Strategies for the Controlled Synthesis of Oligomeric Natural Products

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ABSTRACT

Strategies for the Controlled Synthesis of Oligomeric Natural Products

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1 – Total Syntheses of Helicterin B, Helisorin, and Helisterculin A

The total synthesis of three members of the helicterin family of natural products, helicterin B, helisorin and helisterculin A, was completed from a common, non-biomimetic intermediate. This work featured the development of a complex retro Diels–Alder/Diels–Alder sequence, a Friedel–Crafts ring closure resulting in a highly strained ring-system, an acid-catalyzed hydroxyketone rearrangement, a Lewis acid-promoted dimerization of a bicyclooctene monomer, and the use of a novel phenol protecting group.

2 – Synthetic Studies of an Alternative Diels–Alder Approach Towards the Helicterin and the Yunnaneic Acid Families of Natural Products

Efforts towards the development of an enantioselective synthesis of the helicterin natural products are presented. Given the failure of known methods to achieve this goal, a novel Diels–Alder approach based on a revised biosynthetic proposal was explored. This method achieved a bicyclooctene framework with good stereoselectivity, but its conversion to the natural product core proved challenging. Additionally, a Diels–Alder approach to the core of the yunnaneic acids was developed, one in which the effective reversal of the regiochemical preference of the reaction was achieved.

3 – Small Molecule Inhibitors of Cell Death in a Huntington's Disease Model

A compound based on the core of the helicterin natural products with the ability to prevent cell death in a Huntington's Disease model system was identified. Although its mechanism of action is unknown, its cellular target appears to be distinct from that of prior inhibitors. A number of analogs based on this initial hit were synthesized, and structure-activity relationships were explored.

4 – Synthetic Studies Towards a Biomimetic Approach to the Myrmicarin Alkaloids

The shortest and highest yielding synthesis of the monomeric myrmicarin alkaloids to date has been completed, and the stereochemical complexity of the upper half of the dimeric myrmicarin 430A has been achieved for the first time. Although the dienamine building blocks readily afforded the monomeric natural products under presumed biological conditions, the results of synthetic and theoretical experiments suggest that their dimers are either non-biomimetic or that enzymes are required in the biosynthesis of the higher-order myrmicarins.

5 – Studies on The Mechanism of the Knorr Pyrrole Cyclization

A mechanistic study of the Knorr pyrrole cyclization of an indolizidine-based dienamine to myrmicarin 215B was completed. This cyclization was found to occur exclusively in polar protic solvents, and two solvent molecules were required in the rate-determining step. A revised mechanism for this cyclization is proposed, in which a slow ketone protonation step precedes the cyclization and dehydration steps.

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Chapter 5 – Studies on The Mechanism of the Knorr Pyrrole Cyclization

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A Szüleimnek

CHAPTER 1

Total Syntheses of Helicterin B, Helisorin, and Helisterculin A

1.1 Introduction

The total synthesis of natural products has long served as a driving force for the discovery of new reactions, technologies, and strategies for accessing previously unattainable architectures, and as inspiration for the development of novel medicines. Despite the enormous amount of progress made in the development of synthetic chemistry over the past century, many of the complex scaffolds found in natural products remain inaccessible because the necessary synthetic methods do not yet exist. This issue is especially true for families of oligomeric natural products, where chemists' ability make single compounds at will is still limited.[1] With this challenge in mind, the Snyder research group is interested in developing general approaches toward the selective total synthesis of oligomeric natural product families starting from common intermediates that differ from the presumed biosynthetic building blocks.[2] It is with this goal that the synthetic challenges of the helicterin polyphenols and the myrmicarin alkaloids were undertaken. An account of these endeavors and related projects that arose directly from them will be described in the five chapters of this dissertation.

Helicterins A and B, helisorin, and helisterculins A and B (**1**–**5**, Figure 1) are members of the helicterin and helisterculin family of natural products that were isolated from the fruits of the southeast asian arborescent shrub *Helicteres isora* L. in 1999 and 2000.[3] This plant is an important member of the *Hindu Materia Medica* and the Indonesian *Jamu* medicines, and its fruits are used as anti-convulsants as well to treat colic and abdominalgia. During their isolation, all of these compounds were shown to be air and heat sensitive, and they required a careful handling protocol to prevent their

decomposition.[4] Nonetheless, the isolation chemists showed that these natural products possess weak to mild inhibitory activity against avian myeloblastosis virus reverse transcriptase, and water extracts of the fruits have been reported as having anti-HIV type 1 activity.[5] Structurally, the helicterins and helisterculins are optically active neolignans with a bicyclo[2.2.2]octene core. Similar to other polyphenolic natural products, their architectural complexity likely derives from the oligomerization of a simpler building block, in this case either rosmarinic acid (**6**)[6] or oresbiusin A (**7**)[7], if their unassigned stereogenic centers (highlighted within Figure 1) are of the same absolute chirality. If that assumption holds true, helicterin A (**1**) and B (**2**) are tetramers, whereas helisorin (**3**) and helisterculin A (**4**) are dimeric structures. Prior to our work,[8] no total syntheses or synthetic studies towards any of these natural products had been reported in the literature.

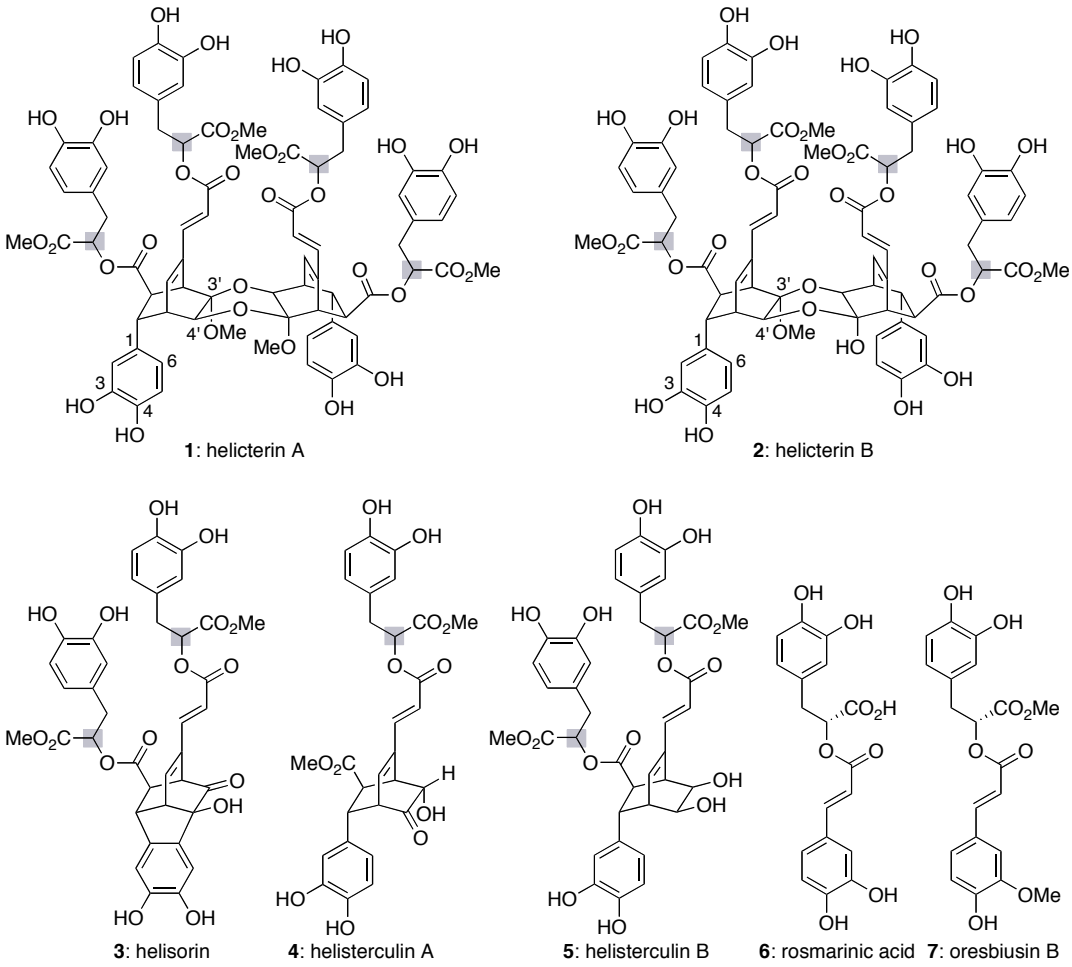
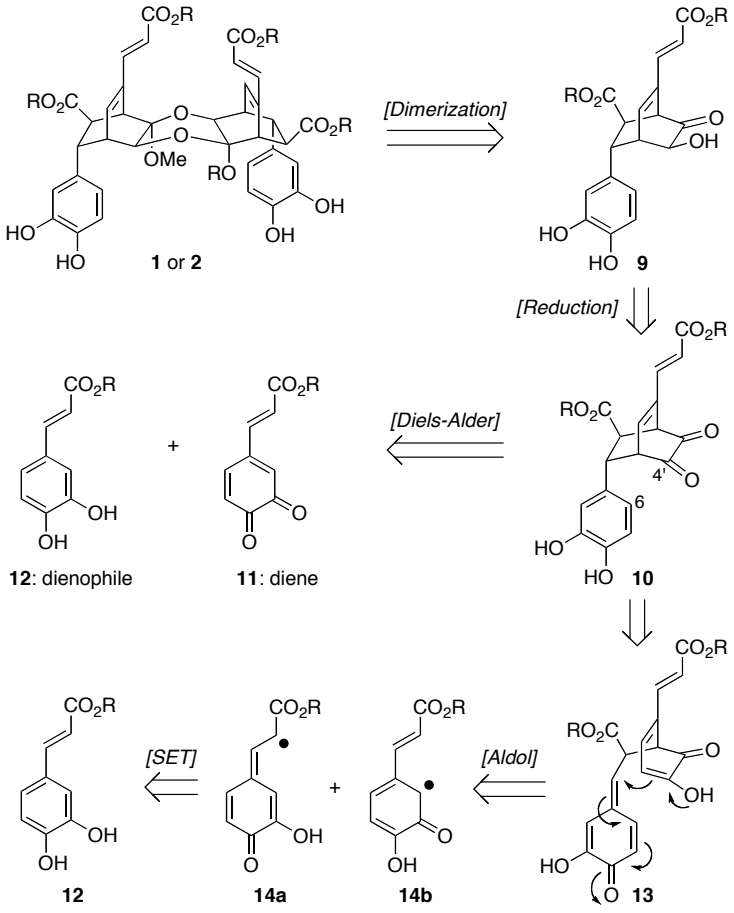


Figure 1. Structures of helicterin family of natural products (**1**–**5**) and putative biosynthetic precursors (**6** and **7**). Unassigned stereocenters are highlighted.

1.2 Biosynthetic Hypothesis and Retrosynthetic Analysis

The proposed biosynthesis of these neolignans[3] served as our initial inspiration for the retrosynthetic analysis shown in Scheme 1. The tetrameric helicterins (**1** and **2**) could be derived from a dimerization of a simpler hydroxyketone precursor such as **9**, which, in turn, could arise from a selective reduction of diketone **10** at the C-4' position. Diketone **10** occupies a central role in this biosynthetic proposal since it could also give

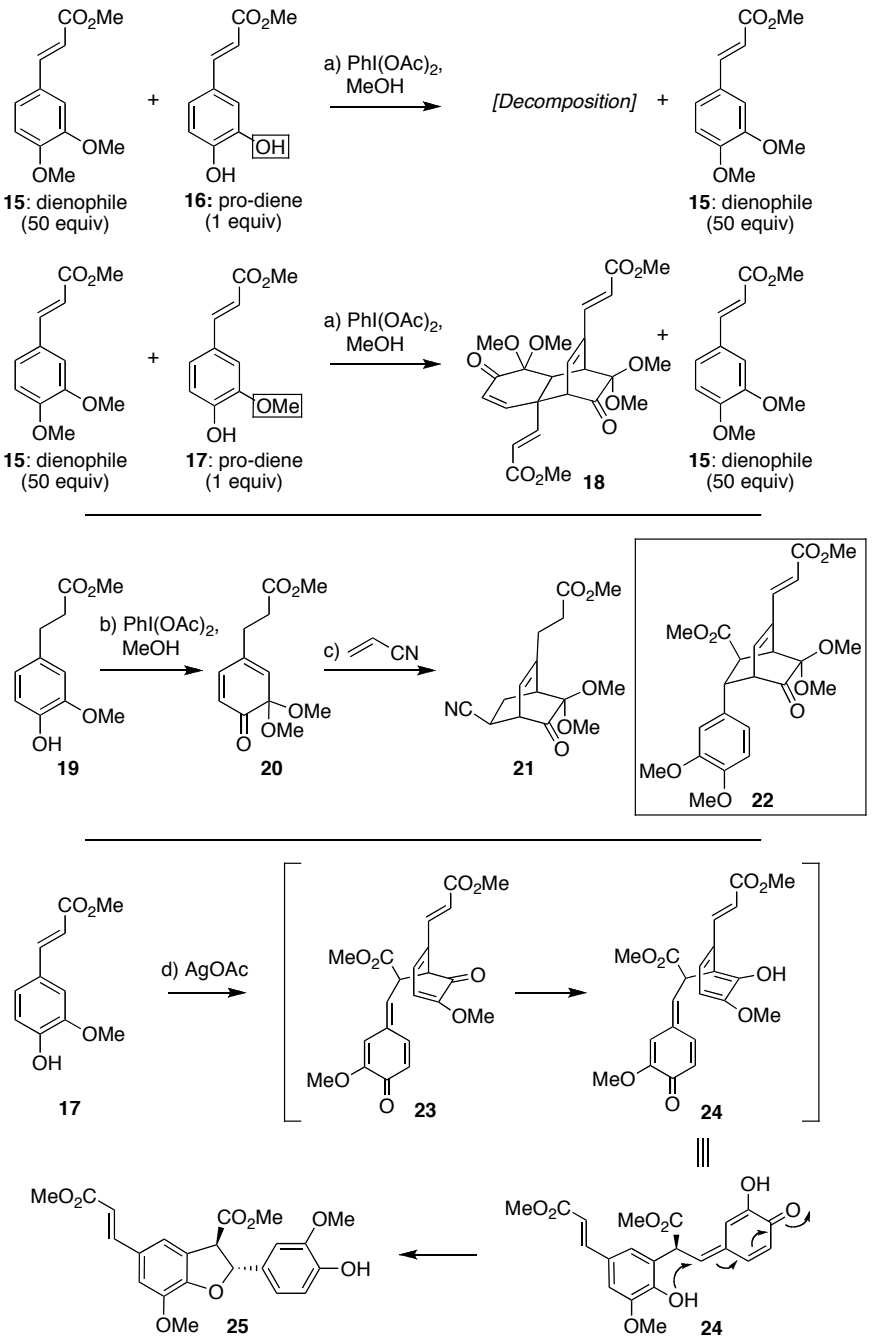
rise to helisorin (**3**, Figure 1) by a Friedel–Crafts union between C-6 and C-4', and to helisterculin A (**4**, Figure 1) by a different oxidation state adjustment. Diketone **10**, in turn, could be derived from a Diels–Alder reaction between monomer **12** and its oxidized form, *o*-benzoquinone **11**, serving as dienophile and diene, respectively.[9]



Scheme 1. Proposed biogenetic routes to helicterin A and B (**1** and **2**).

Overall, although this biosynthetic proposal appears reasonable at first glance, many of the individual steps were anticipated to be quite challenging to achieve in the laboratory if a biomimetic synthesis were undertaken without any of the enzymes that may be involved in catalyzing some of these transformations. For example, dimerizations of hydroxyketones such as **9** to form the 1,4-dioxane rings found in **1** and **2** had not

previously been documented in [2.2.2]-bicyclic systems; in fact, controlled dimerizations of hydroxyketones, in general, have proven difficult to achieve.[10] In addition, the reduction of **10** to **9** requires the regioselective addition of a hydride from the more hindered face of the molecule onto the more hindered of its two ketones. Furthermore, as our initial model studies in Scheme 2 have shown, diketone **16** decomposed upon oxidation with $PhI(OAc)_2$[11] to the *o*-benzoquinone, even when in the presence of a large excess of dienophile **15**, instead of participating in Diels–Alder chemistry to afford the natural product core (**22**).[12a] A commonly employed means of tempering the reactivity of this type *o*-benzoquinones is to mask one of the two ketones as a ketal affording a masked *o*-benzoquinone (MOB).[12] These dienes are well documented to participate in [4+2] cycloaddition reactions and have been successfully employed towards the synthesis of natural products.[13] In model studies seeking to implement such a concept, we found that oxidation of phenol **17** in MeOH produced the MOB that then underwent a near quantitative [4+2] dimerization reaction to afford dimer **18** even in the presence of a large excess of dienophile **15**.[12b–d] Only by using the further altered phenol **19**, in which the side-chain is fully saturated, was a stable MOB (**20**) observed. Furthermore, this diene underwent Diels–Alder reactions only with the simplest of dienophiles in large excess to give bicyclic products such as **21**, and the regiochemical outcome of this event did not match the one desired for the helicterins, placing the electron-withdrawing group incorrectly (**21** *versus* **22**).[14]



Scheme 2. Preliminary model studies to achieve bicyclic natural product core **22**: (a) $PhI(OAc)_2$ (1.1 equiv), $MeOH/CH_2Cl_2$ (6:1), 23 °C, 14 h, 87%; (b) $PhI(OAc)_2$ (1.1 equiv), $MeOH/CH_2Cl_2$ (5:1), 23 °C, 14 h, 97%; (c) acrylonitrile (100 equiv), toluene, 80 °C, 48 h, 43%; (d) AgOAc (1.1 equiv), toluene, 60 °C, 20 h, 20%.

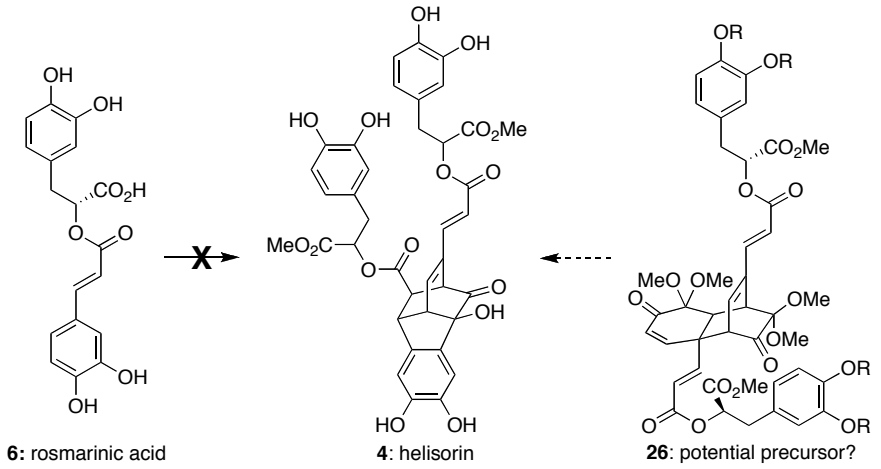
An alternative proposal[3] to account for the formation of diketone core **10** of the natural products is also shown in the bottom of Scheme 1. In this case, a single-electron

transfer (SET) oxidation converting catechol **12** into radical resonance forms **14a** and **14b** that in turn could dimerize to form intermediate **13** prior to cyclization through the indicated mechanism to generate diketone **10**. This sequence invokes two reactions that are unlikely to succeed in a controlled fashion without enzymatic participation: a highly regio- and stereoselective dimerization of a greatly delocalized radical (**14**) and a sufficiently long lifetime of **13** in its dearomatized tautomeric form to allow for the cyclization step to occur. In model studies aimed at testing this hypothesis (Scheme 2), phenol **17** was treated with AgOAc and it was possible to effect the initial radical dimerization to generate intermediate **23**. However, the second bond-formation event occurred from this intermediate's tautomeric aromatic isomer (**24**), which underwent *O*-alkylation to afford dihydrofuran **25** as the major product of the reaction.[15] Thus, a purely biomimetic synthesis of the natural product core did not appear achievable based on these results. Thus, the identification of a different approach was needed.

1.3 Development of an Alternative Diels–Alder Approach and Initial Model Studies

Given the failures in controlling the reactivity of starting materials derived directly from oxidized forms of rosmarinic acid (**6**) and oresbiusin B (**7**), we wondered whether a dimer such as the one that was so readily obtained in Scheme 2 could in fact be the common precursor to enable a controlled synthesis. In other words, a strucure such as

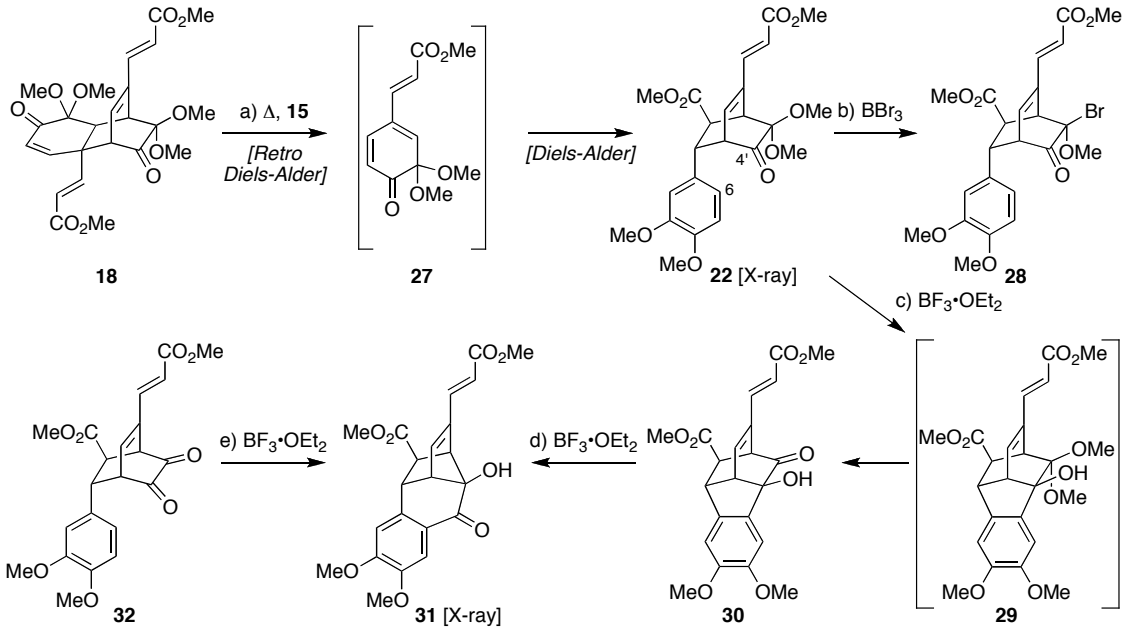
26 (Scheme 3) could be the starting material needed to afford the natural product framework in a retro Diels–Alder/Diels–Alder cascade. Since Diels–Alder reactions are typically kinetically controlled,[16] perhaps this homodimer was the kinetic product of the reaction, whereas the desired bicyclic core was the thermodynamic product that could be accessed if the reaction could be run at a high enough temperature to enable thermodynamic control. Although we had no direct evidence for this hypothesis, we were aware of other examples of retro Diels–Alder/Diels–Alder pathways using dearomatized phenols as dienes in the literature.[17]



Scheme 3. Proposed use of a dimeric form of rosmarinic acid as starting material for the synthesis of the helicterin family of natural products.

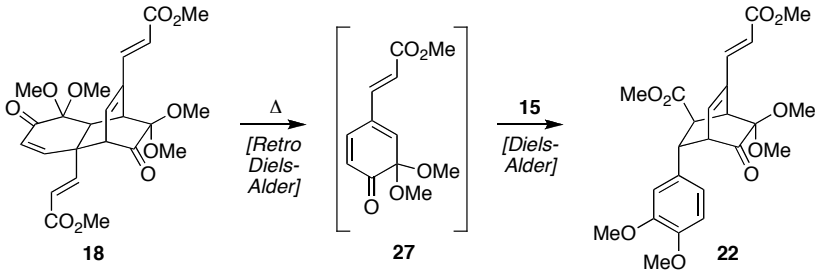
Indeed, as shown in Scheme 4, upon heating to 220°C in mesitylene, model dimer **18** underwent a retro-[4+2] fragmentation unveiling diene **27** that was then trapped by dienophile **15** in a forward [4+2] reaction to afford desired adduct **22** in 44% yield (83% b.r.s.m.) as the only characterizable new product in the reaction mixture. This product was confirmed by NMR spectroscopy and X-ray crystallography to possess the correct regio- and stereochemistry for the natural bicyclic core. As shown in Table 1, this highly

complex example of a domino retro Diels–Alder/Diels–Alder reaction sequence required significant thermal activation, as no product was observed below 160 °C. It is also worth noting that experiments seeking to use microwave irradiation[18] as well as *on water* acceleration effects[19] failed to improve upon the original conditions. As such, though the desired natural product core was formed, the protocol required was far from biomimetic.



Scheme 4. (a) **15** (6.7 equiv), mesitylene, 220 °C, 30 min, 44% (83% b.r.s.m.); (b) BBr_3 (1.0 M in CH_2Cl_2, 6.0 equiv), –78 °C, 1 h, 86%; (c) BF_3•OEt_2 (6.0 equiv), CH_2Cl_2, 0→23 °C, 16 h, 82%; (d) BF_3•OEt_2 (20 equiv), CH_2Cl_2, 23 °C, 16 h, 80%; (e) BF_3•OEt_2 (6.0 equiv), CH_2Cl_2, 0→23 °C, 16 h, 53%.

Table 1. Optimization of retro Diels–Alder/Diels–Alder reaction.



18 **27** **22**

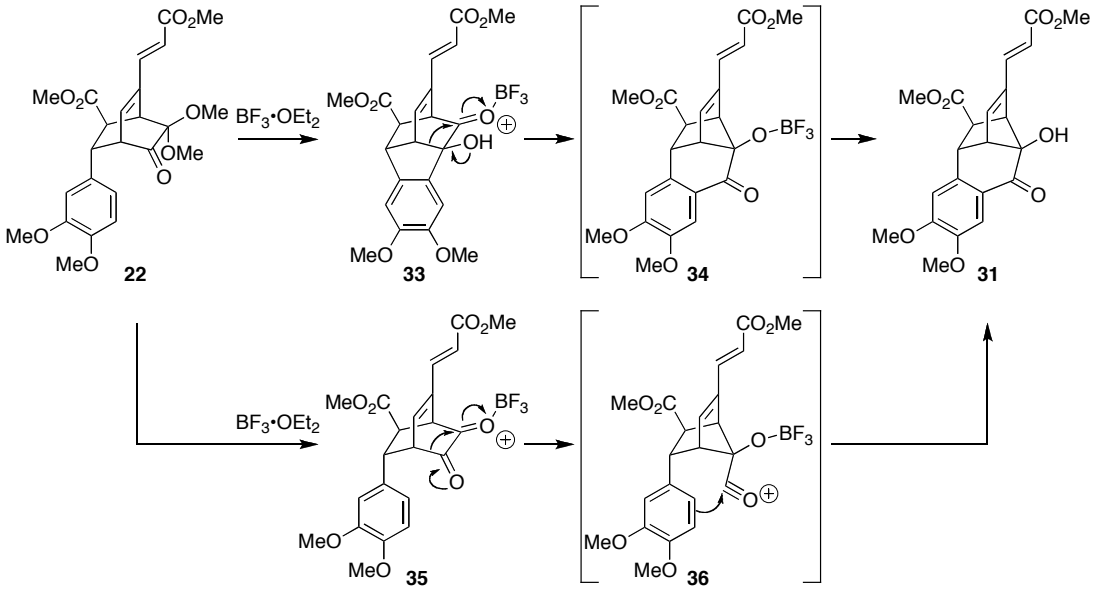
Entry	Heating source	Conditions	**13** (equiv)	Yield (%)[b]
1	μwave	EtOH, 200 °C, 5 min	5.0	0
2	μwave	ethylene glycol, 210 °C, 10 min	5.0	16
3	μwave	toluene/*i*-PrOH, 190 °C, 35 min	5.0	11
4	oil bath[a]	H_2O, LiCl, 160 °C, 60 min	5.0	23
5	oil bath[a]	DMA, 220 °C, 30 min	5.0	26
6	oil bath[a]	mesitylene/H_2O, 220 °C, 30 min	5.0	34
7	oil bath[a]	mesitylene, 220 °C, 30 min	5.0	40
8	oil bath[a]	mesitylene, 220 °C, 30 min	3.3	33
9	oil bath[a]	mesitylene, 220 °C, 30 min	6.7	43
10	oil bath[a]	mesitylene, 220 °C, 30 min	10	42
11	oil bath[a]	mesitylene, 220 °C, 30 min	20	44

[a] Reaction performed in a sealed tube. [b] Isolated yields. DMA = *N*,*N*-dimethylacetamide

With bicyclo[2.2.2]octene **22** in hand, one more step was anticipated to be necessary to reach the diketone, the proposed common precursor to the entire family (cf. **10**, Scheme 1), namely hydrolysis of the dimethyl ketal of **22**. However, conventional methods for ketal hydrolysis (aqueous protic acids, heat) did not succeed, leading instead to recovered starting material or decomposition. The failure of this hydrolysis is not entirely surprising given that this event would have to proceed through a highly destabilized oxocarbenium intermediate, so more forcing conditions were anticipated to be required. As shown in Scheme 4, treatment of **22** with BBr_3 at low temperature under anhydrous conditions led to bromoketal **28** exclusively,[20] indicating that a Lewis acid

could indeed catalyze the formation of the intermediate oxocarbenium. Therefore, in order to ensure that water would be the nucleophile instead of bromide, Diels–Alder product **22** was treated with BF_3•OEt_2 in "wet" CH_2Cl_2 at 0 °C, and the reaction was warmed to ambient temperature and stirred for 16 h. Instead of affording expected diketone **32**, the major product of the reaction was the core of the natural product helisorin (**30**), the structure of which was confirmed by X-ray crystallography. This reactivity turned out to be almost exclusive to BF_3•OEt_2, as other Lewis acids led to the same product in low yield ($FeCl_3$•SiO_2,[21] 13%) or did not afford any desired product [$In(OTf)_3$, $TiCl_4$ and Me_2AlCl]. In addition, the amount of BF_3•OEt_2 used was also critical. Using a large excess of this Lewis acid at the same temperature and in the same solvent with **22** or **30** resulted in a skeletal rearrangement to isomer **31** (*vide infra*). Furthermore, the conversion of **22** to **30** is believed to occur by initial cyclization of C-6 onto C-4' to form intermediate **29** followed by hydrolysis of the dimethyl ketal. When the presumed intermediate diketone **32** that would arise from the alternate order of events was exposed to the conditions that led to **30**, only rearranged isomer **31** was obtained.

Two possible mechanistic pathways for the formation of rearranged product **31** are shown in Scheme 5. Although both account for the formation of the product, there are obvious problems with each sequence. First, upon initial examination, the bond migration events in **33** and **35** do not seem to meet the stereoelectronic requirements for such rearrangements and, second, acylium ion **36** has the capability to simply lose CO prior to ring closure and thereby lead to a different bicyclic product. Therefore, computational analysis of these mechanisms, isotope labeling studies, and/or other experiments are likely necessary before a more conclusive mechanism can be proposed.

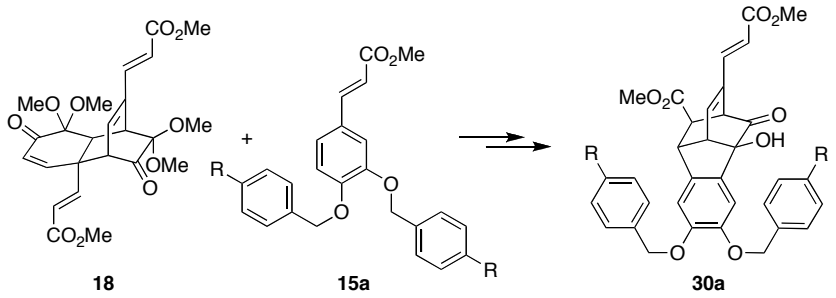


Scheme 5. Proposed mechanisms to account for the formation of **31** originally described in Scheme 4.

1.4 Protecting Group Selection

The model studies described in the previous section demonstrated the chemistries required for the total synthesis of helisorin (**3**). However, one crucial component that had not been addressed was the identification of an appropriate phenol-protecting group. The reaction conditions that had been developed up to this point as well as the known sensitivity of the natural products[3,4] presented a unique combination of challenges. First, the chosen protecting group would have to be stable to heat (>200 °C) and BF_3•OEt_2 over extended periods. Second, its removal would have to avoid the use of strongly nucleophilic and/or basic conditions to avoid ester-hydrolysis and/or racemization of chiral centers within the fully functionalized materials. Finally, it would have to be cleaved cleanly and rapidly up to twelve times and allow for minimal manipulations of the air- and heat-sensitive final natural products.

Table 2. Optimization phenol-protecting group.



18 **15a** **30a**

Entry	R =	Hammett parameter (σ)	Observations
1	H	0	*not stable to* BF_3•OEt_2
2	F	0.06	*not stable to* BF_3•OEt_2
3	NO_2	0.78	*insoluble materials*
4	CN	0.66	*insoluble materials*
5	CF_3	0.54	*balanced*

Based on the above criteria and literature precedent, benzyl ethers seemed ideal.[22] Thus, we attempted to synthesize compound **30** with benzyl-protected phenols (Table 2, entry 1) using the reaction conditions shown in Scheme 4. In the event, this group proved to be unstable during the BF_3•OEt_2 cyclization step and no product was isolated (Table 2, entry 1). Since the benzyl group was most likely being cleaved through a pathway involving a benzyl cation intermediate, we hypothesized that the addition of electron-withdrawing groups[23] onto the protecting group's phenyl ring would destabilize the cationic intermediate and would impart sufficient stability to the benzyl ether to prevent cleavage during the Lewis acid-catalyzed cyclization step, yet still allow it to be cleaved under mild conditions. Addition of a mildly electron-withdrawing fluorine atom (entry 2) did not lead a significant improvement in stability, however strongly electron-withdrawing nitro and cyano groups (entries 3 and 4) did. Unfortunately, the presence of

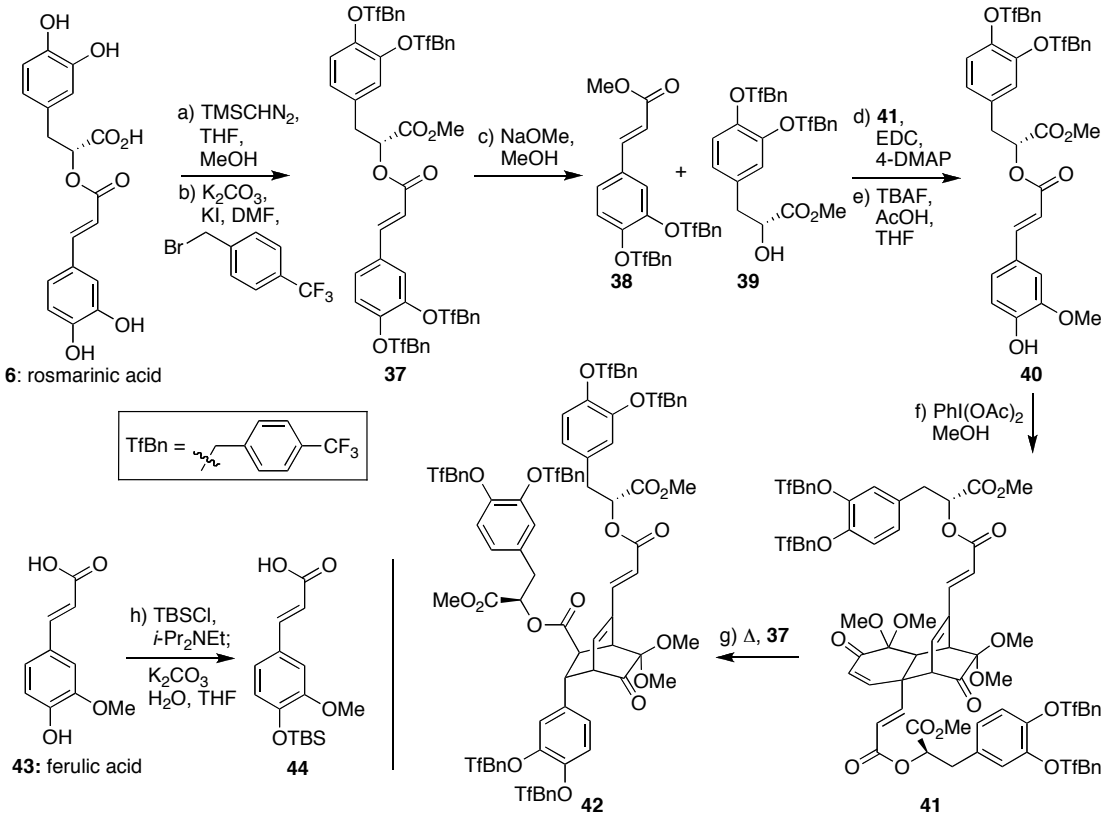
these moieties rendered many of the synthetic intermediates, such as **15c** and **15d**, insufficiently soluble in non-polar organic solvents and difficult to handle. Thus, a slightly less electron deficient trifluoromethyl was used (entry 5, $\sigma = 0.54$), and it was found to have the right balance of desirable properties.[24] Furthermore, model compound **30e** with this group could be successfully and rapidly deprotected at –78 °C with BBr_3.

1.5 Total Synthesis of Helisorin (3)

The stage was now set to apply the newly developed chemistry and protecting group to the synthesis of helisorin (**3**). Starting from commercially available rosmarinic acid (**6**) in Scheme 6, initial chemoselective methyl ester formation was achieved through treatment with $TMSCHN_2$ and was followed by a subsequent alkylation of the four phenol residues using *p*-CF_3-benzyl (TfBn[1]) bromide under Finkelstein conditions to complete the synthesis of **37** in 84% overall yield. Methanolysis of the internal ester linkage within this new product then provided both **38** and **39**, the latter of which was coupled to carboxylic acid **44** under standard conditions to afford intermediate **40**, following silyl ether cleavage.[25] As in the previous model studies, treatment of this phenol with $PhI(OAc)_2$ in MeOH smoothly afforded Diels–Alder dimer **41**, which was then taken into the retro Diels–Alder/Diels–Alder cascade to afford the desired product (**42**) in 38% isolated yield (71% yield based on recovered **37**). Interestingly, this new product (**42**) was generated as a 1:1 mixture of diastereomers, indicating that the stereogenic center present in each component was too remote to control the facial

[1] This abbreviation was originally defined in T. W. Greene, P. G. M. Wuts, *Protective Groups in Organic Synthesis*, John Wiley and Sons: New York, 1999, p. 779.

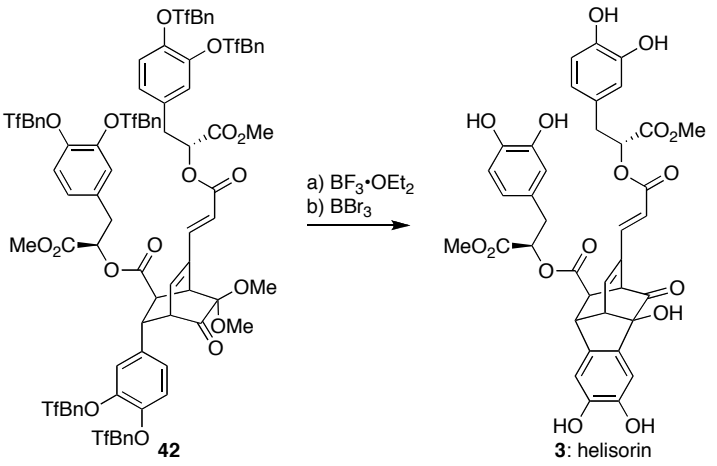
presentation of the two partners in this key event. This outcome also suggested that if a Diels–Alder reaction is indeed part of the biosynthetic dimerization of rosmarinic acid, an enzyme is likely involved in the process, since only a single optically active diastereomer of each natural product has been isolated.



Scheme 6. (a) $TMSCHN_2$ (0.95 equiv), THF/MeOH (10:1), -78 °C, 1 h; (b) TfBnBr (6.0 equiv), K_2CO_3 (6.0 equiv), KI (catalytic), 60 °C, 8 h, 84% overall; (c) NaOMe (1.0 equiv), MeOH/CH_2Cl_2 (1:1), 23 °C, 2 h, 92% **28**, 90% **29**; (d) **31** (2.0 equiv), EDC·HCl (2.0 equiv), 4-DMAP (1.0 equiv), CH_2Cl_2, 23 °C, 3 h; (e) TBAF (2.0 equiv), AcOH, THF, 0 °C, 10 min, 94% overall; (f) $PhI(OAc)_2$ (1.05 equiv), MeOH/CH_2Cl_2 (5:1), 23 °C, 14 h, 99%; (g) **37** (6.7 equiv), mesitylene, 220 °C, 30 min, 38% (71% b.r.s.m.); (h) TBSCl (2.5 equiv), *i*-Pr_2NEt (3.0 equiv), CH_2Cl_2, 23 °C, 14 h, then K_2CO_3 (excess), H_2O, THF, 25 °C, 2 h, 99%. 4-DMAP = 4-dimethylaminopyridine, EDC = 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide, TBAF = tetra-*n*-butylammonium fluoride, TBS = *tert*-butyldimethylsilyl, TMS = trimethylsilyl.

At this stage, the diastereomers of Diels–Alder product **42** were separated via chromatography, and the two isomers were independetly subjected to BF_3•OEt_2 under conditions slightly modified and optimized for this cyclization. As shown in Scheme 7, one of these operations smoothly afforded protected helisorin that was then subjected to

BBr_3 at –78 °C, cleanly cleaving all six *p*-CF_3-benzyl ethers in 30 min and providing a synthetic sample of helisorin (**3**) that was spectroscopically identical to the natural material. This event completed the first synthesis of this natural product, served as a proof-of-concept for using dimer **41** as the starting point for this synthesis, and validated our choice of phenol-protecting group. Additionally, this result also enabled confirmation that absolute configuration of helisorin (**3**) matched that anticipated from the oligomerization of rosmarinic acid (**6**).

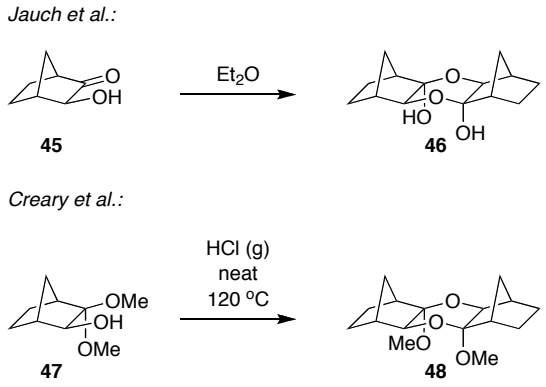


Scheme 7. (a) BF_3•OEt_2 (30 equiv), H_2O (5.0 equiv), C_6H_6, 0→23 °C, 16 h, 53% (82% b.r.s.m.); (b) BBr_3 (1.0 M in CH_2Cl_2, 20 equiv), CH_2Cl_2, -78 °C, 30 min, 77%.

1.6 Model Studies Directed towards Helicterin A (1) and B (2)

We next turned our attention towards the most complex members of the family, helicterin A (**1**) and B (**2**). Based on the biosynthetic hypothesis outlined in Scheme 1, the starting material needed for achieving the central 1,4-dioxane ring system was anticipated

to be a hydroxyketone such as **9** or an equivalent structure. Based on the precedent shown in Scheme 8,[26] in which [2.2.1]-bicyclic hydroxyketone **45** dimerized spontaneously upon standing in Et_2O whereas a [2.2.1]-bicyclic hydroxyketal **47** dimerized when treated with anhydrous HCl gas and heat, this key event was expected to proceed smoothly from similarly functionalized helicterin cores (**57** or **49**) despite the fact that this type of reactivity had never been shown to occur in highly substituted [2.2.2]-bicyclic molecules.

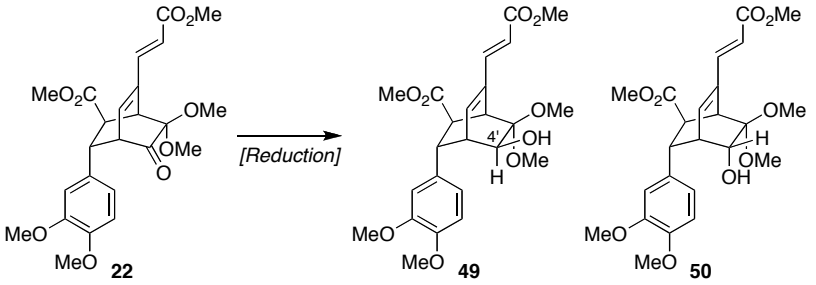


Scheme 8. Precedent for the dimerization of [2.2.1]-bicyclic systems.

Therefore, the main challenge was identified as being the establishment of the key C-4' carbinol stereochemistry. Working with model Diels–Alder adduct **22**, extensive efforts were undertaken towards developing a reduction to afford hydroxyketal **49** (Table 3). Direct reduction with $NaBH_4$ (entry 1) led to the exclusive formation of epimeric hydroxyketone **50**, confirming that the bottom face of the ketone within **22** is hindered by the pendant aryl ring. Luche conditions (entry 2), which have been shown to alter the selectivity of $NaBH_4$ reductions in bicyclic systems,[27] did not alter the outcome of the reaction. Meerwein-Ponndorf-Verley and related reductions (entries 4–9), which are known to be thermodynamically controlled,[28] (with desired epimer **49** predicted to be

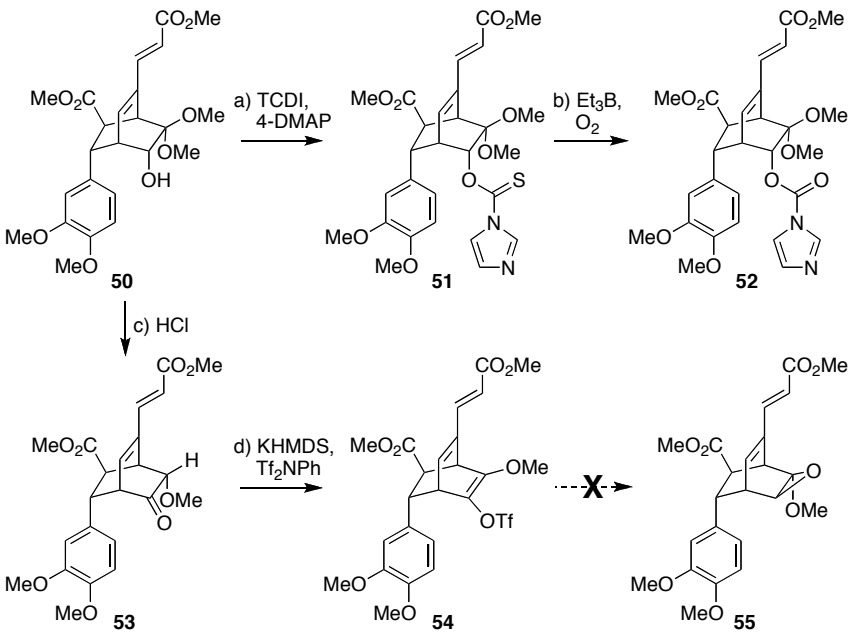
more stable than **50** due to decreased $A_{1,3}$-strain), gave either no reaction, reduction once again to undesired epimer, and/or side-reactions. Additionally, attempts at employing a chiral catalyst (entry 10),[29] alane (entry 11) or single-electron reductions (entries 12 and 13)[30] did not afford the desired product. As such, direct reduction of the ketone within **22** could not be carried out, and reiterated the question about how this key event might occur during the biosynthesis of these natural products.

Table 3. Selected attempts to effect a diastereoselective reduction of Diels–Alder adduct **22** to alcohol **49**.



Entry	Conditions	Result
1	$NaBH_4$, MeOH, 0 °C	**50**[(a)]
2	$NaBH_4$, $CeCl_3$, MeOH, –78 °C	**50**
3	Al(O*i*-Pr)$_3$, *i*-PrOH, 80 °C	*i-Pr ester of* **50**
4	Al(O*i*-Pr)$_3$, toluene/*i*-PrOH (4:1), 80 °C	*i-Pr ester of* **50**
5	Al(O*i*-Pr)$_3$, $(CF_3)_2CHOH$, 80 °C	*no reaction*
6	Al(O*i*-Pr)$_3$, TFA, DCE, 60 °C	**50**
7	*i*-Bu_2AlO*i*-Pr, Et_2O/toluene/CH_2Cl_2 (4:1:1), 23 °C	*no reaction*
8	*i*-Bu_2AlCl, THF, 60 °C	*no reduction*
9	SmI_2(O*t*-Bu), *i*-PrOH, THF, 65 °C	*no reaction*
10	BH_3•THF, CBS-catalyst, THF, 0°C	**50**
11	AlH_3, THF, 23 °C	*decomposition*
12	Li, NH_4Cl, NH_3, –78 °C	*decomposition*
13	SmI_2, *t*-BuOH, THF, 0 °C	*decomposition*

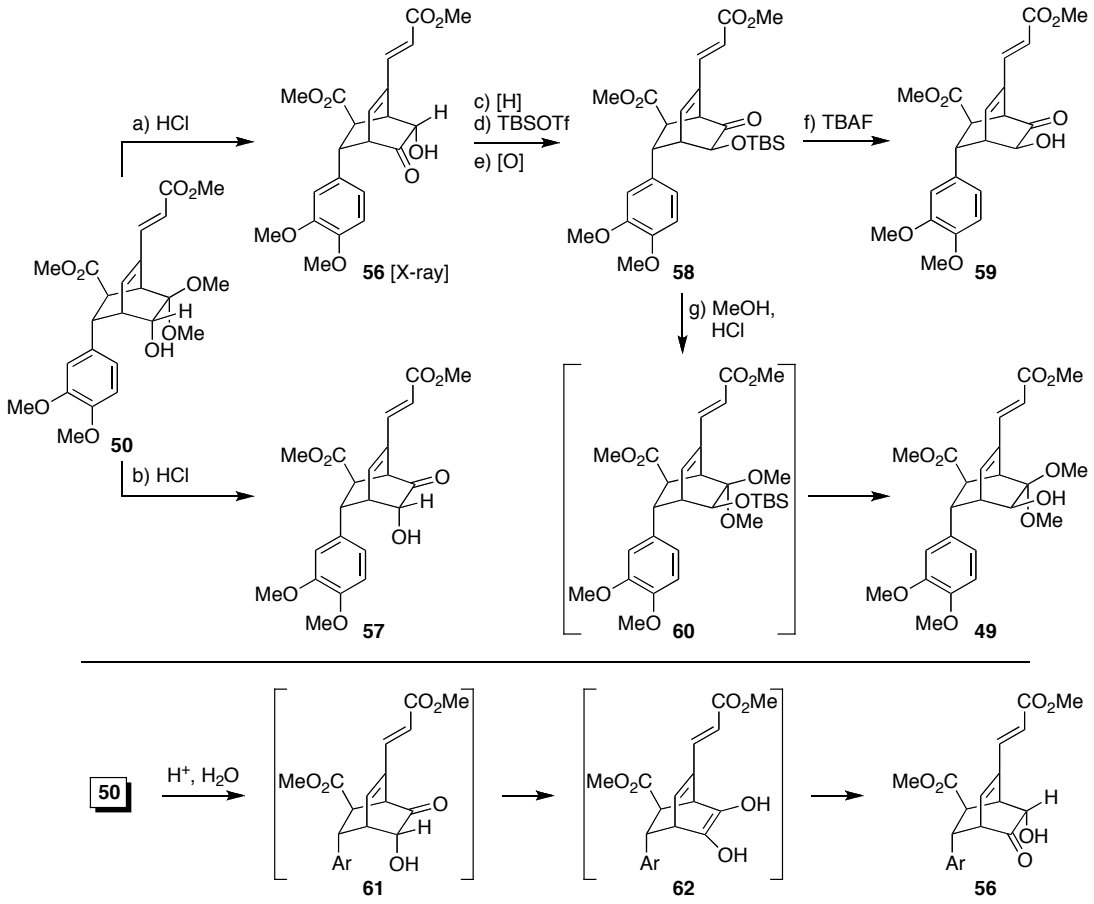
Reagents and conditions: (a) $NaBH_4$ (excess), MeOH/CH_2Cl_2 (4:1), 0 °C, 1 h, 99%.



Scheme 9. (a) TCDI (6.0 equiv), 4-DMAP (1.5 equiv), CH_2Cl_2, 40 °C, 91%; (b) Et_3B (5.0 equiv), *n*-Bu_3SnH (5.0 equiv), O_2 (1 atm), CH_2Cl_2, 0 °C, 1 h, 72%, (c) HCl (g), 100 °C, 45 min, 99%; (d) KHMDS (0.5 M in toluene, 1.3 equiv), Tf_2NPh (2.6 equiv), THF, –78 °C, 10 min, 74%;. 4-DMAP = 4-dimethylaminopyridine, KHMDS = potassium bis(trimethylsilyl)amide, TCDI = 1,1'-thiocarbonyldiimidazole, Tf = trifluoromethanesulfonyl.

Further efforts to achieve the desired C-4' epimer via a different approach are summarized in Scheme 9. Alcohol **50** was readily converted to the Barton–McCombie deoxygenation precursor **51**,[31] a compound that has now been shown to possess interesting biological activity (see Chapter 3). However, despite screening many radical-initiating methods, this intermediate never fragmented to the desired *C*-centered radical to allow potential trapping with a hydride or molecular oxygen.[32] Instead, compounds derived from a thiocarbonyl *C*-centered radical, such as **52**, were consistently isolated. Additionally, alcohol **50** was subjected to an acid catalyzed rearrangement (*vide infra*, Scheme 10) and subsequent enol triflate formation to afford **54**. A reductive Stille reaction[33] followed by a site- and diastereoselective epoxidation was then anticipated to afford intermediate **55**, which could then be opened with acidic MeOH to hydroxyketal

49 or used directly as a dimerization precursor towards helicterin A (**1**) or B (**2**). However, it was found that intermediate **54** underwent a retro [4+2] reaction to give a rearomatized eastern half when treated with Pd or other metal catalysts. Finally, inversion protocols of the alcohol in **50**, either under standard Mitsunobu conditions or attempted displacement of a triflate with KO_2 or $NaNO_2$, proved fruitless.[34]

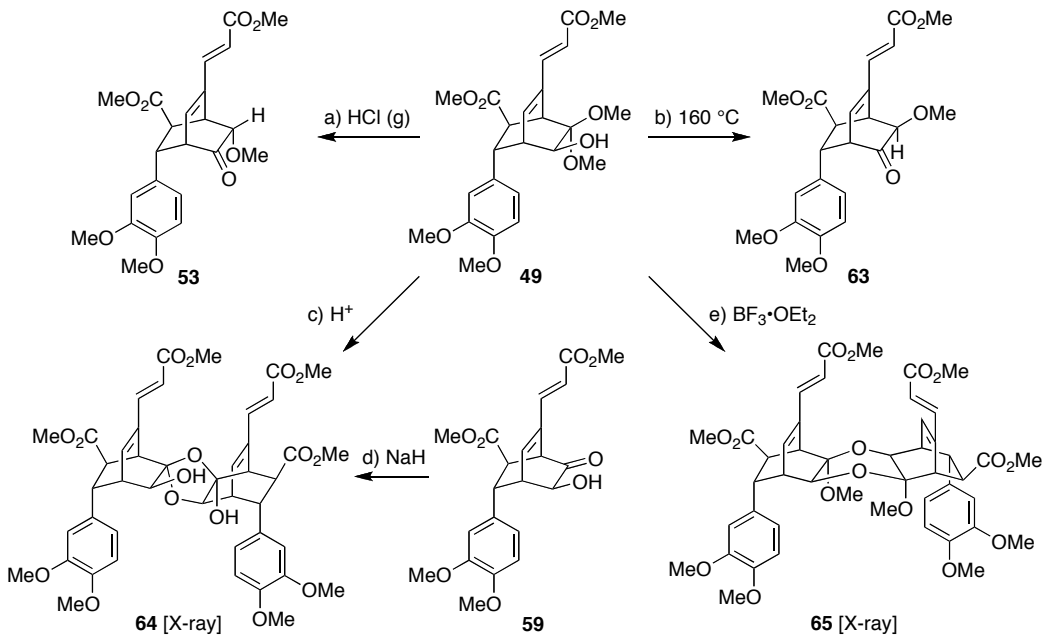


Scheme 10. (a) 0.5 M HCl, H_2O, THF, 23 °C, 14 h, 84%; (b) 0.2 M HCl, H_2O, toluene, 0 °C, 20 h, 86%; (c) $Me_4NBH(OAc)_3$ (5.0 equiv), MeCN/AcOH (10:1), 25 °C, 5 h, 75%; (d) TBSOTf (1.0 equiv), Et_3N (5.0 equiv), CH_2Cl_2, –78→23 °C, 1 h; (e) Dess-Martin periodinane (1.5 equiv), $NaHCO_3$ (10 equiv), CH_2Cl_2, 25 °C, 1 h, 94% over 2 steps; (f) TBAF (1.0 M in THF, 2.0 equiv), AcOH (2.0 equiv), THF, 25 °C, 2 h, 54% (76% b.r.s.m.); (g) 0.4 M HCl, MeOH/$CH(OMe)_3$ (4:1), 25 °C, 14 h, 93%. TBAF = tetrabutylammonium fluoride, TBS = *t*-butyldimethylsilyl, Tf = trifluoromethanesulfonyl.

However, after some experimentation with the undesired epimeric alcohol, a key rearrangement reaction was discovered. As shown in Scheme 10, exposure of intermediate **50** to aqueous HCl resulted in rearranged hydroxyketone **56** via the mechanism detailed at the bottom of the scheme.[35] Although it was possible to affect ketal hydrolysis without rearrangement to give hydroxyketone **57** under carefully controlled conditions, hydroxyketone **56** appeared to be the thermodynamic product of the reaction. To confirm this hypothesis, density-functional theory [B3LYP[36]/6-31+G(d)] calculations were used to compare the energies of the four possible hydroxyketone isomers, and **56** was found to be the most stable by 1.7 kcal/mol. This outcome reflects the minimization of two important steric interactions within the molecule: having an sp^2 center at the C-4' position minimizes 1,3-diaxial strain with the bulky aryl ring, whereas having an H-atom on the top face minimizes 1,3-diaxial-type strain with the pendant α,β-unsaturated ester side chain. In addition, it reflects proton capture by enol **62** from its less hindered, top face.[37]

Hydroxyketone **56** not only corresponds to the core of the natural product helisterculin A (**4**), but it allowed us to access the desired C-4' stereochemistry. Exposure of **56** to $Me_4NBH(OAc)_3$ performed a directed reduction[38] of the ketone in which the hydride was delivered intramolecularly from the bottom face of the molecule. This newly formed alcohol was then selectively protected as a TBS ether, and the unprotected alcohol was oxidized to the corresponding ketone to afford **58**. From here, TBS-deprotection or one-pot ketalization followed by TBS-removal completed the synthesis of dimerization precursors **59** and **49**, respectively.

With these crucial model compounds in hand, model studies towards the final bond constructions found in helicterin A (**1**) and B (**2**) could begin. This work is summarized in Scheme 11. Despite the literature precedent on similar dimerizations[26] (*vide supra* and Scheme 8), hydroxyketone **59** did not dimerize spontaneously upon standing. Its exposure to acidic or basic conditions did afford a dimer (**64**) in near quantitative yield, however its structure did not correspond to the core of the helicterin natural products. Rather, it reflected the bond connections of a related family of natural products, the yunnaneic acids,[39] which will be discussed briefly in Chapter 2. Furthermore, exposure of hydroxyketal **49** to anhydrous HCl gas and heat formed rearranged methoxyketone **53** exclusively, likely via a mechanism analogous to the one described at the bottom of Scheme 10, whereas heating it to 160 °C led to methoxyketone **63** likely through loss of methoxide followed by a hydride shift. Additionally, when this hydroxyketal (**49**) was exposed to acidic conditions in solution, unsymmetrical dimer **64** was formed to the extent that adventitious water was present in the reaction mixture, likely forming **59** as an intermediate. Once again, only through a reagent well removed from biomimetic conditions were we able to effect the desired dimerization. Treatment of hydroxyketal **49** with $BF{\bullet}OEt_2$ at 0 °C in CH_2Cl_2 under strictly anhydrous conditions completed the synthesis of the core of helicterin A (**65**) in good yield (79%), paving the way for the total synthesis of the natural product. Interestingly, exposure of **59** to this or other Lewis acids did not lead to helicterin-like dimers.

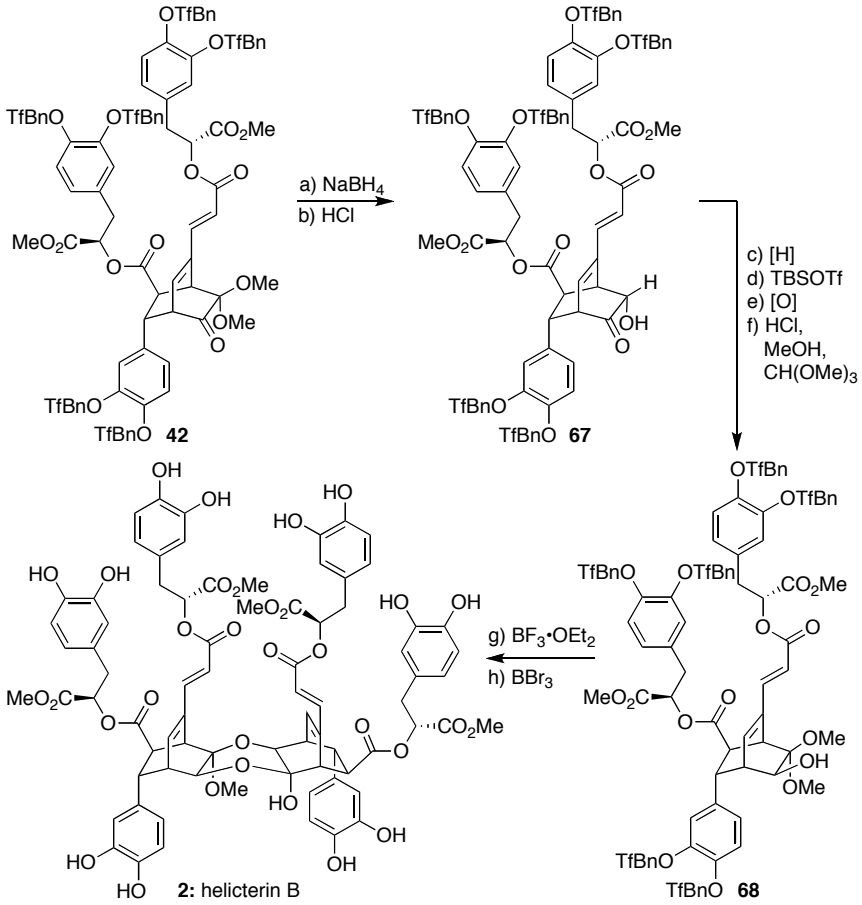


Scheme 11. (a) HCl (g), 100 °C, 45 min, 99%; (b) 160 °C, 4 h, 15% (32% b.r.s.m.); (c) protic acid (catalytic), organic solvent; (d) NaH (10 equiv), THF, 25 °C, 20 min, 99%; (e) BF_3•OEt_2 (4.0 equiv), CH_2Cl_2, 0 °C, 30 min, 79%.

1.7 Total Synthesis of Helicterin B (2)

The reactions and conditions developed in the model studies transferred readily to fully functionalized molecules. As shown in Scheme 12, Diels–Alder adduct **42** was readily converted to hydroxyketone **67**, which in turn was used to prepare dimerization precursor hydroxyketal **68**. This compound was then subjected to BF_3•OEt_2-mediated dimerization to afford protected helicterin A in 67% yield. Low temperature exposure of this intermediate to BBr_3 then cleaved all twelve *p*-CF_3-benzyl ethers and, surprisingly, one of the two mixed ketals within the core in 76% overall yield. Thus, the first total synthesis of helicterin B (**2**) was completed. Efforts to convert this natural product to helicterin A (**1**) by reintroducing the missing methyl group, such as treating **2** with acidic

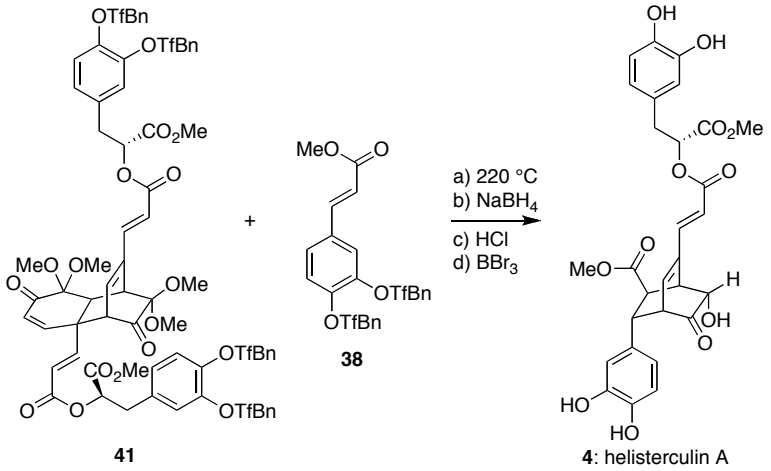
MeOH, proved fruitless. Difficulty in reintroducing that group coupled with the observation that only one of the two ketals was hydrolyzed during the deprotection step, suggests the existence of an intramolecular hydrogen bond between the pseudoaxially disposed hemiketal hydroxy and ketal methoxy groups.



Scheme 12. (a) $NaBH_4$ (1.5 equiv), MeOH/THF (4:1), –30 °C, 1 h; (b) 0.5 M HCl, MeCN/H_2O (100:1), 23 °C, 14 h, 56% overall; (c) $Me_4NBH(OAc)_3$ (5.0 equiv), MeCN/AcOH (80:1), 23 °C, 28 h; (d) TBSOTf (1.05 equiv), Et_3N (5.0 equiv), CH_2Cl_2, –78 °C, 1 h; (e) Dess–Martin periodinane (1.5 equiv), $NaHCO_3$ (excess), CH_2Cl_2, 23 °C, 1 h; (f) 0.4 M HCl MeOH/$CH(OMe)_3$ (4:1), 23 °C, 14 h, 43% overall; (g) BF_3•OEt_2 (8.0 equiv), CH_2Cl_2, 0 °C, 30 min, 67%; (h) BBr_3 (1.0 M in CH_2Cl_2, 20 equiv), CH_2Cl_2, –78 °C, 45 min, 76%. TBS = *t*-butyldimethylsilyl, Tf = trifluoromethanesulfonyl

1.8 Total Synthesis of Helisterculin A (4)

As a final demonstration of the robustness the developed sequences, a third member of the family, helisterculin A (**4**), was prepared using a number of the critical steps discussed above. As shown in Scheme 13, our common starting material, dimer **41**, was subjected to the retro Diels–Alder/Diels–Alder cascade using a different dienophile (**38**) ultimately yielding the bicyclic core of the natural product. This intermediate was then subjected to a reduction followed by an acid-catalyzed ketal cleavage and rearrangement to afford the thermodynamic hydroxyketone. Global phenol deprotection with BBr_3 at low temperature then converted this compound into the natural product (**4**), thereby completing this sequence with an overall yield of 26%.



Scheme 13. (a) **38** (6.7 equiv), mesitylene, 220 °C, 30 min, 44% (78% b.r.s.m.); (b) $NaBH_4$ (1.5 equiv), MeOH/THF (4:1), 0 °C, 1 h, 79%; (c) 0.2 M HCl, MeCN/H_2O (15:1), 23 °C, 2 h, 74%; (d) BBr_3 (1.0 M in CH_2Cl_2, 8.0 equiv), CH_2Cl_2, –78 °C, 30 min, 92%.

1.9 Conclusion

We have developed an approach capable of controllably accessing the major architectures within the helicterin neolignan family, culminating in total syntheses of three natural products (**2**–**4**) as well as providing a potential route to the core of several others (the yunnaneic acids). In the process, the unassigned stereochemistry of their side chains has been established, and their presumed connection to rosmarinic acid has been confirmed. Overall, this work has led to a number of discoveries including the development of a domino retro/forward Diels–Alder sequence with highly functionalized pieces, a unique Friedel–Crafts ring closure resulting in a highly strained ring-structure, an acid-catalyzed hydroxyketone rearrangement, a Lewis acid-promoted dimerization of highly functionalized bicyclo[2.2.2]octene hydroxyketal derivatives, and the use of a novel phenol protecting group to balance chemical reactivity on sensitive scaffolds. The results of these studies suggest that enzymes are used to achieve many of the transformations during the biosynthesis of these compounds. Furthermore, this work illustrates that only through the use of a common intermediate distinct from the biosynthetic starting material could these natural prodcuts be synthesized in the laboratory.

The assistance of Anish Shah during the pursuit of this research project is gratefully aknowledged. He efficiently prepared several batches of material at various stages, and his contribution was greatly appreciated. In addition, Michelle L. Hall (Friesner group) is thanked for performing the computational analysis on the hydroxyketone isomers.

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1.11 Experimental Section

General Procedures. All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Dry tetrahydrofuran (THF), acetonitrile (MeCN), toluene, benzene, diethyl ether (Et_2O), and methylene chloride (CH_2Cl_2) were obtained by passing commercially available pre-dried, oxygen-free formulations through activated alumina columns. Yields refer to chromatographically and spectroscopically (^1H and ^{13}C NMR) homogeneous materials, unless otherwise stated. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Reactions were magnetically stirred and monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent, and cerium sulfate (CAM) and heat as developing agents. SiliCycle silica gel (60, academic grade, particle size 0.040–0.063 mm) was used for flash column chromatography. Preparative thin-layer chromatography (PTLC) separations were carried out on 0.50 mm E. Merck silica gel plates (60F-254). NMR spectra were recorded on Bruker DPX 300, Avance II 400, Avance III 400, and DMX 500 instruments, and calibrated using residual undeuterated solvent as an internal reference ($CDCl_3$: 7.26 ppm for ^1H, 77.0 ppm for ^{13}C; acetone-d_6: 2.05 ppm for ^1H, 29.8 for ^{13}C; methanol-d_4: 3.31 ppm for ^1H, 49.0 for ^{13}C). The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, br = broad, app = apparent. IR spectra were recorded on a Perkin-Elmer 1000 series FT-IR spectrometer. High-resolution mass spectra (HRMS) were recorded in the

Columbia University Mass Spectral Core facility on a JOEL HX110 mass spectrometer using FAB (fast atom bombardment) techniques.

Abbreviations. 4-DMAP = 4-(dimethylamino)pyridine, DMF = *N*,*N*-dimethylformamide, EDC = *N*-ethyl-*N*′-(3-dimethylaminopropyl)carbodiimide, TBAF = tetra-*n*-butylammonium fluoride, TBS = *tert*-butyldimethylsilyl, TMS = trimethylsilyl, Tf = trifluoromethanesulfonyl.

Diels–Alder dimer (18). $PhI(OAc)_2$ (8.58 g, 26.6 mmol, 1.05 equiv) was added to a solution of *trans*-3-methoxy-4-hydroxycinnamic acid methyl ester (**17**, 5.28 g, 25.4 mmol, 1.0 equiv) in MeOH:CH_2Cl_2 (6:1, 35 mL) at 23 °C, and the resultant light yellow solution was stirred at 23 °C for 14 h. Upon completion, the reaction contents were concentrated directly, and the resultant crude yellow oil was purified by flash column chromatography (silica gel, hexanes/EtOAc, 3:2) to give Diels–Alder adduct **18** (5.26 g, 87% yield) as a yellow amorphous solid. **18**: R_f = 0.22 (silica gel, hexanes/EtOAc, 1:1); IR (film) ν_{max} 2950, 1710, 1650, 1635, 1436, 1313, 1196, 1174, 1132, 1050, 733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.22 (d, *J* = 16.0 Hz, 1 H), 6.97 (d, *J* = 16.0 Hz, 1 H), 6.19 (dd, *J* = 7.2, 2.0 Hz, 1 H), 6.17 (d, *J* = 10.0 Hz, 1 H), 6.06 (d, *J* = 15.6 Hz, 1 H), 6.01 (d, *J* = 10.0 Hz, 1 H), 6.00 (d, *J* = 16.4 Hz, 1 H), 3.76 (s, 3 H), 3.74 (s, 3 H), 3.44 (s, 3 H), 3.43 (s, 3 H), 3.40 (app t, *J* = 1.6 Hz, 1 H), 3.35 (s, 1 H), 3.30 (d, *J* = 6.4 Hz, 1 H), 3.22 (s, 3 H), 3.05 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.9, 191.2, 166.7, 166.1, 147.7, 146.1, 141.0, 140.2, 132.4, 128.2, 121.7, 119.8, 97.6, 94.1, 58.2, 51.7, 51.6, 50.6, 50.5, 50.2,

50.0, 48.7, 43.3, 40.6; HRMS (FAB) calcd for $C_{24}H_{28}O_{10}^{+}$ [M^{+}] 476.1682, found 476.1613.

3-Methoxy-4-Hydroxydihydrocinnamic Acid Methyl Ester (19). Concentrated HCl (2 drops) was added to a solution of 3-methoxy-4-hydroxydihydrocinnamic acid (0.225 g, 1.15 mmol, 1.0 equiv) in anhydrous MeOH (10 mL) at 23 °C, and the resultant solution was stirred at 23 °C for 20 h. Upon completion, the reaction contents were concentrated directly, and the resultant crude yellow oil was purified by flash column chromatography (silica gel, hexanes/EtOAc, 3:2) to afford **19** (0.231 g, 96% yield) as a colorless oil. **16**: R_f = 0.63 (silica gel, hexanes/EtOAc, 1:1); IR (film) ν_{max} 3445, 2951, 1731, 1606, 1515, 1434, 1364, 1290, 1234, 1202, 1152, 1121, 1033, 818, 791, 732 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.83 (d, *J* = 8.0 Hz, 1 H), 6.70 (s, 1 H), 6.69 (d, *J* = 9.6 Hz, 1 H), 5.51 (s, 1 H), 3.87 (s, 3 H), 3.67 (s, 3 H), 2.88 (t, *J* = 7.8 Hz, 2 H), 2.60 (t, *J* = 7.8 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.4, 146.4, 144.0, 132.4, 120.8, 114.3, 110.9, 55.8, 51.6, 36.1, 30.7; HRMS (FAB) calcd for $C_{11}H_{14}O_4^{+}$ [M^{+}] 210.0892, found 210.0905.

Diels–Alder adduct 21. $PhI(OAc)_2$ (0.384 g, 1.19 mmol, 1.1 equiv) was added to a solution of **19** (0.228 g, 1.08 mmol, 1.0 equiv) in MeOH:CH_2Cl_2 (5:1, 12 mL) at 23 °C, and the resultant yellow solution was stirred at 23 °C for 1 h. Upon completion, the reaction contents were concentrated directly, and the resultant crude yellow oil was purified by flash column chromatography (silica gel, hexanes/EtOAc, 7:3) to afford the desired orthoquinone monoketal intermediate (0.253 g, 97% yield) as a bright yellow oil.

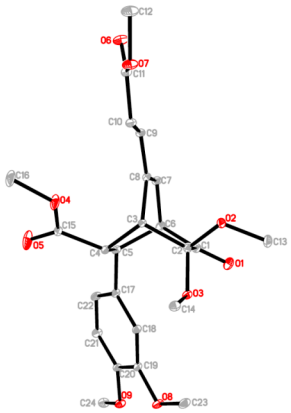
[Note: this product was stored as a 0.2 M solution in toluene at 4 °C to prevent its dimerization]. Acrylonitrile (7.60 mL, 116 mmol, 100 equiv) was then added to a solution of this newly formed orthoquinone monoketal (0.2 M in toluene, 5.8 mL, 1.16 mmol, 1.0 equiv), and the reaction mixture was stirred in a sealed tube at 80 °C for 2 days. Upon completion, the reaction contents were concentrated directly, and the resultant crude yellow oil was purified by flash column chromatography (silica gel, hexanes/EtOAc, 7:3) to afford **21** (0.148 g, 43% yield) as a colorless oil. **21**: R_f = 0.41 (silica gel, hexanes/EtOAc, 1:1); IR (film) ν_{max} 3004, 2969, 2921, 2139, 1740, 1713, 1445, 1422, 1365, 1222, 1091, 1069, 894 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.90 (d, *J* = 6.4 Hz, 1 H), 3.70 (s, 3 H), 3.35 (dd, *J* = 6.4, 2.0 Hz, 1 H), 3.32 (s, 3 H), 3.28 (s, 3 H), 3.13 (ddd, *J* = 10.0, 5.6, 2.0 Hz, 1 H), 3.04 (dd, *J* = 4.8, 2.8 Hz, 1 H), 2.62–2.53 (m, 4 H), 3.13 (ddd, *J* = 13.2, 10.0, 3.0 Hz, 1 H), 1.65 (ddd, *J* = 13.2, 5.2, 3.2 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.8, 172.9, 149.7, 120.7, 117.3, 93.4, 51.9, 50.9, 49.8, 49.2, 42.5, 31.5, 30.0, 26.2, 25.3; HRMS (FAB) calcd for $C_{15}H_{20}O_5N^+$ [M + H^+] 294.1341, found 294.1356.

Dihydrofuran 25. AgOAc (0.452 g, 2.71 mmol, 1.1 equiv) was added to a solution of *trans*-3-methoxy-4-hydroxydihydrocinnamic acid methyl ester (**17**, 0.513 g, 2.46 mmol) in toluene (8 mL) at 23 °C. The reaction mixture was then warmed to 60 °C and stirred for 20 h. Upon completion, the reaction contents were filtered through Celite, concentrated, and purified by flash column chromatography (silica gel, hexanes/EtOAc, 7:3) to afford dihydrobenzofuran **25** (0.105 g, 20% yield) as a white amorphous solid. **25**: R_f = 0.36 (silica gel, hexanes/EtOAc, 7:3); IR (film) ν_{max} 3444, 2952, 1736, 1705, 1634,

1601, 1518, 1496, 1435, 1171, 1145, 1033, 980, 846 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 16.0 Hz, 1 H), 7.26 (s, 1 H), 7.18 (s, 1 H), 6.91–6.86 (m, 3 H), 6.31 (d, *J* = 16.0 Hz, 1 H), 6.10 (d, *J* = 8.4 Hz, 1 H), 5.79 (br s, 1 H), 4.34 (d, *J* = 8.4 Hz, 1 H), 3.90 (s, 3 H), 3.85 (s, 3 H), 3.82 (s, 3 H), 3.79 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6, 167.5, 149.8, 146.7, 146.0, 144.6, 144.6, 131.2, 128.4, 125.6, 119.2, 117.8, 115.3, 114.5, 112.0, 108.7, 87.3, 56.0, 55.8, 55.3, 52.7, 51.5; HRMS (FAB) calcd for $C_{22}H_{22}O_8^+$ [M^+] 414.1315, found 414.1331.

Mixed Diels–Alder Adduct 22. A solution of **18** (1.21 g, 2.54 mmol, 1.0 equiv) and dienophile **15** (3.78 g, 17.0 mmol, 6.7 equiv) in mesitylene (3.0 mL) was carefully degassed 3 times using the freeze-pump-thaw method, and then sealed under argon in a tube equipped with a magnetic stir bar. The reaction solution was stirred at 220 °C (oil bath) for 30 min. After cooling to 23 °C, the reaction contents were purified directly by flash column chromatography (silica gel, hexanses:EtOAc, 4:1→1:1) to afford recovered **15** (3.20 g) alongside a light yellow solid which was recrystallized from Et_2O to provide Diels–Alder adduct **22** (1.00 g, 43% yield, 83% yield based on recovered starting material) as a crystalline white solid. **22**: R_f = 0.36 (silica gel, hexanes/EtOAc, 3:2); m.p. 143.0–143.5 °C; IR (film) ν_{max} 2951, 1735, 1719, 1632, 1519, 1436, 1311, 1287, 1269, 1239, 1195, 1172, 1146, 1062, 1027 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, *J* = 15.6 Hz, 1 H), 6.82–6.77 (m, 3 H), 6.62 (dd, *J* = 6.8, 2.4 Hz, 1 H), 6.11 (d, *J* = 15.6 Hz, 1 H), 3.92 (app t, *J* = 0.2 Hz, 1 H), 3.85 (s, 3 H), 3.84 (s, 3 H), 3.78 (s, 3 H), 3.67 (s, 3 H), 3.58 (dd, *J* = 6.8, 2.8 Hz, 1 H), 3.48 (s, 3 H), 3.44 (dd, *J* = 6.8, 2.0 Hz, 1 H), 3.34 (s, 3 H), 3.30 (dd, *J* = 6.8, 2.4 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.9, 173.3, 167.2, 149.0,

148.1, 141.7, 140.0, 134.3, 133.1, 119.7, 118.2, 111.2, 111.08, 93.8, 56.3, 55.8, 52.4, 51.8, 51.0, 49.9, 47.0, 44.5, 42.4; HRMS (FAB) calcd for $C_{24}H_{28}O_9^+$ [M^+] 460.1733, found 460.1759.



22 [X-ray structure]

Bromoketal 28. BBr_3 (1.0 M in CH_2Cl_2, 0.365 mL, 0.365 mmol, 6.0 equiv) was added to a solution of Diels–Alder adduct **22** (0.028 g, 0.061 mmol, 1.0 equiv) in CH_2Cl_2 (1 mL) at –78 °C, and the reaction was stirred at –78 °C for 1 h. Upon completion, the reaction contents were poured into saturated aqueous $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were then washed with brine (10 mL), dried ($MgSO_4$), and concentrated. The resultant crude material was purified by flash column chromatography (silica gel, hexanes/EtOAc, 2:1) to afford bromoketal **28** (0.027 g, 86% yield) as a thick colorless oil. **28**: R_f = 0.47 (silica gel, hexanes/EtOAc, 1:1); IR (film) ν_{max} 2951, 1735, 1718, 1635, 1519, 1437, 1313, 1247, 1196, 1173, 1148, 1027, 669 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, J = 16.0 Hz, 1 H), 6.79–6.73 (m, 3 H), 6.70 (dd, J = 6.8, 1.6 Hz, 1 H), 6.15 (d, J = 16.0 Hz, 1 H), 4.40 (t, J = 0.2 Hz, 1 H), 3.85 (s, 3 H), 3.84 (s, 3 H), 3.80 (s, 3 H), 3.68 (s, 3 H), 3.68 (s, 3 H), 3.68-3.67 (m, 1 H), 3.52

(dd, J = 6.6, 2.2 Hz, 1 H), 3.46 (dd, J = 6.8, 2.4 Hz, 1 H); LRMS (APCI) calcd for $C_{23}H_{25}BrO_8^+$ [M^+] 508.1, found 508.2.

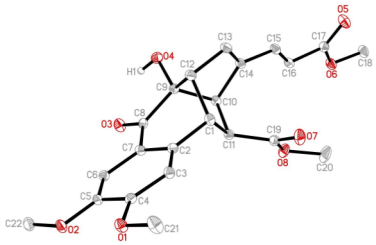
Helisorin Core 30. BF_3•OEt_2 (0.016 mL, 0.130 mmol, 6.0 equiv) was added to a solution of Diels–Alder adduct **22** (0.010 g, 0.022 mmol, 1.0 equiv) in CH_2Cl_2 (0.5 mL) at 0 °C, and the reaction was slowly warmed to 23 °C and stirred from an additional 16 h. Upon completion, the reaction was quenched with saturated aqueous $NaHCO_3$ (10 mL) and extracted with EtOAc (2 × 10 mL). The combined organic layers were then washed with saturated aqueous $NaHCO_3$ (10 mL), brine (10 mL), dried ($MgSO_4$), and concentrated. The resultant thick orange oil was purified by flash column chromatography (silica gel, hexanes/EtOAc, 1:1) to afford compound **30** (7.5 mg, 82% yield) as a colorless solid. **30**: R_f = 0.24 (silica gel, hexanes/EtOAc, 3:7); IR (film) ν_{max} 3462, 2952, 1725, 1631, 1499, 1437, 1306, 1221, 1167, 1116, 1003 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, J = 15.6 Hz, 1 H), 6.82 (app s, 2 H), 6.74 (d, J = 5.2 Hz, 1 H), 6.05 (d, J = 15.6 Hz, 1 H), 4.14 (d, J = 3.6 Hz, 1 H), 3.88 (s, 3 H), 3.88 (s, 3 H), 3.88–3.85 (m, 2 H), 3.77 (s, 3 H), 3.62 (s, 3 H), 3.25 (s, 1 H), 3.09 (d, J = 3.6 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.6, 170.6, 167.0, 150.5, 149.5, 139.9, 138.7, 136.7, 136.4, 132.9, 118.5, 106.6, 105.8, 81.2, 56.1, 56.1, 55.9, 52.2, 51.8, 51.6, 51.4, 42.4; HRMS (FAB) calcd for $C_{22}H_{23}O_8^+$ [M+H^+] 415.1393, found 415.1401.

Diketone 32. Solid $NaHCO_3$ (0.040 g, 0.480 mmol, 10 equiv) and Dess–Martin periodinane (0.041 g, 0.096 mmol, 2.0 equiv) were added sequentially in single portions to a solution of hydroxyketone **56** (0.040 g, 0.048 mmol, 1.0 equiv) in CH_2Cl_2 (1 mL) at

23 °C. The resultant suspension was stirred at 23 °C for 1 h. Upon completion, saturated aqueous Na_2SO_3 (2 mL) was added, and the resultant biphasic mixture was stirred vigorously for 1 h to quench any remaining oxidizing agents. The reaction contents were then poured into water (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL), dried ($MgSO_4$), and concentrated to afford crude diketone **32** (0.037 g, 93% yield) as a thick yellow oil, which was used immediately without further purification. **32**: R_f = 0.15 (silica gel, hexanes/EtOAc, 3:2); IR (film) ν_{max} 2925, 1733, 1717, 1630, 1518, 1437, 1312, 1264, 1196, 1172, 1146, 1025, 809 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.38 (d, *J* = 16.0 Hz, 1 H), 6.78 (app d, *J* = 8.5 Hz, 2 H), 6.58–6.57 (m, 2 H), 6.16 (d, *J* = 15.5 Hz, 1 H), 4.27 (t, *J* = 2.0 Hz, 1 H), 3.87–3.83 (m, 7 H), 3.84 (s, 3 H), 3.83 (s, 3 H), 3.80 (s, 3 H), 3.80–3.78 (m, 1 H), 3.72 (s, 3 H), 3.43 (dd, *J* = 6.0, 2.0 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 187.8, 187.8, 171.4, 166.5, 149.4, 148.6, 139.5, 137.7, 135.2, 131.8, 120.5, 119.2, 111.6, 110.8, 56.5, 55.9, 55.8, 52.9, 52.0, 50.7, 46.8, 45.3; LRMS (FAB) calcd for $C_{22}H_{22}O_8^+$ [M^+] 414.13, found 414.14.

Rearragement Product 31. BF_3•OEt_2 (0.054 mL, 0.434 mmol, 20 equiv) was added to a solution of Diels–Alder adduct **22** (0.010 g, 0.022 mmol, 1.0 equiv) in CH_2Cl_2 (0.5 mL) at 23 °C, and the reaction was stirred at 23 °C for 12 h. Upon completion, the reaction contents were quenched with saturated aqueous $NaHCO_3$ (10 mL) and extracted with EtOAc (2 × 10 mL). The combined organic layers were then washed with saturated aqueous $NaHCO_3$ (10 mL), brine (10 mL), dried ($MgSO_4$), and concentrated. The resultant thick orange oil was purified by flash column chromatography (silica gel,

hexanes/EtOAc, 1:1) to afford a thick yellow oil which was recrystallized from Et_2O to afford **31** (7.5 mg, 88% yield from **22**) as a white crystalline solid. Compound **31** was also obtained from helisorin core **30** under identical reaction conditions (80% yield), and from diketone **32** using 6.0 equiv of BF_3•OEt_2 (53% yield). **31**: R_f = 0.26 (silica gel, hexanes/EtOAc, 3:7); m.p. = 105.8–106.4 °C; IR (film) ν_{max} 3463, 2924, 1734, 1717, 1596, 1308, 1264, 1209, 1114 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.50 (s, 1 H), 7.43 (d, *J* = 16.0 Hz, 1 H), 6.82 (d, *J* = 3.0 Hz, 1 H), 6.62 (d, *J* = 3.0 Hz, 1 H), 5.95 (d, *J* = 16.0 Hz, 1 H), 3.97 (s, 3 H), 3.93 (s, 3 H), 3.90 (s, 1 H), 3.76 (s, 3 H), 3.52 (s, 3 H), 3.52 (s, 3 H), 3.40 (s, 1 H), 3.35 (d, *J* = 4.5 Hz, 1 H), 3.29 (d, *J* = 2.0 Hz, 1 H), 2.90 (dd, *J* = 4.5, 1.5 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.1, 171.5, 167.2, 154.9, 148.6, 145.3, 143.7, 138.6, 138.3, 122.6, 119.3, 109.7, 108.4, 95.9, 61.7, 56.3, 56.2, 54.2, 51.6, 50.1, 42.9; HRMS (FAB) calcd for $C_{22}H_{23}O_8^+$ [M+H^+] 415.1393, found 415.1401.



31 [X-ray structure]

Dienophile 37. TMS-diazomethane (2.0 M in Et_2O, 7.9 mL, 15.8 mmol, 0.95 equiv) was added in small portions over 1 h to a solution of rosmarinic acid (**6**, 6.00 g, 16.7 mmol, 1.0 equiv) in THF:MeOH (10:1, 110 mL) at –78 °C. Upon completion, the reaction contents were allowed to warm to 23 °C over 1 h, concentrated directly and

filtered through a short plug of silica gel (CH_2Cl_2:MeOH, 19:1). The resultant thick brown oil was dried thoroughly under high vacuum to provide the desired ester intermediate that was carried forward without any additional purification. Next, *p*-trifluoromethylbenzyl bromide (7.40 mL, 48.0 mmol, 6.0 equiv), K_2CO_3 (6.60 g, 48.0 mmol, 6.0 equiv), and KI (catalytic) were added sequentially and in single portions to a solution of half of the crude ester just prepared (8.0 mmol, 1.0 equiv) in *N*,*N*-dimethylformamide (30 mL) at 23 °C. The resultant reaction mixture was then stirred at 60 °C for 8 h, and at 23 °C for 16 h. Upon completion, the reaction contents were carefully quenched by the addition of 1 M aqueous HCl (until gas evolution ceased), poured into water (50 mL) and extracted with EtOAc (2 × 100 mL). The combined organic layers were then washed with 1 M aqueous HCl (50 mL), saturated aqueous $NaHCO_3$ (50 mL) and brine (50 mL), dried ($MgSO_4$), and concentrated. The resultant crude material was purified by flash column chromatography (silica gel, hexanes/EtOAc:CH_2Cl_2, 17:1:2→5:4:1) to afford dienophile **37** (6.00 g, 84% yield over 2 steps) as a white amorphous solid. **37**: R_f = 0.45 (silica gel, hexanes/EtOAc:CH_2Cl_2, 3:1:1); IR (film) ν_{max} 1751, 1715, 1625, 1598, 1511, 1324, 1265, 1160, 1120, 1065, 1016, 824, 736 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.66–7.49 (m, 17 H), 7.11–7.08 (m, 2 H), 6.92–6.81 (m, 4 H), 6.29 (d, *J* = 16.0 Hz, 1 H), 5.36 (dd, *J* = 8.0, 4.8 Hz, 1 H), 5.23 (s, 2 H), 5.19 (s, 2 H), 5.17 (s, 2 H), 5.16 (s, 2 H), 3.71 (s, 3 H), 3.18 (dd, *J* = 14.4, 5.0 Hz, 1 H), 3.11 (dd, *J* = 14.4, 8.4 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.1, 166.0, 150.8, 148.6, 148.5, 147.7, 145.5, 141.2, 141.1, 140.7, 140.5, 127.9, 127.2, 127.2, 127.1, 125.8, 125.4, 125.3, 125.3, 123.3, 122.7, 122.2, 116.2, 115.2, 114.9, 114.0, 113.5, 72.8, 70.5,

70.3, 69.9, 52.2, 36.9; HRMS (FAB) calcd for $C_{51}H_{38}F_{12}O_8^+$ [M^+] 1006.2375, found 1006.2424.

Dienophile 38 and Chiral Alcohol 39. Solid NaOMe (0.057 g, 1.05 mmol, 1 equiv) was added in a single portion to a solution of **37** (1.06 g, 1.05 mmol) in methanol:CH_2Cl_2 (1:1, 16 mL) at 23 °C, and the reaction was stirred at 23 °C for 2 h. Upon completion, the reaction contents were quenched with 1 M aqueous HCl (10 mL), poured into water (10 mL) and extracted with EtOAc (2 × 20 mL). The combined organic layers were then washed with saturated aqueous NH_4Cl (20 mL) and brine (20 mL), dried ($MgSO_4$), and concentrated. The resultant crude yellow solid was purified by flash column chromatography (silica gel, hexanes/EtOAc, 7:3) to afford the desired dienophile **38** (0.493 g, 92% yield) as a white amorphous solid alongside chiral alcohol **39** (0.498 g, 90% yield) as a white amorphous solid. **38**: R_f = 0.66 (silica gel, hexanes/EtOAc, 3:2); IR (film) ν_{max} 3004, 2918, 1713, 1422, 1363, 1222, 1126, 665 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.66–7.47 (m, 9 H), 7.13–7.09 (m, 2 H), 6.91 (d, *J* = 8.8 Hz, 1 H), 6.27 (d, *J* = 16.2 Hz, 1 H), 5.24 (s, 2 H), 5.22 (s, 2 H), 3.79 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.4, 150.4, 148.5, 144.1, 140.8, 140.6, 128.2, 127.2, 127.2, 127.1, 127.1, 127.1, 125.5, 125.5, 125.4, 125.4, 123.0, 116.1, 114.0, 113.4, 70.3, 70.0, 51.5; HRMS (FAB) calcd for $C_{26}H_{20}F_6O_4^+$ [M^+] 510.1266, found 510.1261.

39: R_f = 0.34 (silica gel, hexanes/EtOAc, 3:2); $[\alpha]^{22}_D$ = +11.0° (*c* = 0.79, $CHCl_3$); IR (film) ν_{max} 3417, 1720, 1632, 1519, 1421, 1330, 1271, 1239, 1217, 1159, 1142, 1115, 1105, 1068, 1037, 1021, 823 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.64–7.53 (m, 8 H),

6.85 (d, J = 8.4 Hz, 1 H), 6.84 (s, 1 H), 6.75 (dd, J = 8.4, 2.0 Hz, 1 H), 5.19 (s, 2 H), 5.17 (s, 2 H), 4.40 (dd, J = 6.6, 4.2 Hz, 1 H), 3.73 (s, 3 H), 3.04 (dd, J = 14.2, 4.2 Hz, 1 H), 2.87 (dd, J = 14.0, 6.4 Hz, 1 H), 2.69 (br s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.4, 148.4, 147.6, 141.3, 141.2, 130.2, 129.8, 127.3, 127.2, 125.9, 125.5, 125.4, 122.8, 116.5, 115.0, 71.2, 70.5, 70.5, 52.4, 39.9; HRMS (FAB) calcd for $C_{26}H_{22}F_6O_5^+$ [M^+] 528.1371, found 528.1392.

Phenol 40. EDC•HCl (1.41 g, 7.34 mmol, 2.0 equiv) and 4-DMAP (0.448 g, 3.67 mmol, 1.0 equiv) were added sequentially in single portions to a solution of TBS-protected acid **44** (2.26 g, 7.34 mmol, 2.0 equiv) and chiral alcohol **39** (1.94 g, 3.67 mmol, 1.0 equiv) in CH_2Cl_2 (20 mL) at 23 °C, and the resulting mixture was stirred at 23 °C for 3 h. Upon completion, the reaction contents were diluted with EtOAc (30 mL), poured into water (40 mL) and extracted with EtOAc (2 × 50 mL). The combined organic layers were then washed with 1 M aqueous HCl (3 × 30 mL) and brine (30 mL), dried ($MgSO_4$), and concentrated to afford the desired ester as a yellow oil which was carried forward without any additional purification. Next, AcOH (0.6 mL) and TBAF (1.0 M in THF, 7.34 mL, 7.34 mmol, 2.0 equiv) were added sequentially and dropwise over the course of several minutes to a solution of the newly formed ester in THF (20 mL) at 0 °C. After 5 min of stirring at 0 °C, the reaction contents were poured into 1 M aqueous HCl (30 mL) and extracted with EtOAc (2 × 30 mL). The combined organic layers were then washed with brine (30 mL), dried ($MgSO_4$), and concentrated. The resultant crude yellow solid was purified by flash column chromatography (silica gel, hexanes/EtOAc, 7:3) to afford phenol **40** (2.43 g, 94% yield over 2 steps) as a white amorphous solid. **40**: R_f =

0.35 (silica gel, hexanes/EtOAc, 3:2); $[\alpha]^{23}_{D}$ = +36.2° (*c* = 0.65, $CHCl_3$); IR (film) ν_{max} 3413, 3004, 1716, 1422, 1366, 1218, 1092, 902 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 16.4 Hz, 1 H), 7.62–7.58 (m, 4 H), 7.54–7.49 (m, 4 H), 7.06 (dd, *J* = 8.0, 1.6 Hz, 1 H), 7.00 (d, *J* = 1.6 Hz, 1 H) 6.92–6.82 (m, 4 H), 6.31 (d, *J* = 16.0 Hz, 1 H), 5.95 (s, 1 H), 5.37 (ddd, *J* = 8.0, 4.8, 1.2 Hz, 1 H) 5.16 (s, 2 H), 5.15 (s, 2 H), 3.93 (s, 3 H), 3.87 (s, 3 H), 3.18 (dd, *J* = 14.4, 4.8 Hz, 1 H), 3.12 (dd, *J* = 14.4, 8.4 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.2, 166.2, 148.4, 148.4, 147.6, 146.8, 146.2, 141.1, 141.0, 129.7, 127.2, 127.1, 126.5, 125.3, 125.2, 125.2, 123.2, 122.7, 116.1, 114.9, 114.7, 114.0, 109.4, 72.7, 70.4, 70.3, 55.6, 52.2, 36.9; HRMS (FAB) calcd for $C_{36}H_{30}F_6O_8^+$ [M^+] 704.1845, found 704.1864.

Carboxylic Acid 44. *i*-Pr_2NEt (8.07 mL, 46.3 mmol, 3.0 equiv) and TBSCl (5.82 g, 38.6 mmol, 2.5 equiv) were added sequentially in single portions to a solution of 3-methoxy-4-hydroxydihydrocinnamic acid (**43**, 3.00 g, 15.4 mmol, 1.0 equiv) in CH_2Cl_2 (20 mL) at 23 °C, and the reaction mixture was stirred at 23 °C for 14 h. Upon completion, the reaction contents were diluted with EtOAc (60 mL), poured into water (15 mL), washed with 1 M aqueous HCl (2 × 30 mL) and brine (30 mL), dried ($MgSO_4$), and concentrated to afford the desired bis-silylated product as a light yellow oil which was carried forward without any additional purification. Next, the newly formed intermediate was taken up in wet THF (20 mL), solid K_2CO_3 (2.00 g, excess) was added at 23 °C in a single portion, and the resultant slurry was stirred vigourously for 2 h at 23 °C. Upon completion, the reaction contents were diluted with EtOAc (60 mL), poured into water (40 mL), washed with 1 M aqueous HCl (30 mL) and brine (30 mL), dried

($MgSO_4$), and concentrated. The resultant white solid was then dried under high vacuum in a 60 °C oil bath for 3 h to drive off TBSOH and afford the desired carboxylic acid **44** (4.74 g, 99% yield) as a white amorphous solid. **44**: R_f = 0.40 (silica gel, hexanes/EtOAc, 3:2); IR (film) ν_{max} 2956, 2931, 2858, 1679, 1625, 1509, 1418, 1283, 1265, 1205, 1160, 1123, 906, 839, 824, 783 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 11.4 (br s, 1 H), 7.72 (d, *J* = 16.0 Hz, 1 H), 7.07–7.04 (m, 2 H), 6.86 (d, *J* = 8.8 Hz, 1 H), 6.31 (d, *J* = 16.0 Hz, 1 H), 3.85 (s, 3 H), 1.00 (s, 9 H), 0.18 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.0, 151.2, 148.0, 147.1, 127.9, 122.7, 121.1, 115.0, 111.1, 55.4, 25.6, 18.5, –4.6; HRMS (FAB) calcd for $C_{16}H_{25}O_4Si^+$ [M + H^+] 309.1522 and $C_{16}H_{23}O_3Si^+$ [M – OH^+] 291.1416, found 309.1503 and 291.1424.

Diels–Alder Dimer 41. MeOH (10 mL) and $PhI(OAc)_2$ (0.444 g, 1.38 mmol, 1.05 equiv) were added sequentially to a solution of phenol **40** (0.925 g, 1.31 mmol, 1.0 equiv) in CH_2Cl_2 (2 mL) at 0 °C. The resulting yellow solution was allowed to slowly warm to 23 °C, and then stirred for 14 h. Upon completion, the reaction contents were concentrated directly and purified by flash column chromatography (silica gel, hexanes/EtOAc, 7:3) to afford a 1:1 mixture of diastereomeric **41** (0.959 g, 99% yield) as a light yellow amorphous solid. **41**: R_f = 0.22 (silica gel, hexanes/EtOAc, 3:2); IR (film) ν_{max} 3059, 1731, 1718, 1631, 1512, 1421, 1326, 1267, 1220, 1165, 1126, 1065, 1018, 825 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 1:1 mixture of diastereomers) δ 7.63–7.52 (m, 32 H), 7.24 (d, *J* = 14.0 Hz, 1 H), 7.21 (d, *J* = 15.2 Hz, 1 H), 7.03 (d, *J* = 16.0 Hz, 1 H), 6.97 (d, *J* = 15.6 Hz, 1 H), 6.91–6.84 (m, 8 H), 6.80–6.76 (m, 4 H), 6.17 (app dt, *J* = 6.8, 3.4 Hz, 2 H), 6.13–5.96 (m, 7 H), 5.92 (d, *J* = 10.4 Hz, 1 H), 5.30–5.18 (m, 20 H), 3.70 (s, 3 H),

3.69 (s, 3 H), 3.66 (s, 3 H), 3.63 (s, 3 H), 3.40 (m, 10 H), 3.37 (br s, 1 H), 3.32 (m, 5 H), 3.30 (s, 1 H), 3.23 (d, J = 6.8 Hz, 1 H), 3.21 (s, 3 H), 3.17 (s, 3 H), 3.15–3.08 (m, 8 H), 3.02 (s, 3 H), 2.98 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, 1:1 mixture of diastereomers) δ 198.8, 191.1, 170.1, 169.8, 165.6, 165.3, 164.9, 149.2, 149.1, 148.5, 147.7, 145.7, 133.1, 132.8, 130.7, 130.3, 129.9, 129.6, 129.5, 128.7, 128.4, 127.3, 127.2, 125.9, 125.5, 122.9, 122.8, 122.3, 121.0, 120.9, 119.4, 119.0, 116.3, 116.1, 115.1, 97.7, 94.3, 94.2, 77.2, 73.3, 70.5, 58.3, 57.9, 52.3, 52.2, 50.7, 50.6, 50.4, 50.1, 50.0, 49.9, 49.0, 48.9, 43.5, 43.3, 40.7, 36.9; LRMS (MALDI) calcd for $C_{74}H_{63}F_{12}O_{18}Na^+$ [M – H + Na^+] 1490.37, found 1490.46.

Mixed Diels–Alder Product 42. A solution of **41** (1.07 g, 0.728 mmol, 1.0 equiv) and dienophile **37** (4.90 g, 4.87 mmol, 6.7 equiv) in mesitylene (3.0 mL) was carefully degassed 3 times using the freeze-pump-thaw method, and then sealed under argon in a tube equipped with a magnetic stir bar. The reaction mixture was then stirred at 220 °C (oil bath) for 35 min. After cooling the reaction contents to 23 °C, the reaction mixture was purified directly by flash column chromatography (silica gel, hexanes/EtOAc:CH_2Cl_2, 8:1:1→5:4:1) to provide recovered **37** (4.12 g) along with **42** (0.960 g, 38% yield, 71% yield based on recovered starting material) as a light yellow solid. [Note: compound **42** is produced as a 1:1 mixture of chromatographically separable diastereomers; only data pertaining to the diastereomer which leads to the final natural products is provided here]. **42**: R_f = 0.24 (silica gel, hexanes/EtOAc:CH_2Cl_2, 3:1:1); $[\alpha]^{25}_D$ = +63.5° (c = 0.45, $CHCl_3$); IR (film) ν_{max} 1740, 1435, 1367, 1325, 1228, 1246, 1112, 1065, 824 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55–7.43 (m, 24 H), 7.34 (d, J =

16.0 Hz, 1 H), 6.87–6.69 (m, 8 H), 6.58–6.55 (m, 2 H), 6.18 (d, *J* = 15.6 Hz, 1 H), 5.29 (dd, *J* = 7.6, 5.2 Hz, 1 H), 5.18–5.02 (m, 13 H), 4.97 (app s, 2 H), 3.66 (s, 3 H), 3.57 (s, 3 H), 3.37 (app s, 2 H), 3.30 (s, 3 H), 3.28 (s, 3 H), 3.13 (dd, *J* = 14.4, 5.2 Hz, 1 H), 3.08 (dd, *J* = 14.2, 7.8 Hz, 1 H), 3.02 (dd, *J* = 14.2, 4.6 Hz, 1 H), 2.92 (dd, *J* = 14.8, 8.0 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.5, 172.2, 169.3, 165.9, 148.6, 148.5, 148.3, 147.8, 147.8, 142.4, 141.2, 141.0, 140.4, 134.3, 134.1, 130.4, 129.9, 129.5, 127.4, 127.3, 127.2, 127.1, 125.8, 125.5, 122.7, 122.6, 122.3, 120.7, 118.3, 116.1, 114.9, 114.7, 93.9, 77.2, 73.3, 73.0, 70.5, 70.4, 70.3, 55.3, 52.3, 52.3, 51.0, 49.7, 46.7, 44.9, 42.1, 40.0, 36.7; HRMS (FAB) calcd for $C_{88}H_{70}F_{18}O_{17}^{+}$ [M^{+}] 1740.43, found 1739.98.

Helisorin (3). Water (0.012 mL, 0.645 mmol, 5.0 equiv) and BF_3•OEt_2 (0.487 mL, 3.88 mmol, 30 equiv) were added in single portions to a solution of Diels–Alder adduct **42** (0.225 g, 0.129 mmol, 1.0 equiv) in benzene (6 mL) at 0 °C. The resulting yellow solution was then warmed slowly to 23 °C and stirred for an additional 16 h. Upon completion, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (10 mL), poured into water (10 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were then washed with brine (10 mL), dried ($MgSO_4$), and concentrated. The crude orange solid was purified by flash column chromatography (silica gel, toluene:acetone, 19:1) to afford recovered **42** (0.080 g) alongside the protected natural product (0.116 g, 53% yield, 82% yield based on recovered starting material) as a colorless glass. Next, BBr_3 (1.0 M in CH_2Cl_2, 0.283 mL, 0.283 mmol, 20 equiv) was added in a single portion to a solution of this newly formed intermediate (0.024 g, 0.014 mmol, 1.0 equiv) in CH_2Cl_2 (1 mL) at –78 °C, and the reaction was stirred at –78 °C for

30 min. Upon completion, the reaction mixture was quenched at –78 °C with saturated aqueous $NaHCO_3$ (1 mL), re-acidified with 1.0 M HCl (1 mL), warmed to 23 °C, poured into water (10 mL) and extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$), and concentrated. The resultant crude yellow solid was triturated with CH_2Cl_2 (3 × 1 mL) to afford helisorin (**3**, 9.2 mg, 89% yield) as a white solid. [Note: significant decomposition of helisorin (**3**) was observed following its application to silica gel, exposure to air, and/or temperatures above 23 °C]. **3**: R_f = 0.13 (silica gel, CH_2Cl_2:MeOH, 9:1); $[\alpha]^{25}_D$ = +28.3° (*c* = 0.15, MeOH); IR (film) ν_{max} 3415, 1728, 1631, 1515, 1444, 1261, 1160, 1044 cm^{-1}; ^1H NMR (500 MHz, acetone-d_6) δ 7.71 (br s, 4 H), 7.25 (d, *J* = 16.0 Hz, 1 H), 6.80 (s, 1 H), 6.74 (br s, 2 H), 6.72 (d, *J* = 9.0 Hz, 1 H), 6.72 (d, *J* = 3.5 Hz, 1 H), 6.71 (br s, 1 H), 6.68 (d, *J* = 8.0 Hz, 1 H), 6.57 (dd, *J* = 8.0, 2.0 Hz, 1 H), 6.56 (dd, *J* = 8.0, 2.0 Hz, 1 H), 6.04 (d, *J* = 16.0 Hz, 1 H), 5.15 (dd, *J* = 9.2, 6.8 Hz, 1 H), 4.97 (dd, *J* = 9.2, 4.3 Hz, 1 H), 3.97 (br s, 1 H), 3.62 (s, 3 H), 3.64–3.59 (m, 1 H), 3.55 (s, 3 H), 3.51 (d, *J* = 5.0 Hz, 1 H), 6.57 (dd, *J* = 8.0, 2.0 Hz, 1 H), 3.57 (s, 3 H), 3.37 (app s, 2 H), 3.30 (s, 3 H), 3.28 (s, 3 H), 3.05 (dd, *J* = 13.7, 4.3 Hz, 1 H), 3.01 (br s, 1 H), 2.98 (dd, *J* = 14.7, 6.7 Hz, 1 H), 2.97 (dd, *J* = 14.5, 4.5 Hz, 1 H), 2.82 (dd, *J* = 14.0, 9.5 Hz, 1 H); ^{13}C NMR (125 MHz, acetone-d_6) δ 204.7, 170.9, 170.7, 170.3, 166.7, 147.3, 145.9, 145.9, 145.8, 145.0, 145.1, 142.8, 140.7, 138.0, 137.6, 134.8, 128.7, 128.7, 121.9, 121.8, 118.2, 117.4, 117.4, 116.3, 116.2, 111.4, 111.0, 82.0, 75.0, 74.3, 57.5, 53.0, 52.9, 52.7, 52.5, 43.7, 37.6, 37.6; HRMS (FAB) calcd for $C_{38}H_{35}O_{16}^+$ [M + H^+] 747.4531, found 747.4528. All spectroscopic data for this synthetic material match those reported for natural helisorin (**3**).[1]

[1] Y. Tezuka, M. Terazono, T. I. Kusumoto, Y. Kawashima, Y. Hatanaka, S. Kadota, M.

Hydroxyketal 50. $NaBH_4$ (0.090 g, 2.38 mmol, 2.0 equiv) was added in a single portion to a solution of bicyclic ketone **22** (0.550 g, 1.19 mmol, 1.0 equiv) in MeOH:CH_2Cl_2 (5:1, 6 mL) at 0 °C, and the resultant mixture was stirred at 0 °C for 1 h. Upon completion, the reaction contents were diluted with EtOAc (20 mL), poured into water (20 mL), washed with 1 M aqueous HCl (20 mL), saturated aqueous $NaHCO_3$ (20 mL) and brine (20 mL), dried ($MgSO_4$), and concentrated to afford hydroxyketal **50** (0.551 g, 99% yield) as a white amorphous solid. **50**: R_f = 0.51 (silica gel, hexanes/EtOAc, 3:7); IR (film) ν_{max} 3548, 2949, 1717, 1630, 1517, 1436, 1310, 1237, 1194, 1119, 1086, 1056, 911, 868 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, *J* = 15.6 Hz, 1 H), 6.94–6.92 (m, 2 H), 6.80 (d, *J* = 8.8 Hz, 1 H), 6.68 (d, *J* = 6.8 Hz, 1 H), 6.01 (d, *J* = 16.0 Hz, 1 H), 3.89 (s, 3 H), 3.84 (s, 3 H), 3.75 (s, 3 H), 3.70 (d, *J* = 1.2 Hz, 1 H), 3.61 (s, 3 H), 3.58 (ddd, *J* = 8.8, 3.2, 1.2 Hz, 1 H), 3.55 (s, 3 H), 3.42 (dd, *J* = 6.2, 2.2 Hz, 1 H), 3.39 (app d, *J* = 7.6 Hz, 1 H), 3.21 (dt, *J* = 6.8, 0.2 Hz, 1 H), 3.12 (s, 3 H), 2.21 (d, *J* = 8.8 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.7, 167.5, 148.9, 147.6, 142.6, 139.7, 137.6, 133.6, 119.0, 117.3, 111.7, 111.1, 98.9, 72.2, 55.8, 55.7, 52.1, 51.5, 48.9, 48.8, 46.5, 41.6, 41.1, 40.3; HRMS (FAB) calcd for $C_{24}H_{30}O_9^+$ [M^+] 462.1890, found 462.1897.

Thiocarbamate 51. Thiocarbonyl diimidazole (0.069 g, 0.389 mmol, 6.0 equiv) and 4-DMAP (0.012 g, 0.097 mmol, 1.5 equiv) were added to a solution of alcohol **35** (0.030 g, 0.065 mmol, 1.0 equiv) in CH_2Cl_2 (1.0 mL) at 23 °C, and the reaction was stirred at 40 °C in a sealed tube for 48 h. Upon completion, the reaction contents were

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Hattori, T. Namba, T. Kikuchi, K. Tanaka, S. Supriyatna, *Helv. Chim. Acta* **1999**, *82*, 408–417.

poured into saturated aqueous NH_4Cl (15 mL) and extracted with EtOAc (2×10 mL). The combined organic layers were then washed with saturated aqueous $NaHCO_3$ (10 mL), brine (10 mL), dried ($MgSO_4$), and concentrated. The resultant thick orange oil was purified by flash column chromatography (silica gel, hexanes/EtOAc, 2:3) to afford compound **51** (0.032 g, 91% yield) as a white amorphous solid. **51**: R_f = 0.17 (silica gel, hexanes/EtOAc, 3:7); ^{1}H NMR (500 MHz, CDCl3) δ 7.73 (s, 1 H), 7.39 (d, *J* = 16.0 Hz, 1 H), 7.18 (s, 1 H), 6.82 (m, 2 H), 6.73 (m, 2 H), 6.61 (d, *J* = 8.5 Hz, 1 H), 6.07 (d, *J* = 16.0 Hz, 1 H), 5.21 (d, *J* = 3.0 Hz, 1 H), 3.94 (dt, *J* = 15.0, 3.0 Hz, 1 H), 3.81 (s, 3 H), 3.79 (s, 3H), 3.78 (s, 3 H), 3.71 (s, 3 H), 3.71 (m, 1 H), 3.68 (s, 3 H), 3.42 (s, 3 H), 3.35 (d, *J* = 7.5 Hz, 1 H), 3.10 (s, 3 H).

Carbamate 52. Oxygen gas passed through a drying tube was bubbled into a solution of **51** (5.0 mg, 0.0092 mmol, 1.0 equiv), Et_3B (1.0 M in hexanes, 0.046 mL, 0.046 mmol, 5.0 equiv) and nBu_3SnH (0.012 mL, 0.046 mmol, 5.0 equiv) in CH_2Cl_2 (1.0 mL) at 0 °C for 30 min. after which the solution was stirred at 0 °C for an additional 30 min. Upon completion, the reaction was quenched with 1 M aqueous HCl (10 mL) and extracted with EtOAc (2×10 mL). The combined organic layers were then washed with saturated aqueous $NaHCO_3$ (10 mL), brine (10 mL), dried ($MgSO_4$), and concentrated. The crude was purified by flash column chromatography (silica gel, hexanes/EtOAc, 2:3) to afford compound **52** (3.5 mg, 72% yield) as a white amorphous solid. **52**: R_f = 0.14 (silica gel, hexanes/EtOAc, 3:7); ^{1}H NMR (500 MHz, CDCl3) δ 7.51 (s, 1 H), 7.37 (d, *J* = 15.5 Hz, 1 H), 6.87 (m, 2 H), 6.83 (s, 1 H), 6.80 (s,1 H), 6.73 (d, *J* = 7.0 Hz, 1 H), 6.69 (d , *J* = 8.0 Hz, 1 H), 6.05 (d, *J* = 15.5 Hz, 1 H), 4.77 (d, *J* = 3.0 Hz, 1 H), 3.82 (s, 3 H),

3.78 (s, 3 H), 3.77 (m, 2 H), 3.76 (s, 3 H), 3.71 (m, 2 H), 3.67 (s, 3 H), 3.42 (s, 3 H), 3.34 (d, J = 6.0 Hz, 1 H), 3.17 (s, 3 H).

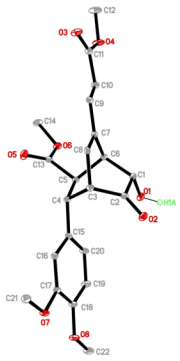
Ketone 53. Anhydrous HCl gas (1 atm, generated in another flask linked via rubber tubing by slowly adding concentrated H_2SO_4 to solid NaCl) was ducted into a round-bottom flask containing alcohol **50** (0.7 mg, 0.0015 mmol) and immersed in a 100 °C oil bath. A positive pressure of HCl was maintained in the reaction flask for 5 min, after which time no further HCl was added. The reaction was then maintained at 100 °C for an additional 40 min. Upon completion, the reaction contents were cooled to 23 °C, affording ketone **53** (0.6 mg, 99% yield) as a light yellow amorphous solid. Alternatively, the same reaction could be performed with alcohol **49** under the same conditions to afford ketone **53** in the same yield. **53**: R_f = 0.38 (silica gel, hexanes/EtOAc, 3:2); IR (film) ν_{max} 2953, 1715, 1631, 1518, 1436, 1264, 1170, 1101, 1026, 811 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, J = 16.0 Hz, 1 H), 6.86 (d, J = 1.6 Hz, 1 H), 6.83–6.77 (m, 2 H), 6.65 (d, J = 6.4 Hz, 1 H), 6.13 (d, J = 15.6 Hz, 1 H), 3.91 (app s, 1 H), 3.85 (s, 3 H), 3.85 (s, 3 H), 3.79 (s, 3 H), 3.71 (s, 3 H), 3.66 (s, 3 H), 3.57 (dd, J = 7.4, 2.2 Hz, 1 H), 3.49 (dd, J = 6.8, 2.0 Hz, 1 H), 3.37 (d, J = 3.6 Hz, 1 H), 3.24 (dd, J = 6.6, 2.6 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.0, 173.7, 167.1, 165.3, 148.9, 148.1, 140.9, 139.8, 135.4, 133.0, 120.3, 118.5, 111.2, 59.0, 56.4, 55.8, 52.3, 51.8, 48.3, 42.8, 39.9; HRMS (FAB) calcd for $C_{23}H_{26}O_8^+$ [M^+] 430.1628, found 430.1635.

Enol Triflate 54. KHMDS (0.5 M in toluene, 0.604 mL, 0.302 mmol, 1.3 equiv) was added dropwise to a solution of Tf_2NPh (0.216 g, 0.604 mmol, 2.6 equiv) and ketone

53 (0.100 g, 0.232 mmol, 1.0 equiv) in THF (5 mL) at –78 °C, and the reaction was stirred at –78 °C for 10 min. Upon completion, the reaction contents were quenched sequentially at –78 °C with water (10 mL) and saturated aqueous $NaHCO_3$ (10 mL). After warming to 23 °C, the mixture was extracted with EtOAc (2 × 20 mL). The combined organic layers were then washed with brine (20 mL), dried ($MgSO_4$), and concentrated. The resultant crude yellow solid was purified by flash column chromatography (silica gel, hexanes/EtOAc, 7:3) to afford enol triflate **54** (0.097 g, 74% yield) as a white amorphous solid. **54**: R_f = 0.37 (silica gel, hexanes/EtOAc, 3:2); IR (film) ν_{max} 2953, 1718, 1632, 1516, 1420, 1205, 1138, 1085, 1027, 878 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34 (d, *J* = 16.0 Hz, 1 H), 6.92 (d, *J* = 5.5 Hz, 1 H), 6.81 (d, *J* = 9.0 Hz, 1 H), 6.72-6.71 (m, 2 H), 6.00 (d, *J* = 16.0 Hz, 1 H), 4.28 (app s, 1 H), 3.88 (s, 1 H), 3.87 (s, 6 H), 3.77 (s, 3 H), 3.62 (s, 3 H), 3.56 (dd, *J* = 6.5, 2.0 Hz, 1 H), 3.44 (dd, *J* = 5.0, 2.0 Hz, 1 H), 3.04 (dd, *J* = 5.0, 2.5 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.9, 167.1, 149.7, 149.2, 148.3, 142.6, 140.5, 140.1, 133.8, 127.8, 119.3, 117.4, 111.4, 110.5, 58.4, 55.9, 55.8, 52.2, 51.7, 48.5, 47.9, 42.2; HRMS (FAB) calcd for $C_{24}H_{26}O_{10}F_3S^+$ [M^+] 563.1199, found 563.1191.

Hydroxyketone 56. Water (0.050 mL) and HCl (4.0 M in dioxane, 0.750 mL) were added sequentially to a solution of alcohol **50** (0.102 g, 0.220 mmol, 1.0 equiv) in THF (5 mL) at 23 °C to obtain a final acid concentration of 0.5 M. The resultant solution was stirred at 23 °C for 14 h. Upon completion, the reaction was poured into EtOAc (30 mL), washed with saturated aqueous $NaHCO_3$ (15 mL) and brine (15 mL), dried ($MgSO_4$), and concentrated. The resultant crude solid was purified by flash column

chromatography (silica gel, hexanes/EtOAc, 3:2) and crystallized from Et_2O to afford the desired hydroxyketone **56** (0.077 g, 84% yield) as a white crystalline solid. **56**: R_f = 0.51 (silica gel, hexanes/EtOAc, 3:7); m.p. = 170.0–170.3 °C; IR (film) ν_{max} 3727, 3456, 2947, 1730, 1629, 1518, 1436, 1312, 1194, 1173, 1026, 811 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, *J* = 15.6 Hz, 1 H), 6.78–6.77 (m, 3 H), 6.65 (dd, *J* = 6.4, 2.0 Hz, 1 H), 6.13 (d, *J* = 15.6 Hz, 1 H), 3.87 (dt, *J* = 3.2, 2.0 Hz, 1 H), 3.83 (s, 6 H), 3.78 (s, 3 H), 3.64 (s, 3 H), 3.61 (dd, *J* = 7.6, 2.4 Hz, 1 H), 3.57 (dd, *J* = 7.2, 2.0 Hz, 1 H), 3.28 (dd, *J* = 6.4, 2.4 Hz, 1 H), 3.23 (d, *J* = 2.0 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.2, 173.7, 167.2, 148.8, 148.1, 140.8, 140.2, 134.7, 132.3, 120.1, 118.6, 111.4, 111.1, 69.8, 55.7, 52.3, 51.8, 49.1, 41.8, 41.8; HRMS (FAB) calcd for $C_{22}H_{24}O_8^+$ [M^+] 416.1471, found 416.1489.



56 [X-ray structure]

Hydroxyketone 57. To a solution of alcohol **50** (0.026 g, 0.056 mmol, 1.0 equiv) in toluene (2 mL) at 0 °C was sequentially added water (0.050 mL) and HCl (4.0 M in dioxane, 0.100 mL). The resultant biphasic solution was then stirred vigorously at 0 °C for 20 h. Upon completion, the reaction contents were quenched with saturated aqueous

$NaHCO_3$ (10 mL), poured into water (10 mL) and extracted with EtOAc (3 × 15 mL). The combined organic layers were then washed with brine (10 mL), dried ($MgSO_4$), and concentrated. The resultant crude oil was purified by flash column chromatography (silica gel, hexanes/EtOAc, 1:1) to afford hydroxyketone **57** (0.020 g, 86% yield) as a colorless oil. **57**: R_f = 0.22 (silica gel, hexanes/EtOAc, 2:3); IR (film) ν_{max} 3727, 3475, 2947, 1730, 1631, 1517, 1435, 1313, 1237, 1172, 1146, 1026, 803 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, *J* = 15.6 Hz, 1 H), 6.93 (d, *J* = 7.2 Hz, 1 H), 6.83–6.79 (m, 3 H), 6.03 (d, *J* = 16.0 Hz, 1 H), 4.05 (app t, *J* = 2.2 Hz, 1 H), 3.88 (s, 3 H), 3.88–3.85 (m, 1 H) 3.85 (s, 3 H), 3.77 (s, 3 H), 3.64 (s, 3 H), 3.64–3.61 (m, 1 H), 3.57–3.54 (m, 2 H), 2.08 (d, *J* = 5.2 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.9, 171.8, 167.0, 149.0, 148.1, 140.8, 140.6, 135.1, 131.8, 119.5, 118.9, 111.9, 110.9, 72.2, 55.9, 52.6, 51.8, 49.3, 47.3, 46.3, 42.5; HRMS (FAB) calcd for $C_{22}H_{24}O_8$ [M^+] 416.1471, found 416.1489.

Computational Details for the Comparison of Hydroxyketone Isomers 56, 57 and Two Others. These calculations were performed at the DFT-B3LYP[2]/6-31+G(d) level in acetonitrile and THF continuum solvents. All four possible isomers were subjected to conformational searching within Macro-Model 6.0 using the OPLS 2001 force field.[3] The lowest energy structures for each possible isomer were then optimized in the gas phase at the B3LYP/6-31+G(d) level within Jaguar 7.0. Single-point solvation calculations, including first-shell correction terms and activation energy, were then

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[2] a) C. Lee, W. Yang, R. G. Parr, *Phys. Rev. B* **1988**, *37*, 785–789; b) A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 5648–5652; c) A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 1372–1377.

[3] W. L. Jorgensen, D. S. Maxwell, J. Tirado-Rives, J. *J. Am. Chem. Soc.* **1996**, *118*, 11225–11236.

performed in acetonitrile and THF continuum solvents. Isomer **56** was the most stable of the four by 1.7 kcal•mol^{-1}.

Ketone 58. AcOH (0.3 mL) and tetramethylammonium triacetoxyborohydride (0.146 g, 0.555 mmol, 3.0 equiv) were added sequentially to a solution of hydroxyketone **56** (0.077 g, 0.185 mmol, 1.0 equiv) in MeCN (3 mL) at 0 °C. The resultant solution was then warmed to 23 °C, and the reaction contents were stirred at 23 °C for 3 h. A second portion of tetramethylammonium triacetoxyborohydride (0.097 g, 0.370 mmol, 2.0 equiv) was then added, and stirring was continued at 23 °C for 2 h. Upon completion, the reaction contents were diluted with EtOAc (30 mL), poured into water (20 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were then washed with saturated aqueous $NaHCO_3$ (2 × 20 mL) and brine (20 mL), dried ($MgSO_4$), and concentrated. The resultant crude yellow solid was purified by flash column chromatography (silica gel, hexanes/EtOAc, 3:7) to afford the desired *anti*-disposed diol (0.066 g, 75% yield) as a white solid. With this step complete, Et_3N (0.110 mL, 0.789 mmol, 5.0 equiv) and TBSOTf (0.036 mL, 0.158 mmol, 1.0 equiv) were added sequentially to a solution of this newly formed *anti*-disposed diol (0.066 g, 0.158 mmol, 1.0 equiv) in CH_2Cl_2 (2 mL) at –78 °C. The reaction contents were then slowly warmed to 23 °C over 1 h with constant stirring. Upon completion, the reaction contents were diluted with EtOAc (30 mL), poured into water (20 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were then washed with saturated aqueous $NaHCO_3$ (20 mL) and brine (20 mL), dried ($MgSO_4$), and concentrated to afford the desired mono-silylated diol as a white solid which was used directly without any additional purification.

With this operation complete, solid $NaHCO_3$ (0.132 g, 1.58 mmol, 10 equiv) and Dess–Martin periodinane (0.134 g, 0.315 mmol, 2.0 equiv) were added sequentially in single portions to a solution of this newly formed intermediate in CH_2Cl_2 (2 mL) at 23 °C. The resultant suspension was stirred at 23 °C for 1 h. Upon completion, saturated aqueous Na_2SO_3 (2 mL) was added, and the resultant biphasic mixture was stirred vigorously for 1 h to quench any remaining oxidizing agents. The reaction contents were then diluted with EtOAc (30 mL), poured into water (20 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (20 mL) and brine (20 mL), dried ($MgSO_4$), and concentrated. The crude product was purified by flash column chromatography (silica gel, hexanes/EtOAc, 7:3) to afford ketone **58** (0.079 g, 94% yield over 2 steps, 71% overall yield from **56**) as a light yellow solid. **58**: R_f = 0.69 (silica gel, hexanes/EtOAc, 3:7); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (d, *J* = 15.5 Hz, 1 H), 6.88 (d, *J* = 6.5 Hz, 1 H), 6.85 (d, *J* = 8.5 Hz, 1 H), 6.77 (d, *J* = 7.5 Hz, 1 H), 6.02 (d, *J* = 15.5 Hz, 1 H), 3.95 (s, 1 H), 3.91 (d, *J* = 2.0 Hz, 1 H), 3.89 (s, 3 H), 3.88 (s, 3 H), 3.76 (s, 3 H), 3.65 (s, 3 H), 3.51 (dd, *J* = 7.0, 2.5 Hz, 1 H), 3.36 (dd, *J* = 6.8, 1.8 Hz, 1 H), 3.08 (dt, *J* = 6.0, 2.5 Hz, 1 H), 0.76 (s, 9 H), –0.08 (s, 3 H), –0.10 (s, 3 H).

Hydroxyketone 59. AcOH (0.012 mL, 0.196 mmol, 2.0 equiv) and TBAF (1.0 M in THF, 0.196 mL, 0.196 mmol, 2.0 equiv) were added sequentially in single portions to a solution of **58** (0.052 g, 0.098 mmol, 1.0 equiv) in THF (2 mL) at 23 °C, and the resultant solution was stirred at 23 °C for 2 h. Upon completion, the reaction contents were poured into EtOAc (20 mL) and washed with saturated aqueous NH_4Cl (15 mL) and brine (15 mL), dried ($MgSO_4$), and concentrated. The resultant crude yellow solid was

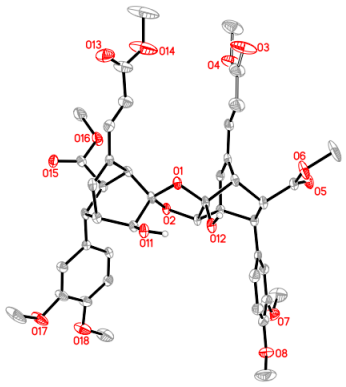
purified by flash column chromatography (silica gel, hexanes/EtOAc, 3:2) to afford recovered **58** (0.015 g) alongside hydroxyketone **59** (0.022 g, 54% yield, 76% yield based on recovered starting material) as a white amorphous solid. **59**: R_f = 0.32 (silica gel, hexanes/EtOAc, 3:7); IR (film) ν_{max} 3728, 3460, 1731, 1631, 1518, 1436, 1313, 1238, 1172, 1089, 1026, 808 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, *J* = 16.0 Hz, 1 H), 6.91 (d, *J* = 6.8 Hz, 1 H), 6.86–6.79 (m, 3 H), 6.06 (d, *J* = 15.6 Hz, 1 H), 4.03 (t, *J* = 1.6 Hz, 1 H), 3.98 (s, 1 H), 3.89 (s, 3 H), 3.88 (s, 3 H), 3.77 (s, 3 H), 3.64 (s, 3 H), 3.55 (dd, *J* = 7.2, 2.8 Hz, 1 H), 3.41 (dd, *J* = 7.2, 2.0 Hz, 1 H), 3.30 (dt, *J* = 6.4, 2.4 Hz, 1 H), 2.55 (d, *J* = 1.6 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.4, 172.2, 167.0, 149.3, 148.4, 141.6, 140.4, 133.0, 131.3, 119.1, 118.5, 111.7, 111.3, 66.9, 56.0, 52.7, 51.8, 46.1, 44.2, 41.6; HRMS (FAB) calcd for $C_{22}H_{25}O_8^+$ [$M+H^+$] 417.1549, found 417.1548.

Hydroxyketal 49. HCl (4.0 M in dioxane, 0.3 mL) was added to a solution of ketone **58** (0.027 g, 0.051 mmol, 1.0 equiv) in MeOH:$CH(OMe)_3$ (4:1, 2.5 mL) at 23 °C, and the resultant solution was stirred at 23 °C for 14 h. Upon completion, the reaction contents were concentrated directly, and the resultant crude yellow solid was purified by flash column chromatography (silica gel, hexanes/EtOAc, 3:2) to afford monomer **49** (0.022 g, 93% yield) as a light yellow solid. **49**: R_f = 0.45 (silica gel, hexanes/EtOAc, 3:7); IR (film) ν_{max} 3525, 2950, 1717, 1628, 1516, 1436, 1240, 1171, 1123, 1083, 1027, 733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, *J* = 15.6 Hz, 1 H), 6.90–6.83 (m, 3 H), 6.78 (d, *J* = 7.2 Hz, 1 H), 6.01 (d, *J* = 16.0 Hz, 1 H), 3.92 (dd, *J* = 6.6, 2.2 Hz, 1 H), 3.90 (s, 3 H), 3.77 (s, 3 H), 3.76 (app s, 1 H), 3.60 (s, 3 H), 3.53 (dd, *J* = 6.8, 2.0 Hz, 1 H), 3.32 (s, 3 H), 3.31 (s, 3 H), 3.26 (dd, *J* = 6.8, 2.8 Hz, 1 H), 2.92 (dt, *J* = 6.8, 2.6 Hz, 1 H),

2.86 (d, J = 6.4 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.8, 167.4, 149.0, 147.9, 142.5, 141.4, 136.8, 132.5, 120.0, 116.4, 111.8, 111.2, 101.9, 68.3, 55.9, 55.8, 52.1, 51.6, 49.8, 49.6, 48.2, 44.3, 41.6, 41.5; HRMS (FAB) calcd for $C_{24}H_{30}O_9^+$ [M^+] 462.1890, found 462.1889.

