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Studies Toward the Synthesis of Salvinorin A and Synthesis of Broad-Spectrum DENV/WNV NS3 Protease Inhibitors

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Studies Toward the Synthesis of Salvinorin A and Synthesis of Broad-Spectrum DENV/WNV NS3 Protease Inhibitors

by

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Dissertation

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To my babies Sophia and Marissa and to my beautiful mother Laura who is watching over us.

Studies Toward the Synthesis of Salvinorin A and Synthesis of Broad-Spectrum DENV/WNV NS3 Protease Inhibitors

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Part I: Salvinorin A is the main active component of the plant *Salvia divinorum*. *Salvia divinorum* is native to the Mazatec region in Northern Oaxaca, Mexico. It has been used by local Mazatec Indians for its hallucinogenic properties in ritual divination and healing ceremonies. It is the first non-alkaloid hallucinogen and the first that is not an agonist of the 5-HT_{2A} receptor. It is a potent, selective agonist of the Kappa opioid receptor (KOR). The aim of our current research is to complete the total synthesis of Salvinorin A, then to synthesize novel analogs not attainable by semi-synthetic methods. The region of the molecule we wish to focus on is the furan ring. Our routes to Salvinorin A were designed to allow for changes to be made to the section of the molecule where the furan is ring late in the synthesis.

Part II: West-Nile Virus (WNV) and Dengue Virus (DENV), both members of the *Flavivirirus* genus, are transmitted to humans by mosquito vectors and are significant causes of human illness worldwide. The majority of people infected with either virus remain asymptomatic, however some of those infected will develop critical and life-threatening diseases West Nile encephalitis or Dengue hemorrhagic fever. As members of the same genus, they share many important biological features including a highly homologous NS3 protease. NS3 is essential for virion replication, making it an ideal target for a broad-spectrum inhibitor of the related viral proteases.

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PART I: STUDIES TOWARD THE SYNTHESIS OF SALVINORIN A

ABSTRACT

Salvinorin A is the main active component of the plant *Salvia divinorum*. *Salvia divinorum* is native to the Mazatec region in Northern Oaxaca, Mexico. It has been used by local Mazatec Indians for its hallucinogenic properties in ritual divination and healing ceremonies. It is the first non-alkaloid hallucinogen and the first that is not an agonist of the 5-HT_{2A} receptor. It is a potent, selective agonist of the Kappa opioid receptor (KOR) with as little as 200mcg required to produce a hallucinogenic effect. Unlike other KOR agonists, it appears to bind to unique residues on the KOR. Several semi-synthetic analogs have been synthesized, focusing on chemical modifications to the C2 and C4 esters and more recent modifications to the furan ring. Two groups have completed the total synthesis of Salvinorin A.

The aim of our current research is to complete the total synthesis of Salvinorin A, then to synthesize novel analogs not attainable by semi-synthetic methods. The region of the molecule we wish to focus on is the furan ring. Our routes to Salvinorin A were designed to allow for changes to be made to the section of the molecule where the furan is ring late in the synthesis.

Chapter 1: S*alvia divinorum:* Identification, Mechanism And Synthetic Work

Salvia divinorum is a hallucinogenic plant native to a small region of the Sierra Mazateca, a mountainous region in the northern part of the state of Oaxaca, Mexico. The binomial name is derived from the latin words "*salvare*" which means "to save" and "*divino*" which means "divine".[1] The Mazatec Indians have used *Salvia divinorum* for its psychoactive properties in various religious and shamanistic ceremonies. Considered a weak hallucinogen, it was used as a mushroom substitute when there were no mushrooms to be gathered.[1] *Salvia divinorum* was also used to induce visions during the preliminary stages of curanderos' informal training, with morning glory seeds and various psilocybin-containing mushrooms used in the latter stages of training.[1,2] The Mazatecs' preferred methods of ingestion were chewing the leaves or making a tea-like infusion from them.[1]

FIRST REPORTS OF *SALVIA DIVINORUM*

The modern discovery of *Salvia divinorum* is the serendipitous consequence of the search for psilocybin-containing mushrooms. In the quest for the fungi, researchers stumbled upon the Mazatec alternative to the hallucinogenic fungi. In 1945, Blas Reko, an Austrian doctor and naturalist reported a magic plant used by the Mazatec Indians whose leaves produced visions.[3] They referred to the leaves as *hojas de adivinacion* (leaves of prophecy). Reko was unable to identify the plant. In 1952, American engineer turned anthropologist Robert J. Weitlaner described how a Mazatec *curandero* used *yerba de Maria* (leaves of Mary) to cure a patient in a small Oaxacan village. In his

account, the *curandero* made an infusion of approximately 50 leaves and had the patient drink it. While under the influence of the leaves, the patient was diagnosed and cured.[4] In 1957 Arturo Gomez-Pompa, Professor of Botanical Pharmacy and Chemistry at National Autonomous University of Mexico (UNAM) was hired as a consultant by the Swiss chemical firm Chemical Industries Basel (CIBA) to obtain samples of recently reported Mexican *hongos alucinogenos* (hallucinogenic mushrooms) for analysis. While exploring for mushrooms, he was introduced to a plant referred to by the locals as *xca Pastora*. He was able to identify it as being a member of the *Salvia* genus, but was unable to further classify it due to the lack of flowers.[5] In 1953, professor, author, a vice president of J. P. Morgan & Co. and amateur mycologist R. Gordon Wasson began visiting the Sierra Mazateca to study the sociological impact of the hallucinogenic mushrooms on the Mazatec Indians.[6] During one of his yearly expeditions he was introduced to a psychotropic plant that the Mazatecs consumed when mushrooms were unavailable. In 1962, he obtained a living sample of the plant and submitted it to University of California Berkeley botanist Carl Epling.[7] Epling and colleague Carlos D. Jativa-M. characterized the plant as a new species of *Salvia* which they named *Salvia divinorum* Epling & Jativa.[8]

ACTIVE COMPOUND IN *SALVIA DIVINORUM*

Decades after the first reports of *Salvia divinorum*, the active component remained unidentified. Albert Hoffman, a Swiss chemist who was the first person to identify and synthesize psilocybin from *Psilocybe* mushrooms[9] and synthesized the semi-synthetic ergotamine derivative lysergic acid[10] spent a considerable amount of time in Mexico researching psychotropic plants and fungi.[11] Hoffman obtained samples of *Salvia*

divinorum from the Mazatec region in Oaxaca but was unable to identify the active component. During his work with LSD and related ergolines, Hoffman found that LSD is sensitive to light and oxygen. After failing to identify the active compound in *Salvia divinorum*, Hoffman surmised that its active component was also unstable, "The active principle of this magical drug is apparently very unstable and could not now be identified".[12]

Jose Luis Diaz, a biochemist/neurophysiologist at UNAM studied the Mazatec Indian's use of *Salvia divinorum* in the 1970s. Due to the fact that existing hallucinogenic natural products and derivatives, including mescaline, ergotamine-derivative lysergic acid diethylamide and psilocybin were alkaloid molecules, he focused his efforts on searching for an alkaloid compound as the active component of the plant. Diaz reported that his lab used Ludy Tenger, a reagent that colorimetrically tests for the presence of alkaloid compounds to study the pharmacologically active extracts from *Salvia divinorum*, but was unable to identify the active component.[13]

The first molecular identification of salvinorin A came in 1982, when a novel *trans*-neoclerodane diterpene was identified as one of the components of *Salvia divinorum*.[14] The authors extracted the compound from 200 g of dried, ground leaves with boiling chloroform, purified the extract by chromatography using chloroform as the eluent and recrystallized from methanol. Ortega and co-workers reported ^{1}H and ^{13}C NMR spectra and an X-ray crystal structure for this new compound, which they named salvinorin. However, they made no mention of the biological activity of this molecule nor

did they speculate that this was the compound that was responsible for the psychotropic activity of *Salvia divinorum*.

In 1984 Valdes and co-workers identified the molecule responsible for the psychotropic activity of *Salvia divinorum*, which the authors named divinorum A.[15] Divinorum A had a sedative effect on mice in Hall's open field test similar to the effect elicited by administration of the plant extract. The authors reported the ^{1}H and ^{13}C NMR spectra and an X-ray crystal structure of divinorum A. Unbeknownst to the authors at the time of submission, this was the same molecule that had been previously identified and named salvinorin by Ortega in 1982. A note was included in the publication crediting Ortega with the original discovery of the molecule.

MOLECULAR TARGET OF SALVINORIN A

In 1994, Daniel Siebert reported on different modes of administration of salvinorin A in human subjects, including chewing *S. divinorum* leaves, absorption through oral mucosa and inhalation of the vaporized compound.[16] Siebert found that inhalation was the most efficient method, with 200-500 μg required to produce a hallucinogenic effect. Siebert then submitted a sample of salvinorin A to NovaScreen Biosciences to screen against a number of receptors, but the molecular target was not identified.

The molecular target of salvinorin A was identified when it was screened against several targets for the National Institute of Mental Health Psychoactive Drug Screening Program.[17] The assay included 5-HT receptors, dopamine receptors, mu, delta and kappa

opioid receptors, histaminergic receptors, 5-HT transporter, norepinephrine transporter, dopamine transporter, vasopressin receptors, prostaglandin receptors, protein kinase C (α-ε), vesicular monoamine transporter (VMAT), γ-amino butyric acid (GABA) receptors, adrenergic receptors, muscarinic receptors, nicotinic receptors, sigma receptors, angiotensin receptors, imidazoline -1 receptor, neurotensin receptor, adenosine receptors and Ca^{2+} channel.

Salvinorin A inhibited [^{3}H]-bremazocine binding to cloned human KOR but did not inhibit binding to μ or δ opioid receptors (MOR and DOR, respectively), nor did it affect any of the other targets. The binding affinity (K_i) was determined to be 16 nM at the KOR and >5,000 nM at MOR and DOR, making salvinorin A the first non-alkaloid compound selective for the KOR. In separate functional assays using cloned human and guinea pig KORs, salvinorin A inhibited forskolin-stimulated adenylate cyclase activity, which categorized it as the first non-alkaloid agonist selective for the KOR. Interestingly, salvinorin A was found to have no affinity for the 5-HT_{2A} serotonin receptor, a known target of classical hallucinogens.

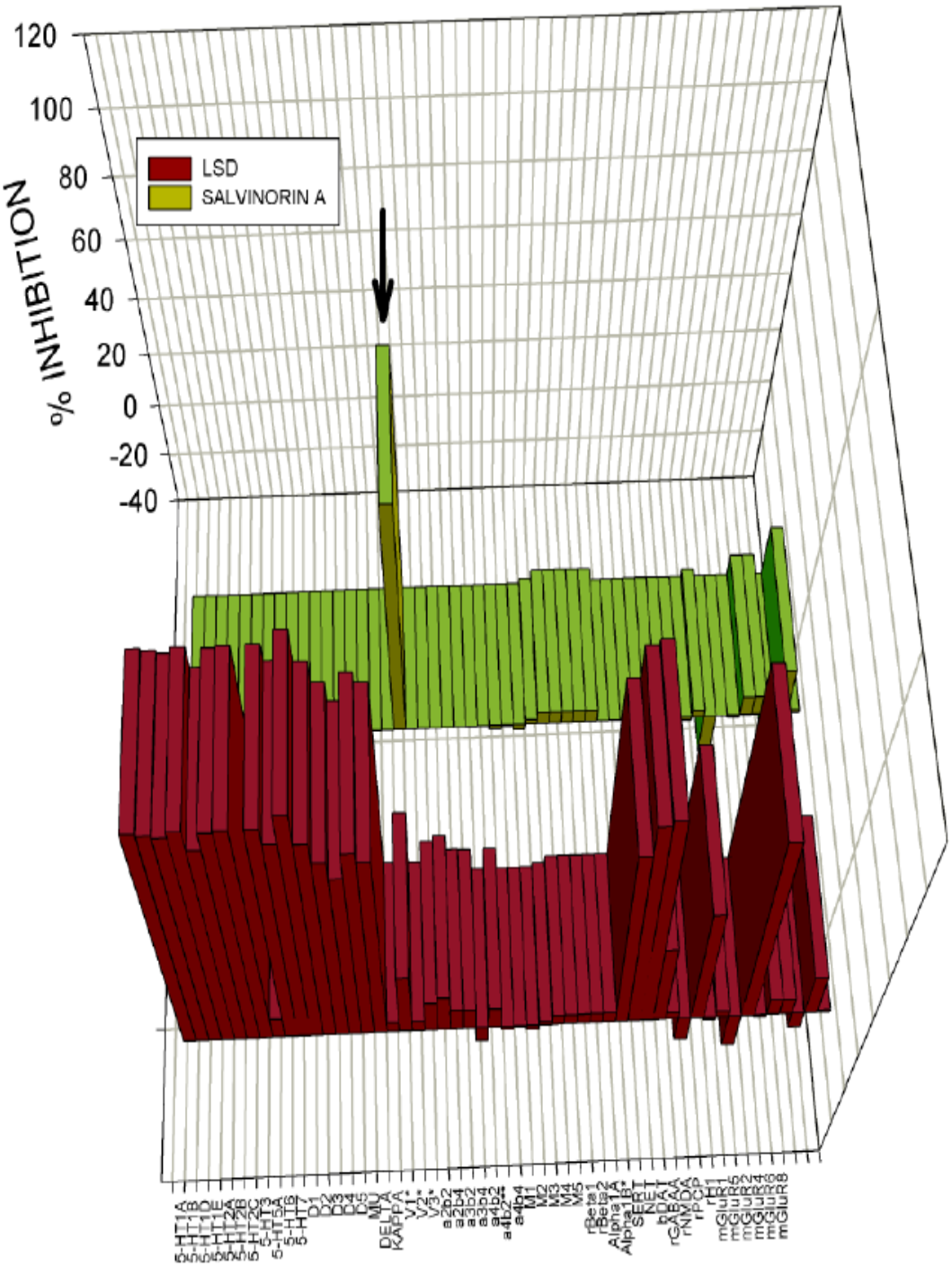


Figure 1.1: Results for Salvinorin A and LSD in receptorome assay

Image from Roth, *et al*. 2002, reprinted with permission

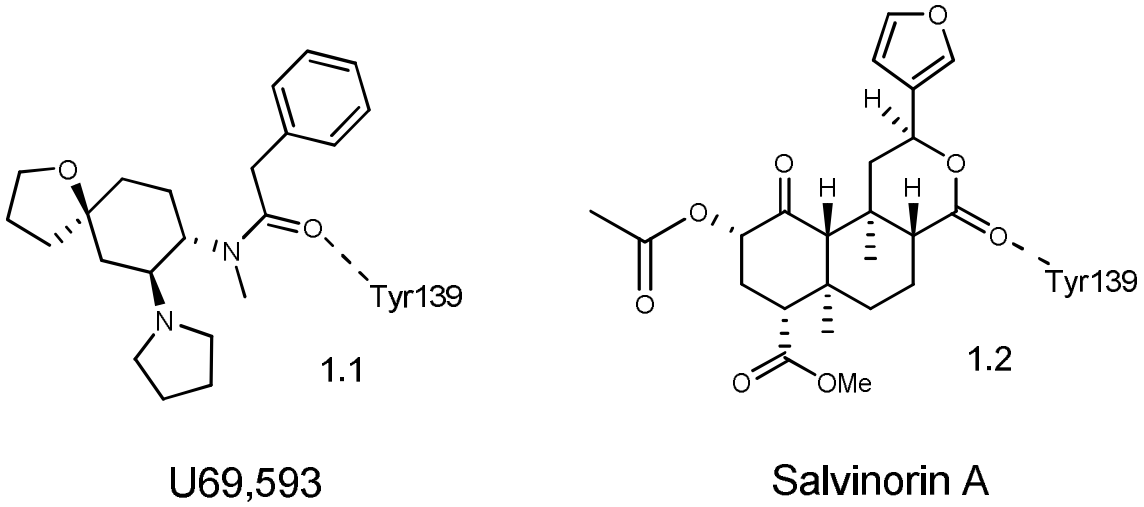


Figure 1.2: Taking advantage of structural similarity - carbonyl used as docking-point

Salvinorin A's unique structure and exceptional selectivity for the kappa receptor prompted researchers to examine the molecular basis for such distinct properties. Due to its dissimilarity to other opioid agonists (i.e. no protonatable nitrogen), Roth and co-workers[17] based molecular modeling interactions on a prior study[18] whereby the carbonyl of U-69,593, (**1.1**) a member of the arylacetamide class of kappa-selective opioid agonists was hydrogen-bonded to Tyr139 in TM III of the KOR. The only structural similarities between U-69593 and salvinorin A (**1.2**) are an aromatic ring and an adjacent carbonyl. Results from analysis of salvinorin A and structurally modified analogs in wild-type KOR and site-directed mutants indicate that salvinorin A interacts with the KOR through different residues not utilized by standard opioid agonists.[19] Studies of the interaction of salvinorin A with chimeric opioid receptors support the hypothesis that salvinorin A interacts with unique residues within the KOR.[20,21]

KAPPA OPIOID RECEPTORS

Kappa opioid receptors, also known as OP2 receptors, are one subtype of a larger family of opioid receptors which includes the μ and δ receptors. Opioid receptors are G-protein coupled receptors (GPCR) which share approximately 60% sequence homology with other opioid receptors.[22] The kappa opioid receptor was identified in 1976 when Martin and co-workers identified three distinguishable subtypes of opioid receptors which are activated by molecules with differing affinities for the receptor subtypes in the chronic spinal dog pain model.[23] The kappa opioid receptor was named after ketocyclazocine (**1.3**), which was found to have high affinity for the kappa receptor and low affinity for the other two identified receptors. Kappa receptors are further sub-classified into κ1, κ2 and κ3 subtypes based on their affinities for different kappa opioid ligands.[24] The endogenous ligand for the KOR is the peptide dynorphin A (**1.4**).[22]

Opioid GPCRs are coupled to the inhibitory G_i/G_o G-protein. Binding of an opioid agonist to an opioid GPCR induces a conformational change in the receptor that triggers the associated, inactive heterotrimeric G-protein to exchange bound guanosine diphosphate (GDP) for guanosine triphosphate (GTP). The α-subunit of this transiently activated G-protein dissociates from the bound β and γ subunits. The dissociated species subsequently affect different signal transduction pathways. The activated G-protein α-subunit inhibits adenylyl cyclase, causing a subsequent decrease in intracellular cyclic-adenosine monophosphate (cAMP).[25] The $G_{\beta\gamma}$ heterodimer activates G protein-coupled inwardly-rectifying potassium channels (GIRK), increasing potassium conductance out of

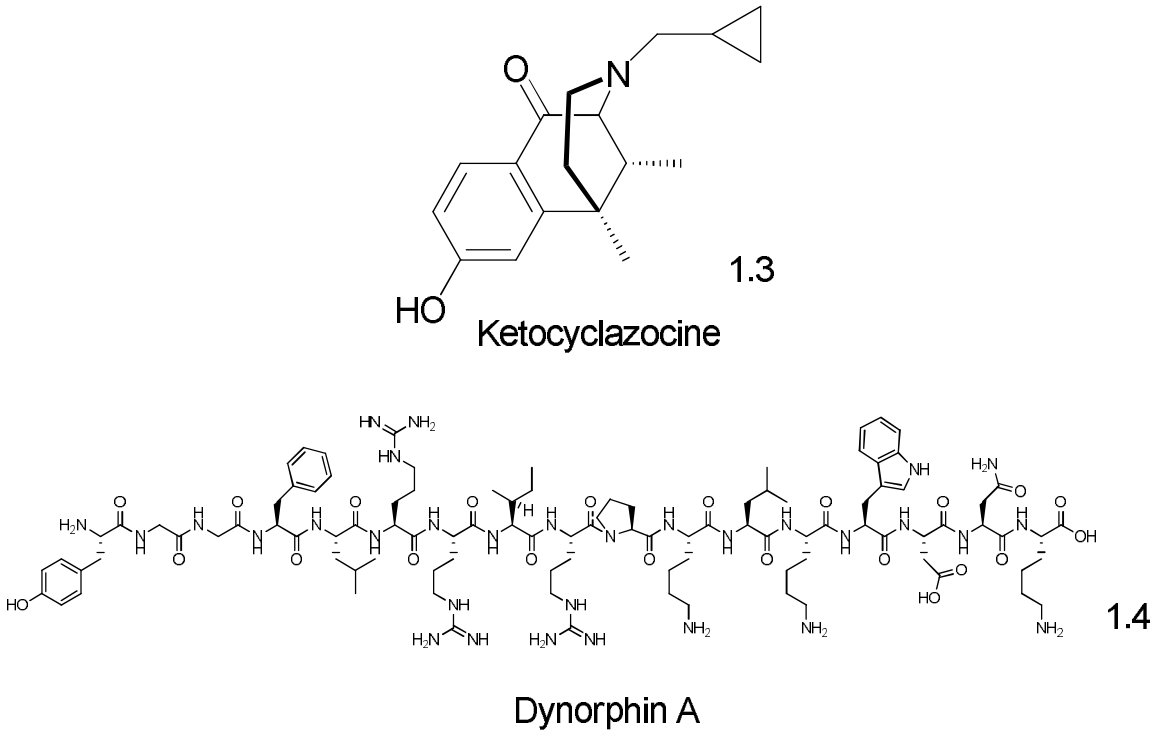


Figure 1.3: Exogenous and endogenous kappa opioid agonists

the cell which causes the cell membrane to become hyperpolarized.[25] Activation of KORs also leads to a reduction of calcium influx through N-type (Neural-type) calcium channels, which is also mediated by G-protein signaling.[26]

PAIN PATHWAY

The pain signal from the periphery to the brain is transmitted through primary and secondary afferent neurons.[27] A pain stimulus in the periphery activates nerve endings of primary nociceptive Aδ and C fibers of primary afferent neurons which innervate all tissue in the periphery. These primary afferent neurons project to the dorsal horn of the spinal cord where their cell bodies are located. In the dorsal horn, they form synapses with second order projection neurons. At the synapse, primary afferents release

neurotransmitters that trigger secondary neurons to relay the pain signal to the brain. Among these neurotransmitters is glutamate, which activates the ionotropic AMPA receptor, resulting in rapid Na^+ entry into the cell and subsequent membrane depolarization. The release of the neurotransmitter substance P augments glutamate's action by activating the neurorokinin-1 receptor which prevents membrane hyperpolarization by inactivating GIRK channels and preventing K^+ from exiting the cell. The net effect is a rapid excitatory post-synaptic potential (EPSP) that relays the pain signal to the brain through secondary neurons.[28]

MECHANISM OF ANALGESIC ACTION

Outside of the brain, opioids exert their antinociceptive effect by inhibiting the transmission of the pain signal through primary and secondary afferent neurons. Opioid receptors are located at terminals of primary afferent neurons in the dorsal horn of the spinal cord, the area that contains neuronal synapses which modulate sensory input to the brain.[28] Opioids inhibit N-type Ca^{2+} channels on the pre-synaptic side which results in modulation of neurotransmitter release and reduction of neuronal excitability.[26, 29] Furthermore, post-synaptic opioid receptor activation triggers the opening of GIRK channels, leading to neuronal hyperpolarization and concomitant reduction the of pain-signal conducting action potential.[30]

STRUCTURAL FEATURES OF SALVINORIN A

Salvinorin A (**1.8**) is a molecule rich in molecular complexity. It is a tricyclic *trans-cis* neoclerodane diterpene which contains 7 chiral centers at C2, C4, C5, C10, C9, C8 and C12. 5 of these stereocenters are contiguous. It also contains a *trans*-decalin ring system (**1.5**), C19 and C20 methyl groups with a 1,3-diaxial interaction, a lactone with an easily epimerizable hydrogen at C8 and a furan ring on C12. The *trans*- designation refers to the configuration of the decalin ring system and *cis*- refers to the relative orientation of C17 and C20 carbons.[31] The neoclerodane designation is due to it having the same absolute stereochemistry as the neoclerodane diterpene clerodin (**1.6**) at C5, C10, C9 and C8.[32] The diterpene classification is related to its biosynthesis and represents a carbon framework assembled from four isoprene (**1.7**) units.[33]

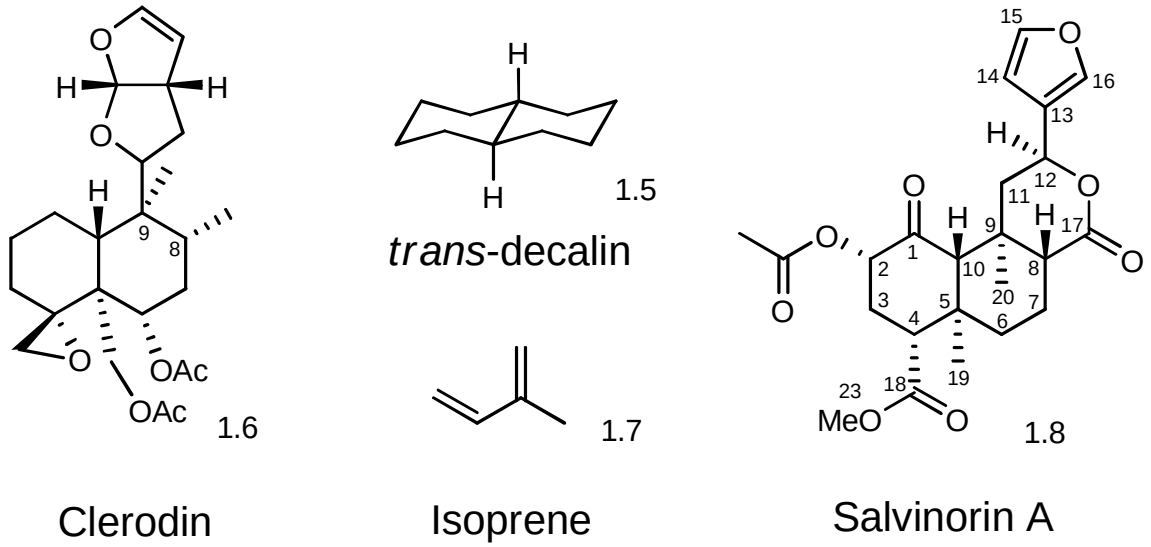
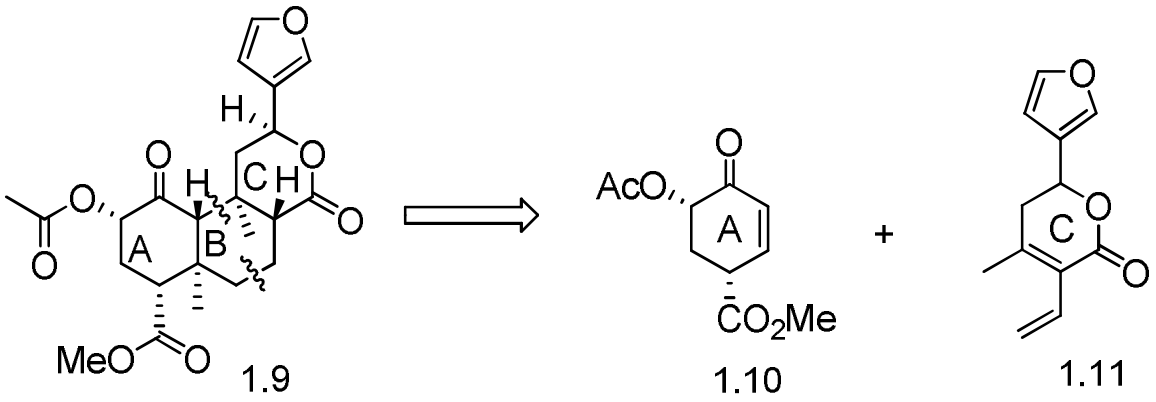


Figure 1.4: Structural features of Salvinorin A

TOTAL AND INCOMPLETE SYNTHESES

Several research groups have attempted to synthesize salvinorin A. Three total syntheses have been completed by two research groups and three partial syntheses have been published.[34-39] Additionally, several analogs have been synthesized semi-synthetically in efforts to develop structure-activity relationship (SAR) data to identify the pharmacophore of salvinorin A.

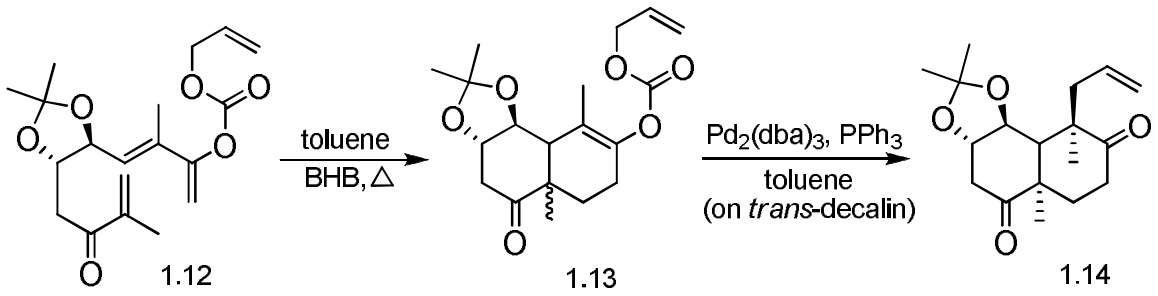
Rook and co-workers envisioned a convergent synthesis whereby the joining of the A and C rings would construct the B ring in the process (Scheme 1.1).[34] Their work yielded the cyclohexenone (**1.10**) and the racemic α,β-unsaturated furanyl-lactone (**1.11**) but did not proceed further.



Scheme 1.1: Rook and co-workers' retrosynthesis

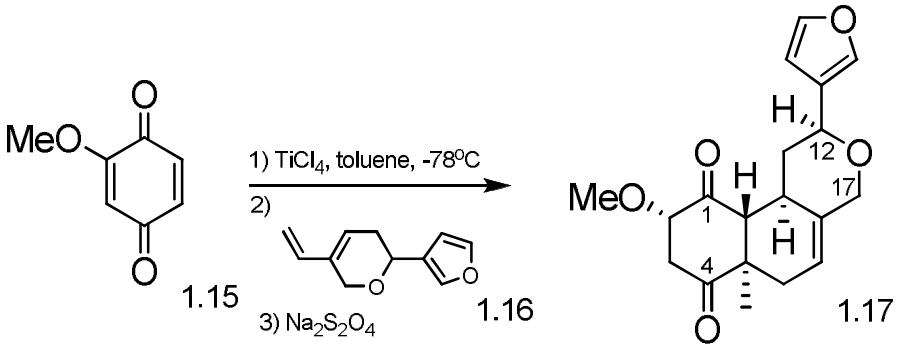
Forsyth and Burns employed an intramolecular Diels-Alder reaction to deliver the *cis*- and *trans*-decalins (**1.13**) in a 1:1 diastereomeric ratio (Scheme 1.2). [35] Subsequent Tsuji allylation on the *trans*-decalin gave the α-allylated product (**1.14**) via a transition

state that favored the creation of a 1,3 diaxial-interaction between two methyl groups over a 1,3-diaxial methyl-allyl interaction. The allylated *cis*-dimethyl product possessed the required stereochemistry for the synthesis of salvinorin A, but no further progress was reported.



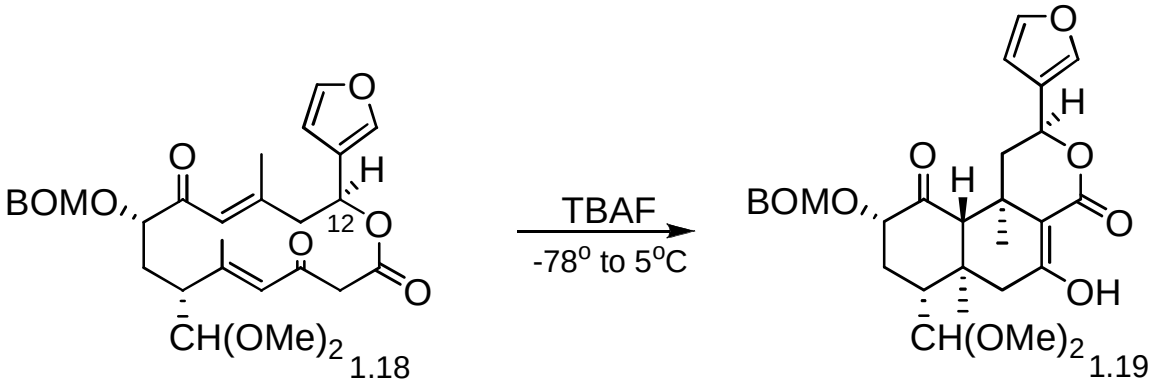
Scheme 1.2: Diels-Alder and Tsuji allylation

Perlmutter and co-workers synthesized the C20-desmethyl salvinorin A analog **1.17**.[36] The key reaction was a titanium-tetrachloride mediated Diels-Alder reaction between 2-methoxy-5-methyl-1,4-benzoquinone (**1.15**) and furanyldihydropyran diene (**1.16**) to give the tricyclic compound **1.17**.



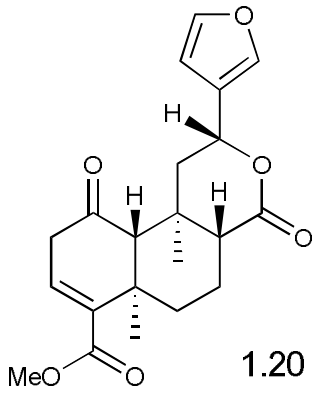
Scheme 1.3 C20 Desmethyl analog

The first total synthesis of salvinorin A was completed by Evans and co-workers in 2007.[37] The synthesis required 33 steps and was achieved in an overall yield of 4 %. The key reaction in the synthesis was an intracellular double Michael addition on the macrocyclic dienone (**1.18**, Scheme 1.4) to give the tricyclic product (**1.19**). In experiments on model systems, the disastereoselectivity (>95%) was controlled by the stereochemistry at the C12-furyl carbon. Five subsequent steps gave 8-*epi* salvinorin B (2-desacetyl salvinorin A) which was epimerized then acetylated to give the final product.



Scheme 1.4: Double intracellular Michael addition

The other two total syntheses of salvinorin A were reported by Hagiwara and co-workers in 2008 and 2009.[38, 39] Both syntheses were similar to a previous synthesis by the Hagiwara group of a similar neoclerodane diterpenoid, methyl barbascoate (**1.17**, Figure **1.5**).[40]

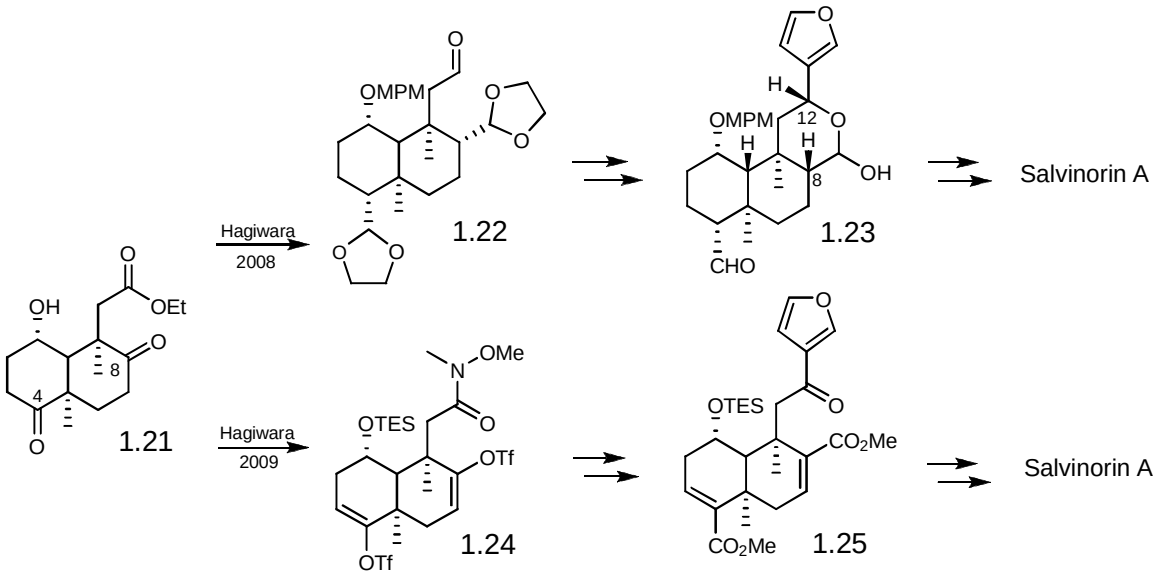


Methyl barbascoate

Figure 1.5: Methyl barbascoate

Both Hagiwara syntheses used the same 6-step approach to arrive at the functionalized bicyclic dione (**1.21**, Scheme 1.5), after which the synthetic schemes diverged. The 2008 synthesis used a dual-Wittig approach for simultaneous C4/C8 homologation.[38] The 2009 synthesis converted the bicyclic dione to the bis-enol triflate (**1.24**) followed by palladium-catalyzed double carbonylation.[39] The 2008 synthesis used a substrate-directed furan addition to obtain the desired C12 stereochemisty in a 3:2 ratio (**1.23**).[38] The 2009 synthesis used K-selectride in a chelation-controlled reduction to obtain a single diastereomer (**1.25**).[39] The 2008 synthesis required 24 steps resulting in a 0.95% overall yield. The improved 2009 synthesis required 17 steps in 2.8% overall

yield. Both routes required an additional step to epimerize C8 to the correct stereochemistry.



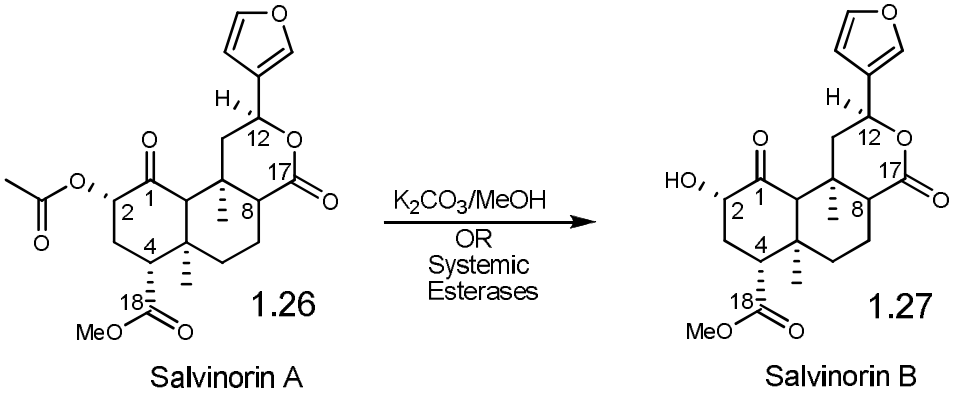
Scheme 1.5: Hagiwara syntheses

SEMI-SYNTHETIC ANALOGS

A litany of analogs of salvinorin A has been synthesized in order to acquire SAR data and attempt to identify the pharmacophore. Owing to the difficulty in synthesizing salvinorin A, the collection of analogs has been produced by chemical modification to the natural product obtained from the leaves of *Salvia divinorum*, i.e. semi-synthetically. The majority of modifications have focused on the C2 ester and the furan ring on C12. Additionally, chemical alterations have been made to C4 ester, and C1 and C17 carbonyls.

C2 Analogs

The hydrolysis of the C2 acetoxy group of salvinorin A (**1.26**) yields the secondary alcohol salvinorin B (**1.27**), an inactive minor natural product isolated from *Salvia divirnorum.*[15, 41] The ester hydrolysis occurs readily *in vivo*[42,43] and is likely the reason for salvinorin's short duration of action. The esterase carboxylesterase has been shown to be the major contributor to salvinorin A metabolism[44] but several cytochrome P450 isoforms and uridine diphosphate-glucuronosyltransferase (UDPGT)-2B7 have also been shown to contribute.[45]

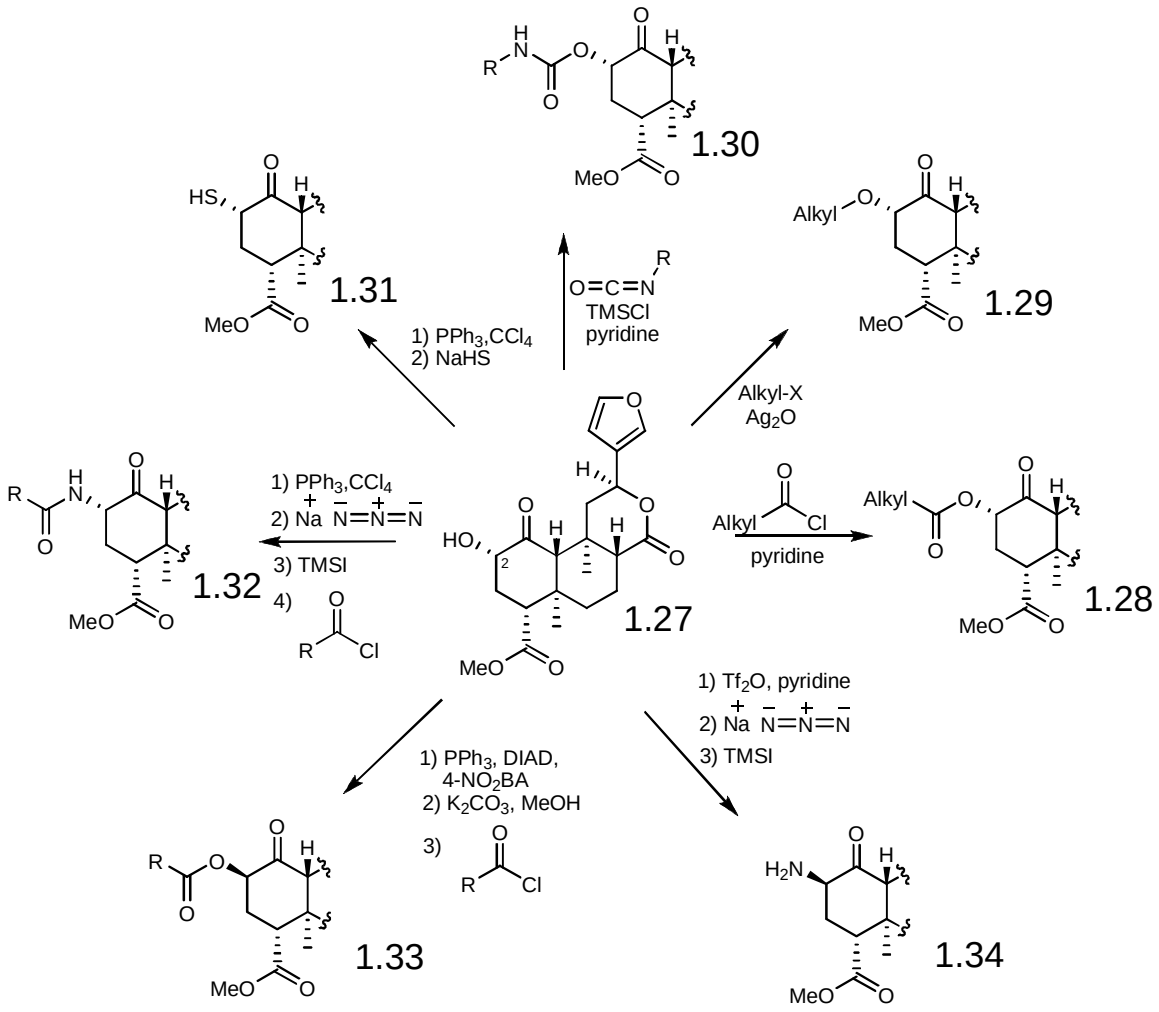


Scheme 1.6: C2 hydrolysis

The C2 hydrolysis (methanolysis, Scheme 1.6) is easily carried out under mild conditions[15] and affects only the C2 ester group of the molecule, resulting in a molecule with a secondary alcohol handle that is ideally suited for chemical modification. This reaction has been utilized by several groups to synthesize C2 analogs (Scheme 1.7) including esters (**1.28**) by reaction with acid chlorides or anhydrides and pyridine[41, 46, 47, 48, 49] and ethers (**1.29**) by reaction with alkyl halides and silver oxide[47] or diisopropylethylamine.[50] Carbamate C2 analogs (**1.30**) have been synthesized by

reaction with isocyanates and chlorotrimethylsilane[46] or DMAP and pyridine.[47] Bikbulatov and co-workers synthesized the C2 thiol (**1.31**) by C2 chlorination followed by reaction with sodium hydrogen sulfide.[51] Subsequent reaction of the C2 thiol with acetic anhydride yielded the 2-thioacetate ester equivalent of salvinorin A.[51] Amides (**1.32**) have also been synthesized using a similar double-inversion approach. Reaction of secondary chloride with sodium azide followed by reduction of the resulting azide with *in situ*-generated iodotrimethylsilane[52] produced the secondary amine handle, which upon reaction with acid chlorides yielded the corresponding amides.[53, 49]

In order to determine the importance of C2 steroechemistry, several C2-inverted stereochemistry analogs of salvinorin A were synthesized. 2-epi Salvinorin A was synthesized by Mitsunobu reaction of salvinorin B followed by reaction with acetic anhydride.[48,53] The Mitsunobu product was also used to synthesize other esters and ethers (**1.33**).[53, 54] Reaction of the trifluoromethanesulfonate ester of salvinorin B with sodium azide followed by reduction to the amine gave inverted-stereochemistry free amine (**1.34**) which was used as a handle for the synthesis of amides.[47] Substituted amines were reacted with the trifluoromethanesulfonate ester of salvinorin B to give C2-alkyl amine analogs.[47]

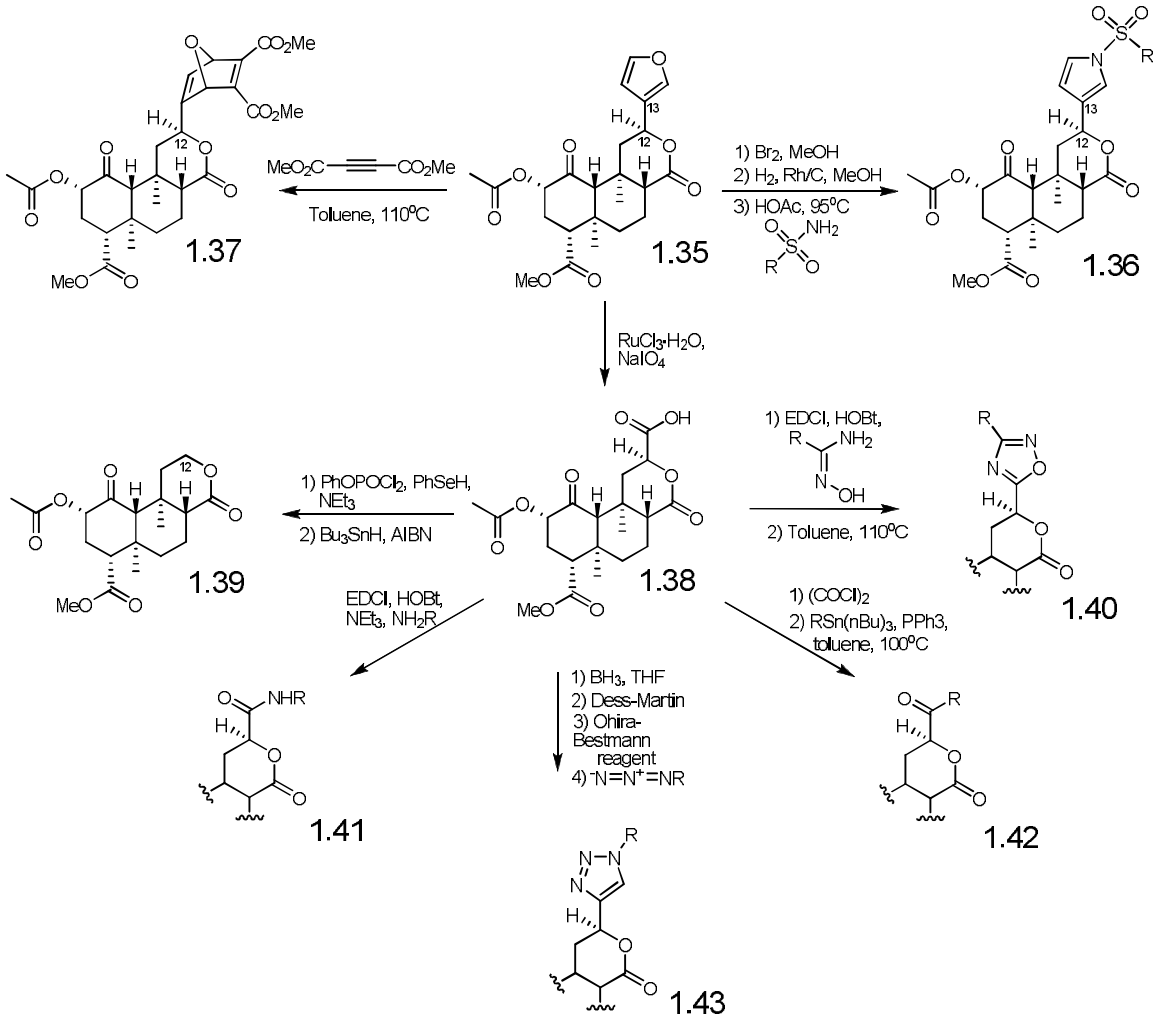


Scheme 1.7: C2 modifications

Furan Ring Analogs

The most recent round of publications of semi-synthetic salvinorin analogs has focused on modifications to, and replacement of the furan ring (Scheme 1.8). The furan ring has been brominated to give the 2-bromofuranyl analog.[54] Reaction with molecular bromine in methanol yielded the 2,5-dimethoxydihydrofuran analog, which upon treatment with $KMnO_4$ yielded the natural products salvicinin A and B.[54] Reaction of the

2,5-dimethoxydihydrofuran compound with different sulfonamides yielded the corresponding N-substituted sulfonylpyrroles (**1.36**).[55] The furan ring of salvinorin A has been used at the diene substrate for a Diels-Alder cycloaddition, with dimethyl acetylene dicarboxylate as the dienophile to give the oxabicycle product (**1.37**).[56]



Scheme 1.8: C12 modifications

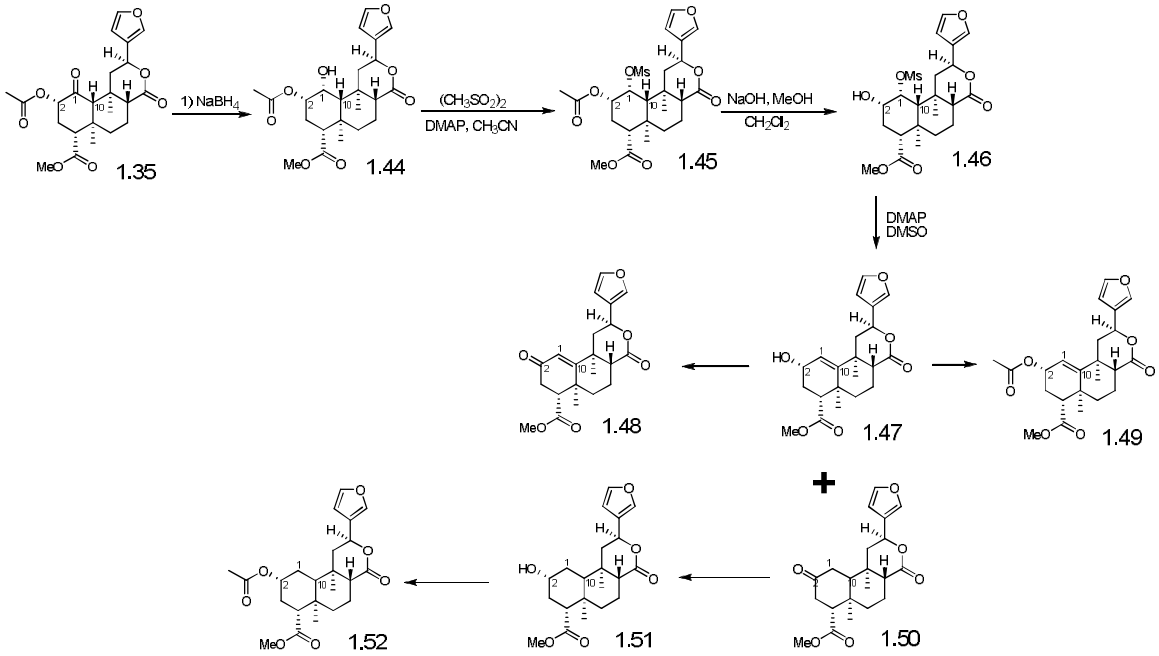
The majority of furan-modified analogs have come from the reaction of salvinorin A (**1.35**) with $RuCl_3 \cdot 3H_2O$ and $NaIO_4$ to give the C13 carboxylic acid (**1.38**), another

versatile handle on which to perform a variety of chemical reactions. Reaction of this acid with phenylchlorophosphate followed by selenophenol produced the selenephenol ester which was then decarbonylated with tri-*n*-butyltin hydride and azobisisobutyronitrile (AIBN) provided the des-furan derivative (**1.39**).[55] Other C12-substituted salvinorin analogs resulting from reaction of the C13 acid include oxazoline, oxazole and oxadiazole (**1.40**).[55] 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDCI) has been used as a coupling reagent to synthesize a variety of amides (**1.41**) and esters.[57] Reaction of the acid with trimethylsilyldiazomethane followed by aliphatic and benzylic amines yielded the corresponding ketones.[58] Conversion to the acid chloride followed by Stille coupling reactions with various aryltributyltin reagents gave the corresponding aryl and heteroaryl ketone compounds (**1.42**).[58] Finally, reduction of the C13 acid to the primary alcohol, followed by oxidation to the aldehyde and conversion to the terminal alkyne by Ohira-Bestmann alkynylation gave the alkyne which was used as a substrate for Huisgen 1,3-dipolar cycloadditions to give substituted triazoles (**1.43**).[59]

C1 Analogs

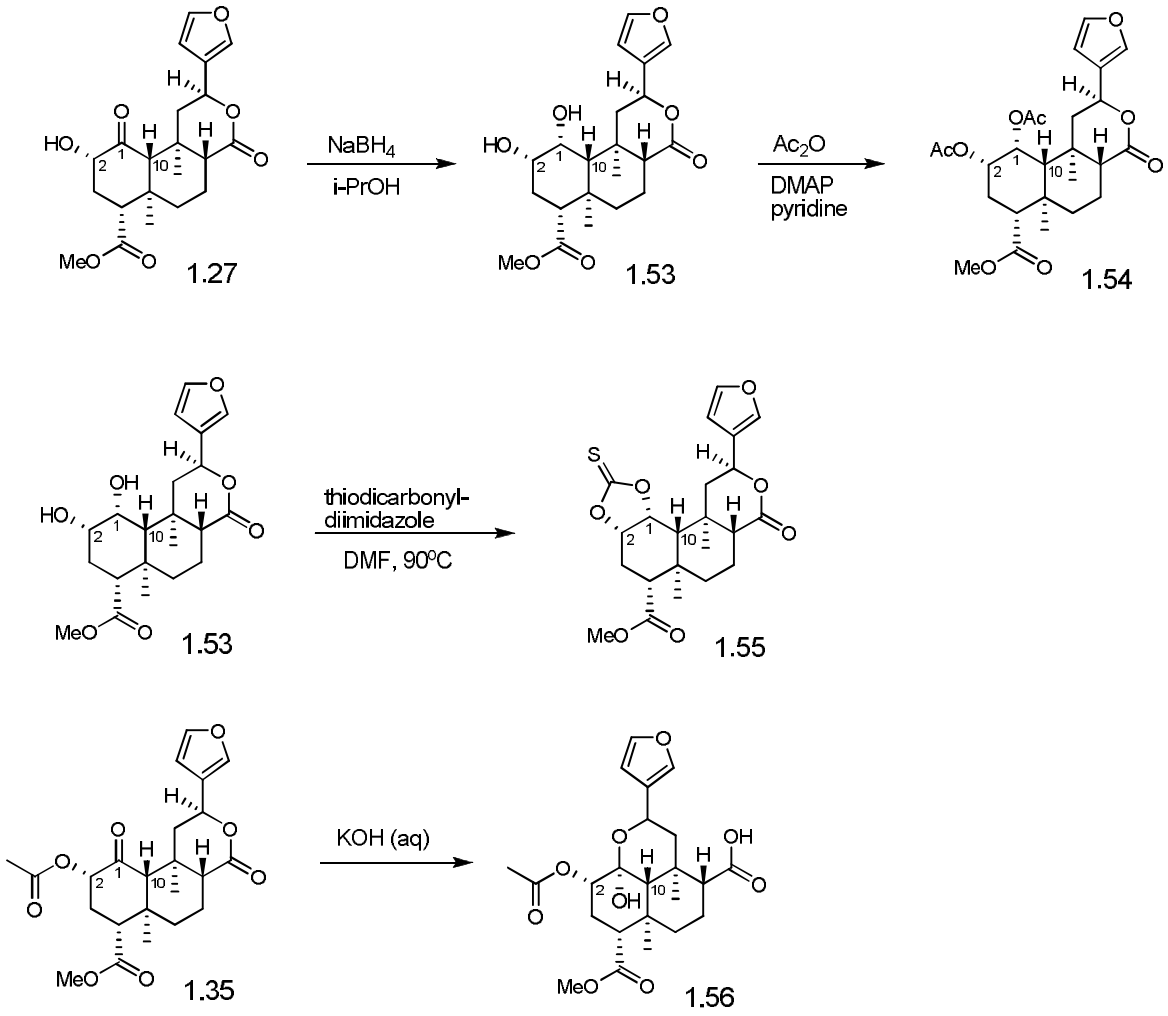
Several C1 analogs were synthesized en route to 1-deoxy salvinorin A (**1.52**).[60] The C1 carbonyl of salvinorin A (**1.35**) was reduced to give the C1 alcohol (**1.44**) which was mesylated (**1.45**) then deacetylated at C2 (**1.46**). Treatment of this mesylate with 4-dimethylaminopyridine (DMAP) produced the C1-C10 elimination product 1-deoxo-1,10-dehydrosalvinorin B (**1.47**). Reactions on this C1-C10 olefin include oxidation of the secondary alcohol to give the enone (**1.48**), and acetylation of the secondary alcohol to give the 1,10-dehydrosalvinorin A (**1.49**). One of the side products of the DMAP-

elimination reaction was 2-keto-1-deoxysalvinorin A (**1.50**) which was reduced to 1-deoxosalvinorin B (**1.51**) and subsequently acetylated to give 1-deoxosalvinorin A (**1.52**).



Scheme 1.9: C1 modifications

The C1 carbonyl of salvinorin B (**1.27**) was reduced to give the C1-C2 *cis*-diol (**1.53**), which was acetylated to give the *cis*-diacetate (**1.54**).[46] This C1-C2 *cis*-diol was used to synthesize the cyclic thionocarbonate (**1.55**) by reaction with thiocarbonyldiimidazole.[61] Treatment of salvinorin A with aqueous KOH gave the stable C1 hemi-acetal (**1.56**).[62]

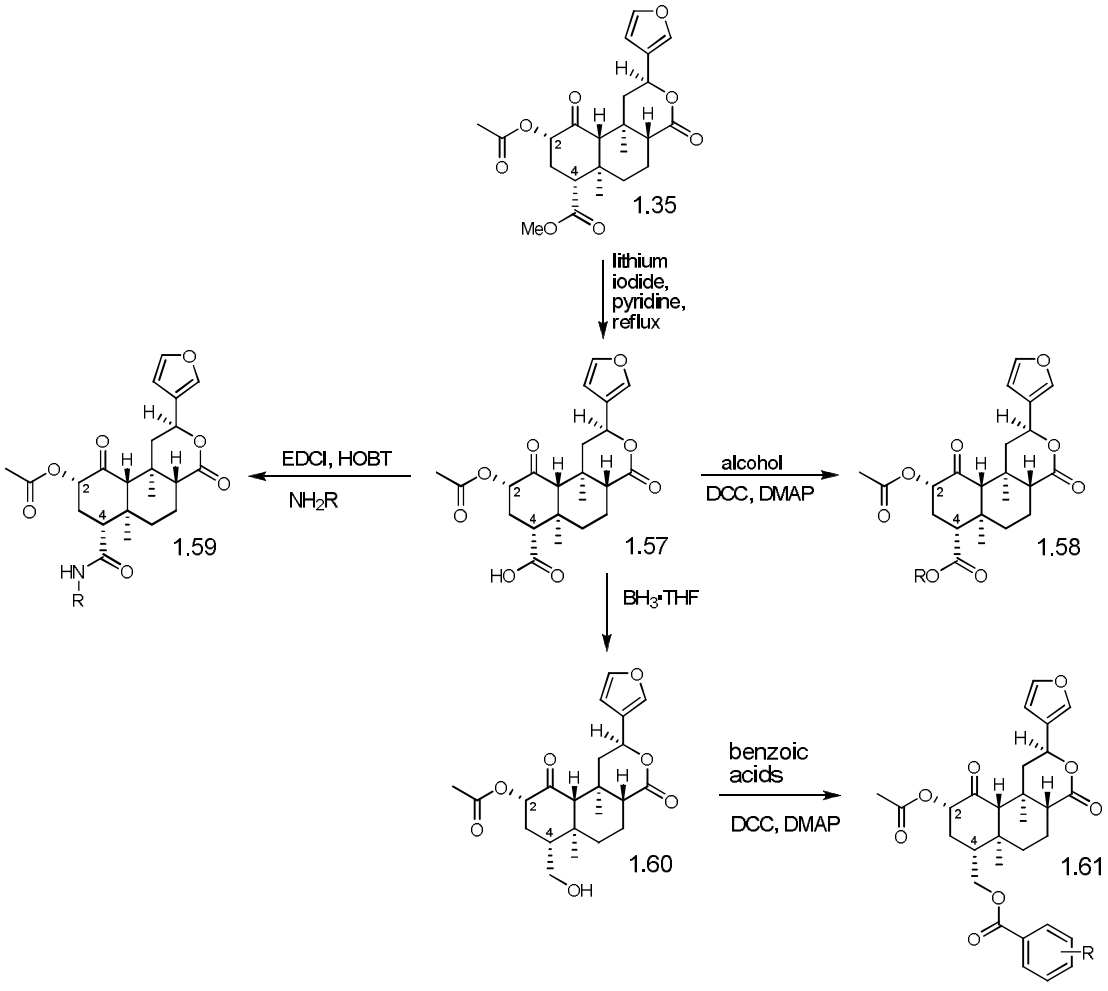


Scheme 1.10: C1 modifications, continued

C4 Analogs

The selective cleavage of C4 ester was accomplished by refluxing salvinorin A and lithium iodide in pyridine.[63] Treatment of the resulting carboxylic acid with DCC, DMAP and different alcohols yielded the corresponding C4 esters (**1.58**).[63] 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI) and 1-hydroxybenzotrizole (HOBT) were

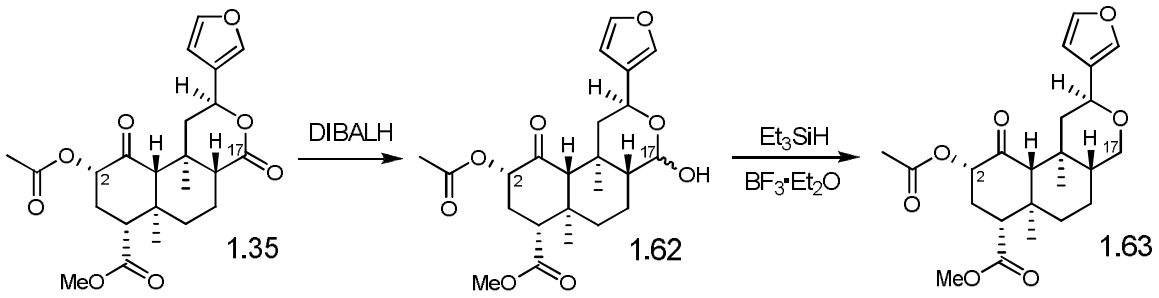
used in conjunction with different amines in dimethylformamide (DMF) to create a series of C4 amides (**1.59**).[63] The C4 carboxylic acid was reduced with borane-THF to give the primary alcohol (**1.60**). The primary alcohol was treated with silver oxide and alkyl, allyl and benzyl halides to synthesize ethers. DCC and DMAP were used to construct benzoate esters (**1.61**) and amino acid derivatives at the primary alcohol.[64]



Scheme 1.11: C4 modifications

C17 Analog

The C17-deoxysalvinorin analog was synthesized by reaction with DIBAL-H to make the hemi-acetal (**1.62**) followed by reaction triethylsilane and borontrifluoride diethyletherate.[61]



Scheme 1.12: C17 Desoxysalvinorin A

SAR SUMMARY

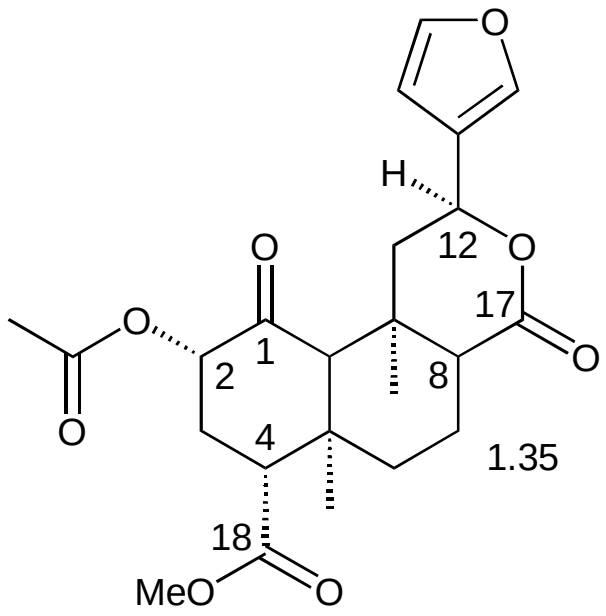
C2 modifications to salvinorin A are the most numerous. The natural stereochemistry is important for retention of activity; 2 epi-Salvinorin A and analogs thereof display significantly reduced affinity for KORs.[46] The exceptions to this are 2-N-methylacetamide and 2-N-ethylacetamide which display affinity comparable to salvinorin A regardless of C2 stereochemistry. Two to four carbon alkanoate ester groups have comparable KOR affinity which decreases rapidly when ester size increases beyond four carbons (>butanoate, isobutanoate ester).[41, 47, 48] Some C2 benzoate esters exhibit selectivity for μ over κ opioid receptors.[46, 48] Bioisosteric replacements are tolerated, including mesylate, -NH_2 carbamate, and thioacetate.[46, 47, 49, 51] Most notably, the 2-

methoxymethyl (MOM) ether derivative displays comparable KOR affinity, higher potency and longer antinociceptive effects *in vivo*.[50, 65]

Most of the C12 modifications were not well-tolerated.[54-57] Reduction of the furan ring results in a 40-fold loss in affinity for the KOR. Removal of the furan ring results in loss of activity.[55] Replacement of the furan ring with sulfonylpyrroles, oxazoles, oxodiazoles and triazoles was also detrimental to KOR affinity.[55] Furan Diels-Alder derivatives displayed significant loss in affinity.[56, 58] 2-allyl and 2-bromofuran derivatives, as well as C12 epi-Salvinorin A, retained affinity for the KOR.[58]

The removal of the C1 ketone did not significantly reduce KOR affinity (4-fold decrease).[60] Reduction to the α-alcohol was also tolerated, (10-fold decrease in affinity) transforming the molecule from a full agonist to an antagonist.[60] The removal of the C17 carbonyl also had no effect on affinity for the KOR, suggesting that neither the C1 nor the C17 carbonyls are required for activity.[60, 61]

Most modifications to the C4 methyl ester were detrimental to the affinity of these molecules for the KOR. Hydrolysis of the C4 methyl ester to the carboxylic acid caused 1,000-fold decrease in affinity.[53] The affinity of the corresponding alcohol for the KOR was reduced 40-fold.[53] The C4 ethyl ester was tolerated but larger esters were not.[63, 64] Amides and N-linked amino acids were not tolerated.[63, 64]



C1: Deoxy analog loses affinity
-OH loses affinity

C2: -OH loses affinity (100-fold less)
Propionate and butanoate ester retain affinity
Larger alkyl esters lose affinity as size increases
Ethyl ether retains affinity but larger alkyl ethers lose affinity
Heterocycles, aromatics, carbamates, amines lose affinity for KOR
Benzoate and p-Bromobenzoate selective for MOR over KOR (~80x)
MOM ether has comparable affinity, potency and efficacy
with improved duration of action
Thiol and thioesters lose affinity
Inversion of stereochemistry has detrimental effect

C4: Methyl ester required for affinity
Amides, ethers, alcohol, amines, acid esters,
amino acids, aldehyde, alcohol lose affinity

C8: Epimer displays17-fold loss of affinity

C12: 2-bromo- and 2-alllylfuran have comparable affinity
Removal of furan loses affinity
Replacement with oxazole, oxazolines lose affinity
Furan Diels-Alder products lose affinity
Amides (aromatic and heterocyclic) lose affinity
Alkyl, heterocyclic and aryl ketones lose affinity

C17: Deoxy analog retains affinity

Figure 1.6: SAR summary

KAPPA AGONISTS AS THERAPEUTICS

The prototypical drugs for severe pain are mu opioid agonists.[66] Unfortunately, there are numerous side-effects associated with mu agonists which include physical dependence, sedation, constipation and respiratory depression.[66] Kappa agonists are devoid of many of the harmful side-effects associated with mu agonists. Kappa agonists display minimal potential for abuse and physical dependence associated with MOR agonists.[67] Additionally, various kappa agonists do not alter respiratory rate nor do they cause constipation.[67]

The primary limitation associated with KOR agonists is their psychotomimetic activity. The side-effects produced by KOR agonists include dysphoria, hallucinations, alteration in the perception of time, derealization and loss of self-control.[68] These actions are a result of activation of KORs located in the brain. A chemically modified analog of Salvinorin A which limits its passage across the blood-brain barrier could limit or eliminate the psychotomimetic properties.

This approach has been previously utilized with some arylacetamides, a class of selective agonists for the kappa opioid receptor. ICI 199,441 (**1.64**) is a selective kappa opioid agonist with >1,000 and >600 fold selectivity for kappa over mu and delta opioid receptors, respectively and a Ki of 0.05 nM.[69] ICI 199,441 exhibits centrally-mediated psychomimetic properties, but the modified, zwitterionic analog ICI 204,448 (**1.65**) retains comparable affinity and selectivity for the kappa receptor while displaying lower CNS penetration (level of radiolabeled drug in brain/dose of drug).[70] Another example of

a peripherally-selective arylacetamide is EMD 61753 (**1.66**) (Asimadoline, Tioga Pharmaceuticals) which entered clinical trials in 2005 and is currently in a phase III clinical trial for diarrhea-predominant irritable bowel syndrome.[71]

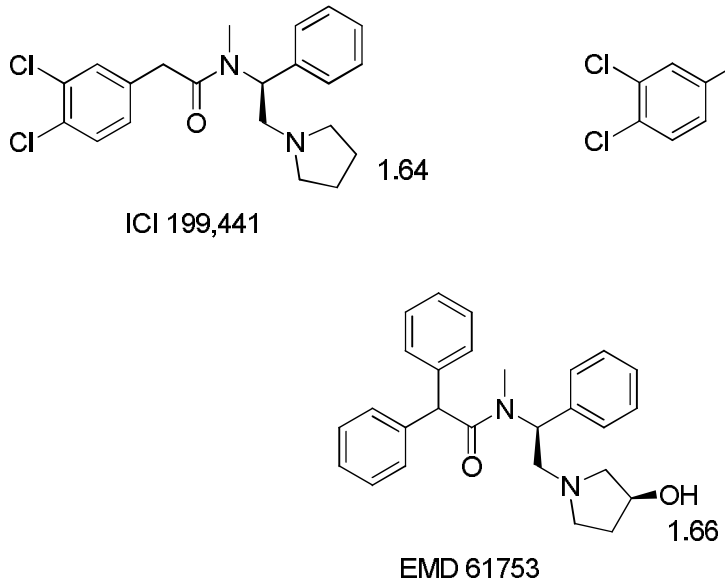


Figure 1.7: Arylacetamides

CONCLUSION

Salvinorin A is a highly potent, selective agonist of the KOR. Its unique structure and novel mode of receptor interaction establish it as the first of a new class of kappa-selective opioid agonists. Chemical modification and SAR data has shed light on the pharmacophore of this remarkable compound. Chemical modification to salvinorin can minimize the shortcomings while preserving the desirable features. Conversion of the C2 acetate ester to the MOM ether has shown that the half-life of salvinorin A can be

extended. Other modifications, such as the inclusion of a protonatable nitrogen, can potentially limit distribution to the periphery in order to eliminate psychotomimetic side effects. Total synthesis of salvinorin A opens the door for a number of previously inaccessible compounds to be made.

Chapter 2: Synthetic Work Towards Salvinorin A

The primary goal of this project is to complete the total synthesis of salvinorin A. Moreover, the syntheses of novel analogs of salvinorin A, especially molecules with substitutions at C12, are also of interest to this project. A total synthesis of this molecule will allow for modifications to be made that are not possible by modifying the natural product. Of the three total syntheses that have been completed (by two groups), neither has gone on to create novel analogs of salvinorin A.[37, 38, 39] The existing collection of analogs of salvinorin A has been arrived at by chemical modification to the natural product isolated from the leaves of *Salvia divinorum*.[41, 46-65] This semi-synthetic approach limits chemical modifications to only the more reactive functional groups of salvinorin A. Certain functional groups, e.g. C19 and C20 methyl groups are essentially permanent due to their relatively low reactivity. The synthetic routes employed in this project were designed to have the advantage of 1) establishing a roadmap to the total synthesis of salvinorin A, 2) allowing novel modifications to be made that are not possible by semi-synthetic methods, 3) allowing established, noteworthy changes from the collection of published semi-synthetic modifications to be made (e.g. 2-MOM ether) in combination with our unprecedented transformations to create novel molecules with enhanced pharmacological properties.

The particular change we focused on was substitution of the furan ring attached to C12. Although semi-synthetic modifications to salvinorin A have been performed on the furan ring, the complete replacement of the furan ring by means of total synthesis has not

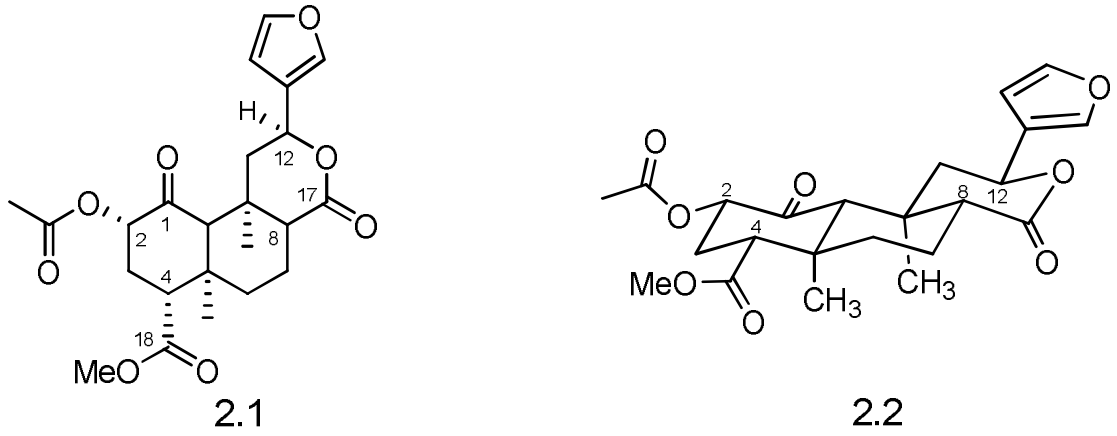


Figure 2.1: 2-D representation and 3-D structure of Salvinorin A

been investigated. With this in mind, our synthetic routes were designed with the requirement that an intermediate be produced relatively late in the synthesis whose structure is amenable to a wide variety of modifications at C12.

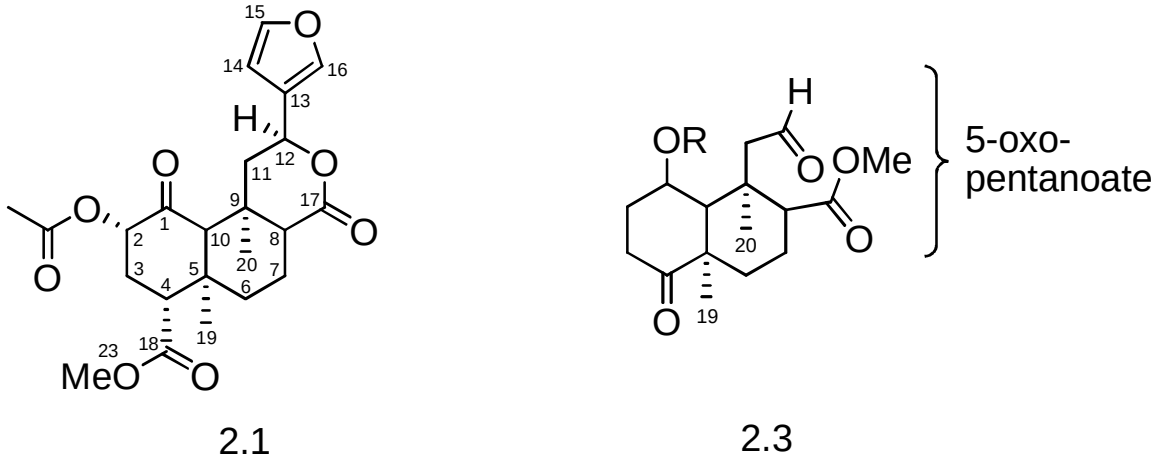


Figure 2.2: Labeled rings of contiguous tricycle and branch-point molecule for Salvinorin A analogs

Salvinorin A (**2.1**) contains 4 rings, three of which are contiguous. The three rings comprising this contiguous tricyclic core are designated A, B and C. Rings A and B

constitute a functionalized *trans*-decalin which is the basis for the numbering of salvinorin carbons. The C ring is a δ-lactone which shares C8 and C9 with the B ring. Our attempts at synthesizing salvinorin A focus on the synthesis of this ABC tricyclic core with subsequent modification to append the functional groups along the periphery of the molecule.

Bicyclic δ-carboxy ester **2.3** was chosen as the primary intermediate. It is theoretically six steps away from salvinorin A. The [4.4.0] bicyclic ring system of **2.3** corresponds to the *trans*-decalin AB ring system of salvinorin A. Moreover, the C19 and C20 diaxial methyl groups are already incorporated into the molecule. The most noteworthy feature of this molecule (**2.3**) is the 5-oxopentanoate moiety. Methyl 5-oxopentanoates such as molecule **2.4** have been employed as precursors to δ-alkylated δ-lactones.[72-75] The most electrophilic functional group on this molecule is the aldehyde, which upon reaction with a nucleophile yields a lactone (**2.5**) with the nucleophile incorporated at the δ-position (Figure 2.3).

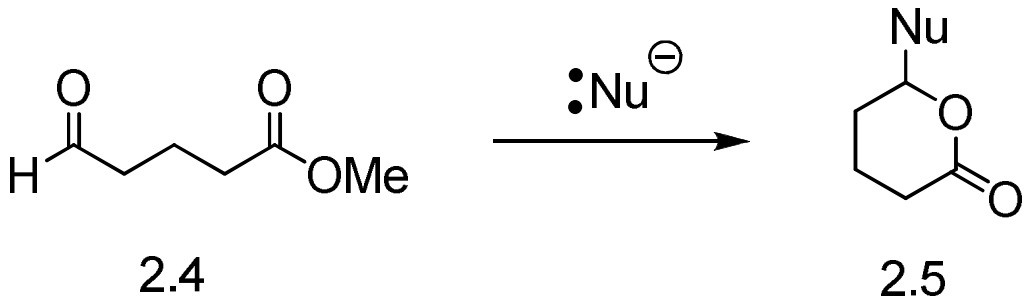


Figure 2.3: δ-lactone from δ-carboxy ester

The utility of compound **2.3** is its ability to give rise to a diverse array of salvinorin analog precursors modified at C12. As illustrated in Figure 2.4, reaction of **2.3**

with 3-furyllithium would give rise to a molecule that is a precursor to salvinorin A (**2.6**). A C12 phenyl-substituted salvinorin analog (**2.7**) can be synthesized by utilizing phenyllithium as the nucleophile. Employing an acetylide anion as the nucleophile will result in a C12 acetylene lactone which upon reaction with an azide leads to the azide alkyne Huisgen cycloaddition product (**2.8**), an important reaction which has been used as the diversification step to make numerous functionalized 1,2,3-triazoles.[76, 77] Zinc-chelated N-(trifluoroacetyl)glycine ester enolate[78] (**2.9**) can be employed as the nucleophile to give the C12-glycine substituted salvinorin analog.

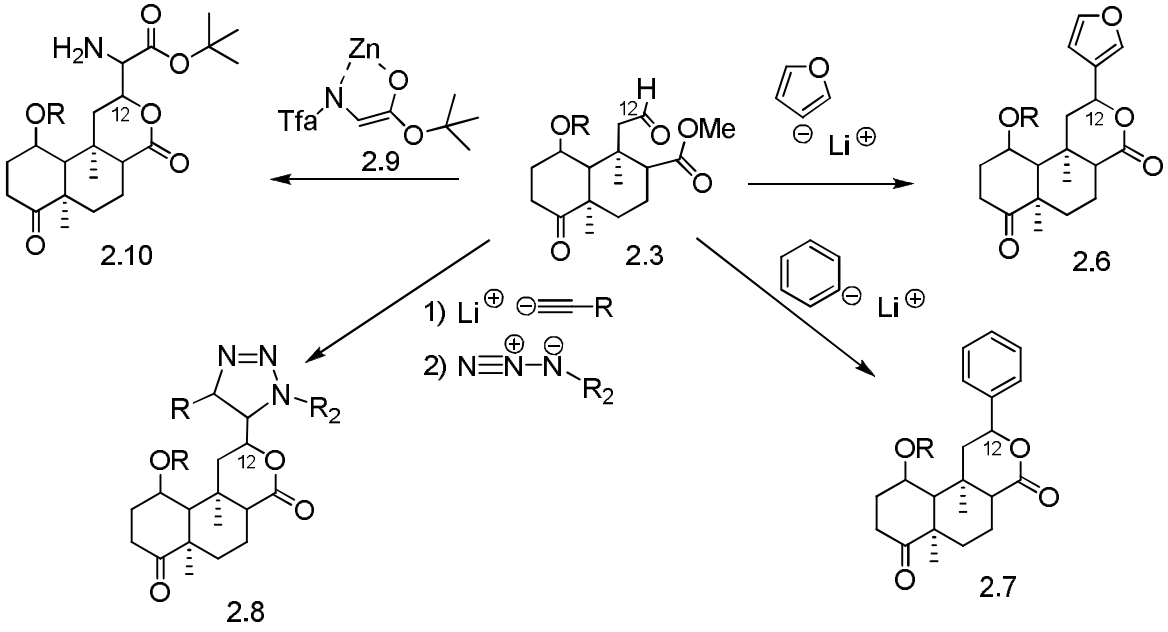


Figure 2.4: Bicyclic δ-carboxy ester reaction wheel of utility

RETROSYNTHETIC ANALYSIS I

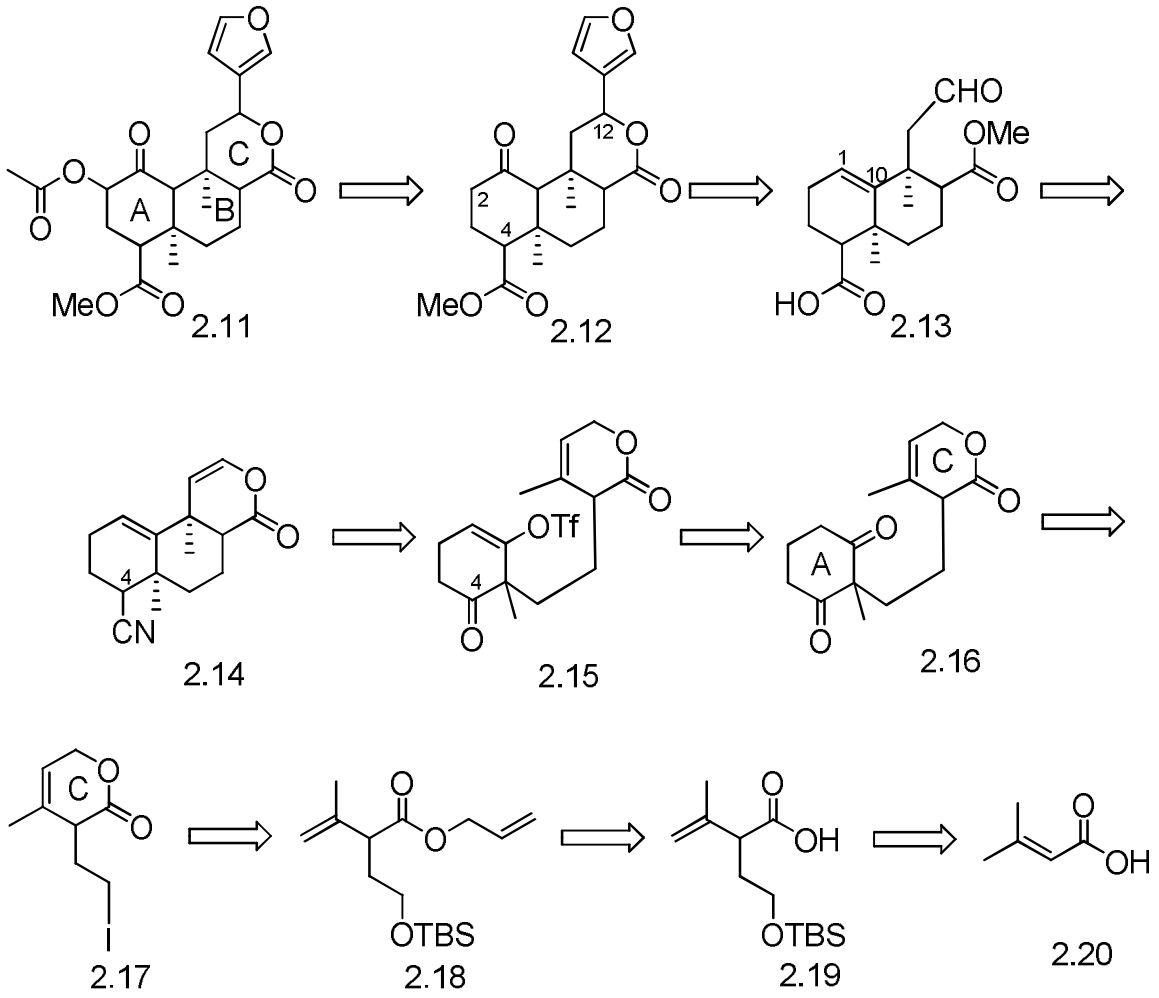


Figure 2.5: Retrosynthesis 1

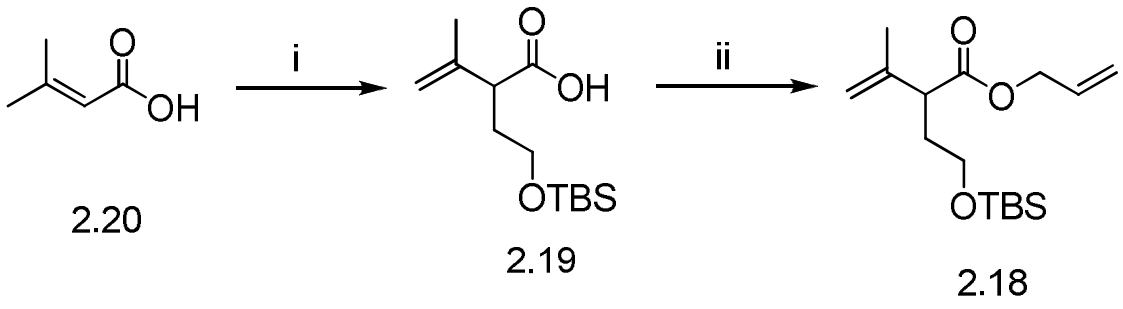
In our original retrosynthesis, salvinorin A would be derived from ketone **2.12**, whereby the C2 acetate would be obtained by a Rubottom oxidation[79] of C2 followed by O-acetylation. Compound **2.12** would come from addition of 3-furanyllithium to the aldehyde of bicyclic δ-carboxy ester **2.13**, which itself comes from methanolysis/ring opening of enol lactone of **2.14**. This tricyclic compound **2.14** is the desired product of an

intramolecular Heck reaction[80] between the vinyl triflate and olefin on **2.15**. This would be the key step of this route. The vinyl triflate would be obtained by enolate formation followed by trifluoromethanesulfonyl-trapping of one of the A-ring ketones on **2.16**. Compound **2.16** would be obtained by alkylating the anion of 2-methyl-1,3-cyclohexadione with iodide **2.17** which in turn would be synthesized via ring-closing metathesis of allyl ester **2.18**. The allylic ester would be obtained by regioselective α-alkylation of 3,3-dimethylacrylic acid **2.20** followed by allyl esterification.

FORWARD ROUTE I

In a forward fashion, 3,3-dimethylacrylic acid (**2.20**) was deprotonated with two equivalents of lithium diisopropyl amide (LDA) to give the lithium dianion which was regioselectively alkylated at the α position[81] with *tert*-butyldimethylsilyl (TBS)-protected 2-iodoethanol.[82] This moved the olefin out of conjugation and into a terminal position, a requirement for a forthcoming metathesis step. Allyl esterification of the alkylated acid **2.19** was initially performed using allyl alcohol and dicyclohexylcarbodiimide[83] as the dehydrative coupling reagent. Although this method did work, complete separation of the ester product from the dicyclohexylurea by-product was difficult by column chromatography. Conversion of the carboxylic acid to the acid chloride followed by alcoholysis[84] with allyl alcohol also yielded the desired product, albeit with an unsatisfactory yield of 18%. Ultimately, alkylation of the cesium salt of the carboxylic acid produced the best result.[85] This was accomplished by refluxing the acid (**2.19**), allyl iodide and cesium carbonate in THF. Allyl esterification transformed the acid into the

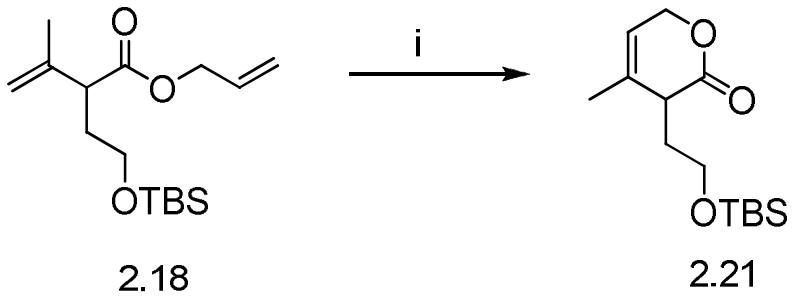
terminal diene ester **2.18**, a substrate for the subsequent ring-closing metathesis (RCM) reaction.



Conditions and reagents: (i) 2 equiv. LDA, THF, -78 °C, $I(CH_2)_2OTBS$, 84%; (ii) Cs_2CO_3, allyl iodide, THF, 80 °C, 86%.

Scheme 2.1: Alkylation and subsequent esterification of dimethylacrylic acid

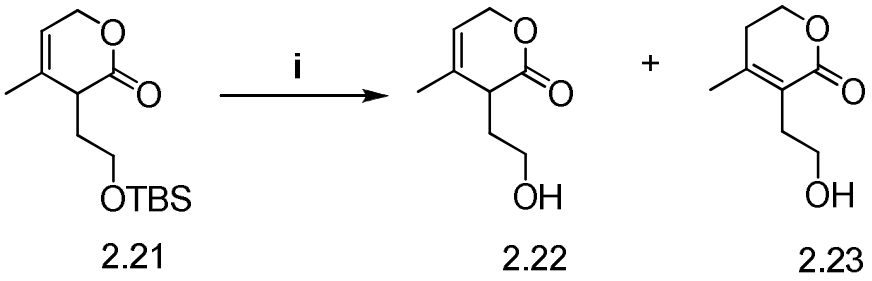
Grubbs' second generation catalyst was employed to transform the diene-ester **2.18** to the β, γ-unsaturated δ-lactone **2.21** via an intramolecular RCM. [86]



Conditions and reagents: (i) Grubbs' II, 10 mol%, CH_2Cl_2, 40 °C, 40%

Scheme 2.2: Grubbs'-catalyzed lactonization

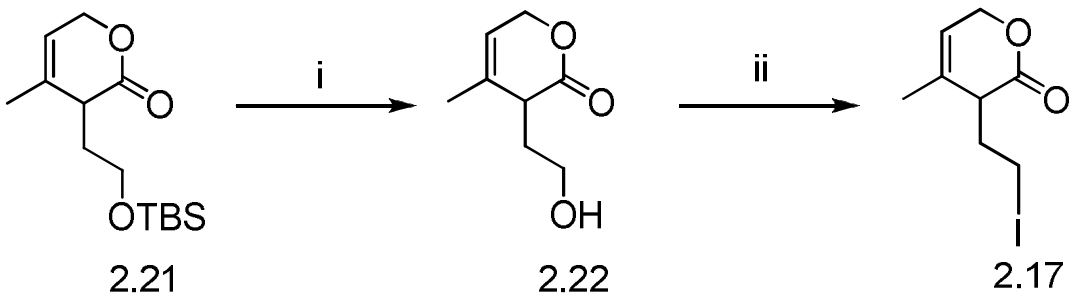
Deprotection of the TBS ether **2.21** using the conventional tetra-*n*-butylammonium fluoride (TBAF)[82] resulted in a mixture of the desired product (**2.22**) and the deprotected, conjugated lactone **2.23**. The retention factor (Rf) of these two lactones was so similar that purification to homogeneity by column chromatography was essentially impossible.



Conditions and reagents: (i) TBAF 1M in THF, 0 °C-rt, 2hrs.

Scheme 2.3: Initial deprotection of TBS ether

Deprotection of the TBS ether (**2.21**) with borontrifluoride diethyletherate ($BF_3 \cdot (OEt)_2$)[87] generated the desired free alcohol lactone **2.22** with better results. Subsequent conversion of the primary alcohol to the iodide **2.17** was accomplished using a modified Appel reaction.[88,89]



Conditions and reagents: (i) $BF_3.(OEt)_2$, CH_3CN, 0 °C, 2hrs, 81%; (ii) PPh_3, I_2, imidazole, CH_3CN/diethyl ether, 0 °C-rt, 6 hrs, 33%.

Scheme 2.4: Improved deprotection of TBS ether

Alkylation of 2-methyl-1,3-cyclohexadione (**2.24**) with our lactone-iodide (**2.17**) using Fuji's conditions[90] was unsuccessful. Several published procedures[90-93] achieved 2-alkylation of 2-methyl-1,3-cyclohexadione, but the alkylating agents employed were methyl-, allyl, or benzyl halides or simple enones, i.e. relatively active alkylating agents. Our primary alkyl halide, lactone **2.17**, is most likely an insufficiently active alkylating agent to achieve alkylation of 2-methyl-1,3-cyclohexadione at the 2-position.

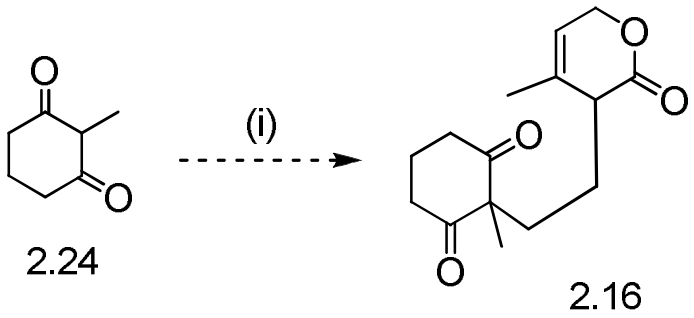


Figure 2.6: Unsuccessful alkylation of 2-methyl-1,3-cyclohexadione with primary alkyl iodide

RETROSYNTHETIC ANALYSIS II

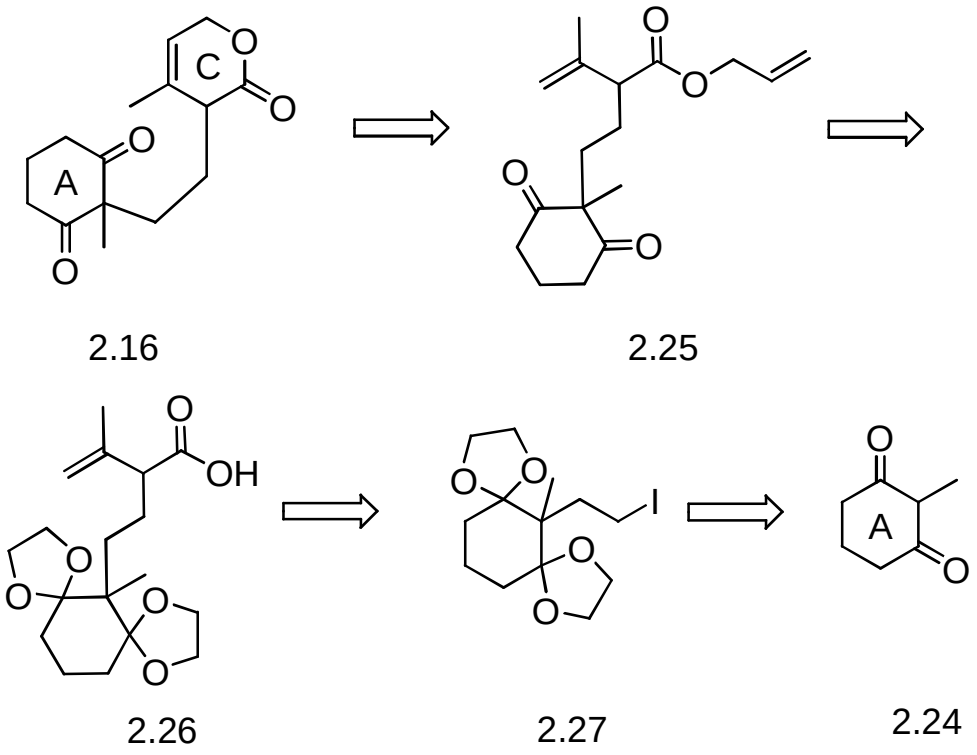
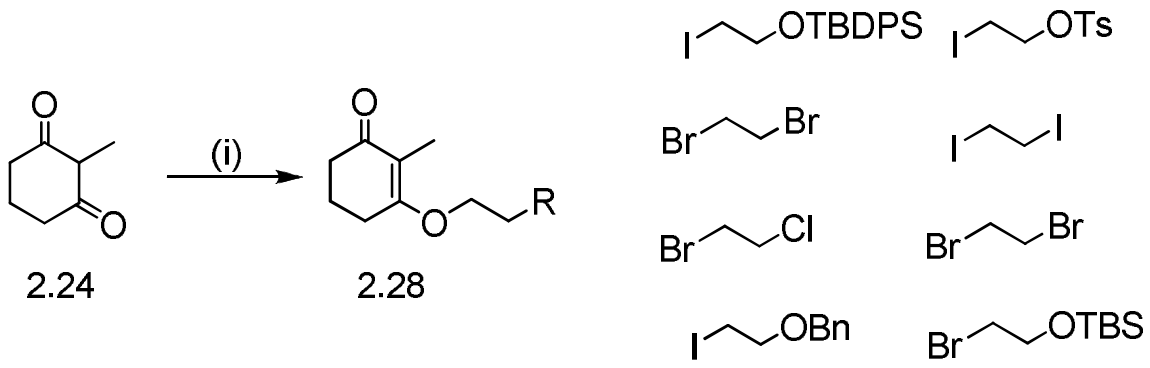


Figure 2.7: Retrosynthesis II

After failing to make the AC bicyclic intermediate **2.16**, the synthetic route was modified. The revised route included **2.16** as an intermediate, but a different approach was designed to arrive at the tethered lactone. Whereas the initial forward route began with the formation of the lactone C-ring then attachment of the A-ring (Retrosynthetic Analysis 1, Figure 2.5), the revised approach began with the A-ring **2.24** then the formation of the C-ring at the end of the sequence to arrive at the common intermediate **2.16**.

FORWARD ROUTE II

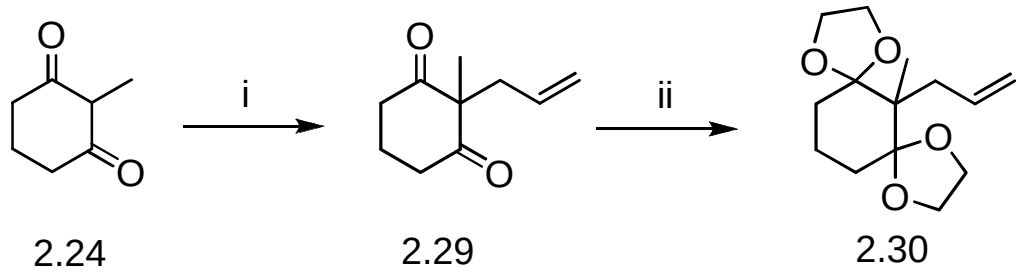
The initial approach in this route was to alkylate 2-methyl-1,3-cyclohexadione (**2.24**) with a two carbon reagent. Several substrates were evaluated, initially in THF then in DMSO and DMF (Scheme 2.5). The desired product was never obtained; invariably the product of these reactions was the O-alkylated enol ether (**2.28**).



Conditions and Reagents: (i) DBU, LiI, alkylating agent, THF, reflux.

Scheme 2.5: Attempts to alkylate 2-methyl-1,3-cyclohexadione

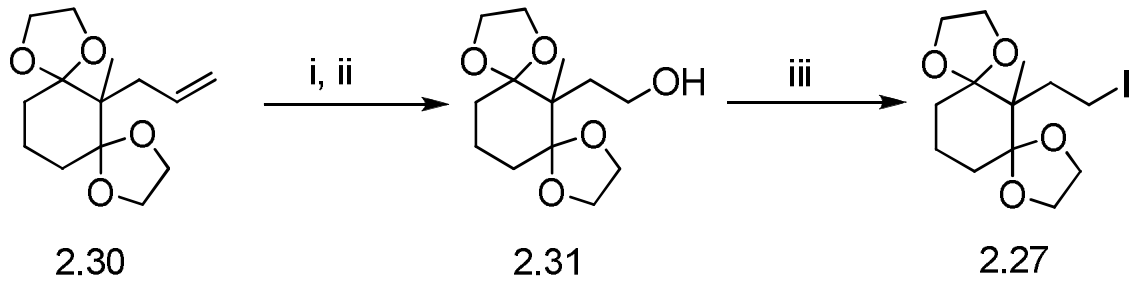
The inability to alkylate 2-methyl-1,3-cyclohexadione with these primary halides and the lactone primary halide **2.17** led us to employ a more reactive alkylating agent, allyl iodide. Following the procedure directly from Fuji's paper[90] the allylation of 2-methyl-1,3-cyclohexadione (**2.24**) was accomplished (Scheme 2.6). Although the yield for this reaction was excellent (93%), the disadvantage to this method was the inclusion of an extra carbon atom. Additional steps, including ketal-protection of the two carbonyls, cleavage of the olefin and an iodination step would add to the total number of synthetic steps of this route.



Conditions and Reagents: (i) DBU, LiI, allyl iodide, THF, 80 °C, 12hrs, 95%; (ii) $(CH_2OH)_2$, $CH(OMe)_3$, *p*-TSA, CH_2Cl_2, 40 °C, 12hrs, 93%.

Scheme 2.6: 2-Methyl-1,3-cyclohexadione alkylation

In order to prevent the reduction of the two ketones during the subsequent borohydride reduction, the carbonyls of the allylated cyclohexadione **2.29** were protected using ethylene glycol under acidic conditions[94] to yield the bis-ketal **2.30**.

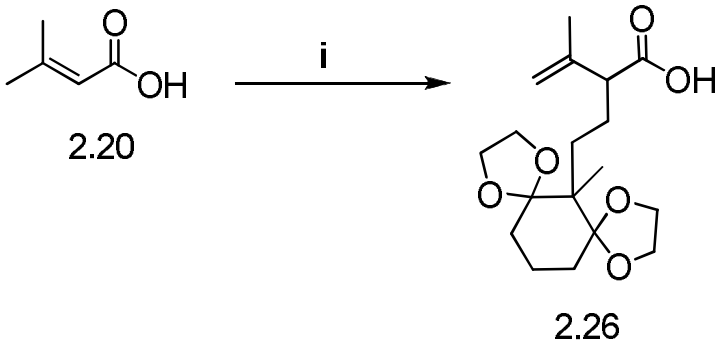


Reagents and Conditions: (i) O_3, -78 °C, CH_2Cl_2; (ii) $NaBH_4$ then NH_4Cl, 45% two steps; (iii) PPh_3, I_2, imidazole, THF, 0 °C-rt, 6 hrs.

Scheme 2.7: Ozonolysis, reduction and iodination

Ozonolysis of the terminal olefin of **2.30** followed by reduction in the same pot by sodium borohydride[95] afforded the primary alcohol **2.31** (Scheme 2.7). The alcohol was then converted to the primary iodide **2.27** using conditions previously employed in Scheme 2.4.[88]

With iodide **2.27** in hand, the next step was alkylation of 3,3-dimethylacrylic acid (**2.20**) with **2.27**. The reaction was attempted several times, albeit unsuccessfully. We eventually learned that the issue was the stability of the iodide; it decomposed rapidly after purification despite being stored at -20 °C. A typical reaction sequence involved synthesizing, purifying and characterizing the iodide on one day, storing it in the freezer overnight, then using it the following day for the subsequent alkylation of 3,3-dimethylacrylic acid. The NMR spectrum of the freshly purified iodide was clean, but NMR analysis of the same sample 24 hours later provided an unintelligible spectrum. This problem was addressed by synthesizing and purifying the iodide early in the morning, then using it immediately for the next step. The result was a two-step aggregate yield of 84% from the primary alcohol **2.31** to the alkylated acid **2.26** (Scheme 2.8).

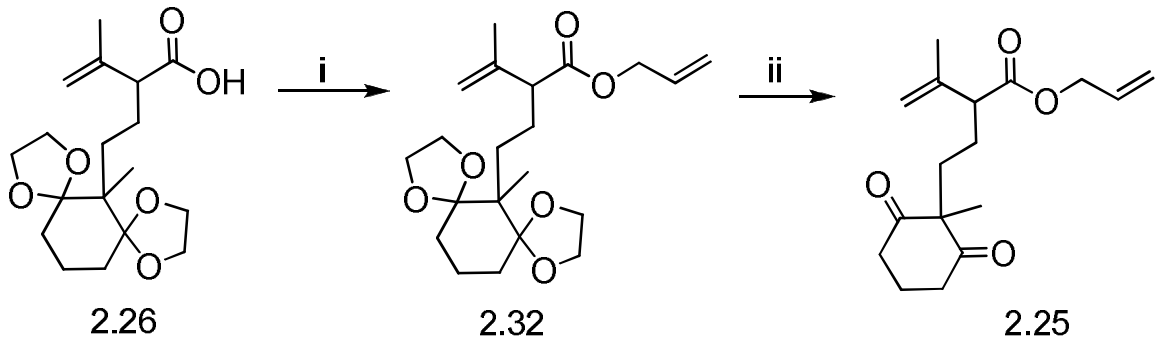


2.20 2.26

Conditions and Reagents: (i) 2 equiv. LDA, -78 °C, then 2.27, 66% from 2.31.

Scheme 2.8: 3,3-Dimethylacrylic acid alkylation

The following step (Scheme 2.9) was the allyl esterification of carboxylic acid **2.26** using previously optimized conditions.[84] Hydrolysis of the bis-ketal (**2.32**) to diketone **2.25** was accomplished using 3:1 1M HCl:acetone at 60 °C.



Conditions and Reagents: (i) Cs_2CO_3, allyl iodide, THF, 65 °C, 16 hrs, 99%; (ii) 3:1 acetone:1M HCl, 60 °C, 3 hrs, 81%

Scheme 2.9: Esterification and deprotection

Once again, we had a viable substrate for the ring-closing metathesis reaction. When the RCM reaction was performed by simply refluxing a mixture of diene and catalyst in CH_2Cl_2, analysis confirmed that the major product was the intermolecular, cross-metathesis triene product **2.33** (R = 1-methyl, 2,6-cyclohexyl). Diluting the reaction to concentrations as low as 0.00001M did not significantly decrease the formation of the undesired intermolecular cross-metathesis product (**2.33**). Figure 2.8 demonstrates how the steric bulk of the disubstituted olefin of compound **2.34** hinders reaction with the sterically crowded Ruthenium carbene of Grubbs' catalyst **(2.35)** as compared to the less hindered monosubstituted olefin.

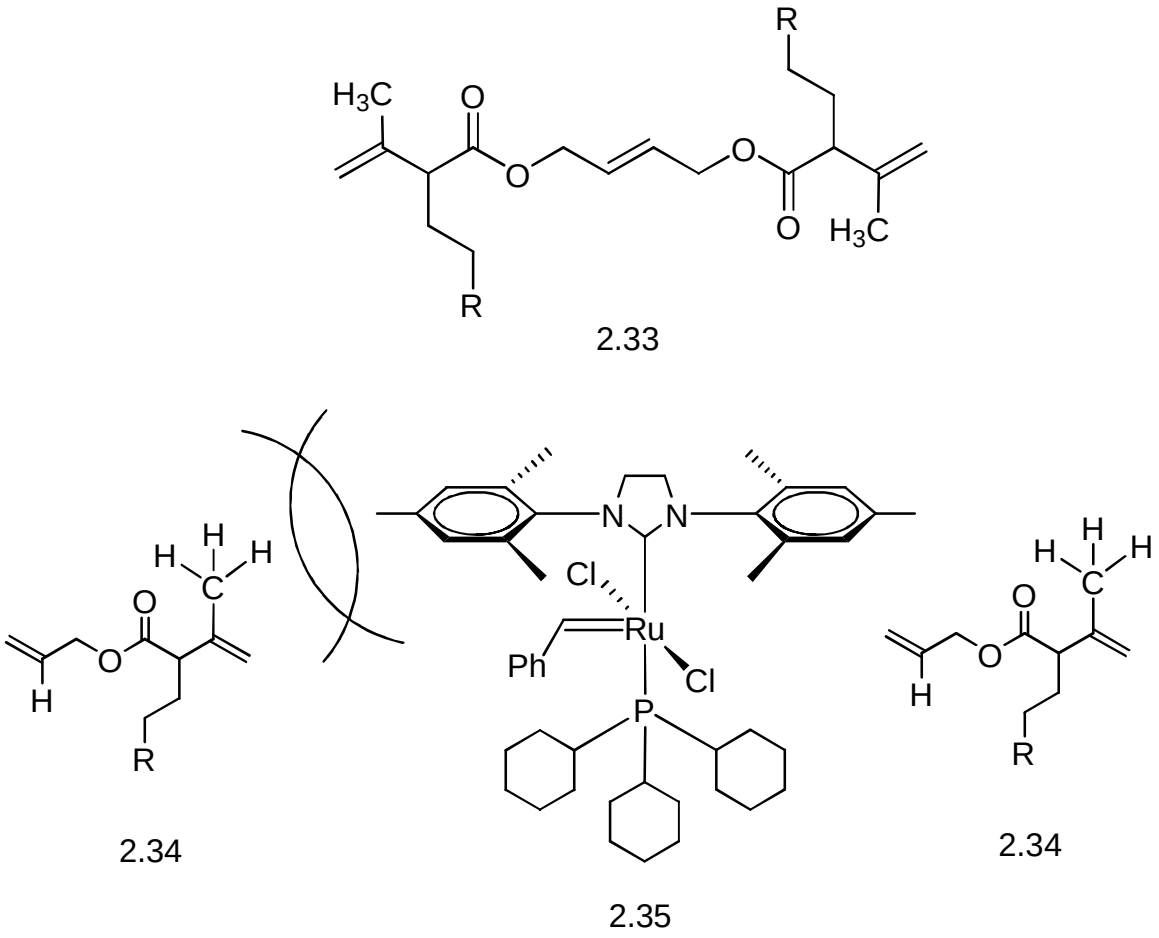
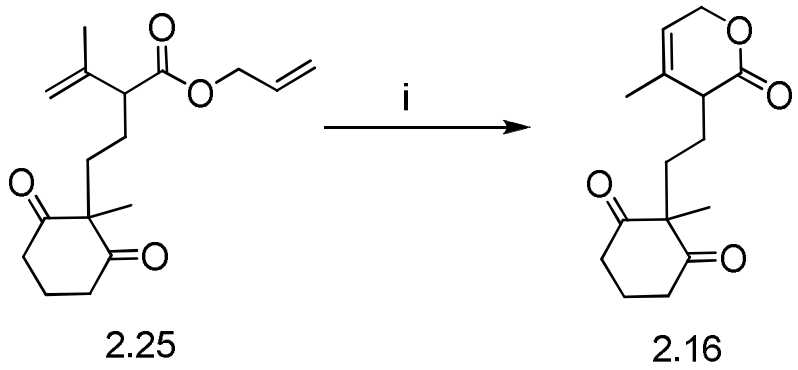


Figure 2.8: Preference for intermolecular cross-metathesis

The problem of intermolecular cross-metathesis was circumvented by the use of a syringe pump which slowly added the substrate to the reaction vessel. The syringe was loaded with a solution of ester and catalyst (reaction did not proceed at room temperature), and was added dropwise over 2 hours to a refluxing solution of catalyst. Intermolecular metathesis was minimized by adding the ester to a heated, "activated" solution of catalyst that presumably catalyzed the desired intramolecular reaction soon after the ester molecules were introduced into this hot solution. 10 mole % of catalyst was divided equally between the reaction vessel and the syringe in the syringe pump. The

introduction of more catalyst with every drop ensured that fresh, active catalyst was present for the duration of the reaction, although the reaction was never attempted with the entire quantity of catalyst in the reaction vessel. This technique improved the reaction yield from ~30% to ~70%.

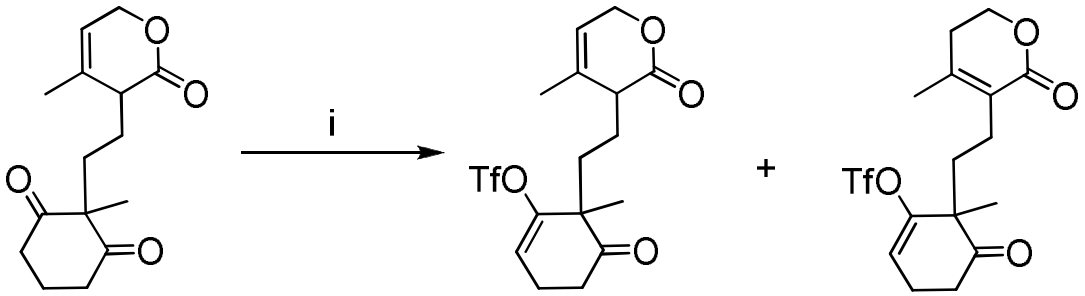


Reagents and Conditions: (i) Grubbs' II, 10 mol%, CH_2Cl_2, 40 °C, 3hrs, 68%.

Scheme 2.10: Ring-closing metathesis

The next step involved the conversion of one of the cyclohexadionedione carbonyl groups to a vinyl triflate. Initially the goal was to synthesize salvinorin A then perform the synthesis asymmetrically. For the purpose of this route, an asymmetric deprotonation was deemed unnecessary. Several conditions for the vinyl triflate synthesis were examined. Using 2,6-di-*tert*-butylpyridine and triflic anhydride resulted in recovery of the cyclohexadionedione starting material. Using phenyl triflimide in combination with LDA, lithium or potassium hexamethyldisilazide also did not produce the vinyl triflate. The successful conditions for vinyl triflate synthesis employed the use of Comins' reagent[96] (N-(5-Chloro-2-pyridyl)bis(trifluoromethanesulfonimide)) in combination with lithium hexamethyldisilazide (Scheme 2.11). In addition to obtaining

lactone **2.36**, the conjugated lactone **2.37** was also observed. The Rf of this product was very close to the Rf of the desired product, making the two compounds almost impossible to separate via column chromatography.

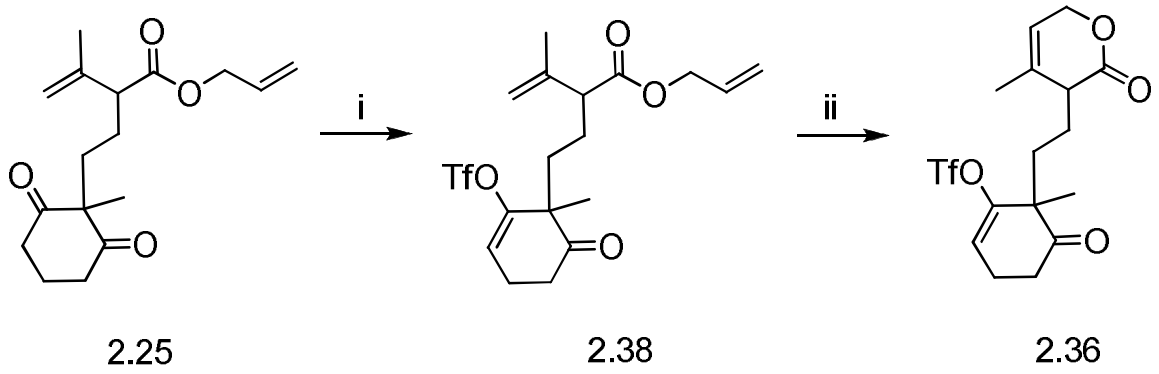


2.16 2.36 2.37

Conditions and Reagents: (i) LiHMDS, N-(5-chloro-2-pyridyl)triflimide, THF, -78 °C-rt, 6 hrs.

Scheme 2.11: Carbonyl to vinyl triflate on lactone

This problem was solved by swapping the order of the RCM and triflate synthesis reactions (Scheme 2.12). The triflate synthesis conditions were applied to the ester **2.25** (before the RCM reaction). The vinyl triflate ester **2.38** was obtained with no olefin conjugation product. The RCM was then performed on this ester to give the lactone vinyl triflate **2.36**. With this compound in hand, the key intramolecular Heck reaction to synthesize the tricyclic core of salvinorin A could be attempted.



Reagents and Conditions: (i) LiHMDS, N-(5-chloro-2-pyridyl)triflimide, THF, -78 °C-rt, 6 hrs, 69%; (ii) Grubbs' II, 10 mol%, CH_2Cl_2, 40 °C, 73%.

