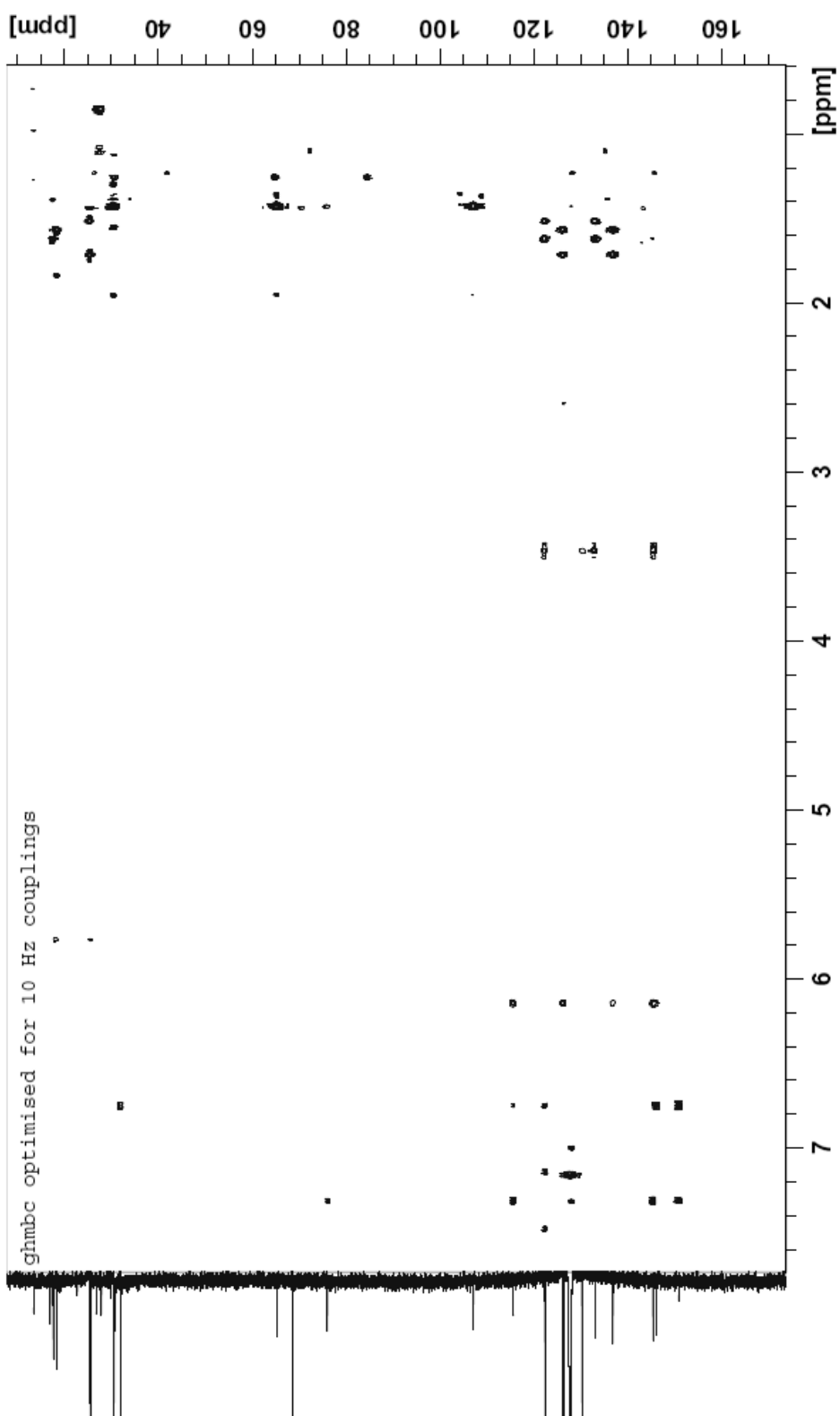


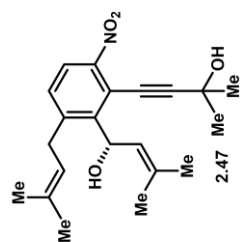
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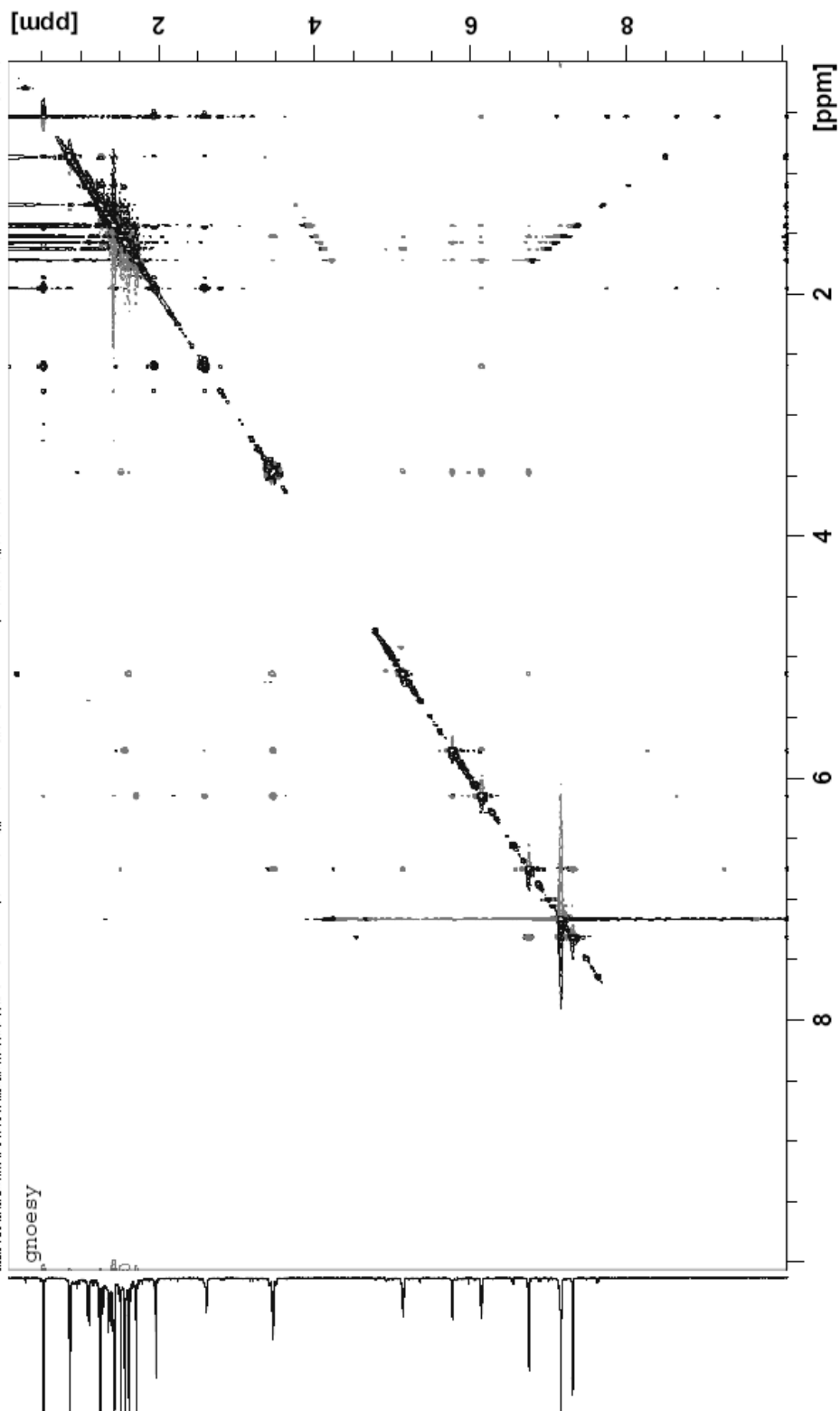


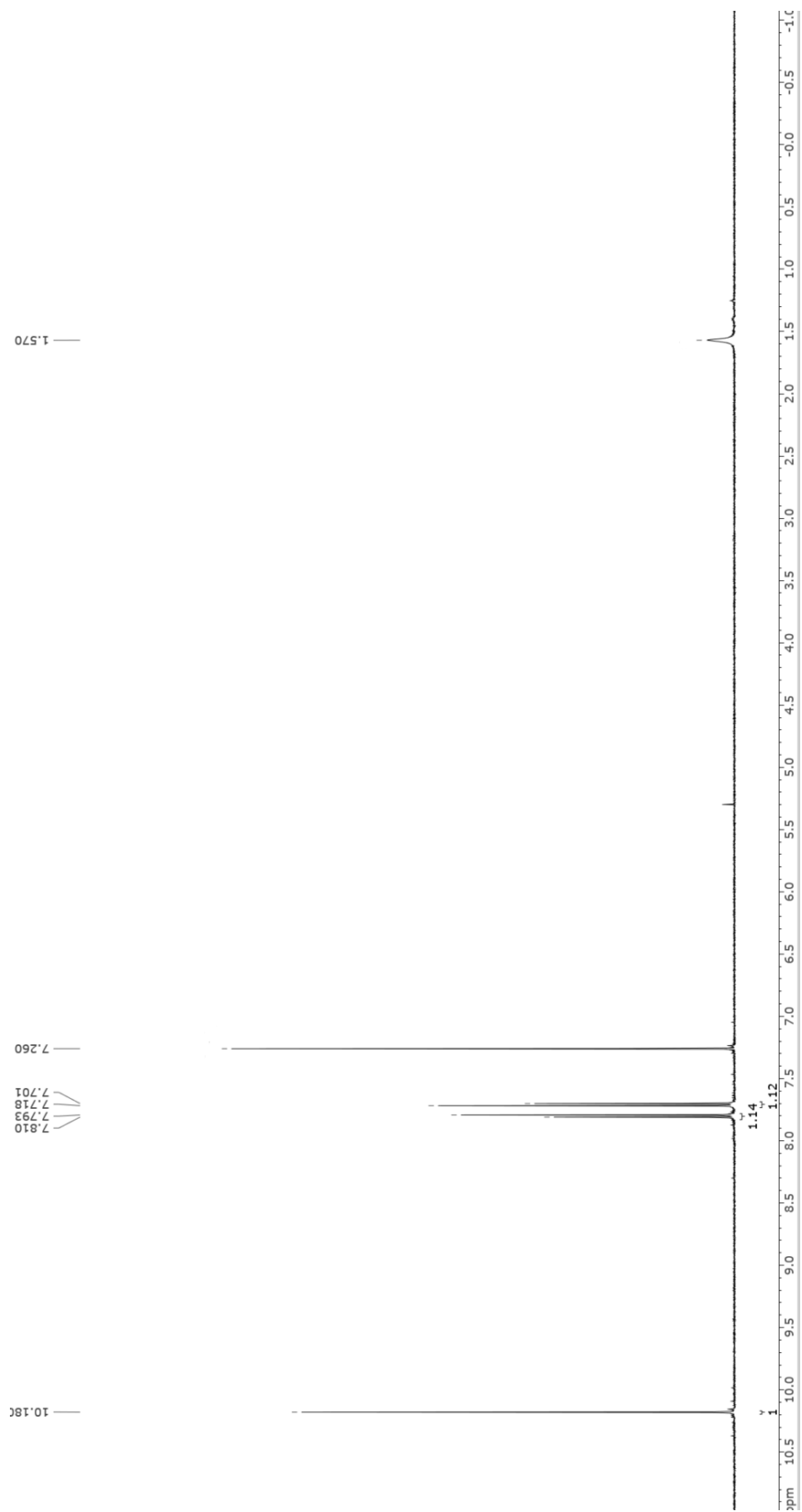
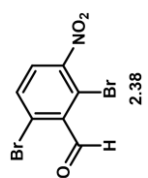
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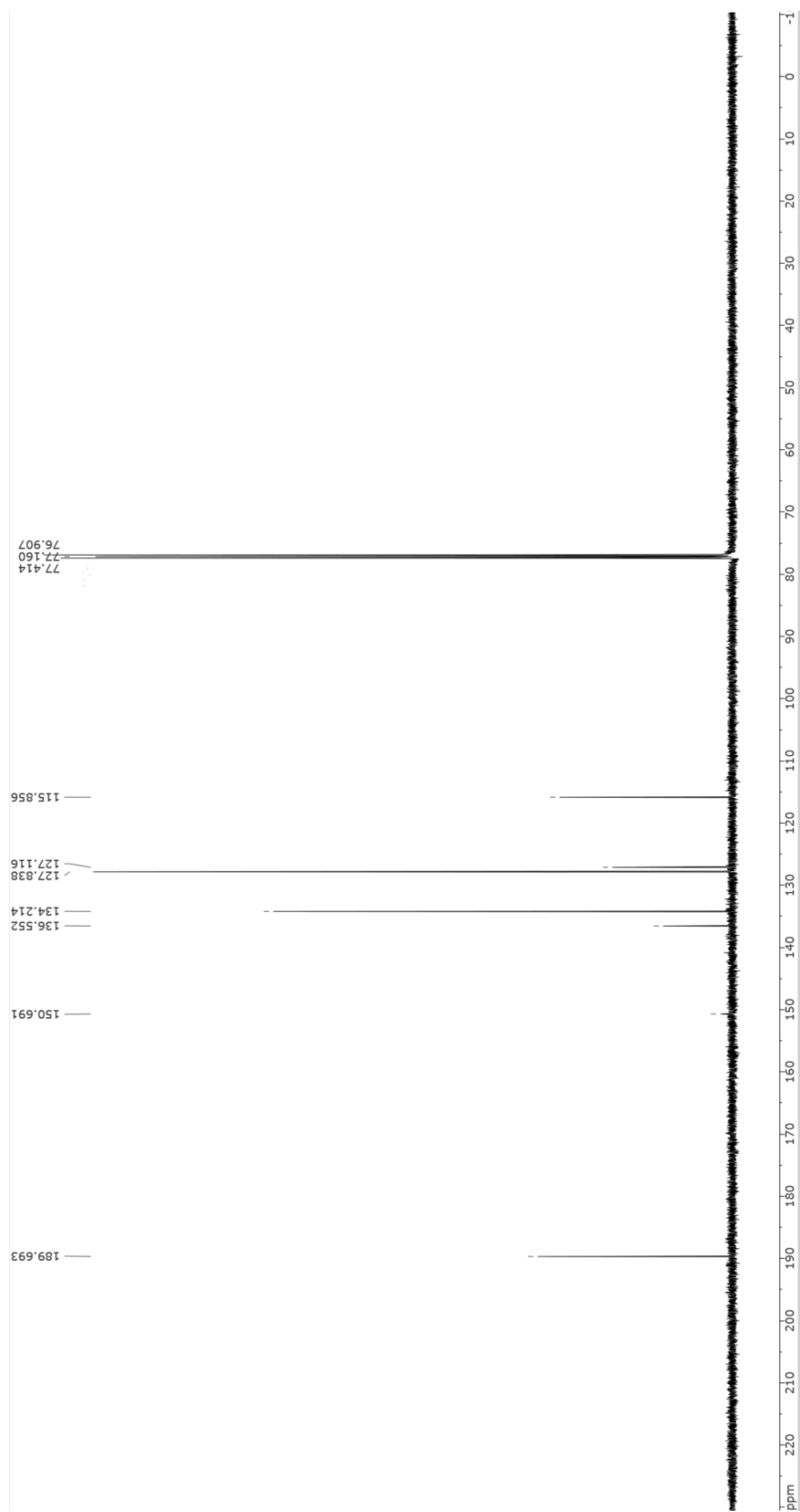
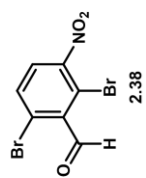


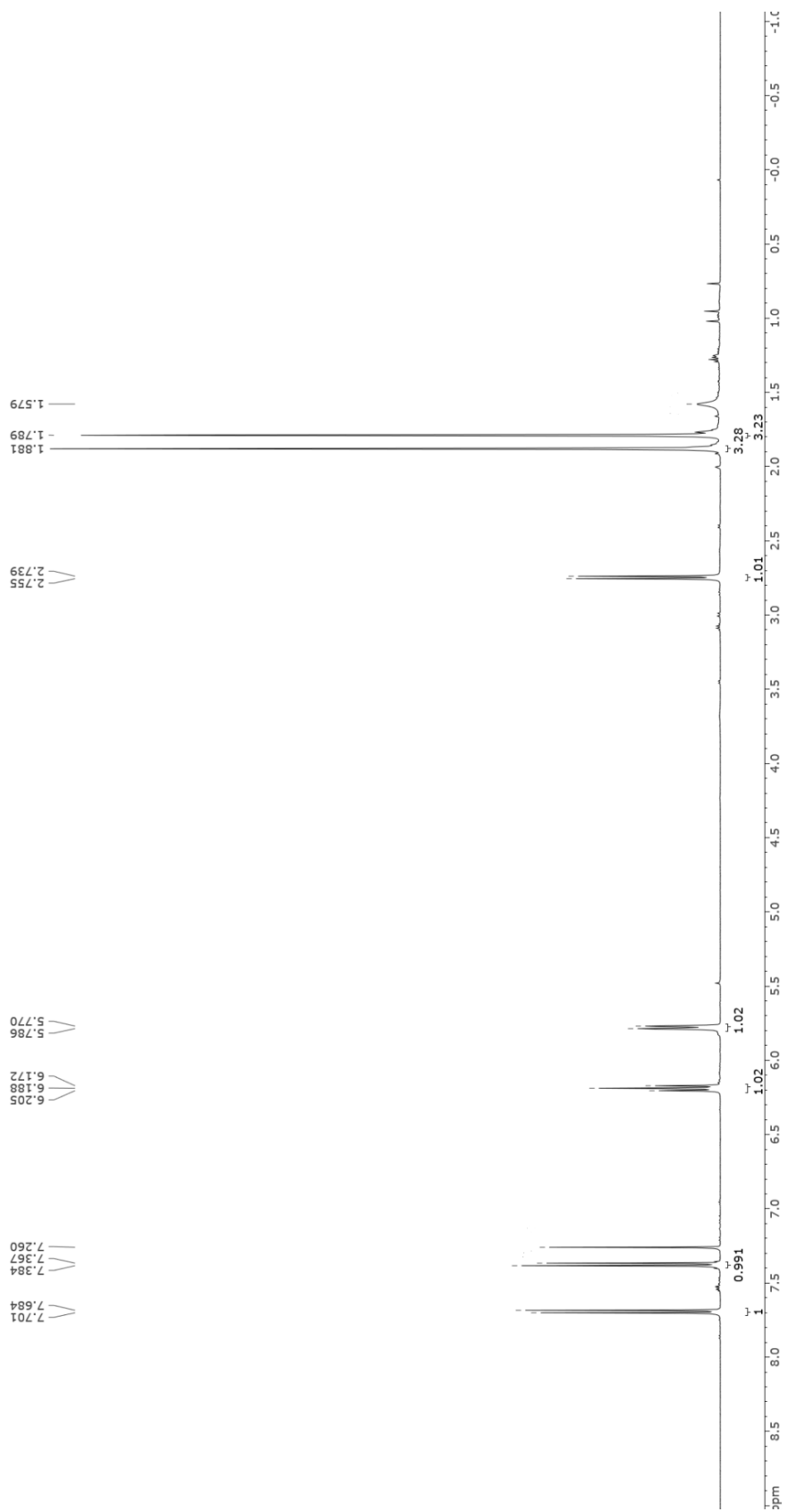
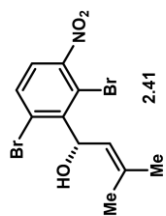


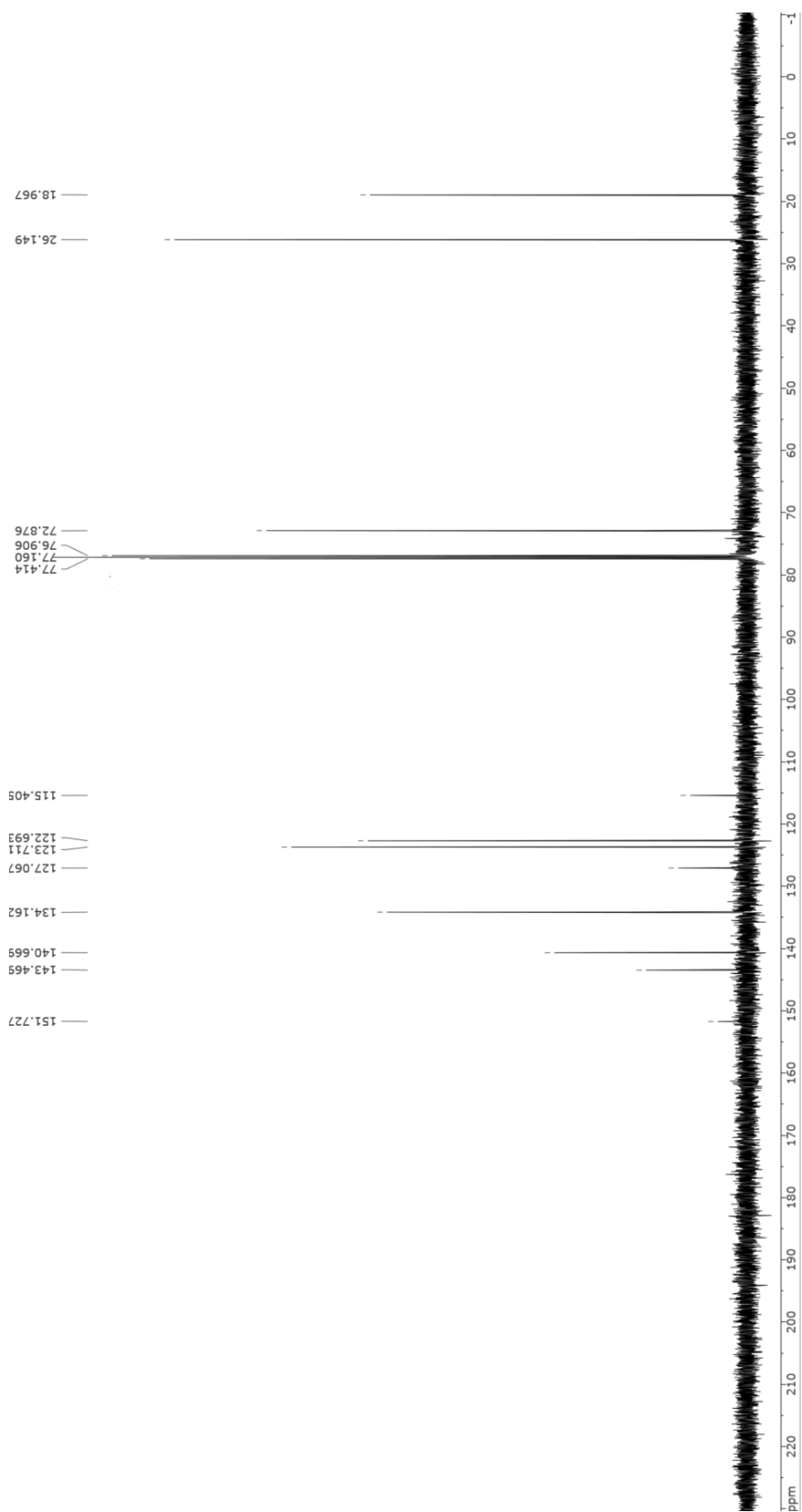
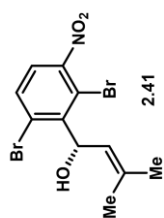
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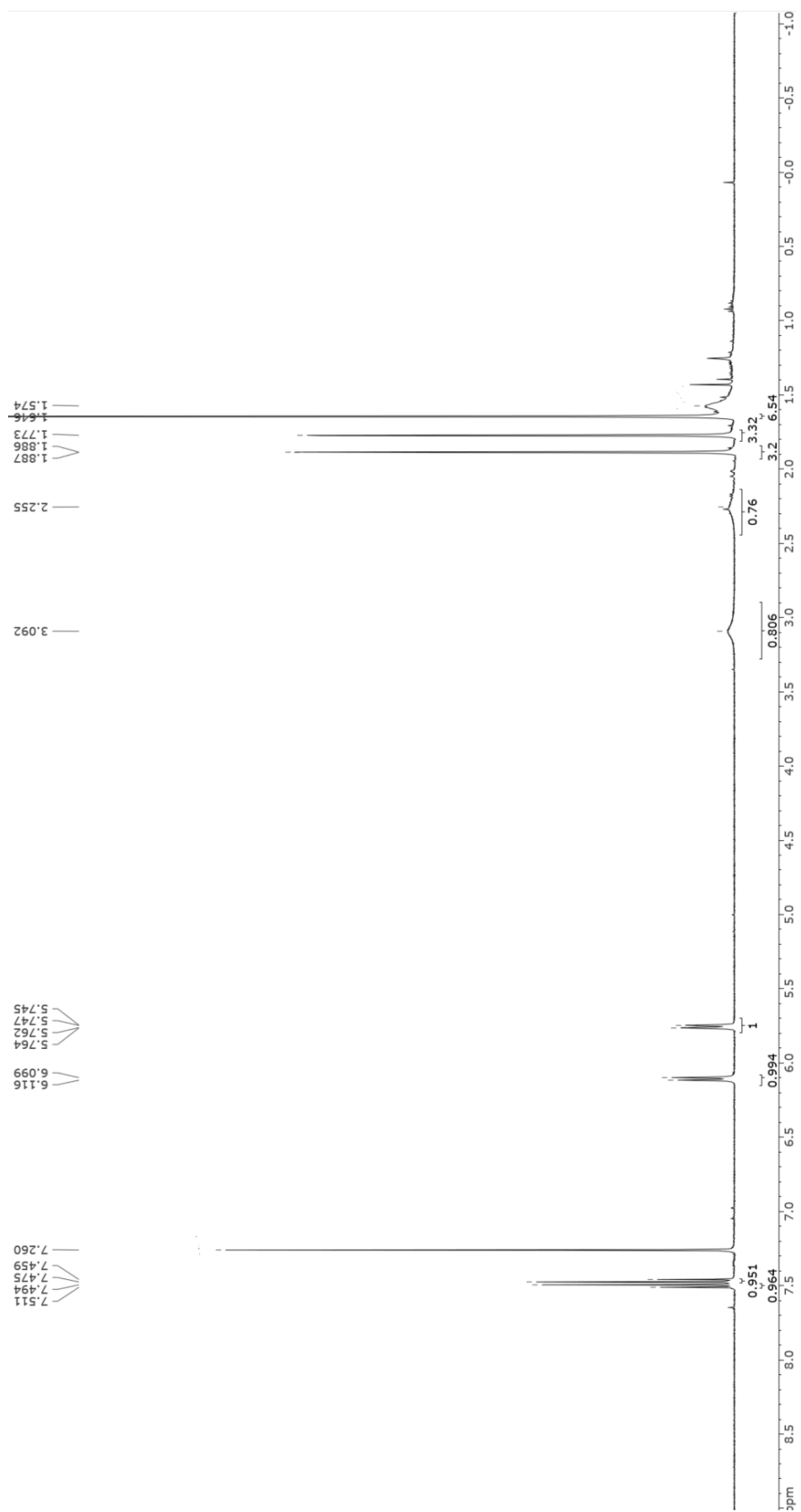
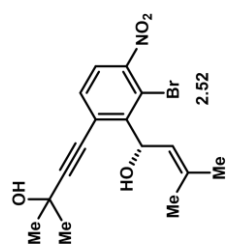


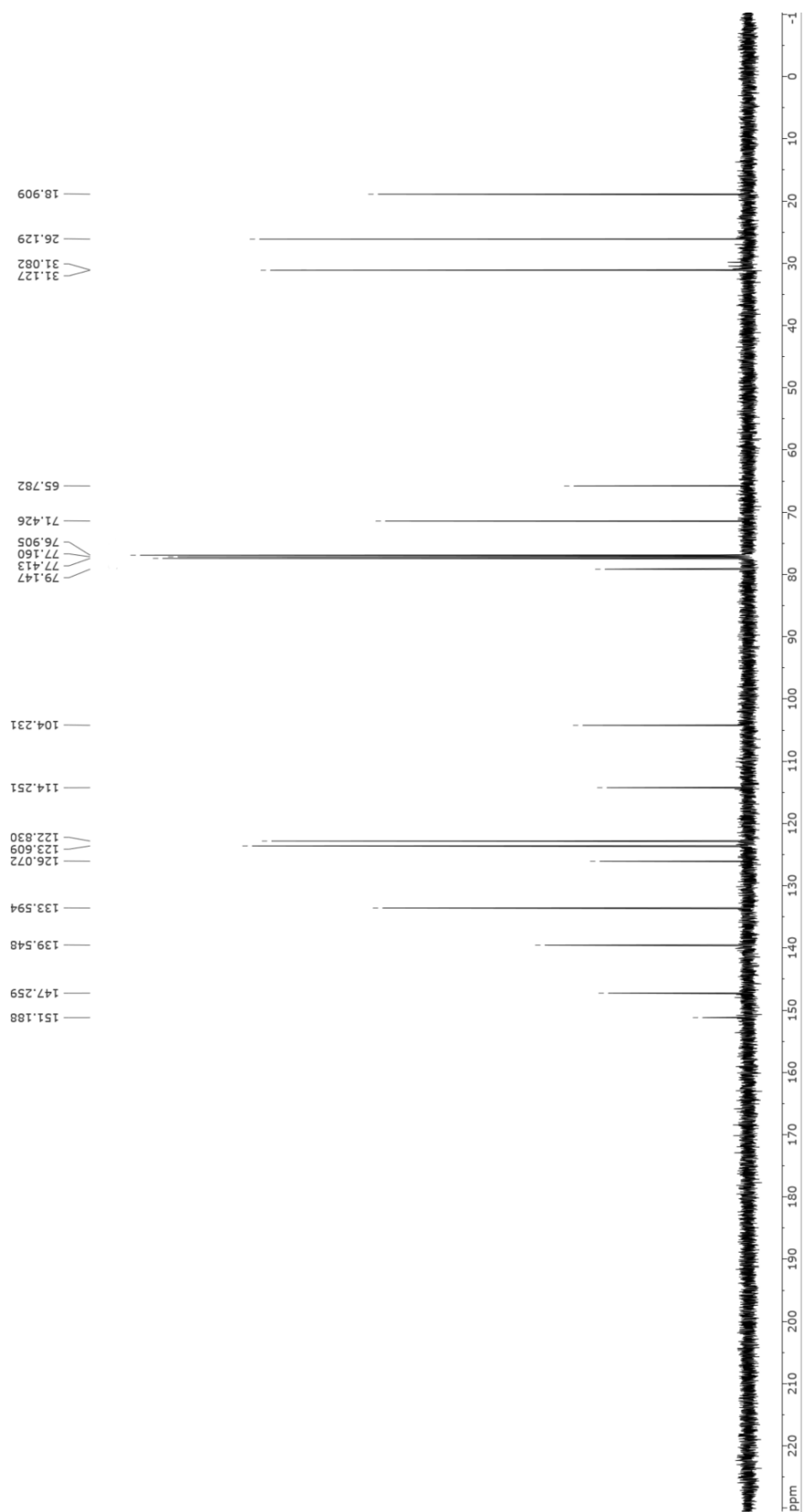
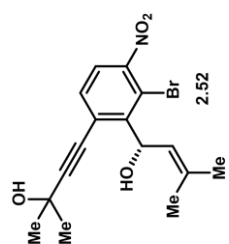


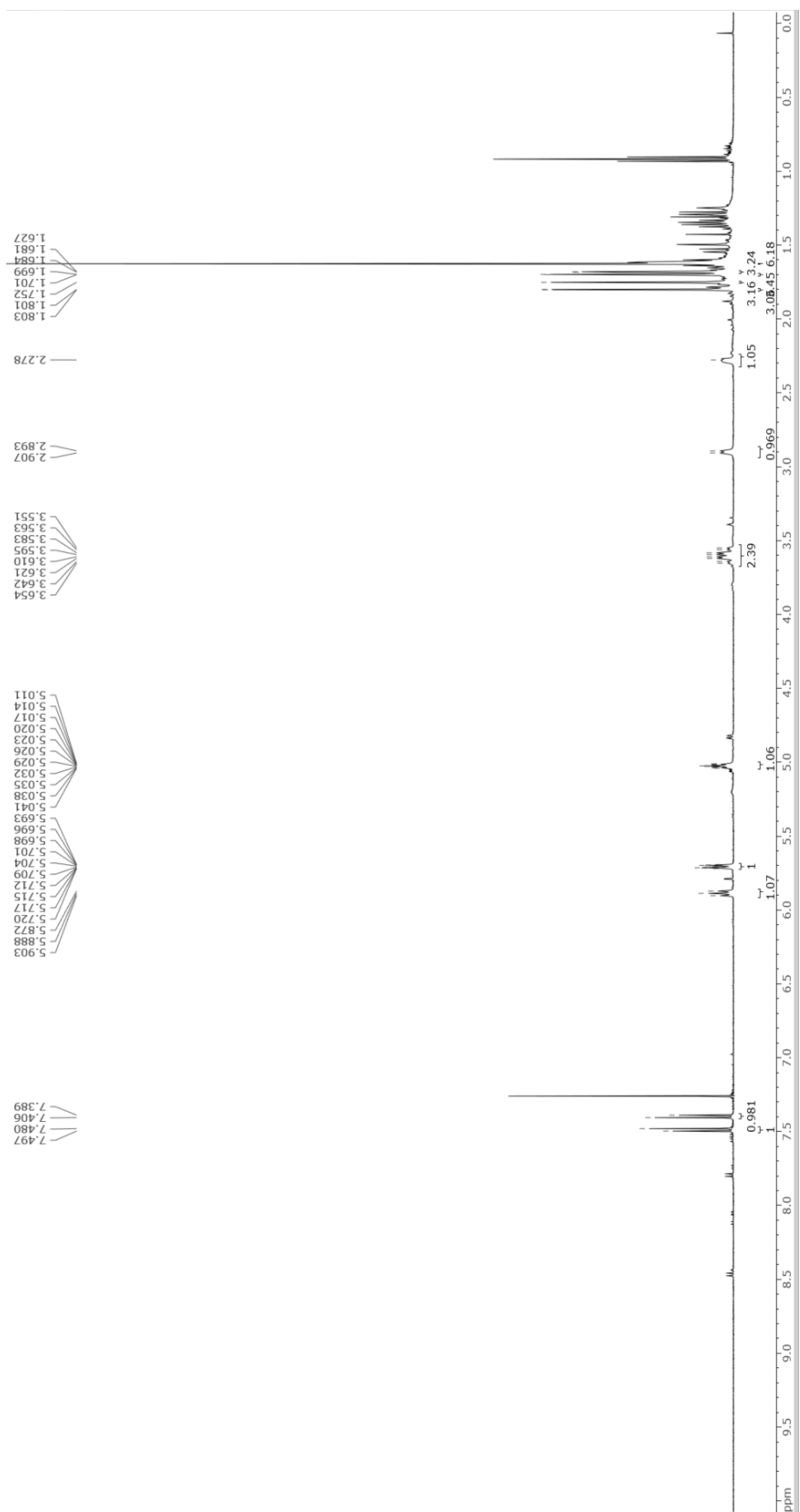
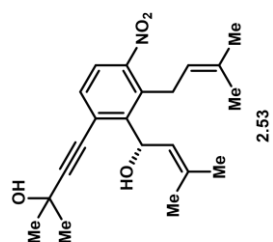


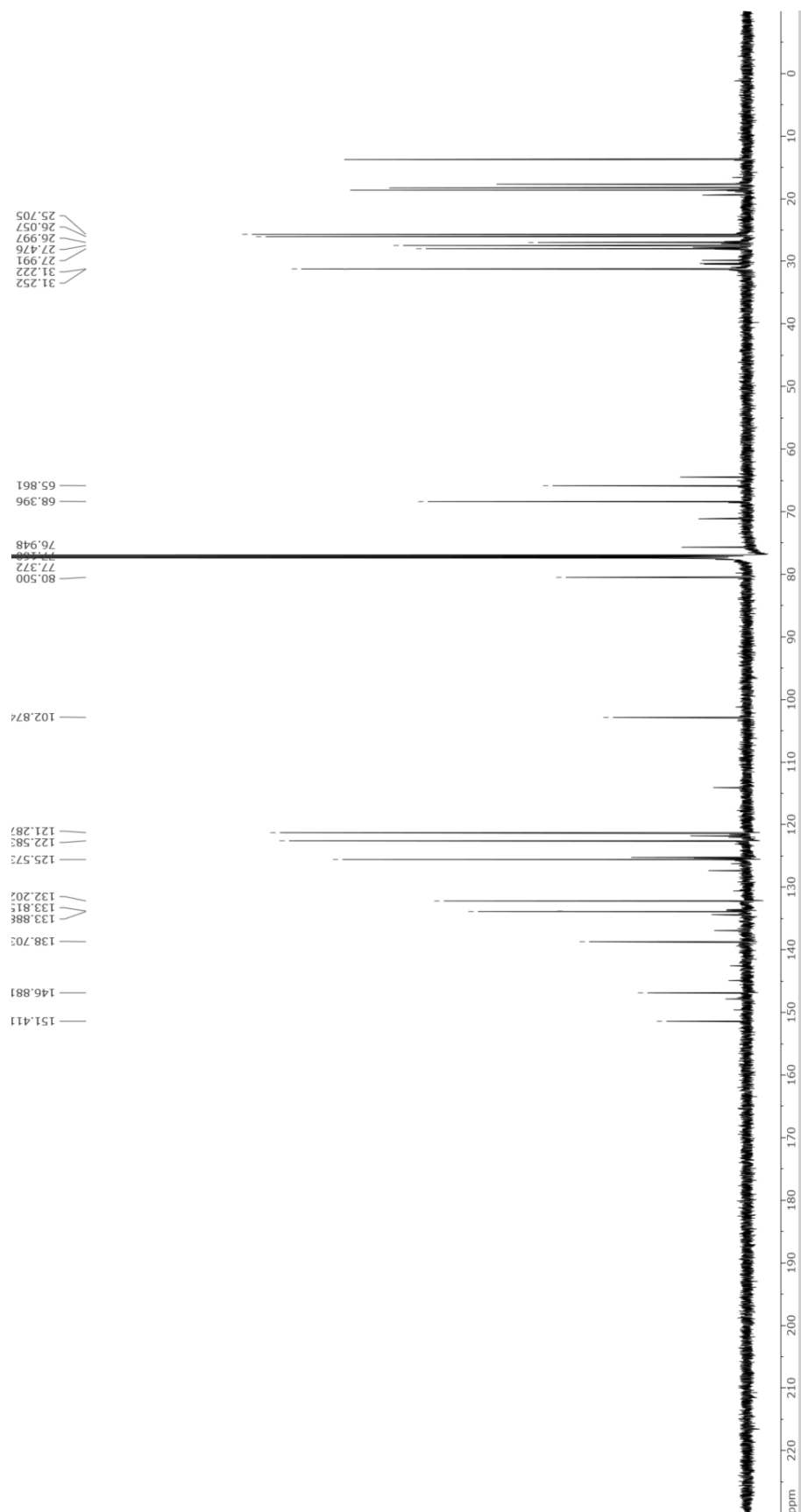
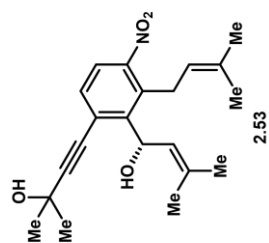


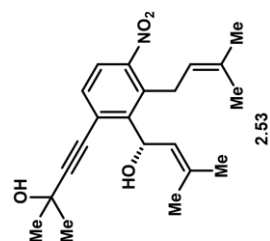




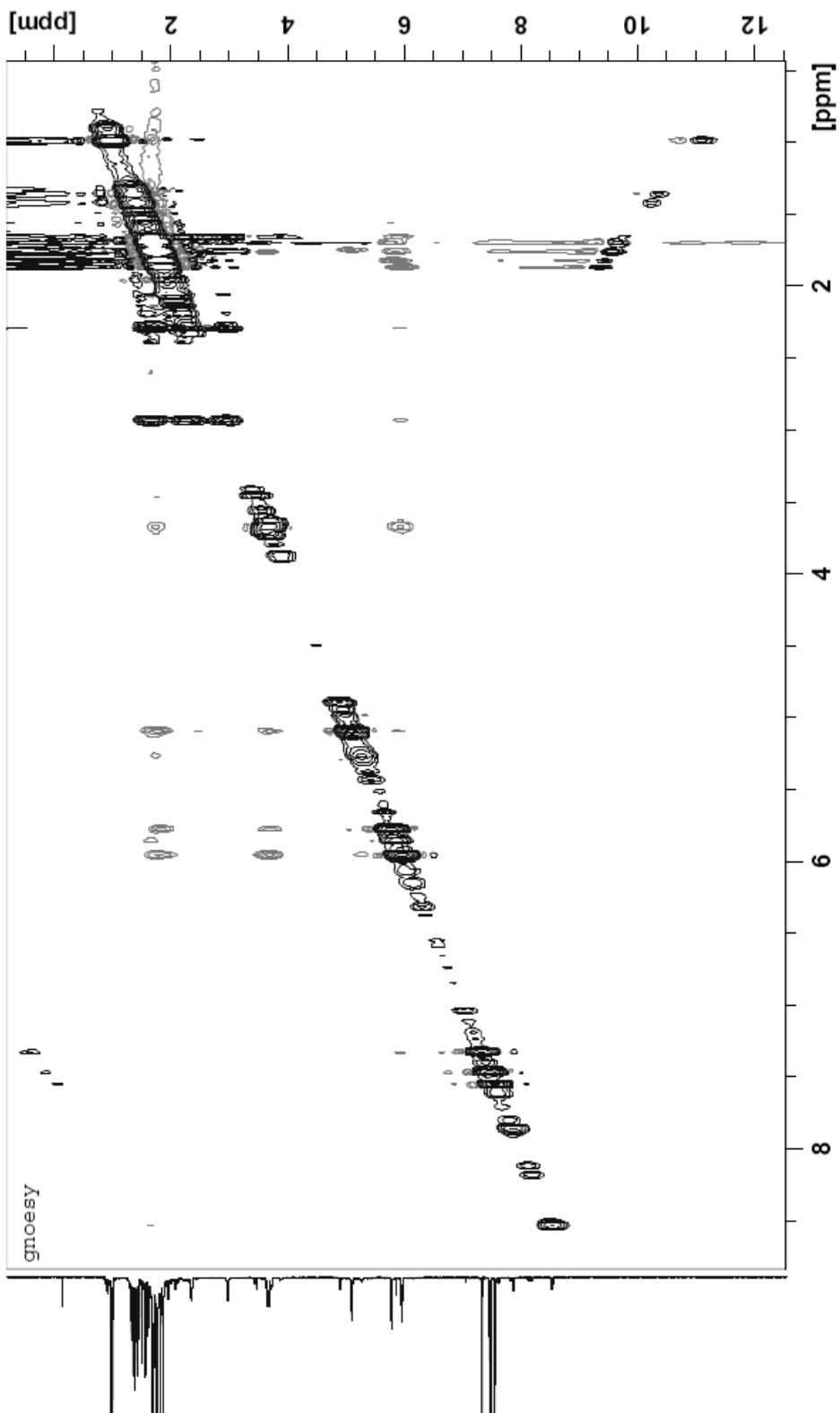


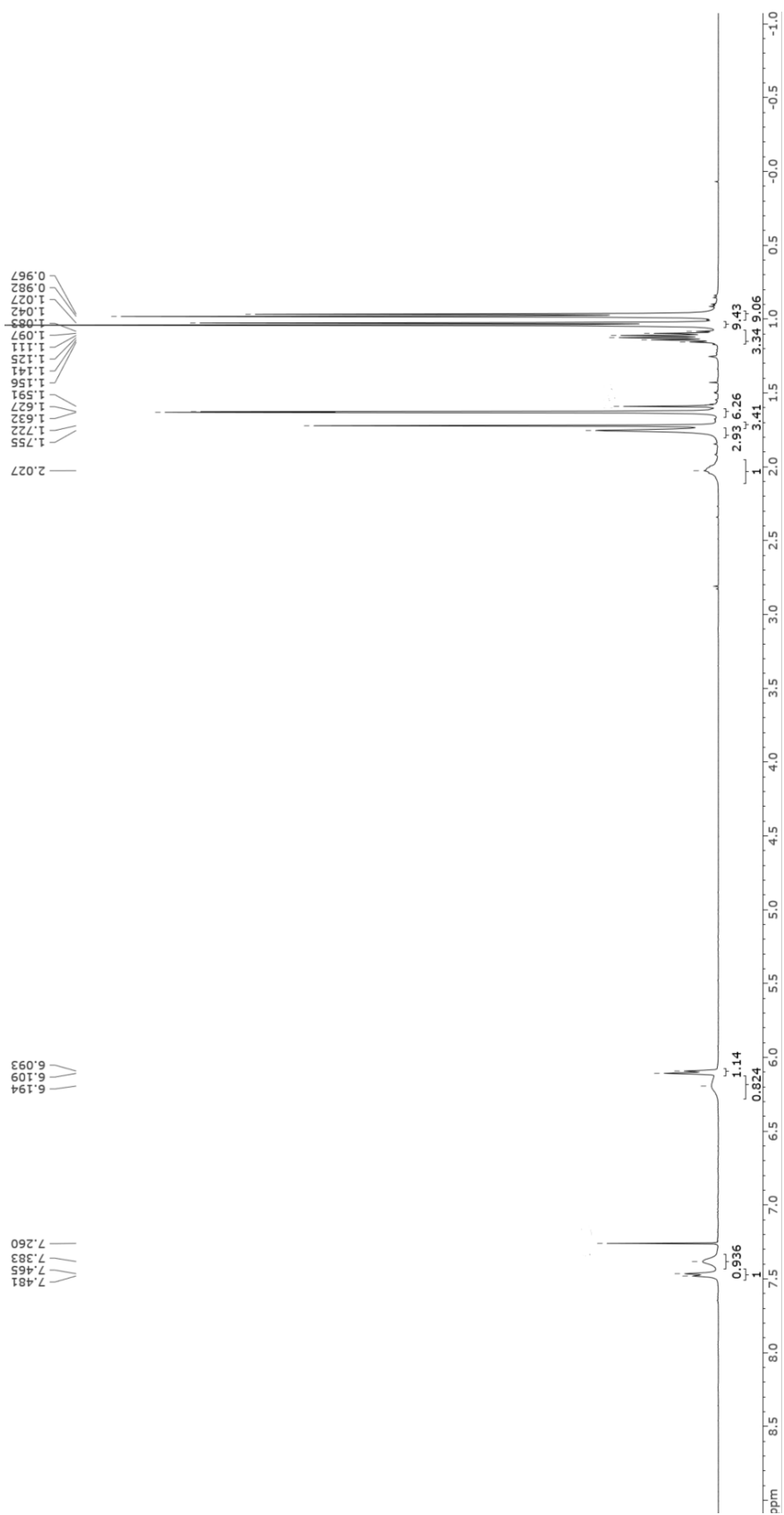
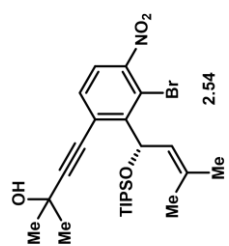


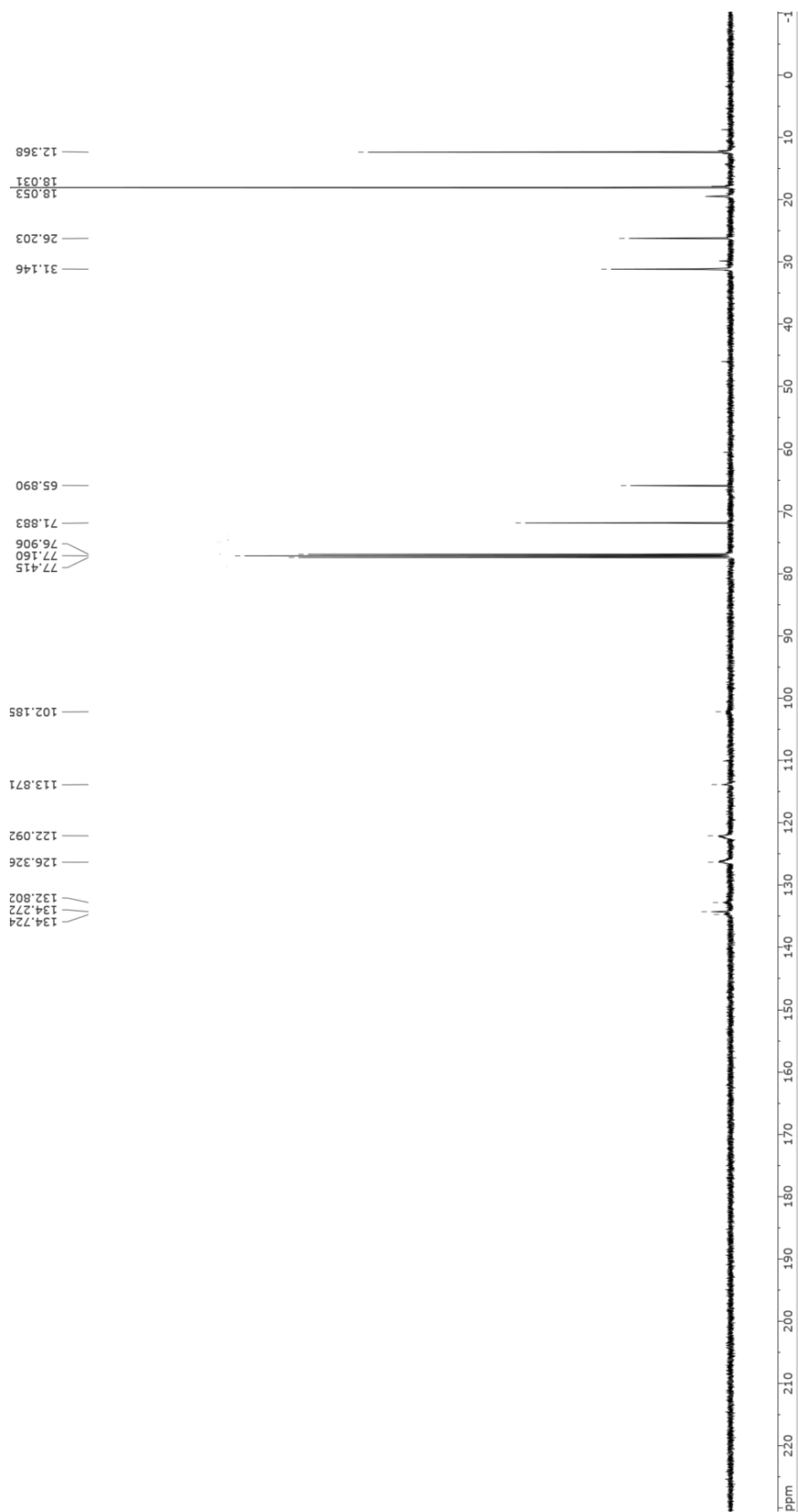
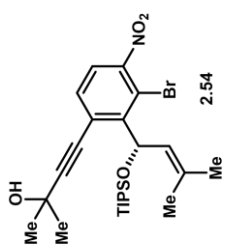


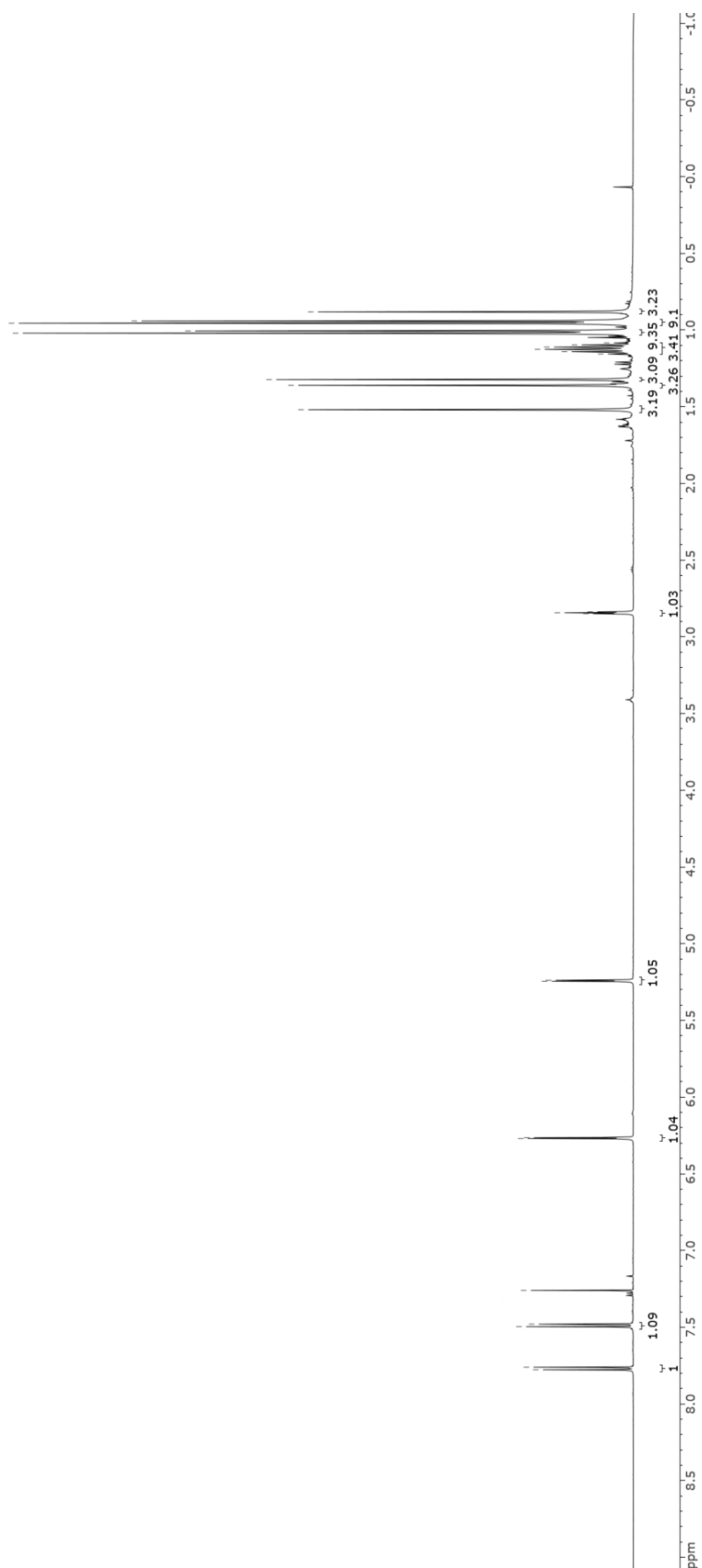
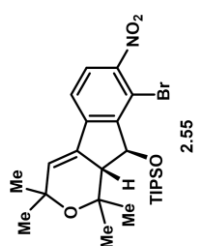


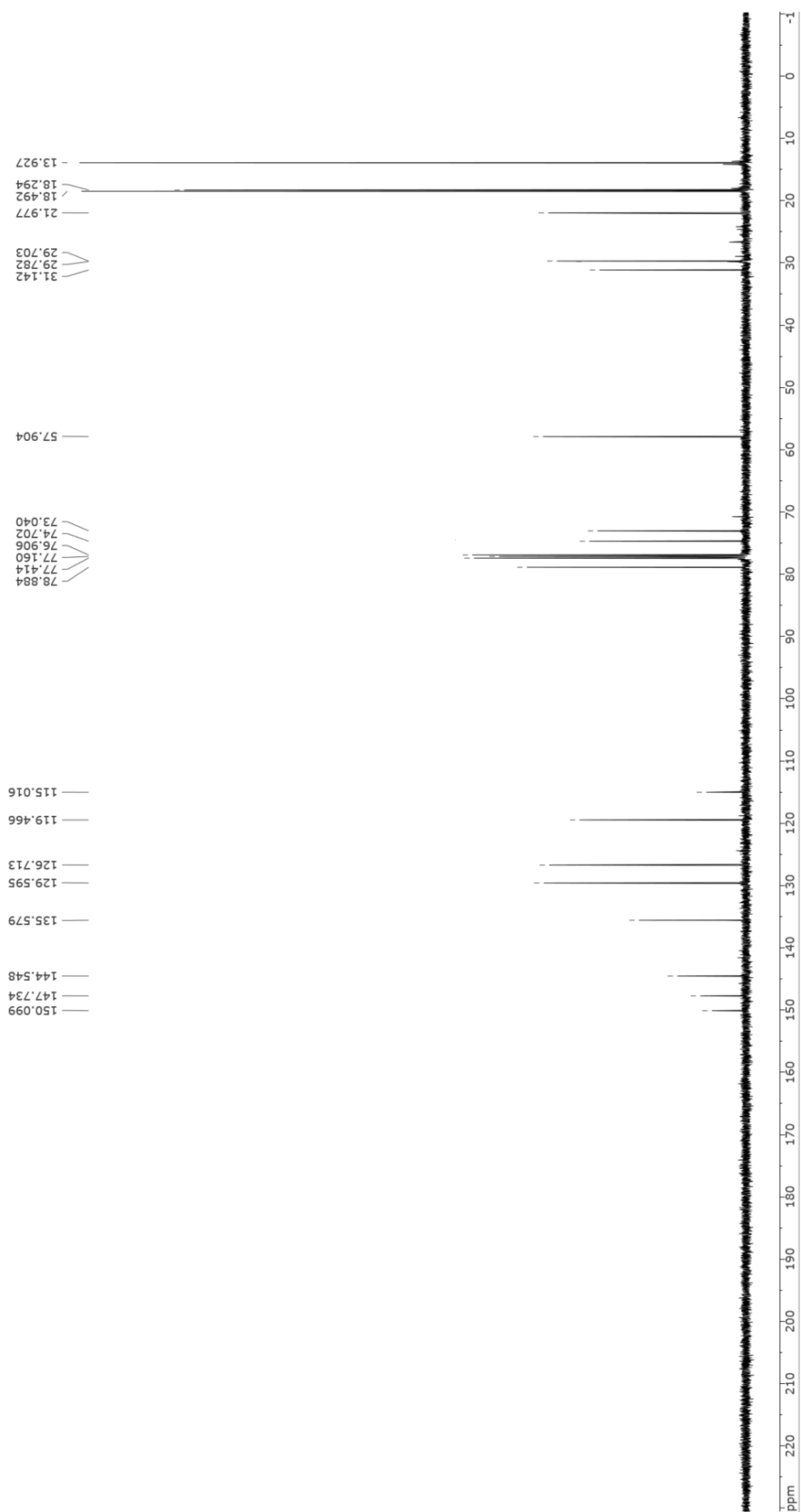
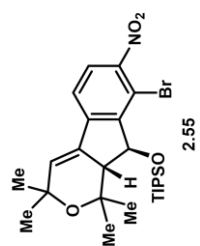
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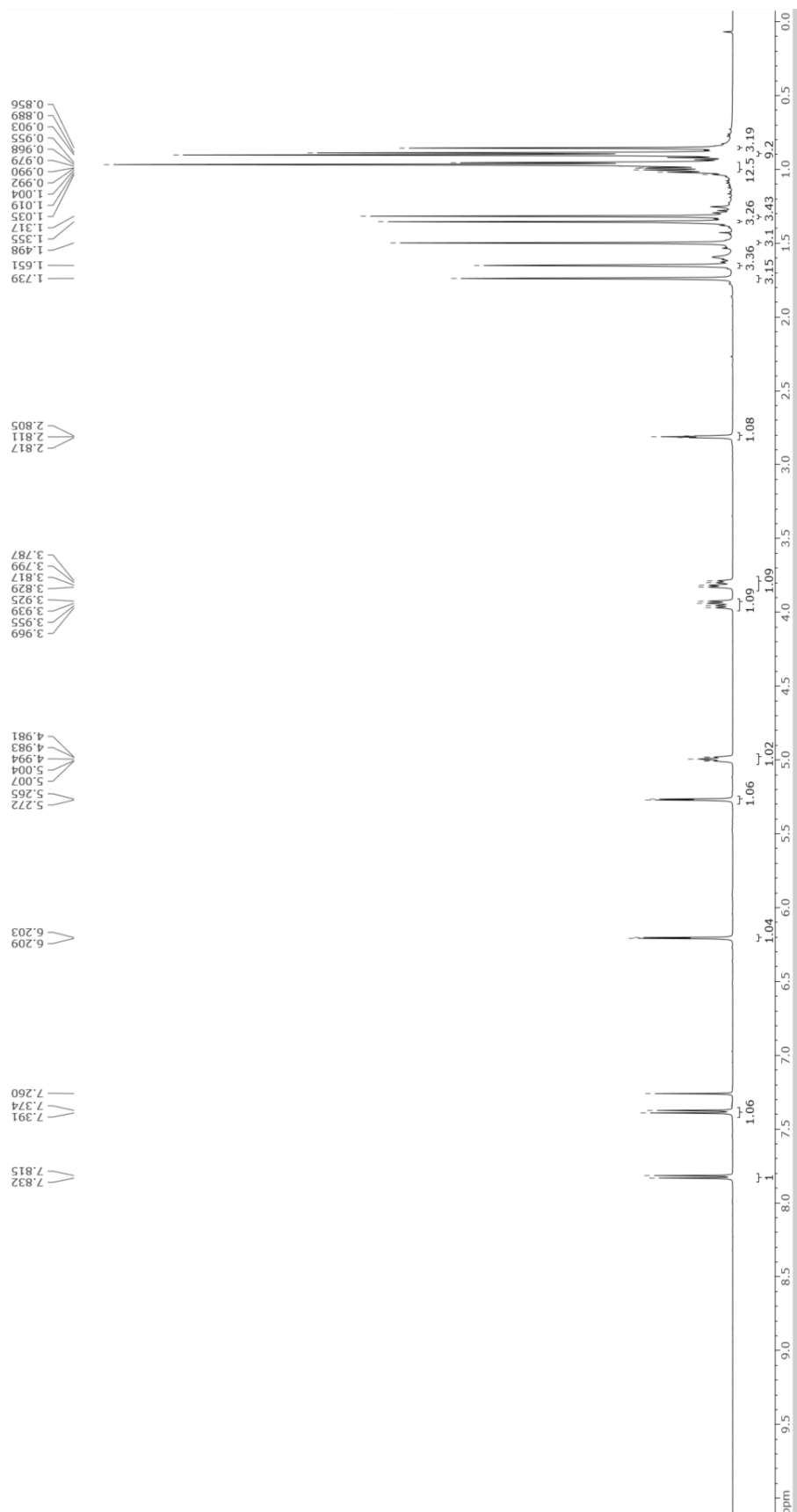
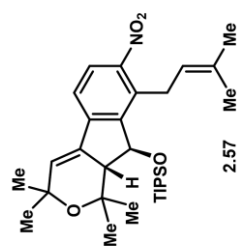


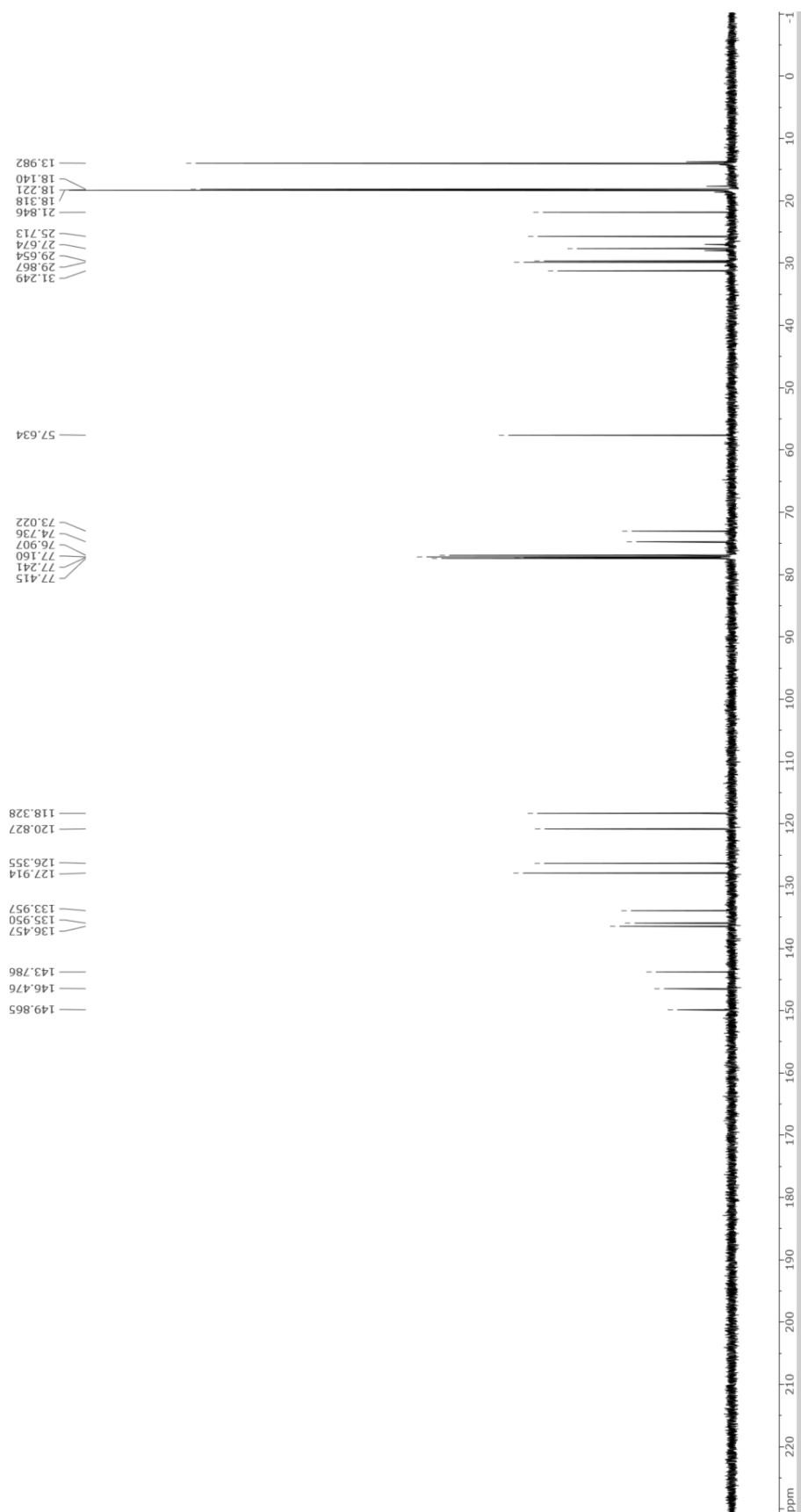
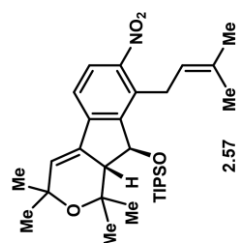


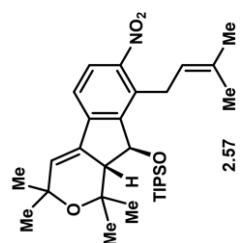




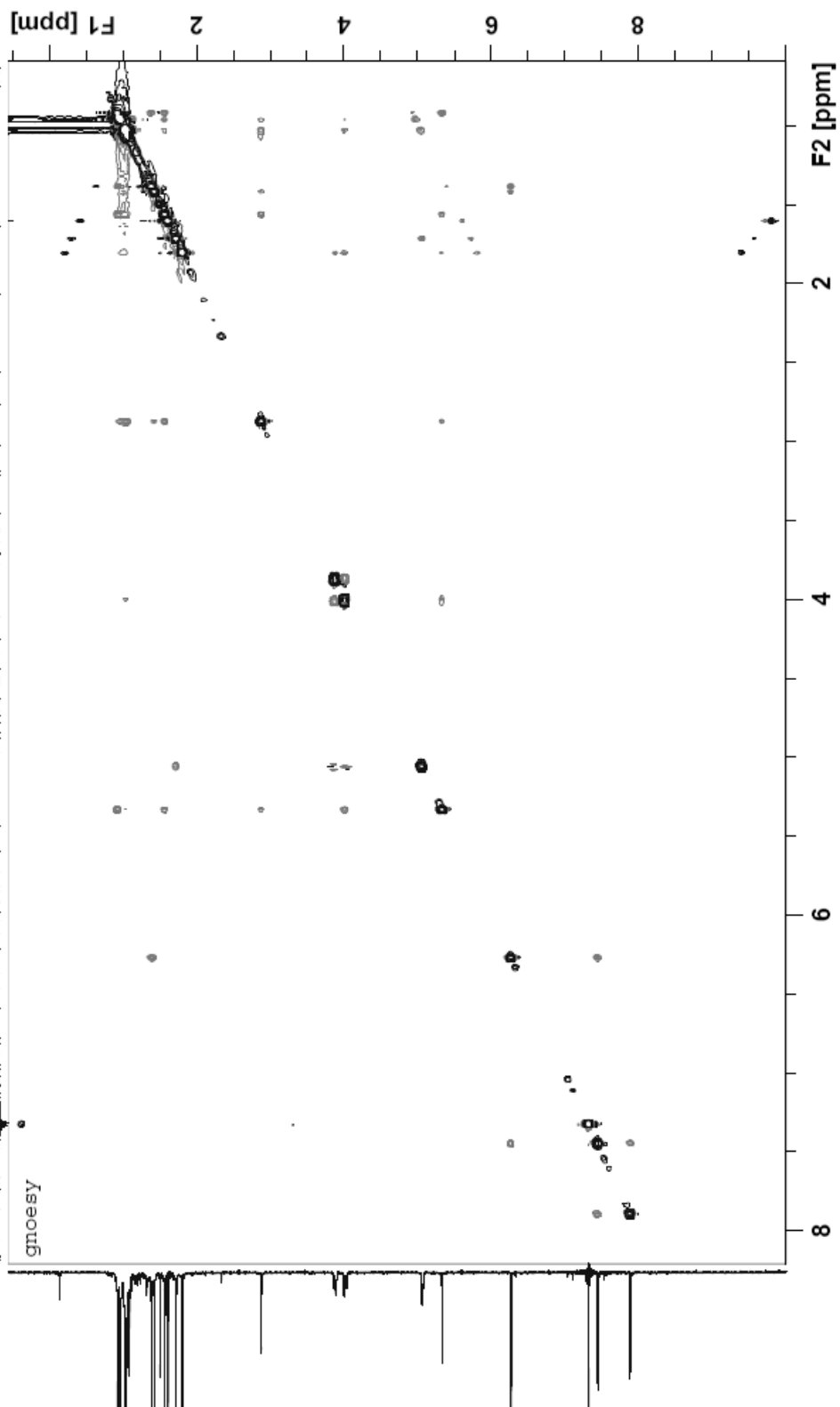


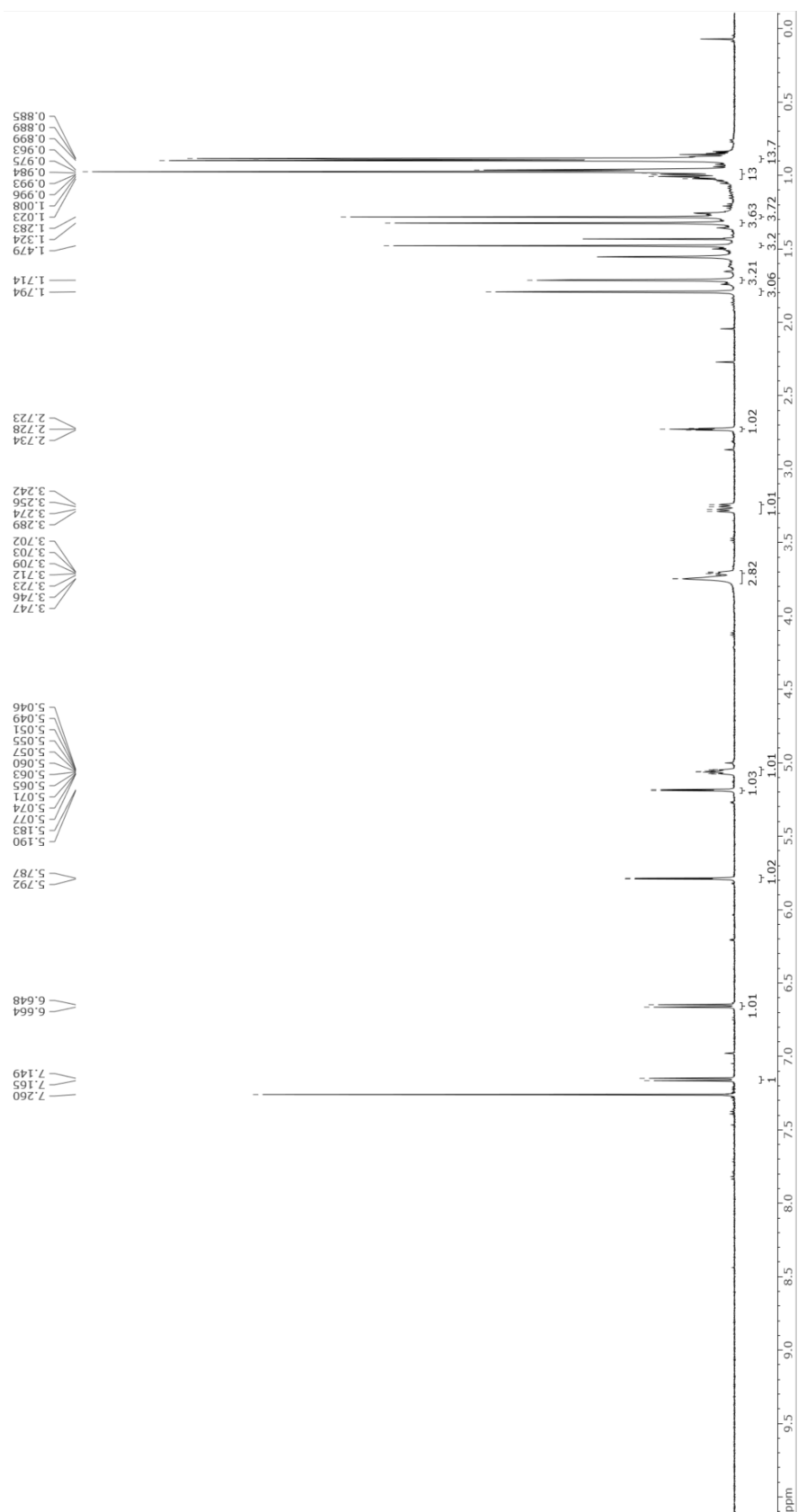
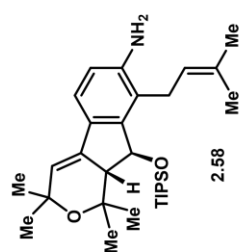