Unsymmetrical Dimer 64. Solid NaH (60% dispersion in mineral oil, 5.8 mg, 0.144 mmol, 10 equiv) was added in a single portion to a solution of hydroxyketone **59** (6.0 mg, 0.014 mmol, 1.0 equiv) in THF (0.5 mL) at 0 °C. The resultant slurry was then warmed to 23 °C and stirred for 20 min. Upon completion, the reaction mixture was carefully quenched with saturated aqueous NH_4Cl (10 mL), poured into water (10 mL) and extracted with EtOAc (3 × 15 mL). The combined organic layers were then washed with brine (10 mL), dried ($MgSO_4$), and concentrated. The resultant crude off-white solid was purified by flash column chromatography (silica gel, hexanes/EtOAc, 1:1) to afford unsymmetrical dimer **64** (6.0 mg, 99% yield) which was recrystallized from $CHCl_3$:Et_2O (2:1) as white needles. **64**: R_f = 0.17 (silica gel, hexanes/EtOAc, 3:7); m.p. = 189.0–189.3 °C; IR (film) ν_{max} 3426, 2904, 1720, 1632, 1518, 1436, 1311, 1238, 1196, 1027, 810 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (d, J = 16.0 Hz, 1 H), 7.28 (d, J = 16.5 Hz, 1 H), 7.00–6.97 (m, 2 H), 6.89 (d, J = 8.0 Hz, 1 H), 6.85–6.80 (m, 3 H), 6.71 (d, J = 6.5 Hz, 1 H), 6.59 (d, J = 6.0 Hz, 1 H), 5.96 (d, J = 15.5 Hz, 1 H), 5.80 (d, J = 15.5 Hz, 1 H), 5.43 (br s, 1 H), 4.14 (d, J = 3.0 Hz, 1 H), 3.88 (s, 6 H), 3.84 (s, 3 H), 3.79 (s, 3 H), 3.79 (s, 3 H), 3.79-3.76 (m, 2 H), 3.73 (s, 3 H), 3.58 (s, 3 H), 3.57 (s, 3 H), 3.53 (dd, J = 6.0, 2.0 Hz, 1 H), 3.45 (dd, J = 5.8, 2.7 Hz, 1 H), 3.34 (dd, J = 6.5, 2.0 Hz, 1 H), 3.25 (dd, J = 6.5, 2.5 Hz, 1 H), 3.16 (s, 1 H), 3.12 (dt, J = 6.5, 3.0 Hz, 1 H), 2.91 (dt, J = 6.5, 2.8 Hz, 1 H),

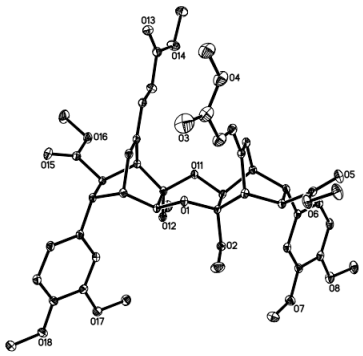
2.51 (br s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.4, 173.3, 167.2, 149.0, 148.0, 142.0, 141.5, 138.6, 138.2, 137.7, 136.9, 132.4, 132.2, 120.4, 119.6, 118.1, 117.5, 112.3, 111.4, 111.3, 111.2, 106.6, 80.7, 71.5, 55.9, 55.9, 55.8, 52.3, 51.6, 51.5, 47.4, 45.0, 44.4, 44.2, 43.9, 43.1, 42.9, 41.7; HRMS (FAB) calcd for $C_{44}H_{48}O_{16}^{+}$ [M^{+}] 832.2942, found 832.2975.



64 [X-ray structure]

Ketone 63. Alcohol **49** (3.5 mg, 0.008 mmol, 1.0 equiv) was heated neat under an argon atmosphere at 160 °C for 4 h. Upon completion, the reaction contents were cooled to 23 °C, concentrated and purified by flash column chromatography (silica gel, hexanes/EtOAc, 3:2) to afford recovered **49** (1.8 mg) alongside **63** (0.5 mg, 15% yield, 32% yield based on recovered starting material) as a colorless oil. **63**: R_f = 0.55 (silica gel, hexanes/EtOAc, 3:7); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, J = 16.0 Hz, 1 H), 6.79 (d, J = 8.4 Hz, 1 H), 6.70–6.64 (m, 3 H), 6.08 (d, J = 15.6 Hz, 1 H), 3.90 (s, 1 H), 3.85 (s, 6 H), 3.78 (s, 3 H), 3.71 (s, 3 H), 3.61 (dd, J = 6.2, 2.2 Hz, 1 H), 3.58 (s, 3 H), 3.54 (d, J = 2.8 Hz, 1 H), 3.49 (dd, J = 6.8, 2.4 Hz, 1 H), 3.01 (dd, J = 6.4, 2.0 Hz, 1 H); LRMS (FAB) calcd for $C_{23}H_{26}O_8^{+}$ [M^{+}] 430.2, found 430.1.

Helicterin A Core 65. BF_3•OEt_2 (0.057 mL, 0.450 mmol, 4.0 equiv) was added in a single portion under strictly anhydrous conditions to a solution of monomer **49** (0.052 g, 0.112 mmol, 1.0 equiv) in CH_2Cl_2 (1 mL) at 0 °C, and the reaction was stirred at 0 °C for 30 min. Upon completion, the reaction contents were quenched at 0 °C with saturated aqueous $NaHCO_3$ (10 mL), poured into water (10 mL) and extracted with EtOAc (2 × 20 mL). The combined organic layers were then washed with brine (20 mL), dried ($MgSO_4$), and concentrated. The resultant crude yellow solid was purified by flash column chromatography (silica gel, hexanes/EtOAc, 3:2) and recrystallized from Et_2O:hexanes (3:1) to afford dimer **65** (0.038 g, 79% yield) as a white crystalline solid. **65**: R_f = 0.51 (silica gel, hexanes/EtOAc, 3:7); m.p. = 215.0–215.8 °C; IR (film) ν_{max} 2950, 1705, 1632, 1517, 1435, 1362, 1234, 1170, 1145, 1026 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, *J* = 15.2 Hz, 2 H), 6.95–6.91 (m, 4 H), 6.80 (d, *J* = 8.4 Hz, 2 H), 5.88 (d, *J* = 15.6 Hz, 2 H), 3.88 (s, 6 H), 3.86 (s, 6 H), 3.80 (s, 6 H), 3.63 (d, *J* = 3.2 Hz, 2 H), 3.57 (s, 6 H), 3.29 (s, 6 H), 3.24 (dd, *J* = 6.4, 2.8 Hz, 2 H), 3.14 (dd, *J* = 6.4, 1.6 Hz, 2 H), 2.79 (dt, *J* = 6.4, 1.6 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.6, 167.7, 148.8, 147.7, 142.9, 139.7, 135.7, 133.0, 120.0, 116.1, 112.2, 111.1, 100.1, 69.1, 55.8, 52.1, 51.6, 49.0, 44.4, 43.2, 42.2, 40.1; HRMS (FAB) calcd for $C_{46}H_{52}O_{16}^+$ [M^+] 860.3255, found 860.3262.



65 [X-ray structure]

Hydroxyketone 67. $NaBH_4$ (0.022 g, 0.586 mmol, 1.5 equiv) was added in a single portion to a solution of Diels–Alder adduct **42** (0.680 g, 0.390 mmol, 1.0 equiv) in MeOH:THF (4:1, 7.5 mL) at –30 °C. The reaction was then stirred at –30 °C for 1 h. Upon completion, the reaction mixture was carefully quenched at –30 °C with 1 M aqueous HCl (15 mL), poured into water (10 mL) and extracted with EtOAc (3 × 30 mL). The combined organic layers were then washed with saturated aqueous $NaHCO_3$ (15 mL) and brine (15 mL), dried ($MgSO_4$), and concentrated. The resultant crude material was then purified by flash column chromatography (silica gel, toluene:acetone, 9:1) to afford the desired intermediate alcohol as a yellow solid. Next, this newly formed alcohol was taken up in MeCN (5 mL), and water (0.050 mL) and HCl (4.0 M in dioxane, 0.750 mL) were then added sequentially at 23 °C to obtain a final acid concentration of 0.5 M. The resultant solution was stirred at 23 °C for 14 h. Upon completion, the reaction contents were diluted with EtOAc (30 mL), poured into water (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were then washed with saturated aqueous $NaHCO_3$ (15 mL) and brine (15 mL), dried ($MgSO_4$), and concentrated. The resultant

crude material was purified by flash column chromatography (silica gel, toluene:acetone, 19:1) to afford **67** (0.370 g, 56% yield over 2 steps) as a light yellow solid. **67**: R_f = 0.44 (silica gel, toluene:acetone, 9:1); $[\alpha]^{25}_D$ = +49.2° (*c* = 0.19, $CHCl_3$); IR (film) ν_{max} 3628, 2928, 1734, 1513, 1324, 1161, 1110, 1066, 1017, 824 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.63–7.43 (m, 24 H), 7.32 (d, *J* = 15.6 Hz, 1 H), 6.86–6.78 (m, 5 H), 6.70–6.65 (m, 3 H), 6.61 (dd, *J* = 6.4, 1.2 Hz, 1 H), 6.53 (dd, *J* = 8.4, 2.0 Hz, 1 H), 6.21 (d, *J* = 15.6 Hz, 1 H), 5.30 (dd, *J* = 7.6, 5.2 Hz, 1 H), 5.15–5.01 (m, 13 H), 3.88 (d, *J* = 2.8 Hz, 1 H), 3.69 (d, *J* = 3.6 Hz, 1 H), 3.66 (s, 3 H), 3.53 (s, 3 H), 3.51 (app d, *J* = 1.6 Hz, 1 H), 3.42 (dd, *J* = 7.6, 2.4 Hz, 1 H), 3.25 (dd, *J* = 6.4, 2.0 Hz, 1 H), 3.14 (dd, *J* =14.4, 5.2 Hz, 1 H), 3.07 (dd, *J* = 14.4, 8.0 Hz, 1 H), 3.00 (dd, *J* = 14.4, 4.4 Hz, 1 H), 2.89 (dd, *J* = 14.8, 8.4 Hz, 1 H), 2.71 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.6, 172.6, 169.9, 169.3, 165.9, 148.5, 147.9, 147.8, 147.7, 141.4, 141.0, 140.4, 134.9, 133.3, 130.8, 130.3, 129.9, 129.5, 129.2, 127.3, 127.3, 127.2, 127.1, 125.8, 125.5, 122.7, 122.5, 122.2, 121.3, 118.7, 116.2, 116.0, 115.0, 114.8, 77.2, 73.3, 73.0, 70.6, 70.4, 70.4, 70.1, 54.7, 52.3, 49.0, 41.8, 41.5, 36.9, 36.7; HRMS (FAB) calcd for $C_{86}H_{67}F_{18}O_{16}^+$ [M + H^+] 1697.41, found 1697.77.

Hydroxyketal 68. AcOH (0.2 mL) and tetramethylammonium triacetoxyborohydride (0.239 g, 0.912 mmol, 3.0 equiv) were added sequentially to a solution of hydroxyketone **67** (0.515 g, 0.303 mmol, 1.0 equiv) in MeCN (10 mL) at 0 °C. The resultant solution was then warmed to 23 °C, and the reaction contents were stirred at 23 °C for 10 h. A second portion of tetramethylammonium triacetoxyborohydride (0.159 g, 0.606 mmol, 2.0 equiv) was then added, and stirring was continued at 23 °C for 4 h. Upon completion, the reaction contents were diluted with EtOAc (20 mL), poured into water (15 mL) and extracted with EtOAc (2 × 20 mL). The

combined organic layers were then washed with saturated aqueous $NaHCO_3$ (2 × 20 mL) and brine (20 mL), dried ($MgSO_4$), and concentrated. The resultant crude orange solid was purified by flash column chromatography (silica gel, toluene:acetone, 9:1) to afford recovered **67** (0.162 g) alongside the desired *anti*-disposed diol product (0.270 g, 52% yield, 76% yield based on recovered starting material) as a colorless, glassy solid. Next, Et_3N (0.082 mL, 0.585 mmol, 5.0 equiv) and TBSOTf (0.028 mL, 0.123 mmol, 1.05 equiv) were added sequentially to a solution of a portion of this newly formed *anti*-disposed diol (0.199 g, 0.117 mmol, 1.0 equiv) in CH_2Cl_2 (3 mL) at –78 °C. The reaction was then slowly warmed to 23 °C over 1 h with constant stirring. Upon completion, the reaction contents were diluted with EtOAc (20 mL), poured into water (15 mL) and extracted with EtOAc (2 × 20 mL). The combined organic layers were then washed with saturated aqueous $NaHCO_3$ (20 mL) and brine (20 mL), dried ($MgSO_4$), and concentrated to afford the desired mono-silylated diol as a white solid which was used directly without any additional purification. With this operation complete, $NaHCO_3$ (0.986 g, 1.17 mmol, 10 equiv) and Dess–Martin periodinane (0.074 g, 0.176 mmol, 1.5 equiv) were added sequentially in single portions to a solution of this newly formed intermediate in CH_2Cl_2 (2 mL) at 23 °C. The resultant suspension was then stirred at 23 °C for 1 h. Upon completion, saturated aqueous Na_2SO_3 (2 mL) was added and the resultant biphasic mixture was stirred vigorously for 1 h to quench any remaining oxidizing agents. The reaction contents were then diluted with EtOAc (20 mL), poured into water (15 mL) and extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (2 × 20 mL) and brine (20 mL), dried ($MgSO_4$), and concentrated to afford the desired crude ketone as a light yellow solid which was carried

forward without any additional purification. Finally, HCl (0.3 mL) was added to a solution of the newly formed crude ketone in MeOH:$CH(OMe)_3$ (4:1, 2.5 mL) at 23 °C, and the resultant solution was stirred at 23 °C for 14 h. Upon completion, the reaction contents were diluted with EtOAc (20 mL), poured into water (15 mL) and extracted with EtOAc (2 × 20 mL). The combined organic layers were then washed with saturated aqueous $NaHCO_3$ (20 mL) and brine (20 mL), dried ($MgSO_4$), and concentrated. The resultant crude yellow solid was purified by flash column chromatography (silica gel, toluene:acetone, 19:1) to afford the desired alcohol **68** (0.148 g, 73% yield over the final 3 steps, 43% overall from **67**) as a light yellow solid. **68**: R_f = 0.28 (silica gel, toluene:acetone, 9:1); $[\alpha]^{25}_D$ = +14.2° (*c* = 0.38, $CHCl_3$); IR (film) ν_{max} 3727, 2953, 1743, 1715, 1623, 1513, 1420, 1324, 1161, 1118, 1066, 824 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.63–7.35 (m, 25 H), 6.93–6.73 (m, 8 H), 6.64–6.61 (m, 2 H), 6.41 (dd, *J* = 8.0, 1.6 Hz, 1 H), 6.14 (d, *J* = 15.6 Hz, 1 H), 5.28 (dd, *J* = 7.2, 5.6 Hz, 1 H), 5.16–4.98 (m, 13 H), 3.82 (app d, *J* = 6.4 Hz, 1 H), 3.72 (s, 1 H), 3.65 (s, 3 H), 3.57 (s, 3 H), 3.54 (app d, *J* = 7.2 Hz, 1 H), 3.26 (s, 3 H), 3.17 (s, 3 H), 3.10 (dd, *J* = 6.8, 4.0 Hz, 1 H), 3.00–2.87 (m, 5 H), 2.85 (d, *J* = 6.4 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.8, 170.0, 169.5, 166.2, 148.7, 148.5, 148.3, 147.7, 147.6, 147.5, 143.3, 141.4, 141.1, 141.0, 137.3, 133.8, 130.3, 129.9, 129.6, 129.4, 129.1, 127.3, 127.2, 127.1, 127.1, 125.8, 125.4, 122.7, 122.7, 122.2, 121.0, 116.5, 116.2, 115.9, 115.4, 114.9, 114.7, 101.9, 77.2, 73.0, 70.5, 70.4, 70.3, 68.6, 52.2, 49.9, 49.7, 47.3, 44.5, 41.7, 41.1, 37.0, 36.6; HRMS (FAB) calcd for $C_{88}H_{72}F_{18}O_{17}^+$ [M^+] 1742.45, found 1742.67.

Helicterin B (2). BF_3•OEt_2 (0.033 mL, 0.262 mmol, 8.0 equiv) was added in a single portion under rigorously anhydrous conditions to a solution of monomer **68** (0.057 g, 0.033 mmol, 1.0 equiv) in CH_2Cl_2 (0.2 mL) at 0 °C, and the resultant solution was stirred at 0 °C for 30 min. Upon completion, the reaction contents were quenched at 0 °C with saturated aqueous $NaHCO_3$ (10 mL) and extracted with EtOAc (2 × 15 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), and concentrated. The resultant crude yellow solid was purified by flash column chromatography (silica gel, toluene:acetone, 19:1) to afford protected helicterin A (0.038 g, 67% yield) as a white amorphous solid. Next, BBr_3 (1.0 M in CH_2Cl_2, 0.126 mL, 0.126 mmol, 18 equiv) was added in a single portion to a solution of protected helicterin A (0.024 g, 0.007 mmol, 1.0 equiv) in CH_2Cl_2 (0.5 mL) at –78 °C, and the resultant solution was stirred at –78 °C for 45 minutes. Upon completion, the reaction mixture was quenched at –78 °C with saturated aqueous $NaHCO_3$ (1 mL), re-acidified with 1.0 M HCl (1 mL), warmed to 23 °C, poured into water (10 mL) and extracted with EtOAc (2 × 10 mL). The combined organic layers were then washed with brine (10 mL), dried ($MgSO_4$), and concentrated. The crude yellow solid was then triturated with CH_2Cl_2 (3 × 1 mL) to afford helicterin B (**2**) (8.0 mg, 76% yield) as a white solid. The natural product was further purified by preparative TLC (silica gel, CH_2Cl_2:MeOH, 4:1). [Note: some decomposition was observed on silica gel]. **2**: R_f = 0.05 (silica gel, CH_2Cl_2:MeOH, 4:1); $[\alpha]^{25}_D$ = +6.5° (*c* = 0.15, CH_3OH); IR (film) ν_{max} 3412, 2924, 1730, 1701, 1627, 1521, 1442, 1363, 1284, 1174, 1117, 816 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 7.26 (d, *J* = 15.5 Hz, 1 H), 7.25 (d, *J* = 15.5 Hz, 1 H), 6.88 (d, *J* = 1.0 Hz, 1 H), 6.82 (d, *J* = 2.5 Hz, 1 H), 6.73 (d, *J* = 8.5 Hz, 1 H), 6.71 (d, *J* = 8.5 Hz, 1 H), 6.71 (br s, 2 H), 6.70 (d, *J* = 7.0

Hz, 1 H), 6.695 (d, *J* = 8.0 Hz, 1 H), 6.64–6.58 (m, 6 H), 6.53 (d, *J* = 1.5 Hz, 1 H), 6.39 (dd, *J* = 8.0, 1.0 Hz, 1 H), 6.34 (d, *J* = 5.0 Hz, 1 H), 6.32 (dd, *J* = 7.8, 1.7 Hz, 1 H), 6.29 (d, *J* = 6.0 Hz, 1 H), 5.93 (d, *J* = 15.5 Hz, 1 H), 5.92 (d, *J* = 15.5 Hz, 1 H), 5.28 (dd, *J* = 8.3, 4.3 Hz, 1 H), 5.27 (dd, *J* = 8.8, 4.3 Hz, 1 H), 4.99 (dd, *J* = 7.5, 4.5 Hz, 1 H), 4.97 (dd, *J* = 8.0, 4.0 Hz, 1 H), 3.83 (d, *J* = 2.0 Hz, 1 H), 3.73 (s, 3 H), 3.71 (s, 3 H), 3.58 (br d, *J* = 1.5 Hz, 2 H), 3.54 (s, 3 H), 3.53 (s, 3 H), 3.48 (dd, *J* = 6.8, 1.8 Hz, 1 H), 3.28 (br s, 1 H), 3.24 (s, 3 H), 3.12–3.08 (m, 3 H), 3.03 (dd, *J* = 14.5, 8.5 Hz, 2 H), 2.99 (dd, *J* = 6.2, 3.7 Hz, 2 H), 2.93 (dd, *J* = 14.8, 3.8 Hz, 1 H), 2.89 (dd, *J* = 14.5, 4.5 Hz, 1 H), 2.80 (dd, *J* = 13.8, 8.7 Hz, 1 H), 2.80 (dd, *J* = 14.0, 8.0 Hz, 1 H), 2.75–2.72 (m, 1 H), 2.66 (dt, *J* = 6.5, 2.8 Hz, 1 H); ^{13}C NMR (75 MHz, CD_3OD) δ 175.8, 175.3, 170.3, 170.3, 172.3, 172.2, 169.3, 169.3, 147.1, 147.,1 146.9, 146.9, 146.9, 146.9, 146.8, 146.6, 146.1, 146.1, 146.1, 146.0, 146.0, 145.8, 143.3, 141.7, 139.3, 137.8, 134.4, 134.3, 129.6, 129.6, 129.3, 129.2, 122.7, 122.6, 122.6, 122.6, 121.7, 121.6, 118.2, 118.0, 117.9, 117.9, 117.4, 117.4, 117.4, 117.2, 117.2, 117.2, 117.2, 117.2, 117.2, 117.2, 102.4, 98.8, 75.8, 75.6, 75.5, 75.4, 71.1, 70.9, 53.5, 53.5, 53.5, 53.5, 50.0, 50.0, 48.0, 46.9, 46.9, 45.5, 45.1, 44.8, 43.8, 42.0, 38.6, 38.6, 38.4, 38.4. All spectroscopic data for this synthetic material match those reported for natural helicterin B (**2**).[4]

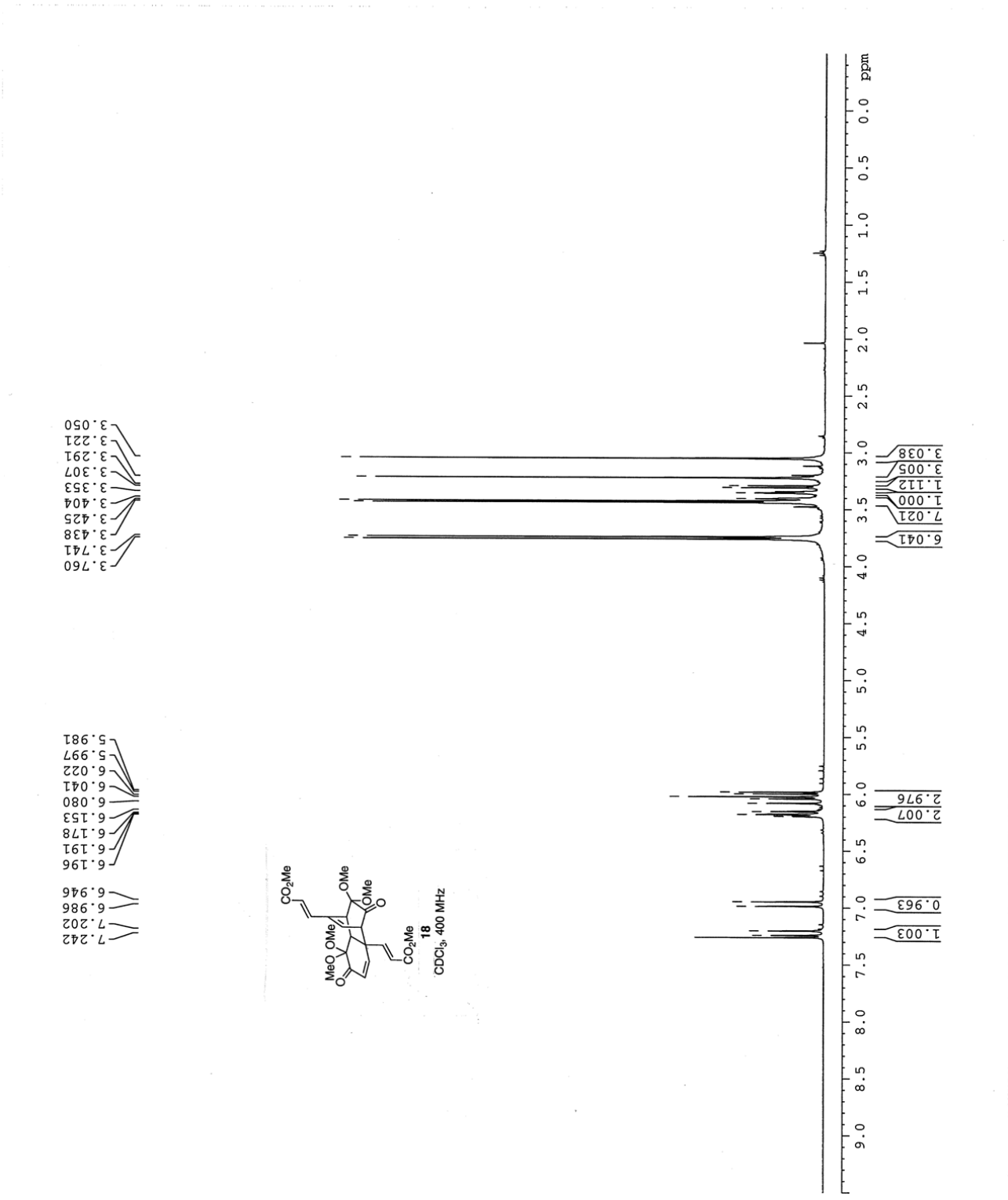
Helisterculin A (4). A solution of **41** (0.190 g, 0.129 mmol, 1.0 equiv) and dienophile **38** (0.441 g, 0.864 mmol, 6.7 equiv) in mesitylene (1.0 mL) was carefully degassed 3 times using the freeze-pump-thaw method, and then sealed under argon in a tube equipped with a magnetic stir bar. The reaction mixture was then stirred at 223 °C

[4] Y. Tezuka, M. Terazono, T. I. Kusumoto, Y. Hatanaka, S. Kadota, M. Hattori, T. Namba, T. Kikuchi, K. Tanaka, S. Supriyatna, *Helv. Chim. Acta* **2000**, *83*, 2908–2919.

(oil bath) for 35 min. After cooling the reaction contents to 23 °C, the reaction mixture was purified directly by flash column chromatography (silica gel, hexanes/EtOAc:CH_2Cl_2, 8:1:1→5:4:1) to provide recovered **38** (1.22 g) alongside the desired Diels–Alder adduct (0.142 g, 44% yield, 78% based on recovered starting material) as a light yellow solid. Next, a portion of this newly formed ketone (0.128 g, 0.103 mmol, 1.0 equiv) was taken up in MeOH:THF (4:1, 5.0 mL) and $NaBH_4$ (6.0 mg, 0.154 mmol, 1.5 equiv) was added in a single portion at 0 °C. The reaction was then stirred at 0 °C for 30 minutes. Upon completion, the reaction mixture was carefully quenched at 0 °C with 1 M aqueous HCl (10 mL), poured into water (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were then washed with saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL), dried ($MgSO_4$), and concentrated. The resultant crude material was then purified by flash column chromatography (silica gel, hexanes/EtOAc, 3:2) to afford the desired intermediate alcohol (0.111 g, 79% yield) as a yellow solid. Next, this newly formed alcohol was taken up in MeCN (2 mL) and a solution of HCl (4.0 M in dioxane, 0.133 mL) was then added at 23 °C to obtain a final acid concentration of 0.2 M. The resultant solution was stirred at 23 °C for 2 h. Upon completion, the reaction contents were diluted with EtOAc (10 mL), poured into water (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were then washed with saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL), dried ($MgSO_4$), and concentrated. The resultant crude material was purified by flash column chromatography (silica gel, hexanes/EtOAc, 3:2) to afford the desired hydroxyketone (0.037 g, 33% yield) as a white amorphous solid. Finally, BBr_3 (1.0 M in CH_2Cl_2, 0.140 mL, 0.140 mmol, 8.0 equiv) was added to a solution this newly

formed intermediate (0.021 g, 0.017 mmol, 1.0 equiv) in CH_2Cl_2 (0.5 mL) at –78 °C, and the reaction was stirred at –78 °C for 30 min. Upon completion, the reaction mixture was quenched at –78 °C with water (1 mL), warmed to 23 °C, poured into water (10 mL) and extracted with EtOAc (2 × 10 mL). The combined organic layers were then washed with brine (10 mL), dried ($MgSO_4$), and concentrated. The resultant crude yellow solid was triturated with CH_2Cl_2 (3 × 1 mL) to afford a 1:1 diastereomeric mixture of helisterculin A (**4**, 8.8 mg, 92% yield) as a white solid. [Note: some decomposition was observed on silica gel]. **4**: R_f = 0.50 (silica gel, CH_2Cl_2:MeOH, 4:1); IR (film) ν_{max} 3412, 2918, 1701, 1627, 1521, 1438, 1284, 1165, 1066, 816 cm^{-1}; ^1H NMR (400 MHz, acetone-d_6) δ 7.64 (br s, 4 H), 7.34 (d, *J* = 15.6 Hz, 1 H), 6.85 (dd, *J* = 7.0, 1.8 Hz, 1 H), 6.82 (br s, 1 H), 6.79 (d, *J* = 2.0 Hz, 1 H), 6.74 (d, *J* = 8.0 Hz, 1 H), 6.70 (d, *J* = 8.0 Hz, 1 H), 6.66 (dd, *J* = 8.2, 1.8 Hz, 1 H), 6.61 (dd, *J* = 8.0, 2.0 Hz, 1 H), 6.12 (d, *J* = 15.6 Hz, 1 H), 5.18 (dd, *J* = 8.6, 4.6 Hz, 1 H), 3.82 (d, *J* = 2.4 Hz, 1 H), 3.78 (d, *J* = 3.2 Hz, 1 H), 3.68 (s, 3 H), 3.59 (s, 3 H), 3.56 (dd, *J* = 7.2, 2.0 Hz, 1 H), 3.46 (dd, *J* = 7.2, 2.4 Hz, 1 H), 3.17 (dd, *J* = 6.6, 2.6 Hz, 1 H), 3.07 (dd, *J* = 14.6, 4.6 Hz, 1 H), 3.00 (dd, *J* = 14.2, 5.4 Hz, 1 H); ^{13}C NMR (75 MHz, acetone-d_6) δ 207.3, 175.1, 171.0, 166.9, 146.2, 146.1, 145.3, 143.5, 141.6, 138.1, 134.1, 129.0, 121.9, 121.1, 118.4, 117.7, 116.7, 116.4, 116.3, 74.5, 70.2, 57.7, 52.7, 52.7, 49.6, 44.2, 43.5, 37.8; HRMS (FAB) calcd for $C_{29}H_{29}O_{12}$ [$M+H^+$] 569.1659, found 569.1656. All spectroscopic data for this synthetic material match those reported for natural helisterculin A (**4**).[5]

[5] Y. Tezuka, M. Terazono, T. I. Kusumoto, Y. Kawashima, Y. Hatanaka, S. Kadota, M. Hattori, T. Namba, T. Kikuchi, K. Tanaka, S. Supriyatna, *Helv. Chim. Acta* **1999**, *82*, 408–417.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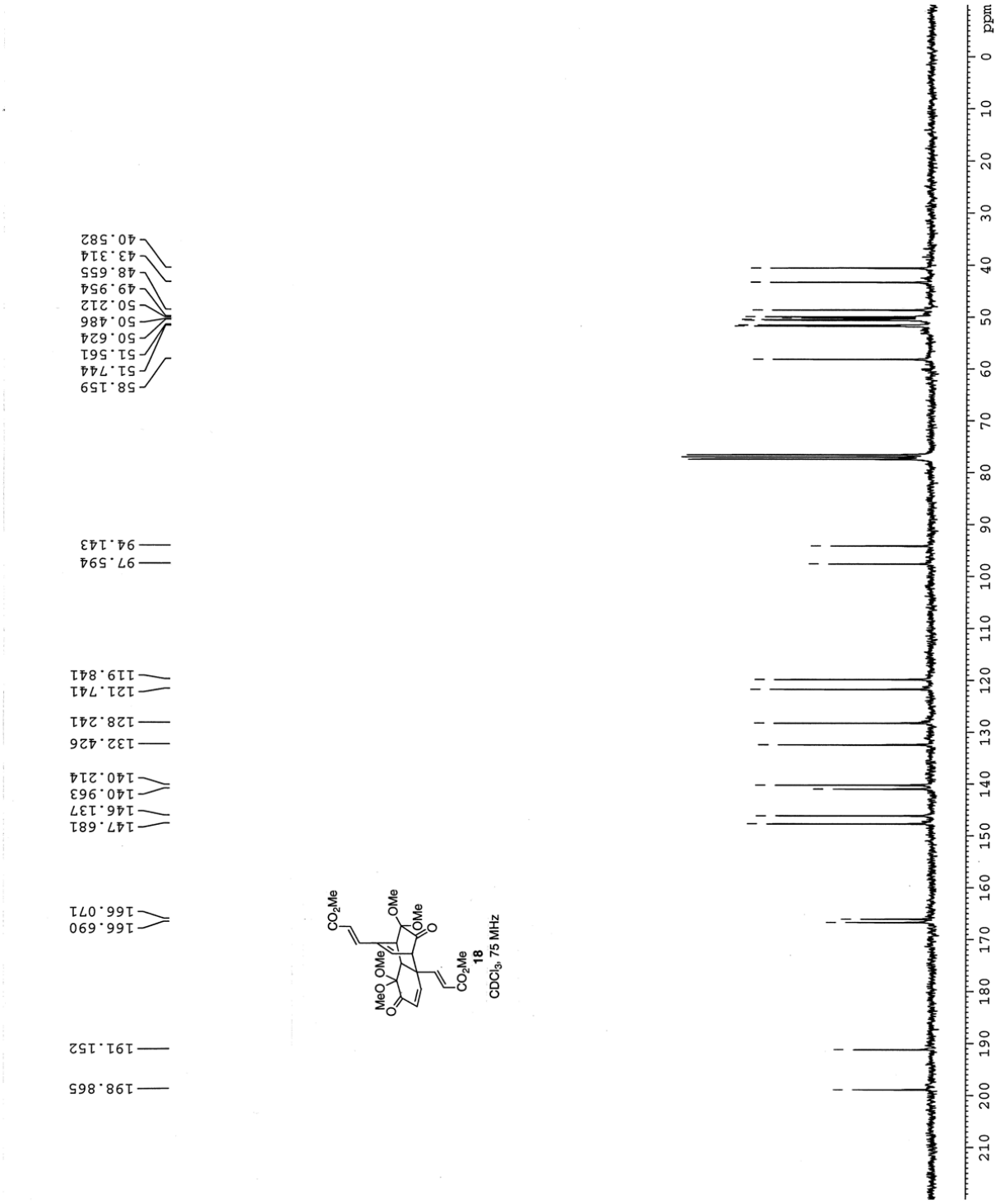
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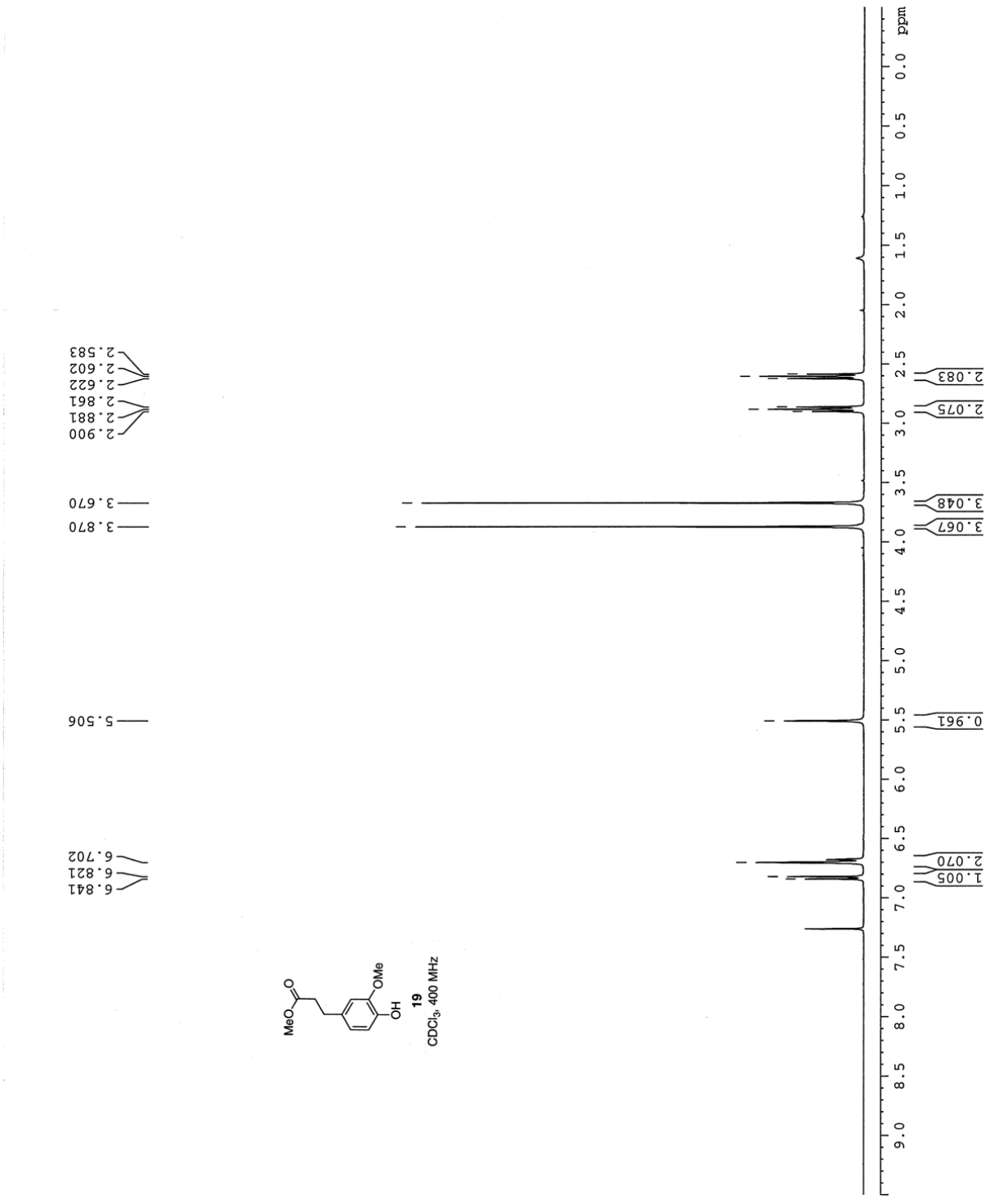
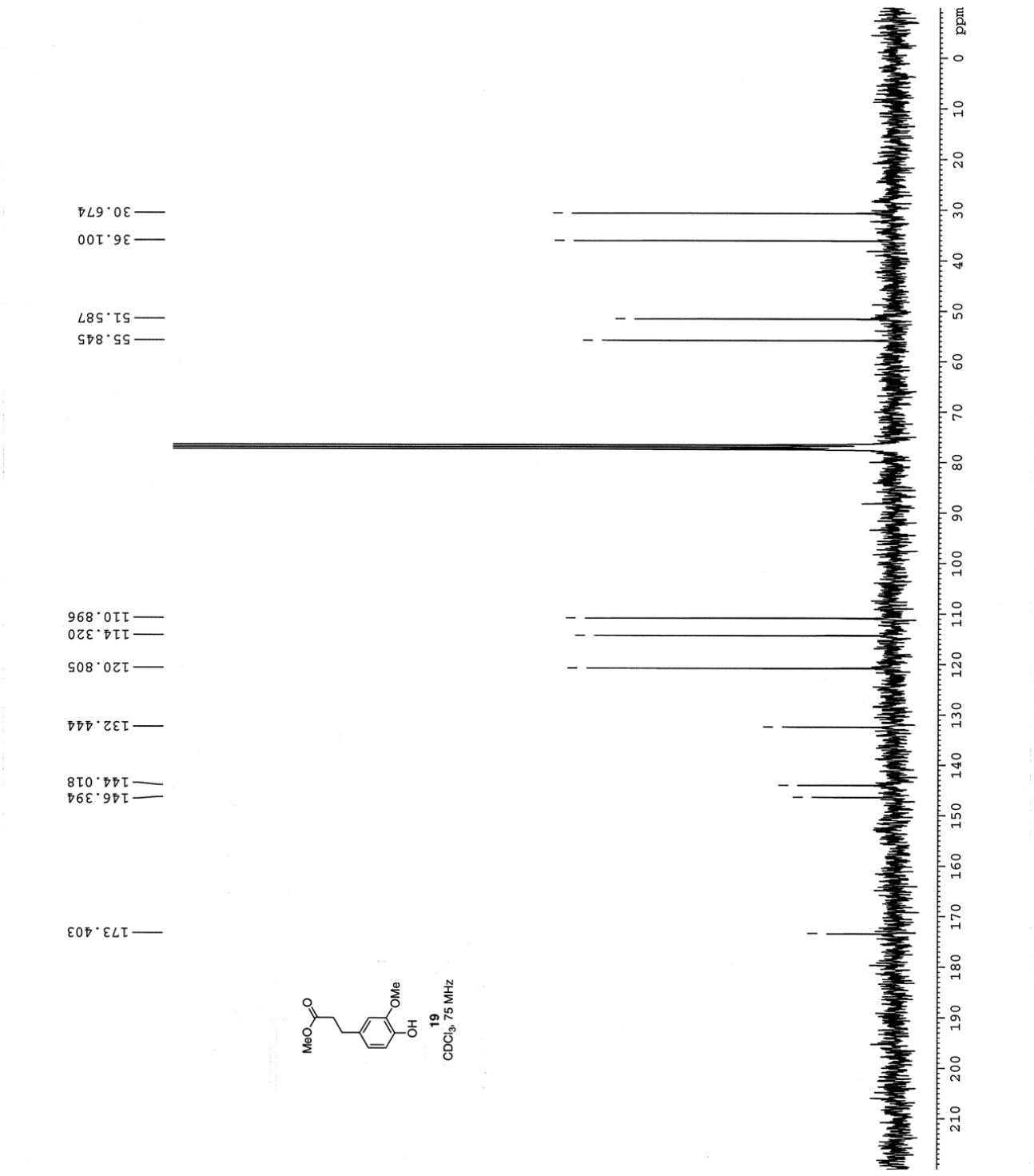
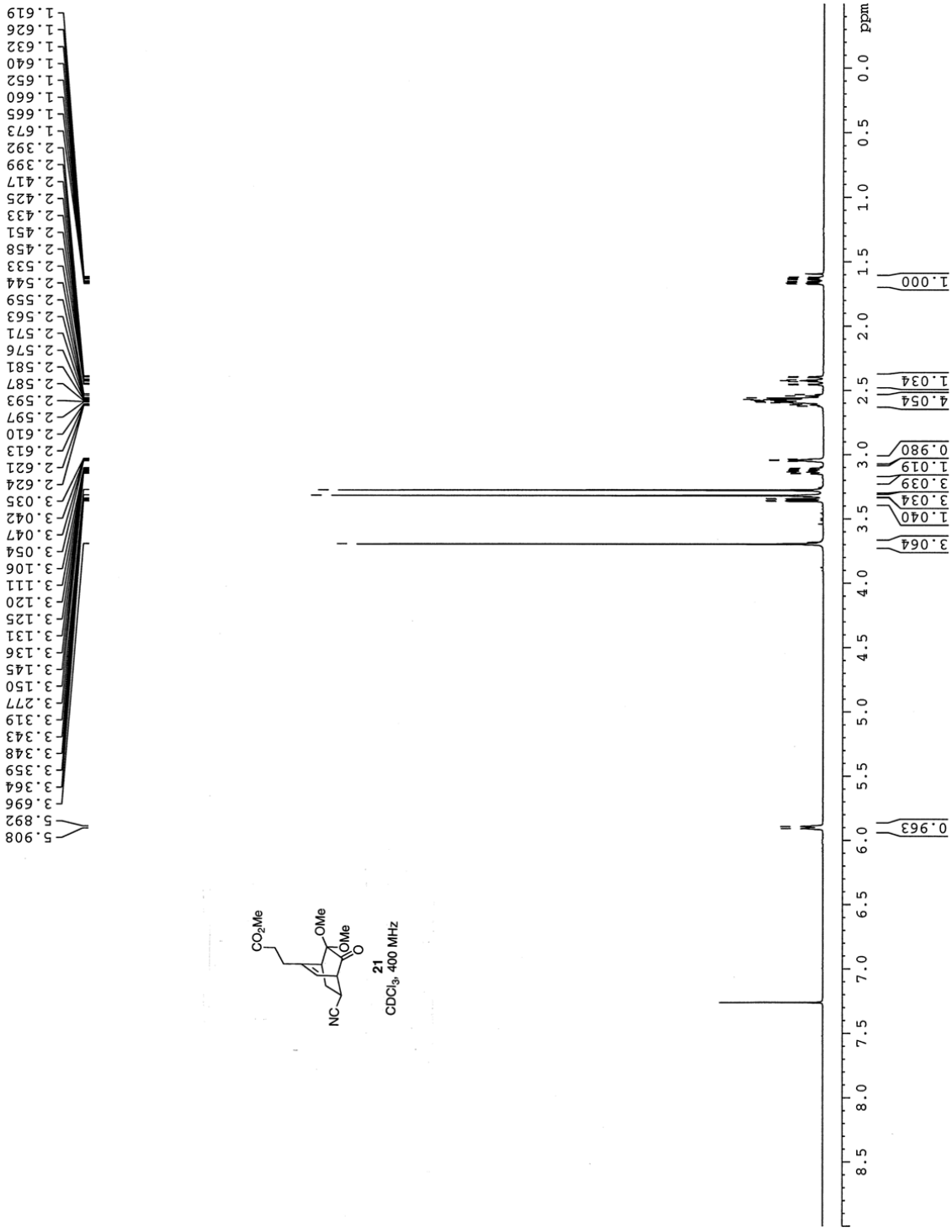
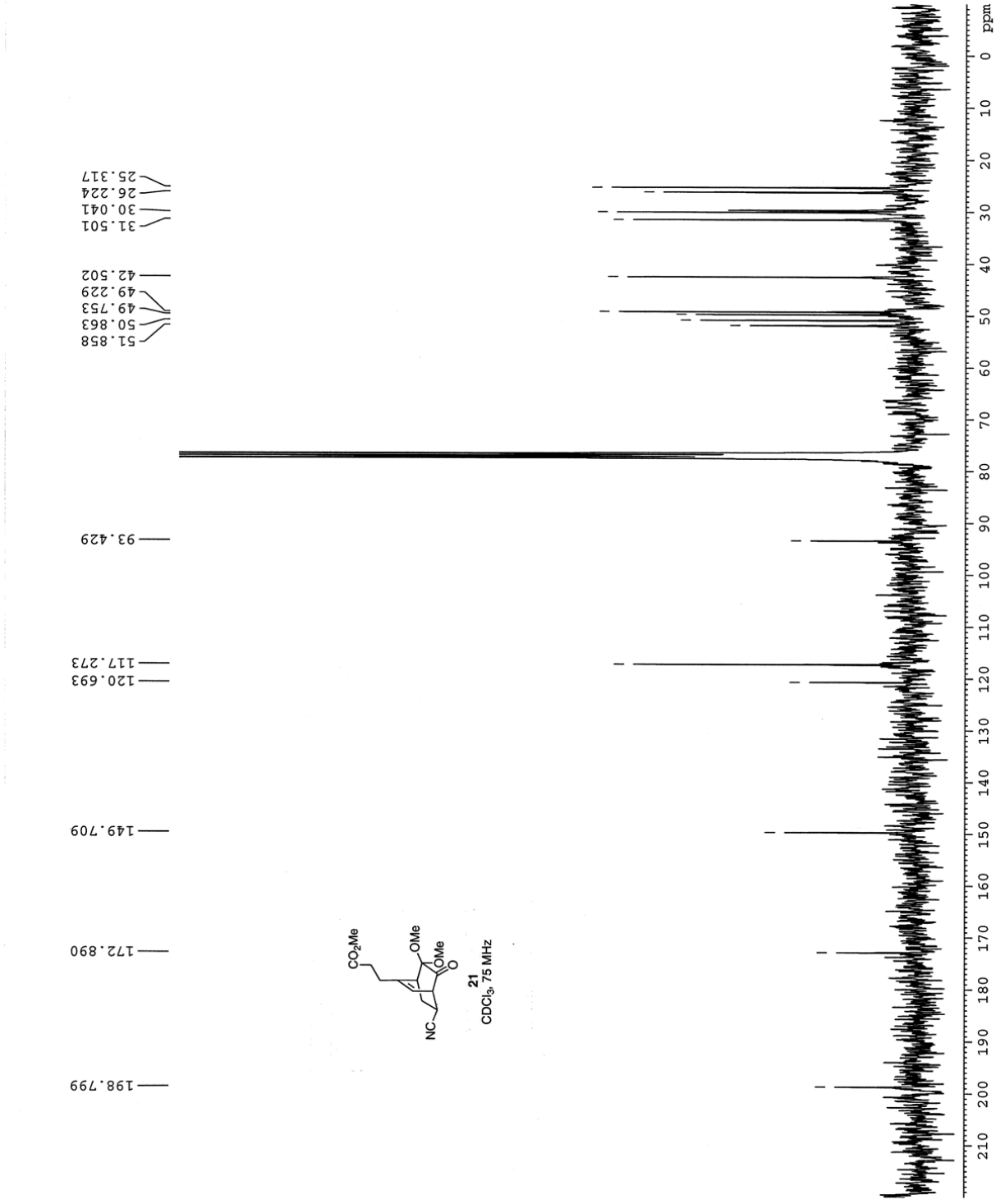
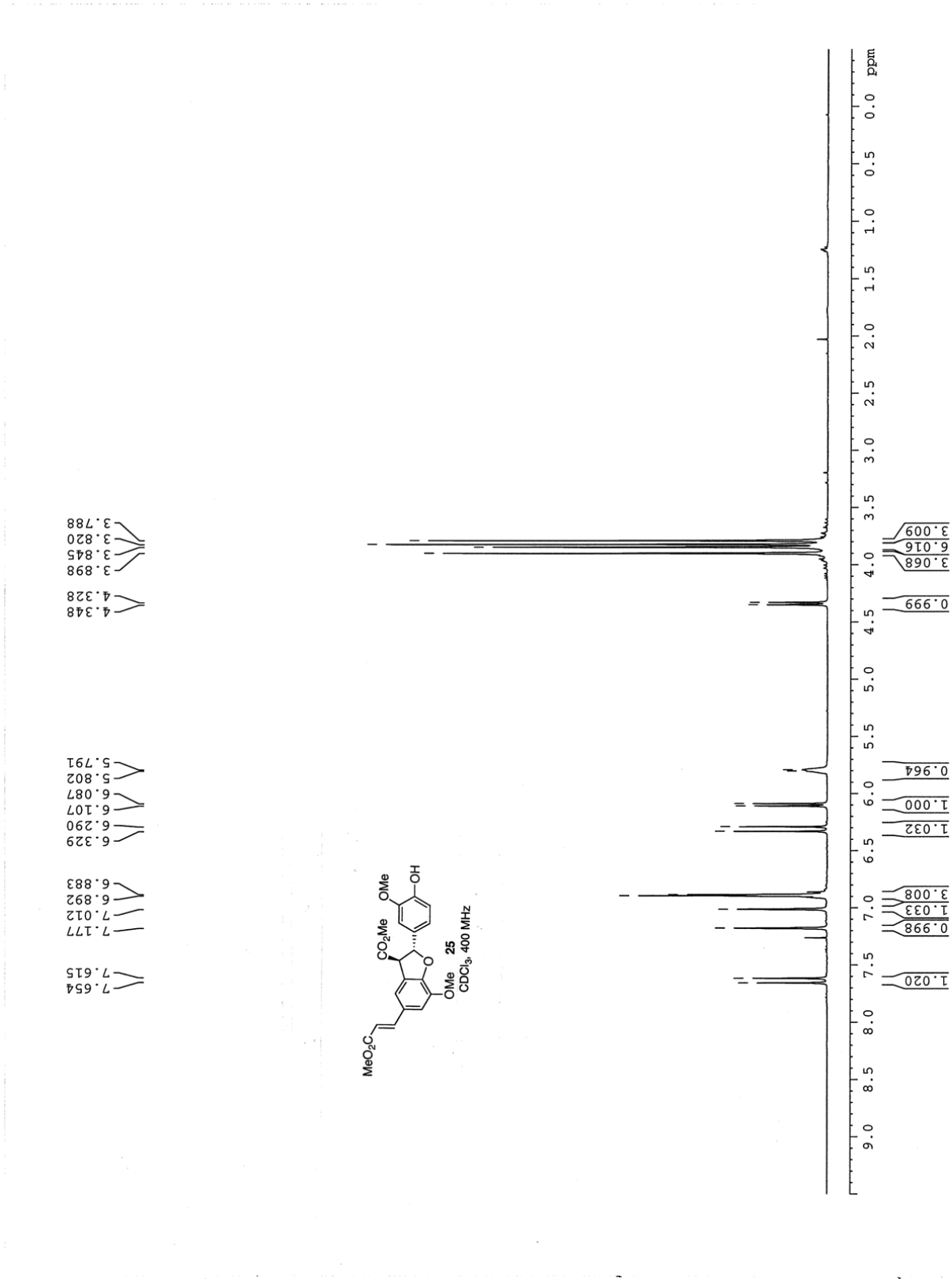
200
210

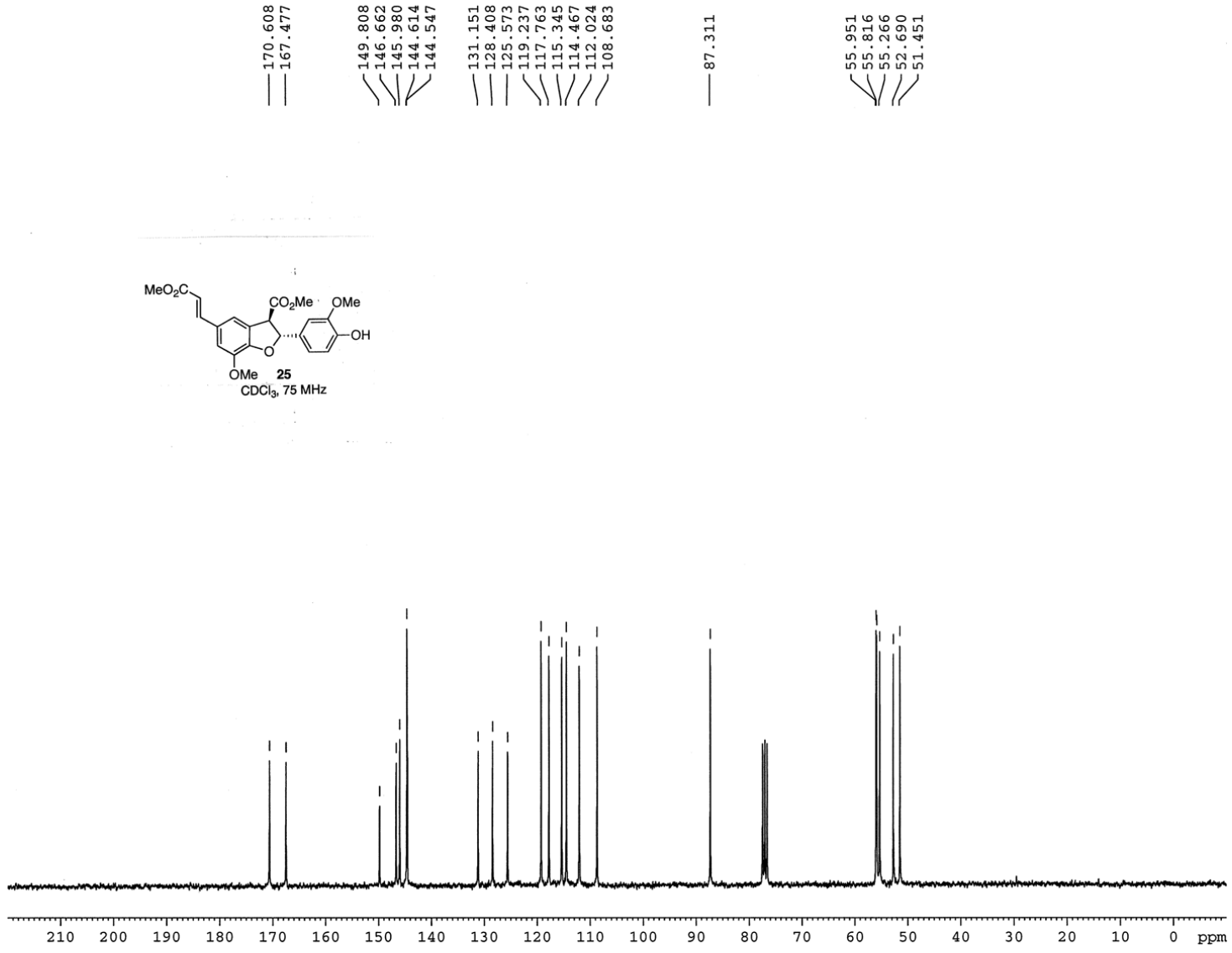

MeO
O
OMe
OH
19
$CDCl_3$, 400 MHz
6.841
6.821
6.702
5.506
3.870
3.670
2.900
2.881
2.861
2.622
2.602
2.583
1.005
2.070
0.961
2.083
2.075
3.048
3.067
ppm

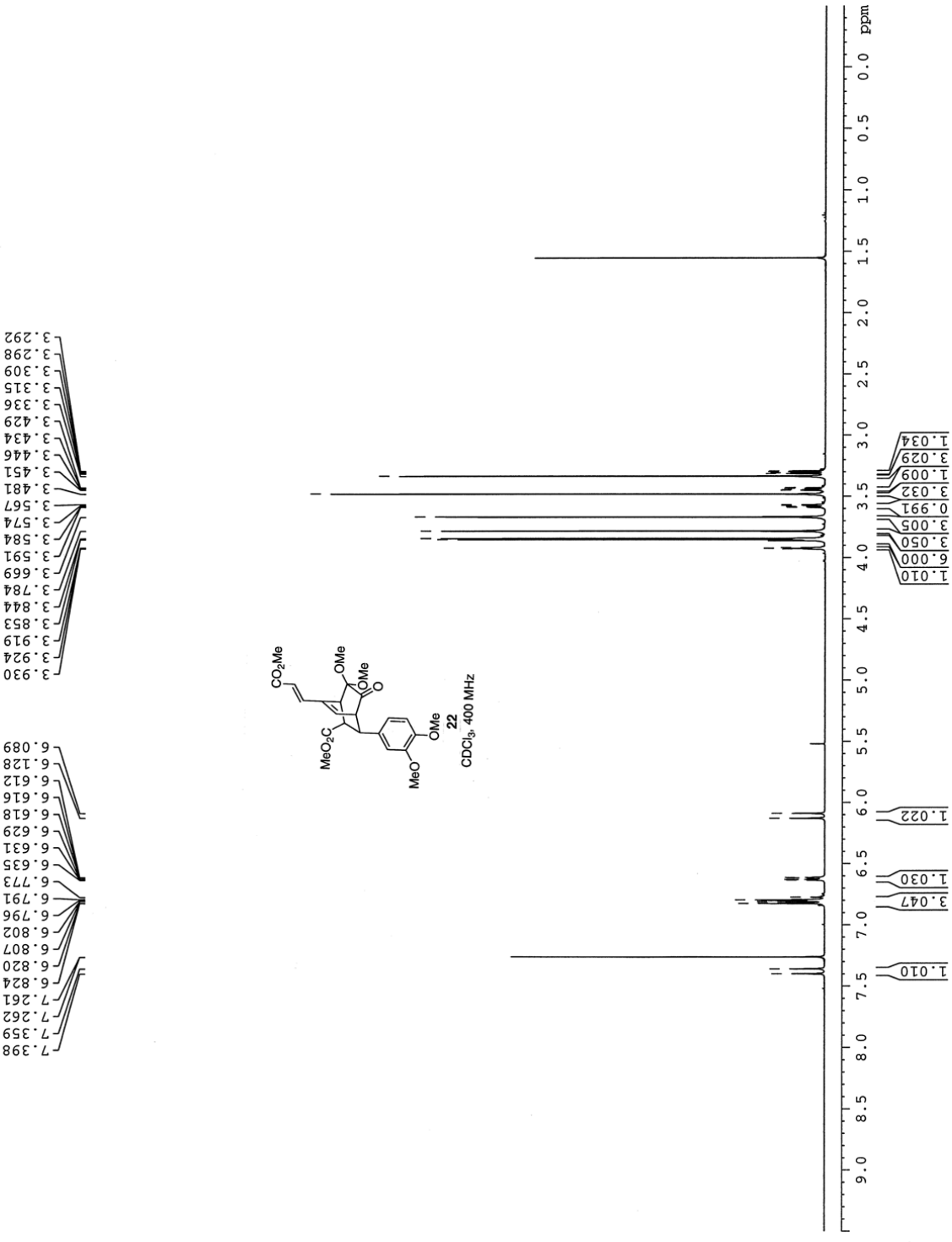

173.403
146.394
144.018
132.444
120.805
114.320
110.896
55.845
51.587
36.100
30.674
MeO
OMe
OH
19
CDCl3, 75 MHz
ppm

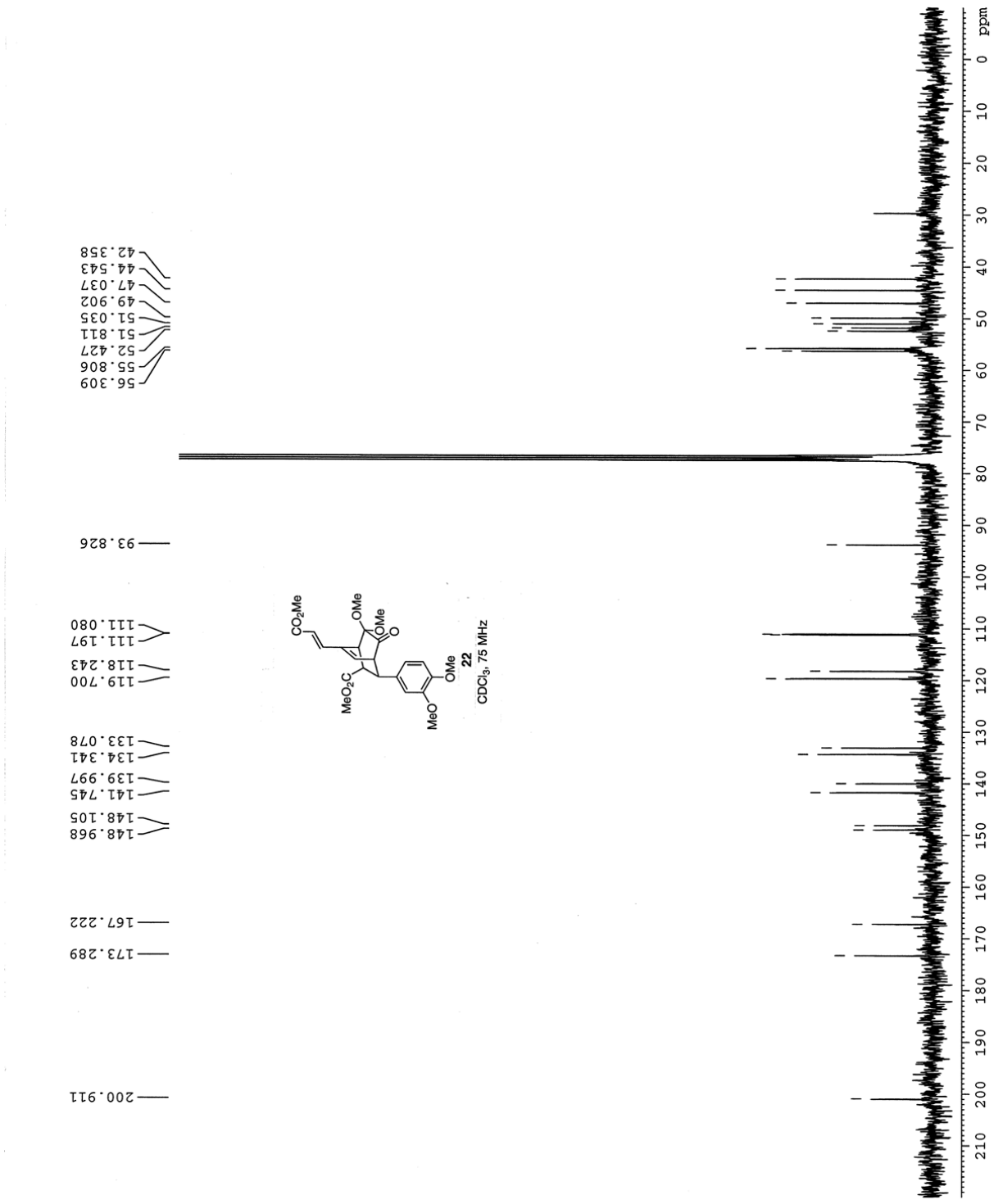

CO2Me
OMe
OMe
O
NC
21
CDCl3, 400 MHz
ppm
0.963
3.064
1.040
3.034
3.039
1.019
0.980
4.054
1.034
1.000


198.799
172.890
149.709
120.693
117.273
93.429
51.858
50.863
49.753
49.229
42.502
31.501
30.041
26.224
25.317
CO2Me
OMe
OMe
O
NC
21
CDCl3, 75 MHz
ppm

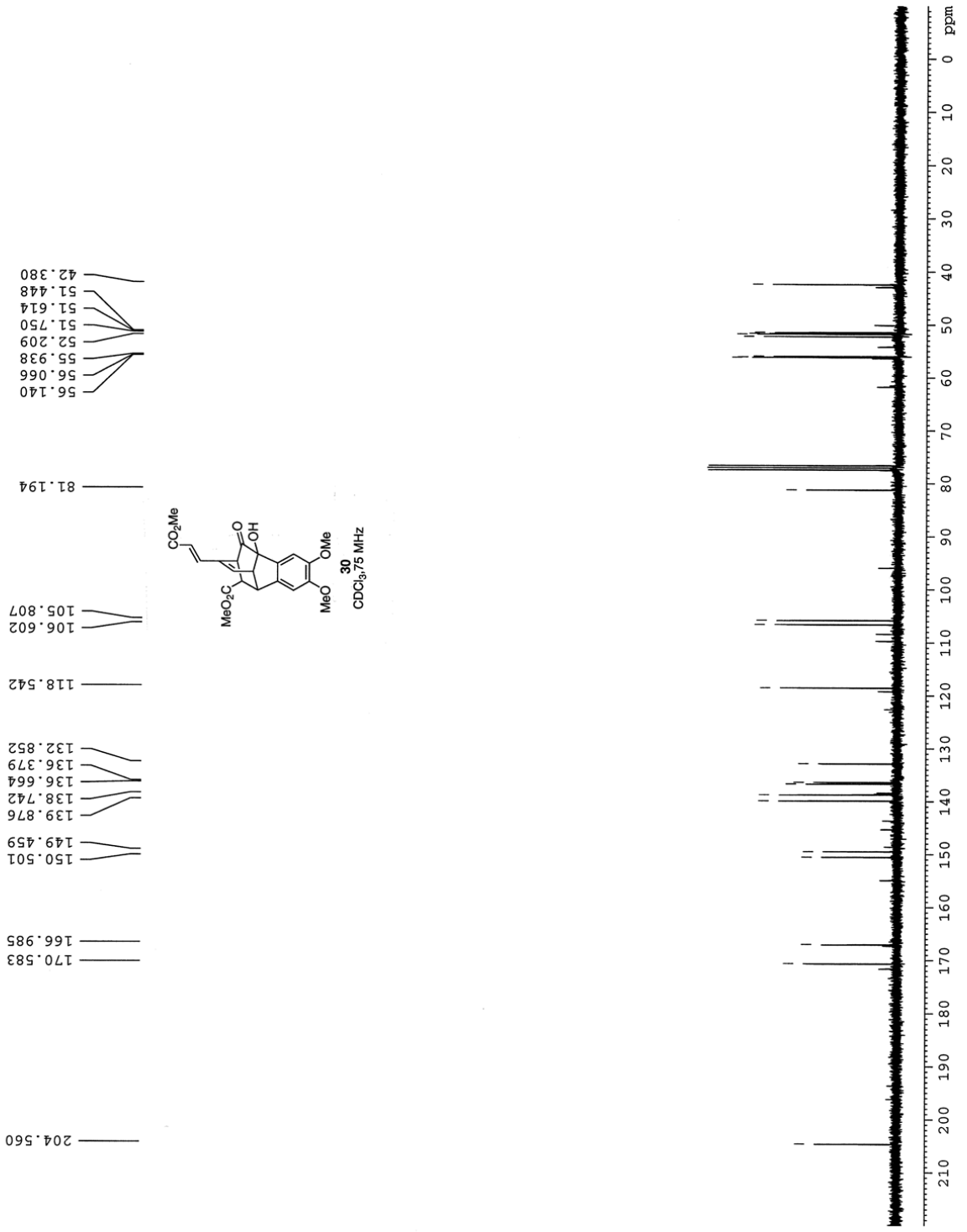

7.654
7.615
7.177
7.012
6.892
6.883
6.329
6.290
6.107
6.087
5.802
5.791
4.348
4.328
3.898
3.845
3.820
3.788
1.020
0.998
1.033
3.008
1.032
1.000
0.964
0.999
3.068
6.016
3.009
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
OMe
OH
CO2Me
OMe
25
CDCl3, 400 MHz
MeO2C

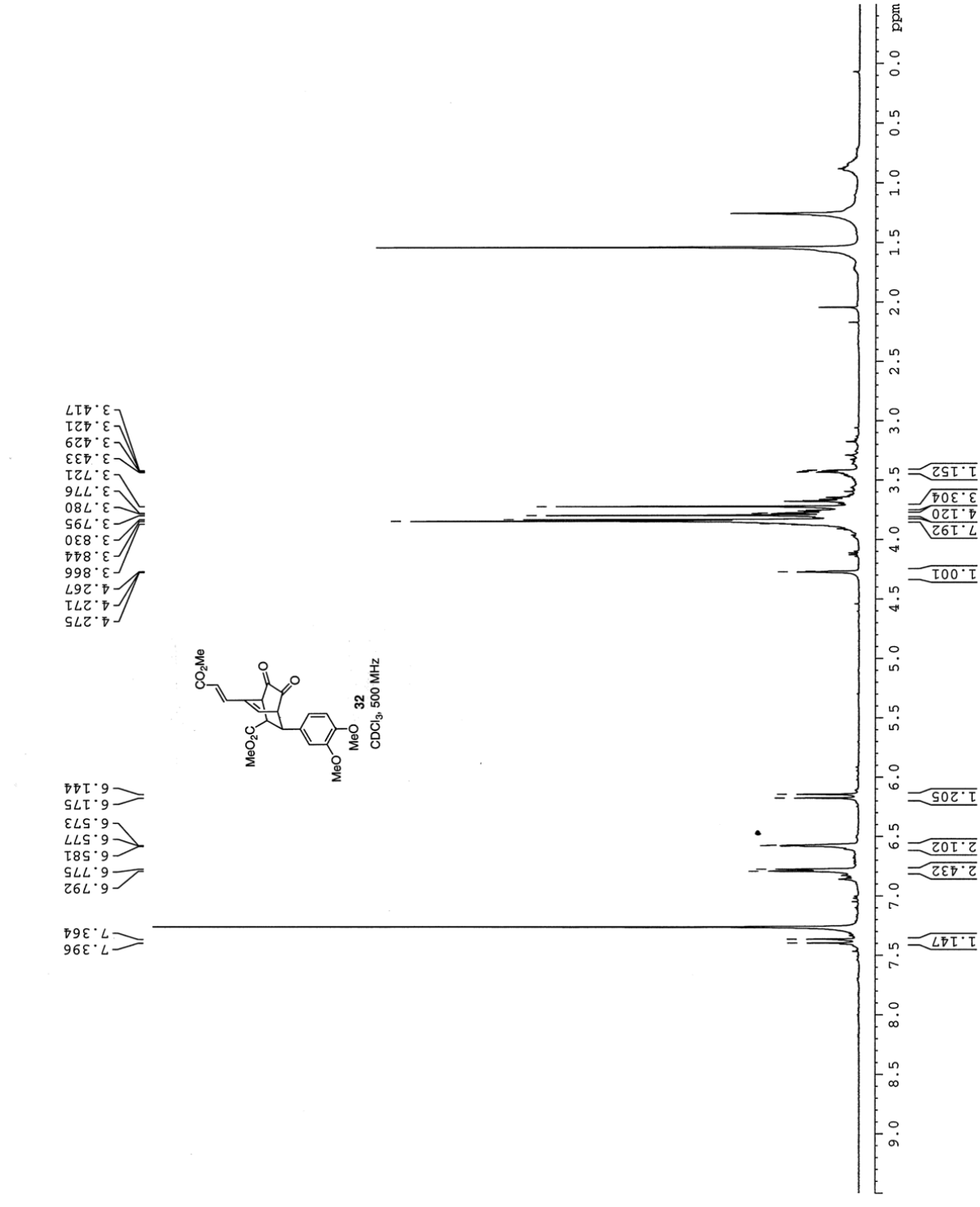

170.608
167.477
149.808
146.662
145.980
144.614
144.547
131.151
128.408
125.573
119.237
117.763
115.345
114.467
112.024
108.683
87.311
55.951
55.816
55.266
52.690
51.451
MeO2C
CO2Me
OMe
OH
OMe
25
CDCl3, 75 MHz
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

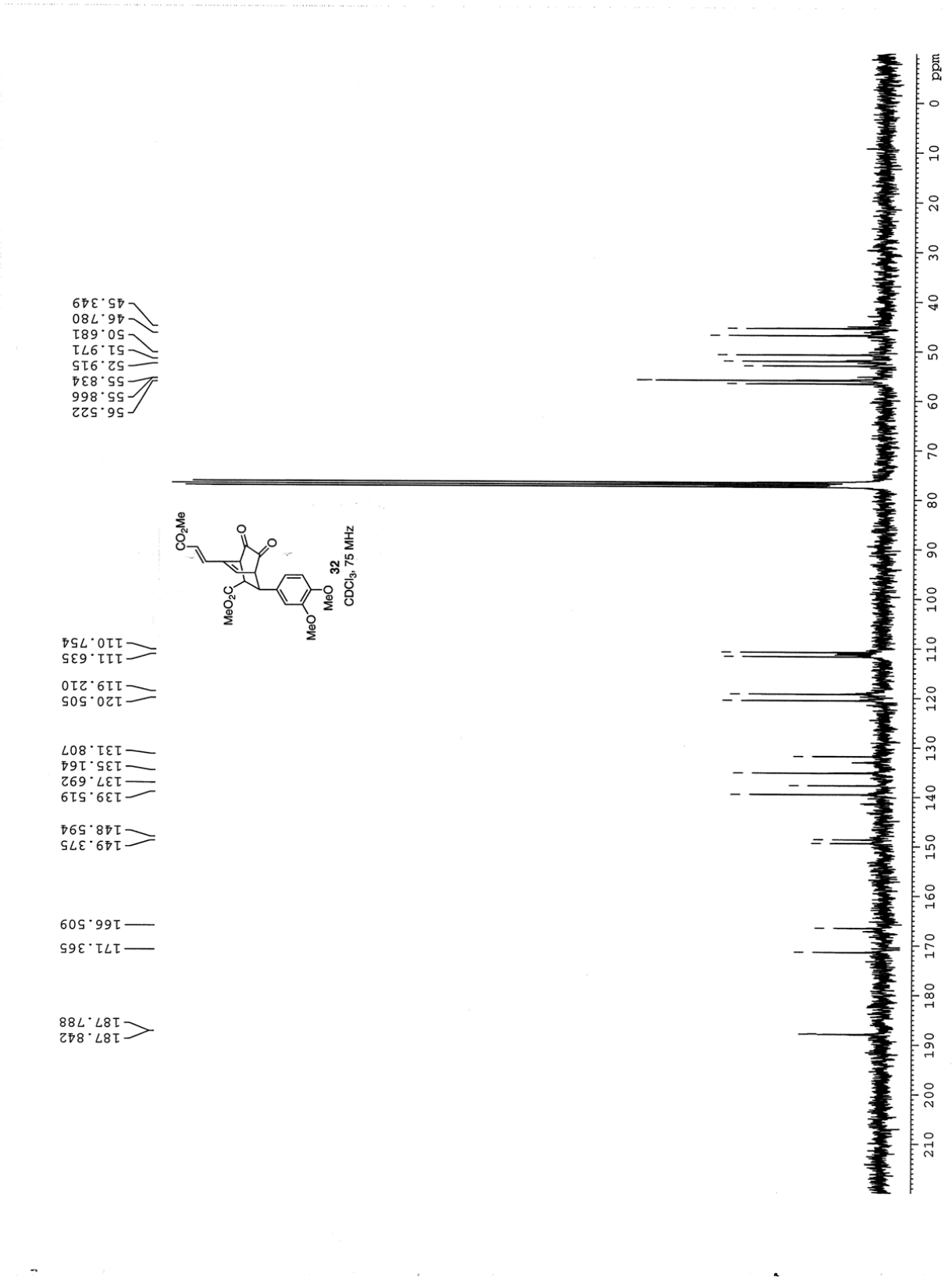

CO2Me
OMe
OMe
O
MeO2C
OMe
MeO
22
CDCl3, 400 MHz
ppm
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
1.010
3.047
1.030
1.022
1.010
6.000
3.050
3.005
0.991
3.032
1.009
3.029
1.034
3.930
3.924
3.919
3.853
3.844
3.784
3.669
3.591
3.584
3.574
3.567
3.481
3.451
3.446
3.434
3.429
3.336
3.315
3.309
3.298
3.292
6.089
6.128
6.612
6.616
6.618
6.629
6.631
6.635
6.773
6.791
6.796
6.802
6.807
6.820
6.824
7.261
7.262
7.359
7.398

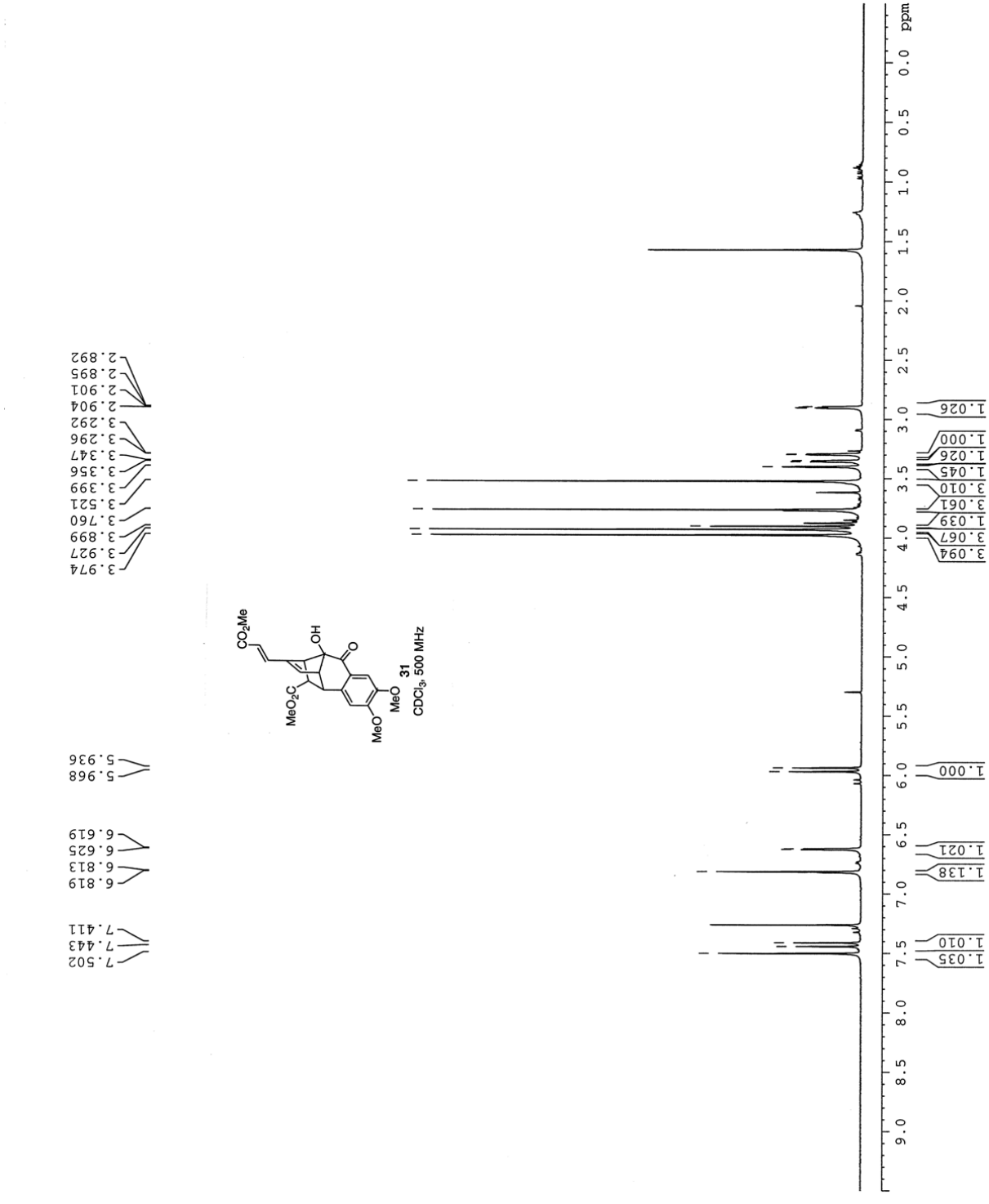

ppm
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
42.358
44.543
47.037
49.902
51.035
51.811
52.427
55.806
56.309
93.826
111.080
111.197
118.243
119.700
133.078
134.341
139.997
141.745
148.105
148.968
167.222
173.289
200.911
CO2Me
OMe
OMe
O
MeO2C
OMe
MeO
22
CDCl3, 75 MHz

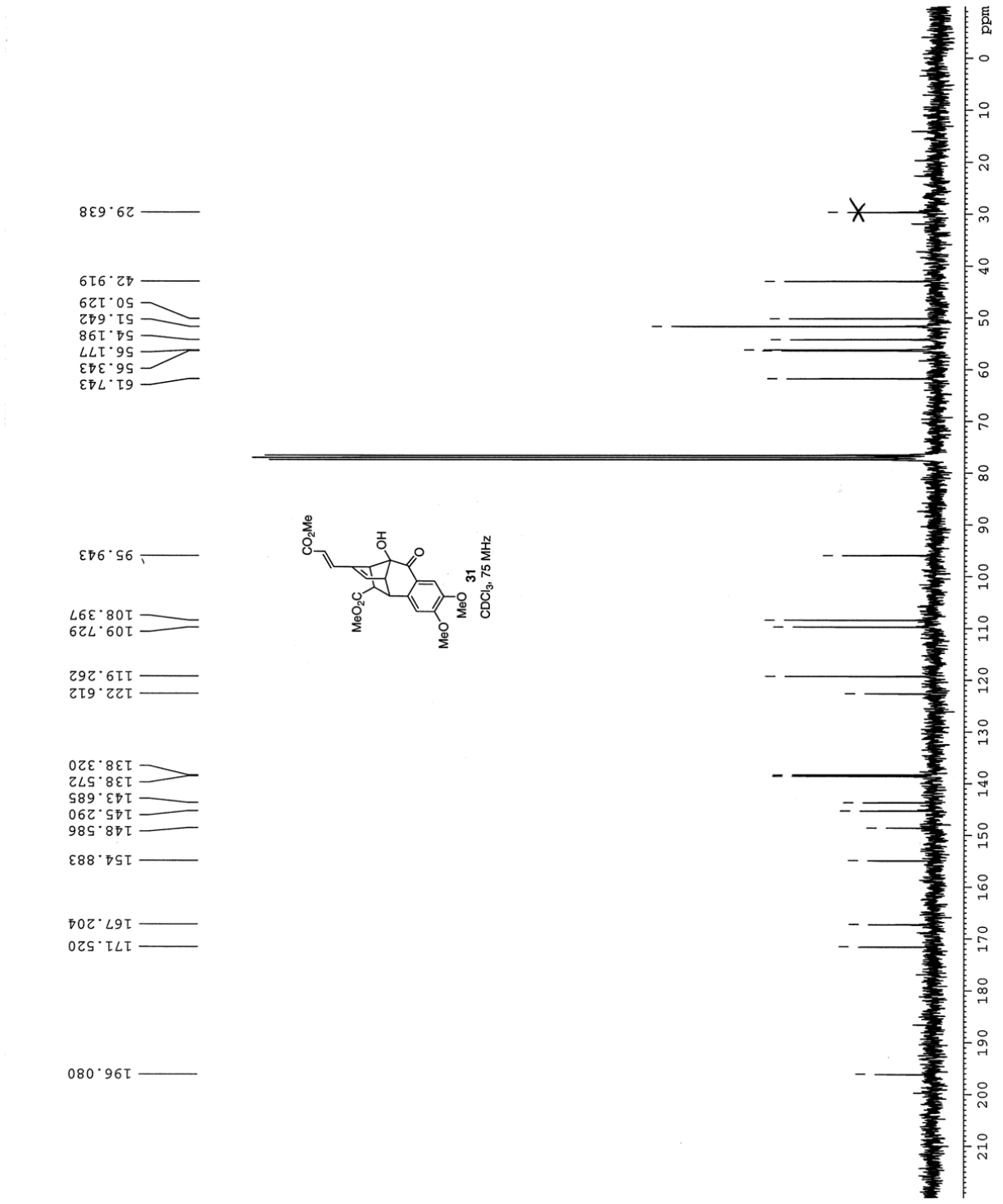

7.329
7.290
6.821
6.744
6.731
6.074
6.035
4.140
4.131
3.878
3.875
3.865
3.852
3.771
3.617
3.249
3.098
3.089
CO2Me
O
OH
OMe
MeO2C
MeO
30
CDCl3, 400 MHz
1.019
2.021
1.013
1.000
1.047
8.042
3.027
2.920
0.919
0.969
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm

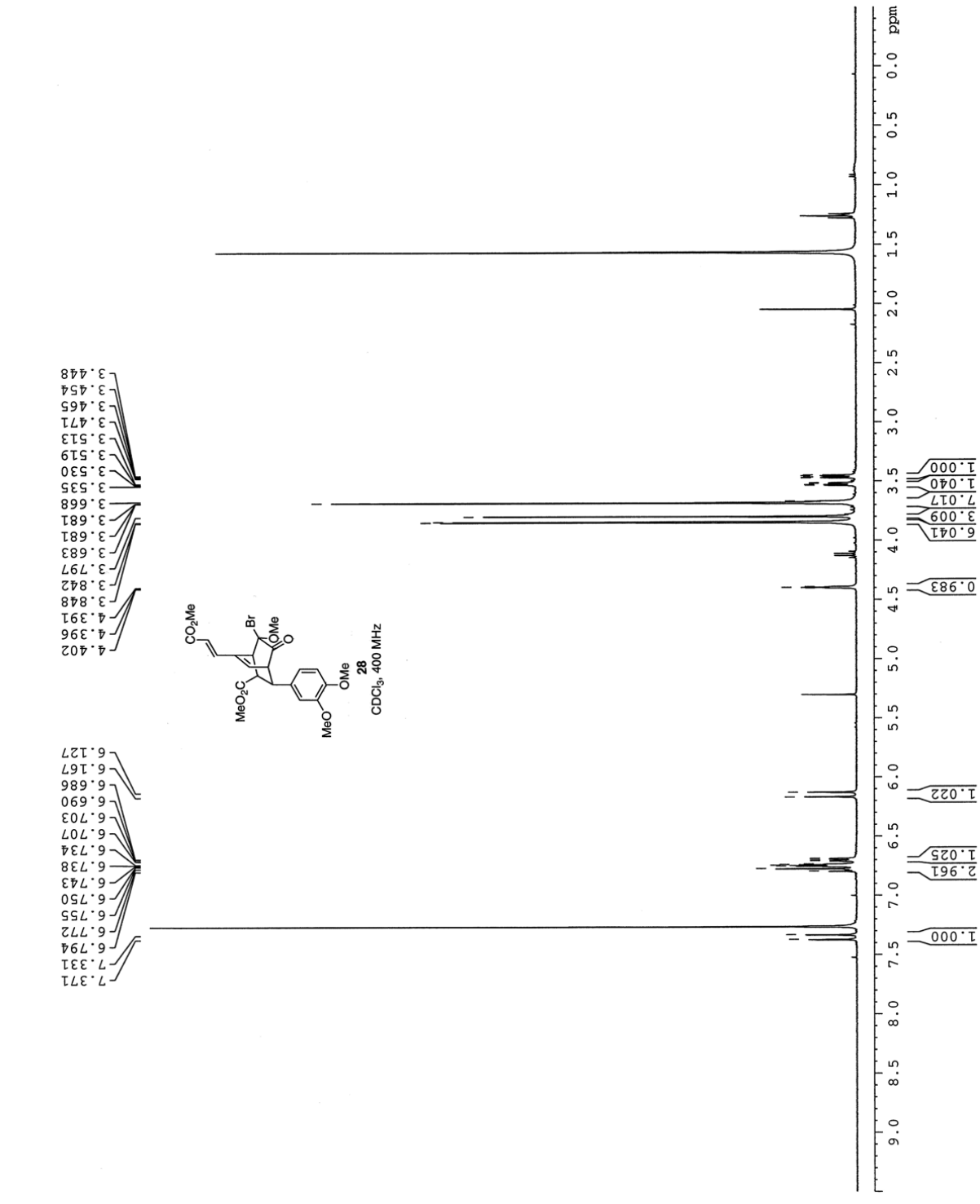

204.560
170.583
166.985
150.501
149.459
139.876
138.742
136.664
136.379
132.852
118.542
106.602
105.807
81.194
56.140
55.938
52.209
51.750
51.614
51.448
42.380
CO2Me
O
OH
OMe
MeO2C
MeO
30
CDCl3,75 MHz
ppm

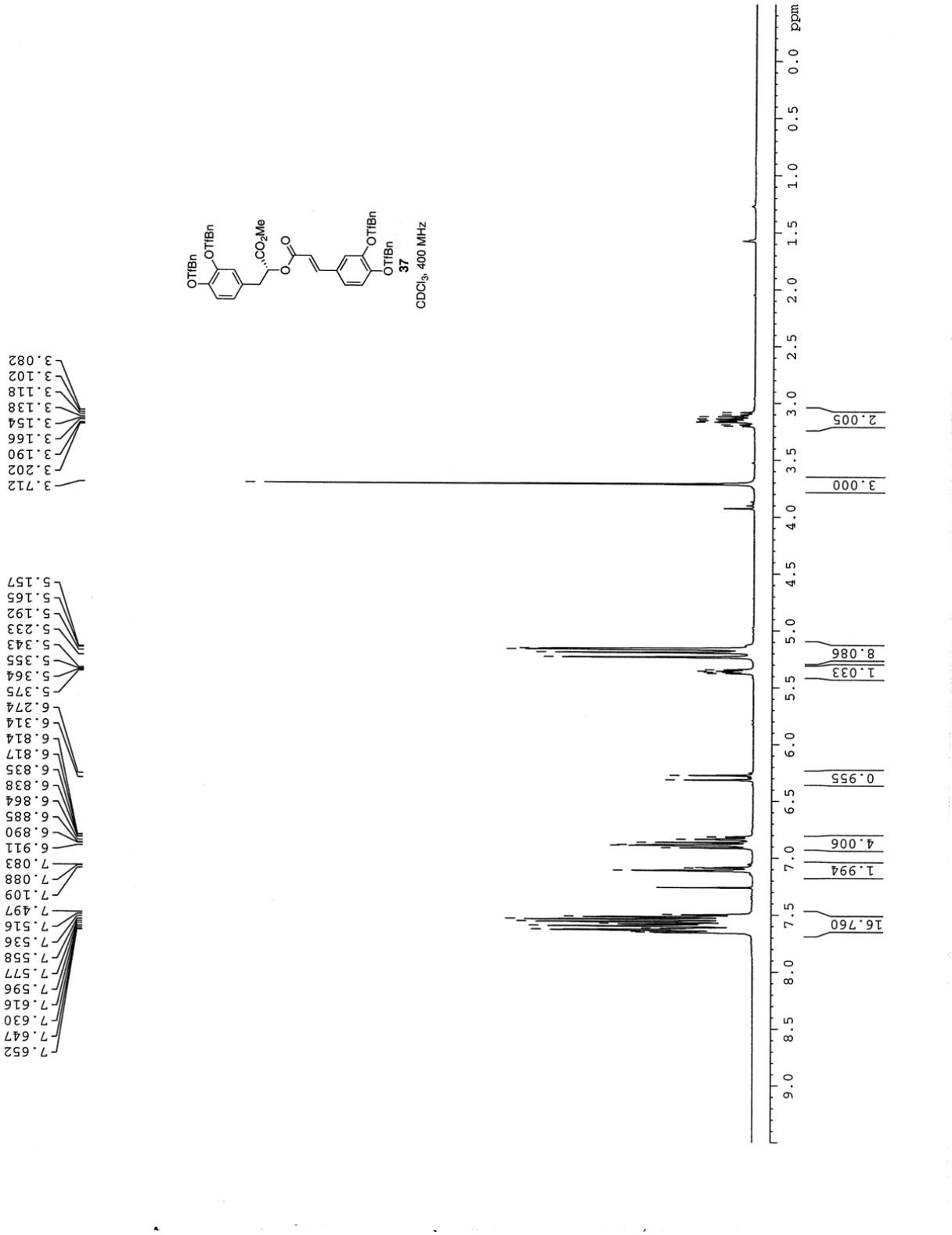

32
CDCl3, 500 MHz
CO2Me
MeO2C
MeO
MeO
7.364
7.396
6.144
6.175
6.573
6.577
6.581
6.775
6.792
4.275
4.271
4.267
3.866
3.844
3.830
3.795
3.780
3.776
3.721
3.433
3.429
3.421
3.417
1.147
2.432
2.102
1.205
1.001
7.192
4.120
3.304
1.152
ppm

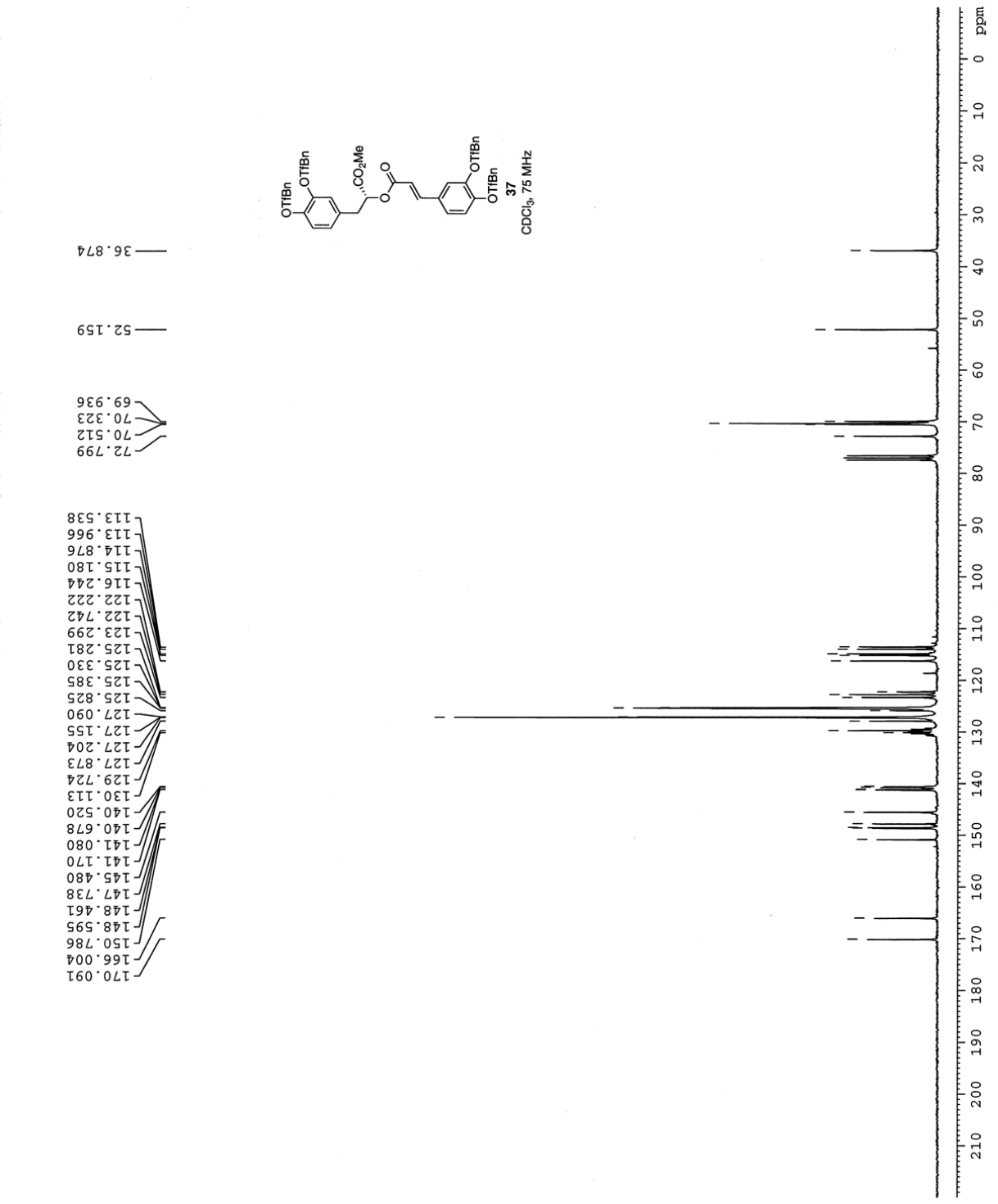

45.349
46.780
50.681
51.971
52.915
55.834
55.866
56.522
110.754
111.635
119.210
120.505
131.807
135.164
137.692
139.519
148.594
149.375
166.509
171.365
187.788
187.842
CO2Me
MeO2C
MeO
MeO
32
CDCl3, 75 MHz
ppm

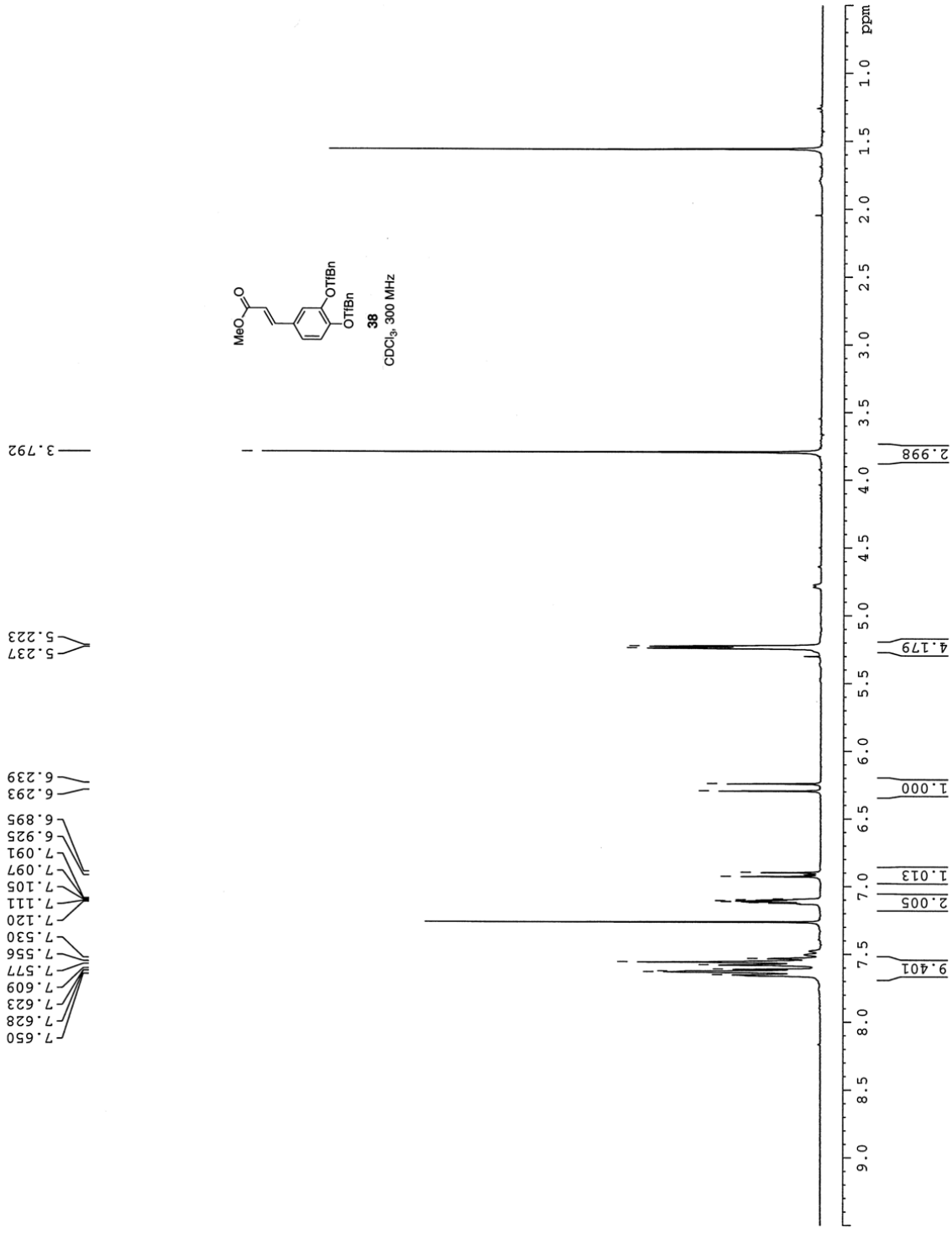

CO2Me
OH
O
MeO2C
MeO
MeO
31
CDCl3, 500 MHz
ppm
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
1.035
1.010
1.138
1.021
1.000
3.094
3.067
1.039
3.061
3.010
1.045
1.026
1.000
1.026
7.502
7.443
7.411
6.819
6.813
6.625
6.619
5.968
5.936
3.974
3.927
3.899
3.760
3.521
3.399
3.356
3.347
3.296
3.292
2.904
2.901
2.895
2.892

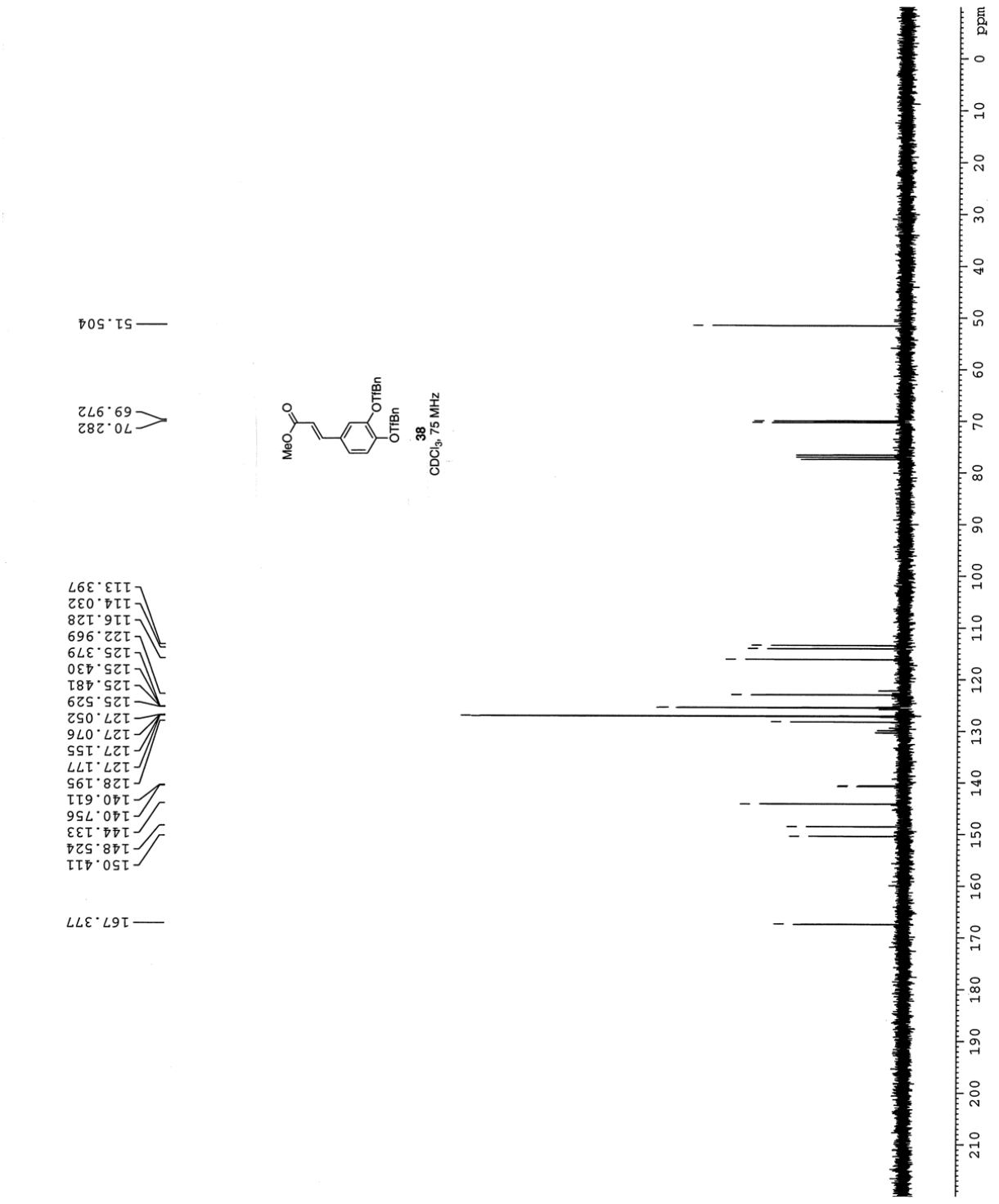

29.638
42.919
50.129
51.642
54.198
56.177
56.343
61.743
95.943
108.397
109.729
119.262
122.612
138.320
138.572
143.685
145.290
148.586
154.883
167.204
171.520
196.080
CO2Me
OH
O
MeO2C
MeO
MeO
31
CDCl3, 75 MHz
ppm

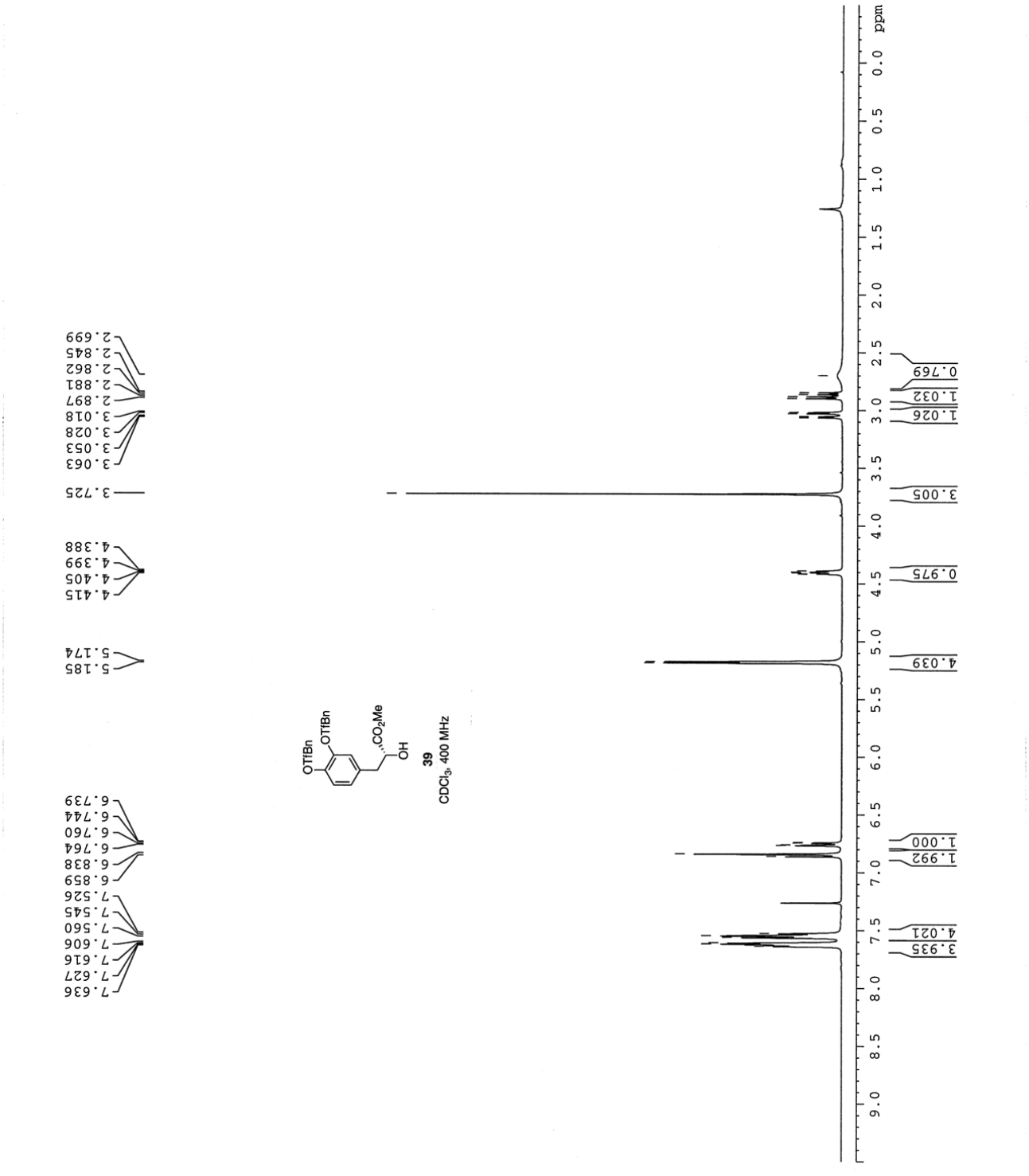

CO2Me
Br
OMe
O
MeO2C
OMe
MeO
28
CDCl3, 400 MHz
7.371
7.331
6.794
6.772
6.755
6.750
6.743
6.738
6.734
6.707
6.703
6.690
6.686
6.167
6.127
4.402
4.396
4.391
3.848
3.842
3.797
3.683
3.681
3.681
3.668
3.535
3.530
3.519
3.513
3.471
3.465
3.454
3.448
1.000
2.961
1.025
1.022
0.983
6.041
3.009
7.017
1.040
1.000
ppm

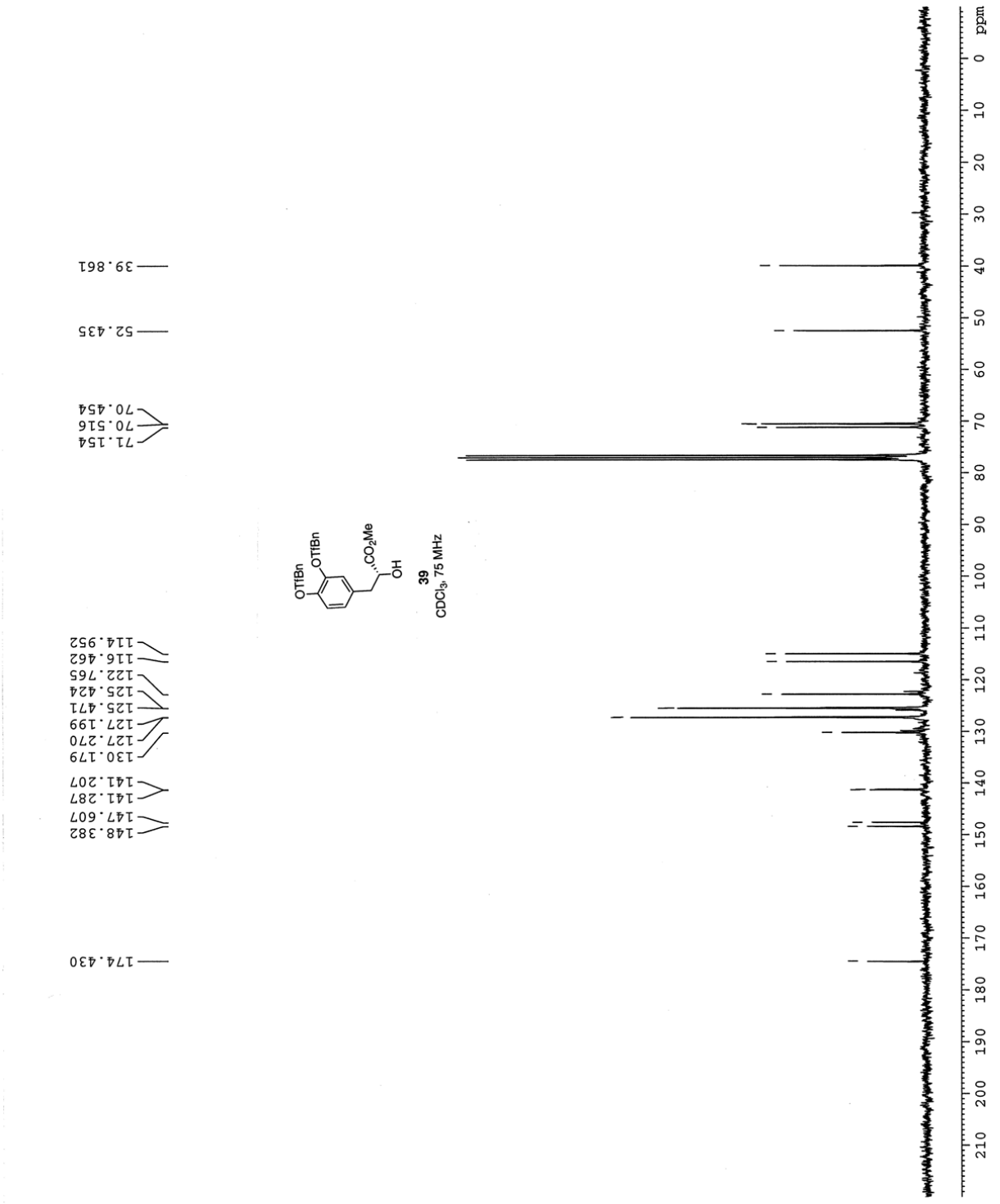

OTfBn
OTfBn
CO2Me
OTfBn
OTfBn
37
CDCl3, 400 MHz
ppm
16.760
1.994
4.006
0.955
8.086
1.033
3.000
2.005

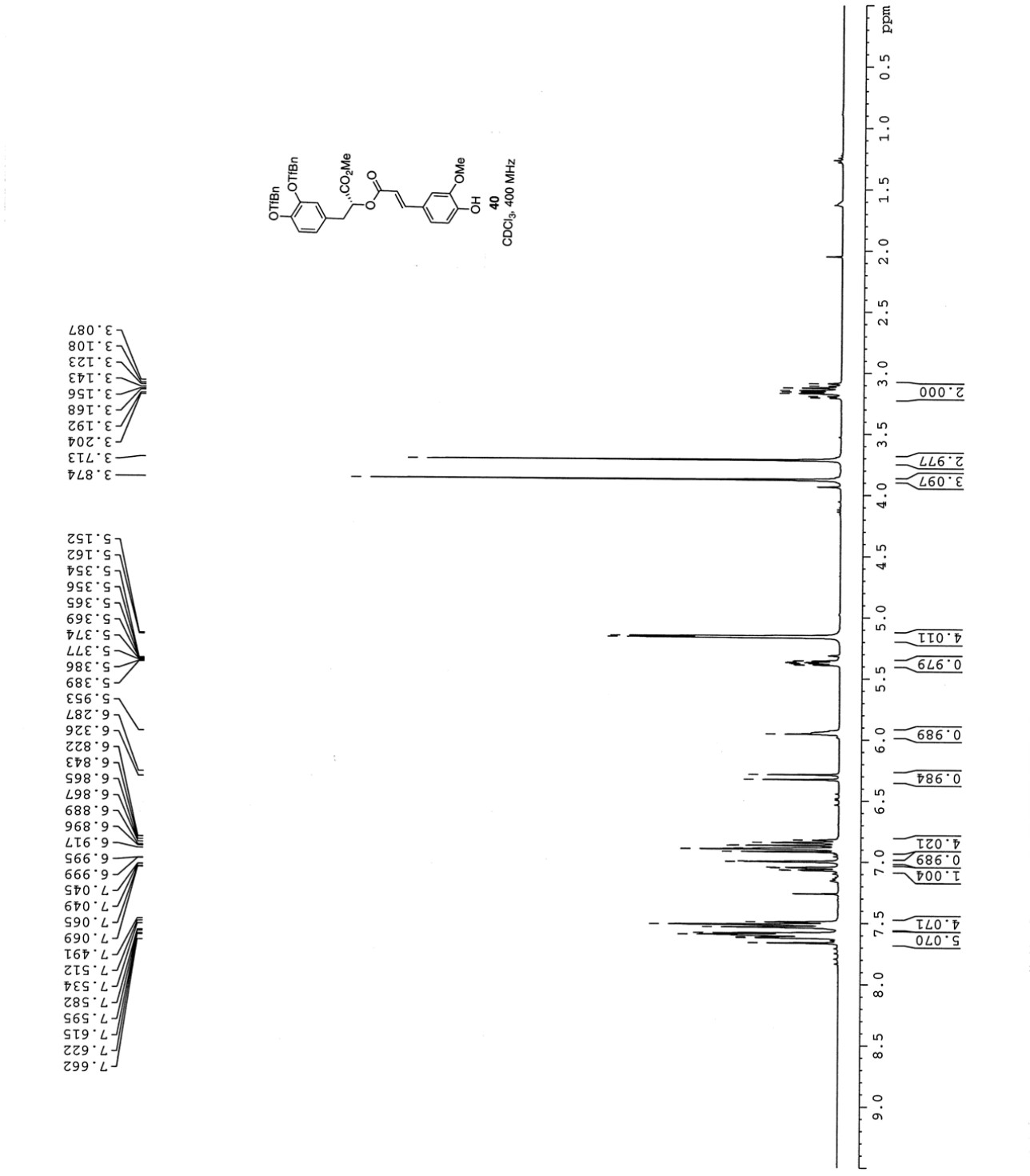

OTfBn
OTfBn
CO2Me
OTfBn
OTfBn
37
CDCl3, 75 MHz
36.874
52.159
69.936
70.323
70.512
72.799
113.538
113.966
114.876
115.180
116.244
122.222
122.742
123.299
125.281
125.330
125.385
125.825
127.090
127.155
127.204
127.873
129.724
130.113
140.520
140.678
141.080
141.170
145.480
147.738
148.461
148.595
150.786
166.004
170.091
ppm

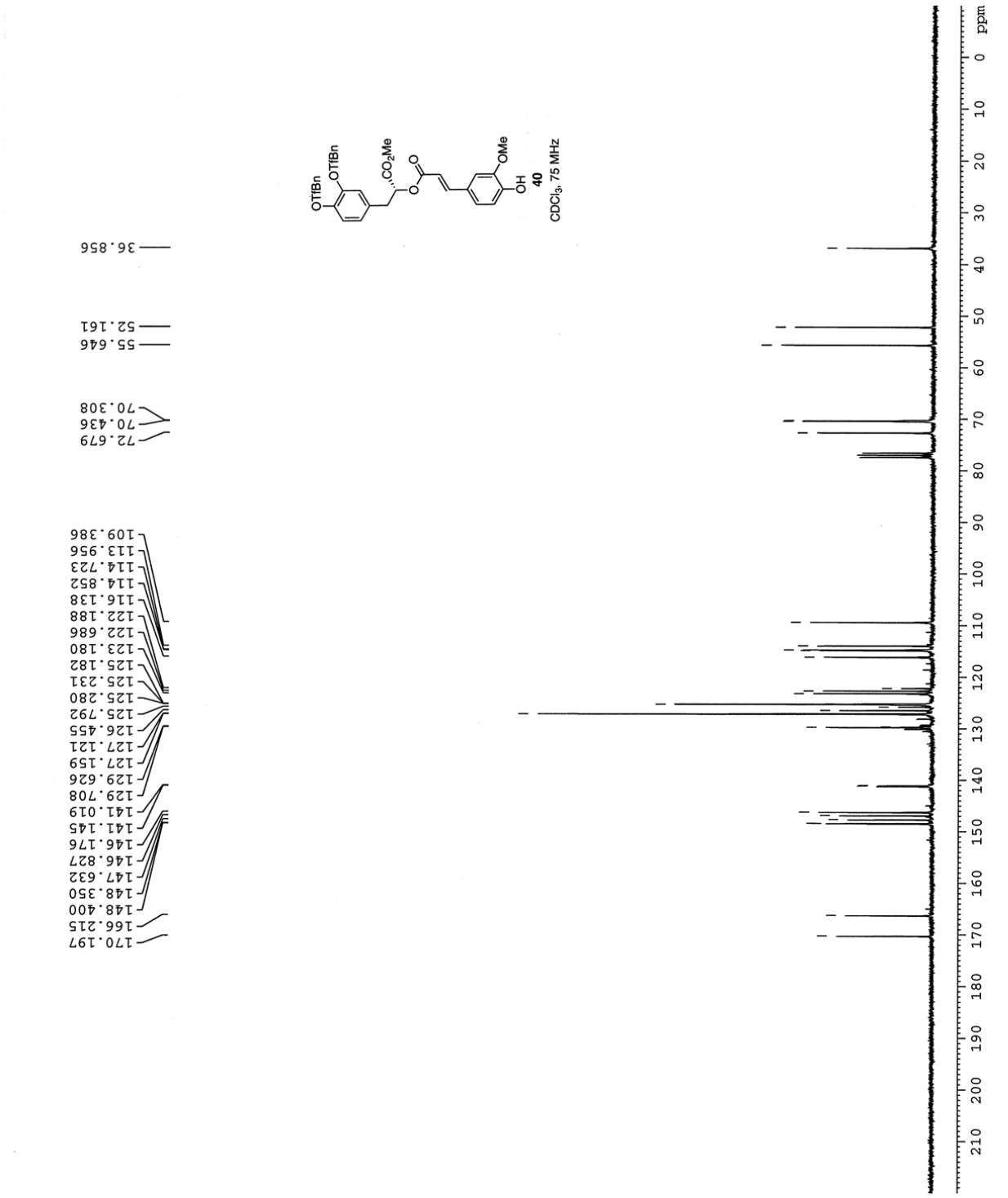

MeO
O
OTfBn
OTfBn
38
CDCl3, 300 MHz
3.792
5.237
5.223
6.293
6.239
6.895
6.925
7.091
7.097
7.105
7.111
7.120
7.530
7.556
7.577
7.609
7.623
7.628
7.650
2.998
4.179
1.000
1.013
2.005
9.401
ppm

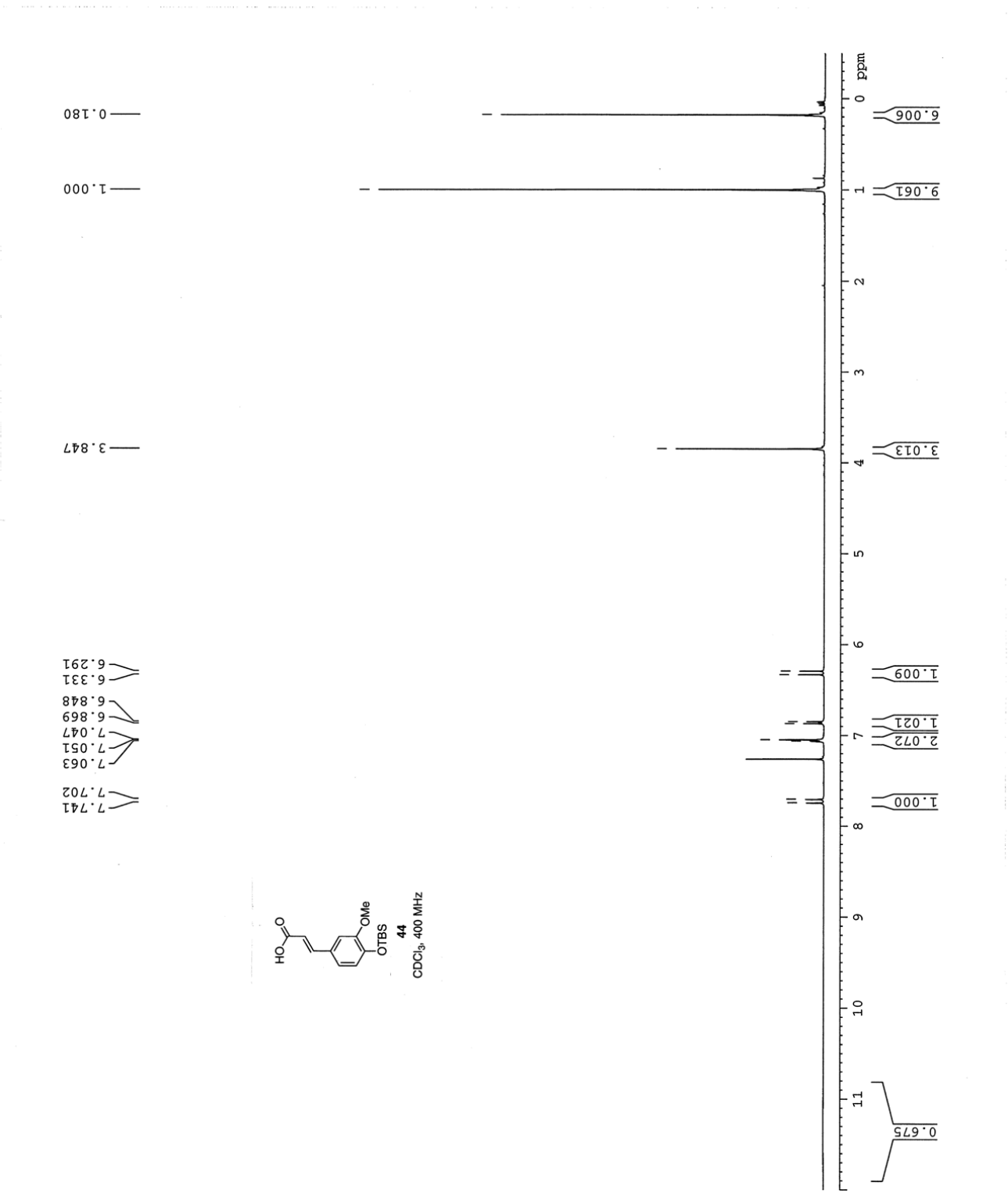

MeO
O
OTfBn
OTfBn
38
CDCl3, 75 MHz
51.504
69.972
70.282
113.397
114.032
116.128
122.969
125.379
125.430
125.481
125.529
127.052
127.076
127.155
127.177
128.195
140.611
140.756
144.133
148.524
150.411
167.377
ppm

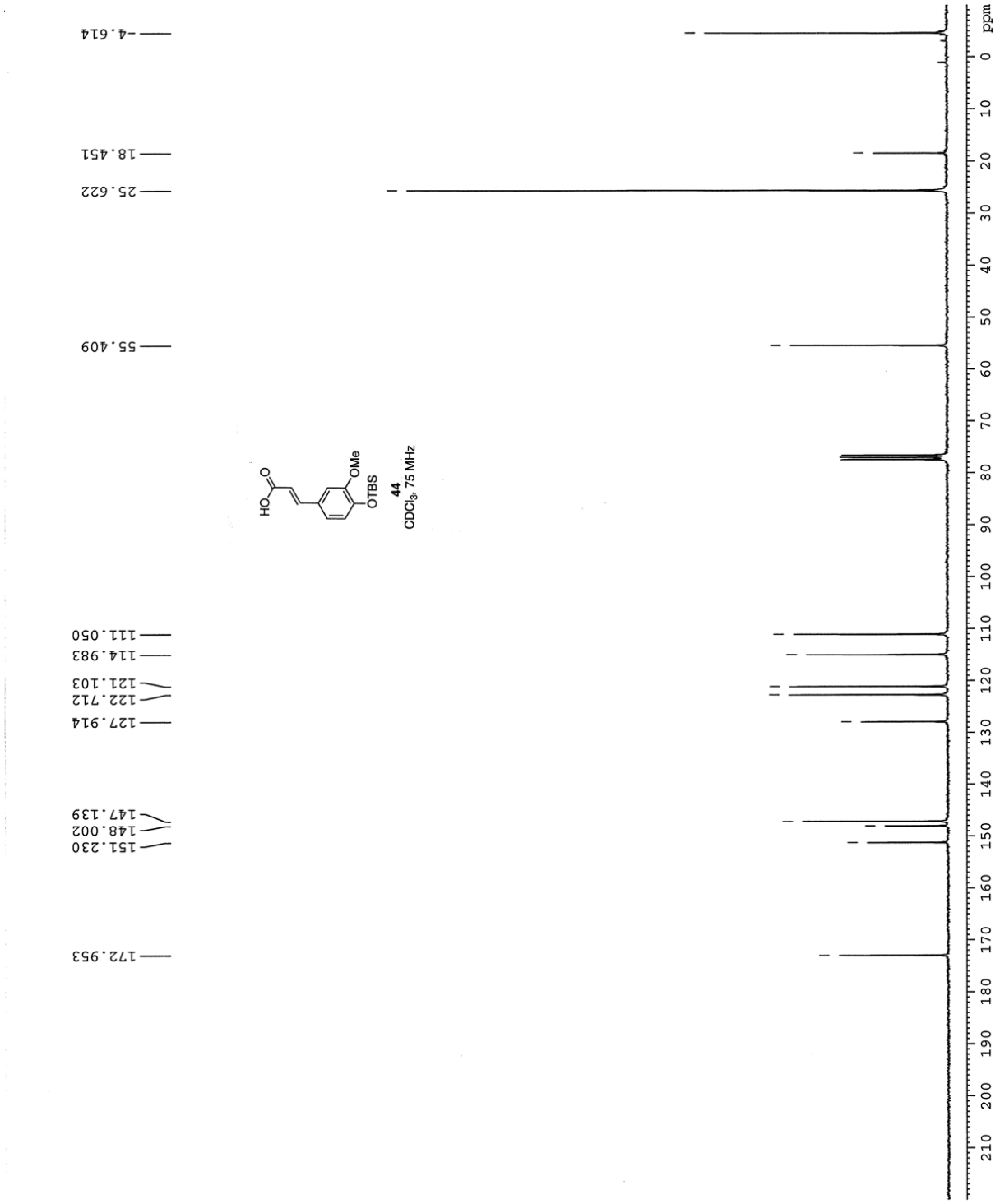

OTfBn
OTfBn
CO2Me
OH
39
CDCl3, 400 MHz
ppm
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0
0.769
1.032
1.026
3.005
0.975
4.039
1.000
1.992
4.021
3.935
2.699
2.845
2.862
2.881
2.897
3.018
3.028
3.053
3.063
3.725
4.388
4.399
4.405
4.415
5.174
5.185
6.739
6.744
6.760
6.764
6.838
6.859
7.526
7.545
7.560
7.606
7.616
7.627
7.636

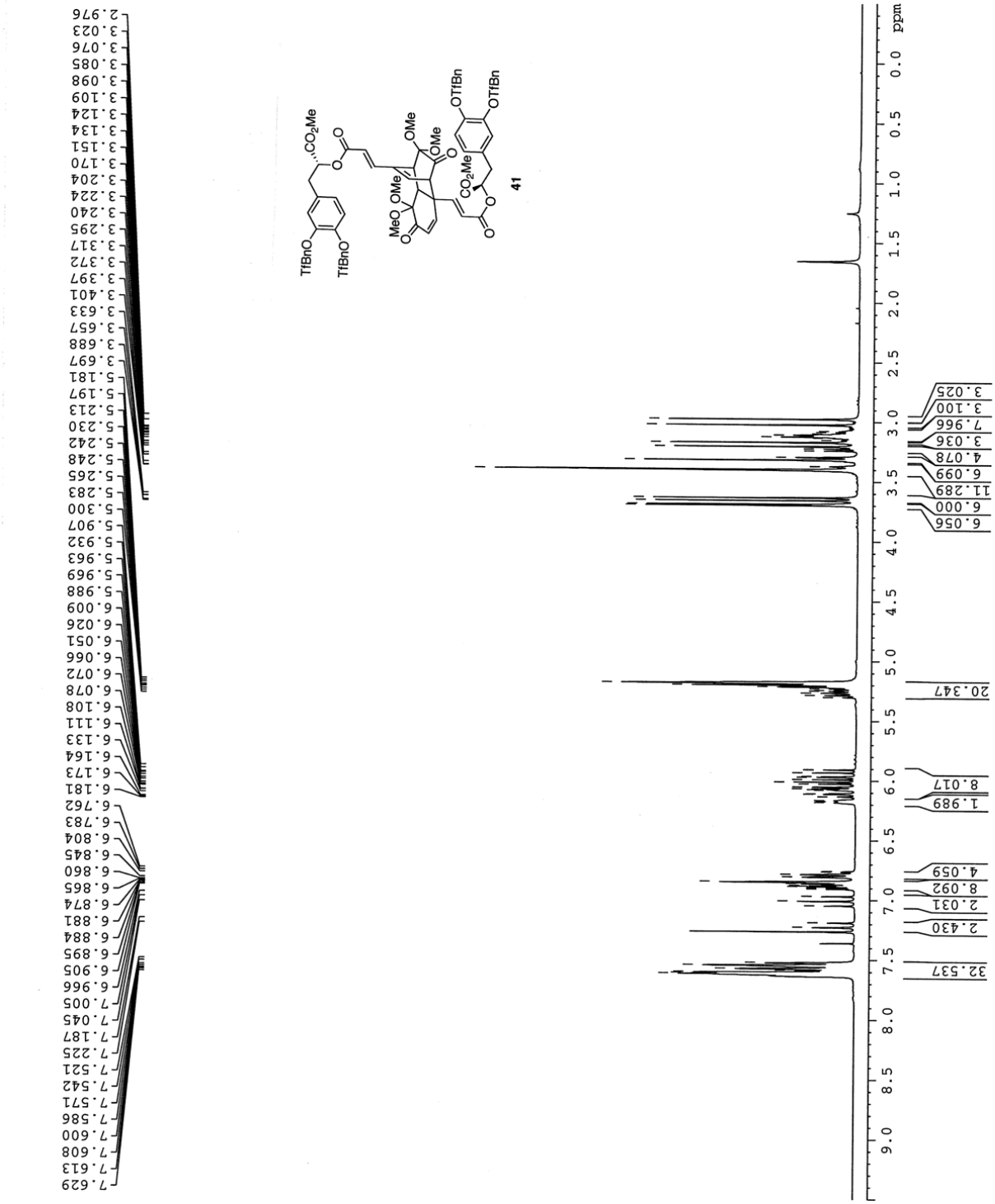

39
CDCl3, 75 MHz
OTfBn
OTfBn
CO2Me
OH
174.430
148.382
147.607
141.287
141.207
130.179
127.270
127.199
125.471
125.424
122.765
116.462
114.952
71.154
70.516
70.454
52.435
39.861
ppm