Scheme 2.12: Carbonyl to vinyl triflate on ester

In efforts to synthesize tricyclic lactone **2.39** via an intramolecular Heck reaction, several reaction conditions were examined. Different combinations of palladium source ($Pd(OAc)_2$, $Pd(tri\text{-}o\text{-}tolylphosphine)_2Cl_2$), base ($NEt_3$, K_2CO_3, KOAc, diisopropylamine), reducing ligand (PPh_3, nBu_4NCl, 1,4-bis(diphenylphospino)butane), solvent (CH_3CN, DMF, DMA, THF) and temperature were screened for the Heck reaction, but none were

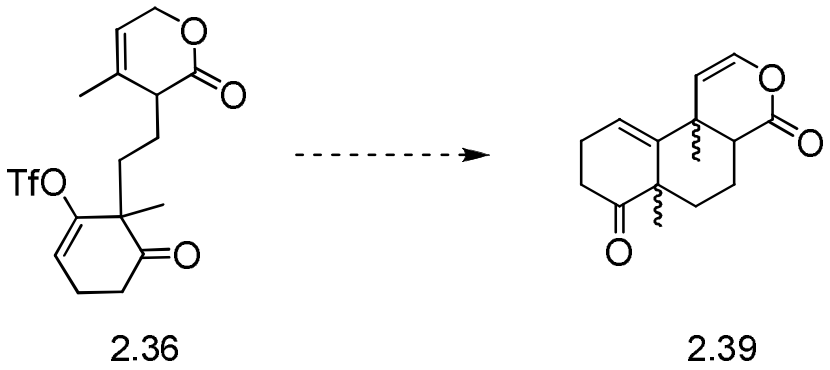


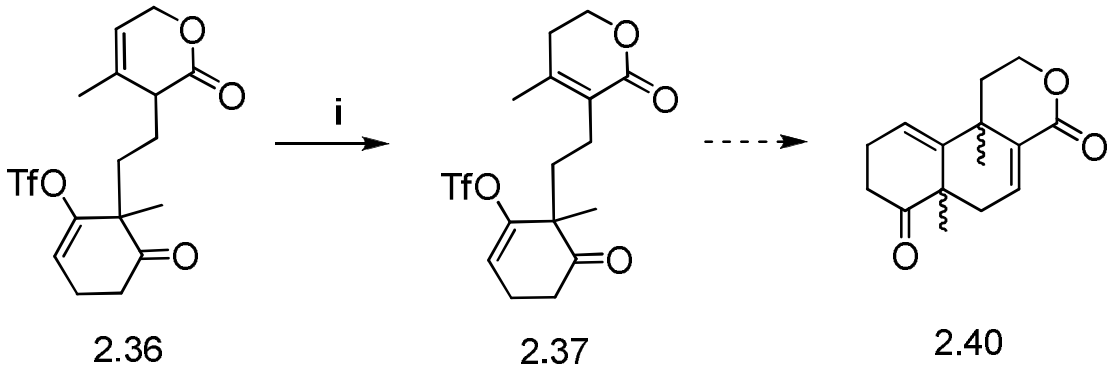
Figure 2.9: Tricyclic lactone from Heck reaction on vinyl triflate

successful (Figure 2.9).[80, 97-100] Of the products obtained, only recovered starting material and the reduced product were positively identified.

After being unable to obtain the desired tricyclic product from substrate **2.36**, a different substrate was examined. A successful Heck reaction on conjugated lactone **2.37** would result in the conjugated tricyclic product **2.40** (Scheme 2.13), which could still be transformed into salvinorin A. The conversion of the lactone vinyl triflate **2.36** to the conjugated lactone **2.37** was accomplished using DBU.[101] The Heck reaction was attempted on the conjugated lactone using the following conditions:

- Cl_2Pd(tri-o-tolylphosphine)$_2$, potassium acetate, dimethyacetamide, 60 °C
- Cl_2Pd(tri-o-tolylphosphine)$_2$,diisopropylamine, dimethyacetamide, 60 °C
- Cl_2Pd(tri-o-tolylphosphine)$_2$,diisopropylamine, dimethyacetamide, 90 °C
- $Pd(OAc)_2$, triphenylphosphine, triethylamine, dimethyacetamide, 80 °C
- $Pd(OAc)_2$, triphenylphosphine, triethylamine, dimethyformamide, 80 °C
- $Pd(OAc)_2$, 1,4-bis(diphenylphospino)butane, triethylamine, dimethyformamide, 80 °C

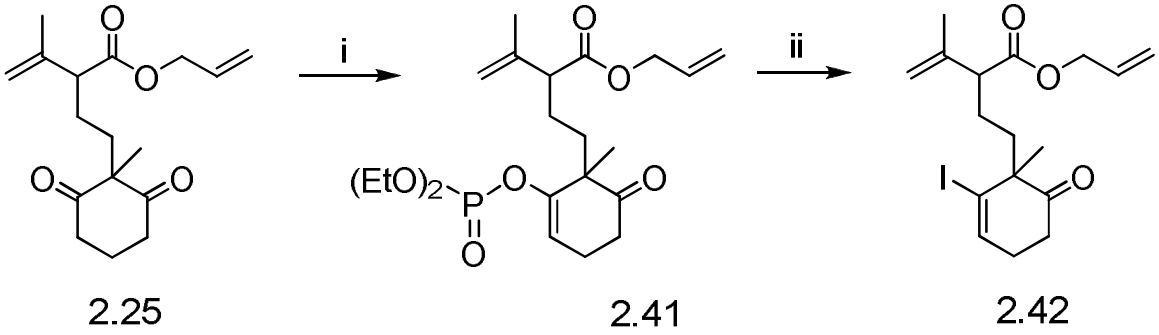
For these reactions, thin layer chromatography (TLC) displayed one new less polar product whose structure was not identified. Analysis by NMR confirmed this was not the desired product.



Reagents and Conditions: (i) DBU, THF, rt, 2.5hrs, 89%.

Scheme 2.13: Conjugation of β,γ-unsaturated lactone

Vinyl iodides are also substrates for Heck reactions.[102] Vinyl iodides are made from carbonyl compounds via a vinyl phosphonate intermediate.[103] Ester **2.25** was converted to the vinyl phosphonate **2.41** which was then converted to vinyl iodide **2.42** (Scheme 2.14).[104] Unfortunately, the best yield for this reaction was prohibitively low (7%), precluding the Heck reaction attempt with a vinyl iodide substrate.



Reagents and Conditions: (i) LiHMDS, diethyl chlorophosphonate, THF, -78 °C-rt, 6 hrs, 69%; (ii) TMSI, CH_2Cl_2, 0 °C, 7%.

Scheme 2.14: Vinyl iodide synthesis

RETROSYNTHETIC ANALYSIS III

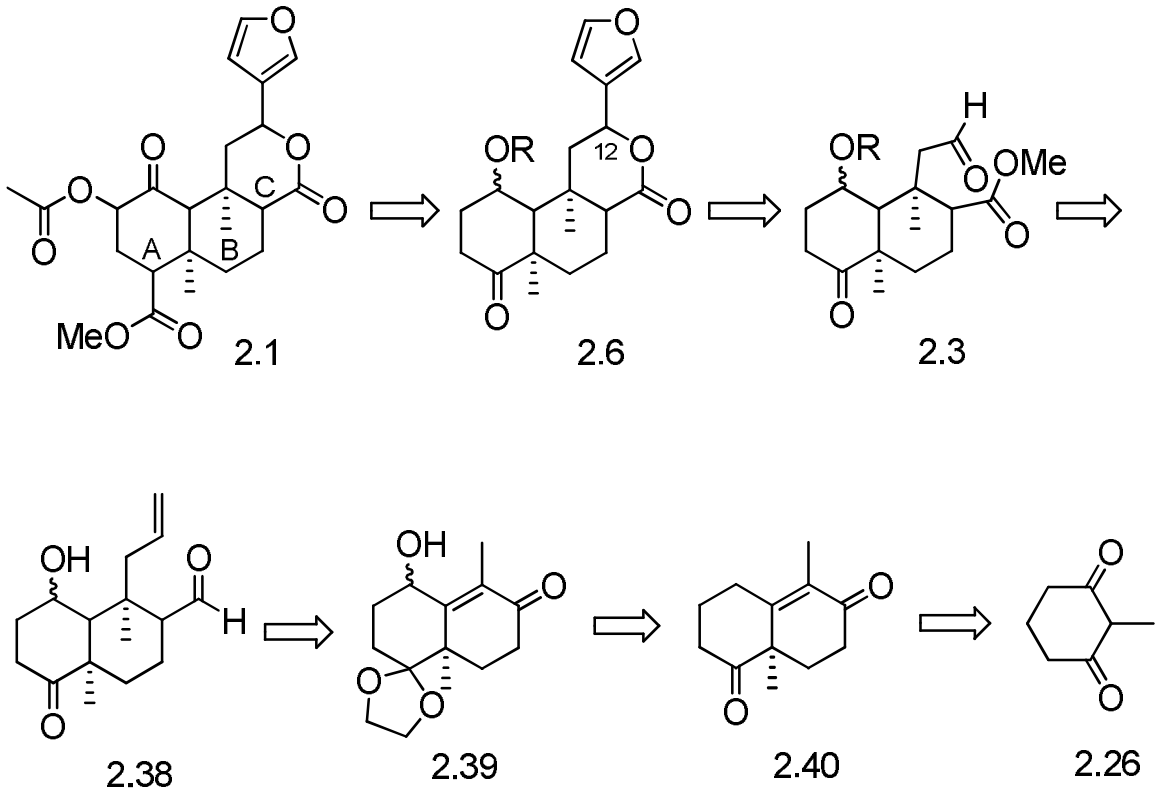


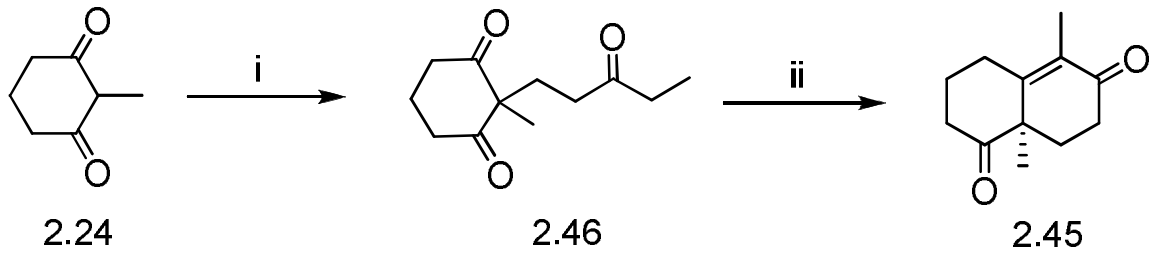
Figure 2.10: Retrosynthesis III

After being unable to complete the key step of the previous routes, an entirely new synthetic approach was undertaken. In keeping with the idea that we wanted a molecule that allowed for C12 substitutions late in the synthesis, a new route was designed that contained the familiar bicyclic δ-carboxy ester **2.3** (Figure 2.10). Whereas the previous routes focused on making the A and C rings first, this new approach began by synthesizing the fused AB-bicyclic compound **2.45** as one of the first steps. 2-methyl-1,3-cyclohexadione (**2.24**) would still become the A-ring of salvinorin A, although by an entirely different approach.

One advantage of this approach is that the stereochemistry at C5 was set very early in the synthesis. The synthesis of compound **2.45** and variations thereof are chemical reactions that are well-established in the chemical literature.[105- 107] Compound **2.45** is a variant of the Wieland–Miescher ketone (WMK), which was the AB-ring basis for many steroid syntheses from the 1950s to the 1970s.[108] The modification to the classic WMK is the inclusion of the C20 methyl group.

FORWARD ROUTE III

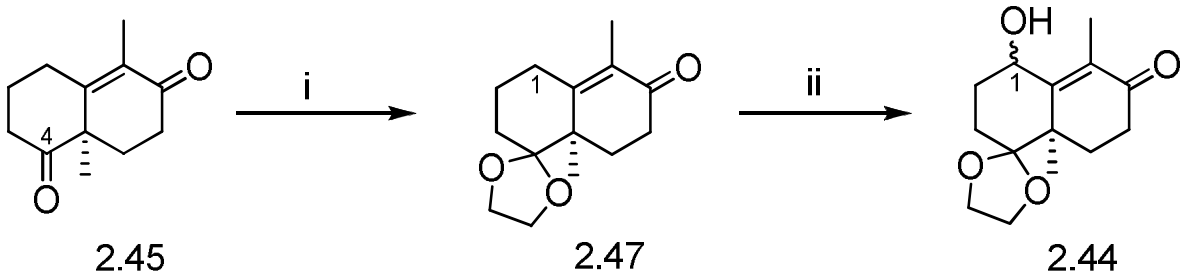
Alkylation of 2-methyl-1,3-cyclohexadione (**2.24**) with the strong electrophile ethyl vinyl ketone was accomplished with the aid of a catalytic amount of potassium hydroxide in methanol (Scheme 2.15). A typical work-up was not necessary for this reaction; removal of methanol under vacuum followed by column chromatography of the resulting thick oil was sufficient. The asymmetric annulation of the resulting triketone **2.46** required a distinct set of reaction conditions.[105] A solution of a stoichiometric amount of D-phenylalanine along with half an equivalent of (1S)-(+)-10-Camphorsulfonic acid in DMF was stirred at room temperature for 24 hours. Each day, the temperature was increased by 10 $^{\circ}$C and after the fifth day the reaction was quenched, worked up and purified.



Reagents and Conditions: (i) KOH, ethyl vinyl ketone, MeOH, 65 °C, 12 hrs, 93%; (ii) D- β-phenylalanine, D-camphorsulfonic acid, DMF, rt-70 °C, 5 days, 90% yield, 84% ee, determined by chiral HPLC.

Scheme 2.15: Synthesis of C12 variant of Wieland-Miescher Ketone

After protecting the C4 ketone of bicyclic ketone **2.45** as the ketal (Scheme 2.16), the C1 allylic alcohol was installed by bubbling oxygen through a heated solution of the enone in 3:1 methanol:20 % KOH.[109]



Reagents and Conditions: (i) $(CH_2OH)_2$, $CH(OMe)_3$, *p*-TSA, CH_2Cl_2, 40 °C, 16 hrs, 89%; (ii) 3:1 MeOH:20%KOH, O_2, 60 °C, 12hrs, 76 %.

Scheme 2.16: Allylic oxidation

The next step in the synthesis was the C12 alkylation of α-methyl enone **2.44** (Figure 2.11). The first reaction we tried was a reductive alkylation using a solution of lithium metal in liquid ammonia. These reaction conditions create what is effectively a solution of free electrons that is denoted by a deep blue color. The solvated electrons

transform an enone into an enolate anion which can be trapped or alkylated at the α position.

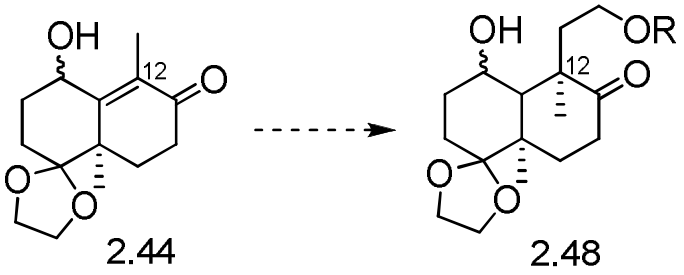
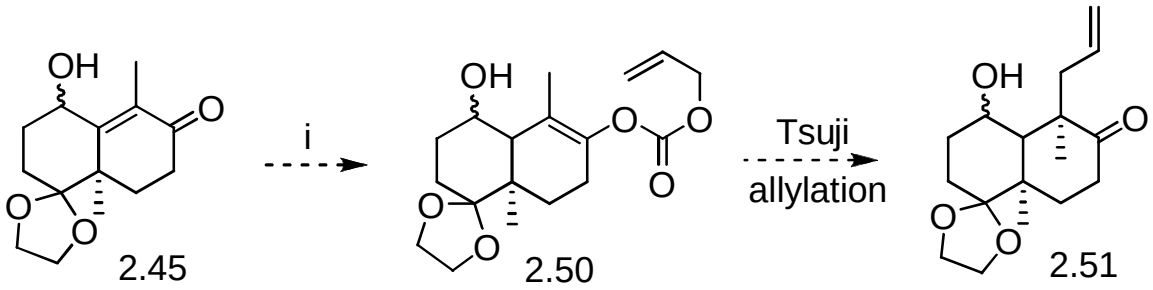


Figure 2.11: Reductive alkylation at C12

The "trapping reagent" used was allyl chloroformate. The resulting allyl vinyl carbonate (**2.49**) was going to be used as a substrate for a Tsuji allylation[110] but the reductive alkylation was unsuccessful (Scheme 2.17).

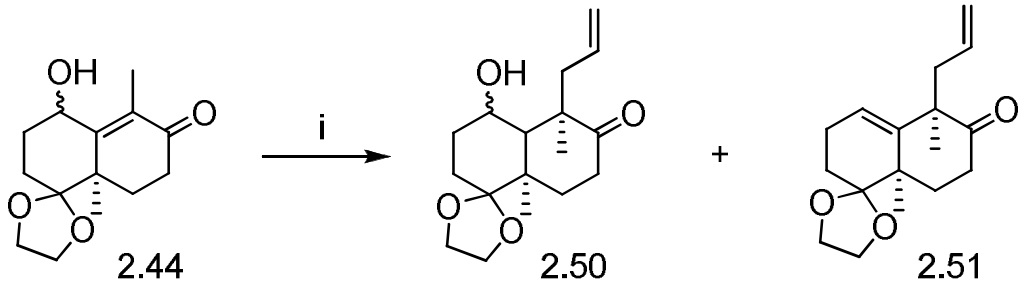


Reagents and Conditions: (i) Li^{o}, NH_3, allyl chloroformate, THF.

Scheme 2.17: Reductive alkylation attempt to synthesize Tsuji allylation substrate

The next approach was to directly obtain the allylated product **2.50** by using allyl iodide as the alkylating agent.[111, 112] Although the reaction worked, the yield was consistently less than 15% (Scheme 2.18). Several modifications were made in attempt to improve the yield. The reaction was run at different temperatures (-33 °C and -78 °C). The

order of addition of lithium and ammonia was swapped. Different lithium sources were utilized (slurry in oil and pure metal strips) .The reaction duration was varied from 10 minutes to 24 hours and in between. Isoprene was added to quench the excess electrons.[111] Methanol or *tert*-butanol was added to aid the protonation of the intermediate radical carbanion. The stoichiometries of lithium and allyl iodide were varied. The concentrations of enone substrate and allyl iodide solutions were changed. The reaction-quenching approach was modified (saturated ammonium chloride and solid ammonium chloride). Allyl iodide was replaced with allyl bromide. Despite these modifications, the yield never improved beyond 35%.

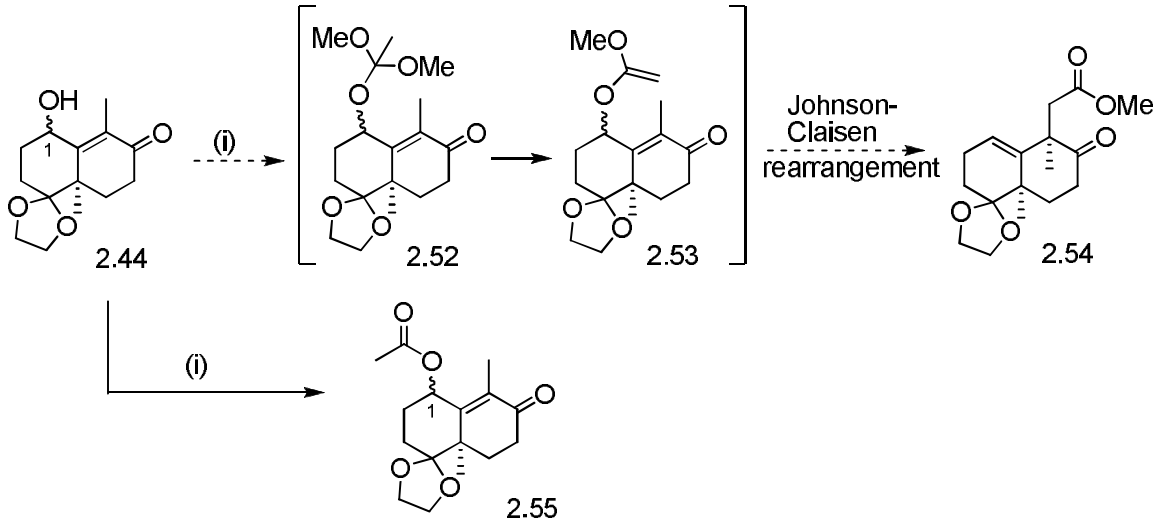


Reagents and Conditions: (i) Li^{o}, NH_3, allyl iodide, THF, 2.50 = 35 %, 2.51 > 60 %.

Scheme 2.18: Reductive alkylation with allyl iodide

The major product (60-70 %) of the reductive alkylation was the elimination product **2.51**. When the secondary alcohol was protected as the TBS ether or the methoxymethyl (MOM) acetal, the relative amount of the elimination product increased (>80%). Ozonolysis at low temperature and short reaction time was attempted on **2.51** to try and take advantage of the steric differences around the two olefins, but ozone reacted with both olefins.

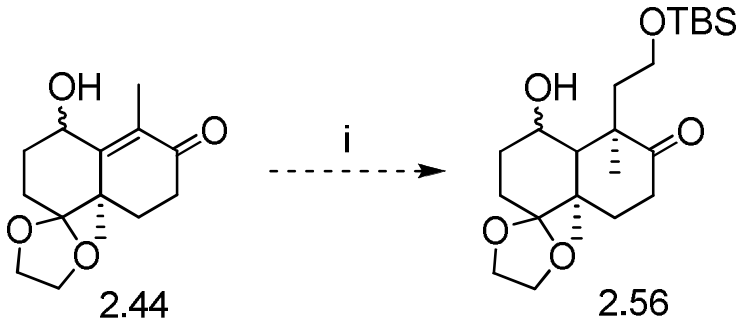
Due to the low yield of the reductive alkylation, alternative non-nucleophilic quaternary carbon-creating approaches were also investigated. The allylic alcohol motif of **2.44** led us to examine the Johnson-Claisen rearrangement.[113] Allylic alcohol **2.44** was reacted with trimethyl orthoacetate with the use of propionic acid as a catalyst, but the desired rearrangement product **2.54** was not observed (Scheme 2.19). The only observed product was the C1 acetate ester **2.55**.



Reagents and Conditions: (i) $CH_3C(OMe)_3$, propionic acid, 90 °C.

Scheme 2.19: Johnson-Claisen rearrangement attempt

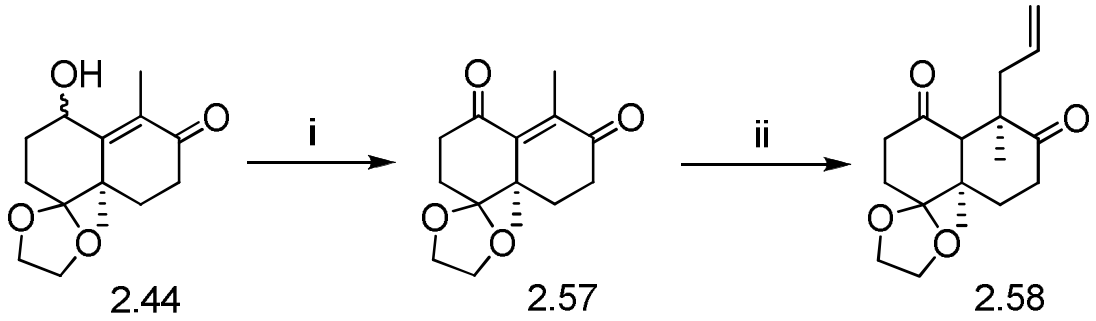
The reductive alkylation was also re-examined using TBS-protected 2-iododethanol as the alkylating agent, but the desired product was not observed (Scheme 2.20).



Reagents and Conditions: (i) Li^o, NH_3, $I(CH_2)_2OTBS$, THF.

Scheme 2.20: Reductive alkylation with a primary alkyl iodide

Finally, a reductive alkylation reaction was attempted using enedione **2.57** as the substrate.[114] The allylic alcohol **2.44** was oxidized to enedione **2.57** using pyridinium chlorochromate (PCC) (Scheme 2.21).[115] Reductive alkylation was then attempted on **2.57**, but the yield was prohibitively low.

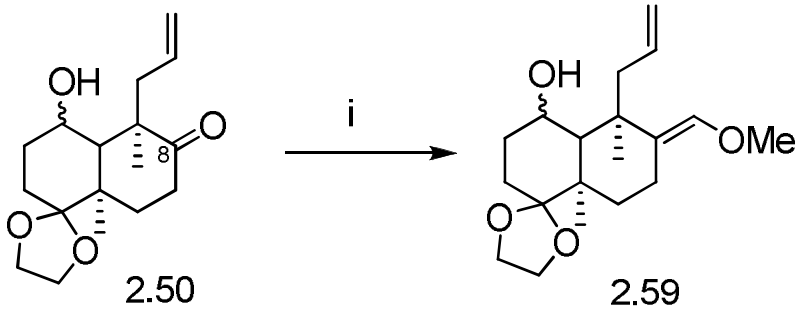


Reagents and Conditions: (i) PCC, CH_2Cl_2, 66%, (ii) Li^o, NH_3, allyl iodide, THF, 6 %.

Scheme 2.21: Oxidation to enedione and subsequent reductive alkylation

Moving forward with compound **2.50**, the next step was the homologation of the C8 ketone (Scheme 2.22). For the synthesis of salvinorin A, C8 would require the conversion of the ketone to an intermediate ester. A Wittig reaction was performed using

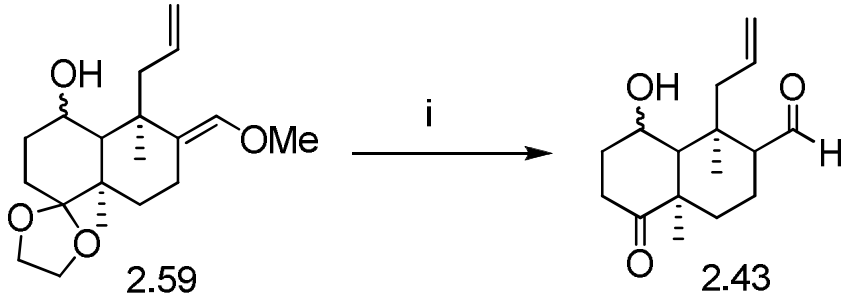
methoxymethyl-phosphonium chloride.[116] Methoxymethyl-phosphonium chloride converts the C8 carbonyl to the aldehyde synthon methyl vinyl ether **2.59**.



Reagents and Conditions: (i) Ph_3PCH_2OMeCl, KOtBu, DMSO,0-60 °C, 12hrs, 72 %.

Scheme 2.22: Wittig homologation

The acid-catalyzed hydrolysis of the methyl vinyl ether yielded the C8 aldehyde and also hydrolyzed the ketal to give ketone-aldehyde **2.43** (Scheme 2.23).

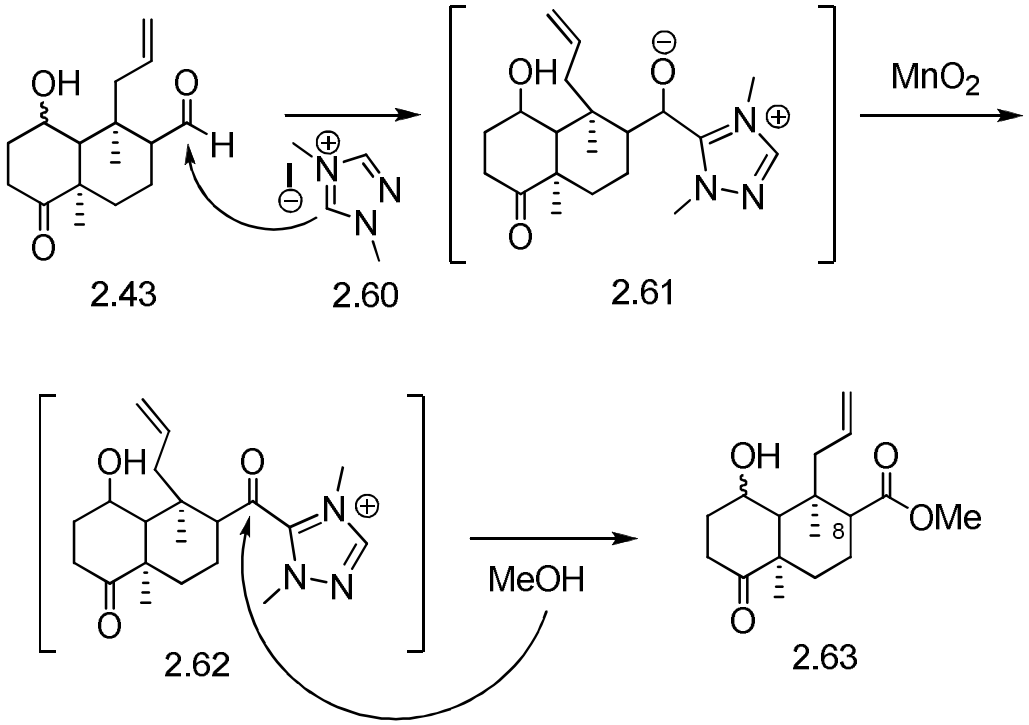


Reagents and Conditions: (i) CH_3CN/3M HCl, 6 hrs, 81 %.

Scheme 2.23: Enol ether hydrolysis

The oxidation of aldehyde **2.43** and the esterification of the intermediate acid were accomplished in one step. The N-heterocyclic carbene (NHC) 1,4-dimethyl-1,2,4-triazolium iodide **2.60** was employed as a catalyst for the transformation (Scheme

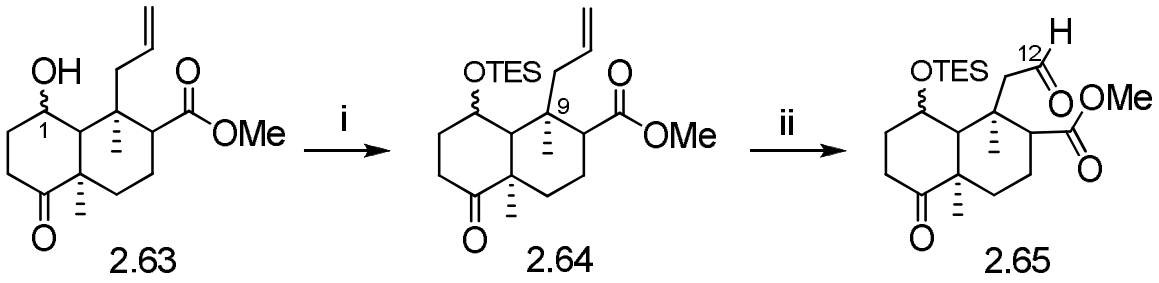
2.24).[117] Upon reaction of the catalyst with aldehyde **2.43**, the transient allylic alcohol **2.61** was generated, which was oxidized by manganese dioxide. Methanol performed a nucleophilic acyl substitution to displace and regenerate the NHC catalyst, yielding methyl ester **2.63** in the process.



Reagents and Conditions: 1,4-dimethyl-1,2,4-triazolium iodide, MnO_2, DBU, MeOH, CH_2Cl_2, 55 %.

Scheme 2.24: NHC-catalyzed oxidation/esterification

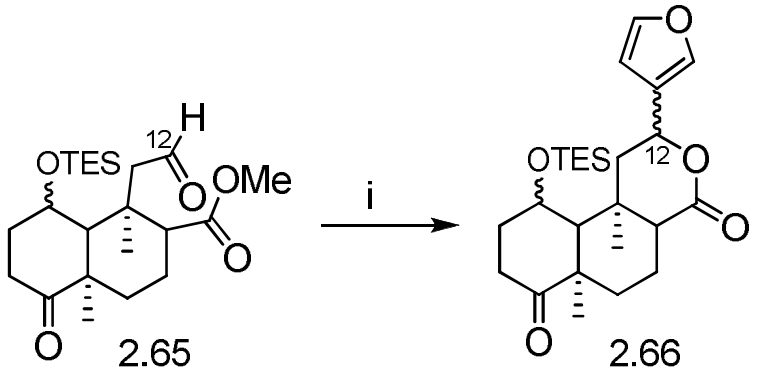
With the installation of the C8 ester complete, one of the requisite components of the C-ring of salvinorin was in place. The C1 secondary alcohol **2.63** was protected as the triethylsilyl (TES) ether to prevent the potential formation of a hemi-acetal in the subsequent step (Scheme 2.25). The ozonolysis of the olefin to yield aldehyde **2.65** gave us the bicyclic δ-carboxy ester **2.65** we required to make C12 analogs of salvinorin A.



Reagents and Conditions: (i) TESOTf, pyridine, DMAP, DMF, 95 °C, 46 %; (ii) O_3, CH_2Cl_2, -78 °C, 83 %.

Scheme 2.25: Ozonolysis to give δ-carboxy ester

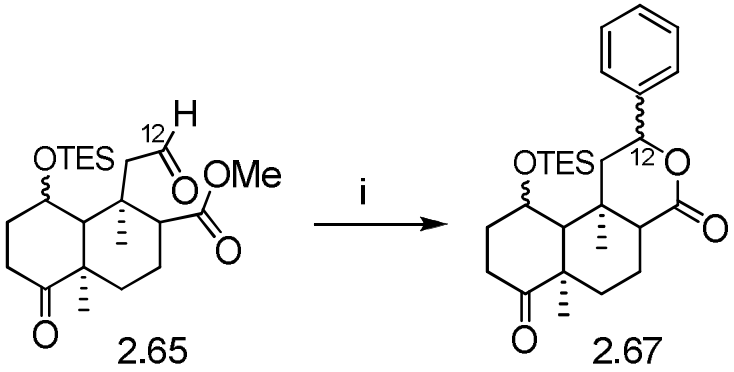
In order to synthesize a compound that is a precursor to salvinorin A, compound **2.65** was reacted with one equivalent of 3-furyllithium to give **2.66** in 53 % yield. The significance of this reaction is that it demonstrates that bicyclic δ-carboxy ester **2.65** can serve as a precursor molecule to salvinorin A.



Reagents and Conditions: (i) 3-furyllithium, -78 °C to rt, 53 %.

Scheme 2.26: Furan addition to δ-carboxy ester

In order to demonstrate the utility of compound **2.65**, it was reacted with phenyllithium to give **2.67**. The successful completion of this reaction exhibits the usefulness of δ-carboxy ester **2.65** as a platform for C12 analogs of salvinorin A.



Reagents and Conditions: (i) phenyllithium, -78 °C to rt, 19 %.

Scheme 2.27: Phenyl addition to δ-carboxy ester

CONCLUSION

The total synthesis of the kappa opioid agonist salvinorin A was attempted via three synthetic routes. Although the approaches employed for these routes were different, the preliminary goal common to the three routes was the synthesis of a common bicyclic δ-carboxy ester intermediate. The value of the bicyclic δ-carboxy ester intermediate is that it serves as a branch point for the synthesis of a variety of salvinorin analogs differing in the functional group bonded to C12. The overwhelming majority of existing C12-modified salvinorin analogs exhibit poor biological activity.[54-59] The capacity for the bicyclic δ-carboxy ester intermediate to accept different nucleophiles makes it an exceptional candidate for the synthesis of novel, chemically diverse C12-modified salvinorin analogs.

Although the first route was unsuccessful, the efforts made toward this route (e.g. di-anion α-alkylation, ring-closing metathesis) established reaction conditions that were

useful for subsequent efforts. The second route achieved the synthesis of the key intramolecular Heck reaction substrate **2.36**. This allowed for the unprecedented endeavor to synthesize a novel tricyclic enol-lactone compound via an intramolecular Heck reaction.

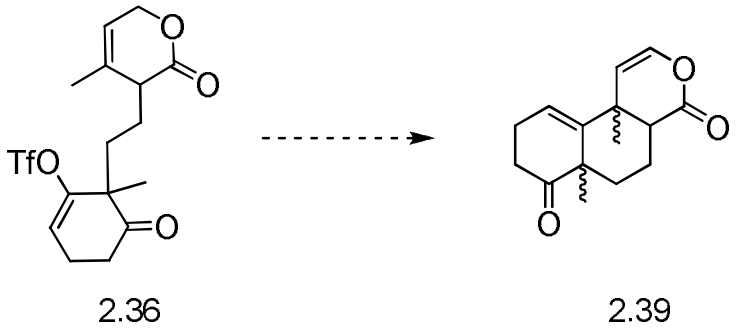


Figure 2.12: Attempt at intramolecular Heck reaction

The third route advanced the furthest and served as proof of principle of our idea that different nucleophiles can be added to the bicyclic δ-carboxy ester intermediate. Compound **2.66** is a precursor to salvinorin A while compound **2.67** features a phenyl ring at C12. Both compounds arise from addition a nucleophile to C12 of carboxy ester **2.65**.

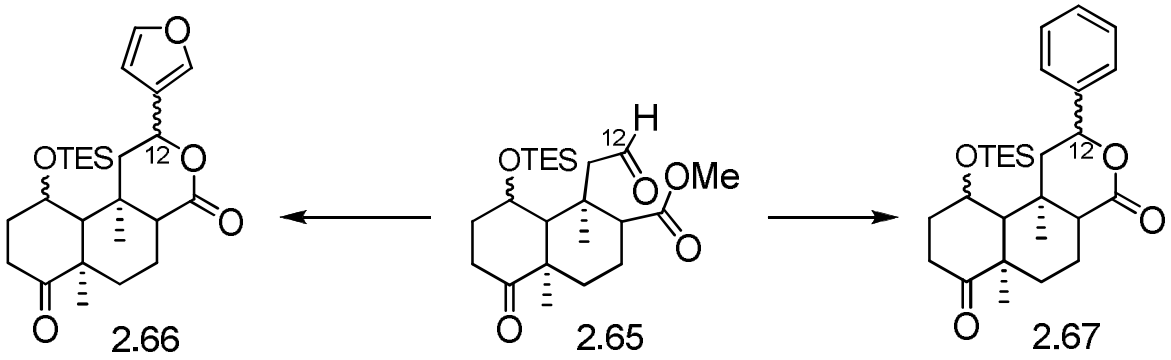


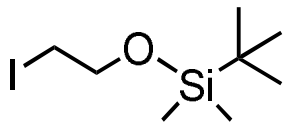
Figure 2.13: Different products from bicyclic δ-carboxy ester intermediate

EXPERIMENTAL

General Procedures

All chemicals were purchased from Acros Organics or Sigma-Aldrich Co. and used without additional purification unless otherwise noted. Innovative Technology solvent drying system was used to obtain anhydrous tetrahydrofuran, dichloromethane and acetonitrile. Reactions were monitored by thin layer chromatography using Silicycle glass backed extra hard 60 Å, F_{254}, 250 μm plates. Enantiomeric excess was measured using a Crawford Scientific Chiralpak AS-H HPLC column. Column chromatography was performed using Silicycle SiliaFlash P60, 230-400 mesh silica gel. ^{1}H and ^{13}C NMR spectra were obtained on JEOL ECX 400 and 500 NMR Spectrometers (400 MHz and 500 MHz, respectively). ^{1}H NMR spectra are reported in parts per million (δ) relative to tetramethylsilane. Coupling constants (J) are reported in Hertz. Unless noted otherwise, all reactions were carried out under N_2 atmosphere. All glassware was dried in an oven at 120 °C.

tert-butyl(2-iodoethoxy)dimethylsilane



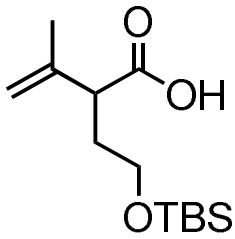
To a solution of 4-dimethylaminopyridine (0.1 g, 0.82 mmol) in CH_2Cl_2 (25 mL) was added 2-iodoethanol (4.37 g, 2 mL, 25 mmol). The resulting solution was cooled to 0 °C and triethylamine (2.83 g, 3.9 mL, 28 mmol, 1.1 equiv.) was added. After 30 minutes

of stirring, a solution of *tert*-butylchlorodimethylsilane (1 M in THF, 28 mL, 28 mmol, 1.1 equiv.) was added and the reaction was warmed to room temperature and allowed to proceed for 16 hours. The resulting precipitate was removed by filtration and the filtrate was concentrated under reduced pressure. The resulting residue was purified by flash chromatography, eluting with 9:1 hexane: ethyl acetate to give 6.52 g of the silyl ether (91%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.83 (t, J = 6.87 Hz, 2H), 3.20 (t, J = 6.87 Hz, 2H), 0.91 (s, 9H), 0.09 (s, 6H)

^{13}C NMR (400 MHz, $CDCl_3$) δ 64.3, 26.0, 18.4, 7.1

2-(2-(tert-butyldimethylsilyloxy)ethyl)-3-methylbut-3-enoic acid (2.19)



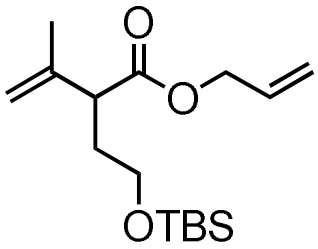
To a solution of diisopropylamine (3.36 g, 4.65 mL, 33.2 mmol, 2.2 equiv.) in THF (20 mL) at -78 °C was added a solution of n-butyllithium (13.3 mL, 2.5 M in hexanes, 2.2 equiv.). The reaction flask was placed into an ice bath and stirred for 15 minutes after which time the flask was placed back into the dry ice/acetone bath. A solution of 3,3-dimethylacrylic acid (1.51 g, 15.1 mmol, 1 equiv.) in THF (20 mL) was added dropwise to the lithium diisopropylamide (LDA) solution and the reaction flask was again placed into an ice bath, stirred for 15 minutes, then placed back into the dry

ice/acetone bath. A solution of *tert*-butyl(2-iodoethoxy)dimethylsilane (4.77 g, 16.6 mmol, 1.1 equiv.) in THF (20 mL) was then added dropwise and the reaction flask was removed from the dry ice/acetone bath and stirred for 16 hours. The reaction was quenched by the addition of 30 mL of saturated NH_4Cl (aq). The organic layer was collected and washed with brine (30 mL), dried with $MgSO_4$, filtered and concentrated under vacuum. The crude product was purified by flash chromatography using 3:1 hexane:ethyl acetate as the eluent to afford 3.28 g of the alkylated acid (84%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.96 (s, 1H), 4.94 (s, 1H), 3.67-3.58 (m, 2H), 3.29 (t, J = 7.45 Hz, 1H), 2.11-1.73 (m, 2H), 1.78 (s, 3H), 0.89 (s, 9H), 0.04 (s, 6H)

^{13}C NMR (400 MHz, $CDCl_3$) δ 180.0, 141.9, 114.6, 60.7, 49.4, 32.8, 26.0, 20.4, 18.3

allyl 2-(2-(tert-butyldimethylsilyloxy)ethyl)-3-methylbut-3-enoate (2.18)



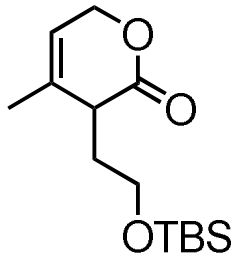
Cesium carbonate (3.35 g, 10.3 mmol, 1.1 equiv.) was added to a solution of acid **2.19** (2.42 g, 9.36 mmol, 1 equiv.) and allyl iodide (1.89 g, 1.03 mL, 1.2 equiv.) in THF (100 mL) in a 250 mL round bottom flask. The flask was equipped with a reflux condenser and the mixture was heated to 65 °C for 6 hours. The mixture was cooled to room temperature and quenched with 80 mL of saturated NH_4Cl (aq). The organic layer was collected and washed with brine (60 mL). The organic layer was dried with $MgSO_4$,

filtered and concentrated under vacuum. The product was purified by flash chromatography using 4:1 hexane:ethyl acetate as the eluent to afford 2.40 g of the allyl ester (86%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.91 (ddt, J = 17.40,10.53, 5.50 Hz, 1H), 5.31 (dd, J = 17.40, 1.83 Hz, 1H), 5.22 (dd, J = 10.53, 1.37 Hz, 1H), 4.91 (s, 1H), 4.90 (s, 1H), 4.58 (m, 2H), 3.59 (t, J = 5.95 Hz, 2H), 3.30 (t, J = 7.33 Hz, 1H), 2.11-1.72 (m, 2H), 1.75 (s, 3H), 0.89 (s, 9H), 0.03 (s, 6H)

^{13}C NMR (400 MHz, $CDCl_3$) δ 173.3, 142.3, 132.3, 118.1, 114.1, 65.2, 60.6, 49.2, 33.1, 26.0, 20.4, 18.3

3-(2-(tert-butyldimethylsilyloxy)ethyl)-4-methyl-3,6-dihydro-2H-pyran-2-one (2.21)



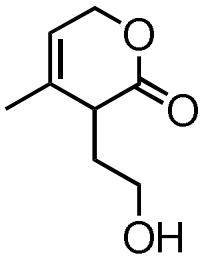
Grubbs' second generation catalyst (0.11 mmol, 90 mg, 4 mol %) was added to a solution of ester **2.18** (0.85 g, 2.8 mmol) and $Ti(OiPr)_4$ (0.24 g, 0.4 mL, 0.3 equiv.) in CH_2Cl_2 (500 mL). The solution was refluxed at 40 $^{\circ}$C for 6 hours. The reaction was then cooled to room temperature and the solution was filtered through a thin pad of silica gel to remove $Ti(OiPr)_4$. The filtered solution was then concentrated under vacuum to give a

dark brown tar which was purified by flash chromatography using 4:1 hexane:ethyl acetate as the eluent to give 0.3 g of the lactone (40%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.66 (d, J = 16.03 Hz, 1H), 4.88 (d, J = 15.57 Hz, 1H), 4.70 (m, 1H), 3.68 (m, 2H), 3.07 (t, J = 2.75 Hz, 1H), 2.86-1.85 (m, 2H), 1.77 (s, 3H), 0.89 (s, 9H), 0.05 (s, 6H)

^{13}C NMR (400 MHz, $CDCl_3$) δ 172.3, 133.8, 117.7, 67.7, 59.8, 42.0, 32.6, 25.9, 20.1, 18.3

3-(2-hydroxyethyl)-4-methyl-3,6-dihydro-2H-pyran-2-one (2.22)

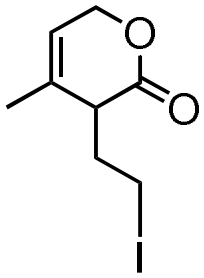


$BF_3{\cdot}(OEt)_2$ was added to a solution of lactone **2.21** (0.35 g, 1.3 mmol) in CH_3CN (10 mL) at 0 °C and stirred for 2 hours. 10 mL of saturated $NaHCO_3$ (aq) was added to the reaction mixture. The organic layer was collected and the aqueous layer was extracted with EtOAc (2 × 10 mL). The organic layers were combined and washed with saturated NaCl (aq), dried with $MgSO_4$, and concentrated under vacuum. The product was purified by flash chromatography using 1:1 hexane:ethyl acetate as the eluent to give 0.16 g of the deprotected alcohol (81%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.65 (dt, J = 2.29, 1.83 Hz, 1H), 4.89 (ddd, J = 15.57, 2.29, 1.83 Hz 1H), 4.71 (ddd, J = 15.57, 2.29, 1.83 Hz 1H), 3.78-3.60 (m, 2H), 3.06 (tt, J=2.29, 1.83 Hz, 1H), 2.18-1.77 (m, 2H), 1.76 (s, 3H)

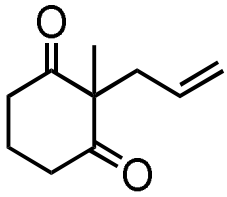
^{13}C NMR (400 MHz, $CDCl_3$) δ 173.3, 134.0, 117.5, 68.1, 59.8, 42.3, 32.5, 27.3, 20.2

3-(2-iodoethyl)-4-methyl-3,6-dihydro-2H-pyran-2-one (2.17)



To a stirred solution of lactone **2.22** (0.17 g, 1.1 mmol) in CH_3CN (5 mL) and diethyl ether (8 mL) at 0 °C was added triphenyl phosphine (0.38 g, 1.43 mmol, 1.1 equiv.), iodine (0.39 g, 1.54 mmol, 1.4 equiv.) and imidazole (0.11 g, 1.65 mmol, 1.5 equiv.). The reaction was allowed to slowly warm to and maintained at room temperature for 6 hours. 20% aqueous $Na_2S_2O_3$ (10 mL) was added to the reaction mixture. The organic layer was collected and the aqueous layer was extracted with EtOAc (2 × 10 mL). The organic layers were combined and washed with saturated NaCl (aq), dried with $MgSO_4$, and concentrated under vacuum. The product was purified by flash chromatography using 3:1 hexane:ethyl acetate as the eluent to give 97 mg of the halide (33%).

2-allyl-2-methylcyclohexane-1,3-dione (2.29)

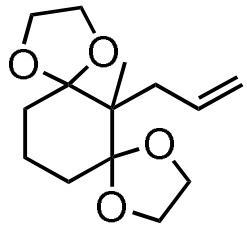


From Bedekar, A. V., Watanabe, T., Tanaka, K., Fuji, K. *Synthesis*. **1995**, 1069-1070.

To a stirred mixture of 2-methyl-1,3-cyclohexadione (15 g, 0.119 mol) and lithium chloride (5.51 g, 0.13 mol, 1.1 equiv.) in THF (200 mL) was added 1,8-diazabicycloundec-7-ene (19.8 g, 19.4 mL, 0.13 mol, 1.1 equiv.). The resulting viscous, white mixture was stirred for 30 minutes at room temperature. Allyl bromide (17.3 g, 12.1 mL, 0.143 mol, 1.2 equiv.) was then added and the reaction mixture was heated to 65 $^{\circ}$C for 8 hours. The reaction was then cooled to room temperature and 50% aqueous NH_4Cl (100 mL) was added. The organic layer was collected and the aqueous layer was extracted with EtOAc (100 mL). The organic layers were combined and washed with saturated NaCl (aq), dried with $MgSO_4$, and concentrated under vacuum. The product was purified by flash chromatography using 2:1 hexane:EtOAc as the eluent to afford 18.8 g of the allylated product (95%).

The NMR spectra matched the values reported in the literature.

6-methyl-6-(prop-2-en-1-yl)-1,4,8,11-tetraoxadispiro[4.1.4^{7}.3^{5}]-tetradecane (2.30)

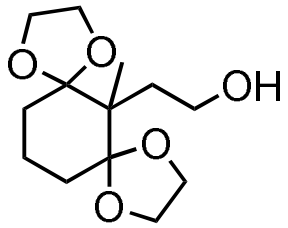


To a solution of 2-allyl-2-methylcyclohexane-1,3-dione **2.29** (20.0 g, 0.12 mol)**,** trimethylorthoformate (95.5 g, 99 mL, 0.9 mol, 7.5 equiv.) and ethylene glycol (67.0 g, 60.2 mL, 1.08 mol, 9 equiv.) in CH_2Cl_2 (700 mL) was added *para*-toluenesulfonic acid hydrate (2.28 g, 12 mmol, 0.1 equiv.). The resulting biphasic mixture was heated to 40 $^{\circ}$C for 16 hours. The flask was cooled to room temperature and 20% aqueous $NaHCO_3$ (200 mL) was added. The organic layer was collected and washed with saturated NaCl (aq), dried with $MgSO_4$, and concentrated under vacuum. The product was purified by flash chromatography using 2:1 hexane:EtOAc as the eluent to afford 28.4 g of bis-ketal (93%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.98 (ddt, J = 10.31, 7.45, 2.86 Hz, 1H), 4.94 (dd, J = 16.61, 2.86 Hz, 1H), 4.89 (dd, J = 10.31, 2.29 Hz, 1H), 4.05-3.85 (m, 8H), 2.35 (d, J = 7.45 Hz, 2H), 1.66-1.53 (m, 6H), 1.16 (s, 3H)

^{13}C NMR (400 MHz, $CDCl_3$) δ 137.7, 114.1, 113.0, 65.3, 63.8, 49.7, 35.0, 30.2, 18.6, 17.2

2-{6-methyl-1,4,8,11- tetraoxadispiro[4.1.4^{7}.3^{5}]tetradecan-6- yl}ethan-1-ol (2.31)

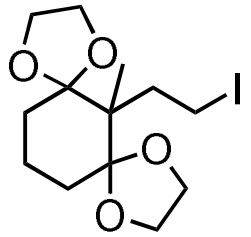


Ozone was bubbled through a solution of olefin **2.30** (9.3 g, 0.036 mol) in CH_2Cl_2 (70 mL) at -78 $^{\circ}$C. After the blue color persisted, the ozone source was removed, the reaction flask was removed from the dry ice/acetone bath and placed into an ice bath. N_2 was bubbled through for 10 minutes. A suspension of sodium borohydride (1.63 g, 0.043 mol, 1.2 equiv.) in isopropanol (70 mL) was added. The resulting mixture was warmed to room temperature and stirred for 8 hours. The reaction flask was then cooled to 0 $^{\circ}$C and saturated aqueous NH_4Cl (100 mL) was added slowly. The flask was warmed to room temperature and stirred for two hours after which the evolution of H_2 gas subsided. The resulting mixture was extracted with CH_2Cl_2 (2 × 100 mL). The organic layers were combined and washed with saturated NaCl (aq), dried with $MgSO_4$, and concentrated under vacuum. The product was purified by flash chromatography using EtOAc as the eluent to give 4.14 g of the primary alcohol (45%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.02-3.96 (m, 8H), 3.71 (t, J = 5.95 Hz, 2H), 1.95 (t, J = 5.95 Hz, 2H), 1.76-1.57 (m, 6H), 1.09 (s, 3H)

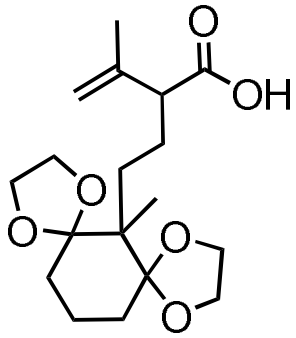
^{13}C NMR (400 MHz, $CDCl_3$) δ 113.0, 64.8, 64.6, 59.6, 49.6, 34.6, 29.6, 18.6, 13.9

6-(2-iodoethyl)-6-methyl-1,4,8,11- tetraoxadispiro[4.1.4^7.3^5]tetradecane (2.27)



A solution of I_2 in THF (25 mL) was added to a stirred solution of alcohol **2.31** (4.14 g, 16 mmol), PPh_3 (4.72 g, 18 mmol, 1.1 equiv.), and imidazole (1.50 g, 22 mmol, 1.4 equiv.) in THF (25 mL) at 0 $^{\circ}$C. The resulting solution is allowed to warm to room temperature and stirred for 6 hours. 20% aqueous $Na_2S_2O_3$ (30 mL) was added to the reaction mixture. The organic layer was collected and the aqueous layer was extracted with EtOAc (2 × 25 mL). The organic layers were combined and washed with saturated NaCl (aq), dried with $MgSO_4$, and concentrated under vacuum. The product was purified by flash chromatography using 2:1 hexane:ethyl acetate as the eluent to give the halide product which was used immediately for the following step.

3-methyl-2-({6-methyl-1,4,8,11- tetraoxadispiro[4.1.4^7.3^5]tetradecan-6- yl}ethyl)but-3-enoic acid (2.26)

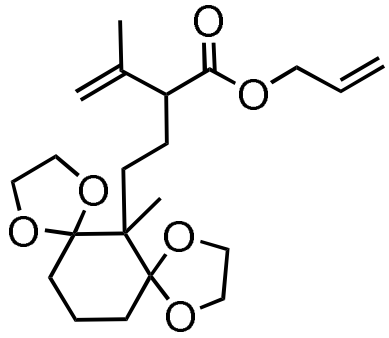


To a solution of diisopropylamine (6.78 g, 9.42 mL, 67 mmol, 4.2 equiv. relative to starting alcohol **2.31** from previous step) in THF (30 mL) at -78 °C was added a solution of n-butyllithium (26.8 mL, 2.5 M in hexanes, 4.2 equiv.). The reaction flask was placed into an ice bath and stirred for 15 minutes after which time the flask was placed back into the dry ice/acetone bath. A solution of 3,3-dimethylacrylic acid (3.21 g, 32 mmol, 2 equiv.) in THF (20 mL) was added dropwise to the lithium diisopropylamide (LDA) solution and the reaction flask was again placed into an ice bath, stirred for 15 minutes, then placed back into the dry ice/acetone bath. A solution of **2.21** from the previous step in THF (20 mL) was then added dropwise and the reaction flask was removed from the dry ice/acetone bath and stirred for 16 hours. The reaction was quenched by the addition of 70 mL of saturated NH_4Cl (aq). The organic layer was collected and washed with saturated aqueous NaCl (600 mL), dried with $MgSO_4$, filtered and concentrated under vacuum. The crude product was purified by flash chromatography using 1:1 hexane:ethyl acetate as the eluent to give 3.59 g of the alkylated acid (66%, based on **2.31**).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.91 (s, 2H), 4.01-3.68 (m, 8H), 2.81 (t, 1H), 2.00-1.89 (m, 2H), 1.78-1.62 (m, 2H), 1.78 (s, 3H), 1.64-1.50 (m, 6H), 1.12 (s, 3H)

^{13}C NMR (400 MHz, $CDCl_3$) δ 200.0, 158.5, 132.9, 112.5, 65.9, 65.4, 65.1, 44.4, 33.7, 29.1, 27.4, 24.7, 22.5, 15.3, 11.0

prop-2-en-1-yl 3-methyl-2-({6-methyl-1,4,8,11- tetraoxadispiro[4.1.4^{7}.3^{5}]tetradecan-6- yl}ethyl)but-3-enoate (2.32)

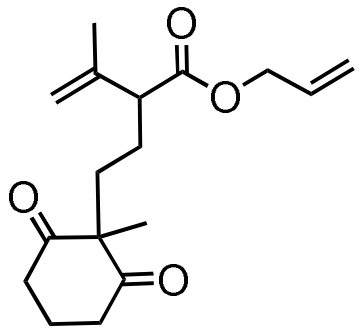


Cesium carbonate (2.49 g, 7.64 mmol, 1.3 equiv.) was added to a solution of acid **2.26** (2.0 g, 5.88 mmol, 1 equiv.) and allyl iodide (1.58 g, 0.86 mL, 1.6 equiv.) in THF (100mL) in a 250 mL round bottom flask. The flask was equipped with a reflux condenser and the mixture was heated to 65 $^{\circ}$C for 16 hours. The mixture was cooled to room temperature and quenched with 80mL of saturated NH_4Cl (aq). The organic layer was collected and washed with brine (60 mL). The organic layer was dried with $MgSO_4$, filtered and concentrated under vacuum. The product was purified by flash chromatography using 1:1 hexane:ethyl acetate as the eluent to afford 2.23 g of the allyl ester (99%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.91 (ddt, J = 17.18, 10.31, 5.73 Hz, 1H), 5.31 (dd, J = 17.18, 2.86 Hz, 1H), 5.21 (dd, J = 10.31, 2.86 Hz, 1H), 4.89-4.87 (m, 2H), 4.57 (d, J = 5.73 Hz, 2H), 4.0-3.84 (m, 8H), 2.92 (t, J = 7.45 Hz, 1H), 1.75 (s, 3H), 1.65-1.50 (m, 10H), 1.11 (s, 3H)

^{13}C NMR (400 MHz, $CDCl_3$) δ 173.6, 142.8, 132.3, 117.9, 113.6, 113.4, 65.2, 65.1, 65.0, 64.1, 54.6, 49.2, 30.1, 29.9, 26.0, 20.3, 18.6, 15.6

prop-2-en-1-yl 3-methyl-2-[(1-methyl-2,6-dioxocyclohexyl)ethyl]but-3-enoate (2.25)

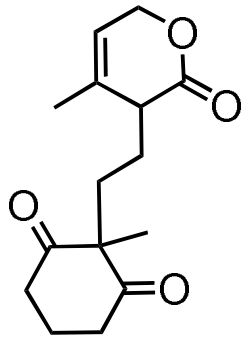


1M HCl (20 mL) is added to a solution of bis-ketal ester **2.32** (0.81 g, 2.12 mmol) in acetone (60 mL). The solution is heated to 60 °C for 3 hours. The reaction is cooled to room temperature and diethyl ether (50 mL) is added to the solution followed by slow addition of saturated aqueous $NaHCO_3$ (50 mL). The organic layer is collected and the aqueous layer is extracted with diethyl ether (2 × 50 mL). The organic layers were combined and washed with saturated NaCl (aq), dried with $MgSO_4$, and concentrated under vacuum. The product was purified by flash chromatography using 2:1 hexane:EtOAc as the eluent to afford 0.50 g of the deprotected diketone (81%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.89 (ddt, J = 17.18, 10.31, 5.73Hz, 1H), 5.30 (dd, J = 17.18, 1.72Hz, 1H), 5.22 (dd, J = 10.31, 1.72 Hz, 1H), 4.92 (s, 1H), 4.88 (s, 1H), 4.61-4.53 (m, 2H), 2.97 (t, J = 7.45 Hz, 1H), 2.74-2.60 (m, 4H), 2.04-1.84 (m, 2H), 1.77-1.71 (m, 2H), 1.71 (s, 3H), 1.62-1.41 (m, 2H), 1.24 (s, 3H)

^{13}C NMR (400MHz, $CDCl_3$) δ 210.1, 172.7, 141.7, 132.1, 118.3, 114.7, 65.3, 65.2, 53.1, 38.0, 34.5, 24.9, 20.0, 19.8, 17.7

2-methyl-2-[2-(4-methyl-2-oxo-3,6-dihydro-2H-pyran-3-yl)ethyl]cyclohexane-1,3-dione (2.16)

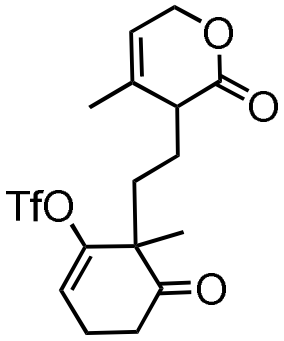


A 1000 mL three-neck round bottom flask containing a solution of Grubbs' second generation catalyst (20 mg, 0.025 mmol, 5 mol %) in 400 mL of CH_2Cl_2 was fitted with a reflux condenser on the middle neck and rubber septa on each of the two outside necks. The solution was heated to 40 °C. A solution of ester **2.25** (0.142 g, 0.49 mmol) and Grubbs' second generation catalyst (20 mg, 0.025 mmol, 5 mol %) in CH_2Cl_2 (60 mL) was drawn into a 60 mL syringe. The syringe was fitted onto a New Era syringe pump which was programmed to deliver the ester/catalyst solution at a rate of 0.5 mL/min. The entire contents of the syringe pump were added over 2 hours and the oil bath was maintained at a temperature of 40 °C for a total time of 3 hours. The reaction was then cooled to room temperature and the solution was filtered through a small pad of silica. The filtered solution was then concentrated under vacuum to give a dark brown tar which was purified by flash chromatography using 1:1 hexane:ethyl acetate as the eluent to give 0.12 g of the lactone (68%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.64 (dt, J = 2.29, 1.72 Hz, 1H), 4.85 (ddd, J = 16.04, 2.29, 1.72 Hz 1H), 4.74 (ddd, J = 16.04, 2.29, 1.72 Hz 1H), 2.92 (tt, J = 2.86, 2.29 Hz, 1H), 2.74-2.60 (m, 4H), 2.10-1.82 (m, 4H), 1.78 (s, 3H), 1.74-1.50 (m, 2H), 1.43 (s, 3H)

^{13}C NMR (400 MHz, $CDCl_3$) δ 209.8, 171.6, 133.5, 117.7, 68.2, 65.4, 44.6, 37.9, 37.8, 32.9, 25.0, 20.2, 19.5, 17.8

6-methyl-6-[2-(4-methyl-2-oxo-3,6-dihydro-2H-pyran-3-yl)ethyl]-5-oxocyclohex-1-en-1-yl trifluoromethanesulfonate (2.36)



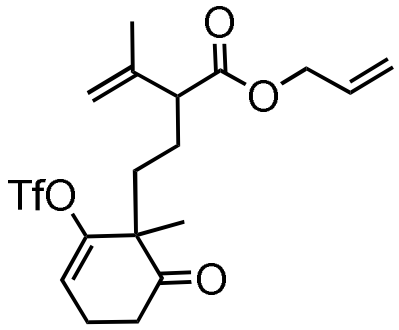
A solution of LiHMDS (0.11 mL, 0.11 mmol, 1.1 equiv., 1 mmol/mL) is added dropwise to a stirred mixture of lactone **2.16** (26 mg, 0.099 mmol, 1 equiv.) and N-(5-chloro-2-pyridyl)triflimide (47 mg, 0.12 mmol, 1.2 equiv.) in THF (3 mL) at -78 °C. The reaction was allowed to warm to room temperature and stirred for 6 hours. The reaction was quenched by the addition of 3 mL of saturated NH_4Cl (aq). Diethyl ether (3 mL) was added and the organic layer was carefully collected. The organic layer was dried with $MgSO_4$, and concentrated under vacuum. The product was purified by flash

chromatography using 3:1 hexane:ethyl acetate as the eluent to give 3 mg of the vinyl triflate (8%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.10 (t, J = 4.01 Hz, 1H), 6.65 (t, J = 1.72 Hz, 1H), 4.86 (ddd, J = 16.61, 2.29, 1.72 Hz 1H), 4.76-4.70 (m, 2H), 2.92 (t, J = 2.83 Hz, 1H), 2.66-2.38 (m, 4H), 1.66-1.32 (m, 4H), 1.30 (s, 3H)

^{13}C NMR (400 MHz, $CDCl_3$) δ 208.2, 171.4, 149.9, 133.7, 117.8, 117.3, 68.2, 52.3, 44.8, 35.8, 32.2, 25.4, 23.2, 20.2, 20.1

prop-2-en-1-yl 3-methyl-2-(2-{1-methyl-6-oxo-2-[(trifluoromethane)sulfonyloxy]cyclohex-2-en-1-yl}ethyl)but-3-enoate (2.38)



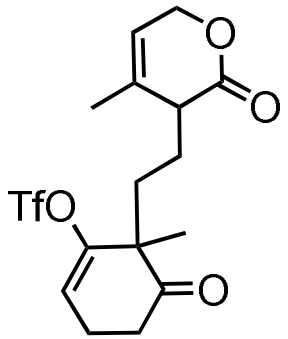
A solution of LiHMDS (1 mmol/mL, 0.99 mL, 0.99 mmol, 1 equiv.) is added dropwise to a stirred mixture of cyclohexadione **2.25** (0.29 g, 0.99 mmol, 1 equiv.) and N-(5-chloro-2-pyridyl)triflimide (0.47 g, 1.19 mmol, 1.2 equiv.) in THF (10 mL) at -78 °C. The reaction was allowed to warm to room temperature and stirred for 6 hours. The reaction was quenched by the addition of 10 mL of saturated NH_4Cl (aq). Diethyl ether (10 mL) was added and the organic layer was collected. The aqueous layer was extracted

with diethyl ether (2 × 10 mL). The organic layers were combined and washed with saturated NaCl (aq), dried with $MgSO_4$, and concentrated under vacuum. The product was purified by flash chromatography using 6:1 hexane:ethyl acetate as the eluent to give 0.29 g of the vinyl triflate (69%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.10 (t, J = 4.01 Hz, 1H), 5.89 (ddt, J = 17.18, 10.88, 5.73, 1H), 5.30 (dd, J = 17.18Hz, 1.72 Hz, 1H), 5.22 (dd, J = 10.88, 1.72 Hz, 1H), 4.94 (s, 1H), 4.88 (s, 1H), 2.97 (t, J = 6.30 Hz), 2.66-2.43 (m, 4H), 1.70 (s, 3H), 1.68-1.60 (m, 2H), 1.43-1.36 (m, 2H), 1.28 (s, 3H)

^{13}C NMR (400 MHz, $CDCl_3$) δ 208.9, 172.8, 150.3, 141.5, 132.1, 118.3, 117.3, 115.0, 65.3, 53.1, 52.5, 36.0, 33.6, 24.8, 23.4, 20.1, 19.7

6-methyl-6-[2-(4-methyl-2-oxo-3,6-dihydro-2H-pyran-3-yl)ethyl]-5-oxocyclohex-1-en-1-yl trifluoromethanesulfonate (2.36)



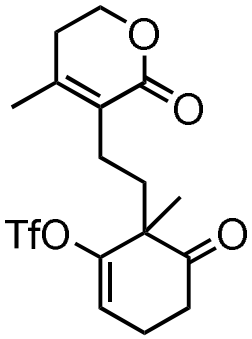
A 500 mL three-neck round bottom flask containing a solution of Grubbs' second generation catalyst (17 mg, 0.02 mmol, 5 mol %) in 200 mL of CH_2Cl_2 was fitted with a reflux condenser on the middle neck and rubber septa on each of the two outside necks. The solution was heated to 40 °C. A solution of ester **2.38** (0.18 g, 0.42 mmol) and

Grubbs' second generation catalyst (17 mg, 0.02 mmol, 5 mol %) in CH_2Cl_2 (60 mL) was drawn into a 60 mL syringe. The syringe was fitted onto a New Era syringe pump which was programmed to deliver the ester/catalyst solution at a rate of 0.5 mL/min. The entire contents of the syringe pump were added over 2 hours and the oil bath was maintained at a temperature of 40 $^{\circ}C$ for a total time of 3 hours. The reaction was then cooled to room temperature and the solution was filtered through a small pad of silica. The filtered solution was then concentrated under vacuum to give a dark brown tar which was purified by flash chromatography using 3:1 hexane:ethyl acetate as the eluent to give 0.12 g of the lactone (73%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.10 (t, J = 4.01 Hz, 1H), 6.65 (t, J = 1.72 Hz, 1H), 4.86 (ddd, J = 16.61, 2.29, 1.72 Hz 1H), 4.76-4.70 (m, 2H), 2.92 (t, J = 2.83 Hz, 1H), 2.66-2.38 (m, 4H), 1.66-1.32 (m, 4H), 1.30 (s, 3H)

^{13}C NMR (400 MHz, $CDCl_3$) δ 208.2, 171.4, 149.9, 133.7, 117.8, 117.3, 68.2, 52.3, 44.8, 35.8, 32.2, 25.4, 23.2, 20.2, 20.1

6-methyl-6-[2-(4-methyl-2-oxo-5,6-dihydro-2H-pyran-3-yl)ethyl]-5-oxocyclohex-1-en-1-yl trifluoromethanesulfonate (2.37)

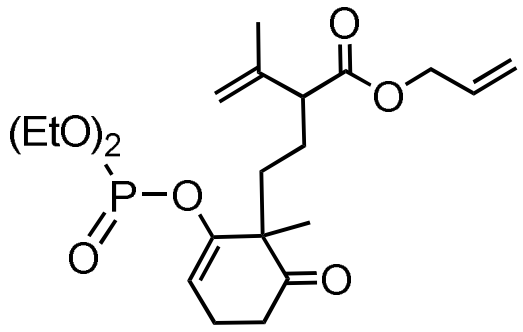


DBU (0.04 mL, 0.27 mmol, 0.6 equiv.) was added so a solution of lactone **2.36** (0.178g, 0.45 mmol) in THF (5 mL) and the resulting solution was stirred at room temperature for 2.5 hours. The reaction mixture was poured into water (5 ml) and the product was extracted with ethyl acetate (2 × 5 mL). The organic layer was with saturated NaCl (aq), dried with $MgSO_4$, and concentrated under vacuum. The product was purified by flash chromatography using 3:1 hexane:ethyl acetate as the eluent to give 0.159 g of the conjugated lactone (89%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.10 (t, J = 4.58 Hz, 1H), 4.27 (t, J = 6.30 Hz, 2H), 2.65-2.61 (m, 2H), 2.50-2.45 (m, 2H), 2.38 (q, J = 5.73 Hz, 2H), 2.25 (td, J = 12.03, 5.15 Hz, 1H), 2.12 (td, J = 12.03, 5.15 Hz, 1H), 1.99 (ddd, J = 12.03, 5.15, 4.58, 1H), 1.95 (s, 3H), 1.71 (ddd, J = 12.03, 5.15, 4.58 Hz, 1H), 1.30 (s, 3H)

^{13}C NMR (400 MHz, $CDCl_3$) δ 208.6, 165.1, 150.6, 150.2, 126.1, 117.1, 65.1, 52.5, 35.7, 35.0, 30.7, 29.8, 22.6, 22.4, 20.4, 19.9

prop-2-en-1-yl 2-({2-[(diethoxyphosphoryl)oxy]-1-methyl-6-oxocyclohex-2-en-1-yl}methyl)-3-methylbut-3-enoate (2.41)

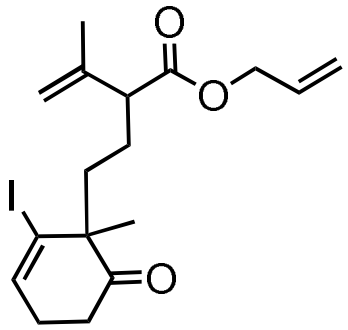


LiHMDS (1 mmol/mL, 1.66 mL, 1.66 mmol, 1.1 equiv.) was added to a stirred solution of ester (0.44 g, 1.51 mmol) in THF (9 mL) at -78 °C. The reaction flask was placed in an ice bath for 10 minutes then returned to the dry ice/acetone bath. Diethyl chloro-phosphonate (0.25 mL, 1.66 mmol, 1.1 equiv.) was added to trap the enolate and the reaction was removed from the dry ice/acetone bath and allowed to warm to room temperature and stirred for 6 hours. Diethyl ether (10 mL) and 10 mL of saturated NH_4Cl (aq) were added and the organic layer was collected. The aqueous layer was extracted with diethyl ether (2 × 10 mL). The organic layers were combined and washed with saturated NaCl (aq), dried with $MgSO_4$, and concentrated under vacuum. The product was purified by flash chromatography using 1:1 hexane:ethyl acetate as the eluent to give 0.31 g of the vinyl phosphonate (69%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.98 (ddt, J = 17.18, 10.88, 5.73 Hz, 1H), 5.90 (t, J = 5.15 Hz, 1H), 5.34 (dd, J = 17.18Hz, 1.72 Hz, 1H), 5.24 (dd, J = 10.88, 1.72 Hz, 1H), 4.63 (m, 2H), 4.19 (m, 4H), 4.13 (t, J = 8.02 Hz, 1H), 2.61-2.45 (m, 2H), 2.39-2.32 (m, 2H), 2.24-1.99 (m, 2H), 1.81 (s, 3H), 1.39-1.33 (m, 8H), 1.26 (s, 3H)

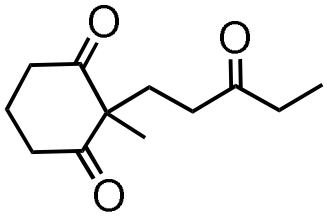
^{13}C NMR (400MHz, $CDCl_3$) δ 211.2, 168.9, 149.5, 144.1, 132.6, 126.7, 118.0, 108.7, 65.0, 64.5, 52.4, 52.3, 36.5, 35.2, 25.7, 23.1, 21.8, 20.2, 16.2

prop-2-en-1-yl 2-[(2-iodo-1-methyl-6-oxocyclohex-2-en-1-yl)methyl]-3-methylbut-3-enoate (2.42)



Iodotrimethylsilane (0.11 mL, 0.78 mmol, 3 equiv.) is added to a solution of vinyl phosphonate **2.41** (0.113 g, 0.26 mmol) in CH_2Cl_2 (3 mL) at 0 °C and stirred for 30 minutes. The resulting mixture is filtered and purified directly by flash chromatography using 2:1 hexane:EtOAc as the eluent to afford the vinyl iodide (7%).

2-methyl-2-(3-oxopentyl)cyclohexane-1,3-dione (2.46)



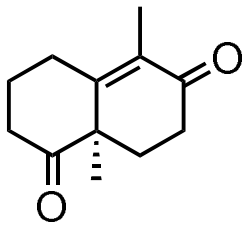
From Scheck, M., Kock, M. A., Waldmann, H. *Tetrahedron*. **2008**, 64, 4792-4802.

A solution of 2-methyl-1,3-cyclohexadione (20 g, 0.159 mol), ethyl vinyl ketone (15.8 mL, 0.159 mol, 1 equiv.) and potassium hydroxide (0.11 g, 1.99 mmol, 0.0125 equiv.) in methanol (700 mL) was heated to 65 °C for 12 hours. The reaction was then

cooled, concentrated under pressure and purified by flash chromatography using 1:1 hexane:ethyl acetate as the eluent to give 31.1 g of the product (93%).

The NMR specta matched the values reported in the literature.

(R)-5,8a-dimethyl-3,4,8,8a-tetrahydronaphthalene-1,6(2H,7H)-dione (2.45)

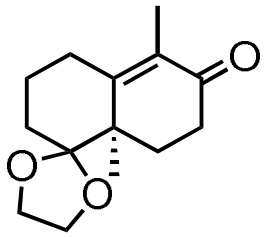


From Hagiwara, H., Uda, H. *Journal of Organic Chemistry*. **1988**, 53, 2308-2311.

A mixture of trione **2.46** (29 g, 0.138 mol), D-phenylalanine (22.8g, 0.138 mol, 1 equiv.) and D-camphorsulfonic acid (16g, 0.069 mol, 0.5 equiv.) in DMF (1.5 L) was stirred for 24 hours at room temperature. The temperature of the reaction was then raised by 10 $^{\circ}$C to 30 $^{\circ}$C and was stirred for 24 hours. The temperature was raised 10 °C every day for four more days. After stirring for 24 hours at 70 $^{\circ}$C, the reaction mixture was then cooled to room temperature. To 100 mL of the DMF reaction solvent was added 1 L of H_2O and 100 mL saturated aqueous $NaHCO_3$. This aqueous suspension was extracted with diethyl ether (2 × 200 mL). This process was repeated with 100 mL aliquots of the reaction solvent (14×). The organic layers were combined and washed with saturated NaCl (aq), dried with $MgSO_4$, and concentrated under vacuum. The product was purified in two batches by flash chromatography using 2:1 hexane:ethyl acetate as the eluent to give 23.8 g of the annulated product (90%).

The NMR specta matched the values reported in the literature.

(R)-5',8a'-dimethyl-3',4',8',8a'-tetrahydro-2'H-spiro[[1,3]dioxolane-2,1'-naphthalen]-6'(7'H)-one (2.47)

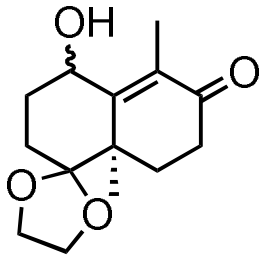


From Hagiwara, H. Uda, H. *Journal of the Chemical Society, Perkin Transactions 1*. **1991**, 8, 1803-1807.

To a solution of ketone **2.45** (14.5 g, 0.075 mol)**,** trimethylorthoformate (8.3 mL, 0.075 mol, 1 equiv.) and ethylene glycol (12.5 mL, 0.225 mol, 3 equiv.) in CH_2Cl_2 (600 mL) was added *para*-toluenesulfonic acid hydrate (1.42 g, 7.5 mmol, 0.1 equiv.). The resulting biphasic mixture was heated to 40 $^{\circ}$C for 16 hours. The flask was cooled to room temperature and 20% aqueous $NaHCO_3$ (200 mL) was added. The organic layer was collected and washed with saturated NaCl (aq), dried with $MgSO_4$, and concentrated under vacuum. The product was purified by flash chromatography using 2:1 hexane:EtOAc as the eluent to afford 15.7 g of ketal (89%).

The NMR specta matched the values reported in the literature.

(R)-4'-hydroxy-5',8a'-dimethyl-3',4',8',8a'-tetrahydro-2'H-spiro[[1,3]dioxolane-2,1'-naphthalen]-6'(7'H)-one (2.44)

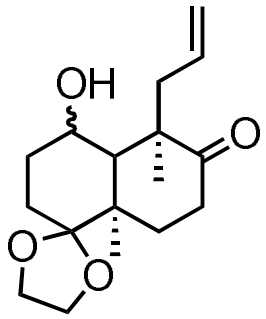


From Nozawa, M., Suka, Y., Hoshi, T., Suzuki, T., Hagiwara, H. *Organic Letters.* **2008**, 10, 1365-1368.

To a stirred solution of enone **2.47** (9.6 g, 0.041 mol) in methanol (300 mL) was added 20% aqueous KOH (100 mL). O_2 was bubbled through and the solution was heated to 60 $^{\circ}$C for 12 hours. The reaction was cooled to 0 $^{\circ}$C and acidified to pH 7 by the addition of 3M HCl. The resulting suspension was extracted with CH_2Cl_2 (2 × 150 mL). The organic layers were collected and washed with saturated NaCl (aq), dried with $MgSO_4$, and concentrated under vacuum. The product was purified by flash chromatography using EtOAc as the eluent to afford 7.9 g of allylic alcohol (76%).

The NMR specta matched the values reported in the literature.

(5'R,8a'R)-5'-allyl-4'-hydroxy-5',8a'-dimethylhexahydro-2'H-spiro[[1,3]dioxolane-2,1'-naphthalen]-6'(7'H)-one (2.50)



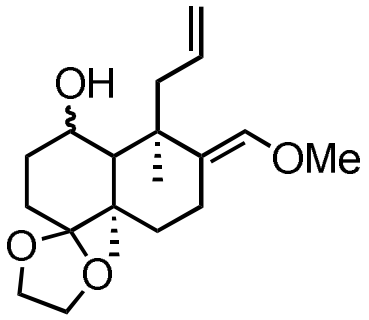
To a refluxing solution of lithium (0.4 g, 58.2 mmol, 3 equiv.) in liquid ammonia (70 mL) was added a solution of enone **2.44** (4.9 g, 19.4 mmol) in THF (45 mL). The resulting solution was stirred for 5 minutes. Allyl iodide (4.5 mL, 49.0 mmol, 2.5 equiv.) was added and the resulting solution was stirred for 10 minutes. The reaction was quenched by the addition of solid NH_4Cl (3 g, 56 mmol). The liquid ammonia was allowed to evaporate. 100 mL of saturated NH_4Cl (aq) and diethyl ether (100 mL) were added and the organic layer was collected. The aqueous layer was extracted with diethyl ether (100 mL). The organic layers were combined and washed with saturated NaCl (aq), dried with $MgSO_4$, and concentrated under vacuum. The product was purified by flash chromatography using 6:1 hexane:ethyl acetate as the eluent to give 2 g of product (35%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.62 (ddt, J = 15.11, 10.07, 4.58 Hz, 1H), 5.02 (d, J = 10.07 Hz, 1H), 4.96, (d, J = 15.11 Hz, 1H), 4.21 (m, 1H), 3.98-3.83 (m, 4H), 2.73-2.60 (m, 2H), 2.28 (ddd, J = 15.57, 5.04, 3.21 Hz, 1H), 2.18-2.10 (m, 2H), 2.04 (d, J = 1.83

Hz, 1H), 1.88 (td, J = 14.20, 4.58 Hz, 1H), 1.79-1.65 (m, 2H), 1.60-1.54 (m, 1H), 1.54 (s, 1H), 1.48 (ddd, J = 13.28, 4.12, 2.75 Hz, 1H), 1.40 (s, 3H)

^{13}C NMR (400 MHz, $CDCl_3$) δ 215.6, 135.4, 117.5, 112.9, 67.1, 65.3, 65.0, 51.9, 46.7, 42.7, 35.1, 32.9, 30.2, 25.6, 24.4, 19.3

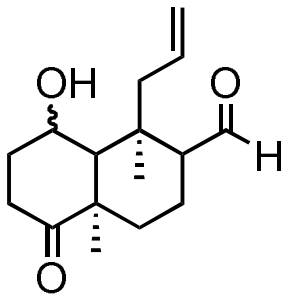
(5'R,8a'R,E)-5'-allyl-6'-(methoxymethylene)-5',8a'-dimethyloctahydro-2'H-spiro[[1,3]dioxolane-2,1'-naphthalen]-4'-ol (2.59)



To a stirred mixture of methoxymethyltriphenylphosphonium chloride (2.16 g, 6.3 mmol, 5 equiv.) in DMSO (7 mL) at 0 °C was added a solution of potassium *tert*-butoxide in THF (1 mmol/mL, 6.3 mL, 5 equiv.). The resulting mixture was stirred for 30 minutes. A solution of ketone **2.50** (0.37 g, 1.26 mmol) in DMSO (3 mL) was added and the reaction was heated to 60 °C for 12 hours. The reaction was cooled to room temperature then 1M HCl (7 mL) and diethyl ether (20 mL) were added. The organic layer was collected and the aqueous layer was extracted with diethyl ether (20 mL). The organic layers were combined and washed with saturated NaCl (aq), dried with $MgSO_4$, and concentrated under vacuum. The product was purified by flash chromatography using 6:1 hexane:ethyl acetate as the eluent to give the methyl vinyl ether. The purified product contained triphenylphosphine oxide; an accurate yield could not be calculated and NMR

spectra of the pure product were not obtained. The subsequent reaction was performed on this mixture.

(1R,4aR)-1-allyl-8-hydroxy-1,4a-dimethyl-5-oxodecahydronaphthalene-2-carbaldehyde (2.43)

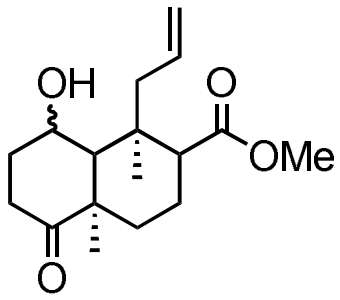


2M HCl (6 mL) is added to a solution of methyl vinyl ether **2.59** (0.29 g, 0.91 mmol) in CH_3CN (18 mL). The solution is stirred at room temperature for 6 hours. Ethyl acetate (20 mL) is added to the solution followed by slow addition of saturated aqueous $NaHCO_3$ (10 mL) to control the evolution of CO_2. The organic layer is collected and the aqueous layer is extracted with diethyl ether (2 × 20 mL). The organic layers were combined and washed with saturated NaCl (aq), dried with $MgSO_4$, and concentrated under vacuum. The product was purified by flash chromatography using 2:1 hexane:EtOAc as the eluent to afford 0.50 g of the deprotected diketone (81%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.84 (d, J = 2.29 Hz, 1H), 5.64-5.55 (m, 1H), 5.04 (d, J = 10.31 Hz, 1H), 4.98 (d, J = 17.18 Hz, 1H), 4.27 (m, 1H), 2.77-2.68 (m, 2H), 2.38-2.34 (m, 1H), 2.19-2.02 (m, 4H), 1.91-1.86 (m, 1H), 1.75-1.65 (m, 2H), 1.49 (s, 3H), 1.42 (s, 3H)

^{13}C NMR (400 MHz, $CDCl_3$) δ 214.3, 204.9, 135.2, 118.1, 66.9, 62.1, 52.3, 50.5, 43.0, 38.8, 37.2, 34.9, 34.7, 24.3, 17.9, 17.0

methyl (1R,4aR)-8-hydroxy-1,4a-dimethyl-5-oxo-1-(prop-2-en-1-yl)-decahydronaphthalene-2-carboxylate (2.63)

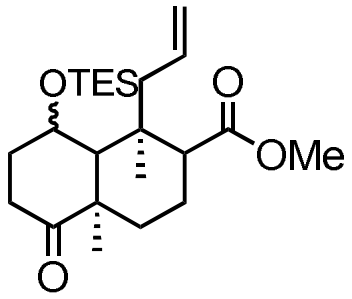


A solution of aldehyde **2.43** (102 mg, 0.39 mmol) in CH_2Cl_2 (2 ml) was added to a flask containing 1,4-dimethyl-1,2,4-triazolium iodide (22 mg, 0.01mmol, 0.25 equiv.) followed by DBU (0.06 ml, 0.42 mmol, 1.1 equiv.). The septum was removed, MnO_2 (170 mg, 1.95 mmol, 5 equiv.) was added and the septum was replaced. Methanol (0.1 mL, 1.95 mmol, 5 equiv.) was then added and the reaction was stirred for 2 hours. The black suspension was filtered through a pipette plugged with cotton with a thin layer of celite on top. The filtrate was then concentrated under vacuum and purified by flash chromatography using 2:1 hexane:EtOAc as the eluent to afford 63 mg of the ester (55%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.86-5.77 (m, 1H), 5.13 (d, J = 5.15 Hz, 1H), 5.10 (d, J = 13.75 Hz, 1H), 4.52 (d, J = 1.72 Hz, 1H), 3.67 (s, 3H), 3.11 (dt, J = 14.32, 6.30 Hz, 1H), 2.43-2.37 (m, 2H), 2.18-2.13 (m, 2H), 2.06-1.98 (m, 2H),1.82-1.61 (m, 4H), 1.53 (s, 3H), 1.46-1.45 (d, J = 3.44 Hz, 1H), 1.37 (s, 3H)

^{13}C NMR (400 MHz, $CDCl_3$) δ 215.5, 174.6, 133.7, 118.9, 65.8, 51.3, 50.2, 50.1, 49.0, 44.4, 41.0, 35.9, 33.9, 32.8, 21.8, 21.3, 21.1

methyl (1R,4aR)-1,4a-dimethyl-5-oxo-1-(prop-2-en-1-yl)-8-[(triethylsilyl)oxy]-decahydronaphthalene-2-carboxylate (2.64)

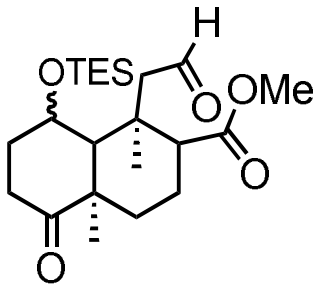


A solution of secondary alcohol **2.63** (48 mg, 0.16 mmol), triethylsilyl trifluoromethane-sulfonate (0.04 mL, 0.19 mmol, 1.2 equiv.) and 4-dimethylaminopyridine (2 mg, 0.016 mmol, 0.1 equiv.) in pyridine (0.013 mL, 0.16 mmol, 1 equiv.) and dimethylformamide (0.6 mL) was heated to 100 °C for 1 hour. The reaction was then cooled to room temperature and quenched by the addition of aqueous ammonium chloride (6 mL). The mixture was extracted with diethyl ether (2 × 5 mL). The organic layers were combined, dried with magnesium sulfate and concentrated under vacuum. The crude product was purified by flash chromatography using 2:1 hexane:EtOAc as the eluent to afford the TES-protected silyl ether (46%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.86-5.76 (m, 1H), 5.14-5.06 (m, 2H), 4.50 (bs, 1H), 3.66 (s, 3H), 3.04 (dt, J = 13.75, 6.30 Hz, 1H), 2.35-2.41 (m, 2H), 2.10-2.17 (m, 2H), 1.96-

2.07 (m, 2H), 1.60-1.74 (m, 3H), 1.56 (s, 1H), 1.51 (s, 3H), 1.32 (s, 3H), 1.01 (t, J = 8.10 Hz, 9H), 0.71 (q, J = 8.02 Hz, 6H)

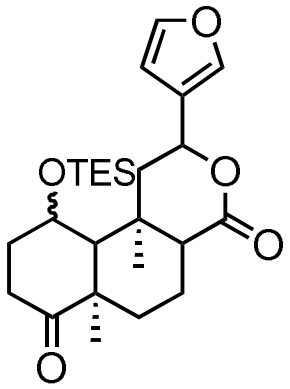
methyl (1R,4aR)-1,4a-dimethyl-5-oxo-1-(2-oxoethyl)-8-[(triethylsilyl)oxy]-decahydronaphthalene-2-carboxylate (2.65)



Ozone gas was bubbled through a solution of olefin **2.64** (38 mg, 0.09 mmol) in CH_2Cl_2 (3 mL) at 0 $^{\circ}$C for 30 seconds. Triphenylphosphine (40 mg, 0.15 mmol, 2.1 equiv.) was then added and the resulting solution was stirred at room temperature for 3 hours. The reaction mixture was purified directly by column chromatography using 2:1 hexane:EtOAc as the eluent to give the aldehyde in 83% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.87 (t, J = 2.29 Hz, 1H), 4.47 (d, J = 2.29 Hz, 1H), 3.70 (s, 3H), 3.01 (dt, J = 14.65, 5.95 Hz, 1H), 2.67 (d, J = 2.29 Hz, 2H), 2.16-1.98 (m, 2H), 1.77-1.53 (m, 7H), 1.49 (s, 3H), 1.34 (s, 3H), 1.10 (t, J = 7.79 Hz, 9H), 0.69 (q, J = 7.79 Hz, 6H)

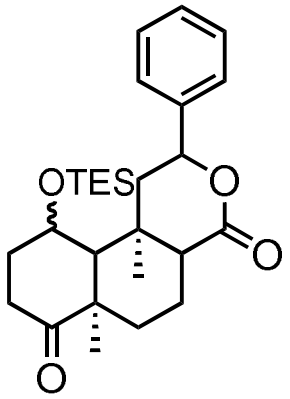
(6aR,10bR)-2-(furan-3-yl)-6a,10b-dimethyl-10-[(triethylsilyl)oxy]-dodecahydro-1H-naphtho[2,1-c]pyran-4,7-dione (2.66)



n-Butyllithium (0.43 mL, 1.07 mmol, 44.6 equiv., 2.5 M) was added to a solution of 3-bromofuran (0.157 g, 1.07 mmol, 44.6 equiv) in THF (3.4 mL) at -78 °C and stirred at that temperature for 30 minutes. 0.08 mL (2.4 %, 0.026 mmol, 1.1 equiv.) of this stock solution was added to a solution of aldehyde **2.65** (10 mg, 0.024 mmol) in THF (1 mL) at -78 °C. The solution was allowed to warm to room temperature and stirred for 2 hours. The reaction was quenched by addition of saturated ammonium chloride (1 mL). The organic layer was removed carefully and the aqueous layer was extracted with diethyl ether (2 mL). The organic layers were combined, dried with magnesium sulfate and purified directly by column chromatography using 4:1 hexane:EtOAc as the eluent to give 4 mg of the furyllactone (53%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (s, 1H), 7.43 (t, J = 1.72 Hz, 1H), 6.40 (s, 1H), 5.54 (dd, J = 11.46, 5.15 Hz, 1H), 4.46 (t, J = 1.15 Hz, 1H), 3.09-3.01 (m, 1H), 2.37 (dd, J = 13.17, 5.73 Hz, 1H), 2.20-2.00 (m, 6H), 1.78-1.62 (m, 3H), 1.44 (s, 3H), 1.25 (s, 3H),

(6aR,10bR)-6a,10b-dimethyl-2-phenyl-10-[(triethylsilyl)oxy]-dodecahydro-1H-naphtho[2,1-c]pyran-4,7-dione (2.67)



Phenyllithium (0.04 mL, 0.08 mmol, 1 equiv., 2 M) was added to a solution of aldehyde **2.65** (32 mg, 0.08 mmol) in THF (2.5 mL) at -78 °C. The solution was slowly allowed to warm to room temperature and stirred for four hours. The reaction was quenched by addition of saturated ammonium chloride (3 mL). The mixture was extracted with diethyl ether (2 × 3 mL). The organic layers were combined, dried with magnesium sulfate and purified directly by column chromatography using 3:1 hexane:EtOAc as the eluent to give 5 mg of the furyllactone (19%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62-7.27 (m, 5H), 5.55 (dd, J = 11.45, 5.50 Hz, 1H), 4.49 (t, J = 2.29 Hz, 1H), 2.46 (dd, J = 13.28, 5.50 Hz, 1H), 2.25-1.88 (m, 6H), 1.57 (s, 1H), 1.56 (s, 3H), 1.48 (s, 3H), 1.34-1.27 (m, 2H)

^{13}C NMR (400MHz, $CDCl_3$) δ 172.5, 145.9, 141.1, 128.8, 128.2, 127.7, 127.5, 126.9, 125.4, 78.8, 78.6, 66.5, 52.9, 52.7, 47.8, 42.7, 38.1, 36.7, 33.1, 32.5, 19.4, 18.9, 17.0, 7.2, 5.4

Chapter 3: Summary/Future Work

SUMMARY

Salvinorin A is the major natural product produced by the plant *Salvia divinorum*.[1] It is native to a region of the Mazatec Mountain in the Mexican state of Oaxaca. *Salvia divinorum* has been used historically by the native Mazatec Indians for its vision-inducing properties.[2] When its vapors are inhaled it produces intense, short-lived hallucinations.[16]

Salvinorin A is a highly selective and potent agonist of the Kappa opioid receptor.[17] As an opioid, it displays anti-nociceptive properties and is devoid of many of the undesirable properties commonly associated with opioid agonists, including sedation, constipation and respiratory depression.[67]

Our goals for this project were to complete the total synthesis of salvinorin A and to develop a process by which C12-modified analogs of salvinorin A could be synthesized. By modifying the structure, we sought to synthesize a molecule with comparable affinity for the KOR and efficacy while trying to minimize the hallucinogenic affects.

Our efforts resulted in the synthesis of the bicyclic δ-carboxy ester **3.2**. Reaction of **3.2** with a nucleophile results in the incorporation of that nucleophile at C12. Upon reacting **3.2** with 3-furanyllithium, we were able to synthesize **3.1**, which is a few steps away from salvinorin A. By using a phenyl anion, we were also able to synthesize **3.3**. This demonstrated that nucleophiles other than the furanyl anion can react with carboxy

ester **3.2**. The successful completion of these two reactions serves as a foundation for the future total synthesis of salvinorin A and the synthesis of C12-modified analogs of salvinorin A.

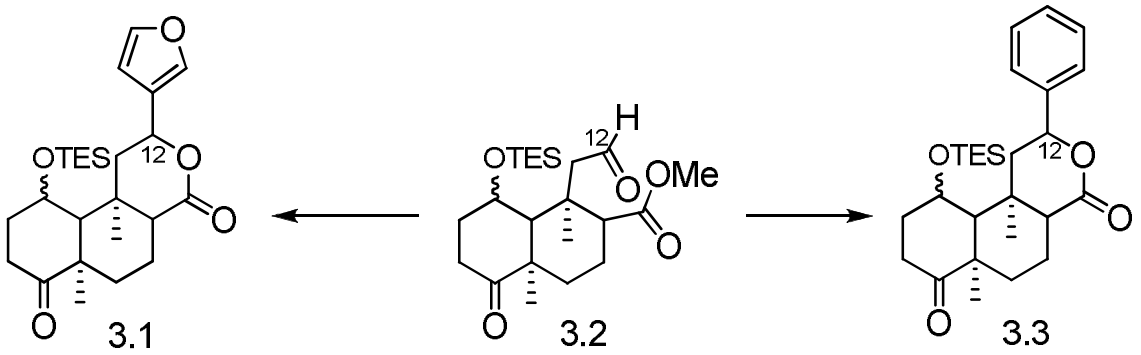


Figure 3.1: Synthesized C12 analogs

FUTURE WORK: TOTAL SYNTHESIS OF SALVINORIN A

Molecule **3.1** is just a few steps away from salvinorin A (**3.4**). In order to complete the synthesis of salvinorin a, modification of carbons 1, 2 and 4 on the A ring of **3.1** will be required. C1 will be converted from a silyl ether to a ketone. C2 will be oxidized to the secondary alcohol followed by acetylation of the resulting alcohol. C4 will be deoxygenated, carboxylated and esterified.

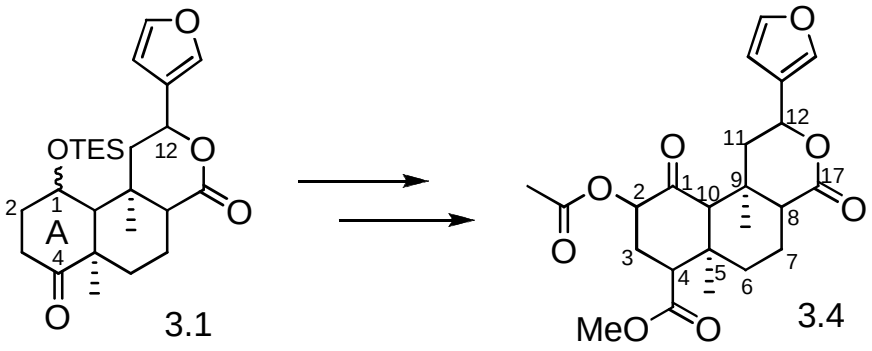


Figure 3.2 Completion of synthesis of salvinorin A

The homologation of C4 can be accomplished with the methoxymethyl triphenylphosphonium Wittig reagent used previously for C8 homologation.[116] This reaction can be performed on **3.1**, but could potentially be performed earlier in the synthesis at the same time as C8 homologation. Hydrolysis of the C4 methyl vinyl ether (**3.5**) would yield an aldehyde which upon oxidation/esterification using the triazolium NHC catalyst[117] previously employed for C8 functionalization would yield the C4 methyl carboxylate (**3.6**).

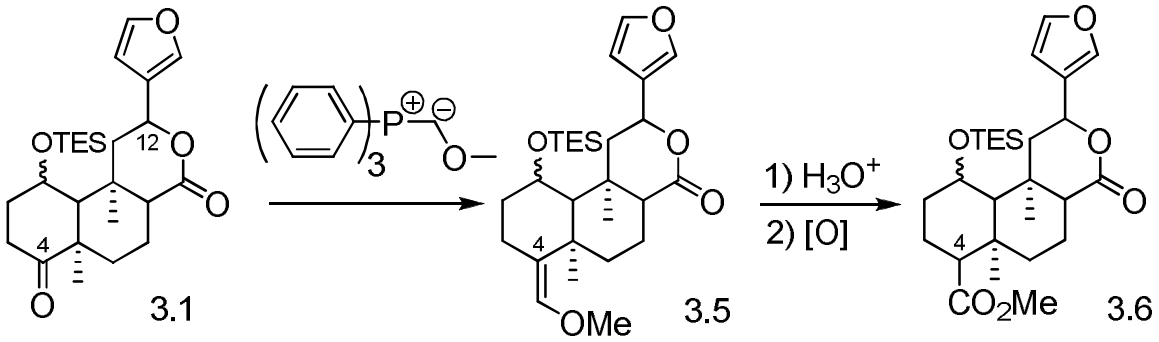


Figure 3.3: C4 Functionalization

Cleavage of the C1 triethylsilyl ether by Olah's reagent (pyridine hydrofluoride)[118] would yield the C1 secondary alcohol, which upon PCC oxidation[115] would give the C1 ketone (**3.7**).

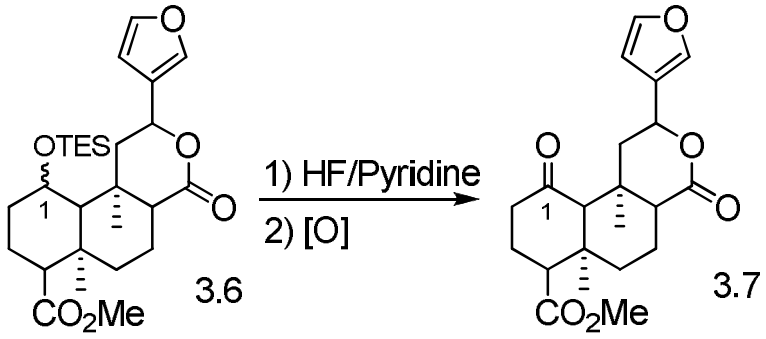


Figure 3.4: C1 Functionalization

In order to functionalize C2, **3.5** would be subjected to Rubottom oxidation conditions.[79] Deprotonation at C2 and subsequent quenching of the resulting enolate with chlorotrimethylsilane would yield an intermediate silyl enol ether. Treatment of the intermediate silyl enol ether with m-chloroperbenzoic acid would give the C2 alcohol, leaving the furanyl olefins unaffected.[38] Acetylation of the C2 alcohol would yield salvinorin A.

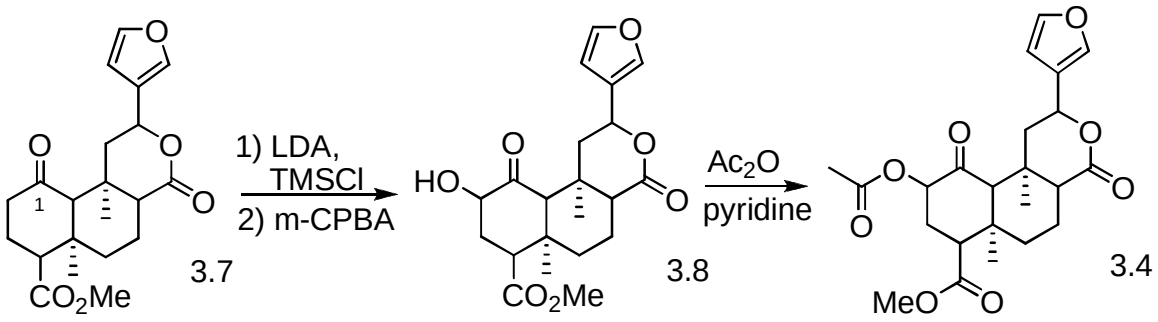


Figure 3.5: C2 Functionalization

FUTURE WORK: C12 SALVINORIN ANALOGS

Although the total synthesis of salvinorin A is appealing, the more noteworthy aspect of this project is the synthesis of C12-modified salvinorin analogs. Every synthetic route was designed with diversification at C12 in mind. The successful syntheses of compounds **3.1** and **3.3** demonstrate that the intermediate bicyclic δ-carboxy ester **3.2** is capable of serving as a foundation for C12-modified salvinorin analogs. As demonstrated in Figure 3.6, δ-carboxy ester **3.2** can be reacted with other nucleophiles to give different C12 salvinorin analogs.

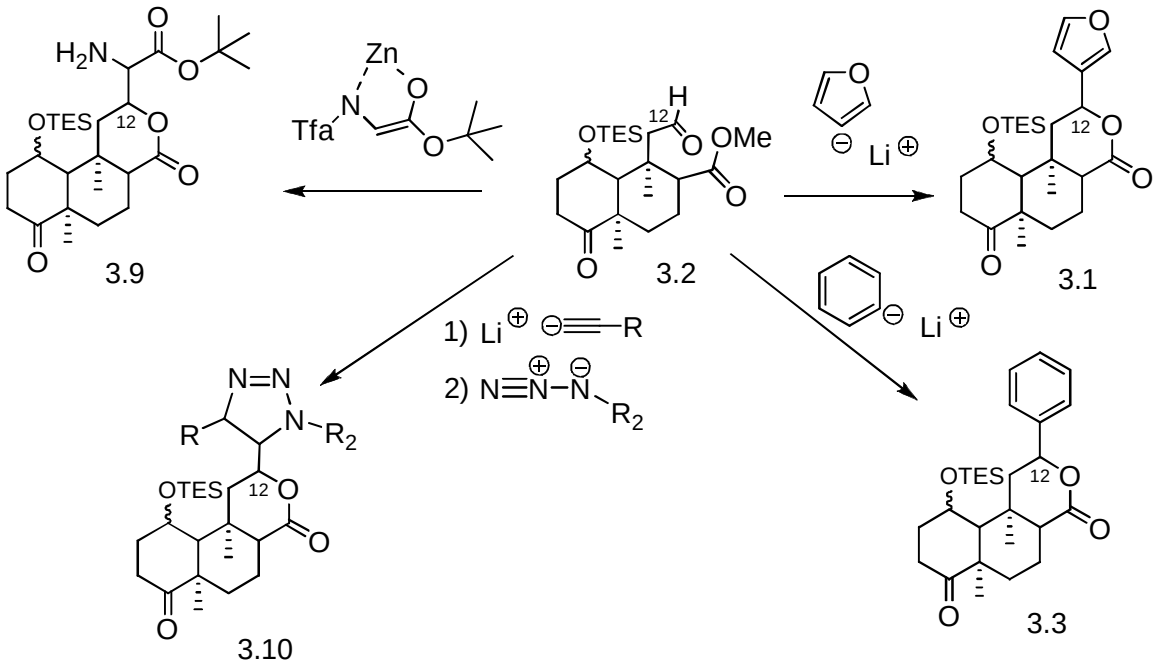


Figure 3.6: Reaction of different nucleophiles with common intermediate

Molecule **3.1** would have to undergo additional chemical transformations in order to be converted into salvinorin A (Figures 3.3-3.6). Similarly, molecules **3.3, 3.9 and 3.10** would require additional synthetic steps to install the C2 and C4 esters that are necessary for the activity of salvinorin A.[41, 53] Ideally, the C12-diversification step would be the final step in the synthesis of these molecules. In order for that to occur, a more "complete" substrate for C12-nucleophilic addition must be synthesized. The ideal substrate for the synthesis of C12-modified salvinorin analogs would be molecule **3.16**, which after addition of the C12 nucleophile would require no additional reaction steps.

If C4 and C8 homologation/oxidation/esterification were to be performed concurrently earlier in the synthesis, the product of these three transformations would be

di-ester **3.13**. This molecule contains the C4 methyl carboxylate and C8 ester that would become later be transformed into the C-ring lactone.

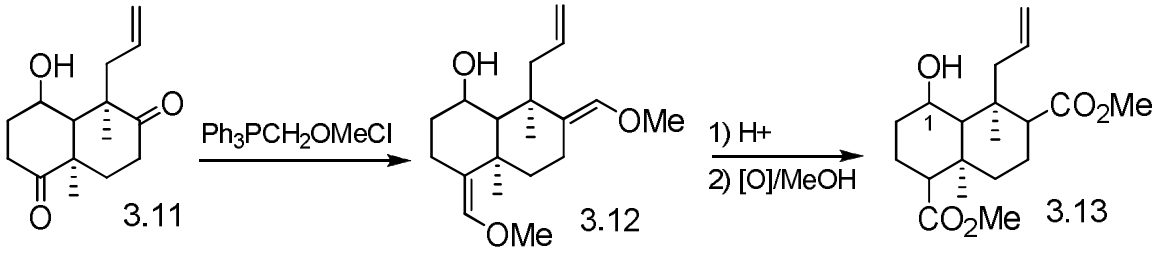


Figure 3.7: Synthesizing a substrate for C12-substitution in final step (part 1)

Oxidation of the C1 secondary alcohol on **3.13** would yield the C1 ketone **3.14**. A modified Rubottom oxidation (*m*-chloroperbenzoic acid, acetic acid, pyridine) would oxidize the silyl enol ether, leaving the terminal olefin unaffected.[119] Subsequent acetylation of the C2 alcohol would give acetate ester **3.15**.

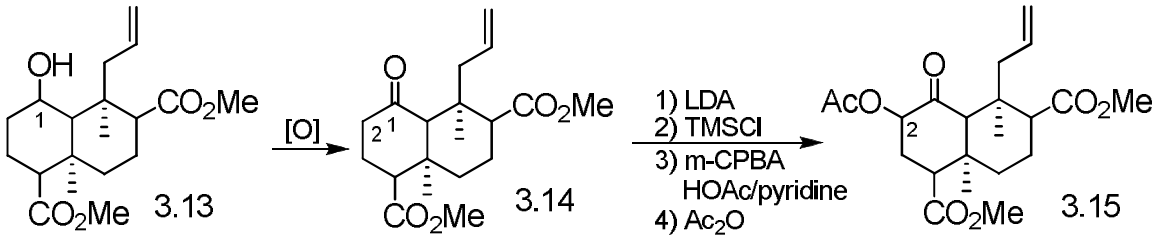


Figure 3.8: Synthesizing a substrate for C12-substitution in final step (part 2)

Ozonolysis of the terminal olefin would give the δ-carboxy ester **3.16**. This molecule is the ideal candidate for the synthesis of an array of C12 salvinorin analogs. As shown previously for molecules **3.1** and **3.3,** a nucleophile (e.g. R^-) would react with C12, the most electrophilic carbon, followed by the formation of the C-ring lactone. Molecule

3.16 is one step away from the total synthesis of salvinorin A and is an excellent candidate for the future creation of a library of C12 salvinorin analogs.

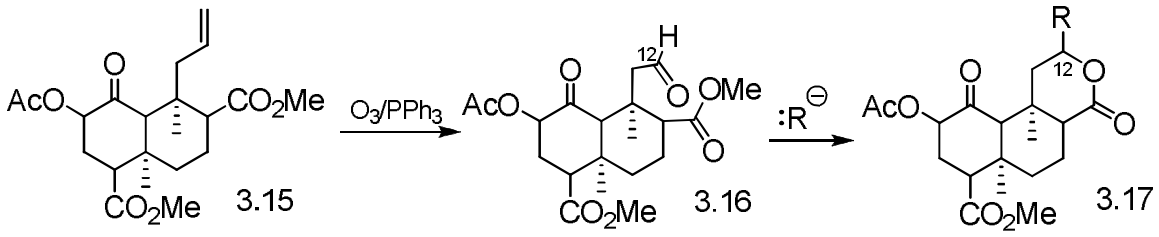


Figure 3.9: Ideal compound for C12 analogs

PART II SYNTHESIS OF BROAD-SPECTRUM DENV/WNV NS3 PROTEASE INHIBITORS

ABSTRACT

West-Nile Virus (WNV) and Dengue Virus (DENV), both members of the *Flavivirirus* genus, are transmitted to humans by mosquito vectors and are significant causes of human illness worldwide. The majority of people infected with either virus remain asymptomatic, however some of those infected will develop critical and life-threatening diseases West Nile encephalitis or Dengue hemorrhagic fever. As members of the same genus, they share many important biological features including a highly homologous NS3 protease. NS3 is essential for virion replication, making it an ideal target for a broad-spectrum inhibitor of the related viral proteases.

Chapter 4: West Nile and Dengue Virus

WEST NILE VIRUS

West Nile Virus is taxonomically classified as a member of the family *Flaviviridae* and the genus *Flavivirus* which also include the related yellow fever, Japanese encephalitis and St. Louis encephalitis viruses. It is a class IV virus, with a positive sense single-strand RNA genome.[120] Phylogenetic analysis of several viral strains has determined there are two distinct lineages (serotypes) of WNV which differ in virulence and geographical distribution and can be distinguished serologically.[121]

WNV is maintained through a mosquito-bird-mosquito transmission cycle (Figure 4.1). Birds are amplifying hosts, and although most birds are not affected by the virus, some North American species are particularly susceptible to WNV-induced mortality[122]. 29 mosquito species have been identified as carriers of the virus, with the *Culex pipiens* species being the primary vector.[123] Humans and other incidental mammalian hosts are dead-end hosts, incapable of achieving a sufficiently high viral titer to retransmit the virus back to a mosquito[124,125]. Horses are particularly susceptible to WNV-induced illness, with a ~40% mortality rate for infected horses.[126]

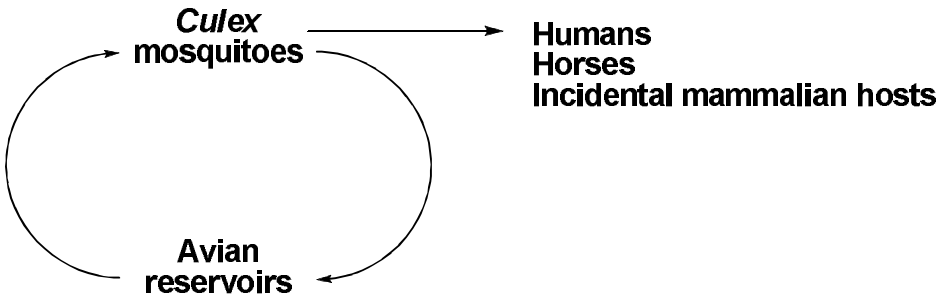


Figure 4.1 WNV Transmission Cycle

West Nile Virus was initially identified in 1937 from a woman in the West Nile district of Uganda.[127] Over the next several decades the virus expanded across the Eastern hemisphere with outbreaks reported in the Mediterranean (1951),[128] Israel (1951),[129] France (1962)[121] and South Africa (1974).[125] After being relatively dormant for 20 years, the virus reemerged in 1994 with West Nile epidemics reported in Algeria (1994),[130] Romania (1996),[131] Russia (1999)[132] and Israel (1999).[133]

In August 1999 WNV made its first appearance in the Western hemisphere during an outbreak in New York City and the surrounding area.[134] Initial studies pointed to the St. Louis encephalitis virus as the cause of the illnesses, but deaths of substantial numbers of birds, which are not affected by St. Louis encephalitis virus, indicated otherwise.[135] After the virus was isolated, its genome was sequenced and researchers determined WNV was the cause of the human and avian illnesses.[136] The 1999 NY outbreak included 62 reported cases and 7 deaths.[134] Since then the virus has rapidly expanded across the country and is currently endemic to the United States with more than 4,000 reported infections and 200 deaths in 2002.[123] Other endemic areas include Australia, Africa and parts of Europe and Asia (Figure 4.2).[121]

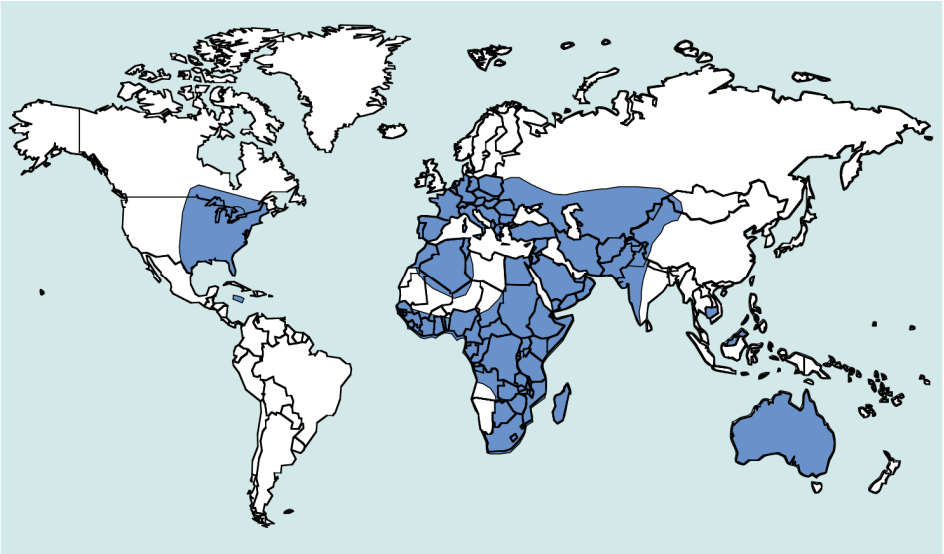


Figure 4.2 Areas with endemic WNV

Image reprinted with permission from Campbell, 2002.