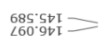




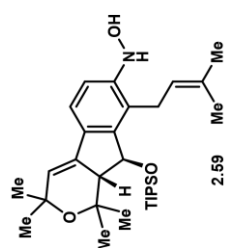
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18.162
14.110

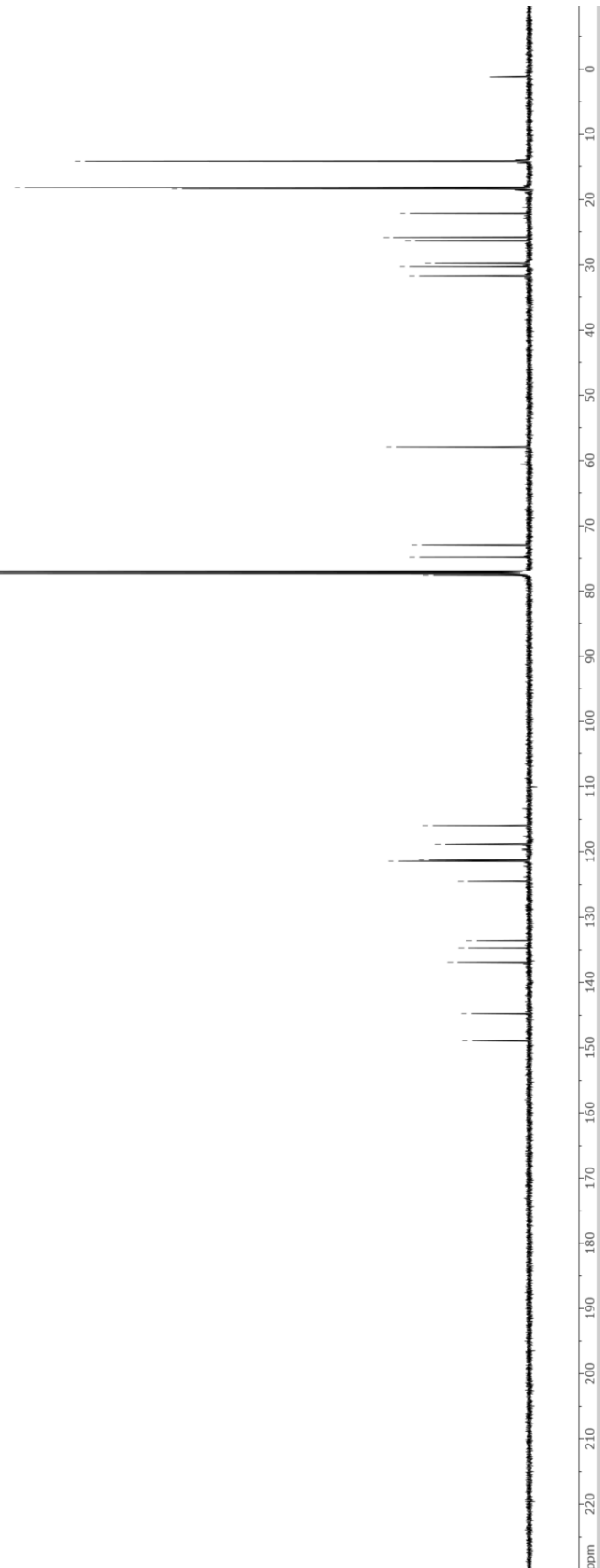
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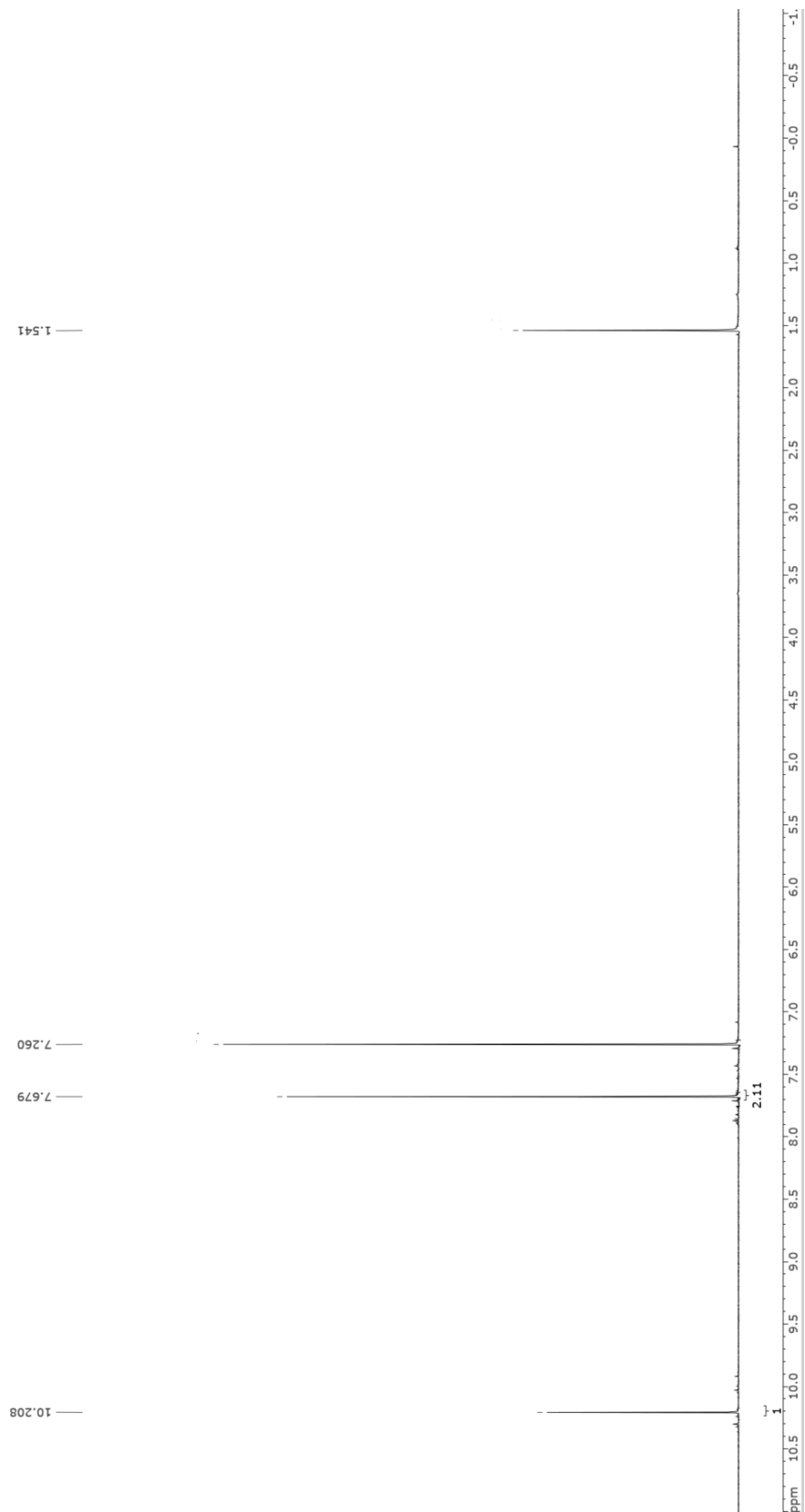
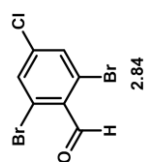
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72.949

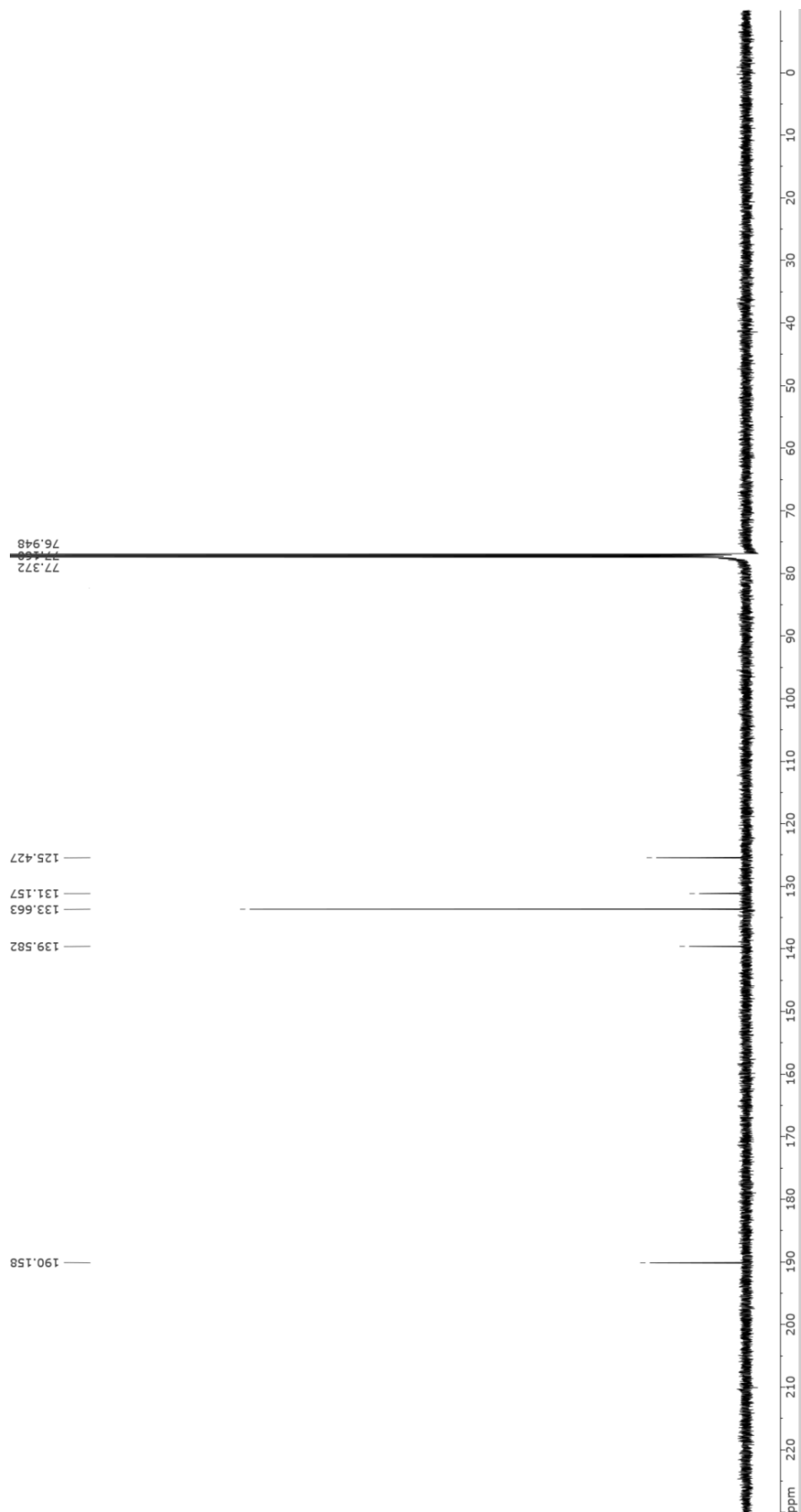
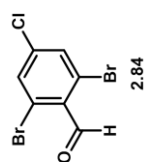
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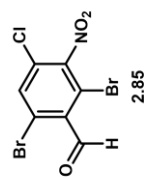
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133.606

144.786
148.961









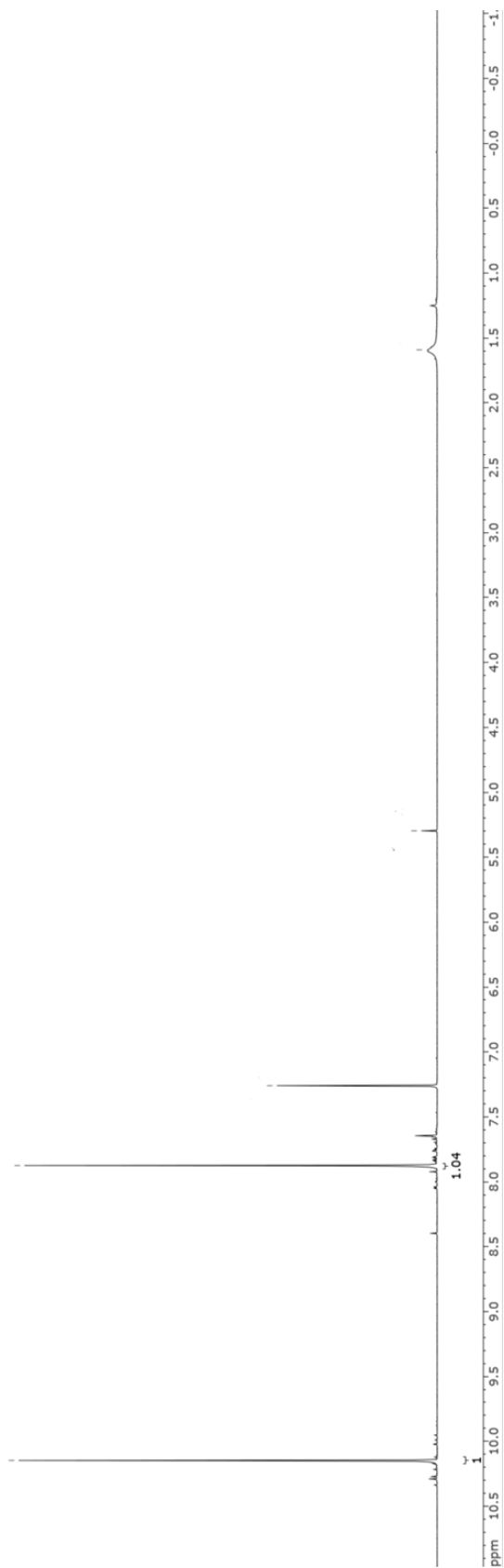
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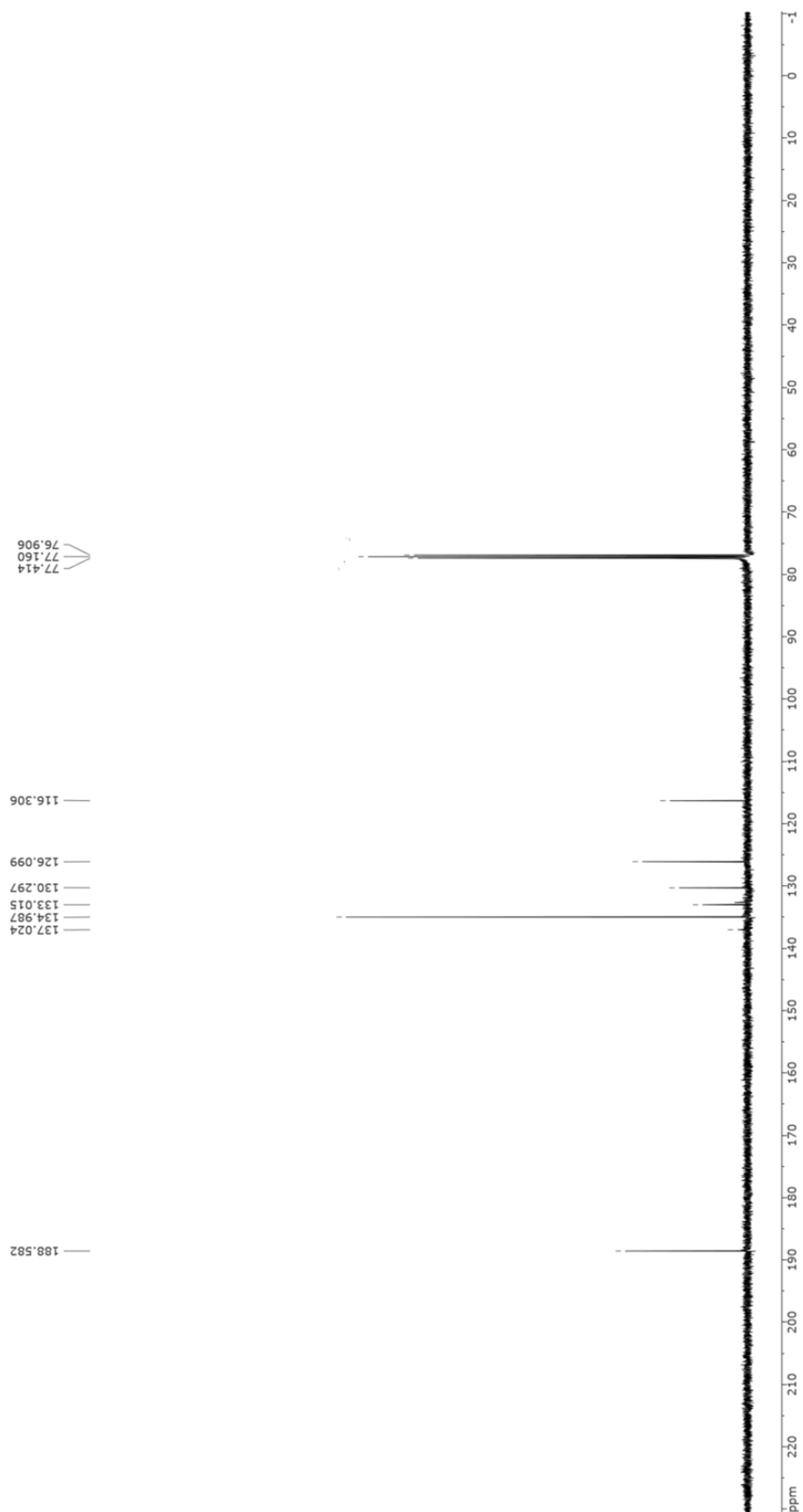
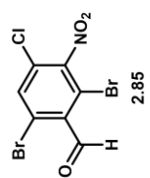
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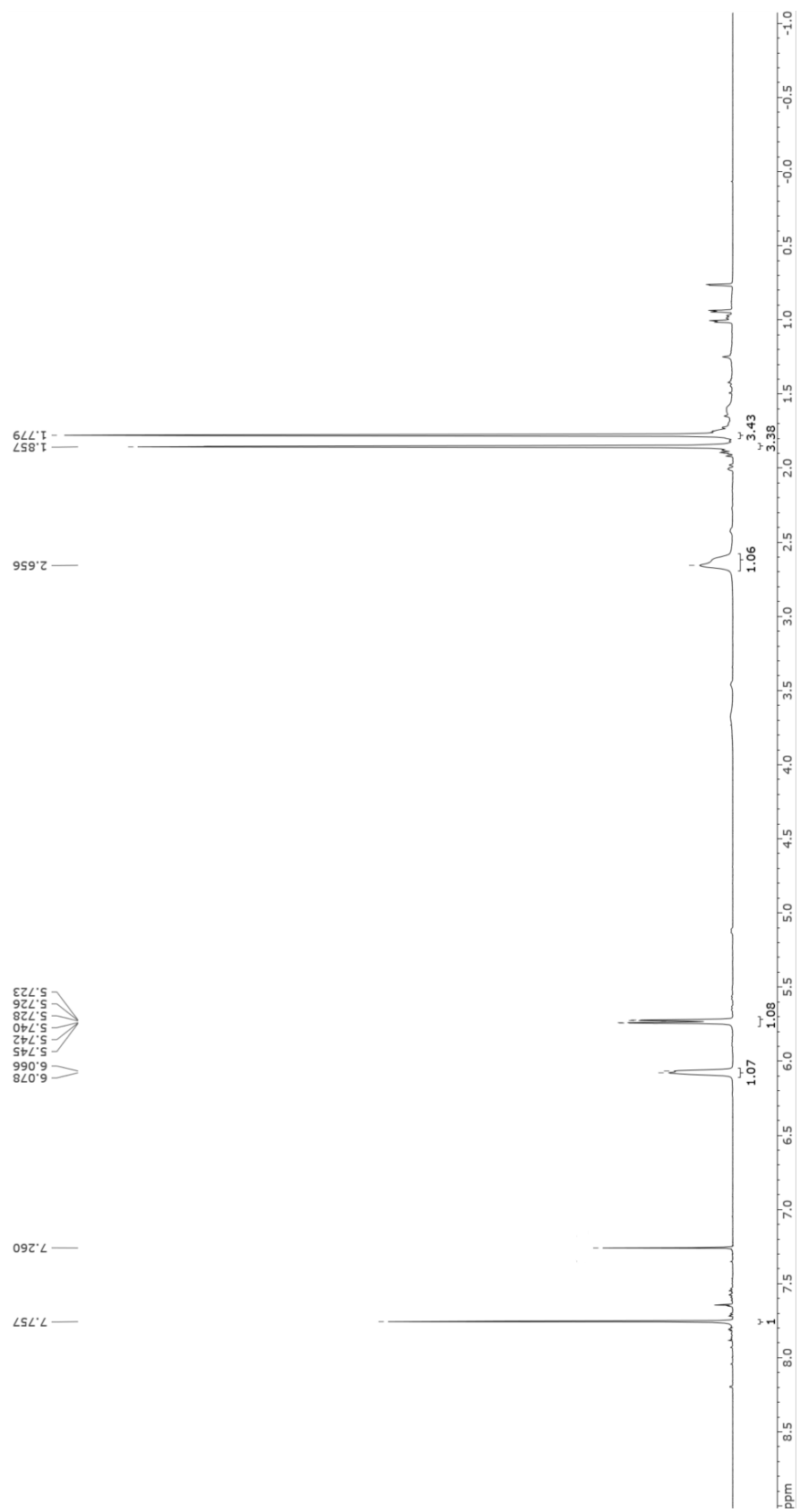
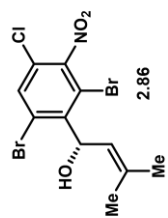
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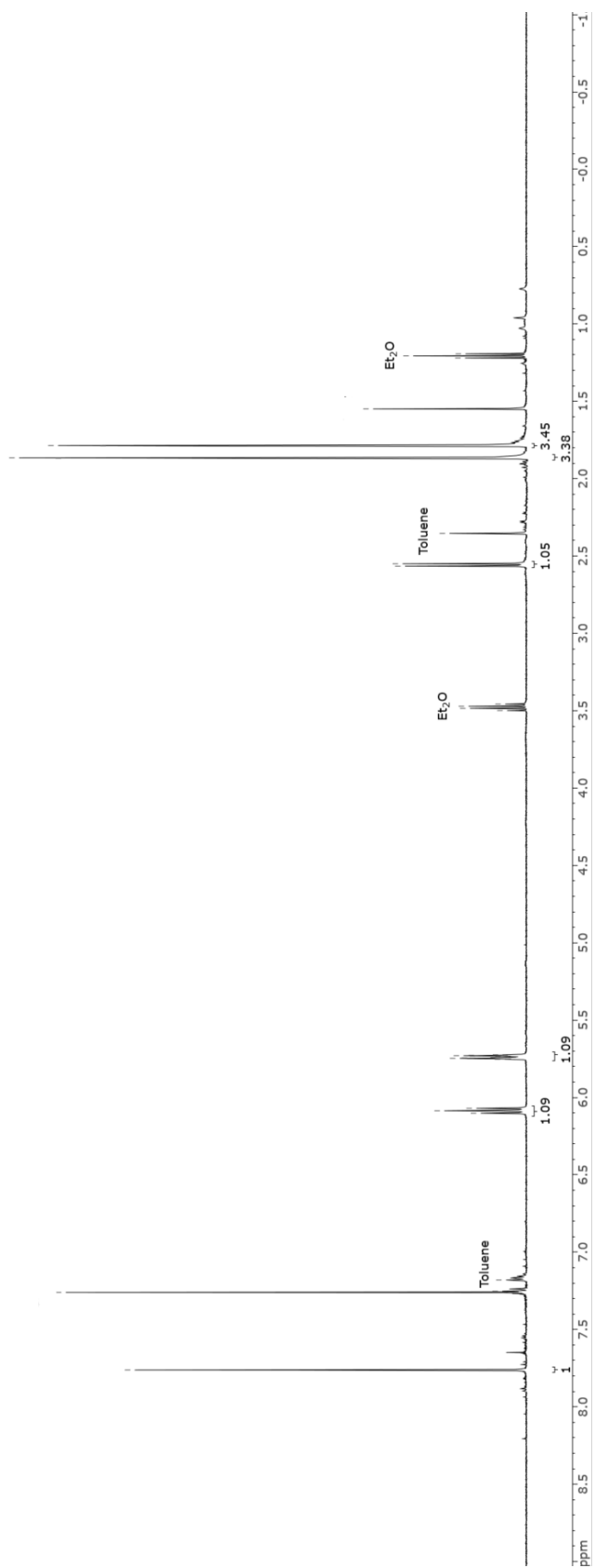
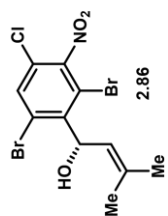
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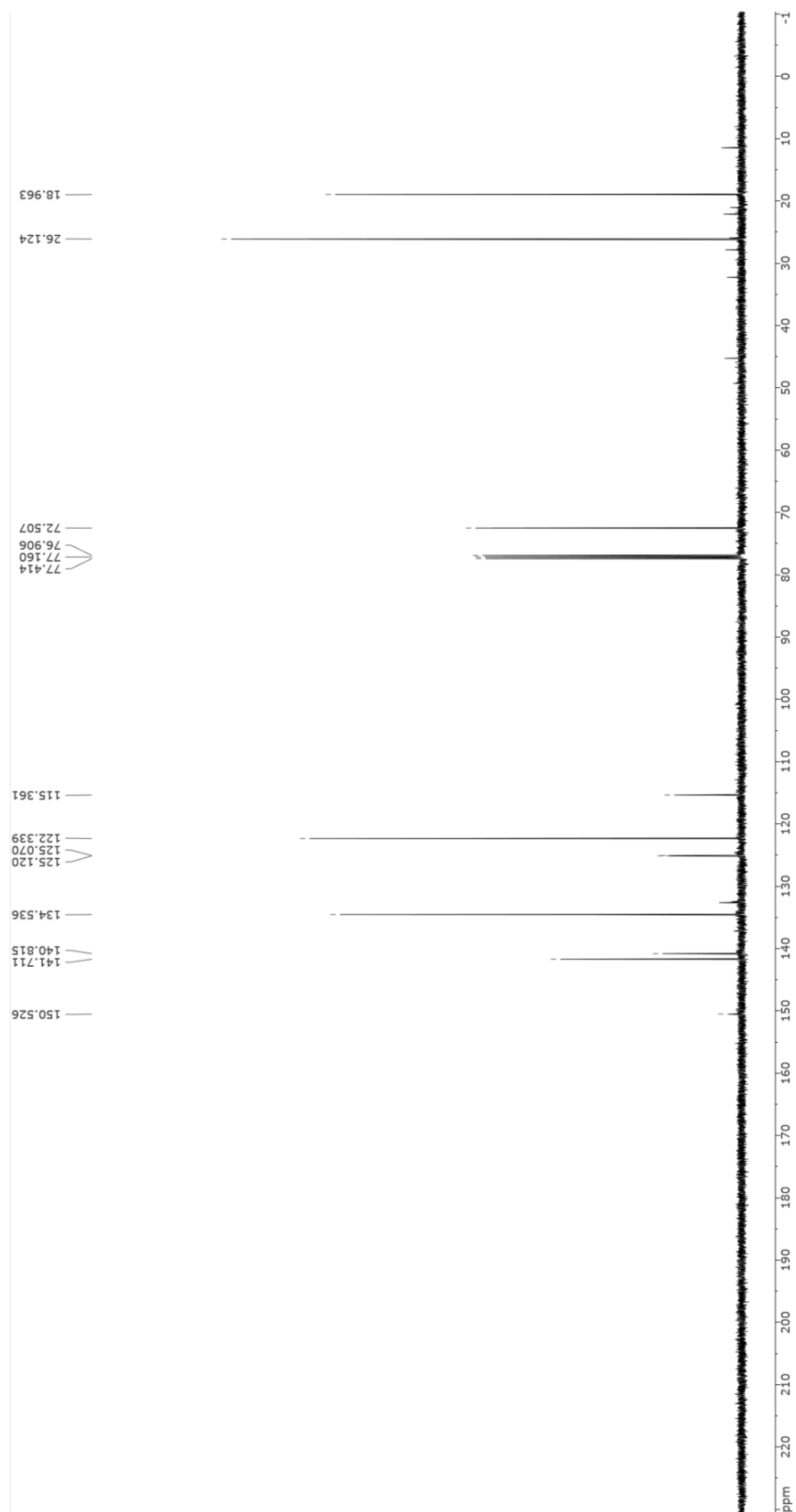
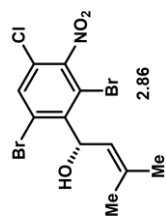
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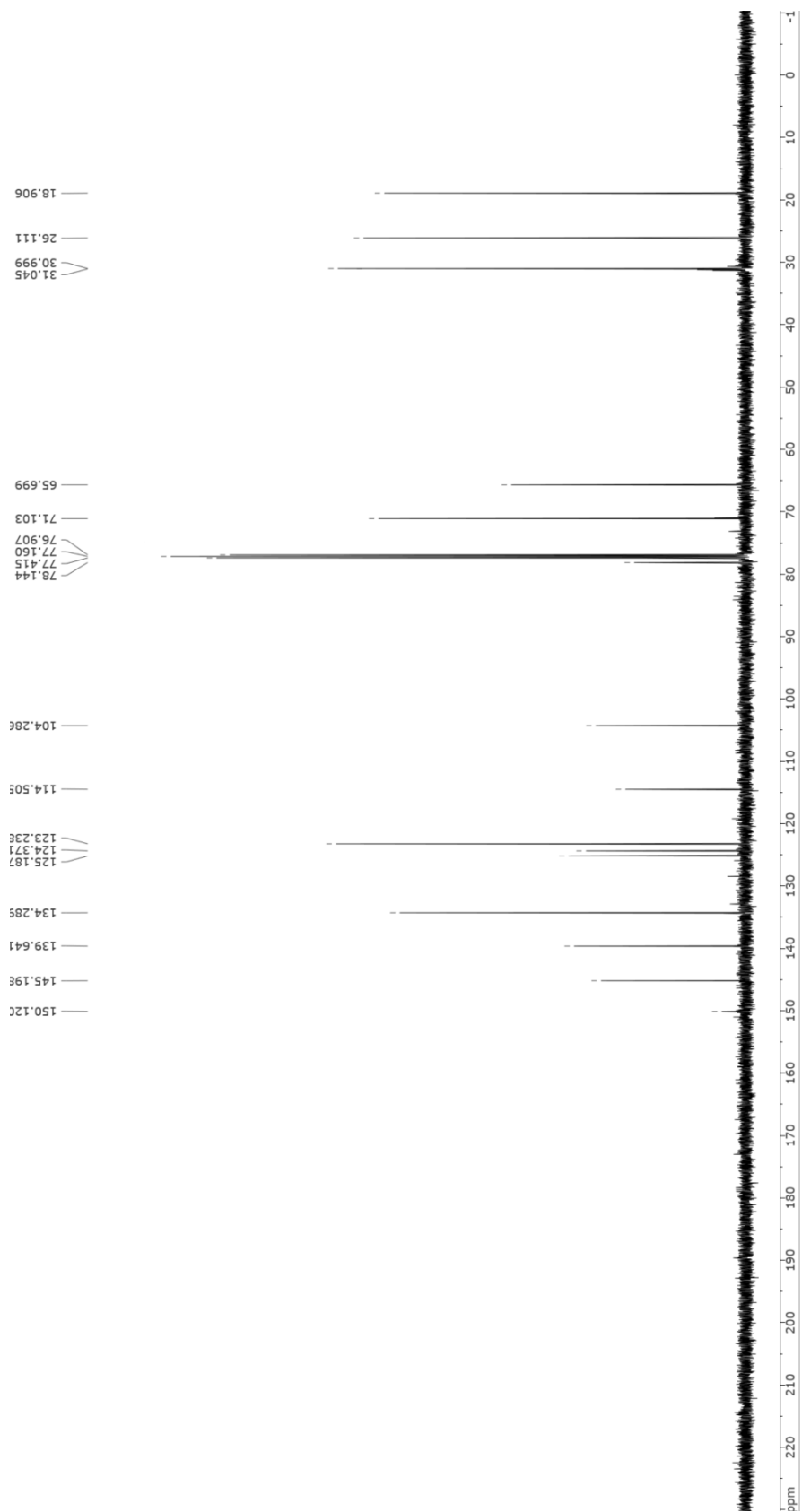
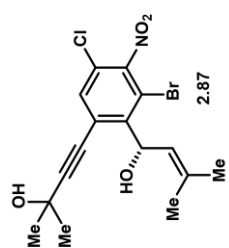


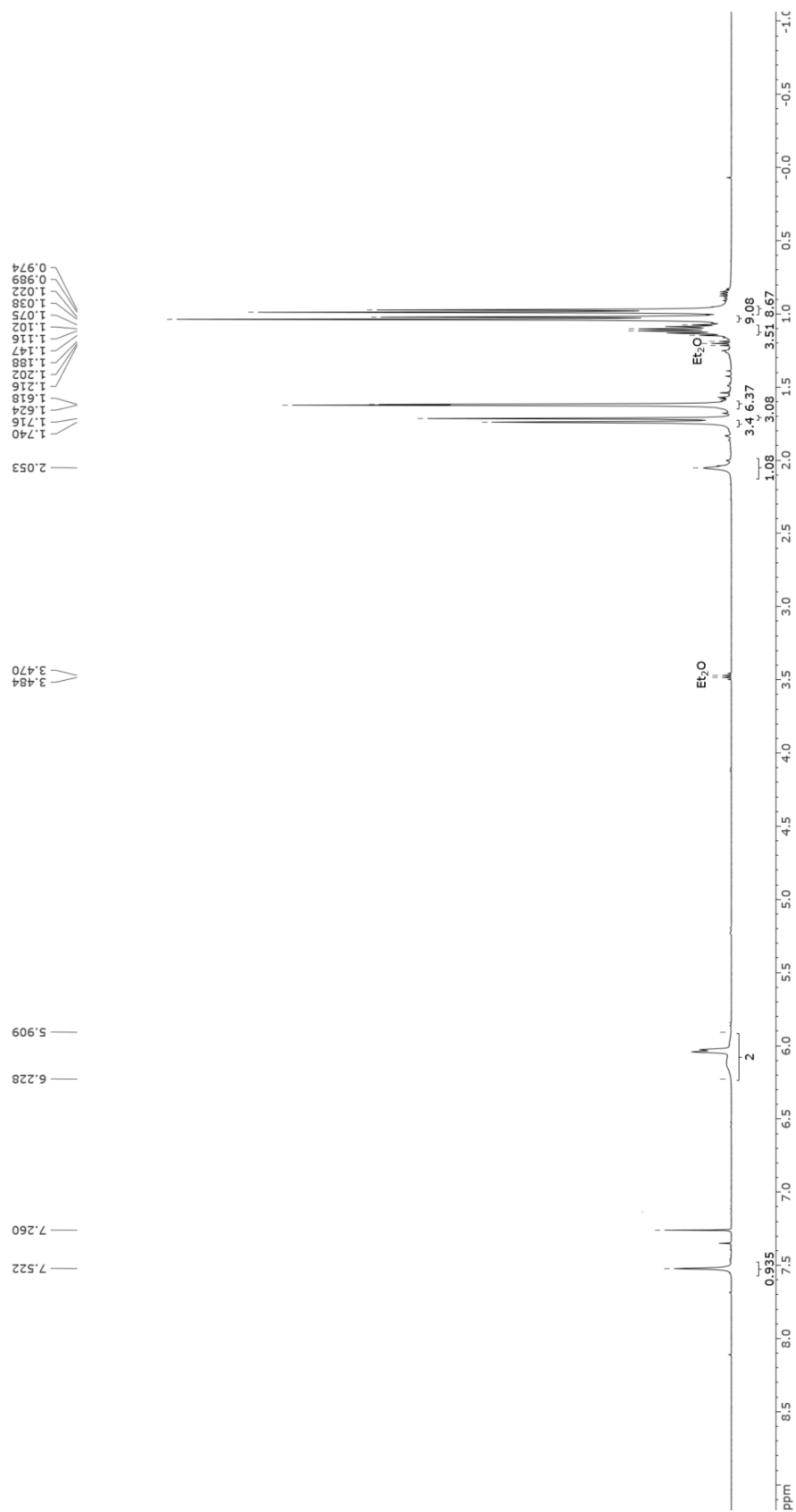
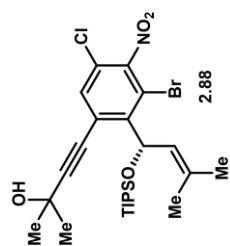


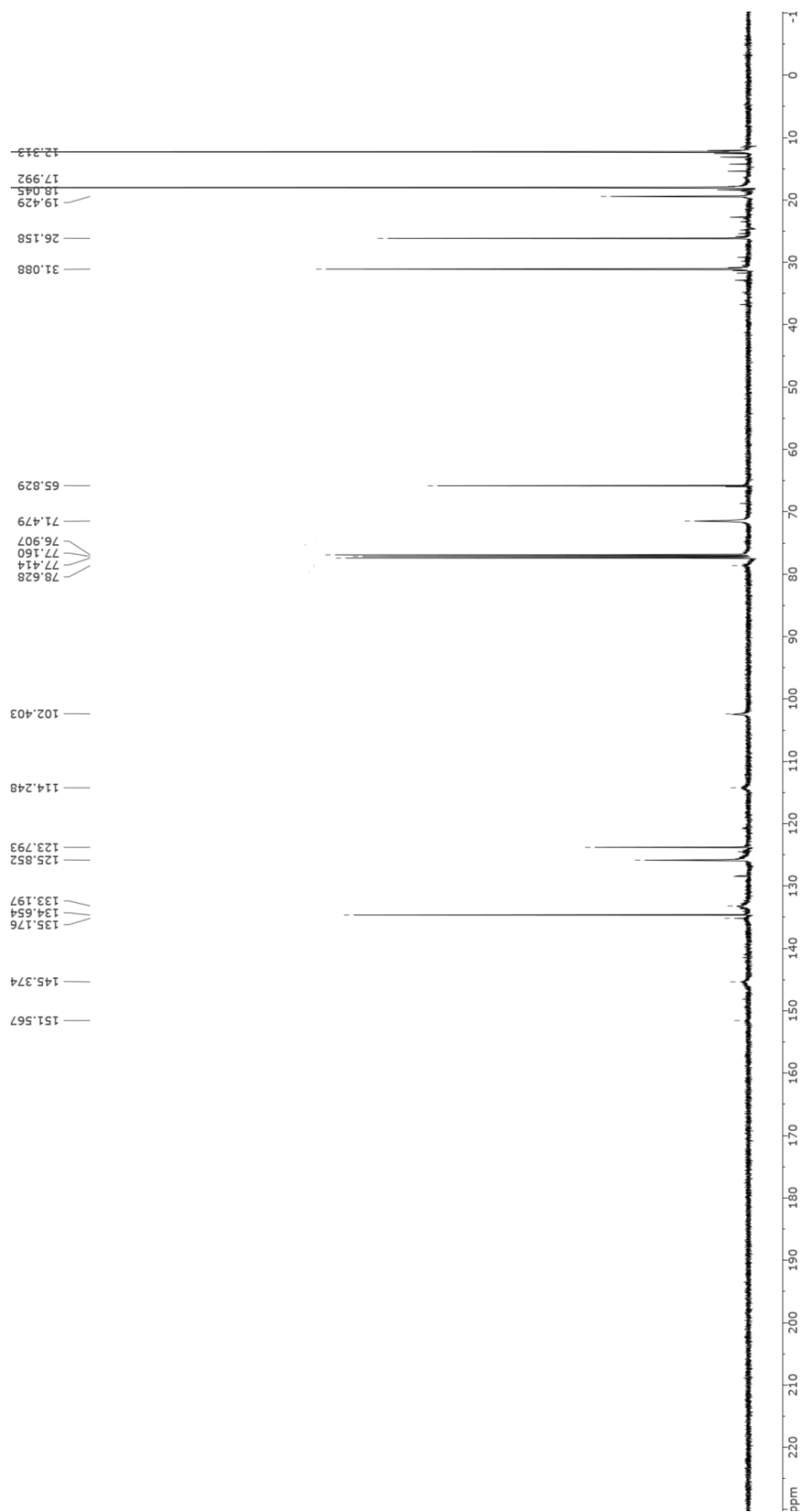
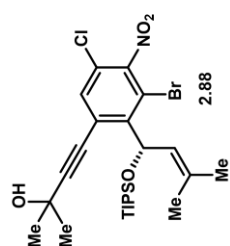


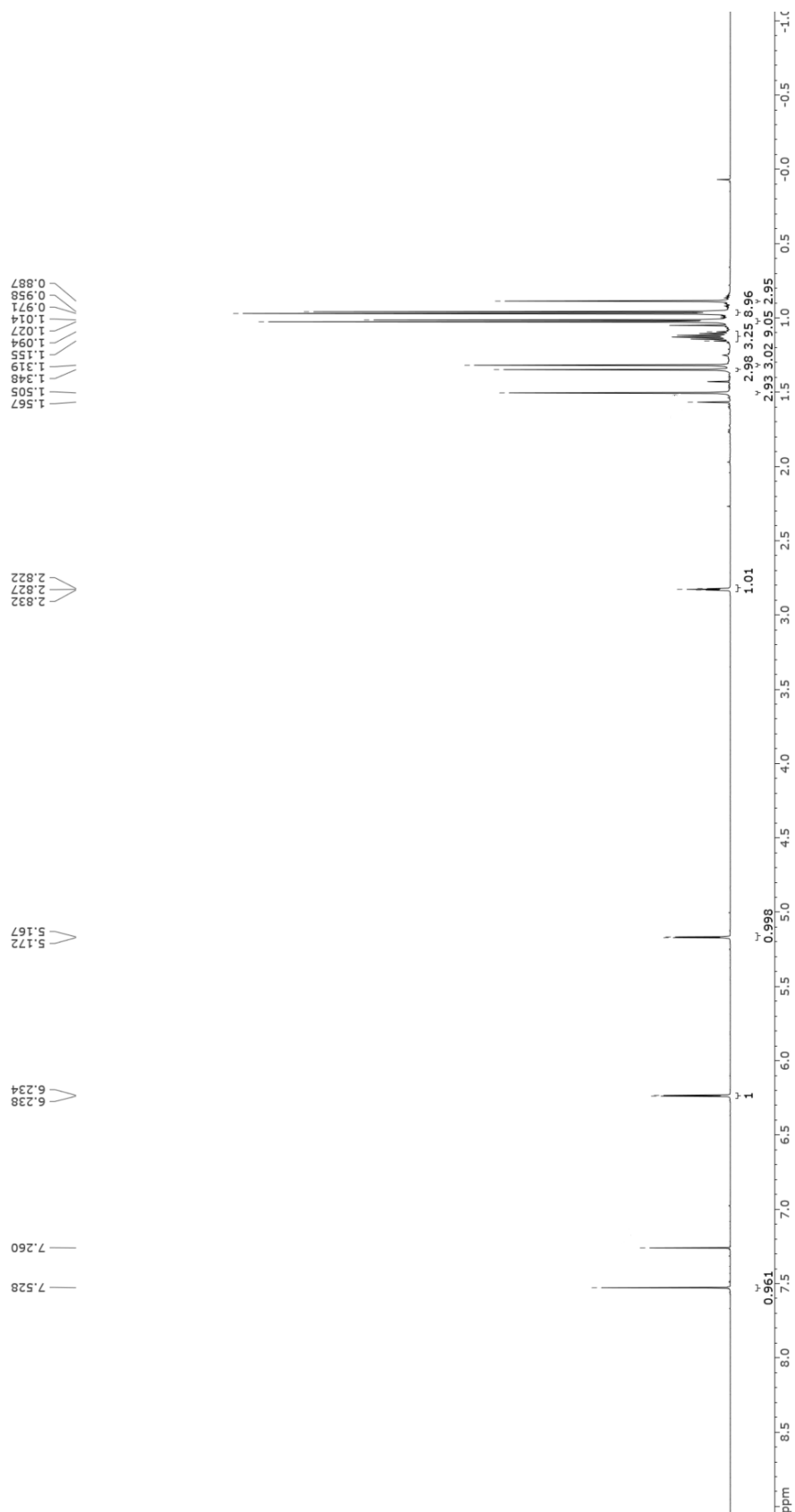
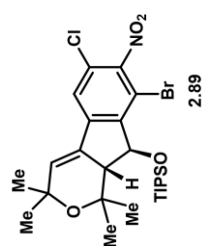


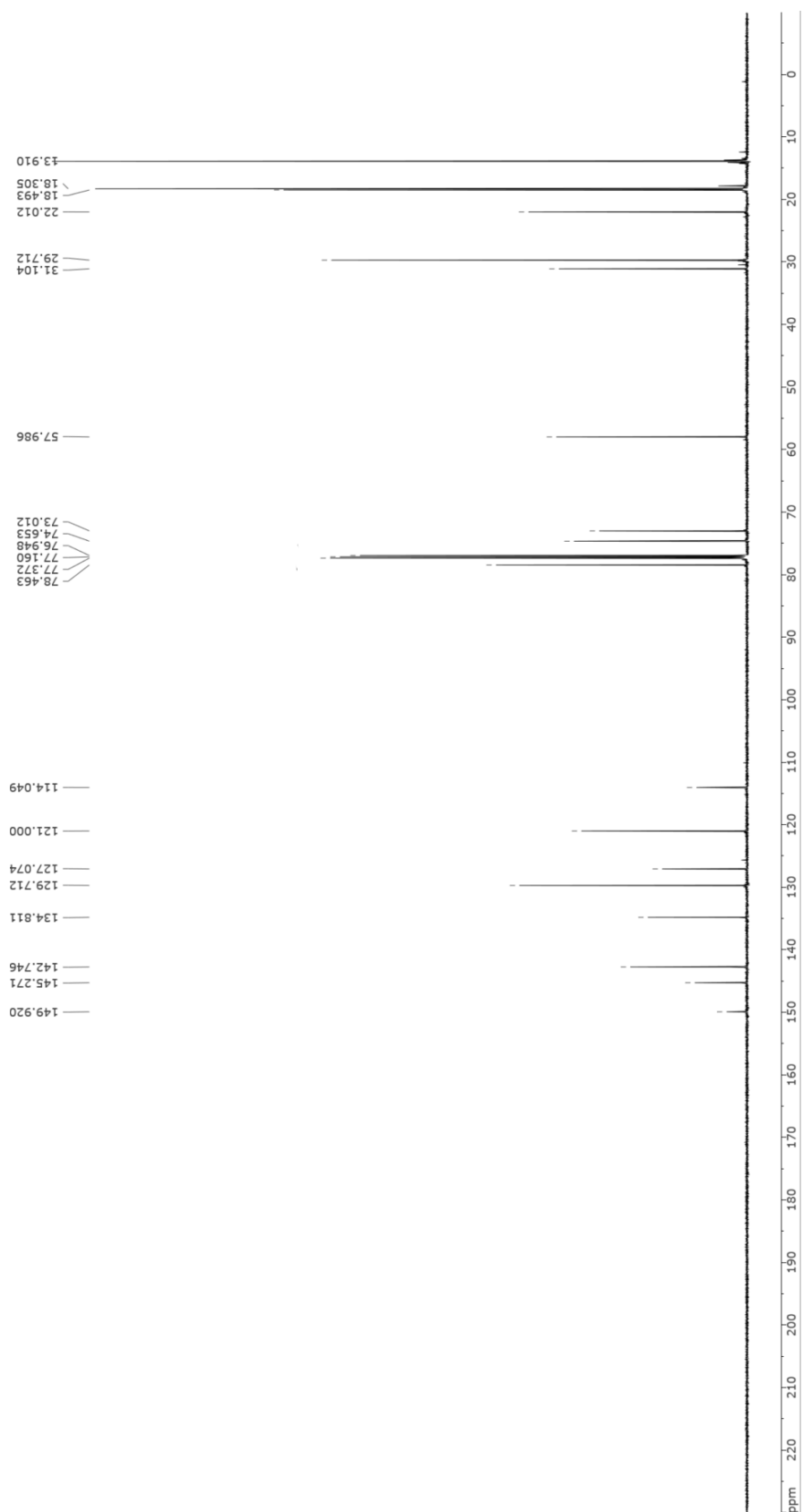
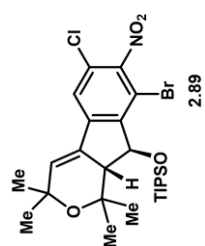


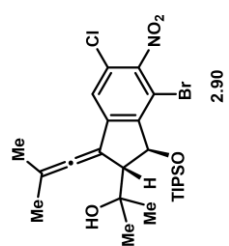




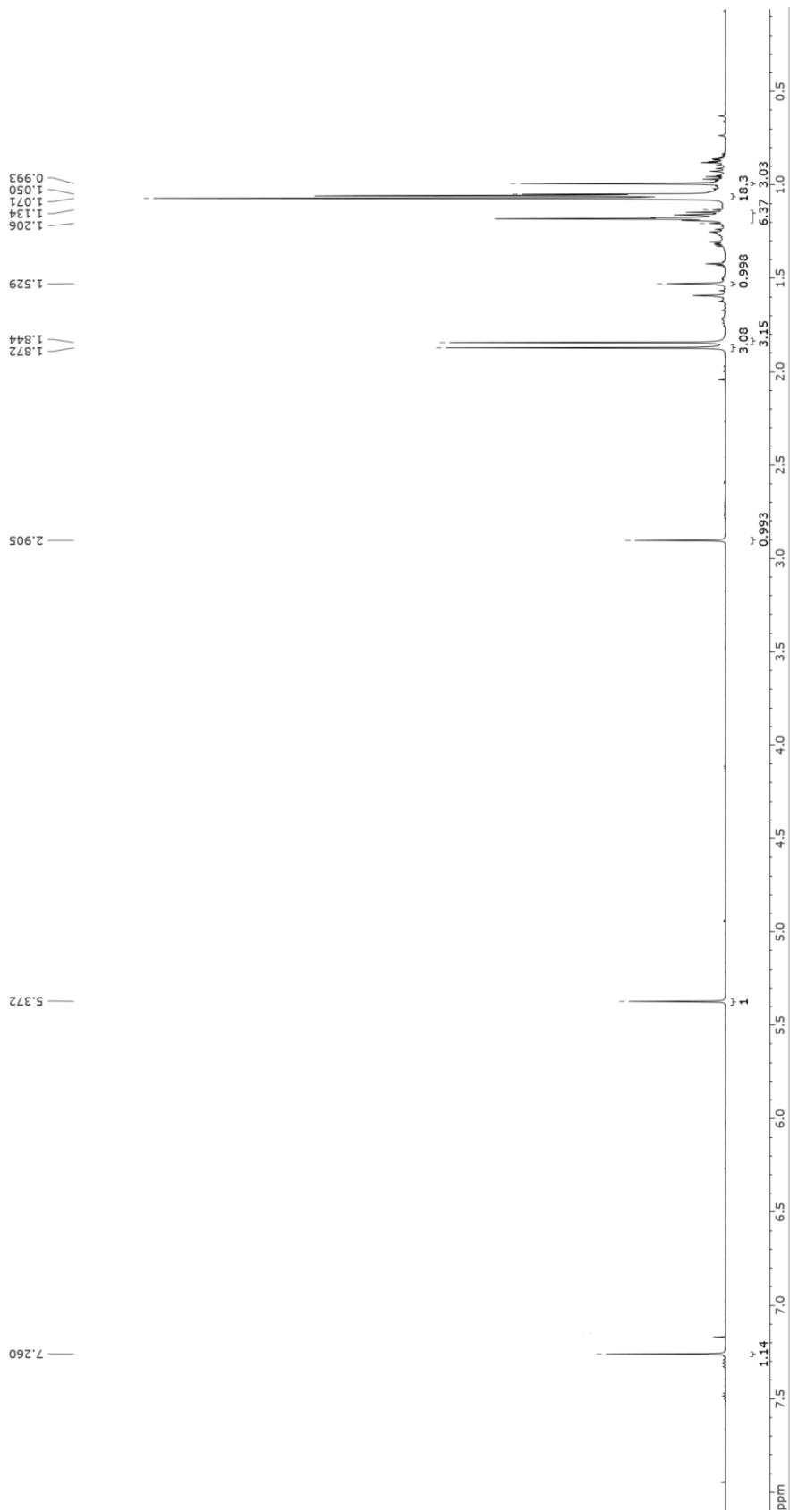


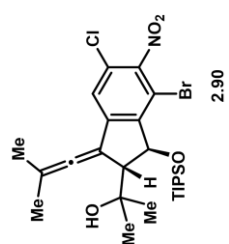




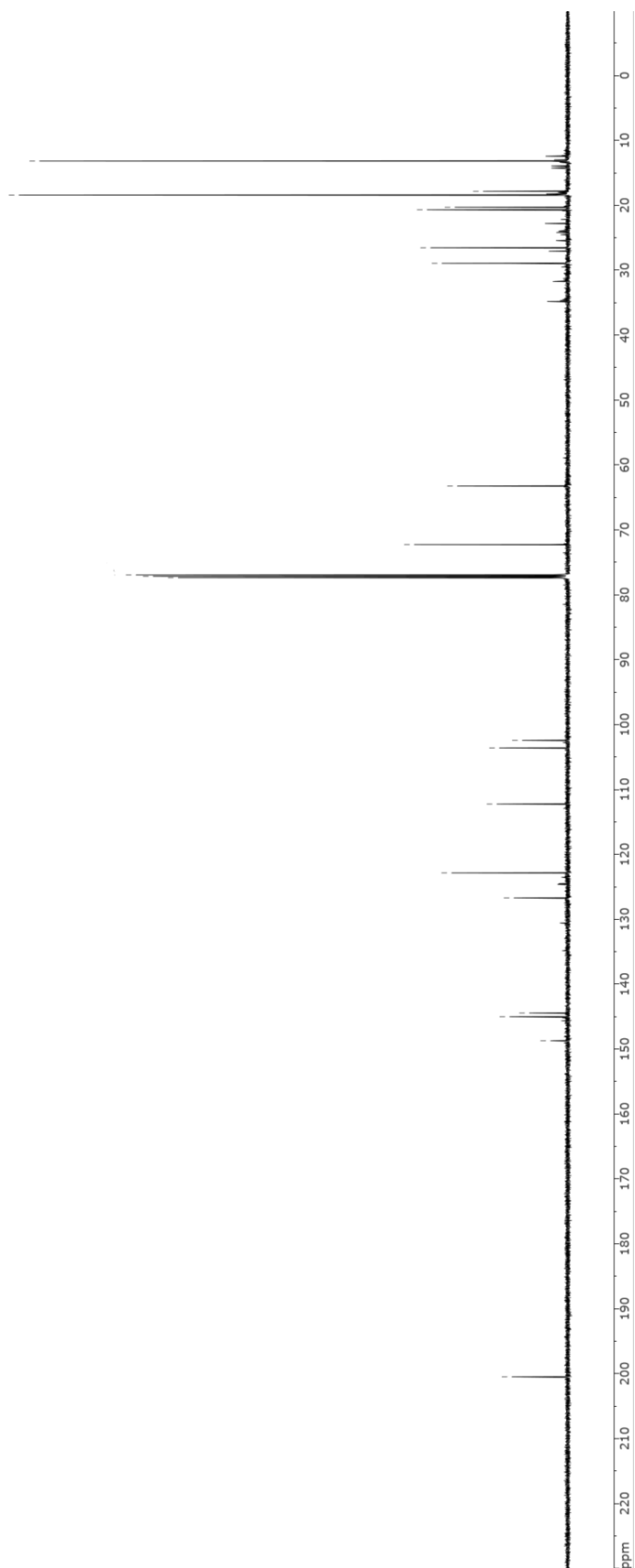
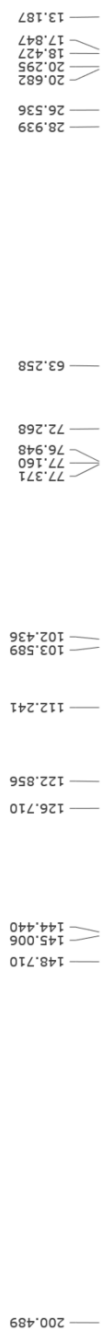


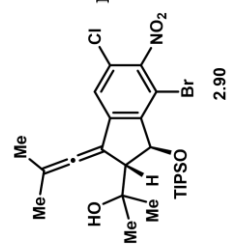
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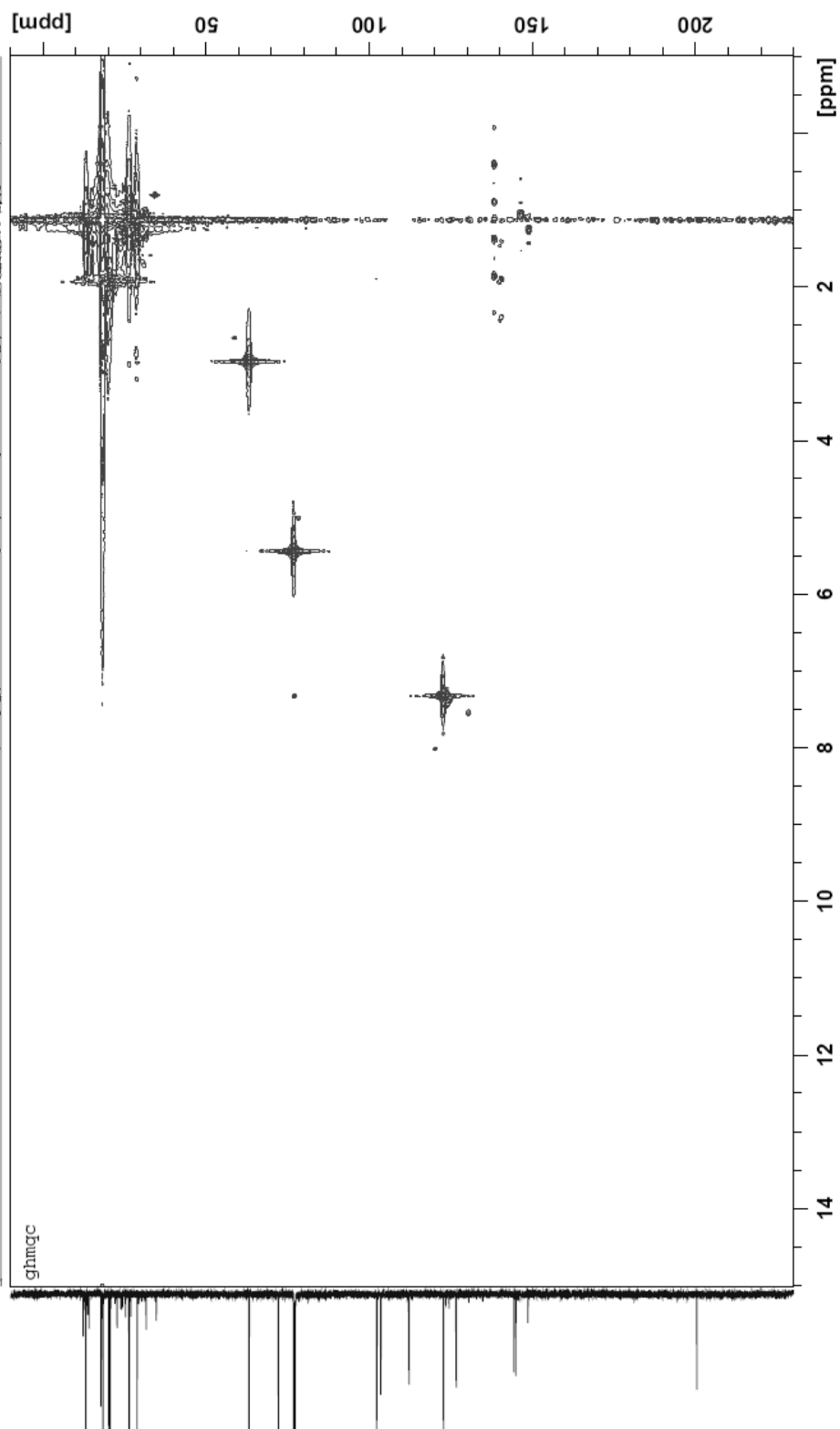


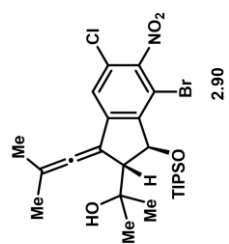
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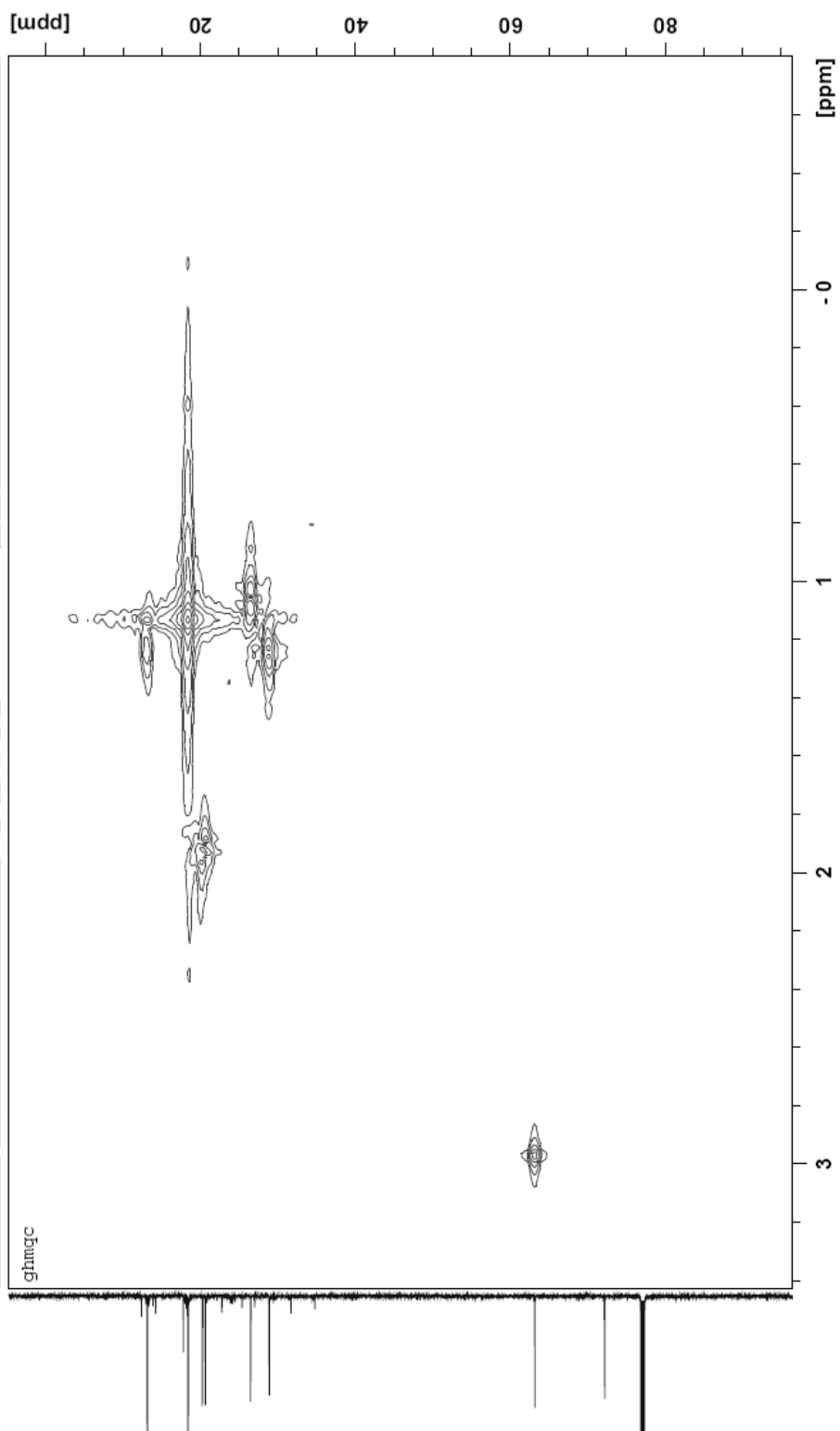
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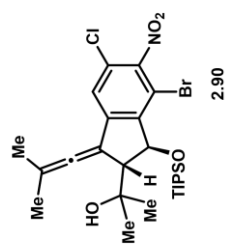




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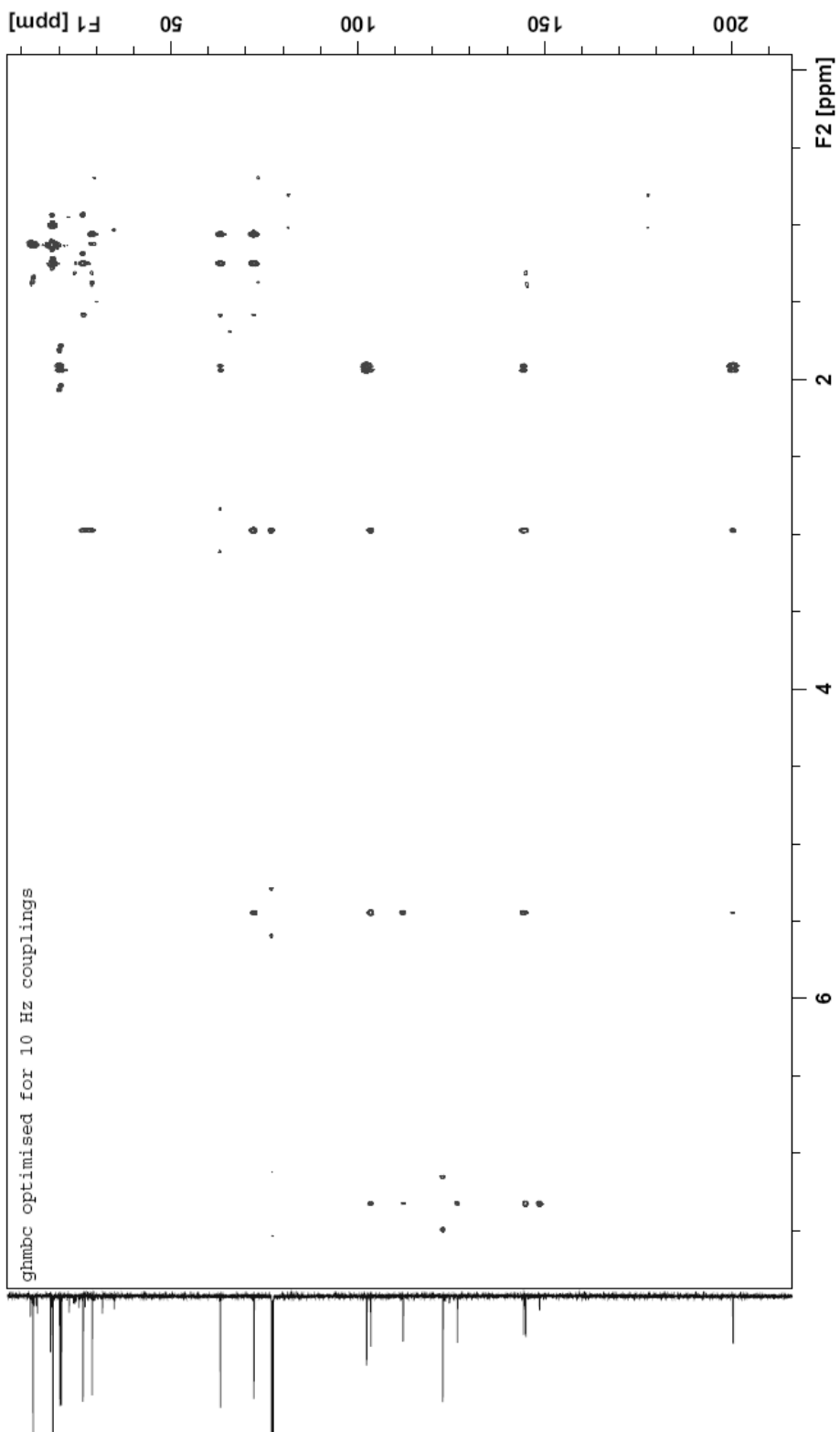
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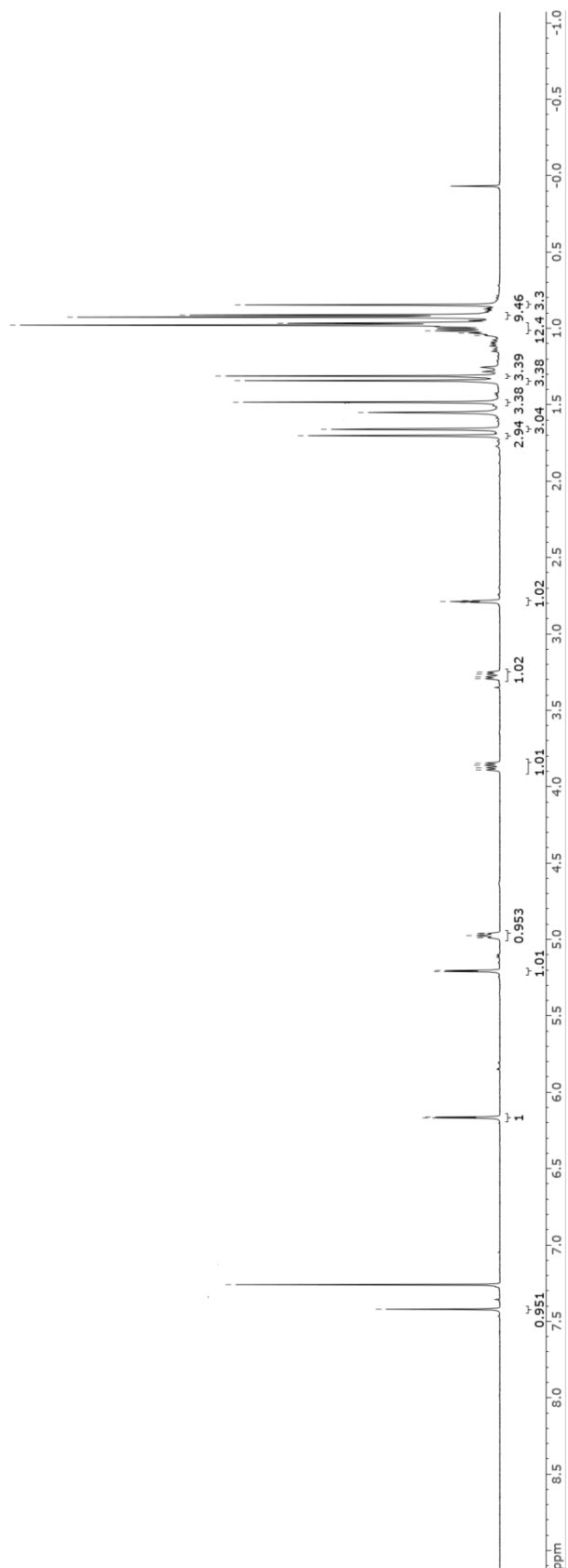
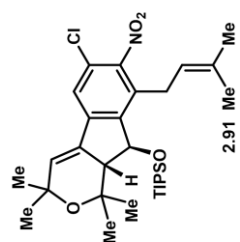


