UNIVERSITY OF CALIFORNIA, SAN DIEGO

The Enantioselective Total Synthesis of (+)-Symbioimine

A dissertation submitted in partial satisfaction of the

requirements for the degree Doctor of Philosophy

in

Organic Chemistry

by

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The Dissertation of Stephen C. Born is approved, and it is acceptable

In quality and form for publication on microfilm and electronically:

Chair

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DEDICATION

I dedicate this work to my family, whose unconditional love and guidance, whether wanted or not, and whether deserved or not, have not just helped form the person I am today, but have also served to instill in me the inspiration to set high goals and the confidence to achieve them.

Moreover, they are not to blame for my ridiculous appearance and behavior while I achieve these goals.

I also dedicate this to Shannon Werner, my erstwhile partner in shenanigans, tomfoolery, and general rambunctiousness, who, while supportive of my work and also sharing the many uncertainties, challenges, and sacrifices for completing this dissertation, above all deserves your sympathy, because she is the one who lives with and puts up with me, my messes, and above all, my love.

EPIGRAPH

Of all the things I miss, I miss my mind the most.

Ozzy Osbourne

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Chapter 2, in full, is unpublished material.

Chapter 3, in full, is a retelling of the material as it appears in *Synlett* **2008**, No. *16*, 2479-2482. Born, Stephen; Kobayashi, Y. The dissertation author was the primary investigator and author of this material.

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Born, S.C.; Kobayashi, Y. "Masked A Stable Synthetic Equivalent of 2,3 Dihydropyridine." *Synlett*, **2008**, *16*, 2479-2482.

Born, S.C.; Bacani, G.; Olsen, E.E.; Kobayashi, Y. "Microwave-Assisted Intramolecular Diels-Alder Reaction towards the Total Synthesis of Symbioimine." *Synlett*, **2008**, *18*, 2877-2881.

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ABSTRACT OF THE DISSERTATION

The Enantioselective Total Synthesis of (+)-Symbioimine

by

Stephen Christopher Born

Doctor of Philosophy in Organic Chemistry

University of California, San Diego, 2009

Professor Yoshihisa Kobayashi, Chair

(+)-Symbioimine is a marine-derived alkaloid isolated by Uemura in 2004 from a culture of *Symbiodinium* sp., a dinoflagellate that is a symbiont of the acoel flatworm *Amphiscolops* sp. This natural product has been found to inhibit osteoclastogenesis in the murine monocytic cell line RAW264 (EC_{50} = 44 μg/mL), suggesting that either it or its analogues may offer a new opening to the development of preventative treatments for osteoporosis. In addition, it has been found to exhibit inhibition of Cycloxygenase (COX-2), suggesting possible use as an antiinflammatory.

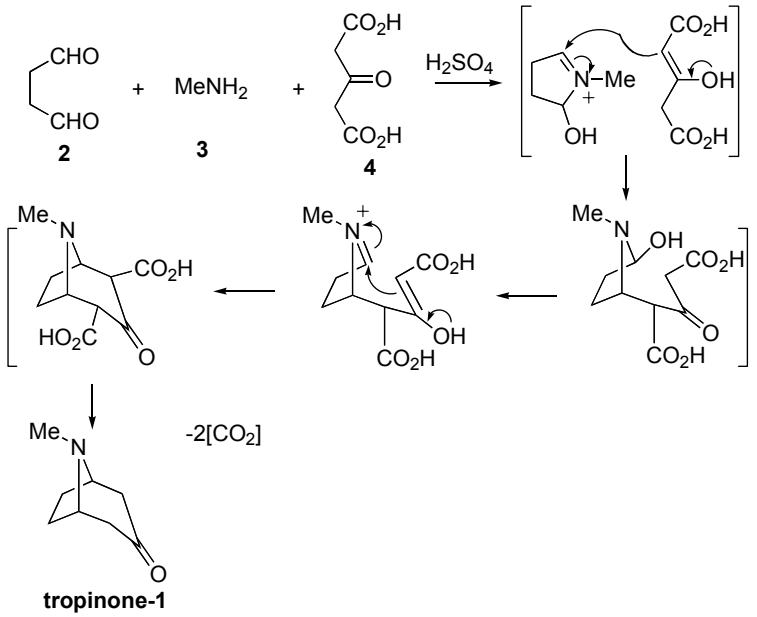
From a structural perspective, the bicyclic cyclohexenyl imine moiety is a unique feature endemic to several marine natural products. While it is postulated that these natural products undergo some version of the Diels-Alder reaction in their biosyntheses,

there has yet to be an investigation that has yielded a general method for its incorporation.

Herein I describe our investigation into and completion of the convergent, biomimetic, enantioselective total synthesis of (+)-Symbioimine, featuring an intramolecular, iminium-activiated Diels-Alder reaction that constructs the 6,6,6-tricyclic iminium framework as a single. Additionally, I will also report on our discoveries into the reactivity of various 2,3-dihydropyridine intermediates, the results of which may assist in the synthesis of the several other structurally similar natural products.

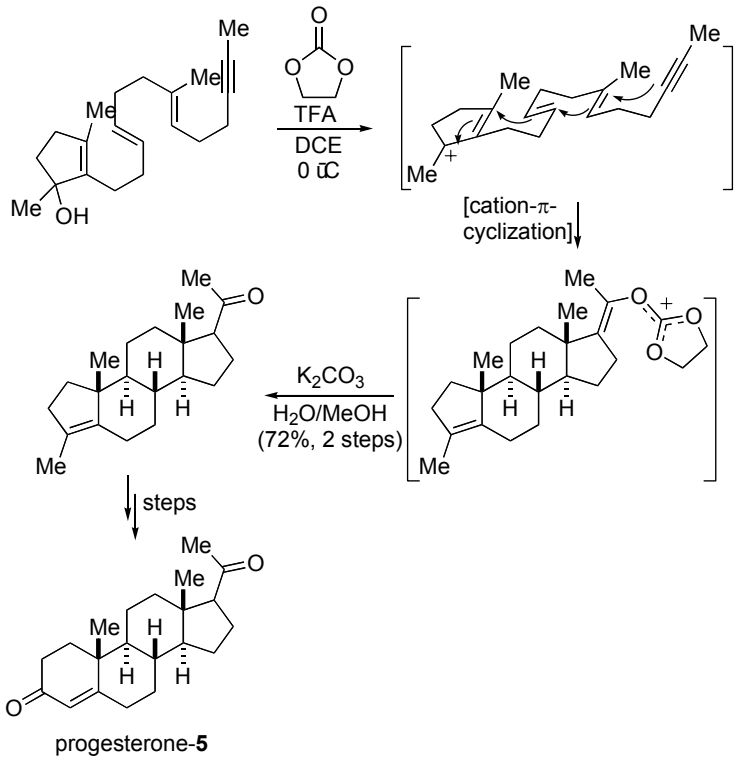
INTRODUCTION

Today, as never before, synthetic chemists are facing Herculean tasks in the construction of natural products, whose continual upsurge in molecular complexity and diversity stem in large part due to the technological advances in both spectroscopy and molecular purification. Although each synthetic endeavor is facilitated by an equally expanding number of technologies endowing tools for our attempts to outsmart these molecular chimeras, the general challenges are still being intensified. The demand continues to rise for solutions and strategies that surpass their predecessors in terms of not just their creativity, but also in their general utility and applicability to unrelated challenges. Not only do we seek to bequeath the next generation of experimentalists with a superior understanding of reaction, mechanism, and synthetic toolbox to tackle their chosen puzzles, but we also aspire, for the present, to be able to probe the chemical biology of complex molecules by gaining efficient access to designed analogues. With all of these objectives at the foremost in our minds, it quickly becomes obvious that our chances of achieving a lucrative outcome are greatly enhanced if we make every effort to improve our efficiency in forging new bonds, particularly carbon–carbon bonds. In this respect, cascade and tandem reactions have long been recognized as providing an admirable set of strategies and tactics, being traced back to the formative years of the practice of total synthesis when, in 1917, Sir Robert Robinson achieved the landmark, one-pot biomimetic synthesis of tropinone **1** from succindialdehyde **2**, methylamine **3**, and either acetone or a salt of acetonedicarboxylic acid **4** (Scheme 1).[1]



Scheme 1. Robinson's Biomimetic Total Synthesis of Tropinone **1**[1]

This 'gold standard' was once again attained in 1971 with W. S. Johnson's synthesis of progesterone **5** wherein a series of cation-π-cyclizations was exploited to assemble the entire carbon framework of this steroid in a single operation (Scheme 2).[2]



Scheme 2. Johnson's Key Cascade Reaction of the Progesterone **5** Framework

If we are to successfully emulate the elegance of these works and concomitantly advance the state of the art, current and future practitioners will need to delve deeply in search of creative insight and, in addition, will be required to hone their comprehension of the kinetics of multi-component transformations as well as the fundamentals of reaction mechanisms.

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[1] Robinson, R. *J. Chem. Soc.* **1917**, 762-768.

[2] (a) Johnson, W. S.; Gravestock, M. B.; Parry, R. J.; Myers, R. F.; Bryson, T. A.; Miles, D. H. *J. Am. Chem. Soc.* **1971**, *93*, 4330-4332. (b) Johnson, W. S.; Gravestock, M. B.; McCarry, B. E. *J. Am. Chem. Soc.* **1971**, *93*, 4332-34; (c) Johnson, W. S.; Gravestock, M. B.; McCarry, B. E.; Parry, R. J.; Ratcliffe, B. E. *J. Am. Chem. Soc.* **1978**, *100*, 4274-84.

CHAPTER 1

Introduction and Background of

Bioactive Iminium Alkaloids

A. Marine-derived Alkaloids as an Engine for Scientific Discovery

Alkaloids are nitrogen-containing compounds that occur naturally not only in plants but also in microorganisms, marine organisms, and animals. They are often useful as drugs or biological probes for physiological studies. As new and more complicated diseases are encountered worldwide, the importance of bioactive alkaloids has increased because of their potential application in chemotherapy.

Fascinating compounds with unique chemical structures and biological activities have been found from marine organisms. However, the true origins or progenitors of these metabolites are not entirely clear.[1] The possible primary producers of the secondary metabolites have been suggested to be microalgae, bacteria, and fungi, and they are carried through symbiosis, association, a food chain, and other forms of nutrient dependency. For instance, palytoxin (PTX) is a potent toxic polyol compound isolated from the zoanthid *Palythoa* sp., the bioorganic origin of which was questioned because of seasonal and regional variations.[2] In 1995, a PTX analogue, osteocin, was isolated from the dinofagellate *Ostreopsis siamensis*, and it has been suggested that its true origin is also microorganisms.[3]

Numerous bioactive nitrogenous compounds, such as peptides, indoles, oxazoles, and thiazoles, have been isolated from marine invertebrates. However, it is still not clear why alkaloids show significant biological activity. This question may never be answered for in vivo systems. In the eco-system, the alkaloidal metabolites of cyanobacteria help to inhibit predation by marine herbivores, such as fish and sea urchins.[4]

Recently, several novel bioactive compounds possessing a cyclic imino group fused with a macrocarbocycle, such as pinnatoxins, gymnodimine, and symbioimine have

been reported. In this chapter, I will summarize the structure, biological activity, and biogenesis of these bioactive iminium alkaloids, as well as those with proposed biosyntheses involving iminium-activated cycloadditions, with an emphasis on symbioimine, including the relevant synthetic efforts by other research groups on its total synthesis.

B. Biosynthetic Diels-Alder Reactions

The Diels-Alder reaction is a powerful reaction for the formation of carbon-carbon bonds in synthetic organic chemistry which allows facile, stereospecific entry into six-membered ring systems. The structures of various secondary metabolites have led to an array of provocative proposals which suggest that nature might also make use of this valuable reaction. An intriguing aspect of many of these biosynthetic proposals involves the possibility of enzymatic catalysis of [4+2] cycloaddition, which would accommodate the stereochemistry extant in the respective natural product. Enzymes generally catalyze reactions by stabilizing the structure and charge of the developing transition state. For most reactions subject to this stratagem of catalysis, both the starting substrate and the product differ significantly from the transition state with respect to structure. Both the product and the starting substrate must bind to the enzyme less tightly than the transition-state structure for catalysis to occur. The transition state in the Diels-Alder reaction is highly ordered and closely resembles the structure of the product. In other words, an enzyme that was designed to stabilize the transition state structure for this reaction would be expected to be inhibited by the product (by tight binding) and turnover (thus, catalysis) would be precluded. Alternatively, the free energy of activation can be lowered by

raising the ground-state energy of the reactants. This might be accomplished in the Diels-Alder reaction by the introduction of torsional strain into the dienophile or diene components, but it is difficult to find solid precedent for this strategy in the literature. The prospect of discovering a Diels-Alderase is therefore especially enticing to mechanistic enzymologists, since it could represent a new mechanism of catalysis in nature.

C. Macrocyclic Iminium Shellfish Poisons (Pinnatoxins)

Shellfish of the genus *Pinna* live mainly in shallow waters of the temperate and tropical zones of the Indian and Pacific Oceans.[5] The adductor muscle of this bivalve is eaten in Japan and China, and food poisoning resulting from its ingestion occurs frequently.[6] Chinese investigators have reported that a toxic extract from *P. attenuata*, referred to as pinnatoxin, is a Ca^{2+} channel activator.[7a] The Uemura group has isolated pinnatoxin A (**1**), a mixture of pinnatoxins B and C (**2**, **3**), and pinnatoxin D (**4**) from *P. muricata* (Figure 1).[7]

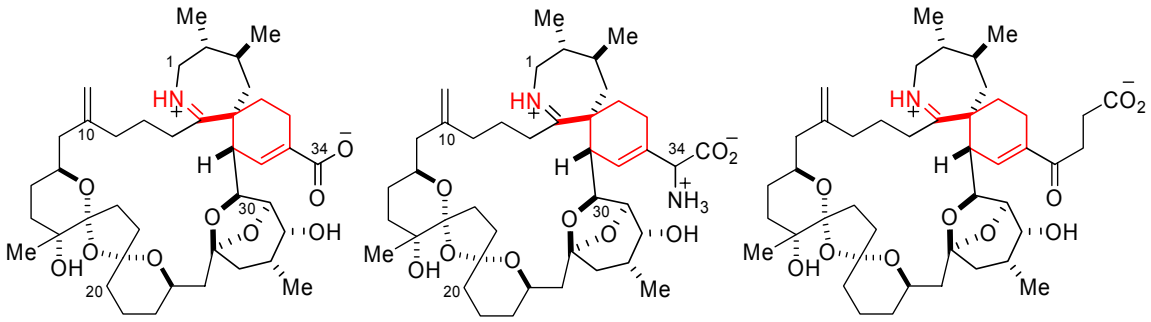
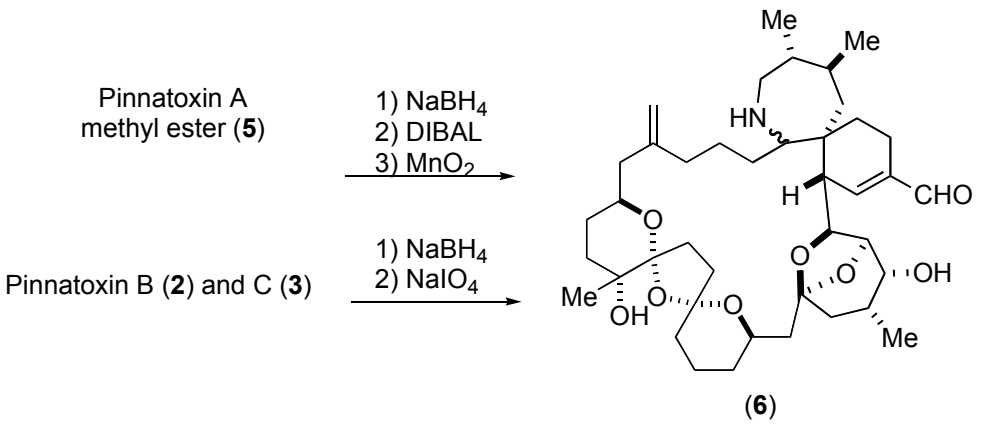


Figure 1. Structure of Pinnatoxins

The structures and stereochemistry of pinnatoxins have been clarified by extensive NMR experiments and positive ion ESI MS/MS spectra.[8] Pinnatoxins consist of a 20-membered carbocyclic ring, i.e., with 5,6-bicyclo, 6,7-azaspiro, and 6,5,6-triketal moieties in their structure. In particular, they contain a carboxylate anion and an iminium cation or an ammonium cation. Pinnatoxin A (**1**) showed potent acute toxicity against mice (LD99 180 μg/kg (ip)) with characteristic neurotoxic symptoms. Recently, Kishi's group achieved the total synthesis of **1** and *ent*-**1**.[9] Interestingly, while natural **1** showed significant acute toxicity, its antipode *ent*-**1** showed no toxicity.[10] This investigation also clarified the stereochemistry of **1**, including its absolute stereochemistry.

Pinnatoxins B (**2**) and C (**3**), the most toxic constituents in the pinnatoxin series, have been isolated from *P. muricata* (as a 1:1 mixture).[7e] The LD99 values of **2** and **3** have been reported to be 22 μg/kg, which makes them as potent as tetrodotoxin, the well known fatal substance found in pufferfish. Although they were obtained in small amounts (~0.3 mg), the structures and relative stereochemistries of the macrocycles in **2** and **3** were successively confirmed by mass spectrometry. Reduction of the imino group in **2** and **3** with $NaBH_4$ followed by oxidative cleavage with $NaIO_4$ provided aldehyde **6** (Scheme 1). The spectroscopic data of **6** derived from **2** and **3** were the same as those of the pinnatoxin A methyl ester (**5**), which was obtained by the reduction of iminium and a carboxylic acid moiety followed by oxidation of the resulting alcohol. Thus, the relative stereochemistry of the macrocyclic core in **2** and **3** was the same as that in pinnatoxin A (**1**).



Scheme 1. Demonstration of Stereochemical Similarity of the Pinnatoxins

Although pinnatoxin D (**4**) showed weaker acute toxicity than the other pinnatoxins (LD50 > 10 μg/MU), **4** showed the strongest cytotoxicity against the murine leukemia cell line P388 (IC50 2.5 μg/mL).

The backbone (**7**) of pinnatoxins and their analogues could be configured from C1 to C34 in a single carbon chain, in a polyketide biogenetic pathway (Figure 2). Based on the structural similarity of the imine moiety adjacent to the spirocyclic core, other macrocyclic imines represented by pinnatoxin may also be biosynthesized via a similar intramolecular Diels–Alder reaction.

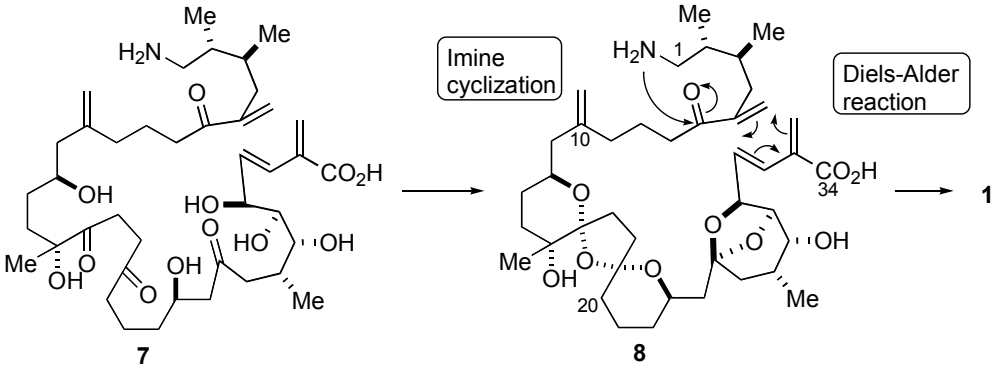


Figure 2. Proposed Biogenesis of Pinnatoxin A (**1**).

D. Other Macrocyclic Iminium Toxins Related to Pinnatoxins

Several shellfish poisons containing a cyclic iminium moiety have been isolated (Figure 3). In their study of shellfish poisons, the Uemura group observed that a moray eel vomits the viscera of the Okinawan bivalve *Pteria penguin* (that must have been fun to work with). Pteriatoxins A (**9**), B, and C (**10**, **11**: a 1:1 mixture) were successively isolated from this shellfish species.[11] Based on the analysis of 2D-NMR spectra and positive ion ESI MS/MS spectra, they were determined to be pinnatoxin analogs that contained a cysteine moiety. Pteriatoxins (**9**–**11**) showed significant acute toxicity against mice with LD99 values of 100 and 8 μg/kg, respectively. The toxic symptoms of pteriatoxins resemble those of pinnatoxins. Extracts from the digestive glands of several *Pinna* sp., including *P. muricata*, *P. attenuata*, *P. atropupurea*, and the commonly eaten shellfish *Atrina pectinata*, all produced the same symptoms of poisoning in mice. These data suggest that Pinna shellfish may become toxic as the result of feeding on toxic organisms such as dinoflagellates. Also, based on the presence of pinnatoxin analogs in both shellfish *Pinna* sp. and *Pteria* sp., the pinnatoxin series may be biosynthesized by microorganisms that are in the food chain of or in a symbiotic relationship with these shellfish.

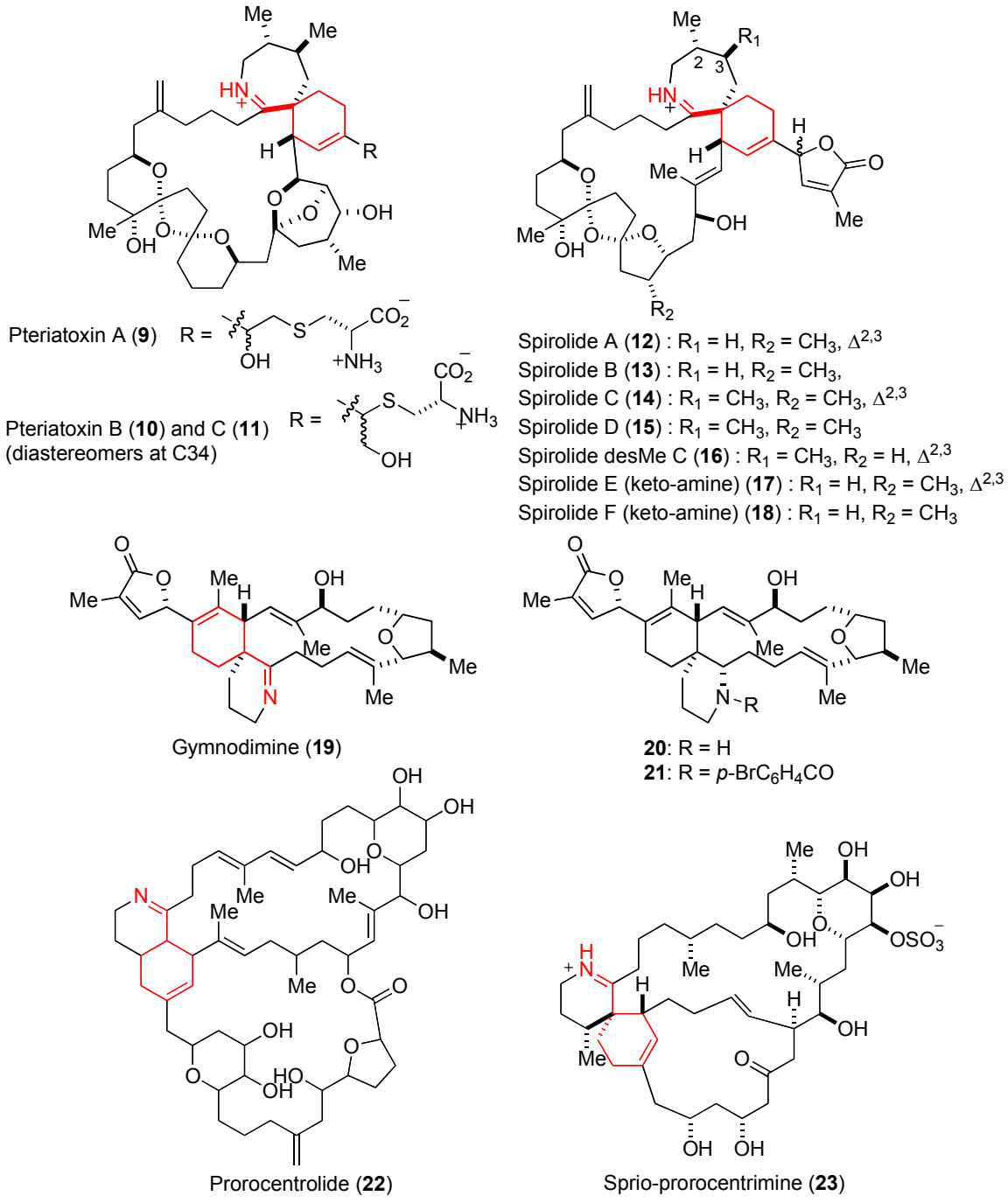


Figure 3. Structures of Polyether Toxins Containing Imine Moieties.

Spirolides, a class of macrocyclic imines, were identified in extracts of the digestive glands of mussels and scallops from the Atlantic coast of Nova Scotia,

Canada.[12] The marine dinoflagellate *Alexandrium ostenfeldi* (Paulsen) Balech and Tangen was identified as the cause of spirolide toxicity in Nova Scotia in the early 1990's.[13] Seven compounds, spirolides A–D (**12**–**15**) and 13-demethyl C (**16**), which show toxicity against mice, and the keto amine derivatives E and F (**17** and **18**), have been isolated and structurally characterized from shellfish extracts and cultured dinoflagellate isolates from Nova Scotia. The spirolide family contains a 5-5-6 trispiroketal ring system. Recently, the relative stereochemistry of spirolides B (**13**), D (**15**), and 13-demethyl C (**16**), except for one chiral center, has been determined from 2D NMR data analysis and a molecular modeling method, which showed that these compounds have the same relative stereochemistry as pinnatoxins in the region of their common structure.[14]

Other known marine toxins possessing a cyclic imine moiety are gymnodimine, centrimine, and proro-centrimine. Gymnodimine (**19**) was isolated from the New Zealand oyster *Tiostrea chilensis* and the dinoflagellate *Gymnodinium* sp., and its structure was established.[15] The MLD (minimum lethal dose) of **19** was 450 μg/kg, and this compound also showed potent ichthyotoxicity against the fish *Tanichthys albonubes* at 0.1 ppm. The absolute stereostructure of gymnodimine (**19**) has been established by an X-ray crystal structure analysis of the *p*-bromobenzamide derivative **21** derived from gymnodamine (**20**).[16] Gymnodimine B, which contains an exocyclic methylene at C-17 and an allylic hydroxyl group at C-18, was also isolated from the same dinoflagellate.[17]

Recently, synthetic work by Kishi et al. have demonstrated the biosynthetic proposal of an iminium-activated intramolecular Diels-Alder reaction, as shown in Figure 4. TBS and Alloc deprotection of (**A**) gave the cyclic iminium intermediate (**B**), which upon gentle heating under buffered aquous condtions gave the Diels-Alder adducts (**C**) as

a mixture of open and closed amino ketones, which upon stirring under molecular sieves in benzene yielded a 1:1 mixture of diasteromeric cyclic imines (**D**).

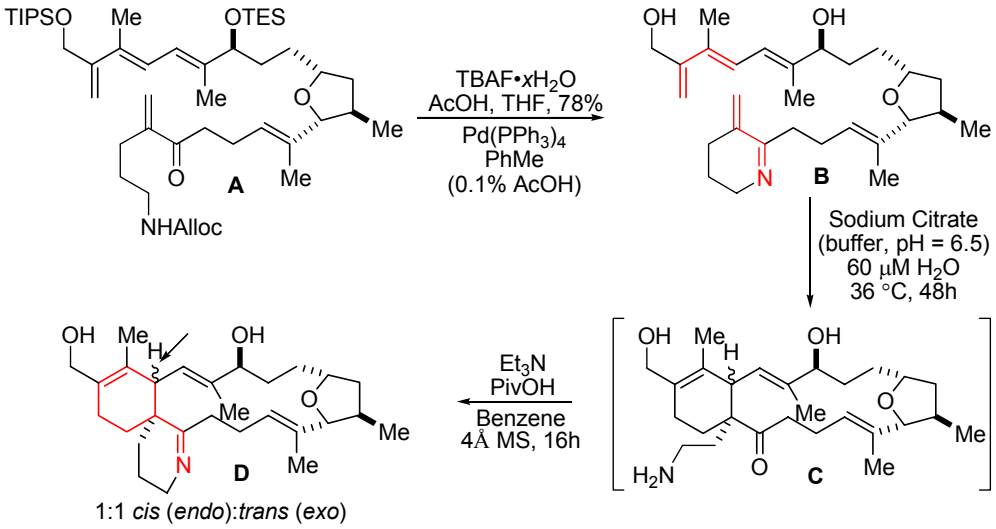


Figure 4. Iminium-Activated IMDA Towards Gymnodimine by Kishi

Prorocentrolide (**22**), a toxic marine macrolide that incorporates a hexahydroisoquinoline moiety, was isolated from the cultured dinoflagellate *Prorocentrium lima*.[18] This dinoflagellate produces diarrhetic shellfish poisoning toxins such as okadaic acid and dinophysistoxins (DTXs).[19] Recently, the prorocentrolide derivative spiro-prorocentrimine (**23**) was isolated from a cultured benthic *Prorocentrium* sp. in Taiwan, and its relative stereochemistry was established by X-ray crystallographic analysis.[20] Compound **23** was much less toxic than other cyclic iminium toxins.

It should be noted that both the keto amine derivatives spirolide E and F (**17** and **18**),[12e] in which this ring has been opened, and the reduced form (**20**) of gymnodimine (**19**)[16] were inactive. Although the pharmacological action of these iminium compounds has not yet been fully defined, the cyclic imine functionality may be essential and may

act as a pharmacophore of macrocyclic iminium compounds, e.g., pinnatoxins and spirolides.

E. Norzoanthamine, A Significant Inhibitor of Osteoporosis

Osteoporosis is caused by an imbalance between bone resorption and bone formation, which results in bone loss and fractures after mineral flux occurs. The frequency of fracture is significantly increased in patients with osteoporosis, and hip fracture in elderly patients with osteoporosis is a very serious problem because it often limits their quality of life. Therefore, in addition to preventing the loss of bone mass, maintenance of the mechanical strength of bone tissue is a very important point to consider in the development of novel antiosteoporotic drugs.[21] Norzoanthamine (**24**),[22a] zoanthamine (**25**), and its homologues were isolated from *Zoanthus* sp.[22] The relative stereochemistry of norzoanthamines was determined by X-ray analysis. Furthermore, the absolute stereochemistry of norzoanthamine was determined by a modified Mosher's method, as shown in Figure 5.[23]

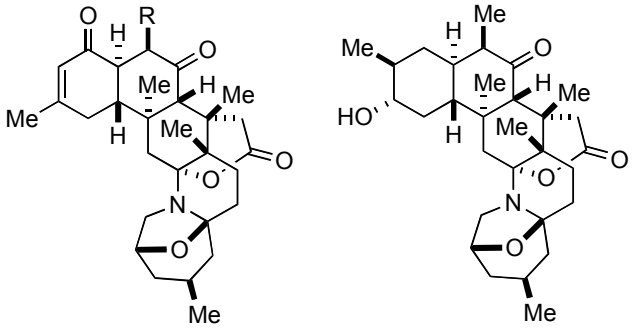
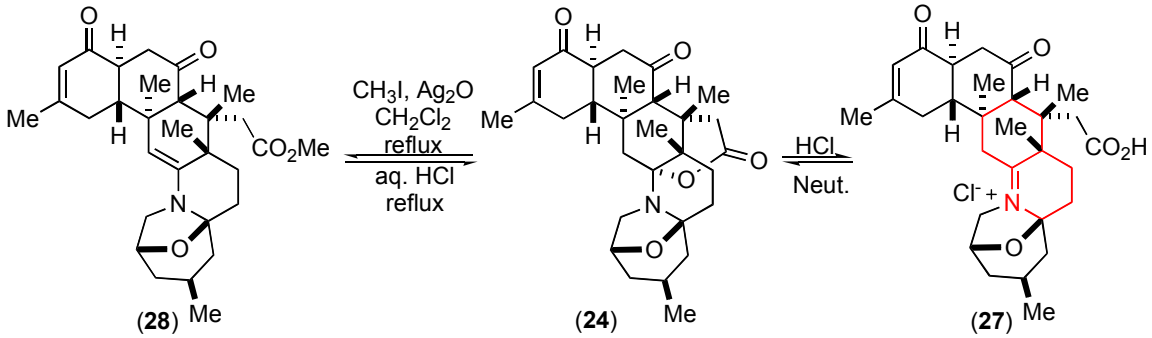


Figure 5. Structure of Norzoanthamine Derivatives.

IL-6 is known to stimulate osteoclast formation, and the suppression of IL-6 secretion can be effective in the prevention of osteoporosis. Norzoanthamine and its HCl salt inhibit IL-6 induction at values of 13 and 4.7 μg/mL, respectively.[23] Furthermore, norzoanthamine and its HCl salt, both of which counteract decreases in bone weight and strength in ovariectomized mice, may be good candidates for antiosteoporotic drugs.[24]

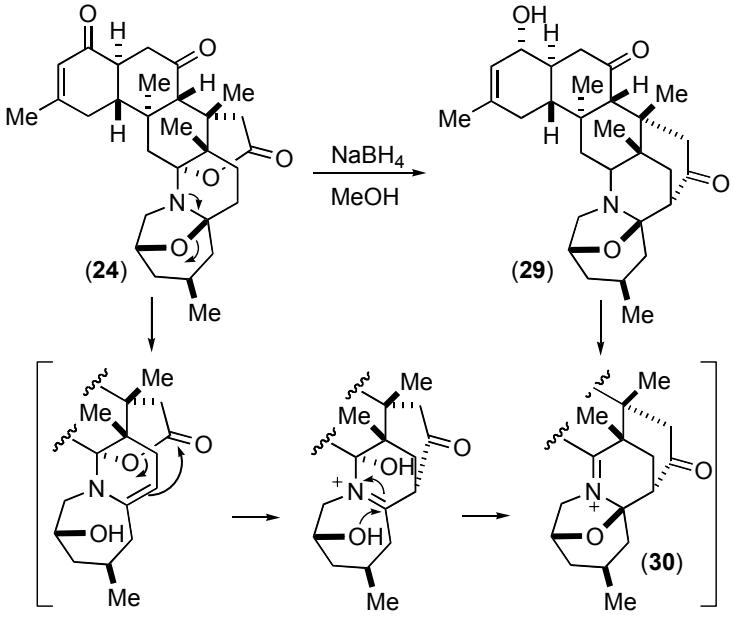
The effect of norzoanthamine HCl on bone weight and strength was tested in ovariectomized mice, an animal model of postmenopausal osteoporosis.[23,25] Norzoanthamine HCl (0.08 mg/kg/day, p.o.) significantly suppressed the decrease in femoral weight caused by ovariectomy without an in crease in uterine weight. These results suggest that the mode of action of norzoanthamine HCl differs from that of estrogen.[26] In ovariectomized mice treated with norzoanthamine HCl, the primary spongiosa did not significantly increase, and the morphology of the metaphysis remained nearly normal.

Equilibration between the lactone structure and iminium structure has been examined.[23b] The NMR spectrum of norzoanthamine HCl salt in CD_3OD implied the presence of an iminium structure (**27**, $\delta_{C\text{-}10}$ = 193.3) but not the lactone structure **24** in norzoanthamine (Scheme 2). The zwitter-iminium structure was also demonstrated by transformation into methyl ester **28** by the treatment of **24** with $CH_3I–Ag_2O$. On the other hand, hydrolysis of **28** with aqueous HCl led to the recovery of **24**. Zooxathellamine (**26**), isolated from the cultured symbiotic dinoflagellate *Symbiodinium* sp., also adopted a zwitterion structure with carboxylate and iminium moieties in D_2O based on their ^{13}C chemical shifts, but had a lactone structure in either $CDCl_3$ or CD_3OD.[27]



Scheme 2. Norzoanthamine Equilibration

During a structural study of norzoanthamine (**24**), Uemura had found an intriguing rearrangement reaction.[23] Reduction of **24** with $NaBH_4$ in MeOH gave two derivatives, deoxydihydronorzoanthamine (**29**) and deoxynorzoanthamine (**30**). The proposed mechanism of this rearrangement reaction is shown in Scheme 3.



Scheme 3. An Interesting Structural Rearrangement of Norzoathamine (**24**)

Based on their molecular formulas, zoanthamines have been regarded as terpenoids; however, the biogenetic pathway of zoanthamines remains unclear. As described above, marine organisms usually produce "super-carbon-chain molecules" with a terminal amino group. Uemura had proposed a polyketide biogenetic pathway (**31→25**) for zoanthamines, as shown in Figure 6. Furthermore, a feeding experiment with a labeled compound suggested a biosynthetic pathway for zooxathellamine (**26**). This pathway was similar to one that they had previously suggested.

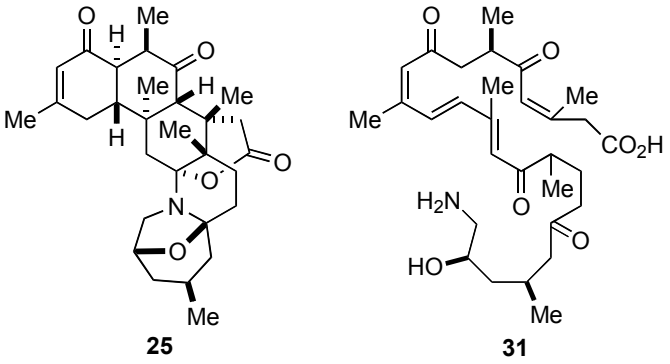


Figure 6. Proposed Biogenesis of Zoanthamine (**25**).

Recently, a total synthesis of norzoanthamine (**24**) has been achieved using an intramolecular Diels–Alder reaction as a key step to construct the requisite chiral triene.[28] This synthesis may be a powerful tool for advancing the study of norzoanthamine as a therapeutic drug.

F. Symbioimine, A Potential Osteoclastogenesis Inhibitor

Symbioimine (**32**) is a marine-derived alkaloid isolated by Uemura in 2004 from a culture of *Symbioidinium* sp., a dinoflagellate that is a symbiont of the acoel flatworm

Amphiscolops sp. (Figure 7).[29] This species of dinoflagellate is a type of zooxanthellae, and is found in a variety of marine invertebrates, producing several bioactive large polyol compounds such as the zooxanthellatoxins (ZTX)[30] and zooxanthellamides.[31] In addition to its structural elucidation, Uemura also demonstrated **32** to inhibit osteoclastogenesis of the murine monocytic cell line RAW264 (EC_{50} = 44 μg/mL) while maintaining cell viability at concentrations up to 100 μg/mL, suggesting that **32** or its analogues may offer a new opening to the development of preventative treatments for osteoporosis. Additional studies have shown that **32** inhibits cyclooxygenase-2 (COX-2), showing potential use as an anti-inflammatory agent. Neosymbioimine (**33**), isolated from the same organism, was reported in 2005.[32]

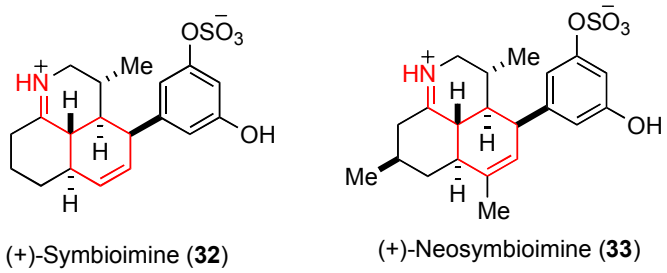


Figure 7. Structures of Symbioimine (**32**) and Neosymbioimine (**33**).

G. Symbioimine Biosynthesis - Uemura

The unique 6,6,6-tricyclic iminium framework of **32** has initiated several hypotheses regarding its biogenic origin, all of which are variations of the intramolecular Diels-Alder reaction of a cyclic, conjugated iminium ion precursor. This proposed disconnection is shared among numerous other marine alkaloids bearing a polycyclic iminium ion, which include gymnodimine, the pinnatoxins and pteriatoxins, the

prorocentrolides, and the terrestrial himbacine.[33] A general method to access these diverse and complex frameworks would be highly desirable in the investigation of their biological action. In the initial study, Uemura and co-workers suggested plausible biosynthetic pathway A of **32** based on an *exo*-selective intramolecular Diels–Alder reaction akin to the conversion of *trans*-enone precursor **34** into **32** as shown in Figure 8. It should be noted that a stereocenter on the methyl group in the acyclic precursor must control the face selectivity in addition to the *endo*/*exo* selectivity.

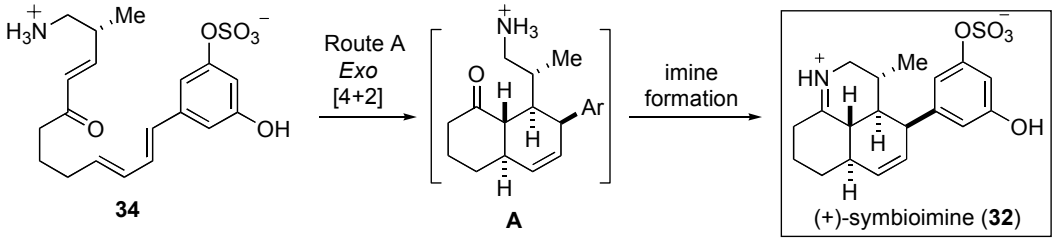


Figure 8. Uemura's Proposed Biosyntheses of Symbioimine (**32**)

H. Symbioimine Biosynthesis – Alternative

Given the aqueous conditions of its putative biosynthesis, it seemed unlikely to us that the Diels-Alder cyclization of **34** would proceed with *exo* selectivity without an aid of an enzyme, for two reasons. First, due to the aqueous conditions the hydrophobic nature of the carbon framework of **34** would serve to compress the molecular transition state to its most compact form, orienting itself into an *endo*-type transition state; Second, the stabilizing π-π stacking interaction between the diene and dienophile further lowers the free-energy barrier to an *endo*-transition state: the well known '*Endo* Rule'. The

alternative *endo*-selective Diels-Alder cyclization from *trans*-enone **34**, however, does not occur given the observation of the relative stereochemistry in symbioimine.

An alternative solution, depicted as Route B in Figure 9, consists of an *endo*-selective cyclization of the cyclic iminium species **35** derived from *cis*-enone **C**, followed by a thermodynamically favorable epimerization of the resultant *cis*-fused ring system **B** to an all-*trans*-fused arrangement seemed more reasonable. Moreover, one has to wonder why nature would incorporate such a potentially powerful self-activating biosynthon unless it served a purpose. And given the evolutionary pressure for life to abhor waste, it could be proposed that such self-activation allows the intrammolecular Diels-Alder reaction to occur *without* the aid of an enzyme. This observation is further strengthened by Kishi's success in using an iminium-activated intramolecular Diels-Alder reaction in his synthesis of the gymnodimine (**19**) framework, and, more importantly, doing so under buffered (pH = 6.9) aqueous conditions at a mild, 35 ˚C.

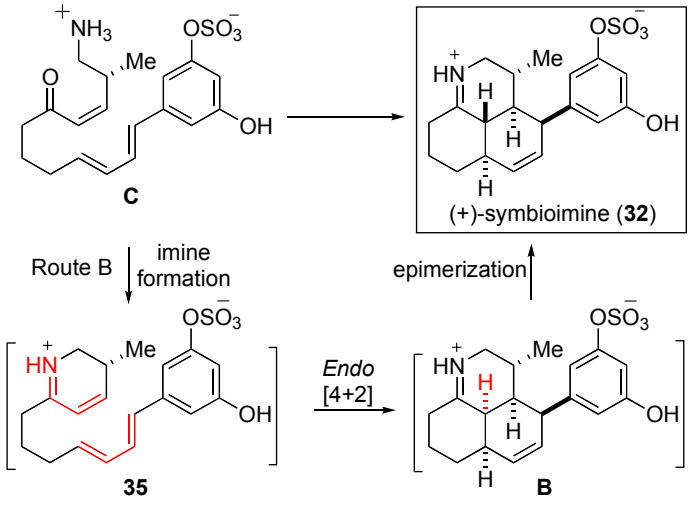


Figure 9. Alternative Proposal to the Biosynthesis of Symbioimine (**32**)

Symbioimine's unknown biosynthesis, in addition to its unique bioactivity and lack of natural abundance, merits an investigation that is uniquely suited to a total synthesis effort. Beyond the goals of developing a short, convergent, enantioselective synthesis of symbioimine amenable to analog development (the usual total synthesis boilerplate), and beyond finding an answer to the seemingly academic question of whether symbioimine's framework derives from a *trans*-enone *exo*- versus a cyclic iminium-activated *endo*-Diels-Alder reaction, there is a unique opportunity to recognize and marvel at nature's resourcefulness in taking advantage of the structural complexity offered by the [4+2] cycloaddition, especially by the simple, purposeful construction of a framework that self-activates its own intramolecular cycloaddition, presumably without the aid of a putative Diels-Alderase. To discover an equitable solution to symbioimine's biosynthesis has ramifications beyond its own construction: throughout this chapter I've illustrated an entire class of related natural products whose own biosyntheses, in addition to any future synthetic synthetic endeavors directed at them, would stand to directly benefit from such a methodological insight. A damned good reason if I ever heard one.

H. Relevant Synthetic Work

While our investigation was in progress, Uemura had published a similar idea, and Snider reported a model study in which a cyclic *N*-acyl iminium ion underwent a selective intramolecular Diels–Alder reaction followed by epimerization.[34] Additional studies by Maier and Uemura have explored alternative, non-biomimetic cycloaddition strategies to overcome the inherent poor orbital overlap, with the former group achieving a racemic synthesis of symbioimine (**32**), and the later demonstrating a high-yielding *exo*-

selective Diels-Alder reaction to give (+)-**36** (Figure 10) from (**1'**).[35] While these studies do illustrate the use of the Diels-Alder reaction in the synthesis of the symbioimine framework, neither address nor support either of the proposed biosyntheses of the 6,6,6-tricyclic iminium framework, nor could ever serve as a practical source of material for biological evaluation.

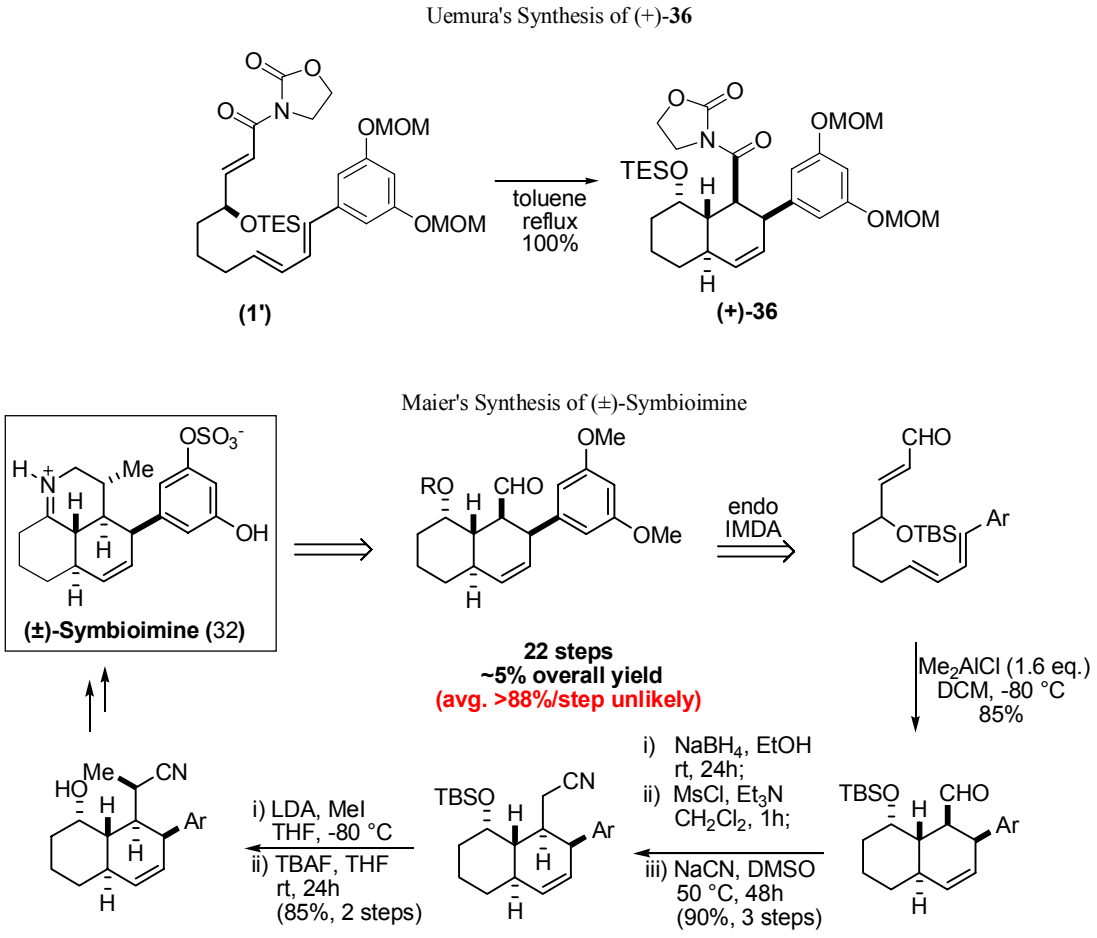


Figure 10. Alternative Cycloaddition Synthetic Work by Maier and Uemura.

In the interim, two additional syntheses have been published; Snider and co-workers reported the second racemic total synthesis of **32** based on their strategy of the cycloaddition of a cyclic *N*-acyl iminium ion (Figure 11),[36a] and most recently the first

enantioselective synthesis of (+)-**32** by Thomson (Figure 12).[36b] The Snider group does justice in proving the validity of the biomimetic proposal favoring iminium formation as a precuror to the intramolecular Diels-Alder reaction, as well as illustrating that oftentimes a biomimetic approach can be much more efficient in both yield and brevity than Maier's approach, as evidenced by taking 10 less steps in their synthetic route.

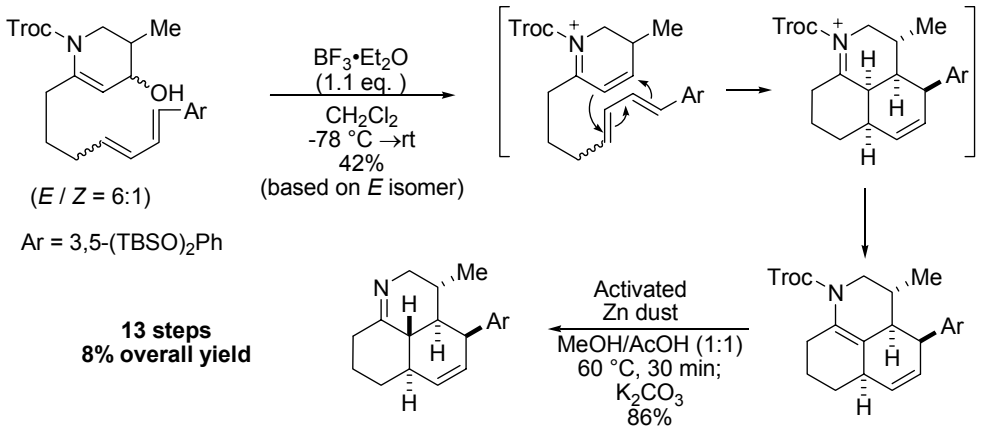


Figure 11. Biomimetic Synthetic Work by Snider.

Thomson's work, in addition, lays further claim to this biosynthetic proposal of an iminium-activated *endo*-selective intramolecular Diels-Alder reaction, doing so in a comparable number of steps, even enantioselectively, though in an unequitable manner that fails to prove useful to other molecular targets in the same class.

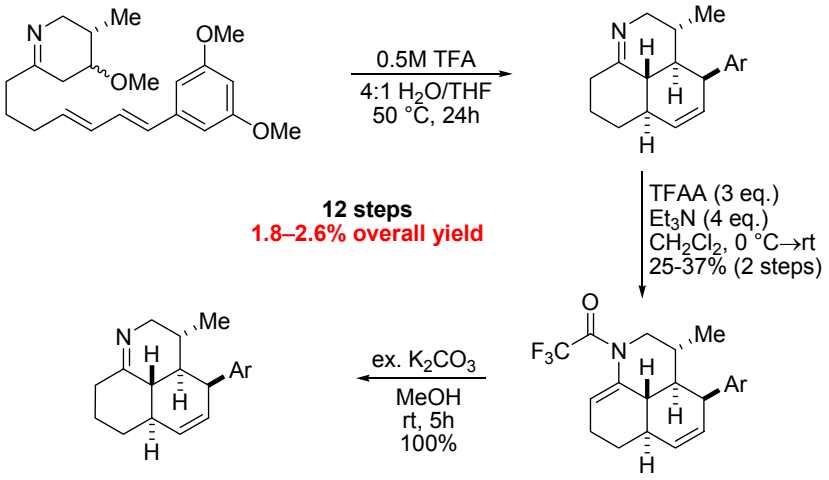


Figure 12. Biomimetic Synthetic Work by Thomson.

Of the biomimetic Diels-Alder reactions investigated, both suffer from low yields in part from the relative dearth of information regarding the inherent reactivity of the postulated reactive intermediate. The topic of this thesis is to report the synthetic adventures experienced whilst designing and creating a convergent approach to (+)-symbiomine **32.**

I. Iminium-activated Cycloadditions: the Manzamine and the Galbulimina Alkaloids

The manzamines are a growing group of cytotoxic marine sponge alkaloids that possess unusual polycyclic diamine skeletons. Among this group are manzamine A (**37**), and B (**38**),[37] ircinal A (**39**) and B (**40**),[38] ircinol A (**41**) and B (**42**),[39] keramaphidin B (**43**),[40] xestocycamine (**44**)[41] and ingenamine (Figure 13).[42] The ircinals **39** and **40** were proposed to be biosynthetic precursors to the manzamines A and B. In fact, Ircinal A was chemically transformed to Manzamine A through a Pictet-Spengler cyclization with tryptamine and subsequent oxidation with DDQ. Ircinols A and B are antipodes of the

alcoholic forms of Ircinals A and B, and represent the first alkaloids in this class of compounds to possess the opposite absolute configuration to that of the manzamines. Keramphidin B (**43**) was also postulated as a manzamine biosynthetic precursor through formation of an ircinal from hydrolysis of the N2-C3 bond of the imino form of **43**.

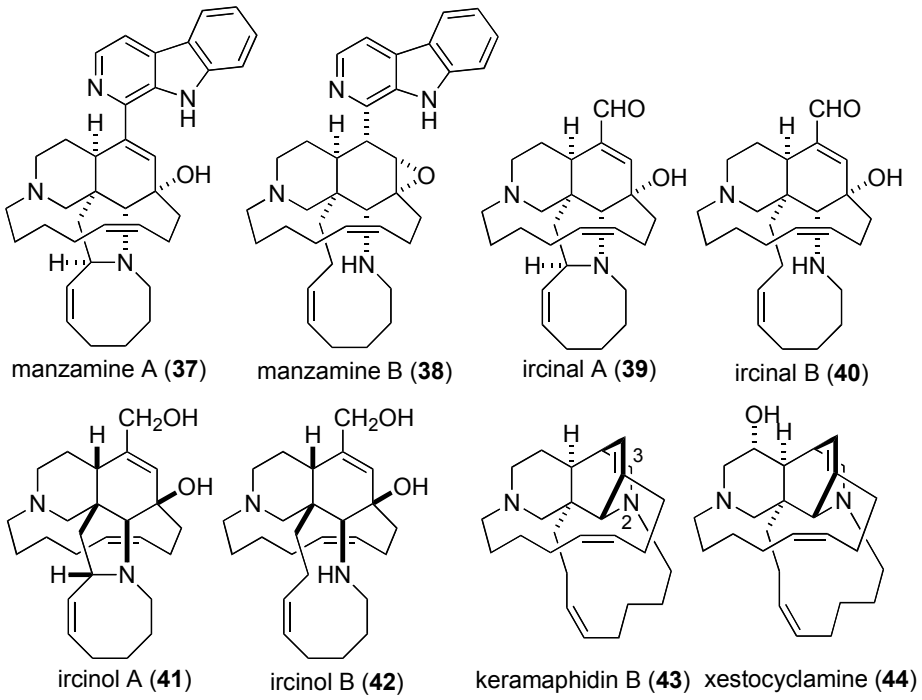
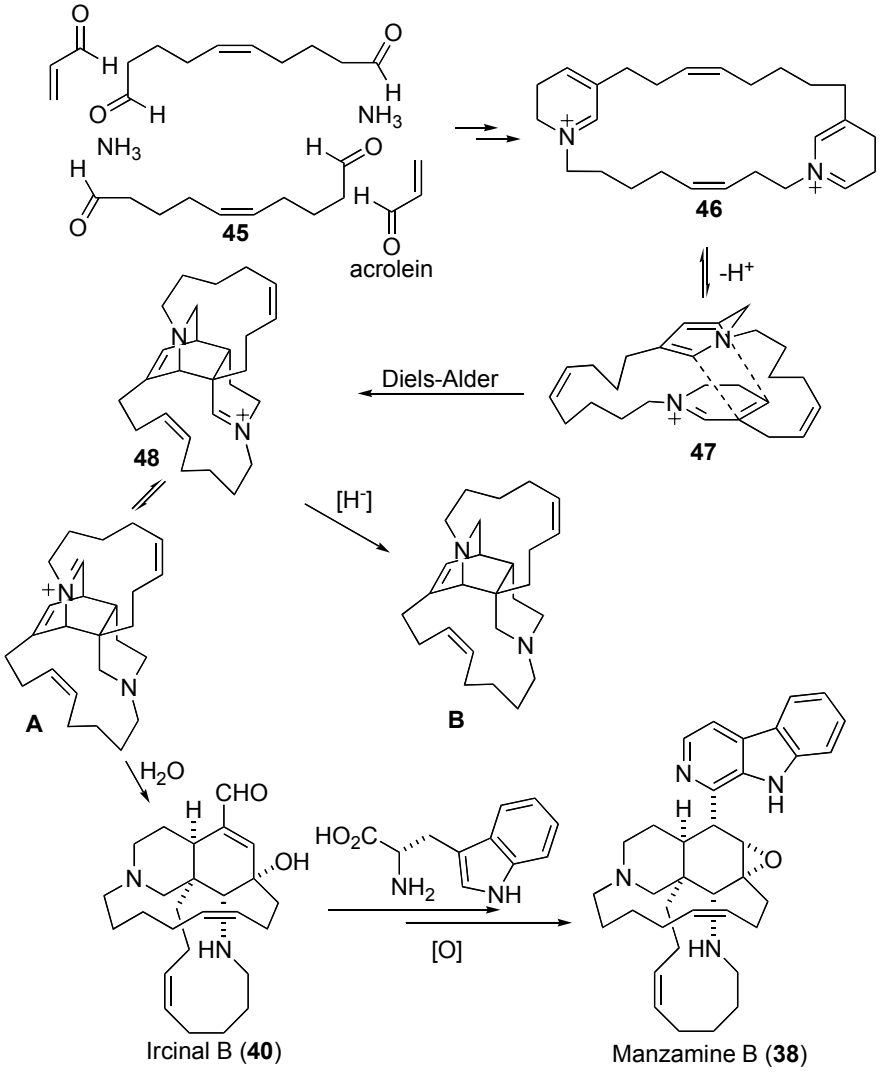


Figure 13. Manazmine Alkaloids

In 1992, Baldwin and Whitehead outlined an elegant unified biogenesis for the manzamines (Scheme 4).[43] Manzamine B (**38**) was envisioned to be derived from four building blocks: ammonia, the C_{10} unit **45**, a C_3 unit (acrolein), and tryptophan. The key step for the proposed biogenesis was an intramolecular *endo*-Diels-Alder reaction of the bis-dihydropyridinium species (**46→47→48**). The intermediacy of **46** was supported by the isolation of the bispyridinium macrocycles cyclostellattamines A-F from the marine

sponge *Stelletta maxima*.[44] Later, Baldwin et al. expanded their biosynthetic proposal to include keramaphidin B.[45]



Scheme 4. Proposed Biosynthesis by Baldwin et al. of Manzamine B (**38**).

Baldwin et al. completed a biomimetic total synthesis of keramaphidin B (**43**) by dissolving the proposed intermediate **46** in a methanol/Tris buffer solution followed by reduction with $NaBH_4$ to provide a small amount of **43** (Figure 14).[46] The low yield of **43** was rationalized as a reflection of the inclination of intermediate **47** to disproportionate.

The researchers further argued that *in vivo*, a Diels-Alderase could limit the conformational mobility of the substrate, which would not only minimize the change in entropy toward the transition state but would also obviate the intrinsic problem of disproportionation.

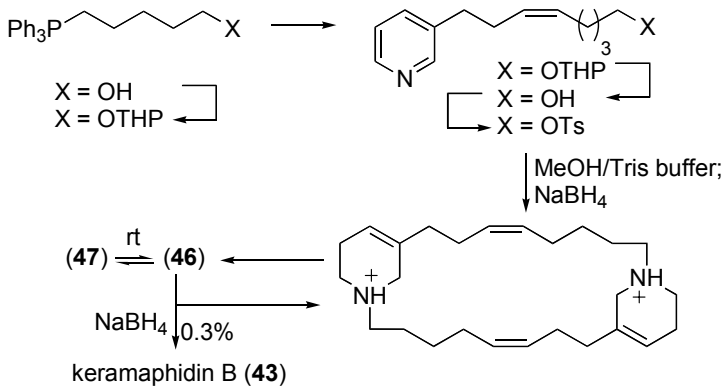


Figure 14. Biomimetic Synthesis of Keramaphidin B (**43**) by Baldwin et al.

In 1995 the Baldwin group also published a general biosynthetic proposal to explain the formation of the type I Galbulimina alkaloids.[47] So far 28 Galbulimina alkaloids have been isolated and they appear to fall into four classes based upon their structures. Class I consists of four tetracyclic lactones as shown in Figure 15.

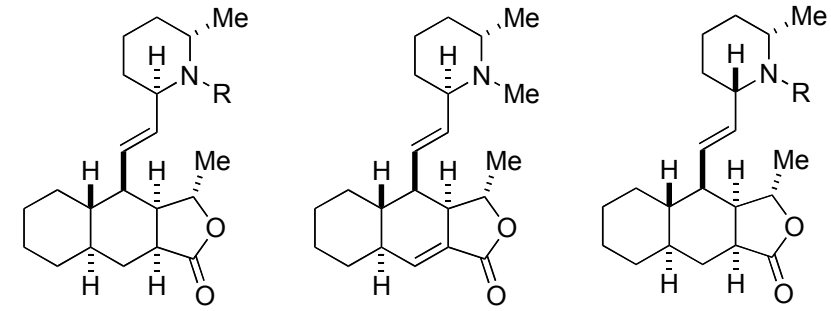
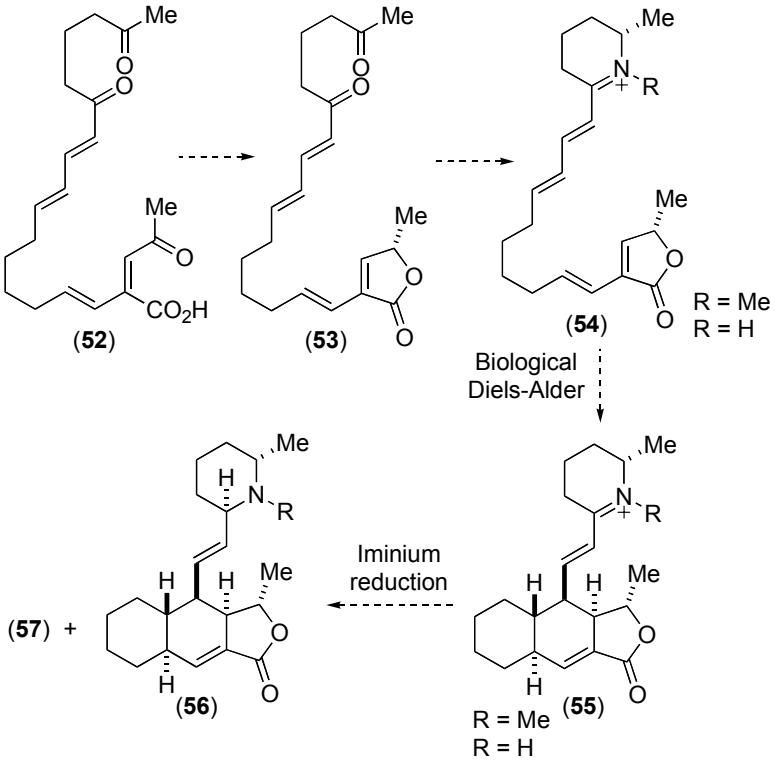


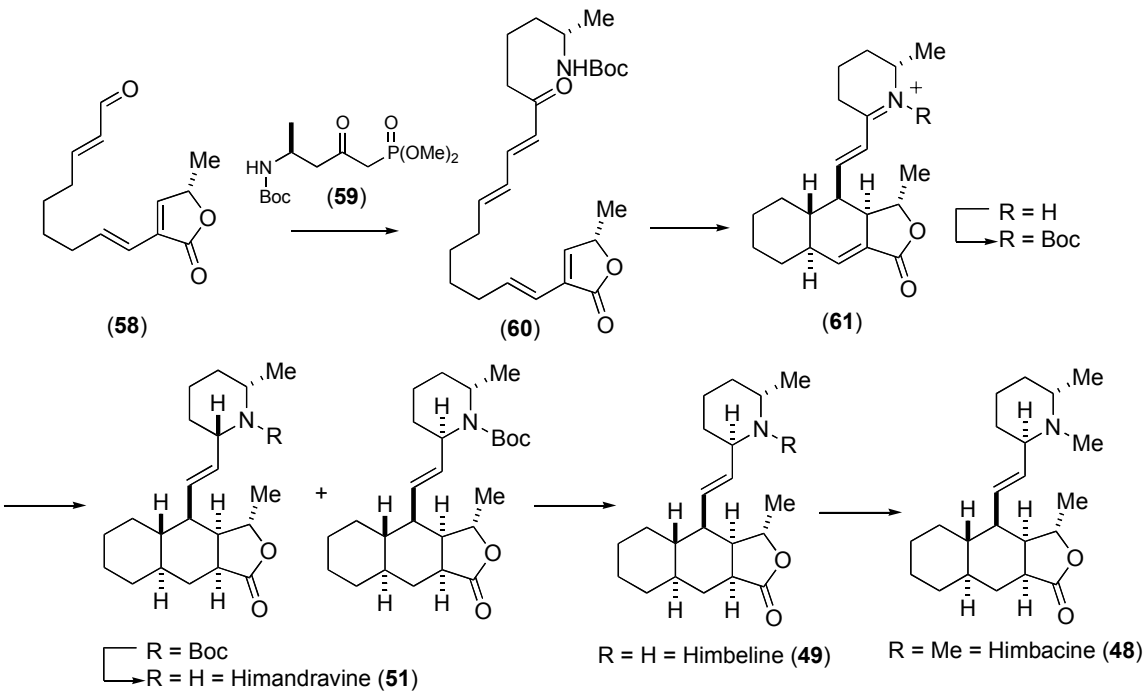
Figure 15. The Galbulimia Type 1 Alkaloids **48**- **51**

The proposed biosynthetic pathway for the Galbulimina Class I alkaloids postulates ketide (**52**) formation from nine acetates and a pyruvate via standard polyketide biosynthesis. Reductive lactonization would result in butenolide (**53**), which on reductive amination followed by iminium ion formation via *N*-methylation or *N*-protonation would provide the Diels–Alder precursor (**54**). Intramolecular Diels–Alder cycloaddition via an *endo* transition state with facial selection controlled by the butenolide methyl group, would afford tetracycle (**55**). Finally, hydride reduction of the iminium from either the α or β face would furnish either the himbacine (*trans*-piperidine ring) precursor (**56**) or the himandravine (*cis*-piperidine ring) precursor (**57**) (Scheme 5).



Scheme 5. Proposed Biosynthesis of the Galbulimina Type I Alkaloids.

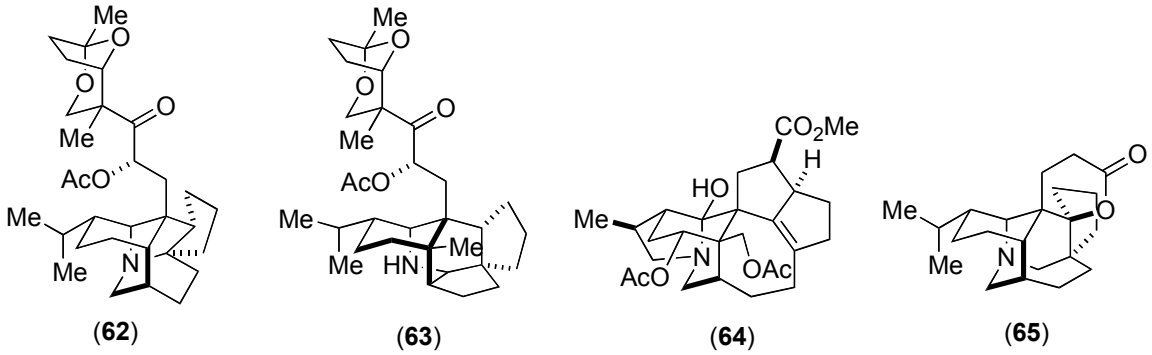
Having completed a successful model study which demonstrated the feasibility of the key Diels–Alder cycloaddition, the Baldwin group next focused their attention towards a total synthesis of the Galbulimina Class I alkaloids.[48] Unlike the model system, which utilised Gassman's Diels–Alder chemistry, Tchabanenko et al. employed an alternative iminium ion activated biomimetic Diels–Alder process.[49] Thus, the key intermediate (**60**) was successfully prepared by an olefination of known aldehyde (**58**) and Horner–Emmons reagent (**59**). Treatment of tetraene (**60**) with trifluoroacetic acid at 0 ˚C effected Boc-cleavage and condensation to the desired iminium species (**61**) R = H, that after quenching at room temperature with sodium cyanoborohydride successfully revealed the desired type I core of the Galbulimina alkaloids, as a mixture of diastereoisomers. Further straightforward chemical steps successfully yielded enantiomerically pure synthetic himbeline (**49**), himbacine (**48**) and himandravine (**51**), all of which had spectroscopic data matching that of the naturally occurring substances (Scheme 6).



Scheme 6. Synthesis of the Himandravine, Himbeline and Himbacine by Baldwin.

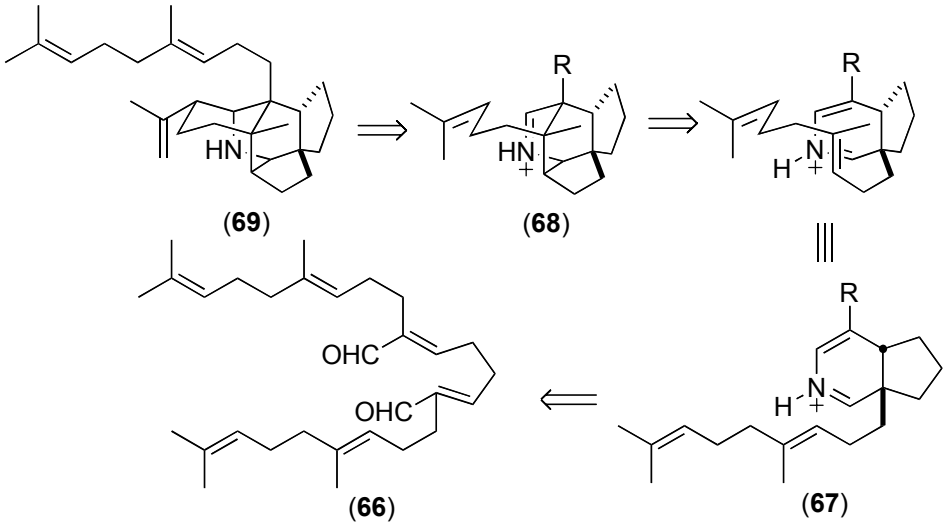
J. Iminium-activated Cyloadditions: Daphniphyllum Alkaloids

The daphniphylline alkaloids are a growing class of polycyclic natural products that were first isolated in 1909 from the deciduous tree Yuzurha (*Daphniphyllum macropodium*). The four different skeletal classes of daphniphylline alkaloids are represented by daphniphylline (**62**), secodadaphnipylline (**63**), yuzurimine (**64**), and daphnilactone A (**65**) as shown in Scheme 7.



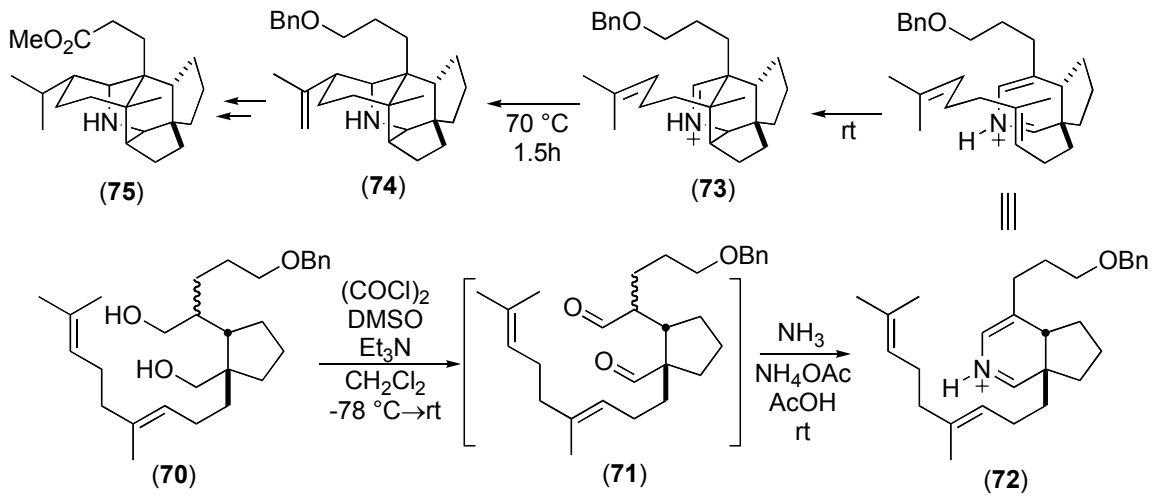
Scheme 7. Representative Daphniphylline Alkaloids (**62)**-(**66)**.

Early work on the biosynthesis of daphniphylline (**62**) established its mevalonate origin via a squalene-like intermediate.[50] Later, Ruggeri and Heathcock devised a biosynthetic proposal for the construction of the complex polycyclic ring systems of the daphniphyllum alkaloids through a hetero-Diels-Alder cyclization (Scheme 8).[51] They proposed that the squalene-derived dialdehyde (**66**) might condense with an amine equivalent and after a process of enamine isomerization and condensation would provide the dihydropyridine derivative (**67**). A catalyzed intramolecular hetero-Diels-Alder reaction of (**67**) would give the tetrahydropyridine (**68**). Subsequent enelike cylciztion of (**68**) would give the pentacyclic compound proto-daphnipylline (**69**), a proposed precursor to daphniphylline.



Scheme 8. Proposed Biosynthesis of the Daphniphyllum Alkaloids

To explore the proposed biosynthesis, Heathcock et al. completed a biomimetic total synthesis of **75** (Scheme 9).[52] The synthesis utilizes a one-pot procedure that was also used to synthesize five dapniphyllum alkaoids.[53] Oxidation of the 1,5-diol (**70**) to the dialdehyde (**71**) was accomplished through a Swern oxidation. The crude reaction mixture was treated with ammonia followed by acetic acid and ammonium acetate to produce the azadiene (**72**). An intramolecular Diels-Alder reaction furnished the imine (**73**). Heating the acetic acid solution of the imine then facilitated an intramolecular aza—Prins cyclization and gave (**74**) in 82% yield. Subsequent redox steps gave methyl homosecodaphniphyllate (**75**) after 9 steps in 48% overall yield.



Scheme 9. Heathcock's Biomimetic Total Synthesis of Homosecodaphniphyllate (**75**).

K. Conclusion

The rapidly accumulating body of knowledge in this field suggests that nature indeed utilized the Diels-Alder construction to generate a complex array of natural products. Of these, a question has arisen that revolves around whether or not such an IMDA occurs spontaneously (via an iminium-activated intermediate like gymnodimine by Kishi and Baldwin or through an enone as proposed for the pinnatoxins by Uemura), or by way of a hypothetical Diels-Alderase. In many cases, such as in the endiandric acids,[54] lucidene,[55] and asatone,[56] current experimental evidence argues that the putative biosynthetic Diels-Alder cyclization reactions are not enzyme-mediated, but occur spontaneously in the producing organism in a stereorandom fashion and give rise to racemic products. For the natural products that are enantiomerically pure, there is growing evidence that the Diels-Alder reactions might be enzyme-mediated. The experimental evidence for the enzyme involvement is, however, circumstantial for virtually all of these systems. The three systems in which the strongest and most direct

experimental support for the existence of a Diels-Alderase are: a) the enzymatic activity observed for cell-free extracts of *Aldernaria solani* that leads to the production of solanapyrone A,[57] b) lovastatin nonaketide synthase that leads to the production of lovastatin,[58] and c) macrophomate synthatse that leads to the production of macrphomic acid.[59] Despite the impressive and difficult experimental work that the authors of these publications have gathered, in the quest for proving the existence of a Diels-Alderase, rigorous proof that the purified or partially purified (in the case of solanapyrone) proteins are catalyzing the pericyclic Diels-Alder reaction remains to be rigorously established. This account of my research experience regarding the biomimetic total synthethsis of symbioimine may shed some light on this topic, at least as how it might pertain to dinoflagellate alkaloid biosynthesis.

L. References and Notes

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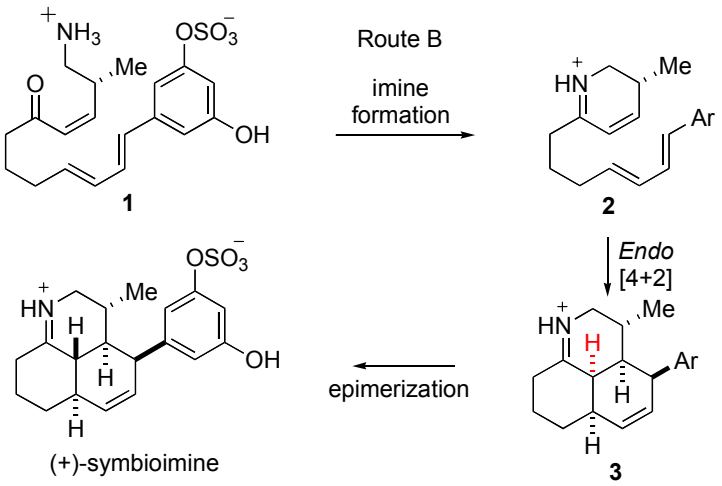
CHAPTER 2

Adventures in *cis*-Enone Synthesis

A. Synopsis

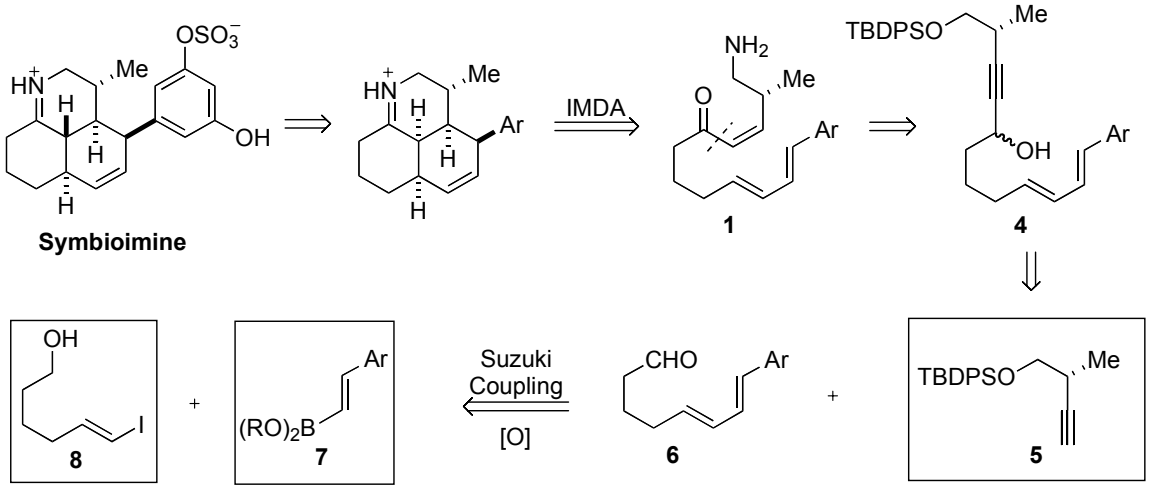
Our synthesis of symbioimine began with an eye towards construction of the *cis*-enone framework **1** that we deemed necessary for intramolecular imine formation **2** and subsequent iminium-activated Diels-Alder cycloaddition **3** that we had proposed in response to Uemura's biosynthetic claim for symbioimine (Scheme 10).



Scheme 10. Route B of the Proposed Biosyntheses of Symbioimine

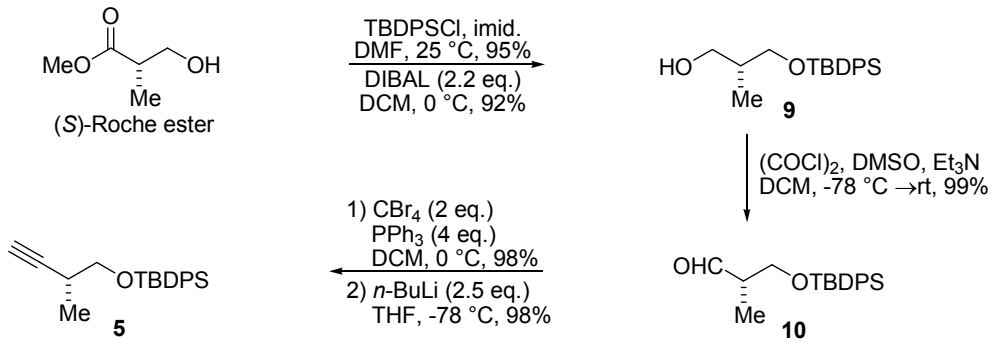
B. Lindlar Reduction

Of the many methodologies developed to construct *cis*-enones, we felt that the Lindlar reduction of an alkyne would enable us to come to a more simplified retron that would enable us to quickly assemble a convergent approach, as shown in Scheme 11. The synthesis of **1** from **4** can be achieved from a sequence of Lindlar reduction, allylic oxidation, and a functional group interconversion. Propargylic alcohol **4** can be produced from addition of lithiated alkyne **5** to aryl diene aldehyde **6**. Aryl diene aldehyde **6** can be produced from the Suzuki coupling of vinyl iodide **8** and vinyl boronate ester **7**, followed by alcohol oxidation.



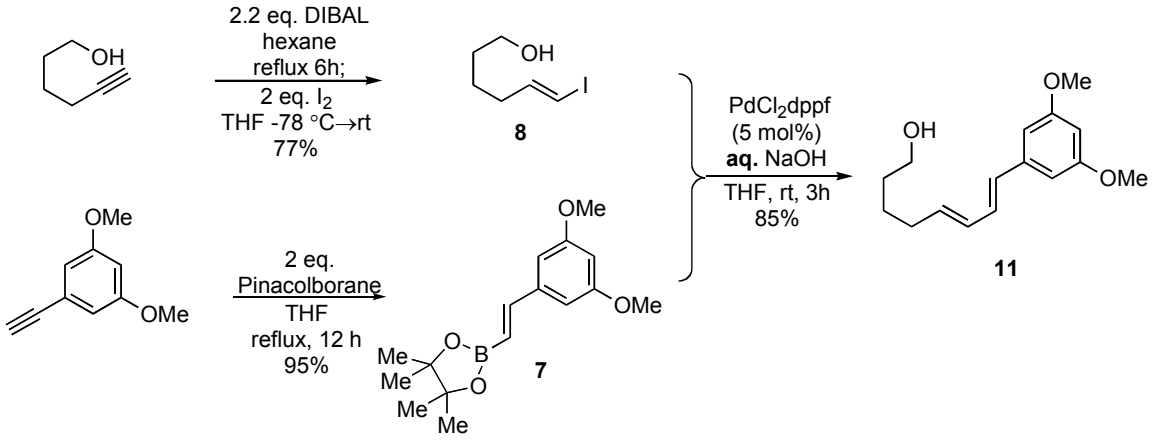
Scheme 11. Retrosynthesis of *cis*-Enone **1** Featuring the Lindlar Reduction of **4**

The synthesis of fragment **5** began from commercially available (*S*)-Roche ester, which was protected with TBDPSCl in 95% yield, and the ester completely reduced to the alcohol to yield **9** in 92% yield. This then was oxidized using the Swern reaction[1] to produce the aldehyde **10**, to be placed under the Corey-Fuchs sequence of acetylene formation.[2] First, dibromo-olefination with triphenylphosphine and carbon tetrabromide gave the desired product, which then underwent C-H insertion after lithiation with *n*-BuLi, that, after quenching gave alkyne **5** in quite excellent yield over the 3 steps (Scheme 12).



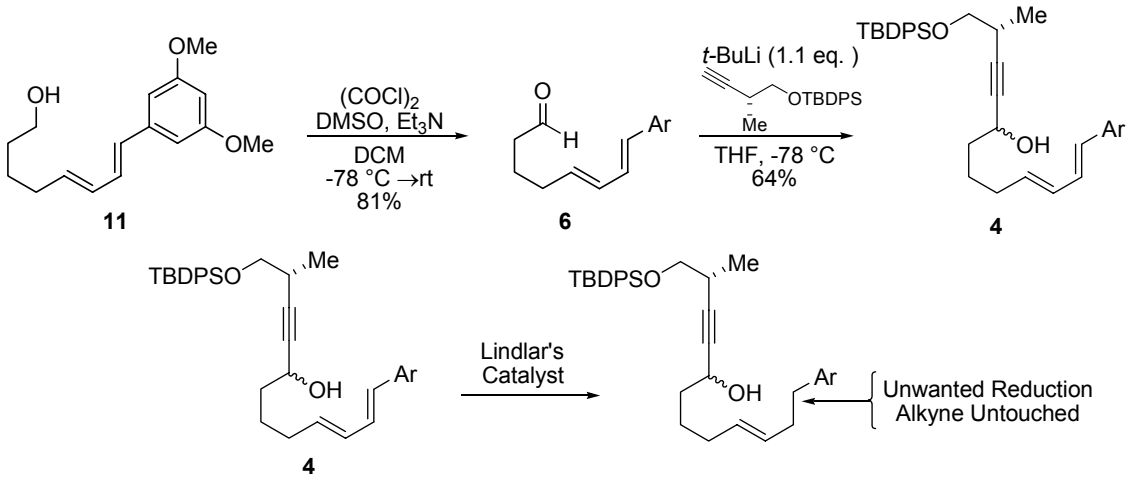
Scheme 12. Synthesis of Fragment **5**

The synthesis of vinyl iodide **8** was straightforward in a single pot transformation by hydroalumination of commercially available 5-hexyn-1-ol, and trapping the subsequent alkenyl aluminate with iodine at -78 °C in 77% yield (Scheme 13). Its coupling partner, Pinacol boronate **7**, was likewise constructed in a single step by hydroboration of commercially available 3,5-dimethoxy phenylacetylene with two equivalents of pinacolborane under refluxing THF, overnight, in 95% yield. Both of these were coupled via Suzuki coupling with a catalytic 5 mol% of $PdCl_2$(dppf), several equivalents of aqueous NaOH, in THF to give the aryl dienol **11** in 85% yield.



Scheme 13. Coupling Fragments **7** and **8** to Give Diene **11**

Construction of propargylic alcohol **4** began by oxidation of alcohol **11** using the Swern method to yield the aldehyde **6** in 81% yield (Scheme 14). Subsequent addition of the lithiated chiral acetylene (by *t*-BuLi) to **6** in THF at -78 °C gave **4** in 64% yield as a racemic mixture. This then set the stage for performing the Lindlar reduction. Lindlar's catalyst is a combination of 5% palladium metal, poisoned by the presence of lead (which prevents palladium from over-reduction to the alkane), on a solid support $CaCO_3$. Propargylic alcohol **4**, unfortunately, did not undergo the desired reduction; rather, the benzylic olefin was reduced to the alkane. This lack of reactivity is assumed to be steric in origin, as several catalyst sources were used, all giving the same result.

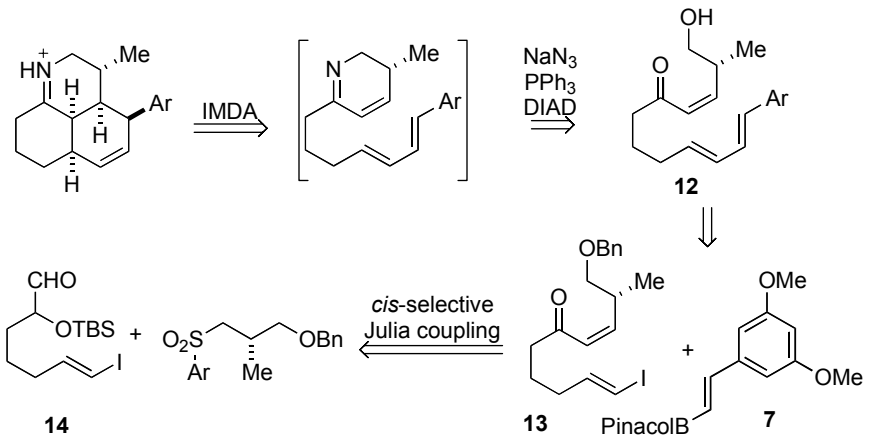


Scheme 14. Attempt at Lindlar Reduction of Alkyne **4**

While not quite a dead end, the relative simplicity of this system and subsequent ease of substrate modification allowed us to try for a *cis*-selective modified Julia olefination approach to the desired *cis*-enone framework.

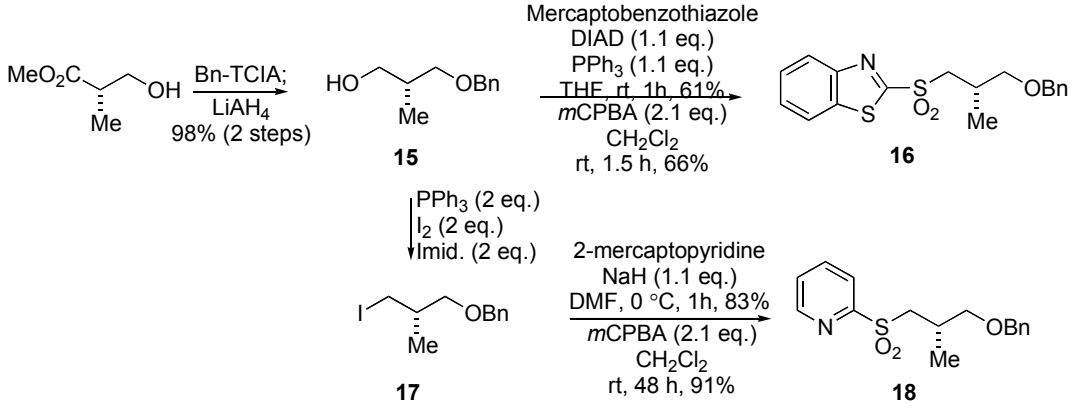
C. Modified Julia coupling

Difficulty with the prior system disallowed any experiments that would have explored [4+2] cycloadditions. To remedy this, a different approach for *cis*-enone synthesis was undertaken, as shown in Scheme 15. From the desired *cis*-enone **12**, a Suzuki coupling connection could be derived from fragments **13** and the aforementioned **7**. Fragment **13** was planned to come from a modified Julia-Kocienski coupling from aldehyde **14** and a chiral sulfone fragment. The aryl group of the sulfone can be varied to manipulate the *cis*:*trans* ratio. At the time, mercaptobenzothiazole was on hand, and sulfones from the material were known to give a 2:1 *cis*:*trans* ratio when using LiHMDS as a base, which wasn't necessarily a bad thing since we could explore both modes of Diels-Alder cycloaddition, both the *endo*-selective iminium-activiated IMDA and a thermally-driven *exo*-selective IMDA through the *trans*-enone. Later, 2-mercaptopyridine was obtained, the sulfones of which were much more *cis*-selective.



Scheme 15. Retrosynthesis Featuring Modified Julia Coupling of **14** and **15**

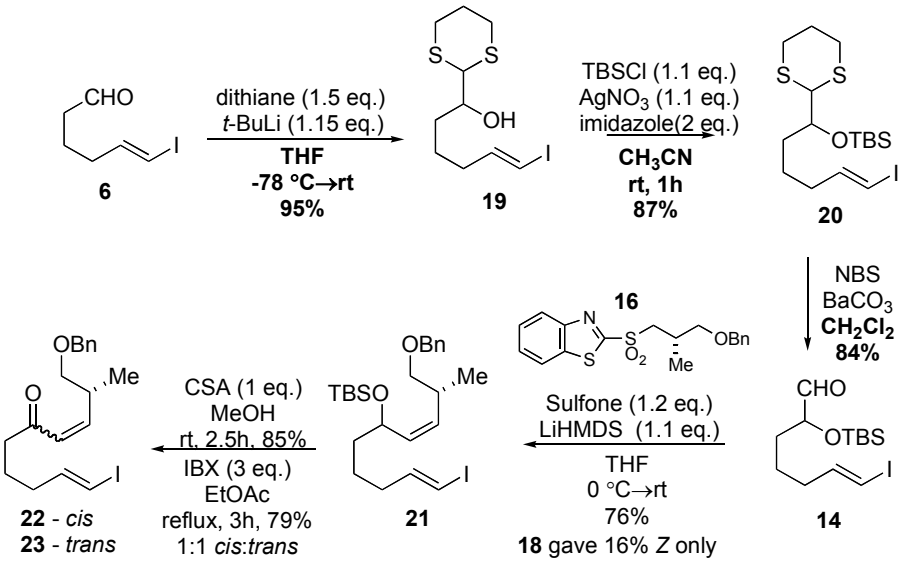
Sulfone synthesis began with benzyl protection of the chiral (*S*)-Roche ester by way of the activated trichloroacetimidate in order to avoid potential racemization, followed by reduction with $LiAlH_4$ to give compound **15** in 98% yield over two steps (Scheme 16). Mitsunobu substitution of the primary alcohol with mercaptobenzothiazole to give the aryl sulfide, and its subsequent oxidation to the sufone **16** with a couple equivalents of *m*-CPBA in 66% yield (2 steps) set the stage for the Julia olefination. The other aryl sulfone, starting from the same chiral starting material, diverges from alcohol **15** to the alkyl iodide **17** by treatment with iodine and triphenylphosphine, followed by its displacement by the 2-mercaptopyridine's thiolate generated by deprotonation with NaH produced the sulfide in 83% yield. Again, sulfone oxidation with two equivalents of *m*-CPBA gave the desired chiral material **18** in 91% yield.



Scheme 16. Synthesis of Modified Julia-Kocienski Sulfones **16** and **18**

With sulfones **16** and **18** in hand, construction of aldehyde **14** began from the aforementioned aldehyde **6**, as shown in Scheme 17. Addition of lithiated dithiane in THF at –78 ˚C gave secondary alcohol **19** in 95% yield, followed by TBS protection to give the silyl ether **20** in 87% yield. Deprotection of the dithiane with NBS furnished

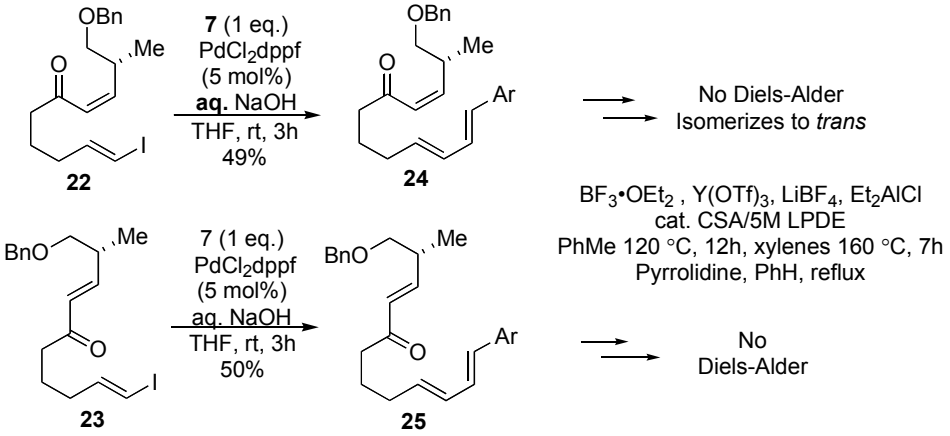
aldehyde **14** in 84%. Deprotonation of sulfone **16** with LiHMDS in THF at 0 ˚C and the addition of aldehyde **14** gave **21** as a mixture of olefinic isomers in 76% yield, which were separated after CSA deprotection and subsequent IBX oxidation in 85% and 79% yields, respectively, observing a 2:1 *cis*:*trans* ratio. Sulfone **18** exclusively produced *cis*-material, albeit in 16% yield.



Scheme 17. Julia Olefination of Aldehyde **14**

With both isomers in hand, Suzuki couplings with the vinyl pinacol boronate ester (**7**) and both the *cis*-(**22**) and *trans*-(**23**) gave their respective coupled products in 49% and 50% yield (Scheme 18). Extensive experimentation with known Diels-Alder conditions gave no product whatsoever. Amongst the conditions tried were by heating, both 120 ˚C in toluene overnight, or 160 ˚C in xylenes for the day had no effect other than *cis*→*trans* isomerization. At the higher temperatures, migration of the enone down a carbon to become a trisubstituted olefin, and destroying the chiral center, was observed. An entire book of Lewis acidic conditions, from $BF_3 \cdot OEt_2$ and $Et_2AlCl/EtAlCl_2$, to

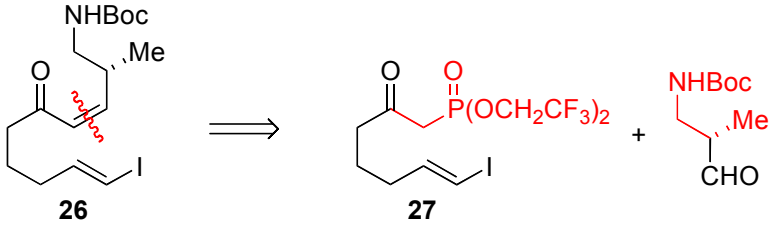
iminium-activation by pyrrolidine did nothing more than waste material and taunt my resolve.