Most people infected with WNV (60-80%) remain asymptomatic, and people of advanced age are at highest risk for developing severe symptoms.[137] Once a human is infected with WNV, the virus incubates for 2-14 days before symptoms appear. Uncomplicated WN fever affects approximately 20% of infected people, and less than 1% of infected individuals will go on to develop more severe diseases.[138] The severe, neuroinvasive diseases include 1) West Nile meningitis – inflammation of the membranes surrounding the brain and spinal cord, 2) West Nile encephalitis – inflammation of the brain, and 3) acute flaccid paralysis – sudden onset of paralysis of the limbs. Post-recovery, meningitis and encephalitis patients continue to display persistent physical, cognitive and functional symptoms which linger several months after the acute illness.[140,141]

There is no current vaccine or viral-specific treatment for WN meningitis/encephalitis. Although standard anti-viral therapies, including nucleoside analogs[141] and interferon-α[142] have been effective in vitro, neither has shown to be effective in human patients.

DENGUE VIRUS

Like WNV, DENV is a member of the *Flaviviridae* family and the *Flavivirus* genus. The virus exists as four infectious viral serotypes (DENV-1, DENV-2, DENV-3, DENV-4) which are differentiated by the amino acid sequence of the surface glycoprotein E and can be identified by analysis of the neutralizing antibody.[143] Infection with one serotype will confer lifetime immunity to that particular serotype and temporary immunity to a different serotype.[144] However, prior infection of one serotype leaves an individual more susceptible to illness from other serotypes.[145] Dengue virus infection triggers a spectrum of clinical presentations which range from asymptomatic infection to classical dengue fever to the more serious and sometimes fatal dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS).

DENV life cycle is maintained via transmission between mosquitoes and both human and non-human primates (Figure 4.3).[144] The mosquito vector includes several species of the *Aedes* genus, with *aegypti* species being the major transmitter. An infective *A. aegypti* mosquito is capable of infecting several people in one blood meal.[146] Additionally, an infected mosquito can transfer the virus to its progeny.[143]

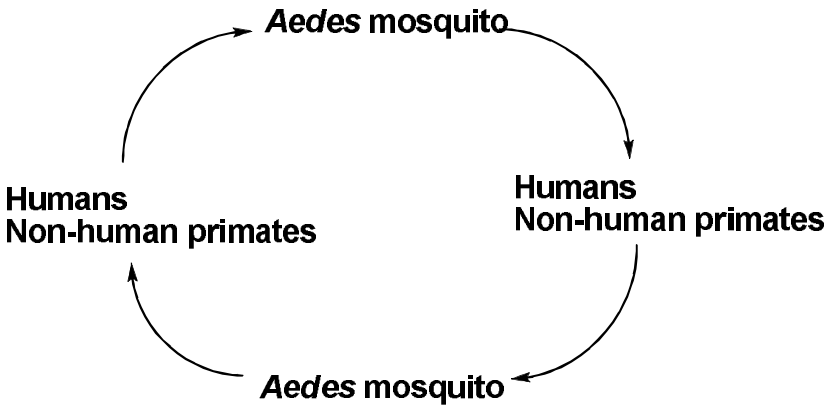


Figure 4.3 DENV Transmission Cycle

DENV is endemic to more than 110 countries, with more than half the world's population living in areas at elevated risk for DENV transmission (Figure 4.4).[147,148] The most affected areas are tropical regions including Southern and Central America, the Caribbean and most of Southeast Asia. The World Health Organization estimates there are 50-100 million cases of dengue fever every year with 500,000 people hospitalized with the more serious dengue hemorrhagic fever (DHF) and 25,000 deaths resulting from DENV-associated illnesses.[149,150]

The areas of the U.S. most vulnerable to DENV are areas to which *Aedes aegpyti* is indigenous, including Hawaii and the southeast from Texas to South Carolina. Outbreaks of DENV have occurred several times in Hawaii with the most recent occurring in 2001.[151] In 1999, 14 cases of dengue infection were confirmed in the Mexican border town of Laredo, Texas.[152] The most recent reports of DENV infection occurred in Key West, Florida in 2009-2010 with 28 confirmed DENV infections.[153]

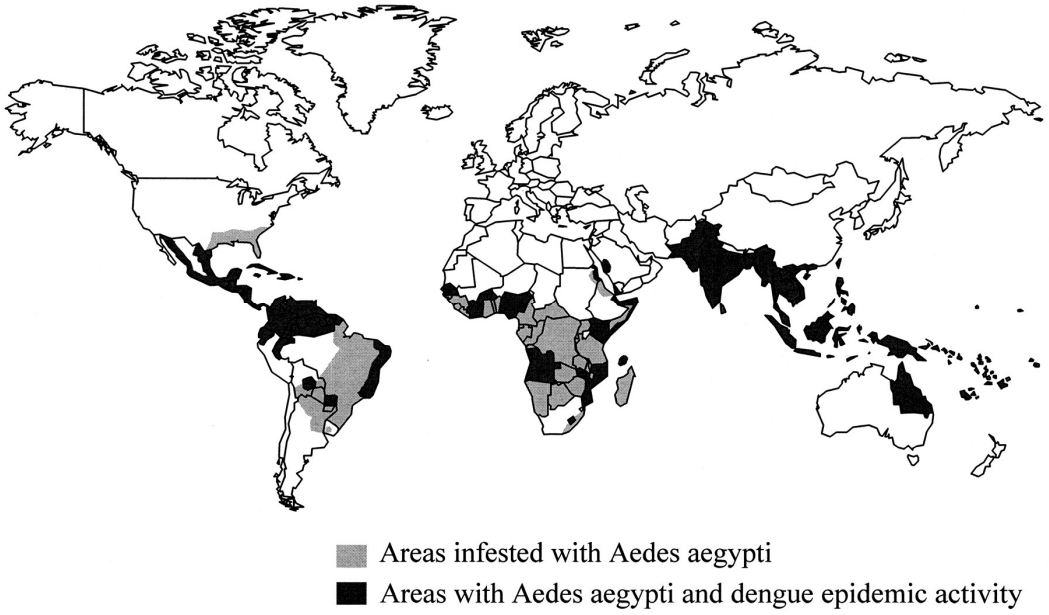


Figure 4.4 Areas with DENV and mosquito vector

Image reprinted with permission from Gubler and Meltzer, 1999

Once a human is infected with DENV the virus incubates for a period 3-14 days, after which the person can then remain asymptomatic or go on to develop a range of clinical manifestations varying in severity.[146] Dengue fever (DF) symptoms include fever, rash, nausea, muscle and joint pain.[154] It is during the febrile period that the viral titer can reach a sufficient level to be transmitted to an uninfected mosquito.[146] DF can progress to DHF which is diagnosed by fever, low platelet count, plasma leakage and hemorrhagic manifestations including skin, nasal, gastrointestinal and uterine bleeding.[155] If vasculature leakage persists, DHF can progress further to a critical stage termed Dengue Shock Syndrome where a patient's temperature falls below normal and blood pressure falls to dangerously low levels.[147]

There is no specific drug or vaccine for the treatment of DHF. Treatment of DHF includes hydration and fluid management to compensate for the vascular plasma leakage.[156] One of the difficulties in developing a vaccine is that it would have to be effective against all four serotypes.[157] Current approaches to developing a therapeutic against DENV include classical antiviral targets: inhibition of viral entry,[158] inhibition of RNA synthesis,[159] inhibition of N-terminal RNA capping[160] and inhibition of viral proteolytic processing.[161]

FLAVIVIRUS (WNV AND DENV) STRUCTURAL DETAILS/ BASIC VIROLOGY

As members of the *Flavivirus* genus, WNV and DENV share certain biological properties, including the identity of proteins encoded by the genome. The viruses are spherical in shape, 50nm in diameter and exhibit icosahedral symmetry. The surface is composed of an arrangement of membrane protein and envelope glycoprotein anchored within a lipid bilayer. Enclosed within is the nucleocapsid which contains a ~11 kb positive RNA sense-strand viral genome that encodes for 3 structural proteins: capsid protein (C), membrane protein (M), envelope protein (E), and 7 non-structural (NS) proteins: NS1, NS2A, NS2B, NS3, NS4A, NS4B, NS4B, NS5. The genome is comprised of a single, long open reading frame flanked by 5' and '3 non-coding regions.[162] The genes are ordered: 5' non-coding region-C-M-E-NS1-NS2A-NS2B-NS3-NS4A-NS4B-NS4B-NS5-3' non-coding region and are translated as a single polyprotein that is co- and post-translationally cleaved by both host and viral proteases.[156]

NS3 PROTEASE

NS3 is a multi-functional protein which serves as a component of the viral replicase and contains a nucleotide triphosphatase domain , a helicase domain and an N-terminal chymotrypsin-like serine protease.[163,164] DENV and WNV NS3 proteases share 56-65 % sequence homology (dependent on serotypes).[165,166] Their functional protease is comprised of three strictly-conserved amino acid residues (His-51, Asp-75 and Ser-135) spatially arranged to form the protease catalytic triad.[165,167] NS2B is a cofactor of NS3 that stabilizes the structure of NS3 and provides some of the surface of the substrate-binding site.[168] Binding of the NS2B cofactor is required for NS3 protease activity.[169] NS3 requires two consecutive basic residues (P1 and P2) at the cleavage site.[167] NS3 cleaves the translated viral polyprotein via a chymotrypsin-like mechanism at 6 sites with similar but distinct sequences for DENV and WNV.[165,170] X-ray crystal structures have been obtained for WNV[165,168] and DENV[171,172,173] with and without peptide-based inhibitors. NS3 is required for polyprotein processing and viral replication, making the protease an appealing target for small molecule-based inhibition.[169,174]

DENV AND WNV NS3 INHIBITORS

The initial identification of DENV NS3 protease inhibitors was reported in 2001 by Leung and coworkers who synthesized a series of peptidic α-keto amides (**4.1**) based on DENV NS3 substrates.[175] Upon nucleophilic attack by the protease, Ser-135 and the α-keto compound (**4.2**) generate a covalently bonded tetrahedral intermediate (**4.3**) that mimics the transition state structure of substrate cleavage. Although the formation of the

tetrahedral intermediate is reversible, stabilization by non-covalent interactions within the enzyme bring about tight-binding, slow dissociation and subsequent protease inhibition.[176]

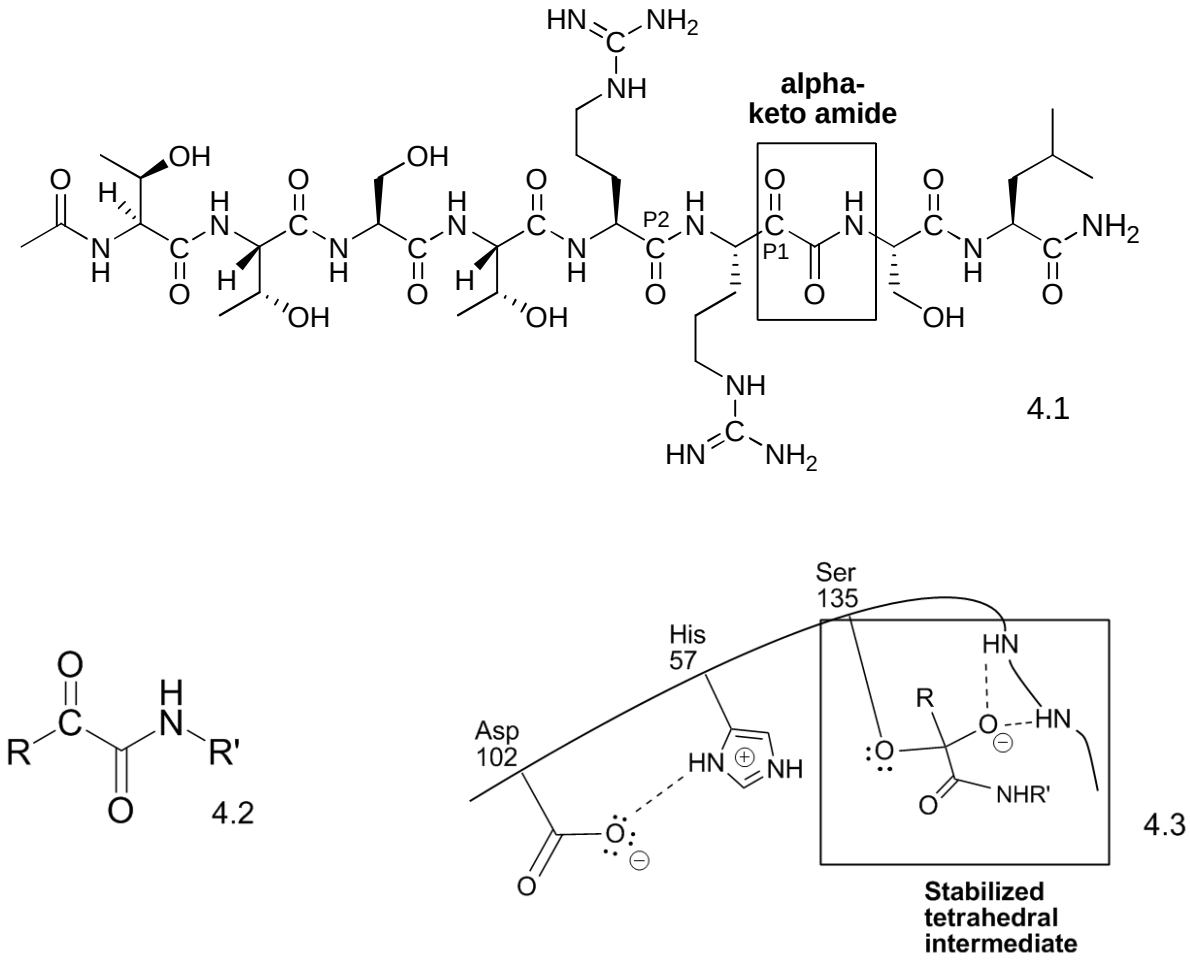


Figure 4.5: α-Keto amide DENV NS3 inhibitor and stabilized intermediate

Making use of the fact that DENV NS3 protease cleaves at basic residues, Ganesh and coworkers (2005) screened several guanidine small molecules as potential protease inhibitors.[177] They identified three compounds that displayed modest inhibitory concentration of both DENV and WNV NS3 proteases.

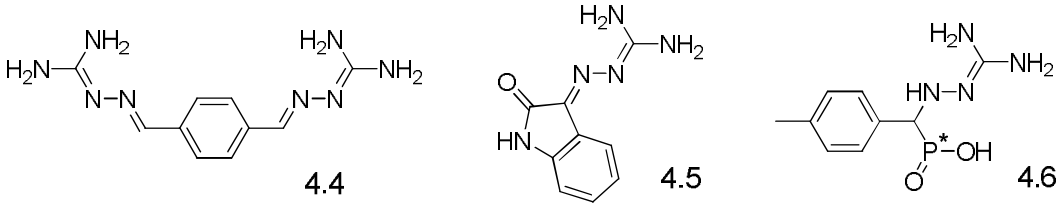


Figure 4.6: Guanidine DENV and WNV NS3 inhibitors

Yin and coworkers[178] (2006) identified three DENV NS3 protease inhibitors based on a known tetrapeptide substrate sequence.[179] The active inhibitors they identified (Bz-Nle-Lys-Arg-Arg-R) contained electrophilic C-terminal aldehyde, boronic acid or trifluoromethylketone, which also act as transition state analogs.

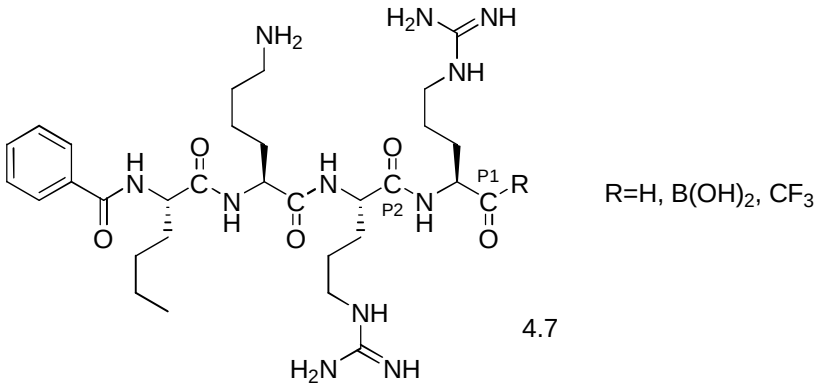


Figure 4.7: Transition-state analog DENV NS3 inhibitors

Lim and coworkers (2011) discovered a series of peptidomimetic WNV NS3 protease inhibitors.[180] By replacing the P1 arginine of a known substrate with decarboxylated, N-functionalized arginine peptoid mimics, they identified several novel competitive inhibitors.

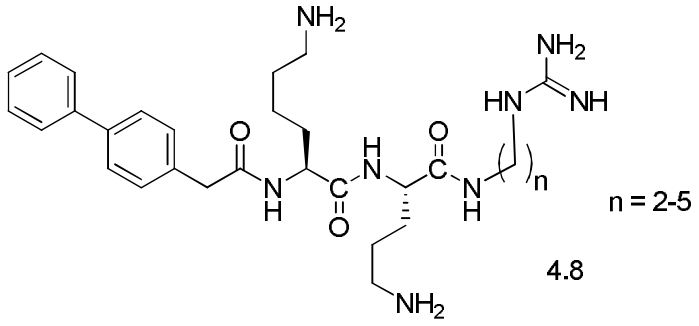


Figure 4.8: Decarboxylated arginine peptoid WNV NS3 inhibitors

Yang and coworkers (2011) utilized an *in vitro* high throughput screen of 41,600 compounds and obtained three compounds (**4.9**-**4.11**) that inhibited DENV NS3 protease.[181] **4.10** and **4.11** were found to be cytotoxic, leaving compound **4.9** as the only candidate from the HTS. Compound **4.9** also inhibited viral RNA replication but not viral translation (in addition to protease function, NS3 also contains a replicase domain[163,164]). They proposed that **4.9** did not act by inhibition of NS3 at the proteolytic active site, but rather by a novel mechanism of action of that involved interruption of protein-protein interactions between NS3 and the NS2B cofactor.

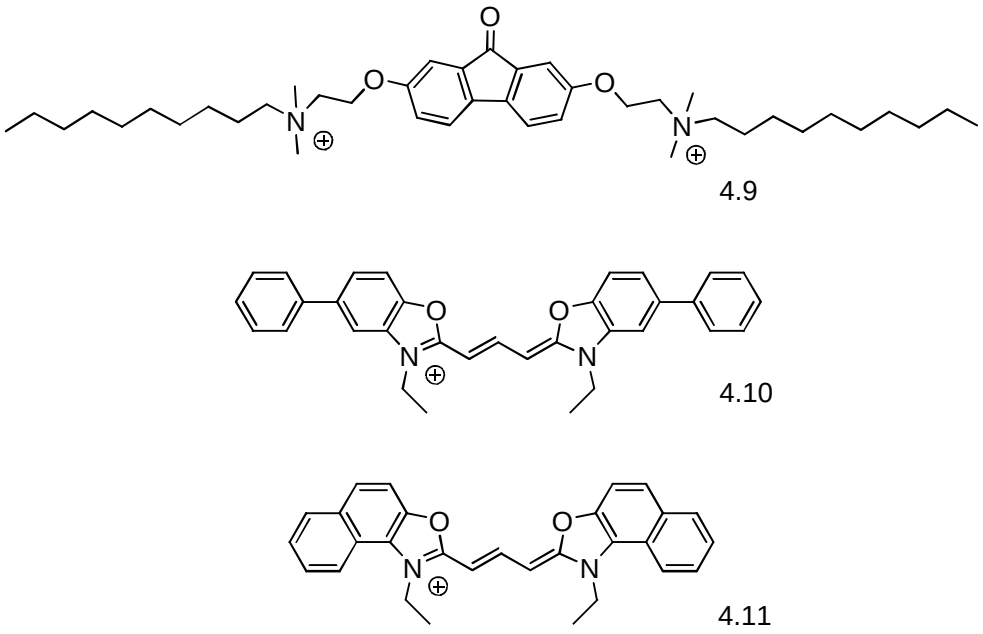
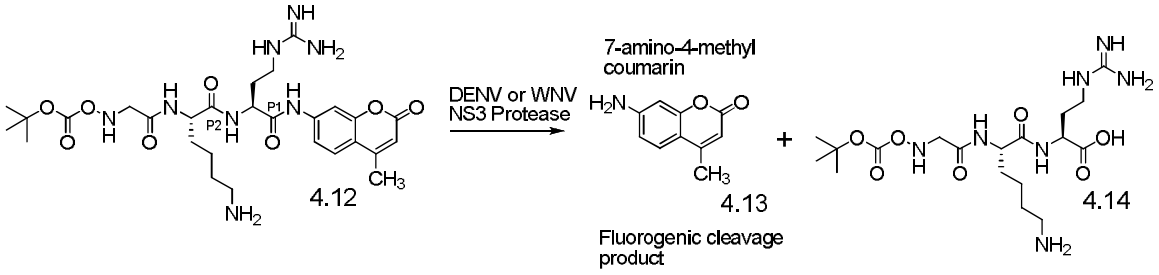


Figure 4.9:DENV NS3 inhibitors identified by HTS

BROAD-SPECTRUM NS3 INHIBITORS

Owing to the sequence homology and structural similarity of DENV and WNV NS3 proteases, Dr. Stanley Watowich and co-workers sought "broad-spectrum" small molecule inhibitors of the related proteases.[166] An initial high-throughput *in silico* screen was performed using the EUDOC docking program[182] on a subset of a Mayo Clinic virtual chemical library containing ~200,000 compounds. The compounds were screened against previously reported DENV-2 NS3 protease crystal structures (PDB identifiers 1BEF and 1DF9).[183,184] Only commercially available compounds that are neutral at pH 7.4 were considered. Twenty compounds were purchased from Sigma-Aldrich based on results from the EUDOC virtual screen.

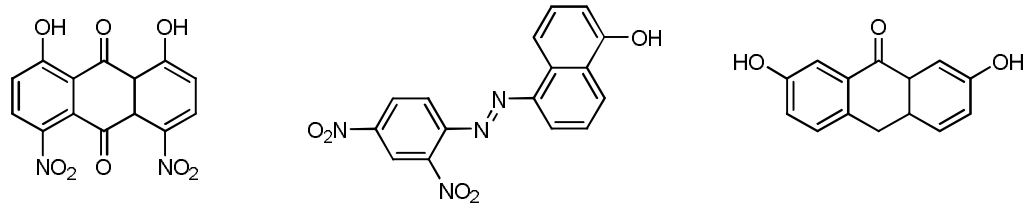


Scheme 4.1: NS3 cleavage at P1 to liberate AMC fluorophore

The molecules were then assayed *in vitro* to assess their ability to inhibit DEN2V NS3 protease.[185] The assay measured the ability of the compounds to inhibit the cleavage of Boc-Gly-Lys-Arg-AMC (**4.12**), a dibasic substrate for NS3.[186] The protease-catalyzed cleavage at P1 of the substrate was measured by monitoring the fluorescence of liberated 7-amino-4-methyl coumarin (AMC, **4.13**, Scheme 1).[187] The five best NS3 inhibitors were then tested for their ability to inhibit viral replication in an ELISA-like cell-based replication assay. Of those five molecules, **ARDP0006** (Figure 4.10) displayed the lowest EC_{50} (4.2 μM).

A subsequent structure similarity search of **ARDP0006** prompted the purchase of twenty-six structurally similar compounds. Among the twenty-six compounds were other anthraquinones, anthracenone **6A60,** and structurally dissimilar phenyldiazenylnaphthalene **6A49**. This set of compounds was examined for the ability to inhibit DEN2V NS3 protease. **6A49** and **6A60** displayed the lowest inhibition constants, K_i = 15 μM and 7 μM, respectively. The set of molecules was then tested for the ability to inhibit WNV NS3 protease. **6A49** and **6A60** displayed comparable activity for the inhibition of WNV NS3 protease, with K_i values of 34 μM and 11 μM, respectively.

6A60 and **6A49** were chosen as scaffolds for the synthesis of chemical libraries of potential broad-spectrum inhibitors of DENV and WNV NS3.



ARDP0006 6A49 6A60

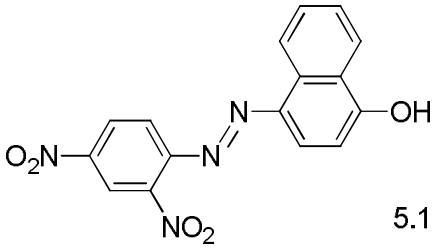
Figure 4.10 Lead Compounds

CONCLUSION

The Flaviviruses WNV and DENV represent serious health threats to humans worldwide. WNV and DENV are transmitted to humans by mosquito vectors and cause West Nile meningitis/encephalitis and Dengue hemorrhagic fever, respectively. There is no specific treatment, neither drug nor vaccine, to combat these viruses. As members of the same genus, Dengue and West Nile viruses share important features including an NS3 protease with >50% sequence homology. The NS3 protease is required for post-translational processing of the viral polyprotein, making it an excellent target for inhibition. Several different chemotherapeutic approaches targeting NS3 have been investigated, including peptidic transition-state analogs, reversible small-molecule inhibitors, de-carboxylated amino acid analogs and small molecules that disrupt essential protein-protein interactions. Owing to the substantial sequential and structural similarity of the two proteases, Watowich and coworkers performed a series of *in silico* and *in vitro*

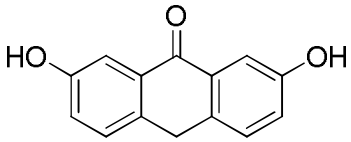
experiments and identified two lead molecules with distinct chemical structures that inhibit both DENV and WNV proteases. We seek to synthesize a library of structurally related compounds based on these two lead molecules in order to identify small molecule, broad-spectrum inhibitors of both DENV and WNV NS3 proteases with improved biological activity.

CHAPTER 5: SYNTHESIS OF ANALOGS OF LEAD COMPOUND 6A49



5.1

6A49



5.2

6A60

Figure 5.1: Lead compounds

Of the two lead compounds, 6A49 and 6A60, the former was chosen for the relative ease by which analogs could be synthesized. The diazene functional group linking the two aromatic rings of 6A49 is comprised of two sp^2-hybridized nitrogen atoms with both C-N-N bond angles of approximately 120°. The nitrogens' unhybridized 2p-orbitals form a π-bond between the two atoms which prevents rotation about the N-N bond. The C-N-N bond angles and relative positions of the pendant aromatic rings can be maintained by replacing the sp^2-hybridized nitrogen atoms with isosteric functional groups that mimic the bond angles and spatial arrangement provided by the diazene nitrogens.[188] The olefin of stilbene **5.3**, amide **5.4** and imine functional group of compound **5.5** are relatively straightforward synthetic replacements for the diazenyl functional group of **5.2** which would preserve the 120° bond angles.

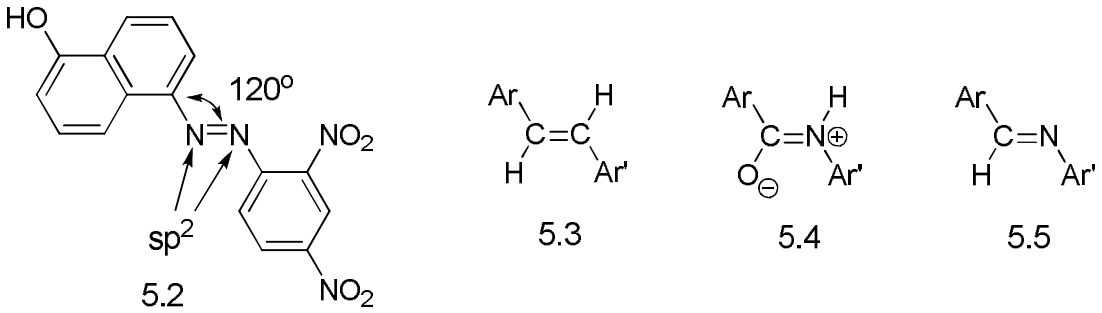


Figure 5.2: Bioisosteric replacecements of diazene

STILBENES

Stilbenes (e.g. **5.3**) possess the noteworthy ability of being able to bind to different receptors, and as such they are considered to be "privileged structures".[189,190] There are several examples of pharmacologically active stilbenes in the literature. 4,4'-diisothiocyanostilbene-2,2'disulfonic acid (DIDS) inhibits human immunodeficiency virus (HIV) type-1 growth by inhibiting surface glycoprotein CD4.[191] (E)-3-methoxy-5-hydroxystilbene and other structurally similar stilbenes inhibit the growth of several clinically relevant bacteria.[192] The cis-stilbene Combretastatin A-4 is a tubulin polymerization inhibitor which affects vascular endothelial cells in tumors.[193] The most extensively investigated stilbene, resveratrol (2,5,4'-trihydroxystilbene) has been the subject of a considerable amount of research and has been linked to several functions including cardio-protective effects[194] anti-ageing effects,[195] anti-inflammatory[196] and anti-carcinogenic effects.[197]

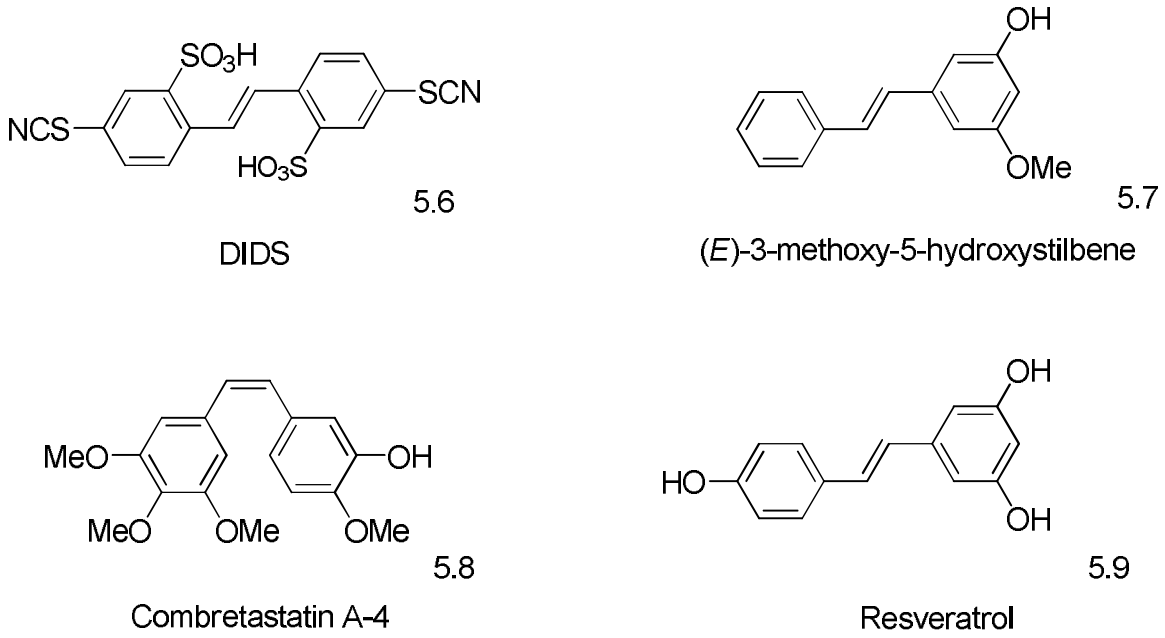
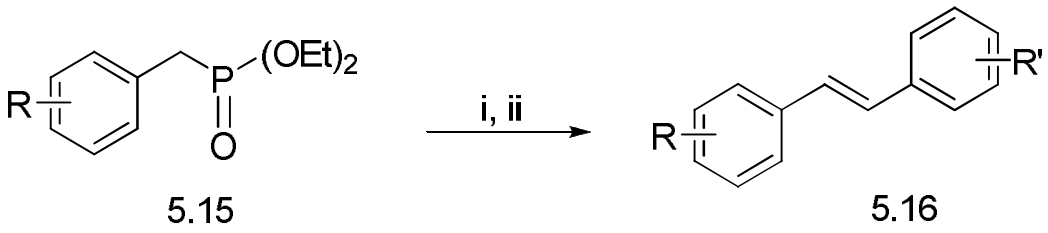


Figure 5.3: Pharmacologically active stilbenes

The desired stilbene analogs were synthesized via Horner-Wadsworth-Emmons (HWE) reactions[198,199] between aromatic dialkyl benzylphosphonate esters and aromatic aldehydes. The HWE reactions were run at 0 °C in dimethylformamide employing sodium hydride as the base (Scheme 5.1).



Conditions and Reagents: (i) NaH, DMF, 0 °C (ii) aromatic aldehyde

Scheme 5.1: General HWE reaction for the synthesis of stilbenes

The five dialkyl arylphosphonate esters employed in the syntheses of the stilbenes are listed in Figure 5.4. In addition to stilbenes, the dialkyl naphthylphosphonate esters **5.13** and **5.14** were used to synthesize 1-styrylnaphthalene analogs.

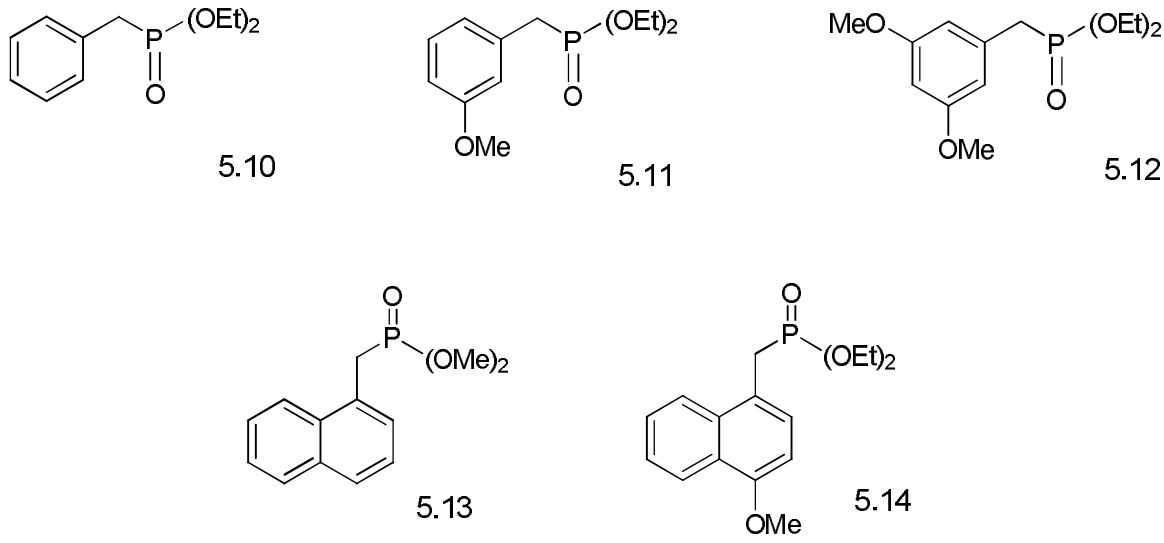


Figure 5.4: HWE phosphonate reagents

The mechanism of the Horner-Wadsworth-Emmons reaction (Figure 5.5) involves deprotonation of a benzyl phosphonate (**5.15**) to give phosphoryl-stabilized carbanion **5.17**. The carbanion then nucleophilically attacks either face of aromatic aldehyde **5.18** to give two intermediate oxyanions **5.20** and **5.24**. These oxyanions then rearrange to form the two equilibrating oxaphosphatene intermediates **5.21** and **5.25**. The subsequent collapse of the oxaphosphatene into the alkene products is slow, allowing the equilibrium to favor the more stable *anti*-diaryloxaphosphatene **5.21**.[200] As a result, the formation of (E)-alkene **5.22** is favored over (Z)-alkene **5.26**.

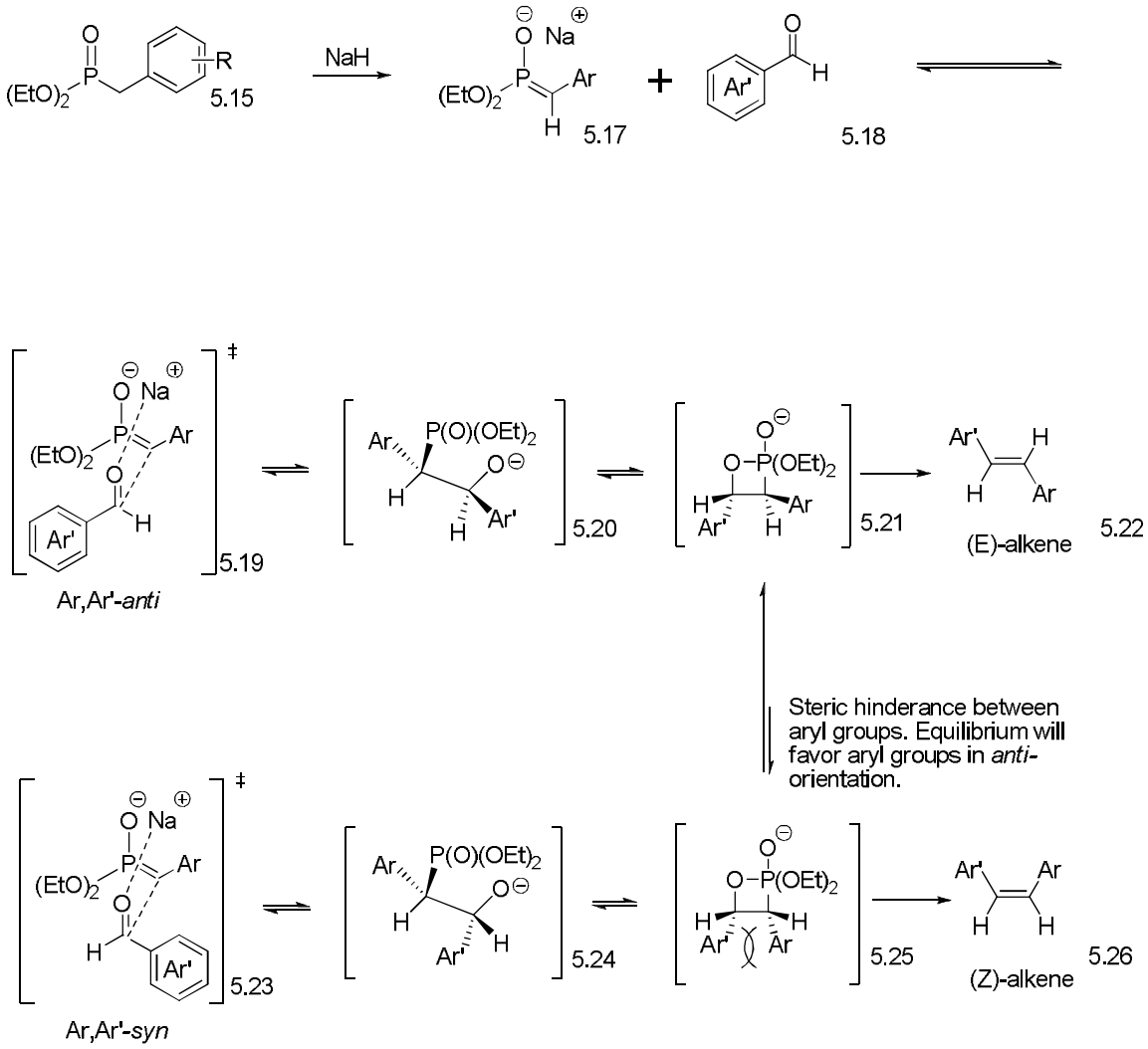


Figure 5.5: HWE mechanism

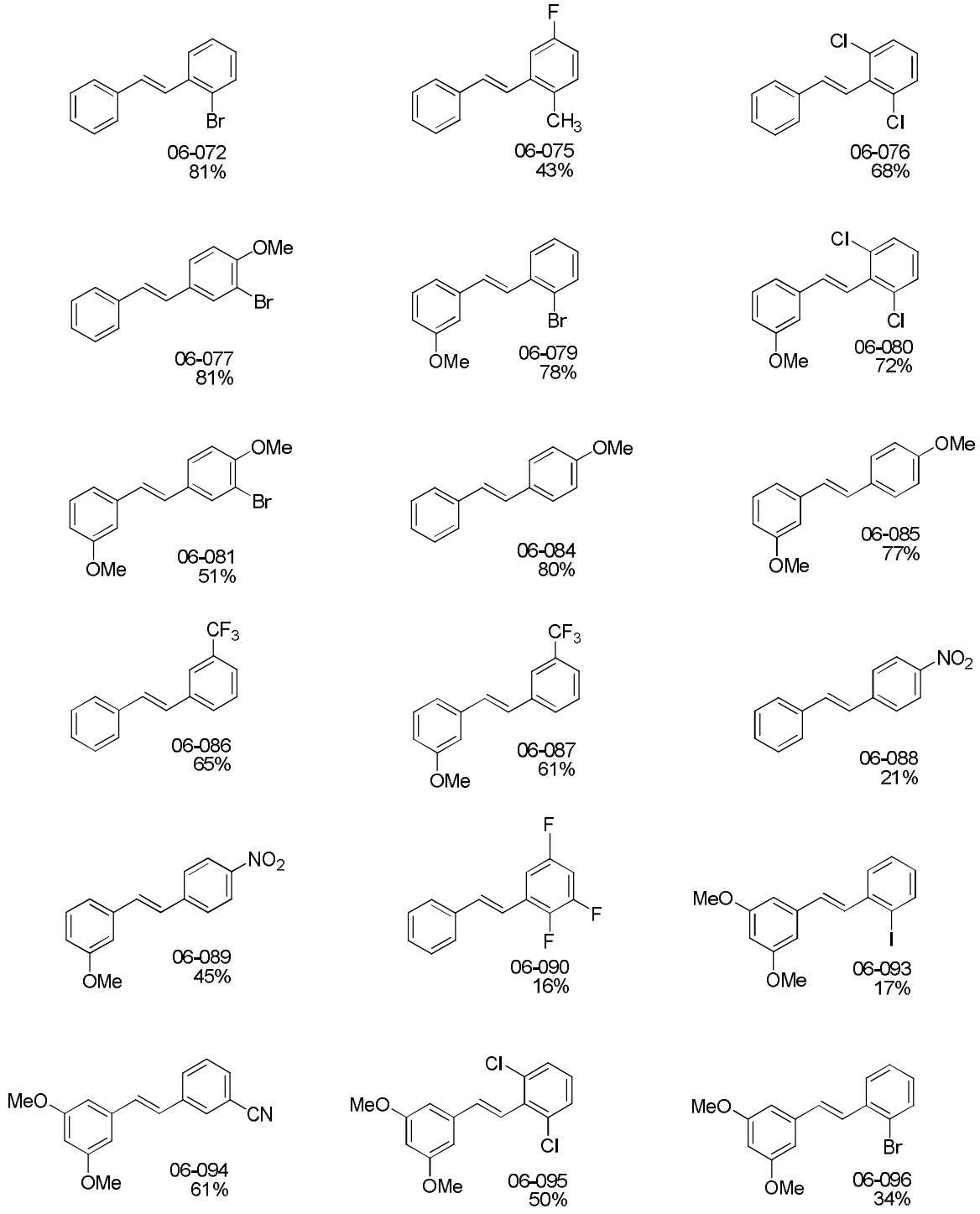


Figure 5.6: Synthesized stilbenes

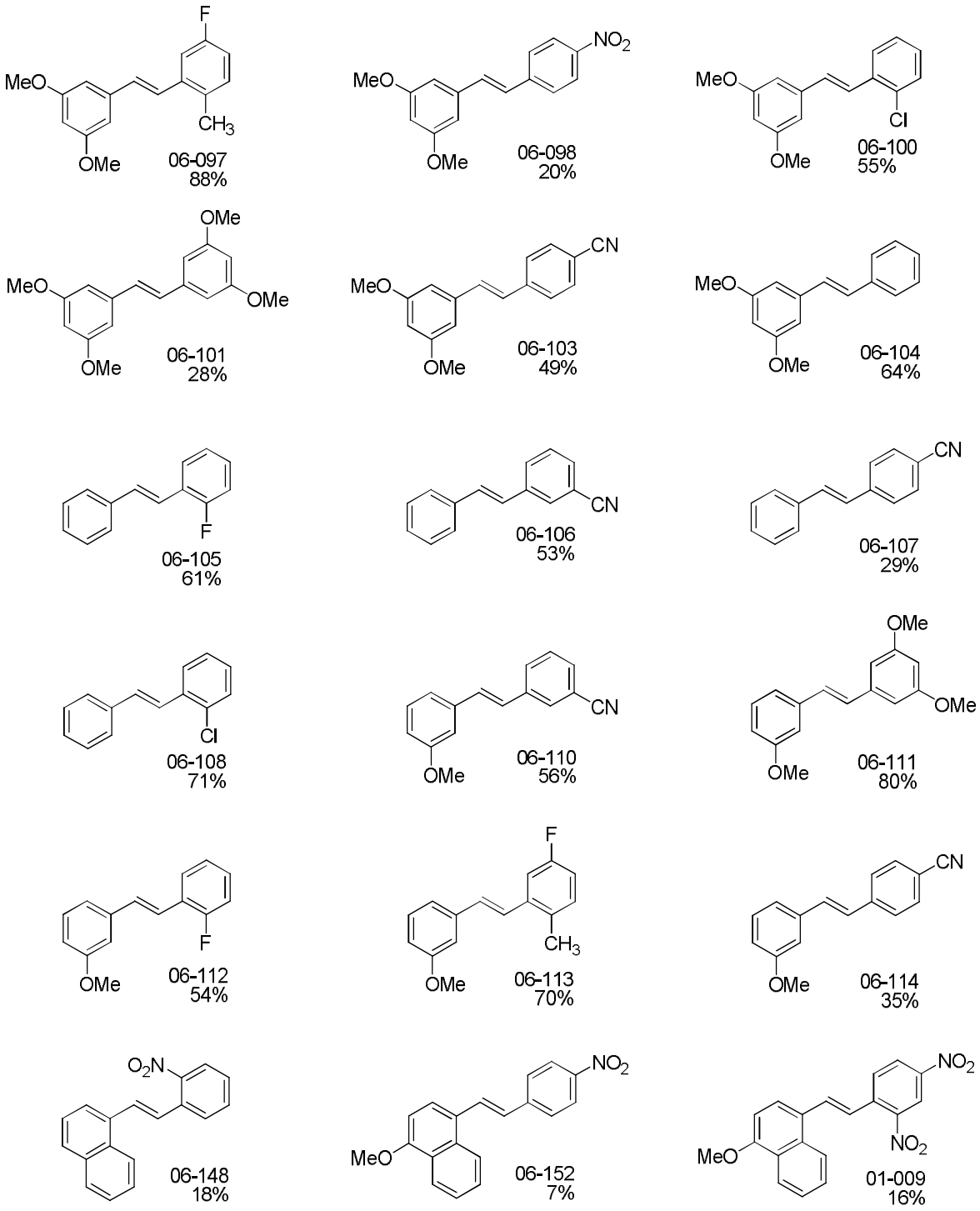
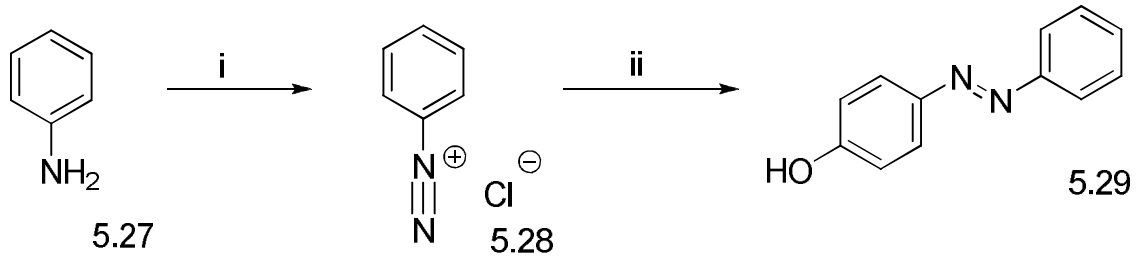


Figure 5.7: Synthesized stilbenes and styrylnaphthalenes

DIARYLDIAZENES

Additionally, we synthesized compounds whose structures more closely resembled that of lead compound 6A49. A series of unsymmetrical diaryldiazenes were synthesized via diazotization-coupling reactions between anilines and phenols.[201,202] Diaryldiazenes represent a large group of synthetic organic dyes and the diazotization-coupling reaction is a well-established reaction used extensively in the dyes and pigments industry.[201] The general diazotization-coupling reaction involves treating aniline (**5.27**) with hydrochloric acid and sodium nitrite in order to obtain an intermediate benzene diazonium chloride (**5.28**). Subsequent addition of phenol in $NaOH/H_2O/EtOH$ results in reaction at the *para*- position of phenol to yield the unsymmetrical diaryldiazene **5.29**.



Conditions and Reagents: (i) HCl, $NaNO_2$, 0 °C, 20 minutes (ii) phenol, NaOH, EtOH, 0 °C, 1 hour

Scheme 5.2: Diazotization-coupling reaction

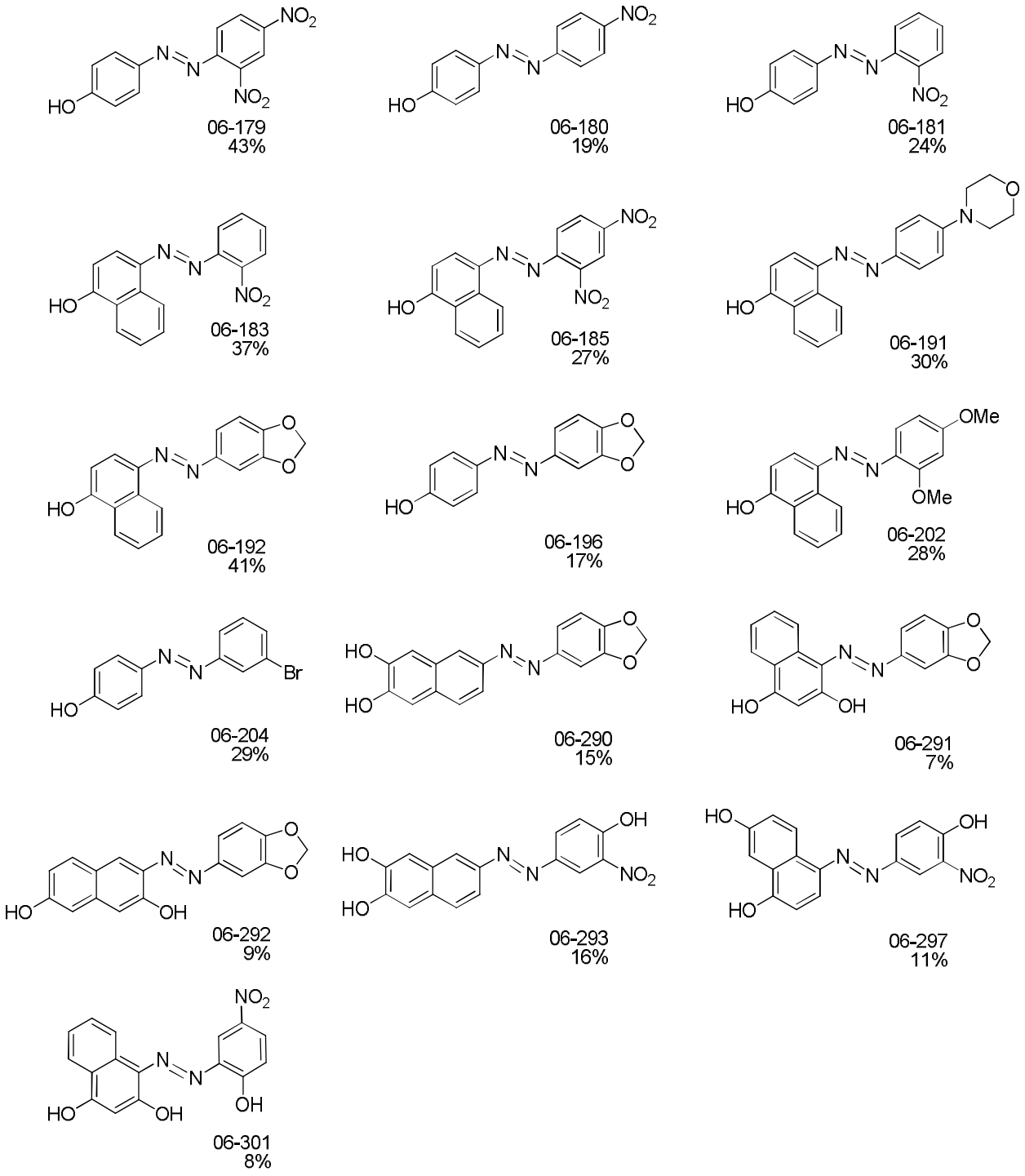


Figure 5.8: Synthesized diaryldiazenes

RESULTS

The synthesized compounds were evaluated for activity in the lab of Dr. Stan Watowich. The stilbenes and diaryldiazenes were assessed for their ability to inhibit DENV and WNV NS3 protease cleavage of Boc-Gly-Arg-Arg-AMC, Boc-Gly-Lys-Arg-AMC and Ac-Asp-Phe-Ala-Ser-Gly-Lys-Arg-AMC substrates. In summary, for the determination of inhibition constants, four different concentrations of stilbene or diaryldiazene were mixed with buffer, NS3 and six different concentrations of peptide substrate. Initial reaction velocities were determined by the measurement, in increments of five minutes, of liberated AMC fluorescence which was then converted to concentration units by serial dilution/linear regression analysis of AMC. [166]

The stilbene compounds did not exhibit inhibitory activity against either protease. Many of these compounds displayed poor water-solubility. The inhibition constants of lead compound **6A49** against DENV and WNV NS3 were 15 and 34 μM, respectively. The inhibition constant of our synthesized compound **06-185** against DENV NS3 was 119 μM (WNV not tested). Analyses of lead compound **6A49** confirmed the structures were identical. Interestingly, removing one of the aromatic rings in going from **06-185** to **06-179** reduced activity almost 10-fold, suggesting that the second aromatic ring of the naphthyl group interacts favorably with the protease. Compound **06-301** displayed inhibitory activity against WNV NS3 essentially equal to the lead compound: 28 vs. 34 μM, respectively.

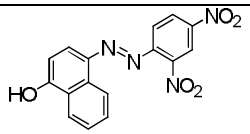
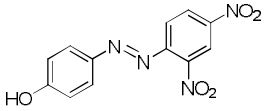
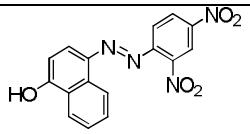
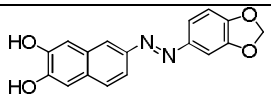
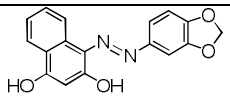
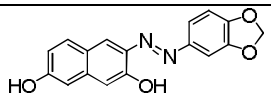
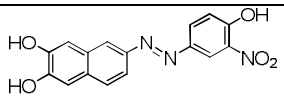
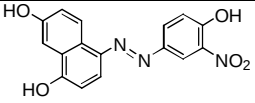
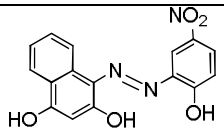
Compound	Structure	DENV Ki	Ki WNV (μM)
6A49		**15**	**34**
06-179		**1110**	*****
06-185		**119**	*****
06-290		**75**	*****
06-291		**229**	**214**
06-292		**92**	**110**
06-293		**432**	*****
06-297		**358**	*****
06-301		**142**	**28**

Table 5.1: Ki values for compounds with NS3 inhibitory activity, * = not tested

CONCLUSION

A series of stilbenes and diaryldiazenes was synthesized based on the structurally similar lead compound **6A49**.The styrylnaphthalene compounds (**06-148**, **06-152** and **01-009**) displayed the poorest yields, which is probably due to steric hinderance of the aromatic rings of the naphthyl phosphonate ester.

The diazotization-coupling reaction was employed for a variety of electron-rich and electron-poor anilines with no significant difference in yields. Phenol and naphthol also showed no significant difference in yields. The reactions involving naphthalenediols, however resulted in especially low yields. This can be attributed to the fact that the naphthalenediols can react at multiple positions around the naphthalene ring system; TLCs for these reactions displayed multiple spots.

The iterations of synthesis and analysis of these molecules has led us to a class of compounds, naphthalenediol diazenes which consistently show inhibitory activity against NS3. Three of these compounds, **06-290**, **06-292** and **06-301** were equal or better inhibitors of DENV or WNV NS3 than lead compound **6A49**. Continued efforts will lead us to synthesize compounds with improved activity against both DENV and WNV NS3 proteases.

EXPERIMENTAL

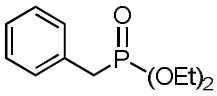
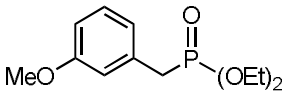
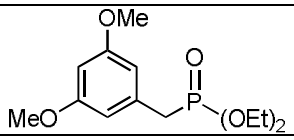
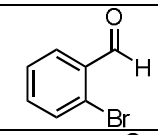
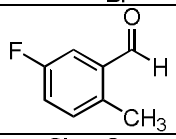
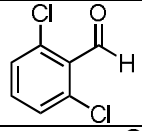
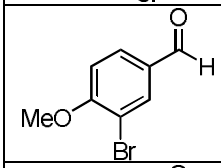
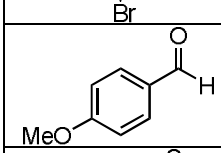
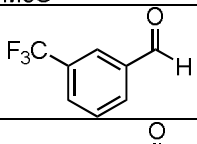
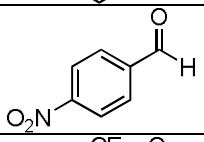
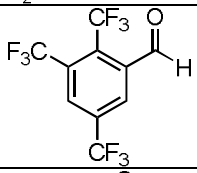
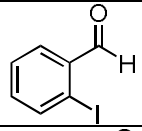
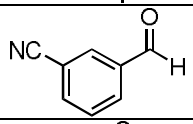
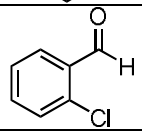
General procedures

All chemicals were purchased from Acros Organics or Sigma-Aldrich Co. and used without additional purification unless otherwise noted. Reactions were monitored by

thin layer chromatography using Silicycle glass backed extra hard 60 Å, F_{254}, 250 μm plates. Column chromatography was performed using Silicycle SiliaFlash P60, 230-400 mesh silica gel. ^{1}H and ^{13}C NMR spectra were obtained on a JEOL ECX 500 NMR Spectrometer (500 MHz). ^{1}H NMR spectra are reported in parts per million (δ) relative to tetramethylsilane. Coupling constants (J) are reported in Hertz. Unless noted otherwise, all reactions were carried out under N_2 atmosphere. All glassware was dried in an oven at 120 °C.

General procedure for the synthesis of stilbenes

A stirred solution of diethyl arylphosphonate (0.48 mmol, 1.2 equiv.) in THF (3 mL) was cooled to 0 °C. The rubber septum was removed and NaH (0.48 mmol, 1.2 equiv.) was added and the septum was replaced. After stirring for 20 minutes at 0 °C, a solution of aldehyde (0.4 mmol, 1 equiv.) in THF (3 mL) was added and the reaction was monitored by TLC. The reaction was quenched by the addition of a saturated aqueous solution of ammonium chloride (5 mL) and extracted with EtOAc (3 × 5 mL). The organic layers were combined and washed with brine (10 mL), dried with Na_2SO_4 and concentrated under vacuum. The stilbenes were then purified by column chromatography. Table **5.2** depicts the diethylbenzylphosphonates and aromatic aldehydes used to synthesize the corresponding stilbenes **06-072** to **06-114**.

			
	**06-072** **81%**	**06-079** **78%**	**06-096** **34%**
	**06-075** **43%**	**06-113** **70%**	**06-097** **88%**
	**06-076** **68%**	**06-080** **72%**	**06-095** **50%**
	**06-077** **81%**	**06-081** **51%**	-
	**06-084** **80%**	**06-085** **77%**	-
	**06-086** **65%**	**06-087** **61%**	-
	**06-088** **21%**	**06-089** **45%**	**06-098** **20%**
	**06-090** **16%**	-	-
	-	-	**06-093** **17%**
	**06-106** **53%**	**06-110** **56%**	**06-094** **61%**
	**06-108** **71%**	-	**06-100** **55%**

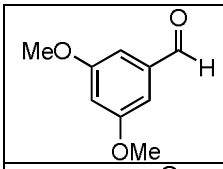
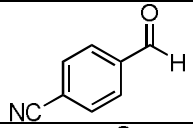
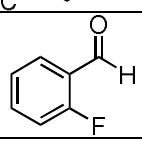
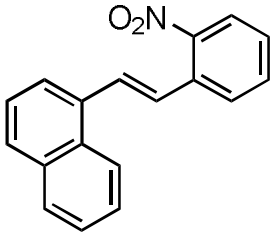
	**06-104** **64%**	**06-111** **80%**	**06-101** **28%**
	**06-107** **29%**	**06-114** **35%**	**06-103** **49%**
	**06-105** **61%**	**06-112** **54%**	**-**

Table 5.2: Dialkylphosphonates and aromatic aldehydes used to synthesize the corresponding stilbenes

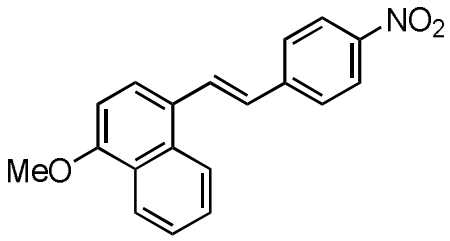
(E)-1-(2-nitrostyryl)naphthalene (06-148)



A stirred solution of diethyl (4-methoxynaphthalen-1-yl)methylphosphonate (0.712 g, 2.84 mmol, 1.2 equiv.) in THF (10 mL) was cooled to 0 °C. The rubber septum was removed and LiHMDS (0.9 M, 3.16 mL, 2.84 mmol, 1.2 equiv.) was added and the septum was replaced. After stirring for 20 minutes at 0 °C, a solution of 2-nitrobenzaldehyde (0.35 g, 2.37 mmol, 1 equiv.) in THF (10 mL) was added and the reaction was monitored by TLC. The reaction was quenched by the addition of a saturated aqueous solution of ammonium chloride (20 mL) and extracted with EtOAc (3 × 10 mL). The organic layers were combined and washed with brine (20 mL), dried with Na_2SO_4 and concentrated under vacuum. The resulting residue was purified by flash

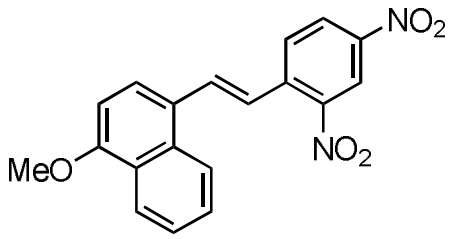
chromatography, eluting with 4:1 hexane: ethyl acetate to give 0.11 g of the naphthylstyrene (18%).

(E)- 1-methoxy-4-(4-nitrostyryl)naphthalene (06-152)



A stirred solution of diethyl-1-naphthylphosphonate (0.25 g, 0.81 mmol, 1.1 equiv.) in THF (5 mL) was cooled to 0 °C. The rubber septum was removed and KOtBu (1.0 M, 0.81 mL, 0.81 mmol, 1.1 equiv.) was added and the septum was replaced. After stirring for 20 minutes at 0 °C, a solution of 4-nitrobenzaldehyde (0.11 g, 0.74 mmol, 1 equiv.) in THF (5 mL) was added and the reaction was monitored by TLC. The reaction was quenched by the addition of a saturated aqueous solution of ammonium chloride (10 mL) and extracted with EtOAc (3 × 5 mL). The organic layers were combined and washed with brine (10 mL), dried with Na_2SO_4 and concentrated under vacuum. The resulting residue was purified by flash chromatography, eluting with 4:1 hexane: ethyl acetate to give 0.02 g of the naphthylstyrene (7%).

(E)- 1-(2,4-dinitroxtyryl)-4-methoxynaphthalene (01-009)

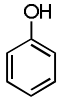
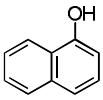
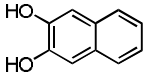
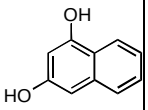
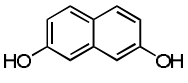
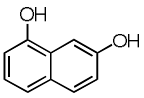
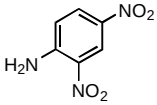
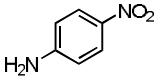
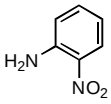
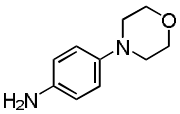
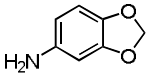
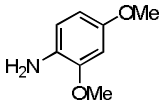


A stirred solution of diethyl-1-naphthylphosphonate (0.25 g, 0.81 mmol, 1.1 equiv.) in THF (5 mL) was cooled to 0 °C. The rubber septum was removed and KOtBu (1.0 M, 0.81 mL, 0.81 mmol, 1.1 equiv.) was added and the septum was replaced. After stirring for 20 minutes at 0 °C, a solution of 2,4-dinitrobenzaldehyde (0.15 g, 0.74 mmol, 1 equiv.) in THF (5 mL) was added and the reaction was monitored by TLC. The reaction was quenched by the addition of a saturated aqueous solution of ammonium chloride (10 mL) and extracted with EtOAc (3 × 5 mL). The organic layers were combined and washed with brine (10 mL), dried with Na_2SO_4 and concentrated under vacuum. The resulting residue was purified by flash chromatography, eluting with 4:1 hexane: ethyl acetate to give 0.04 g of the naphthylstyrene (16%).

General procedure for the synthesis of diaryldiazenes

To a stirred suspension of aniline (0.51 g, 5.5 mmol), in hydrochloric acid (15 mL, 1.1 mol/L) at 0 °C was added a solution of sodium nitrite (0.4 g, 5.8 mmol, 1.05 equiv.) in water (28 mL). After stirring for 20 min at 0 °C, the resulting solution was added dropwise to a solution of phenol (5.5 mmol, 1 equiv.) in sodium hydroxide (0.22 g, 5.5 mmol), ethanol (40 mL) and water (120 mL) at 0 °C. The resulting brightly colored mixture was stirred vigorously for 2 hours, after which time the solid was collected in a

Buchner funnel and washed with water (3 × 10 mL). The filter paper was placed in the dark and allowed to dry overnight. The diaryldiazenes were then purified by column chromatography. Table **5.3** depicts the phenols and aromatic aldehydes used to synthesize the corresponding diaryldiazenes.

						
	**06-179 43%**	**06-185 30%**	-	-	-	-
	**06-180 19%**	-	-	-	-	-
	**06-181 24%**	**06-183 37%**	-	-	-	-
	-	**06-191 30%**	-	-	-	-
	**06-196 17%**	**06-192 41%**	**06-290 15%**	**06-291 7%**	**06-292 9%**	-
	-	**06-202 28%**	-	-	-	-

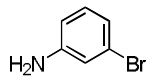
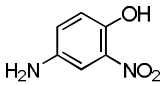
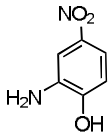
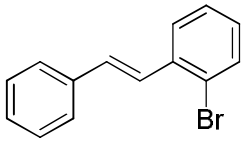
	**06-204 29%**	-	-	-	-	-
	-	-	**06-293 16%**	-	-	**06-297 11%**
	-	-	-	**06-301 8%**	-	-

Table 5.3: Anilines and phenols used to synthesize the corresponding diaryldiazenes

NMR Data

(E)-1-bromo-2-styrylbenzene (06072)

81% yield

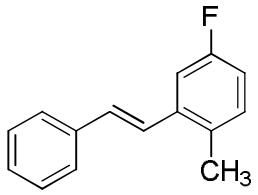


^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (dd, J = 8.02, 1.72 Hz, 1H), 7.59 (dd, J = 8.02, 1.15 Hz, 1H), 7.56 (d, J = 7.45 Hz, 2H), 7.47 (d, J = 16.61 Hz, 1H), 7.38 (t, J = 6.87 Hz, 2H), 7.30 (dt, J = 8.02, 7.45 Hz, 2H), 7.12 (td, J = 7.45, 1.72 Hz, 1H), 7.04 (d, J = 16.04 Hz, 1H)

^{13}C NMR (500 MHz, $CDCl_3$) δ 137.3, 137.2, 133.2, 131.6, 129.0, 128.9, 128.3, 127.7, 127.6, 127.0, 126.9, 124.3

(E)-4-fluoro-1-methyl-2-styrylbenzene (06075)

43% yield

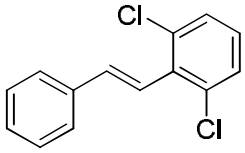


^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (d, J = 2.04 Hz, 2H), 7.36 (t, J = 7.45 Hz, 2H), 7.30-7.24 (m, 3H), 7.12 (dd, J = 8.02, 6.30 Hz, 1H), 6.99 (d, J = 16.04 Hz, 1H), 6.87 (td, J = 8.59, 2.86 Hz, 1H), 2.38 (s, 3H)

^{13}C NMR (500 MHz, $CDCl_3$) δ 162.6, 160.7, 138.1, 131.7, 131.4, 131.0, 128.8, 128.0, 126.8, 125.6, 114.3, 114.1, 111.8, 111.6, 19.3

(E)-1,3-dichloro-2-styrylbenzene (06076)

68% yield

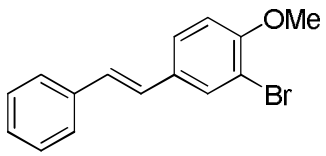


^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (d, J = 7.45 Hz, 2H), 7.39 (td, J = 7.45, 1.15 Hz, 2H), 7.35 (d, J = 8.02 Hz, 2H), 7.32 (tt, J = 7.22, 1.15 Hz, 1H), 7.19-7.13 (m, 2H), 7.12 (t, J = 8.02Hz, 1H)

^{13}C NMR (500MHz, $CDCl_3$) δ 137.1, 136.9, 134.7, 128.9, 128.7, 128.5, 128.2, 126.9, 122.7

(E)-2-bromo-1-methoxy-4-styrylbenzene (06077)

81% yield

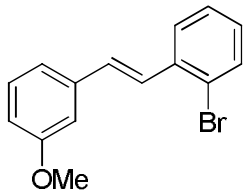


^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, J = 2.29Hz, 1H), 7.49 (dt, J = 7.33, 1.37 Hz, 2H), 7.40 (dd, J = 8.24, 2.29 Hz, 1H), 7.36 (t, J = 7.33 Hz, 2H), 7.27 (tt, J = 7.33, 0.92 Hz, 1H), 6.99 (bs, 2H), 6.89 (d, J = 8.24 Hz, 1H), 3.92 (s, 3H)

^{13}C NMR (500MHz, $CDCl_3$) δ 155.4, 137.2, 131.7, 131.1, 128.8, 128.0, 127.7, 127.0, 126.8, 126.5, 112.2, 112.0, 56.4

(E)-1-bromo-2-(3-methoxystyryl)benzene (06079)

78% yield

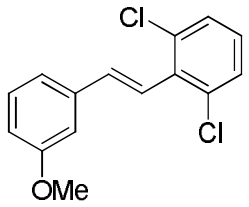


^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (dd, J = 7.45, 1.15 Hz, 1H), 7.58 (dd, J = 8.02, 1.15 Hz, 1H), 7.45 (d, J = 16.04 Hz, 1H), 7.32-7.27 (m, 2H), 7.15 (d, J = 7.45Hz, 1H), 7.11 (dt, J = 7.45, 1.72 Hz, 1H), 7.08 (t, J = 1.72 Hz, 1H), 7.00 (d, J = 16.04 Hz, 1H), 6.85, (dd, J = 8.02, 1.72 Hz, 1H), 3.85 (s, 3H)

^{13}C NMR (500 MHz, $CDCl_3$) δ 160.0, 138.6, 137.1, 133.2, 131.4, 129.8, 129.0, 127.9, 127.7, 126.8, 124.3, 119.6, 113.7, 112.3, 55.4

(E)-1,3-dichloro-2-(3-methoxystyryl)benzene (06080)

72% yield

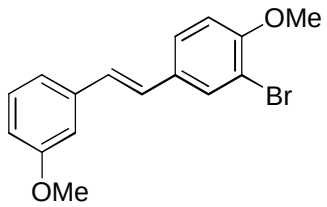


^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (d, J = 8.24 Hz, 2H), 7.31 (t, J = 7.79 Hz, 1H), 7.15 (dt, J = 7.79, 1.37 Hz, 1H), 7.13-7.09 (m, 3H), 7.08 (t, J = 2.29 Hz, 1H), 6.87 (dd, J = 8.24, 2.29 Hz, 1H), 3.86 (s, 3H)

^{13}C NMR (500 MHz, $CDCl_3$) δ 160.0, 138.3, 137.0, 134.7, 129.8, 128.7, 128.2, 123.0, 119.6, 114.1, 112.1, 55.4

(E)-2-bromo-1-methoxy-4-(3-methoxystyryl)benzene (06081)

51% yield



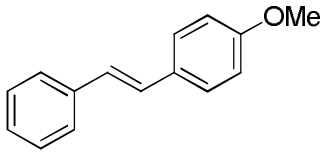
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, J = 1.72 Hz, 1H), 7.38 (dd, J = 8.59, 1.72 Hz, 1H), 7.26 (t, J = 7.45 Hz, 1H), 7.08 (d, J = 7.45 Hz, 1H), 7.01 (bs, 1H), 6.95 (d, J = 5.15 Hz,

2H), 6.84, (d, J = 8.02 Hz, 1H), 6.81 (dd, J = 8.59, 2.86 Hz, 1H), 3.90 (s, 3H), 3.84 (s, 3H)

^{13}C NMR (500 MHz, $CDCl_3$) δ 160.0, 155.5, 138.7, 131.6, 131.1, 129.8, 127.9, 127.2, 127.0, 119.2, 113.4, 112.2, 112.0, 111.7, 56.4, 55.3

(E)-1-methoxy-4-styrylbenzene (06084)

80% yield

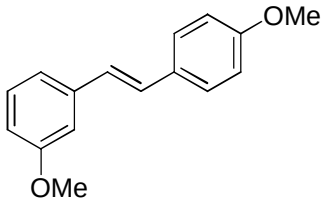


^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (d, J = 7.45 Hz, 2H), 7.46 (d, J = 8.59 Hz, 2H), 7.35 (t, J = 8.02 Hz, 2H), 7.23 (t, J = 7.45 Hz, 1H), 7.07 (d, J = 16.61 Hz, 1H), 6.98 (d, J = 16.61 Hz, 2H), 6.90 (d, J = 8.59 Hz, 2H), 3.84 (s, 3H)

^{13}C NMR (500 MHz, $CDCl_3$) δ 159.4, 137.7, 130.2, 128.7, 128.3, 127.8, 127.3, 126.7, 126.3, 114.2, 55.4

(E)-3,4'-(ethene-1,2-diyl)bis(methoxybenzene) (06085)

77% yield

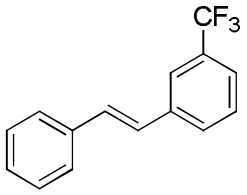


^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (d, J = 8.59 Hz, 2H), 7.25 (t, J = 8.02 Hz, 1H), 7.08 (d, J = 8.02 Hz, 1H), 7.04 (d, J = 16.61 Hz, 1H), 7.02 (bs, 1H), 6.94 (d, J = 16.61 Hz, 1H), 6.88 (d, 8.59 Hz, 2H), 6.79, (dd, J = 8.02, 2.29 Hz, 1H), 3.82 (s, 3H), 3.80 (s, 3H)

^{13}C NMR (500 MHz, $CDCl_3$) δ 160.0, 159.5, 139.2, 130.1, 129.7, 128.6, 127.9, 126.6, 119.1, 114.2, 113.0, 111.6, 55.4, 55.3

(E)-1-styryl-3-(trifluoromethyl)benzene (06086)

65% yield

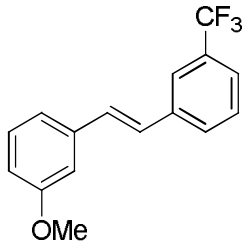


^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (bs, 1H), 7.66 (d, J = 7.45 Hz, 1H), 7.54-7.44 (m, 4H), 7.38 (t, J = 8.02 Hz, 2H), 7.29 (t, J = 7.45 Hz, 1H), 7.17 (d, J = 16.61 Hz, 1H), 7.10 (d, J = 16.61 Hz, 1H)

^{13}C NMR (500 MHz, $CDCl_3$) δ 138.2, 136.8, 131.3, 131.1, 130.6, 129.7, 129.2, 128.9, 128.3, 127.2, 126.8, 125.3, 124.2, 124.1, 123.2

(E)-1-methoxy-3-(3-(trifluoromethyl)styryl)benzene (06087)

61% yield

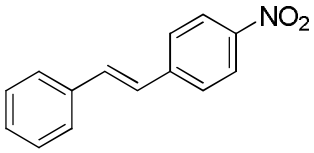


^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (s, 1H), 7.46 (d, J = 7.45 Hz, 1H), 7.44 (t, J = 7.45 Hz, 1H), 7.28 (t, J = 8.02 Hz, 1H), 7.14-7.09 (m, 3H), 7.05 (t, J = 1.72 Hz, 1H), 6.84 (dd, J = 8.02, 1.72 Hz, 1H), 3.84 (s, 3H)

^{13}C NMR (500 MHz, $CDCl_3$) δ 160.0, 138.2, 138.1, 131.6, 131.3, 131.1, 130.8, 130.5, 129.9, 129.7, 129.2, 127.5, 123.5, 124.2, 123.2, 119.5, 114.0, 112.0, 55.3

(E)-1-nitro-4-styrylbenzene (06088)

21% yield

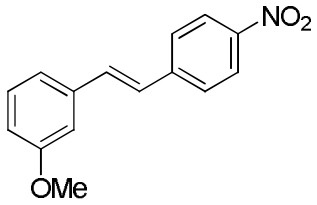


^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 (d, J = 9.16 Hz, 2H), 7.64 (d, J = 9.16 Hz, 2H), 7.56 (d, J = 7.45 Hz, 2H), 7.41 (t, J = 7.45 Hz, 2H), 7.34 (t, J = 7.45 Hz, 1H), 7.28 (d, J = 16.04 Hz, 1H), 7.15 (d, J = 16.04 Hz, 1H)

^{13}C NMR (500MHz, $CDCl_3$) δ 146.8, 143.9, 136.3, 133.4, 129.8, 129.0, 128.9, 128.7, 128.1, 127.1, 127.0, 126.4, 124.2, 123.7

(E)-1-methoxy-3-(4-nitrostyryl)benzene (06089)

45% yield

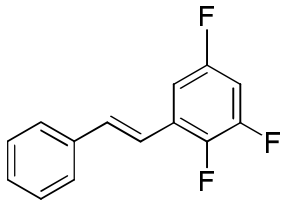


^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20 (d, J = 8.59 Hz, 2H), 7.61 (d, J = 8.59 Hz, 2H), 7.31 (t, J = 8.02 Hz, 1H), 7.22 (d, J = 16.61 Hz, 1H), 7.14 (s, 1H), 7.11 (d, J = 16.61 Hz, 1H), 7.06 (t, J = 1.76 Hz, 1H), 6.88 (dd, J = 7.45, 1.72 Hz, 1H), 3.56 (s, 3H)

^{13}C NMR (500 MHz, $CDCl_3$) δ 160.1, 146.9, 143.8, 137.7, 133.3, 130.0, 127.0, 126.7, 124.2, 119.8, 114.5, 112.4, 55.4

(E)-1,2,5-trifluoro-3-styrylbenzene (06090)

16% yield

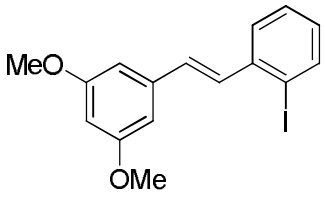


^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (d, J = 7.45 Hz, 2H), 7.39 (t, J = 7.45 Hz, 2H), 7.32 (t, J = 7.45 Hz, 1H), 7.21 (d, J = 16.61 Hz, 1H), 7.16 (d, J = 16.61 Hz, 1H), 7.11-7.07 (m, 1H), 6.84-6.78 (m, 1H)

^{13}C NMR (500 MHz, $CDCl_3$) δ 136.3, 133.3, 133.2, 128.9, 128.8, 127.0, 119.0, 107.8, 107.6, 104.2, 104.1, 104.0, 103.9

(E)-1-(2-iodostyryl)-3,5-dimethoxybenzene (06093)

17% yield

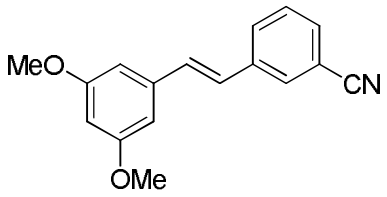


^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (dd, J = 8.02, 1.15 Hz, 1H), 7.60 (dd, J = 8.02, 1.15 Hz, 1H), 7.34 (t, J = 8.02 Hz, 1H), 7.28 (d, J = 16.04 Hz, 1H), 6.95 (td, J = 7.45, 1.72 Hz, 1H), 6.88 (d, J = 16.04 Hz, 1H), 6.71 (d, J = 2.29 Hz, 2H), 6.43 (t, J = 2.29 Hz, 1H), 3.84 (s, 6H)

^{13}C NMR (500 MHz, $CDCl_3$) δ 161.1, 140.3, 139.7, 139.0, 133.1, 131.7, 129.2, 128.5, 126.5, 105.0, 100.6, 100.3, 55.5

(E)-3-(3,5-dimethoxystyryl)benzonitrile (06094)

61% yield

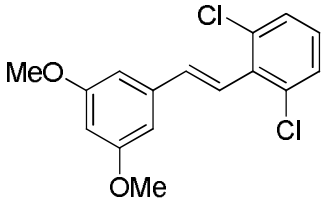


^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.72 (d, J = 7.79 Hz, 1H), 7.54 (d, J = 7.79 Hz, 1H), 7.46 (t, J = 7.79 Hz, 1H), 7.10 (d, J = 16.49 Hz, 1H), 7.03 (d, J = 16.49 Hz, 1H), 6.67 (d, J = 2.29 Hz, 2H), 6.44 (t, J = 1.83 Hz, 1H), 3.84 (s, 6H)

^{13}C NMR (500 MHz, $CDCl_3$) δ 161.1, 138.5, 138.4, 131.4, 130.9, 130.7, 130.0, 129.6, 126.8, 118.9, 113.0, 104.9, 100.7, 55.5

(E)-1,3-dichloro-2-(3,5-dimethoxystyryl)benzene (06095)

50% yield

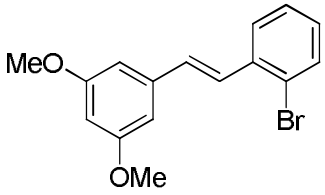


^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (s, 1H), 7.35 (d, J = 8.24 Hz, 1H), 7.12 (d, J = 8.24 Hz, 1H), 7.09 (s, 2H), 6.70 (d, J = 2.29 Hz, 2H), 6.45 (t, J = 2.29 Hz, 1H), 3.84 (s, 6H)

^{13}C NMR (500 MHz, $CDCl_3$) δ 161.1, 138.8, 137.1, 134.7, 134.5, 128.7, 128.1, 123.2, 104.9, 100.7, 55.5

(E)-1-(2-bromostyryl)-3,5-dimethoxybenzene (06096)

34% yield

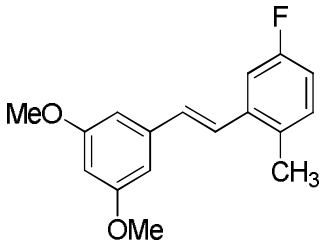


^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (d, J = 7.79 Hz, 1H), 7.58 (d, J = 7.79 Hz, 1H), 7.43 (d, J = 16.03 Hz, 1H), 7.31 (t, J = 7.79 Hz, 1H), 7.12 (t, J = 7.79 Hz, 1H), 6.96 (d, J = 16.03 Hz, 1H), 6.71 (d, J = 2.73 Hz, 2H), 6.43 (t, J = 2.73 Hz, 1H), 3.84 (s, 6H)

^{13}C NMR (500 MHz, $CDCl_3$) δ 161.1, 139.1, 137.1, 133.2, 131.5, 129.0, 128.0, 127.7, 126.9, 124.3, 105.1, 100.4, 55.5

(E)-2-(3,5-dimethoxystyryl)-4-fluoro-1-methylbenzene (06097)

88% yield

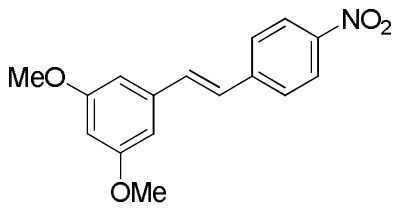


^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (dd, J = 9.74, 2.29 Hz, 1H), 7.22 (dd, J = 16.04, 1.72 Hz, 1H), 7.11 (dd, J = 8.59, 5.73 Hz, 1H), 6.91 (d, J = 16.04 Hz, 1H), 6.87 (td, J = 8.02, 2.29 Hz, 1H), 6.67 (d, J = 2.29 Hz, 2H), 6.42 (t, J = 2.29 Hz, 1H), 3.84 (s, 6H), 2.37 (s, 3H)

^{13}C NMR (500M Hz, $CDCl_3$) δ 162.6, 161.1, 160.3, 139.3, 137.9, 137.8, 131.7, 131.6, 131.5, 131.0, 126.2, 114.4, 114.3, 111.9, 111.7, 104.9, 100.1, 55.5, 19.3

(E)-1,3-dimethoxy-5-(4-nitrostyryl)benzene (06098)

20% yield

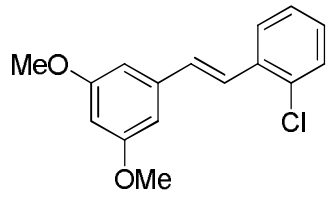


^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 (d, J = 8.70 Hz, 2H), 7.64 (d, J = 8.70 Hz, 2H), 7.20 (d, J = 16.49 Hz, 1H), 7.12 (d, J = 16.49 Hz, 1H), 6.70 (d, J = 2.29 Hz, 2H), 6.47 (t, J = 2.29 Hz, 1H), 3.85 (s, 6H)

^{13}C NMR (500 MHz, $CDCl_3$) δ 161.2, 146.9, 143.8, 138.2, 133.54, 127.0, 126.8, 124.2, 105.2, 101.1, 55.5

(E)-1-(2-chlorostyryl)-3,5-dimethoxybenzene (06100)

55% yield



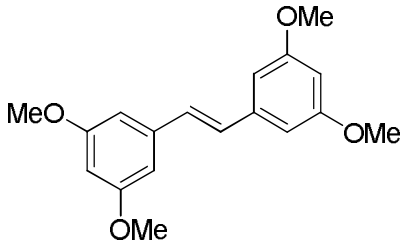
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (dd, J = 7.79, 1.37 Hz, 1H), 7.49 (d, J = 16.49 Hz, 1H), 7.39 (dd, J = 7.79, 1.37 Hz, 1H), 7.27 (td, J = 7.79, 1.37 Hz, 1H), 7.20 (td, J = 7.79,

1.83 Hz, 1H), 7.01 (d, J = 16.49 Hz, 1H), 6.71 (d, J = 6.71 Hz, 2H), 6.43 (t, J = 2.29 Hz, 1H), 3.84 (s, 6H)

^{13}C NMR (500 MHz, $CDCl_3$) δ 161.1, 139.2, 135.2, 133.6, 131.3, 129.9, 128.7, 127.0, 126.6, 125.4, 105.0, 100.4, 55.5

(E)-1,2-bis(3,5-dimethoxyphenyl)ethane (06101)

28% yield

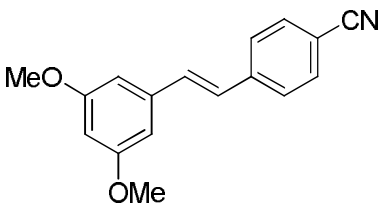


^{1}H NMR (500 MHz, $CDCl_3$) δ 7.02 (s, 2H), 6.67 (d, J = 2.29 Hz, 4H), 6.41 (t, J = 2.29 Hz, 2H), 3.84 (s, 12H)

^{13}C NMR (500 MHz, $CDCl_3$) δ 161.1, 139.2, 129.4, 129.3, 129.1, 105.4, 104.7, 104.6, 100.3, 100.1, 55.8, 55.6, 55.4, 55.1

(E)-4-(3,5-dimethoxystyryl)benzonitrile (06103)

49% yield

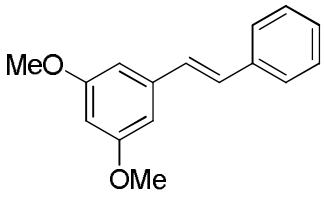


^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (d, J = 8.59 Hz, 2H), 7.56 (d, J = 8.59 Hz, 2H), 7.13 (d, J = 16.61 Hz, 1H), 7.04 (d, J = 16.61 Hz, 1H), 6.67 (d, J = 2.29 Hz, 2H), 6.44 (t, J = 2.29 Hz, 1H), (t, J = 2.29 Hz, 1H), 3.83 (s, 6H)

^{13}C NMR (500 MHz, $CDCl_3$) δ 161.1, 141.7, 138.3, 132.6, 132.4, 127.3, 127.0, 119.1, 110.8, 105.1, 100.9, 55.5

(E)-1,3-dimethoxy-5-styrylbenzene (06104)

64% yield

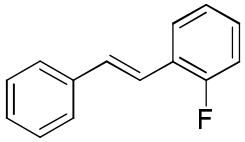


^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (d, J = 7.79 Hz, 2H), 7.36 (t, J = 7.79 Hz, 2H), 7.26 (t, J = 7.79 Hz, 1H), 7.10 (d, J = 16.49 Hz, 1H), 7.04 (d, J = 16.49 Hz, 1H), 6.68 (d, J = 2.29 Hz, 2H), 6.41 (t, J = 2.29 Hz, 1H), 3.84 (s, 3H)

^{13}C NMR (500 MHz, $CDCl_3$) δ 161.1, 139.4, 137.2, 129.3, 128.8, 128.7, 127.9, 126.7, 104.7, 100.1, 55.5

(E)-1-fluoro-2-styrylbenzene (06105)

61% yield

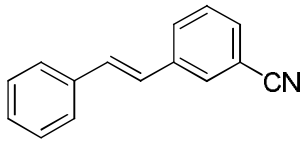


^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (t, J = 8.02 Hz, 1H), 7.54 (d, J = 7.45 Hz, 2H), 7.37 (t, J = 7.45 Hz, 1H), 7.28 (d, J = 8.02 Hz, 1H), 7.27 (d, J = 16.61 Hz, 1H), 7.22 (t, J = 7.45 Hz, 1H), 7.18 (d, J = 16.61 Hz, 1H), 7.14 (t, J = 8.02 Hz, 1H), 7.07 (t, J = 8.02 Hz, 1H)

^{13}C NMR (500 MHz, $CDCl_3$) δ 161.5, 159.5, 137.3, 131.0, 130.9, 128.9, 128.8, 128.1, 127.1, 127.0, 126.8, 125.3, 125.2, 124.3, 124.2, 121.0, 120.9, 116.0, 115.8

(E)-3-styrylbenzonitrile (06106)

53% yield

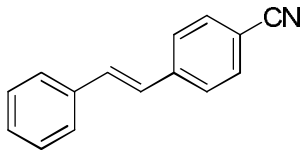


^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.71 (d, J = 7.45 Hz, 1H), 7.53 (d, J = 8.02 Hz, 2H), 7.45 (t, J = 7.45 Hz, 1H), 7.39 (t, (J = 8.02 Hz, 2H), 7.32 (d, J = 7.45 Hz, 1H), 7.15 (d, J = 16.61 Hz, 1H), 7.05 (d, J = 16.61 Hz, 1H)

^{13}C NMR (500 MHz, $CDCl_3$) δ 138.7, 136.4, 131.4, 130.8, 130.7, 130.0, 129.6, 129.0, 128.8, 128.6, 126.9, 126.3, 118.9, 113.0

(E)-4-styrylbenzonitrile (06107)

29% yield

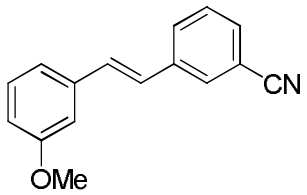


^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (d, J = 8.02 Hz, 2H), 7.58 (d, J = 8.02 Hz, 2H), 7.53 (d, J = 7.45 Hz, 2H), 7.39 (t, J = 7.45 Hz, 2H), 7.32 (t, J = 7.45 Hz, 1H), 7.21 (d, J = 16.04 Hz, 1H), 7.09 (d, J = 16.04 Hz, 1H)

^{13}C NMR (500 MHz, $CDCl_3$) δ 141.9, 136.4, 132.6, 132.5, 129.0, 128.8, 127.0, 126.9, 126.8, 119.2, 110.7

(E)-3-(3-methoxystyryl)benzonitrile (06110)

56% yield

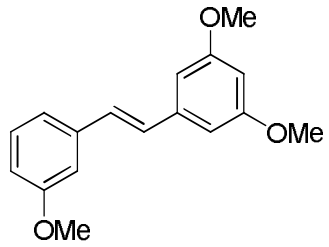


^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.72 (d, J = 7.79 Hz, 1H), 7.53 (d, J = 7.79 Hz, 1H), 7.45(t, J = 7.79 Hz, 1H), 7.31 (t, J = 8.24 Hz, 1H), 7.16-7.02 (m, 4H), 6.87 (d, J = 8.24 Hz, 1H), 3.86 (s, 3H)

^{13}C NMR (500 MHz, $CDCl_3$) δ 160.0, 138.6, 137.9, 131.3, 130.8, 130.7, 130.0, 129.9, 129.6, 126.6, 119.6, 118.9, 114.2, 113.0, 112.1, 55.4

(E)-1,3-dimethoxy-5-(3-methoxystyryl)benzene (06111)

80% yield

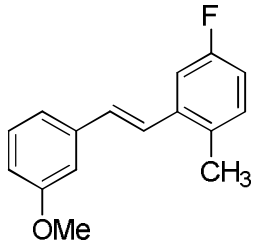


^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (d, J = 7.79 Hz, 1H), 7.11 (d, J = 7.79 Hz, 1H), 7.06-7.04 (m, 3H), 6.84 (dd, J = 8.24, 1.83 Hz, 1H), 6.67 (d, J = 2.29 Hz, 2H), 6.40 (t, J = 2.29 Hz, 1H), 3.85 (s, 3H), 3.84 (s, 6H)

^{13}C NMR (500 MHz, $CDCl_3$) δ 161.1, 160.0, 139.3, 138.7, 129.8, 129.2, 129.1, 119.4, 113.5, 111.9, 104.7, 100.1, 55.5, 55.4

(E)-4-fluoro-2-(3-methoxystyryl)-1-methylbenzene (06113)

70% yield

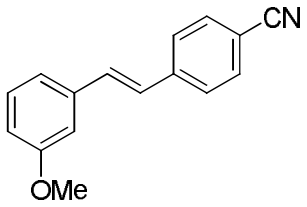


^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31-7.23 (m, 3H), 7.13 (t, J = 8.02 Hz, 2H), 7.05 (s, 1H), 6.96 (d, J = 16.61 Hz, 1H), 6.86 (dddd, J = 16.61, 8.59, 2.29 Hz, 2H), 3.86 (s, 3H), 2.38 (s, 3H)

^{13}C NMR (500 MHz, $CDCl_3$) δ 126.6, 160.7, 160.1, 138.8, 138.1, 138.0, 131.8, 131.7, 131.5, 131.4, 131.0, 129.9, 129.4, 128.7, 126.0, 125.9, 121.7, 119.5, 114.4, 114.3, 114.0, 113.7, 113.5, 112.3, 111.9, 111.7, 55.4, 55.0, 19.3

(E)-4-(3-methoxystyryl)benzonitrile (06114)

35% yield

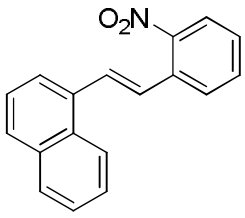


^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (d, J = 8.02 Hz, 1H), 7.56 (d, J = 8.02 Hz, 1H), 7.30 (t, J = 8.02 Hz, 1H), 7.17 (d, J = 16.61 Hz, 7.12 (d, J = 7.45 Hz, 1H), 7.8-7.04 (m, 2H), 6.87 (dd, J = 7.45, 1.72 Hz), 3.85 (s, 3H)

^{13}C NMR (500 MHz, $CDCl_3$) δ 160.0, 141.8, 137.8, 132.6, 132.4, 129.9, 127.1, 127.0, 119.7, 119.2, 114.3, 112.3, 110.7, 55.4

(E)-1-(2-nitrostyryl)naphthalene (06148)

18% yield

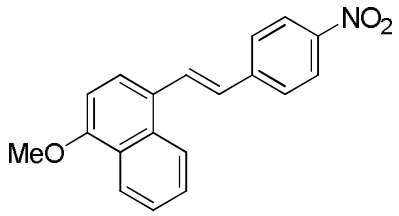


^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20 (d, J = 8.02 Hz, 1H), 8.01 (d, J = 8.59 Hz, 1H), 7.89 (d, J = 8.02 Hz, 2H), 7.86 (d, J = 15.46 Hz, 1H), 7.84 (d, J = 8.59 Hz, 1H), 7.80 (d, J = 6.30 Hz, 1H), 7.67 (t, J = 7.45 Hz, 1H), 7.64 (d, J = 15.46 Hz, 1H), 7.56 (td, J = 6.30, 1.15 Hz, 1H), 7.52 (t, J =7.45 Hz, 2H), 7.45 (td, J = 8.02, 1.15 Hz, 1H)

^{13}C NMR (500 MHz, $CDCl_3$) δ 148.1, 134.1, 133.8, 133.4, 133.3, 131.4, 131.0, 129.1, 128.9, 128.7, 128.3, 126.7, 126.5, 126.1, 125.9, 124.9, 124.6, 123.6

(E)-1-methoxy-4-(4-nitrostyryl)naphthalene (06152)

7% yield

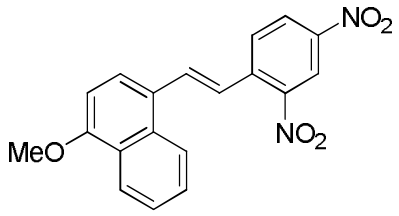


^{1}H NMR (500 MHz, $CDCl_3$) δ 8.34 (d, J = 8.02 Hz, 1H), 8.25 (d, J = 8.59 Hz, 2H), 8.16 (d, J = 8.59 Hz, 1H), 8.01 (d, J = 16.04 Hz, 1H), 7.75 (d, J = 8.02 Hz, 1H), 7.70 (d, J = 8.59 Hz, 2H), 7.61 (td, J = 8.59, 1.15 Hz, 1H), 7.54 (td, J = 8.02, 1.15 Hz, 1H), 7.15 (d, J = 16.04 Hz, 1H), 6.88 (d, J = 8.02 Hz, 1H), 4.06 (s, 3H)

^{13}C NMR (500 MHz, $CDCl_3$) δ 156.4, 146.6, 144.6, 132.3, 130.4, 127.2, 126.8, 126.3, 125.7, 125.6, 124.8, 124.3, 123.2, 122.8, 103.9, 55.8

(E)-1-(2,4-dinitrostyryl)-4-methoxynaphthalene (01009)

16% yield

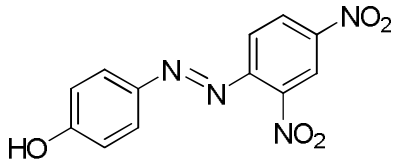


^{1}H NMR (500 MHz, $CDCl_3$) δ 8.31 (dd, J = 7.79, 1.37 Hz, 1H), 8.14 (d, J = 7.79 Hz, 1H),7.69 (t, J = 8.70 Hz, 2H), 7.62 (s, 1H), 7.58-7.48 (m, 2H), 7.43 (d, J = 15.57 Hz, 1H), 7.24 (d, J = 2.75 Hz, 1H), 6.93 (dd, J = 8.70, 2.75 Hz, 1H), 6.86 (d, J = 8.24 Hz, 1H)

^{13}C NMR (500 MHz, $CDCl_3$) δ 146.2, 129.6, 129.4, 127.7, 126.8, 125.6, 124.5, 123.4, 122.6, 121.0, 119.8, 109.9, 104.0, 91.3, 55.6

4-((2,4-dinitrophenyl)diazenyl)phenol (06179)

43% yield

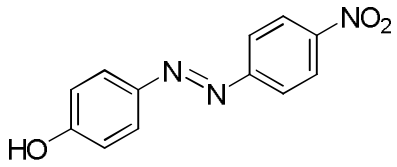


^{1}H NMR (500 MHz, $CDCl_3$) δ 8.31 (d, J = 1.83 Hz, 1H), 8.20 (dd, J = 8.24, 1.83 Hz, 1H), 8.10 (d, J = 8.24 Hz, 1H), 7.96 (d, J = 8.70 Hz, 2H), 7.00 (d, J = 8.70 Hz, 2H)

^{13}C NMR (500 MHz, acetone-d6) δ 162.9, 155.1, 146.1, 144.1, 142.1, 127.9, 127.2, 126.4, 117.6, 116.4

4-((4-nitrophenyl)diazenyl)phenol (06180)

19% yield

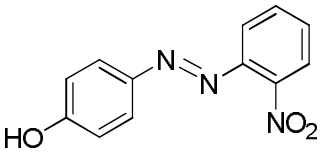


^{1}H NMR (500 MHz, $CDCl_3$) δ 8.37 (d, J = 9.16 Hz, 2H), 7.99 (d, J = 9.16 Hz, 2H), 7.94 (d, J = 8.70 Hz, 2H), 6.99 (d, J =8.70 Hz, 2H)

^{13}C NMR (500 MHz, acetone-d6) δ 162.0, 156.1, 148.4, 146.4, 125.9, 125.8, 125.0, 124.8, 123.2, 123.0, 116.3, 116.0

4-((2-nitrophenyl)diazenyl)phenol (06181)

24% yield

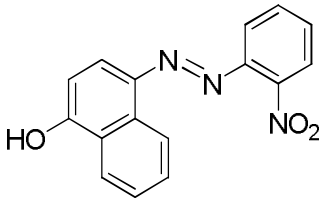


^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92-7.87 (m, 3H), 7.68-7.65 (m, 2H), 7.56-7.51 (m, 1H), 6.98-6.93 (m, 2H)

^{13}C NMR (500 MHz, $CDCl_3$) δ 159.6, 147.4, 147.2, 145.6, 133.1, 129.6, 126.1, 124.1, 118.6, 116.1

4-((2-nitrophenyl)diazenyl)naphthalen-1-ol (06183)

37% yield

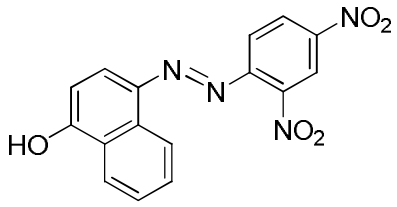


^{1}H NMR (500 MHz, $CDCl_3$) δ 8.45 (d, J = 8.24 Hz, 1H), 8.27 (dd, J = 8.70, 1.37 Hz, 1H), 8.19 (d, J = 8.24 Hz, 2H), 7.74-7.68 (m, 3H), 7.57 (td, J = 8.24, 0.92 Hz, 1H), 7.09 (td, J = 8.24, 1.37 Hz, 1H), 6.83 (d, J = 10.53 Hz, 1H)

^{13}C NMR (500 MHz, $CDCl_3$) δ 184.8, 140.3, 137.1, 136.7, 134.9, 133.1, 132.7, 132.1, 130.4, 129.3, 126.4, 126.3, 123.8, 123.3, 121.2, 116.6

4-((2,4-dinitrophenyl)diazenyl)naphthalen-1-ol (06185)

27% yield

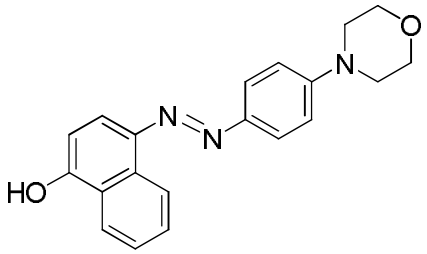


^{1}H NMR (500 MHz, $CDCl_3$) δ 9.21 (d, J = 2.75 Hz, 1H),8.52 (d, J = 2.75 Hz, 1H), 8.50 (d, J = 2.29 Hz, 1H), 8.45 (dd, J = 7.33, 0.92 Hz, 1H), 8.32 (d, J = 9.16 Hz, 1H), 8.22 (dd, J = 7.79, 1.37 Hz, 1H), 7.76 (dt, J = 7.33, 1.37 Hz, 1H), 7.70 (d, J = 10.53 Hz, 1H), 7.65 (td, J = 7.79, 0.92 Hz, 1H), 6.90 (d, J = 10.53 Hz, 1H)

^{13}C NMR (500 MHz, CD_2Cl_2) δ 143.9, 134.1, 133.5, 133.0, 131.4, 131.1, 130.6, 130.5, 130.2, 126.3, 123.8, 123.7, 123.2, 117.2

4-((4-morpholinophenyl)diazenyl)naphthalen-1-ol (06191)

30% yield

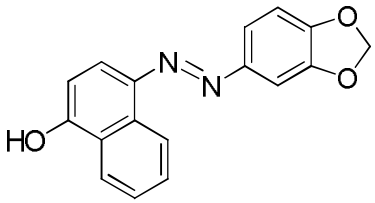


^{1}H NMR (500 MHz, $CDCl_3$) δ 8.98 (d, J = 8.59 Hz, 1H), 8.32 (d, J = 8.02 Hz, 1H), 7.95 (d, J = 9.16 Hz, 2H), 7.85 (d, J = 8.02 Hz, 1H), 7.68 (ddd, J = 6.87, 6.83, 1.15 Hz, 1H), 7.59 (ddd, J = 6.87, 6.30, 1.15 Hz, 1H), 7.13 (d, J = 9.16 Hz, 2H), 7.05 (d, J = 8.59 Hz, 1H), 3.83 (t, J = 4.58 Hz, 4H), 3.34 (t, J = 4.58 Hz, 4H)

^{13}C NMR (500 MHz, acetone-d6) δ 158.8, 156.0, 153.2, 146.2, 141.1, 133.0, 127.1, 125.3, 124.9, 124.2, 123.1, 122.3, 114.5, 112.6, 108.4, 108.2, 66.4, 48.0

4-(benzo[d][1,3]dioxol-5-yldiazenyl)naphthalen-1-ol (06192)

41% yield

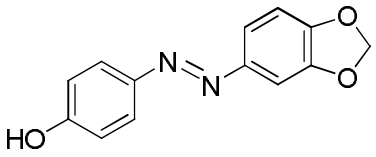


^{1}H NMR (500 MHz, $CDCl_3$) δ 8.77 (d, J = 2.86 Hz, 1H), 8.42 (d, J = 7.45 Hz, 1H), 8.07 (dd, J = 8.59, 2.86 Hz, 1H), 7.65 (td, J = 7.45, 1.15 Hz, 1H), 7.53 (d, J = 7.45 Hz, 1H), 7.47 (td, J = 7.45, 1.15 Hz, 1H), 7.11 (d, J = 9.74 Hz, 1H), 7.04 (d, J = 9.16 Hz, 1H), 6.95 (d, J = 9.74 Hz, 1H), 4.12 (s, 2H)

^{13}C NMR (500 MHz, $CDCl_3$) δ 179.5, 153.0, 142.6, 137.5, 134.6, 133.5, 132.3, 131.0, 128.3, 127.9, 127.6, 126.9, 123.3, 121.2, 110.8, 110.5, 57.0

4-(benzo[d][1,3]dioxol-5-yldiazenyl)phenol (06196)

17% yield

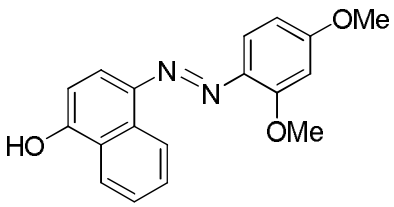


^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (d, J = 8.59 Hz, 2H), 7.52 (dd, J = 8.02, 1.72 Hz, 1H), 7.40 (d, J = 2.29 Hz, 1H), 6.92 (m, 3H), 6.05 (s, 2H)

^{13}C NMR (500 MHz, $CDCl_3$) δ 157.9, 149.9, 148.8, 148.7, 147.1, 124.7, 122.9, 115.8, 107.9, 101.8, 99.0

4-((2,4-dimethoxyphenyl)diazenyl)naphthalen-1-ol (06202)

28% yield

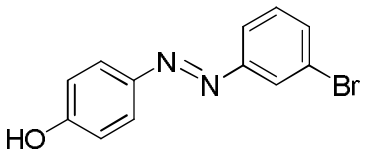


^{1}H NMR (500 MHz, $CDCl_3$) δ 8.45 (d, J = 8.24 Hz, 1H), 8.20 (d, J = 7.33 Hz, 1H), 7.70 (d, J = 10.53 Hz, 1H), 7.66 (t, J = 7.79 Hz, 1H), 7.50 (t, J = 7.79 Hz, 1H), 7.36 (d, J = 3.21 Hz, 1H), 6.85 (d, J = 9.16 Hz, 1H), 6.73 (d, J = 10.07 Hz, 1H), 6.55 (dd, J = 8.70, 3.21 Hz, 1H), 3.92 (s, 3H), 3.87 (s, 3H)

^{13}C NMR (500 MHz, $CDCl_3$) δ 154.7, 151.5, 134.9, 127.8, 126.6, 126.0, 125.4, 124.5, 121.7, 120.8, 108.7, 100.9, 56.5, 56.1

4-((3-bromophenyl)diazenyl)phenol (06204)

29% yield

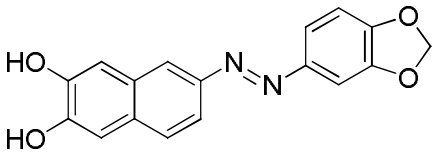


^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (t, J = 1.72 Hz, 1H), 7.88 (d, J = 8.59 Hz, 2H), 7.83 (dt, J = 8.02, 1.72 Hz, 1H), 7.56 (dt, J = 8.02, 1.72 Hz, 1H), 7.01 (t, J = 8.02 Hz, 1H), 6.94 (d, J = 8.59 Hz, 2H),

^{13}C NMR (500 MHz, $CDCl_3$) δ 158.8, 153.7, 146.9, 133.1, 130.5, 125.4, 124.4, 123.2, 122.8, 116.0

6-(benzo[d][1,3]dioxol-5-yldiazenyl)naphthalene-2,3-diol (06290)

15% yield

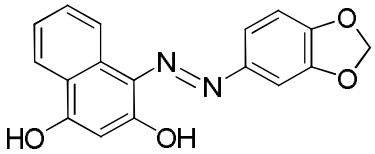


^{1}H NMR (500 MHz, $CDCl_3$) δ 8.33 (d, J = 8.02 Hz, 1H), 7.44 (d, J = 6.87 Hz, 1H), 7.38 (td, J = 6.87, 1.15 Hz, 2H), 7.33 (td, J = 7.45, 1.15 Hz, 1H), 7.11 (s, 1H), 7.02 (dd, J = 8.02, 2.29 Hz, 1H), 6.87 (d, J = 8.02 Hz, 1H), 6.73 (s, 1H)

^{13}C NMR (500 MHz, $CDCl_3$) δ 169.0, 149.4, 147.8, 147.2, 137.7, 129.0, 128.8, 128.0, 127.5, 126.4, 126.3, 121.2, 115.5, 112.6, 108.8, 102.0, 98.2

4-(benzo[d][1,3]dioxol-5-yldiazenyl)naphthalene-1,3-diol (06291)

7% yield

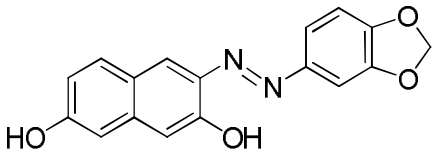


^{1}H NMR (500 MHz, DMSO-D6) δ 8.40 (d, J = 8.02 Hz, 1H), 7.94 (d, J = 8.02 Hz, 1H), 7.60 (td, J = 6.87, 1.15 Hz, 1H), 7.44 (td, J = 6.87, 1.15 Hz, 1H), 7.41 (d, J = 2.29 Hz, 1H), 7.09 (dd, J = 8.02, 2.29 Hz, 1H), 7.00 (d, J = 8.02 Hz, 1H), 6.12 (s, 1H), 6.10 (s, 2H)

^{13}C NMR (500 MHz, DMSO-D6) δ 176.8, 165.0, 149.2, 146.0, 139.2, 134.1, 130.5, 127.2, 126.2, 123.9, 123.8, 122.1, 111.7, 109.3, 104.5, 102.2, 97.9

3-(benzo[d][1,3]dioxol-5-yldiazenyl)naphthalene-2,7-diol (06292)

9% yield

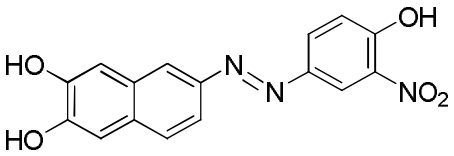


^{1}H NMR (500 MHz, acetone-D6) δ 8.17 (d, J = 2.29 Hz, 1H), 7.83 (d, J = 8.59 Hz, 1H),7.73 (d, J = 8.59 Hz, 1H), 7.54 (d, J = 1.72 Hz, 1H), 7.50 (dd, J = 8.02, 2.29 Hz, 1H), 7.06 (d, J = 8.02 Hz, 1H), 7.05 (dd, J = 8.59, 2.86 Hz, 1H), 6.88 (d, J = 9.16 Hz, 1H), 6.18 (s, 2H)

^{13}C NMR (500 MHz, acetone-D6) δ 160.4, 157.8, 157.0, 149.7, 149.5, 145.4, 136.0, 135.4, 130.4, 123.1, 120.1, 117.1, 116.0, 108.4, 104.4, 102.5, 97.9

6-((4-hydroxy-3-nitrophenyl)diazenyl)naphthalene-2,3-diol (06293)

16% yield

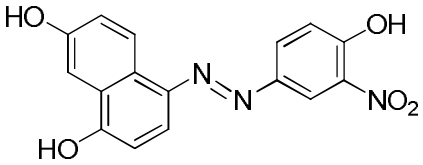


^{1}H NMR (500 MHz, $CDCl_3$) δ 8.33 (d, J = 2.86 Hz, 1H), 8.30 (d, J = 8.02 Hz, 1H), 7.93 (dd, J = 9.16, 2.86 Hz, 1H), 7.44-7.39 (m, 2H), 7.37 (dd, J = 7.45, 1.72 Hz, 1H), 7.30 (d, J = 9.16 Hz, 1H), 7.11 (s, 1H)

^{13}C NMR (500 MHz, $CDCl_3$) δ 171.3, 153.4, 147.7, 135.7, 130.0, 128.5, 128.4, 127.7, 127.3, 127.0, 126.5, 123.2, 121.7, 121.6, 117.0, 112.6

4-((4-hydroxy-3-nitrophenyl)diazenyl)naphthalene-1,7-diol (06297)

11% yield

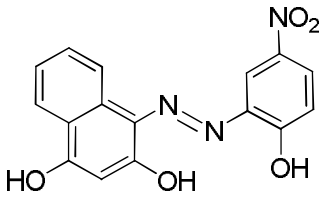


^{1}H NMR (500 MHz, DMSO-D6) δ 10.88 (s, 1H), 9.90 (s, 1H), 8.77 (d, J = 9.16Hz, 1H), 8.41 (d, J = 2.29 Hz, 1H), 8.19 (dd, J = 8.59, 2.29 Hz, 1H), 7.65 (d, J = 8.02 Hz, 1H), 7.48 (d, J = 1.63 Hz, 1H), 7.33 (d, J = 9.16 Hz, 1H), 7.28 (dd, J = 8.02, 2.29 Hz, 1H), 6.94 (d, J = 8.59 Hz, 1H)

^{13}C NMR (500 MHz, DMSO-D6) δ 156.9, 155.7, 154.0, 145.3, 140.2, 137.9, 129.0, 127.6, 126.6, 125.1, 120.7, 120.3, 119.7, 111.4, 108.9, 104.3

4-((2-hydroxy-5-nitrophenyl)diazenyl)naphthalene-1,3-diol (06301)

8% yield



^{1}H NMR (50 0MHz, DMSO-D6) δ 12.1 (s, 1H), 12.0 (s, 1H), 8.48 (d, J =2.86 Hz, 1H), 8.30 (d, J = 8.12 Hz, 1H), 7.93-7.90 (m, 2H), 7.66 (td, J = 7.45, 1.15 Hz, 1H), 7.48 (t, J = 7.45 Hz, 1H), 7.09 (d, J = 8.59 Hz, 1H), 6.03 (t, J = 8.02 Hz, 1H)

^{13}C NMR (500 MHz, DMSO-D6) δ 181.1, 166.5, 152.5, 141.1, 133.7, 131.6, 131.0, 129.8, 127.5, 125.1, 124.1, 122.3, 121.1, 115.8, 109.6, 105.1

CHAPTER 6: FUTURE DIRECTIONS

ANALOGS OF LEAD COMPOUND 6A60

Of the two lead compounds, only analogs of **6A49** were synthesized. Bromoanthracenone **6.2** with its aromatic halide handle can serve as the branch point molecule for the synthesis of a number of analogs.