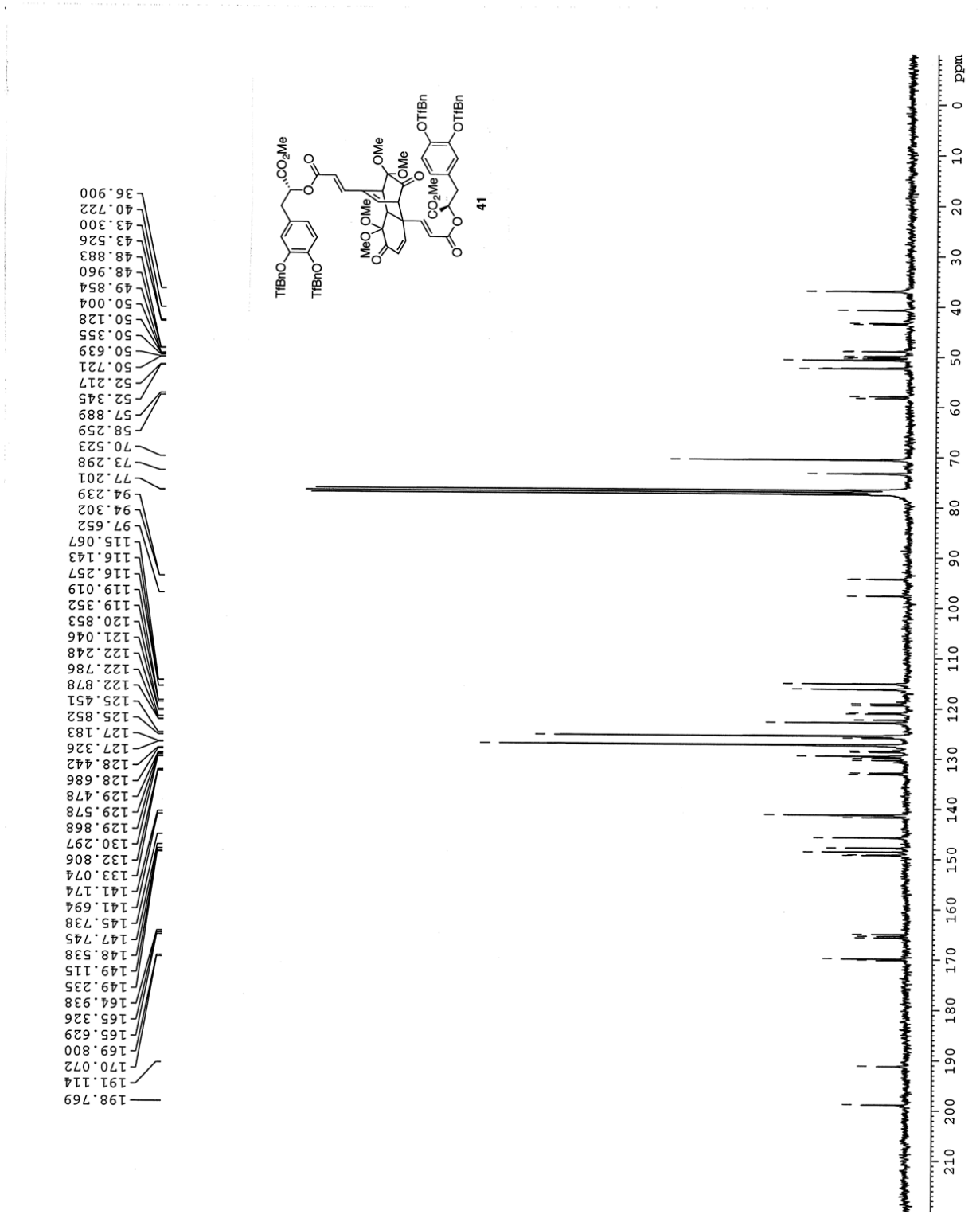

OTfBn
OTfBn
CO2Me
OMe
OH
40
CDCl3, 400 MHz
ppm
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
2.000
3.097
2.977
4.011
0.979
0.989
0.984
4.021
0.989
1.004
4.071
5.070
3.874
3.713
3.204
3.192
3.168
3.156
3.143
3.123
3.108
3.087
5.389
5.386
5.377
5.374
5.369
5.365
5.356
5.354
5.162
5.152
5.953
6.287
6.326
6.822
6.843
6.865
6.867
6.889
6.896
6.917
6.995
6.999
7.045
7.049
7.065
7.069
7.491
7.512
7.534
7.582
7.595
7.615
7.622
7.662

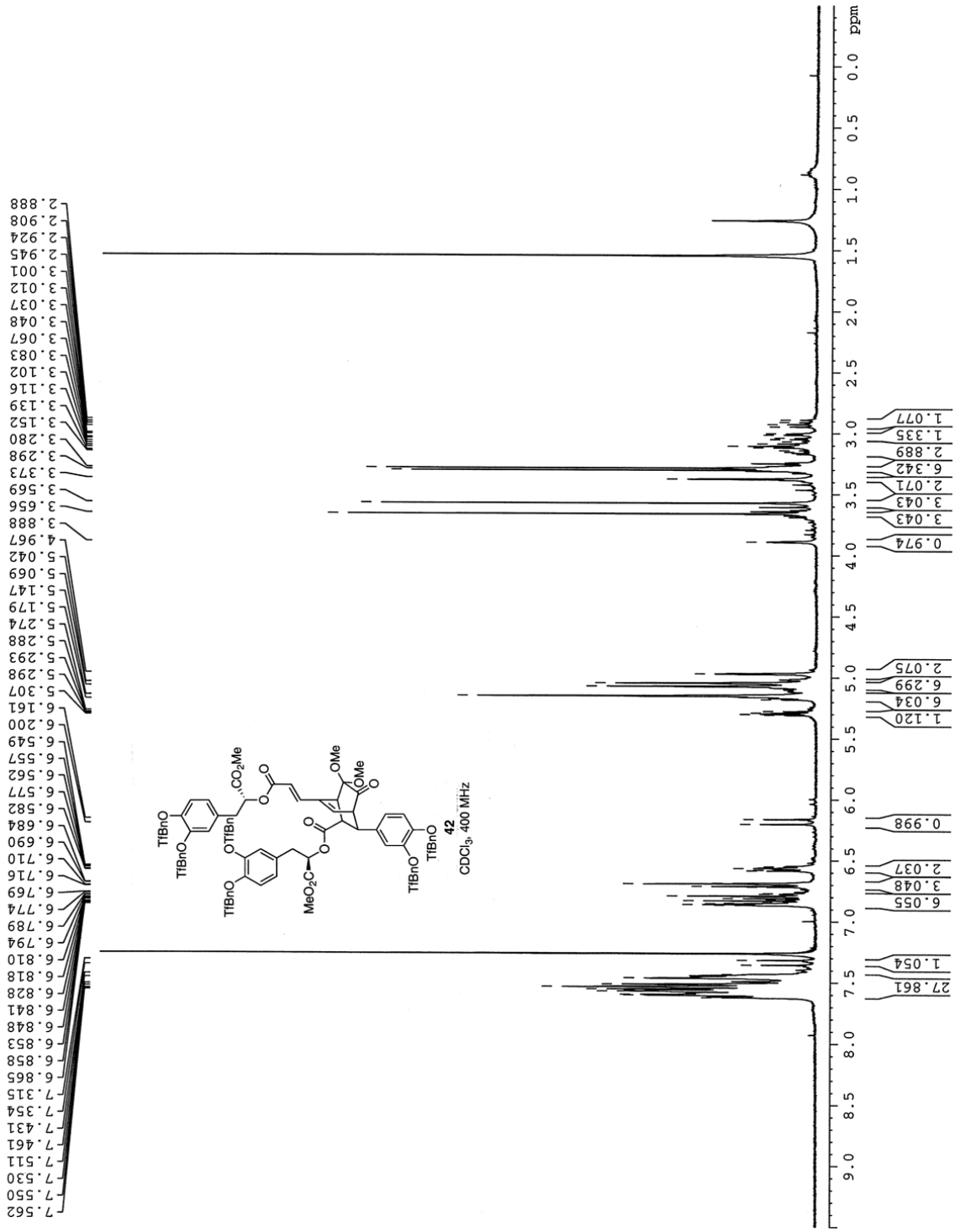

OTfBn
OTfBn
CO2Me
O
O
OMe
OH
40
CDCl3, 75 MHz
36.856
52.161
55.646
70.308
70.436
72.679
109.386
113.956
114.723
114.852
116.138
122.188
122.686
123.180
125.182
125.231
125.280
125.792
126.455
127.121
127.159
129.626
129.708
141.019
141.145
146.176
146.827
147.632
148.350
148.400
166.215
170.197
ppm

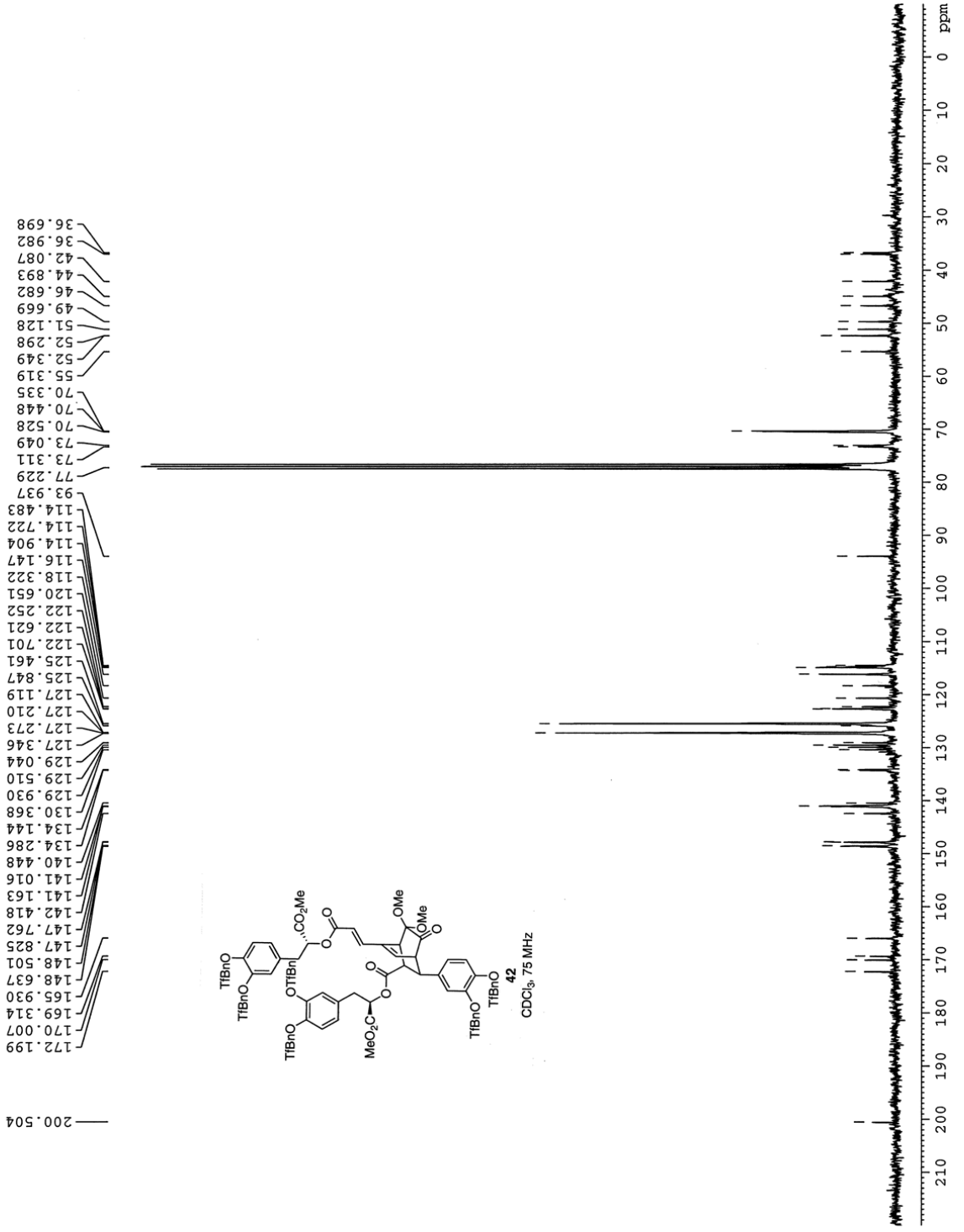

0.180
1.000
3.847
6.291
6.331
6.848
6.869
7.047
7.051
7.063
7.702
7.741
HO
O
OMe
OTBS
44
CDCl3, 400 MHz
ppm
0
1
2
3
4
5
6
7
8
9
10
11
6.006
9.061
3.013
1.009
1.021
2.072
1.000
0.675

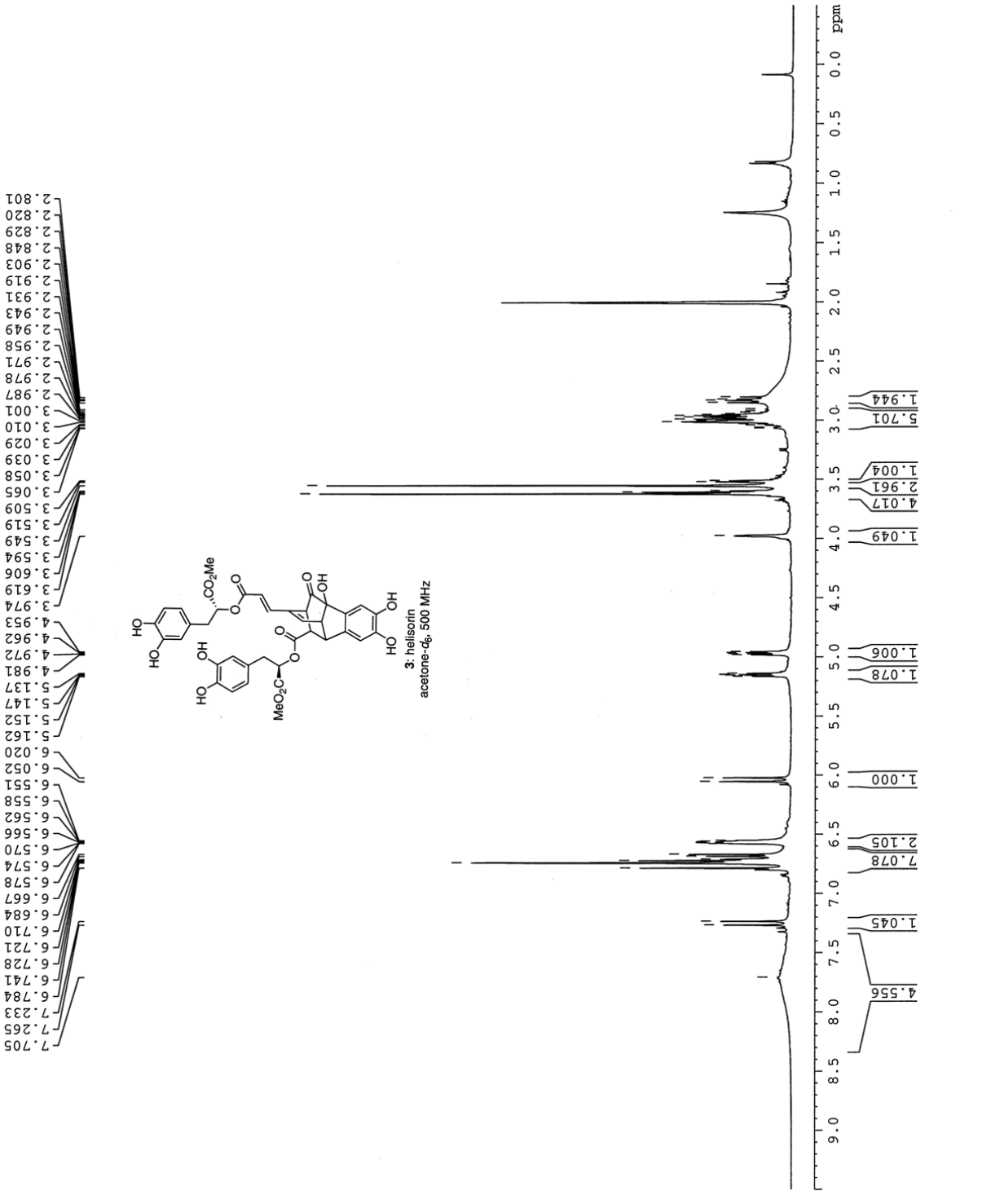

-4.614
18.451
25.622
55.409
111.050
114.983
121.103
122.712
127.914
147.139
148.002
151.230
172.953
HO
O
OMe
OTBS
44
CDCl3, 75 MHz
ppm

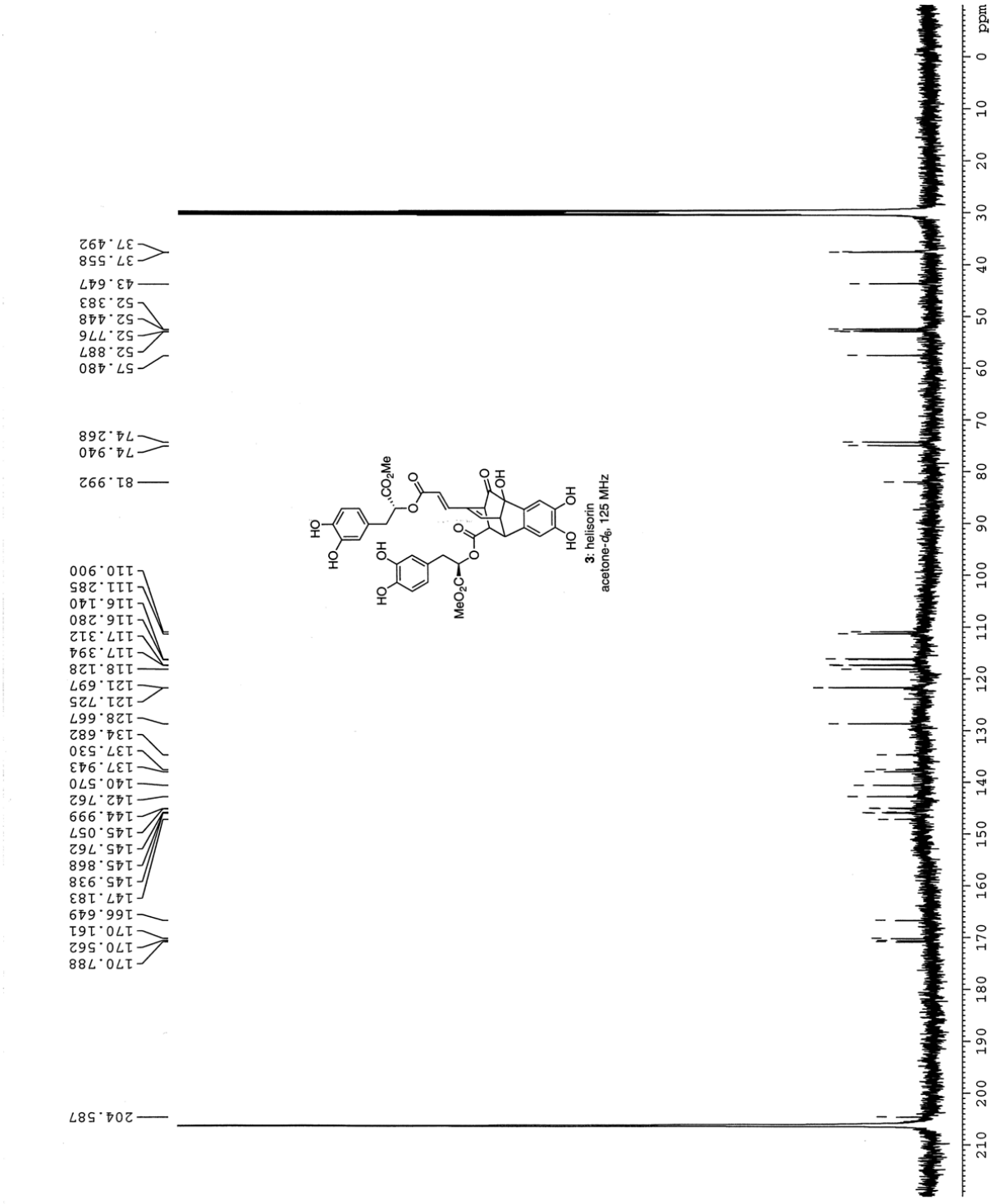

TfBnO
TfBnO
CO2Me
OMe
OMe
MeO OMe
OTfBn
OTfBn
CO2Me
41
ppm
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
32.537
2.430
2.031
8.092
4.059
1.989
8.017
20.347
6.056
6.000
11.289
6.099
4.078
3.036
7.966
3.100
3.025

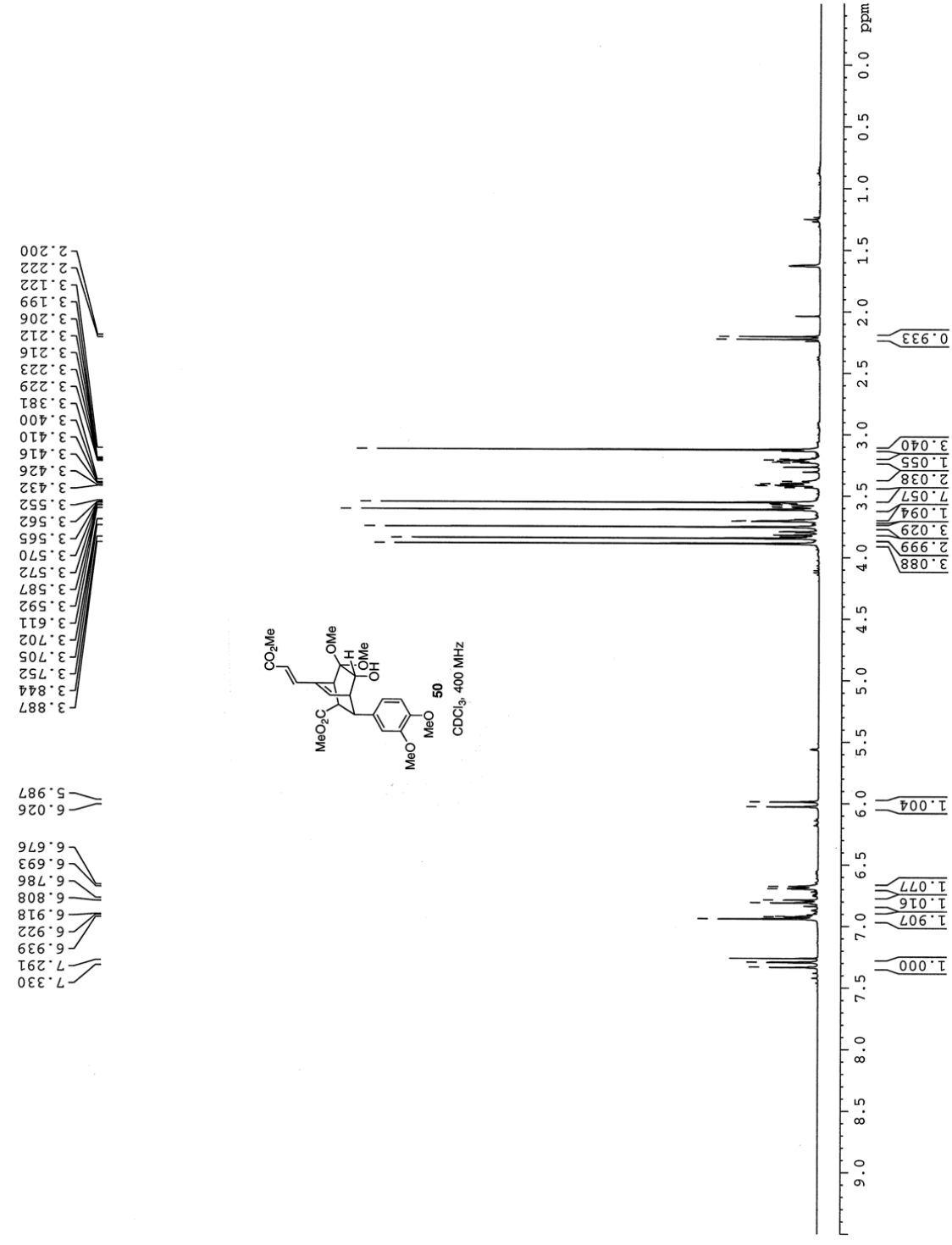

198.769
191.114
170.072
169.800
165.629
165.326
164.938
149.235
149.115
148.538
147.745
145.738
141.694
141.174
133.074
132.806
130.297
129.868
129.578
129.478
128.686
128.442
127.326
127.183
125.852
125.451
122.878
122.786
122.248
121.046
120.853
119.352
119.019
116.257
116.143
115.067
97.652
94.302
94.239
77.201
73.298
70.523
58.259
57.889
52.345
52.217
50.721
50.639
50.355
50.128
50.004
49.854
48.960
48.883
43.526
43.300
40.722
36.900
TfBnO
TfBnO
CO2Me
OMe
OMe
MeO
OMe
OTfBn
OTfBn
CO2Me
41
ppm

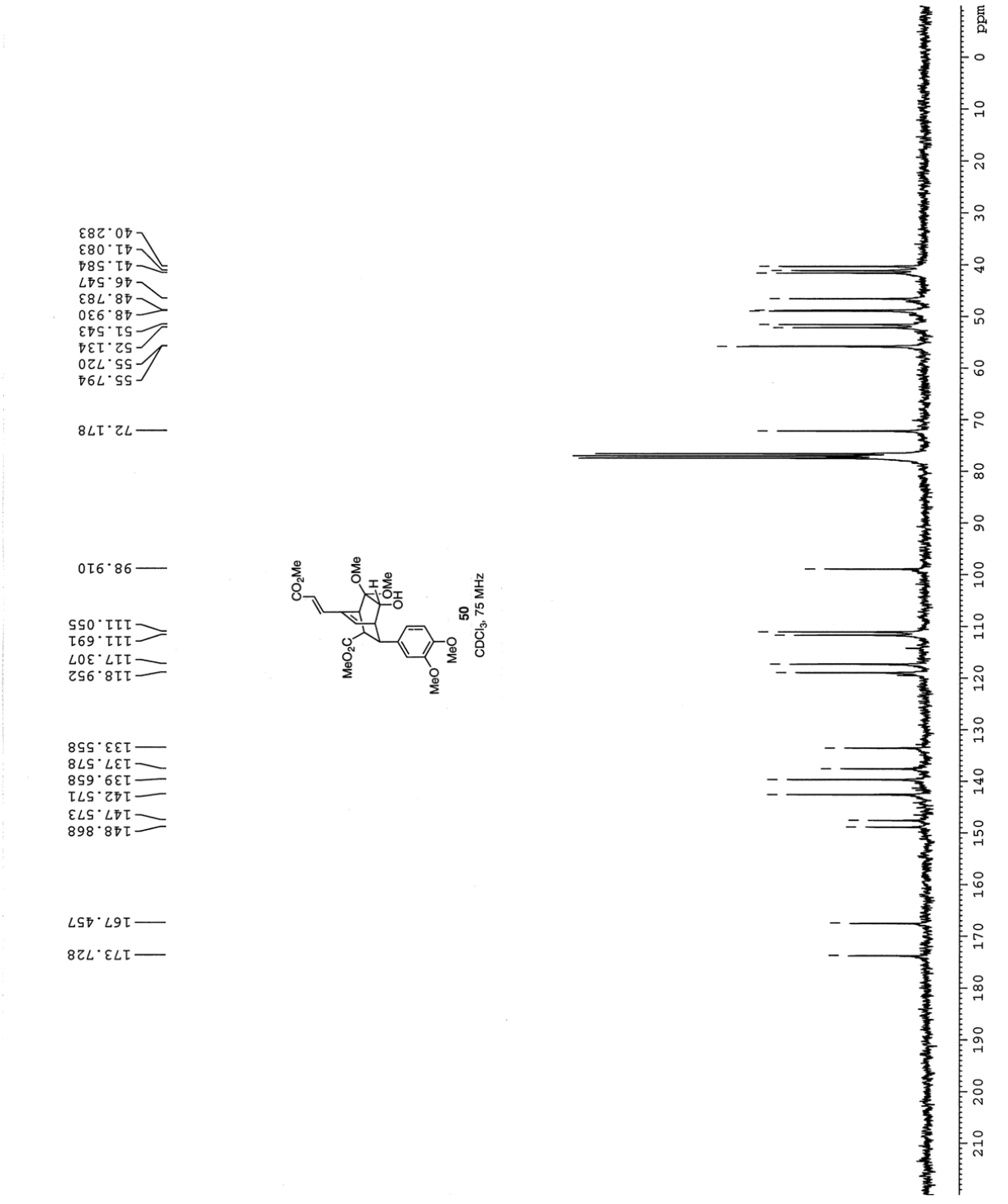

TfBnO
TfBnO
OTfBn
CO2Me
OMe
OMe
O
MeO2C
TfBnO
TfBnO
TfBnO
42
CDCl3, 400 MHz
ppm
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
27.861
1.054
6.055
3.048
2.037
0.998
1.120
6.034
6.299
2.075
0.974
3.043
3.043
2.071
6.342
2.889
1.335
1.077
7.562
7.550
7.530
7.511
7.461
7.431
7.354
7.315
6.865
6.858
6.853
6.848
6.841
6.828
6.818
6.810
6.794
6.789
6.774
6.769
6.716
6.710
6.690
6.684
6.582
6.577
6.562
6.557
6.549
6.200
6.161
5.307
5.298
5.293
5.288
5.274
5.179
5.147
5.069
5.042
4.967
3.888
3.656
3.569
3.373
3.298
3.280
3.152
3.139
3.116
3.102
3.083
3.067
3.048
3.037
3.012
3.001
2.945
2.924
2.908
2.888

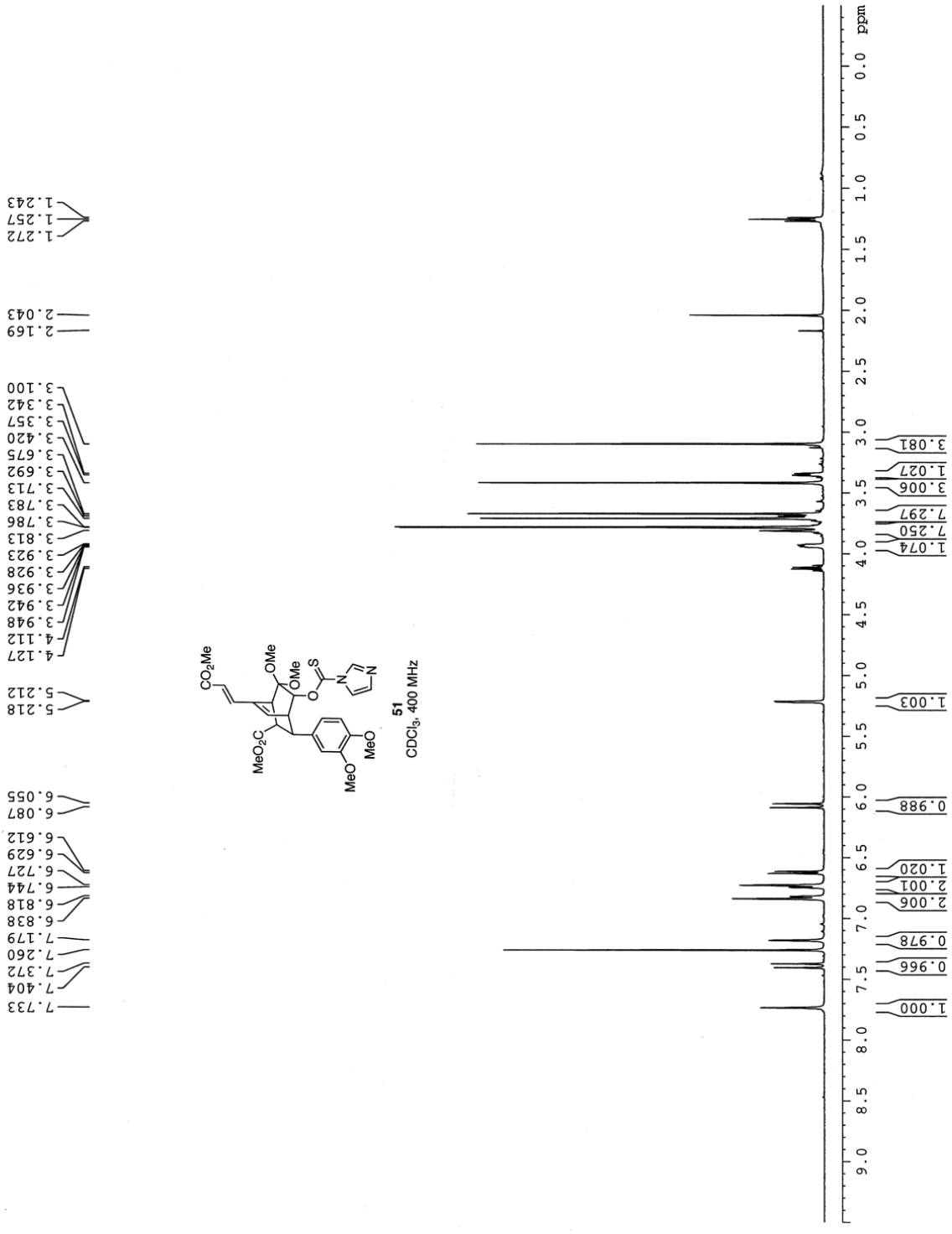

TfBnO
TfBnO
OTfBn
CO2Me
TfBnO
MeO2C
OMe
OMe
TfBnO
TfBnO
42
CDCl3, 75 MHz
ppm
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
200.504
172.199
170.007
169.314
165.930
148.637
148.501
147.825
147.762
142.418
141.163
141.016
140.448
134.286
134.144
130.368
129.930
129.510
129.044
127.346
127.273
127.210
127.119
125.847
125.461
122.701
122.621
122.252
120.651
118.322
116.147
114.904
114.722
114.483
93.937
77.229
73.311
73.049
70.528
70.448
70.335
55.319
52.349
52.298
51.128
49.669
46.682
44.893
42.087
36.982
36.698

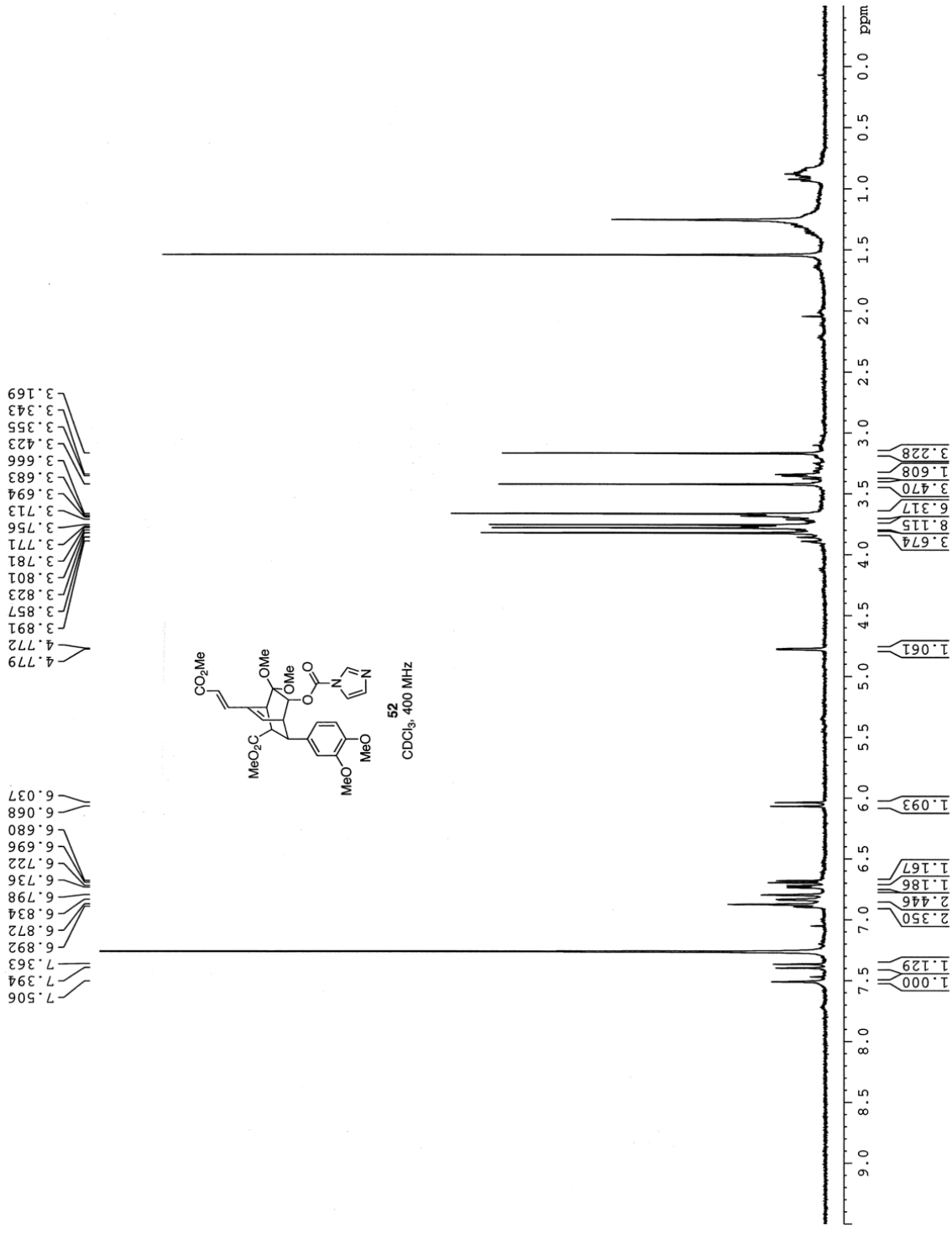

3: hellsorin
acetone-d_6, 500 MHz
ppm

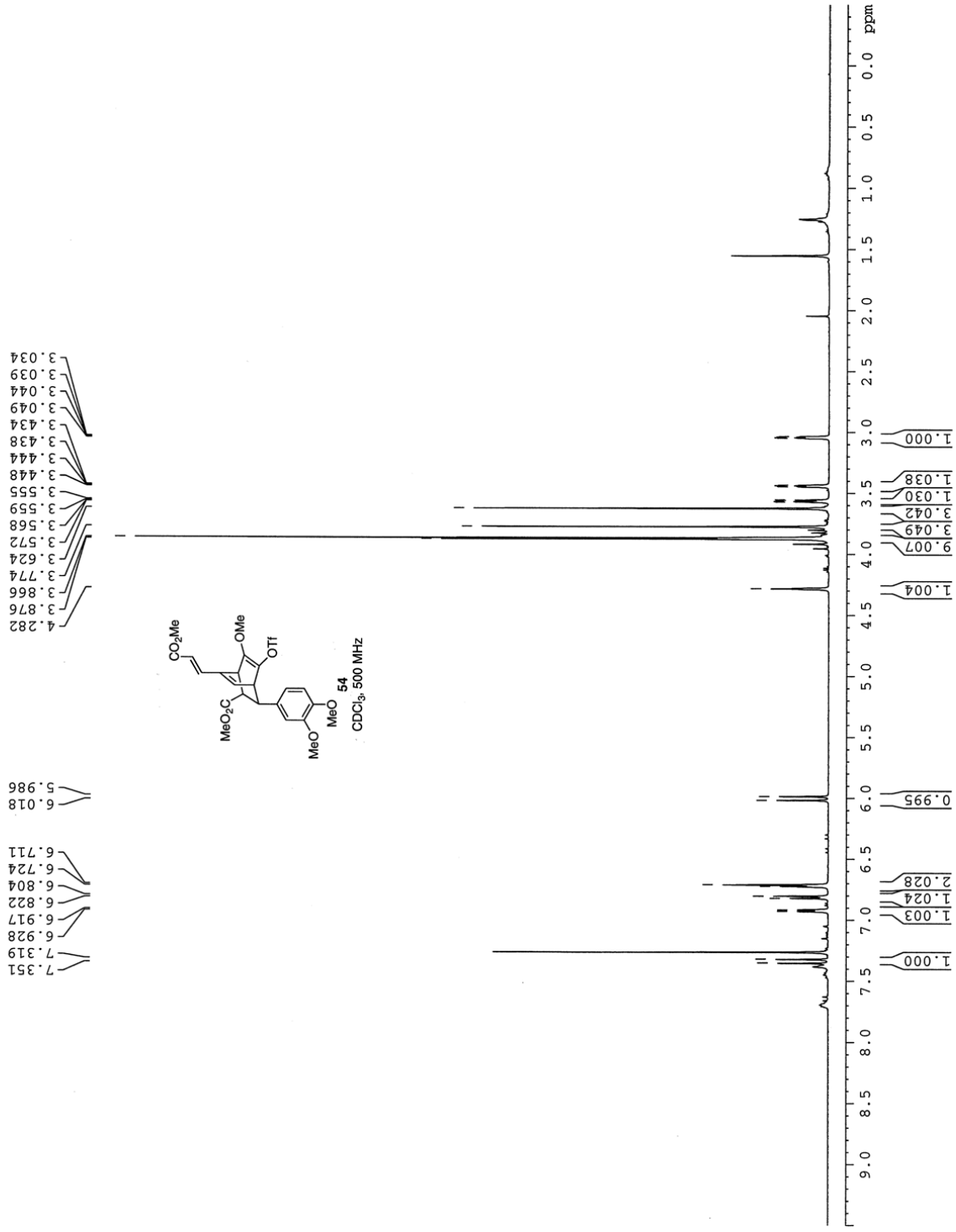

204.587
170.788
170.562
170.161
166.649
147.183
145.938
145.868
145.762
145.057
144.999
142.762
140.570
137.943
137.530
134.682
128.667
121.725
121.697
118.128
117.394
117.312
116.280
116.140
111.285
110.900
81.992
74.940
74.268
57.480
52.887
52.776
52.448
52.383
43.647
37.558
37.492
HO
HO
CO2Me
O
O
O
OH
OH
HO
O
MeO2C
OH
HO
3: helisorin
acetone-d6, 125 MHz
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
ppm

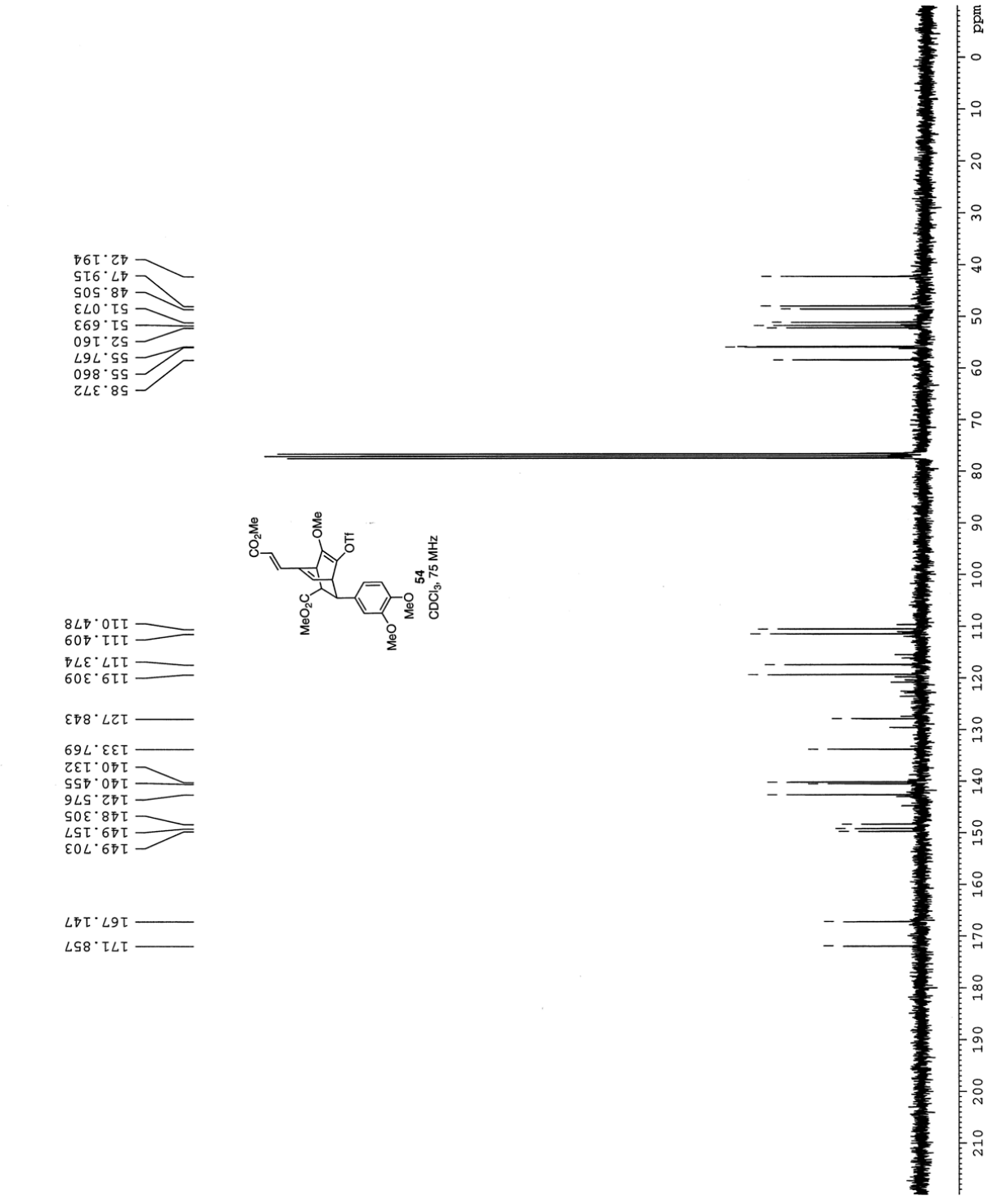

CO2Me
OMe
H
OMe
OH
MeO2C
MeO
MeO
50
CDCl3, 400 MHz
ppm
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
1.000
1.907
1.016
1.077
1.004
3.088
2.999
3.029
1.094
7.057
2.038
1.055
3.040
0.933
7.330
7.291
6.939
6.922
6.918
6.808
6.786
6.693
6.676
6.026
5.987
3.887
3.844
3.752
3.705
3.702
3.611
3.592
3.587
3.572
3.570
3.565
3.562
3.552
3.432
3.426
3.416
3.410
3.400
3.381
3.229
3.223
3.216
3.212
3.206
3.199
3.122
2.222
2.200

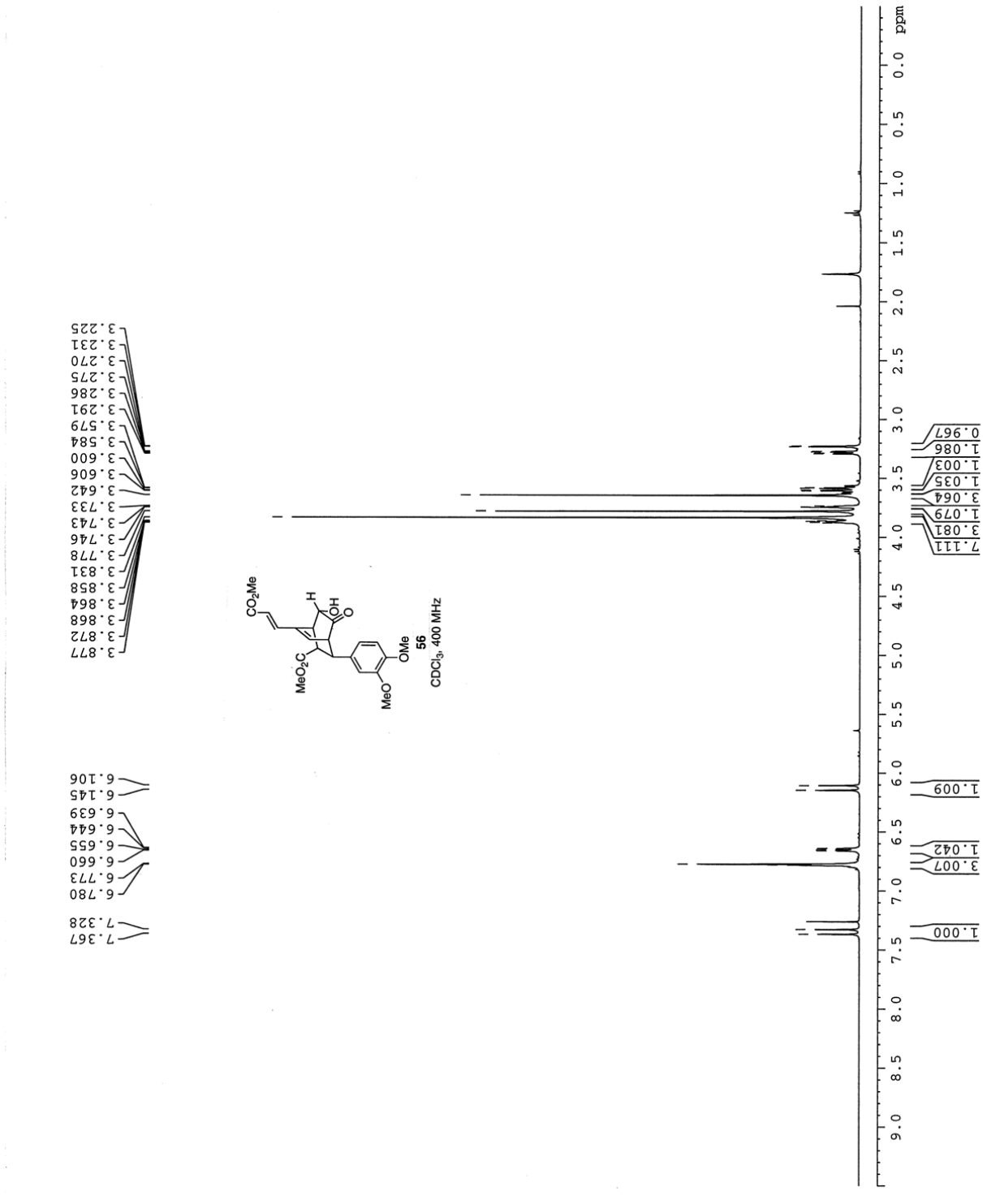

CO2Me
OMe
H
OMe
OH
MeO2C
MeO
MeO
50
CDCl3, 75 MHz
ppm
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
40.283
41.083
41.584
46.547
48.783
48.930
51.543
52.134
55.720
55.794
72.178
98.910
111.055
111.691
117.307
118.952
133.558
137.578
139.658
142.571
147.573
148.868
167.457
173.728

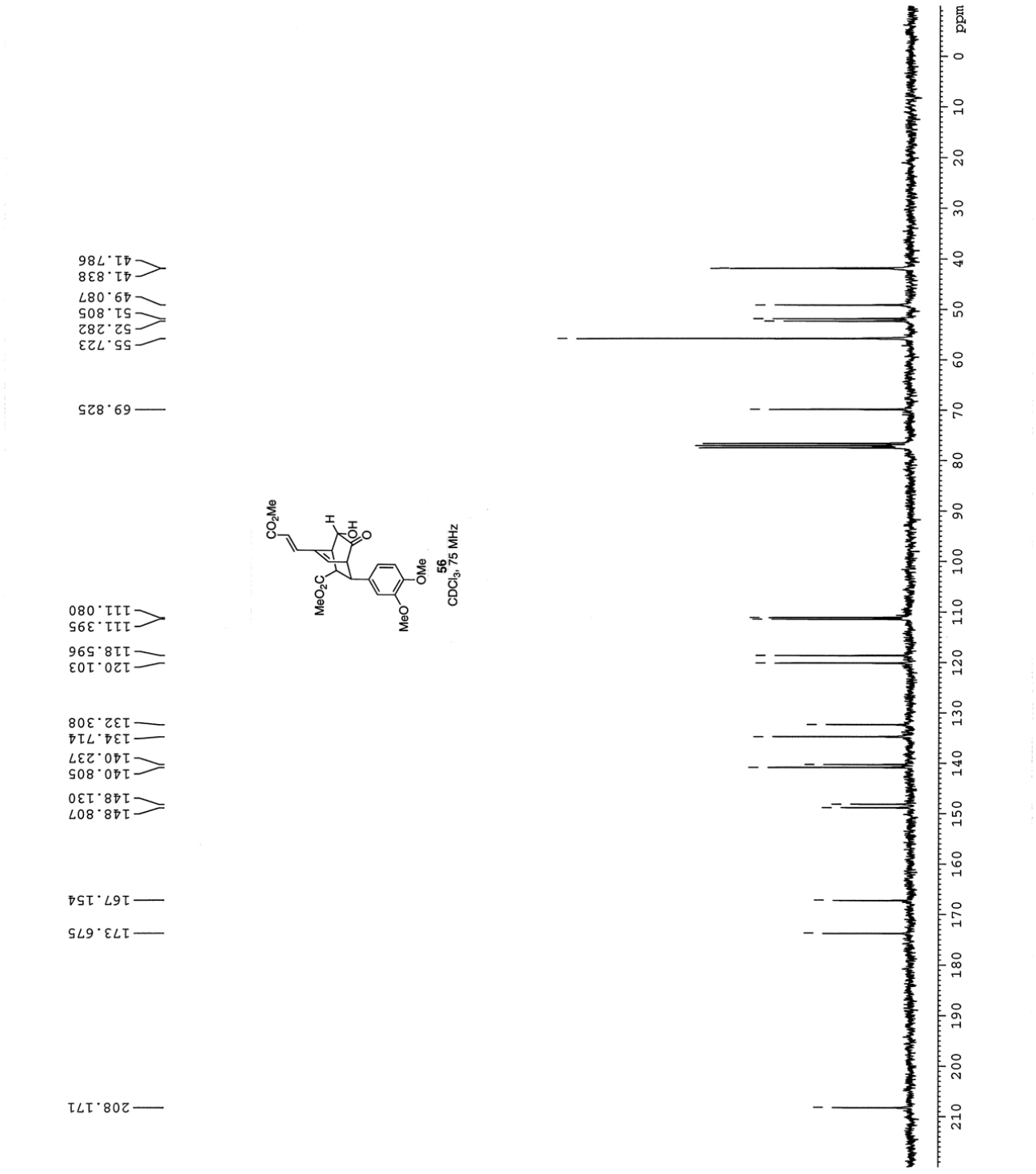

51
CDCl3, 400 MHz
CO2Me
OMe
OMe
O
S
N
N
MeO2C
MeO
MeO
1.272
1.257
1.243
2.169
2.043
3.100
3.342
3.357
3.420
3.675
3.692
3.713
3.783
3.786
3.813
3.923
3.928
3.936
3.942
3.948
4.112
4.127
5.212
5.218
6.055
6.087
6.612
6.629
6.727
6.744
6.818
6.838
7.179
7.260
7.372
7.404
7.733
1.000
0.966
0.978
2.006
2.001
1.020
0.988
1.003
1.074
7.250
7.297
3.006
1.027
3.081
ppm

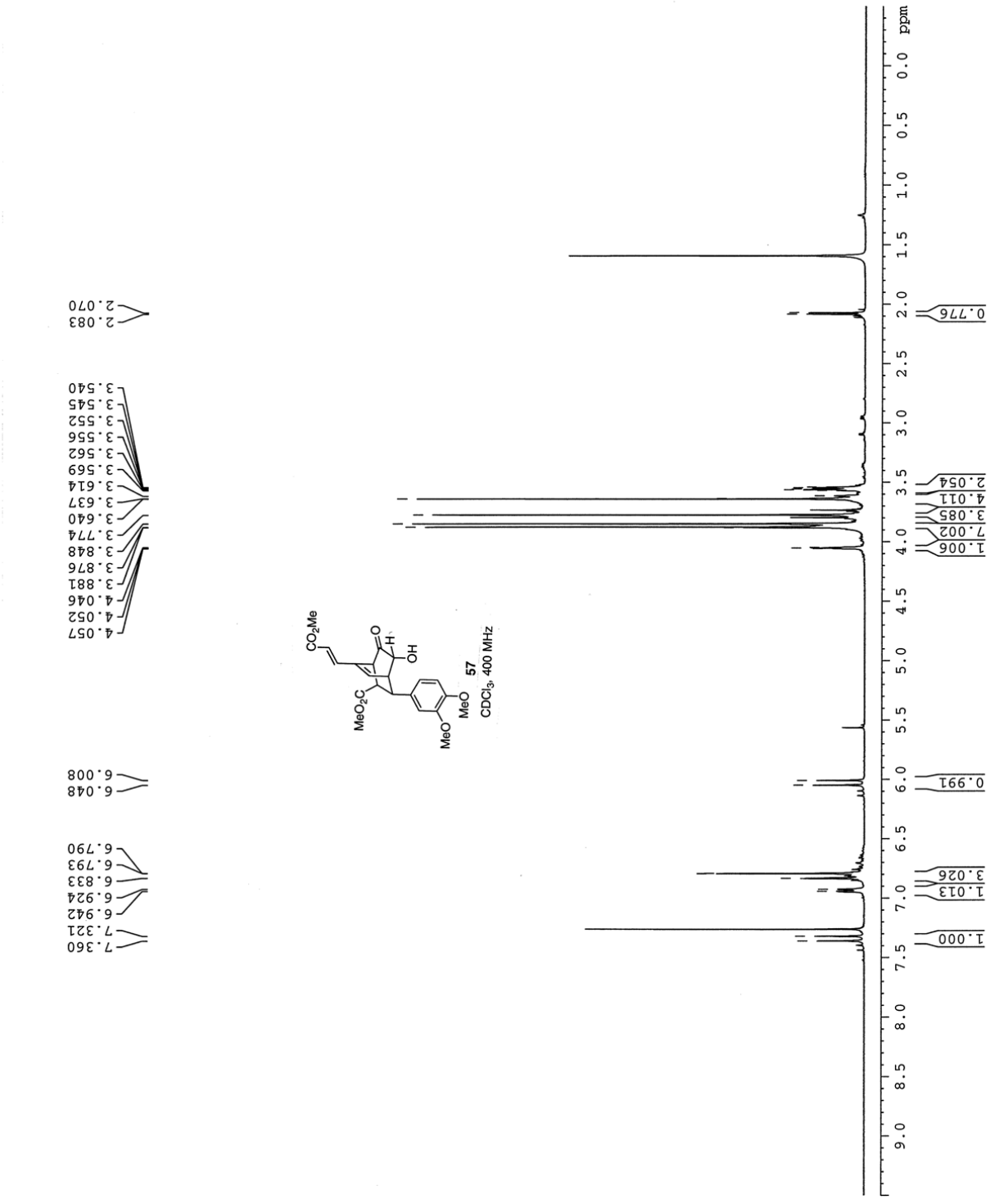

52
CDCl3, 400 MHz
CO2Me
OMe
OMe
O
N
N
MeO2C
MeO
MeO
7.506
7.394
7.363
6.892
6.872
6.834
6.798
6.736
6.722
6.696
6.680
6.068
6.037
4.779
4.772
3.891
3.857
3.823
3.801
3.781
3.771
3.756
3.713
3.694
3.683
3.666
3.423
3.355
3.343
3.169
1.000
1.129
2.350
2.446
1.186
1.167
1.093
1.061
3.674
8.115
6.317
3.470
1.608
3.228
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm

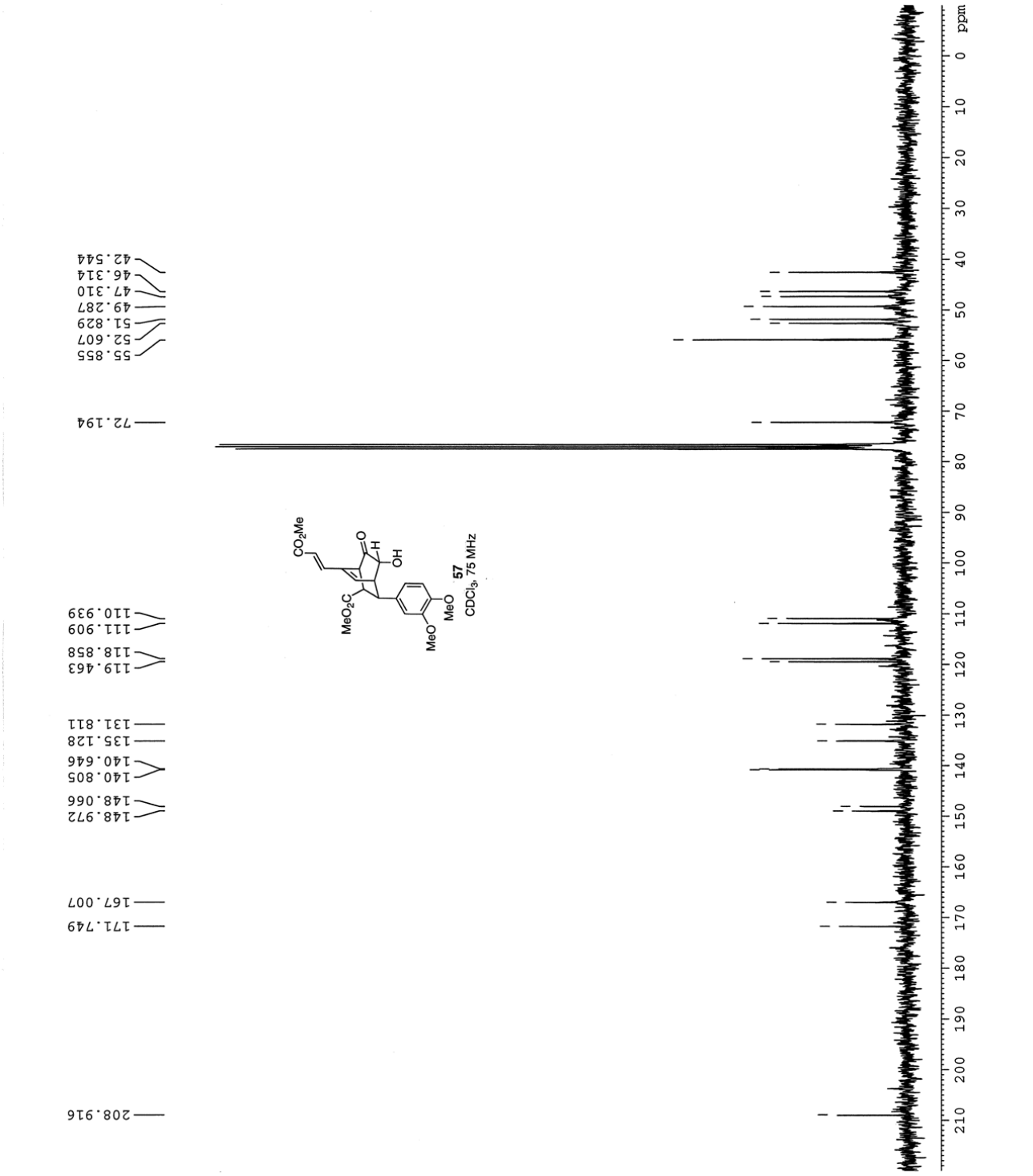

CO2Me
OMe
OTf
MeO2C
MeO
MeO
54
CDCl3, 500 MHz
4.282
3.876
3.866
3.774
3.624
3.572
3.568
3.559
3.555
3.448
3.444
3.438
3.434
3.049
3.044
3.039
3.034
6.018
5.986
7.351
7.319
6.928
6.917
6.822
6.804
6.724
6.711
1.000
1.003
1.024
2.028
0.995
1.004
9.007
3.049
3.042
1.030
1.038
1.000
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm

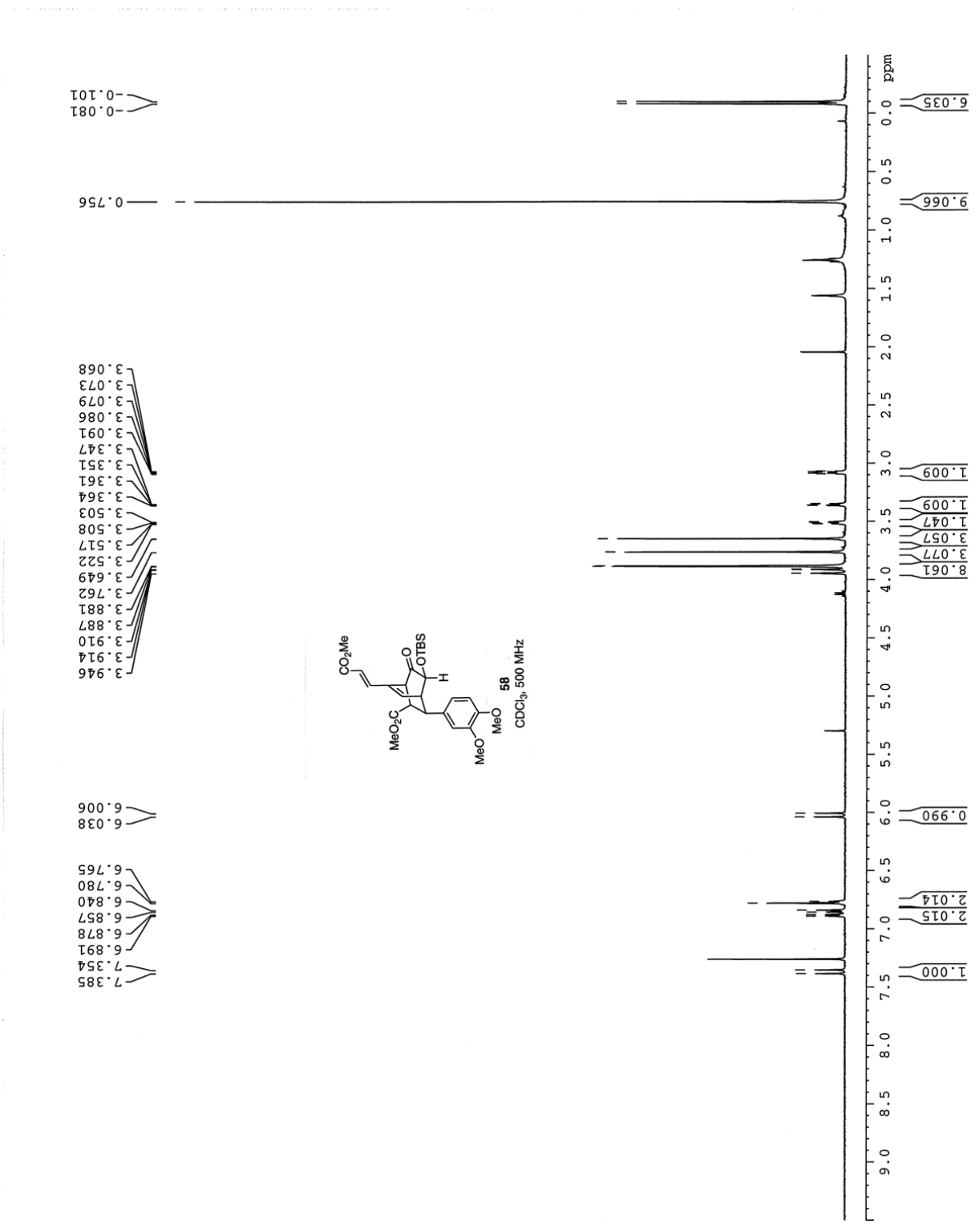

CO2Me
OMe
OTf
MeO2C
MeO
MeO
54
CDCl3, 75 MHz
ppm
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
42.194
47.915
48.505
51.073
51.693
52.160
55.767
55.860
58.372
110.478
111.409
117.374
119.309
127.843
133.769
140.132
140.455
142.576
148.305
149.157
149.703
167.147
171.857

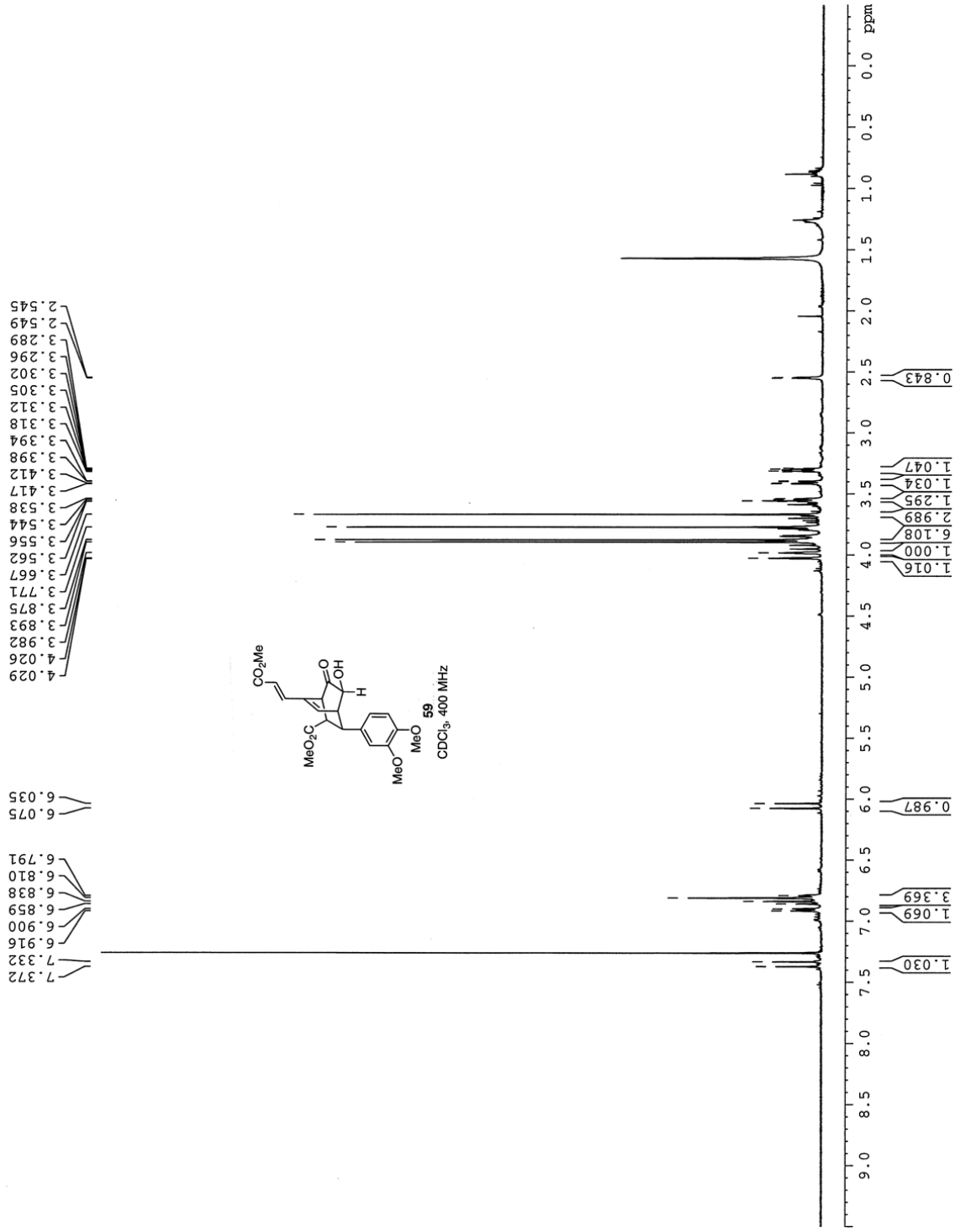

3.225
3.231
3.270
3.275
3.286
3.291
3.579
3.584
3.600
3.606
3.642
3.733
3.743
3.746
3.778
3.831
3.858
3.864
3.868
3.872
3.877
6.106
6.145
6.639
6.644
6.655
6.660
6.773
6.780
7.328
7.367
CO2Me
MeO2C
OMe
MeO
H
OH
O
56
CDCl3, 400 MHz
0.967
1.086
1.003
1.035
3.064
1.079
3.081
7.111
1.009
1.042
3.007
1.000
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm


208.171
173.675
167.154
148.807
148.130
140.805
140.237
134.714
132.308
120.103
118.596
111.395
111.080
69.825
55.723
52.282
51.805
49.087
41.838
41.786
CO2Me
H
OH
O
MeO2C
OMe
MeO
56
CDCl3, 75 MHz
ppm


CO2Me
O
H
OH
MeO2C
MeO
MeO
57
CDCl3, 400 MHz
ppm
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
1.000
1.013
3.026
0.991
1.006
7.002
3.085
4.011
2.054
0.776
7.360
7.321
6.942
6.924
6.833
6.793
6.790
6.048
6.008
4.057
4.052
4.046
3.881
3.876
3.848
3.774
3.640
3.637
3.614
3.569
3.562
3.556
3.552
3.545
3.540
2.083
2.070


42.544
46.314
47.310
49.287
51.829
52.607
55.855
72.194
110.939
111.909
118.858
119.463
131.811
135.128
140.646
140.805
148.066
148.972
167.007
171.749
208.916
CO2Me
O
H
OH
MeO2C
MeO
MeO
57
CDCl3, 75 MHz
ppm


CO2Me
O
OTBS
H
MeO2C
MeO
MeO
58
CDCl3, 500 MHz
ppm
-0.101
-0.081
0.756
3.068
3.073
3.079
3.086
3.091
3.347
3.351
3.361
3.364
3.503
3.508
3.517
3.522
3.649
3.762
3.881
3.887
3.910
3.914
3.946
6.006
6.038
6.765
6.780
6.840
6.857
6.878
6.891
7.354
7.385
6.035
9.066
1.009
1.009
1.047
3.057
3.077
8.061
0.990
2.014
2.015
1.000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7.332
6.916
6.900
6.859
6.838
6.810
6.791
6.075
6.035
4.029
4.026
3.982
3.893
3.875
3.771
3.667
3.562
3.556
3.544
3.538
3.417
3.412
3.398
3.394
3.318
3.312
3.305
3.302
3.296
3.289
2.549
2.545
CO2Me
O
OH
H
MeO2C
MeO
MeO
59
CDCl3, 400 MHz
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1.034
1.295
2.989
6.108
1.000
1.016
0.987
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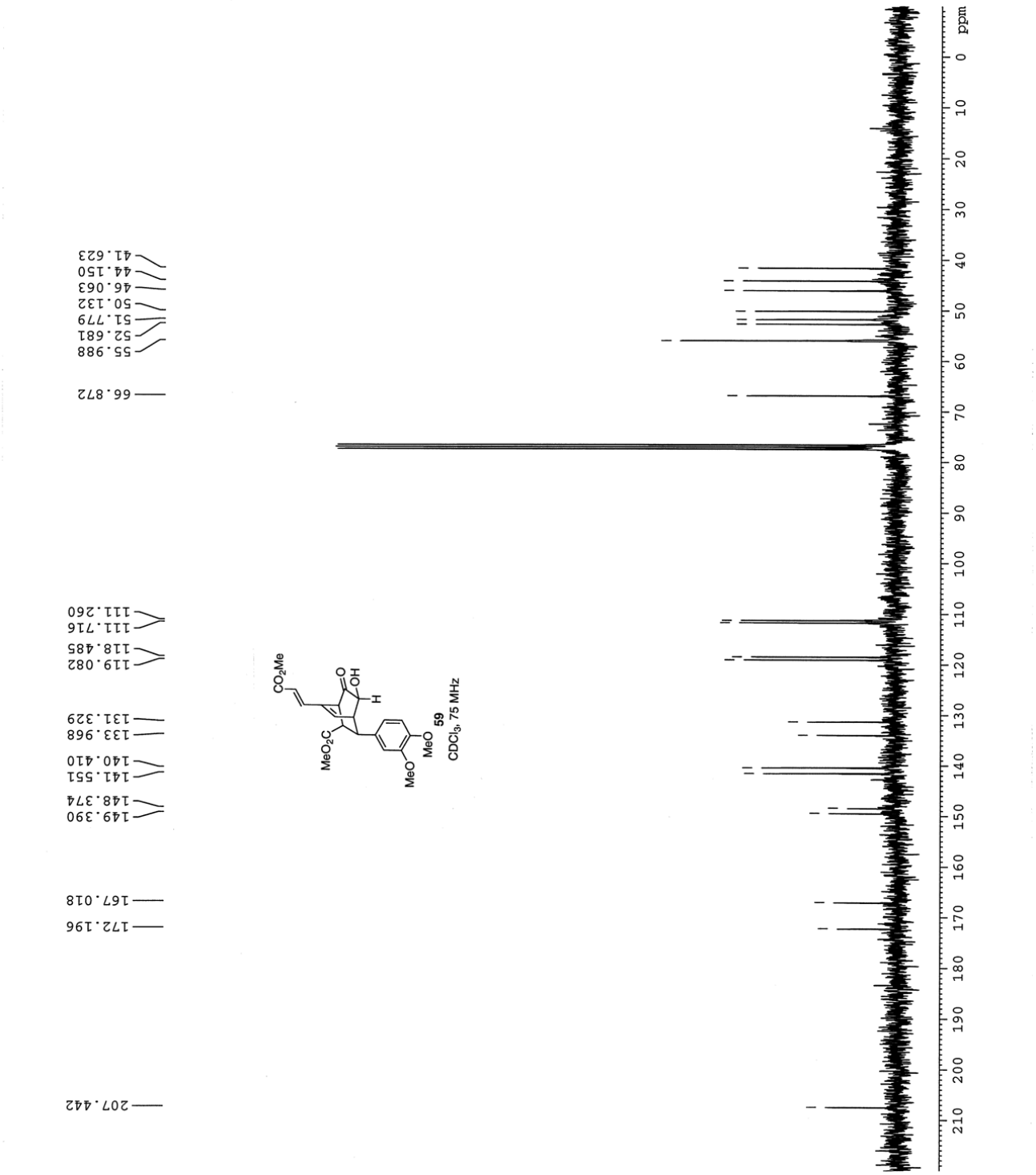
1.030
ppm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172.196
167.018
149.390
148.374
141.551
140.410
133.968
131.329
119.082
118.485
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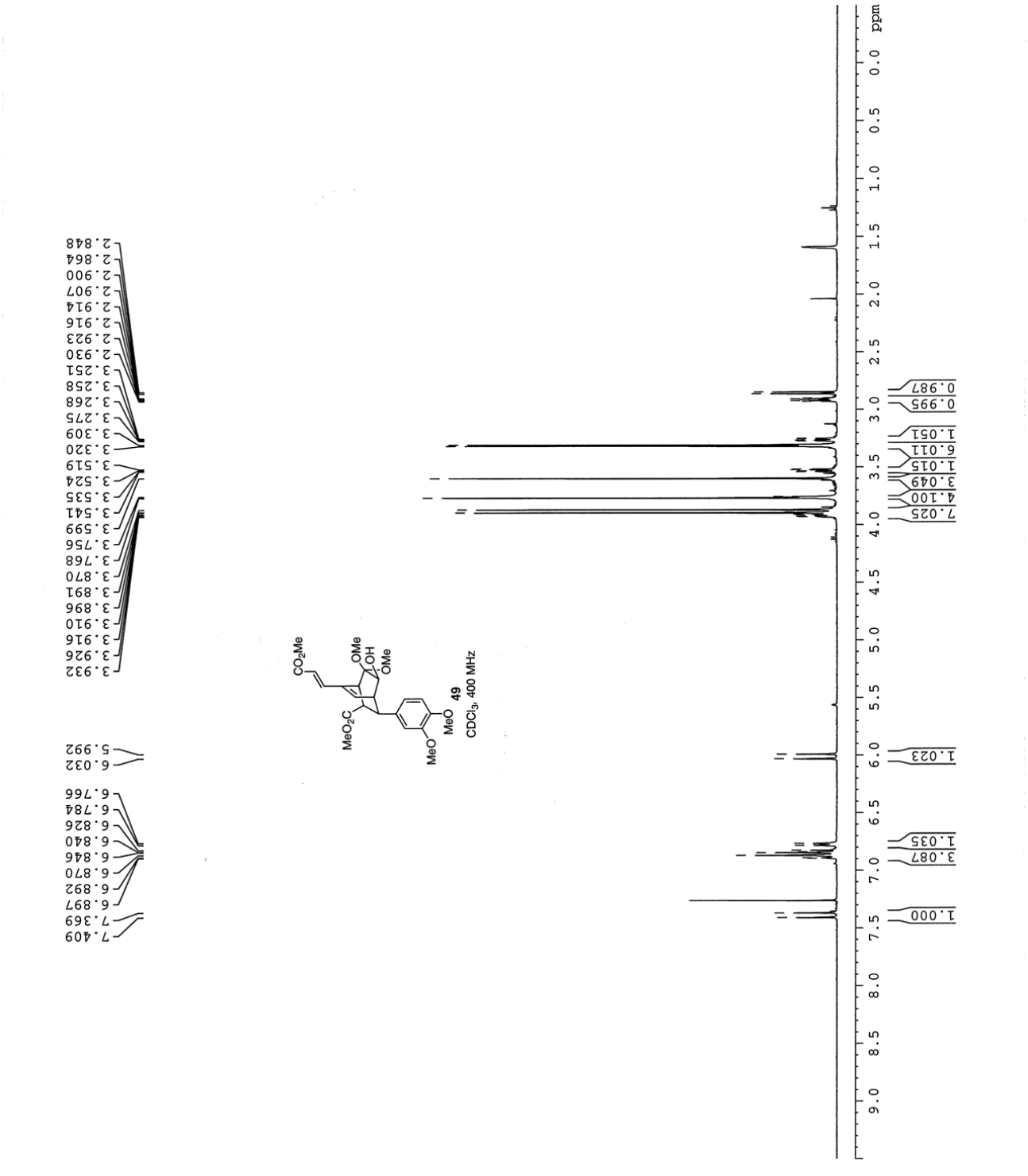
111.260
66.872
55.988
52.681
51.779
50.132
46.063
44.150
41.623
CO2Me
O
OH
H
MeO2C
MeO
MeO
59
CDCl3, 75 MHz
ppm


CO2Me
OMe
OH
OMe
MeO2C
MeO
MeO
49
CDCl3, 400 MHz
ppm
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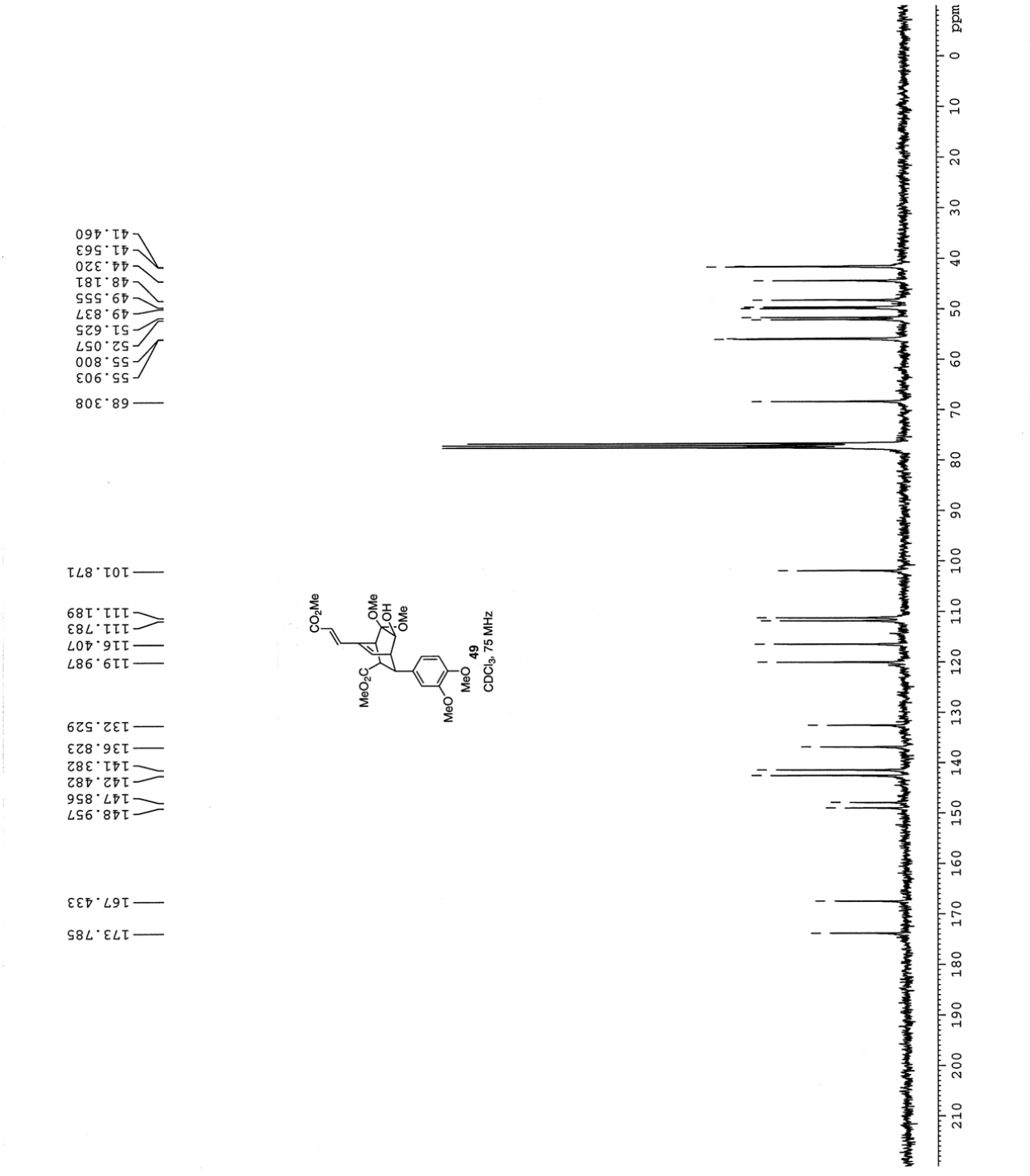
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
1.000
3.087
1.035
1.023
7.025
4.100
3.049
1.015
6.011
1.051
0.995
0.987
7.409
7.369
6.897
6.892
6.870
6.846
6.840
6.826
6.784
6.766
6.032
5.992
3.932
3.926
3.916
3.910
3.896
3.891
3.870
3.768
3.756
3.599
3.541
3.535
3.524
3.519
3.320
3.309
3.275
3.268
3.258
3.251
2.930
2.923
2.916
2.914
2.907
2.900
2.864
2.848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41.563
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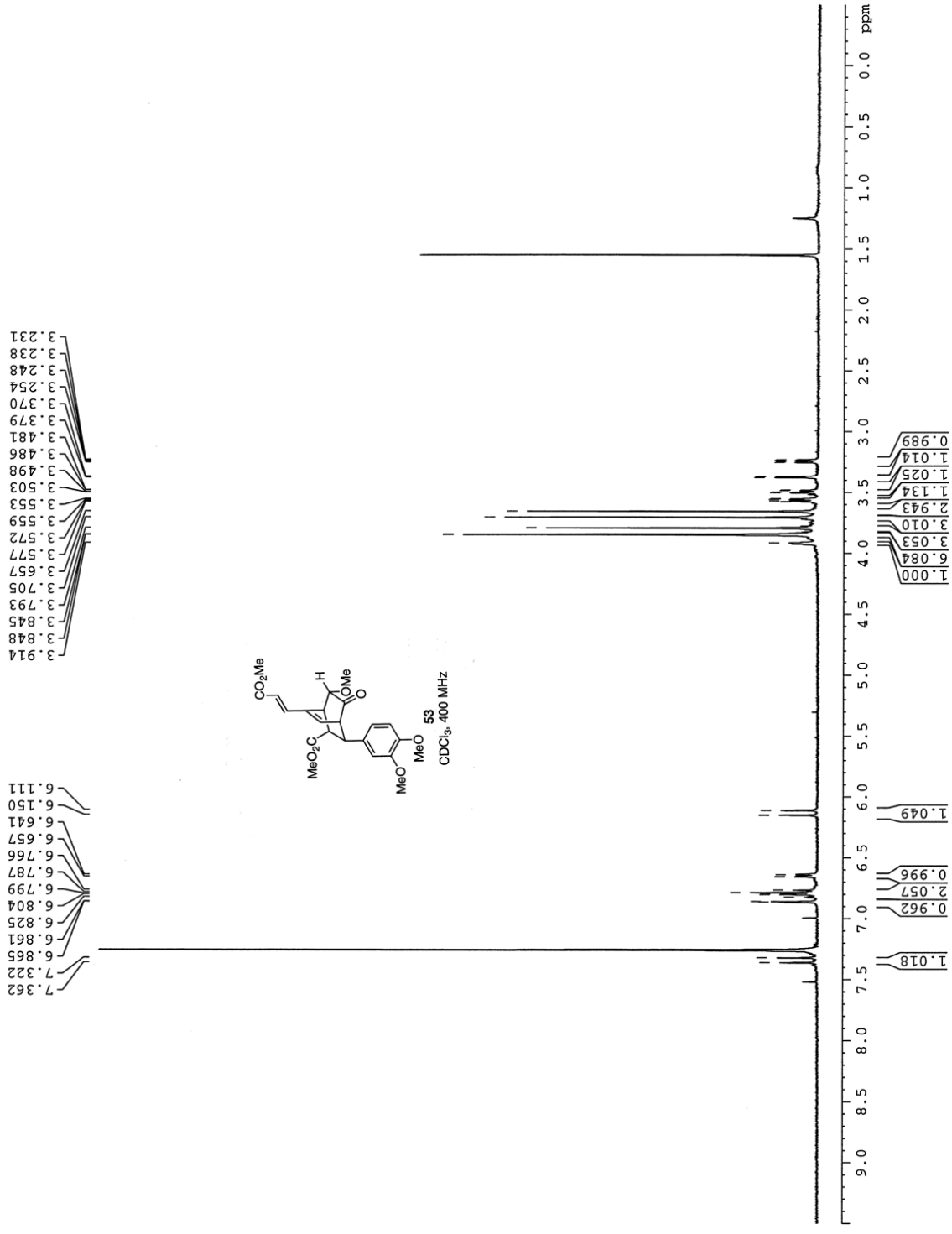
48.181
49.555
49.837
51.625
52.057
55.800
55.903
68.308
101.871
111.189
111.783
116.407
119.987
132.529
136.823
141.382
142.482
147.856
148.957
167.433
173.785
CO2Me
OMe
OH
OMe
MeO2C
MeO
MeO
49
CDCl3, 75 MHz
ppm


CO2Me
H
OMe
O
MeO2C
MeO
MeO
53
CDCl3, 400 MHz
3.914
3.848
3.845
3.793
3.705
3.657
3.577
3.572
3.559
3.553
3.503
3.498
3.486
3.481
3.379
3.370
3.254
3.248
3.238
3.231
7.362
7.322
6.865
6.861
6.825
6.804
6.799
6.787
6.766
6.657
6.641
6.150
6.111
1.000
6.084
3.053
3.010
2.943
1.134
1.025
1.014
0.989
1.049
0.962
2.057
0.996
1.018
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
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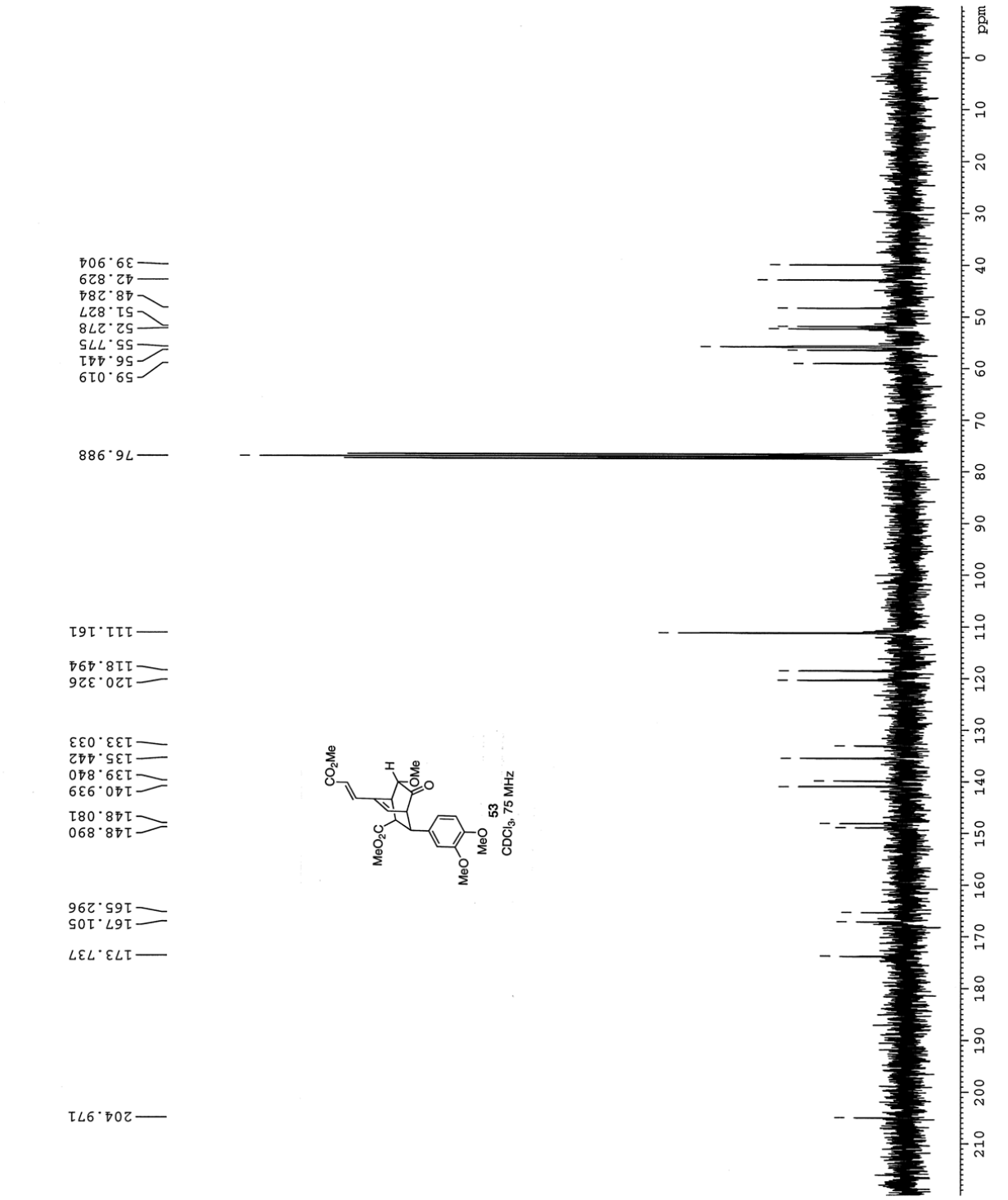
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm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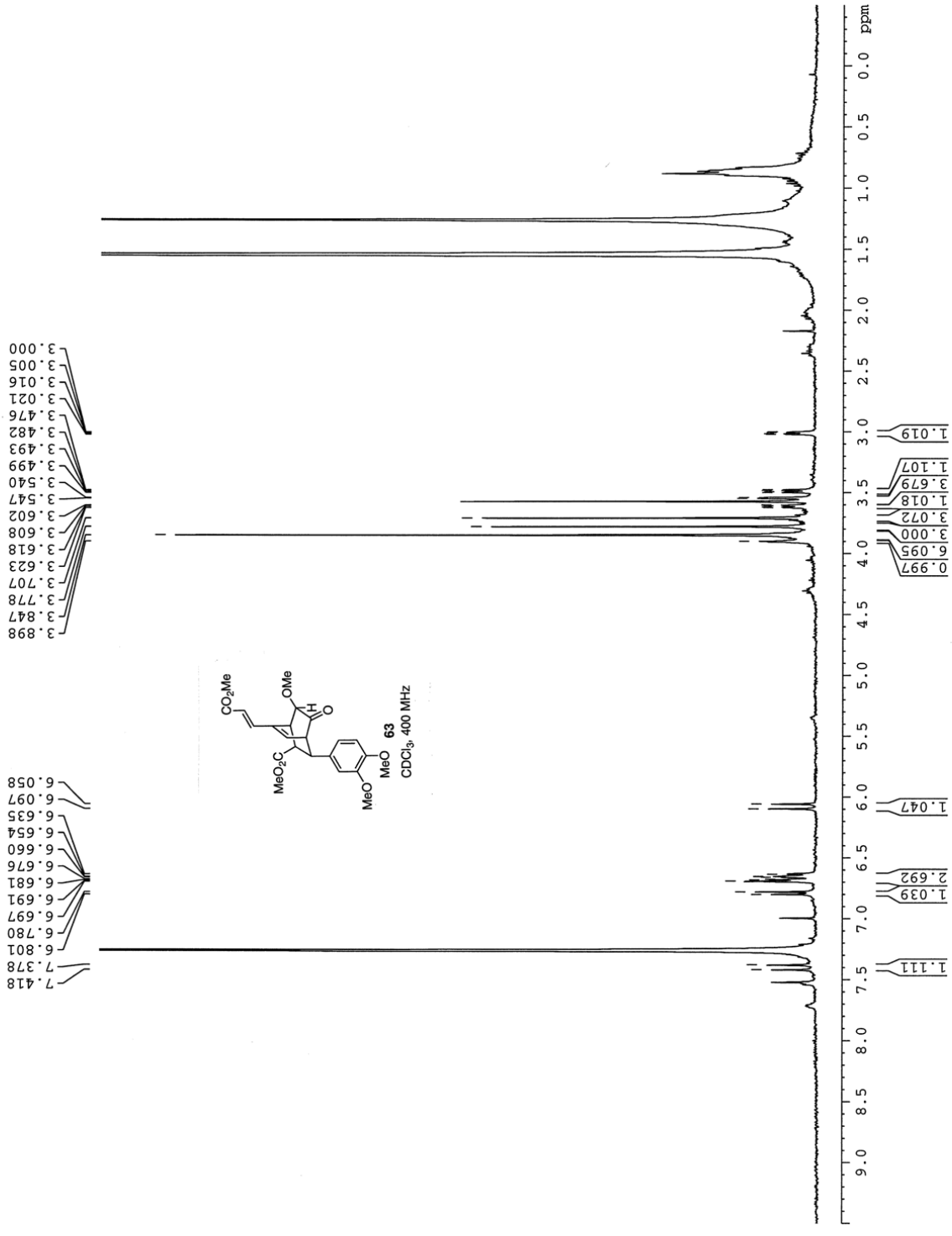
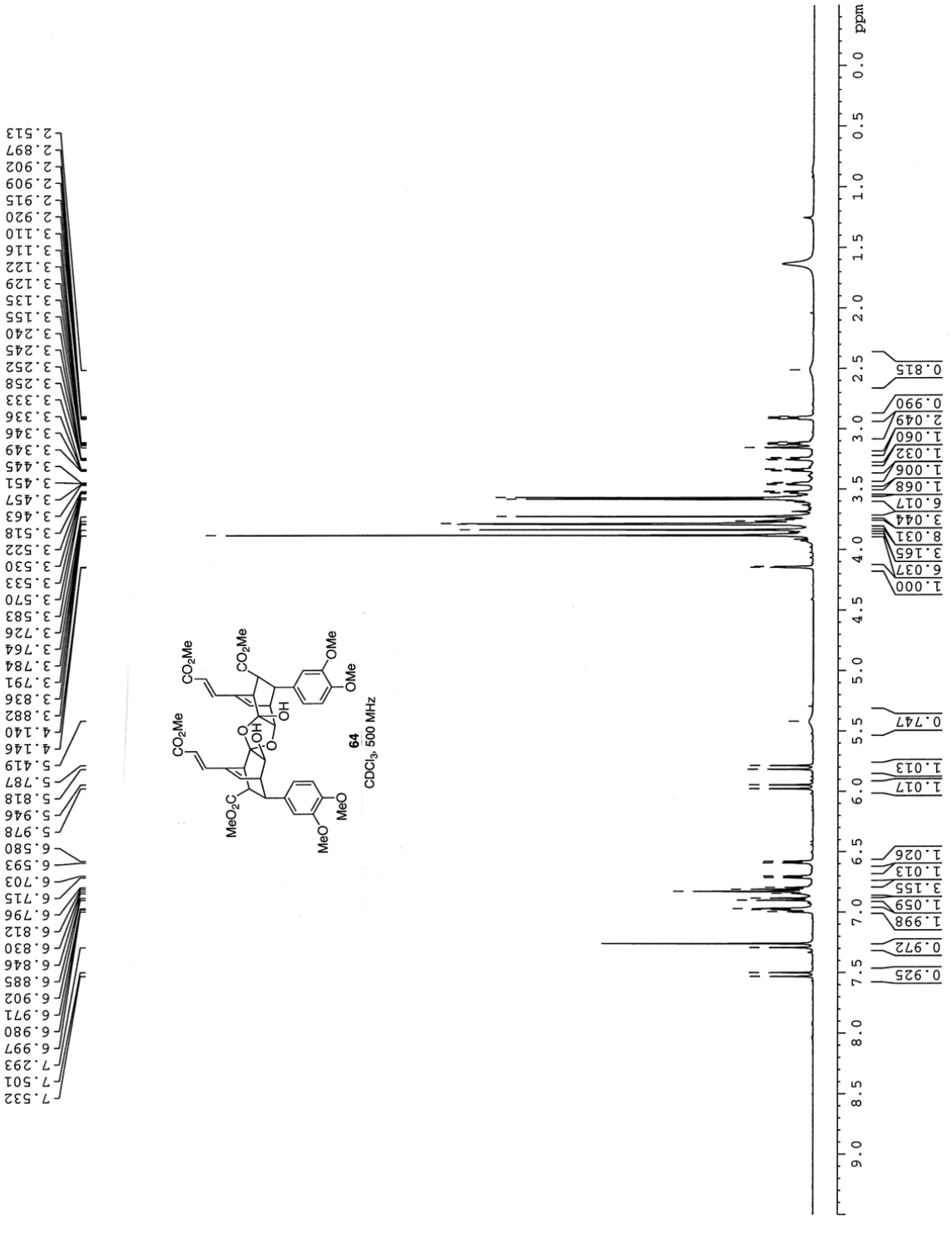
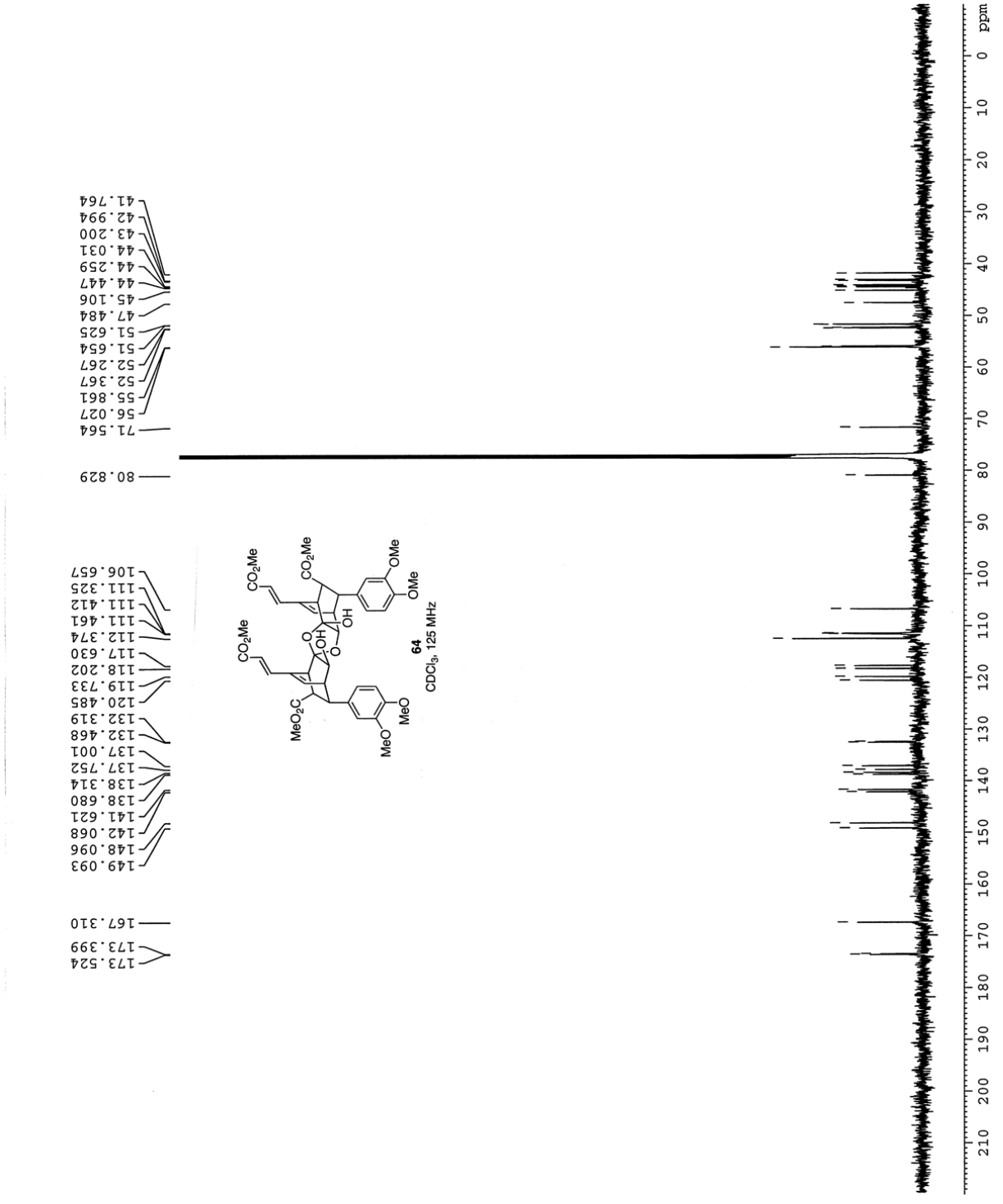
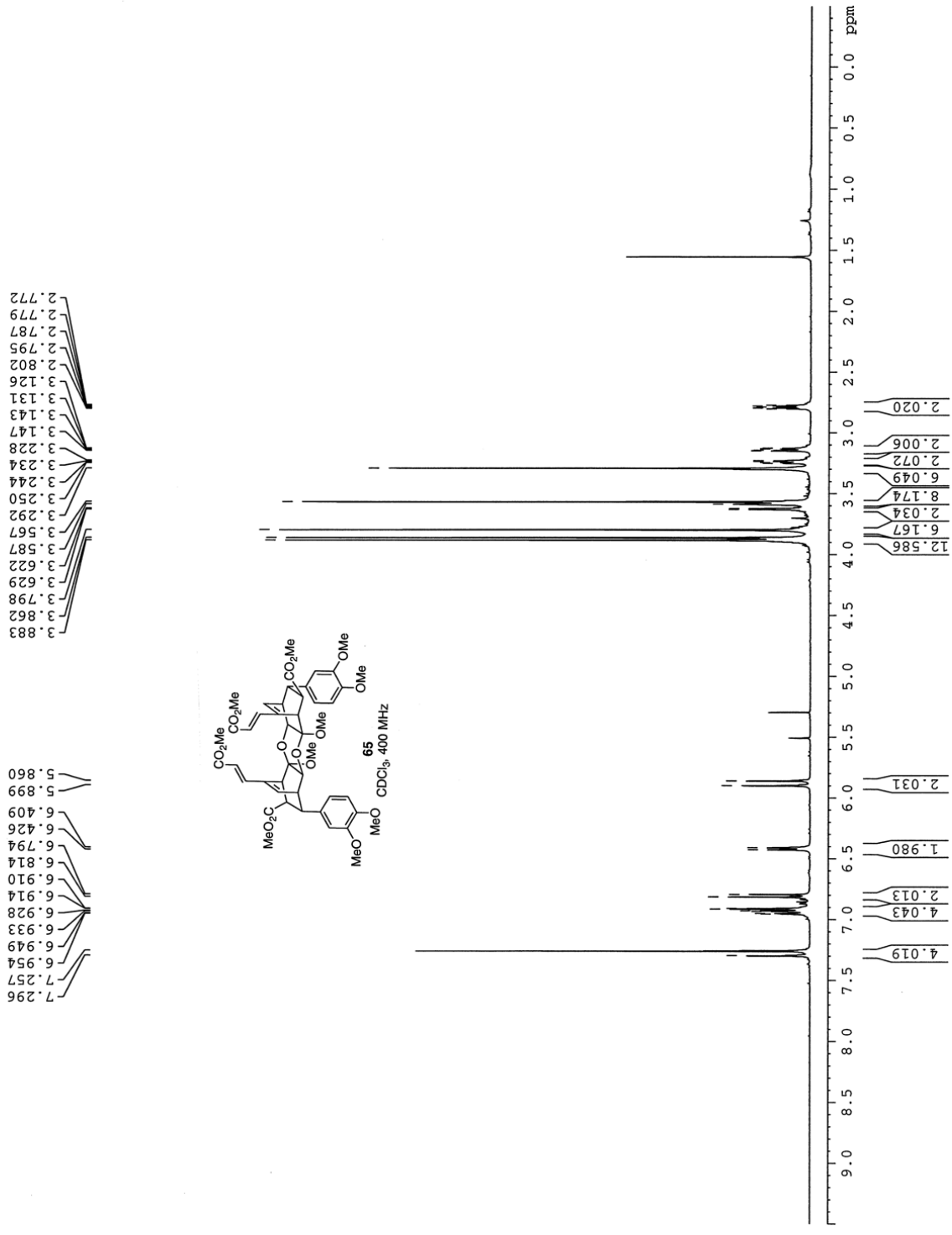
173.737
167.105
165.296
148.890
148.081
140.939
139.840
135.442
133.033
120.326
118.494
111.161
76.988
59.019
56.441
55.775
52.278
51.827
48.284
42.829
39.904
ppm
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
CO2Me
H
OMe
O
MeO2C
MeO
MeO
53
CDCl3, 75 MHz


63
CDCl3, 400 MHz
ppm


64
CDCl3, 500 MHz
ppm


41.764
42.994
43.200
44.031
44.259
44.447
45.106
47.484
51.625
51.654
52.267
52.367
55.861
56.027
71.564
80.829
106.657
111.325
111.412
111.461
112.374
117.630
118.202
119.733
120.485
132.319
132.468
137.001
137.752
138.314
138.680
141.621
142.068
148.096
149.093
167.310
173.399
173.524
CO2Me
CO2Me
OMe
OMe
OH
O
OH
O
CO2Me
MeO2C
MeO
MeO
64
CDCl3, 125 MHz
ppm


65
CDCl3, 400 MHz
CO2Me
CO2Me
CO2Me
OMe
OMe
OMe
OMe
MeO2C
MeO
MeO
ppm
12.586
6.167
2.034
8.174
6.049
2.072
2.006
2.020
4.019
4.043
2.013
1.980
2.031
7.296
7.257
6.954
6.949
6.933
6.928
6.914
6.910
6.814
6.794
6.426
6.409
5.899
5.860
3.883
3.862
3.798
3.629
3.622
3.587
3.567
3.292
3.250
3.244
3.234
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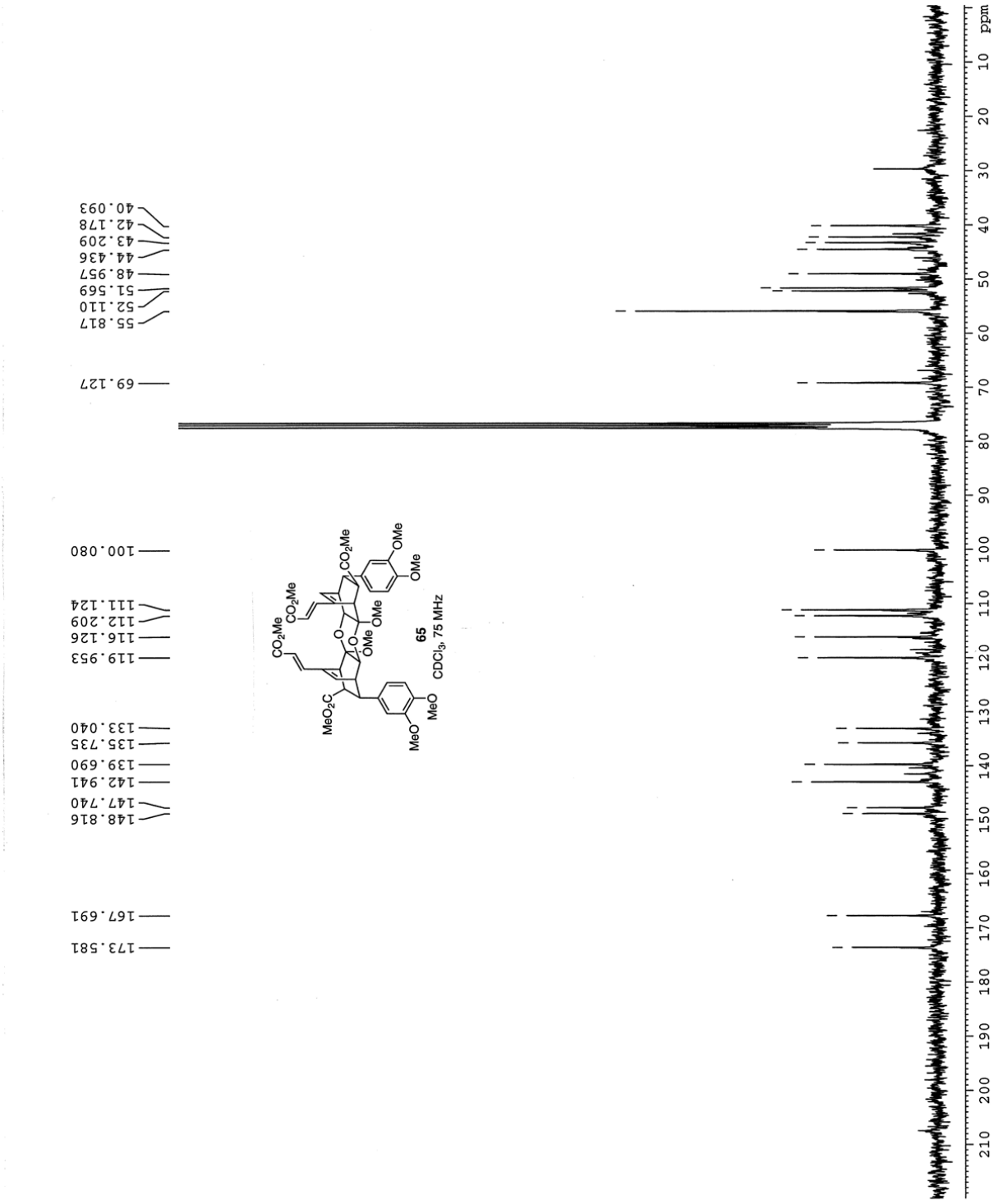
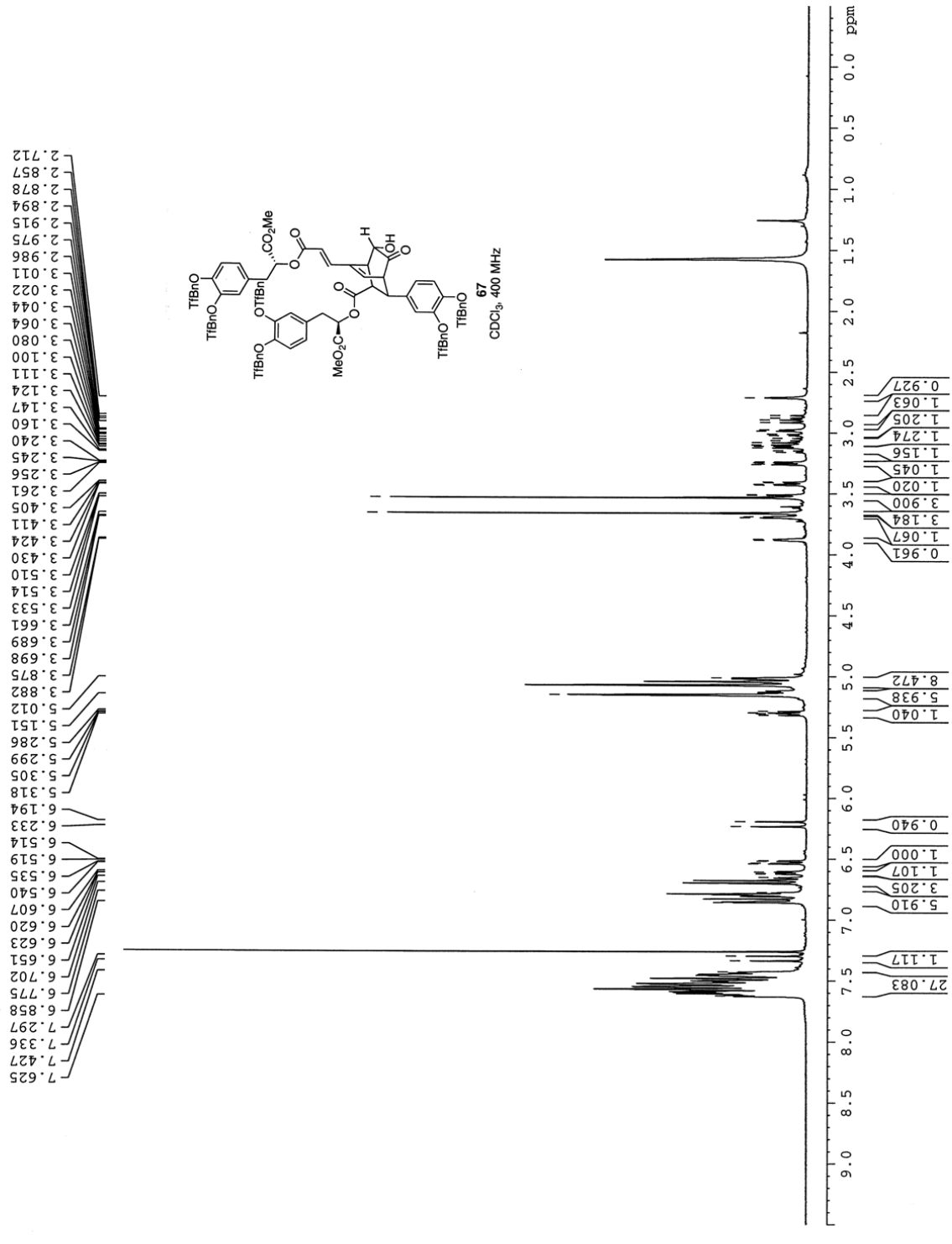
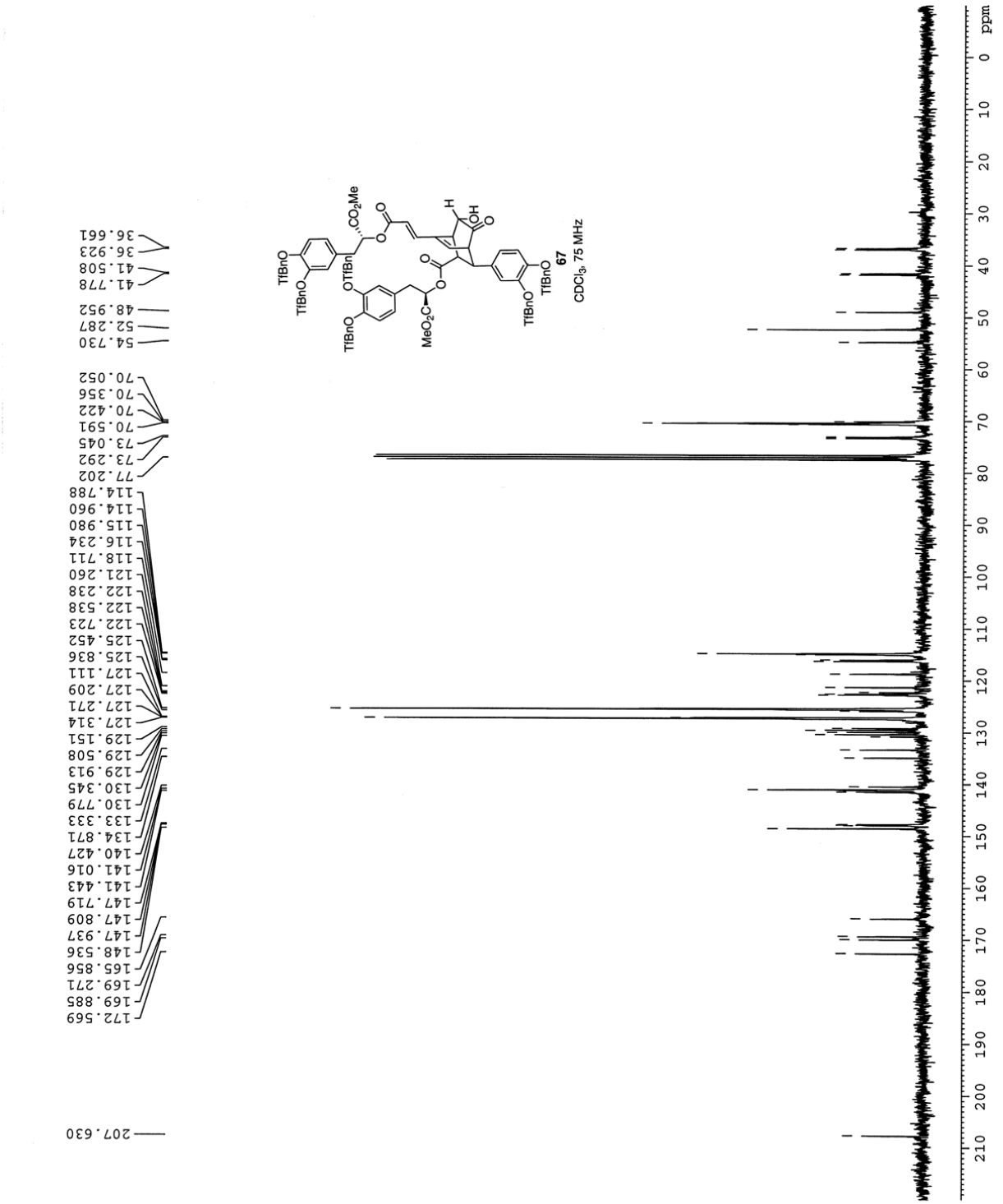
3.147
3.143
3.131
3.126
2.802
2.795
2.787
2.779
2.772


40.093
42.178
43.209
44.436
48.957
51.569
52.110
55.817
69.127
100.080
111.124
112.209
116.126
119.953
133.040
135.735
139.690
142.941
147.740
148.816
167.691
173.581
ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
65
CDCl3, 75 MHz


TfBnO
TfBnO
TfBnO
OTfBn
CO2Me
MeO2C
TfBnO
TfBnO
OH
H
67
CDCl3, 400 MHz
ppm
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
27.083
1.117
5.910
3.205
1.107
1.000
0.940
1.040
5.938
8.472
0.961
1.067
3.184
3.900
1.020
1.045
1.156
1.274
1.205
1.063
0.927


TfBnO
TfBnO
OTfBn
CO2Me
TfBnO
MeO2C
H
OH
O
TfBnO
TfBnO
67
CDCl3, 75 MHz
ppm
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
207.630
172.569
169.885
169.271
165.856
148.536
147.937
147.809
147.719
141.443
141.016
140.427
134.871
133.333
130.779
130.345
129.913
129.508
129.151
127.314
127.271
127.209
127.111
125.836
125.452
122.723
122.538
122.238
121.260
118.711
116.234
115.980
114.960
114.788
77.202
73.292
73.045
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70.356
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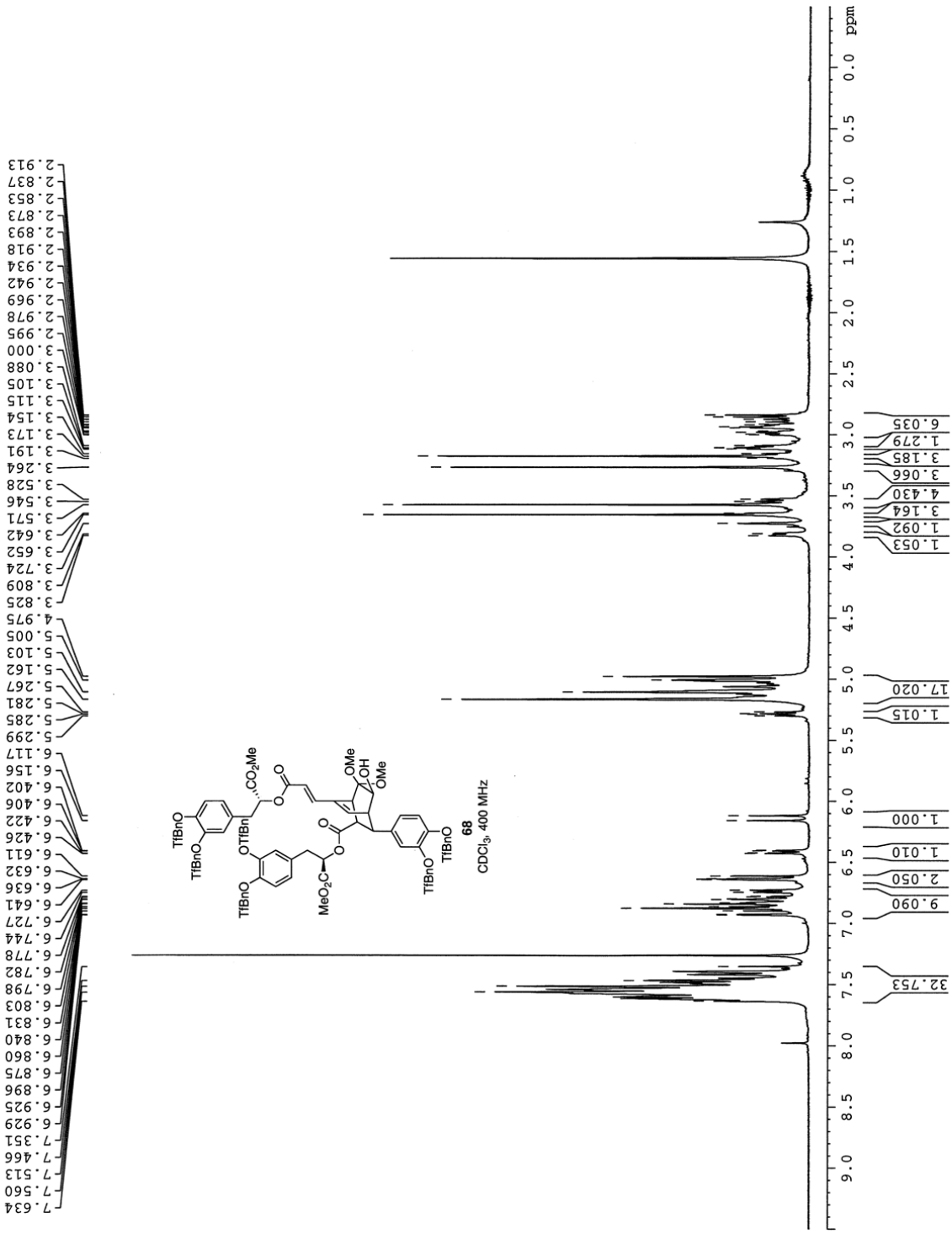
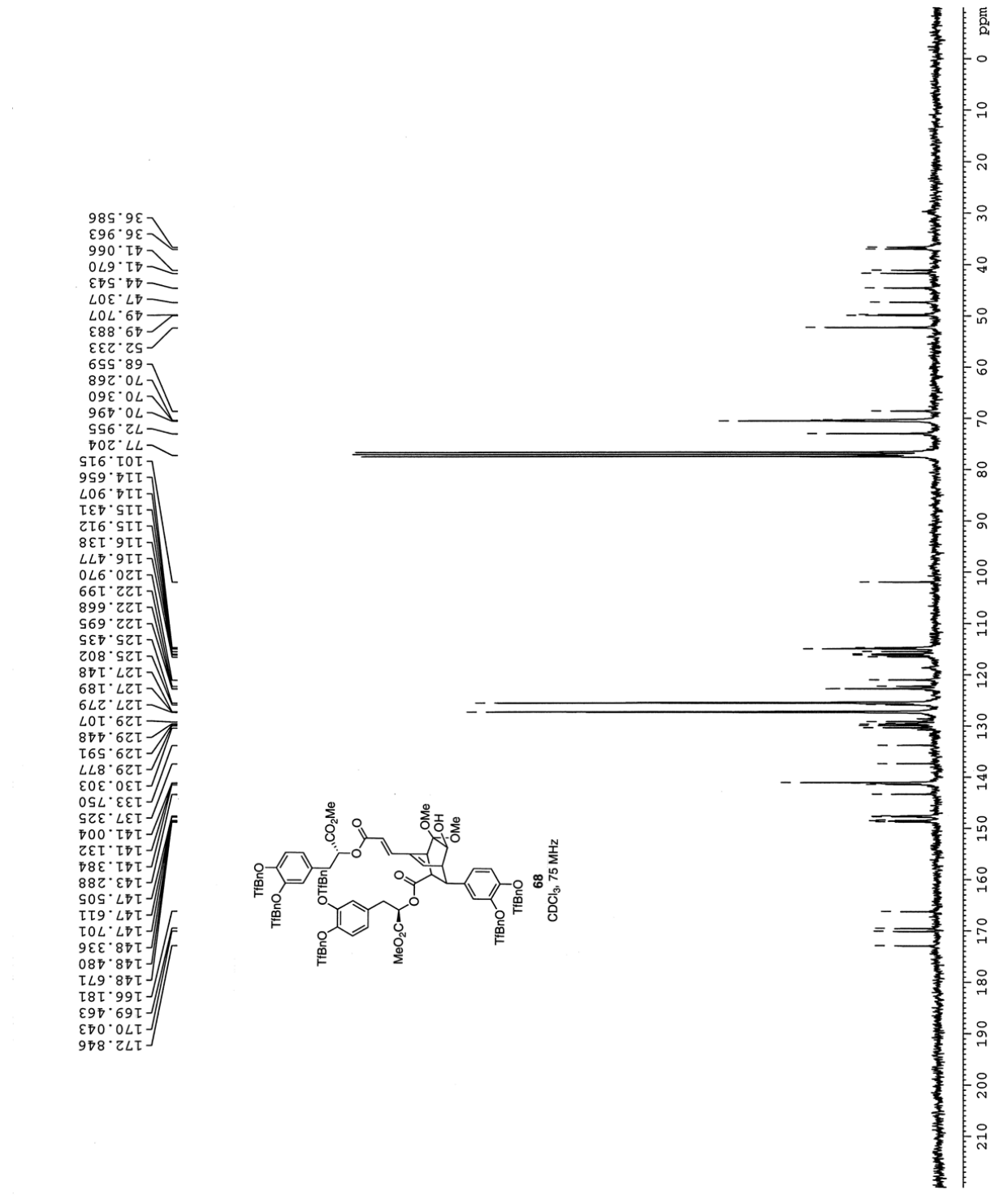
54.730
52.287
48.952
41.778
41.508
36.923
36.661


68
CDCl3, 400 MHz
TfBnO
OTfBn
CO2Me
OMe
OH
OMe
MeO2C
ppm
32.753
9.090
2.050
1.010
1.000
17.020
1.015
1.053
1.092
3.164
4.430
3.066
3.185
1.279
6.035


172.846
170.043
169.463
166.181
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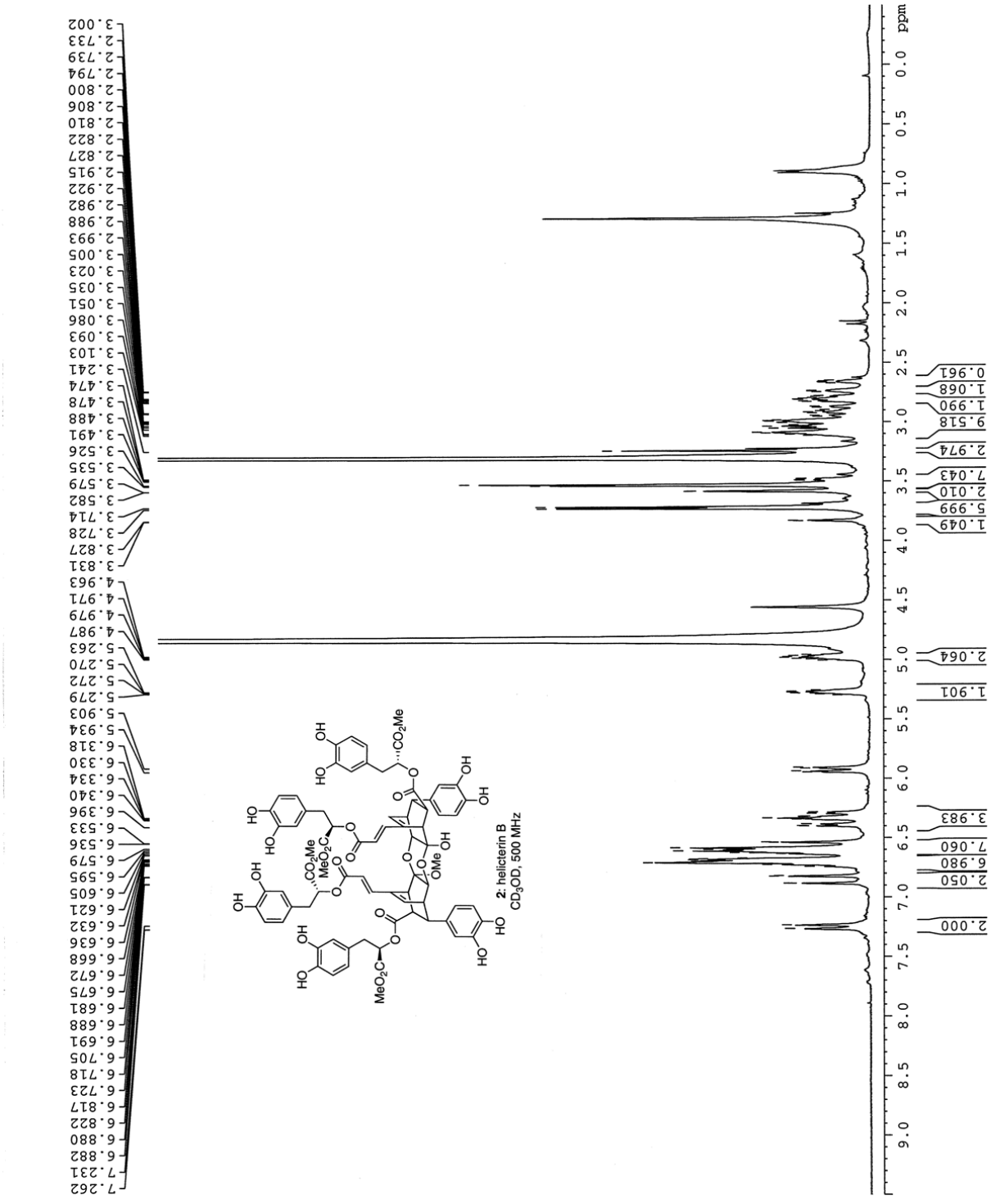
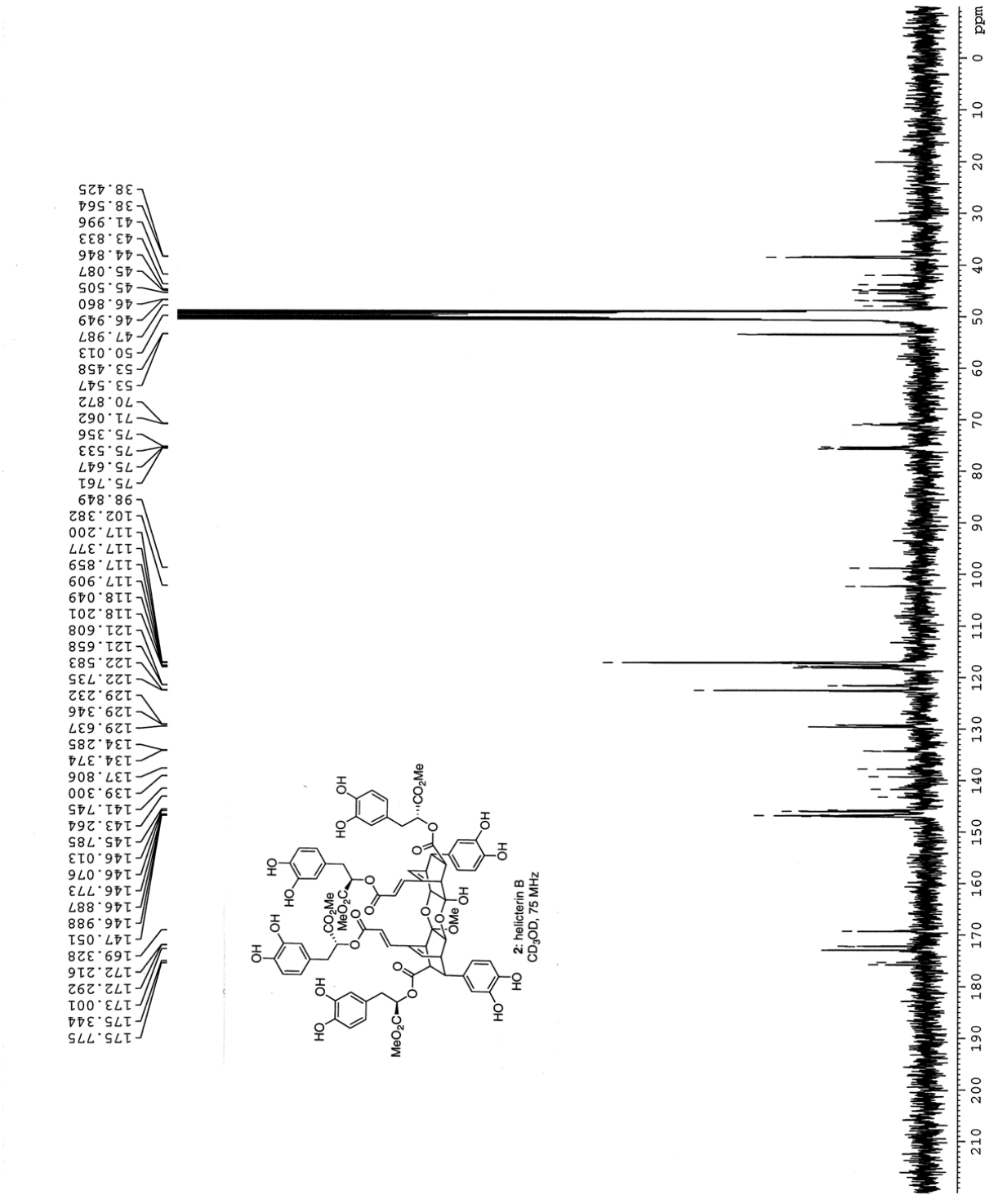
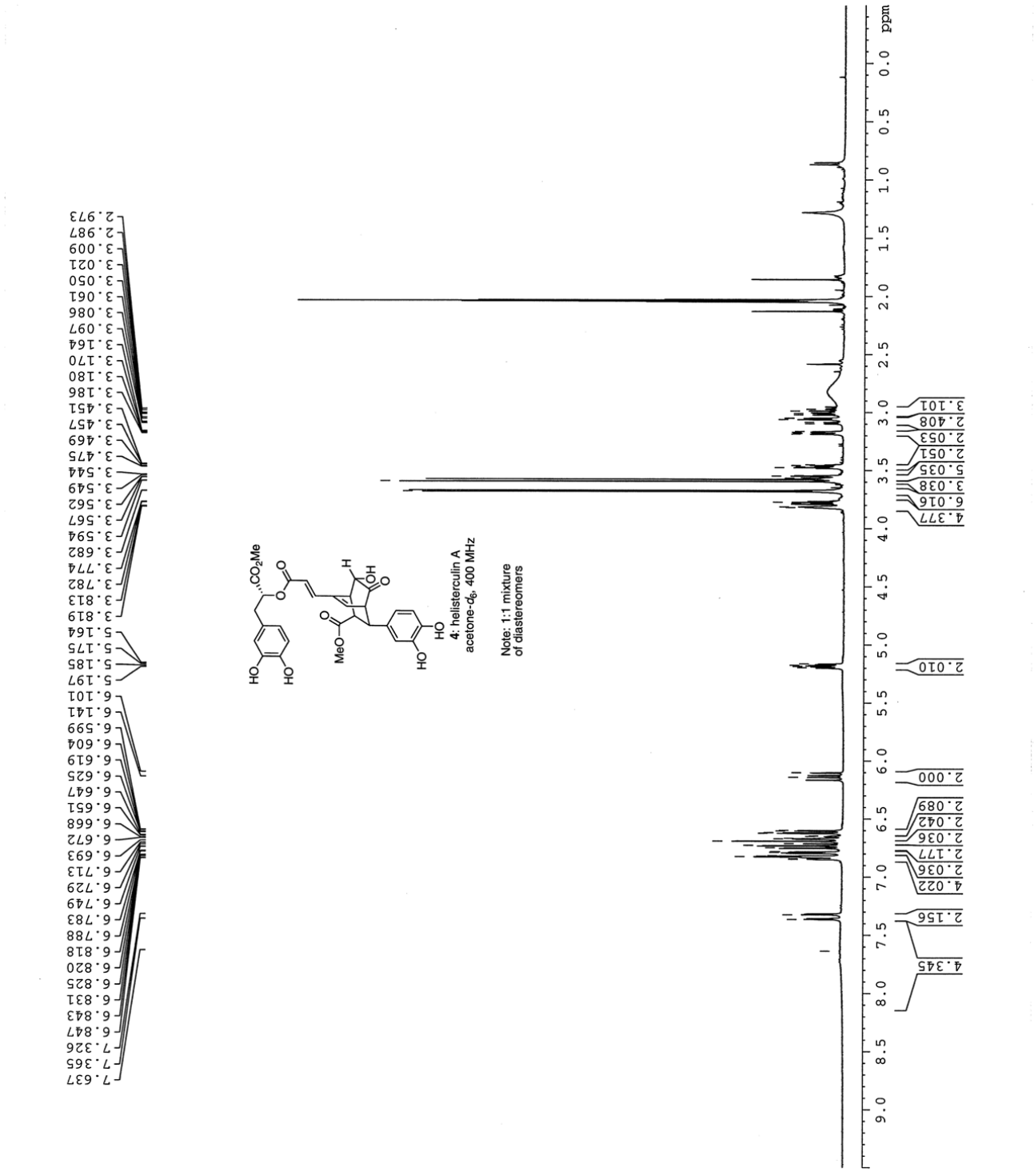
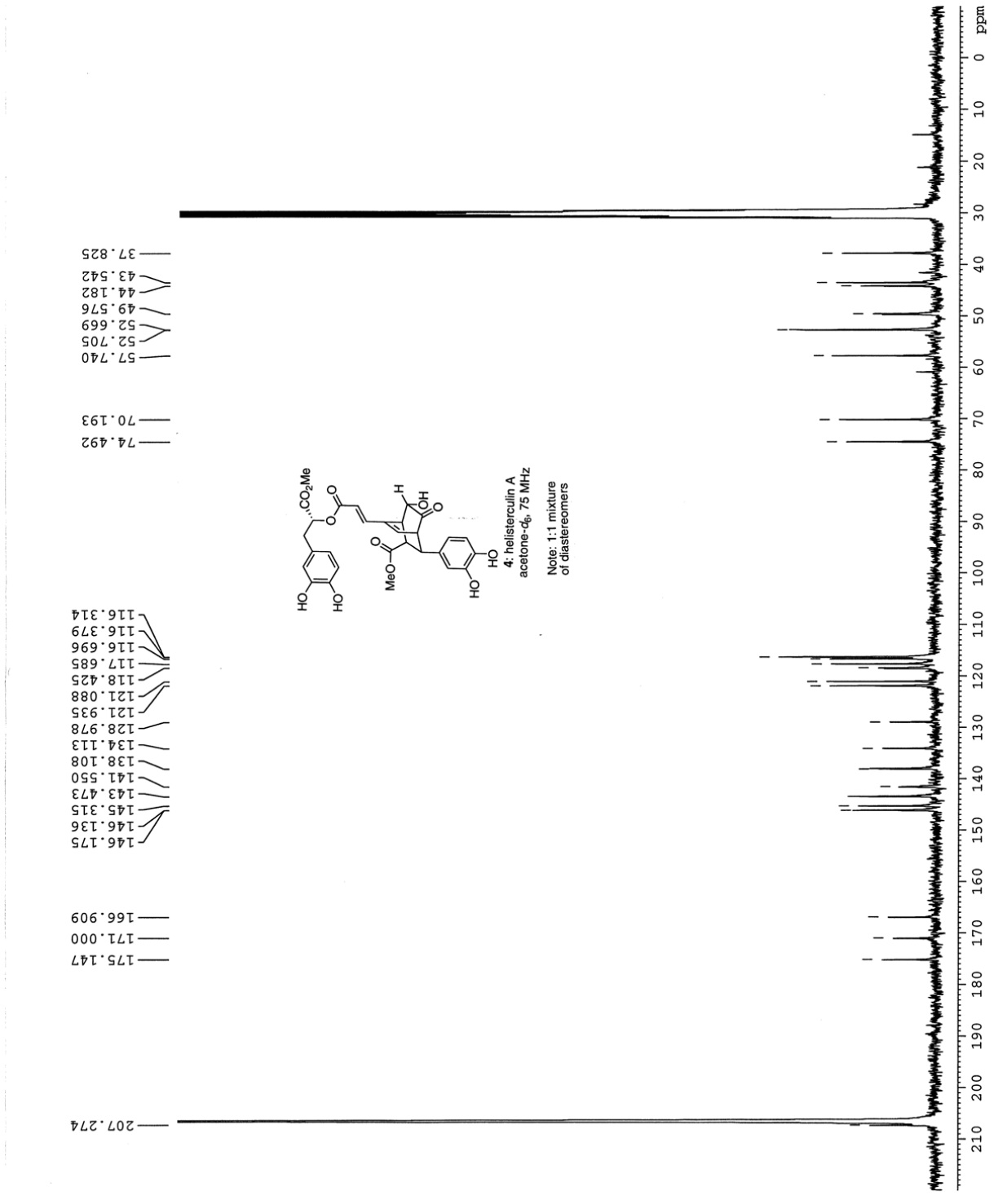
148.336
147.701
147.611
147.505
143.288
141.384
141.132
141.004
137.325
133.750
130.303
129.877
129.591
129.448
129.107
127.279
127.189
127.148
125.802
125.435
122.695
122.668
122.199
120.970
116.477
116.138
115.912
115.431
114.907
114.656
101.915
77.204
72.955
70.496
70.360
70.268
68.559
52.233
49.883
49.707
47.307
44.543
41.670
41.066
36.963
36.586
TfBnO
TfBnO
OTfBn
CO2Me
TfBnO
MeO2C
OMe
OH
OMe
TfBnO
TfBnO
68
CDCl3, 75 MHz
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
ppm


2: helicterin B
CD3OD, 500 MHz
ppm


175.775
175.344
173.001
172.292
172.216
169.328
147.051
146.988
146.887
146.773
146.076
146.013
145.785
143.264
141.745
139.300
137.806
134.374
134.285
129.637
129.346
129.232
122.735
122.583
121.658
121.608
118.201
118.049
117.909
117.859
117.377
117.200
102.382
98.849
75.761
75.647
75.533
75.356
71.062
70.872
53.547
53.458
50.013
47.987
46.949
46.860
45.505
45.087
44.846
43.833
41.996
38.564
38.425
2: helicterin B
CD3OD, 75 MHz
ppm
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210


4: helisterculin A
acetone-d_6, 400 MHz
Note: 1:1 mixture
of diastereomers
ppm


4: helisterculin A
acetone-d_6, 75 MHz
Note: 1:1 mixture
of diastereomers
207.274
175.147
171.000
166.909
146.175
146.136
145.315
143.473
141.550
138.108
134.113
128.978
121.935
121.088
118.425
117.685
116.696
116.379
116.314
74.492
70.193
57.740
52.705
52.669
49.576
44.182
43.542
37.825
ppm

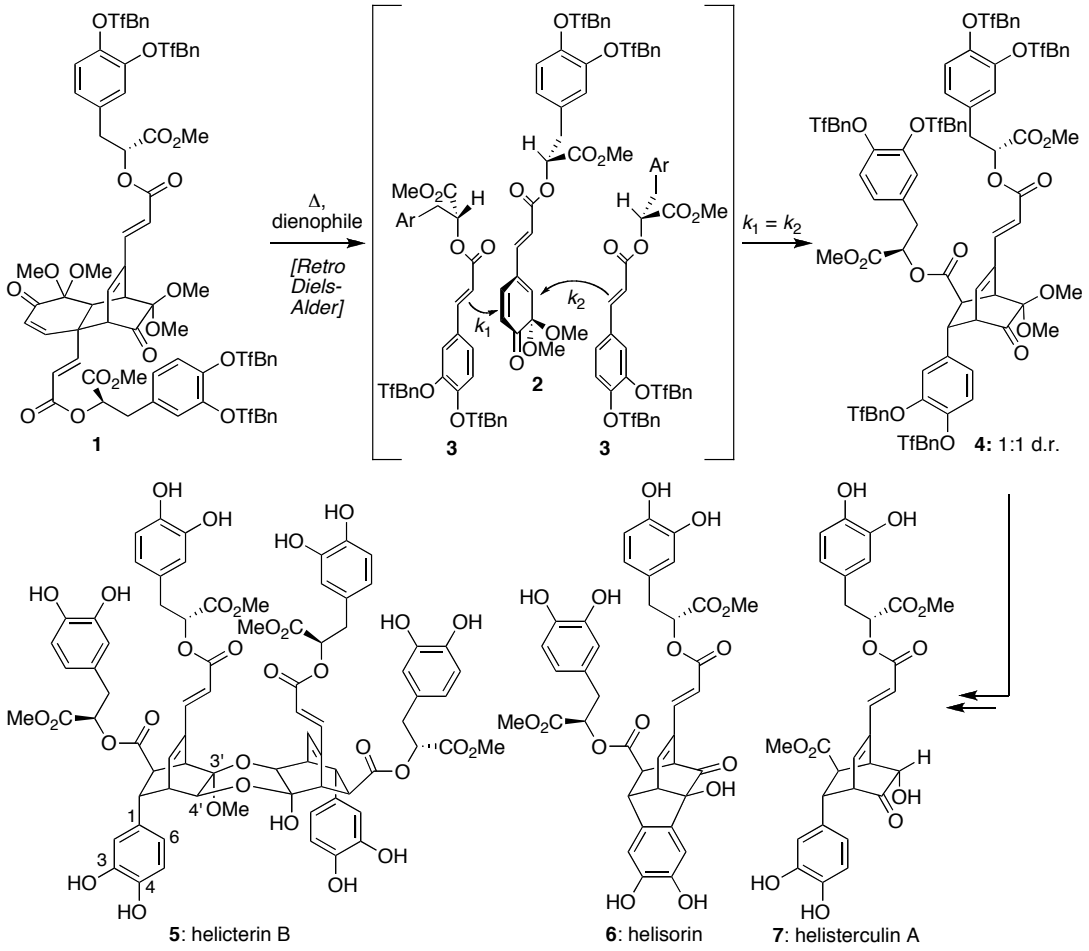
CHAPTER 2

Synthetic Studies of an Alternative Diels–Alder Approach Towards the Helicterin and the Yunnaneic Acid Families of Natural Products

2.1 Introduction

Chapter 1 described the total synthesis of three members of the helicterin family of natural products[1] (**5**–**7**, Scheme 1) via a sequence that was inspired by their biogenetic proposal, but one that ultimately required the development of several non-biomimetic transformations.[2] Perhaps the best example of such a non-biomimetic transformation is the retro Diels–Alder/Diels–Alder reaction sequence that generated the common core for all of these natural products. Additionally, as shown in Scheme 1, this non-diastereoselective reaction afforded a 1:1 mixture of diastereomers of adduct **4** due to the apparent ineffectiveness of the remote chiral center with the diene (**2**) and/or dienophile (**3**) in directing the facial approach of the two components. Though the diastereomers of product **4** were separable by standard chromatography, the synthesis of the helicterin natural products could be greatly improved through the development a stereoselective version of this Diels–Alder reaction sequence that would enable access to **3** as a single diastereoisomer. Efforts directed towards this goal will be the principal topic of this chapter.[3]

Furthermore, during model studies of hydroxyketone dimerizations described in Chapter 1, a reaction that could potentially access the central ketal linkages found in the yunnaneic acids[4] (**55**–**58**, Figure 1) was discovered. In the second part of this chapter, a further extension of Diels–Alder-based construction of bicyclo[2.2.2]octenes will be described within the context of studies targeted towards the core of this related family of neolignan natural products.