Scheme 18. Attempt to Make Lemonade From Lemons

The failure of observing any desired reaction despite the variety and strength of the conditions applied were not without benefit, however. Merely, they increased our assertion that the biosynthesis of the symbiomine framework must come from some activiated intermediate that can better tolerate the Diels-Alder conditions, like the internally conjugated cyclic iminium moiety where the *cis*-conformation is locked by the imine formation. This then, raised the importance of having the amine in place upon construction of the *cis*-enone and diene, so as to take advantage of iminium-activation to drive the desired Diels-Alder. Additionally, we needed a method of *cis*-enone formation that would be more tolerable to a protected amine on the chiral fragment. At the time, the Paterson group had accomplished the total synthesis of the marine natural product, discodermolide[3], which contained a *cis*-enone that was made by using the Still-Gennari

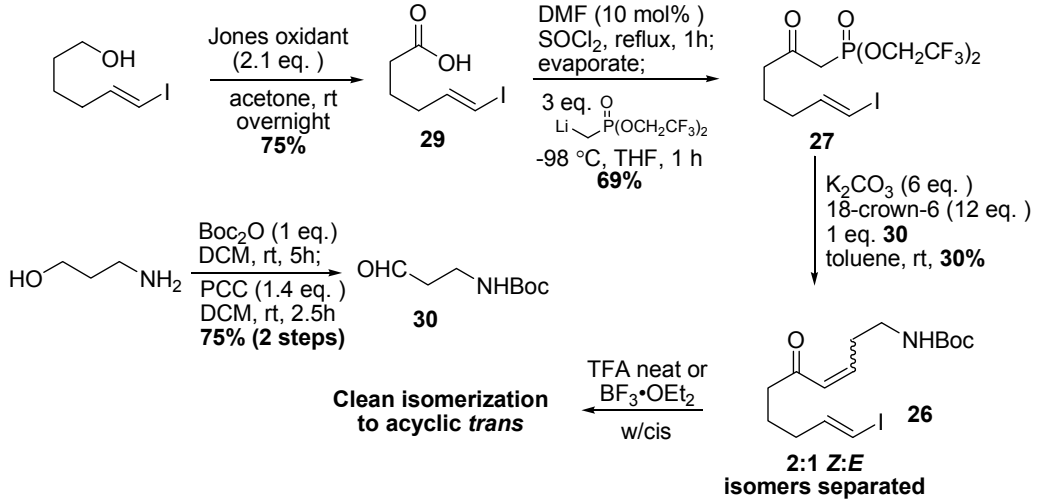
cis-selective bis-(trifluroroethanol) phosphonate coupling partner.[4] Our use of such functionality can be seen in Scheme 19.



Scheme 19. Retrosynthesis Featuring the Still-Gennari Olefination

Synthesis of the Still-Gennari phosphonate began from the aforementioned vinyl iodo alcohol, that upon treatment under the Jones oxidation protocol gave carboxylic acid **29** in 75% yield (Scheme 20). This then was readily converted to the phosphonate by way of the acid chloride, first by refluxing for 1 hour in thionyl chloride and a touch of DMF, followed by evaporation to dryness, dissolved in THF and cooled to –98 ˚C, whereupon addition of an excess of the lithiated phosphonate (by *n*-BuLi) gave the bis(trifluoroethanol) phosphonate **27** in 69% yield. This material, then, upon mixing with an excess of potassium carbonate and 18-crown-6 ether (to solublize the carbonate by sequestering the potassium ion) in toluene was added the aldehyde **30** (produced from commercially available 1,3-aminopropanol, Boc protected and subsequently oxidized by PCC in 75% yield over two steps). Unfortuantely, while more *cis*-selective than the Julia-Kocienski sulfone generated from mercaptobenzothiazole, the Still-Gennari reaction suffered in yield, producing **26** 30%, with 2:1 *Z*:*E* selectivity prior to purification. While these conditions were not productive enough for us to continue extending the carbon framework, it still gave us an opportunity to examine intramolecular imine formation.

Unfortunately, any method used to deprotect the amine's Boc group served to induce *cis*→*trans* isomerization of the enone.

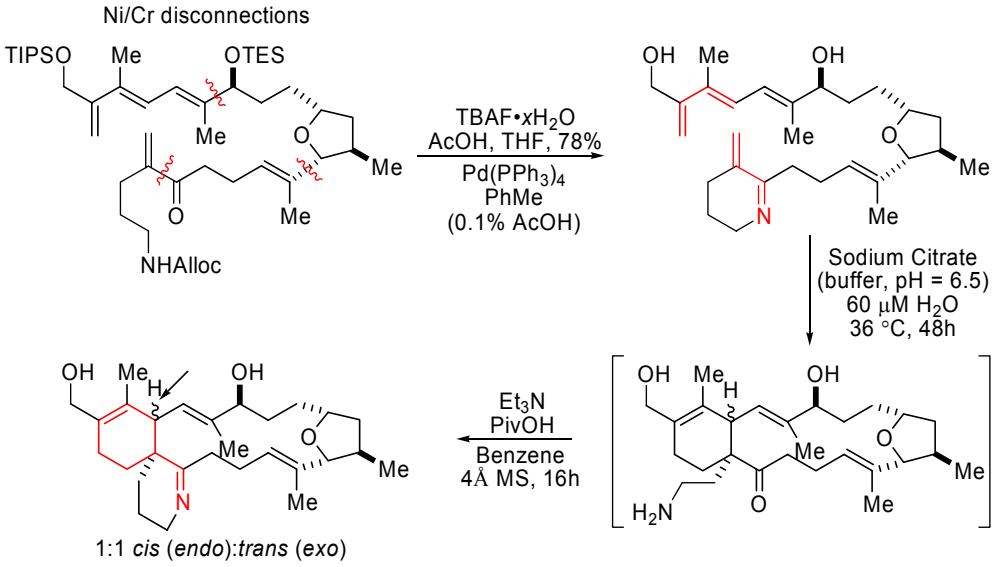


Scheme 20. Still-Gennari Olefination and Failed Imine Formation

D. Nozaki-Hiyama-Kishi reaction

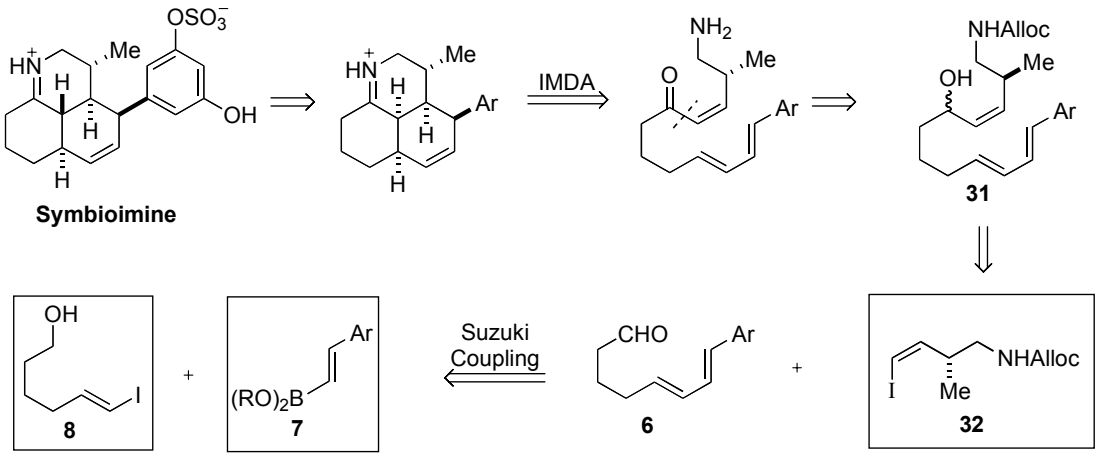
Clearly, a more neutral deprotection condition was needed, and as luck would have it, solutions to both issues were to be resolved simultaneously upon reading Kishi's publication of his progress on gymnodimine (Scheme 21). In this work, Kishi constructs each allylic alcohol by way of a nickel-catalyzed organochromium addition of a vinyl iodide or vinyl bromide to the corresponding aldehyde, called the Nozaki-Hiyama-Kishi reaction.[5] Reading more about such organometallic species, it was observed that the *E*/*Z* olefinic relationship of the vinyl halide was maintained in the reaction product. Additionally, organochromium species are selective for aldehydes, and would not deprotonate a carbamate, unlike the corresponding vinyl lithium species. More significant, however, is that the Kishi group has the same approach towards creation of

gymnodimine's tricyclic system, in that an activated cyclic iminium species is serving as the dienophile in an intramolecular Diels-Alder reaction. Here, of the variety of protecting group strategies they employed (Boc, Teoc, Alloc), it seemed that the allyloxycarbonyl (alloc) allowed them to obtain the desired condensation product just prior to their Diels-Alder reaction.



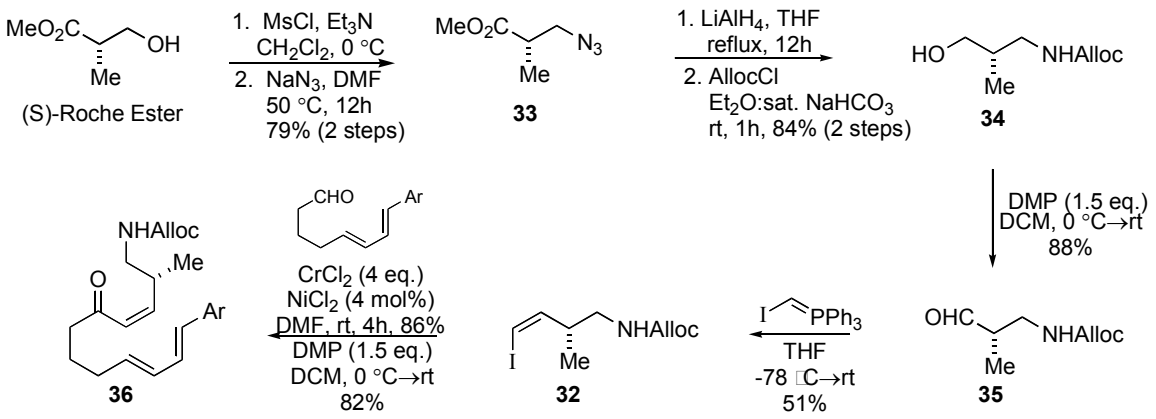
Scheme 21. Iminium-Activated Intramolecular Diels-Alder of Gymnodimine

To that end, application of the Nozaki-Hiyama-Kishi (ironically named NHK) reaction to our system can be observed in the retrosynthesis depicted in Scheme 22. Allyl alcohol **31** could be oxidized and deprotected to afford our desired reaction substrate, and prior to that, its construction by the NHK reaction can be seen by the coupling of known aldehyde **6** and *cis*-vinyl iodide **32**.



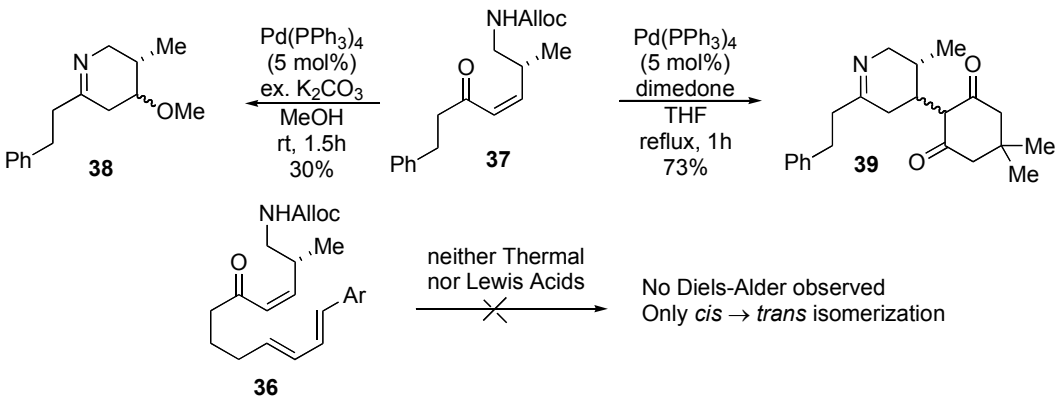
Scheme 22. Retrosynthesis Featuring the Nozaki-Hiyama-Kishi (NHK) Reaction

Synthesis of the chiral fragment **32** began by way of the commercially available (*S*)-Roche ester, as shown in scheme 23. Mesylation, followed by substitution with sodium azide gave azido-ester **33** in 79% over two steps. This then, was reduced by $LiAlH_4$ and subsequently *N*-protected by Allyl chloroformate under biphasic conditions to give the protected amino alcohol **34** in 84% yield over two steps. Oxidation of **34** with the Dess-Martin Periodinane produced aldehyde **35** in 88% yield, upon which a Wittig olefination was performed with an ylide generated from iodomethyl-triphenylphosphonium iodide deprotonated with NaHMDS, at –78 ˚C, to afford the desired *cis*-vinyl iodide **32** in 51% yield. This then, was taken onwards to the NHK reaction. Aldehyde **7** was weighed in a flask, and placed in anaerobic glovebox whereupon pre-weighed $CrCl_2$ (very hydroscopic) and $NiCl_2$ was added to it. Removal from the glove box, charging with DMF, and adding the *cis*-vinyl iodide immediately gave the corresponding *cis*-allyl alcohol as a mixture of isomers, which upon oxidation with DMP gave *cis*-enone **37** in 86% and 82%, respectively.



Scheme 23. Synthesis of Fragment **37** and Coupling to Produce Framework **38**

Prior to further experimentation with *cis*-enone **36**, model studies with *cis*-enone **37** (derived from the coupling and oxidation of *cis*-**32** and commercially available hydrocinnemaldehyde in similar yields) were undertaken to explore which alloc deprotection methodologies were amendable to our condensation needs (Scheme 24). Unfortunately, the results were a mixture of good and bad: imine formation readily occurred, but the electrophilic nature of 2,3-dihydropyridine meant that any potential nucleophile would trap it, as evidenced by both methanol-**38** and dimedone-**39** adducts. Moreover, exposure of **36** to all of the aforementioned Diels-Alder conditions failed to realize any Diels-Alder products; just *cis*→*trans* isomerization.

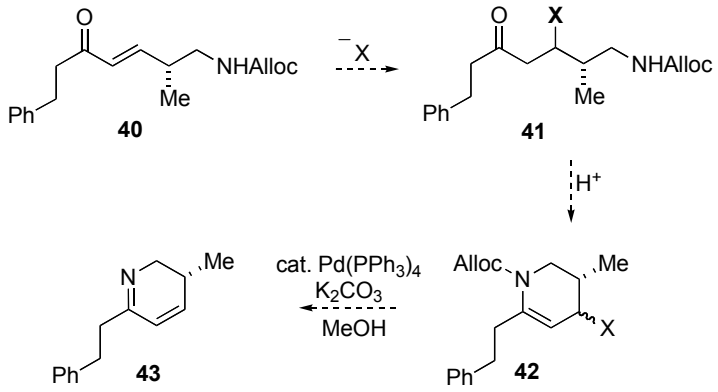


Scheme 24. Imine Formation + Conjugate Addition; No Diels-Alder Observed

E. Equitable solutions / Conclusion

Clearly, a synthesis of clean 2,3-dihydropyridine was needed whereupon the π-allyl acceptor needed in the alloc deprotection would not add to 2,3-dihydropyridine. While thinking about this problem at the ACS national meeting in San Francisco, I outlined what the necessary desired steps for such a transformation, and summarily came upon a solution not only to the endemic problem of alloc deprotection, but more importantly one which obviated the need for undertaking *cis*-selective olefination (Scheme 25). From a model system lacking the aryl diene, it was clear that we needed to isolate 2,3-dihydropyrdine **43** in a manner that avoided both acidic and basic conditions. From *trans*-olefin **40**, conjugate addition of a suitable nucleophile would give ketone **41**, thus allowing free bond rotation to occur such that under catalytic acidic conditions an allyl carbamate would be free to condense on the resulting ketone, isomerizing to *N*-acyl enamine **42**. This 'masked' 2,3-dihydropyridine could then be deprotected, the resulting enamine kicking out the nucleophile, which would then, rather than trap the nascent 2,3-dihydropyridine **43**, would attack the Pd π-allyl complex, allowing $Pd^{(0)}$ to be catalytic in

nature. As you will see in the subsequent chapter, this realization proved to be key in developing the necessary methodology to obtain 2,3-dihydropyridine.



Scheme 25. Isomerization Regime Change Starts in Our Minds

F. Acknowledgments

The first section in the chapter on the application of the Lindlar reduction to the synthesis of the carbon framework of symbioimine was undertaken by Erin Olson, who is graciously acknowledged for her contribution to this work.

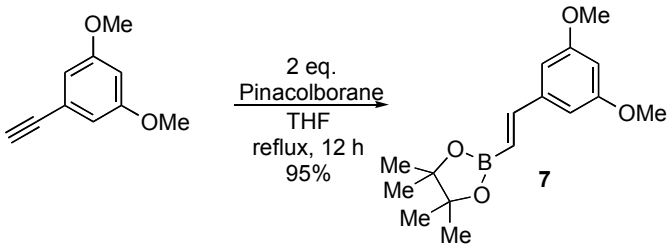
G. Experimental Section

Material and Methods

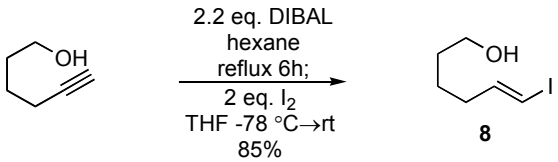
All reagents were commercially obtained (Aldrich, Fisher) at highest commercial quality and used without further purification except where noted. Organic solutions were concentrated by rotary evaporation below 45 ˚C at approximately 20 mmHg. Tetrahydofuran (THF), methanol (MeOH), chloroform ($CHCl_3$), dichloromethane (DCM), ethyl acetate (EtOAc), acetonitrile (CH_3CN), and acetone were purchased as reagent grade and used without further purification. Reactions were run under an inert N_2

atmosphere unless otherwise noted. Yields refer to chromatographically and spectroscopically (^{1}H- and ^{13}C-NMR) homogeneous materials, unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254), visualized with UV light and stained with cerium molybdate solution and heat. E. Merck silica gel (60A, particle size 0.040-0.063 mm) was used for flash chromatography. Preperative thin-layer chromatography separations were carried out on 0.50 mm E. Merck silica gel plates (60F-254). NMR spectra were recorded on Varian Mercury 300, 400 and/or Unity 500 MHz instruments and calibrated using the residual undeuterated solvent as an internal reference. Chemical shifts (δ) are reported in parts per million (ppm) and coupling constants (*J*) are reported in hertz (Hz). The following abbreviations are used to designate multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Mass spectra (MS) and high-resolution mass spectra (HRMS) were recorded on a Finnigan LCQDECA mass spectrometer under electrospray ionization (ESI) or atmospheric pressure chemical ionization (APCI) conditions, or on a Thermo-Finnegan Mat900XL mass spectrometer under electron impact (EI), chemical ionization (CI), or fast atom bombardment (FAB) conditions. X-ray data were recorded on a Bruker SMART APEX CCD X-ray diffractometer. Specific optical rotations were recorded on a Jasco P-1010 polarimeter and the specific rotations were calculated based on the equation $[\alpha]^{25}_{D} = (100 \cdot \alpha)/(l \cdot c)$, where the concentration c is in g/100 mL and the path length *l* is in decimeters.

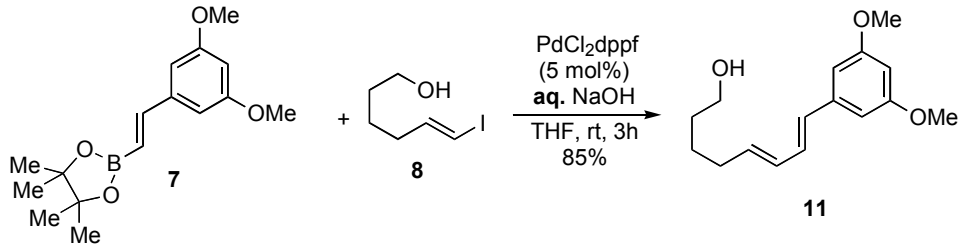
Procedures and Spectral Data



2-(3,5-Dimethoxystyryl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane 7: BH_3-THF (1.0M THF, 48 ml, 48 mmol) was added to a flame-dried, 250 mL round bottom flask, cooled to 0 ˚C, and pinacol (5.585 g, 47.26 mmol) slowly added. After 2 hours, the reaction was allowed to warm to room temperature for 2 additional hours, whereupon commercially available 3,5-dimethoxy phenyleacetylene (3.83 g, 23.63 mmol) was added, and refluxed overnight. Upon cooling to 0 ˚C, the reaction was quenched by the addition of sat. NH_4Cl. After separation, the aqueous layer was extracted 3x with EtOAc, the combined organics washed with brine, and dried over Na_2SO_4. Evaporation, followed by purification over silica (15:1 Hexane:EtOAc, R_F = 0.4) gave the title compound **7** as a white waxy solid (6.51 g, 95% yield). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.30 (d, *J* = 18.0 Hz, 1H), 6.63 (d, *J* = 2.5 Hz, 2H), 6.40 (t, *J* = 2.5 Hz, 1H), 6.12 (d, *J* = 18.0 Hz, 1H, 3.77 (s, 6H), 1.29 (s, 12H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 160.5, 149.5, 149.1, 117.9, 104.8, 101.25, 83.4, 55.3, 24.9. ^{13}C-NMR (100 MHz, $CDCl_3$) δ. HRMS $C_{16}H_{23}BO_4$: [M] calcd 290.1689, obsd $[M + Na]^+$ = 313.1582.

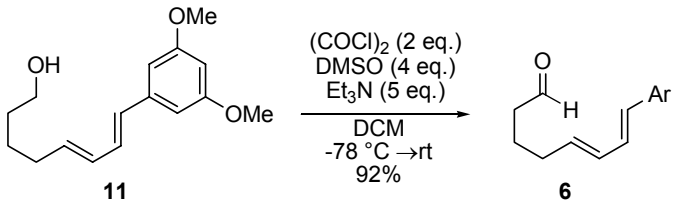


(*E*)-6-Iodohex-5-en-1-ol 8: DIBAL (1.0M hexane, 234 ml, 234 mmol) was added to a flame-dried, 1 L round bottom flask, and cooled to 0 ˚C. 5-hexyn-1-ol (10.0 g, 101.88 mmol) was added dropwise, and the solution warmed to reflux for 6 hours. After evaporation of solvent, 130 ml THF was added and the solution was cooled to –78 ˚C. Iodine (28.44 g, 112.07 mmol) in 100 ml THF was added dropwise and the solution allowed to reach room temperature. The reaction was quenched by addition to a 0 ˚C, 1:1 solution of 1M HCl:EtOAc (400 mL) slowly (exothermic), the solution turning to a clear light yellow color. After separation, the aqueous is extracted 3x 100 mL with EtOAc, washed with sat. $NaHCO_3$, brine, and dried over Na_2SO_4. Evaporation *in vacuo* and subsequent purification on silica (2:1 Hexane:EtOAc, R_f = 0.3) gave **8** (19.57 g, 85% yield) as a clear oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.45 (dt, *J* = 7.5 Hz, 1H), 5.99 (d, *J* = 16.0, 1H), 3.60 (m, 2H), 2.10 (q, *J* = 7.0 Hz, 2H), 1.75 (m, 4H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 146.5, 75.1, 62.8, 36.0, 32.1, 24.8. MS $C_6H_{11}IO$: calcd 225.99, obsd $[M + H]^+$ = 226.97.



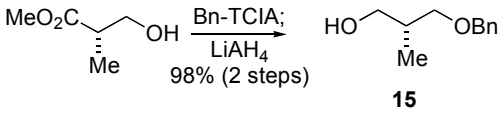
(5*E*,7*E*)-8-(3,5-Dimethoxyphenyl)octa-5,7-dien-1-ol 11: To a 250 mL round bottom flask was added vinyl iodide **8** (8.68 g, 38.40 mmol, 1.2 equiv.), pinacol boronate **7** (9.285 g, 32.0 mmol, 1.0 equiv.), and THF (160 mL, degassed with N_2) under an inert N_2 atmosphere at room temperature. $PdCl_2dppf{\cdot}CH_2Cl_2$ (1.30 g, 1.60 mmol, 0.05 equiv.) and 15% NaOH (25.6 ml, 3.0 equiv.) were added, and the reaction allowed to stir for 3h

until the vinyl iodide had been consumed as observed by TLC. The reaction was quenched by addition of brine and EtOAc, separated, and the aqueous extracted 2x with EtOAc. The combined organics were dried over Na_2SO_4, evaporated to dryness, and purified over silica (5:1 to 3:1 Hexane:EtOAc, $R_f = 0.4$) to yield the aryl diene alcohol **11** (7.13 g, 85% yield). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 6.70 (dd, *J* = 11.0, 16.0 Hz, 1H), 6.51 (d, *J* = 2.0 Hz, 1H), 6.35 (d, *J* = 15.5 Hz, 1H), 6.32 (t, *J* = 2.5 Hz, 1H), 6.18 (dd, *J* = 10.0, 14.5 Hz, 1H), 5.81 (dt, *J* = 7.5, 15.0 Hz, 1H), 3.77 (s, 6H), 3.64 (t, *J* = 6.5 Hz, 2H), 2.16 (q, *J* = 6.5 Hz, 2H), 1.59 (m, 2H), 1.49 (q, *J* = 7.5 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 160.8, 139.6, 135.7, 130.7, 130.1, 129.8, 104.1, 99.5, 62.8, 55.3, 32.58, 32.2, 25.4. MS $C_{16}H_{23}BO_4$: calcd 262.16, obsd $[M + H]^+ = 263.14$.



(5*E*,7*E*)-8-(3,5-Dimethoxyphenyl)octa-5,7-dienal 6: $(COCl)_2$ (13.5 mL, 141.56 mmol, 2 equiv.) and DCM (350 mL) were added to a 1 L round bottom flask, and cooled to –78 ˚C. DMSO (20 mL, 283.12 mmol, 4 equiv.) was added dropwise, noting the evolution of CO, and allowed to react for 10 minutes. Alcohol (**11**) (16.0 g, 70.78 mmol, 1 equiv.) was added with continued stirring for 15 minutes, whereupon Et_3N (49.3 ml, 353.9 mmol, 5 equiv.) was added and the solution warmed to room temperature, 1h. The reaction was quenched with water (300 ml), separated, and the aqueous layer extracted 2x with EtOAc. The combined organics were washed with water, brine, and dried over Na_2SO_4. Evaporation to dryness and purification over silica (3:1 Hexane:EtOAc, R_f=

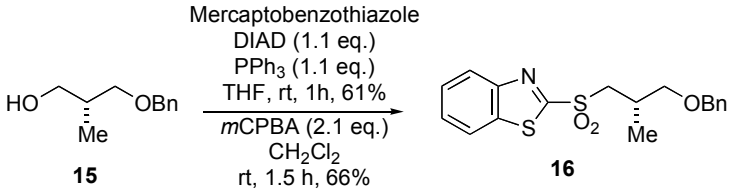
0.33) gave aldehyde **6** (14.59 g, 92%) as a clear oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.76 (s, 1H), 6.69 (dd, *J* = 10.5, 15.0 Hz, 1H), 6.51 (s, 2H), 6.37 (d, *J* = 15.5 Hz, 1H), 6.32 (s, 1H), 6.18 (dd, *J* = 10.5, 15.0 Hz 1H), 5.75 (dt, *J* = 7.5 Hz, 1H), 3.78 (s, 6H), 2.45 (t, *J* = 7.0 Hz, 2H), 2.18 (q, *J* = 6.5 Hz, 2H), 1.76 (q, *J* = 7.0 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 202.3, 160.8, 139.4, 134.3, 131.4, 130.6, 129.5, 128.3, 55.3, 43.1, 32.0, 21.5. HRMS $C_{16}H_{20}O_3$: calcd 260.1412, obsd $[M -2H]^-$ = 258.1255.



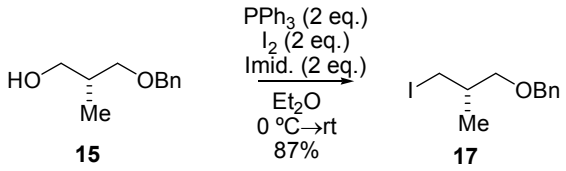
15

(*R*)-3-(Benzyloxy)-2-methylpropan-1-ol 15: To the (*S*)-Roche ester (11.25 g, 95.2 mmol, 1.0 equiv.) in DCM (475 mL) at 0 ˚C was added benzyl trichloroacetimidate (BTCA, 25.25 g, 100 mmol, 1.05 eq.), and trifluoromethanesulfonic acid (0.84 ml, 9.52 mmol, 0.1 eq.), and allowed to warm to room temperature over 1 hour. Upon consumption of the alcohol, the reaction was quenched with water, separated, and the aqueous extracted twice with EtOAc. The combined organics were washed with brine, evaporated to dryness, and the crude material added dropwise to a solution of $LiAlH_4$ (3.61 g, 1.0 eq.) in THF (360 mL) at 0 ˚C. The reaction was then quenched using the Fieser method (for 3.6 g. of $LiAlH_4$, add 3.6 mL water, 3.6 mL of 15% NaOH, and 3x3.6 mL of water), followed by addition of excess K_2CO_3, which, after 30 min, was filtered, and the filtrate evaporated to give compound (**15**) (16.82 g, 98% yield) which needed no further purification. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.32 (m, 5H), 450 (s, 1H), 3.59 (dd, 8.8, 8.8 Hz, 1H), 3.41 (t, 8.0 Hz, 1H), 2.73 (bs, 1H), 2.04 (m, 1H), 0.87 (d, 6.8 Hz, 3H);

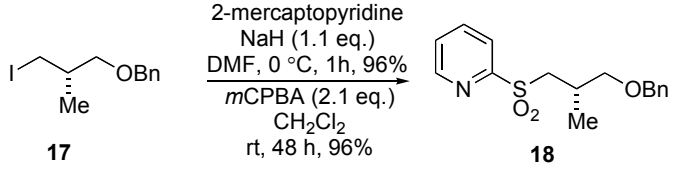
^{13}C-NMR (100 MHz, $CDCl_3$) δ 137.8, 128.2, 127.5, 127.3, 75.1, 73.2, 67.5, 35.6, 13.6. MS $C_{11}H_{16}O_2$: calcd 180.12, obsd $[M + H]^+$ = 181.14.



2-((*S*)-3-(Benzyloxy)-2-methylpropylsulfonyl)benzo[*d*]thiazole 16: Alcohol **15** (200 mg, 1.11 mmol, 1.0 equiv.) was added to a solution of diisopropylazodicarboxylate (DIAD, 245 mg, 1.22 mmol, 1.1 equiv.) and triphenylphosphine (320 mg, 1.22 mmol, 1.1 equiv.) in THF (6 ml) at room temperature, followed by 2-mercaptobenzothiazole (200 mg, 1.22 mmol, 1.1 equiv.) and allowed to stir for 1 hour. The reaction was quenched by the addition of water, diluted with EtOAc, separated, and the aqueous layer extracted twice with EtOAc. The combined organics were washed with brine, dried over Na_2SO_4, and evaporated to dryness. This crude material was then dissolved in DCM (8 mL), and *m*-CPBA (405 mg, 2.1 equiv.) added, stirring for 1.5h. The reaction was then quenched by the sat. $NaHCO_3$, extracted 3x with EtOAc, the combined organics washed with brine, dried over Na_2SO_4, and evaporated to dryness, followed by purification over silica (3:1 Hexane:EtOAc, R_f = 0.45) to give sulfone **16** (164 mg, 41% yield over two steps) as a white solid. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.20 (d, *J* = 8.7 Hz, 1H), 8.01 (d, *J* = 7.2 Hz, 1H), 7.62 (dt, *J* = 5.7 Hz, 2H), 7.28 (m, 5H), 4.44 (d, *J* = 2.7 Hz, 2H), 3.86 (dd, *J* = 4.8, 14.4 Hz, 1H), 3.51 (dd, *J* = 5.1, 15.5 Hz, 1H), 3.38 (dt, *J* = 5.4 Hz, 2H), 2.60 (m, 1H), 1.19 (d, *J* = 6.6 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 166.4, 152.6, 137.9, 136.7, 128.3, 128.2, 127.6, 127.5, 125.4, 122.3, 73.3, 72.9, 57.8, 29.4, 17.1.

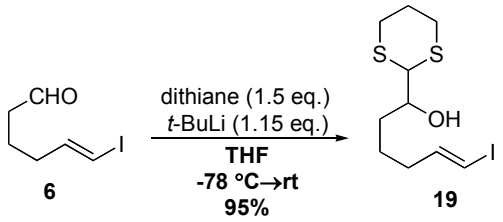


1-(((*S*)-3-Iodo-2-methylpropoxy)methyl)benzene 17: To a ml round bottom flask containing alcohol **15** (1.40 g, 7.77 mmol, 1 equiv.) and Et_2O (70 mL) at 0 ˚C was added iodine (3.94 g, 15.54 mmol, 2.0 equiv.) and triphenylphosphine (4.07 g, 15.54 mmol, 2.0 equiv.), and imidazole (1.06 g, 15.54 mmol, 2.0 equiv.). After 1 hour, the reaction was quenched by the addition of water and diluted with EtOAc. After separation, the aqueous layer was extracted 2x with EtOAc, and the combined organics washed with brine, dried over Na_2SO_4, and evaporated to dryness. Purification over silica (9:1 Hexane:EtOAc, Rf = 0.6) produced alkyl iodide **17** (1.96 g, 87% yield) as a clear oil. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.32 (m, 5H), 4.50 (s, 2H), 3.38 (dd, J = 5.0, 9.5 Hz, 1H), 3.31 (m, 3H), 1.77 (m, 1H), 0.98 (d, J = 7.0 Hz, 3H).



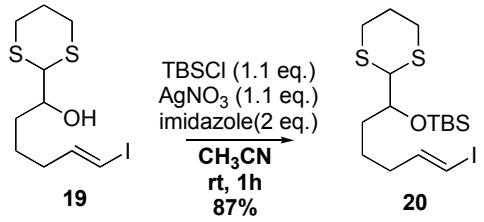
2-((*S*)-3-(Benzyloxy)-2-methylpropylsulfonyl)pyridine 18: To a ml round bottom flask containing 2-mercaptopyridine (0.311 g, 2.80 mmol, 1.0 eq.), DMF (5.3 mL) at 0 ˚C was added NaH (120 mg, 1.1 equiv.), followed by alkyl iodide **17** (775 mg, mmol, 1.0 equiv.). After 1 hr, the reaction was quenched with water (50 mL), and extracted three times with EtOAc. The combined organics were washed with brine, dried over Na_2SO_4, and evaporated to dryness. This crude material was then dissolved in DCM (5 mL), and *m*-CPBA (1.014 g, 5.88 mmol, 2.1 eq.) added, stirring for 1.5h. The reaction

was then quenched by the sat. $NaHCO_3$, extracted 3x with EtOAc, the combined organics washed with brine, dried over Na_2SO_4, and evaporated to dryness, followed by purification over silica (2:a Hexane:EtOAc, $R_f = 0.25$) to give sulfone **18** (0.786 g, 92% yield over two steps) as a white solid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.70 (m, 1H), 8.07 (d, *J* = 8.0 Hz, 1H), 7.92 (t, *J* = 7.6 Hz, 1H), 7.50 (t, *J* = 6.0 Hz, 1H), 7.27 (m, 5H), 4.42 (d, *J* = 4.8 Hz, 2H), 3.67 (dd, *J* = 4.4, 14.0 Hz, 1H), 3.43 (dd, *J* = 4.8, 6.4 Hz, 1H), 3.34 (t, *J* = 8.0 Hz, 1H), 3.24 (dd, *J* = 7.6, 14.4 Hz, 1H), 2.45 (m, 1H), 1.10 (d, *J* = 6.4 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 158.0, 150.0, 137.9, 128.2, 127.4, 127.3, 127.1, 121.8, 73.6, 72.9, 55.0, 29.2, 17.3. MS $C_{16}H_{19}NO_3S$: calcd 305.11, obsd $[M + H]^+$ = 306.00.

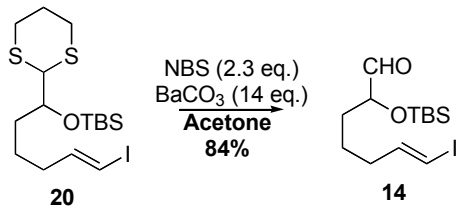


(*E*)-1-(1,3-Dithian-2-yl)-6-iodohex-5-en-1-ol 19: To a solution of 1,3-dithiane (6.9 g, 57.495 mmol, 1.5 equiv.) in THF (100 mL) at –78 ˚C was added *t*-BuLi (1.7 M, 26 mL, 1.15 equiv.) dropwise, and allowed to stir for 5 min. Aldehyde **6** (8.59 g, 38.33 mmol, 1.0 equiv.) was added dropwise, and the reaction allowed to warm to room temperature, where it was quenched by the addition of sat. NH_4Cl, separated, and the aqueous phase extracted 3x with EtOAc. The combined organics were washed with brine, dried over Na_2SO_4, and evaporated to dryness. The crude material was purified over silica (5:1 Hexane:EtOAc, $R_f = 0.15$), giving alcohol **19** (12.54 g, 95% yield) as a clear oil. The ^{1}H-NMR (500 MHz, $CDCl_3$) δ 6.48 (dt, *J* = 7.5 Hz, 1H), 5.99 (d, *J* = 14.0

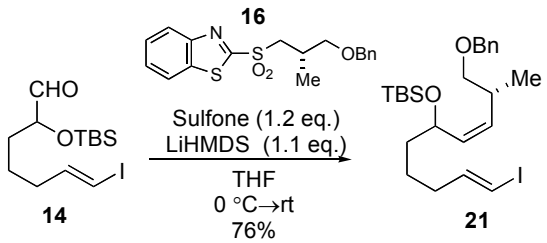
Hz, 1H), 3.83 (m, 2H), 2.90 (m, 2H), 2.73 (m, 2H), 2.08 (m, 3H), 1.93 (m, 1H), 1.80 (m, 2H), 1.62 (m, 2H), 1.51 (m, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 146.0, 74.9, 71.6, 52.1, 35.7, 33.1, 30.2, 25.5, 24.5, . MS $C_{10}H_{17}IOS_2$: calcd 343.98, obsd $[M - OH]^+$ = 326.99.



((*E*)-1-(1,3-Dithian-2-yl)-6-iodohex-5-enyloxy)(*tert*-butyl)dimethylsilane 20: A ml round bottom flask containing alcohol **19** (6.6 g, 19.17 mmol, 1 equiv.) in CH_3CN (66 mL) at room temperature was added TBSCl (3.18 g, 21.08 mmol, 1.1 equiv.), $AgNO_3$ (3.58 g, 21.08 mmol, 1.1 equiv.) and pyridine (7.58 g, 95.85 mmol, 5.0 equiv.). The reaction was stirred for 1h, whereupon the reaction was quenched by addition of water and diluted with EtOAc. After separation, the aqueous phase was extracted 3x with EtOAc, the combined organics washed with brine, dried over Na_2SO_4, and concentrated to dryness. The crude material was purified over silica (9:1 Hexane:EtOAc, R_f = 0.7) to afford silyl ether **20** (12.74 g, 87% yield) as a clear oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.48 (dt, *J* = 7.2 Hz, 1H), 5.98 (d, *J* = 14.1 Hz, 1H), 4.13 (d, *J* = 4.8 Hz, 1H), 3.80 (q, *J* = 4.8 Hz, 1H), 2.82 (m, 4H), 2.05 (m, 4H), 1.83 (m, 2H), 1.62 (m, 2H), 0.90 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 146.4, 75.1, 74.4, 54.7, 36.2, 33.8, 30.9, 30.7, 26.6, 26.1, 25.9, 23.9, -4.1, -4.2. MS $C_{16}H_{31}IOS_2Si$: calcd 458.06, obsd $[M - OTBS]^+$ = 327.08.

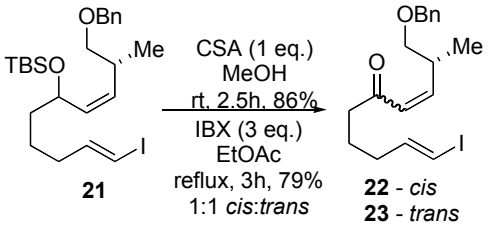


2-(*t*-Butyldimethylsilyl ether)-7-iodo-6-heptenaldehyde 14: A ml round bottom flask containing silyl ether **20** (1.0 g, 3.18 mmol, 1 equiv.) in acetone (100 mL) was added $BaCO_3$ (6.02 g, 30.52 mmol, 14 equiv.) and NBS (0.894 g, 5.02 mmol, 2.3 equiv.). The reaction was stirred at room temperature for 30 min, whereupon the reaction was quenched by addition of water and diluted with EtOAc. After separation, the aqueous phase was extracted 3x with EtOAc, the combined organics washed with brine, dried over Na_2SO_4, and concentrated to dryness. The crude material was purified over silica (9:1 Hexane:EtOAc, $R_f = 0.55$) to afford aldehyde **14** (0.674 g, 84% yield) as a clear oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.60 (s, 1H), 6.45 (dt, J = 6.9 Hz, 1H), 5.99 (d, J = 14.4 Hz, 1H), 3.94 (t, J = 6.6 Hz, 1H), 2.05 (q, J = 6.9 Hz, 2H), 1.58 (q, J = 6.9 Hz, 2H), 1.48 (m, 2H), 0.90 (s, 9H), 0.05 (s, 6H). MS $C_{13}H_{25}IO_2Si$: calcd 368.07, obsd $[M - CHO]^+$ = 338.38.



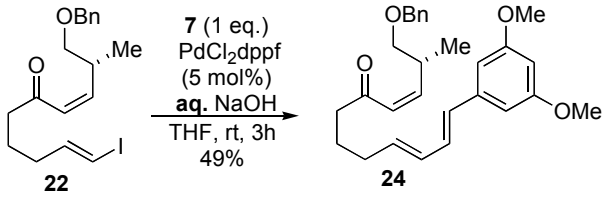
((2*R*,3*Z*,9*E*)-1-(Benzyloxy)-10-iodo-2-methyldeca-3,9-dien-5-yloxy)(*tert*-butyl)dimethylsilane 21: In a 25 ml round bottom flask was added sulfone **16** (355 mg, 0.982 mmol, 1.1 equiv.), THF (8 mL) cooled to 0 ˚C, LiHMDS (1M, 1.1 ml, 1.2 eq.) for

1h, followed by aldehyde **14** (328 mg, 0.892 mmol, 1 equiv.) and the reaction allowed to warm to room temperature. The reaction was quenched by addition of water and diluted with EtOAc. After separation, the aqueous phase was extracted 3x with EtOAc, the combined organics washed with brine, dried over Na_2SO_4, and concentrated to dryness. The crude material was purified over silica (9:1 Hexane:EtOAc, $R_f = 0.66$) to afford olefinic **21** (348 mg, 76% yield) as a mixture of isomers. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.31 (m, 5H), 6.51-6.41 (m, 1H), 6.01-5.89 (m, 1H), 5.54-5.30 (m, 2H), 4.49 (s, 2H), 4.01 (d, *J* = 5.7 Hz, 1H), 3.36-3.22 (m, 2H), 2.47 (q, *J* = 6.6 Hz, 1H), 2.03 (t, *J* = 6.6 Hz, 2H), 1.45-1.37 (m, 5H), 1.01 (d, *J* = 6.6 Hz, 2H), 0.85 (s, 9H), 0.01 (s, 6H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 146.5, 138.6, 134.3, 132.8, 128.2, 127.5, 127.4, 38.0, 37.6, 36.4, 35.9, 35.9, 25.8, 25.7, 24.1, 18.1, 17.1, -3.0, -4.8. MS $C_{24}H_{39}IO_2Si$: calcd [M] = 514.18, obsd $[M + NH_4]^+ = 531.90$.



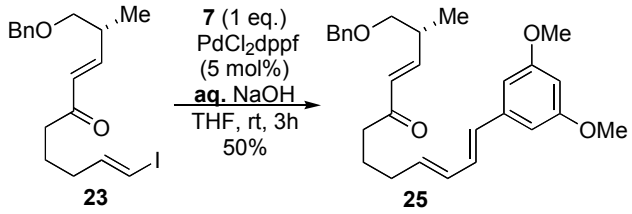
(*R*,9*E*)-1-(Benzyloxy)-10-iodo-2-methyldeca-3,9-dien-5-one 22, 23: A silyl ether **21** (56 mg, 0.108 mmol, 1 equiv.) walked into a bar, surrounded by an ocean of MeOH (1 mL), went up to the barkeep and asked for CSA (27 mg, 0.114 mmol, 1.05 equiv.). After imbibing the acid, the silyl ether danced for 2.5 hrs, whereupon it was quenched by addition of sat. $NaHCO_3$ and diluted with EtOAc. After separation, the aqueous phase was extracted 3x with EtOAc, the combined organics washed with brine,

dried over Na_2SO_4, and concentrated to dryness. The crude material was dissolved in EtOAc (2mL), IBX (91 mg, 0.324mmol, 3.0 equiv.) added, and the solution refluxed for 3h. Upon cooling, the solution was filtered, and the filtrate evaporated to dryness. The crude material was purified over silica (9:1 Hexane:EtOAc, R_f =0.4 (cis), 0.2 (trans)) to afford enone ***cis*-22**, ***trans*-23** (29 mg, 68% yield, 1:1 *cis*:*trans*, over 2 steps) as a clear oil. *cis*-**22**: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.30 (m, 5H), 6.45 (dt, *J* = 6.9 Hz, 1H), 6.12 (d, *J* = 11.4 Hz, 1H), 5.99 (d, *J* = 14.7 Hz, 1H), 5.96 (t, *J* = 9.0 Hz, 1H), 4.49 (s, 2H), 3.75 (m, 1H), 3.47 (d, *J* = 3.9 Hz, 1H), 3.36 (dd, *J* = 2.1, 7.2 Hz, 2H), 2.44 (t, *J* = 7.2 Hz, 2H), 2.05 (q, *J* = 6.9, Hz, 2H), 1.67 (q, *J* = 7.5 Hz, 2H), 1.54 (s, 6H), 1.02 (d, *J* = 6.9 Hz, 3H). MS $C_{18}H_{23}IO_2$: calcd 398.07, obsd $[M + Na]^+$ = 420.95. *trans*-**23**: ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.31 (m, 5H), 6.78 (dd, *J* = 7.2, 16.4 Hz, 1H), 6.46 (dt, *J* = 7.2 Hz, 1H), 6.09 (d, *J* = 16.0 Hz, 1H), 5.99 (d, *J* = 14.8 Hz, 1H), 4.49 (s, 2H), 3.39 (d, *J* = 6.4 Hz, 2H), 2.64 (m, 1H), 2.52 (t, *J* = 7.2 Hz, 2H), 2.06 (q, *J* = 8.0 Hz, 2H), 1.70 (q, *J* = 7.6 Hz, 2H), 1.07 (d, *J* = 6.8 Hz, 3H).

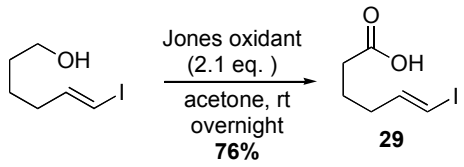


(*R*,3*Z*,9*E*,11*E*)-2-((Benzyloxy)methyl)-12-(3,5-dimethoxyphenyl)dodeca-3,9,11-trien-5-one 24: *cis*-enone **22** (83 mg, 0.208 mmol, 1.0 equiv.) in THF (2 mL) at room temperature was subjected to addition of pinacol boronate **7** (86 mg, 0.291 mmol, 1.4 equiv.), $PdCl_{2(}$(dppf)·DCM (8.5 mg, 0.0104 mmol, 0.05 equiv.) and 15% NaOH (1 mL, >3 equiv.). After stirring for 3 hours, the reaction was diluted with brine, separated,

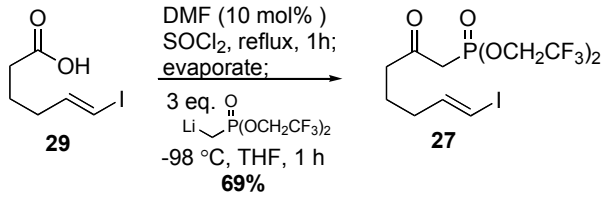
and the aqueous phase extracted 2x with EtOAc. The combined organics washed with brine, dried over Na_2SO_4, and concentrated to dryness. The crude material was purified over silica (4:1 Hexane:EtOAc, R_f = 033) to afford *cis*-enone **24** (50 mg, 49% yield) as a clear oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.25 (m, 5H), 6.69 (dd, *J* = 10.4, 15.6 Hz, 1H), 6.51 (d, *J* = 1.8 Hz, 2H), 6.35 (d, *J* = 16.0 Hz, 1H), 6.32 (s, 1H), 6.17 (dd, *J* = 10.5, 15.2 Hz, 1H), 6.13 (d, *J* = 11.7 Hz, 1H), 5.94 (dd, *J* = 9.6, 11.4 Hz, 1H), 5.76 (dt, *J* = 7.2 Hz, 1H), 4.48 (s, 2H), 3.78 (s, 6H), 3.36 (m, 2H), 2.47 (t, *J* = 7.5 Hz, 2H), 2.15 (q, *J* = 7.2 Hz, 2H), 1.72 (q, *J* = 7.5 Hz, 2H), 1.02 (d, *J* = 6.6 Hz, 3H). MS $C_{28}H_{34}O_4$: calcd 434.25, obsd $[M + H]^+$ = 435.14.



(*R*,3*E*,9*E*,11*E*)-1-(Benzyloxy)-12-(3,5-dimethoxyphenyl)-2-methyldodeca-3,9,11-trien-5-one 25: Made as described for *cis*-enone **24**, in 50% yield. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.25 (m, 5H), 6.79 (dd, *J* = 6.8, 16.0 Hz, 1H), 6.70 (dd, *J* = 7.8, 15.2 Hz, 1H), 6.51 (d, *J* = 2.0 Hz, 2H), 6.36 (d, *J* = 15.6 Hz, 1H), 6.32 (t, *J* = 2.0 Hz, 1H), 6.18 (dd, *J* = 10.0, 14.4 Hz, 1H), 6.11 (d, *J* = 16.0 Hz, 1H), 5.78 (dt, *J* = 6.8 Hz, 1H), 4.49 (s, 2H), 3.78 (s, 6H), 3.39 (d, *J* = 6.8 Hz, 2H), 2.64 (m, 1H), 2.55 (t, *J* = 7.2 Hz, 2H), 2.16 (q, *J* = 7.2 Hz, 2H), 1.74 (q, *J* = 7.6 Hz, 2H), 1.07 (d, *J* = 6.8 Hz, 3H). MS $C_{28}H_{34}O_4$: calcd 434.25, obsd $[M + Na]^+$ = 457.15.

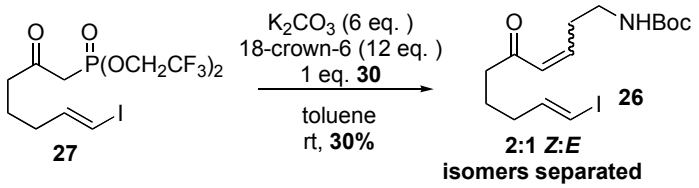


(*E*)-6-Iodohex-5-enoic acid 29: Vinyl iodide **8** (226 mg, 1.0 mmol, 1 equiv.) was added to a 10 mL round bottom flask, followed by acetone (3.4 mL) and the Jones oxidant (0.79 mL, 2.67M, 2.1 equiv.) to stir at room temperature overnight. The reaction was diluted with EtOAc and water, separated, and the aqueous layer extracted 3x with EtOAc. The combined organics were washed with brine, dried over Na_2SO_4, and evaporated to dryness, whereupon purification over silica (1:1 Hexane:EtOAc, R_f = 0.25-0.50) produced carboxylic acid **29** (181 mg, 76% yield) as a clear oil. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 6.46 (dt, *J* = 6.5, 1H), 6.04 (d, *J* = 14.0 Hz, 1H), 2.34 (t, *J* = 7.5 Hz, 1H), 2.10 (q, *J* = 7.5 Hz, 2H), 1.72 (q, *J* = 7.5 Hz, 2H); MS $C_6H_9IO_2$: calcd 239.96, obsd [M - Na]$^-$ = 238.99.



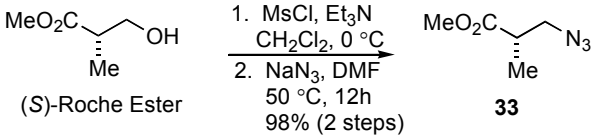
7-Iodo-6-en-1-Bis-(trifluoroethoxy)-β-ketophosphonate 27: To a solution of thionyl chloride (17 mL) and DMF (26 μL, .357 mmol, 0.1 equiv.) was added a solution of carboxylic acid **29** (859 mg, 3.57 mmol, 1 equiv.) in DCM (1 mL). The solution was refluxed for 1h, and evaporated to dryness. In another flask containing bis(trifluoroethanol) methyl phosphonate (1.856 g, 7.14 mmol, 2.0 equiv.) in THF (35 mL) at –98 ˚C, LiHMDS (1M, 7.14 mL, 2.0 equiv.) was added and allowed to stir for 10

minutes, whereupon the crude acid chloride in THF (3 mL) was added. After 1h at -78 ˚C, the solution was quenched with 30 mL of sat. NH_4Cl, separated, and the aqueous phase extracted 3x with EtOAc. The combined organics were washed with brine, dried over Na_2SO_4, and evaporated to dryness, whereupon purification over silica (5:1 Hexane:EtOAc, R_f = 0.75) produced β-ketophosphonate **27** (1.29 g, 69% yield) as a clear oil. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 6.45 (dt, *J* = 7.5 Hz, 1H), 5.99 (d, *J* = 16.0 Hz, 1H), 4.50 (q, *J* = 8.5 Hz, 4H), 3.17 (t, *J* = 7.5 Hz, 1H), 2.41 (q, *J* = 7.0, Hz, 2H), 2.10 (q, *J* = 7.0 Hz, 2H), 1.75 (q, *J* = 7.5 Hz, 2H). MS $C_{11}H_{14}IO_4P$: calcd 481.96, obsd $[M + H]^+$ = 482.72.



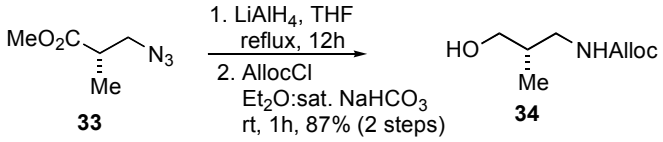
***tert*-Butyl (9*E*)-10-iodo-5-oxodeca-3,9-dienylcarbamate 26**: To a solution of β-ketophosphonate **27** (0.367 g, 0.7625 mmol, 1 equiv.) in toluene (12 mL) at room temperature was added K_2CO_3 (0.632 g, 4.575 mmol, 6 equiv.), 18-crown-6 (2.40 g, 9.15 mmol, 12 equiv.), and *N*-(*t*-Butoxycarbonyl)-aminopropanal (100 mg, 0.7625 mmol, 1 equiv.) to stir over 3 h. The reaction was quenched with water, separated, and the aqueous phase extracted twice with EtOAc. The combined organics were washed with brine, dried over Na_2SO_4, evaporated to dryness, and purified over silica (2:1 Hexane:EtOAc, R_f = 0.45 (*cis*), 0.35 (*trans*)) to produce the enone **26** (91 mg., 30%; reaction product was 2:1 *cis*:*trans*) as a clear oil. ***Cis*-26**: ^{1}H-NMR (500 MHz, $CDCl_3$) δ 6.45 (dt, *J* = 7.5 Hz, 1H), 6.19 (d, *J* = 16.0 Hz, 1H), 6.06 (m, 1H), 5.99 (d, *J* = 14.5 Hz, 1H), 4.79 (bs, 1H), 3.23 (m, 2H), 2.73 (q, *J* = 6.5 Hz, 2H), 2.44 (t, *J* = 7.5 Hz, 2H), 2.06

(q, *J* = 7.5 Hz, 2H), 1.68 (q, *J* = 6.5 Hz, 2H), 1.40 (s, 9H). ***Trans*-26**: ^{1}H-NMR (500 MHz, $CDCl_3$) δ 6.73 (dt, *J* = 7.5 Hz, 1H), 6.45 (dt, *J* = 7.5 Hz, 1H), 6.10 (d, *J* = 16.0 Hz, 1H), 5.98 (d, *J* = 14.0 Hz, 1H), 4.61 (bs, 1H), 3.25 (m, 2H), 2.51 (t, *J* = 7.5 Hz, 2H), 2.38 (q, *J* = 7.0 Hz, 2H), 2.05 (q, *J* = 7.0 Hz, 2H), 1.68 (q, *J* = 7.0, Hz, 2H), 1.40 (s, 9H). MS $C_{15}H_{24}INO_3$: calcd 393.08, obsd $[M + Na]^+$ = 415.92.

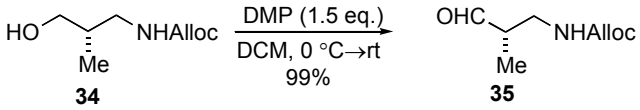


(*S*)-methyl 3-azido-2-methylpropanoate 33: Methanesulfonyl chloride (17.18 g, 150 mmol, 1.50 equiv.) was added dropwise to a solution of the (*S*)-Roche ester (11.813 g, 100 mmol, 1.0 equiv.) and triethylamine (20.24 g, 200 mmol, 2.0 equiv.) in DCM (400 mL) at 0 ˚C. After stirring for 2 h, the reaction was quenched and subsequently washed with sat. $NaHCO_3$, water, brine, dried over $MgSO_4$, and evaporated to dryness, whereupon purification over silica (1:1 Hexane:EtOAc, R_f = 0.45) to produce the mesylate in quantitative yield. This then, was added to a round bottom flask containing DMF (99 mL). Sodium azide (19.33 g, 297.37 mmol, 3.0 equiv.) was added, followed by heating to 60 ˚C overnight. The reaction was quenched with water (600 mL), and the aqueous phase extracted 4x with Et_2O. The combined organics were washed with brine, dried over Na_2SO_4, evaporated to dryness, and purified over silica (5:1 Hexane:EtOAc, R_f = 0.66) to produce the azide **33** (9.71 g., 98%) as a clear volatile oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.72 (s, 3H), 3.54 (dd, *J* = 7.2, 12.0 Hz, 1H), 3.38 (dd, *J* = 5.6, 12.4 Hz,

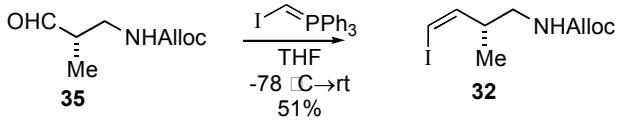
1H), 2.69 (m, 1H), 1.21 (d, J = 7.2 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 174.3, 53.7, 52.0, 39.6, 14.7. MS $C_5H_9N_3O_2$: calcd 143.07, obsd $[M - N_2+H]^+$ = 115.88.



Allyl (*S*)-3-hydroxy-2-methylpropylcarbamate 34: Azide **33** (10.0 g, 69.86 mmol, 1 equiv.) was added to a 0 ˚C solution of $LiAlH_4$ (5.30 g, 139.72 mmol, 2 equiv.) in THF (175 mL). The reaction was warmed and refluxed overnight. Upon cooling, the reaction was then quenched using the Fieser method (for 5.6 g. of $LiAlH_4$, add 5.6 mL water, 5.6 mL of 15% NaOH, and 3 x 5.6 mL of water), followed by addition of excess K_2CO_3, which, after 30 min, was filtered, and the filtrate evaporated to give the pure amino alcohol (5.42 g, 87%). The amino alcohol (1.0 g, 11.218 mmol, 1.0 equiv.) was dissolved in 1:1 sat. $NaHCO_3$:Et_2O (56 mL) at room temperature, and allyl chloroformate (1.5 mL, 14.0 mmol, 1.25 equiv.) added dropwise. After 2 h, organic was separated, and the aqueous phase extracted twice with EtOAc. The combined organics were washed with brine, dried over Na_2SO_4, evaporated to dryness, and purified over silica (2:1 Hexane:EtOAc, R_f = 0.40) to produce allyl carbamate **34** (1.94 g., 87% over 2 steps) as a clear oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.91 (m, 1H) 5.27 (dd, J = 17.2, 10.8 Hz, 2H), 5.12 (s, 1H), 4.57 (d, J = 6.0 Hz, 2H), 3.22 (d, J = 6.8 Hz, 2H), 3.03 (d, J = 7.2 Hz, 2H), 0.86 (s, 6H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 157.8, 132.6, 117.9, 68.2, 65.9, 47.6, 36.8, 22.4. HRMS $C_8H_{15}NO_3$: calcd 173.1046, obsd [M] = 173.1044.

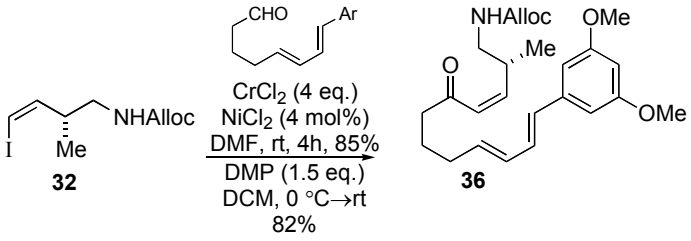


Allyl (*S*)-2-formylpropylcarbamate 35: Alcohol **34** (1.35 g, 7.8 mmol, 1 equiv.) in DCM (7.8 mL) at 0 ˚C was treated to oxidation by DMP (4.962 g, 11.70 mmol, 1.5 equiv.). The reaction was allowed to warm to room temperature, and after 3 h, was quenched by the addition of water. Separation was followed by extraction of the aqueous phase 3x with EtOAc. The combined organics were washed with brine, dried over Na_2SO_4, evaporated to dryness, and purified over silica (2:1 Hexane:EtOAc, $R_f = 0.25$) to produce aldehyde **35** (1.321 g., 99%) as a clear oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.66 (s, 1H), 5.88 (m, 1H), 5.24 (dd, J = 17.2, 10.4 Hz, 2H), 5.13 (s, 1H), 4.53 (d, J = 5.2 Hz, 2H), 3.37 (m, 2H), 2.65 (m, 1H), 1.15 (d, J = 7.2 Hz, 3H) ^{13}C-NMR (100 MHz, $CDCl_3$) δ 203.8, 156.3, 132.7, 117.7, 65.6, 47.0, 40.9, 11.2. MS $C_8H_{13}NO_3$: HRMS calcd 194.0788, obsd $[M + Na]^+$ = 194.0787.



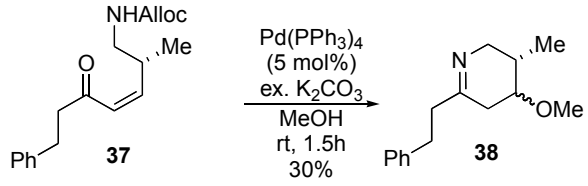
Allyl (*R*,*Z*)-4-iodo-2-methylbut-3-enylcarbamate 32: NaHMDS (1.0M, 6.5 mL, 1.1 equiv.) was added to a room temperature solution of iodomethyltrimethylphosphonium iodide (3.096 g, 5.84 mmol, 1.0 equiv.) in THF (30 mL) and stirred for 1 h. Upon cooling to –78 ˚C, aldehyde **35** (1.0 g, 5.84 mmol, 1.0 equiv.) in THF (1 mL) was added and allowed to warm to room temperature. The reaction was quenched with sat. NH_4Cl, diluted with EtOAc, separated, and the aqueous

phase extracted twice with EtOAc. The combined organics were washed with brine, dried over Na_2SO_4, evaporated to dryness, and purified over silica (5:1 Hexane:EtOAc, R_f = 0.50) to produce *cis*-vinyl iodide **32** (0.929 g., 54%) as a clear oil. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 6.26 (d, *J* = 17.5 Hz, 1H), 5.95 (t, *J* = 8.0 Hz, 1H), 5.89 (m, 1H), 5.28 (d, *J* = 17.0 Hz, 1H), 5.18 (d, *J* = 10.5 Hz, 1H), 4.75 (bs, 1H), 4.53 (s, 2H), 3.23 (dt, 6.0, 13.5 Hz, 1H), 3.09 (dt, 5.5 Hz, 1H), 2.72 (m, 1H), 1.01 (d, *J* = 7.0 Hz, 3H). MS $C_9H_{14}INO_2$: calcd 295.01, obsd $[M + H]^+$ = 295.87.



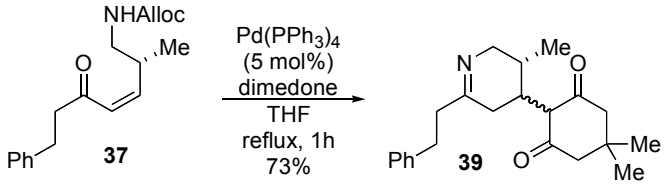
***cis*-Enone 36**: A round bottom flask was charged with aldehyde **6** (165 mg., 0.63 mmol, 1.0 equiv.), and inside a glove box $CrCl_2$ (300 mg, 2.52 mmol, 4 equiv.) and $NiCl_2$ (4 mg, 0.025 mmol, 0.04 equiv.) was added. Taken out of the glove box, DMF (4.5 mL) and *cis*-vinyl iodide **32** (215 mg., 0.693 mmol, 1.1 equiv.) was added at room temperature. Immediate exothermic behavior was observed, and after 4 hours, the reaction was quenched with sat. sodium serinate and stirred for 30 min. The solution was diluted with water and EtOAc, separated, and the aqueous extracted 4x with EtOAc. The combined organics were washed with brine, dried over Na_2SO_4, evaporated to dryness. This crude material then was oxidized by submitting it to a 0 ˚C solution of DMP (340 mg., 0.80 mmol, 1.5 equiv.) in DCM (5.5 mL). After warming to room temperature and stirring for 3h, the reaction was quenched with water, diluted with EtOAc, separated, and

the aqueous phase extracted 3x with EtOAc. The combined organics were washed with brine, dried over Na_2SO_4, evaporated to dryness, and purified over silica (3:1 Hexane:EtOAc, $R_f = 0.33$) to produce *cis*-enone **36** (187 mg., 70% over 2 steps) as a clear oil. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 6.69 (dd, J = 10.5, 15.0 Hz, 1H), 6.51 (s, 2H), 6.36 (d, J = 15.5 Hz, 1H), 6.32 (s, 1H), 6.18 (d, J = 11.5 Hz, 2H), 5.88 (m, 1H), 5.78 (m, 1H), 5.29 (bs, 1H), 5.25 (d, J = 17.5 Hz, 1H), 5.16 (d, J = 11.0 Hz, 1H), 4.51 (d, J = 5.0 Hz, 2H), 3.77 (s, 6H), 3.46 (m, 1H), 3.16 (m, 2H), 2.48 (t, J = 6.5 Hz, 2H), 2.15 (q, J = 7.0, Hz, 2H), 1.72 (q, J = 7.0 Hz, 2H), 0.99 (d, J = 6.5 Hz, 3H). Alcohol = MS $C_{25}H_{33}NO_5$: calcd 427.24, obsd $[M + H]^+$ = 428.05.



(*S*)-2,3,4,5-Tetrahydro-4-methoxy-3-methyl-6-phenethylpyridine 38: The alloc-protected model *cis*-enone **37** (10 mg., 0.030 mmol, 1.0 equiv.) was dissolved in MeOH (0.6 mL) at room temperature, whereupon $Pd(PPh_3)_4$ (1.73 mg., 0.0015 mmol, 0.05 equiv.) and excess K_2CO_3 (20 mg., 0.15 mmol, 5.0 equiv.) was added. After stirring for 1.5h, the reaction was filtered over celite, concentrated, and diluted with EtOAc and water. After separation, the aqueous phase was extracted 2x with EtOAc, the combined organics washed with brine, dried over Na_2SO_4, and evaporated to give the crude cyclic imine methanol-adduct **37** (1.8 mg., 30% yield) as a clear oil. ***Cis*-37**: ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.25 (m, 3H), 7.16 (m, 2H), 6.17 (d, J = 11.0 Hz, 1H), 5.90 (m, 1H), 5.80 (t, J = 11.0 Hz, 1H), 5.25 (d, J = 16.0 Hz, 1H), 5.16 (d, J = 11.0 Hz, 1H),

4.52 (d, J = 4.5 Hz, 2H), 3.44 (m, 1H), 3.13 (m, 2H), 2.91 (t, J = 8.0 Hz, 2H), 2.79 (q, J = 6.5 Hz, 2H), 0.99 (d, J = 6.5 Hz, 3H). **38**: ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.26 (t, J = 7.0 Hz, 2H), 7.17 (m, 3H), 3.78 (dd, J = 4.5, 17.0 Hz, 1H), 3.50 (m, 1H), 3.24 (s, 3H), 3.10 (m, 2H), 2.85 (t, J = 7.5 Hz, 2H), 2.52 (dd, J = 4.5, 17.5 Hz, 1H), 2.46 (t, J = 8.5 Hz, 1H), 2.23 (d, J = 5.5 Hz, 1H), 2.00 (dd, J = 8.0, 14.8 Hz, 1H), 1.66 (m, 1H), 0.96 (d, J = 6.5 Hz, 3H). MS $C_{15}H_{21}NO$: calcd 231.16, obsd $[M + H]^+$ = 232.17.



2-((*R*)-2,3,4,5-Tetrahydro-3-methyl-6-phenethylpyridin-4-yl)-5,5-dimethylcyclohexane-1,3-dione 39: The alloc-protected model *cis*-enone (10 mg., 0.030 mmol, 1.0 equiv.) was dissolved in THF (0.3 mL) at room temperature, whereupon $Pd(PPh_3)_4$ (1.73 mg., 0.0015 mmol, 0.05 equiv.) and dimedone (12.6 mg., 0.90 mmol, 3.0 equiv.) was added. After refluxing for 1 h, the reaction was diluted with EtOAc and water. After separation, the aqueous phase was extracted 2x with EtOAc, the combined organics washed with brine, dried over Na_2SO_4, and evaporated to give the crude cyclic imine dimedone-adduct **39** (4 mg., 73% yield) as a clear oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.25 (m, 3H), 7.17 (m, 2H), 2.96 (dd, J = 4.4, 11.6 Hz, 1H), 2.84 (s, 1H), 2.72 (m, 2H), 2.50 (d, J = 11.2 Hz, 1H), 2.29 (s, 3H), 2.20 (s, 3H), 2.17 (dd, J = 2.8, 12.8 Hz, 1H), 1.97 (t, J = 8.8 Hz, 1H), 1.39 (dd, J = 3.2, 12.4 Hz, 1H), 1.19 (d, J = 7.2 Hz, 2H), 1.06 (d, J = 3.6 Hz, 3H). MS $C_{22}H_{29}NO_2$: calcd 339.22, obsd $[M + H]^+$ = 340.19.

H. References and Notes

[1] (a) Omura, K.; Swern, D. *Tetrahedron* **1978***, 34*, 1651. (b) Mancuso, A. J.; Brownfain, D. S.; Swern, D. *J. Org. Chem.* **1979**, *44*, 4148–4150.

[2] Corey, E.J.; Fuchs, P.L. *Tetrahedron Lett.* **1972**, 3769-3772.

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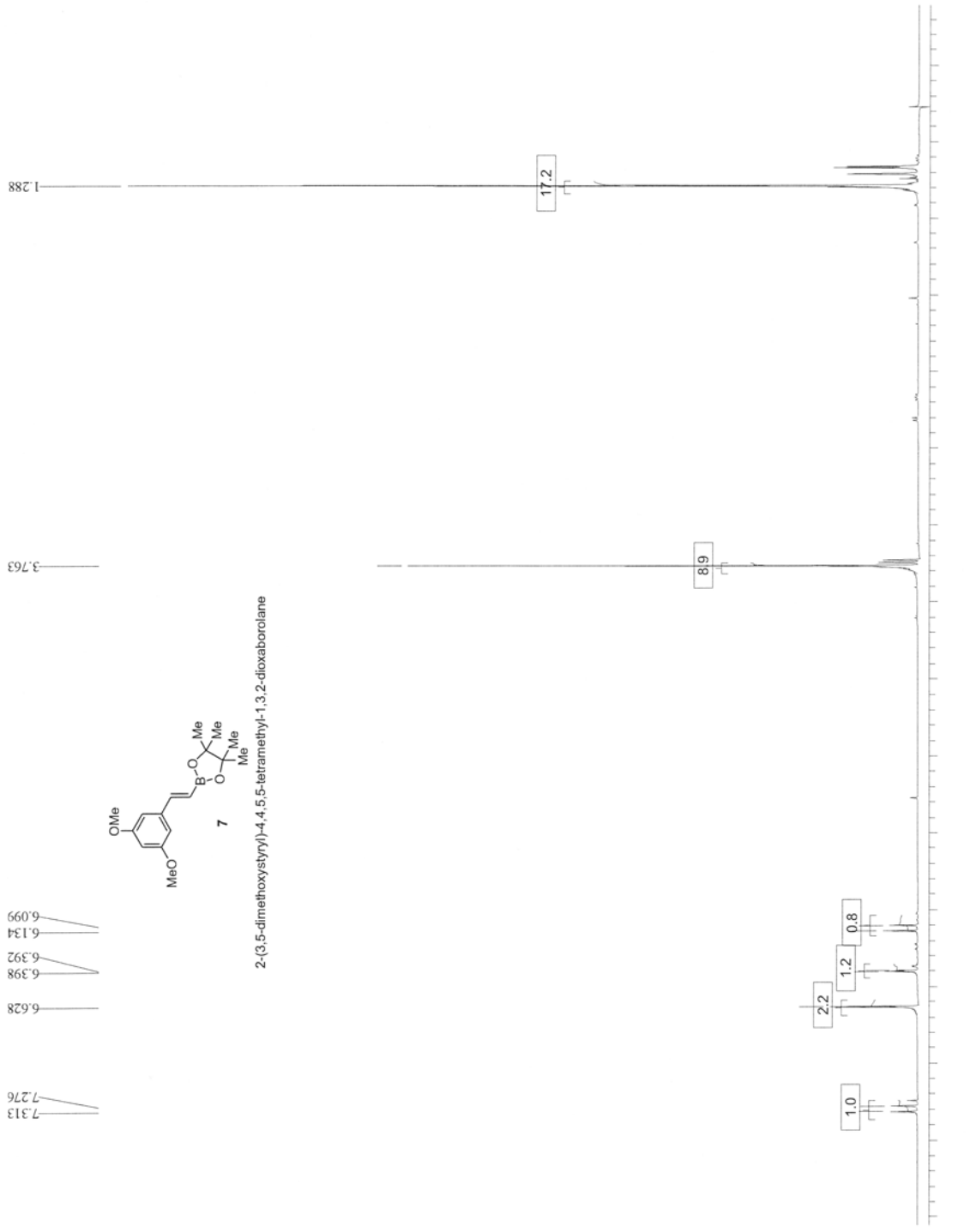
[4] Still, W.C.; Gennari, C., *Tetrahedron Lett.* **1983**, *24*, 4405

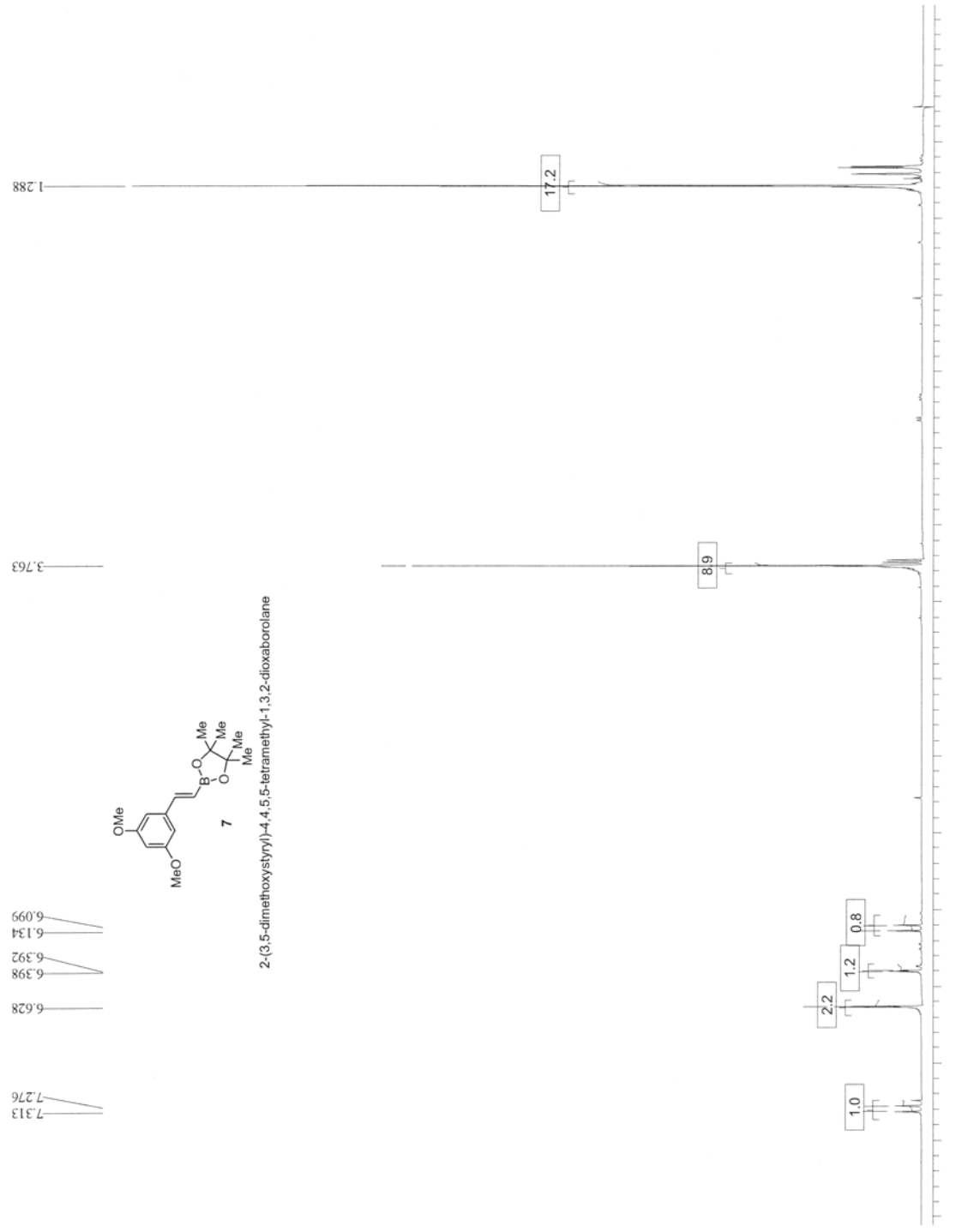
[5] (a) Okude, Y.; Hirano, S.; Hiyama, T.; Nozaki, H. J. Am. Chem. Soc. **1977**, *9*, 3179-3181. (b) Taki, K.; Kimura, K.; Kuroda, T.; Hiyama, T.; Nozaki, H. *Tetrahedron Lett.* **1983**, *47*, 5281-5284. (c) Jin, H.; Uenishi, J.; Christ, W. J.; Kishi, Y. *J. Am. Chem. Soc.* **1986**, *108*, 5644-6646.

Chapter 2

Selected Spectra



Spectrum 1. ^{1}H NMR spectrum of compound **7** in $CDCl_3$



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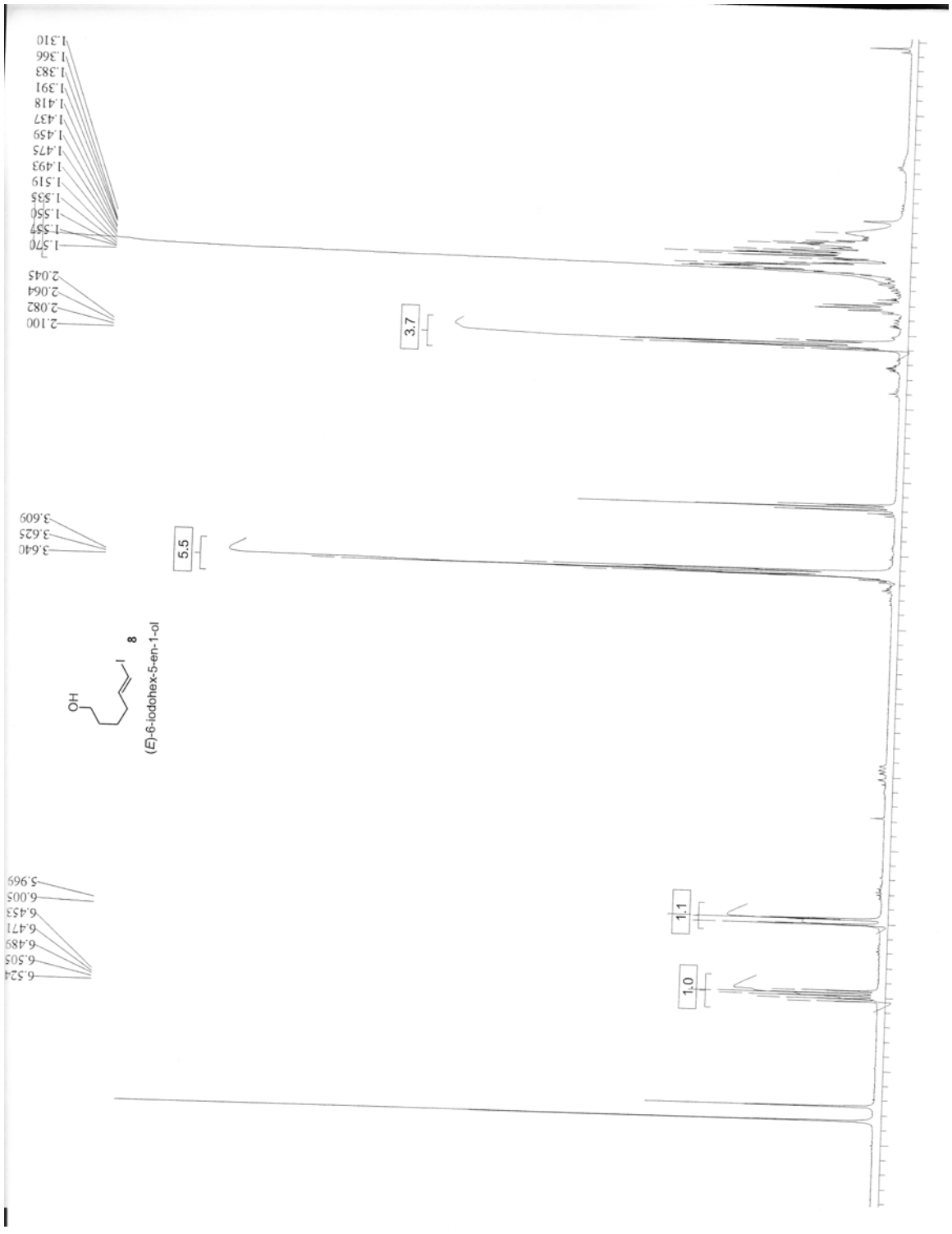

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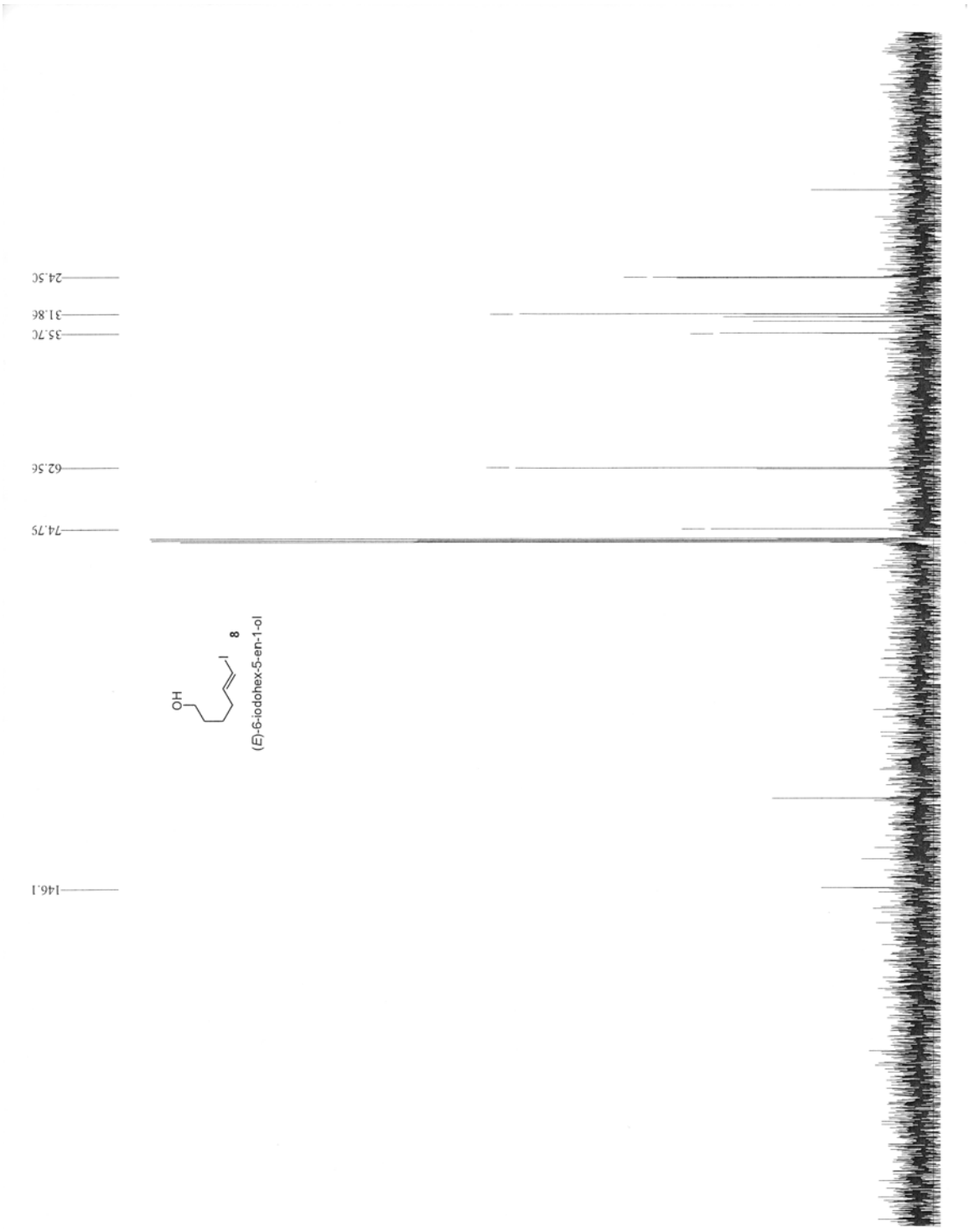

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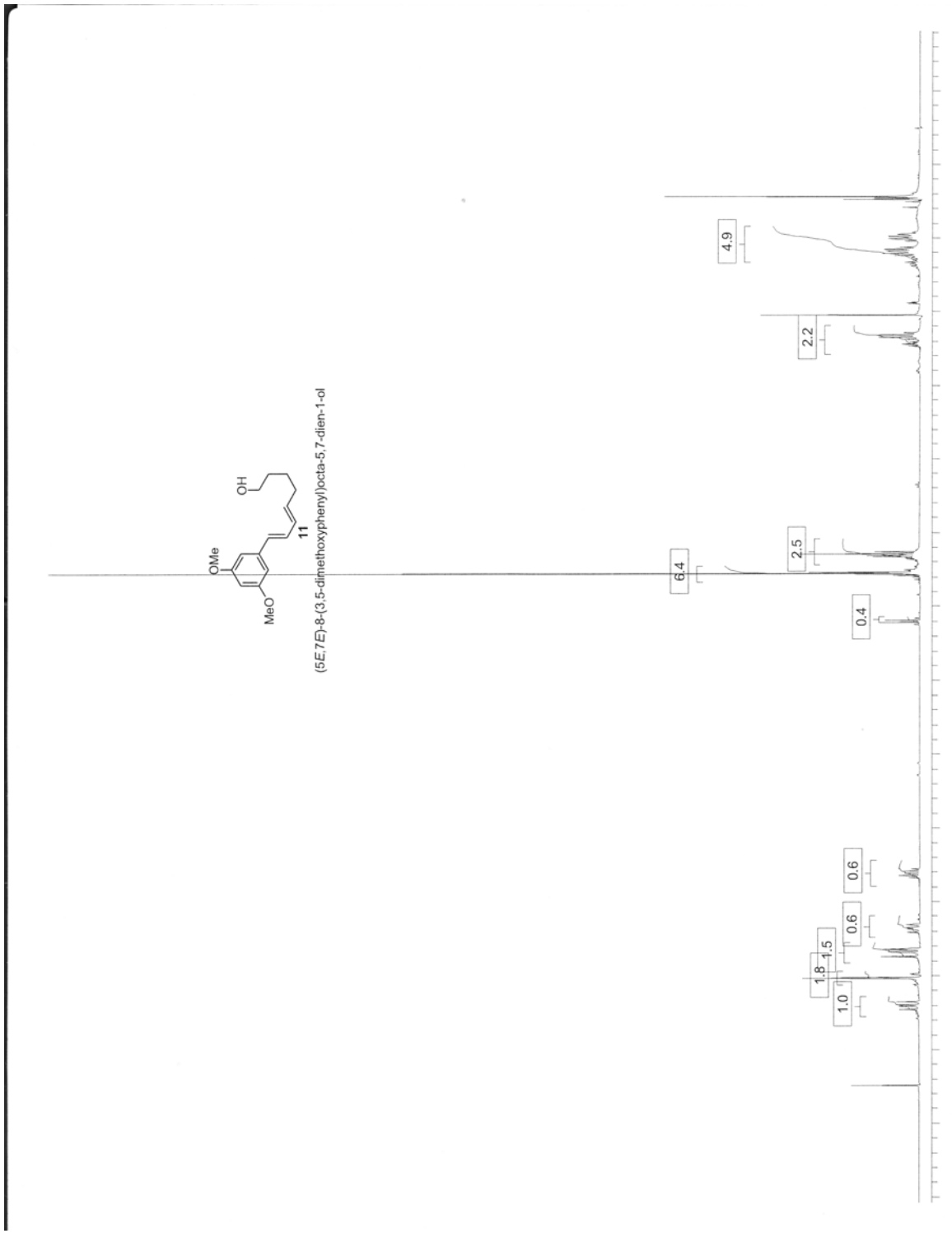

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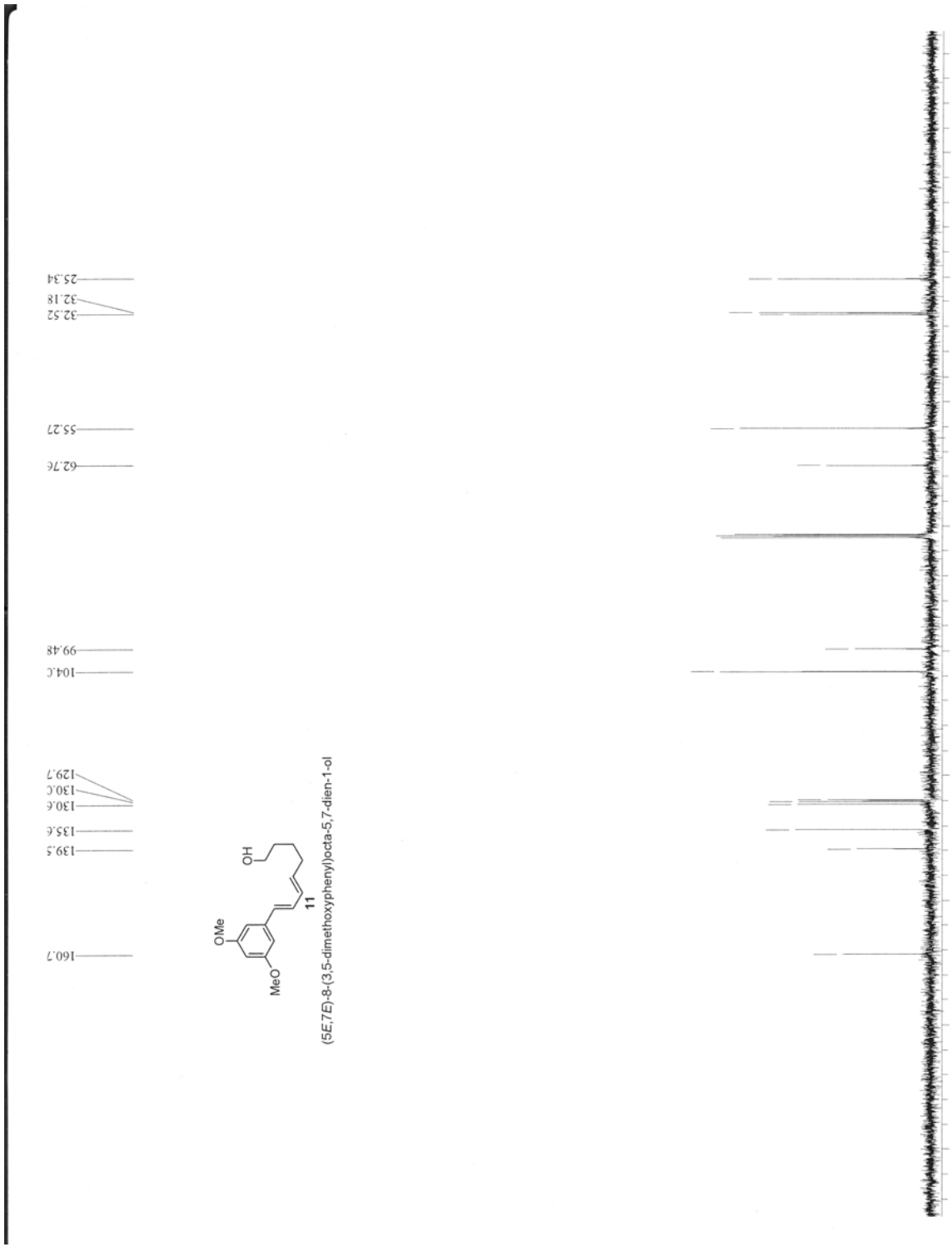

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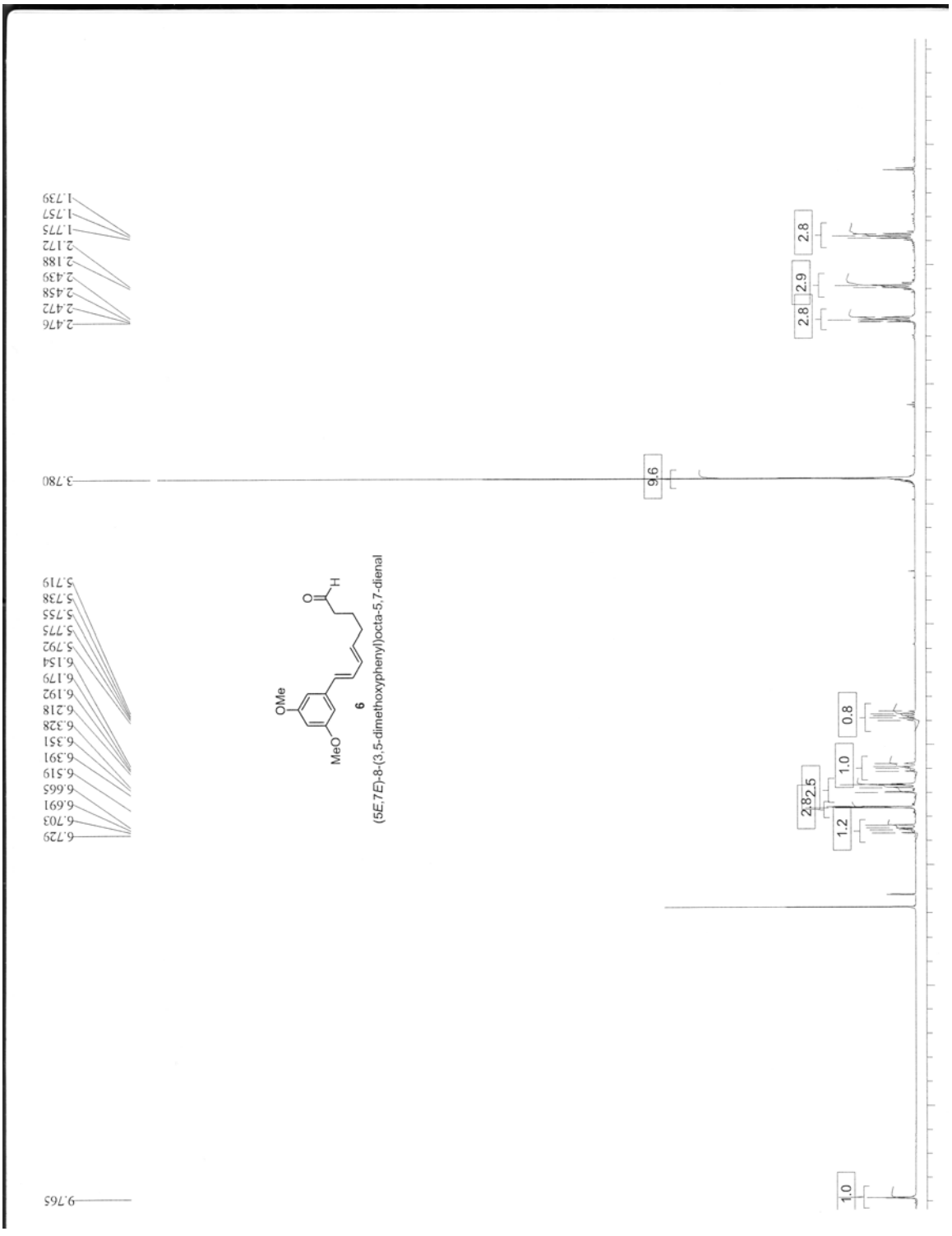
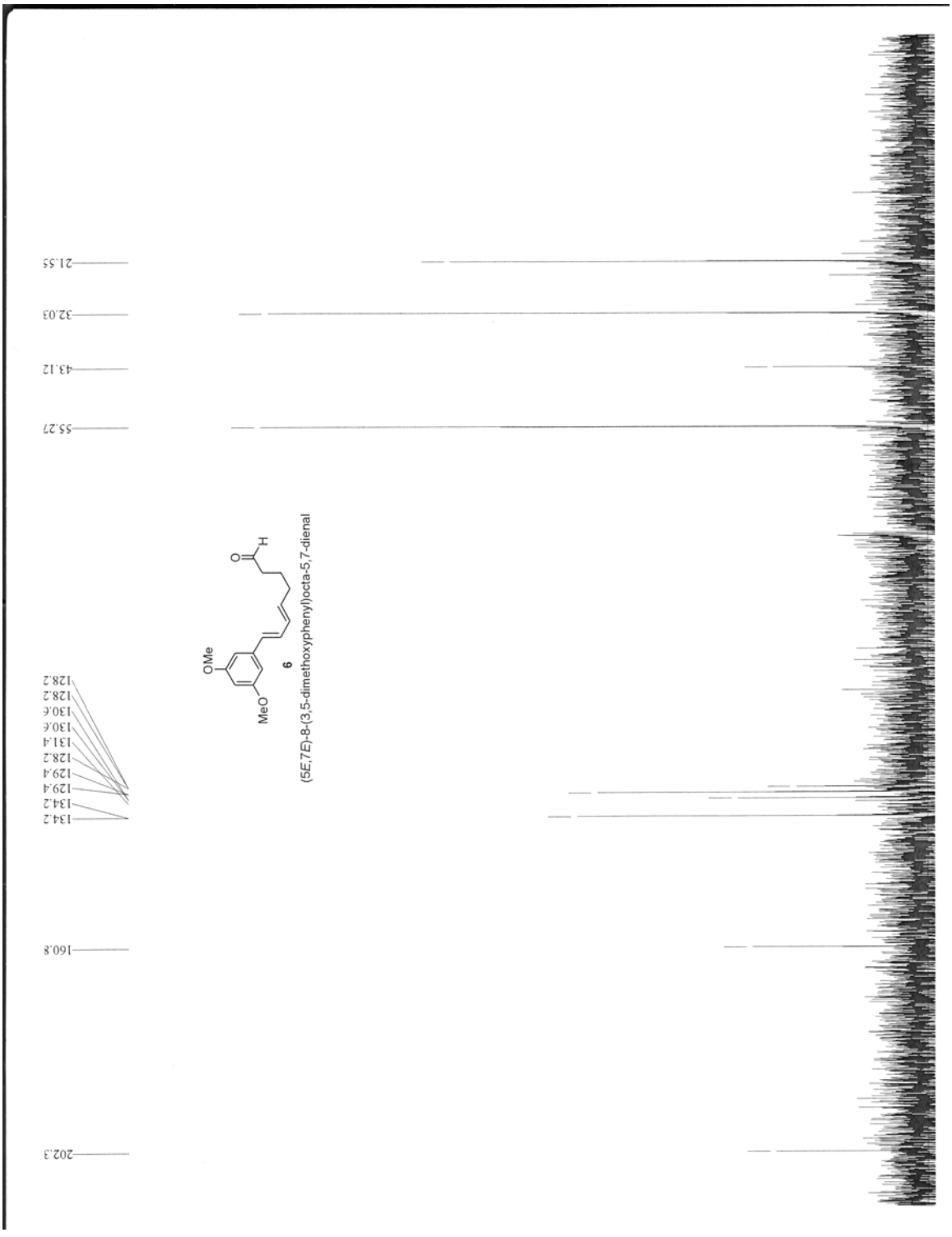