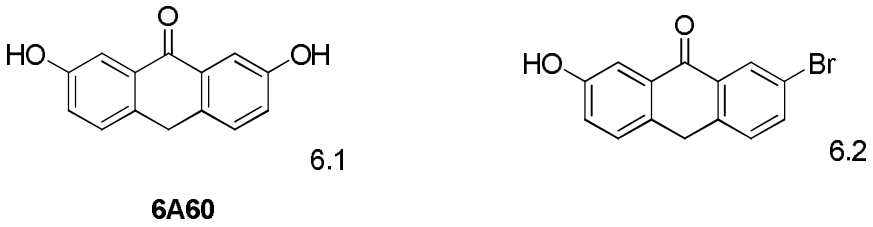


Figure 6.1: 6A60 and halide analog

Bromoanthracenone **6.2** can be synthesized beginning with the commercially available 2-bromonaphthalene (**6.3**) as the starting material. Oxidation to bromonaphthoquinone **6.4** can be achieved using a Ruthenium terpyridine catalyst and hydrogen peroxide as the terminal oxidant.[203] Subsequent Diels-Alder [4+2] cycloaddition of **6.4** with Danishefsky's diene (**6.6)**, will yield anthracenedione **6.7**.[204]

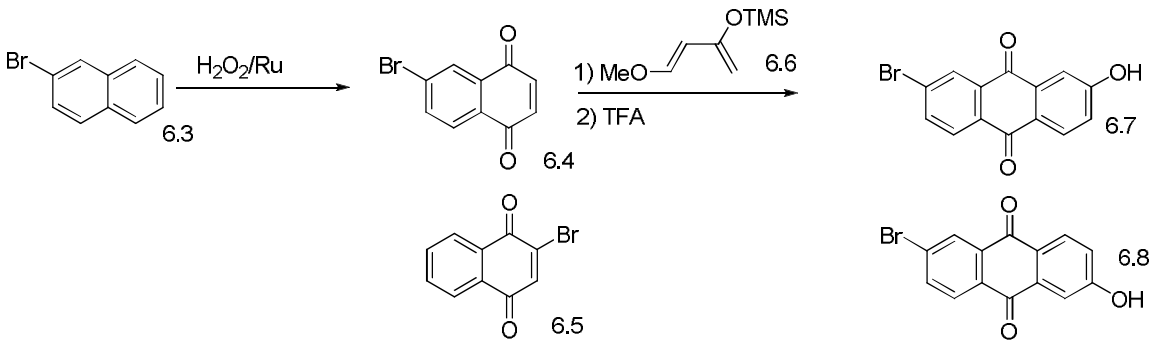


Figure 6.2: Synthesis of bromoanthracene dione

Reduction of bromoanthracenone dione **6.7** to anthracenone **6.1** can be accomplished using tin (II) chloride in acetic acid/hydrochloric acid.[205] The aromatic halide handle can be used to append a variety of different groups via coupling reactions such as the Suzuki coupling reaction.[206]

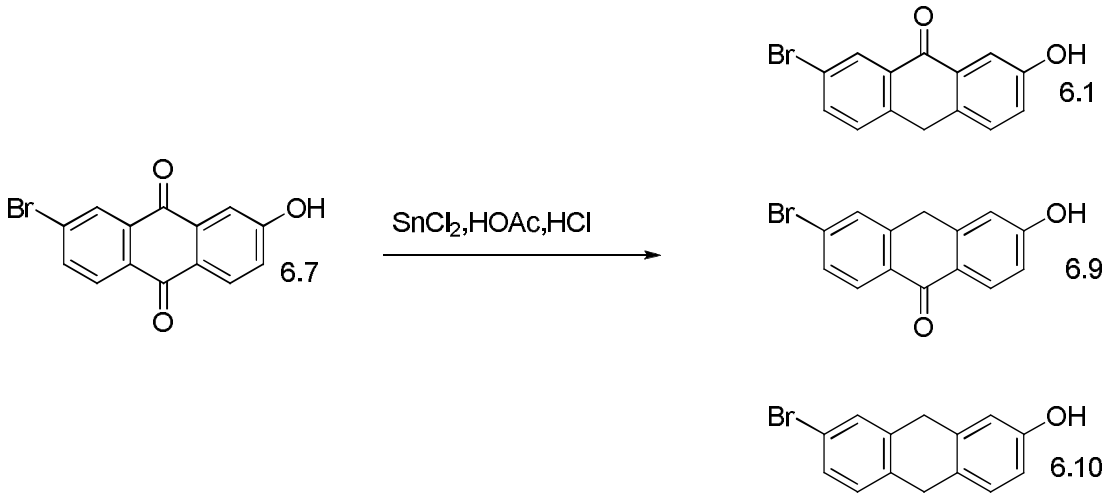


Figure 6.3: Synthesis of bromoanthracenone

MODIFICATIONS TO EXISTING MOLECULES

One noteworthy feature of the biologically active molecules is that each one contained an aromatic hydroxyl group (e.g. **6.11**). Many of the stilbenes included one or more aromatic methyl ethers (e.g. **6.12**), which is a less effective hydrogen bond donor than a hydroxyl group. The existing collection of compounds containing an aromatic methyl ether can be demethylated to give phenolic compounds by reacting them with boron tribromide.[207] This transformation would also increase the solubility that plagued some of the stilbene compounds.

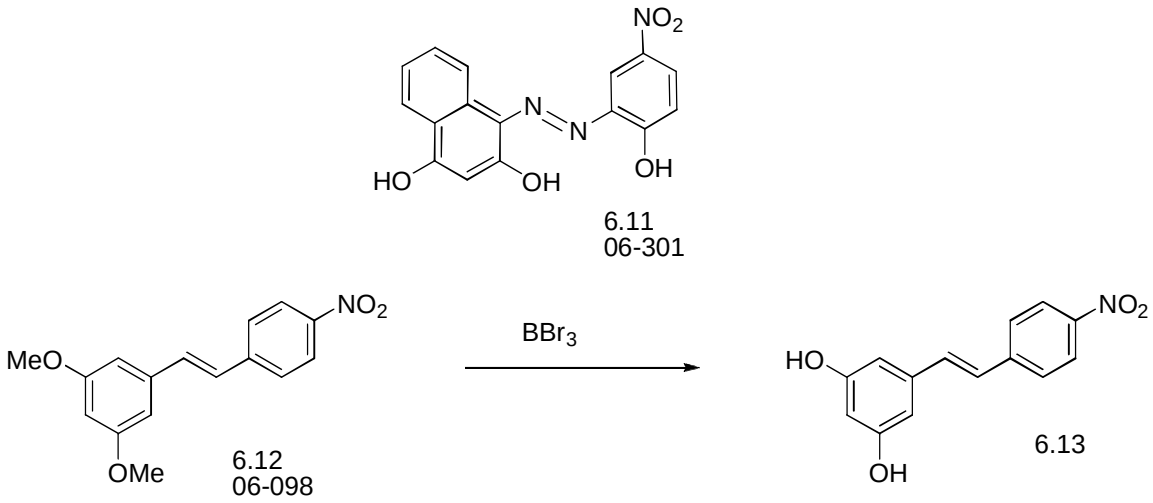


Figure 6.4: Demethylation of aromatic methyl ethers

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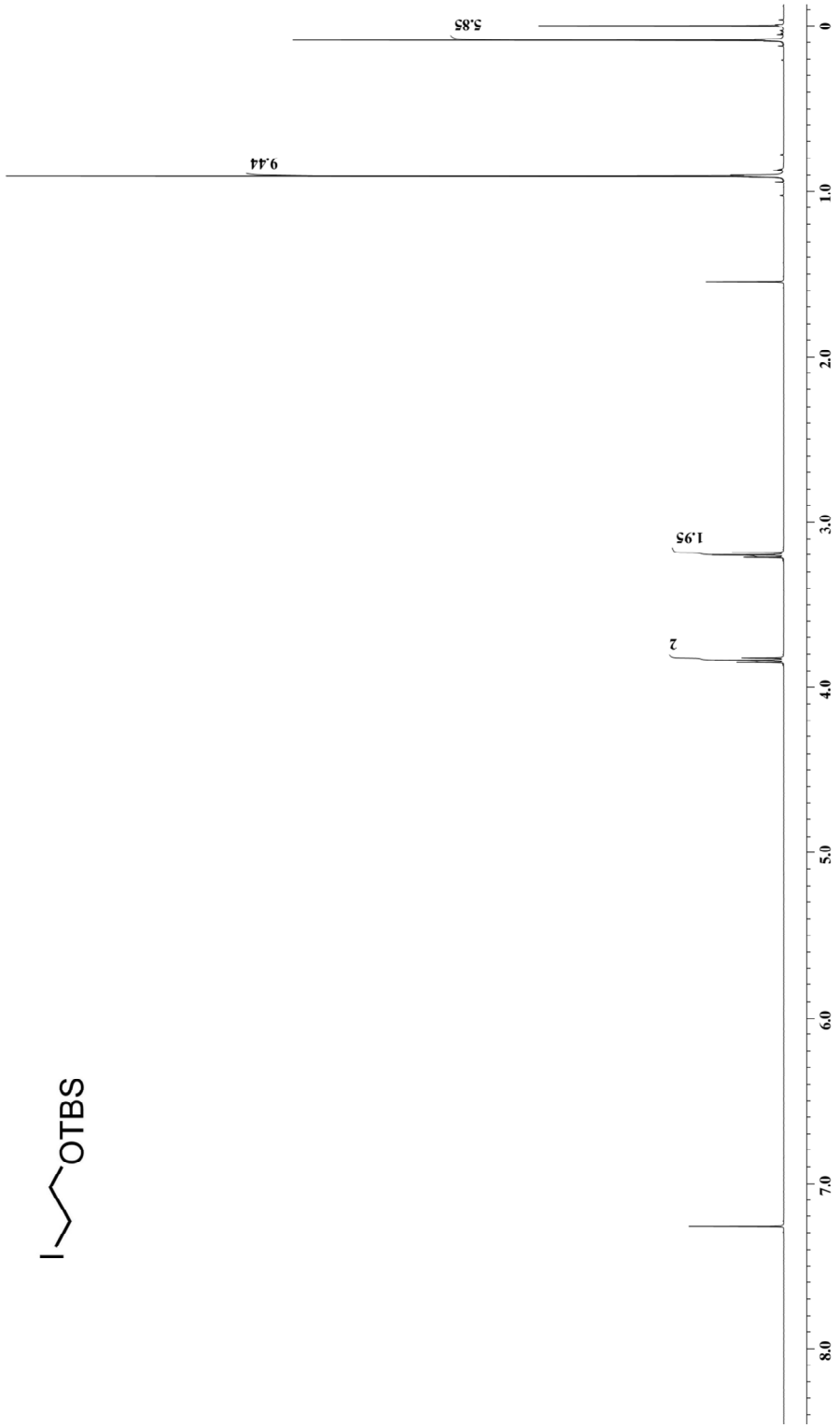
Appendix

SPECTRAL DATA: ^{1}H-NMR, ^{13}C-NMR AND CHIRAL HPLC RESULTS

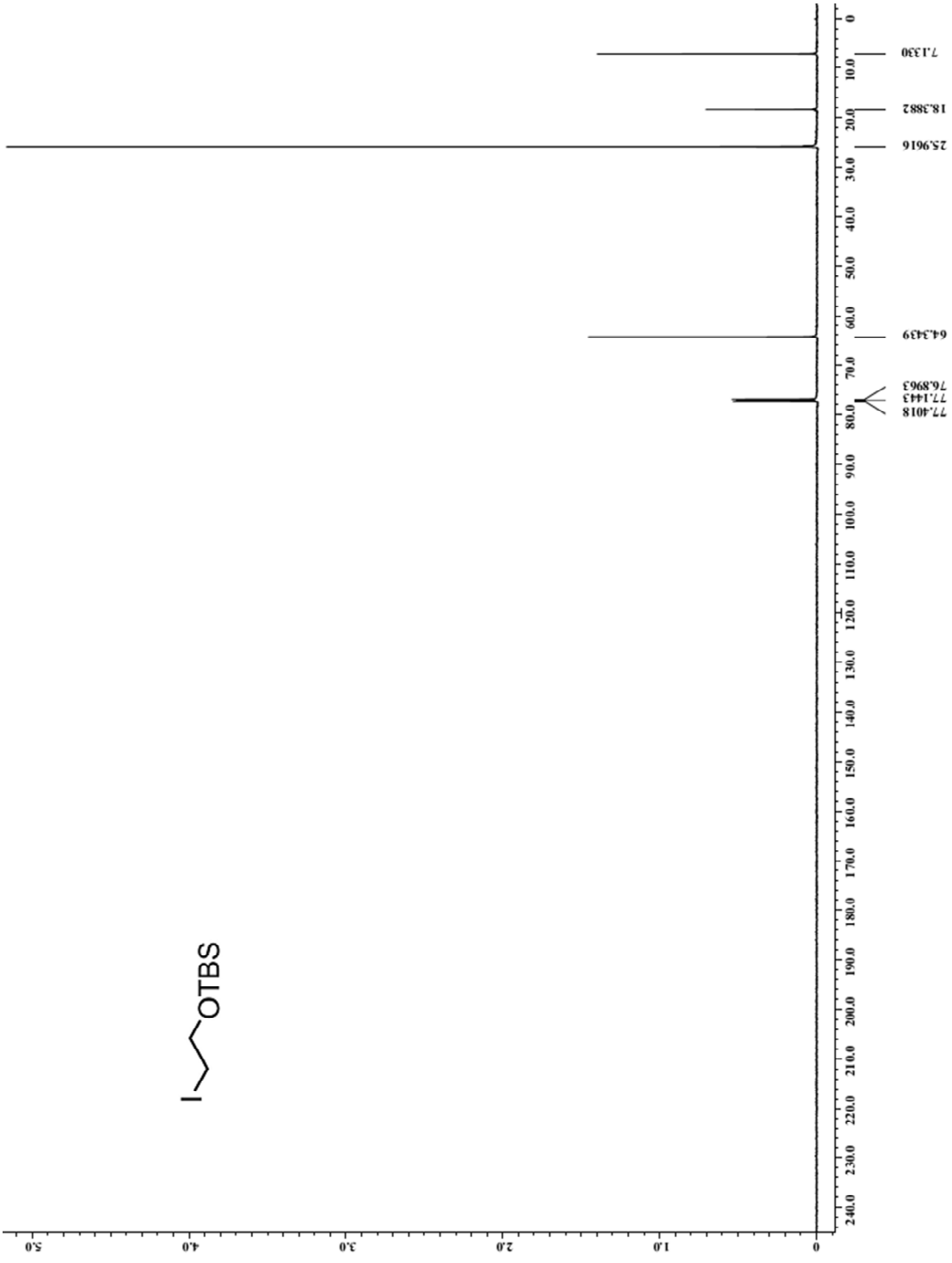
^{1}H-NMR Spectrum (400 MHz, $CDCl_3$)

tert-butyl(2-iodoethoxy)dimethylsilane



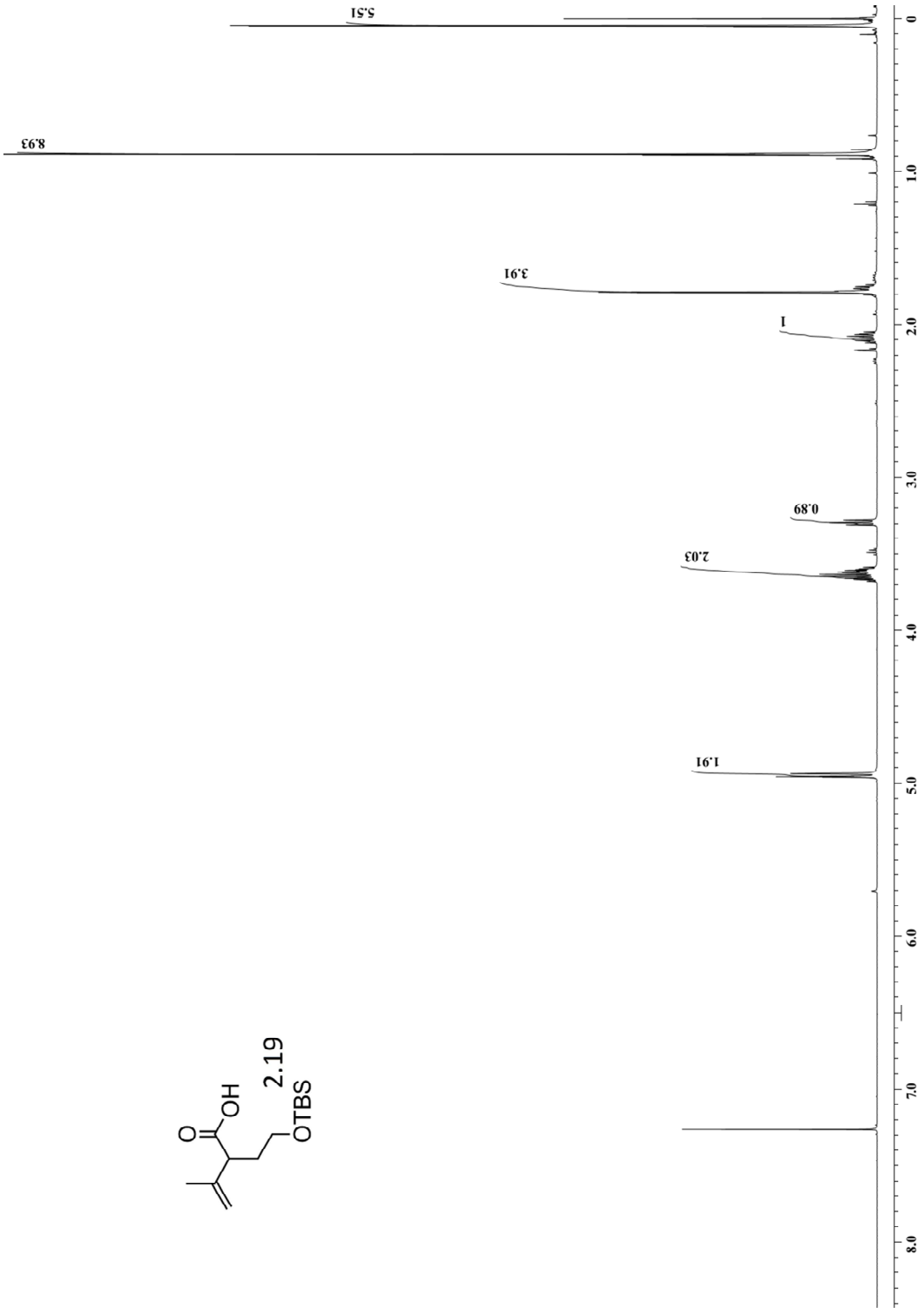
^{13}C-NMR Spectrum (400 MHz, $CDCl_3$)

tert-butyl(2-iodoethoxy)dimethylsilane



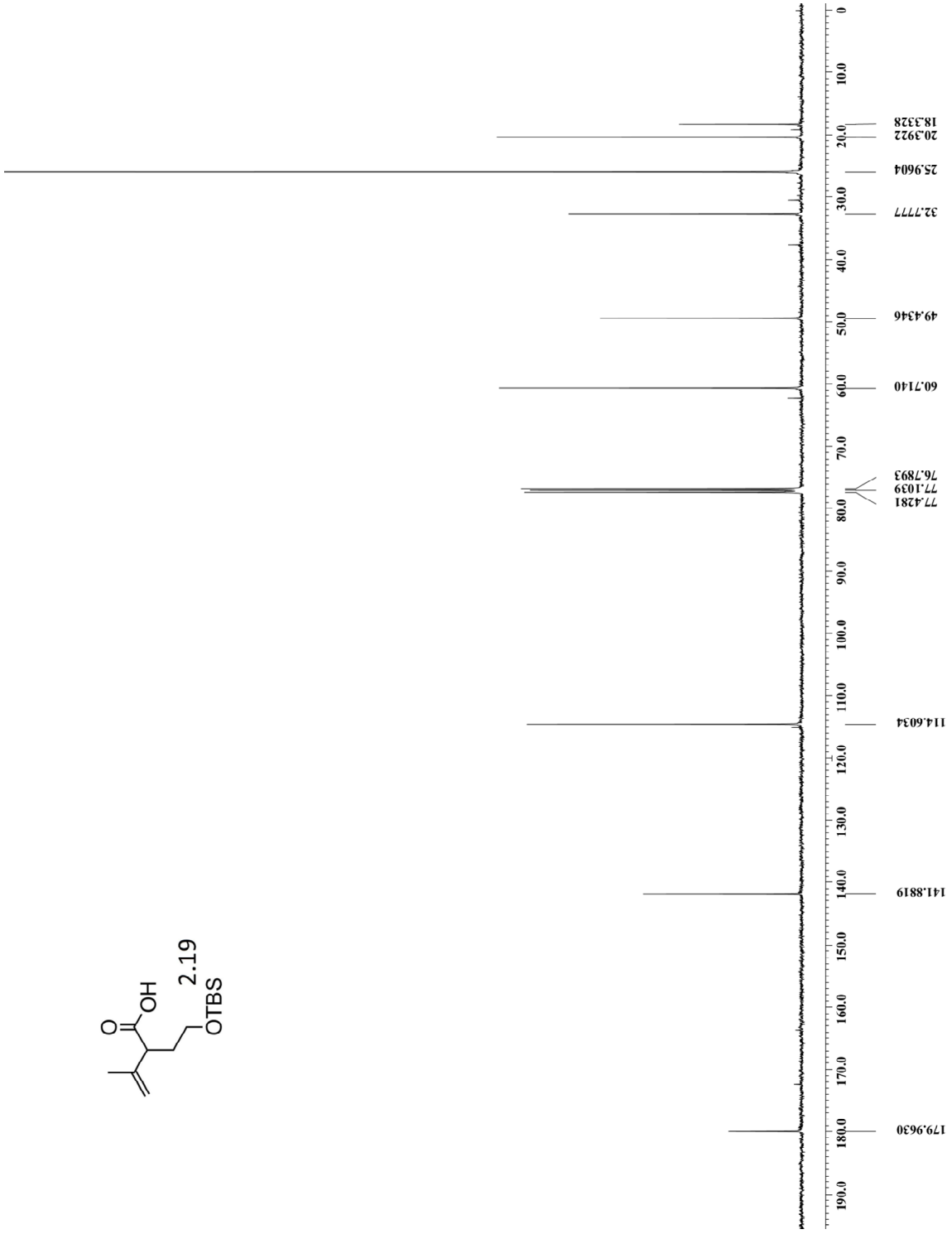
^{1}H-NMR Spectrum (400 MHz, $CDCl_3$)

2-(2-(tert-butyldimethylsilyloxy)ethyl)-3-methylbut-3-enoic acid



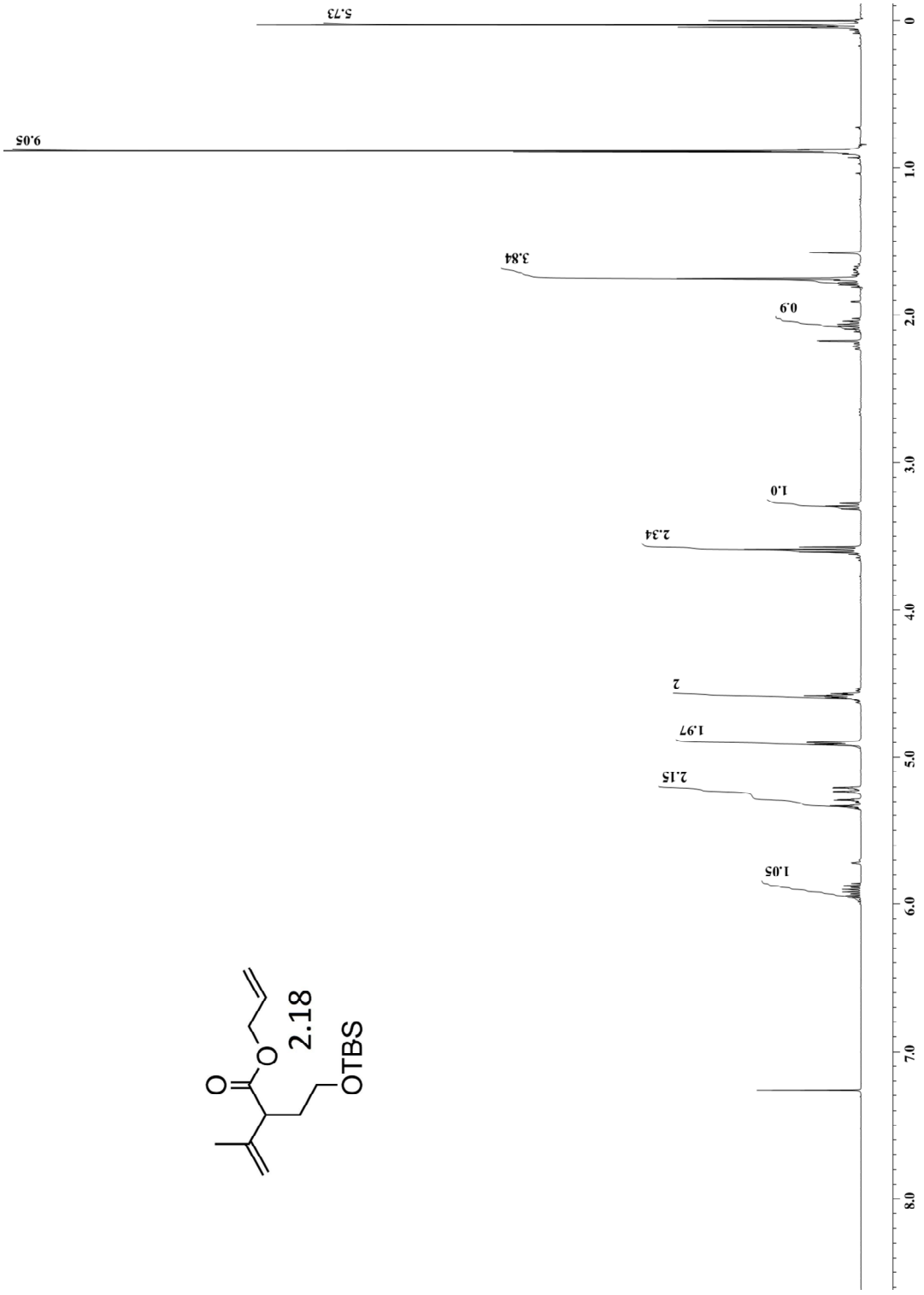
^{13}C-NMR Spectrum (400 MHz, $CDCl_3$)

2-(2-(tert-butyldimethylsilyloxy)ethyl)-3-methylbut-3-enoic acid



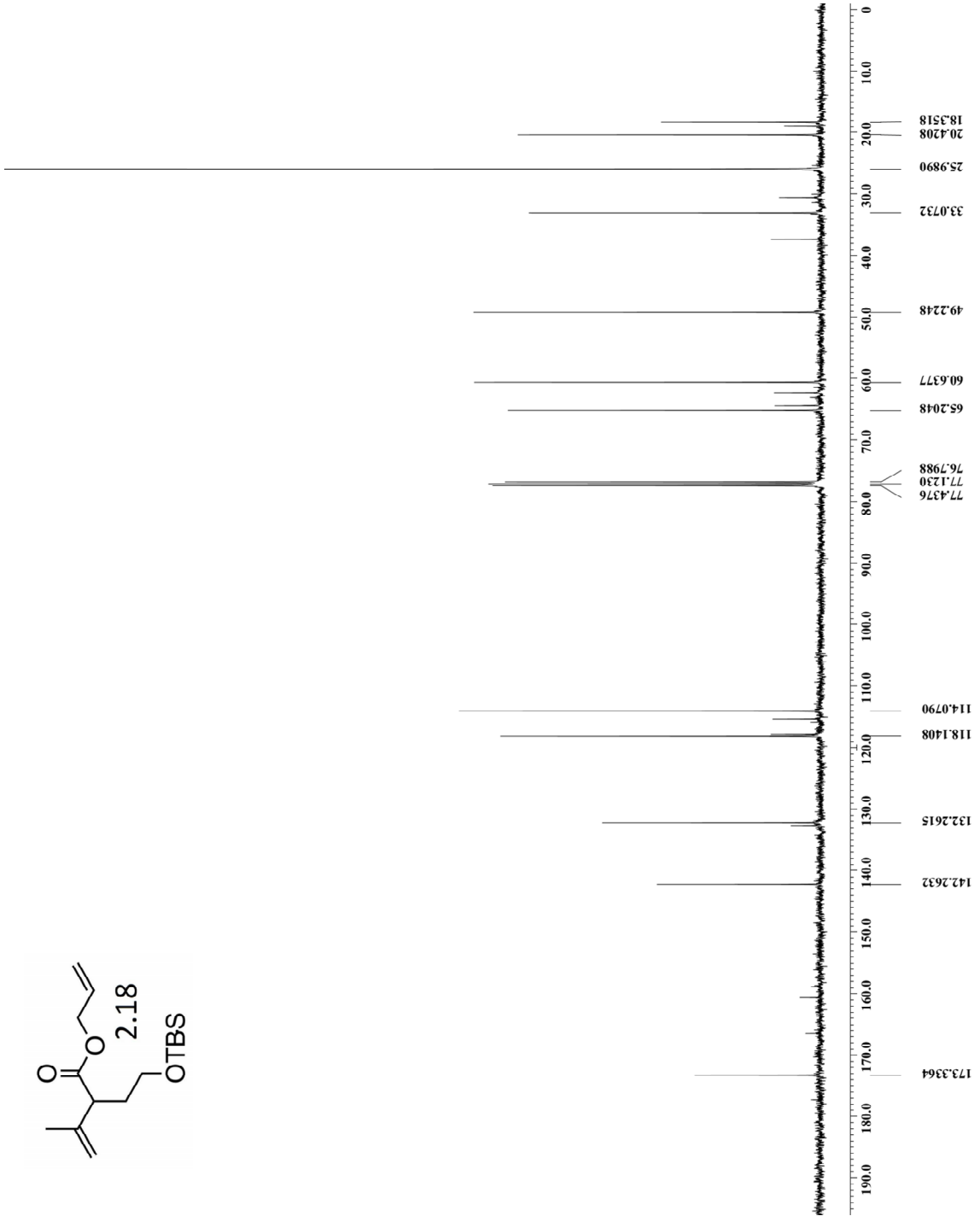
^{1}H-NMR Spectrum (400 MHz, $CDCl_3$)

allyl 2-(2-(tert-butyldimethylsilyloxy)ethyl)-3-methylbut-3-enoate



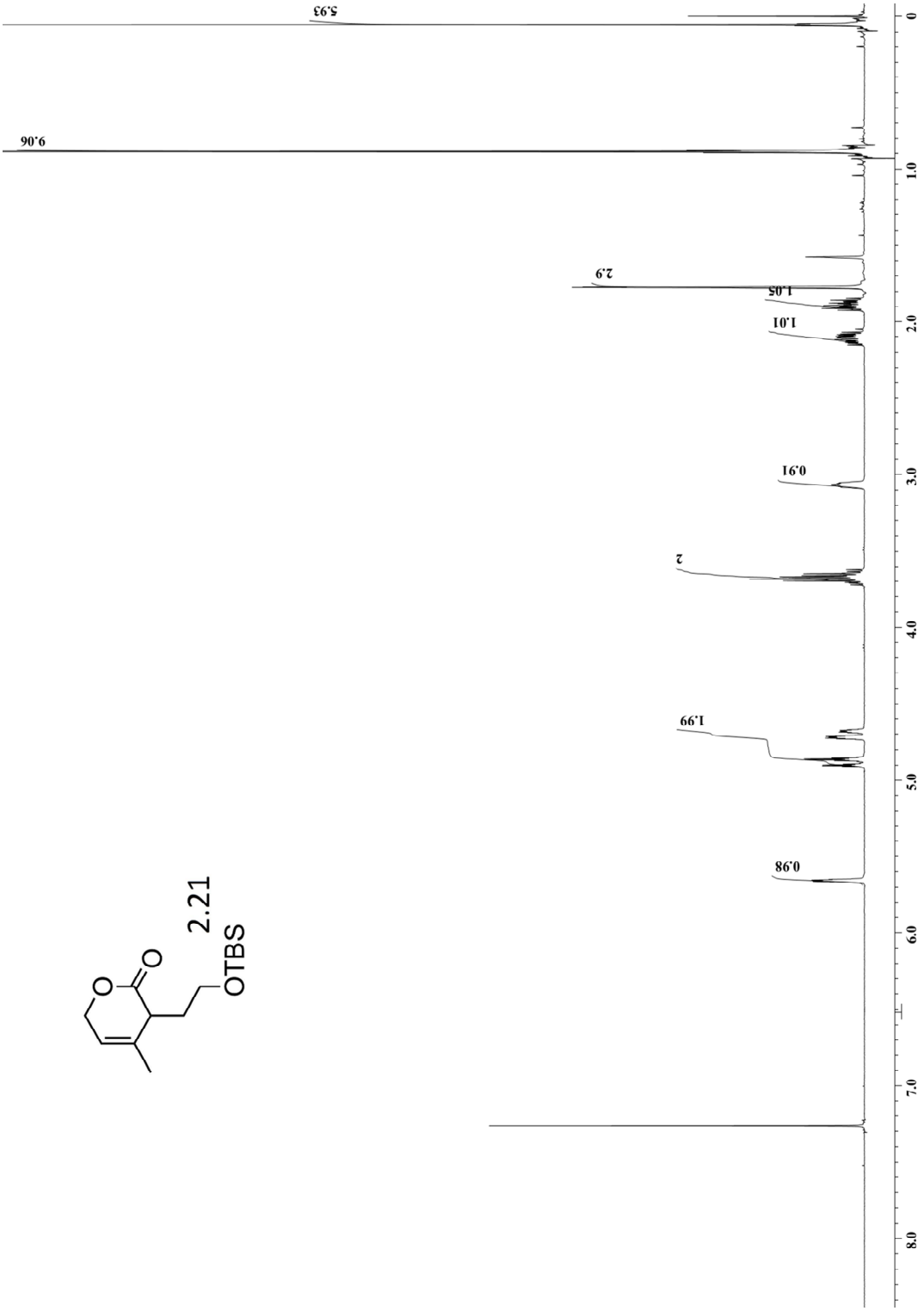
^{13}C-NMR Spectrum (400 MHz, $CDCl_3$)

allyl 2-(2-(tert-butyldimethylsilyloxy)ethyl)-3-methylbut-3-enoate



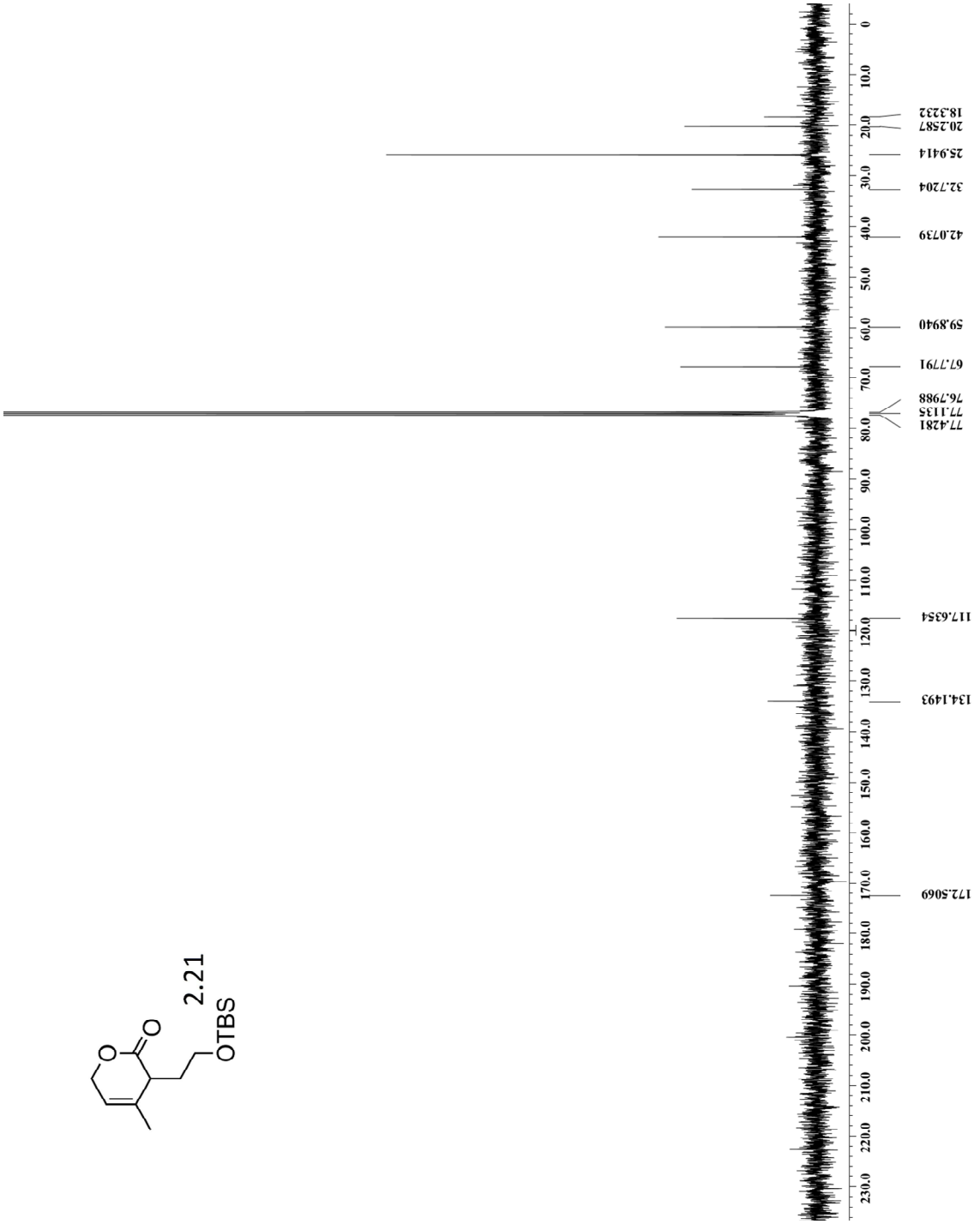
^{1}H-NMR Spectrum (400 MHz, $CDCl_3$)

3-(2-(tert-butyldimethylsilyloxy)ethyl)-4-methyl-3,6-dihydro-2H-pyran-2-one



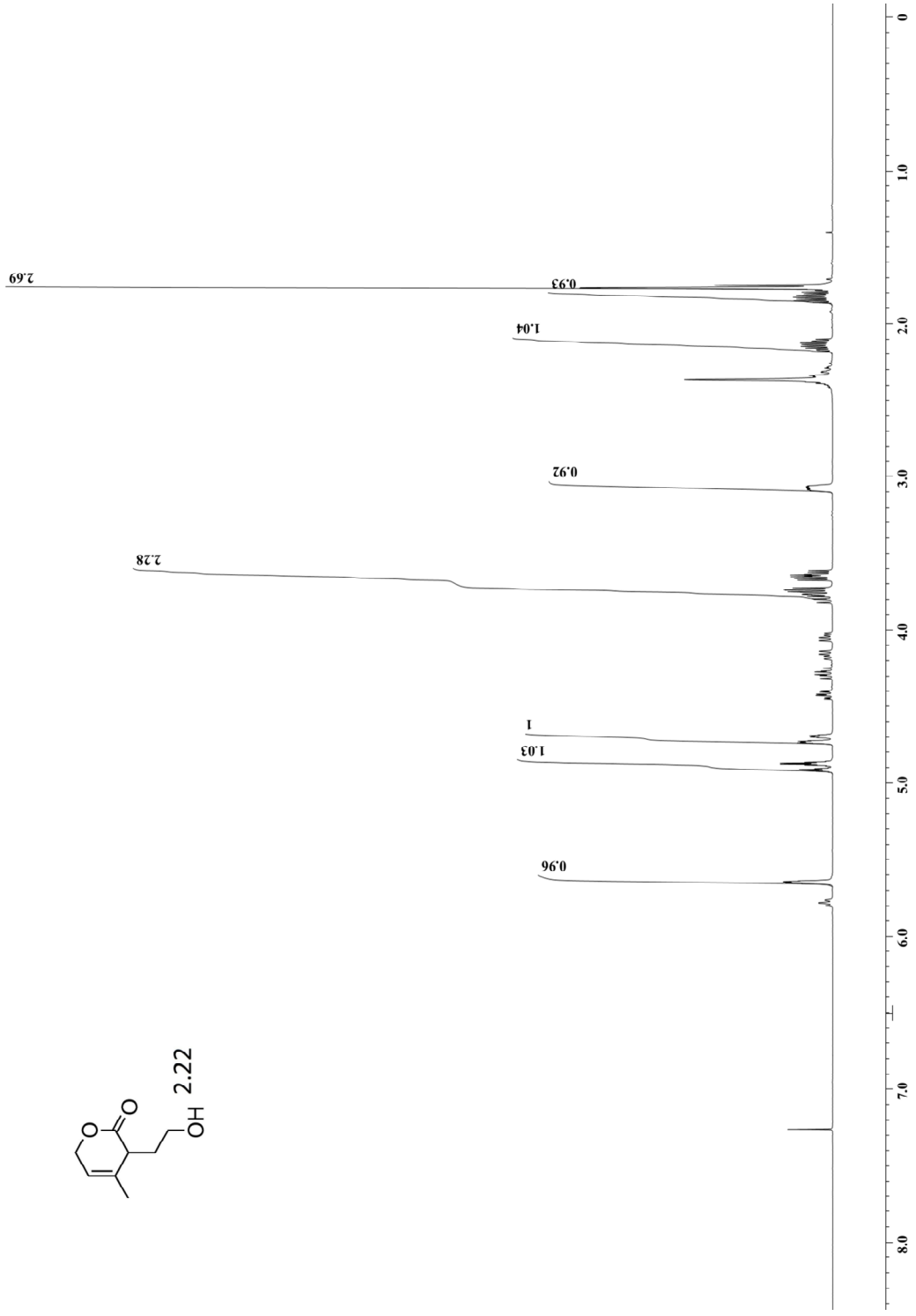
^{13}C-NMR Spectrum (400 MHz, $CDCl_3$)

3-(2-(tert-butyldimethylsilyloxy)ethyl)-4-methyl-3,6-dihydro-2H-pyran-2-one



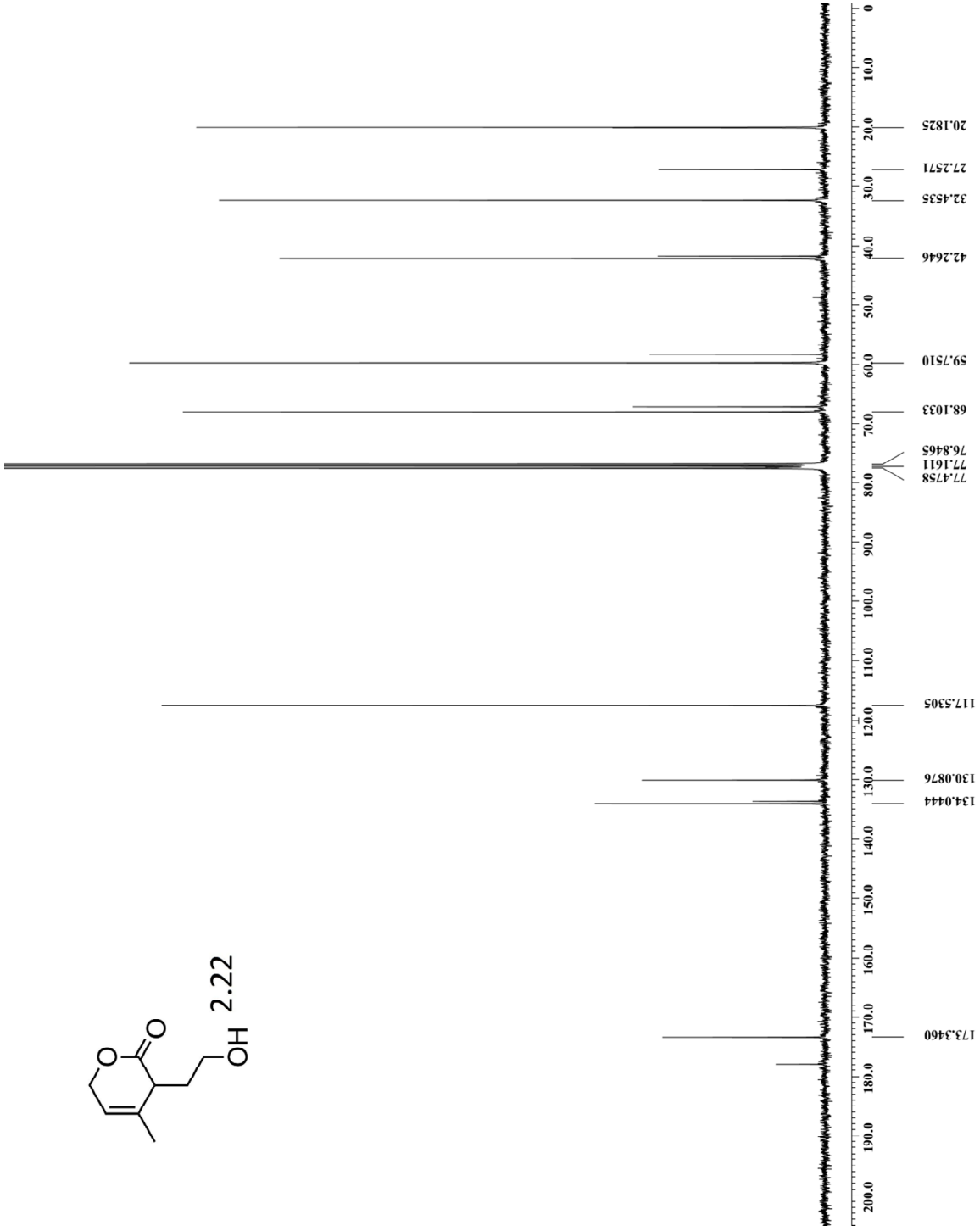
^{1}H-NMR Spectrum (400 MHz, $CDCl_3$)

3-(2-hydroxyethyl)-4-methyl-3,6-dihydro-2H-pyran-2-one



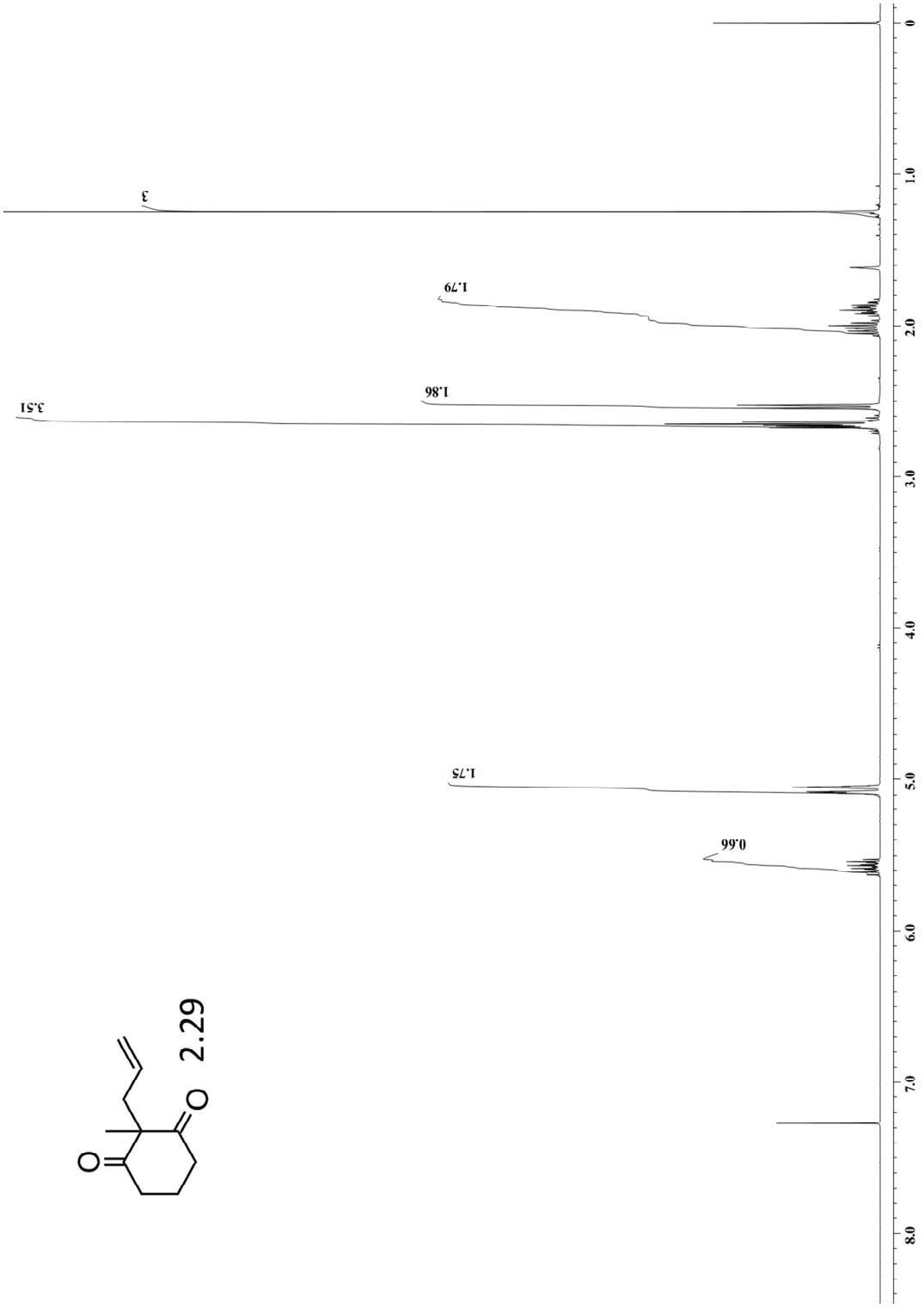
^{13}C-NMR Spectrum (400 MHz, $CDCl_3$)

3-(2-hydroxyethyl)-4-methyl-3,6-dihydro-2H-pyran-2-one



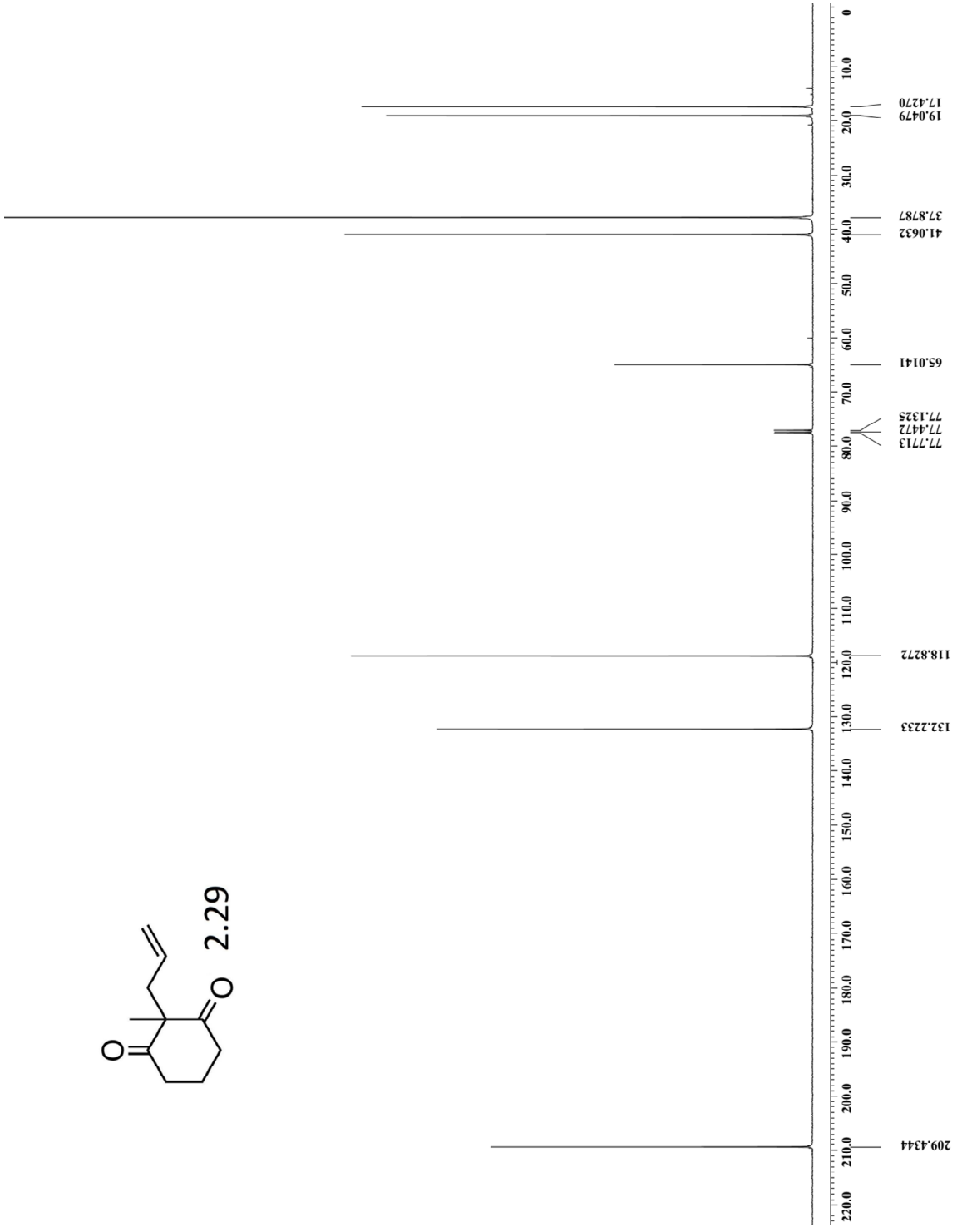
^{1}H-NMR Spectrum (400 MHz, $CDCl_3$)

2-allyl-2-methylcyclohexane-1,3-dione



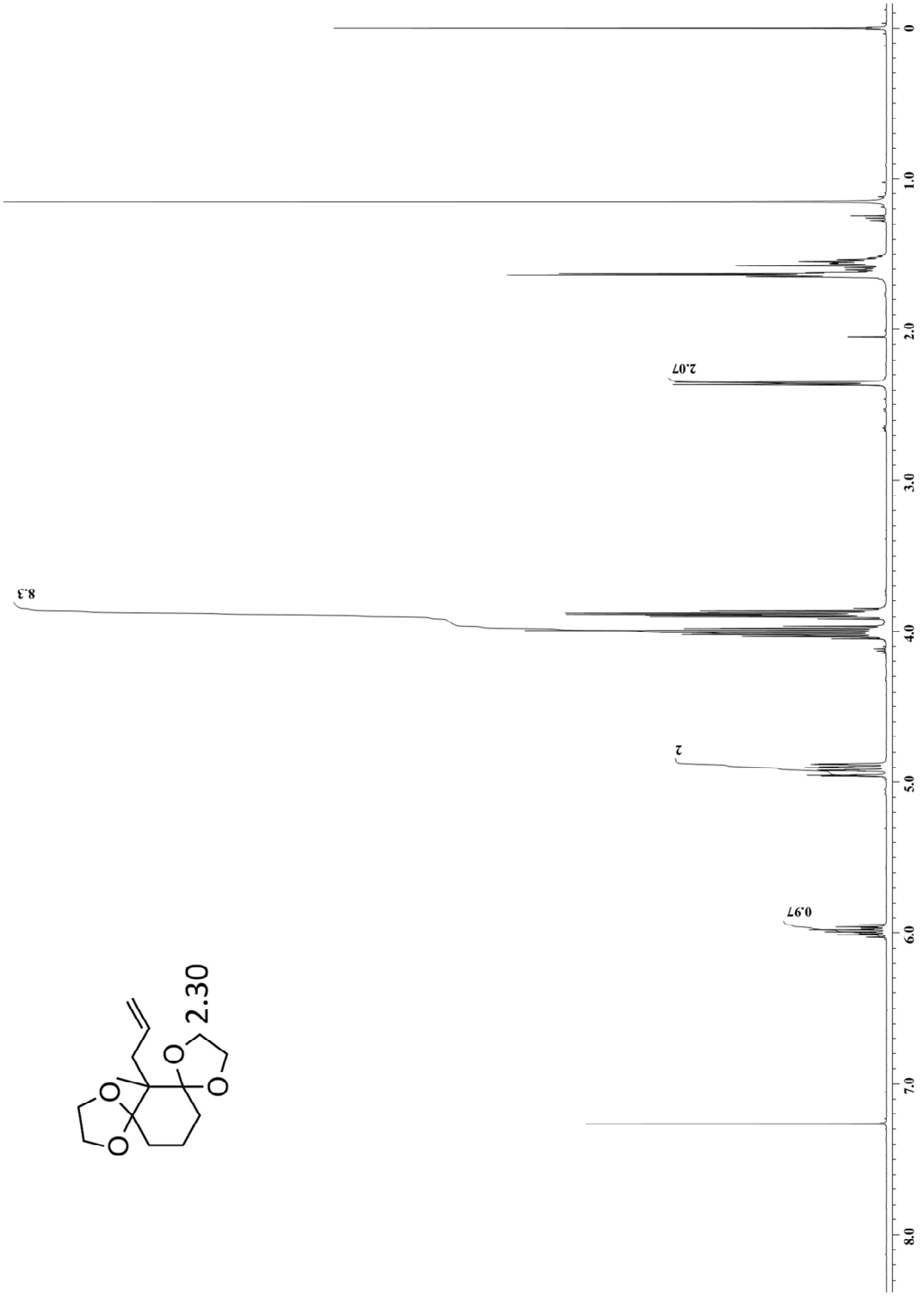
^{13}C-NMR Spectrum (400 MHz, $CDCl_3$)

2-allyl-2-methylcyclohexane-1,3-dione



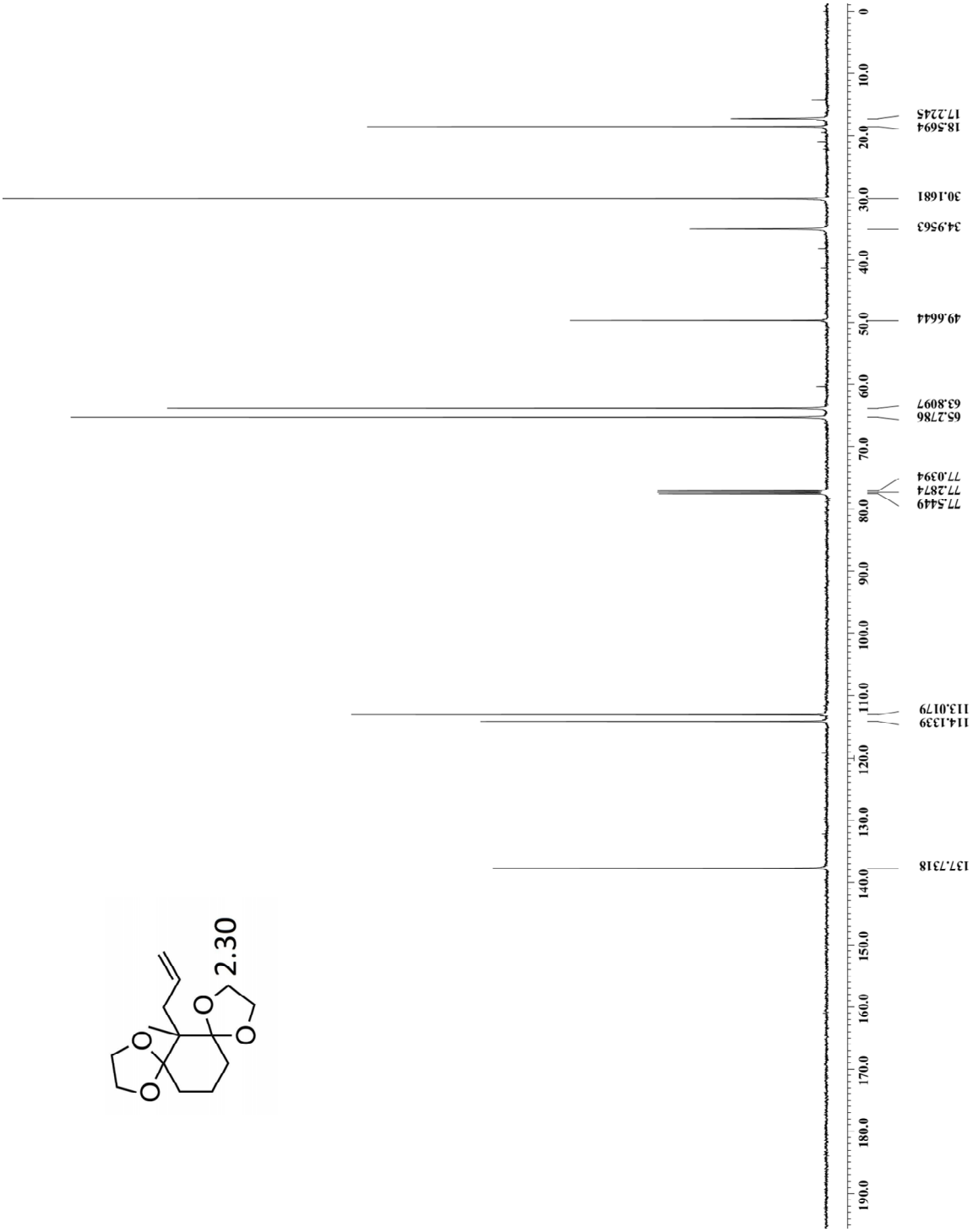
^{1}H-NMR Spectrum (400 MHz, $CDCl_3$)

6-methyl-6-(prop-2-en-1-yl)-1,4,8,11-tetraoxadispiro[4.1.47.35]-tetradecane



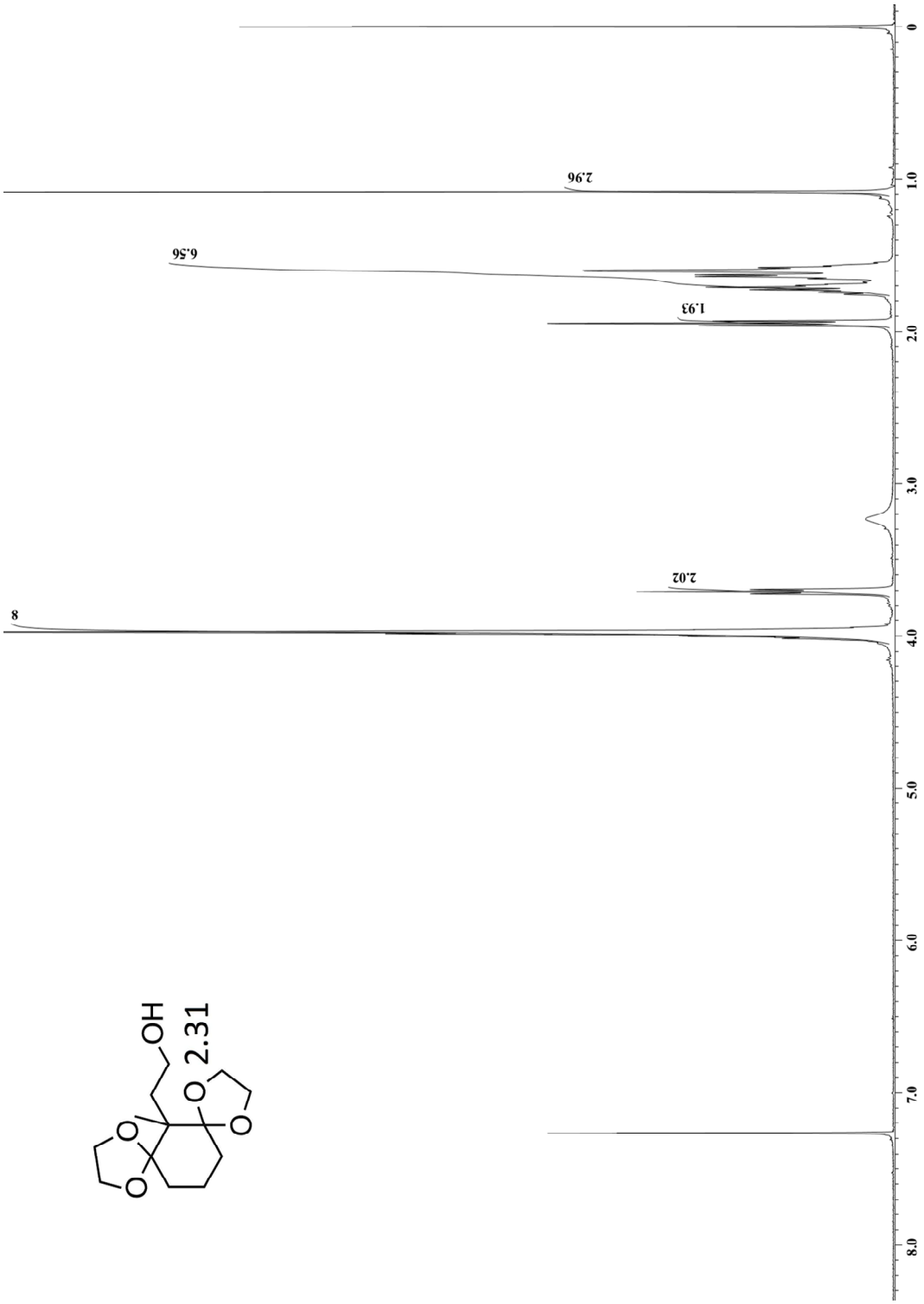
^{13}C-NMR Spectrum (400 MHz, $CDCl_3$)

6-methyl-6-(prop-2-en-1-yl)-1,4,8,11-tetraoxadispiro[4.1.47.35]-tetradecane



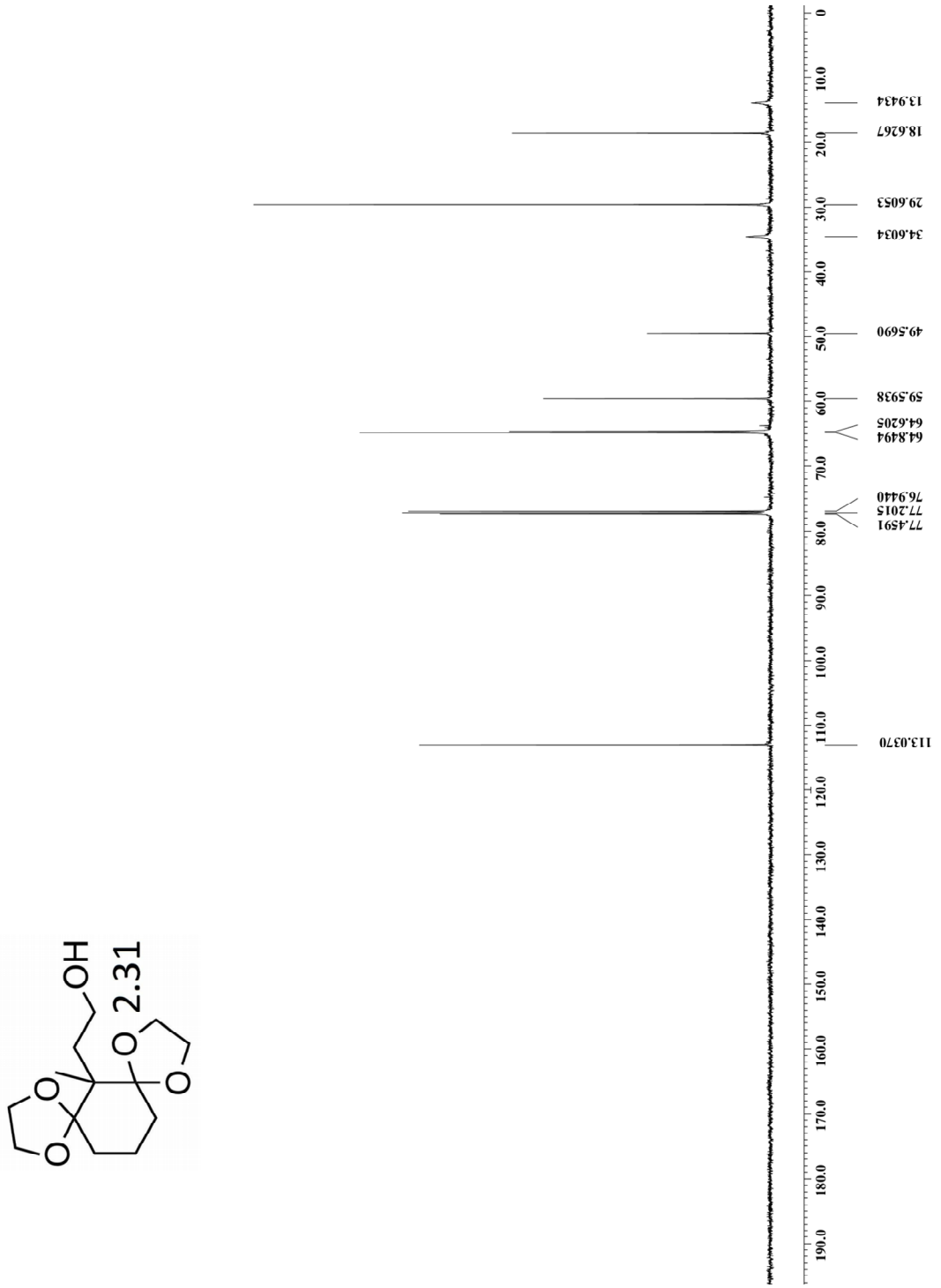
^{1}H-NMR Spectrum (400 MHz, $CDCl_3$)

2-{6-methyl-1,4,8,11- tetraoxadispiro[4.1.47.35]tetradecan-6- yl}ethan-1-ol



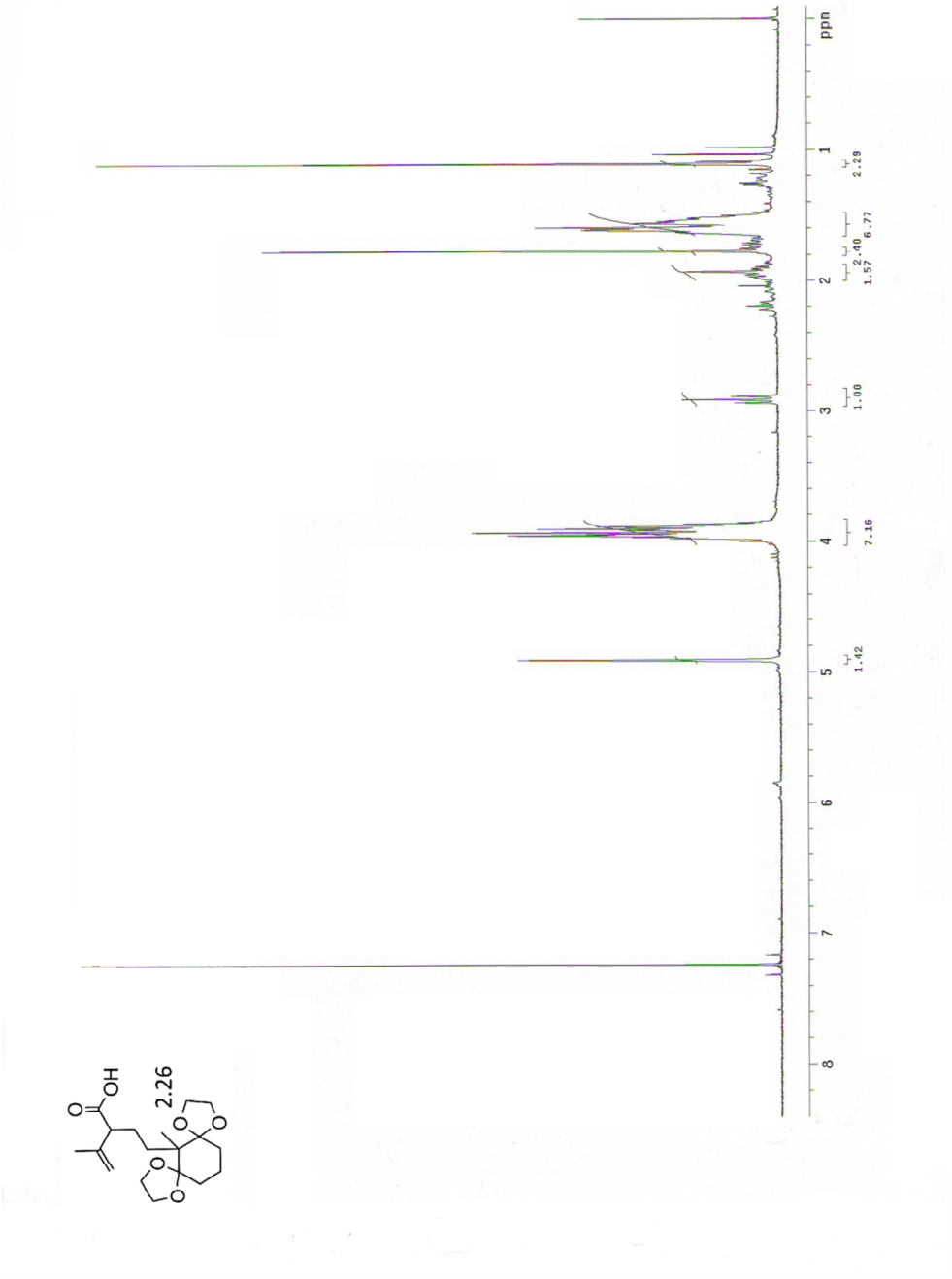
^{13}C-NMR Spectrum (400 MHz, $CDCl_3$)

2-{6-methyl-1,4,8,11- tetraoxadispiro[4.1.47.35]tetradecan-6- yl}ethan-1-ol



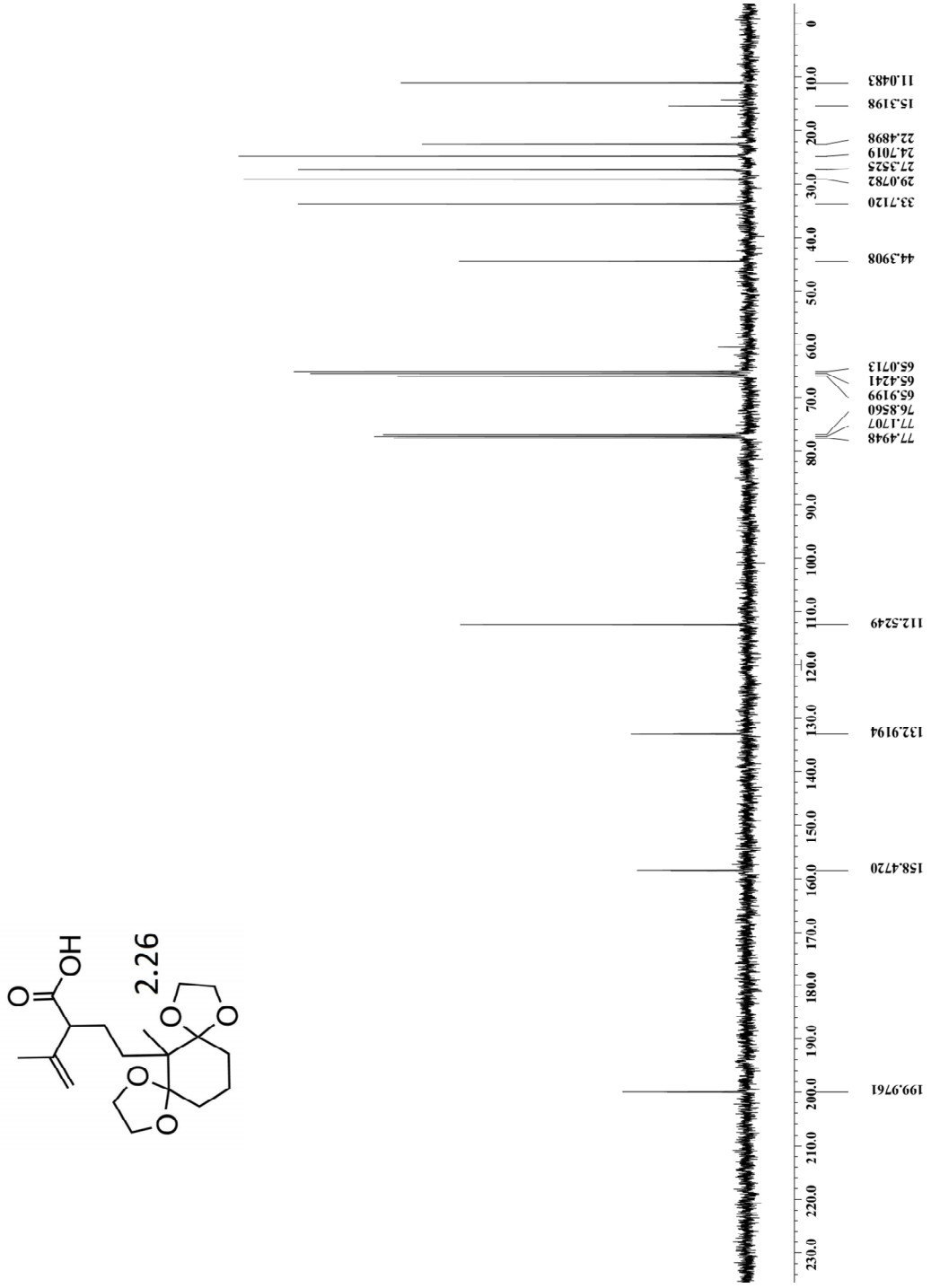
^{1}H-NMR Spectrum (300 MHz, $CDCl_3$)

3-methyl-2-({6-methyl-1,4,8,11- tetraoxadispiro[4.1.47.35]tetradecan-6- yl}ethyl)but-3-enoic acid



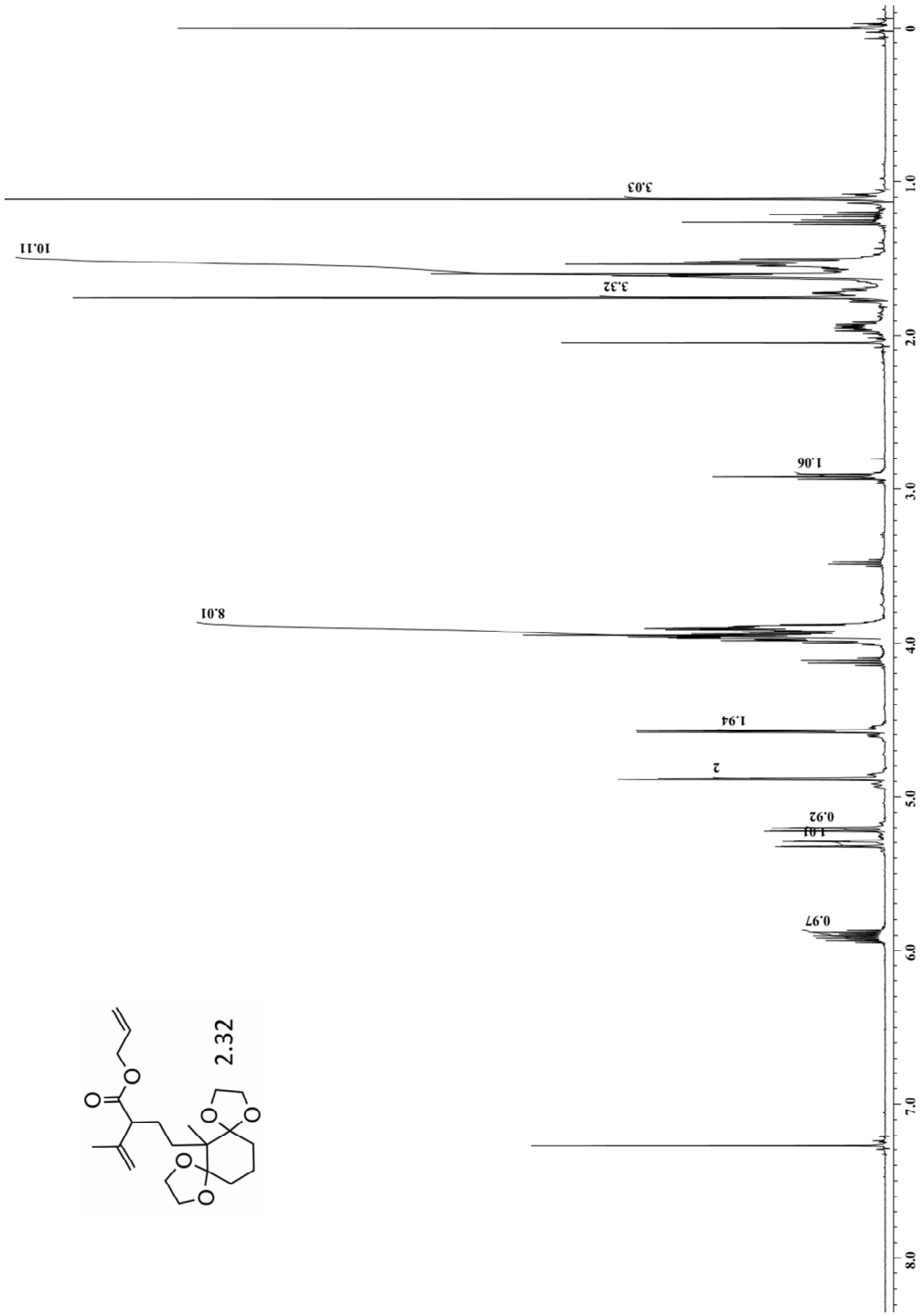
^{13}C-NMR Spectrum (400 MHz, $CDCl_3$)

3-methyl-2-({6-methyl-1,4,8,11- tetraoxadispiro[4.1.47.35]tetradecan-6- yl}ethyl)but-3-enoic acid



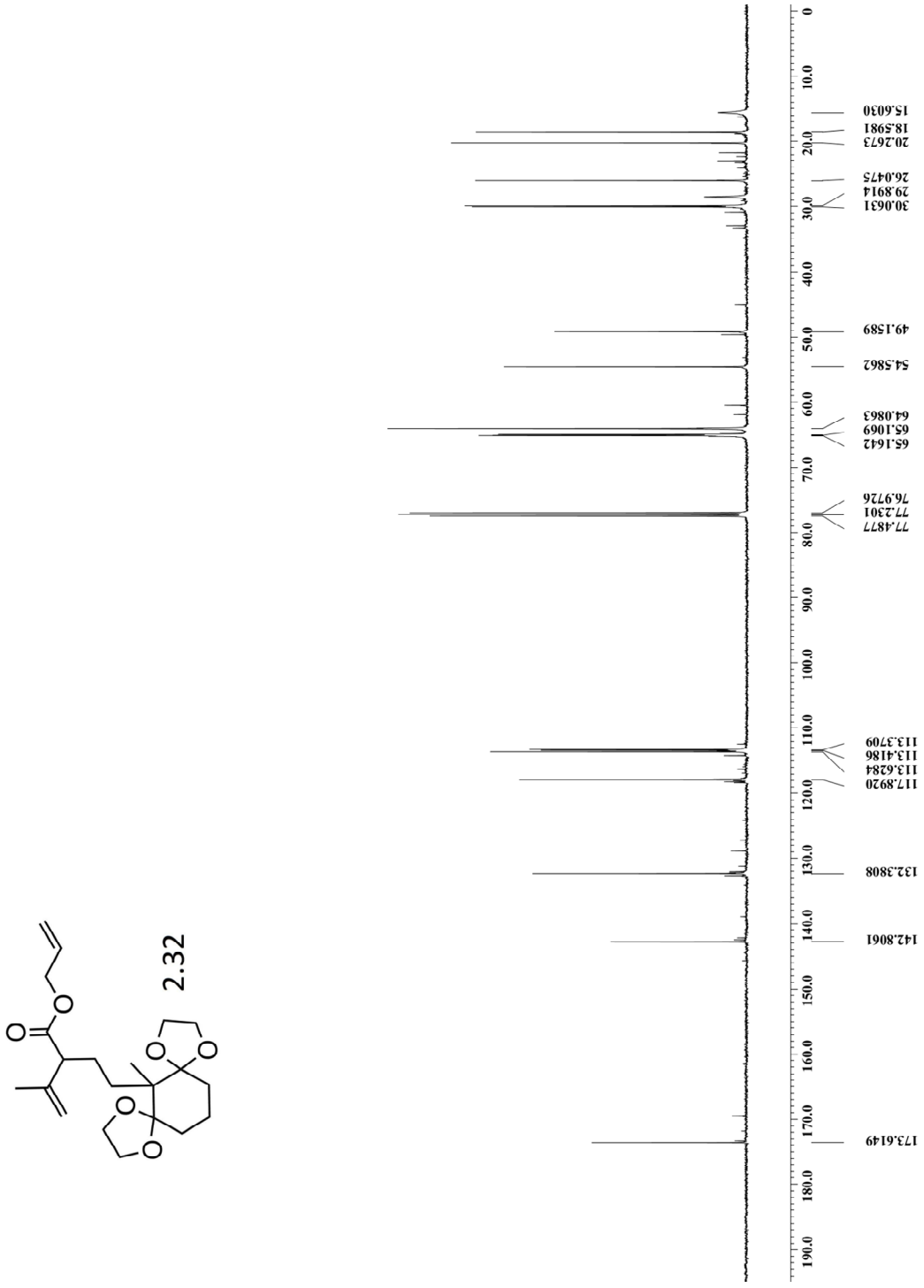
^{1}H-NMR Spectrum (400 MHz, CDCl3)

prop-2-en-1-yl 3-methyl-2-({6-methyl-1,4,8,11- tetraoxadispiro[4.1.47.35]tetradecan-6-yl}ethyl)but-3-enoate



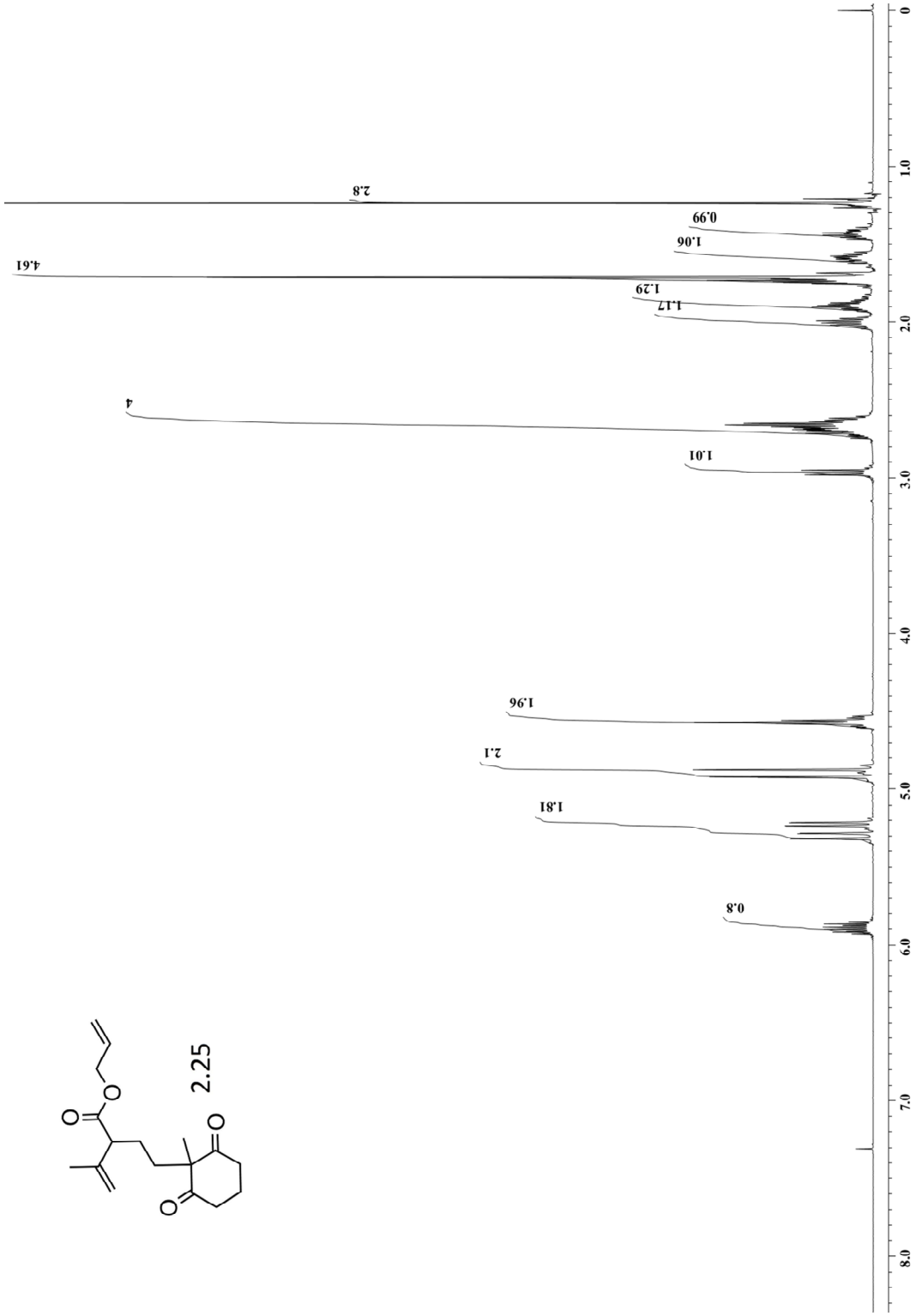
^{13}C-NMR Spectrum (400 MHz, CDCl3)

prop-2-en-1-yl 3-methyl-2-({6-methyl-1,4,8,11- tetraoxadispiro[4.1.47.35]tetradecan-6-yl}ethyl)but-3-enoate



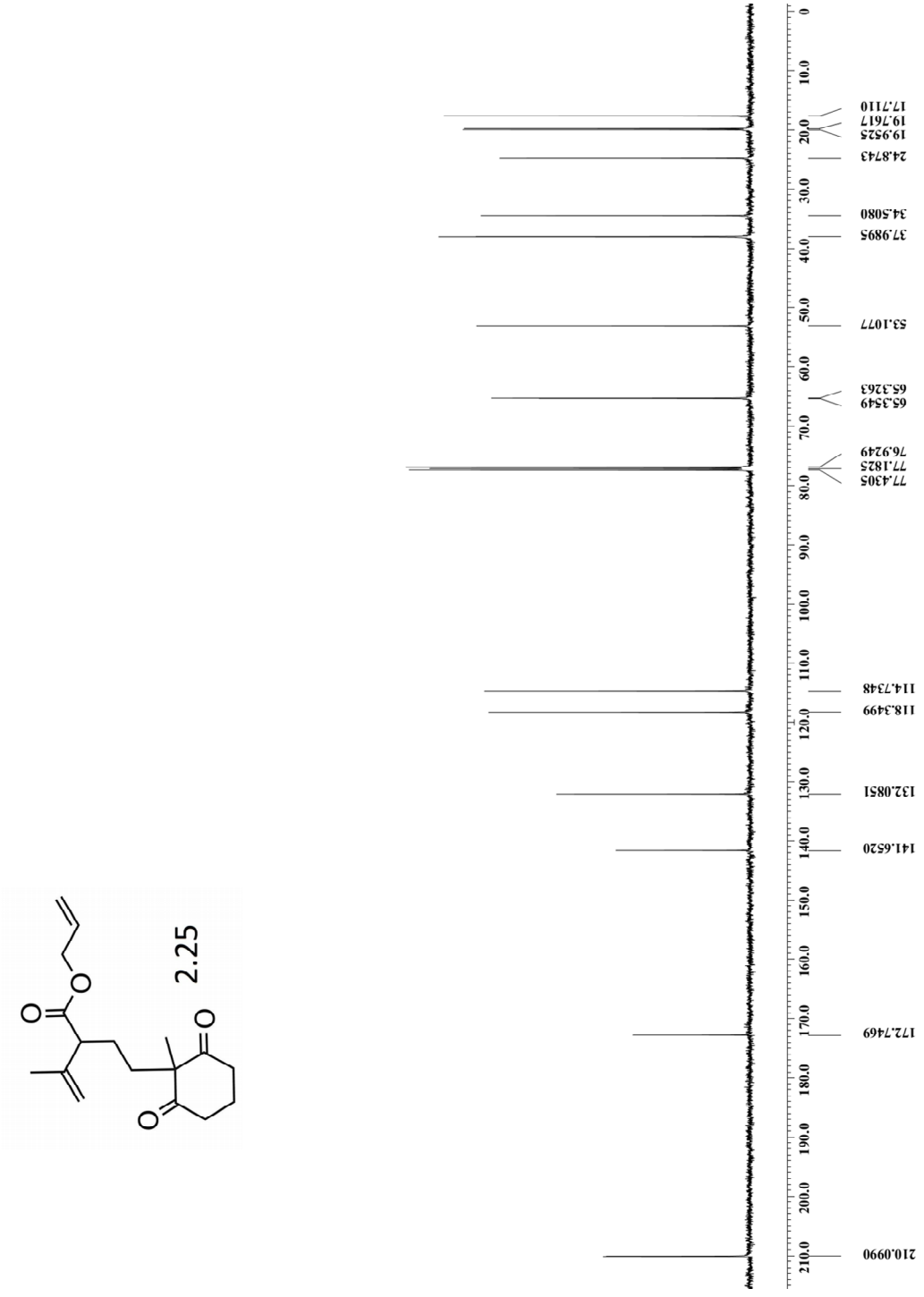
1H-NMR Spectrum (400 MHz, CDCl3)

prop-2-en-1-yl 3-methyl-2-[(1-methyl-2,6-dioxocyclohexyl)ethyl]but-3-enoate



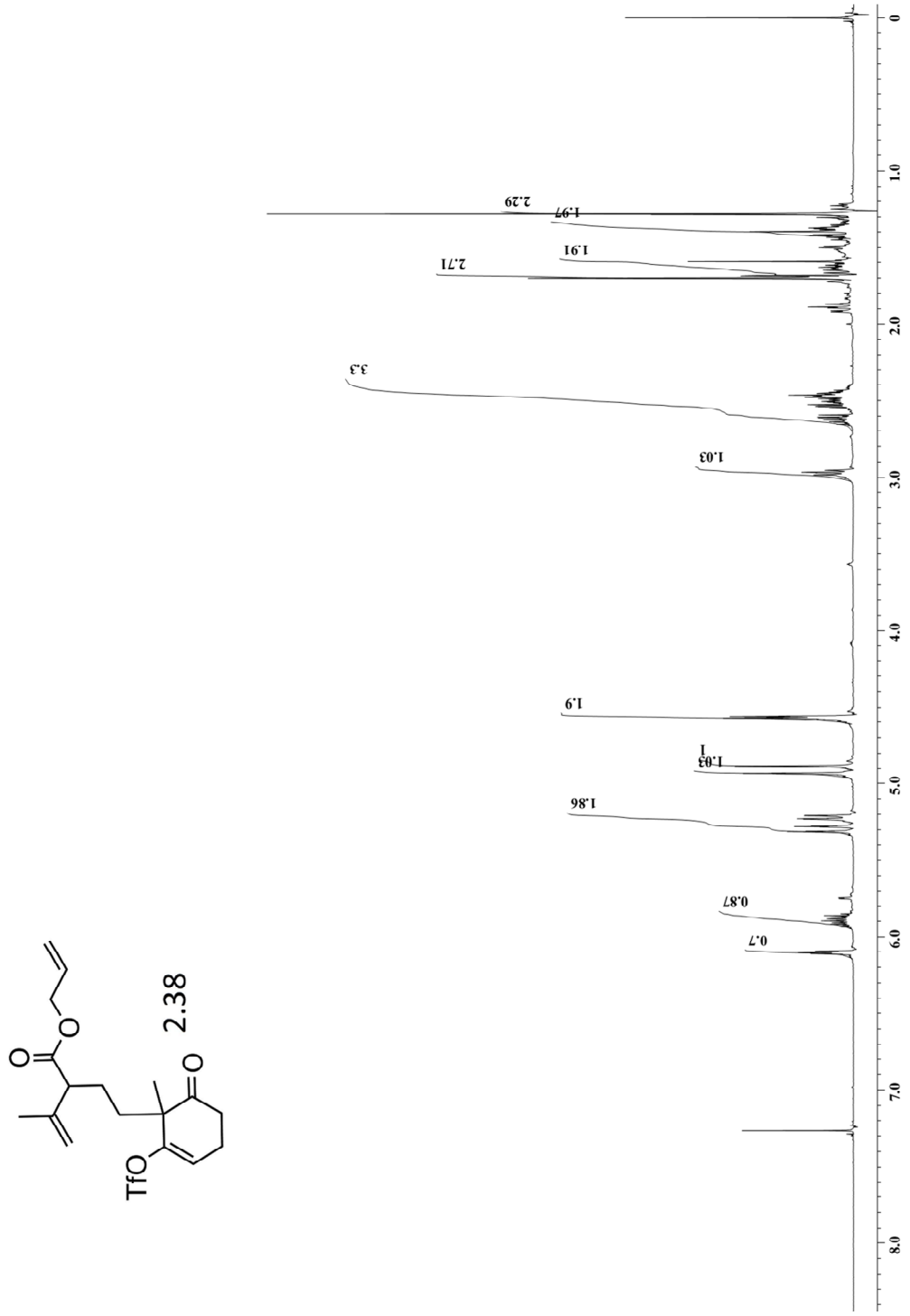
^{13}C-NMR Spectrum (400 MHz, CDCl3)

prop-2-en-1-yl 3-methyl-2-[(1-methyl-2,6-dioxocyclohexyl)ethyl]but-3-enoate



^{1}H-NMR Spectrum (400 MHz, CDCl3)

prop-2-en-1-yl 3-methyl-2-(2-{1-methyl-6-oxo-2-[(trifluoromethane)sulfonyloxy]cyclohex-2-en-1-yl}ethyl)but-3-enoate

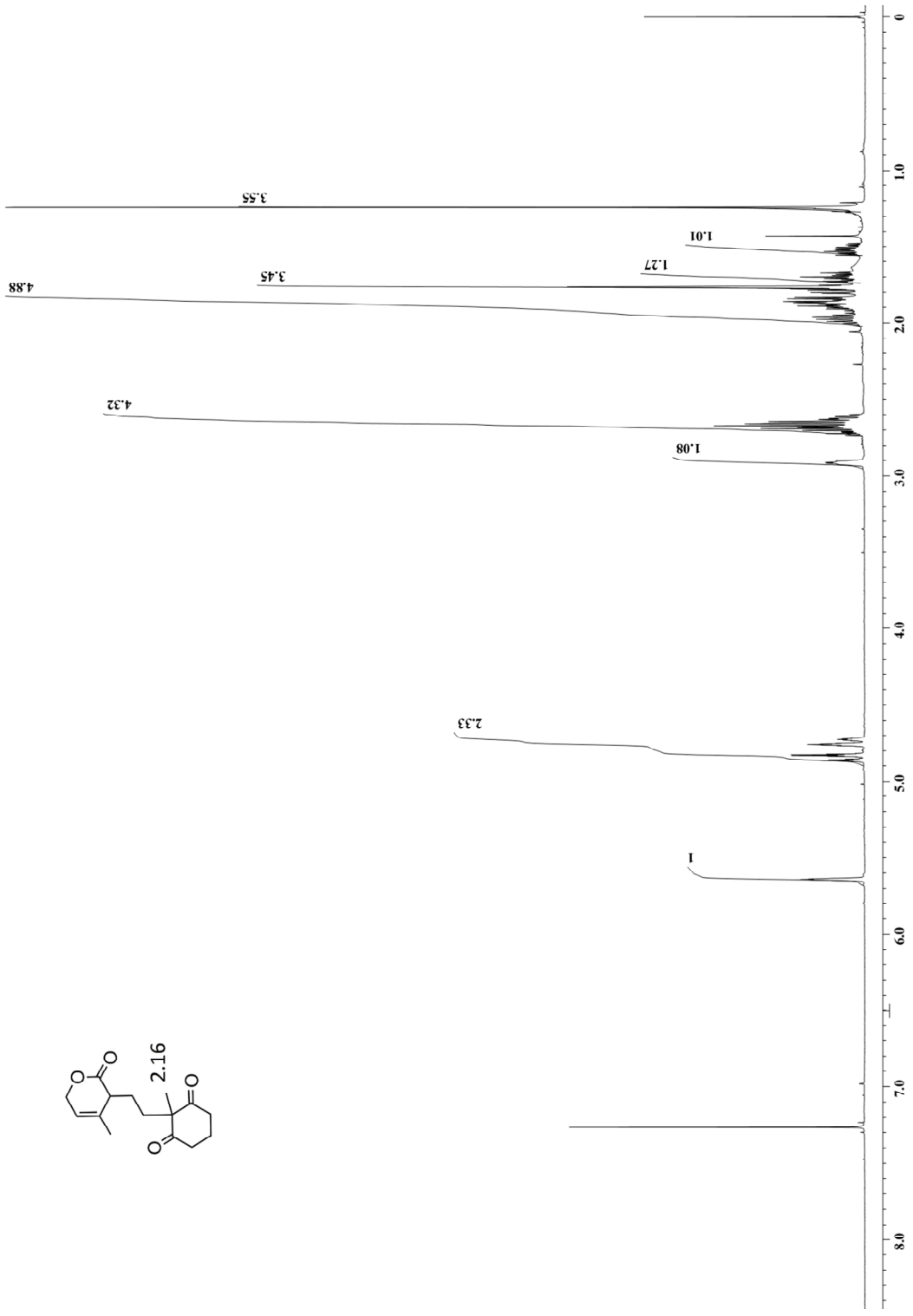


^{13}C-NMR Spectrum (400 MHz, CDCl3)

prop-2-en-1-yl 3-methyl-2-(2-{1-methyl-6-oxo-2-[(trifluoromethane)sulfonyloxy]cyclohex-2-en-1-yl}ethyl)but-3-enoate

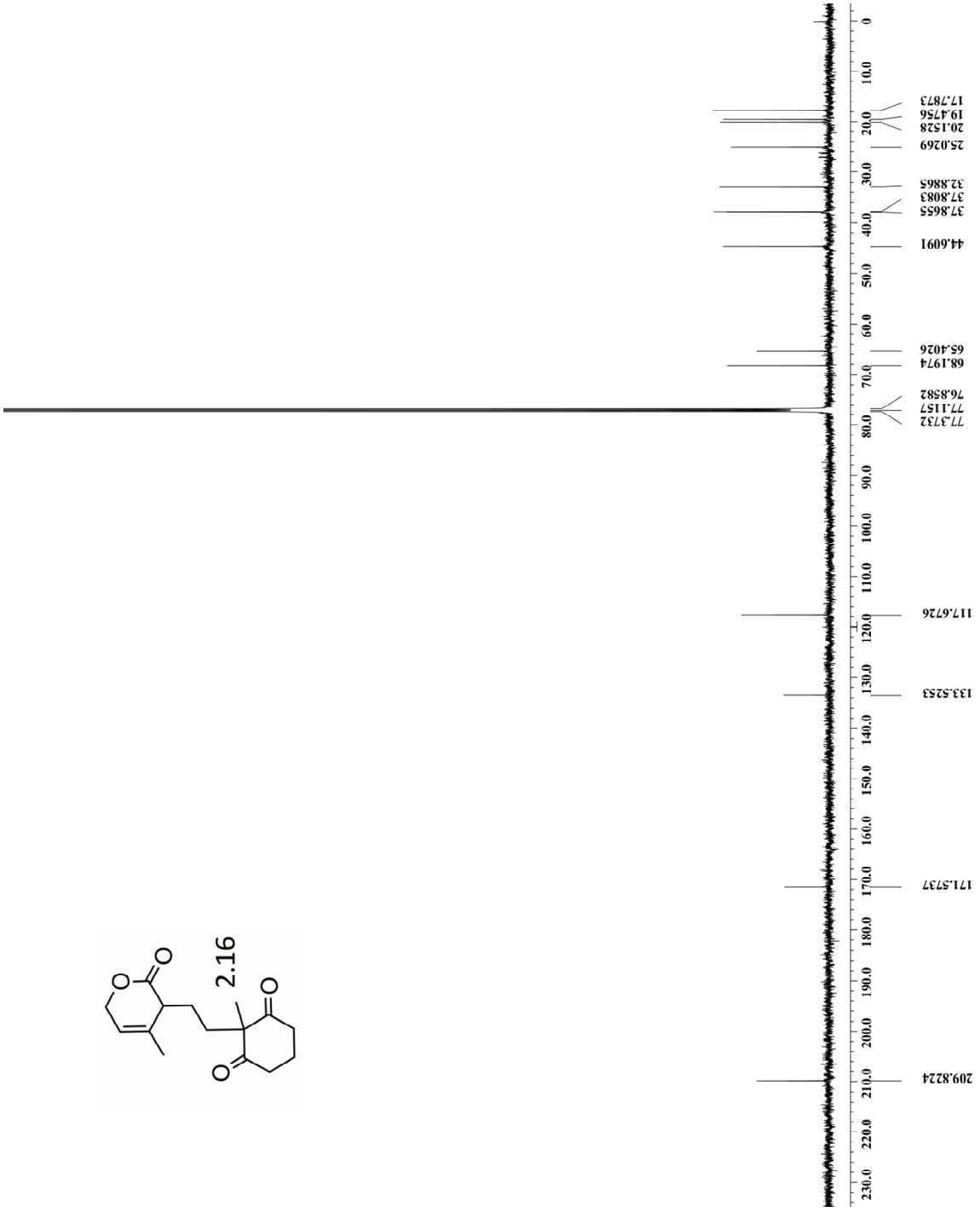
^{1}H-NMR Spectrum (400 MHz, CDCl3)

2-methyl-2-[2-(4-methyl-2-oxo-3,6-dihydro-2H-pyran-3-yl)ethyl]cyclohexane-1,3-dione



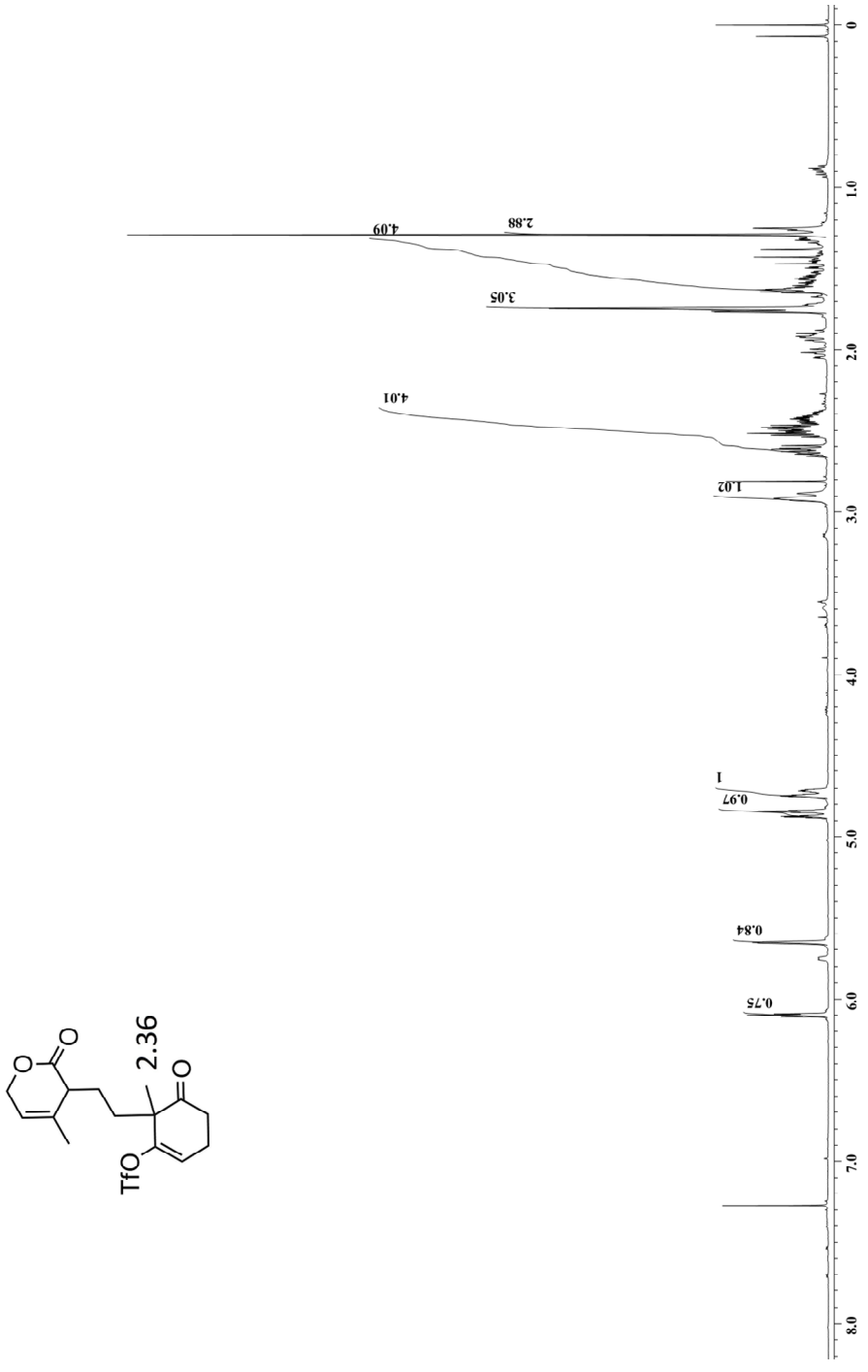
^{13}C-NMR Spectrum (400 MHz, CDCl3)

2-methyl-2-[2-(4-methyl-2-oxo-3,6-dihydro-2H-pyran-3-yl)ethyl]cyclohexane-1,3-dione



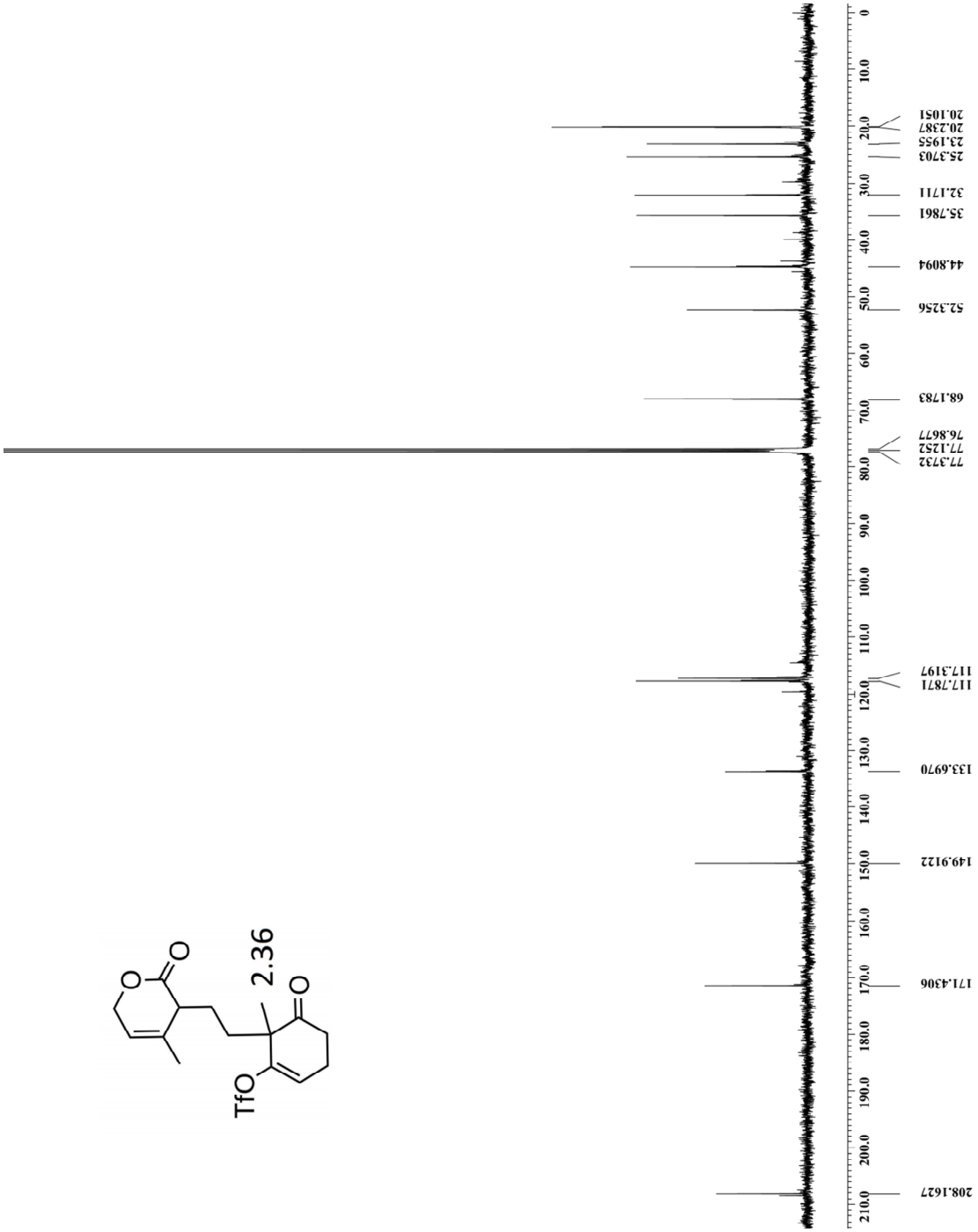
^{1}H-NMR Spectrum (400 MHz, CDCl3)

6-methyl-6-[2-(4-methyl-2-oxo-3,6-dihydro-2H-pyran-3-yl)ethyl]-5-oxocyclohex-1-en-1-yl trifluoromethanesulfonate



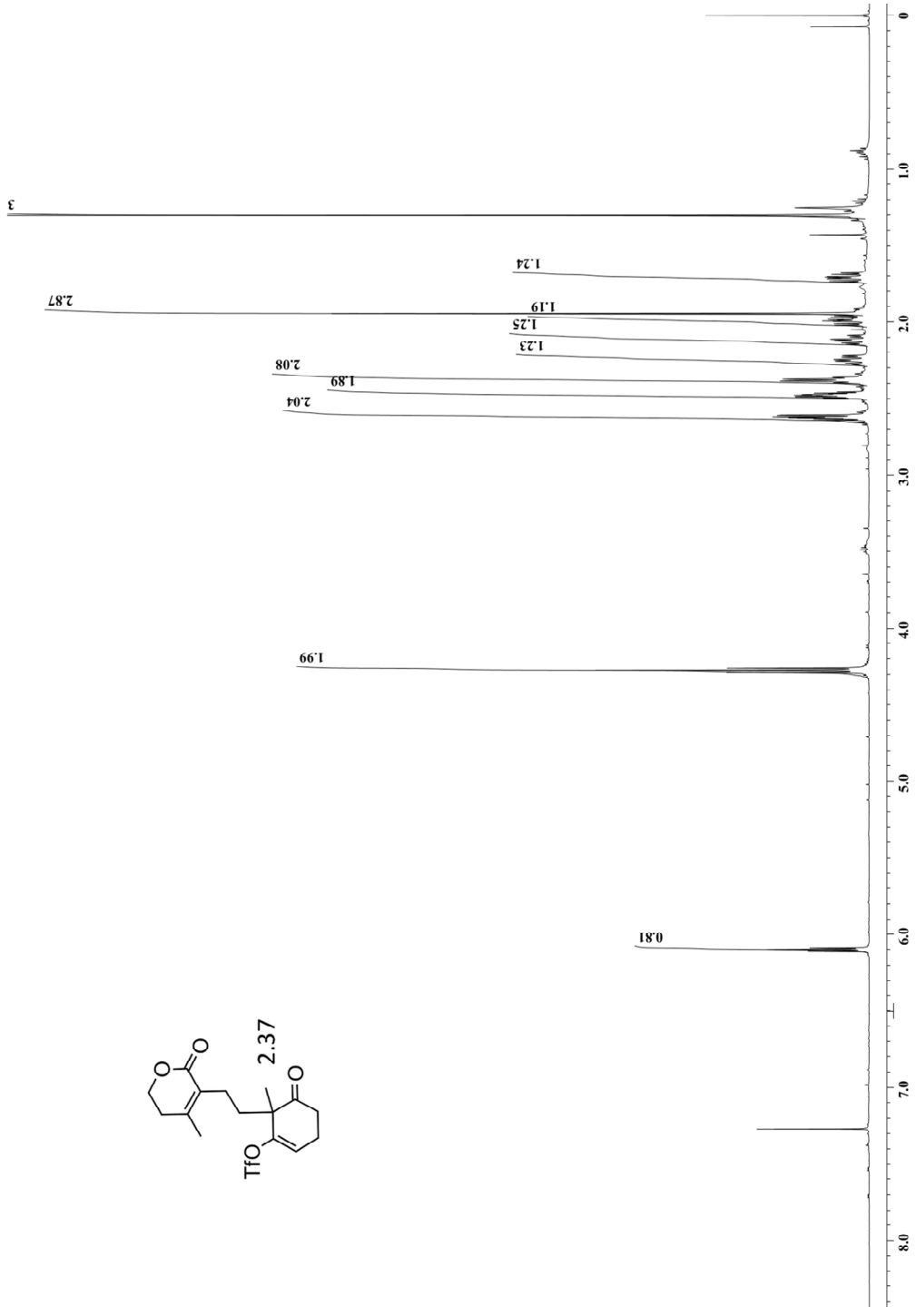
^{13}C-NMR Spectrum (400 MHz, CDCl3)

6-methyl-6-[2-(4-methyl-2-oxo-3,6-dihydro-2H-pyran-3-yl)ethyl]-5-oxocyclohex-1-en-1-yl trifluoromethanesulfonate



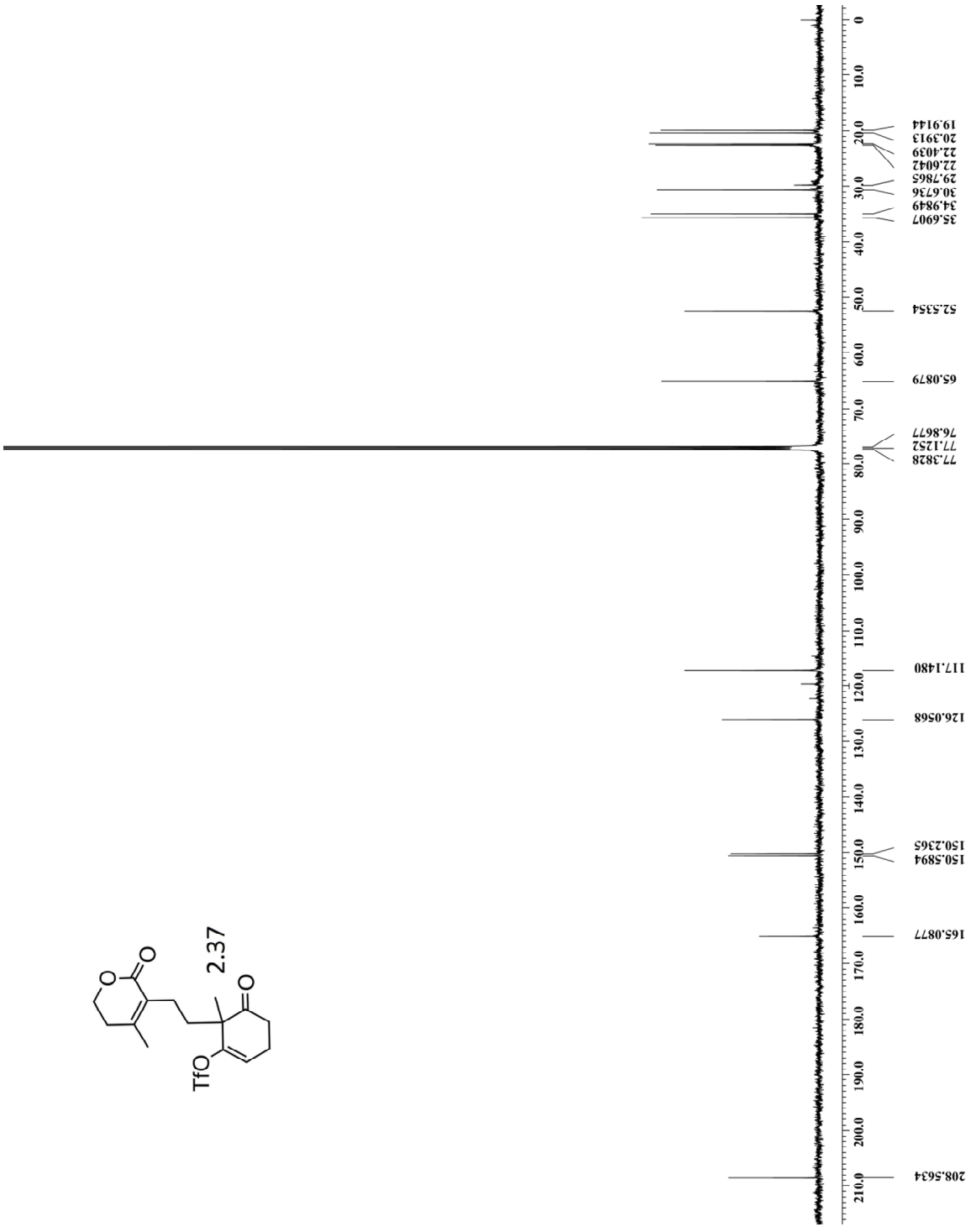
^{1}H-NMR Spectrum (400 MHz, CDCl3)