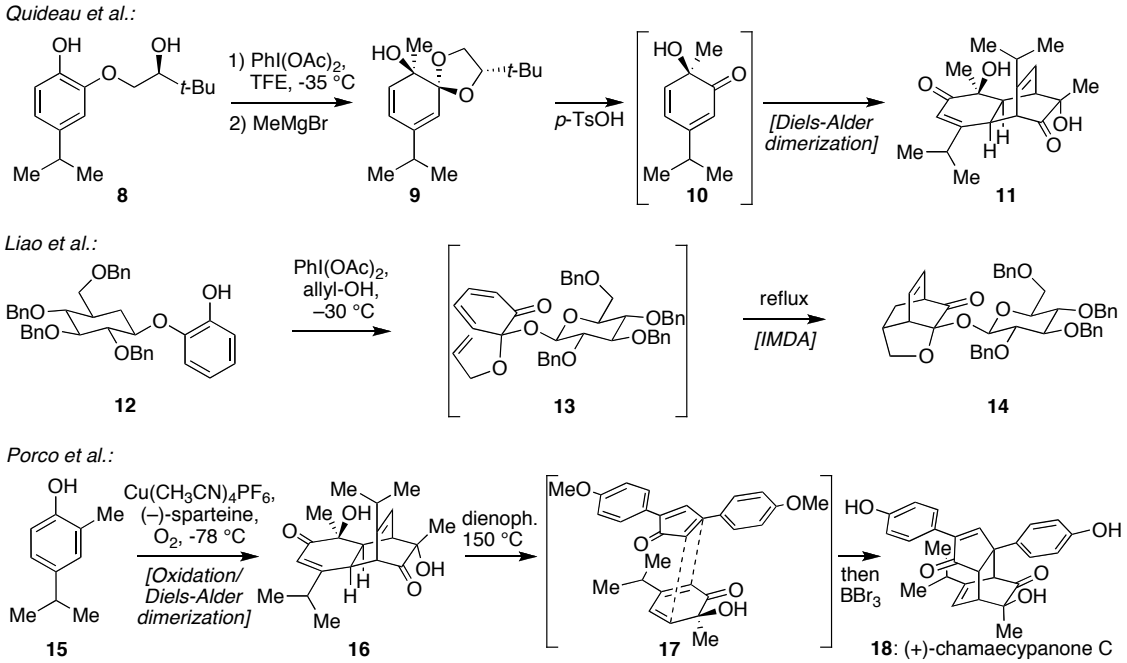


Scheme 1. Summary of the total synthesis of three helicterin neolignans (**5**–**7**) that was described in detail in Chapter 1.

2.2 State of the Art of Diasteroselective Synthesis of Bicyclo[2.2.2]octenes

Scheme 2 presents the leading literature examples for the diastereoselective construction of [2.2.2] bicycles through Diels–Alder reactions of *o*-benzoquinones and *o*-benzoquinols. The first of these methods, originally reported by Quideau and coworkers,[5] begins with a phenol bearing a chiral alcohol auxiliary (**8**), which, upon oxidation with a

hypervalent iodine reagent, led to the enantioselective formation of a chiral cyclic ketal that enabled a diastereoselective addition of a methyl Grignard reagent to afford intermediate **9**. Subsequently, the ketal chiral auxiliary was hydrolyzed, and the resultant *o*-quinol (**10**) underwent a Diels–Alder dimerization *in situ* to generate bicyclo[2.2.2]octene derivative **11** as a single diastereomer. A related chiral auxiliary-based approach was utilized by the Liao group[6] in which one of the hydroxyls of a catechol was functionalized with a perbenzylated β-D-glucose chiral auxiliary (**12**). Following oxidative dearomatization, a stereocontrolled addition of allyl alcohol leads to masked *o*-benzoquinone **13**, which underwent an intramolecular, diastereospecific Diels–Alder cycloaddition to afford bicyclic product **14**. Finally, the Porco group has developed an asymmetric Cu(II)-catalyzed oxidative dearomatization of phenol **15** directed by a (–)-sparteine ligand.[7] Under the reaction conditions employed, the resultant *o*-quinol underwent a 1,2-methyl shift followed by the diastereoselective formation of dimer **16**. This material was subsequently taken forward into a diastereoselective retro Diels–Alder/Diels–Alder sequence similar to the one described for the helicterins with an *in situ* generated dienophile, which, upon phenol deprotection, completed the total synthesis of (+)-chamaecypanone C (**18**).[8]



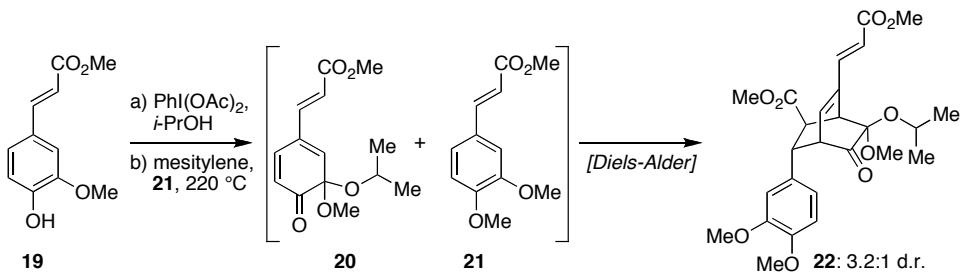
Scheme 2. Selected precedent for diastereoselective Diels–Alder reactions of *o*-benzoquinones and *o*-benzoquinols relevant to the helicterin family of natural products.[5–8]

The three examples described above and illustrated in Scheme 2 offer several ideas as starting points for the development of a diastereoselective route to the core of the helicterin family of natural products. As these examples demonstrate, the challenge could be approached as follows. First, a chiral center within the dearomatized phenol (i.e. the Diels–Alder diene) must be generated in a stereoselective way. In the first two examples,[5–6] this chiral center is a mixed ketal. Its diastereoselective formation is directed, in Quideau's work, by the face-selective intramolecular cyclization of a pendant chiral alcohol and, in Liao's work, by the face-selective approach of the allyl alcohol external nucleophile due to the presence of the chiral auxiliary. In Porco's work,[7,8] this chiral center is a tertiary carbinol formed by the stereoselective introduction of a hydroxyl directed by a chiral catalyst. After it is generated, this new chiral center must be able to direct the facial presentation of the diene and dienophile to afford a

diastereoselective Diels–Alder cycloaddition. In the Quideau and Porco examples, this is possible due to the proximity of this stereogenic center to the Diels–Alder diene, whereas in the Liao case, the Diels–Alder reaction is intramolecular and stereospecific. If these two key aspects can be addressed, then a stereoselective construction of the helicterin core should be possible.

2.3 Efforts Towards a Diastereoselective Route to the Helicterin Core

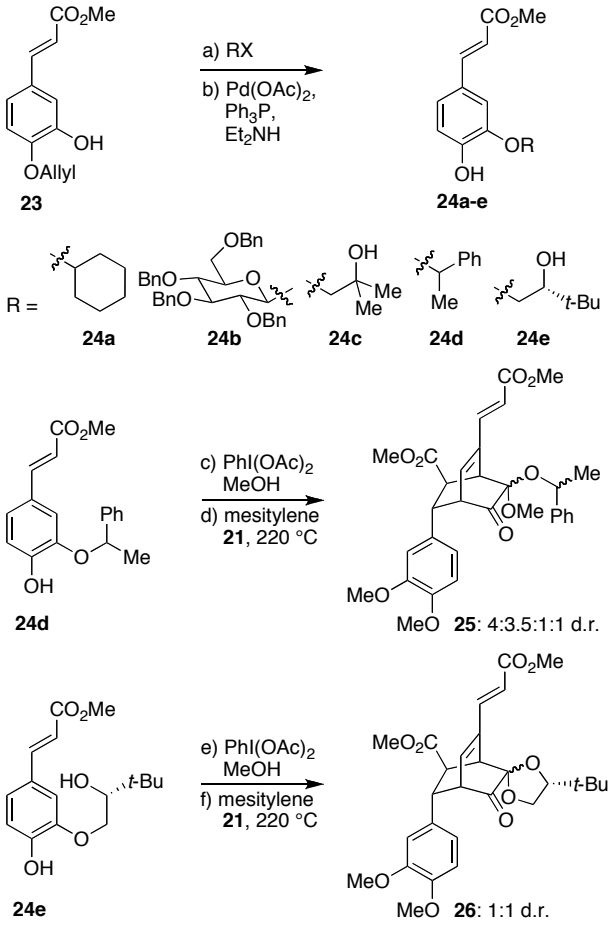
In order to implement the ideas discussed above it was necessary to establish whether or not a chiral center within the masked *o*-benzoquinone could control the diastereoselectivity of the reaction under the domino retro Diels–Alder/Diels–Alder conditions previously developed for the synthesis of the helicterin core. As shown in Scheme 3, phenol **19** was treated with $PhI(OAc)_2$[9] in *i*-PrOH to generate mixed ketal intermediate **20**,[10] which then dimerized according to expectations based on previous work with the MeOH adduct.[2] Although this dimerization already showed some degree of diastereoselectivity due to the presence of the mixed ketal chiral center, it was nonetheless taken forward into the real test reaction. Upon heating to 220 °C, the dimer fragmented to reveal diene **20** which then reacted with dienophile **21** to afford Diels–Alder adduct **22** as a 3.2:1 ratio of diastereomers, where the major product is presumed to be the one drawn in the Scheme based on the larger size of the *i*-Pr group within the mixed ketal. Although this selectivity was not perfect, it nonetheless suggested that a stereoselective synthesis of the core was possible if the mixed ketal could be formed asymmetrically.



Scheme 3. (a) $PhI(OAc)_2$ (1.1 equiv), *i*-PrOH/CH_2Cl_2 (6:1), 23 °C, 14 h, 99%; (b) **21** (6.7 equiv), mesitylene, 220 °C, 30 min., 17%.

Despite much effort with similar model studies, significant improvement of this initial level of selectivity proved impossible. For instance, the use of bulkier alcohols in the oxidation step (cyclohexanol, 2-butanol, 3-pentanol or 2,4-dimethyl-3-pentanol), albeit not used as solvent due to their elevated boiling temperatures, did not produce any isolable products and led to decomposition of the starting material. Thus, an alternative method for accessing such mixed ketals was developed; that route is shown in Scheme 4. Starting from mono-allylated catechol **23**,[11] the bulkier group was introduced first by a Mitsunobu displacement (**24a** and **24d**),[12] a glycosylation reaction (**24b**)[6] or an epoxide opening (**24c** and **24e**).[5] Following deallylation,[13] the resultant phenol (**24a** or **24b)** was exposed to oxidant in MeOH in an attempt to generate the mixed ketal. Unfortunately, no Diels–Alder products were isolated from either of these reactions. Additionally, no product was isolated from the oxidative dearomatization of intermediate **24c**. Furthermore, when racemic *s*-phenethyl ether **24d** was subjected to oxidative dearomatization followed by a retro [4+2]/[4+2] cycloaddition with dienophile **21**, the bicyclic product obtained (**25**) showed a 4:3.5:1:1 ratio of diastereomers. This result indicated that the chiral center within the *s*-phenethyl ether did not induce significant stereoselection during the formation of the mixed ketal (diastereoselectivity of approximately 4:3.5) and that the *s*-phenethyl group in this mixed ketal did not

significantly improve the selectivity of the Diels–Alder reaction compared with the *i*-Pr group discussed above (diastereoselectivity of approximately 4:1). Finally, the use of a chiral cyclic ketal (**24e**) similar to Quideau's report (*vide supra*) provided no selectivity in the Diels–Alder step, affording a 1:1 mixture of diastereomers of adduct **26**.



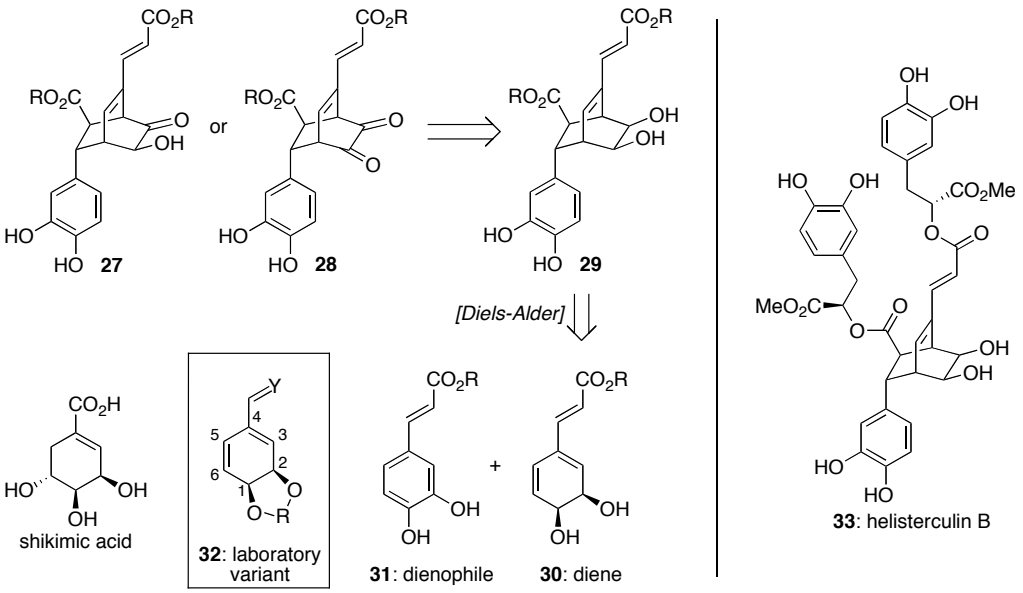
Scheme 4. (a) **24a** and **24d**: R-OH (1.2 equiv), DIAD (1.2 equiv), PPh_3 (1.2 equiv), toluene/THF (2:1), 23 °C, 36 h, 52–65%; **24b**: D-Glu(OAc)$_4$(α-OCNHCCl$_3$) (3.0 equiv), BF_3•OEt_2 (1.2 equiv), CH_2Cl_2, 23 °C, 18 h, 99%, then NaH (5.0 equiv), MeOH, 23 °C, 3 h, then NaH (5.0 equiv), BnBr (5.0 equiv), DMF, 0→23 °C, 33% overall; **24c** and **24e**: epoxide (4.0 equiv), K_2CO_3 (2.0 equiv), DMF, 100 °C, 24 h, 50–65%; (b) $Pd(OAc)_2$ (0.2 equiv), PPh_3 (0.3 equiv), THF/Et_2NH/H_2O (5:2:1), 23 °C, 16 h, 52–99%; (c) $PhI(OAc)_2$ (1.05 equiv), MeOH/CH_2Cl_2 (11:1), –40→23 °C, 2 h, 75%; (d) **21** (5.0 equiv), mesitylene, 220 °C, 30 min, 52%; (e) $PhI(OAc)_2$ (1.05 equiv), CF_3CH_2OH, –40→–10 °C, 1.25 h, 39%; (d) **21** (6.7 equiv), mesitylene, 220 °C, 30 min, 45%. DIAD = diisopropylazodicarboxylate, DMF = *N*,*N*-dimethylformamide

2.4 A New Biogenetic Hypothesis

In addition to the failure of the biomimetic approaches discussed in Chapter 1 to afford the natural core, the inability of the remote chiral centers within rosmarinic acid derivatives to control the diastereoselectivity of the Diels–Alder cycloaddition (Scheme 1) and the observation that a chiral center closer to the reactive center could induce some measure of stereocontrol in model systems (Schemes 3 and 4) led us to reexamine past hypotheses concerning the biosynthetic construction of the helicterin family. Specifically, an alternative Diels–Alder-based biosynthetic proposal that could account for the formation of these molecules without invoking enzymatic participation seemed particularly appealing given the paucity of evidence regarding the existence of true Diels–Alderases.[14] Although such enzymes have been proposed to account for the formation of many natural products, only a small number of them have been identified, and the biochemical or mechanistic evidence regarding their biosynthetic role is limited.

An alternative proposal for the biosynthesis of the bicyclo[2.2.2]octene core of the helicterins is shown in Scheme 5. This hypothesis involves a Diels–Alder reaction between diene **30** and dienophile **31** to produce bicyclic adduct **29**, a compound which represents the core of the natural product helisterculin B (**33**).[1a] If diene **30** could be synthesized by the plant as a single enantiomer, then perhaps its reaction with **31** would occur with facial selectivity to arrive at **29** as a single diastereomer without enzyme participation. This diol (**29**) could also give rise to hydroxyketone **27**, the precursor to helicterin B (**5**) and helisterculin A (**7**), and diketone **28**, the precursor to helisorin (**6**), through simple oxidation state adjustments. The possibility of a diene such as **30** being

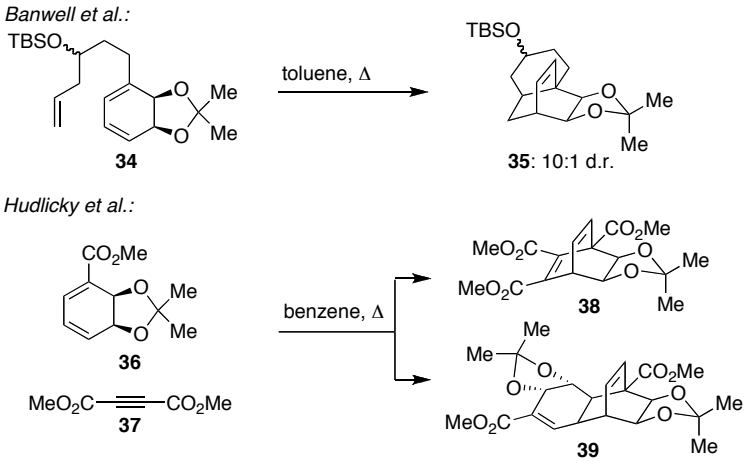
part of the biosynthesis of the helicterins is not entirely inconceivable. Lignan and neolignan polyphenolic natural products, such as the helicterins, the yunnaneic acids, rosmarinic acid, caffeic acid and many others, are believed to derive from the amino acids tyrosine and phenylalanine,[15] both of which are synthesized in plants via the shikimate pathway.[16] This pathway obtains its name from shikimic acid (Scheme 5), a chiral trihydroxylated cyclohexene carboxylic acid that is, in principle, one dehydration step away from a diene such as **30**. Although an appealing biogenetic alternative, the ideas listed above are circumstantial at best, and no direct evidence can be posited from the literature regarding the validity of the above hypothesis. Nonetheless, we decided to investigate their feasibility in the laboratory.



Scheme 5. An alternative biogenetic hypothesis for the construction of the helicterin core.

2.5 Development of a Stereoselective Diels–Alder Synthesis of the Helicterin Core

Although molecules of type **32** prepared as single enantiomers have been described in the literature,[17] no precedent for their participation in Diels–Alder chemistry had been documented prior to our work. More broadly, only a limited number of examples of related dienes derived from dihydroxylated benzenes[18] participating in [4+2] cycloadditions have been reported, two of which are illustrated in Scheme 6. In the first, 3-alkyl substituted diene **34** underwent an intramolecular Diels–Alder reaction in refluxing toluene with the pendant alkene to afford a bicyclic product (**35**) in 44% yield.[19] This example demonstrated the thermal stability of this type of diene and that their use leads to high facial selectivity. However, it was perhaps less relevant because the reaction is intramolecular, and both the diene and dienophile components are electronically different from the desired union for the helicterin core. The second example is electronically more similar to the targeted reaction, with a cycloaddition occurring between an electron-poor diene and an electron-poor dienophile, and it proceeded in refluxing benzene with excellent diastereoselectivity to afford the desired product (**38**).[20] However, this product was formed as a 2:1 mixture of alongside dimer **39**, suggesting that self-dimerization may once again be an important issue.

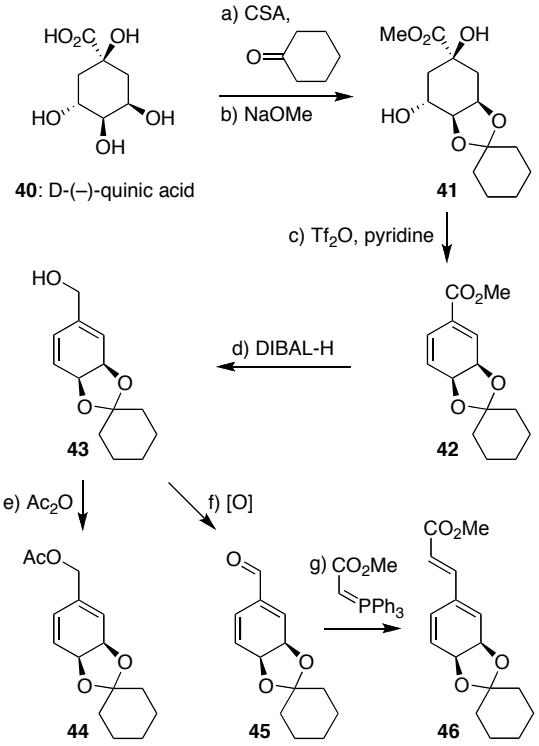


Scheme 6. Representative examples of Diels–Alder reactions of dihydroxylated benzene derivatives.

With this promising literature precedent in mind, the 4-substituted cyclohexadienediol derivatives of type **32** (Scheme 6) necessary for testing this synthetic proposal were synthesized. In contrast to enzymatic dihydroxylations of substituted benzenes that produce 3-substituted or 3,4-, 3,5- and 3,6-disubstituted cyclohexadiene diols (**32** numbering) in one step,[18] greater than four steps have typically been required to produce 4-substituted dienes from commercially available starting materials.[17] Thus, an improved protocol was desired.

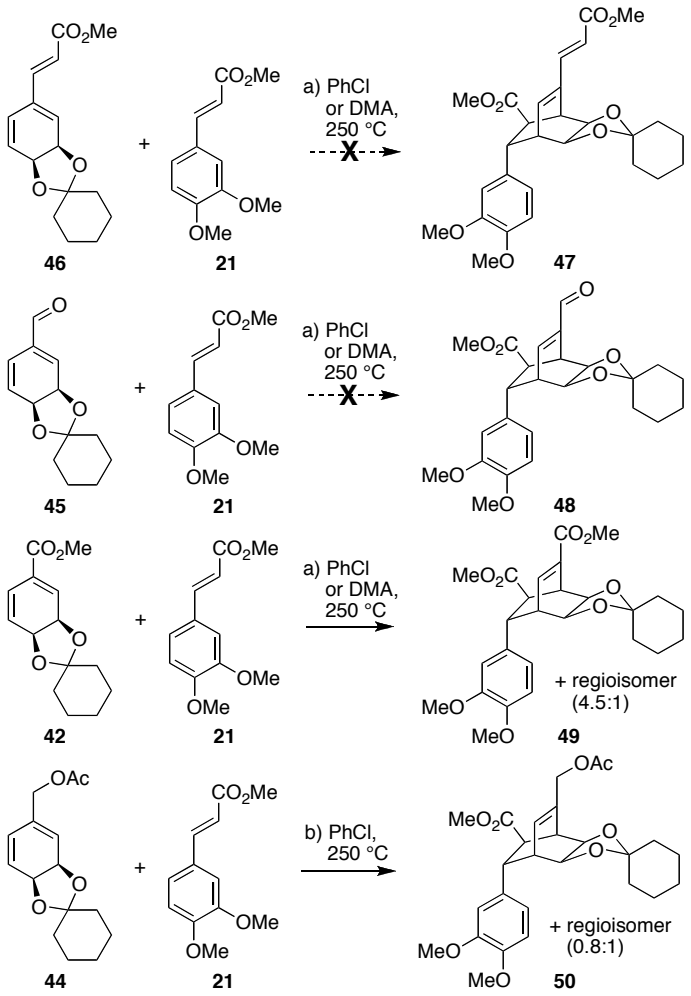
As shown in Scheme 7, a three-step reaction sequence to prepare chiral diene **42** from D-(–)-quinic acid (**40**) was developed. The final elimination to regioselectively generate the desired diene had been carried out is a two-step sequence in previous cases. By careful control of the reaction conditions, it was possible to achieve these events in a single step via a double triflation/elimination sequence that achieved the necessary diene in 44% yield. Following protection of the *syn*-1,2-diol as a cyclohexanone ketal and formation of the methyl ester, diol **41** was first converted to the *bis*-

trifluoromethanesulfonate in the presence of only a slight excess of pyridine at low temperature. Additional base was then added to effect a tandem double elimination to afford diene **42**. Of note, the use of stronger bases in this step, such as imidazole, led to deprotonation of **42** at the 2-position followed by a third elimination to afford an aromatic phenol. With protected cyclohexadiene diol **42** in hand, a series of standard transformations provided compounds **44**–**46**. Compounds **42** and **44**–**46** are stable to silica gel chromatography and can be stored for several weeks at ambient temperature or below.



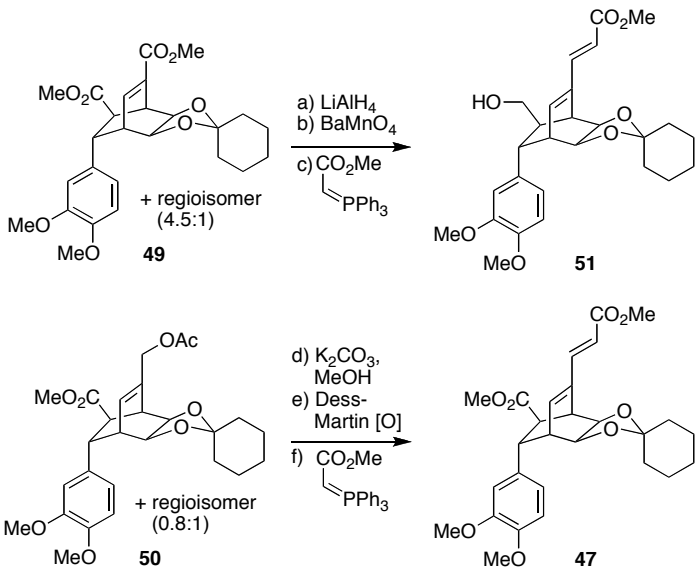
Scheme 7. (a) CSA (0.1 equiv), cyclohexanone (5.0 equiv), toluene, reflux, 14 h, 78%; (b) NaOMe (0.1 equiv), MeOH, 23 °C, 14 h, 82%; (c) Tf_2O (2.2 equiv), pyridine (3.2 equiv), CH_2Cl_2, 0→23 °C, 2 h, then pyridine (15 equiv), 23 °C, 24 h, 44%; (d) DIBAL-H (3.0 equiv), THF, 0 °C, 30 min, 93%; (e) Ac_2O (3.0 equiv), pyridine (5.0 equiv), CH_2Cl_2, 23 °C, 14 h, 50%; (f) Dess-Martin periodinane (2.0 equiv), CH_2Cl_2, 23 °C, 76%; (g) Ph_3PCHCO_2Me (1.5 equiv), CH_2Cl_2, 23 °C, 18 h, 82%. CSA = (±)-camphorsulfonic acid, DIBAL-H = diisobutylaluminum hydride, Tf = trifluoromethanesulfonyl

Scheme 8 shows efforts towards the development of a diastereoselective Diels–Alder reaction using chiral dienes **42** and **44**–**46** with the ultimate goal of synthesizing the core of the natural product helisterculin B (**47**). In a direct approach, triene **46** was heated to temperatures of up to 250 °C in the presence of dienophile **21** in chlorobenzene or *N*,*N*-dimethylacetamide (DMA) but no desired product (**47**) was formed. Thus, a more indirect route to **47** was sought.



Scheme 8. (a) **21** (5.0 equiv), 250 °C, μwave, 3 h, PhCl: 7% or DMA: 12%; (b) **21** (5.0 equiv), PhCl, 250 °C, μwave, 6 h, 12%. DMA = *N*,*N*-dimethylacetamide

Aldehyde **45** also did not afford the desired product (**48**) under the same reaction conditions. However, when heated to 250 °C in the presence of 5 equivalents of **21**, ester **42** underwent a Diels–Alder reaction to afford the desired bicyclo[2.2.2]octene product (**49**) as a 4.5:1 ratio of regioisomers with respect to the dienophile, but with complete facial selectivity. The yield of this reaction was 7% when run in chlorobenzene and 12% when run in DMA. Furthermore, a significant amount of the dimer of **42** was also isolated from the reaction mixture. This latter compound could be resubjected to a retro Diels–Alder/Diels–Alder cascade in the presence of **21** under the same reaction conditions to afford a small amount of **49**, but the efficiency of this process was far lower than that of the direct reaction between **42** and **21**. Finally, treatment of acetate **44** under the same reaction conditions afforded product **50** in 15% yield as a 0.8:1 ratio of regioisomers with respect to the dienophile, with the desired isomer shown being the minor product, but again with complete facial selectivity. The use of Lewis acids, other solvents or lower temperatures in either of these reactions afforded lower or no yield of products. Nonetheless, bicyclo[2.2.2]octenes **49** and **50** were generated with high degrees of facial selectivity, albeit once again only under relatively harsh, non-biomimetic conditions and in even lower yield. Furthermore, compounds **49** and **50** were still well removed from the core of the helicterin natural products, and our ability to convert them into the target natural core (**47**) was still uncertain.

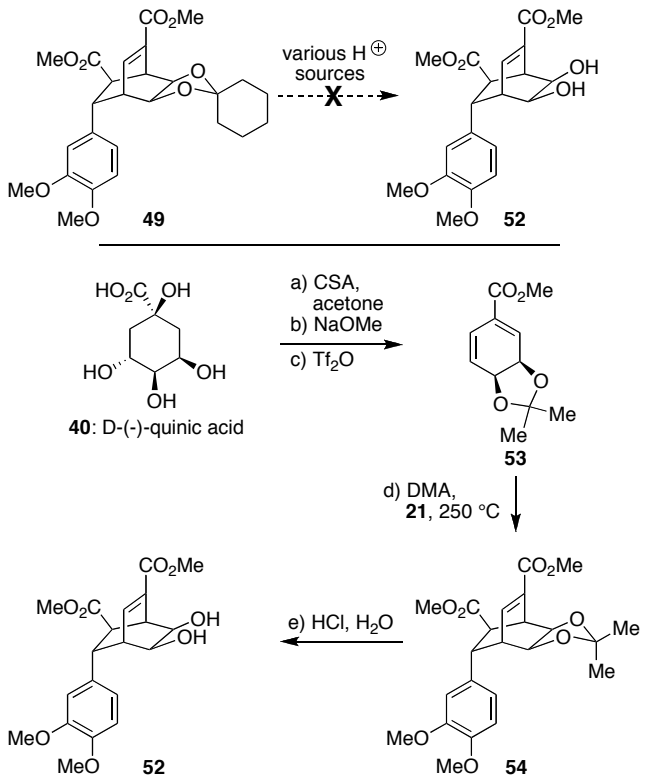


Scheme 9. (a) $LiAlH_4$ (2.0 equiv), THF, 0 °C, 30 min; (b) $BaMnO_4$ (excess), CH_2Cl_2, 23 °C, 18 h; (c) Ph_3PCHCO_2Me (2 equiv), toluene, 60 °C, 5 h, 50% overall; (d) K_2CO_3 (cat), MeOH, 23 °C, 14 h; (e) Dess-Martin periodinane (2.0 equiv), CH_2Cl_2, 23 °C, 1 h; (f) Ph_3PCHCO_2Me (2.0 equiv), toluene, 60 °C, 5 h, 73% overall.

Since the Diels–Alder reaction to afford the desired adduct (**47**) directly did not succeed, we sought to explore whether adducts **49** or **50** could instead be converted into the natural product core. Diels–Alder adduct **49** was transformed to intermediate **51** using a three step homologation process of the α,β-unsaturated methyl ester (Scheme 9). However, the first step in this sequence also reduced the other methyl ester in the molecule, and would likely not be compatible with fully functionalized materials (cf. **33**, Scheme 5). Alternatively, Diels–Alder adduct **50** was converted to the desired natural product core (**51**) using a three step sequence. However, this adduct was synthesized by a highly unselective Diels–Alder reaction in which the desired product was the minor diastereomer. As a final model study, Diels–Alder adduct **49** was subjected to various conditions to effect the hydrolysis of the diol-protecting group and reveal diol **52**. As

shown in Scheme 10, however, exposure of **49** to various protic acid sources in aqueous solvents with or without heating led to varying amounts of recovered starting material and decomposition. However, a switch to a more labile protecting group solved the problem. Bicyclic adduct **54** was synthesized using much of the previously developed chemistry, and its exposure to aqueous HCl effected hydrolysis of the acetonide protecting group to reveal diol **52**.

Though a potential stereoselective synthesis of the helicterin natural products (**5**–**7** and **33**) seemed possible, it was only through a low-yielding and non-regioselective Diels–Alder reaction occurring at a very high temperature that the desired framework could be accessed. Whether the combination of these elements will eventually lead to a first total synthesis of helisterculin B (**33**) remains to be seen. Nevertheless, this outcome suggests that if this revised biosynthetic proposal is accurate, enzymatic participation likely does play a very important role in the construction of the bicyclic core of these natural products.



Scheme 10. (a) CSA (0.1 equiv), acetone, 40 °C, 48 h, 96%; (b) NaOMe (0.1 equiv), MeOH, 23 °C, 14 h, 80%; (c) Tf_2O (2.2 equiv), pyridine (3.2 equiv), CH_2Cl_2, 0-23 °C, 2 h, then pyridine (15 equiv), 23 °C, 24 h, 38%; (d) **14** (5.0 equiv), DMA, 250 °C, μwave, 3 h, 15%; (e) HCl (1 M H_2O) / THF (1:1), 23 °C, 48 h, 86%. CSA = (±)-camphorsulfonic acid, DMA = *N*,*N*-dimethylacetamide, Tf = trifluoromethanesulfonyl

2.6 The Yunnaneic Acid Natural Products

After completing the synthesis of the helicterin natural products (**5**–**7**, Scheme 1),[2] we turned our attention towards the yunnaneic acids[4] (**55**–**58**, Figure 1), a related family of neolignan natural products. These molecules are hexamers and trimers of caffeic acid, respectively, that were isolated from the roots of *Salvia yunnanensis* collected in Yunnan, China in 1996 and have been shown to exhibit uremic toxin-decreasing activity.

Earlier model studies towards the helicterins, discussed in Chapter 1, had revealed a promising lead for the synthesis of the central ketal linkage of the dimeric natural products, yunnaneic acid A (**55**) and B (**56**), from a simple monomeric hydroxyketone. But before such a dimerization reaction could be attempted, we sought to address the question of how to synthesize the yunnaneic acid bicyclic core (**59**), whose regioselectivity is reversed with respect to the dienophile in the Diels–Alder reaction that achieved the core of the helicterins and thereby constitutes an *exo*-product. This challenge necessitated a modified version of that key cycloaddition reaction.

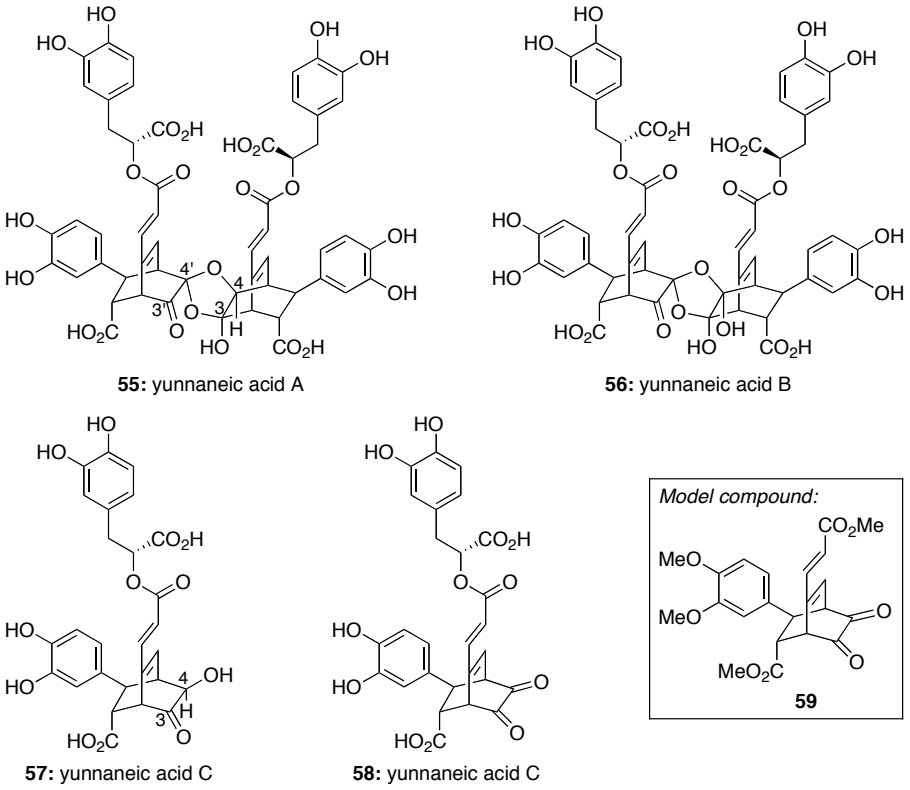
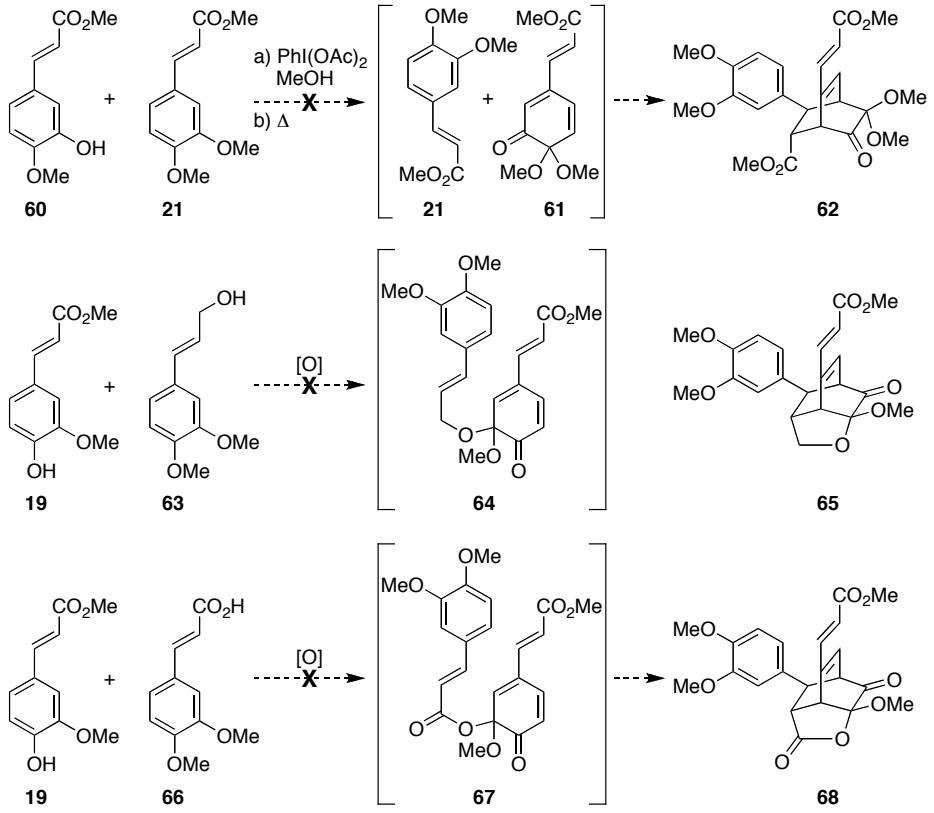


Figure 1. The yunnaneic acid neolignans and their corresponding core structure targeted during model studies.

2.7 An Alternative Diels–Alder Strategy to Achieve Regiochemical Reversal

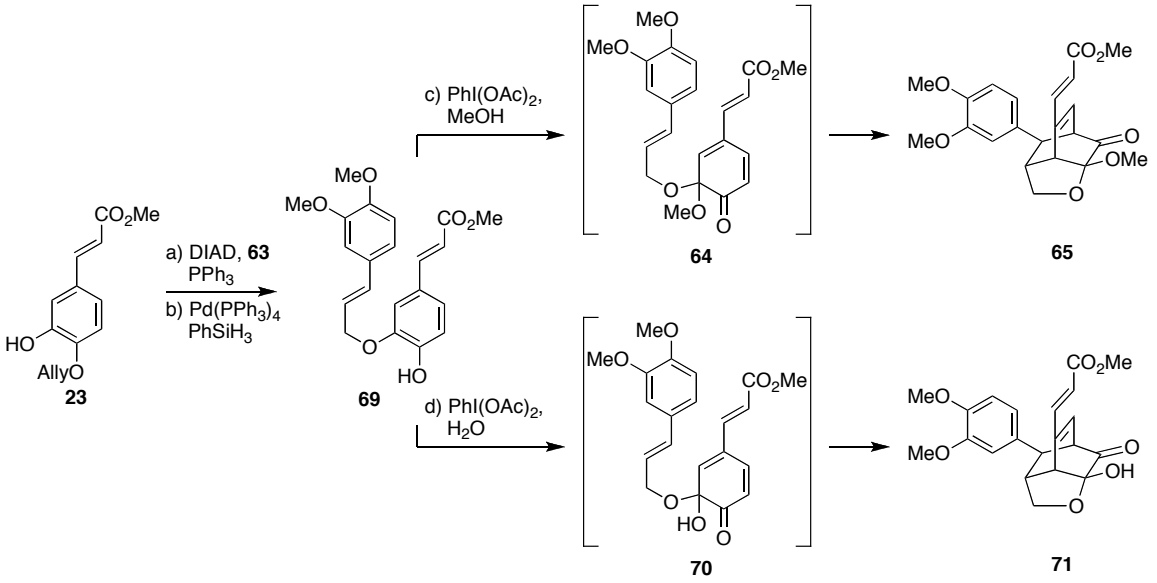
The helicterin work[2] described in Chapter 1 clearly established that Diels–Alder reactions between the masked *o*-benzoquinone derived from phenol **19** and dienophile **21** leads to helicterin-like *endo*-products. We wondered whether switching the position of the free phenol and the methoxy group in the starting material (**60** *vs.* **19**, Scheme 11) would have an effect on the regio- and *endo*/*exo*-selectivity of the Diels–Alder reaction. As in the case of the helicterin core, exposure of phenol **60** to hypervalent iodine oxidation conditions smoothly afforded a Diels–Alder dimer of masked *o*-benzoquinone **61**, even in the presence of large excess of the dienophile (**21**). However, upon heating, no new bicyclic products were produced, indicating that dimer either did not undergo a retro Diels–Alder fragmentation to reveal intermediate **61** or that this *o*-benzoquinone derivative did not undergo a Diels–Alder reaction with dienophile **21**. Therefore, it became necessary to develop a radically different approach towards the desired Diels–Alder regio- and stereochemical outcome.



Scheme 11. (a) $PhI(OAc)_2$ (1.1 equiv), $MeOH/CH_2Cl_2$ (5:1), 23 °C, 14 h, 99%; (b) **21** (6.7 equiv), mesitylene, 220 °C, 30 min.

Cognizant of the Liao group's work towards a diastereoselective synthesis of bicyclo[2.2.2]octenes shown in Scheme 2,[6] we sought to implement a related strategy for the construction of the yunnaneic acid core. As shown in Scheme 11, phenol **19** was oxidized with a hypervalent iodine reagent in the presence of several equivalents of dienophile **63** or **66**, hoping to arrive at intermediates such as **64** and **67**, which would then undergo stereospecific intramolecular Diels–Alder reactions to afford products **65** and **68**, respectively. Unfortunately, despite several attempts with various oxidants in various polar and non-polar solvents, no desired products were obtained from any of these reactions. In every case, these reactions led to complete consumption of the phenol

starting material, and no byproducts consistent with the formation of intermediates such as **64** and **67** were ever isolated. This observation prompted us to conclude that such mixed ketal intermediates were likely not being formed at all. This outcome can most likely be attributed to the poor nucleophilicity of alcohol **63** and, especially, carboxylic acid **66**, compounded by the relatively small excess of these compounds that can be added to the reaction mixture (*versus* using them as co-solvent). In order to test this hypothesis, we decided to pre-form the needed C–O bond, then perform the oxidation in which the smaller alcohol is solvent or co-solvent. As shown in Scheme 12, a Mitsunobu reaction[12] between allylated catechol **23** and allylic alcohol **69** afforded a 2:1 mixture of the desired linear and S_N2' adducts. Following chromatographic separation of these isomers, allyl group cleavage under carefully controlled conditions[21] completed the synthesis of phenol **69**. Exposure of this intermediate to $PhI(OAc)_2$ in MeOH generated mixed ketal **64**, which underwent an intramolecular Diels–Alder reaction to afford product **65** in 66% yield. Additionally, exposure of phenol **69** $PhI(OAc)_2$ in aqueous dioxane generated hemiketal **70**, which also underwent an intramolecular Diels–Alder reaction to complete the synthesis of adduct **71** in 64% yield. Unfortunately, an analogous strategy with carboxylic acid derivative **66** was unsuccessful due to the occurrence of ester hydrolysis during the oxidation step. Nevertheless, this work completed the synthesis of the carbogenic core of the yunnaneic acids and achieved the effective reversal of the Diels–Alder reaction's regio- and stereochemical preference.



Scheme 12. (a) **63** (1.2 equiv), DIAD (1.5 equiv), PPh_3 (1.5 equiv), THF, 0 °C, 1.5 h, 65%; (b) $Pd(PPh_3)_4$ (0.03 equiv), $PhSiH_3$ (1.5 equiv), CH_2Cl_2, 23 °C, 5 h, 53%; (c) $PhI(OAc)_2$ (1.1 equiv), $MeOH/CH_2Cl_2$ (5:1), 60 °C, 1.25 h, 66%; (d) $PhI(OAc)_2$ (1.1 equiv), 1,4-dioxane/H_2O/CH_2Cl_2 (4:2:1), 80 °C, 45 min., 64%.

2.8 Conclusion

Given the failure of more traditional methods for the stereoselective synthesis of the bicyclic core of the helicterin natural products (**5**–**7** and **33**), a new approach based on a revised biosynthetic proposal was investigated. The reaction sequence developed began with the shortest and most efficient synthesis to date of a chiral dihydroxylated benzene derivative as a single enantiomer. This intermediate was then used in the key Diels–Alder cycloaddition to afford the bicyclic natural product core. Although the reaction displayed a limited substrate scope and gave the desired products in low yield, it occurred with complete facial selectivity and provided access to enantiopure materials. In addition, the reaction took place under non-biomimetic conditions (high temperature, non-polar

solvents), suggesting that even if the revised biogenetic hypothesis is correct, enzymatic catalysis is still likely necessary to effect the biosynthesis of the natural product core via this route.

In addition, a Diels–Alder approach to the core of the yunnaneic acids (**55**–**58**) was also developed, wherein the tethering of the dienophile to the pro-diene was key. Upon exposure to an oxidant in an alcoholic or aqueous solvent, this intermediate underwent an intramolecular [4+2] cycloaddition. This accomplished the reversal of the regiochemical preference of the reaction and thereby completed the synthesis of the natural product core.

Fellow graduate student Daniel R. Griffith has contributed to the chemistry presented in this chapter by exploring the Mitsunobu and deallylation steps presented in Scheme 12. Since then, he has developed a synthetic route and has completed the synthesis of several of the yunnaneic acid natural products, which will be reported in due course.

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2.10 Experimental Section

General Procedures. All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Dry THF (THF), acetonitrile (MeCN), toluene, benzene, diethyl ether (Et_2O), and methylene chloride (CH_2Cl_2) were obtained by passing commercially available pre-dried, oxygen-free formulations through activated alumina columns. Yields refer to chromatographically and spectroscopically (^1H and ^{13}C NMR) homogeneous materials, unless otherwise stated. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Reactions were magnetically stirred and monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent and cerium sulfate (CAM) and heat as developing agents. SiliCycle silica gel (60, academic grade, particle size 0.040–0.063 mm) was used for flash column chromatography. Preparative thin-layer chromatography (PTLC) separations were carried out on 0.50 mm E. Merck silica gel plates (60F-254). NMR spectra were recorded on Bruker DPX 300, Avance II 400, Avance III 400, and DMX 500 instruments, and calibrated using residual undeuterated solvent as an internal reference ($CDCl_3$: 7.26 ppm for ^1H, 77.0 ppm for ^{13}C). The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, br = broad, app = apparent. IR spectra were recorded on a Perkin-Elmer 1000 series FT-IR spectrometer. High-resolution mass spectra (HRMS) were recorded in the Columbia University Mass Spectral Core facility on a JOEL HX110 mass spectrometer using FAB (fast atom bombardment) techniques.

Abbreviations. DIBAL-H = diisobutylaluminum hydride, DMA = *N*,*N*-dimethylacetamide, DMF = *N*,*N*-dimethylformamide, Tf = trifluoromethanesulfonyl.

Diels-Alder Adduct 22. $PhI(OAc)_2$ (0.093 g, 0.288 mmol, 1.2 equiv) was added to a solution of **19** (0.050 g, 0.240 mmol, 1.0 equiv) in *i*-PrOH/CH_2Cl_2 (2:1, 3 mL) at 0 °C, and the resultant yellow solution was stirred at 0 °C for 5 h, then at 23 °C for another 2 days. Upon completion, the reaction contents were concentrated directly and the resultant crude yellow oil was purified by flash column chromatography (silica gel, hexanes/EtOAc, 7:3) to afford the desired dimeric product (0.127 g, 99% yield) as a yellow oil. A solution of this dimer (0.033 g, 0.062 mmol, 1.0 equiv) and dienophile **21** (0.138 g, 0.620 mmol, 10.0 equiv) in mesitylene (1.0 mL) was carefully degassed 3 times using the freeze-pump-thaw method, and then sealed under argon in a tube equipped with a magnetic stir bar. The reaction solution was stirred at 220 °C (oil bath) for 1.5 h. After cooling to 23 °C, the reaction contents were purified directly by flash column chromatography (silica gel, hexanes/EtOAc, 4:1→7:3) to afford Diels–Alder adduct **22** (0.010 g, 17% yield) as a 3.2:1 ratio of diastereomers. **22**: R_f = 0.37 (silica gel, hexanes/EtOAc, 3:2); ^{1}H NMR (400 MHz, $CDCl_3$, major isomer only) δ 7.38 (d, *J* = 15.7 Hz, 1 H), 6.86–6.74 (m, 3 H), 6.58 (dd, *J* = 6.7, 1.9 Hz, 1 H), 6.10 (d, *J* = 15.8 Hz, 1 H), 4.43 (app septet, *J* = 6.2 Hz, 1 H), 3.88 (t, *J* = 2.0 Hz, 1 H), 3.84 (s, 3 H), 3.84 (s, 3 H), 3.80 (s, 3 H), 3.66 (s, 3 H), 3.55 (dd, *J* = 7.0, 2.4 Hz, 1 H), 3.50 (s, 3 H), 3.29 (dd, *J* = 7.0, 1.9 Hz, 1 H), 3.26 (dd, *J* = 6.6, 2.5 Hz, 1 H), 1.12 (d, *J* = 6.2 Hz, 3 H), 0.85 (d, *J* = 6.1 Hz, 3 H).

General Procedure for Mitsunobu Reaction (for the synthesis of 24a and 24d): To a solution of the known starting phenol **23** (1.0 equiv) and diisopropyl-azodicarboxylate (1.2 equiv) in toluene (0.1–0.2 M in phenol) at 23 °C was added a solution of alcohol (R-OH, 1.2 equiv) and PPh_3 (1.2 equiv) in THF (0.2–0.4 M) such that the final toluene/THF ratio was 2:1. The reaction was stirred at 23 °C for 36 h. Upon completion, the reaction contents were concentrated directly and purified by flash column chromatography (silica gel, hexanes/EtOAc, 4:1) to afford the desired products in 52–65% yield.

Glycosylation (for the synthesis of 24b): *Trichloroacetimidate* – D-Glucose pentaacetate (0.080 g, 0.230 mmol, 1.0 equiv) was dissolved in trichloroacetonitrile (1 mL), K_2CO_3 (0.317 g, 2.30 mmol, 10.0 equiv) was added, and the reaction was stirred at 60 °C for 16 h. Upon cooling, the reaction was diluted with CH_2Cl_2 (20 mL) and water (10 mL), and the layers were separated. The organic phase was washed with brine (10 mL), dried ($MgSO_4$), and concentrated to afford the crude trichloroacetimidate (0.101 g, 89% yield) as a colorless oil. *Glycosylation* – Phenol **23** (0.024 g, 0.102 mmol, 1.0 equiv) and the crude trichloroacetimidate (0.101 g, 0.205 mmol, 2.0 equiv) were dissolved in CH_2Cl_2 (0.5 mL). Activated powdered 4 Å molecular sieves were then added, and the mixture was stirred at 23 °C for 1 h. Catalytic BF_3•OEt_2 (0.0026 mL, 0.020 mmol, 0.2 equiv) was then added, and the reaction was stirred at 23 °C for 5 h. The reaction was then quenched with saturated aqueous $NaHCO_3$ (10 mL) and extracted with EtOAc (20 mL). The organic phase was then washed with brine (10 mL), dried ($MgSO_4$), and concentrated. The crude product was then purified by flash column chromatography

(silica gel, hexanes/EtOAc, 9:1→7:3) to afford the desired glycosylated product (0.041 g, 71% yield). *Deacetylation/benzylation* – The acetylated glycoside (0.041 g, 0.073 mmol, 1.0 equiv) was dissolved in MeOH (1.0 mL) and sodium hydride (60%, excess) was added. The resulting yellow solution was stirred at 23 °C for 3 h, after which it was neutralized by the addition of Amberlite-120IR-H resin, filtered and concentrated. This crude product was then taken up in DMF (1.0 mL) and cooled to 0 °C. Sodium hydride (60%, 0.015 g, 0.363 mmol, 5.0 equiv) was added followed by benzyl bromide (0.043 mL, 0.363 mmol, 5.0 equiv), and the reaction was stirred at 23 °C for 24 h. Upon completion, the reaction was quenched with water (10 mL) and extracted with Et_2O (3×10 mL). The organic phase was dried ($MgSO_4$) and concentrated. The crude product was then purified by flash column chromatography (silica gel, hexanes/EtOAc, 9:1→7:3) to afford the desired product (0.026 g, 47% yield).

General Procedure for Epoxide Opening (for the synthesis of 24c and 24e): Phenol **23** (1.0 equiv) and the epoxide (4.0 equiv) were dissolved in DMF (0.1 M in phenol). K_2CO_3 (2.0 equiv) was then added, and the reaction was stirred in a sealed flask at 100 °C for 24 h. Upon completion, the reaction contents were poured into aqueous 1 M HCl and extracted with Et_2O (3×). The combined organic layer was then washed with water and brine, dried ($MgSO_4$), and concentrated. The crude product was then purified by flash column chromatography (silica gel, hexanes/EtOAc, 9:1→7:1) to afford the desired alcohols in 50–65% yield.

General Procedure for Allyl Group Removal: Allylated starting material (1.0 equiv), $Pd(OAc)_2$ (0.2 equiv) and PPh_3 (0.3 equiv) were dissolved in a mixture of $THF/Et_2NH/H_2O$ (5:2:1, 0.05–0.1 M in starting material). The reaction was stirred in a sealed flask at 23 °C for 16 h. Upon completion, the reaction mixture was diluted with EtOAc then washed with 1 M aqueous HCl and brine. The crude product was purified by flash column chromatography (silica gel, hexanes/EtOAc, 7:3) to afford the desired product in 52–99% yield.

24a: R_f = 0.58 (silica gel, hexanes/EtOAc, 1:1); ^{1}H NMR (300 MHz, $CDCl_3$) 7.60 (d, *J* = 15.9 Hz, 1 H), 7.07–7.04 (m, 2 H), 6.92 (d, *J* = 8.0 Hz, 1 H), 6.27 (d, *J* = 15.9, 1 H), 5.95 (s, 1 H), 4.36–4.27 (m, 1 H), 3.80 (s, 3 H), 2.08–1.99 (m, 2 H), 1.86–1.75 (m, 2 H), 1.64–1.30 (m, 6 H).

24b: R_f = 0.30 (silica gel, hexanes/EtOAc, 7:3); ^{1}H NMR (300 MHz, $CDCl_3$) 7.57 (d, *J* = 15.9 Hz, 1 H), 7.41–7.17 (m, 22 H), 6.98 (d, *J* = 8.3 Hz, 1 H), 6.23 (d, *J* = 16.0, 1 H), 4.99–4.54 (m, 9 H), 3.81 (s, 3 H), 3.77–3.72 (m, 5 H), 3.55–3.51 (m, 1 H).

24c: R_f = 0.26 (silica gel, hexanes/EtOAc, 3:2); ^{1}H NMR (300 MHz, $CDCl_3$) 7.98 (br s, 1 H), 7.55 (d, *J* = 15.9 Hz, 1 H), 7.05 (dd, *J* = 8.2, 1.8 Hz, 1 H), 6.92 (d, *J* = 8.2 Hz, 1 H), 6.90 (d, *J* = 1.8 Hz, 1 H), 6.21 (d, *J* = 15.9, 1 H), 3.82 (s, 2 H), 3.79 (s, 3 H), 1.39 (s, 6 H).

24d: R_f = 0.32 (silica gel, hexanes/EtOAc, 7:1); ^{1}H NMR (400 MHz, $CDCl_3$) 7.48 (d, *J* = 16.0 Hz, 1 H), 7.40–7.28 (m, 5 H), 7.02 (dd, *J* = 8.2, 1.8 Hz, 1 H), 6.91 (d, *J* = 8.2 Hz, 1 H), 6.86 (d, *J* = 1.8 Hz, 1 H), 6.10 (d, *J* = 16.0 Hz, 1 H), 5.99 (s, 1 H), 5.36 (q, *J* = 6.5 Hz, 1 H), 3.76 (s, 3 H), 1.71 (d, *J* = 6.5 Hz, 1 H).

24e: R_f = 0.21 (silica gel, hexanes/EtOAc, 3:1); ^{1}H NMR (500 MHz, $CDCl_3$) 7.60 (d, *J* = 15.9 Hz, 1 H), 7.11 (dd, *J* = 8.2, 1.9 Hz, 1 H), 7.06 (d, *J* = 1.9 Hz, 1 H), 6.93 (d, *J* = 8.3 Hz, 1 H), 6.27 (d, *J* = 15.9 Hz, 1 H), 4.25 (dd, *J* = 9.9, 2.2 Hz, 1 H), 3.89 (t, *J* = 9.6 Hz, 1 H), 3.79 (s, 3 H), 3.74 (dd, *J* = 9.2, 2.2 Hz, 1 H), 1.01 (s, 9 H).

Diels–Alder Adduct 25. A solution of $PhI(OAc)_2$ (0.045 g, 0.141 mmol, 1.05 equiv) in MeOH/CH_2Cl_2 (0.2 mL) was added to a solution of **24d** (0.040 g, 0.134 mmol, 1.0 equiv) in MeOH (2.0 mL) at –40 °C, and the resultant yellow solution was stirred while slowly warming to 23 °C over 2 h, then at 23 °C for another 14 h. Upon completion, the reaction contents were concentrated directly and the resultant crude yellow oil was purified by flash column chromatography (silica gel, hexanes/EtOAc, 4:1) to afford the desired diastereomeric mixture of dimeric product (0.033 g, 75% yield) as a yellow oil. A solution of this dimer (0.032 g, 0.049 mmol, 1.0 equiv) and dienophile **21** (0.054 g, 0.244 mmol, 5.0 equiv) in mesitylene (0.3 mL) was carefully degassed 3 times using the freeze-pump-thaw method, and then sealed under argon in a tube equipped with a magnetic stir bar. The reaction solution was stirred at 220 °C (oil bath) for 30 min. After cooling to 23 °C, the reaction contents were purified directly by flash column chromatography (silica gel, hexanes/EtOAc, 4:1→7:3) to afford Diels–Alder adduct **25** (0.014 g, 52% yield) as a 4:3.5:1:1 ratio of diastereomers. **25**: R_f = 0.22 (silica gel, hexanes/EtOAc, 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) 4:3.5:1:1 d.r.

Diels–Alder Adduct 26. A solution of $PhI(OAc)_2$ (0.174 g, 0.539 mmol, 1.05 equiv) in 1,1,1-trifluoroethanol (2.0 mL) was added to a solution of **24e** (0.151 g, 0.513

mmol, 1.0 equiv) in the same solvent (10 mL) at –40 °C, and the resultant yellow solution was stirred –40 °C for 30 min, then warmed to –10 °C over another 30 min. Powdered $NaHCO_3$ (excess) was then added, and the reaction was stirred at –10 °C for another 15 min, after which it was concentrated directly. The resultant mixture was taken up in CH_2Cl_2 (20 mL), filtered and concentrated. The crude was purified by flash column chromatography (silica gel, hexanes/EtOAc, 3:2) to afford the desired diastereomeric mixture of dimeric product (0.058 g, 39% yield) as a yellow oil. A solution of this dimer (0.025 g, 0.043 mmol, 1.0 equiv) and dienophile **21** (0.064 g, 0.286 mmol, 6.7 equiv) in mesitylene (0.3 mL) was carefully degassed 3 times using the freeze-pump-thaw method, and then sealed under argon in a tube equipped with a magnetic stir bar. The reaction solution was stirred at 220 °C (oil bath) for 30 min. After cooling to 23 °C, the reaction contents were purified directly by flash column chromatography (silica gel, hexanes/EtOAc, 4:1→7:3) to afford Diels–Alder adduct **26** (0.020 g, 45% yield) as a 1:1 ratio of diastereomers. **26**: R_f = 0.33 (silica gel, hexanes/EtOAc, 3:1); ^{1}H NMR (400 MHz, $CDCl_3$) 1:1 d.r.

Improved Synthesis of Diene 42. D-(–)-quinic acid (6.0 g, 31.2 mmol, 1.0 equiv) was dissolved in toluene (2.0 mL), and the flask was equipped with a magnetic stir bar and a Dean-Stark apparatus. Cyclohexanone (6.1 mL, 156 mmol, 5.0 equiv) and (±)-camphorsulfonic acid (0.0024 g, 0.010 mmol, 0.1 equiv) were then added. The reaction was stirred at reflux for 14 h during which water was removed from the reaction using the Dean-Stark apparatus. Upon completion, the reaction contents were then poured into saturated aq. $NaHCO_3$ (15 mL) and extracted with CH_2Cl_2 (2×10 mL). The combined

organic phase was dried ($MgSO_4$) and concentrated. Pure product was obtained by triturating the crude residue with Et_2O to afford the desired lactone (6.17 g, 78% yield) as a white solid. This lactone (2.0 g, 7.87 mmol, 1.0 equiv) was dissolved in anhydrous MeOH (50.0 mL), and NaOMe (0.042 g, 0.787 mmol, 0.1 equiv) was added. The reaction was stirred at 23 °C for 14 h. The reaction contents were then poured into saturated aq. NH_4Cl (200 mL) and extracted with CH_2Cl_2 (2×100 mL). The combined organic phase was dried ($MgSO_4$), concentrated and purified by flash column chromatography (silica gel, hexanes/EtOAc, 7:3→1:1) to afford the desired known diol **41** (1.84 g, 82% yield). This intermediate (**41**, 0.062 g, 0.252 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (2.0 mL), and the resulting solution was cooled to 0 °C. Pyridine (0.065 mL, 0.806 mmol, 3.2 equiv) was added followed by Tf_2O (0.156 mL, 0.554 mmol, 2.2 equiv) dropwise. The resulting yellow solution was stirred at 23 °C for 2 h, then more pyridine (0.305 mL, 3.78 mmol, 15.0 equiv) was added and stirring was continued at 23 °C for 24 h. Upon completion, the reaction contents were concentrated to near dryness and purified directly by flash column chromatography (silica gel, hexanes/EtOAc, 19:1) to afford known diene **42** (0.020 g, 38% yield). **42**: R_f = 0.50 (silica gel, hexanes/EtOAc, 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) 6.87 (dt, *J* = 3.7, 1.1 Hz, 1 H), 6.53 (d, *J* = 9.9 Hz, 1 H), 6.06 (dd, *J* = 9.9, 3.7 Hz, 1 H), 4.81 (dd, *J* = 8.8, 3.7 Hz, 1 H), 4.64 (ddd, *J* = 9.1, 4.2, 0.7 Hz, 1 H), 3.80 (s, 3 H), 1.64–1.58 (m, 8 H), 1.40 (m, 2 H). All spectroscopic data for this material matches those previously reported.

Alcohol 43. Dienyl ester **42** (0.008 g, 0.032 mmol, 1.0 equiv) was dissolved in THF (0.5 mL) and cooled to 0 °C. DIBAL-H solution (1.0 M toluene, 0.096 mL, 0.096

mmol, 3.0 equiv) was added and the reaction was stirred at 0 °C for 30 min. Upon completion, the reaction contents were quenched with a mixture of aqueous 1 M HCl and saturated NH_4Cl (1:1, 5 mL) and extracted with EtOAc (10 mL). The organic phase was then washed with saturated aq. $NaHCO_3$ (5 mL) and brine (5 mL), dried ($MgSO_4$), and concentrated to afford alcohol **43** (0.0075 g, 93% yield) as a colorless oil. **43**: R_f = 0.07 (silica gel, hexanes/EtOAc, 4:1); ^{1}H NMR (500 MHz, $CDCl_3$) 5.97 (s, 2 H), 5.87 (s, 1 H), 4.67 (s, 2 H), 4.17 (d, J = 3.4 Hz, 2 H). 1.63–1.40 (m, 9 H).

Acetate 44. Alcohol **43** (0.025 g, 0.113 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (1.0 mL). Pyridine (0.045 mL, 0.562 mmol, 5.0 equiv) and Ac_2O (0.032 mL, 0.337 mmol, 3.0 equiv) were added, and the reaction was stirred at 23 °C for 16 h. Upon completion, the reaction contents were concentrated directly and purified by flash column chromatography (silica gel, hexanes/EtOAc, 19:1) to afford acetate **44** (0.015 g, 50% yield) as a colorless oil. **44**: R_f = 0.36 (silica gel, hexanes/EtOAc, 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) 6.00–5.89 (m, 3 H), 4.67 (m, 2 H), 4.59 (dd, J = 18.3, 12.9 Hz, 2 H), 2.09 (s, 3H), 1.63–1.59 (m, 6 H), 1.42–1.39 (m, 2 H).

Aldehyde 45. Alcohol **43** (0.0075 g, 0.030 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (1.0 mL), and the solution was cooled to 0 °C. Dess-Martin periodinane (0.025 g, 0.060 mmol, 2.0 equiv) was added, and the reaction was stirred at 23 °C for 1.5 h. Excess oxidant was quenched by adding saturated aq. Na_2SO_3 (3 mL) and stirring for 15 min. The reaction contents were then diluted with EtOAc (10 mL) and washed with saturated aq. $NaHCO_3$ (2×5 mL) and brine (5 mL). The organic layer was then dried ($MgSO_4$) and

concentrated. The crude product was purified by flash column chromatography (silica gel, hexanes/EtOAc, 4:1) to afford aldehyde **45** (0.005 g, 76% yield) as a colorless oil. **45**: R_f = 0.37 (silica gel, hexanes/EtOAc, 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) 9.52 (d, *J* = 0.5 Hz, 1 H), 6.65 (dt, *J* = 3.5, 1.0 Hz, 1 H), 6.54 (d, *J* = 9.9 Hz, 1 H), 6.14 (dd, *J* = 9.9, 4.0 Hz, 1 H), 4.92 (dd, *J* = 8.8, 3.5 Hz, 1 H), 4.72 (ddd, *J* = 8.7, 4.1, 0.6 Hz, 1 H), 1.65–1.25 (m, 8 H).

Triene 46. Aldehyde **45** (0.027 g, 0.123 mmol, 1.0 equiv) and the Wittig reagent (Ph_3PCHCO_2Me) (0.061 g, 0.184 mmol, 1.5 equiv) were dissolved in CH_2Cl_2 (3.0 mL), and the reaction was stirred at 23 °C for 18 h. Upon completion, the reaction contents were concentrated directly and purified by flash column chromatography (silica gel, hexanes/EtOAc, 19:1→9:1) to afford triene **46** (0.028 g, 82% yield) as a colorless oil. **46**: R_f = 0.40 (silica gel, hexanes/EtOAc, 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) 7.27 (d, *J* = 16.0 Hz, 1 H), 6.27 (d, *J* = 10.0 Hz, 1 H), 6.14–6.07 (m, 3 H), 4.78 (dd, *J* = 8.6, 4.0 Hz, 1 H), 4.67 (ddd, *J* = 8.6, 3.8, 0.7 Hz, 1 H), 3.77 (s, 3 H), 1.64–1.58 (m, 6 H), 1.40 (m, 2 H).

Diels-Alder Adduct 49. A solution of diene **42** (0.004 g, 0.016 mmol, 1.0 equiv) and dienophile **21** (0.018 g, 0.080 mmol, 5.0 equiv) in chlorobenzene (0.3 mL) was carefully degassed 3 times using the freeze-pump-thaw method, and then sealed under argon in a microwave pressure vessel equipped with a magnetic stir bar. The reaction solution was stirred at 250 °C in a microwave reactor for 3 h. After cooling to 23 °C, the reaction contents were purified directly by flash column chromatography (silica gel, hexanes/EtOAc, 4:1→7:3) to afford Diels–Alder adduct **49** (0.0005 g, 7% yield) as a

4.5:1 ratio of regioisomers. The same procedure was used to conduct the reaction in *N*,*N*-dimethylacetamide to afford product **49** in 12% yield. **49**: R_f = 0.31 (silica gel, hexanes/EtOAc, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) 7.35 (d, *J* = 6.8 Hz, 1 H), 6.83 (d, *J* = 8.0 Hz, 1 H), 6.80–6.74 (m, 2 H), 4.44 (dd, *J* = 7.2, 3.6 Hz, 1 H), 4.31 (dd, *J* = 7.2, 2.8 Hz, 1 H), 3.97 (dt, *J* = 1.8, 1.6 Hz, 1 H), 3.89 (s, 3 H), 3.87 (s, 3 H), 3.78 (s, 3 H), 3.65 (s, 3 H), 3.31 (dt, *J* = 6.8, 3.2 Hz, 1 H), 3.20 (dd, *J* = 6.6, 2.6 Hz, 1 H), 2.86 (dd, *J* = 6.6, 1.8 Hz, 1 H), 1.54–1.25 (m, 8 H).

Diels-Alder Adduct 50. A solution of diene **44** (0.005 g, 0.019 mmol, 1.0 equiv) and dienophile **21** (0.021 g, 0.095 mmol, 5.0 equiv) in chlorobenzene (0.3 mL) was carefully degassed 3 times using the freeze-pump-thaw method, and then sealed under argon in a microwave pressure vessel equipped with a magnetic stir bar. The reaction solution was stirred at 250 °C in a microwave reactor for 6 h. After cooling to 23 °C, the reaction contents were purified directly by flash column chromatography (silica gel, hexanses/EtOAc, 4:1→7:3) to afford Diels–Alder adduct **50** (0.0005 g, 7% yield) as a 0.8:1 ratio of regioisomers. **50**: R_f = 0.39 (silica gel, hexanes/EtOAc, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$, integration of 1.0 per H for major diastereomer, 0.8 per H for minor diastereomer) 6.84–6.81 (m, 1.8 H), 6.78–6.72 (m, 3.6 H), 6.28 (d, *J* = 4.8 Hz, 0.8 H), 5.99 (d, *J* = 6.4 Hz, 1 H), 4.67 (ddd, *J* = 18.2, 13.0, 1.2 Hz, 2 H), 4.61 (d, *J* = 1.2 Hz, 1.6 H), 4.39–4.35 (m, 1.8 H), 4.30–4.26 (m, 1.8 H), 3.90 (s, 3 H), 3.88 (s, 2.4 H), 3.87 (s, 3 H), 3.87 (s, 2.4 H), 3.68 (s, 2.4 H), 3.67 (s, 3 H), 3.43 (ddd, *J* = 5.6, 2.8, 1.6 Hz, 1 H), 3.53 (m, 0.8 H), 3.25 (dd, *J* = 6.6, 2.2 Hz, 0.8 H), 3.22 (dd, *J* = 6.6, 2.6 Hz, 1 H), 3.10 (dt,

J = 6.8, 3.2 Hz, 0.8 H), 3.04 (m, 1 H), 2.81 (dd, *J* = 6.6, 1.8 Hz, 0.8 H), 2.78 (dd, *J* = 7.0, 1.4 Hz, 1 H), 2.10 (s, 3 H), 2.08 (s, 2.4 H), 1.54–1.26 (m, 8 H).

Bicyclic Alcohol 51. Diels-Alder adduct **49** (0.013 g, 0.028 mmol, 1.0 equiv) was dissolved in THF (0.5 mL) and cooled to 0 °C. $LiAlH_4$ solution (1.0 M Et_2O, 0.055 mL, 0.055 mmol, 2.0 equiv) was added and the reaction was stirred at 0 °C for 1 h. Upon completion, the reaction contents were quenched with saturated aq. potassium sodium tartrate (5 mL) stirring vigorously for 14 h. The mixture was poured into saturated aq. $NaHCO_3$ (10 mL) and extracted with EtOAc (2×5 mL). The organic phase was then dried ($MgSO_4$) and concentrated to afford the desired diol. This compound was dissolved in CH_2Cl_2 (0.5 mL) and finely ground $BaMnO_4$ (excess) was added. The reaction was stirred at 23 °C for 16 h. Upon completion, the reaction contents were filtered through Celite and concentrated to afford the desired aldehyde. This crude product and the Wittig reagent (Ph_3PCHCO_2Me) were dissolved in toluene (0.5 mL) at stirred at 60 °C for 5 h. Upon completion, the reaction contents were concentrated directly and purified by flash column chromatography (silica gel, hexanes/EtOAc, 4:1→1:1) to afford bicyclic alcohol **51** (0.007 g, 50% yield overall) as a colorless oil. **51**: R_f = 0.23 (silica gel, hexanes/EtOAc, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) 7.50–7.44 (d, *J* = 15.7 Hz, 1 H), 6.85–6.75 (m, 3 H), 6.61 (d, *J* = 6.4 Hz, 1 H), 6.07 (d, *J* = 15.7 Hz, 1 H), 4.44 (dd, *J* = 7.1, 3.5 Hz, 1 H), 4.29 (dd, *J* = 7.1, 3.0 Hz, 1 H), 3.89 (s, 3 H), 3.87 (s, 3 H), 3.83 (dd, *J* = 6.9, 1.6 Hz, 1 H), 3.77 (s, 3 H), 3.58 (br s, 1 H), 3.51 (br s, 1 H), 3.48–3.44 (m, 1 H), 3.25–3.19 (m, 1 H), 3.09–3.07 (m, 1 H), 1.50–1.30 (m, 8 H).

Helisterculin B Core 47. Diels-Alder adduct **50** (0.8:1 d.r., 0.0011 g, 0.0023 mmol, 1.0 equiv) was dissolved in MeOH (1.0 mL) and K_2CO_3 (catalytic) was added. The reaction was stirred at 23 °C for 14 h. Upon completion, the reaction mixture was poured into saturated aq. NH_4Cl (10 mL) and extracted with EtOAc (2×5 mL). The organic phase was then dried ($MgSO_4$) and concentrated to afford the desired alcohol. This compound was dissolved in CH_2Cl_2 (0.5 mL). Dess-Martin periodinane (0.002 g, 0.0045 mmol, 2.0 equiv) was added, and the reaction was stirred at 23 °C for 1 h. Excess oxidant was quenched by adding saturated aq. Na_2SO_3 (3 mL) and stirring for 15 min. The reaction contents were then diluted with EtOAc (10 mL) and washed with saturated aq. $NaHCO_3$ (2×5 mL) and brine (5 mL). The organic layer was then dried ($MgSO_4$) and concentrated to afford the desired aldehyde. This crude product and the Wittig reagent (Ph_3PCHCO_2Me) were dissolved in toluene (0.5 mL) at stirred at 60 °C for 5 h. Upon completion, the reaction contents were concentrated directly and purified by preparative TLC (silica gel, hexanes/EtOAc, 7:3, run up three times) to afford pure bicyclic core **47** (0.0003 g, 73% yield overall) and its regioisomer as a colorless oils. **47**: R_f = 0.48 (silica gel, hexanes/EtOAc, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) 7.39 (d, *J* = 15.8 Hz, 1 H), 6.83 (d, *J* = 8.2 Hz, 1 H), 6.78–6.74 (m, 2 H), 6.64 (d, *J* = 6.5 Hz, 1 H), 5.99 (d, *J* = 15.8 Hz, 1 H), 4.47 (d, *J* = 7.2, 3.4 Hz, 1 H), 4.30 (*J* = 6.9, 2.7 Hz, 1 H), 3.89 (s, 3 H), 3.87 (s, 3 H), 3.76 (s, 3 H), 3.76–3.73 (m, 1 H), 3.63 (s, 3 H), 3.32 (dd, *J* = 6.2, 2.5 Hz, 1 H), 3.23 (dt, *J* = 6.7, 3.1 Hz, 1 H), 2.90 (dd, *J* = 6.3, 1.9 Hz, 1 H), 1.49–1.39 (m, 6 H), 1.32 (m, 2 H).

Diene 53. D-(–)-quinic acid (0.020 g, 0.104 mmol, 1.0 equiv) was dissolved in anhydrous acetone (2.0 mL), and (±)-CAMPHORSULFONIC ACID (0.0024 g, 0.010

mmol, 0.1 equiv) was added. The reaction was stirred in a sealed flask at 40 °C for 48 h. Upon completion, the reaction contents were then poured into saturated aq. $NaHCO_3$ (15 mL) and extracted with CH_2Cl_2 (2×10 mL). The combined organic phase was dried ($MgSO_4$) and concentrated to afford the desired lactone product that was used without further purification. This lactone (0.067 g, 0.315 mmol, 1.0 equiv) was dissolved in anhydrous MeOH (4.0 mL), and NaOMe (0.0017 g, 0.032 mmol, 0.1 equiv) was added. The reaction was stirred at 23 °C for 14 h. The reaction contents were then poured into saturated aq. NH_4Cl (15 mL) and extracted with CH_2Cl_2 (2×10 mL). The combined organic phase was dried ($MgSO_4$), concentrated and purified by flash column chromatography (silica gel, hexanes/EtOAc, 7:3→1:1) to afford the desired product (0.062 g, 80% yield). This diol (0.062 g, 0.252 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (2.0 mL), and the resulting solution was cooled to 0 °C. Pyridine (0.065 mL, 0.806 mmol, 3.2 equiv) was added followed by Tf_2O (0.156 mL, 0.554 mmol, 2.2 equiv) dropwise. The resulting yellow solution was stirred at 23 °C for 2 h, then more pyridine (0.305 mL, 3.78 mmol, 15.0 equiv) was added and stirring was continued at 23 °C for 24 h. Upon completion, the reaction contents were concentrated to near dryness and purified directly by flash column chromatography (silica gel, hexanes/EtOAc, 19:1) to afford diene **53** (0.020 g, 38% yield). **53**: R_f = 0.39 (silica gel, hexanes/EtOAc, 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) 6.86 (dt, J = 3.6, 1.0 Hz, 1 H), 6.54 (d, J = 10.0 Hz, 1 H), 6.04 (dd, J = 10.0, 4.0 Hz, 1 H), 4.81 (dd, J = 8.9, 3.7 Hz, 1 H), 4.64 (ddd, J = 8.8, 4.0, 0.6 Hz, 1 H), 3.80 (s, 3 H), 1.41 (s, 3 H), 1.39 (s, 3 H).

Diels-Alder Adduct 54. A solution of diene **53** (0.004 g, 0.019 mmol, 1.0 equiv) and dienophile **21** (0.021 g, 0.095 mmol, 5.0 equiv) in DMA (0.3 mL) was carefully degassed 3 times using the freeze-pump-thaw method, and then sealed under argon in a microwave pressure vessel equipped with a magnetic stir bar. The reaction solution was stirred at 250 °C in a microwave reactor for 3 h. After cooling to 23 °C, the reaction contents were purified directly by preparative TLC (silica gel, hexanses/EtOAc, 9:1 then 1:1) to afford Diels–Alder adduct **54** (0.0012 g, 15% yield) as a 0.8:1 ratio of regioisomers. **54**: R_f = 0.17 (silica gel, hexanes/EtOAc, 3:2); ^{1}H NMR (400 MHz, $CDCl_3$, major diastereomer only) 7.35 (d, *J* = 7.0 Hz, 1 H), 6.83 (d, *J* = 8.0 Hz, 1 H), 6.81–6.74 (m, 2 H), 4.45 (dd, *J* = 7.2, 3.4 Hz, 1 H), 4.33 (dd, *J* = 6.9, 2.3 Hz, 1 H), 3.96 (m, 1 H), 3.89 (s, 3 H), 3.87 (s, 3 H), 3.78 (s, 3 H), 3.65 (s, 3 H), 3.29 (dt, *J* = 6.9, 2.9 Hz, 1 H), 3.21 (dd, *J* = 6.8, 2.6 Hz, 1 H), 2.86 (dd, *J* = 6.6, 2.0 Hz, 1 H), 1.24 (s, 3 H), 1.21 (s, 3 H).

Bicyclic Diol 52. Diels-Alder adduct **54** (0.0012 g, 0.0028 mmol) was dissolved in THF (0.1 mL), and aqueous 1 M HCl (0.1 mL) was added. The reaction was stirred at 23 °C for 48 h. Upon completion, the reaction contents were taken up in Et_2O (5 mL), poured into saturated aq. $NaHCO_3$ (10 mL) and extracted with EtOAc (2×5 mL). The organic phase was then dried ($MgSO_4$), concentrated and purified by preparative TLC (silica gel, hexanes/EtOAc, 2:3) to afford the desired diol **52** (0.0009 g, 86% yield) as a colorless oil. **52**: R_f = 0.05 (silica gel, hexanes/EtOAc, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) 7.47 (d, *J* = 7.0 Hz, 1 H), 6.85–6.73 (m, 3 H), 4.19 (s, 1 H), 4.08 (s, 1 H), 3.89 (s, 3 H), 3.87 (s, 3 H), 3.80 (s, 3 H), 3.64 (s, 3 H), 3.57–3.54 (m, 1 H), 3.17–3.13 (m, 2 H), 2.95–2.91 (m, 1 H), 2.46 (d, *J* = 5.4 Hz, 1 H), 2.26 (d, *J* = 6.0 Hz, 1 H).

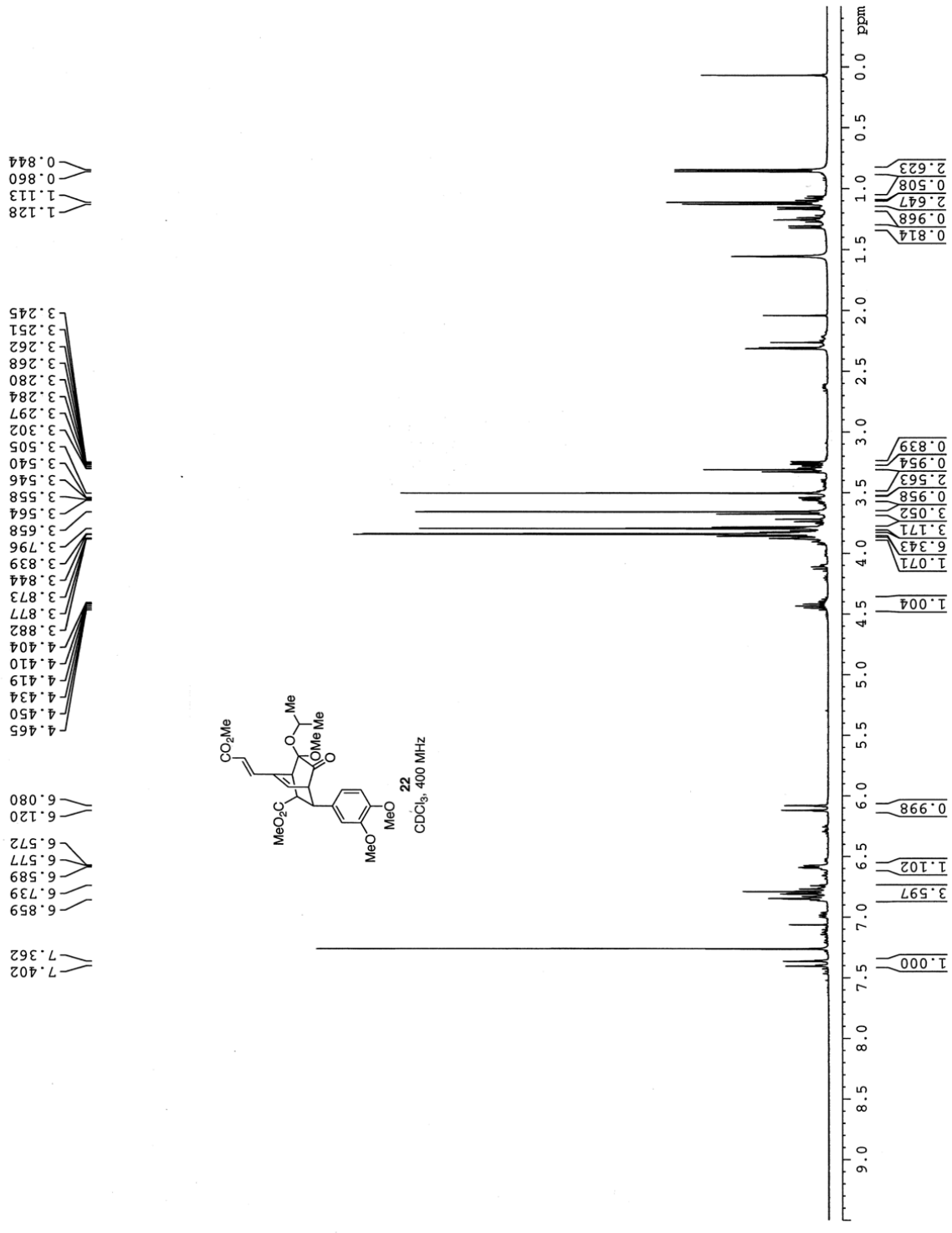
Allylic Alcohol 63. Ester **21** (1.82 g, 8.19 mmol, 1.0 equiv) was dissolved in THF (20.0 mL), and the resulting solution was cooled to –78 °C. DIBAL-H solution (1.0 M toluene, 20.5 mL, 20.5 mmol, 2.5 equiv) was then added, and the reaction was slowly warmed to 23 °C over the period of 3 h with stirring. Upon completion, the reaction was cooled back to 0 °C and poured into a vigorously stirring mixture of hexanes (140 mL) / saturated aq. $MgSO_4$ (6 mL). This initially biphasic mixture was stirred at 23 °C for 1 h, after which it was filtered, washing the salts with EtOAc (50 mL). The filtrate was concentrated to afford the desired allylic alcohol **63** (1.57 g, 99% yield) without further purification. **63:** R_f = 0.43 (silica gel, hexanes/EtOAc, 3:7); ^{1}H NMR (300 MHz, $CDCl_3$) 6.97–6.86 (m, 2 H), 6.82 (d, *J* = 8.0 Hz, 1 H), 6.56 (d, *J* = 15.7 Hz, 1 H), 6.25 (dt, *J* = 15.8, 5.9 Hz, 1 H), 4.32 (td, *J* = 5.9, 1.3 Hz, 2 H), 3.90 (s, 3 H), 3.89 (s, 3 H), 1.38 (t, *J* = 5.9 Hz, 1 H).

Phenol 69. Allyl-protected phenol **23** (0.020 g, 0.085 mmol, 1.0 equiv), allylic alcohol **63** (0.020 g, 0.102 mmol, 1.2 equiv) and PPh_3 (0.034 g, 0.128 mmol, 1.5 equiv) were dissolved in THF (1.0 mL), and the resulting solution was cooled to 0 °C. DEAD (40%, 0.057 mL, 0.128 mmol, 1.5 equiv) was then added dropwise, and the reaction was stirred at 0 °C for 1.5 h. The reaction contents were then concentrated directly and purified by flash column chromatography (silica gel, hexanes/EtOAc, 9:1→4:1) to afford the desired ether product (0.023 g, 65% yield) along with its branched isomer (S_N2' product, 0.011 g, 32% yield). The linear ether product (0.219 g, 0.534 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (3.0 mL) followed by the addition of $PhSiH_3$ (0.098 mL, 0.800

mmol, 1.5 equiv) and $Pd(PPh_3)_4$ (0.018 g, 0.017 mmol, 0.03 equiv). The reaction was stirred at 23 °C for 5 h. Upon completion, the reaction contents were poured into aq. 1 M HCl (10 mL) and extracted with EtOAc (2×10 mL). The combined organic phase was washed with brine (5 mL), dried ($MgSO_4$) and concentrated. The crude product was purified by flash column chromatography (silica gel, hexanes/EtOAc, 9:1→4:1) to afford phenol **69** (0.105 g, 53% yield, 34% yield overall). **69:** R_f = 0.36 (silica gel, hexanes/EtOAc, 3:2); ^{1}H NMR (300 MHz, $CDCl_3$) 7.62 (d, *J* = 15.9 Hz, 1 H), 7.12–7.06 (m, 2 H), 7.01–6.91 (m, 3 H), 6.85 (app d, *J* = 2.6 Hz, 1 H), 6.68 (d, *J* = 15.9 Hz, 1 H), 6.28 (dt, *J* = 15.9, 6.2 Hz, 2 H), 5.97 (br s, 1 H), 4.77 (dd, *J* = 6.2, 1.1 Hz, 2 H), 3.92 (s, 3 H), 3.89 (s, 3 H), 3.79 (s, 3 H).

Diels-Alder Adduct 65. Phenol **69** (0.028 g, 0.076 mmol, 1.0 equiv) was dissolved in MeOH (5.0 mL), and the resulting solution was heated to 60 °C. A solution of $PhI(OAc)_2$ (0.027 g, 0.083 mmol, 1.1 equiv) in CH_2Cl_2 (1.0 mL) was then added dropwise over the course of 15 min. The reaction was the stirred at 60 °C for an additional 1 h. Upon completion, the reaction contents were concentrated directly and purified by flash column chromatography (silica gel, hexanes/EtOAc, 4:1→7:3) to afford Diels-Alder product **65** (0.020 g, 66% yield) as a white amorphous solid. **65:** R_f = 0.24 (silica gel, hexanes/EtOAc, 3:2); ^{1}H NMR (400 MHz, $CDCl_3$) 7.44 (d, *J* = 15.9 Hz, 1 H), 6.75 (d, *J* = 8.3 Hz, 1 H), 6.53 (d, *J* = 2.0 Hz, 1 H), 6.45 (dd, *J* = 8.1, 2.3 Hz, 1 H), 6.32 (d, *J* = 6.3 Hz, 1 H), 6.18 (d, *J* = 15.9, 1 H), 4.32 (dd, *J* = 8.3, 3.3 Hz, 1 H), 4.01 (d, *J* = 8.3 Hz, 1 H), 3.85 (s, 3 H), 3.82 (s, 3 H), 3.81 (s, 3 H), 3.75 (dd, *J* = 4.2, 1.9 Hz, 1 H), 3.57 (s, 3 H), 3.43 (dd, *J* = 6.7, 3.0 Hz, 1 H), 3.40 (br s, 1 H), 2.82 (br s, 1 H).

Diels-Alder Adduct 71. Phenol **69** (0.096 g, 0.259 mmol, 1.0 equiv) was dissolved in a mixture of 1,4-dioxane/water (2:1, 6.0 mL), and the resulting solution was heated to 80 °C. A solution of $PhI(OAc)_2$ (0.092 g, 0.285 mmol, 1.1 equiv) in CH_2Cl_2 (1.0 mL) was then added dropwise over the course of 15 min. The reaction was the stirred at 80 °C for an additional 30 min. Upon completion, the reaction contents were concentrated directly and purified by flash column chromatography (silica gel, hexanes/EtOAc, 4:1→1:1) to afford Diels-Alder product **71** (0.064 g, 64% yield) as a white amorphous solid. **71:** R_f = 0.14 (silica gel, hexanes/EtOAc, 3:2); ^{1}H NMR (400 MHz, $CDCl_3$) 7.43 (d, *J* = 15.8 Hz, 1 H), 6.76 (d, *J* = 8.2 Hz, 1 H), 6.53 (s, 1 H), 6.47 (d, *J* = 8.3 Hz, 1 H), 6.28–6.21 (m, 2 H), 4.38 (dd, *J* = 8.2, 2.9 Hz, 1 H), 4.32 (q, *J* = 7.1 Hz, 1 H), 3.95–3.91 (m, 2 H), 3.85 (s, 3 H), 3.82 (s, 3 H), 3.80 (s, 3 H), 3.73 (m, 1 H), 3.51 (dd, *J* = 7.1, 2.6 Hz, 1 H), 3.43 (br s, 1 H).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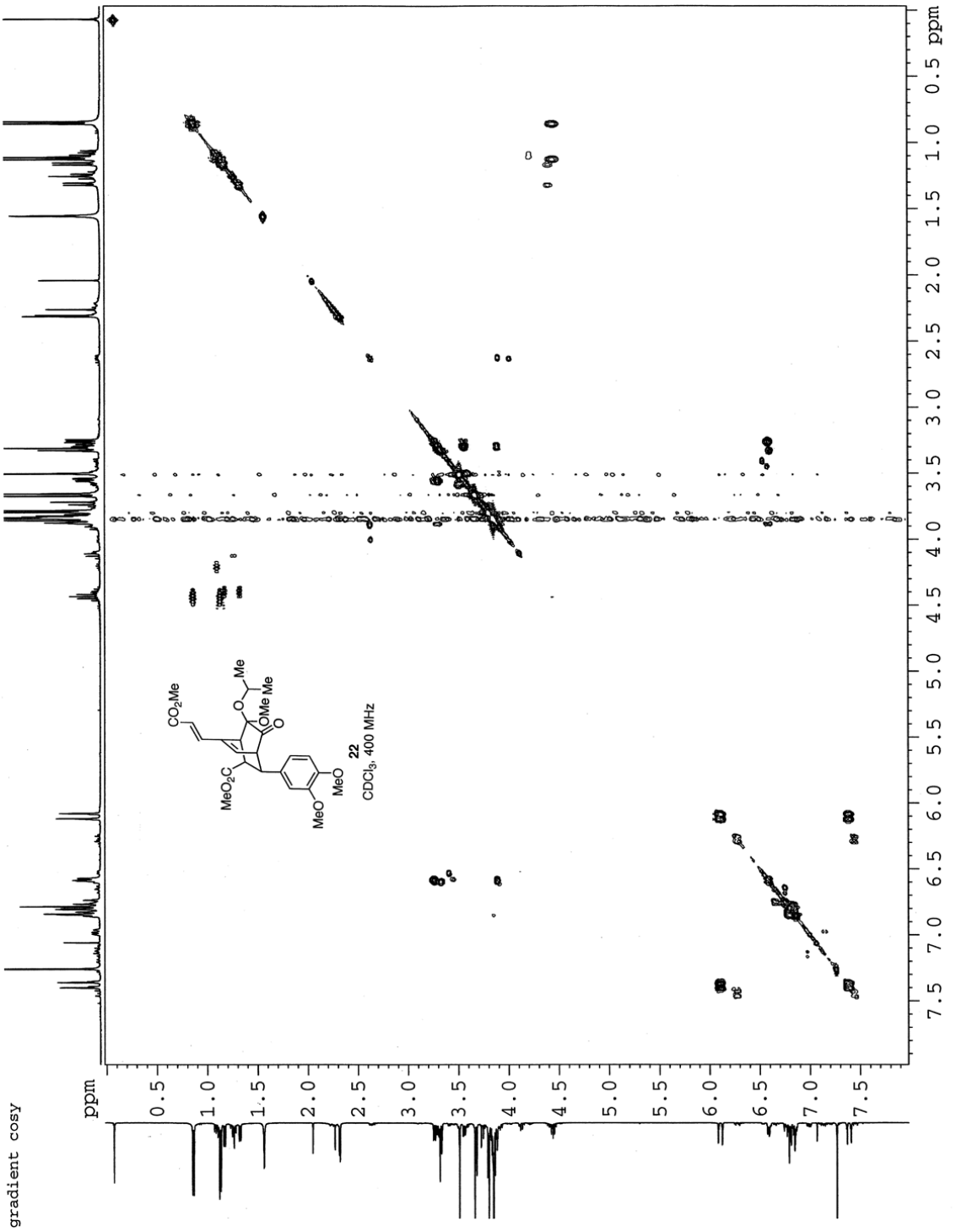
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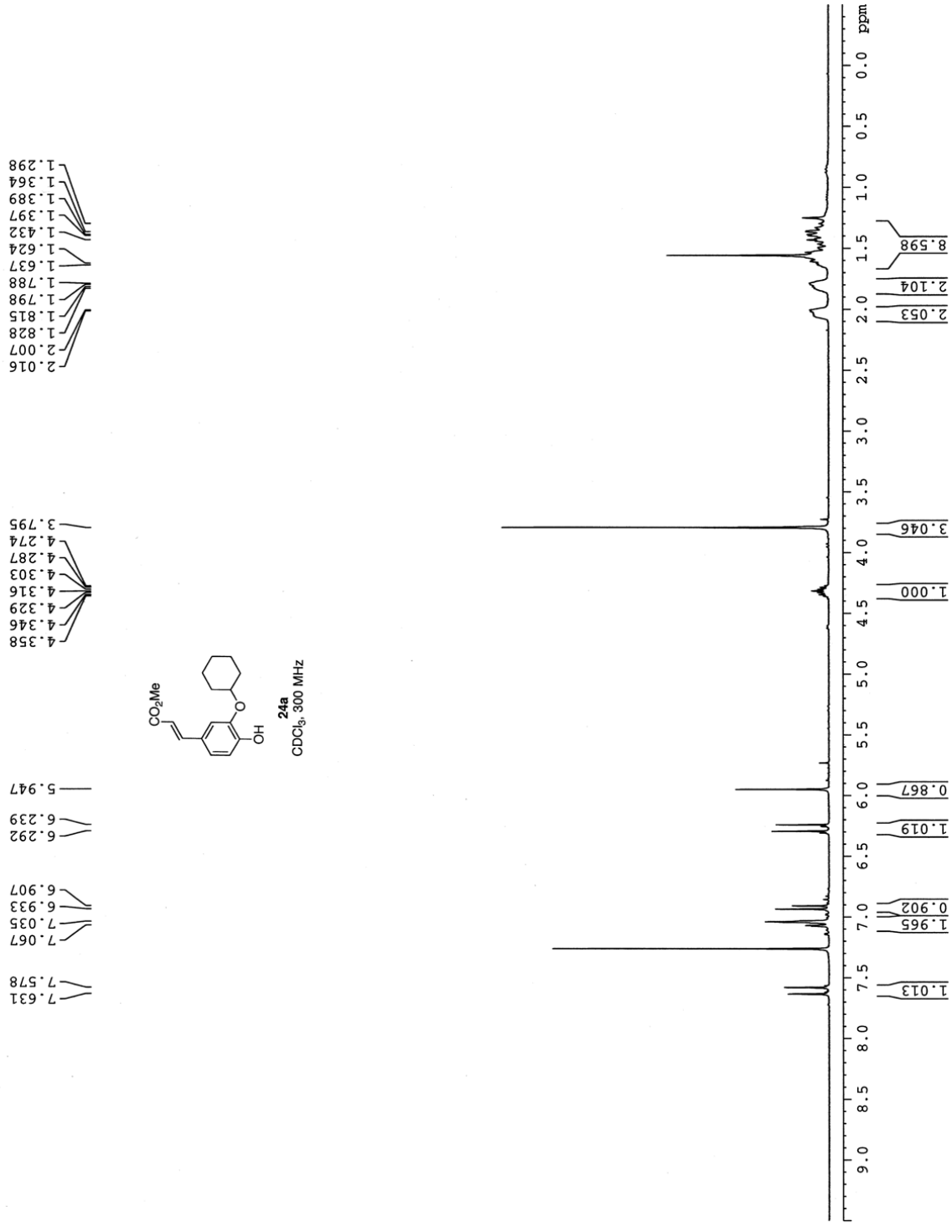
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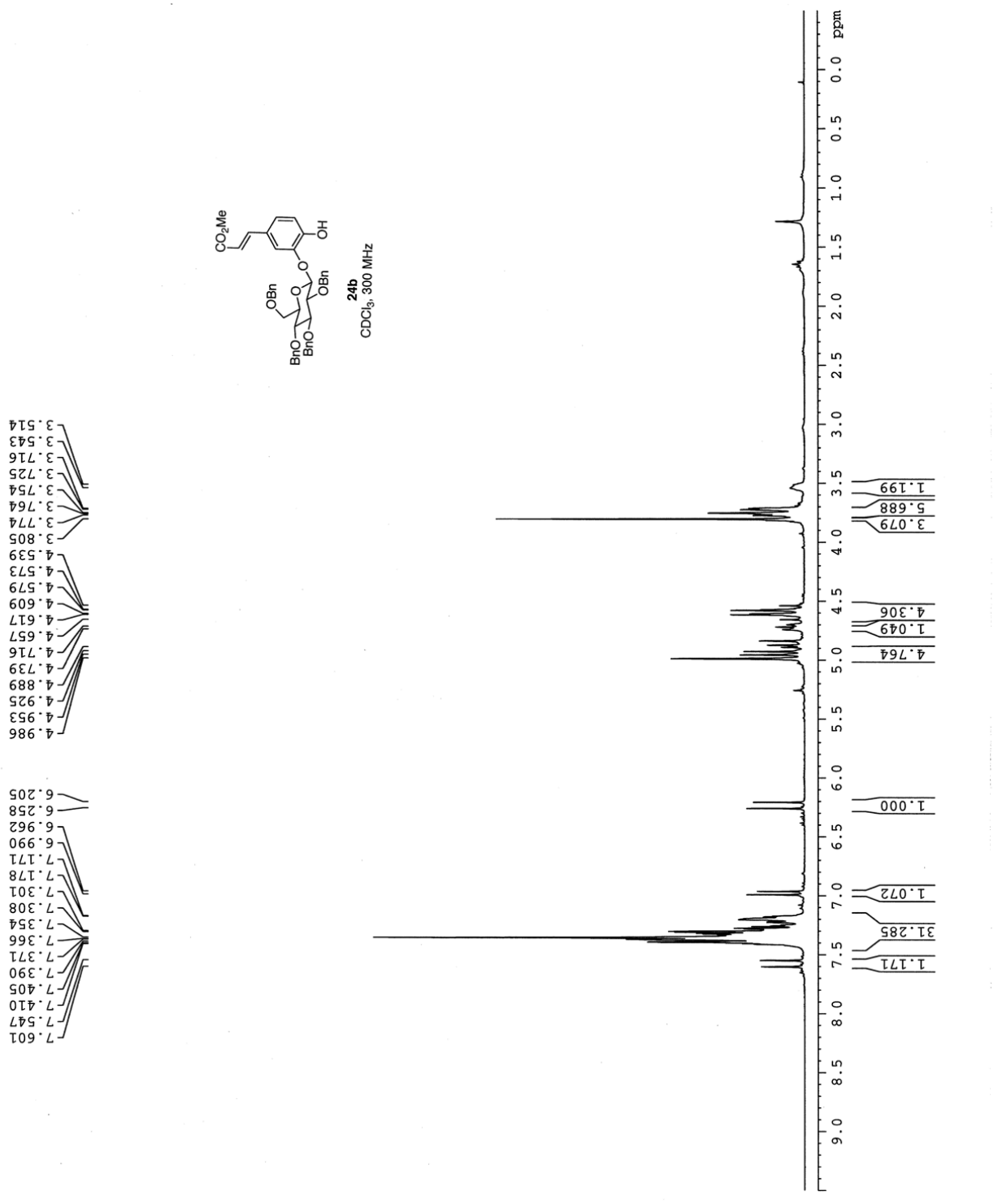
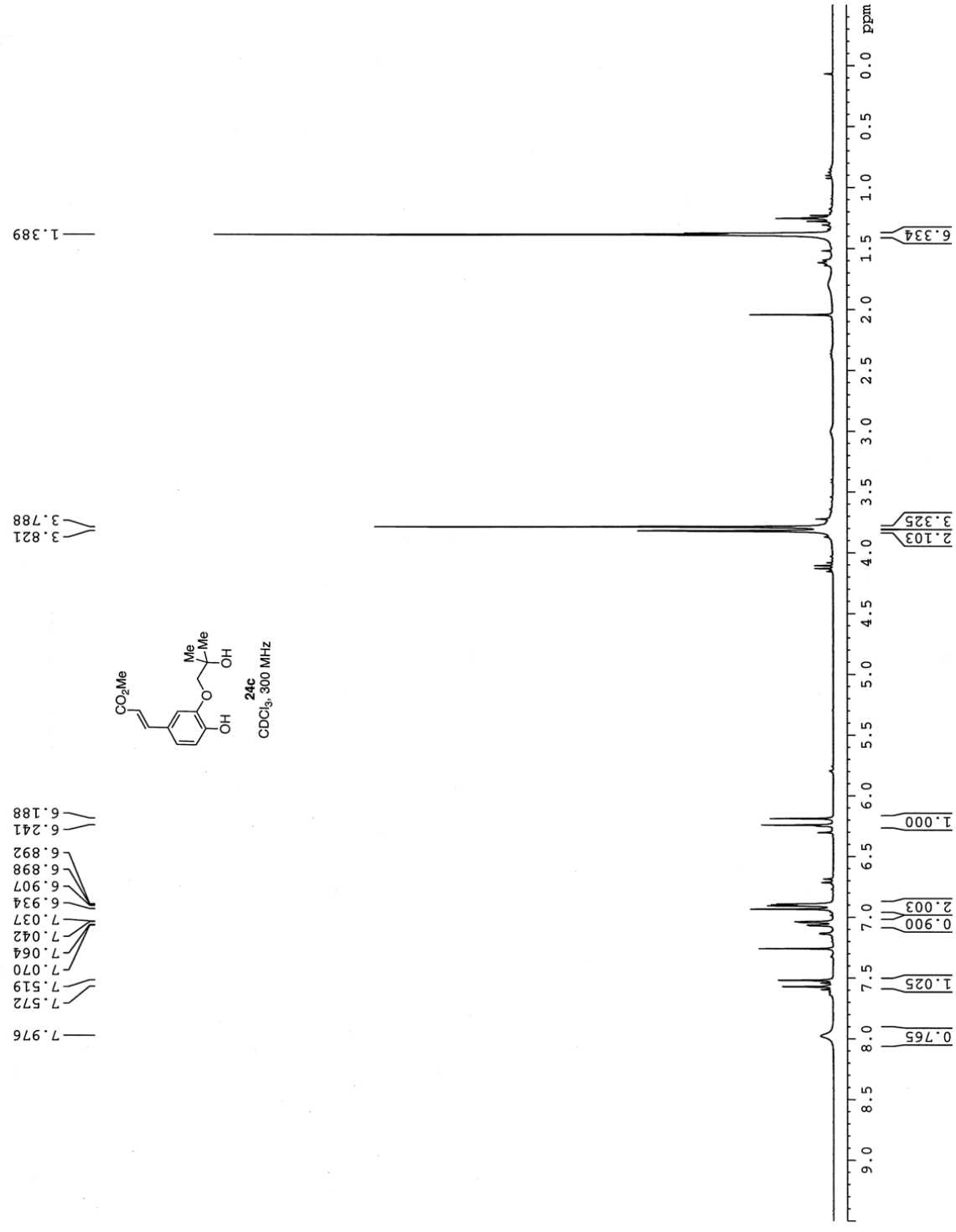
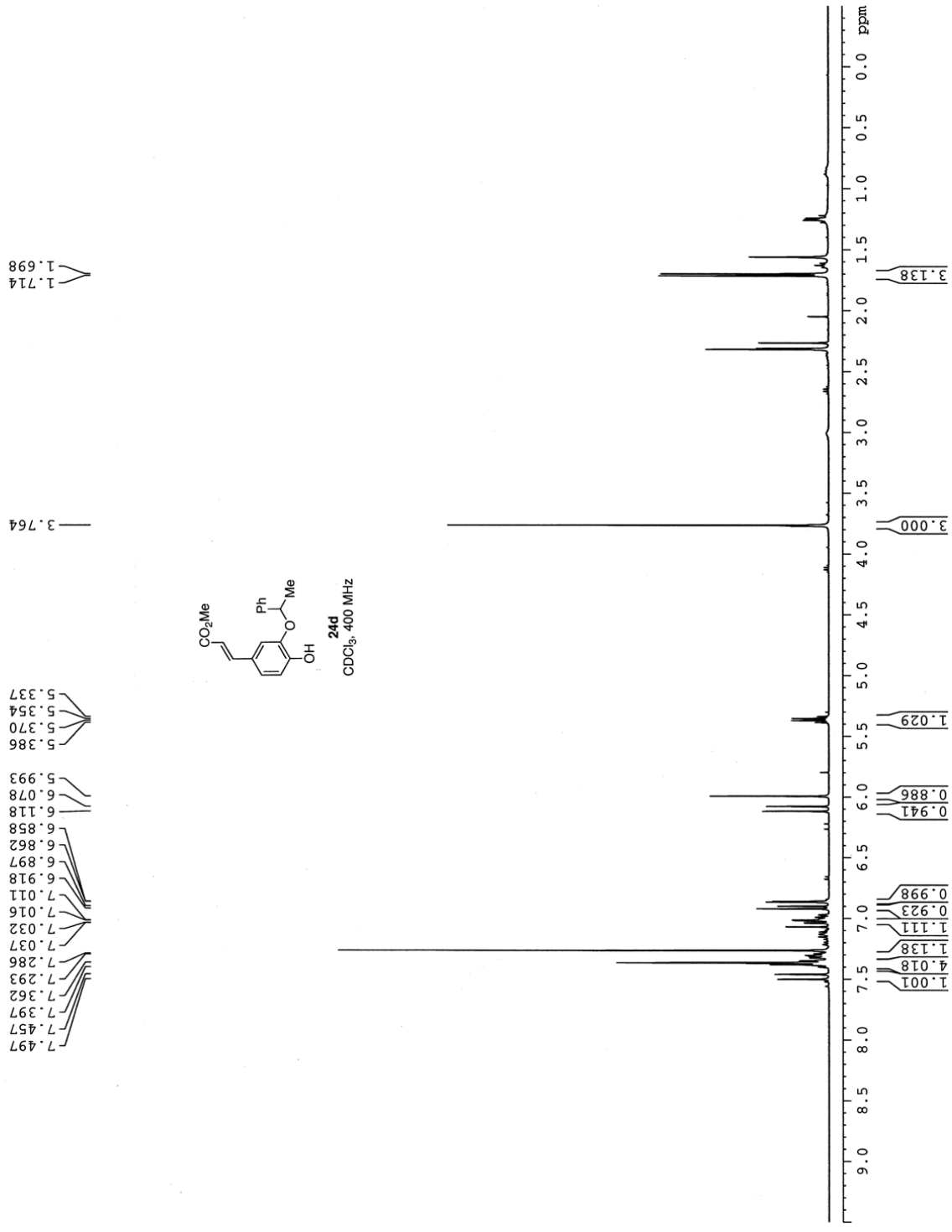
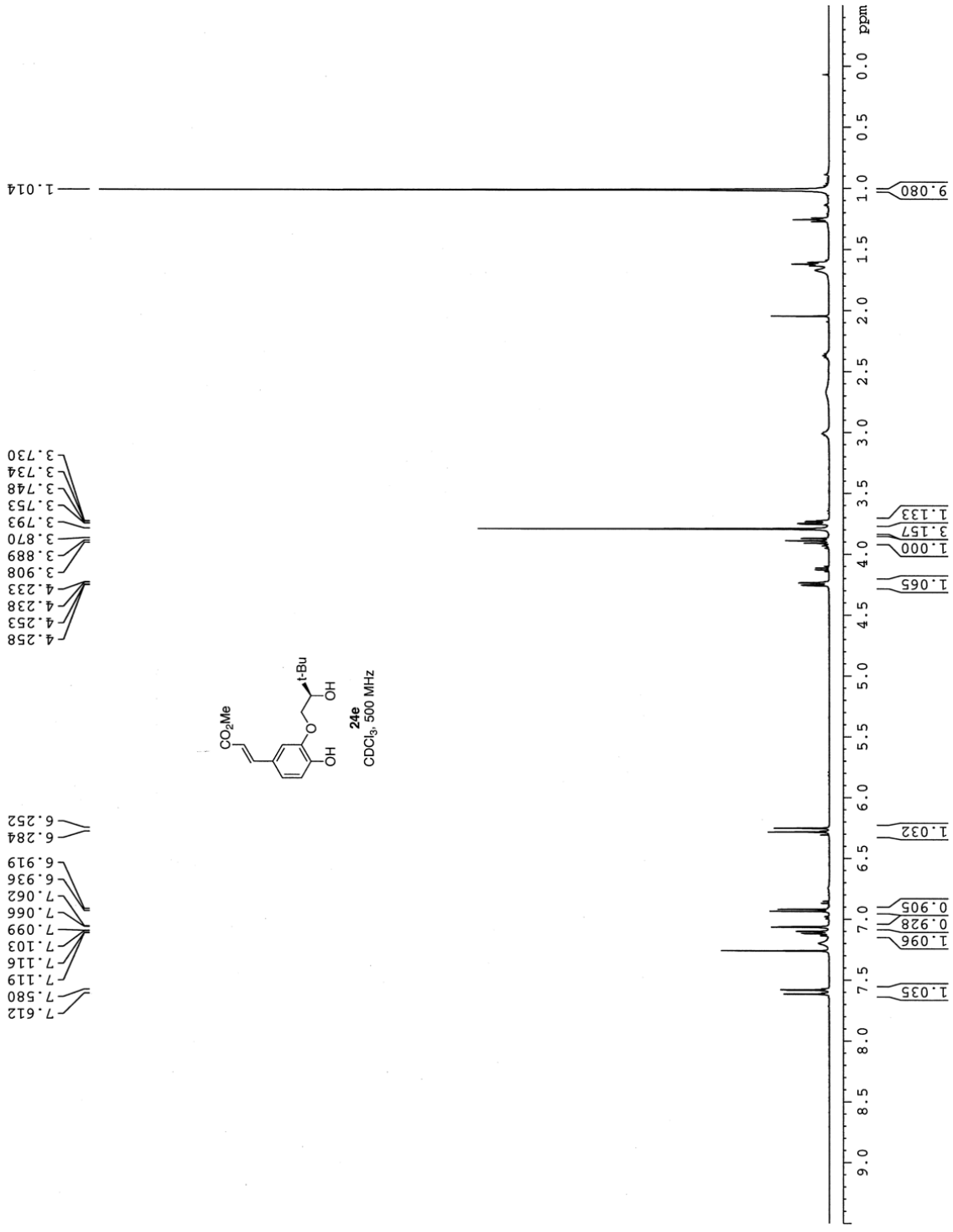
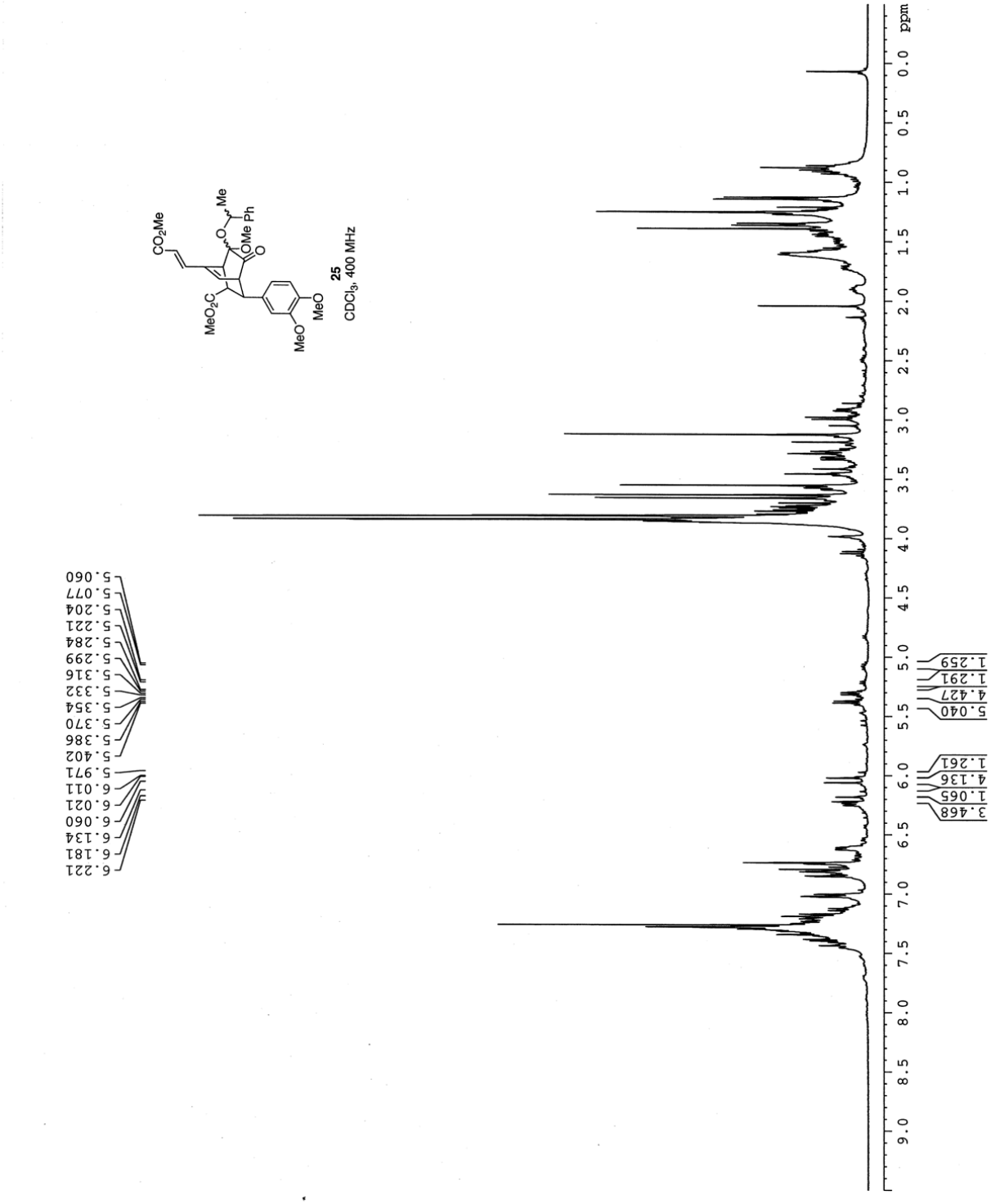
6.933
6.907
6.292
6.239
5.947
4.358
4.346
4.329
4.316
4.303
4.287
4.274
3.795
2.016
2.007
1.828
1.815
1.798
1.788
1.637
1.624
1.432
1.397
1.389
1.364
1.298