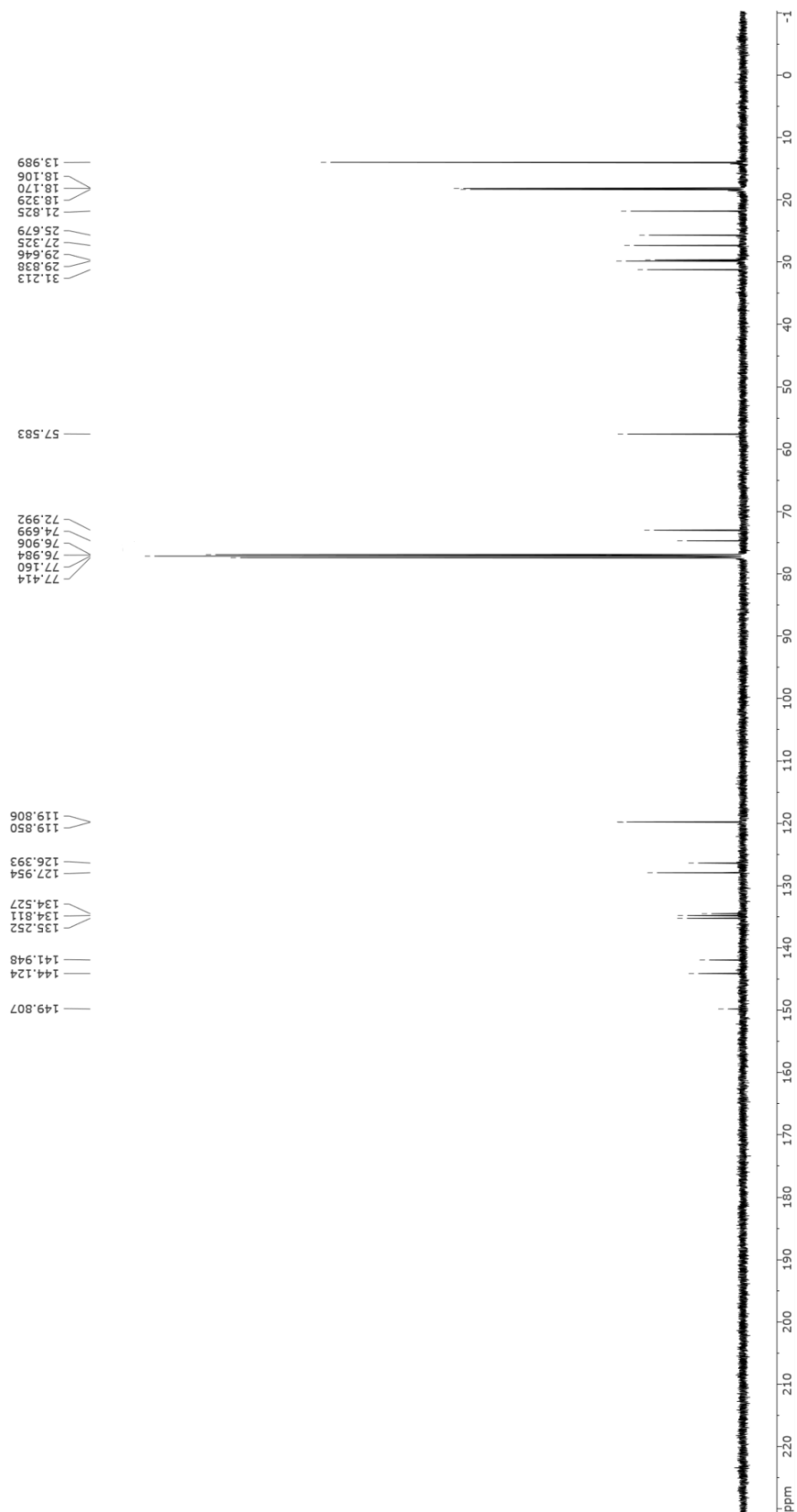
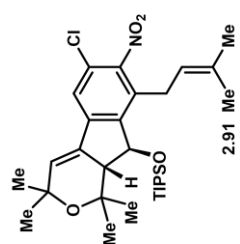


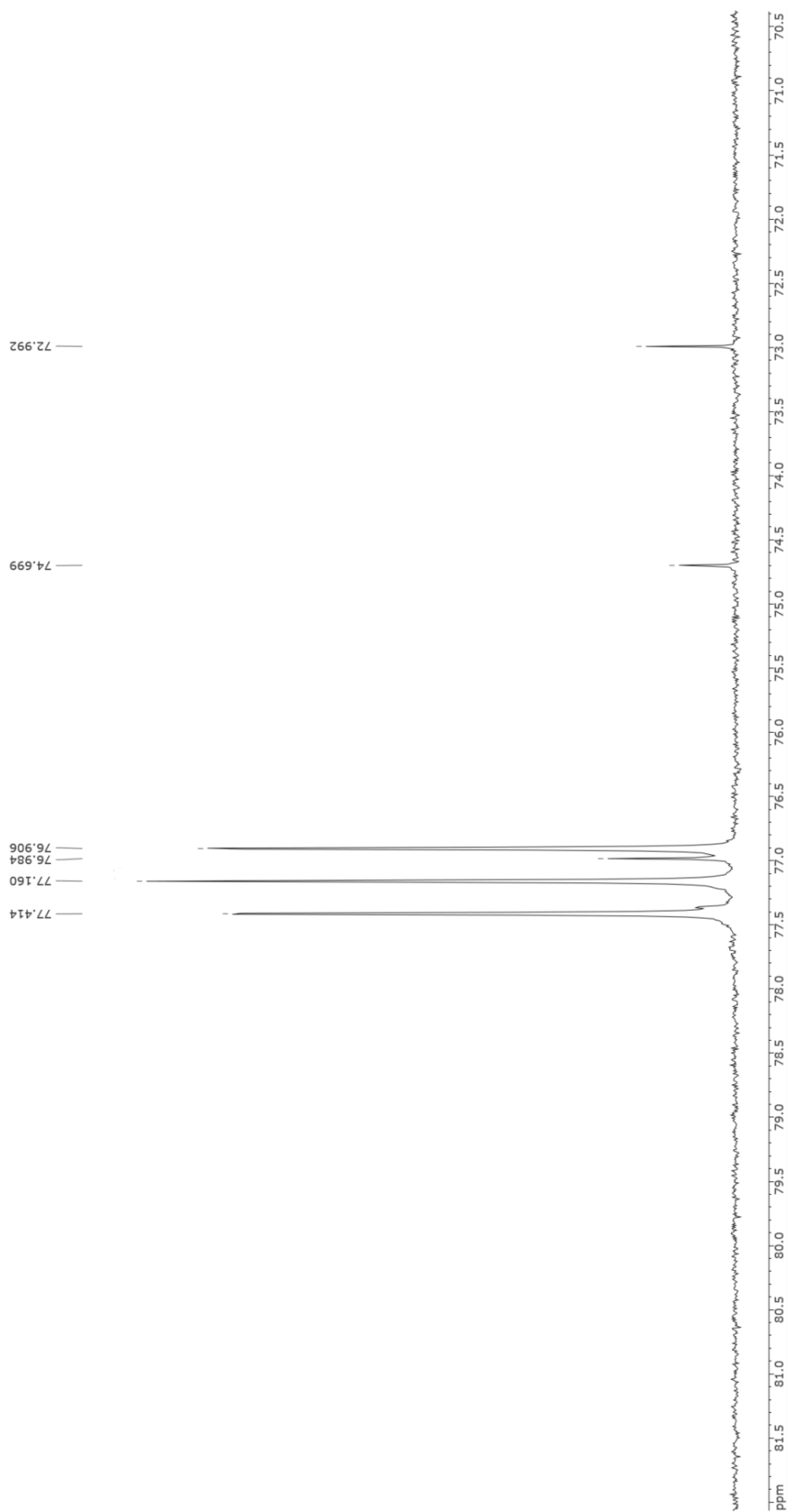
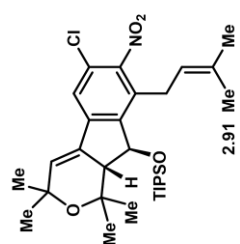
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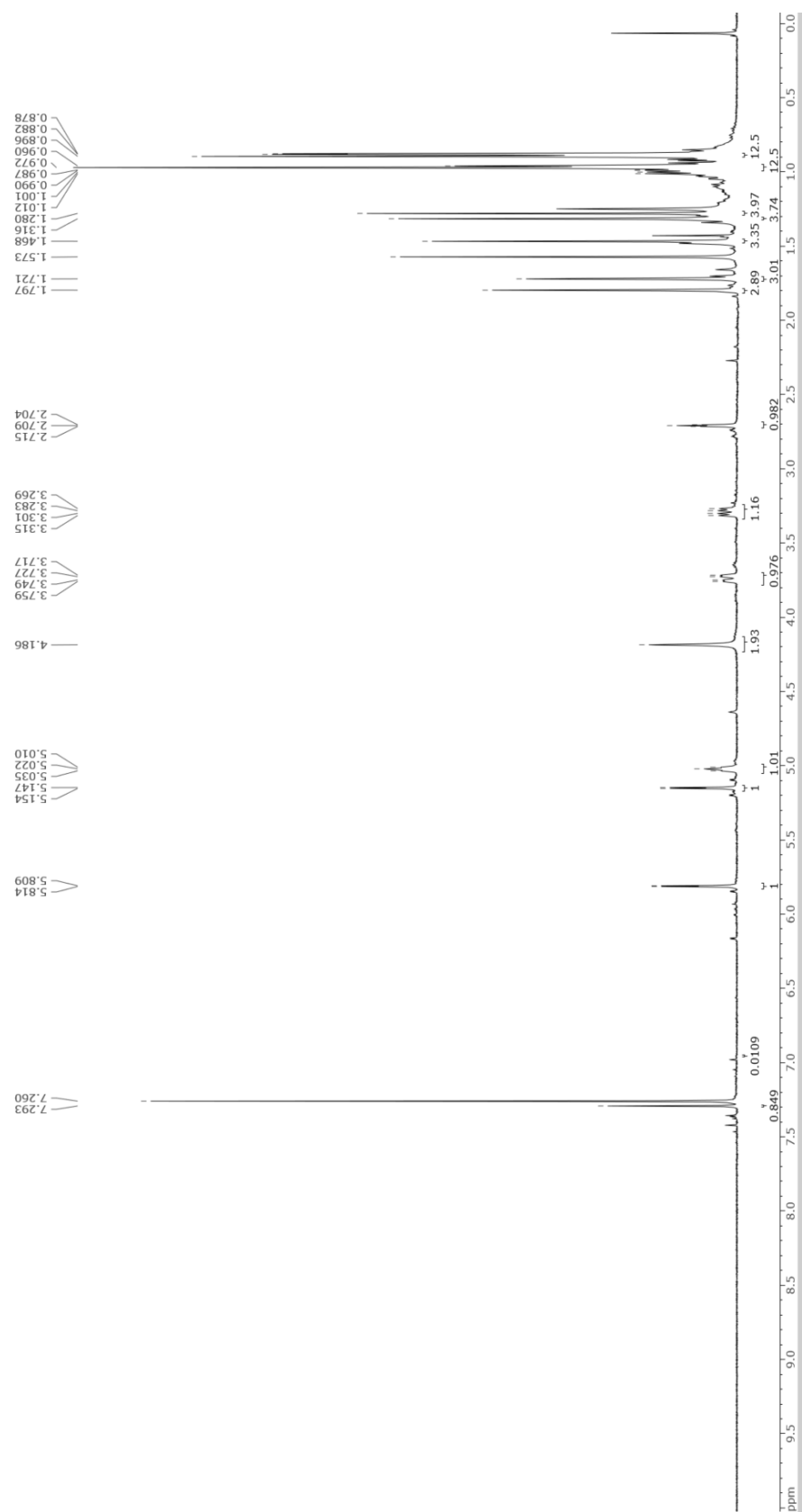
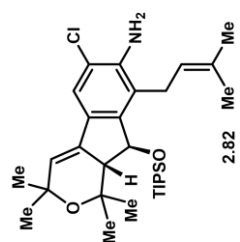
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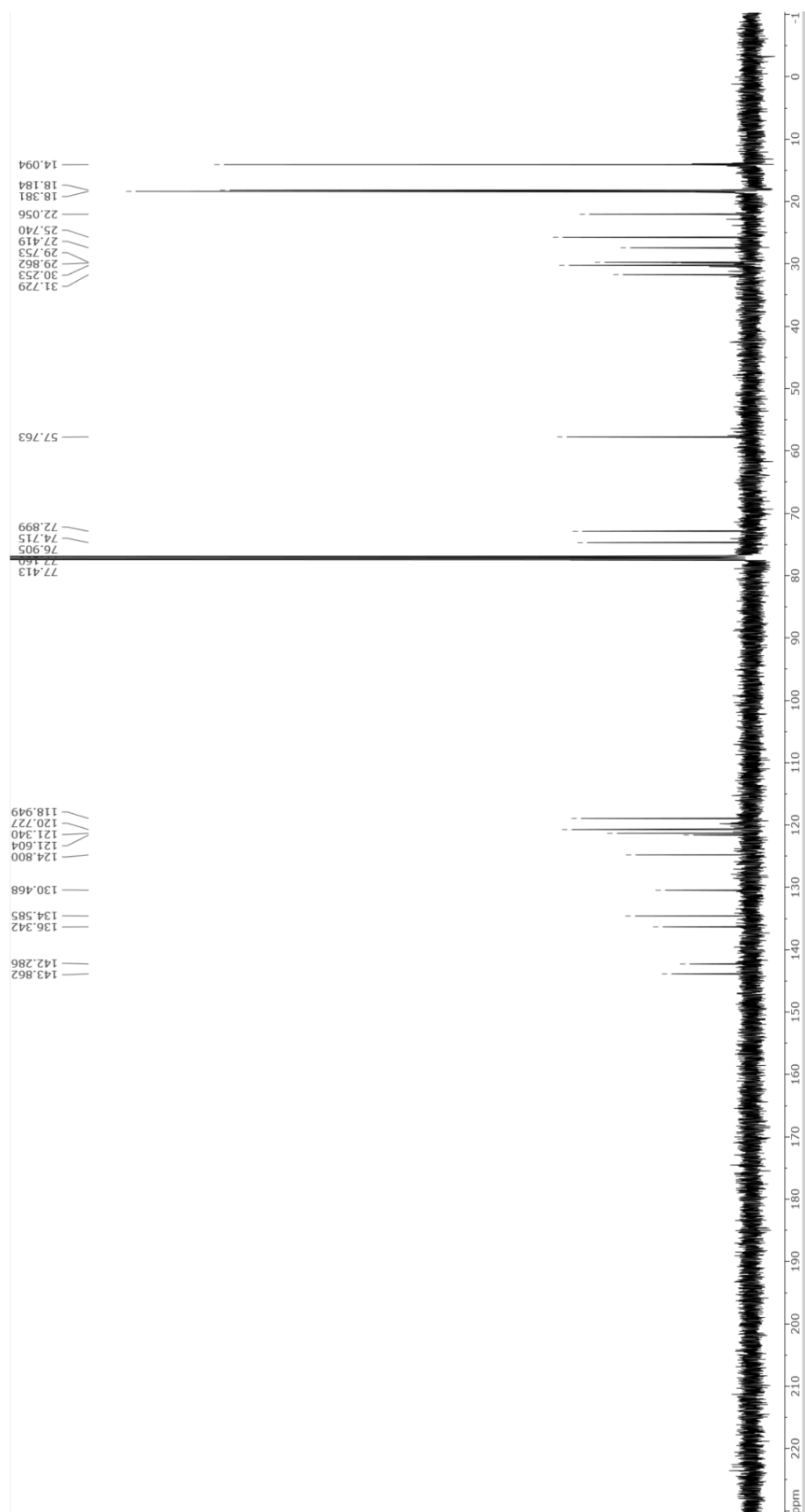
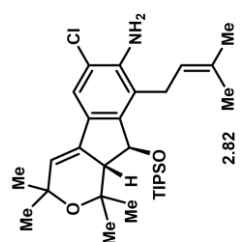


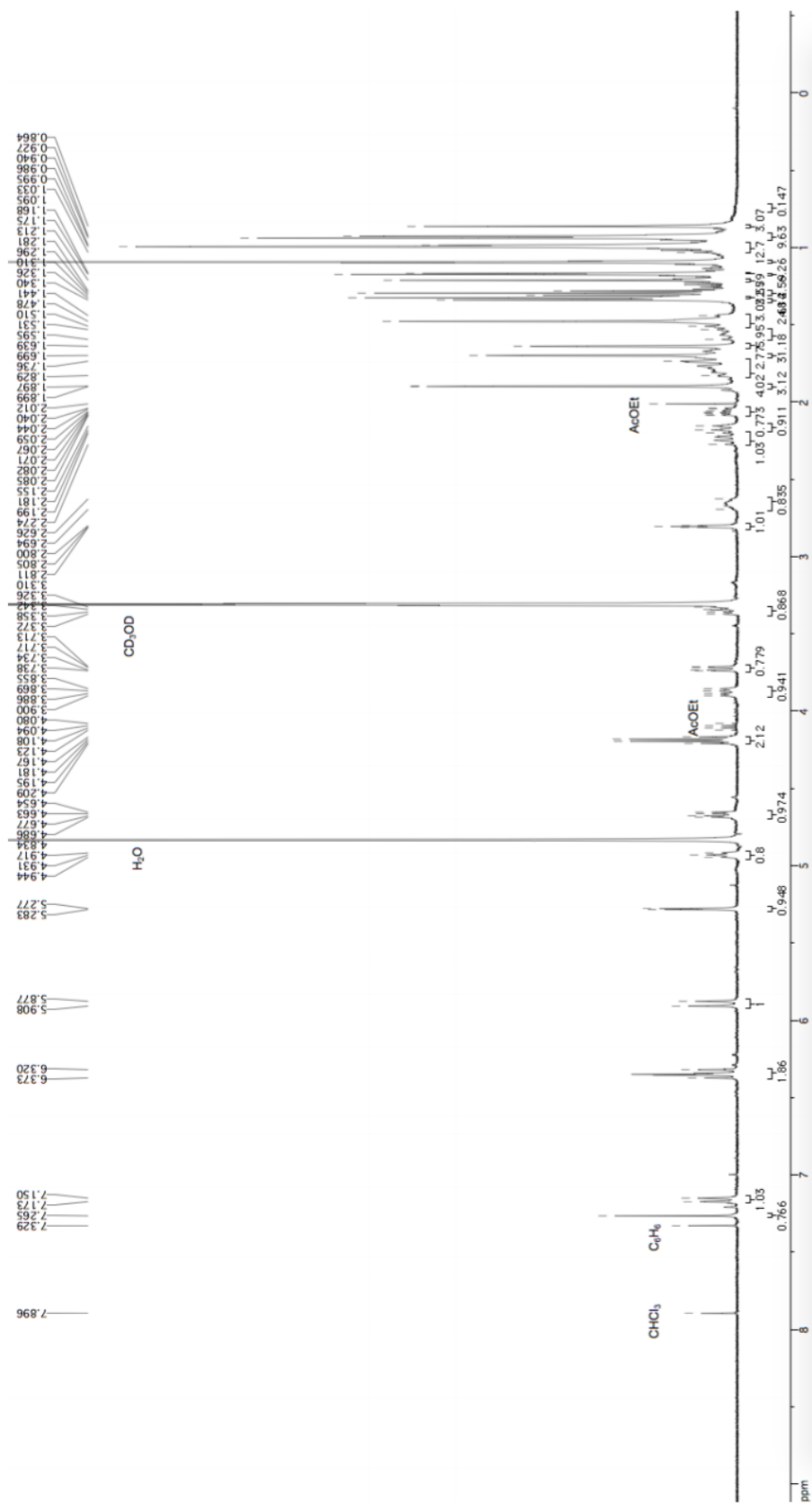
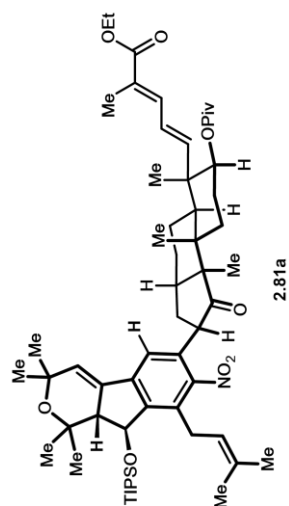


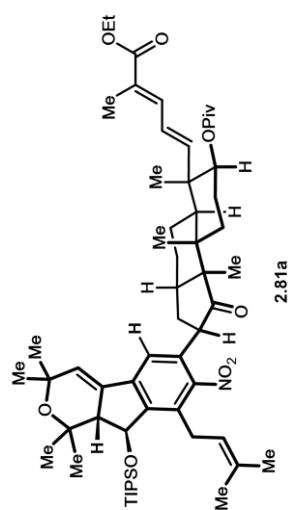




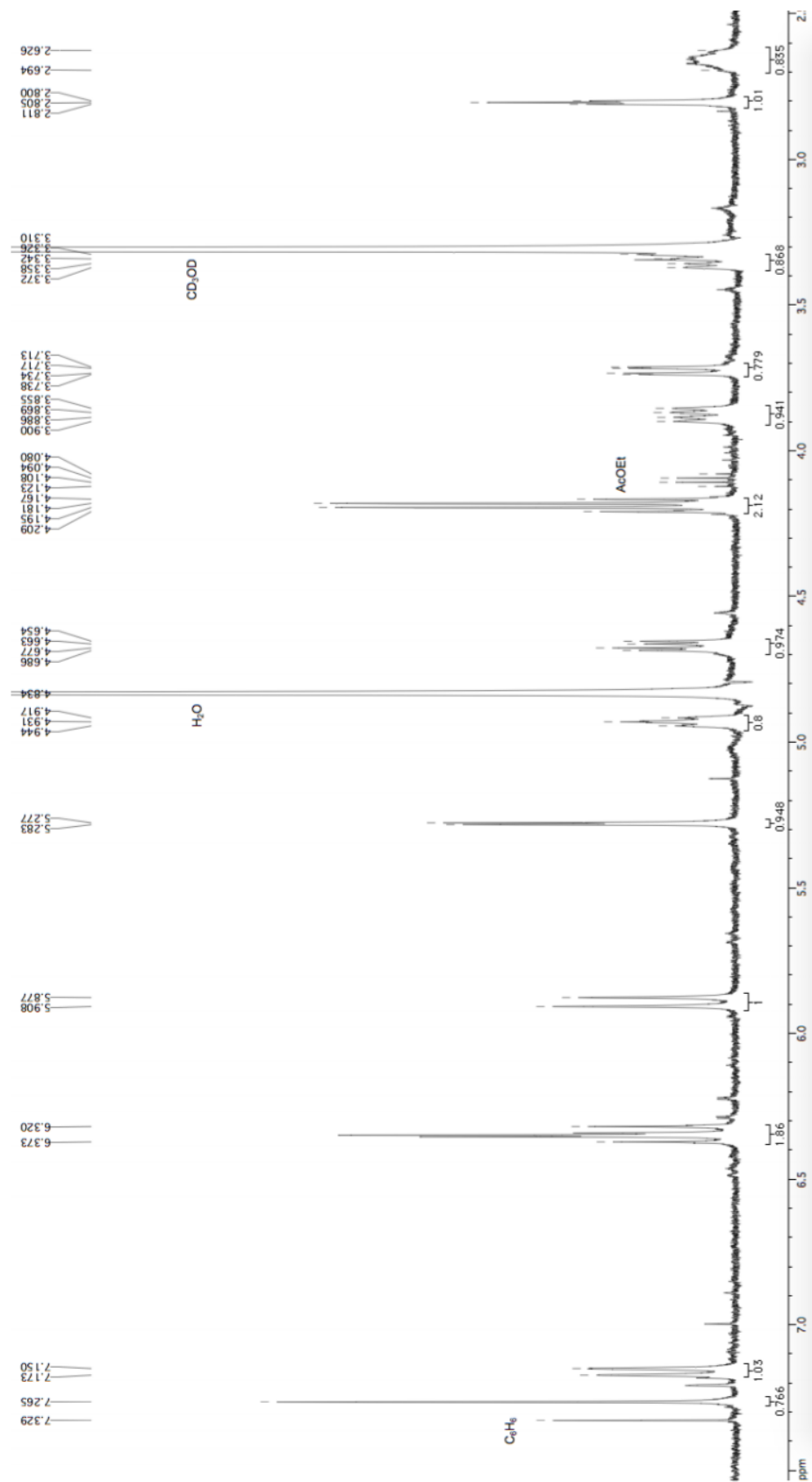


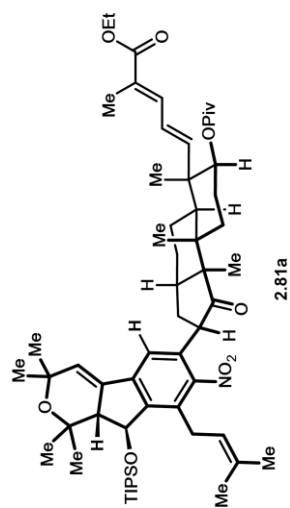




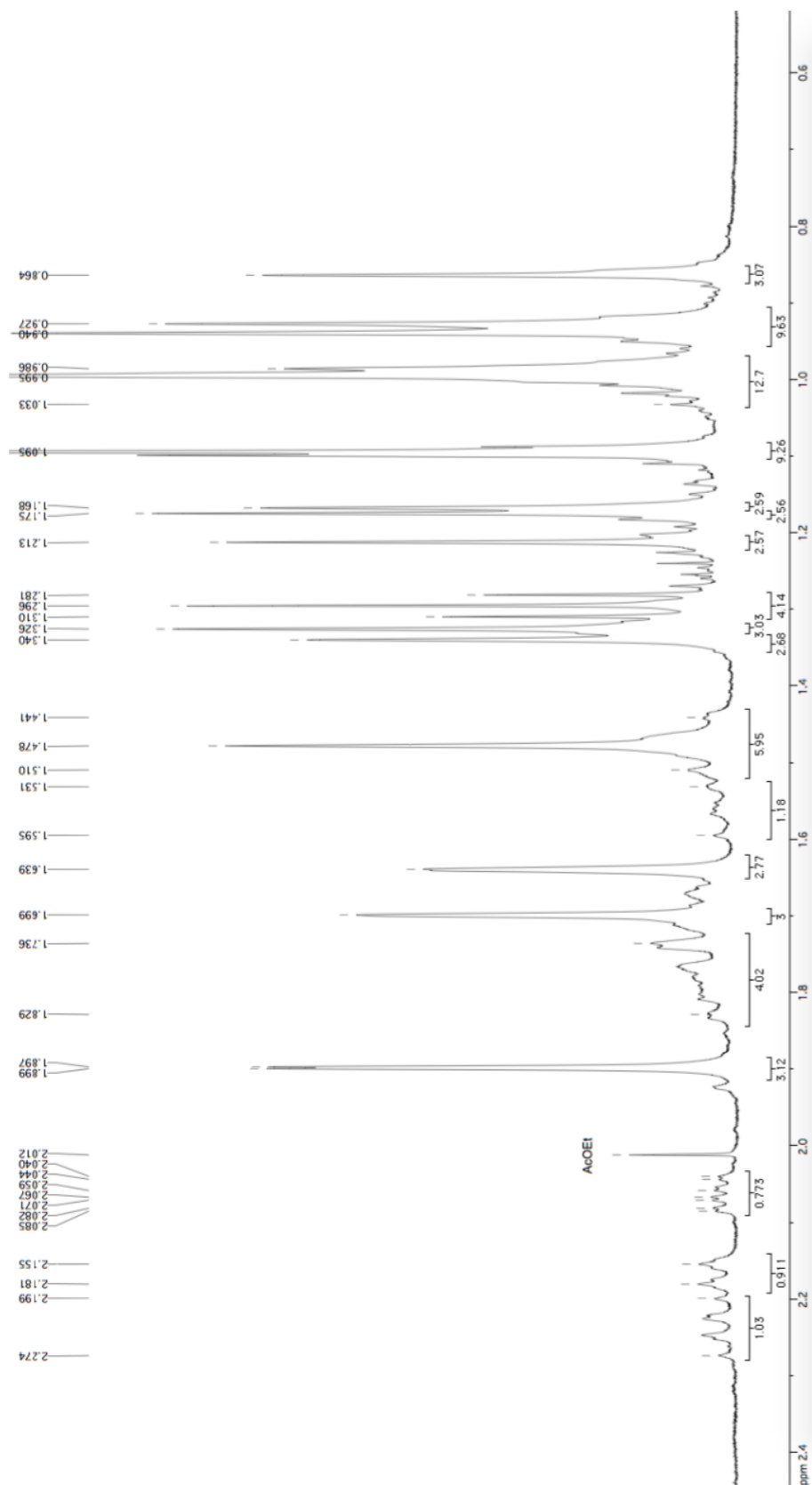


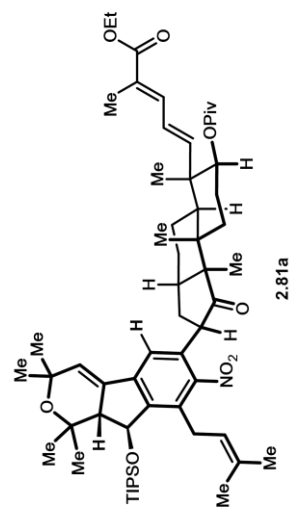
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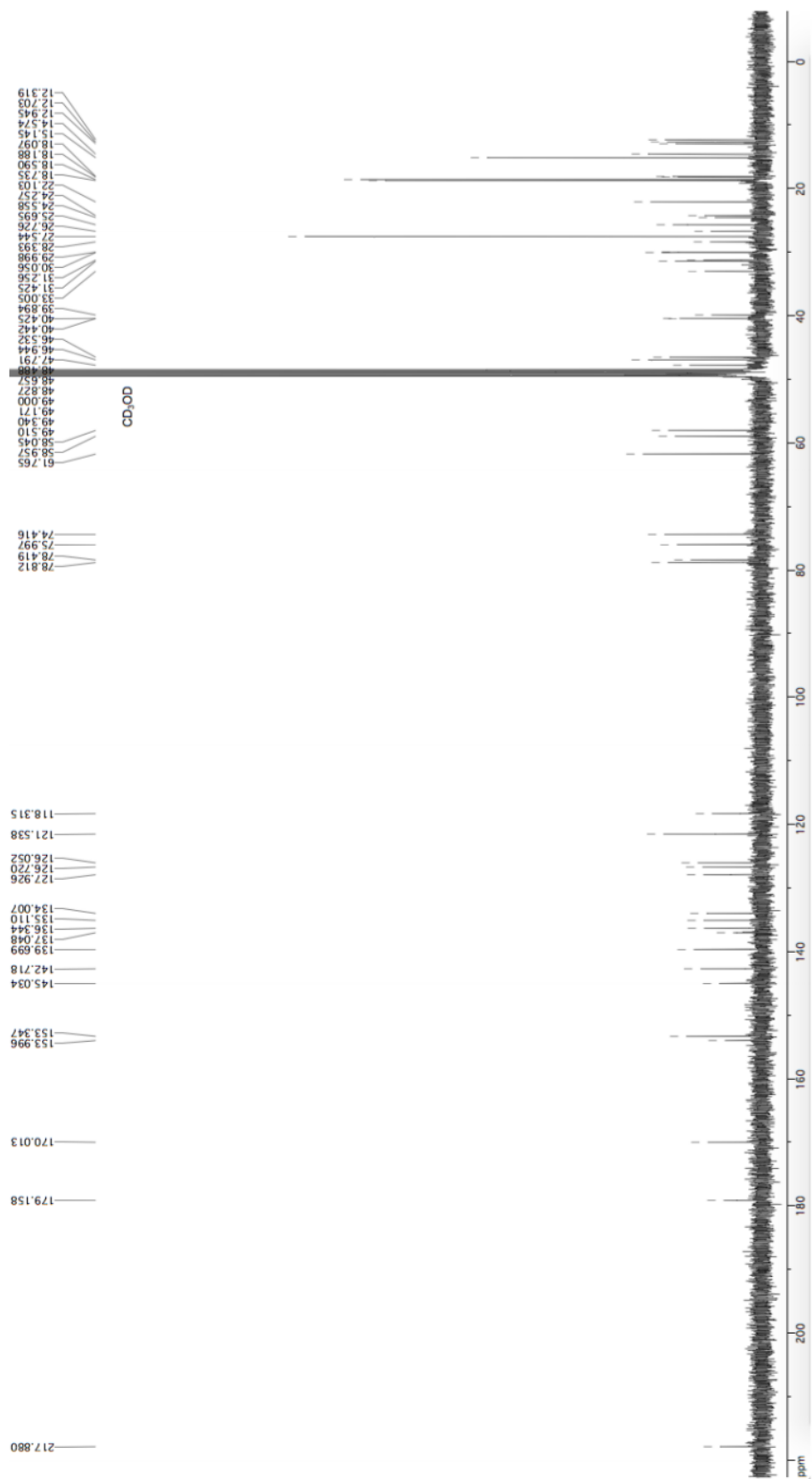


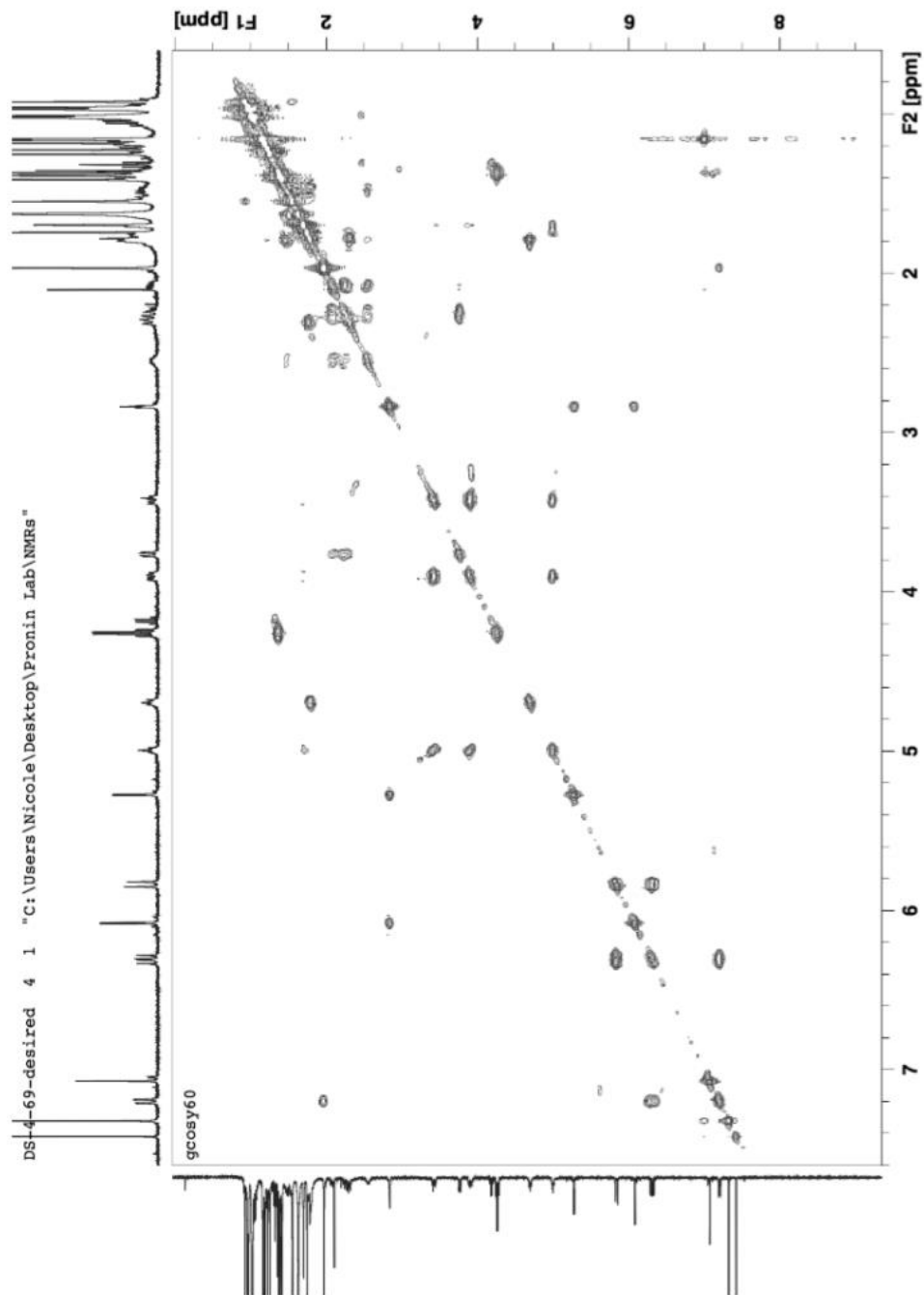
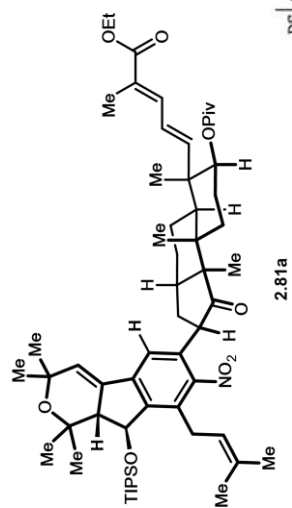
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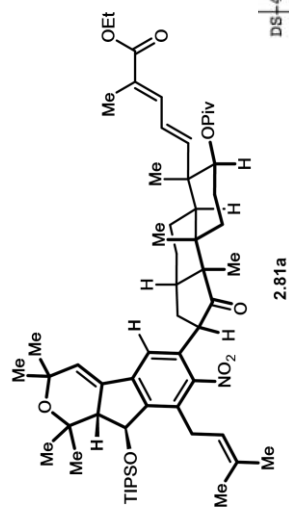




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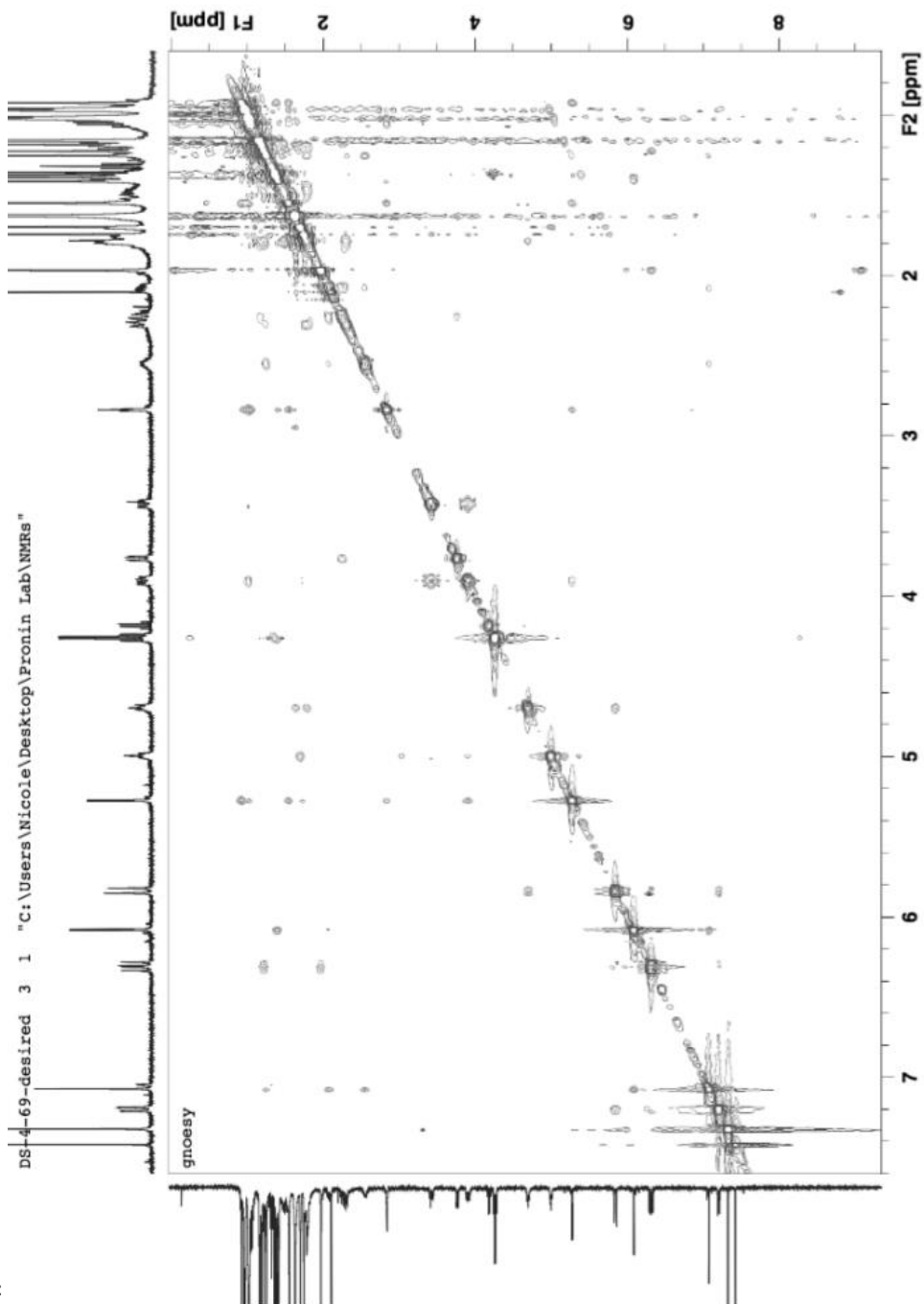


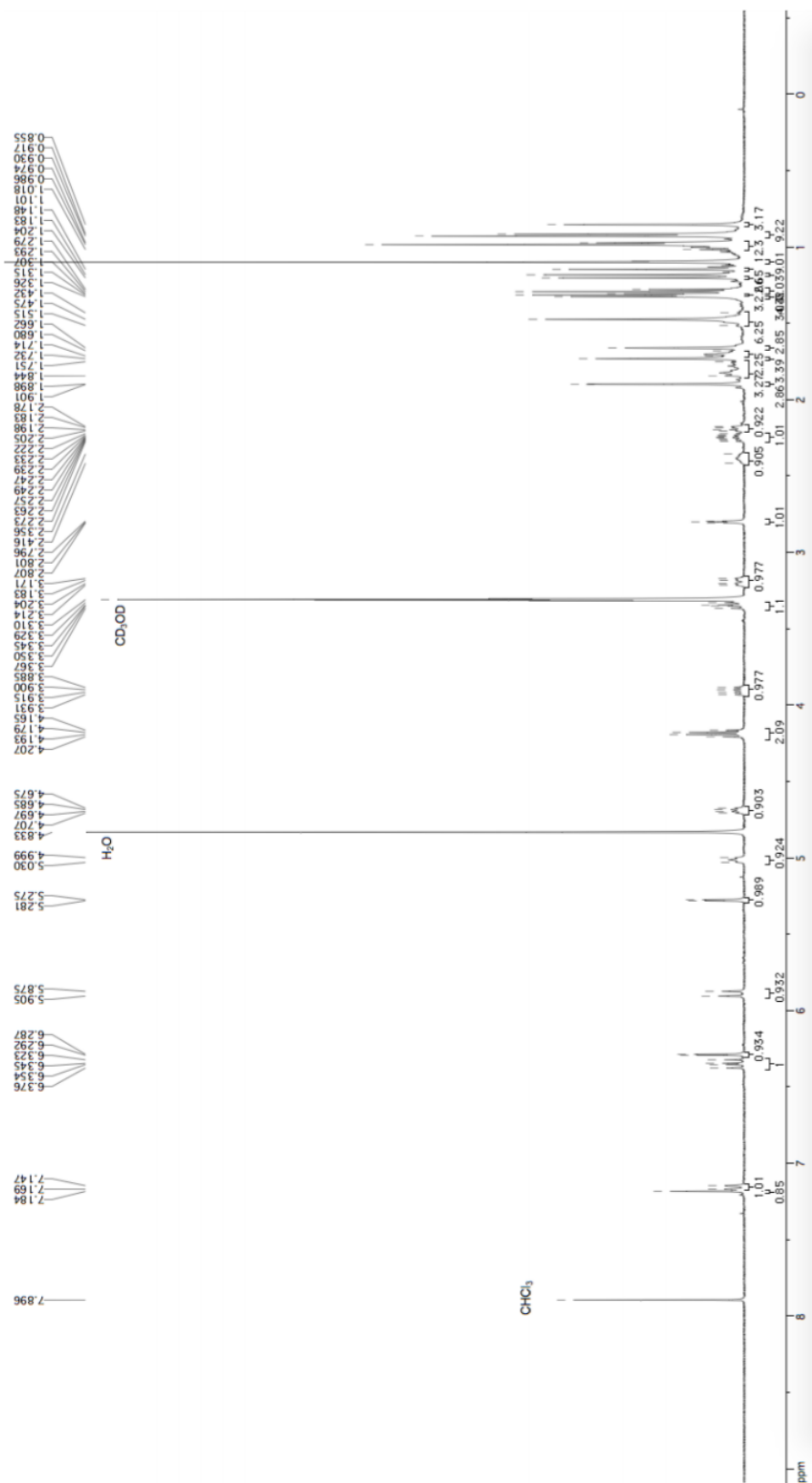
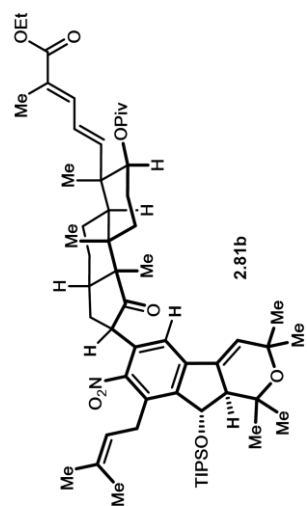


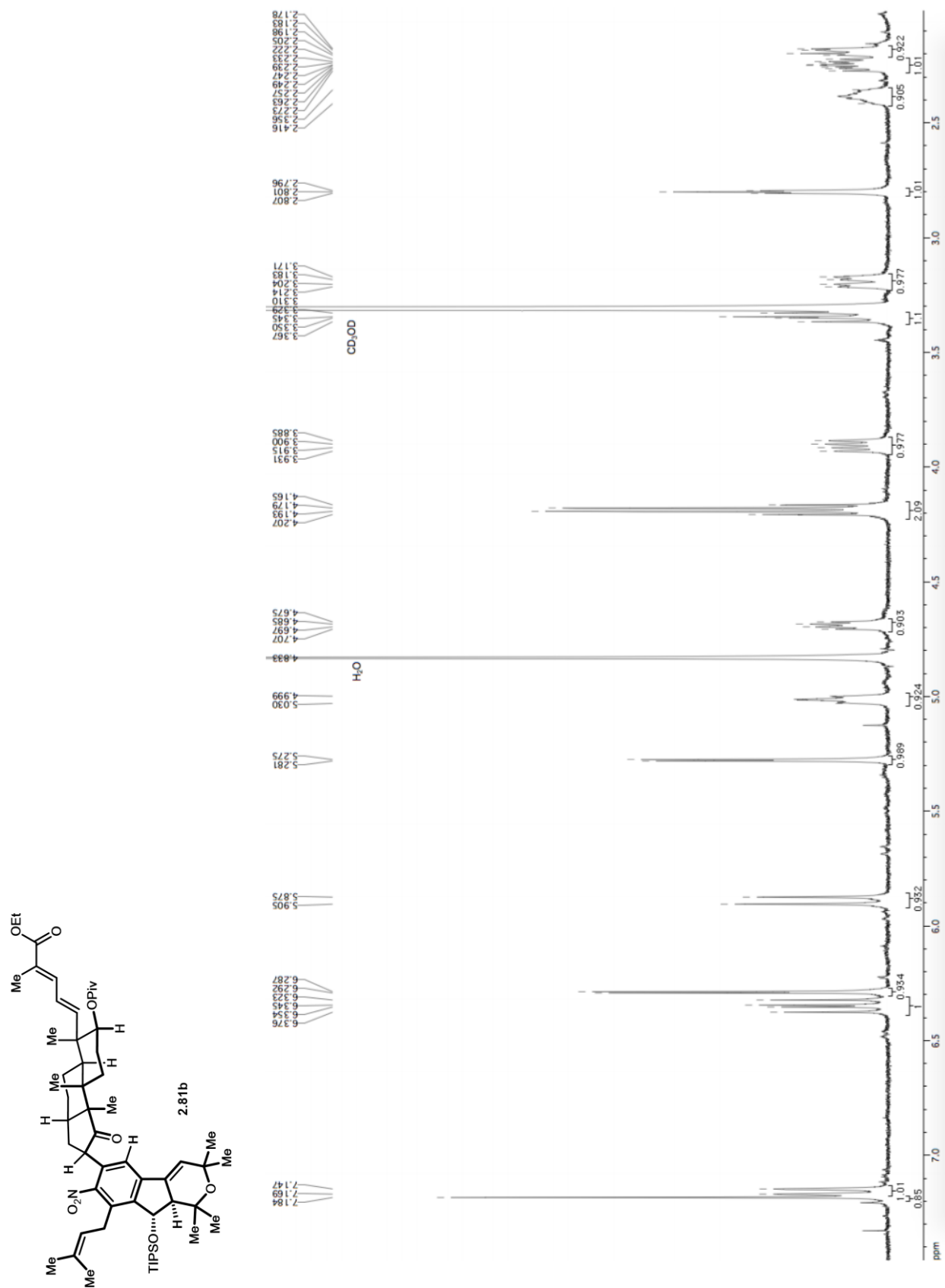


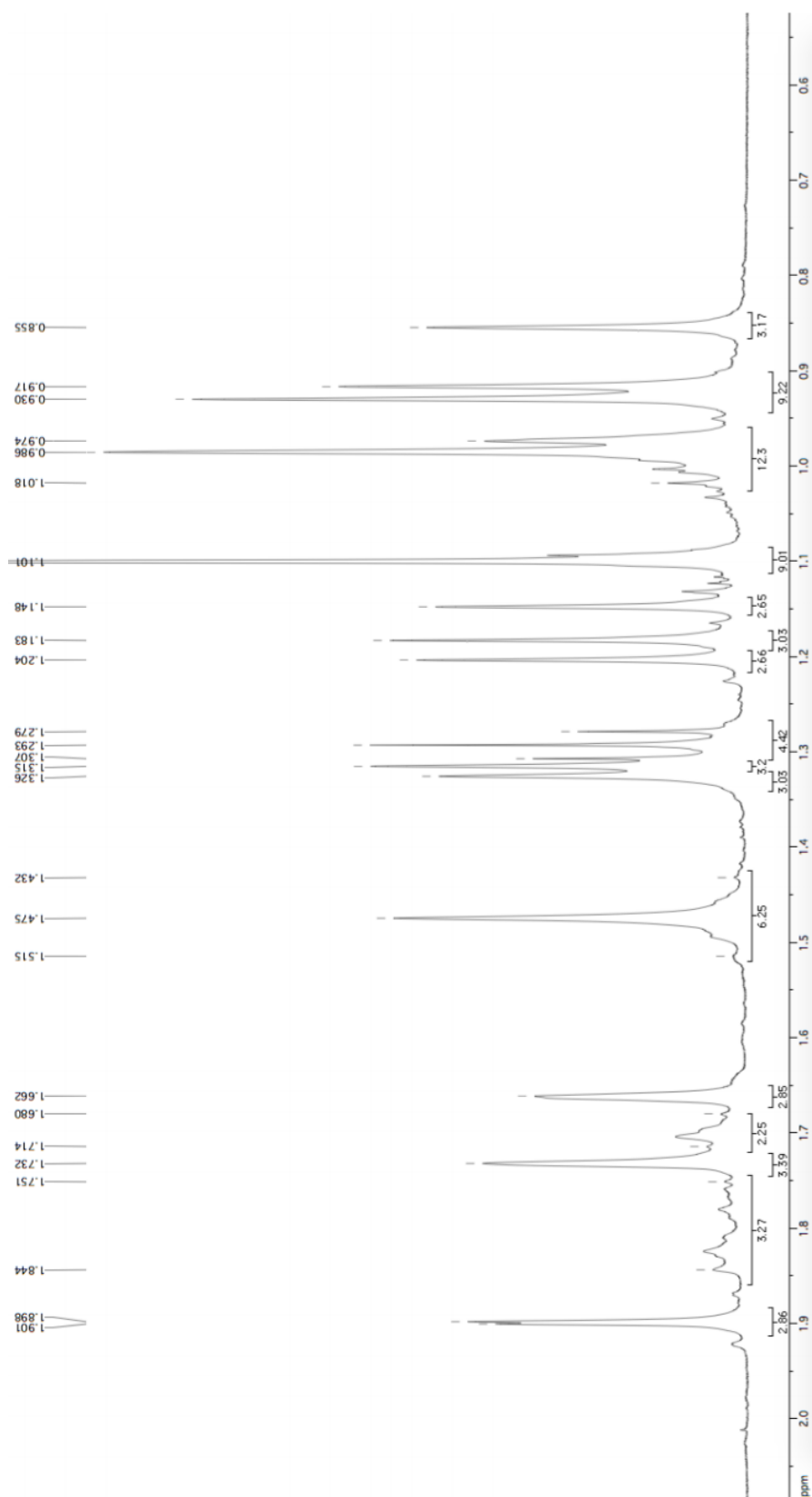
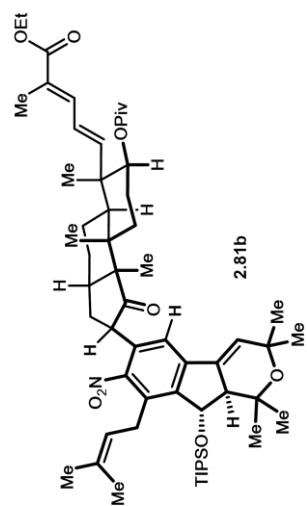
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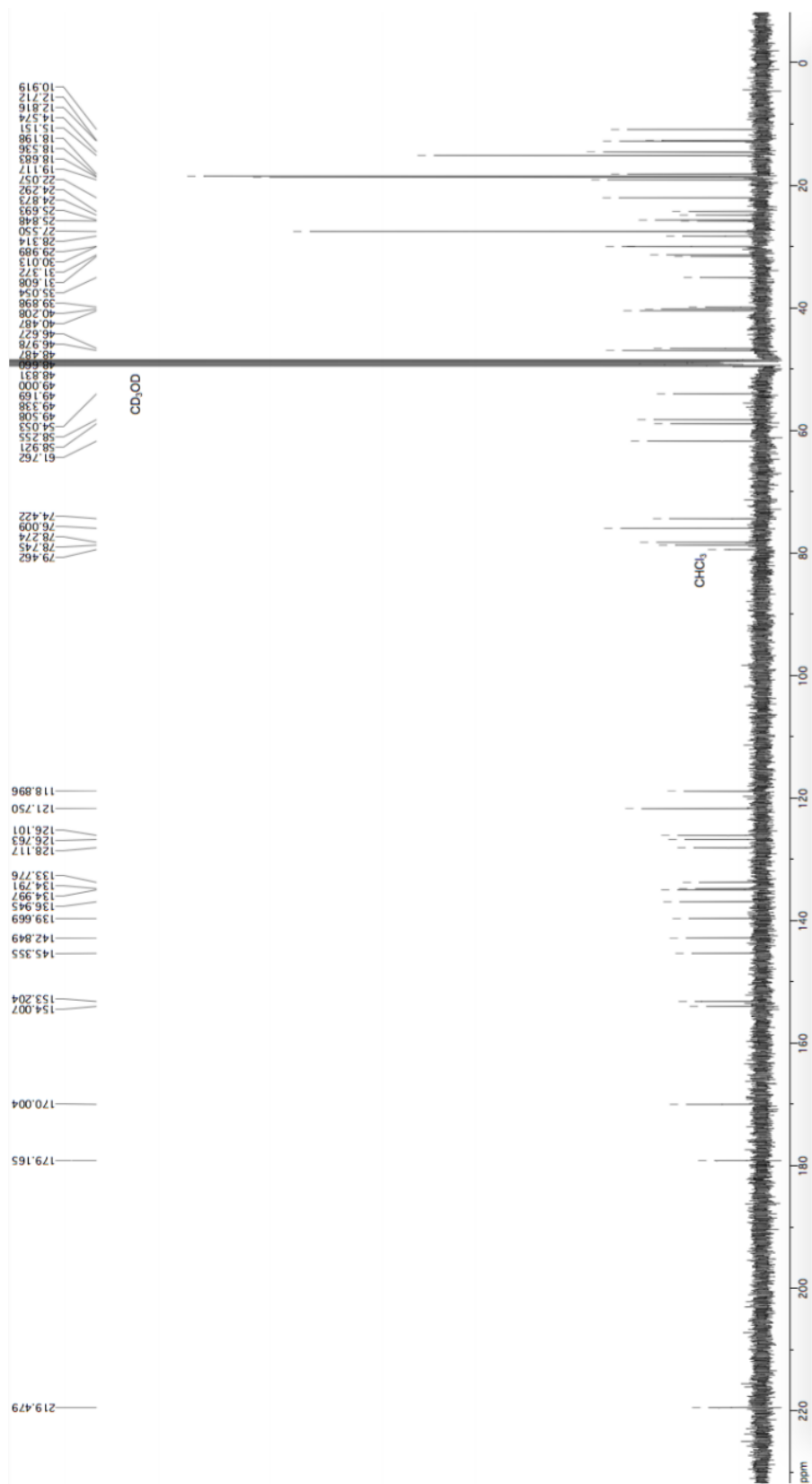
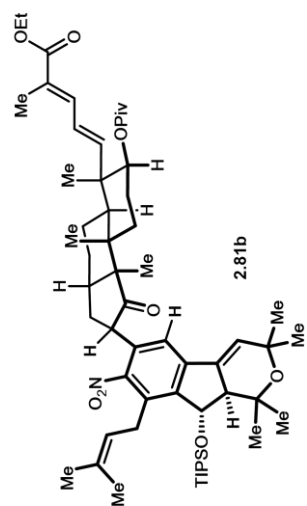
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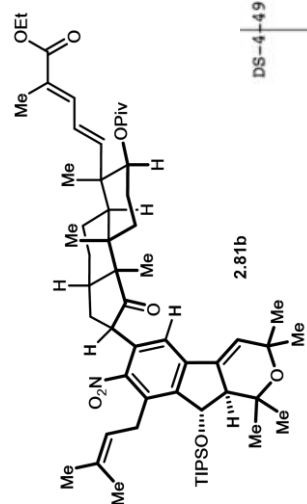




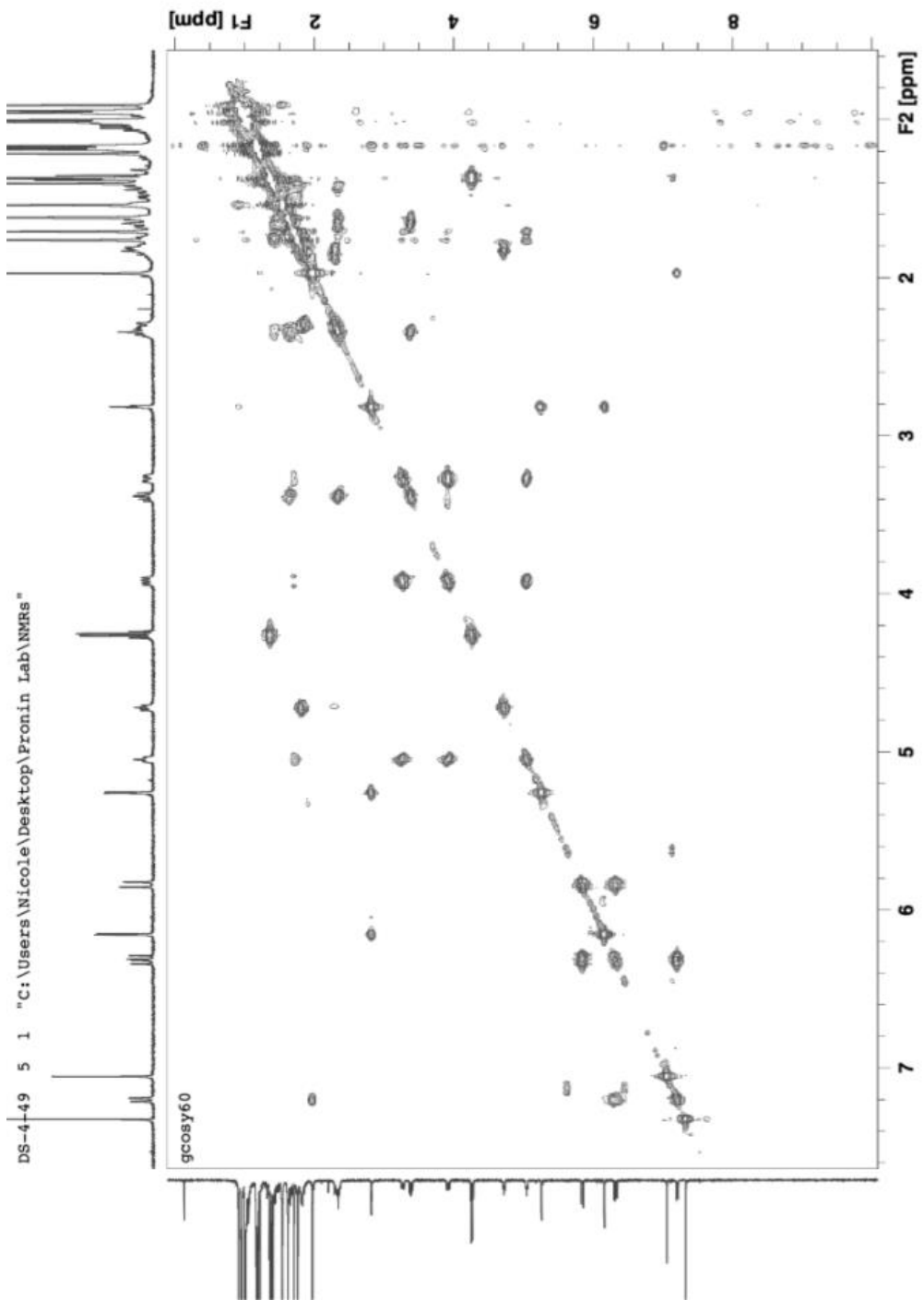


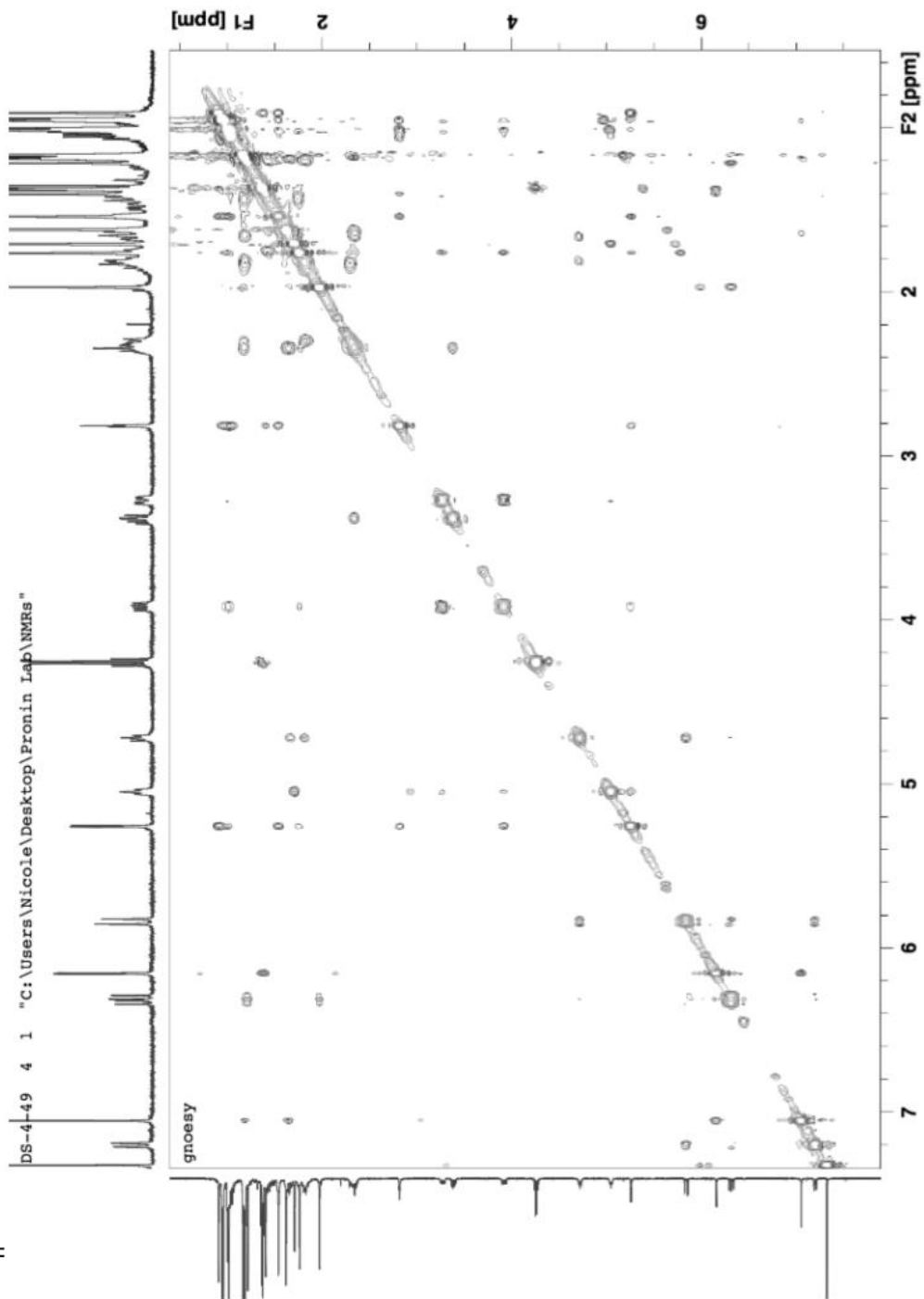
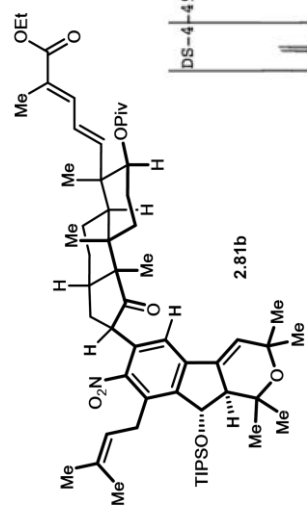


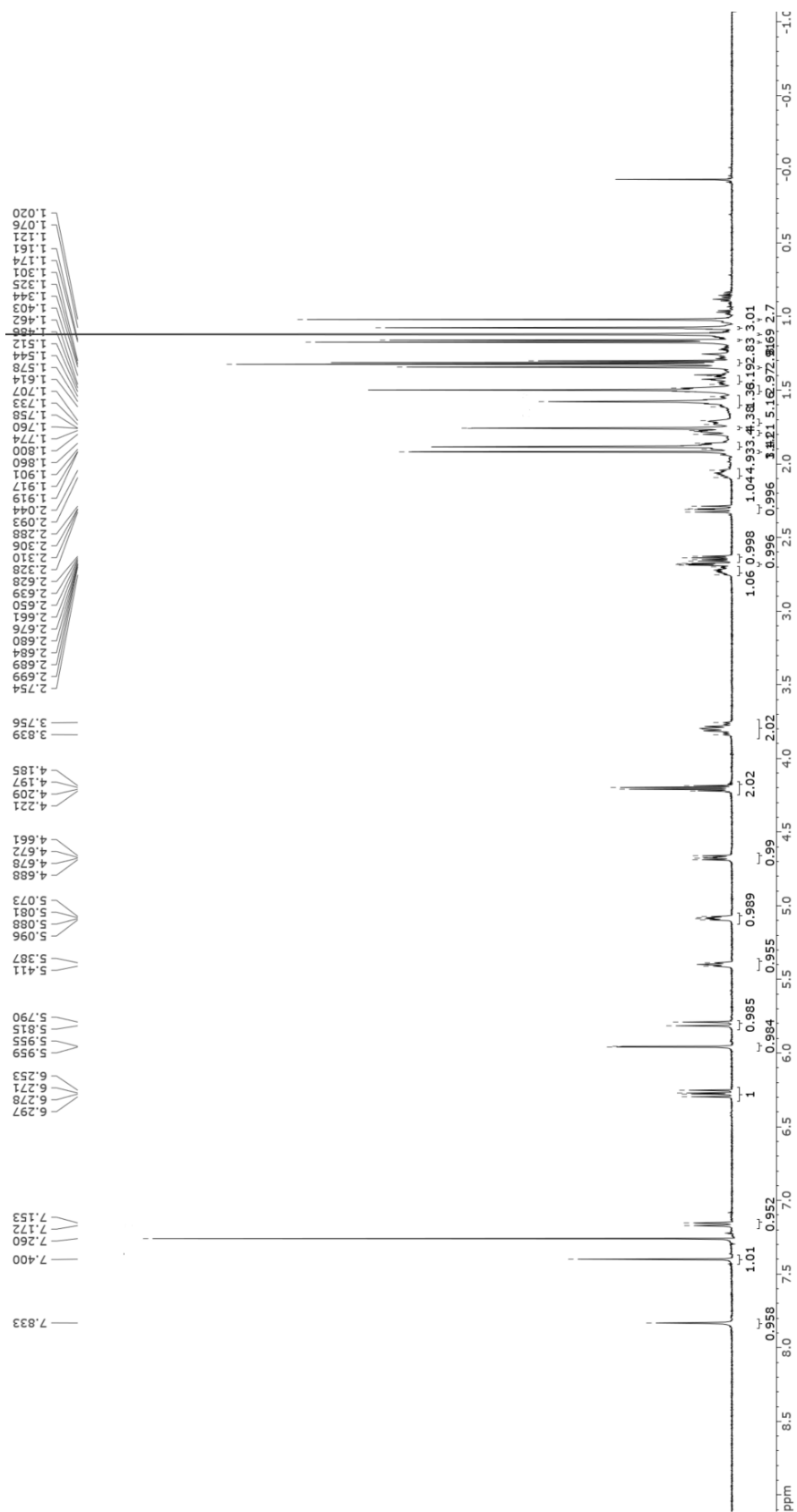
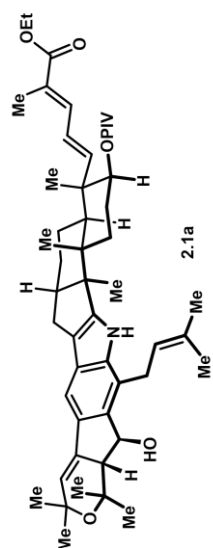