6-methyl-6-[2-(4-methyl-2-oxo-5,6-dihydro-2H-pyran-3-yl)ethyl]-5-oxocyclohex-1-en-1-yl trifluoromethanesulfonate



^{13}C-NMR Spectrum (400 MHz, CDCl3)

6-methyl-6-[2-(4-methyl-2-oxo-5,6-dihydro-2H-pyran-3-yl)ethyl]-5-oxocyclohex-1-en-1-yl trifluoromethanesulfonate

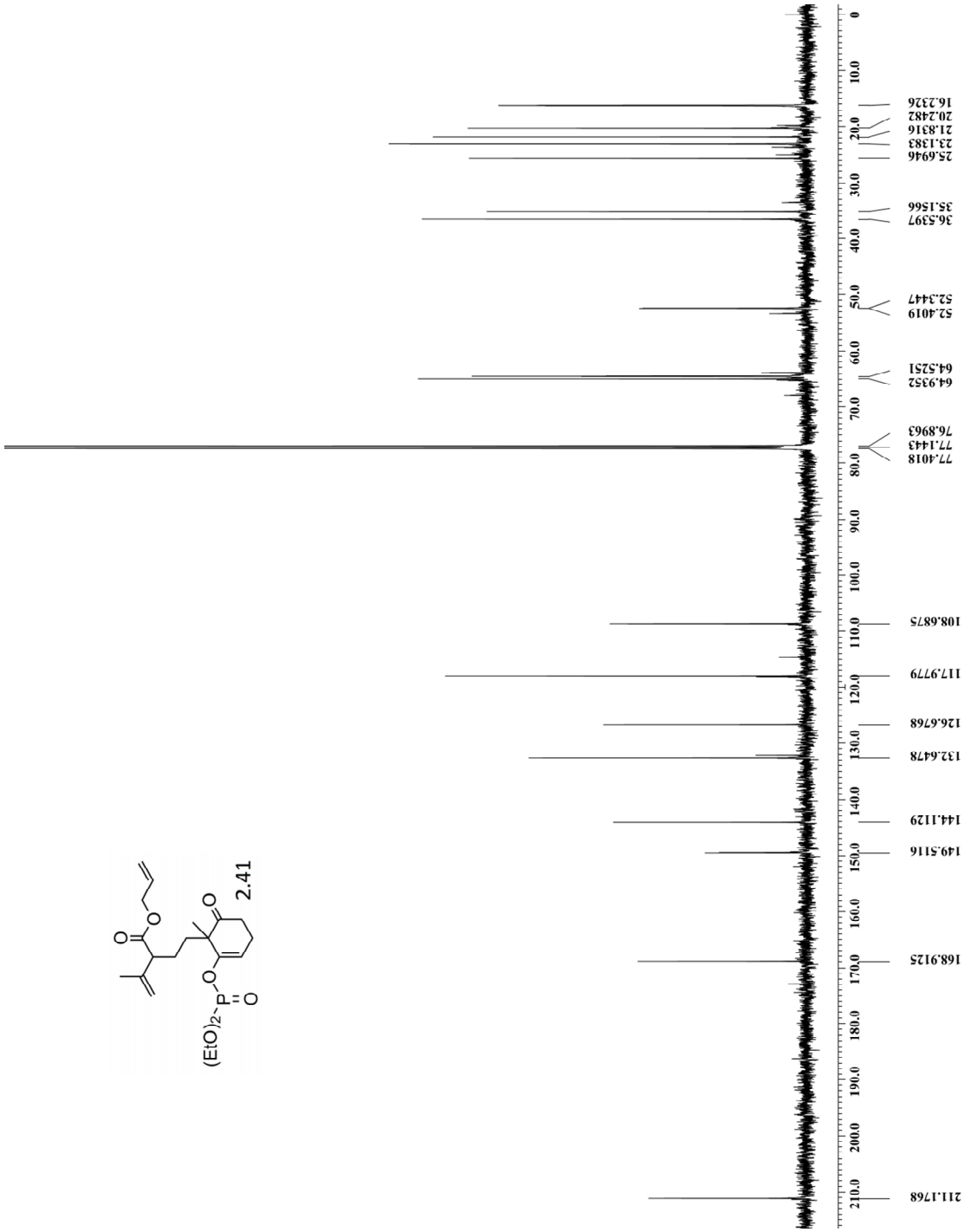


^{1}H-NMR Spectrum (400 MHz, CDCl3)

prop-2-en-1-yl 2-({2-[(diethoxyphosphoryl)oxy]-1-methyl-6-oxocyclohex-2-en-1-yl}methyl)-3-methylbut-3-enoate

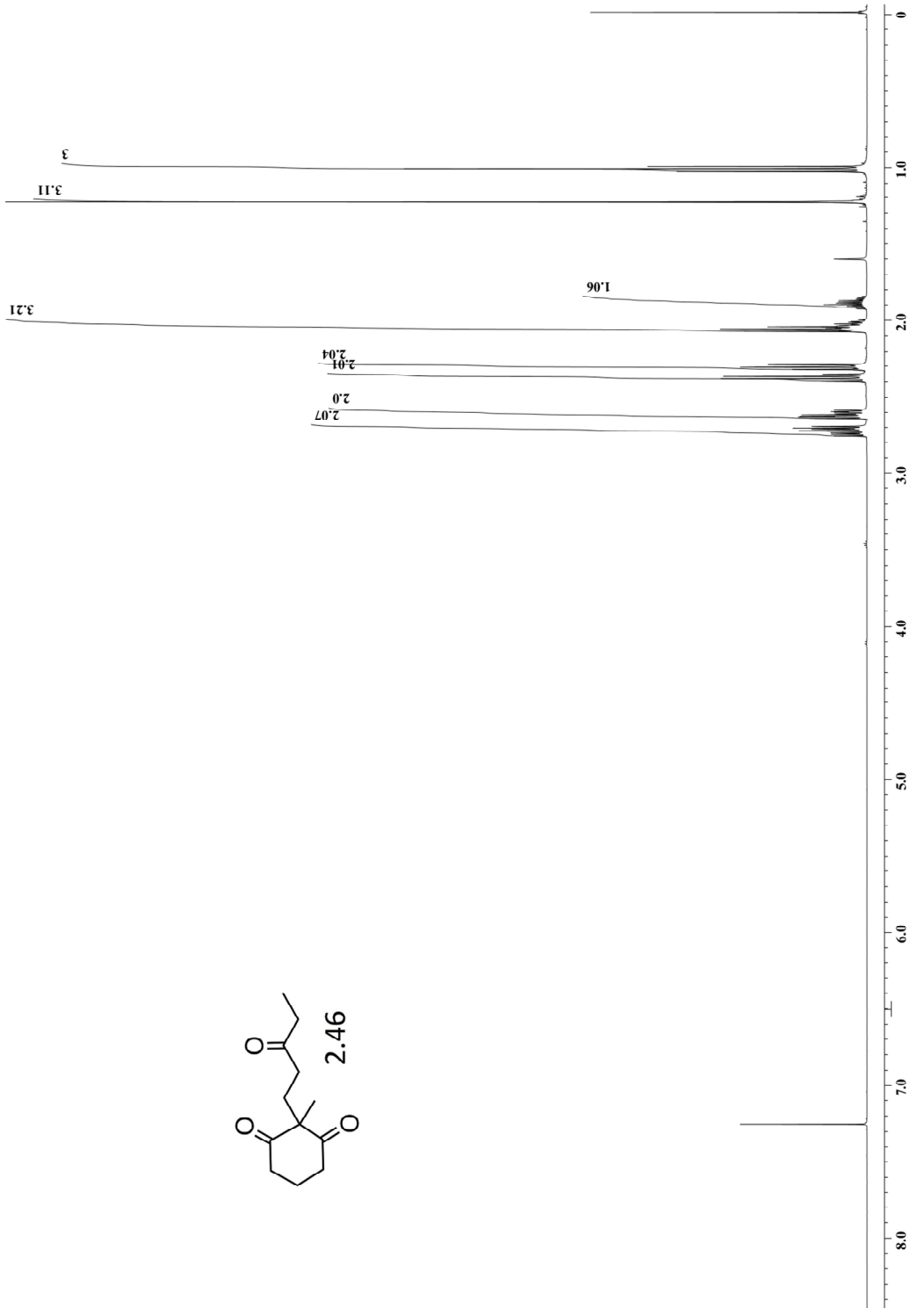
^{13}C-NMR Spectrum (400 MHz, CDCl3)

prop-2-en-1-yl 2-({2-[(diethoxyphosphoryl)oxy]-1-methyl-6-oxocyclohex-2-en-1-yl}methyl)-3-methylbut-3-enoate



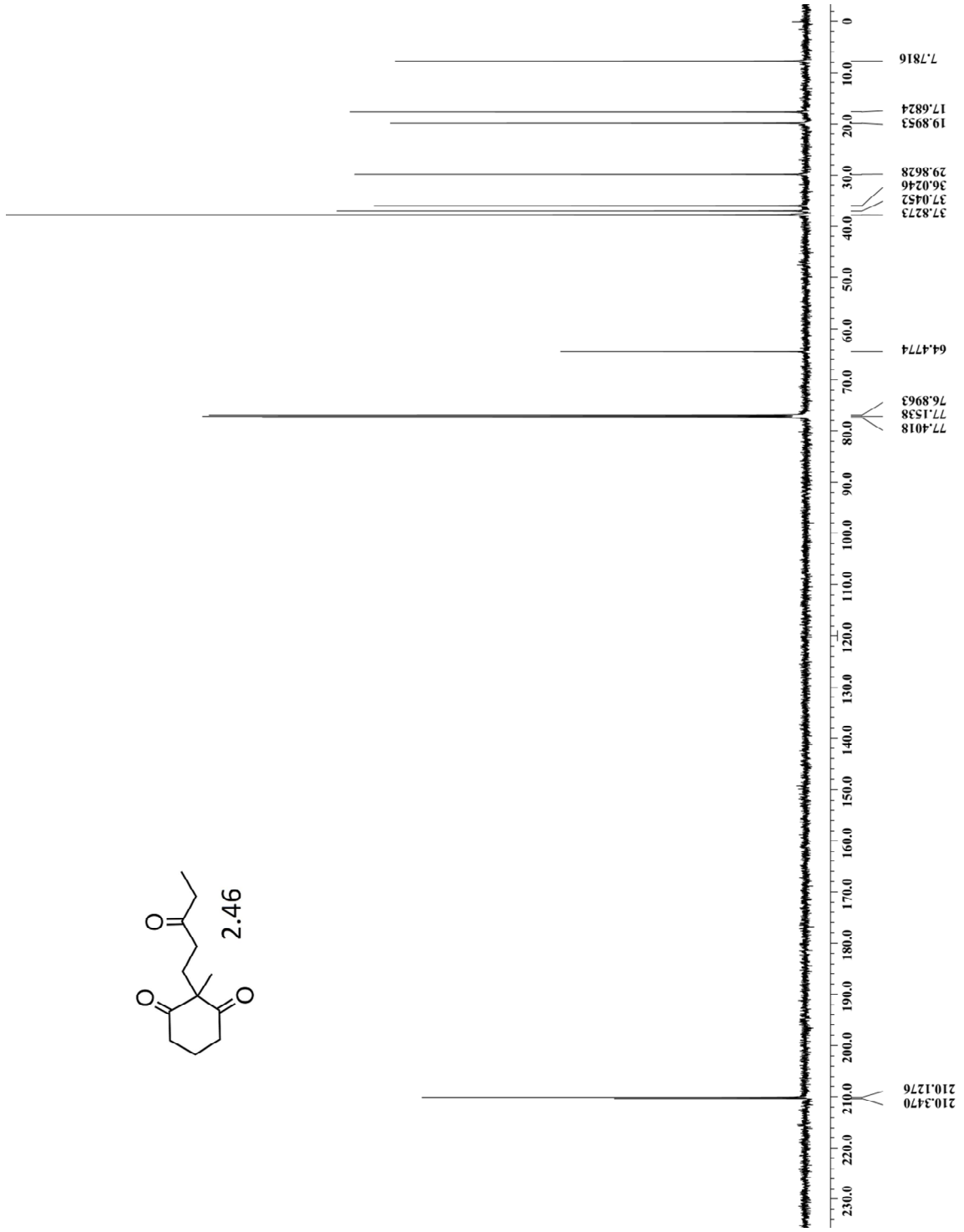
^{1}H-NMR Spectrum (400 MHz, CDCl3)

2-methyl-2-(3-oxopentyl)cyclohexane-1,3-dione



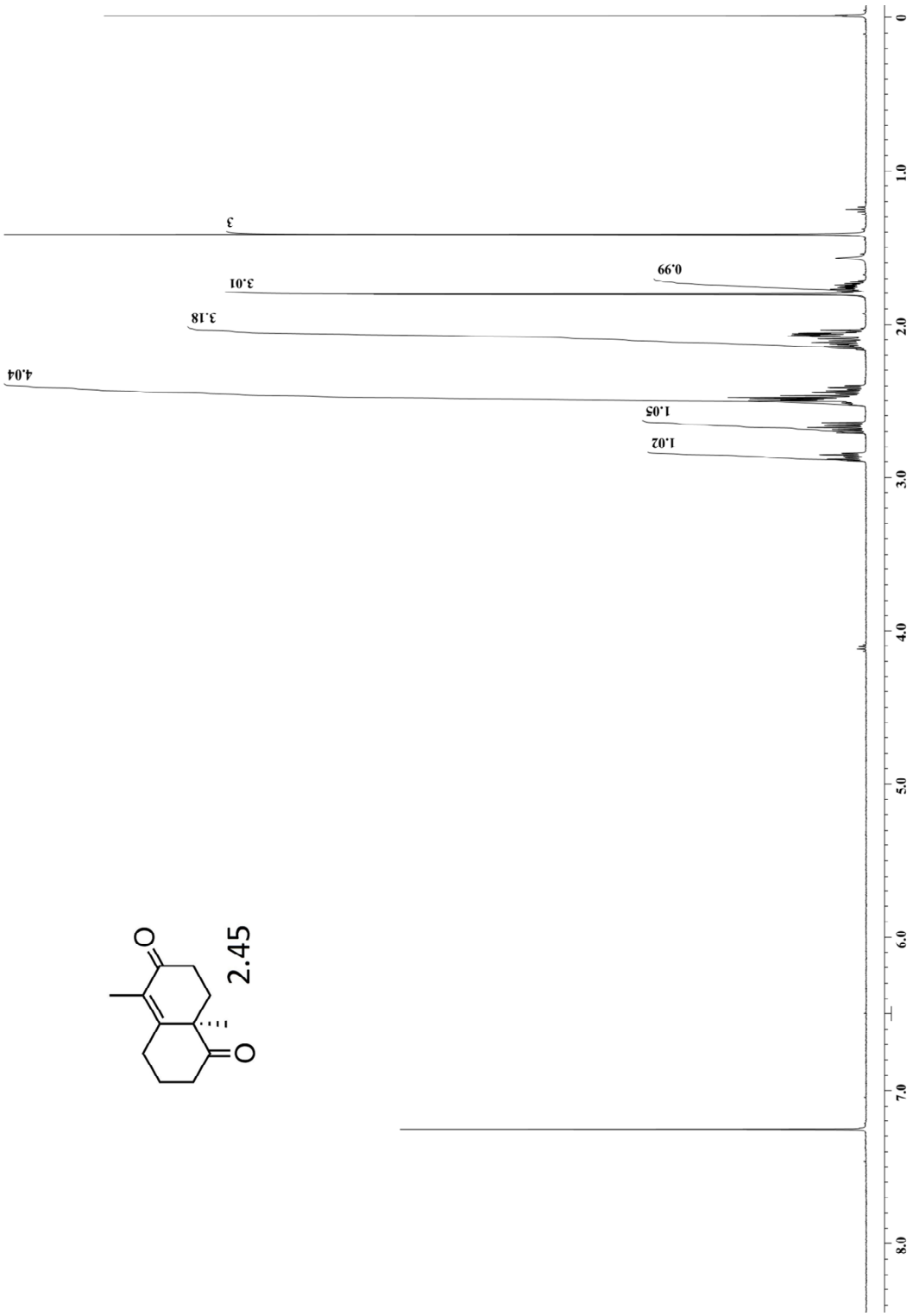
^{13}C-NMR Spectrum (400 MHz, CDCl3)

2-methyl-2-(3-oxopentyl)cyclohexane-1,3-dione



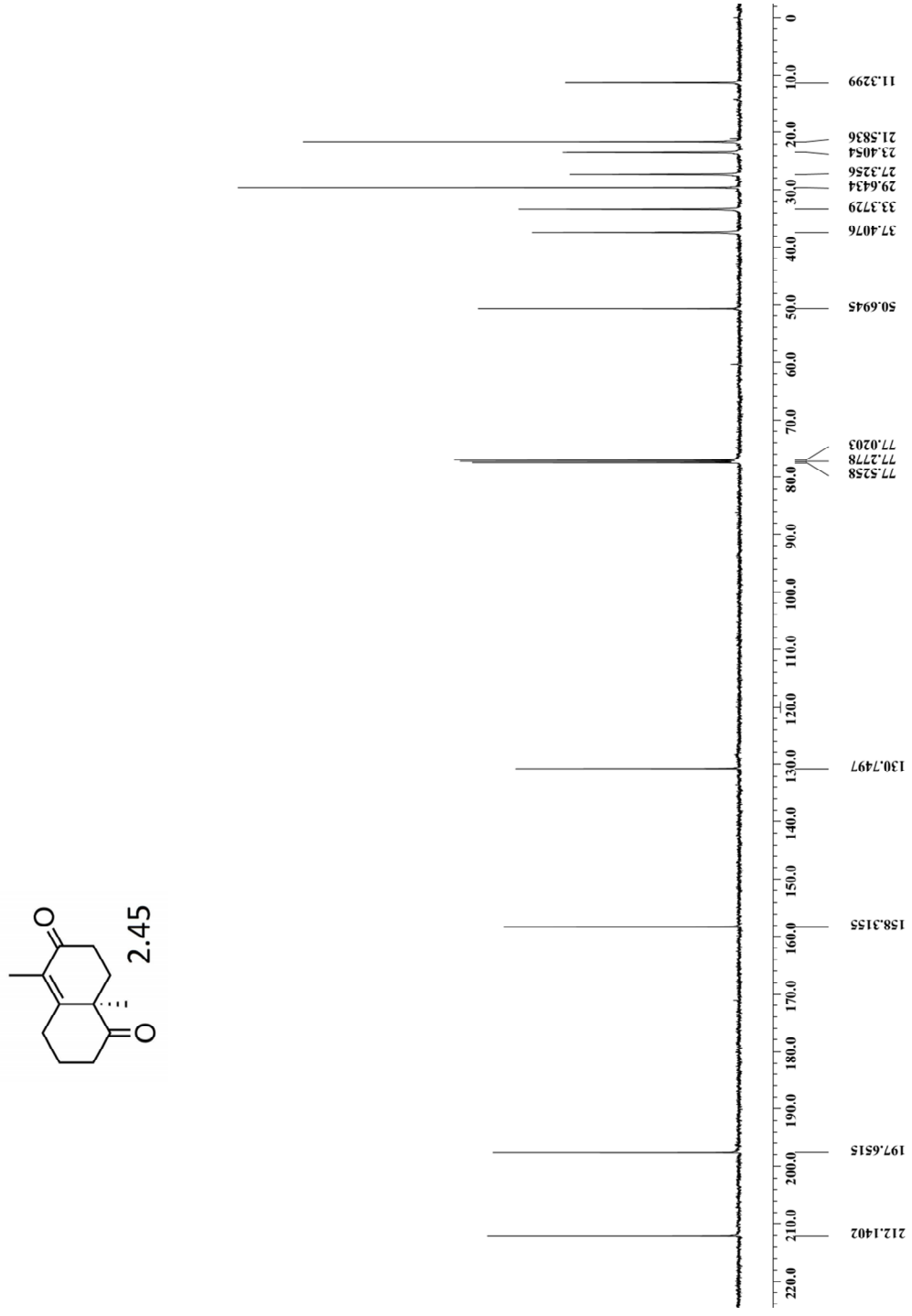
^{1}H-NMR Spectrum (400 MHz, CDCl3)

(R)-5,8a-dimethyl-3,4,8,8a-tetrahydronaphthalene-1,6(2H,7H)-dione



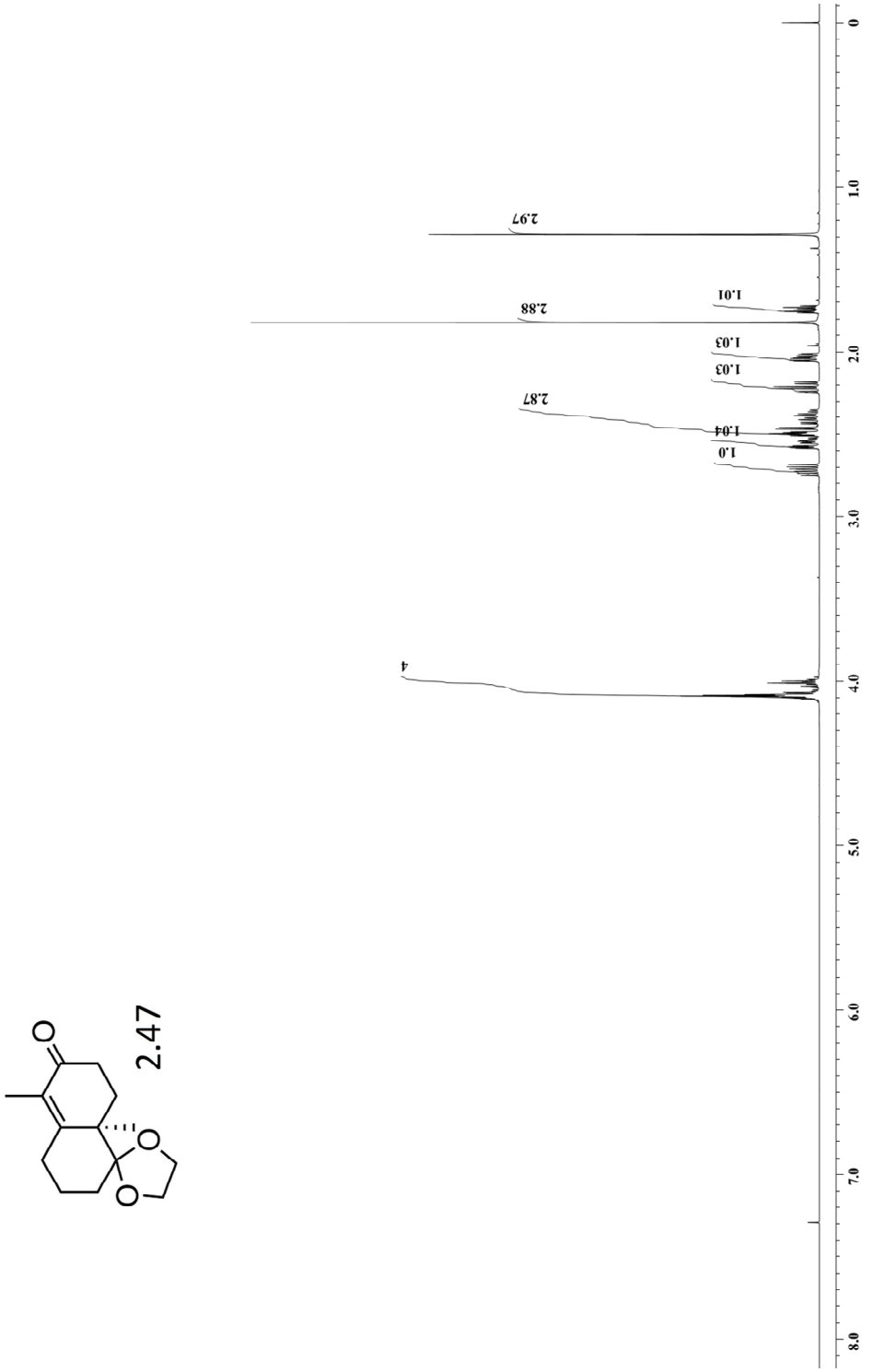
^{13}C-NMR Spectrum (400 MHz, CDCl3)

(R)-5,8a-dimethyl-3,4,8,8a-tetrahydronaphthalene-1,6(2H,7H)-dione



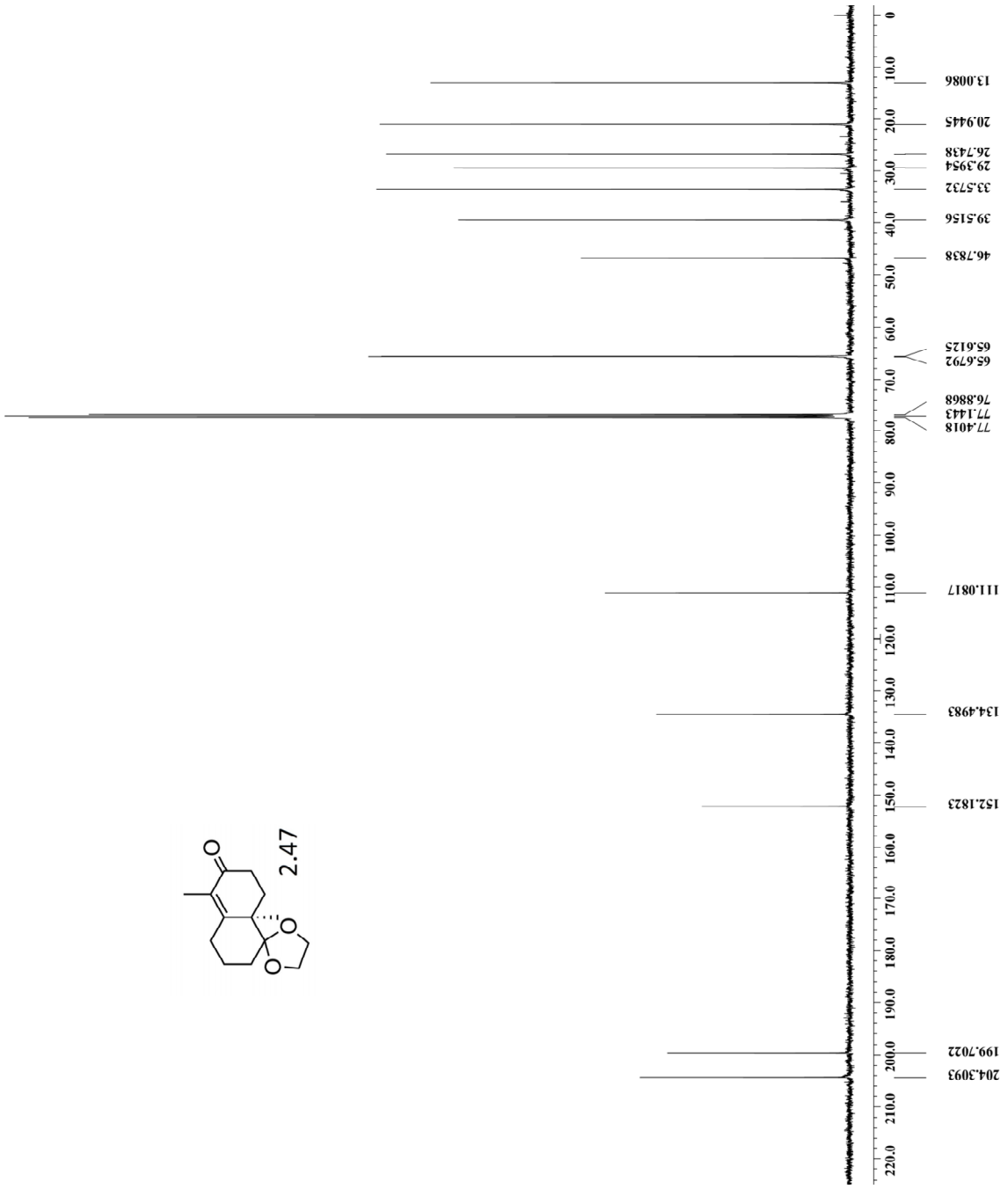
^{1}H-NMR Spectrum (400 MHz, CDCl3)

(R)-5',8a'-dimethyl-3',4',8',8a'-tetrahydro-2'H-spiro[[1,3]dioxolane-2,1'-naphthalen]-6'(7'H)-one



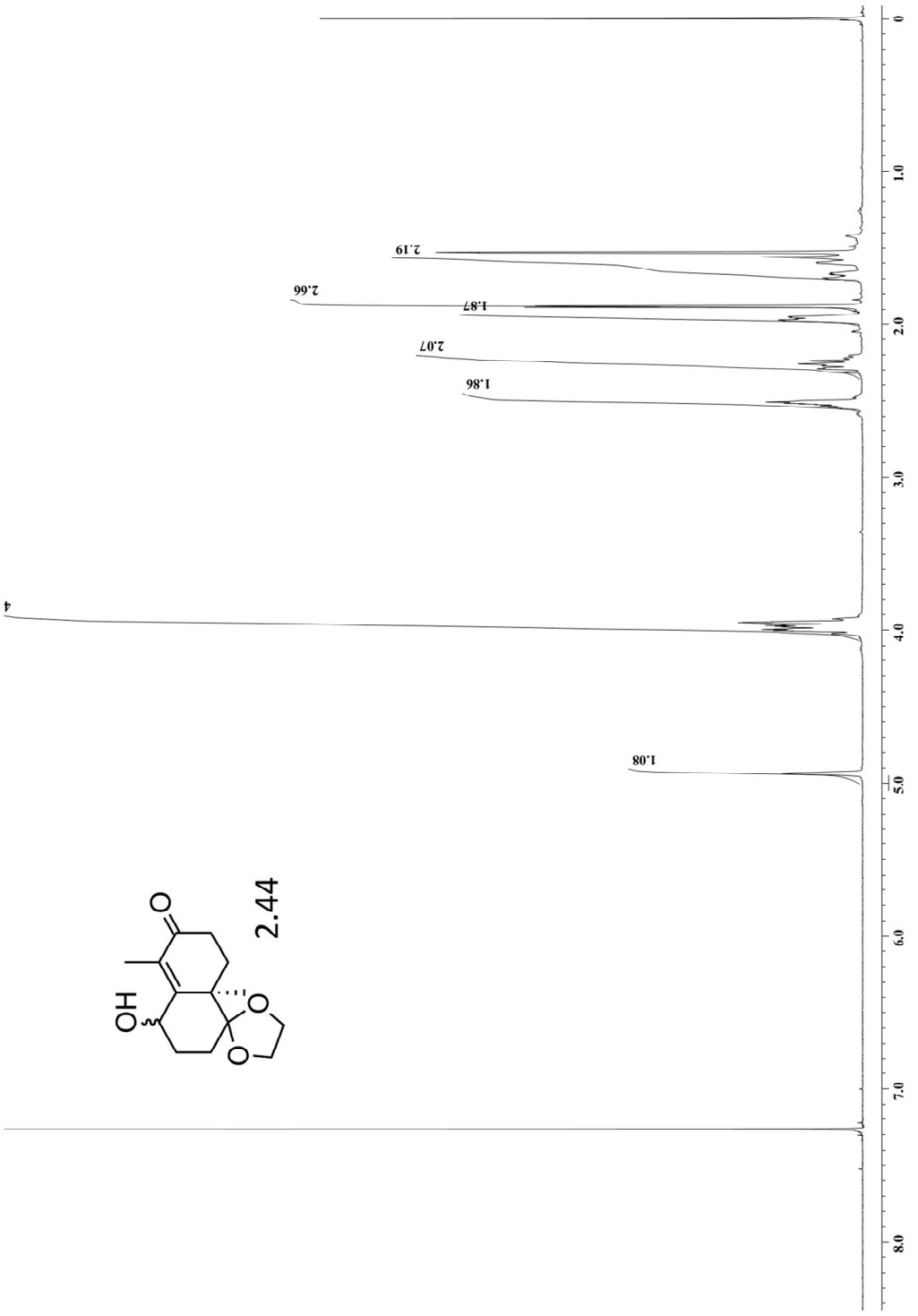
^{13}C-NMR Spectrum (400 MHz, CDCl3)

(R)-5',8a'-dimethyl-3',4',8',8a'-tetrahydro-2'H-spiro[[1,3]dioxolane-2,1'-naphthalen]-6'(7'H)-one



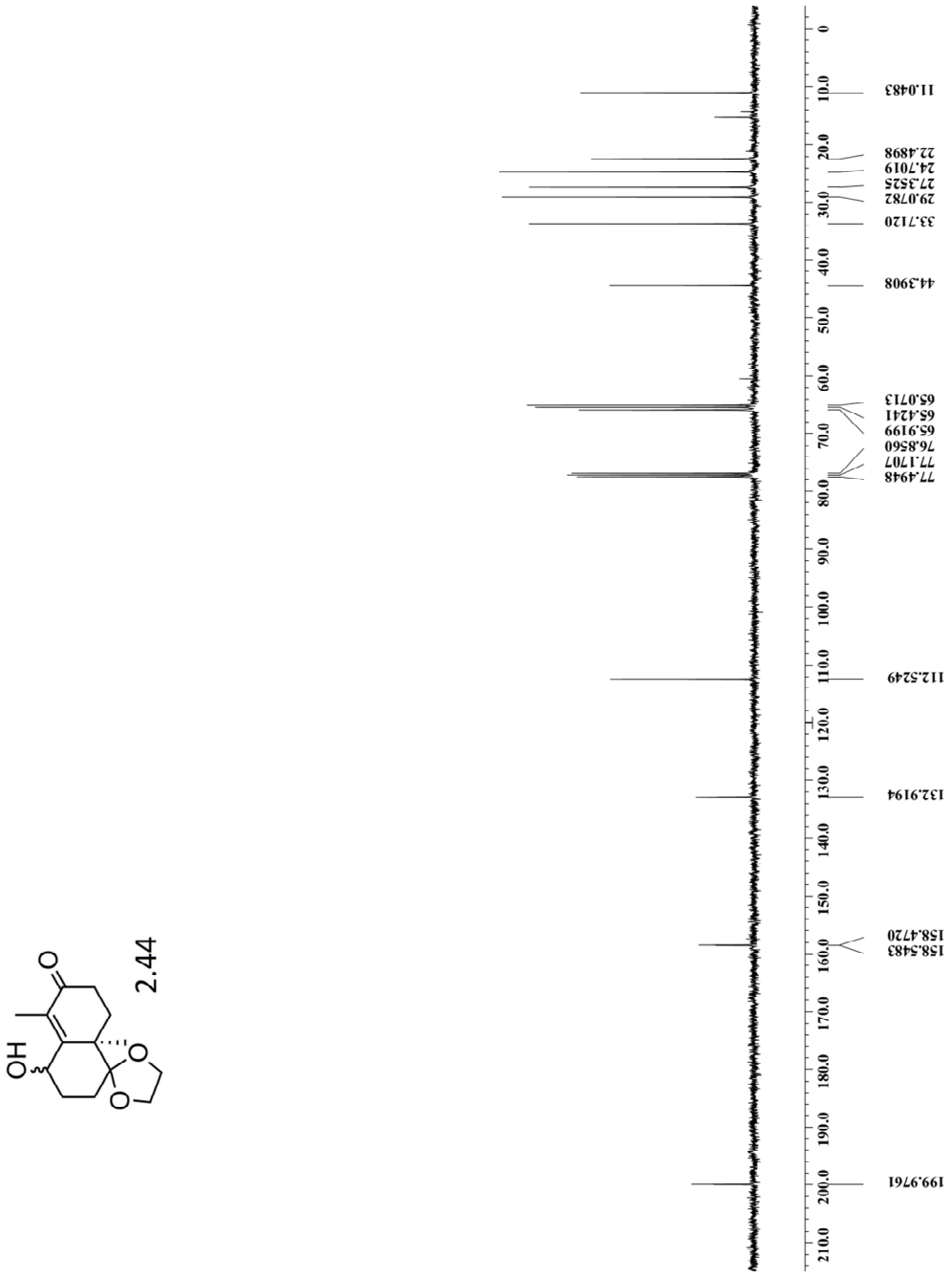
^{1}H-NMR Spectrum (400 MHz, CDCl3)

(R)-4'-hydroxy-5',8a'-dimethyl-3',4',8',8a'-tetrahydro-2'H-spiro[[1,3]dioxolane-2,1'-naphthalen]-6'(7'H)-one



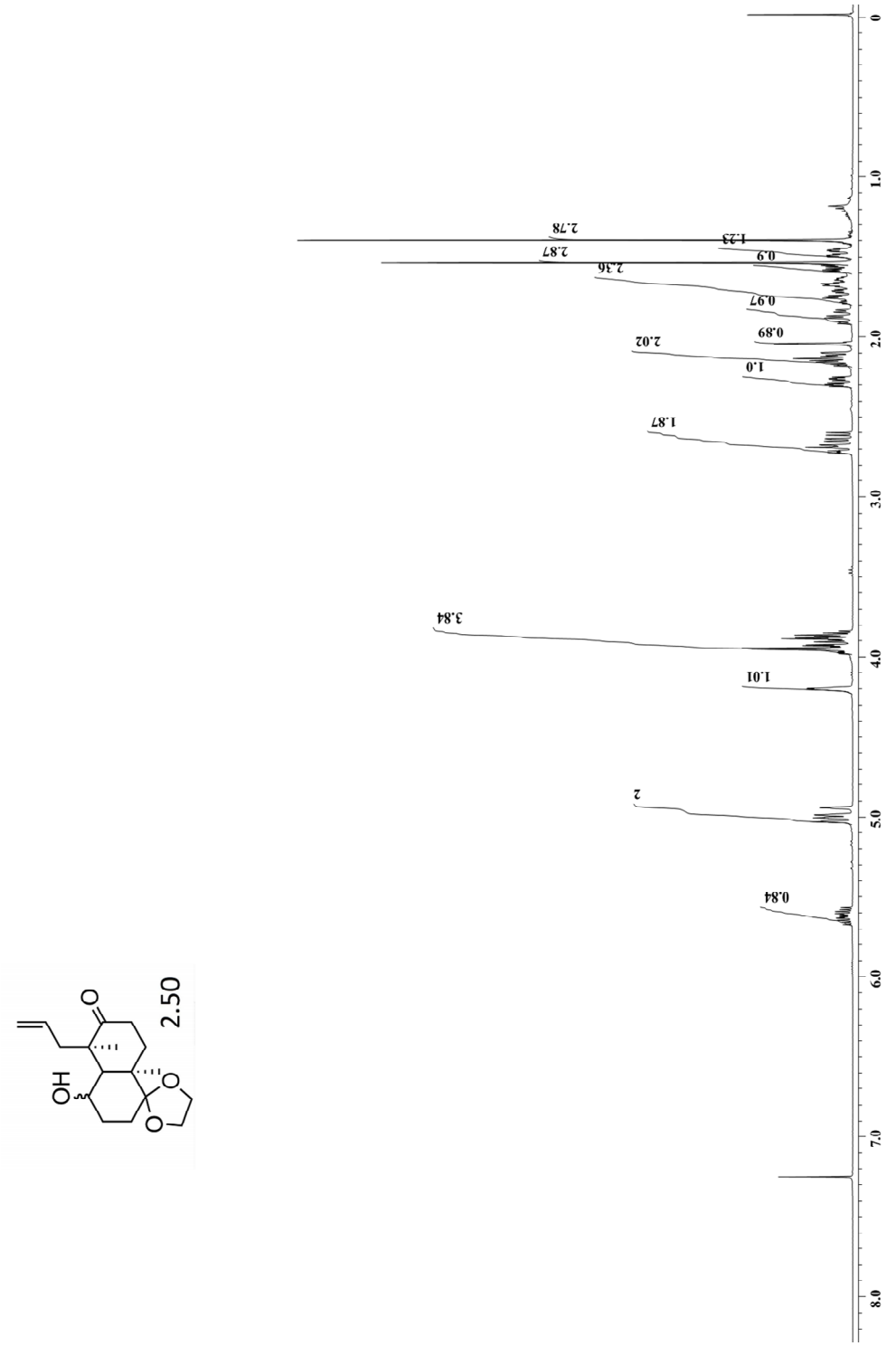
^{13}C-NMR Spectrum (400 MHz, CDCl3)

(R)-4'-hydroxy-5',8a'-dimethyl-3',4',8',8a'-tetrahydro-2'H-spiro[[1,3]dioxolane-2,1'-naphthalen]-6'(7'H)-one



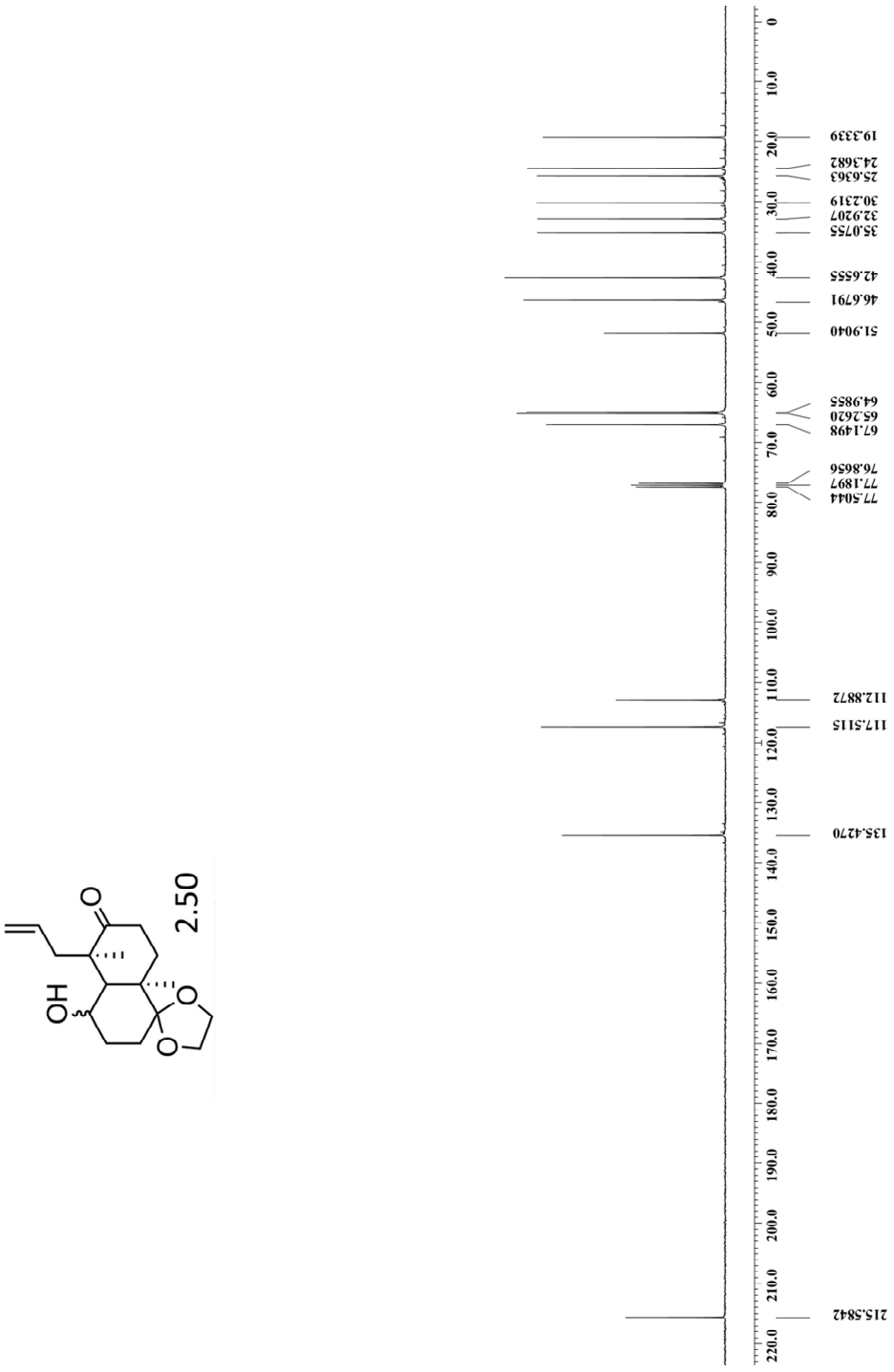
^{1}H-NMR Spectrum (400 MHz, CDCl3)

(5'R,8a'R)-5'-allyl-4'-hydroxy-5',8a'-dimethylhexahydro-2'H-spiro[[1,3]dioxolane-2,1'-naphthalen]-6'(7'H)-one



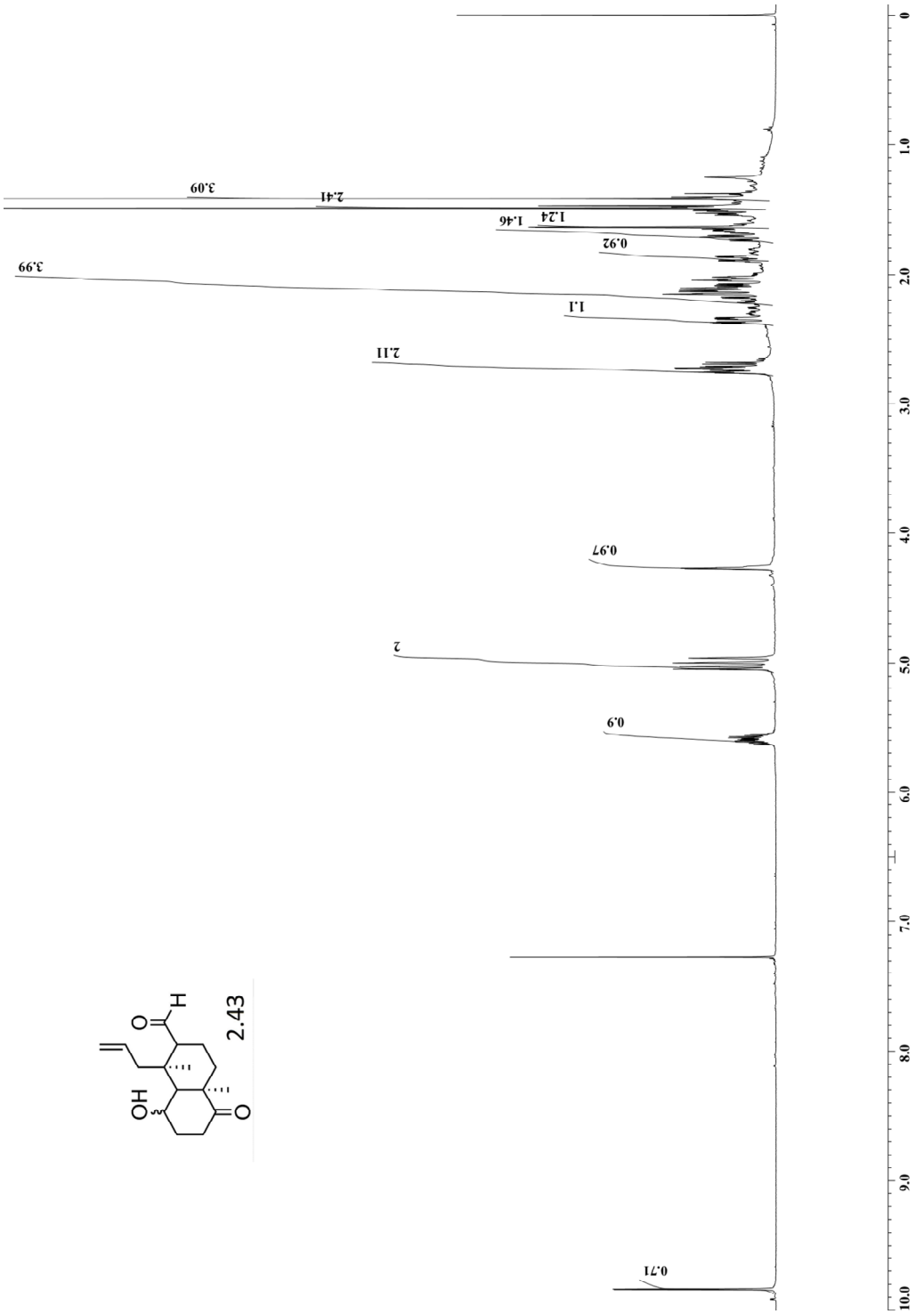
^{13}C-NMR Spectrum (400 MHz, CDCl3)

(5'R,8a'R)-5'-allyl-4'-hydroxy-5',8a'-dimethylhexahydro-2'H-spiro[[1,3]dioxolane-2,1'-naphthalen]-6'(7'H)-one



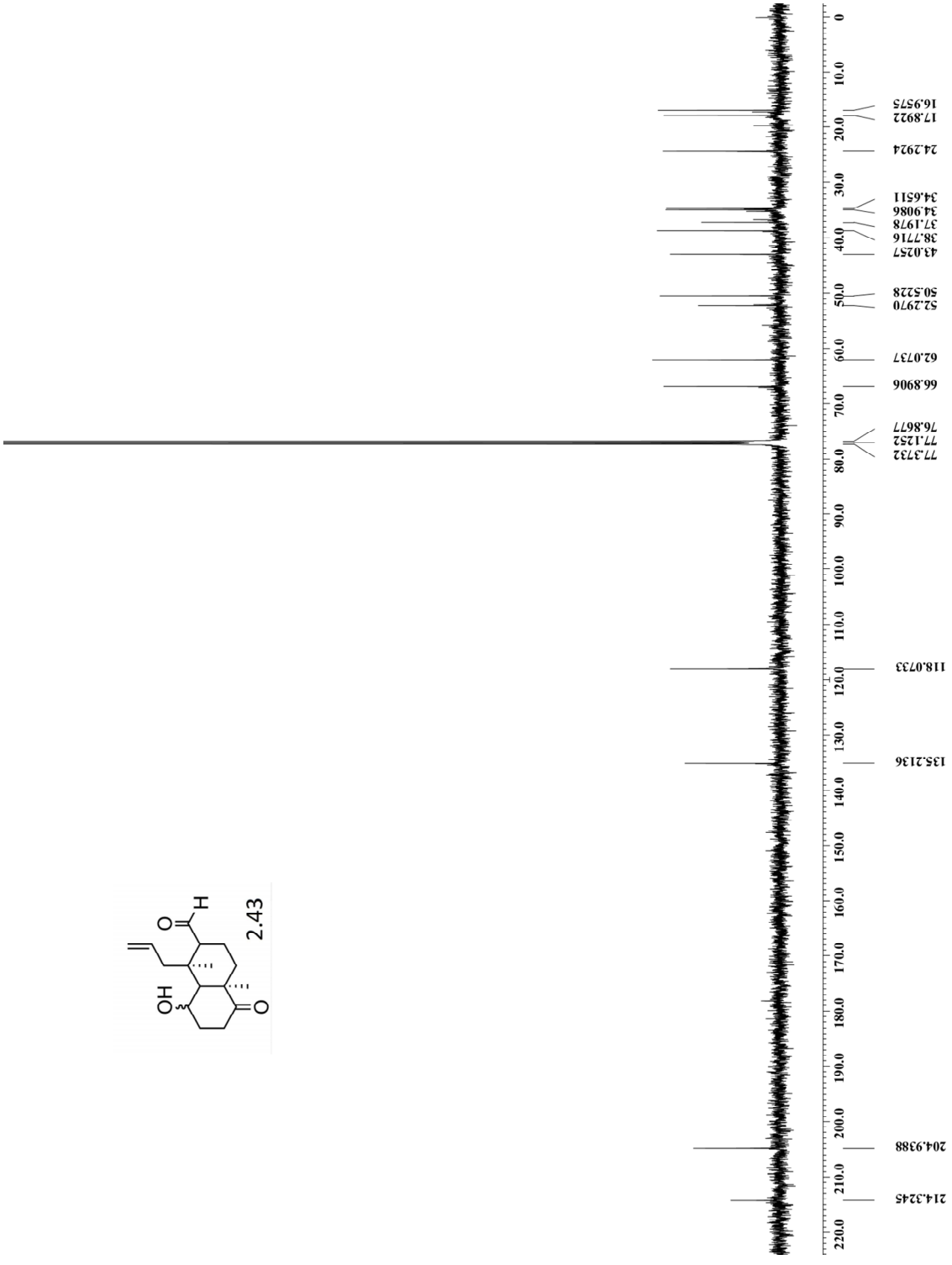
^{1}H-NMR Spectrum (400 MHz, CDCl3)

(1R,4aR)-1-allyl-8-hydroxy-1,4a-dimethyl-5-oxodecahydronaphthalene-2-carbaldehyde



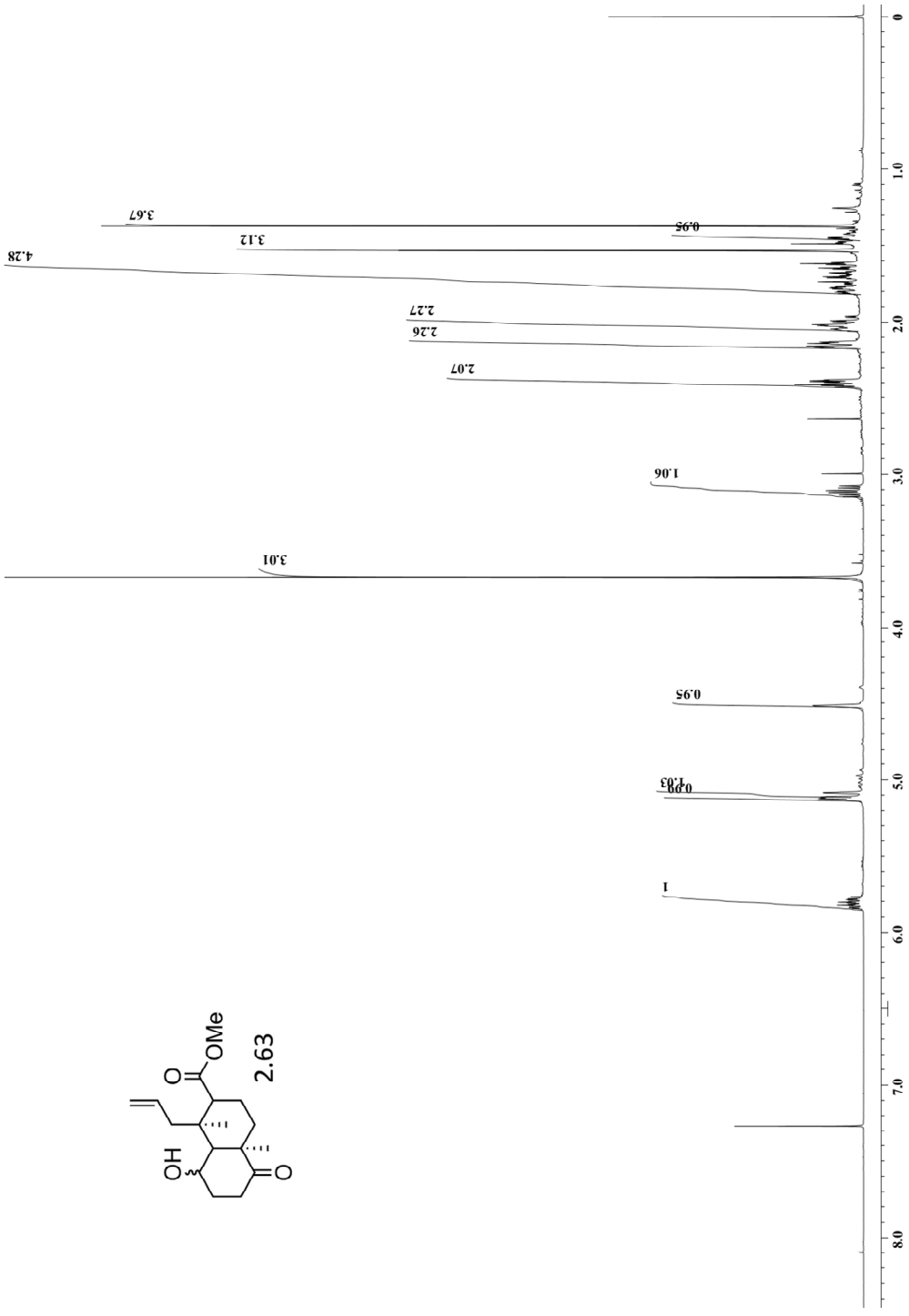
^{13}C-NMR Spectrum (400 MHz, CDCl3)

(1R,4aR)-1-allyl-8-hydroxy-1,4a-dimethyl-5-oxodecahydronaphthalene-2-carbaldehyde



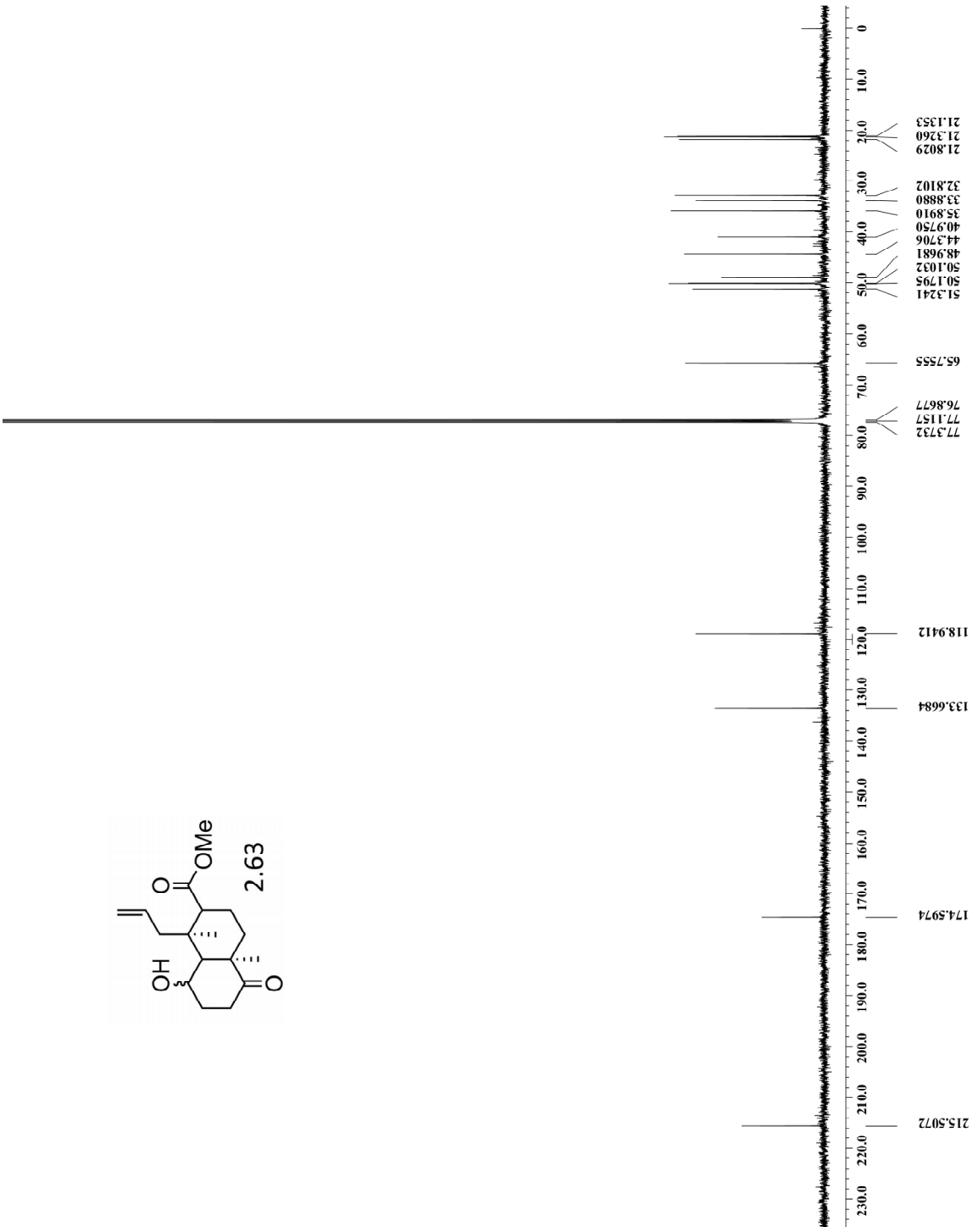
^{1}H-NMR Spectrum (400 MHz, CDCl3)

methyl (1R,4aR)-8-hydroxy-1,4a-dimethyl-5-oxo-1-(prop-2-en-1-yl)-decahydronaphthalene-2-carboxylate



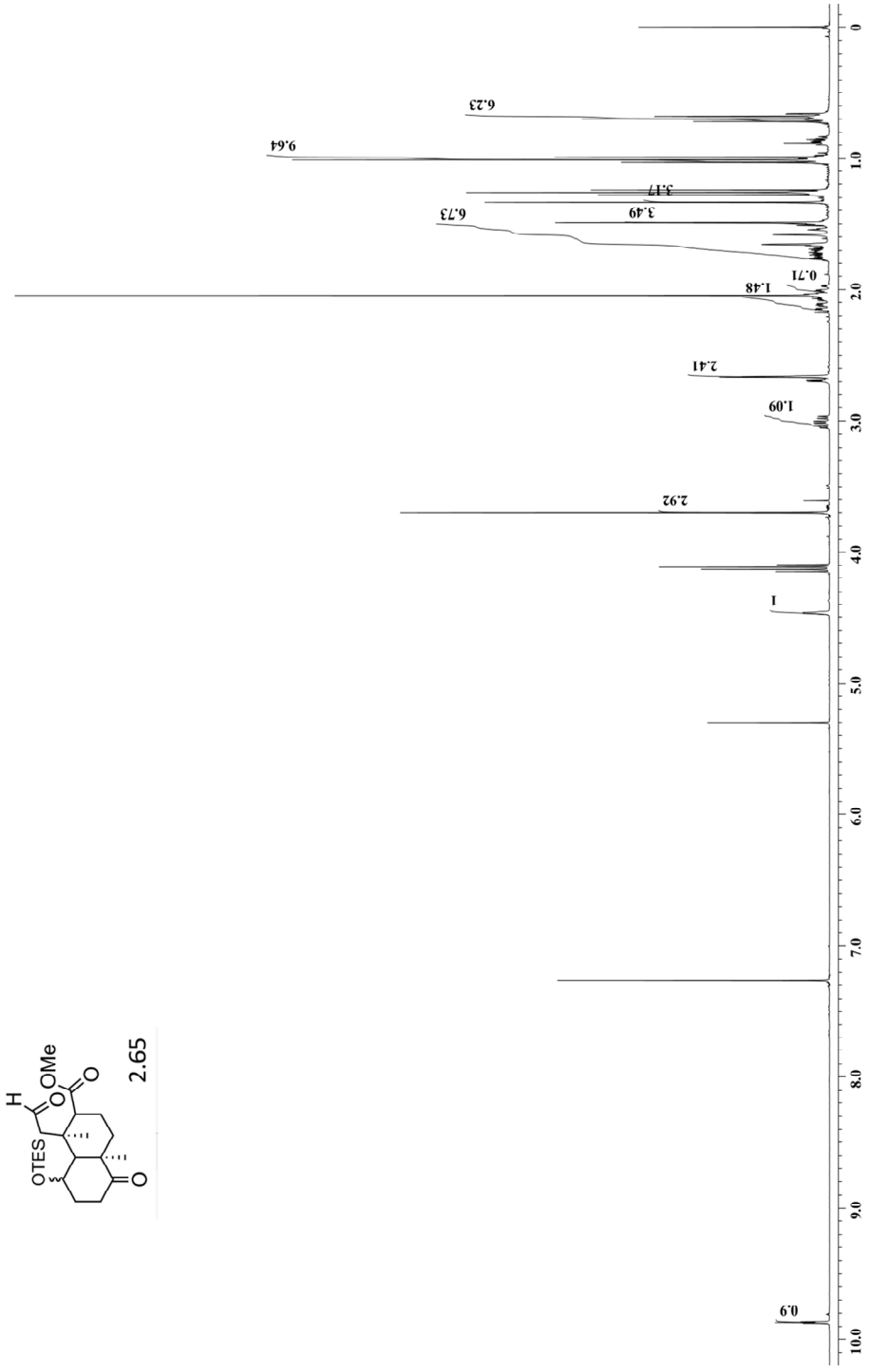
^{13}C-NMR Spectrum (400 MHz, CDCl3)

methyl (1R,4aR)-8-hydroxy-1,4a-dimethyl-5-oxo-1-(prop-2-en-1-yl)-decahydronaphthalene-2-carboxylate



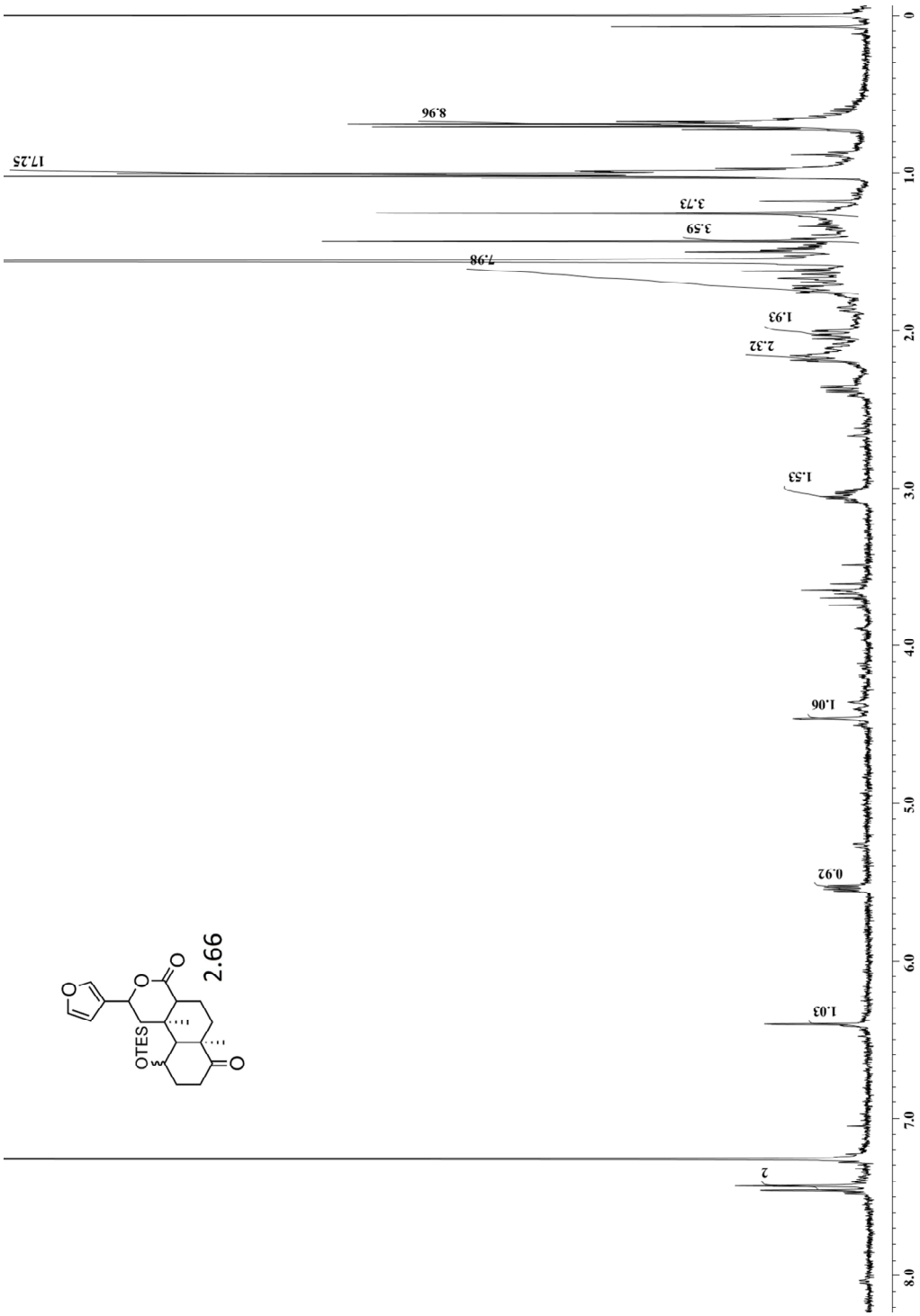
^{1}H-NMR Spectrum (400 MHz, CDCl3)

methyl (1R,4aR)-1,4a-dimethyl-5-oxo-1-(2-oxoethyl)-8-[(triethylsilyl)oxy]-decahydronaphthalene-2-carboxylate



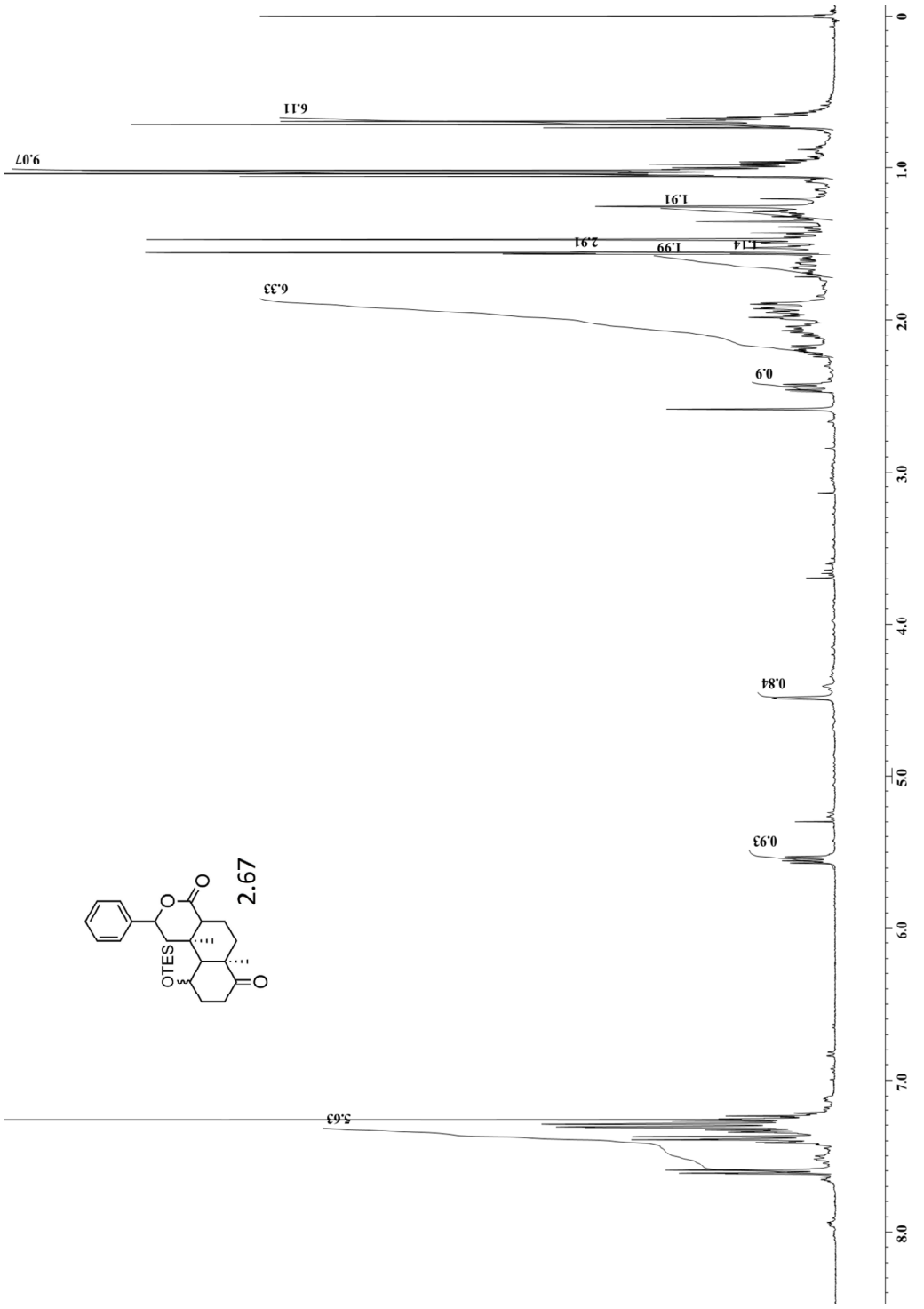
^{1}H-NMR Spectrum (400 MHz, $CDCl_3$)

(6aR,10bR)-2-(furan-3-yl)-6a,10b-dimethyl-10-[(triethylsilyl)oxy]-dodecahydro-1H-naphtho[2,1-c]pyran-4,7-dione



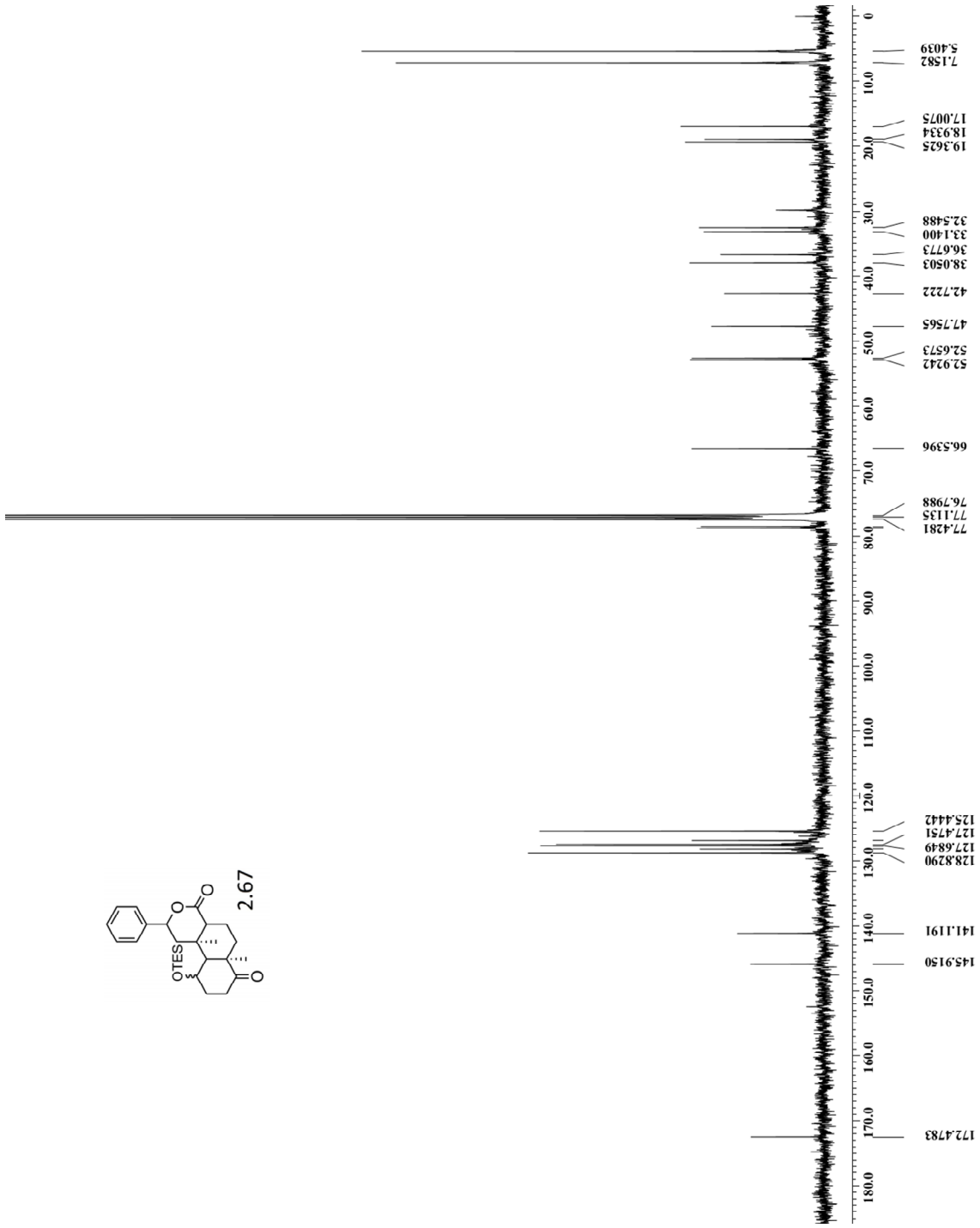
^{1}H-NMR Spectrum (400 MHz, $CDCl_3$)

(6aR,10bR)-6a,10b-dimethyl-2-phenyl-10-[(triethylsilyl)oxy]-dodecahydro-1H-naphtho[2,1-c]pyran-4,7-dione



^{13}C-NMR Spectrum (400 MHz, $CDCl_3$)

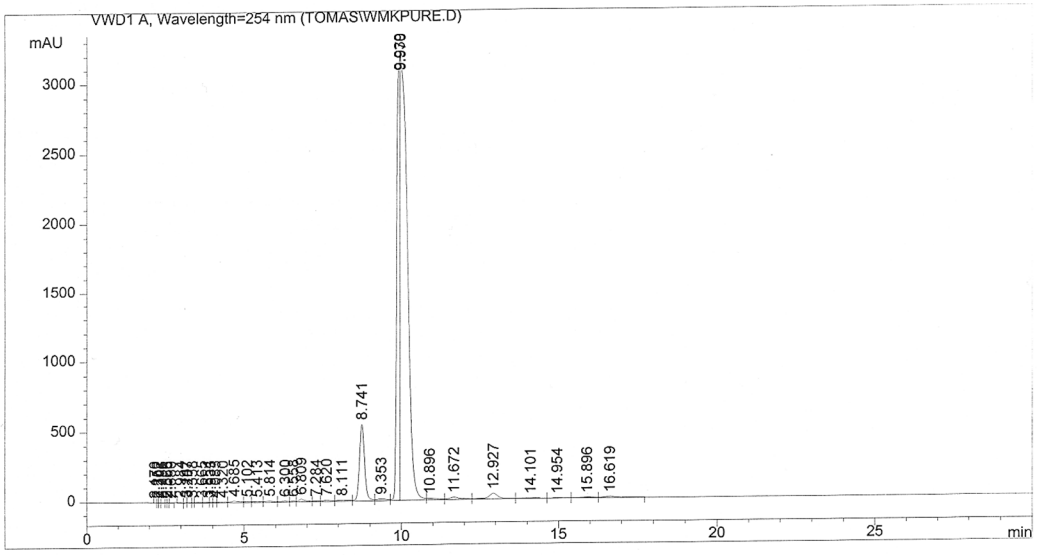
(6aR,10bR)-6a,10b-dimethyl-2-phenyl-10-[(triethylsilyl)oxy]-dodecahydro-1H-naphtho[2,1-c]pyran-4,7-dione



Data File C:\HPCHEM\1\DATA\TOMAS\WMKPURE.D Sample Name: channproduct

Injection Date : 4/9/2012 10:37:18 PM
Sample Name : channproduct Vial : 1
Acq. Operator : Tomas Inj Volume : 10 µl

Method : C:\HPCHEM\1\METHODS\TOMAS_01.M
Last changed : 4/6/2012 1:20:41 PM by Tomas
Chiralpak AS-H 4.6 x 250 mm 5 uM, 10 uL
EtOH/Hexanes 1:9, isocratic, 1 mL/min, 30 min.



Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Sample Amount : 1.00000 [ng/ul] (not used in calc.)

Signal 1: VWD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	2.170	VV	0.0741	10.49552	1.75605	0.0125
2	2.252	VV	0.0422	6.43049	2.14624	7.679e-3
3	2.302	VV	0.0607	11.72729	2.36891	0.0140
4	2.386	VB	0.1016	22.52819	2.80694	0.0269
5	2.526	BV	0.0524	13.24653	3.47793	0.0158
6	2.568	VB	0.0495	14.50328	3.69131	0.0173
7	2.680	BB	0.1182	40.06498	4.24056	0.0478
8	2.984	BP	0.1338	57.49563	5.91609	0.0687
9	3.147	VV	0.0593	37.12325	9.38507	0.0443

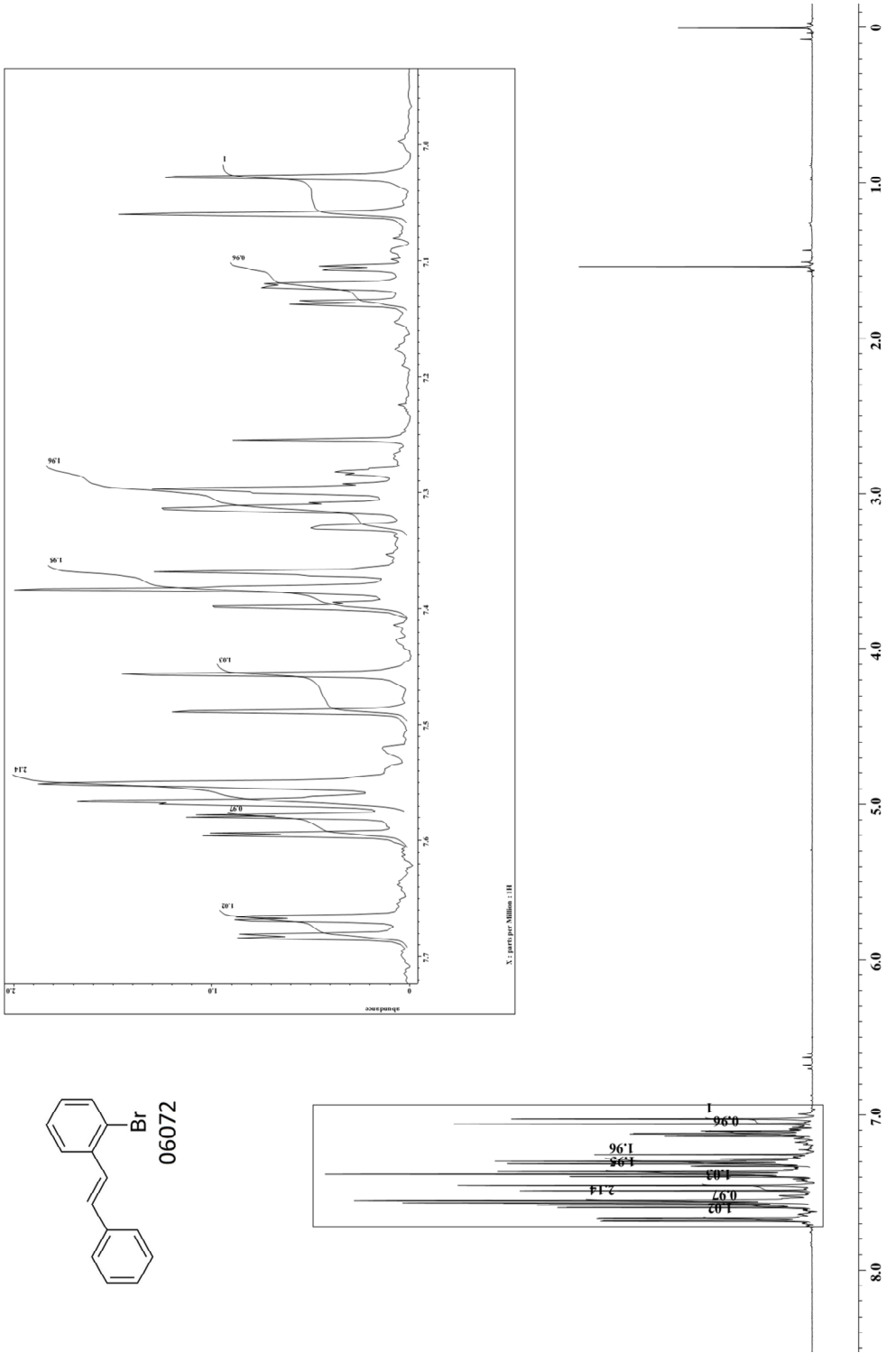
Data File C:\HPCHEM\1\DATA\TOMAS\WMKPURE.D Sample Name: channproduct

Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
10	3.207	VV	0.0996	61.29060	7.93746	0.0732
11	3.358	VV	0.0700	35.08467	6.31118	0.0419
12	3.665	VV	0.1806	93.89799	6.24297	0.1121
13	3.854	VV	0.1494	78.97922	6.38750	0.0943
14	3.933	VV	0.0879	44.99681	6.33697	0.0537
15	4.085	VV	0.0890	45.53803	6.32983	0.0544
16	4.320	VV	0.2385	135.89157	7.14974	0.1623
17	4.685	VV	0.2241	259.37909	14.96309	0.3097
18	5.102	VV	0.1792	116.67339	8.81409	0.1393
19	5.413	VV	0.2532	156.69073	7.61512	0.1871
20	5.814	VV	0.2791	211.16623	9.94193	0.2522
21	6.300	VV	0.2465	174.06163	9.00865	0.2078
22	6.558	VV	0.1637	98.31537	8.71265	0.1174
23	6.809	VV	0.2234	361.00183	22.17170	0.4311
24	7.284	VV	0.1811	108.73553	7.23921	0.1298
25	7.620	VV	0.2818	214.96297	10.46898	0.2567
26	8.111	VV	0.3625	247.63022	8.40959	0.2957
27	8.741	VV	0.1745	6227.88623	549.11603	7.4367
28	9.353	VV	0.3136	322.58456	13.72270	0.3852
29	9.939	VV	0.0854	2.17792e4	3191.28735	26.0064
30	9.970	VV	0.1893	5.03433e4	3201.95142	60.1148
31	10.896	VV	0.3047	313.39450	12.47822	0.3742
32	11.672	VV	0.3701	479.53430	17.93847	0.5726
33	12.927	VV	0.3381	953.05334	40.35462	1.1380
34	14.101	VV	0.6050	152.82585	2.98311	0.1825
35	14.954	VV	0.4576	85.76310	2.22916	0.1024
36	15.896	VV	0.4225	177.56789	5.78022	0.2120
37	16.619	VB	0.3661	252.26917	10.08551	0.3012
Totals :				8.37452e4	7237.75656	

*** End of Report ***

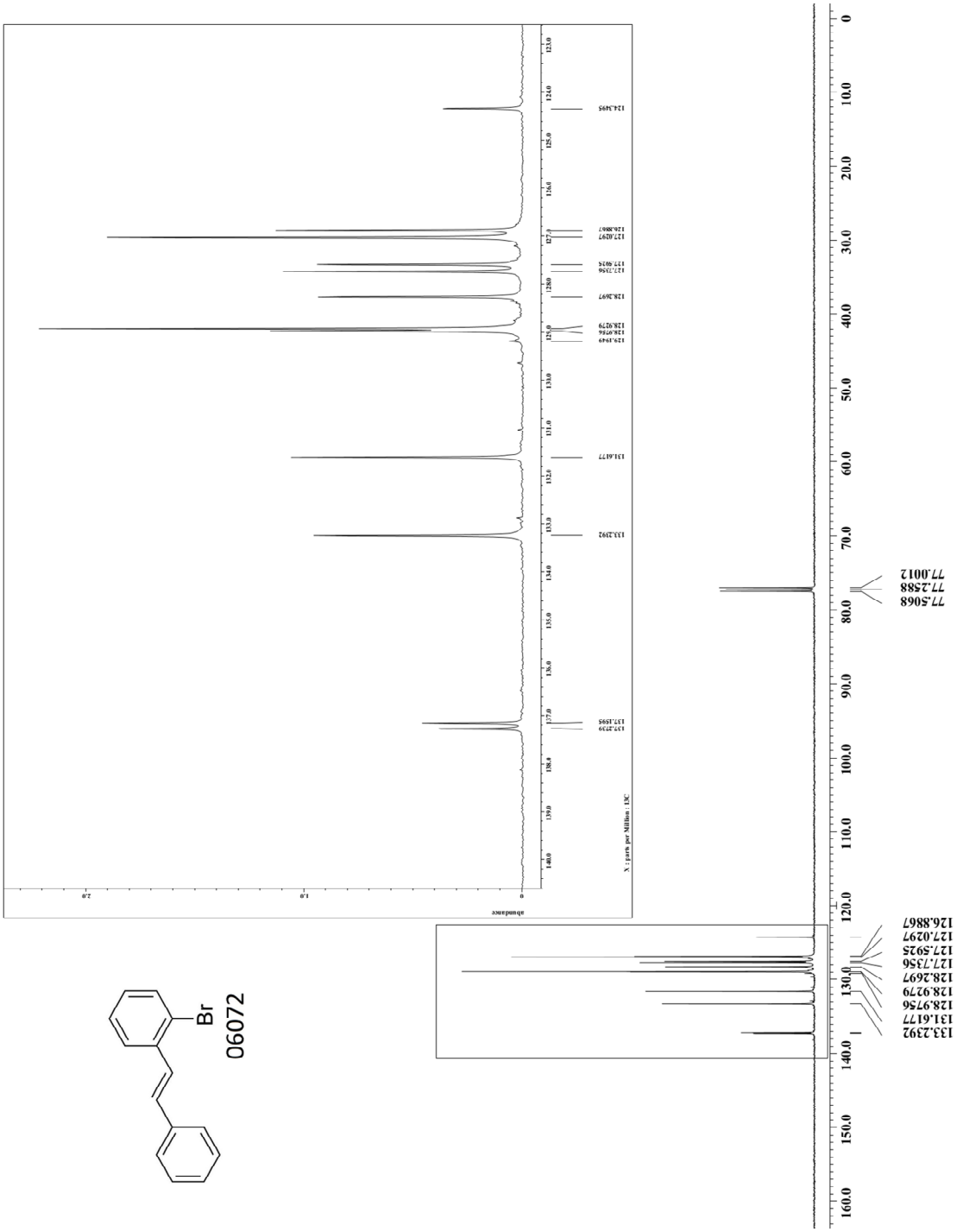
^{1}H-NMR Spectrum (500 MHz, $CDCl_3$)

(E)-1-bromo-2-styrylbenzene



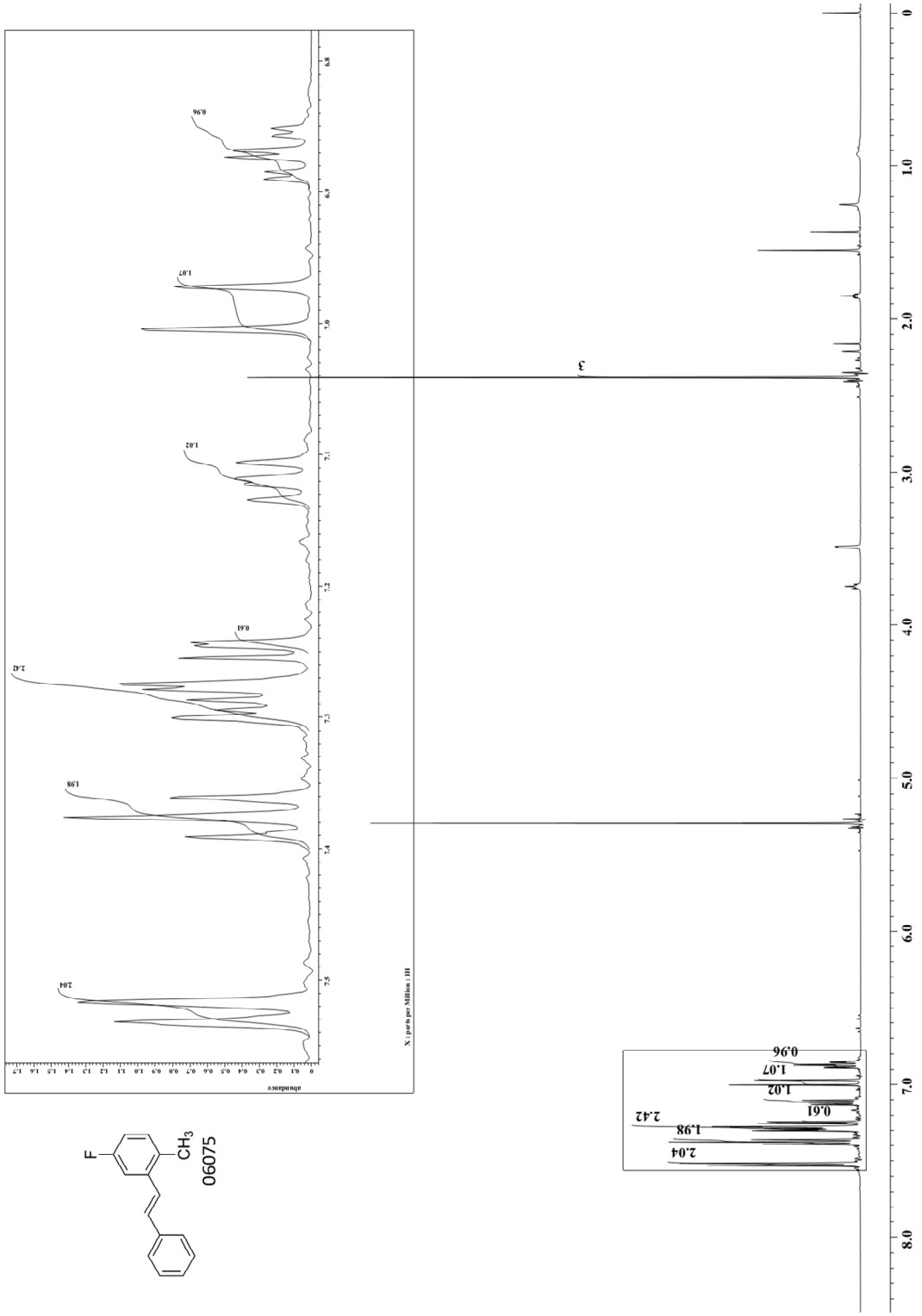
^{13}C-NMR Spectrum (500 MHz, $CDCl_3$)

(E)-1-bromo-2-styrylbenzene



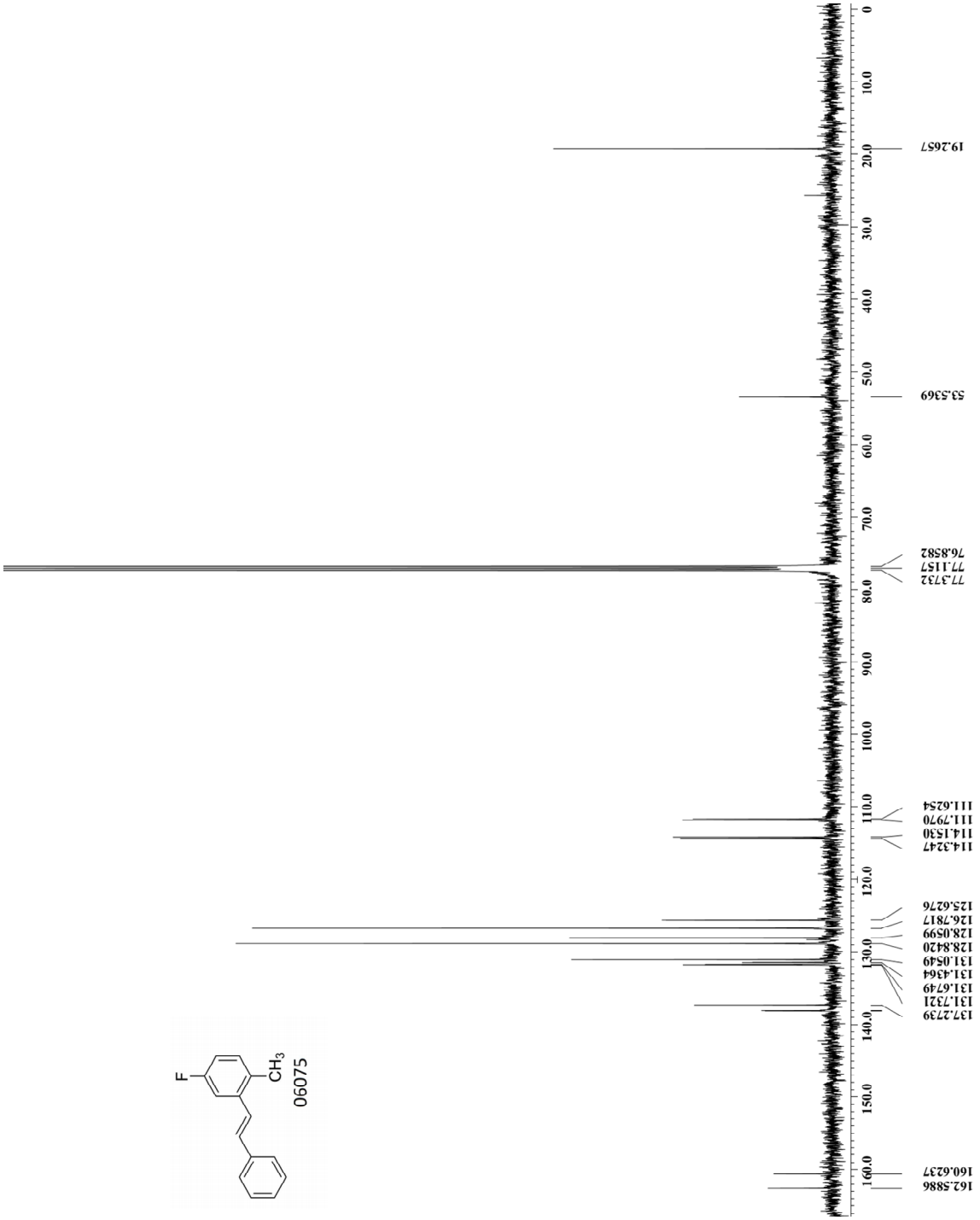
^{1}H-NMR Spectrum (500 MHz, $CDCl_3$)

(E)-4-fluoro-1-methyl-2-styrylbenzene



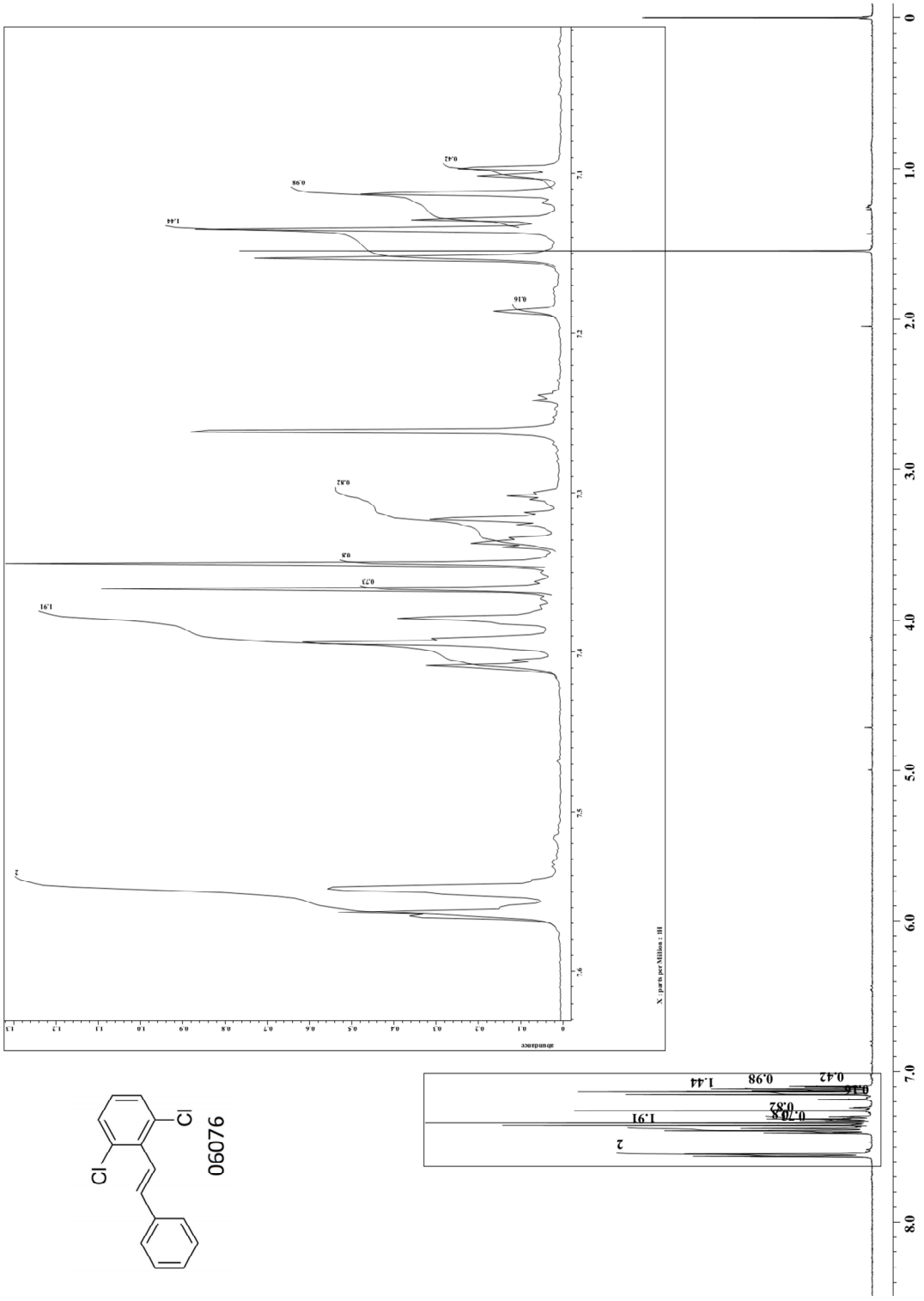
^{13}C-NMR Spectrum (500 MHz, $CDCl_3$)

(E)-4-fluoro-1-methyl-2-styrylbenzene



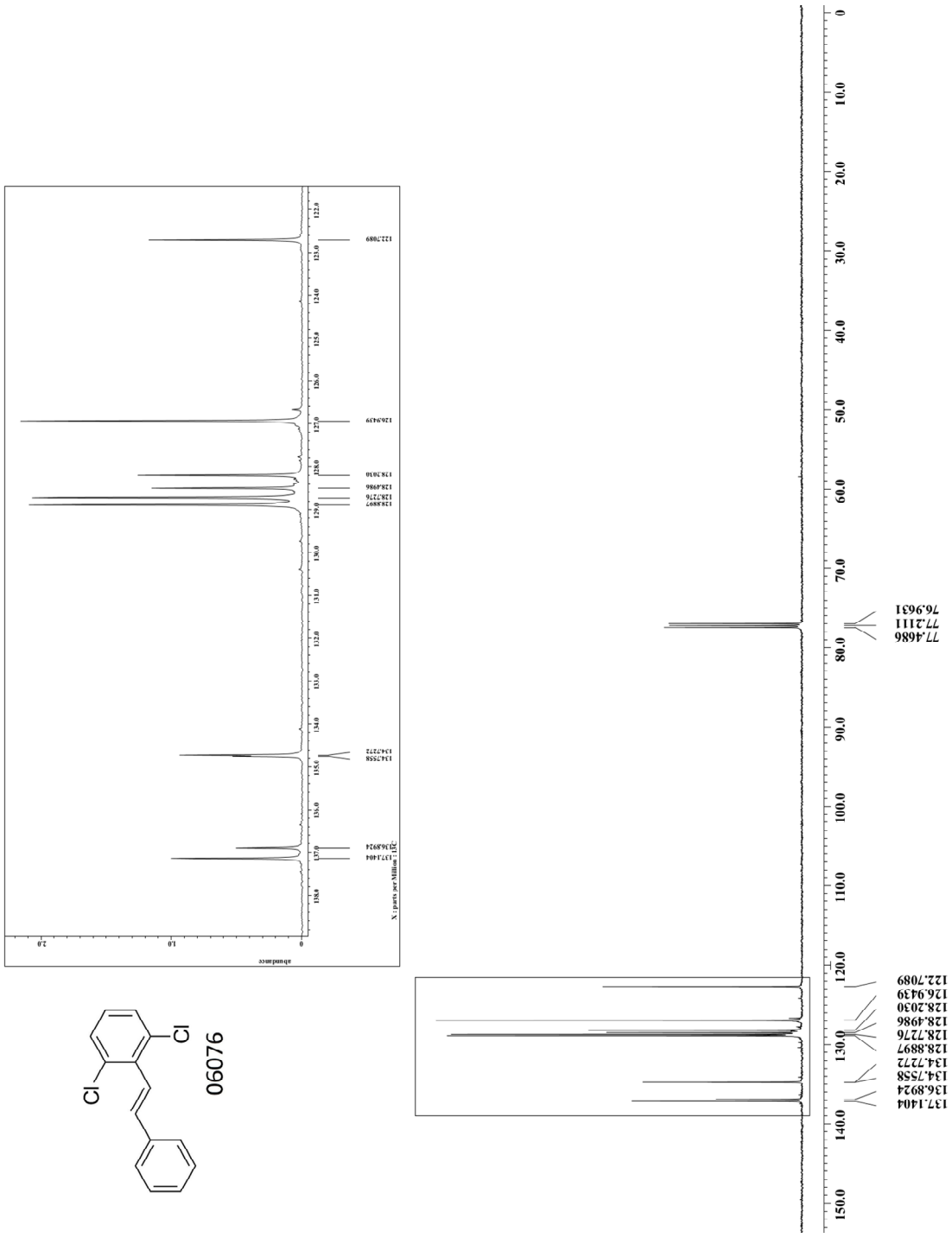
^{1}H-NMR Spectrum (500 MHz, $CDCl_3$)

(E)-1,3-dichloro-2-styrylbenzene



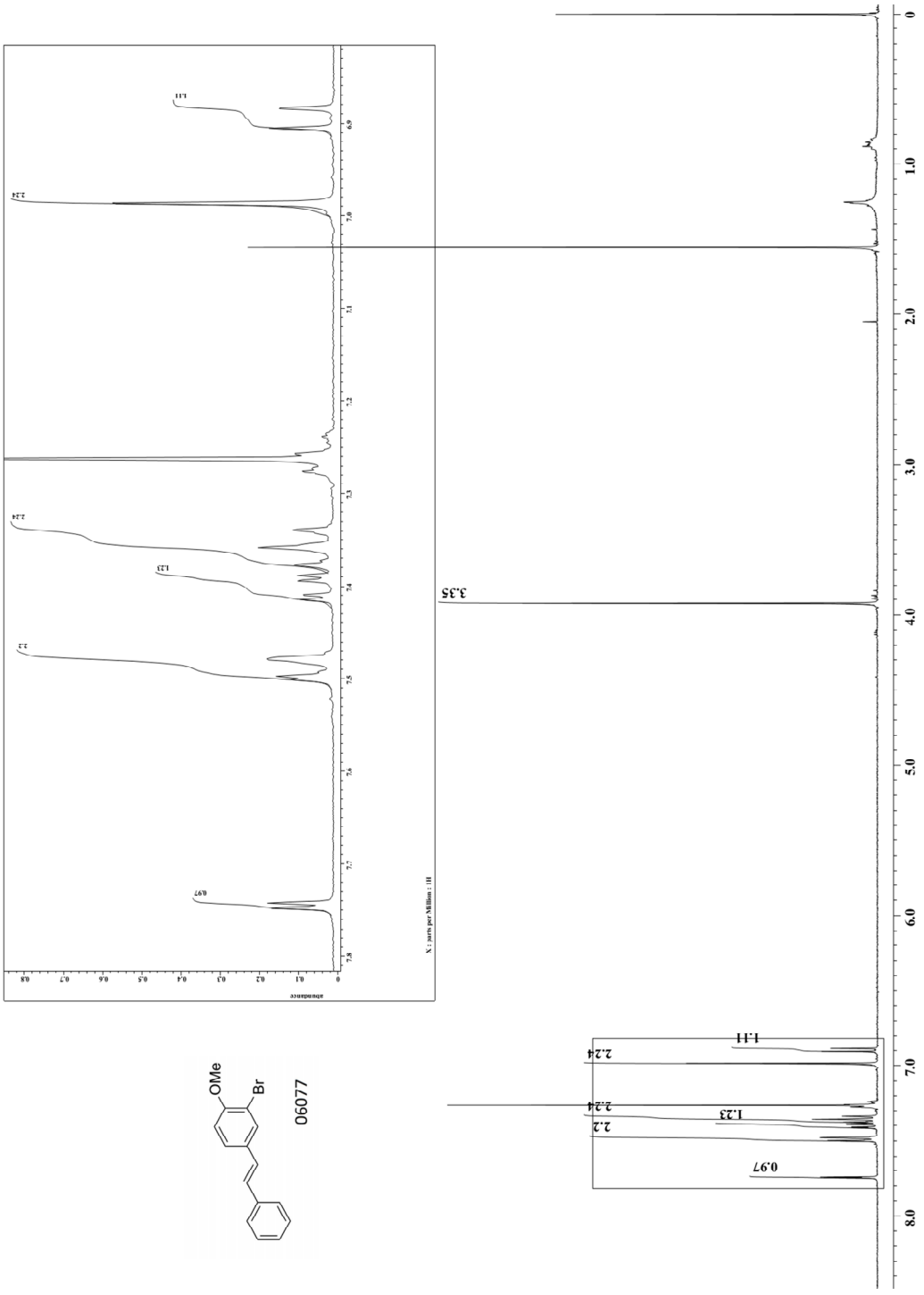
^{13}C-NMR Spectrum (500 MHz, $CDCl_3$)

(E)-1,3-dichloro-2-styrylbenzene



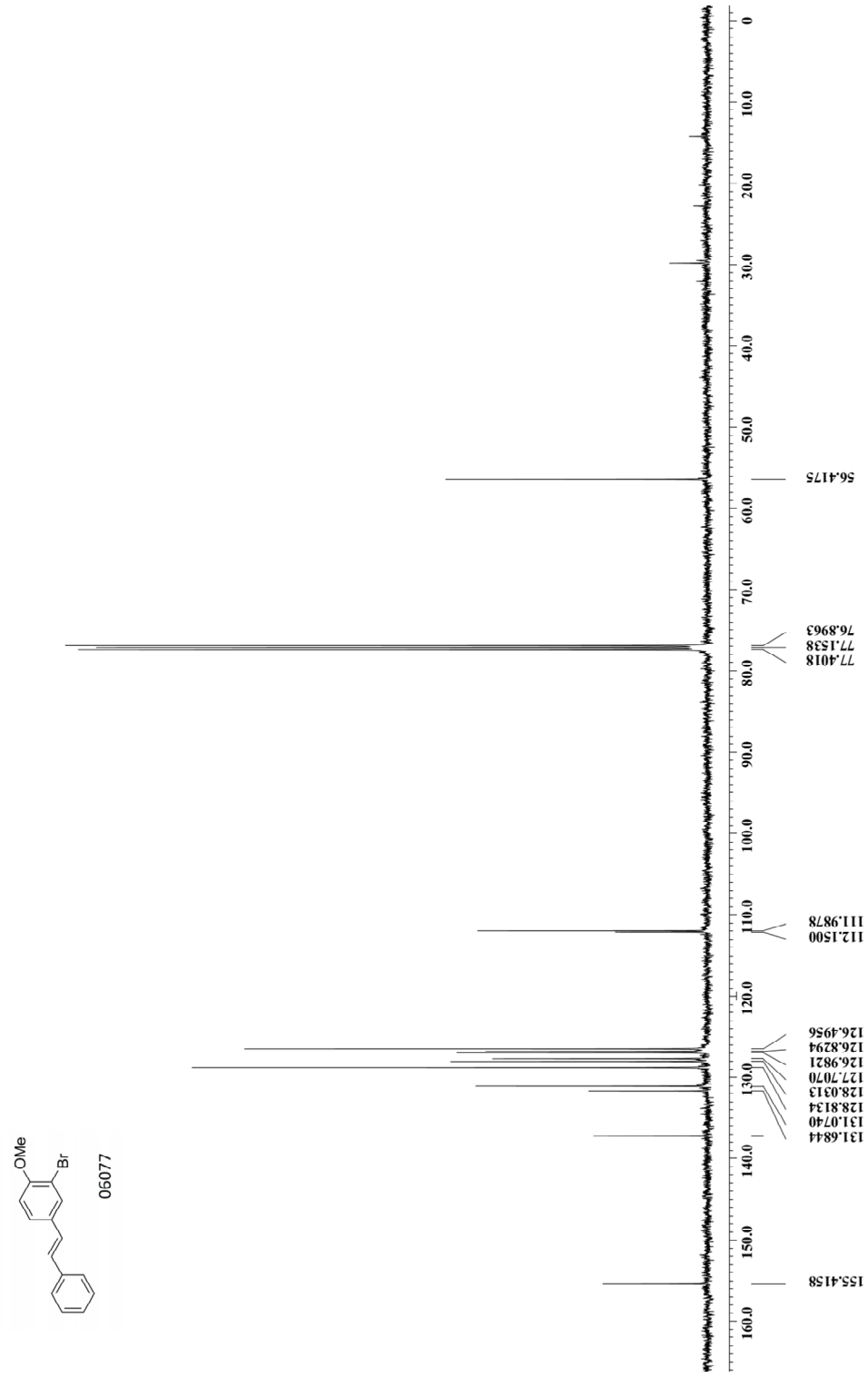
^{1}H-NMR Spectrum (500 MHz, $CDCl_3$)

(E)-2-bromo-1-methoxy-4-styrylbenzene



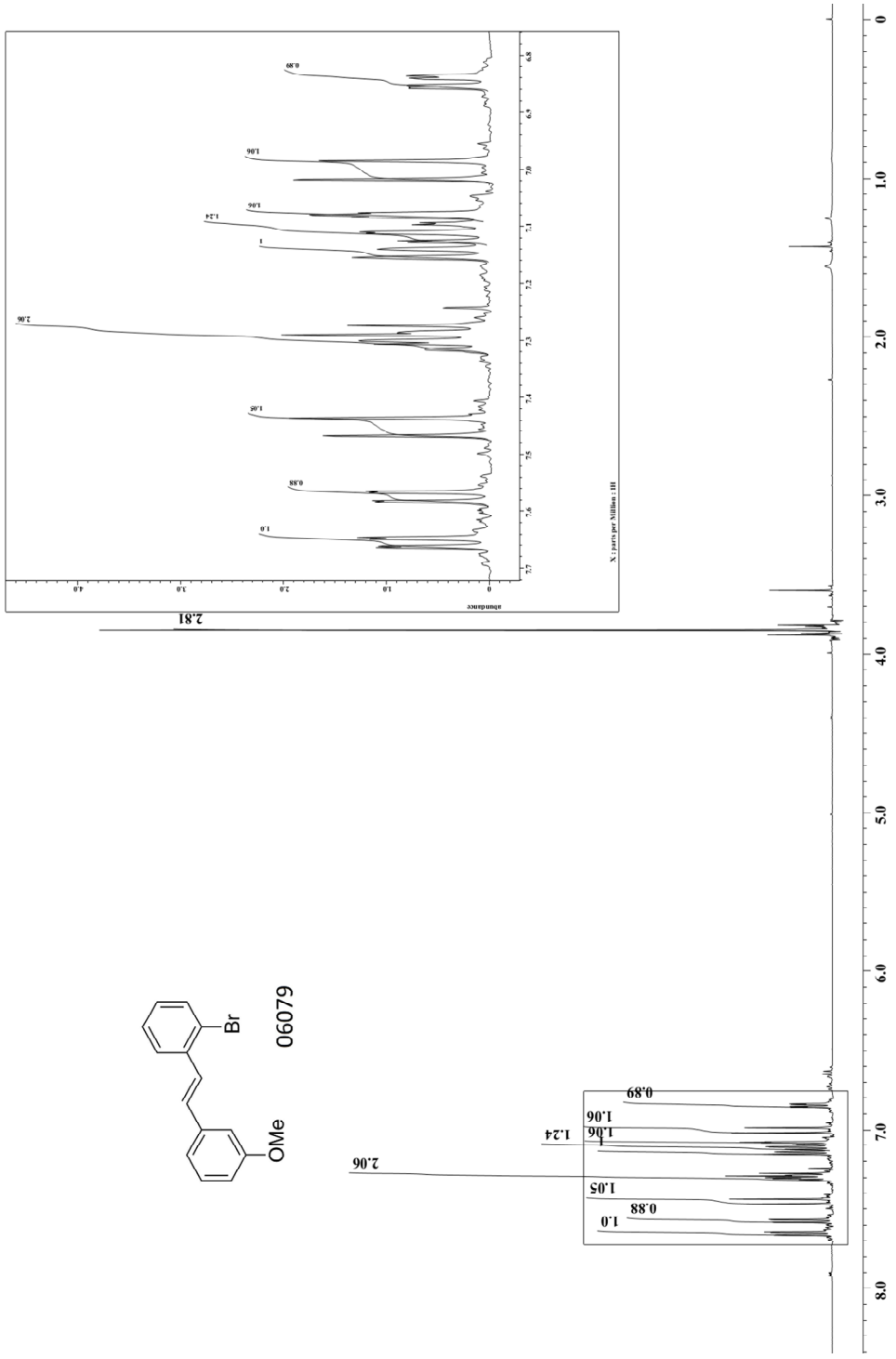
^{13}C-NMR Spectrum (500 MHz, $CDCl_3$)