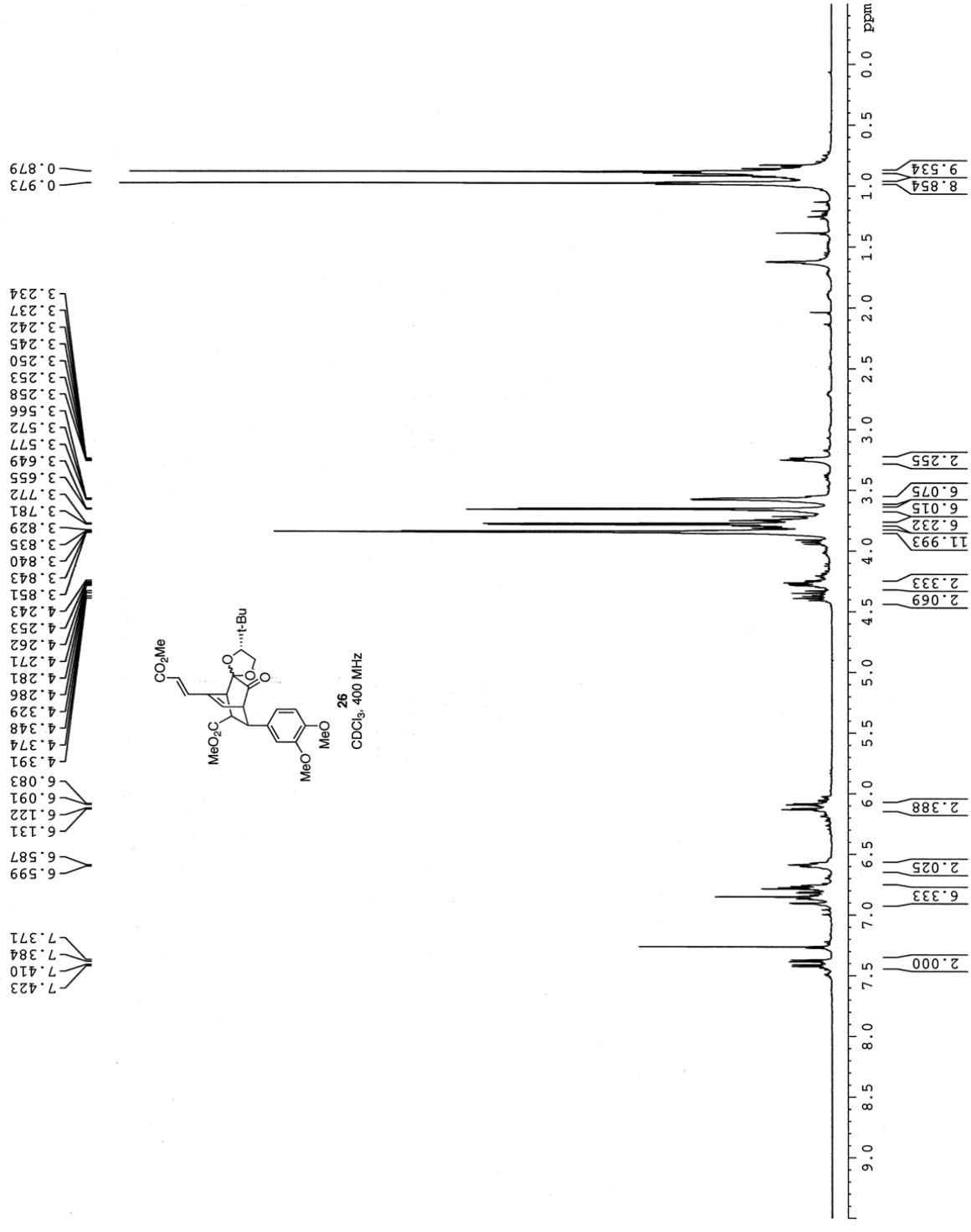

CO2Me
OH
OBn
OBn
BnO
BnO
24b
CDCl3, 300 MHz
ppm
1.171
31.285
1.072
1.000
4.764
1.049
4.306
3.079
5.688
1.199

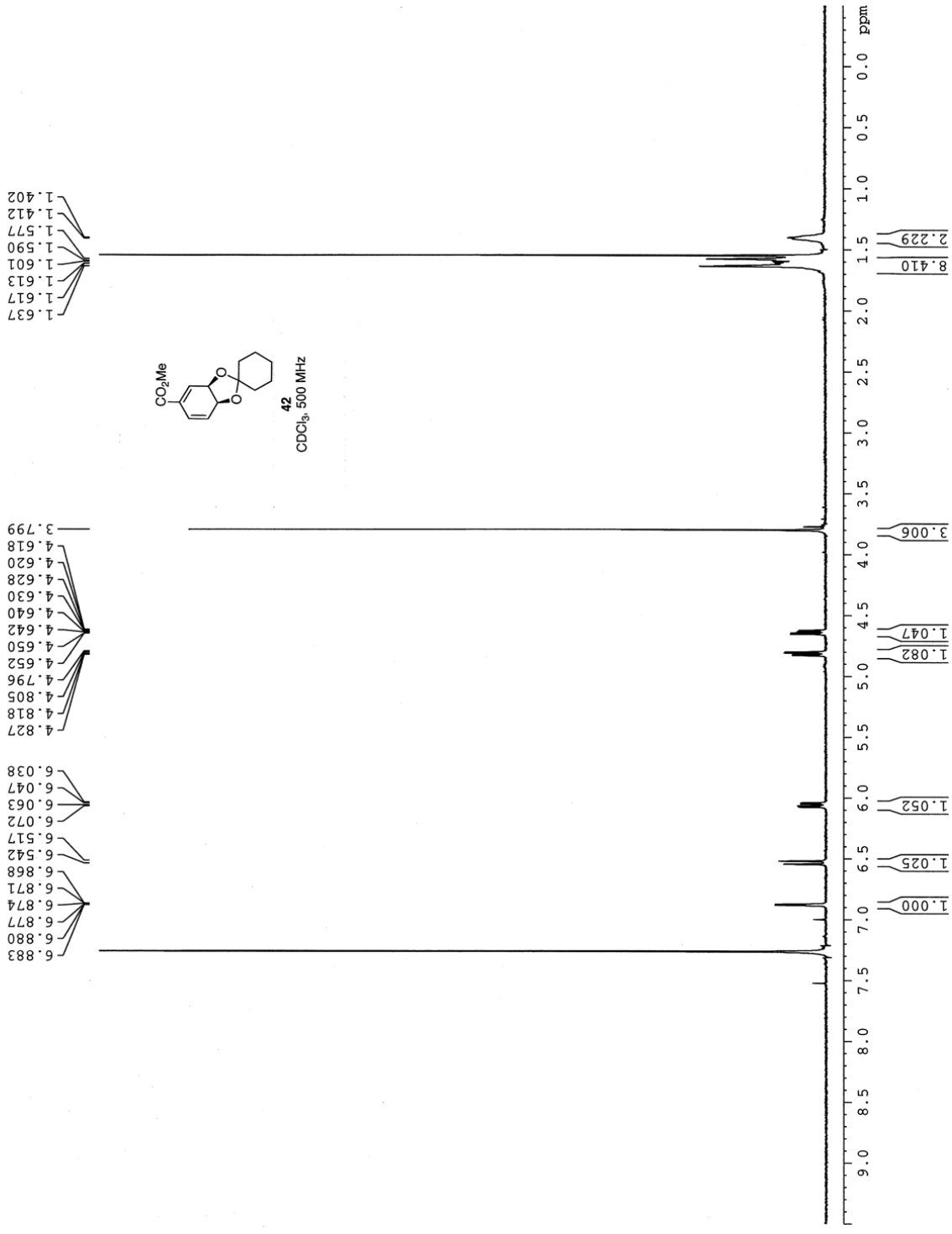

24c
CDCl3, 300 MHz
CO2Me
OH
O
Me
Me
OH
ppm
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
0.765
1.025
0.900
2.003
1.000
2.103
3.325
6.334
7.976
7.572
7.519
7.070
7.064
7.042
7.037
6.934
6.907
6.898
6.892
6.241
6.188
3.821
3.788
1.389

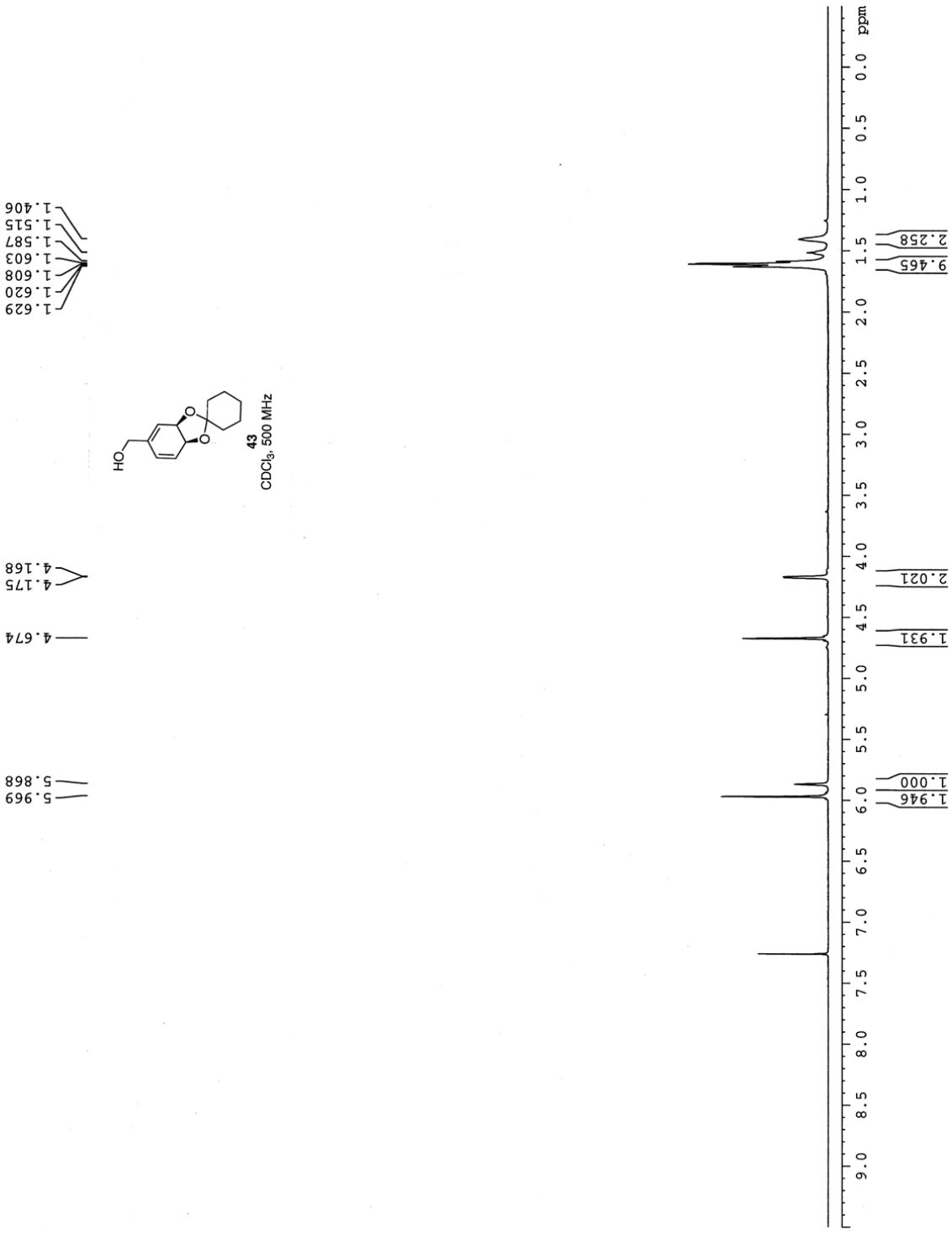

24d
CDCl3, 400 MHz
CO2Me
Ph
Me
O
OH
ppm
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
1.001
4.018
1.138
1.111
0.923
0.998
0.941
0.886
1.029
3.000
3.138
7.497
7.457
7.397
7.362
7.293
7.286
7.037
7.032
7.016
7.011
6.918
6.897
6.862
6.858
6.118
6.078
5.993
5.386
5.370
5.354
5.337
3.764
1.714
1.698

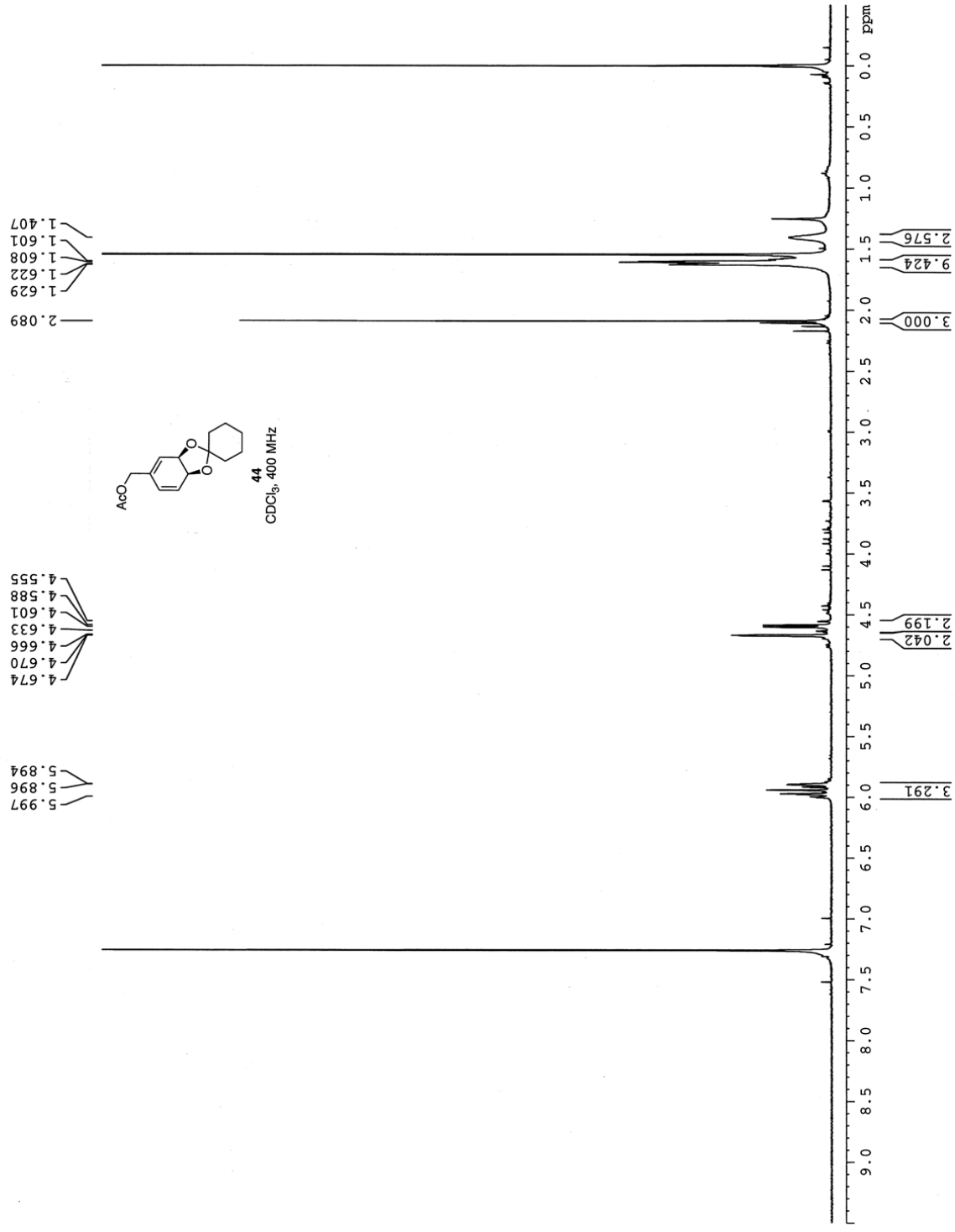

24e
CDCl3, 500 MHz
CO2Me
t-Bu
OH
OH
O
1.014
9.080
1.133
3.157
1.000
1.065
1.032
0.905
0.928
1.096
1.035
7.612
7.580
7.119
7.116
7.103
7.099
7.066
7.062
6.936
6.919
6.284
6.252
4.258
4.253
4.238
4.233
3.908
3.889
3.870
3.793
3.753
3.748
3.734
3.730
ppm

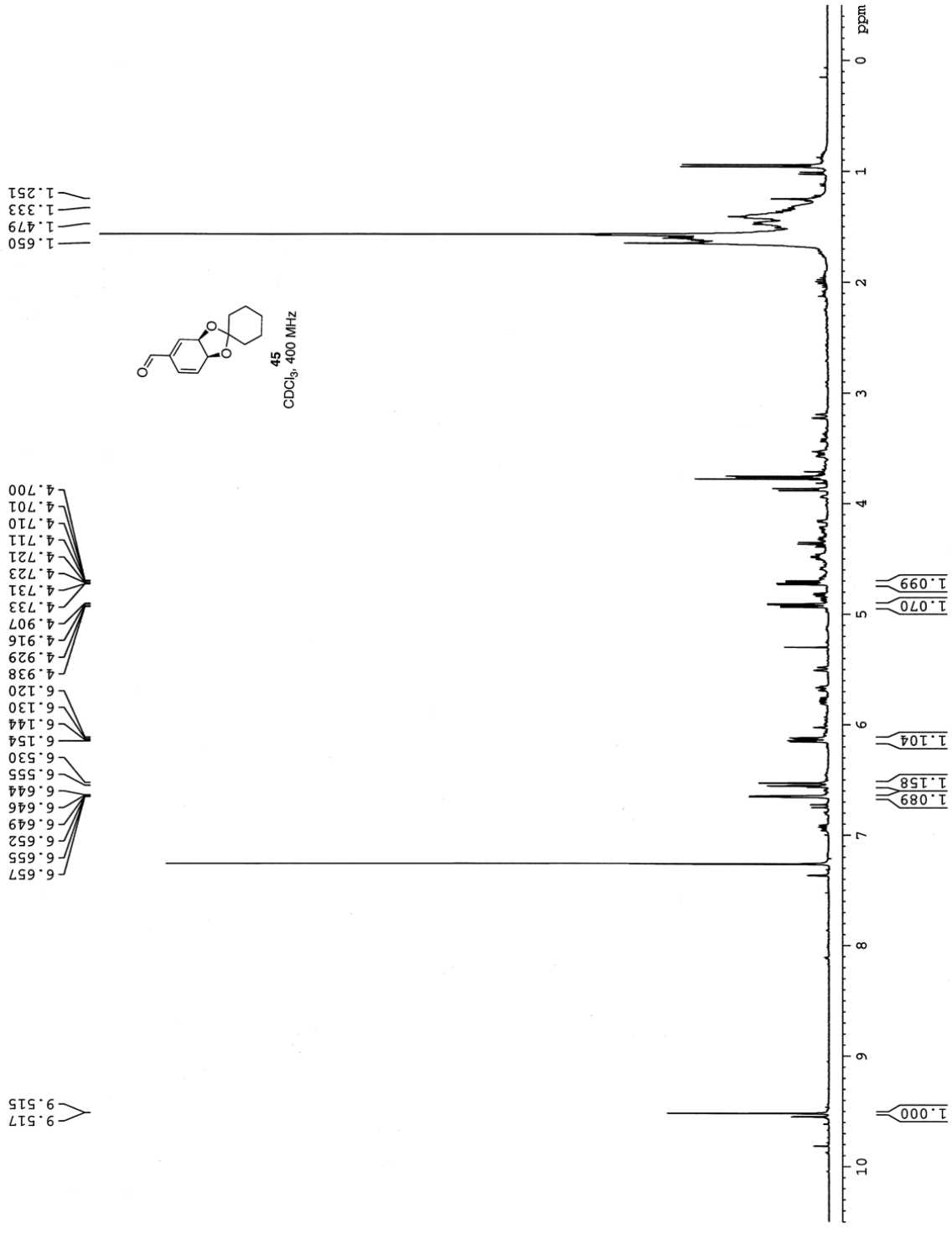

CO2Me
Me
OMe Ph
O
O
MeO2C
MeO
MeO
25
CDCl3, 400 MHz
6.221
6.181
6.134
6.060
6.021
6.011
5.971
5.402
5.386
5.370
5.354
5.332
5.316
5.299
5.284
5.221
5.204
5.077
5.060
3.468
1.065
4.136
1.261
5.040
4.427
1.291
1.259
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm

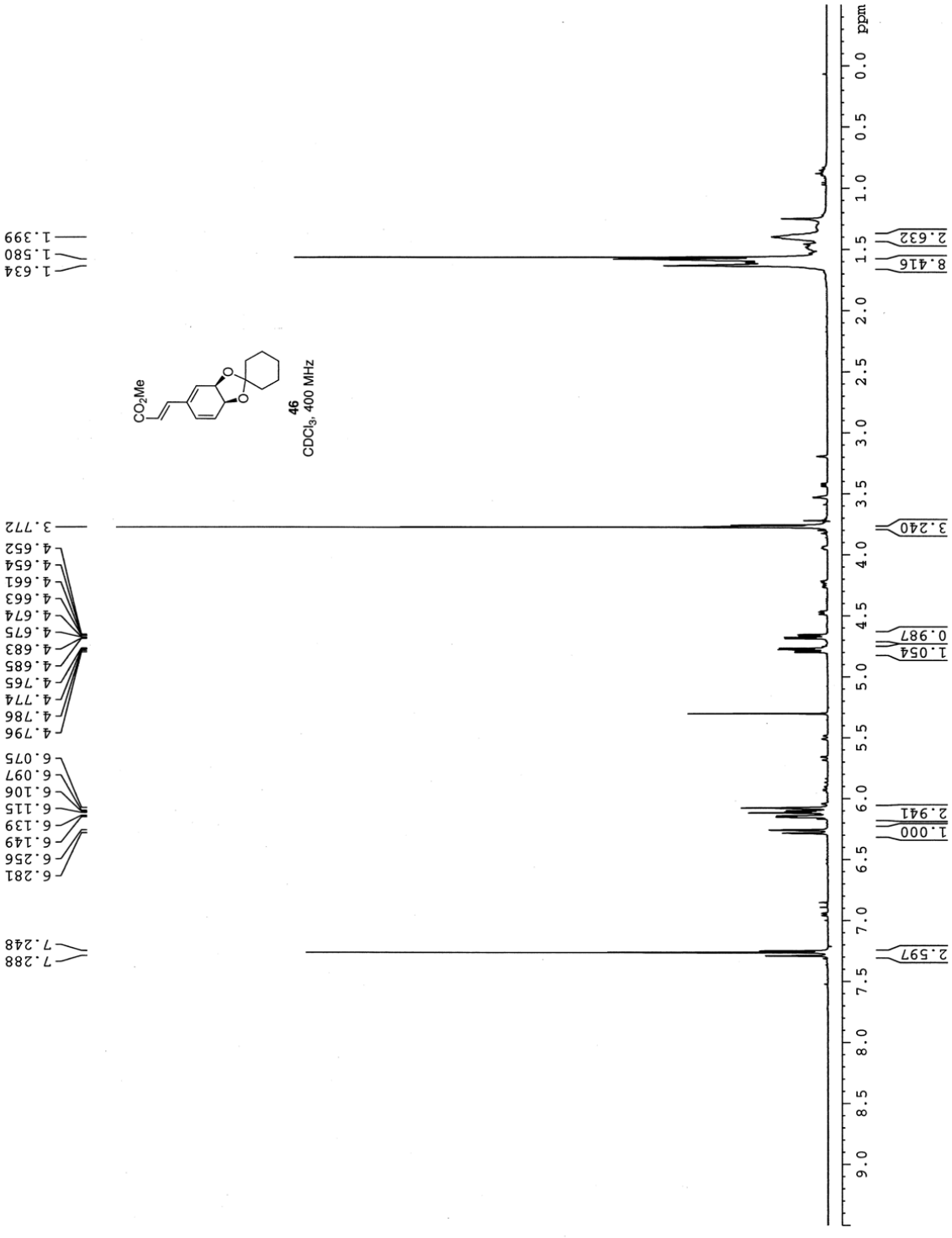

26
CDCl3, 400 MHz
CO2Me
t-Bu
MeO2C
MeO
MeO
ppm
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
2.000
6.333
2.025
2.388
2.069
2.333
11.993
6.232
6.015
6.075
2.255
8.854
9.534
0.973
0.879
7.423
7.410
7.384
7.371
6.599
6.587
6.131
6.122
6.091
6.083
4.391
4.374
4.348
4.329
4.286
4.281
4.271
4.262
4.253
4.243
3.851
3.843
3.840
3.835
3.829
3.781
3.772
3.655
3.649
3.577
3.572
3.566
3.258
3.253
3.250
3.245
3.242
3.237
3.234

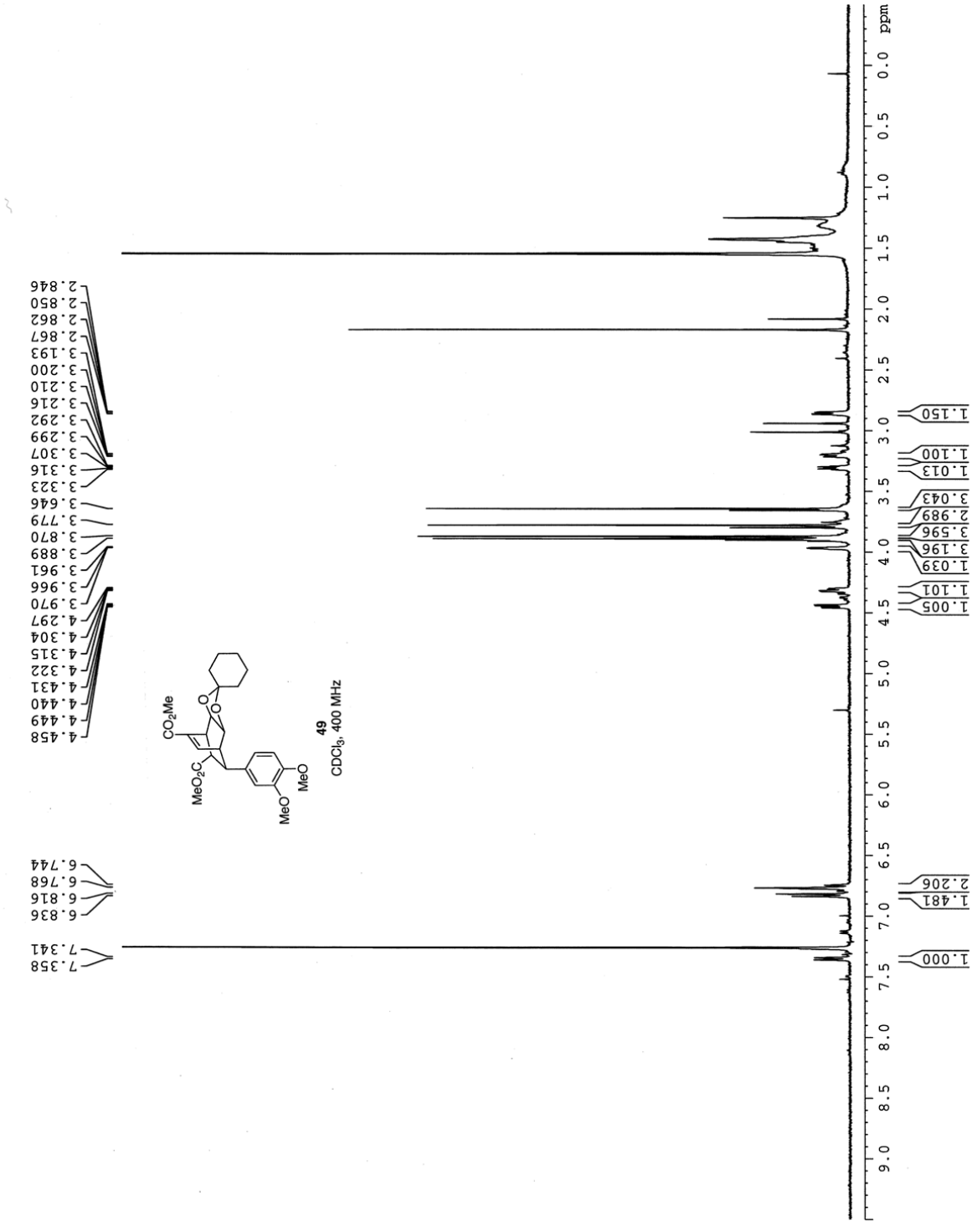

CO2Me
42
CDCl3, 500 MHz
ppm
1.000
1.025
1.052
1.082
1.047
3.006
8.410
2.229
6.883
6.880
6.877
6.874
6.871
6.868
6.542
6.517
6.072
6.063
6.047
6.038
4.827
4.818
4.805
4.796
4.652
4.650
4.642
4.640
4.630
4.628
4.620
4.618
3.799
1.637
1.617
1.613
1.601
1.590
1.577
1.412
1.402

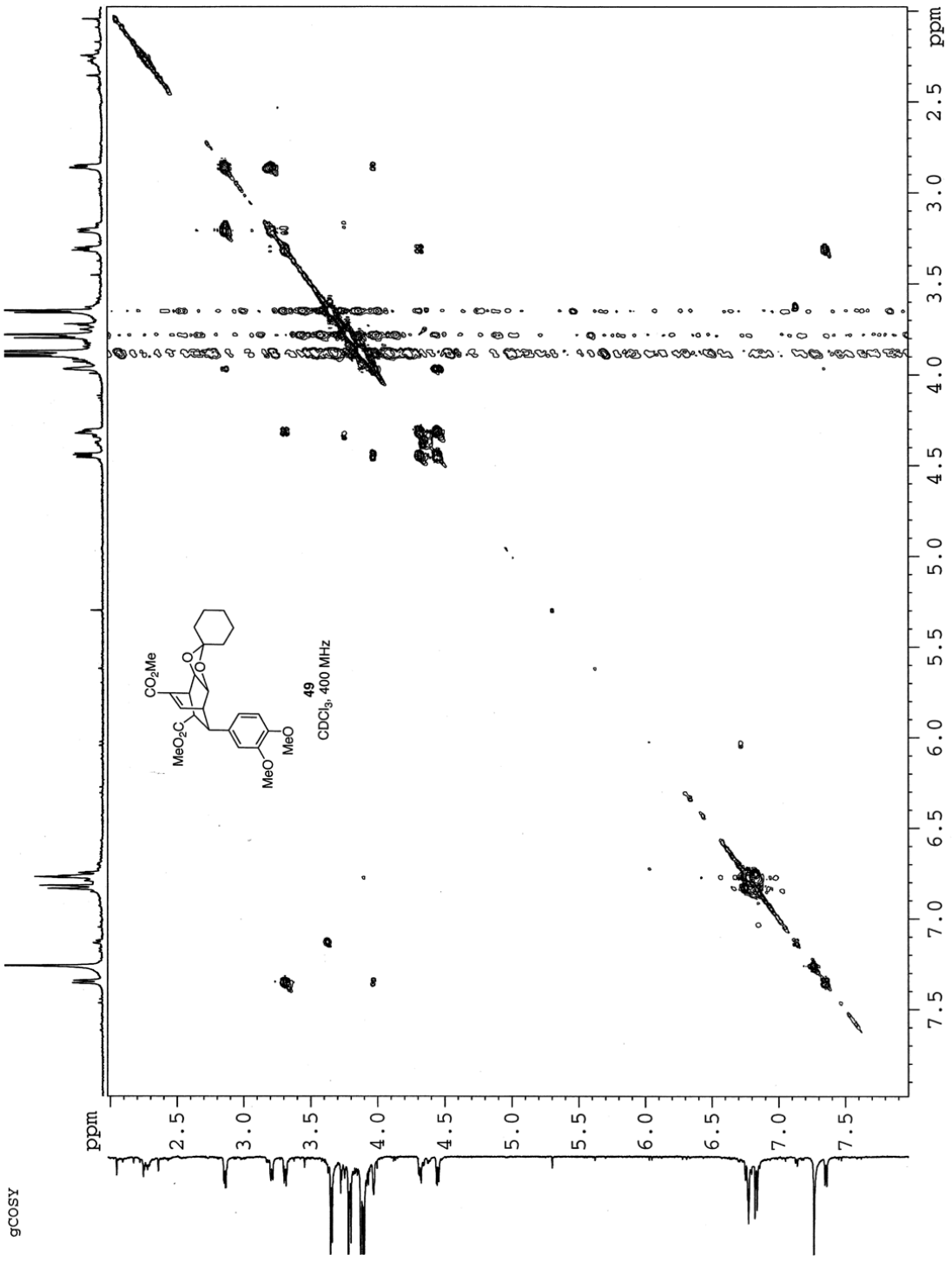

43
CDCl3, 500 MHz
HO
1.406
1.515
1.587
1.603
1.608
1.620
1.629
4.168
4.175
4.674
5.868
5.969
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
1.946
1.000
1.931
2.021
9.465
2.258

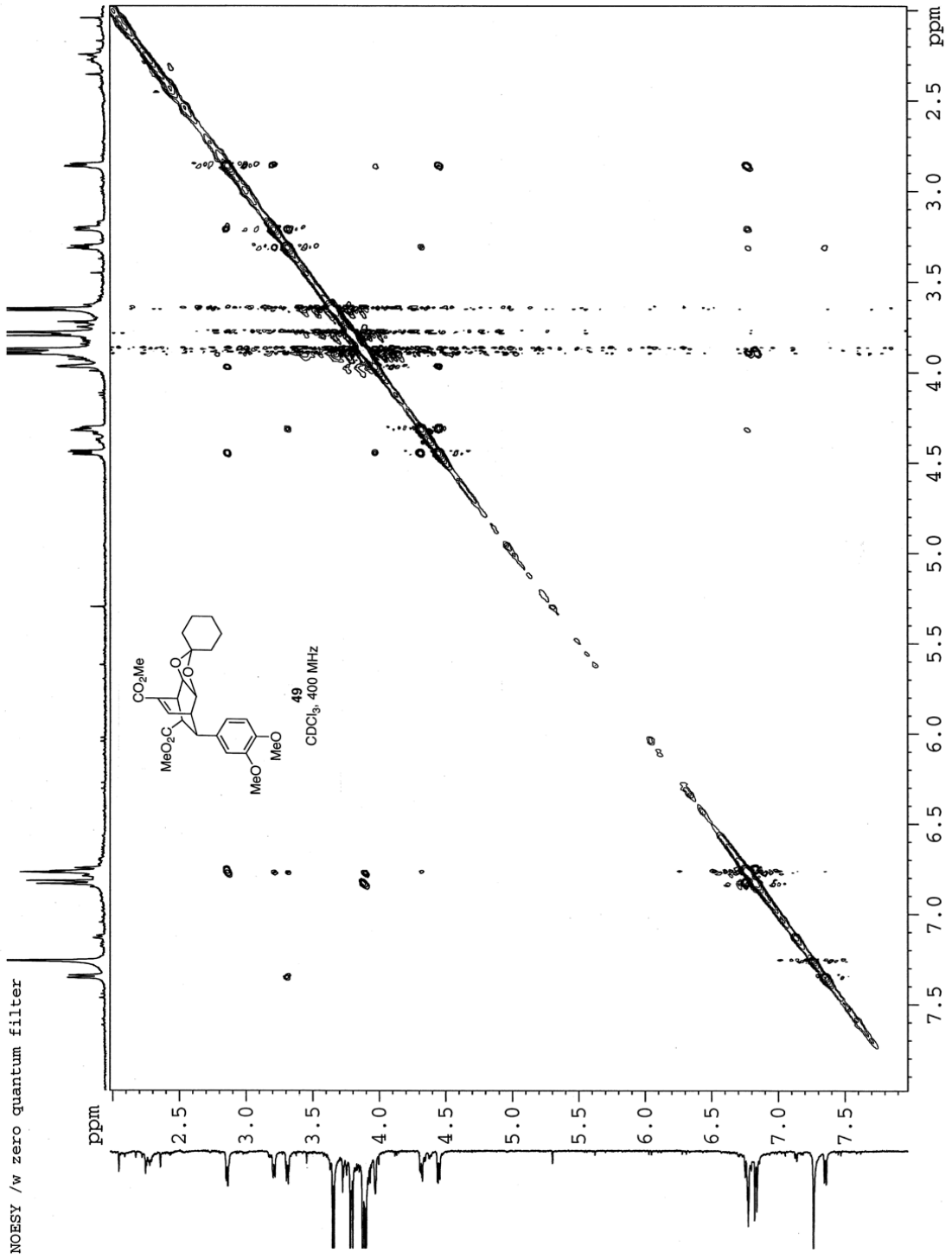

AcO
44
CDCl3, 400 MHz
1.407
1.601
1.608
1.622
1.629
2.089
4.555
4.588
4.601
4.633
4.666
4.670
4.674
5.894
5.896
5.997
2.576
9.424
3.000
2.199
2.042
3.291
ppm

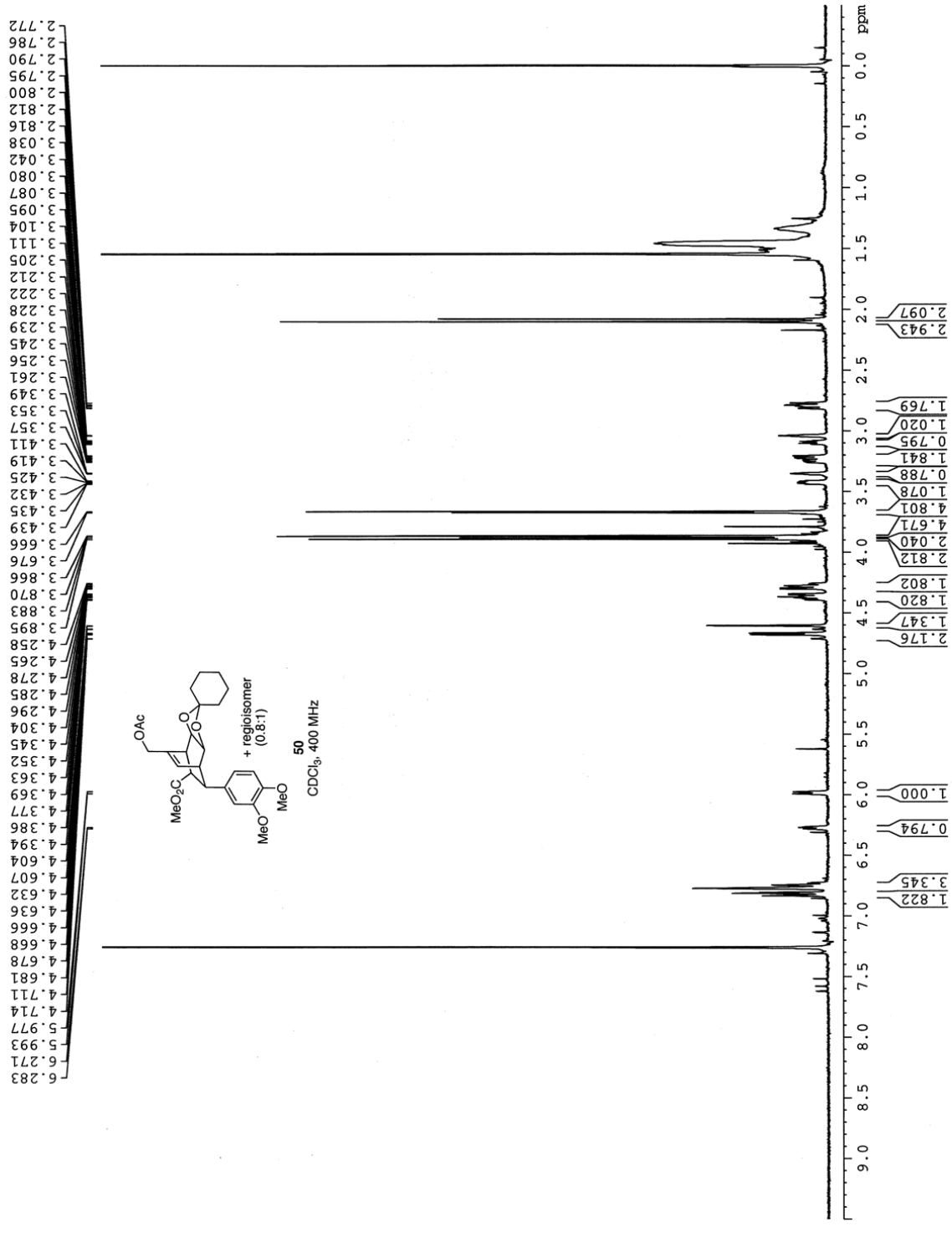

45
CDCl3, 400 MHz
9.517
9.515
6.657
6.655
6.652
6.649
6.646
6.644
6.555
6.530
6.154
6.144
6.130
6.120
4.938
4.929
4.916
4.907
4.733
4.731
4.723
4.721
4.711
4.710
4.701
4.700
1.650
1.479
1.333
1.251
1.000
1.104
1.158
1.089
1.099
1.070
ppm

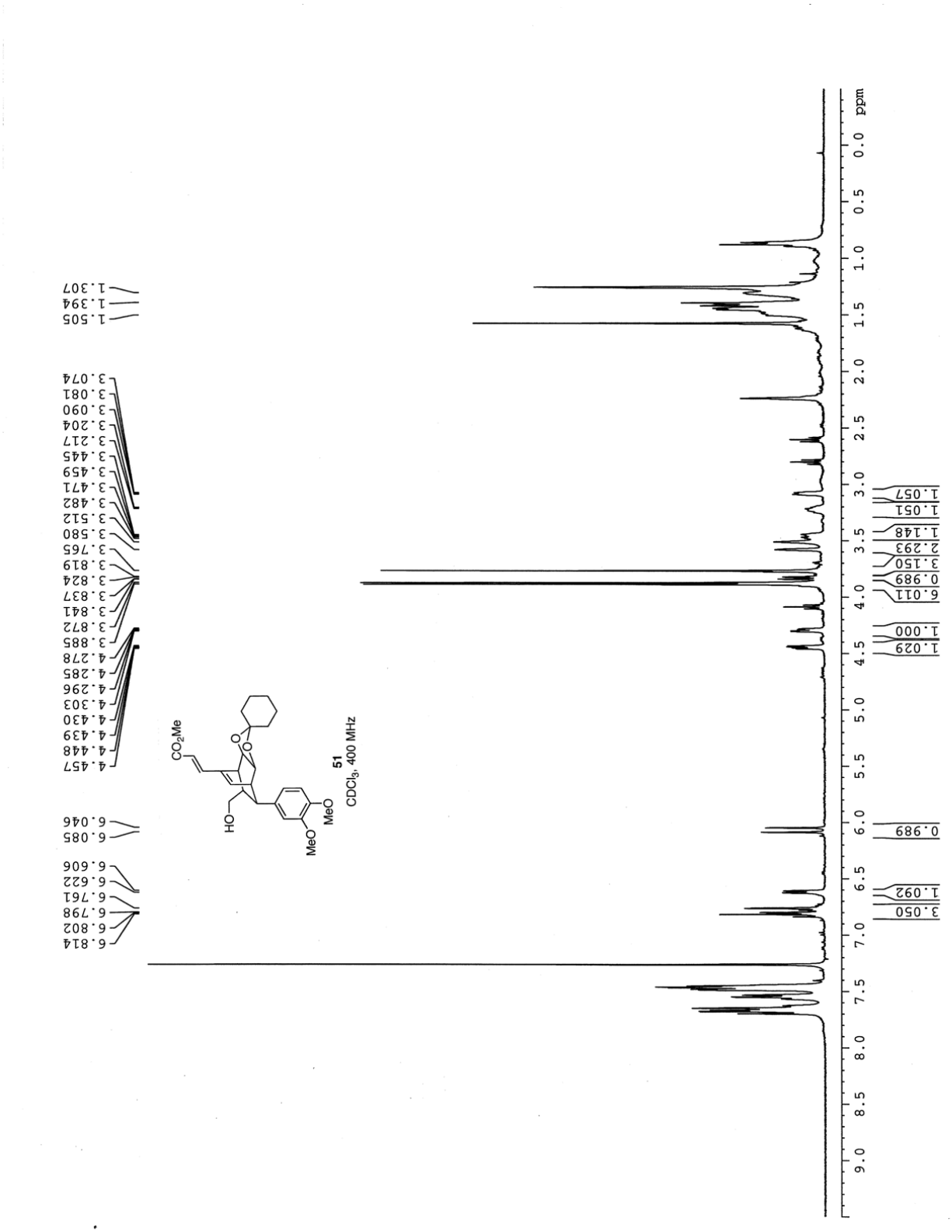

CO2Me
46
CDCl3, 400 MHz
ppm
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
2.597
1.000
2.941
0.987
1.054
3.240
8.416
2.632
7.288
7.248
6.281
6.256
6.149
6.139
6.115
6.106
6.097
6.075
4.796
4.786
4.774
4.765
4.685
4.683
4.675
4.674
4.663
4.661
4.654
4.652
3.772
1.634
1.580
1.399

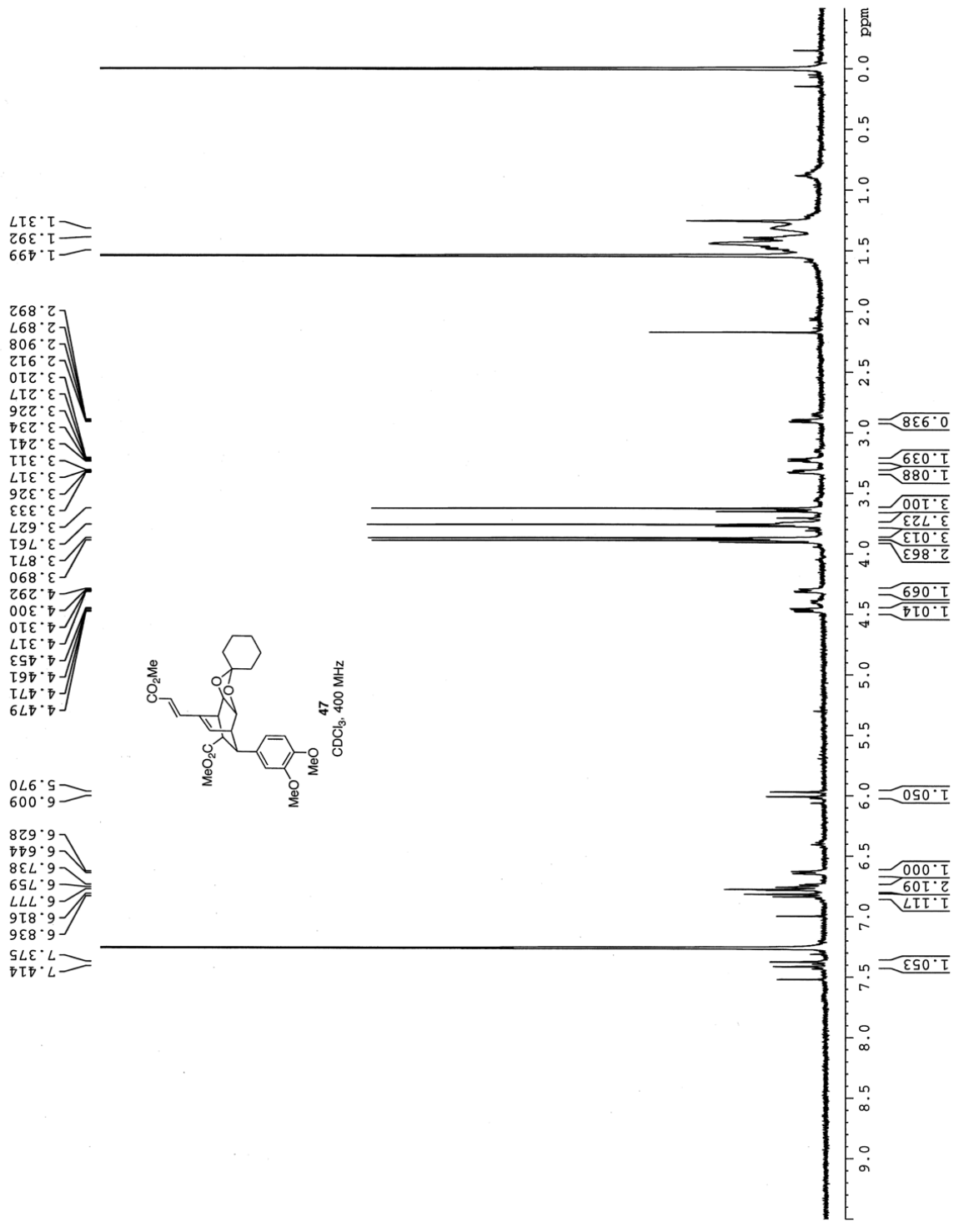

49
CDCl3, 400 MHz
CO2Me
MeO2C
MeO
MeO
ppm
1.000
1.481
2.206
6.744
6.768
6.816
6.836
7.341
7.358
1.150
1.100
1.013
3.043
2.989
3.596
3.196
1.039
1.101
1.005
4.458
4.449
4.440
4.431
4.322
4.315
4.304
4.297
3.970
3.966
3.961
3.889
3.870
3.779
3.646
3.323
3.316
3.307
3.299
3.292
3.216
3.210
3.200
3.193
2.867
2.862
2.850
2.846

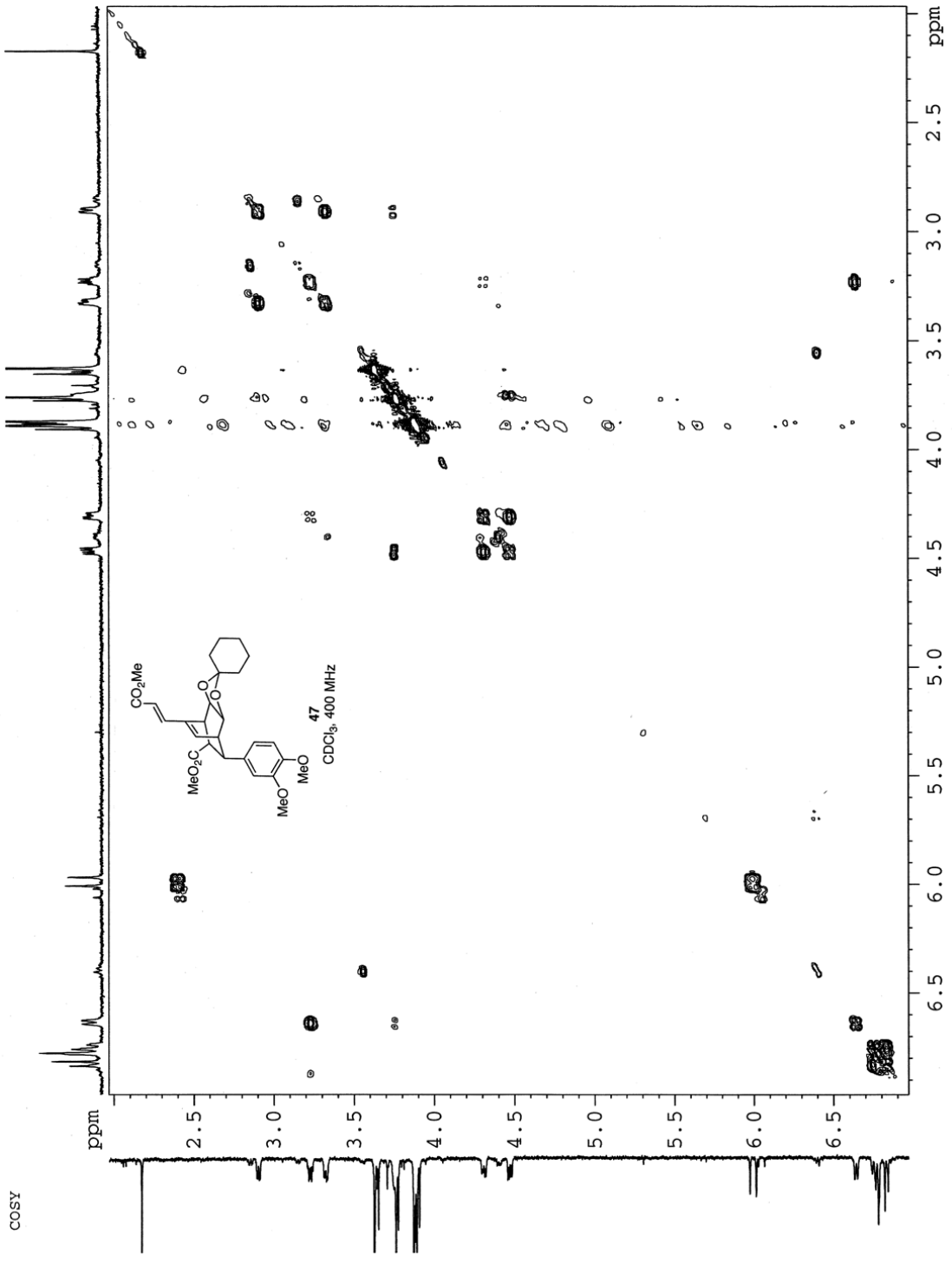

gCOSY
ppm
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
CO2Me
MeO2C
MeO
MeO
49
CDCl3, 400 MHz

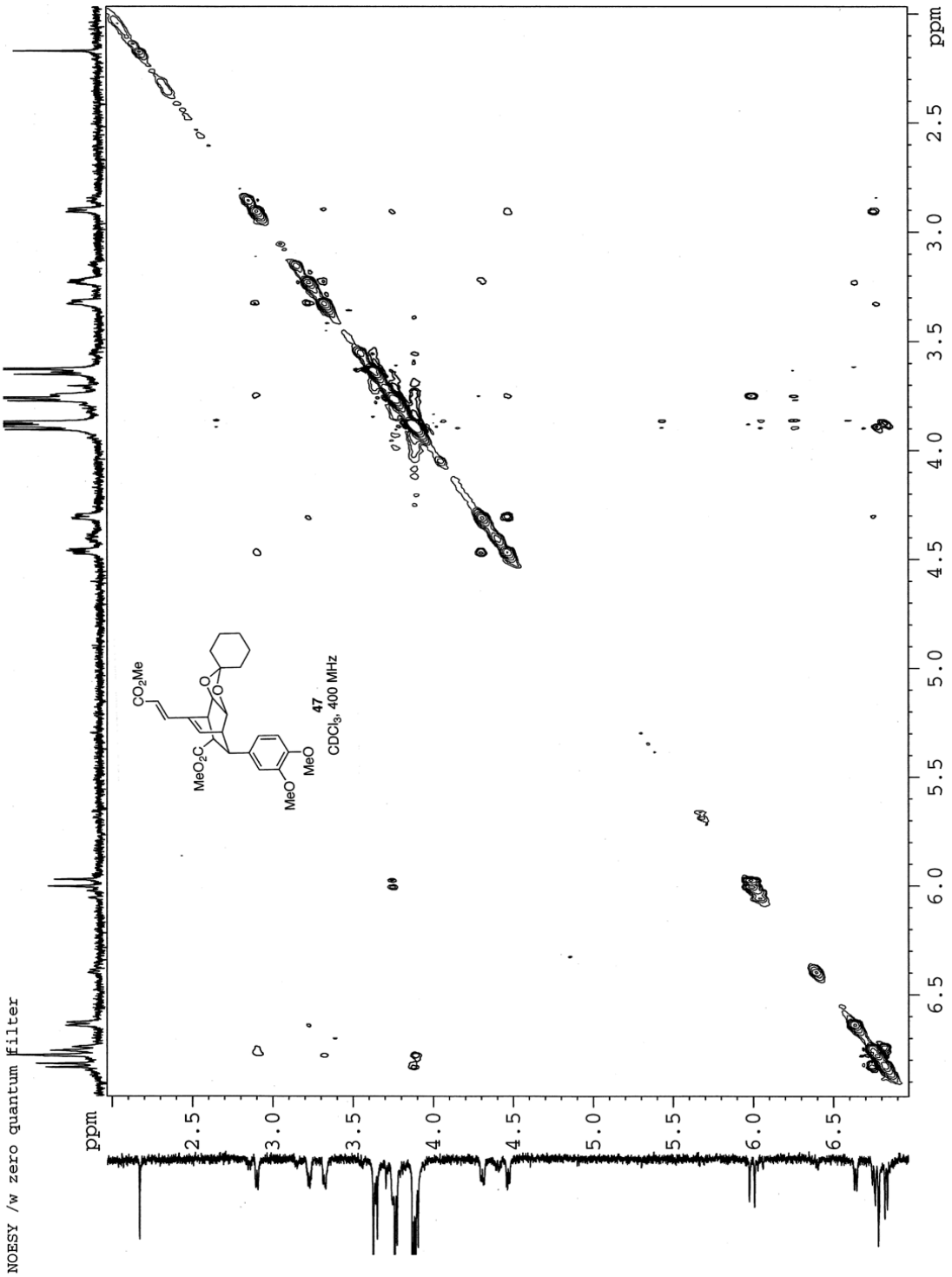

NOESY /w zero quantum filter
ppm
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
CO2Me
MeO2C
MeO
MeO
49
CDCl3, 400 MHz

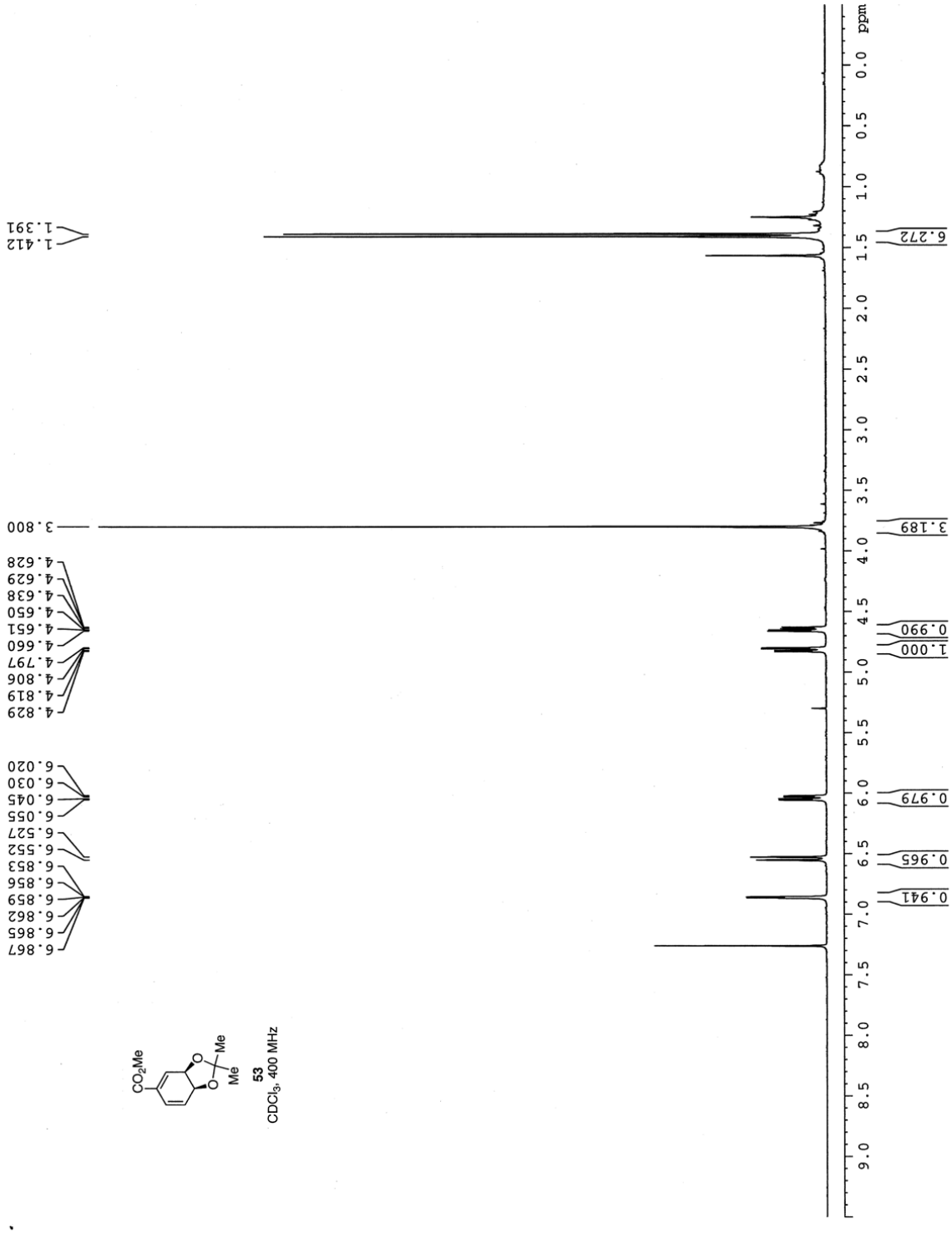

OAc
MeO2C
MeO
MeO
+ regioisomer
(0.8:1)
50
CDCl3, 400 MHz
ppm

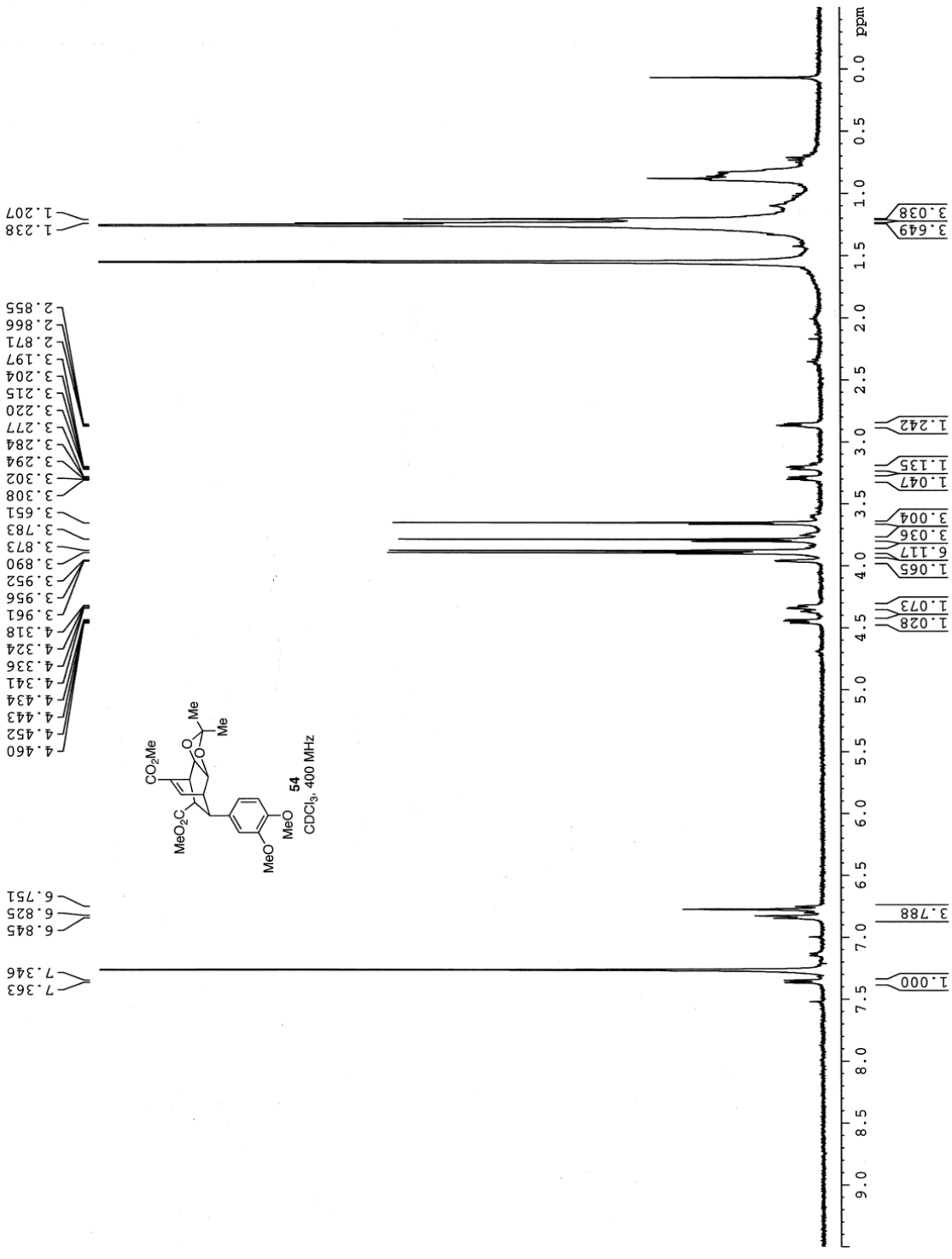

CO2Me
HO
MeO
MeO
51
CDCl3, 400 MHz
ppm

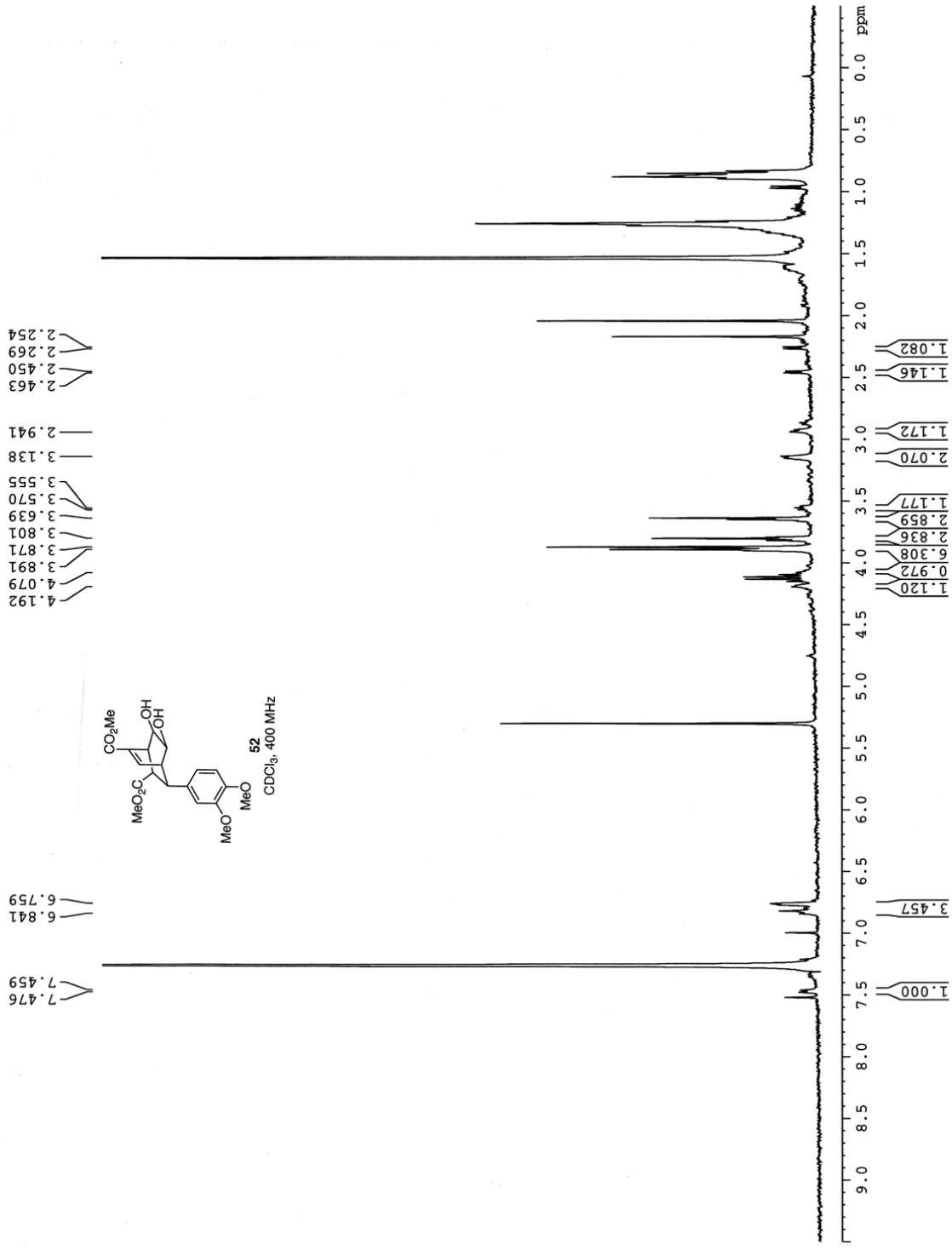

47
CDCl3, 400 MHz
CO2Me
MeO2C
MeO
MeO
ppm

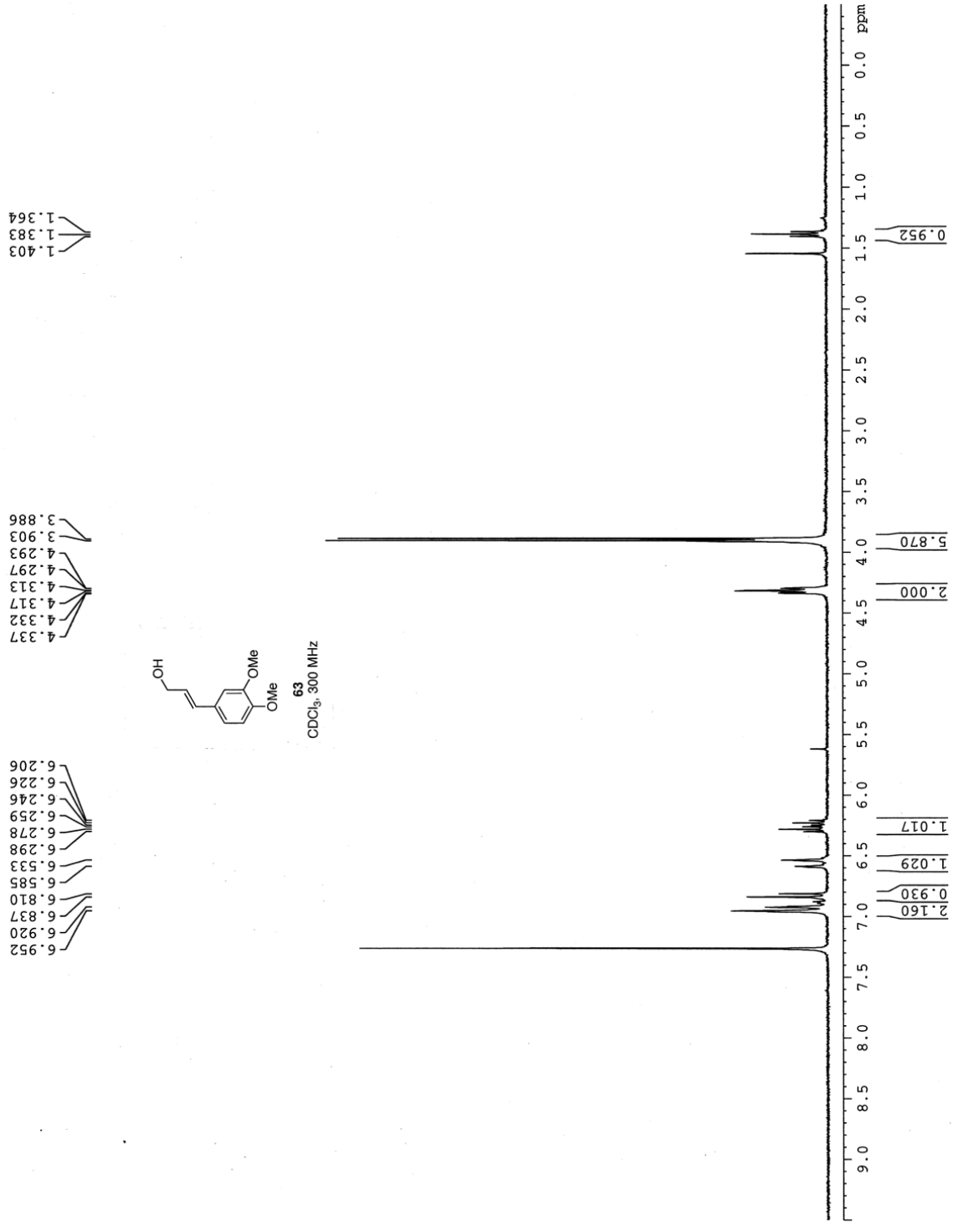

cosy
ppm
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
CO2Me
MeO2C
MeO
MeO
47
CDCl3, 400 MHz

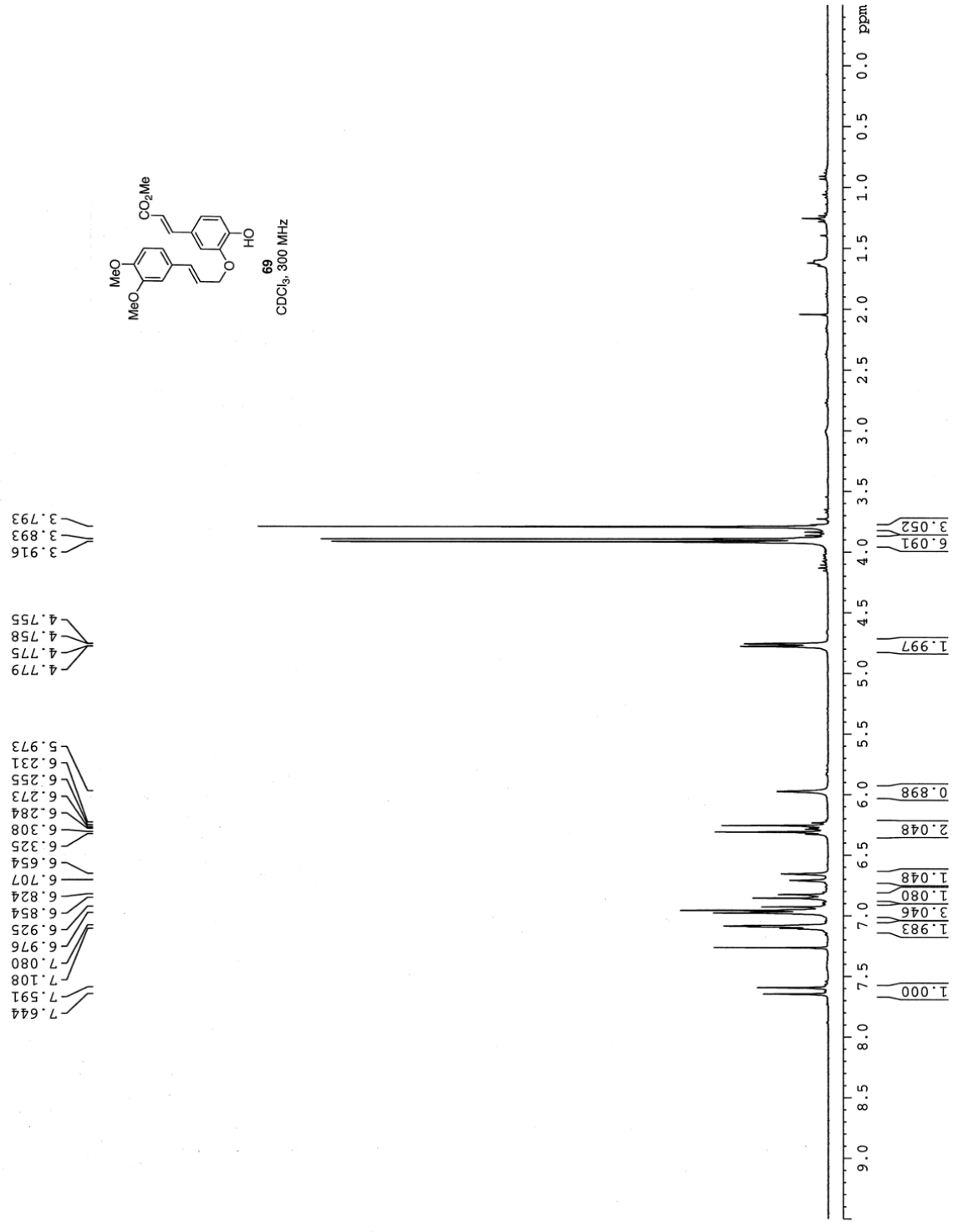

NOESY /w zero quantum filter
ppm
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
CO2Me
MeO2C
MeO
MeO
47
CDCl3, 400 MHz

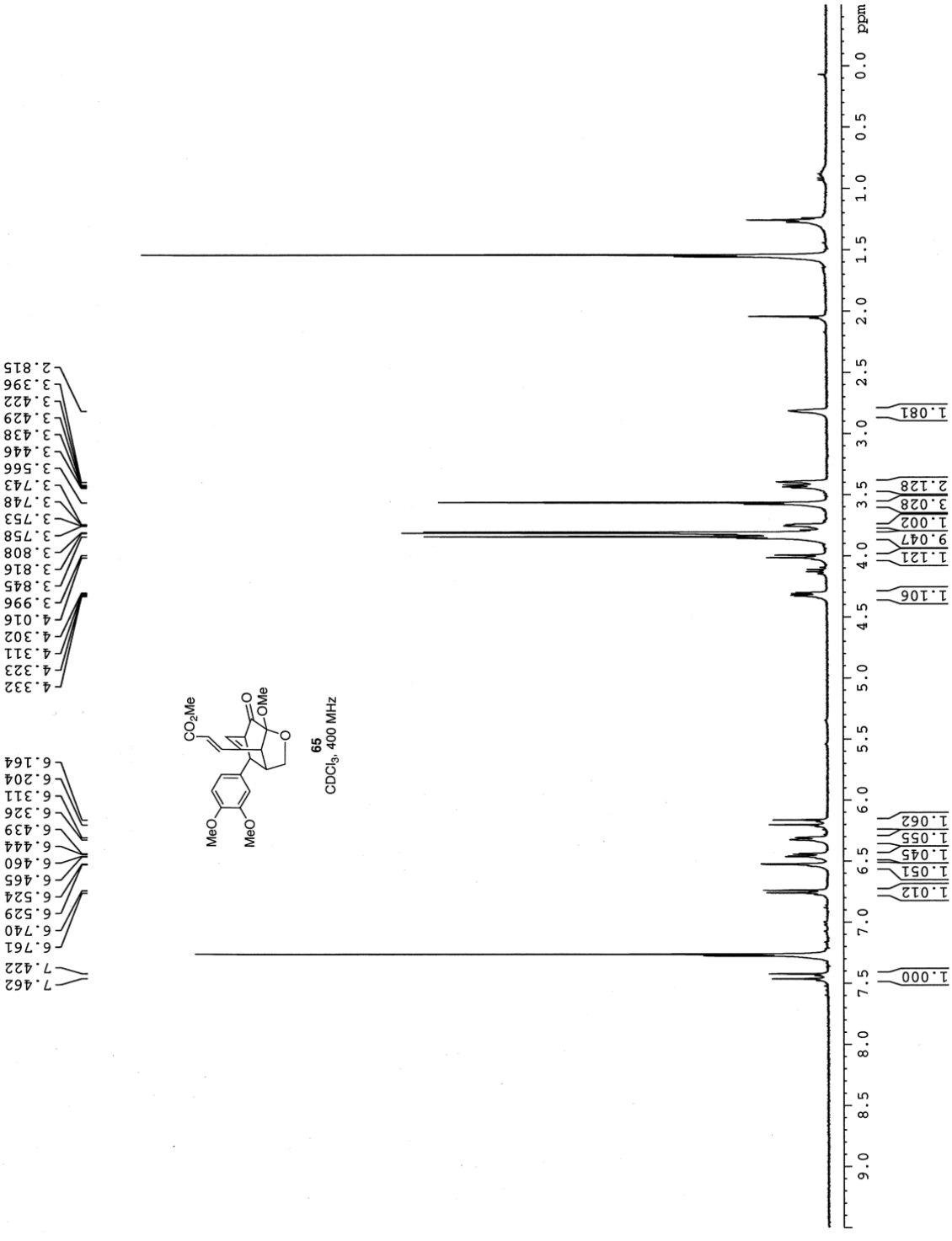

CO2Me
Me
Me
53
CDCl3, 400 MHz
6.867
6.865
6.862
6.859
6.856
6.853
6.552
6.527
6.055
6.045
6.030
6.020
4.829
4.819
4.806
4.797
4.660
4.651
4.650
4.638
4.629
4.628
3.800
1.412
1.391
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
6.272
3.189
0.990
1.000
0.979
0.965
0.941


54
CDCl3, 400 MHz
CO2Me
MeO2C
MeO
MeO
Me
Me
ppm


52
CDCl3, 400 MHz
MeO2C
CO2Me
OH
OH
MeO
MeO
7.476
7.459
6.841
6.759
4.192
4.079
3.891
3.871
3.801
3.639
3.570
3.555
3.138
2.941
2.463
2.450
2.269
2.254
1.000
3.457
1.120
0.972
6.308
2.836
2.859
1.177
2.070
1.172
1.146
1.082
ppm


63
CDCl3, 300 MHz
OH
OMe
OMe
6.952
6.920
6.837
6.810
6.585
6.533
6.298
6.278
6.259
6.246
6.226
6.206
4.337
4.332
4.317
4.313
4.297
4.293
3.903
3.886
1.403
1.383
1.364
0.952
5.870
2.000
1.017
1.029
0.930
2.160
ppm


CO2Me
HO
MeO
MeO
69
CDCl3, 300 MHz
ppm
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
1.000
1.983
3.046
1.080
1.048
2.048
0.898
1.997
6.091
3.052
7.644
7.591
7.108
7.080
6.976
6.925
6.854
6.824
6.707
6.654
6.325
6.308
6.284
6.273
6.255
6.231
5.973
4.779
4.775
4.758
4.755
3.916
3.893
3.793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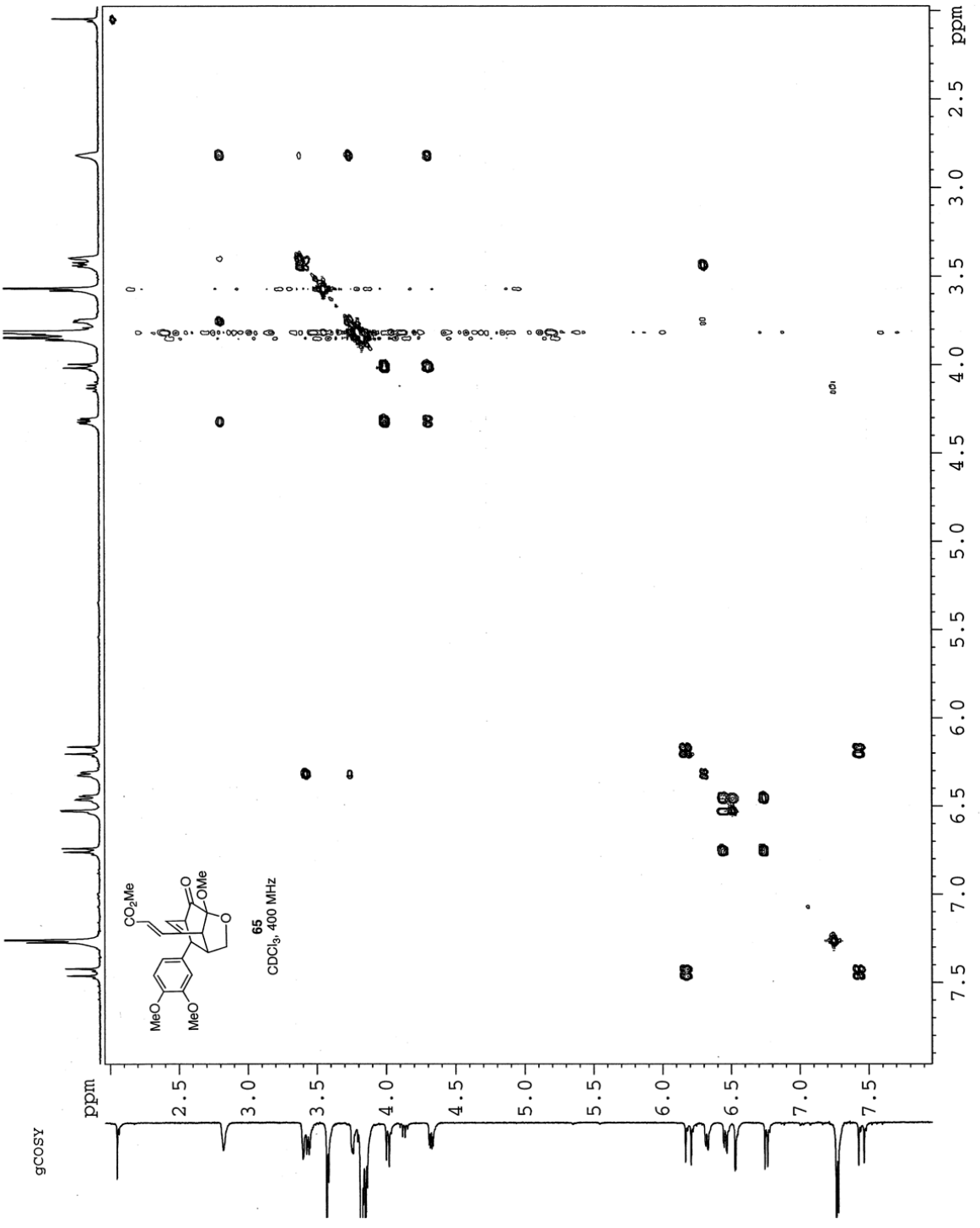
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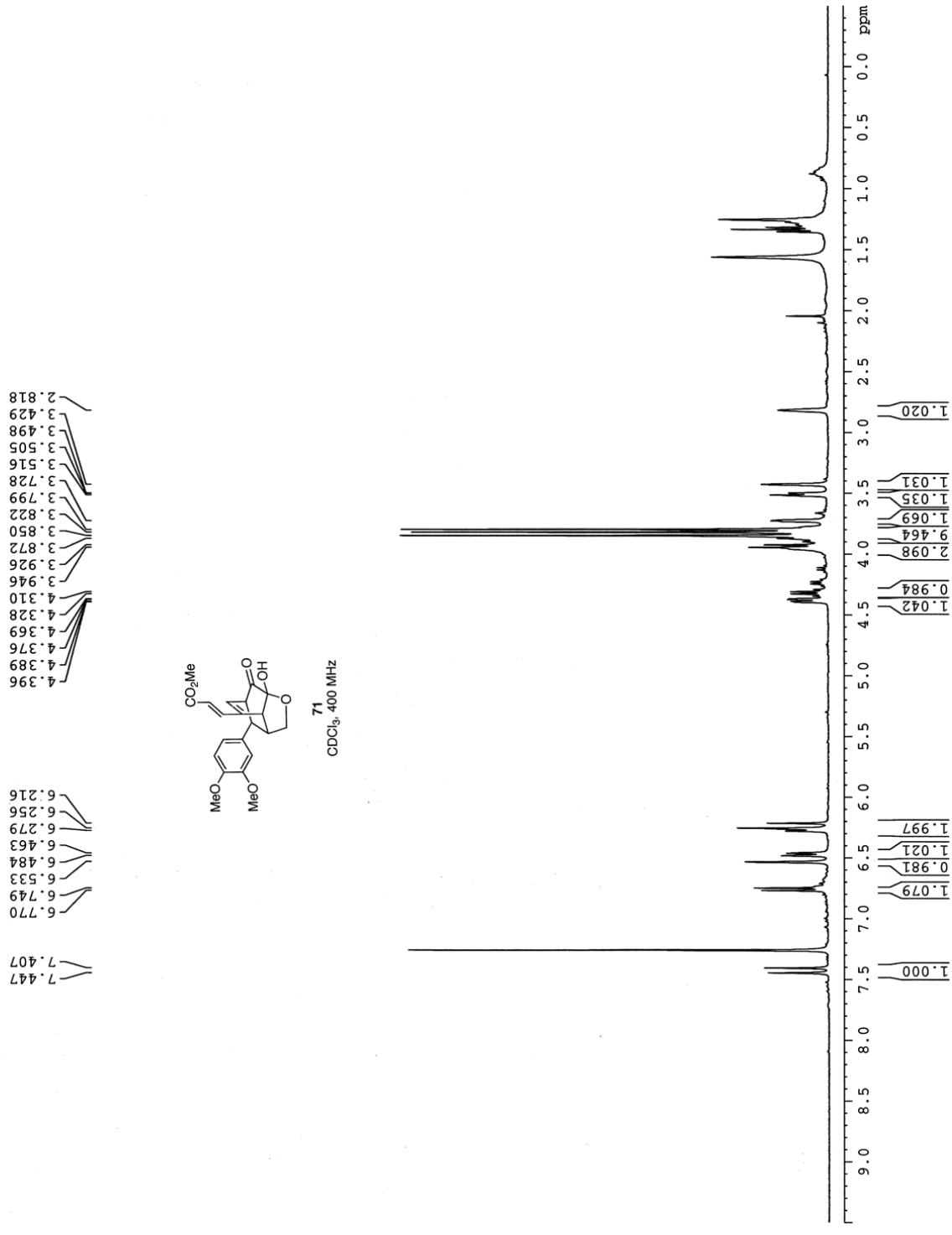
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CHAPTER 3

Small Molecule Inhibitors of Cell Death in a Huntington's Disease Model

3.1 Introduction

Helicteres isora Linn. is a large arborescent shrub native to South- and Southeast Asia, and its parts are used in a variety of traditional medicines throughout the region. An important component of the *Hindu Materia Medica* and the Indonesian *Jamu* medicines, its extracts are used as anti-parasitic, anti-pyretic, anti-spasmodic and anti-convulsant agents and for the treatment of various abdominal illnesses.[1] In the laboratory, bark and root extracts of *H. isora* have been shown to possess significant hypoglycemic effect in rats,[2] whereas fruit extracts were reported to have inhibitory activity against reverse transcriptase from the tumor-causing avian myeloblastosis virus (AMV-RT)[3] and anti-human immunodeficiency virus-type 1 (HIV-1) activity.[4] Tezuka and coworkers examined the constituents of water extracts of the fruits and isolated natural products helicterins A and B, helisterculins A and B, and helisorin (**1**–**5**, Figure 1), all of which showed mild to weak anti-AMV-RT activity.[5]

Having completed the synthesis of three members of the helicterin family of natural products[6] (**2**, **3** and **5**, see Chapter 1 for details), studies were initiated to determine whether their unique molecular frameworks might possess additional biochemical activity beyond that originally described by the isolation chemists. The final natural products, many of the synthetic intermediates, and several compounds that were synthesized during our efforts towards the total synthesis, were sent to collaborators for further testing. From these screens, a compound based on the natural bicyclic core was identified to have micromolar inhibition of cell-death in a Huntington's disease model. As a result, synthetic work to probe structure-activity relationships (SAR) of this initial

hit was carried out. Our efforts have discovered several more active analogs, exhibiting low-micromolar potency, one based on a switch from an imidazole to a 1,2,3-triazole heterocycle and two based on the incorporation of natural product-like rosmarinic acid side-chains into the lead compound.[7]

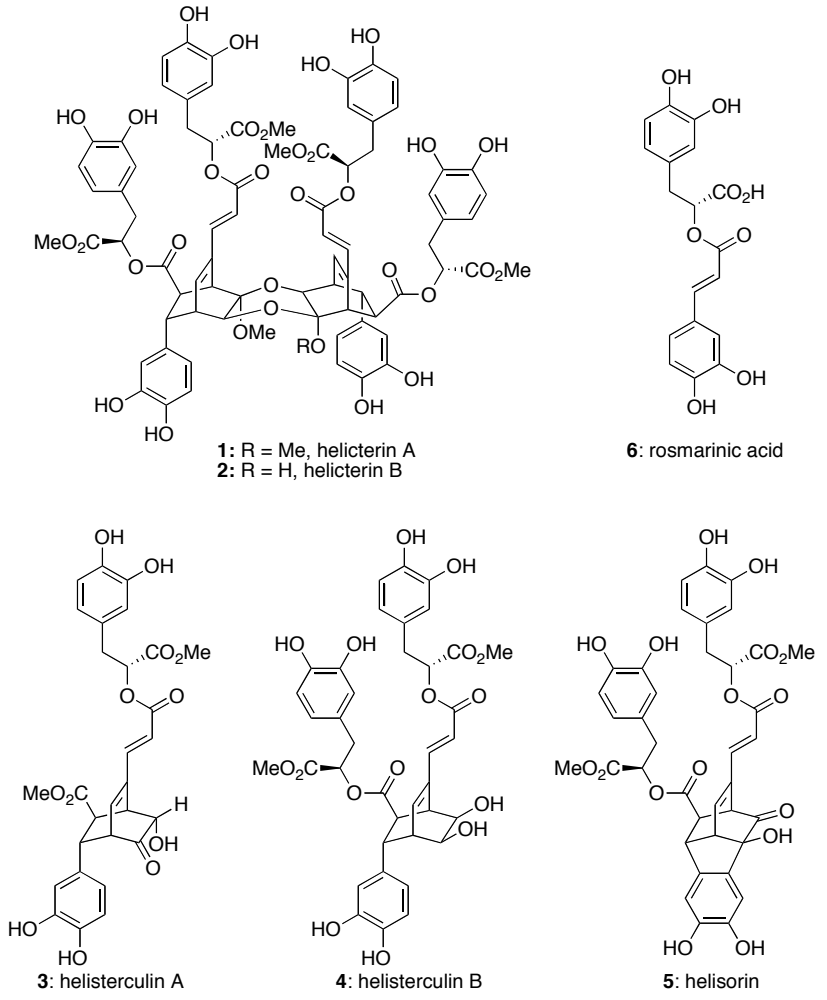


Figure 1. The helicterin family of natural products (**1**–**4**) and their presumed biogenetic precursor, rosmarinic acid (**6**).

3.2 Huntington's Disease and High-Throughput Anti-Neurodegenerative Screening

Huntington's disease (HD) is a progressive and ultimately fatal brain disorder caused by the expansion of a CAG repeat in the huntingtin gene.[8] This mutation results in the expression of the huntingtin protein (Htt) with an expanded *N*-terminal polyglutamine region (Poly Q, >35 glutamine repeats), a structural change that causes the protein to fold incorrectly and form insoluble aggregates.[9] The presence of mutant Htt protein ultimately causes neuronal cell death in the striatum and cortex regions of the brain by a mechanism that is still not fully understood, although considerable evidence suggests that it occurs through an apoptotic pathway.[10] A number of different model systems have established that the Exon 1 portion of Htt containing the expanded Poly Q repeat is sufficient to induce pathology.[11]

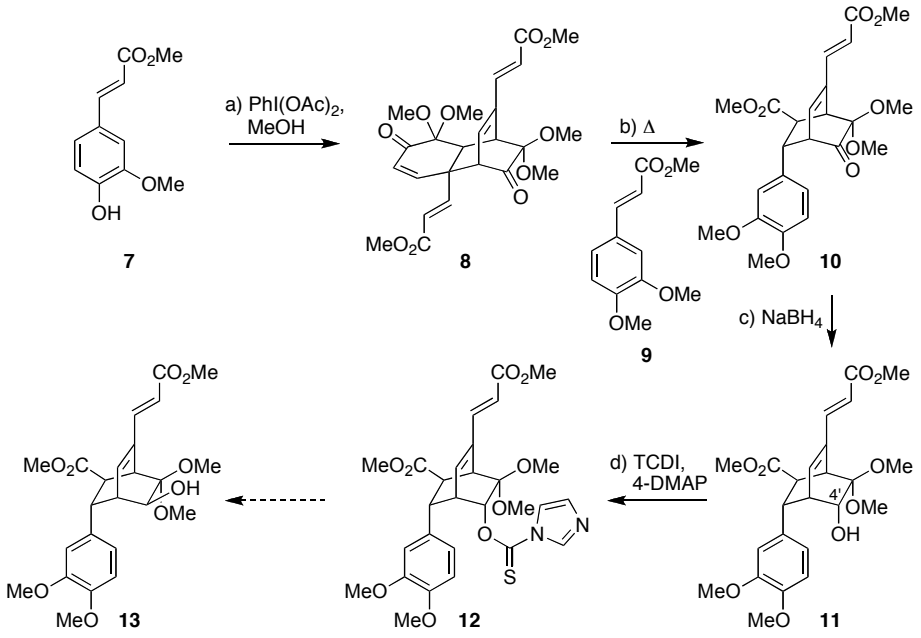
At present, no anti-neurodegenerative therapy for HD exists, with existing treatments intended only to control the symptoms of the disease.[8] As a result, the development of small molecules capable of reversing the neurodegenerative effects of HD is the subject of ongoing research, and several screens have been developed for the identification of lead compounds.[12] One of these assays, originally developed by Schweitzer *et al.* in 2004,[13] has recently been adapted by Stockwell and coworkers[14] into a high-throughput format and was used to discover five structurally distinct inhibitors of cell death induced by mutant Htt. Subsequent Huisgen [3+2] cycloaddition chemistry[15] was employed to identify the cellular target of these inhibitors as protein disulfide isomerase (PDI), an enzyme that was found to have an important role in mutant Htt-induced apoptosis.

In this high-throughput screening system, PC12 rat cells were transfected with an ecdysone-responsive expression vector containing the Exon 1 portion of Htt, with either wild-type (Q25) or mutant (Q103) Poly Q repeats, fused to enhanced green fluorescent protein (EGFP). Protein expression was induced by the ecdysone-analog tebufenozide, after which Q103 cells were observed to accumulate perinuclear inclusion bodies (protein aggregation) and undergo apoptosis. At 48 h post-induction, cell viability was quantified using the fluorescent indicator Alamar blue. Compounds that showed maximum cell viabilities higher than the negative control (pure dimethylsulfoxide, DMSO) are considered to be active, and concentrations at which they produce 50% (EC_{50}) and 100% (EC_{100}) of their maximum cell viability were calculated.

3.3 Screening of Helicterin-Core Compounds

Of the initial set of ten compounds in the helicterin series that were screened in this assay, which included natural products, advanced compounds, and some available intermediates, a single hit was obtained in the form of thiocarbonylimidazole derivative **12**. This compound was originally synthesized[16] as a racemate in an effort to access hydroxyketone **13** (Scheme 1); however, the planned free-radical fragmentation of its thiocarbamate moiety and subsequent capture by molecular oxygen[17] did not succeed, as was noted in Chapter 1. Nonetheless, as shown in Figure 1, **12** demostrated a dose-dependent ability to restore the viability of cells expressing the mutant huntingtin gene (Q103) with EC_{50} = 6.2 μM, rescuing up to 82% of the cells at a concentration of EC_{100} = 8.7 μM, while showing no toxicity to normal cells (Q25) until much higher

concentrations (>17 μM). Additionally, this compound showed a mechanism of action distinct from the five previously identified molecules (*vide supra*), as it did not exhibit inhibitory activity against PDI. Thus, given the unique structure of **12**, its unknown mechanism of action and the general paucity of literature information regarding the biological activity of such thiocarbonylimidazole derivatives, efforts towards identifying the structural features of **12** required for activity (SAR) and designing a more active compound were initiated. The hope was that these endeavors would ultimately provide a probe for the identification of enzymes and/or pathways involved in the pathogenesis of HD as well as a lead structure for the eventual development of anti-neurodegenerative therapies.



Scheme 1. Synthesis of bicyclic core (**10**) and lead compound (**12**): (a) $PhI(OAc)_2$ (1.1 equiv), $MeOH/CH_2Cl_2$ (6:1), 23 °C, 14 h, 87%; (b) **9** (6.7 equiv), mesitylene, 220 °C, 30 min, 44% (83% b.r.s.m.); (c) $NaBH_4$ (excess), $MeOH/CH_2Cl_2$ (4:1), 0 °C, 1 h, 99%; (d) TCDI (6.0 equiv), 4-DMAP (1.5 equiv), CH_2Cl_2, 40 °C, 91%. 4-DMAP = 4-dimethylaminopyridine, TCDI = 1,1'-thiocarbonyldiimidazole

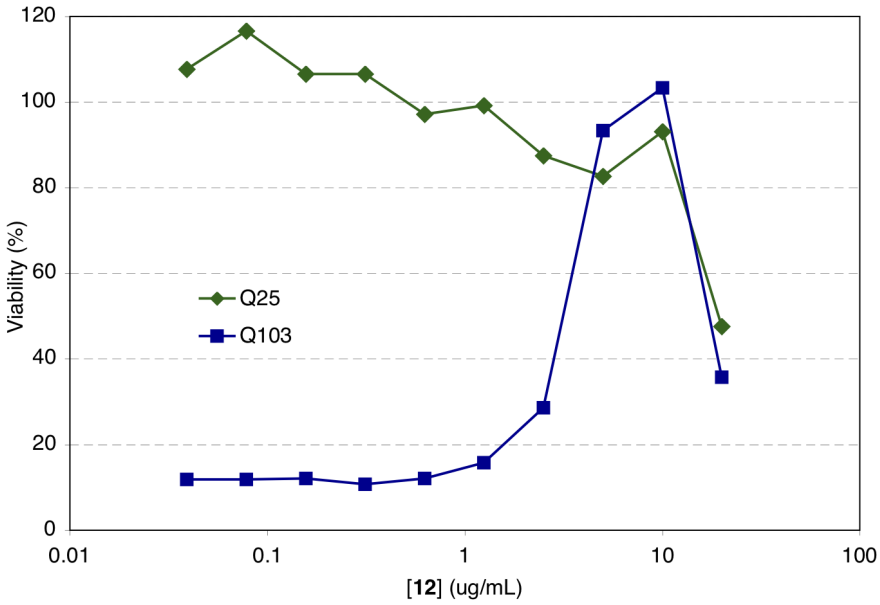


Figure 2. Viability of PC12 cells expressing wild-type (Q25) and mutant (Q103) huntingtin gene at various concentrations of the lead compound (**12**).

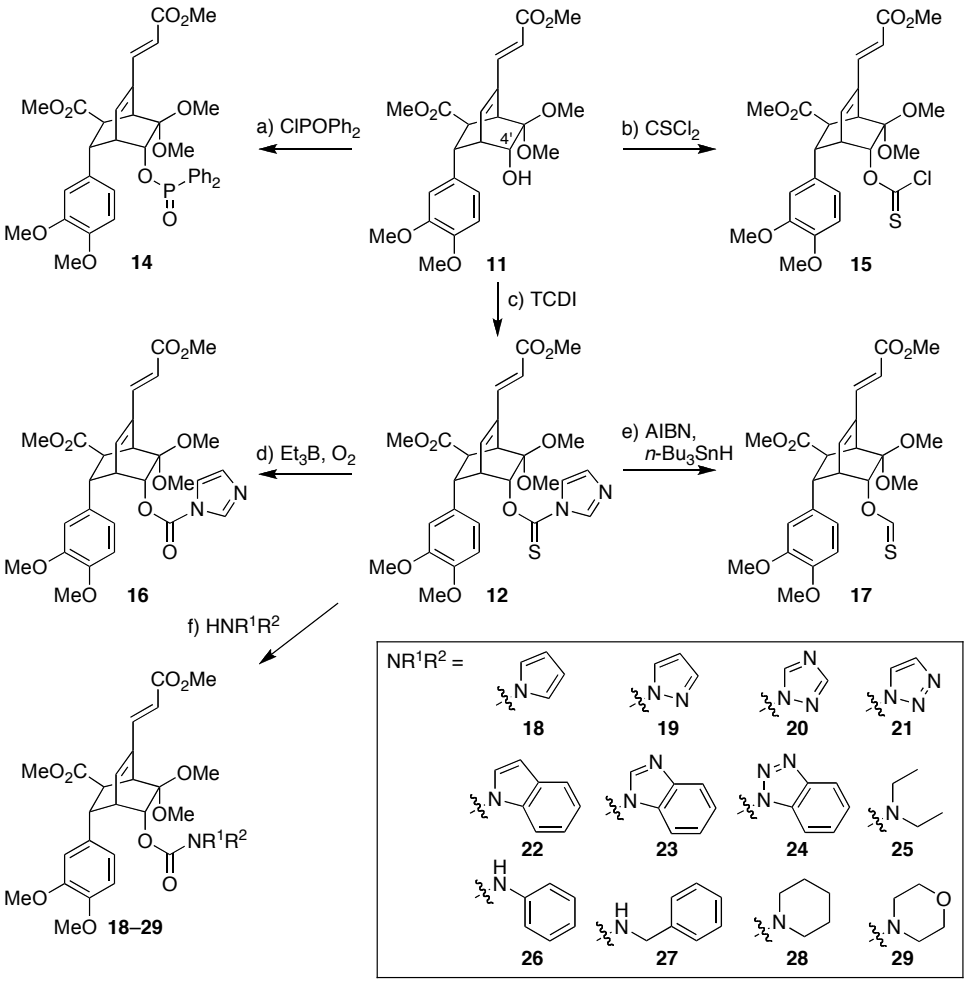
3.4 Optimization of the Carbonylimidazole Moiety

Most of the ten compounds in the initial round of testing, such as **8**, **10** and **11** (Scheme 1), contained the bicyclic core of the helicterin natural products and were completely inactive. As a result, we concluded that the presence of the bicyclo[2.2.2]octene by itself could not be responsible for activity, and that the α,β,δ,γ-unsaturated ester was likely not behaving as a Michael acceptor in the target enzyme. In addition, initial control experiments also showed that thiocarbonyldiimidazole (TCDI) itself and aliphatic alcohol-derived thiocarbonylimidazolides were also inactive. Therefore, the unique bicyclic molecular framework and the presence of the thiocarbonylimidazole moiety within **12** were likely acting in combination to prevent mutant-Htt induced cell death.

Thus, early synthetic efforts were directed towards deciphering the specific role of the thiocarbonylimidazolide moiety in the observed activity of the lead compound (**12**). Based on its structure and reactivity, we hypothesized that this group could be binding to a pocket within an enzyme, as a hydrogen bond acceptor through the thiocarbonyl sulfur and/or the free imidazole nitrogen, or that it could be forming a covalent link with an enzyme through a free-radical reaction or an acyl substitution in which the imidazole was acting as a leaving group. As shown in Scheme 2, a number of different thiocarbonyl, carbonyl and phosphinate analogs were synthesized and tested in an attempt to answer this question. Phosphinate ester **14** was accessed in one step from alcohol **11** and was completely inactive. Turning our attention to the role of the sulfur atom, its replacement with oxygen was accomplished by exposure of the lead (**12**) to Et_3B under an O_2 atmosphere (**16**), and this also ablated all activity. Next, chloride analog **15** was synthesized from **11** by treatment with thiophosgene, and it showed no activity. Reduced analog **17** was accessed under reductive radical conditions from **12**, and this compound showed some cell rescue (42%) at a higher concentration (EC_{50} = 14.9 μM) than the lead compound. Finally, in an effort to optimize the substituent on the thiocarbonyl group, *N*-linked analogs **18**–**29** were synthesized by treatment of the lead (**12**) with the desired amine and heating. Of these, only **20**, **21**, **24** and **29** showed activity, and only 1,2,3-triazole variant **21** was more active than the lead (EC_{50} = 3.6 μM, 81% max. viability).

The inactivity of **14** suggested that simple steric bulk at C-4' (see **11**, helicterin A numbering) was not an important factor for activity, although the diphenylphosphinate could simply be too bulky for the binding pocket. However, a number of other analogs with steric properties similar to the lead (**18**–**20**, **25**, **28** and **29**) were inactive or very

weakly active. The thiocarbonylimidazolide group in the lead (**12**) is not likely to be a covalent inhibitor based on acyl substitution chemistry, given that the chloride (**15**) and the carbonyl (**16**) were both inactive, and it is also not likely to participate in free-radical chemistry since a number of thiocarbonyl analogs that can also readily undergo radical reactions (**17**–**20**, **22**, **23** and **25**–**29**) were also inactive or very weakly active. If hydrogen-bonding to the thiocarbonyl is important, the increased length of the C=S bond compared to the C=O bond (1.61 *vs.* 1.21 Å) could explain why analog **16** was inactive. Finally, although the exact mechanism of cell rescue remains unclear, this activity in these compounds appears to be dependent upon the presence of a heterocycle containing a hydrogen-bond acceptor across the ring from the acylated *N*-atom, as seen in the lead (**12**) as well as active compounds **20**, **21**, **24** and **29**. Overall, however, only the imidazole and triazole-containing analogs (**12**, **20** and **21**) were capable of producing maximum cell viabilities near or above 80%.



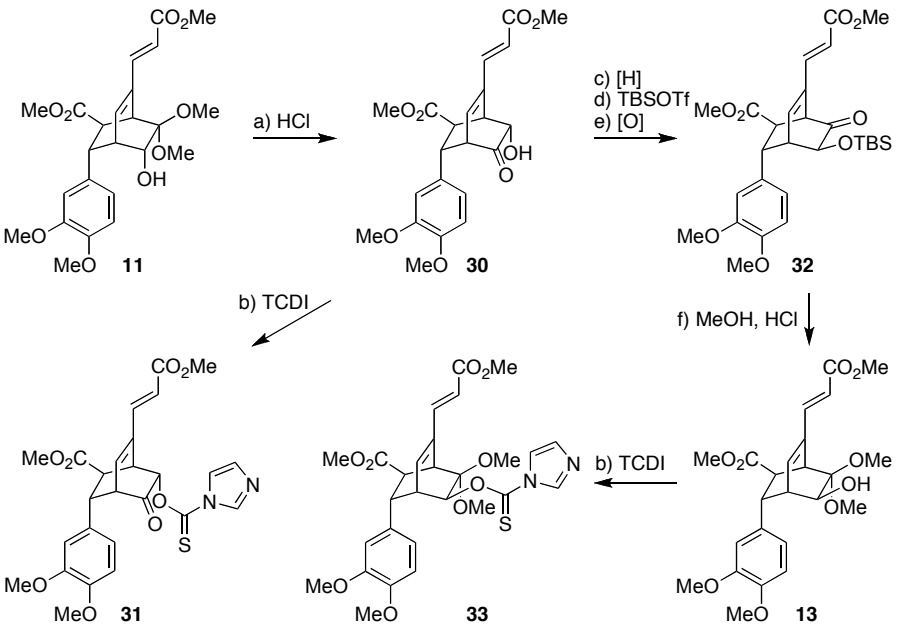
Scheme 2. (a) $ClPOPh_2$ (5.0 equiv), Et_3N (10 equiv), 4-DMAP (catalytic), DCE/THF (1:1), 60 °C, 48 h, 89%; (b) $CSCl_2$ (5.0 equiv), NaH (1.3 equiv), THF, 23 °C, 48 h, 17%; (c) TCDI (6.0 equiv), 4-DMAP (1.5 equiv), CH_2Cl_2, 40 °C, 91%; (d) Et_3B (5.0 equiv), *n*-Bu_3SnH (5.0 equiv), O_2 (1 atm), CH_2Cl_2, 0 °C, 1 h, 72%; (e) AIBN (6.0 equiv), Ph_2Se_2 (4.0 equiv), *n*-Bu_3SnH (6.0 equiv), toluene, 80 °C, 36 h; (f) **18** and **26**: HNR^1R^2 (10 equiv), K_2CO_3 (5.0 equiv), 4-DMAP (cat.), DMF, 60 °C, 18 h, 9–41%; **19**–**25** and **27**–**29**: HNR^1R^2 (5.0 equiv), 4-DMAP (cat.), CH_2Cl_2, 40 °C, 16 h, 22–80%. AIBN = 2,2'-azobisisobutyronitrile, DCE = 1,2-dichloroethane, 4-DMAP = 4-dimethylaminopyridine, TCDI = 1,1'-thiocarbonyldiimidazole

Table 1. Activity data for analogs in Scheme 2 compared to the lead (**12**) and DMSO negative control.

Compound	EC_{50} (μM)	EC_{100} (μM)	Max. viability (%)
12	6.2	8.7	82
14	-	-	29
15	-	-	24
16	-	-	32
17	14.9	39.5	42
18	-	-	29
19	-	-	29
20	12.0	34.9	78
21	3.6	8.7	81
22	-	-	25
23	-	-	30
24	10.5	16.0	41
25	-	-	27
26	-	-	28
27	-	-	27
28	-	-	30
29	11.8	17.8	47
DMSO	-	-	32

- indicates no activity since viability was below negative control

With this information in hand, we sought to study the influence of the stereochemistry of the thiocarbonylimidazole group as well as its positioning on the bicyclic core. Alcohols **30** and **13** were accessed using chemistry developed within for the synthesis of the helicterin natural products[6] and functionalized under standard conditions to afford analogs **31** and **33**, respectively, as shown in Scheme 3. Hydroxyketone analog **31** was completely inactive, suggesting that the thiocarbonylimidazolide is required to be on the proximal (C-4') position on the [2.2.2] bicycle. Additionally, analog **33**, the C-4' epimer of lead compound **12**, showed good potency (EC_{50} = 1.9 μM) but with a low maximum cell viability ratio (52%) suggesting that the thiocarbonylimidazole is required to have α-stereochemistry for optimal activity.



Scheme 3. (a) 0.5 M HCl, H_2O, THF, 23 °C, 14 h, 84%; (b) TCDI (6.0 equiv), 4-DMAP (1.5 equiv), CH_2Cl_2, 40 °C, 50–58%; (c) $Me_4NBH(OAc)_3$ (5.0 equiv), MeCN/AcOH (10:1), 25 °C, 5 h, 75%; (d) TBSOTf (1.0 equiv), Et_3N (5.0 equiv), CH_2Cl_2, –78→23 °C, 1 h; (e) Dess-Martin periodinane (1.5 equiv), $NaHCO_3$ (10 equiv), CH_2Cl_2, 25 °C, 1 h, 94% over 2 steps; (f) 0.4 M HCl, MeOH/$CH(OMe)_3$ (4:1), 25 °C, 14 h, 93%. 4-DMAP = 4-dimethylaminopyridine, TCDI = 1,1'-thiocarbonyldiimidazole, TBS = *t*-butyldimethylsilyl, Tf = trifluoromethanesulfonyl

Table 2. Activity data for analogs in Scheme 3 compared to the lead (**12**) and DMSO negative control.

Compound	EC_{50} (μM)	EC_{100} (μM)	Max. viability (%)
12	6.2	8.7	82
31	-	-	28
33	1.9	8.7	52
DMSO	-	-	32

- indicates no activity since viability was below negative control

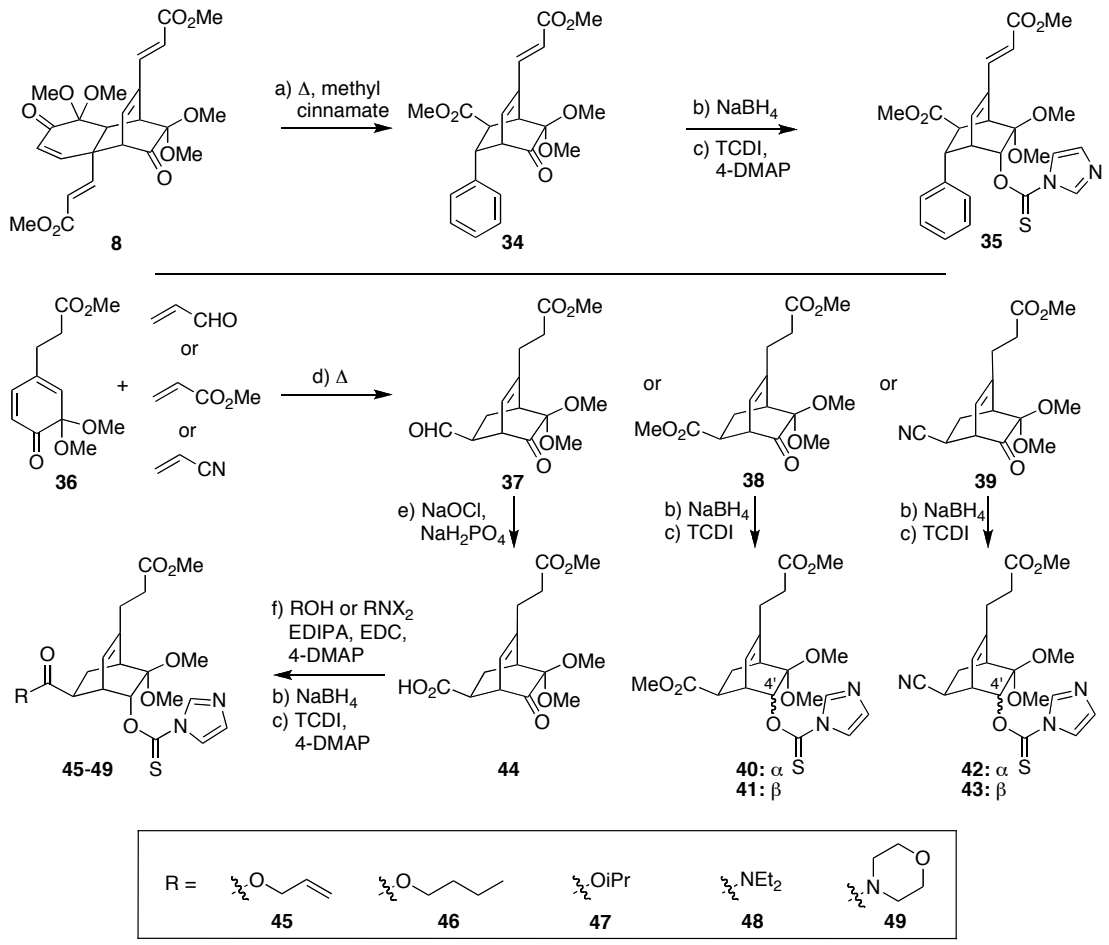
3.5 Activity of Modified Bicyclic Frameworks

In order to probe whether modifications of the aryl ring within the lead compound are tolerated, phenyl substituted analog **35** was synthesized according to the previously described sequence (Scheme 4). When tested, this compound had reduced activity (EC_{50}

= 13.3 μM) and a lower maximum cell rescue (62%), suggesting that the oxygen atoms within the protected-cathecol ring of the lead could enable certain interactions with the enzyme. In addition, we sought to determine whether complete removal of the aryl ring and simplification of the bicyclic core as well as removal of the conjugated alkene and potential Michael acceptor would have an effect on activity. Therefore, bicyclic products **37**–**39** were readily accessed by a Diels–Alder cycloaddition between stable monomeric diene **36** and acrolein, methyl acrylate or acrylonitrile, respectively.[6] Due to the absence of the aromatic ring, the reduction of **38** and **39** proceeded non-selectively to afford a mixture of epimeric alcohols at C-4'. These mixtures were then treated with thiocarbonyldiimidazole under standard conditions followed by separation of the resulting diastereomers through preparative TLC to afford analogs **40**–**43**. When tested, each of these compounds showed significant activity, with EC_{50} values for **42** and **43** of 3.3 and 4.4 μM, respectively. However, all of these analogs produced shallow dose-response curves, reaching their maximum effect at much higher concentrations. Additionally, no significant difference in the activity of C-4' epimers was measured in this simplified molecular framework.

To evaluate the effect of different electron withdrawing groups attached to the bicyclic core, aldehyde **37** was converted to carboxylic acid **44**, which in turn was coupled to various alcohols and amines. Subsequent reduction, thiocarbonylimidazole formation and isolation of the major α-epimer afforded analogs **45**–**49**, as shown in Scheme 4. Some of these compounds were active, with **45** and **47** being almost as active as the lead (EC_{50} = 6.2 and 6.7 μM), albeit their maximum viability values were significantly lower (46 and 50%). These overall results not only confirmed the finding

that the aromatic ring is beneficial, but the activity of **45**-**49** also confirmed that the α,β,δ,γ-unsaturated ester within the lead compound is not acting as a Michael acceptor.



Scheme 4. (a) methyl cinnamate (6.7 equiv), mesitylene, 220 °C, 30 min, 87%; (b) $NaBH_4$ (excess), $MeOH/CH_2Cl_2$ (4:1), 0 °C, 1 h, 76–98%; (c) TCDI (6.0 equiv), 4-DMAP (1.5 equiv), CH_2Cl_2, 40 °C, 27%; (d) electrophile (100 equiv), toluene, 80 °C, 2 days, 43–77%; (e) NaOCl (5.0 equiv), NaH_2PO_4 (5.0 equiv), DMSO/water (6:1), 23 °C, 30 min, 99%; (f) ROH (2.0 equiv) or R_2NH (4.0 equiv), EDC•HCl (2.0 equiv), *i*-Pr_2NEt (4.0 equiv), 4-DMAP (1.0 equiv), CH_2Cl_2, 23 °C, 4 h, 37–63%. 4-DMAP = 4-dimethylaminopyridine, DMSO = dimethyl sulfoxide, EDC•HCl = *N*-(3-Dimethylaminopropyl)-*N′*-ethylcarbodiimide hydrochloride, TCDI = 1,1'-thiocarbonyldiimidazole

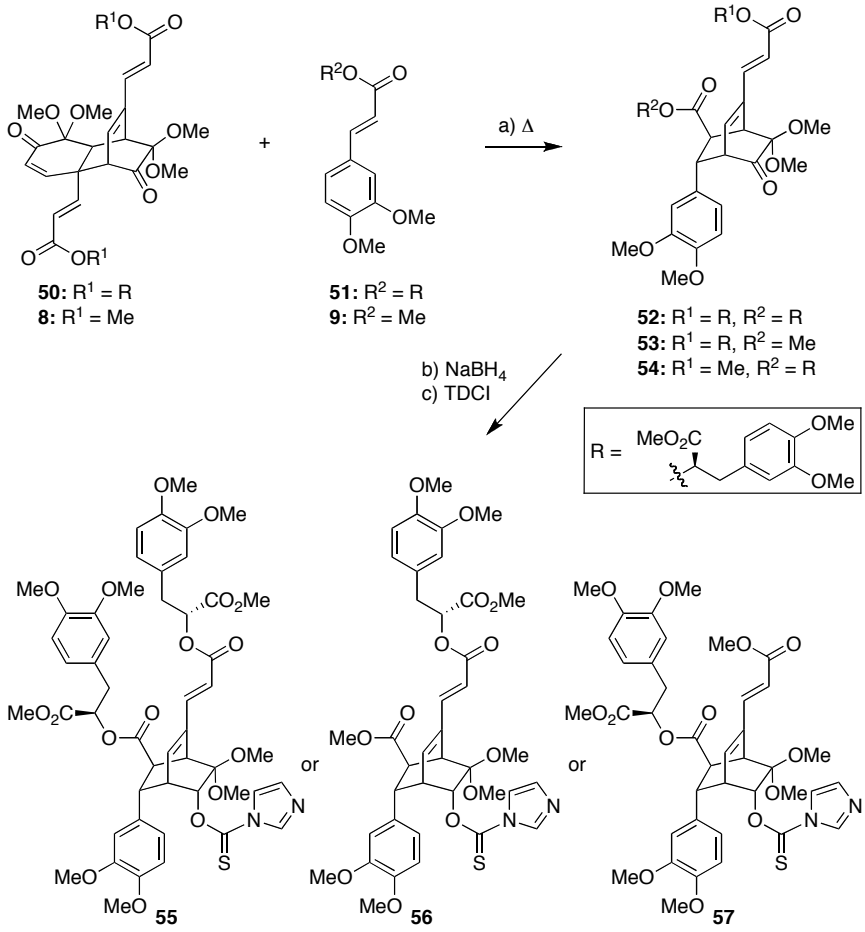
Table 3. Activity data for analogs in Scheme 4 compared to the lead (**12**) and DMSO negative control.

Compound	EC_{50} (μM)	EC_{100} (μM)	Max. viability (%)
12	6.2	8.7	82
35	13.3	19.5	62
40	11.8	22.8	85
41	10.8	22.8	77
42	4.4	24.7	64
43	3.3	24.7	73
45	6.2	10.8	46
46	13.3	20.8	47
47	6.7	10.7	50
48	-	-	30
49	-	-	29
DMSO	-	-	32

- indicates no activity since viability was below negative control

3.6 Activity of Natural Product Architectures

Finally, we were interested in evaluating natural product-like architectures in the HD assay. As shown in Scheme 5, analogs based on the lead structure (**12**) bearing different combinations of the methyl ether-protected natural product side-chain were synthesized as inseparable mixtures of diastereomers with respect to the stereochemistry of the bicyclo[2.2.2]octene core (**55**–**57**). Although these compounds have molecular weights that are well above those of typical small molecule drugs,[18] **55** and **57** proved to be some of the most active in the entire series (3.7 and 4.3 μM).



Scheme 5. (a) **51** or **9** (6.7 equiv), mesitylene, 220 °C, 30 min; (b) $NaBH_4$ (excess), $MeOH/CH_2Cl_2$ (4:1), 0 °C, 1 h, 2–25% (2 steps); (c) TCDI (6.0 equiv), 4-DMAP (1.5 equiv), CH_2Cl_2, 40 °C, 57–64%. 4-DMAP = 4-dimethylaminopyridine, TCDI = 1,1'-thiocarbonyldiimidazole

Table 4. Activity data for analogs in Scheme 5 compared to the lead (**12**) and DMSO negative control.

Compound	EC_{50} (μM)	EC_{100} (μM)	Max. viability (%)
12	6.2	8.7	82
55	3.7	10.1	41
56	8.0	12.8	62
57	4.3	6.4	63
DMSO	-	-	32

- indicates no activity since viability was below negative control

3.7 Conclusion

In conclusion, we have identified and synthesized a series of compounds based on the core of the helicterin natural products with the ability to prevent cell death in an HD model system. Our SAR studies have revealed that a thiocarbonylimidazole or a thiocarbonyl-1,2,3-triazole moiety appended to the bicyclic core was necessary for activity, and replacement of the sulfur atom or removal of the heterocycle led to loss of activity. Certain modifications of the left and upper sides of the bicyclo[2.2.2]octene core were tolerated, albeit at the price that they led to reduced potency. Finally, analogs bearing natural product side-chains (in protected form) turned out to possess good potency within this series.

Most of the active compounds in this collection do not meet several of Lipinski's Rule of Five used for predicting acceptable pharmacokinetics[18ab] and the even more stringent requirements for compounds active in the central nervous system,[18c] especially by having a molecular weight above 500 and more than 10 hydrogen-bond acceptors. In addition, the calculated octanol/water partition coefficient (clogP) of the lead is 4.49±0.6,[19] a value that is close to the upper limit of 5. Thus, they may not constitute potential therapeutics in their current form. Nonetheless, they may serve as important tools for the discovery of novel enzymes and cellular pathways involved in the pathology of HD. Indeed, current efforts in the Stockwell research group are aimed at identifying the cellular target of these molecules. That information coupled with the early stage SAR and syntheses described in this chapter may ultimately become a starting point for the development of an anti-neurodegenerative therapy for the treatment of HD.

The work described in this chapter would not have been possible without the contribution of several talented individuals. Anish Shah played a pivotal role by synthesizing many of the analogs shown in the box in Scheme 2, the analogs shown in Scheme 3 and several of the analogs shown in Scheme 4. In addition, he prepared the samples and set up several rounds of testing in the Stockwell laboratory. Matthew E. Welsch is also acknowledged for synthesizing several analogs shown in Scheme 4 and all of the compounds in Scheme 5. Finally, Professor Brent R. Stockwell and group members Anna Kaplan and Kristina DiPietrantonio are thanked for conducting the biological testing and data analysis.

3.8 References

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3.9 Experimental Section

General Procedures. All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Dry tetrahydrofuran (THF), acetonitrile (MeCN), toluene, benzene, diethyl ether (Et_2O), and methylene chloride (CH_2Cl_2) were obtained by passing commercially available pre-dried, oxygen-free formulations through activated alumina columns. Yields refer to chromatographically and spectroscopically (^1H and ^{13}C NMR) homogeneous materials, unless otherwise stated. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. . Reactions were magnetically stirred and monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent and cerium sulfate (CAM) and heat as developing agents. SiliCycle silica gel (60, academic grade, particle size 0.040–0.063 mm) was used for flash column chromatography. Preparative thin-layer chromatography (PTLC) separations were carried out on 0.50 mm E. Merck silica gel plates (60F-254). NMR spectra were recorded on Bruker DPX 300, Avance II 400, Avance III 400 and DMX 500 instruments and calibrated using residual undeuterated solvent as an internal reference ($CDCl_3$: 7.26 ppm for ^1H, 77.0 ppm for ^{13}C). The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, br = broad, app = apparent. IR spectra were recorded on a Perkin-Elmer 1000 series FT-IR spectrometer. Mass spectra (LRMS) were recorded in the Columbia University Mass Spectral Core facility using an APCI (atmospheric pressure chemical ionization) technique. HPLC traces were obtained on a Shimadzu instrument.

Abbreviations. 4-DMAP = 4-(dimethylamino)pyridine, DMF = *N*,*N*-dimethylformamide, EDC•HCl = *N*-(3-Dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride, TBS = *tert*-butyldimethylsilyl, Tf = trifluoromethanesulfonyl.

General Procedure A for the Synthesis of Bicyclic Cores 10, 34, 52–54. *Oxidative Dearomatization and Dimerization:* $PhI(OAc)_2$ (1.1 equiv) was added to a solution of the starting phenol (1.0 equiv) in MeOH:CH_2Cl_2 (5:1, 0.05–0.1 M in starting phenol) at 23 °C, and the resultant light yellow solution was stirred at 23 °C for 14 h. Upon completion, the reaction contents were concentrated directly and the resultant crude yellow oil was purified by flash column chromatography (silica gel, hexanes/EtOAc) to give the desired Diels–Alder dimer. *Retro Diels–Alder/Diels–Alder Reaction:* A solution of the dimer (1.0 equiv) and dienophile (5–6.7 equiv) in mesitylene (0.1–0.4 M in starting dimer) was carefully degassed 3 times using the freeze-pump-thaw method, and then sealed under argon in a tube equipped with a magnetic stir bar. The reaction solution was stirred at 220 °C (oil bath) for 30 min. After cooling to 23 °C, the reaction contents were purified directly by flash column chromatography (silica gel, hexanses:EtOAc) to afford recovered dienophile alongside the desired Diels–Alder.

General Procedure B for the Synthesis of Bicyclic Cores 37–39. *Oxidative Dearomatization:* $PhI(OAc)_2$ (1.1 equiv) was added to a solution of the 4-hydroxy-3-methoxydihydrocinnamic acid methyl ester (1.0 equiv) in MeOH:CH_2Cl_2 (5:1, 0.05–0.1 M in starting phenol) at 23 °C, and the resultant yellow solution was stirred at 23 °C for 1 h. Upon completion, the reaction contents were concentrated directly and the resultant

crude yellow oil was purified by flash column chromatography (silica gel, hexanes/EtOAc, 7:3) to afford the desired orthoquinone monoketal intermediate **36** (97% yield) as a bright yellow oil. [Note: this product was stored as a 0.2 M solution in toluene at 4 °C to prevent its dimerization]. *Diels-Alder Cycloaddition:* Dienophile (100 equiv) was then added to a solution of this newly formed orthoquinone monoketal (**36**, 0.2 M in toluene, 1.0 equiv), and the reaction mixture was stirred in a sealed tube at 80 °C for 2 days. Upon completion, the reaction contents were concentrated directly and the resultant crude yellow oil was purified by flash column chromatography (silica gel, hexanes/EtOAc) to afford the Diels–Alder adduct.

General Procedure C for Ketone Reduction: $NaBH_4$ (2.0 equiv) was added in a single portion to a solution of bicyclic ketone **(**1.0 equiv) in MeOH:CH_2Cl_2 (5:1, 0.1–0.2 M in starting ketone) at 0 °C, and the resultant mixture was stirred at 0 °C for 1 h. Upon completion, the reaction contents were diluted with EtOAc, washed with 1 M aqueous HCl, saturated aqueous $NaHCO_3$ and brine (20 mL), dried ($MgSO_4$), and concentrated to afford the desired hydroxyketal product, as a single diastereomer or an inseparable mixture of epimers, that was used without further purification.

General Procedure D for the Formation of Thiocarbonylimidazolide Analogs. Thiocarbonyldiimidazole (6.0 equiv) and 4-DMAP (1.5 equiv) were added to a solution of alcohol (1.0 equiv) in CH_2Cl_2 (0.05–0.1 M in starting material) at 23 °C, and the reaction was stirred at 40 °C in a sealed tube for 48 h. Upon completion, the reaction contents were poured into saturated aqueous NH_4Cl and extracted with EtOAc (2×). The

combined organic layers were then washed with saturated aqueous $NaHCO_3$, brine, dried ($MgSO_4$), and concentrated. The resultant thick orange oil was purified by flash column chromatography (silica gel, hexanes/EtOAc) to afford the desired product. If necessary, this product was subjected to preparative TLC (silica gel, hexanes/EtOAc) to increase purity and/or to separate diastereomers. The purity of the final compound was assessed using reverse-phase HPLC (Shimadzu Epic C18 5μ 250×9.6 mm, water/MeCN, 30%, 0.9 mL/min, UV detector at 270 nm).

Alcohol 11. Diels–Alder product **10** was prepared from phenol **7** according to General Procedure A in 38% overall yield. Alcohol **11** was prepared from **10** according to General Procedure C in 99% yield.

Lead Compound 12. Prepared from alcohol **11** according to General Procedure D in 91% yield. **12:** R_f = 0.17 (silica gel, hexanes/EtOAc, 3:7); IR (film) ν_{max} 3132, 2950, 2836, 1720, 1633, 1519, 1436, 1391, 1286, 1231, 1173, 1027, 940, 871, 764, 654 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.73 (s, 1 H), 7.39 (d, *J* = 16.0 Hz, 1 H), 7.18 (s, 1 H), 6.82 (m, 2 H), 6.73 (m, 2 H), 6.61 (d, *J* = 8.5 Hz, 1 H), 6.07 (d, *J* = 16.0 Hz, 1 H), 5.21 (d, *J* = 3.0 Hz, 1 H), 3.94 (dt, *J* = 15.0, 3.0 Hz, 1 H), 3.81 (s, 3 H), 3.79 (s, 3H), 3.78 (s, 3 H), 3.71 (s, 3 H), 3.71 (m, 1 H), 3.68 (s, 3 H), 3.42 (s, 3 H), 3.35 (d, *J* = 7.5 Hz, 1 H), 3.10 (s, 3 H); LRMS (FAB) [$M+H^+$] calc. for $C_{28}H_{32}N_2O_9S$ 573.63, found 573.05; HPLC t_R = 6.73 min.