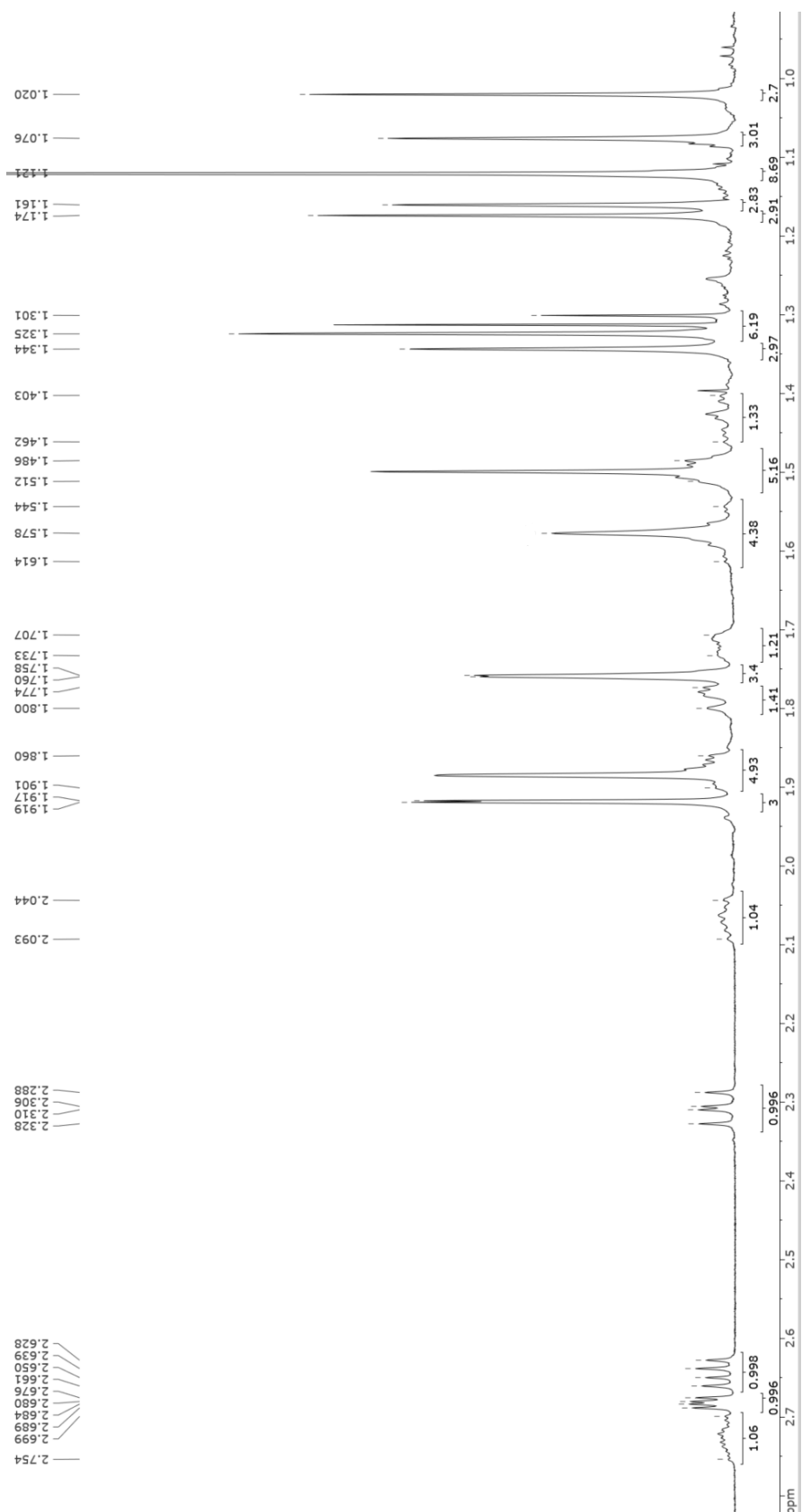
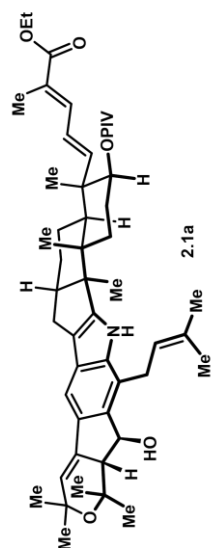


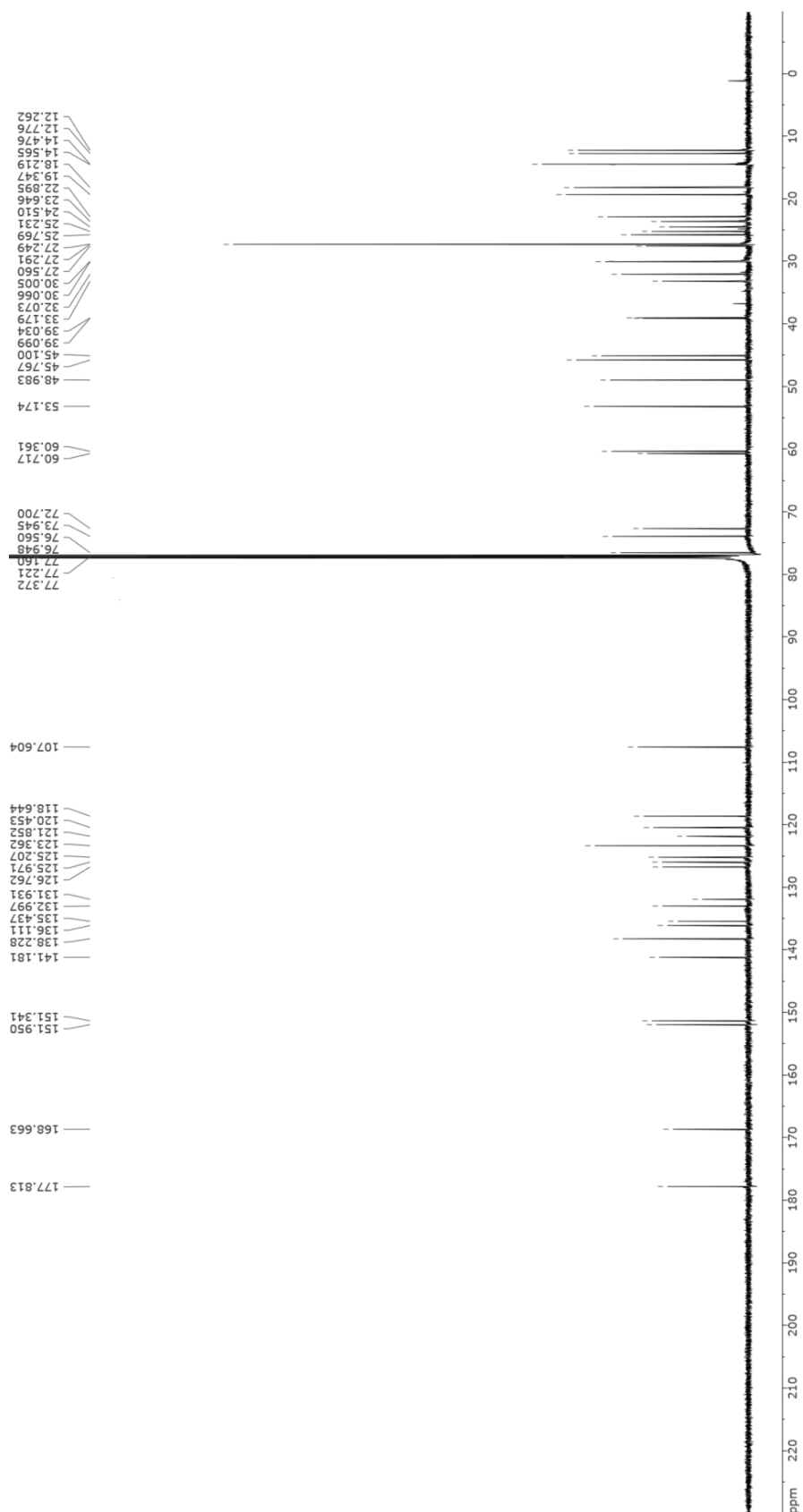
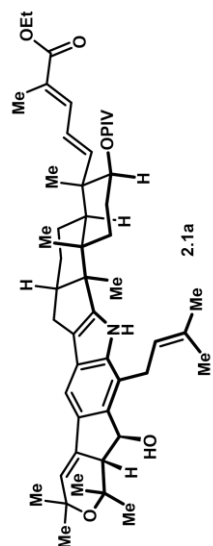
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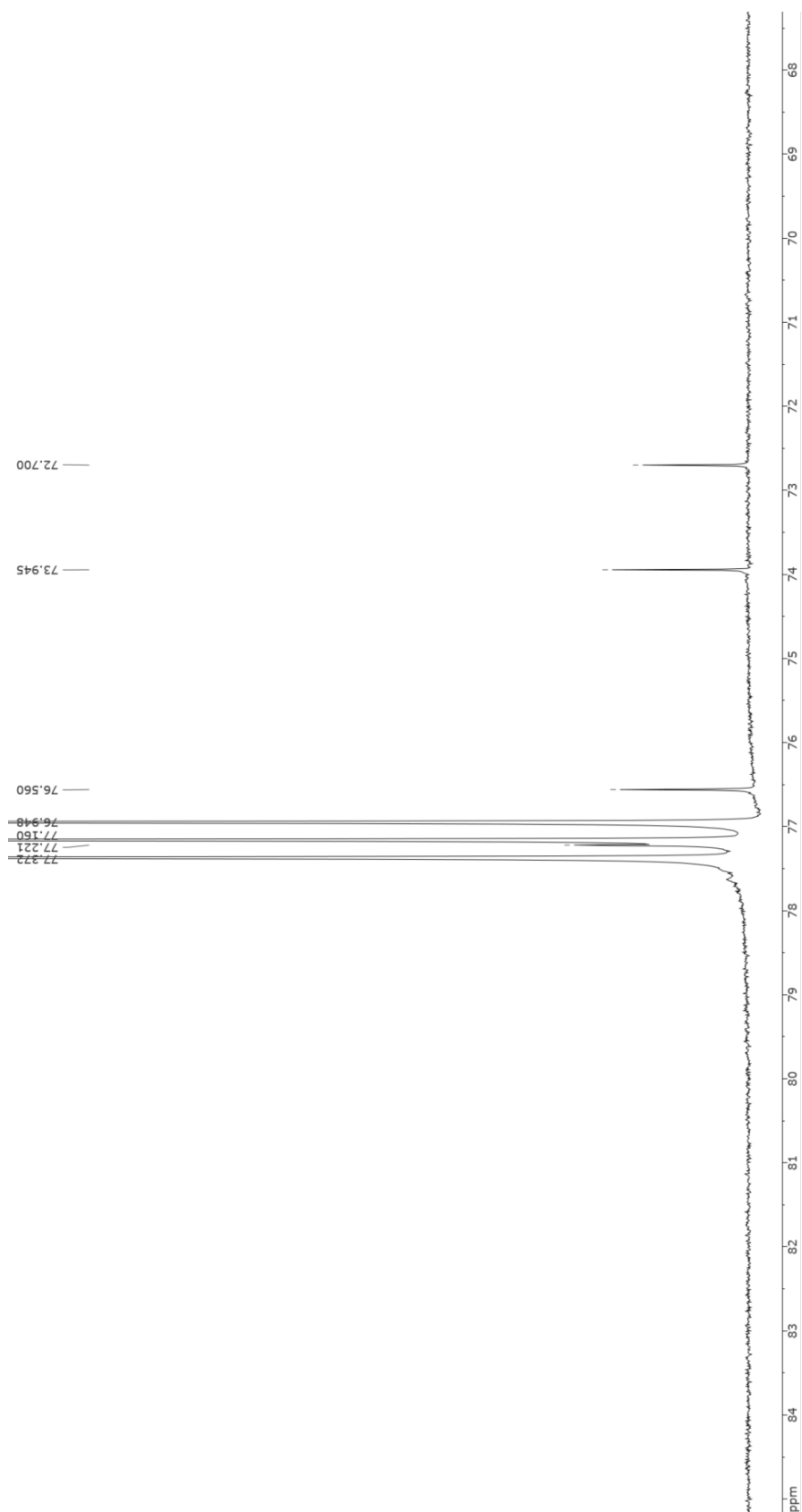
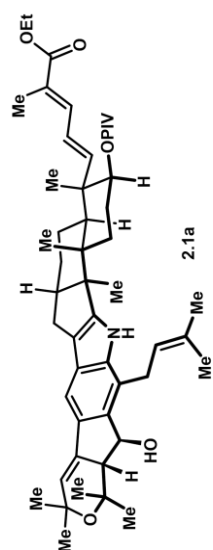


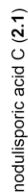


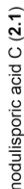




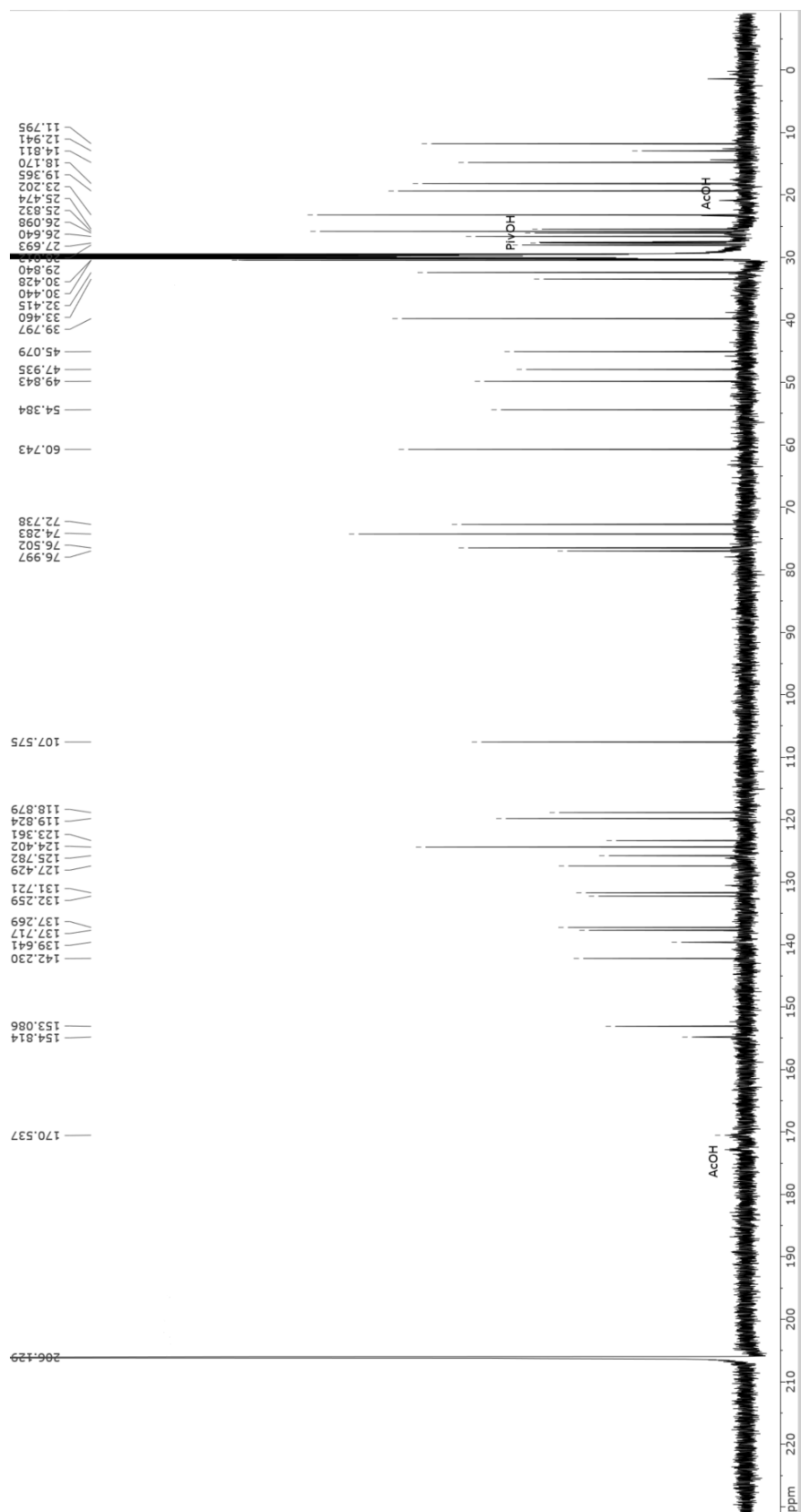
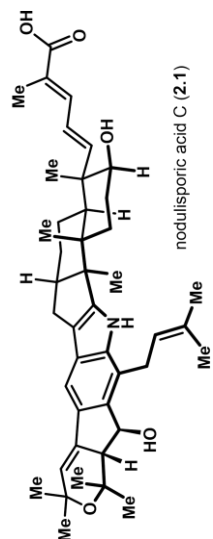


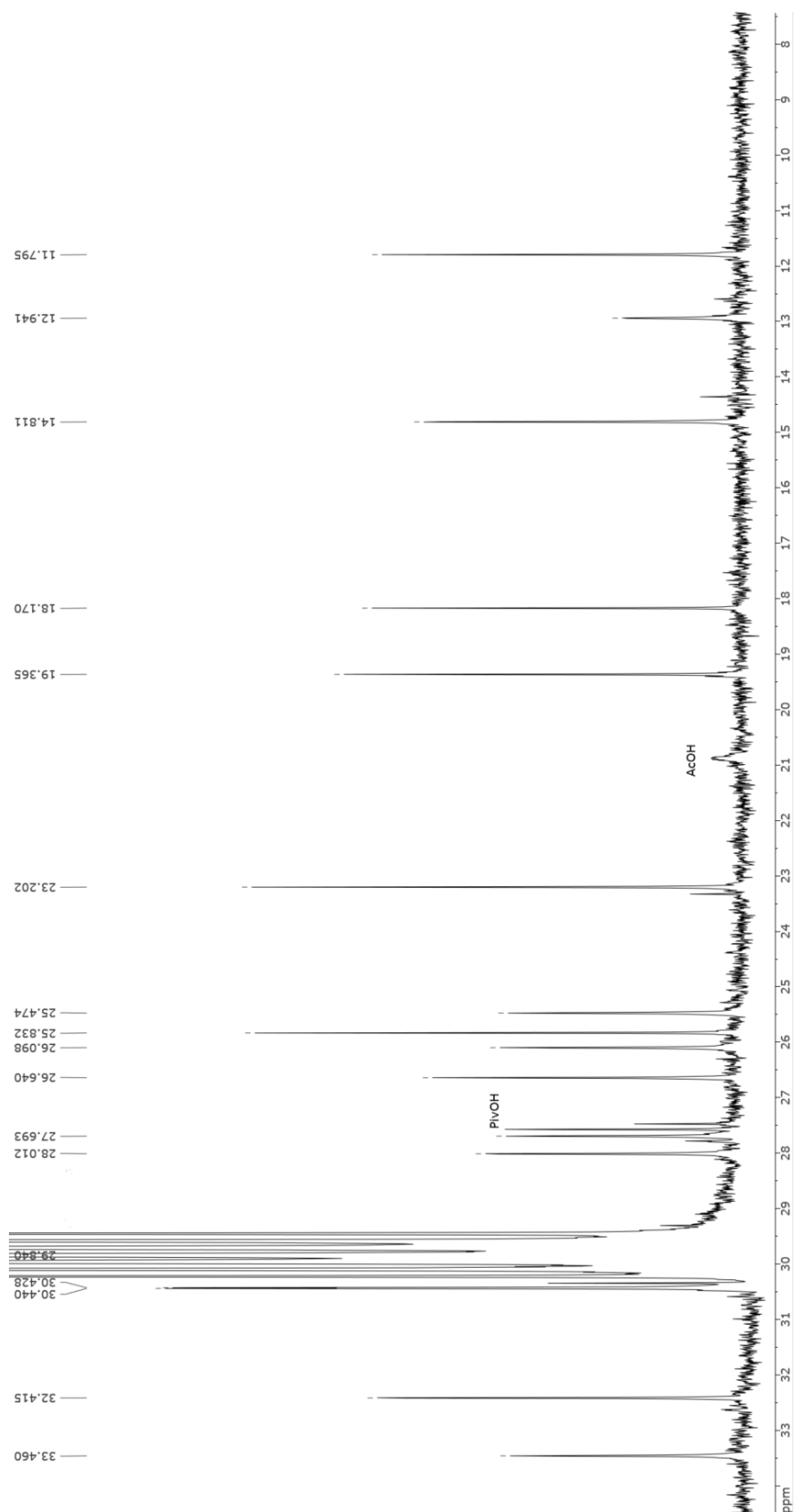
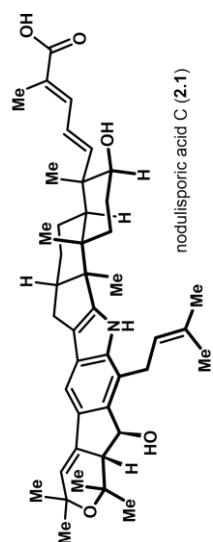


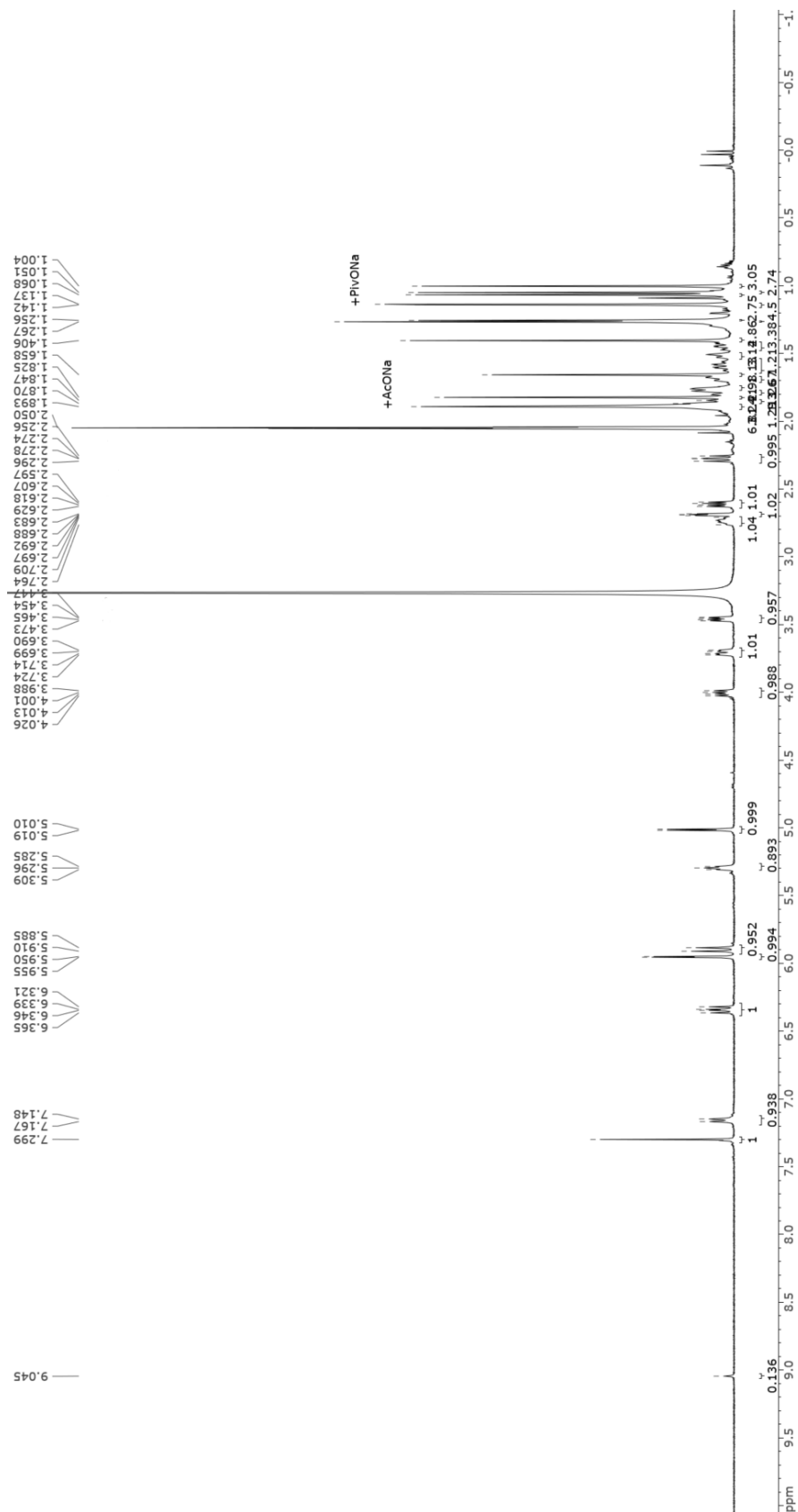
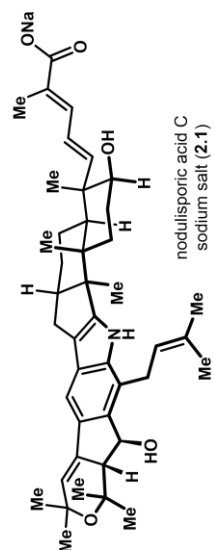




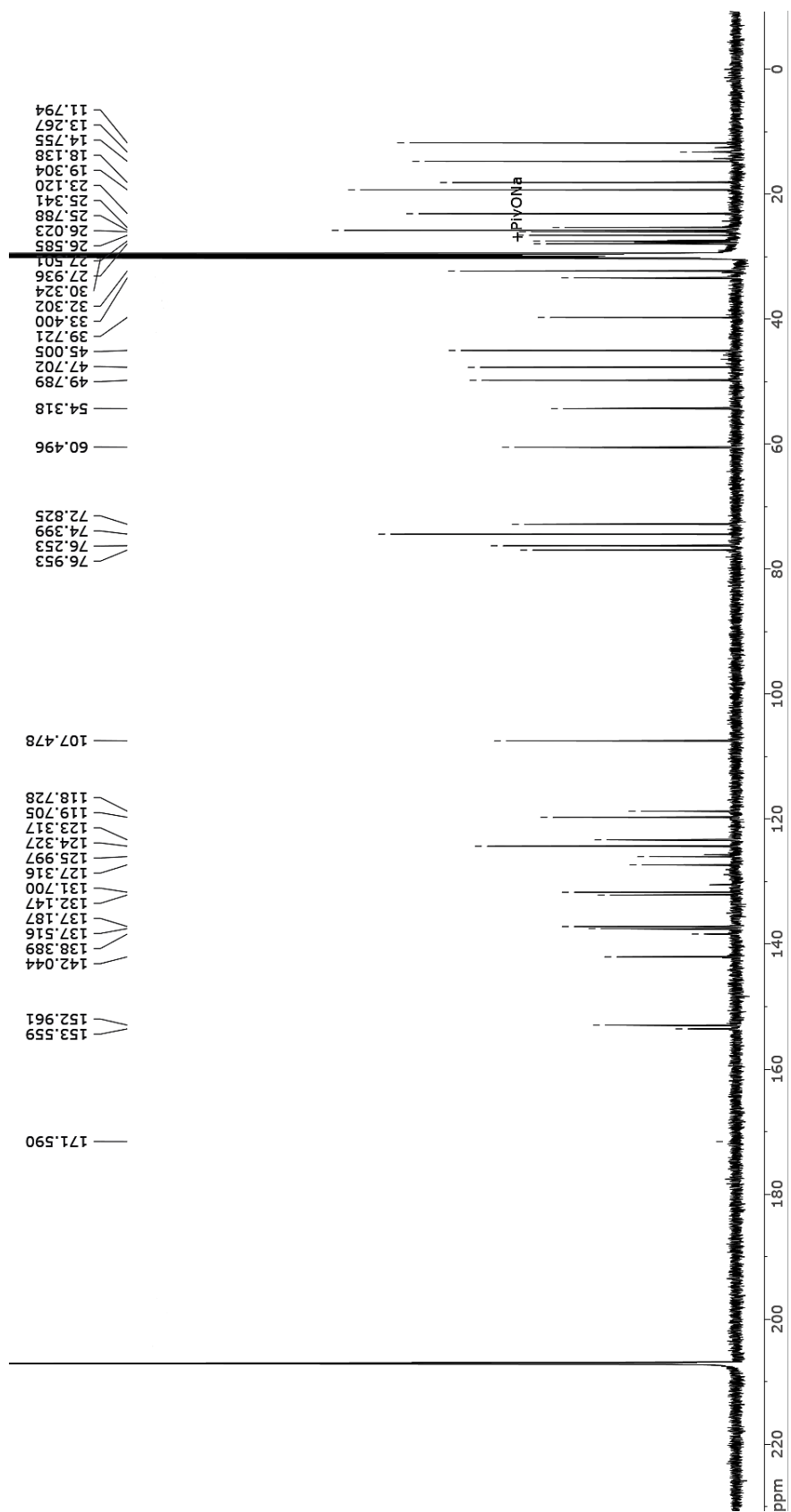
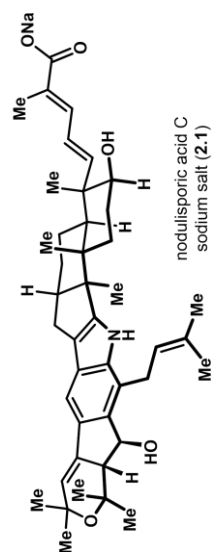
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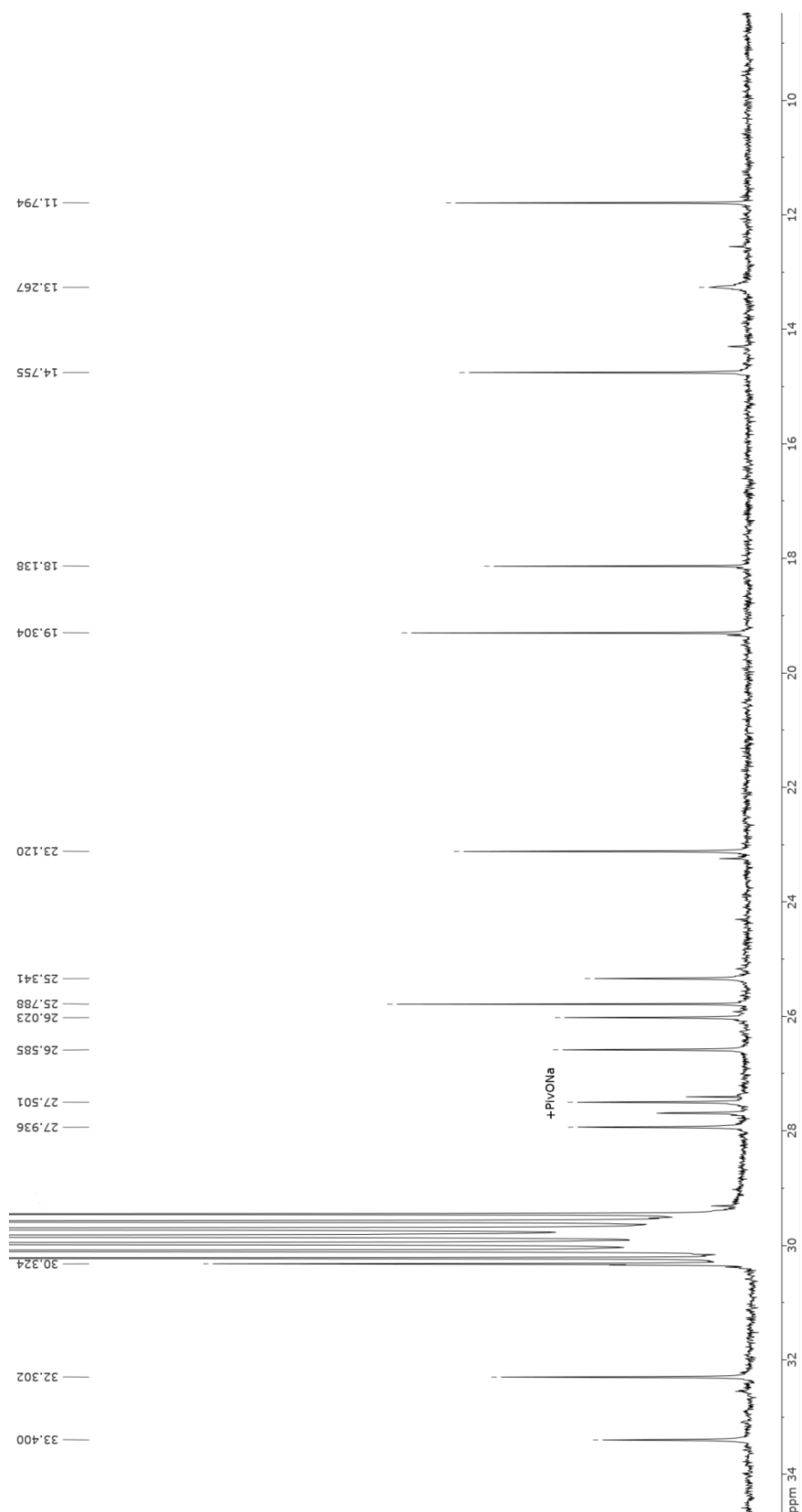
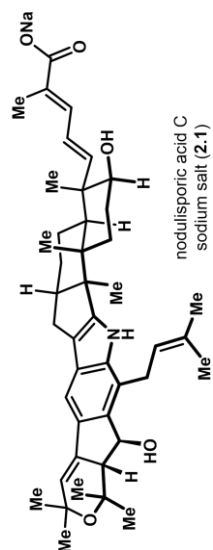




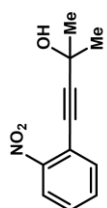




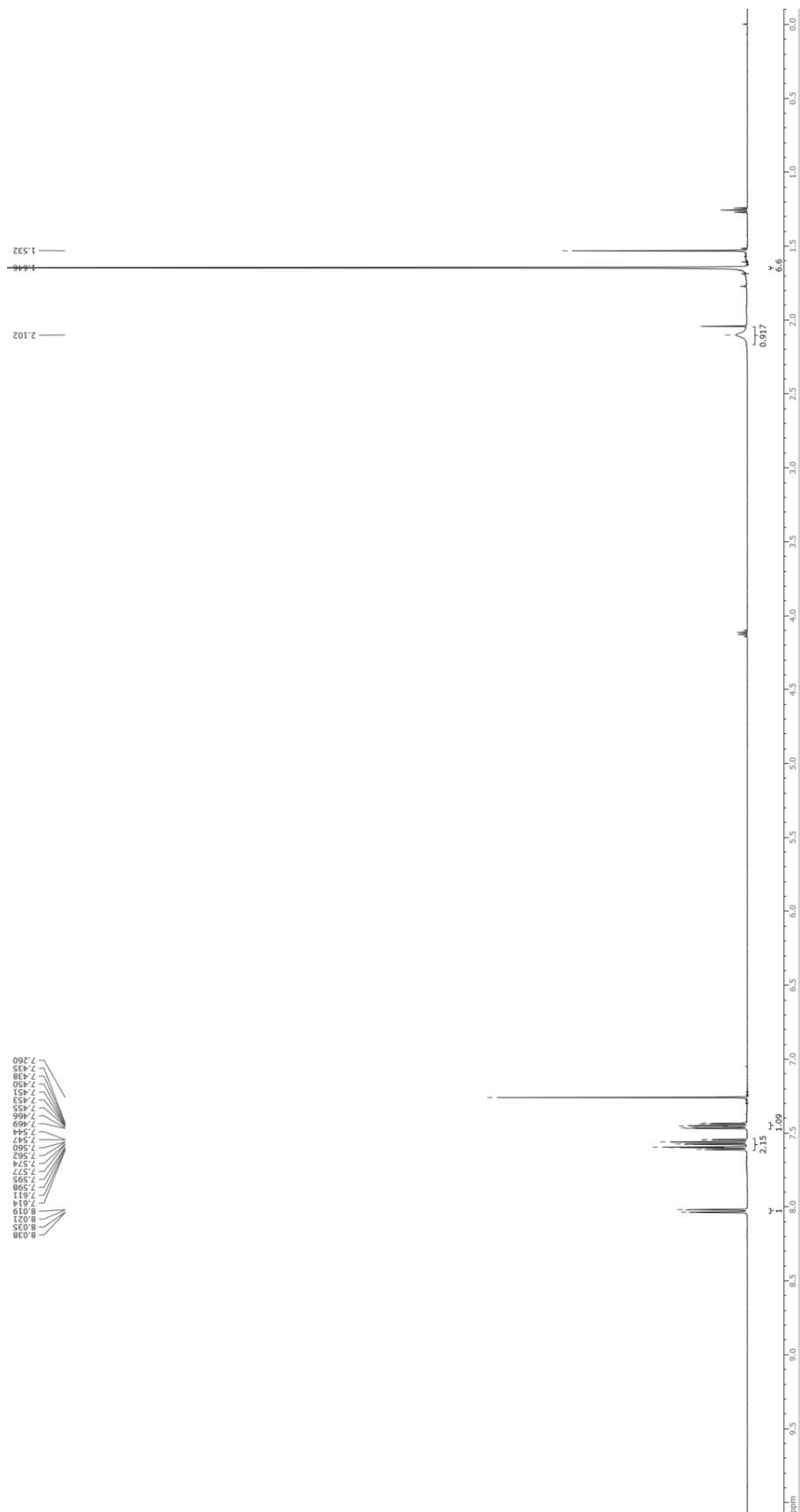


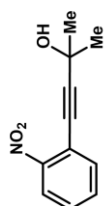


Appendix B: NMR Spectra for Chapter 3

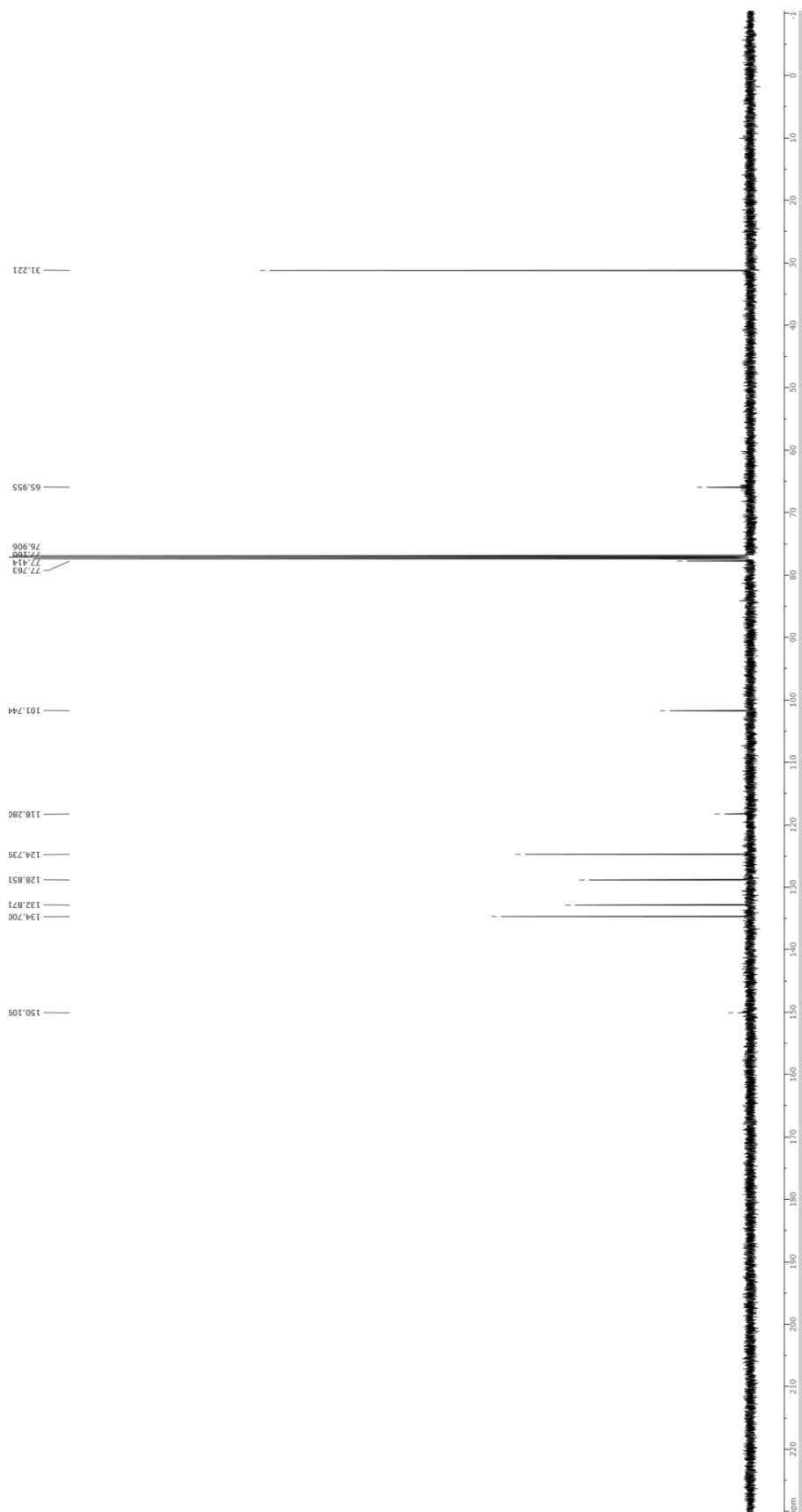


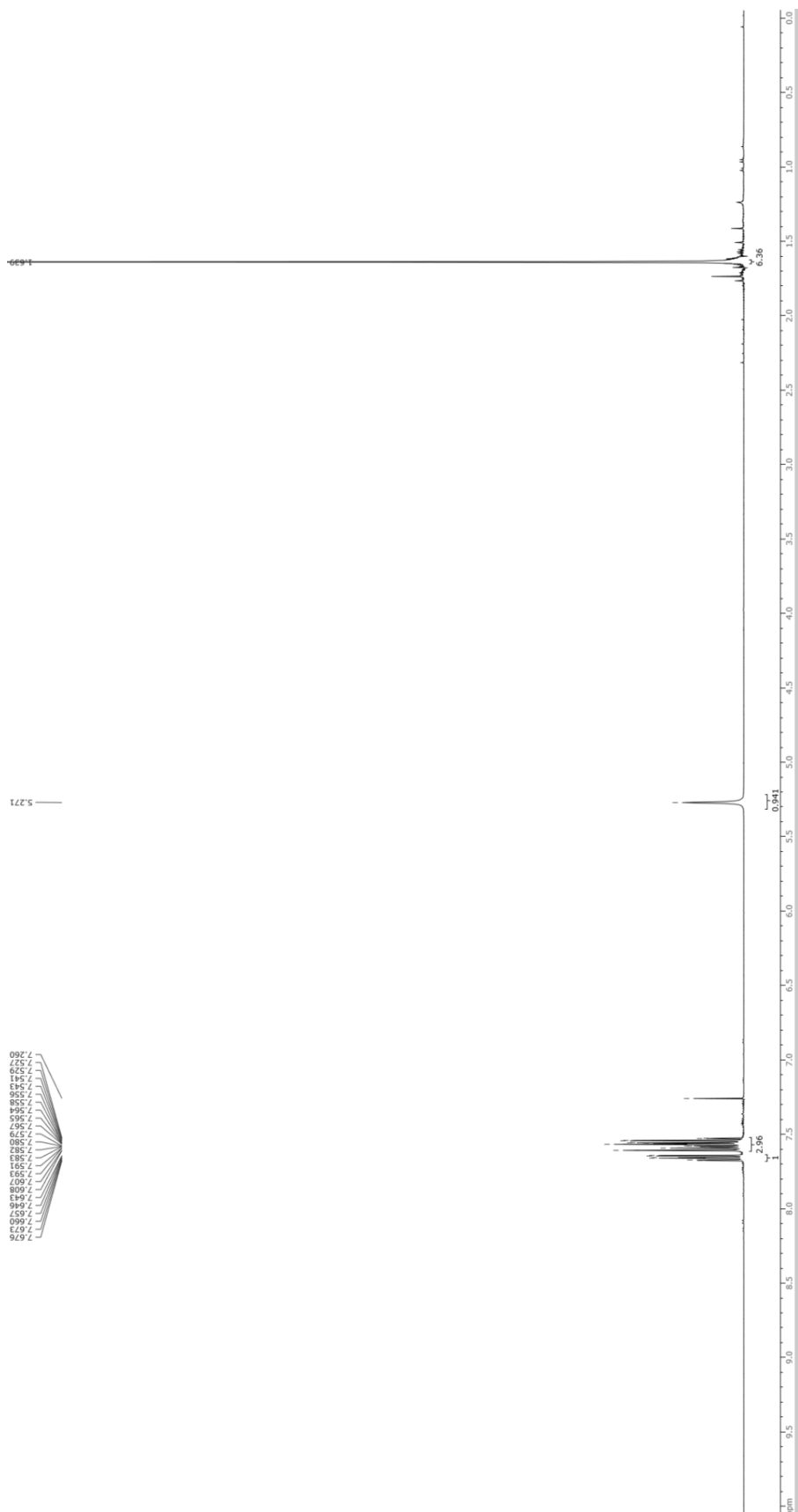
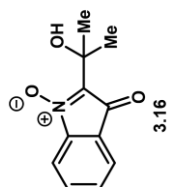
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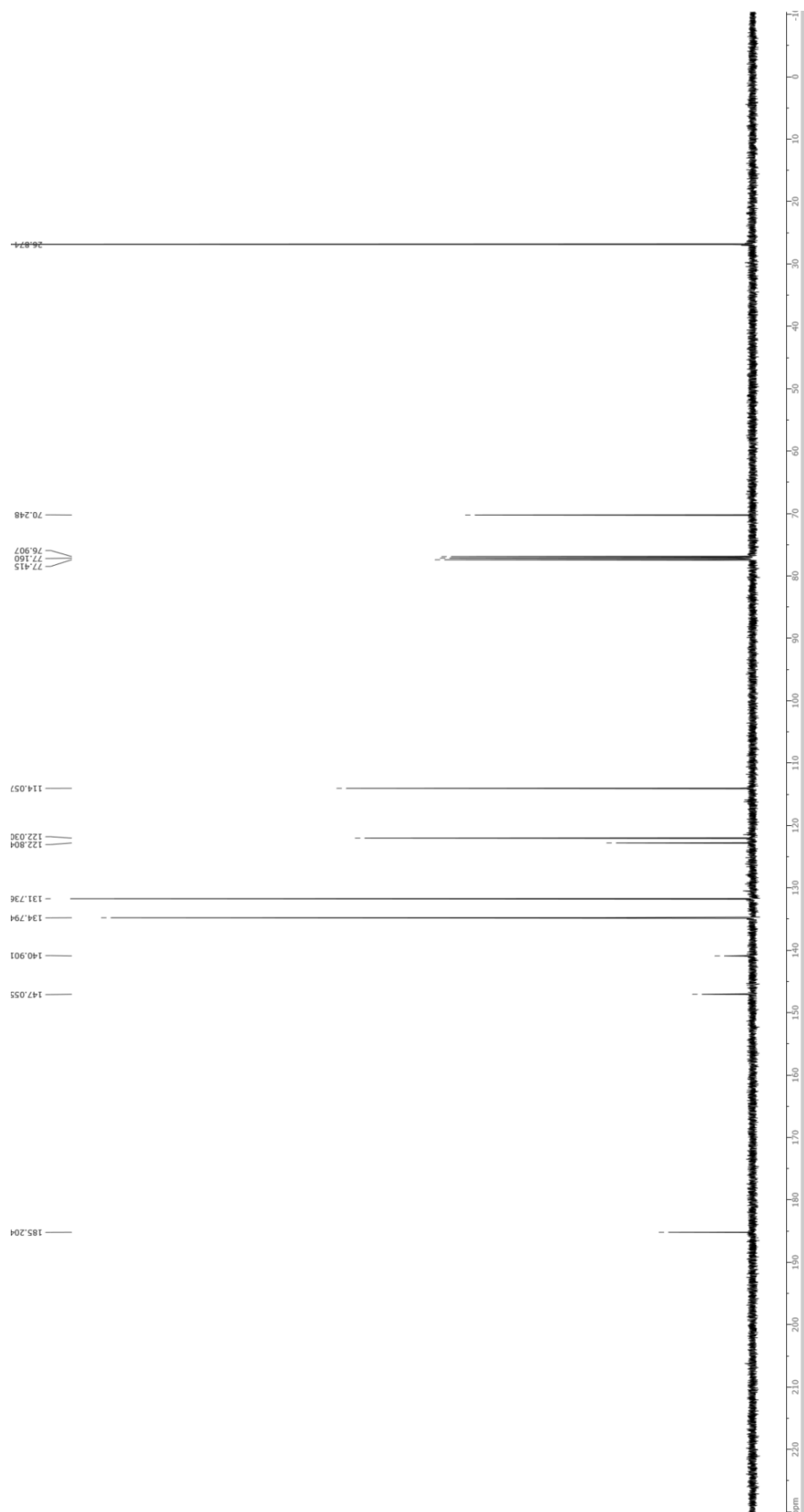
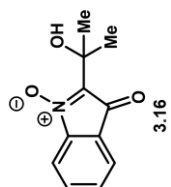


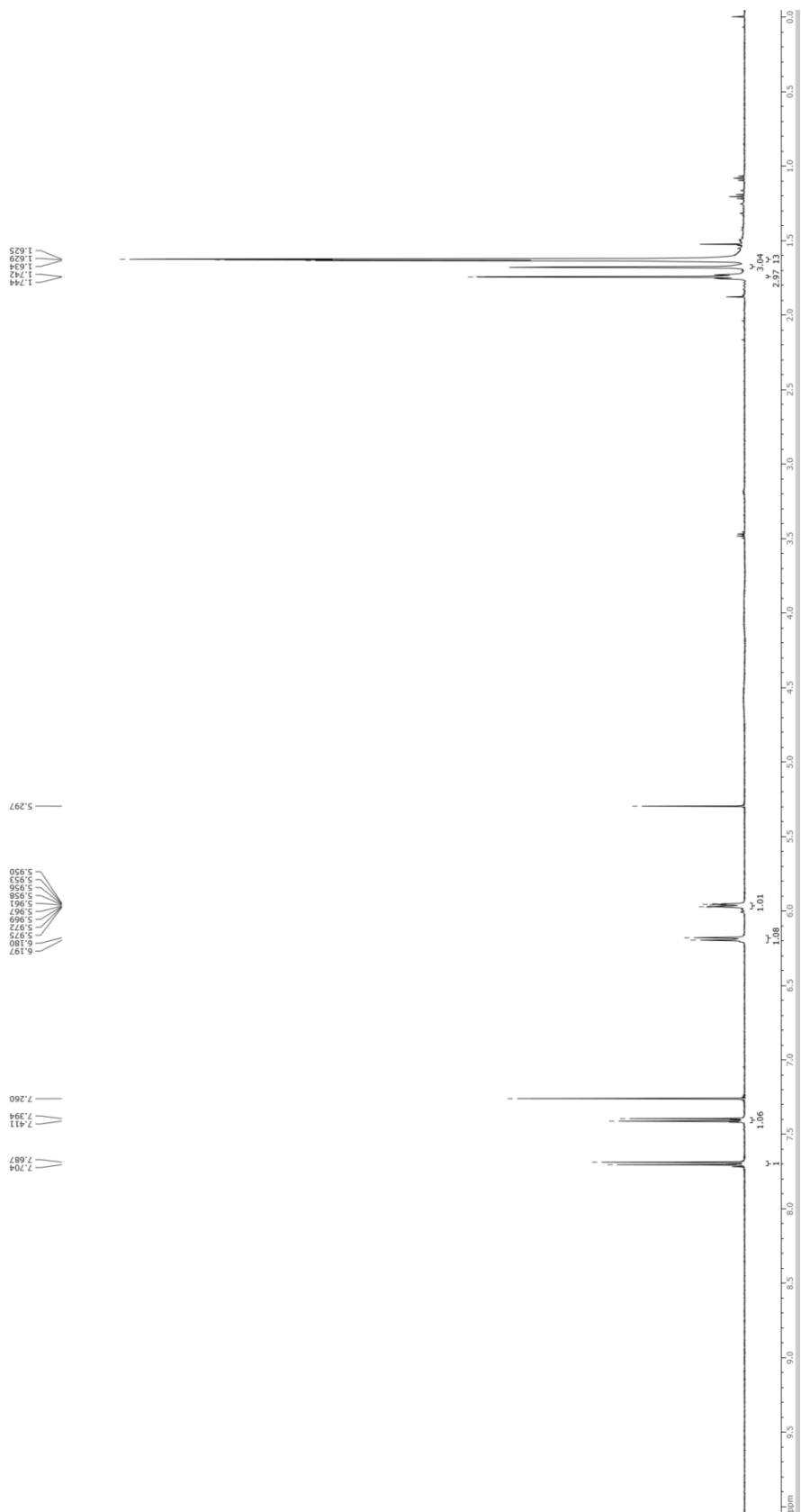
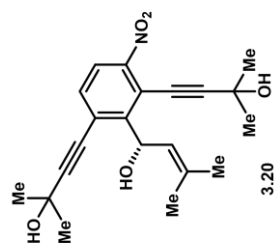


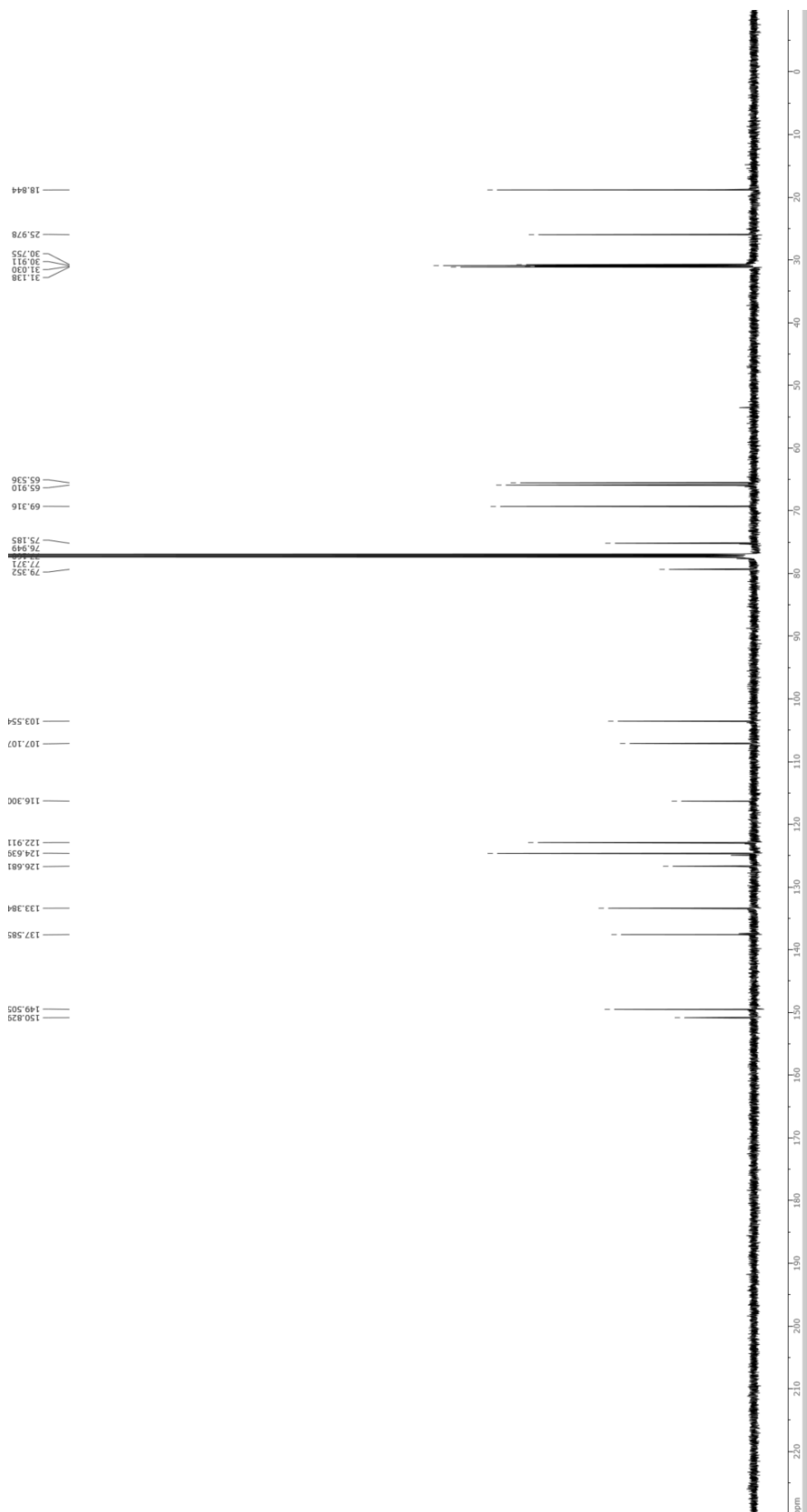
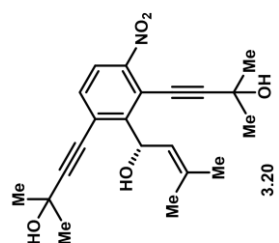
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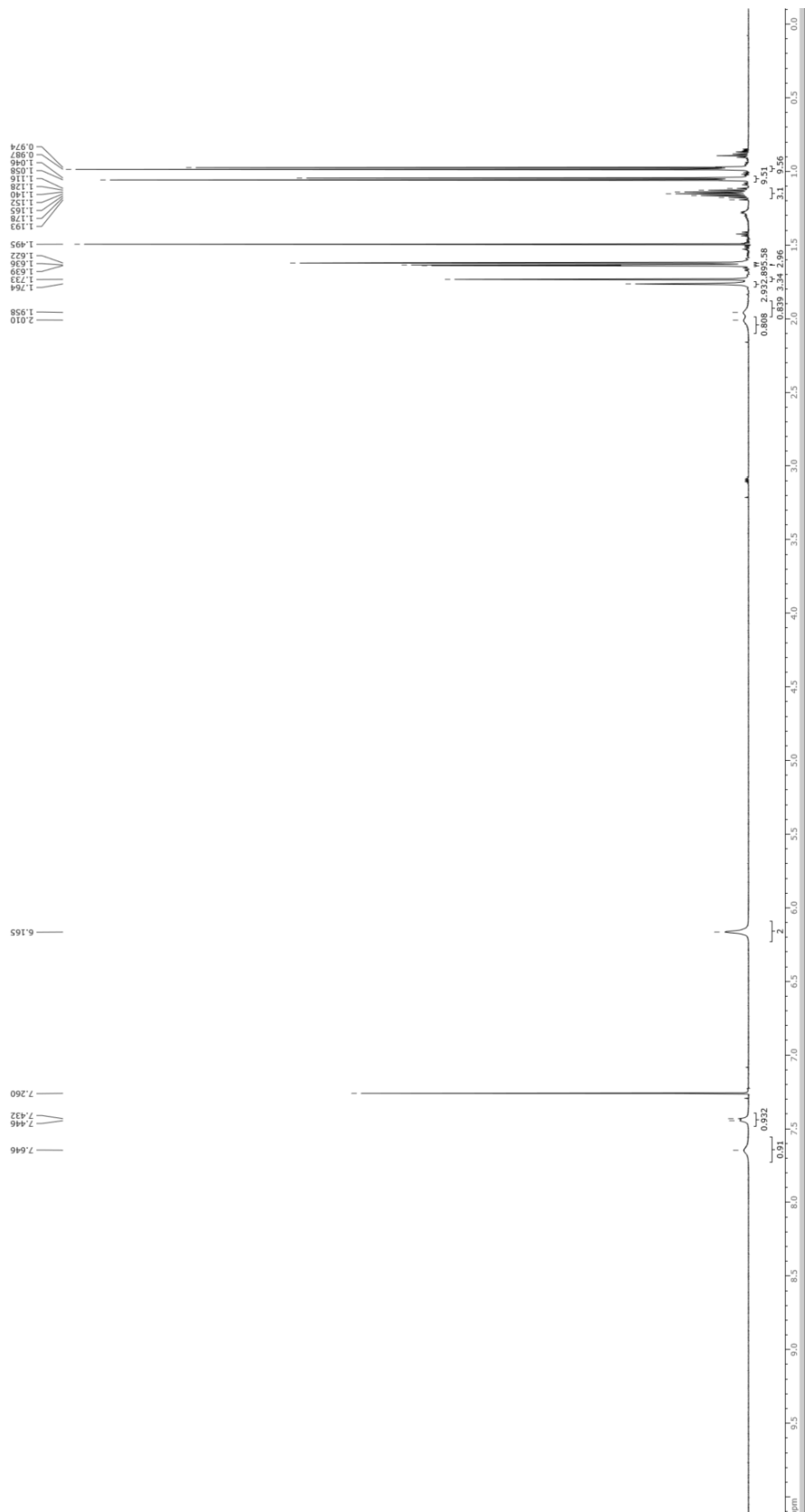
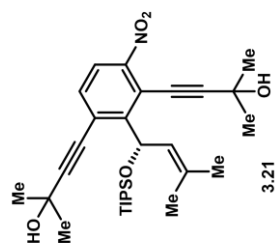


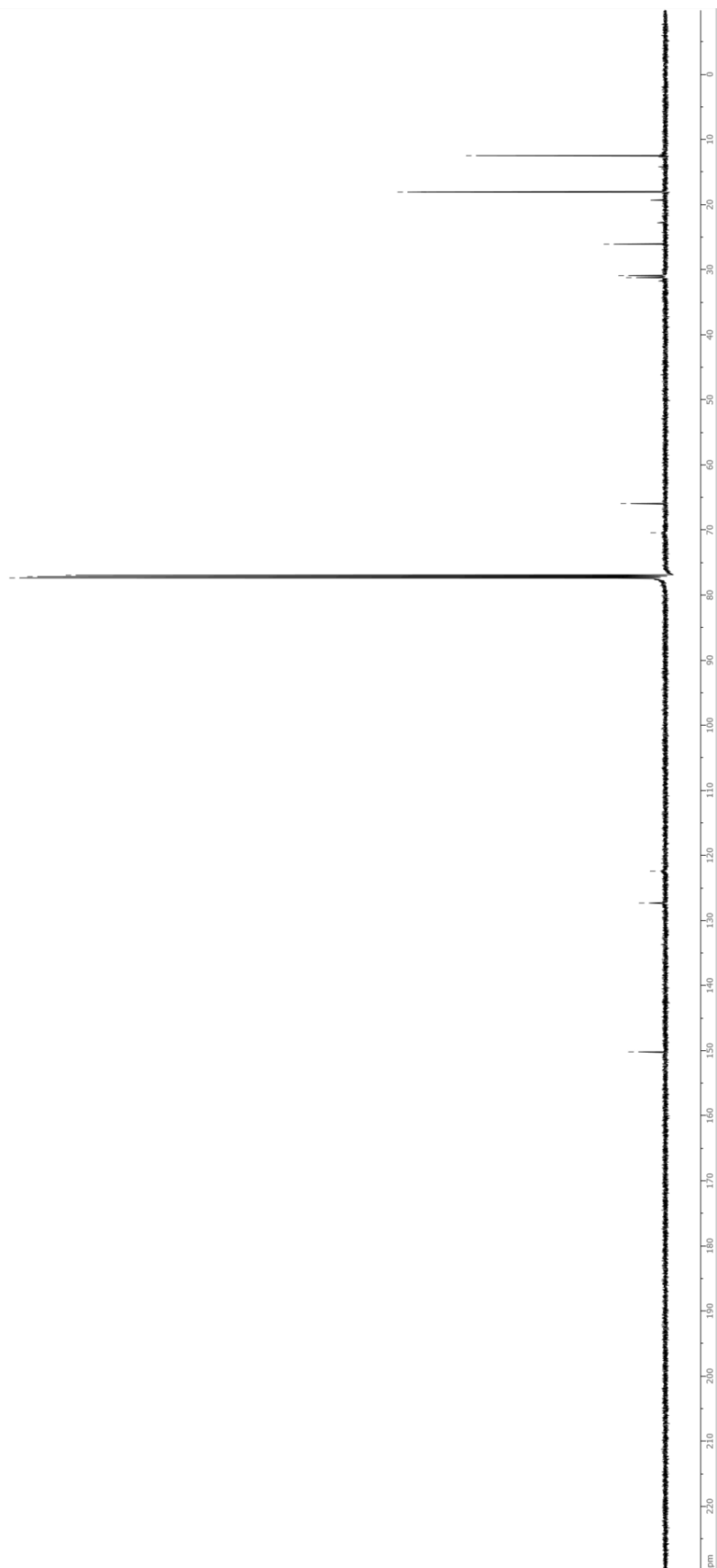
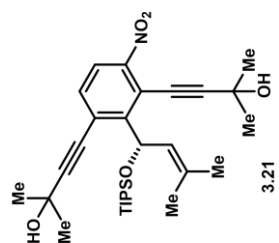


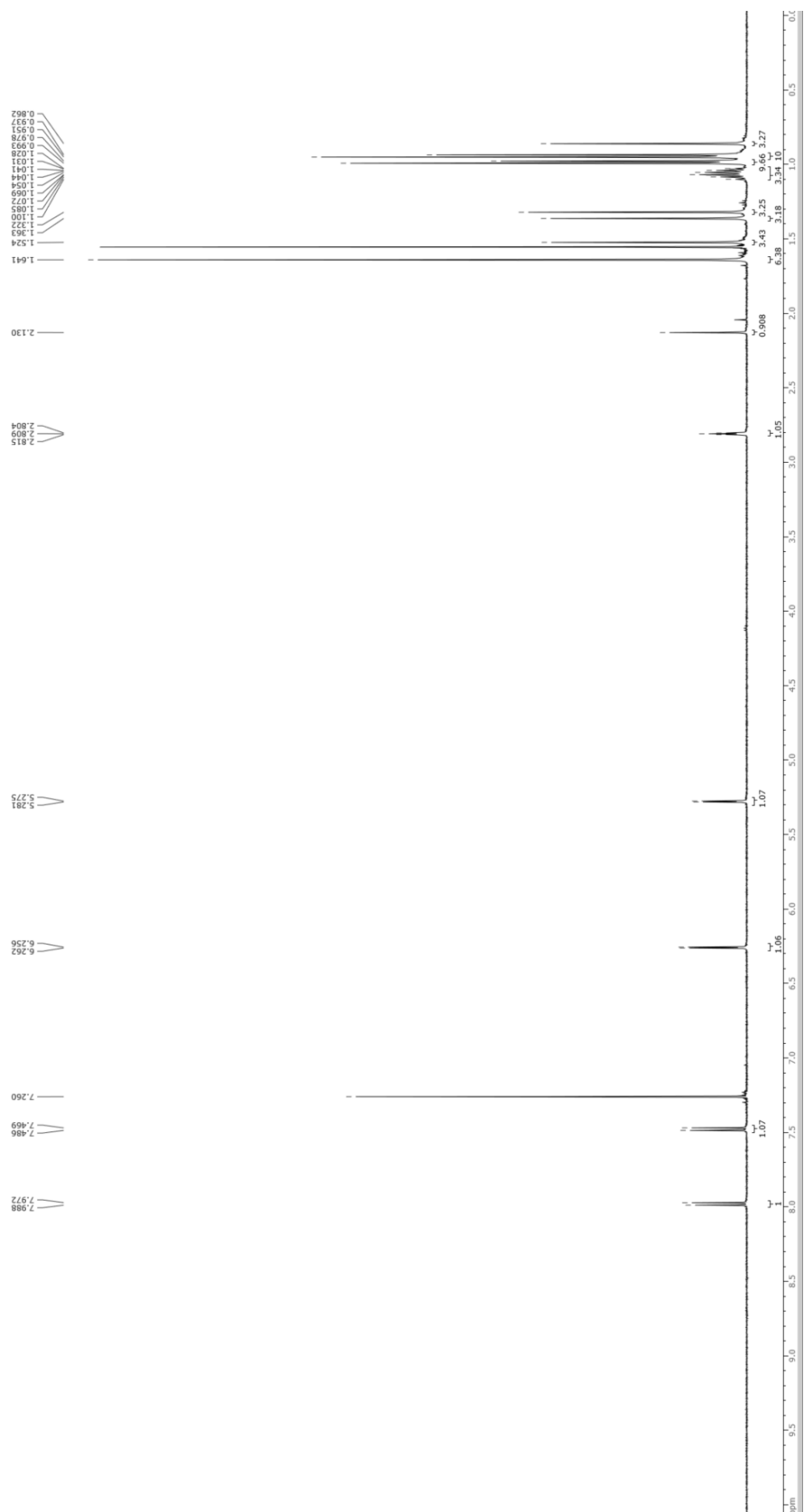
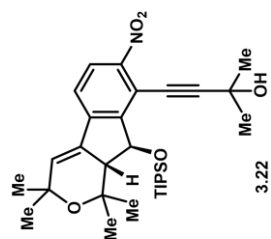


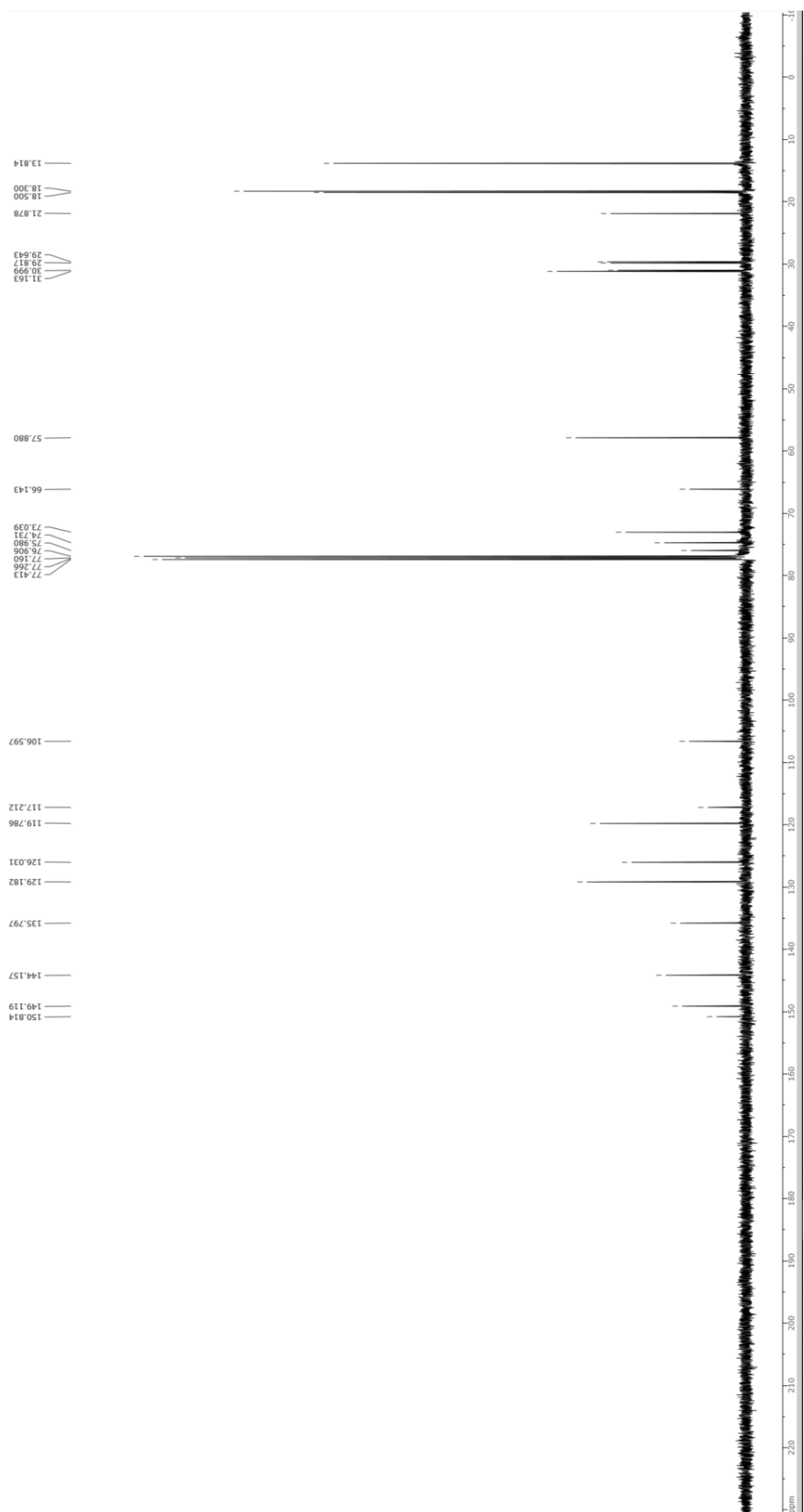
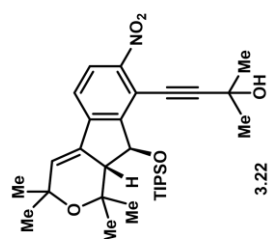