Spectrum 7. ^{1}H NMR spectrum of compound **6** in $CDCl_3$



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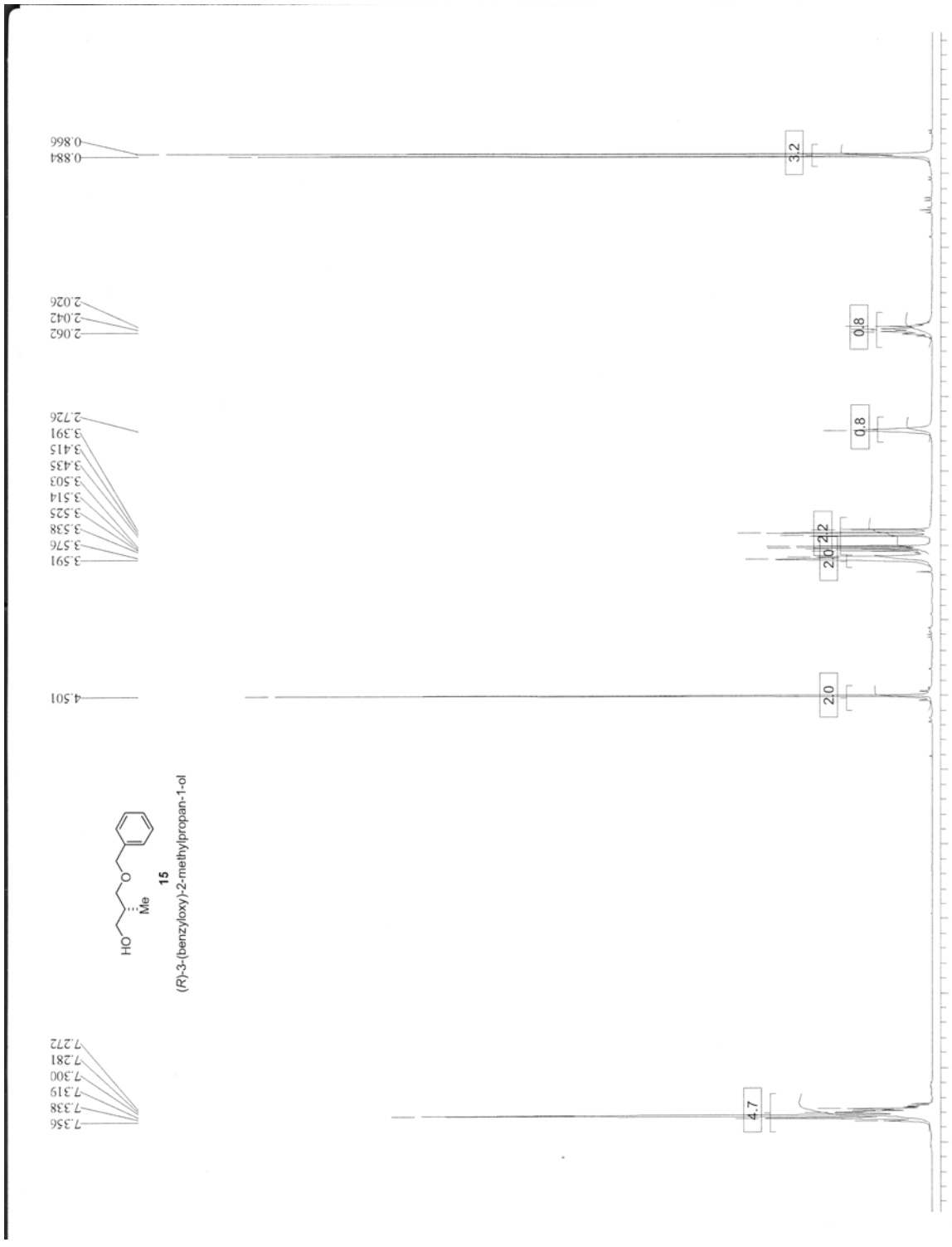

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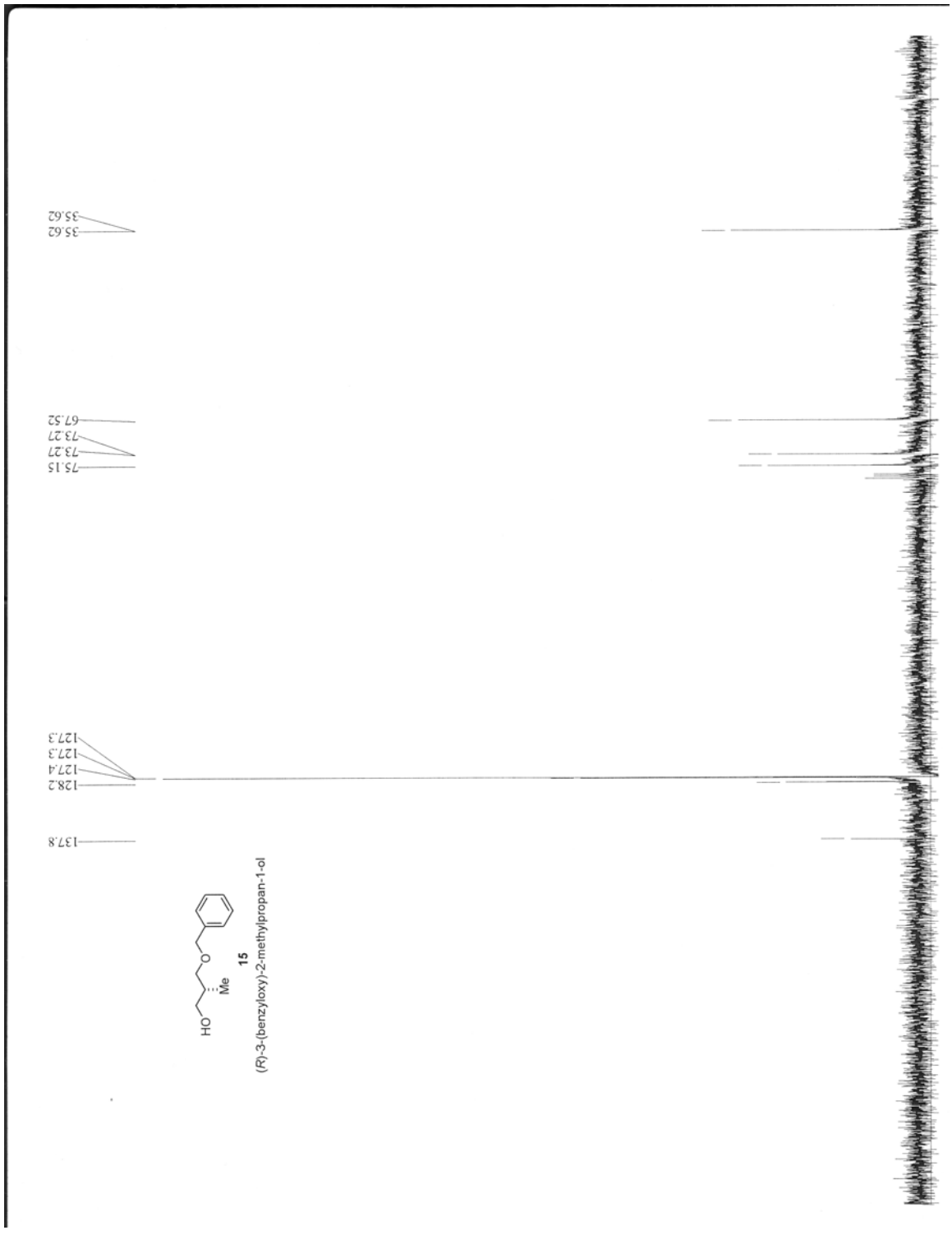

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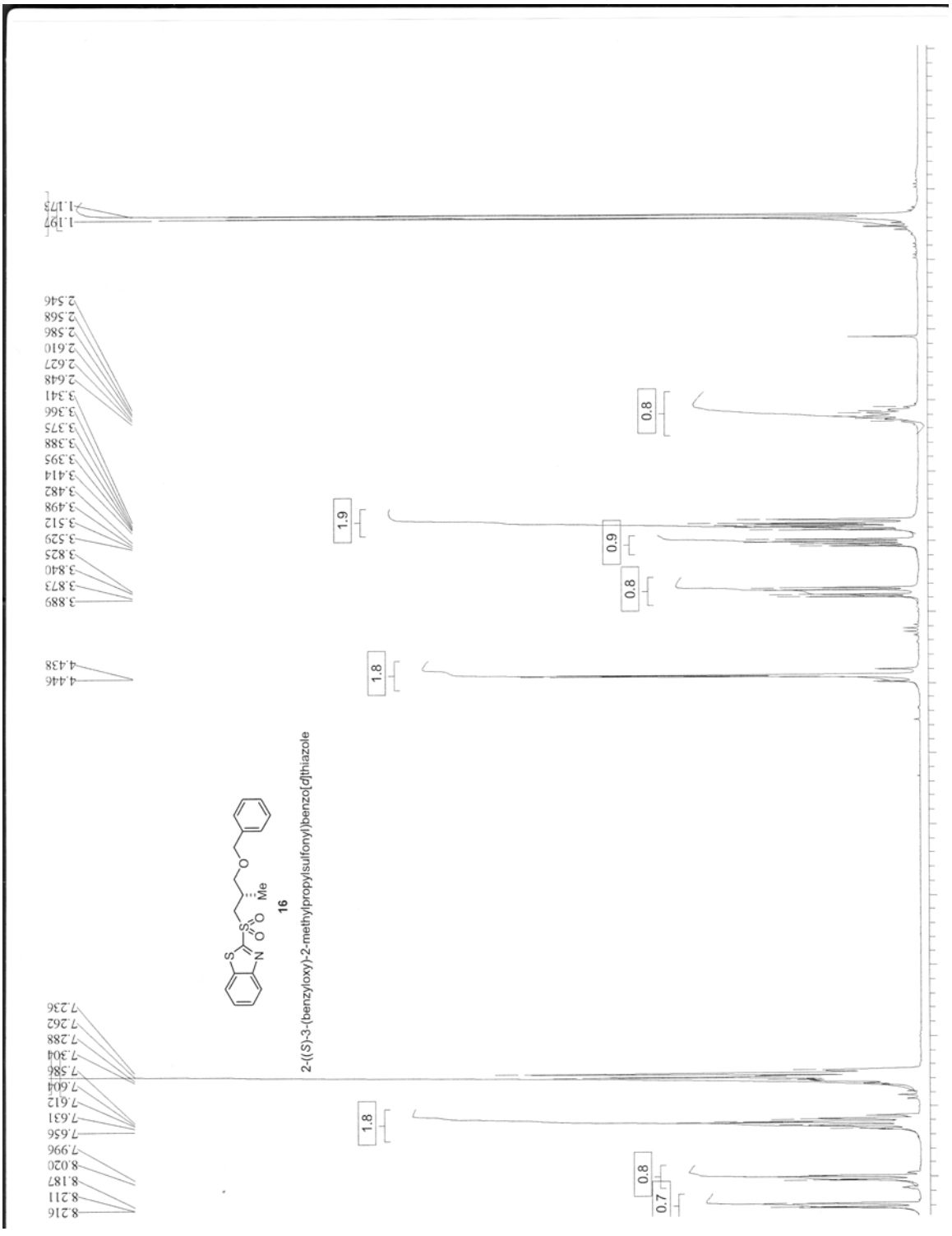

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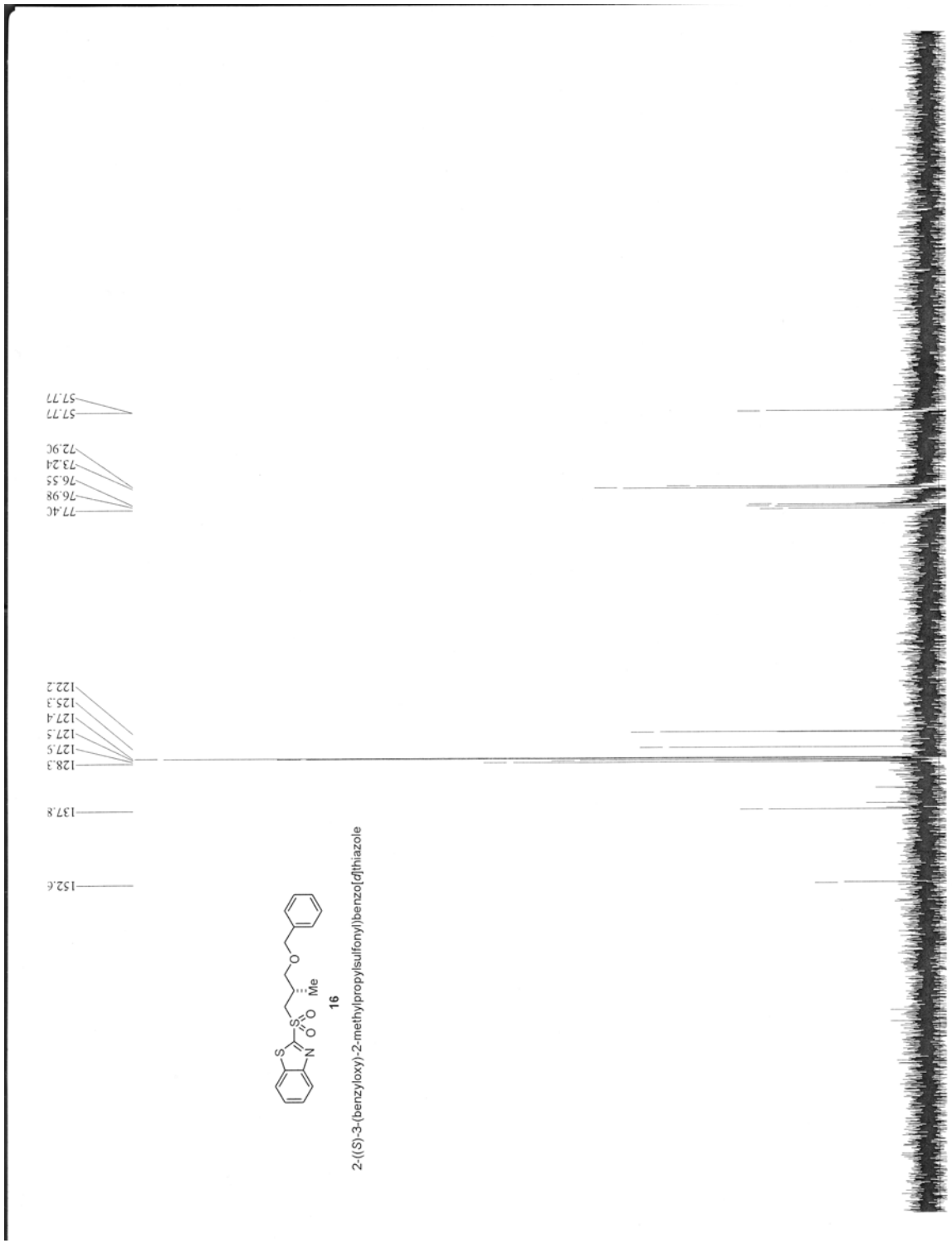

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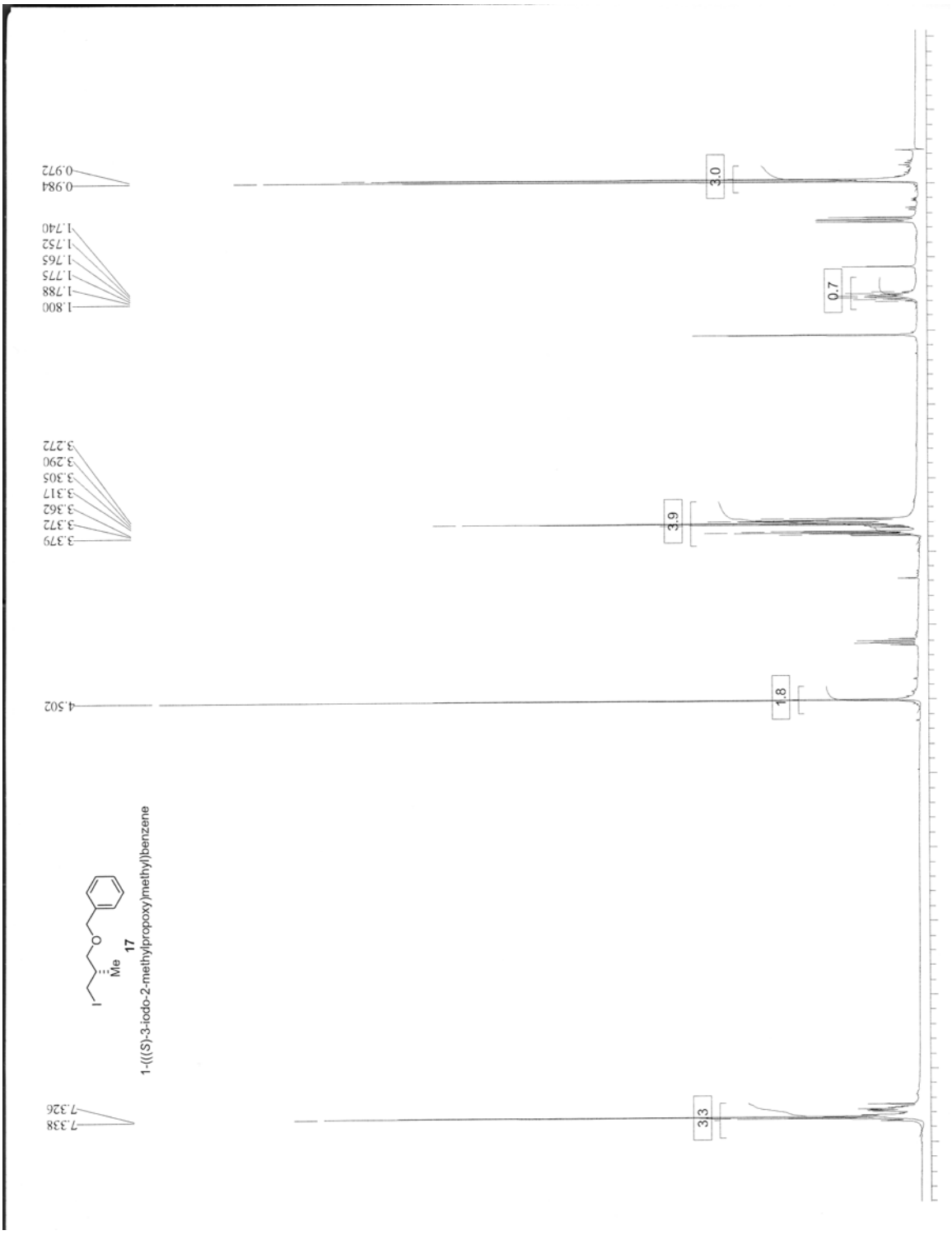

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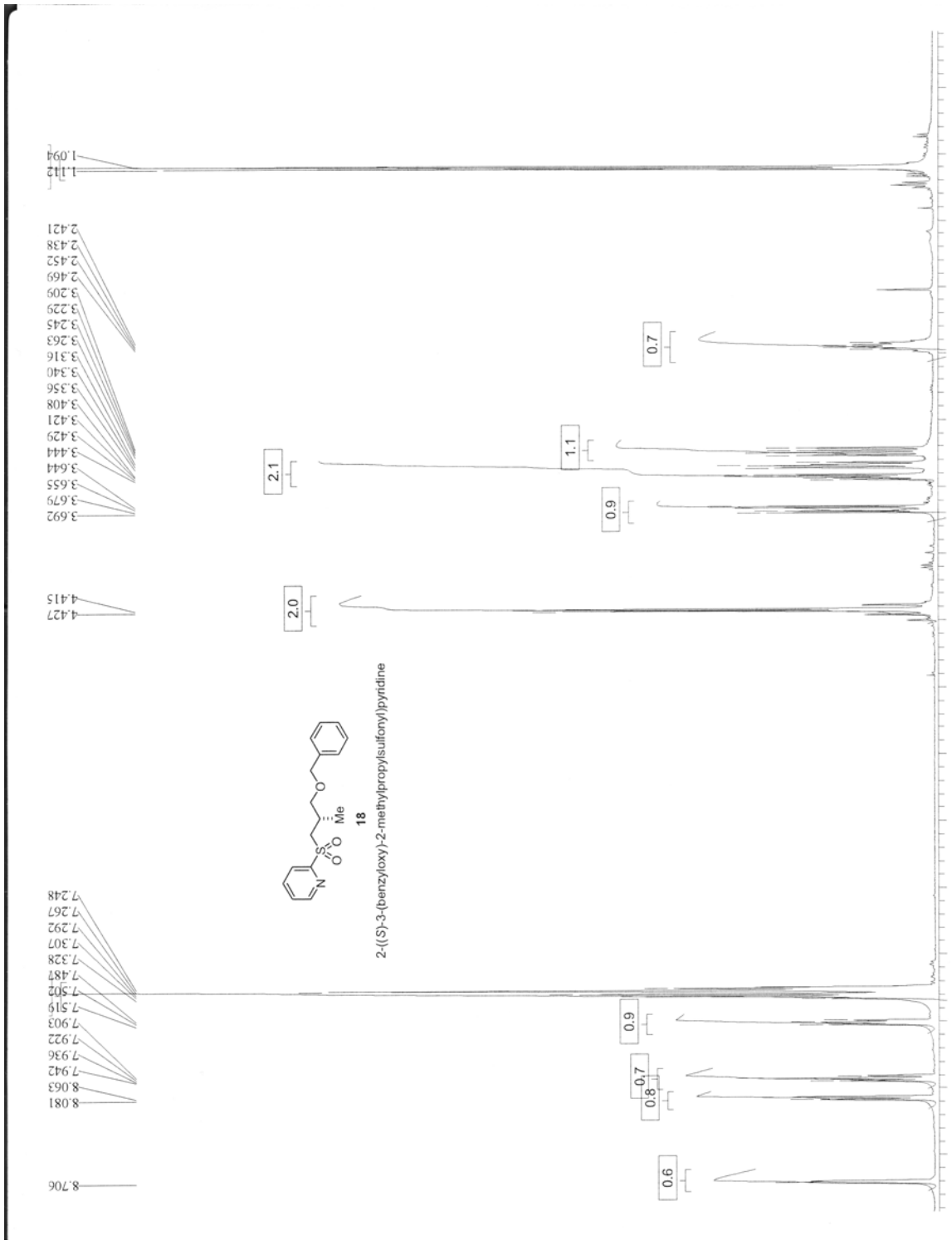

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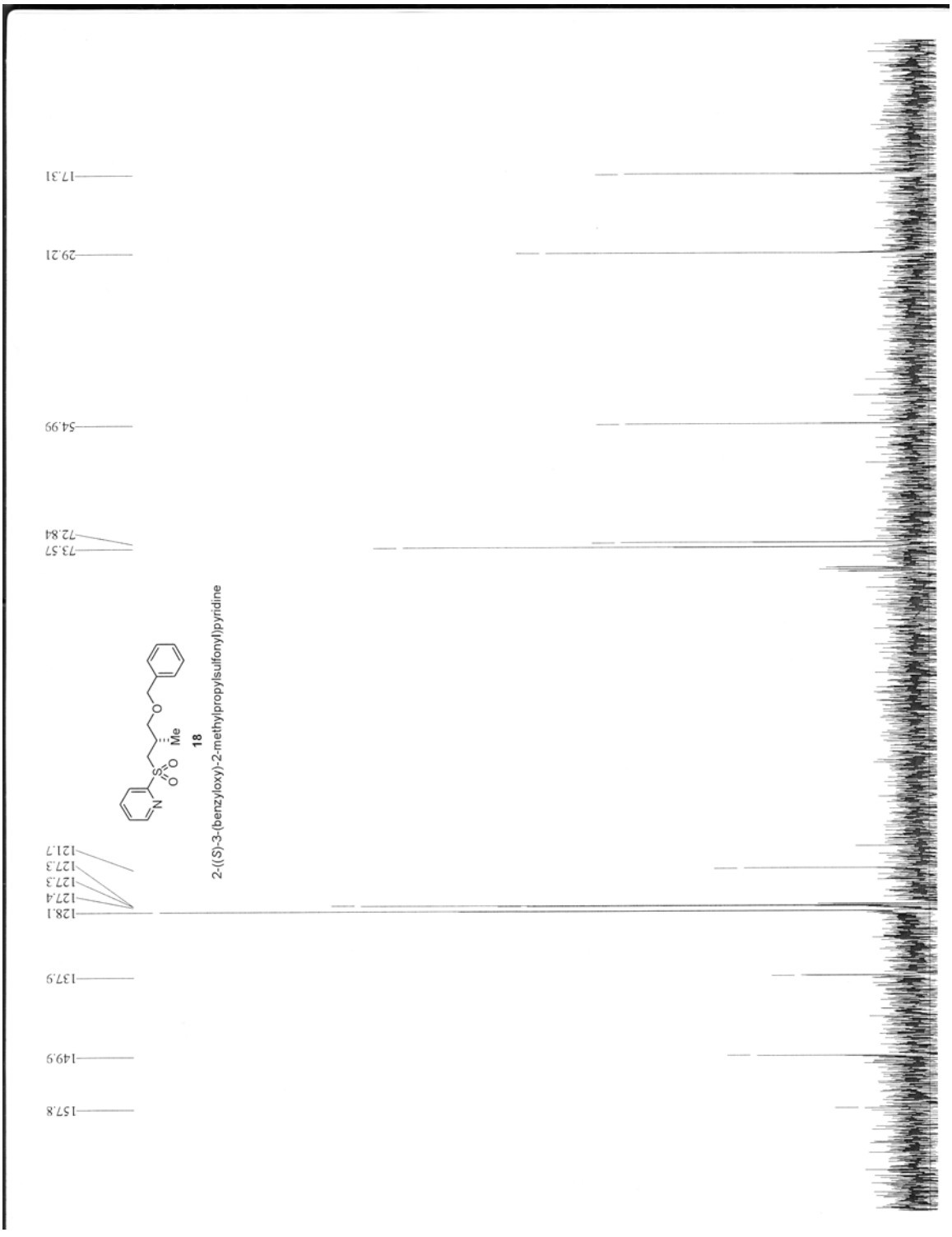

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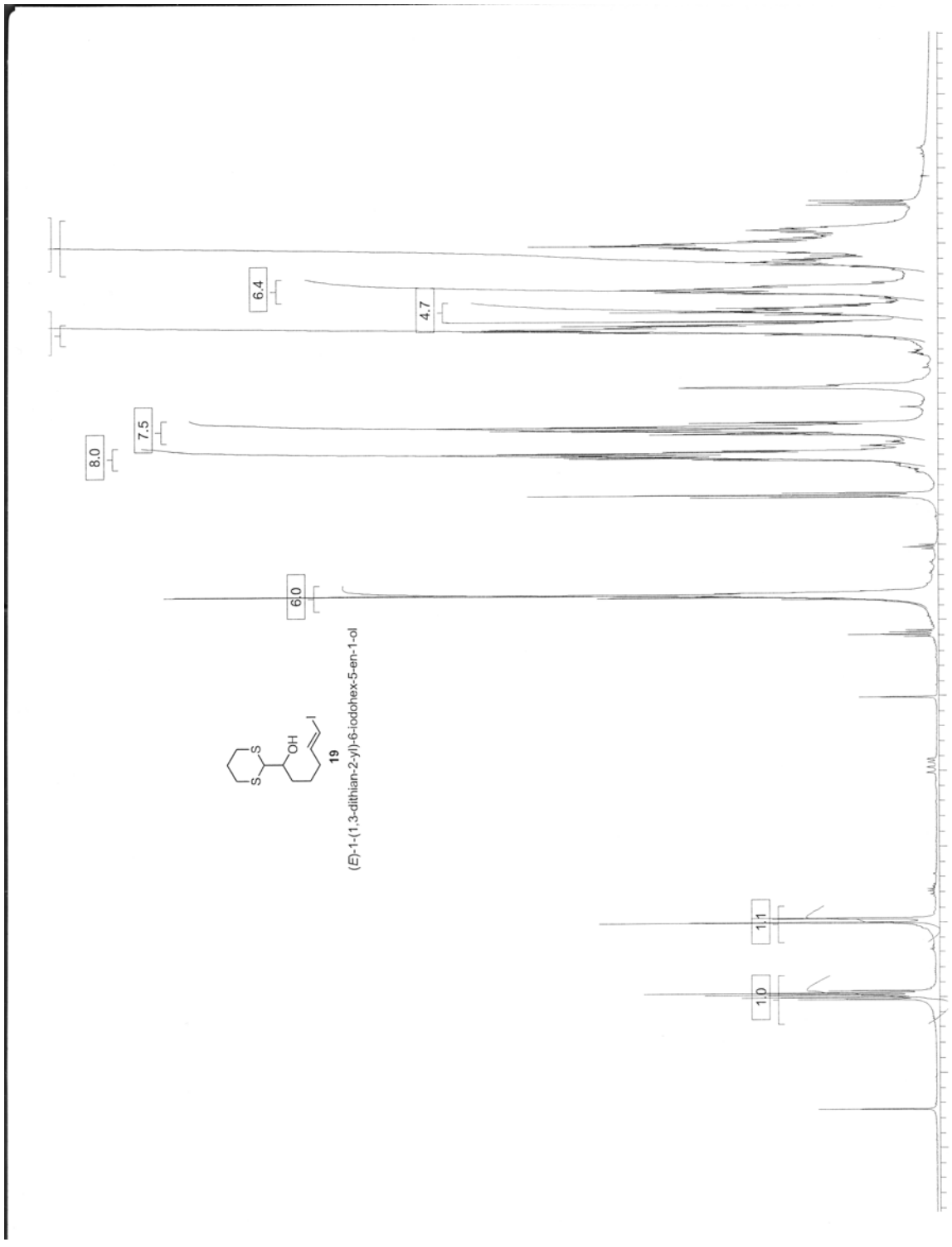

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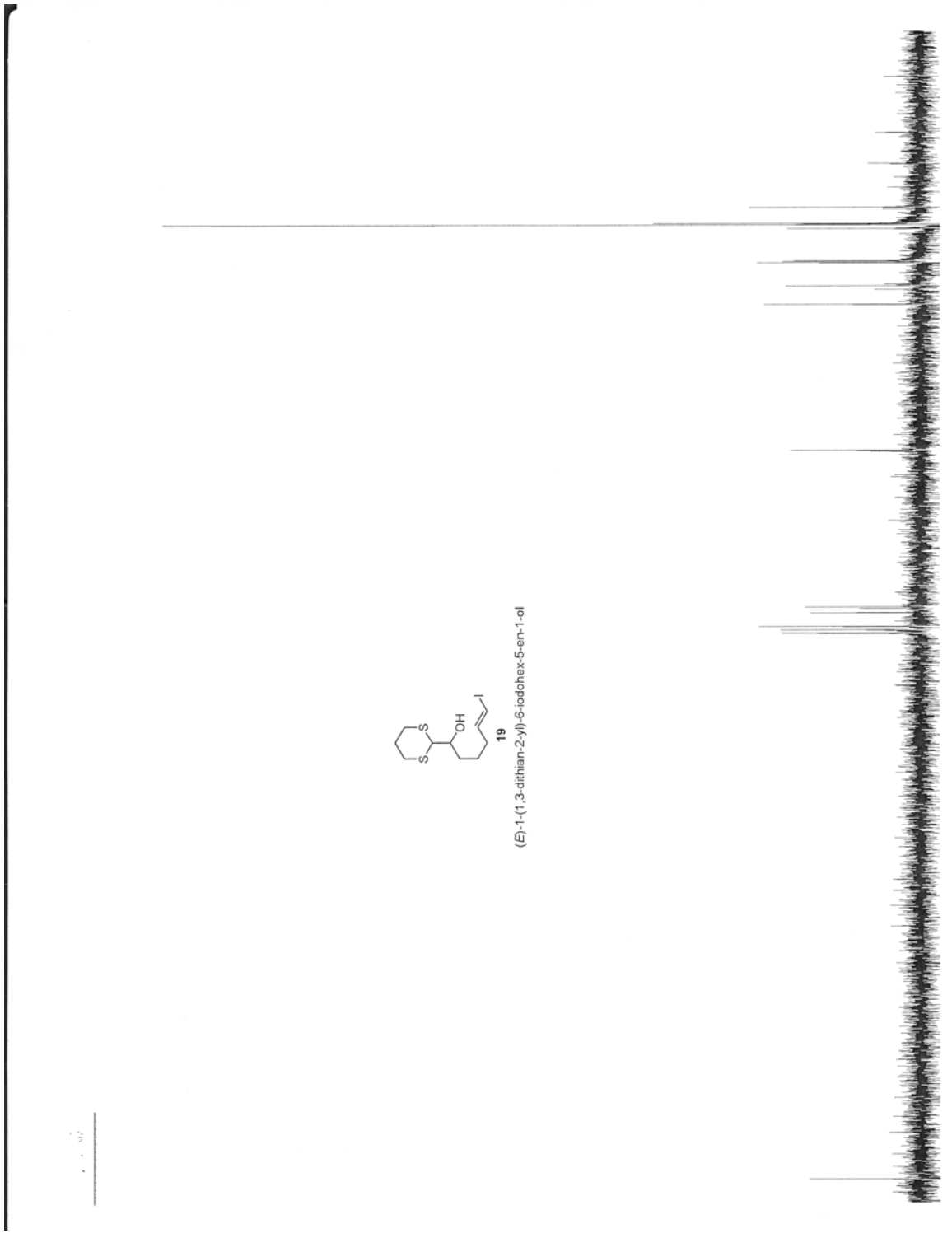

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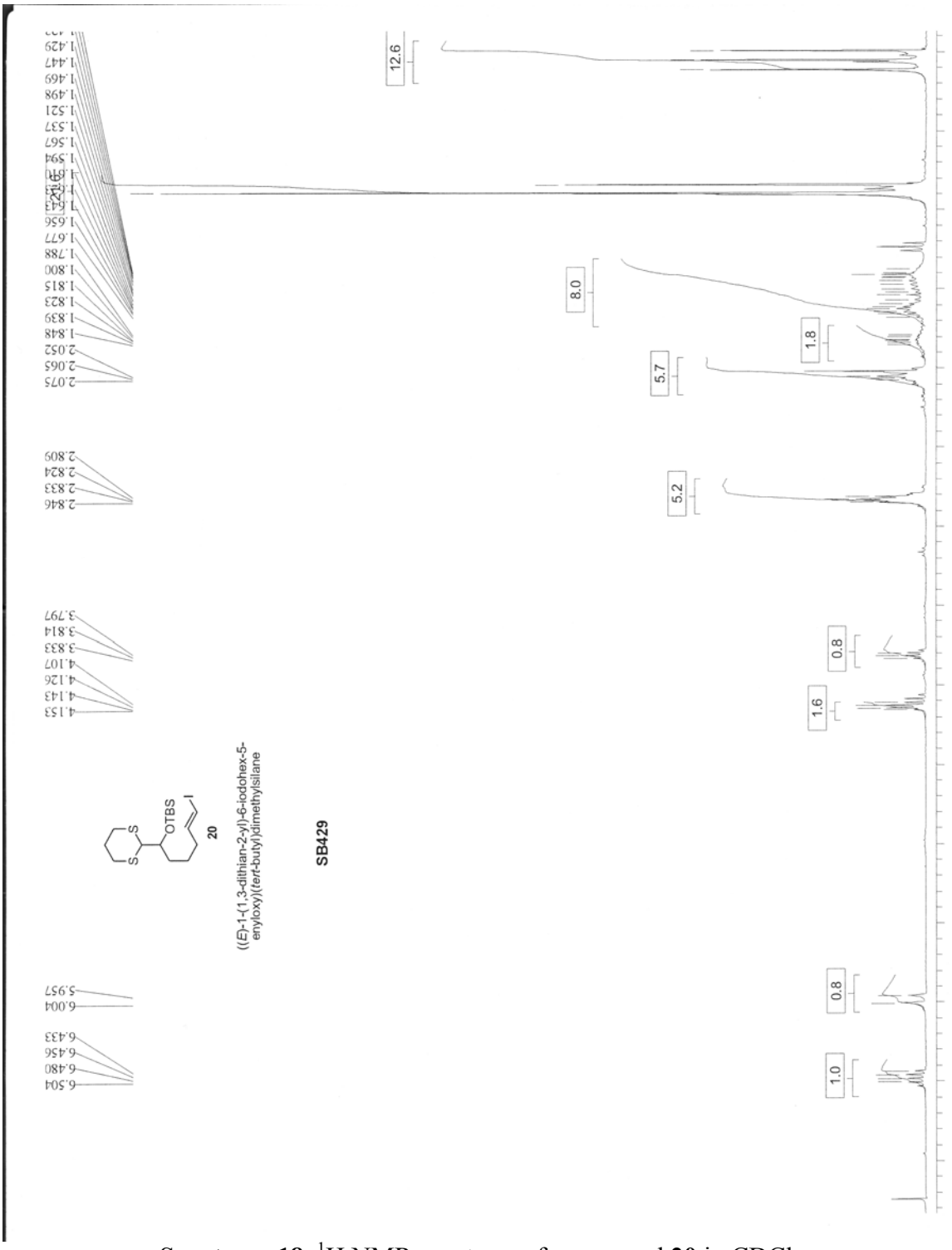

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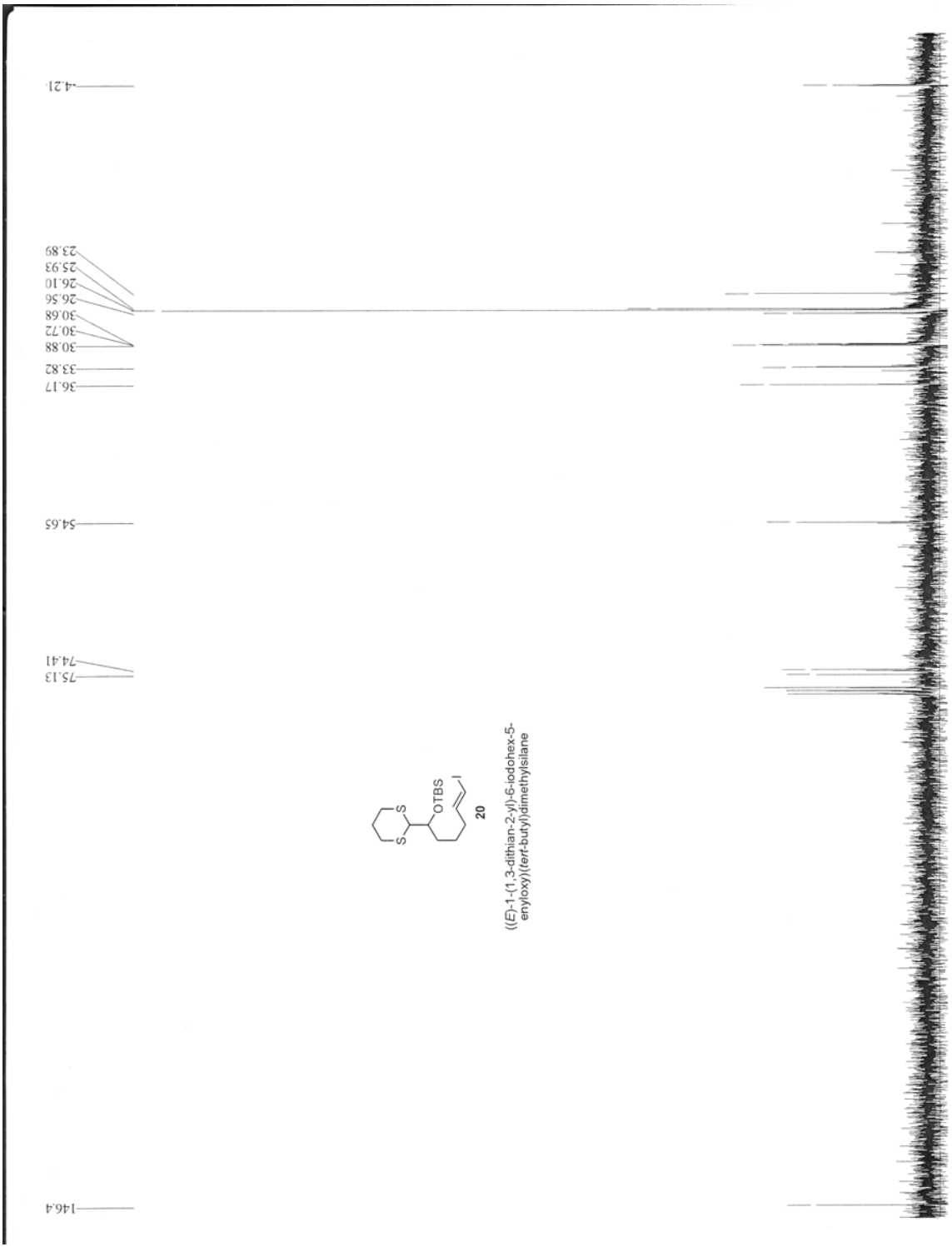

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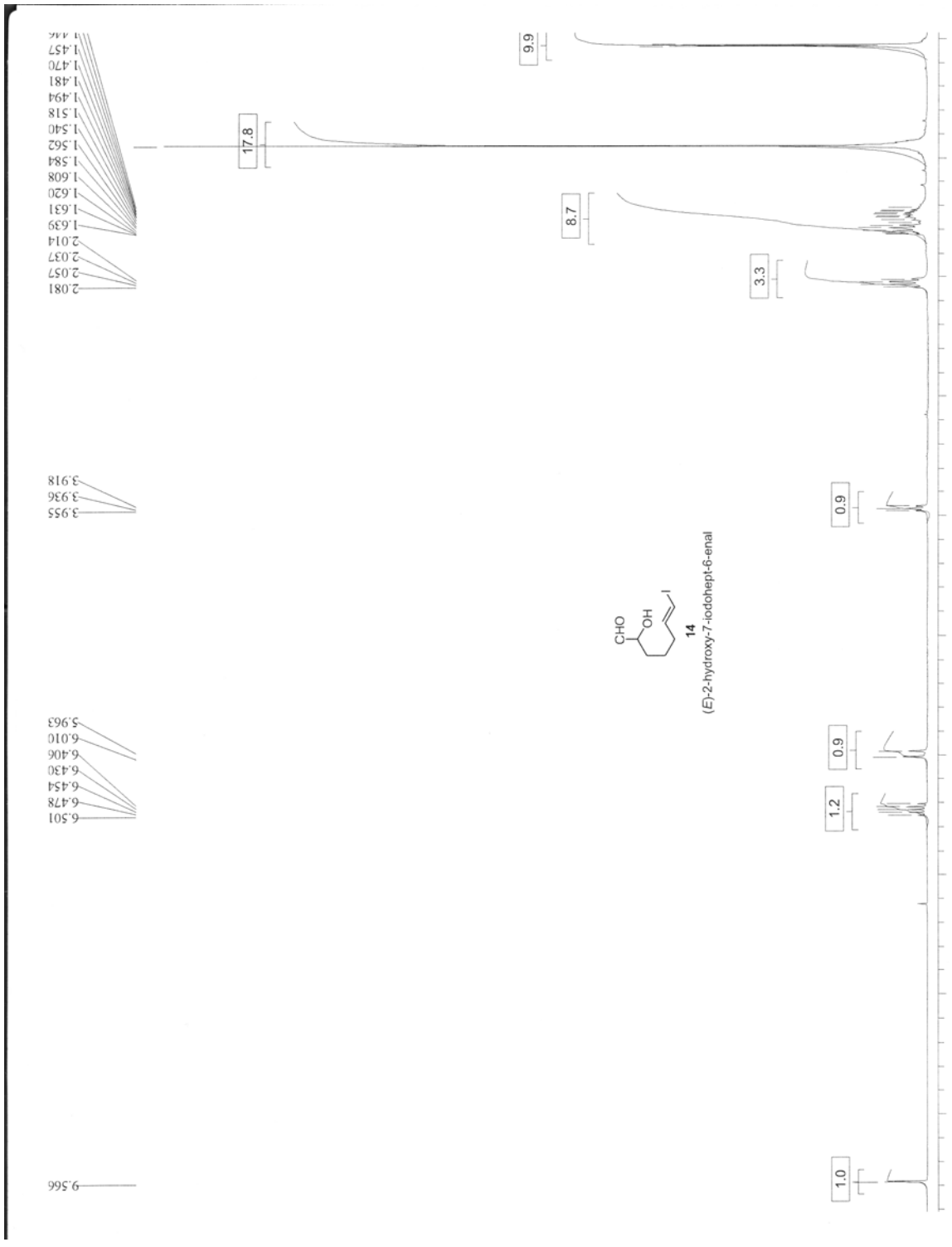

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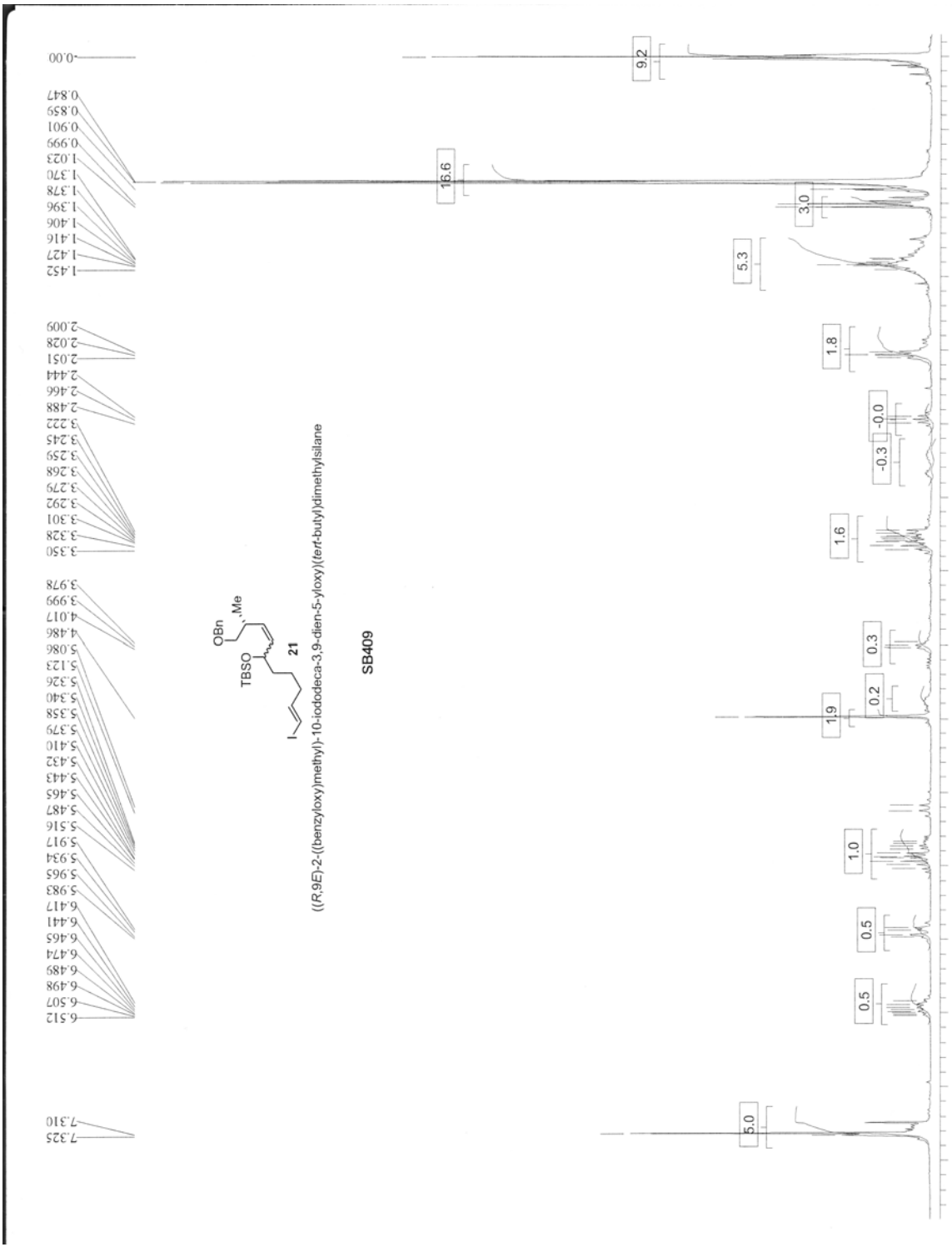
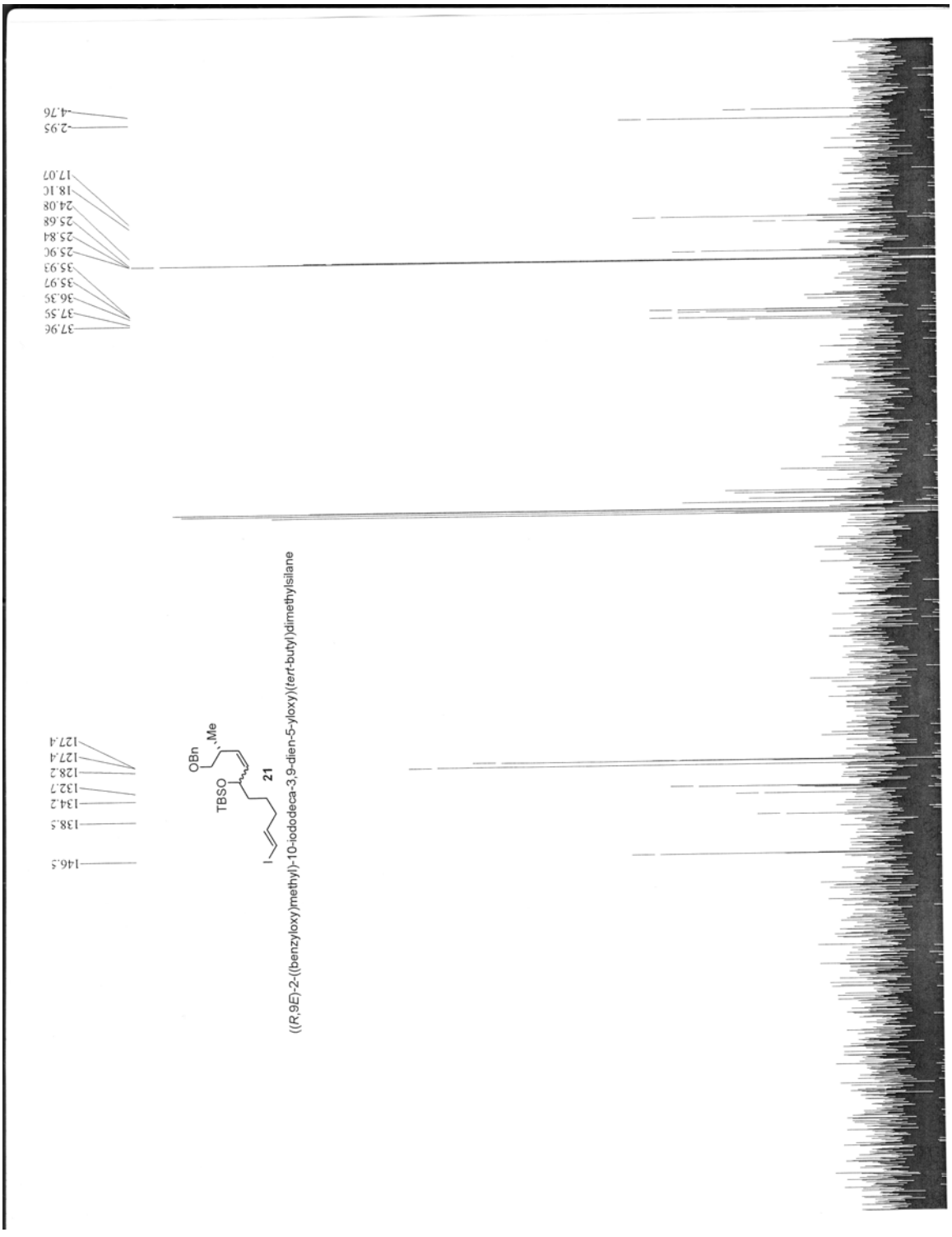
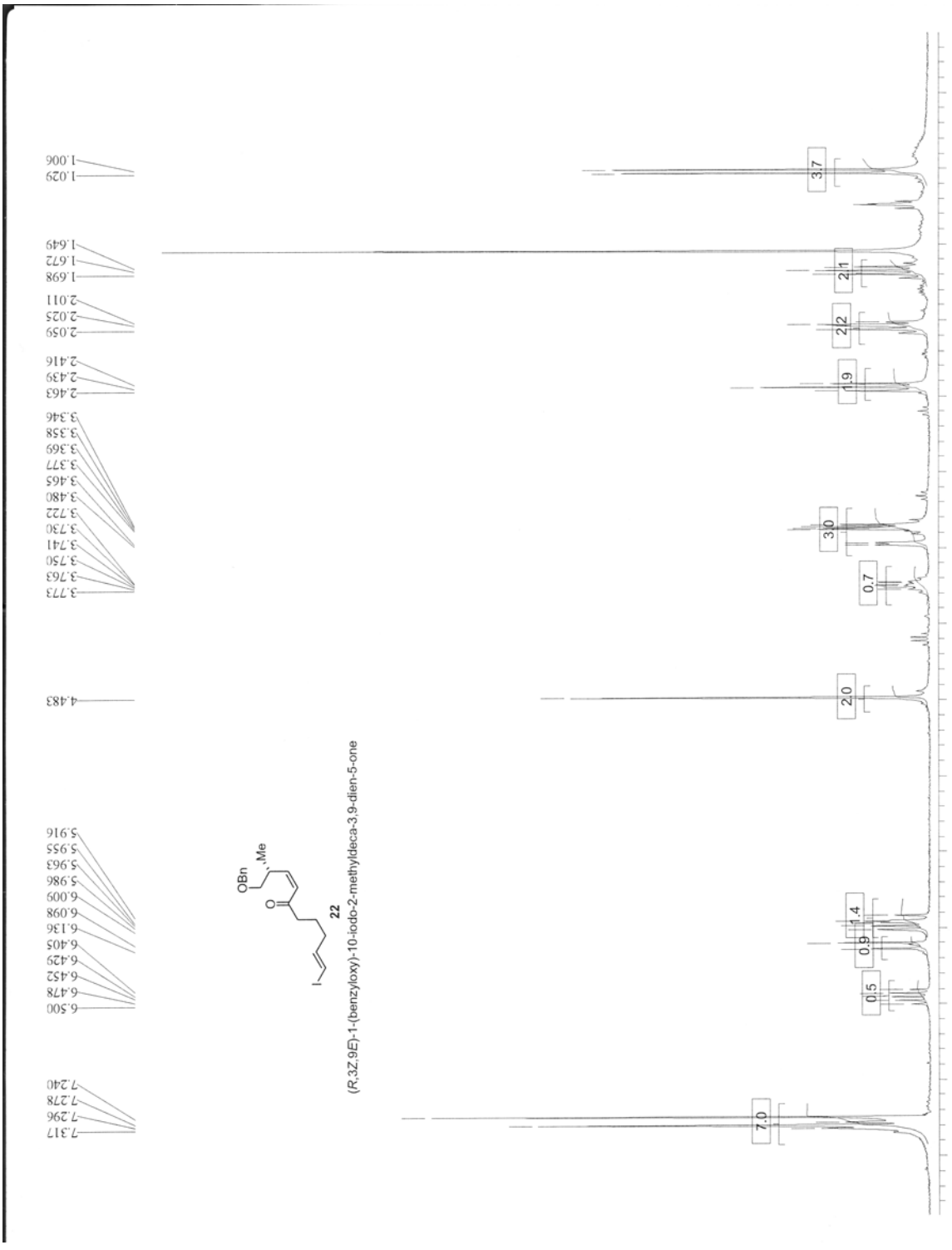


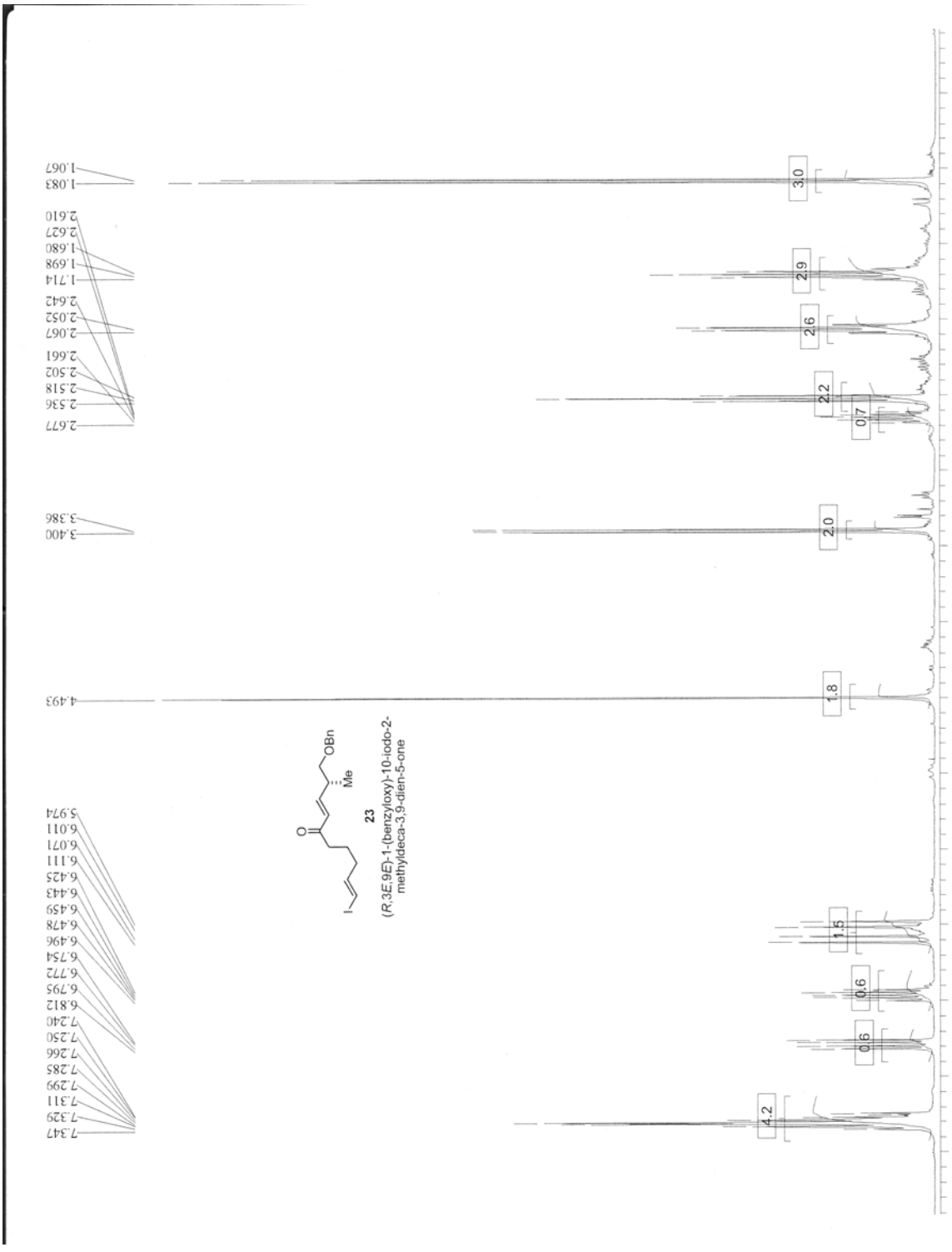
Spectrum 21. ^{1}H NMR spectrum of compound **21** in $CDCl_3$



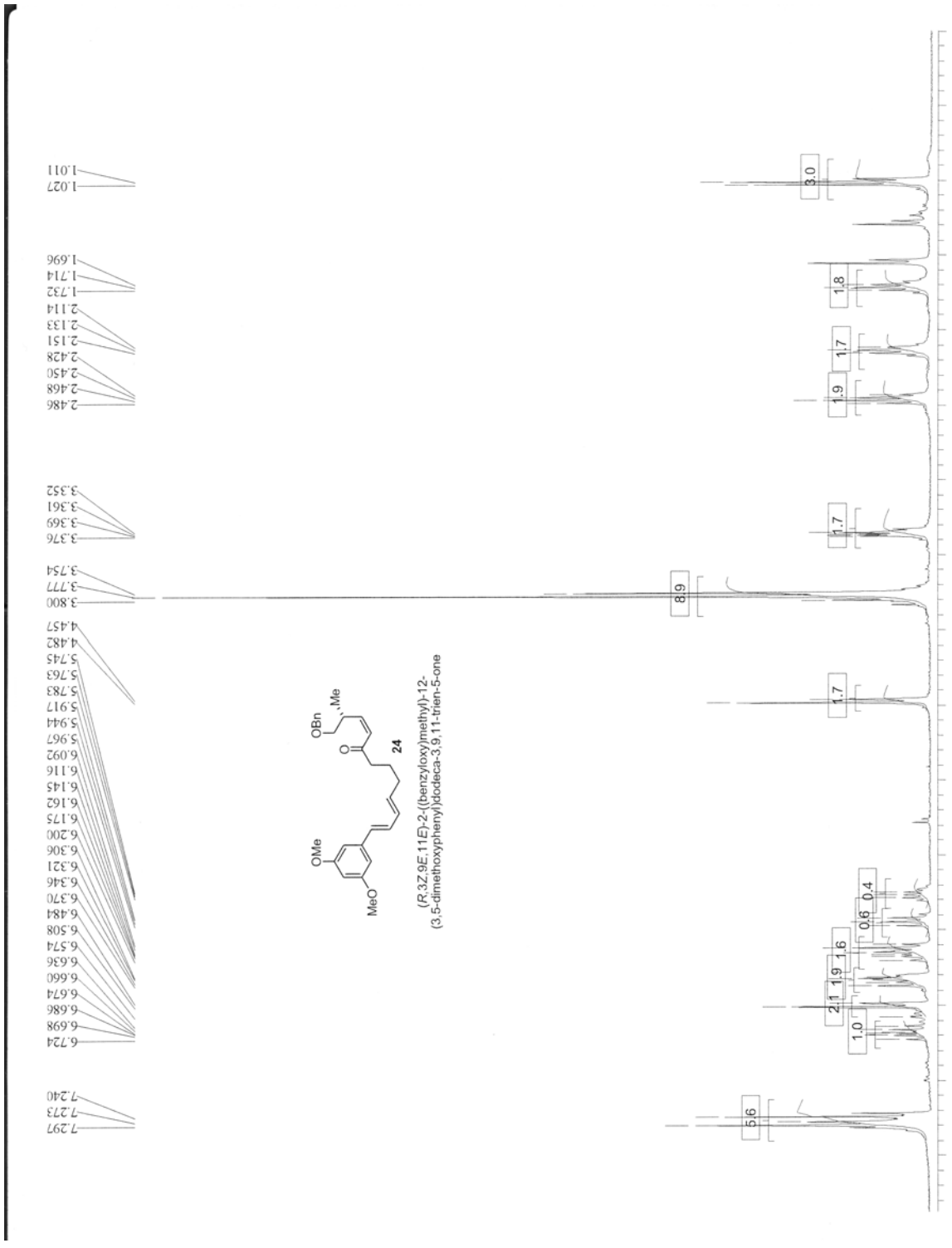
Spectrum 22. ^{13}C NMR spectrum of compound **21** in $CDCl_3$



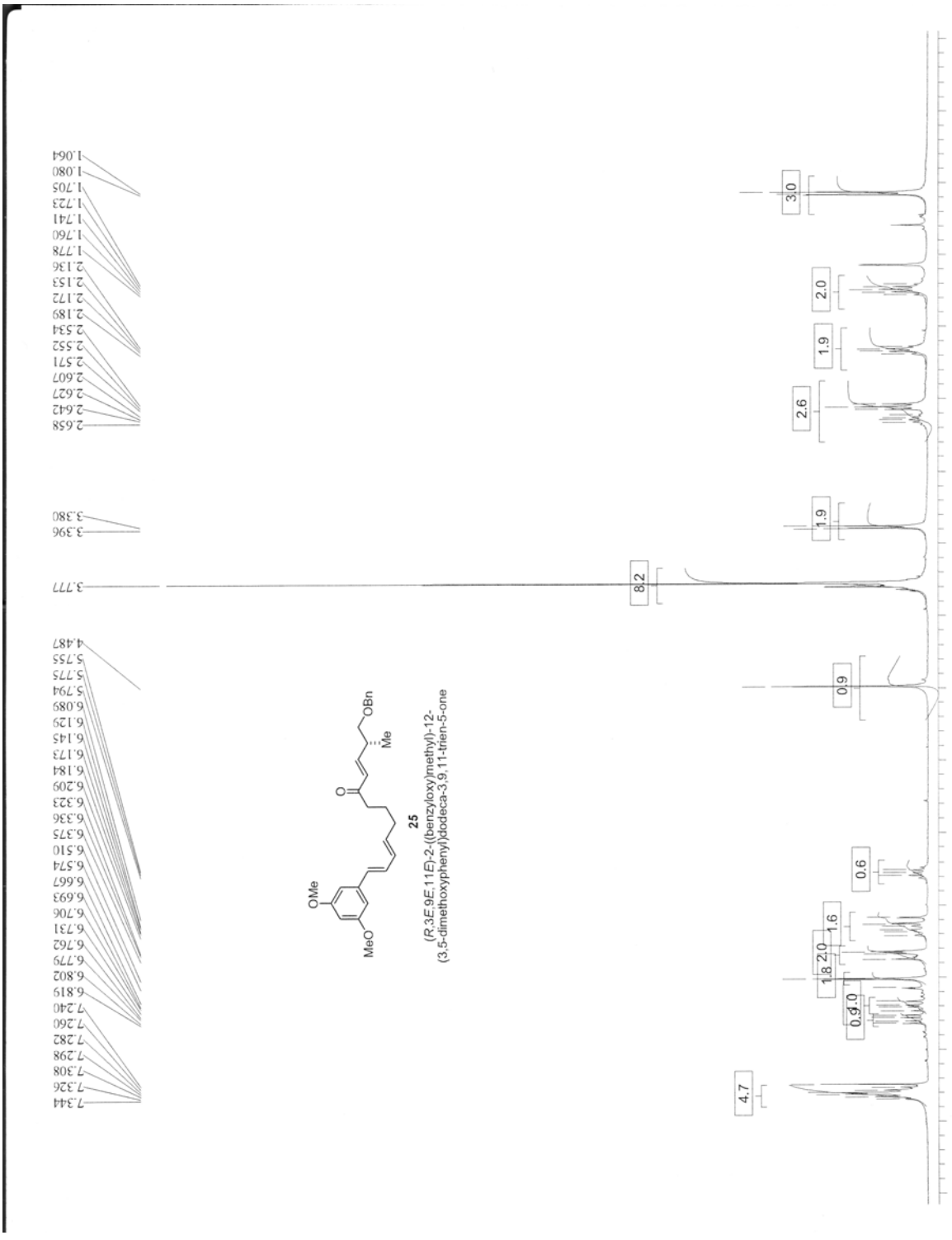
Spectrum 23. ^{1}H NMR spectrum of compound **22** in $CDCl_3$



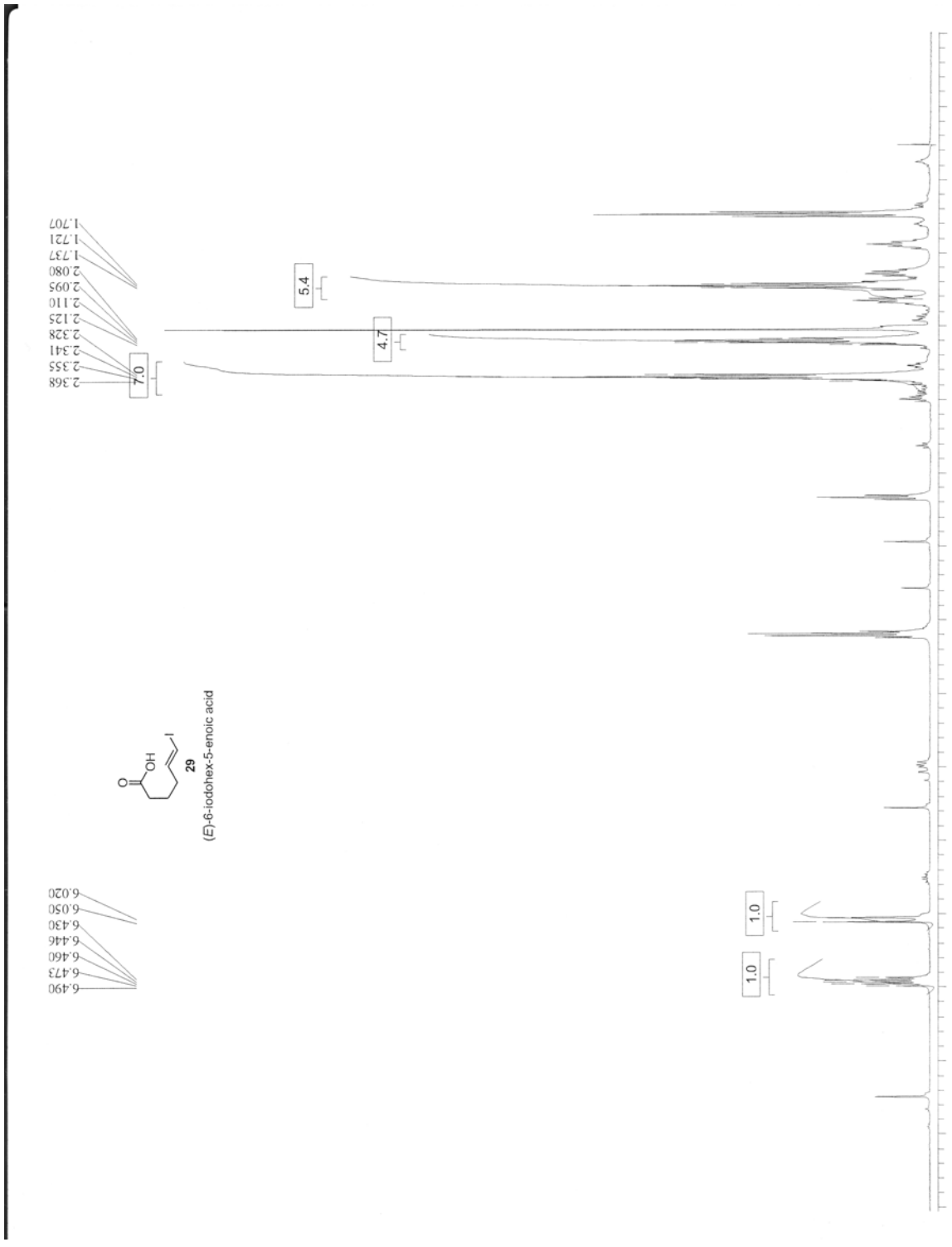
Spectrum 24. ^{1}H NMR spectrum of compound **23** in $CDCl_3$



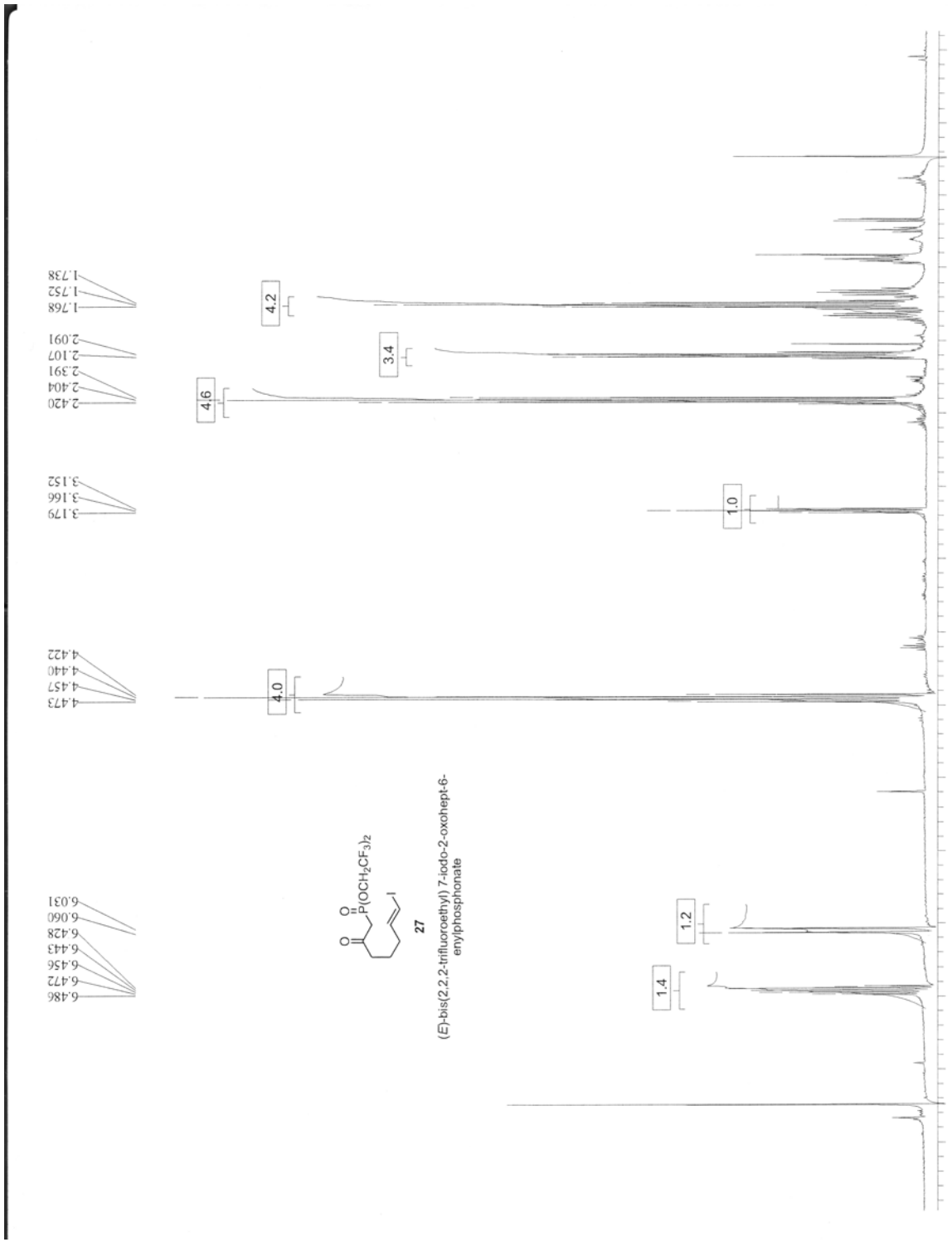
Spectrum 25. ^{1}H NMR spectrum of compound **24** in $CDCl_3$



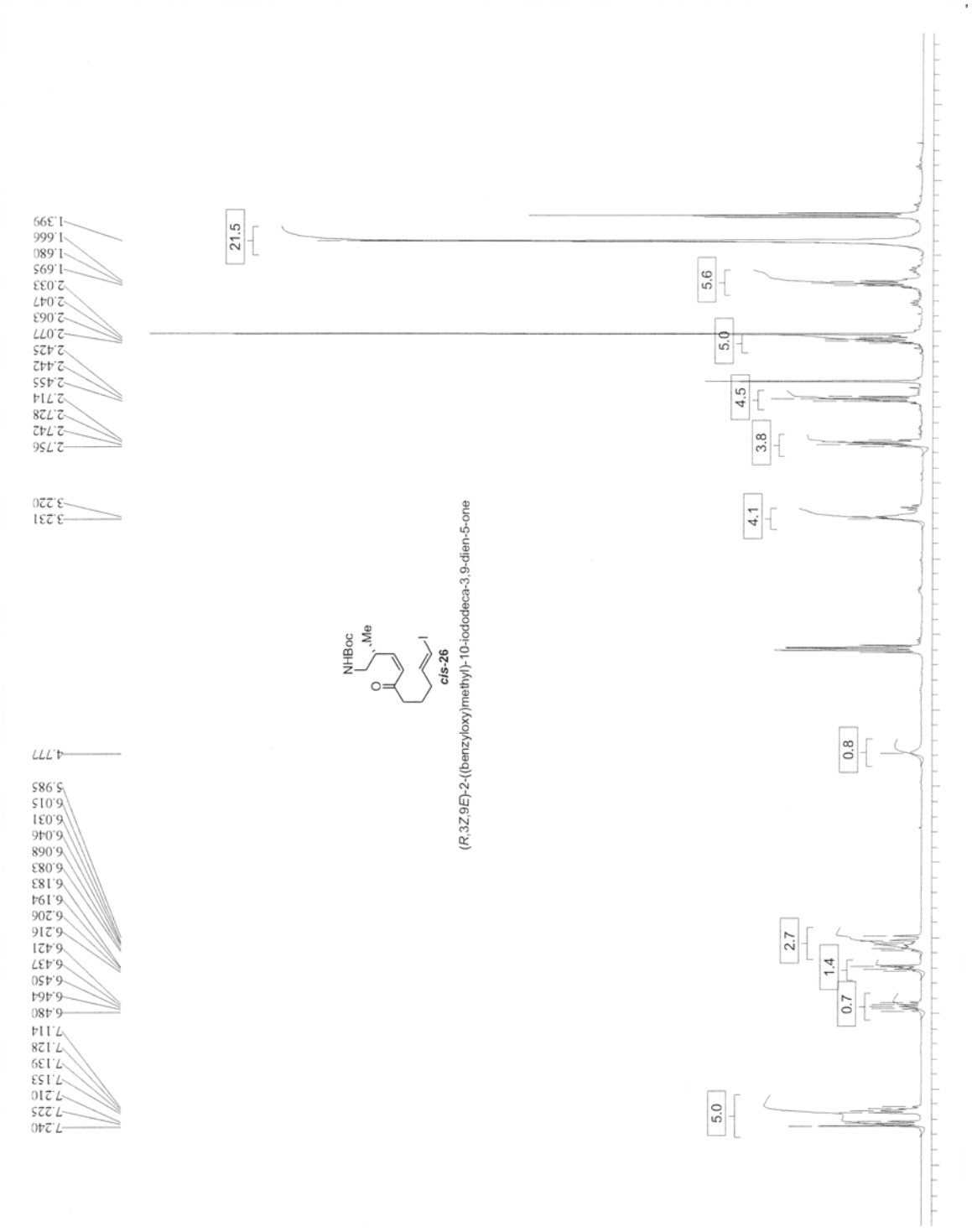
Spectrum 26. ^{1}H NMR spectrum of compound **25** in $CDCl_3$



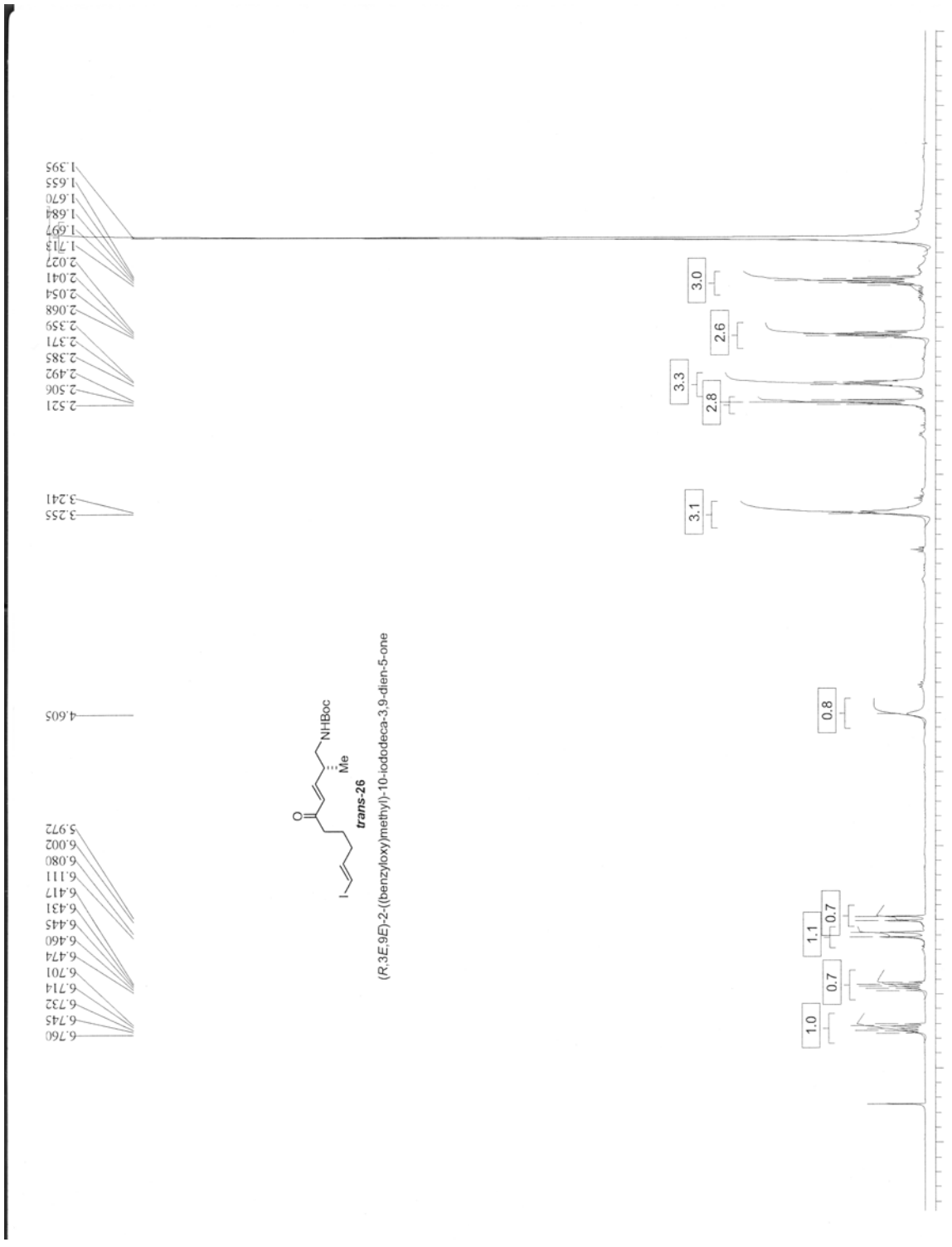
Spectrum 27. ^{1}H NMR spectrum of compound **29** in $CDCl_3$



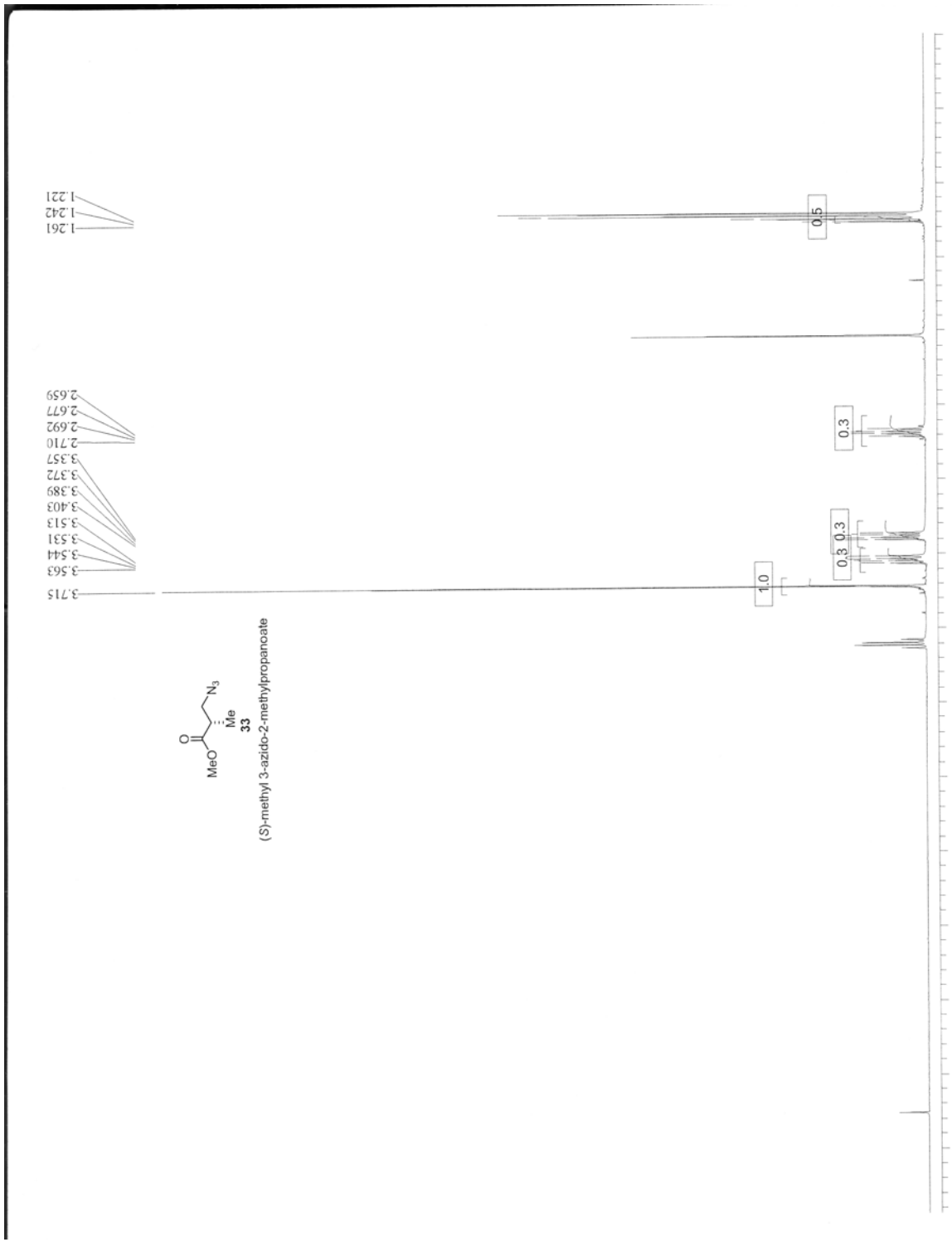
Spectrum 28. ^{1}H NMR spectrum of compound **27** in $CDCl_3$



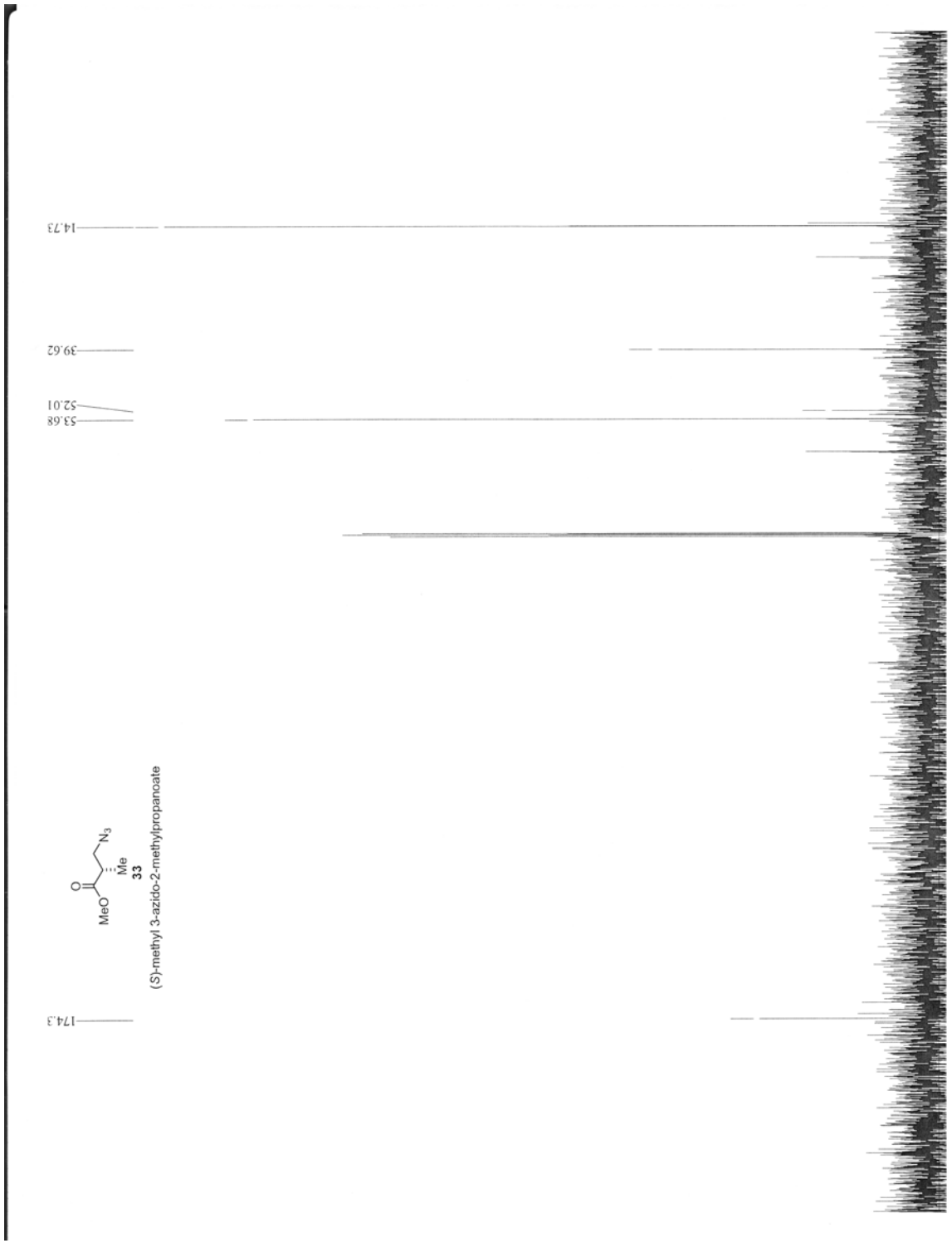
Spectrum 29. ^{1}H NMR spectrum of compound **26-*cis*** in $CDCl_3$



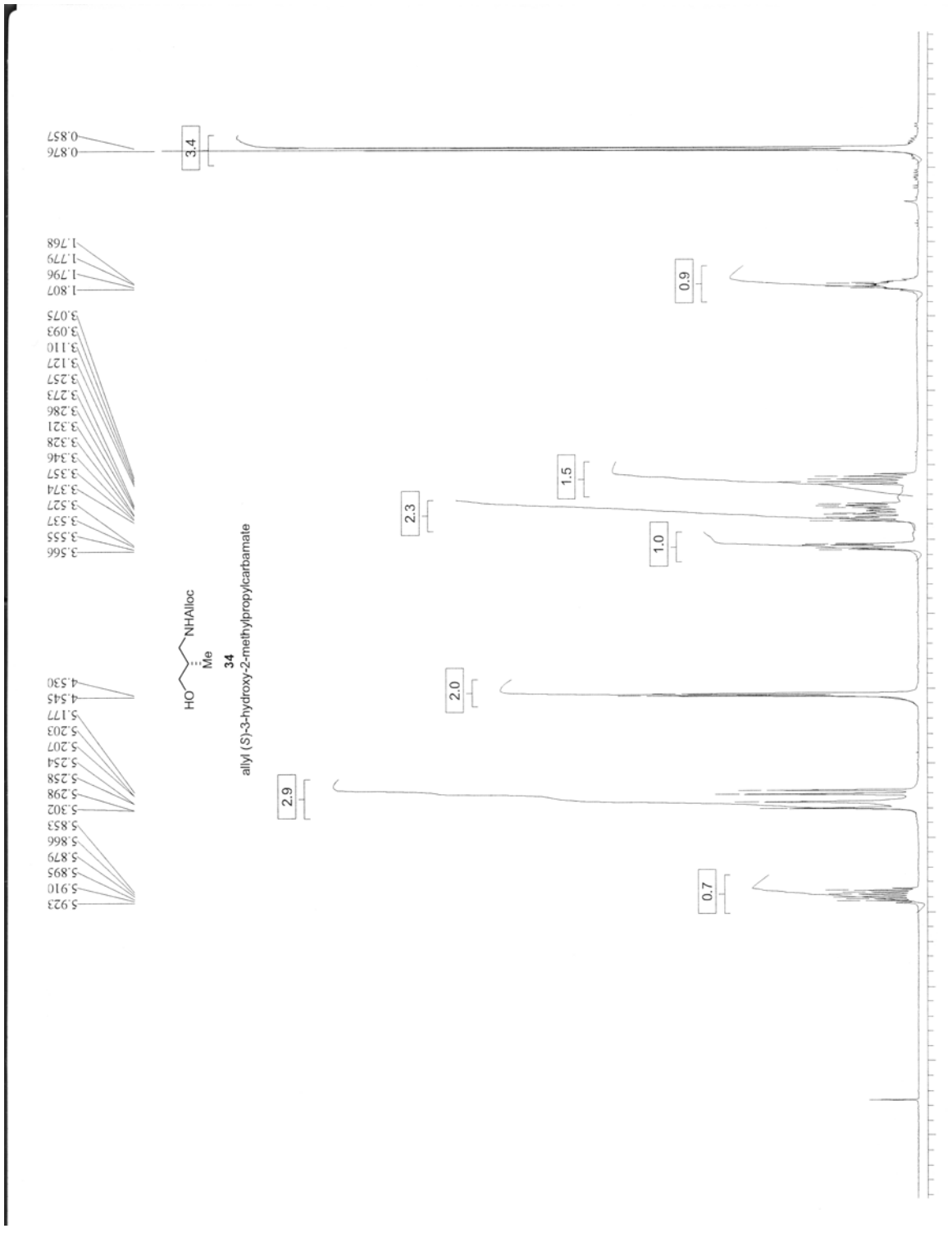
Spectrum 30. ^{1}H NMR spectrum of compound **26-*trans*** in $CDCl_3$



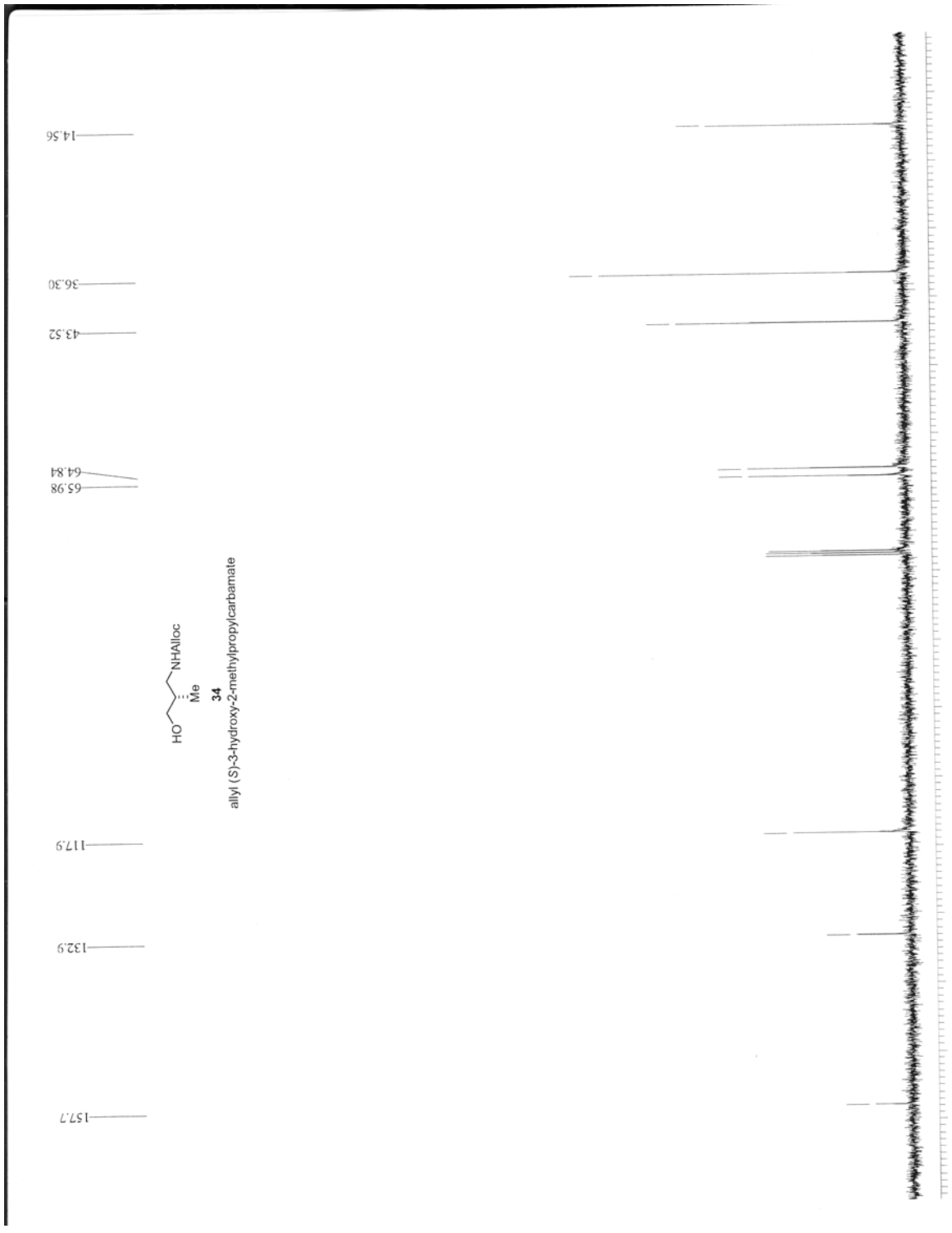
Spectrum 31. ^{1}H NMR spectrum of compound **33** in $CDCl_3$