Diphenylphosphinate 14. Diphenylphosphinic chloride (0.020 mL, 0.108 mmol,

5.0 equiv), Et_3N (0.030 mL, 0.216 mmol, 10 equiv), and 4-DMAP (catalytic) were sequentially added to a solution of alcohol **11** (0.010 g, 0.022 mmol, 1.0 equiv) in 1,2-dichloroethane/THF (1:1, 1.0 mL) at 25 °C, and the resultant reaction mixture was stirred at 60 °C in a sealed tube for 48 h. Upon completion, the reaction contents were quenched with 1 M aqueous HCl (10 mL) and extracted with EtOAc (2×10 mL). The combined organic layers were then washed with saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL), dried ($MgSO_4$), and concentrated. The crude was purified by flash column chromatography (silica gel, hexanes/EtOAc, 3:7) to afford phosphinate **14** (0.013 g, 89% yield) as a white amorphous solid. **14**: R_f = 0.22 (silica gel, hexanes:EtOAc, 3:7); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 (m, 2 H), 7.49–7.32 (m, 5 H), 7.29 (d, *J* = 15.6 Hz, 1 H), 7.28–15 7.18 (m, 2 H), 7.03–6.97 (m, 4 H), 6.60 (d, *J* = 7.5 Hz,1 H), 6.57 (d, *J* = 6.9 Hz, 1 H), 5.96 (d, *J* = 15.6 Hz, 1 H), 4.57 (dd, *J* = 12.0, 3.0 Hz, 1 H), 3.78 (m, 1 H), 3.77 (s, 3 H), 3.75 (s, 3 H), 3.74 (s, 3 H), 3.69 (app s, 1 H), 3.59 (s, 3 H), 3.56 (dd, *J* = 7.2, 2.1 Hz, 1 H), 3.43 (s, 3 H), 3.26 (d, *J* = 6.9Hz, 1 H), 3.11 (s, 3 H), 2.96 (dt, *J* = 6.9, 2.4 Hz, 1 H); LRMS (FAB) calc. for $C_{36}H_{40}O_{10}P$ [M+H$^+$] 663.2, found 663.0.

Thiophosgene Derivative 15. Alcohol **11** (0.010 g, 0.022 mmol, 1.0 equiv) was dissolved in THF (0.5 mL) and cooled to 0 °C. NaH (60%, 0.0011 g, 0.028 mmol, 1.3 equiv) was added followed by thiophosgene (0.0083 mL, 0.108 mmol, 5.0 equiv), and the reaction was stirred at 23 °C for 48 h. The reaction was quenched with saturated aqueous NH_4Cl (10 mL) and extracted with EtOAc (10 mL). The organic layer was washed with brine (10 mL), dried ($MgSO_4$), and concentrated. The product was isolated by preparative TLC (hexanes/EtOAc, 1:1, run 2×) to afford analog **15** (0.002 g, 17% yield, 42%

b.r.s.m.). **15:** R_f = 0.41 (silica gel, hexanes/EtOAc, 2:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, *J* = 16.0 Hz, 1 H), 6.92 (d, *J* = 2 Hz, 1 H), 6.86 (d, *J* = 8.8 Hz, 1 H), 6.77 (d, *J* = 8.4 Hz, 1 H), 6.74 (d, *J* = 8.8 Hz, 1 H), 5.99 (d, *J* = 16.0 Hz, 1 H), 4.65 (d, *J* = 3.2, 1 H), 3.88 (s, 3 H), 3.84 (s, 3 H), 3.76 (s, 3 H), 3.68 (s, 1 H), 3.65 (s, 3 H), 3.62 (d, *J* = 8.8 Hz, 1 H), 3.47 (dd, *J* = 6.2, 3.0 Hz, 1 H), 3.37 (s, 3 H), 3.28 (d, *J* = 6.0 Hz, 1 H), 3.14 (s, 3 H); LRMS (FAB) calc. for $C_{25}H_{30}ClO_9S$ [M+H$^+$] 542.02, found 541.95.

Carbamate 16. Oxygen gas passed through a drying tube was bubbled into a solution of **12** (5.0 mg, 0.0092 mmol, 1.0 equiv), Et_3B (1.0 M in hexanes, 0.046 mL, 0.046 mmol, 5.0 equiv) and nBu_3SnH (0.012 mL, 0.046 mmol, 5.0 equiv) in CH_2Cl_2 (1.0 mL) at 0 °C for 30 min. after which the solution was stirred at 0 °C for an additional 30 min. Upon completion, the reaction was quenched with 1 M aqueous HCl (10 mL) and extracted with EtOAc (2×10 mL). The combined organic layers were then washed with saturated aqueous $NaHCO_3$ (10 mL), brine (10 mL), dried ($MgSO_4$), and concentrated. The crude was purified by flash column chromatography (silica gel, hexanes/EtOAc, 2:3) to afford compound **16** (3.5 mg, 72% yield) as a white amorphous solid. **16**: R_f = 0.14 (silica gel, hexanes/EtOAc, 3:7); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (s, 1 H), 7.37 (d, *J* = 15.5 Hz, 1 H), 6.87 (m, 2 H), 6.83 (s, 1 H), 6.80 (s, 1 H), 6.73 (d, *J* = 7.0 Hz, 1 H), 6.69 (d , *J* = 8.0 Hz, 1 H), 6.05 (d, *J* = 15.5 Hz, 1 H), 4.77 (d, *J* = 3.0 Hz, 1 H), 3.82 (s, 3 H), 3.78 (s, 3 H), 3.77 (m, 2 H), 3.76 (s, 3 H), 3.71 (m, 2 H), 3.67 (s, 3 H), 3.42 (s, 3 H), 3.34 (d, *J* = 6.0 Hz, 1 H), 3.17 (s, 3 H).

Thioformyl Derivative 17. Starting material **12** (20.0 mg, 0.036 mmol, 1.0

equiv) was dissolved in degassed toluene (1.0 mL). To this solution were added AIBN (23.6 mg, 0.144 mmol, 4.0 equiv), Ph_2Se_2 (45.0 mg, 0.144 mmol, 4.0 equiv) and nBu_3SnH (57.1 μL, 0.216 mmol, 6.0 equiv). The reaction mixture was stirred at 80 °C under an Ar atmosphere for 18 hours, at which point 2 μL of H_2O were added and the reaction was allowed to proceed at 80 °C for another 45 minutes. Additional AIBN (2.0 equiv) were then added to the reaction mixture, and the reaction was stirred at 80 °C for another 15 hours. Upon completion, the crude reaction mixture was concentrated directly and purified by flash column chromatography (silica gel, hexanes/EtOAc, 8:2) to afford the desired thioformyl analog **17** as a yellow oil. **17:** R_f= 0.49 (silica gel, hexanes:EtOAc, 3:7); IR (film) ν_{max} 3000, 2909, 2360, 2321, 1654, 1513, 1436, 1317, 1021, 953 cm^{-1}; ^1H NMR (500 MHz,$CDCl_3$) δ 7.48 (s, 1 H), 7.35 (d, *J* = 16.0 Hz, 1 H), 6.98 (d, *J* = 2.0 Hz, 1 H), 6.93 (d, *J* = 8.5 Hz, 1 H), 6.78 (d, *J* = 8.0 Hz, 1 H), 6.70 (d, *J* = 6.5 Hz, 1 H), 6.03 (d, *J* = 16.0 Hz, 1 H), 4.77 (app s, 1 H), 3.89 (s, 3 H), 3.85 (s, 3 H), 3.84 (m, 1 H), 3.78 (s, 3 H), 3.76 (m, 1 H), 3.62 (s, 3 H), 3.60 (d, *J* = 6.5 Hz, 1 H), 3.48 (s, 3 H), 3.30 (d, *J* = 6.5 Hz, 1 H), 3.12 (s, 3 H); LRMS (APCI) calc. for $C_{25}H_{31}O_9S$ $[M+H^+]$ 507.57, found 507.55.

General Procedure E for Heterocycle Substitution (18 and 26). The parent compound (**12**, 1.0 equiv) was dissolved in DMF. To this solution were added sequentially K_2CO_3 (5.0 equiv), *N*-nucleophile (10.0 equiv) and 4-DMAP (catalytic). The resultant reaction mixture was stirred at 60 °C for 18 hours. Upon completion, the reaction contents were diluted with Et_2O and then washed twice with H_2O. The combined organic layers were dried ($MgSO_4$), filtered and concentrated to afford a crude oil. This material was purified by preparative TLC (silica gel, hexanes/EtOAc) to yield the desired analog.

General Procedure F for Heterocycle Substitution (19–25 and 27–29). The parent compound (**12**, 1.0 equiv) was dissolved in CH_2Cl_2 under Ar. To this solution was added 4-DMAP (catalytic) and *N*-nucleophile (5.0 equiv). The resultant reaction mixture was stirred at 40 °C for 16 hours. Upon completion, the reaction contents were diluted with EtOAc and then washed once with saturated aqueous NH_4Cl, twice with saturated aqueous $NaHCO_3$, and once with brine. The combined organic layers were dried ($MgSO_4$), filtered and concentrated to afford a crude yellow oil. This material was purified by preparative TLC (silica gel, hexanes/EtOAc) to yield the desired analog.

Analog 18. Prepared from **12** according to General Procedure E in 9% yield. **18:** R_f = 0.21 (silica gel, hexanes/EtOAc, 3:7); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, *J* = 15.6 Hz, 1 H), 6.96 (br, 1 H), 6.81 (d, *J* = 7.6 Hz, 1 H), 6.77 (m, 2 H), 6.60 (d, *J* = 8.4 Hz, 1 H), 6.07 (s, 1 H), 6.03 (m, 2 H), 5.31 (d, *J* = 3.2 Hz, 1 H), 3.92 (m, 1 H), 3.78 (s, 3 H), 3.77 (s, 3 H), 3.71 (s, 1 H), 3.70 (s, 3 H), 3.69 (s, 1 H), 3.67 (s, 3 H), 3.39 (s, 3 H), 3.33 (d, *J* = 6.8 Hz, 1 H), 3.11 (s, 3 H); LRMS (APCI) calc. for $C_{29}H_{33}NO_9$ [M–S] 539.22, found 539.60; HPLC t_R = 15.46 min.

Analog 19. Prepared from **12** according to General Procedure F in 46% yield. **19:** R_f = 0.52 (silica gel, hexanes/EtOAc, 3:7); IR (film) ν_{max} 3004, 2918, 2361, 1657, 1437, 1316, 1022, 953, 706 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (s, 3 H), 7.33 (d, *J* = 4.4 Hz, 1 H), 6.79 (t, *J* = 14.8 Hz, 3 H), 6.59 (m, 1 H), 6.15 (m, 1 H), 6.06 (d, *J* = 20.8 Hz, 1 H), 5.38 (d, *J* = 4.0 Hz, 1 H), 3.92 (m, 1 H), 3.81 (s, 1 H), 3.78 (s, 6 H), 3.73 (s, 1 H),

3.70 (s, 3 H), 3.67 (s, 3 H), 3.42 (s, 3 H), 3.36 (d, *J* = 10.8 Hz, 1 H), 3.12 (s, 3 H); LRMS (APCI) calc. for $C_{28}H_{32}N_2O_9$ [M–S] 540.21, found 540.51; HPLC t_R = 5.52 min.

Analog 20. Prepared from **12** according to General Procedure F in 51% yield. **20:** R_f = 0.24 (silica gel, hexanes/EtOAc, 3:7); IR (film) ν_{max} 2961, 2848, 2361, 1861, 1720, 1630, 1552, 1413, 1261, 1091, 1009, 800 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.05 (m, 1 H), 7.89 (m, 1 H), 7.39 (d, *J* = 16 Hz, 1 H), 6.83 (d, *J* = 7.2 Hz, 1 H), 6.75 (s, 2 H), 6.62 (m, 1 H), 6.08 (d, *J* = 16.0 Hz, 1 H), 5.29 (d, *J* = 3.2 Hz, 1 H), 3.94-3.92 (m, *J* = 9.2 Hz, 1 H), 3.83 (s, 1 H), 3.78 (s, 6 H), 3.72 (s, 3 H), 3.70 (s, 1 H), 3.67 (s, 3 H), 3.45 (s, 3 H), 3.39 (dd, *J* = 11.6, 3.6 Hz, 1 H), 3.12 (s, 3 H); LRMS (APCI) calc. for $C_{27}H_{30}N_3O_9S$ [M–H] 572.17, found 572.88.

Analog 21. Prepared from **12** according to General Procedure F in 65% yield. **21:** R_f = 0.21 (silica gel, hexanes/EtOAc, 3:7); IR (film) ν_{max} 2952, 2918, 2849, 2360, 2239, 1734, 1653, 1559, 1437, 1243, 1173, 1048, 672 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, *J* = 15.6 Hz, 1 H), 6.82 (d, *J* = 6.8 Hz, 1 H), 6.73 (m, 2 H), 6.62 (d, *J* = 7.6 Hz, 1 H), 6.07 (d, *J* = 15.6 Hz, 1 H), 5.21 (d, *J* = 2.8 Hz, 1 H), 3.93 (m, 1 H), 3.81 (s, 1 H), 3.78 (s, 6 H), 3.72 (s, 3 H), 3.69 (s, 1 H), 3.68 (s, 3 H), 3.42 (s, 3 H), 3.35 (d, *J* = 7.2 Hz, 1 H), 3.10 (s, 3 H); LRMS (APCI) calc. for $C_{27}H_{30}N_3O_9S$ [M–H] 572.17, found 572.77; HPLC t_R = 6.75 min.

Analog 22. Prepared from **12** according to General Procedure F in 39% yield. **22:** R_f = 0.55 (silica gel, hexanes/EtOAc, 3:7); ^1H NMR (400 MHz, $CDCl_3$) δ 8.33 (br, 1 H),

7.71 (br, 1 H), 7.39 (m, 2 H), 7.17 (m, 2 H), 7.79 (d, *J* = 7.2 Hz, 1 H), 6.66 (m, 2 H), 6.46 (d, *J* = 3.6 Hz, 1 H), 6.07 (d, *J* = 16.0 Hz, 1 H), 5.98 (d, *J* = 8.4 Hz, 1 H), 5.44 (d, *J* = 3.2 Hz, 1 H), 4.20 (m, 1 H), 3.84 (s, 1 H), 3.78 (s, 3 H), 3.74 (s, 1 H), 3.70 (s, 3 H), 3.68 (s, 3 H), 3.52 (s, 3 H), 3.33 (s, 4 H), 3.13 (s, 3 H); LRMS (APCI) calc. for $C_{33}H_{35}NO_9$ [M–S] 589.23, found 589.64; HPLC t_R = 11.93 min.

Analog 23. Prepared from **12** according to General Procedure F in 42% yield. **23:** R_f = 0.44 (silica gel, hexanes/EtOAc, 3:7); IR (film) ν_{max} 2920, 2850, 2360, 1726, 1463, 1259, 688 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.34 (s, 1 H), 8.26 (d, *J* = 6.6 Hz, 1 H), 7.67 (dd, *J* = 5.4, 2.4 Hz, 1 H), 7.41 (d, *J* = 16.5 Hz, 1 H), 7.30 (m, 2 H), 6.77 (d, *J* = 6.9 Hz, 1 H), 6.72 (d, *J* = 8.4 Hz, 1 H), 6.66 (s, 1 H), 6.12 (m, 1 H), 6.06 (s, 1 H), 5.35 (d, *J* = 3.3 Hz, 1 H), 4.11 (m, 1 H), 3.85 (s, 1 H), 3.78 (s, 3 H), 3.72 (s, 1 H), 3.71 (s, 3 H), 3.68 (s, 3 H), 3.52 (s, 3 H), 3.37 (s, 3 H), 3.33 (s, 1 H), 3.12 (s, 3 H); LRMS (APCI) calc. for $C_{32}H_{35}N_2O_9S$ [$M+H^+$] 623.69, found 623.12; HPLC t_R = 12.75 min.

Analog 24. Prepared from **12** according to General Procedure F in 22% yield. **24:** R_f = 0.43 (silica gel, hexanes/EtOAc, 3:7); IR (film) ν_{max} 2987, 2950, 2836, 2354, 1720, 1633, 1518, 1453, 1388, 1270, 1174, 1027, 982, 871, 770, 734 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, *J* = 8.3 Hz, 1 H), 8.02 (d, *J* = 8.2 Hz, 1 H), 7.51 (t, *J* = 7.7 Hz, 1 H), 7.42 (m, 2 H), 6.79 (d, *J* = 7.2 Hz, 1 H), 6.67 (m, 1 H), 6.65 (s, 1 H), 6.10 (d, *J* = 15.8 Hz, 1 H), 6.00 (d, *J* = 8.3 Hz, 1 H), 5.45 (d, *J* = 3.4 Hz, 1 H), 4.21–4.17 (m, 1 H), 3.87 (s, 1 H), 3.80 (s, 3 H), 3.76 (m, 1 H), 3.70 (s, 3 H), 3.67 (s, 3 H), 3.57 (s, 3 H), 3.32 (d, *J* = 7.3

Hz, 1 H), 3.27 (s, 3 H), 3.19 (s, 3 H); LRMS (APCI) calc. for $C_{31}H_{33}N_3O_9$ [M–S] 591.22, found 591.63; HPLC t_R = 11.03 min.

Analog 25. Prepared from **12** according to General Procedure F in 59% yield. **25:** R_f = 0.63 (silica gel, hexanes/EtOAc, 3:7); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, *J* = 15.8 Hz, 1 H), 6.87 (s, 1 H), 6.82 (m, 1 H), 6.75 (m, 2 H), 6.01 (d, *J* = 15.8 Hz, 1 H), 5.31 (d, *J* = 2.8 Hz, 1 H), 3.89 (dd, *J* = 5.5, 2.4 Hz, 1 H), 3.86 (s, 3 H), 3.83 (s, 3 H), 3.76 (s, 3 H), 3.73 (s, 1 H), 3.66 (s, 3 H), 3.58 (dd, *J* = 7.0, 2.0 Hz, 1 H), 3.40 (s, 3 H), 3.38–3.32 (m, 1 H), 3.05 (s, 3 H), 2.80–2.71 (m, 1 H), 2.44–2.35 (m, 1 H), 1.25 (s, 2 H), 1.04 (t, *J* = 7.1 Hz, 3 H), 0.86 (t, *J* = 7.1 Hz, 3 H); LRMS (APCI) calc. for $C_{29}H_{39}NO_9$ [M–S] 545.26, found 545.86; HPLC t_R = 11.93 min.

Analog 26. Prepared from **12** according to General Procedure E in 41% yield. **26:** R_f = 0.63 (silica gel, hexanes/EtOAc, 3:7); IR (film) ν_{max} 2917, 2839, 2361, 1648, 1461, 1257, 1017, 791 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (s, 1 H), 7.40 (d, *J* = 15.6 Hz, 1 H), 7.17 (br, 1 H), 7.02 (s, 1 H), 6.89 (s, 1 H), 6.78 (m, 1 H), 6.72 (m, 1 H), 6.63 (d, *J* = 8.4 Hz, 1 H), 6.10 (s, 1 H), 6.06 (m, 1 H), 6.02 (s, 1 H), 5.38 (m, 1 H), 3.91 (s, 3 H), 3.88 (s, 1 H), 3.87 (s, 3 H), 3.80 (s, 3 H), 3.74 (m, 1 H), 3.72 (s, 1 H), 3.70 (m, 2 H), 3.51 (s, 3 H), 3.38 (s, 3 H), 3.20 (s, 1 H), 3.15 (s, 3 H), 3.11 (s, 3 H).

Analog 27. Prepared from **12** according to General Procedure F in 50% yield. **27:** R_f = 0.59 (silica gel, hexanes/EtOAc, 3:7); IR (film) ν_{max} 2952, 2836, 2362, 1720, 1631, 1605, 1589, 1518, 1436, 1252, 1169, 1027, 916, 871, 733 cm^{-1}; ^{1}H NMR (400 MHz,

$CDCl_3$) δ 7.38 (s, 1 H), 7.33 (d, *J* = 9.2 Hz, 1 H), 7.29 (s, 1 H), 7.07 (d, *J* = 8.0 Hz, 2 H), 6.95 (s, 1 H), 6.92 (m, 1 H), 6.71 (d, *J* = 6.8 Hz, 1 H), 6.63 (d, *J* = 8.4 Hz, 1 H), 6.03 (d, *J* = 15.6 Hz, 1 H), 5.34 (d, *J* = 3.6 Hz, 1 H), 4.48 (dd, *J* = 14.8, 6.0 Hz, 1 H), 4.29 (dd, *J* = 14.8, 5.2 Hz, 1 H), 3.89 (s, 3 H), 3.77 (s, 3 H), 3.75 (s, 1 H), 3.66 (s, 1 H), 3.62 (s, 6 H), 3.47 (m, 1 H), 3.41 (s, 3 H), 3.34 (s, 1 H), 3.29 (d, *J* = 6.8 Hz, 1 H), 3.16 (s, 3 H), 3.09 (s, 1 H); LRMS (APCI) calc. for $C_{32}H_{38}NO_9$ [M+H^+–S] 580.26, found 580.08; HPLC t_R = 10.17 min.

Analog 28. Prepared from **12** according to General Procedure F in 80% yield. **28:** R_f = 0.76 (silica gel, hexanes/EtOAc, 3:7); IR (film) ν_{max} 2947, 2835, 2360, 1720, 1632, 1518, 1443, 1244, 1173, 1028, 892, 733, 668 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, *J* = 16.0 Hz, 1 H), 6.89 (s, 1 H), 6.76 (m, 3 H), 5.99 (d, *J* = 15.6 Hz, 1 H), 5.34 (d, *J* = 3.2 Hz, 1 H), 3.88 (s, 3 H), 3.84 (s, 3 H), 3.76 (s, 3 H), 3.70 (s, 1 H), 3.67 (s, 3 H), 3.58 (d, *J* = 6.8 Hz, 1 H), 3.47 (m, 1 H), 3.34 (s, 3 H), 3.29 (m, 2 H), 3.10 (s, 3 H), 2.57 (m, 1 H), 1.49 (m, 2 H), 1.26 (t, *J* = 7.2 Hz, 1.4 H), 1.18–1.12 (m, 2 H); LRMS (APCI) calc. for $C_{30}H_{39}NO_9S$ [M+H^+–S] 558.27, found 558.53; HPLC t_R = 8.76 min.

Analog 29. Prepared from **12** according to General Procedure F in 64% yield. **29:** R_f = 0.51 (silica gel, hexanes/EtOAc, 3:7); IR (film) ν_{max} 2952, 2836, 2357, 1720, 1632, 1518, 1436, 1463, 1436, 1287, 1243, 1169, 1117, 1028, 978, 896, 734 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, *J* = 15.8 Hz, 1 H), 6.89 (s, 1 H), 6.77 (s, 1 H), 6.76 (m, 2 H), 6.0 (d, *J* = 15.8 Hz, 1 H), 5.34 (d, *J* = 3.2 Hz, 1 H), 3.88 (s, 3 H), 3.84 (s, 3 H), 3.76 (s, 3 H), 3.71 (s, 1 H), 3.67 (s, 3 H), 3.56 (dd, *J* = 7.32, 1.94 Hz, 1 H), 3.34 (s, 3 H), 3.30

(m, 2 H), 3.20–3.18 (m, 1 H), 3.14 (d, J = 6.8 Hz, 1 H), 3.09 (s, 4 H), 2.79 – 2.75 (m, 1 H); LRMS (APCI) calc. for $C_{29}H_{37}NO_{10}$ [M–S] 559.24, found 559.79; HPLC t_R = 15.56 min.

Hydroxyketone 30. Water (0.050 mL) and HCl (4.0 M in dioxane, 0.750 mL) were added sequentially to a solution of alcohol **11** (0.102 g, 0.220 mmol, 1.0 equiv) in THF (5 mL) at 23 °C to obtain a final acid concentration of 0.5 M. The resultant solution was stirred at 23 °C for 14 h. Upon completion, the reaction was poured into EtOAc (30 mL), washed with saturated aqueous $NaHCO_3$ (15 mL) and brine (15 mL), dried ($MgSO_4$), and concentrated. The resultant crude solid was purified by flash column chromatography (silica gel, hexanes/EtOAc, 3:2) to afford the desired hydroxyketone **30** (0.077 g, 84% yield) as a white solid.

Analog 31. Prepared from hydroxyketone **30** according to General Procedure D in 50% yield. **31:** R_f = 0.13 (silica gel, hexanes/EtOAc, 3:7); IR (film) ν_{max} 3126, 2951, 2838, 2360, 1828, 1728, 1634, 1519, 1436, 1298, 1169, 1064, 1024, 902, 869, 767 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.63 (s, 1 H), 7.34 (d, J = 15.8 Hz, 1 H), 7.11 (s, 1 H), 6.93 (s, 1 H), 6.88 (m, 2 H), 6.83 (m, 1 H), 6.80 (s, 1 H), 6.15 (d, J = 15.8 Hz, 1 H), 4.86 (d, J = 3.8 Hz, 1 H), 4.05 (m, 1 H), 3.99 (dd, J = 6.7, 1.6 Hz, 1 H), 3.92 (s, 3 H), 3.88 (s, 3 H), 3.79 (s, 3 H), 3.69 (s, 3 H), 3.53–3.48 (m, 2 H); LRMS (APCI) $C_{26}H_{26}N_2O_8S$ [M^+] 526.14, found 526.77.

Hydroxyketal 13. AcOH (0.3 mL) and tetramethylammonium triacetoxyborohydride (0.146 g, 0.555 mmol, 3.0 equiv) were added sequentially to a solution of hydroxyketone **30** (0.077 g, 0.185 mmol, 1.0 equiv) in MeCN (3 mL) at 0 °C. The resultant solution was then warmed to 23 °C, and the reaction contents were stirred at 23 °C for 3 h. A second portion of tetramethylammonium triacetoxyborohydride (0.097 g, 0.370 mmol, 2.0 equiv) was then added, and stirring was continued at 23 °C for 2 h. Upon completion, the reaction contents were diluted with EtOAc (30 mL), poured into water (20 mL), and extracted with EtOAc (3 × 20 mL). The combined organic layers were then washed with saturated aqueous $NaHCO_3$ (2 × 20 mL) and brine (20 mL), dried ($MgSO_4$), and concentrated. The resultant crude yellow solid was purified by flash column chromatography (silica gel, hexanes/EtOAc, 3:7) to afford the desired *anti*-disposed diol (0.066 g, 75% yield) as a white solid. With this step complete, Et_3N (0.110 mL, 0.789 mmol, 5.0 equiv) and TBSOTf (0.036 mL, 0.158 mmol, 1.0 equiv) were added sequentially to a solution of this newly formed *anti*-disposed diol (0.066 g, 0.158 mmol, 1.0 equiv) in CH_2Cl_2 (2 mL) at –78 °C. The reaction contents were then slowly warmed to 23 °C over 1 h with constant stirring. Upon completion, the reaction contents were diluted with EtOAc (30 mL), poured into water (20 mL), and extracted with EtOAc (3 × 20 mL). The combined organic layers were then washed with saturated aqueous $NaHCO_3$ (20 mL) and brine (20 mL), dried ($MgSO_4$), and concentrated to afford the desired monosilylated diol as a white solid which was used directly without any additional purification. With this operation complete, solid $NaHCO_3$ (0.132 g, 1.58 mmol, 10 equiv) and Dess–Martin periodinane (0.134 g, 0.315 mmol, 2.0 equiv) were added sequentially in single portions to a solution of this newly formed intermediate in CH_2Cl_2 (2 mL) at 23 °C. The

resultant suspension was stirred at 23 °C for 1 h. Upon completion, saturated aqueous Na_2SO_3 (2 mL) was added and the resultant biphasic mixture was stirred vigorously for 1 h to quench any remaining oxidizing agents. The reaction contents were then diluted with EtOAc (30 mL), poured into water (20 mL), and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (20 mL) and brine (20 mL), dried ($MgSO_4$), and concentrated. The crude product was purified by flash column chromatography (silica gel, hexanes/EtOAc, 7:3) to afford ketone **32** (0.079 g, 94% yield over 2 steps, 71% overall yield from **30**) as a light yellow solid. HCl (4.0 M in dioxane, 0.3 mL) was added to a solution of ketone **32** (0.027 g, 0.051 mmol, 1.0 equiv) in MeOH:$CH(OMe)_3$ (4:1, 2.5 mL) at 23 °C, and the resultant solution was stirred at 23 °C for 14 h. Upon completion, the reaction contents were concentrated directly and the resultant crude yellow solid was purified by flash column chromatography (silica gel, hexanes/EtOAc, 3:2) to afford hydroxyketal **13** (0.022 g, 93% yield) as a light yellow solid.

Analog 33. Prepared from hydroxyketal **13** according to General Procedure D in 58% yield. **33:** R_f = 0.21 (silica gel, hexanes/EtOAc, 3:7); IR (film) ν_{max} 2950, 2836, 2359, 2342, 1719, 1632, 1518, 1465, 1389, 1288, 1172, 1027, 993, 870, 810, 734, 688 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.21 (br, 1 H), 7.52 (br, 1 H), 7.44 (d, *J* = 15.9 Hz, 1 H), 6.99 (s, 1 H), 6.96 (m, 2 H), 6.89 (m, 1 H), 6.71 (d, *J* = 6.3 Hz, 1 H), 6.09 (d, *J* = 15.6 Hz, 1 H), 5.83 (d, *J* = 2.5 Hz, 1 H), 3.93 (s, 3 H), 3.90 (s, 3 H), 3.80 (s, 3 H), 3.64 (s, 3 H), 3.56 (dd, *J* = 6.4, 4.3 Hz, 1 H), 3.40 (dd, *J* = 6.4, 3.6, 1 H) 3.33 (s, 3 H), 3.25 (s, 3

H), 3.13–3.10 (m, 1 H); LRMS (APCI) calc. for $C_{28}H_{32}N_2O_9S$ [M^+] 572.18, found 572.66; HPLC t_R = 6.58 min.

Analog 35. Prepared from **8** according to General Procedures A (87% yield), C (95% yield), and D (27% yield). **35:** R_f = 0.55 (silica gel, hexanes/EtOAc, 1:2); IR (film) ν_{max} 3130, 2950, 2917, 2848, 1720, 1634, 1287, 12321195, 1117, 1025, 999 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.63 (s, 1 H), δ 7.41 (d, 16 Hz, 1H), 7.31 (s, 1H), 7.17 (t, *J* = 7.9 Hz, 2 H), 7.12 (s, 1 H), 7.00 (t, *J* = 7.2 Hz, 1 H), 6.83 (s, 1 H), 6.78 (d, *J* = 7.2 Hz, 1 H), 6.1 (d, *J* = 15.6 Hz, 1 H), 5.31 (d, *J* = 3.3 Hz, 1 H), 3.9 (m, 1 H), 3.86 (s, 1 H), 3.80 (s, 3 H), 3.78 (m, 1 H), 3.7 (s, 3 H), 3.45 (s, 3 H), 3.12 (s, 3 H); HPLC t_R = 9.76 min.

Diels–Alder Adducts 37, 38 and 39. Prepared according to General Procedure B in 66%, 76% and 43% yield, respectively.

Analogs 40 and 41. Prepared from **38** according to General Procedures C (76% yield), and D (40% yield) as 1.2:1 mixture of diastereomers that were separated by preparative TLC. **40:** R_f = 0.25 (silica gel, hexanes/EtOAc, 3:7); ^1H-NMR (300 MHz, $CDCl_3$) δ 8.38 (s, 1 H), 7.68 (s, 1 H), 7.05 (s, 1 H), 5.75 (d, *J* = 6.6 Hz, 1 H), 5.23 (d, *J* = 3.3 Hz, 1 H), 3.67 (s, 3 H), 3.63 (s, 3 H), 3.27 (s, 3 H), 3.25 (s, 1 H), 3.16 (s, 1 H), 3.05 (s, 3 H), 2.90 (m, 1 H), 2.82 (s, 1 H), 2.54 (s, 1 H), 2.49 (s, 3 H), 2.15 (m, 1 H).

41: R_f = 0.25 (silica gel, hexanes/EtOAc, 3:7); ^1H-NMR (300 MHz, $CDCl_3$) δ 8.30 (s, 1 H), 7.62 (s, 1 H), 7.03 (s, 1 H), 5.68 (d, *J* = 5.7 Hz, 1 H), 5.46 (d, *J* = 2.7 Hz, 1

H), 3.68 (s, 3 H), 3.63 (s, 3 H), 3.30 (s, 1 H), 3.25 (s, 3 H), 3.20 (s, 3 H), 2.84 (m, 1 H), 2.53 (s, 3 H), 2.09 (t, J = 12.6 Hz, 1 H), 1.58 (s, 4 H), 1.54–1.48 (m, 1 H).

Analogs 42 and 43. Prepared from **39** according to General Procedures C (77% yield) and D (49% yield) as 1.3:1 mixture of diastereomers that were separated by preparative TLC. **42:** R_f = 0.28 (silica gel, hexanes/EtOAc, 3:7); IR (film) ν_{max} 2957, 2850, 2361, 2239, 1737, 1553, 1467, 1391, 1287, 1230, 1119, 1048, 998, 802 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.36 (s, 1 H), 7.65 (s, 1 H), 7.06 (s, 1 H), 5.92 (d, J = 6.4 Hz, 1 H), 5.24 (d, J = 3.2 Hz, 1 H), 3.70 (s, 3 H), 3.26 (s, 3 H), 3.05 (s, 3 H), 3.01 (m, 1 H), 2.89 (s, 1 H), 2.55 (s, 3 H), 2.33 (t, J = 10.4 Hz, 1 H), 1.56 – 1.51 (m, 1 H), 1.26 (m, 1.6 H); LRMS (APCI) calc. for $C_{19}H_{24}N_3O_5S$ [M+H^+] 406.47, found 406.02; HPLC t_R = 5.86 min.

43: R_f = 0.28 (silica gel, hexanes/EtOAc, 3:7); IR (film) ν_{max} 2952, 2849, 2359, 2239, 1734, 1653, 1559, 1437, 1393, 1289, 1172, 1048, 672 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.29 (s, 1 H), 7.60 (s, 1 H), 7.03 (s, 1 H), 5.85 (d, J = 6.0 Hz, 1 H), 5.39 (d, J = 3.2 Hz, 1 H), 3.71 (s, 3 H), 3.24 (s, 3 H), 3.18 (s, 3 H), 2.93 (m, 2 H), 2.59 (m, 4 H), 2.31 (t, J = 3.2 Hz, 1 H), 1.45–1.40 (m, 1 H), 1.26 (m, 1 H); LRMS (APCI) calc. for $C_{19}H_{24}N_3O_5S$ [M+H^+] 406.47, found 406.02; HPLC t_R = 5.41 min.

Carboxylic Acid 44. A mixture of $NaClO_2$ (0.145 g, 1.61 mmol, 5.0 equiv) and NaH_2PO_4 (0.251 g, 1.61 mmol, 5.0 equiv) in water (1.0 mL) was added to a solution of aldehyde **37** (0.095 g, 0.321 mmol, 1.0 equiv) in DMSO (6.0 mL). The resulting mixture was stirred at 23 °C for 30 min. Upon completion, the reaction was quenched with 1 M

HCl (2 mL), diluted with water (10 mL), and extracted with Et_2O (3×10 mL). The combined organic layer was washed once with water (10 mL), dried ($MgSO_4$), and concentrated to yield **44** (0.100 g, 99% yield).

General Procedure G for Ester Formation (45–47). To a solution of carboxylic acid **44** (1.0 equiv) and alcohol (2.0 equiv) in CH_2Cl_2 (0.3 M in carboxylic acid), diisopropylethylamine (4.0 equiv), EDC•HCl (2.0 equiv) and 4-DMAP (1.0 equiv) were added sequentially in single portions. The resulting mixture was stirred at 23 °C for 4 h. Upon completion, the reaction was quenched with saturated aqueous $NaHCO_3$, diluted with water, and extracted with EtOAc (3×). The combined organic layer was washed with brine, dried ($MgSO_4$), concentrated, and purified by flash column chromatography (silica gel, hexanes/EtOAc, 6:1) to give the desired ester product (**45**–**47**).

Analog 45. Prepared from carboxylic acid **44** according to General Procedures G (63% yield), C (98% yield), and D (58% yield). **45:** R_f = 0.13 (silica gel, hexanes/EtOAc, 1:2); IR (film) ν_{max} 2952, 2360, 2342, 1736, 1466, 1388, 1328, 1286, 1232 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.41 (s, 1 H), 7.71 (s, 1 H), 7.08 (s, 1 H), 5.92 (m, 1 H), 5.78 (d, *J* = 6.4 Hz, 1 H), 5.26 (m, 3 H), 4.56 (m, 2 H), 3.71 (s, 3 H), 3.36 (m, 1 H), 3.11 (s, 3 H), 2.95 (m, 1 H), 2.86 (s, 1 H), 2.5 (s, 3 H), 2.17 (m, 1 H), 1.68 (m, 1 H); LRMS (APCI) calc. for $C_{22}H_{29}N_2O_7S$ [$M+H^+$] 465.18, found 464.80.

Analog 46. Prepared from carboxylic acid **44** according to General Procedures G (52% yield), C (83% yield), and D (43% yield). **46:** R_f = 0.69 (silica gel, hexanes/EtOAc,

1:2); IR (film) ν_{max} 2956, 2360, 2342, 1736, 1466, 1388, 1287, 1232 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.33 (s, 1 H), 7.64 (s, 1 H), 7.06 (s, 1 H), 7.51 (d, *J* = 6.0 Hz, 1 H), 5.51 (d, *J* = 3.2 Hz, 1 H), 4.07 (m, 2 H), 3.72 (s, 3 H), 3.55 (t, 3 H), 3.30 (m, 1 H), 3.29 (s, 3 H), 3.20 (s, 1 H), 2.89 (s, 1 H), 2.83 (m, 1 H), 2.56 (s, 4 H), 2.12 (m, 2 H), 1.60 (m, 3 H), 1.41 (m, 4 H).

Analog 47. Prepared from carboxylic acid **44** according to General Procedures G (63% yield), C (89% yield), and D (38% yield). **47:** R_f = 0.64 (silica gel, hexanes/EtOAc, 1:2); IR (film) ν_{max} 3583, 3117, 2951, 2917, 2835, 2359, 2342, 1732, 1388, 1286, 1230, 1108 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.33 (s, 1 H), 7.65 (s, 1 H), 7.05 (s, 1 H), 5.71 (d, *J* = 6.4 Hz, 1 H), 5.51 (d, 2.8 Hz), 5.00 (s, *J* = 4.3 Hz, 1 H), 3.72 (s, 3 H), 3.37 (m, 5 H), 3.20 (s, 3 H), 2.89 (s, 1 H), 2.80 (m, 1 H), 2.52 (s, 4 H), 2.11 (m, 1 H), 1.54 (m, 1 H), 1.29 (s, 1H), 1.23 (t, *J* = 5.8 Hz, 6 H); LRMS (APCI) calc. for $C_{22}H_{31}N_2O_7S$ $[M+H^+]$ 467.20, found 466.84.

General Procedure H for Amide Formation (48 and 49). To a solution of carboxylic acid **44** (1.0 equiv) in CH_2Cl_2 (0.3 M), EDC•HCl (2.0 equiv) and 4-DMAP (catalytic) were added sequentially, and the solution was stirred at 23 °C for 5 min before the addition of the desired amine (4.0 eq). The resulting mixture was stirred at 23 °C for an additional 6 h. Upon completion, the reaction was quenched with saturated aqueous $NaHCO_3$, diluted with water, and extracted with EtOAc (3×). The combined organic layers were washed once with brine, dried ($MgSO_4$), concentrated, and purified by flash column chromatography (silica gel, hexanes/EtOAc, 6:1).

Analog 48. Prepared from carboxylic acid **44** according to General Procedures H (37% yield), C (68% yield), and D (36% yield). **48:** R_f = 0.16 (silica gel, hexanes/EtOAc, 1:2); IR (film) ν_{max} 3729, 3584, 2917, 2849, 2360, 23242, 1738, 1641, 1463, 1388, 1286 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.34 (s, 1 H), 7.65 (s, 1 H), 7.06 (s, 1 H), 5.76 (d, 5.6 Hz, 1 H), 4.45 (d, 3.2 Hz, 1 H), 3.71 (s, 3 H), 3.41 (m, 3 H), 3.33 (s, 3 H), 3.21 (s, 3 H), 2.91 (s, 2 H), 2.59 (s, 4 H), 2.05 (m, 2 H) 1.49 (m, 2 H), 1.46 (m, 4 H); LRMS (APCI) calc. for $C_{23}H_{34}N_3O_6S$ $[M+H^+]$ 480.2, found 480.1.

Analog 49. Prepared from carboxylic acid **44** according to General Procedures H (43% yield), C (81% yield), and D (47% yield). **49:** R_f = 0.13 (silica gel, hexanes/EtOAc, 1:2); IR (film) ν_{max} 3584, 2917, 2360, 1736, 1645, 1388, 1329, 1287, 1231, 1113 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.34 (s, 1 H), 7.64 (s, 1 H), 7.06 (s, 1 H), 5.78 (d, *J* = 6.0 Hz, 1 H), 5.43 (d, *J* = 3.2 Hz, 1 H), 3.68 (m, 8 H), 3.57 (s, 4 H), 3.30 (s, 3 H), 3.20 (m, 4 H), 2.92 (t, *J* = 8.3 Hz, 1 H), 2.58 (s, 4 H), 2.06 (m, 2 H), 1.50 (m, 2 H), 1.49 (s, 5 H); LRMS (APCI) calc. for $C_{23}H_{32}N_3O_7S$ $[M+H^+]$ 494.21, found 494.07; HPLC t_R = 4.30 min.

Analog 55. Prepared as a 1:1 mixture of diastereomers with respect to the bicyclo[2.2.2]octene core from dimer **50** and dienophile **51** according to General Procedures A, C (20% yield over 2 steps), and D (59% yield). **55:** IR (film) ν_{max} 2954, 2836, 1744, 1720, 1632, 1517, 1464, 1391, 1230, 1026, 807, 734 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.69 (d, *J* = 7.4 Hz, 1 H), 7.39 (d, *J* = 3.9 Hz, 0.5 H), 7.34 (d, *J* = 3.9 Hz, 0.5 H), 6.68 (m, 11.5 H), 6.222 (d, *J* = 15.9 Hz, 0.5 H), 5.90 (d, *J* = 15.6 Hz, 0.5 H), 5.22

(m, 1.5 H), 5.13 (dd, *J* = 9.0 Hz, 4.5 Hz, 0.5 H), 3.88 (m, 2 H), 3.80 (m, 2 H), 3.74 (m, 8 H), 3.69 (s, 2 H), 3.66 (s, 1.5 H), 3.38 (s, 1 H), 3.32 (s, 2 H), 3.17 (m, 2.5 H), 3.11 (s, 2 H), 3.07 (s, 2 H), 3.00 (m, 1 H); LRMS (APCI) calc. for $C_{50}H_{57}N_2O_{17}S$ [M+H$^+$] 989.35, found 989.51; HPLC t_R = 10.75 min.

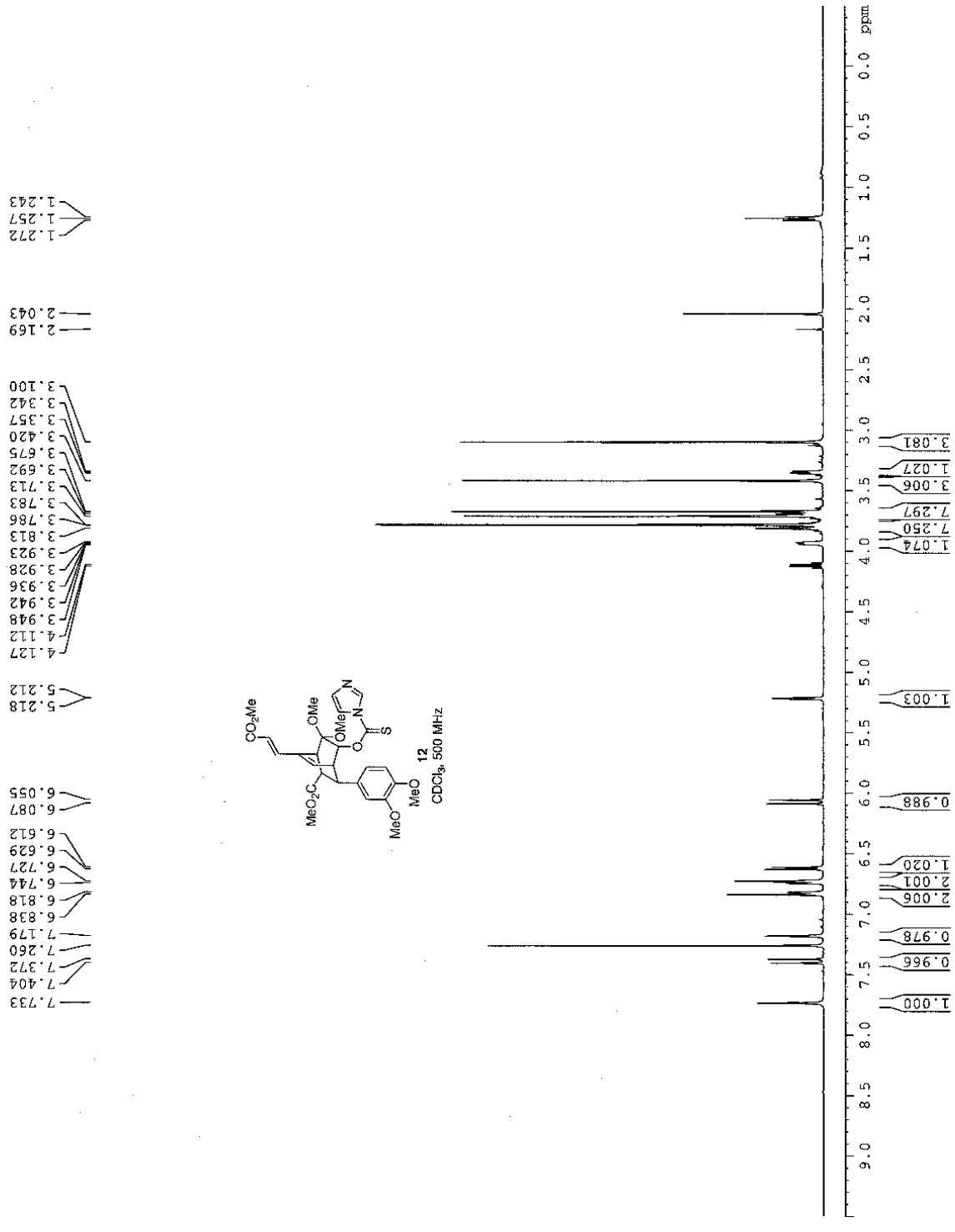
Analog 56. Prepared as a 1:1 mixture of diastereomers with respect to the bicyclo[2.2.2]octene core from dimer **50** and dienophile **9** according to General Procedures A (36% yield), C (65% yield), and D (64% yield). **56:** IR (film) ν_{max} 3000, 2953, 2836, 1735, 1720, 1632, 1518, 1465, 1332, 1233, 1159, 1027, 939, 830, 734, 700 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (s, 1 H), 7.74 (s, 0.5 H), 7.38 (s, 0.5 H), 7.20 (d, *J* = 0.9 Hz, 1 H), 6.81 (m, 7 H), 6.63 (d, *J* = 8.4 Hz), 6.12 (d, *J* = 3 Hz, 0.5 H), 6.07 (d, *J* = 3 Hz, 0.5 H), 5.34 (m, 1 H), 5.22 (d, *J* = 3.3 Hz), 3.95 (m, 1.5 H), 3.90 (m, 6.5 H), 3.81 (br s, 4 H), 3.77 (s, 2 H), 3.75 (s, 2 H), 3.73 (s, 3 H), 3.68 (s, 2 H), 3.63 (br s, 1.5 H), 3.44 (s, 3 H), 3.36 (m, 1 H), 3.19 (m, 2 H), 3.10 (s, 3 H). LRMS (APCI) calc. for $C_{39}H_{45}N_2O_{13}S$ [M+H$^+$] 781.28, found 781.29; HPLC t_R = 8.42 min.

Analog 57. Prepared as a 1:1 mixture of diastereomers with respect to the bicyclo[2.2.2]octene core from dimer **8** and dienophile **51** according to General Procedures A (12% yield), C (18% yield), and D (57% yield). **56:** IR (film) ν_{max} 2951, 2836, 1743, 1720, 1633, 1518, 1465, 1312, 1233, 1172, 1026, 998, 951, 802 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.4 Hz,1 H), 7.38 (d, *J* = 5.7 Hz, 0.5 H), 7.33 (d, *J* = 5.7 Hz, 0.5 H), 7.14 (d, *J* = 1.2 Hz, 1 H), 6.71 (m, 8 H), 6.18 (d, *J* = 15.6 Hz, 0.5 H), 5.76 (d, *J* = 15.6 Hz, 0.5 H), 5.23 (br s, 1.5 H), 5.12 (dd, *J* = 9.1 Hz, 4.3 Hz, 0.5 H), 4.00

(m, 1 H), 3.86 (m, 5 H), 3.82 (s, 3 H), 3.79 (m, 5 H), 3.74 (m, 6 H), 3.37 (br s, 1.5 H), 3.32 (br s, 2 H), 3.12 (s, 2 H), 3.08 (s, 2 H), 3.02 (s, 1 H). LRMS (APCI) calc. for $C_{39}H_{45}N_2O_{13}S$ [M+H$^+$] 781.28, found 781.07; HPLC t_R = 8.73 min.

Cell culture and transfection.[1] A PC12 model of Huntington's disease for screening was used. PC12 cells transfected with pBWN, an ecdysone-responsive expression vector containing DNA inserts encoding Exon 1 of human huntingtin (including a proline-rich segment and either 25 or 103 mixed CAG and CAA repeats, EGFP and a neomycin-resistance gene) were propagated (37 °C, 9.5% CO_2) in complete medium: DMEM high-glucose, 25 mM HEPES (Mediatech no. 15-018-CV), 10% (v/v) Cosmic calf serum (HyClone no. SH30087.03), penicillin and streptomycin, 2 mM glutamine and 500 μg•ml^{-1} active geneticin (G418). For transgene expression, tebufenozide was added to the above medium (200 nM final concentration from 1 mM stock in 85% ethanol). Q103 cells were observed to accumulate perinuclear inclusion bodies (protein aggregation) and undergo apoptosis. At 48 h post-induction, cell viability was quantified using the fluorescent indicator Alamar blue. Compounds that showed maximum cell viabilities higher than the negative control (pure dimethylsulfoxide, DMSO) were considered to be active, and concentrations at which they produce 50% (EC_{50}) and 100% (EC_{100}) of their maximum viability were calculated.

[1] B. G. Hoffstrom, A. Kaplan, R. Letso, R. S. Schmid, G. J. Turmel, Donald C. Lo, B. R. Stockwell, *Nature Chem. Bio.* **2010**, *6*, 900–906.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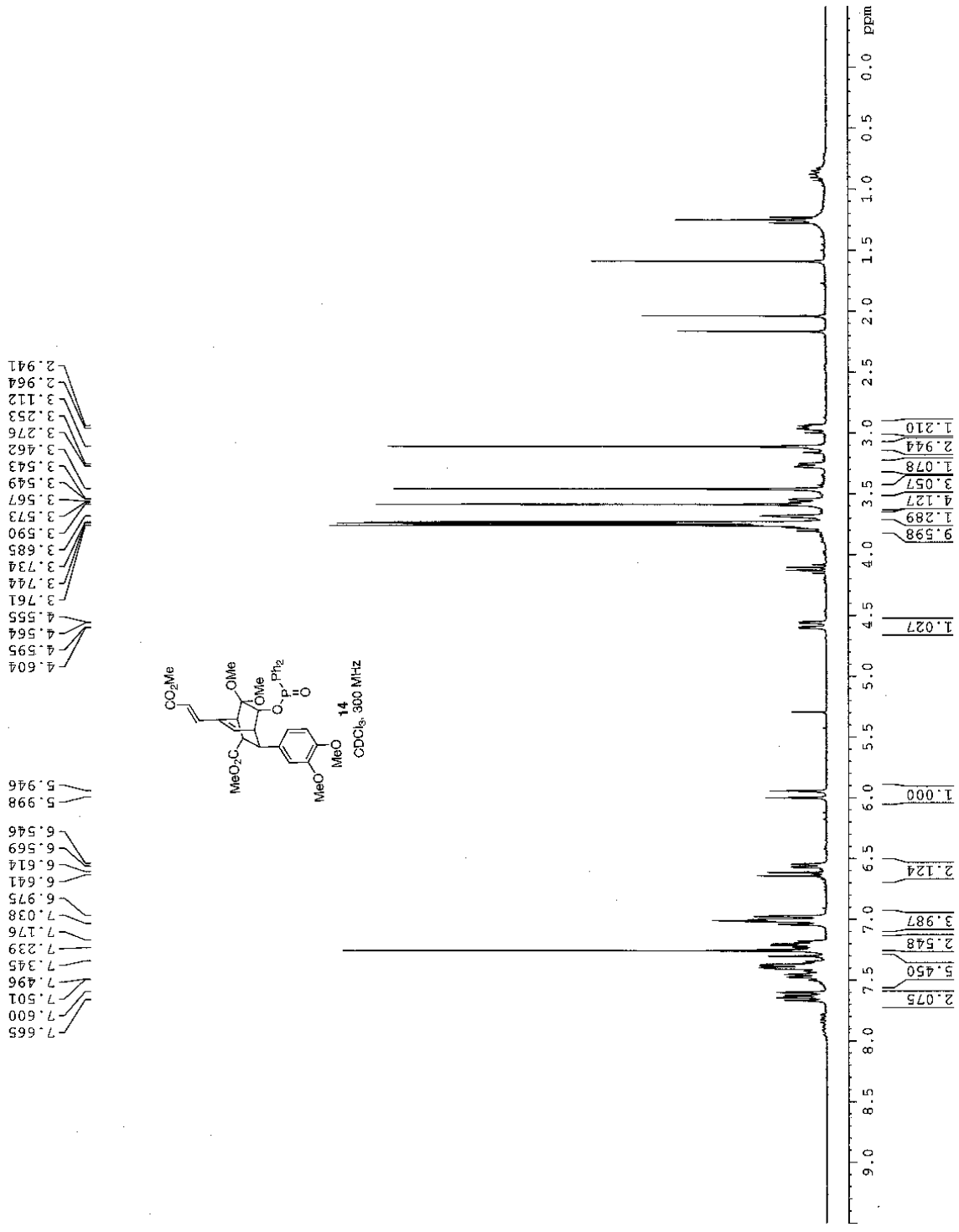
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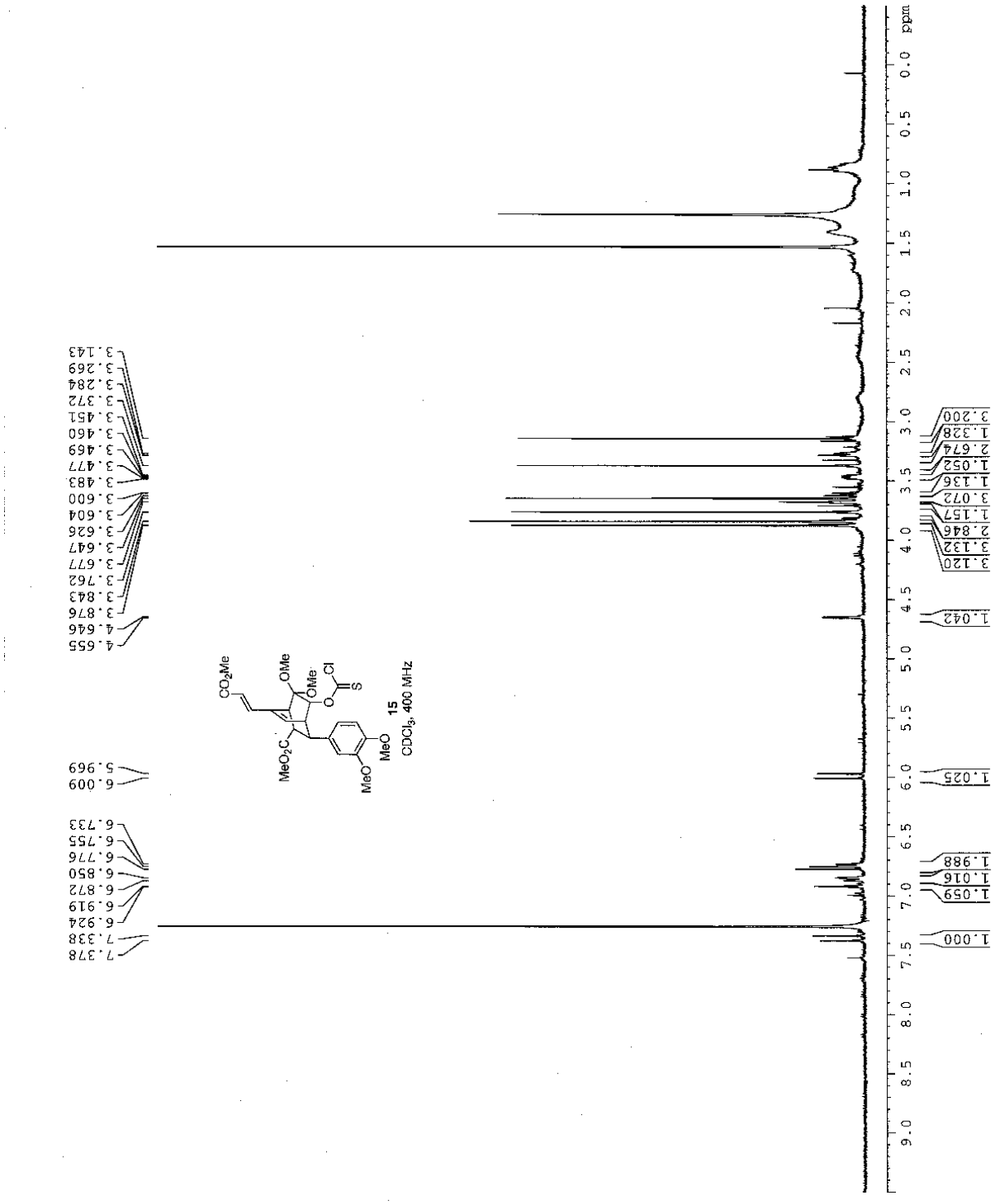
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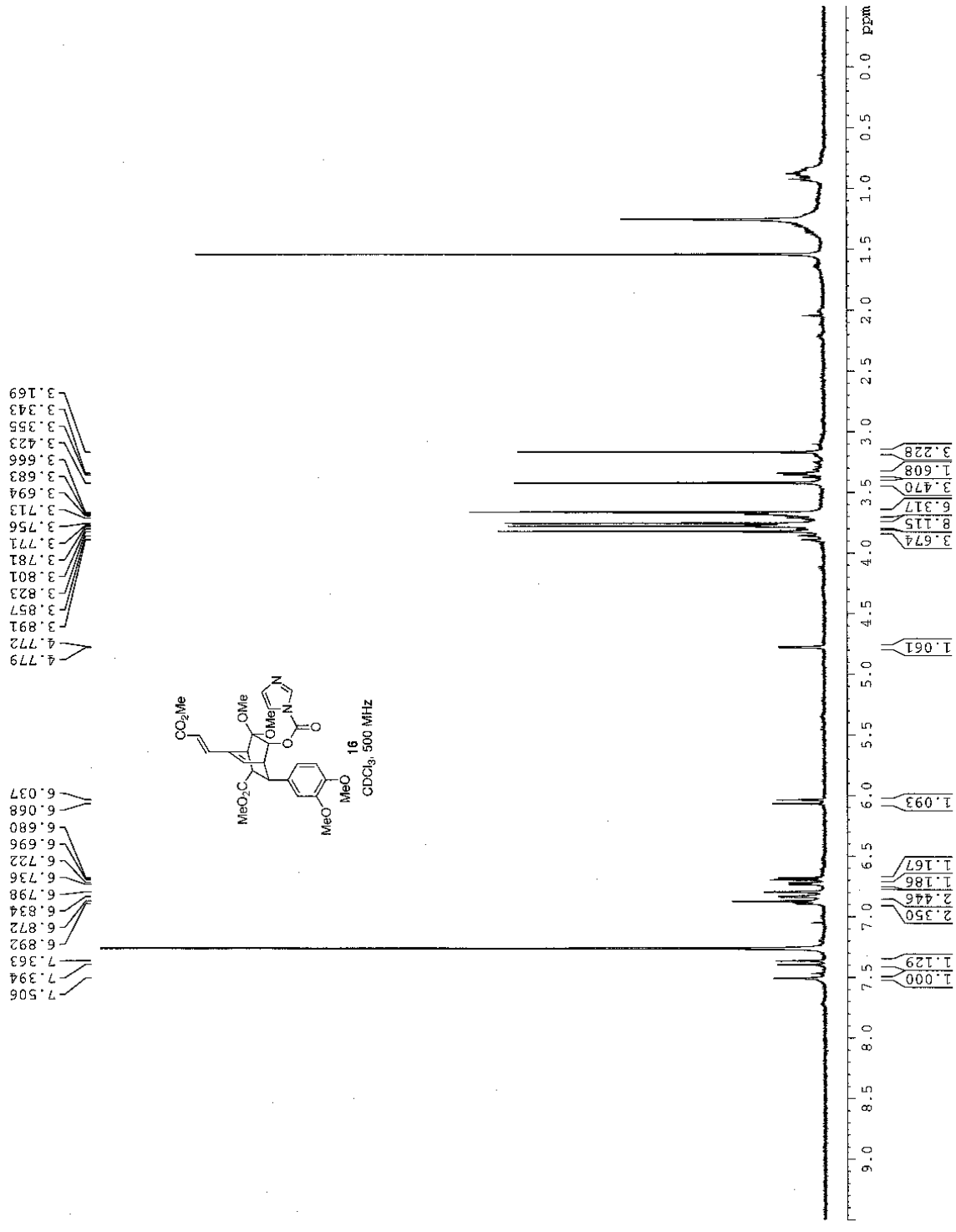
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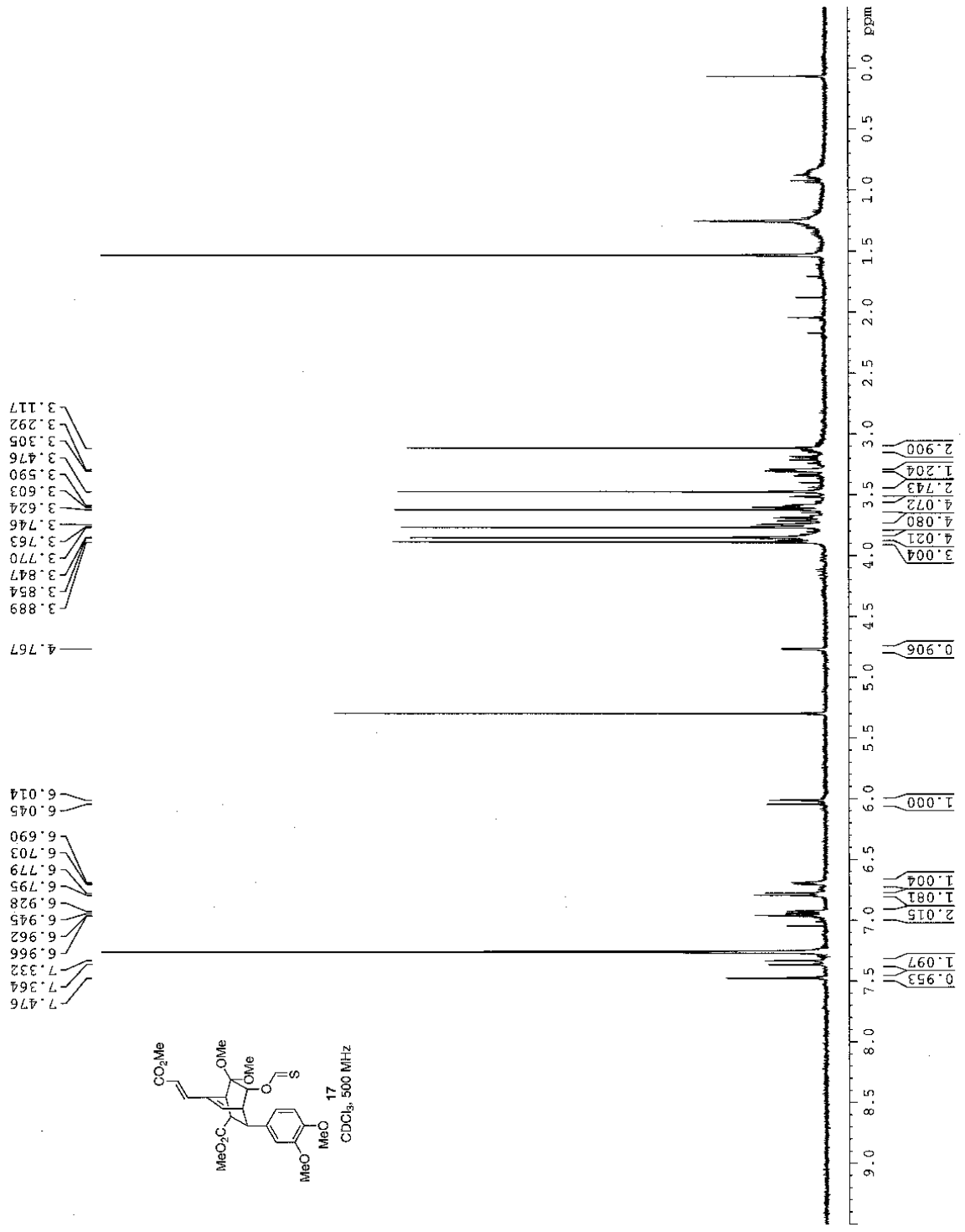
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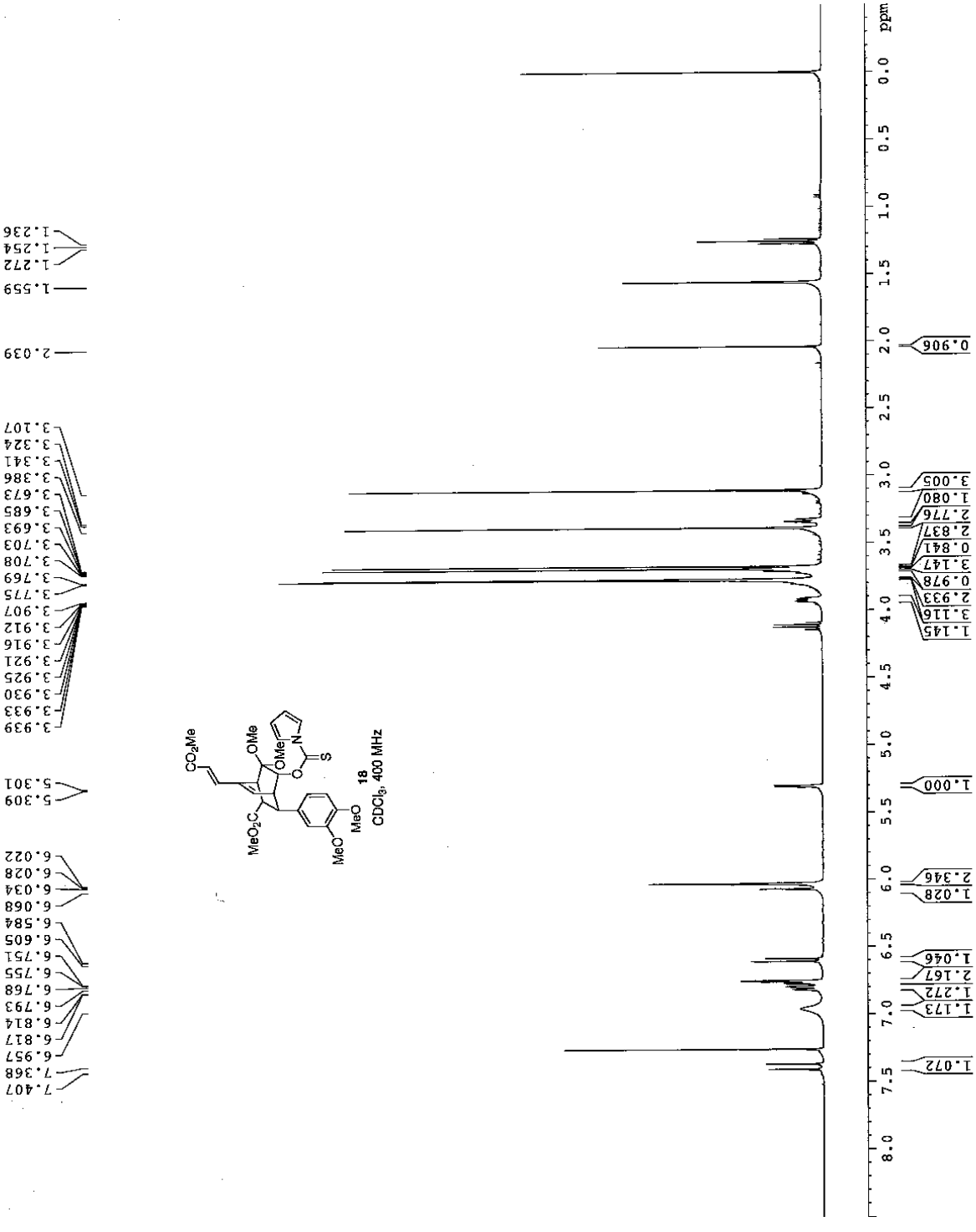
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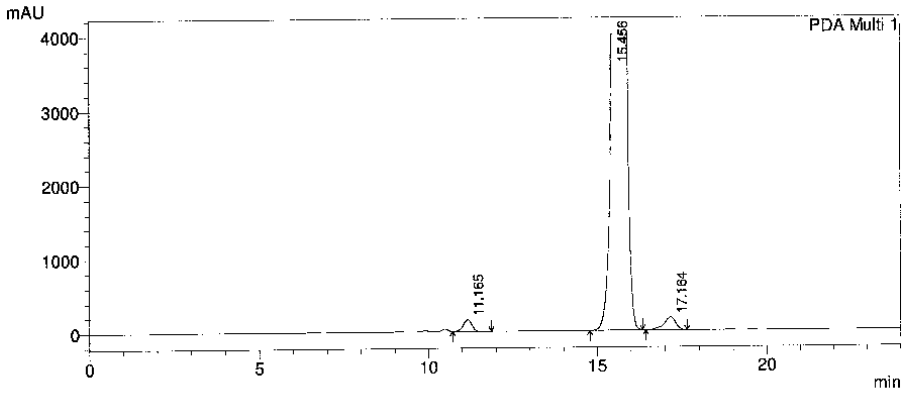

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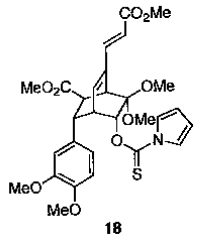

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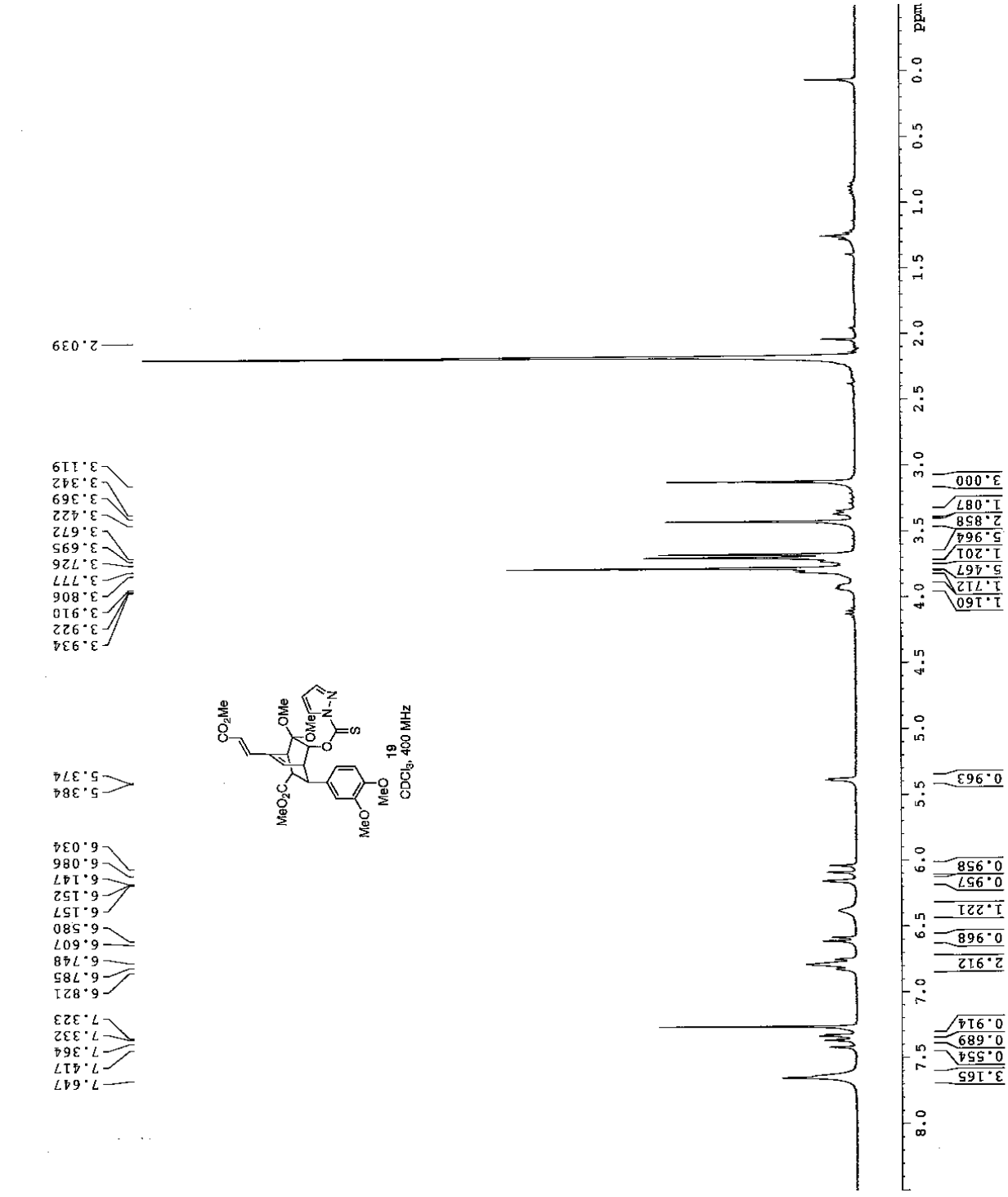
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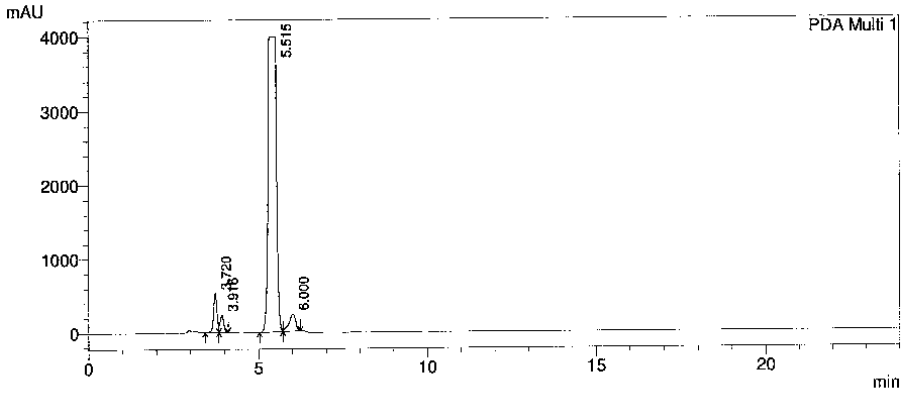

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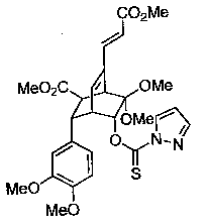

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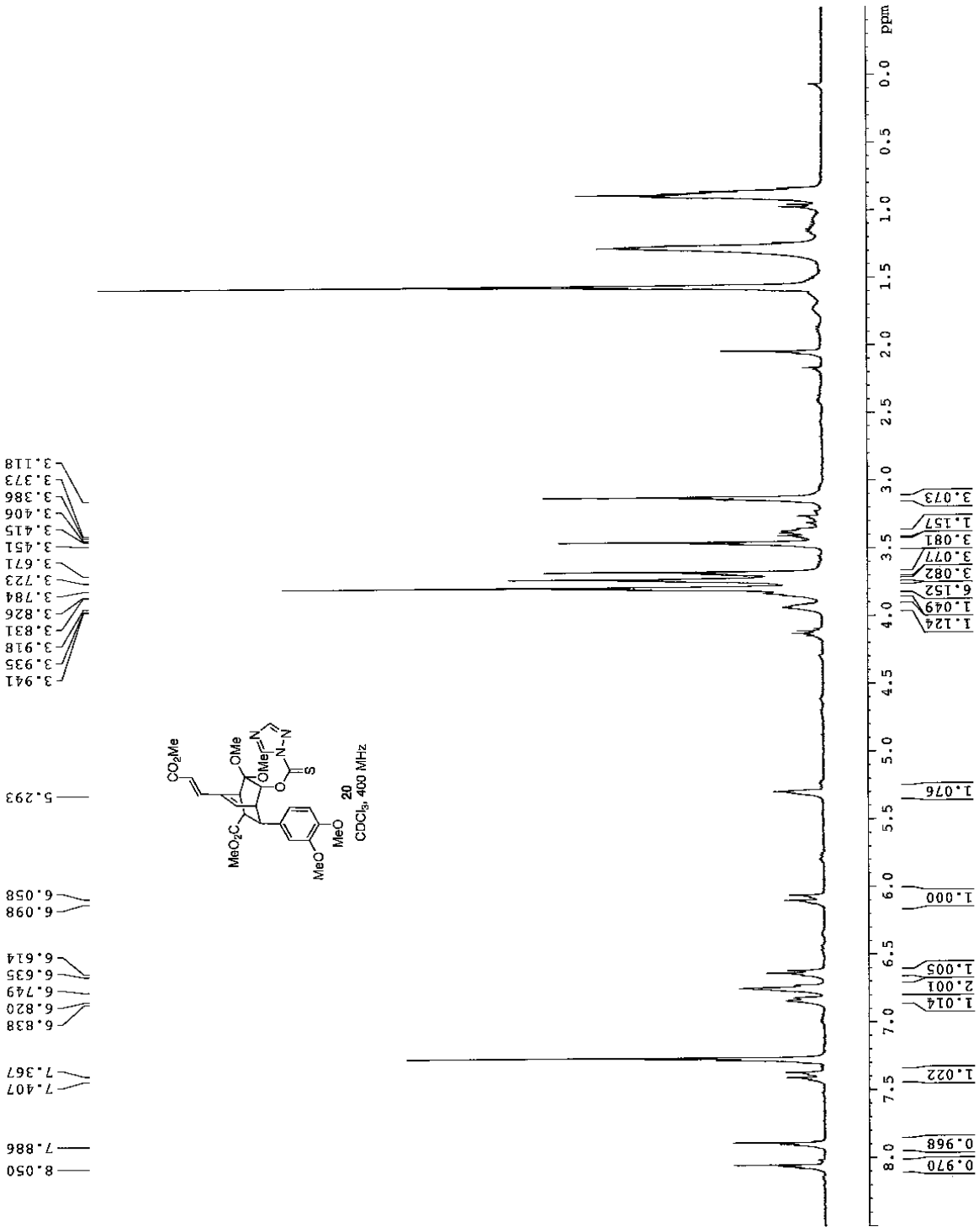
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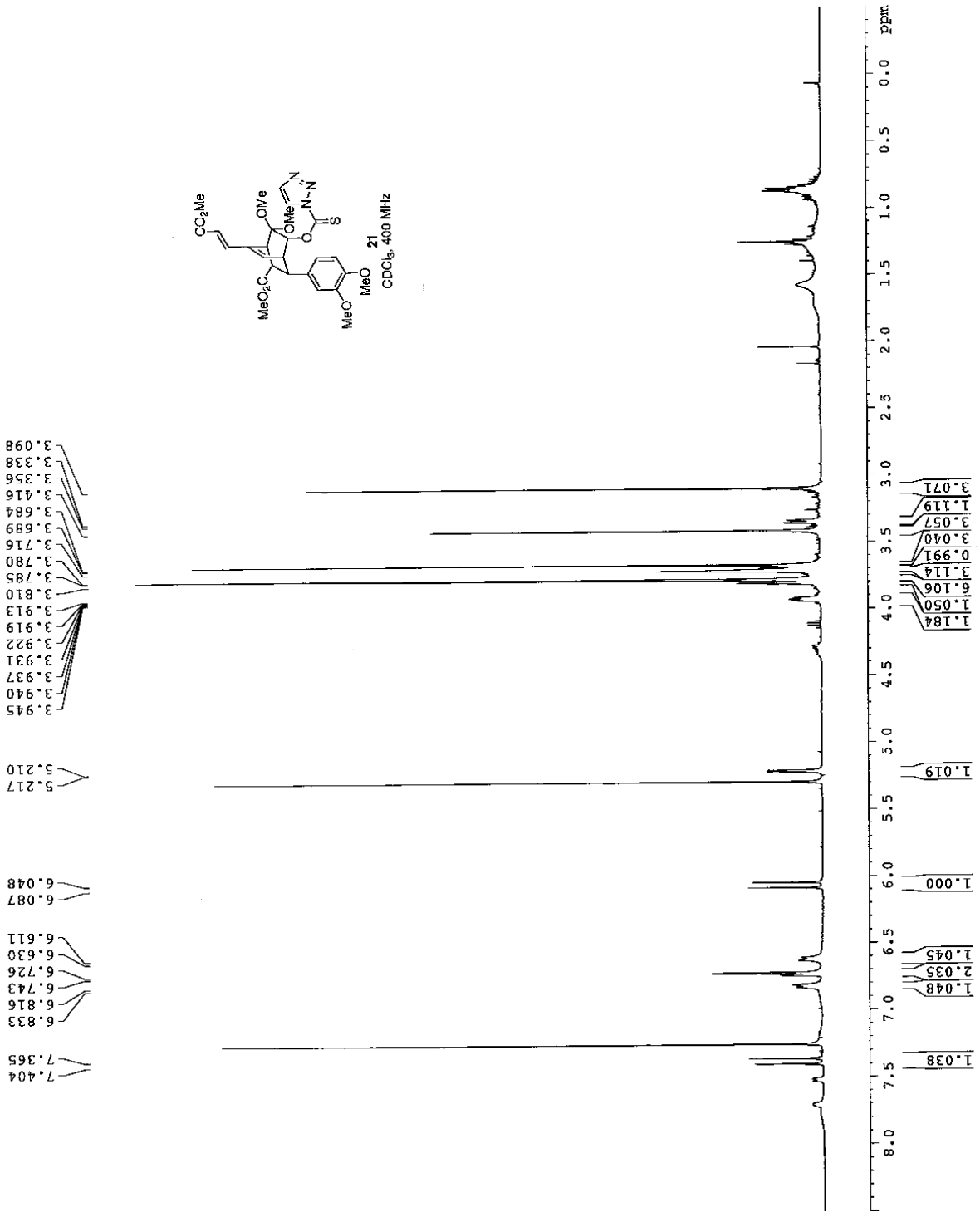
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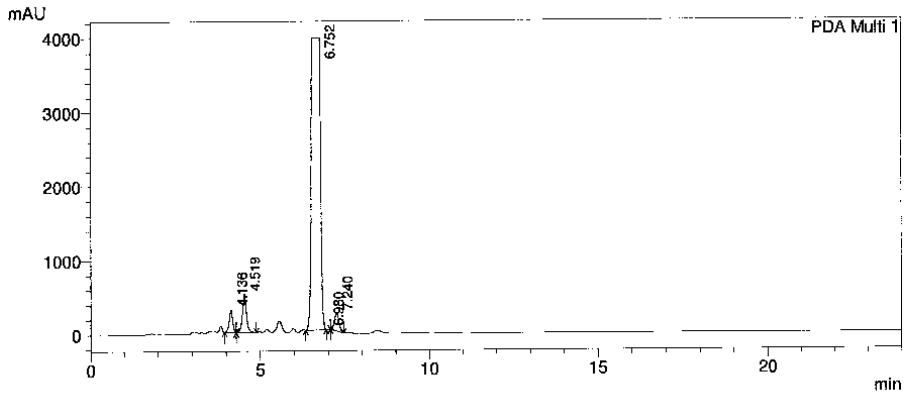

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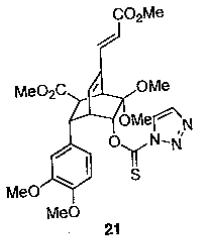

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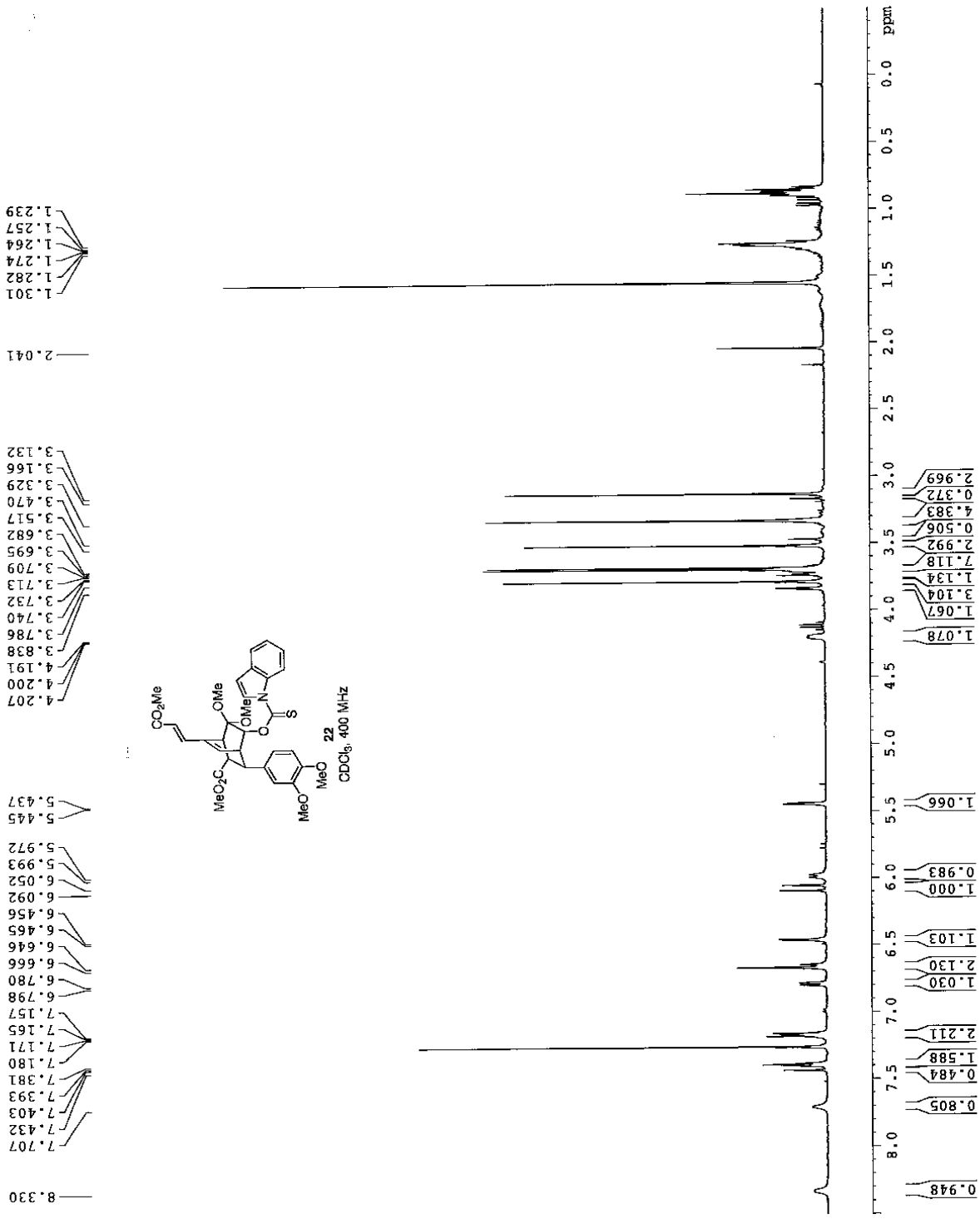
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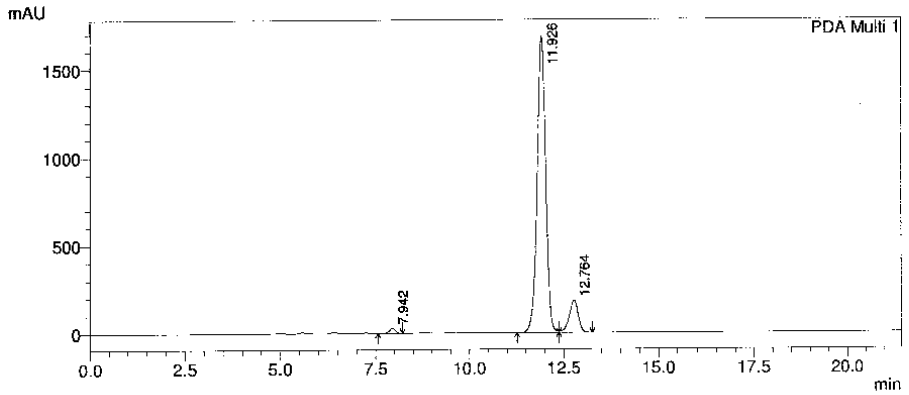

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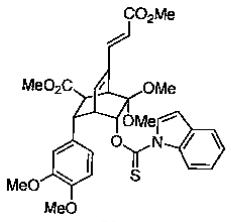

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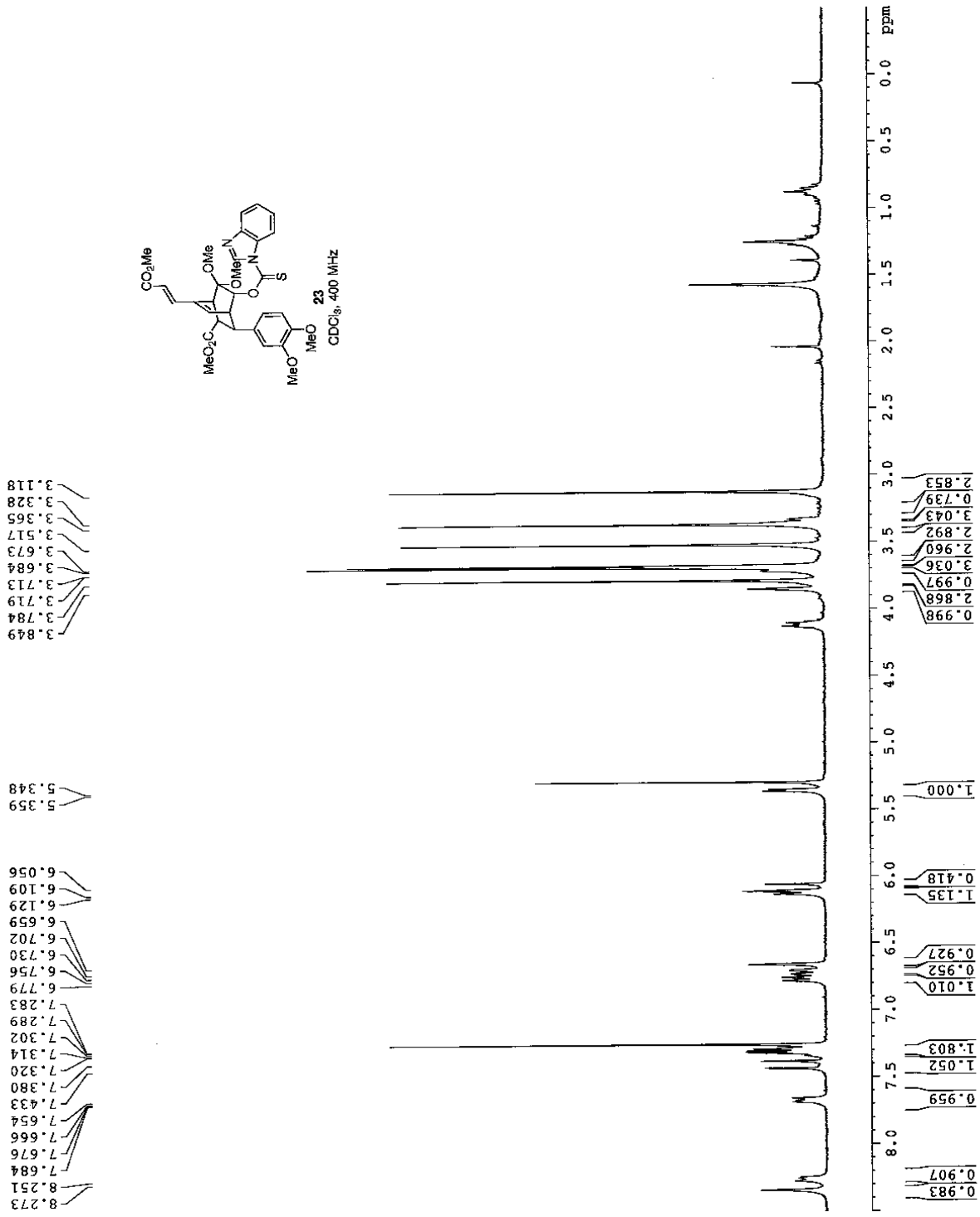
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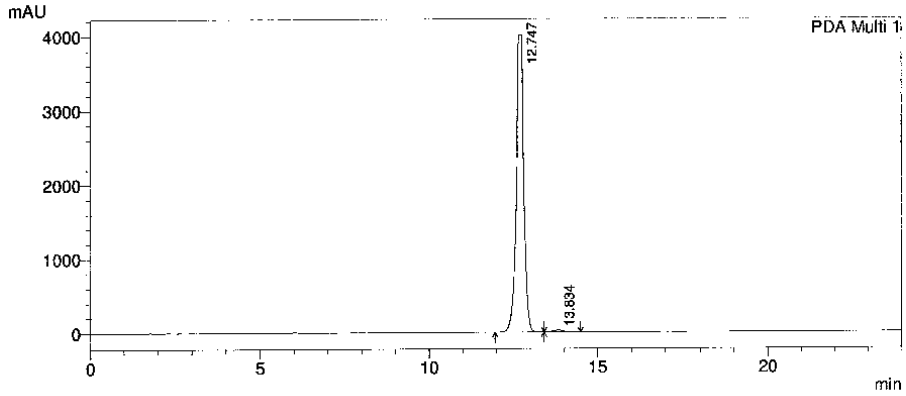

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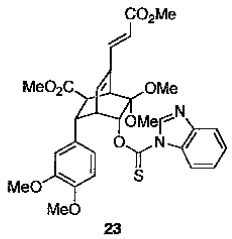
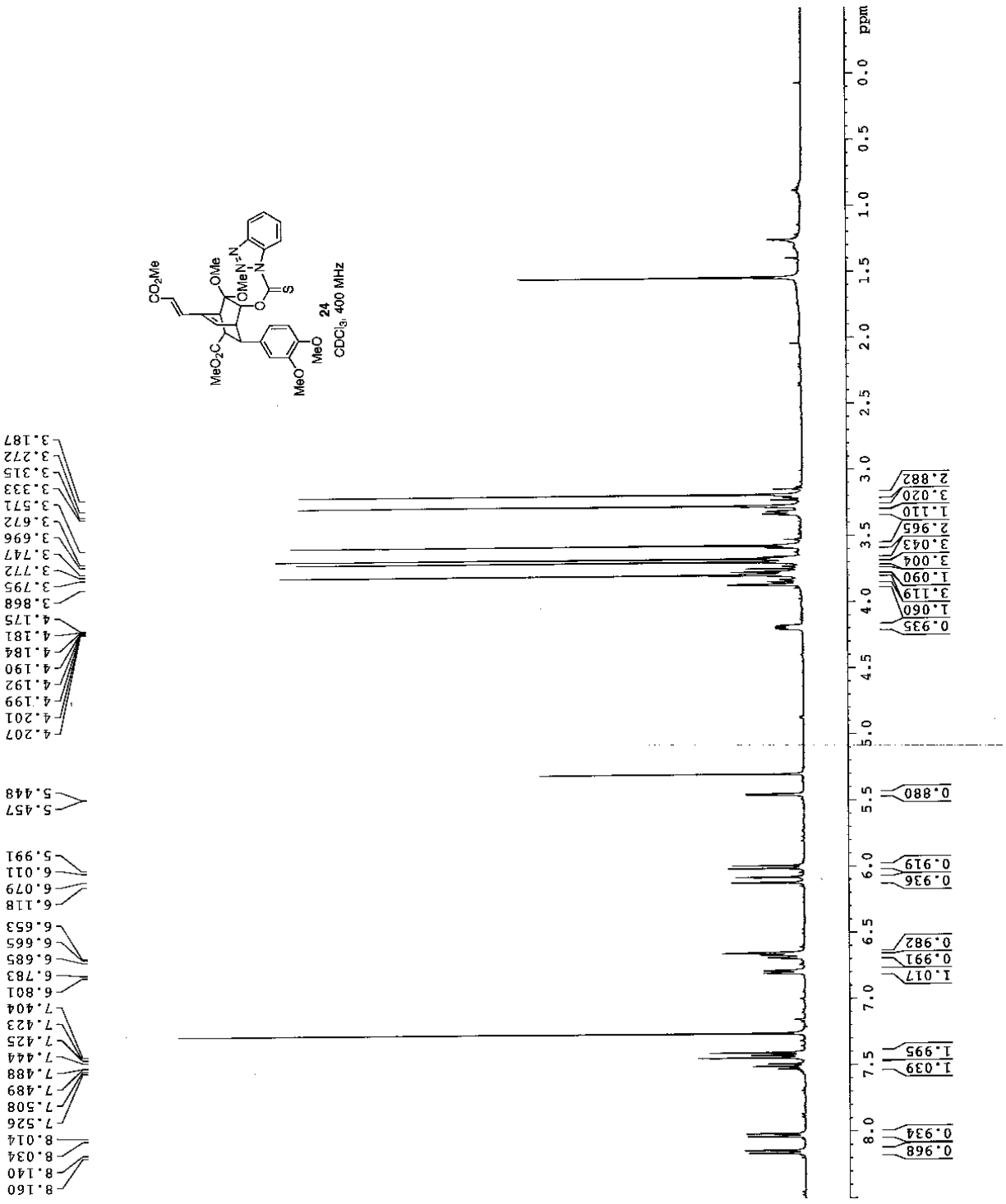
Peak#	Ret. Time	Area	Height	Area %	Height %
1	12.747	62829014	4000560	99.216	99.340
2	13.834	496556	26569	0.784	0.660
Total		63325570	4027129	100.000	100.000

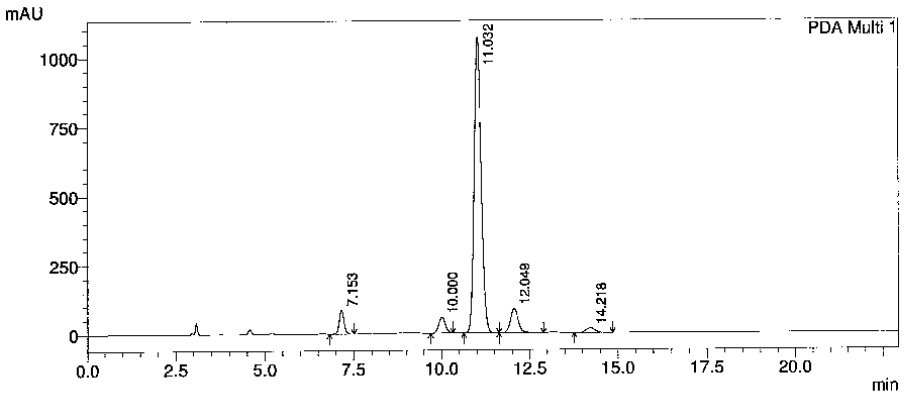


23


CO2Me
OMe
OMe
N
N
S
O
MeO2C
MeO
MeO
24
CDCl3, 400 MHz
ppm

2/21/2011 15:31:39 1 / 1

<Chromatogram>

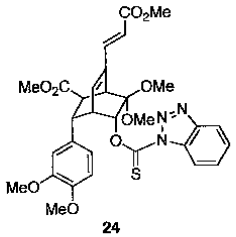


1 PDA Multi 1/270nm 4nm

PeakTable

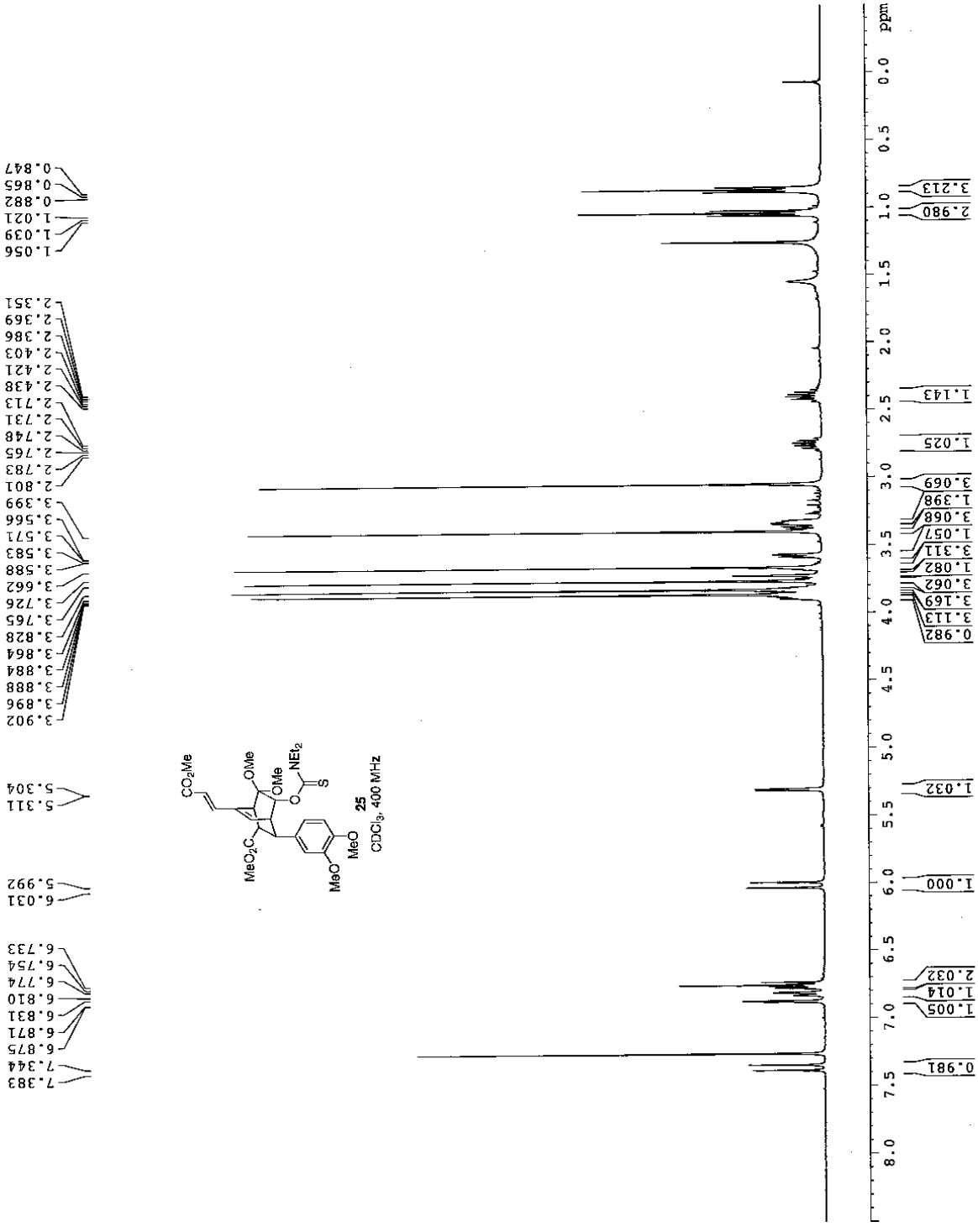
PDA Ch1 270nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	7.153	795348	87157	4.424	6.592
2	10.000	734461	57852	4.086	4.376
3	11.032	14738252	1070646	81.986	80.983
4	12.049	1389624	89082	7.730	6.738
5	14.218	318862	17321	1.774	1.310
Total		17976546	1322058	100.000	100.000



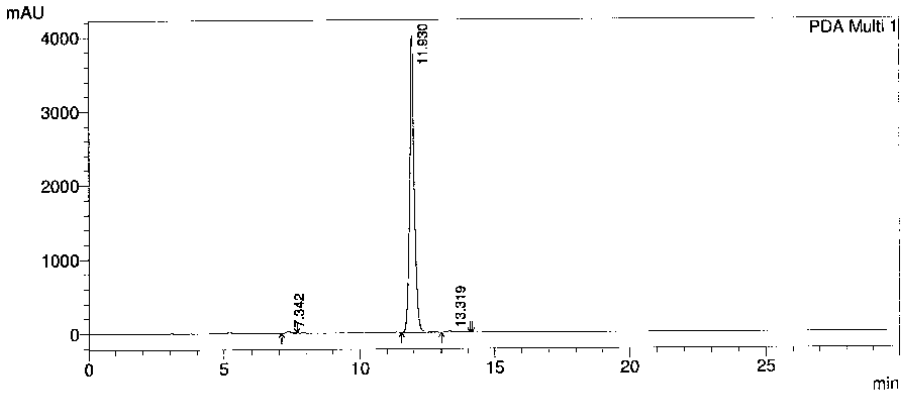
24

C:\LabSolutions\Data\matt\Lead\2as14.lcd


CO2Me
OMe
OMe
NEt2
O
S
MeO2C
MeO
MeO
25
CDCl3, 400 MHz
ppm
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
0.847
0.865
0.882
1.021
1.039
1.056
2.351
2.369
2.386
2.403
2.421
2.438
2.713
2.731
2.748
2.765
2.783
2.801
3.399
3.566
3.571
3.583
3.588
3.662
3.726
3.765
3.828
3.864
3.884
3.888
3.896
3.902
5.304
5.311
5.992
6.031
6.733
6.754
6.774
6.810
6.831
6.871
6.875
7.344
7.383
0.981
1.005
1.014
2.032
1.000
1.032
0.982
3.113
3.169
3.062
1.082
3.311
1.057
3.068
1.398
3.069
1.025
1.143
2.980
3.213

2/21/2011 15:34:28 1 / 1

<Chromatogram>

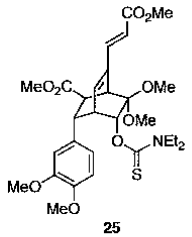


1 PDA Multi 1/270nm 4nm

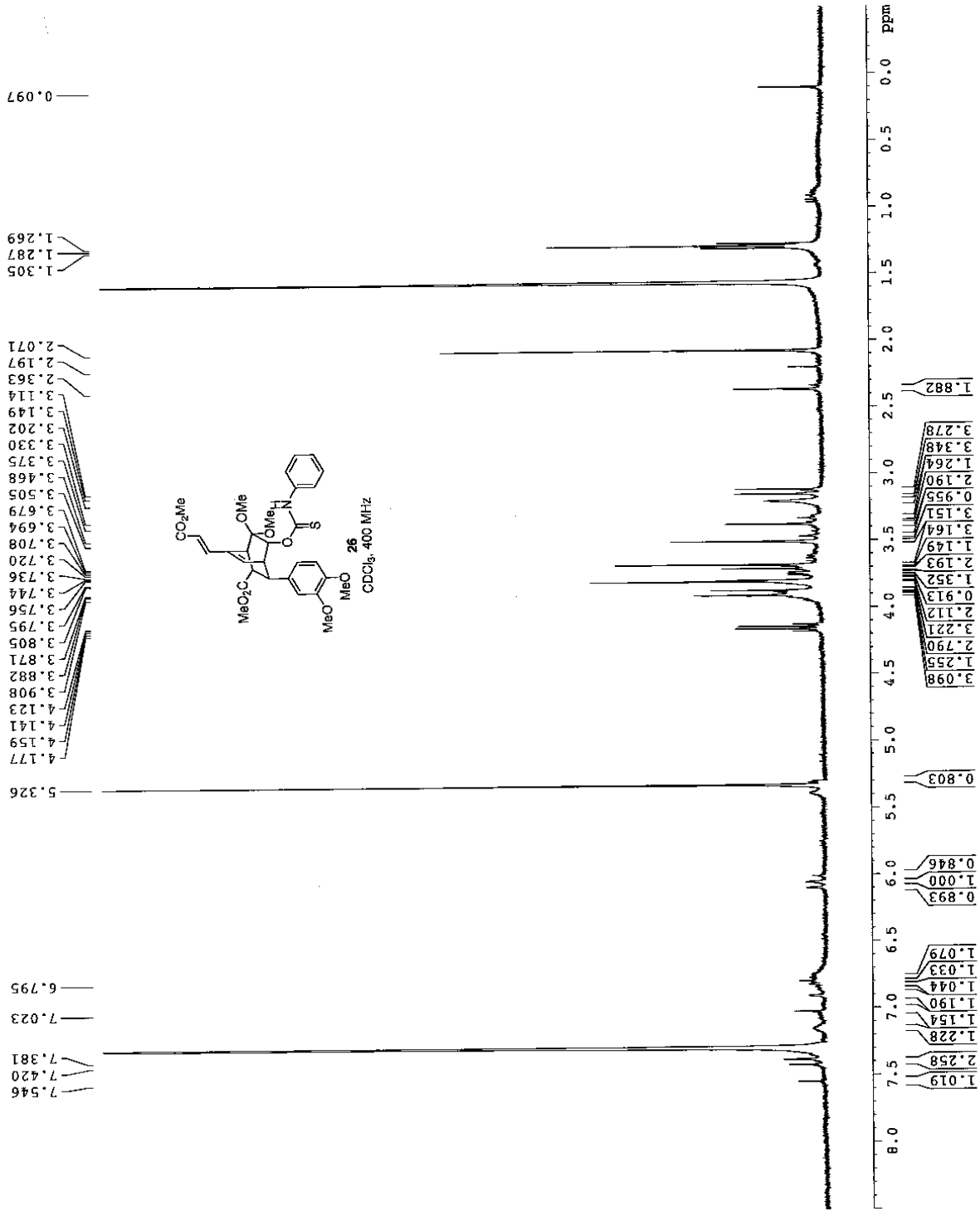
PeakTable

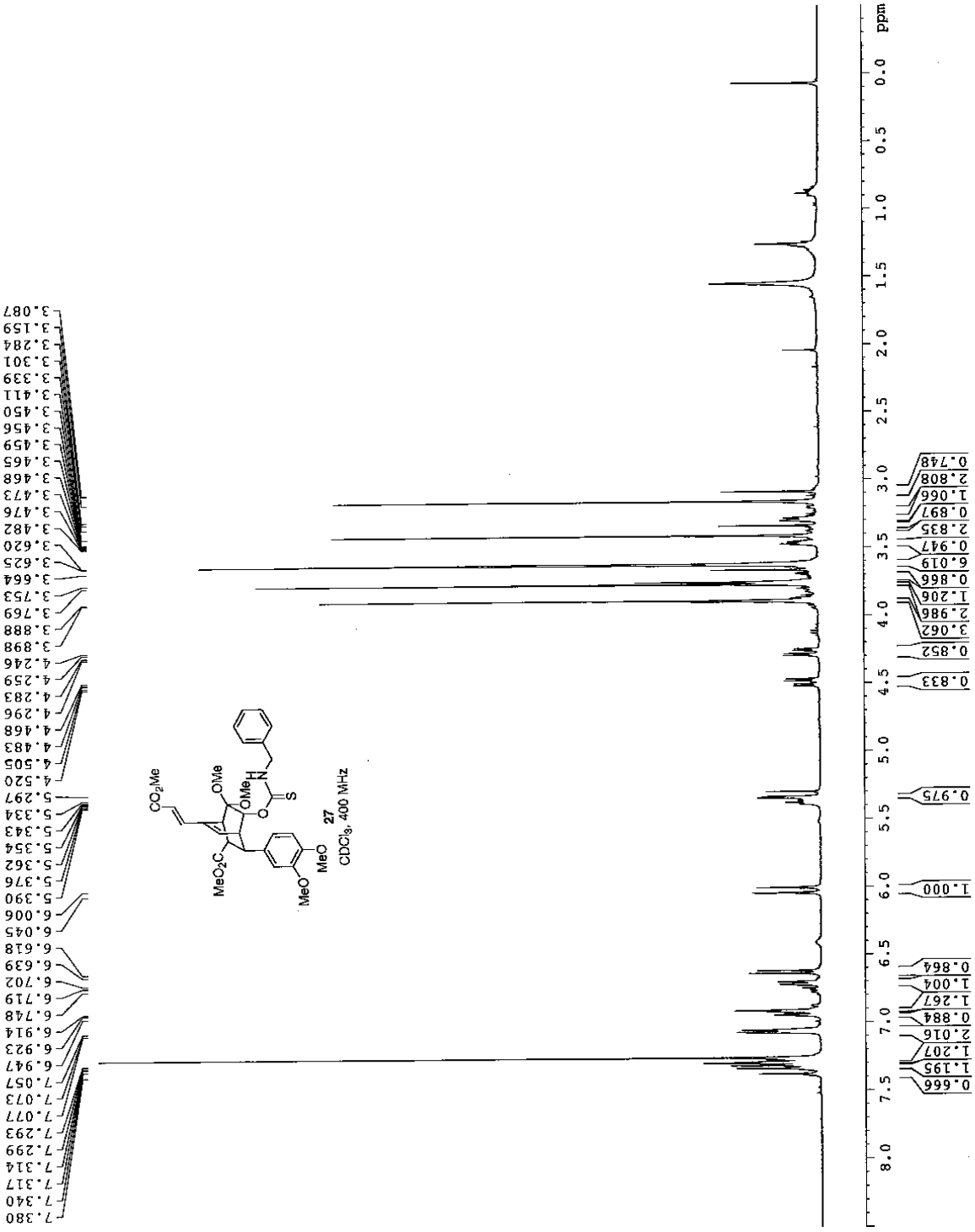
PDA Ch1 270nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	7.342	236854	27746	0.497	0.687
2	11.930	47205267	3997520	99.010	98.958
3	13.319	235179	14337	0.493	0.355
Total		47677300	4039603	100.000	100.000



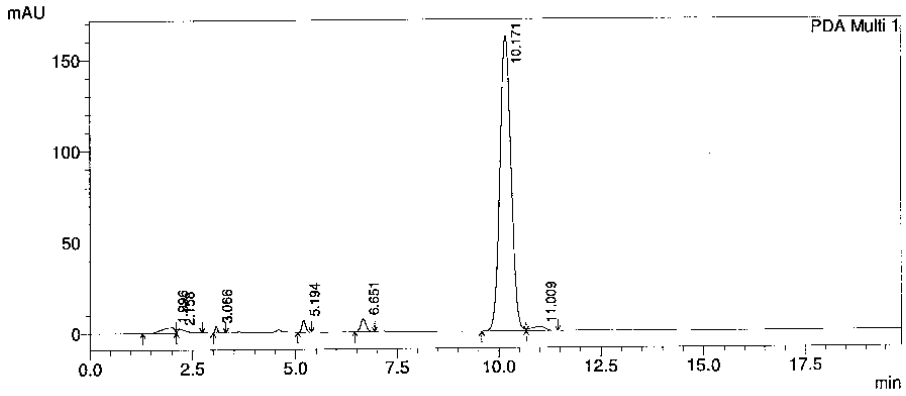
25


26
CDCl3, 400 MHz
ppm


CO2Me
OMe
OMe
N
H
O
S
MeO2C
MeO
MeO
27
CDCl3, 400 MHz
ppm
0.666
1.195
1.207
2.016
0.884
1.267
1.004
0.864
1.000
0.975
0.833
0.852
3.062
2.986
1.206
0.866
6.019
0.947
2.835
0.897
1.066
2.808
0.748

2/21/2011 15:37:59 1 / 1

<Chromatogram>

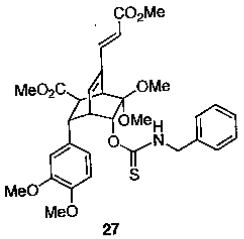


1 PDA Multi 1/270nm 4nm

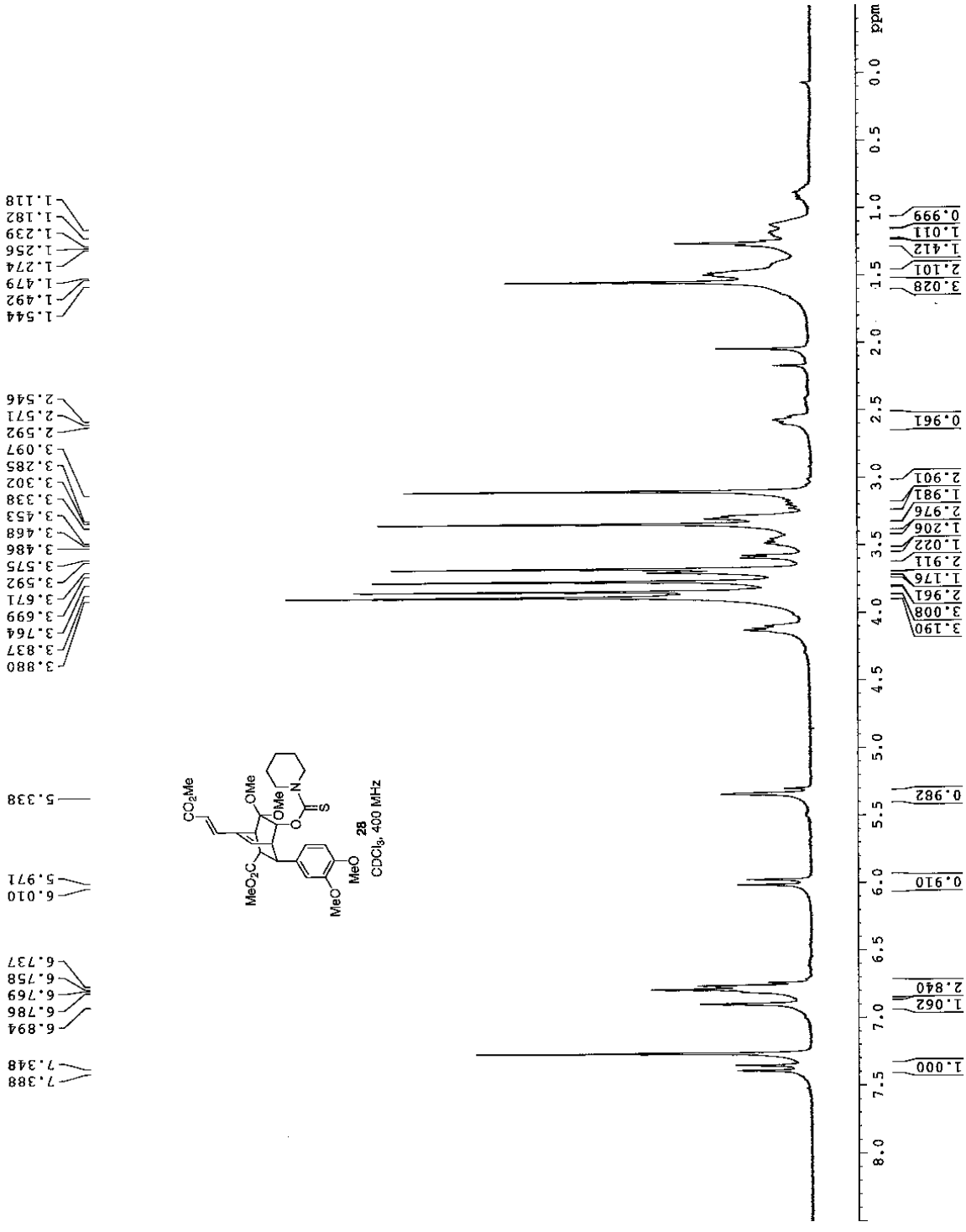
PeakTable

PDA Ch1 270nm 4nm

Peak#	Rct. Time	Area	Height	Area %	Height %
1	1.996	69718	3117	2.075	1.665
2	2.158	29914	2126	0.891	1.135
3	3.066	14914	3548	0.444	1.895
4	5.194	43346	6630	1.290	3.541
5	6.651	62287	7089	1.854	3.786
6	10.171	3085992	162358	91.868	86.718
7	11.009	52974	2357	1.577	1.259
Total		3359145	187225	100.000	100.000

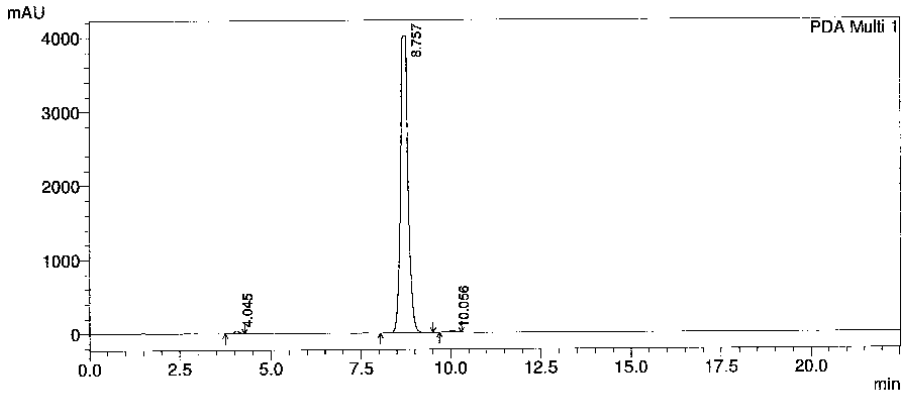


27


CO2Me
OMe
OMe
N
S
O
MeO2C
MeO
MeO
28
CDCl3, 400 MHz
ppm

2/21/2011 15:54:53 1 / 1

<Chromatogram>

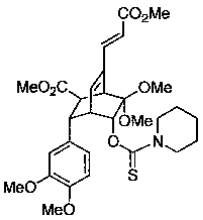


1 PDA Multi 1/270nm 4nm

PeakTable

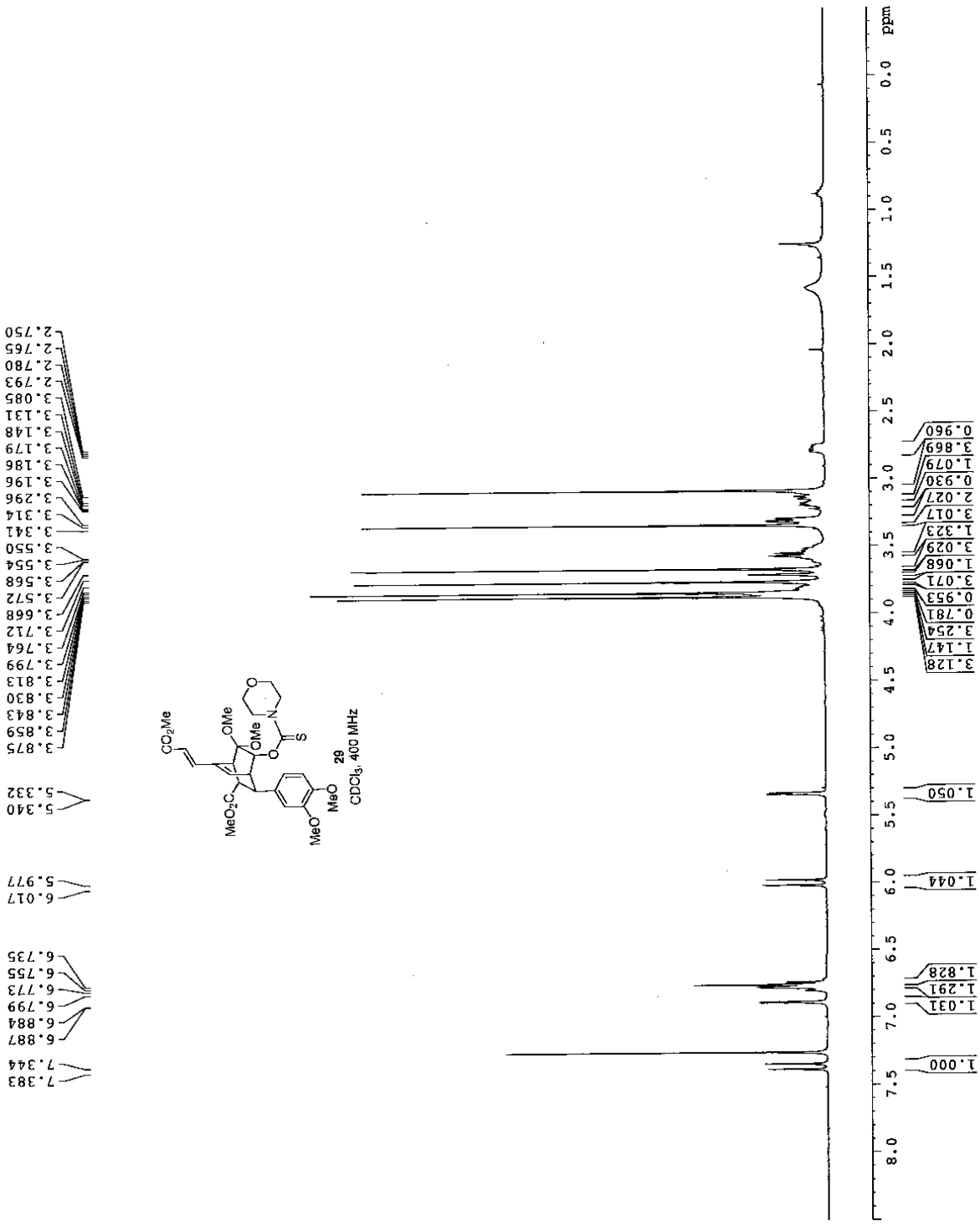
PDA Ch1 270nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	4.045	384998	40535	0.640	0.999
2	8.757	59389940	4000452	98.753	98.595
3	10.056	365142	16467	0.607	0.406
Total		60140080	4057454	100.000	100.000



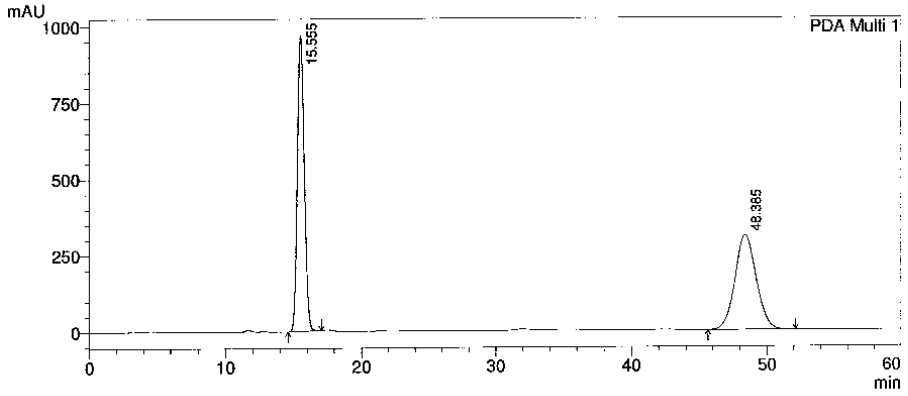
28

C:\LabSolutions\Data\matt\Lead\2as44.lcd


CO2Me
OMe
OMe
MeO2C
MeO
MeO
29
CDCl3, 400 MHz
ppm

2/21/2011 16:06:27 1 / 1

<Chromatogram>

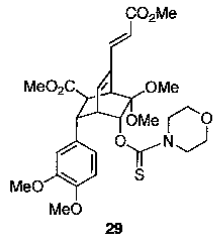


1 PDA Multi 1/270nm 4nm

PeakTable

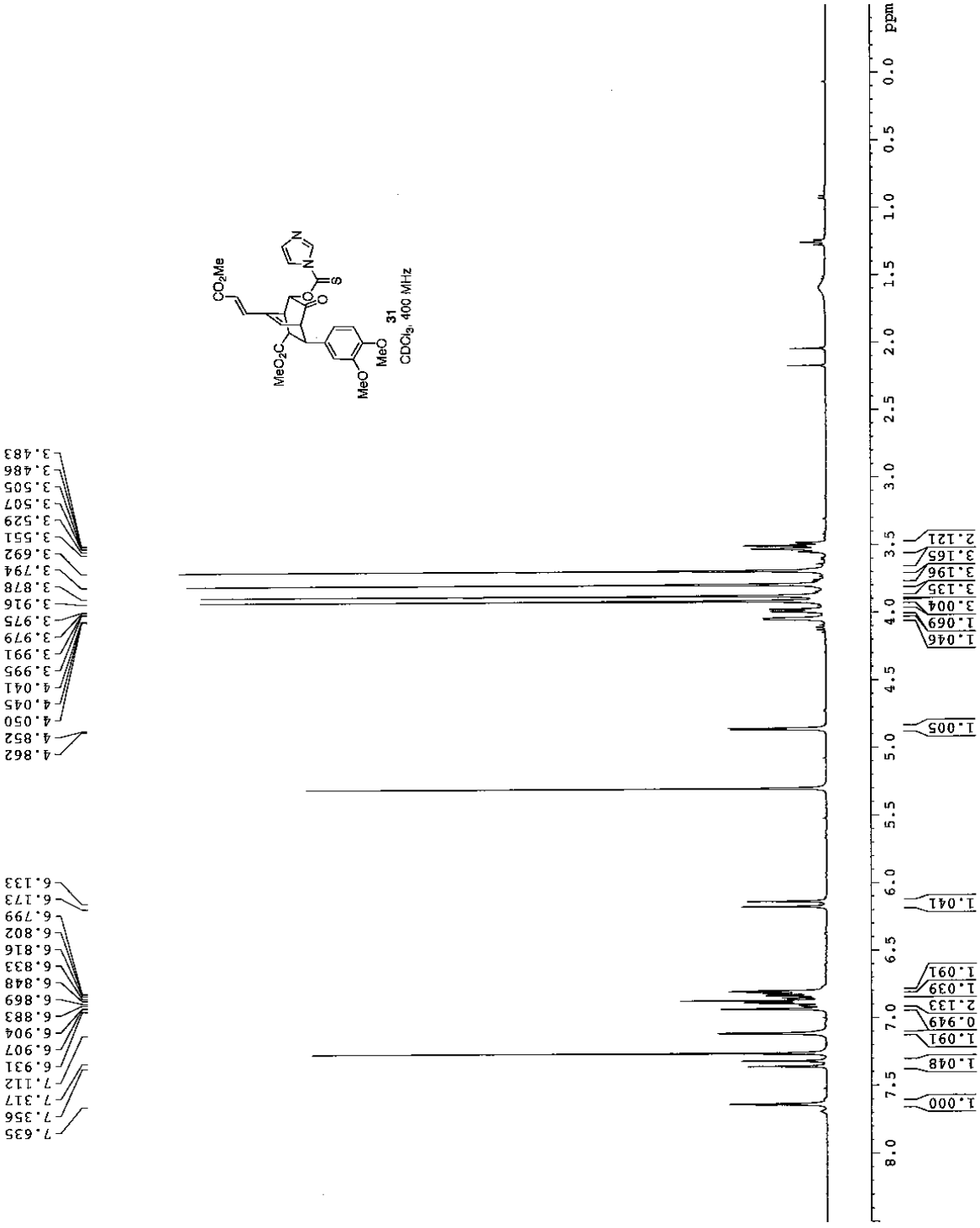
PDA Ch1 270nm 4nm

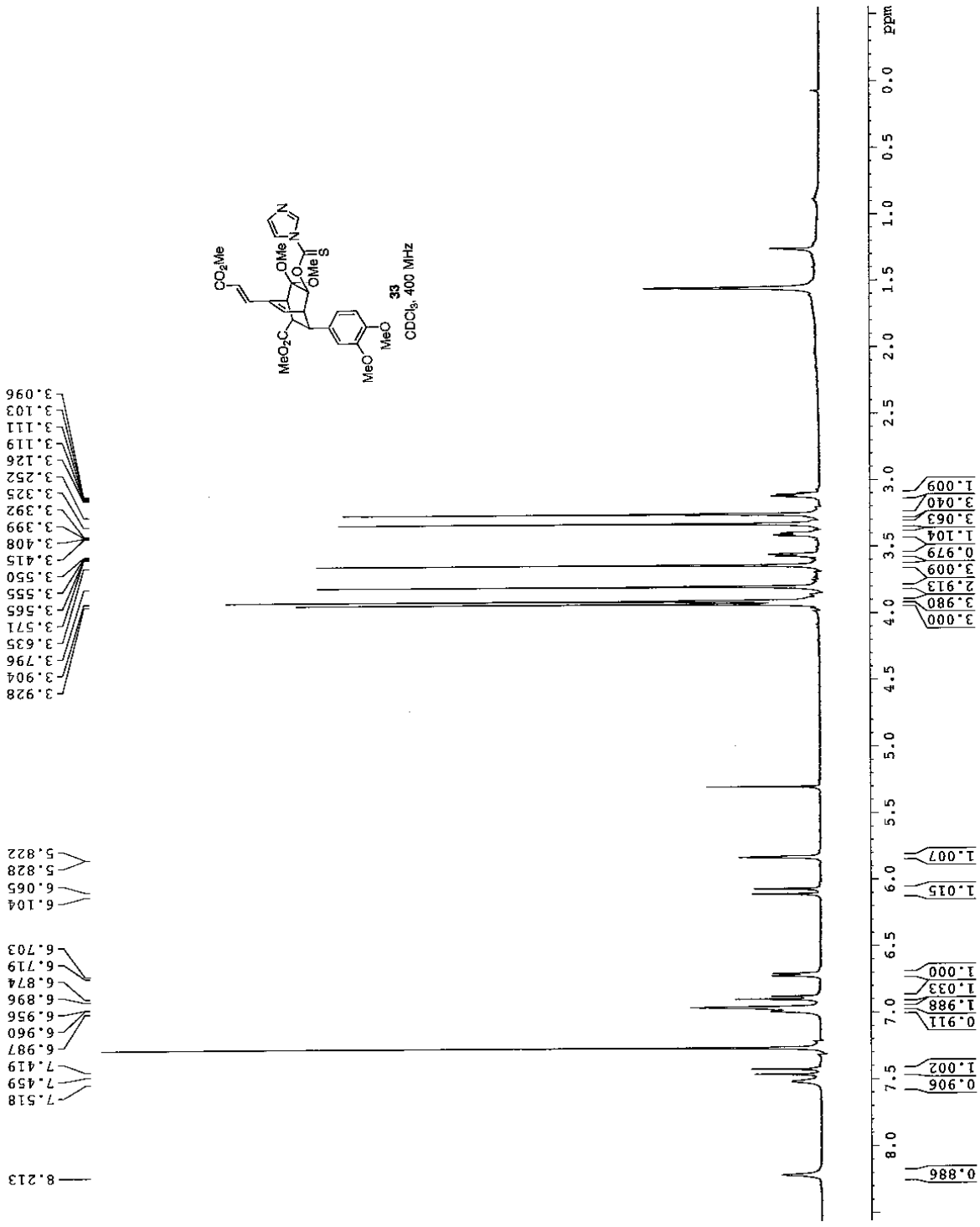
Peak#	Ret. Time	Area	Height	Area %	Height %
1	15.555	33668984	967800	49.986	75.675
2	48.385	33688464	311090	50.014	24.325
Total		67357448	1278890	100.000	100.000