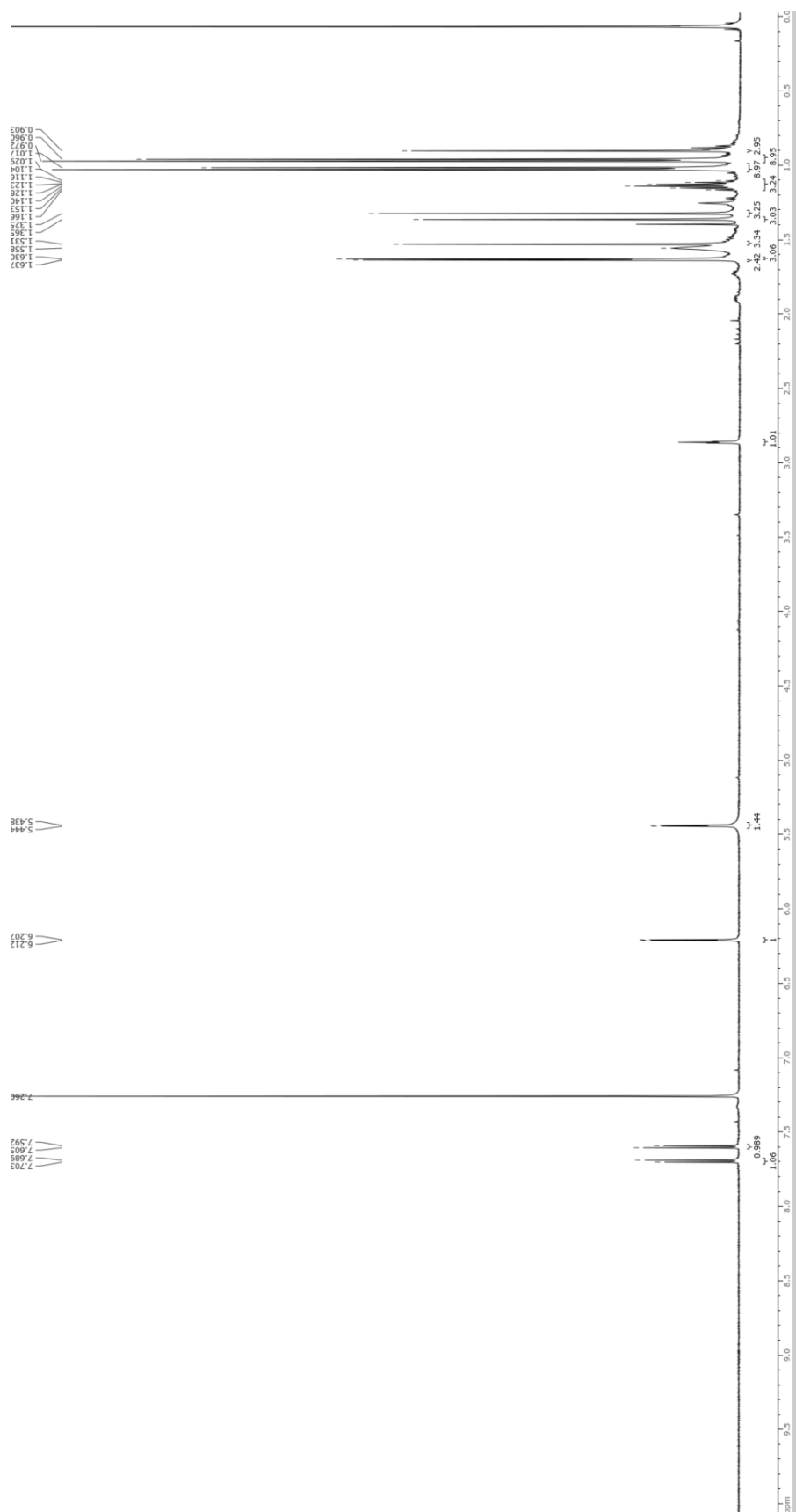
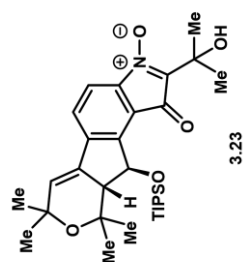


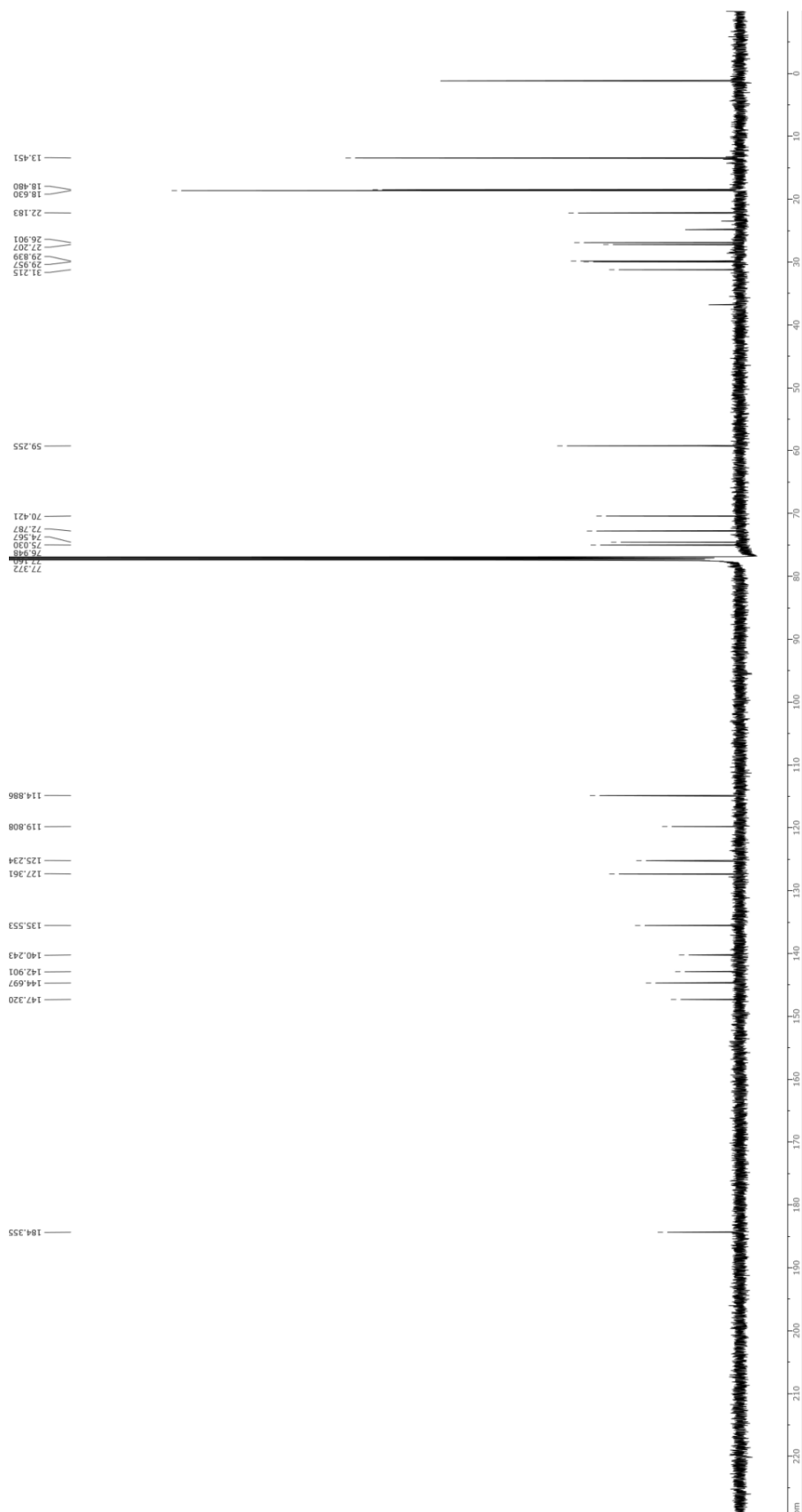
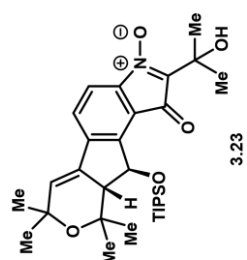




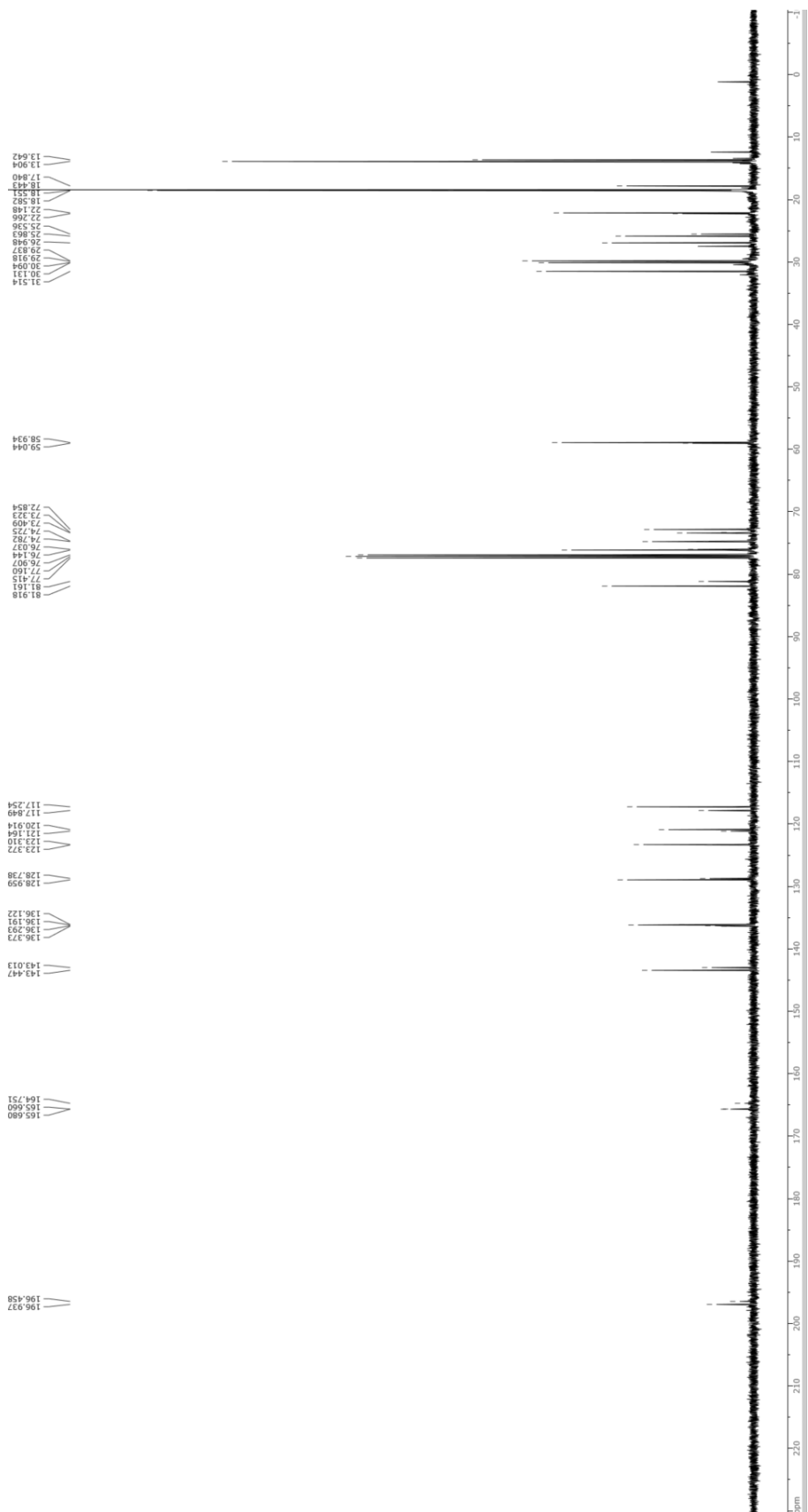
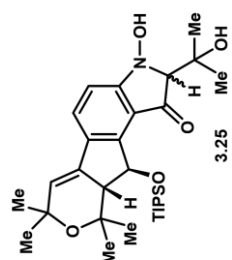


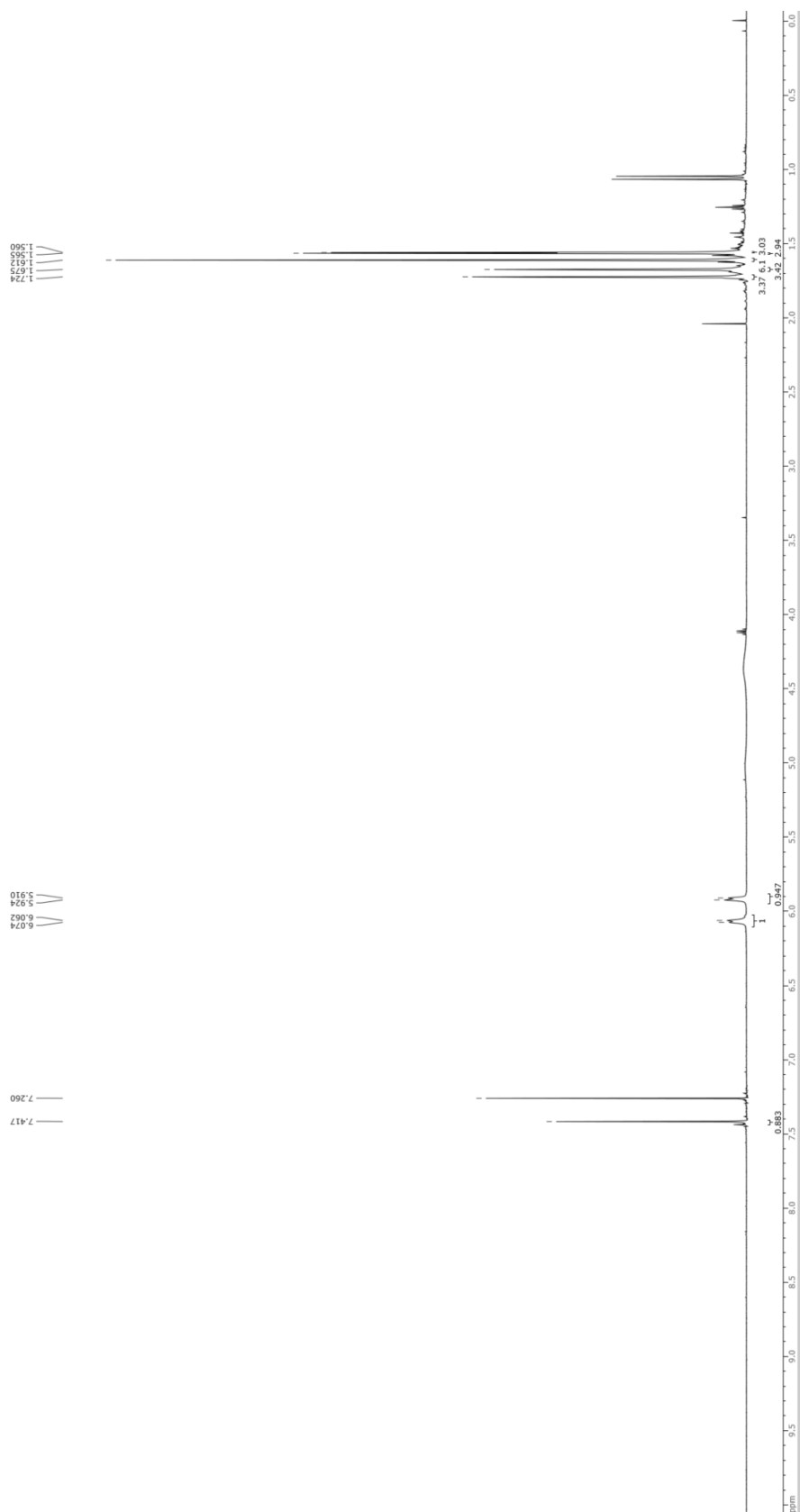
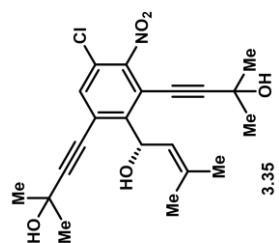




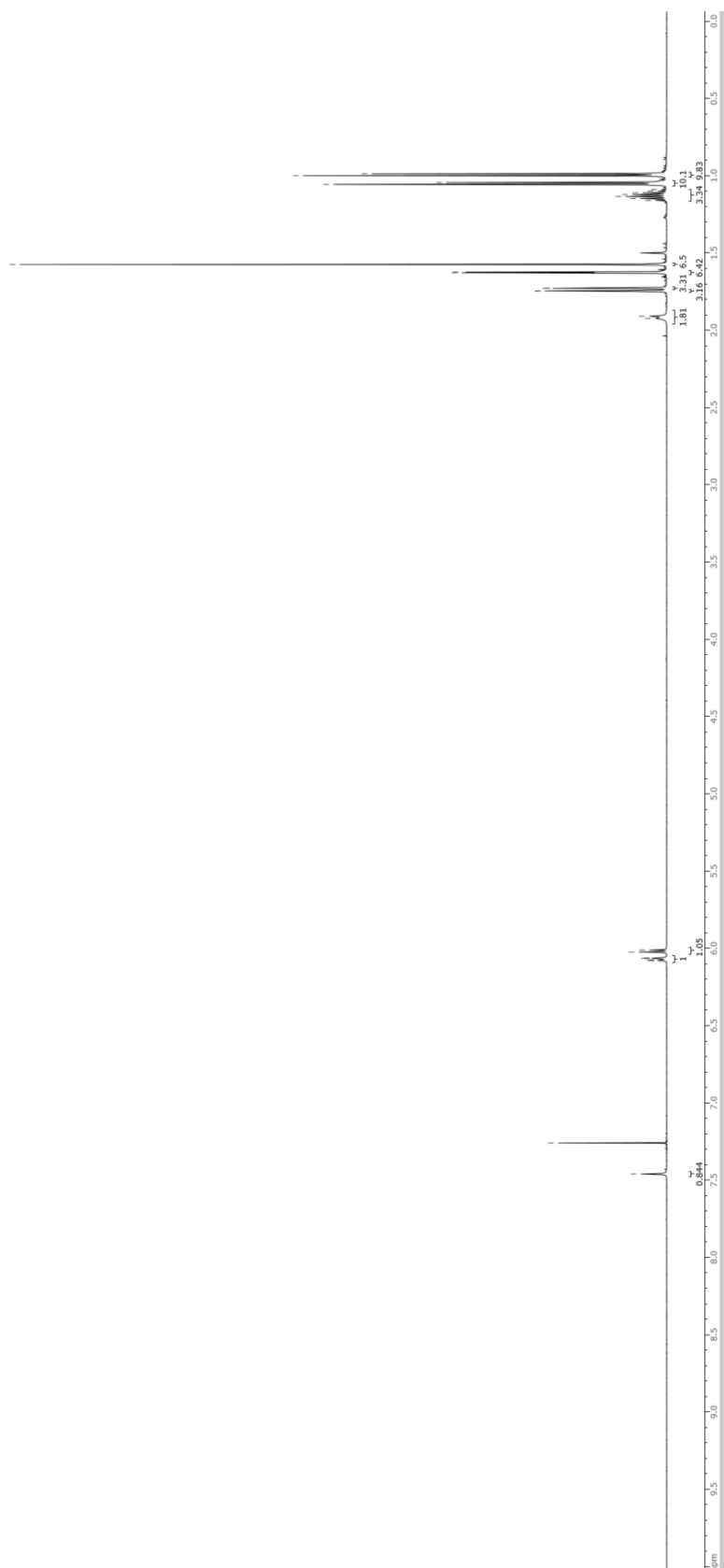
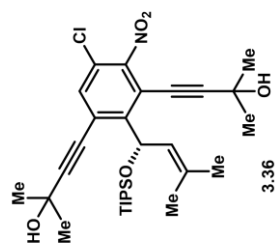


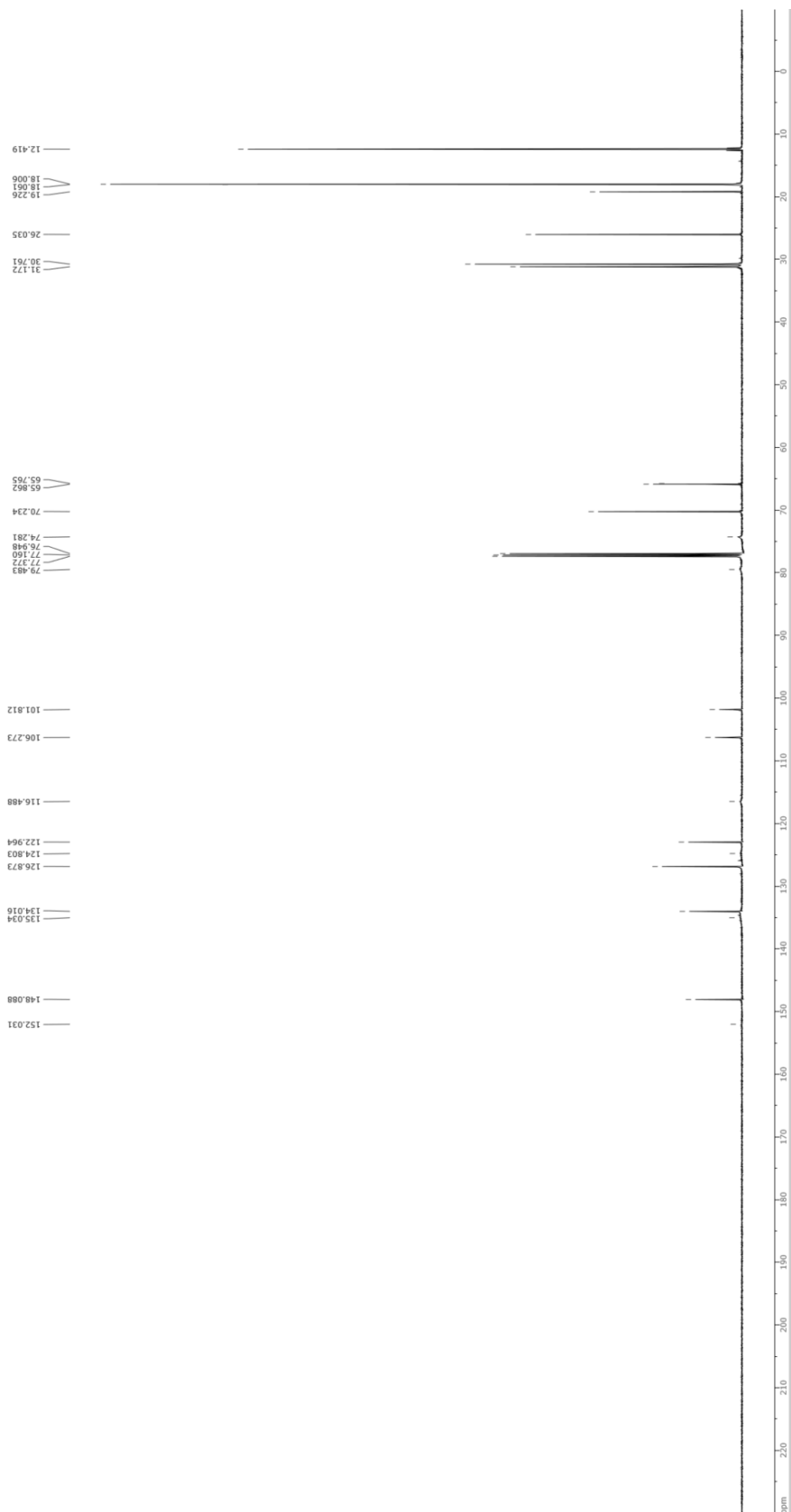
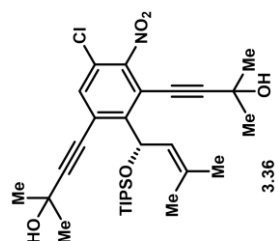


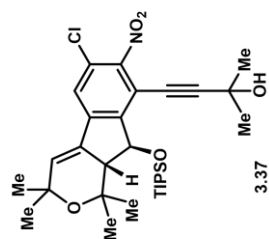












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1.138
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1.130
1.127
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1.113
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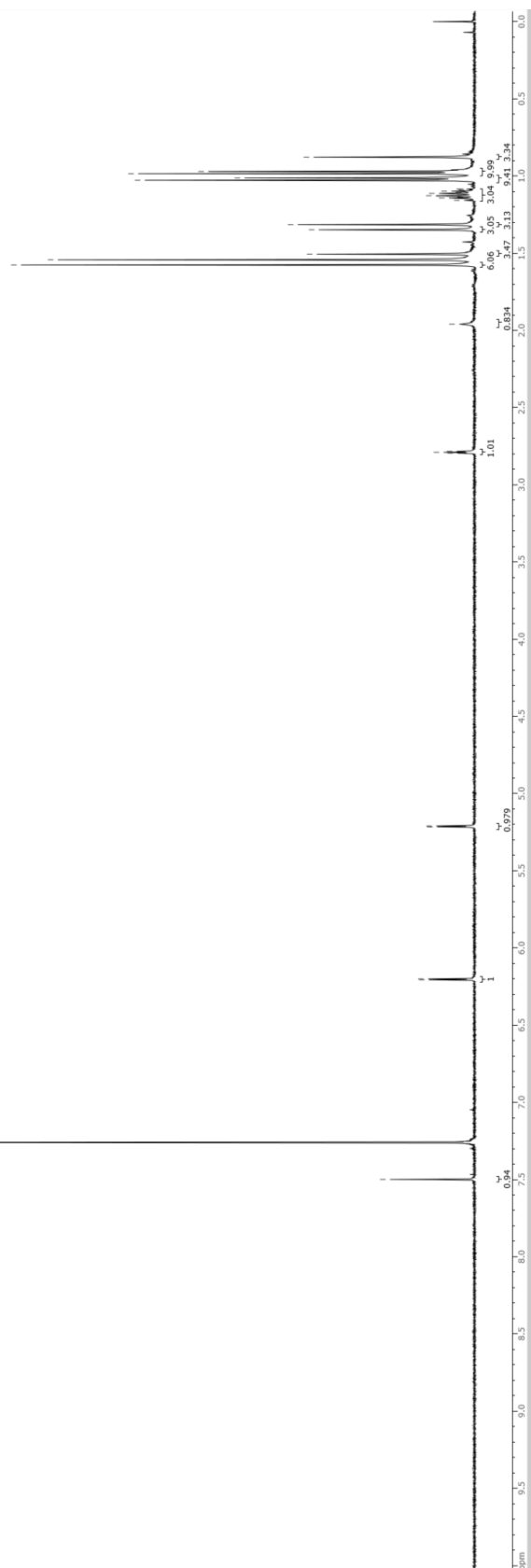
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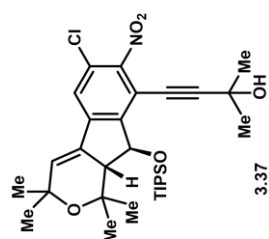
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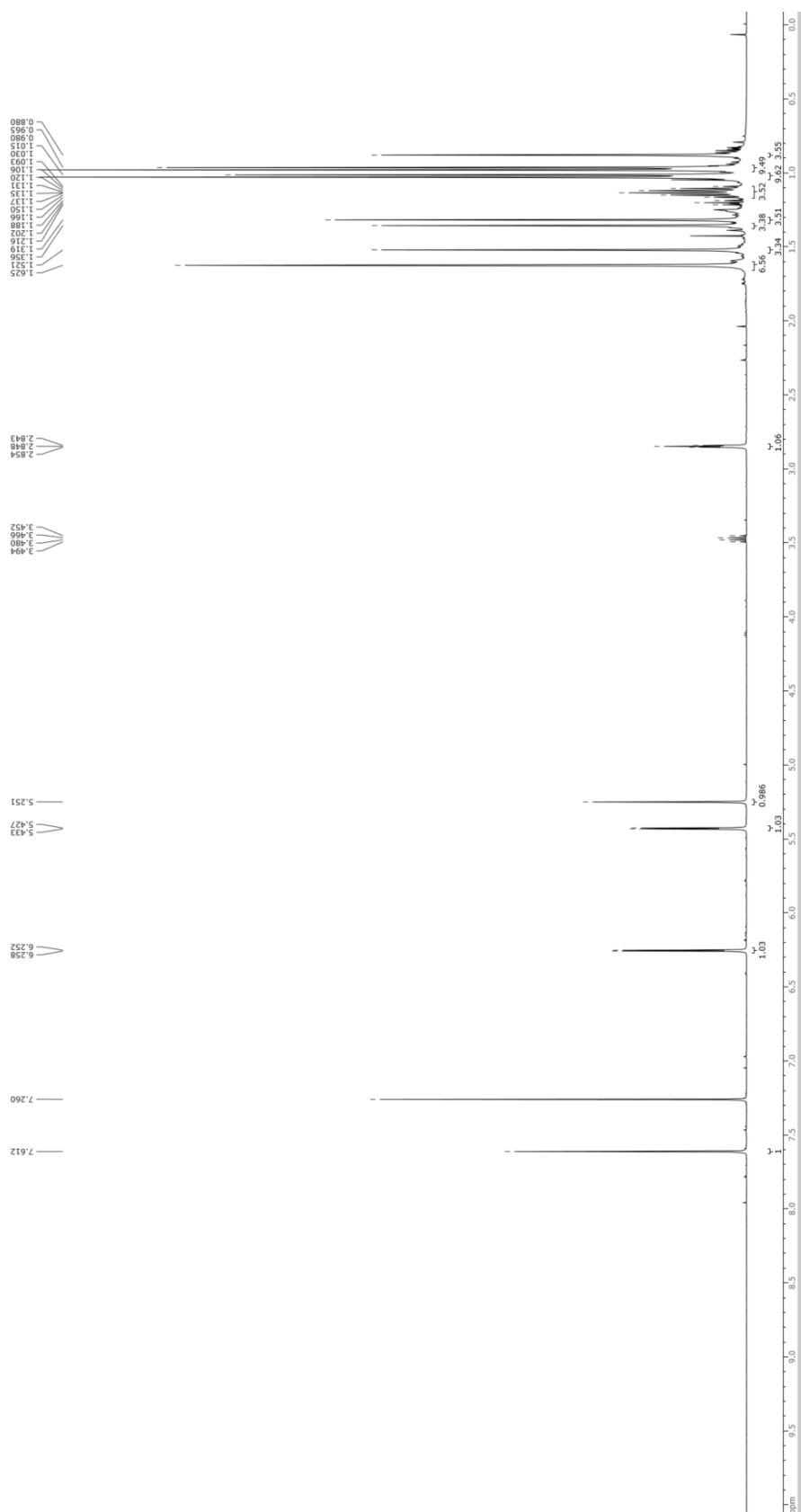
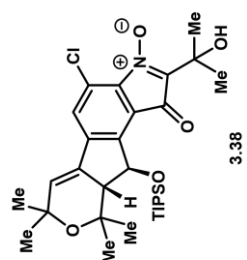
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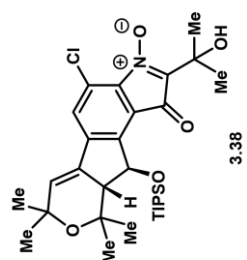
7.260

7.499

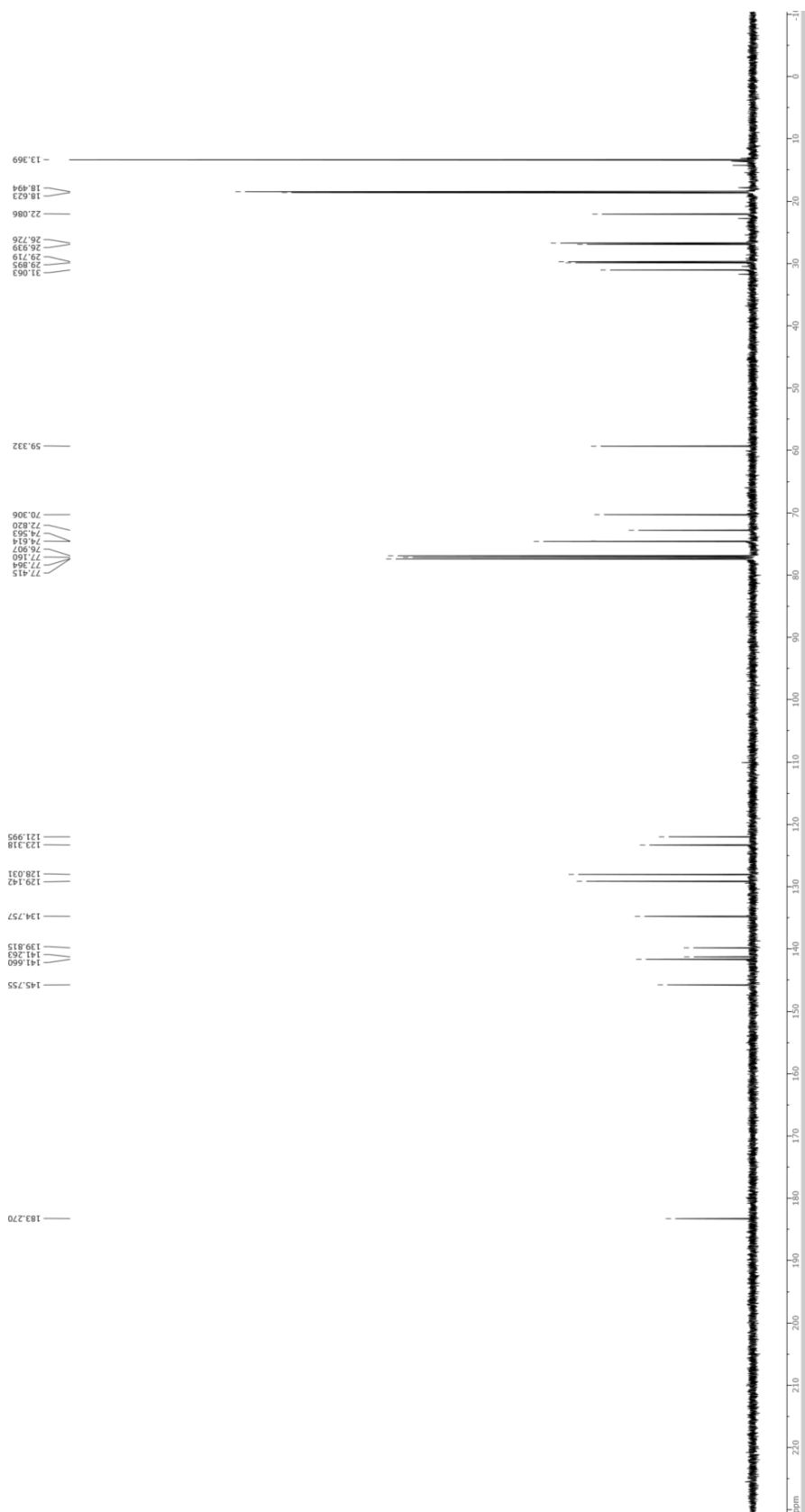


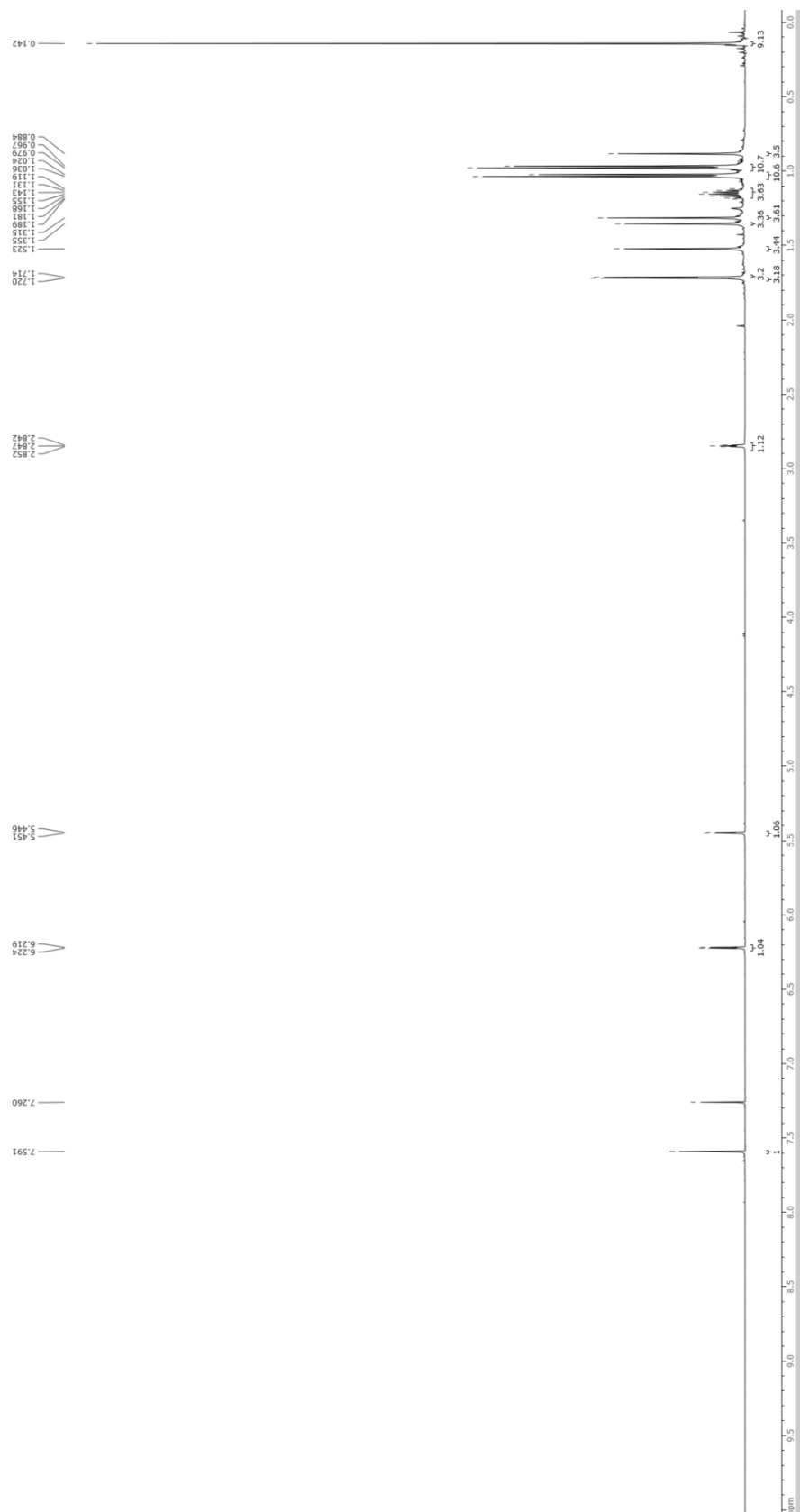
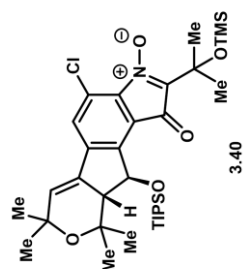


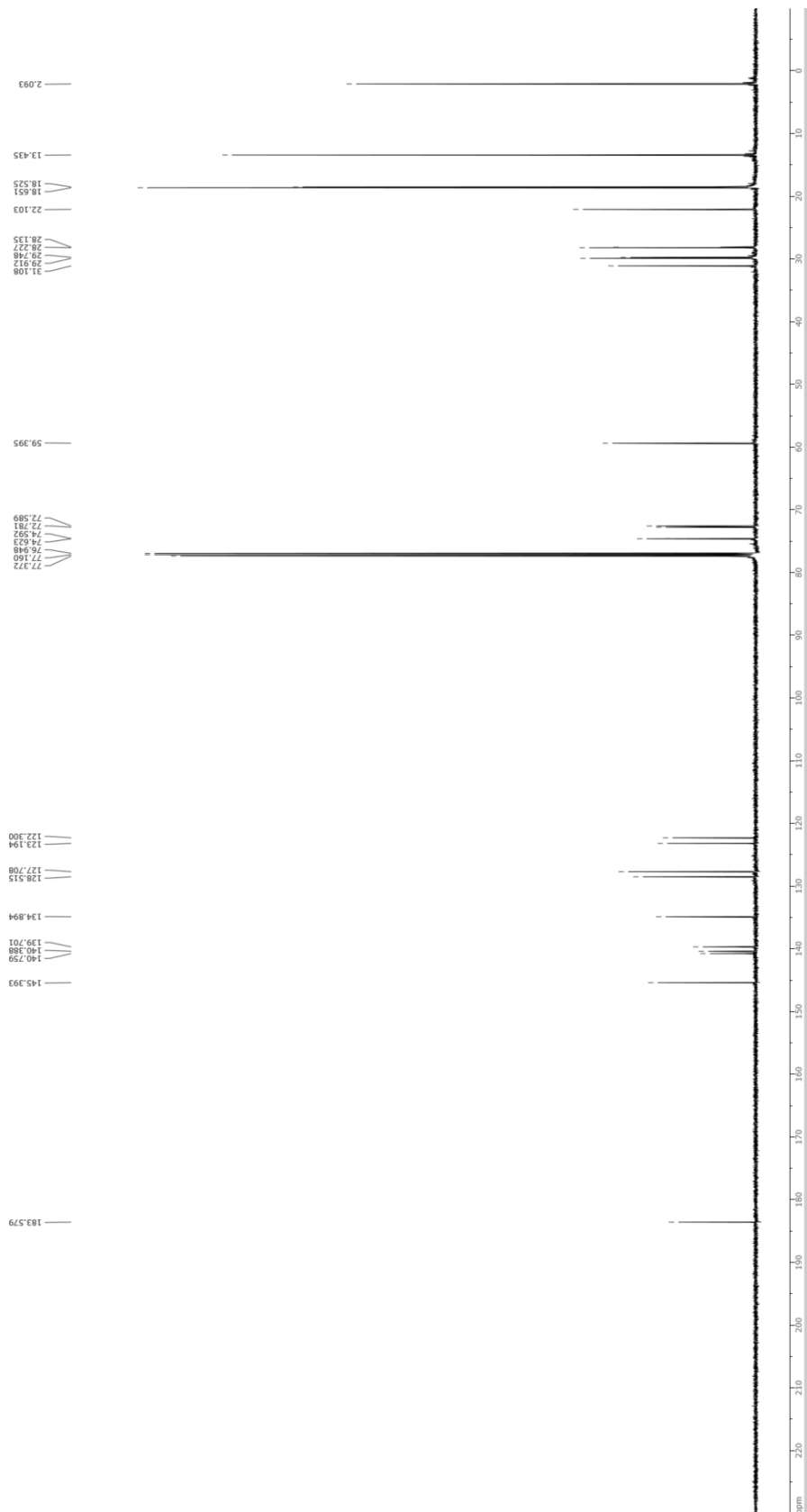
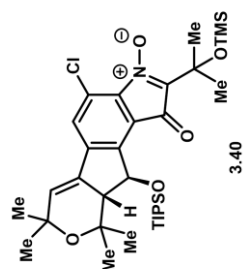


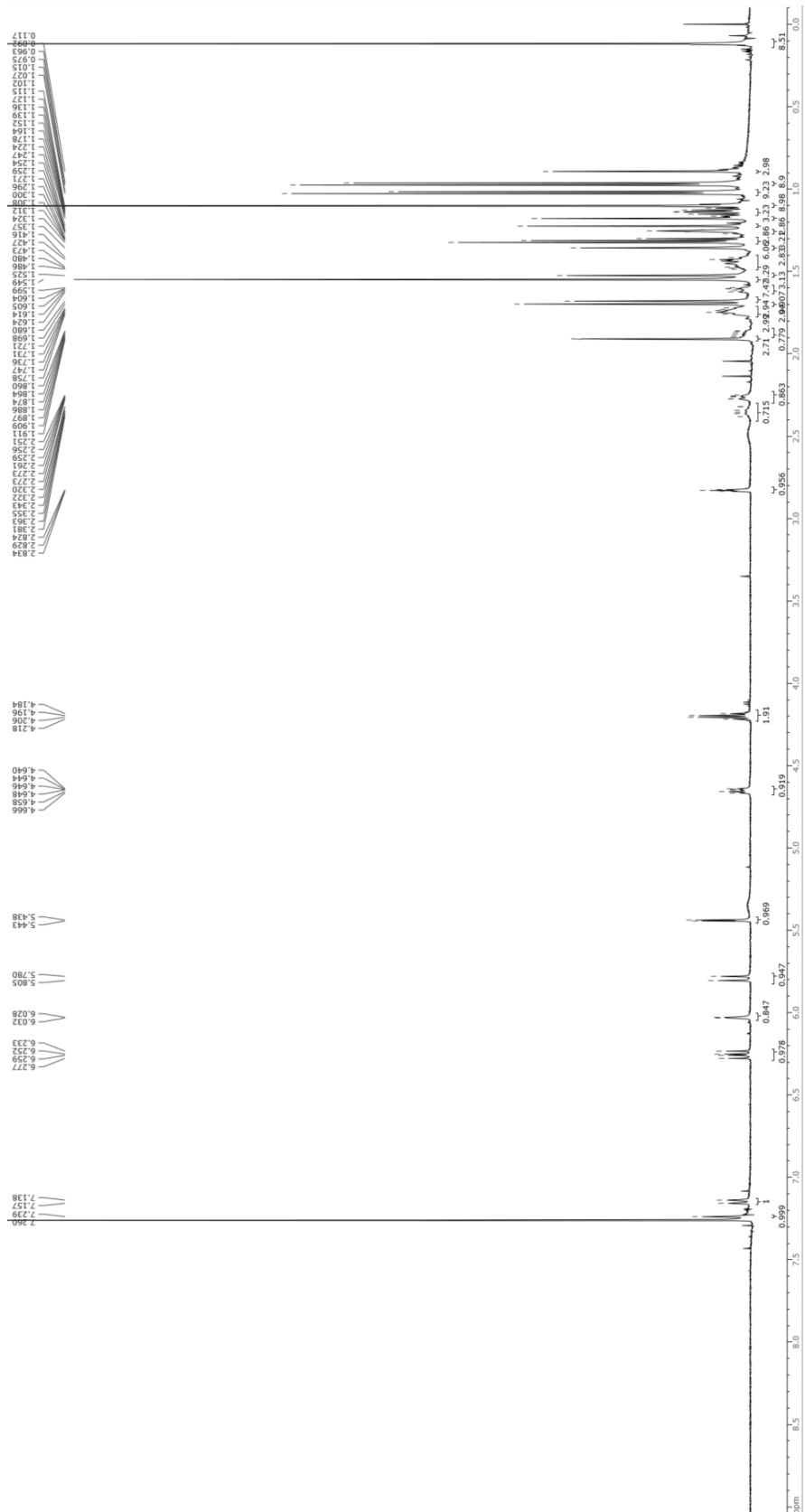


3.38

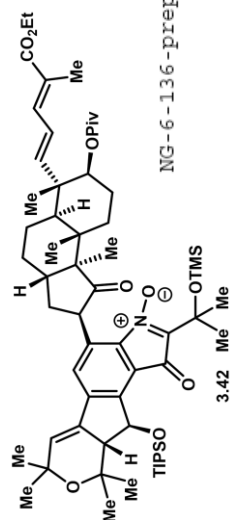






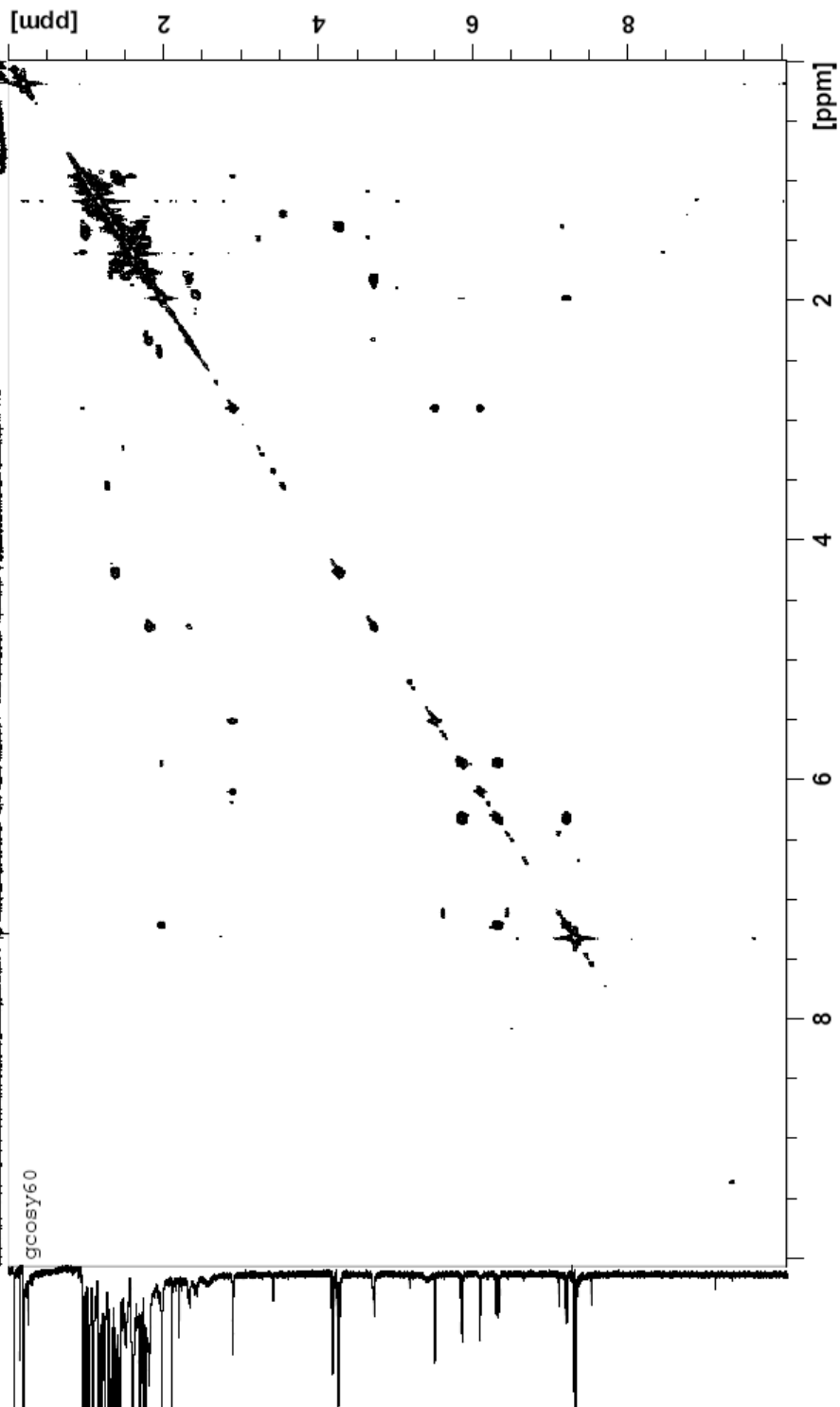


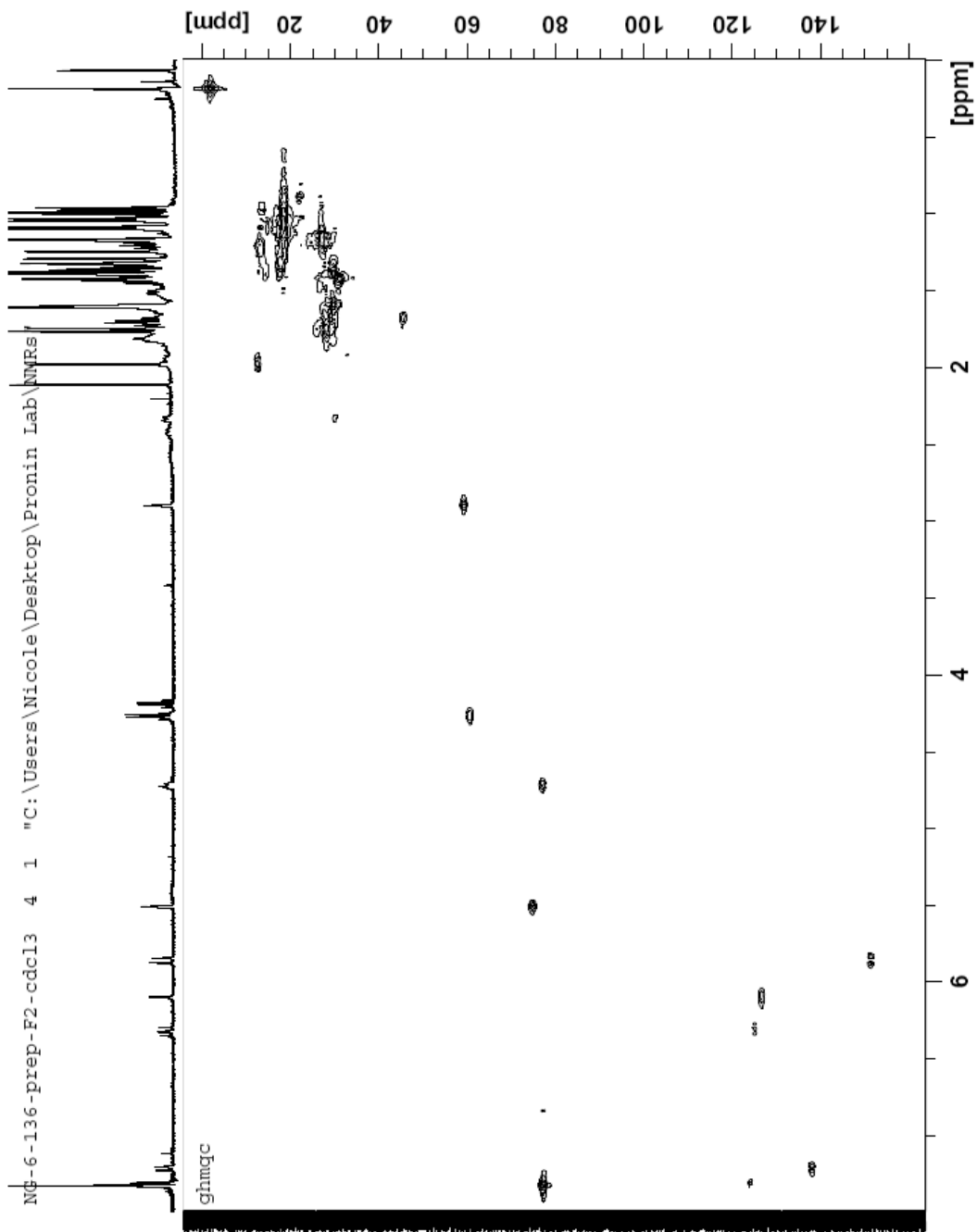
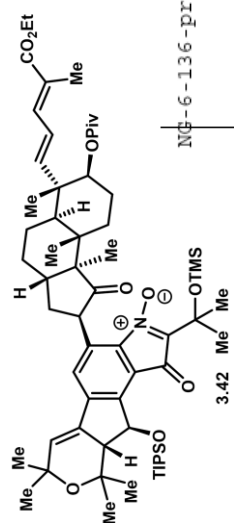




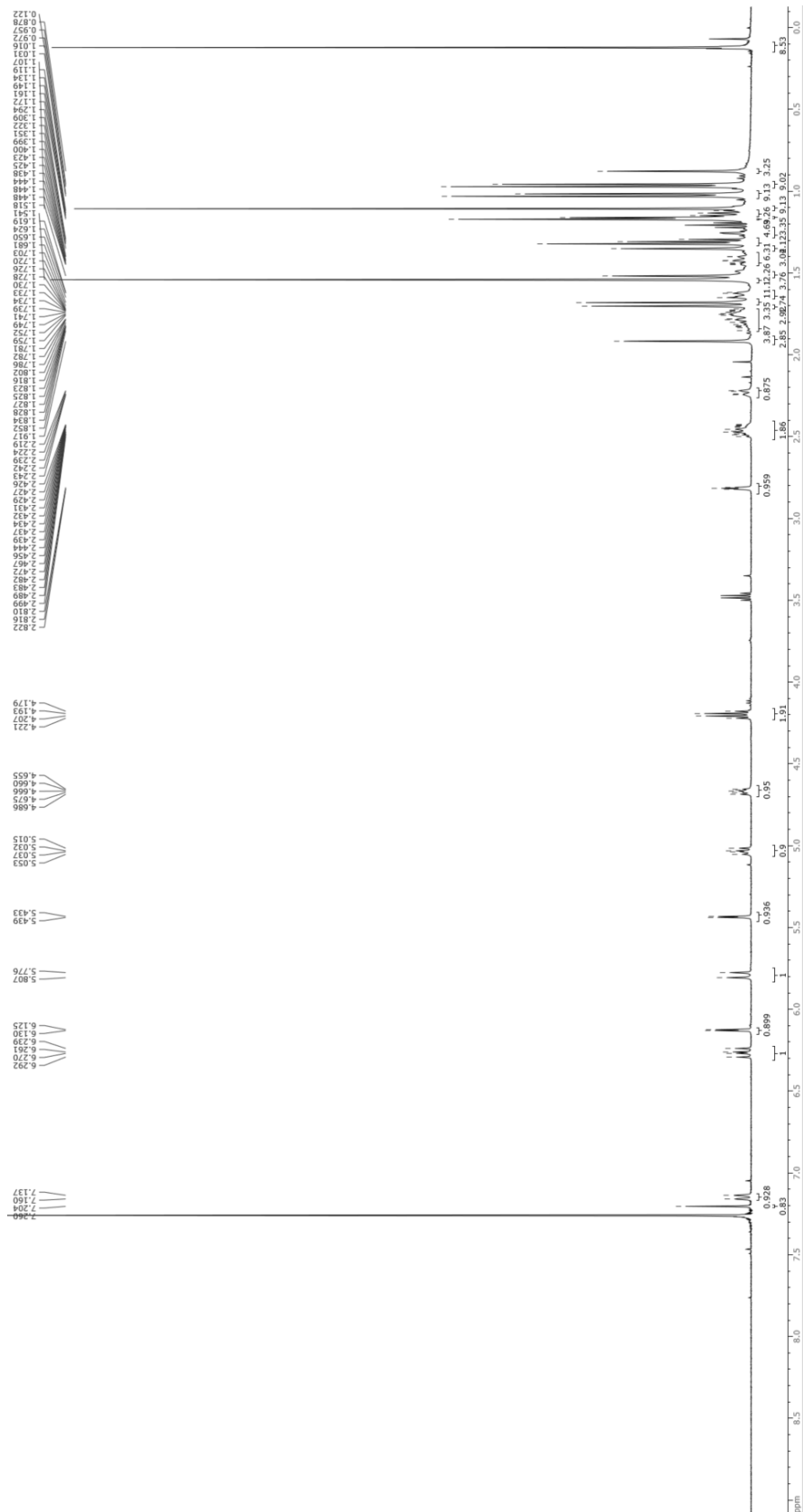
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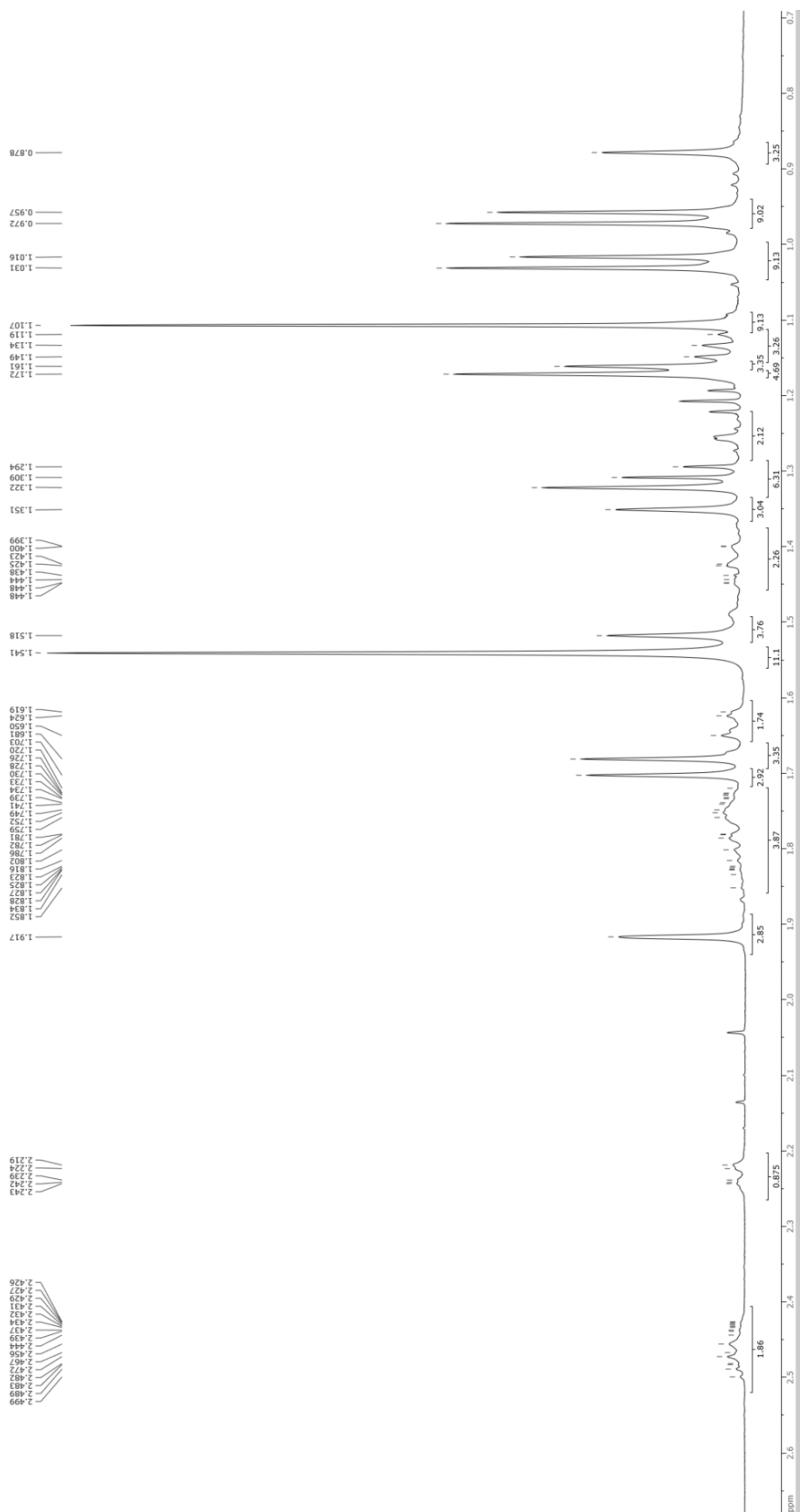
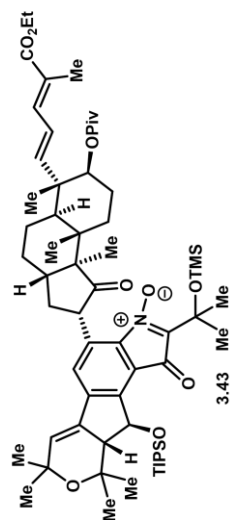
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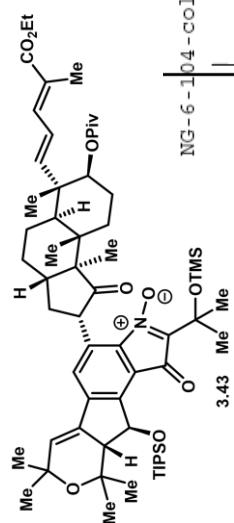




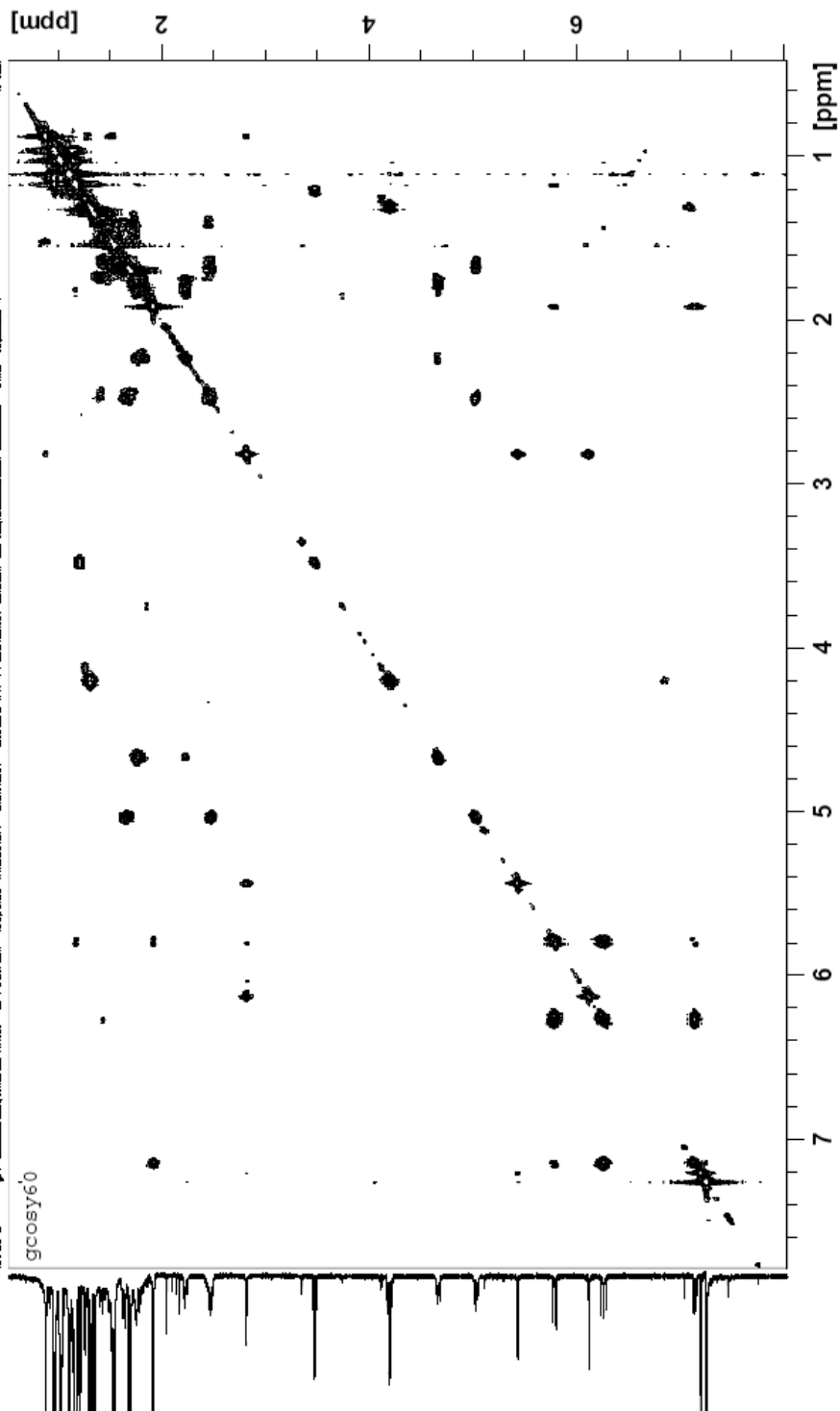


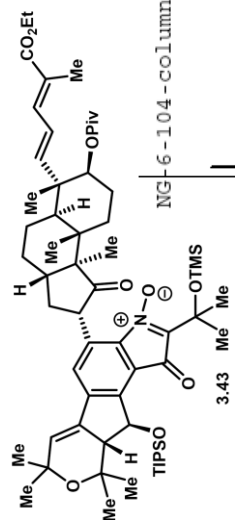




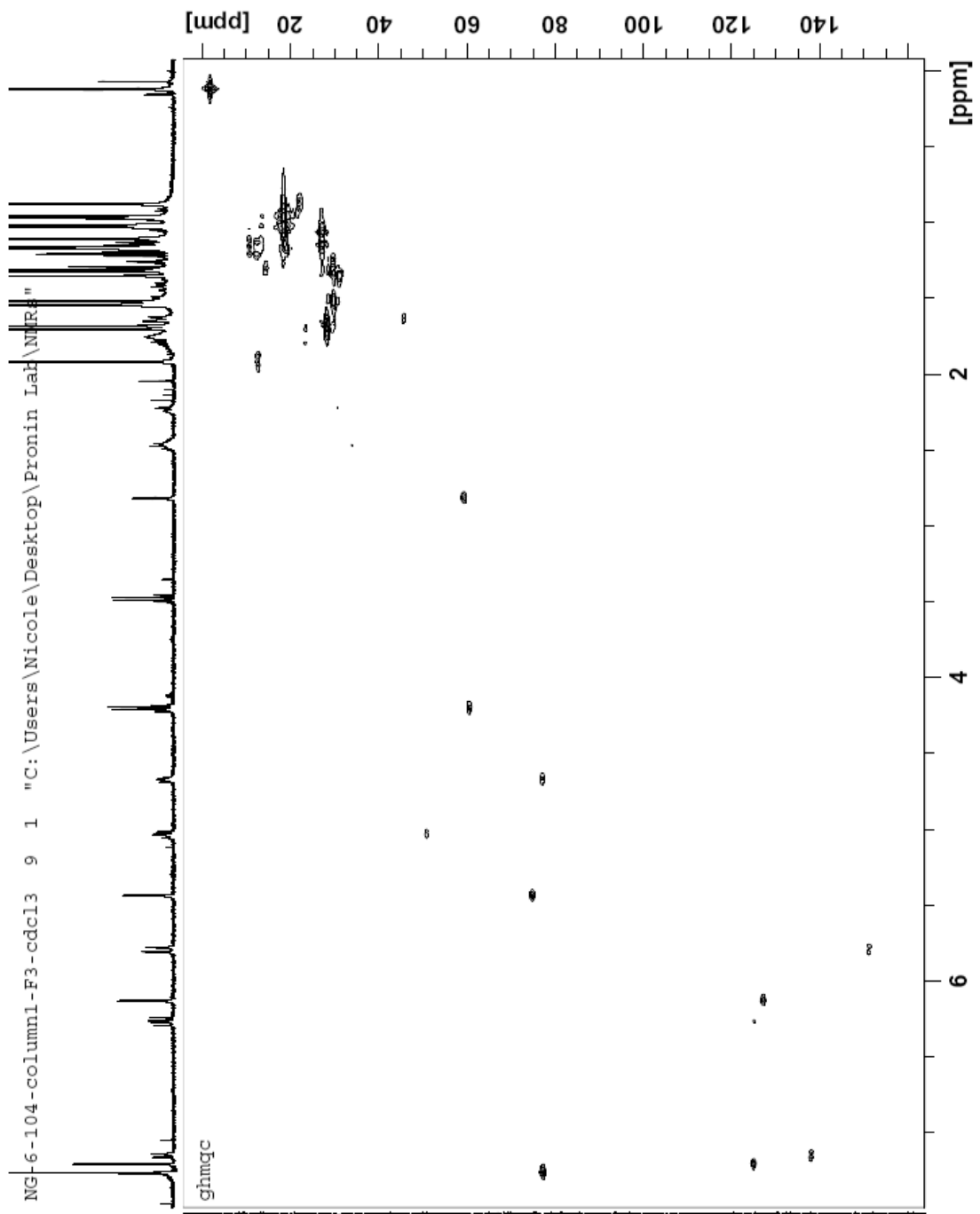


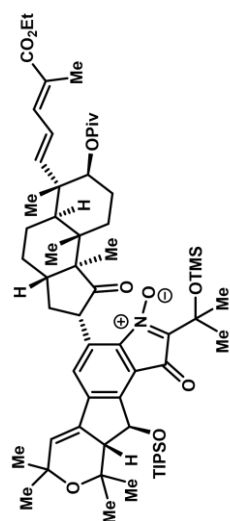
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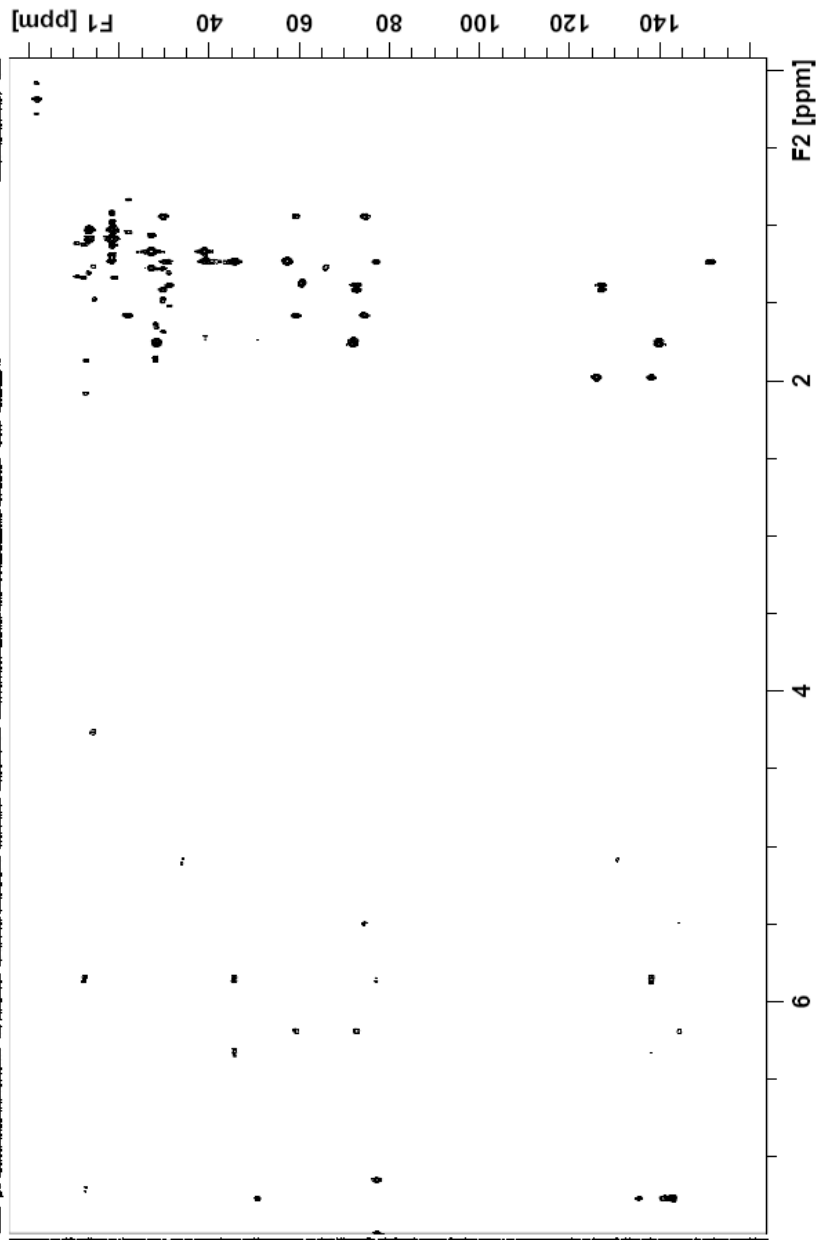