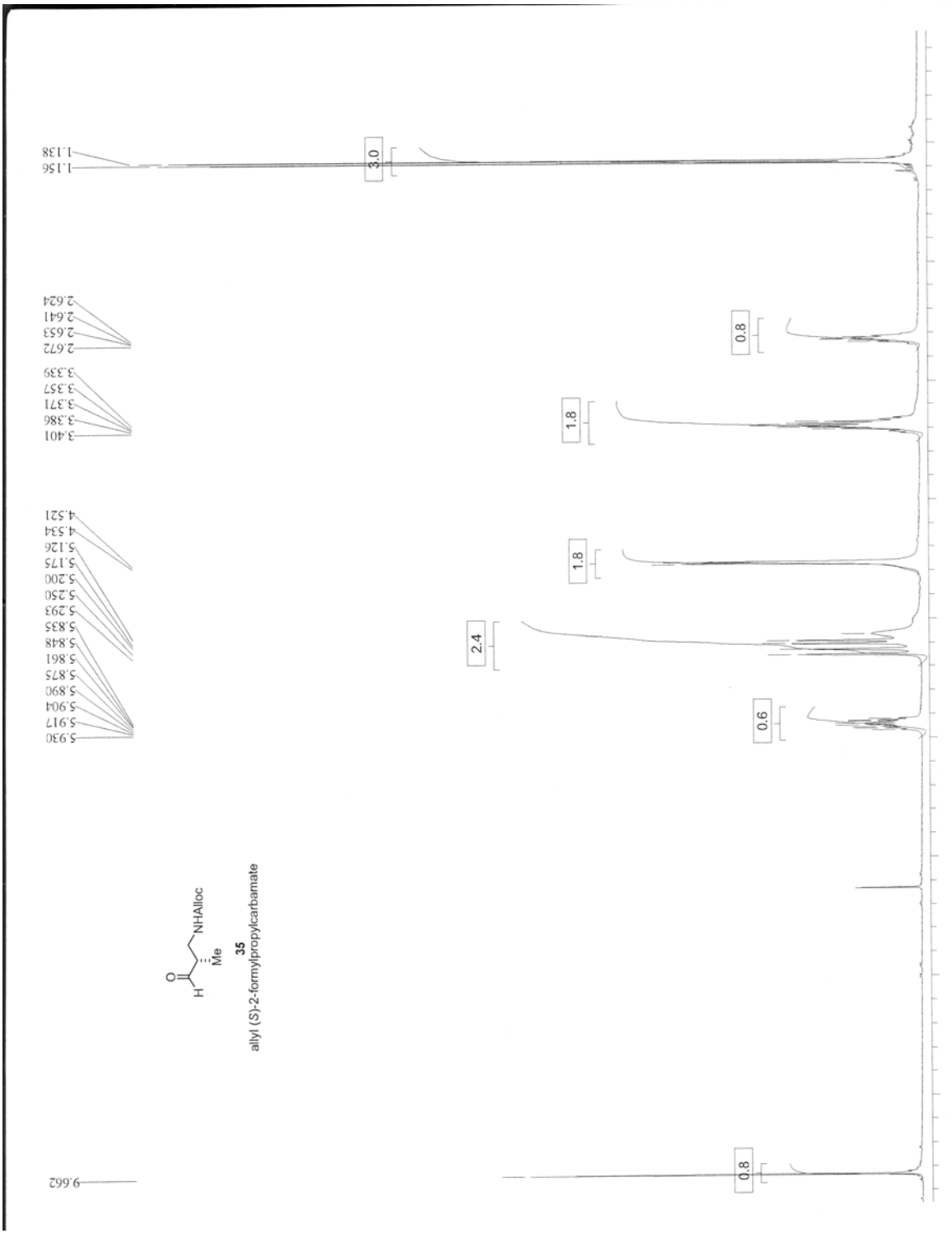
Spectrum 32. ^{13}C NMR spectrum of compound **33** in $CDCl_3$



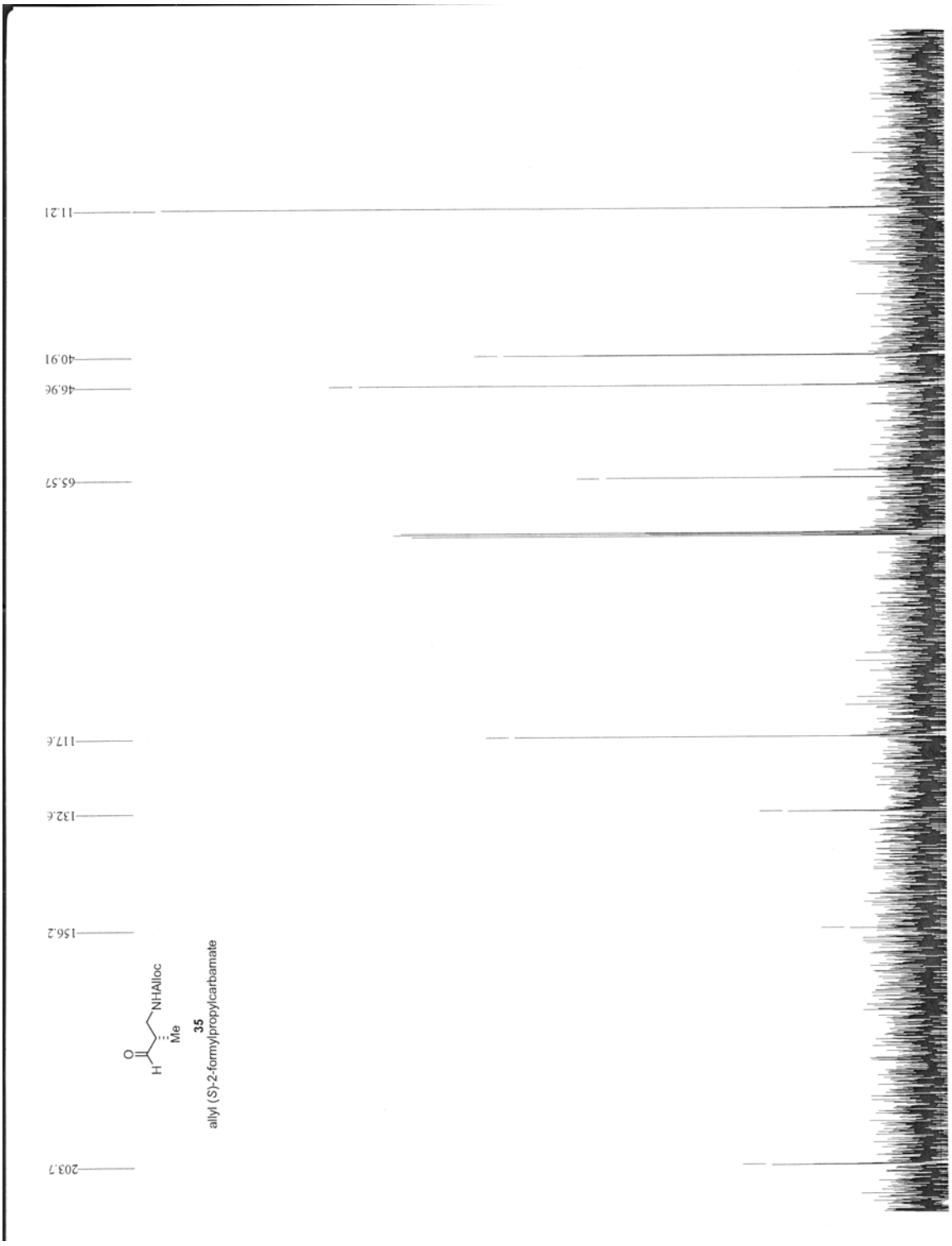
Spectrum 33. ^{1}H NMR spectrum of compound **34** in $CDCl_3$



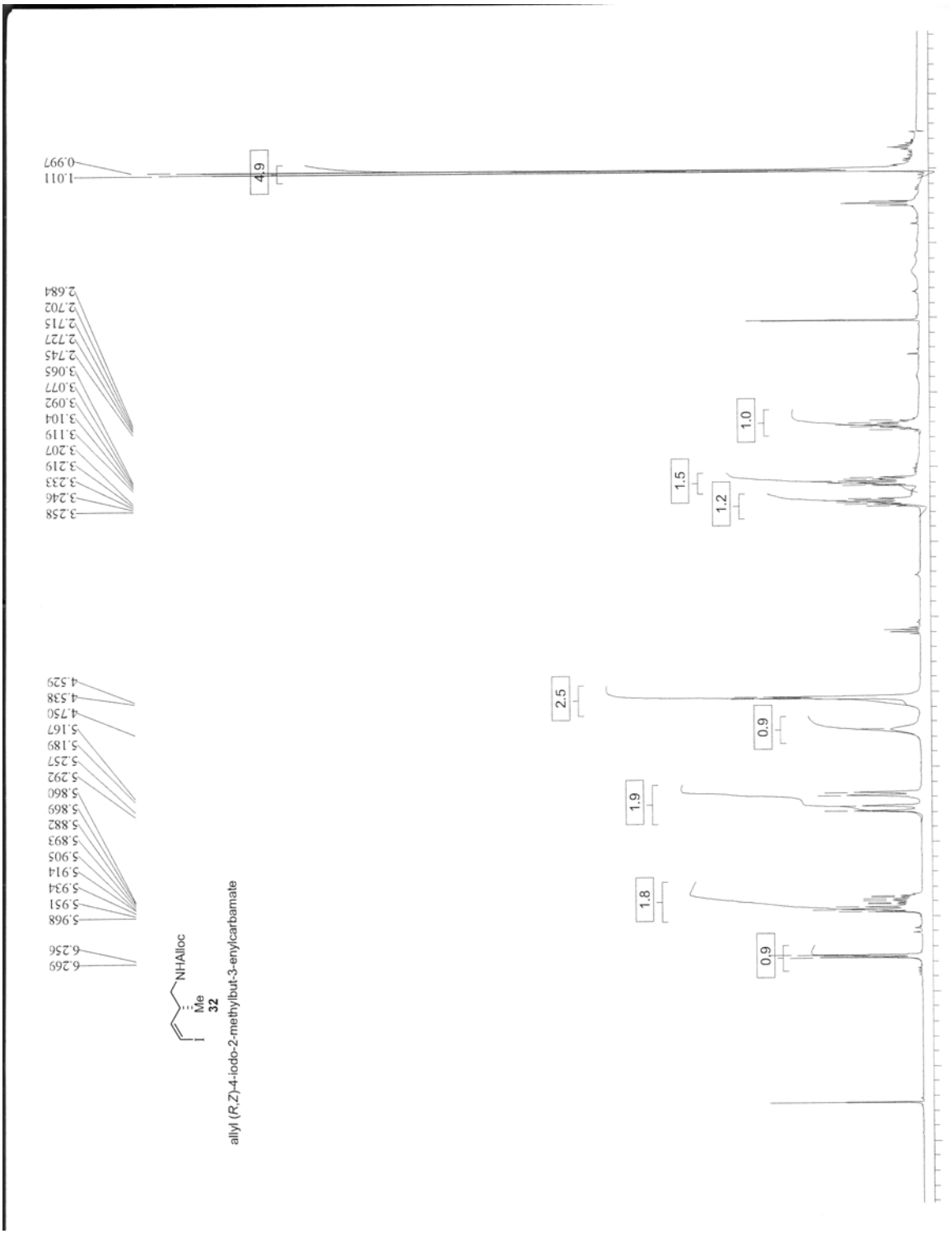
Spectrum 34. ^{13}C NMR spectrum of compound **34** in $CDCl_3$



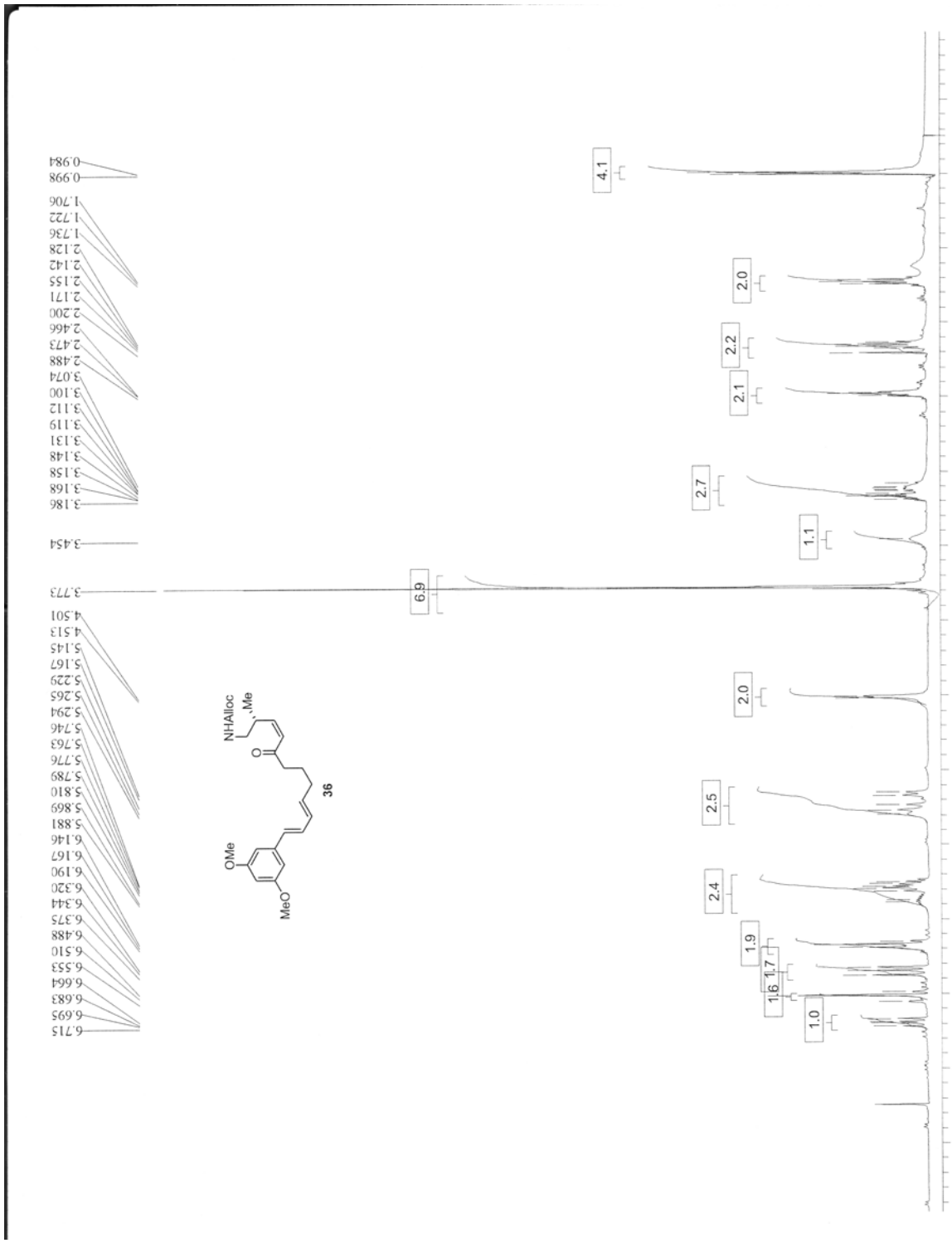
Spectrum 35. ^{1}H NMR spectrum of compound **35** in $CDCl_3$



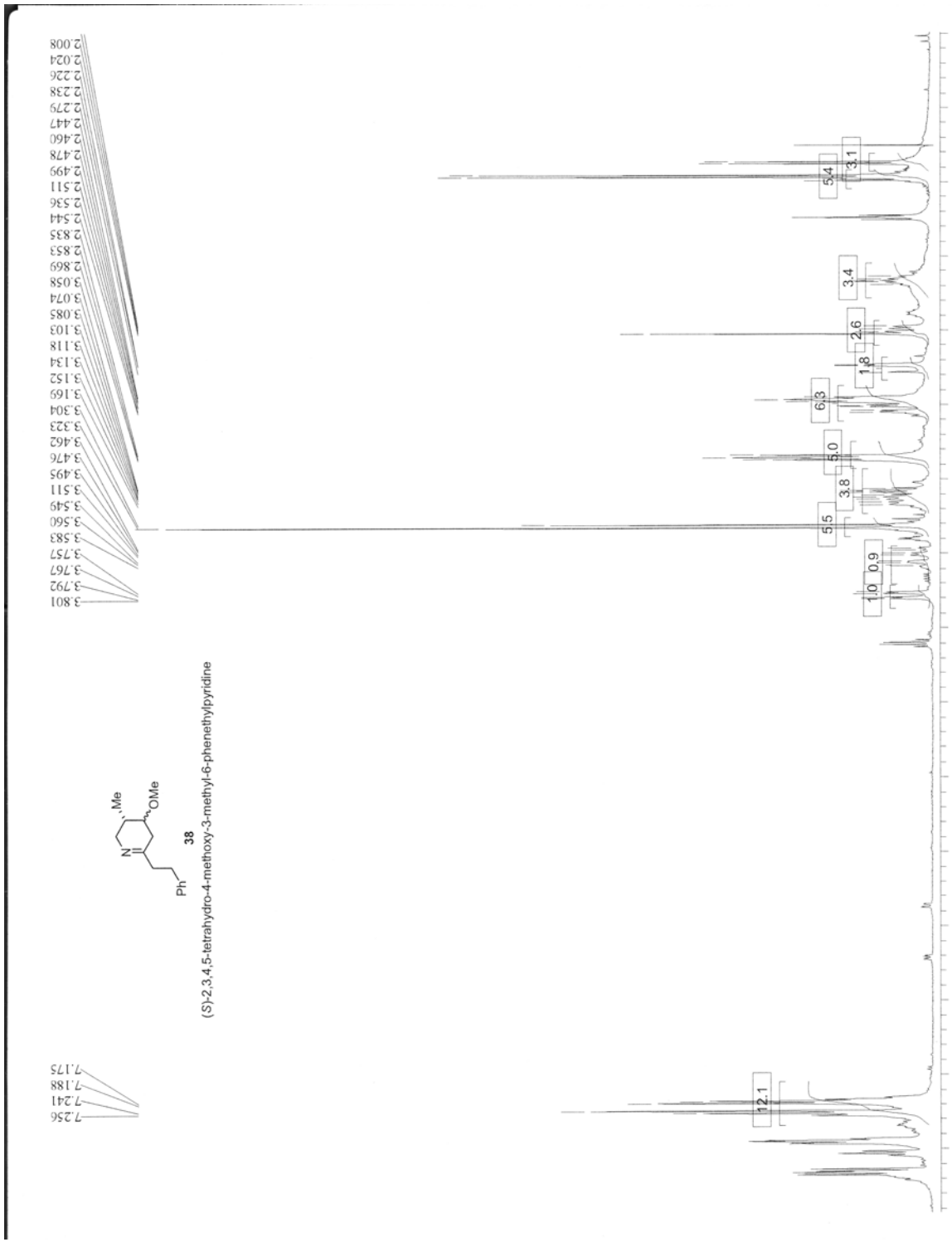
Spectrum 36. ^{13}C NMR spectrum of compound **35** in $CDCl_3$



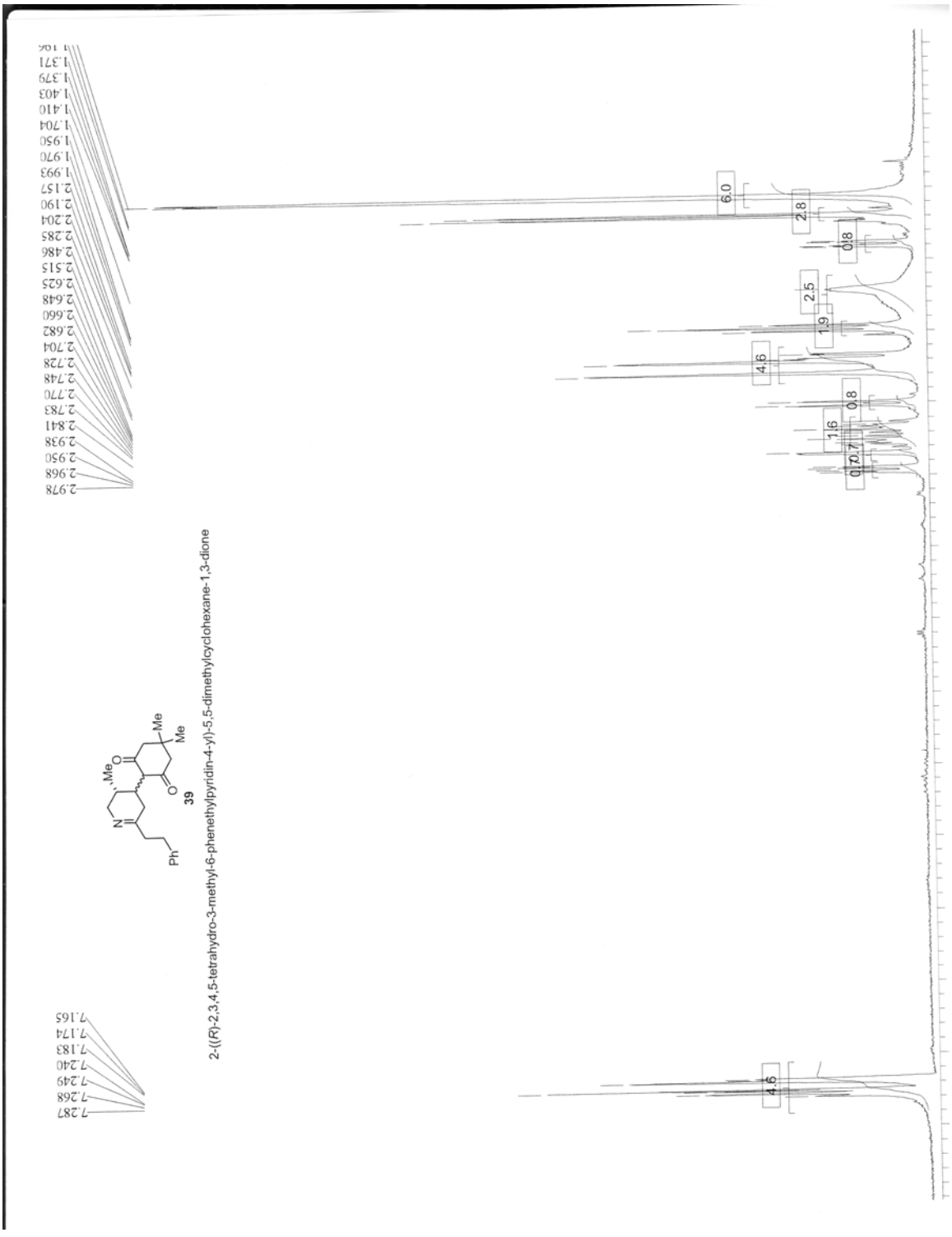
Spectrum 37. ^{1}H NMR spectrum of compound **32** in $CDCl_3$



Spectrum 38. ^{1}H NMR spectrum of compound **36** in $CDCl_3$



Spectrum 39. ^{1}H NMR spectrum of compound **38** in $CDCl_3$



Spectrum 40. ^{1}H NMR spectrum of compound **39** in $CDCl_3$

CHAPTER 3

The Unmasking of 2,3-Dihydropyridine

A. What is 2,3-Dihydropyridine?

2,3-Dihydropyridine has been implicated as a versatile intermediate in the proposed biosynthesis of alkaloids, highlighted by the biomimetic syntheses of a variety of natural products such as Keramaphidin B and Manzamine A,[1] as well as intermediates in the reactions of pyridines (Figure 16).[2]

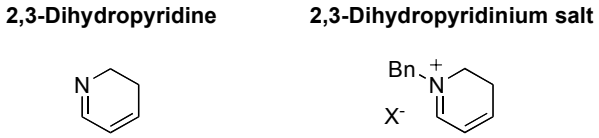


Figure 16. Structures of 2,3-Dihydripyridines

The stability of 2,3-dihydropyridine is assured so long as an alkyl or electron-withdrawing group (e.g., acyl) is attached to the nitrogen atom, effectively preventing the facile oxidation for aromatization. While *N*-alkyl 2,3-dihydropyridinium salt is well documented, and even isolable,[1a,c] there is scant information on the synthesis and physical properties of an *N*-unprotected 2,3-dihydropyridine, other than that they are highly unstable.[3] This is surprising, given the potential number of chemical transformations that such an intermediate can provide.

B. Relevance to Symbioimine

The significance of a 2,3-dihydropyridine intermediate can clearly be seen in our proposed biosynthesis of symbioimine **1**, in which the intramolecular Diels-Alder reaction of a chiral 2,3-dihhydropyridine intermediate **5**, followed by *cis*→*trans* decaline isomerization of **6** nicely zips up the tricyclic imine framework of **1** as shown in Route B of Figure 17. It is an alternative route to the originally proposed biosynthetic pathway

(Route A) which describes an *exo*-Diels-Alder reaction from the linear *trans*-enone **2**, followed by cyclic imine formation of **3** to form **1**.

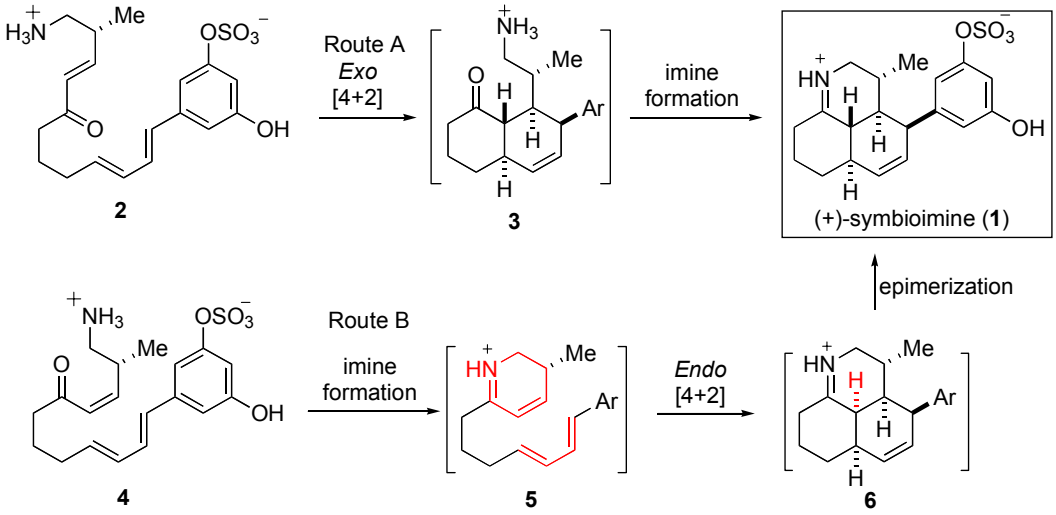


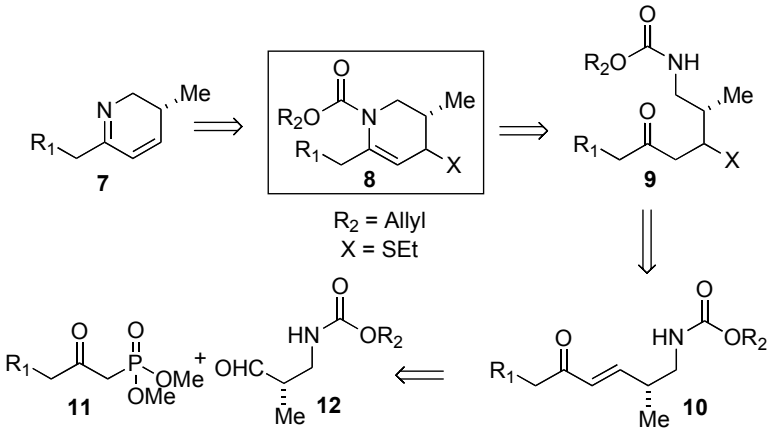
Figure 17. Proposed Biosynthetic Pathway of Symbioimine **1**

C. Problems, Solutions. Building a Model

Our initial approach to 2,3-dihydropyridine necessitated a preexisting *cis*-enone geometry to facilitate the intramolecular imine formation, directly generating the dihydropyridine. Unfortunately, under most *N*-deprotection conditions, we found that the *cis*-enone is highly susceptible to isomerizing to the more thermodynamically stable *trans*-enone.[4] As a result, the imine formation by intramolecular cyclization was inhibited. In the instances where we could form the cyclic imine (by Alloc deprotection) conjugate addition from the nucleophilic π-acceptor, be it from a reagent (dimedone) or solvent (methanol), prevented the isolation of pure 2,3-dihydropyridine.

Due to its inherent instability and predisposition to isomerization and oxidation, the generation of 2-alkyl-2,3-dihydropyridine **7** from a precursor (Scheme 26) necessitated very mild, neutral conditions. We designed masked compound **8** as the

stable synthetic equivalent. The aza-1,3-diene moiety of **7** is masked by formal 1,4-addition of nucleophile X. The deprotection of carbamate **8** will induce the elimination of X^- to regenerate the aza-1,3-diene moiety. An appropriate scavenger must trap the resulting X^- immediately, otherwise **7** will react with X^- to form a 1,4-adduct.



Scheme 26. Design of a Masked 2,3-Dyhydropyridine

We anticipated an alloc group (R_2=Allyl) could be the best candidate for the carbamate **8**, because the eliminated X^- will be scavenged by highly electrophilic Pd-π-allyl complex, concomitantly regenerating Pd(0) for the catalytic cycle. Compound **8** will be formed readily by dehydration of acyclic aminoketone **9**. Ketone **9** will be obtained by 1,4-addition of thiolate (X = SEt) to *trans*-enone **10**, which will be readily formed by condensation of phosphonate **11** and aminoaldehyde **12**. This approach is unique in obviating the need for using problematic *cis*-selective olefination methodologies. For the application to the synthesis of symbiomime, we planned a synthesis of masked compound **14** as a synthetic equivalent of 2,3-dihydropyridine **13** as shown in Figure 18.

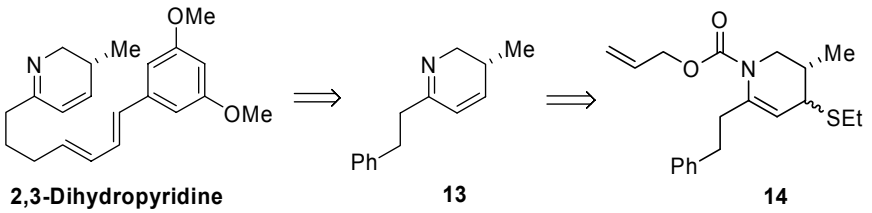
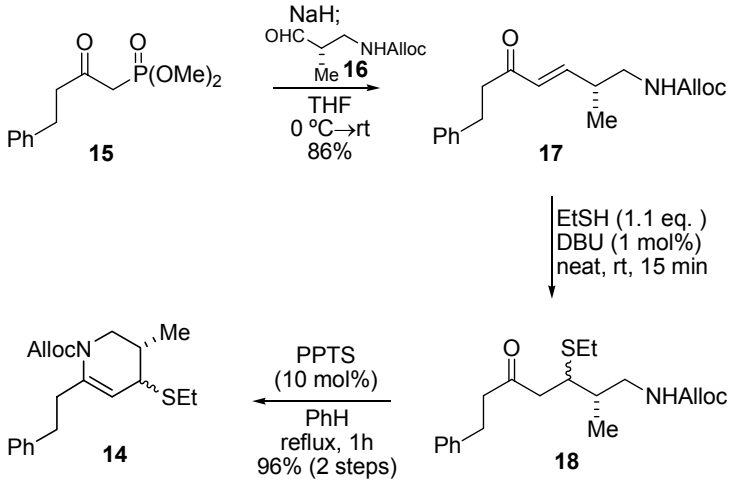


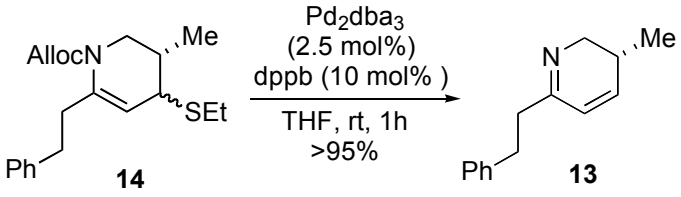
Figure 18. Design of Model 2,3-Dihydropyridine **13**

The masked 2,3-dihydropyridine **14** was prepared in three steps in good yields as shown in Scheme 27. Beginning from commercially available β-ketophosphonate **3**, a Horner-Wadsworth-Emmons olefination with aldehyde **4** yielded the exclusive *trans*-isomer **5** in very good yield. Next, treatment of *trans*-enone **5** with ethanethiol in the presence of a catalytic amount of DBU under solvent-free condition gave the conjugate adduct **6** as a 1:1 diastereomixture. Taking the material directly on to the subsequent cyclodehydration step without purification, treatment with 10 mol% of PPTS under dilute refluxing benzene yielded the masked 2,3-dihydropyrdine **2** as a single regioisomer for an enanine moiety in excellent yield.



Scheme 27. Synthesis of the Masked 2,3-Dihydropyridine **14**.

The inherent reactivity of 2,3-dihydropyridine suggests that of the many protecting groups for amines commonly in use today, not all deprotection conditions are created equal. A brief survey of the more common protecting groups found that the deprotection conditions of allyloxy carbonyl (alloc) group of **14** were sufficiently mild to produce the desired product, and depending on the concentration (0.5 M), allowed the palladium loading to be dropped to an effective 2.5 mol% (Scheme 28) to yield the stable (>48 hr at 25 °C in $CDCl_3$) 2,3-dihydropyrdine **1**.[9] It was found that dihydropyridine **13** decomposes upon purification with silica, but that catalyst removal via Celite filtration and subsequent high vacuum drying to remove allyl ethyl sulfide yielded the desired product essentially free of impurities as shown in Scheme 2.

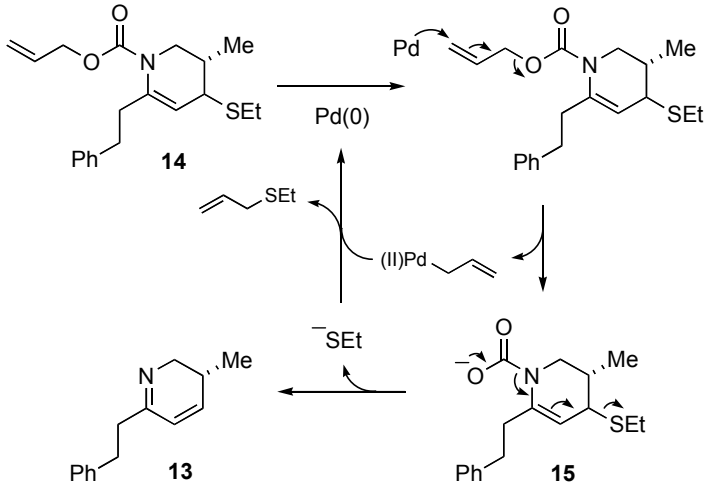


Scheme 28. Unmasking the 2,3-Dihydropyridine Equivalent **14**.

D. Unmasking Mechanism

The unmasking step of **14** to obtain **13** is quite unique, because of the reaction mechanism (Scheme 29). The alloc deprotection begins by the nucleophilic attack of Pd (0) on the allyl carbamate of the masked 2,3-dihydropyridine **14**, generating the Pd-π-allyl complex and carbamylate **15**, which spontaneously undergoes decarboxylation. The resulting enamine induces an elimination of ethanethiolate to form **13**. There is no need for the addition of an external nucleophile (such as diethylamine, pyrrolidine, or dimedone) to intercept the Pd-π-allyl system and regenerate Pd(0) for the catalytic cycle.

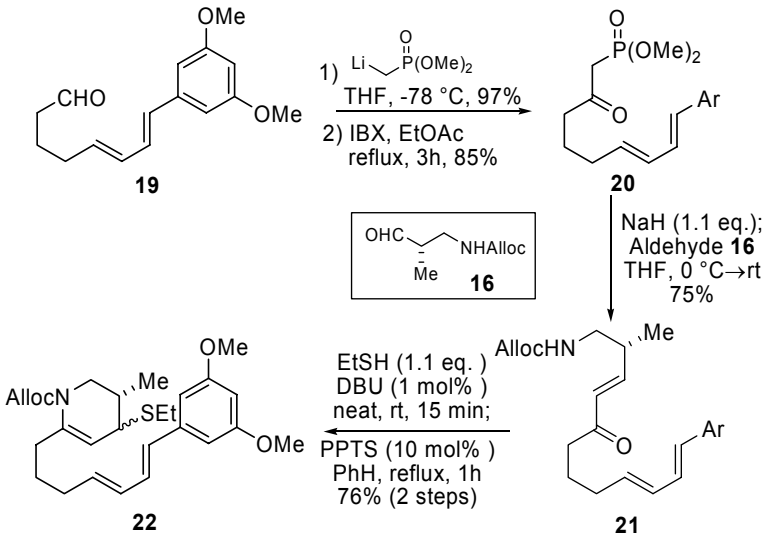
Instead, the extruded ethanethiolate can serve in this capacity as well as help avoiding an unwanted formation of conjugate adducts of **13**.



Scheme 29. Mechanism of $Pd^{(0)}$-catalyzed Unmasking Step

E. Construction of Symbioimine Framework, Unmasking, and Diels-Alder reaction.

Construction of the masked 2,3-dihydropyridine framework of symbioimine began with the addition of a lithiated phosphonate to aldehyde **19** at -78 °C, followed by IBX oxidation of the newly formed secondary alcohol to give β-ketophosphonate **20** in 83% yield (over two steps), as shown in Scheme 30. Horner-Wadsworth-Emmons olefination by way of deprotonating **20** and the addition of chiral aldehyde **16** gave the exclusive *trans*-enone **21** in 75% yield. Taking this on in the same way as the model system, conjugate addition of ethanethiol catalyzed by diazabicycloundecane (DBU) under neat, room temperature conditions quickly gave a crude material that was dissolved in benzene and refluxed with 10 mol% of pyridinium *p*-toluenesulfonate (PPTS) for an hour, producing the condensation product and masked 2,3-dihydropyridine **22** in 76% (over two steps).

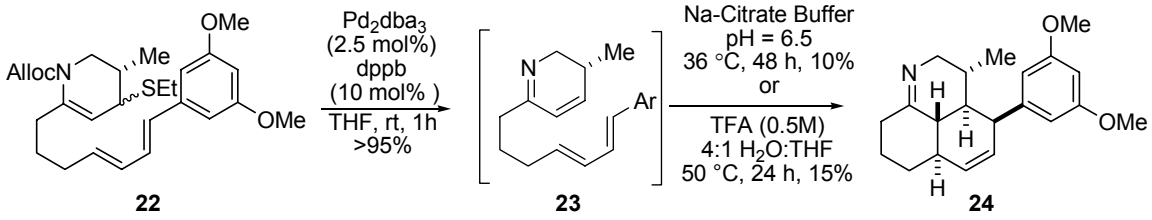


Scheme 30. Construction of Masked Dihydropyridine **22**.

Subsequent unmasking using 5 mol% of $Pd(dppb)_2$ (generated in situ from Pd_2dba_3 and diphenylphosphinobutane (dppb)), the Alloc group was deprotected, with the resulting enamine kicking out ethanethiol to give 2,3-dihydropyridine **23** in essentially quantitative yield (Scheme 31). Again, stability issues regarding the basic imine disallowed purification over silica or alumina, though the only impurity present after filtration of the solution over celite was 7.5 mol% of dibenzylideneacetone (dba) from the palladium source. Given the thermal instability of 2,3-dihydropyridine, conventional heating was avoided and instead, a wide variety of Lewis acids were tried to facilitate the intramolecular Diels-Alder reaction. Unfortunately, after employing an extensive array of Lewis acids, such as $BF_3{\cdot}OEt_2$, $AlCl_3$, $MeAlCl_2$, Me_2AlCl, $TiCl_4$, $SnCl_4$, etc., I came to the conclusion that Lewis-acid activation is poor with nitrogenous substrates, and more suited to oxygenated species. At the time, Snider had published his favorable model study of an *N*-acyl imminum-activated Diels-Alder reaction for symbioimine, but

unfortunately no acylating species could directly activate 2,3-dihydropyridine, and no acylation products were observed from the crude material. Brønsted acid mediated imine-activation was examined, and inspired by the success Kishi had had with Gymnodimine, the identical conditions were employed, as illustrated in Scheme 6.

After unmasking the 2,3-dihydropyridine **22**, subsequent exposure to aqueous sodium citrate buffer (pH = 6.5) and its heating at 36 °C for 48 hr ensued. Initially, the 2,3-dihydropyridine was insoluble in the aqueous conditions, but given five minutes it emulsified and slowly went into solution over the next 10 minutes. Upon quenching and extraction, a roughly 10% yield of Diels-Alder adduct **24** was observed by crude ^{1}H-NMR. A year later, in his publication of the enantioselective synthesis of symbioimine **1**, Thomson reported his success in subjecting his Diels-Alder precursor to a 0.5M TFA solution of 4:1 H_2O:THF, at elevated temperatures overnight. Repetition of these conditions, however, failed to meet his reported yields.



22 **23** **24**

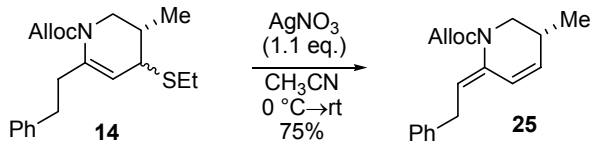
Scheme 31. The Unmasking of **22** and Subsequent Diels-Alder Reaction

The recalcitrance of the pure 2,3-dihydropyridine **23** to listen to its maker and get with the program was met with frustration. Trying to understand its feelings, a closer examination of its delocalized π-systems revealed that it was in fact bi-polar. No,

seriously. If one examines a dienophile, the β-carbon is uniquely electron deficient due to the electron withdrawing presence of a carbonyl (or imine in this case), and is often described as having a small orbital coefficient. Under the usual mode of Diels-Alder cycloadditons, such a small orbital coefficient is favored to react with the more electron rich, larger orbital coefficient end of the coupling diene. Unfortunately, the more electron rich end of the coupling diene in the symbioimine framework is poised to react with the more electron rich α-carbon of the dienophile. Essentially, the system is bi-polar, and doesn't want to interact in a manner condusive to producing the tricyclic ring system.

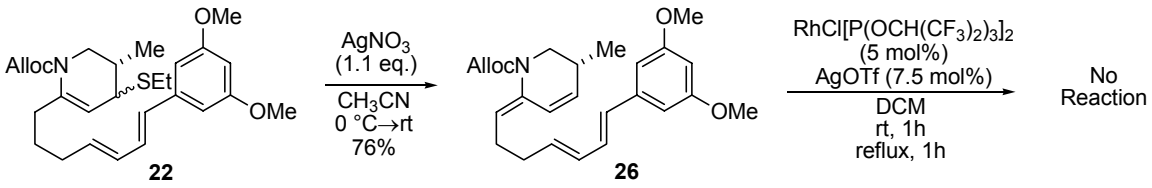
F. Alternative Substrate Modification, and Attempts at a Diels-Alder reaction

A solution to this poor orbital overlap would be to decrease the electron polarity of the diene or dienophile. In the case of our masked 2,3-diydropyridine, experimentation in sulfur activation led to the discovery of a silver-mediated, ethanethiol-eliminated isomerziation (Scheme 32). Treatment of masked model **14** with silver nitrate in acetonitrile produced an exo-olefinic product **25** in 75% yield, whose *cis*-relationship with the carbon framework of the heterocycle was assigned on the observation of an NOE between benzylic (δ 3.22 ppm) and the adjacent vinylic proton (δ 5.97 ppm).



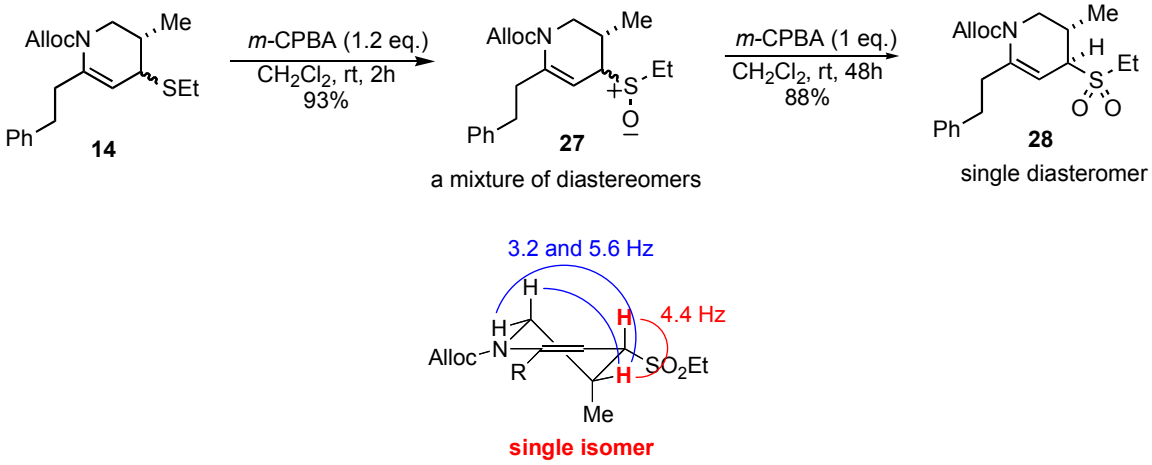
Scheme 32. Silver-Mediated Elimination of Ethanethiol From **23**

This isomerized material neatly presents a *cis*-olefin that, with the proper framework, can more readily participate in an intramolecular Diels-Alder reaction due to conformational restraint induced by the *cis*-exo olefin. Application of this isomerization method to the masked 2,3-dihydropyridine **22** produced the desired tetra-ene **26** in 76% yield (Scheme 33). Again, a wide variety of conditions were explored to induce the [4+2] cycloaddition, including thermal and both Lewis- and Brønsted acid-mediated conditions. Attempts at using cationic-Rhodium catalysis were also ineffective.



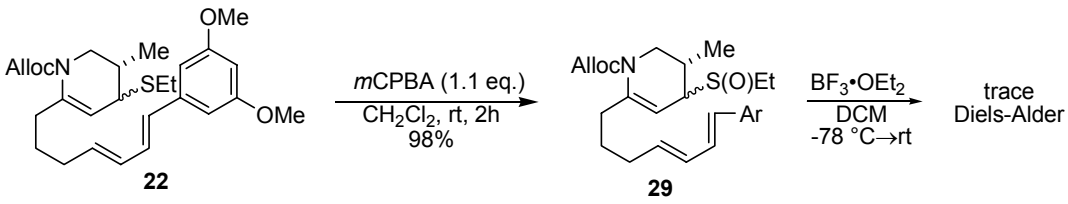
Scheme 33. Silver-Mediated Elimination of Ethanethiol From **22**, and Failed Diels-Alder

Alternative methods to activate the ethyl sulfide such as oxidizing it to the sulfone were employed. Oxidation of sulfide **14** with *m*-CPBA in dichloromethane produced sulfoxide **27** in 93% yield, with a further equivalent of oxidant produced the sulfone **28** in 88% yield as a single isomer (Scheme 34).



Scheme 34. Oxidizing Allyl Ethyl Sulfide **14**.

Application of this oxidation to the symbioimine framework is illustrated in Scheme 35. Oxidation of ethyl sulfide **22** with 1.1 equivalents of *m*-CPBA in dichloromethane produced sulfoxide **29** 98% yield. Of all the [4+2] cycloaddition conditions tried, only Lewis acid-activation with $BF_3{\cdot}OEt_2$ produced any observable Diels-Alder products, and even then only trace amounts (<5%).



Scheme 35. Oxidizing Allyl Ethyl Sulfide **22**, and Failed Diels-Alder Reaction

G. Conclusion

In conclusion, we have described the synthesis of a stable synthetic equivalent of 2,3-dihydropyridine and a unique mechanism in the unmasking step. The masked 2,3-

dihydropyridine **2** was obtained via a high yielding three-step process from a *trans*-enone. In the unmasking step, the thiol served to regenerate the catalyst by intercepting the Pd-π-allyl intermediate. The 2,3-dihydropyridine **1** generated by this strategy has direct applications as a biomimetic intermediate in the synthesis of several classes of alkaloid natural products. Utilization of this methodology in the total synthesis of symbioimine gave poor yields of the intramolecular Diels-Alder adduct, suggesting to us that the formation of 2,3-dihydropyridine should occur under the Diels-Alder conditions to minimize potentially fatal side-reactions. Alternative modification to the masked 2,3-dihydropyridine system by silver-induced thiol-elimination/olefin isomerization and sulfide→sulfone oxidation was found to be unproductive in producing useful quantities of [4+2]-cycloaddition product. Despite these setbacks, however, we did discover a mild method of producing the 2,3-dihydropyrdine heterocycle from a stable, masked precursor. In addition, the methodology used to access the *trans*-enones was seen to be quite useful in examining various thermal conditions for [4+2] cycloaddition, the extant to which will be covered in the subsequent chapter.

H. Acknowledgments

In addition to thanking the University of California for financial support, we also thank Dr. Yongxuan Su for Mass Spectroscopy and Dr. Anthony Mrse for help with NOESY experiments.

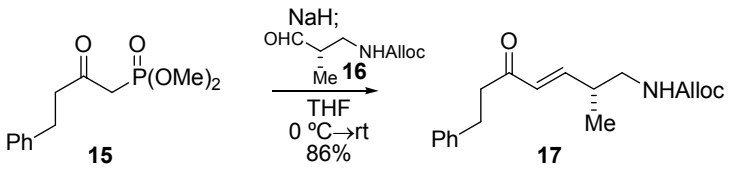
I. Experimental Section

Materials and Methods

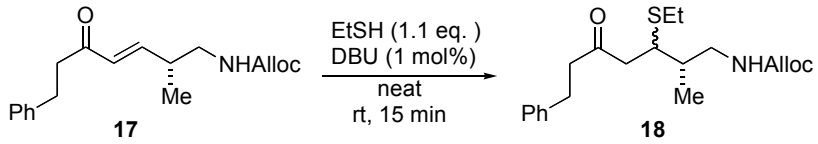
All reagents were commercially obtained (Aldrich, Fisher) at highest commercial quality and used without further purification except where noted. Organic solutions were concentrated by rotary evaporation below 45 ˚C at approximately 20 mmHg. Tetrahydofuran (THF), methanol (MeOH), chloroform ($CHCl_3$), dichloromethane (DCM), ethyl acetate (EtOAc), acetonitrile (CH_3CN), and acetone were purchased as reagent grade and used without further purification. Reactions were run under an inert N_2 atmosphere unless otherwise noted. Yields refer to chromatographically and spectroscopically (^{1}H- and ^{13}C-NMR) homogeneous materials, unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254), visualized with UV light and stained with cerium molybdate solution and heat. E. Merck silica gel (60A, particle size 0.040-0.063 mm) was used for flash chromatography. Preperative thin-layer chromatography separations were carried out on 0.50 mm E. Merck silica gel plates (60F-254). NMR spectra were recorded on Varian Mercury 300, 400 and/or Unity 500 MHz instruments and calibrated using the residual undeuterated solvent as an internal reference. Chemical shifts (δ) are reported in parts per million (ppm) and coupling constants (*J*) are reported in hertz (Hz). The following abbreviations are used to designate multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Mass spectra (MS) and high-resolution mass spectra (HRMS) were recorded on a Finnigan LCQDECA mass spectrometer under electrospray ionization (ESI) or atmospheric pressure chemical ionization (APCI) conditions, or on a Thermo-Finnegan Mat900XL mass spectrometer under electron

impact (EI), chemical ionization (CI), or fast atom bombardment (FAB) conditions. X-ray data were recorded on a Bruker SMART APEX CCD X-ray diffractometer. Specific optical rotations were recorded on a Jasco P-1010 polarimeter and the specific rotations were calculated based on the equation $[\alpha]^{25}_{D} = (100 \cdot \alpha)/(l \cdot c)$, where the concentration c is in g/100 mL and the path length *l* is in decimeters.

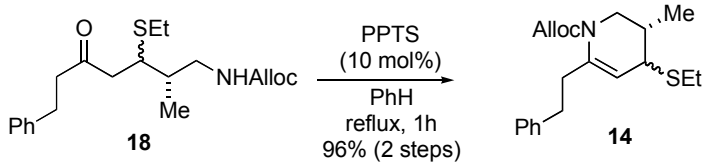
Procedures and Spectral Data



Allyl (*R*,*E*)-2-methyl-5-oxo-7-phenylhept-3-enylcarbamate 17: In a 10 mL round bottom flask was added β-ketophosphonate **15** (120 mg., 0.467 mmol, 1.0 equiv.), THF (2 mL) cooled to 0 ˚C, NaH (19 mg, 0.513 mmol, 1.1 equiv.) for 15 min, followed by aldehyde **16** (80 mg., 0.467mmol, 1 equiv.) and the reaction allowed to warm to room temperature. The reaction was quenched by addition of water and diluted with EtOAc. After separation, the aqueous phase was extracted 3x with EtOAc, the combined organics washed with brine, dried over Na_2SO_4, and concentrated to dryness. The crude material was purified over silica (2:1 Hexane:EtOAc, $R_f = 0.40$) to afford olefinic **17** (121 mg., 86% yield) as a colorless oil. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.26 (m, 2H), 7.18 (m, 3H), 6.27 (dd, *J* = 7.5, 16.0 Hz, 1H), 6.08 (d, *J* = 16.0 Hz, 1H), 5.91-5.85 (m, 1H), 5.26 (d, *J* = 17.0 Hz, 1H), 5.18 (d, *J* = 10.0 Hz, 1H), 4.72 (bs, 1H), 4.52 (d, *J* = 5.0 Hz, 2H), 3.22 (q, *J* = 6.0 Hz, 1H), 3.14-3.06 (m, 1H), 2.92 (t, *J* = 7.0 Hz, 2H), 2.85 (t, *J* = 7.0 Hz, 2H), 2.51 (q, *J* = 7.0 Hz, 1H), 1.04 (d, *J* = 6.5 Hz, 3H).

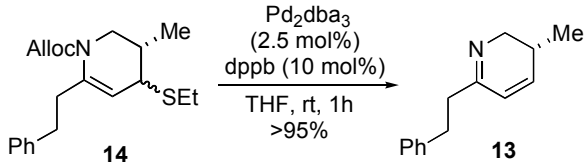


Allyl (*S*)-3-(ethylthio)-2-methyl-5-oxo-7-phenylheptylcarbamate 18: In a 10 mL round bottom flask containing *trans*-enone **17** (1.10 g, 3.65 mmol, 1.0 equiv.), ethanethiol (0.30 ml, 4.02 mmol, 1.1 equiv.) and DBU (5.5 µl, 0.365 mmol, 1 mol%) were added at room temperature. After stirring for 15 minutes, the excess ethanethiol was evaporated *in vacuo* and the resulting crude material **18** (1.326 g., 100% by ^{1}H-NMR) carried on into the next reaction. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.26 (t, 7.0 Hz, 2H), 7.16 (d, J = 8.0 Hz, 3H), 5.93-5.87 (m, 1H), 5.28 (d, J = 17.5 Hz, 1H), 5.19 (d, J = 10.5 Hz, 1H), 5.05 + 4.96 (bs, 1H), 5.34 (s, 2H), 3.29 (q, J = 6.0 Hz, 1H), 3.21-3.19 (m, 2H), 3.11-3.05 (m, 2H), 3.02-2.98 (m, 1H), 2.89 (t, J = 7.5 Hz, 2H), 2.81-2.71 (m, 2H), 2.62-2.57 (m, 2H), 1.95-1.85 (m, 1H), 1.18 (t, J = 7.5 Hz, 3H), 0.93 + 0.86 (d, J = 7.0 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 210.8, 170.4, 128.4, 128.3, 126.1, 117.6, 65.5, 47.7, 45.4, 45.2, 44.2, 43.5, 37.9, 37.5, 29.5, 26.7, 14.9, 14.4.



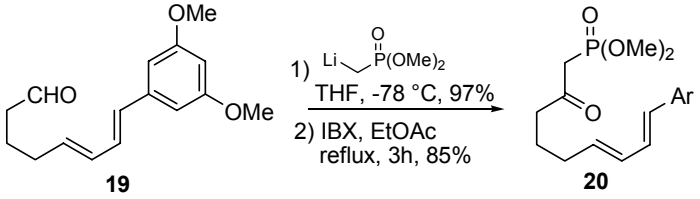
(*S*)-Allyl 4-(ethylthio)-3,4-dihydro-3-methyl-6-phenethylpyridine-1(2*H*)-carboxylate 14: To a 50 ml round bottom flask containing crude **18** (1.326 g, 3.65 mmol, 1.0 equiv.), PPTS (92 mg, 0.365 mmol, 10 mol%) and benzene (36 ml) were added, and

the resulting solution stirred at reflux for 1 hour. Upon cooling, the reaction was quenched by addition of sat. $NaHCO_3$. After separation, the aqueous phase was extracted 3x with EtOAc, the combined organics washed with brine, dried over Na_2SO_4, and concentrated to dryness. The crude material was purified over silica (5:1 Hexane:EtOAc, $R_f = 0.33$) to afford the masked dihydropyridine **14** (1.21 g., 96% yield over two steps) as a colorless oil. (1:1 dr): ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.24 (t, *J* = 9.2 Hz, 2H), 7.16 (m, 3H), 5.95 (m, 1H), 5.34 (dd, *J* = 17.2 Hz, 2H), 4.94 (d, *J* = 21.6 Hz, 1H), 4.64 (s, 2H), 3.75 (q, *J* = 12.8 Hz, 1H), 3.31 (m, 1H), 3.15 and 2.99 (dd, *J* = 12.4 Hz, 1H; m, 1H), 2.84 (t, *J* = 7.2 Hz, 2H), 2.69 (t, *J* = 7.2 Hz, 2H), 2.44 (p, *J* = 8.0 Hz, 2H), 2.12 and 1.92 (m, 1H), 1.20 (t, *J* = 8.0 Hz, 3H), 1.06 and 0.99 (d, *J* = 6.8 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 141.5, 139.9, 138.8, 132.5, 128.5, 128.4, 125.7, 118.1, 112.7, 66.4, 48.5, 45.1, 37.0, 34.7, 33.5, 26.5, 15.2, 14.9. HRMS: m/z calcd for $C_{20}H_{27}NO_2S$: 345.1757, found: 345.1755



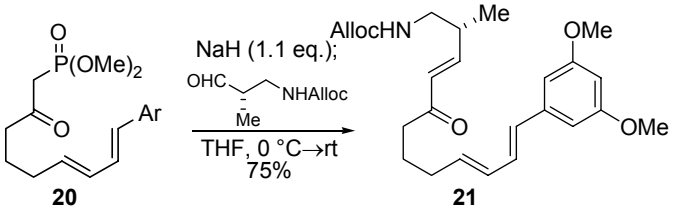
(*R*)-2,3-Dihydro-3-methyl-6-phenethylpyridine 13: To a 10 ml round bottom flask containing masked dihydropyridine **14** (20 mg., 0.058 mmol, 1.0 equiv.) in THF (0.6 mL) at room temperature, $Pd_2dba_3{\cdot}CHCl_3$ (1.33 mg., 0.00145 mmol, 2.5 mol%) and dppb (2.47 mg., 0.0058 mmol, 10 mol%) were added and the solution allowed to stir until the consumption of **14** was comfirmed by TLC, ~1 h. The solution was diluted with THF, filtered over celite, and evaporated *in vacuo* to give crude 2,3-dihydropyridine **13** in quantitative yield free of impurities other than 7.5 mol% dba. ^{1}H-NMR (400 MHz,

$CDCl_3$) δ 7.26 (t, 2H), 7.20 (m, 3H), 6.23 (dd, *J* = 3.5, 9.6 Hz, 1H), 5.88 (dd, *J* = 2.5, 10.0 Hz, 1H), 3.69 (dd, *J* = 7.0, 15.5 Hz, 1H), 3.16 (dd, *J* = 12.5, 16.0 Hz, 1H), 2.86 (t, *J* = 7.8 Hz, 2H), 2.56 (t, *J* = 8.8 Hz, 2H), 1.97 (m, 1H), 0.99 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.3, 142.7, 141.5, 128.6, 128.3, 125.9, 121.7, 53.4, 35.7, 32.6, 30.4, 17.3. HRMS: m/z calcd for $C_{14}H_{19}N$: 199.1356, found 199.1357.



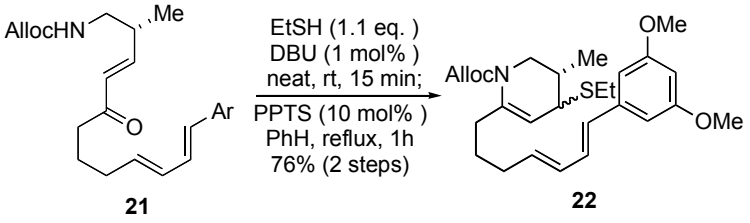
(6*E*, 8*E*)-9-(3,5-Dimethyoxyphenyl)-2-oxo dimethyl nonaphonsphonate 20: To a 100 ml round bottom flask containing dimethyl methylphosphonate (1.985 g., 16.0 mmol, 2.0 equiv.) and THF (47 ml) cooled to –78 ˚C, *n*-BuLi (1.3M, 6.78 ml, 1.1 equiv.) was added, and allowed to stir for 15 minutes, whereupon the addition of aldehyde **19** (2.085 g, 8.0 mmol, 1.0 equiv.) in THF (5 ml) was added. The reaction was allowed to stir warming to room temperature, whereupon the reaction was quenched by addition of water and diluted with EtOAc. After separation, the aqueous phase was extracted 3x with EtOAc, the combined organics washed with brine, dried over Na_2SO_4, and concentrated to dryness. The crude material was purified over silica (1% MeOH/DCM, R_f = 0.10) to afford the 2˚ alcohol **20** (2.983 g, 97% yield) as a colorless oil. Subsequent oxidation began by its dilution with EtOAc (52 mL) and the addition of IBX (6.518 g, 23.28 mmol, 3 equiv.), with the resulting solution refluxed for 3 hours. Upon cooling, the solution was filtered, evaporated *in vacuo*, and purified over silica silica (100% EtOAc, R_f = 0.33) to

afford β-ketophosphonate **20** (2.522 g, 85% yield) as a colorless oil. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 6.67 (dd, *J* = 10.0, 15.5, 1H), 6.49 (d, *J* = 2.0 Hz, 2H), 6.34 (d, *J* = 15.5 Hz, 1H), 6.30 (s, 1H), 6.16 (dd, *J* = 10.5, 15.0 Hz, 1H), 5.74 (dt, *J* = 7.0 Hz, 1H), 3.76 (s, 6H), 3.05 (d, *J* = 22.0 Hz, 2H), 2.61 (t, *J* = 7.0 Hz, 2H), 2.13 (q, *J* = 7.5, 14.5 Hz, 2H), 1.70 (q, *J* = 7.5 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 201.6, 160.8, 139.4, 134.6, 131.2, 130.4, 129.5, 55.2, 53.0, 43.2, 41.9, 40.6, 31.8, 22.7. MS $C_{19}H_{27}O_6P$: calcd [M] = 382.1540, obsd [M] = 382.1542.



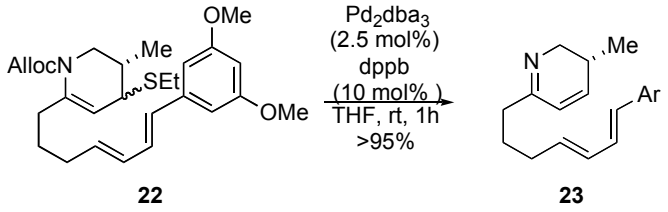
Allyl (*R*,3*E*,9*E*,11*E*)-12-(3,5-dimethoxyphenyl)-2-methyl-5-oxododeca-3,9,11-trienylcarbamate 21: To a 50 ml round bottom flask containing β-ketophosphonate **20** (2.12 g., 5.55 mmol, 1.0 equiv.), THF (22 mL) cooled to 0 ˚C, NaH (0.235 mg., 5.83 mmol, 1.1 equiv.) for 15 min, followed by the chiral aldehyde (0.95 g., 5.55 mmol, 1.0 equiv.) and the reaction allowed to warm to room temperature. The reaction was quenched by addition of water and diluted with EtOAc. After separation, the aqueous phase was extracted 3x with EtOAc, the combined organics washed with brine, dried over Na_2SO_4, and concentrated to dryness. The crude material was purified over silica (3:1 Hexane:EtOAc, R_f = 0.40) to afford olefinic **21** (1.78 g., 75% yield) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.71 (dd, *J* = 10.4, 15.2 Hz, 1H), 6.68 (dd, *J* = 8.0, 16.0 Hz, 1H), 6.52 (d, *J* = 2.0 Hz, 2H), 6.37 (d, *J* = 16.0 Hz, 1H), 6.34 (t, *J* = 2.4 Hz, 1H),

6.19 (dd, *J* = 10.8, 15.2 Hz, 1H), 6.10 (d, *J* = 15.6 Hz, 1H), 5.79 (dt, *J* = 7.2, 1H), 5.28 (d, *J* = 17.2 Hz, 5.19 (d, *J* = 10.4 Hz, 1H), 4.82 (bs, 1H), 4.53 (d, *J* = 5.6 Hz, 2H), 3.79 (s, 6H), 3.27-3.11 (m, 2H), 2.56 (t, *J* = 7.6 Hz, 2H), 2.17 (q, *J* = 7.6 Hz, 2H), 1.75 (q, *J* = 7.6 Hz, 2H), 1.07 (d, *J* = 6.8 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 200.2, 160.8, 156.2, 148.4, 139.5, 134.9, 132.7, 131.1, 130.4, 130.1, 129.6, 117.7, 104.2, 99.6, 65.6, 55.3, 45.7, 39.4, 37.4, 32.2, 23.4, 16.8. IR (film) = 2934, 1697, 1588, 1524, 1456, 1425, 1248, 1152. $[\alpha]_D^{25}$ = +187 (*c* = 0.1, MeOH). MS $C_{25}H_{33}NO_5$: calcd [M] = 427.24, obsd [M + H]$^+$ = 428.04.



(*S*)-Allyl 4-(ethylthio)-3,4-dihydro-6-((4*E*,6*E*)-7-(3,5-dimethoxyphenyl)hepta-4,6-dienyl)-3-methylpyridine-1(2*H*)-carboxylate 22: In a 5 ml round bottom flask containing *trans*-enone **21** (100 mg., 0.233 mmol, 1.0 equiv.), ethanethiol (19 µl, 0.256 mmol, 1.1 equiv.) and DBU (0.3 µl, 0.0023 mmol, 1 mol%) were added at room temperature. After stirring for 15 minutes, the excess ethanethiol was evaporated *in vacuo* and the resulting crude material (114 mg., 100% by ^{1}H-NMR) carried on into the next reaction. Diluted with benzene (4.7 mL), after the addition of PPTS (6.6 mg, 0.023 mmol, 10 mol%) the solution was refluxed for 1 hour, whereupon the reaction was quenched by addition of sat. $NaHCO_3$. After separation, the aqueous phase was extracted 3x with EtOAc, the combined organics washed with brine, dried over Na_2SO_4, and

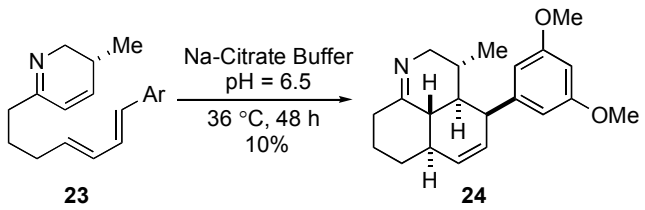
concentrated to dryness. The crude material was purified over silica (9:1 Hexane:EtOAc, $R_f = 0.25$) to afford masked dihydropyridine **22** (83 mg., 76% yield over two steps) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.71 (dd, *J* = 10.0, 15.2 Hz, 1H), 6.53 (d, *J* = 2.4 Hz, 2H), 6.37 (d, *J* = 15.6 Hz, 1H), 6.34 (t, *J* = 2.0 Hz, 1H), 6.19 (dd, *J* = 11.2, 15.2 Hz, 1H), 5.94 (m, 1H), 5.80 (dt, *J* = 8.8 Hz, 1H), 5.32 (d, *J* = 17.2 Hz, 1H), 5.23 (d, *J* = 10.4 Hz, 1H), 5.01 (d, *J* = 4.0 Hz, 1H), 4.62 (m, 2H), 3.80 (s, 6H), 3.73 (dd, *J* = 2.8, 12.8 Hz, 1H), 3.40 (m, 1H), 2.94 (t, *J* = 5.2 Hz, 1H), 2.58 (q, *J* = 7.6 Hz, 1H), 2.54 (q, *J* = 7.6 Hz, 1H), 2.11 (q, *J* = 8.0 Hz, 2H), 1.97 (m, 1H), 1.52 (q, *J* = 7.6 Hz, 2H), 1.25 (m, 3H), 1.01 (d, *J* = 6.8 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 199.2, 160.8, 140.4, 139.6, 135.7, 135.6, 132.4, 130.7, 130.1, 129.9, 118.0, 112.3, 104.1, 99.5, 66.4, 55.3, 49.0, 45.9, 34.7, 34.2, 32.1, 27.4, 24.1, 16.9, 14.9. MS $C_{27}H_{37}NO_4S$: calcd [M] = 471.24, obsd $[M + Na]^+ = 494.15$.



22 **23**

(*R*)-2,3-Dihydro-6-((4*E*,6*E*)-7-(3,5-dimethoxyphenyl)hepta-4,6-dienyl)-3-methylpyridine 23: To a 10 ml round bottom flask containing masked dihydropyridine **22** (30 mg, 0.0636 mmol, 1.0 equiv.) in THF (0.15 ml) at room temperature, $Pd_2dba_3{\cdot}CHCl_3$ (1.75 mg, 0.00159 mmol, 2.5 mol%) and dppb (2.77 mg, 0.00636 mmol, 10 mol%) were added and the solution allowed to stir until the consumption of **22** was comfirmed by TLC, ~1 h. The solution was diluted with THF, filtered over celite, and

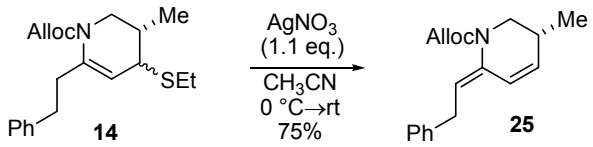
evaporated *in vacuo* to give crude 2,3-dihydropyridine **23** (21 mg) in quantitative yield free of impurities other than 7.5 mol% dba. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.71 (dd, *J* = 10.4, 15.2 Hz, 1H), 6.52 (s, 2H), 6.36 (d, *J* = 15.6 Hz, 1H), 6.33 (s, 1H), 6.20 (m, 2H), 5.87 (d, *J* = 9.6 Hz, 1H), 5.82 (dt, *J* = 7.2, 14.4 Hz, 1H), 3.80 (s, 6H), 3.66 (dd, 6.8, 15.6 Hz, 1H), 3.16 (dd, *J* = 12.0, 15.2 Hz, 1H), 2.56 (m, 1H), 2.29 (t, *J* = 7.6 Hz, 2H), 2.19 (m, 2H), 1.68 (q, *J* = 6.8 Hz, 2H), 1.01 (d, *J* = 7.2 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 160.8, 142.7, 139.6, 135.4, 130.8, 130.1, 129.8, 128.4, 121.6, 104.1, 99.5, 55.3, 38.3, 32.4, 30.3, 26.0, 17.3. MS $C_{21}H_{27}NO_2$: calcd [M] = 325.20, obsd $[M + H]^+$ = 326.26.



23 24

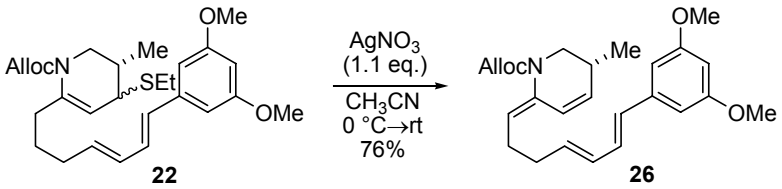
(3*R*,3a*R*,4*S*,4*S*,6a*R*)-3,3a,4,6a,7,8,9-Heptahydro-4-(3,5-dimethoxyphenyl)-3-methyl-2*H*-benzo[*de*]quinoline 24: To a 5 ml round bottom flask containing 2,3-dihydropyridine **23** (21 mg, 0.0636 mmol, 1.0 equiv.), a sodium citrate buffer solution (pH = 6.5, 1 mL) was added, stirring for 48 h at 36 ˚C. Upon cooling, the solution was quenched by the addition of sat. $NaHCO_3$ and diluted with EtOAc. After separation, the aqueous phase was extracted 3x with EtOAc, the combined organics washed with brine, dried over Na_2SO_4, and concentrated to dryness. The crude material was purified over silica (5% MeOH/DCM, R_f = 0.15) to afford the Diels-Alder cycloadduct **24** (2 mg., 10% yield) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.45 (d, *J* = 1.2 Hz, 2H), 6.35 (t, *J* = 2.0 Hz, 1H), 5.76 (d, *J* = 9.6 Hz, 1H), 5.66 (ddd, *J* = 1.6, 4.8, 10.0 Hz, 1H), 3.77 (s,

6H), 3.65 (t, *J* = 4.8 Hz, 1H), 3.58 (dd, *J* = 4.4, 17.6 Hz, 1H), 2.98 (dt, *J* = 2.9, 17.0 Hz, 1H), 2.37 (dt, *J* = 2.0, 12.4, 1H), 2.14 (t, *J* = 13.6 Hz, 1H), 2.05 (t, *J* = 5.6 Hz, 2H), 1.97-1.91 (m, 2H), 1.69-1.54 (m, 2H), 1.40 (dq, *J* = 4.0, 13.6, 1H), 1.12 (m, 1H), 1.02 (d, *J* = 6.0 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 171.5, 160.2, 142.5, 132.1, 129.6, 108.9, 97.8, 57.1, 55.2, 44.6, 43.3, 43.1, 40.4, 37.5, 31.9, 27.5, 25.8, 16.9. IR (film) 2932, 1589, 1488, 1457, 1425, 1204, 1153. $[\alpha]_D^{25}$ = +210 (*c* = 1.0, MeOH). MS $C_{21}H_{27}NO_2$: calcd [M] = 325.20, obsd $[M + H]^+$ = 326.18.



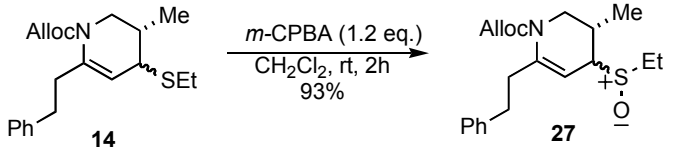
(*R*,2*E*)-Allyl 5,6-dihydro-5-methyl-2-(2-phenylethylidene)pyridine-1(2*H*)-carboxylate 25: To a 10 mL round bottom flask containing masked dihydropyridine **14** (28 mg., 0.081 mmol, 1.0 equiv.) and CH_3CN (1 mL) stirring at 0 ˚C was added silver nitrate (15.1 mg., 0.0891 mmol, 1.1 equiv.). The solution was allowed to warm to room temperature and stirred to completion, ~30 min. The solution was quenched by the addition of sat. $NaHCO_3$ and diluted with EtOAc. After separation, the aqueous phase was extracted 3x with EtOAc, the combined organics washed with brine, dried over Na_2SO_4, and concentrated to dryness. The crude material was purified over silica (3:1 hexanes:EtOAc, R_f = 0.45) to afford exo-olefinic **25** (17 mg., 75% yield) as a clear oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.29-7.14 (m, 5H), 6.41 (dd, *J* = 2.4, 10.0 Hz, 1H), 5.89 (m, 1H), 5.78-5.75 (m, 2H), 5.41 (d, *J* = 17.2 Hz, 1H), 5.15 (d, *J* = 10.0 Hz, 1H), 4.60 (d, *J* = 5.6 Hz, 2H), 4.01 (dd, *J* = 4.8, 13.2 Hz, 1H), 3.56 (m, 2H), 3.11 (dd, *J* = 8.0, 13.2 Hz,

1H), 3.56 (m, 2H), 3.11 (dd, *J* = 8.0, 12.8 Hz, 1H), 2.49 (m, 1H), 1.01 (d, *J* = 7.2 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 155.0, 140.2, 134.0, 132.8, 132.7, 128.4, 128.3, 126.0, 122.2, 120.2, 117.4, 66.2, 49.6, 32.7, 30.5, 17.7. HRMS $C_{18}H_{21}NO_2$: calcd [M] = 283.1567, obsd $[M]^+$ = 283.1569.

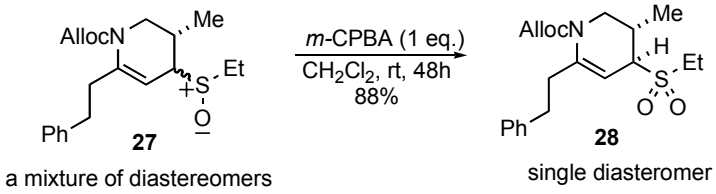


(*R*,2*E*)-Allyl 5,6-dihydro-2-((4*E*,6*E*)-7-(3,5-dimethoxyphenyl)hepta-4,6-dienylidene)-5-methylpyridine-1(2*H*)-carboxylate 26: To a screw cap vial containing masked dihydropyridine **22** (35.5 mg., 0.075 mmol, 1.0 equiv.) in CH_3CN (1 mL) at 0 ˚C was added silver nitrate (14.0 mg., 0.0825 mmol, 1.1 equiv.). After warming to room temperature, the solution was quenched by the addition of sat. $NaHCO_3$ and diluted with EtOAc. After separation, the aqueous phase was extracted 3x with EtOAc, the combined organics washed with brine, dried over Na_2SO_4, and concentrated to dryness. The crude material was purified over silica (2:1 hexanes:EtOAc, R_f = 0.40) to afford exo-olefinic **26** (23 mg., 76% yield) as a clear oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.70 (dd, *J* = 11.0, 15.5 Hz, 1H), 6.51 (d, *J* = 2.0 Hz, 2H), 6.36 (d, *J* = 15.0 Hz, 1H), 6.32 (t, *J* = 1.5 Hz, 1H), 6.29 (d, *J* = 10.0 Hz, 1H), 6.20 (dd, *J* = 10.5, 15.0 Hz, 1H), 5.92 (m, 1H), 5.83 (dt, *J* = 7.0, 14.0 Hz, 1H), 5.70 (d, *J* = 10.5 Hz, 1H), 5.61 (s, 1H), 5.28 (d, *J* = 17.0 Hz, 1H), 5.18 (d, *J* = 10.5 Hz, 1H), 4.60 (d, *J* = 5.0 Hz, 2H), 3.97 (dd, *J* = 4.5, 12.5 Hz, 1H), 3.77 (s, 6H), 3.07 (dd, *J* = 8.5, 13.0 Hz, 1H), 2.46 (s, 1H), 2.34-2.24 (m, 4H), 0.98 (d, *J* = 7.5 Hz, 3H);

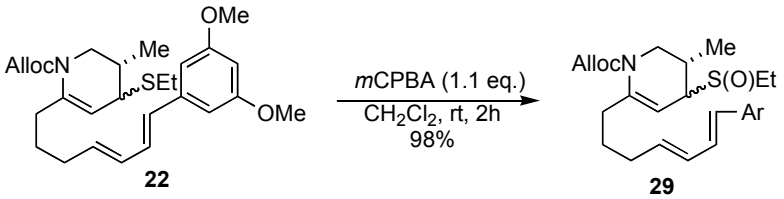
^{13}C-NMR (100 MHz, $CDCl_3$) δ 160.8, 152.7. 139.5, 134.8, 133.3, 132.9, 132.3, 130.0, 130.3, 129.7, 117.2, 104.4, 104.1, 99.5, 66.1, 55.2, 49.6, 32.9, 30.4, 26.6, 17.7.



(*S*)-Allyl 4-(ethylsulfinyl)-3,4-dihydro-3-methyl-6-phenethylpyridine-1(2*H*)-carboxylate 27: *m*-CPBA (30.0 mg., 0.174 mmol, 1.2 equiv.) was added to a 10 mL round bottom flask containing a room temperature solution of masked dihydropyridine **14** (50 mg., 0.145 mmol, 1.0 equiv.) in dichloromethane (1.5 mL). The reaction was allowed to stir to completion, ~2h, whereupon the solution was quenched by the addition of sat. $NaHCO_3$ and diluted with EtOAc. After separation, the aqueous phase was extracted 3x with EtOAc, the combined organics washed with brine, dried over Na_2SO_4, and concentrated to dryness. The crude material was purified over silica (1:1 hexanes:EtOAc, R_f = 0.35) to afford sulfoxide **27** (48.7 mg., 93% yield) as a mixture of diastereomers. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.25-7.05 (m, 5H), 5.97-5.89 (m, 1H), 5.36-5.20 (m, 2H), 4.96 + 4.91 (d, *J* = 3.6 Hz, 1H), 4.66-4.60 (m, 2H), 4.41 (t, *J* = 3.6 Hz, 1H), 3.82-3.73 (m, 1H), 3.56-3.42 (m, 1H), 3.4003.10 (m, 1H), 3.0802.98 (m, 2H), 2.89-2.21 (m, 4H), 1.32-1.19 (m, 3H), 1.02 (t, *J* = 6.8 Hz, 3H).



(3*S*,4*R*)-Allyl 4-(ethylsulfonyl)-3,4-dihydro-3-methyl-6-phenethylpyridine-1(2*H*)-carboxylate 28: *m*-CPBA (550.0 mg., 3.183 mmol, 2.2 equiv.) was added to a 25 mL round bottom flask containing a room temperature solution of masked dihydropyridine **14** (500 mg., 1.447 mmol, 1.0 equiv.) in dichloromethane (14.5 mL). The reaction was allowed to stir overnight, whereupon the solution was quenched by the addition of sat. $NaHCO_3$ and diluted with EtOAc. After separation, the aqueous phase was extracted 3x with EtOAc, the combined organics washed with brine, dried over Na_2SO_4, and concentrated to dryness. The crude material was purified over silica (1:1 hexanes:EtOAc, $R_f = 0.55$) to afford sulfone **28** (473 mg., 88% yield) as a single diastereomer. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.27-7.10 (m, 5H), 6.0-5.88 (m, 1H), 5.33 (d, $J = 17.1$ Hz, 1H), 5.26 (d, $J = 10.2$ Hz, 1H), 4.95 (d, $J = 3.9$ Hz, 1H), 4.65 (d, $J = 5.7$ Hz, 2H), 3.57-3.45 (m, 2H), 3.16-3.07 (m, 2H), 2.83-2.69 (m, 3H), 2.62 (dq, $J = 1.8, 7.5, 15.0$ Hz, 2H), 2.52-2.46 (m, 1H), 1.28 (t, $J = 7.5$ Hz, 3H), 1.08 (d, $J = 6.6$ Hz, 3H).



(*S*)-Allyl 4-(ethylsulfoxide)-3,4-dihydro-6-((4*E*,6*E*)-7-(3,5-dimethoxyphenyl)hepta-4,6-dienyl)-3-methylpyridine-1(2*H*)-carboxylate 29: *m*-

CPBA (5.4 mg., 0.033 mmol, 1.1 equiv.) was added to a screw cap vial containing a room temperature solution of masked dihydropyridine **22** (14 mg., 0.030 mmol, 1.0 equiv.) in dichloromethane (0.2 mL). The reaction was allowed to stir for 4h, whereupon the solution was quenched by the addition of sat. $NaHCO_3$ and diluted with EtOAc. After separation, the aqueous phase was extracted 3x with EtOAc, the combined organics washed with brine, dried over Na_2SO_4, and concentrated to dryness. The crude material was purified over silica (2:1 hexanes:EtOAc, $R_f = 0.05$) to afford sulfoxide **29** (11.7 mg., 98% yield) as a mixture of diastereomers. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.61 (m, 1H), 6.49 (s, 2H), 6.33 (m, *J* = 15.5 Hz, 1H), 6.33 (s, 1H), 6.14 (m, 1H), 5.89 (m, 1H), 5.76 (m, 1H), 5.29 (d, *J* = 16.5 Hz, 1H), 5.21 (d, *J* = 7.5 Hz, 1H), 5.01 (s, 1H), 4.59 (s, 2H), 3.77 (s, 6H), 3.64-3.52 (m, 1H), 2.99 + 2.91 (s, 1H), 2.79-2.57 (m, 3H), 2.46 (bs, 1h), 2.10 (bt, 2H), 1.52 (t, *J* = 7.0 Hz, 2H), 1.36-1.32 (m, 3H), 1.24 (m, 1H), 1.04 (m, 3H). MS $C_{27}H_{37}NO_5S$: calcd [M] = 487.24, obsd $[M + Na]^+ = 509.97$.

J. References and Notes

[1] (a) Baldwin, J.E.; Spring, D.R.; Whitehead, R.C., *Tetrahderon Lett.* **1998**, *39*, 5417-5420. (b) Baldwin, J.E.; Claridge, T.D.W.; Culshaw, A.J.; Heupel, F.A.; Lee, V.; Spring, D.R.; Whitehead, R.C., *Chem. Eur. J.* **1999**, *5*, 3154-3161. (c) Jakubowicz, K.; Abdeljelil, K.B.; Herdemann, M.; Martin, M.-T.; Gateau-Olesker, A.; Al-Mourabit, A.; Marazano, C.; Das, B.C., *J. Org. Chem.* **1999**, *64*, 7381-7387. (d) Herdemann, M.; Al-Mourabit, A.; Martin, M.-T.; Marazano, C., *J. Org. Chem.* **2002**, *67*, 1890-1897. (e) Ruggeri, R.B.; Hansen, M.M.; Heathcock, C.H. *J. Am. Chem. Soc.* **1988**, *110*, 8734-8736.

[2] Jones, G. Pyridines and their benzoderivatives: synthesis. In Comprehensive Hetereocyclic Chemistry II; Katritzky, A.; Rees, C.W.; Scriven, E.F.V.; Eds.; Pergamon: Oxford, 1996, 5, 167-243.

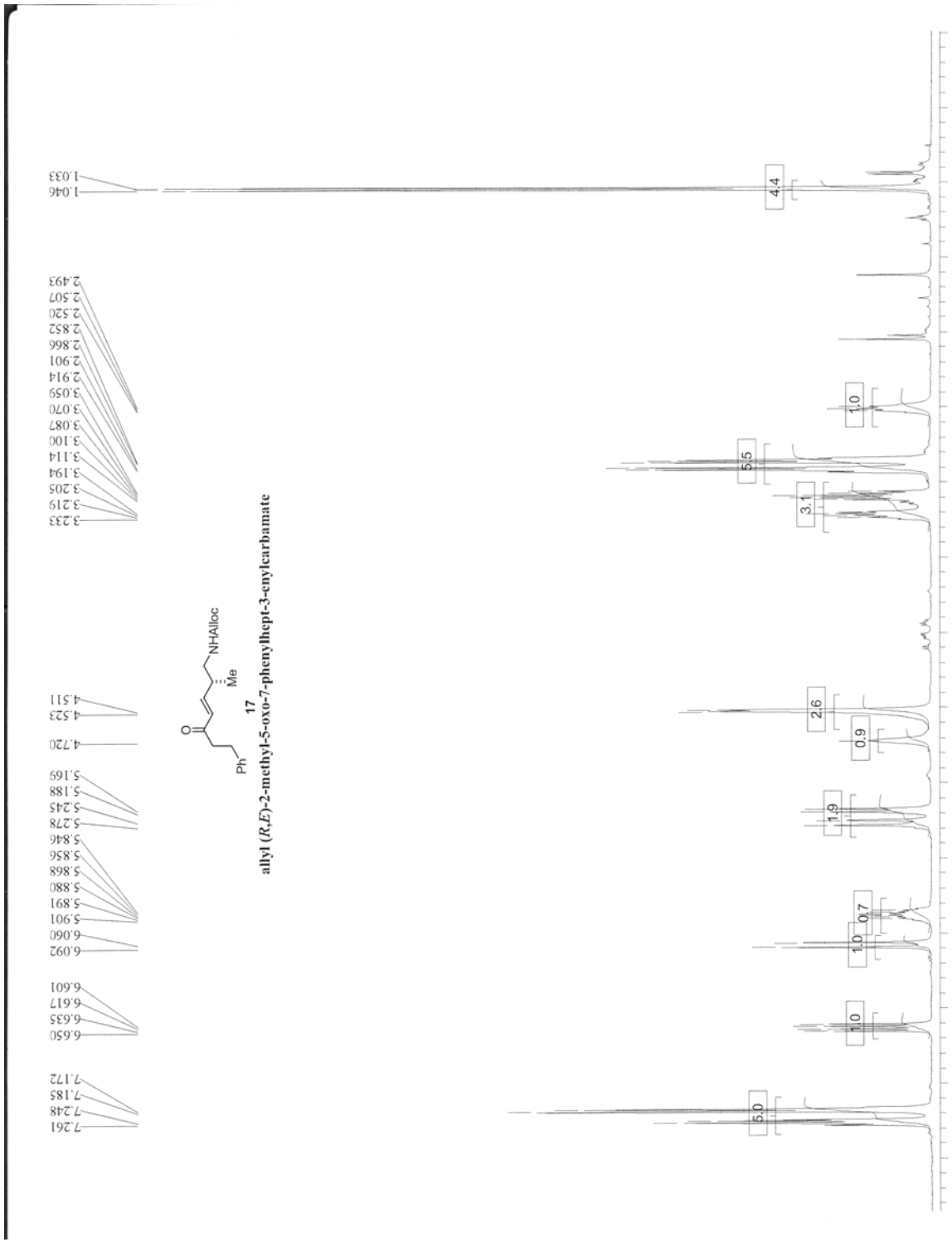
[3] (a) Hasan, I.; Fowler, F.W., *J. Am. Chem. Soc.* **1978**, *100*, 6696-6699. (b) Lasne, M.; Ripoll, J.; Guillemin, J.; Denis, J. *Tetrahedron Lett.* **1984**, *35*, 3847-3848.

[4] Under thermal (>100 °C), Bronsted/Lewis acid (TfOH, TFA, CSA/TsOH, BF_3OEt, $MeAlCl_2$, Et_2AlCl, $EtAlCl_2$, etc), basic (NaOEt, NaOH, LDA, etc.), or nucleophilic conditions (dimedone, piperidine, NaSEt, etc.).