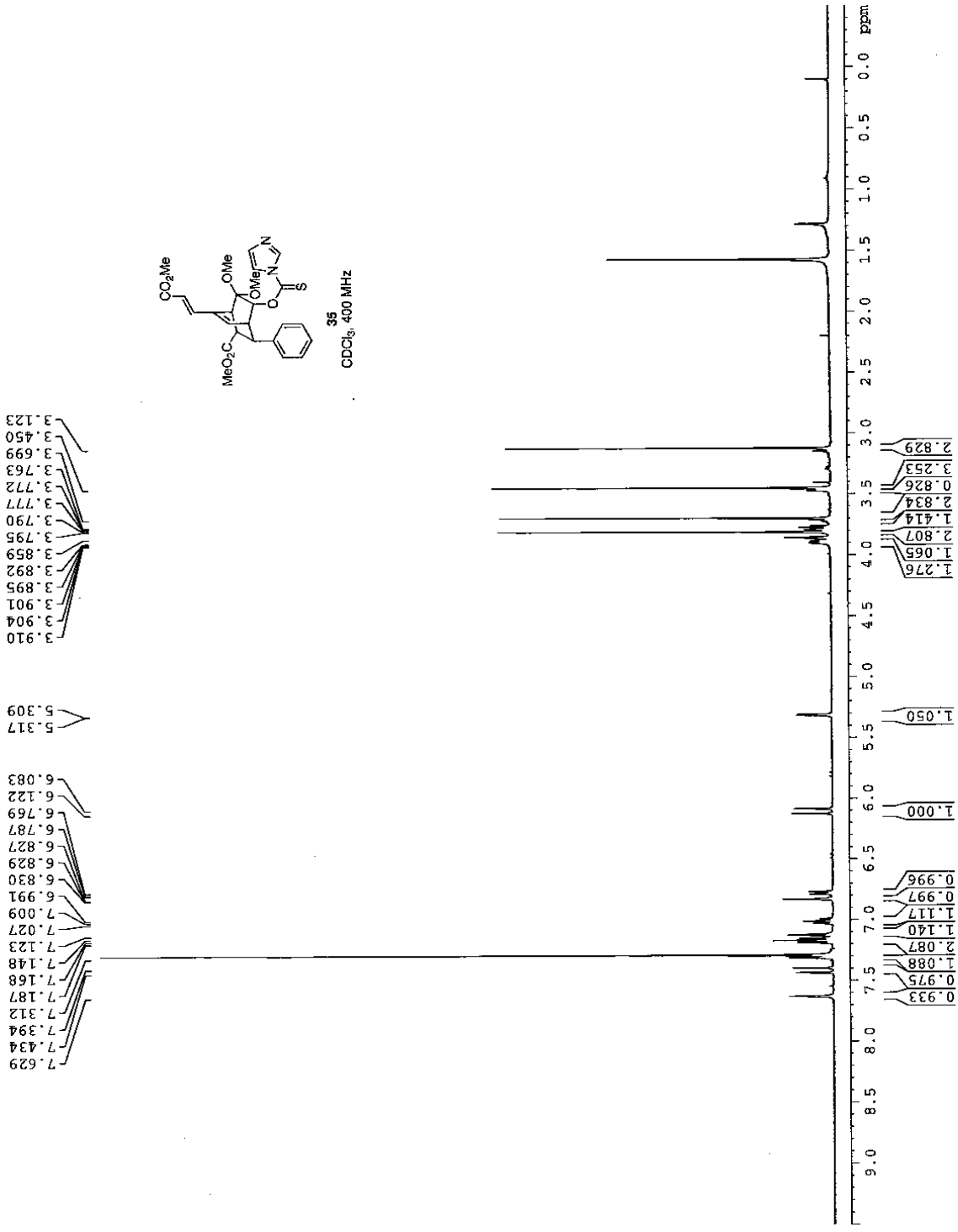


29

C:\LabSolutions\Data\matt\2as19.lcd

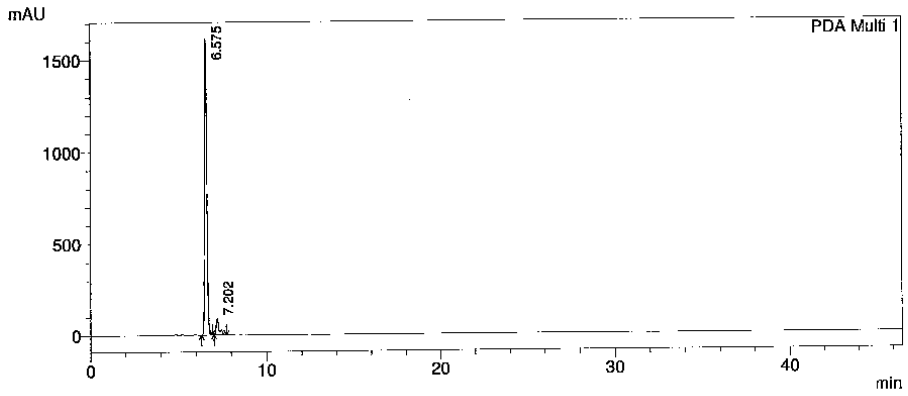

CO2Me
MeO2C
MeO
MeO
S
O
O
N
N
31
CDCl3, 400 MHz
ppm
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
1.000
1.048
1.091
0.949
2.133
1.039
1.091
1.041
1.005
1.046
1.069
3.004
3.135
3.196
3.165
2.121
7.635
7.356
7.317
7.112
6.931
6.907
6.904
6.883
6.869
6.848
6.833
6.816
6.802
6.799
6.173
6.133
4.862
4.852
4.050
4.045
4.041
3.995
3.991
3.979
3.975
3.916
3.878
3.794
3.692
3.551
3.529
3.507
3.505
3.486
3.483


33
CDCl3, 400 MHz
CO2Me
OMe
OMe
S
MeO2C
MeO
MeO
8.213
7.518
7.459
7.419
6.987
6.960
6.956
6.896
6.874
6.719
6.703
6.104
6.065
5.828
5.822
3.928
3.904
3.796
3.635
3.571
3.565
3.555
3.550
3.415
3.408
3.399
3.392
3.325
3.252
3.126
3.119
3.111
3.103
3.096
ppm
0.886
0.906
1.002
0.911
1.988
1.033
1.000
1.015
1.007
1.009
3.040
3.063
1.104
0.979
3.009
2.913
3.980
3.000


35
CDCl3, 400 MHz
ppm

2/21/2011 14:59:54 1 / 1

<Chromatogram>

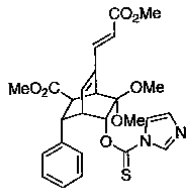


1 PDA Multi 1/254nm 4nm

PeakTable

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	6.575	13478863	1614319	92.755	94.806
2	7.202	1052805	88436	7.245	5.194
Total		14531668	1702754	100.000	100.000



35

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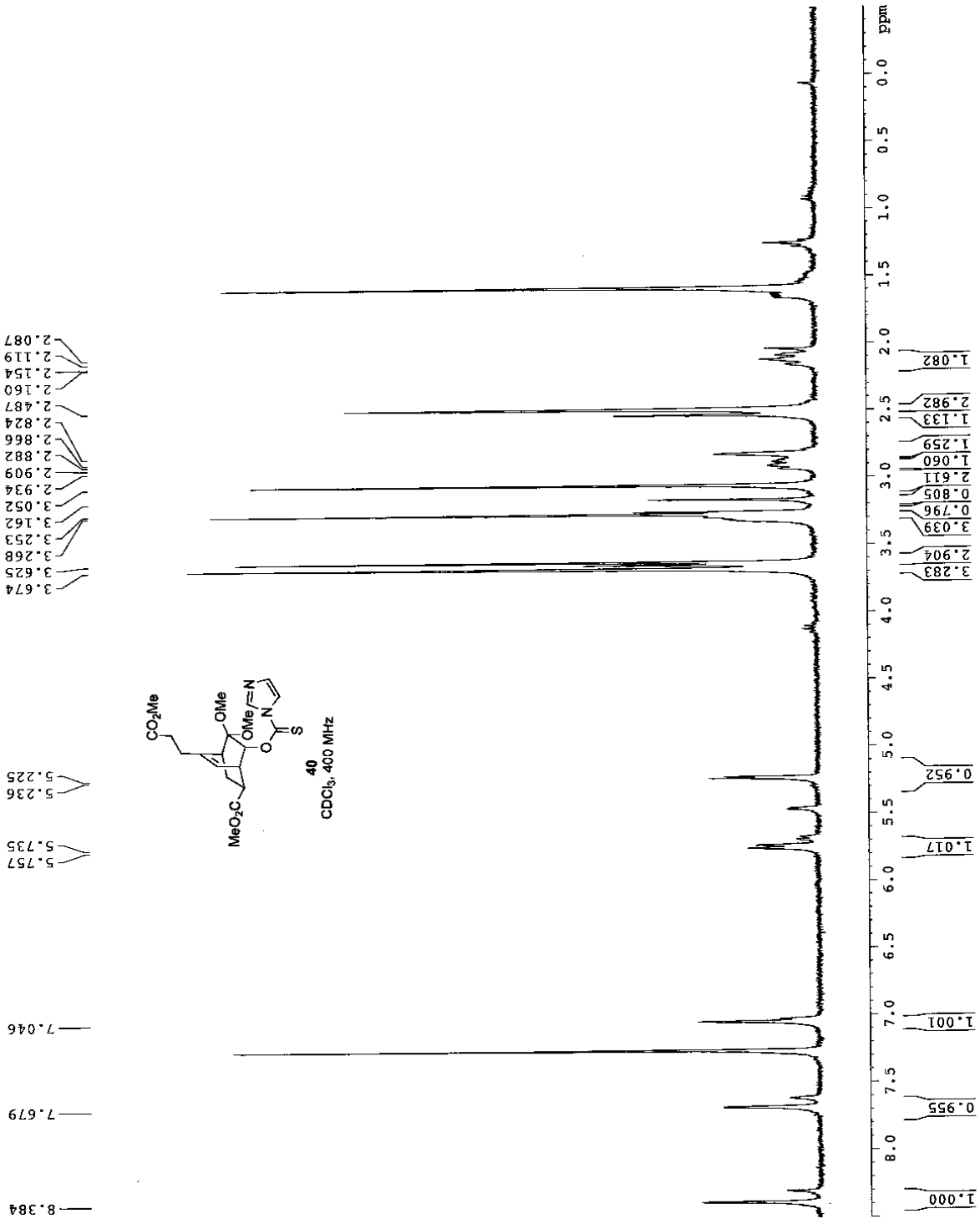
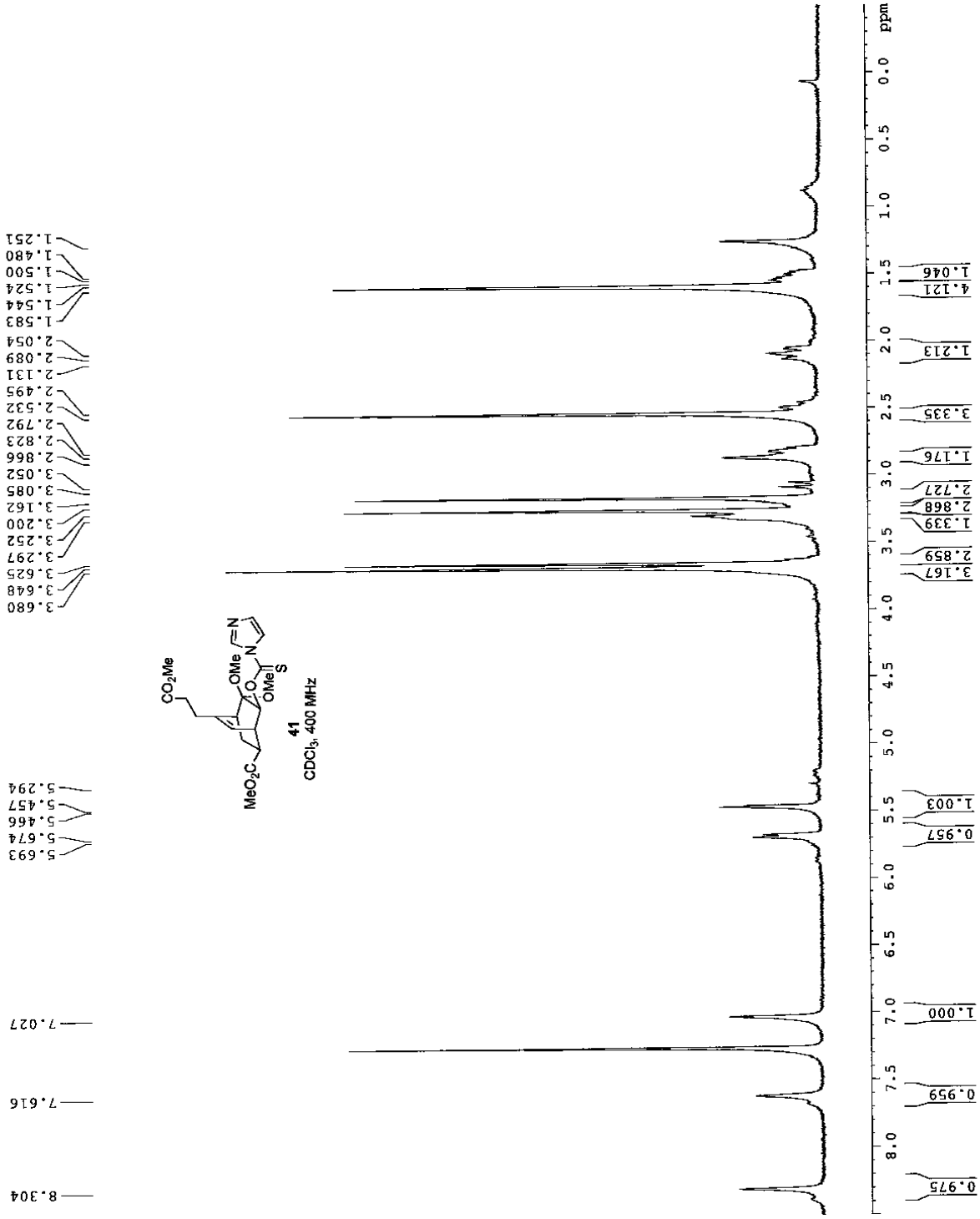
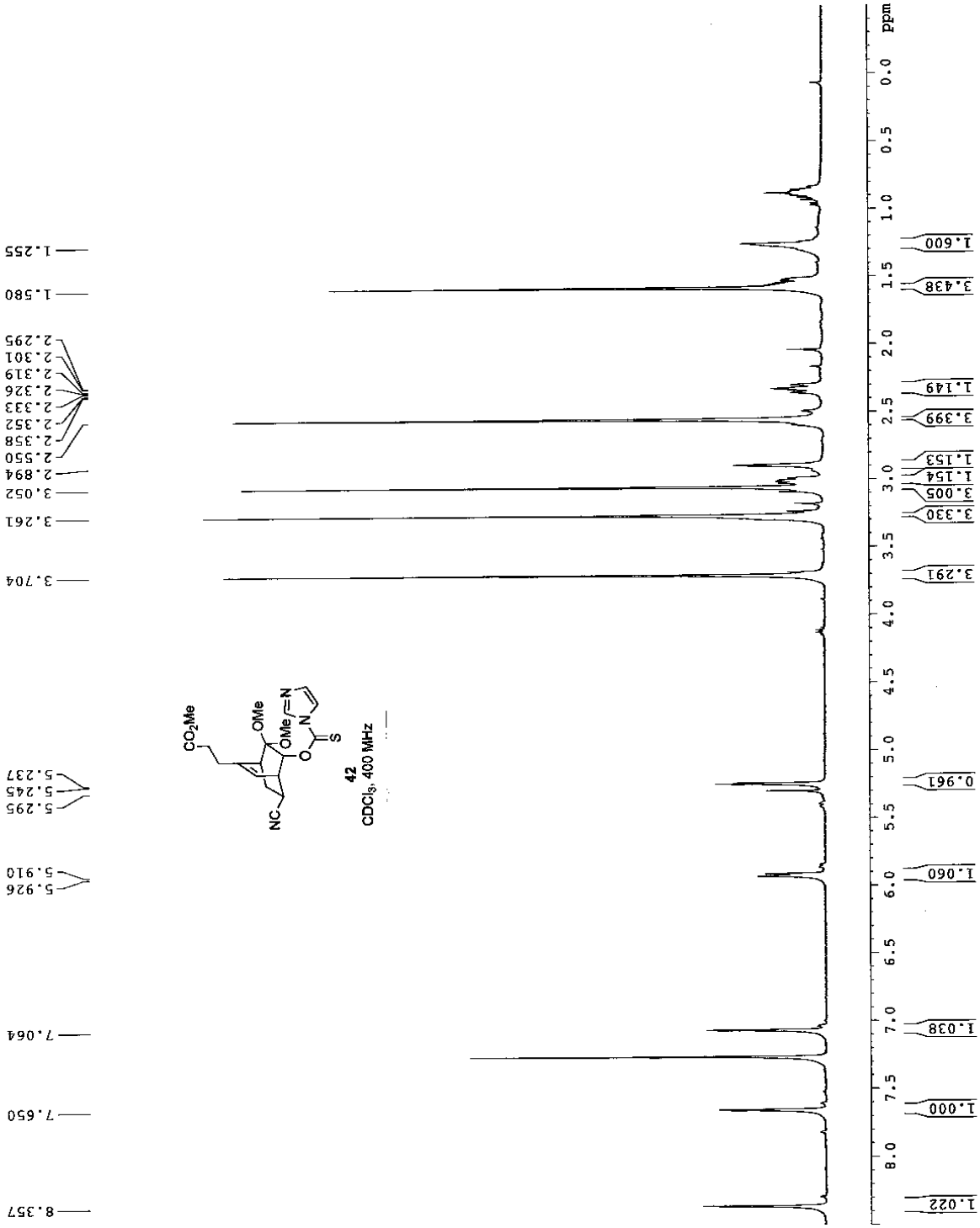
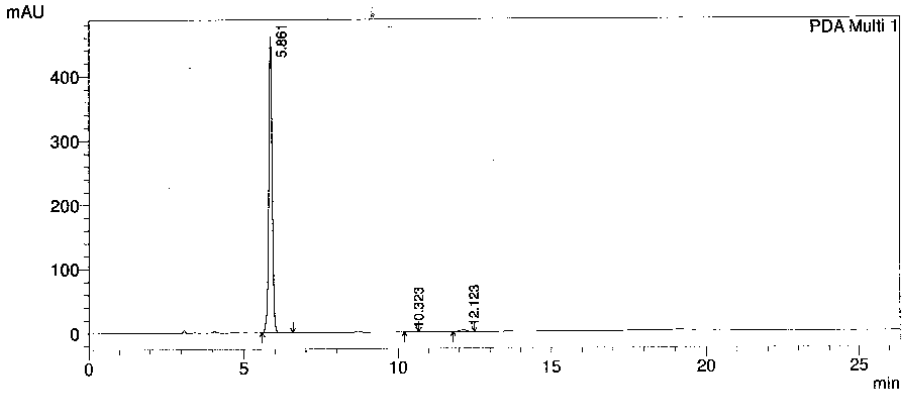

8.384
7.679
7.046
5.757
5.735
5.236
5.225
3.674
3.625
3.268
3.253
3.162
3.052
2.934
2.909
2.882
2.866
2.824
2.487
2.160
2.154
2.119
2.087
CO2Me
OMe
OMe
N
S
O
MeO2C
40
CDCl3, 400 MHz
1.000
0.955
1.001
1.017
0.952
3.283
2.904
3.039
0.796
0.805
2.611
1.060
1.259
1.133
2.982
1.082
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm


41
CDCl3, 400 MHz
CO2Me
OMe
N
O
OMe
S
MeO2C
ppm


1.255
1.580
2.295
2.301
2.319
2.326
2.333
2.352
2.358
2.550
2.894
3.052
3.261
3.704
5.237
5.245
5.295
5.910
5.926
7.064
7.650
8.357
CO2Me
OMe
OMe
N
N
O
S
NC
42
CDCl3, 400 MHz
ppm
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
1.022
1.000
1.038
1.060
0.961
3.291
3.330
3.005
1.154
1.153
3.399
1.149
3.438
1.600

2/21/2011 15:46:26 1 / 1

<Chromatogram>

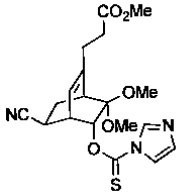


1 PDA Multi 1/270nm 4nm

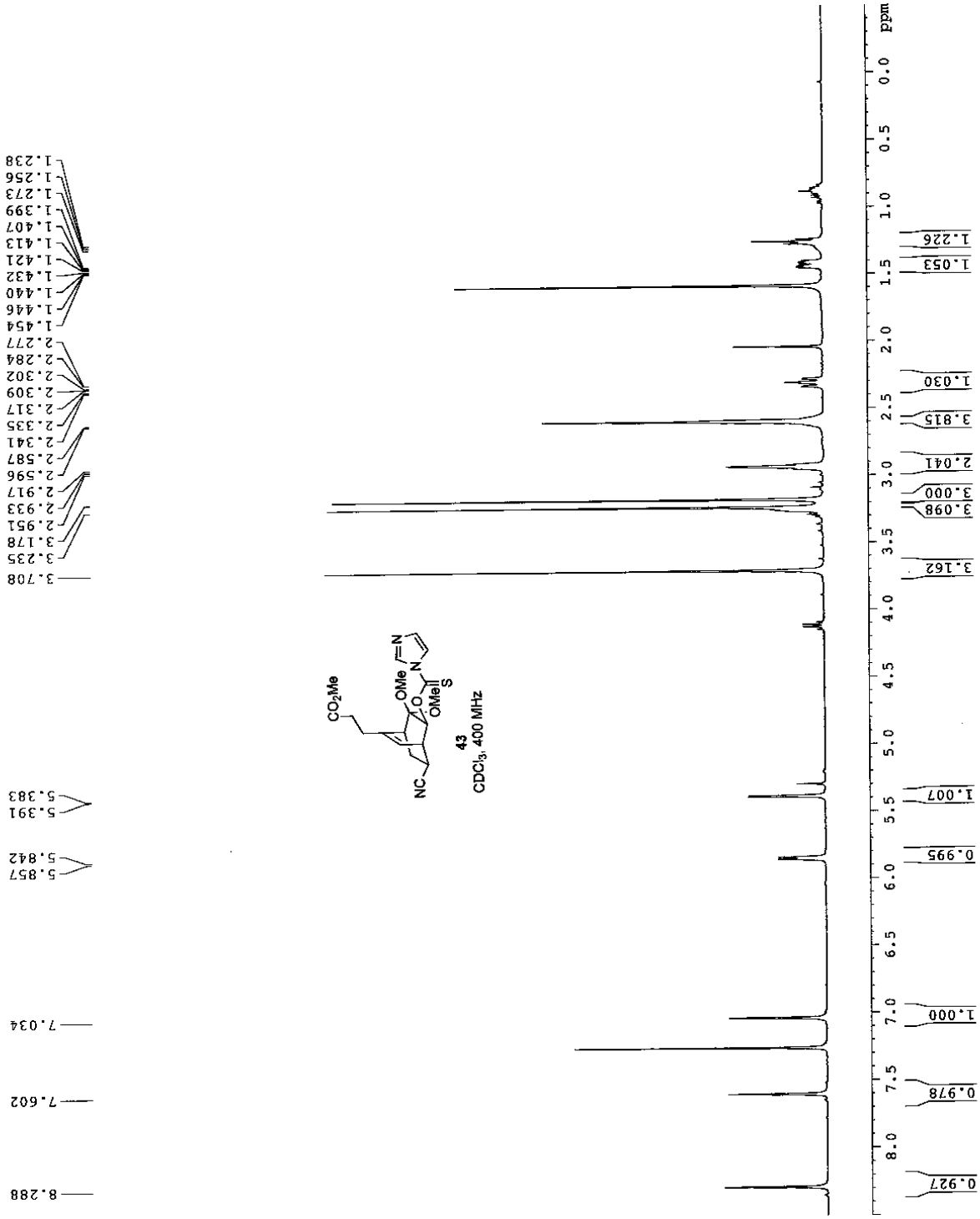
PeakTable

PDA Ch1 270nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	5.861	3483058	460907	98.736	99.348
2	10.323	1296	100	0.037	0.021
3	12.123	43278	2923	1.227	0.630
Total		3527632	463930	100.000	100.000

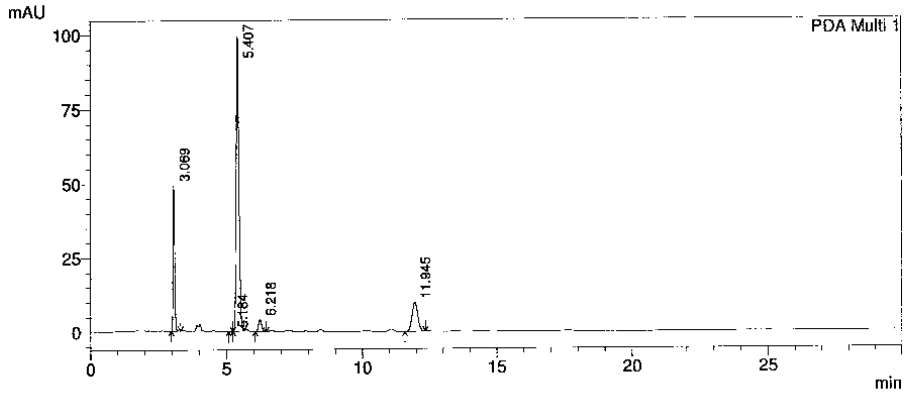


42


CO2Me
OMe
OMe
S
NC
43
CDCl3, 400 MHz
ppm
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
1.226
1.053
1.030
3.815
2.041
3.000
3.098
3.162
1.007
0.995
1.000
0.978
0.927
1.238
1.256
1.273
1.399
1.407
1.413
1.421
1.432
1.440
1.446
1.454
2.277
2.284
2.302
2.309
2.317
2.335
2.341
2.587
2.596
2.917
2.933
2.951
3.178
3.235
3.708
5.383
5.391
5.842
5.857
7.034
7.602
8.288

2/21/2011 15:42:03 1 / 1

<Chromatogram>

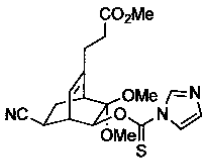


1 PDA Multi 1/270nm 4nm

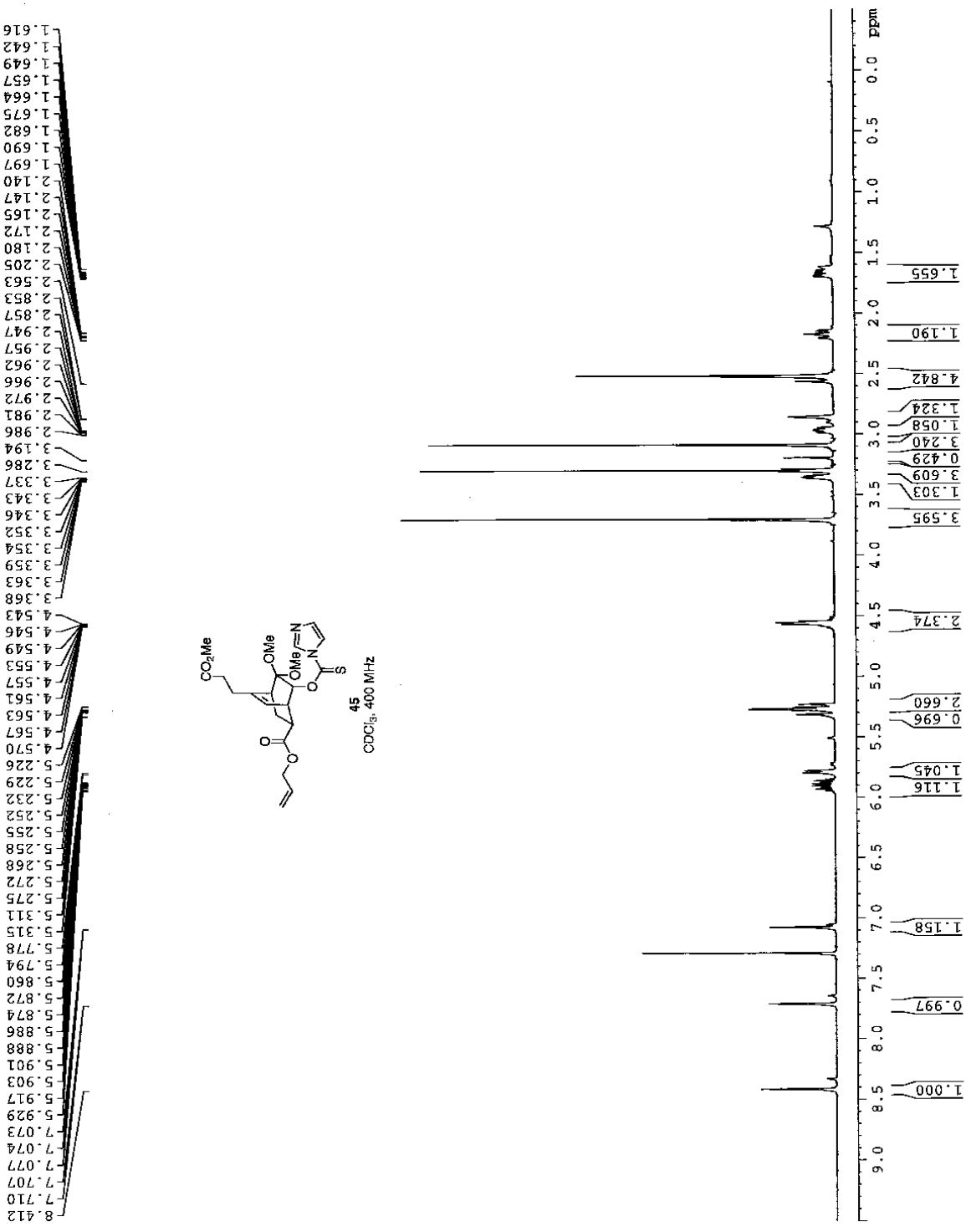
PeakTable

PDA Ch1 270nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	3.069	191233	49326	18.463	30.405
2	5.184	623	108	0.060	0.067
3	5.407	667346	98894	64.432	60.958
4	6.218	31706	4092	3.061	2.523
5	11.945	144837	9813	13.984	6.049
Total		1035744	162234	100.000	100.000

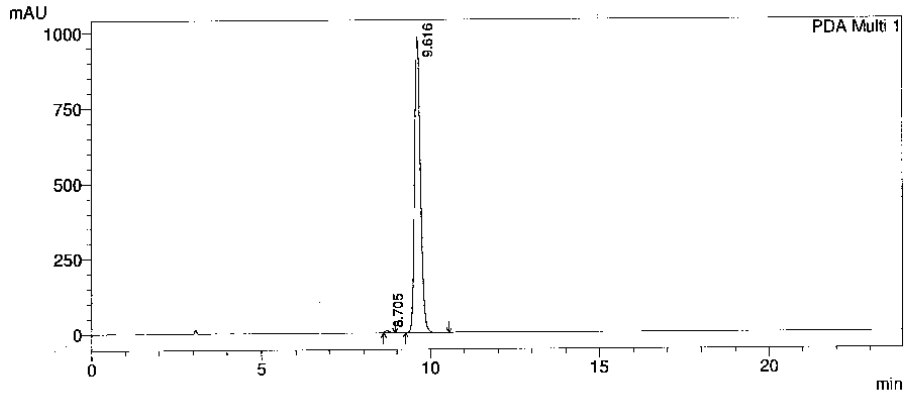


43


45
CDCl3, 400 MHz
ppm

2/21/2011 15:29:25 1 / 1

<Chromatogram>

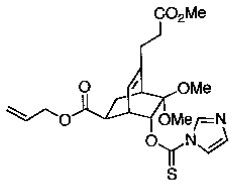


1 PDA Multi 1/270nm 4nm

PeakTable

PDA Ch1 270nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	8.705	65543	6889	0.548	0.695
2	9.616	11887492	984572	99.452	99.305
Total		11953035	991461	100.000	100.000



45

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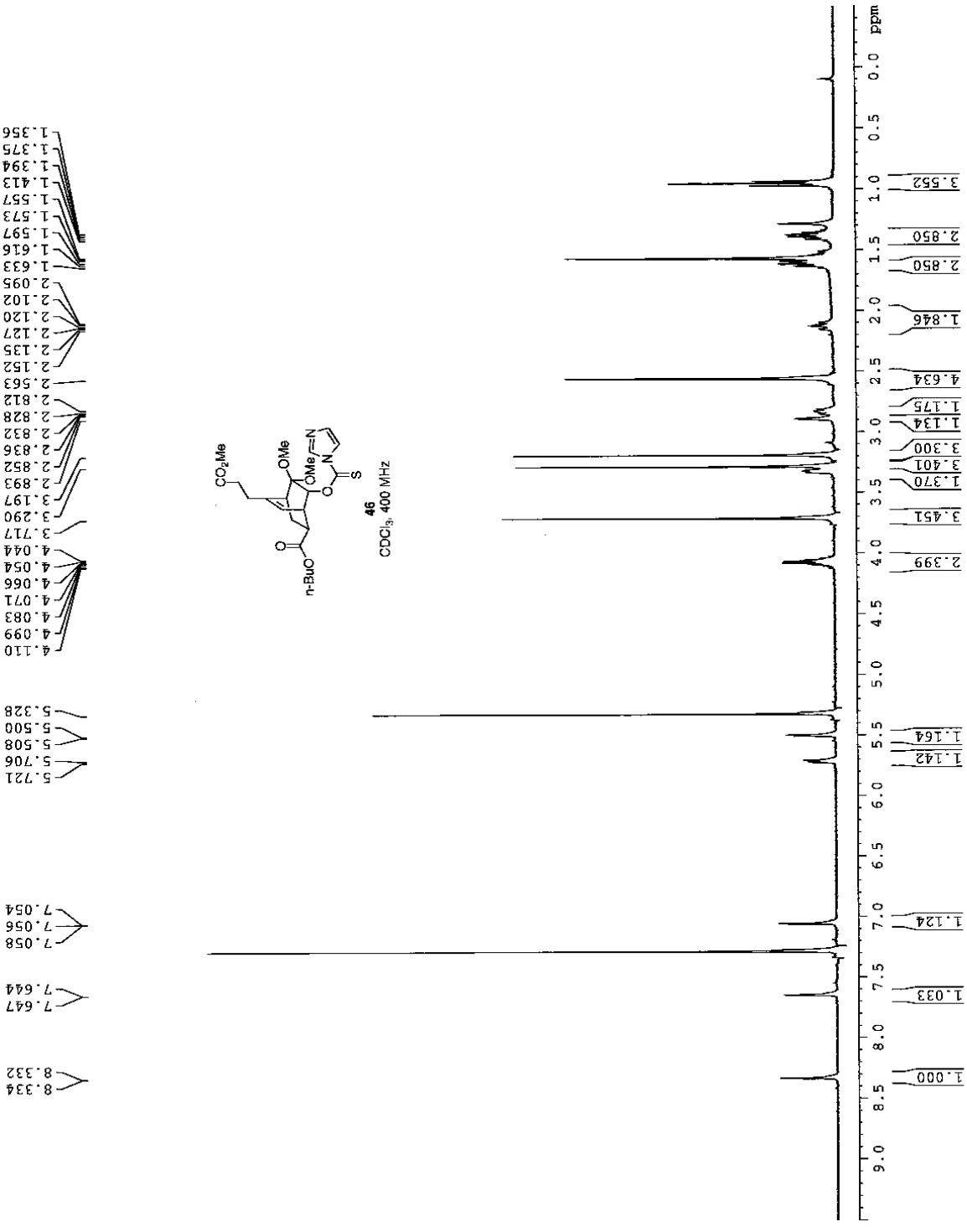
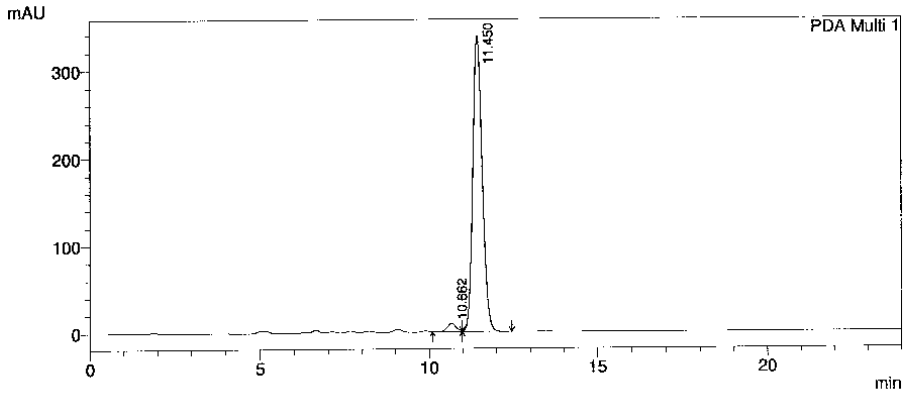

CO2Me
OMe
OMe
N
S
O
O
n-BuO
46
CDCl3, 400 MHz
ppm
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0
3.552
2.850
2.850
1.846
4.634
1.175
1.134
3.300
3.401
1.370
3.451
2.399
1.164
1.142
1.124
1.033
1.000
1.356
1.375
1.394
1.413
1.557
1.573
1.597
1.616
1.633
2.095
2.102
2.120
2.127
2.135
2.152
2.563
2.812
2.828
2.832
2.836
2.852
2.893
3.197
3.290
3.717
4.044
4.054
4.066
4.071
4.083
4.099
4.110
5.328
5.500
5.508
5.706
5.721
7.054
7.056
7.058
7.644
7.647
8.332
8.334

2/21/2011 15:16:25 1 / 1

<Chromatogram>

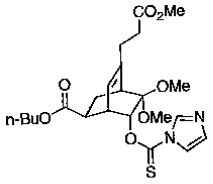


1 PDA Multi 1/270nm 4nm

PeakTable

PDA Ch1 270nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	10.662	173383	9375	2.552	2.698
2	11.450	6620952	338158	97.448	97.302
Total		6794335	347534	100.000	100.000



46

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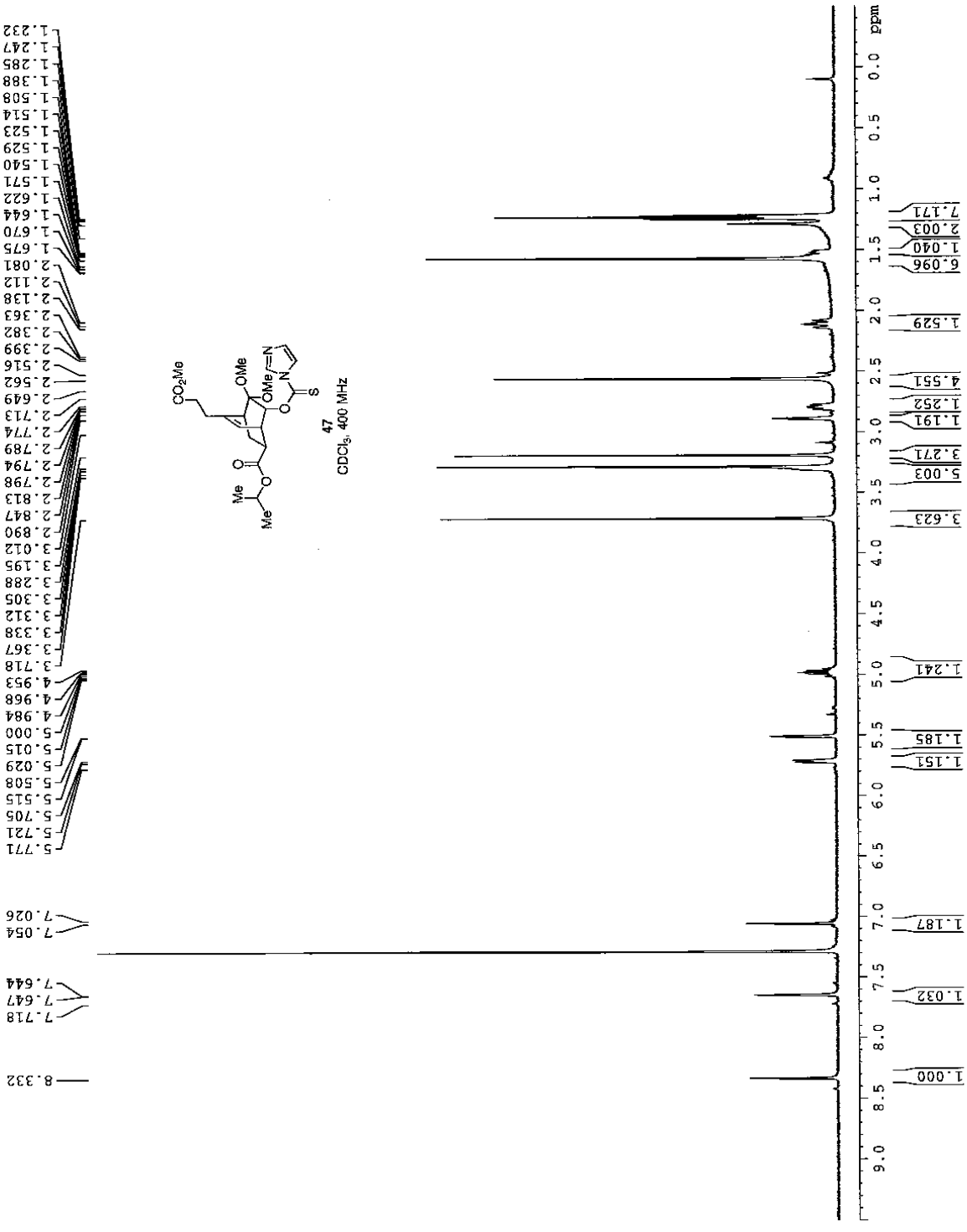
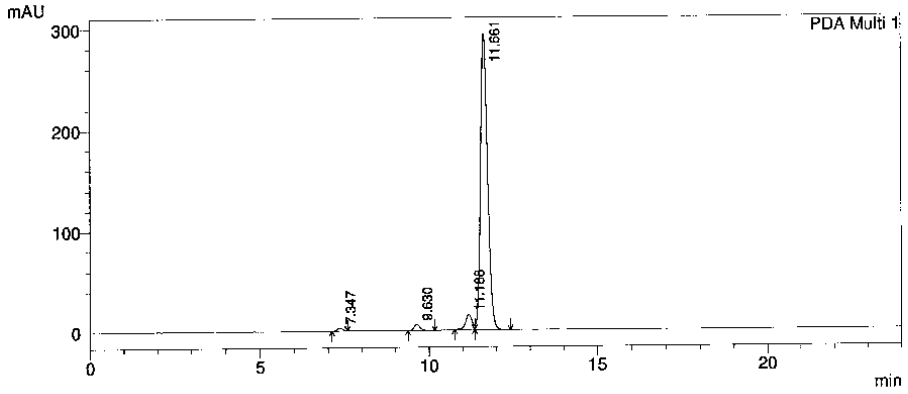

CO2Me
OMe
OMe
N
S
Me
Me
47
CDCl3, 400 MHz
ppm
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0
7.171
2.003
1.040
6.096
1.529
4.551
1.252
1.191
3.271
5.003
3.623
1.241
1.185
1.151
1.187
1.032
1.000
1.232
1.247
1.285
1.388
1.508
1.514
1.523
1.529
1.540
1.571
1.622
1.644
1.670
1.675
2.081
2.112
2.138
2.363
2.382
2.399
2.516
2.562
2.649
2.713
2.774
2.789
2.794
2.798
2.813
2.847
2.890
3.012
3.195
3.288
3.305
3.312
3.338
3.367
3.718
4.953
4.968
4.984
5.000
5.015
5.029
5.508
5.515
5.705
5.721
5.771
7.026
7.054
7.644
7.647
7.718
8.332

2/21/2011 15:20:51 1 / 1

<Chromatogram>

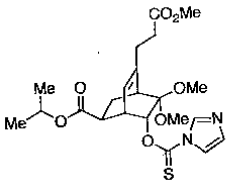


1 PDA Multi 1/270nm 4nm

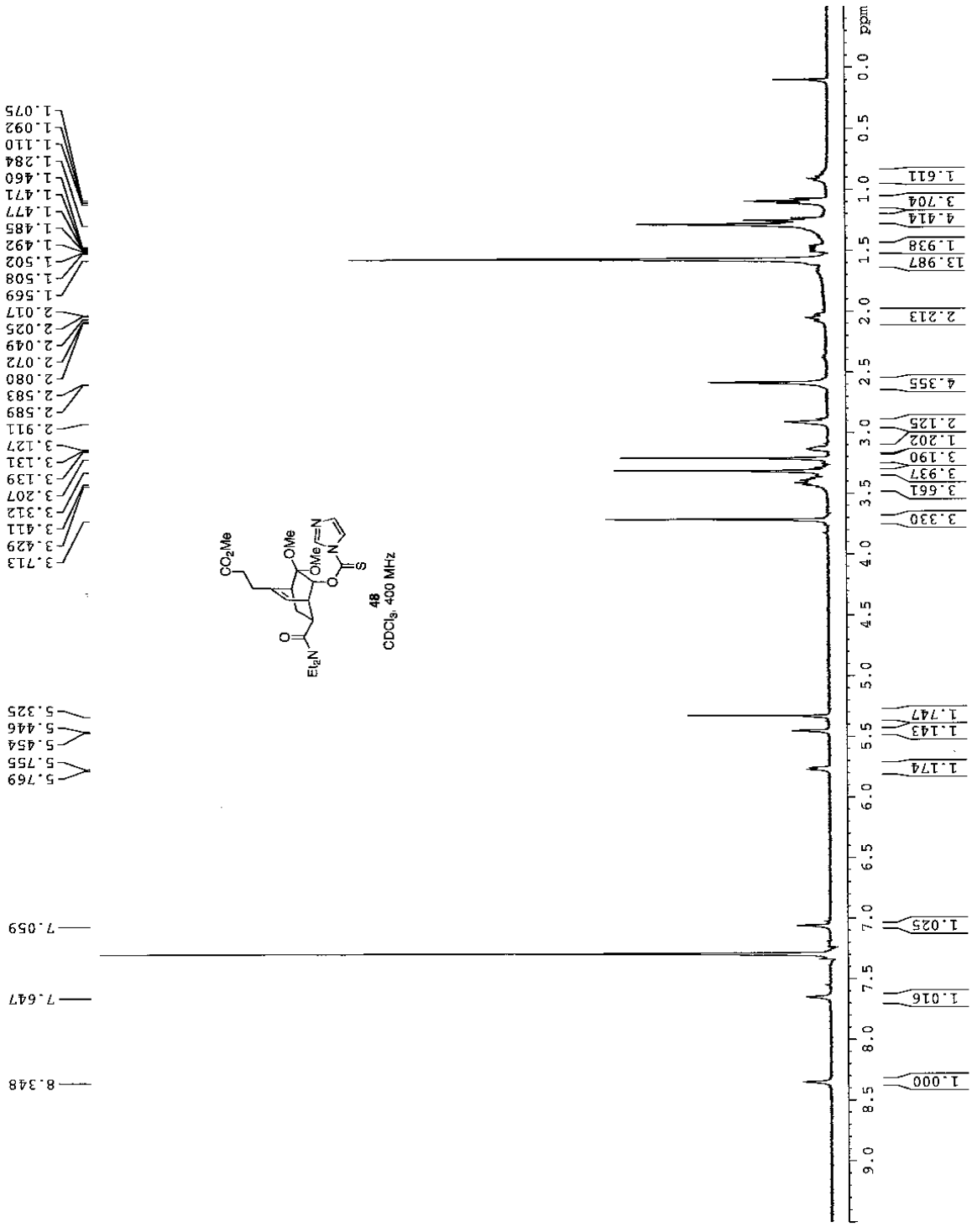
PeakTable

PDA Ch1 270nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	7.347	34548	2980	0.764	0.940
2	9.630	75875	6051	1.677	1.908
3	11.188	202480	14825	4.476	4.676
4	11.661	4210580	293219	93.083	92.476
Total		4523482	317075	100.000	100.000

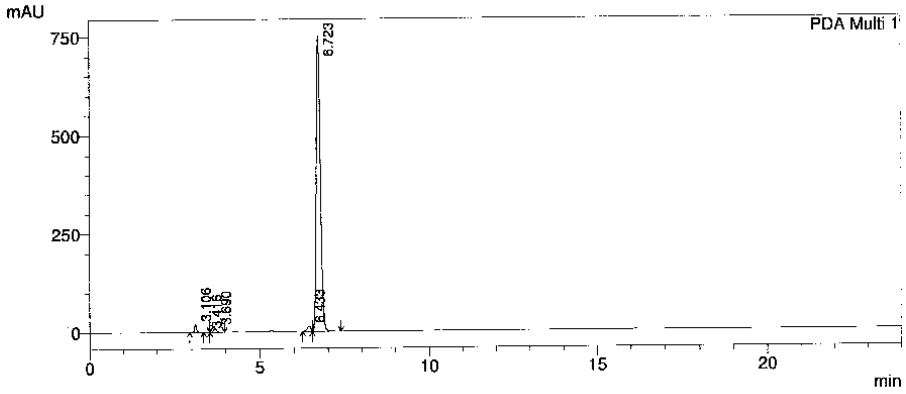


47


48
CDCl3, 400 MHz
ppm

2/21/2011 16:01:45 1 / 1

<Chromatogram>

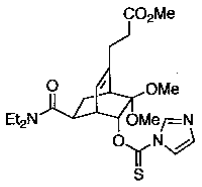


1 PDA Multi 1/270nm 4nm

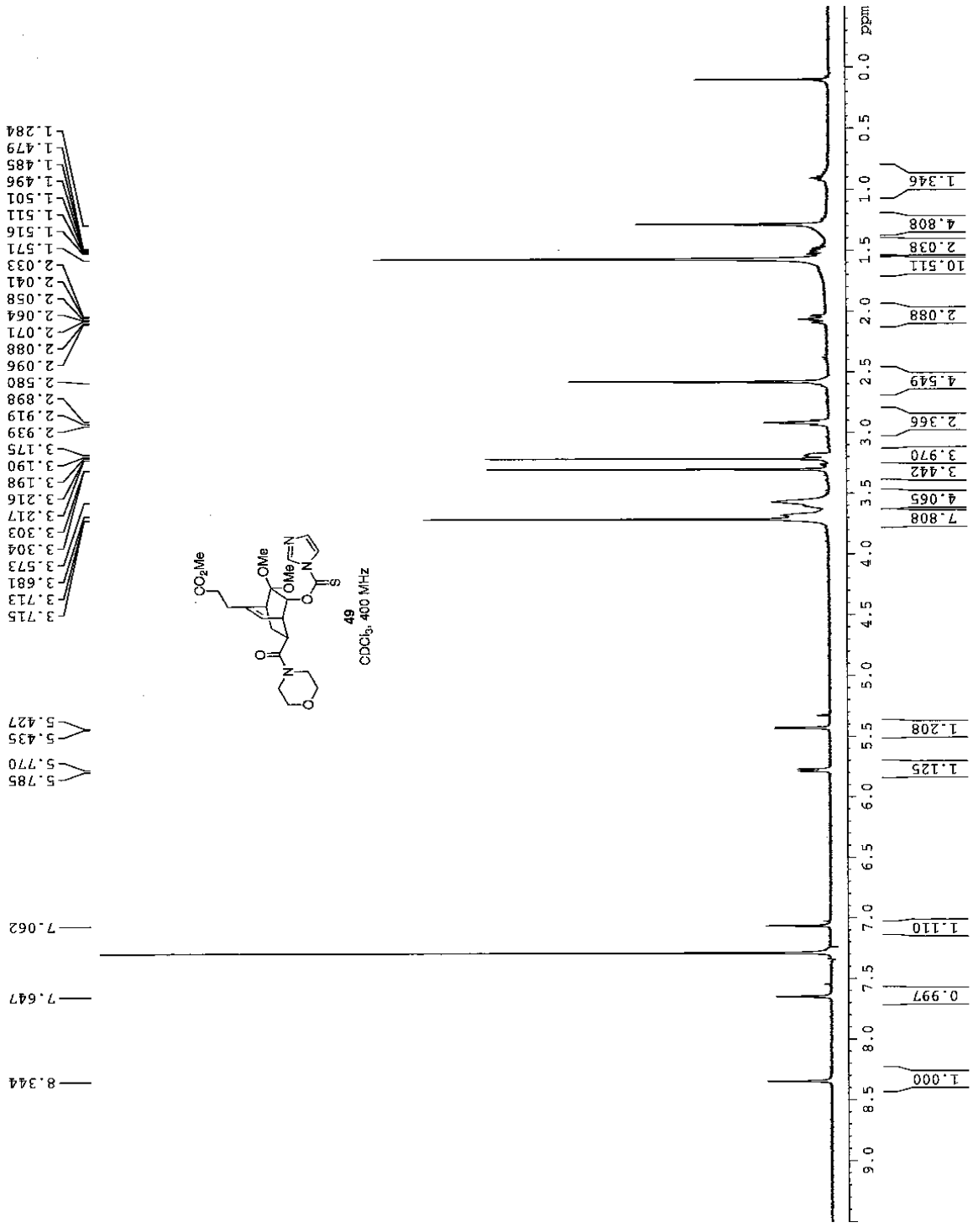
PeakTable

PDA Ch1 270nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	3.106	90412	19660	1.370	2.476
2	3.416	2957	615	0.045	0.077
3	3.690	57264	9977	0.868	1.257
4	6.433	99414	12641	1.506	1.592
5	6.723	6349299	751064	96.211	94.598
Total		6599347	793957	100.000	100.000

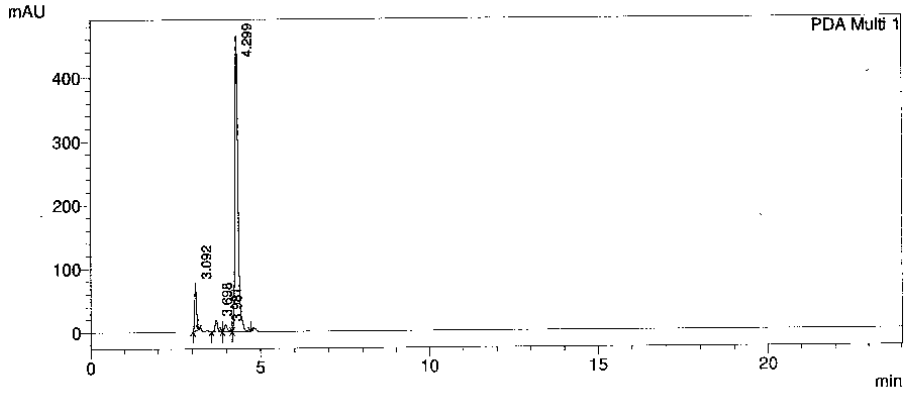


48


49
CDCl3, 400 MHz
CO2Me
OMe
OMe
N
O
S
O
N
O
8.344
7.647
7.062
5.785
5.770
5.435
5.427
3.715
3.713
3.681
3.573
3.304
3.303
3.217
3.216
3.198
3.190
3.175
2.939
2.919
2.898
2.580
2.096
2.088
2.071
2.064
2.058
2.041
2.033
1.571
1.516
1.511
1.501
1.496
1.485
1.479
1.284
1.000
0.997
1.110
1.208
1.125
7.808
4.065
3.442
3.970
2.366
4.549
2.088
10.511
2.038
4.808
1.346
ppm

2/21/2011 16:07:55 1 / 1

<Chromatogram>

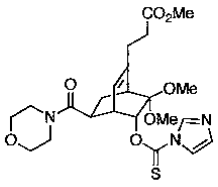


1 PDA Multi 1/270nm 4nm

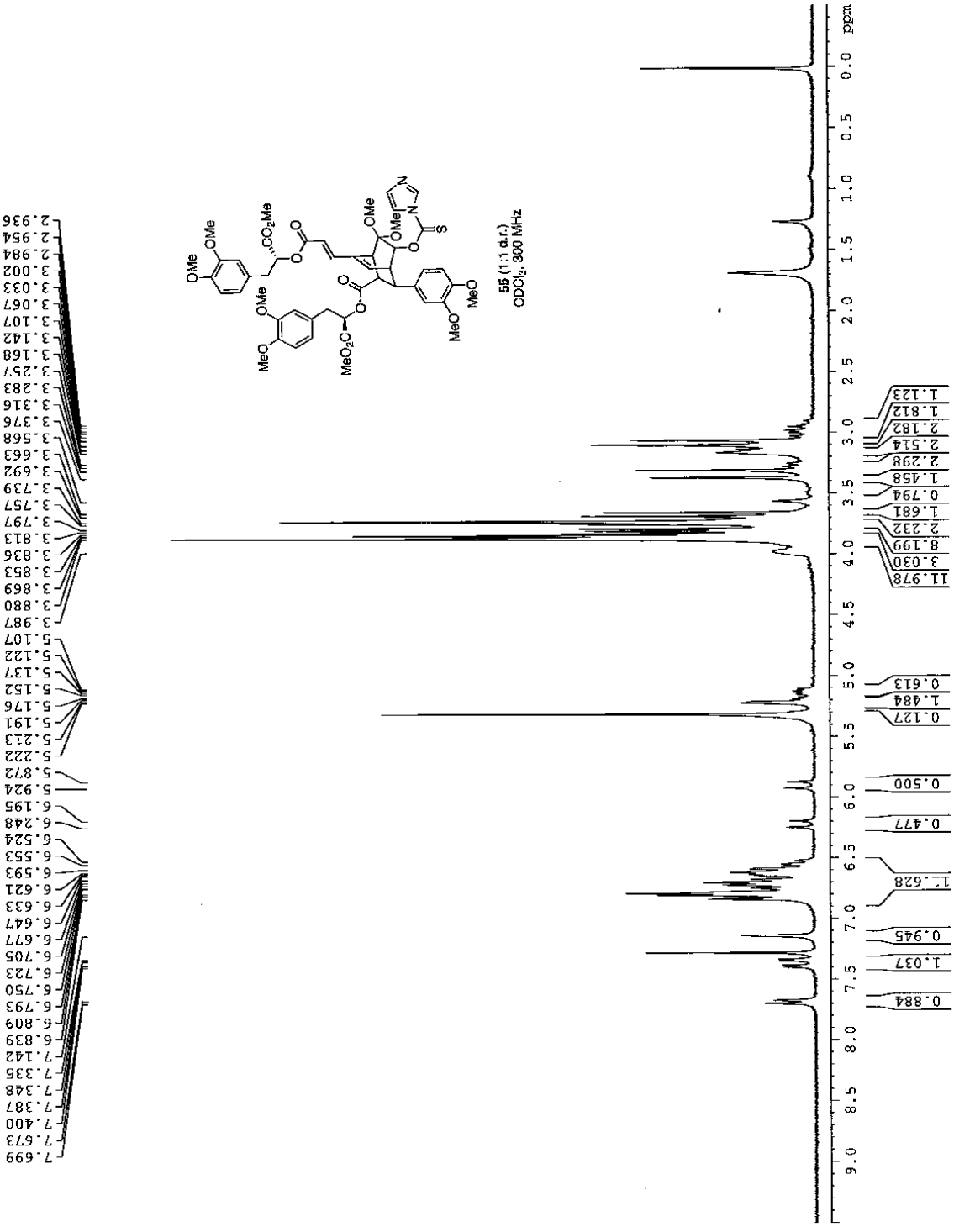
PeakTable

PDA Ch1 270nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	3.092	279921	75374	8.720	13.262
2	3.698	96773	18856	3.015	3.318
3	3.981	67490	11311	2.103	1.990
4	4.299	2765773	462807	86.162	81.430
Total		3209957	568348	100.000	100.000

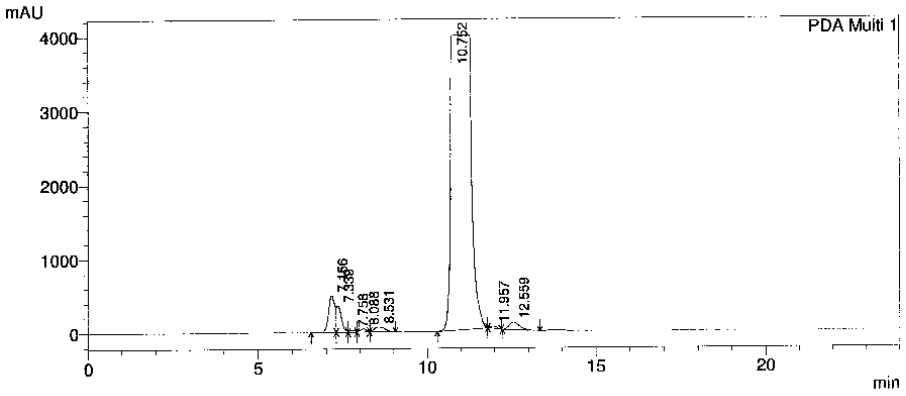


49


55 (1:1 d.r.)
CDCl3, 300 MHz
OMe
OMe
CO2Me
OMe
OMe
MeO
MeO2C
MeO
MeO
N
N
S
O
ppm
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
11.978
3.030
8.199
2.232
1.681
0.794
1.458
2.298
2.514
2.182
1.812
1.123
0.127
1.484
0.613
0.500
0.477
11.628
0.945
1.037
0.884
7.699
7.673
7.400
7.387
7.348
7.335
7.142
6.839
6.809
6.793
6.750
6.723
6.705
6.677
6.647
6.633
6.621
6.593
6.553
6.524
6.248
6.195
5.924
5.872
5.222
5.213
5.191
5.176
5.152
5.137
5.122
5.107
3.987
3.880
3.869
3.853
3.836
3.813
3.797
3.757
3.739
3.692
3.663
3.568
3.376
3.316
3.283
3.257
3.168
3.142
3.107
3.067
3.033
3.002
2.984
2.954
2.936

2/26/2011 14:20:22 1 / 1

<Chromatogram>

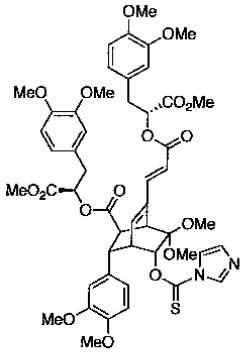


1 PDA Multi 1/270nm 4nm

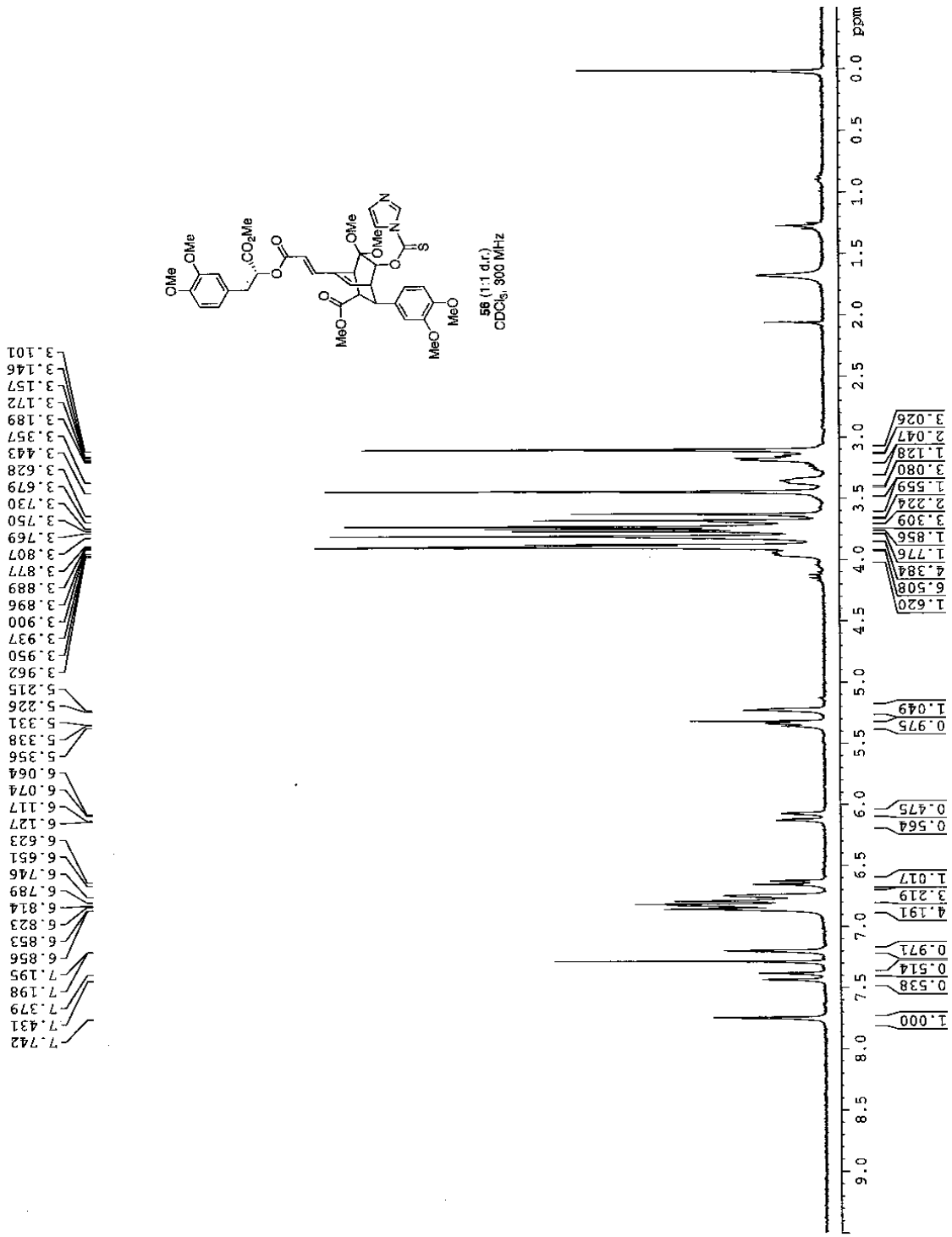
PeakTable

PDA Ch1 270nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	7.156	6612563	495266	3.666	9.721
2	7.339	3461113	352874	1.919	6.926
3	7.758	277067	21682	0.154	0.426
4	8.088	576274	44586	0.320	0.875
5	8.531	1447092	64294	0.802	1.262
6	10.752	165313535	3983073	91.655	78.176
7	11.957	369676	29084	0.205	0.571
8	12.559	2308119	104123	1.280	2.044
Total		180365439	5094983	100.000	100.000

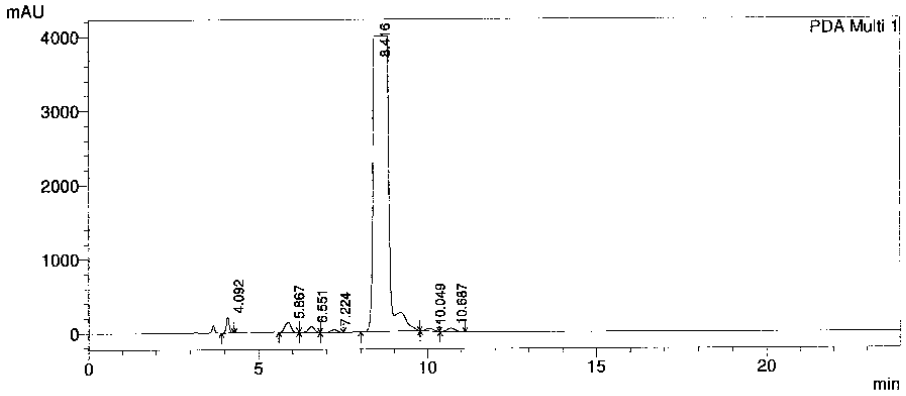


55 (1:1 d.r.)


56 (1:1 d.r.)
CDCl3, 300 MHz
ppm

2/26/2011 14:25:16 1 / 1

<Chromatogram>

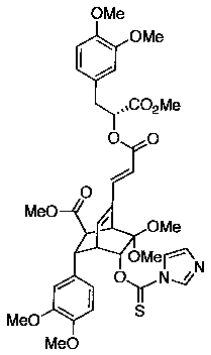


1 PDA Multi 1/270nm 4nm

PeakTable

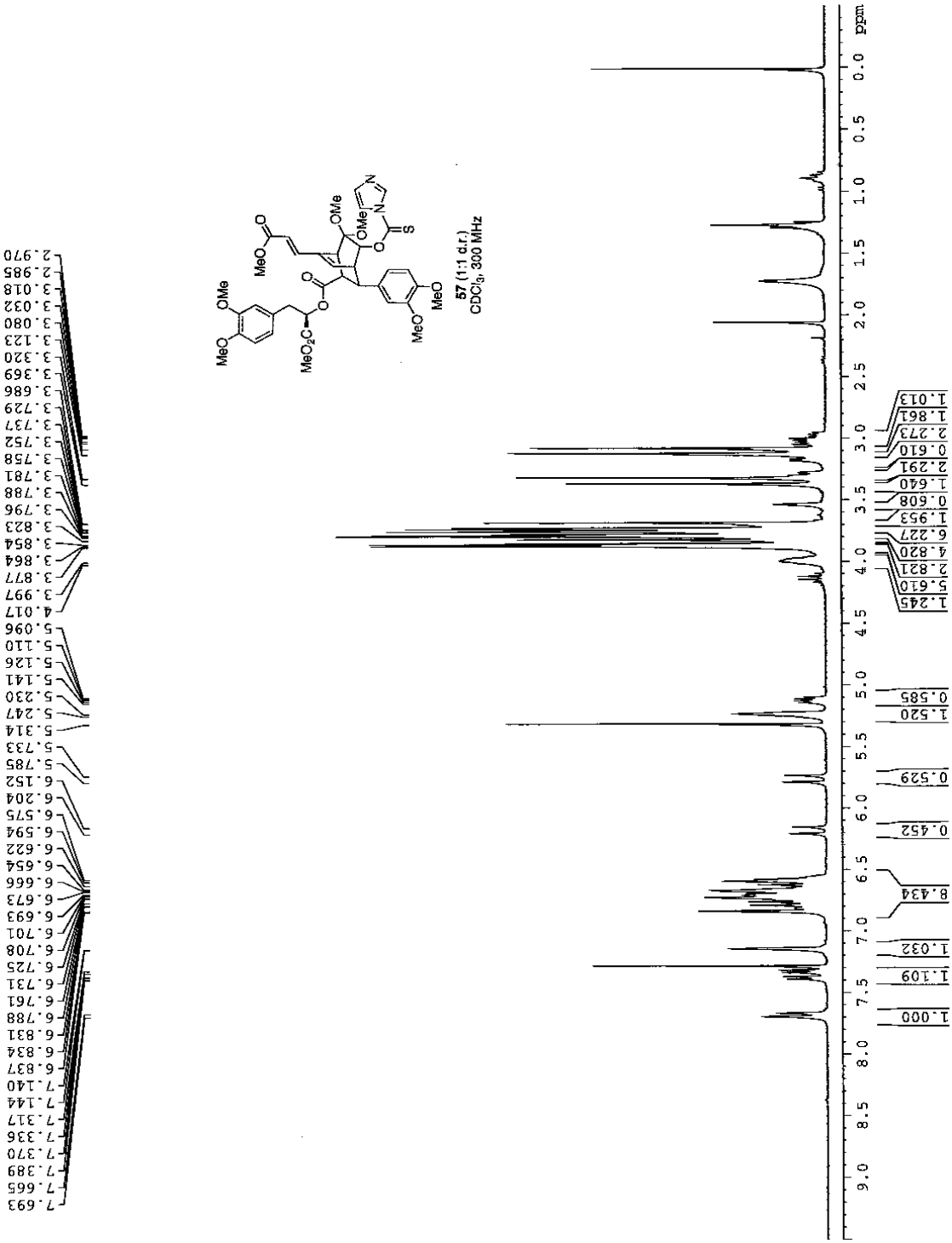
PDA Ch1 270nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	4.092	1229669	217449	0.925	4.793
2	5.867	1633813	131525	1.229	2.899
3	6.551	960900	80663	0.723	1.778
4	7.224	498511	37986	0.375	0.837
5	8.416	127274998	3986585	95.754	87.865
6	10.049	566249	36537	0.426	0.805
7	10.687	754774	46421	0.568	1.023
Total		132918913	4537166	100.000	100.000



56 (1:1 *d.r.*)

C:\LabSolutions\Data\matt\Lead\8mew18.lcd


57 (1:1 d.r.)
CDCl3, 300 MHz
MeO
OMe
MeO2C
OMe
MeO
MeO
OMe
N
N
S
O
ppm
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
1.000
1.109
1.032
8.434
0.452
0.529
1.520
0.585
1.245
5.610
2.821
4.820
6.227
1.953
0.608
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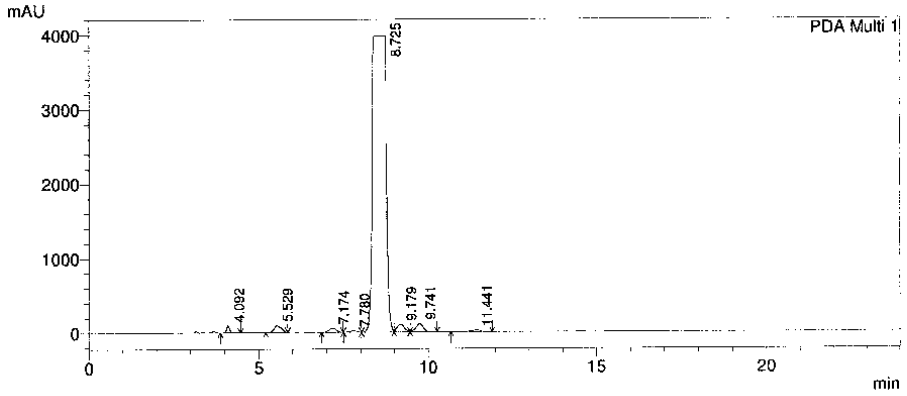
0.610
2.273
1.861
1.013

2/26/2011 14:04:39 1 / 1

<Chromatogram>

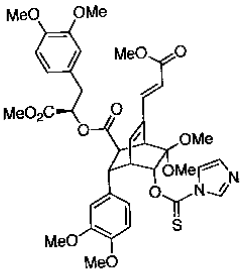


1 PDA Multi 1/254nm 4nm

PeakTable

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	4.092	581021	97085	0.490	2.165
2	5.529	1372553	94209	1.158	2.101
3	7.174	798060	56428	0.673	1.258
4	7.780	260901	21628	0.220	0.482
5	8.725	111807617	3976897	94.309	88.691
6	9.179	1576061	103619	1.329	2.311
7	9.741	1693425	111027	1.428	2.476
8	11.441	464871	23123	0.392	0.516
Total		118554509	4484015	100.000	100.000



57 (1:1 d.r.)

CHAPTER 4

Synthetic Studies Toward a Biomimetic Approach to the Myrmicarin Alkaloids

4.1 Introduction

The myrmicarin alkaloids (**1**–**7**, Figure 1) were isolated over a decade ago from the poison glands of several African ant species of the *Myrmicaria* genus by Francke and co-workers.[1] These oligomeric natural products represent the first examples of naturally occurring pyrrolo[2,1,5-*cd*]indolizidines, and the higher molecular weight dimeric and trimeric myrmicarins (**5**–**7**) represent some of the most complex alkaloids ever isolated from an insect. As an example of this complexity, myrmicarin 430A (**5**) displays a series of five contiguous stereocenters, one of which is quaternary, arranged around a pentasubstituted cyclopentane ring. Additionally, this molecule proved to be extremely sensitive to air, silica gel, and alumina, such that it was impossible to isolate and its structure had to be deduced from a series of two-dimensional NMR experiments on the crude poison gland extract, of which **5** was only a minor component.[1c]

The overall level of structural complexity of the myrmicarin alkaloids along with their marked fragility provide a unique set of challenges for chemists and an exceptional opportunity to test and discover new synthetic methodologies. The Snyder research group has been interested in the development of unified strategies towards the controlled synthesis of entire families of oligomeric natural products,[2] and we became interested in applying some of the lessons learned from previous syntheses to the myrmicarin family. This chapter details the completion of the shortest and most efficient total syntheses of the monomeric myrmicarin alkaloids (**1**–**4**) to date predicated upon a revised biosynthetic hypothesis, and our efforts to implement the ideas of that hypothesis towards a synthesis

of the dimeric member of the family, myrmicarin 430A (**5**). Although ultimately unsuccessful, these efforts have culminated in the achievement of the stereochemical complexity around the central cyclopentane ring of **5**, have questioned whether a biomimetic synthesis of this molecule is feasible in the laboratory, and have inspired future work towards this target.[3]

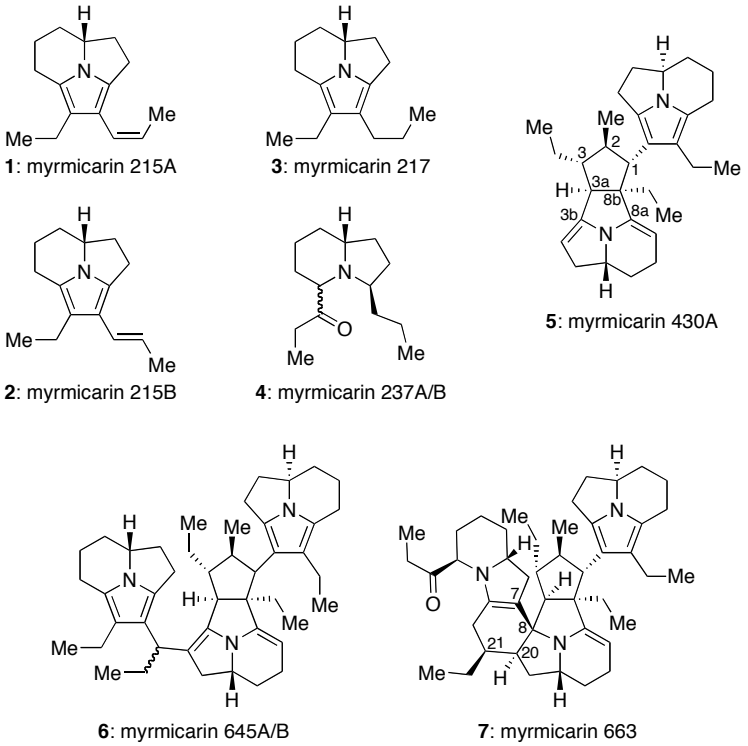


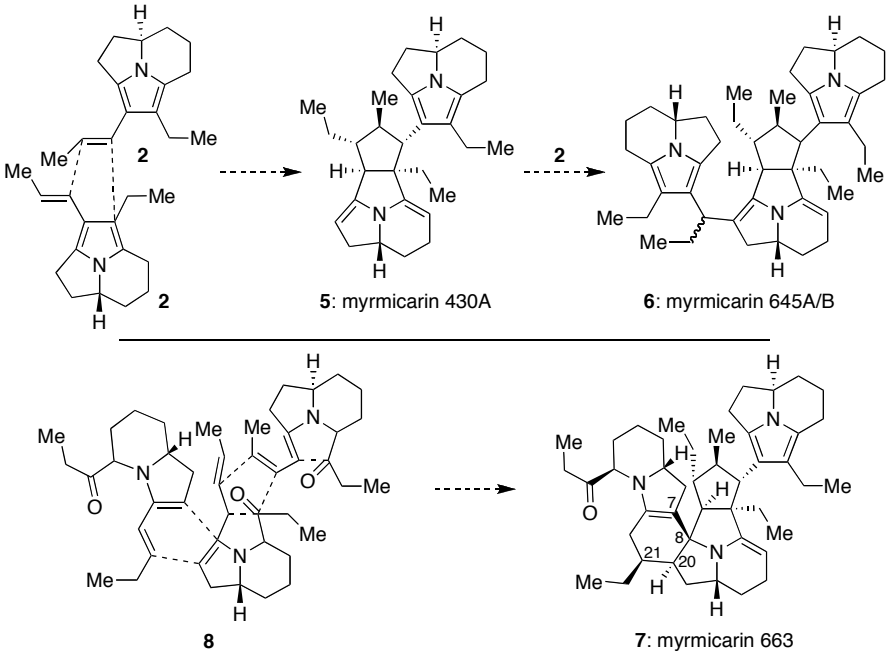
Figure 1. The myrmicarin family of alkaloid natural products.

4.2 Biosynthetic Hypotheses for the Myrmicarin Alkaloids

Several biosynthetic hypotheses have been advanced for the myrmicarin natural products, as shown in Scheme 1. In the first, proposed by Movassaghi and coworkers,[4]

dimeric myrmicarin 430A (**5**) could be derived from the union of two myrmicarin 215B (**2**) monomers through one of three possible pathways: azafulvenium chemistry, cycloaddition chemistry, or free-radical chemistry. In either of the first two pathways, it was proposed that a molecule of **2** could be activated by protonation of the alkene or ionization of a corresponding C-3 leaving group to afford an azafulvenium intermediate. This species could then electrophilically attack the alkene of a second molecule of **2** followed by a cyclization reaction or it could participate in a concerted [6π+2π] cycloaddition to generate the cyclopentane ring of myrmicarin 430A (**5**). In the third pathway, a sequence of events analogous to the azafulvenium pathway could proceed via a benzylic free radical intermediate generated by the addition of a hydrogen radical to the alkene of **2**. Finally, according to this biogenetic hypothesis, the addition of another activated molecule of **2** to the dimer (**5**) could lead to the formation of trimeric myrmicarin 645 (**6**).

In the second biosynthetic hypothesis proposed by the isolation chemists,[1b] shown in the bottom half of Scheme 2, trimeric myrmicarin 663 (**7**) could be derived from the union of indolizidine starting materials shown within **8**. This proposal was predicated upon the observation of molecules of mass 233 during mass spectrometry on the crude poison gland extracts.[5] However, such indolizidine monomers have not been isolated, and their exact structure and the chemical pathway by which they could unite to make trimer **7** were not specifically defined.



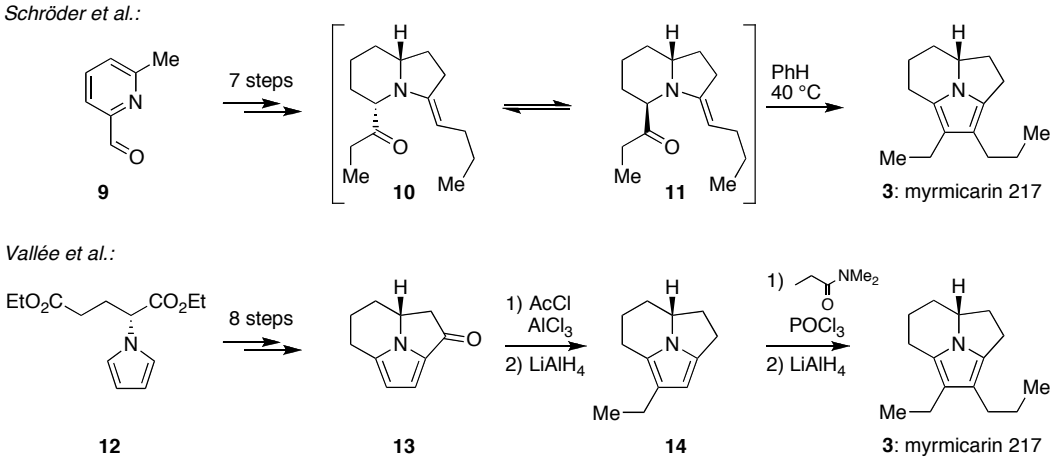
Scheme 1. Previous biosynthetic proposals to account for the formation of the higher-order myrmicarin alkaloids.

4.3 Previous Synthetic Efforts Towards the Myrmicarin Alkaloids

A number of racemic and enantioselective syntheses of the monomeric members of the family (**1**–**4**) have been completed.[1a,6] The first synthesis of myrmicarin 217 (**3**) was accomplished by Schröder and Francke in 1998.[6a] Here, enamine **10** was prepared from pyridine derivative (**9**) and was found to be configurationally and chemically unstable, undergoing epimerization at C-5 and cyclodehydration to form myrmicarin 217 (**3**) in 53% yield upon heating in benzene for 2 days. Unclear was which of the two isomers (**10** or **11**) or both were undergoing the cyclization reaction to afford the natural product.

In the first enantioselective synthesis of myrmicarin 217 (**3**) published in 2000,[6b,c] Vallée and coworkers introduced the pyrrole subunit early on by condensing the diethyl

ester of glutamic acid with tetrahydro-2,5-dimethoxyfuran to afford intermediate **12**. From this, another eight steps were required to afford tricyclic intermediate **13**, which subsequently underwent a Friedel–Crafts acylation and $LiAlH_4$ reduction followed by a Vilsmeier–Haack formalytion and another $LiAlH_4$ reduction to afford the natural product.

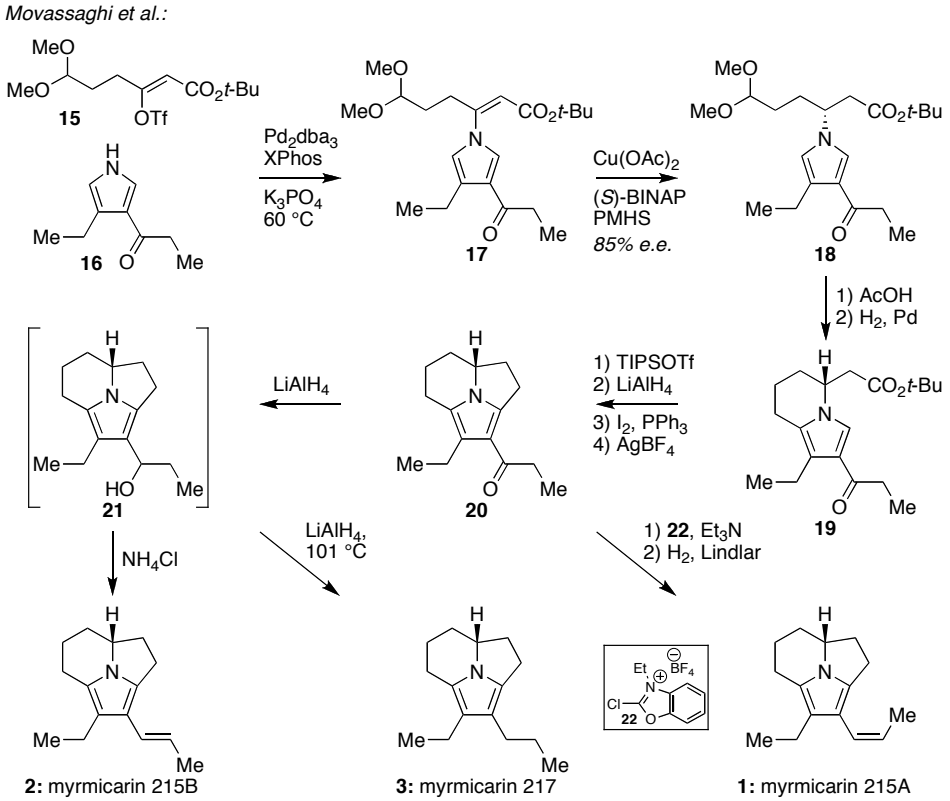


Scheme 2. Previous syntheses of myrmicarin 217 (**3**).

The first synthesis of myrmicarin 215A (**1**) and 215B (**2**) was completed by Movassaghi and Ondrus in 2005.[6e] They also employed a strategy that introduces the pyrrole unit early on in the synthesis. As shown in Scheme 3, a Pd-mediated coupling between triflate **15** and pyrrole **16** afforded *N*-vinyl pyrrole **17**. This intermediate was then subjected to an enantioselective hydrogenation protocol to afford product **18** with 85% e.e. From here, a series of standard Friedel–Crafts cyclizations inspired by the Vallée work (*vide supra*) afforded tricyclic ketone **20**, which was then converted in several additional steps to myrmicarin 215A (**1**), 215B (**2**) and 217 (**3**).

Finally, [3+2] cycloaddition reactions between quinolizidine-based azomethine ylides and electron-deficient alkynes was successfully used to access a variety of

pyrrolo[2,1,5-*de*]quinolizidines.[7] However this type of reaction failed with the corresponding indolizidine-based azomethine ylides and did not ultimately lead to the synthesis of the tricyclic myrmicarin natural products.



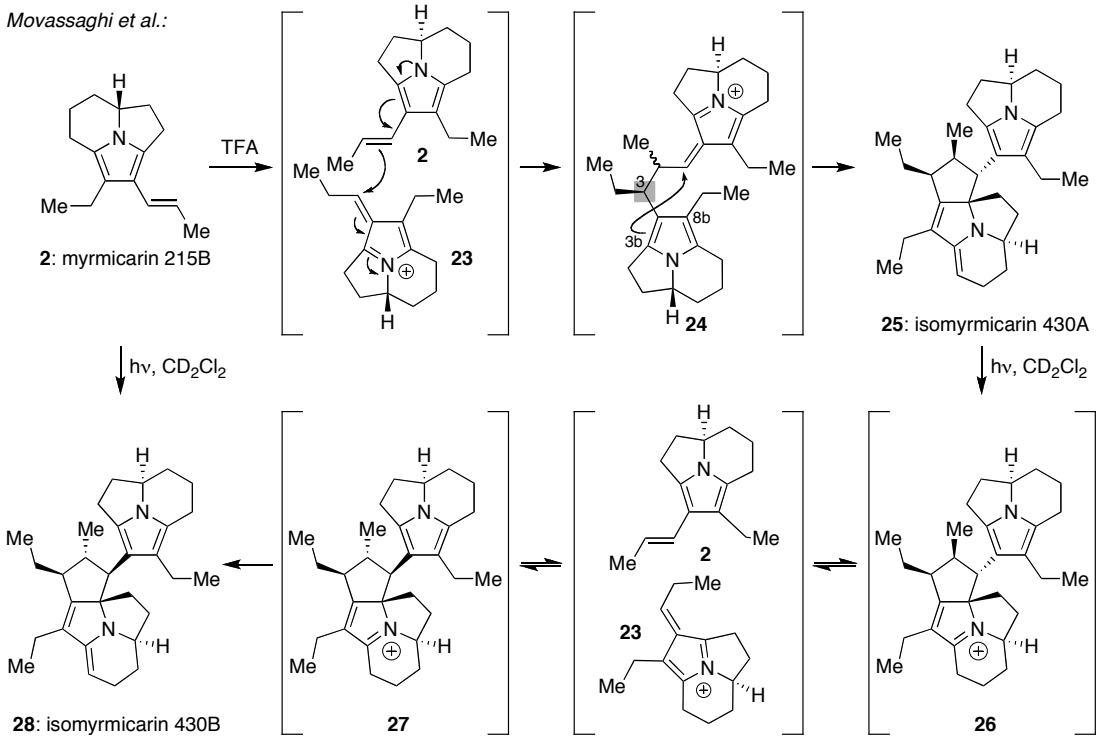
Scheme 3. Movassaghi's enantioselective synthesis of the monomeric tricyclic myrmicarin alkaloids (**1**–**3**).

However, despite significant efforts, particularly by the Movassaghi group[4,8] as summarized in Scheme 4, none of the higher-order natural products have yet been achieved in the laboratory. Inspired by their biogenetic proposal for the higher order myrmicarins (*vide supra*), the tricyclic natural product (**2**) was treated with an equivalent

of TFA in benzene, which led to protonation to afford presumed azafulvenium intermediate **23**. Although this intermediate was never observed or characterized in the reaction mixture, it was assumed to exist as the *Z*-azafulvenium based on steric considerations, as it is shown in Scheme 4. Unprotonated **2** served as a nucleophile to form the first C–C bond by attack from the less-hindered convex face of **23**. This operation set the stereochemistry of the newly formed ethyl group at C-3 incorrectly (see intermediate **24** *vs.* **5**, Figure 1), and, subsequently, the second C–C bond formation occurred from the undesired C-3b position of the pyrrole to afford an epimeric and regioisomeric product, isomyrmicarin 430A (**25**). When this product was exposed to slowly generated HCl by irradiation of **25** dissolved in CD_2Cl_2 (residual H_2O in the solvent ensured that HCl and not DCl was the active acid source), a new heptacyclic product (**28**) was generated in which the stereochemical arrangement of the methyl and aryl substituents along the cyclopentane backbone had been reversed. Deuterium labeling studies confirmed that the conversion of **25** to **28** occurred through complete reversal of the reaction to tricyclic monomers **2** and **23**, and product **28** thus appeared to be a thermodynamic sink for the acid-promoted dimerization of myrmicarin 215B (**2**). As a result, it was also possible to convert **2** to **28** directly under the same reaction conditions. Additionally, when myrmicarin 215A (**1**) was treated with protic acids, it underwent a slow isomerization to 215B (**2**), which then led to dimers **25** and/or **28.**

Further studies by these researchers using a conformationally restricted electrophilic component, in which the ethyl group and the benzylic methylene of the 5-membered ring of **2** were linked by an O–Si–O bridge,[4] and other structural variants of

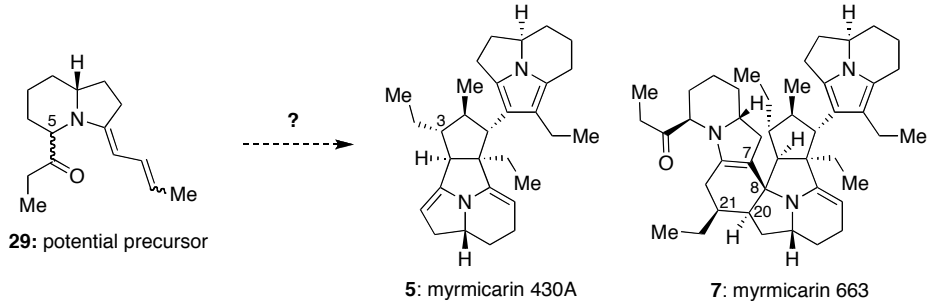
starting material **2**[8d] were unproductive in altering the reactivity of the dimerization components and ultimately led to products analogous to **25** and **28**. The crucial question that remained unanswered, however, was that of the effect of the C-3 ethyl group stereochemistry on the regiochemical outcome of second C–C bond forming event, since these prior approaches were never able to access the correct epimer at that critical position in any amount.



Scheme 4. Summary of Movassaghi's efforts towards myrmicarin 430A (**5**, Figure 1).

4.4 A Novel Biomimetic Approach

Given the failure of previous approaches to access the correct C-3 ethyl group stereoisomer (see **5**, Figure 1, or **24**, Scheme 4, for numbering), its influence on regiochemical outcome of the cyclization step was unknown (*vide supra*). We wondered whether having that ethyl group in the α-orientation would bias the conformation of the intermediate azafulvenium such that the cyclization would occur from the desired C-8b position. Therefore, a new approach towards dimeric molecules that would enable access to the desired C-3 epimer was required. Based on past experience with the helicterin[2d] and yunnaneic acid natural products (Chapters 1 and 2) as well as other oligomeric natural product families synthesized in the Snyder group,[2bc] we sought an alternative, unique building block by looking for anomalous structural features within the higher molecular weight myrmicarins (**5**–**7**). Specifically, we wondered if myrmicarin 663 (**7**), whose structure is inconsistent with the direct oligomerization of myrmicarin 215 (**1** or **2**), could provide the needed design elements.



29: potential precursor

5: myrmicarin 430A

7: myrmicarin 663

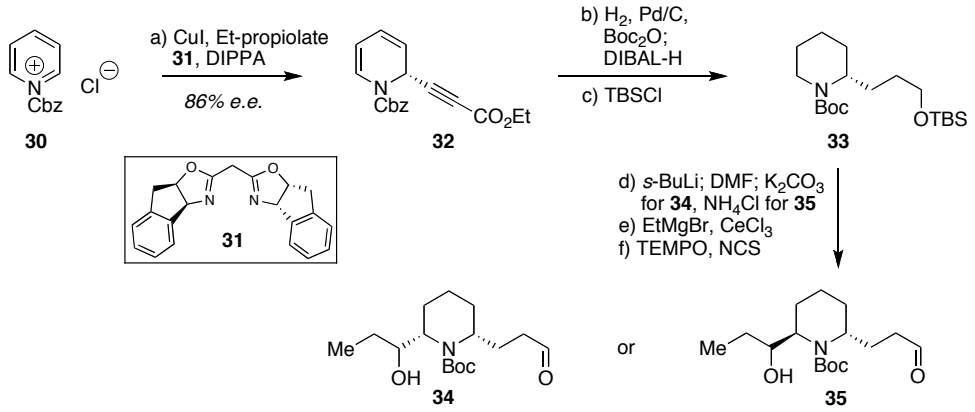
Scheme 5. Proposed building block for the synthesis of the higher-order myrmicarin alkaloids inspired by structural features within **7**.

Upon careful examination, retrosynthetic cleavage of the C-7–C-8 and the C-20–C-21 bonds within myrmicarin 663 (**7**, Scheme 5) suggested that a starting material such as **29**, which is structurally related to the biosynthetic precursors proposed by the isolation chemists (**8**, Scheme 1), could be a potential precursor to the higher-order members of the family (**5**–**7**). Additionally, this material could also be a precursor to the monomeric myrmicarins (**1**–**4**) and thereby constitute a unified approach towards the entire family of these natural products, which was a crucial consideration in its proposal as a building block. At this stage, however, the stereochemistry at C-5 and the alkene isomer of **29** needed to afford the correct dimerization epimer were unclear. Thus we set out to design a synthesis capable of accessing all four possible variants of the building block, using chemoselective reactions to enable efficient syntheses.

4.5 Preparation of Dienamine Building Blocks and Total Synthesis of the Monomeric Myrmicarin Alkaloids

Our synthesis began with the Cu-catalyzed asymmetric addition of ethyl propiolate to pyridinium salt **30** using variant of a protocol originally developed by Ma and co-workers.[9] (Scheme 6). This event afforded intermediate **32** in 84% yield and established the first stereogenic center with 86% e.e. Subsequent one-pot global reduction and protecting group exchange, followed by *t*-butyldimethylsilyl (TBS) protection of the free alcohol, afforded piperidine derivative **33**. This set the stage for the first point of divergence in the sequence, in which *s*-BuLi deprotonation of the piperidine C-6 position

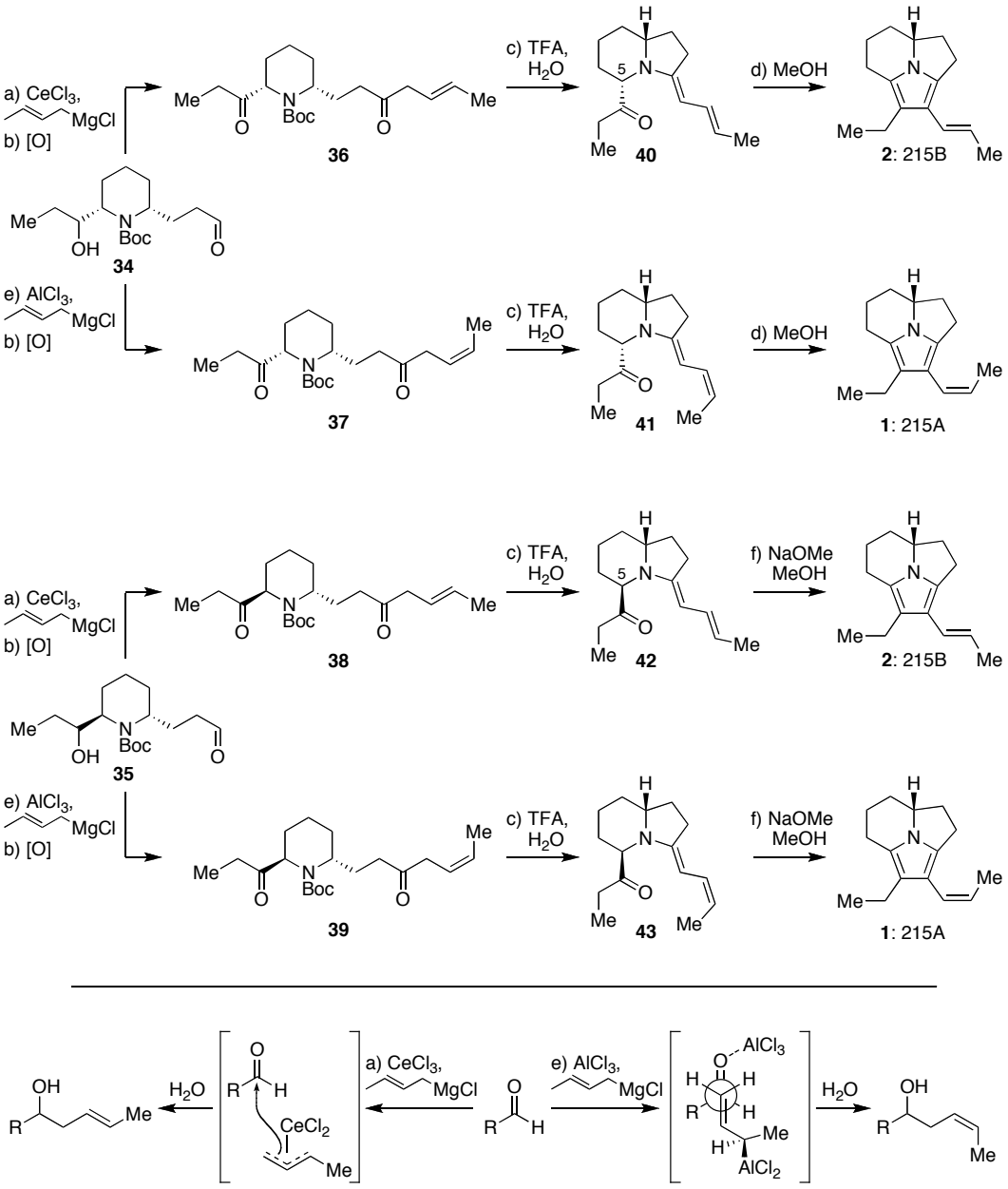
and *N*,*N*-dimethylformamide (DMF) quench of the resulting alkyllithium afforded an aldehyde[10] that was either epimerized *in situ* by addition of basic MeOH to afford the *cis*-disubstituted piperidine derivative or simply subjected to acidic work-up to afford the *trans*-disubstituted piperidine derivative. Each of these epimeric aldehydes was then elaborated independently to intermediates **34** and **35** by the one-pot addition of ethyl-Grignard reagent and subsequent deprotection of the TBS-protected alcohol followed by the chemoselective oxidation of the resulting primary alcohol.[11] Notably, the epimerization reaction described above occurred with a high degree of selectivity (>10:1) following the formylation of piperidine **33**. When that same reaction was attempted after the transformation of the formyl to an ethyl ketone, the ratio of *cis*/*trans* piperidine epimers obtained from the epimerization dropped to 3:2.



Scheme 6. (a) Cbz-Cl (5.0 equiv), CuI (0.1 equiv), **31** (0.12 equiv), DIPPA (5.0 equiv), ethyl propiolate (5.0 equiv), CH_2Cl_2, -65 °C, 14 h, 84%, 86% e.e.; (b) H_2 (1 atm), Pd/C (10 %, 0.05 equiv), Boc_2O (1.3 equiv), EtOAc, 23 °C, 16 h, 84 %; concentrate; DIBAL-H (1.1 equiv), THF, –78 °C, 45 min; 0 °C, 15 min, 98 %; (c) TBSCl (1.3 equiv), imidazole (2.0 equiv), CH_2Cl_2, 23 °C, 12 h, 98%; (d) *s*-BuLi (1.8 equiv), TMEDA (2.2 equiv), Et_2O, –78→40 °C, 1 h; DMF (10 equiv), –78→40 °C, 1.5 h; K_2CO_3/MeOH or NH_4Cl, 90% for **34**, 97% for **35**; (e) $CeCl_3$ (1.5 equiv), EtMgBr (3.0 M in Et_2O, 1.5 equiv), THF, –40 °C; HCl (1.0 M in H_2O, 2.0 equiv), 3 h, 70% for **34**, 89% for **35**; (f) TEMPO (0.05 equiv), NCS (1.0 equiv), *n*-Bu_4NCl (0.1 equiv), NaBr (1.0 equiv), CH_2Cl_2, pH 8.6 aqueous buffer, 0 °C, 1.5 h, 93 % for **34**, 96% for **35**. Boc_2O = di-*t*-butyldicarbonate, Cbz = carboxybenzyl, DIBAL-H = di-isobutylaluminum hydride, DIPPA = diisopropylpropylamine, TBS = *t*-butyldimethylsilyl, DMF = *N*,*N*-dimethylformamide, TEMPO = 2,2,6,6-tetramethyl-1-piperidinyloxy free radical, NCS = *N*-chlorosuccinimide, TMEDA = *N*,*N*,*N*',*N*'-tetramethylethylenediamine

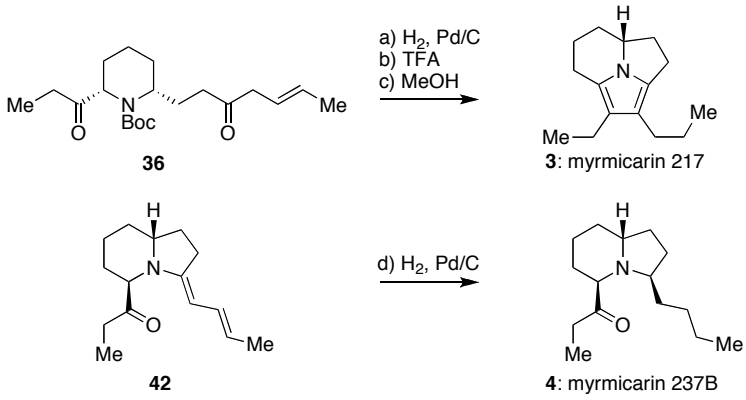
With this first stereodivergence secured, we next turned our attention to the selective linear crotylation of aldehydes **34** and **35**. We anticipated that this would provide selectively access both the *E*- and the *Z*-isomer of the desired β,γ-unsaturated ketone, which would in turn lead to the *E*- and the *Z*-isomer of the desired dienamine building block (**29**). An alternative approach of adding a 1-butenyl group nucleophile to these aldehydes, which then would lead to the corresponding α,β-unsaturated ketones, would only allow access to the *E*-isomer of building block **29**. As shown in Scheme 7, the crotylation approach proved successful. Exposure of aldehyde **34** and **35** to the crotylcerium reagent[12] prepared from $CeCl_3$ and 2-butenylmagnesium chloride afforded the linear *E*-isomers (6:1 α:γ, 8:1 *E*/*Z*), while use of the crotylaluminum reagent[13] from $AlCl_3$ furnished the linear *Z*-isomers (4:1 α:γ, > 15:1 *Z*/*E*). Subsequent Dess–Martin oxidation of the resultant diastereomeric mixture of diols and separation of the minor branched isomer through chromatography afforded rapid and highly selective access to **36–39** in 26–36% overall yield from commercially available starting materials. It is important to note that the original publication on the use of the crotylaluminum reagent used above reported the major product to be the *E*-isomer, even though no details were given on the stereochemical assignment. Our implementation of this methodology, however, led almost exclusively to the *Z*-isomer, even on substrates included in the original report. As shown at the bottom of Scheme 7, an open transition state with a branched crotylaluminum reagent could account for the observed outcome. The proposed transition state structure is consistent with the observation that at least twice as much $AlCl_3$ as Grignard reagent was required for the reaction to proceed with high selectivity for both the linear and the *Z*-alkene product. In addition, a similar rationale has been

invoked to explain other *Z*-selective Lewis acid-mediated linear crotylations.[14] In contrast, the crotylcerium reagent forms an η^3-complex[15] that reacts with the aldehyde through its less hindered side to afford a linear, *E*-alkene product.



Scheme 7. (a) $CeCl_3$ (3.0 equiv), 2-butenylmagnesium chloride (3.0 equiv), THF, –78→40 °C, 3 h; (b) Dess–Martin periodinane (3.0 equiv), CH_2Cl_2, –10 °C, 1.5 h, 71% over 2 steps, *E*/*Z* = 8:1 for **36**, 66% over two steps, *E*/*Z*=8:1 for **38**; (c) TFA/CH_2Cl_2/H_2O (4:4:1), 0 °C, 1 h, 99%; (d) MeOH, 23 °C, 1 h, 99%; (e) $AlCl_3$ (6.0 equiv), 2-butenylmagnesium chloride (3.0 equiv), THF, –78→0 °C, 1 h, 62% [two steps, (e) and (b)], *E*/*Z* > 15:1 for **37**, 72% [two steps, (e) and (b)], *E*/*Z* > 15:1 for **39**; (f) NaOMe (10 equiv), MeOH, 50 °C, 1 h, 85%. TFA = trifluoroacetic acid.

Finally, with diketones **36**–**39** in hand, *N*-Boc deprotection of each isomer with TFA in the presence of H_2O (in order to prevent alkene-isomerization into conjugation),[16] followed by a cold NaOH work-up, afforded dienamine building blocks **40**–**43** in near quantitative yield. Contrary to their monoenamine counterparts (**10** and **11**, Scheme 2),[5] these dienamines were configurationally and chemically stable, such that they did not undergo epimerization at C-5 or spontaneous cyclization to form pyrroles in non-polar solvents, even upon heating at temperatures above 80 °C for several days. However, in polar protic solvents, **40**–**43** readily cyclized to afford myrmicarins 215A (**1**) and 215B (**2**). Indeed, for **40** and **41**, simple dissolution in degassed MeOH achieved quantitative cyclizations in less than one hour, whereas **42** and **43** required heating in NaOMe/MeOH to 50 °C for one hour to affect initial epimerization at C-5 followed by cyclodehydration to afford the tricyclic natural products in 85% yield. Thus, these reactions completed the shortest and most efficient syntheses of **1** and **2** to date (10 steps, 29% and 31% overall yield).



Scheme 8. (a) H_2 (1 atm), Pd/C (10%, 0.1 equiv), EtOAc, 23 °C, 1 h, 99%; (b) TFA/CH_2Cl_2/H_2O (4:4:1), 0 °C, 1 h, 99%; (c) MeOH, 23 °C, 1 h, 99%; (d) H_2 (1 atm), Pd/C (10%, 0.1 equiv), EtOAc, 23 °C, 1 h, 37%. TFA = trifluoroacetic acid

In addition, this sequence enabled the synthesis of myrmicarin 217 (**3**) as well as myrmicarin 237B (**4**), thereby confirming that this route represents a universal approach to the monomeric tricyclic and bicyclic myrmicarin alkaloids (**1**–**4**, Scheme 8). More importantly, however, our ability to arrest or affect the cyclodehydration of dienamine building blocks **40**–**43** through solvent control gave us the means to explore their dimerization chemistry.

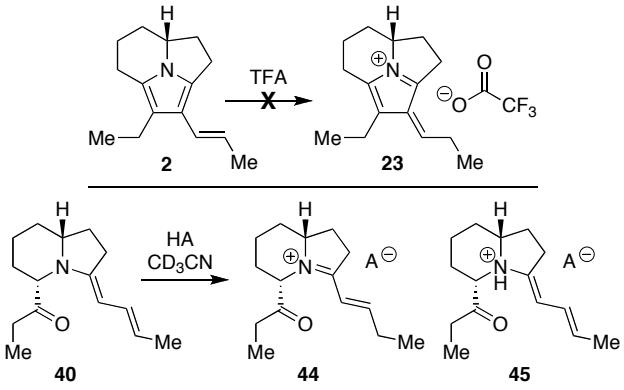
4.6 Explorations into the Dimerization of the Dienamine Building Blocks

Given the ease with which compounds such as **40** and **41** cyclized to the monomeric natural products (**1** and **2**) under biomimetic conditions (polar protic solvent), we sought to determine whether a related biomimetic dimerization could afford the higher-order myrmicarins (**5**–**8**). If successful, we hoped to firmly establish the biogenetic origin of these molecules as well as clarify the details of Francke hypothesis[1b] (**8**, Scheme 1). Unfortunately, despite numerous attempts, characterizable dimeric materials were never observed. Indeed, stirring various combinations of compounds **40**–**43** in acidic, neutral or basic buffers led exclusively to recovered starting materials with varying degrees of alkene isomerization and C-5 epimerization as well as to cyclization products **1** and **2**.

Thus, it appeared that a stepwise approach was needed to accomplish controlled dimerization, and we sought to identify a method to stoichiometrically and regioselectively protonate dienamines **40**–**43** at the γ-position to afford the corresponding extended iminium ions.[17] As indicated in Scheme 4, previous work by Movassaghi and

Ondrus demonstrated that myrmicarin 215 (**1** or **2**) cannot be stoichiometrically protonated to give a stable *Z*-azafulvenium (**23**), even though that structure is the presumed electrophile in the dimerization of **1** or **2**.[8] Therefore, efforts to identify a suitable solvent and acid combination to generate the extended iminium were initiated. After much experimentation, acetonitrile was identified as the best solvent for this protonation event, and a clear trend with respect to acid strength[18] emerged. As shown in Table 1, solutions of dienamine **40** in CD_3CN were added to 1.1 equivalents of various acids also in CD_3CN at ambient temperature, and the reactions were monitored by ^1H NMR. Weak acids such as acetic and dichloroacetic acid (entries 1 and 2) led only to alkene isomerization, whereas strong acids such as methanesulfonic acid (entry 4) led exclusively to *N*-protonated product **45**. TFA (entry 3) turned out to have just the right pK_a value to effect a stoichiometric γ-protonation and quantitatively generate iminium ion **44**. This protonated species was sufficiently stable in solution to enable full NMR characterization, and key nOe correlations revealed that it exists exclusively as the *E*-isomer in an s-*trans* conformation in solution, which is the conformational equivalent to a prohibitively strained *E*-azafulvenium ion.

Table 1. Regioselective protonation of dienamine **40** to form iminium ion **44**.

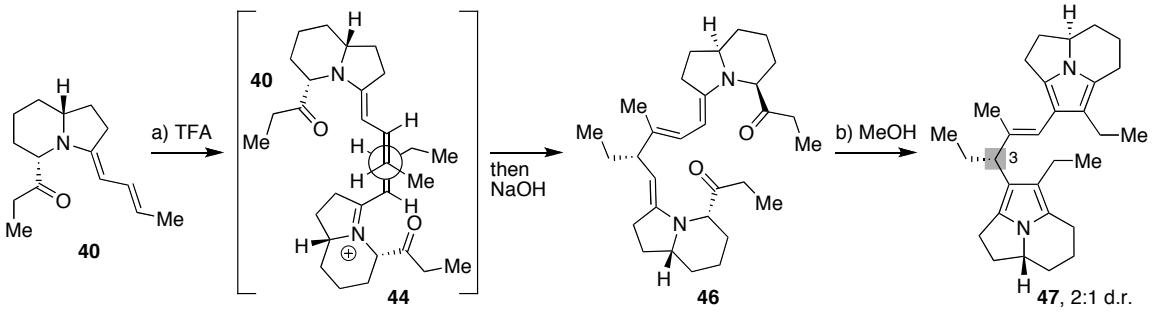


Entry	HA	pK_a	Result
1	AcOH	4.8	*alkene isomerization*
2	$CHCl_2CO_2H$	1.3	*alkene isomerization*
3	TFA	-0.25	**44**
4	$MeSO_3H$	-2.6	**45**

Reagents and conditions: *HA* (1.1 equiv), CD_3CN, 23 °C.

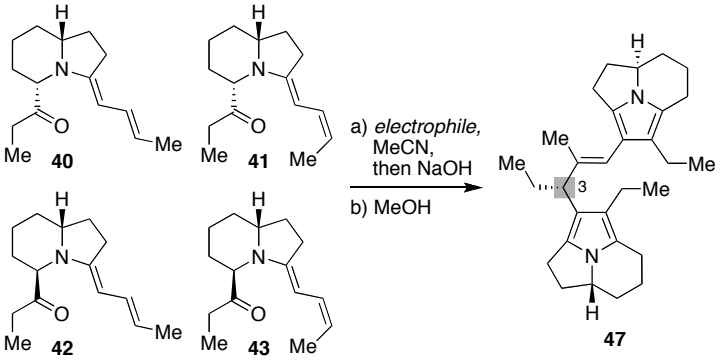
Having developed a method to stoichiometrically protonate dienamines to form corresponding iminium ions, we began to explore dimerizations. Following extensive experimentation (*vide infra*), Scheme 9 shows the optimized sequence developed for this process. A freshly prepared solution of dienamine **40** in MeCN was added to a solution of 0.5 equivalents of TFA at ambient temperature. After stirring for 30 min, the reaction was quenched with cold aqueous NaOH, and dimeric product **46** was observed as a complex mixture of diastereomers. Due to its extreme sensitivity to silica and alumina (neutral and basic), this compound was immediately taken forward, without further purification or characterization, into a degassed MeOH-mediated *bis*-cyclization reaction to afford hexacyclic product **47** as a 2:1 mixture of isomers in 54% yield. Although highly air-sensitive, this intermediate was purified on neutral alumina, and the diastereomeric

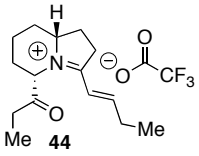
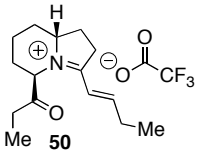
mixture was subjected to characterization by two-dimensional NMR techniques. These experiments, particularly two-dimensional nOe measurements, revealed that **47** was produced in a 2:1 epimeric ratio at the critical C-3 position and that the major product contained the ethyl group in the desired α-orientation (Scheme 9). The stereochemical outcome of this reaction can be explained by the preferred conformation of the extended iminium electrophile (**44**, *vide supra*). Similar to the dimerization of myrmicarin 215B (**2**), the stereochemistry in the major product results from the preferred approach of the nucleophile (**40**) onto the convex face of the electrophile (**44**). However, the difference in conformation of **44** (*E*-alkene), in contrast to the protonated form of myrmicarin 215 (**23**, Scheme 4, *Z*-azafulvenium), leads to the reversed C-3 ethyl group orientiation. Additionally, the increased conformational flexibility in both nucleophile and electrophile as well as a less sterically demanding environment near the electrophilic site compared with the dimerization of **2** is likely the reason for the reduced level of diastereoselectivity.



Scheme 9. (a) TFA (1.0 equiv), MeCN, 23 °C, 1 h; 1 M NaOH, 0 °C; (b) MeOH, 23 °C, 3 h, 54% over 2 steps. TFA = trifluoroacetic acid

Table 2. Optimization of the diastereoselectivity of the dimerization of various combinations of dienamines **40**–**43**.



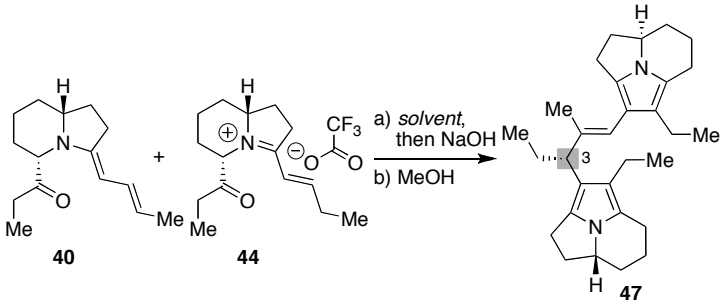
Entry	Electrophile	Nucleophile	d.r.
1		**40**	2:1
2		**41**	1:1.2
3		**42**	1.3:1
4		**43**	1:1
5		**40**	1:1.5
6		**42**	1:1.2
7		**43**	1:1.2

Reagents and conditions: (a) **44**/**50** (1.0 equiv), MeCN, 23 °C, 1 h; 1 M NaOH, 0 °C; (b) MeOH, 23 °C, 3 h or NaOMe (10 equiv), MeOH, 50 °C, 3 h.

In order to optimize the diastereomeric ratio of this dimerization, investigations into the effect of using various nucleophile/electrophile combinations (see Table 2) as well various as solvent and temperature (see Table 3) were carried out. However, every alteration led either to no improvement or to reversal of selectivity, with the d.r. for this reaction ranging from 2:1 to 1:1.5. Additionally, attempts to react dienamines **40**–**43** directly with myrmicarin 215A or 215B (**1** or **2**) were unproductive. Nonetheless, the two diastereomers of **47** were separable by reverse-phase HPLC to afford the desired epimer in pure form. Alternatively, it was also possible to perform a kinetic resolution of intermediate **46** as the major C-3 α-ethyl epimer underwent *bis*-cyclization faster than the

minor C-3 β-ethyl epimer. Using *i*-PrOH instead of MeOH allowed for a sufficiently slow overall rate that **47** could be enriched to a 5:1 d.r., albeit in reduced yield (12%). This secured access to the previously unattainable C-3 α-ethyl isomer through a sequence that was dependent on our ability to access stable dienamine building blocks, form stable iminium species from them, affect a regioselective dimerization, and use solvent changes to control the timing of the cyclodehydration.

Table 3. Optimization of solvent and temperature for the dimerization of dienamine **40**.



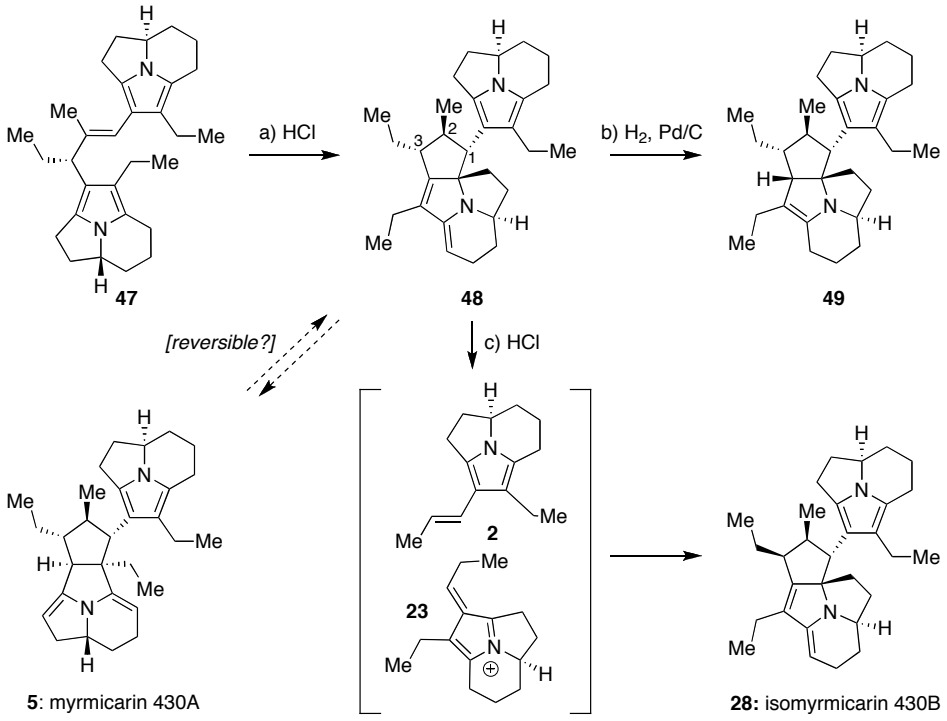
Entry	Solvent	Temperature (°C)	d.r.
1	MeCN	23	23
2	MeCN	0	2:1
3	MeCN	–20→0	2:1
4	DMF	23	1:1
5	DMSO	23	2:1
6	$MeNO_2$	23	2:1

Reagents and conditions: (a) **40** (1.0 equiv), **44** (1.0 equiv), *solvent*, *temperature*, 1 h; 1 M NaOH, 0 °C; (b) MeOH, 23 °C, 3 h.

4.7 Synthetic and Theoretical Studies Directed Towards Myrmicarin 430A (5)

The remaining question to address at this stage was whether this previously unattainable ethyl group stereochemistry could influence the regiochemistry of the final ring closure. Thus, a method of activation for the alkene within **47** was needed. Movassaghi and co-workers had previously shown that a hexacyclic compound such as **47**, albeit with the opposite ethyl-group stereochemistry, could be induced to cyclize in photochemically–irradiated CH_2Cl_2.[8c] Furthermore, the azafulvenium intermediate resulting from the protonation of a hexacycle such as **47** is a presumed intermediate in the TFA-mediated dimerization of myrmicarin 215B (**2**, Scheme 4). As such, many protic acids (TFA, $MeSO_3H$, AcOH, HBr/AcOH, HCl), Lewis acids [BF_3•OEt_2, $In(OTf)_3$, $Sc(OTf)_3$, $Pd(OAc)_2$, $AuCl(PPh_3)$] as well as photochemical (with and without triplet sensitizers) and radical (AIBN/*n*-Bu_3SnH, AIBN/Ph_6Sn_2, BPO) conditions were screened to effect the cyclization of hexacycle **47**. Of all the methods attempted, most led to recovered starting material or decomposition, and only HCl proved capable of activating the alkene within **47**. As shown in Scheme 10, when treated with an ethereal solution of HCl in CH_2Cl_2 at 23 °C for 1 h and then worked up with base, ^{1}H NMR spectroscopy of the crude reaction mixture showed the exclusive conversion to hexacyclic compound **48**, the regio- and stereochemistry of which was determined from nOe correlations in **48** and reduced product **49**. Thus, the cyclopentane core of **48** had the *trans*/*trans* C-1–C-2/C-2–C-3 disposed backbone analogous to myrmicarin 430A (**5**), but was the result of the undesired regiochemical pyrrole attack onto the azafulvenium intermediate. As such, the

stereochemistry of the C-3 ethyl group was seemingly incapable of influencing the site of pyrrole attack in the ring closure reaction.



Scheme 10. (a) HCl (1.0 M in Et_2O, 20 equiv), CH_2Cl_2, 23 °C, 1 h, 60%; (b) H_2, Pd/C (10%, 0.8 equiv), C_6D_6, 0.5 h, 40%; (c) HCl (1.0 M in Et_2O, 20 equiv), CH_2Cl_2 or THF, 23 °C, 5 h.

The C-2 or C-5 acylation of simple pyrroles is generally considered a kinetic outcome, whereas the C-3 or C-4 acylation is often theremodynamic, and it has been possible to convert the kinetic product to the thermodynamic one under strongly acidic conditions and heat.[19] We consequently wondered if a similar situation was occurring with **48**, where this regioisomeric cyclization was perhaps a kinetic outcome, and myrmicarin 430A (**5**) could be accessed under thermodynamic conditions. Unfortunately, all attempts to isomerize **48** into **5** under strongly acidic conditions both with and without heating led to either recovered starting material or decomposition. Furthermore, attempting the cyclization of **47** with HCl both at –20 °C and 0 °C led only to variable

mixtures of starting material **47** and regiochemical cyclization product **48**. Finally, as shown in Scheme 10, exposure of **47** to HCl for prolonged periods (5 h or longer) at ambient temperature or for any period of thime at elevated temperatures (60–100 °C in THF or 1,4-dioxane) led to isomyrmicarin 430B (**28**) in accordance with the reversibility reported by Movassaghi (Scheme 4),[8c] indicating that this latter compound is likely the most stable isomer among heptacycles **25**, **28** and **48**.

In order to gain a better understanding of the energetic landscape linking hexacyclic starting material **47**, the undesired regiochemical cyclization product **48** and myrmicarin 430A (**5**), a series of *ab initio* calculations were performed on the protonated forms of these molecules. Figure 2 depicts an energy plot of equilibrium geometries derived from B3LYP[20]/6-31G(d) optimizations of the hexacyclic azafulvenium **50**, in its two rotameric forms about the C-3/C-3b bond (**50a** and **50b**), the two competing transitions states (**51** and **53**) and the two cyclization products (**52** and **54**). The results of these calculations indicate that the geometric difference between starting azafulvenium rotamers (**50a** and **50b**) is small with the major distinction arising from differences in the dihedral angle defined by carbon atoms 2-3-3a-8b (84° and 69°, respectively). Additionally, although the starting material rotamer **50a** leading to the natural product is lower in energy, the two transition states are essentially isoenergetic. Significantly, however, the undesired cyclization product (**52**) is thermodynamic by 2.9 kcal/mol, and it is almost 5 kcal/mol lower in energy than the natural product precursor (**54**) arising from C-8b ring closure.

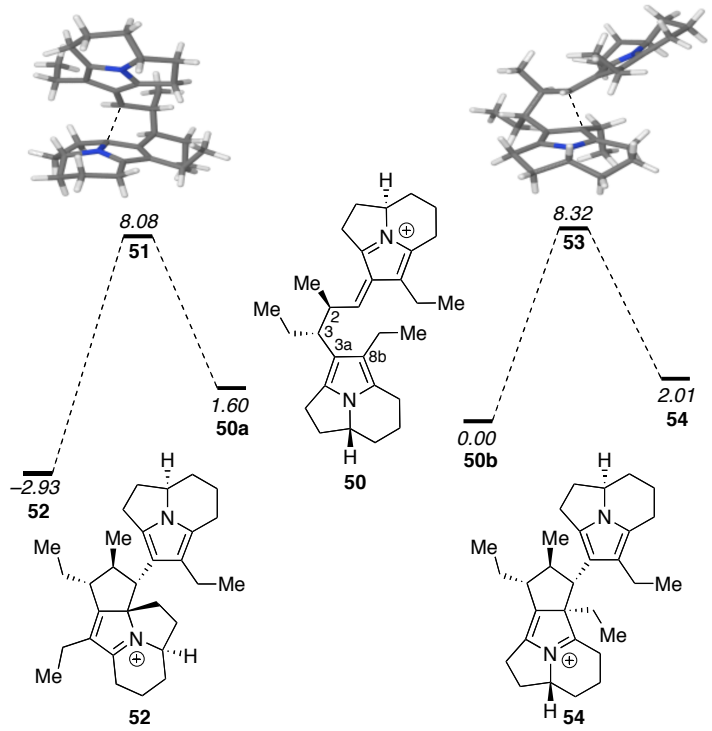
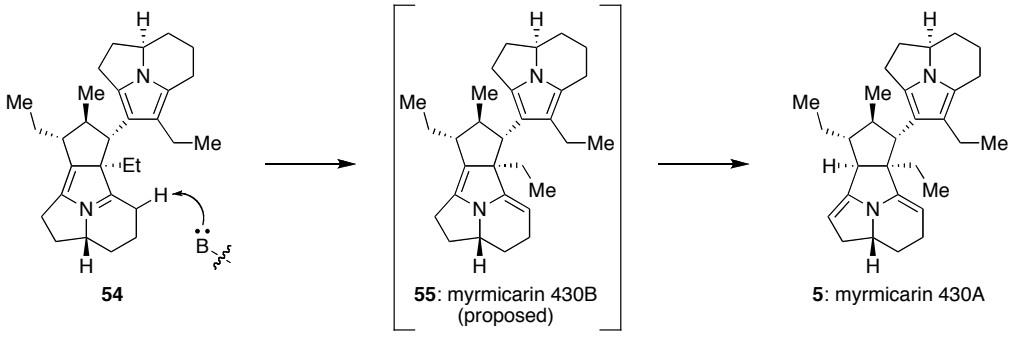


Figure 2. Potential energy surface of the acid-catalyzed cyclization of hexacycle **47**. All values are ΔG in kcal/mol and were obtained from B3LYP/6-31G(d) calculations.

Thus, the observed cyclization from **47** to **48** not only reflects a thermodynamic preference of the reaction, but there also appears to be no kinetic preference for the formation of the natural product heptacycle (**5**). As such, the collated results from the chemical experiments outlined in Scheme 10 and the computational analysis shown in Figure 2 strongly suggest that the synthesis of **5** is impossible under simple protic acid conditions from **47** or by any reaction in which its protonated form (**50**) is an intermediate. Consequently, either intermediates such as **47** are not biomimetic or enzyme participation determines the outcome of the cyclization reaction during biosynthesis. If enzymes are involved in this cyclization, their contribution can take one or more of several forms. An enzyme could prevent rotation about the C-2–C-3 bond in

the intermediate azafulvenium (**50**) and thereby prevent the molecule entering the undesired cyclization pathway. An enzyme could also stabilize the transition state (**53**) and the product **(54**) of the cyclization leading to the natural material sufficiently that this pathway could become kinetically and/or thermondynamically favored. Finally, the cyclization could be coupled to a regiospecific and irreversible protonation event, as shown in Scheme 11, that could trap **54** as enamine **55**, which has been proposed by the isolation chemists as the structure for myrmicarin 430B,[5] but could not be characterized due to its tendency to spontaneously convert to myrmicarin 430A (**5**) upon standing. This final hypothesis is particularly appealing given that once formed, **5** would first have to isomerize back to the less stable **55** prior to protonation at C-8 and, therefore, is not likely to rearrange to **48** under acidic conditions.



Scheme 11. Proposed regiospecific and irreversible deprotonation of **54** to afford myrmicarin 430A (**5**).

4.8 Conclusion

We have developed an efficient enantioselective route to dienamine building blocks **40**–**43**, and have completed the shortest and highest-yielding synthesis to date of four monomeric myrmicarin alkaloids (**1**–**4**). Our studies suggest that, given the ease with which some of them cyclize to form pyrroles under biomimetic conditions, mono- and dienamines derived from oxidation of myrmicarin 237A or 237B (**4**) could be the biosynthetic precursors to the tricyclic pyrroloindolizidine members of the family (**1**–**3**). Furthermore, we have been able to achieve controlled acid-mediated dimerizations of dienamines **40**–**43** that provided access to the crucial C-3 ethyl group stereochemistry found in the higher order myrmicarins (**5**–**7**) for the first time. Further HCl-mediated cyclization of such a dimeric compound led to a product that resulted from a regioisomeric attack of the nucleophilic pyrrole, indicating that the C-3 stereochemistry does not influence the regiochemical outcome of the final bond formation. Nevertheless, the stereochemistry around the central cyclopentane ring matched that for myrmicarin 430A (**5**). Our results question whether hexacyclic intermediate **47** is biomimetic and, as such, suggest that methods other than acid-catalysis are needed if this intermediate is to be converted into the natural product in the laboratory.

The research presented in this chapter was conducted as a collaborative effort with fellow graduate student Adel M. ElSohly. Ideas, plans, synthetic intermediates, experimental results and conclusions were discussed and shared on a regular basis, and work was attributed with the goal of maximizing the overall efficiency of the team. Adel is acknowledged for performing the calculations.