(E)-2-bromo-1-methoxy-4-styrylbenzene



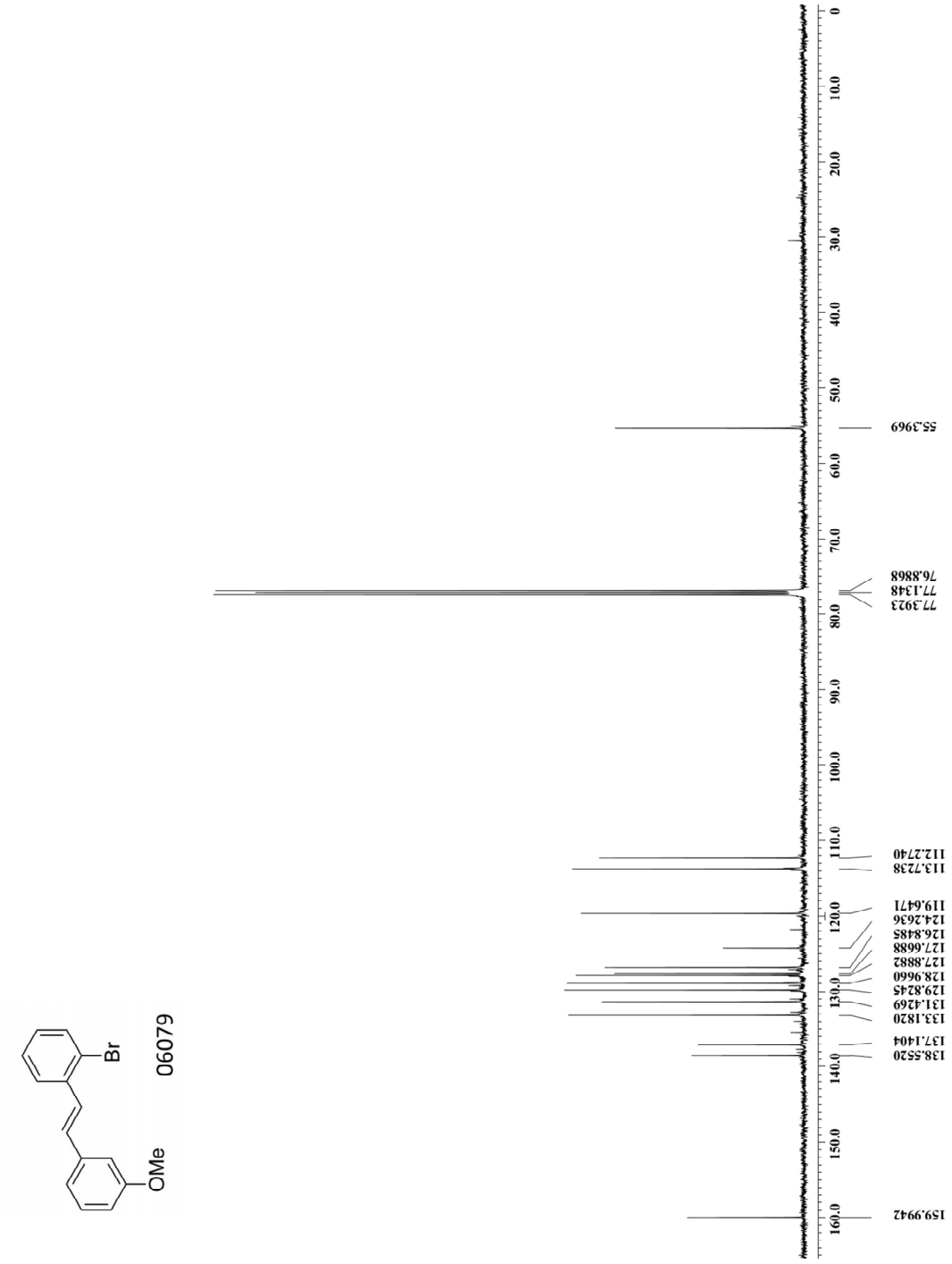
^{1}H-NMR Spectrum (500 MHz, $CDCl_3$)

(E)-1-bromo-2-(3-methoxystyryl)benzene



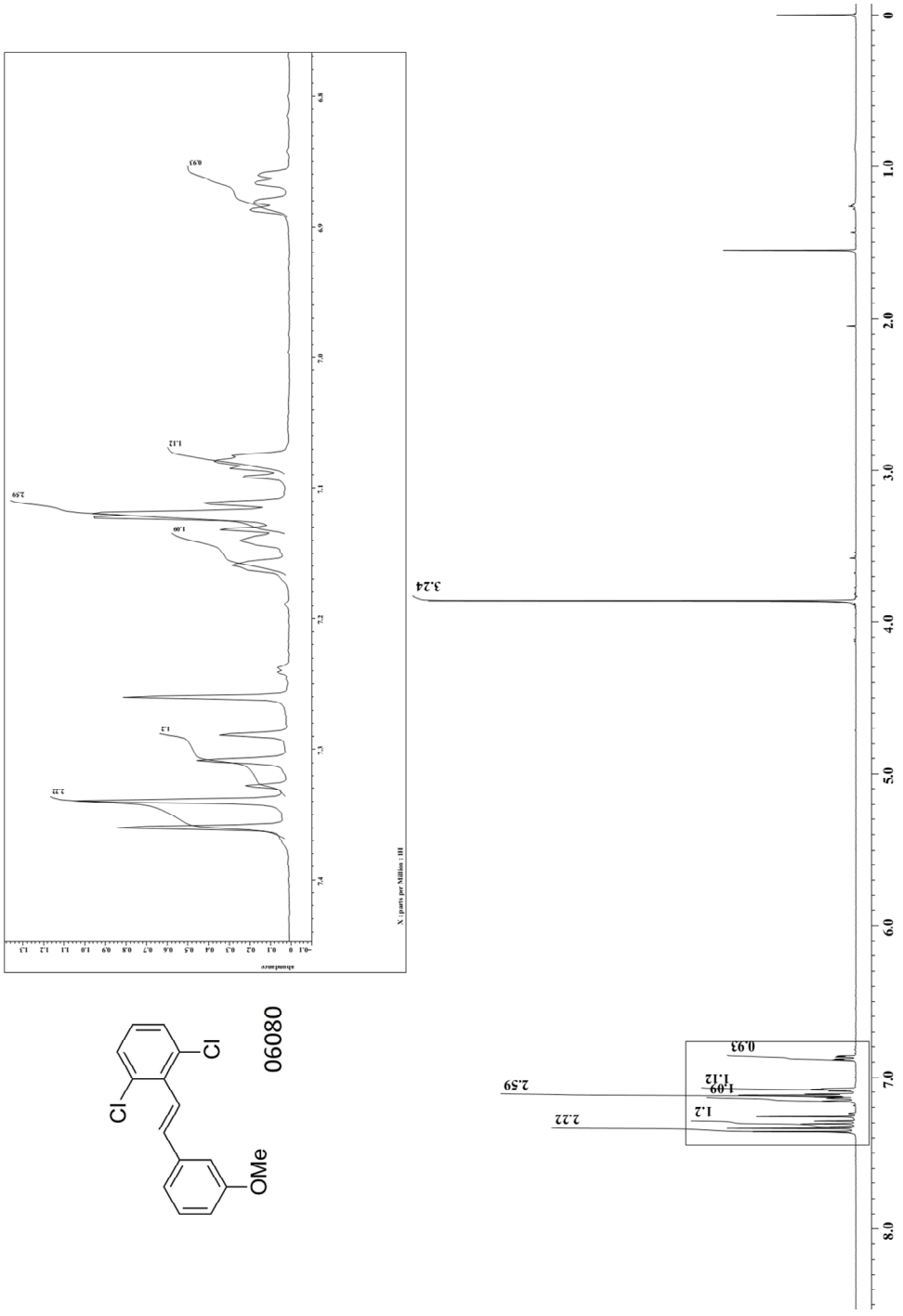
^{13}C-NMR Spectrum (500 MHz, $CDCl_3$)

(E)-1-bromo-2-(3-methoxystyryl)benzene



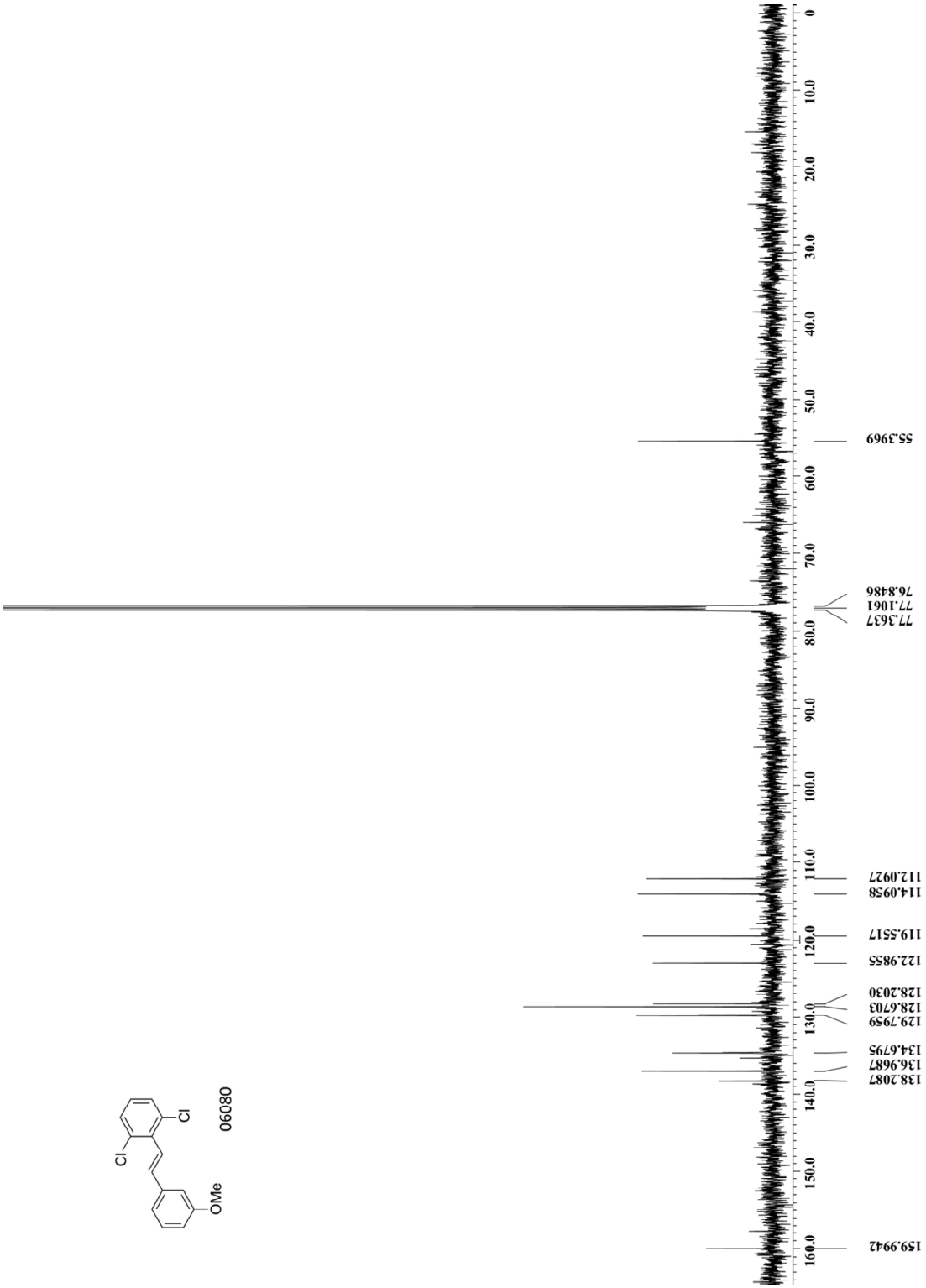
^{1}H-NMR Spectrum (500 MHz, $CDCl_3$)

(E)-1,3-dichloro-2-(3-methoxystyryl)benzene



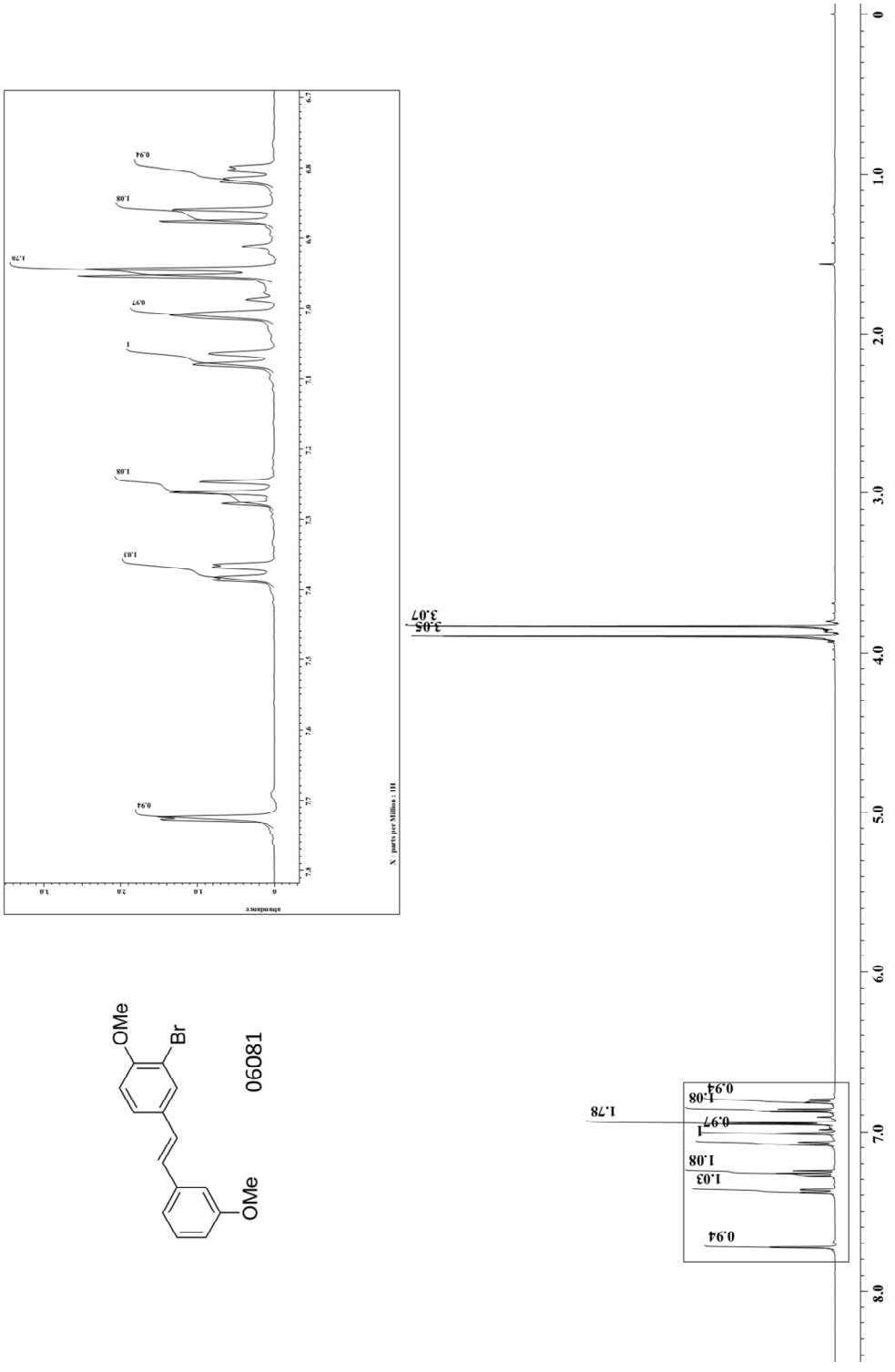
^{13}C-NMR Spectrum (500 MHz, $CDCl_3$)

(E)-1,3-dichloro-2-(3-methoxystyryl)benzene



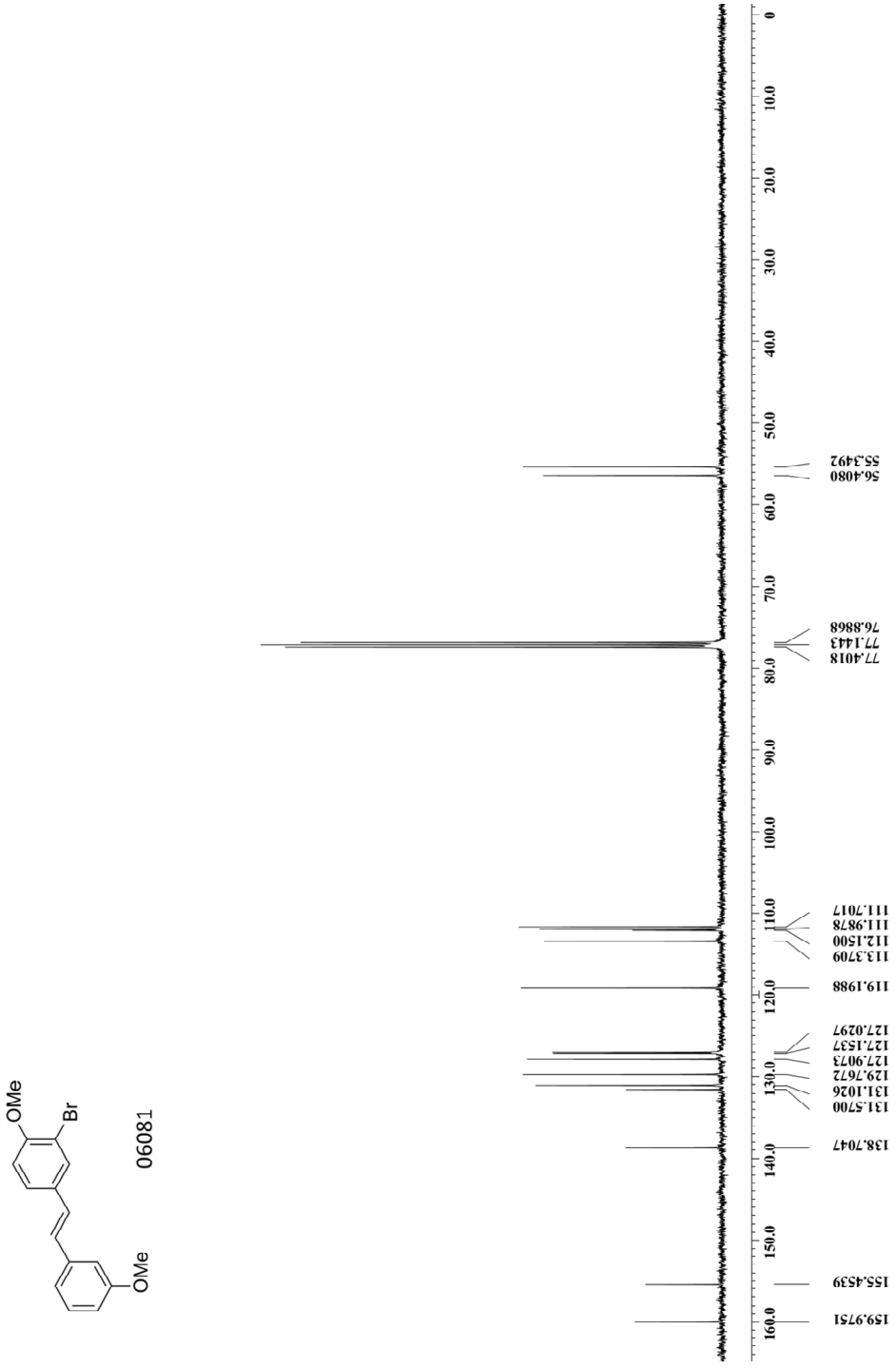
^{1}H-NMR Spectrum (500 MHz, $CDCl_3$)

(E)-2-bromo-1-methoxy-4-(3-methoxystyryl)benzene



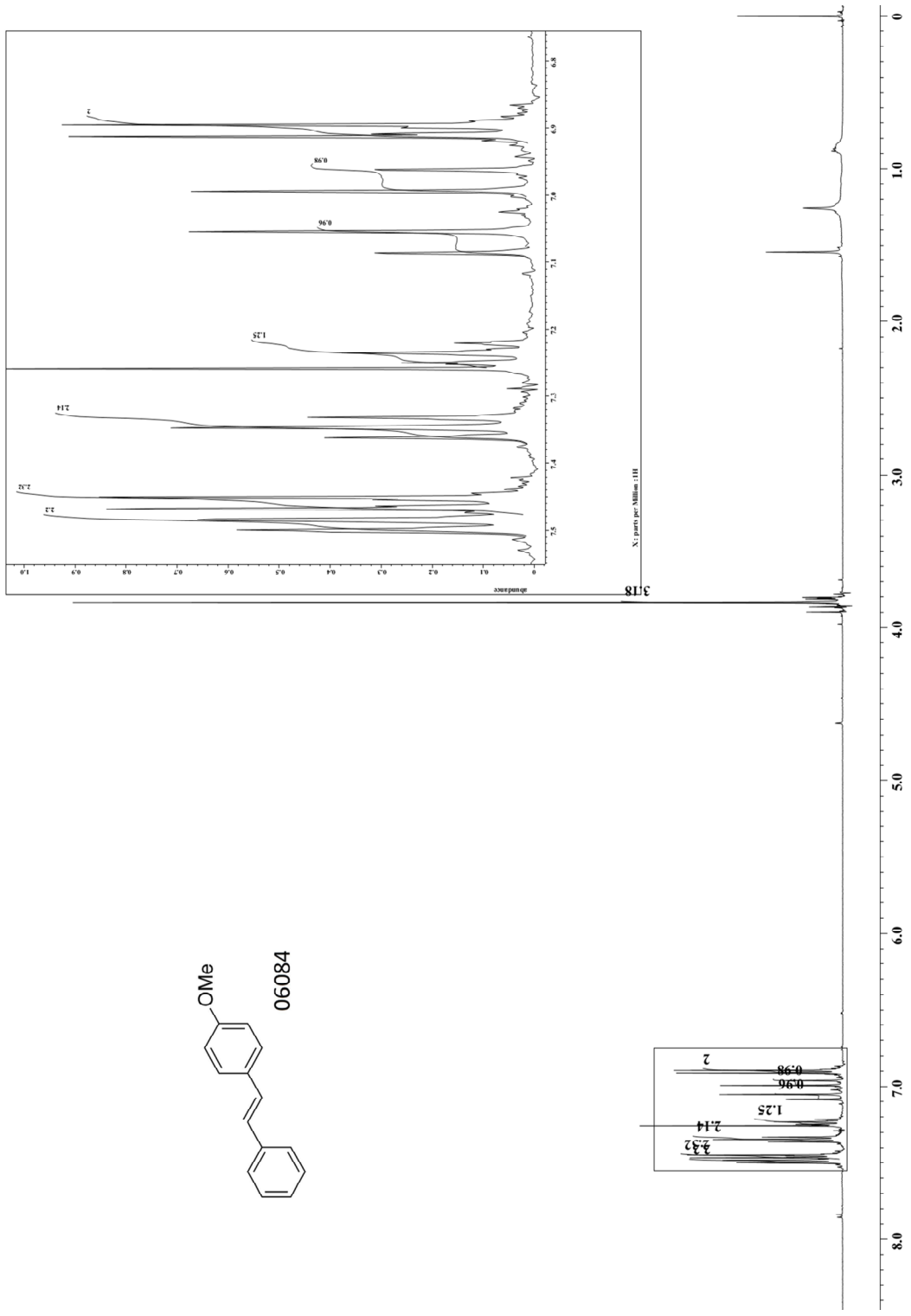
^{13}C-NMR Spectrum (500 MHz, $CDCl_3$)

(E)-2-bromo-1-methoxy-4-(3-methoxystyryl)benzene



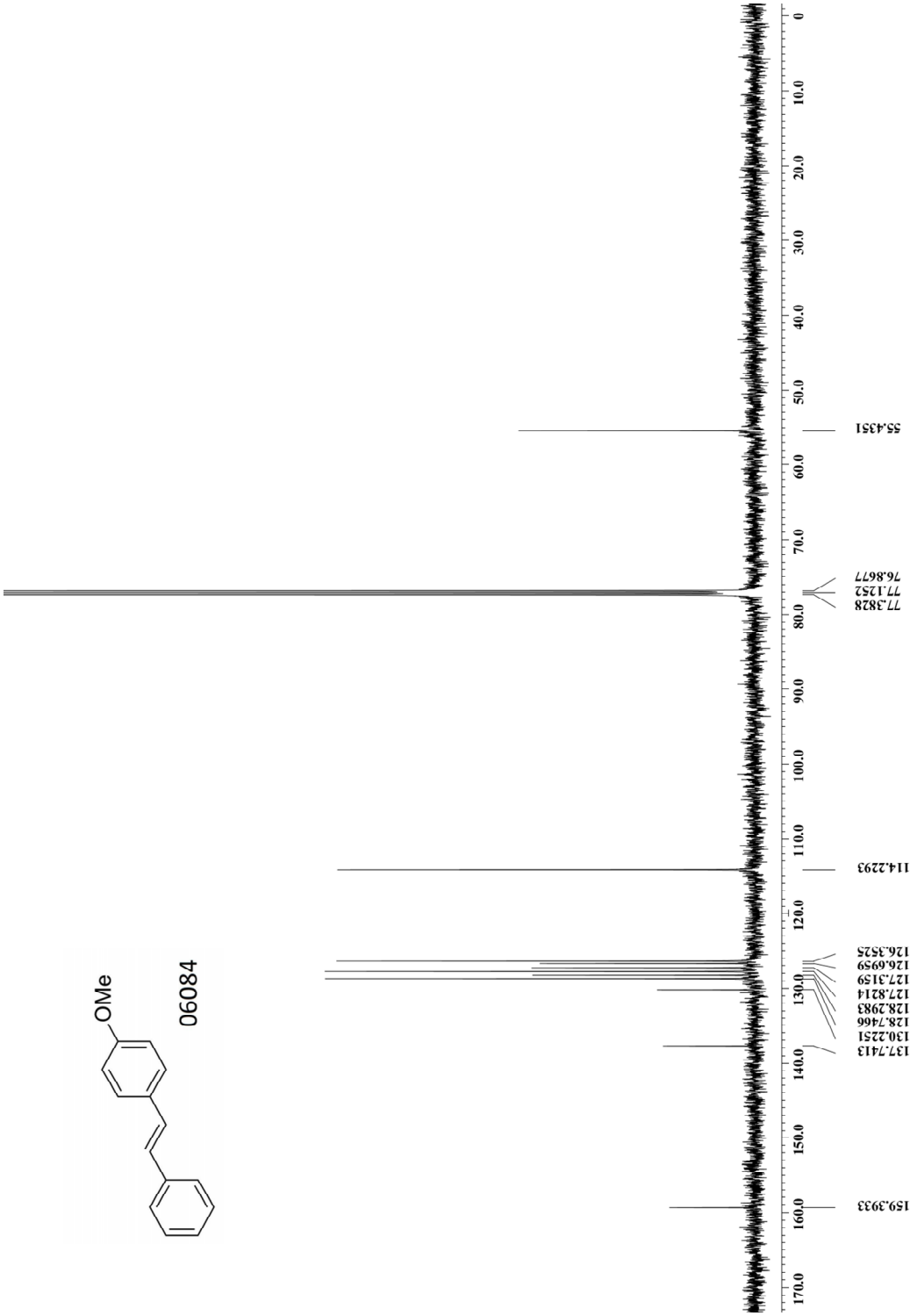
^{1}H-NMR Spectrum (500 MHz, $CDCl_3$)

(E)-1-methoxy-4-styrylbenzene



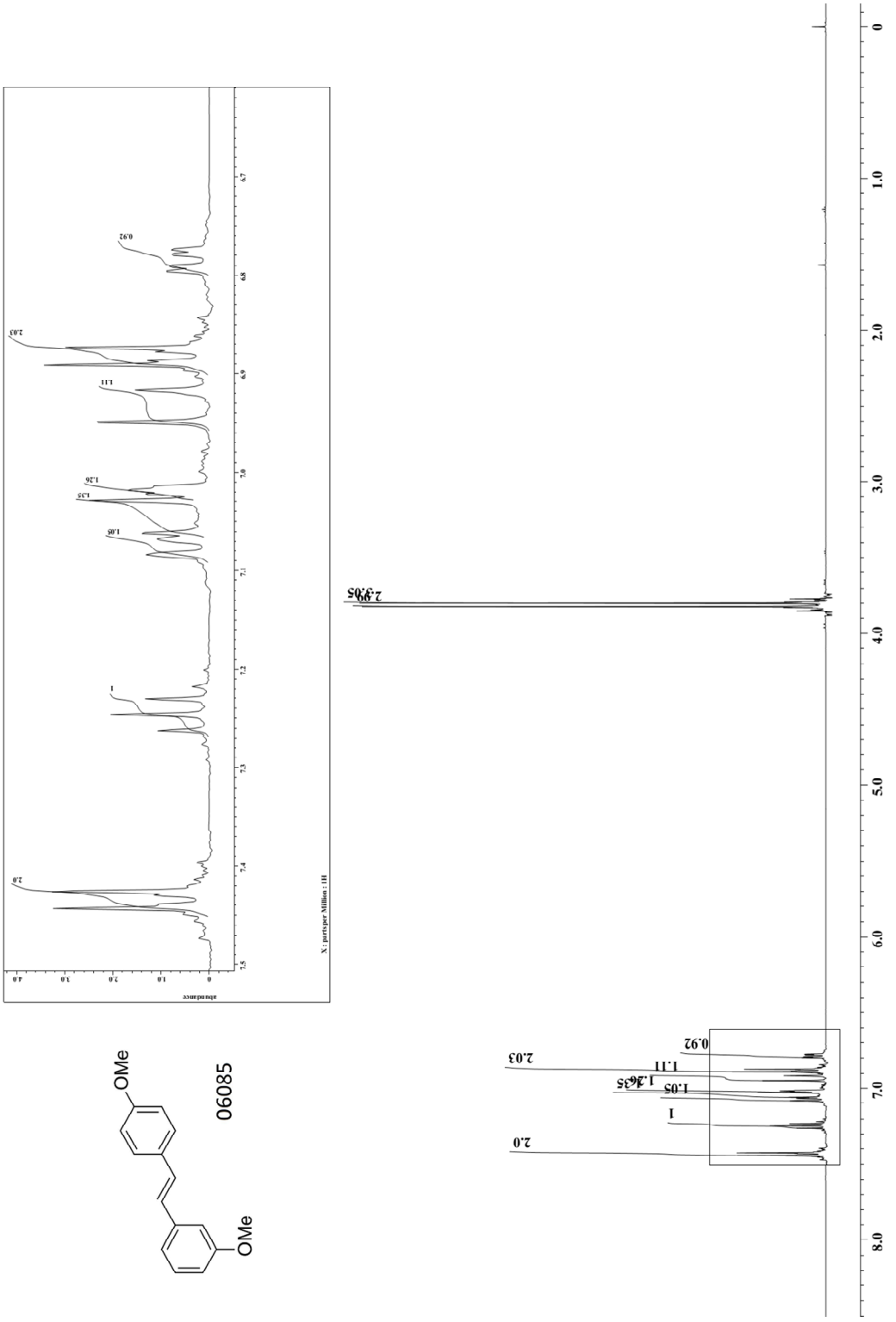
^{13}C-NMR Spectrum (500 MHz, $CDCl_3$)

(E)-1-methoxy-4-styrylbenzene



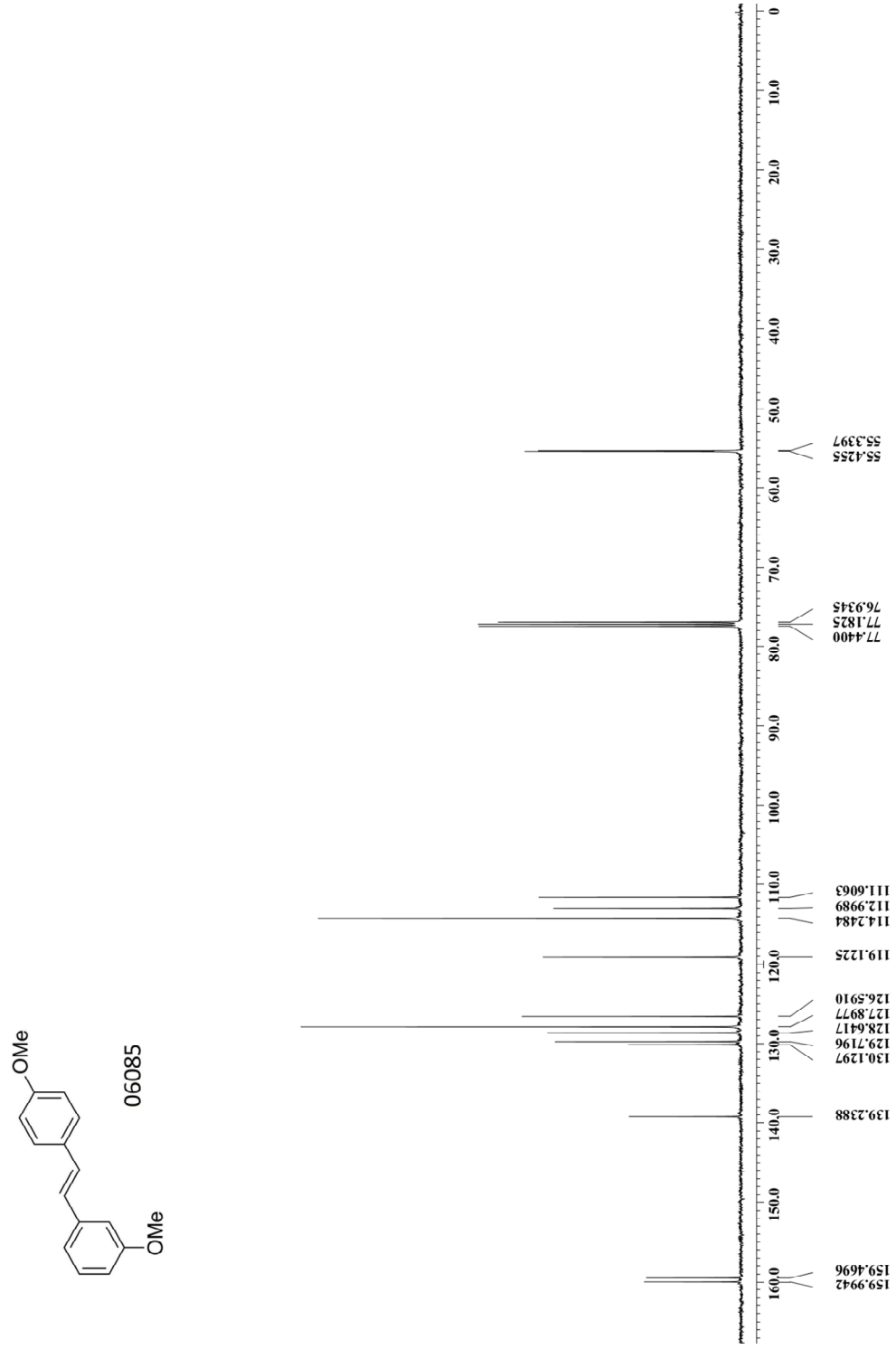
^{1}H-NMR Spectrum (500 MHz, $CDCl_3$)

(E)-3,4'-(ethene-1,2-diyl)bis(methoxybenzene)



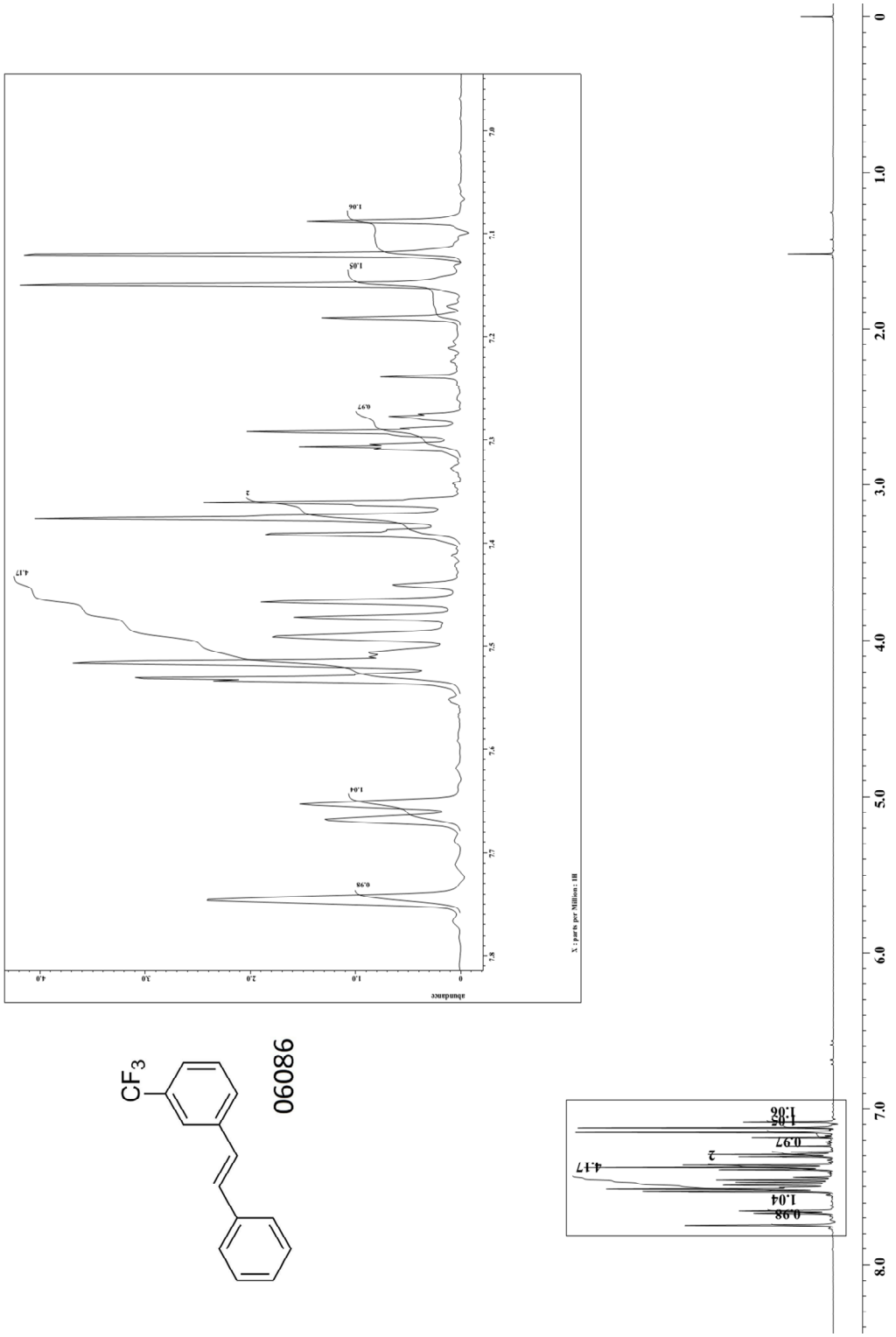
^{13}C-NMR Spectrum (500 MHz, $CDCl_3$)

(E)-3,4'-(ethene-1,2-diyl)bis(methoxybenzene)



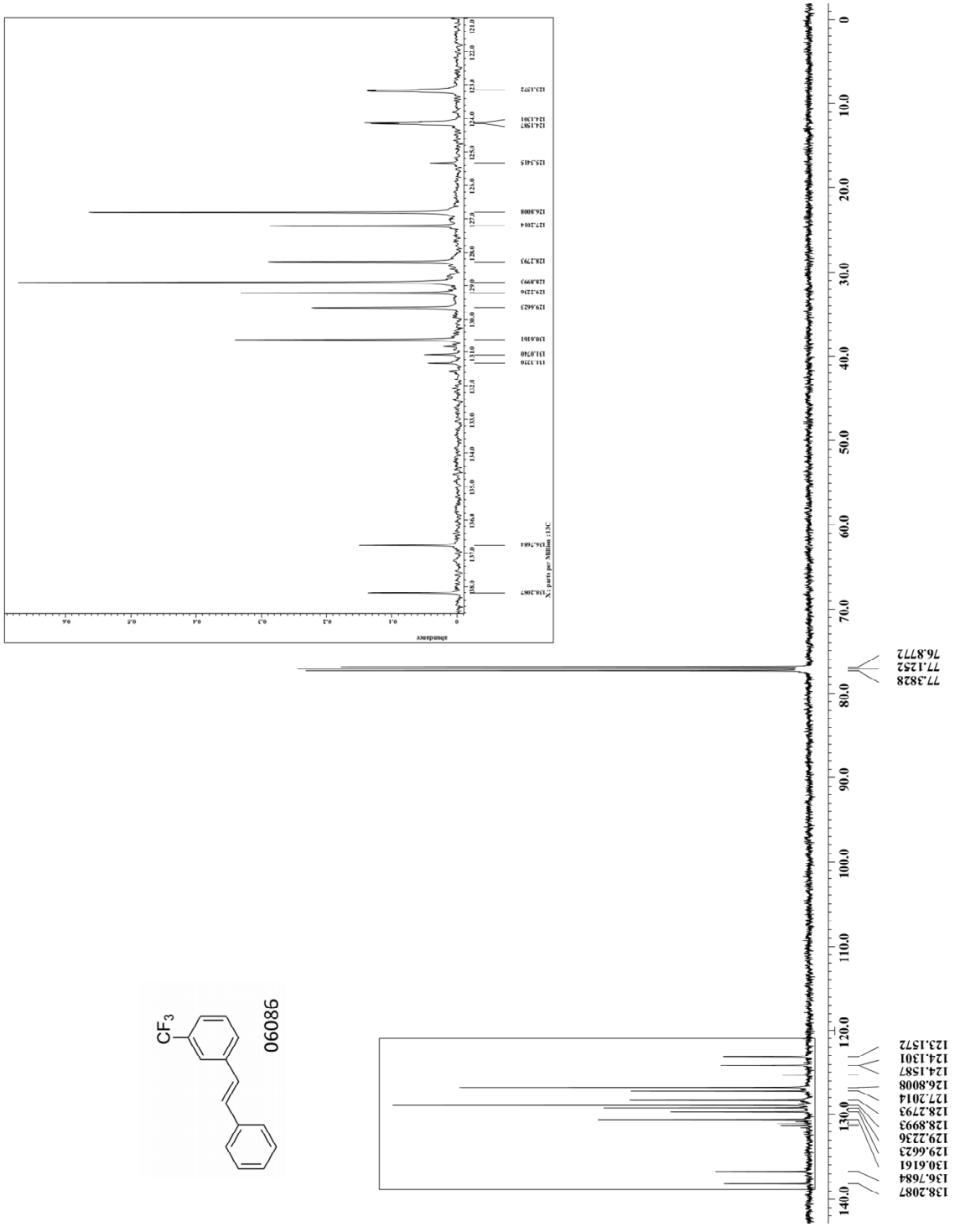
^{1}H-NMR Spectrum (500 MHz, $CDCl_3$)

(E)-1-styryl-3-(trifluoromethyl)benzene



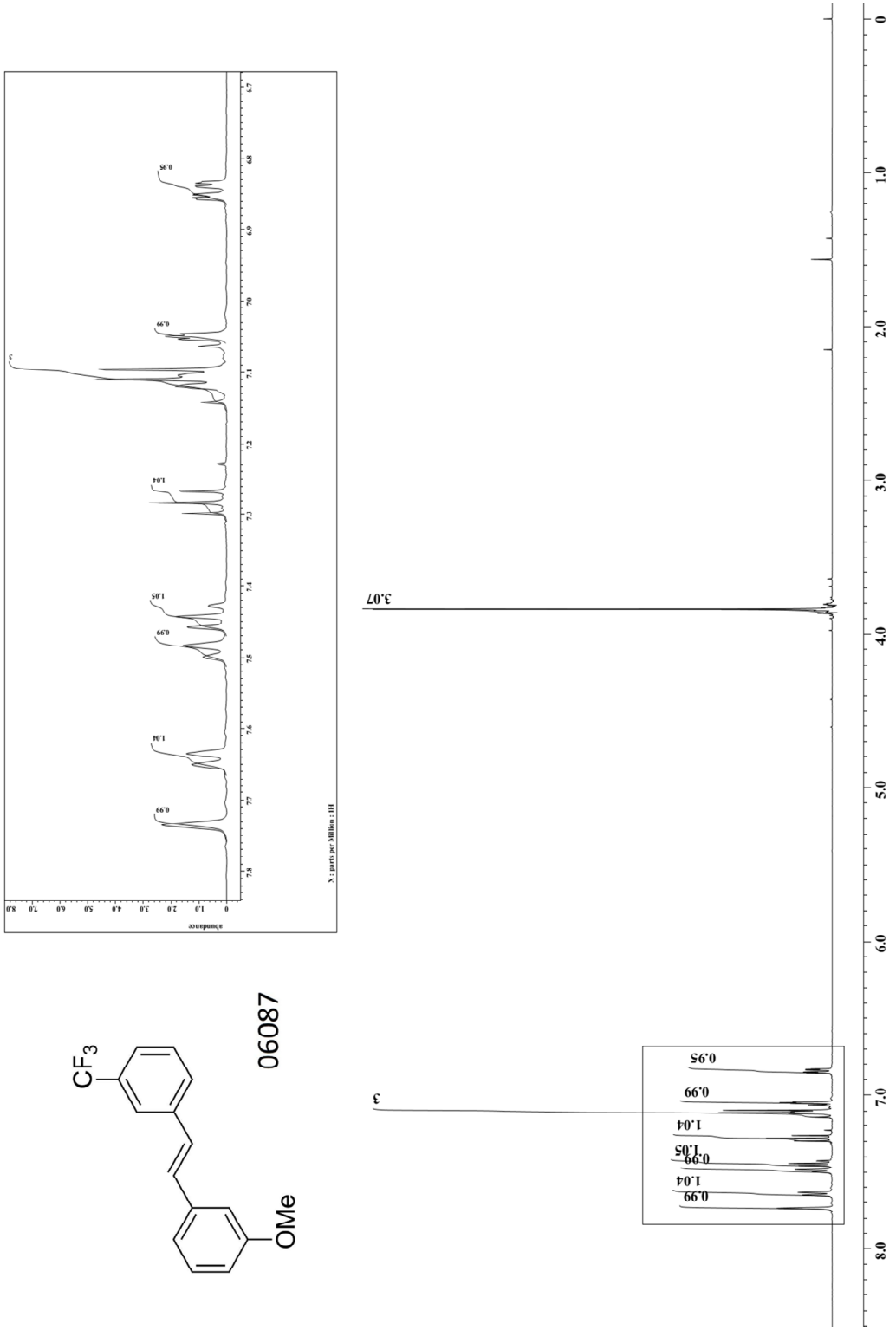
^{13}C-NMR Spectrum (500 MHz, $CDCl_3$)

(E)-1-styryl-3-(trifluoromethyl)benzene



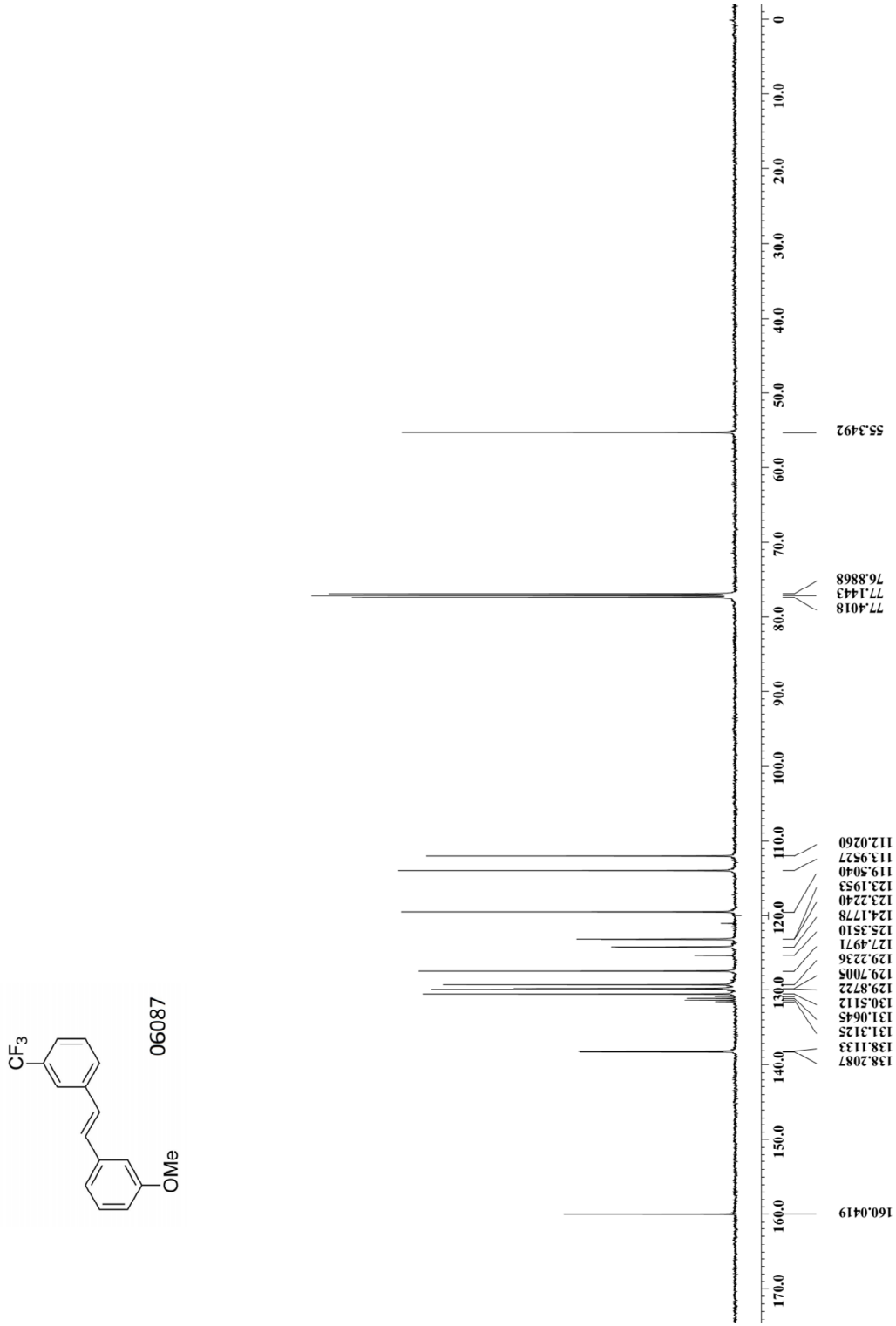
^{1}H-NMR Spectrum (500 MHz, $CDCl_3$)

(E)-1-methoxy-3-(3-(trifluoromethyl)styryl)benzene



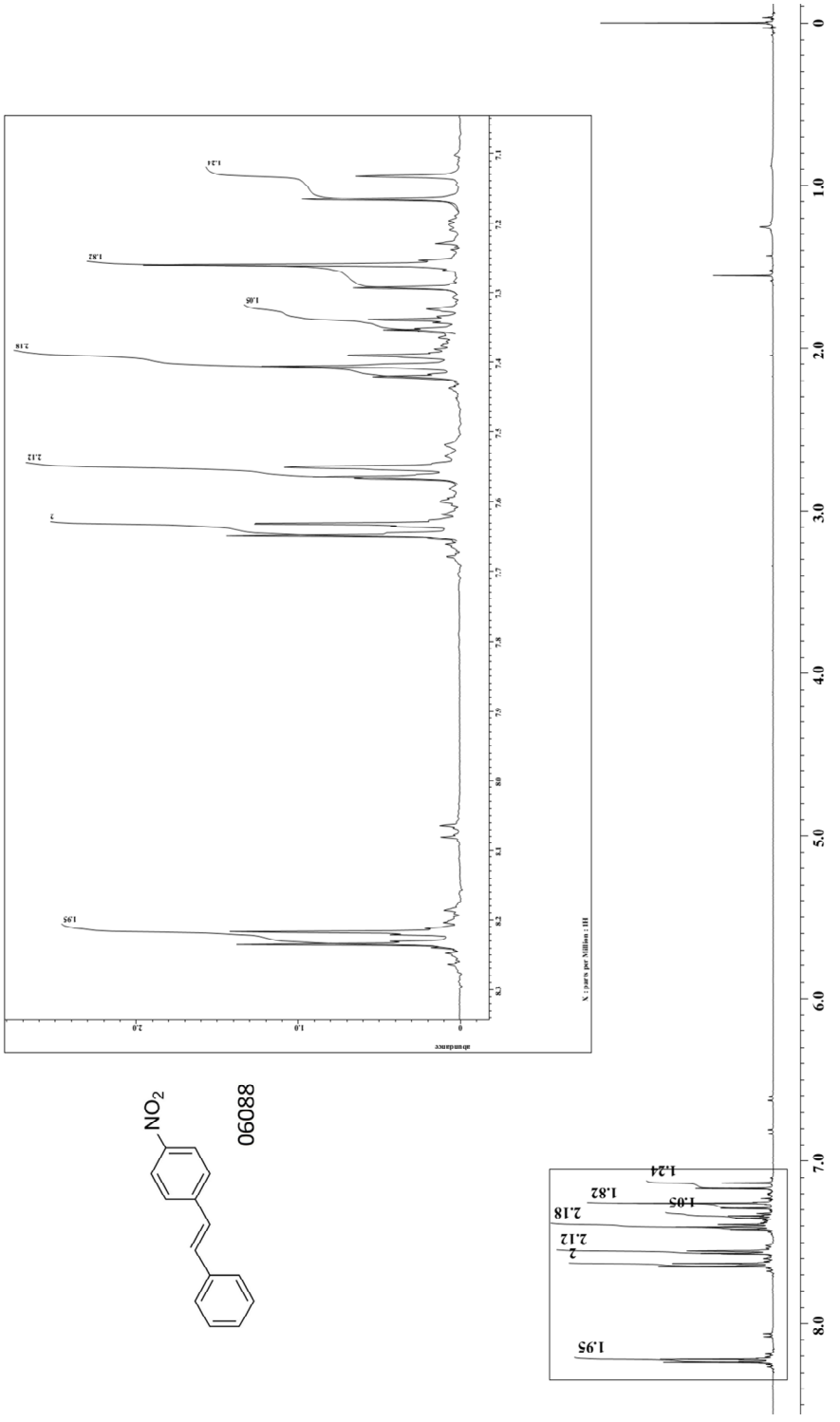
^{13}C-NMR Spectrum (500 MHz, $CDCl_3$)

(E)-1-methoxy-3-(3-(trifluoromethyl)styryl)benzene



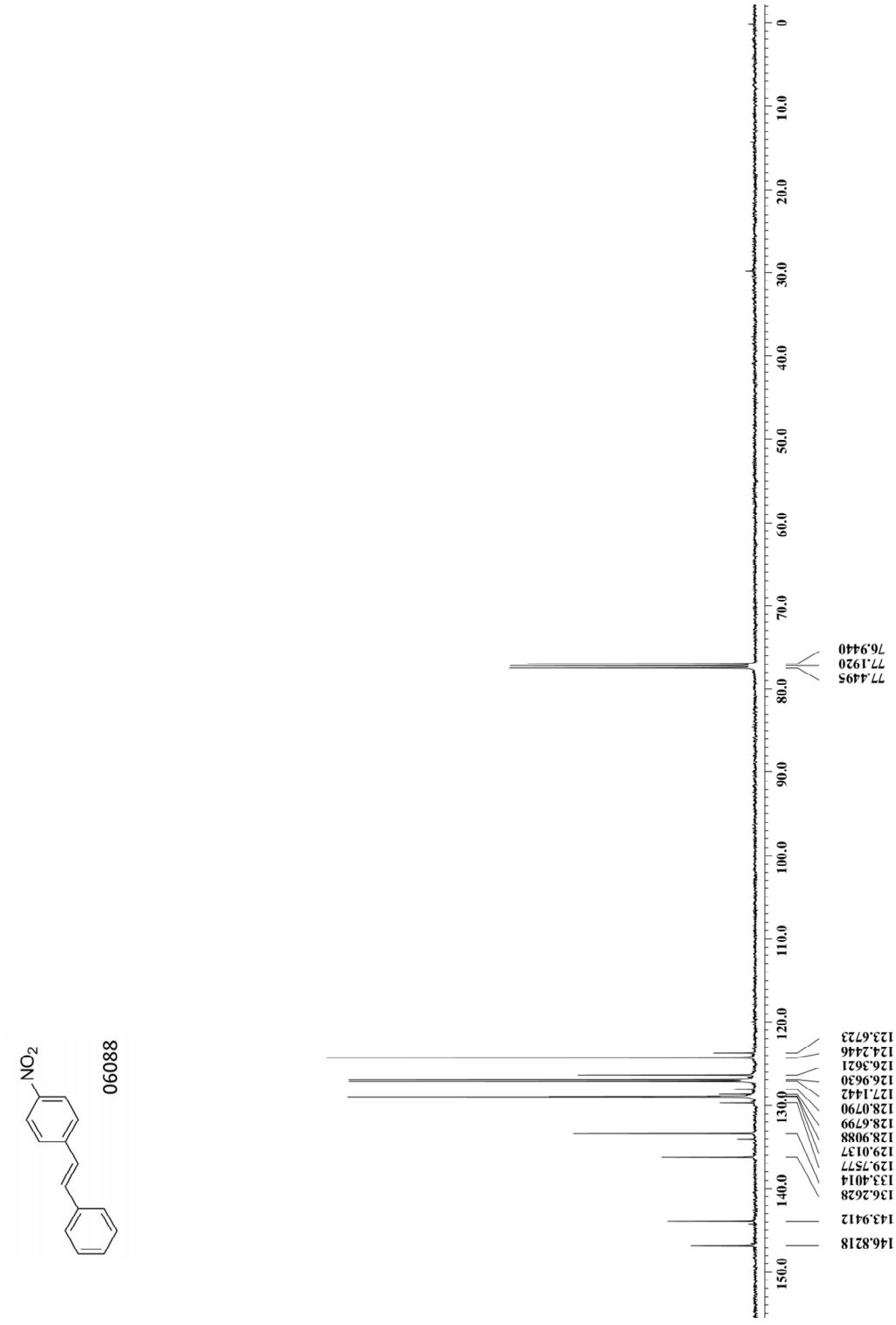
^{1}H-NMR Spectrum (500 MHz, $CDCl_3$)

(E)-1-nitro-4-styrylbenzene



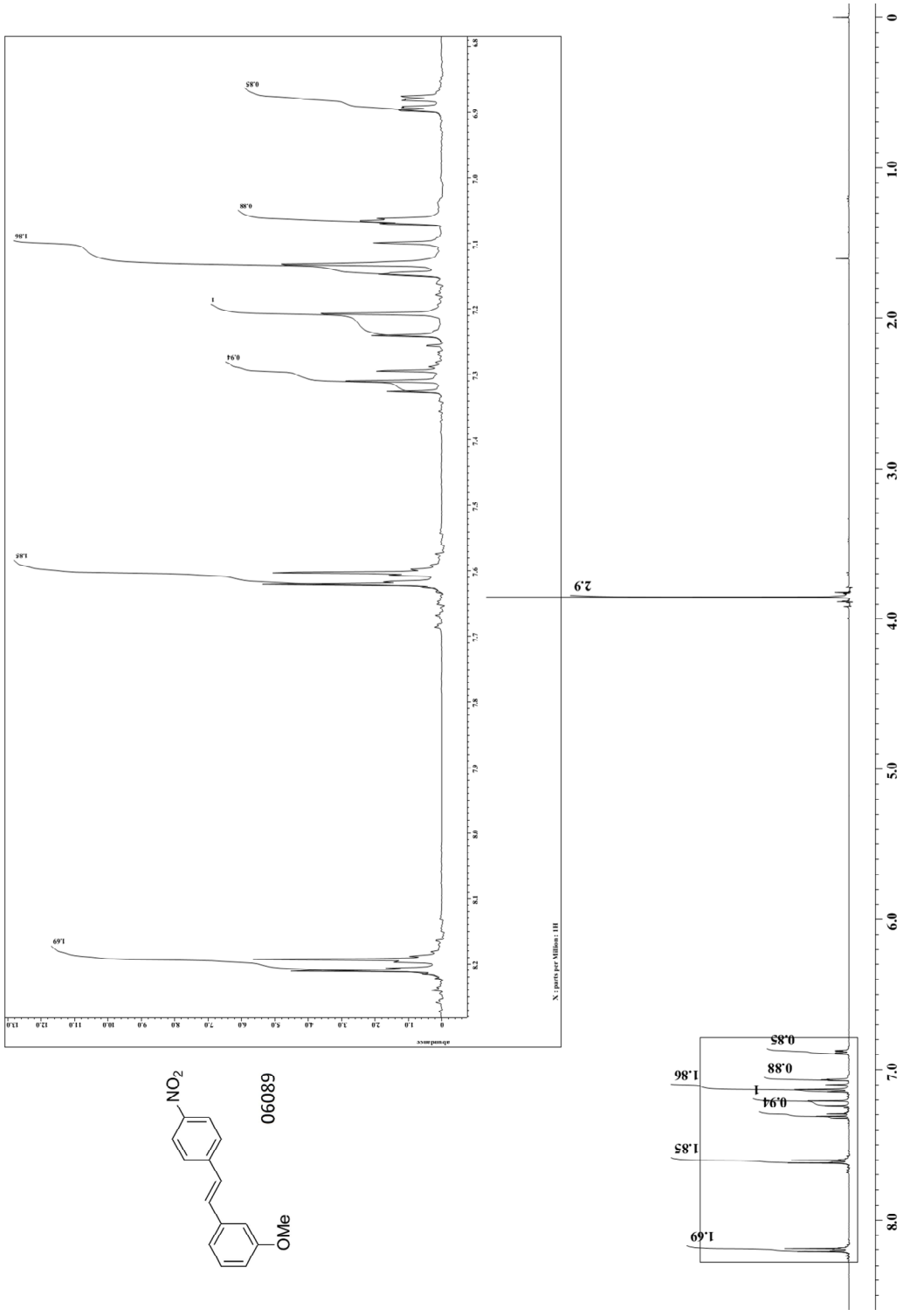
^{13}C-NMR Spectrum (500 MHz, $CDCl_3$)

(E)-1-nitro-4-styrylbenzene



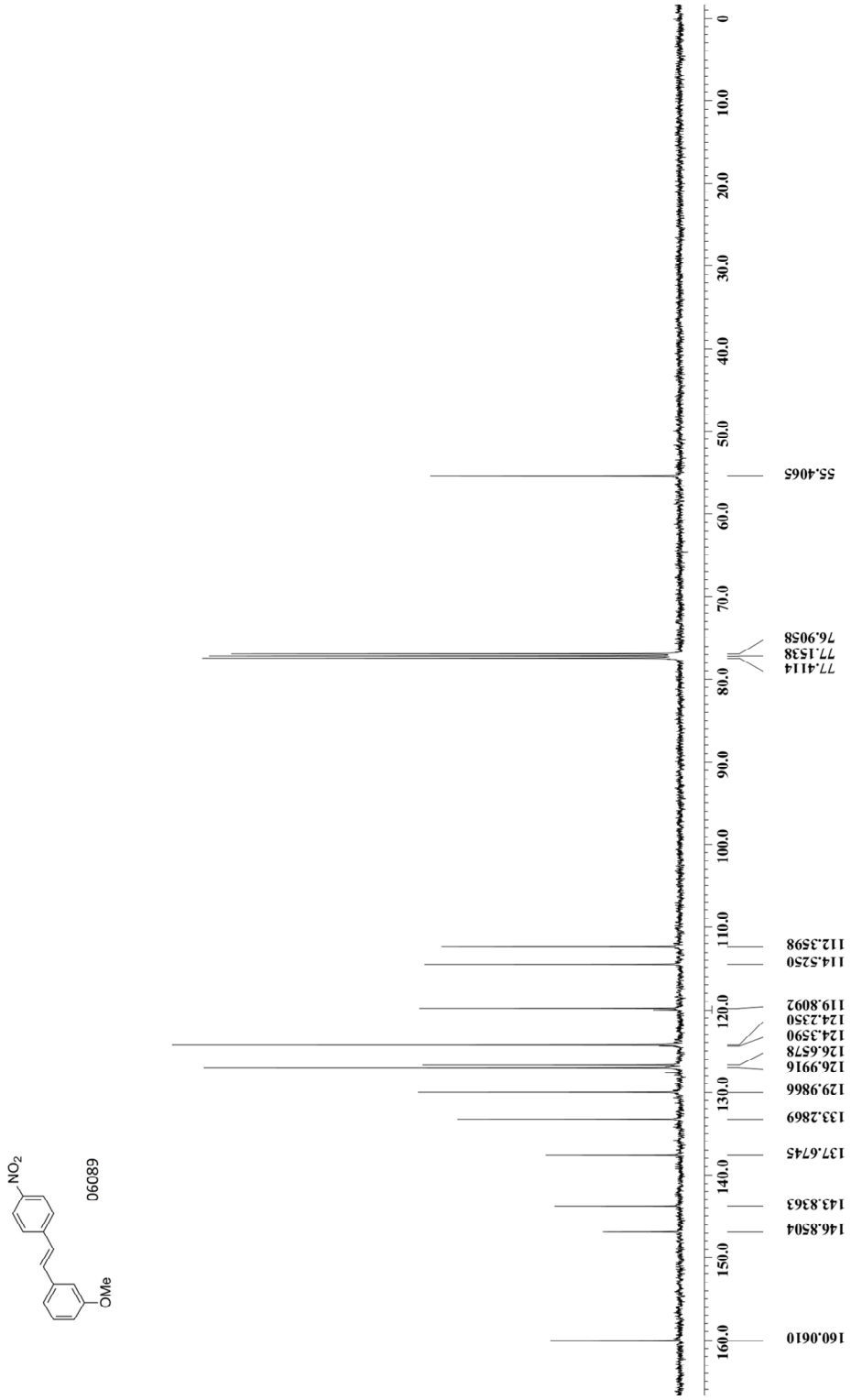
^{1}H-NMR Spectrum (500 MHz, $CDCl_3$)

(E)-1-methoxy-3-(4-nitrostyryl)benzene



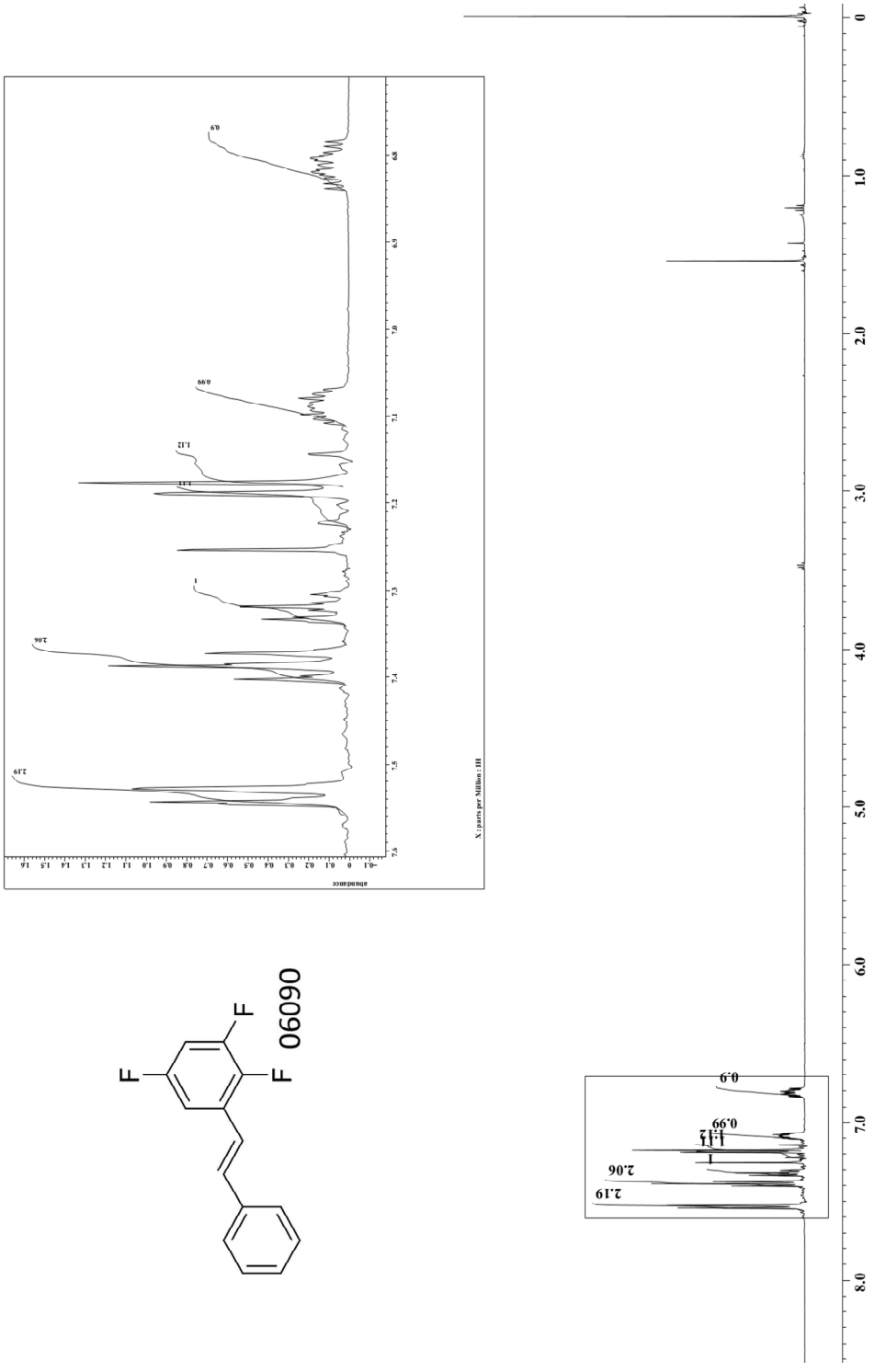
^{13}C-NMR Spectrum (500 MHz, $CDCl_3$)

(E)-1-methoxy-3-(4-nitrostyryl)benzene



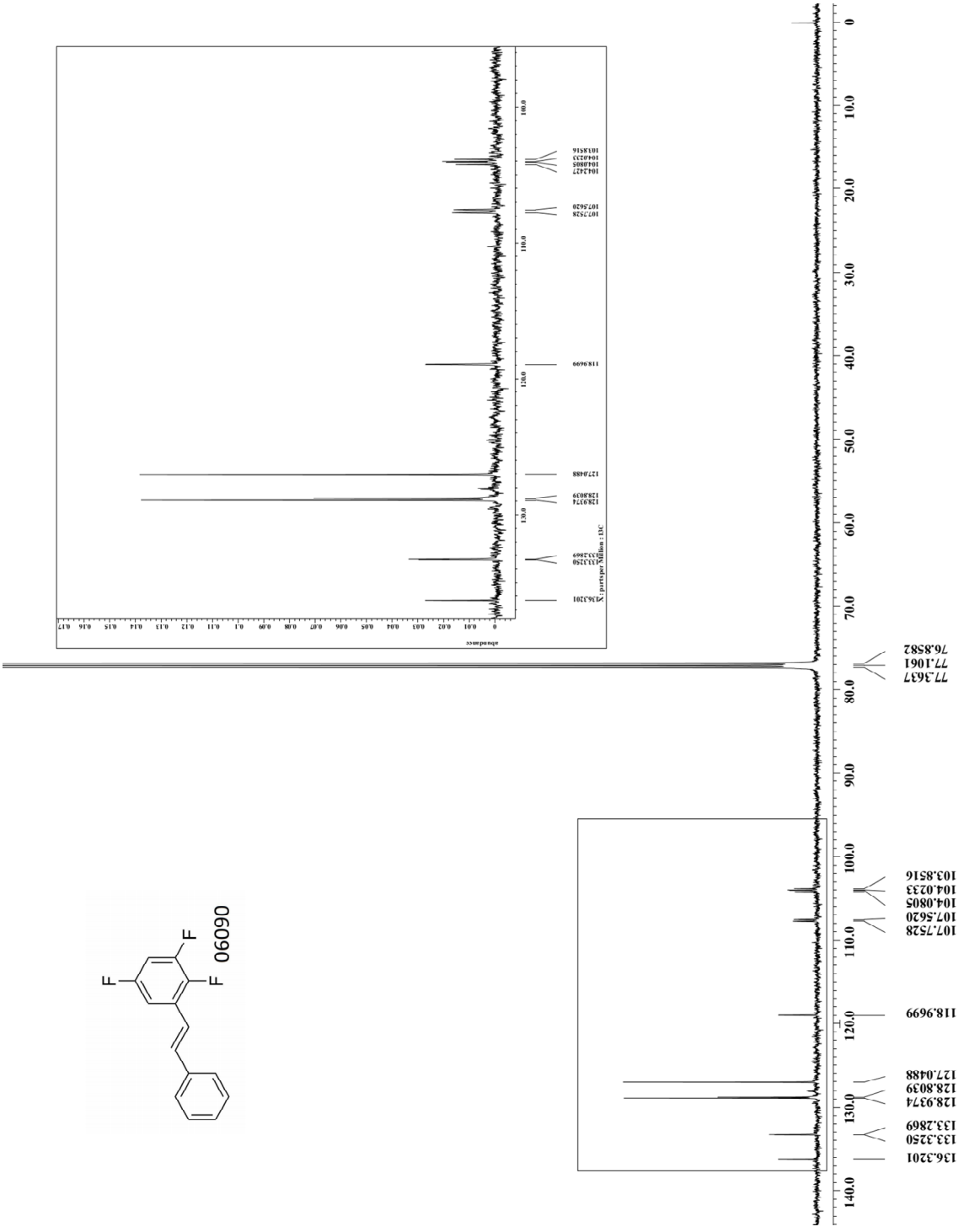
^{1}H-NMR Spectrum (500 MHz, $CDCl_3$)

(E)-1,2,5-trifluoro-3-styrylbenzene



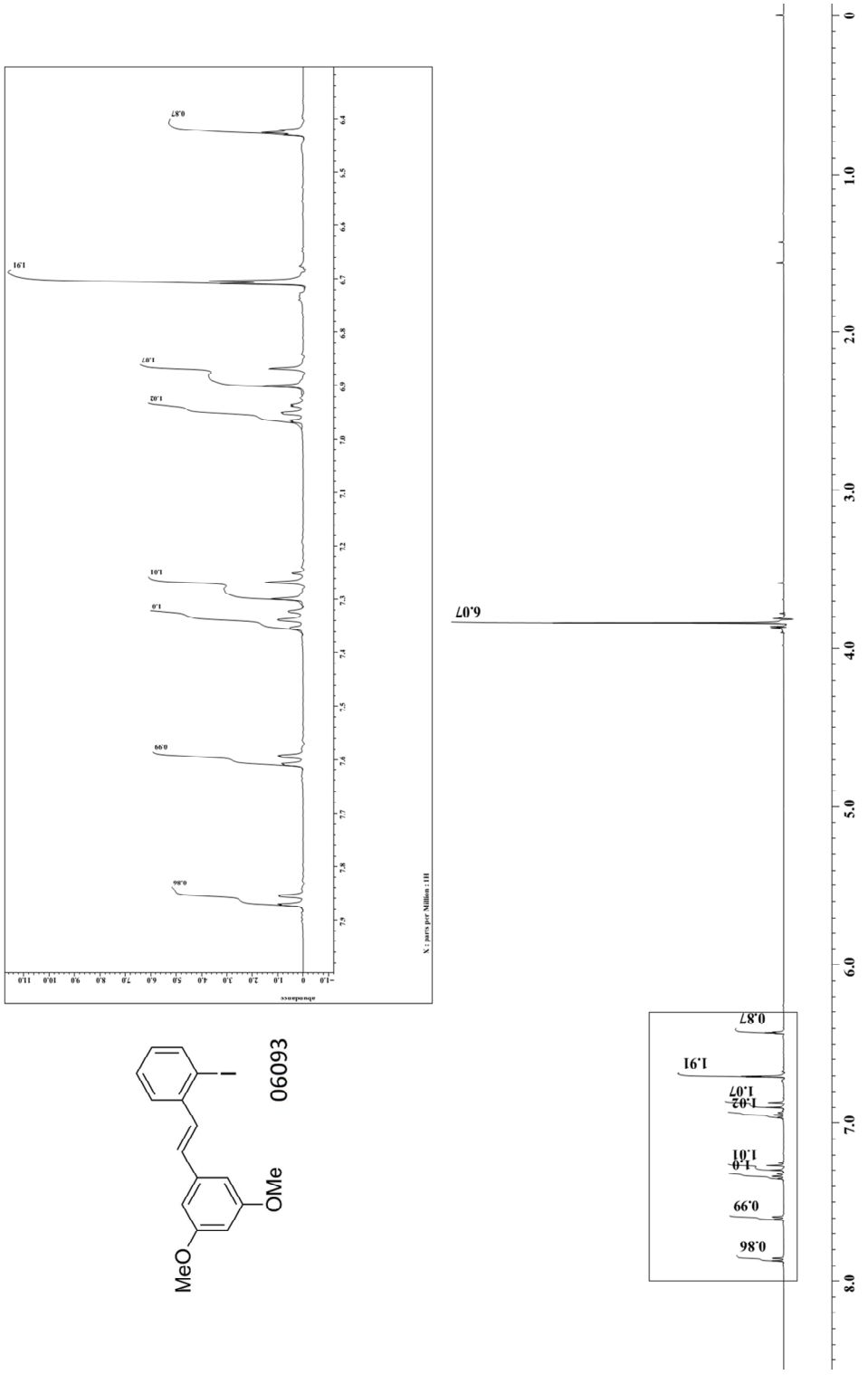
^{13}C-NMR Spectrum (500 MHz, $CDCl_3$)

(E)-1,2,5-trifluoro-3-styrylbenzene



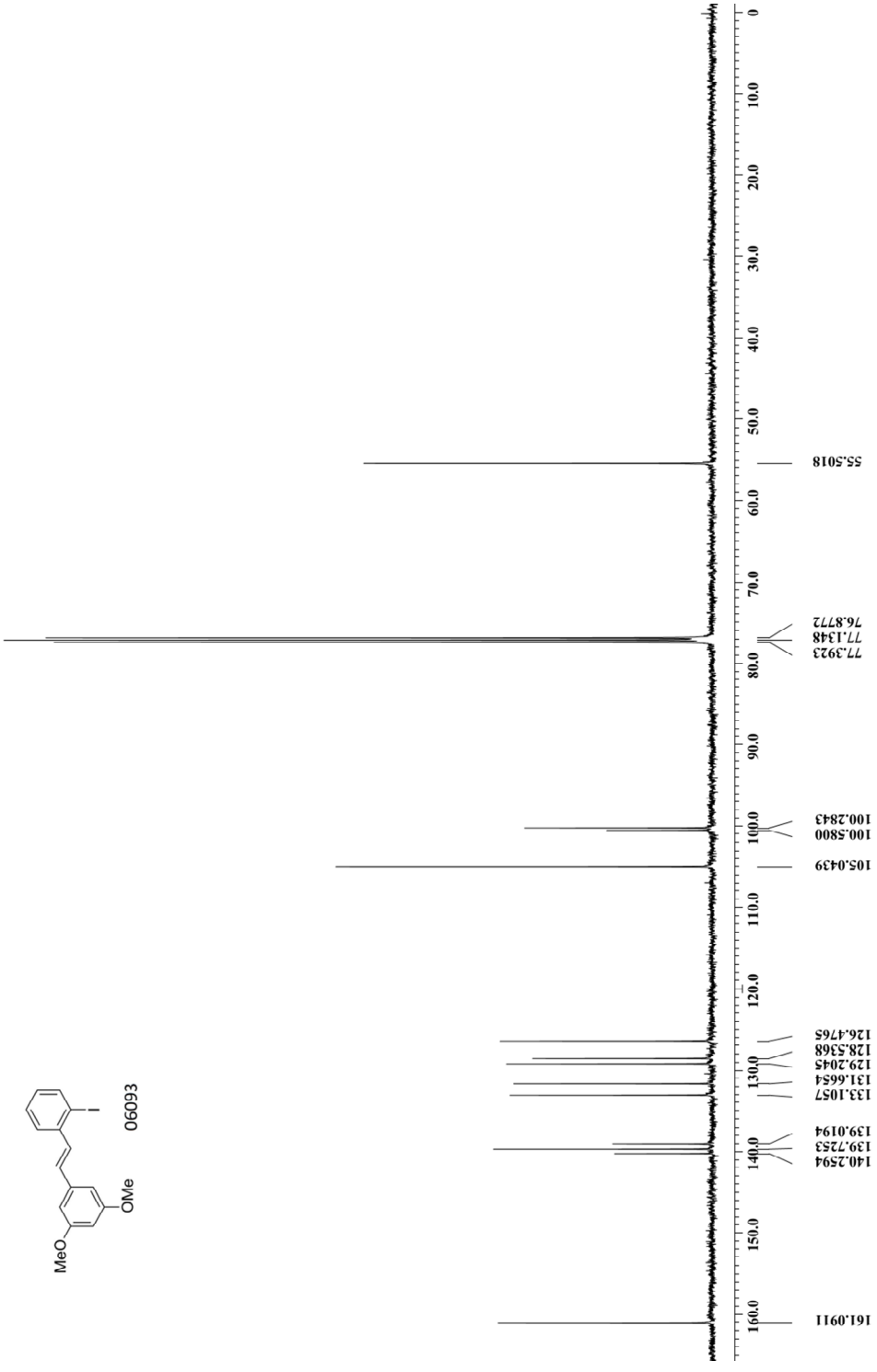
^{1}H-NMR Spectrum (500 MHz, $CDCl_3$)

(E)-1-(2-iodostyryl)-3,5-dimethoxybenzene



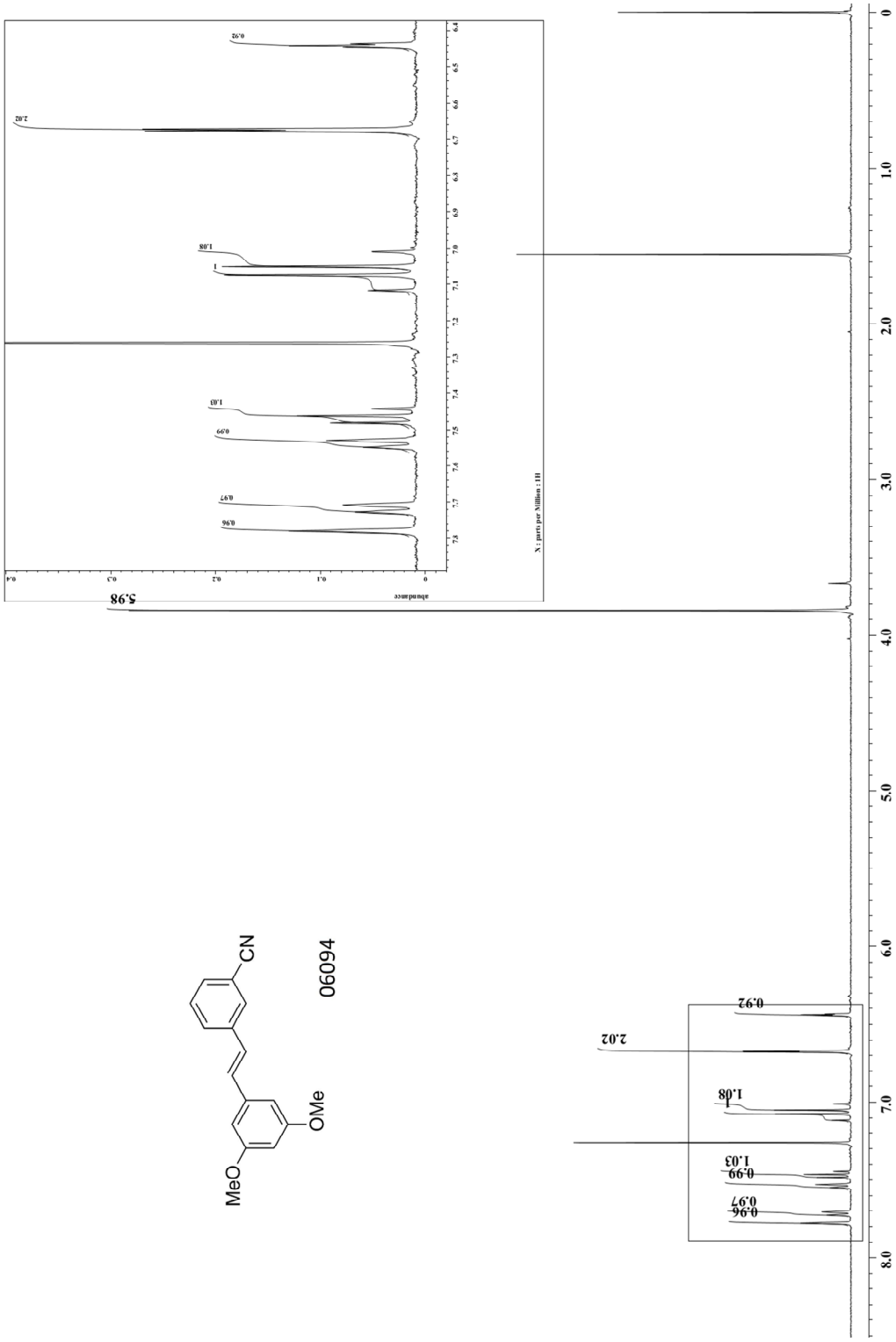
^{13}C-NMR Spectrum (500 MHz, $CDCl_3$)

(E)-1-(2-iodostyryl)-3,5-dimethoxybenzene



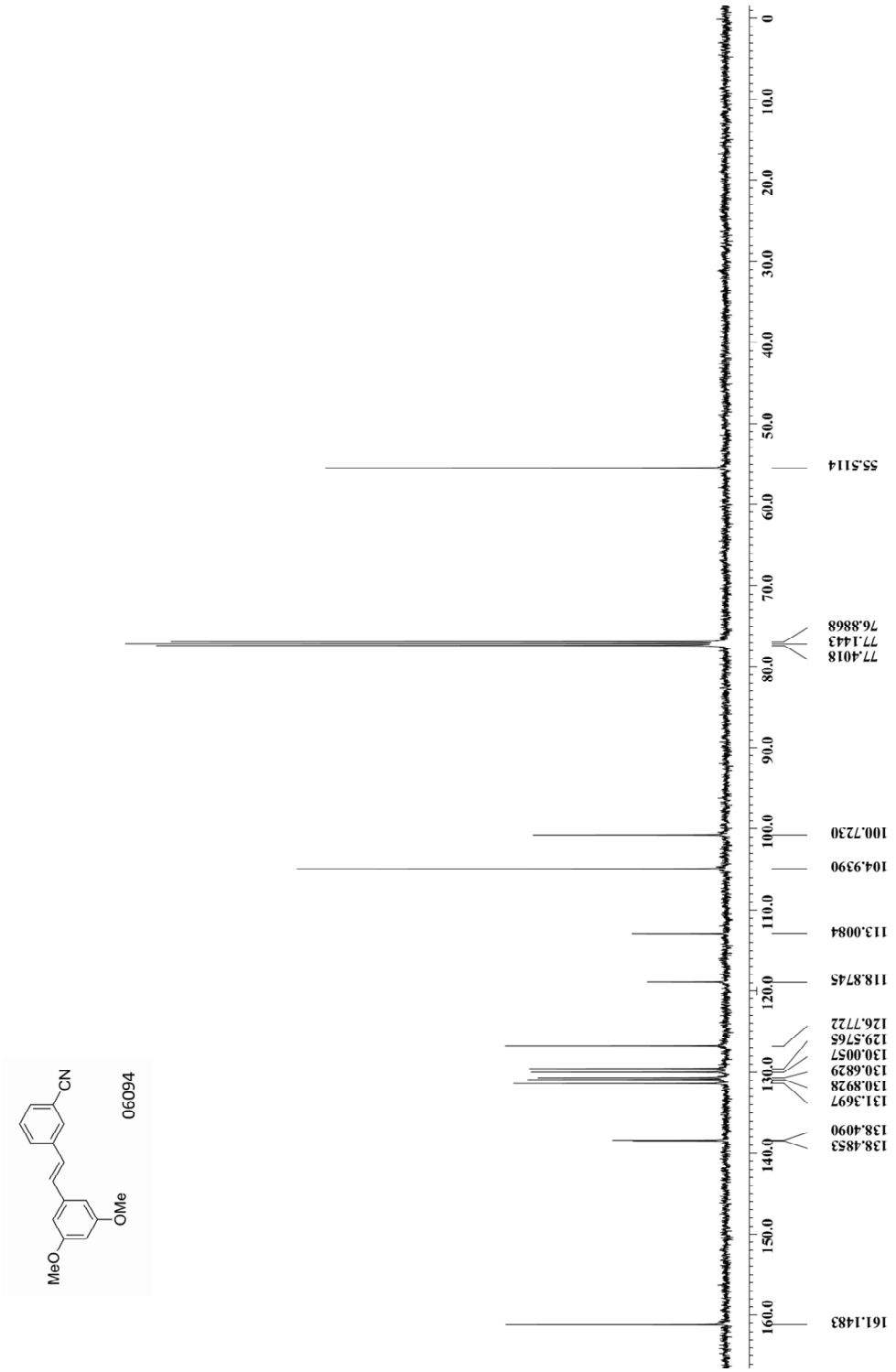
^{1}H-NMR Spectrum (500 MHz, $CDCl_3$)

(E)-3-(3,5-dimethoxystyryl)benzonitrile



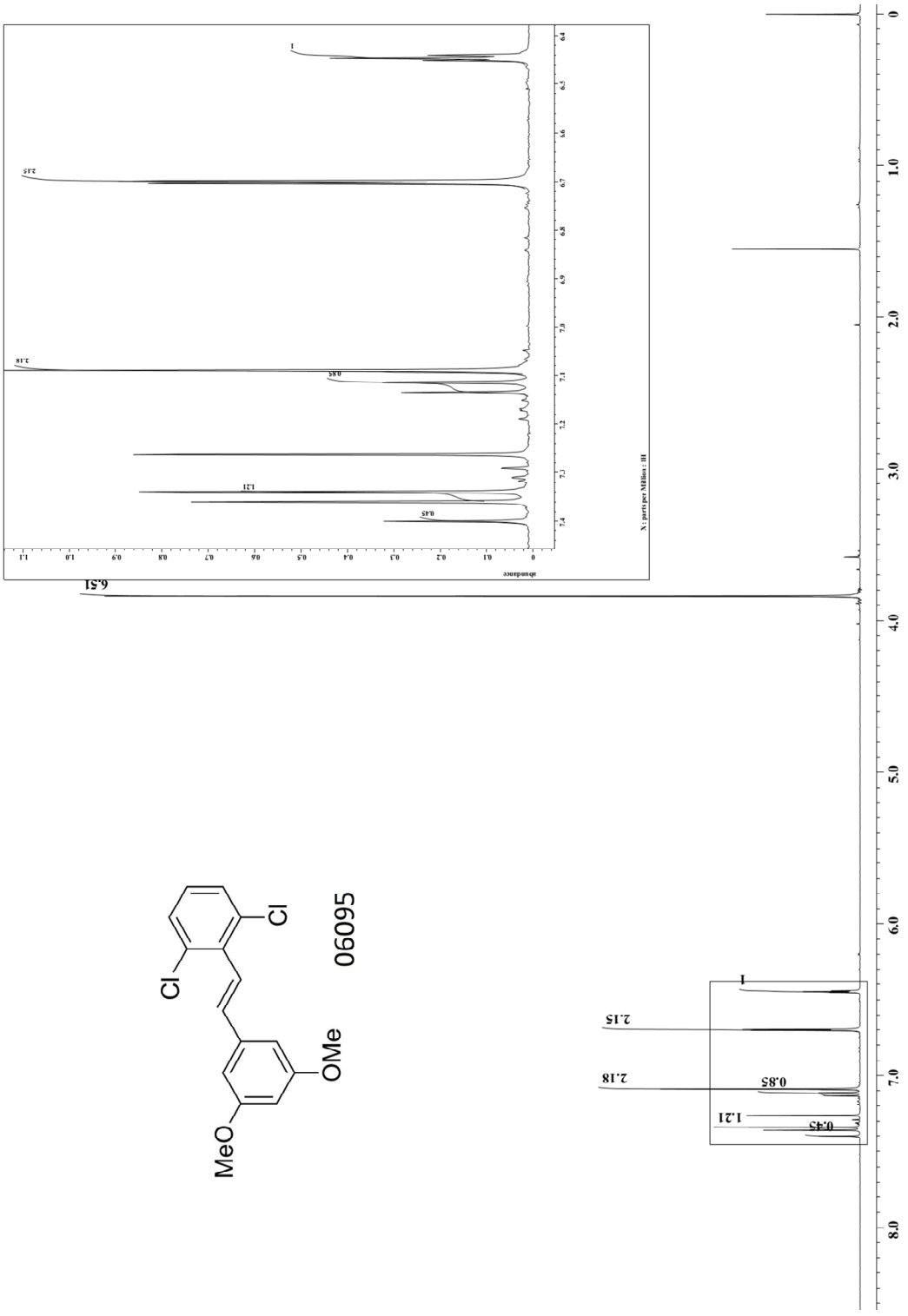
^{13}C-NMR Spectrum (500 MHz, $CDCl_3$)

(E)-3-(3,5-dimethoxystyryl)benzonitrile



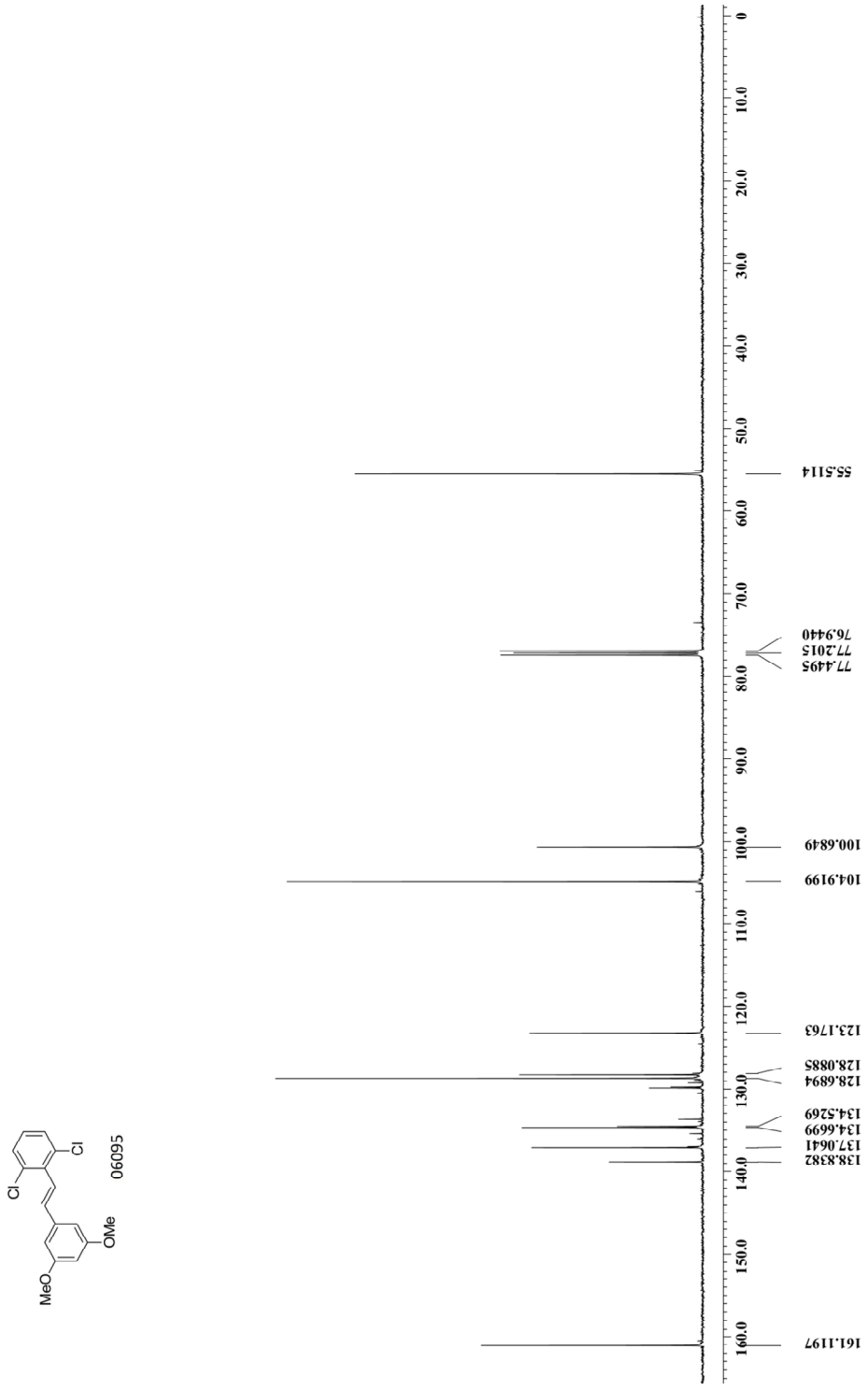
^{1}H-NMR Spectrum (500 MHz, $CDCl_3$)

(E)-1,3-dichloro-2-(3,5-dimethoxystyryl)benzene



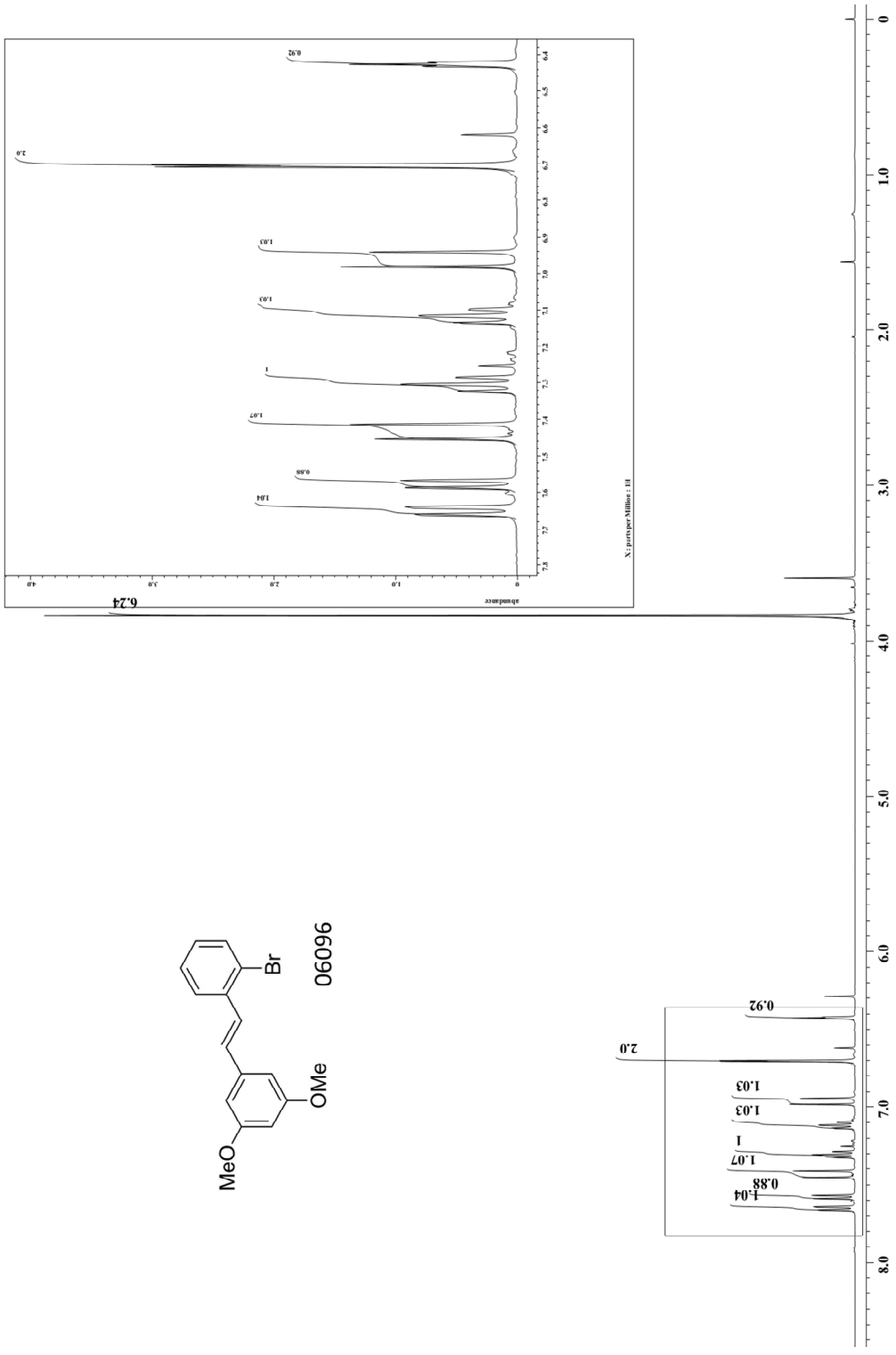
^{13}C-NMR Spectrum (500 MHz, $CDCl_3$)

(E)-1,3-dichloro-2-(3,5-dimethoxystyryl)benzene



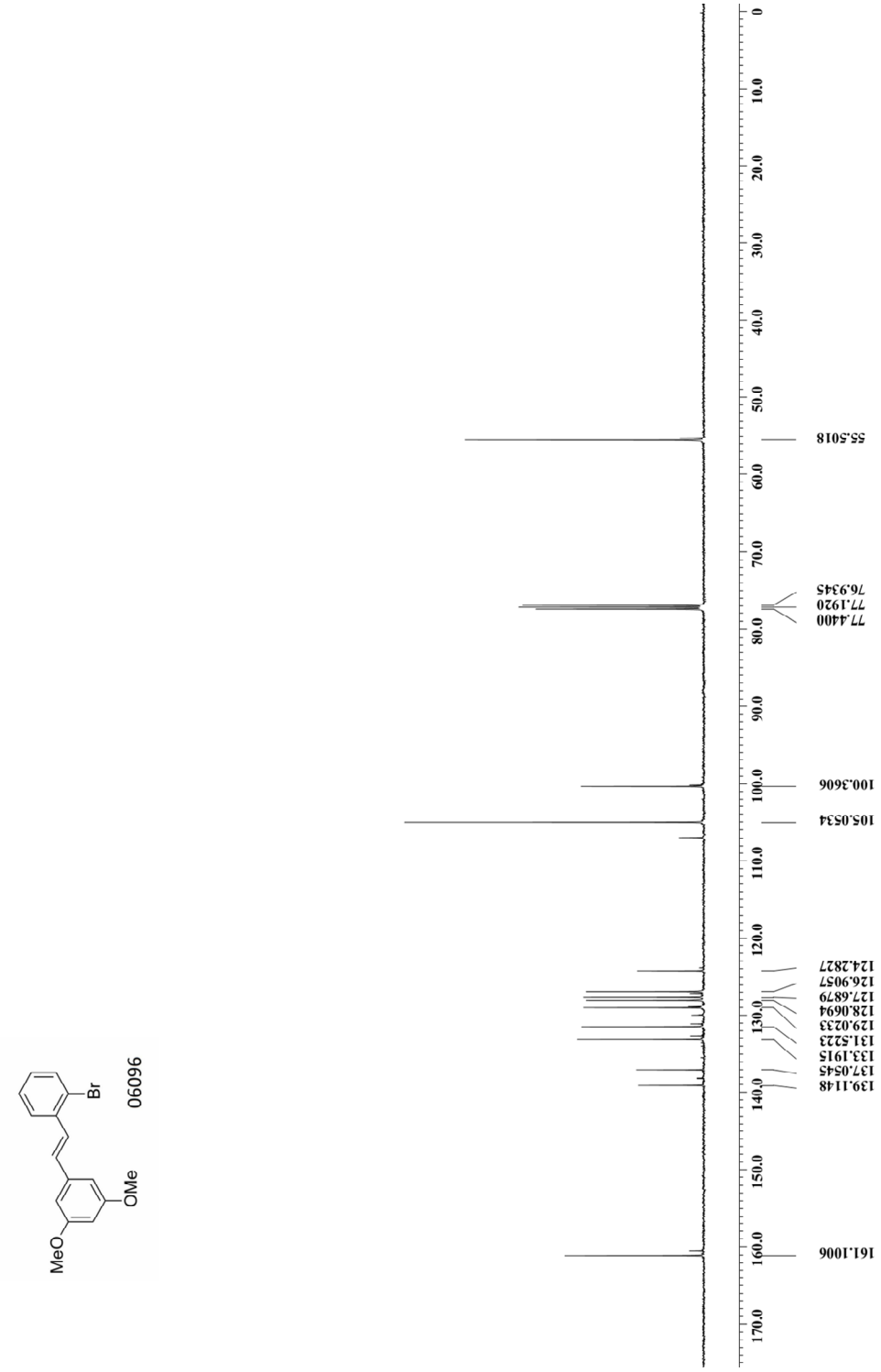
^{1}H-NMR Spectrum (500 MHz, $CDCl_3$)

(E)-1-(2-bromostyryl)-3,5-dimethoxybenzene



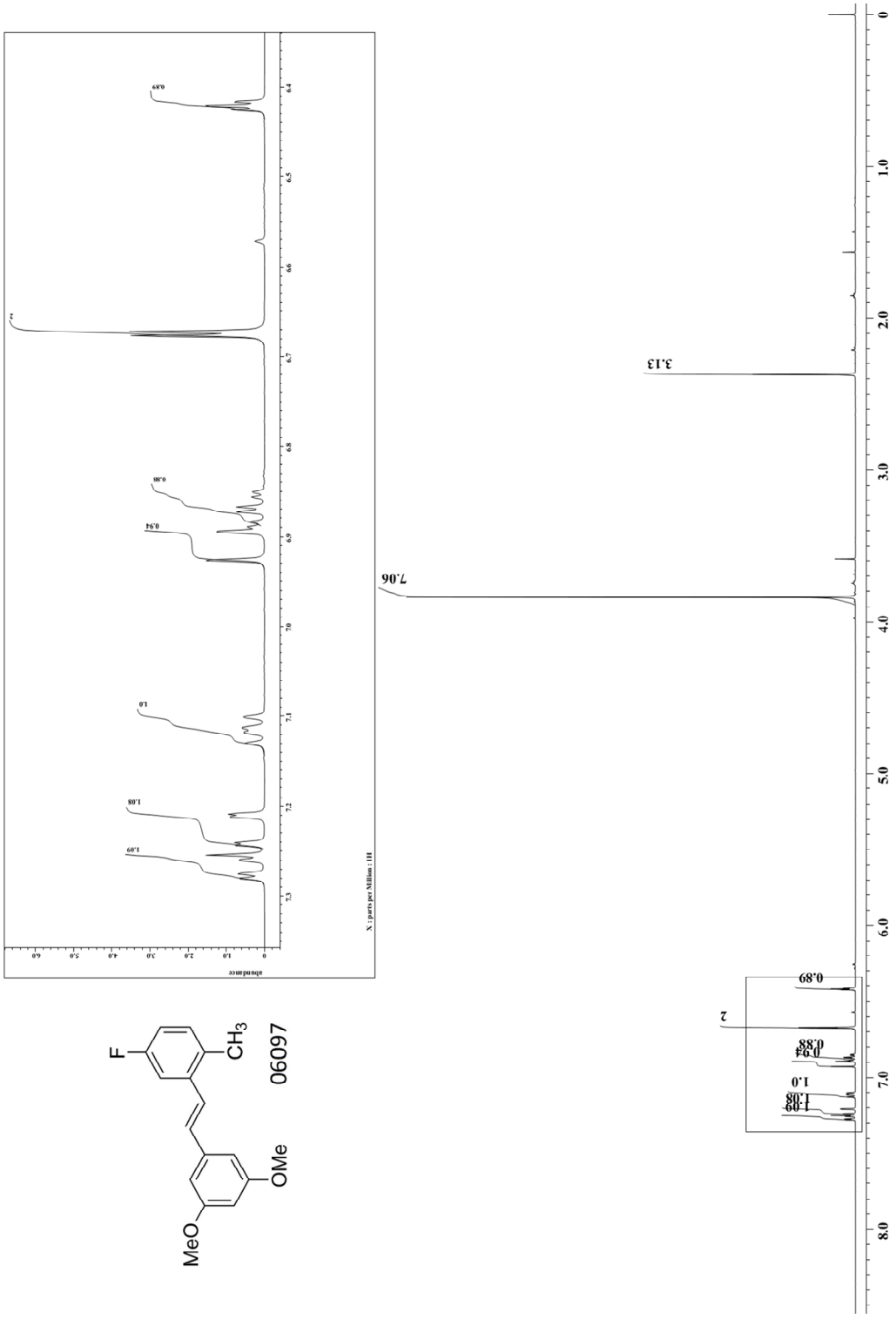
^{13}C-NMR Spectrum (500 MHz, $CDCl_3$)

(E)-1-(2-bromostyryl)-3,5-dimethoxybenzene



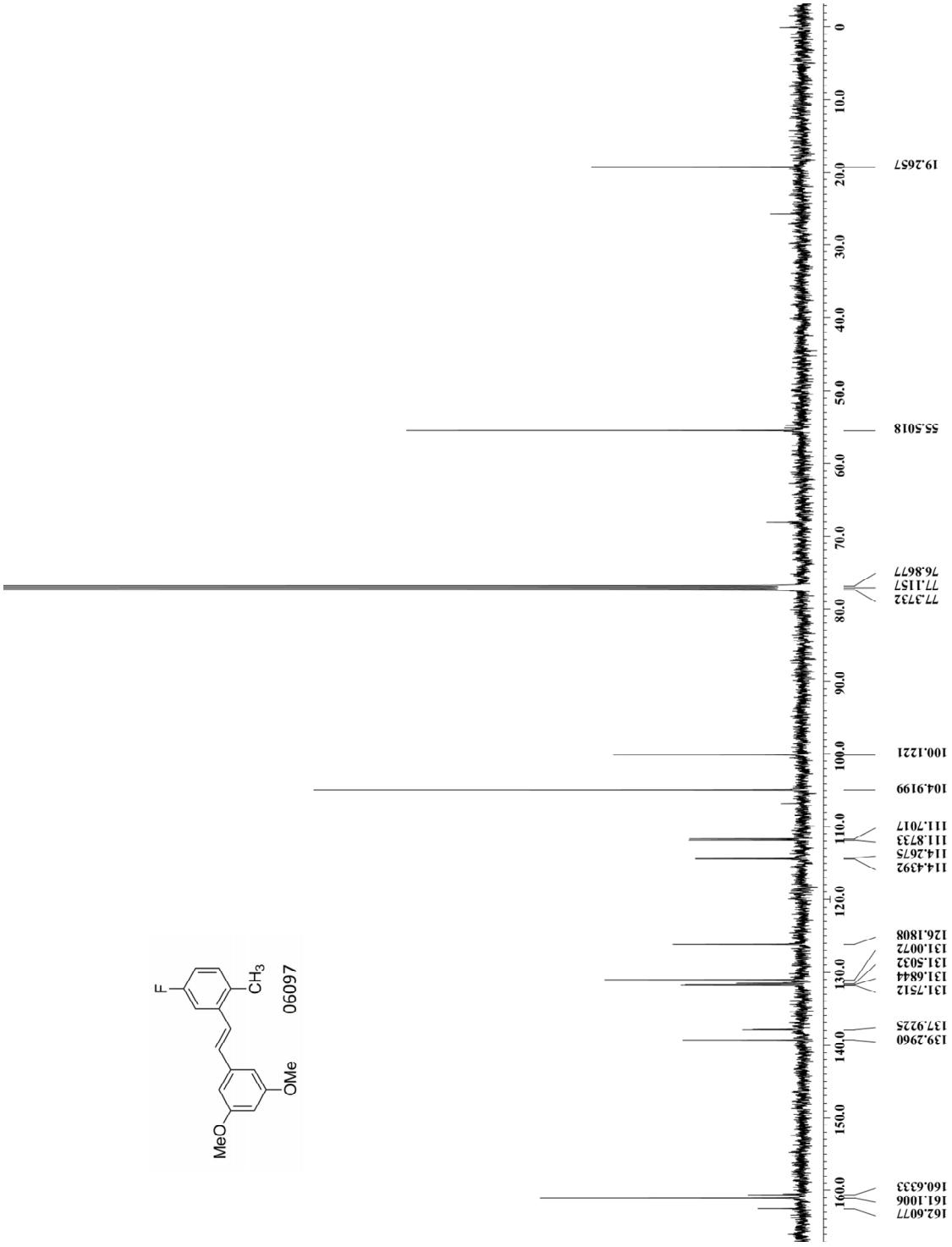
^{1}H-NMR Spectrum (500 MHz, $CDCl_3$)

(E)-2-(3,5-dimethoxystyryl)-4-fluoro-1-methylbenzene



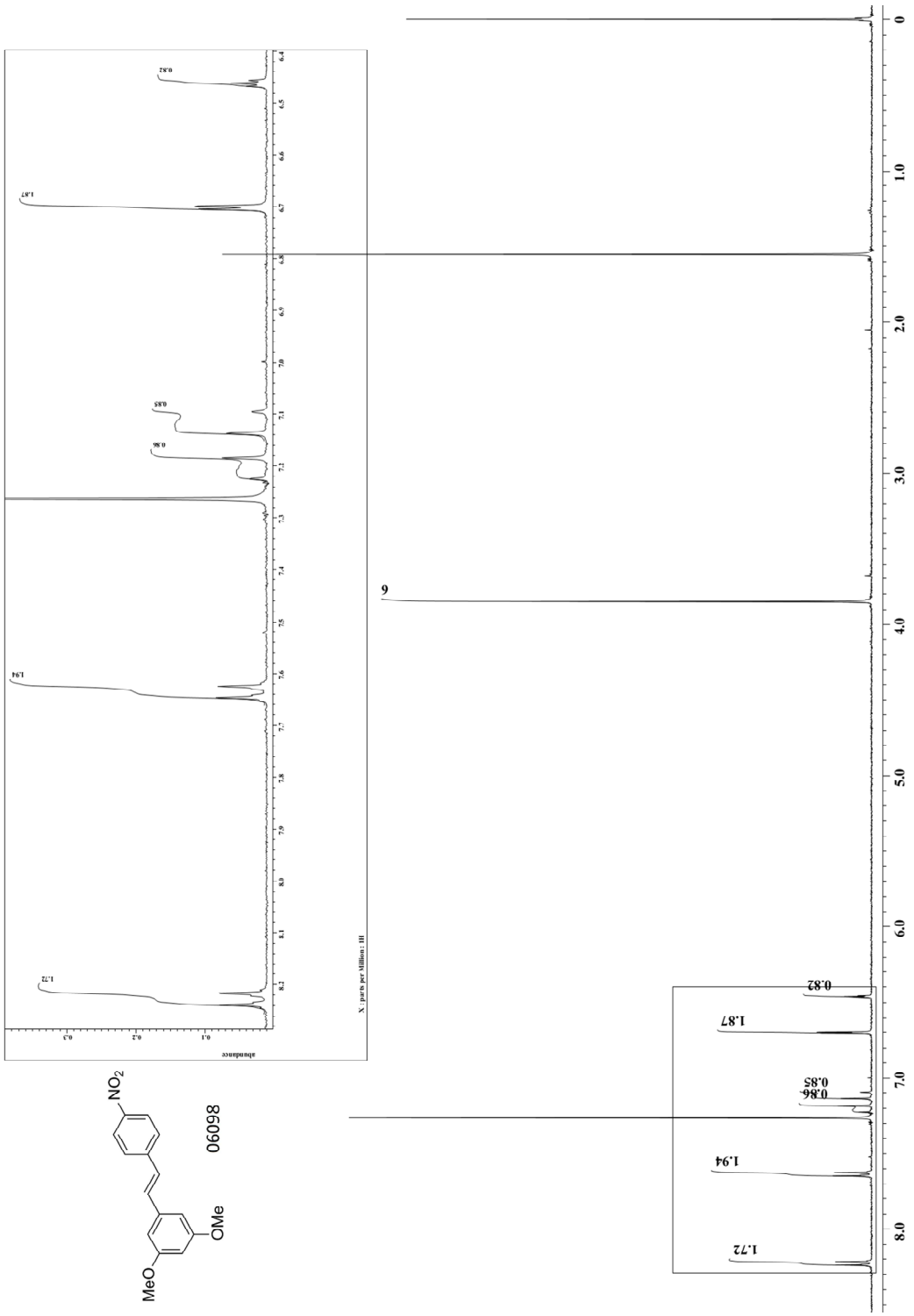
^{13}C-NMR Spectrum (500 MHz, $CDCl_3$)

(E)-2-(3,5-dimethoxystyryl)-4-fluoro-1-methylbenzene



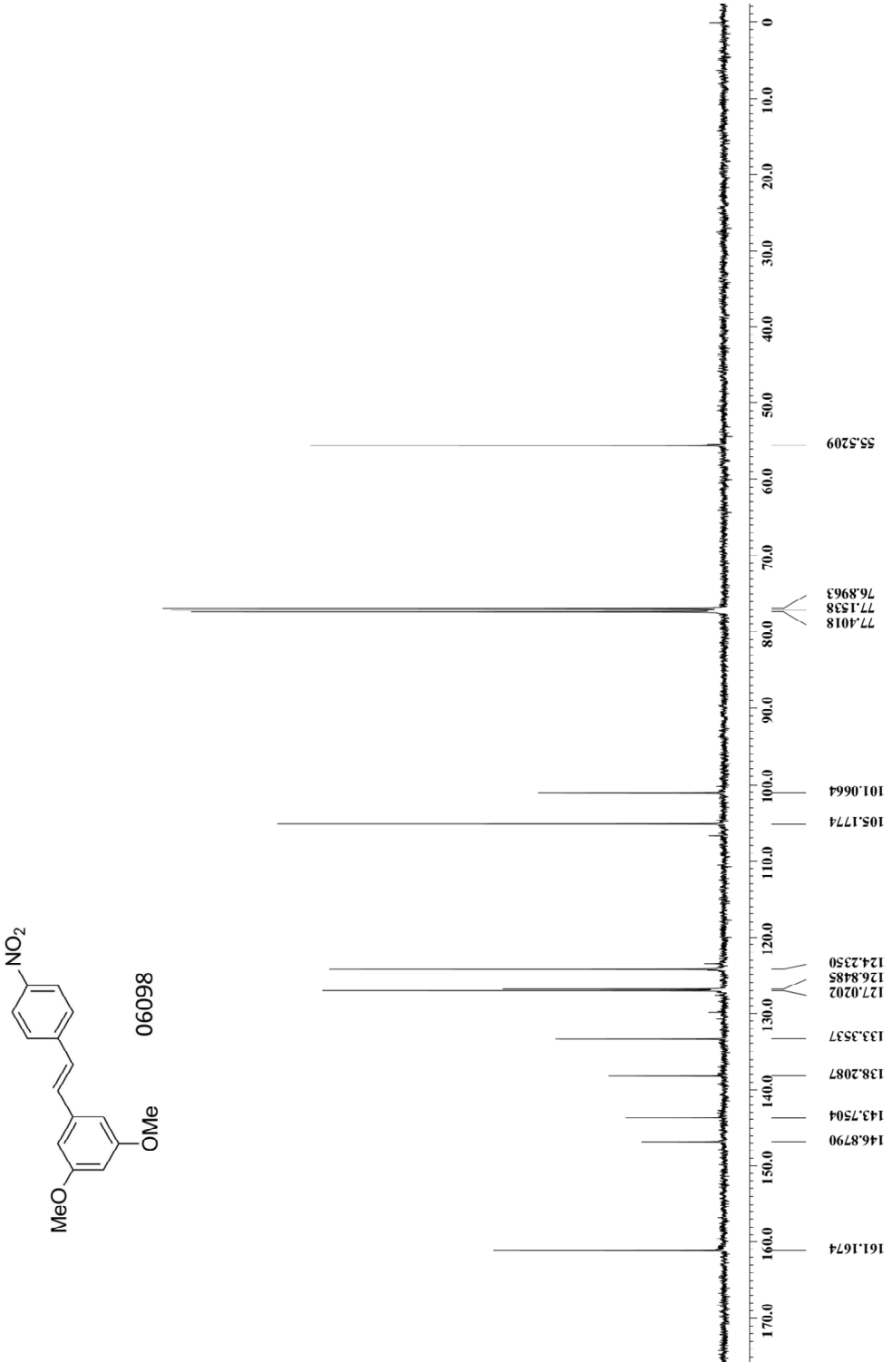
^{1}H-NMR Spectrum (500 MHz, $CDCl_3$)