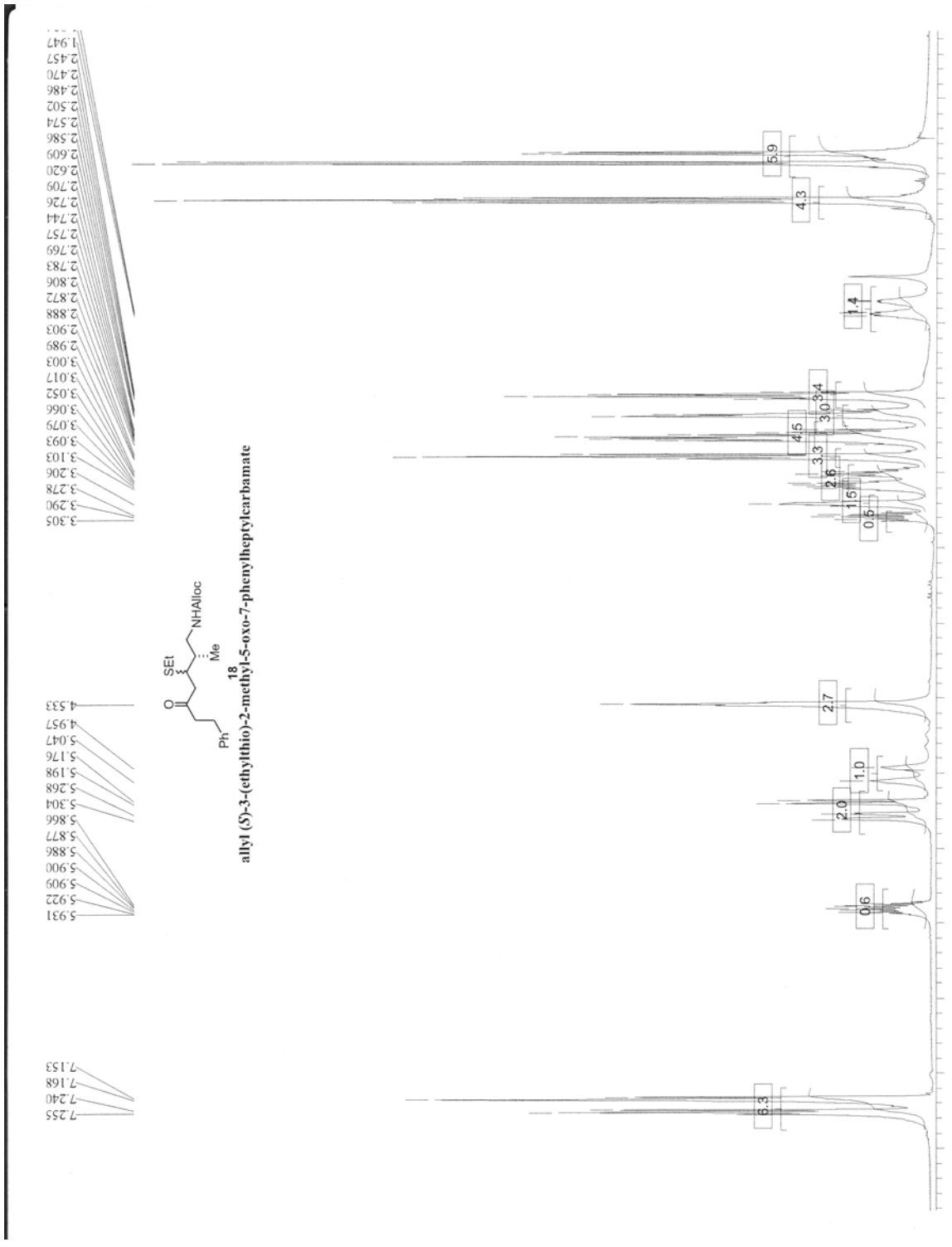
Chapter 3

Selected Spectra

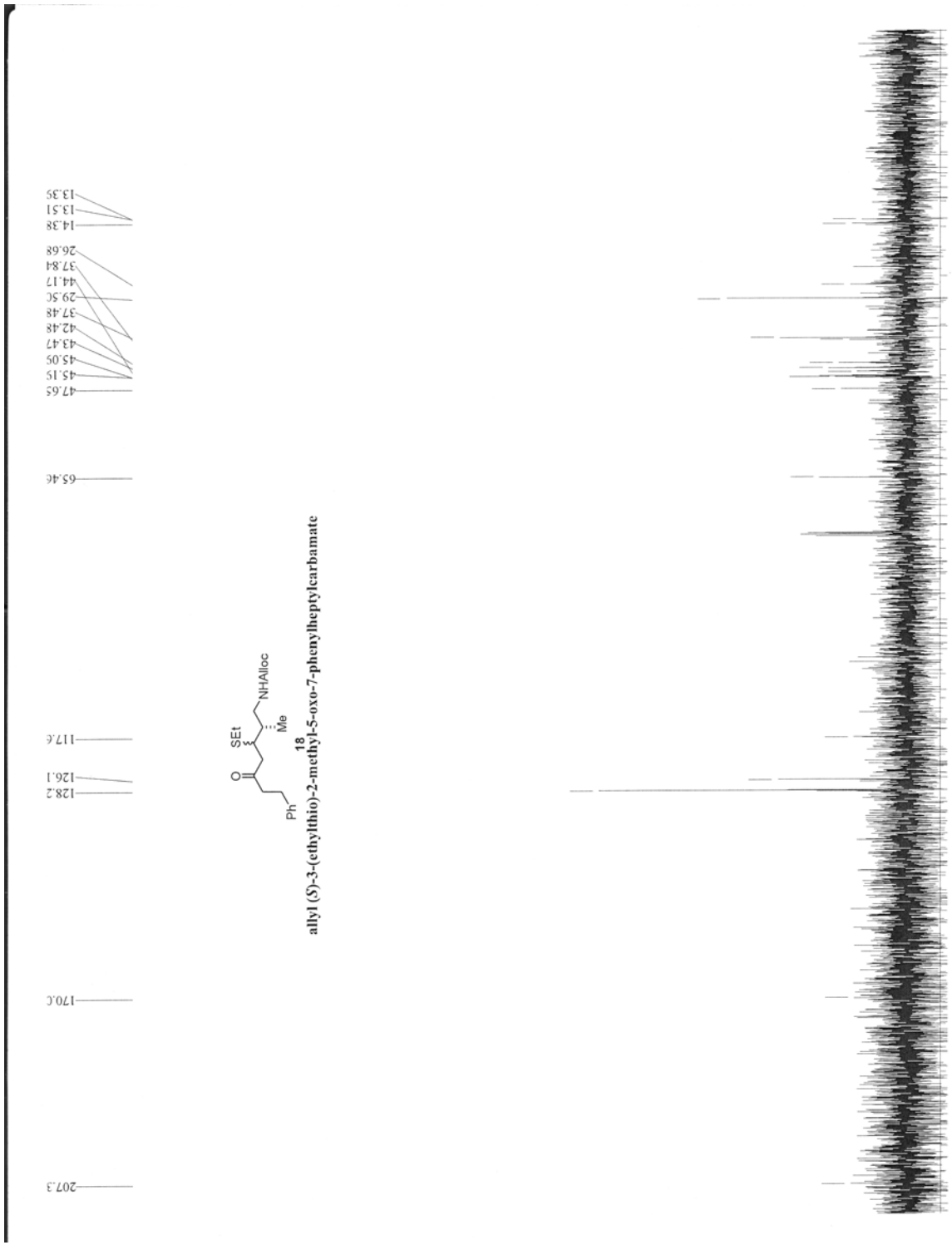
Spectrum Page



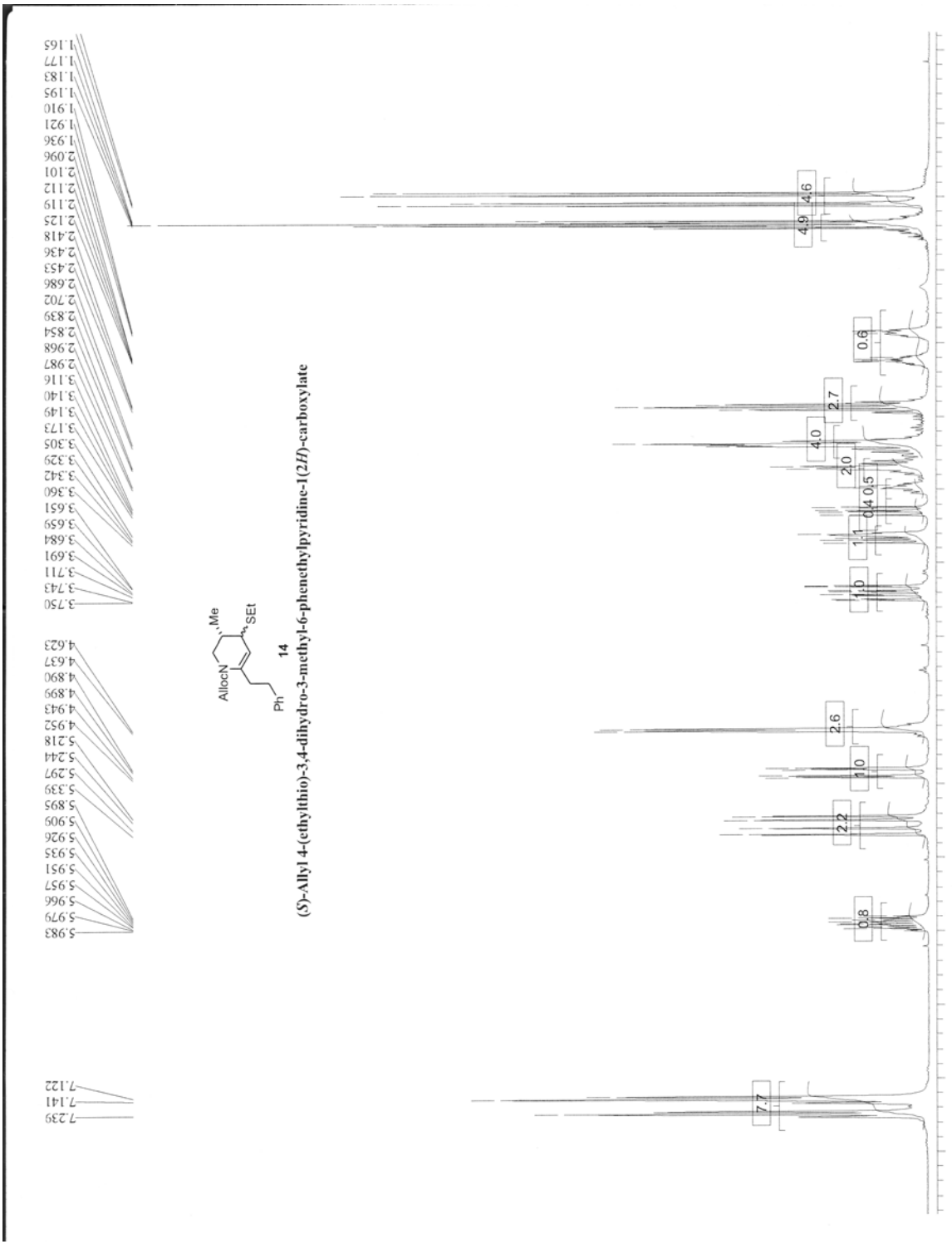
Spectrum 41. ^{1}H NMR spectrum of compound **17** in $CDCl_3$



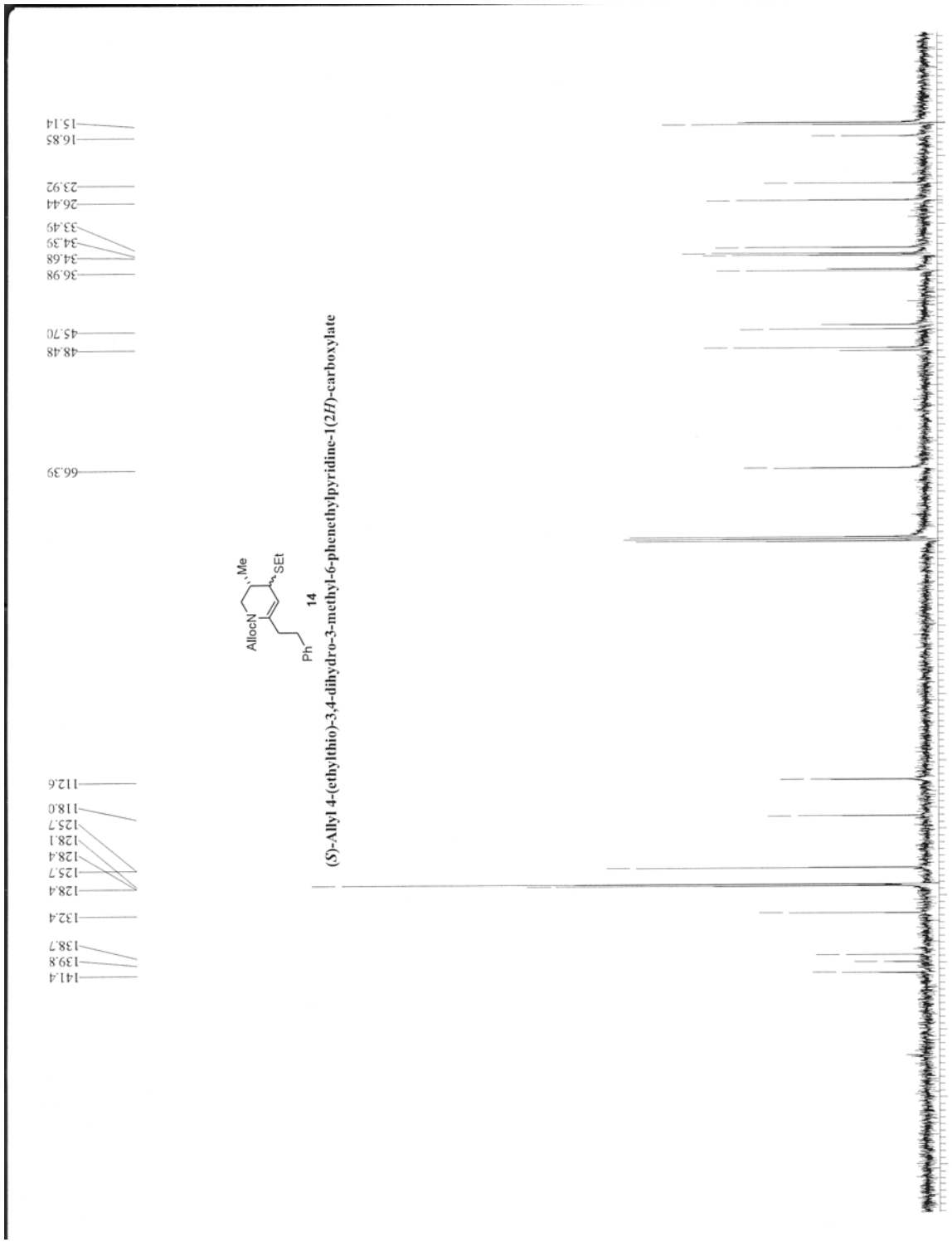
Spectrum 42. ^{1}H NMR spectrum of compound **18** in $CDCl_3$



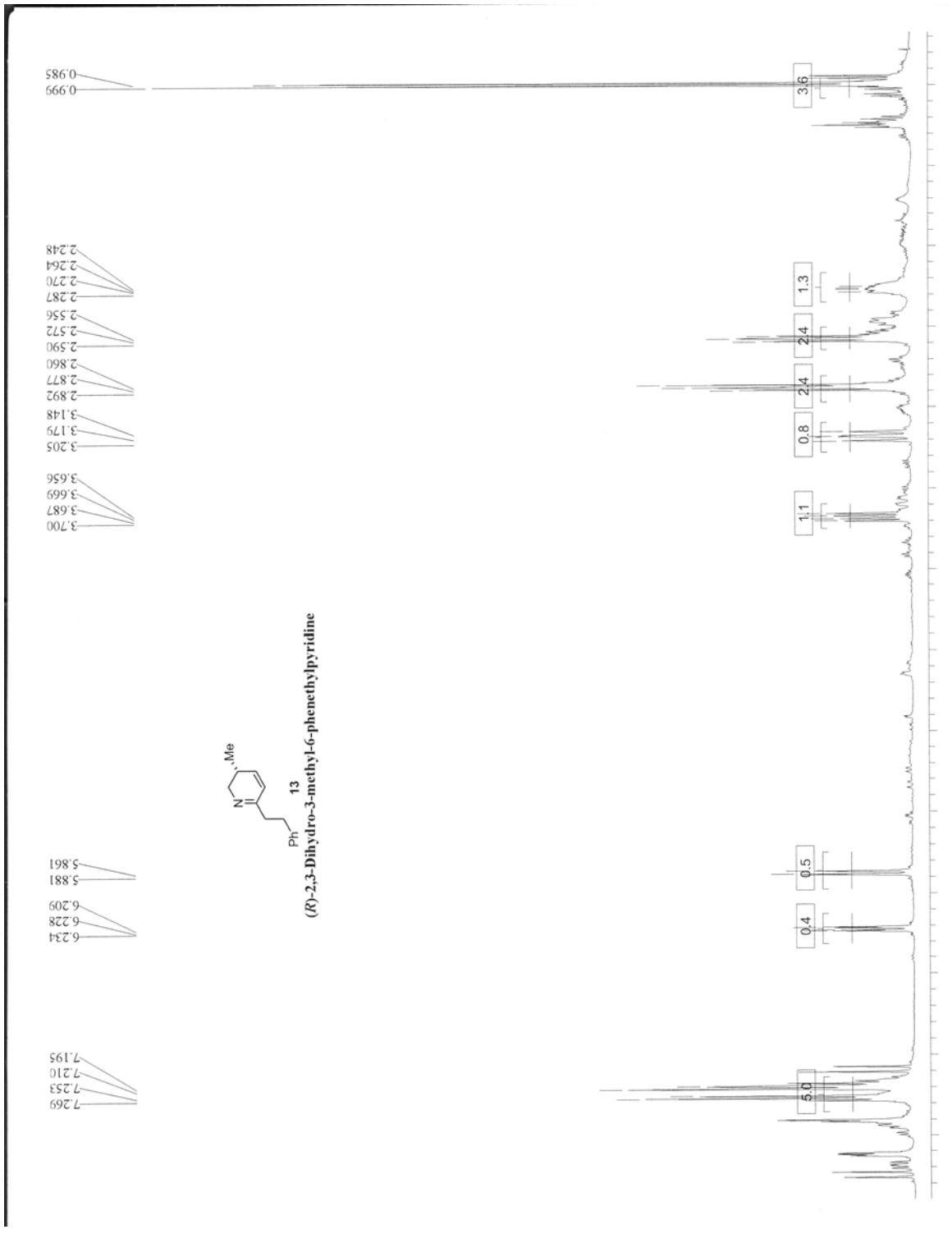
Spectrum 43. ^{13}C NMR spectrum of compound **18** in $CDCl_3$



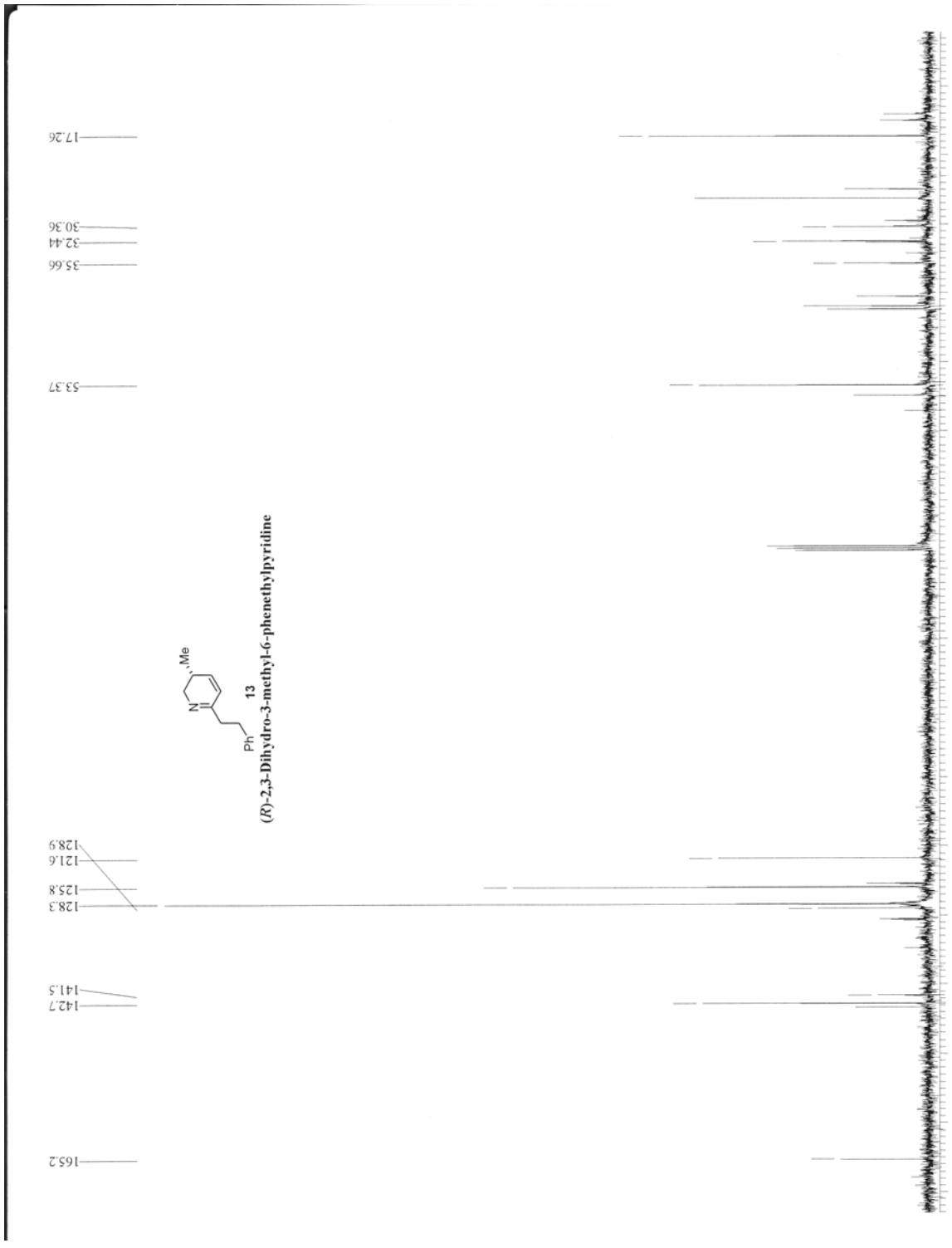
Spectrum 44. ^{1}H NMR spectrum of compound **14** in $CDCl_3$



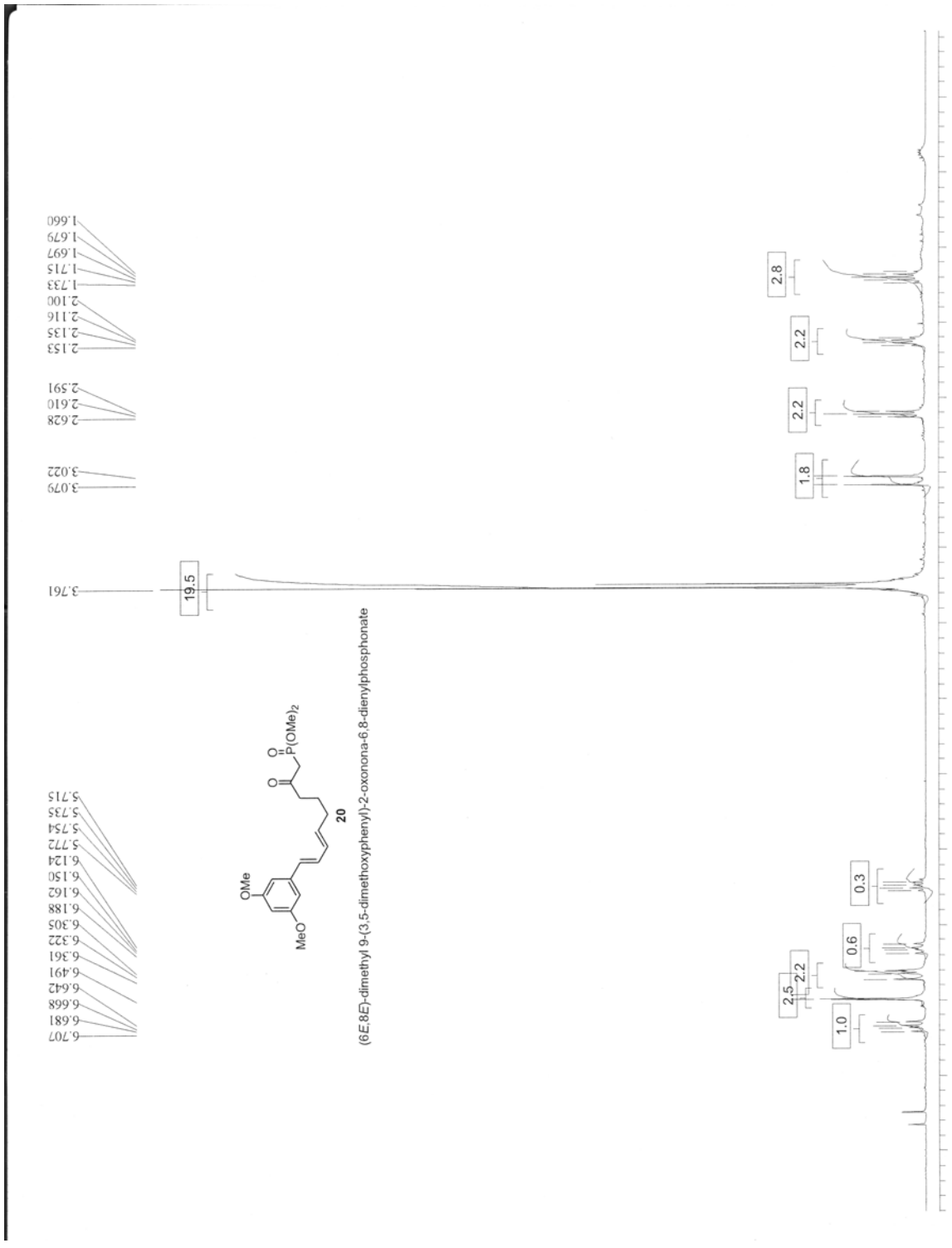
Spectrum 45. ^{13}C NMR spectrum of compound **14** in $CDCl_3$



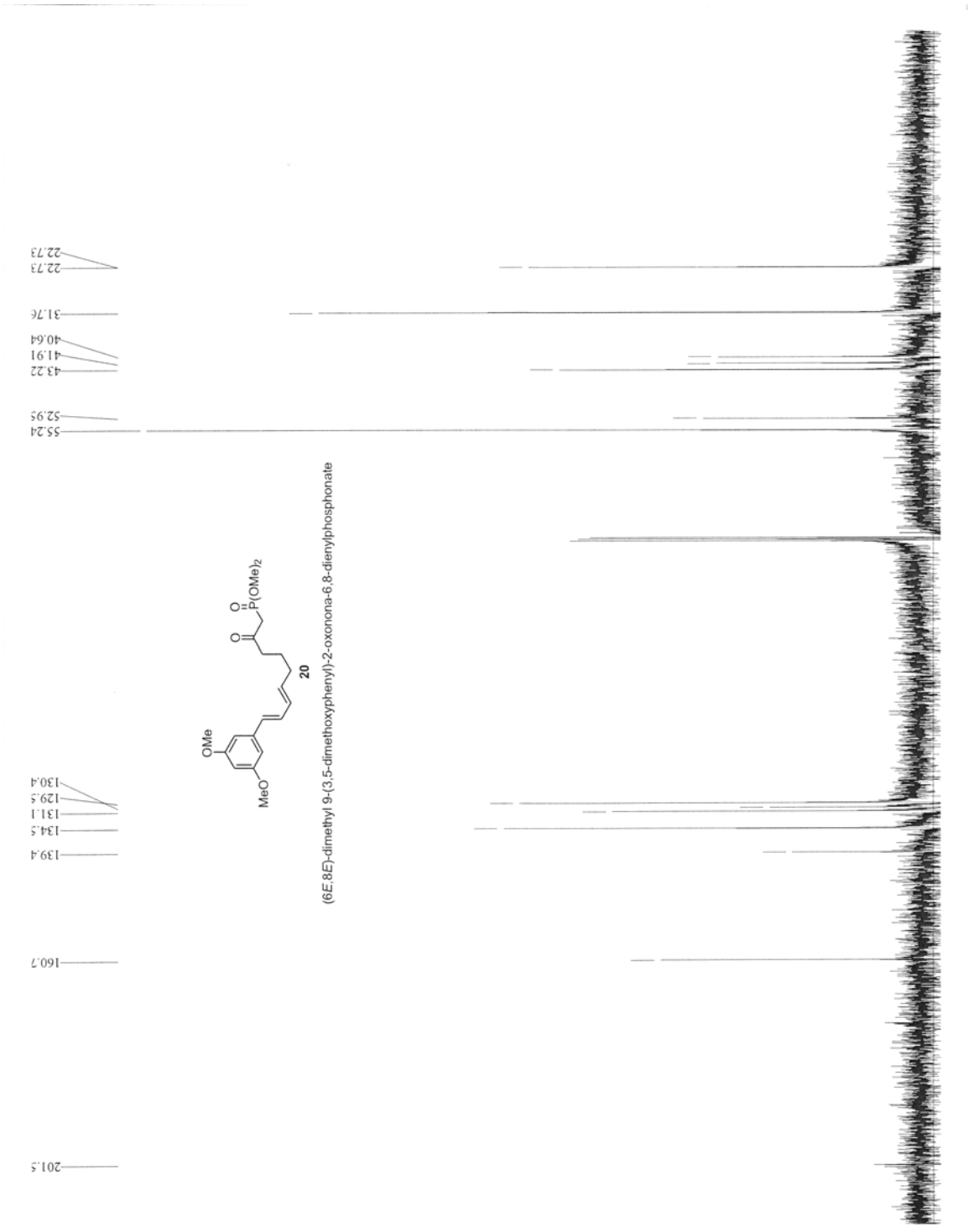
Spectrum 46. ^{1}H NMR spectrum of compound **13** in $CDCl_3$



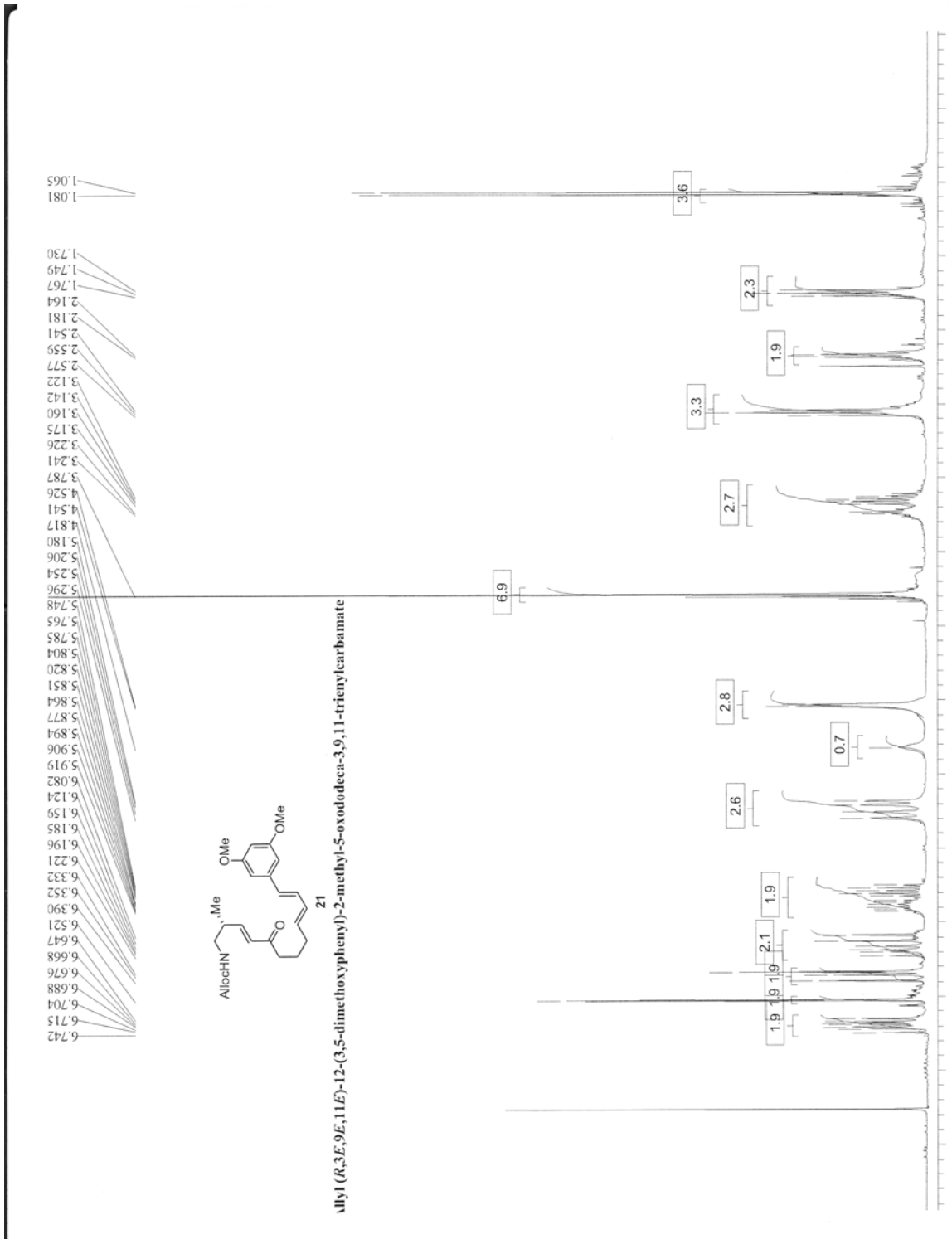
Spectrum 47. ^{13}C NMR spectrum of compound **13** in $CDCl_3$



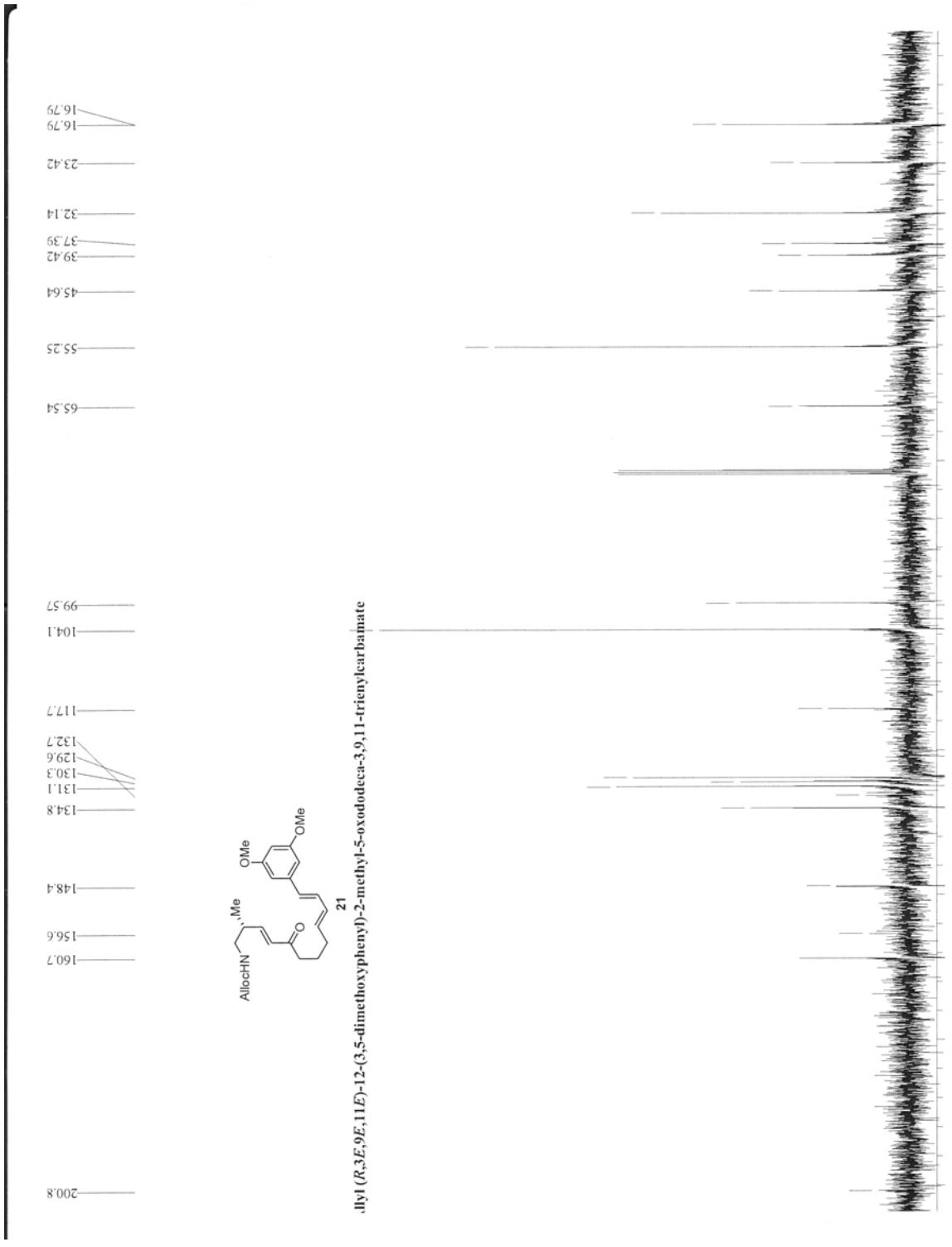
Spectrum 48. ^{1}H NMR spectrum of compound **20** in $CDCl_3$



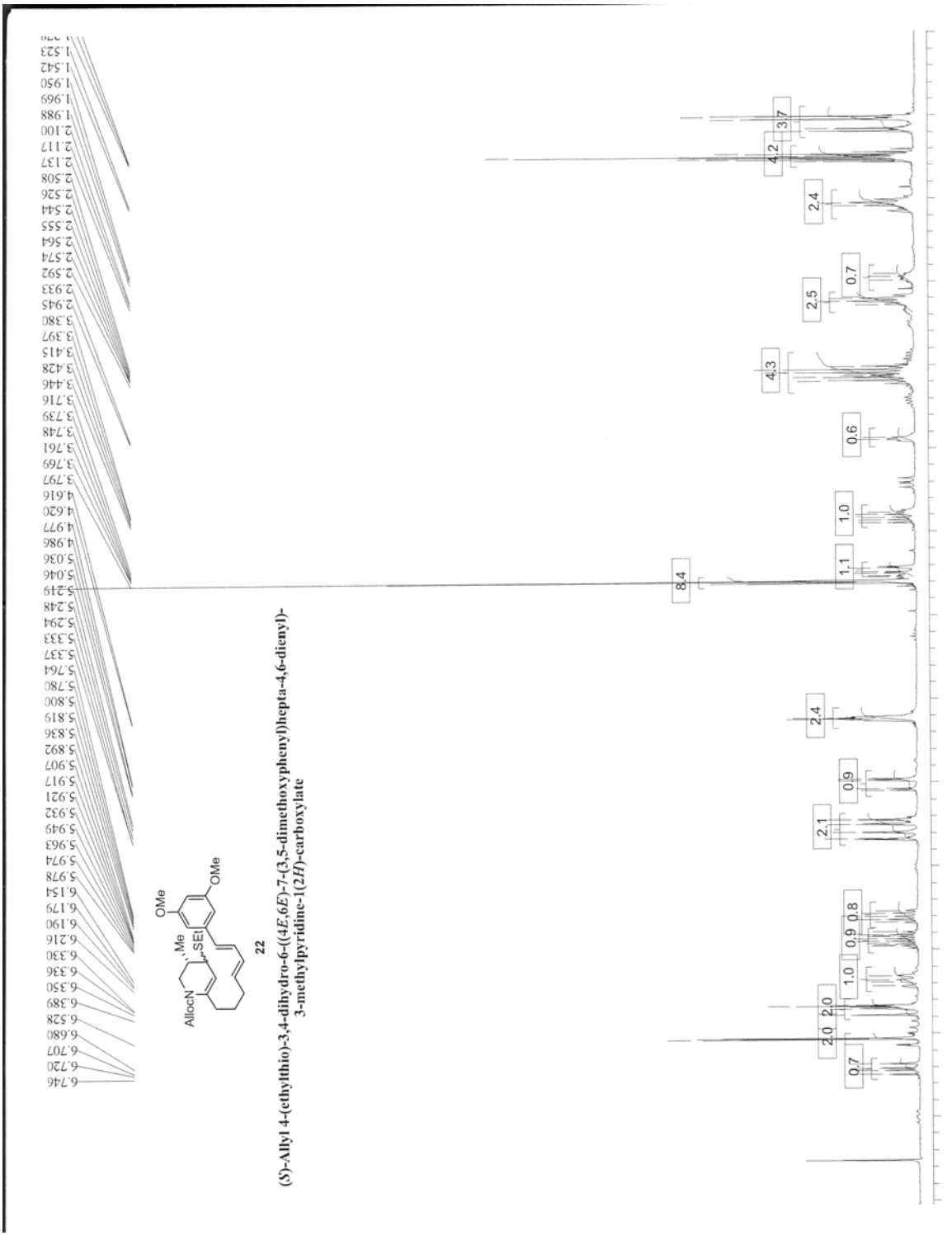
Spectrum 49. ^{13}C NMR spectrum of compound **20** in $CDCl_3$



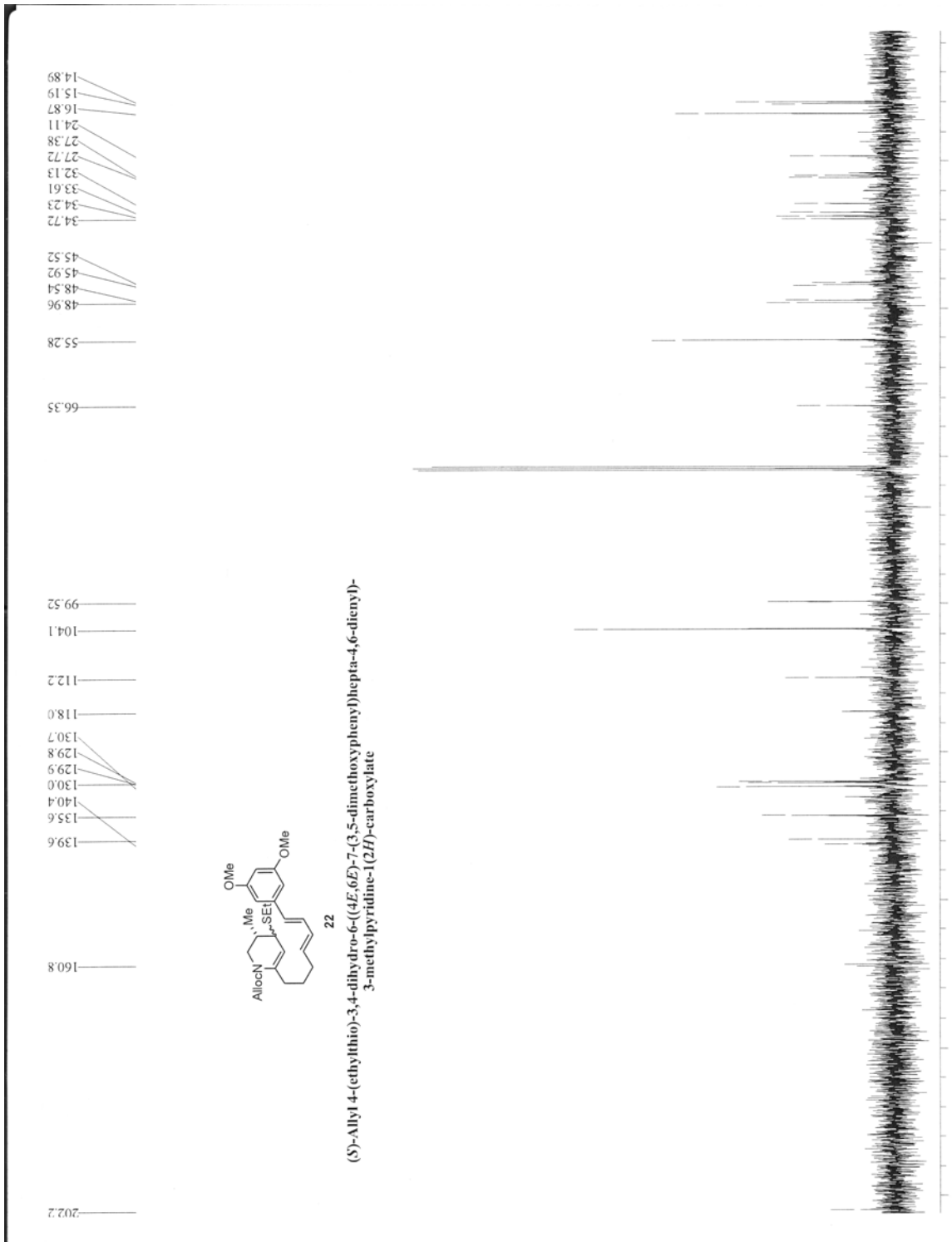
Spectrum 50. ^{1}H NMR spectrum of compound **21** in $CDCl_3$



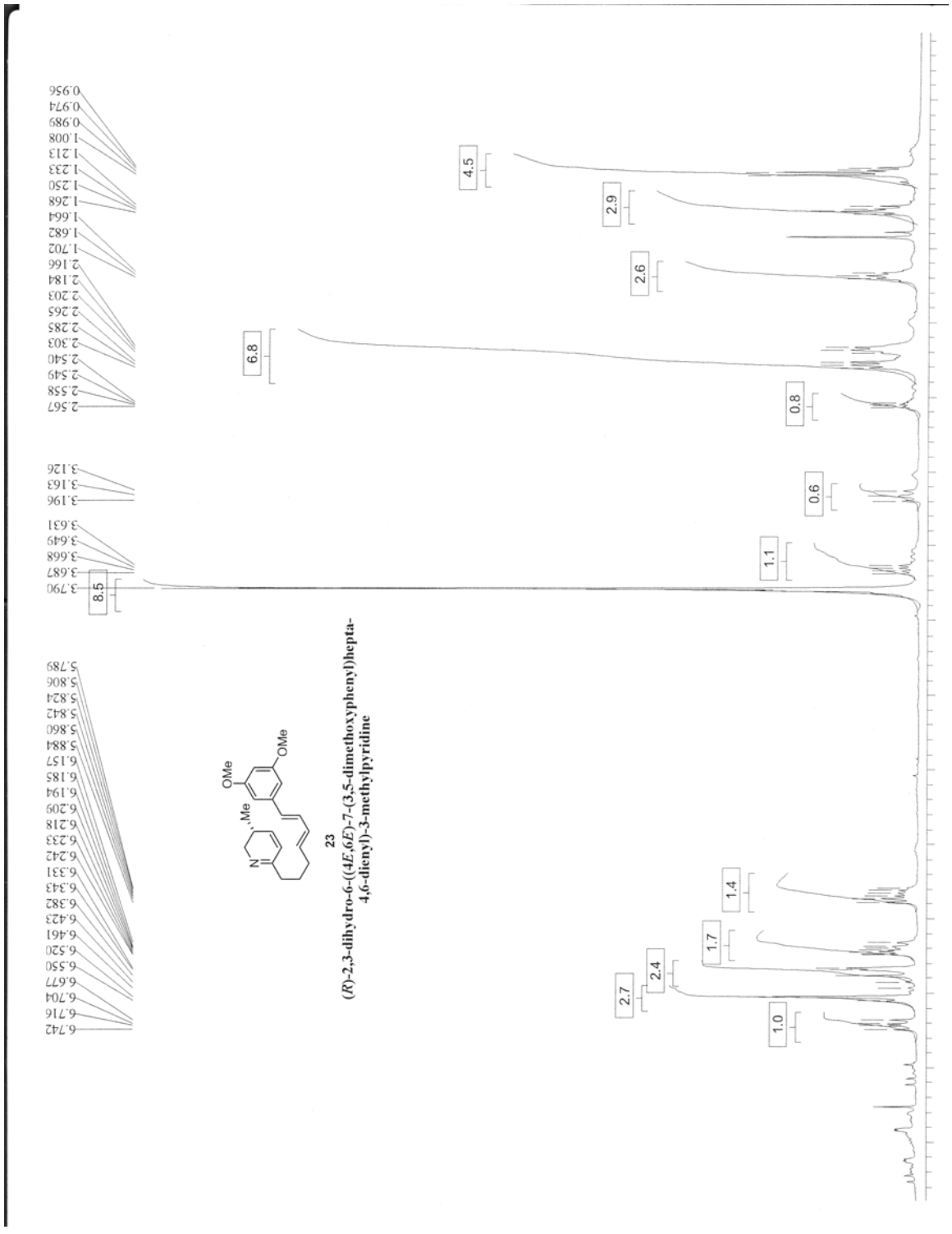
Spectrum 51. ^{13}C NMR spectrum of compound **21** in $CDCl_3$



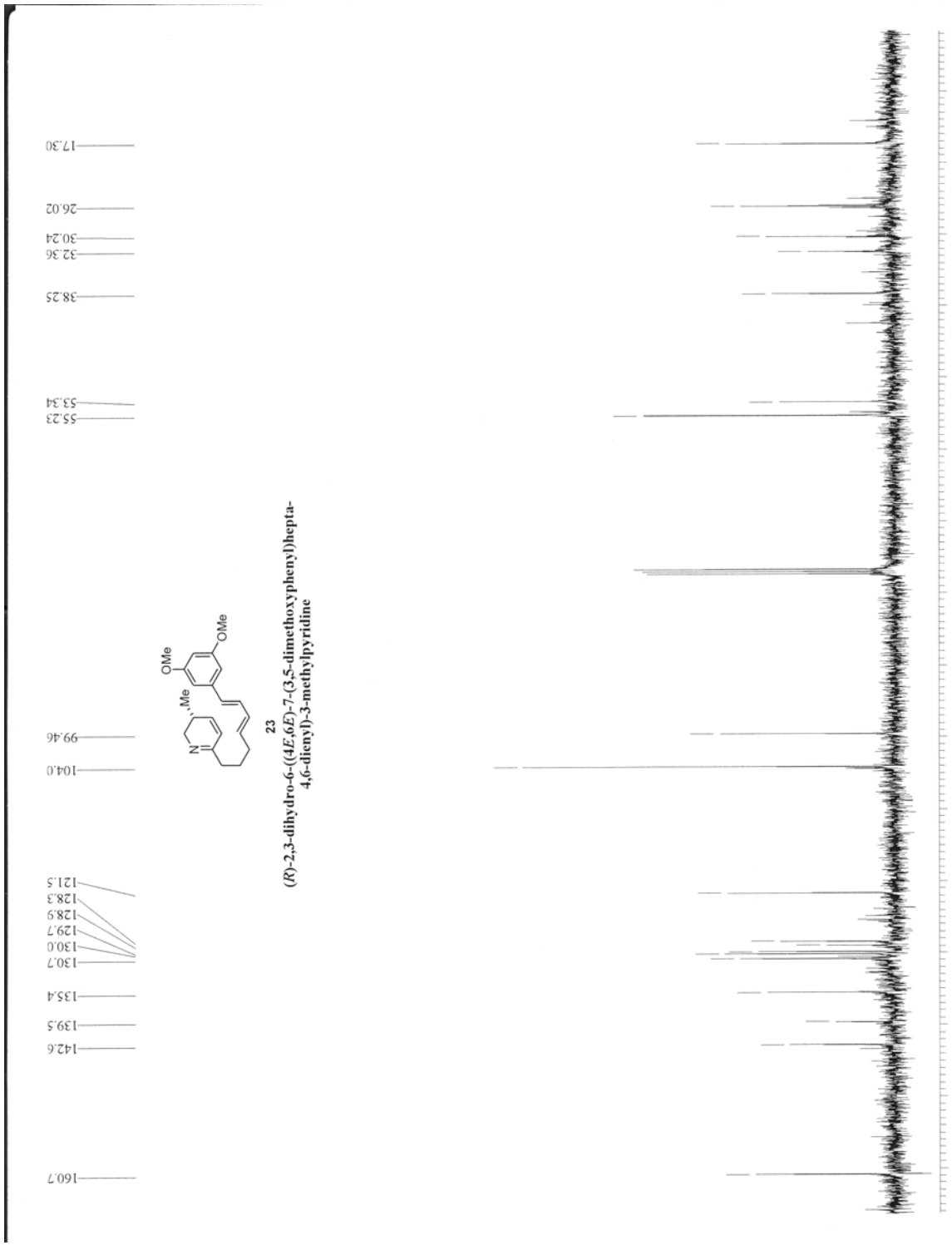
Spectrum 52. ^{1}H NMR spectrum of compound **22** in $CDCl_3$



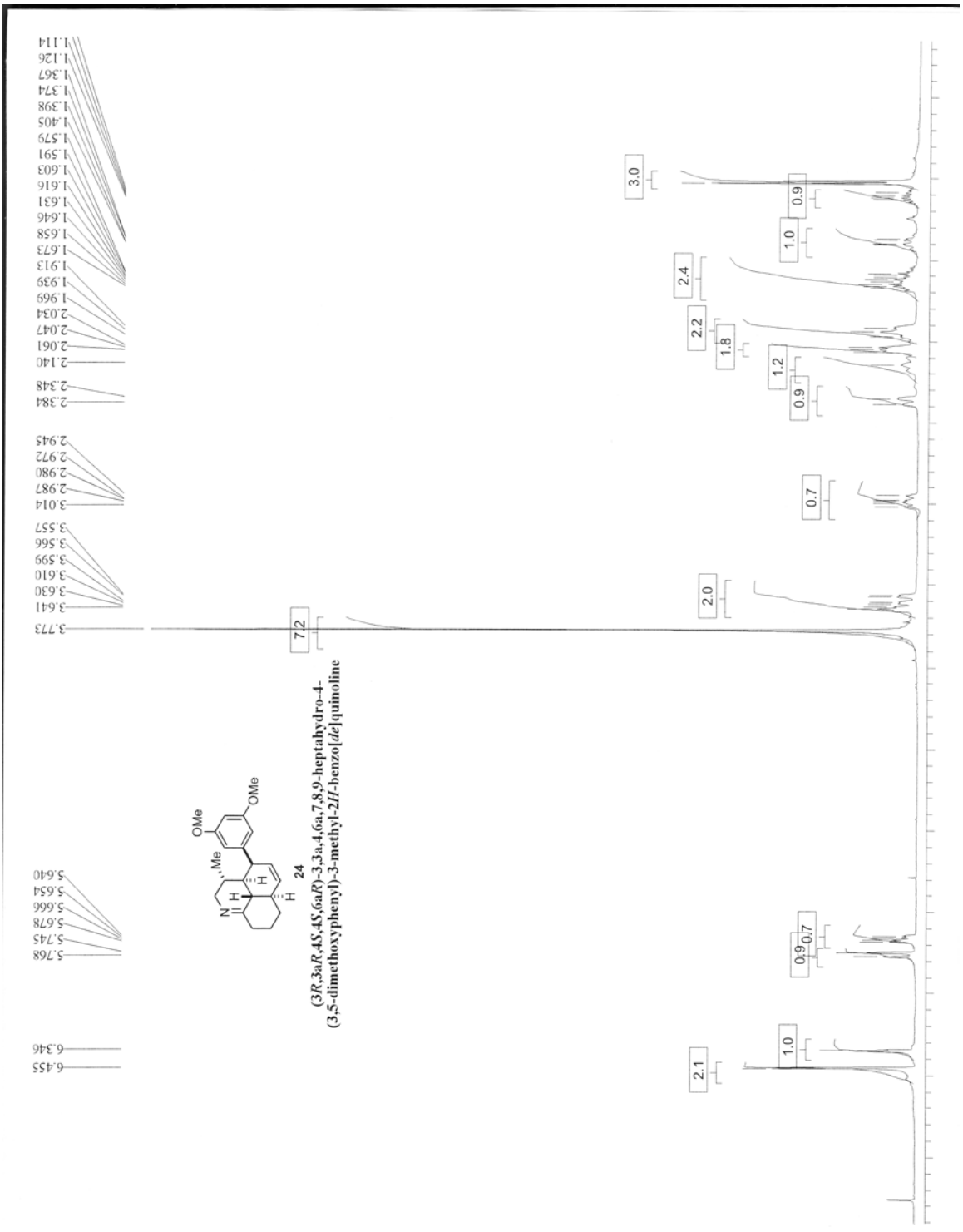
Spectrum 53. ^{13}C NMR spectrum of compound **22** in $CDCl_3$



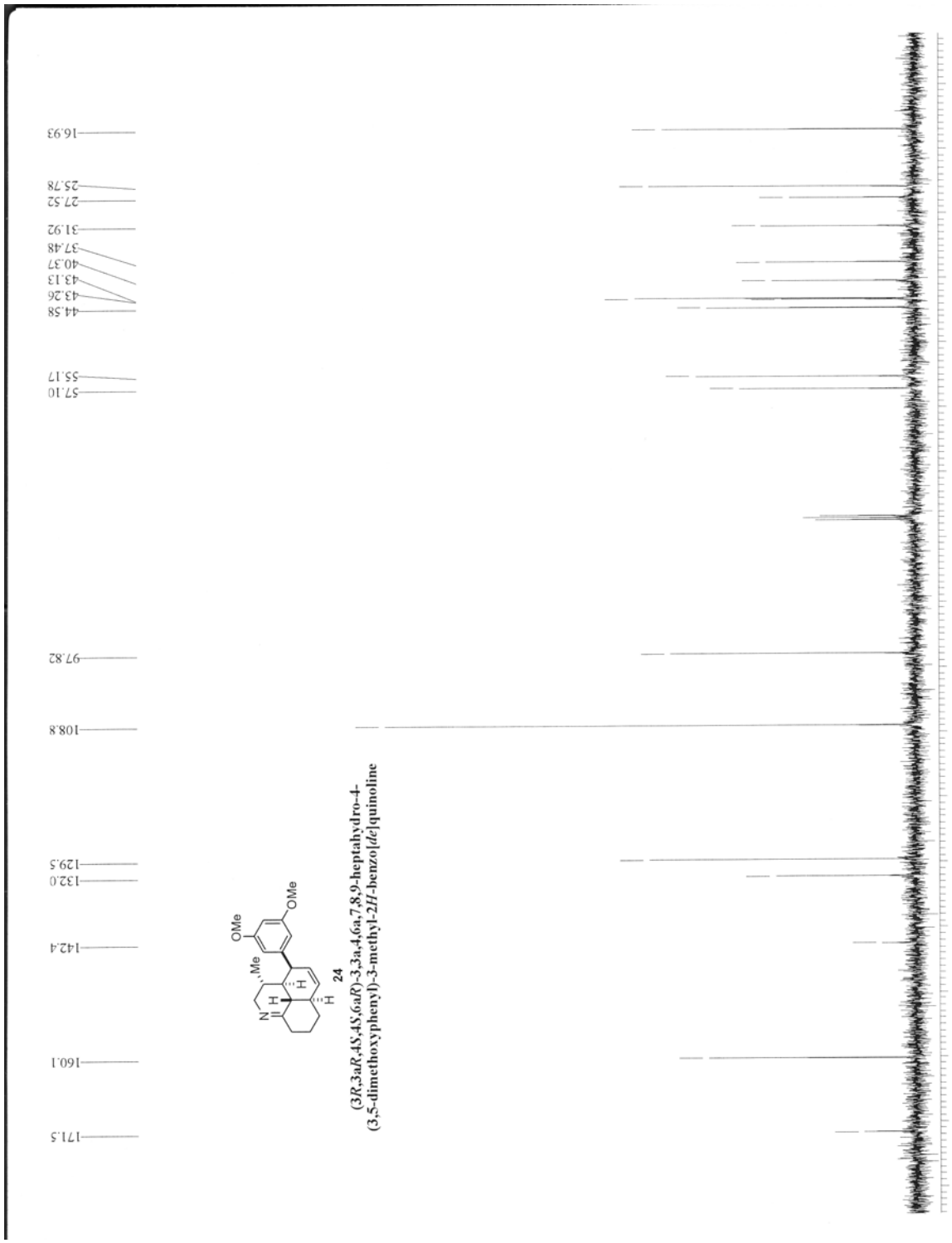
Spectrum 54. ^{1}H NMR spectrum of compound **23** in $CDCl_3$



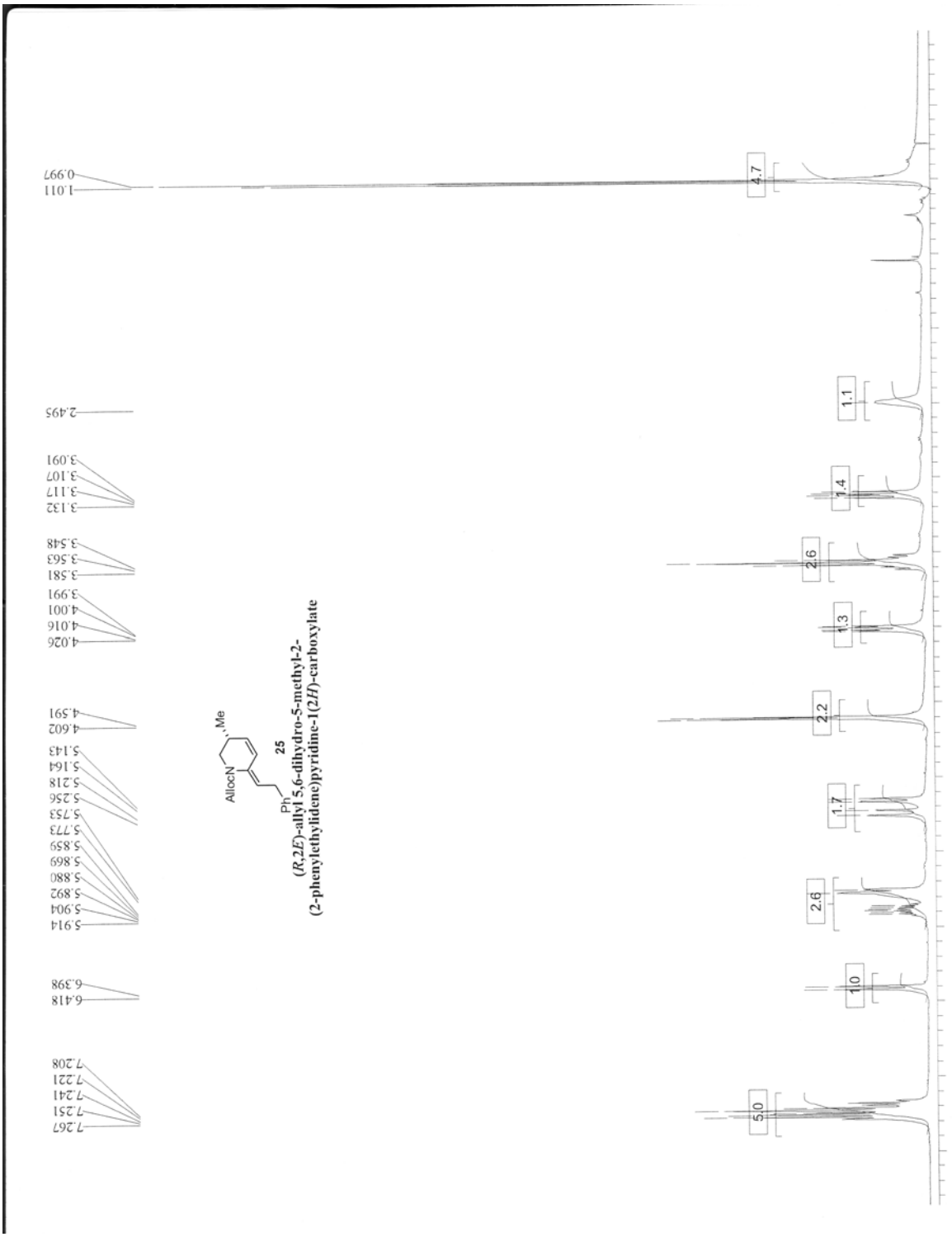
Spectrum 55. ^{13}C NMR spectrum of compound **23** in $CDCl_3$



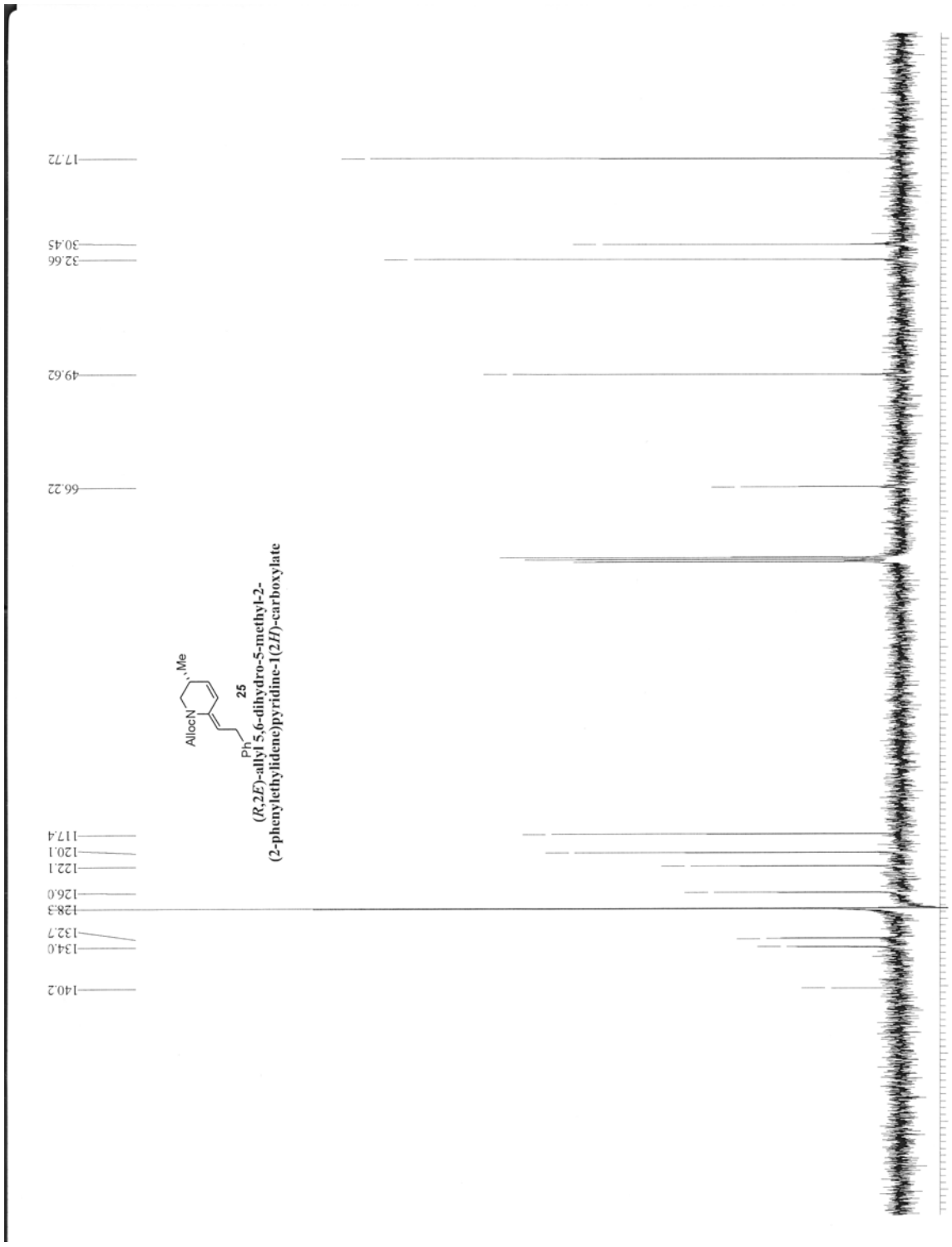
Spectrum 56. ^{1}H NMR spectrum of compound **24** in $CDCl_3$



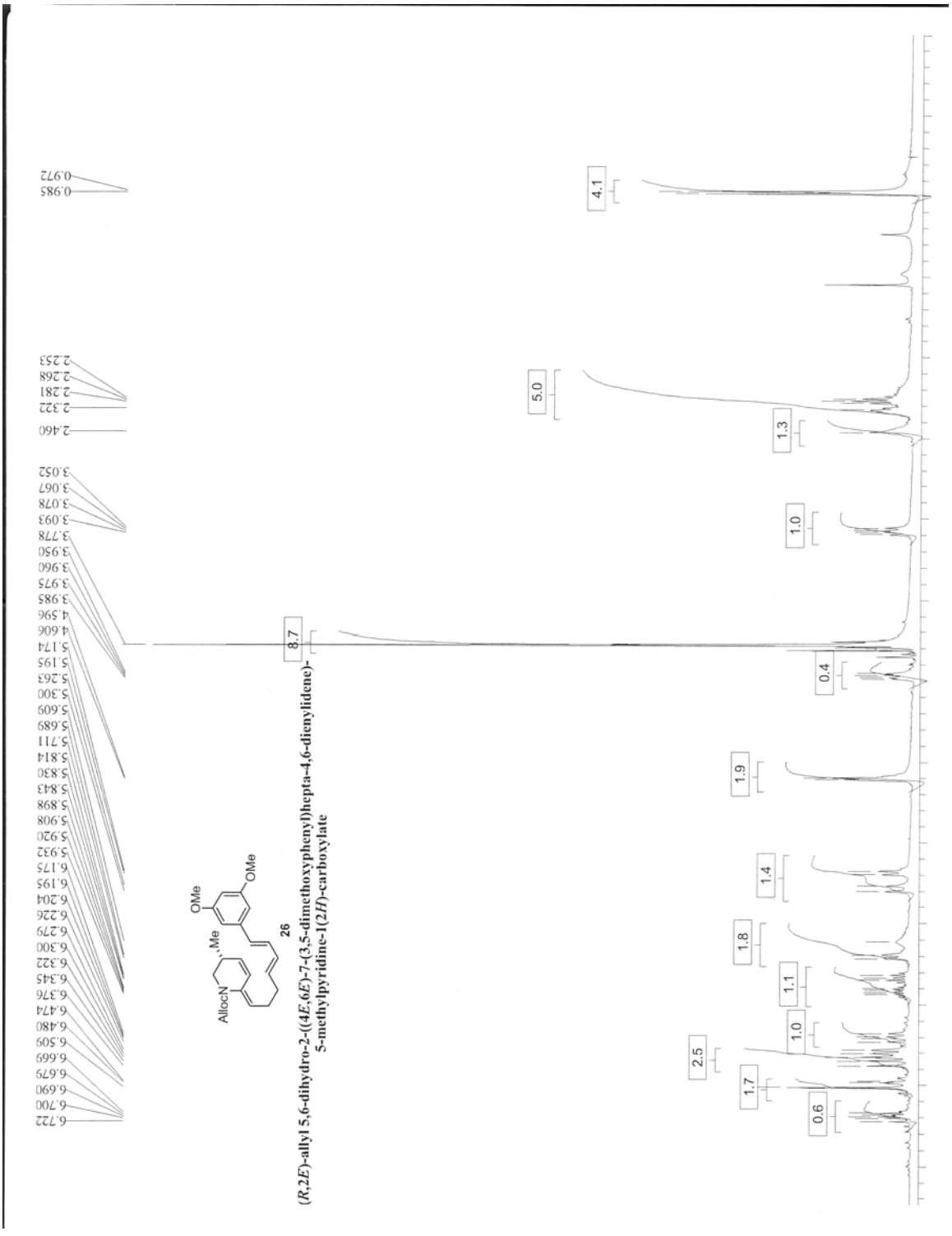
Spectrum 57. ^{13}C NMR spectrum of compound **24** in $CDCl_3$



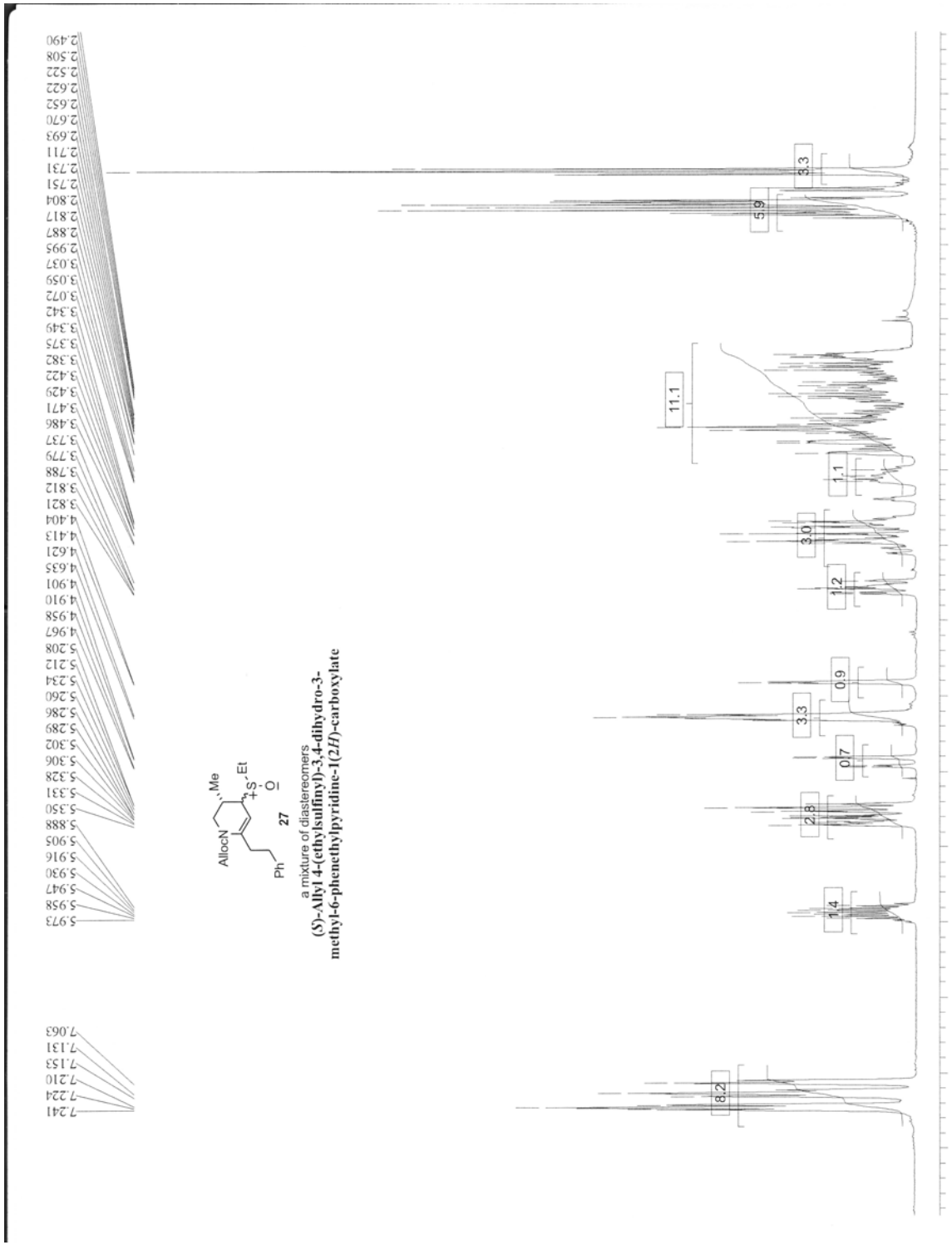
Spectrum 58. ^{1}H NMR spectrum of compound **25** in $CDCl_3$



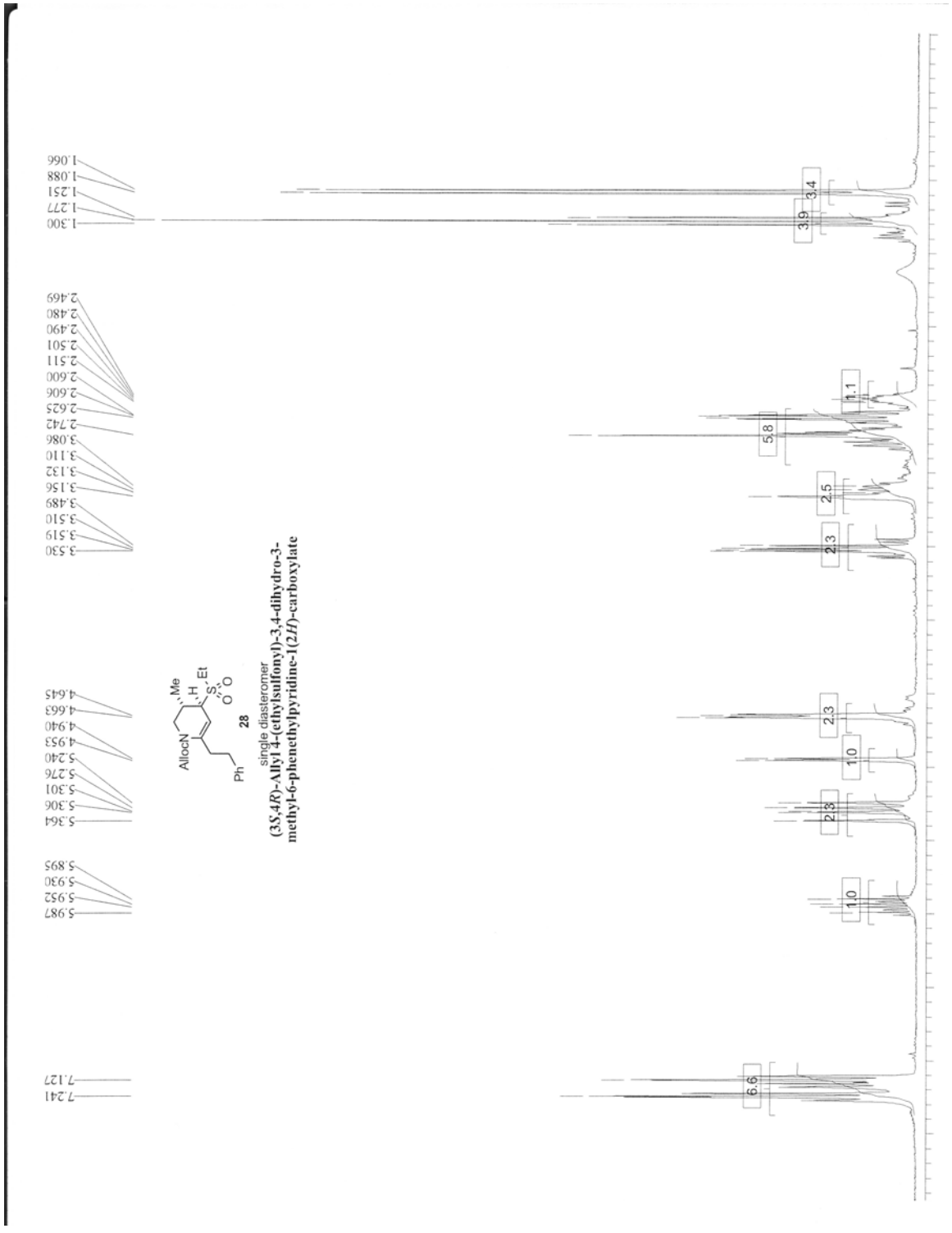
Spectrum 59. ^{13}C NMR spectrum of compound **25** in $CDCl_3$



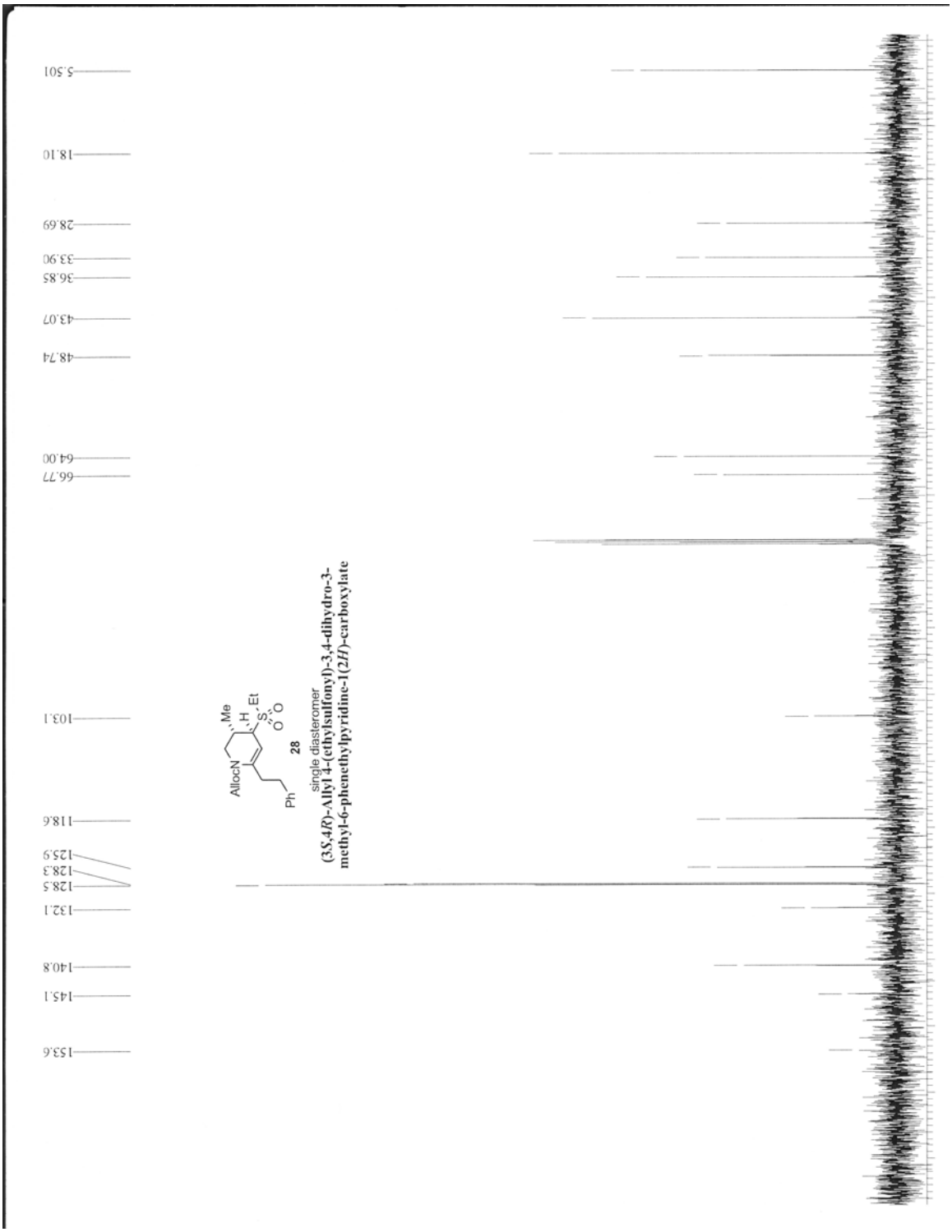
Spectrum 60. ^{1}H NMR spectrum of compound **26** in $CDCl_3$



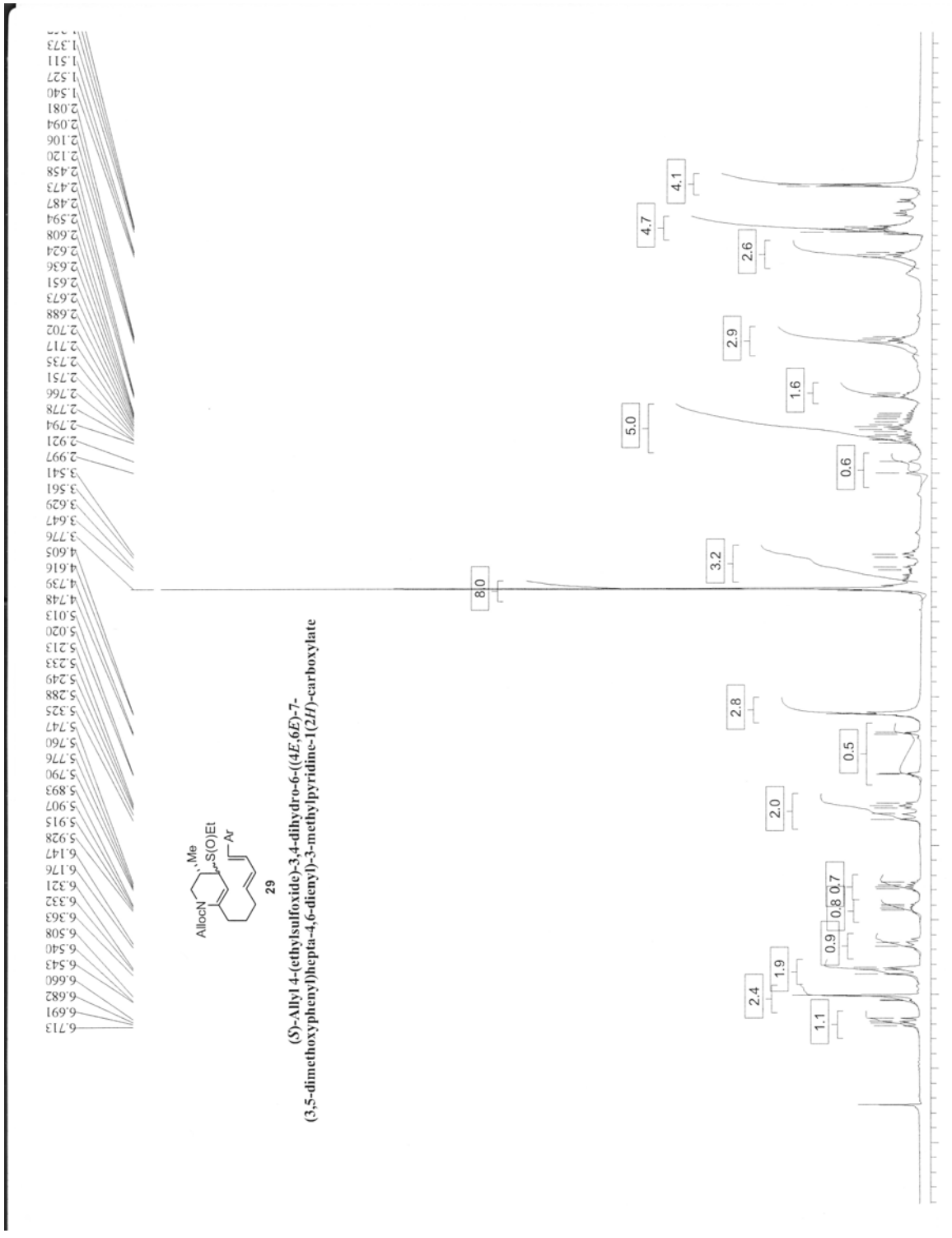
Spectrum 61. ^{1}H NMR spectrum of compound **27** in $CDCl_3$



Spectrum 62. ^{1}H NMR spectrum of compound **28** in $CDCl_3$



Spectrum 63. ^{13}C NMR spectrum of compound **28** in $CDCl_3$



Spectrum 64. ^{1}H NMR spectrum of compound **29** in $CDCl_3$

CHAPTER 4

Examination of a Thermal Diels-Alder Reaction of *Trans*-enones

A. Microwaves: More Than A Kitchen Appliance

Microwave chemistry is the science of applying microwave irradiation to chemical reactions. Microwaves act as high frequency electric fields and will generally heat any material containing mobile electric charges, such as polar molecules in a solvent or conducting ions in a solid. Polar solvents are heated as their component molecules are forced to rotate with the field and lose energy in collisions. Semiconducting and conducting samples heat when ions or electrons within them form an electric current and energy is lost due to the electrical resistance of the material. Microwave heating in the laboratory began to gain wide acceptance following papers in 1986[1], although the use of microwave heating in chemical modification can be traced back to the 1950s.

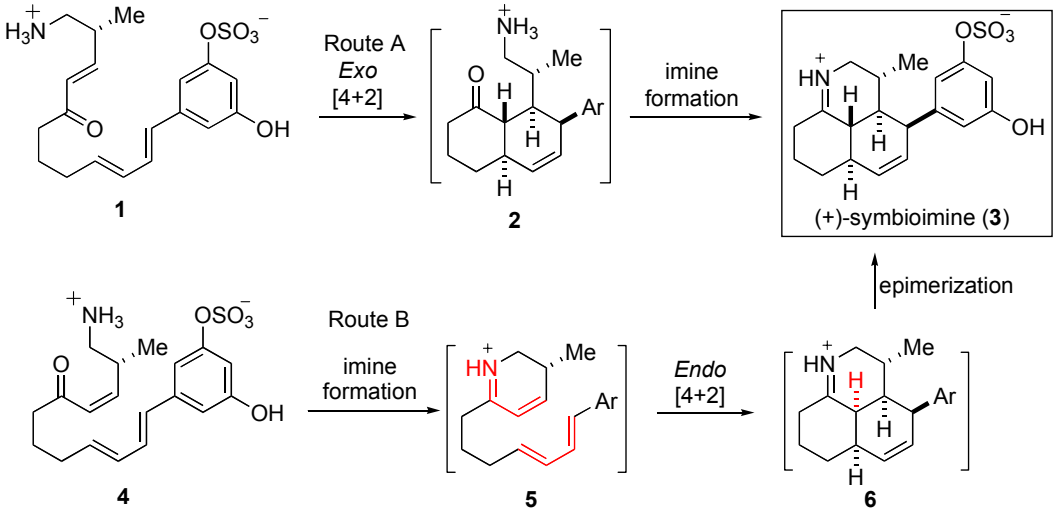
Conventional heating usually involves the use of a sand or oil bath, which heats the walls of the reactor by convection or conduction. The core of the sample takes much longer to achieve the target temperature, e.g. when heating a large sample of ceramic bricks.

Microwave heating is able to heat the target compounds without heating the entire furnace or oil bath, which saves time and energy. It is also able to heat sufficiently thin objects throughout their volume (instead of through its outer surface), in theory producing more uniform heating. However, due to the design of most microwave ovens and to uneven absorption by the object being heated, the microwave field is usually non-uniform and localized superheating occurs (hot on the outside, cold in the middle). Nowadays much of these design problems have been overcome, and the appearance of small, benchtop microwave systems designed to generate continuous, uniform microwave fields to compeltely eliminate localized superheating. More importantly, microwave

heating can have certain benefits over conventional heating as observed by reaction rate acceleration, which can allow milder reaction conditions, as well as providing higher chemical yields. My personal favorite, however, is the ability to channel an entire day's cumulation of little frustrations and stresses into your reaction and just nuking the hell out of it.

B. Uemura's Proposed Biosynthesis and Background

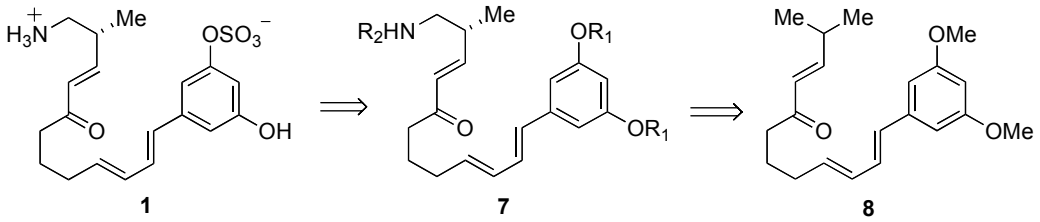
In his publication of the isolation of symbioimine **3**, Uemura proposed that the biosynthesis of the 6,6,6-tricyclic iminium ring system began with an intramolecular *exo*-Diels-Alder reaction between the *trans*-enone and the diene, followed by imine formation by condensation of the terminal amine with the resulting ketone (Scheme 36)



Scheme 36. Proposed Biosyntheses of Symbioimine **3**

Uemura's proposed biosynthetic pathway seems reasonable except the *exo*-

selectivity in the intramolecular Diels-Alder reaction. A synthesis of a similar type of octalone has been reported to exclusively afford an *endo*-adduct by the intramolecular Diels-Alder reaction of a *trans*-enone precursor.[2] On the other hand, the attempt of this Diels-Alder reaction with a nonionic model compound **7** under conventional conditions was unsuccessful as reported by Maier (Scheme 237).[3] Interestingly, only slow decomposition of the substrate was observed, and even the *endo*-adduct was not formed, probably due to the steric hindrance. Therefore, the validity of the biosynthetic route remained to be verified.



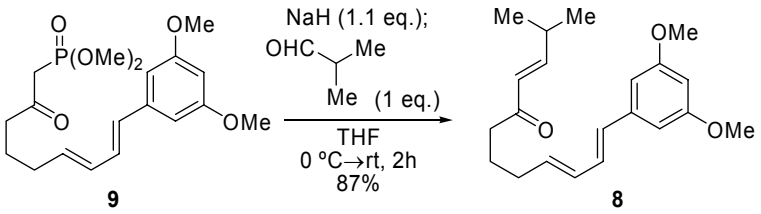
Scheme 37. Design of a Precursor for the Intramolecular Diels-Alder Reaction

C. Model system synthesis

Based on our own preliminary results (A: R^1 = Me, R^2 = Alloc), we decided to investigate on the feasibility of the intramolecular Diels-Alder reaction without the terminal amino group in **7**, the reason of which is to avoid a decomposition pathway initiated by elimination of an amino group from the γ-amino-*trans*-enone moiety, and also simplify the analysis of the Diels-Alder products because the possible products are two diastereomers (*endo*/*exo*) instead of four. Although this model compound **8** would not provide a cycic imine moiety of symbioimine, we expected that useful information

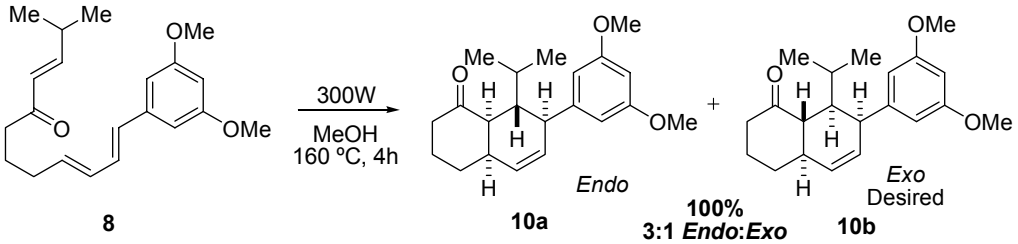
regarding the stereoselectivity in the Diels-Alder reaction could be obtained.

The synthesis of *trans*-enone **8** was accomplished in a similar fashion as illustrated in the previous chapter. Deprotonation of β-ketophosphonate **9** by barium hydroxide and its resulting Horner-Wadsworth-Emmons olefination with isobutyraldehyde gave *trans*-enone **8** in good yield.[4]



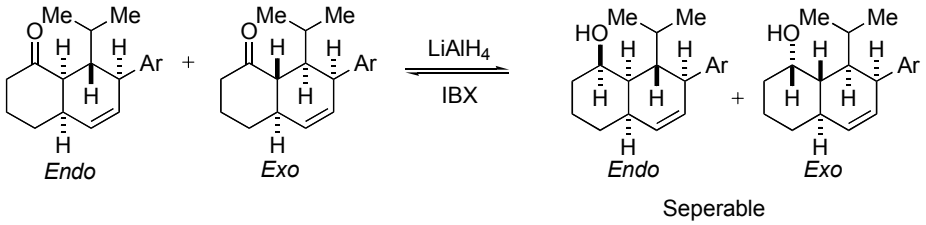
Scheme 38. Synthesis of *trans*-enone **8**

With *trans*-enone **8** in hand, we embarked on the intramolecular Diels-Alder reaction (Scheme 39). As reported by Maier previously,[2a] we found that the Diels-Alder reaction of **8** does not proceed by conventional heating or treatment with Lewis acid.[5] To our delight, microwave-assisted heating of **8** at 160 ˚C in methanol (boiling point ~65 ˚C) did provide the Diels-Alder adducts **10a** and **10b** quantitatively with a 3:1 *endo/exo* ratio.[6,7] The *exo*-adduct **10a** has the corresponding stereochemistry to that of symbioimine.



Scheme 39. Intramolecular Diels-Alder Reaction of *trans*-Enone **8**

Although these compounds are inseparable by SiO_2 chromatography, we fortunately found the separation of the corresponding alcohols possible. The reduction of **10** with $LiAlH_4$ gave a separable mixture of secondary alcohols. After separation, these are oxidized to **10a** and **10b** by IBX, individually (Scheme 40).



Scheme 40. Separation of the Diastereomers **10a** and **10b**

The relative stereochemistry of the Diels-Alder products **10a** and **10b** was established by analysis of coupling constants of a proton (H^4) at an angular position and by a NOE experiment after isolation of each adduct as shown in Figure 19. Importantly, we confirmed that octalones **10a** and **10b** are kinetic products, which are directly formed by Diels-Alder reaction of **10**. Isomerization of the epimerizable stereocenter was not observed. The assignments of the ^1H and ^{13}C-NMR chemical shifts were established by

COSY experiments.

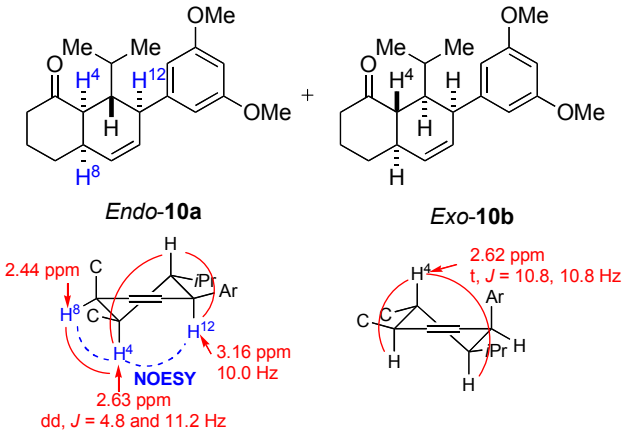
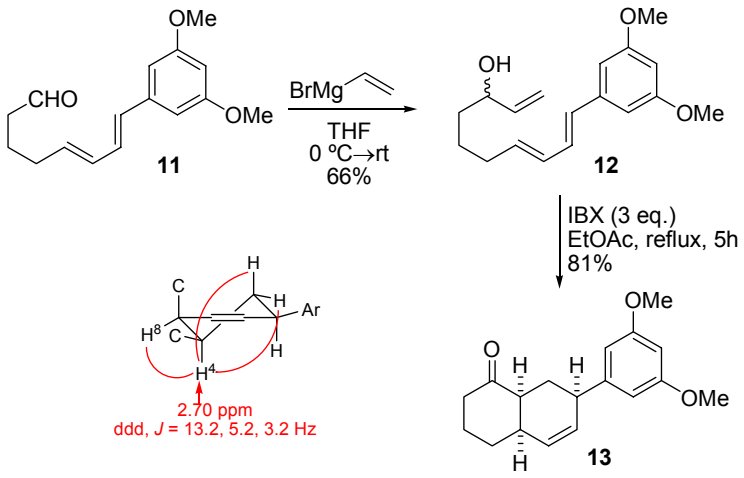


Figure 19. Assignment of Stereochemistry of Diels-Alder Adducts **10a** and **10b**

Importantly, the intramolecular Diels-Alder reaction of *trans*-enone **8** was efficiently accelerated by microwave-assisted heating, although any other conventional methods were not as effective. We speculated a steric interaction between phenyl and isopropyl groups in the transition state of the Diels-Alder reaction would be the origin of the difficulty.

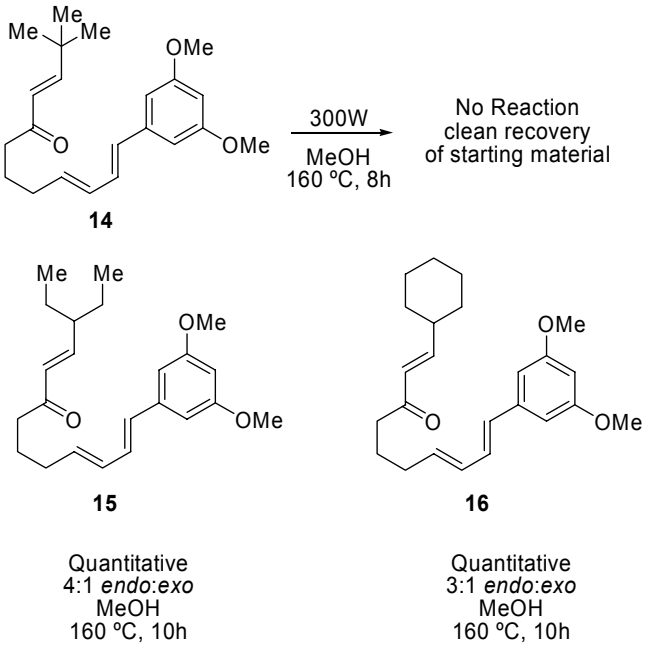
To analyze this steric inhibition, as a control experiment, we investigated the intramolecular Diels-Alder reaction of a vinyl ketone derivative of **8**. Allyl alcohol **12** was obtained by addition of vinylmagnesium bromide to aldehyde **11** (Scheme 41). The IBX oxidation of **12** by heating at 80 ˚C for 3 hours gave a mixture of the corresponding enone (not shown) and *endo*-Diels-Alder adduct **13** (*endo*/*exo* = 4:1).[8] The enone intermediate was readily converted completely into **13** by further heating at 80 ˚C. Indeed, the Diels-Alder reaction was significantly facilitated compared with that of *trans*-

enone **8**, suggesting steric hindrance as the determining factor of the reaction rate. The relative stereochemistry of major adduct **13** was established by analysis of coupling constants as shown below.



Scheme 41. Intramolecular Diels-Alder Reaction of Vinyl Ketone

The impact of steric substitution on the γ-position on the Diels-Alder reaction was undertaken to determine the scope of these microwave conditions. *t*-Butyl *trans*-enone **14**, and branched *trans*-enones **15** and **16** were made using β-ketophosphonate **9** and their respective aldehydes. Application of the microwave conditions to **14** were unsuccessful, even up to 190 °C (Scheme 42). Branched *trans*-enones **15** and **16**, on the other hand, while sluggish, fully converted to their respective products in quantitavie yield.

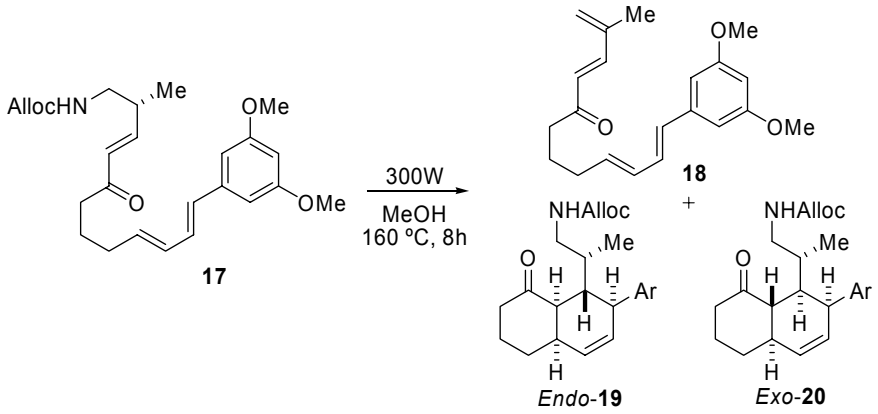


Scheme 42. Steric Scope of Microwave Conditions

D. Synthesis of Symbioimine Framework and Diels-Alder Reaction

Application of the microwave-assisted Diels-Alder reaction to the symbioimine framework in the form of chiral *trans*-enone **17** (whose synthesis was described in the previous chapter) produced a complex mixture which consisted of a moderate yield of amine-eliminated adduct **18**, as well as Diels-Alder products **19** and **20** in an 8:1 *endo*:*exo* ratio as an inseparable mixture (Scheme 43). Using a combination of 1:1 ethanol:water as the reaction solvent, and heating to 190 ˚C for 15 minutes produced a 25% yield of the Diels-Alder adducts in a similar 8:1 ratio, with the mass balance being the remaining unreacted starting material. Clearly decomposition occurs under prolonged reaction times. Despite the opportunity presented to do multiple, short lasting experiments under the higher temperature conditions, the 8:1 ratio favoring the unwanted diasteromer is clearly unacceptable. On the bright side, however, these results illustrate

that such a high $\Delta G^{\ddagger}$ barrier to the [4+2] cycloaddition would induce natural selection to find an alternative method in its construction, assuming a putative Diels-Alderase were not involved.



Scheme 43. Intramolecular Diels-Alder Reaction of *trans*-Enone **17**

E. Conclusions

As Uemura suggested in his proposed biosynthesis of symbioimine, the intramolecular Diels-Alder reaction of *trans*-enone linear precursor is possible. In our hands, the reaction proceeded very cleanly under microwave-assisted heating conditions (MeOH, 160 ˚C, 4 h), although the *endo*/*exo* selectivity was moderate (3:1). The stereochemistry of each adduct was unambiguously determined by NMR analysis. We anticipated the steric interaction in the transition state of the Diels-Alder reaction to be significant between the substituents at the termini of the diene and the dienophile, subsequently slowing the rate of reaction, an observation confirmed by examining the steric scope of the microwave conditions. A higher selectivity of the unwanted Diels-Alder diastereomer generated from the chiral precursor was also observed. Therefore, most likely, if an *exo*-selective Diels-Alder reaction is the biosynthetic route then it must

clearly be catalyzed by an enzyme.

F. Acknowledgements

In addition to thanking the University of California for financial support, I would also thank Dr. Yongxuan Su for Mass Spectroscopy and Dr. Anthony Mrse for help with NOESY experiments. The section pertaining to the model Diels-Alder cycloaddition using the vinyl enone was undertaken by Genesis Bacani, an undergraduate member of our laboratory, and is graciously acknowledged for his contribution to this work. I'd like to acknowledge Yoshi's instruction, guidance, and patience in helping me understand and assign the complex NOESY experimental data. Most importantly, this work would have not been possible if it weren't for the Molinski group's gracious permission of my use of their microwave reactor, with special thanks to Colin Skepper for taking the time to instruct me in its proper use.

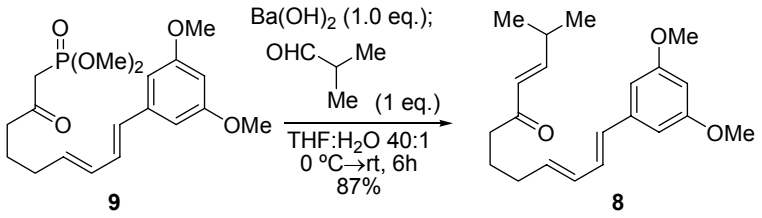
G. Experimentals

Materials and Methods

All reagents were commercially obtained (Aldrich, Fisher) at highest commercial quality and used without further purification except where noted. Organic solutions were concentrated by rotary evaporation below 45 ˚C at approximately 20 mmHg. Tetrahydofuran (THF), methanol (MeOH), chloroform ($CHCl_3$), dichloromethane (DCM), ethyl acetate (EtOAc), acetonitrile (CH_3CN), and acetone were purchased as reagent grade and used without further purification. Reactions were run under an inert N_2 atmosphere unless otherwise noted. Yields refer to chromatographically and

spectroscopically (^{1}H- and ^{13}C-NMR) homogeneous materials, unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254), visualized with UV light and stained with cerium molybdate solution and heat. E. Merck silica gel (60A, particle size 0.040-0.063 mm) was used for flash chromatography. Preperative thin-layer chromatography separations were carried out on 0.50 mm E. Merck silica gel plates (60F-254). NMR spectra were recorded on Varian Mercury 300, 400 and/or Unity 500 MHz instruments and calibrated using the residual undeuterated solvent as an internal reference. Chemical shifts (δ) are reported in parts per million (ppm) and coupling constants (*J*) are reported in hertz (Hz). The following abbreviations are used to designate multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad. Mass spectra (MS) and high-resolution mass spectra (HRMS) were recorded on a Finnigan LCQDECA mass spectrometer under electrospray ionization (ESI) or atmospheric pressure chemical ionization (APCI) conditions, or on a Thermo-Finnegan Mat900XL mass spectrometer under electron impact (EI), chemical ionization (CI), or fast atom bombardment (FAB) conditions. X-ray data were recorded on a Bruker SMART APEX CCD X-ray diffractometer. Specific optical rotations were recorded on a Jasco P-1010 polarimeter and the specific rotations were calculated based on the equation $[\alpha]^{25}_{D} = (100 \cdot \alpha)/(l \cdot c)$, where the concentration c is in g/100 mL and the path length *l* is in decimeters.