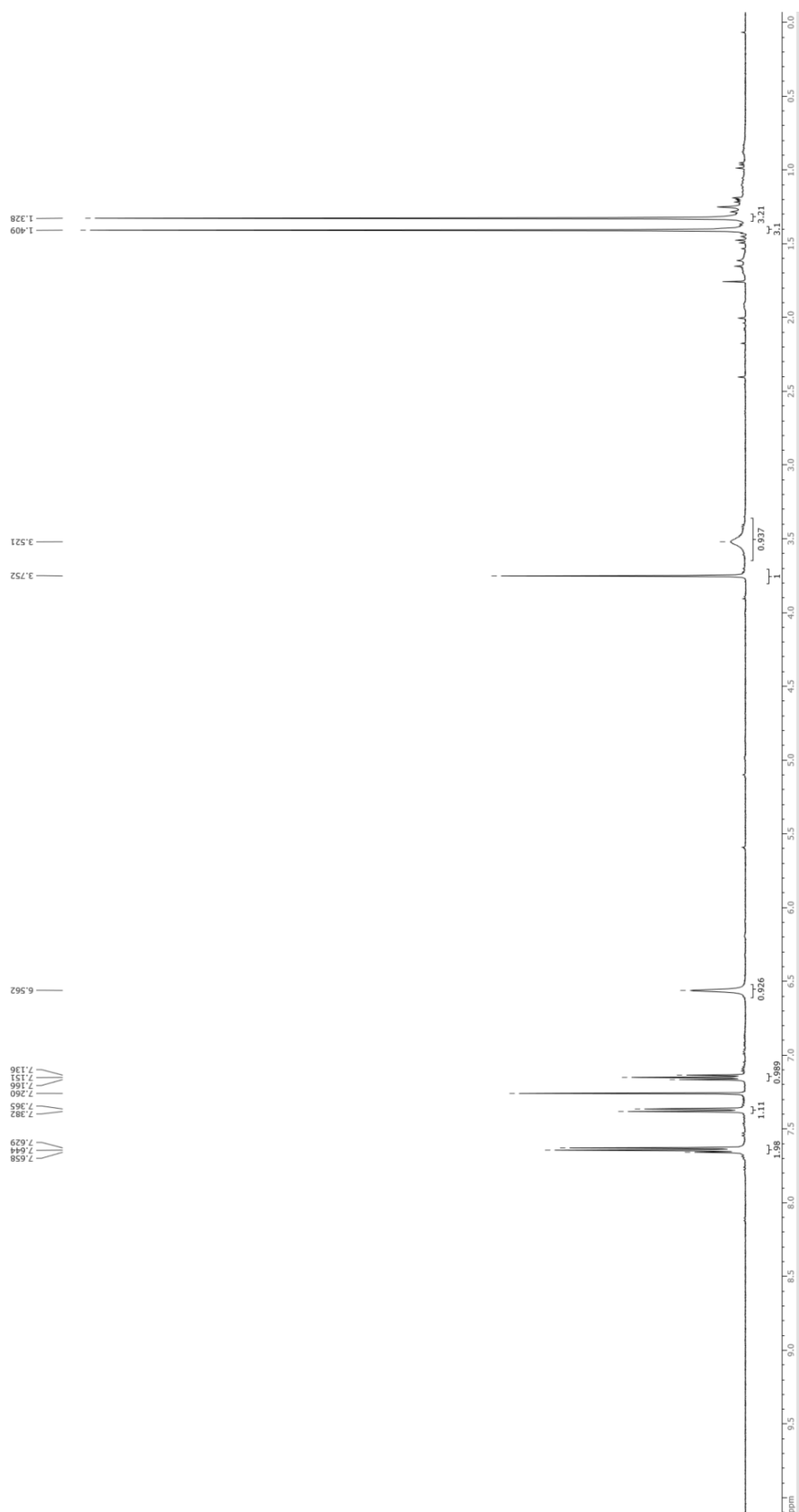
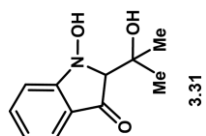


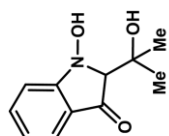
HMBC optimized for 10 Hz coupling

3.43

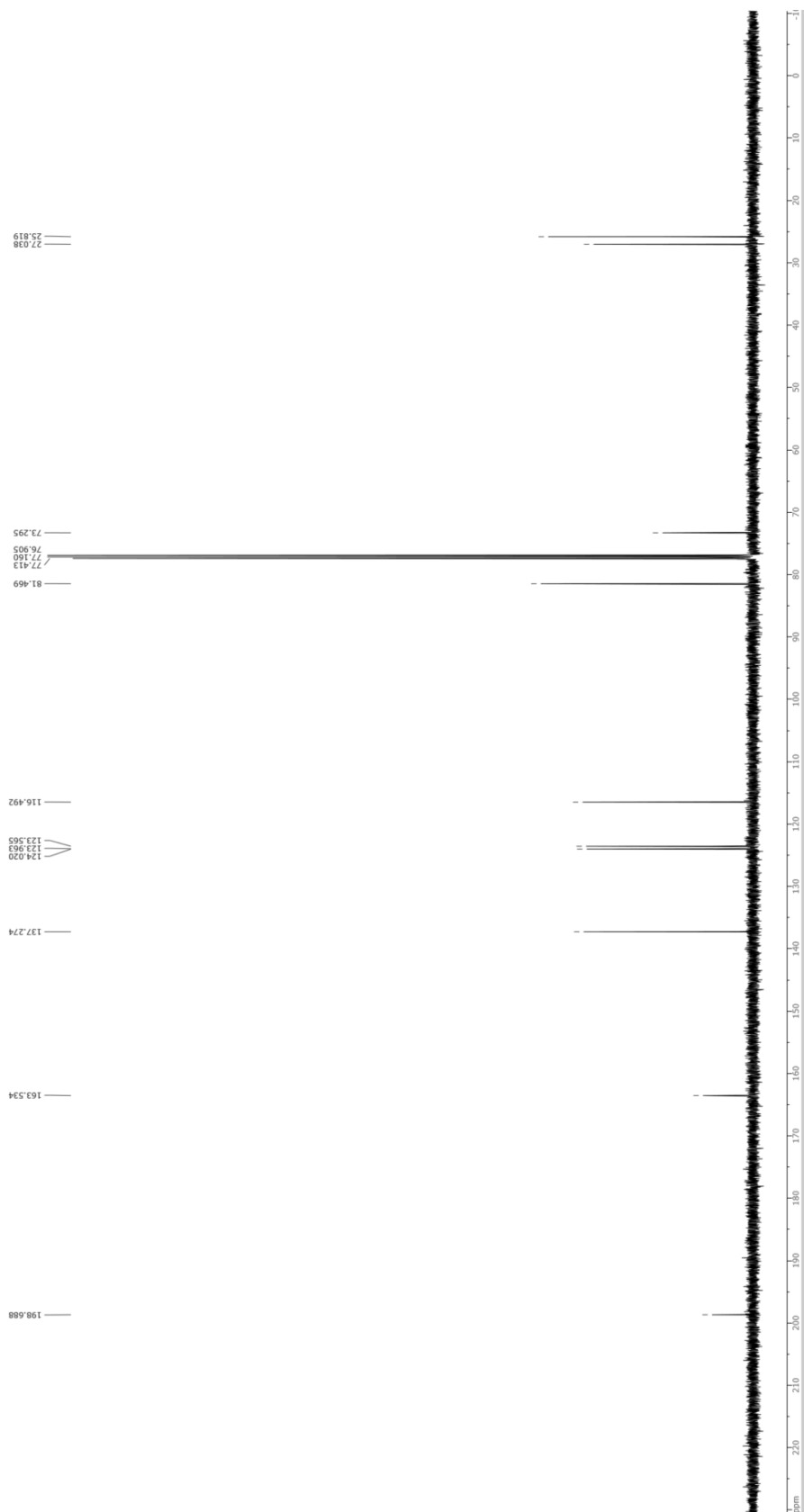
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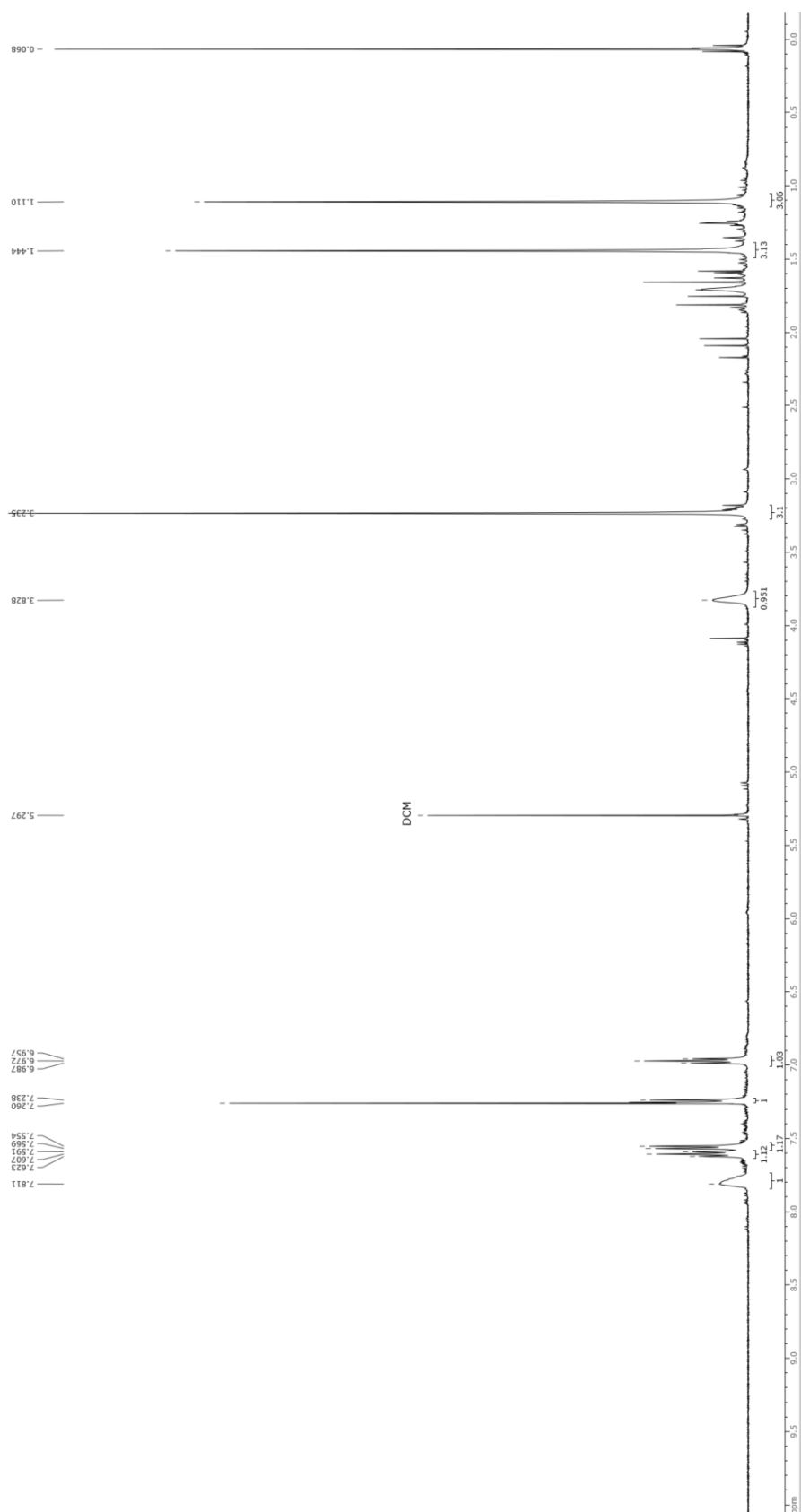
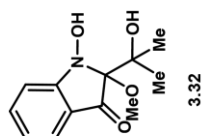


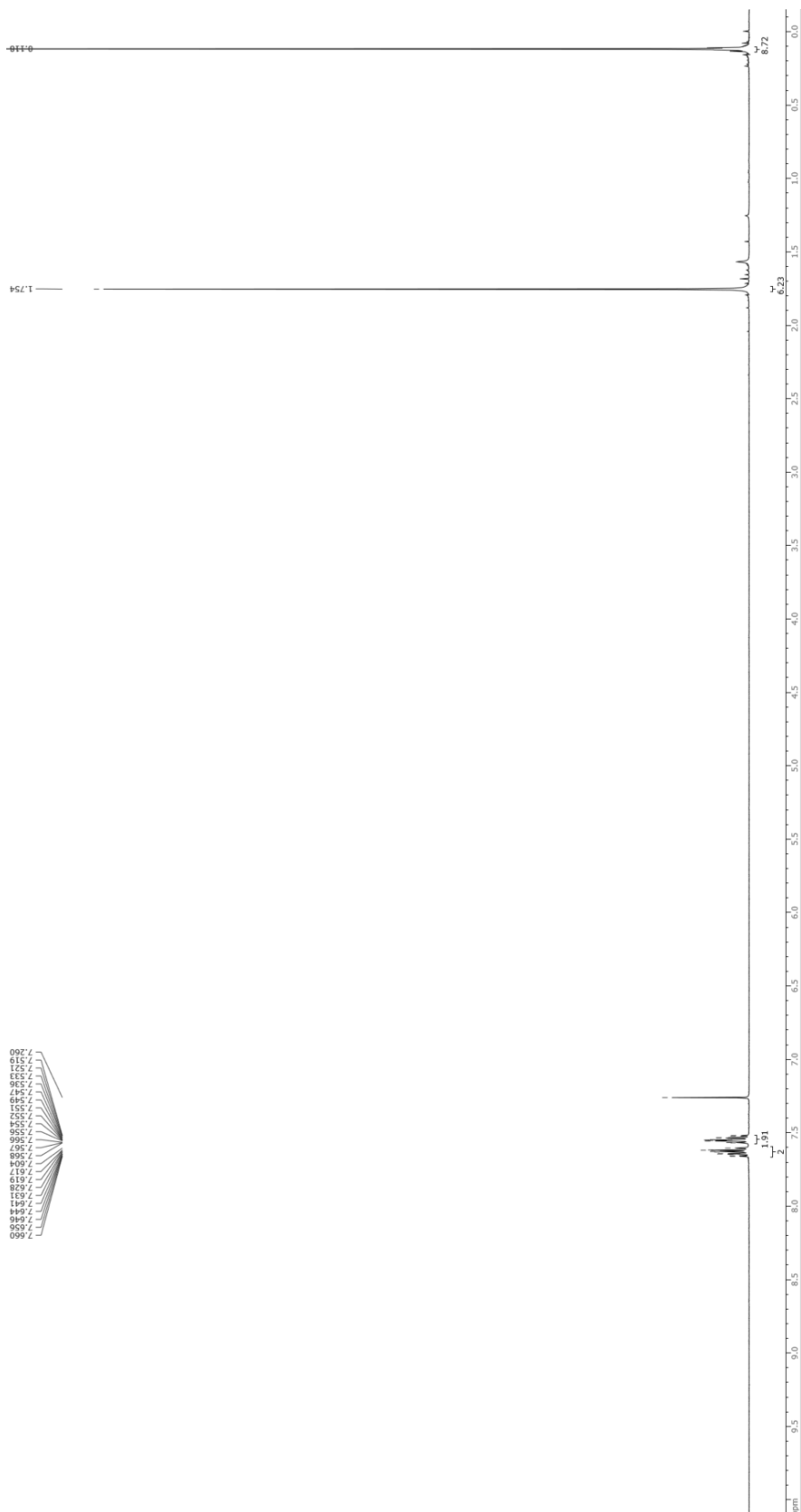
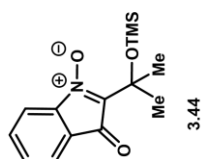


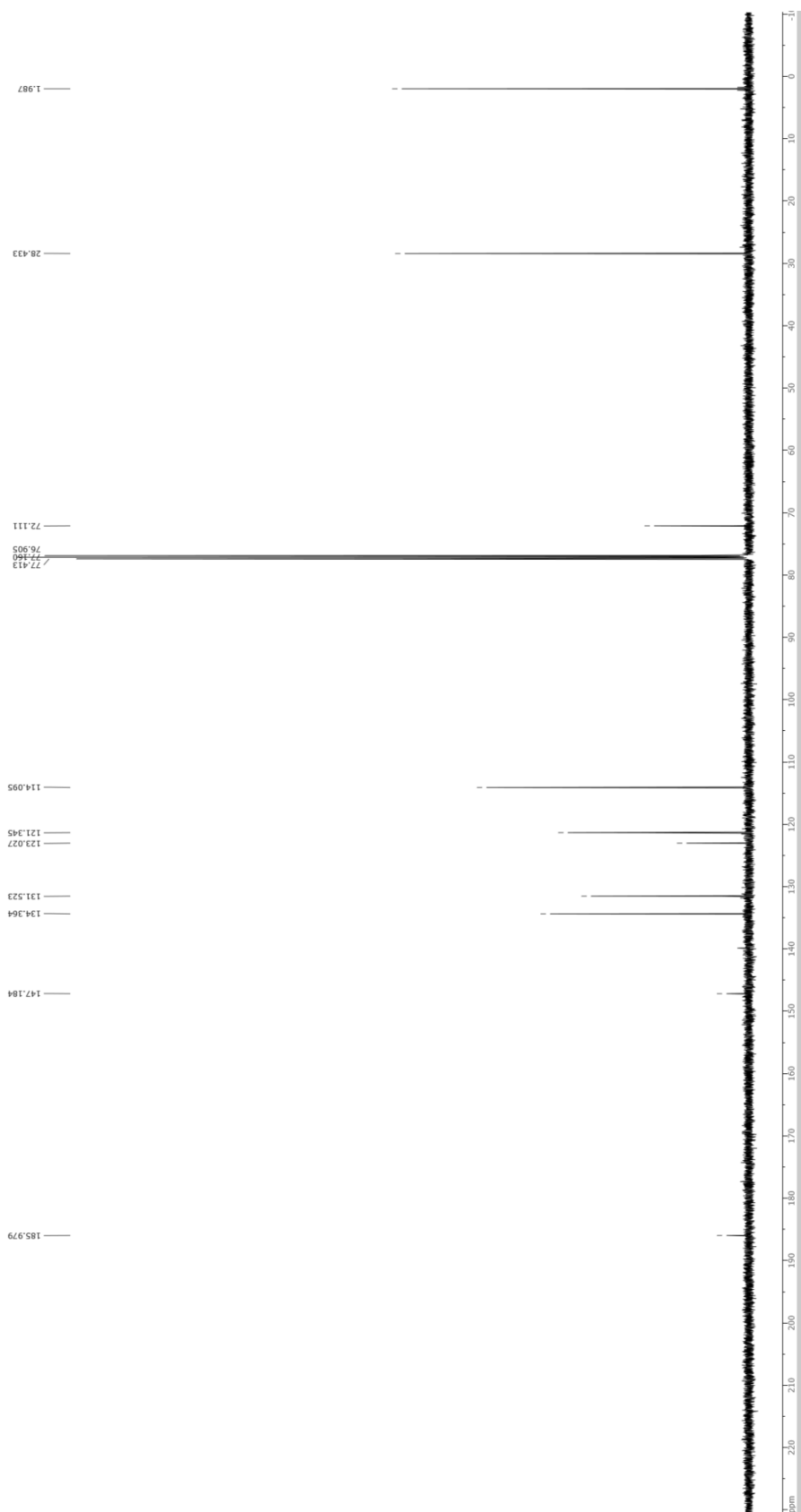
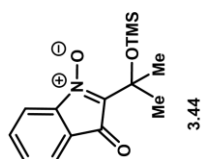


3.31







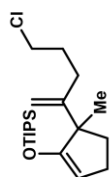


Appendix C: NMR Spectra for Chapter 4

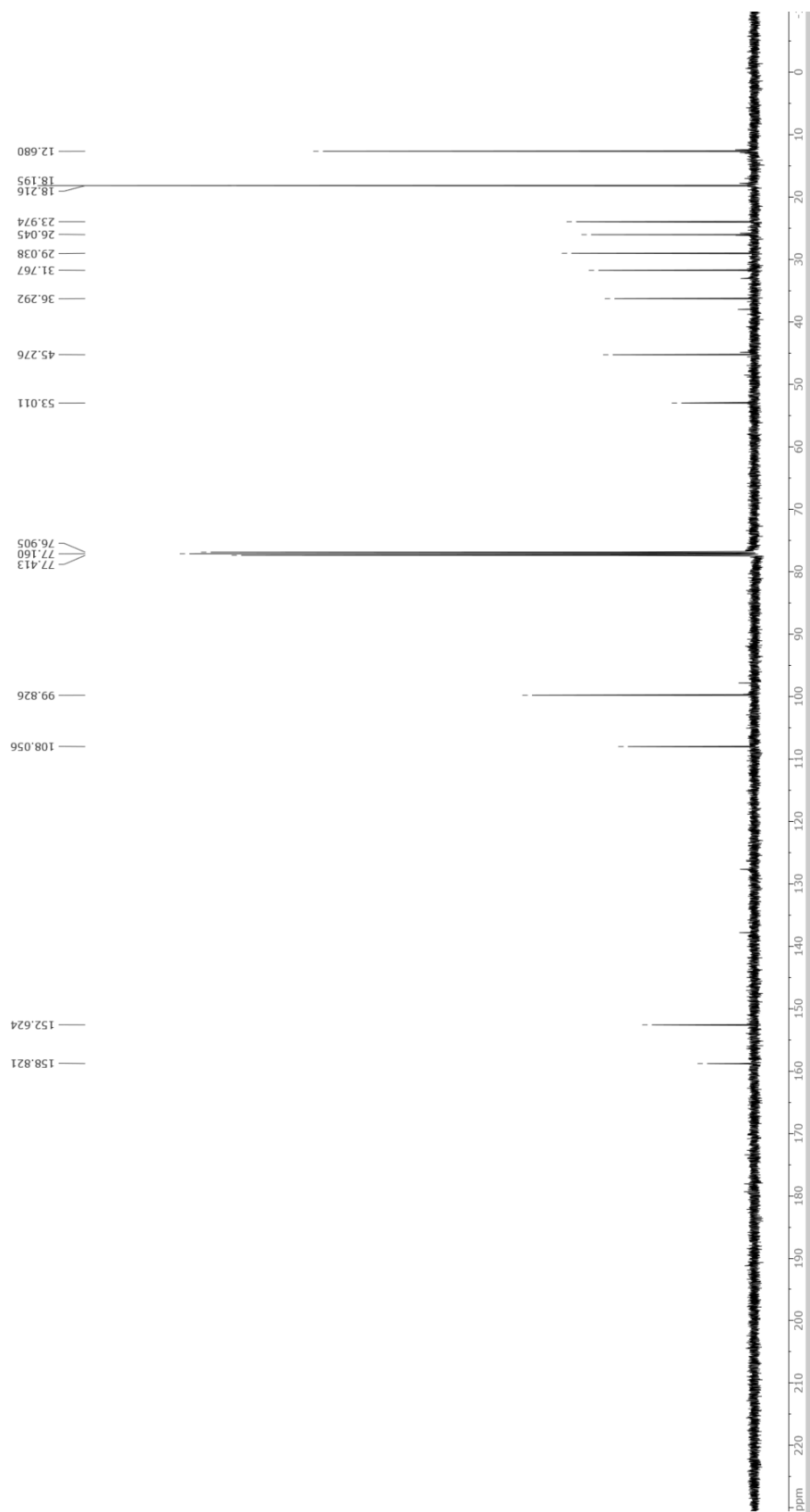


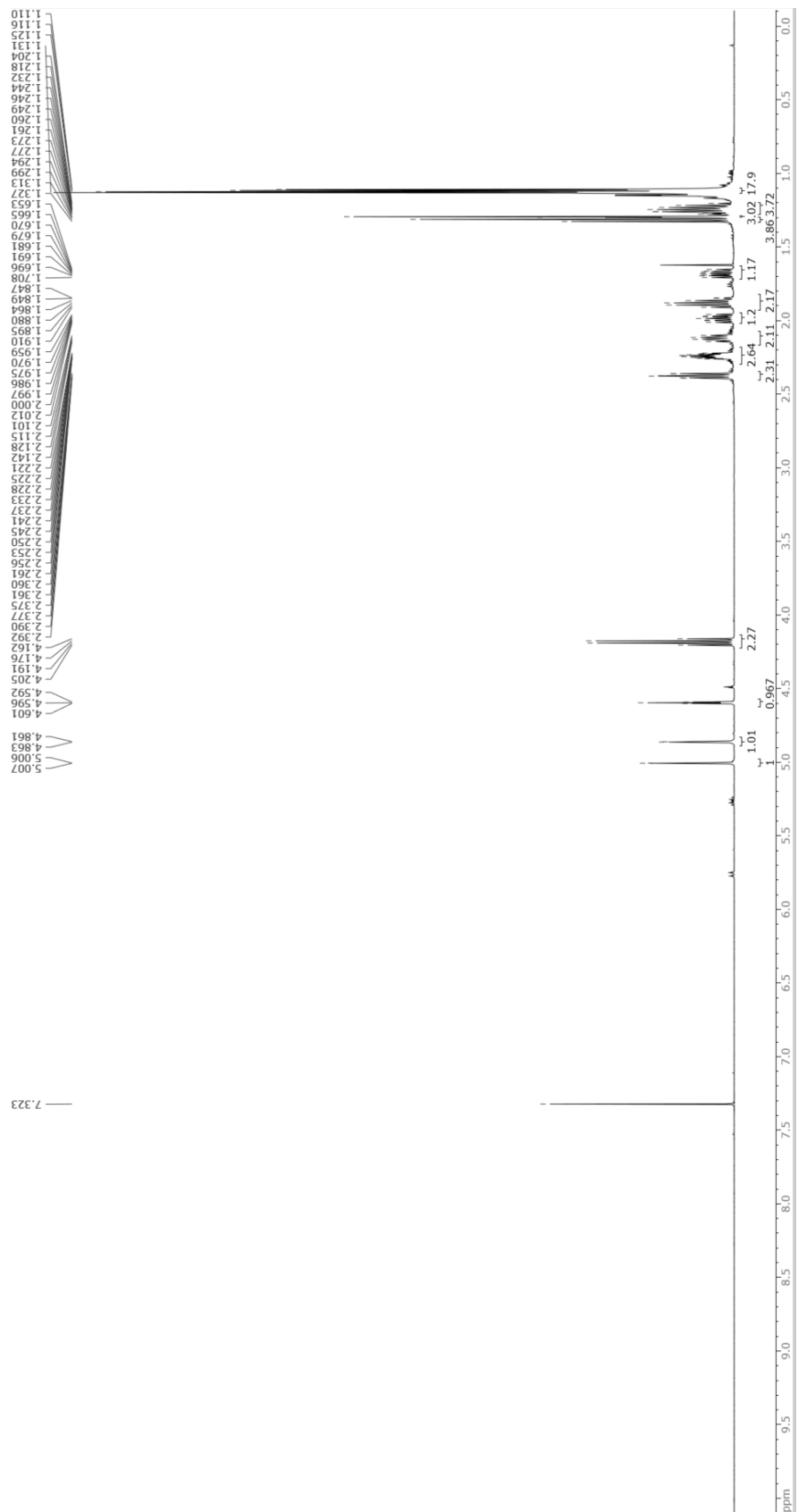
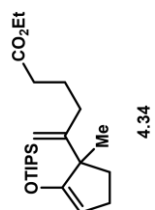


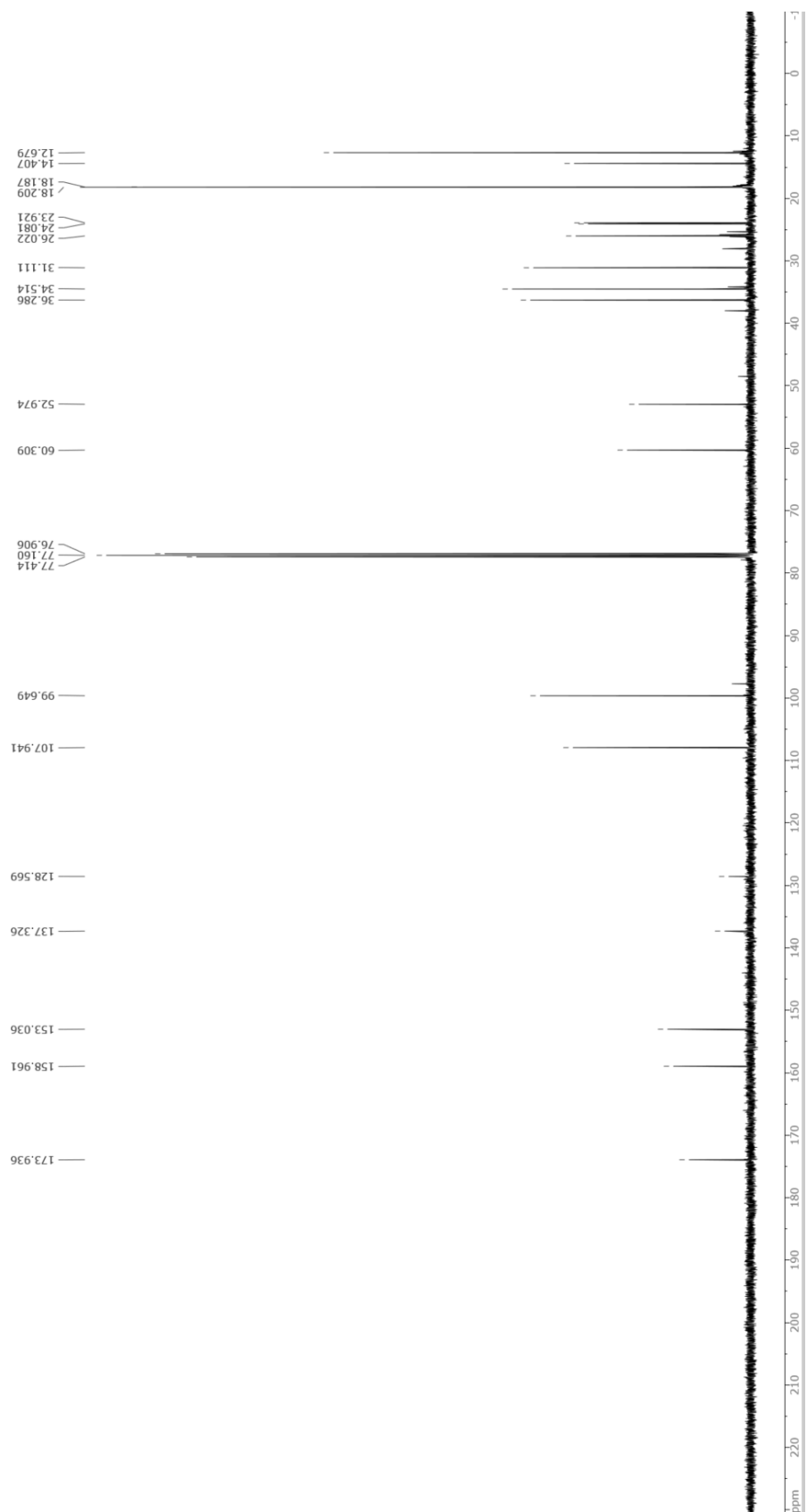
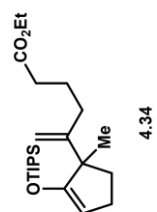


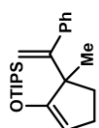


4.32

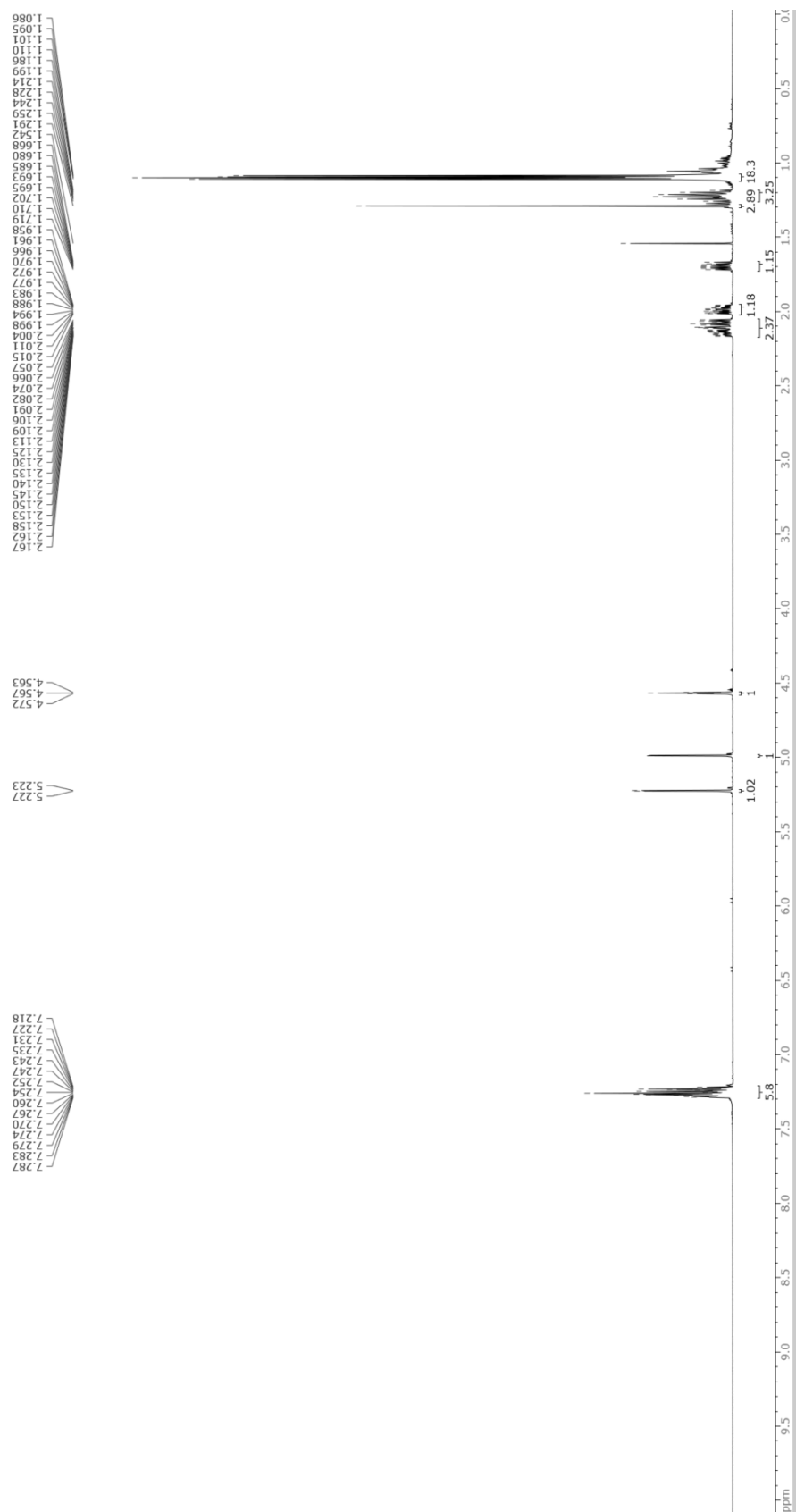




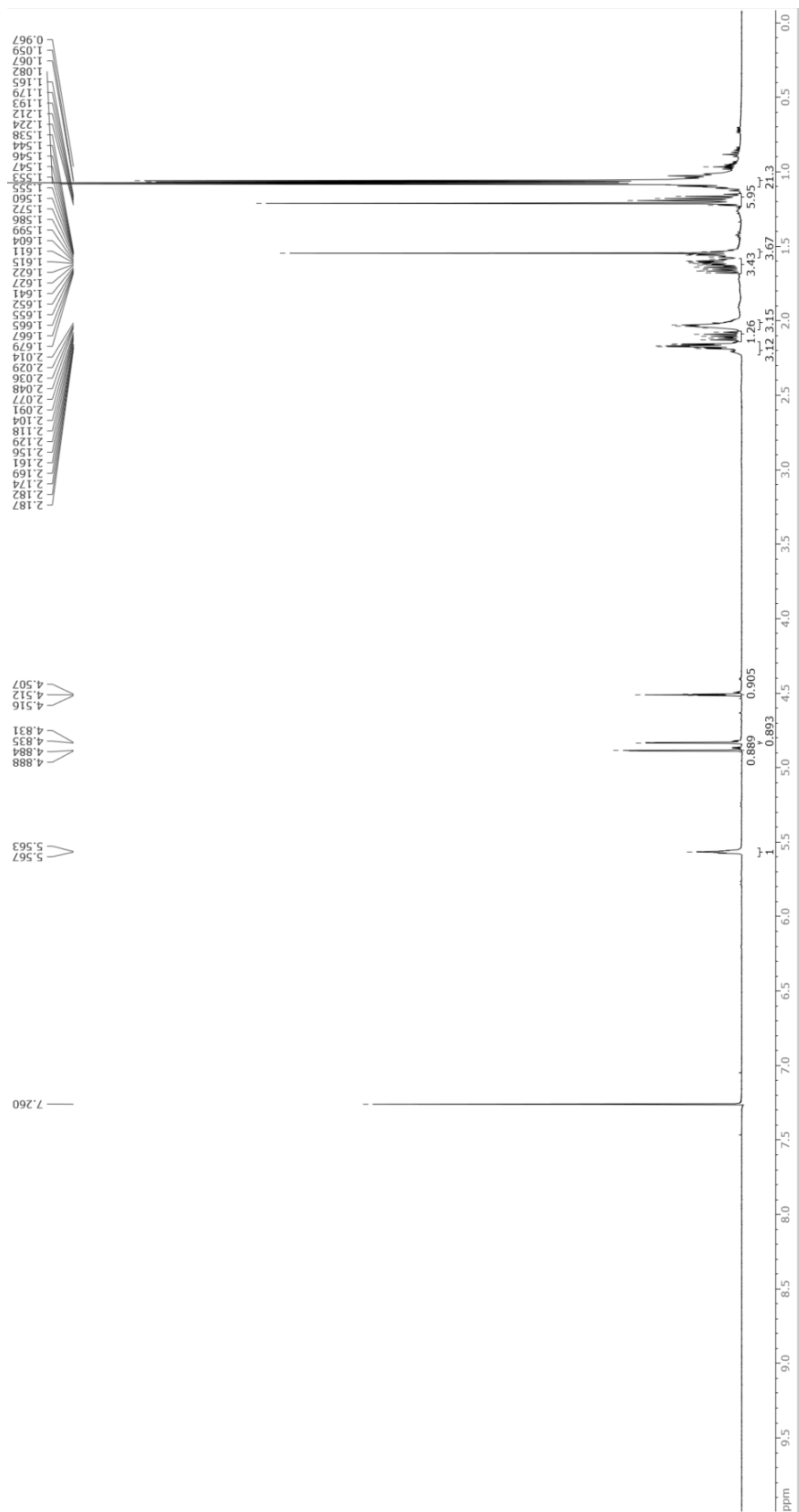
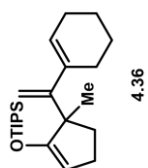


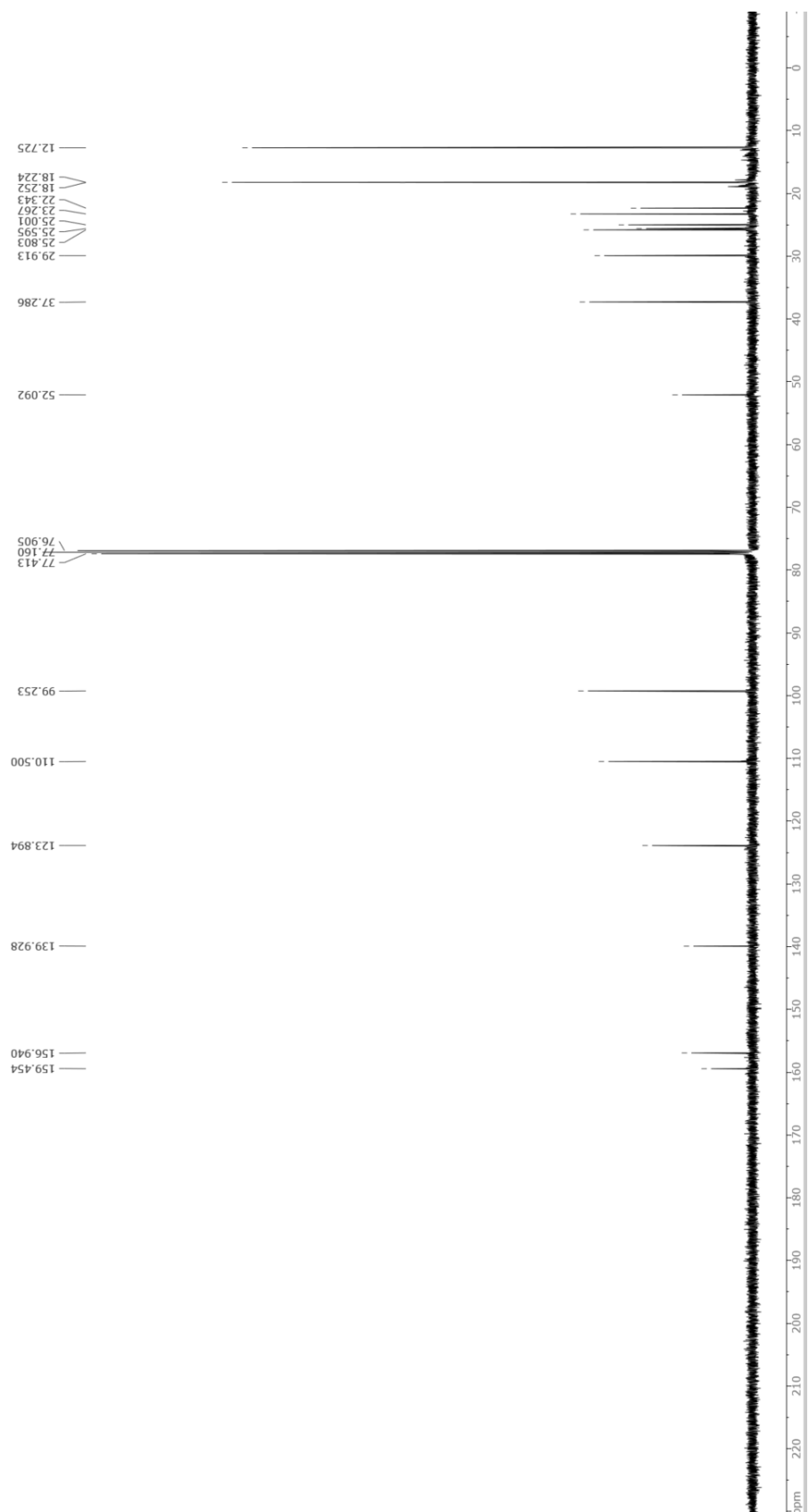
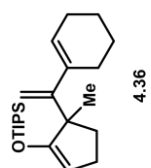


4.35



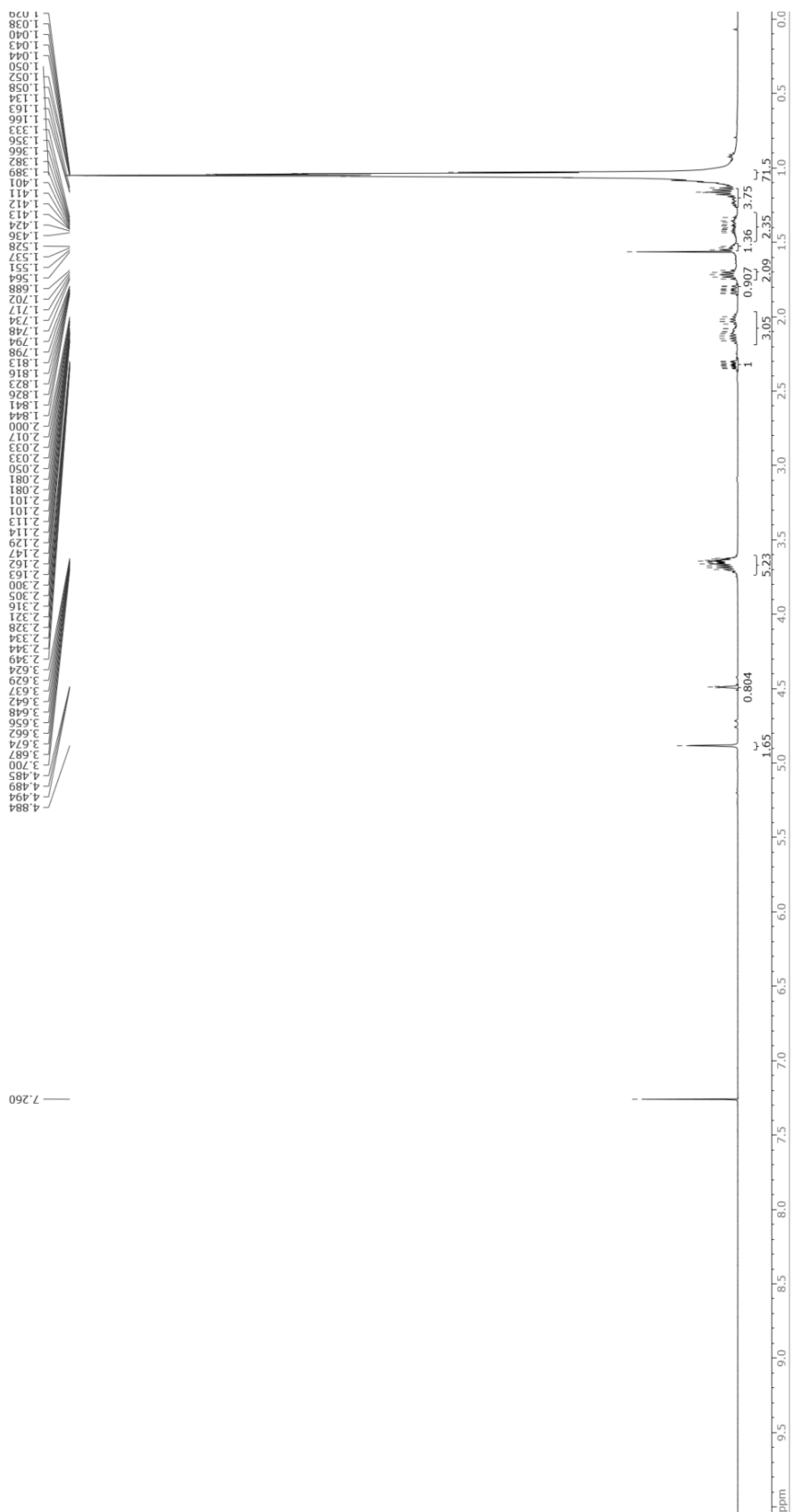
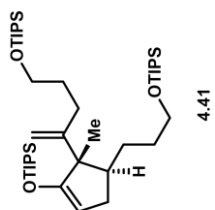


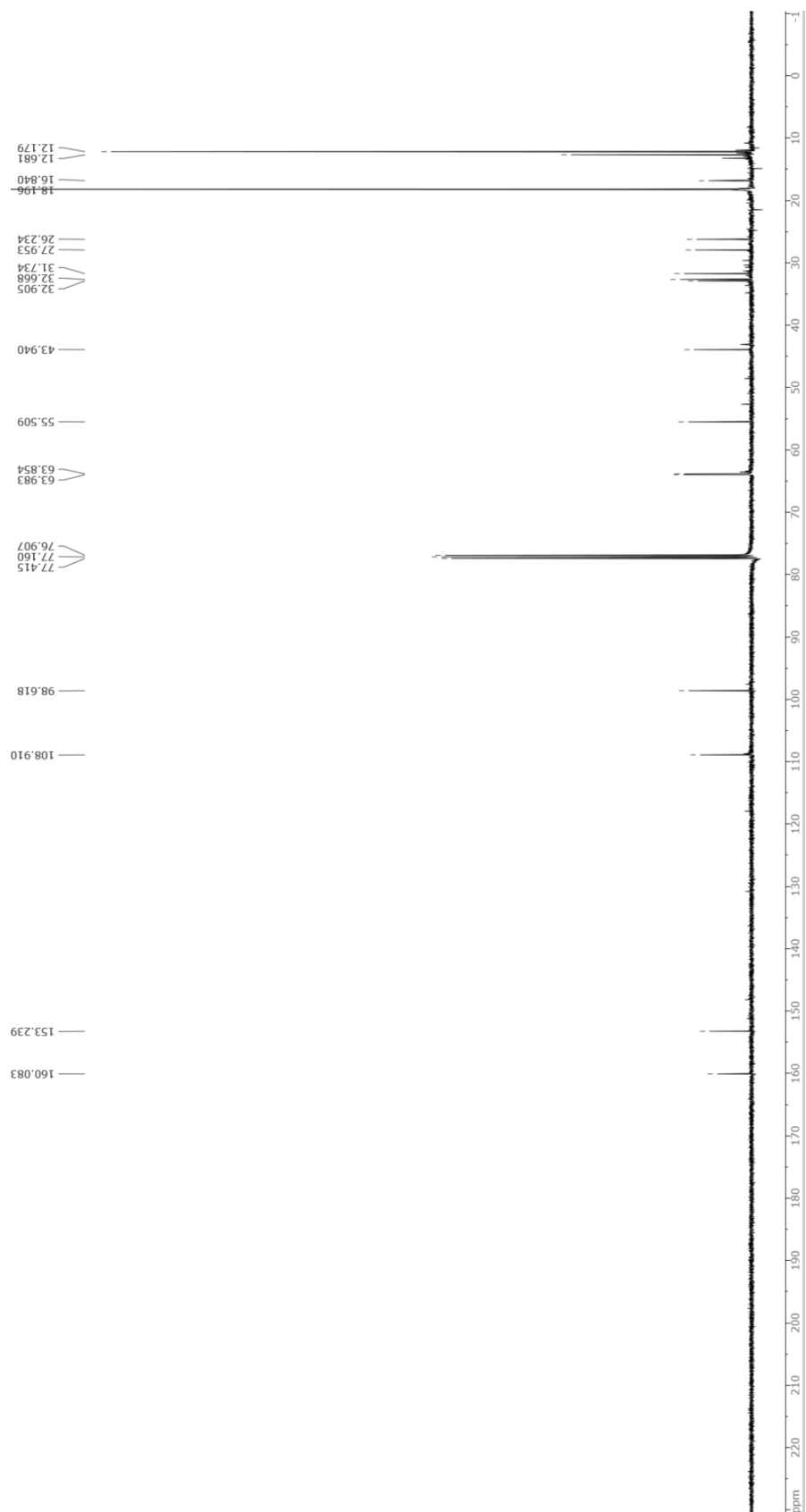
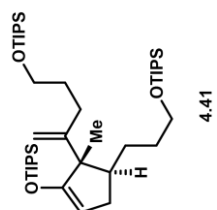


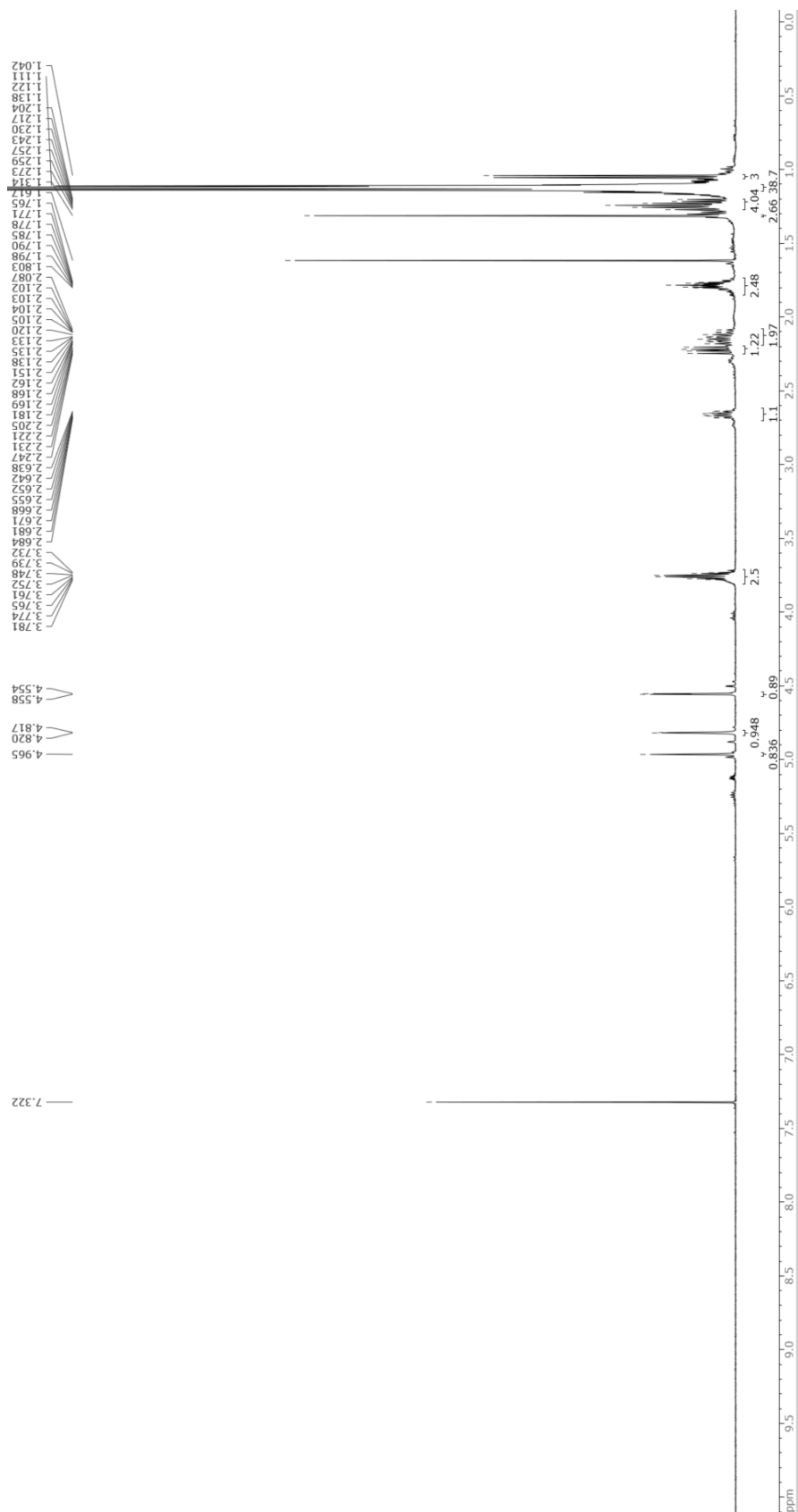
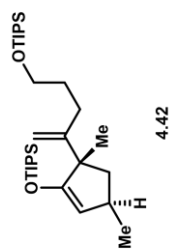


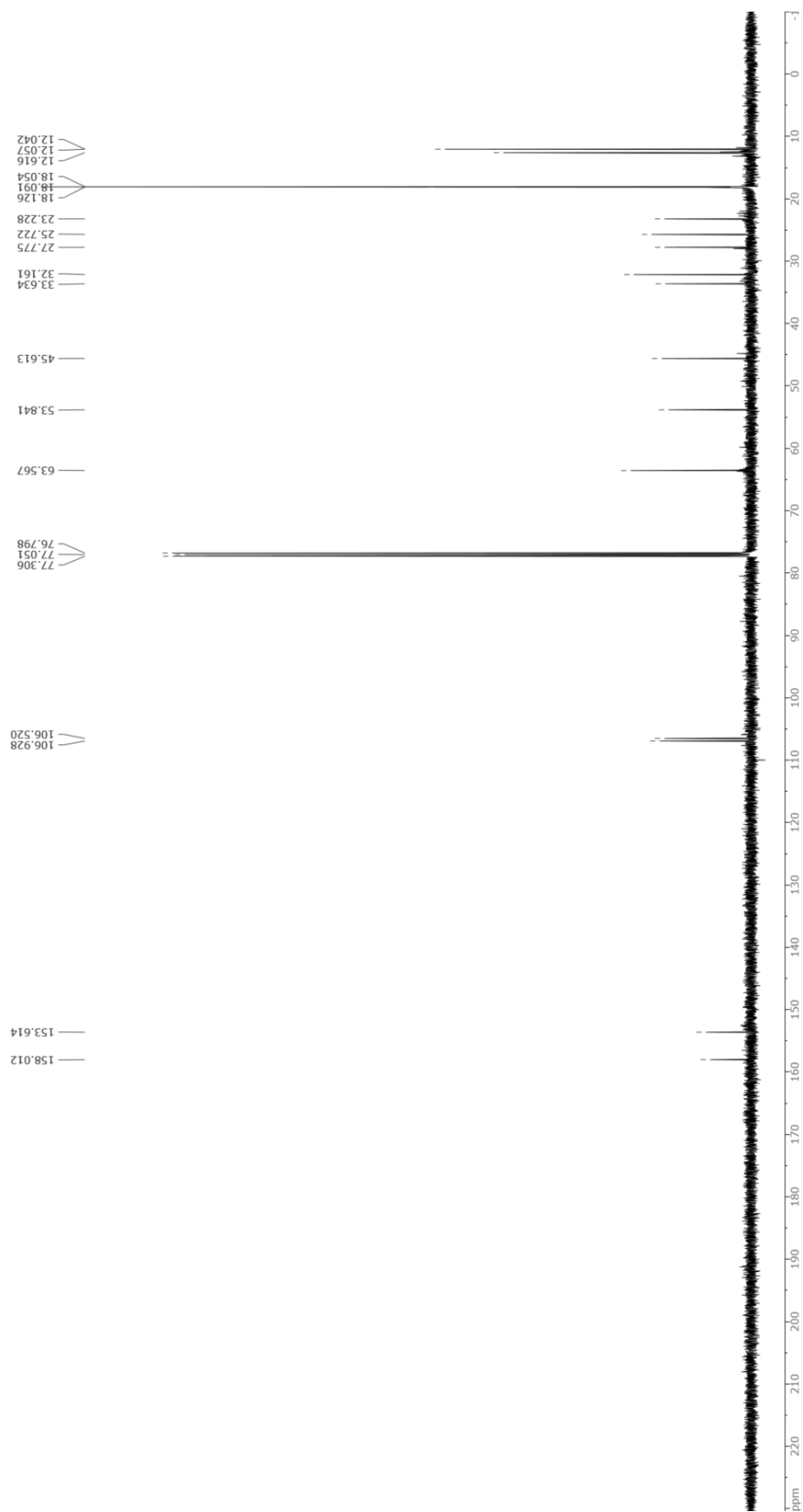
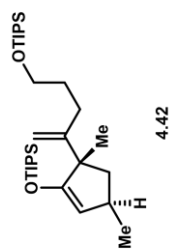


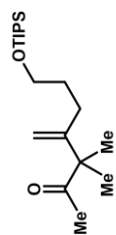




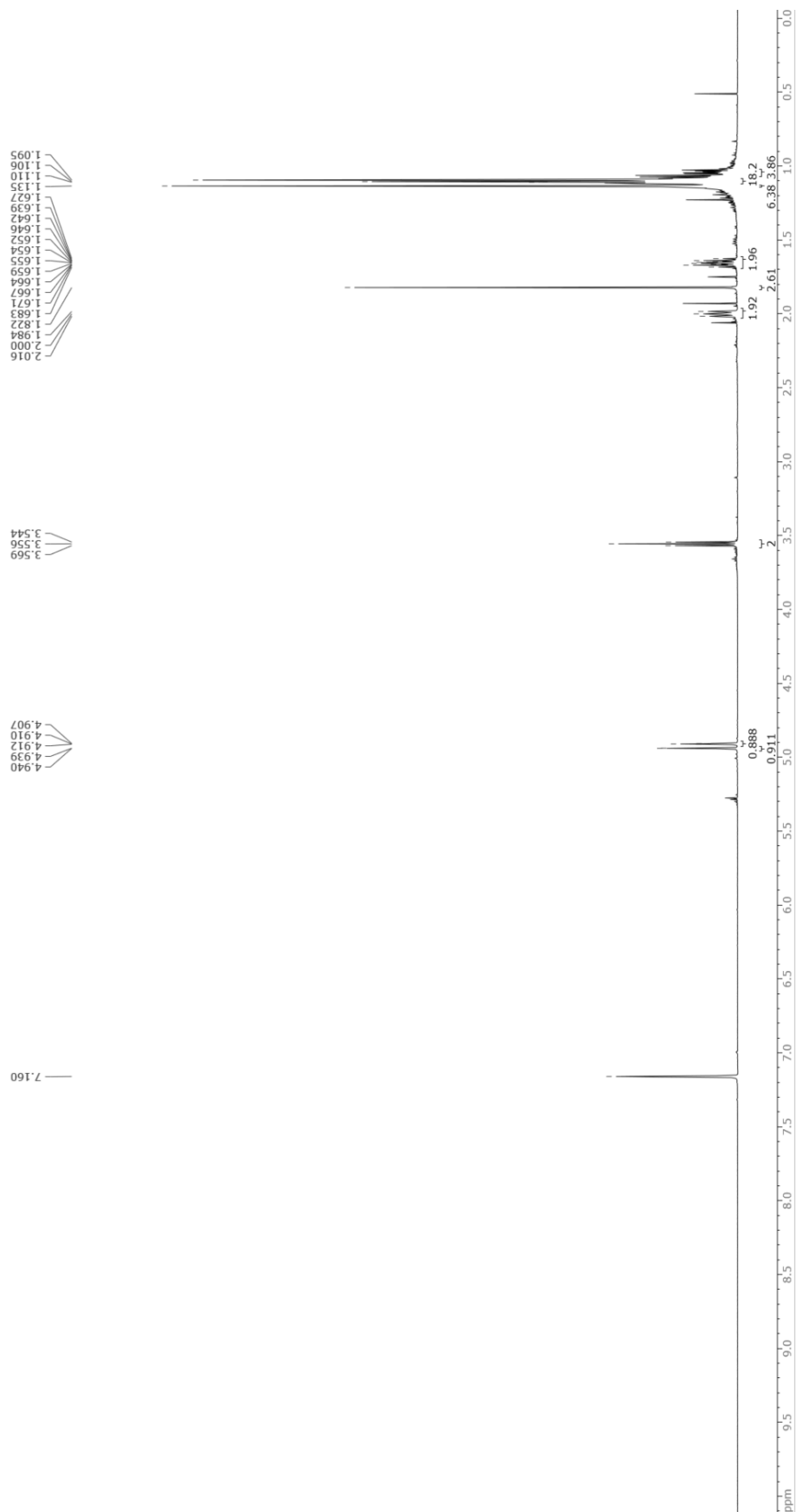


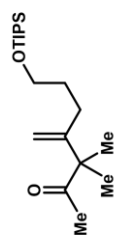




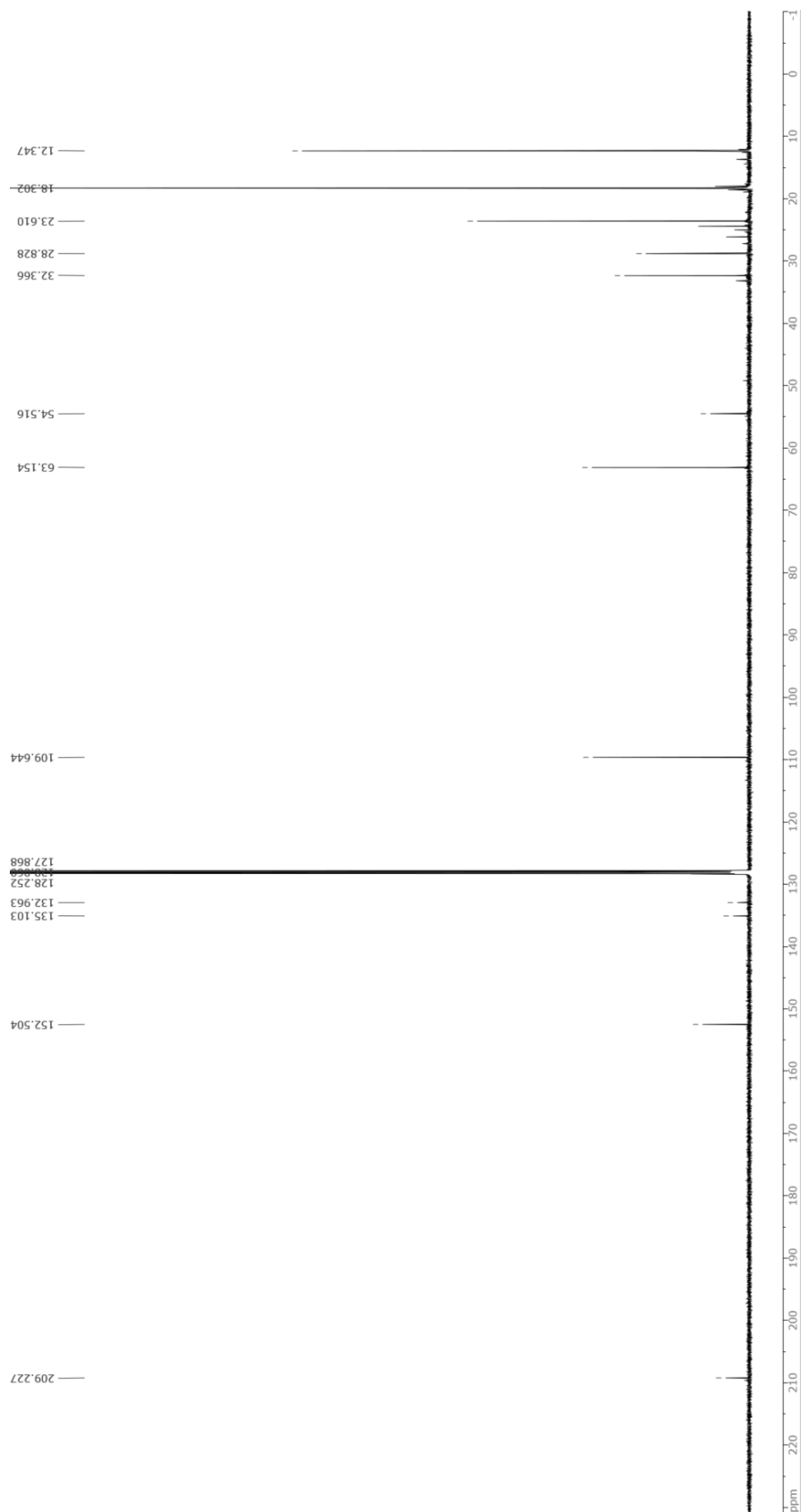


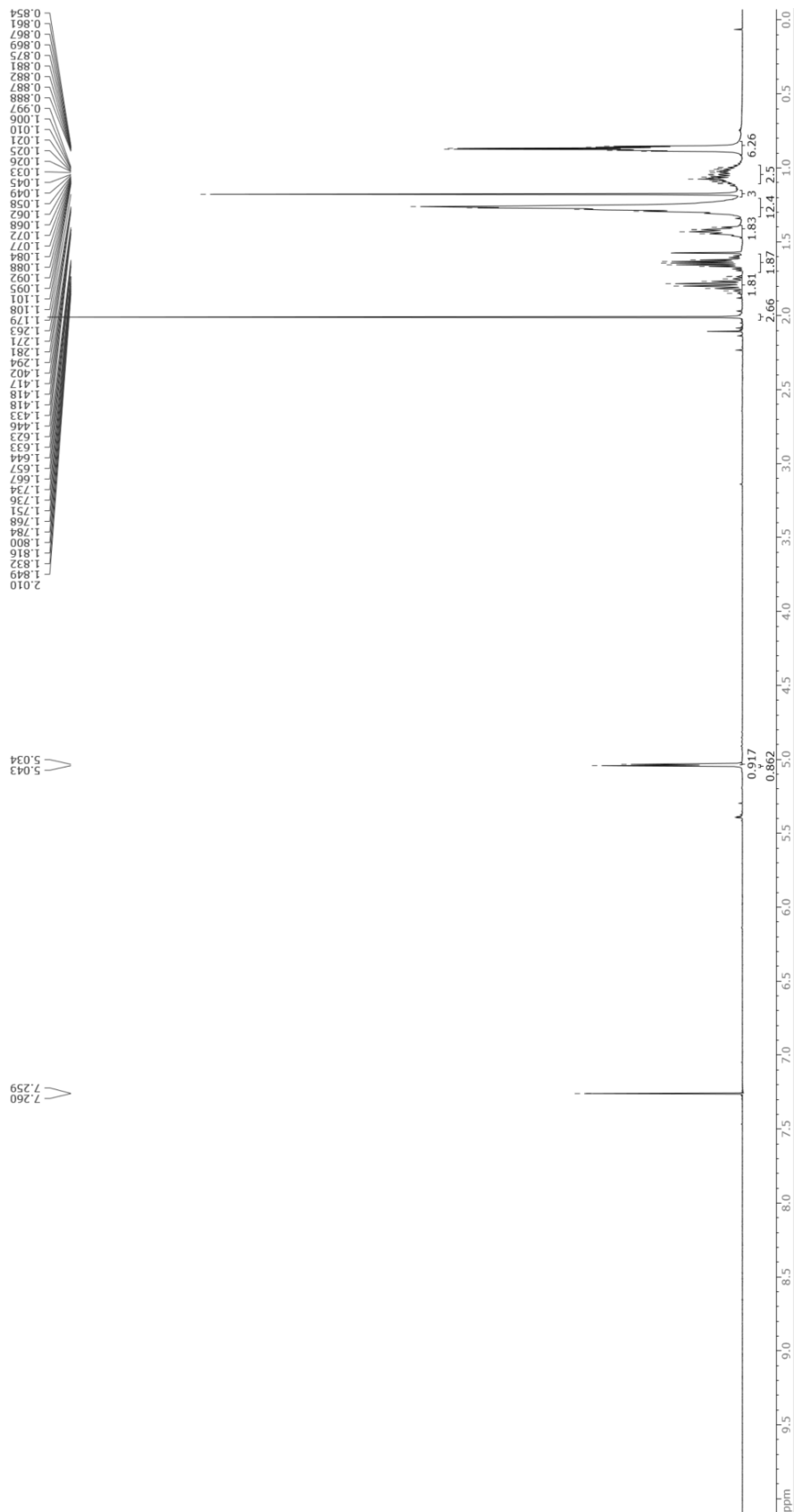
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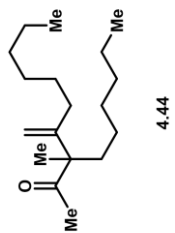