(E)-1,3-dimethoxy-5-(4-nitrostyryl)benzene



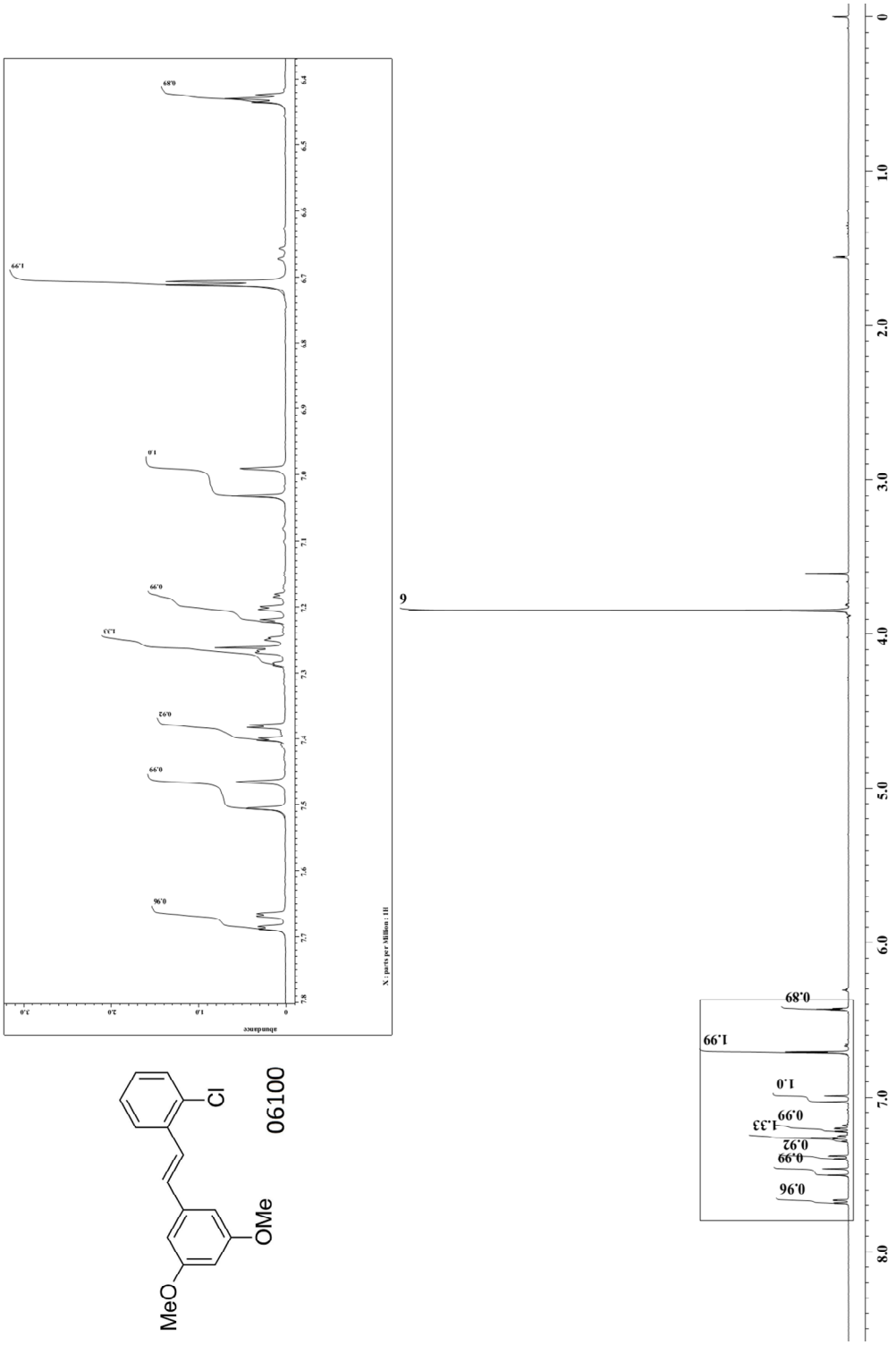
^{13}C-NMR Spectrum (500 MHz, $CDCl_3$)

(E)-1,3-dimethoxy-5-(4-nitrostyryl)benzene



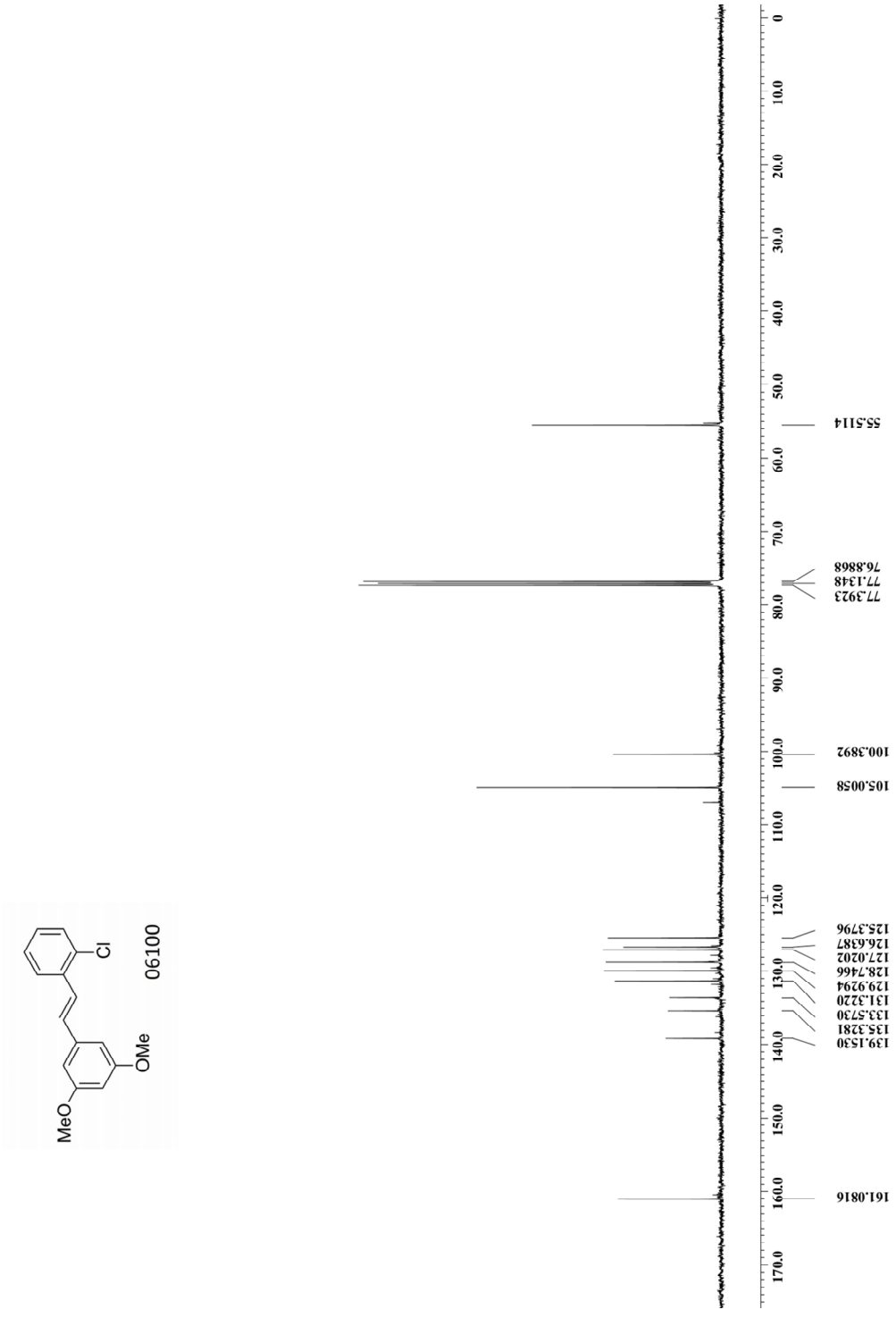
^{1}H-NMR Spectrum (500 MHz, $CDCl_3$)

(E)-1-(2-chlorostyryl)-3,5-dimethoxybenzene



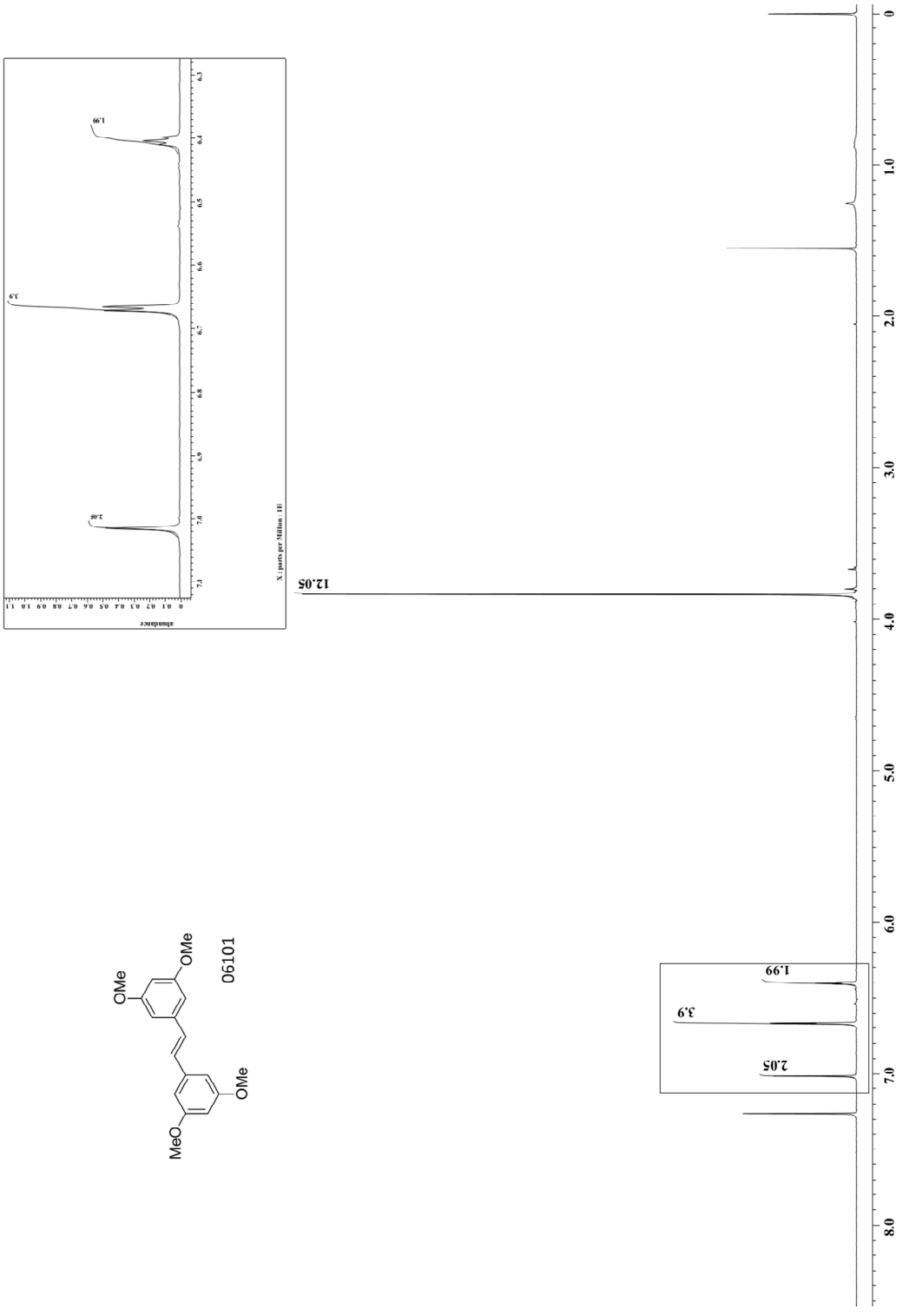
^{13}C-NMR Spectrum (500 MHz, $CDCl_3$)

(E)-1-(2-chlorostyryl)-3,5-dimethoxybenzene



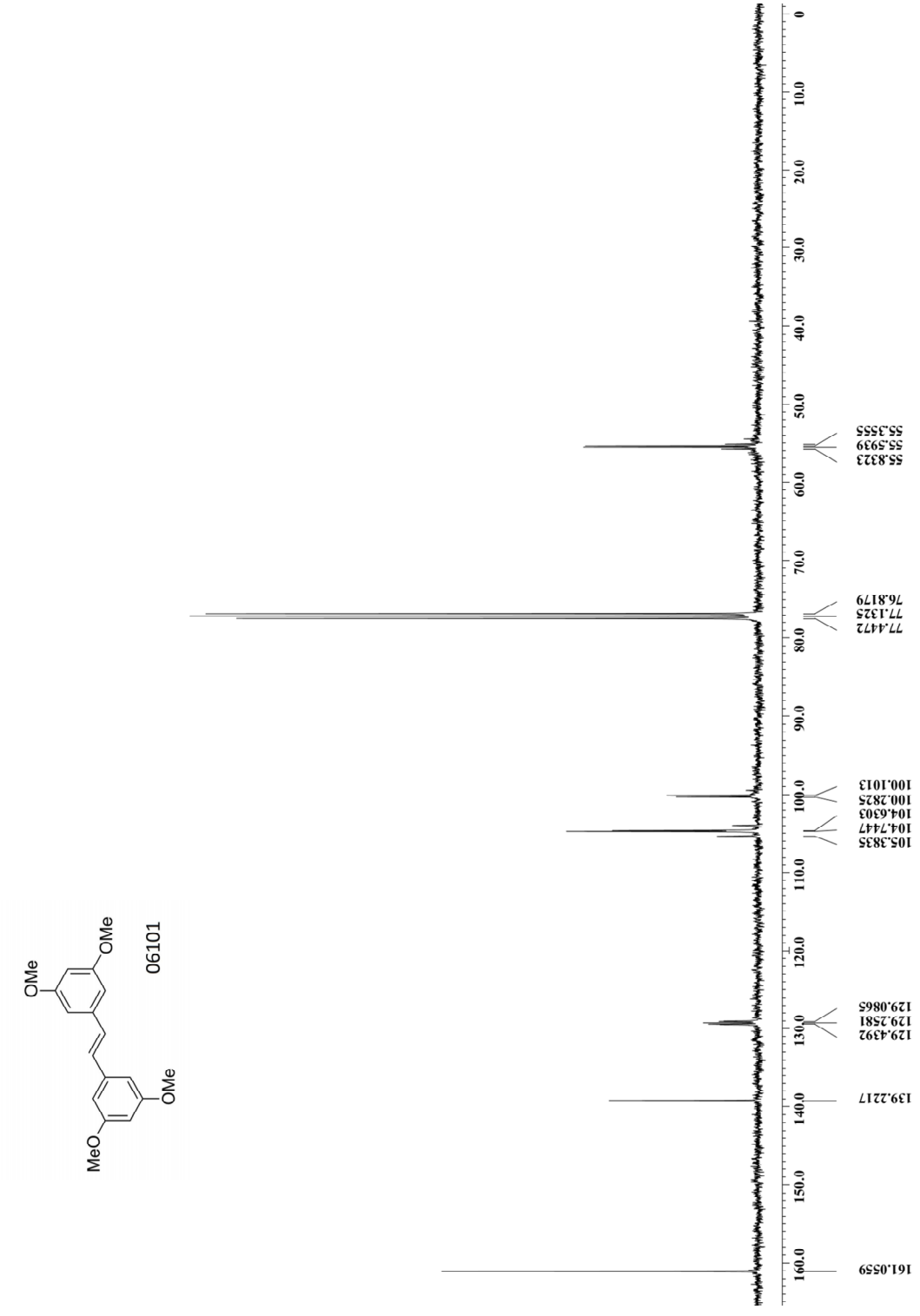
^{1}H-NMR Spectrum (500 MHz, $CDCl_3$)

(E)-1,2-bis(3,5-dimethoxyphenyl)ethane



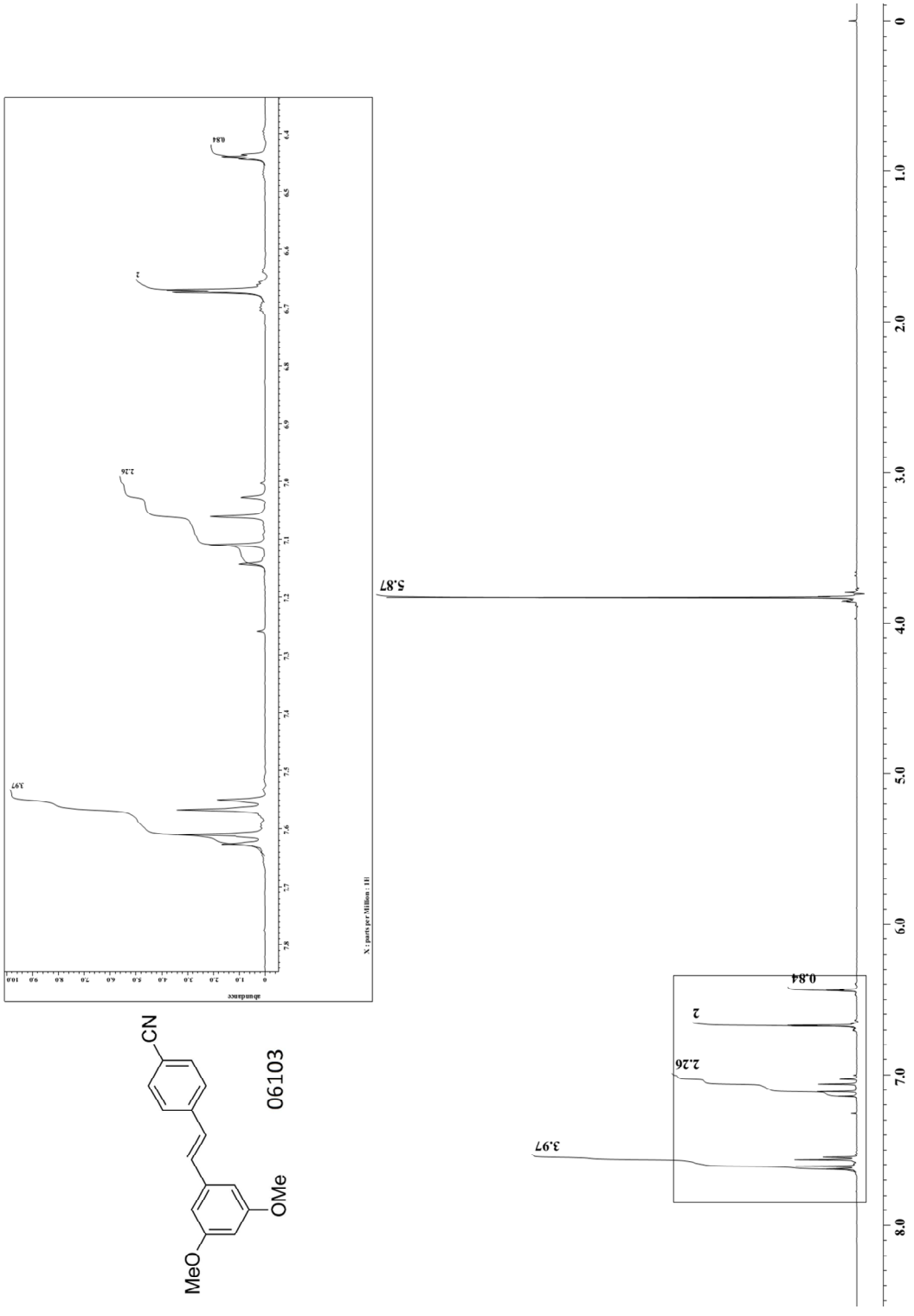
^{13}C-NMR Spectrum (500 MHz, $CDCl_3$)

(E)-1,2-bis(3,5-dimethoxyphenyl)ethane



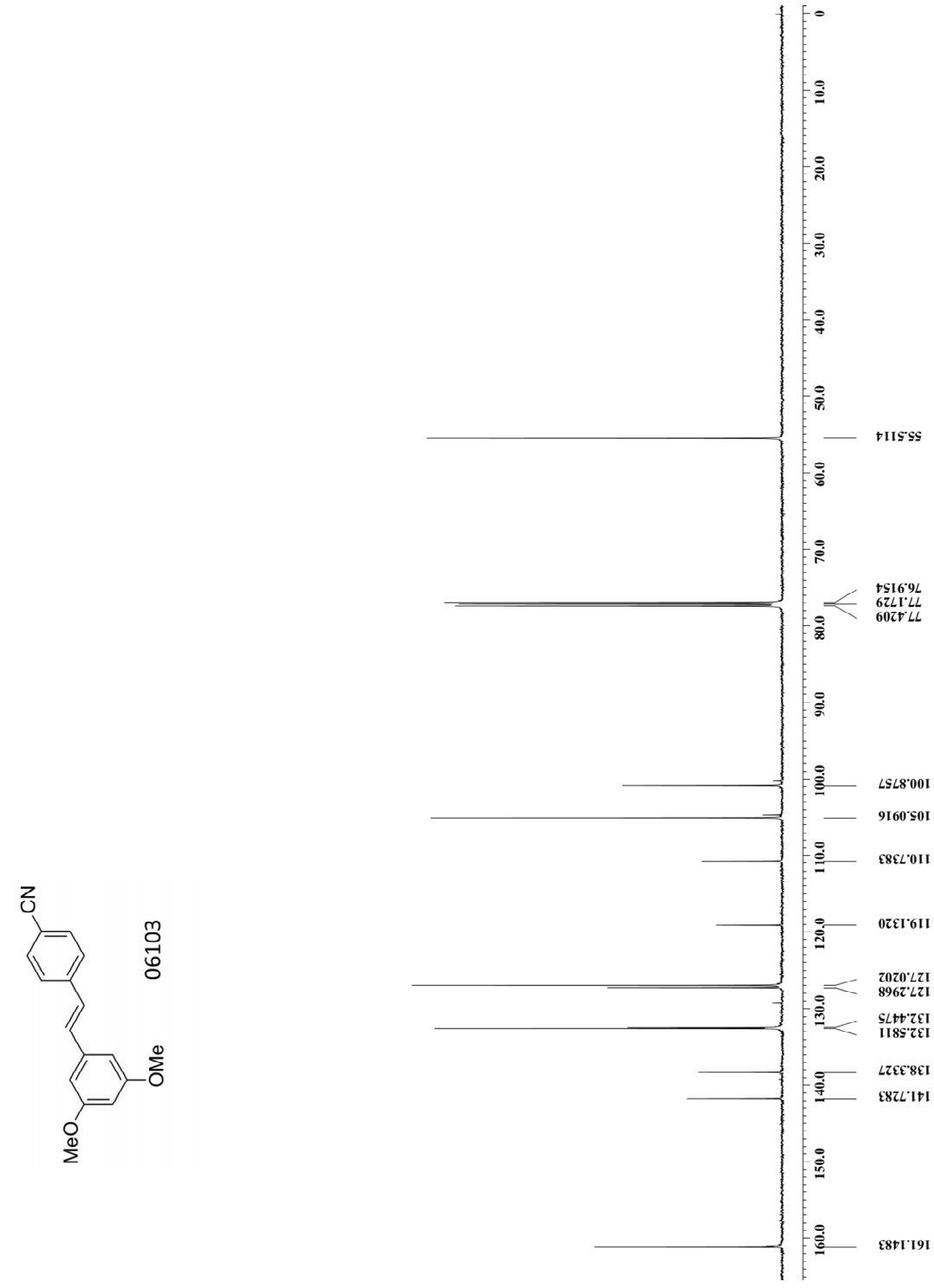
^{1}H-NMR Spectrum (500 MHz, $CDCl_3$)

(E)-4-(3,5-dimethoxystyryl)benzonitrile



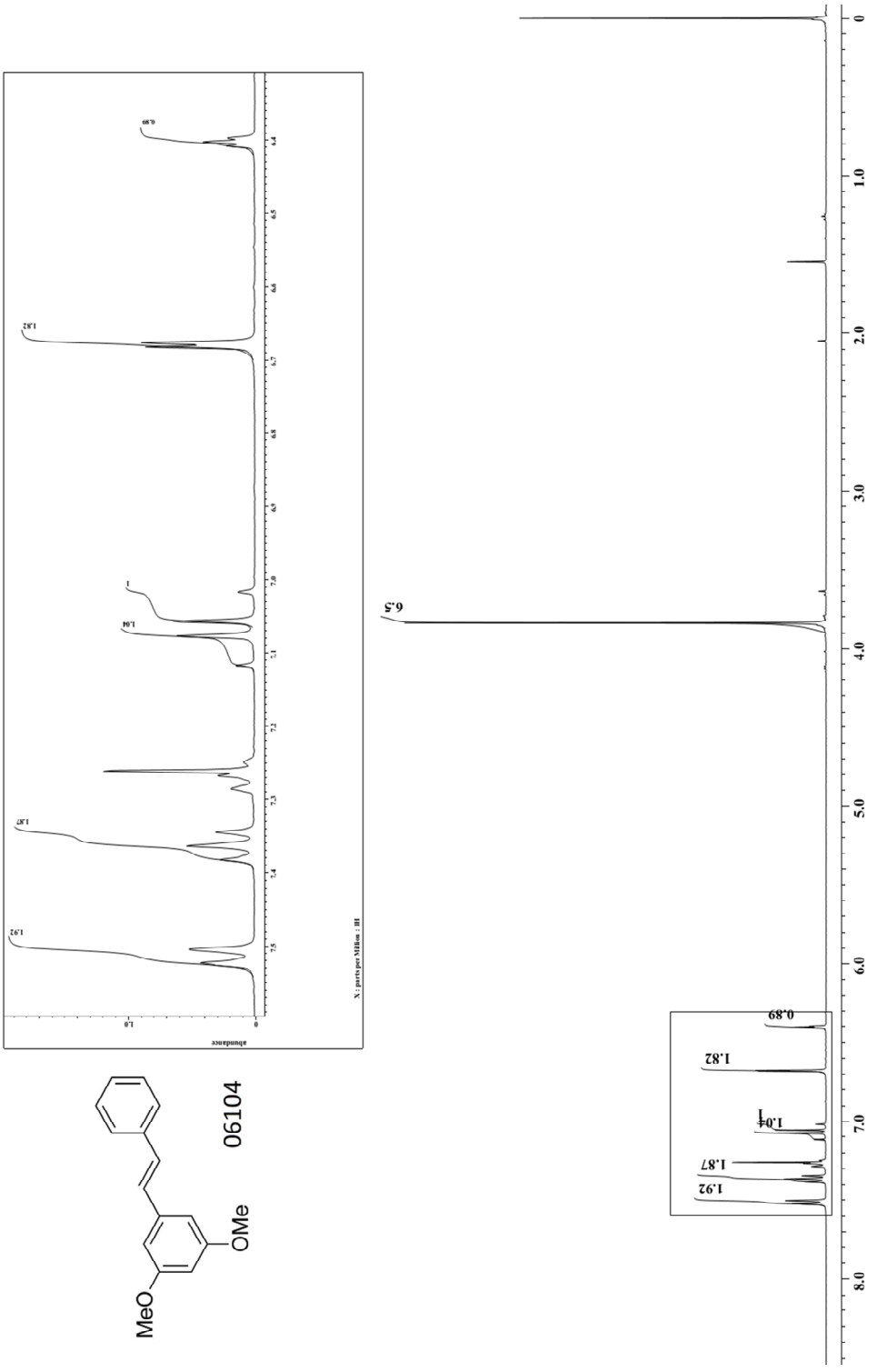
^{13}C-NMR Spectrum (500 MHz, $CDCl_3$)

(E)-4-(3,5-dimethoxystyryl)benzonitrile



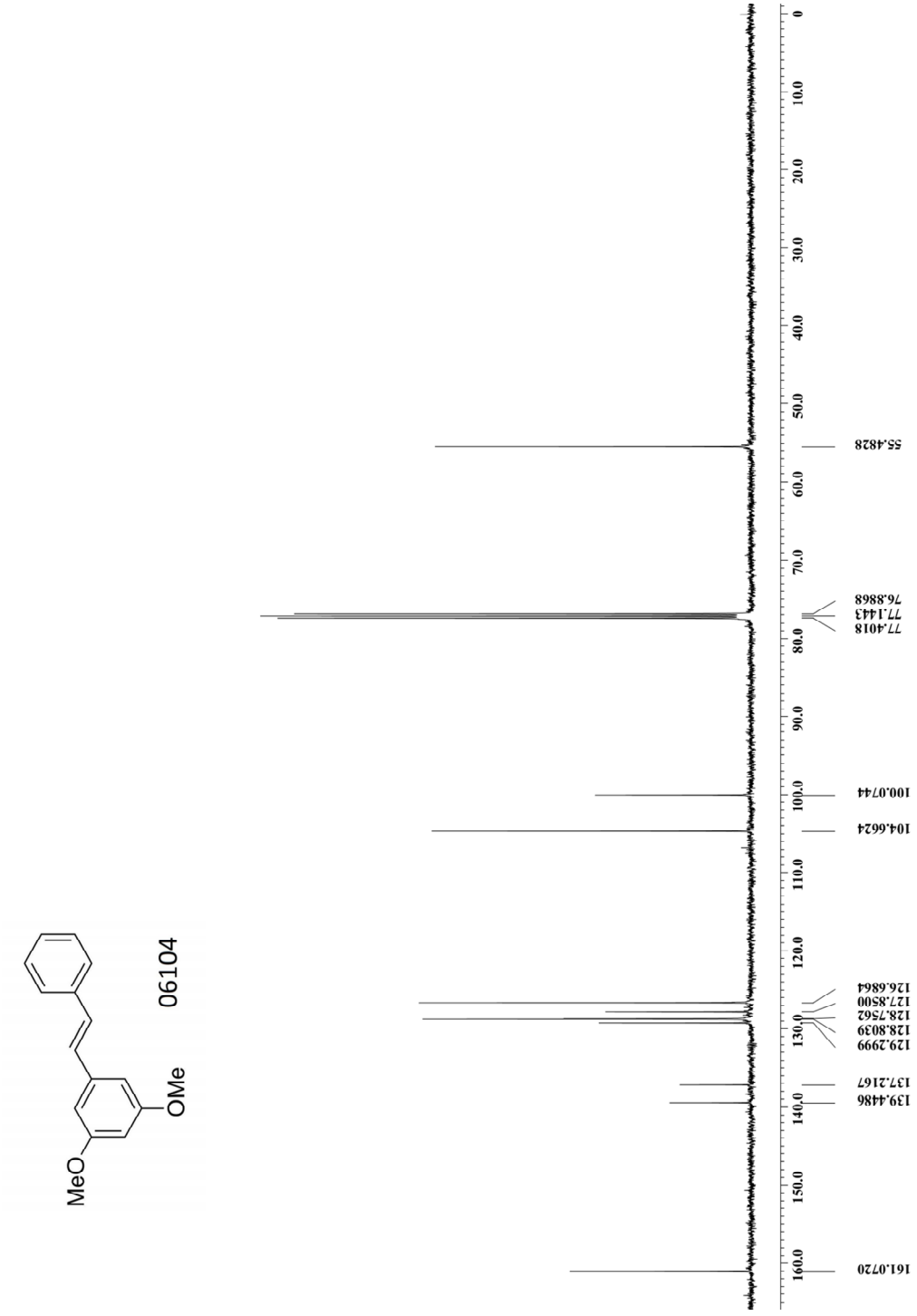
^{1}H-NMR Spectrum (500 MHz, $CDCl_3$)

(E)-1,3-dimethoxy-5-styrylbenzene



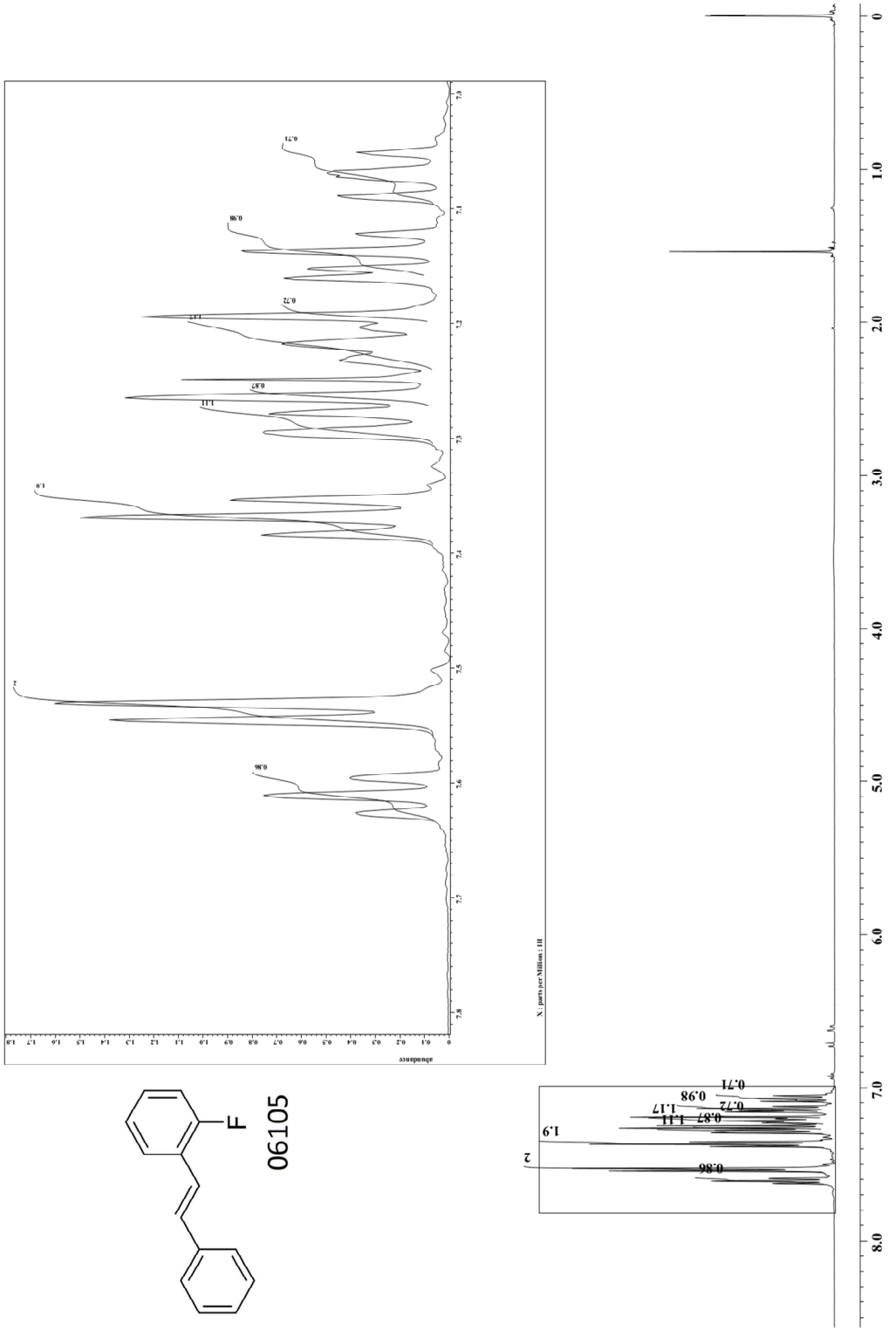
^{13}C-NMR Spectrum (500 MHz, $CDCl_3$)

(E)-1,3-dimethoxy-5-styrylbenzene



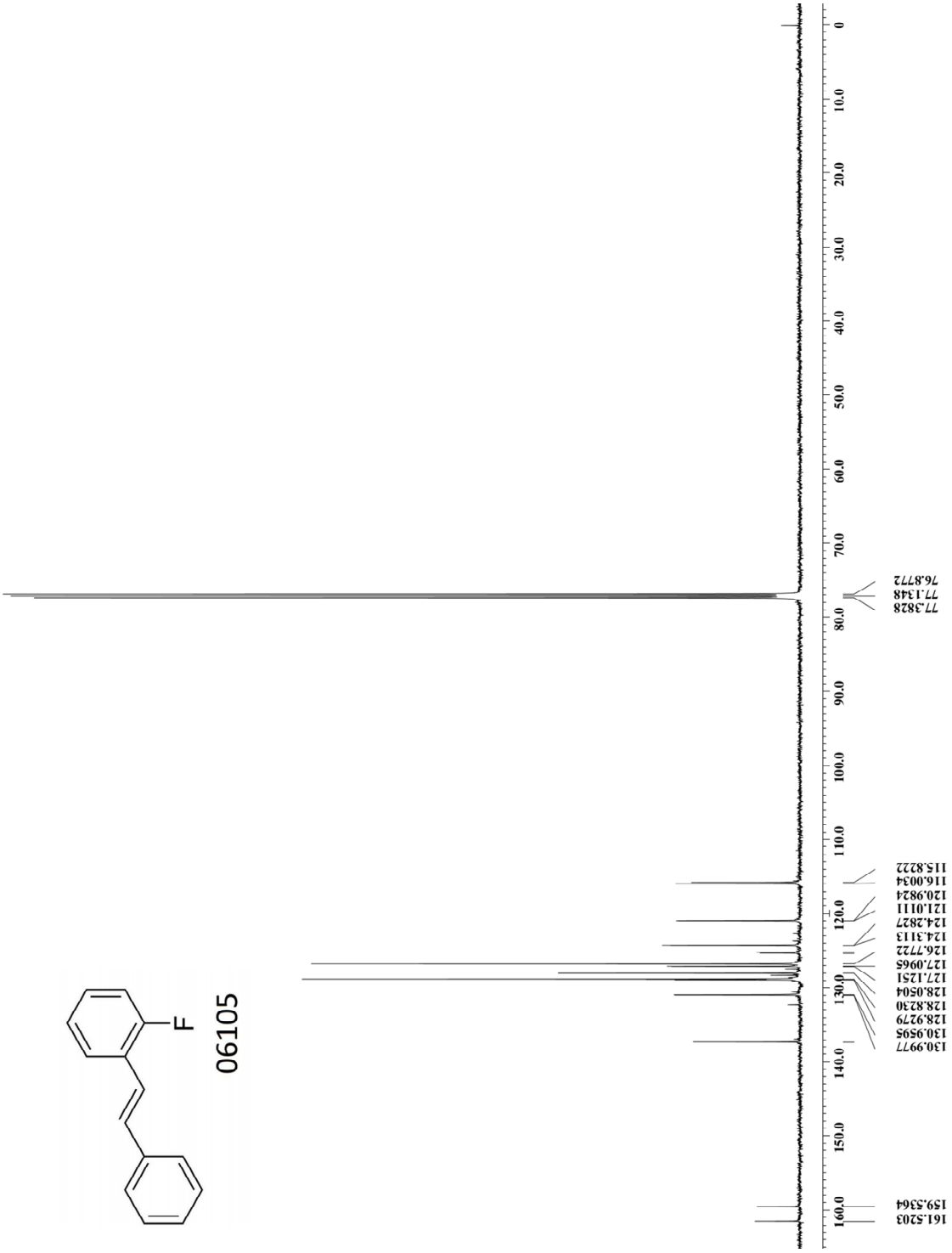
^{1}H-NMR Spectrum (500 MHz, $CDCl_3$)

(E)-1-fluoro-2-styrylbenzene



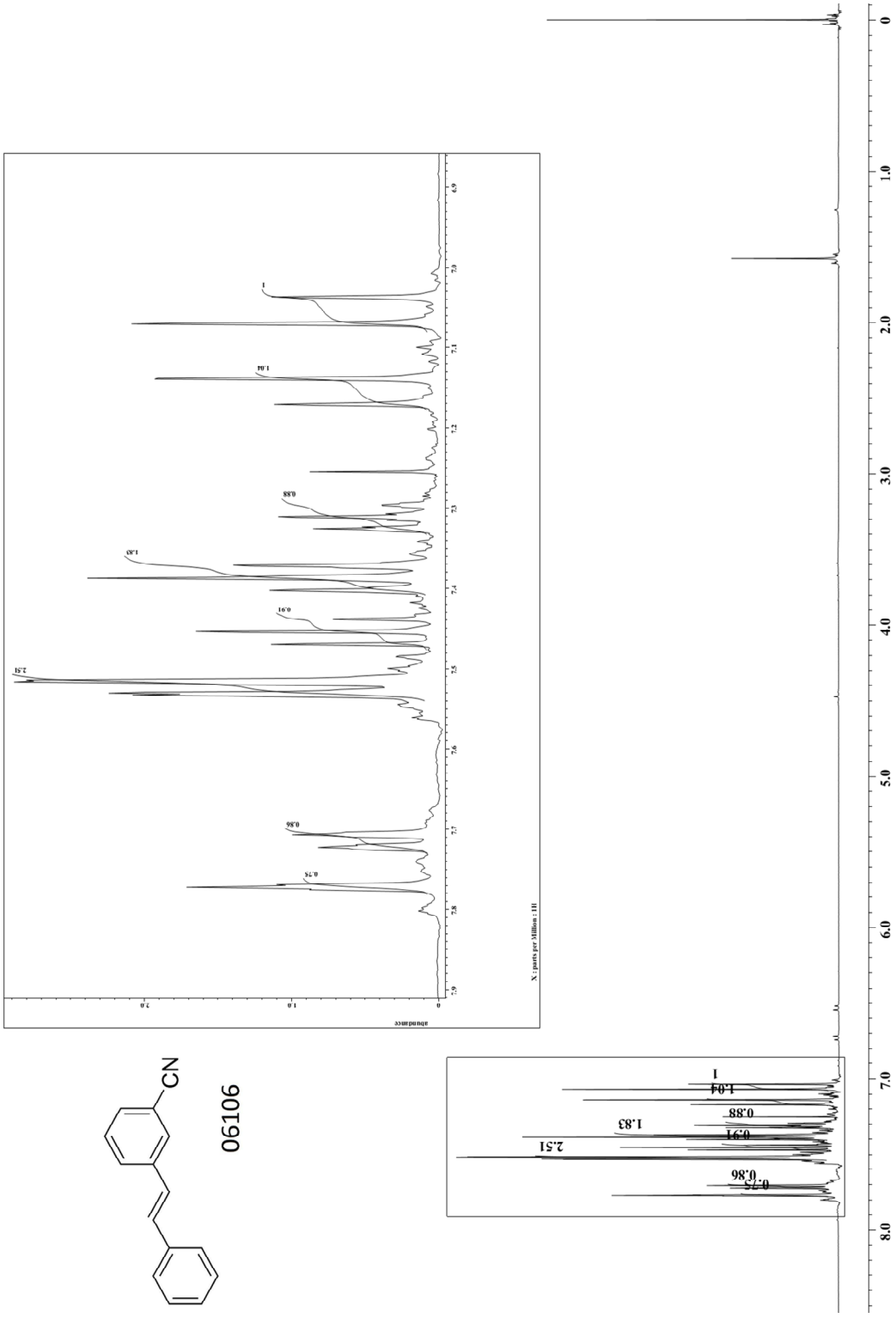
^{13}C-NMR Spectrum (500 MHz, $CDCl_3$)

(E)-1-fluoro-2-styrylbenzene



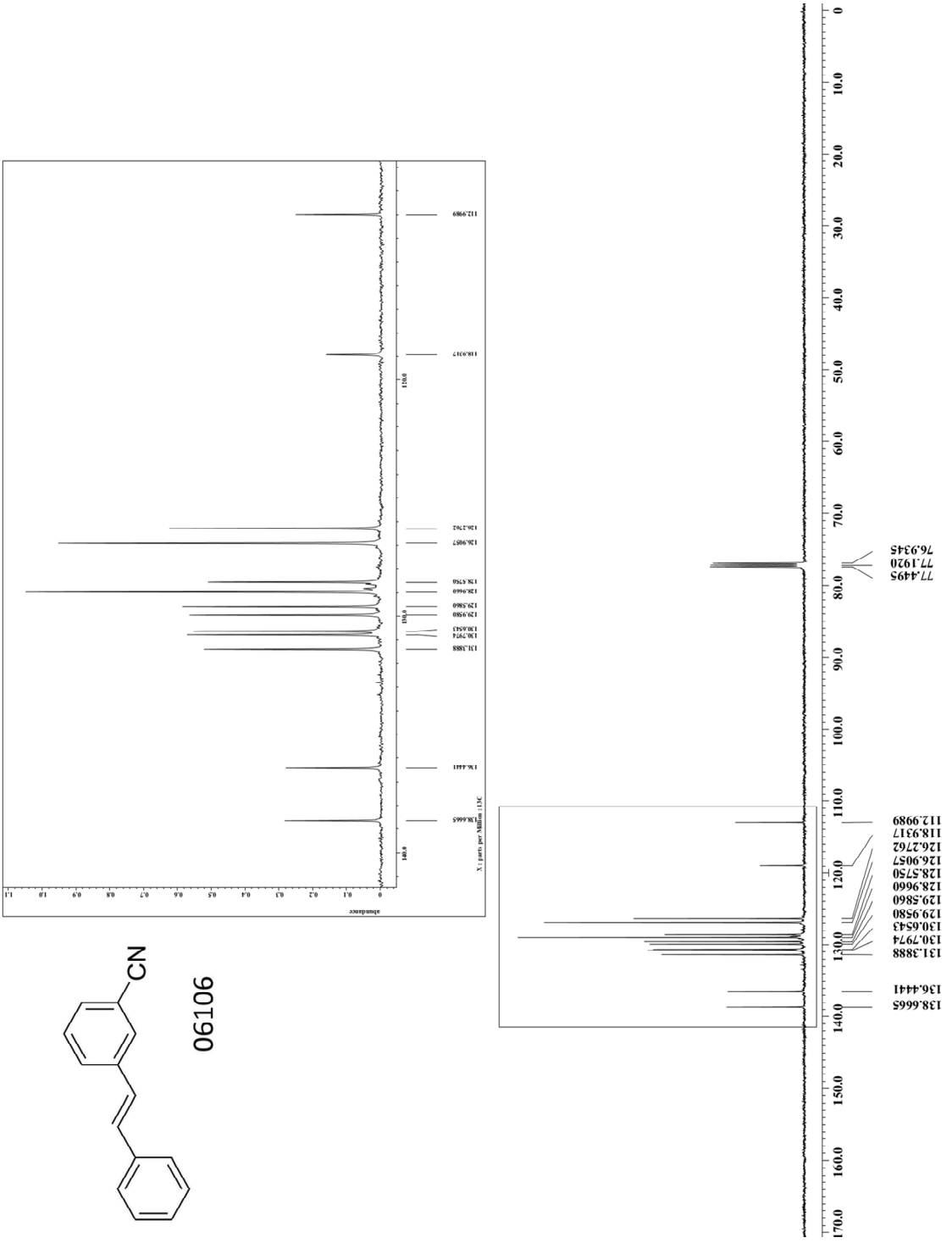
^{1}H-NMR Spectrum (500 MHz, $CDCl_3$)

(E)-3-styrylbenzonitrile



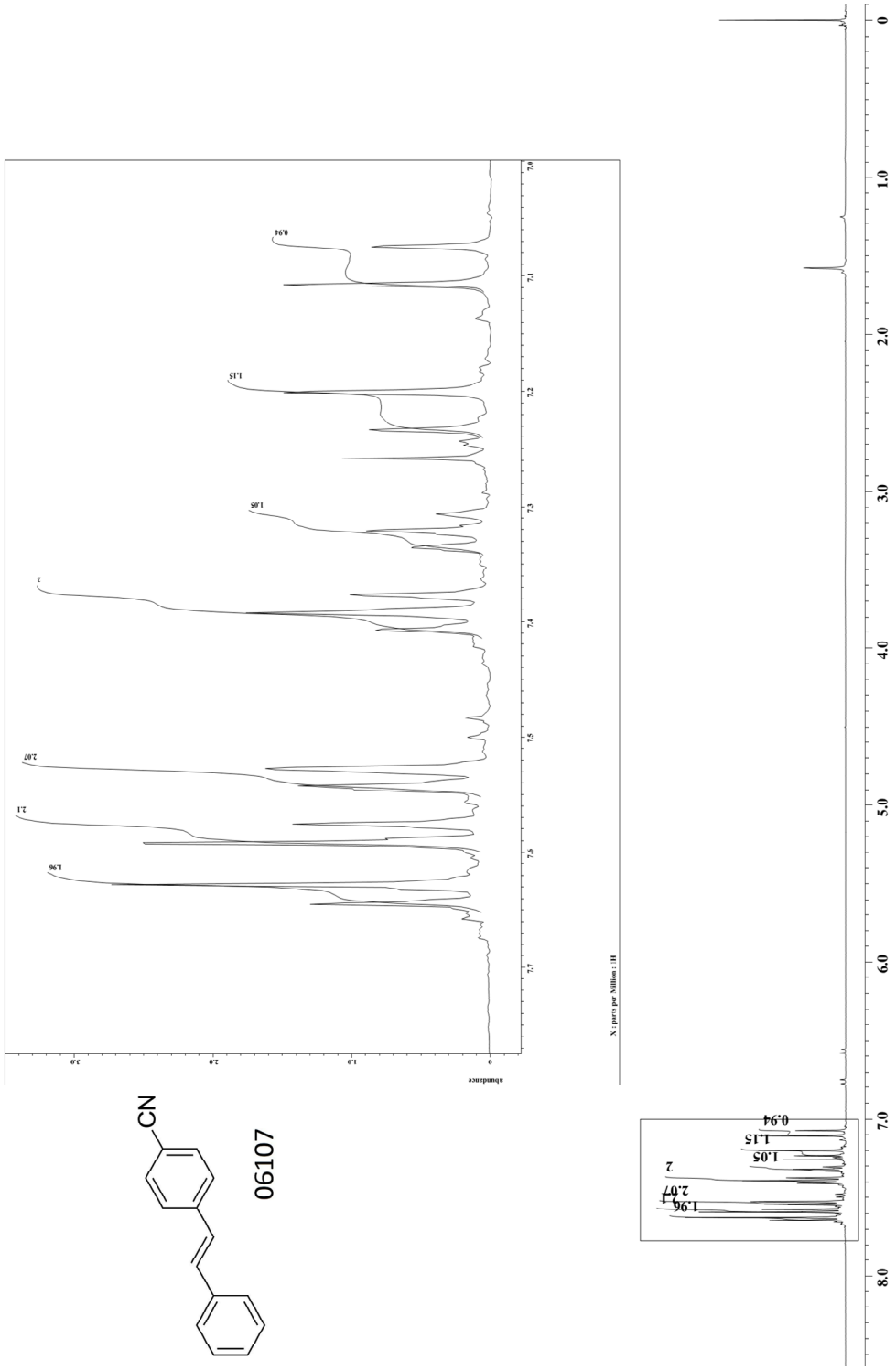
^{13}C-NMR Spectrum (500 MHz, $CDCl_3$)

(E)-3-styrylbenzonitrile



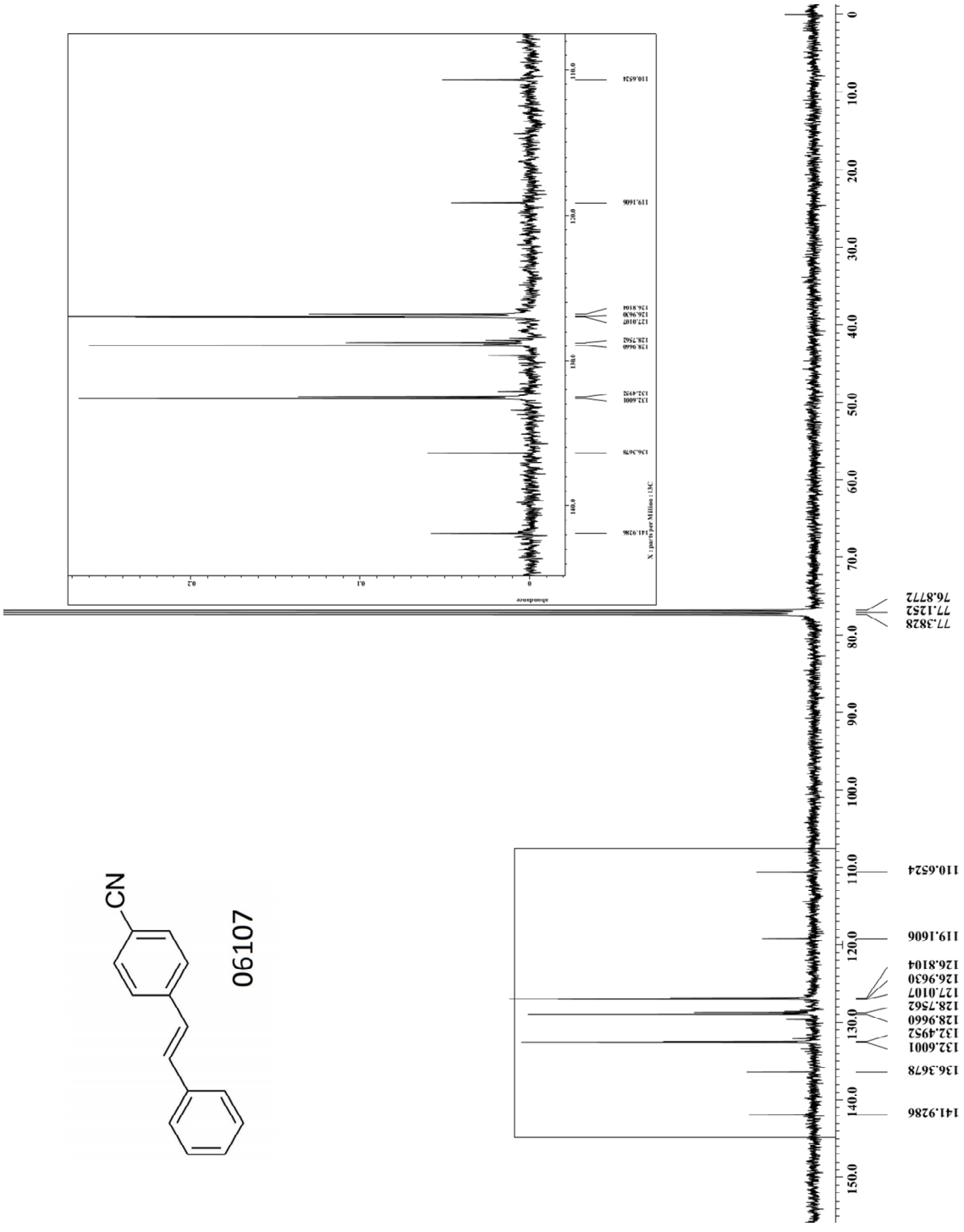
^{1}H-NMR Spectrum (500 MHz, $CDCl_3$)

(E)-4-styrylbenzonitrile



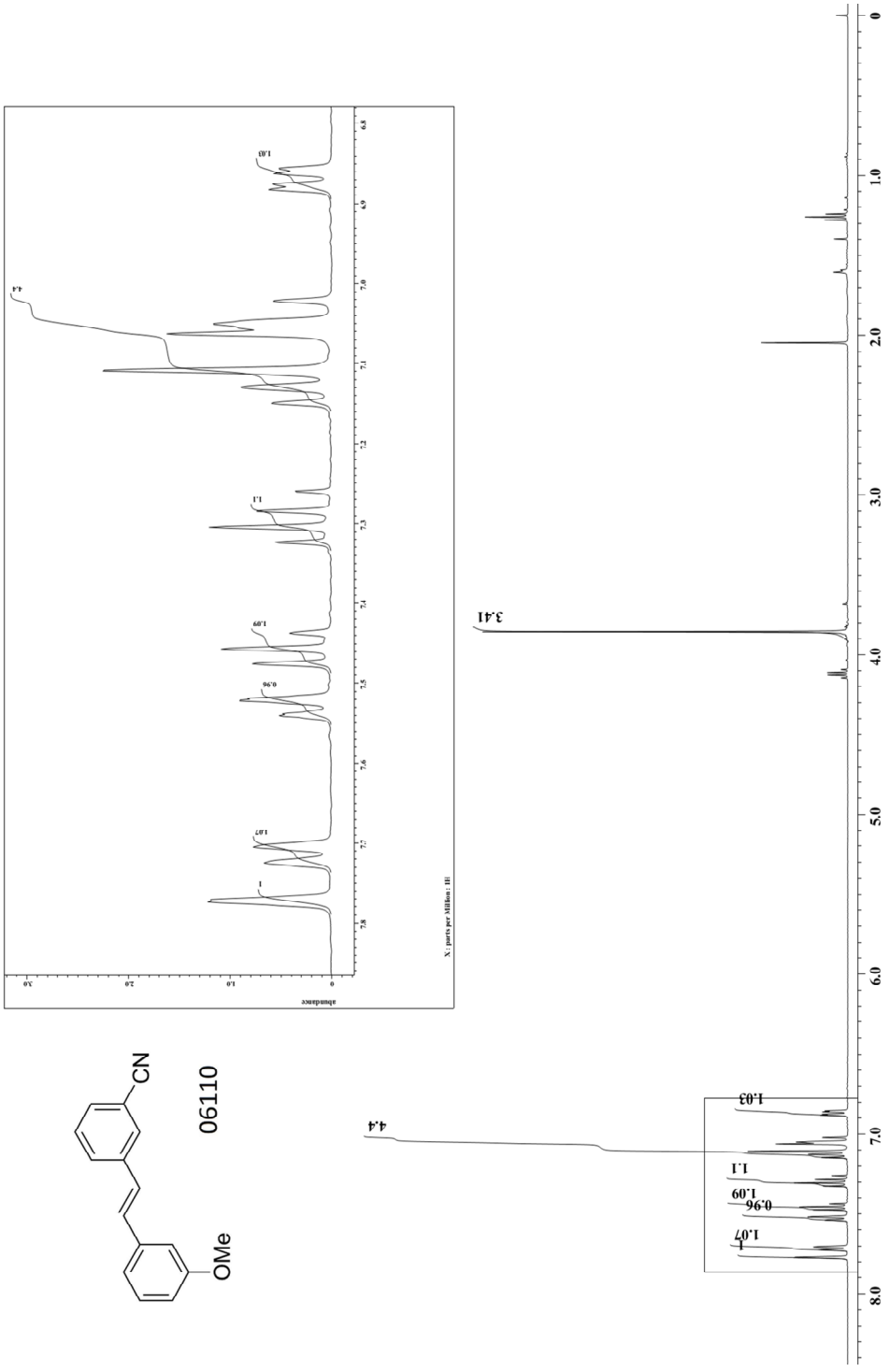
^{13}C-NMR Spectrum (500 MHz, $CDCl_3$)

(E)-4-styrylbenzonitrile



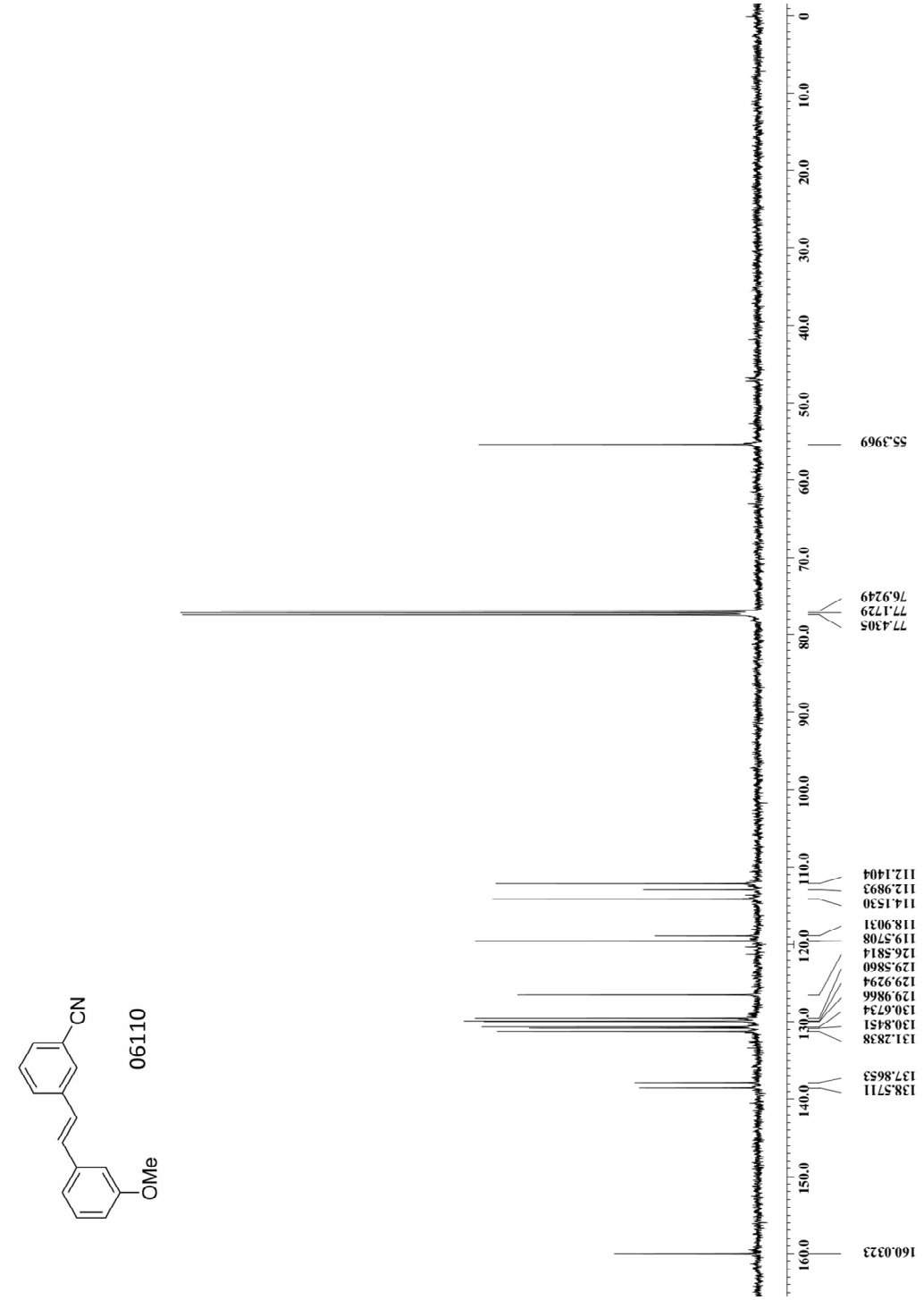
^{1}H-NMR Spectrum (500 MHz, $CDCl_3$)

(E)-3-(3-methoxystyryl)benzonitrile



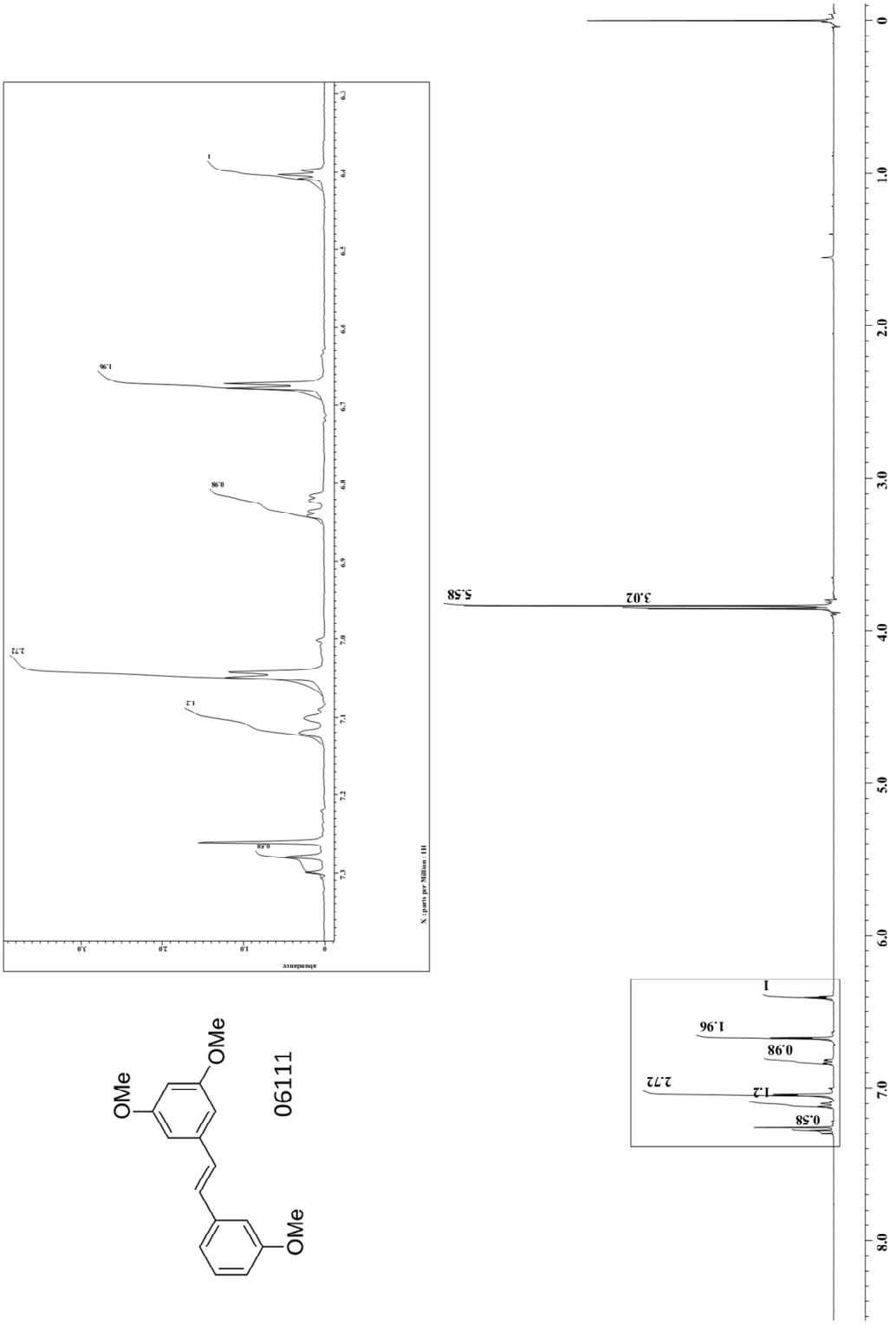
^{13}C-NMR Spectrum (500 MHz, $CDCl_3$)

(E)-3-(3-methoxystyryl)benzonitrile



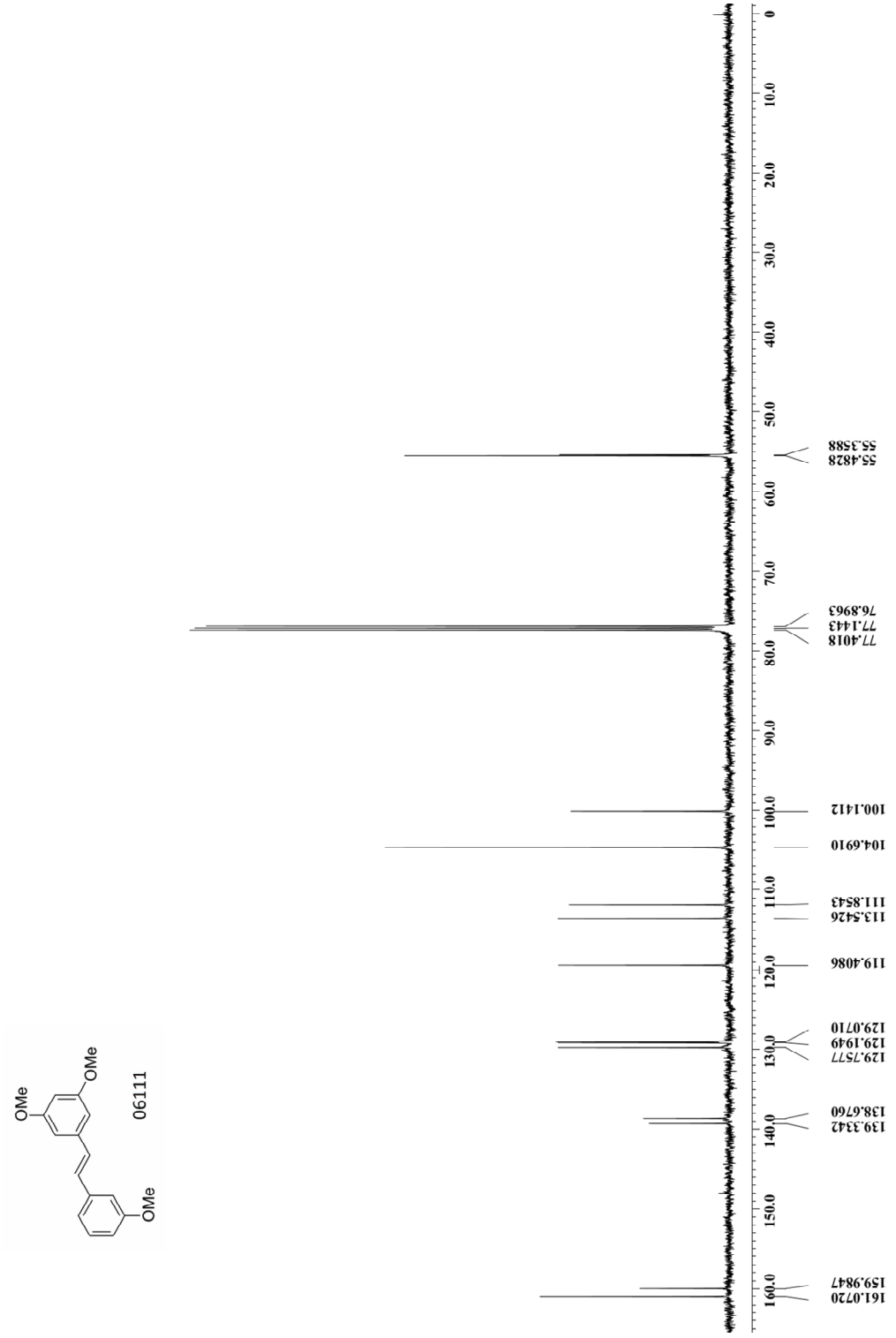
^{1}H-NMR Spectrum (500 MHz, $CDCl_3$)

(E)-1,3-dimethoxy-5-(3-methoxystyryl)benzene



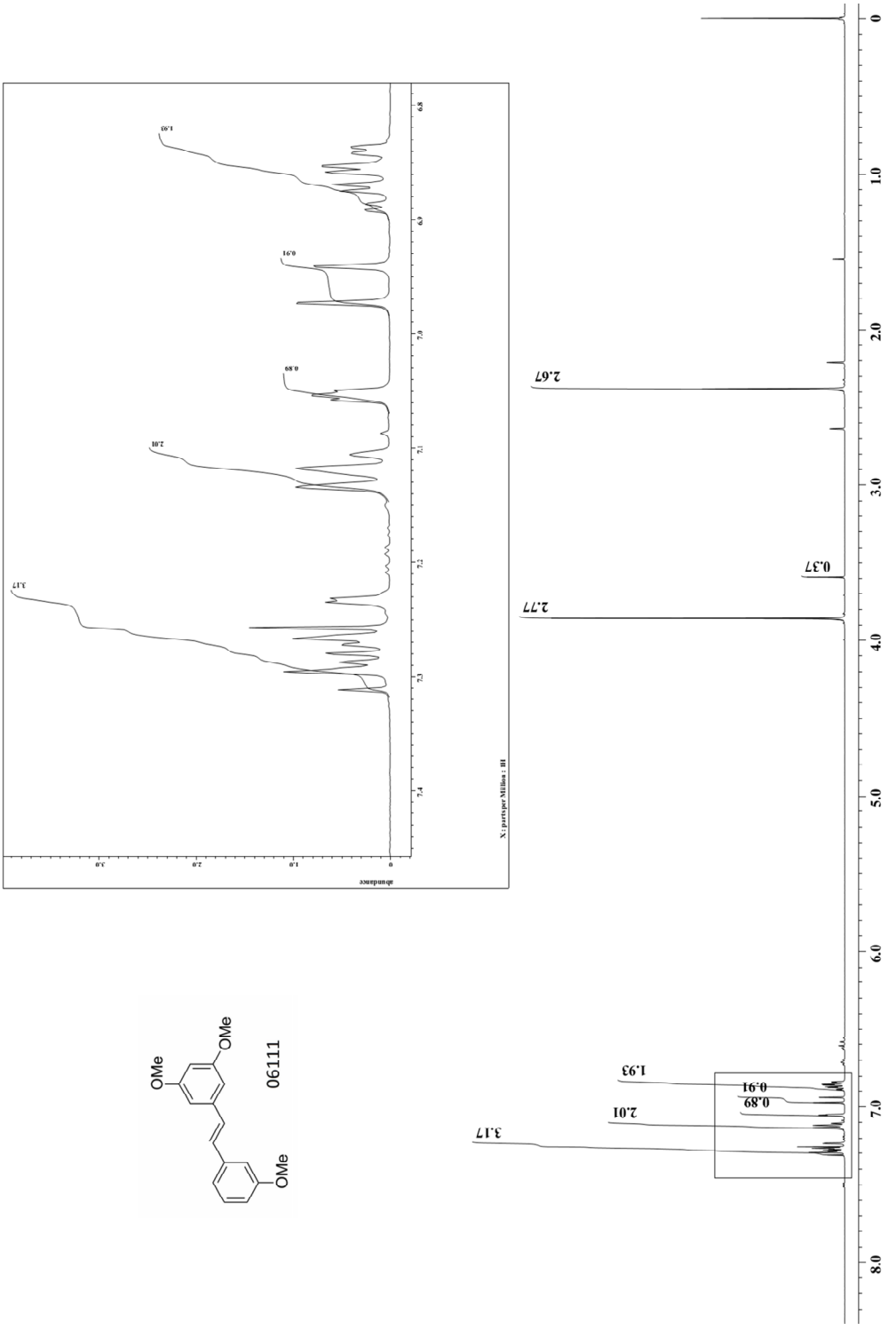
^{13}C-NMR Spectrum (500 MHz, $CDCl_3$)

(E)-1,3-dimethoxy-5-(3-methoxystyryl)benzene



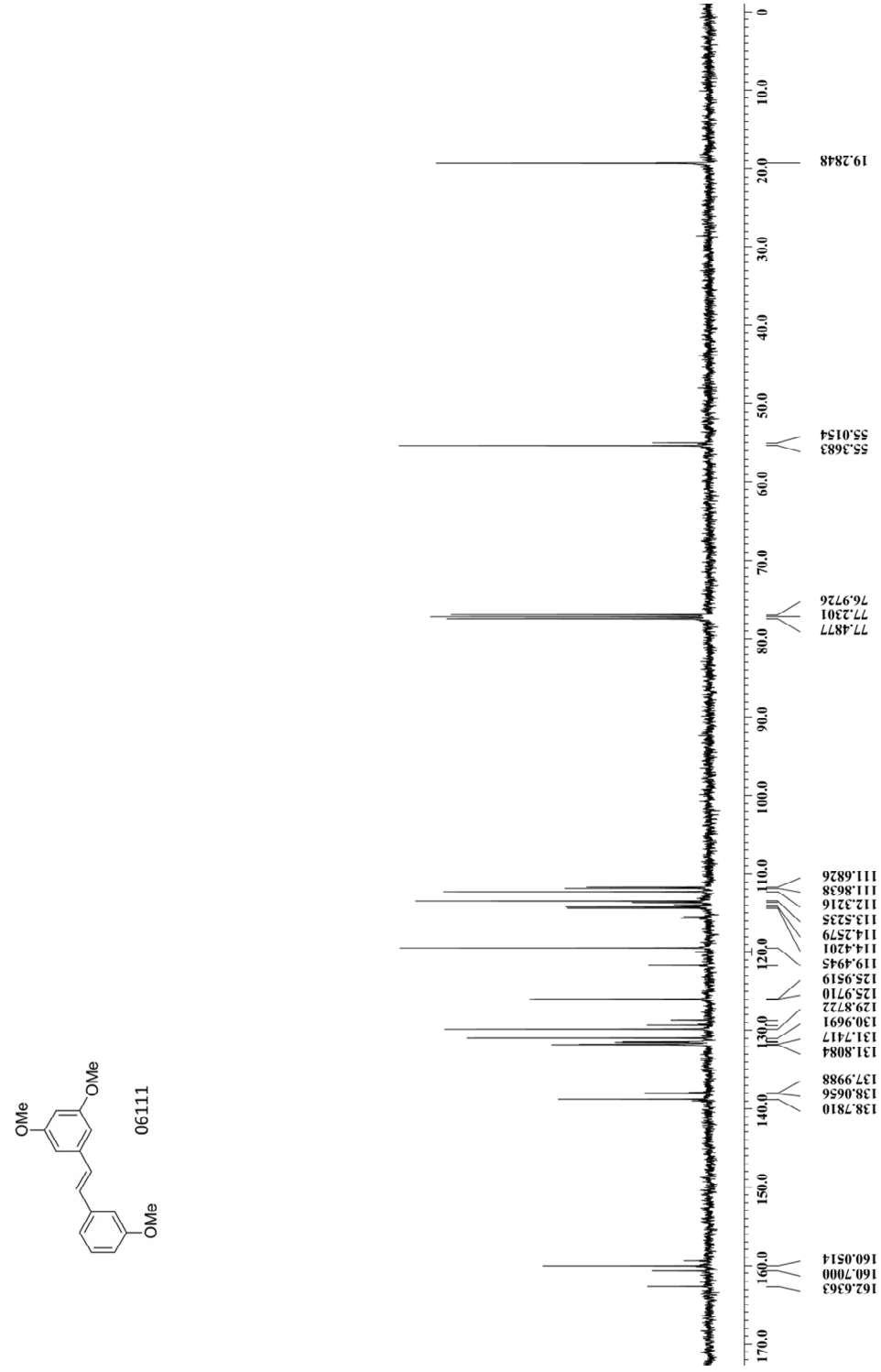
^{1}H-NMR Spectrum (500 MHz, $CDCl_3$)

(E)-4-fluoro-2-(3-methoxystyryl)-1-methylbenzene



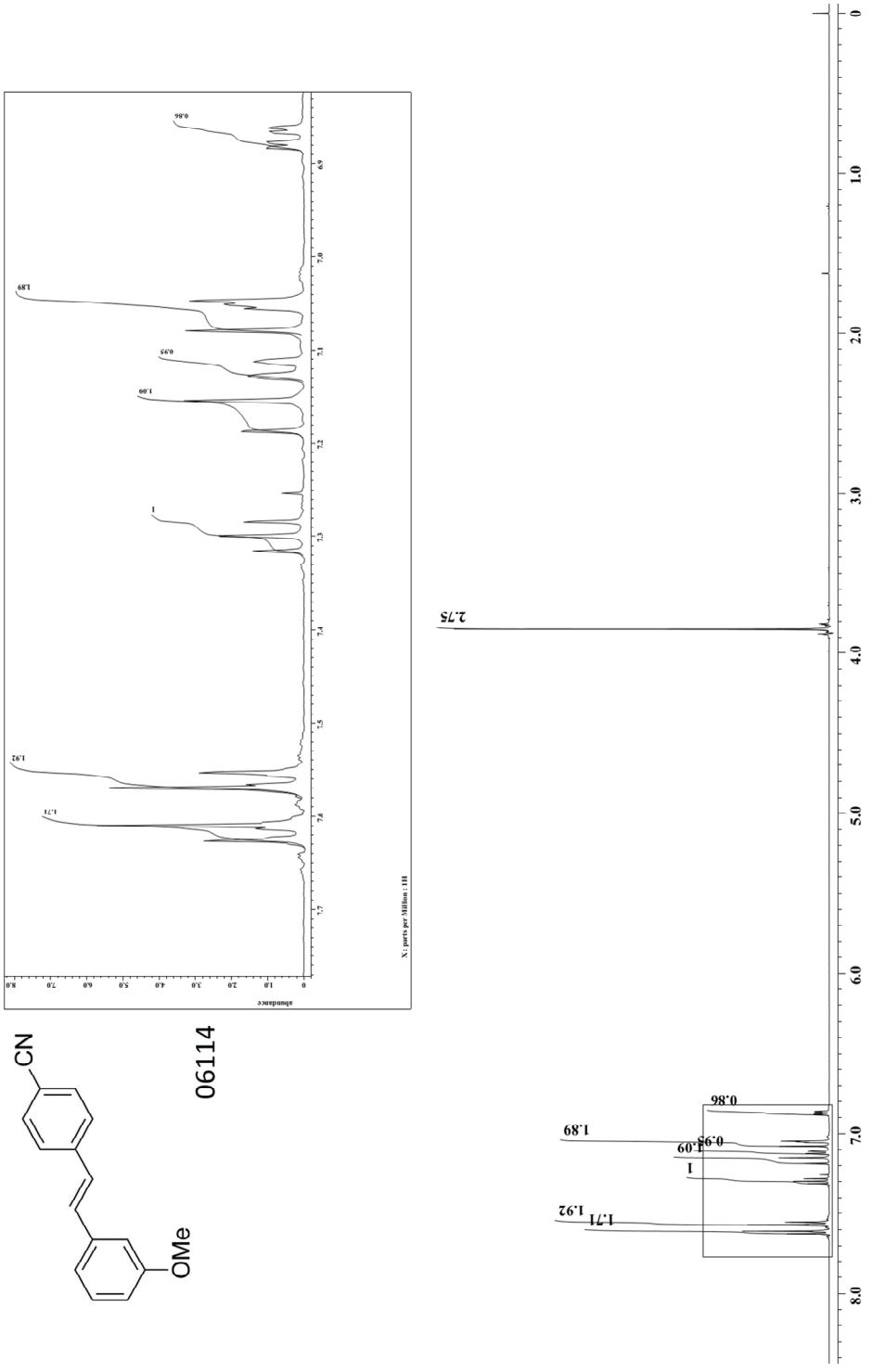
^{13}C-NMR Spectrum (500 MHz, $CDCl_3$)

(E)-4-fluoro-2-(3-methoxystyryl)-1-methylbenzene



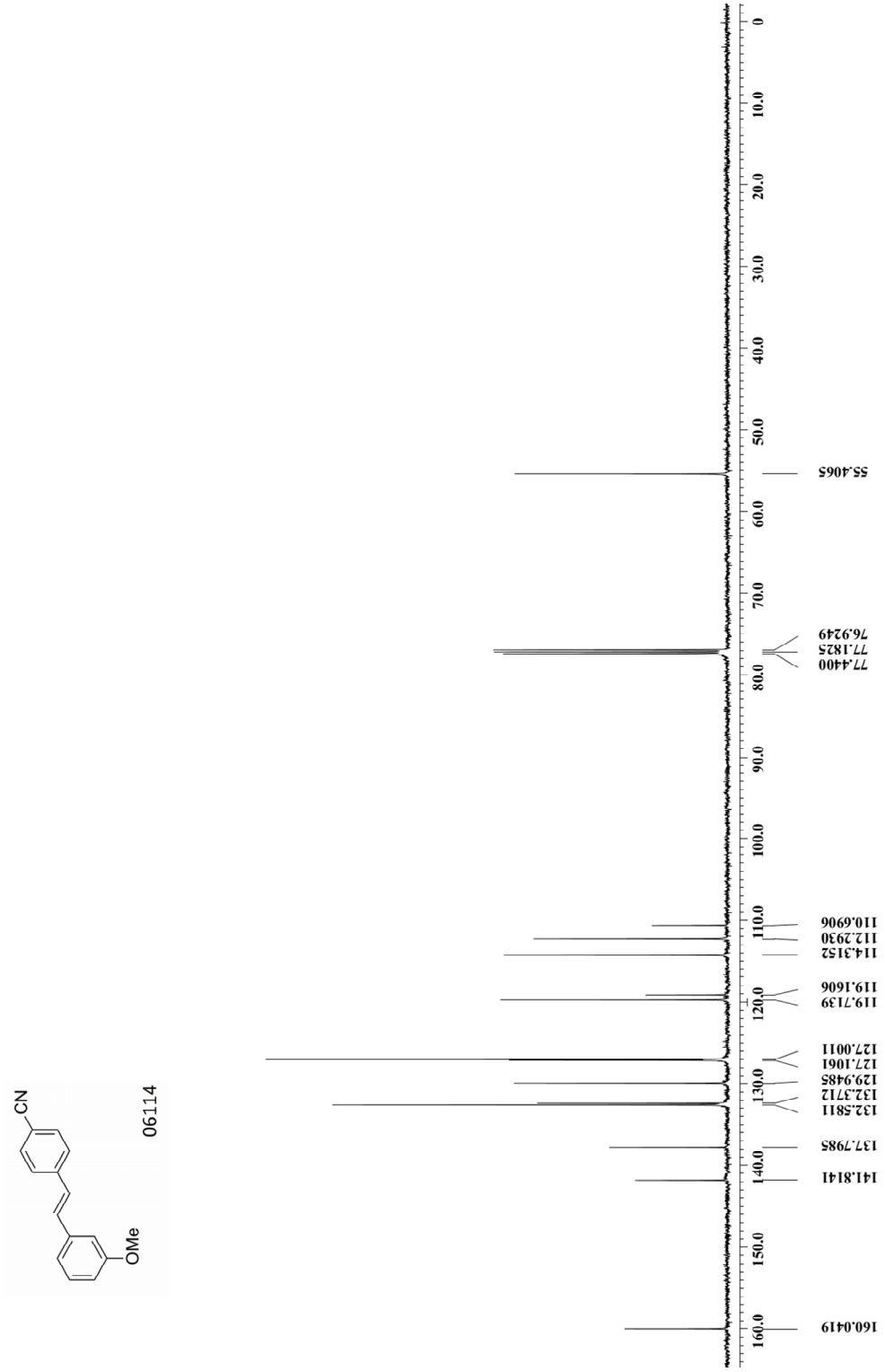
^{1}H-NMR Spectrum (500 MHz, $CDCl_3$)

(E)-4-(3-methoxystyryl)benzonitrile



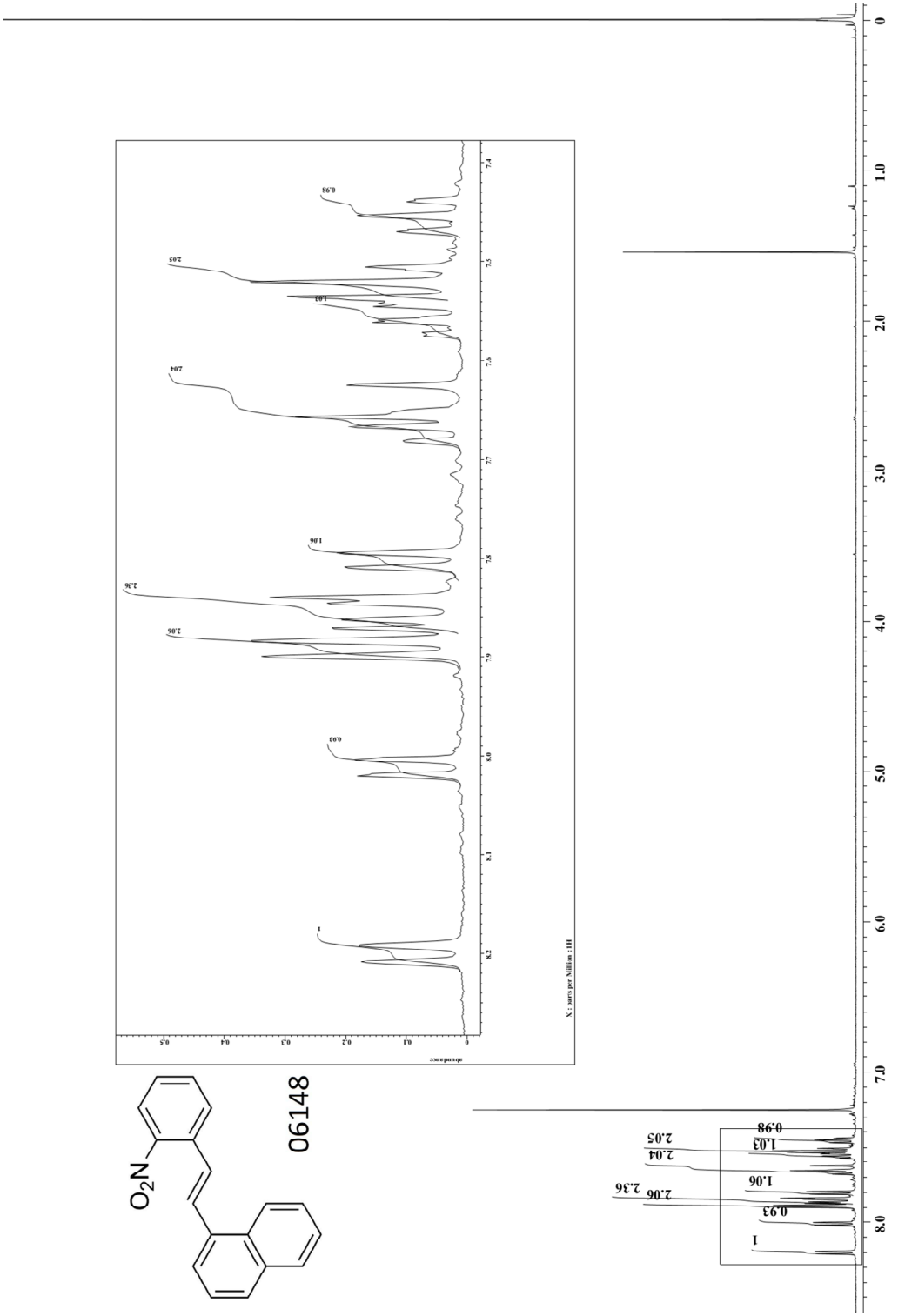
^{13}C-NMR Spectrum (500 MHz, $CDCl_3$)

(E)-4-(3-methoxystyryl)benzonitrile



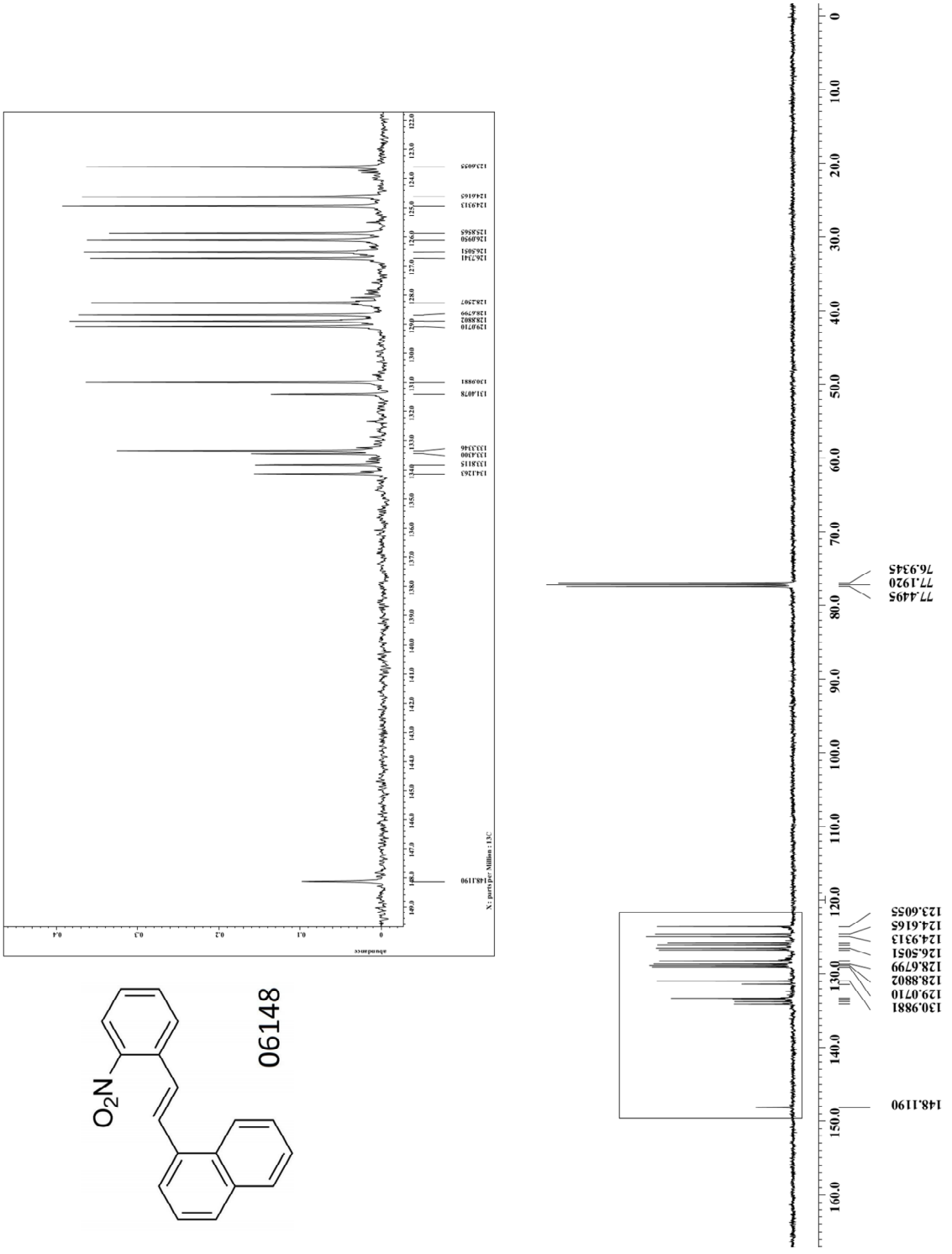
^{1}H-NMR Spectrum (500 MHz, $CDCl_3$)

(E)-1-(2-nitrostyryl)naphthalene



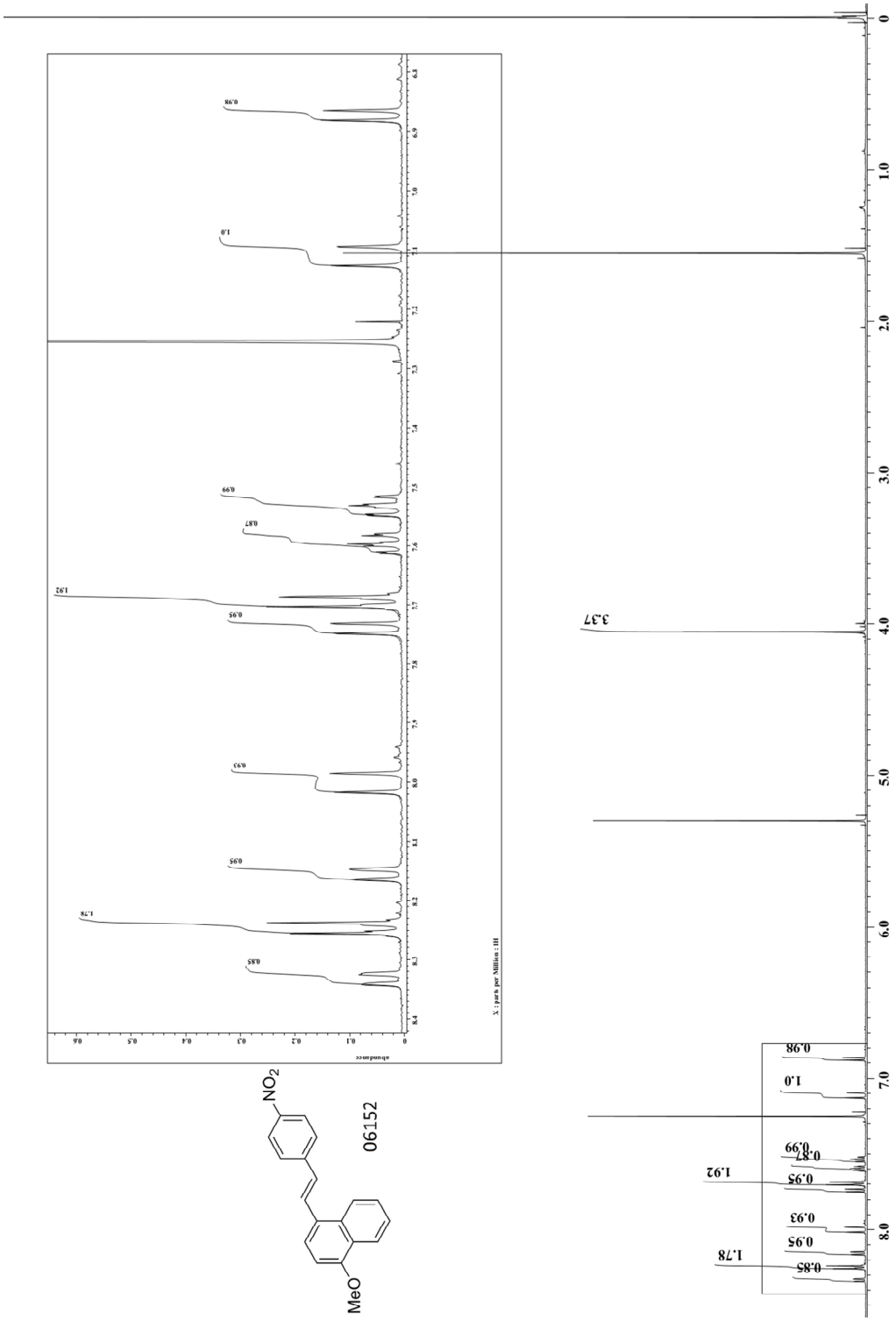
^{13}C-NMR Spectrum (500 MHz, $CDCl_3$)

(E)-1-(2-nitrostyryl)naphthalene



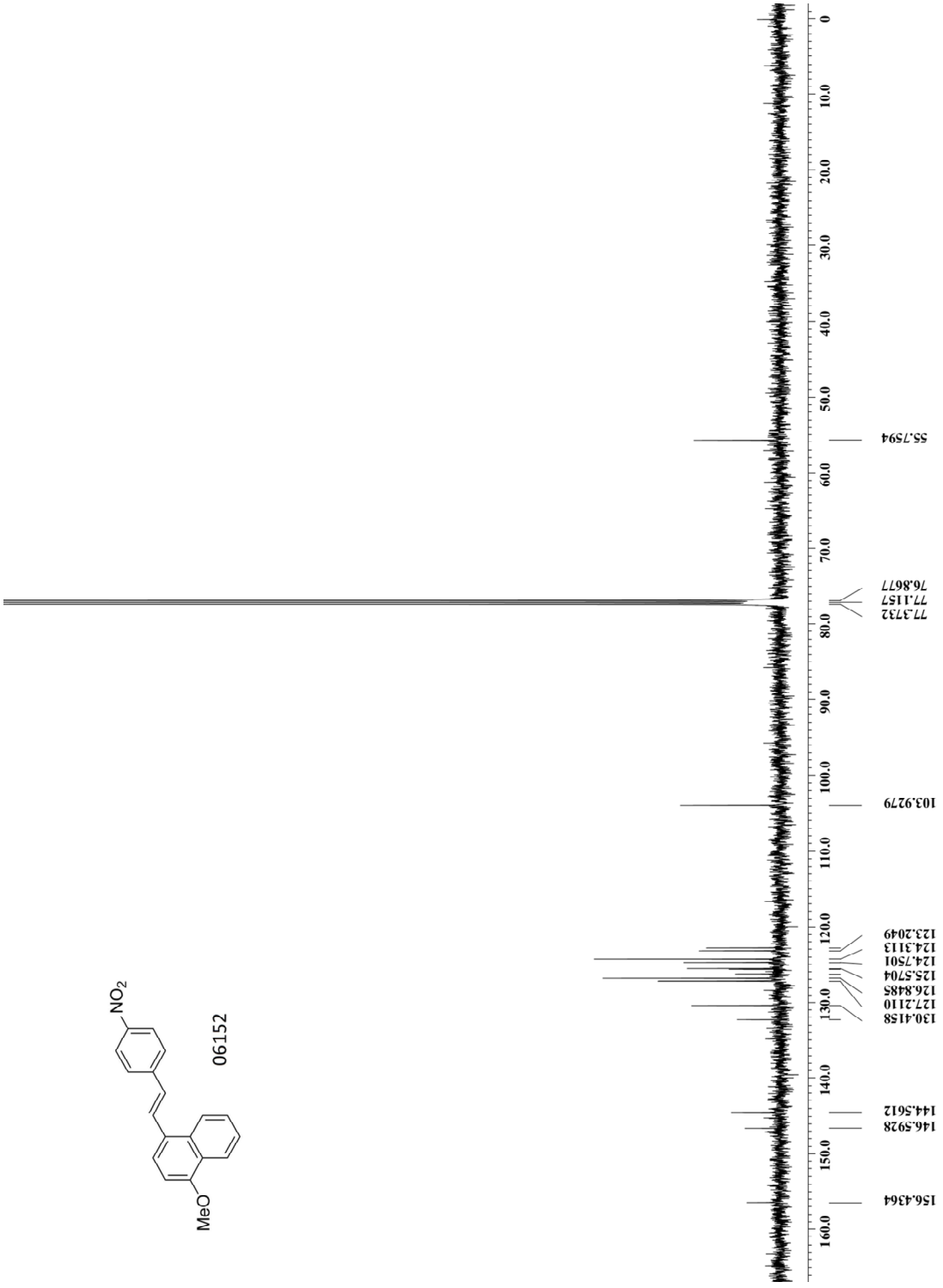
^{1}H-NMR Spectrum (500 MHz, $CDCl_3$)

(E)-1-methoxy-4-(4-nitrostyryl)naphthalene



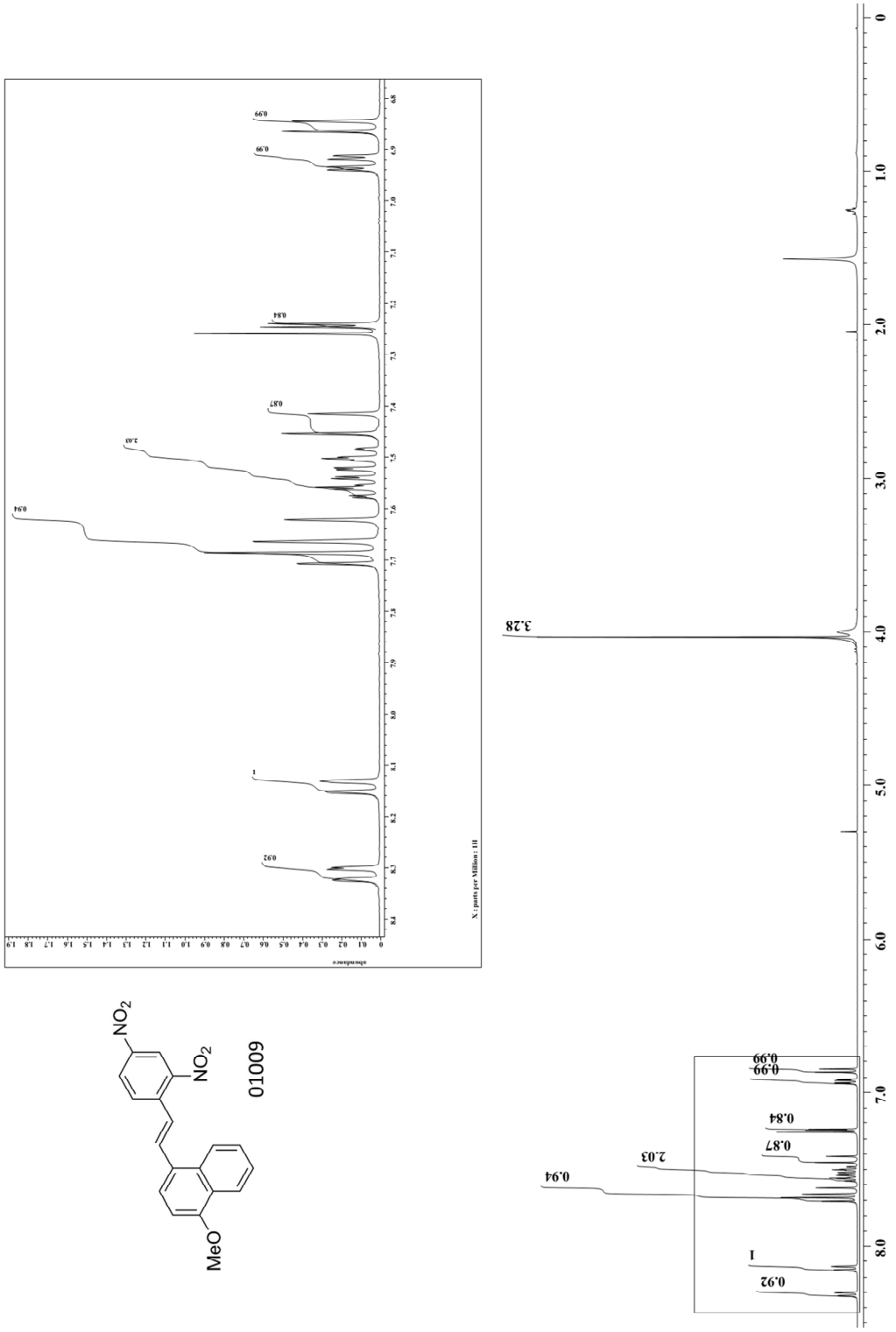
^{13}C-NMR Spectrum (500 MHz, $CDCl_3$)

(E)-1-methoxy-4-(4-nitrostyryl)naphthalene



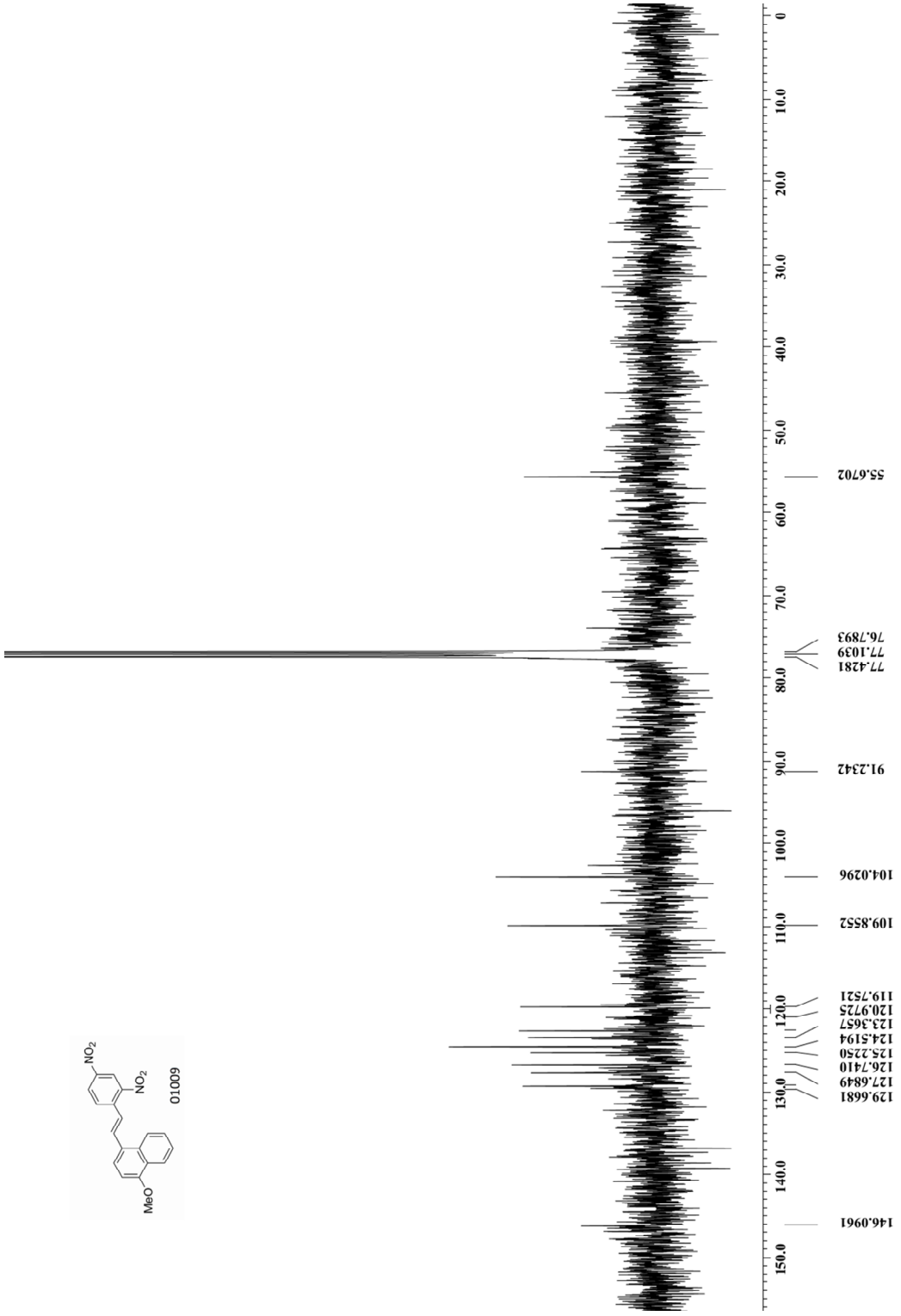
^{1}H-NMR Spectrum (500 MHz, $CDCl_3$)

(E)-1-(2,4-dinitrostyryl)-4-methoxynaphthalene



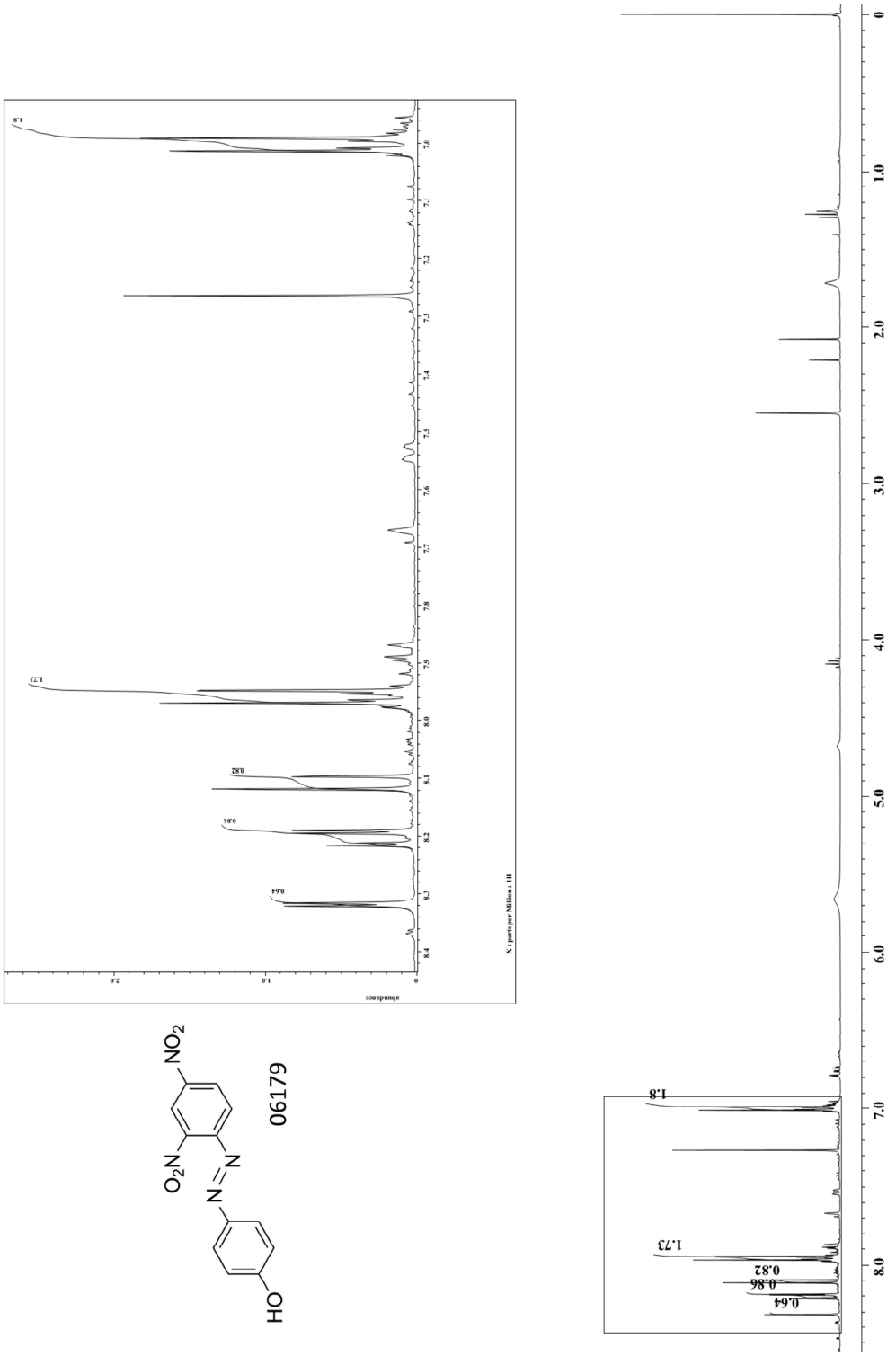
^{13}C-NMR Spectrum (500 MHz, $CDCl_3$)

(E)-1-(2,4-dinitrostyryl)-4-methoxynaphthalene



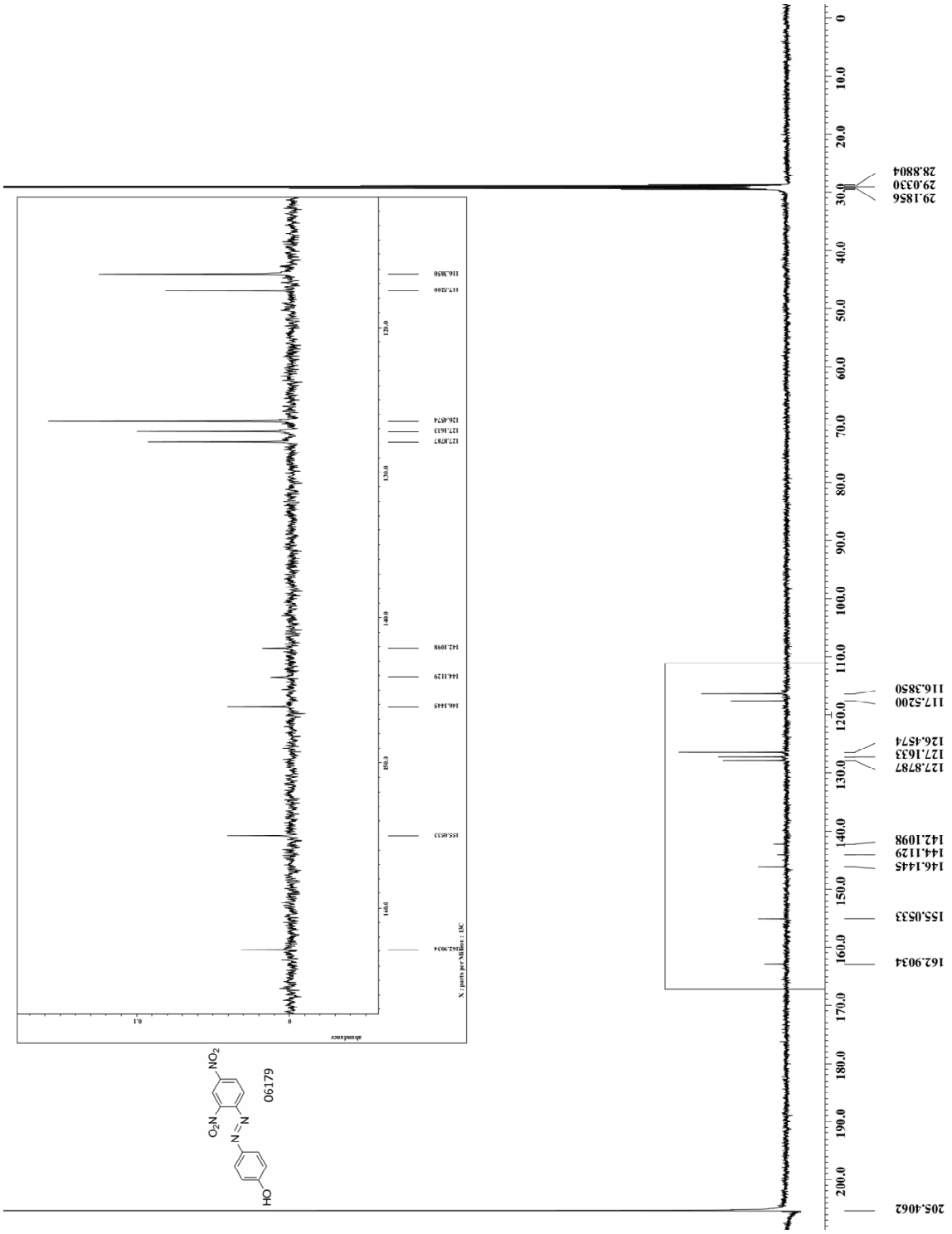
^{1}H-NMR Spectrum (500 MHz, $CDCl_3$)