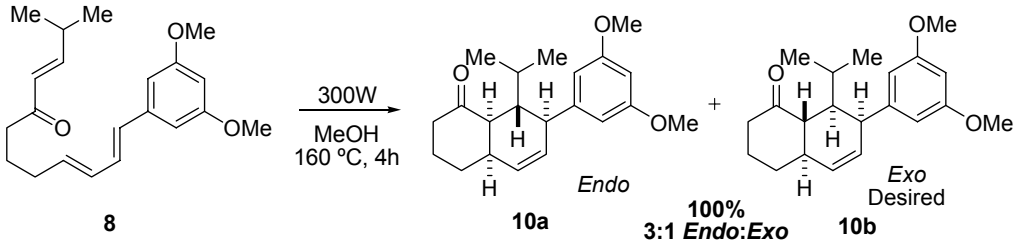
Procedures and Spectral Data



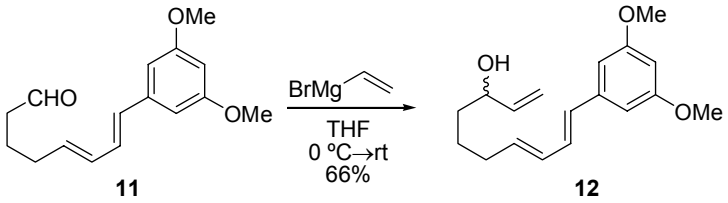
9 **8**

(3E,9E,11E)-12-(3,5-dimethoxyphenyl)-2-methyldodeca-3,9,11-trien-5-one 8:

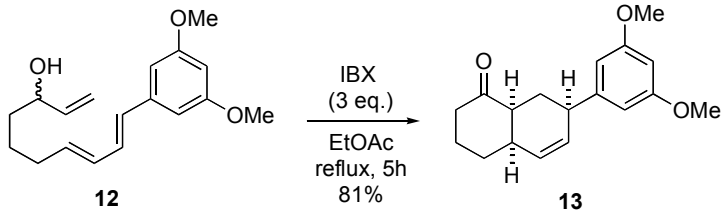
$Ba(OH)_2 \bullet 8H_2O$ (413 mg., 1.31 mmol, 1.0 equiv.) was added to a 0 ˚C solution of β-ketophosphonate **20** (500 mg., 1.31 mmol, 1.0 equiv.) in THF:H_2O (40:1, 13.1 mL) and allowed to stir for 30 min. Isobutyraldehyde (95 mg, 1.31 mmol, 1.0 equiv.) was then added, and the solution allowed to warm to room temperature, stirring for 6 hours. Upon completion, the solution was diluted with DCM, and $MgSO_4$ was added with additional stirring for 30 min. Filtration over Celite and subsequent purification over silica (5:1 Hexane:EtOAc, R_F = 0.45) gave the title compound **8** as a clear oil (3.76 mg., 87% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.77 (dd, *J* = 7.0, 16.0 Hz, 1H), 6.70 (dd, *J* = 11.0, 16.0 Hz, 1H), 6.51 (d, *J* = 2.5 Hz, 2H), 6.35 (d, *J* = 15.5 Hz, 1H), 6.32 (t, *J* = 1.5 Hz, 1H), 6.18 (dd, *J* = 10.5, 15.0 Hz, 1H), 6.02 (d, *J* = 16.0 Hz, 1H), 5.78 (dt, *J* = 7.0, 14.5 Hz, 1H), 3.78 (s, 6H), 2.55 (t, *J* = 7.5 Hz, 2H), 2.44 (m, 1H), 2.16 (q, *J* = 6.5 Hz, 2H), 1.74 (q, 6.5 Hz, 2H), 1.05 (d, *J* = 6.5 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.8, 160.8, 153.4, 139.5, 135.1, 131.1, 130.3, 129.7, 127.5, 104.1, 99.6, 55.3, 39.2, 32.2, 21.3. HRMS: *m/z* calcd for $C_{21}H_{28}O_3$: 328.2038, found 328.2036.



(4a*R*,7*S*,8*R*,8a*R*)-2,3,4,4a,8,8a-hexahydro-8-isopropyl-7-(3,5-dimethoxyphenyl) naphthalen-1(7*H*)-one 10a, (3*E*,9*E*,11*E*)-12-(3,5-dimethoxyphenyl)-2-methyldodeca-3,9,11-trien-5-one 10b: A microwave tube containing *trans*-enone **8** (20 mg., 0.0608 mmol, 1.0 equiv.) in MeOH (1.2 mL) was heated to 160 ˚C for 4 hours. Upon cooling, the methanol was evaporated *in vacuo* to give the Diels-Alder adducts ***endo*-10a** and ***exo*-10b** in quantitative yield in a 3:1 ratio. No purification was necessary. **Endo DA** : ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.34 (d, *J* = 2.0 Hz, 2H), 6.30 (t, *J* = 1.5 Hz, 1H), 5.70 (dq, *J* = 2.8, 5.2, 10.0 Hz, 1H), 5.47 (d, *J* = 9.6 Hz, 1H), 3.77 (s, 6H), 3.15 (dd, *J* = 2.4, 10.0 Hz, 1H), 2.61 (dd, *J* = 4.8, 11.2 Hz, 1H), 2.52 (dt, *J* =6.0, 12.8 Hz, 1H), 2.45-2.41 (m, 1H), 2.31-2.26 (m, 2H), 2.05 (ddd, *J* = 3.2, 5.2, 12.4 Hz, 1H), 1.89 (dd, *J* = 3.6, 13.2 Hz, 1H), 1..80-1.60 (m, 3H), 0.79 (d, *J* = 7.2 Hz, 3H), 0.77 (d, *J* = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.70, 147.8, 131.6, 128.6, 106.8, 97.6, 55.2, 52.9, 46.0, 43.1, 40.3, 40.00, 29.4, 29.0, 26.6, 19.9, 17.7. **Exo DA**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.44 (s, 2H), 6.32 (s, 1H), 5.83 (dq, *J* = 9.6 Hz, 1H), 5.64 (d, *J* = 9.6 Hz, 1H), 3.77 (s, 6H), 3.07 (d, 1H), 2.62 (t, 1H), 2.49 (h, 1H), 2.36 (t, 1H), 2.20 (t, 1H), 2.13 (d, 1H), 2.06 (dd, 1H), 1.82 (t, 1H), 1.78 (q, 1H), 1.73 (dt, 2H), 0.69 (d, 3H), 0.43 (d, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 212.6, 160.4, 144.6, 131.0, 129.5, 108.6, 97.8, 51.8, 45.6, 43.9, 43.2, 42.1, 33.0, 28.2, 27.0, 19.5, 19.0.

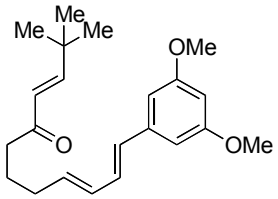


(7*E*,9*E*)-10-(3,5-dimethoxyphenyl)deca-1,7,9-trien-3-ol 12: Vinyl magnesium bromide (1.0M THF, 0.93 mL, 0.93 mmol, 2.0 equiv.) was added to a 0 ˚C solution of aldehyde **11** (108 mg., 0.415 mmol, 1.0 equiv.) in THF (4 mL), and the solution allowed to warm to room temperature. After 1h, the reaction was quenched by addition of sat. NH_4Cl and diluted with EtOAc. After separation, the aqueous phase was extracted 3x with EtOAc, the combined organics washed with brine, dried over Na_2SO_4, and concentrated to dryness. The crude material was purified over silica (2:1 hexanes:EtOAc, $R_f = 0.33$) to afford the vinyl alcohol **12** (78 mg., 66% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 6.70$ (dd, $J = 10.4, 15.6$ Hz, 1H), 5.10 (d, $J = 2.4$ Hz, 2H), 6.35 (d, $J = 15.2$ Hz, 1H), 6.32 (t, $J = 2.0$ Hz, 1H), 6.18 (dd, $J = 10.0, 14.7$ Hz, 1H), 5.89-5.77 (m, 2H), 5.21 (d, $J = 17.2$ Hz, 1H), 5.10 (d, $J = 10.4$ Hz, 1H), 4.10 (d, $J = 6.8$ Hz, 1H), 3.78 (s, 6H), 2.16 (q, $J = 6.4$ Hz, 2H), 1.57-1.45 (m, 4H).



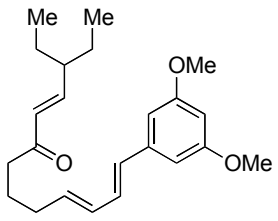
(4a*R*,7*R*,8a*S*)-2,3,4,4a,8,8a-hexahydro-7-(3,5-dimethoxyphenyl)naphthalen-1(7*H*)-one 13: IBX (226 mg., 0.81 mmol, 3.0 equiv.) was added to a room temperature solution of vinyl alcohol **12** (78 mg., 0.270 mmol, 1.0 equiv.) in 1.8 mL of EtOAc, and

heated to reflux for 3h. Upon cooling, the solution was filtered, concentrated *in vacuo*, and purified over silica (5:1 hexane:EtOAc $R^f = 0.40$) to provide the Diels-Alder adduct **13** (62 mg., 81% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.31 (s, 1H), 5.88 (dq, *J* = 10.0 Hz, 1H), 5.72 (d, *J* = 10.4 Hz, 1H), 3.78 (s, 6H), 3.40 (ddd, *J* = 2.4, 6.0, 11.2 Hz, 1H), 2.70 (dq, *J* = 3.2, 5.2, 13.2 Hz, 1H), 2.45 (bq, 1H), 2.30 (m, 2H), 2.04-1.96 (m, 1H), 1.92-1.83 (m, 2H), 1.76 (dd, *J* = 11.2, 13.2 Hz, 1H), 1.66-1.55 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.8, 147.6, 130.9, 129.8, 105.3, 98.0, 50.2, 43.1, 38.5, 37.2, 32.1, 38.3, 24.8.



14

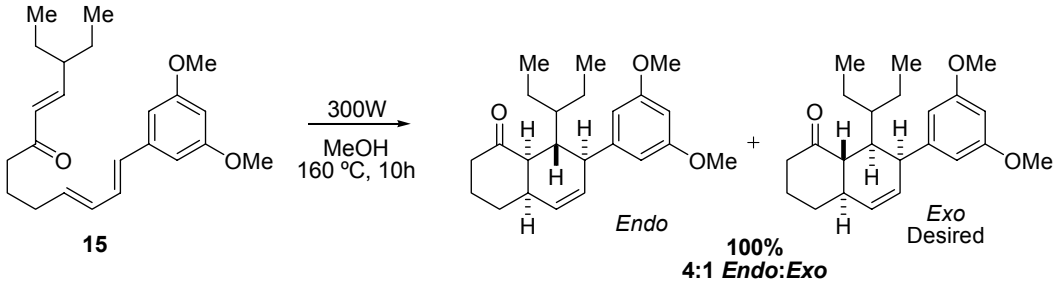
(3*E*,9*E*,11*E*)-12-(3,5-dimethoxyphenyl)-2,2-dimethyldodeca-3,9,11-trien-5-one 14: Made in similar fashion to *trans*-enone **8**. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.80 (d, *J* = 16.0 Hz, 1H), 6.70 (dd, *J* = 10.0, 15.6 Hz, 1H), 6.51 (d, *J* = 2.4 Hz, 2H), 6.35 (d, *J* = 15.6 Hz, 1H), 6.32 (t, *J* = 2.4 Hz, 1H), 6.18 (dd, *J* = 10.4, 15.2 Hz, 1H), 5.99 (d, *J* = 16.0 Hz, 1H), 5.78 (dt, *J* = 6.8, 14.4 Hz, 1H), 3.77 (s, 6H), 2.55 (t, *J* = 7.6 Hz, 2H), 2.16 (q, *J* = 6.8 Hz, 2H), 1.74 (q, *J* = 7.2 Hz, 2H), 1.06 (s, 9H).



15

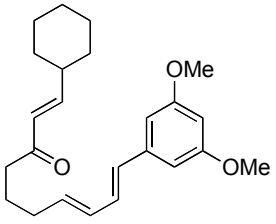
(4*E*,10*E*,12*E*)-3-ethyl-13-(3,5-dimethoxyphenyl)trideca-4,10,12-trien-6-one

15: Made in similar fashion to *trans*-enone **8**. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.80 (dd, *J* = 10.4, 15.6 Hz, 1H), 6.56 (dd, *J* = 9.2, 15.6 Hz, 1H), 6.51 (d, *J* = 2.0 Hz, 2H), 6.36 (d, *J* = 15.2 Hz, 1H), 6.32 (t, *J* = 2.4 Hz, 1H), 6.18 (dd, *J* = 10.8, 15.6, 1H), 6.04 (d, *J* = 16.0 Hz, 1H), 5.78 (dt, *J* = 6.8, 14.4 Hz, 1H), 3.78 (s, 6H), 2.55 (t, *J* = 7.6 Hz, 2H), 2.17 (q, *J* = 7.2 Hz, 2H), 1.99-1.90 (m, 1H), 1.75 (q, *J* = 7.2 Hz, 2H), 1.54-1.43 (m, 2H), 1.38-1.27 (m, 2H), 0.83 (t, *J* = 7.6 Hz, 6H).



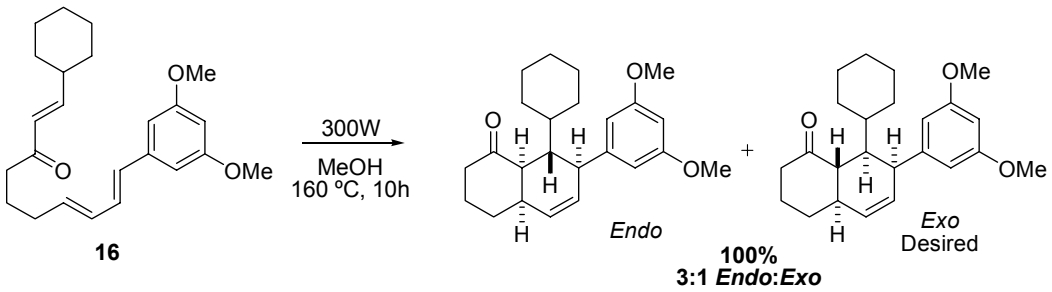
(4a*R*,7*S*,8*R*,8a*R*)-2,3,4,4a,8,8a-hexahydro-7-(3,5-dimethoxyphenyl)-8-(pentan-3-yl)naphthalen-1(7*H*)-one and (4a*R*,7*S*,8*S*,8a*S*)-2,3,4,4a,8,8a-hexahydro-7-(3,5-dimethoxyphenyl)-8-(pentan-3-yl)naphthalen-1(7*H*)-one 15-DA: A microwave tube containing *trans*-enone **15** (33 mg., 0.111 mmol, 1.0 equiv.) in MeOH (2.2 mL) was heated to 160 ˚C for 10 hours. Upon cooling, the methanol was evaporated *in vacuo* to give the Diels-Alder adducts in quantitative yield in a 4:1 ratio. No purification was necessary. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.34 (d, *J* = 2.4 Hz, 2H), 6.30 (t, *J* = 2.0 Hz, 1H), 5.71 (dq, *J* = 2.0, 4.8, 9.6 Hz, 1H), 5.47 (d, *J* = 9.6 Hz, 1H), 3.77 (s, 6H), 3.17 (dd, *J* = 2.4, 10.0 Hz, 1H), 2.67 (dd, *J* = 4.8, 11.6 Hz, 1H), 2.54-2.40 (m, 4H), 2.34 (d, *J* = 13.2

Hz, 1H), 2.06 (dq, *J* = 2.8, 6.0, 12.8, 1H), 1.92 (dt, *J* = 6.0, 14.0 Hz, 1H), 1.81-1.61 (m, 2H), 1.24-1.12 (m, 4H), 1.00-0.79 (m, 6H), 0.72 (q, *J* = 6.8 Hz, 6H).



16

(1*E*,7*E*,9*E*)-1-cyclohexyl-10-(3,5-dimethoxyphenyl)deca-1,7,9-trien-3-one 16: Made in similar fashion to *trans*-enone **8**. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.74 (dd, *J* = 6.8, 16.4, 1H), 6.70 (dd, *J* = 10.0, 15.2 Hz, 1H), 6.51 (d, *J* = 2.4, 2H), 6.36 (d, *J* = 16.0 Hz, 1H), 6.32 (t, *J* = 2.0 Hz, 1H), 6.18 (dd, *J* = 10.4, 15.2 Hz, 1H), 6.02 (dd, *J* = 1.2, 16.0 Hz, 1H), 5.78 (dt, *J* = 7.2, 14.4 Hz, 1H), 3.78 (s, 6H), 2.54 (t, *J* = 7.6 Hz, 2H), 2.16 (q, *J* = 6.8, 3H), 1.74 (m, 8H), 1.29-1.11 (m, 7H).



16

100%
3:1 *Endo*:*Exo*

(4a*R*,7*S*,8*R*,8a*R*)-8-cyclohexyl-2,3,4,4a,8,8a-hexahydro-7-(3,5-dimethoxyphenyl)naphthalen-1(7*H*)-one) and (4a*R*,7*S*,8*S*,8a*S*)-8-cyclohexyl-2,3,4,4a,8,8a-hexahydro-7-(3,5-dimethoxyphenyl)naphthalen-1(7*H*)-one 16-DA: A microwave tube containing *trans*-enone 16 (26 mg., 0.0705 mmol, 1.0 equiv.) in MeOH (1.4 mL) was heated to 160 ˚C for 10 hours. Upon cooling, the methanol was evaporated

in vacuo to give the Diels-Alder adducts in quantitative yield in a 3:1 ratio. No purification was necessary. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.34 (d, *J* = 2.4 Hz, 2H), 6.31 (d, *J* = 2.0 Hz, 1H), 5.70 (dq, *J* = 2.8, 5.2, 10.0 Hz, 1H, *Endo*), 5.47 (d, *J* = 9.6 Hz, 1H, *Endo*), 5.82 (dq, *J* = 2.4, 4.8, 9.2 Hz, *Exo*), 5.63 (dt, *J* = 1.6, 9.6 Hz, 1H, *Exo*), 3.78 (s, 6H), 3.19 (dd, *J* = 2.0, 10.0 Hz, 1H), 2.63 (dd, *J* = 4.4, 11.6 Hz, 1H), 2.61-2.38 (m, 3H), 2.32-2.15 (m, 3H), 1.88 (dd, *J* = 4.0, 13.6 Hz, 1H), 1.77-1.60 (m, 7H), 1.52 (bs, 2H), 1.43 (m, 2H), 1.01 (d, *J* = 4.8 Hz, 6H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 215.6, 160.7, 131.7, 128.6, 106.8, 97.8, 55.3, 53.1, 45.9, 43.0, 40.3, 40.2, 40.1, 30.7,29.4, 28.3, 27.2,26.6, 26.4, 14.2.

H. References and Notes

[1] Gedye, R.; Smith F.; Westaway; K.; Ali, H.; Baldisera, L. *Tetrahedron Lett.* **1986**, *3*, 279-282.

[2] (a) Gras, J.-L.; Bertrand, M. *Tetrahedron Lett.* **1979**, 4549-4552. (b) Gras, J.-L. *J. Org. Chem.* **1981**, *46*, 3738-3741. (c) Taber, D. F.; Kong, S.; Malcom, S. C. *J. Org. Chem.* **1998***, 63*, 7953-7956. (d) Coe, J. W.; Roush, W. R. *J. Org. Chem.* **1989**, *54*, 915-930. (e) Frankowski, K. J.; Golden, J. E.; Zeng, Y.; Lei, Y.; Aubé, J. *J. Am. Chem. Soc.* **2008**, *127*, 6018-6019.

[3] (a) Varseev, G. N.; Maier, M. E. *Angew. Chem. Int. Ed.* **2006**, *45*, 4767-4771. (b) Sammakia showed an interesting method to prepare an octalone core structure of dihydrocompactin, see: Sammakia, T.; Johns, D. M.; Kim, G.; Berliner, M. A. *J. Am. Chem. Soc.* **2005**, *127*, 6504-6505.

[4] Preparation of β-ketophosphonate: Hosokawa, S.; Seki, M.; Fukuda, H.; Tatsuta, K. *Tetrahedron Lett.* **2006**, *47*, 2439-2442.

[5] Attempted Diels-Alder reaction of **11** under conventional conditions: (a) xylene, reflux, 2 d, and (b) $MeAlCl_2$, CH_2Cl_2, -78 ˚C.

[6] Microwave instrument: CEM Dicovery Labmate microwave system.

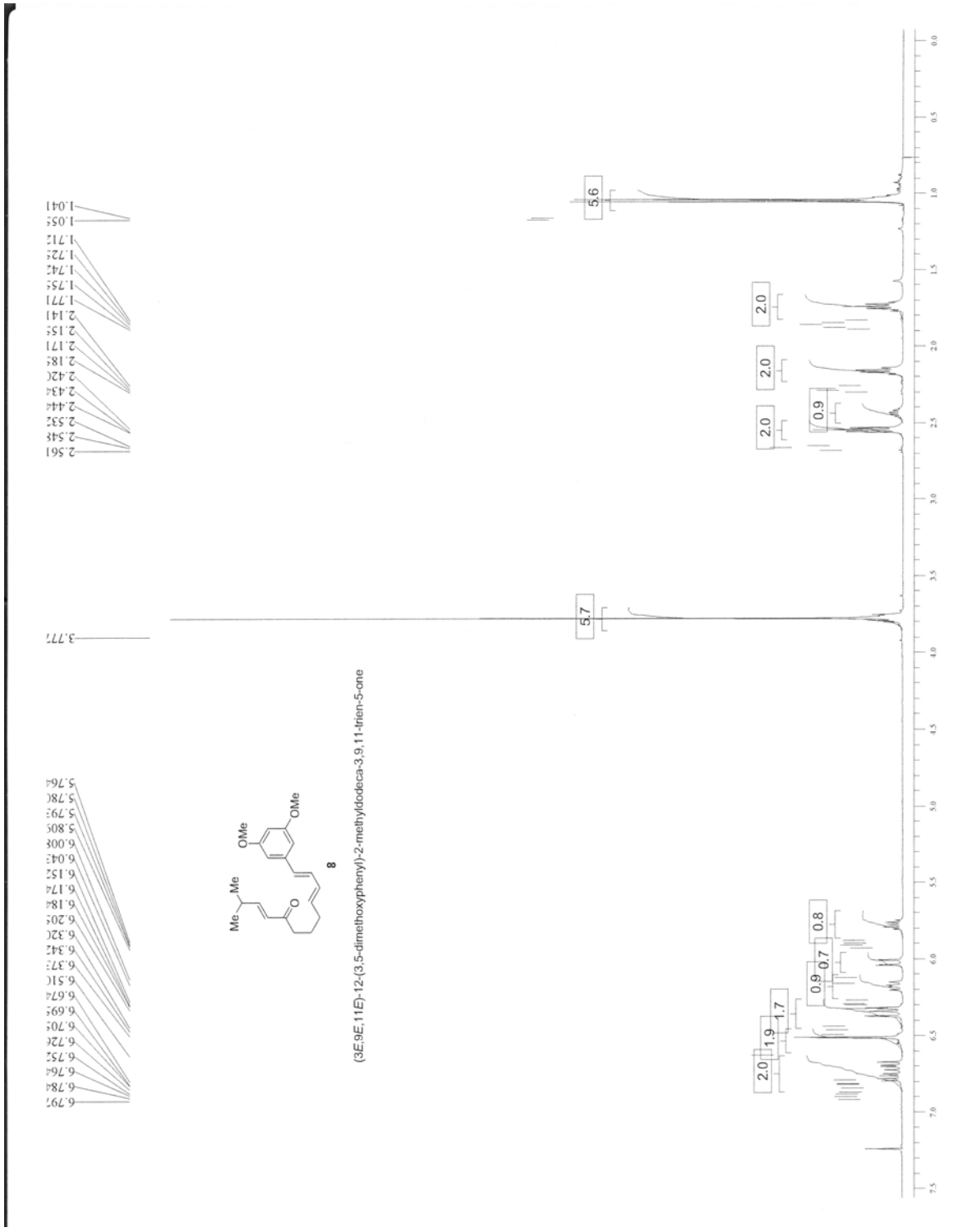
[7] Microwave-assisted heating of **11** in ethanol provided the Diels-Alder adducts **12a** and **12b** in 69% with *exo*/*endo* = 1:2.

[8] The minor diastereomer was assumed to be the *exo*-adduct. We do not exclude the possibility of epimerization of the major kinetic *endo*-adduct **14** to the minor *exo*-adduct under the reaction conditions.

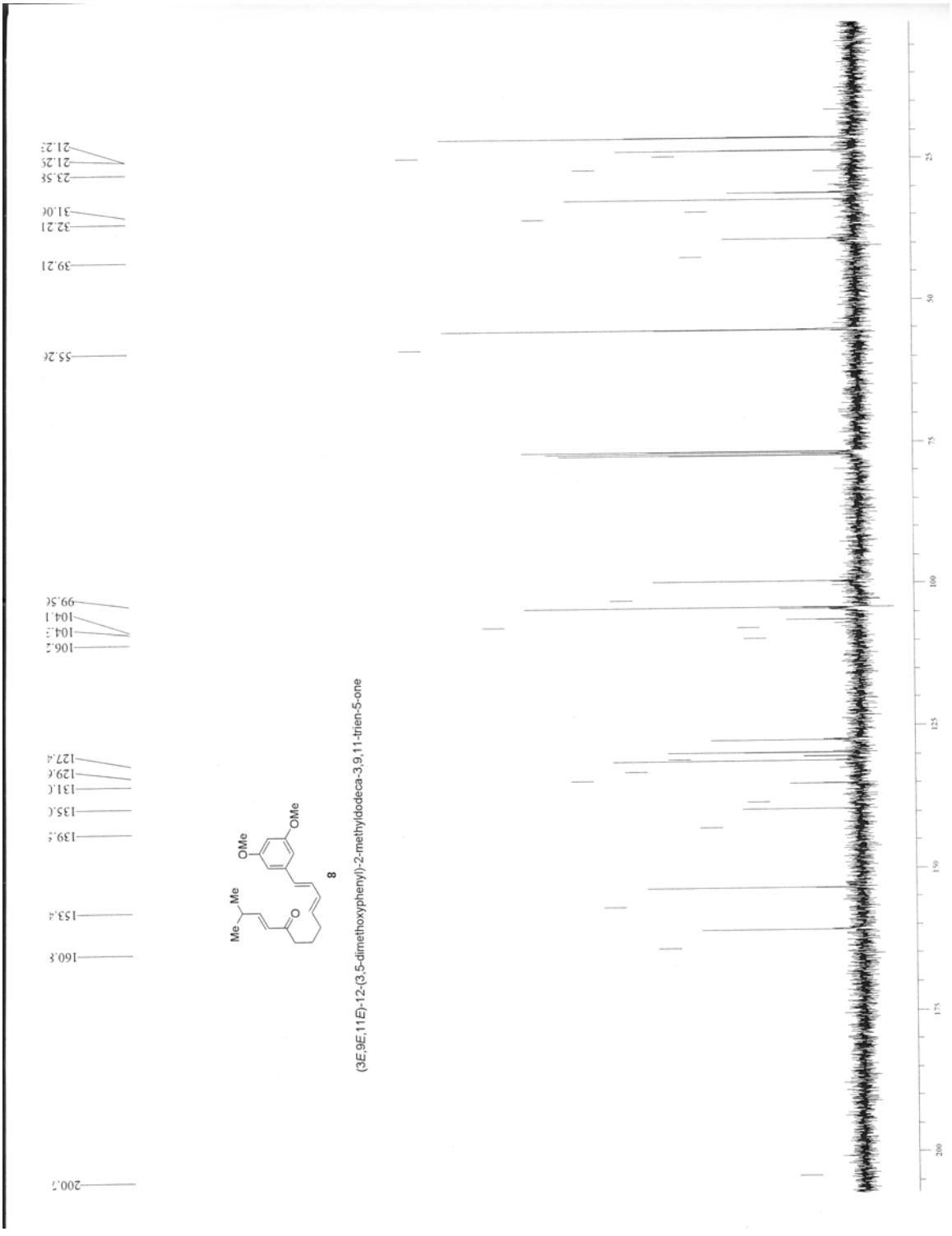
Chapter 4

Selected Spectra

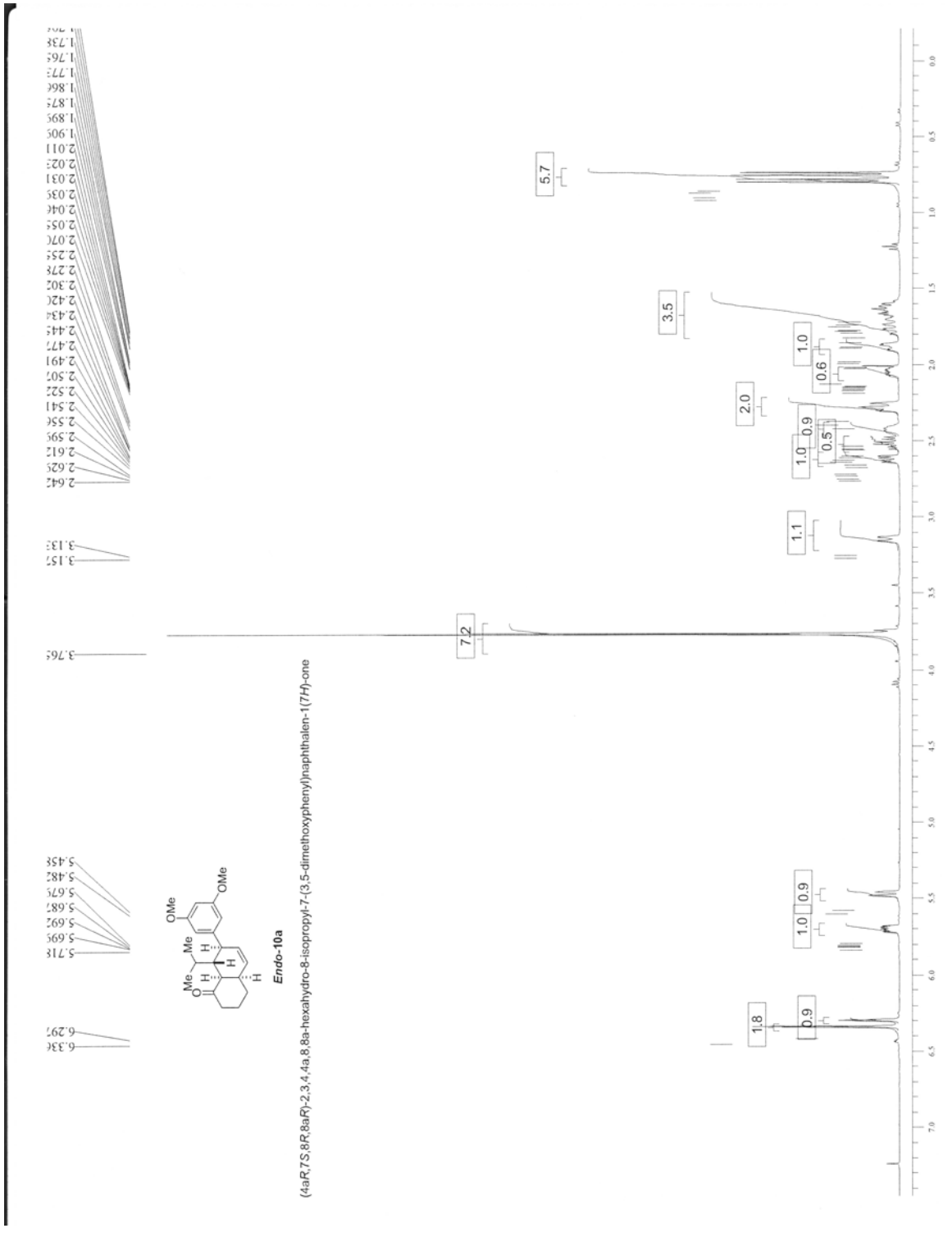
Spectrum Page



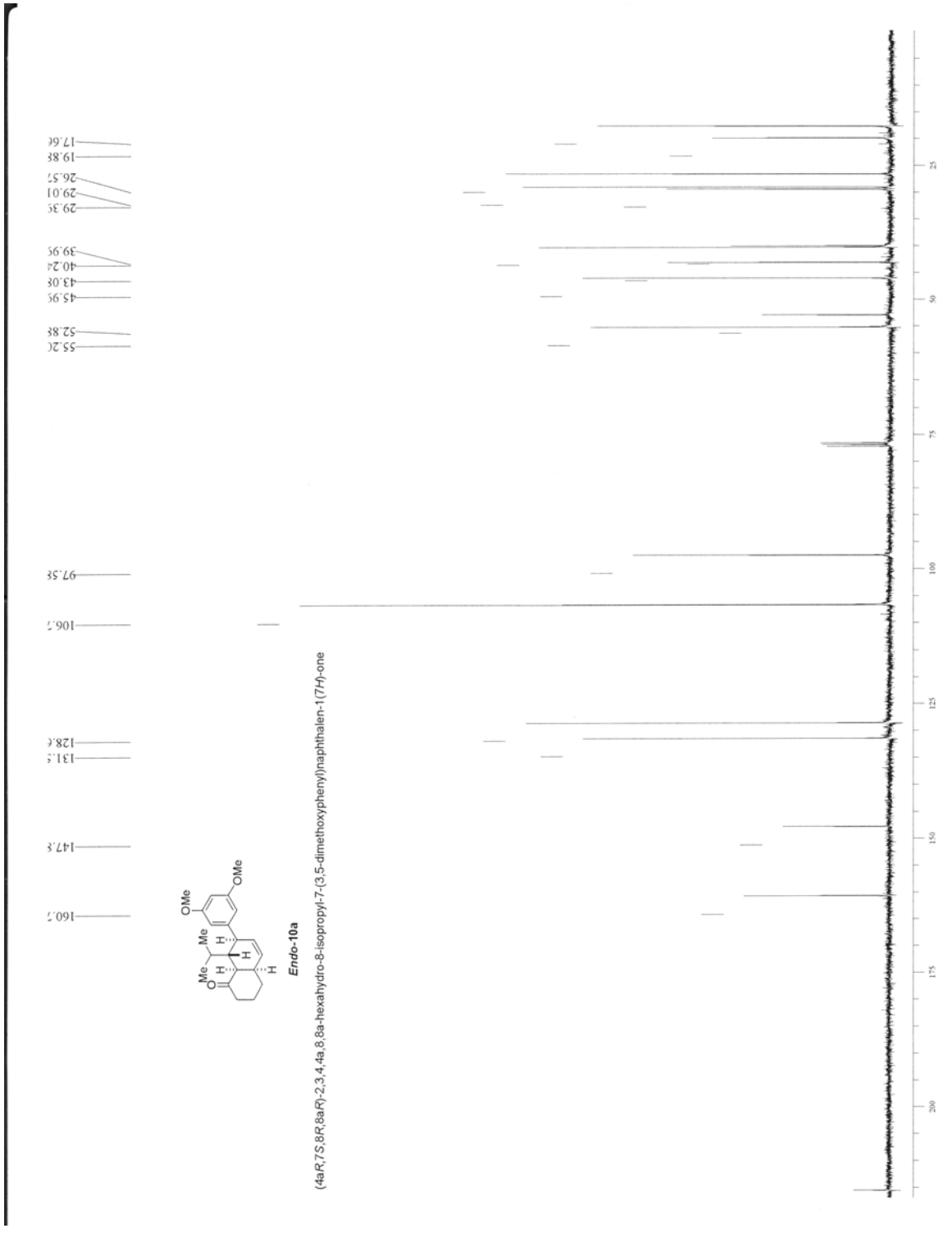
Spectrum 65. ^{1}H NMR spectrum of compound **8** in $CDCl_3$



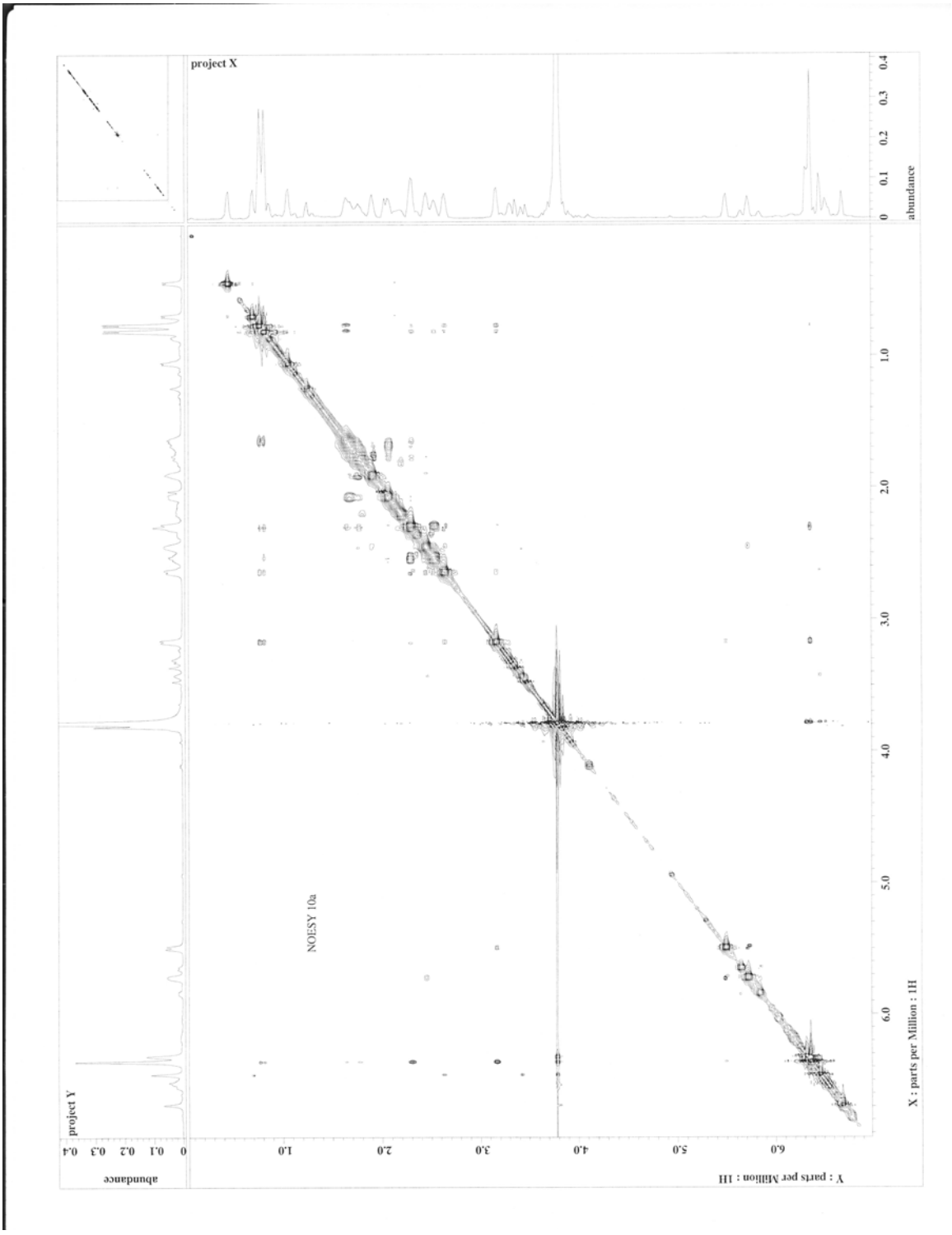
Spectrum 66. ^{13}C NMR spectrum of compound **8** in $CDCl_3$



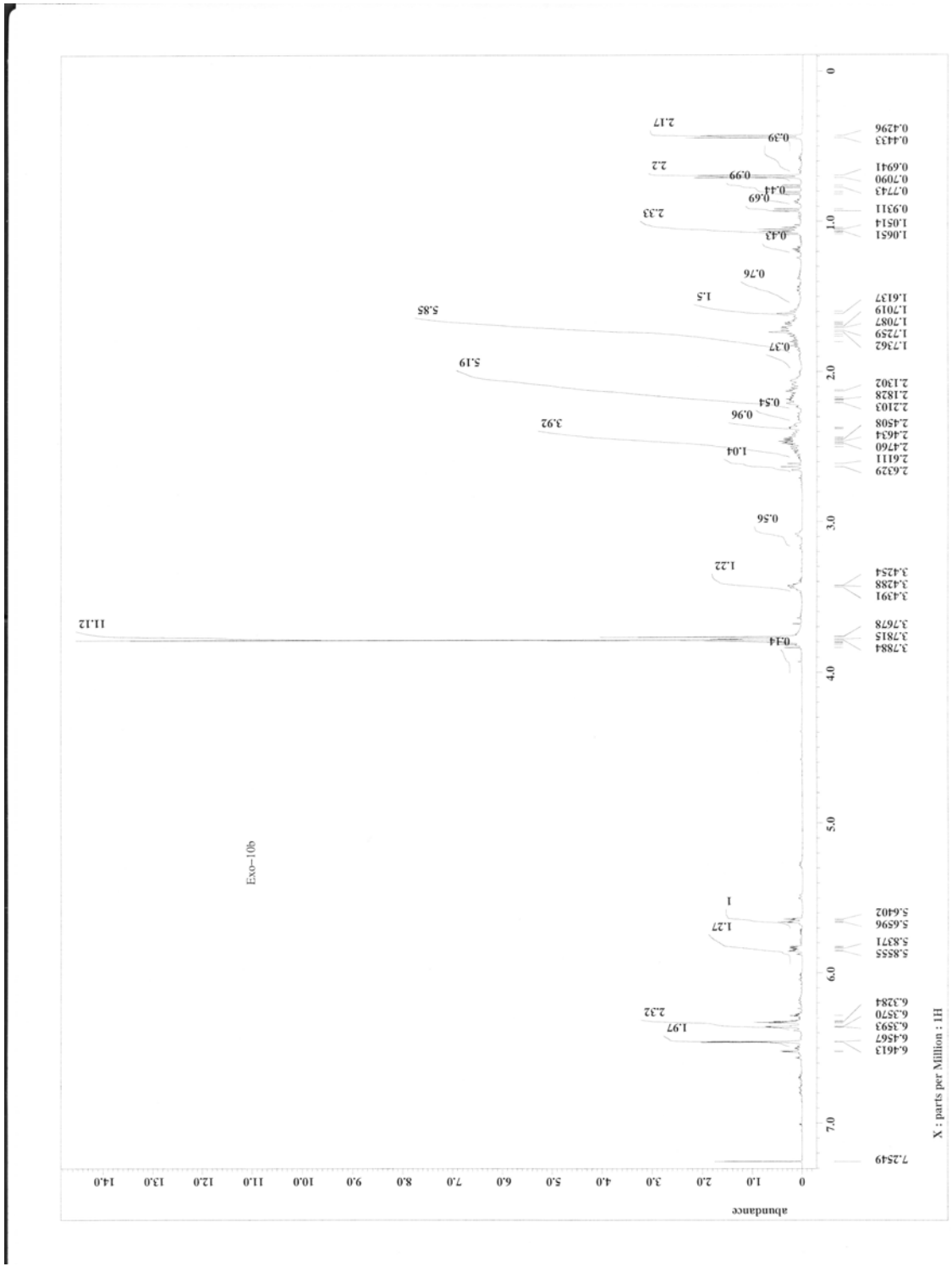
Spectrum 67. ^{1}H NMR spectrum of compound **10a** in $CDCl_3$



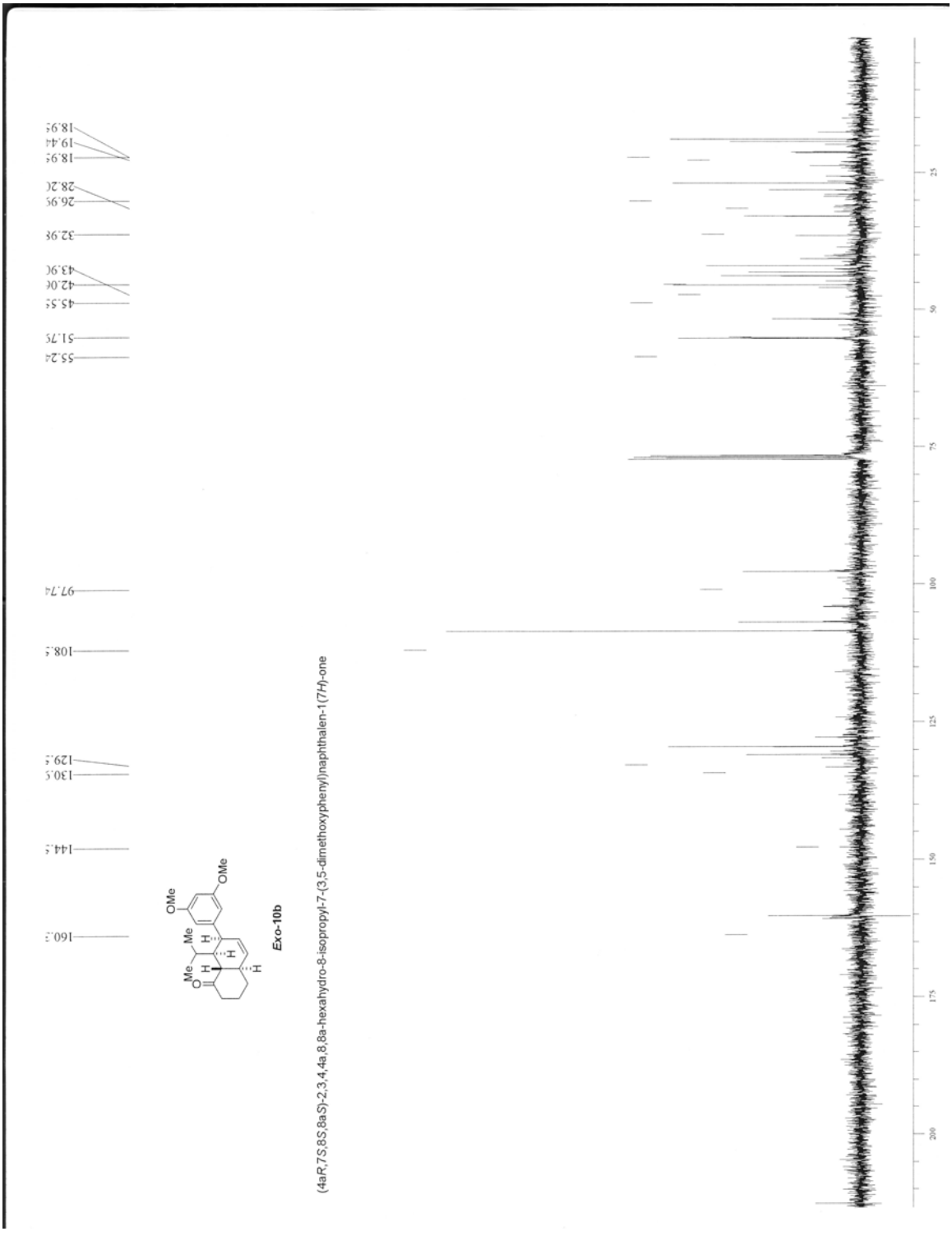
Spectrum 68. ^{13}C NMR spectrum of compound **10a** in $CDCl_3$



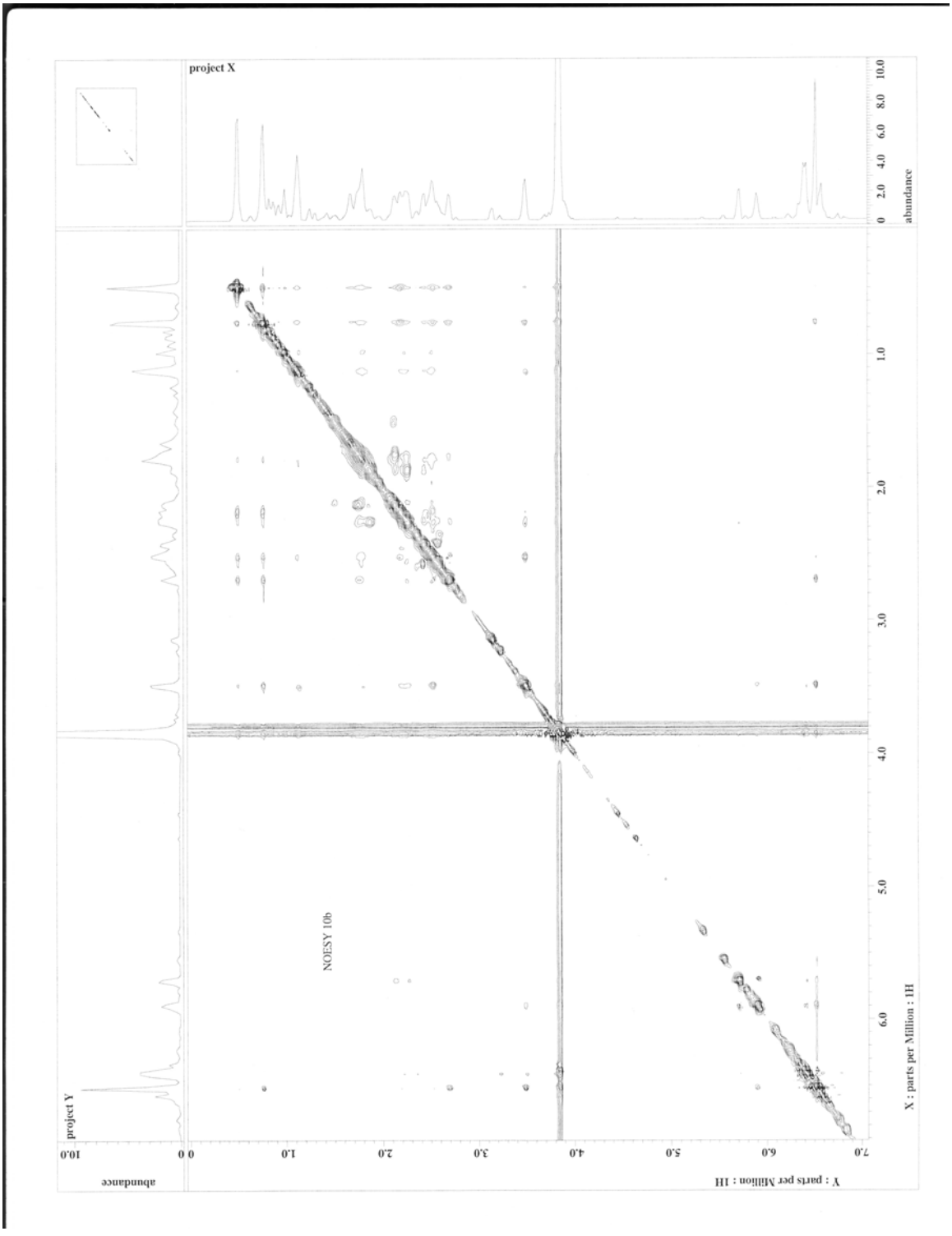
Spectrum 69. NOESY spectrum of compound **10a** in $CDCl_3$



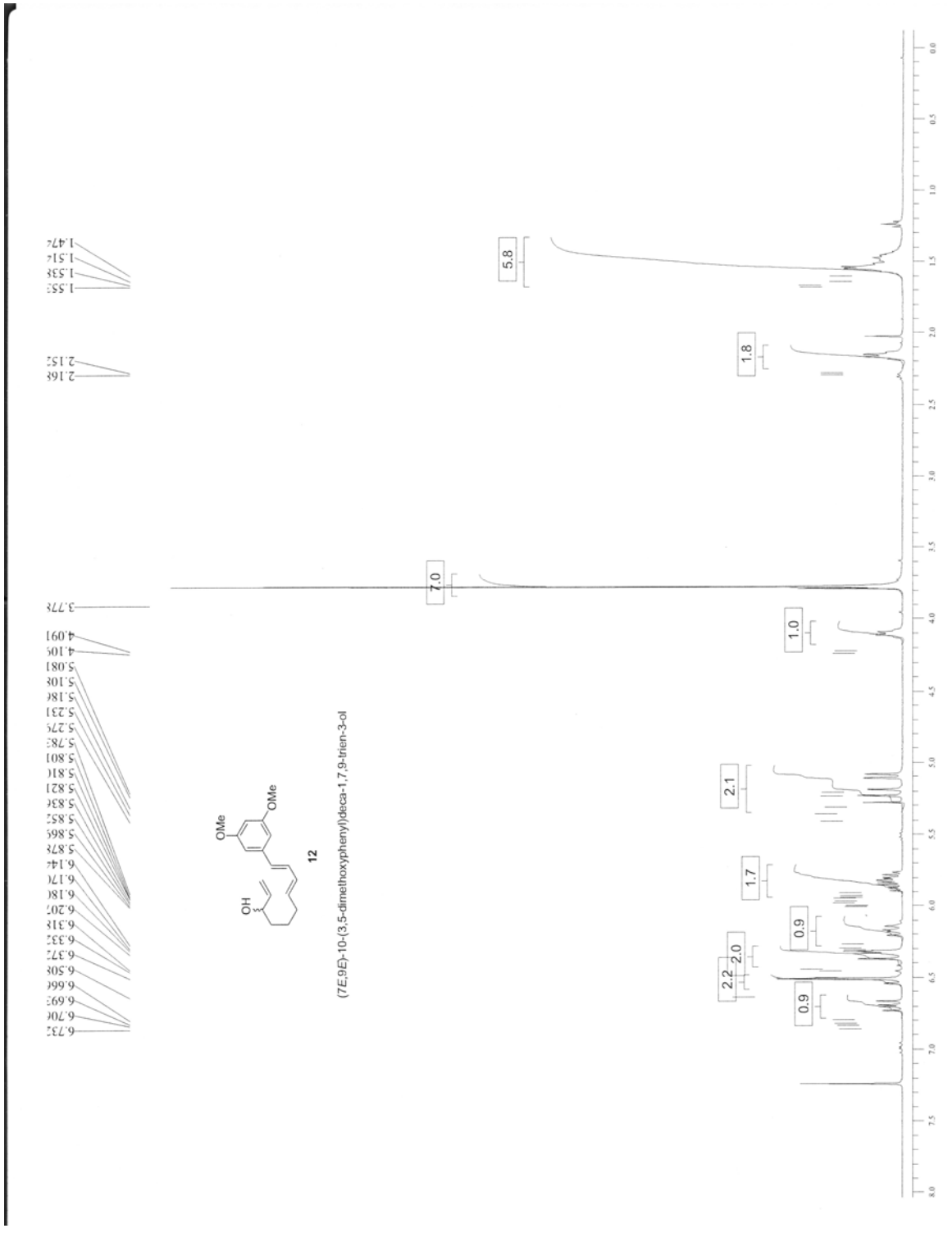
Spectrum 70. ^{1}H NMR spectrum of compound **10b** in $CDCl_3$



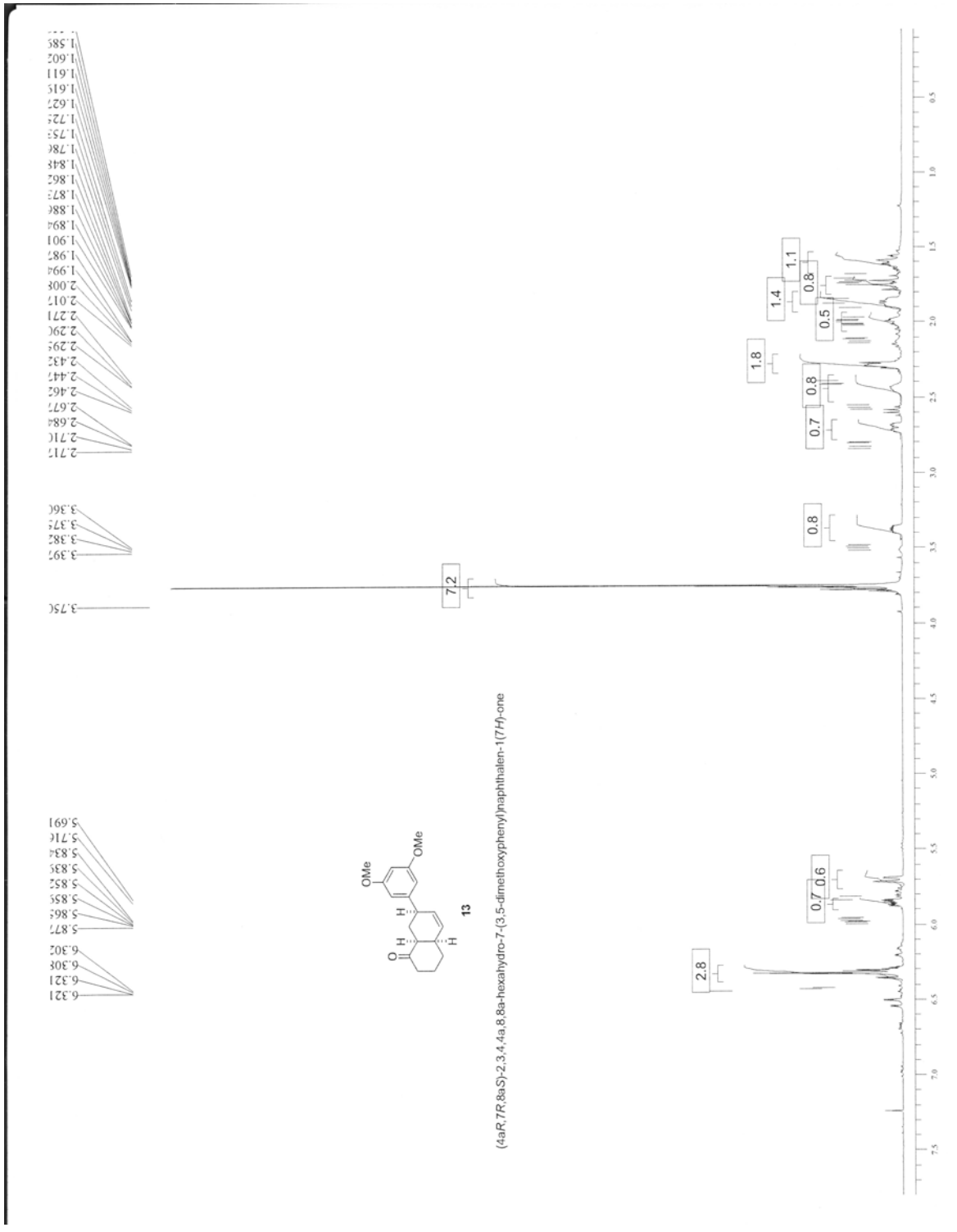
Spectrum 71. ^{13}C NMR spectrum of compound **10b** in $CDCl_3$



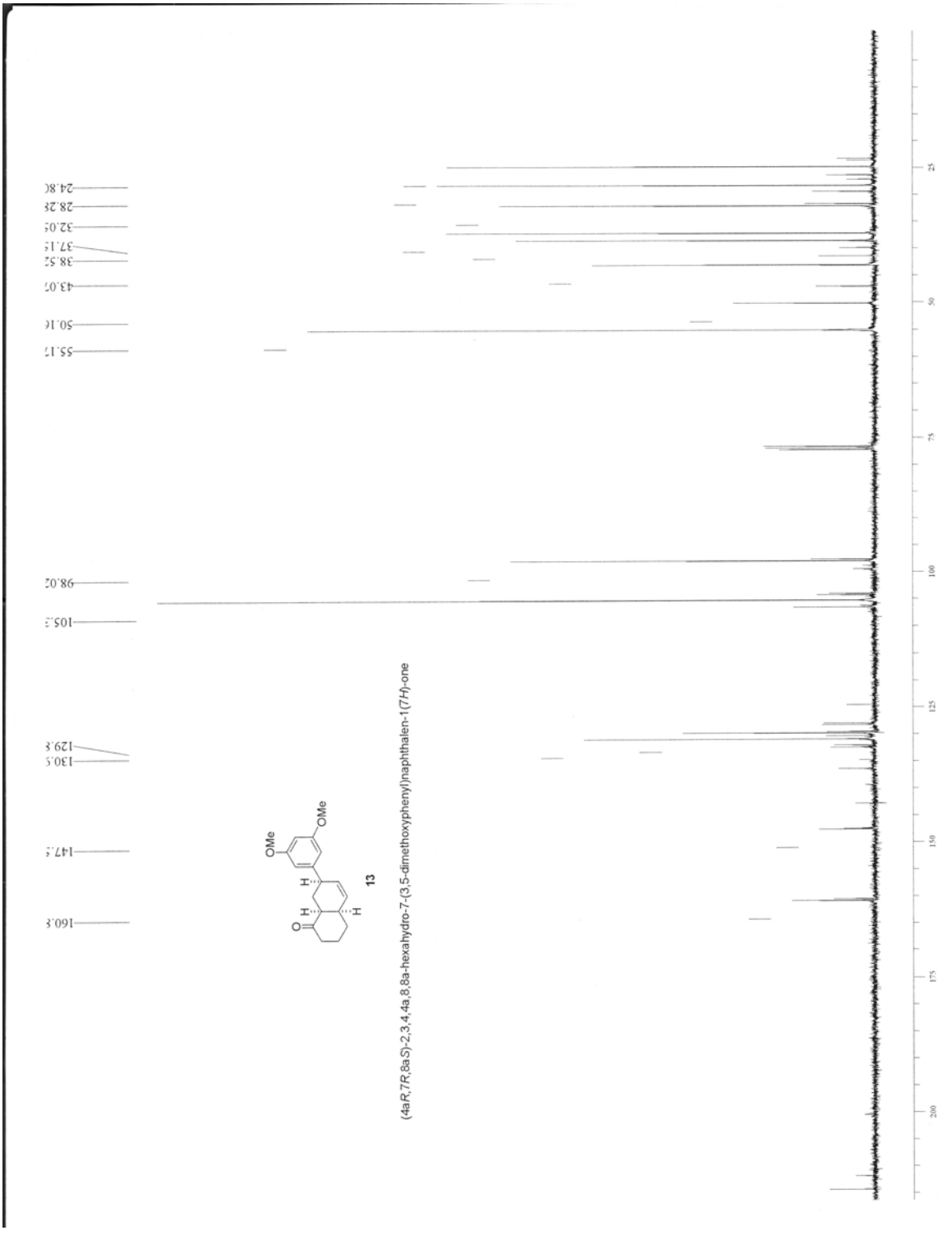
Spectrum 72. NOESY spectrum of compound **10b** in $CDCl_3$



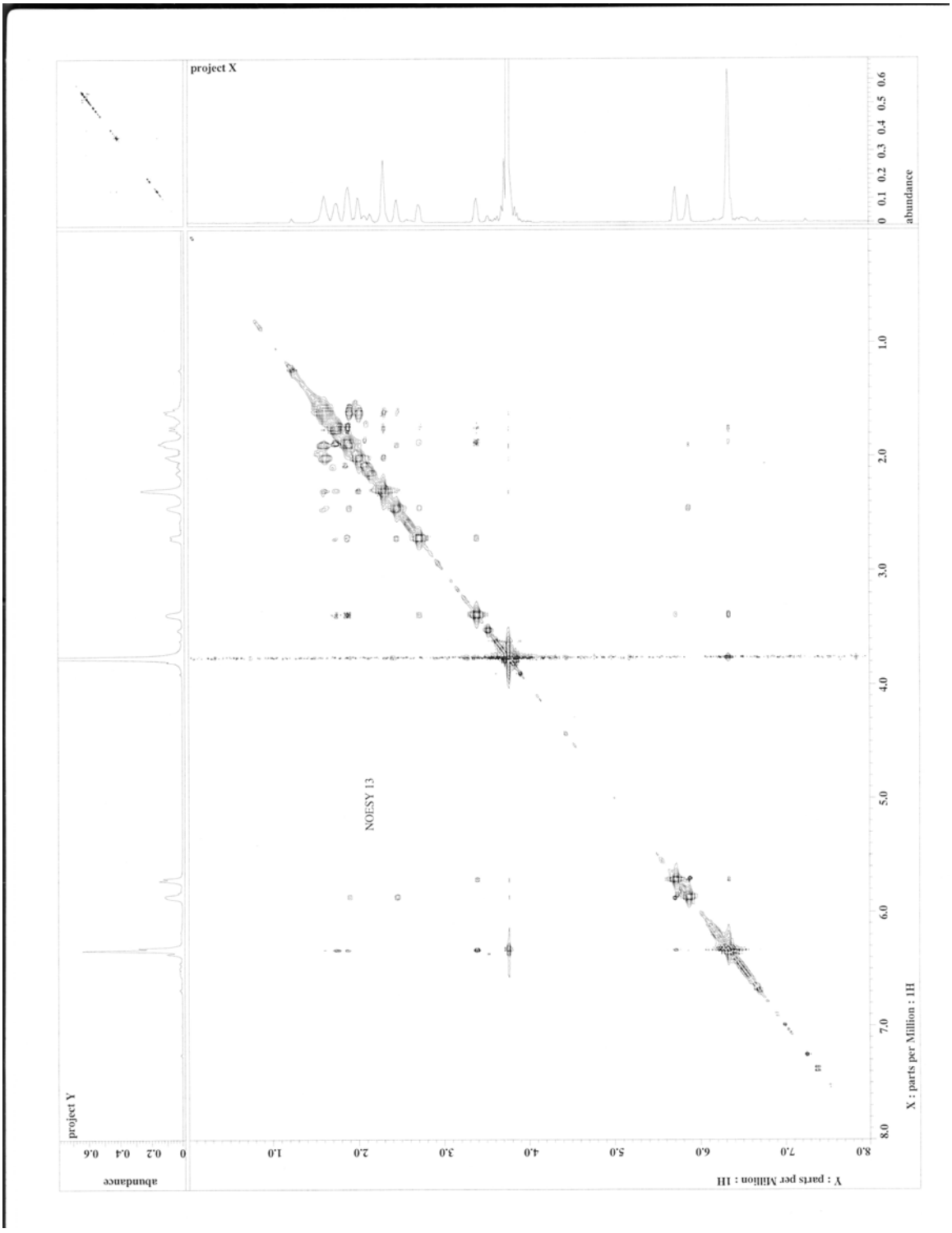
Spectrum 73. ^{1}H NMR spectrum of compound **12** in $CDCl_3$



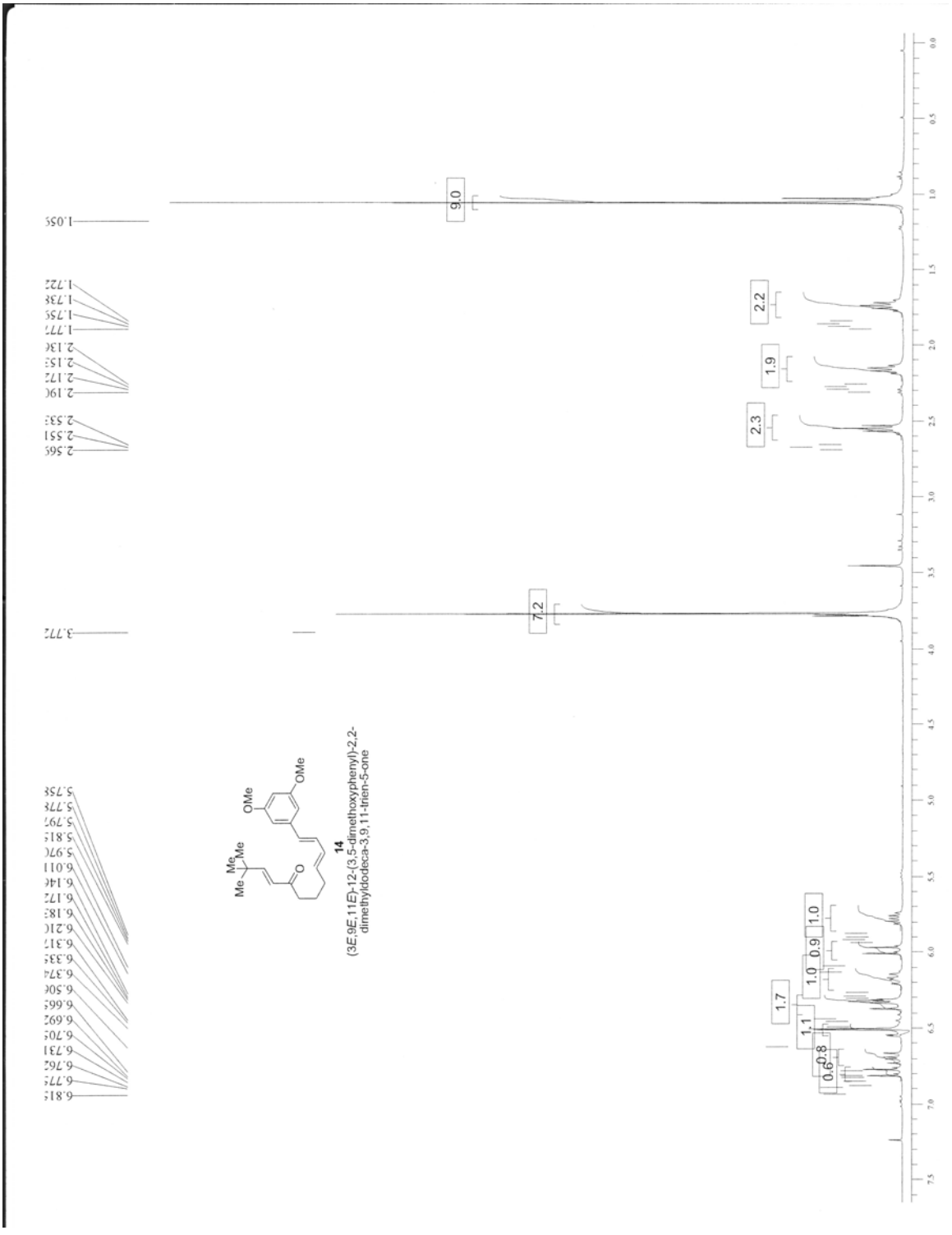
Spectrum 74. ^{1}H NMR spectrum of compound **13** in $CDCl_3$



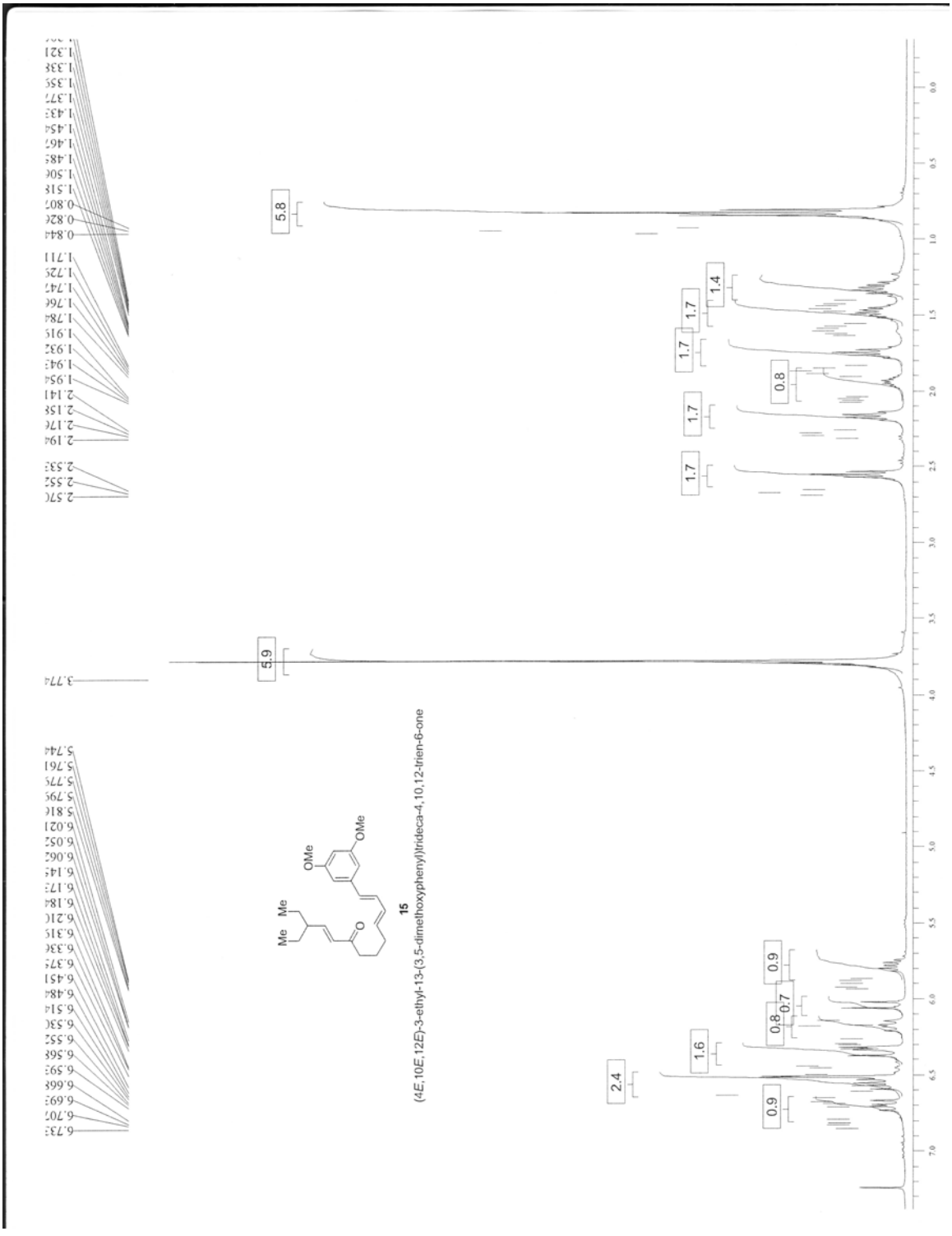
Spectrum 75. ^{13}C NMR spectrum of compound **13** in $CDCl_3$



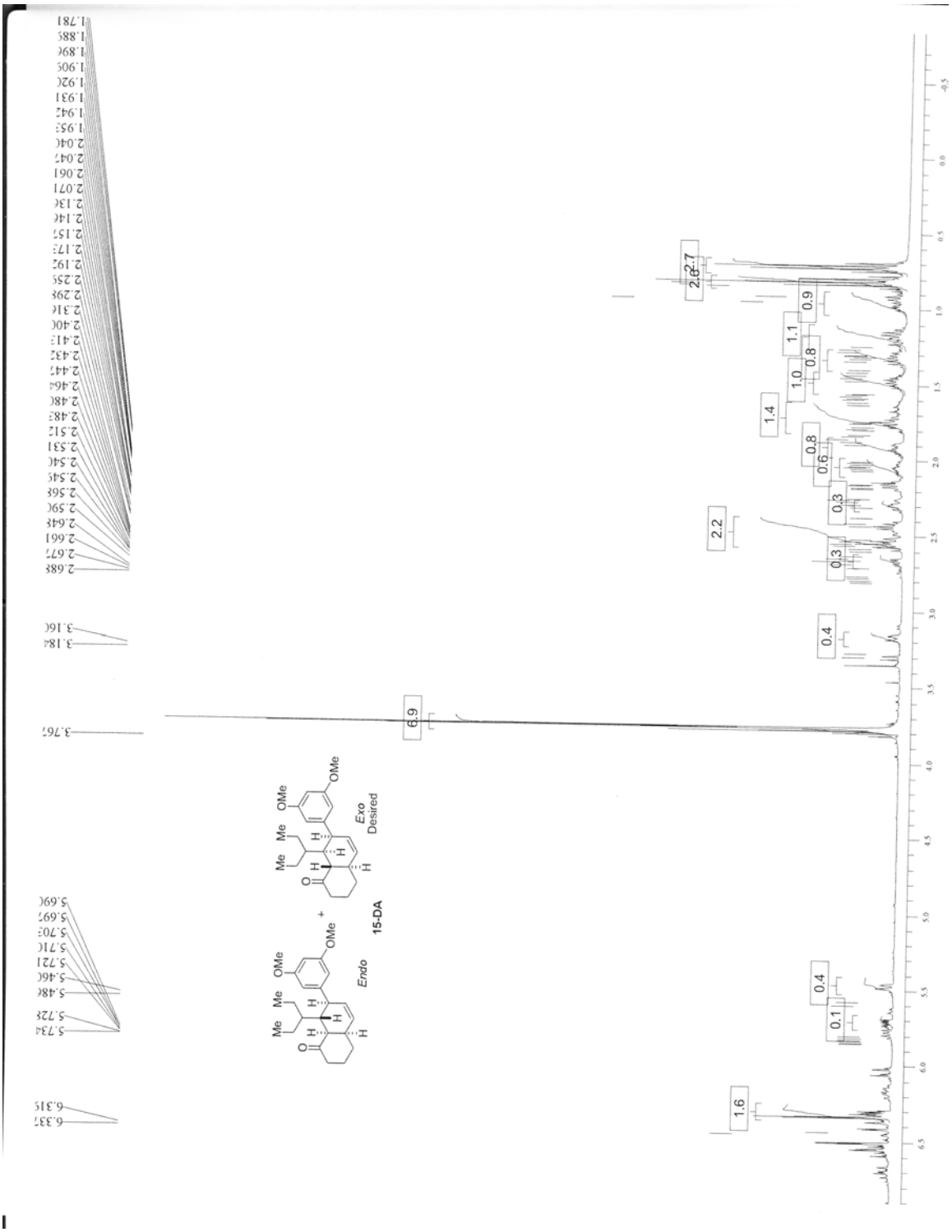
Spectrum 76. NOESY spectrum of compound **13** in $CDCl_3$



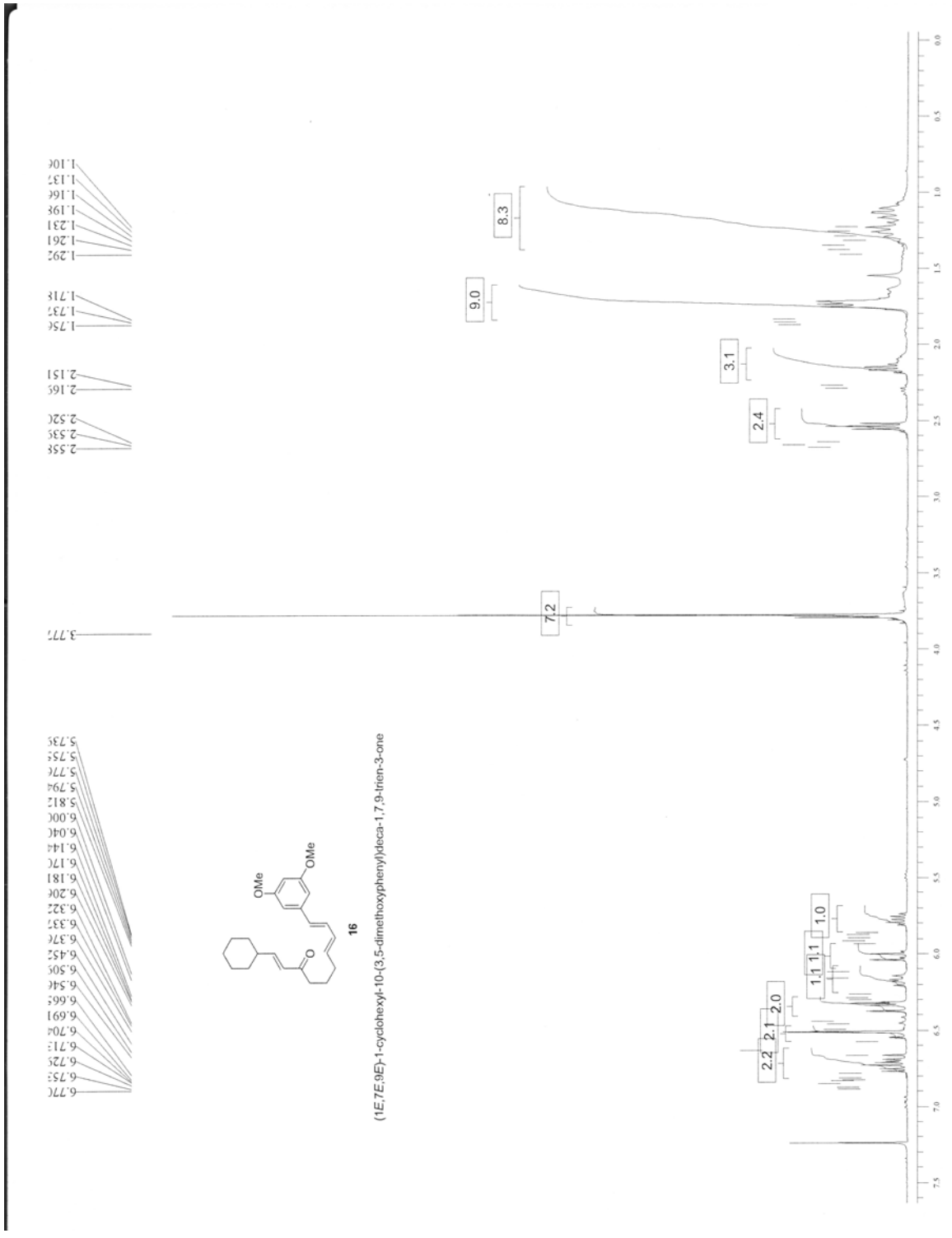
Spectrum 77. ^{1}H NMR spectrum of compound **14** in $CDCl_3$



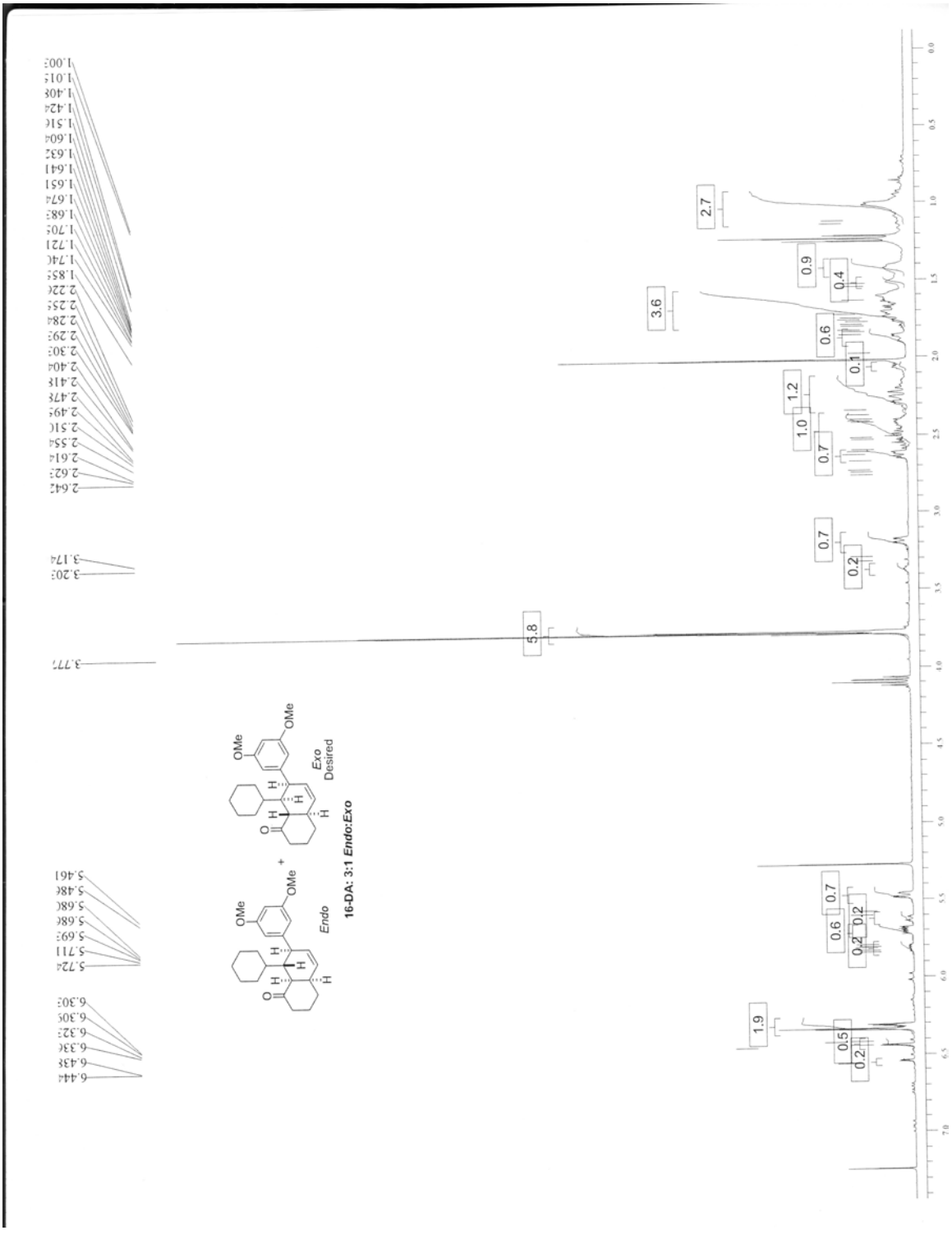
Spectrum 78. ^{1}H NMR spectrum of compound **15** in $CDCl_3$



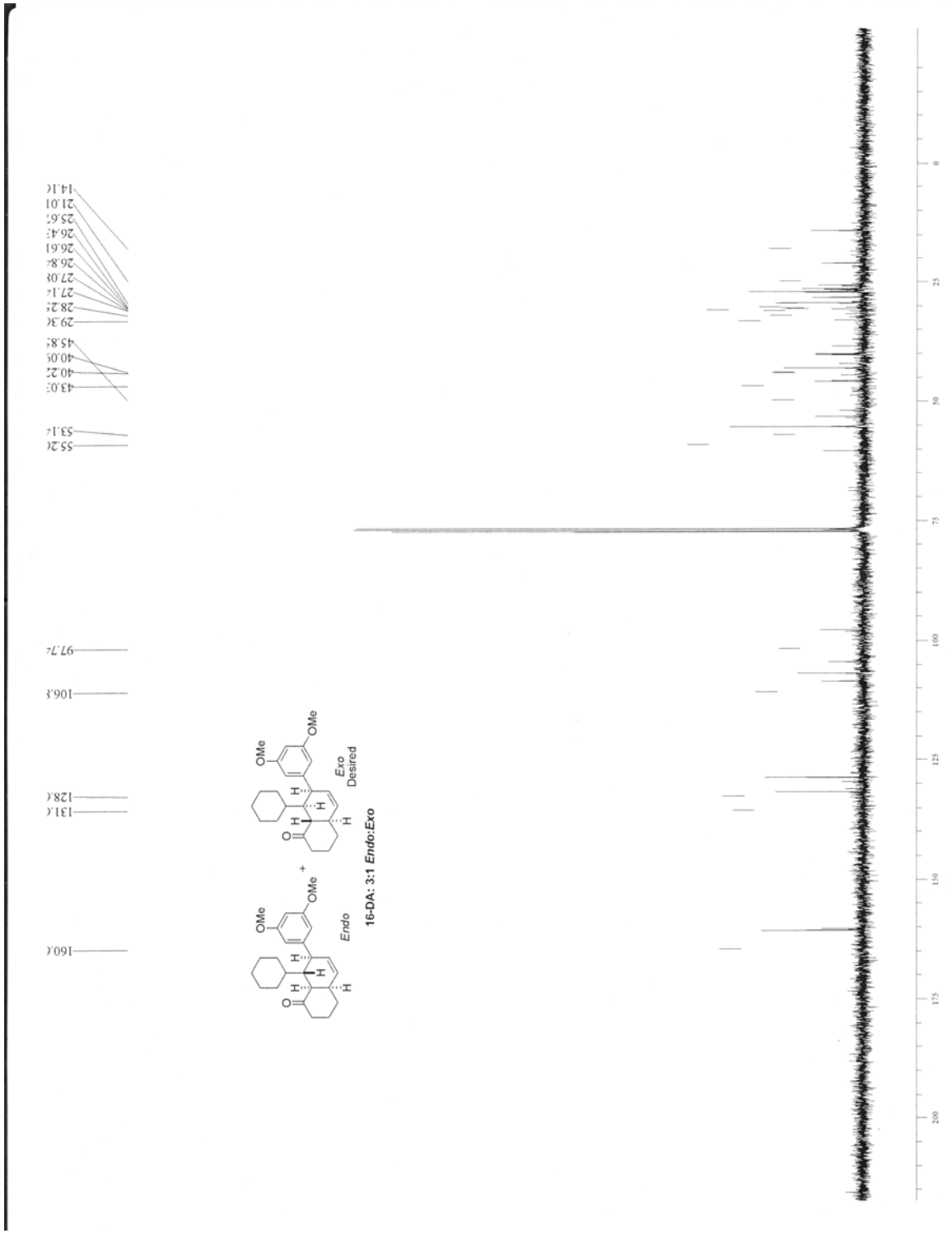
Spectrum 79. ^{1}H NMR spectrum of compound **15-DA** in $CDCl_3$



Spectrum 80. ^{1}H NMR spectrum of compound **16** in $CDCl_3$



Spectrum 81. ^{1}H NMR spectrum of compound **16-DA** in $CDCl_3$



Spectrum 82. ^{13}C NMR spectrum of compound **16-DA** in $CDCl_3$

CHAPTER 5

Explorations of Vinyl Oxocarbenium Ions in the Diels-Alder Reaction

A. What is a Vinyl Oxocarbenium?

Vinyl oxocarbenium ions can be described as allylic cations that are substituted at one terminus by at least one oxygen atom such as **1**. In the broadest sense, the literature is replete with examples of the cycloaddition chemistry of such species, particularly their behavior as dienophiles in the Diels-Alder reaction. This is the case because any α,β-unsaturated carbonyl compound that is complexed to a Lewis acid can be represented in one of its resonance forms as a vinyl oxocarbenium ion (Fig. 20).

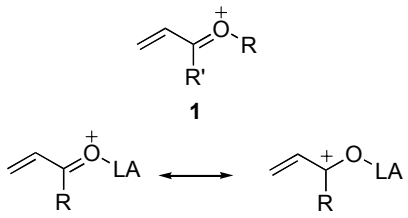


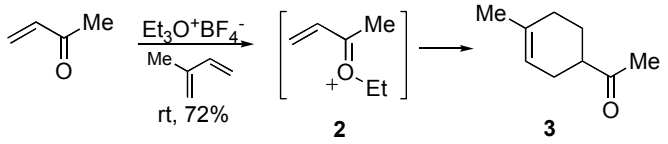
Figure 20. Vinyl Oxocarbenium

The [4+2] cycoaddition or Diels-Alder reaction is perhaps the most effective way of constructing six-membered ring systems. The reaction has been well studied since it was discovered in 1928.[1] Extensive research in the area of stereo- and regiocontrol, as well as application to the synthesis of natural products, has been conducted during the last few decades.[2] In an ordinary or 'normal' Diels-Alder reaction, the interaction between the HOMO of an electron-rich diene and the LUMO of an electron-poor dienophile is a major factor in determining the rate and regiochemical outcome of the reaction. Since there is no other carbon-based electron-withdrawing group better than a carbocation, an olefin bearing an adjacent carbocation would be expected to act as an excellent dienophile. Diels-Alder reactions involving allylic cations as dienophiles are referred to as ionic Diels-Alder reactions. Many variations on this theme are possible,

and in this chapter, I'll illustrate relevant examples in which those cation 'substituents' are further stabilized by one or more alkoxy groups.[3] This variety of activation for symbioimine's [4+2] cycloaddition could prove to be biosynthetically informative in regards to whether or not its amine functionality is necessarily present for an *endo*-selective intramolecular Diels-Alder reaction to occur from a cyclic *cis*-dienophile precursor produced from a primary alcohol.

B. History and Use in [4+2] Cycloadditions

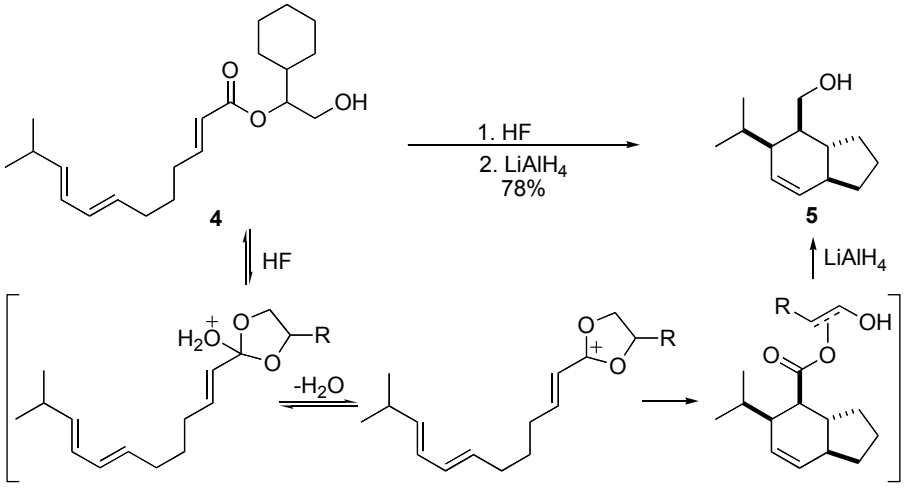
What appears to be the first example of an oxocarbenium ion in a [4+2] cycloaddition reaction came from the Sasaki laboratory in 1982.[4] They showed that methyl vinyl ketone underwent a [4+2] cycloaddition reaction with isoprene at room temperature in the presence of triethyloxonium tetrafluoroborate to afford cycloadduct **3** in 72% yield. It is not clear, however, that the vinyl oxocarbenium ion **2** was an intermediate in the reaction (Scheme 44).



Scheme 44. The First Example of an Oxocarbenium Ion in a [4+2] Cycloaddition

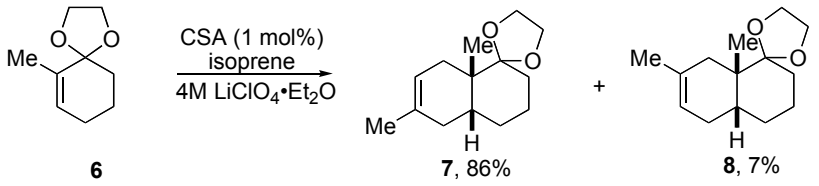
Subsequently, Roush and co-workers convincingly demonstrated the intermediacy of an oxocarbenium ion in certain intramolecular Diels-Alder reactions catalyzed by hydrofluoric acid.[5] For example, treatment of **4** with HF in acetonitrile at room

temperature resulted in a cycloadduct as a mixture of esters, which upon reduction gave alcohol **5** in 78% overall yield (Scheme 45).



Scheme 45. HF-Activated Vinyl Oxocarbenium Ion

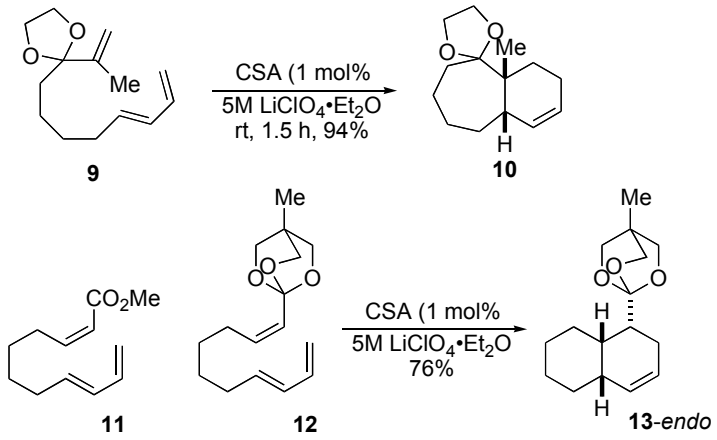
Grieco and co-workers demonstrated that the ethylene ketals of various α,β-unsaturated ketones would react with dienes in 4 M $LiClO_4$ in ether in the presence of a catalytic amount of camphorsulfonic acid (CSA).[6] For example, the ethylene acetal of 2-methyl-2-cyclohexanone (**6**) afforded the cycloadducts **7** and **8** in 86 and 7% yields, respectively, upon reaction with isoprene (Scheme 46). The reactions took place between room temperature and 0 ˚C.



Scheme 46. Use of Ethylene Ketals in Oxocarbenium-Activated [4+2] Cycloadditons

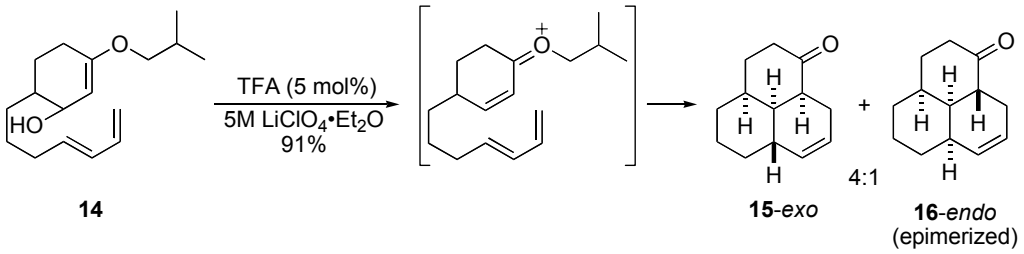
Additional examples more analogous to the symbioimine framework have

demonstrated the general utility of the method. Treatment of **9** with catalytic CSA in 5 M $LiClO_4$ gave cycloadduct **10** in 94% yield as a single stereoisomer. The ketone corresponding to **9** required a reaction temperature near 200 ˚C to undergo cycloaddition. Similarly, while the methyl ester **11** was known to react at high temperatures but with little selectivity to afford a Diels-Alder cycloadduct, the reaction of the orthoester **12** in 5 M $LiClO_4$ led to **13** in 76% yield as the only product (Scheme 47).



Scheme 47. Orthoester Activation in [4+2] Cycloadditions

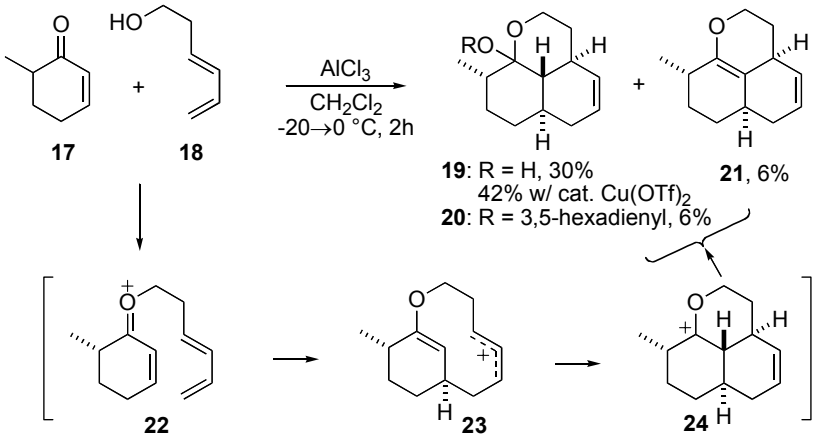
A different approach to vinyl oxocarbenium ioins using the same reaction conditions was also introduced by the Grieco group. In this case, readily prepared hydroxy enol ethers were exposed to acid in 5 M $LiClO_4$ in ether to generate oxocarbenium ions, which underwent rapid cycloaddition.[7] For example, the reaction of **14** produced cycloadducts **15** and **16** in a ratio of 4:1 in 91% yield (Scheme 48). The former cycloadduct was the result of an *exo* transition state and the latter from an *endo* transition state followed by a post-cyclization epimerization (Just like our proposed biosynthesis of Symbioimine!). With but one exception, it appeared that all of the intramolecular cycloadditions studied in this work proceeded in a concerted fashion.