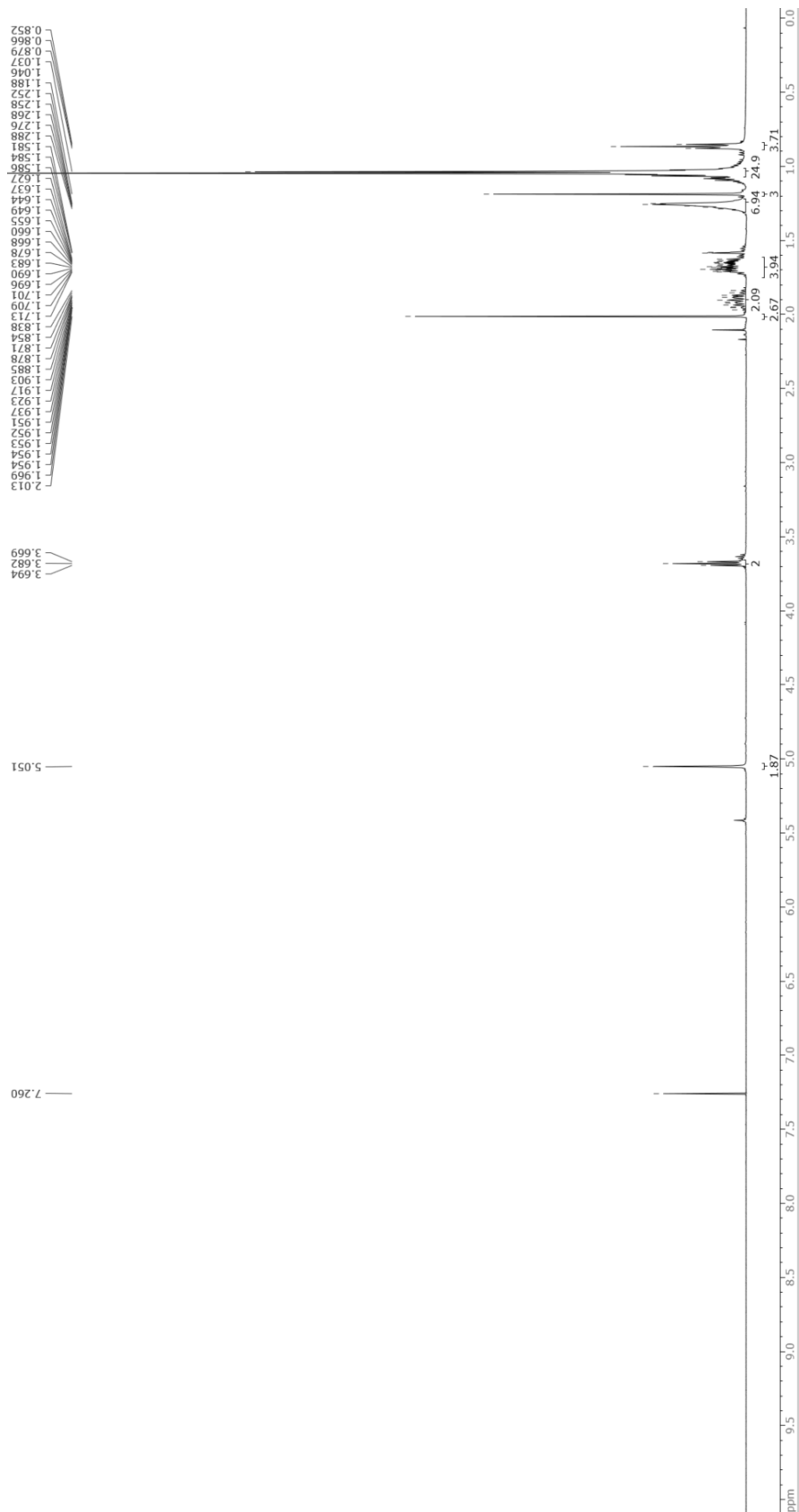


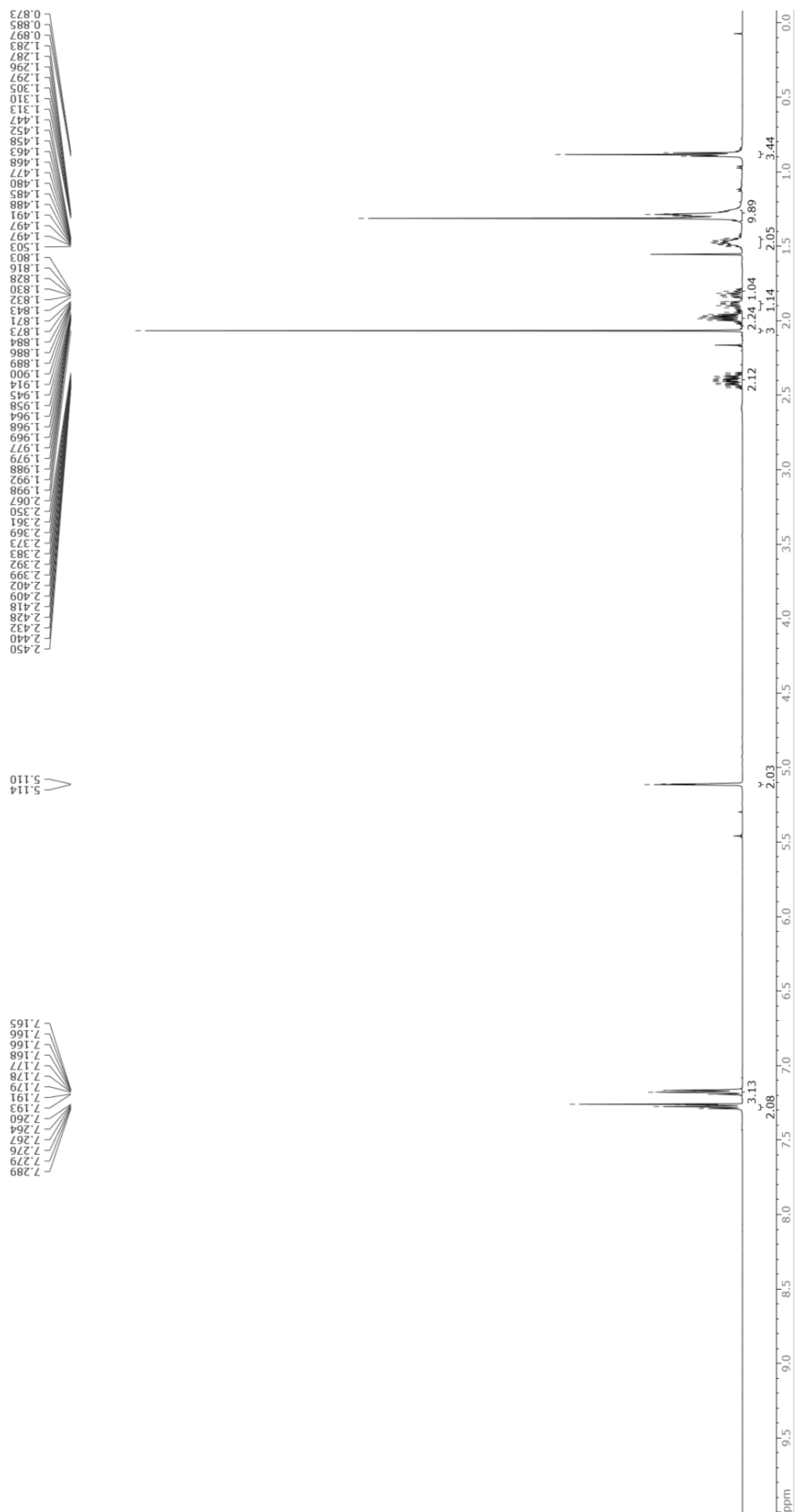
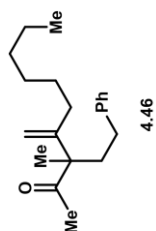
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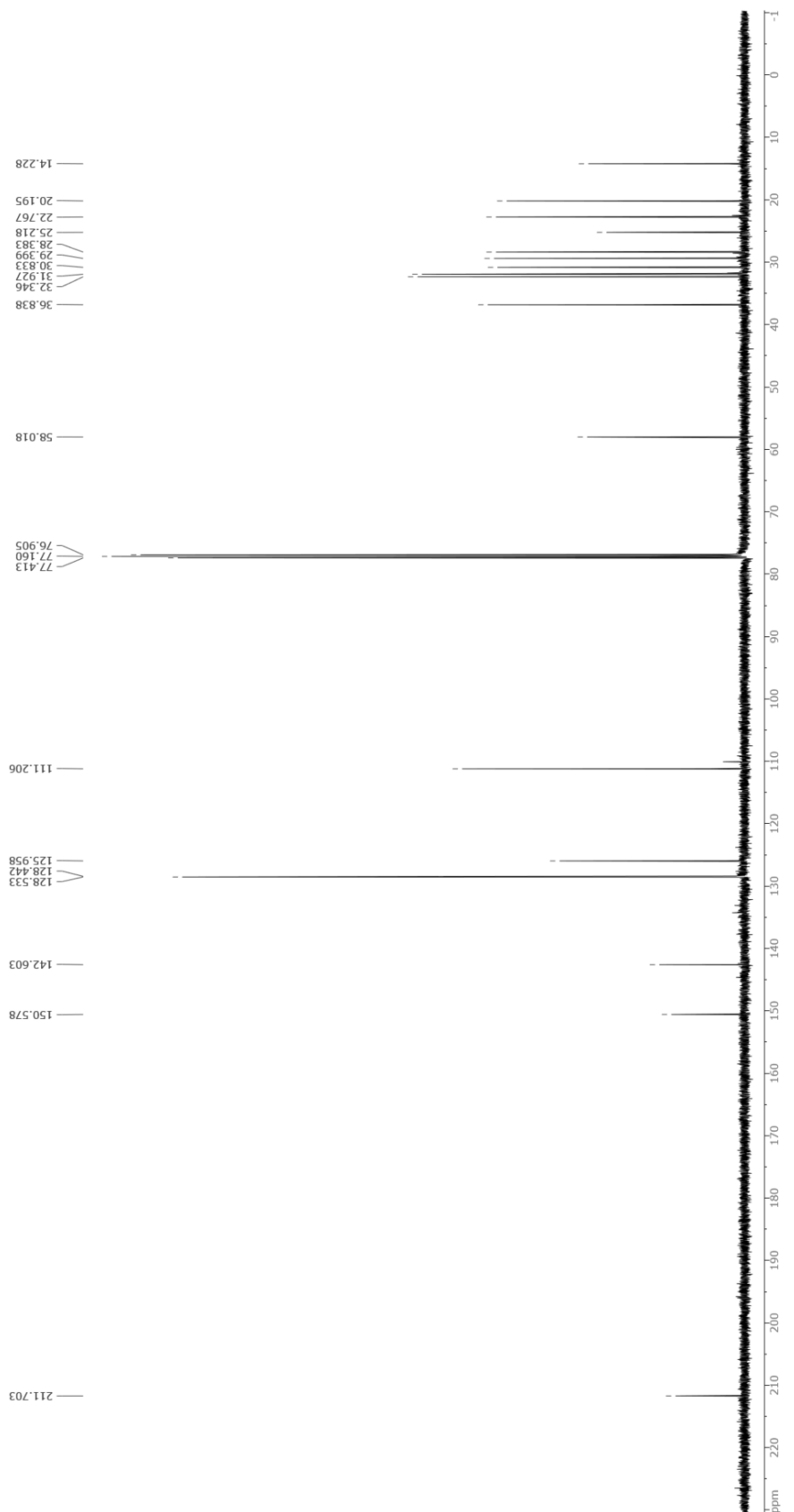
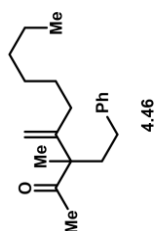


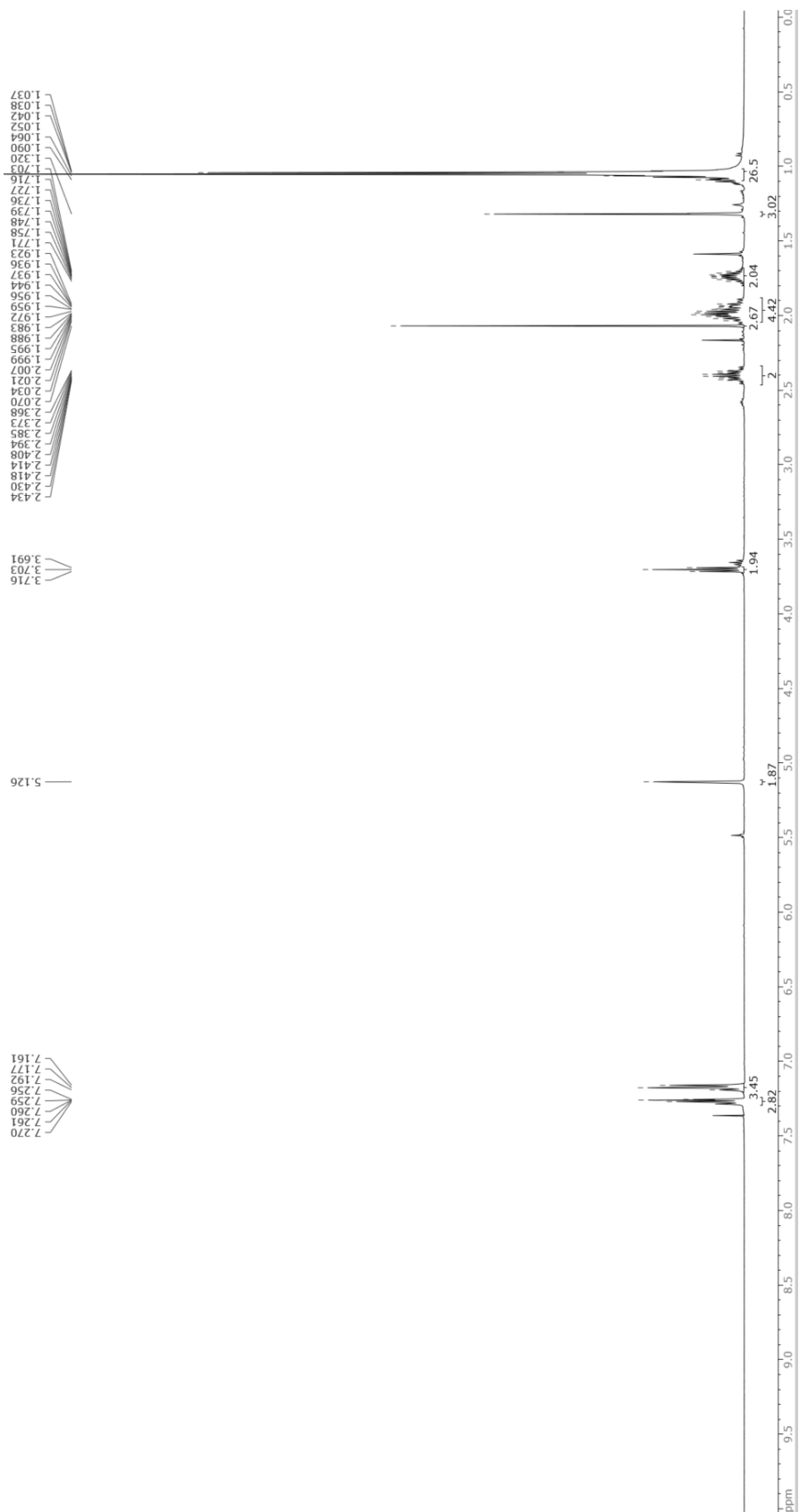


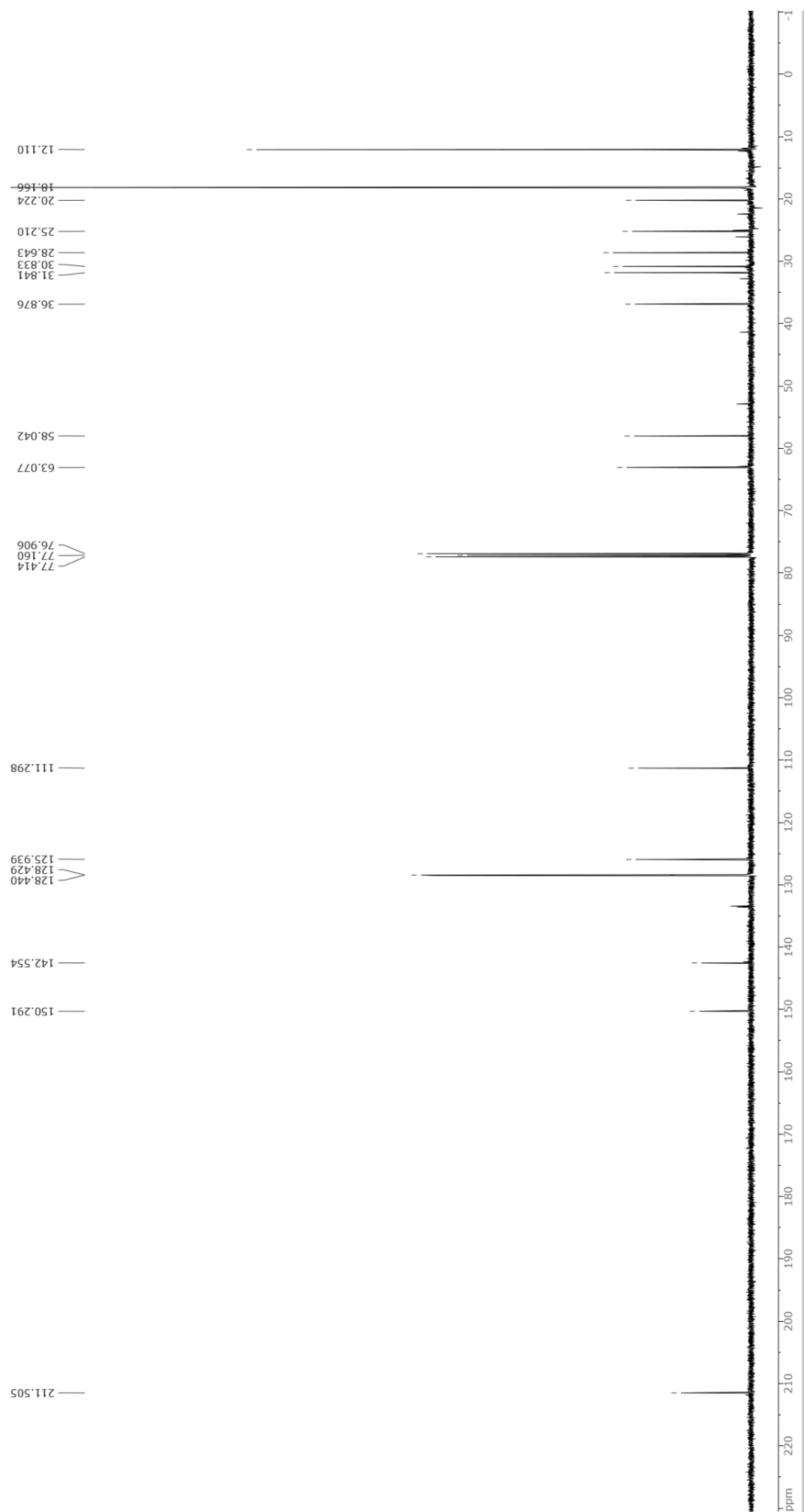
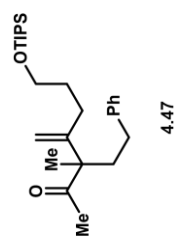


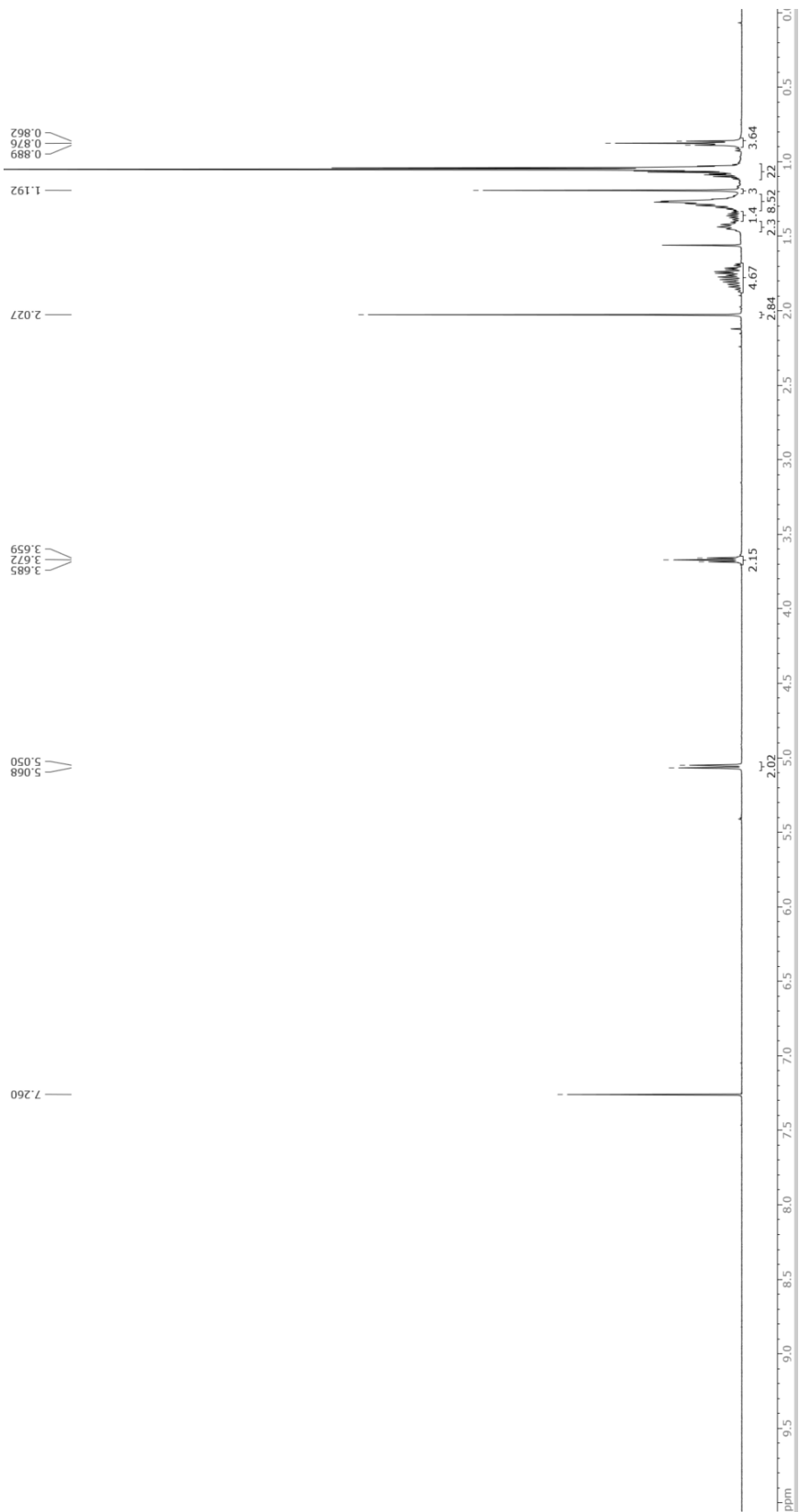


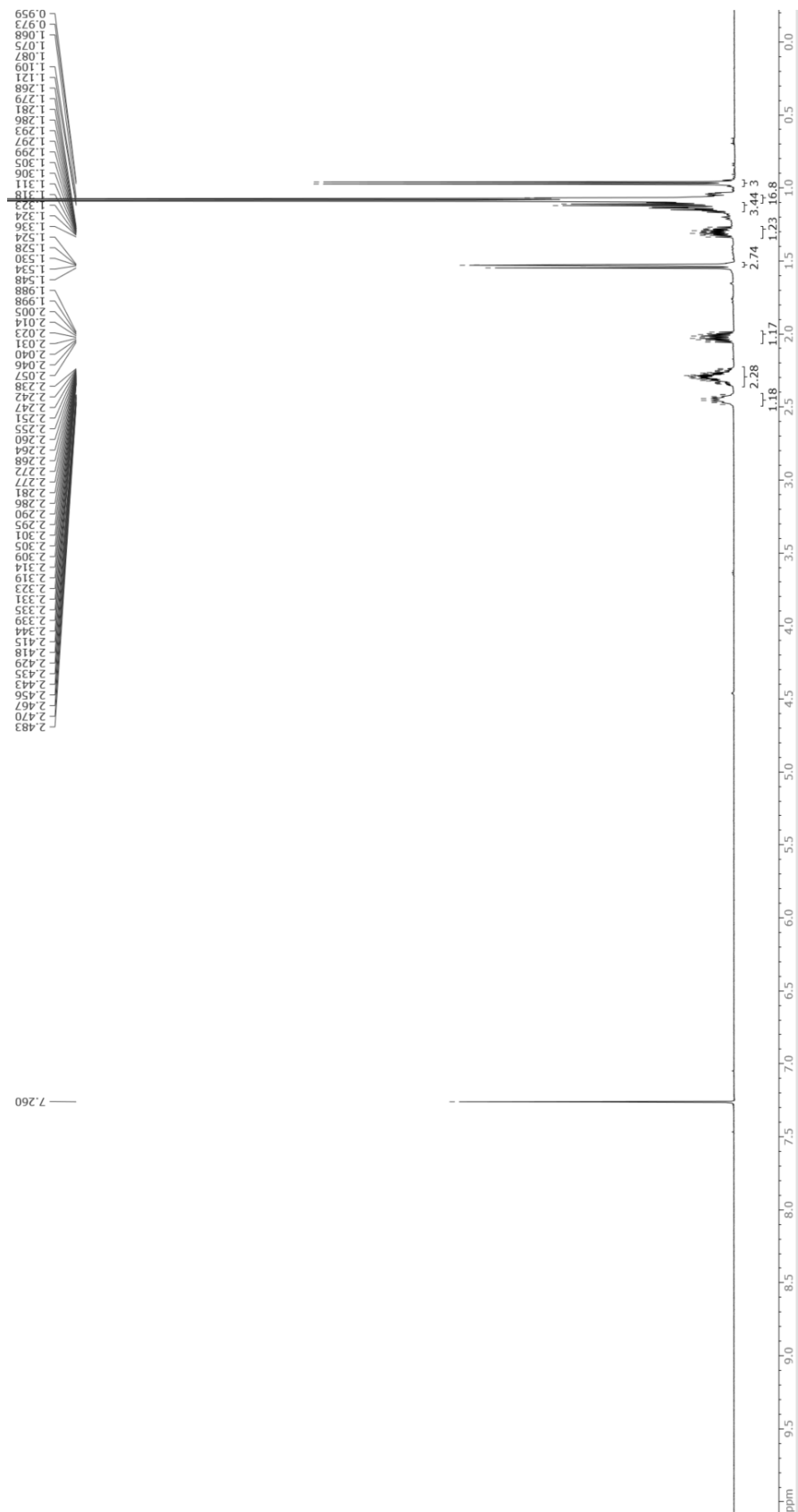
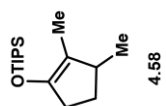


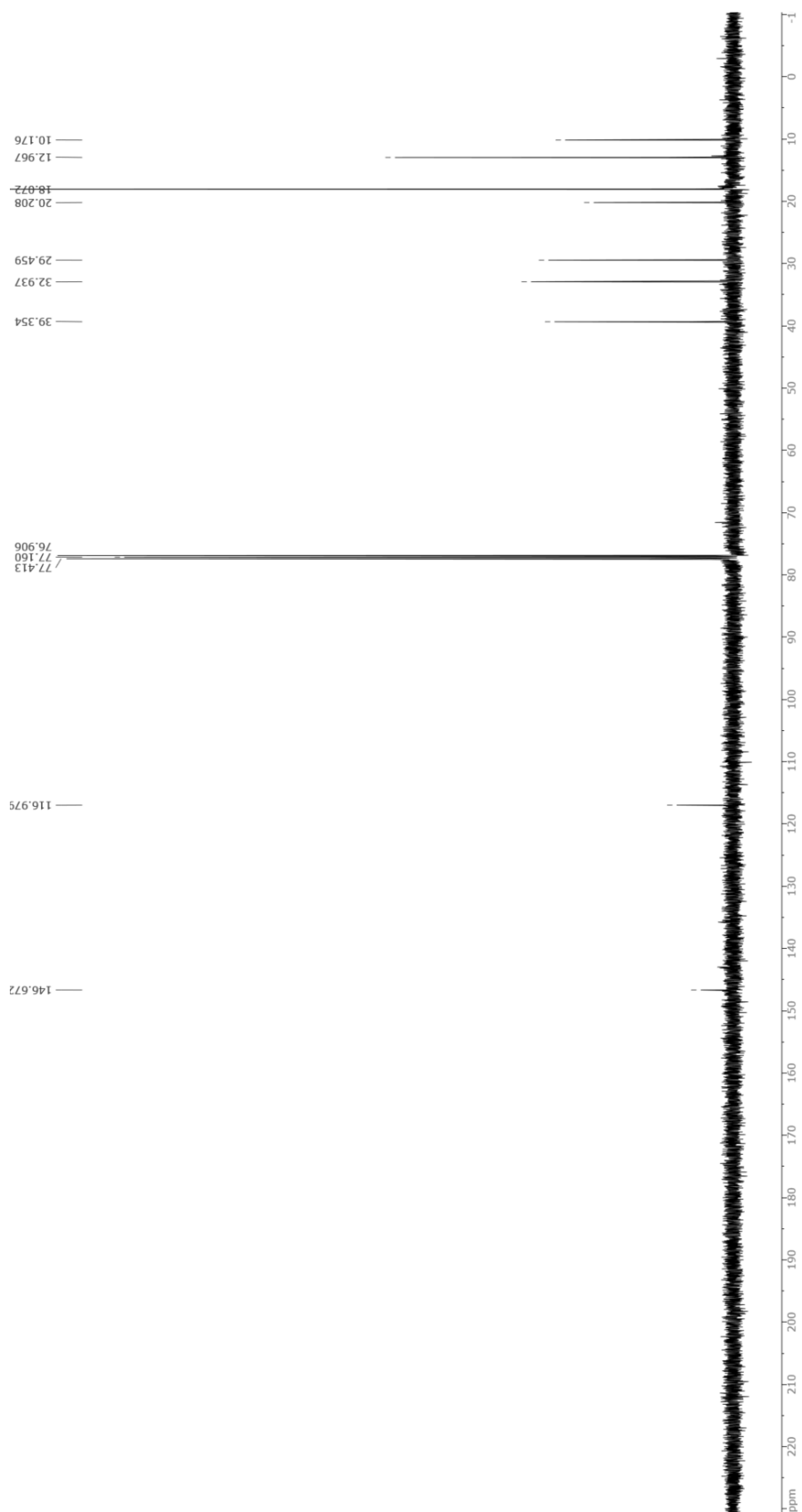
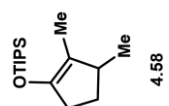


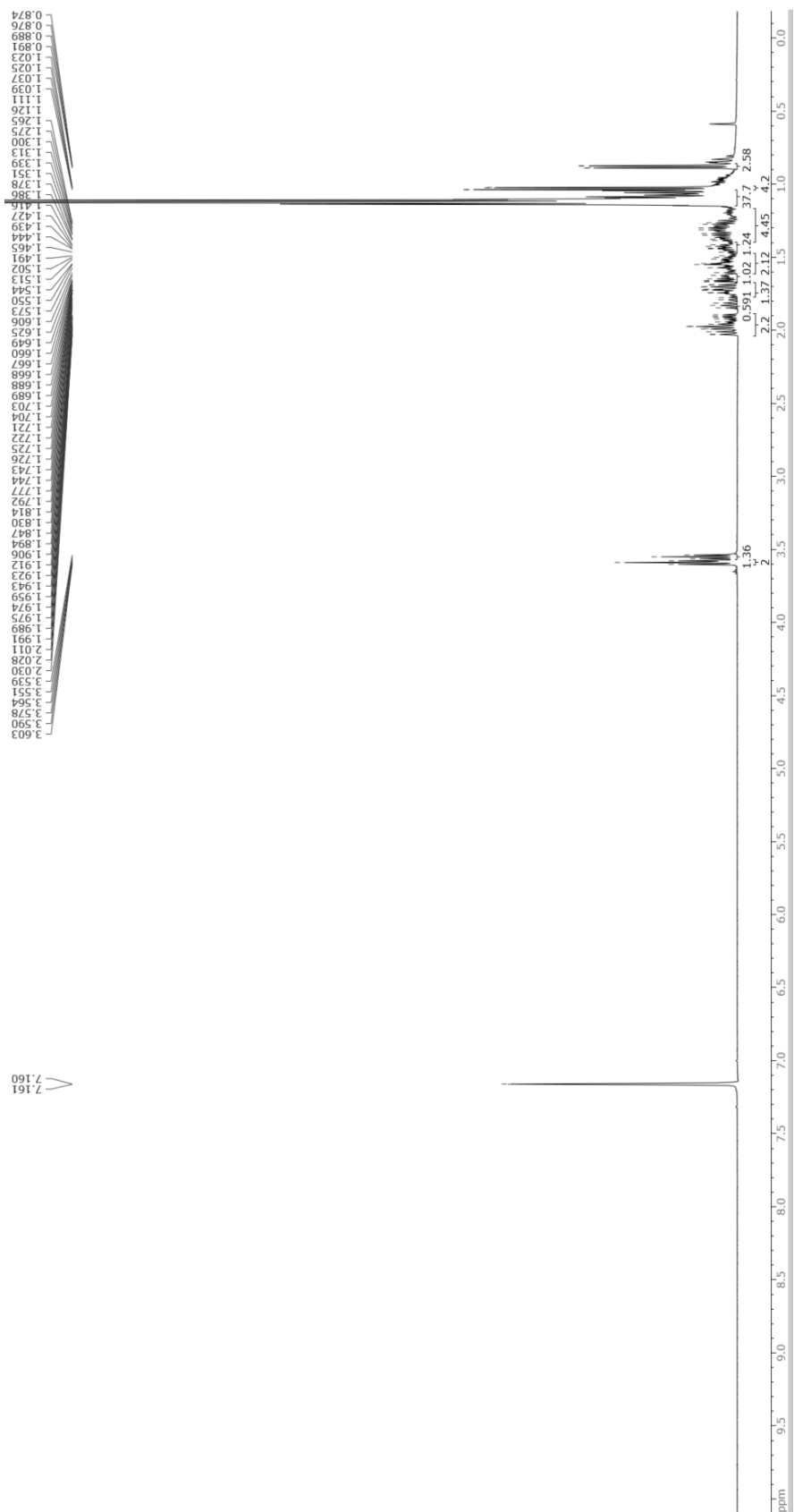
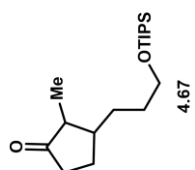


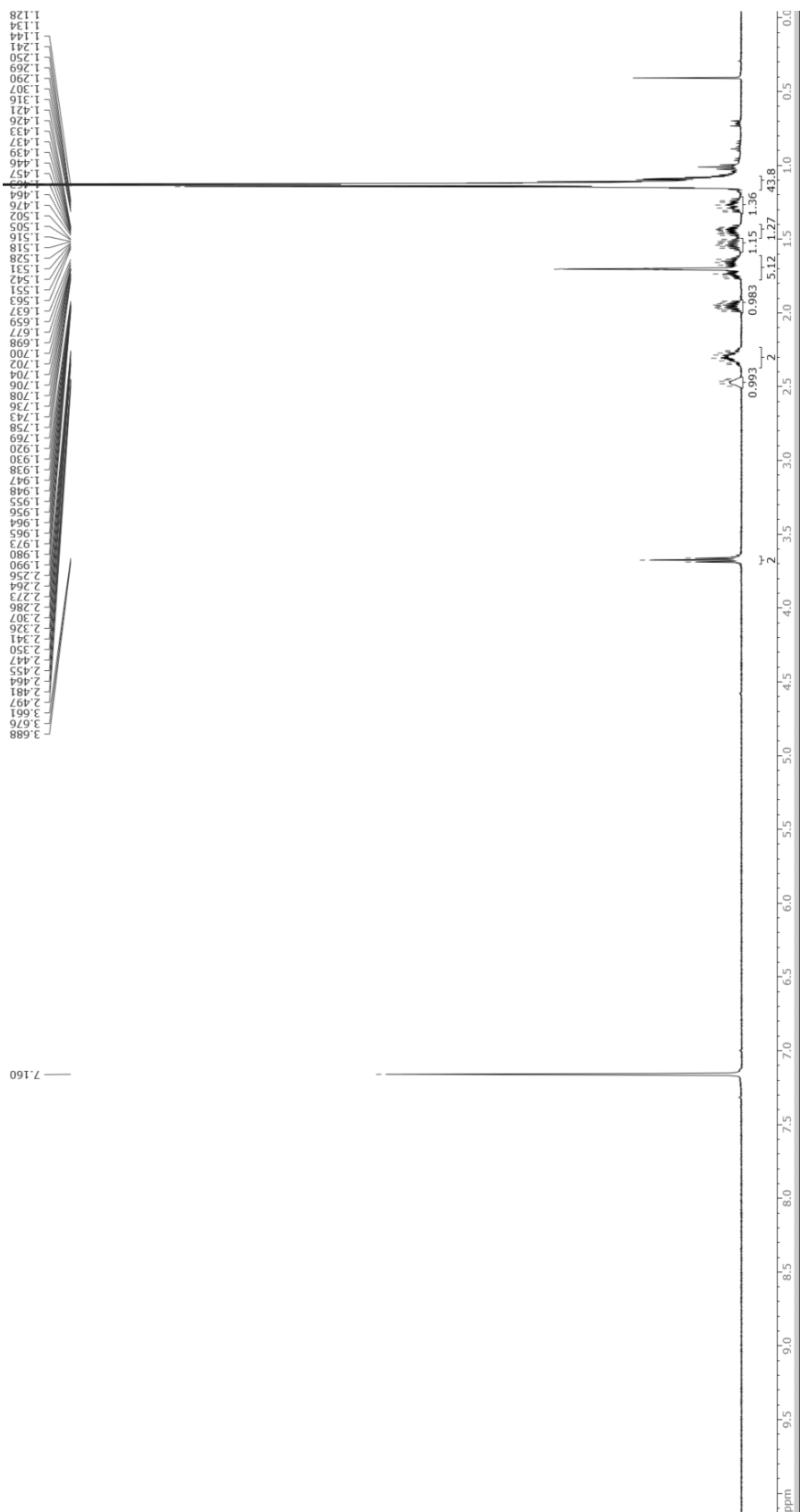
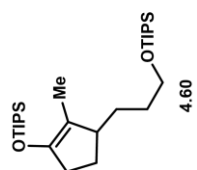


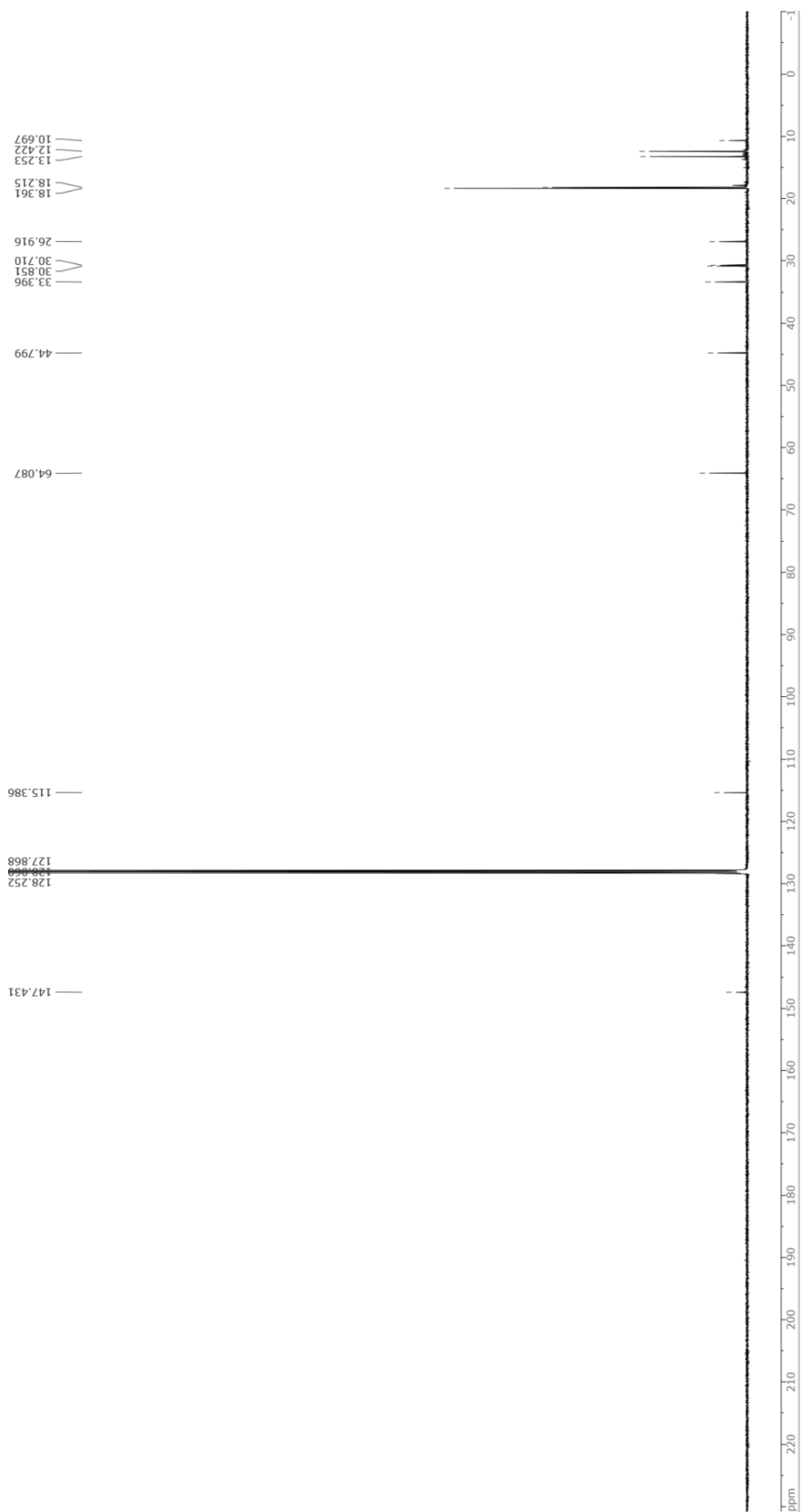
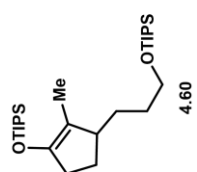


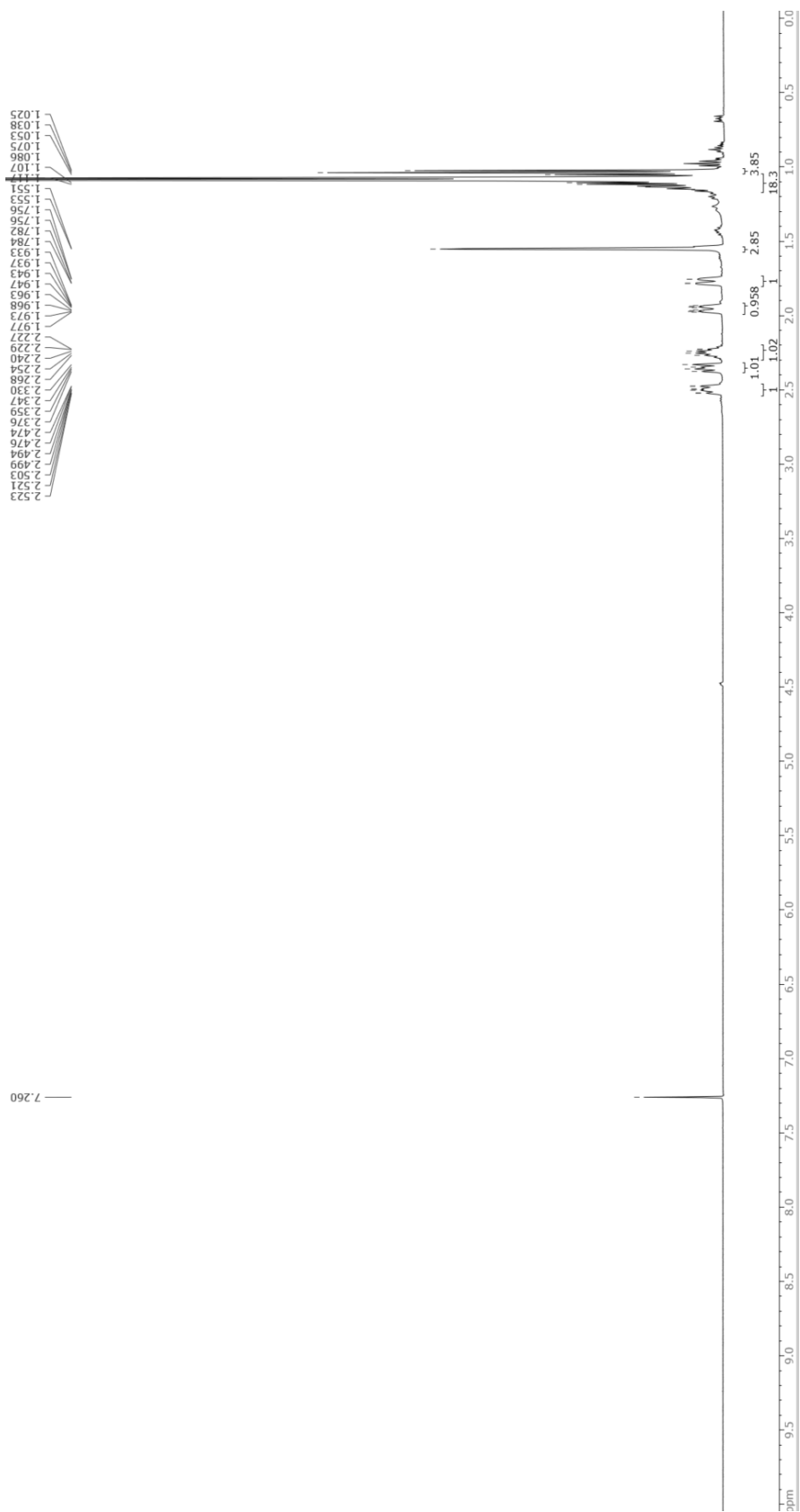
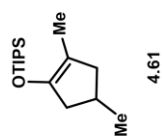


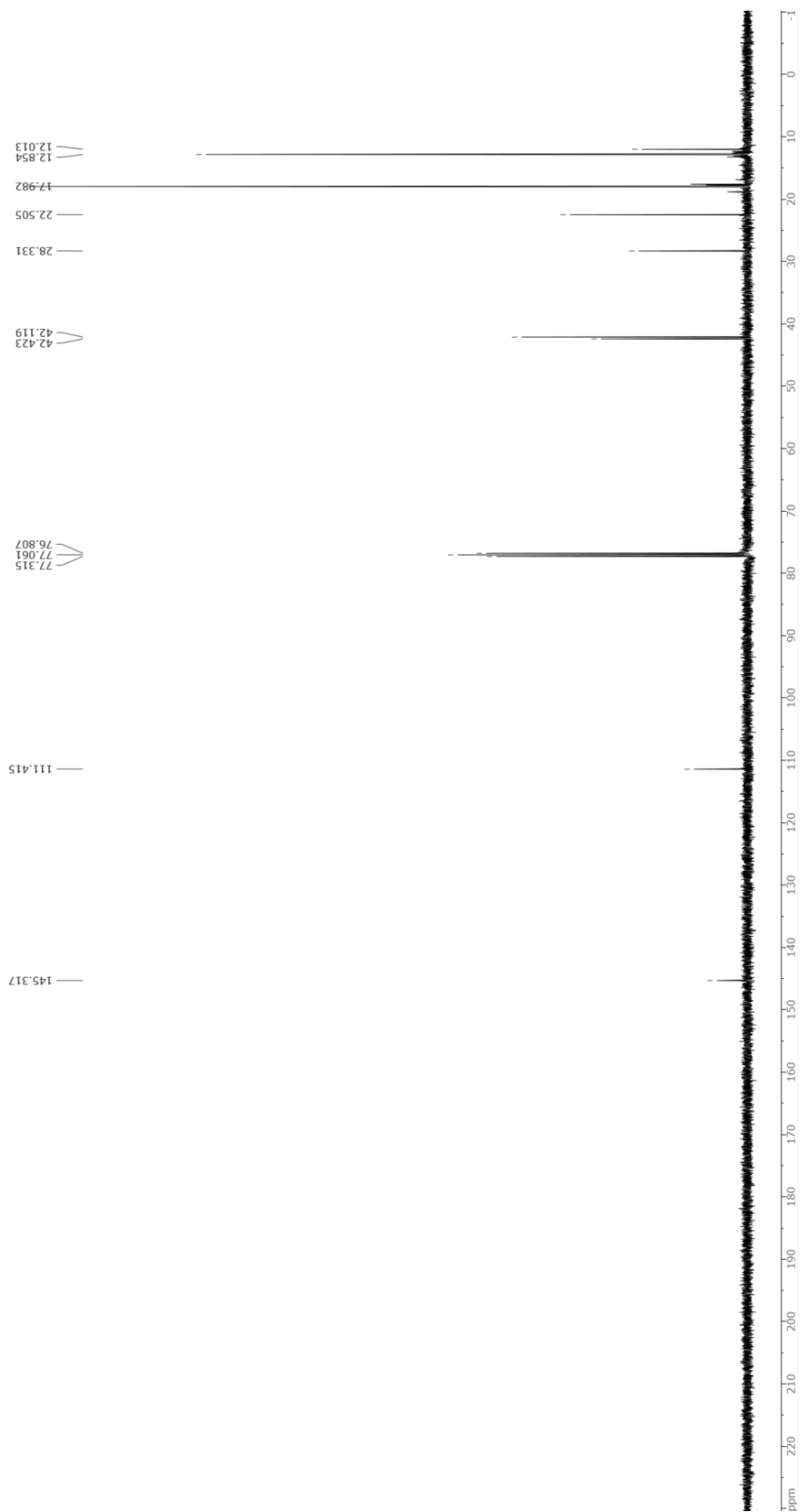
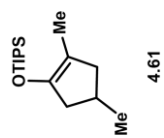


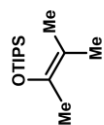




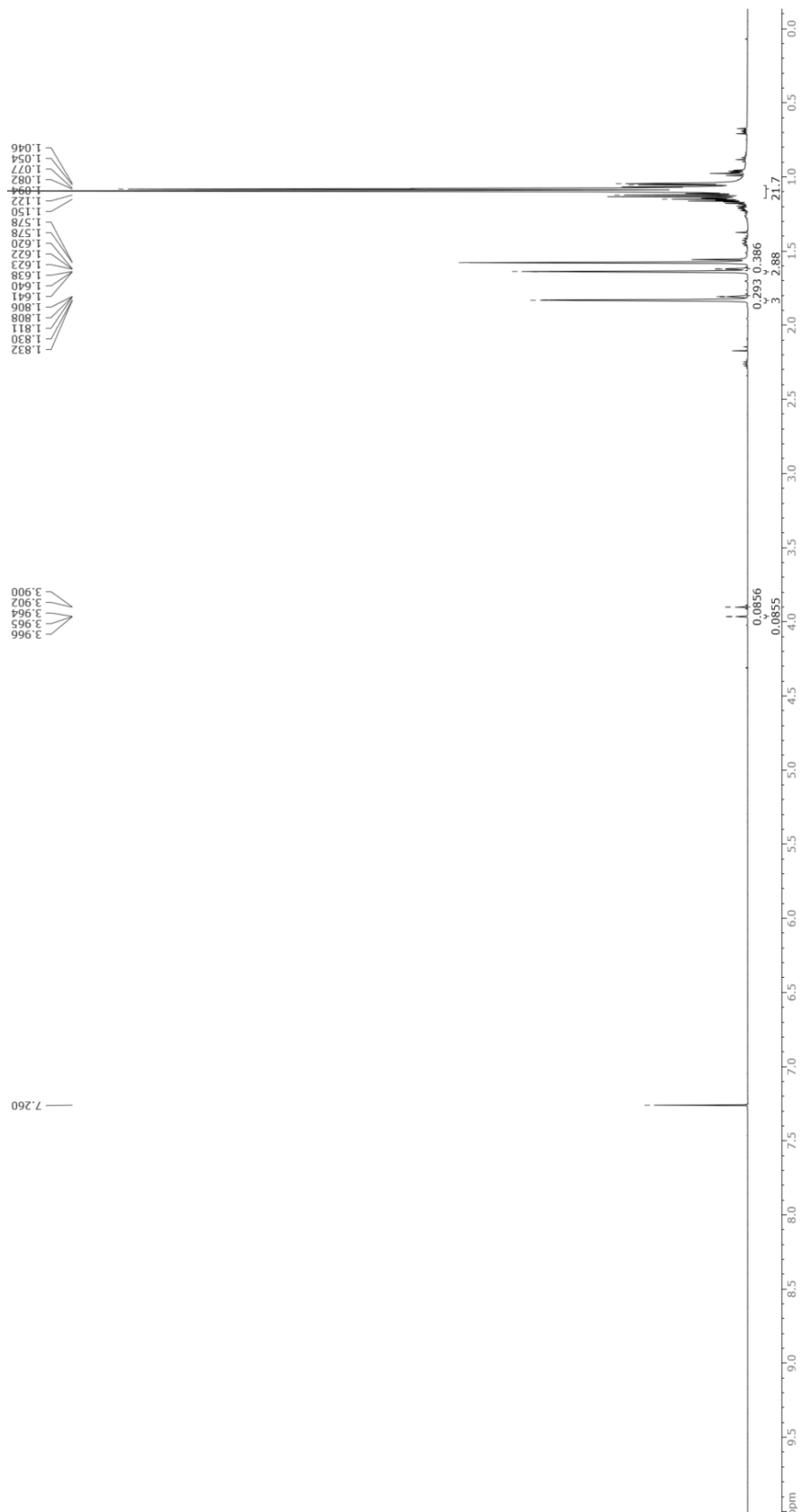




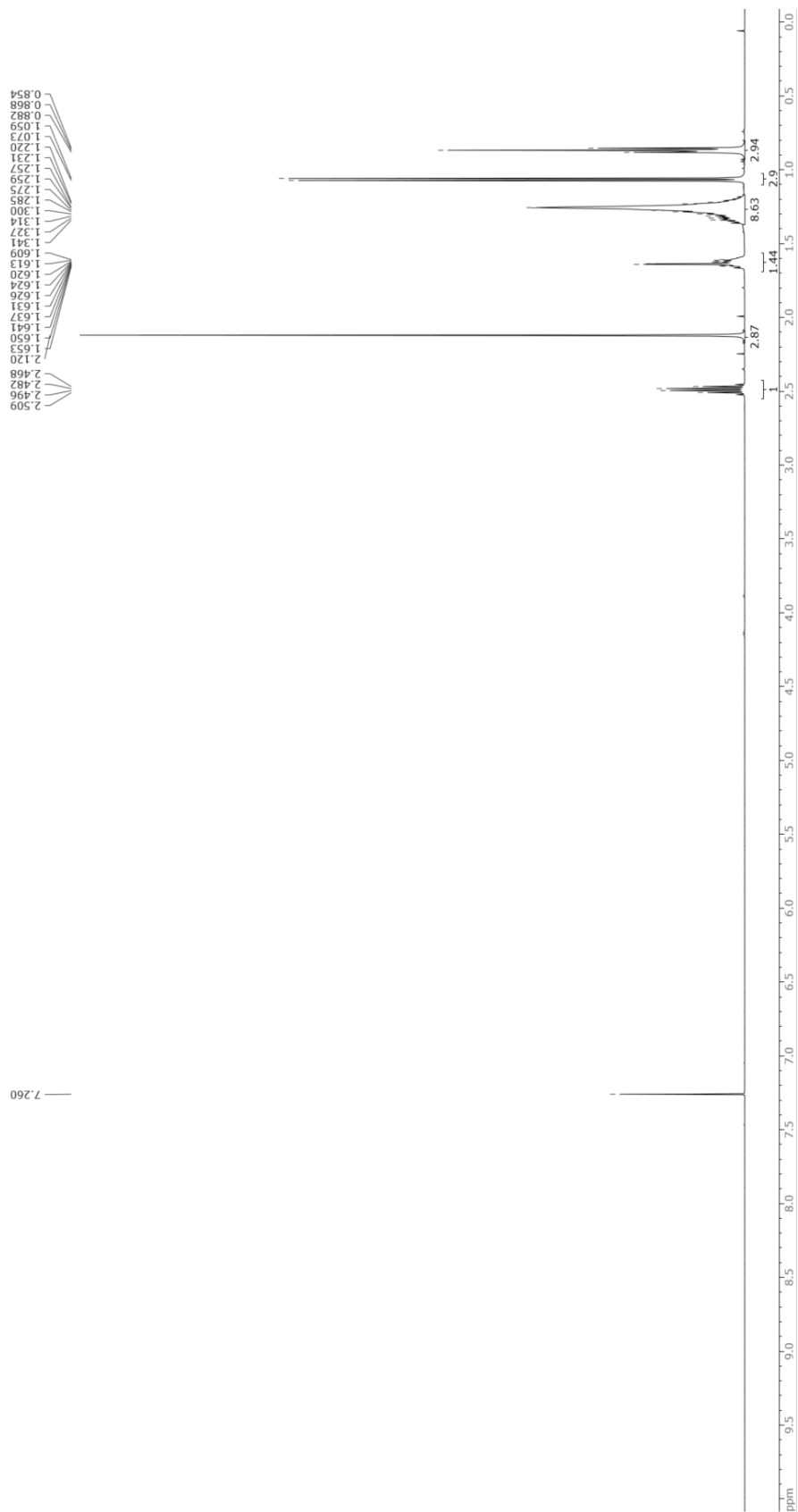
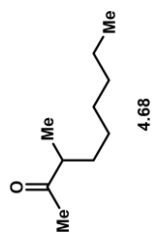


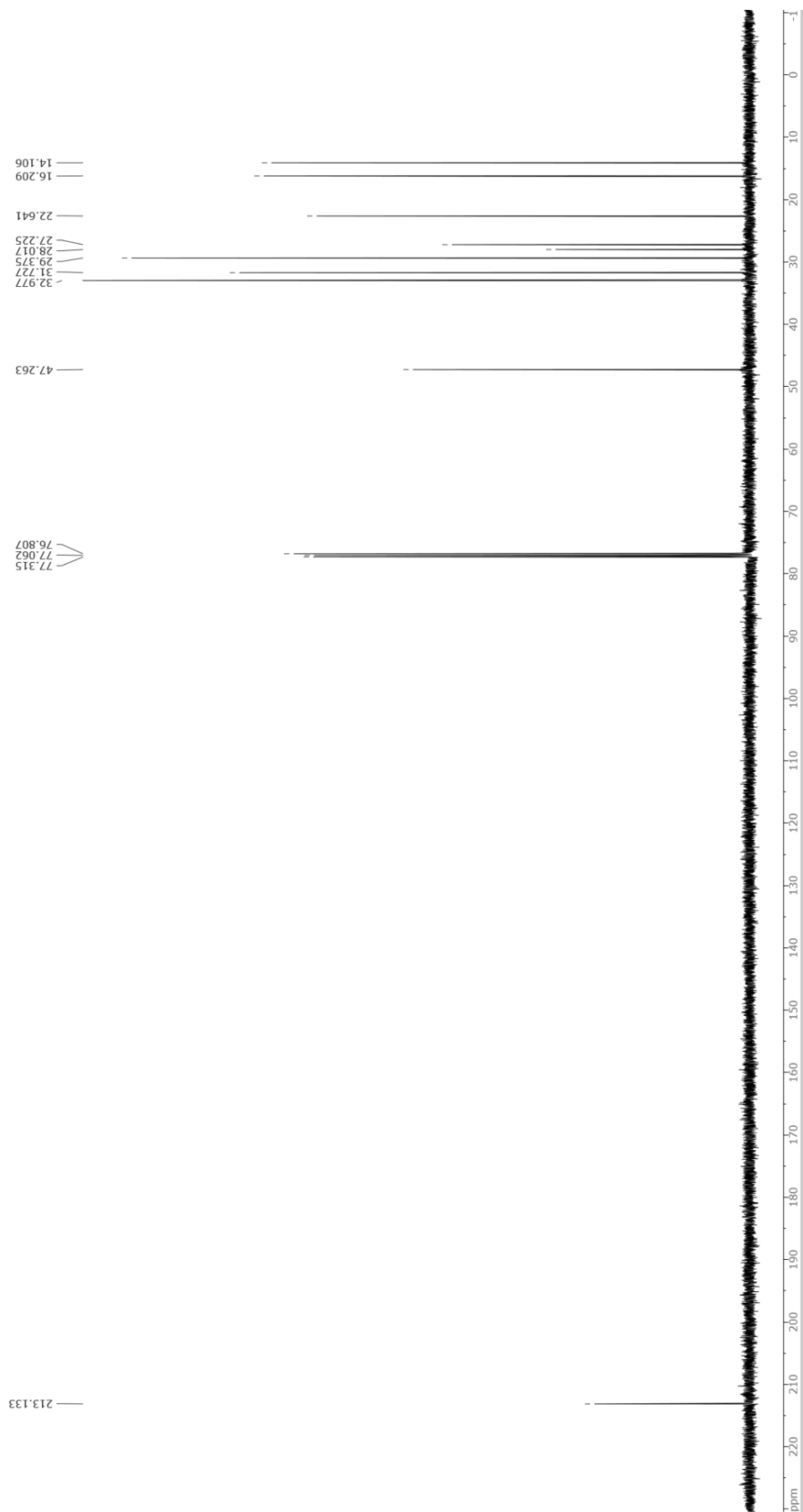
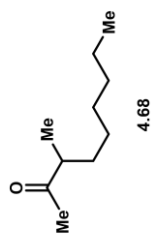


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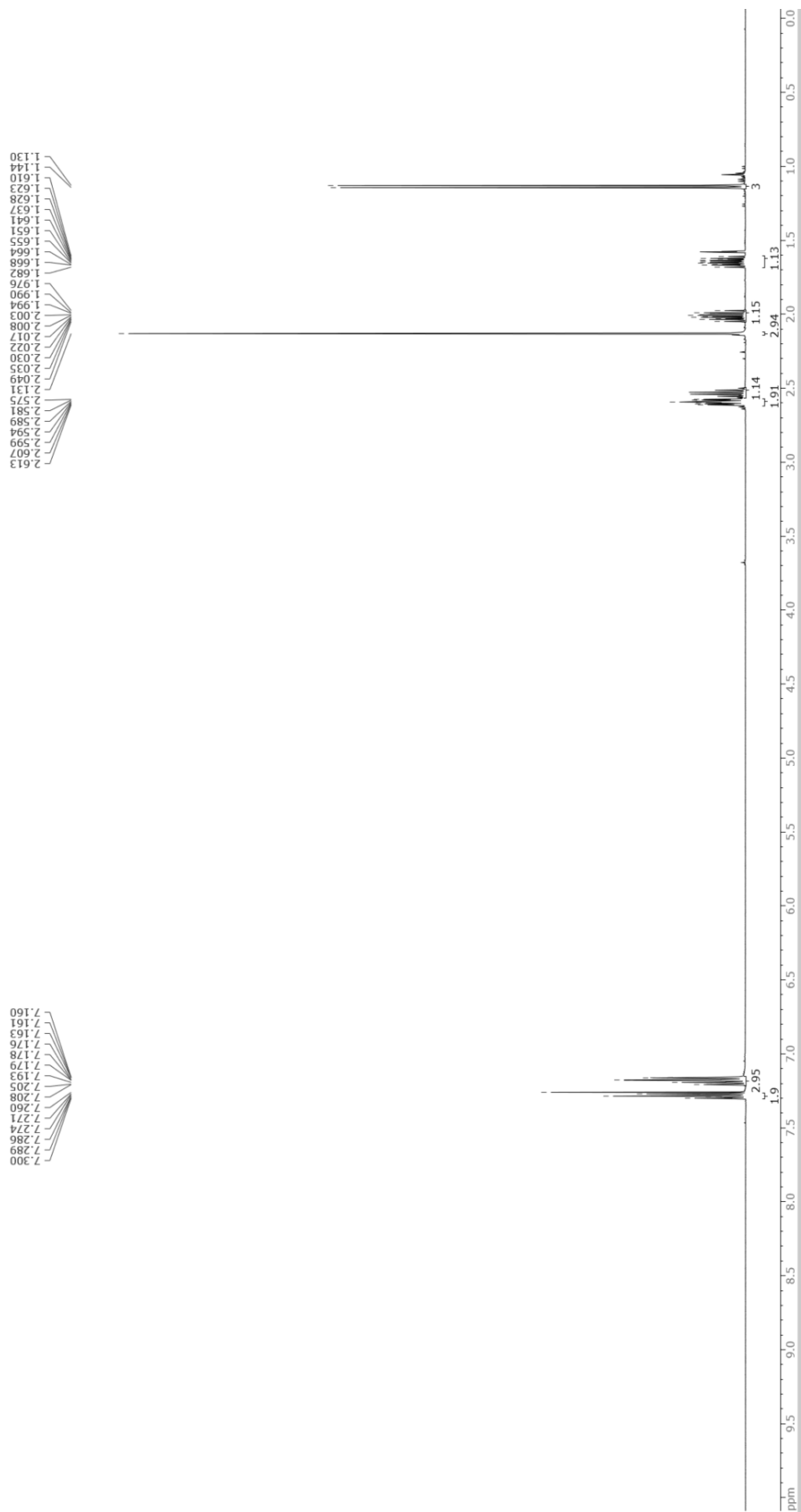
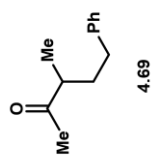


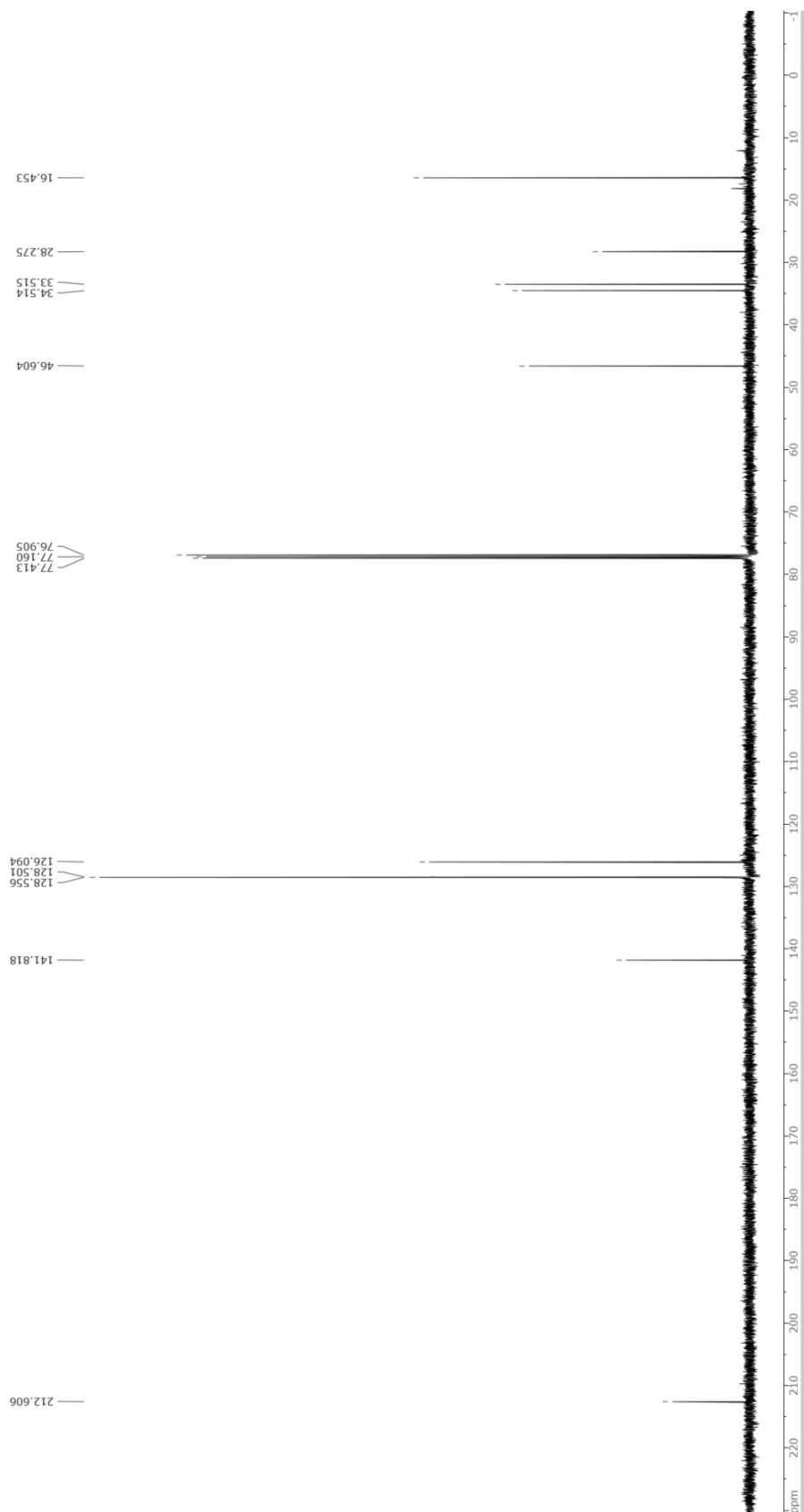
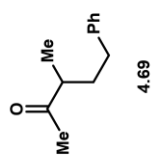