-4-((2,4-dinitrophenyl)diazenyl)phenol



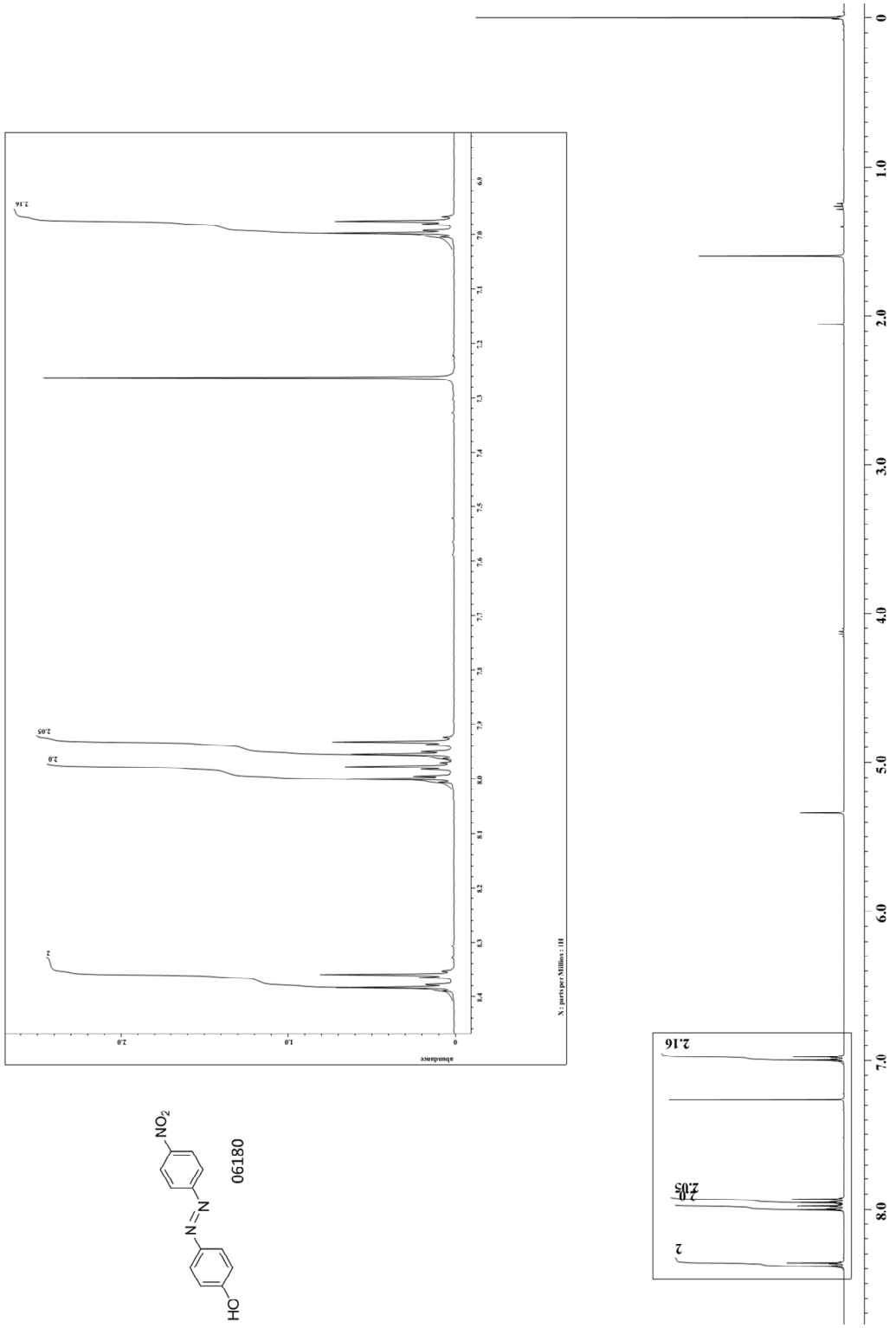
^{13}C-NMR Spectrum (500 MHz, acetone-d6)

4-((2,4-dinitrophenyl)diazenyl)phenol



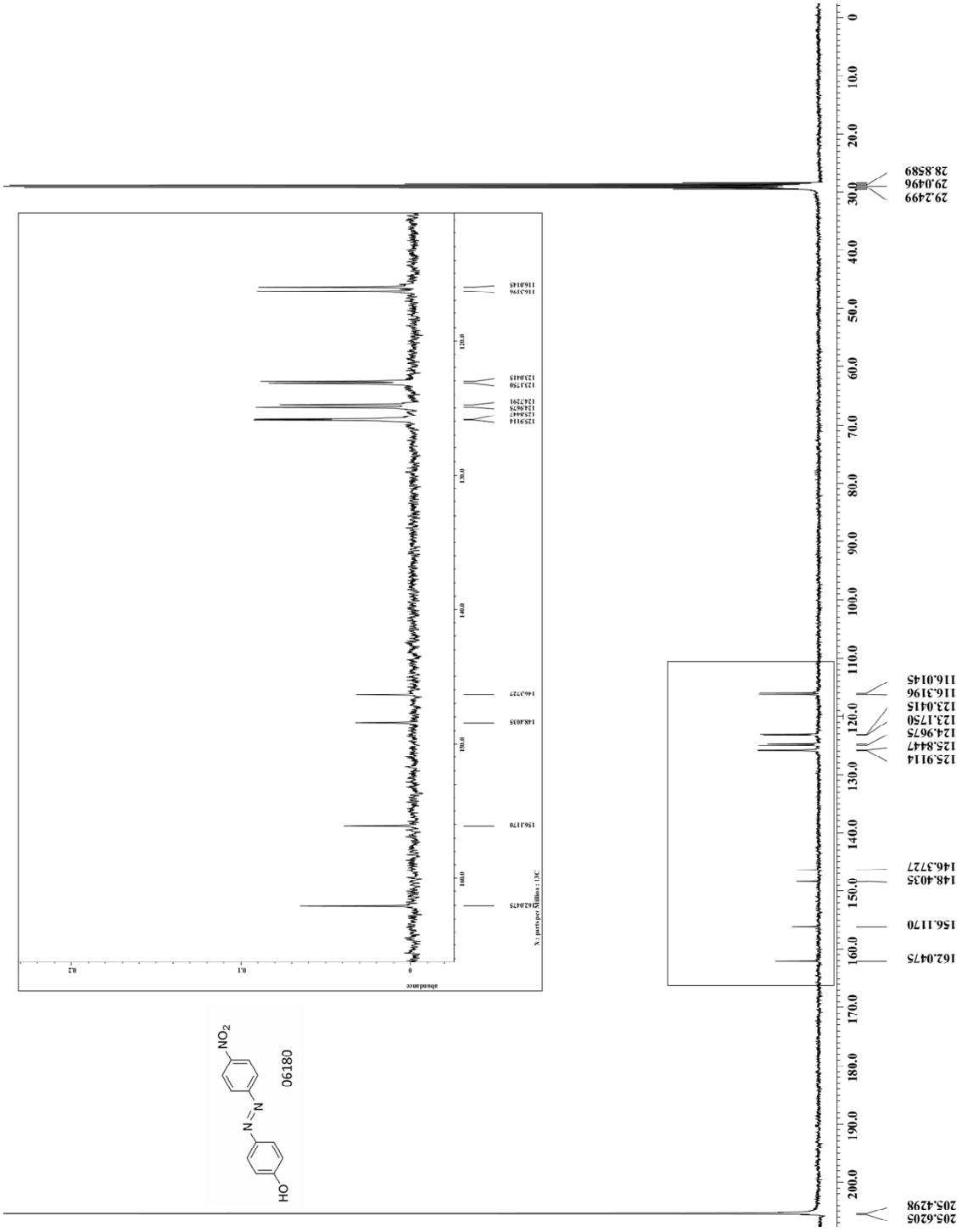
^{1}H-NMR Spectrum (500 MHz, $CDCl_3$)

4-((4-nitrophenyl)diazenyl)phenol



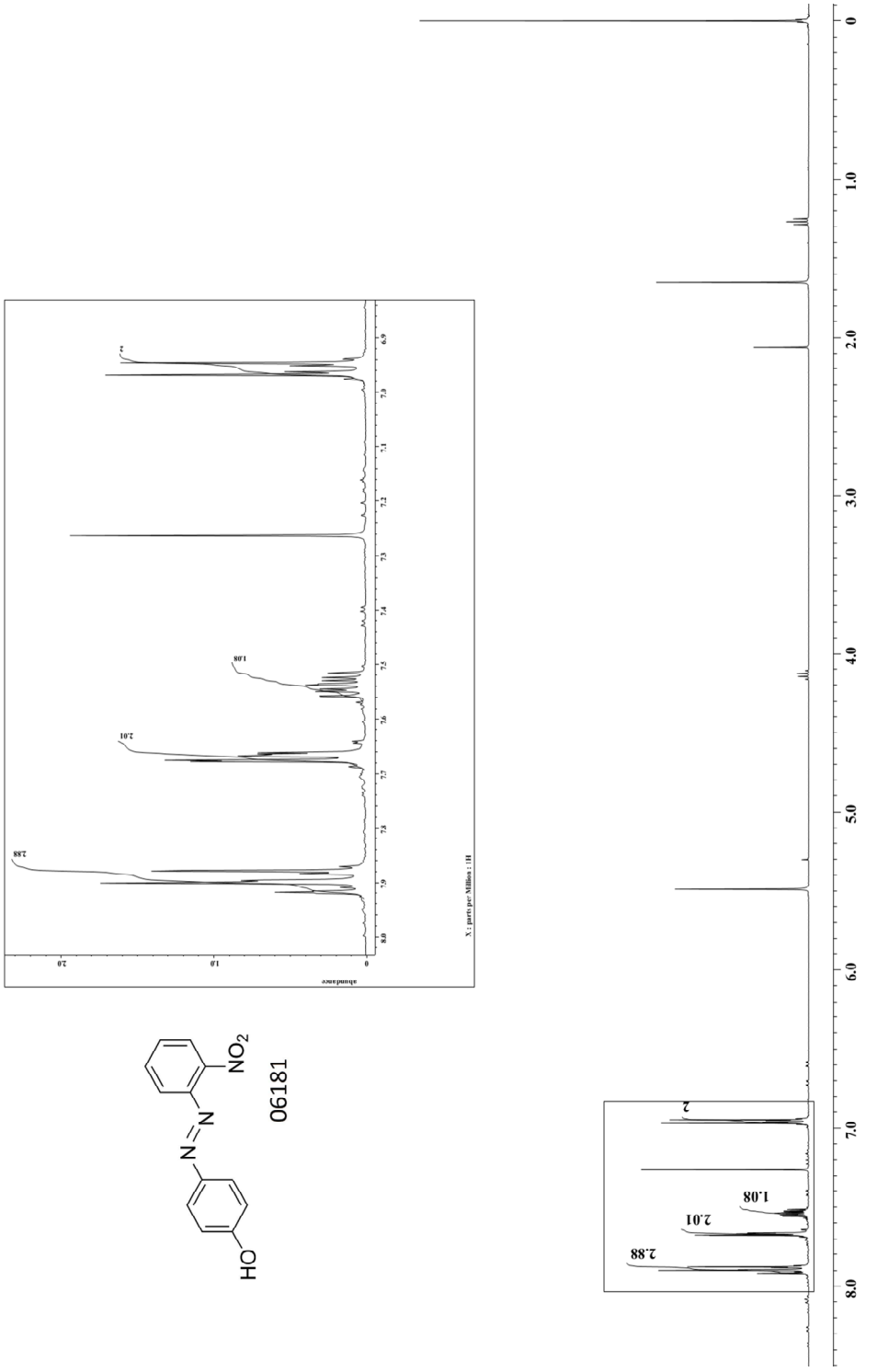
^{13}C-NMR Spectrum (500 MHz, acetone-d6)

4-((4-nitrophenyl)diazenyl)phenol



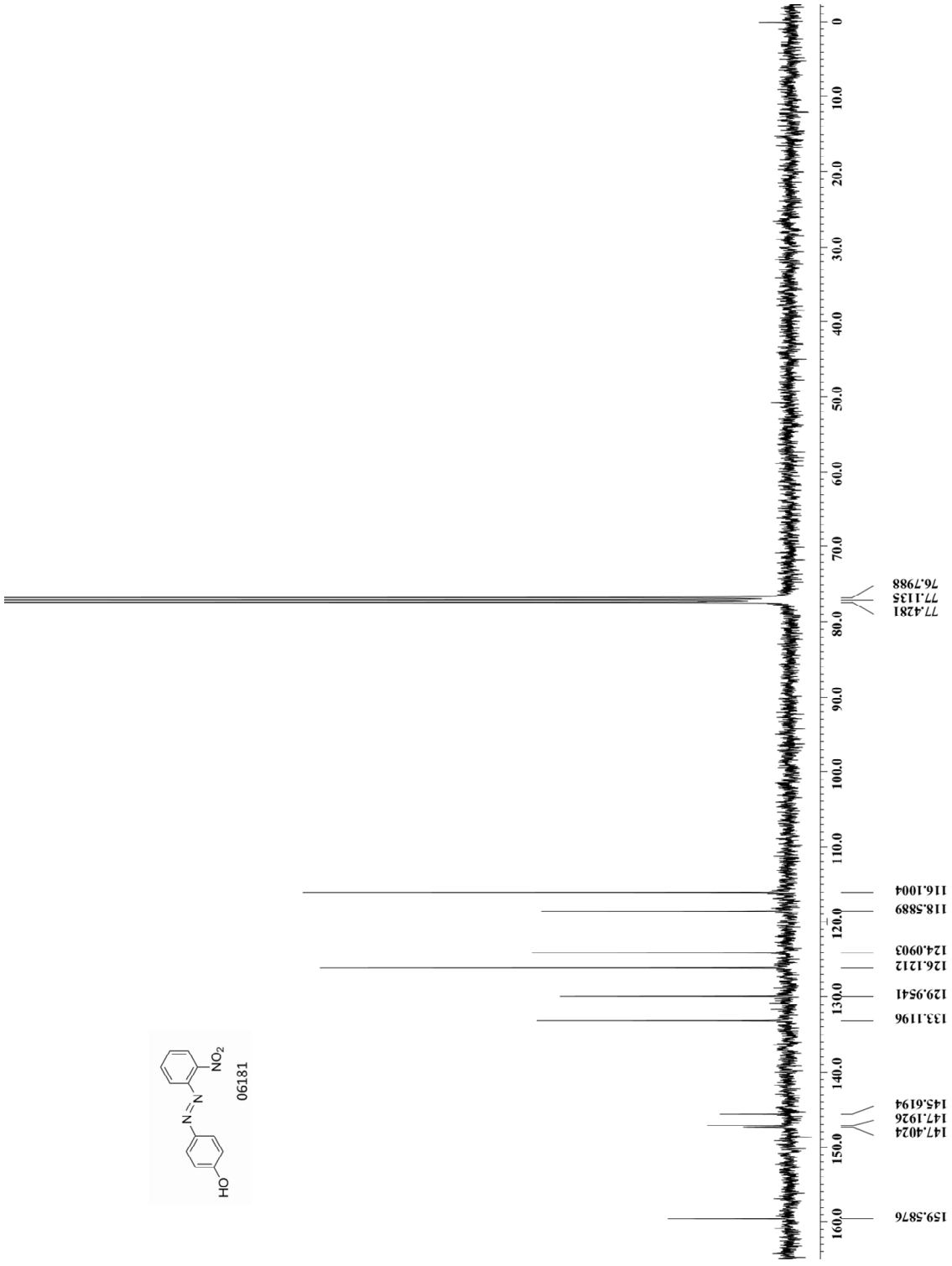
^{1}H-NMR Spectrum (500 MHz, $CDCl_3$)

4-((2-nitrophenyl)diazenyl)phenol



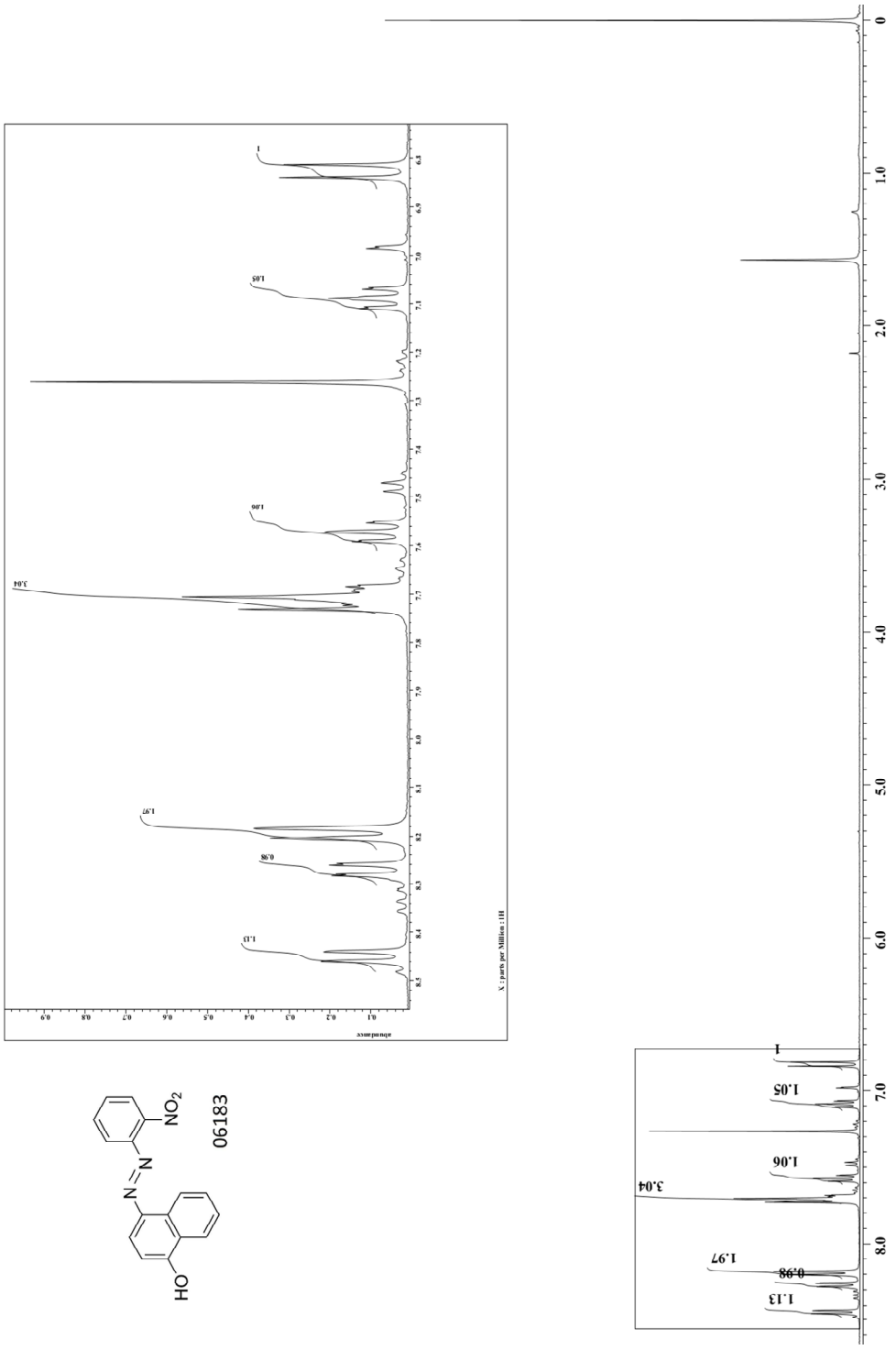
^{13}C-NMR Spectrum (500 MHz, $CDCl_3$)

4-((2-nitrophenyl)diazenyl)phenol



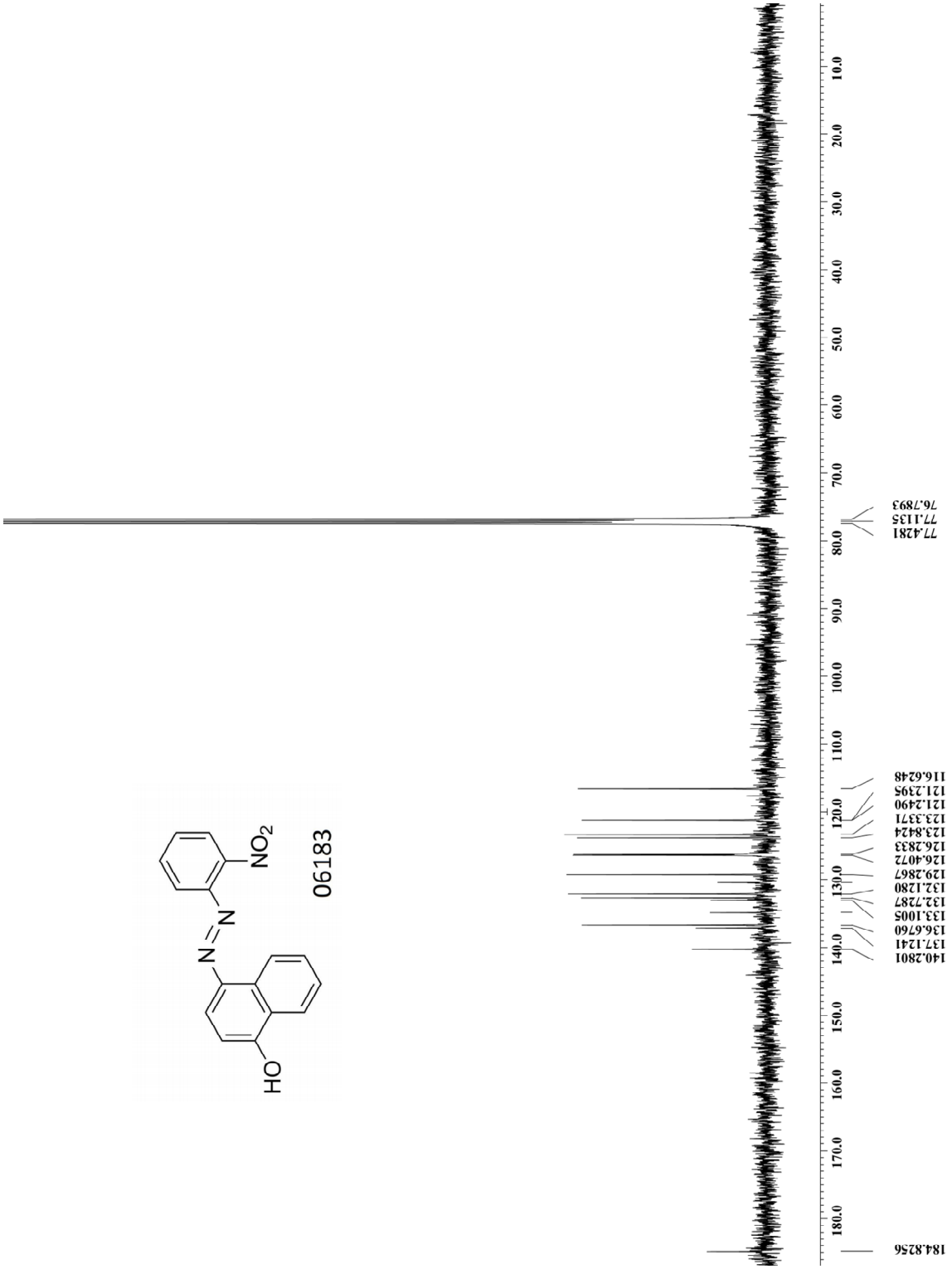
^{1}H-NMR Spectrum (500 MHz, $CDCl_3$)

4-((2-nitrophenyl)diazenyl)naphthalen-1-ol



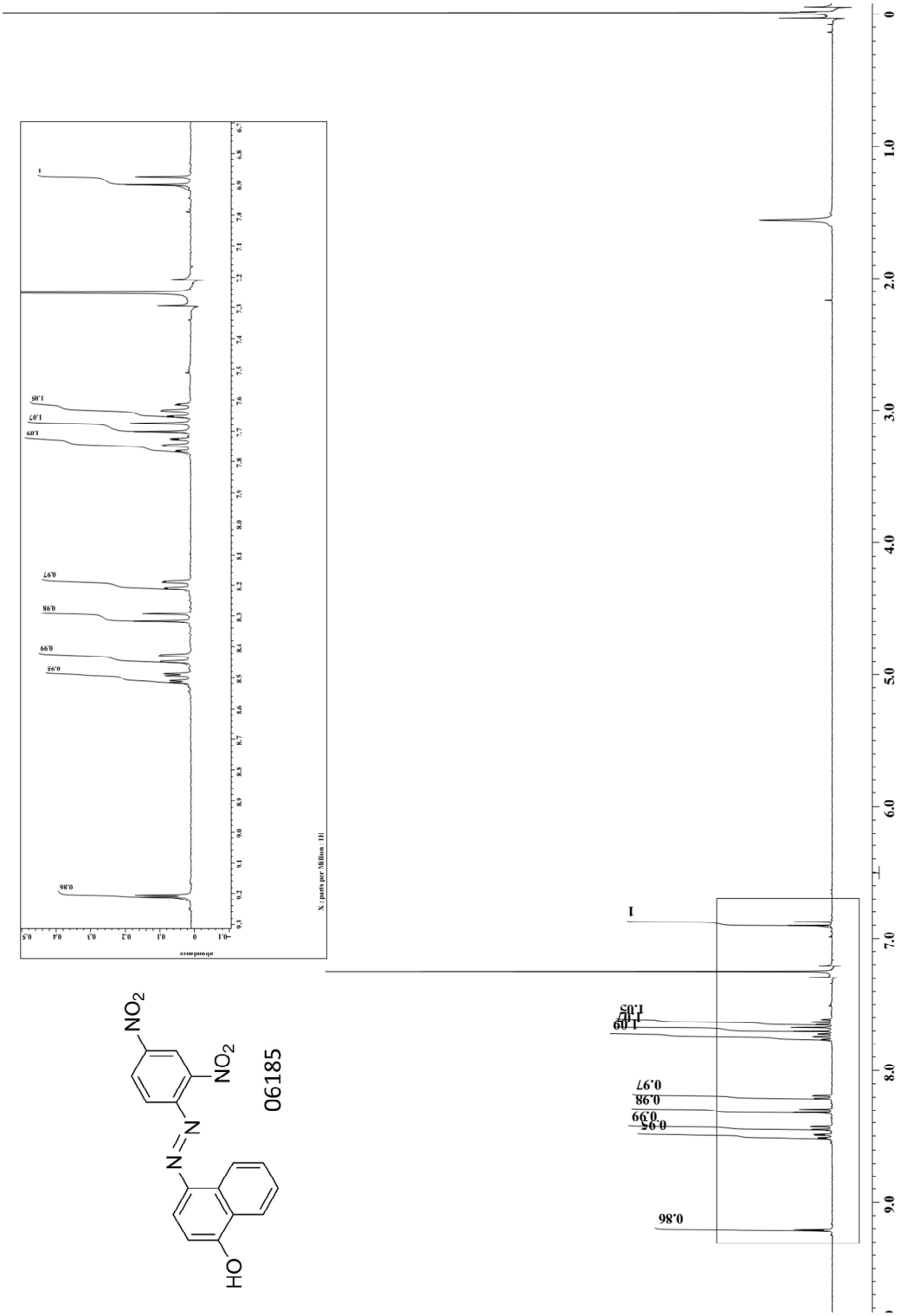
^{13}C-NMR Spectrum (500 MHz, $CDCl_3$)

4-((2-nitrophenyl)diazenyl)naphthalen-1-ol



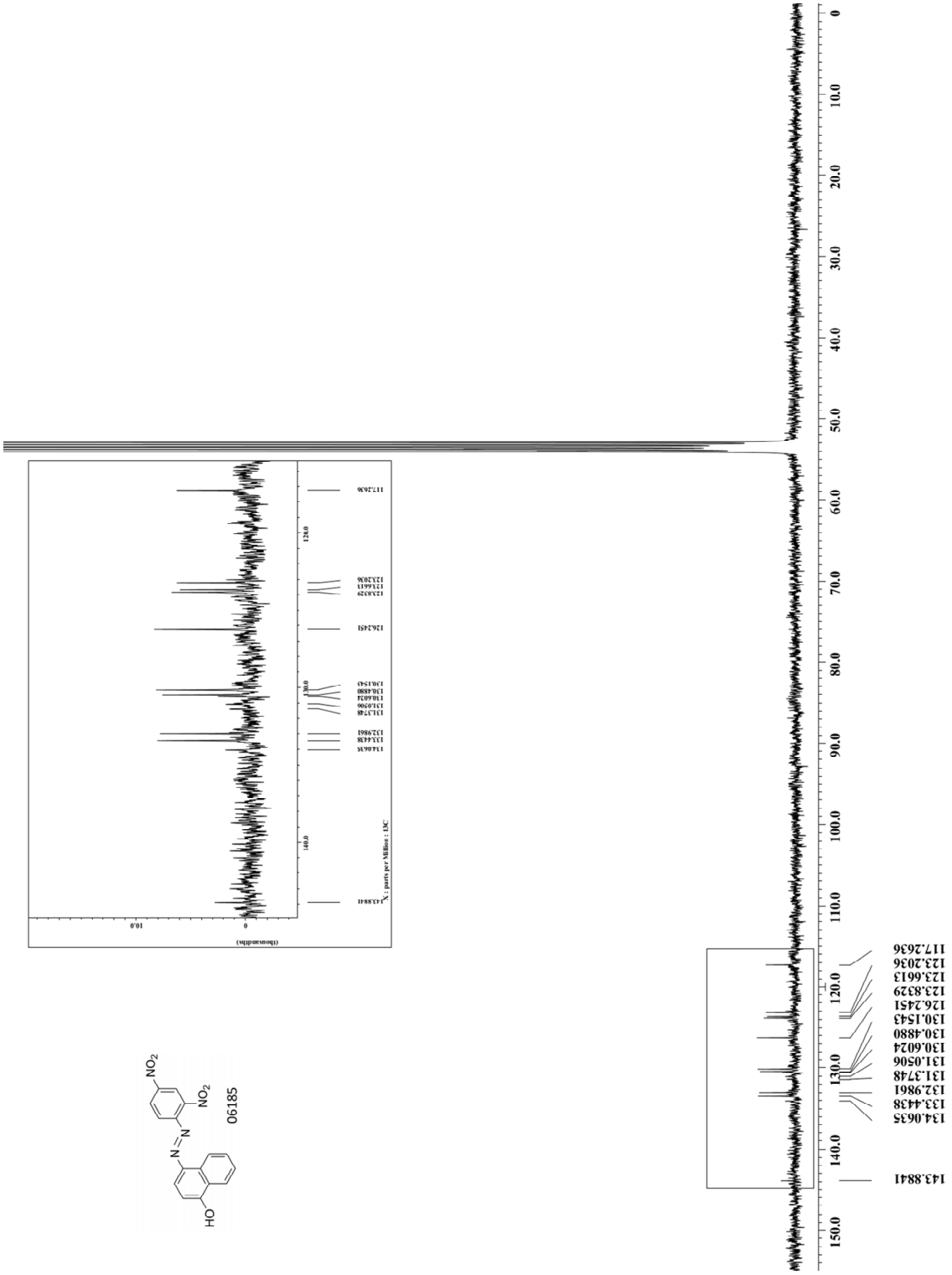
^{1}H-NMR Spectrum (500 MHz, $CDCl_3$)

4-((2,4-dinitrophenyl)diazenyl)naphthalen-1-ol



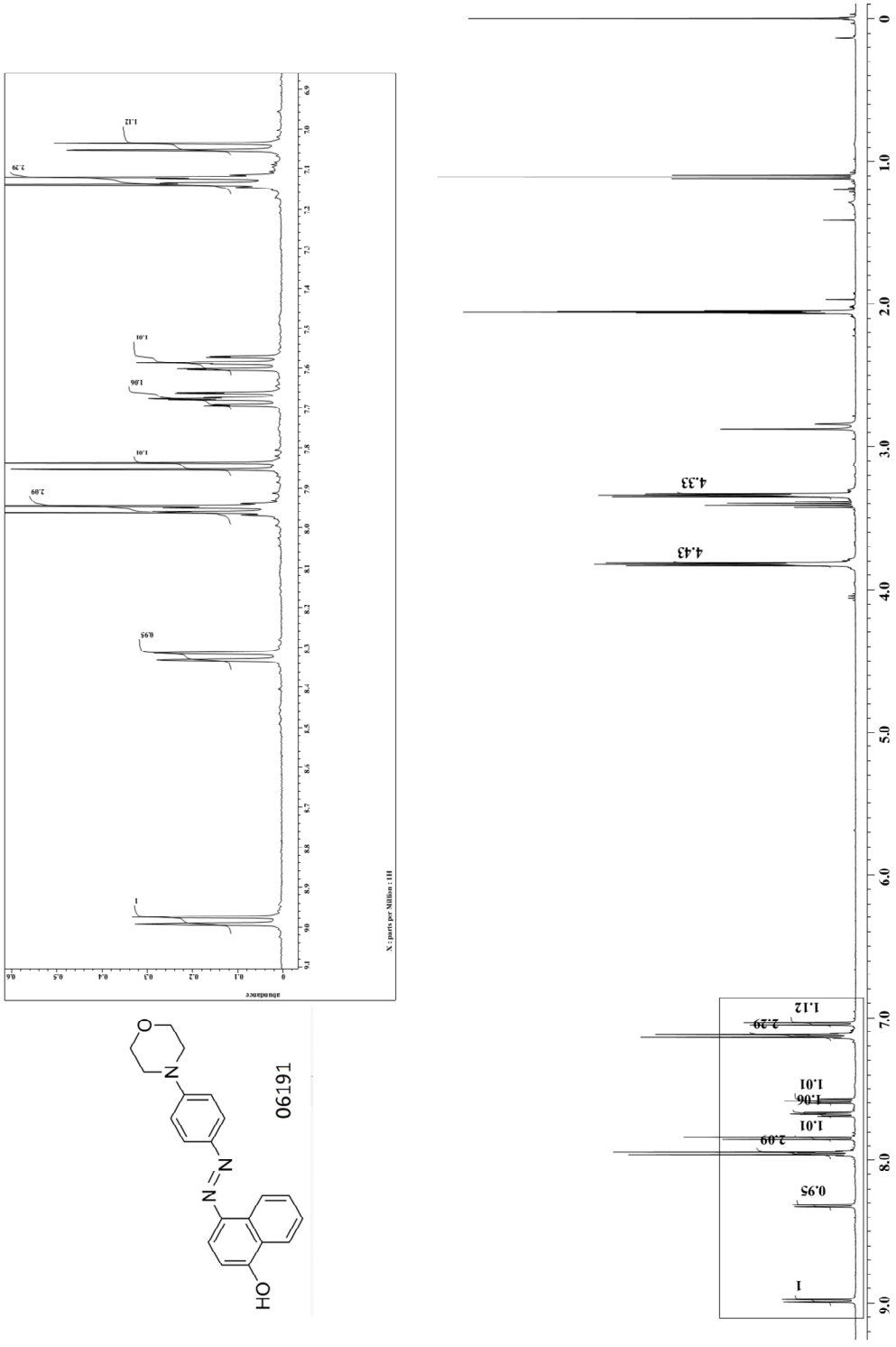
^{13}C-NMR Spectrum (500 MHz, $CDCl_3$)

4-((2,4-dinitrophenyl)diazenyl)naphthalen-1-ol



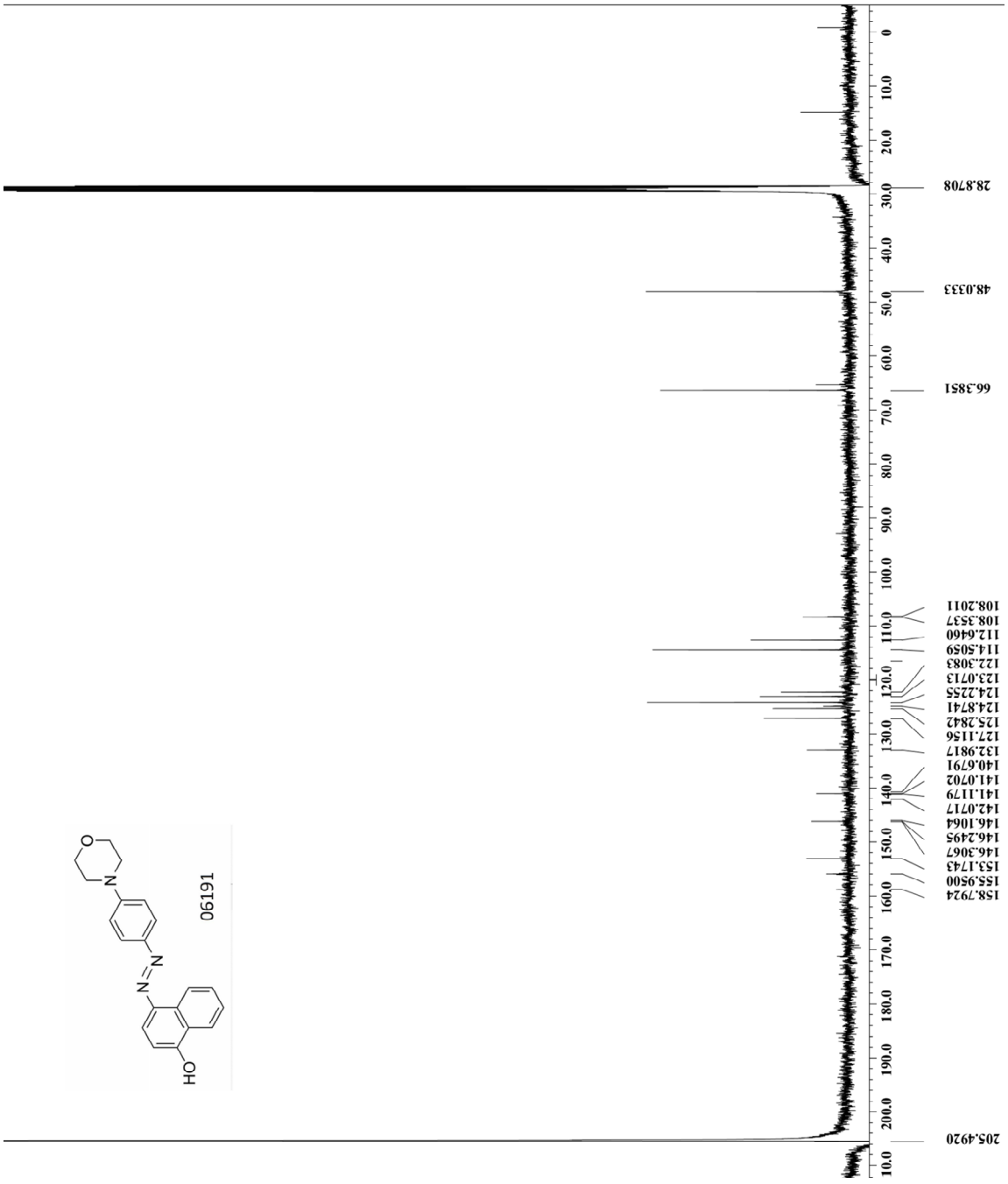
^{1}H-NMR Spectrum (500 MHz, $CDCl_3$)

4-((4-morpholinophenyl)diazenyl)naphthalen-1-ol



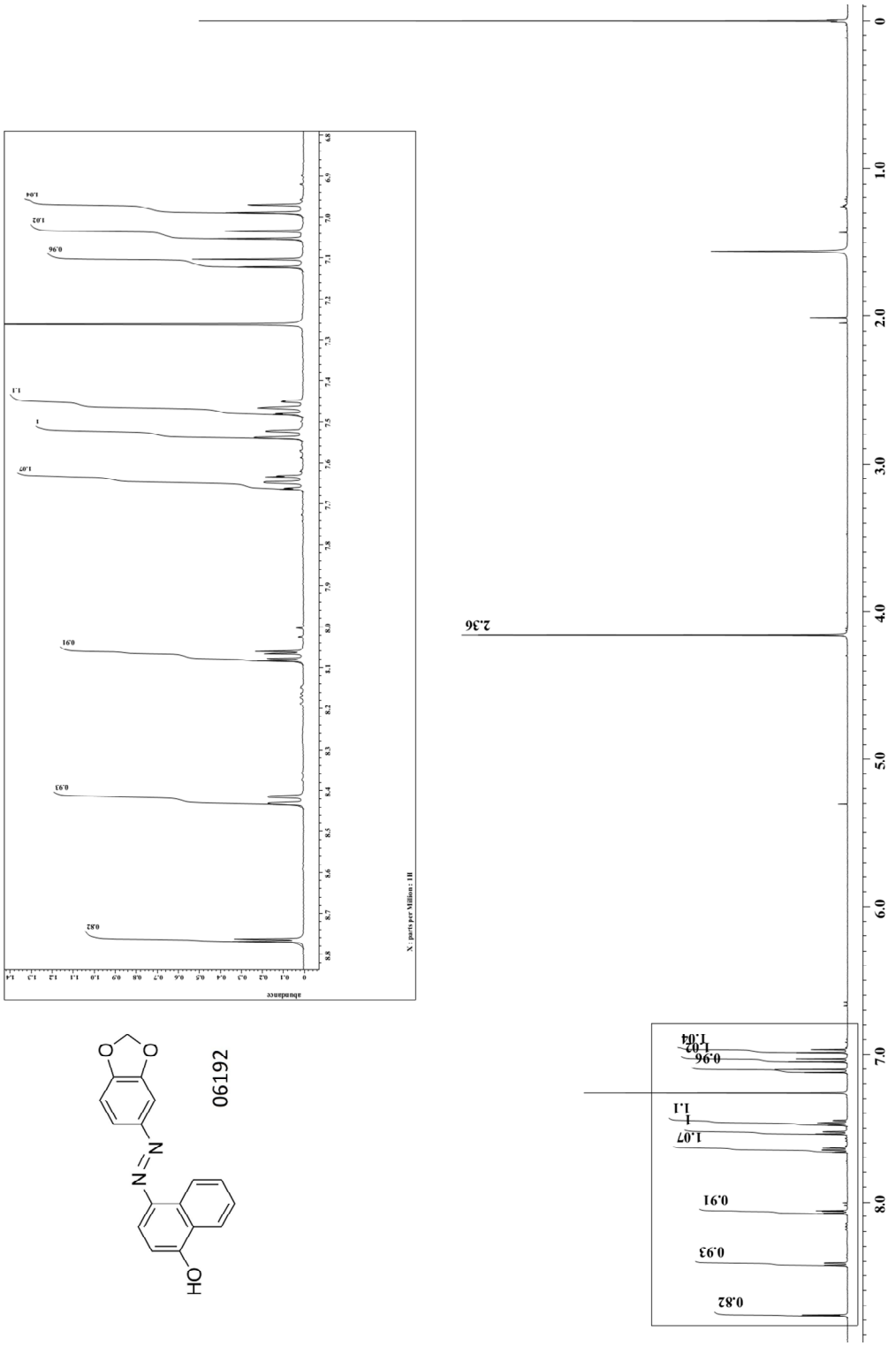
^{13}C-NMR Spectrum (500 MHz, acetone-d6)

4-((4-morpholinophenyl)diazenyl)naphthalen-1-ol



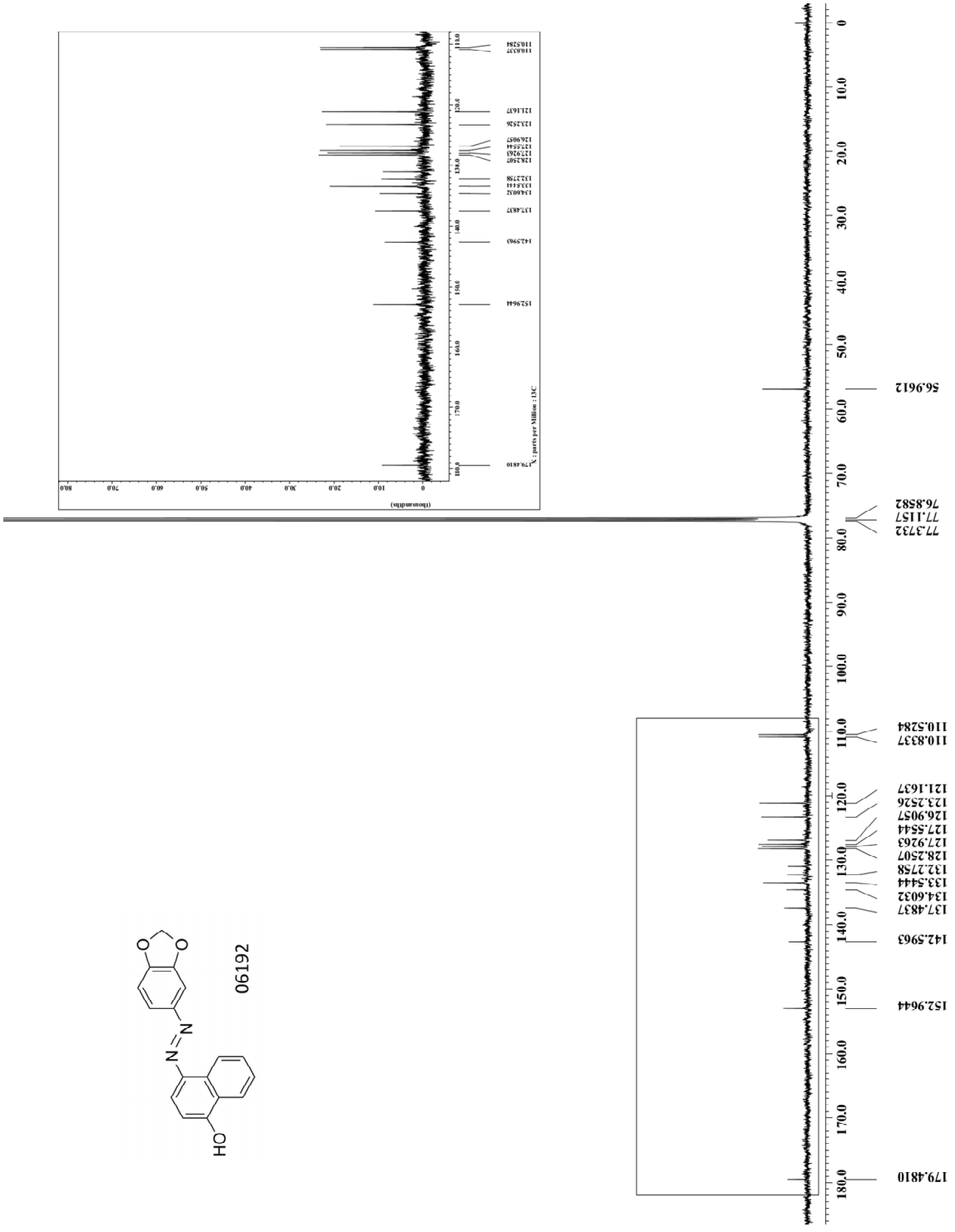
^{1}H-NMR Spectrum (500 MHz, $CDCl_3$)

4-(benzo[d][1,3]dioxol-5-yldiazenyl)naphthalen-1-ol



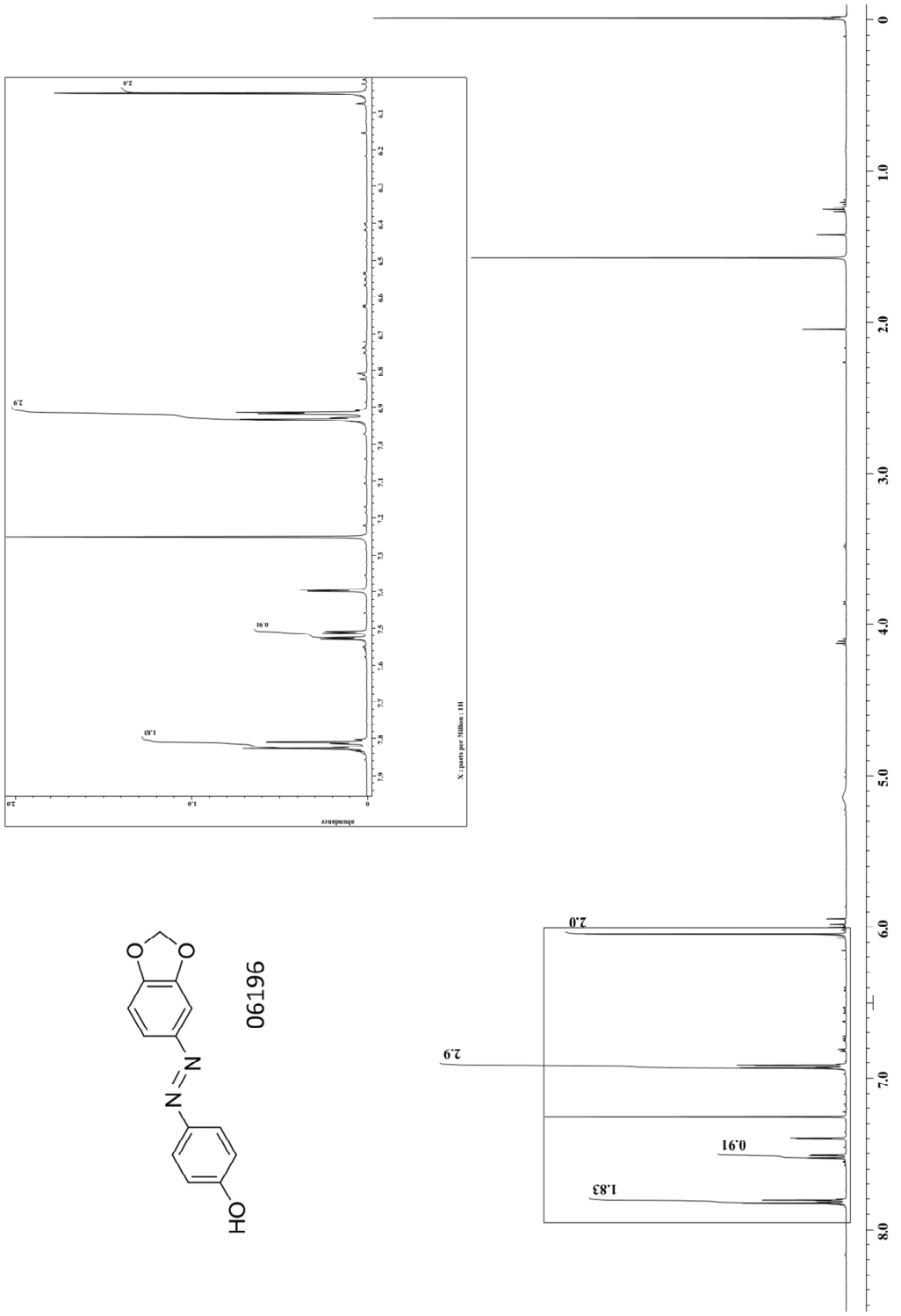
^{13}C-NMR Spectrum (500 MHz, $CDCl_3$)

4-(benzo[d][1,3]dioxol-5-yldiazenyl)naphthalen-1-ol



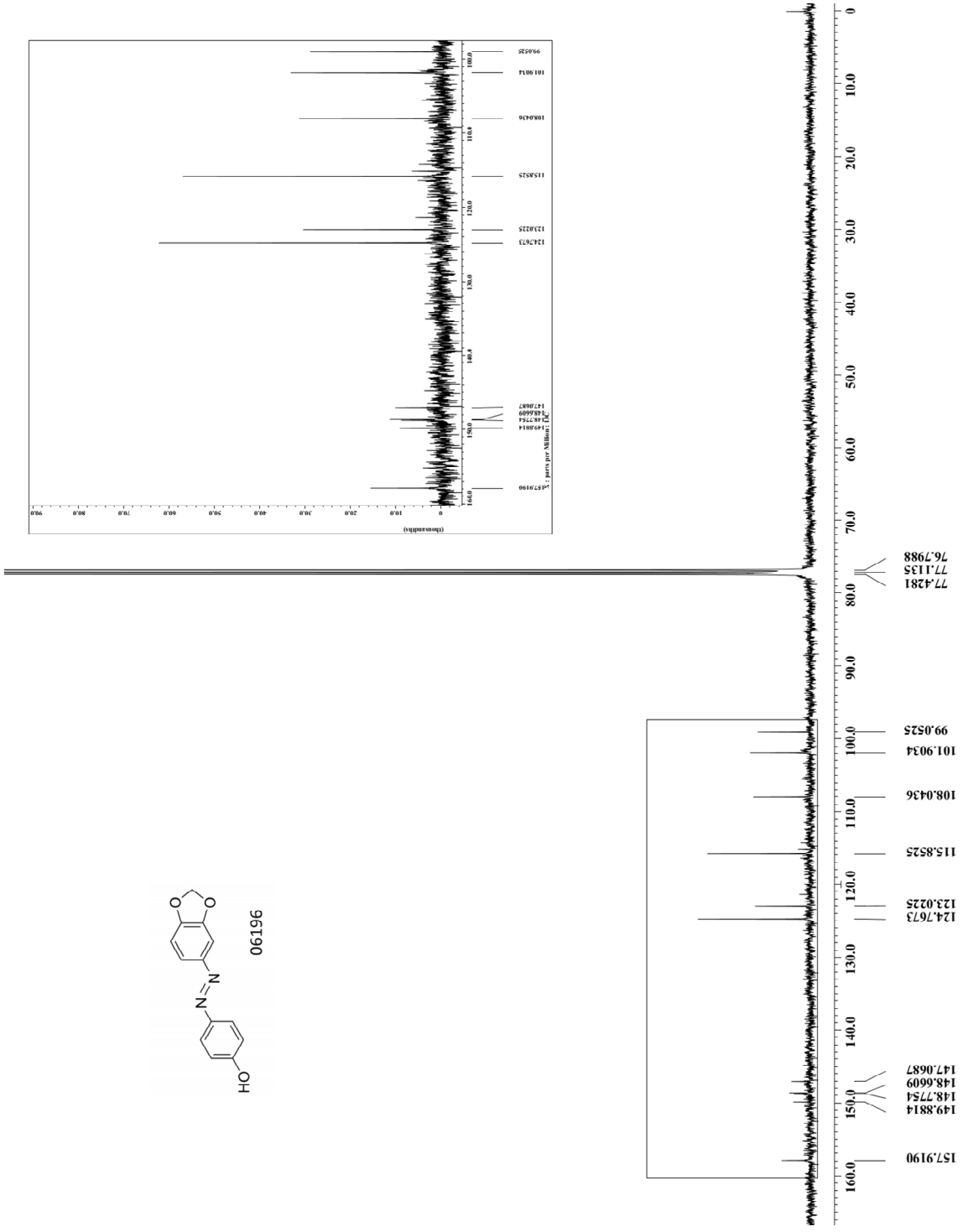
^{1}H-NMR Spectrum (500 MHz, $CDCl_3$)

4-(benzo[d][1,3]dioxol-5-yldiazenyl)phenol



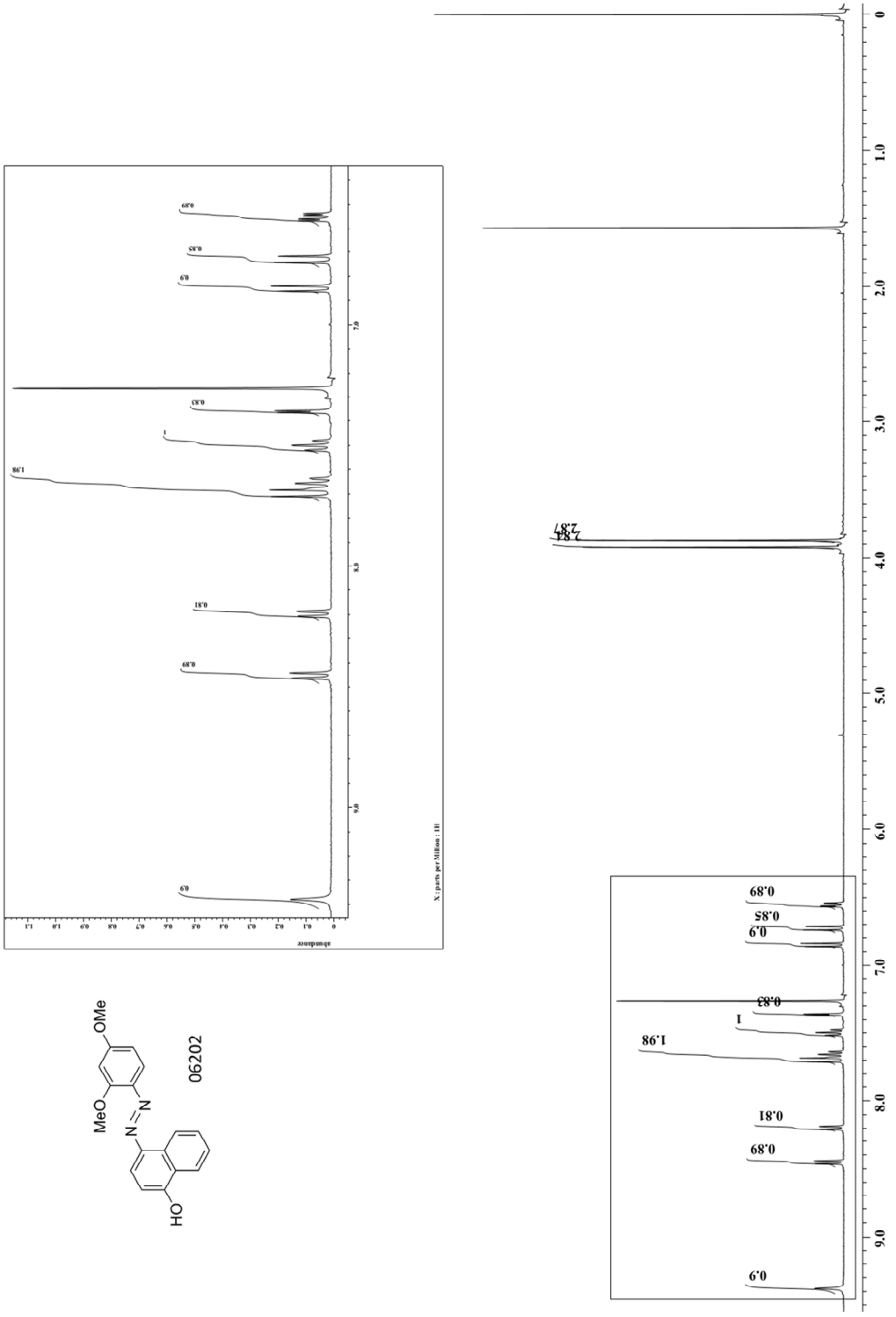
^{13}C-NMR Spectrum (500 MHz, $CDCl_3$)

4-(benzo[d][1,3]dioxol-5-yldiazenyl)phenol



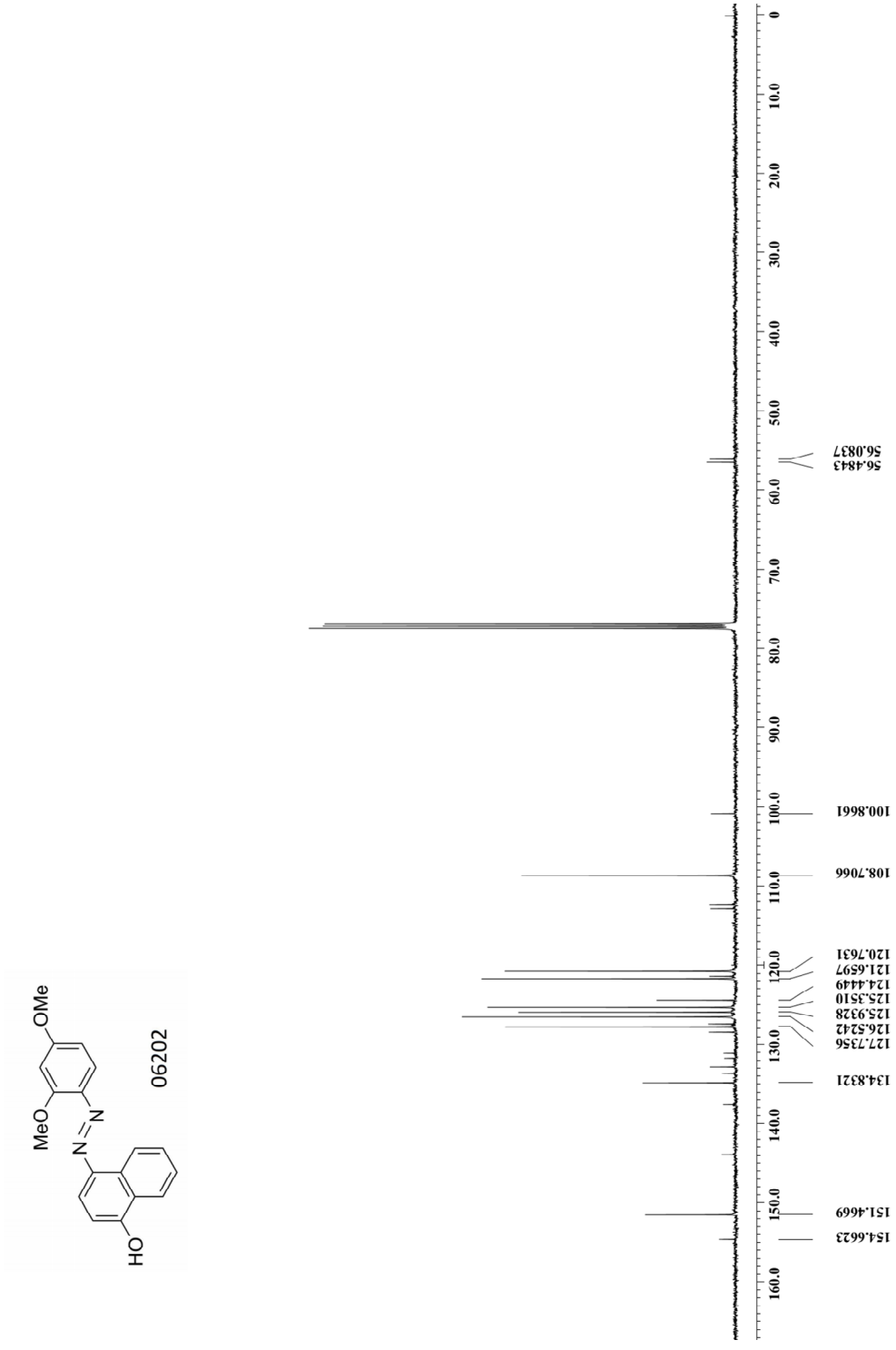
^{1}H-NMR Spectrum (500 MHz, $CDCl_3$)

4-((2,4-dimethoxyphenyl)diazenyl)naphthalen-1-ol



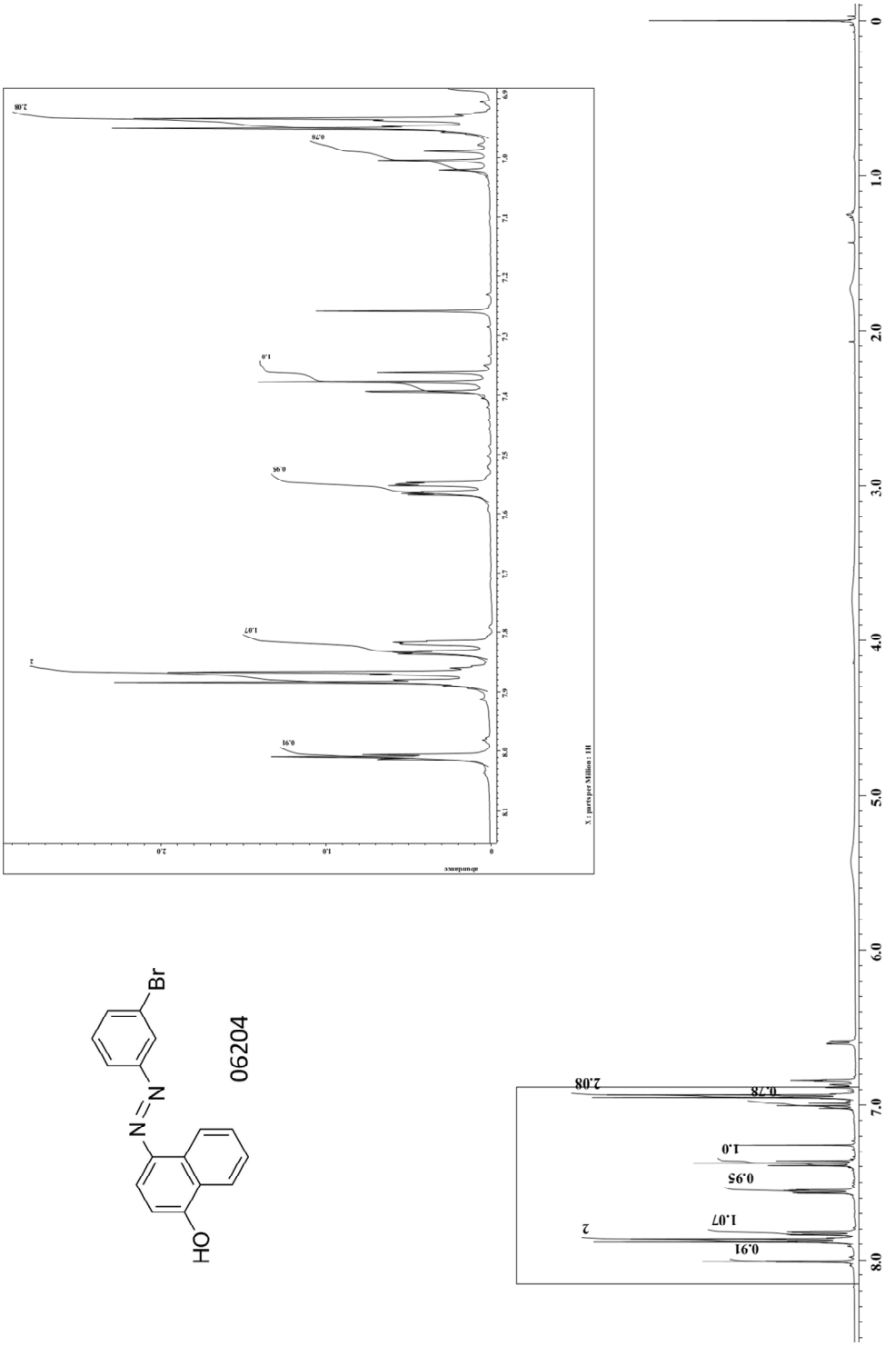
^{13}C-NMR Spectrum (500 MHz, $CDCl_3$)

4-((2,4-dimethoxyphenyl)diazenyl)naphthalen-1-ol



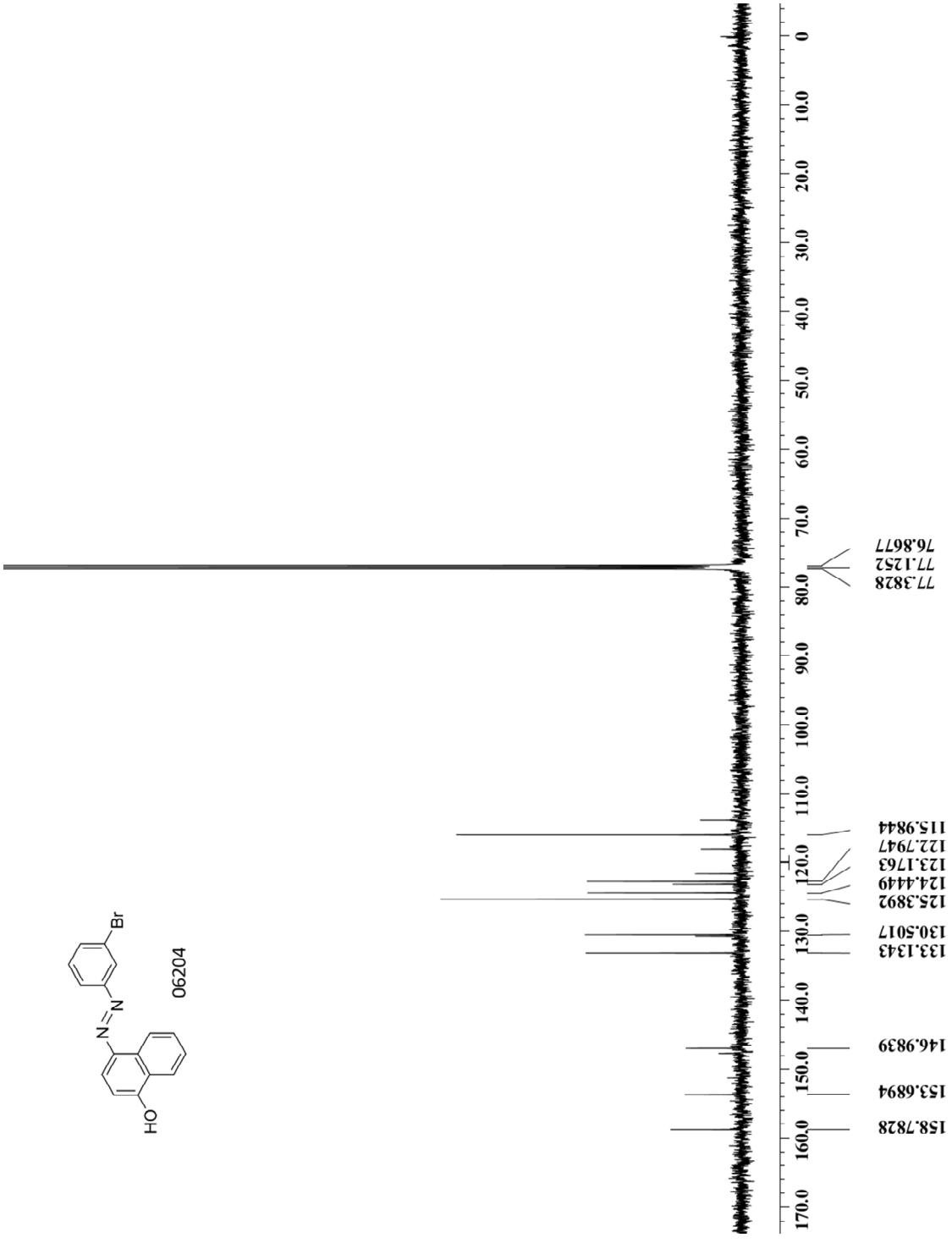
^{1}H-NMR Spectrum (500 MHz, $CDCl_3$)

4-((3-bromophenyl)diazenyl)phenol



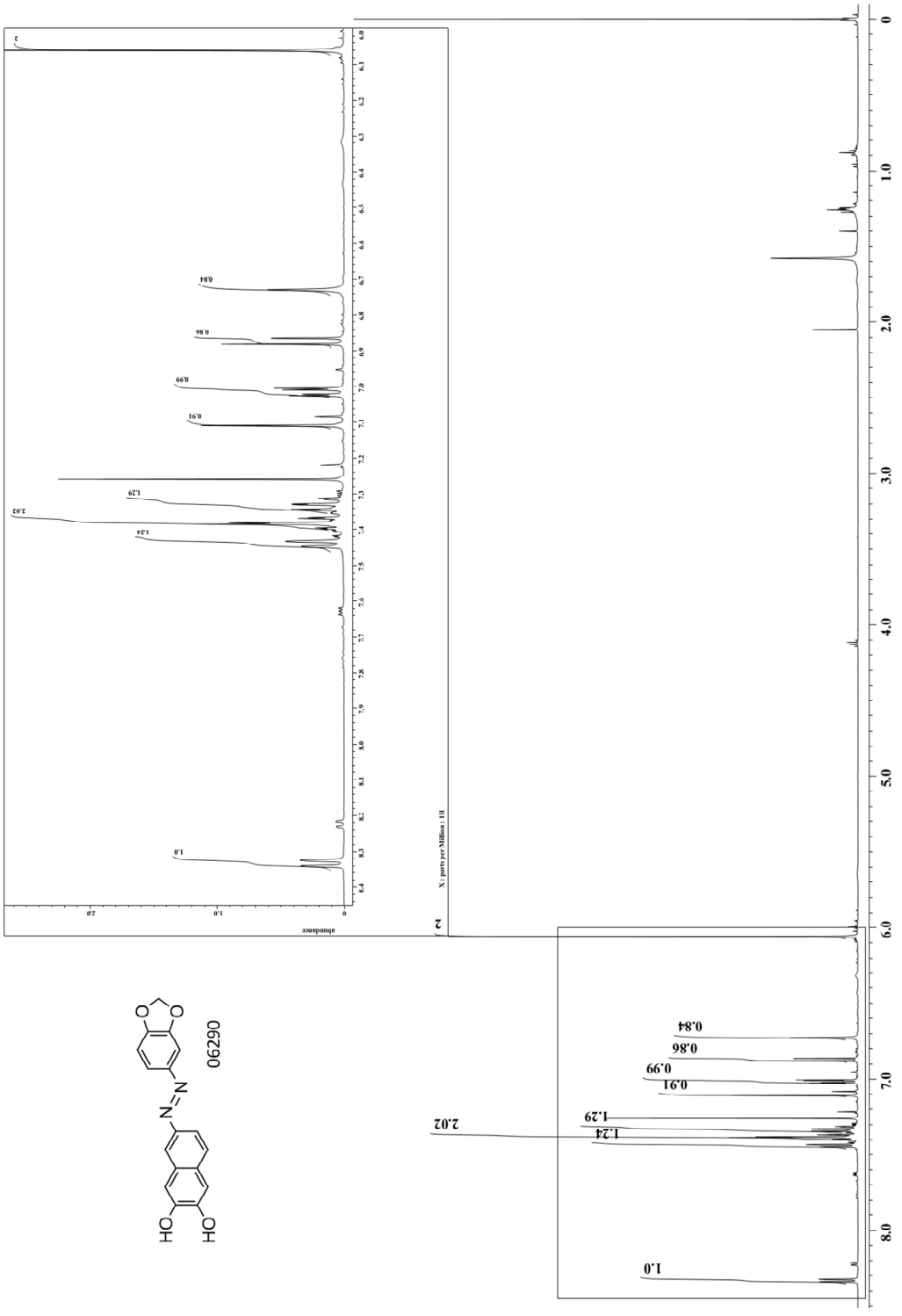
^{13}C-NMR Spectrum (500 MHz, $CDCl_3$)

4-((3-bromophenyl)diazenyl)phenol



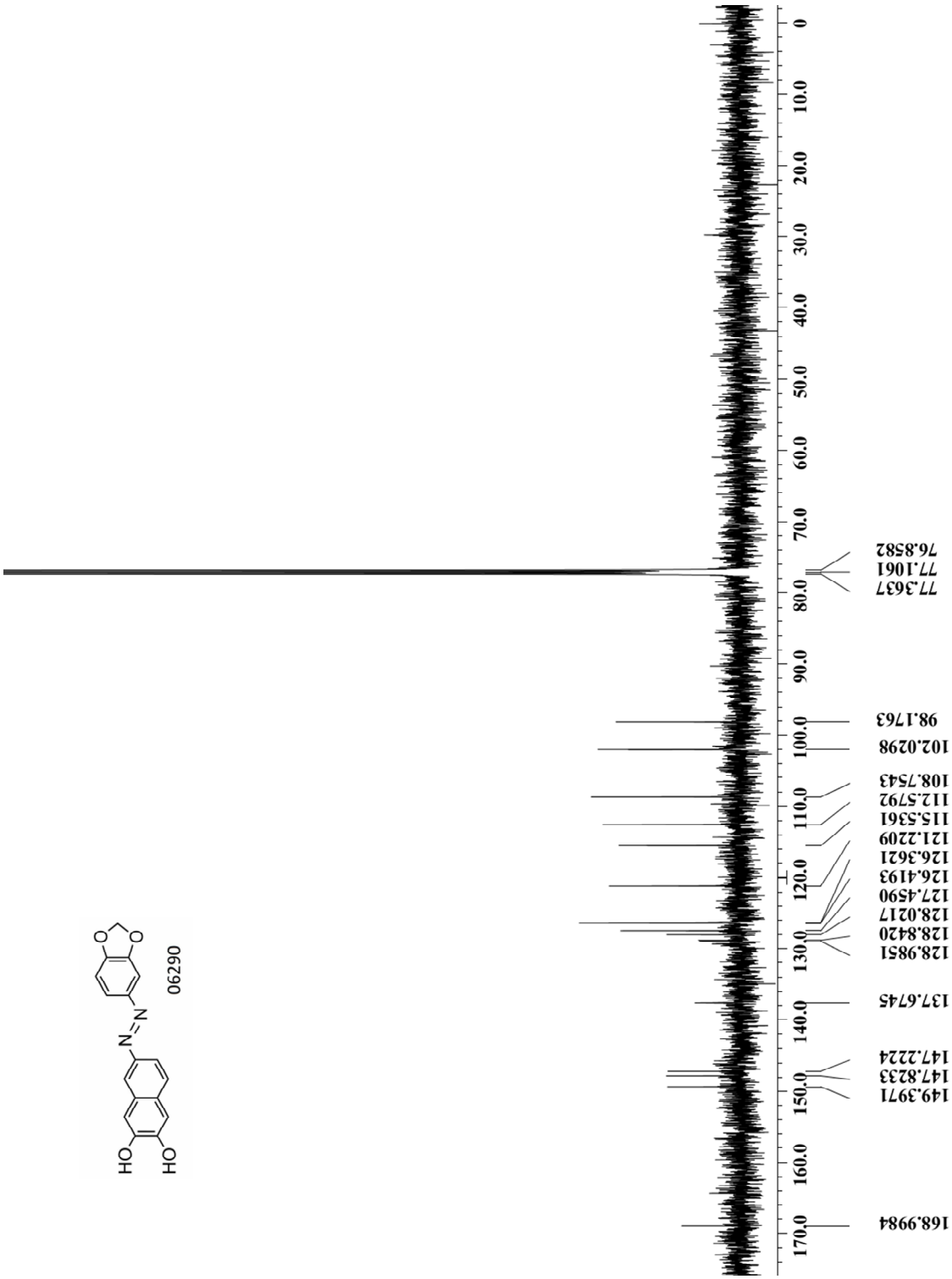
^{1}H-NMR Spectrum (500 MHz, $CDCl_3$)

6-(benzo[d][1,3]dioxol-5-yldiazenyl)naphthalene-2,3-diol



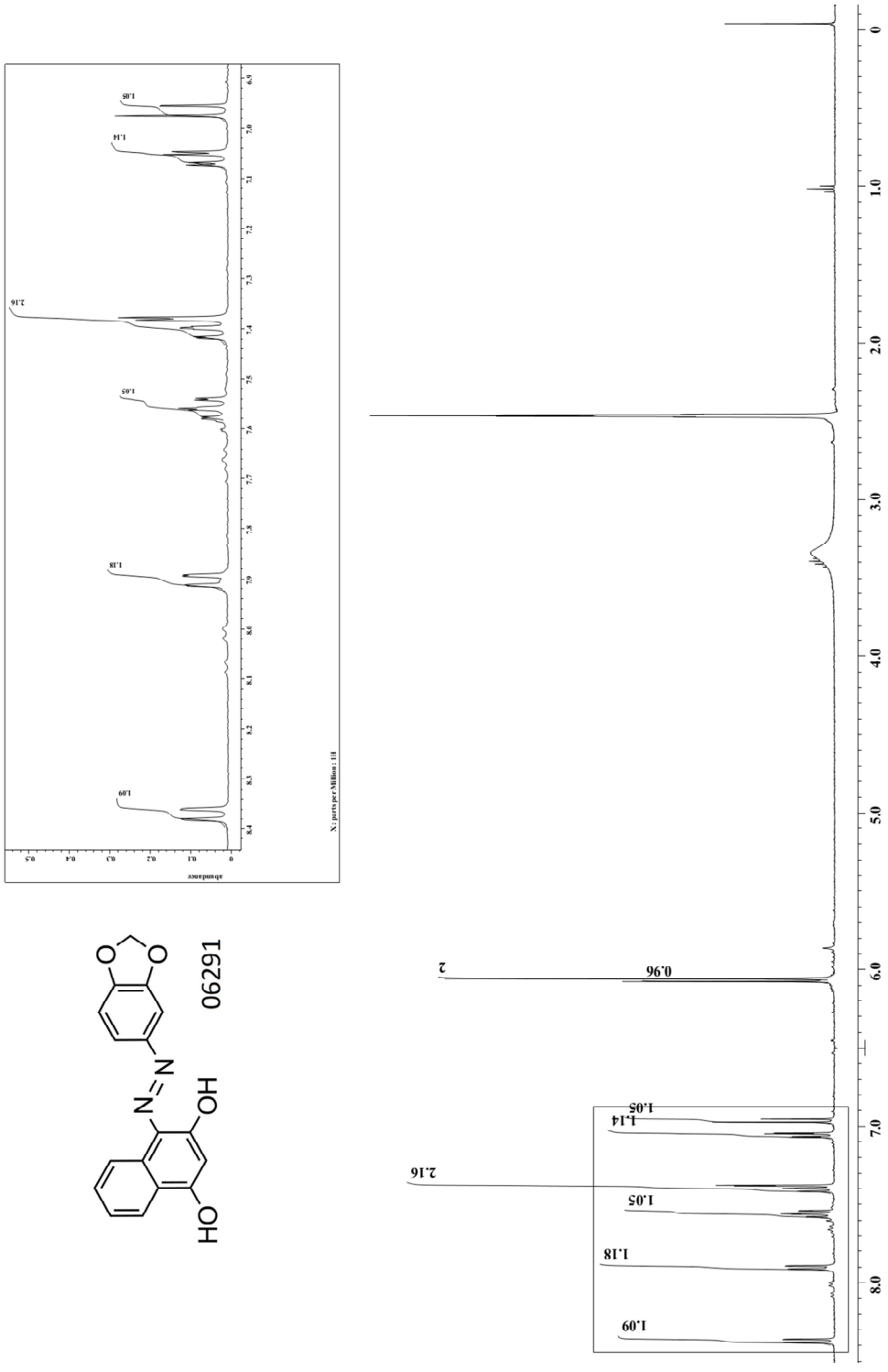
^{13}C-NMR Spectrum (500 MHz, $CDCl_3$)

6-(benzo[d][1,3]dioxol-5-yldiazenyl)naphthalene-2,3-diol



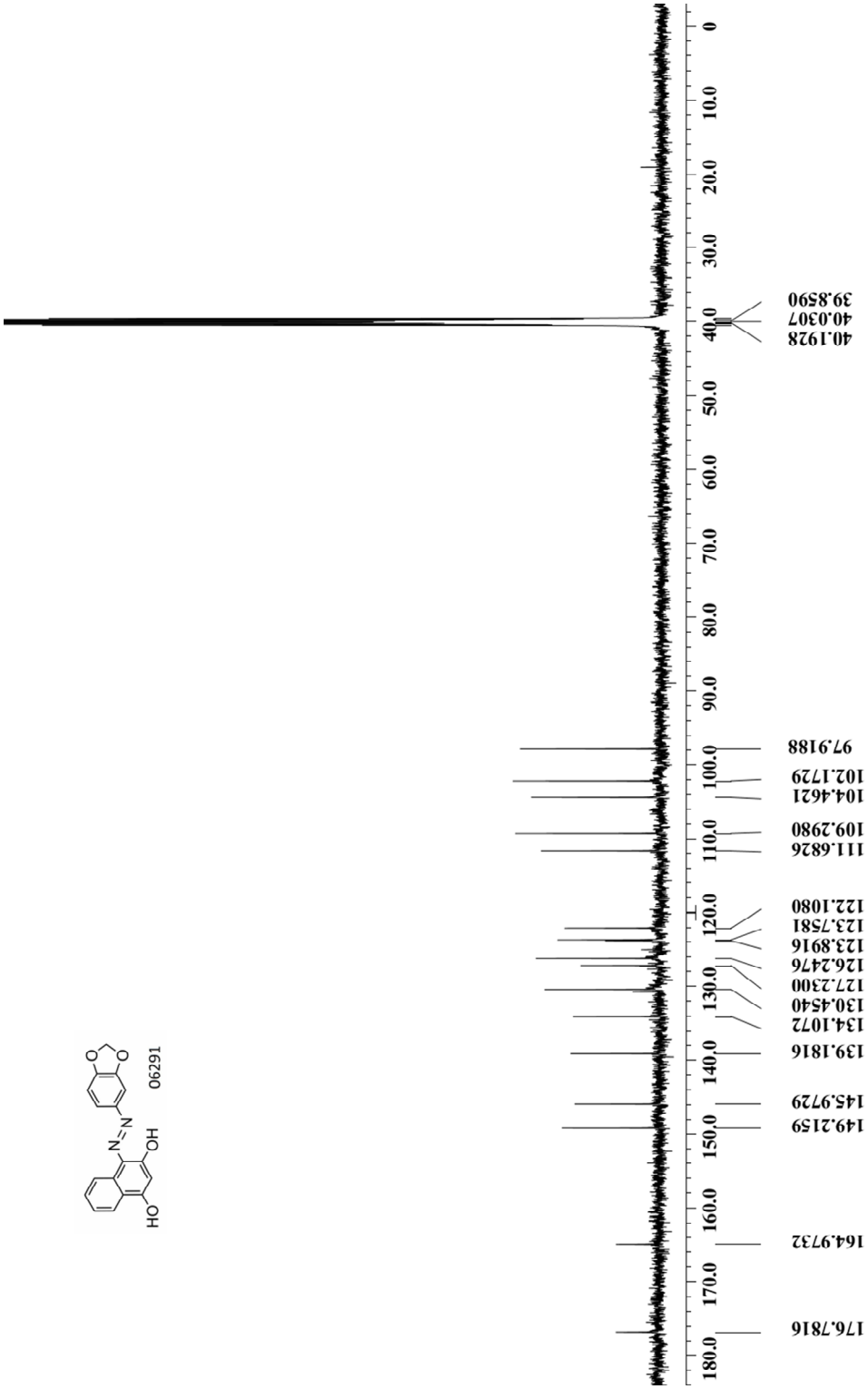
^{1}H-NMR Spectrum (500 MHz, DMSO-d6)

4-(benzo[d][1,3]dioxol-5-yldiazenyl)naphthalene-1,3-diol



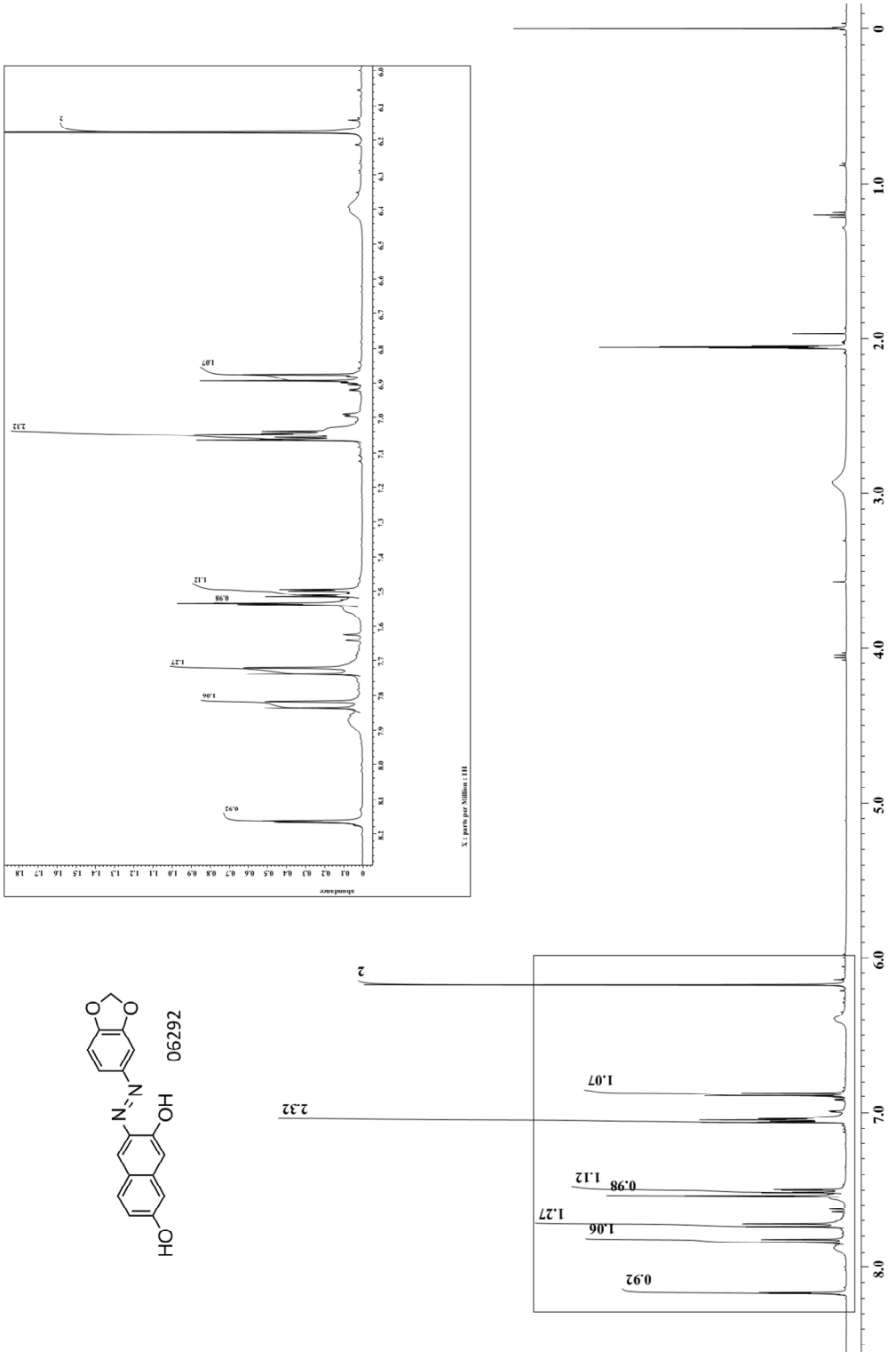
^{13}C-NMR Spectrum (500 MHz, DMSO-d6)

4-(benzo[d][1,3]dioxol-5-yldiazenyl)naphthalene-1,3-diol



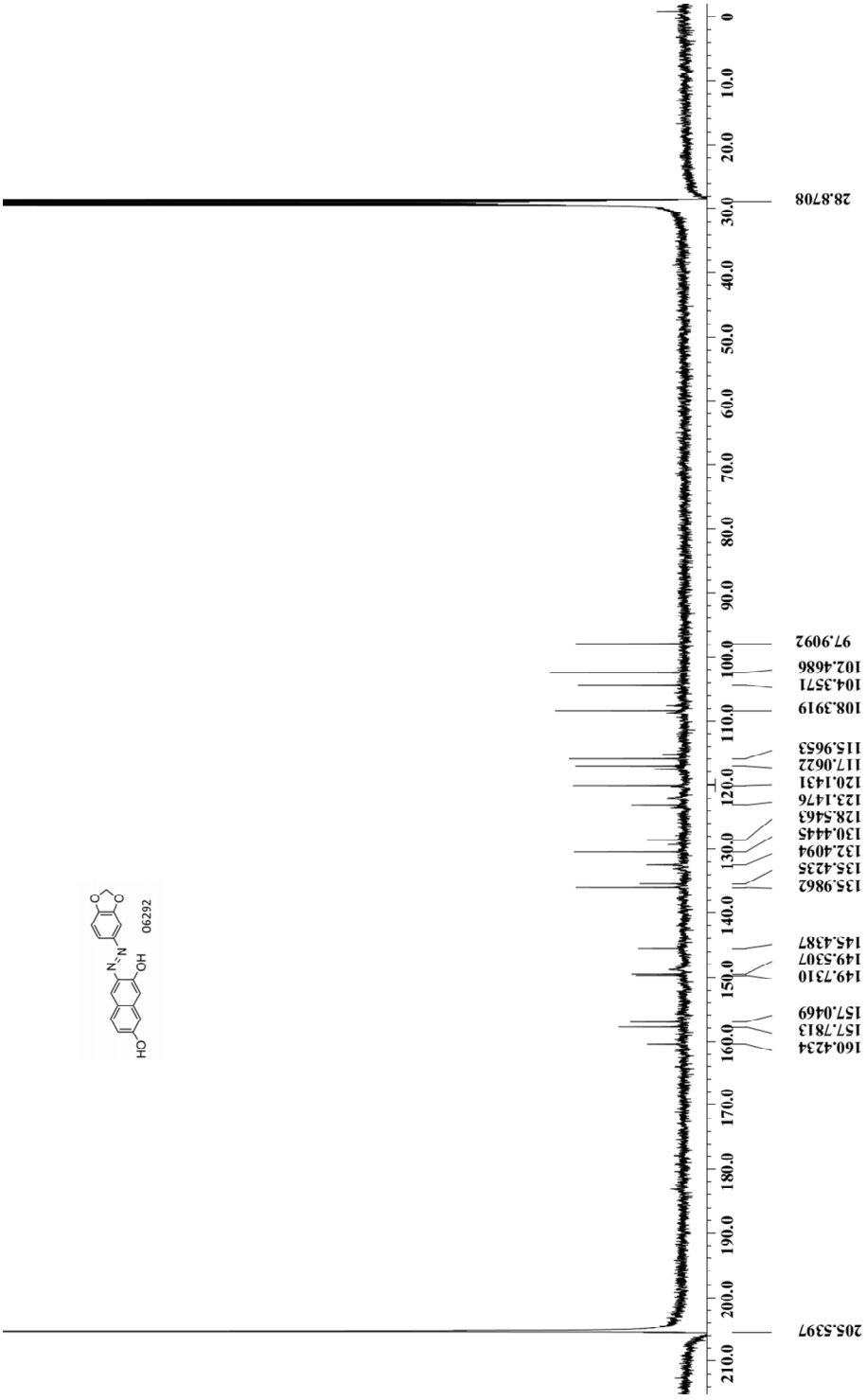
H NMR (500MHz, acetone-D6)

3-(benzo[d][1,3]dioxol-5-yldiazenyl)naphthalene-2,7-diol



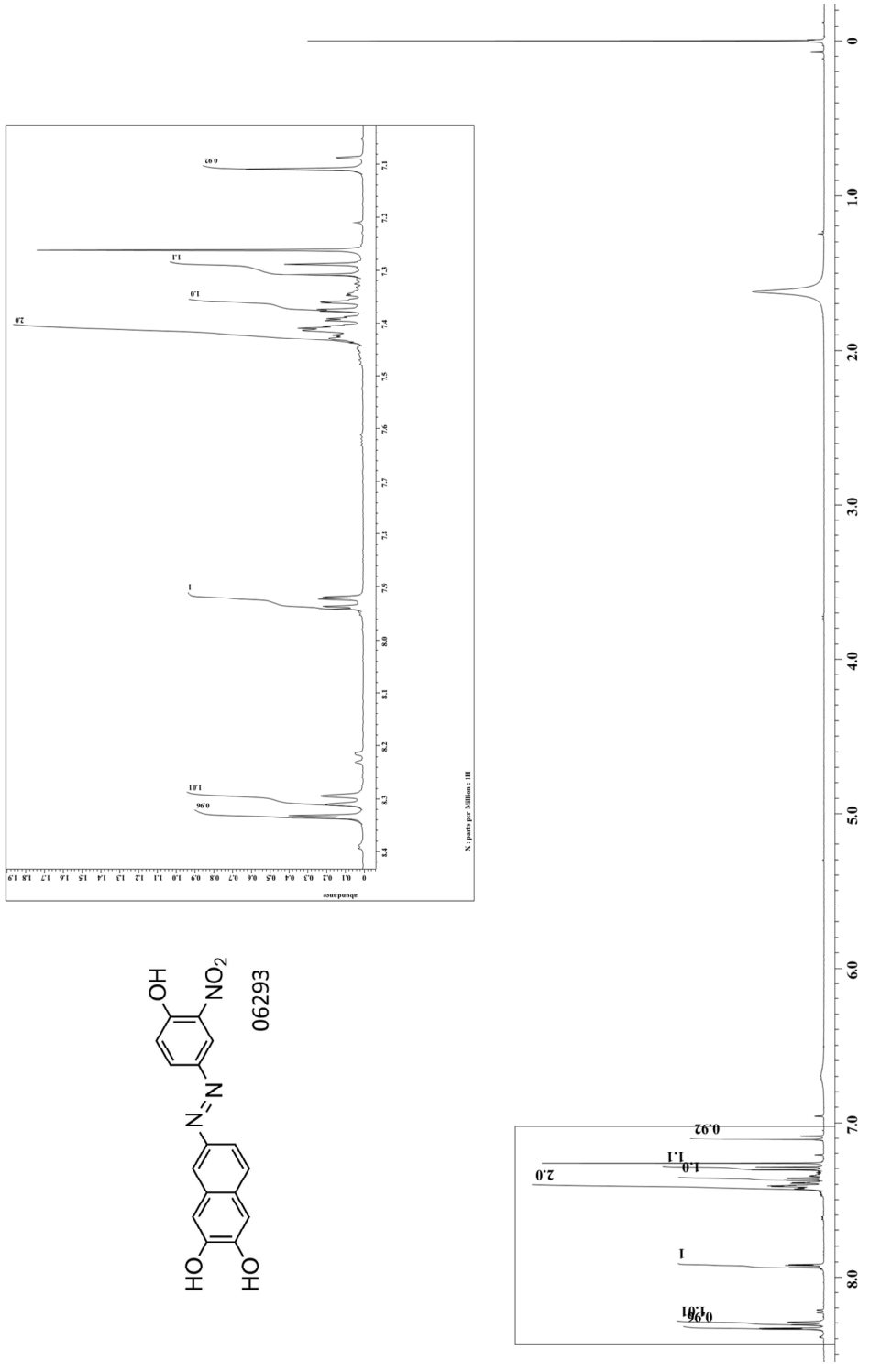
^{13}C-NMR Spectrum (500 MHz, acetone-d6)

3-(benzo[d][1,3]dioxol-5-yldiazenyl)naphthalene-2,7-diol



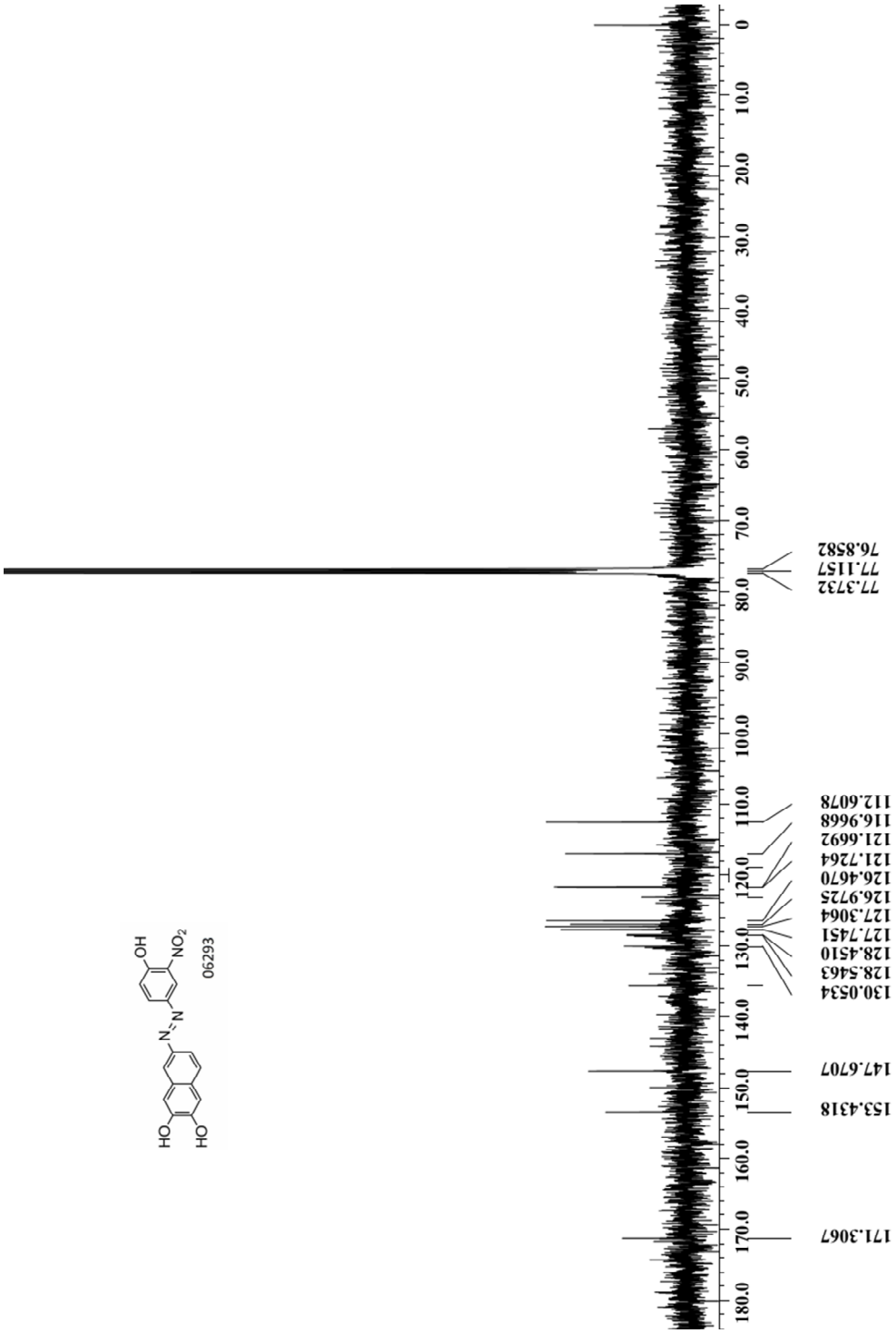
^{1}H-NMR Spectrum (500 MHz, $CDCl_3$)

6-((4-hydroxy-3-nitrophenyl)diazenyl)naphthalene-2,3-diol



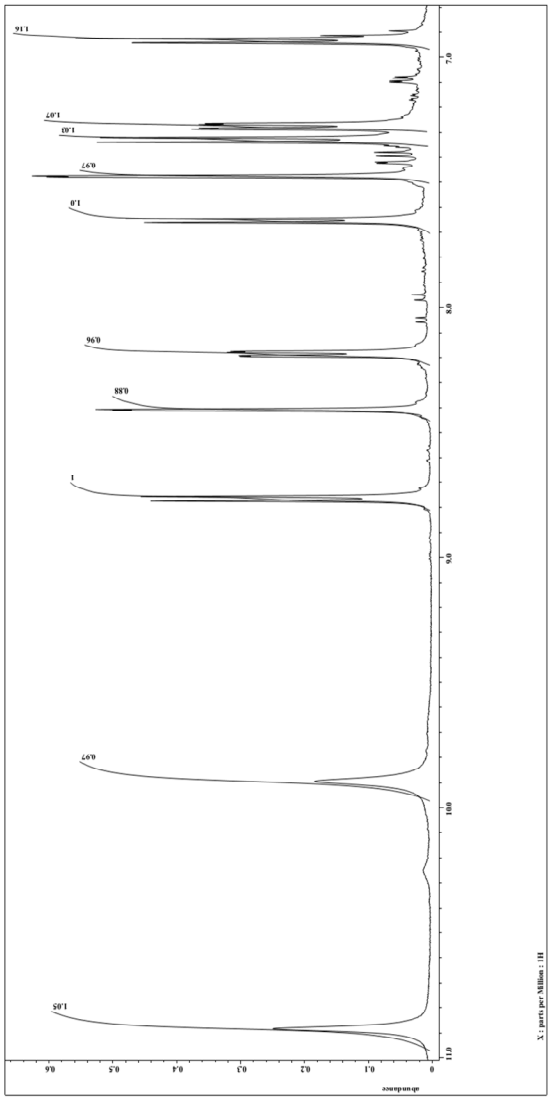
^{13}C-NMR Spectrum (500 MHz, $CDCl_3$)

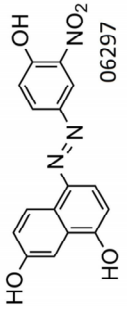
6-((4-hydroxy-3-nitrophenyl)diazenyl)naphthalene-2,3-diol

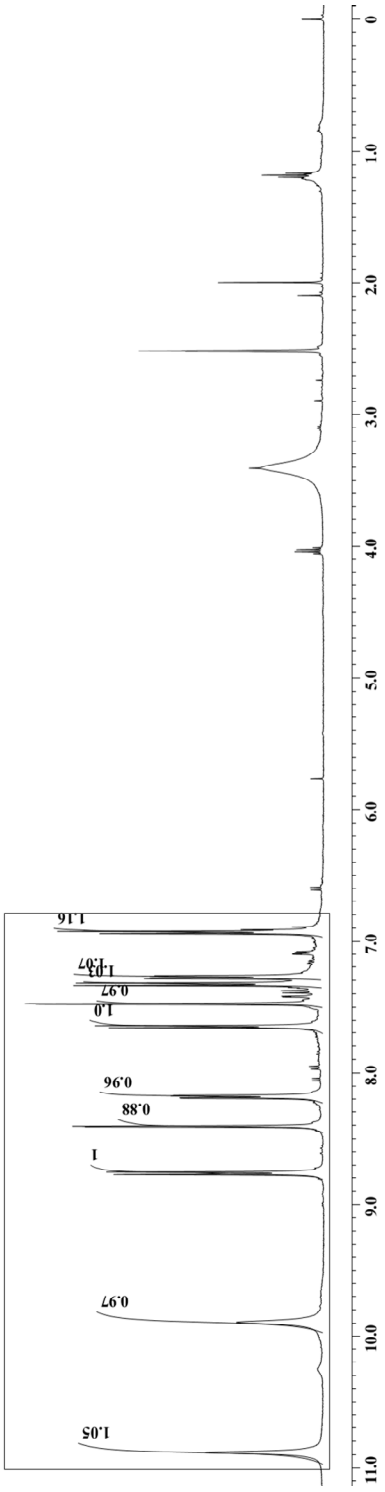


^{1}H NMR Spectrum (500MHz, DMSO-D6)

4-((4-hydroxy-3-nitrophenyl)diazenyl)naphthalene-1,7-diol

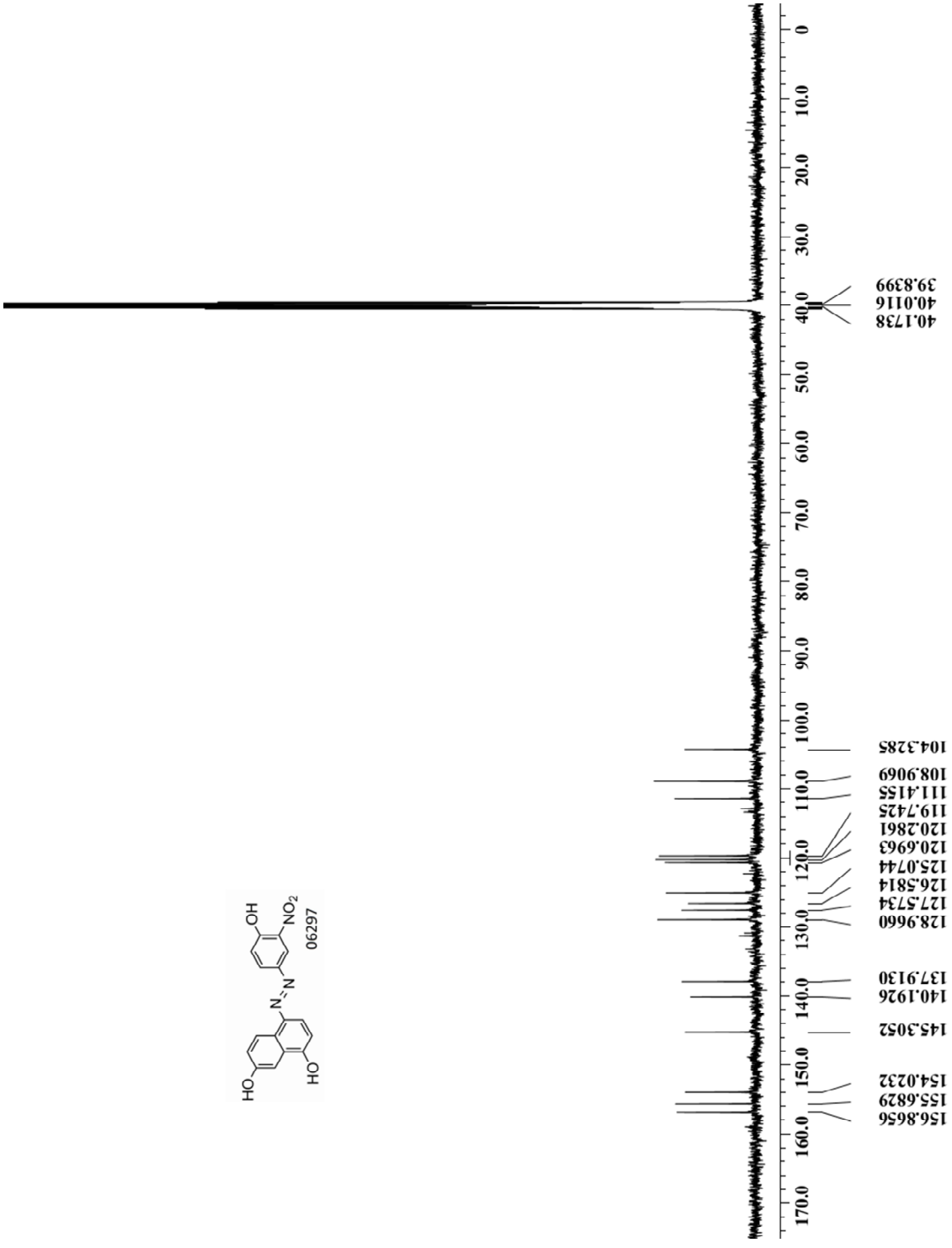






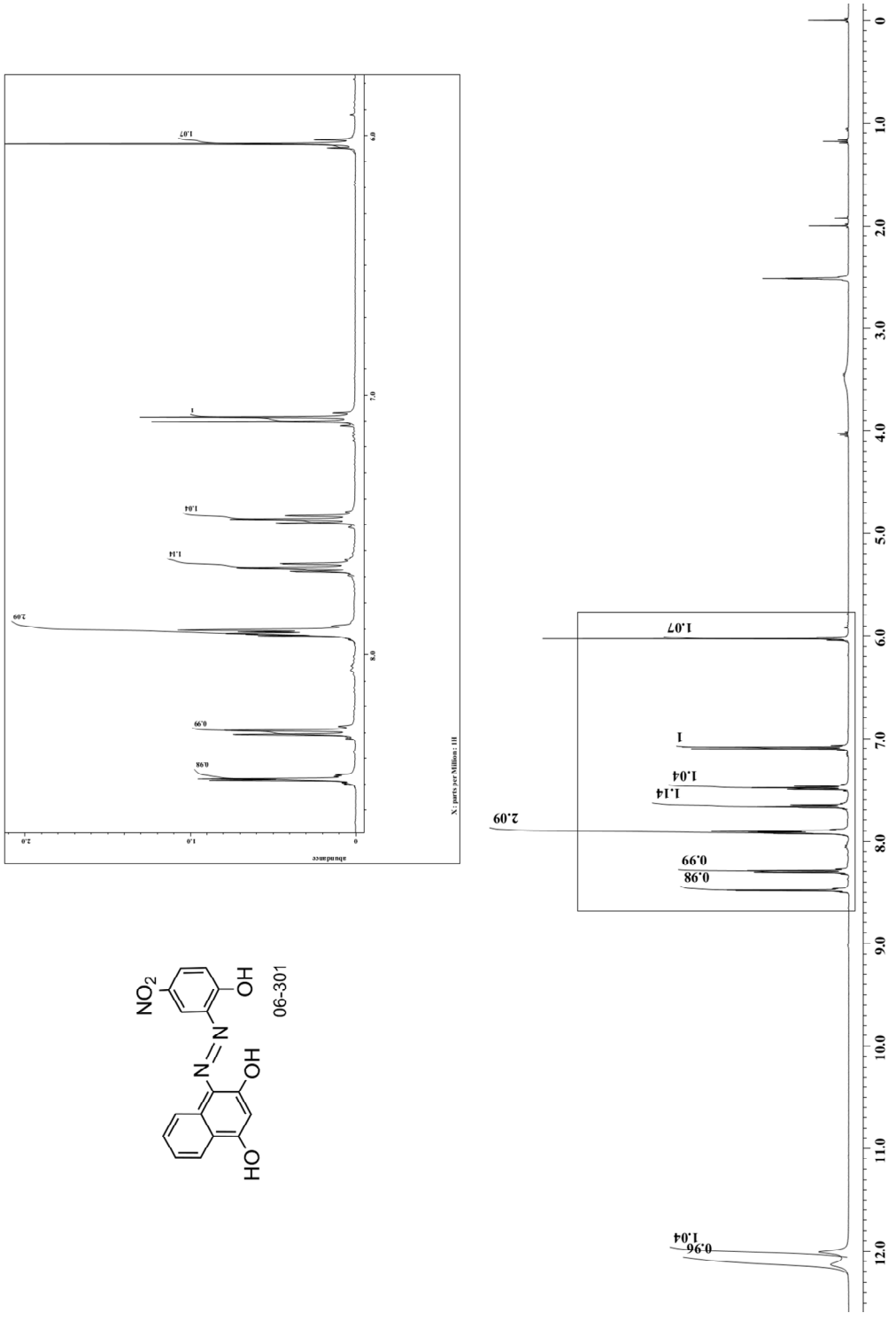
^{13}C NMR Spectrum (500MHz, DMSO-D6)

4-((4-hydroxy-3-nitrophenyl)diazenyl)naphthalene-1,7-diol



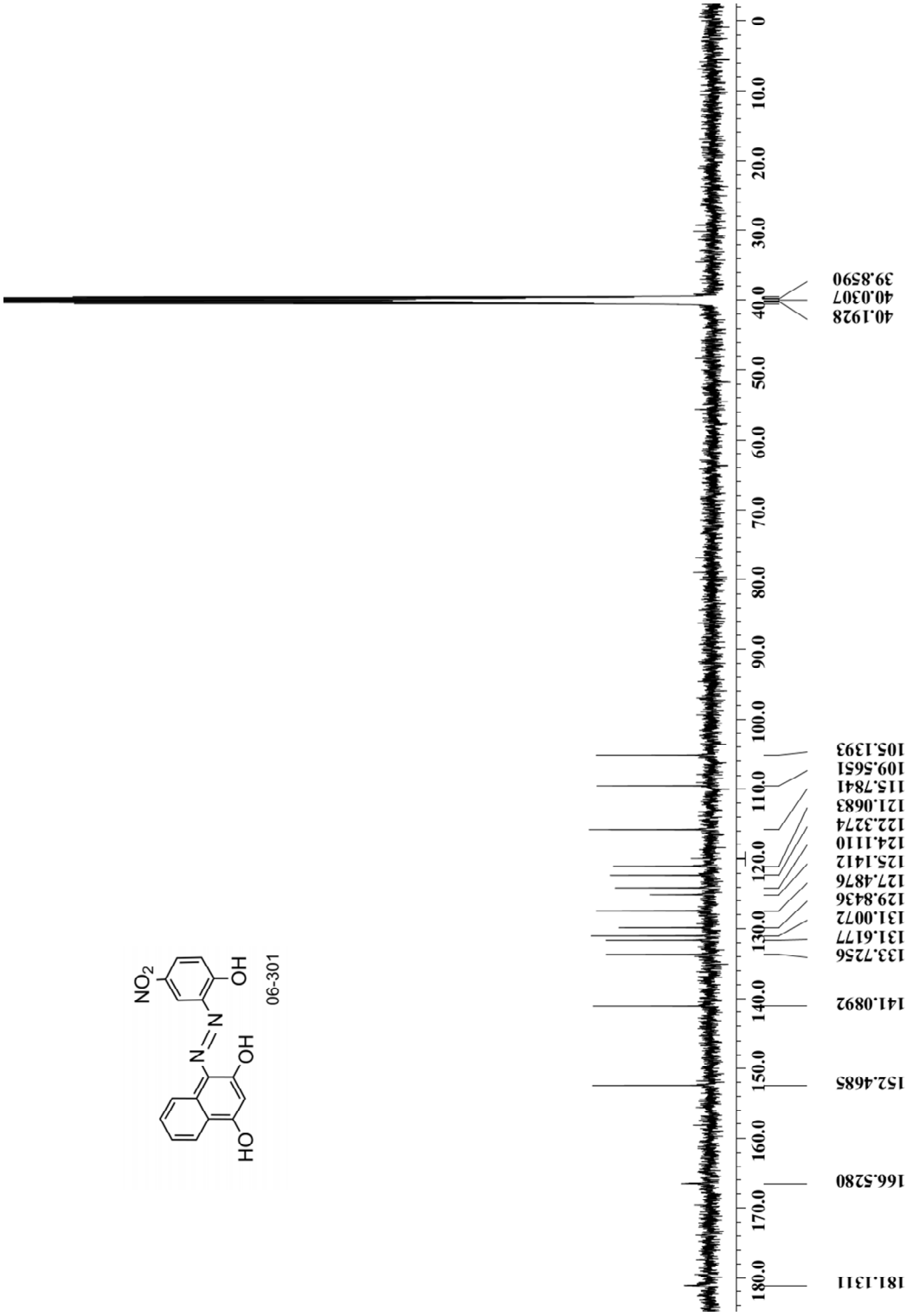
^{1}H NMR Spectrum (500MHz, DMSO-D6)

4-((2-hydroxy-5-nitrophenyl)diazenyl)naphthalene-1,3-diol



^{13}C NMR Spectrum (500MHz, DMSO-D6)

4-((2-hydroxy-5-nitrophenyl)diazenyl)naphthalene-1,3-diol



Vita

Tomas Vasquez was born in San Benito, Texas and raised in Hebbronville, Texas by his parents Tomas and Laura J. Vasquez (dec.). He has two daughters named Sophia Michelle Vasquez and Marissa Isabel Vasquez. Tomas received his Bachelor of Science from Texas A&M University Kingsville. After earning his undergraduate degree, he worked for Economy Polymers and Chemicals in Houston, Texas then decided to return to graduate school. He received his Master of Science in Chemistry from Texas A&M University Kingsville where he researched the catalytic asymmetric alkylation of indanones under the tutelage of Dr. Apu Bhattacharya. He continued his graduate studies at the University of Texas Medical Branch under the supervision of Dr. Scott Gilbertson where he worked on the total synthesis of Salvinorin A and synthesized broad-spectrum inhibitors of West Nile and Dengue Virus NS3 proteases.

Publications:

- Bhattacharya, A., Patel, N. C., Vasquez, T., Tichkule, R., Parmar, G., Wu, J. "Surfactant-mediated solvent-free dealkylative cleavage of ethers and esters and trans-alkylation under neutral conditions", Tetrahedron Letters 2006, 47, 565-567.
- Bhattacharya, A., Vasquez, T., Ramirez, T., Plata, R. E., Wu, J. "Pseudoenzymatic catalyst-substrate interactions in ion-pair mediated chiral phase transfer catalysis" Tetrahedron Letters 2006, 47, 5581-5583.

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This dissertation was typed by Tomas Vasquez.