14 **15**-*exo* **16**-*endo* (epimerized)

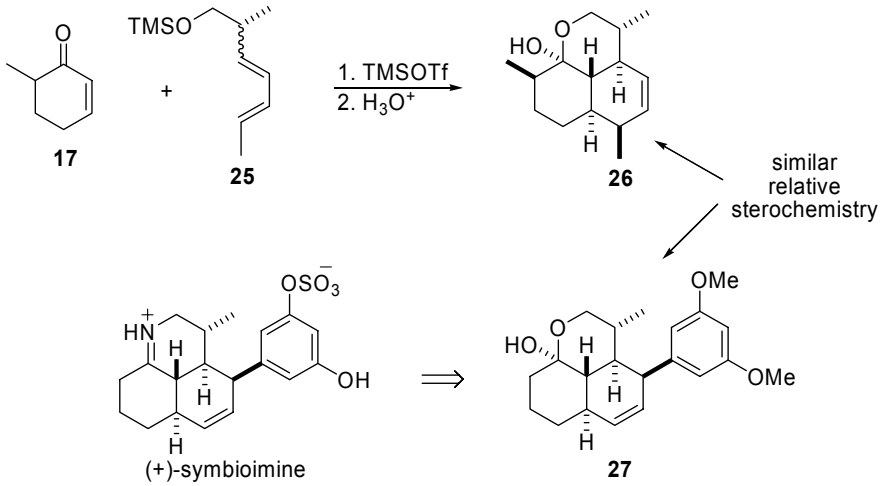
Scheme 48. Hydroxy Enol Ethers serve as Vinyl Oxocarbenium Precursors

All of the cycloaddition reactions discussed up to this point have involved intermolecular or intramolecular reactions in which the diene is connected to the vinyl oxocarbenium ion via a tether of carbon atoms. However, several examples exist of intramolecular cycloadditions in which the diene is joined to the vinyl oxocarbenium ion via the oxygen of the oxocarbenium intermediate. For example during the course of the synthesis of an analogue of artemisinic acid, Haynes and co-workers examined the Lewis acid catalyzed ionic Diels-Alder reaction of 6-methyl-2-cycloexenone **17** and hydroxy diene **18**.[8] In the presence of $AlCl_3$, enone **17** reacted with diene **18** to provide *trans*-fused octalin **19** (30%), acetal **20** (6%) and dehydration product **21** (6%) (Scheme 49). When the reaction was catalyzed by $Cu(OTf)_2$ in MeCN, **19** (42%) and variable amounts of **20** (up to 8%) were obtained. The relative stereochemistry of **19** was established by X-ray crystallography.[9] The mechanism of this reaction was proposed to involve the formation of a vinyloxocarbenium ion (**22**) followed by a cyclization to form **23**, which underwent ring closure to afford **24**. This cation then proceeded to the products isolated.



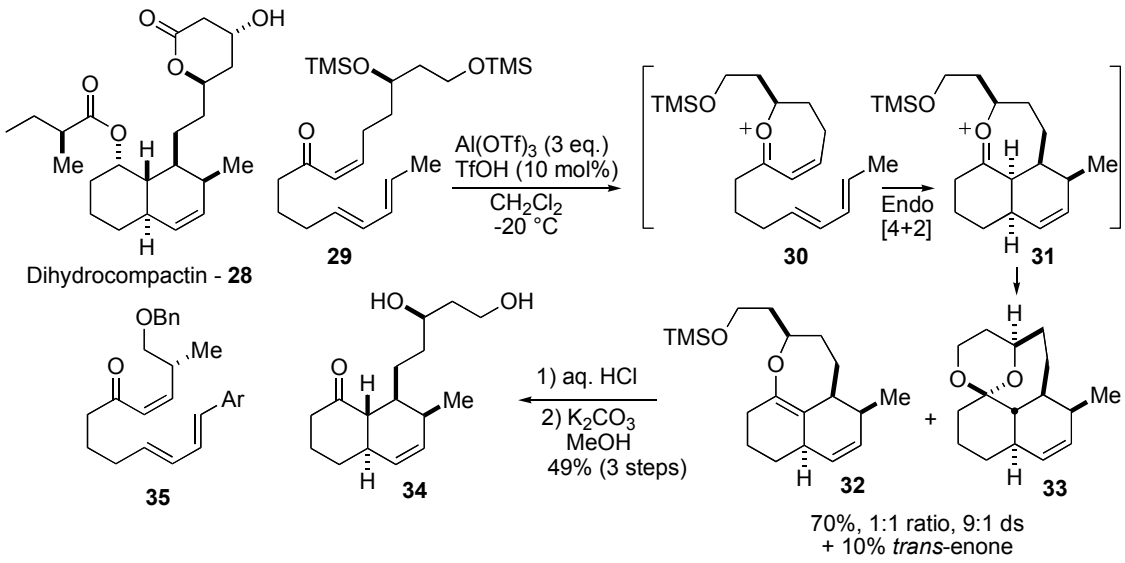
Scheme 49. Vinyl Oxocarbenium Ion Generation Using an Oxygenated Tether

Additionally, the reaction of a mixture of TMS ethers (TMS activation popularized by Gassman)[10] of (2R)-2-methylheptadien-1-ols (E/Z mixture at position 3) with racemic 6-methyl-2-cyclohexenone afforded a mixture of cycloadducts in 25% yield which upon hydrolysis afforded **25** as a single, enantiomerically pure compound (Scheme 7).[11] The formation of **26** supports the idea of an *endo*-transition state in the cycloaddition process in which initial attack on the dienophile occurs on the face *cis* to the methyl group. This contrasts with the initial mechanistic formulation in which attack was assumed to occur *trans* to the methyl group (see Scheme 50). In any case, the result bodes well for the development and application of relative stereocontrol in reactions of this type, as I was hoping when applying this mode of activation of [4+2] cycloadditions to the symbioimine framework (**27**).



Scheme 50. Use of TMS-Ethers in the Generation of Vinyl Oxocarbenium Ions

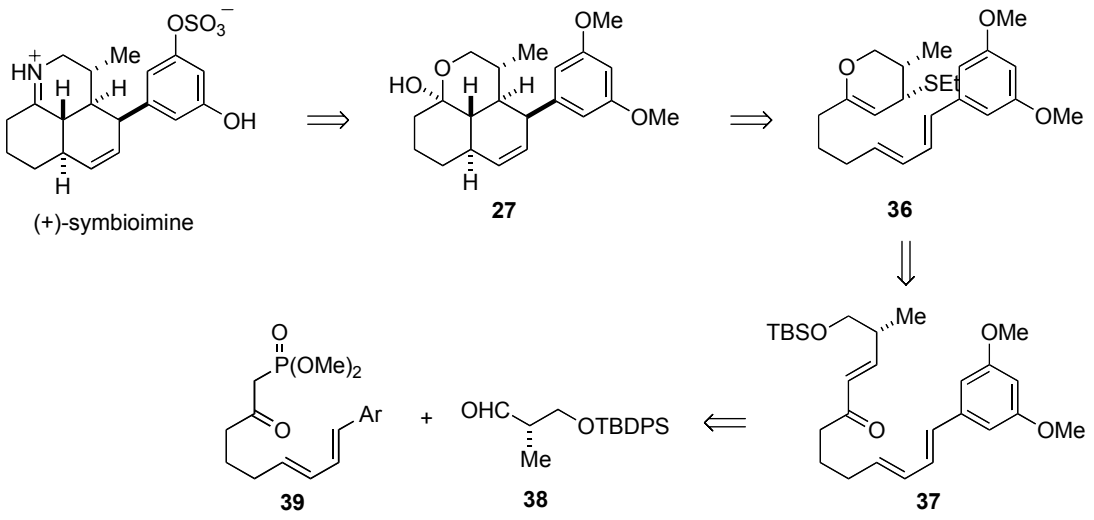
Recently, a synthesis of (+)-dihydrocompactin **28** featuring an oxonium-activated intramolecular Diels-Alder reaction was reported.[12] As seen in Scheme 51, the similarities between the frameworks and stereochemistries of dihydrocompactin **28** and symbioimine are striking. From the *cis*-enone substrate **29**, treatment with either TMSOTf (5 mol%) or Al(OTf) (3 eq.) and TfOH (10 mol%) in CH_2Cl_2 at –20 ˚C gave a 9:1 dr of cycloadducts **32** and **33** in 70% yield as in 1;1 ratio, as well as 10% of the *trans*-isomerized starting material. The mixture of **32** and **33** was then subjected to aqueous acid to cleave the cyclic enol ether, followed by K_2CO_3 in MeOH to induce a *cis* to *trans*-decalin isomerization, yielding bicycle 34 in 49% yield (3 steps).



Scheme 51. Synthesis of Dihydrocompactin Featuring a Vinyl Oxocarbenium Ion Intermediate in a [4+2] Cycloaddition

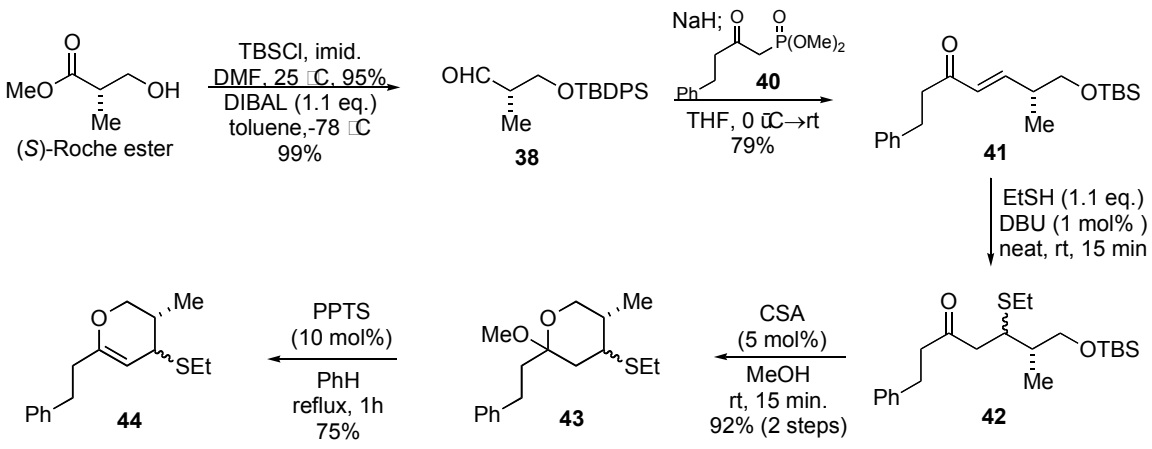
C. Hypothesis, Retrosynthesis and Construction of Model System

While the γ-proton of **35** was particularly prone to inducing *trans*-isomerization, prohibiting us from using this methodology, it was predicted that a *cis*-relationship could be masked and appropriately produced much in the same way as was described in the previous chapter. As illustrated in Scheme 52, cyclic enol ether **36** with a suitable leaving group could furnish the vinyl oxocarbenium intermediate upon activation and elimination of the sulfide, which would then undergo a [4+2] cycloaddition to yield **27**. Enol ether **36** could readily be obtained from *trans*-enone **37** by the familiar conjugate addition of EtSH followed by condensation; **37** itself can also be constructed using the methods previously mentioned from aldeyde **38** and β-ketophosphonate **39**.



Scheme 52: Retrosynthesis of Vinyl Oxocarbenium Precursor

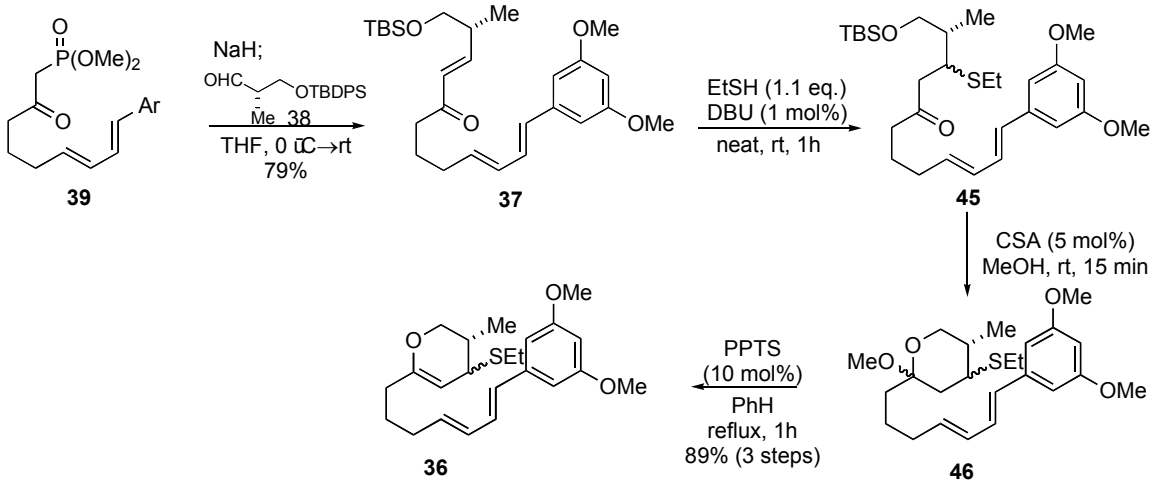
To confirm the validity of the proposed synthetic route with a simpler system, the construction of masked vinyl oxocarbenium **44** began with the commercially available (*S*)-Roche ester, whose TBS protection and subsequent DIBAL reduction produced aldehyde **38** 99% yield (two steps). Horner-Wadsworth-Emmons olefination with β-ketophosphonate **40** gave *trans*-enone **41** in 79% yield. Using the methodology from Chapter 3, quick conjugate addition of ethanethiol catalyzed by DBU, followed by a one pot camphorsulfonic acid-catalyzed sequential silyl-ether deprotection/intramolecular acetal formation sequence produced heterocycle **43** in 92% yield over the two steps. PPTS-catalyzed elimination of methanol and the resulting oxonium isomerization to the enol ether produced **44** in 75% yield.



Scheme 53: Construction of Model Masked Vinyl Oxocarbenium **44**

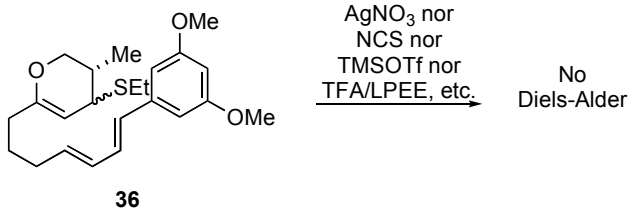
D. Construction of the Symbioimine Framework and Attempted Diels-Alder Reaction

After the synthetic route to a masked vinyl oxocarbenium ion was confirmed, the construction of the symbioimine framework (Scheme 54) could begin in earnest. Horner-Wadsworth-Emmons olefination of aldehyde **38** with β-ketophosphonate **39** produced *trans*-enone **37** in 79% yield. Application of the proceeding methodology was uneventful, with DBU-catalyzed conjugate addition of ethanethiol to **37** producing ethyl sulfide **45**, followed by CSA-catalyzed silyl-ether methanolysis and acetal formation, and PPTS-catalyzed condensation/elimination of methanol gave the desired masked vinyl oxocarbenium compound **36** in 89% over the three steps.



Scheme 54: Construction of Masked Vinyl Oxocarbenium **36**

With masked vinyl oxocarbenium **36** containing the symbioimine framework in hand, its submission to all known sulfide-activation / vinyl oxocarbenium forming [4+2] cycloaddition conditions were undertaken (Scheme 55). Unfortunately, not even the slightest evidence of a Diels-Alder adduct was observed, save for extensive decomposition of the vinyl oxocarbenium heterocycle and the unreacted presence of the diene system.



Scheme 55: Application of [4+2] Cycloaddition Methods to the Symbioimine Framework

E. Conclusions

Despite the promising precedence of vinyl oxocarbenium-activated Diels-Alder reactions in natural product synthesis, its biomimetic-like application to the unique cyclic system and diene of the symbioimine framework was disappointing. On the flipside, this disappointing result does reinforce the importance of the terminal amine's and its potential ability to self-activate the proposed [4+2] cycloaddition.

F. Acknowledgements

In addition to thanking the University of California for financial support, we also thank Dr. Yongxuan Su for Mass Spectroscopy and Dr. Anthony Mrse for instruction on the 500 MHz Jeol NMR spectrometer.

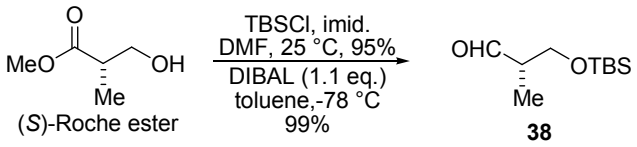
G. Experimentals

Materials and Methods

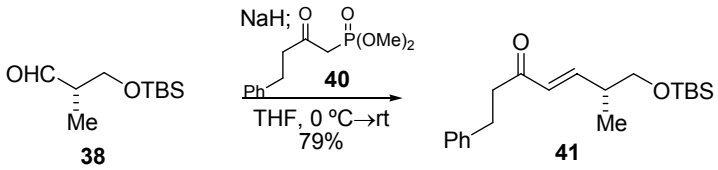
All reagents were commercially obtained (Aldrich, Fisher) at highest commercial quality and used without further purification except where noted. Organic solutions were concentrated by rotary evaporation below 45 ˚C at approximately 20 mmHg. Tetrahydofuran (THF), methanol (MeOH), chloroform ($CHCl_3$), dichloromethane (DCM), ethyl acetate (EtOAc), acetonitrile (CH_3CN), and acetone were purchased as reagent grade and used without further purification. Reactions were run under an inert N_2 atmosphere unless otherwise noted. Yields refer to chromatographically and spectroscopically (^{1}H- and ^{13}C-NMR) homogeneous materials, unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254), visualized with UV light

and stained with cerium molybdate solution and heat. E. Merck silica gel (60A, particle size 0.040-0.063 mm) was used for flash chromatography. Preperative thin-layer chromatography separations were carried out on 0.50 mm E. Merck silica gel plates (60F-254). NMR spectra were recorded on Varian Mercury 300, 400 and/or Unity 500 MHz instruments and calibrated using the residual undeuterated solvent as an internal reference. Chemical shifts (δ) are reported in parts per million (ppm) and coupling constants (*J*) are reported in hertz (Hz). The following abbreviations are used to designate multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Mass spectra (MS) and high-resolution mass spectra (HRMS) were recorded on a Finnigan LCQDECA mass spectrometer under electrospray ionization (ESI) or atmospheric pressure chemical ionization (APCI) conditions, or on a Thermo-Finnegan Mat900XL mass spectrometer under electron impact (EI), chemical ionization (CI), or fast atom bombardment (FAB) conditions. X-ray data were recorded on a Bruker SMART APEX CCD X-ray diffractometer. Specific optical rotations were recorded on a Jasco P-1010 polarimeter and the specific rotations were calculated based on the equation $[\alpha]^{25}_{D} = (100 \cdot \alpha)/(l \cdot c)$, where the concentration c is in g/100 mL and the path length *l* is in decimeters.

Procedures and Spectral Data

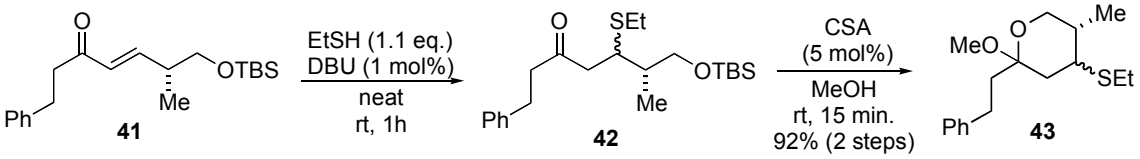


(*S*)-3-(*t*-butyldimethylsilyl ether)-2-methylpropanal 38: *t*-Butyldimethylsilyl chloride (2.81 g, 18.62 mmol, 1.1 equiv.) was added to a 0 ˚C solution of the (*S*)-Roche ester (2.0 g, 16.93 mmol, 1.0 equiv.) and imidazole (1.73 g, 25.4 mmol, 1.5 equiv.) in DMF (12 mL). After warming to room temperature and stirring for 1h, the reaction was diluted with EtOAc and 1M HCl. The layers were separated, and the organic washed with sat. $NaHCO_3$ and brine, followed by drying over Na_2SO_4. Upon evaporation *in vacuo*, the crude material was purified over silica (5:1 hexane:EtOAc, R_f = 0.75) to give the silyl ether (3.93 g, 100%) as a clear oil. Subsequently, DIBAL-H (1.5M, 1.13 mL, 4.859 mmmol, 1.13 equiv.) was slowly added dropwise to a solution of ester **38** (1.0 g, 4.30 mmol, 1.0 equiv.) in toluene (43 mL) at –78 ˚C. After 2h at –78 ˚C, the reaction was quenched by the addition of a sat. sodium potassium tartrate solution and allowed to warm to room temperature. The layers were separated, and the aqueous extracted twice with EtOAc. The combined organics were washed with brine, dried over Na_2SO_4, and evaporated *in vacuo* to give a crude material that was readily purified over silica (9:1 hexane:EtOAc R_f = 0.75) to give aldehyde **38** (0.835 g, 95% yield) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.74 (s, 1H), 3.83 (dq, *J* = 5.2, 10.4 Hz, 2H), 2.53 (s, *J* = 6.8, Hz, 1H), 1.09 (d, *J* = 7.2 Hz, 3H), 0.87 (s, 9H), 0.05 (s, 6H).



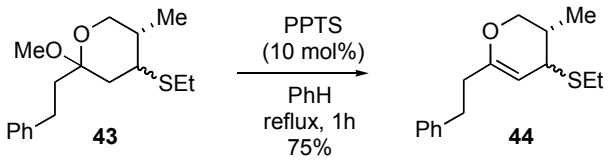
(*R*,*E*)-7-(*t*-butyldimethylsilyl ether)-6-methyl-1-phenylhept-4-en-3-one 41: Sodium Hydride (135 mg, 3.37 mmol, 1.05 equiv.) was added to a 0 ˚C solution of β-

ketophosphonate **40** (688 mg, 3.21 mmol, 1.0 equiv.) in THF (13 mL) and allowed to stir for 1h, whereupon aldehyde **38** (650 mg, 3.21 mmol, 1.0 equiv.) in THF (1 mL) was added, allowing the reaction to warm to room temperature. The reaction was quenched by the addition of water and diluted with EtOAc. The layers were separated, and the aqueous extracted twice with EtOAc. The combined organics were washed with brine, dried over Na_2SO_4, and evaporated *in vacuo* to give a crude material that was readily purified over silica (15:1 hexane:EtOAc $R_f = 0.25$) to give *trans*-enone **41** (0.880 g, 83% yield) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.26 (m, 2H), 7.18 (m, 3H), 6.77 (dd, J = 7.6, 16.4Hz, 1H), 6.09 (d, J = 16.4 Hz, 1H), 3.50 (d, J = 6.8 Hz, 2H), 2.94-2.83 (m, 4H), 2.51-2.44 (m, 1H), 1.02 (d, J = 6.8 Hz, 3H), 0.86 (s, 9H), 0.01 (s, 6H).



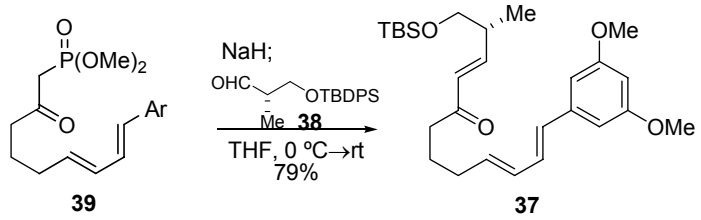
(5*S*)-4-(ethylthio)-tetrahydro-2-methoxy-5-methyl-2-phenethyl-2*H*-pyran 43: DBU (4.5 μL, 0.0311 mmol, 1 mol%) was added to a round bottom flask containing *trans*-enone **41** (1.035 g, 3.11 mmol, 1.0 equiv.) and ethanethiol (0.25 mL, 3.42 mmol, 1.1 equiv.) neat at room temperature. After 10 minutes the reaction was complete, and the volatile contents removed *in vacuo* to give ethylsulfide **42** in quantitative yield. To this material, then, was added MeOH (30 mL), and camphorsulfonic acid (72 mg, 0.031 mmol, 10 mol%), and allowed to stir until the starting material was consumed, <10 minutes. After evaporation of the solvent *in vacuo* and dilution with sat. $NaHCO_3$ and EtOAc, the layers were separated, and the aqueous layer extracted twice with EtOAc.

The combined organics were washed with brine, dried over Na_2SO_4, and evaporated *in vacuo* to give a crude material which upon purification over silica (9:1 hexanes:EtOAc, Rf = 0.20) produced methyl acetal **43** (842 mg, 92% yield over 2 steps) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.26 (m, 2H), 7.17 (m, 3H), 3.57 (dd, *J* = 4.8, 11.6 Hz, 1H), 3.28 (t, *J* = 11.6 Hz, 1H), 3.18 (s, 3H), 2.73-2.59 (m, 2H), 2.55 (q, *J* = 7.2 Hz, 2H), 2.22 (dd, *J* = 4.0, 13.2 Hz, 1H), 2.00 (dd, *J* = 4.8, 12.4 Hz) + 1.96 (dd, *J* = 5.6, 12.4 Hz) = 1H, 1.82 (dd, *J* = 6.4, 11.6 Hz) + 1.78 (dd, *J* = 6.0, 12.0 Hz) = 1H, 1.62 (d, *J* = 13.2 Hz, 1H), 1.24 (t, *J* = 7.6 Hz, 3H), 0.98 (d, *J* = 6.4 Hz, 3H).

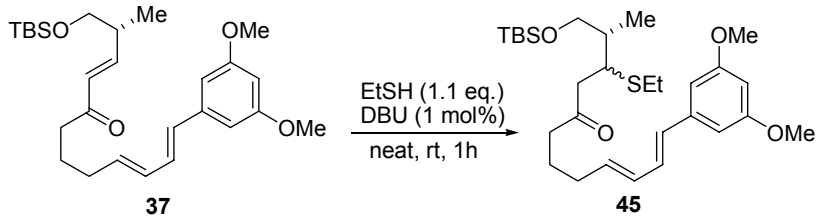


(*S*)-4-(ethylthio)-3,4-dihydro-3-methyl-6-phenethyl-2*H*-pyran 44: PPTS (2.8 mg, 0.011 mmol, 10 mol%) was added to a solution of methyl acetal **43** (32 mg, 0.109 mmol, 1.0 equiv.) in benzene (1.1 mL), which was refluxed until the starting material was consumed. Upon cooling, the solution was quenched by the addition of sat. $NaHCO_3$, the layers separated, and the aqueous phase extracted twice with EtOAc. The combined organics were washed with brine, dried over Na_2SO_4, and evaporated *in vacuo* to give a crude material, which upon purification over silica gel (9:1 hexanes:EtOAc, R_f = 0.40) gave cyclic enol ether **44** (25 mg, 89% yield) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.26 (t, *J* = 7.2 Hz, 2H), 7.17 (d, *J* = 5.6 Hz, 3H), 4.50 (d, *J* = 4.0 Hz, 1H), 4.12 (dd, *J* = 2.8, 10.4 Hz, 1H), 3.70 (dd, *J* = 5.6, 10.8 Hz, 1H), 2.92 (t, *J* = 4.4 Hz, 1H), 2.77

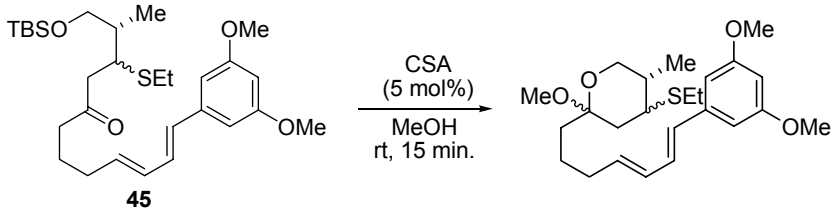
(t, *J* = 8.4 Hz, 2H), 2.46 (m, 2H), 2.31 (t, *J* = 8.0 Hz, 2H), 1.92-1.82 (bs, 1H), 1.21 (t, *J* = 7.2 Hz, 3H), 1.02 (d, *J* = 6.8 Hz, 3H).



(*R*,3*E*,9*E*,11*E*)-2-(*t*-butyldimethylsilylethermethyl)-12-(3,5-dimethoxyphenyl) dodeca-3,9,11-trien-5-one 37: Sodium Hydride (44 mg, 1.10 mmol, 1.05 equiv.) was added to a 0 ˚C solution of β-ketophosphonate **39** (400 mg, 1.046 mmol, 1.0 equiv.) in THF (4 mL) and allowed to stir for 1h, whereupon aldehyde **38** (211 mg, 1.046 mmol, 1.0 equiv.) in THF (1 mL) was added, allowing the reaction to warm to room temperature. The reaction was quenched by the addition of water and diluted with EtOAc. The layers were separated, and the aqueous extracted twice with EtOAc. The combined organics were washed with brine, dried over Na_2SO_4, and evaporated *in vacuo* to give a crude material that was readily purified over silica (9:1 hexane:EtOAc R_f = 0.20) to give *trans*-enone **37** (0.379 g, 79% yield) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.78 (dd, *J* = 7.6, 16.4 Hz, 1H), 6.70 (dd, *J* = 10.8, 16.0 Hz, 1H), 6.51 (d, *J* = 2.0 Hz, 2H), 6.35 (d, *J* = 15.2 Hz, 1H), 6.18 (dd, *J* = 10.4, 15.2 Hz, 1H), 6.08 (d, *J* = 15.6 Hz, 1H), 5.77 (dt, *J* = 7.2, 14.8 Hz, 1H), 3.78 (s, 6H), 3.51 (d, *J* = 6.4 Hz, 2H), 2.55 (t, *J* = 7.2 Hz, 2H), 2.48 (q, *J* = 6.8, 13.6 Hz, 1H), 2.16 (q, *J* = 6.8 Hz, 2H), 1.74 (q, *J* = 7.2 Hz, 2H), 0.86 (s, 9H), 0.05 (s, 6H).

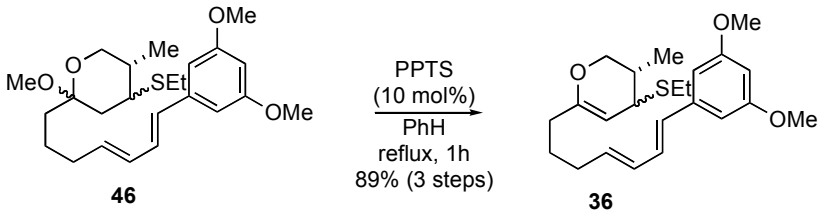


(2*S*,9*E*,11*E*)-2-(*t*-butyldimethylsilylethermethyl)-3-(ethylthio)-12-(3,5-dimethoxyphenyl)dodeca-9,11-dien-5-one 45: A solution of DBU (0.53 μL, 4.0 μmol, 1 mol%) in THF (10 μL) was added to a screw cap vial containing *trans*-enone **37** (177 mg., 0.386 mmol, 1.0 equiv.) and ethanethiol (32 μL, 0.424 mmol, 1.1 equiv.) neat at room temperature. After 20 minutes the reaction was complete, and the volatile contents removed *in vacuo* to give ethylsulfide **45** (201 mg, >99%) as a diastereomixture, which was carried on into the next reaction without further purification. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.69 (dd, *J* = 10.4, 15.6 Hz, 1H), 6.51 (s, 2.0 Hz, 2H0, 6.36 (d, *J* = 16.0 Hz, 1H), 6.32 (t, *J* = 2.0 Hz, 1H), 6.17 (dd, *J* = 10.4, 14.8 Hz, 1H), 5.76 (dt, *J* = 7.2, 14.8 Hz, 1H), 3.78 (s, 6H), 3.62 (dd, *J* = 7.6, 10.4 Hz, 1H), 3.51-3.45 (m, 2H), 3.31 (q, *J* = 4.4 Hz, 1H), 2.62-2.43 (m, 6H), 2.14 (q, *J* = 7.2 Hz, 2H), 1.20 (q, *J* = 7.2 Hz, 3H), 0.90 + 0.83 (d, *J* = 6.8 Hz, 3H).



(*S*)-4-(ethylthio)-tetrahydro-2-methoxy-2-((4*E*,6*E*)-7-(3,5-dimethoxyphenyl)hepta-4,6-dienyl)-5-methyl-2*H*-pyran 46: Camphorsulfonic acid (9 mg, 0.0386 mmol, 10 mol%) was added to a room temperature solution of ethyl sulfide

45 (201 mg, 0.386 mmol, 1.0 equiv.) in MeOH (3.9 mL), allowing to stir until the starting material was consumed, ~20 minutes. After evaporation of the solvent *in vacuo* and dilution with sat. $NaHCO_3$ and EtOAc, the layers were separated, and the aqueous layer extracted twice with EtOAc. The combined organics were washed with brine, dried over Na_2SO_4, and evaporated *in vacuo* to give crude **46** in quantitative yield, of suitable purity to carry on into the subsequent reaction. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.69 (dd, *J* = 10.5, 15.6Hz, 1H), 6.51 (d, *J* = 2.1 Hz, 2H), 6.35 (d, *J* = 16.0 Hz, 1H), 6.32 (d, *J* = 1.8 Hz, 1H), 6.17 (dd, *J* = 10.5, 15.0 Hz, 1H), 5.78 (dt, *J* = 6.9, 14.1 Hz, 1H), 3.78 (s, 6H), 3.53 (dd, *J* = 4.5, 11.4 Hz, 1/2H), 3.45 (d, *J* = 11.1 Hz, 1/2H), 3.35-3.20 (m, 1H), 3.13 + 3.12 (s, 3H), 2.64 (dt, *J* = 4.5, 12.3 Hz, 1/2H), 2.52 (dq, *J* = 3.3, 7.5, 14.7 Hz, 2H), 2.13 (q, *J* = 4.5 Hz, 2H), 1.81 (dd, *J* = 4.2, 13.2 Hz, 1H), 1.64-1.39 (m, 5H), 1.24 (m, 3H), 1.04 (d, *J* = 7.2 Hz) + 0.96 (d, *J* = 6.6 Hz) = 3H.



46 **36**

(*S*)-4-(ethylthio)-3,4-dihydro-6-((4*E*,6*E*)-7-(3,5-dimethoxyphenyl)hepta-4,6-dienyl)-3-methyl-2*H*-pyran 36: PPTS (9.5 mg, 0.0386 mmol, 10 mol%) was added to a solution of methyl acetal **46** (162 mg, 0.386 mmol, 1.0 equiv.) in benzene (4 mL), which was refluxed until the starting material was consumed. Upon cooling, the solution was quenched by the addition of sat. $NaHCO_3$, the layers separated, and the aqueous phase extracted twice with EtOAc. The combined organics were washed with brine, dried over

Na_2SO_4, and evaporated *in vacuo* to give a crude material, which upon purification over silica gel (9:1 hexanes:EtOAc, $R_f = 0.40$) gave cyclic enol ether **36** (133 mg, 89% yield over 3 steps) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ6.70 (dd, *J* = 10.4, 15.6 Hz, 1H), 6.51 (d, *J* = 2.0 Hz, 2H), 6.35 (d, *J* = 16.0 Hz, 1H), 6.32 (t, *J* = 2.4 Hz, 1H), 6.17 (dd, *J* = 10.4, 15.2 Hz, 1H), 5.79 (dt, *J* = 7.2, 14.4 Hz, 1H), 4.64 (d, *J* = 4.8 Hz) + 4.53 (d, *J* = 3.6 Hz) = 1H, 4.10 (d, *J* = 7.2 Hz, 1H), 3.78 (s, 6H), 3.73-3.66 (m, 1H), 3.32 (t, *J* = 4.4 Hz) + 2.95 (t, *J* = 4.4 Hz) = 1H, 2.55 (m, 2H), 2.21 (m, 1H), 2.12 (q, *J* = 7.2 Hz, 2H), 2.02 (q, *J* = 7.6 Hz, 2H), 1.58 (m, 2H), 1.24 (t, *J* = 6.8 Hz, 3H), 1.04 (d, *J* = 4.4 Hz) + 1.02 (d, *J* = 4.4 Hz) = 3H.

H. References and Notes

[1] Diels, O.; Alder, K. *Liebigs Ann. Chem.* **1928**, *460*, 98-122.

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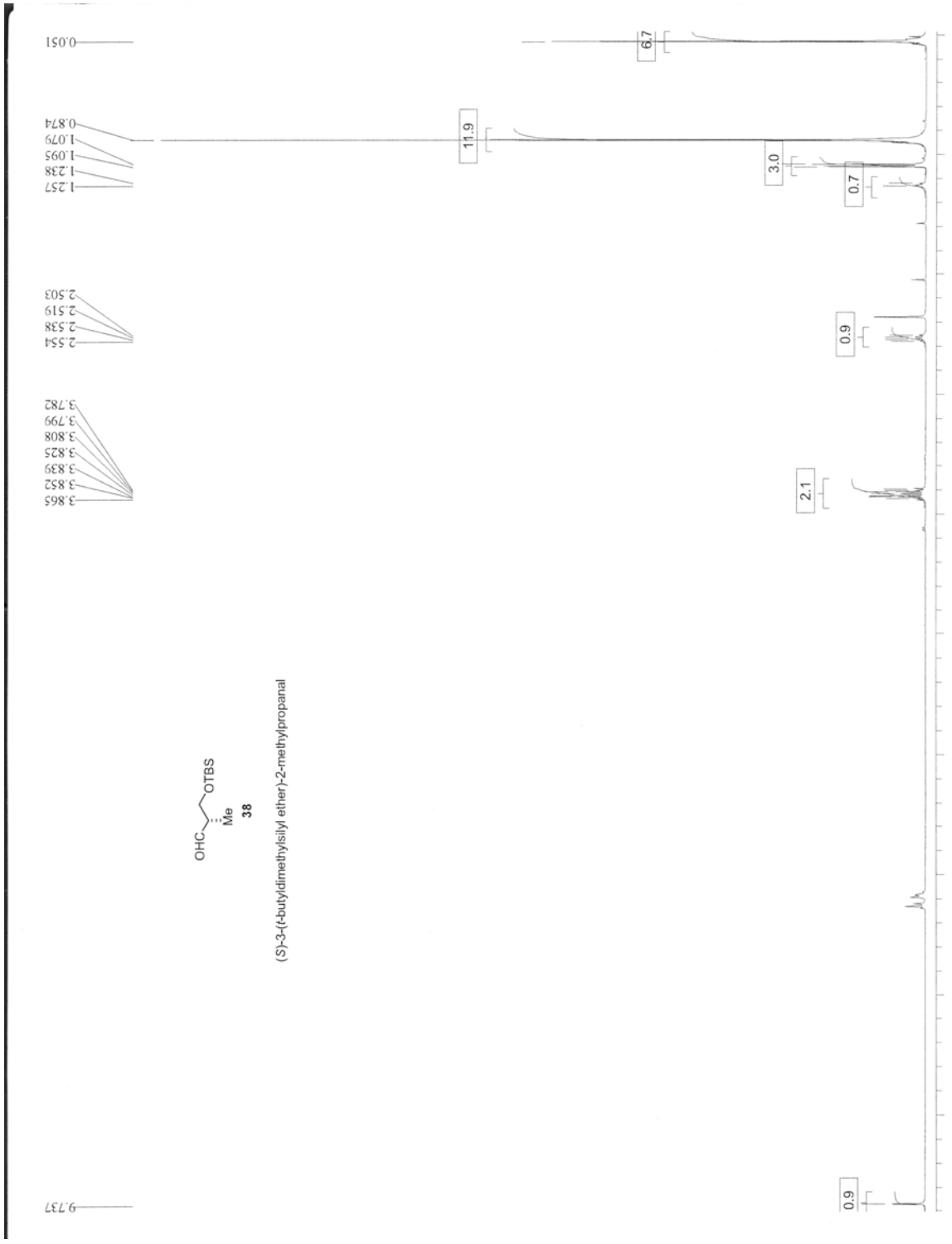
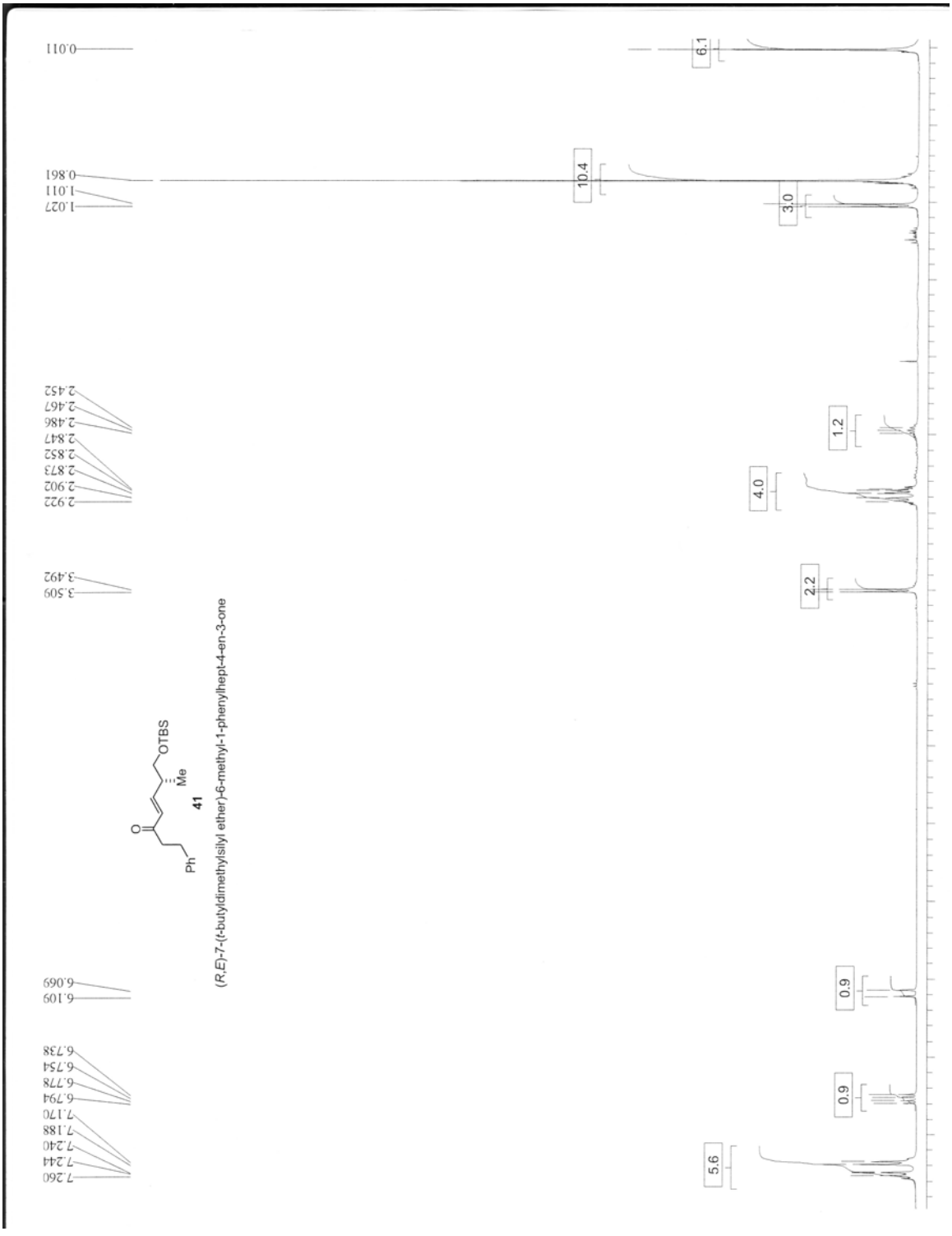
Chapter 5

Selected Spectra

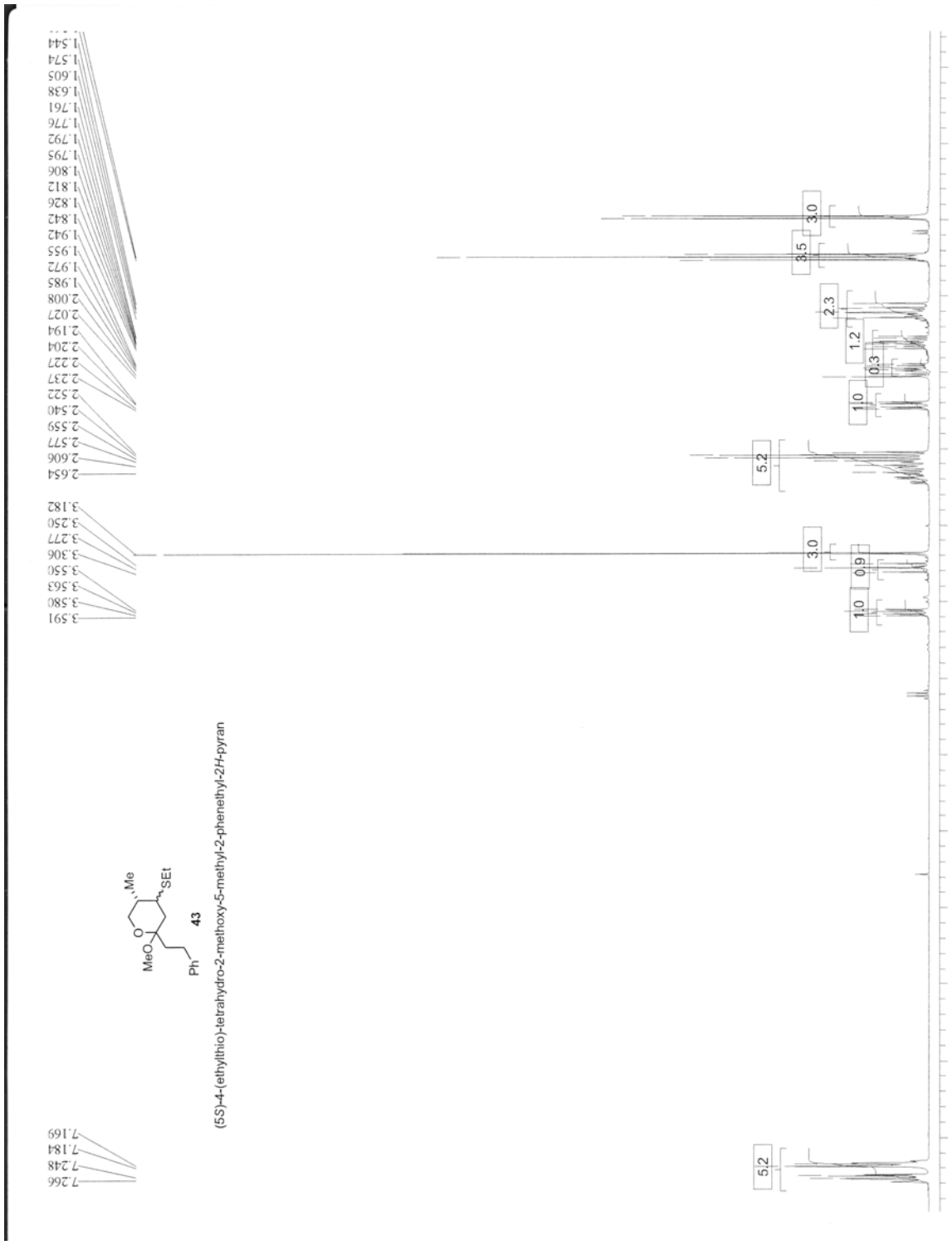
Spectrum Page



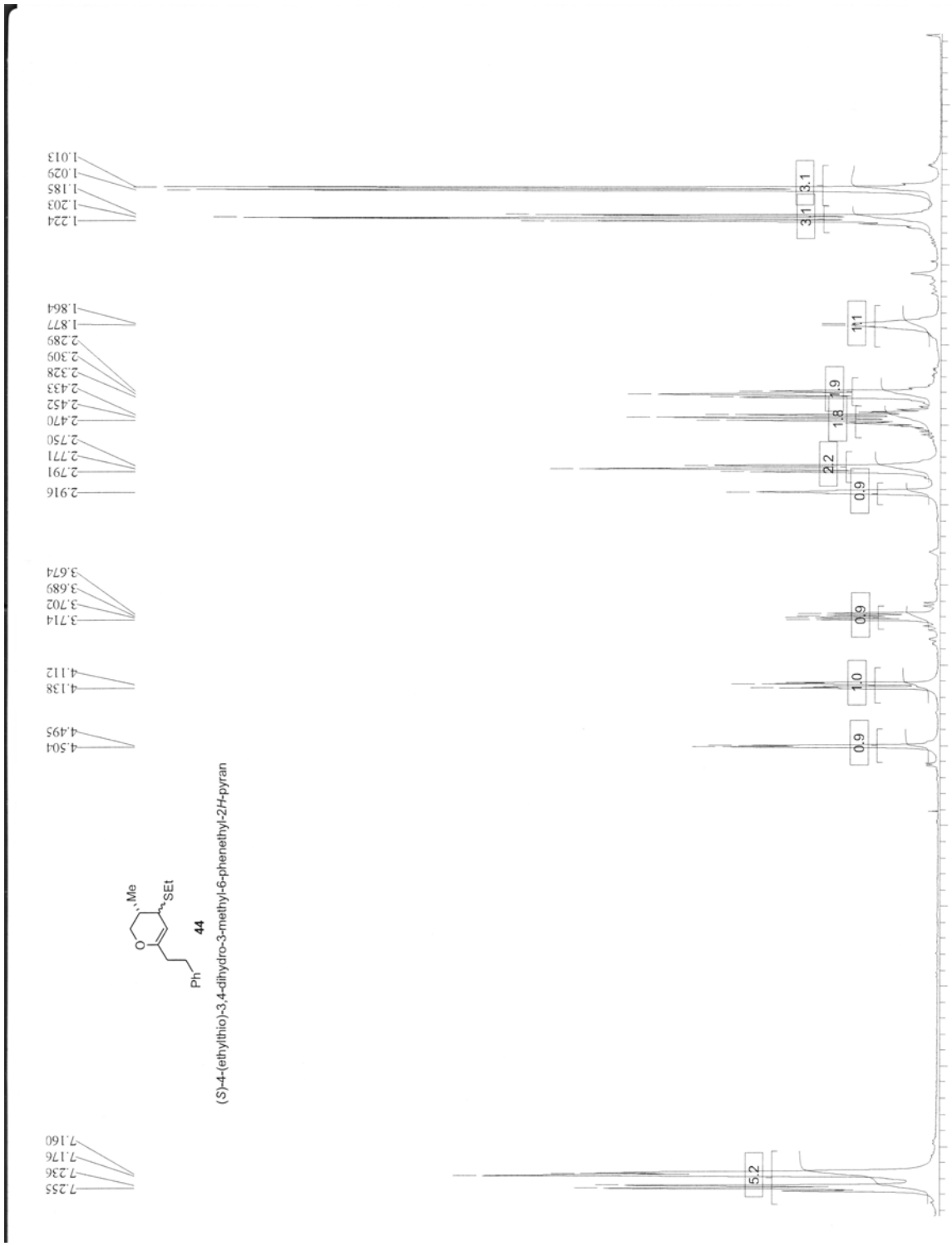
Spectrum 83. ^{1}H NMR spectrum of compound **38** in $CDCl_3$



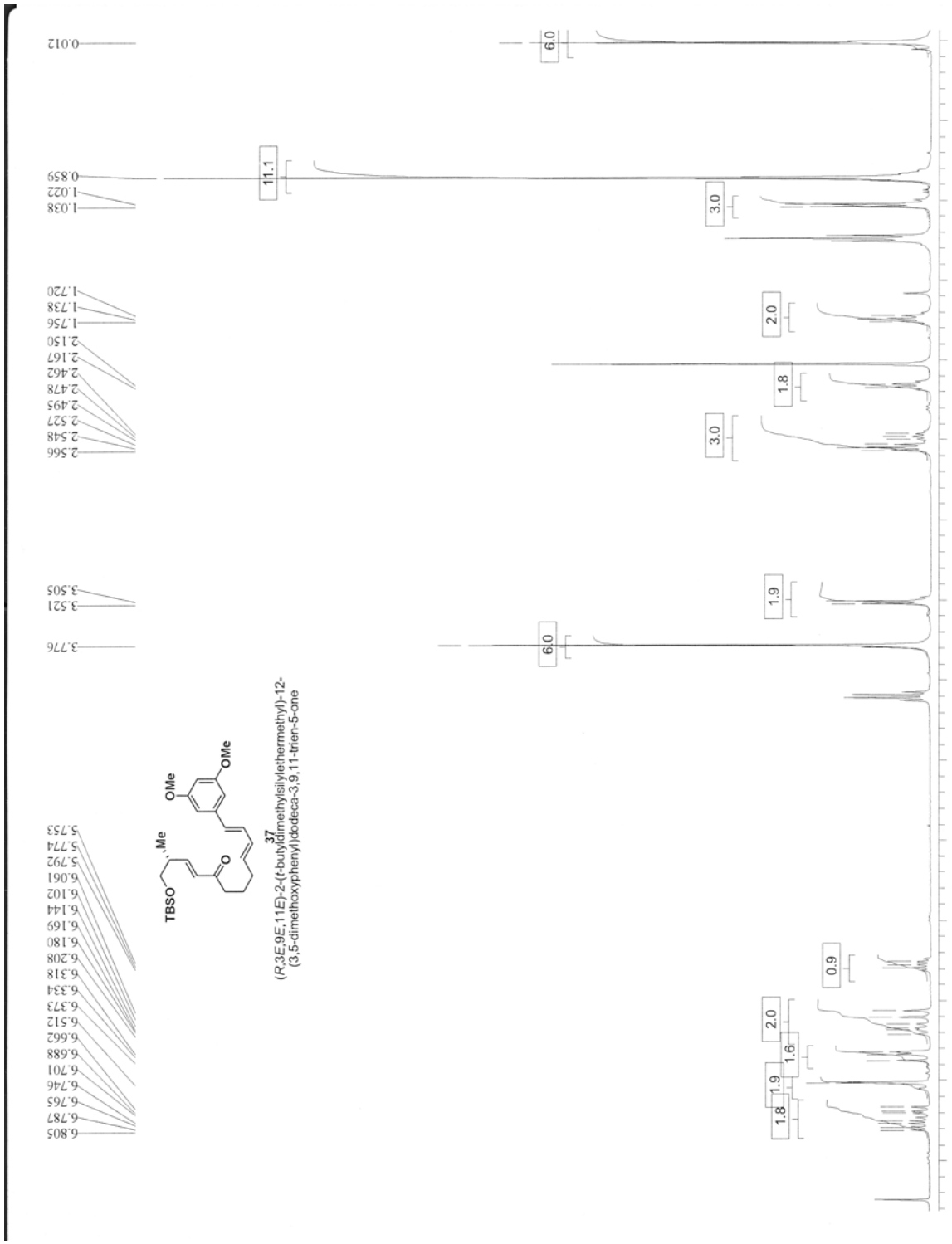
Spectrum 84. ^{1}H NMR spectrum of compound **41** in $CDCl_3$



Spectrum 85. ^{1}H NMR spectrum of compound **43** in $CDCl_3$

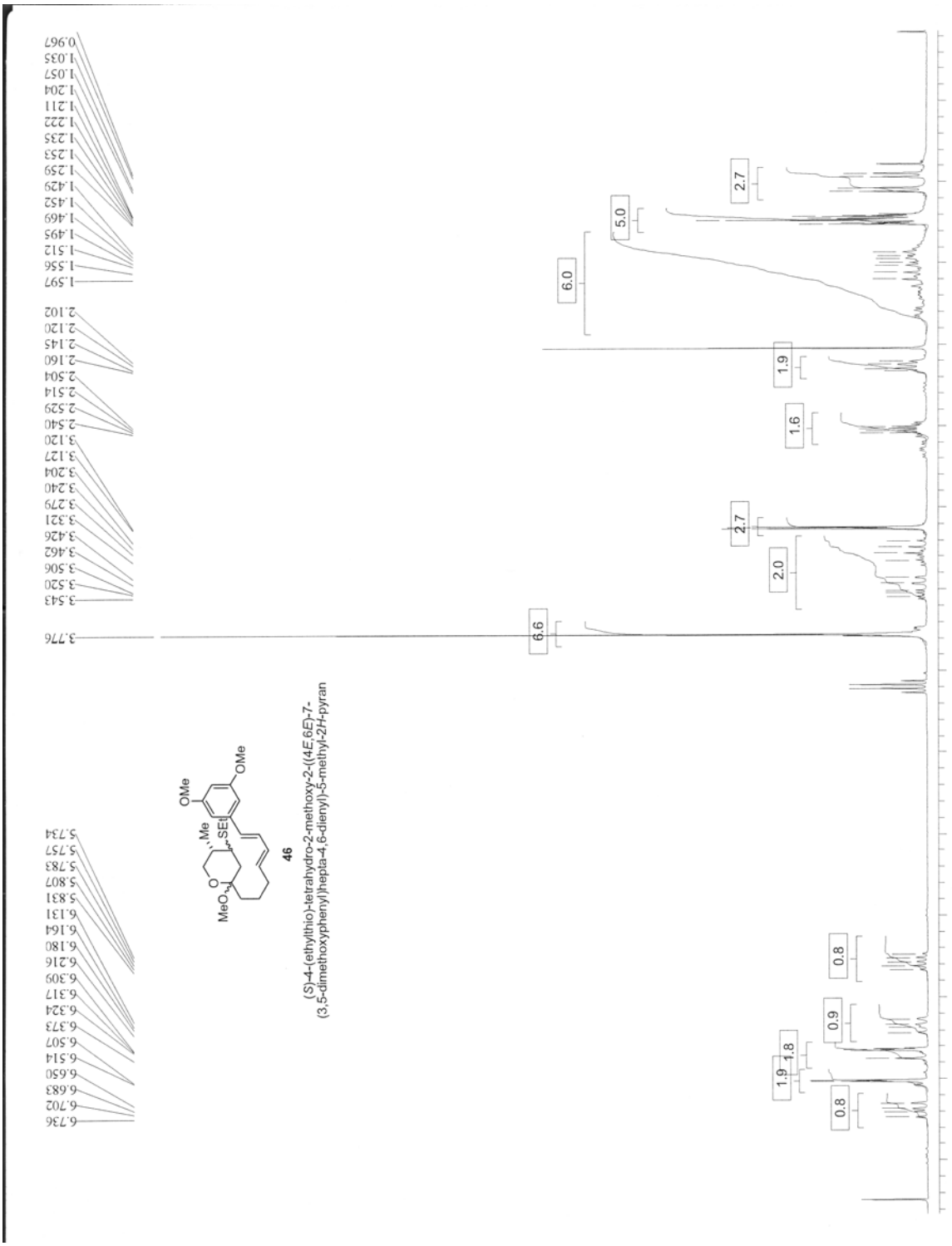


Spectrum 86. ^{1}H NMR spectrum of compound **44** in $CDCl_3$

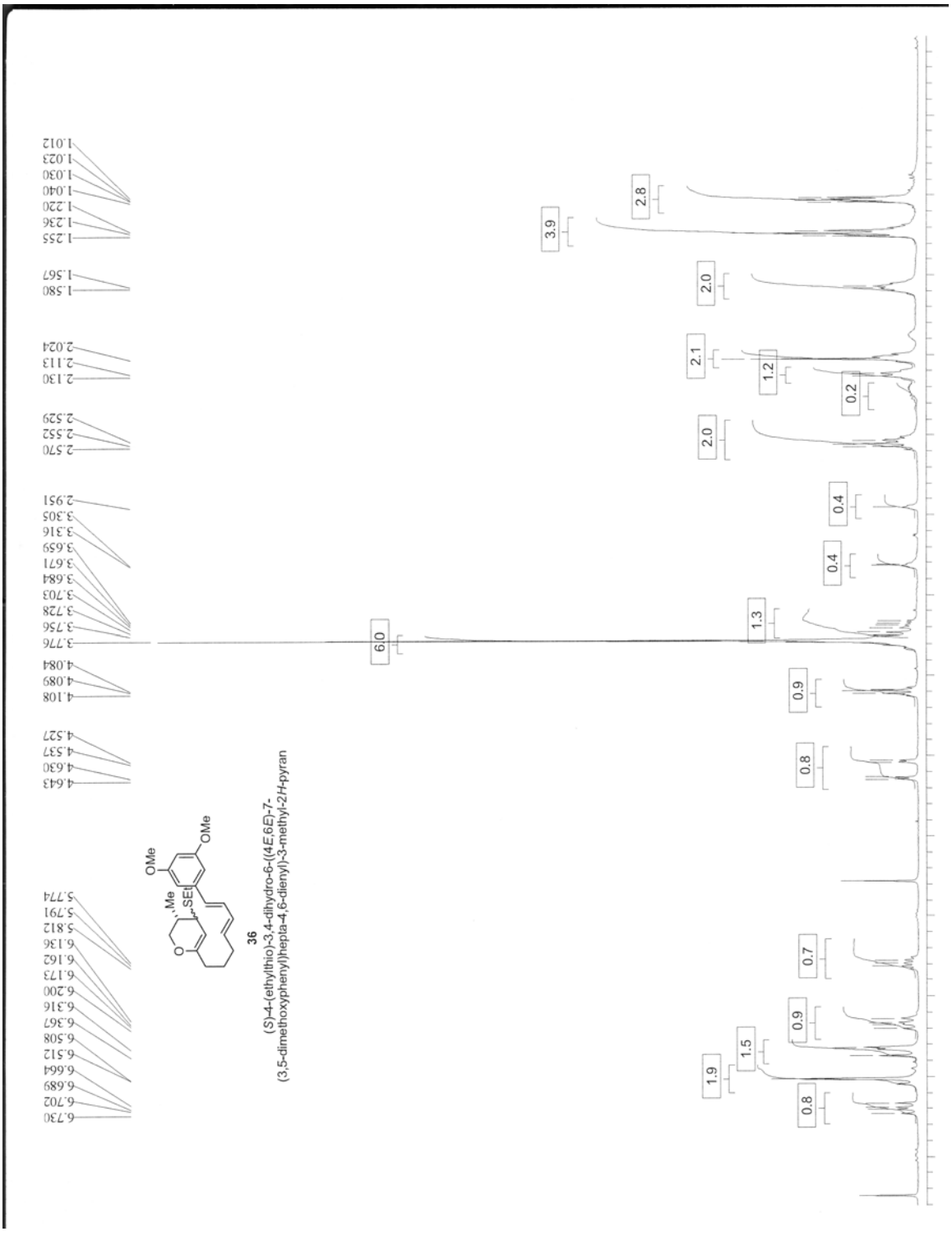


Spectrum 87. ^{1}H NMR spectrum of compound **37** in $CDCl_3$

Spectrum 88. ^{1}H NMR spectrum of compound **45** in $CDCl_3$



Spectrum 89. ^{1}H NMR spectrum of compound **46** in $CDCl_3$



Spectrum 90. ^{1}H NMR spectrum of compound **36** in $CDCl_3$

CHAPTER 6

Brønsted Acids Revisited and the Symbioimine Endgame

A. Inspiration Strikes: Heathcock's Homosecodaphniphyllate Synthesis

Upon spending time researching the literature for references of dihydropyridine and iminium-activated Diels-Alder cycloadditions, I had the joy to come across Heathcock's impressive biomimetic total syntheses of several *Daphniphyllum* alkaloids, exemplified by the synthesis of homosecodaphniphyllate (**1**) shown in Figure 21.[1] Oxidation of diol **2** by the Swern method, immediately followed by blowing a stream of ammonia over the solution gave the condensation 3,4-dihydropyridine **3**. Upon evaporation, the addition of ammonium acetate and acetic acid at room temperature activated the imine and nearly instantaneously produced an aza-Diels-Alder adduct **4** with the internal trisubstituted olefin of the homogeranyl group; subsequent heating served to drive an aza-Prins reaction with the remaining trisubstituted olefin to produce **5**.

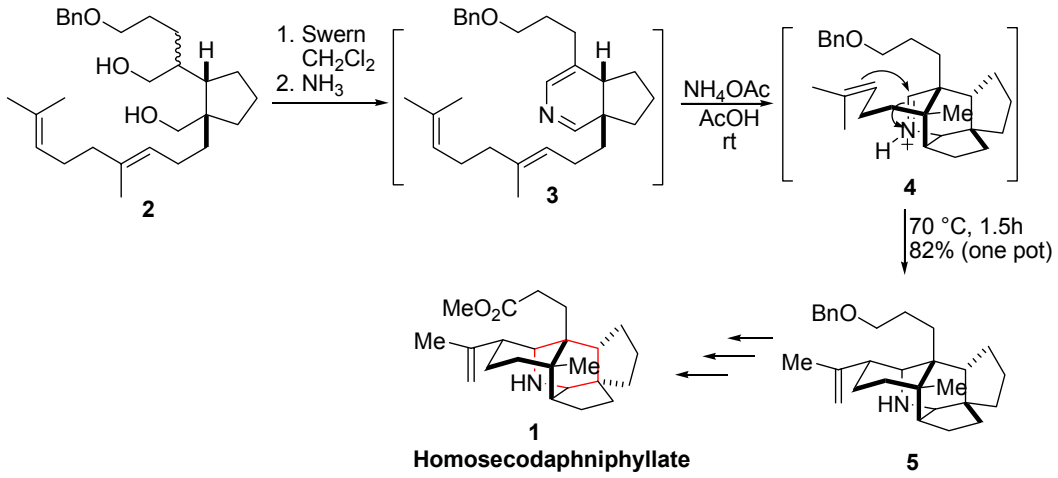


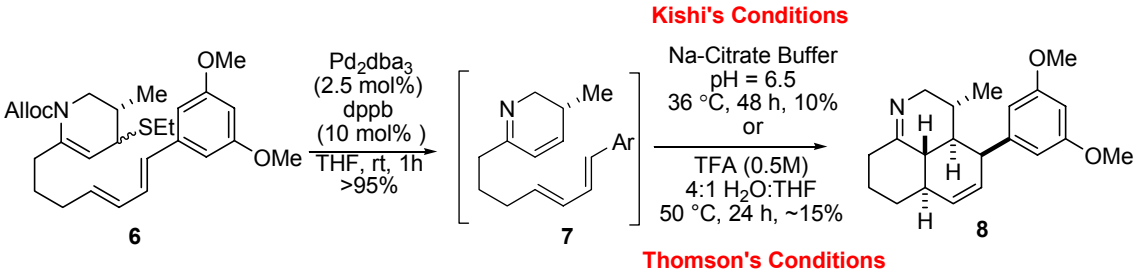
Figure 21. The Key Cascade Sequence of Homosecodaphniphyllate (**1**) by Heathcock

What struck me beyond the use of such a simple acid, was the incremental benefit in yield that the addition of ammonium acetate had over the course of the cascade

sequence. What role did the ammonium acetate play? "Little to none..," Heathcock writes, suggesting that "The excess acetate ion may stabilize the cationic intermediates in the reaction." This one sentence lit up a mighty light bulb over my head, as it started me thinking about the relative instability of the 2,3-dihydropyridine **7** produced from the masked precursor **6** that I observed over the course of exploring Diels-Alder methodologies, and how I might be able to circumnavigate this global issue in the synthesis of symbioimine (Scheme 56).

B. Experience with Brønsted Acid-Mediated Iminium Activation

What was particularly frustrating in my experience with Brønsted acid-mediated iminium activation of 2,3-dihydropyridine to undergo a Diels-Alder reaction was not that it didn't work, rather, that it worked so very badly, and without any clue as to *why* or *what* could be causing the decomposition of material. As depicted in Scheme 1, the most successful efforts in our for an *endo*-selective iminium-activated intramolecular Diels-Alder reaction were paltry at best. Unmasking **6** with $Pd_2dba_3 \cdot CHCl_3$ (2.5 mol%) and the dppb ligand (10 mol%) in THF at room temperature produced 2,3-dihydropyridine **7** in essentially quantitative yield, albeit with an inconsequential 7.5 mol% impurity of dibenzylideneacetone derived from the Pd-catalyst. Subjection of **7** to either Kishi's or Thomson's Diels-Alder conditions (reported for gymnodimine and symbioimine, respectively) only produced the desired Diels-Alder adduct **8** in 10% and 15% yield, with an unidentified messy mixture of products, respectively (illustrating the completion of the formal total synthesis of symbioimine, because compound **8** was reported by Thomson, although the yield is not satisfactory.).



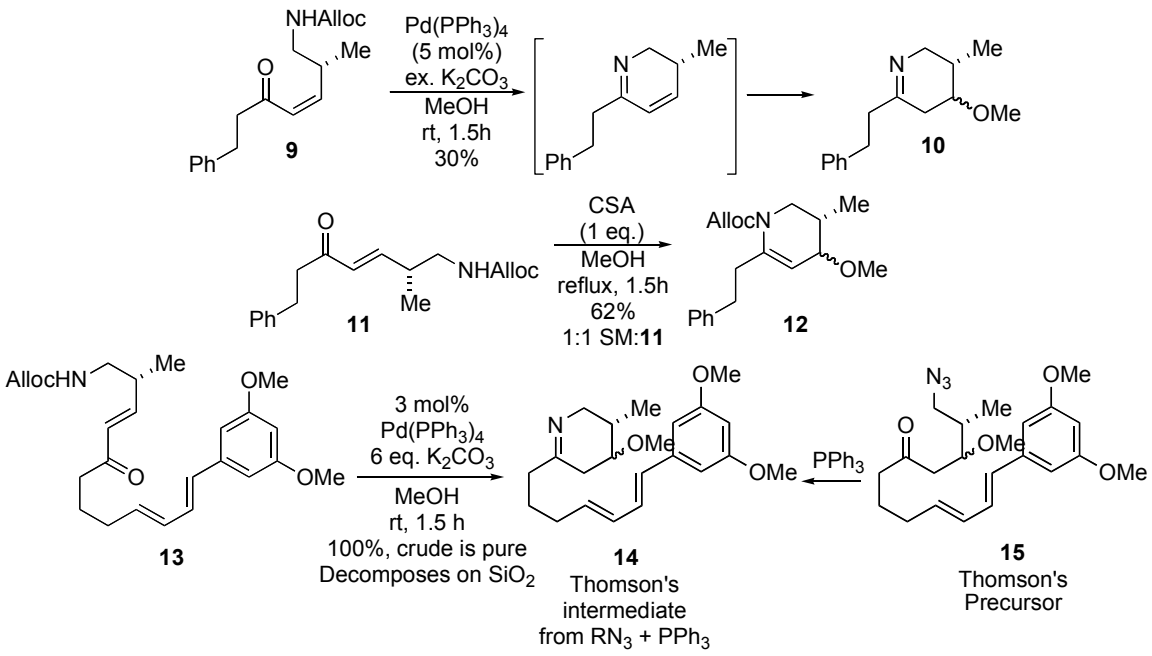
Scheme 56. Brønsted Acid-Mediated Taunting of 2,3-Dihydropyridine **7**

The mistake I had made in understanding this quandary was the assumption that once the imine picked up a proton, it was 'activated' for an immediate [4+2] cycloaddition. How naïve of me, never to think that it might take two to tango, insofar as one cycloaddition partner needing to be in its correct orientation *with respect* to the other. Focusing solely on iminium-formation, I neglected to think of how long might such an intermediate might be stable under the reaction conditions. Yes, there are still steric obstacles to overcome, a situation common to Diels-Alder cycloadditions remedied by thermal activation (typically refluxing toluene overnight), but anathema to our intermediate. How do you stabilize such an intermediate, yet still have it be available for the opportune moment of cycloaddition? This is where Heathcock's words and chemistry cleared both metal and chemical fugues. The solution was to use an acid that could also serve as a reversible stabilization agent under the reaction conditions.

C. Acetic Acid is Our Friend

Early on in our investigation, while examining amine protection strategies using the model system, it was discovered that while the alloc group could be readily deprotected by palladium catalysis in basic methanol, even forming the cyclic imine from

the *cis*-enone **9** and thus 2,3-dihydropyridine, the nature of the conditions resulted in a conjugate addition of methanol, effectively trapping the 2,3-dihydropyrdine as the cyclic imine **10** (Scheme 57). While not much use to us at that juncture, later on we realized that a suitable, potentially reversible 1,4-selective nucleophile addition would allow for free bond rotation of the original double bond and permit a condensation event between the amine-carbamate and the resultant ketone. The attractiveness of such a situation lies in the avoidance of laborious *cis*-selective methodologies and permits a more facile *trans*-enone approach. Before settling on ethanethiol as the desired 1,4-selective, reversible nucleophile, it was observed that *trans*-enone **11** would, to a limited degree undergo this one pot transformation of conjugate addition of methanol followed by condensation mediated by 1 equivalent of camphorsulfonic acid (CSA) in refluxing methanol to produce the Alloc-masked dihydropyridine methanol-adduct **12** as a 62% 1:1 mixture of starting material and **12**. Much later, while inquiring into whether or not one could isolate the free amine *trans*-enone by alloc deprotection of its allyl carbamate **13**, it was discovered that while the free amine was not isolable, its presence in basic methanol allowed for the formation of the cyclic imine methanol-adduct **14**, which happened to be the Diels-Alder precursor made by Thomson from **15** in his enantioselective synthesis of (+)-symbioimine.



Scheme 57. An Amine-Containing *trans*-Enone Can Be Tricked Into Cyclizing

The exact mechanism of this two-step conjugate addition/condensation was originally thought to occur first by the conjugate addition of methoxide, followed by alloc deprotection, condensation and imine formation. The conjugate addition was found not to occur in the absence of palladium, and the starting material was recovered in its entirety. Repetition of the experiment using an excess of K_2CO_3 and refluxing the methanolic solution gave a minor amount of the methanol-adduct, with the remainder of the material having decomposed. Instead, it seems the first, necessary step is the alloc deprotection, whereupon the free amine can add in conjugate fashion intermolecularly, allowing the free bond rotation need for condensation/imine formation. The dimer can then be cleaved by elimination of the amine at the β-position after base-catalyzed (either by methoxide or potassium amide) enamine isomerization, which eliminates the amine

and forms 2,3-dihydropyridine, which is subsequently trapped by methanol. The only drawback to this method is that the purification of resulting basic imine is understandably problematic, as only decomposition products are observed upon contact with both silica (pre-treated with Et_3N) and basic alumina. Fortunately, filtering the reaction solution through a plug of Celite removes the palladium catalyst, and subsequent evaporation *in vacuo* gives a high-yielding product whose crude ^{1}H- and ^{13}C-NMR spectra are impeccable.

This discovery was advantageous as it obviated the construction of the smelly masked 2,3-dihydropyridine, allowing direct access to a potential Diels-Alder precursor (the same as used by Thomson). Moreover, further investigation allowed the Pd catalyst loading to be dropped to 0.5 mol% and only two equivalents of K_2CO_3 were necessary to promote the desired reaction in timely fashion (Scheme 58). Subjection of this material to Heathcock's Diels-Alder conditions produced the desired *endo*-selective cycloaddition/epimerization adduct **8** in ~25% yield (structure confirmed by ^{1}H-NMR comparison to Thomson's material) (1st attempt in Scheme 58), with the majority of the remaining material determined to be the aromatized product by oxidation of 2,3-dihydropyridine, pyridine **18** (DA:pyr ≈ 1:2), plus a minor amount of unidentified decomposition product. The mechanism of producing the 2,3-dihydropyridnium cation **19** starts by protonation of the imine as well as the methyl ether giving **14a**, followed by the iminium's isomerization to an enamine **14b**, and the subsequent elimination of methanol to produce the desired reactive intermediate **19** (Figure 22).

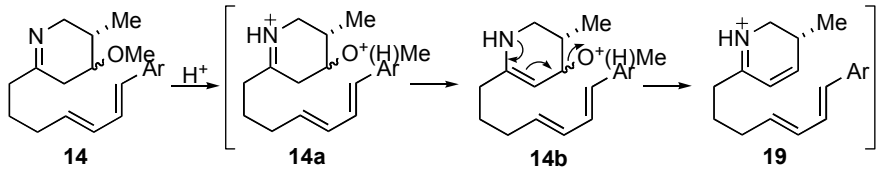
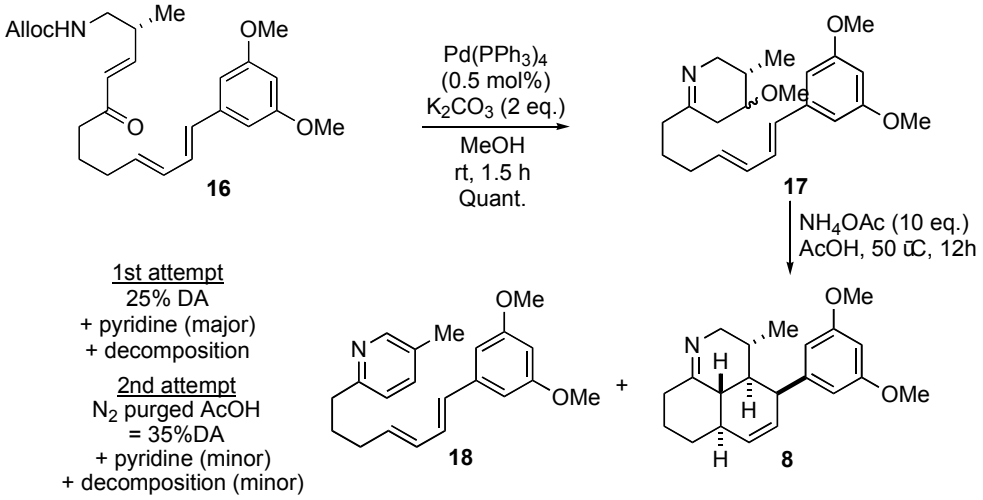


Figure 22. Mechanism of 2,3-Dihydropyridinium Formation From **14**

The discovery and use of the Heathcock conditions proved to be a great lead, as it nearly doubled by previous best yield (15% from 2,3-Dihydropyridine and Thomson's conditions in Scheme 56). The cause of the problematic pyridine formation suggested the presence of oxygen in the solvent, whose resolution by a rigorous purging of solvent by N_2 gas for 30 min was satisfactorily observed by an increase in yield of the Diels-Alder adduct **8** to 35% (2nd attempt in Scheme 58), coupled with a significant decrease in amount of pyridine **18** (DA:pyr ≈1.5:1), in addition to the presence of decomposed material.

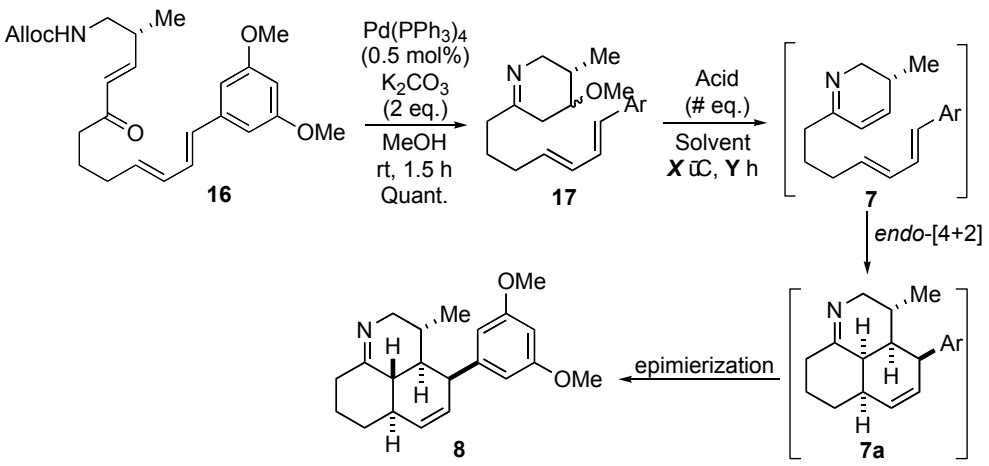


Scheme 58. Subjecting **16** to Brønsted Acid Diels-Alder Conditions, Obtaining **8**

D. Screening the Variables

While the purging of AcOH with N_2 helped in reducing the oxidation of the 2,3-dihydropyridine intermediate, the yield still too low to be practical. On the plus side, however, the relative increase in yield from isolated 2,3-dihyropyridine to this system is significant, as was also the increase from the N_2 purging, because it illustrated that in allowing the imposition of more control and stability to the reaction conditions, one can realize a (potential) increase in yield. Moreover, it illustrated the need for the reactive intermediate to be reversibly stabilized under the reaction conditions to prolong its lifetime. Kishi's idealistic biomimetic conditions as well as Thomson's aqueous TFA serve to be no more than black boxes to throw reactions into and hope for a beneficial outcome, as evidenced by the observed yields with the isolated 2,3-dihydropyridine. Very telling was the repetition of Thomson's conditions with his own Diels-Alder precursor: in my hands the best I could obtain was ~15% yield after hydrolysis of the trifluoracetamide formed to ease purification of the crude Diels-Alder adduct, relative to his reported 36%.

To that end, the variables of acid, equivalents thereof, solvent, temperature, and reaction duration were screened in the hope of observing a trend that may serve as a guide in determining how best to increase the yield of the Diels-Alder adduct while minimizing oxidation to pyridine and 2,3-dihydropyridine decomposition (Scheme 59 and Table 1).



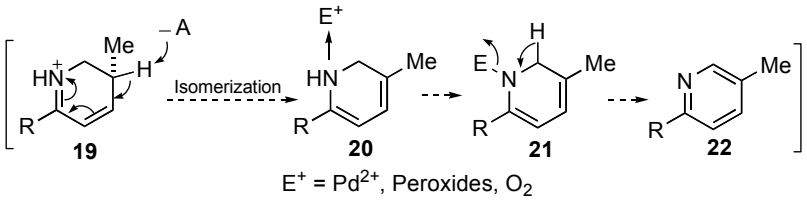
Scheme 59. Experimental Determination of Optimum Diels-Alder Condtions

Table 1. Screening the Variables for the Diels-Alder Reaction

# Equiv.	Acid	Solvent	˚C
1-10	AcOH	AcOH	
	Cl-AcOH	CH_3CN	
	aq. HCl	MeOH	-78
	TFA	CH_2Cl_2	0
	CSA	$(CH_2Cl)_2$	rt
	MsOH	$MeNO_2$	35
	$MsOH/P_2O_5$	H_2O	50
	H_2SO_4	$CH_3CN:H_2O$ 1:1	80
	TfOH	Dioxane	

From our benchmark of 35% yield using acetic acid as both acid and solvent, in surveying the Brønsted acid conditions it became readily apparent that oxidation of 2,3-dihydropyridine to pyridine **18** became the most significant competing reaction. The strength of the acid was not a determining factor in pyridine formation; instead, acids beyond the strength of TFA (pH < 0) did not produce any Diels-Alder adduct and only decomposed material was observed. This could be attributed to isomeriazation of 2,3-dihydropyridinium cation **19** to enamine **20** (1,2-Dihydropyridine) and the subsequent protonation of the amine by the stong acid, effectively shutting down the availability of 2,3-dihydropyridine to serve as a nucleophile (Scheme 60). At the time, despite rigorous N_2 purging of the solvents examined, pyridine adduct **22** was consistently observed, indicating that the oxidant (E in **20** and **21**) might be something else entirely rather than oxygen. Possible sources of oxidant could be explained by the presence of a trace amount of residual palladium from the previous reaction (alloc deprotection), or the presence of peroxides in the solvent, the both of which could be mechanistically understood to coordinate/covalently bond with the nitrogen's lone pair (like **21**),

facilitating ring aromatization to pyridine **22**. Given the observation of pyridine **22** in reaction products from chlorinated solvents such as CH_2Cl_2 and $(CH_2Cl)_2$, which are known to contain little, if any peroxides, it seemed to leave the presence of trace palladium as the only explainable source of redox potential in the system.

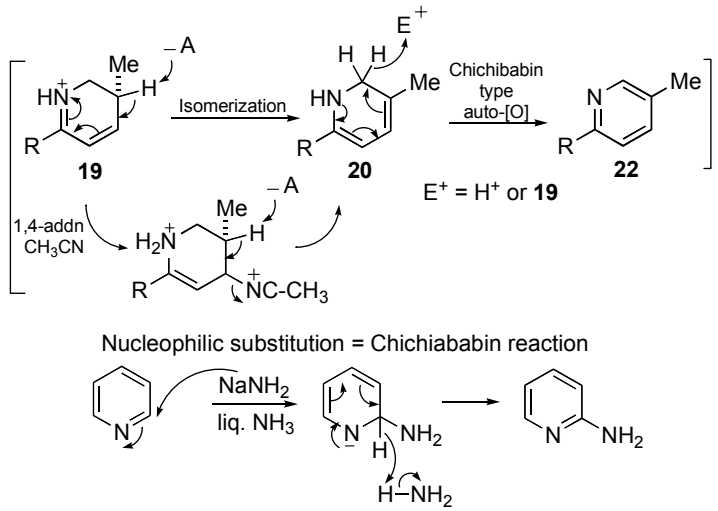


Scheme 60. 2,3-Dihydropyridine Auto-Oxidation via Pd^{2+}/Peroxide/O_2 Mechanism

A timely donation of Sili-Thiol, a commercially available thiol-based solid phase palladium scavenger on silica-support, enabled me to quickly rule out the presence of trace palladium as the oxidation agent, still observing the same 3:1 ratio of Diels-Alder (DA) adduct:pyridine with or without its addition to the work up procedure, especially since the catalyst loading the previous step was already in the low ppm range.

An additional explanation then was necessary to account for the oxidation of 2,3-dihydropyridine, but from what? The only conclusion that I could come to was a solution offered by an undergraduate organic chemistry textbook, in the form of Chichiababin-type reaction. The Chichiababin reaction, as taught in undergraduate organic chemistry, is the method of nucleophilic addition to the 2-position in pyridines (Scheme 61). The resulting dihydropyridine, analogous to intermediate **20** in Scheme 60, could push its electrons through the ring, eliminating a hydride and auto-oxidizing itself. 1,2-Dihydropyridine **20** itself could come from two possible routes, one being direct enamine

isomerization from the 2,3-dihydropyridinium **19**, or, hypothetically, by way of conjugate addition of the solvent or conjugate base of the acid, followed by elimination to form the trisubstutited olefin at the 4,5-position of **19**. The higher ratios of pyridine observed in reaction products somewhat correlates to the solvent's ability to possibly behave as a stabilization agent. Use of 5 equivalents of TFA in acetonitrile at 50 ˚C overnight would give a clean 3:1 ratio of the desired Diels-Alder adduct to pyridine, whereas dioxane under similar conditions gave exclusively the pyridine side product, and the best solvent of all was a tie between CH_2Cl_2 and $(CH_2Cl)_2$, giving consistently clean >5:1 Diels-Alder:pyridine product ratios with the complete absence of any decomposition products. Given the poor ability of the conjugate base of trifluoroacetic acid to serve in any capacity as a stabilizing agent of the 2,3-dihydropyrdinium intermediate, let alone the solvent itself, the choice of Diels-Alder precursor is of the utmost importance to ensure a long enough life for the reactive intermediate and to prevent the dispropostionation reaction by decreasing the concentration of 2,3-DHP in the reaction mixture. The fortuitous selection of the trapped 2,3-dihydropyrdine methanol-adduct as a the Diels-Alder precursor could not have been more timely, as the eliminated methanol can serve as the desired reversible stabilizing agent, and given that it comes from the solvent in the previous reaction, such utility is highly atom economical.

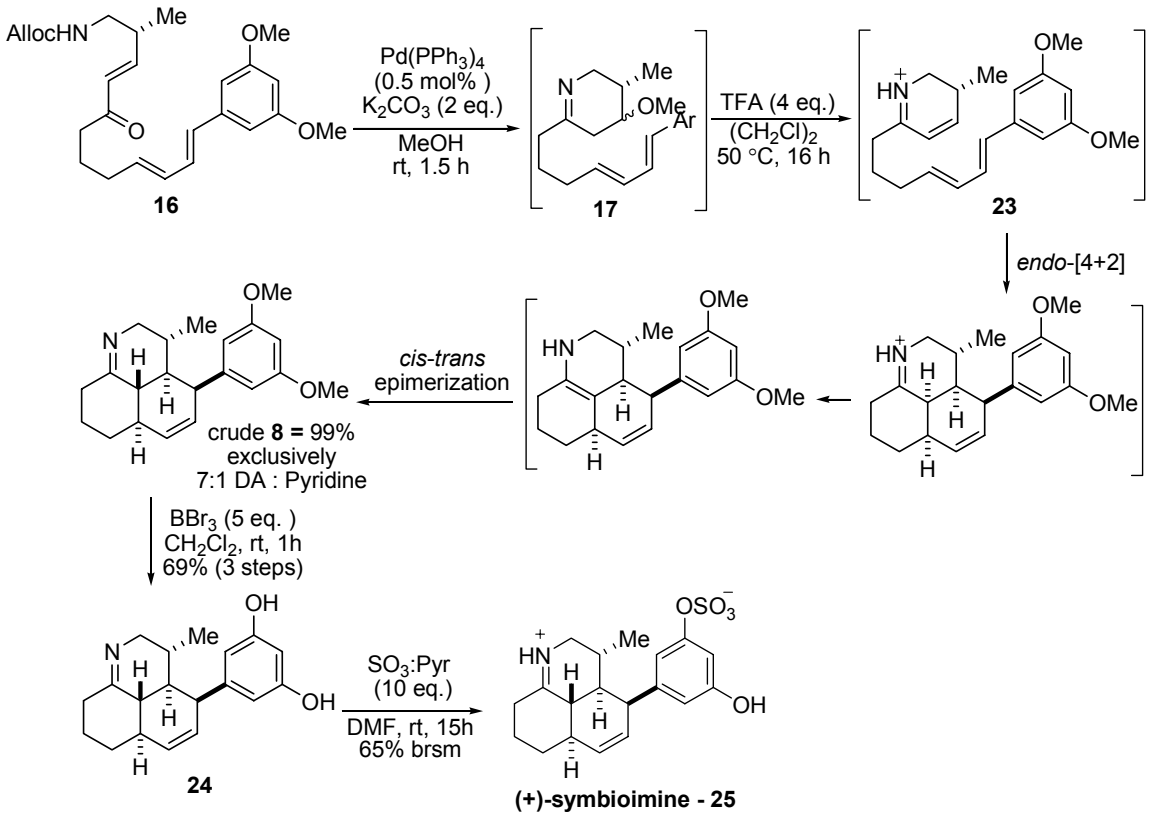


Scheme 61. 2,3-Dihydropyridine Auto-Oxidation via Chichibabin-Type Mechanism

E. Symbioimine Endgame

With apparent success in the survey of Brønsted acid-mediated Diels-Alder reaction conditions, selection of TFA as the acid, in 4-5 equivalents, in a 0.025M N_2 purged $(CH_2Cl)_2$ solution of the cyclic imine methanol-adduct **17**, being set to stir overnight at 50 ˚C furnished crude **8** as a 7:1 ratio of the desired *endo*-selective Diels-Alder adduct:pyridine side product in 99% yield, with ^{1}H- and ^{13}C-NMR spectra completely devoid of any decomposition material (Scheme 62), and subsequent analysis indicating that the *cis*→*trans* dehydrodecalone epimerization had also occurred, most likely via an enamine form. Given the problematic nature of chromatographing basic imines (**8** is also air sensitive) over silica or alumina (purification over basic alumina is adequate, but some decomposition occurs, the mass balance of which does not account for its lack of presence in the crude ^{1}H-NMR spectra) the material was carried on into the deprotection of the methyl aryl ethers by boron tribromide, which, upon an excess of

BBr_3 in CH_2Cl_2 at room temperature for 1 hour gave, after purification over neutral alumina, catechol **24** in 69% yield (over 3 steps) as a white, bench stable, crystalline solid. At this point, catechol **24** was obtained in an overall 27% yield over 10 steps (From either 3,5-dimethylphenyl acetylene or 5-hexyn-1-ol), in comparison to Snider (4.5% overall yield in 12 steps) and Thomson (4.6% overall yield in 12-13 steps). Subsequent bis-sulfation with an excess of SO_3·Pyr in DMF was stirred at room temperature overnight. Evaporation of the solvent *in vacuo* is followed by addition of aquous phosphate buffer (pH = 7) in order to hydrolyze the remaining excess SO_3 as well as cleave the bis-sulfate to the desired mono-sulfate. Evaporation of the aqueous solution gave a white crystalline solid that upon purification on silica in 25% MeOH/$CHCl_3$ produced (+)-symbioimine **25** in 50%, in addition to the recovery of catechol **24** which could be resubmitted to the reaction conditions, providing a 65% yield, brsm.



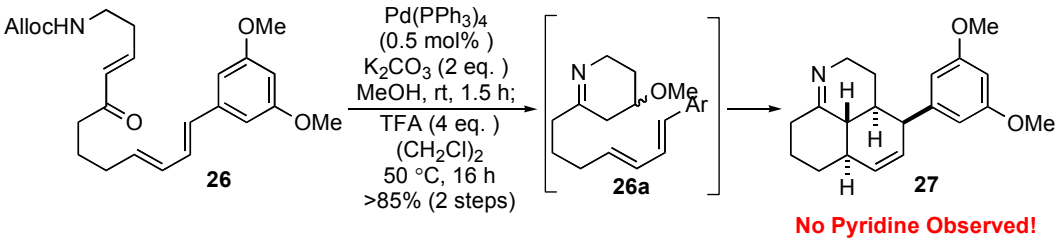
Scheme 62. Endgame of the Total Synthesis of Symbioimine (**25**)

F. 2,3-Dihydropyridinium Studies

Further investigation into the nascent ability of 2,3-dihydropyridine **23** to auto-oxidize itself to pyridine was undertaken with an eye to see if a *gem*-dimethyl substituted 2,3-dihydropyridine would undergo auto-oxidation (seemingly impossible), or given that auto-oxidation is the major competing reaction under Brønsted-acid catalysis, and understanding that such a disubstituted 2,3-dihydropyridine would be impervious to auto-oxidation, thus allowing for harsher Diels-Alder conditions potentially be used.

In addition to a *gem*-dimethyl analog, a desmethyl analog would also be worth constructing to observe if the lack of additional sterics imposed by the chiral methyl

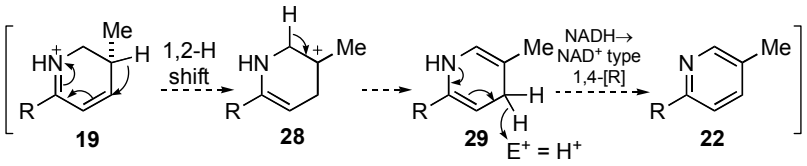
group in the natural material might allow for a gentler reaction environment and still be conducive to allow the [4+2] cycloaddition to occur. Surprisingly, while identical conditions were used to facilitate the alloc deprotection of **226** and its subsequent Brønsted acid-mediated iminium-activated intramolecular Diels-Alder reaction, no pyridine material whatsoever was observed in the resulting crude ^{1}H-NMR, cleanly producing the desired cycloadduct **27** in >85% yield (Scheme 63).



Scheme 63. Synthesis of Desmethyl 3,5-Dimethoxy-Symbioimine **27**

This lack of pyridine formation runs counter to what was expected given our existing understanding of the behavior of the reactive 2,3-dihydropyridinium intermediate (illustrated previously in Scheme 61). With the incorporation of an additional proton at the γ-position, in addition to the lack of a steric hinderance for its deprotonation by the conjugate base, it was expected that we would observe more pyridine formation, if anything. In examining the difference between the two 2,3-dihydropyridinium species (**23** vs. **26a)**, we can obviously tell that the presence of the methyl group has an effect on auto-oxidation. Conformational analysis to determine if release of potential ring strain might in some way act as a thermodynamic driving force for auto-oxidation is extremely far-fetched. The difference between the two is hinted at by the reaction conditions. The

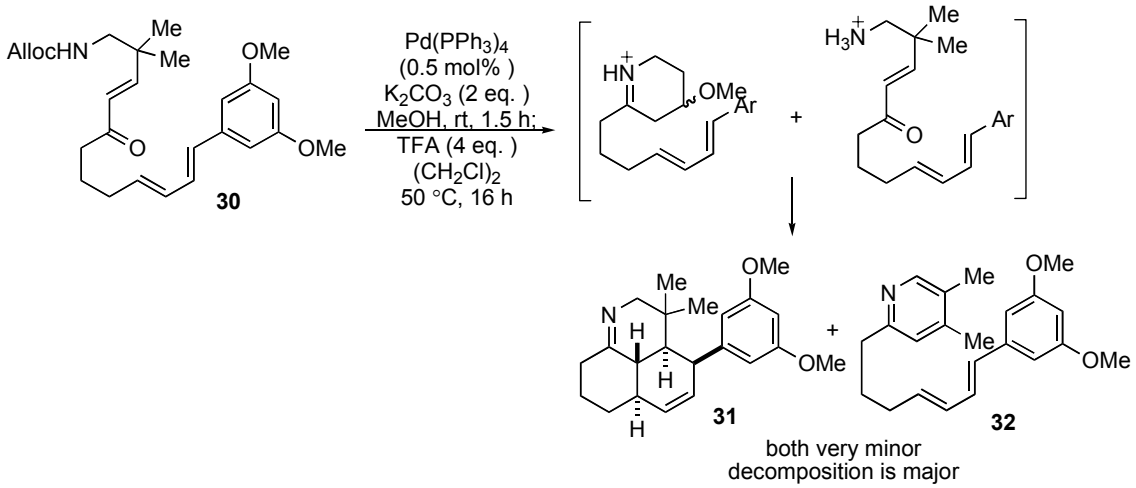
2,3-dihydropyridinium cation by resonance is effectively a heteroatom-destablized allyl cation. Given the carbocation-like lack of electron density at the 4-position of **19**, it wouldn't be odd at all to propose that a 1,2-hydride shift could easily occur to leave a stable 3˚ carbocation **28**, as illustrated in Scheme 64**.** Deprotonation from the adjacent carbon bearing the more electronegative atom would give a 1,4-dihydropyridine, a structural unit endemic throughout nearly all biological life forms on the planet in the form the NADH/NAD^+ redox system. NADH is a 1,4-dihydropyridine whose nitrogen eliminates a hydride from the 4-position thus inducing aromatization as a by-product. Like NADH, 1,4-Dihydropyridine **29** can be ascribed the same reactivity, auto-oxidizing itself at the exclusion of a hydride. This hydride then will float off and reduce anything in need of its electrons, and given the excess of acid in solution, it would not be surprising if hydrogen gas was a byproduct (or **29** may reduce **19**).