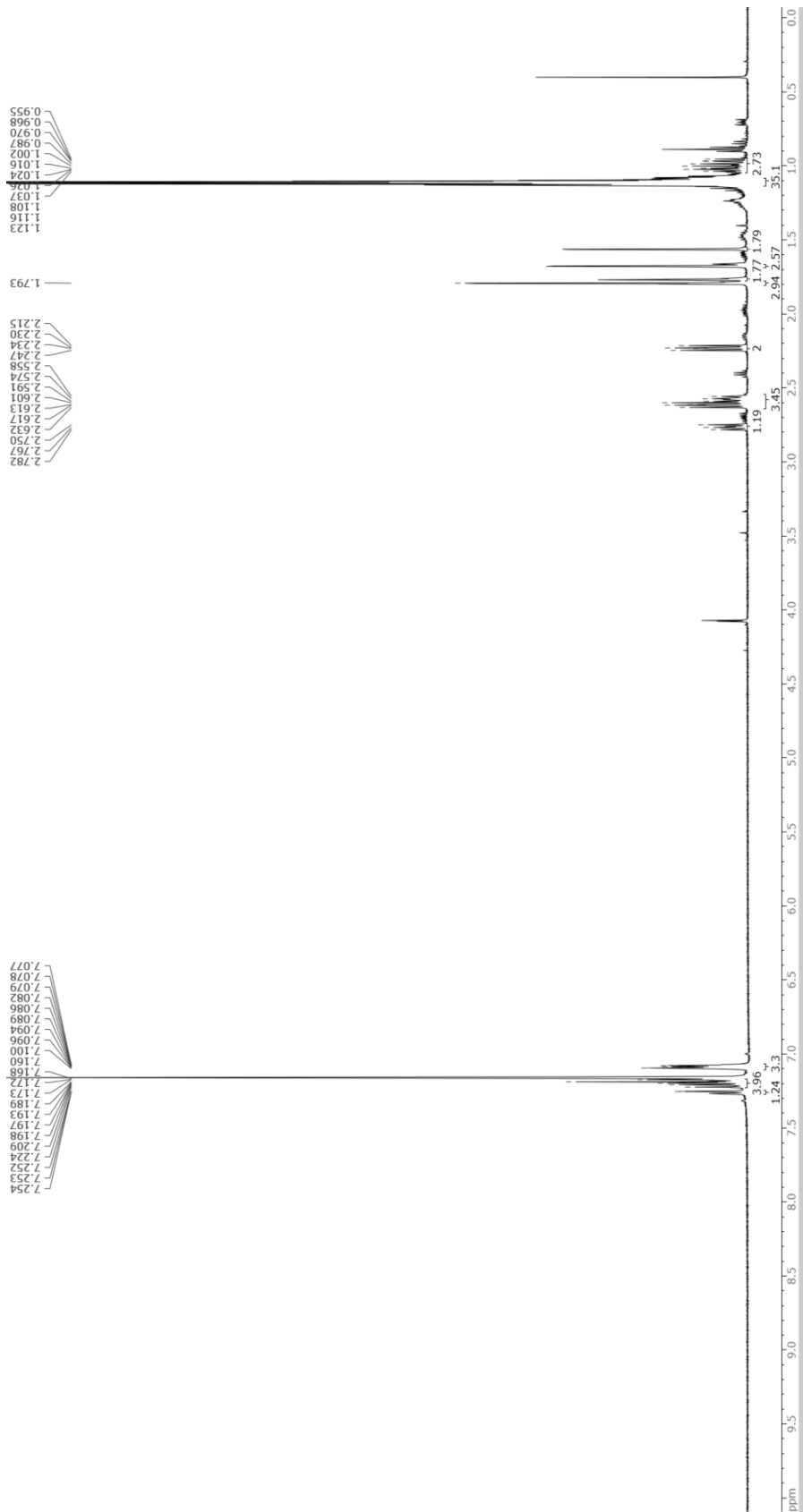


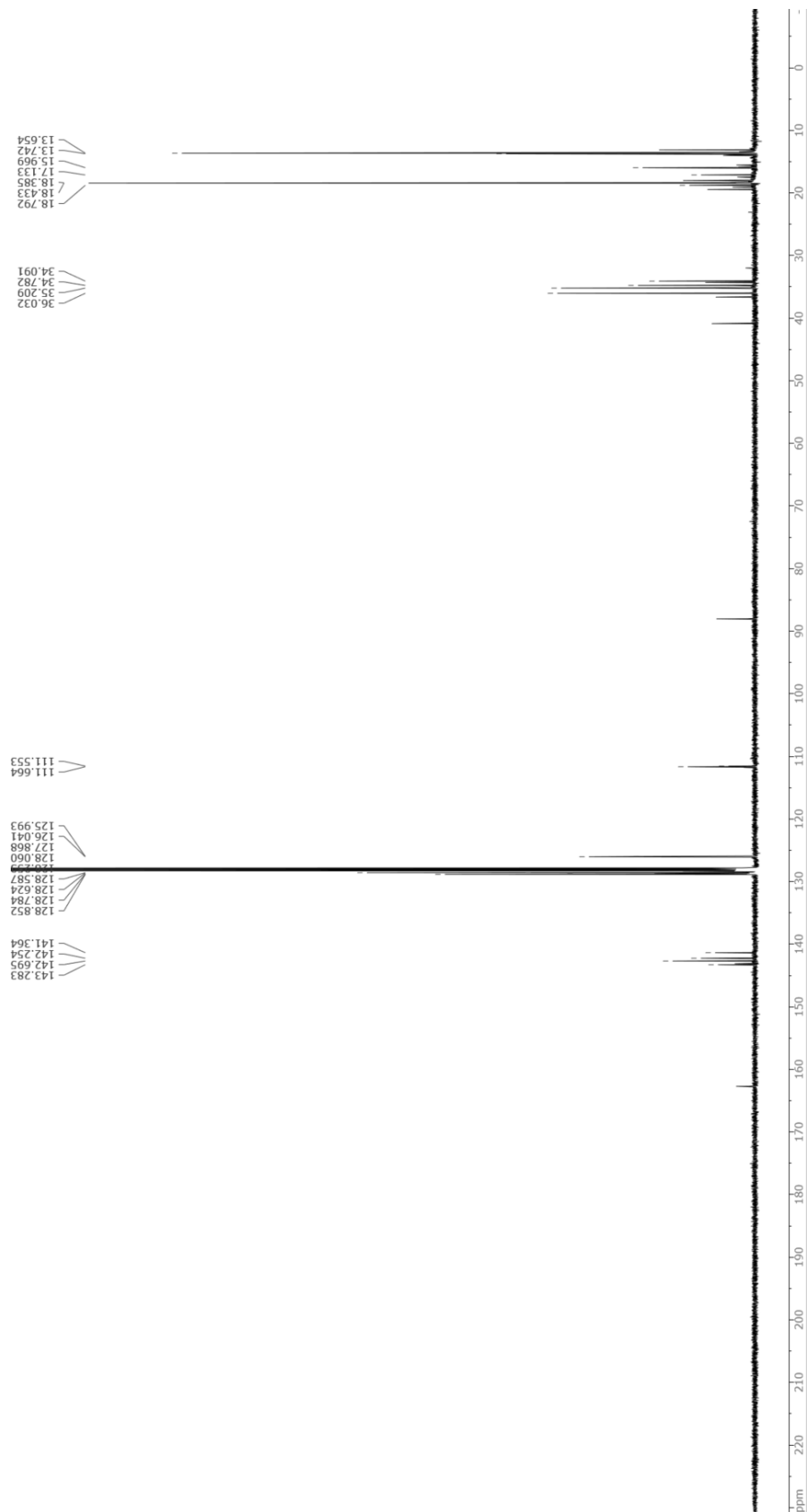


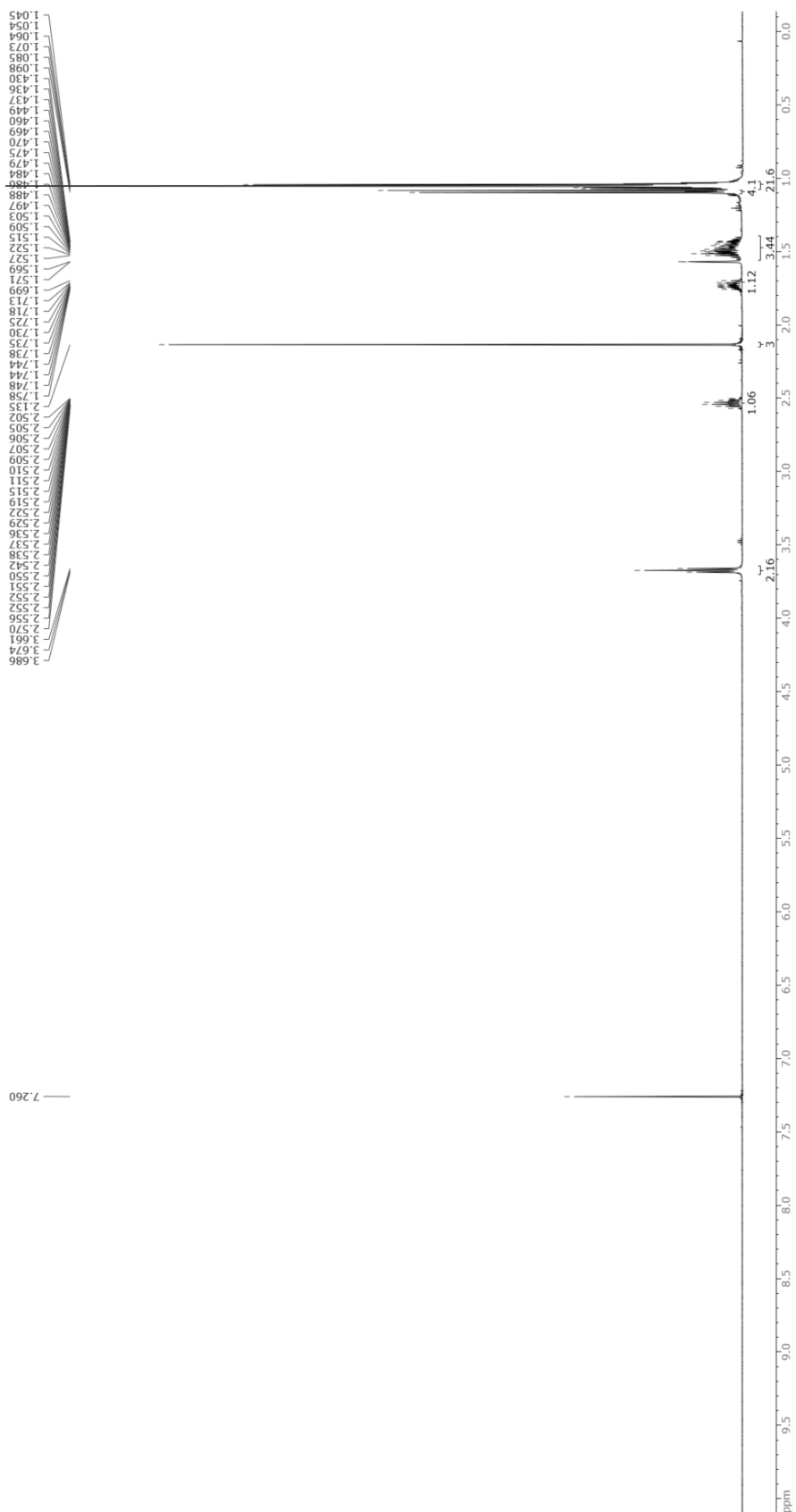
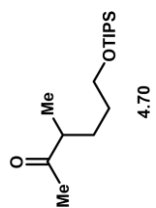


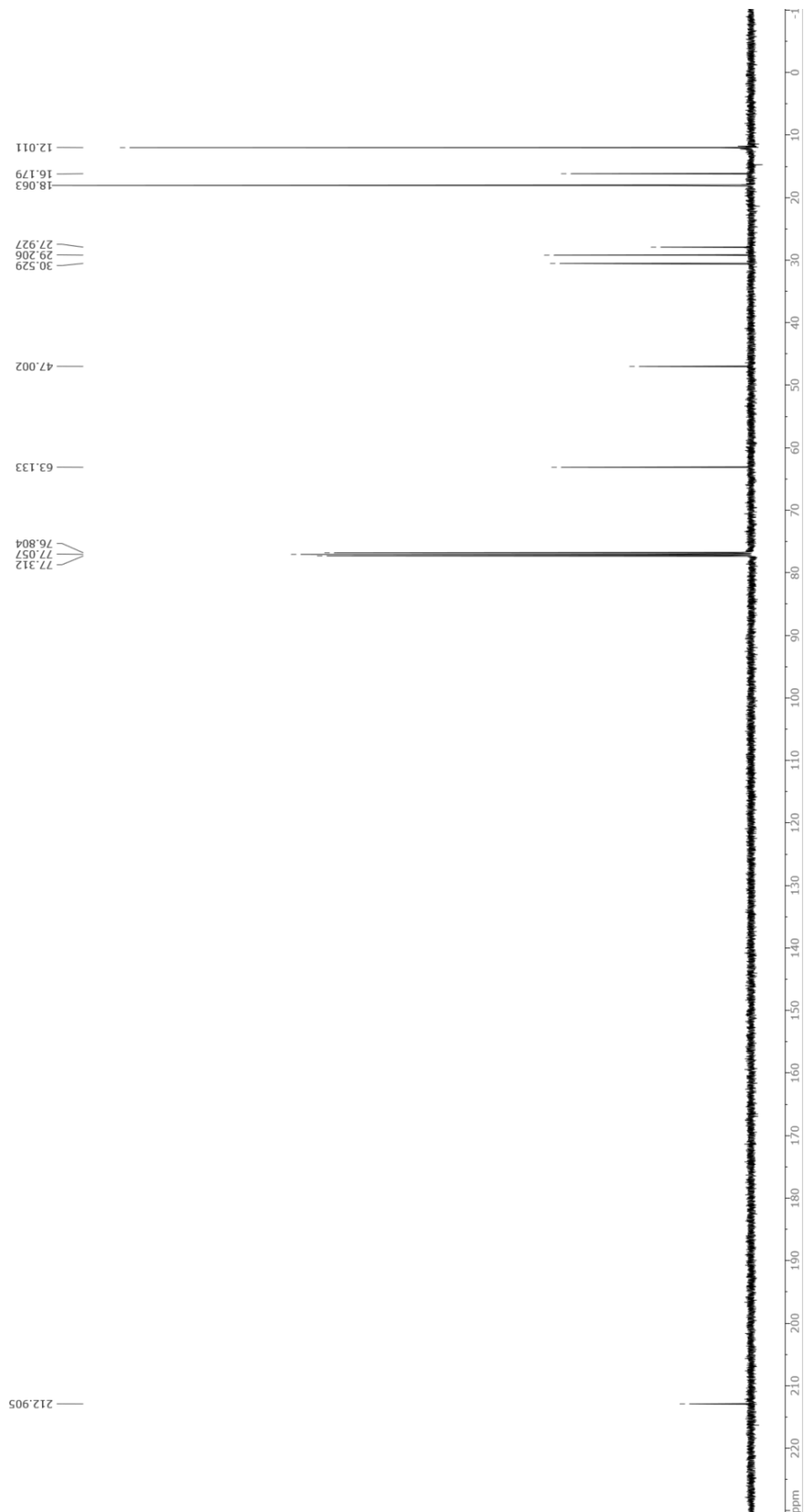
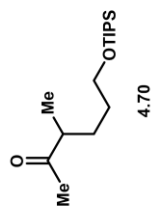


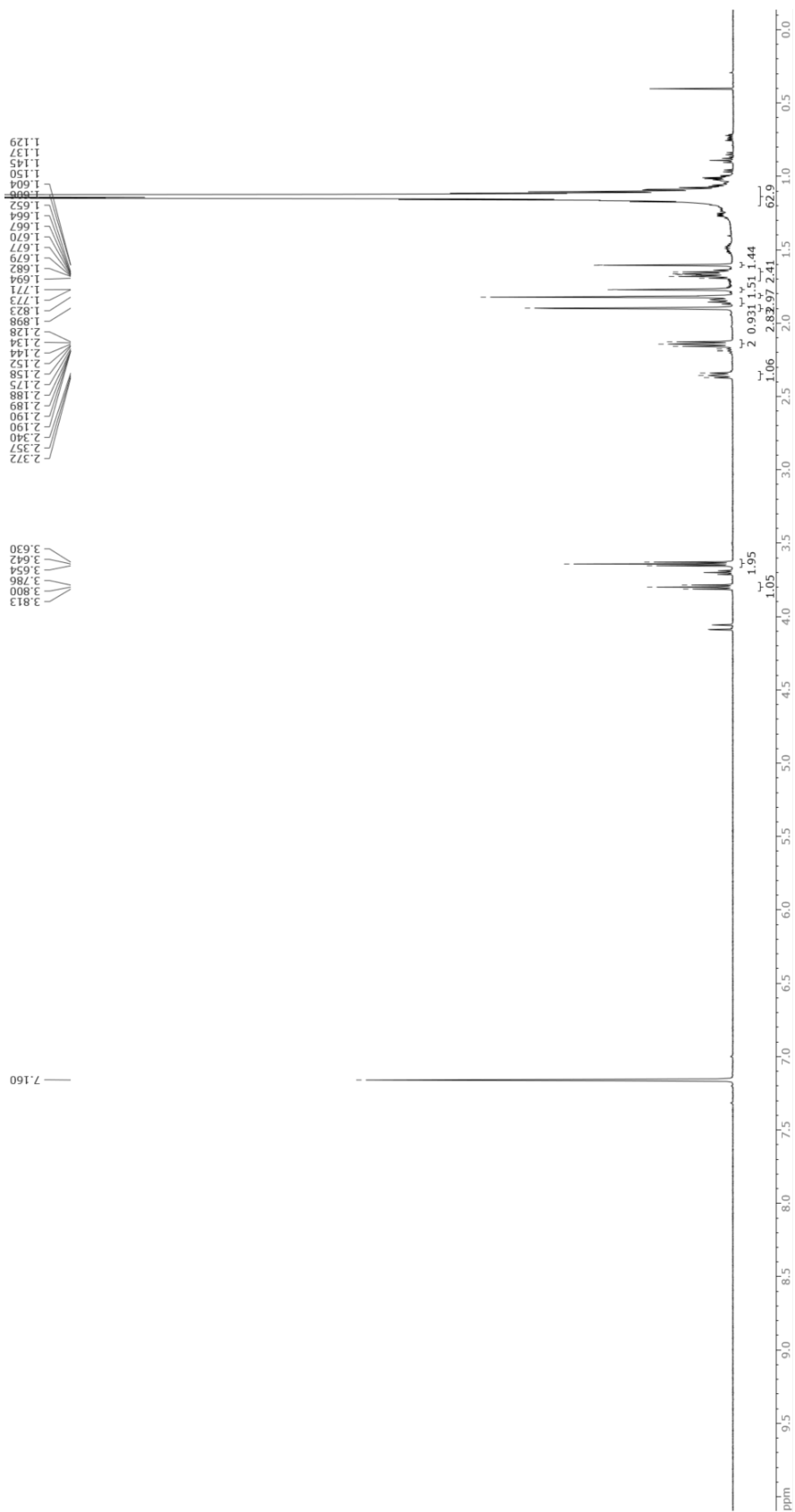
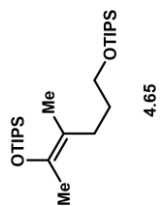




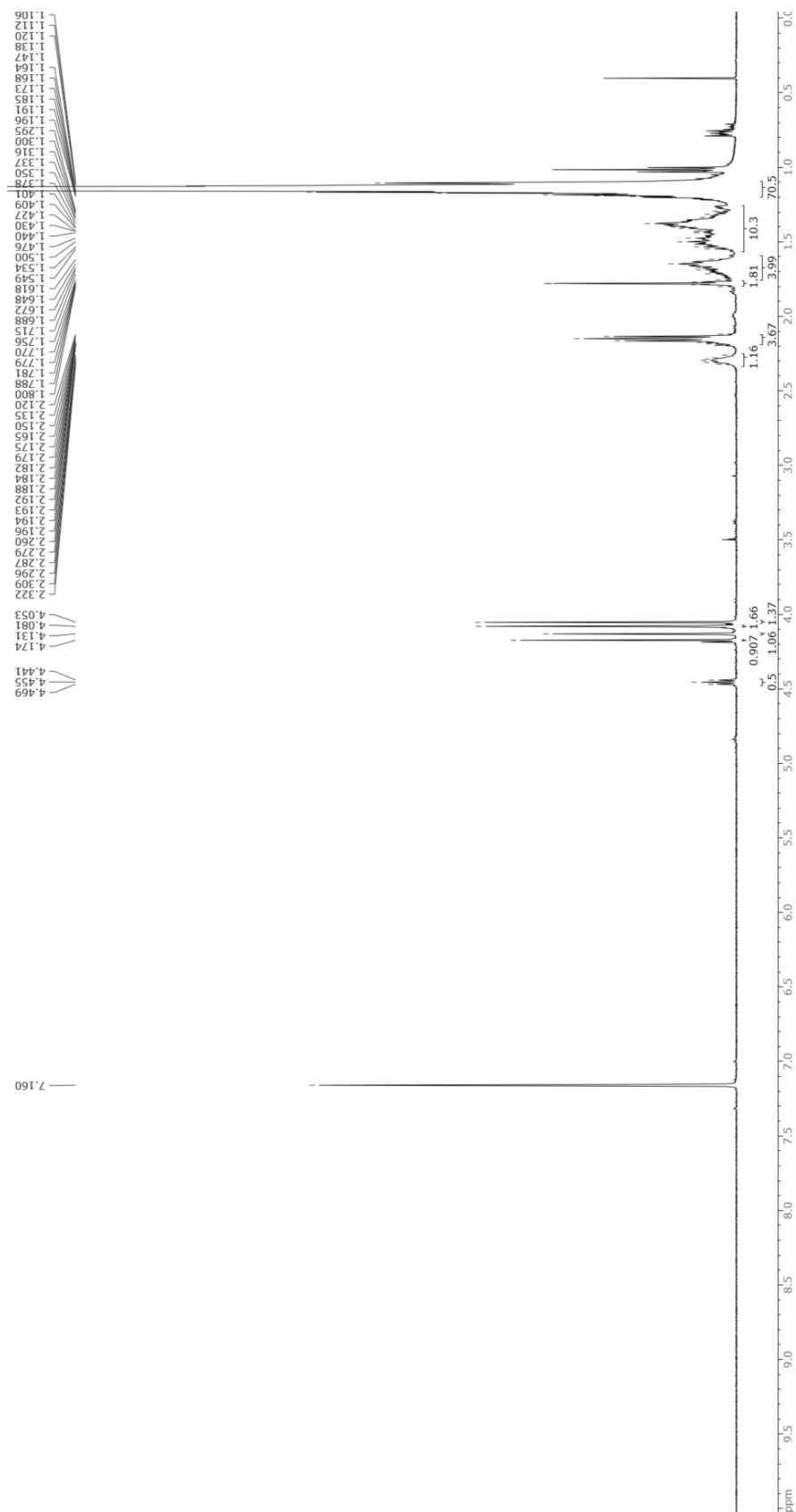
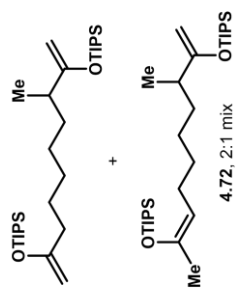


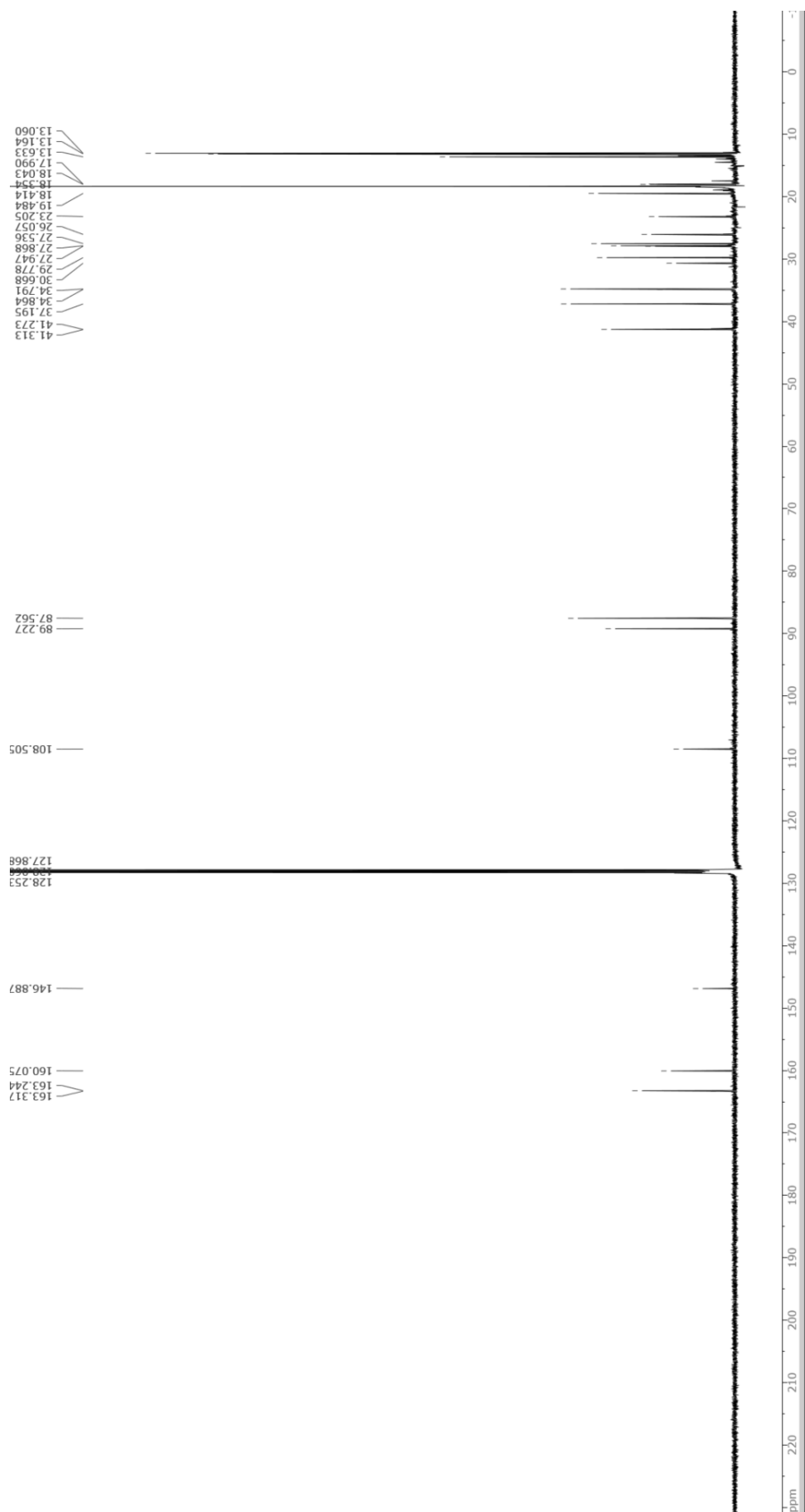
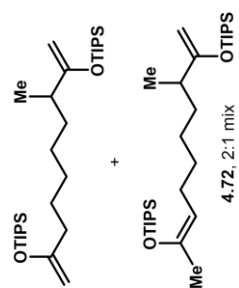


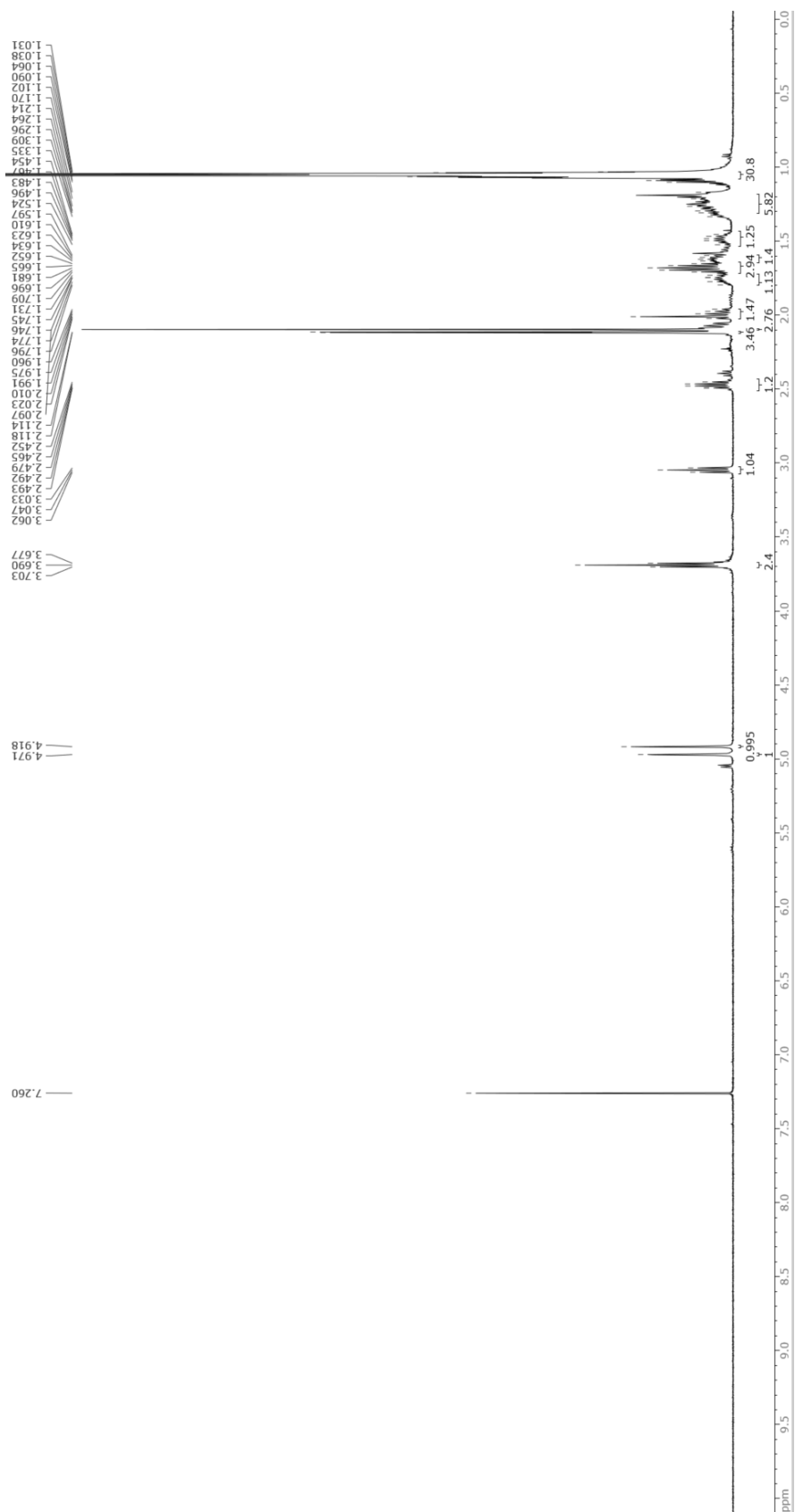


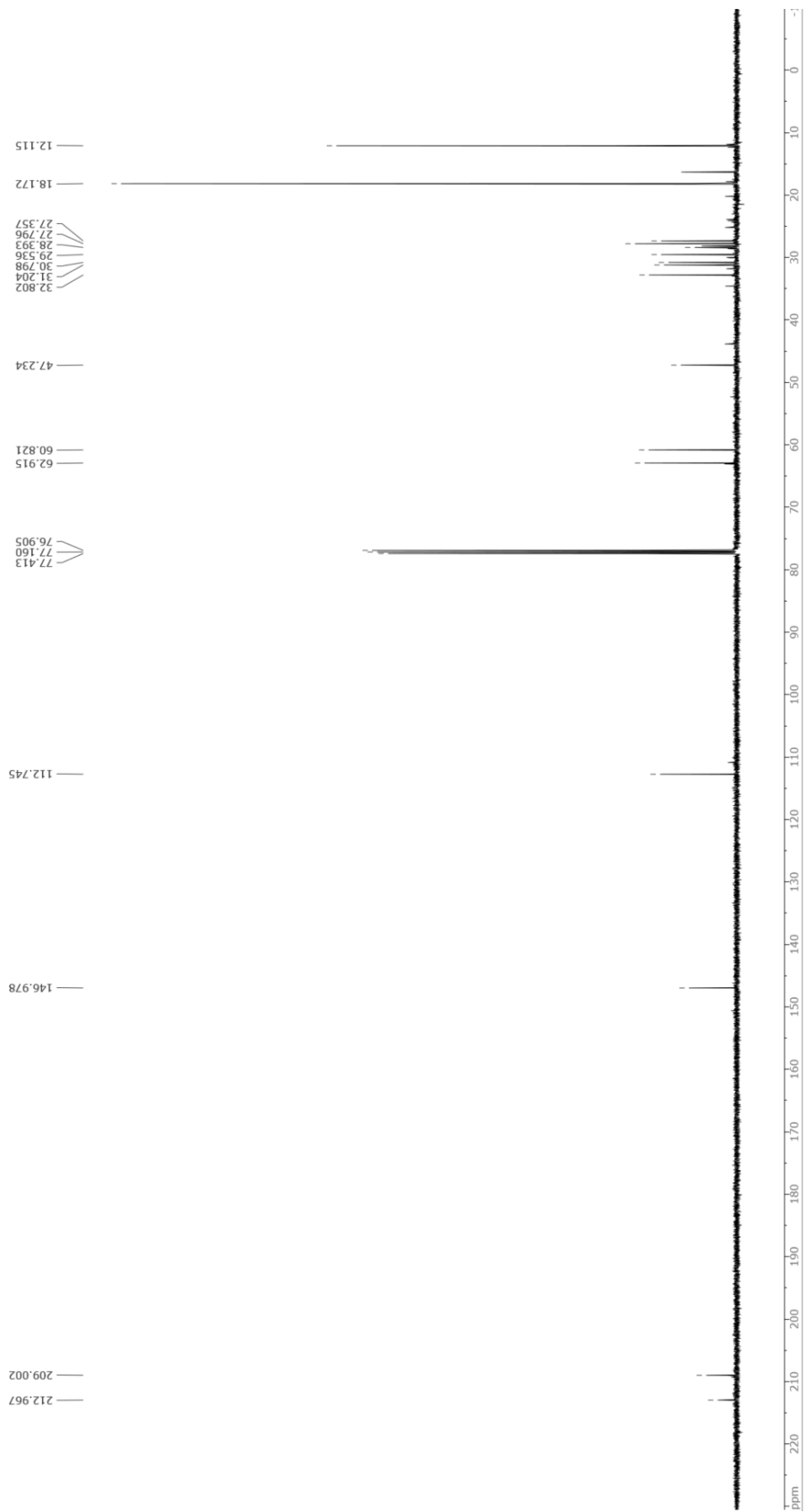
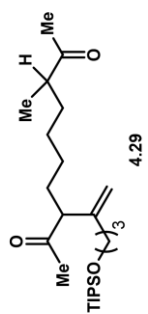














Appendix D: X-ray Crystallographic Data for 2.89 and 2.90

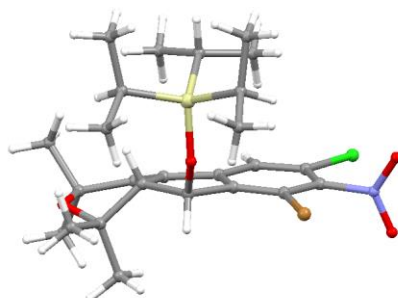


Table 1. Crystal data and structure refinement for **2.89**.

Identification code	svp8 (Nicole Godfrey)
Empirical formula	C ₂₅ H ₃₇ BrClNO ₄ Si
Formula weight	559.00
Temperature	133(2) K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	<i>P</i> $\bar{1}$
Unit cell dimensions	<i>a</i> = 8.6052(4) Å α = 72.9449(6)°. <i>b</i> = 10.8224(6) Å β = 78.4844(7)°. <i>c</i> = 16.0638(8) Å γ = 73.8845(6)°.
Volume	1362.58(12) Å ³
Z	2
Density (calculated)	1.362 Mg/m ³
Absorption coefficient	1.680 mm ⁻¹
F(000)	584
Crystal color	colorless
Crystal size	0.490 x 0.068 x 0.067 mm ³
Theta range for data collection	1.337 to 28.874°
Index ranges	-11 ≤ <i>h</i> ≤ 11, -13 ≤ <i>k</i> ≤ 14, -20 ≤ <i>l</i> ≤ 21
Reflections collected	16448
Independent reflections	6472 [R(int) = 0.0169]
Completeness to theta = 25.500°	99.8 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7458 and 0.6090
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	6472 / 0 / 308
Goodness-of-fit on F ²	1.040
Final R indices [I > 2sigma(I) = 5958 data]	R1 = 0.0249, wR2 = 0.0620

R indices (all data, 0.74 Å)
Largest diff. peak and hole

R1 = 0.0285, wR2 = 0.0639
0.461 and -0.245 e.Å⁻³

Table 2. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for svp8. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Br(1)	6183(1)	4133(1)	4124(1)	17(1)
Cl(1)	124(1)	3103(1)	4458(1)	19(1)
Si(1)	5853(1)	6543(1)	1471(1)	15(1)
O(1)	1303(1)	10570(1)	2624(1)	20(1)
O(2)	5541(1)	6784(1)	2467(1)	18(1)
O(3)	4312(2)	1667(1)	4289(1)	32(1)
O(4)	3373(1)	2229(1)	5519(1)	27(1)
N(1)	3595(2)	2466(1)	4716(1)	18(1)
C(1)	2650(2)	9631(1)	3042(1)	17(1)
C(2)	2873(2)	8344(1)	2759(1)	15(1)
C(3)	4228(2)	7125(1)	3110(1)	14(1)
C(4)	3338(2)	6018(1)	3509(1)	13(1)
C(5)	3977(2)	4715(1)	3932(1)	13(1)
C(6)	2952(2)	3845(1)	4235(1)	14(1)
C(7)	1310(2)	4261(1)	4115(1)	14(1)
C(8)	637(2)	5576(1)	3726(1)	14(1)
C(9)	1671(2)	6454(1)	3430(1)	13(1)
C(10)	1287(2)	7892(1)	3048(1)	14(1)
C(11)	-146(2)	8763(1)	3060(1)	17(1)
C(12)	-268(2)	10236(2)	2762(1)	21(1)
C(13)	4102(2)	10256(2)	2661(1)	23(1)
C(14)	2350(2)	9425(2)	4039(1)	20(1)
C(15)	-887(2)	10797(2)	1867(1)	34(1)
C(16)	-1418(2)	10930(2)	3432(1)	34(1)
C(17)	4161(2)	6152(2)	1072(1)	22(1)
C(18)	3715(2)	4830(2)	1585(1)	27(1)
C(19)	2618(2)	7280(2)	902(1)	29(1)
C(20)	6318(2)	8122(2)	704(1)	22(1)
C(21)	7619(3)	8587(2)	974(1)	41(1)
C(22)	6712(3)	8124(2)	-269(1)	39(1)

C(23)	7590(2)	5019(2)	1537(1)	20(1)
C(24)	8057(2)	4552(2)	687(1)	31(1)
C(25)	9098(2)	5126(2)	1854(1)	37(1)

Table 3. Bond lengths [Å] and angles [°] for svp8.

Br(1)-C(5)	1.8846(13)
Cl(1)-C(7)	1.7305(14)
Si(1)-O(2)	1.6545(11)
Si(1)-C(20)	1.8829(16)
Si(1)-C(23)	1.8865(16)
Si(1)-C(17)	1.8928(16)
O(1)-C(1)	1.4437(17)
O(1)-C(12)	1.4527(18)
O(2)-C(3)	1.4161(16)
O(3)-N(1)	1.2176(17)
O(4)-N(1)	1.2247(17)
N(1)-C(6)	1.4712(18)
C(1)-C(13)	1.522(2)
C(1)-C(14)	1.529(2)
C(1)-C(2)	1.5407(19)
C(2)-C(10)	1.5165(19)
C(2)-C(3)	1.5457(19)
C(3)-C(4)	1.5146(18)
C(4)-C(5)	1.3823(19)
C(4)-C(9)	1.3998(19)
C(5)-C(6)	1.3862(19)
C(6)-C(7)	1.3937(19)
C(7)-C(8)	1.3846(19)
C(8)-C(9)	1.3982(19)
C(9)-C(10)	1.4643(19)
C(10)-C(11)	1.329(2)
C(11)-C(12)	1.504(2)
C(12)-C(15)	1.527(2)
C(12)-C(16)	1.528(2)
C(17)-C(18)	1.537(2)
C(17)-C(19)	1.541(2)
C(20)-C(21)	1.526(2)
C(20)-C(22)	1.532(2)
C(23)-C(25)	1.529(2)

C(23)-C(24)	1.534(2)
O(2)-Si(1)-C(20)	105.40(6)
O(2)-Si(1)-C(23)	103.43(6)
C(20)-Si(1)-C(23)	115.61(7)
O(2)-Si(1)-C(17)	118.56(6)
C(20)-Si(1)-C(17)	108.26(7)
C(23)-Si(1)-C(17)	105.98(7)
C(1)-O(1)-C(12)	120.13(11)
C(3)-O(2)-Si(1)	139.45(9)
O(3)-N(1)-O(4)	125.62(13)
O(3)-N(1)-C(6)	117.88(12)
O(4)-N(1)-C(6)	116.49(12)
O(1)-C(1)-C(13)	104.67(11)
O(1)-C(1)-C(14)	111.77(12)
C(13)-C(1)-C(14)	109.85(12)
O(1)-C(1)-C(2)	105.98(11)
C(13)-C(1)-C(2)	111.20(12)
C(14)-C(1)-C(2)	113.00(12)
C(10)-C(2)-C(1)	108.10(11)
C(10)-C(2)-C(3)	106.09(11)
C(1)-C(2)-C(3)	118.70(11)
O(2)-C(3)-C(4)	111.49(11)
O(2)-C(3)-C(2)	114.63(11)
C(4)-C(3)-C(2)	103.78(11)
C(5)-C(4)-C(9)	120.02(12)
C(5)-C(4)-C(3)	127.83(12)
C(9)-C(4)-C(3)	112.14(12)
C(4)-C(5)-C(6)	118.73(12)
C(4)-C(5)-Br(1)	120.95(10)
C(6)-C(5)-Br(1)	120.30(10)
C(5)-C(6)-C(7)	121.23(13)
C(5)-C(6)-N(1)	119.54(12)
C(7)-C(6)-N(1)	119.21(12)
C(8)-C(7)-C(6)	120.68(12)
C(8)-C(7)-Cl(1)	120.48(10)

C(6)-C(7)-Cl(1)	118.84(10)
C(7)-C(8)-C(9)	117.85(12)
C(8)-C(9)-C(4)	121.34(13)
C(8)-C(9)-C(10)	129.74(13)
C(4)-C(9)-C(10)	108.87(12)
C(11)-C(10)-C(9)	129.27(13)
C(11)-C(10)-C(2)	121.32(13)
C(9)-C(10)-C(2)	108.47(12)
C(10)-C(11)-C(12)	121.48(13)
O(1)-C(12)-C(11)	112.86(12)
O(1)-C(12)-C(15)	104.73(13)
C(11)-C(12)-C(15)	109.90(13)
O(1)-C(12)-C(16)	109.02(13)
C(11)-C(12)-C(16)	110.22(13)
C(15)-C(12)-C(16)	109.96(14)
C(18)-C(17)-C(19)	111.09(14)
C(18)-C(17)-Si(1)	115.12(11)
C(19)-C(17)-Si(1)	116.63(11)
C(21)-C(20)-C(22)	110.02(15)
C(21)-C(20)-Si(1)	113.75(12)
C(22)-C(20)-Si(1)	115.27(12)
C(25)-C(23)-C(24)	110.91(14)
C(25)-C(23)-Si(1)	114.46(12)
C(24)-C(23)-Si(1)	113.21(11)

Table 4. Anisotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for svp8. The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2} U^{11} + \dots + 2 h k a^* b^* U^{12}]$

	U11	U22	U33	U23	U13	U12
Br(1)	10(1)	19(1)	21(1)	-6(1)	-4(1)	-1(1)
Cl(1)	15(1)	16(1)	27(1)	-4(1)	-4(1)	-6(1)
Si(1)	12(1)	18(1)	14(1)	-6(1)	0(1)	-5(1)
O(1)	22(1)	14(1)	24(1)	-1(1)	-7(1)	-5(1)
O(2)	12(1)	26(1)	17(1)	-9(1)	2(1)	-6(1)
O(3)	33(1)	18(1)	43(1)	-14(1)	-9(1)	3(1)
O(4)	25(1)	29(1)	22(1)	4(1)	-6(1)	-6(1)
N(1)	14(1)	16(1)	25(1)	-3(1)	-6(1)	-3(1)
C(1)	19(1)	15(1)	18(1)	-4(1)	-3(1)	-5(1)
C(2)	16(1)	16(1)	13(1)	-5(1)	-1(1)	-6(1)
C(3)	14(1)	17(1)	13(1)	-6(1)	1(1)	-6(1)
C(4)	13(1)	16(1)	12(1)	-7(1)	0(1)	-4(1)
C(5)	9(1)	18(1)	15(1)	-8(1)	-3(1)	-1(1)
C(6)	15(1)	14(1)	14(1)	-5(1)	-3(1)	-2(1)
C(7)	13(1)	15(1)	16(1)	-6(1)	-1(1)	-6(1)
C(8)	11(1)	17(1)	16(1)	-6(1)	-2(1)	-2(1)
C(9)	13(1)	14(1)	12(1)	-6(1)	-1(1)	-2(1)
C(10)	16(1)	15(1)	13(1)	-4(1)	-2(1)	-6(1)
C(11)	16(1)	17(1)	18(1)	-5(1)	-2(1)	-3(1)
C(12)	20(1)	15(1)	28(1)	-5(1)	-6(1)	-2(1)
C(13)	26(1)	22(1)	23(1)	-4(1)	-2(1)	-12(1)
C(14)	25(1)	18(1)	20(1)	-8(1)	-3(1)	-5(1)
C(15)	39(1)	23(1)	39(1)	4(1)	-22(1)	-8(1)
C(16)	26(1)	26(1)	50(1)	-19(1)	0(1)	0(1)
C(17)	17(1)	30(1)	22(1)	-11(1)	-2(1)	-6(1)
C(18)	26(1)	35(1)	29(1)	-14(1)	0(1)	-16(1)
C(19)	19(1)	41(1)	31(1)	-18(1)	-7(1)	-3(1)
C(20)	22(1)	21(1)	22(1)	-4(1)	0(1)	-5(1)
C(21)	47(1)	41(1)	40(1)	4(1)	-9(1)	-31(1)
C(22)	62(1)	29(1)	20(1)	1(1)	2(1)	-13(1)
C(23)	17(1)	21(1)	19(1)	-5(1)	0(1)	-3(1)

C(24)	35(1)	26(1)	24(1)	-9(1)	0(1)	4(1)
C(25)	18(1)	43(1)	53(1)	-19(1)	-10(1)	1(1)

Table 5. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for svp8.

	x	y	z	U(eq)
H(2)	3072	8563	2103	17
H(3)	4665	7299	3586	17
H(8)	-490	5872	3662	17
H(11)	-1116	8448	3263	20
H(13A)	4289	10385	2022	35
H(13B)	5075	9669	2916	35
H(13C)	3879	11117	2800	35
H(14A)	2056	10290	4180	30
H(14B)	3344	8883	4292	30
H(14C)	1459	8970	4285	30
H(15A)	-912	11748	1664	50
H(15B)	-1989	10669	1919	50
H(15C)	-157	10334	1445	50
H(16A)	-1007	10572	4002	51
H(16B)	-2508	10776	3488	51
H(16C)	-1476	11887	3234	51
H(17)	4640	6013	476	26
H(18A)	4711	4120	1651	41
H(18B)	3004	4620	1265	41
H(18C)	3144	4907	2167	41
H(19A)	1958	7367	1464	43
H(19B)	1980	7072	541	43
H(19C)	2935	8117	594	43
H(20)	5292	8826	751	27
H(21A)	7407	8515	1607	62
H(21B)	7589	9515	656	62
H(21C)	8697	8030	833	62
H(22A)	7726	7461	-359	59
H(22B)	6842	9006	-620	59
H(22C)	5820	7906	-450	59

H(23)	7176	4289	1993	24
H(24A)	7121	4320	560	46
H(24B)	8974	3769	758	46
H(24C)	8374	5266	201	46
H(25A)	9673	5712	1385	56
H(25B)	9825	4241	2012	56
H(25C)	8763	5492	2370	56

Table 6. Torsion angles [°] for svp8.

C(20)-Si(1)-O(2)-C(3)	100.53(15)
C(23)-Si(1)-O(2)-C(3)	-137.68(14)
C(17)-Si(1)-O(2)-C(3)	-20.80(17)
C(12)-O(1)-C(1)-C(13)	173.50(12)
C(12)-O(1)-C(1)-C(14)	-67.65(16)
C(12)-O(1)-C(1)-C(2)	55.87(16)
O(1)-C(1)-C(2)-C(10)	-58.58(14)
C(13)-C(1)-C(2)-C(10)	-171.76(12)
C(14)-C(1)-C(2)-C(10)	64.16(15)
O(1)-C(1)-C(2)-C(3)	-179.33(11)
C(13)-C(1)-C(2)-C(3)	67.49(16)
C(14)-C(1)-C(2)-C(3)	-56.59(16)
Si(1)-O(2)-C(3)-C(4)	69.20(18)
Si(1)-O(2)-C(3)-C(2)	-48.32(19)
C(10)-C(2)-C(3)-O(2)	126.74(12)
C(1)-C(2)-C(3)-O(2)	-111.49(13)
C(10)-C(2)-C(3)-C(4)	4.91(13)
C(1)-C(2)-C(3)-C(4)	126.68(12)
O(2)-C(3)-C(4)-C(5)	57.48(18)
C(2)-C(3)-C(4)-C(5)	-178.62(13)
O(2)-C(3)-C(4)-C(9)	-124.04(12)
C(2)-C(3)-C(4)-C(9)	-0.14(15)
C(9)-C(4)-C(5)-C(6)	3.0(2)
C(3)-C(4)-C(5)-C(6)	-178.63(13)
C(9)-C(4)-C(5)-Br(1)	-175.36(10)
C(3)-C(4)-C(5)-Br(1)	3.0(2)
C(4)-C(5)-C(6)-C(7)	0.4(2)
Br(1)-C(5)-C(6)-C(7)	178.79(10)
C(4)-C(5)-C(6)-N(1)	-177.78(12)
Br(1)-C(5)-C(6)-N(1)	0.59(18)
O(3)-N(1)-C(6)-C(5)	-83.07(17)
O(4)-N(1)-C(6)-C(5)	96.09(16)
O(3)-N(1)-C(6)-C(7)	98.69(16)
O(4)-N(1)-C(6)-C(7)	-82.15(16)

C(5)-C(6)-C(7)-C(8)	-3.2(2)
N(1)-C(6)-C(7)-C(8)	175.02(12)
C(5)-C(6)-C(7)-Cl(1)	176.58(11)
N(1)-C(6)-C(7)-Cl(1)	-5.22(17)
C(6)-C(7)-C(8)-C(9)	2.4(2)
Cl(1)-C(7)-C(8)-C(9)	-177.38(10)
C(7)-C(8)-C(9)-C(4)	1.1(2)
C(7)-C(8)-C(9)-C(10)	-175.83(13)
C(5)-C(4)-C(9)-C(8)	-3.8(2)
C(3)-C(4)-C(9)-C(8)	177.59(12)
C(5)-C(4)-C(9)-C(10)	173.68(12)
C(3)-C(4)-C(9)-C(10)	-4.93(15)
C(8)-C(9)-C(10)-C(11)	16.4(2)
C(4)-C(9)-C(10)-C(11)	-160.79(15)
C(8)-C(9)-C(10)-C(2)	-174.71(13)
C(4)-C(9)-C(10)-C(2)	8.09(15)
C(1)-C(2)-C(10)-C(11)	33.62(18)
C(3)-C(2)-C(10)-C(11)	161.94(13)
C(1)-C(2)-C(10)-C(9)	-136.31(12)
C(3)-C(2)-C(10)-C(9)	-7.99(14)
C(9)-C(10)-C(11)-C(12)	169.62(14)
C(2)-C(10)-C(11)-C(12)	2.0(2)
C(1)-O(1)-C(12)-C(11)	-21.22(18)
C(1)-O(1)-C(12)-C(15)	-140.75(13)
C(1)-O(1)-C(12)-C(16)	101.61(15)
C(10)-C(11)-C(12)-O(1)	-10.5(2)
C(10)-C(11)-C(12)-C(15)	106.02(17)
C(10)-C(11)-C(12)-C(16)	-132.63(16)
O(2)-Si(1)-C(17)-C(18)	-64.55(13)
C(20)-Si(1)-C(17)-C(18)	175.58(11)
C(23)-Si(1)-C(17)-C(18)	50.97(13)
O(2)-Si(1)-C(17)-C(19)	68.26(14)
C(20)-Si(1)-C(17)-C(19)	-51.61(14)
C(23)-Si(1)-C(17)-C(19)	-176.21(12)
O(2)-Si(1)-C(20)-C(21)	49.67(14)
C(23)-Si(1)-C(20)-C(21)	-63.86(15)

C(17)-Si(1)-C(20)-C(21)	177.48(13)
O(2)-Si(1)-C(20)-C(22)	178.08(13)
C(23)-Si(1)-C(20)-C(22)	64.55(15)
C(17)-Si(1)-C(20)-C(22)	-54.11(15)
O(2)-Si(1)-C(23)-C(25)	-54.30(13)
C(20)-Si(1)-C(23)-C(25)	60.36(14)
C(17)-Si(1)-C(23)-C(25)	-179.73(12)
O(2)-Si(1)-C(23)-C(24)	177.25(11)
C(20)-Si(1)-C(23)-C(24)	-68.09(13)
C(17)-Si(1)-C(23)-C(24)	51.82(13)

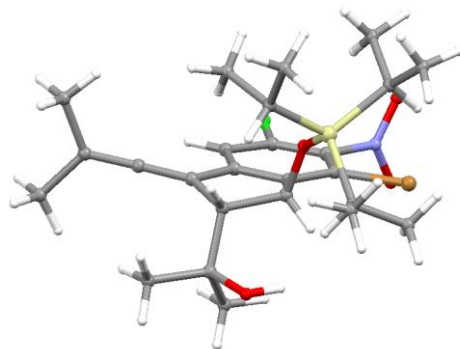


Table 1. Crystal data and structure refinement for **2.90**.

Identification code	svp9 (Nicole Godfrey)
Empirical formula	C ₂₅ H ₃₇ BrClNO ₄ Si
Formula weight	559.00
Temperature	133(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	<i>P</i> 2 ₁ 2 ₁ 2 ₁
Unit cell dimensions	<i>a</i> = 7.9555(7) Å $\alpha = 90^\circ$. <i>b</i> = 16.5243(15) Å $\beta = 90^\circ$. <i>c</i> = 21.253(2) Å $\gamma = 90^\circ$.
Volume	2793.9(4) Å ³
<i>Z</i>	4
Density (calculated)	1.329 Mg/m ³
Absorption coefficient	1.639 mm ⁻¹
<i>F</i> (000)	1168
Crystal color	colorless
Crystal size	0.372 x 0.281 x 0.098 mm ³
Theta range for data collection	1.561 to 26.371°
Index ranges	-9 ≤ <i>h</i> ≤ 9, -20 ≤ <i>k</i> ≤ 20, -26 ≤ <i>l</i> ≤ 24
Reflections collected	15707
Independent reflections	5691 [<i>R</i> (int) = 0.0471]
Completeness to theta = 25.500°	99.9 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7456 and 0.5129
Refinement method	Full-matrix least-squares on <i>F</i> ²
Data / restraints / parameters	5691 / 0 / 309
Goodness-of-fit on <i>F</i> ²	1.076

Final R indices [$I > 2\sigma(I)$ = 5125 data]	R1 = 0.0734, wR2 = 0.1781
R indices (all data, 0.80 Å)	R1 = 0.0799, wR2 = 0.1815
Absolute structure parameter	0.18(2)
Largest diff. peak and hole	0.945 and -0.646 e.Å ⁻³

Table 2. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for svp9. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Br(1)	7004(1)	8622(1)	617(1)	37(1)
Cl(1)	772(4)	7900(2)	1625(2)	55(1)
Si(1)	8186(4)	11155(2)	1128(1)	32(1)
O(1)	9665(8)	9892(5)	2817(3)	41(2)
O(2)	6899(8)	10472(3)	1418(3)	25(1)
O(3)	2987(16)	8074(5)	228(4)	81(4)
O(4)	3913(10)	7071(4)	760(4)	50(2)
N(1)	3562(11)	7776(5)	700(4)	41(2)
C(1)	4925(11)	9989(5)	2670(4)	21(2)
C(2)	6784(11)	10152(5)	2547(3)	20(2)
C(3)	7087(12)	9849(5)	1865(3)	20(2)
C(4)	5635(10)	9276(5)	1753(4)	20(2)
C(5)	5388(11)	8762(5)	1255(4)	23(2)
C(6)	3877(13)	8333(5)	1227(4)	31(2)
C(7)	2638(11)	8430(6)	1681(5)	33(2)
C(8)	2866(13)	8974(5)	2165(4)	30(2)
C(9)	4378(11)	9386(5)	2197(4)	18(2)
C(10)	3997(12)	10315(5)	3105(4)	26(2)
C(11)	3159(13)	10679(6)	3548(4)	33(2)
C(12)	2296(13)	11477(7)	3440(6)	52(3)
C(13)	3061(16)	10342(8)	4211(5)	49(3)
C(14)	7951(12)	9754(6)	3032(4)	28(2)
C(15)	7747(14)	10164(7)	3673(4)	38(2)
C(16)	7745(14)	8838(6)	3070(4)	37(2)
C(17)	7728(19)	12120(7)	1533(6)	54(3)
C(18)	8150(30)	12897(7)	1192(6)	79(5)
C(19)	5930(20)	12210(9)	1746(10)	92(7)
C(20)	10475(15)	10846(10)	1296(6)	60(4)
C(21)	11740(20)	11495(12)	1356(9)	98(6)
C(22)	11081(18)	10184(10)	886(7)	72(5)

C(23)	7681(16)	11105(7)	263(4)	44(3)
C(24)	8710(20)	11676(8)	-149(5)	75(5)
C(25)	5798(19)	11159(10)	150(5)	69(4)

Table 3. Bond lengths [Å] and angles [°] for svp9.

Br(1)-C(5)	1.882(9)
Cl(1)-C(7)	1.727(10)
Si(1)-O(2)	1.644(6)
Si(1)-C(17)	1.849(12)
Si(1)-C(23)	1.883(10)
Si(1)-C(20)	1.925(13)
O(1)-C(14)	1.456(12)
O(2)-C(3)	1.409(9)
O(3)-N(1)	1.208(12)
O(4)-N(1)	1.204(11)
N(1)-C(6)	1.473(11)
C(1)-C(10)	1.300(12)
C(1)-C(9)	1.480(11)
C(1)-C(2)	1.526(12)
C(2)-C(14)	1.535(12)
C(2)-C(3)	1.552(10)
C(3)-C(4)	1.513(12)
C(4)-C(5)	1.372(11)
C(4)-C(9)	1.386(11)
C(5)-C(6)	1.397(13)
C(6)-C(7)	1.388(14)
C(7)-C(8)	1.378(13)
C(8)-C(9)	1.384(13)
C(10)-C(11)	1.302(13)
C(11)-C(12)	1.504(14)
C(11)-C(13)	1.515(14)
C(14)-C(16)	1.525(14)
C(14)-C(15)	1.529(12)
C(17)-C(19)	1.50(2)
C(17)-C(18)	1.512(16)
C(20)-C(21)	1.48(2)
C(20)-C(22)	1.48(2)
C(23)-C(25)	1.520(19)
C(23)-C(24)	1.526(15)

O(2)-Si(1)-C(17)	107.1(5)
O(2)-Si(1)-C(23)	101.7(4)
C(17)-Si(1)-C(23)	116.8(6)
O(2)-Si(1)-C(20)	109.7(5)
C(17)-Si(1)-C(20)	109.2(7)
C(23)-Si(1)-C(20)	111.8(6)
C(3)-O(2)-Si(1)	133.5(6)
O(4)-N(1)-O(3)	124.8(9)
O(4)-N(1)-C(6)	119.0(9)
O(3)-N(1)-C(6)	116.2(8)
C(10)-C(1)-C(9)	126.5(8)
C(10)-C(1)-C(2)	126.8(8)
C(9)-C(1)-C(2)	106.7(7)
C(1)-C(2)-C(14)	113.3(7)
C(1)-C(2)-C(3)	104.7(7)
C(14)-C(2)-C(3)	113.3(7)
O(2)-C(3)-C(4)	105.7(7)
O(2)-C(3)-C(2)	112.2(6)
C(4)-C(3)-C(2)	103.3(7)
C(5)-C(4)-C(9)	120.3(8)
C(5)-C(4)-C(3)	128.2(8)
C(9)-C(4)-C(3)	111.1(7)
C(4)-C(5)-C(6)	118.0(8)
C(4)-C(5)-Br(1)	122.3(7)
C(6)-C(5)-Br(1)	119.7(6)
C(7)-C(6)-C(5)	121.6(8)
C(7)-C(6)-N(1)	118.7(9)
C(5)-C(6)-N(1)	119.7(9)
C(8)-C(7)-C(6)	120.0(9)
C(8)-C(7)-Cl(1)	119.7(8)
C(6)-C(7)-Cl(1)	120.3(7)
C(7)-C(8)-C(9)	118.2(9)
C(8)-C(9)-C(4)	121.9(8)
C(8)-C(9)-C(1)	128.3(8)
C(4)-C(9)-C(1)	109.8(7)

C(1)-C(10)-C(11)	175.7(10)
C(10)-C(11)-C(12)	121.9(10)
C(10)-C(11)-C(13)	121.9(9)
C(12)-C(11)-C(13)	116.1(9)
O(1)-C(14)-C(16)	105.8(8)
O(1)-C(14)-C(15)	108.0(8)
C(16)-C(14)-C(15)	112.4(8)
O(1)-C(14)-C(2)	106.8(7)
C(16)-C(14)-C(2)	113.3(7)
C(15)-C(14)-C(2)	110.1(8)
C(19)-C(17)-C(18)	105.7(13)
C(19)-C(17)-Si(1)	114.3(10)
C(18)-C(17)-Si(1)	117.8(10)
C(21)-C(20)-C(22)	111.5(13)
C(21)-C(20)-Si(1)	117.9(12)
C(22)-C(20)-Si(1)	113.2(10)
C(25)-C(23)-C(24)	113.7(12)
C(25)-C(23)-Si(1)	111.2(8)
C(24)-C(23)-Si(1)	114.7(8)

Table 4. Anisotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for svp9. The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2} U^{11} + \dots + 2 h k a^* b^* U^{12}]$

	U11	U22	U33	U23	U13	U12
Br(1)	45(1)	41(1)	24(1)	-12(1)	3(1)	9(1)
Cl(1)	27(1)	48(2)	89(2)	-15(2)	-14(2)	-12(1)
Si(1)	42(2)	30(1)	23(1)	2(1)	2(1)	-15(1)
O(1)	14(3)	81(6)	29(4)	-14(4)	2(3)	-3(3)
O(2)	20(3)	30(3)	26(3)	7(2)	0(3)	-7(3)
O(3)	131(9)	49(5)	63(6)	-19(4)	-68(7)	13(6)
O(4)	51(5)	28(4)	71(6)	-21(4)	-21(4)	5(3)
N(1)	42(5)	32(4)	50(5)	-18(4)	-21(4)	4(4)
C(1)	20(4)	22(4)	22(4)	-2(3)	0(3)	-1(3)
C(2)	21(5)	19(4)	19(4)	0(3)	-4(3)	-7(3)
C(3)	20(4)	22(4)	19(3)	-1(3)	1(4)	-5(4)
C(4)	14(4)	23(4)	24(4)	1(3)	-2(3)	5(3)
C(5)	17(4)	25(4)	26(4)	-2(3)	-5(3)	3(3)
C(6)	36(5)	26(4)	30(5)	-5(4)	-17(4)	9(4)
C(7)	21(5)	29(5)	48(5)	1(4)	-9(4)	-1(3)
C(8)	26(5)	31(4)	32(4)	1(3)	-6(4)	-6(4)
C(9)	17(4)	16(4)	22(4)	2(3)	-2(3)	3(3)
C(10)	22(5)	23(4)	32(4)	-3(4)	3(4)	-4(4)
C(11)	20(5)	38(5)	42(5)	-15(4)	-3(4)	-1(4)
C(12)	28(6)	42(6)	86(8)	-28(6)	-13(6)	7(5)
C(13)	35(6)	73(8)	40(5)	-22(5)	17(5)	-16(6)
C(14)	19(4)	46(5)	19(4)	1(3)	-1(4)	-3(4)
C(15)	29(6)	62(7)	25(4)	-6(4)	-5(4)	3(5)
C(16)	33(6)	45(6)	33(5)	13(4)	-7(4)	7(5)
C(17)	70(9)	33(6)	59(7)	-3(5)	-11(7)	2(6)
C(18)	139(15)	42(7)	55(7)	5(6)	-19(10)	-32(10)
C(19)	80(12)	37(7)	160(18)	-24(9)	-48(13)	19(8)
C(20)	27(6)	95(11)	57(7)	13(7)	3(5)	-14(7)
C(21)	58(10)	113(14)	123(14)	24(12)	-11(10)	-29(11)
C(22)	42(8)	115(13)	58(8)	22(8)	21(6)	20(8)
C(23)	69(9)	44(6)	20(4)	2(4)	5(5)	-13(6)

C(24)	154(16)	54(7)	18(5)	6(5)	8(7)	-38(9)
C(25)	75(10)	101(12)	30(5)	-4(6)	-14(6)	37(9)

Table 5. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for svp9.

	x	y	z	U(eq)
H(1)	9790	9689	2458	62
H(2A)	6974	10750	2558	24
H(3A)	8196	9570	1823	24
H(8A)	2010	9063	2469	36
H(12A)	1106	11430	3555	78
H(12B)	2391	11626	2996	78
H(12C)	2828	11894	3701	78
H(13A)	1886	10229	4317	74
H(13B)	3520	10738	4507	74
H(13C)	3715	9840	4235	74
H(15A)	6636	10036	3845	58
H(15B)	7856	10751	3623	58
H(15C)	8619	9967	3960	58
H(16A)	6602	8708	3209	56
H(16B)	8556	8617	3372	56
H(16C)	7945	8600	2654	56
H(17A)	8425	12119	1925	65
H(18A)	9347	12901	1085	118
H(18B)	7895	13360	1465	118
H(18C)	7479	12935	807	118
H(19A)	5545	11699	1929	138
H(19B)	5225	12350	1384	138
H(19C)	5860	12639	2062	138
H(20A)	10430	10597	1725	72
H(21A)	11375	11882	1678	147
H(21B)	11860	11774	952	147
H(21C)	12822	11260	1478	147
H(22A)	10384	9702	951	108
H(22B)	12252	10058	990	108

H(22C)	11008	10353	445	108
H(23A)	8008	10547	128	53
H(24A)	9891	11658	-19	113
H(24B)	8283	12229	-103	113
H(24C)	8617	11509	-590	113
H(25A)	5222	10747	402	103
H(25B)	5562	11069	-297	103
H(25C)	5396	11697	272	103

Table 6. Torsion angles [°] for svp9.

C(17)-Si(1)-O(2)-C(3)	-101.2(8)
C(23)-Si(1)-O(2)-C(3)	135.8(8)
C(20)-Si(1)-O(2)-C(3)	17.2(9)
C(10)-C(1)-C(2)-C(14)	74.7(11)
C(9)-C(1)-C(2)-C(14)	-105.3(8)
C(10)-C(1)-C(2)-C(3)	-161.3(9)
C(9)-C(1)-C(2)-C(3)	18.6(8)
Si(1)-O(2)-C(3)-C(4)	-161.0(6)
Si(1)-O(2)-C(3)-C(2)	87.1(9)
C(1)-C(2)-C(3)-O(2)	92.9(8)
C(14)-C(2)-C(3)-O(2)	-143.2(7)
C(1)-C(2)-C(3)-C(4)	-20.5(8)
C(14)-C(2)-C(3)-C(4)	103.5(8)
O(2)-C(3)-C(4)-C(5)	70.6(10)
C(2)-C(3)-C(4)-C(5)	-171.4(8)
O(2)-C(3)-C(4)-C(9)	-102.1(7)
C(2)-C(3)-C(4)-C(9)	15.9(9)
C(9)-C(4)-C(5)-C(6)	-2.9(12)
C(3)-C(4)-C(5)-C(6)	-175.0(8)
C(9)-C(4)-C(5)-Br(1)	177.1(6)
C(3)-C(4)-C(5)-Br(1)	5.1(12)
C(4)-C(5)-C(6)-C(7)	1.3(13)
Br(1)-C(5)-C(6)-C(7)	-178.7(7)
C(4)-C(5)-C(6)-N(1)	180.0(8)
Br(1)-C(5)-C(6)-N(1)	-0.1(11)
O(4)-N(1)-C(6)-C(7)	-87.8(12)
O(3)-N(1)-C(6)-C(7)	93.6(13)
O(4)-N(1)-C(6)-C(5)	93.5(12)
O(3)-N(1)-C(6)-C(5)	-85.1(13)
C(5)-C(6)-C(7)-C(8)	1.5(14)
N(1)-C(6)-C(7)-C(8)	-177.2(8)
C(5)-C(6)-C(7)-Cl(1)	179.0(7)
N(1)-C(6)-C(7)-Cl(1)	0.4(12)
C(6)-C(7)-C(8)-C(9)	-2.6(13)

Cl(1)-C(7)-C(8)-C(9)	179.8(7)
C(7)-C(8)-C(9)-C(4)	1.1(13)
C(7)-C(8)-C(9)-C(1)	-179.4(8)
C(5)-C(4)-C(9)-C(8)	1.8(12)
C(3)-C(4)-C(9)-C(8)	175.1(7)
C(5)-C(4)-C(9)-C(1)	-177.8(7)
C(3)-C(4)-C(9)-C(1)	-4.5(9)
C(10)-C(1)-C(9)-C(8)	-8.9(14)
C(2)-C(1)-C(9)-C(8)	171.2(8)
C(10)-C(1)-C(9)-C(4)	170.7(9)
C(2)-C(1)-C(9)-C(4)	-9.3(9)
C(1)-C(2)-C(14)-O(1)	174.3(7)
C(3)-C(2)-C(14)-O(1)	55.2(9)
C(1)-C(2)-C(14)-C(16)	58.2(10)
C(3)-C(2)-C(14)-C(16)	-60.9(10)
C(1)-C(2)-C(14)-C(15)	-68.7(10)
C(3)-C(2)-C(14)-C(15)	172.2(8)
O(2)-Si(1)-C(17)-C(19)	-29.6(13)
C(23)-Si(1)-C(17)-C(19)	83.6(13)
C(20)-Si(1)-C(17)-C(19)	-148.4(12)
O(2)-Si(1)-C(17)-C(18)	-154.6(11)
C(23)-Si(1)-C(17)-C(18)	-41.4(14)
C(20)-Si(1)-C(17)-C(18)	86.6(13)
O(2)-Si(1)-C(23)-C(25)	49.9(10)
C(17)-Si(1)-C(23)-C(25)	-66.3(11)
C(20)-Si(1)-C(23)-C(25)	167.0(10)
O(2)-Si(1)-C(23)-C(24)	-179.3(10)
C(17)-Si(1)-C(23)-C(24)	64.5(12)
C(20)-Si(1)-C(23)-C(24)	-62.2(12)