Scheme 64. 2,3-Dihydropyridine Auto-Oxidation via 1,2-H^+ Shift, + 1,4-H Elimination

To examine this hypothesis, it would be reasonable to assume that a more electron-rich migrating group that could still leave a 3˚ carbocation would be all the more likely to participate in the auto-oxidation process than a mono-substituted or desmethyl substrate. To that end, *trans*-enone **30** was constructed quite readily using the existing methodology, and its subsequent exposure to the selected Diels-Alder cycloaddition

conditions failed to give any Diels-Alder product, with the majority of the material decomposed, and only the faintest traces of a pyridine adduct present (Scheme 65). Repeating the experiment at 80 ˚C for 16h produced a small isolable amount of Diels-Alder adduct, and while some trace pyridine-type material was observed in the crude ^{1}H-NMR, upon silica purification the material was lost despite rigorous attention to detail. While this isn't an unreasonable outcome, given the sterically demanding environment to induce a Diels-Alder cycloaddition, I still expected to see substantially more dimethyl pyridine **31**.



Scheme 65. Synthesis of Dimethyl Analog **31**, Dimethylpyridine **32**

G. Horizons

With the total synthesis of symbioimine **25** completed, application of the key cycloaddition conditions should naturally be applied to Neosymbioimine **33** (Figure 3)**.** Disconnection to the Diels-Alder precuror would give the masked dihydropyridine methanol-adduct **34**, which is constructed in a step from readily obtainable *trans*-enone **35**. The *trans*-enone in turn can be derived from β-ketophosphonate **36**, which is

constructed in two parts, one being a chiral methyl substituted vinyl iodide **37**, and our vinyl pinacol boronate **38**.

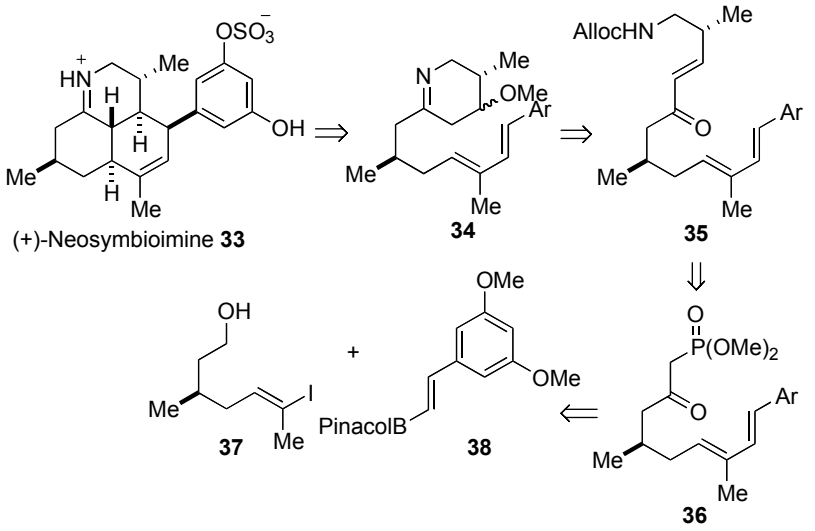


Figure 3. Retrosynthtetic Analysis of (+)-Neosymbioimine **33**

H. Conclusions

There are many facets that contribute to the success of this flavor of Diels-Alder cycloaddition chemistry. First and foremost, selection of the proper cycloaddition precursor that has a reversible means of stabilizing the 2,3-dihydropyridinium ion is key. The polar aprotic, non-coordinating nature of the CH_2Cl_2 and $(CH_2Cl)_2$ solvents and their ability to stabilize, yet not coordinate to, the 2,3-dihydropyridinium transition state is also very significant, in addition to the use of trifluoroacetic acid as a non-nucleophilic iminium-activating source. The accumulation of these variables serves as a general iminium-activated intramolecular Diels-Alder condition that can be readily applied to the synthesis of all of the cyclohexanyl cyclic iminium natural products such as pinnatoxin,

gymnodimine, and the spirolides. Further investigation into the reactivity of substituted and unsubstituted 2,3-dihydropyridines illustrates the significance of substitution at the γ-position and its proton's ability to potentially undergo a 1,2-hydride shift. Fortunately, and perhaps, not coincidentally, nature has cleared that γ-carbon of any substitution in all of the related natural products. Their synthesis and subsequent bioactivity elucidation is only a matter of time, and hopefully, the work described herein might hasten that day to the happiness of all future graduate students tasked with their construction.

I. Acknowledgments

In addition to thanking the University of California for financial support, we also thank Dr. Yongxuan Su for Mass Spectroscopy and Dr. Anthony Mrse for help with NOESY experiments as well as Armando Uribe for the timely donation of Sili-Thiol. Above all, I'd like to acknowledge Yoshi's instruction, guidance, and dedication to my graduate education.

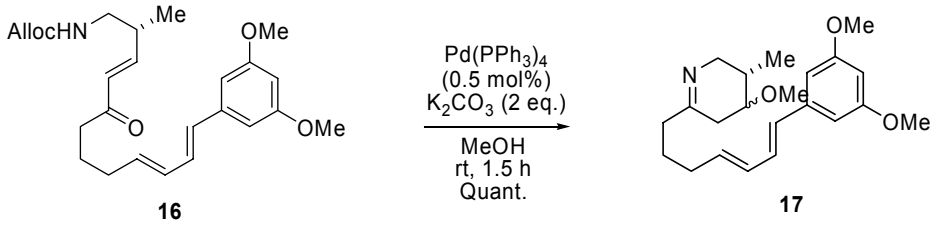
J. Experimental Section

Materials and Methods

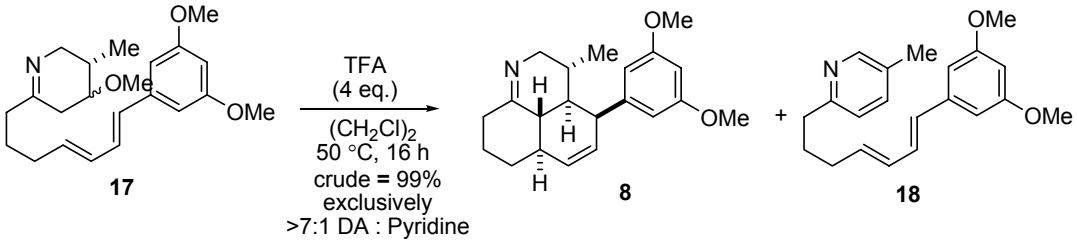
All reagents were commercially obtained (Aldrich, Fisher) at highest commercial quality and used without further purification except where noted. Organic solutions were concentrated by rotary evaporation below 45 ˚C at approximately 20 mmHg. Tetrahydofuran (THF), methanol (MeOH), chloroform ($CHCl_3$), nitromethane ($MeNO_2$), dichloromethane (DCM), ethyl acetate (EtOAc), acetonitrile (CH_3CN),

dioxane and acetone were purchased as reagent grade and used without further purification. Reactions were run under an inert N_2 atmosphere unless otherwise noted. Yields refer to chromatographically and spectroscopically (^{1}H- and ^{13}C-NMR) homogeneous materials, unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254), visualized with UV light and stained with cerium molybdate solution and heat. E. Merck silica gel (60A, particle size 0.040-0.063 mm) was used for flash chromatography. Preperative thin-layer chromatography separations were carried out on 0.50 mm E. Merck silica gel plates (60F-254). NMR spectra were recorded on Varian Mercury 300, 400 and/or Unity 500 MHz instruments and calibrated using the residual undeuterated solvent as an internal reference. Chemical shifts (δ) are reported in parts per million (ppm) and coupling constants (*J*) are reported in hertz (Hz). The following abbreviations are used to designate multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, q = quintet, m = multiplet, br = broad. Mass spectra (MS) and high-resolution mass spectra (HRMS) were recorded on a Finnigan LCQDECA mass spectrometer under electrospray ionization (ESI) or atmospheric pressure chemical ionization (APCI) conditions, or on a Thermo-Finnegan Mat900XL mass spectrometer under electron impact (EI), chemical ionization (CI), or fast atom bombardment (FAB) conditions. X-ray data were recorded on a Bruker SMART APEX CCD X-ray diffractometer. Specific optical rotations were recorded on a Jasco P-1010 polarimeter and the specific rotations were calculated based on the equation $[\alpha]^{25}_{D} = (100 \cdot \alpha)/(l \cdot c)$, where the concentration c is in g/100 mL and the path length *l* is in decimeters.

Procedures and Spectral Data

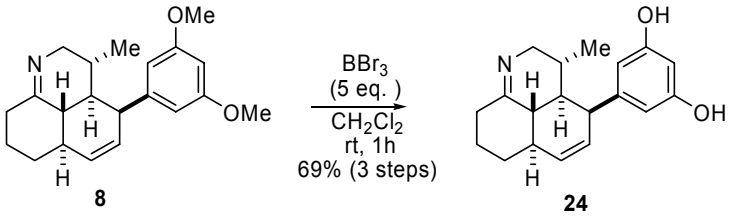


(S)-2,3,4,5-tetrahydro-4-methoxy-6-((4E,6E)-7-(3,5-dimethoxyphenyl)hepta-4,6-dienyl)-3-methylpyridine 17: Tetrakis(triphenylphosphine) palladium (0) (2.8 mg, 2.4 μmol, 0.5 mol %) and K_2CO_3 (139 mg, 0.968 mmol, 2.0 equiv.) was added to a room temperature solution of the *trans*-enone **16** (207 mg, 0.484 mmol, 1.0 equiv.) in MeOH (5 mL). After stirring for 1.5 h, the reaction was diluted with EtOAc, filtered over Celite, and diluted with 1:1 sat. $NaHCO_3$:brine. The layers were separated, the aqueous extracted twice with EtOAc, and the combined organics dried over Na_2SO_4. Evaporation *in vacuo* produced the crude methanol adduct **17** (173 mg, 100%, 1:1 diastereomeric mixture) as a colorless oil, and carried on into the next reaction. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.71 (dd, *J* = 10.4, 15.2 Hz, 1H), 6.53 (d, *J* = 2.0 Hz, 2H), 6.35 (d, *J* = 16.0 Hz, 1H), 6.34 (s, 1H), 6.19 (dd, *J* = 10.4, 15.2 Hz, 1H), 5.82 (dt, *J* = 7.2, 14.8 Hz, 1H), 3.80 (s, 6H), 3.74 (t, *J* = 6.4 Hz, 1H), 3.43 (q, *J* = 6.0 Hz, 1H), 3.50 (d, *J* = 8.4 Hz, 3H), 3.10 (m, 1H), 2.26 (d, *J* = 4.8 Hz, 1H), 2.18 (q, *J* = 8.4 Hz, 3H), 1.85 (q, *J* = 3.6 Hz, 3H), 1.68 (m, 3H), 0.98 (d, *J* = 6.8 Hz) + 0.90 (d, *J* = 6.4 Hz) = 3H; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 169.5, 161.1, 139.9, 135.8, 131.1, 130.4, 130.1, 104.4, 99.8, 78.9, 56.26, 55.5, 54.1, 40.2, 33.1, 32.7, 30.3, 26.1, 15.5. IR (film) 2929, 2837, 1666, 1587, 1456, 1425, 1355, 1295. HRMS $C_{22}H_{31}NO_3$: calcd $[M+H]^+$ = 358.2377, obsd $[M + H]^+$ = 358.2375.



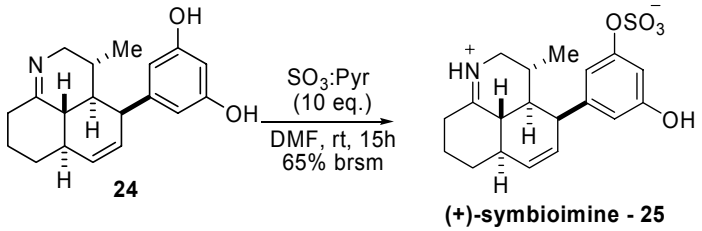
(3R,3aR,4S,4S,6aR)-3,3a,4,6a,7,8,9-heptahydro-4-(3,5-dimethoxyphenyl)-3-methyl-2H-benzo[de]quinoline 8 and 2-((4E,6E)-7-(3,5-dimethoxyphenyl)hepta-4,6-dienyl)-5-methylpyridine 18: TFA (149 mL, 0.22 mmol, 4.0 equiv.) was added to a a room temperature solution of methanol adduct 17 (173 mg, 0.484 mmol, 1.0 equiv.) in N_2 degassed 1,2-dichloroethane (19 mL), and heated to 50 °C for 16h. Upon cooling, the solution was diluted with EtOAc and 1:1 sat. $NaHCO_3$:brine. The layers were separated, the aqueous extracted twice with EtOAc, and the combined organics dried over Na_2SO_4. Evaporation *in vacuo* produced the crude Diels-Alder adduct **8** and pyridine **18** (150 mg, 99%) in a 7:1 ratio as a colorless oil, and carried on into the next reaction. Diels-Alder adduct **8**: ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.45 (d, J = 1.2 Hz, 2H), 6.35 (t, J = 2.0 Hz, 1H), 5.76 (d, J = 9.6 Hz, 1H), 5.66 (ddd, J = 1.6, 4.8, 10.0 Hz, 1H), 3.77 (s, 6H), 3.65 (t, J = 4.8 Hz, 1H), 3.58 (dd, J = 4.4, 17.6 Hz, 1H), 2.98 (m, 1H), 2.33-2.40 (m, 1H), 2.08-2.20 (m, 2H), 2.02-2.08 (m, 2H), 1.97-1.91 (m, 2H), 1.69-1.54 (m, 2H), 1.34-1.45 (m, 1H), 1.06-1.16 (m, 1H), 1.02 (d, J = 6.0 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 171.5, 160.2, 142.5, 132.1, 129.6, 108.9, 97.8, 57.1, 55.2, 44.6, 43.3, 43.1, 40.4, 37.5, 31.9, 27.5, 25.8, 16.9. IR (film): 2932, 2837, 15889, 1488, 1457, 1425, 1295, 1204, 1153. $[\alpha]_D^{25}$ = +215 (c = 1.0, MeOH). HRMS $C_{21}H_{27}NO_2$: calcd $[M + H]^+$ = 326.2120, obsd $[M + H]^+$ = 326.2115. Pyridine **18**: ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.36 (s, 1H), 7.40 (d, J = 6.4 Hz, 1H), 7.04 (d, J = 8.0 Hz, 1H), 6.72 (dd, J = 15.6 Hz, 1H), 6.53 (s, 2H), 6.36 (d, J = 16.4

Hz, 1H), 6.34 (s, 1H), 6.20 (dd, *J* = 15.2 Hz, 1H), 5.85 (dt, *J* = 7.2, 14.4 Hz, 1H), 3.80 (s, 6H), 2.78 (t, *J* = 8.8 Hz, 2H), 2.29 (s, 3H), 2.21 (q, *J* = 6.8 Hz, 2H), 1.85 (q, *J* = 7.2 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 160.8, 156.0, 149.6, 139.6, 136.9, 135.7, 133.0, 130.8, 130.1, 129.9, 122.2, 104.1, 99.6, 55.3, 37.3, 32.4, 29.5, 18.0. HRMS $C_{21}H_{25}NO_2$: calcd [M] = 323.1880, obsd $[M + H]^+$ = 323.1878.



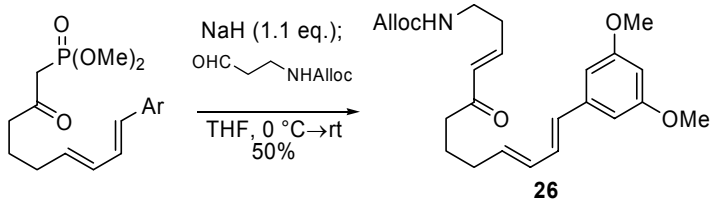
5-((3R,3aR,4S,4S,6aR)-3,3a,4,6a,7,8,9-heptahydro-3-methyl-2H-benzo[de]quinolin-4-yl)benzene-1,3-diol 24: BBr_3 (1.0M DCM, 2.4 mL, 5.0 equiv.) was added to a 0 °C solution of Diels-Alder adduct (150 mg, 0.461 mmol, 1.0 equiv.) in DCM (9.4 mL) and allowed to warm to room temperature, 1h, before quenching with a 1:1 sat. $NaHCO_3$:brine solution. The layers were separated, the aqueous extracted twice with EtOAc, and the combined organics dried over Na_2SO_4. Evaporation *in vacuo* produced a crude material which was purified over neutral alumina (7.5% to 25% MeOH/$CHCl_3$, R_f = 0.15 in 15%) to give pure catechol **24** (99 mg, 69 % yield over 3 steps from *trans*-enone **16**) as a white crystalline solid. ^{1}H-NMR (400 MHz, CD_3OD) δ 6.28 (d, *J* = 2.0 Hz, 2H), 6.16 (t, *J* = 2.4 Hz, 1H), 5.77 (d, *J* = 10.0 Hz, 1H), 5.67 (ddd, *J* = 2.4, 4.8, 9.6 Hz, 1H), 3.58-3.62 (m, 1H), 3.52 (dd, *J* = 4.0, 16.4 Hz, 1H), 3.04 (ddd, *J* = 2.8, 10.4, 16.0 Hz, 1H), 2.34 (dt, *J* = 2.0, 11.2 Hz, 1H), 2.18 (t, *J* = 11.6 Hz, 1H), 1.94-2.08 (m, 3H), 1.60-1.76 (m, 3H), 1.47-1.54 (m, 1H), 1.17-1.21 (m, 1H), 1.08 (d, *J* = 6.4

Hz, 3H); ^{13}C-NMR (100 MHz, DMSO) δ 170.5, 158.5, 142.58, 132.0, 130.6, 109.1, 101.5, 57.0, 44.6, 43.2, 43.1, 37.5, 32.0, 28.2, 26.1, 17.3. $[\alpha]_D^{25}$ = +235 (*c* = 1.0, MeOH). IR (film): 3245, 2926, 1665, 1599, 1449, 1336, 1156. HRMS $C_{19}H_{23}NO_2$: calcd [M] = 297.1723, obsd $[M]^+$ = 297.1719.

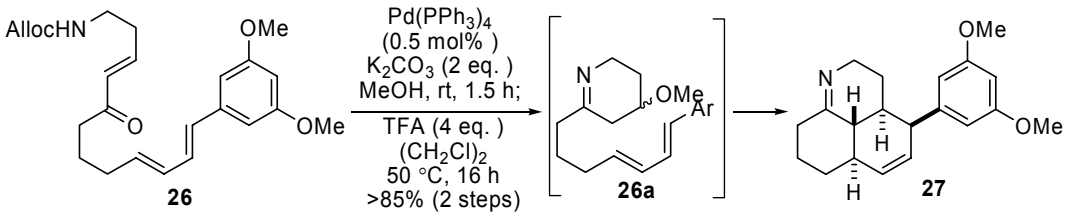


(+)-Symbioimine 25: SO_3·Pyr (154 mg, 0.965 mmol, 10.0 equiv.) was added to a room temperature solution of catechol **24** (28.7 mg, 0.0965 mmol, 1.0 equiv.) and in DMF (4.8 mL) and stirred overnight. Upon concentration *in vacuo*, the crude material was quenched by addition of phosphate buffer (pH = 7) and again concentrated *in vacuo* to give a crude material that was purified over silica (25% MeOH/$CHCl_3$, R_f = 0.20) to give (+)-symbioimine **25** (18 mg, 50% yield) as a crystalline solid, and the remainder of the material being catechol **24**, which was resubmitted to the reaction conditions to give a 65% yield brsm. ^{1}H-NMR (400 MHz, DMSO) δ 12.84 (bs, 1H), 9.36 (s, 1H), 6.64 (t, *J* = 1.8 Hz, 1H), 6.54 (t, *J* = 1.8 Hz, 1H), 6.41 (d, *J* = 1.8 Hz, 1H), 5.80 (d, *J* = 9.8 Hz, 1H), 5.67 (ddd, *J* = 2.4, 4.3, 9.8 Hz, 1H), 3.65 (t, *J* = 4.3 Hz, 1H), 3.58 (dd, *J* = 4.7, 14.3 Hz, 1H), 3.13 (dd, *J* = 12.0, 14.3 Hz, 1H), 2.68-2.62 (m, 2H), 2.52 (dd, *J* = 11.1, 12.0 Hz, 1H), 2.38 (ddd, *J* = 2.4, 12.0, 12.9 Hz, 1H), 2.08-2.01 (m, 1H), 1.94 (dd, *J* = 2.3, 12.9 Hz, 1H), 1.77 (dt, *J* = 4.3, 11.1 Hz, 1H), 1.69-1.63 (m, 1H), 1.50 (dq, *J* = 4.2, 12.9 Hz, 1H), 1.24 (dddq, *J* = 4.7, 6.1, 11.1, 12.0 Hz, 1H), 1.05 (d, *J* = 6.1 Hz, 3H); ^{13}C-NMR (100

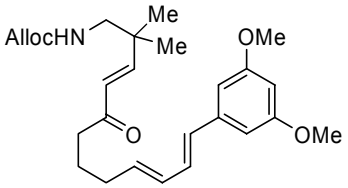
MHz, DMSO) δ 188.0, 157.3, 154.2, 139.9, 130.4, 129.6, 112.8, 111.8, 106.0, 49.8, 41.7, 41.5, 41.0, 40.3, 33.4, 29.7, 26.2, 24.4, 15.6. $[\alpha]_D^{25}$ = +245 (*c* = 0.10, DMSO). IR (film): 3445, 1688, 1605, 1520, 1449, 1259, 1240, 1140. HRMS $C_{19}H_{24}NO_5S$: calcd $[M + H]^+$ = 378.1370, obsd $[M + H]^+$ = 378.1375.



Allyl (3E,9E,11E)-12-(3,5-dimethoxyphenyl)-5-oxododeca-3,9,11-trienylcarbamate 26: Produced in a similar fashion as Ch. 3-21, (146 mg, 50% yield) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.72 (d, *J* = 15.6 Hz, 1H), 6.70 (d, *J* = 15.2 Hz, 1H), 6.55 (s, 1H), 6.36 (d, *J* = 16.0 Hz, 1H), 6.32 (t, *J* = 2.4 Hz, 1H), 6.26-6.08 (m, 2H), 5.88 (m, 1H), 5.77 (dt, *J* = 14.8, 6.8 Hz, 1H), 5.23 (dd, *J* = 10.4, 17.2 Hz, 2H), 4.93 (bs, 1H), 4.53 (d, *J* = 4.8 Hz, 2H), 3.77 (s, 1H), 3.31 (q, *J* = 6.0 Hz, 2H), 2.54 (t, *J* = 7.6 Hz, 2H), 2.41 (q, *J* = 6.8 Hz, 2H), 2.16 (q, *J* = 6.8 Hz, 2H), 1.73 (q, *J* = 7.6 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 200.0, 160.8, 156.1, 143.0, 139.4, 134.9, 132.7, 131.9, 131.1, 130.3, 129.6, 117.6, 104.1, 99.5, 65.5, 55.2, 39.3, 32.9, 32.1, 23.4. HRMS $C_{24}H_{31}NO_5$: calcd $[M+ Na]^+$ = 413.2094, obsd $[M + Na]^+$ = 436.2098.



2,3,4,5-tetrahydro-4-methoxy-6-((4E,6E)-7-(3,5-dimethoxyphenyl)hepta-4,6-dienyl)-3,3-dimethylpyridine 26a and (3aS,4S,4S,6aR)-3,3a,4,6a,7,8,9-heptahydro-4-(3,5-dimethoxyphenyl)-2H-benzo[de]quinoline 27: Produced as similar to **17**: (78 mg, 0.189 mmol) **26** to methanol adduct **26a**. **26a**: ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.69 (dd, *J* = 15.2 Hz, 1H), 6.52 (s, 2H), 6.34 (d, *J* = 15.6 hz, 1H), 6.31 (s, 1H), 6.17 (dd, *J* = 15.2 Hz, 1H), 5.79 (dt, *J* = 7.2, 14.7 Hz, 1H), 3.77 (s, 6H), 3.49 (m, 2H), 3.33 (s, 3H), 2.45 (dd, *J* = 4.8, 17.6 Hz, 1H), 2.16 (m, 4H), 2.06 (dd, *J* = 7.2, 18.0 Hz, 1H), 1.84 (m, 1H), 1.66 (q, *J* = 7.6 Hz, 2H), 1.50 (m, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 169.0, 160.7, 139.5, 130.7, 130.1, 129.7, 104.0, 99.5, 72.6, 55.2, 47.4, 39.9, 35.8, 32.4, 26.7, 25.7. HRMS $C_{21}H_{29}NO_3$: calcd $[M + H]^+$ = 344.2200, obsd $[M + H]^+$ = 434.2218. Produced as similar to **8**: (60 mg. 0.175 mmol) **26a** to Diels-Alder adduct **27** (50 mg, 85% over two steps), which had been purified over basic alumina (3:1 hexanes:EtOAc, R_f = 0.20). Diels-Alder adduct **27**: ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.36 (s, 1H), 6.32 (d, *J* = 10.0 Hz, 1H), 5.68 (dt, *J* = 3.6, 10.0 Hz, 1H0, 3.78 (s, 6H), 3.67 (dd, *J* = 3.6, 17.6 Hz, 1H), 3.47 (s, 1H), 3.41 (m, 1H), 2.53 (d, *J* = 14.4 Hz, 1H), 2.18-1.87 (m, 5H), 1.63 (m, 2H), 1.39 (dq, *J* = 3.2, 12.4, 25.2 Hz, 1H), 0.76 (dq, *J* = 4.8, 12.4, 25.2 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 160.3, 142.4, 132.8, 128.7, 108.3, 97.9, 55.3, 48.8, 45.8, 42.4, 41.2, 37.1, 36.9, 31.5, 25.8, 25.7. HRMS $C_{20}H_{25}NO_2$: calcd $[M + H]^+$ = 312.1958, obsd $[M + H]^+$ = 312.1962.



30

Allyl (3E,9E,11E)-12-(3,5-dimethoxyphenyl)-2,2-dimethyl-5-oxododeca-3,9,11-trienylcarbamate 30: Produced in a similar fashion as Ch. 3-21, (76 mg, 64% yield) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.71 (dd, *J* = 16.0 Hz, 1H), 6.52 (d, *J* = 2.4 Hz, 2H), 6.37 (d, *J* = 16.0 Hz, 1H), 6.33 (s, 1H), 6.19 (dd, *J* = 14.8 Hz, 1H), 6.03 (d, *J* = 16.0 Hz, 1H), 5.92-5.75 (m, 2H), 5.23 (dd, *J* = 10.4, 17.2 Hz, 1H), 4.76 (s, 1H), 4.52 (d, *J* = 4.8 Hz, 2H), 3.78 (s, 6H), 3.15 (d, *J* = 6.8 Hz, 2H), 2.57 (t, *J* = 7.2 Hz, 2H), 2.17 (q, *J* = 7.2 Hz, 2H), 1.07 (s, 6H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 200.4, 160.8, 156.4, 152.5, 139.4, 132.7, 131.1, 130.3, 129.6, 128.0, 117.7, 104.1, 99.5, 65.5, 55.2, 50.4, 39.4, 38.4, 32.1, 24.1, 23.4. HRMS $C_{26}H_{35}NO_5$: calcd [M] = 441.2510, obsd [M] = 441.2503.

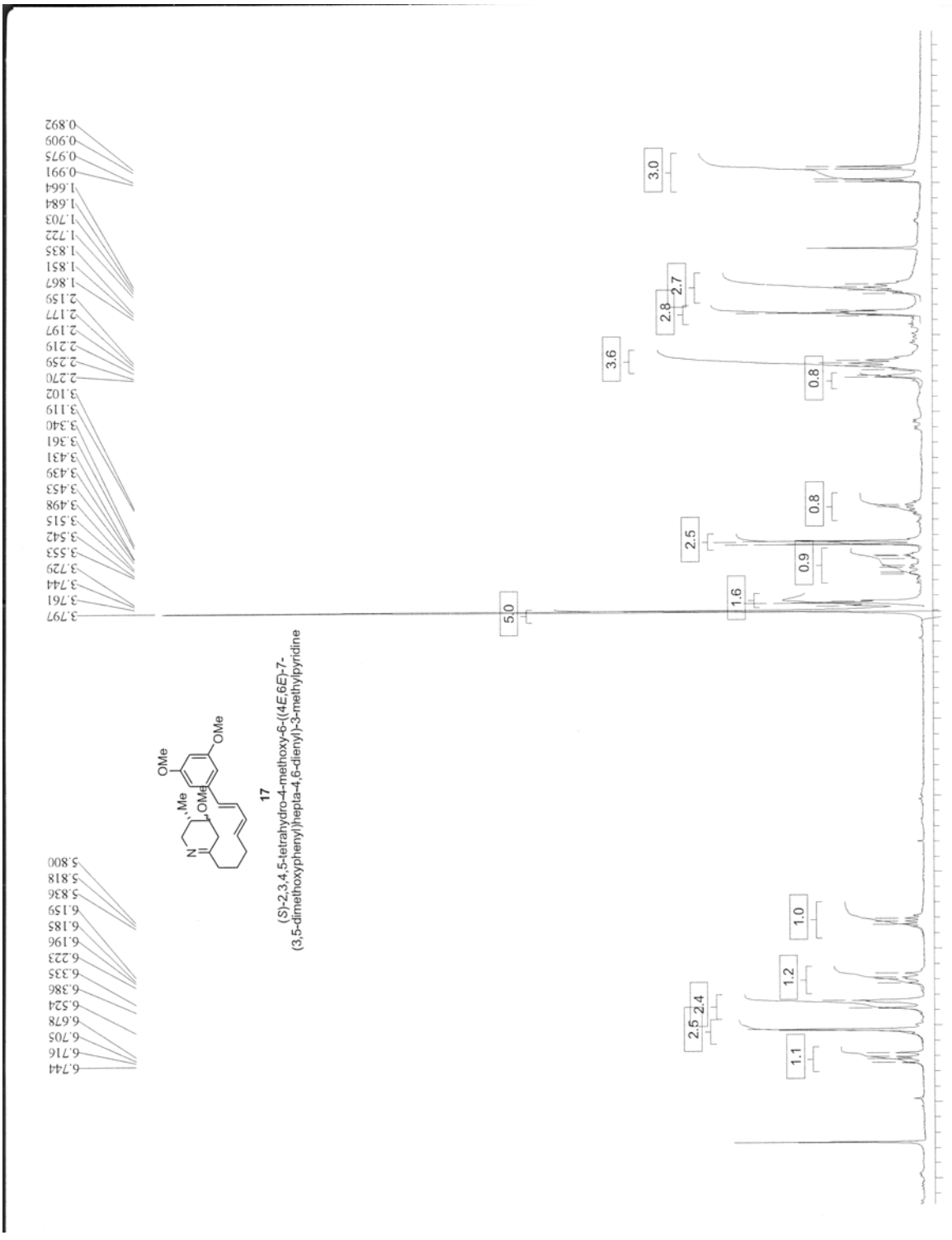
K. References and Notes

[1] Heathcock, C. H.; Hansen M, M.; Ruggeri, R. B.; Kath, J. C. *J. Org. Chem.* **1992**, *57*, 2544-2553.

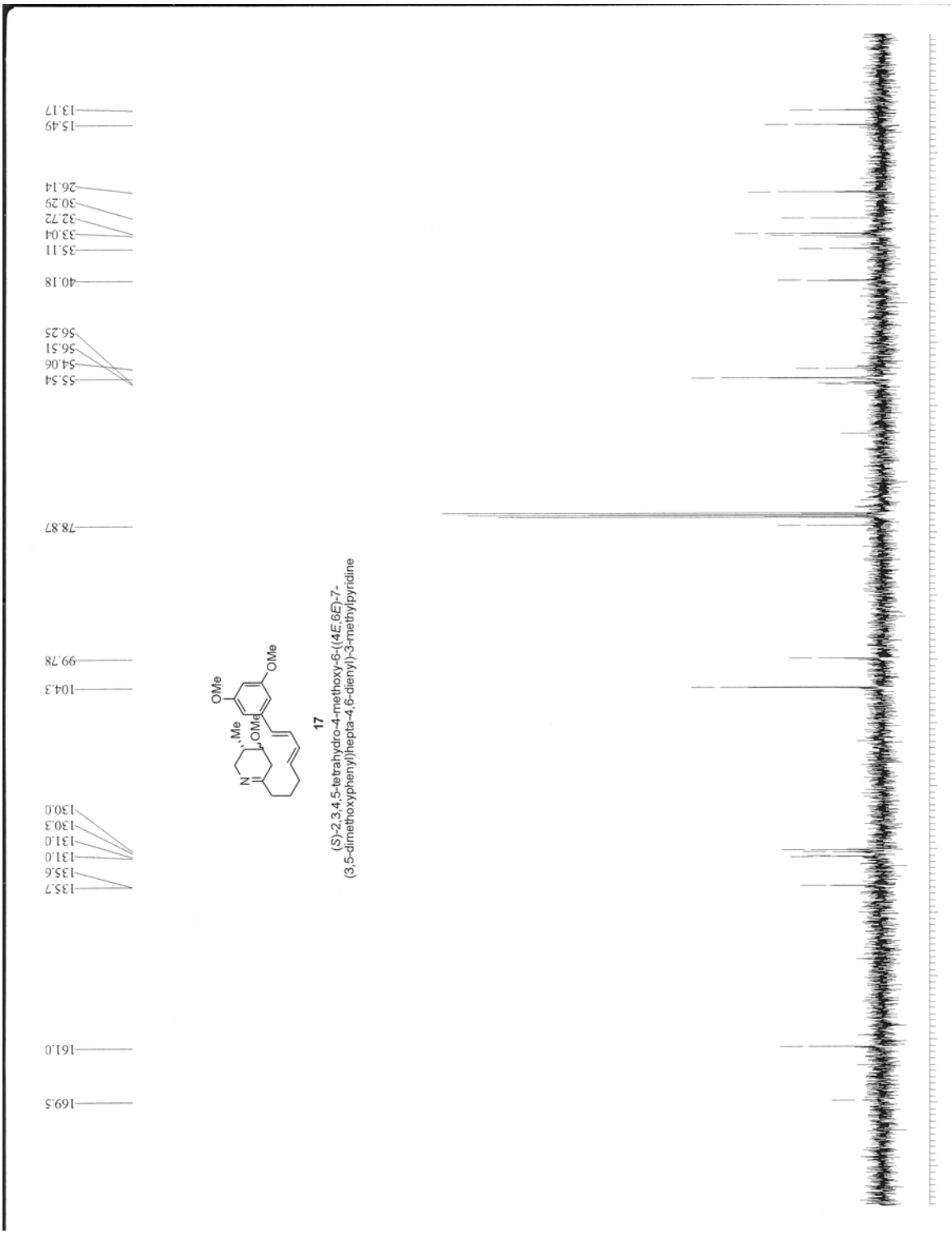
Chapter 6

Selected Spectra

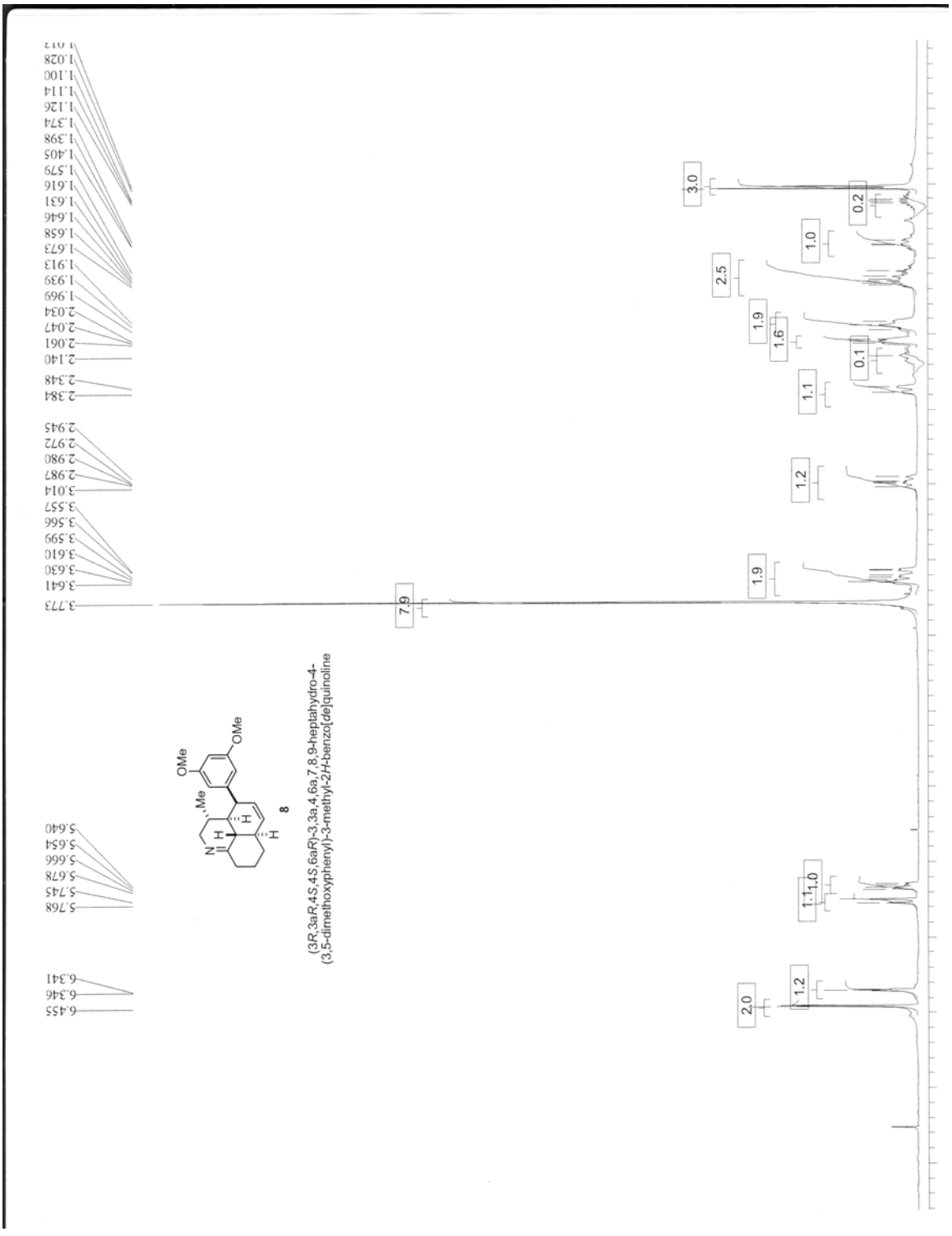
Spectrum Page



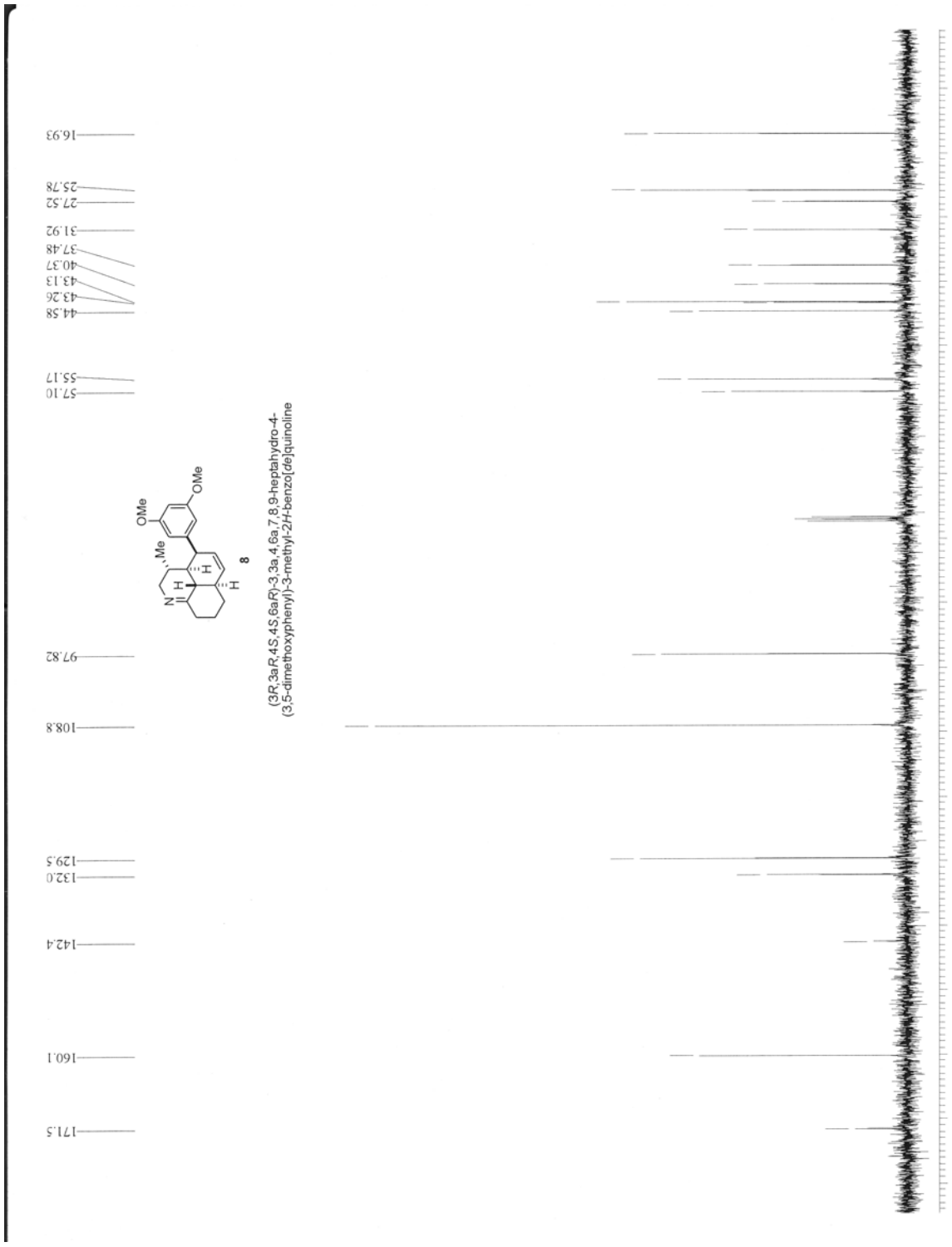
Spectrum 91. ^{1}H NMR spectrum of compound **17** in $CDCl_3$



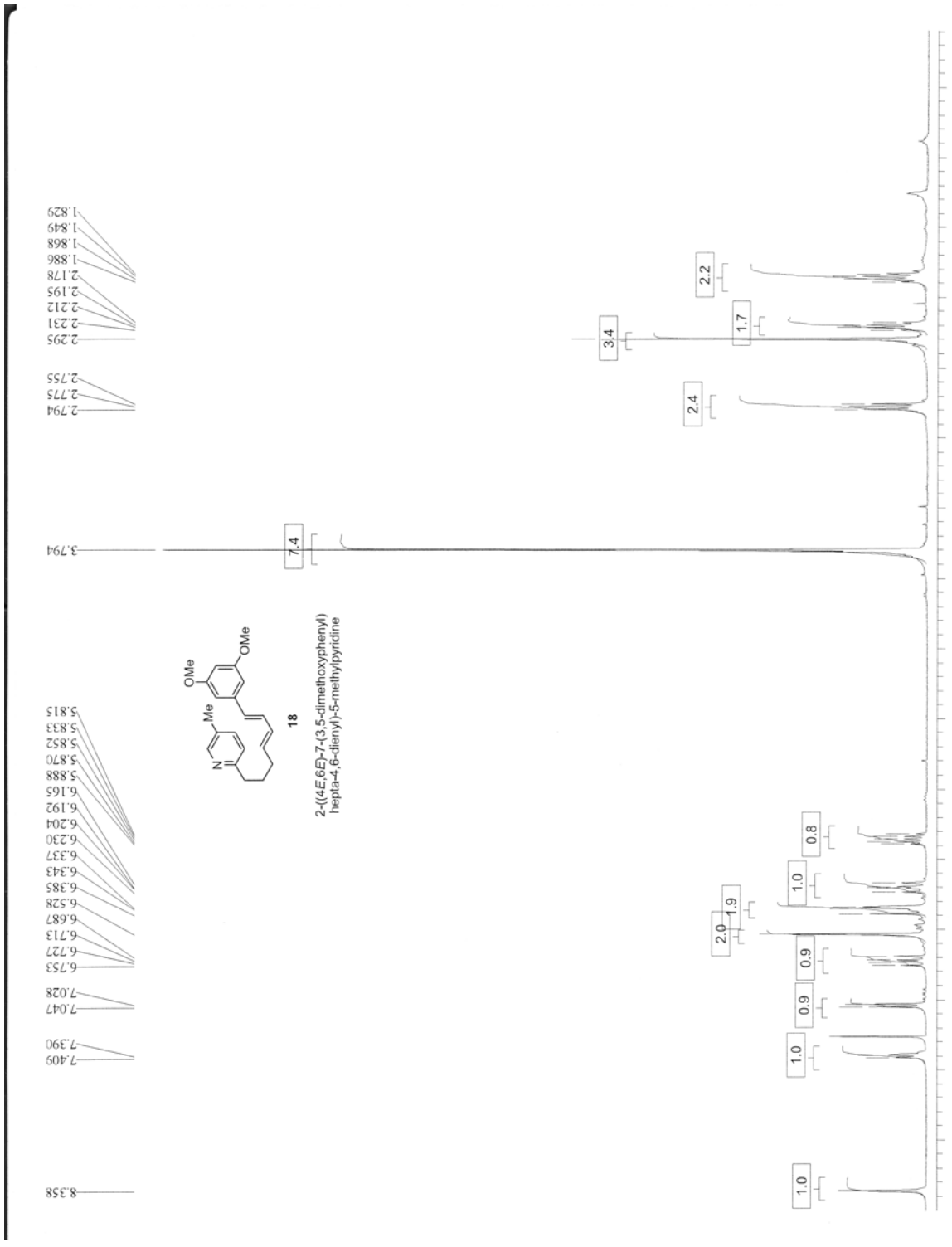
Spectrum 92. ^{13}H NMR spectrum of compound **17** in $CDCl_3$



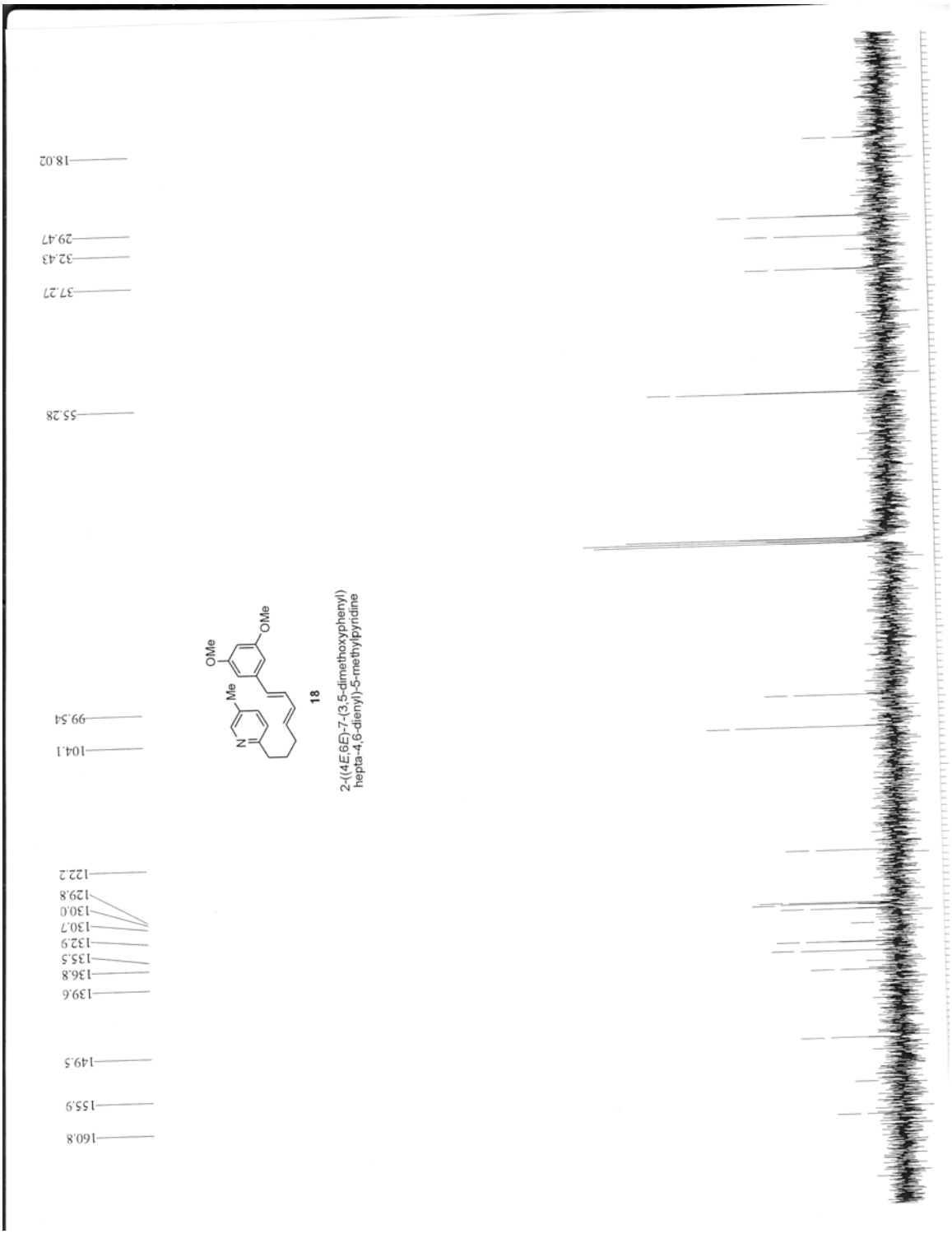
Spectrum 93. ^{1}H NMR spectrum of compound **8** in $CDCl_3$



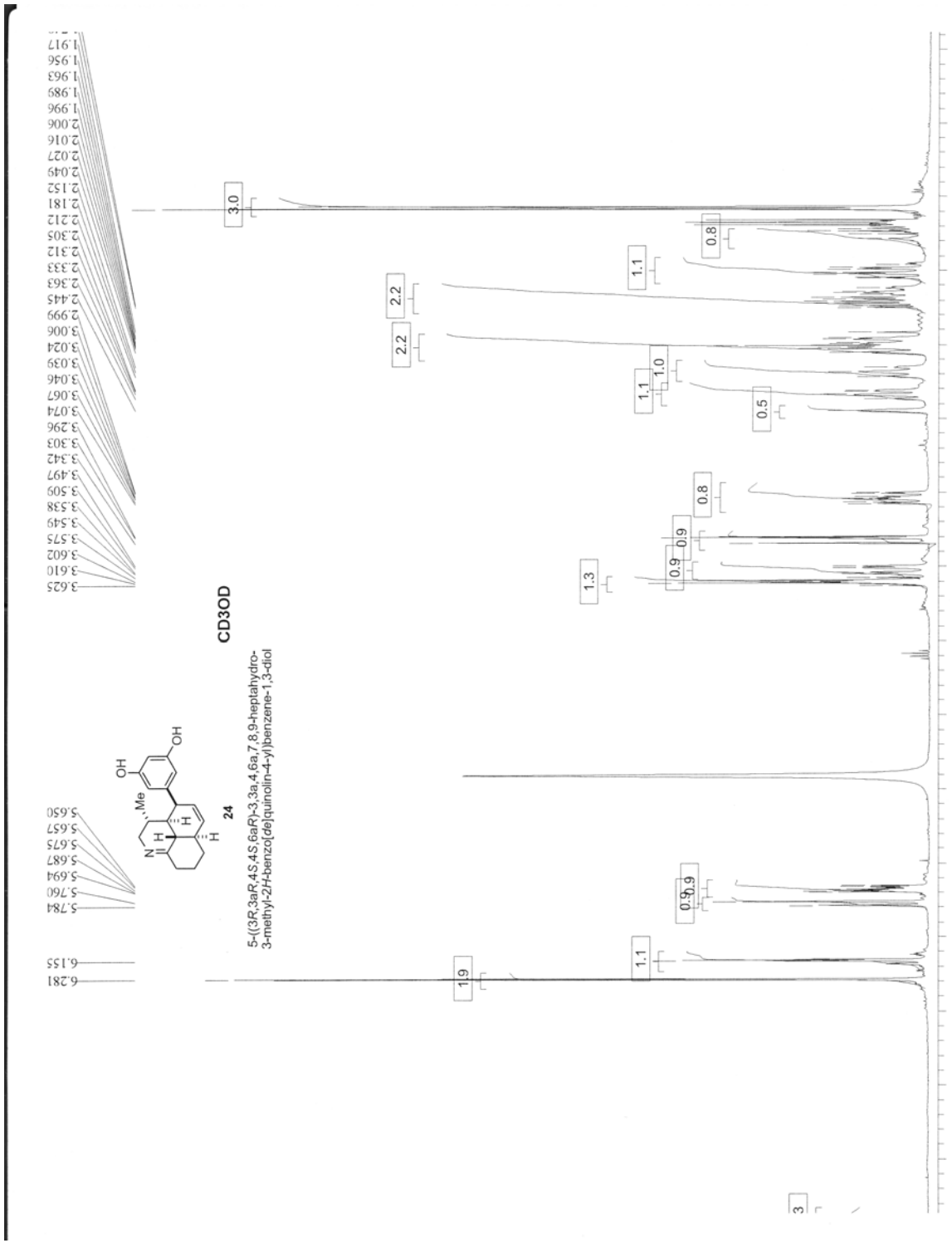
Spectrum 94. ^{13}C NMR spectrum of compound **8** in $CDCl_3$



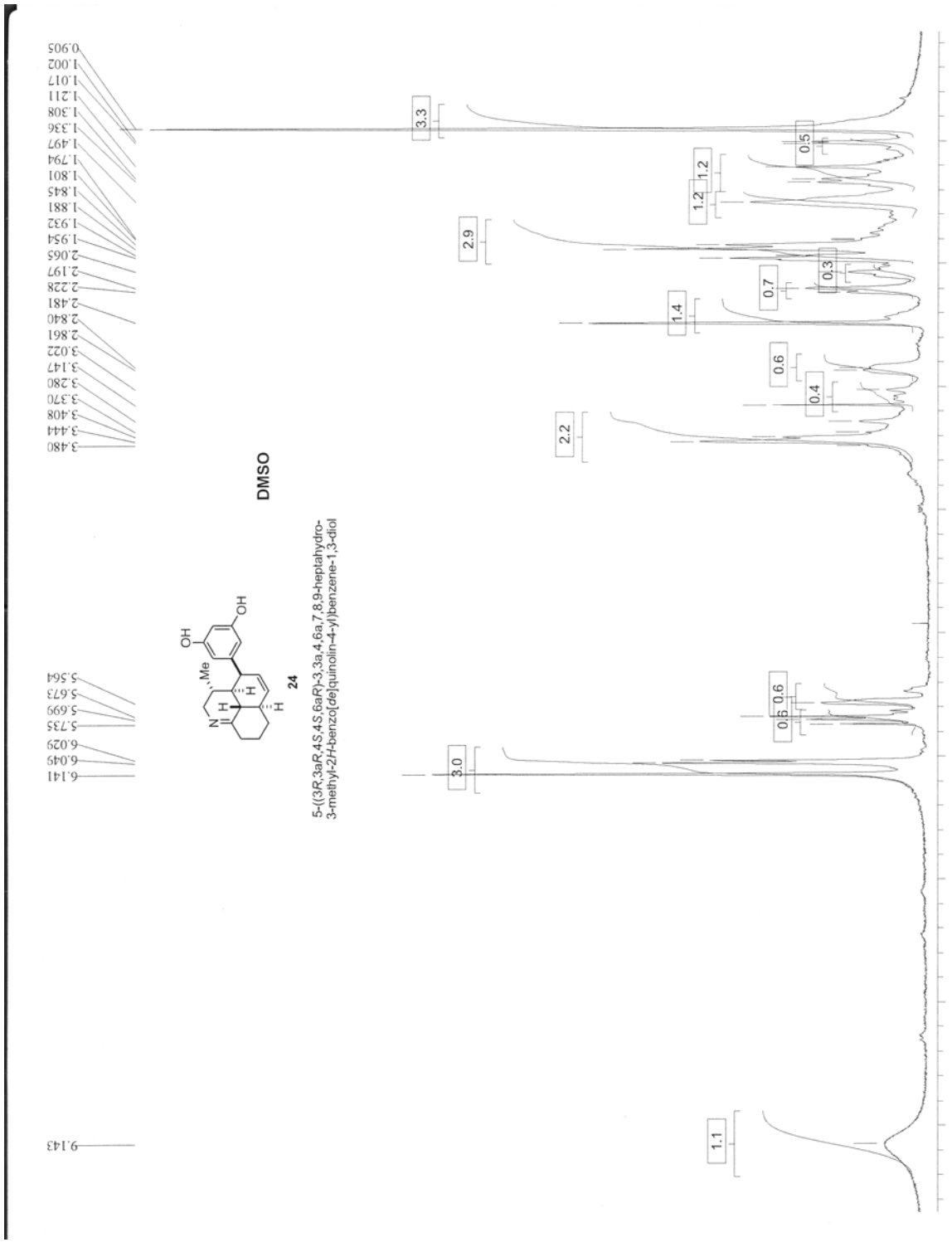
Spectrum 95. ^{1}H NMR spectrum of compound **18** in $CDCl_3$



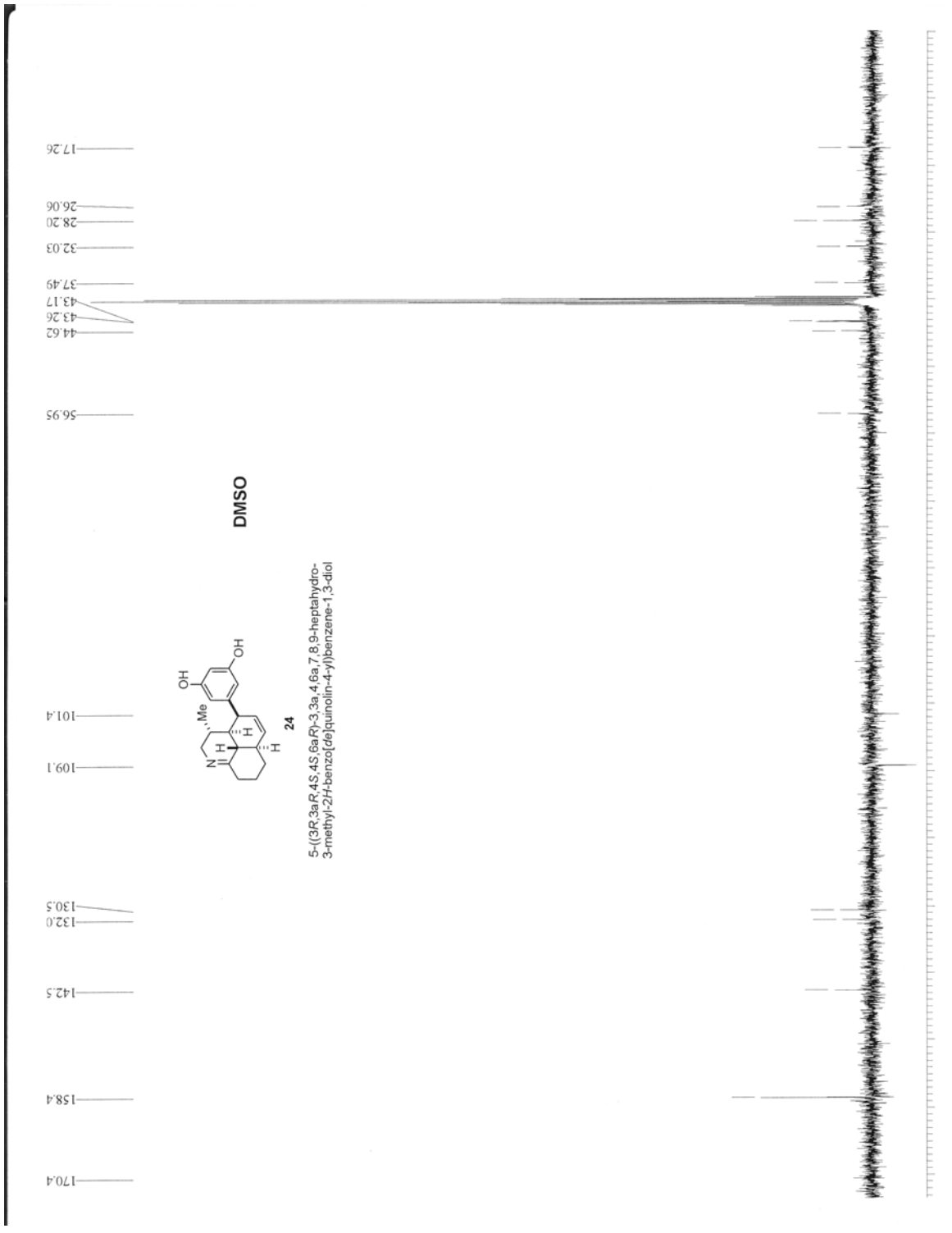
Spectrum 96. ^{13}C NMR spectrum of compound **18** in $CDCl_3$



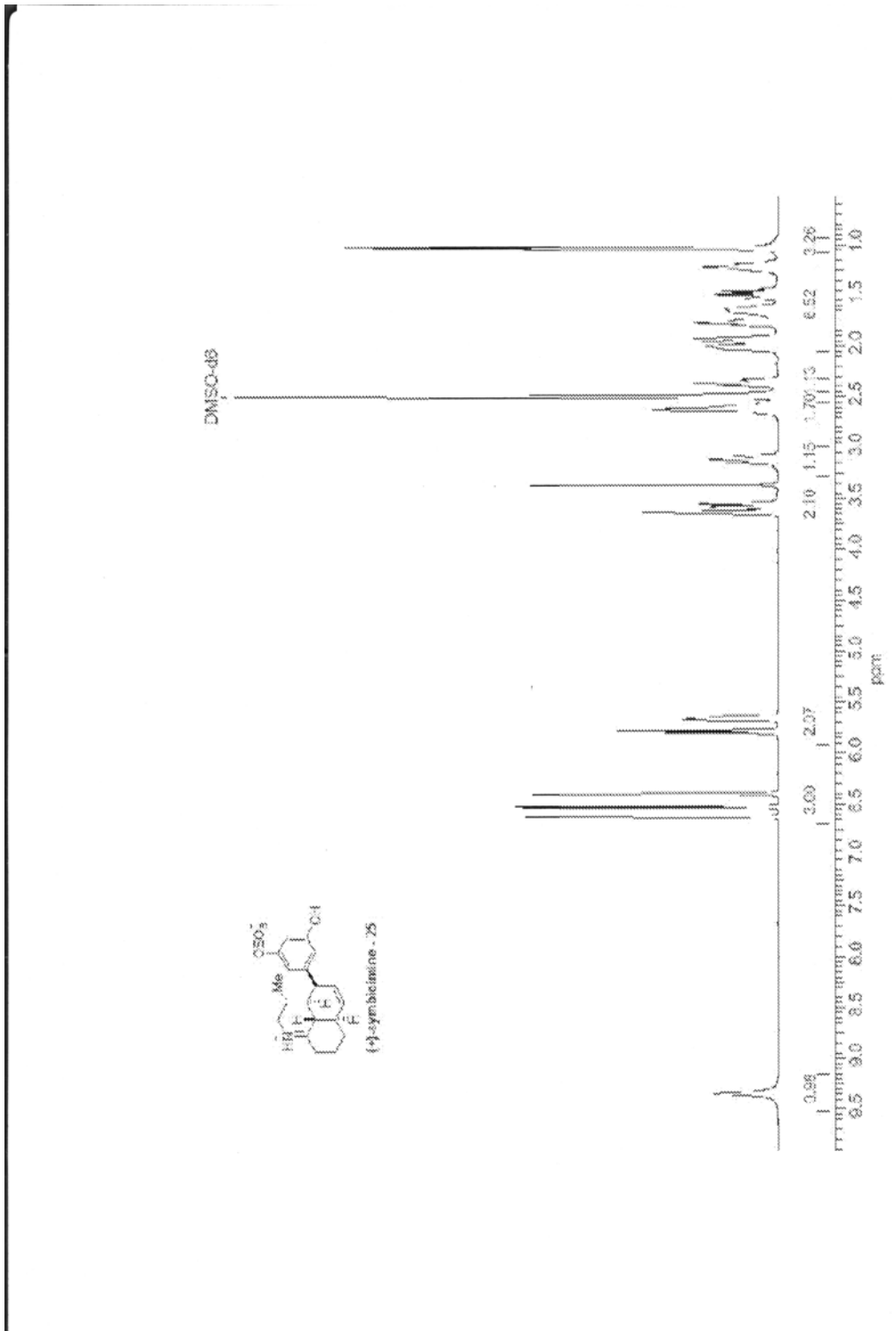
Spectrum 97. ^{1}H NMR spectrum of desulfo-symbioimine **24** in CD_3OD



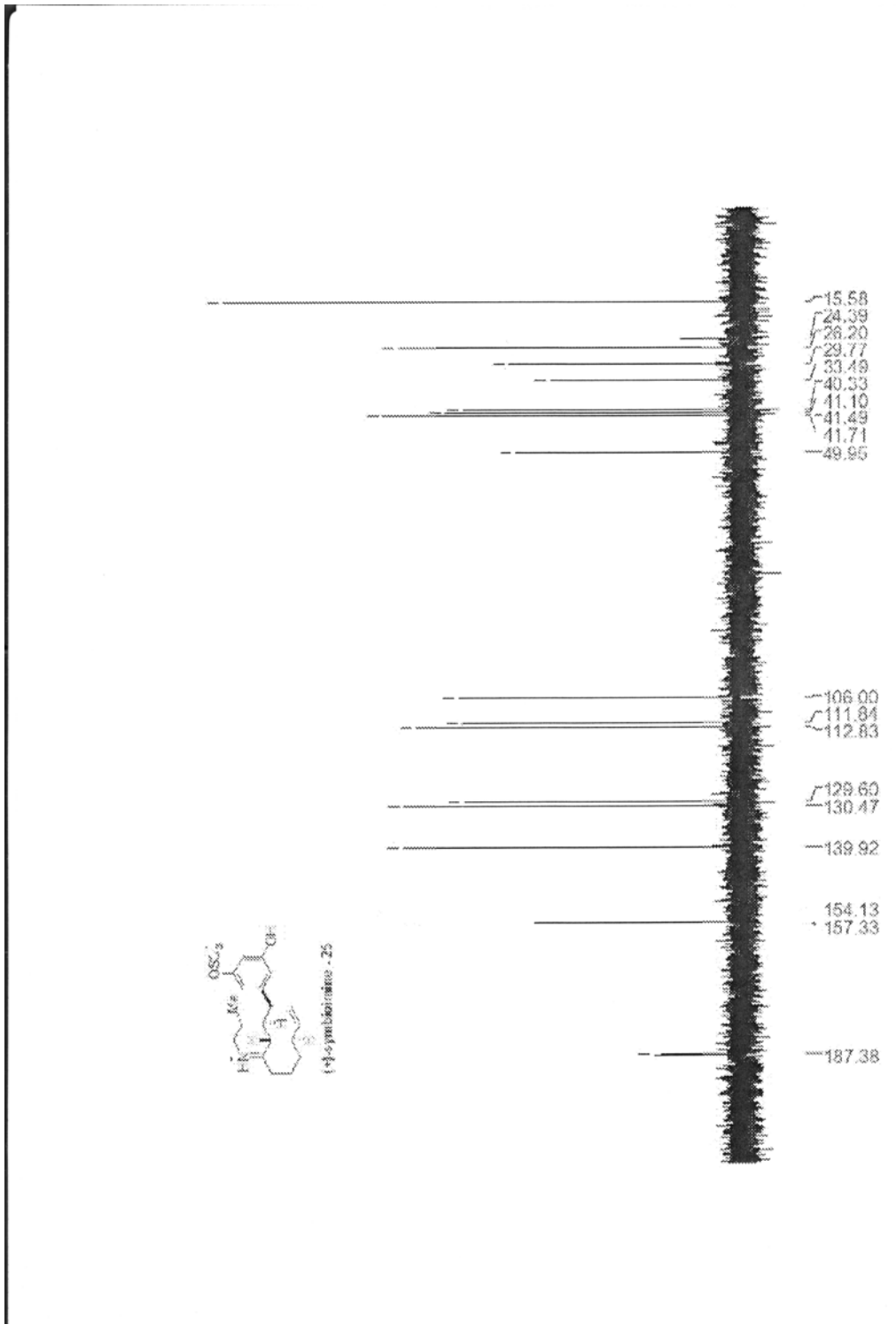
Spectrum 98. ^{1}H NMR spectrum of desulfo-symbioimine **24** in DMSO



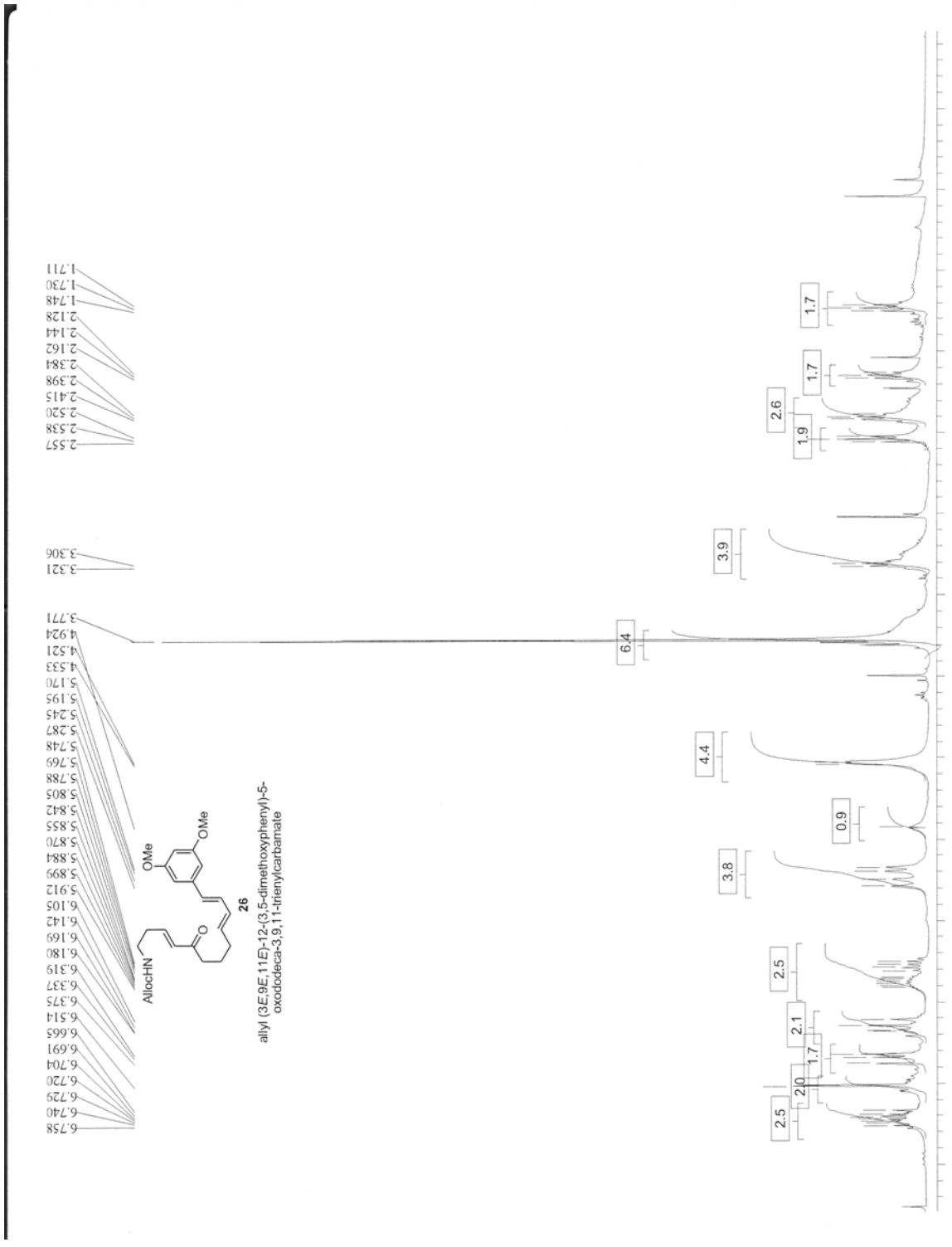
Spectrum 99. ^{13}C NMR spectrum of desulfo-symbioimine **24** in DMSO



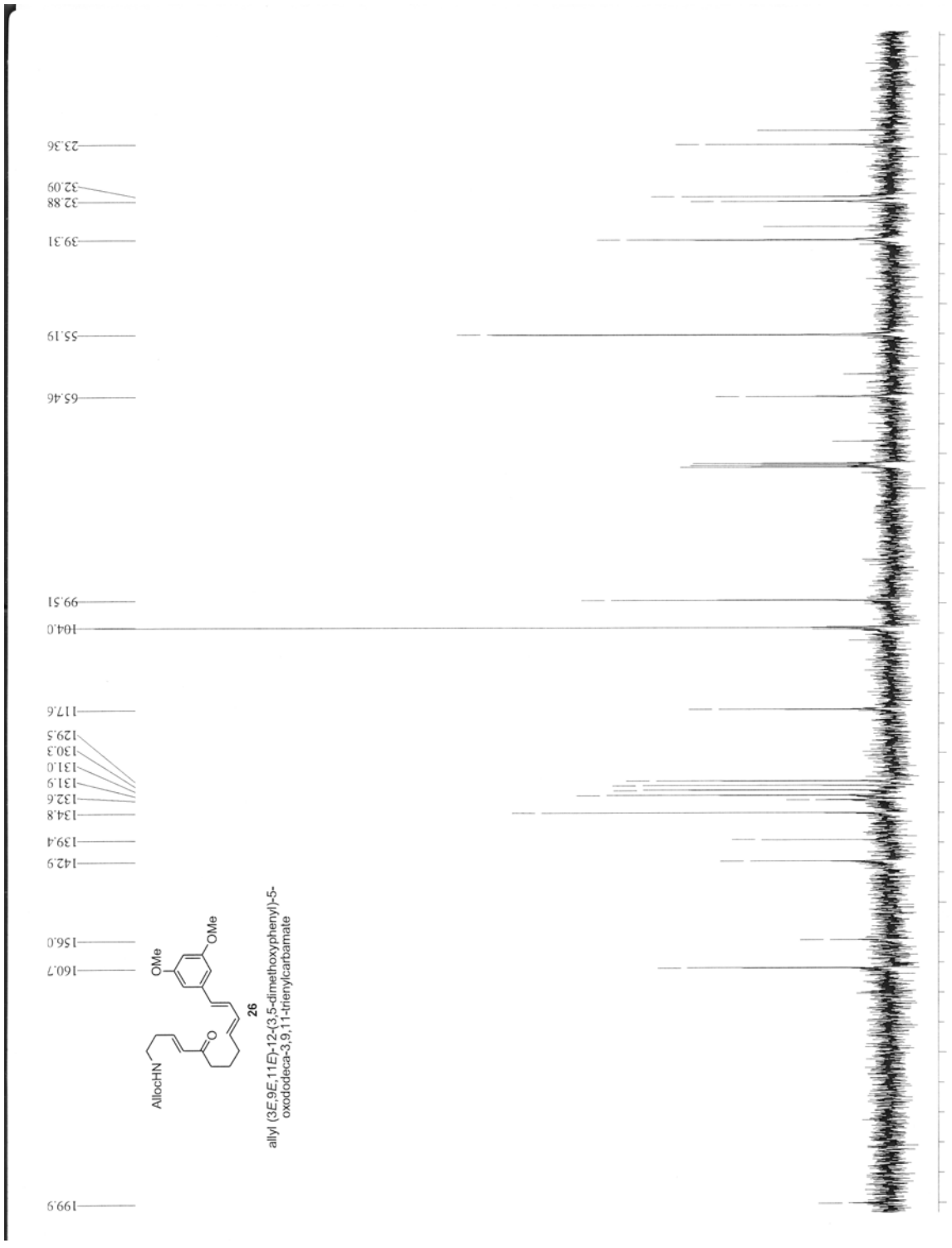
Spectrum 100. ^{1}H NMR spectrum of (+)-Symbioimine **25** in DMSO



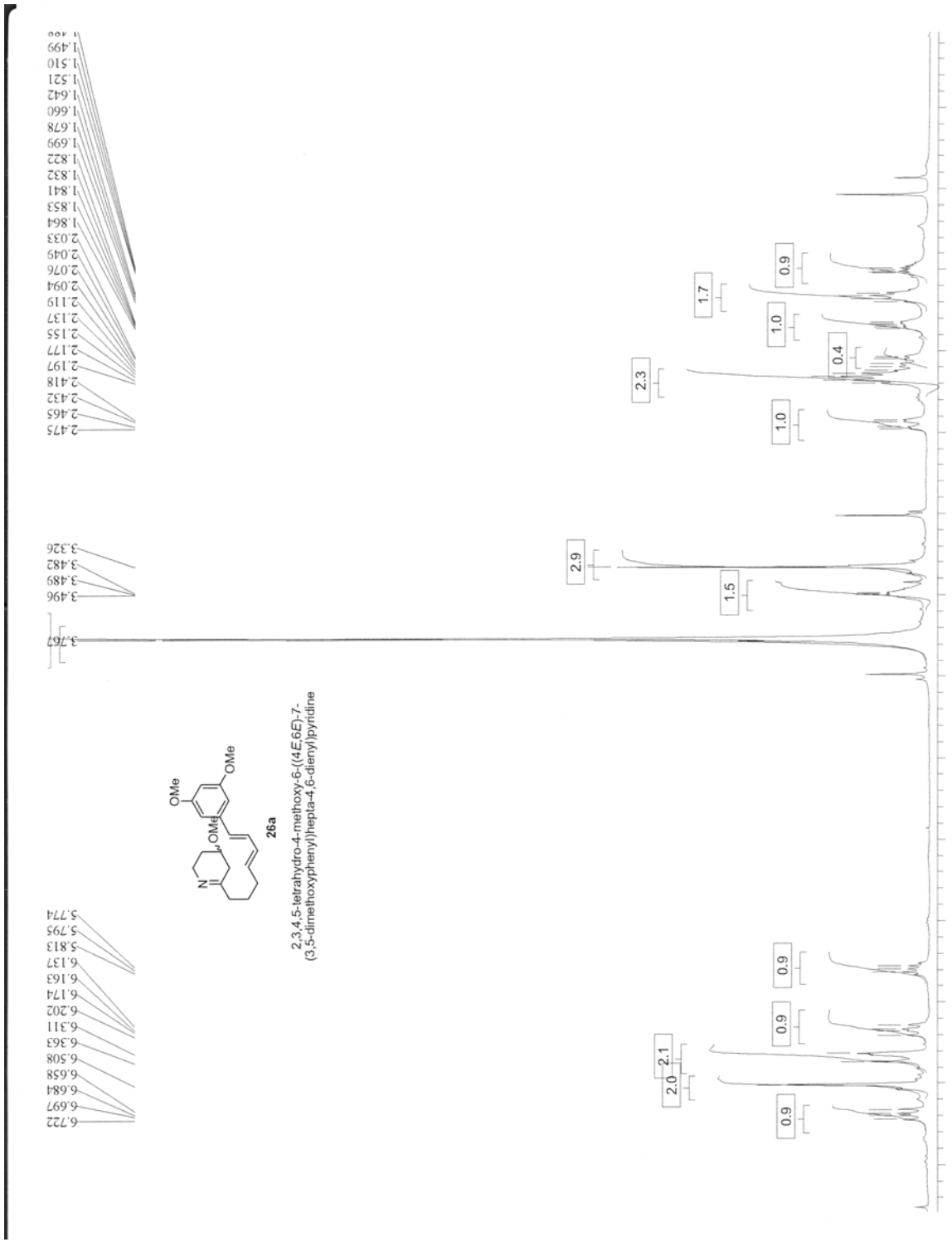
Spectrum 101. ^{13}C NMR spectrum of (+)-Symbioimine **25** in DMSO



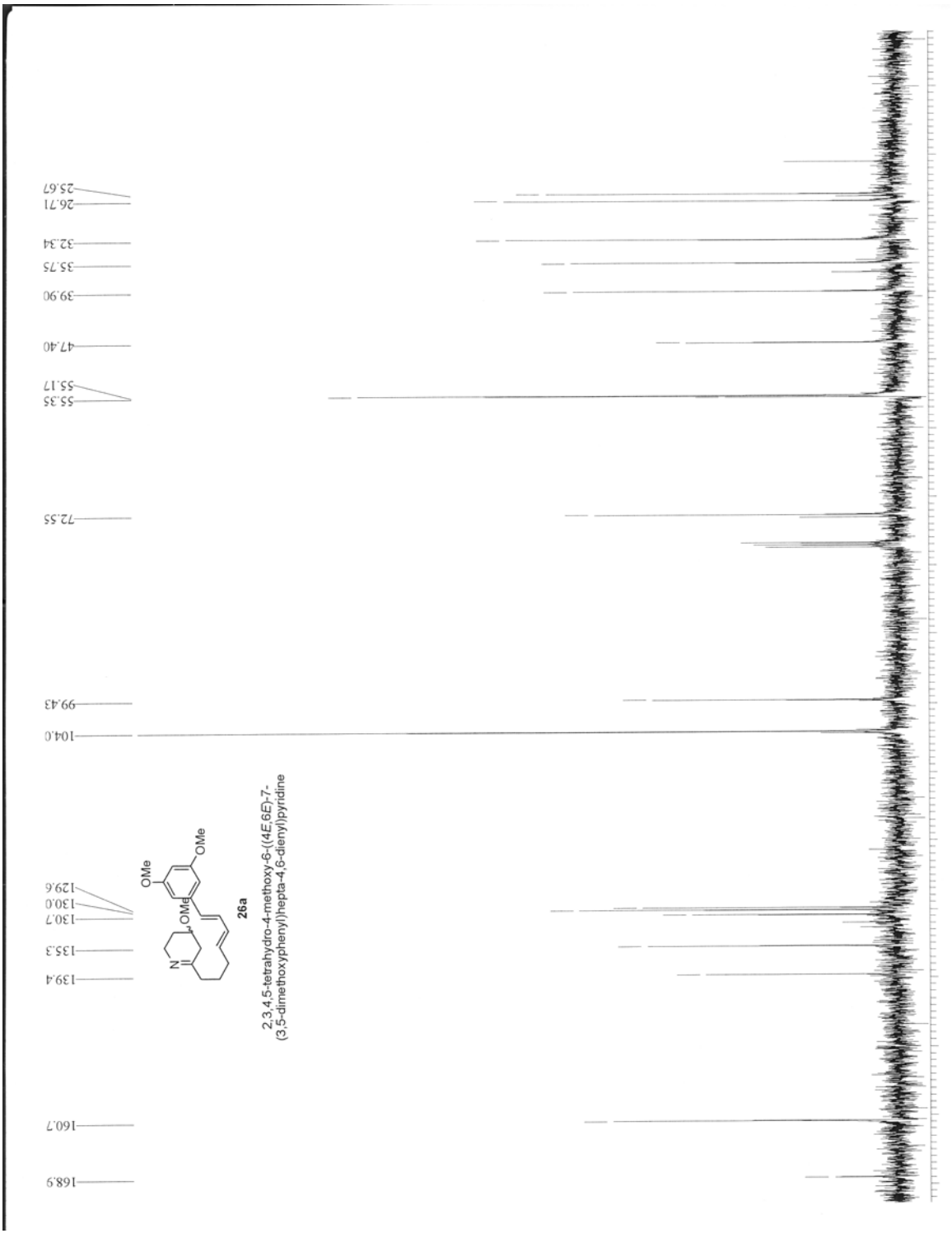
Spectrum 102. ^{1}H NMR spectrum of compound **26** in $CDCl_3$



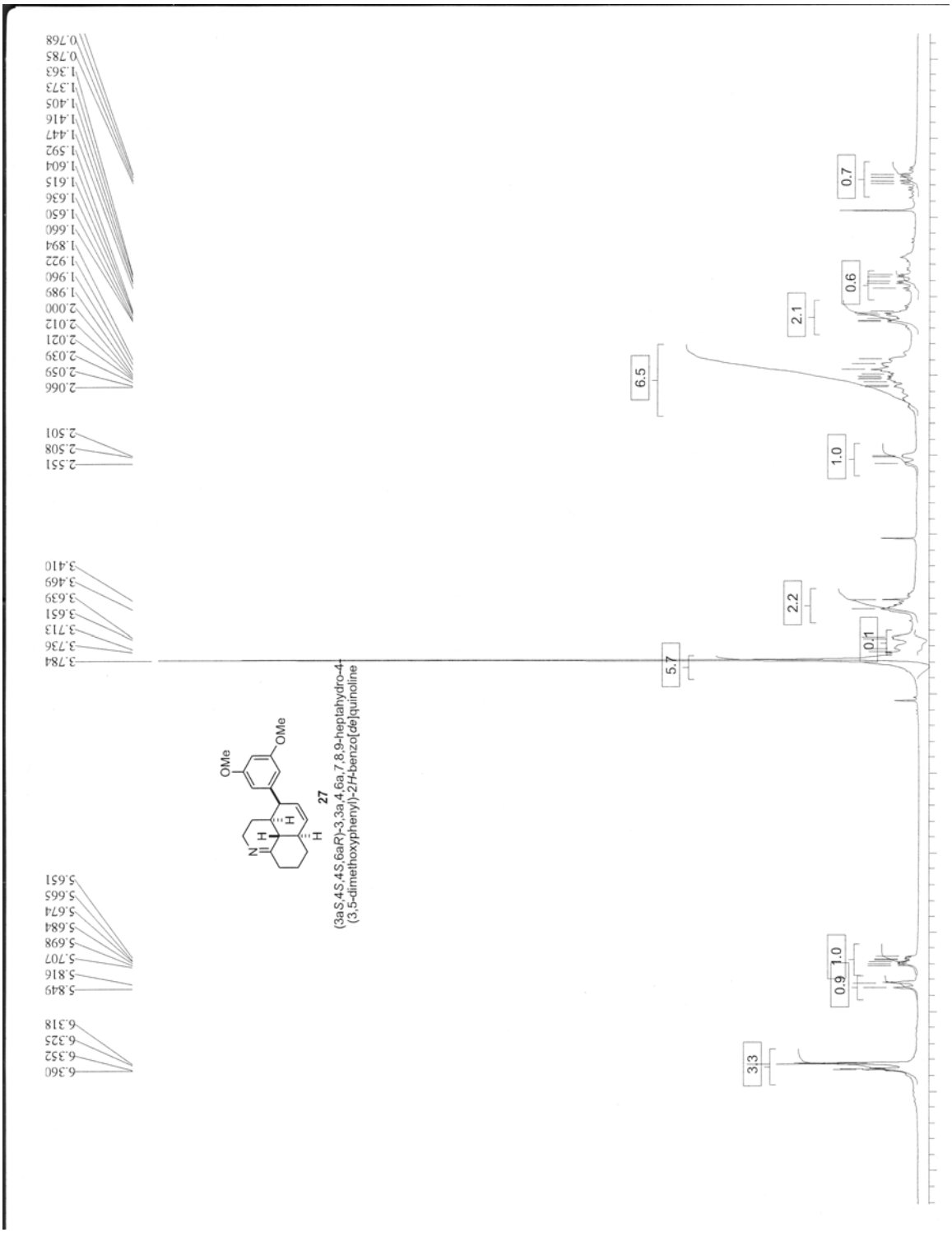
Spectrum 103. ^{13}C NMR spectrum of compound **26** in $CDCl_3$



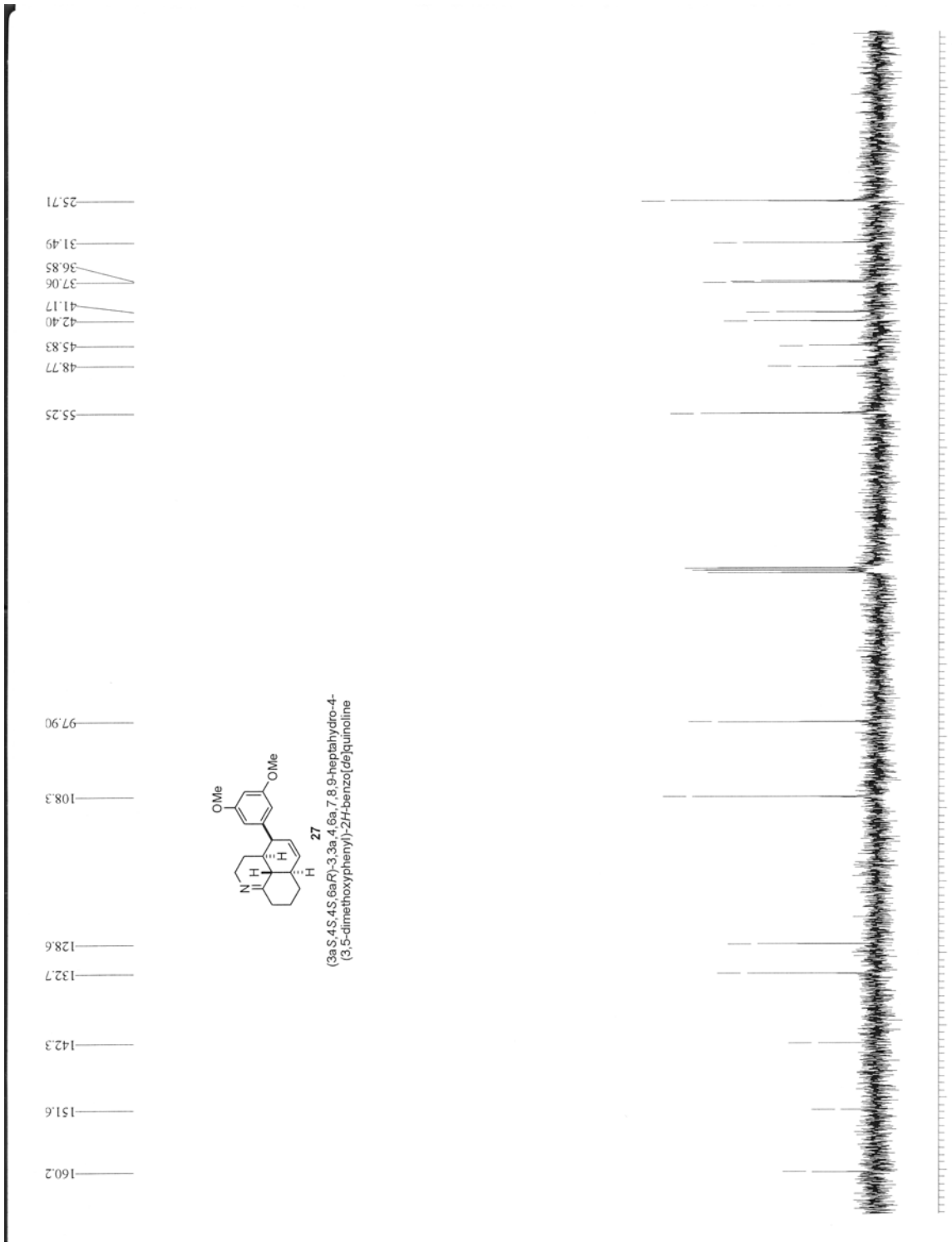
Spectrum 104. ^{1}H NMR spectrum of compound **26a** in $CDCl_3$



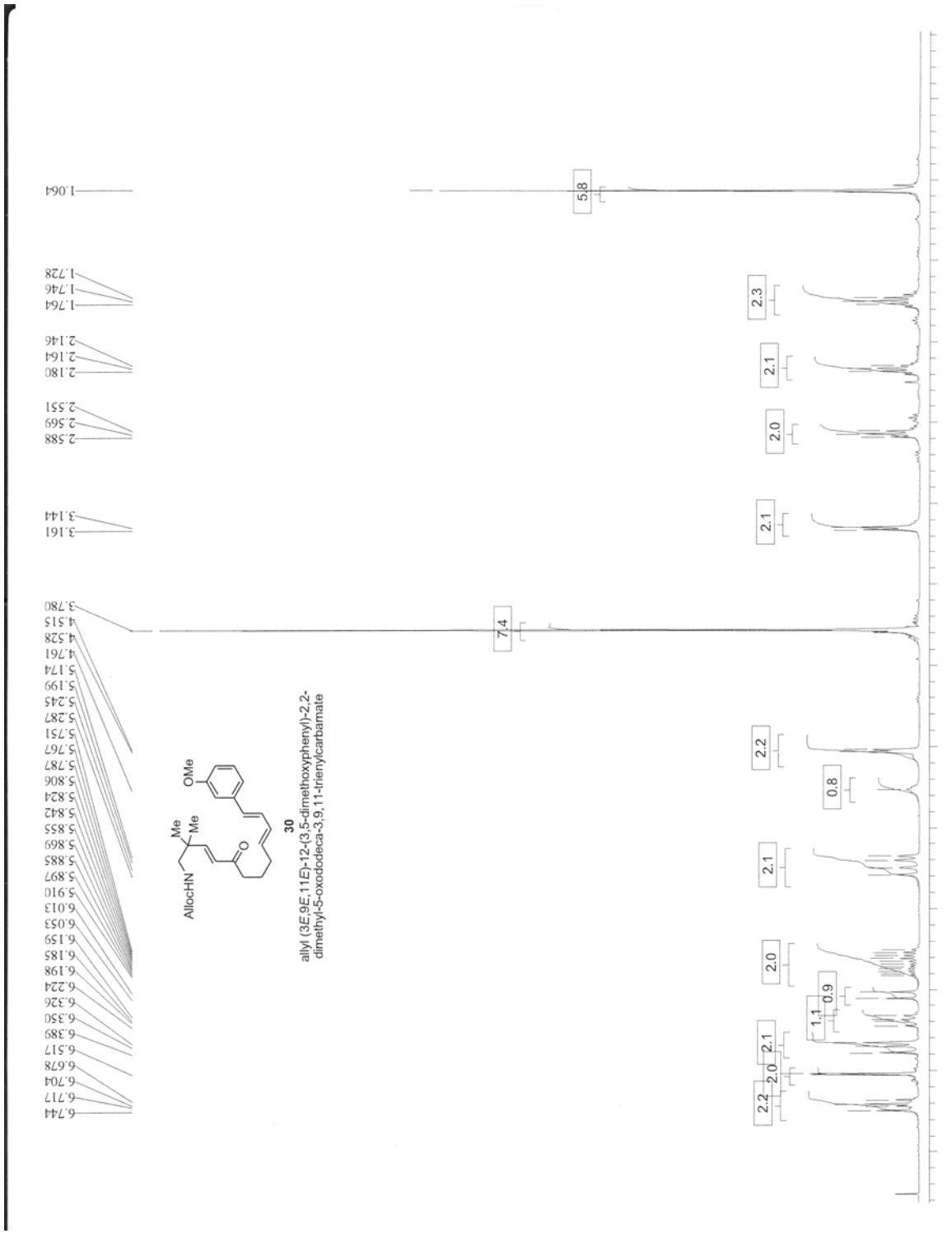
Spectrum 105. ^{13}C NMR spectrum of compound **26a** in $CDCl_3$



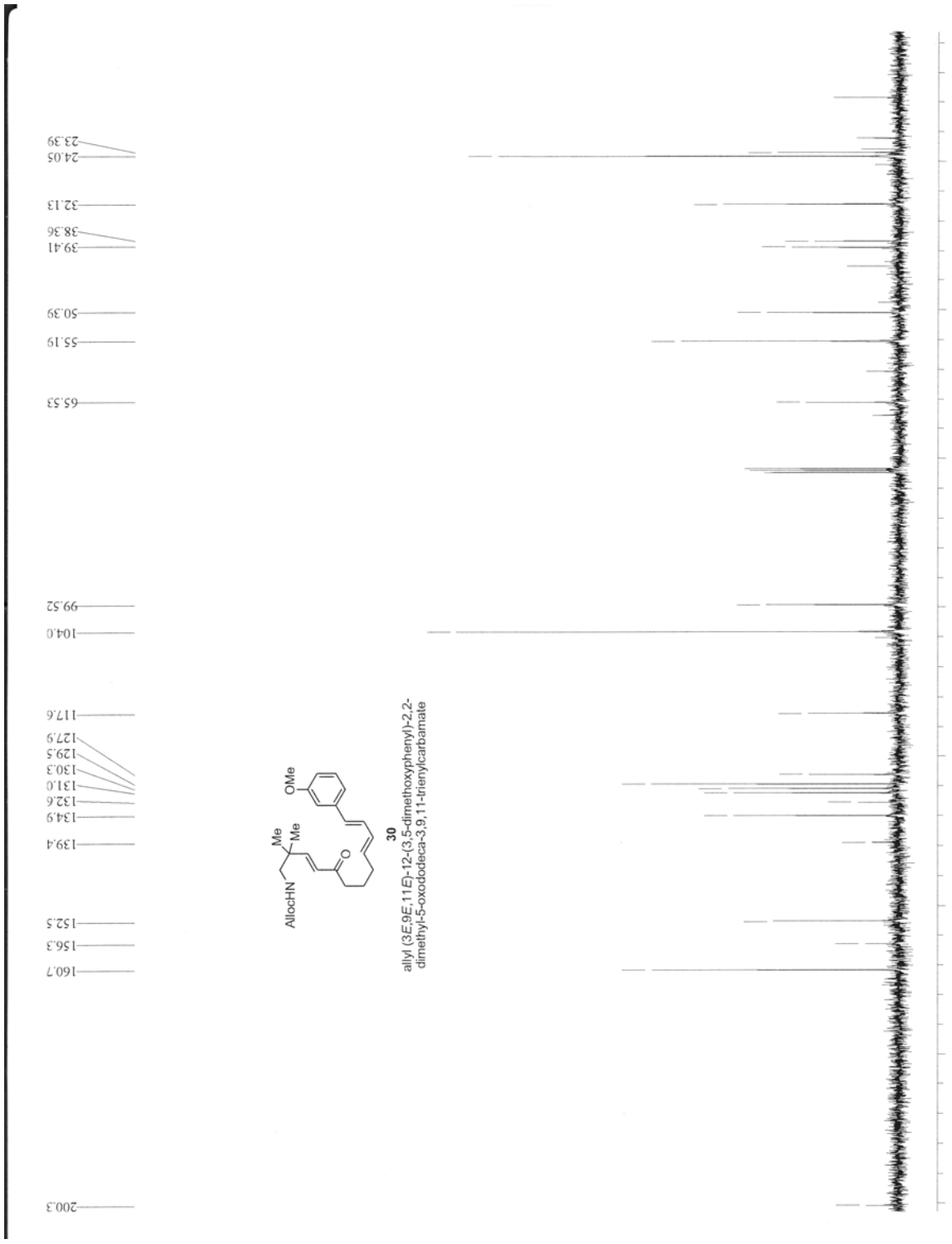
Spectrum 106. ^{1}H NMR spectrum of compound **27** in $CDCl_3$



Spectrum 107. ^{13}C NMR spectrum of compound **27** in $CDCl_3$



Spectrum 108. ^{1}H NMR spectrum of compound **30** in $CDCl_3$



Spectrum 109. ^{13}C NMR spectrum of compound **30** in $CDCl_3$