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4.10 Experimental Section

General Procedures. All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Dry tetrahydrofuran (THF), toluene, benzene, diethyl ether (Et_2O), and methylene chloride (CH_2Cl_2) were obtained by passing commercially available pre-dried, oxygen-free formulations through activated alumina columns. Acetonitrile (MeCN) was dried and stored over 3 Å molecular sieves. Yields refer to chromatographically and spectroscopically (^1H and ^{13}C NMR) homogeneous materials, unless otherwise stated. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Reactions were magnetically stirred and monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent and cerium sulfate (CAM) or aqueous $KMnO_4$, and heat as developing agents. SiliCycle silica gel (60, academic grade, particle size 0.040–0.063 mm) was used for flash column chromatography. Where stated, Aldrich neutral alumina was used for flash chromatography. NMR spectra were recorded on Bruker DPX 300, Avance II 400, Avance III 400 and DMX 500 instruments and calibrated using residual undeuterated solvent as an internal reference ($CDCl_3$: 7.26 ppm for ^1H, 77.0 ppm for ^{13}C; C_6D_6: 7.16 ppm for ^1H, 128.06 for ^{13}C). The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, br = broad, app = apparent. IR spectra were recorded on a Perkin-Elmer 1000 series FT-IR spectrometer. High-resolution mass spectra (HRMS) were recorded in the Columbia University Mass Spectral Core facility on a JOEL HX110 mass spectrometer using FAB (fast atom bombardment) or APCI (atmospheric pressure chemical ionization) techniques.

Abbreviations. BEMP = 2-*tert*-butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2-diazaphosphorine, Boc = *tert*-butyloxycarbonyl, Cbz = carboxybenzyl, DIBAL-H = diisobutylaluminum hydride, DIPPA = diisopropylpropylamine, DMF = *N,N*-dimethylformamide, NCS = *N*-chlorosuccinimide, TBS = *tert*-butyldimethylsilyl, TEMPO = 2,2,6,6-tetramethyl-1-pieridinyloxy free radical, TFA = trifluoroacetic acid, THF = tetrahydrofuran, TMEDA = *N,N,N',N'*-tetramethylethylenediamine.

Ligand 31. (1*S*,2*R*)-(–)-*cis*-1-Amino-2-indanol (1.08 g, 7.24 mmol, 2.1 equiv) and diethyl malonimidate dihydrochloride (0.80 g, 3.46 mmol, 1.0 equiv) were taken up in CH_2Cl_2 (80 mL), and the resulting suspension was refluxed for 16 h. Upon completion, the reaction contents were poured into water (160 mL) and extracted with CH_2Cl_2 (4 × 40 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The resultant crude product was recrystallized from *i*-PrOH (100 mL). The mother liquor was concentrated, and a second recrystallization was performed with *i*-PrOH (30 mL) to provide ligand **S1** (0.853 g from first crop, 0.071 g from second crop, 81% yield overall) as thin white needles. **S1**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47–7.45 (m, 2 H), 7.27–7.22 (m, 6 H), 5.57 (d, J = 8.0 Hz, 2 H), 5.34 (ddd, J = 8.0, 7.0, 1.8 Hz, 2 H), 3.39 (dd, J = 18.0, 7.2 Hz, 2 H), 3.26 (s, 2 H), 3.16 (dd, J = 18.0, 1.2 Hz, 2 H).

Dienecarbamate 32. To a stirred solution of ligand **31** (0.094 g, 0.285 mmol, 0.12 equiv) in CH_2Cl_2 (3.0 mL) at 23 °C was added CuI (0.047 g, 0.248 mmol, 0.1 equiv) and the resultant suspension was stirred at 23 °C for 5 min during which time the suspension turned pink/purple. This suspension was then cooled to –78 °C and stirred for 10 min. Ethyl propiolate (1.25 mL,

12.4 mmol, 5.0 equiv) was added dropwise as a neat liquid followed by freshly distilled diisopropylpropylamine (2.27 mL, 12.4 mmol, 5.0 equiv). The resultant peach colored suspension was stirred at –78 °C for 45 min. In a separate flask, a solution of pyridine (0.2 mL, 2.48 mmol, 1.0 equiv) in CH_2Cl_2 (2.0 mL) was cooled to –40 °C and benzyl chloroformate (1.75 mL, 12.4 mmol, 5.0 equiv) was added dropwise with vigorous stirring. The resultant thick, white slurry (**30**) was warmed to 0 °C and stirred for 20 min before cooling to –78 °C. To this suspension was then added the above Cu-complex solution via cannula and the resulting green suspension was stirred at –65 °C for 14 h. Upon completion, the reaction contents were quenched at –65 °C with saturated aqueous $NaHCO_3$ (15 mL) and then warmed to 0 °C, at which point the reaction mixture turned dark red. The reaction mixture was then extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated. The resultant dark red oil was purified by flash column chromatography (silica gel, hexanes/EtOAc, 19:1) to afford compound **32** (0.650 g, 84% yield) as a yellow oil. **32:** R_f = 0.40 (silica gel, hexanes/EtOAc, 4:1, CAM stain); $[\alpha]^{22}_D$ = +510.0° (*c* = 0.18, CH_2Cl_2); IR (film) ν_{max} 1705, 1386, 1325, 1234, 1103, 998, 976, 716, 696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46–7.34 (m, 5 H), 6.86 and 6.76 (rotamers, d, *J* = 7.6 Hz, 1 H), 6.06 (dd, *J* = 9.2, 5.6 Hz, 1 H), 5.82 and 5.72 (rotamers, d, *J* = 5.4 Hz, 1 H), 5.60 and 5.54 (rotamers, t, *J* = 6.8 Hz, 1 H), 5.41 and 5.36 (rotamers, t, *J* = 6.4 Hz, 1 H), 5.35–5.22 (m, 2 H), 4.23 (q, *J* = 7.0 Hz, 2 H), 1.32 (t, *J* = 7.0 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.2, 153.0, 152.7, 135.4, 128.6, 128.5, 128.3, 128.1, 125.4, 124.8, 124.0, 123.7, 116..4, 115.9, 105.5, 105.4, 83.8, 74.9, 68.6, 68.4, 62.1, 43.9, 43.4, 14.0; HRMS (FAB) calc. for $C_{18}H_{17}NO_4^+$ [M^+] 311.1158, found 311.1170; HPLC (Daicel Chiralpak AD-H 250 × 4.6 mm, hexanes/*i*-PrOH, 9:1, 1 mL/min, UV detector at 300 nm) $t_{R,minor}$ = 6.9 min, $t_{R,major}$ = 7.3 min, ee = 86%. [Note: this reaction has been performed on up to 7.7 mmol scale

without loss of enantioselectivity or yield, and on up to 24.8 mmol scale without loss of enantioselectivity, albeit in a somewhat reduced yield (77%). In order to obtain both high yield and high enantioselectivity, the purity of the CuI utilized (purified according to W. L. F. Armarego, D. D. Perrin, *Purification of Laboratory Chemicals*, **1998**, 4th ed.) as well as careful control of reaction temperature proved crucial. Compound **32** turns brown upon extended exposure to air (>15 min) and should be used immediately in the next reaction.]

Silylated piperidine derivative 33. Dienecarbamate **32** (2.55 g, 8.19 mmol, 1.0 equiv) was dissolved in EtOAc (80 mL) and then Pd/C (10 wt %, 0.436 g, 0.410 mmol, 0.05 equiv) and Boc_2O (2.14 g, 9.83 mmol, 1.2 equiv) were added at 23 °C. The reaction vessel was then purged three times with H_2 gas and stirred under a H_2 atmosphere for 16 h at 23 °C. Upon completion, the reaction mixture was filtered through a pad of Celite and concentrated directly to afford the desired *N*-Boc-protected piperidine ester intermediate. [Note: the purity of **32** and the quality of the Pd reagent greatly affected the rate of the final reduction of an enecarbamate intermediate.] Taken forward without any additional purification, this newly formed intermediate was dissolved in THF (50 mL) and the resultant solution was cooled to –78 °C. DIBAL-H (1.0 M in toluene, 20.5 mL, 20.5 mmol, 2.5 equiv) was then added dropwise. After stirring for 45 min at –78 °C, the reaction contents were warmed to 0 °C and then stirred for an additional 15 min. Upon completion, the reaction mixture was poured into a stirred biphasic mixture of hexanes (300 mL) and saturated aqueous $MgSO_4$ (50 mL) at 0 °C, warmed to 23 °C, and stirred for an additional 1 h with solid $MgSO_4$ being added periodically to maintain a free-flowing suspension. This mixture was then filtered, concentrated, and purified by flash column chromatography (silica gel, hexanes/EtOAc, 1:1) to afford the desired primary alcohol intermediate as a colorless liquid.

[Note: quenching the reaction under basic conditions (NaOH or Rochelle's salt) resulted in cyclization of the alcohol onto the Boc group.] Finally, the newly formed alcohol was dissolved in CH_2Cl_2 (50 mL) and imidazole (0.781 g, 11.5 mmol, 1.4 equiv) and TBSCl (1.48 g, 9.83 mmol, 1.2 equiv) were added sequentially at 23 °C. The resultant reaction solution was stirred for 16 h at 23 °C. Upon completion, the reaction contents were poured into saturated aqueous $NaHCO_3$ (50 mL) and extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The resultant yellow residue was purified by flash column chromatography (silica gel, hexanes/EtOAc, 19:1) to afford the TBS-protected piperidine derivative **33** (2.34 g, 80% yield over 3 steps) as a colorless liquid. **33**: R_f = 0.38 (silica gel, hexanes/EtOAc, 4:1, CAM stain); $[\alpha]^{22}_D$ = +17.9° (*c* = 1.02, CH_2Cl_2); IR (film) ν_{max} 2932, 2857, 1693, 1416, 1364, 1255, 1166, 1101, 836, 775 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.21 (br s, 1 H), 3.98 (br d, *J* = 10.0 Hz, 1 H), 3.63 (t, *J* = 5.4 Hz, 2 H), 2.76 (t, *J* = 12.6 Hz, 1 H), 1.78–1.68 (m, 1 H), 1.63–1.34 (m, 9 H), 1.46 (s, 9 H), 0.90 (s, 9 H), 0.06 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.1, 79.0, 62.9, 50.1, 38.5, 29.6, 28.6, 28.5, 25.9, 25.6, 19.0, 18.3, –5.3; HRMS (FAB) calc. for $C_{19}H_{39}NO_3Si^+$ [M+H^+] 358.2777, found 358.2766.

***Cis*-Piperidine-Derived Aldehyde 34.** TBS-protected piperidine derivative **33** (2.64 g, 7.37 mmol, 1.0 equiv) was dissolved in Et_2O (40 mL) and then TMEDA (2.43 mL, 16.2 mmol, 2.2 equiv) was added at 23 °C. The reaction contents were then cooled to –78 °C and *s*-BuLi (1.4 M in cyclohexane, 9.5 mL, 1.8 equiv) was added dropwise. The resultant pale yellow solution was allowed to warm to –40 °C over 1 h, then stirred at that temperature for an additional 1 h before cooling back to –78 °C. DMF (5.7 mL, 73.7 mmol, 10.0 equiv) was then added quickly in a single portion and the resultant solution was slowly warmed to –40 °C. After stirring for an

additional 1.5 h at –40 °C, the reaction contents were quenched by the addition of MeOH (50 mL) and warmed to 23 °C. Excess K_2CO_3 was then added, and the reaction was stirred at 23 °C for 2 h. Upon completion, the reaction contents were poured into saturated aqueous NH_4Cl (100 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated to afford a crude yellow oil. This material was purified by flash column chromatography (silica gel, hexanes/EtOAc, 19:1) to afford the desired *cis*-piperidine aldehyde product (2.31 g, 81% yield) as a colorless oil along with some mixed *cis*- and *trans*-piperidine material (0.270 g, 10% yield). The mixed fractions were recycled by resubjecting to K_2CO_3 (excess) in MeOH (6 mL) for 2 h at 23 °C. Work-up and purification as above afforded a second batch of *cis*-piperidine product (0.246 g, 91% yield for this step), which was combined with the product from above (2.56 g overall, 90% yield). [Note: careful control of reaction temperature is essential, as reaction temperatures above –40 °C led to large amounts of cyclization of the resultant alkoxide onto the neighboring Boc group.] Next, anhydrous $CeCl_3$ (3.33 g, 13.5 mmol, 1.3 equiv) was suspended in THF (50 mL). The resultant white slurry was stirred at 23 °C for 2 h, cooled to 0 °C, and a solution of *cis*-piperidine aldehyde (3.99 g, 10.3 mmol, 1.0 equiv) in THF (10 mL) was added via cannula. This mixture was stirred at 0 °C for 30 minutes, cooled to –40 °C, and then EtMgBr (3.0 M in Et_2O, 4.5 mL, 13.5 mmol, 1.3 equiv) was added dropwise via syringe. The resultant reaction mixture was slowly warmed to 0 °C and quenched with 1.0 M aqueous HCl (20.6 mL, 20.6 mmol, 2.0 equiv). The mixture was diluted with water (12 mL) and MeOH (12 mL) and was stirred at 23 °C for an additional 3 hours. The reaction contents were then extracted with CH_2Cl_2 (2 × 60 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated to afford the crude product as a thick oil. Purification of this material by flash column chromatography (silica gel, hexanes/EtOAc,

7:3→1:1) afforded the desired diol (2.17 g, 70% yield) as a thick colorless oil and as a single diastereoisomer based on ^{1}H NMR analysis. Finally, a portion of this diastereomerically pure diol (0.681 g, 2.26 mmol, 1.0 equiv) was dissolved in a 1:1 mixture of CH_2Cl_2 (20 mL) and aqueous pH 8.6 buffer ($NaHCO_3/K_2CO_3$, 20 mL) at 23 °C. The resultant biphasic mixture was then cooled to 0 °C and then NaBr (0.233 g, 2.26 mmol, 1.0 equiv), *n*-Bu_4NCl (0.031 g, 0.113 mmol, 0.05 equiv) and TEMPO (0.018 g, 0.113 mmol, 0.05 equiv) were added sequentially. Solid NCS (0.302 g, 2.26 mmol, 1.0 equiv) was then added in three equal portions, 15 min apart, to the vigorously stirred biphasic mixture. The bright resultant yellow reaction was stirred at 0 °C for an additional 1 h (to give a total of 1.5 h of stir time). Upon completion, the reaction contents were poured into water (40 mL) and extracted with CH_2Cl_2 (2 × 30 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated. The resultant crude product was then purified by flash column chromatography (silica gel, hexanes/EtOAc, 4:1→3:2) to afford aldehyde **34** as a colorless oil (0.629 g, 93% yield, 59% overall from **33**). **34**: R_f = 0.52 (silica gel, hexanes/EtOAc, 4:1, $KMnO_4$ stain); IR (film) ν_{max} 3414, 2934, 2874, 1723, 1660, 1455, 1408, 1366, 1321, 1172, 1069, 975 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.77 (s, 1 H), 4.17 (br dd, *J* = 13.6, 6.4 Hz, 1 H), 3.99 (td, *J* = 7.2, 2.4 Hz, 1 H), 3.60 (br s, 1 H), 2.46 (ddd, *J* = 17.6, 14.2, 7.4 Hz, 2 H), 2.05–2.01 (m, 1 H), 1.92 (dq, *J* = 14.0, 7.2 Hz, 1 H), 1.80–1.31 (m, 9 H), 1.44 (s, 9 H), 0.98 (t, *J* = 7.4 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.0, 155.8, 79.7, 74.5, 54.7, 49.7, 41.6, 28.4, 28.2, 27.4, 27.0, 23.8, 15.3, 10.6; HRMS (FAB) calc. for $C_{16}H_{30}NO_4^+$ [M+H$^+$] 300.2175, found 300.2172.

***Trans*-Piperidine-Derived Aldehyde 35.** TBS-protected piperidine derivative **33** (4.60 g, 12.9 mmol, 1.0 equiv) was reacted with *s*-BuLi as described above in the synthesis of

aldehyde **12**. However, upon completion of the formylation, the reaction contents were quenched at –40 ºC with saturated aqueous NH_4Cl (70 mL). The mixture was then allowed to warm to 23 °C and was extracted with Et_2O (2 × 50 mL). The combined organic layers were washed with brine (30 mL), dried ($MgSO_4$), filtered and concentrated to afford the crude product as a yellow oil. Purification of this material by flash column chromatography (silica gel, hexanes/EtOAc, 9:1) to afford the *trans*-piperidine aldehyde product (4.80 g, 97% yield) as a colorless oil. Next, a portion of this product (0.266 g, 0.690 mmol, 1.0 equiv) was reacted with EtMgBr in the presence of $CeCl_3$ according to the procedure described above in the second part of the synthesis of aldehyde **12** to afford the desired *trans*-piperidine diol (0.185 g, 89% yield) as a 1.2:1 mixture of diastereomers about the secondary carbinol. Finally, this product (0.185 g, 0.614 mmol, 1.0 equiv) was oxidized using TEMPO as detailed above to afford the desired aldehyde **35** (0.176 g, 96% yield, 83% overall from **33**) as a 1.2:1 mixture of diastereomers about the secondary carbinol. **35**: R_f = 0.54 (silica gel, hexanes/EtOAc, 4:1, $KMnO_4$ stain); IR (film) ν_{max} 3401, 2934, 2873, 1724, 1668, 1429, 1392, 1366, 1252, 1167, 1116, 1073, 873 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, integration of 1.0 per H for minor diastereomer, 1.2 per H for major diastereomer) δ 9.79 (app t, *J* = 1.2 Hz, 2 H), 4.13–4.04 (m, 2.2 H), 3.94 (ddd, *J* = 13.6, 6.0, 5.4 Hz, 1 H), 3.81 (ddd, *J* = 10.8, 5.4, 2.6 Hz, 1.2 H), 3.60 (ddd, *J* = 16.0, 5.4, 2.6 Hz, 1 H), 3.33 (td, *J* = 7.8, 4.4 Hz, 1 H), 3.04 (br d, *J* = 9.2 Hz, 1.2 H), 2.49–2.39 (m, 4.4 H), 2.11–1.99 (m, 2.2 H) 1.81–1.35 (m, 21 H), 1.44 (s, 9 H), 1.43 (s, 10.8 H). 0.99 (t, *J* = 7 Hz, 3 H), 0.97 (t, *J* = 7.2 Hz, 3.6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.7, 201.6, 157.2, 156.5, 80.5, 80.3, 74.2, 72.9, 57.7, 57.3, 54.4, 53.5, 41.1, 40.8, 28.4, 27.8, 27.7, 26.6, 25.1, 24.5, 23.3, 19.6, 17.7, 10.9, 10.2; HRMS (FAB) calc. for $C_{16}H_{30}NO_4^+$ [M+H^+] 300.2175, found 300.2162.

***Trans*-alkene 36.** A suspension of pre-dried $CeCl_3$ (1.85 g, 7.51 mmol, 3.0 equiv) in dry THF (40 mL) was cooled to 0 °C, and a solution of 2-butenylmagnesium chloride (0.5 M in THF, 15.0 mL, 7.51 mmol, 3.0 equiv) was added dropwise via syringe. The resulting intense orange-red solution was stirred for 30 min at 0 °C and then was cooled to –78 °C. A solution of aldehyde **34** (0.75 g, 2.50 mmol, 1.0 equiv) in THF (10 mL) was then added dropwise, and the resultant pale orange solution was allowed to warm to –40 °C over the course of 45 min. The reaction contents were then stirred at –40 °C for an additional 3 h and quenched by the addition of 10% aqueous AcOH (15 mL). The resultant biphasic mixture was warmed to 23 °C and extracted with Et_2O (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The crude product was used directly in the next reaction without any additional purification. [Note: proper drying of $CeCl_3$ is extremely important for the success of this reaction. The intense orange-red color is an indication that the desired crotylcerium reagent has been formed. When cooled to –78 °C, the suspension turns brown if the crotylcerium reagent has not been formed, which leads exclusively to the branched crotylation product.] Next, the crude product from above was dissolved in CH_2Cl_2 (20 mL) and cooled to –10 °C. Dess–Martin periodinane (3.18 g, 7.51 mmol, 3.0 equiv) was then added in a single portion and the reaction contents were allowed to warm slowly to 0 °C over 1.5 h. Upon completion, the reaction mixture was quenched at 0 °C by first diluting with EtOAc (10 mL) and then adding saturated aqueous Na_2SO_3 (15 mL). After stirring vigorously at 23 °C for 15 minutes, the reaction contents were then extracted with EtOAc (3 × 10 mL). The combined organic layers were washed sequentially with saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL), dried ($MgSO_4$), and concentrated. The resultant crude residue was purified by flash column chromatography (silica gel, Et_2O/hexanes, 1:9→3:19) to afford *trans*-alkene **36** (0.620 g, 8:1 *E*/*Z* ratio, 71% yield over 2 steps) as a colorless oil. **36**: R_f =

0.21 (silica gel, hexanes/EtOAc, 4:1, $KMnO_4$ stain); $[\alpha]^{22}_D$ = –38.6° (*c* = 0.20, CH_2Cl_2); IR (film) ν_{max} 2974, 2939, 1716, 1684, 1400, 1366, 1254, 1172, 1078, 874 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.59–5.48 (m, 2 H), 4.65 (br s, 1 H), 4.16 (m, 1 H), 3.10 (d, 2.8 Hz, 2 H), 2.61–2.38 (m, 4 H), 2.16–2.08 (m, 1 H), 1.74 (dtd, *J* = 14.4, 8.8, 6.0 Hz, 1 H), 1.68 (dd, *J* = 3.6, 1.2 Hz, 3 H), 1.67–1.42 (m, 6 H), 1.45 (s, 9 H), 1.05 (t, 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.6, 209.1, 155.6, 129.5, 123.2, 80.1, 77.2, 59.0, 50.0, 46.7, 39.7, 31.8, 28.4, 27.8, 24.5, 18.0, 15.9, 7.9; HRMS (FAB) calc. for $C_{20}H_{34}NO_4^+$ [M+H^+] 352.2488, found 352.2483.

***Cis*-alkene 37.** A solution of 2-butenylmagnesium chloride (0.5 M in THF, 9.56 mL, 4.78 mmol, 3.0 equiv) was diluted with dry THF (7.5 mL) and cooled to –78 °C. A solution of $AlCl_3$ (2.0 M in Et_2O, freshly prepared before use, 5.75 mL, 11.5 mmol, 6.0 equiv) was then added dropwise at –78 °C, leading to the formation of a white precipitate. After stirring for 10 min at –78 °C, a solution of aldehyde **34** (573 mg, 1.91 mmol, 1.0 equiv) in THF (2.5 mL) was added dropwise, and after 5 min of additional stirring, the reaction contents were immediately warmed to 0 °C by exchanging the dry ice/acetone bath with one made from ice and water. After stirring for 1 h at 0 °C, the reaction was quenched with saturated aqueous NH_4Cl (10 mL) and extracted with Et_2O (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to afford the desired intermediate, which was carried forward without additional purification. [Note: slow warming from –78 °C leads to diminished *E*/*Z* selectivity.] The crude product from above was dissolved in CH_2Cl_2 (8 mL) and cooled to –10 °C. Dess–Martin periodinane (2.43 g, 5.73 mmol, 3.0 equiv) was then added in a single portion and the reaction contents were allowed to warm slowly to 0 °C over 1.5 h. Upon completion, the reaction mixture was quenched at 0 °C by first diluting with EtOAc (10 mL) and then adding saturated aqueous

Na_2SO_3 (15 mL). After stirring vigorously at 23 °C for 15 minutes, the reaction contents were then extracted with EtOAc (3 × 10 mL). The combined organic layers were washed sequentially with saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL), dried ($MgSO_4$), and concentrated. The crude residue was carefully purified by flash column chromatography (silica gel, Et_2O/hexanes, 1:9→3:19), affording *cis*-alkene **37** (0.416 g, >15:1 *Z*/*E* ratio, 62% yield over 2 steps) as a colorless oil. **37:** R_f = 0.21 (silica gel, hexanes/EtOAc, 4:1, $KMnO_4$ stain); $[\alpha]^{22}_D$ = –45.6° (*c* = 0.525, CH_2Cl_2); IR (film) ν_{max} 2974, 2939, 1716, 1684, 1455, 1400, 1366, 1325, 1254, 1172, 1078, 874 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.66 (dqt, *J* = 10.8, 6.4, 1.6 Hz, 1 H), 5.58 (dtq, *J* = 10.8, 6.8, 1.6 Hz, 1 H), 4.65 (br s, 1 H), 4.17 (m, 1 H), 3.19 (d, *J* = 7.2 Hz, 2 H), 2.62–2.38 (m, 4 H), 2.16–2.08 (m, 1 H), 1.75 (dtd, *J* = 14.0, 8.4, 6.0 Hz, 1 H), 1.70–1.42 (m, 6 H), 1.62 (dd, *J* = 6.8, 1.2 Hz, 3 H), 1.45 (s, 9 H), 1.05 (t, 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.5, 208.5, 155.6, 127.5, 122.1, 80.1, 77.2, 59.0, 50.0, 41.3, 39.8, 31.8, 28.4, 27.8, 24.6, 15.9, 13.0, 7.9; HRMS (FAB) calc. for $C_{20}H_{34}NO_4^+$ [M+H^+] 352.2488, found 352.2489.

***Trans*-alkene 38.** This compound was prepared following the same general procedure as described for **36** above, ultimately affording *trans*-alkene **38** (0.244 g, ~8:1 *E*/*Z* ratio, 66% yield over 2 steps) as a colorless oil. **38:** R_f = 0.21 (silica gel, hexanes/EtOAc, 4:1, $KMnO_4$ stain); $[\alpha]^{22}_D$ = +14.2° (*c* = 1.16, CH_2Cl_2); IR (film) ν_{max} 2924, 2853, 1712, 1689, 1681, 1452, 1392, 1365, 1306, 1252, 1163, 1067 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.53 (m, 2 H), 4.05 (br s, 1 H), 3.81 (br s, 1 H), 3.08 (d, *J* = 5.6 Hz, 2 H), 2.48 (m, 3 H), 2.36 (dq, *J* = 17.2, 7.2 Hz, 1 H), 1.97–1.85 (m, 2 H), 1.77–1.45 (m, 6 H) 1.68 (d, *J* = 4.8 Hz, 3 H), 1.40 (s, 9 H), 1.06 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.7, 208.4, 155.9, 129.8, 122.9, 80.7, 77.2, 60.0,

52.3, 46.8, 39.1, 31.3, 28.2, 26.1, 24.4, 18.0, 16.7, 8.0; HRMS (FAB) calc. for $C_{20}H_{34}NO_4^+$ [M+H$^+$] 352.2488, found 352.2476.

***Cis*-alkene 39.** This compound was prepared following the same general procedure described for **37** above, ultimately affording *cis*-alkene **39** (0.270 g, >15:1 *Z*/*E* ratio, 72% over 2 steps) as a colorless oil. **39:** R_f = 0.21 (silica gel, hexanes/EtOAc, 4:1, $KMnO_4$ stain); $[\alpha]^{22}_D$ = +18.7° (*c* = 1.07, CH_2Cl_2); IR (film) ν_{max} 2975, 2937, 1716, 1686, 1393, 1365, 1304, 1253 1166, 1119 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.68 (dqt, *J* = 10.8, 6.8, 1.6 Hz, 1 H), 5.57 (dtq, *J* = 10.8, 6.8, 1.6 Hz, 1 H), 4.07 (br s, 1 H), 3.83 (br s, 1 H), 3.18 (d, *J* = 6.8 Hz, 2 H), 2.57–2.45 (m, 3 H), 2.37 (dq, *J* = 17.2, 7.2 Hz, 1 H), 1.96–1.88 (m, 2 H), 1.80–1.46 (m, 6 H) 1.63 (dd, *J* = 6.8, 1.6 Hz, 3 H), 1.41 (s, 9 H), 1.07 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.5, 208.2, 155.9, 127.8, 121.8, 80.8, 77.2, 60.0, 52.3, 41.5, 39.3, 31.3, 28.2, 26.1, 24.4, 16.7, 13.0, 8.0; HRMS (FAB) calc. for $C_{20}H_{34}NO_4^+$ [M+H$^+$] 352.2488, found 352.2506.

General Procedure for *N*-Boc Deprotection. To a solution of the alkene starting material (**36**–**39**, 0.030 g, 0.085 mmol, 1.0 equiv) in CH_2Cl_2 (0.40 mL) was added water (0.10 mL) at 0 °C and the resultant biphasic mixture was stirred vigorously for 5 min before TFA (0.40 mL) was added dropwise. The resultant mixture was stirred vigorously at 0 °C for 1 h and then was diluted with CH_2Cl_2 (5 mL). The reaction contents were then poured into a separatory funnel containing an ice-cold 1 M NaOH / 0.5 M K_2CO_3 solution (7 mL) and was shaken vigorously for 20 sec. The resultant layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic layers were then dried (Na_2SO_4), filtered, and concentrated to afford dienamines **40**–**43** (0.020 g, 99% yield) as light yellow to orange oils. [Note: vigorous

shaking of the separatory funnel is necessary to ensure complete deprotonation of the amine. When not shaken vigorously enough, the resultant products exhibit reduced *E*/*Z* ratios. The use of saturated $NaHCO_3$ in this operation led to poor mass recoveries, even following multiple extractions. These compounds were found to be unstable to isolation on neutral or basic alumina or Et_3N-deactivated silica gel.]

Dienamine 40: pale yellow oil, 8:1 *E*/*Z* ratio; $[\alpha]^{22}_D$ = +94.5° (*c* = 0.480, CH_2Cl_2); IR (film) ν_{max} 2935, 2855, 1710, 1652, 1619, 1455, 1376, 1309, 1270, 1104 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 6.10 (ddq, *J* = 14.8, 12.0, 1.6 Hz, 1 H), 5.32 (dq, *J* = 14.8 Hz, 6.8 Hz, 1 H), 5.04 (d, *J* = 10.4 Hz, 1 H), 3.29 (dd, *J* = 11.6, 4.4 Hz, 1 H), 2.58 (dq, *J* = 18.4 Hz, 7.6 Hz, 1 H), 2.45–2.32 (m, 2 H, including dq, *J* =18.4, 7.6 Hz, 1 H), 2.19–2.10 (m, 2 H), 1.71 (dd, *J* = 6.8, 1.6 Hz, 3 H), 1.59–1.45 (m, 2 H), 1.41–1.34 (m, 2 H), 1.16–1.08 (m, 5 H, includes t, *J* = 7.2 Hz, 3 H), 0.92–0.85 (m, 2 H); ^{13}C NMR (100 MHz, C_6D_6) δ 212.7, 147.0, 129.1, 120.4, 98.0, 67.2, 61.6, 30.6, 28.9, 28.3, 28.1, 26.6, 23.1, 18.6, 8.3; HRMS (FAB) calc. for $C_{15}H_{24}NO^+$ [M+H^+] 234.1858, found 234.1849.

Dienamine 41: pale yellow oil, >15:1 *Z*/*E* ratio; $[\alpha]^{22}_D$ = +88.8° (*c* = 0.335, CH_2Cl_2); IR (film) ν_{max} 2936, 2855, 1711, 1642, 1605, 1456, 1388, 1338, 1257, 1225, 1200, 1148, 1076, 940, 830, 713 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 6.12 (tq, *J* = 10.4, 1.6 Hz, 1 H), 5.25 (dq, *J* = 10.4, 6.8 Hz, 1 H), 5.2 (d, *J* = 11.2 Hz, 1 H), 3.30 (dd, *J* = 11.2, 4.4 Hz, 1 H), 2.56 (dq, *J* = 18.0, 7.2 Hz, 1 H), 2.42–2.30 (m, 2 H, including dq, *J* = 18.0, 7.2 Hz, 1 H), 2.22–2.09 (m, 2 H), 1.74 (dd, 6.8, 1.6 Hz, 3 H), 1.59–1.34 (m, 4 H), 1.19–1.07 (m, 5 H, includes td, *J* = 7.6, 0.4 Hz, 1 H), 0.93–0.85 (m, 2 H); ^{13}C NMR (100 MHz, C_6D_6) δ 212.6, 148.6, 127.0, 117.4, 93.6, 67.2, 61.6,

30.6, 28.9, 28.3, 27.9, 26.7, 23.1, 13.3, 8.3; HRMS (FAB) calc. for $C_{15}H_{24}NO^+$ [M+H$^+$] 234.1858, found 234.1869.

Dienamine 42: orange oil, 5:1 *E*/*Z* ratio; IR (film) ν_{max} 2934, 2863, 1712, 1649, 1579, 1456, 1395, 1376, 1271 cm^{-1}; ^{1}H NMR (400 MHz, C_6D_6) δ 6.26 (ddq, *J* = 14.8, 10.4, 1.6 Hz, 1 H), 5.38 (dq, *J* = 14.8, 6.8 Hz, 1 H), 4.87 (d, *J* = 10.4 Hz, 1 H), 3.83 (d, *J* = 5.6 Hz, 1 H), 3.25 (dddd, *J* = 11.2, 8.0, 6.0, 3.2 Hz, 1 H), 2.47 (ddt, *J* = 16.0, 8.8, 2.0 Hz, 1 H), 2.25 (dtd, *J* = 15.6, 9.6, 1.2 Hz, 1 H), 2.11 (dq, *J* = 18.0, 7.2 Hz, 1 H), 1.95 (dq, *J* = 18.0, 7.2 Hz, 1 H), 1.87 (dd, *J* = 6.8, 1.6 Hz, 3 H), 1.83–1.77 (m, 1 H), 1.58 (dddd, *J* = 11.6, 9.2, 6.0, 2.4 Hz, 1 H), 1.44–1.37 (m, 1 H), 1.35–1.10 (m, 4 H), 1.09–0.98 (m, 1 H), 0.92 (t, *J* = 7.2 Hz, 3 H), 0.77 (tdd, *J* = 16.0, 12.4, 3.2 Hz, 1 H); ^{13}C NMR (100 MHz, C_6D_6) δ 210.5, 147.3, 130.4, 116.2, 91.4, 59.7, 58.5, 33.5, 32.1, 29.6, 27.6, 25.2, 20.9, 18.8, 7.8; HRMS (FAB) calc. for $C_{15}H_{24}NO^+$ [M+H$^+$] 234.1858, found 234.1849.

Dienamine 43: orange oil, 8:1 *Z*/*E* ratio; $[\alpha]^{22}_D$ = +165.5° (*c* = 0.565, CH_2Cl_2); IR (film) ν_{max} 2934, 2862, 1712, 1634, 1603, 1456, 1395, 1260, 1198, 1150, 1114 cm^{-1}; ^{1}H NMR (400 MHz, C_6D_6) δ 6.29 (tq, *J* = 11.2, 2.0 Hz, 1 H), 5.24 (dq, *J* = 11.2, 6.8 Hz, 1 H), 5.05 (d, *J* = 11.2 Hz, 1 H), 3.94 (d, *J* = 5.2 Hz, 1 H), 3.29 (dddd, *J* = 11.2, 8.4, 5.6, 3.2 Hz, 1 H), 2.49 (ddt, *J* = 16.0, 9.2, 2.4 Hz, 1 H), 2.26 (dtd, *J* = 16.0, 9.2, 1.6 Hz, 1 H), 2.12 (dq, *J* = 18.0, 7.2 Hz, 1 H), 1.98 (dq, 18.0, 7.2 Hz, 1 H), 1.84 (dd, *J* = 6.8, 1.6 Hz, 3 H), 1.82–1.78 (m, 1 H), 1.58 (dddd, *J* = 11.6, 9.2, 6.0, 2.4 Hz, 1 H), 1.43–1.12 (m, 4 H), 1.09–0.97 (m, 1 H), 0.94 (t, *J* = 7.2 Hz, 3 H), 0.77 (tdd, *J* = 16.0, 12.4, 3.6 Hz, 1 H); ^{13}C NMR (100 MHz, C_6D_6) δ 210.3, 149.0, 128.0 (obtained from HSQC), 113.3, 87.2, 59.6, 58.7, 33.6, 32.1, 29.5, 27.7, 25.1, 20.8, 13.4, 7.8; HRMS (FAB) calc. for $C_{15}H_{24}NO^+$ [M+H$^+$] 234.1858, found 234.1865.

(–)-Myrmicarin 215A (1). Freshly prepared **41** (0.020 g, 0.085 mmol, 1.0 equiv) was dissolved in degassed MeOH (1 mL, sparged with Ar for at least 20 min) at 23 °C, and after standing for 1 h, the solvent was removed to afford myrmicarin 215A (**1**, 0.019 g, 99% yield) as a white crystalline solid (0.019 g, 99% yield). Alternatively, freshly prepared **43** (0.020 g, 0.085 mmol, 1.0 equiv) was dissolved in degassed MeOH (1 mL) and NaOMe (0.046 g, 0.85 mmol, 10 equiv) was added at 23 °C. The resultant mixture was then stirred at 50 °C for 1 h, cooled to 23 °C, diluted with water (5 mL), and poured into a separatory funnel containing CH_2Cl_2 (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL), and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The resultant crude residue was purified with a short plug of neutral alumina (Et_2O/pentane, 1:9) to afford myrmicarin 215A (**1**, 0.016 g, 85% yield) as a crystalline solid. **1**: $[\alpha]^{22}_D$ = –25.7° (*c* = 0.280, CH_2Cl_2); IR (film) ν_{max} 2926, 2850, 1638, 1442, 1321, 1198, 960 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 6.65 (dd, *J* = 11.2, 1.6 Hz, 1 H), 5.63 (dq, *J* = 11.2, 6.8 Hz, 1 H), 3.33 (tdd, *J* = 10.4, 5.2, 3.6 Hz, 1 H), 2.68–2.54 (m, 3 H), 2.49 (dd, *J* = 14.8, 8.0 Hz, 1 H), 2.39 (ddd, *J* = 18.8, 12.0, 7.2 Hz, 1 H), 1.97 (dt, *J* = 12.0, 6.0 Hz, 1 H), 1.89 (dd, *J* = 7.2, 1.6 Hz, 3 H), 1.73–1.65 (m, 1 H), 1.58–1.47 (m, 2 H), 1.43–1.31 (m, 2 H), 1.29 (t, *J* = 7.6 Hz, 3 H), 0.83 (tdd, *J* = 13.6, 10.8, 3.2 Hz, 1 H); ^{13}C NMR (100 MHz, C_6D_6) δ 128.9, 124.4, 122.0, 120.5, 119.1, 112.5, 55.3, 37.5, 30.1, 27.3, 22.6, 20.6, 19.0, 16.4, 15.5; HRMS (FAB) calc. for $C_{15}H_{21}N^+$ [M^+] 215.1674, found 215.1673. All spectroscopic data for this synthetic material matched those reported by Francke *et al.*[1] [Note: our observed $[\alpha]^{22}_D$ value is

[1] F. Schröder, S. Franke, W. Francke, H. Baumann, M. Kaib, J. M. Pasteels, D. Daloze, *Tetrahedron* **1996**, *52*, 13539–13546.

lower than the value reported by Movassaghi *et al.*[2] However, chiral HPLC of a derivative of starting material **15** demonstrated that no loss of enantiopurity had occurred prior to these steps.]

(+)-Myrmicarin 215B (2). This compound was prepared via the methods described for the synthesis of **1** from either **40** (99% yield) or **42** (85% yield). **2**: $[\alpha]^{22}_{D}$ = +28.2° (*c* = 0.440, CH_2Cl_2); IR (film) ν_{max} 2925, 2850, 1653, 1430, 1321, 959 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 6.65 (dd, *J* = 15.6, 1.6 Hz, 1 H), 5.88 (dq, *J* = 15.6, 6.4 Hz, 1 H), 3.26 (tdd, *J* = 10.4, 5.2, 3.6 Hz, 1 H), 2.70–2.51 (m, 4 H), 2.37 (ddd, *J* = 16.0, 12.0, 6.8 Hz, 1 H), 1.99–1.91 (m, 1 H), 1.93 (dd, *J* = 6.8, 1.6 Hz, 3 H), 1.73–1.65 (m, 1 H), 1.57–1.45 (m, 2 H), 1.42–1.27 (m, 1 H), 1.31 (t, *J* = 7.6 Hz, 3 H), 0.83 (tdd, *J* = 13.2, 10.8, 2.4 Hz, 1 H); ^{13}C NMR (100 MHz, C_6D_6) δ 128.2, 125.7, 121.1, 118.9, 118.4, 113.6, 55.0, 36.8, 29.9, 25.9, 22.8, 20.5, 19.2, 18.9, 16.6; HRMS (FAB) calc. for $C_{15}H_{21}N^+$ [M^+] 215.1674, found 215.1682. All spectroscopic data for this synthetic material matched those reported by Francke *et al.*[1] [Note: our observed $[\alpha]^{22}_{D}$ value is lower than the value reported by Movassaghi *et al.*[2] However, chiral HPLC of a derivative of starting material **14** demonstrated that no loss of enantiopurity had occurred prior to these steps.]

(+)-Myrmicarin 217 (3). *Cis*-piperidine diketone starting material (**36** or **37**, 1.0 equiv) was dissolved in EtOAc (0.1 M in starting material) at 23 °C, and Pd/C (10 wt % 0.1 equiv) was then added. The reaction was then purged with H_2 three times and was stirred under an H_2 atmosphere at 23 °C for 1 h. The reaction contents were then filtered through a pad of Celite, concentrated, and used without further purification. This diketone intermediate was elaborated according to procedures detailed above to afford myrmicarin 217 (**3**, 97% yield over 3 steps). **3**:

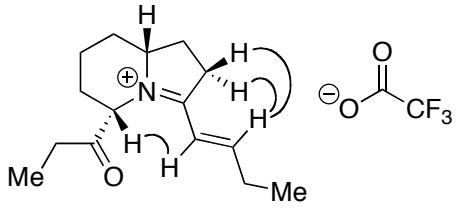
[2] A. E. Ondrus, M. Movassaghi, *Org. Lett.* **2005**, *7*, 4423–4426.

$[\alpha]^{22}_{D}$ = +66.1° (*c* = 0.260, CH_2Cl_2); IR (film) ν_{max} 2956, 2926, 2850, 1456, 1436, 1320, 1260, 1077, 1017, 799 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 3.33 (tdd, *J* = 10.8, 5.2, 3.6 Hz, 1 H), 2.67–2.53 (m, 7 H), 2.44 (ddd, *J* = 16.0, 11.6, 6.4 Hz, 1 H), 2.01 (dtd, *J* = 11.6, 5.2, 1.6 Hz, 1 H), 1.82–1.69 (m, 3 H), 1.64–1.53 (m, 2 H), 1.48–1.35 (m, 1 H), 1.30 (t, *J* = 7.6 Hz, 3 H), 1.07 (t, *J* = 7.2 Hz, 3 H), 0.88 (tdd, *J* = 13.6, 11.2, 2.8 Hz, 1 H); ^{13}C NMR (100 MHz, C_6D_6) δ 127.5, 121.3, 118.1, 113.8, 55.0, 37.3, 30.2, 28.2, 25.1 (2 C), 23.0, 20.8, 18.9, 16.6, 14.6; HRMS (FAB) calc. for $C_{15}H_{22}N^+$ $[M-H]^+$ 216.1752, found 216.1753. All spectroscopic data for this synthetic material matched those reported by Francke *et al.*[1]

Myrmicarin 237B (4). Dienamine **42** (0.013 g, 0.056 mmol, 1.0 equiv) was dissolved in EtOAc (1 mL) at 23 °C, and Pd/C (10 wt %, 0.006 g, 0.006 mmol, 0.1 equiv) was then added. The reaction was then purged with H_2 three times and was stirred under an H_2 atmosphere at 23 °C for 1 h. The reaction contents were then filtered through a pad of Celite, concentrated, and purified by passing through a short plug of neutral alumina (pentane/Et_2O, 9:1) to afford myrmicarin 237B (**4**, 0.005 g, 37% yield) as an opaque oil and as a 10:1 mixture of epimers at C-5. **4**: ^1H NMR (400 MHz, C_6D_6) δ 3.06 (dd, *J* = 5.2, 2.4 Hz, 1 H), 2.85–2.74 (m, 2 H), 2.64 (dq, *J* = 18.0, 7.4 Hz, 1 H), 2.43 (dq, *J* = 18.0, 7.4 Hz, 1 H), 2.01 [dddt, *J* = 13.2 (d), 3.6 (t), 2.4 (d), 1.2 (d), 1 H], 1.81 (dq, *J* = 12.4, 8.8 Hz, 1 H), 1.75–1.67 (m, 1 H), 1.58 (tt, *J* = 12.6, 4.0 Hz, 1 H), 1.50–0.91 (m, 12 H), 1.10 (t, *J* = 7.2 Hz, 3 H), 0.92 (t, *J* = 7.4 Hz, 3 H); ^{13}C NMR (100 MHz, C_6D_6) δ 212.7, 62.5, 59.2, 57.5, 35.7, 32.4, 29.6, 28.8, 28.5, 27.0, 23.6, 21.3, 19.3, 14.5, 8.5. All spectroscopic data for this synthetic material matched those reported by Francke *et al*.[3]

[3] W. Francke, F. Schröder, F. Walter, V. Sinnwell, H. Baumann, M. Kaib, *Liebigs Ann.* **1995**, 965–977.

Iminium Ion 44. A solution of freshly prepared dienamine **40** (0.005 g, 0.021 mmol, 1.0 equiv) in CD_3CN (0.2 mL) was added dropwise to a solution of TFA (1.6 μL, 0.021 mmol, 1.0 equiv) in CD_3CN (0.1 mL) dropwise under argon with stirring. The transfer was quantitated with CD_3CN washes (2 × 0.1 mL), affording a pale yellow solution. ^{1}H NMR analysis showed exclusive conversion to compound **44**. [Note: These protonated species were found to be stable for >24 h as anhydrous solutions in CD_3CN at 23 °C. Attempts to isolate these salts via concentration of the solution resulted in complete decomposition of the materials.] **44:** ^{1}H NMR (300 MHz, CD_3CN) δ 7.36 (dt, *J* = 15.6, 6.3 Hz, 1 H), 6.18 (d, *J* = 15.6 Hz, 1 H), 5.14 (br s, 1 H), 4.38 (br m, 1 H), 3.46 (dd, *J* = 18.9, 9.6 Hz, 1 H), 3.12 (m, 1 H), 2.70 (q, 7.2 Hz, 2 H), 2.52–2.37 (m, 4 H), 2.29–2.17 (m, 1 H), 2.14–2.03 (m 1 H), 1.92–1.65 (m, 2 H), 1.62–1.46 (m, 1 H), 1.44–1.27 (m, 1 H), 1.08 (t, *J* = 7.2 Hz, 3 H), 1.07 (t, *J* = 7.2 Hz, 3 H).



23

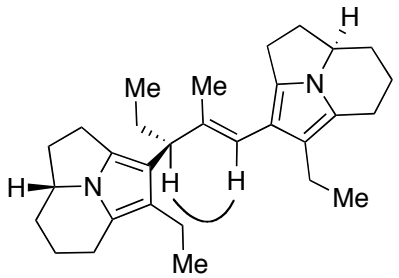
—— NOESY correlations

Iminium Ion 50. Prepared from dienamine **42** or **43** according to the procedure described for iminium ion **44** above. **50:** ^{1}H NMR (300 MHz, CD_3CN, selected peaks only) δ 7.36 (dt, *J* = 15.4, 6.4 Hz, 1 H), 6.47 (d, *J* = 15.5 Hz, 1 H), 5.23 (d, *J* = 5.9 Hz, 1 H), 4.17 (m, 1 H), 1.03 (t, *J* = 7.4 Hz, 3 H), 0.96 (t, *J* = 7.1 Hz, 3 H).

Ammonium Ion 45. A solution of freshly prepared dienamine **40** (0.005 g, 0.021 mmol, 1.0 equiv) in CD_3CN (0.2 mL) was added dropwise to a solution of $MeSO_3H$ (1.4 μL, 0.021 mmol, 1.0 equiv) in CD_3CN (0.1 mL) dropwise under argon with stirring. The transfer was completed with 2 × 0.1 mL washes of CD_3CN, affording a pale yellow solution. ^{1}H NMR analysis showed exclusive conversion to the *N*-protonated compound. **45:** ^{1}H NMR (400 MHz, CD_3CN) δ 5.76 (dqt, *J* = 15.2, 6.8, 2.0 Hz, 1 H), 5.37 (dtq, *J* = 15.2, 6.8, 2.0 Hz, 1 H), 5.13 (br m, 1 H), 3.31–2.99 (m, 4 H), 2.69 (qd, *J* = 7.2, 2.8 Hz, 2 H), 2.48–2.39 (m, 2 H), 2.29–2.18 (m, 1 H), 2.12–2.03 (m, 1 H), 1.91–1.79 (m, 1 H), 1.71 (dq, *J* = 6.4, 1.6 Hz, 3 H), 1.59–1.47 (m, 1 H), 1.44–1.32 (m, 1 H), 1.10–1.01 (m, 1 H), 1.07 (t, *J* = 7.2 Hz, 3 H).

Hexacyclic Alkene 47. A solution of freshly prepared dienamine **40** (53 mg, 0.227 mmol, 1.0 equiv) in CH_3CN (0.6 mL) was added dropwise to a solution of TFA (8.8 μL, 0.114 mmol, 0.5 equiv) in CH_3CN (0.2 mL) at 23 °C. The resulting yellow solution was stirred for 30 min at 23 °C. Upon completion, the reaction contents were diluted with CH_2Cl_2 (10 mL) and poured into ice-cold aqueous 1 M NaOH (10 mL). The layers were separated and the aqueous layer was extracted once more with CH_2Cl_2 (10 mL). The combined organic layers were then dried (Na_2SO_4) and concentrated to afford dimer **46** as a thick orange oil. Taken forward without any additional purification, this newly formed intermediate was immediately taken up in degassed MeOH (1 mL) and stirred for 3 h at 23 °C. The reaction contents were then concentrated directly, and the resultant residue was purified through a plug of neutral alumina (pentane/Et_2O, 9:1, 20 mL) to afford hexacycle **47** as a colorless oil that slowly formed a white solid upon standing under high vacuum; this material was a 2:1 mixture of diastereomers based on ^{1}H NMR analysis. This diastereomeric mixture was then further purified via semi-preparative

HPLC (Shimadzu Epic C18 5μ 250 × 9.6 mm, water/MeCN, 40% for 5 min, 40%→0% over 30 min, 0% for 25 min, UV detector at 280 nm) $t_{R,\ minor}$ = 47 min, $t_{R,\ major}$ = 48 min) to afford pure hexacycle **47**. Alternatively, crude dimer **46** was taken up in degassed *i*-PrOH (1 mL) and the reaction mixture was stirred for 4.5 h at 23 °C. **47** was then isolated, as detailed above, as a 5:1 mixture of diastereomers resulting from kinetic resolution. [Note: this compound was stored for several days in degassed benzene under an Ar atmosphere at –20 °C with minimal decomposition.] **47:** IR (film) ν_{max} 2955, 2923, 2849, 1456, 1420, 1321, 1082, 1018, 801 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 6.67 (s, 1 H), 3.56 (app t, *J* = 7.6 Hz, 1 H), 3.39–3.29 (m, 2 H), 2.93–2.85 (m, 2 H), 2.78–2.61 (m, 7 H), 2.50 (dd, *J* = 14.4, 8.0 Hz, 1 H), 2.50–2.39 (m, 2 H), 2.18–2.04 (m, 3 H), 1.99–1.95 (m, 1 H), 1.94 (d, *J* = 0.8 Hz, 3 H), 1.76–1.70 (m, 3 H), 1.61–1.49 (m, 3 H), 1.41–1.33 (m, 2 H), 1.42 (t, *J* = 7.6 Hz, 3 H), 1.39 (t, *J* = 7.6 Hz, 3 H), 1.22 (t, *J* = 7.6 Hz, 3 H), 0.98–0.81 (m, 2 H); ^{13}C NMR (100 MHz, C_6D_6) δ 136.6, 128.7, 126.9, 122.1, 122.0, 118.7, 118.7, 118.2, 116.6, 113.8, 55.2, 54.9, 49.3, 37.5, 37.4, 30.2, 30.0, 27.6, 27.3, 26.8, 23.0, 22.7, 20.8, 20.7, 19.2, 19.0, 16.5, 16.5, 16.0, 13.6; HRMS (FAB) calc. for $C_{30}H_{42}N_2^+$ [M^+] 430.3348, found 430.3326.

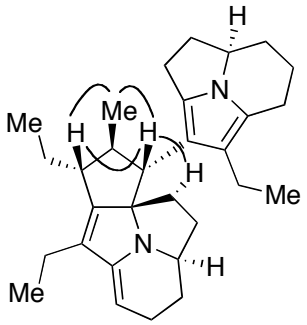


47

— NOESY correlations

Heptacyclic Dienamine 48. Hexacycle **47** (5.0 mg, 0.012 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (1.0 mL), and a solution of HCl (1.0 M in Et_2O, 0.232 mL, 20.0 equiv) was

added quickly. The initially bright yellow solution slowly became darker while stirring at 23 °C for 45 min. The reaction contents were then quenched by the addition of 240 mg of resin-bound BEMP and stirred for 20 min. The reaction mixture was then filtered and concentrated to afford crude heptacyclic dienamine **48** as a brown oil, which was carried forward without further purification. Pure samples could be obtained after purification on Et_3N-deactivated silica gel (Et_3N/hexanes, 0.6%→2.5%), affording **48** (3.0 mg, 60% yield) as a pale yellow oil. **48**: IR (film) ν_{max} 2957, 2928, 2854, 1650, 1453, 1321, 1168, 1089, 960 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 4.74 (dd, *J* = 7.1, 3.1 Hz, 1 H), 3.41–3.31 (m, 1 H), 3.17–3.09 (m, 1 H), 3.02–2.92 (m, 1 H), 2.79–2.40 [m, 7 H, including 2.51 (d, *J* = 8.5 Hz, 1 H)], 2.32 (ddd, *J* = 15.2, 7.6, 1.4 Hz, 1 H), 2.20–1.89 (m, 6 H), 1.81–1.60 (m, 8 H), 1.42–0.82 [m, 16 H, including 1.39 (t, *J* = 7.5 Hz, 3 H), 1.30 (t, *J* = 7.4 Hz, 3 H), 1.13 (d, *J* = 7.4 Hz, 3 H)]; LRMS (APCI) calc. for $C_{30}H_{43}N_2^+$ [M+H^+] 431.34, found 431.36. [Note: this compound was found to be extremely sensitive, and extensive decomposition was observed within hours after isolation in degassed benzene.]

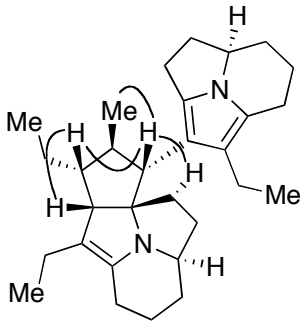


48

— NOESY correlations

Heptacyclic Enamine 49. Crude heptacyclic dienamine **48** (5.0 mg, 0.012 mmol, 1.0 equiv) was dissolved in degassed benzene (0.4 mL) at 23 °C, and Pd/C (10 wt %, 0.010 g, 0.009 mmol, 0.8 equiv) was then added. The reaction was then purged with H_2 three times and was

stirred under an H_2 atmosphere at 23 °C for 45 min. The reaction contents were then filtered through a pad of Celite, concentrated, and purified on a short plug of Et_3N-deactivated silica gel (1.25% Et_3N in hexanes) to afford enamine **49** (1.2 mg, 24% yield over 2 steps) as a yellow oil. **49:** IR (film) ν_{max} 2955, 2924, 2851, 1647, 1458, 1376, 1320 cm^{-1}; HRMS (FAB) calc. for $C_{30}H_{45}N_2^+$ [M+H$^+$] 433.3583, found 433.3591. ^{1}H NMR (400 MHz, C_6D_6) δ 3.58–3.48 (m, 1 H), 3.24 (d, *J* = 8.0 Hz, 1 H), 3.07 (ddd, *J* = 15.3, 11.0, 6.3 Hz, 1 H), 2.87 (dd, *J* = 15.2, 7.8 Hz, 1 H), 2.72–2.61 (m, 4 H), 2.52–2.31 [m, 4 H, including 2.47 (d, *J* = 11.6 Hz, 1 H)], 2.20–2.06 (m, 6 H), 1.95–1.75 (m, 2 H), 1.75–1.44 (m, 6 H), 1.42–1.17 [m, 7 H, including 1.34 (t, *J* = 7.6 Hz, 3 H)], 1.16–0.80 [m, 11 H, including 1.13 (t, *J* = 7.1 Hz, 3 H), 1.10 (t, *J* = 7.4 Hz, 3 H), 1.04 (d, *J* = 6.5 Hz, 3 H)]; ^{13}C NMR (100 MHz, C_6D_6) δ 142.7, 129.3, 123.0, 117.2, 113.2, 111.3, 83.6, 58.8, 57.4, 55.8, 55.2, 55.1, 42.2, 37.7, 37.1, 30.1, 28.3, 27.6, 27.5, 24.4, 23.0, 22.5, 21.0, 20.6, 20.1, 18.9, 17.3, 16.9, 14.8, 14.5. The complete list of peaks in the carbon spectrum was obtained with the aid of an HMBC spectrum.



49

— NOESY correlations

Computational Details. Initial geometries were obtained with the PM3 semi-empirical method[4] using the GAMESS program package.[5] Geometries were then further refined at the B3LYP/6-31G(d) level of theory using a medium integration grid. Geometries were considered converged when maximum Cartesian gradients fell below 4.5×10^{-4} hartree/Bohr. In order to ensure that a larger basis set did not affect the conclusions drawn from these calculations, single point energy computations were undertaken on the structures obtained from the aforementioned geometry optimizations using Pople's 6-311+G(d,p) split-valence triple-ζ basis set, and solvent effects were also computed with this basis set using a Poisson-Boltzmann model with dichloromethane as the solvent[6] (dielectric constant = 8.93, probe radius = 2.33). To ensure that the obtained geometries were stationary points, analytic frequency calculations were undertaken, and thermodynamic parameters were obtained from those calculations. The Gibbs energies obtained therein were used to construct the potential energy surface plot within Figure 3 of the main text, as neither the use of a larger basis set nor the inclusion of solvation effects alters the conclusions drawn from this study. Electronic energies and Cartesian coordinates are reported below for myrmicarin 430A (**5**), myrmicarin 430B (**55**, proposed structure), **28**, and **48**–**54**. In addition, Gibbs energies are provided for compounds **50**–**54**.

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Computed Equilibrium Geometries

Myrmicarin 430A (5)

E(SCF) = -1277.980077

C	-3.3282815377	-4.5317094523	-0.1913236491
C	-3.1101132923	-3.6806404270	0.8903044319
C	-3.8373904183	-2.4605363242	0.5983267165
C	-4.4504028945	-2.6126401151	-0.6418533561
N	-4.1068049219	-3.8555738901	-1.0848143990
C	-4.4254325270	-4.5580431252	-2.3115201722
C	-4.2178303672	-6.0199336488	-1.8480303971
C	-3.1008926772	-5.9185982425	-0.7529068621
C	-5.7815750112	-4.0414772104	-2.7967768213
C	-5.7322117038	-2.4941922318	-2.8247576587
C	-5.4862549163	-1.8549483026	-1.4321846171
C	-2.3072430423	-3.9375267719	2.1419729427
C	-2.4524712491	-5.3479602773	2.7665553392
C	-3.8690360979	-5.6819287180	3.2341958878
C	-1.4018158635	-5.3239530559	3.8938720140
C	-4.0063960494	-1.2637067718	1.5007846354
C	-5.1643238966	-1.4045567992	2.5073289192
C	-1.0852284066	-6.6614910028	4.5887505380
C	-0.6531618031	-7.8163884758	3.6755890330
C	-0.1748068140	-4.6251038409	3.2446614944
C	0.5416391232	-3.6548974626	4.1395265088
N	0.0659481514	-2.3738628339	3.8238125443
C	-0.3231064693	-2.2983941256	2.4842715305
C	-0.7355331823	-3.7130750880	2.0665701459
C	-0.1537505241	-4.1086205301	0.6922955453
C	1.3728147872	-4.0323933607	0.5617943032
C	1.5252288276	-3.6204345937	5.0484200382
C	1.8284743858	-2.1734384061	5.4176386512
C	0.8546116009	-1.3375494489	4.5130215424
C	-0.2186075585	-1.1508720560	1.7906870167
C	0.4650848784	0.0462351854	2.4229122035
C	1.5012490324	-0.4089185257	3.4747132539
H	-3.6706566775	-4.3127445776	-3.0787288972
H	-3.9464985421	-6.6890827374	-2.6704765965
H	-5.1434653751	-6.3942691935	-1.3944017109
H	-2.1061281871	-6.0263143275	-1.2102524248
H	-3.1948959067	-6.7144196775	-0.0071840777
H	-6.0094348047	-4.4315408468	-3.7958295438
H	-6.5738413566	-4.3857466848	-2.1177505397
H	-4.9307506128	-2.1884397094	-3.5118077708
H	-6.6653461606	-2.0982107538	-3.2412697053
H	-5.2049342392	-0.8018195938	-1.5604084455
H	-6.4364098872	-1.8441479479	-0.8762883453
H	-2.6671834913	-3.2355873324	2.9057936846
H	-2.1473935266	-6.0927036047	2.0167732154
H	-3.9298878023	-6.6961371011	3.6474408875
H	-4.5806685027	-5.6114266168	2.4051450658
H	-4.1970628760	-4.9839577816	4.0158176377
H	-1.7896451831	-4.6488893317	4.6714160650
H	-3.0737661645	-1.0698863142	2.0430124407
H	-4.1828453756	-0.3717134556	0.8840365335
H	-5.2535038355	-0.5105151342	3.1372867708
H	-6.1202799101	-1.5513184960	1.9904996671
H	-5.0127295058	-2.2677256504	3.1656411060
H	-0.3008854481	-6.4779837620	5.3364737175
H	-1.9691495126	-6.9765973040	5.1596991411
H	-0.4067693391	-8.7030115013	4.2708115908
H	-1.4475109974	-8.1021469631	2.9766351399
H	0.2345359377	-7.5664625991	3.0825757193
H	0.5163472480	-5.3789727126	2.8561877404
H	-0.4808757110	-5.1319048799	0.4632221331
H	-0.6116729307	-3.4718850547	-0.0725147886
H	1.6820561575	-4.3382522632	-0.4447990614
H	1.7318798043	-3.0122607683	0.7289913038
H	1.8865426042	-4.6884734870	1.2742971109
H	2.0504882980	-4.4725714545	5.4612295558
H	1.6436640937	-1.9619594869	6.4792354291
H	2.8804025919	-1.9102772887	5.2308638934
H	0.1758944104	-0.7427760623	5.1376051248
H	-0.5577712570	-1.0962358163	0.7613514241
H	-0.2580803125	0.7330988121	2.8920516188
H	0.9733699738	0.6349916649	1.6486202301
H	1.9491569766	0.4532260558	3.9832504079
H	2.3117380617	-0.9493196477	2.9679319003

Myrmicarin 430B (55, proposed structure)

E(SCF) = -1277.971197

C	-1.1862072137	-0.4102159583	2.7072133697
C	-1.4074554705	-1.1912004562	1.5739512108
C	-0.7030254287	-2.4386952193	1.7991115248
C	-0.0848629340	-2.3657216044	3.0434006414
N	-0.3825454041	-1.1319104945	3.5422509182
C	-0.0158741183	-0.4899994480	4.7884992377
C	-1.1535328426	0.5521624597	4.9034108266
C	-1.5181117937	0.8852062234	3.4168344030
C	0.1832959420	-1.5918772832	5.8311708572
C	1.1459079452	-2.6511646665	5.2424562333
C	0.6012260729	-3.3422980687	3.9644194818
C	-2.2140044180	-0.8711042890	0.3392162619
C	-0.6953053180	-3.6494417522	0.8997833306
C	-1.9101559224	-4.5780001270	1.0888834385
C	-3.5605121885	-0.1089816874	0.5944378444
C	-3.9822708736	0.5456342426	-0.7776599512
C	-4.3585783784	2.0418341690	-0.6751462953
C	-5.6135218589	2.3238409551	0.1587679251
C	-2.7854957655	0.2538584422	-1.6479612227
C	-2.6543134847	-0.3731417270	-2.8352416986
N	-1.4377786545	-1.0437718650	-2.9040890446
C	-0.6278851002	-0.7872787150	-1.8068039325
C	-1.5234695118	-0.0335644400	-0.8096344202
C	-0.8016860042	1.2174433518	-0.2521292987
C	-0.3942149949	2.2552178617	-1.3024708939
C	-3.3318614754	-0.5910908522	-4.1644921467
C	-2.1031057980	-0.7941306121	-5.1126432217
C	-1.0218230546	-1.4744585386	-4.2266175055
C	0.6926385641	-1.0485915196	-1.8767883048
C	1.2875707085	-1.5417223916	-3.1856447957
C	0.4543574272	-1.0933401118	-4.4162999847
C	-4.6330956117	-1.0220626623	1.1955134225
H	0.9451298068	0.0374073342	4.6589564326
H	-2.0186765627	0.0956054153	5.3994480497
H	-0.8595329205	1.4365887568	5.4771197987
H	-2.5659429677	1.1845548736	3.3197510163
H	-0.9116862023	1.7272405423	3.0519027777
H	-0.7851832581	-2.0500198886	6.0752279810
H	0.5963000529	-1.1773620930	6.7584639530
H	1.3674956701	-3.4153561009	5.9961258153
H	2.0998137222	-2.1569848100	5.0108317155
H	-0.1121659005	-4.1253277278	4.2643153068
H	1.4216943141	-3.8667994643	3.4578998657

H	-2.4846595494	-1.8248895894	-0.1313701211
H	0.2198860840	-4.2274405894	1.0857297699
H	-0.6375460683	-3.3336411998	-0.1485059754
H	-2.8483503119	-4.0504640895	0.8823307461
H	-1.9640907471	-4.9500293688	2.1189843398
H	-1.8549649859	-5.4449459286	0.4181786491
H	-3.3687621129	0.7014227128	1.3084545981
H	-4.8652462543	0.0186194241	-1.1679552493
H	-4.5105680507	2.4249891006	-1.6933279132
H	-3.5096593944	2.6054417490	-0.2656208757
H	-5.4853753573	2.0208238486	1.2046338885
H	-6.4824384389	1.7829658446	-0.2375656541
H	-5.8581843011	3.3927354784	0.1539695499
H	-1.4506272463	1.6977473863	0.4894632589
H	0.0838327959	0.8799173456	0.3008157989
H	0.3191145011	1.8331149905	-2.0178168468
H	-1.2653199934	2.6090332294	-1.8654577058
H	0.0796020750	3.1222006080	-0.8261549354
H	-3.9592983752	-1.4934692660	-4.1493237640
H	-3.9647919310	0.2465162177	-4.4691910158
H	-1.7359651727	0.1855400149	-5.4422362503
H	-2.3483969162	-1.3782804252	-6.0049232302
H	-1.1143294414	-2.5706992754	-4.3028753229
H	1.3430414694	-0.8693833787	-1.0273947908
H	2.3097510548	-1.1566378125	-3.2954395338
H	1.3842861351	-2.6391436738	-3.1963822750
H	0.5295535560	-0.0033048916	-4.5228111120
H	0.8530050148	-1.5434970517	-5.3329728110
H	-4.8935403000	-1.8285748919	0.4972970018
H	-4.2775882893	-1.4855423456	2.1231224602
H	-5.5533768132	-0.4710548200	1.4227741432

Compound 28

E(SCF) = -1277.984209

C	-4.0111098942	0.3223225416	3.1851388222
C	-2.6599775779	0.4155836933	2.8597927070
C	-2.3156246732	-0.8213229318	2.1890982506
C	-3.4584236981	-1.6140740356	2.1385233993
N	-4.4425727374	-0.9017262992	2.7592985929
C	-5.8433028197	-1.1992195297	2.9836873567
C	-6.4043366511	0.2329329513	3.1570860444
C	-5.2092190227	1.0423726689	3.7653314989
C	-6.3023168731	-2.1150831865	1.8468041063
C	-5.3130387746	-3.3019574740	1.7511022358
C	-3.8560095183	-2.8792251514	1.4215771981
C	-1.6962933028	1.5460603321	3.1110036322
C	-0.9637422435	-1.2005693697	1.6364648466
C	-0.0669308790	-1.9370377684	2.6501766369
C	-1.9174518487	2.3538483697	4.4312081468
C	-1.0865964002	3.6824265959	4.2674934096
C	-1.8624904016	4.9656828137	4.6472045525
C	-2.2650924478	5.0501374380	6.1234284066
C	-0.6845886864	3.6374727962	2.8173220390
C	-1.5461251224	2.6775750256	2.0352733866
N	-0.7284606274	2.4006600103	0.8452791294
C	0.3142728287	3.3507443794	0.7805177287
C	0.4141289160	3.9797534577	2.1151264046
C	1.5649744509	4.8434251983	2.5523299953
C	1.4393462387	6.3123514084	2.1042788259
C	-2.8692619053	3.2050475874	1.4185406351
C	-3.0078219001	2.4131391094	0.0992058317
C	-1.5467549447	2.1198616978	-0.3555706430
C	0.9925782137	3.5970980715	-0.3591841723
C	0.4791539535	2.9772746337	-1.6362638396
C	-1.0636941977	2.9265339080	-1.5734156519
C	-1.5589382395	1.5472608964	5.6820405702
H	-5.9540550004	-1.7485357341	3.9344411718
H	-6.6615978547	0.6454844652	2.1739810482
H	-7.3007956761	0.2619935061	3.7841908674
H	-5.2642884509	2.1014269647	3.4961470198
H	-5.2323766784	0.9926517982	4.8645090189
H	-6.3186402056	-1.5526826694	0.9030437581
H	-7.3184532883	-2.4834499032	2.0308849998
H	-5.6577792492	-4.0169201679	0.9955817476
H	-5.3265179767	-3.8356299841	2.7116394566
H	-3.7669780452	-2.7228051226	0.3357307900
H	-3.1794384677	-3.7100734131	1.6581259894
H	-0.6905580631	1.1107331177	3.1783404993
H	-0.4419810220	-0.3034489755	1.2827389569
H	-1.0981395136	-1.8423431797	0.7544616319
H	-0.5419095243	-2.8624857673	2.9968440259
H	0.1216542650	-1.3150506458	3.5329157912
H	0.9024049468	-2.1965196711	2.2065301811
H	-2.9796510456	2.6286247861	4.4923938017
H	-0.1912198271	3.6370108201	4.9055231088
H	-2.7585817288	5.0423606361	4.0158682817
H	-1.2390219001	5.8335943691	4.3942482306
H	-1.3876256245	4.9837398582	6.7787439122
H	-2.9519753817	4.2442010195	6.4060411590
H	-2.7680668045	6.0004179064	6.3370963831
H	1.6454747663	4.8104436637	3.6466189718
H	2.4991187220	4.4246304879	2.1567022517
H	1.3563766297	6.3873618241	1.0150955583
H	0.5465143949	6.7761922636	2.5384091594
H	2.3138079796	6.8926151065	2.4214878804
H	-3.7377488983	3.0808862762	2.0715339540
H	-2.7565023976	4.2760565891	1.2108808738
H	-3.5667964288	2.9700367199	-0.6614055420
H	-3.5385940960	1.4739905978	0.2807936128
H	-1.4479800575	1.0533561994	-0.5951370914
H	1.7995080874	4.3214702897	-0.3795339148
H	0.8728257438	1.9592402555	-1.7942065925
H	0.7983486985	3.5658456852	-2.5047931411
H	-1.4872417861	2.4792332060	-2.4812082612
H	-1.4408508832	3.9559625853	-1.5105590868
H	-1.7528258432	2.1141776435	6.5999169393
H	-2.1393205782	0.6189125281	5.7268713958
H	-0.4952849701	1.2755238809	5.6774092795

Compound 48

E(SCF) = -1277.979562

C	0.1511195677	2.2327931821	-1.2701077352
C	-0.7570316226	1.9803721513	-0.0533594633
N	0.0173847849	1.5475434592	1.1330622894
C	1.4225264231	1.4871602048	1.0711018693
C	2.0823296144	1.2325353304	-0.0785047532
C	1.2852448550	1.1895956640	-1.3595211458
C	1.9415284300	1.7965072158	2.4244899980
C	0.9165985327	2.2902527365	3.1547077410
C	-0.3582938448	2.2985016487	2.3375746463
C	-1.4356871591	1.6814607986	3.3250657172
C	-0.6665663056	1.4978024232	4.6807150404
C	0.5618180185	2.4634258739	4.6097428240
C	-1.5363441287	3.2365631443	0.4420059031

C	-0.8031715862	3.6590755905	1.7315873715
C	-2.1641042890	0.4479757798	2.8625804165
C	-1.6277440577	-0.8168314709	2.6448117119
N	-2.6485632953	-1.6207107759	2.2349078889
C	-3.8444548645	-0.9674439739	2.1885030092
C	-3.5801144199	0.3469922670	2.5683644018
C	-2.2907758276	-2.9891069499	1.9176840742
C	-0.9662852618	-3.1151996659	2.7095426225
C	-0.3774635579	-1.6629507353	2.6997130401
C	-3.5132871690	-3.8583096793	2.2197847165
C	-4.7359437079	-3.2391273574	1.4976310528
C	-5.0813254982	-1.8007428366	1.9698731562
C	-4.6218393322	1.4306044492	2.6976887623
C	-5.2549601808	1.5464191284	4.0970389394
C	-1.5638917876	1.6851236959	5.9039260057
C	1.6379797039	2.1991385208	5.6731659514
C	2.5858505893	3.3823180520	5.9072126839
C	3.3795855740	1.5323840652	2.7895138759
C	3.7043429634	0.0376868097	2.9677579361
H	-2.0723325123	-3.0668970559	0.8387324782
H	-1.1843742440	-3.4177387241	3.7411539100
H	-0.2853437484	-3.8534963619	2.2748321654
H	0.2590937047	-1.5009003093	1.8192035254
H	0.2470741658	-1.4729867430	3.5781490536
H	-3.6851316314	-3.8921728426	3.3045036377
H	-3.3535580365	-4.8875308950	1.8771209159
H	-5.6145996898	-3.8801358749	1.6326579061
H	-4.5243912389	-3.2252999022	0.4192788766
H	-5.6504248126	-1.8666705200	2.9096597702
H	-5.7608437339	-1.3350275364	1.2440324488
H	-2.1872559152	2.4624386267	3.4943992707
H	-4.1896575364	2.4027530968	2.4254080402
H	-5.4201852339	1.2488314515	1.9652066681
H	-4.5003469021	1.7841049025	4.8545901121
H	-6.0191416009	2.3334868457	4.1225003175
H	-5.7308492134	0.6035783598	4.3905809050
H	-0.2601451638	0.4778651660	4.7029293049
H	0.1761248323	3.4871489647	4.7629730074
H	1.1421685068	1.9662242990	6.6243254196
H	2.2061371554	1.2998307718	5.4038710614
H	3.0819629336	3.7004312795	4.9835576748
H	2.0370584084	4.2486975193	6.2961726404
H	3.3643264219	3.1286015466	6.6360651215
H	3.6473445913	2.0756513753	3.6992030344
H	4.0202288309	1.9382778201	1.9939555830
H	3.4503688532	-0.5261693539	2.0648174253
H	4.7713321308	-0.1068308850	3.1745458347
H	3.1366672042	-0.3920095362	3.8014842395
H	-1.4244010942	4.2628770659	2.4017286922
H	0.0916456218	4.2445790970	1.4851683787
H	-2.5757549802	2.9711810811	0.6645953719
H	-1.5564785553	4.0325920847	-0.3107005692
H	-1.4661650173	1.1823733916	-0.3048582909
H	3.1656909879	1.1830791860	-0.0987358086
H	0.8522393527	0.1925209516	-1.5460154220
H	1.9270105202	1.4092610016	-2.2212339066
H	0.6077802205	3.2277385854	-1.1877954037
H	-0.4668315617	2.2333093211	-2.1766098347
H	-1.9669437932	2.7058727545	5.9457659919
H	-1.0275559504	1.4995225080	6.8418550517
H	-2.4101250374	0.9901581218	5.8658049655

Compound 49

E(SCF) = -1279.202202

C	-5.4985803080	-1.3683327664	2.0863491284
C	-4.1380683966	-0.7328977958	2.2183433329
N	-3.0453509555	-1.5341217762	2.0645838081
C	-2.9245047267	-2.9250457505	1.6723029005
C	-4.2244928925	-3.6278009647	2.0713457060
C	-5.4128634366	-2.8080406952	1.5126941226
C	-3.6573125528	0.4924335743	2.6747353109
C	-2.2177636208	0.3865461954	2.8074216709
C	-1.8861558543	-0.9111158993	2.4292225631
C	-1.5682672974	-3.2810185381	2.3298168902
C	-0.7746191617	-1.9303901507	2.3380462108
C	-1.3003245695	1.4610700520	3.3371660299
C	-0.3774610735	2.2087113420	2.3275419461
C	0.7845428269	2.8265217433	3.1920073918
C	0.5796783685	2.2413271128	4.6422636763
C	-0.3200922693	1.0041088591	4.4400958100
N	0.3045709453	1.2760818721	1.3806675182
C	1.6759006940	1.6149785573	1.3910972121
C	2.0248517071	2.4586246423	2.3873800263
C	2.5722536009	1.0349640462	0.3231268550
C	1.7904132740	0.5896053720	-0.9314776151
C	0.5488052106	1.4672732343	-1.1059355068
C	-0.4110195323	1.2515631855	0.0712801704
C	-1.0975105371	3.1924524980	1.3854327170
C	-1.5232417125	2.3302324604	0.1856329745
C	3.3818047176	3.1157163402	2.5242217205
C	4.5434634876	2.2518406494	3.0509549107
C	-1.0139932505	0.5003560103	5.7066139083
C	1.8295035493	1.9639751343	5.4877137720
C	2.5027959959	3.2142128774	6.0667191050
C	-4.5223550970	1.6735372901	3.0403440444
C	-4.9469799012	1.7063432465	4.5209087891
H	-2.8233006786	-2.9883863570	0.5755476049
H	-1.7398960407	-3.6114262488	3.3616381888
H	-1.0429466729	-4.0822987654	1.8004939765
H	-0.1841538622	-1.8151353855	1.4182314718
H	-0.0681699761	-1.8802315885	3.1715351223
H	-4.2879833247	-3.6949320956	3.1662285668
H	-4.2496227556	-4.6498425838	1.6750711678
H	-6.3556569075	-3.3296216948	1.7131977773
H	-5.3118020554	-2.7589112445	0.4194308635
H	-5.9784500187	-1.4110017165	3.0760965376
H	-6.1688785257	-0.7673026386	1.4578556339
H	-1.9326511422	2.2393971455	3.7911805229
H	-4.0047059789	2.6109046333	2.7983543112
H	-5.4254489936	1.6665514270	2.4149278224
H	-4.0736608401	1.7490724884	5.1813159104
H	-5.5776505903	2.5785810514	4.7342828452
H	-5.5138086915	0.8060464563	4.7854811609
H	0.3010640361	0.1954311843	4.0284950970
H	-0.0295981251	2.9792140295	5.1912633537
H	1.5459449191	1.3165112340	6.3281265272
H	2.5436957549	1.3848194248	4.8915590681
H	2.8207978669	3.9126231656	5.2858161311
H	1.8147812373	3.7539987712	6.7295737231
H	3.3893284639	2.9502788970	6.6560067351
H	3.2836010092	4.0035190109	3.1612109103
H	3.6877607979	3.5033937588	1.5394271793
H	4.6758843056	1.3533085131	2.4384715709
H	5.4843193082	2.8156283028	3.0224343296

H	4.3808796961	1.9282341692	4.0828757863
H	-1.9365886906	3.7080609671	1.8656650624
H	-0.3796579784	3.9584321437	1.0638725525
H	-2.4896790201	1.8562623490	0.3786676907
H	-1.6158147138	2.9127669065	-0.7382342277
H	-0.8711901284	0.2621654231	-0.0472740727
H	3.3125570901	1.7976243199	0.0481705418
H	1.4738669977	-0.4573798476	-0.8289479087
H	2.4394063673	0.6349255710	-1.8138610751
H	0.8469595004	2.5248651810	-1.1611278229
H	0.0236512818	1.2343792255	-2.0407185776
H	-1.6003039545	1.3015331854	6.1769458852
H	-0.2977687008	0.1341126161	6.4512670232
H	-1.7001333494	-0.3207654572	5.4725977326
H	0.6915530904	3.9205955740	3.2495025279
H	3.1485039548	0.1903724488	0.7250397940

Compound 50a

E(SCF) = -1278.400309 Gibbs Energy = -1277.783449

C	-1.8123542833	-2.3270548217	-3.8814073335
C	-2.9408806214	-3.0356029246	-3.0891871486
N	-2.1504979709	-3.8510297974	-2.1729817581
C	-0.8519662820	-3.4753836463	-2.0185328388
C	-0.6035642570	-2.2635688402	-2.8871684519
C	-0.2036994077	-4.4767795501	-1.2880443048
C	-1.1916539070	-5.5119930774	-1.0549988482
C	-2.3849936210	-5.0858395427	-1.6407295863
C	-3.9298284958	-3.9615981262	-3.8008802608
C	-4.6566701385	-4.8190230350	-2.7409646242
C	-3.7042153003	-5.7495296107	-1.9450650388
C	1.2567717094	-4.3641451548	-0.8694275932
C	2.1064803149	-5.6382391386	-1.0512959274
C	2.1068910789	-6.1722441974	-2.4878496133
C	-1.0464413245	-6.8767640218	-0.4214569426
C	-1.0904573261	-6.9112954543	1.1158478308
C	1.3394584613	-3.7945651219	0.5805832906
C	2.7544639476	-3.3030172578	0.9795268219
C	0.3931275773	-2.6352889298	0.6881309206
C	-0.3957610484	-2.2780972363	1.7507360064
C	-1.2302314188	-1.0564775025	1.8573031308
C	-1.8280977282	-1.0776293732	3.0857241374
N	-1.4166561380	-2.2629442578	3.7121300683
C	-0.5662914996	-2.9796088517	3.0041858133
C	-1.7664748059	-2.8007881253	5.0318779142
C	-2.0756431294	-1.6156444825	5.9467513176
C	-3.1246558155	-0.7190031981	5.2482307513
C	-2.6275198540	-0.1048688236	3.9133550578
C	-0.1071955591	-4.1568380197	3.8237302953
C	-0.5611274379	-3.7427792185	5.2650263103
C	-1.3354479051	0.0335904671	0.8276049811
C	-0.1516343931	1.0214830472	0.8428913304
H	-2.6839820229	-3.3946492228	4.9078164786
H	0.2469556749	-3.1957881052	5.7632618683
H	-0.8201033853	-4.6047330373	5.8835489557
H	0.9700497172	-4.3286215965	3.7555662146
H	-0.6029537331	-5.0777383336	3.4897655195
H	-1.1566576324	-1.0513957298	6.1542614894
H	-2.4628352709	-1.9755012989	6.9052400665
H	-3.4221331204	0.0942697830	5.9165763846
H	-4.0279791821	-1.3151306266	5.0638531950
H	-1.9914352841	0.7636713523	4.1332105155
H	-3.4788398866	0.2820559965	3.3420535209
H	0.4207466388	-1.9395615126	-0.1473393971
H	-1.4265804396	-0.4146140517	-0.1695354914
H	-2.2675674232	0.5861123036	0.9931010176
H	-0.0686704347	1.5225752815	1.8130114899
H	0.7997703966	0.5141124175	0.6491016284
H	-0.2867059034	1.7909888428	0.0757857909
H	1.0344862525	-4.5802665567	1.2798171361
H	1.7020872353	-3.5947479662	-1.5209663683
H	1.7616711800	-6.4191292519	-0.3621064071
H	3.1406455058	-5.4163074731	-0.7616925455
H	2.4985830298	-5.4230154916	-3.1867076228
H	1.0989641317	-6.4407097770	-2.8190306258
H	2.7396769753	-7.0623665570	-2.5687919904
H	-1.8614371963	-7.5080135097	-0.7960233477
H	-0.1257557054	-7.3637897316	-0.7626208016
H	-0.2247171690	-6.3985243777	1.5511271057
H	-1.9990686147	-6.4254651296	1.4916880161
H	-1.0795016596	-7.9435428844	1.4840743113
H	-0.6199408072	-1.3172383233	-2.3251328373
H	0.3570572106	-2.3023803955	-3.4104870028
H	-2.1109477902	-1.3412389315	-4.2489898760
H	-1.5367797200	-2.9411105110	-4.7463403045
H	-3.5113576372	-2.2936775274	-2.5083674059
H	-4.2080581178	-6.0887226592	-1.0311067004
H	-3.5128639875	-6.6577631452	-2.5338491273
H	-5.4312090650	-5.4278672447	-3.2182437591
H	-5.1769050283	-4.1460552613	-2.0457131567
H	-3.3899085095	-4.6057318590	-4.5080445878
H	-4.6528920814	-3.3749309972	-4.3779110582
H	3.4640446564	-4.1350253360	0.9639069673
H	2.7606732605	-2.8752401587	1.9876775730
H	3.1169722830	-2.5367738113	0.2846034834

Compound 50b

E(SCF) = -1278.402608 Gibbs Energy = -1277.785993

C	-0.0189628786	-1.0061612046	1.8500618961
C	-0.0443606287	-2.4249843286	1.5632857315
C	-1.4382144106	-2.8634131282	1.8181073628
C	-2.1404493144	-1.7660571627	2.2290039681
N	-1.2316906983	-0.6948607362	2.2571303650
C	-1.4395578578	0.7060041945	2.6419388766
C	-0.2471459915	1.3679890467	1.9110546610
C	0.8318418810	0.2360199619	1.8177647457
C	-2.8940667251	1.0599092682	2.3304800832
C	-3.8057333920	0.0034810544	2.9981773096
C	-3.5932644092	-1.4371751090	2.4611532909
C	0.9859967186	-3.1982175008	1.1038389669
C	-1.9693758575	-4.2559309075	1.6244299165
C	-1.6125969688	-5.2147795893	2.7776370793
C	2.3579345776	-2.7613348758	0.6956479951
C	3.3862275119	-3.7848078016	1.2653737397
C	4.8488305228	-3.3514633551	1.0198282235
C	5.8729034896	-4.4089536701	1.4457196719
C	3.0619947509	-4.1118435010	2.7158985343
C	2.6398783208	-5.3697249353	3.1494738184
N	2.4603448620	-5.2985724411	4.4951133350
C	2.7935529742	-4.0710834686	4.9934353681
C	3.1595369481	-3.2829716844	3.9031646046
C	3.6420731208	-1.8553581522	4.0236124345
C	5.1087613740	-1.7163655105	4.4757179530

C	2.4804449811	-6.8122076273	2.7273325595
C	2.6632741258	-7.5653762778	4.0894731490
C	2.1715114957	-6.5617662951	5.1636445761
C	2.8665347986	-3.9153644300	6.4916744248
C	2.3861515989	-5.1892127643	7.2378320660
C	2.8169553215	-6.5058664338	6.5500965954
C	2.3826224915	-2.6485883909	-0.8500418391
H	-1.2910747513	0.7683439659	3.7299631906
H	-0.5508334909	1.6711497857	0.9030734909
H	0.1215938135	2.2522635401	2.4350652874
H	1.4410690646	0.3120565504	0.9133394263
H	1.5203925982	0.2543681100	2.6735477304
H	-3.0515199065	1.0822308709	1.2440151825
H	-3.1255933457	2.0576993936	2.7166010428
H	-3.6245494905	0.0203305634	4.0809738912
H	-4.8556022085	0.2761243089	2.8569430542
H	-4.1266155524	-1.5478396131	1.5067058436
H	-4.0497287134	-2.1570461296	3.1488414033
H	0.7655681548	-4.2496320823	0.9226812252
H	-3.0590694482	-4.2084008814	1.5173389210
H	-1.5928665410	-4.6656752471	0.6782776190
H	-0.5283429305	-5.2918182134	2.9142331440
H	-2.0422251709	-4.8658540416	3.7221412792
H	-2.0061075465	-6.2160972746	2.5742657288
H	2.5704982787	-1.7742222686	1.1178691074
H	3.2304989328	-4.7156206600	0.6974712941
H	5.0481378791	-2.4114273056	1.5485237611
H	4.9879736452	-3.1392974462	-0.0473381847
H	5.7250076581	-5.3462407754	0.8953029819
H	5.7980042795	-4.6321042621	2.5147308731
H	6.8922110602	-4.0642711017	1.2418489095
H	3.0064055100	-1.3172347160	4.7419536959
H	3.5207100663	-1.3321486539	3.0672640264
H	5.7903707013	-2.2058535352	3.7723888339
H	5.2634781991	-2.1768111177	5.4571624549
H	5.3981462376	-0.6618301873	4.5521864580
H	1.4882350860	-7.0227059044	2.3015643293
H	3.2194433772	-7.1288220003	1.9845974790
H	2.1225737235	-8.5153499570	4.1239055221
H	3.7273853473	-7.7749565004	4.2481597484
H	1.0816749747	-6.6602050247	5.2907357343
H	3.9077750347	-3.7081997136	6.7758754913
H	2.2877583261	-3.0484775837	6.8377798756
H	1.2900959111	-5.1797194169	7.3115941408
H	2.7646000336	-5.1620398060	8.2648286178
H	3.9102336796	-6.5477294022	6.4525162559
H	2.5072109608	-7.3673995533	7.1515730940
H	3.3590535336	-2.2909289327	-1.1884874937
H	1.6235680291	-1.9472121101	-1.2127374996
H	2.1975803149	-3.6214524387	-1.3196002985

Compound 51

E(SCF) = -1278.39282 Gibbs Energy = -1277.773113

C	-1.9408946579	-2.1352381252	-3.1989947037
C	-2.9074852987	-2.7196619573	-2.1383134041
N	-2.0181493756	-3.6643716521	-1.4468711061
C	-0.6613953194	-3.3745893278	-1.5425634854
C	-0.5107445647	-2.2660779186	-2.5827989040
C	0.0171272533	-4.6161191452	-1.2983406921
C	-0.9565028585	-5.5981252024	-1.0296979185
C	-2.2215344883	-4.9664579082	-1.1768315697
C	-4.1498418219	-3.4726921064	-2.6241166907
C	-4.6585399593	-4.4165972015	-1.5176151778
C	-3.6202455301	-5.5106704249	-1.1788245650
C	1.4919681993	-4.5083006151	-0.9722884250
C	2.3357397655	-5.7888901357	-0.9724945773
C	2.4772664261	-6.4241284819	-2.3610994533
C	-0.8103435702	-7.0638189711	-0.6914711282
C	-0.8063730835	-7.3929380462	0.8114824631
C	1.4327782299	-3.7643444131	0.3935717104
C	2.7631945414	-3.1489586173	0.8576050127
C	0.3622896604	-2.6757722967	0.2720562510
C	-0.5105390948	-2.3239201542	1.3328447968
C	-1.2364166090	-1.0532552158	1.4596784518
C	-1.9414514306	-1.0942929637	2.6407117933
N	-1.6923459363	-2.3317340448	3.2056726978
C	-0.8375572667	-3.0786171482	2.4944793502
C	-2.1568401129	-2.9077927196	4.4666062873
C	-2.4284316240	-1.7542453608	5.4329385944
C	-3.3466684408	-0.7291039442	4.7280357750
C	-2.7069291543	-0.0918978830	3.4671161456
C	-0.5318210867	-4.3289660924	3.2891813174
C	-1.0356747886	-3.9417548336	4.7203975456
C	-1.1418601721	0.1431093840	0.5493721595
C	0.1112108010	1.0087060939	0.7876475002
H	-3.1060412254	-3.4310645831	4.2735334353
H	-0.2206469710	-3.4708644375	5.2815557615
H	-1.3838667415	-4.8069381208	5.2899128796
H	0.5296498942	-4.5908045166	3.2905751740
H	-1.0770405783	-5.1975314434	2.8986655917
H	-1.4809054712	-1.2846475389	5.7295021050
H	-2.9074685440	-2.1298054190	6.3431588702
H	-3.6196475535	0.0685179766	5.4257091562
H	-4.2826633025	-1.2320968885	4.4503567005
H	-2.0165092416	0.7038795381	3.7805577580
H	-3.4819522642	0.4026142518	2.8691982915
H	0.6784550118	-1.8397757156	-0.3464768728
H	-1.1682607140	-0.1745664638	-0.5000073811
H	-2.0343806341	0.7647760075	0.6903958756
H	0.1345498670	1.3874014450	1.8149993324
H	1.0323918850	0.4372125664	0.6275262201
H	0.1242450839	1.8689450977	0.1095095016
H	1.1033614739	-4.4980341488	1.1370808251
H	1.9411188927	-3.8174519104	-1.7046777376
H	1.9201598872	-6.5132485023	-0.2616494347
H	3.3357822192	-5.5405049547	-0.5973484616
H	2.9715995125	-5.7374044569	-3.0580766022
H	1.5048104542	-6.6868289488	-2.7932494766
H	3.0797227509	-7.3368876931	-2.3135018445
H	-1.6390505062	-7.6080679215	-1.1632330455
H	0.0978947327	-7.4623018469	-1.1514538934
H	0.0453237209	-6.9285281280	1.3208787496
H	-1.7236887083	-7.0419519980	1.2991505042
H	-0.7394375090	-8.4749202070	0.9675907267
H	-0.1878870465	-1.3146997127	-2.1463734493
H	0.2314265068	-2.5291070214	-3.3431277242
H	-2.1885883454	-1.1038423072	-3.4648547172
H	-2.0063803592	-2.7377824208	-4.1116773672
H	-3.2056495860	-1.9457346429	-1.4181323175
H	-3.8573473937	-5.9780103049	-0.2142512959
H	-3.6705775901	-6.3213772853	-1.9194909229
H	-5.5948774200	-4.8917800334	-1.8252713660
H	-4.8853461964	-3.8301388094	-0.6176000834

H	-3.9006068762	-4.0531872353	-3.5227887458
H	-4.9267112955	-2.7560347117	-2.9093168508
H	3.5238282593	-3.9230547672	1.0020192156
H	2.6427419552	-2.6207323004	1.8093309538
H	3.1471498018	-2.4339942774	0.1200152241

Compound 52

E(SCF) = -1278.411939 Gibbs Energy = -1277.790663

C	-2.1992772586	-1.9689966466	-2.3590323183
C	-3.0534257197	-2.9428875173	-1.4949635520
N	-2.0335294307	-3.9241211638	-1.0526970077
C	-0.6450284801	-3.4774112005	-1.2331721730
C	-0.8386467712	-2.6866749380	-2.5578859821
C	0.1050577743	-4.7762853237	-1.2449577609
C	-0.7732041103	-5.8251026543	-1.1568338515
C	-2.1070979834	-5.2351225303	-1.1312526225
C	-4.1951439370	-3.6832877115	-2.1978051379
C	-4.6022912049	-4.9218204789	-1.3831434706
C	-3.4303413281	-5.9194576739	-1.2723847092
C	1.5475283916	-4.5187852096	-0.9133088967
C	2.4703768624	-5.7089338471	-0.6209687211
C	2.9821250427	-6.4256180790	-1.8771707547
C	-0.5447225455	-7.3134846240	-1.0673288954
C	-0.7060363660	-7.8891832724	0.3526132286
C	1.3257456912	-3.5373479692	0.2944233278
C	2.5478543801	-2.7013821468	0.6689252038
C	0.0829651596	-2.6519774620	-0.0852462992
C	-0.7421738094	-2.1827113607	1.0806715061
C	-1.0829111110	-0.8006838694	1.3599347486
C	-1.7905044555	-0.7772502826	2.5592572528
N	-1.8979270213	-2.0741726314	2.9647181710
C	-1.2668754903	-2.9425513268	2.1275966937
C	-2.4770783151	-2.6546374714	4.1684591020
C	-2.3877790948	-1.6017383836	5.2748393682
C	-2.9918122600	-0.2811598655	4.7400854637
C	-2.2340478204	0.3000962952	3.5166833232
C	-1.3530734440	-4.3192351388	2.7503846050
C	-1.6839807697	-3.9812723807	4.2431175251
C	-0.6665395054	0.4268141405	0.5857906639
C	0.6743913691	1.0359025894	1.0387031031
H	-3.5409741608	-2.8746401324	3.9832240302
H	-0.7506111892	-3.8191862831	4.7944154681
H	-2.2408171875	-4.7778118522	4.7444744559
H	-0.4325774086	-4.9048004207	2.6647907856
H	-2.1575062258	-4.9275957479	2.3085668581
H	-1.3382133667	-1.4559241585	5.5638501237
H	-2.9321212131	-1.9338199562	6.1655619658
H	-3.0093440874	0.4702942970	5.5359548434
H	-4.0394595449	-0.4663080223	4.4664344633
H	-1.3488156684	0.8462029460	3.8720957307
H	-2.8640186725	1.0473394602	3.0181467206
H	0.4706500610	-1.7609528568	-0.5899787106
H	-0.6061870483	0.2029357046	-0.4883436702
H	-1.4491368698	1.1904743494	0.6795938437
H	0.6400192453	1.3139894235	2.0976600065
H	1.4988816019	0.3253585193	0.9119897228
H	0.9121662414	1.9365677497	0.4610914266
H	1.0490985517	-4.1578187689	1.1549076830
H	1.9887438775	-3.9277196499	-1.7331801503
H	1.9627053612	-6.4142325950	0.0488067787
H	3.3354054636	-5.3366560147	-0.0600257120
H	3.5922237267	-5.7521112158	-2.4899961664
H	2.1660044514	-6.7921332663	-2.5110566308
H	3.6063909014	-7.2841407494	-1.6090110322
H	-1.2498039836	-7.8201322596	-1.7401590311
H	0.4510091643	-7.5516155926	-1.4467190007
H	0.0226871779	-7.4522863583	1.0433443230
H	-1.7056597270	-7.7006150439	0.7609561662
H	-0.5524138407	-8.9726865859	0.3399137414
H	-0.0145319135	-1.9965867876	-2.7522992062
H	-0.8942132522	-3.3912454307	-3.3961334380
H	-2.0625165415	-1.0240922012	-1.8270025604
H	-2.6841767595	-1.7437397218	-3.3131945401
H	-3.4258278603	-2.4377872646	-0.5979835956
H	-3.5726070835	-6.6117041658	-0.4325220750
H	-3.3703238612	-6.5567302387	-2.1659453461
H	-5.4576356679	-5.4236023343	-1.8444942844
H	-4.9217102744	-4.6112260730	-0.3805699112
H	-3.8778756291	-3.9833871296	-3.2064310245
H	-5.0427946659	-3.0015887205	-2.3184228099
H	3.3855320176	-3.3252396738	0.9969091846
H	2.3009511837	-2.0236691925	1.4931523617
H	2.8898061021	-2.0949380260	-0.1791630582

Compound 53

E(SCF) = -1278.392392 Gibbs Energy = -1277.772739

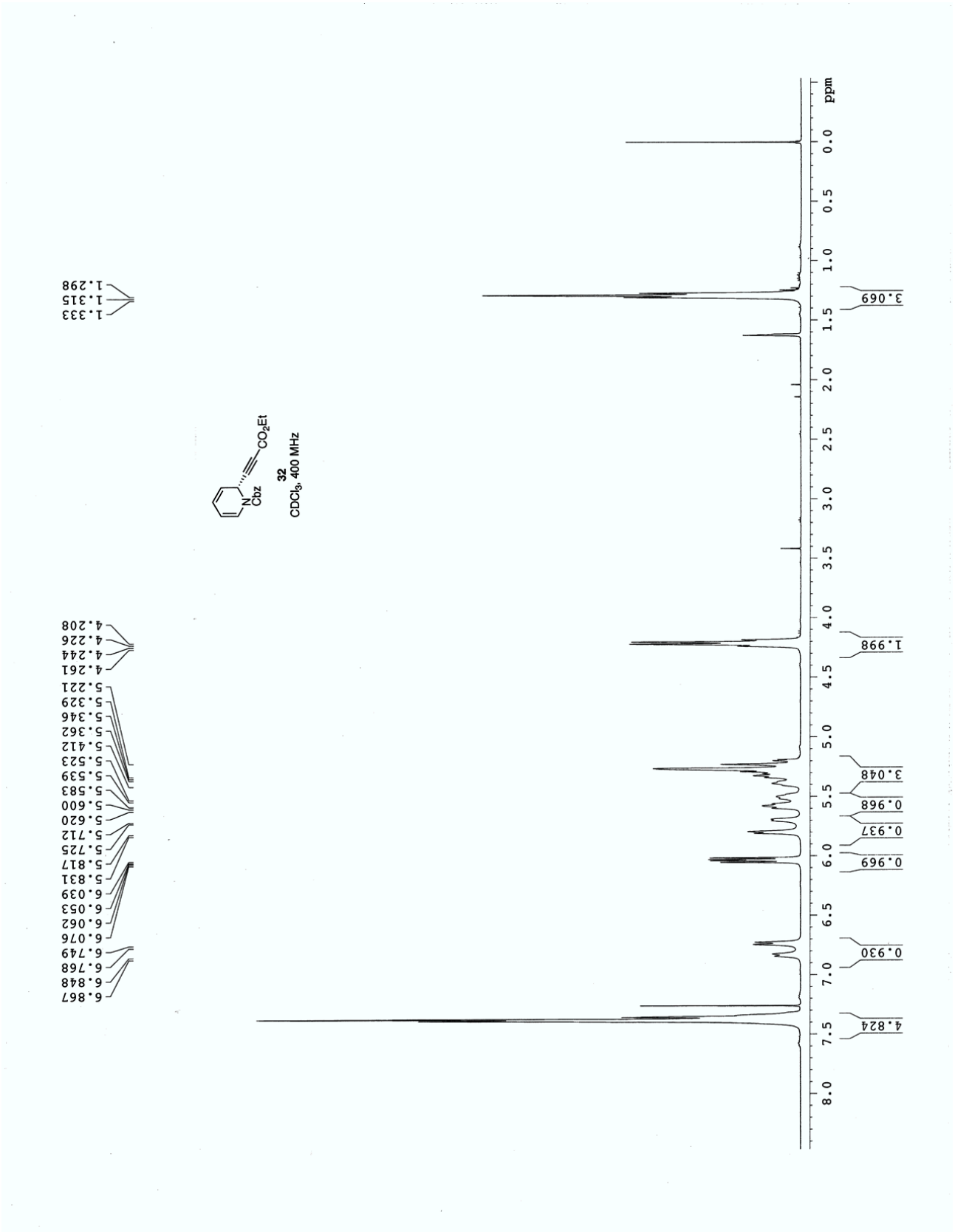
C	0.8309230642	-3.1293487094	3.9850397483
C	-0.0822040203	-2.2577710035	3.1607157218
N	-0.6429946882	-1.1556931095	3.7798748413
C	-0.4063100052	-0.5908027448	5.1076756857
C	0.0420977736	-1.7313857398	6.0221097740
C	1.2149042953	-2.4724794704	5.3375606858
C	-0.6776187376	-2.3547399222	1.9225758778
C	-1.6618029952	-1.2719033439	1.8203253375
C	-1.5905009571	-0.5570119213	3.0466056495
C	-1.7405871402	0.1605033285	5.3252704886
C	-2.2154363085	0.5381907448	3.8812588323
C	-2.5052463907	-1.0318798897	0.7058120728
C	-3.7951596151	-0.2121046627	0.8022933659
C	-4.9311070527	-1.1242292052	1.3074576955
C	-0.4321671440	-3.4358611979	0.9047044535
C	-1.4306813858	-4.6074886429	0.9858214320
C	-4.1112139354	0.4540102617	-0.5859145544
C	-4.5517428510	1.9326699112	-0.5001449934
C	-5.8846608520	2.1557907608	0.2223711546
C	-2.8577815373	0.2205730367	-1.3893126443
C	-1.5371075678	0.2751449806	-0.7298993227
C	-0.6393804406	-0.4274686407	-1.6031894083
N	-1.3781704117	-0.8879915964	-2.6139247282
C	-2.7096123271	-0.5167060976	-2.5334859995
C	0.8550861091	-0.5498501623	-1.6993957453
C	1.2930180098	-1.4719299478	-2.8698488622
C	0.4284795912	-1.3194796220	-4.1453892800
C	-1.0201483299	-1.6681531106	-3.7985288565
C	-3.4088460796	-1.0636551308	-3.7539896705
C	-2.2059187920	-1.3110490678	-4.7288048907
C	-1.0196963256	1.3809044430	0.1712586367
C	-0.6320007508	2.6642880171	-0.5841770414
H	0.4170512685	0.1352512332	5.0266002338
H	-2.4718150057	-0.5124104123	5.7871591909
H	-1.6285172108	1.0349015179	5.9707385200
H	-3.3055859959	0.5693690003	3.8066663703

H	-1.8429796747	1.5299271313	3.5900637887
H	-0.7963864090	-2.4168812531	6.2037921326
H	0.3592350765	-1.3351332542	6.9922801988
H	1.6078330757	-3.2455388029	6.0049008467
H	2.0320524341	-1.7563667301	5.1773780645
H	0.3214007095	-4.0827025848	4.1828661976
H	1.7405600690	-3.3851385881	3.4287229385
H	-2.5638261609	-1.8533636571	-0.0035536089
H	0.5849425165	-3.8253266597	1.0358362825
H	-0.4612990457	-3.0061285843	-0.1057045462
H	-2.4613301905	-4.2678304790	0.8328227326
H	-1.3866734236	-5.0917883875	1.9670581037
H	-1.2059371790	-5.3641566898	0.2258466415
H	-3.6481193711	0.5857501651	1.5374660601
H	-4.9311396424	-0.1024780837	-1.0588043564
H	-4.6303553002	2.3167514644	-1.5252300446
H	-3.7648635494	2.5251239612	-0.0154738451
H	-5.8355473657	1.8687870853	1.2790990429
H	-6.6922249471	1.5789011053	-0.2442887598
H	-6.1701509009	3.2121509431	0.1859854813
H	-1.7690227038	1.6322757392	0.9272593997
H	-0.1523518936	0.9987577442	0.7248139660
H	0.1592868785	2.4817613359	-1.3195707608
H	-1.4914835370	3.0819632421	-1.1187127031
H	-0.2657385980	3.4248013865	0.1142137779
H	-3.9348005572	-2.0046932536	-3.5418232162
H	-4.1420451164	-0.3702538484	-4.1740343136
H	-1.9802582867	-0.3893477064	-5.2770828108
H	-2.4116353596	-2.0985975266	-5.4576541607
H	-1.0756936703	-2.7345833372	-3.5332829761
H	1.2770369086	-0.9123537957	-0.7538929814
H	1.2742860318	0.4569293284	-1.8439779684
H	2.3423523027	-1.2688020492	-3.1050559683
H	1.2468138577	-2.5185613789	-2.5403080023
H	0.4797449360	-0.2914313910	-4.5262543353
H	0.8026067599	-1.9806486775	-4.9334241099
H	-5.1055285310	-1.9542188625	0.6123636500
H	-4.7005212190	-1.5496558093	2.2895205267
H	-5.8644592563	-0.5586267207	1.3904882810

Compound 54

E(SCF) = -1278.404143 Gibbs Energy = -1277.782794

C	-1.1407783858	-0.3948653420	2.6717393015
C	-1.4390607241	-1.1729453775	1.5511045942
C	-0.7251657997	-2.4273706911	1.7164517815
C	-0.0304826671	-2.3607112052	2.9195919800
N	-0.2889176835	-1.1259734191	3.4400126961
C	0.1205929249	-0.5131052051	4.6969494156
C	-1.0190568505	0.5164488734	4.8833077677
C	-1.4546552695	0.8811849171	3.4237111858
C	0.3597608253	-1.6398442231	5.7033226453
C	1.3014402039	-2.6825554362	5.0564948681
C	0.7086080823	-3.3485595302	3.7870966849
C	-2.2984725518	-0.8471632564	0.3724323173
C	-0.8135390704	-3.6477393192	0.8331104503
C	-2.0227962561	-4.5533865834	1.1375126303
C	-3.6414500170	-0.0770410690	0.6201519530
C	-4.0871450071	0.4999909454	-0.7813217942
C	-4.5229037963	1.9848690440	-0.7687826602
C	-5.7830216105	2.2531987003	0.0597137444
C	-2.8745452367	0.2184538883	-1.6275736074
C	-2.6658359743	-0.3319060816	-2.8422926441
N	-1.3478673114	-0.8621737202	-2.8352467711
C	-0.6939872392	-0.6867702245	-1.7214749332
C	-1.6174276374	0.0372487790	-0.7907353282
C	-0.9549929711	1.3242263696	-0.2268636991
C	-0.5544070597	2.3655461187	-1.2788025473
C	-3.2357912304	-0.6024756158	-4.2111753803
C	-1.9448864413	-0.8151100408	-5.0728373212
C	-0.9411806281	-1.4846768426	-4.1037339020
C	0.7551063538	-1.0403650351	-1.6509729601
C	1.2432311747	-1.7922508508	-2.9176447587
C	0.5733411396	-1.3062549048	-4.2266027383
C	-4.6937574921	-0.9683749774	1.2832355240
H	1.0720901718	0.0191102118	4.5379872519
H	-1.8575935194	0.0434190545	5.4073731415
H	-0.7065971318	1.3906607764	5.4608486961
H	-2.5095882701	1.1679656604	3.3784822960
H	-0.8729845841	1.7370783190	3.0521627285
H	-0.5978838018	-2.1039444829	5.9757856137
H	0.8066107926	-1.2438900318	6.6216784131
H	1.5494552511	-3.4631228750	5.7829646810
H	2.2468186613	-2.1851870458	4.8007545794
H	0.0131672767	-4.1428846999	4.0936918155
H	1.5090506276	-3.8517118686	3.2304569578
H	-2.5704219490	-1.7911854341	-0.1152264609
H	0.1057380093	-4.2375017642	0.9418192731
H	-0.8510506339	-3.3552339064	-0.2272061916
H	-2.9681224484	-4.0138205208	1.0082042754
H	-1.9898184374	-4.9097174218	2.1726105015
H	-2.0377578444	-5.4294608046	0.4784528233
H	-3.4405994642	0.7697428730	1.2866036480
H	-4.9322434642	-0.0880112751	-1.1632989292
H	-4.6991636822	2.2998076526	-1.8055977165
H	-3.6981506210	2.6066771885	-0.3977706935
H	-5.6318220076	2.0264919573	1.1209075160
H	-6.6287632518	1.6524199868	-0.2949890370
H	-6.0708095349	3.3069338340	-0.0125454628
H	-1.6462266261	1.7815013082	0.4857757031
H	-0.0833899676	1.0105982957	0.3591345937
H	0.1791242240	1.9776625061	-1.9956345264
H	-1.4207788887	2.7176141361	-1.8482126491
H	-0.1005547023	3.2348956537	-0.7923508178
H	-3.8577785446	-1.5074344349	-4.2163961041
H	-3.8514969960	0.2195611868	-4.5825726356
H	-1.5534496660	0.1536868346	-5.4032223552
H	-2.1297790444	-1.4269796221	-5.9583615570
H	-1.1762608861	-2.5552220296	-4.0241796625
H	0.9478593308	-1.6189674011	-0.7386340316
H	1.3122824382	-0.1008194858	-1.5180642787
H	2.3291517605	-1.6866340008	-2.9946611046
H	1.0445070391	-2.8643111806	-2.7960444805
H	0.8061336952	-0.2499248397	-4.4143096509
H	0.9529771912	-1.8803446906	-5.0772739742
H	-4.9501067881	-1.8202809355	0.6409349885
H	-4.3244035495	-1.3642065035	2.2347744766
H	-5.6161776268	-0.4133309639	1.4828634382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N
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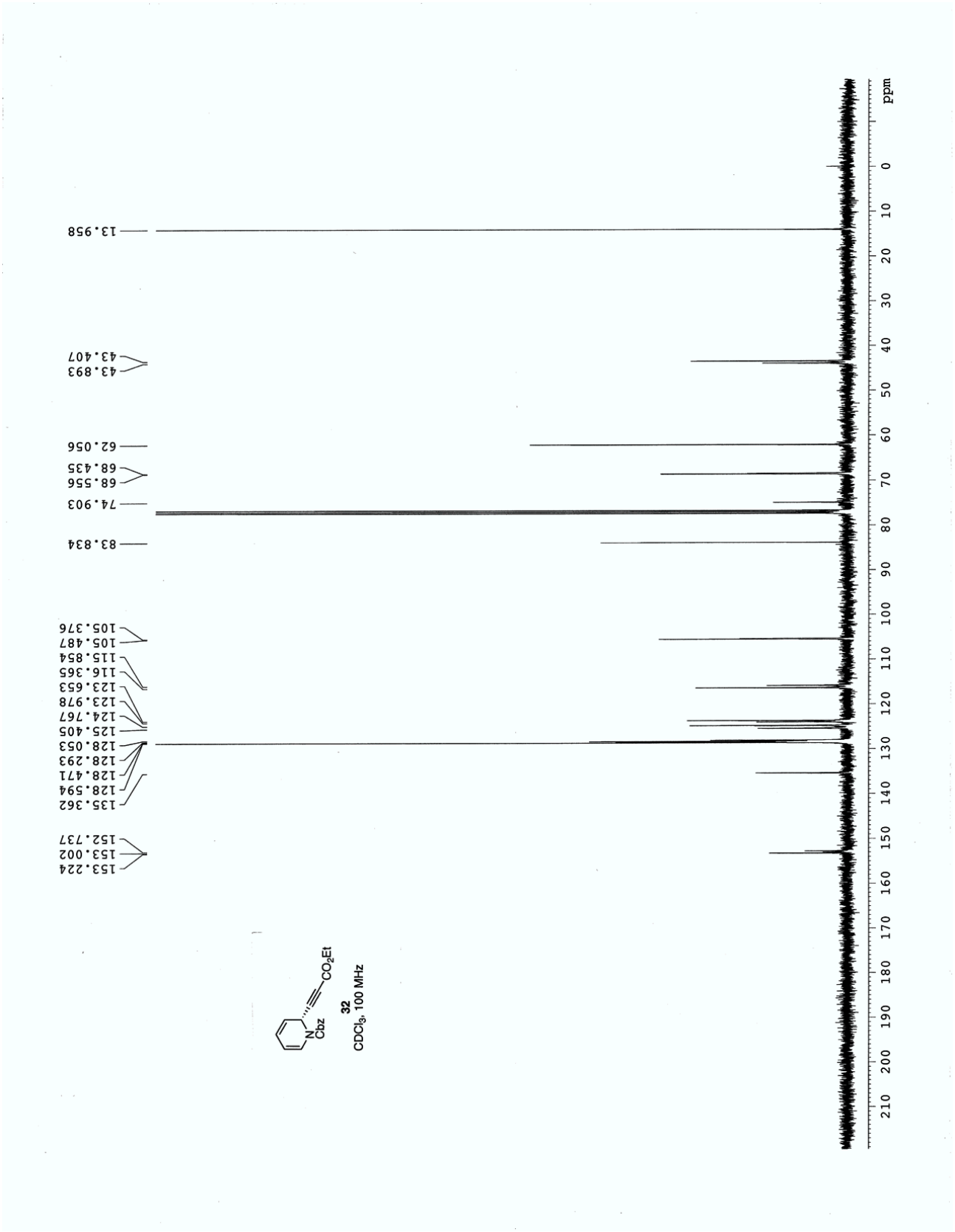
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CO2Et
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ppm

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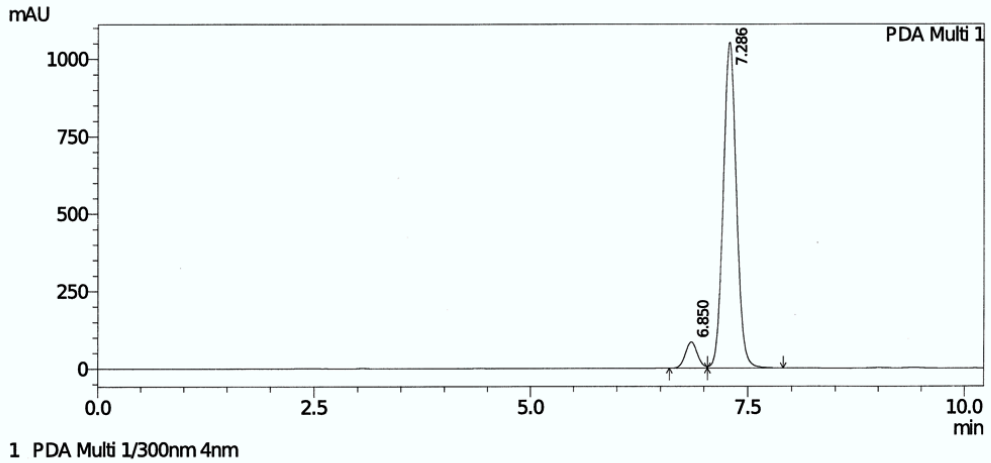

1 PDA Multi 1/300nm 4nm

PeakTable

PDA Ch1 300nm 4nm

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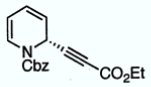
Total		11876455	1136417	100.000	100.000



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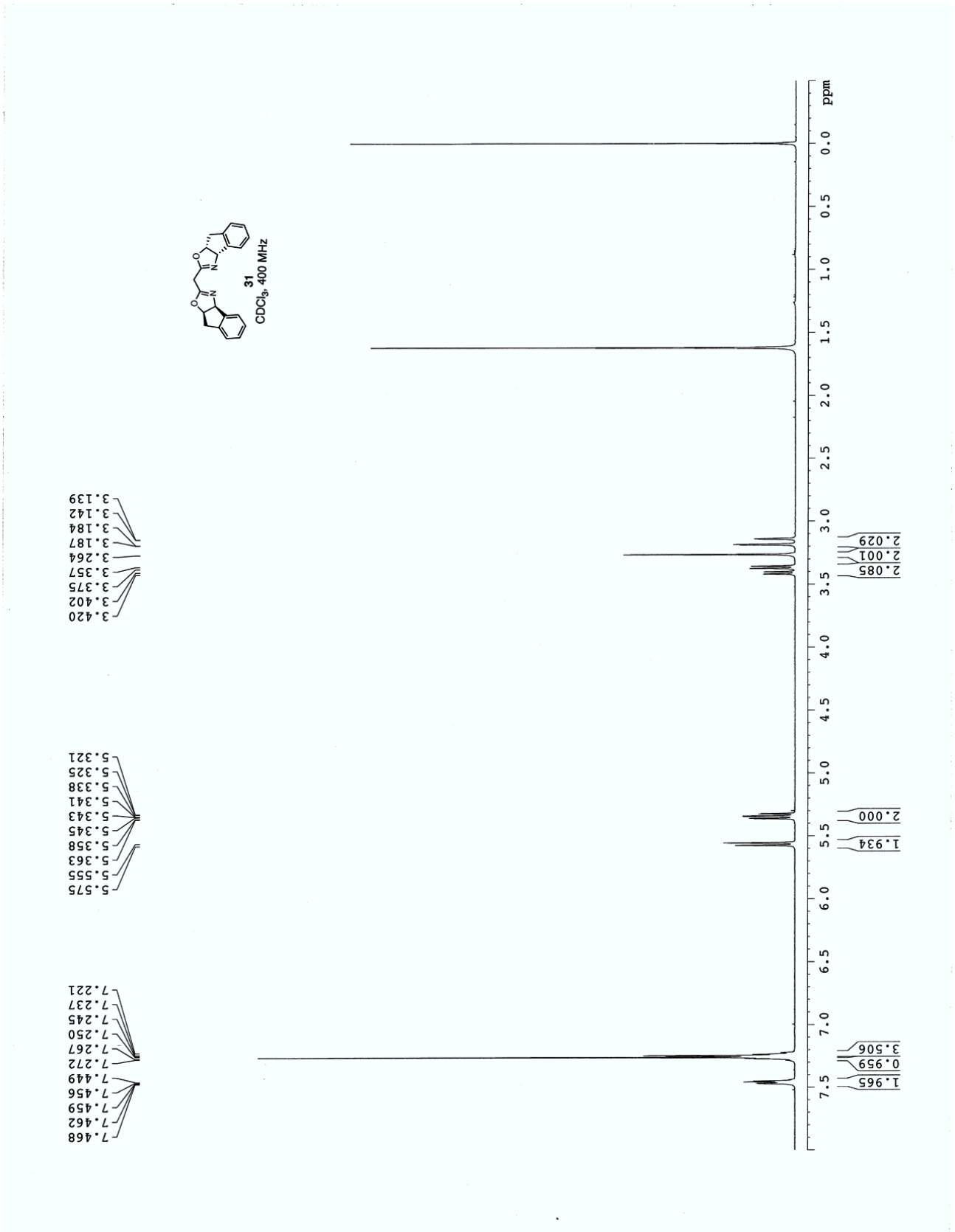
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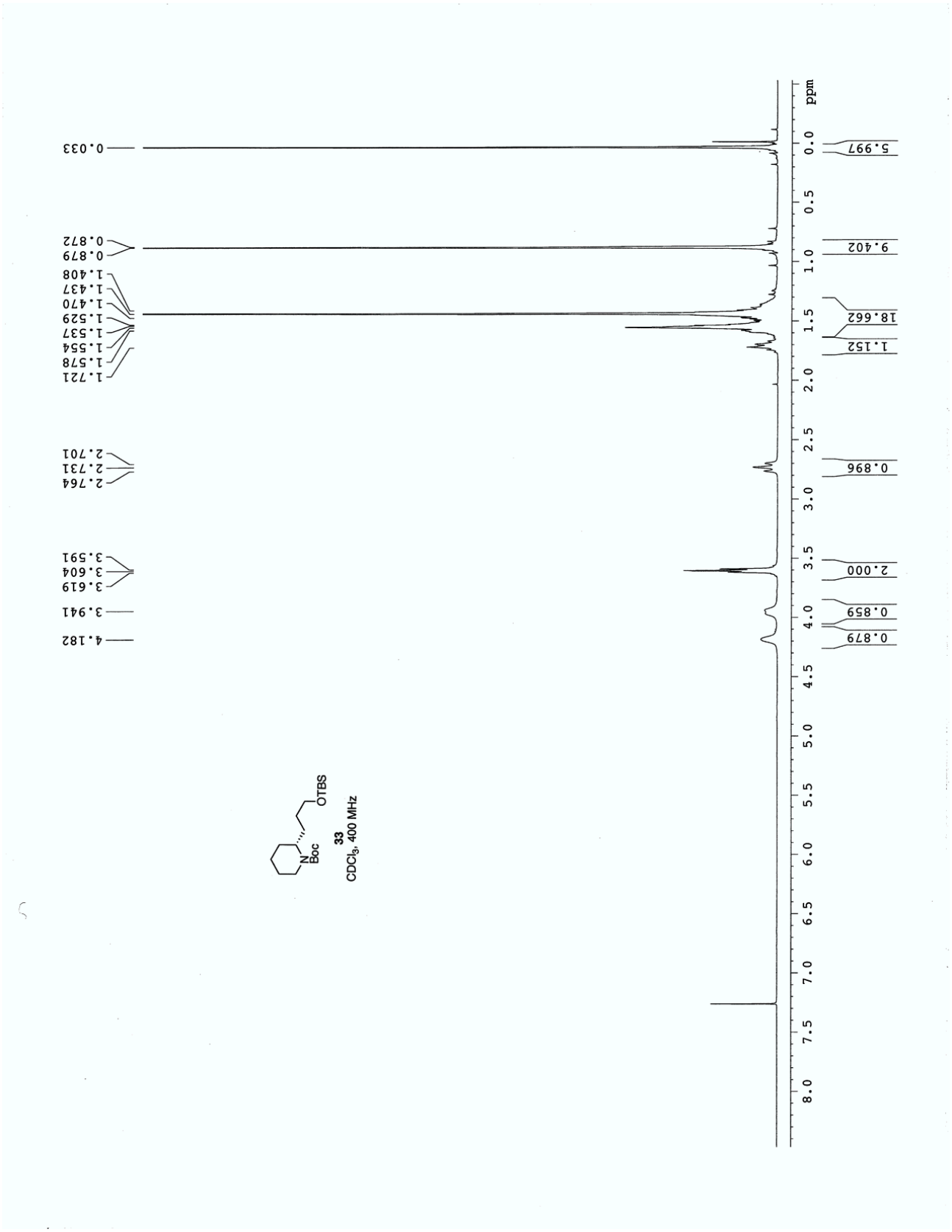
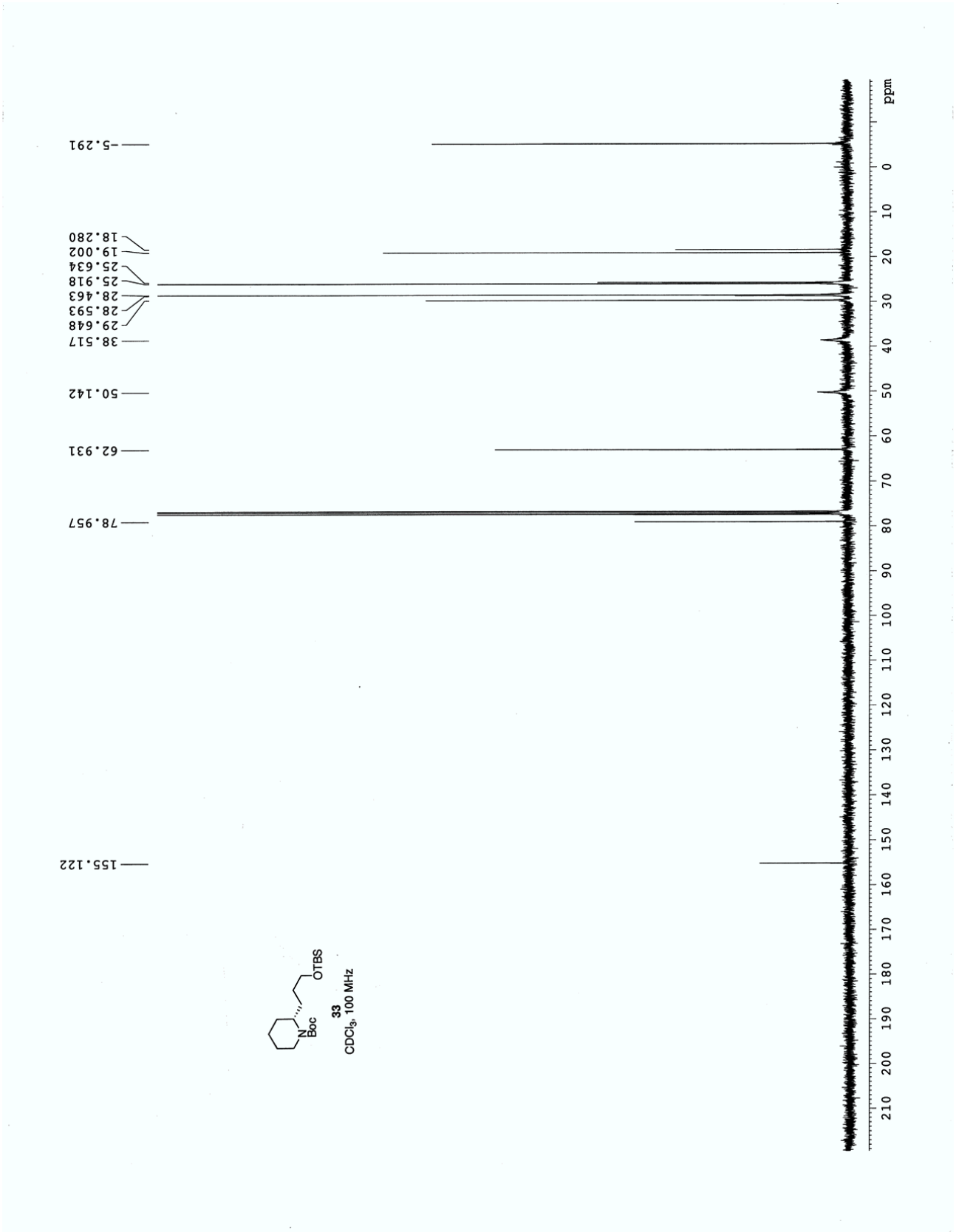
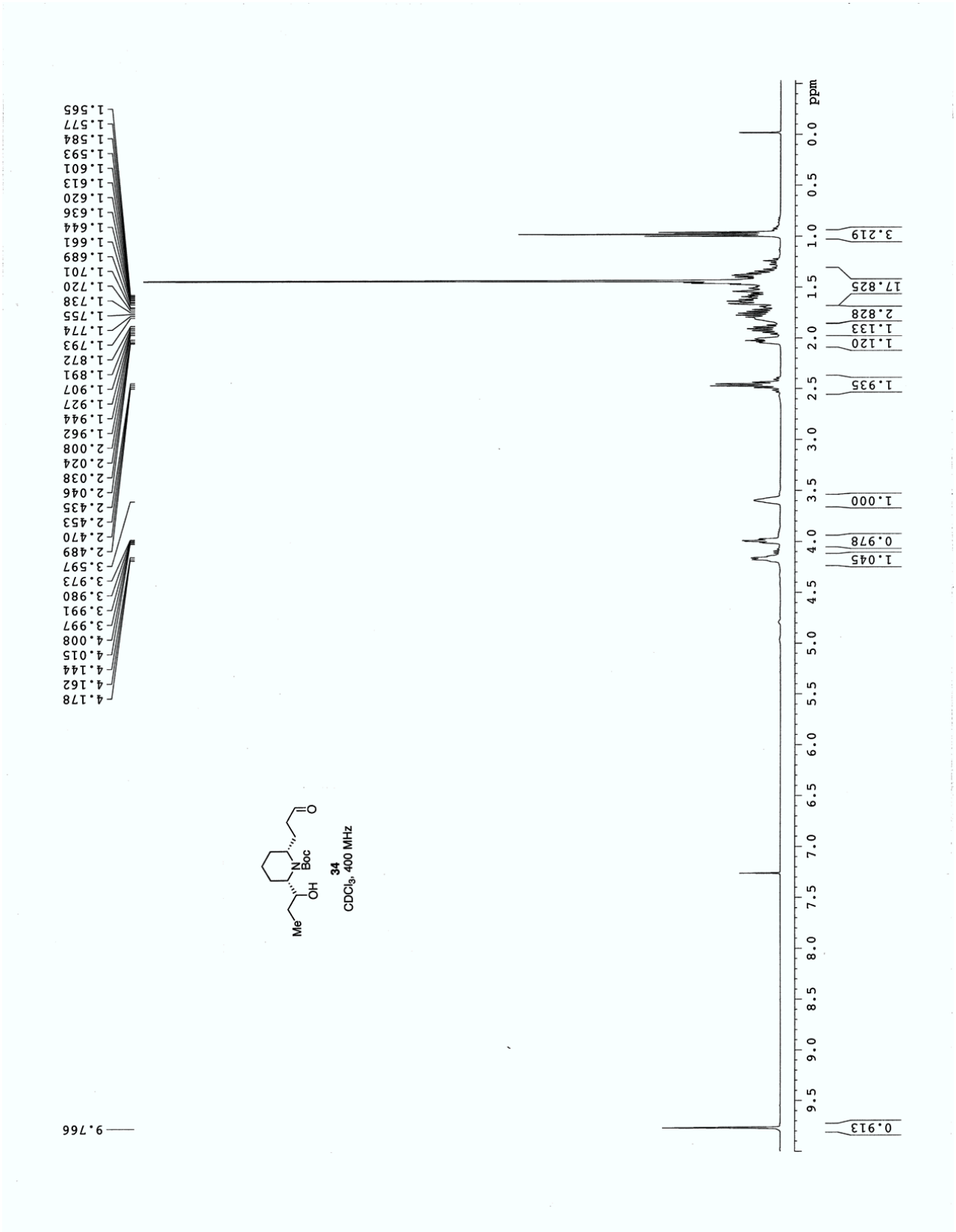
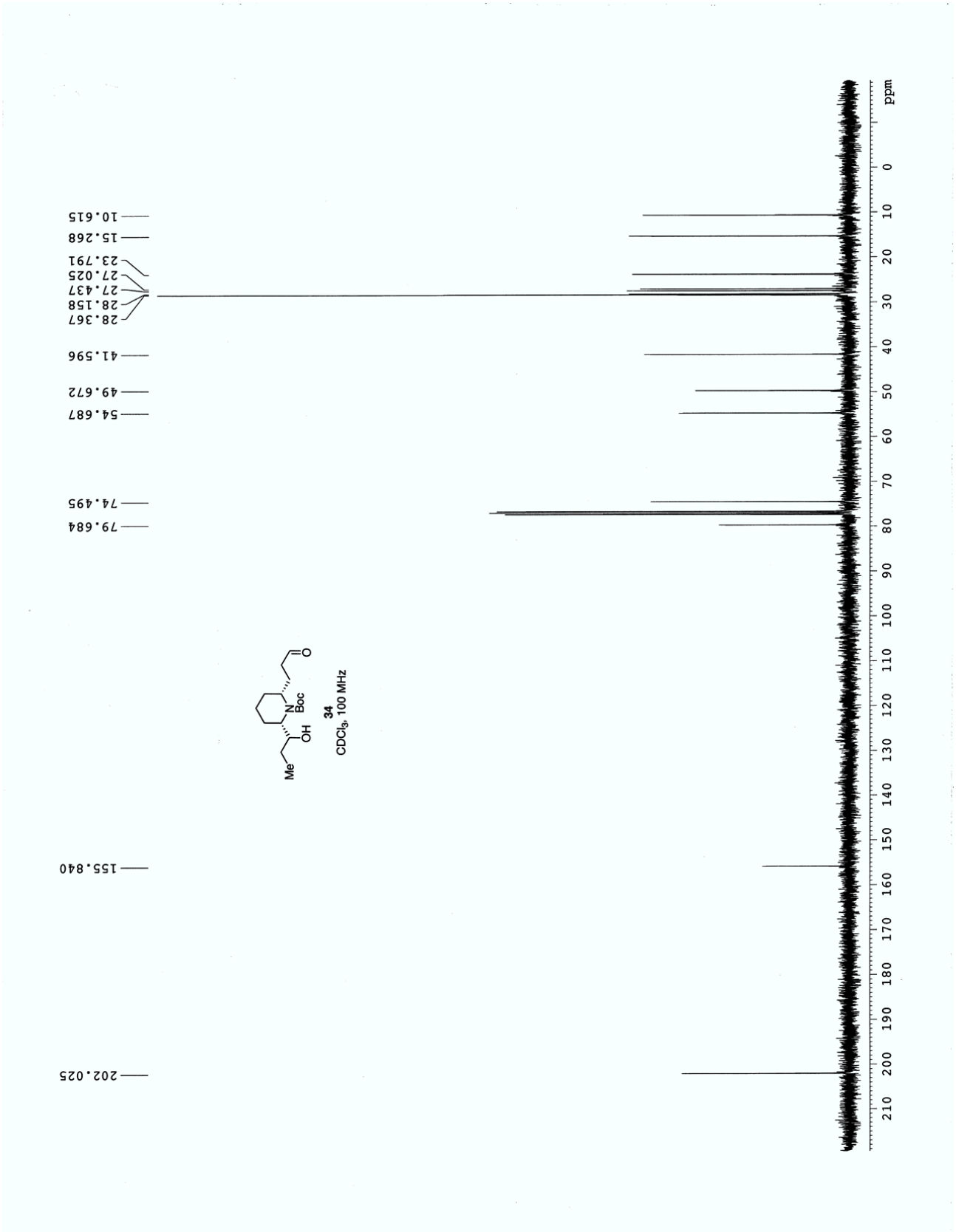
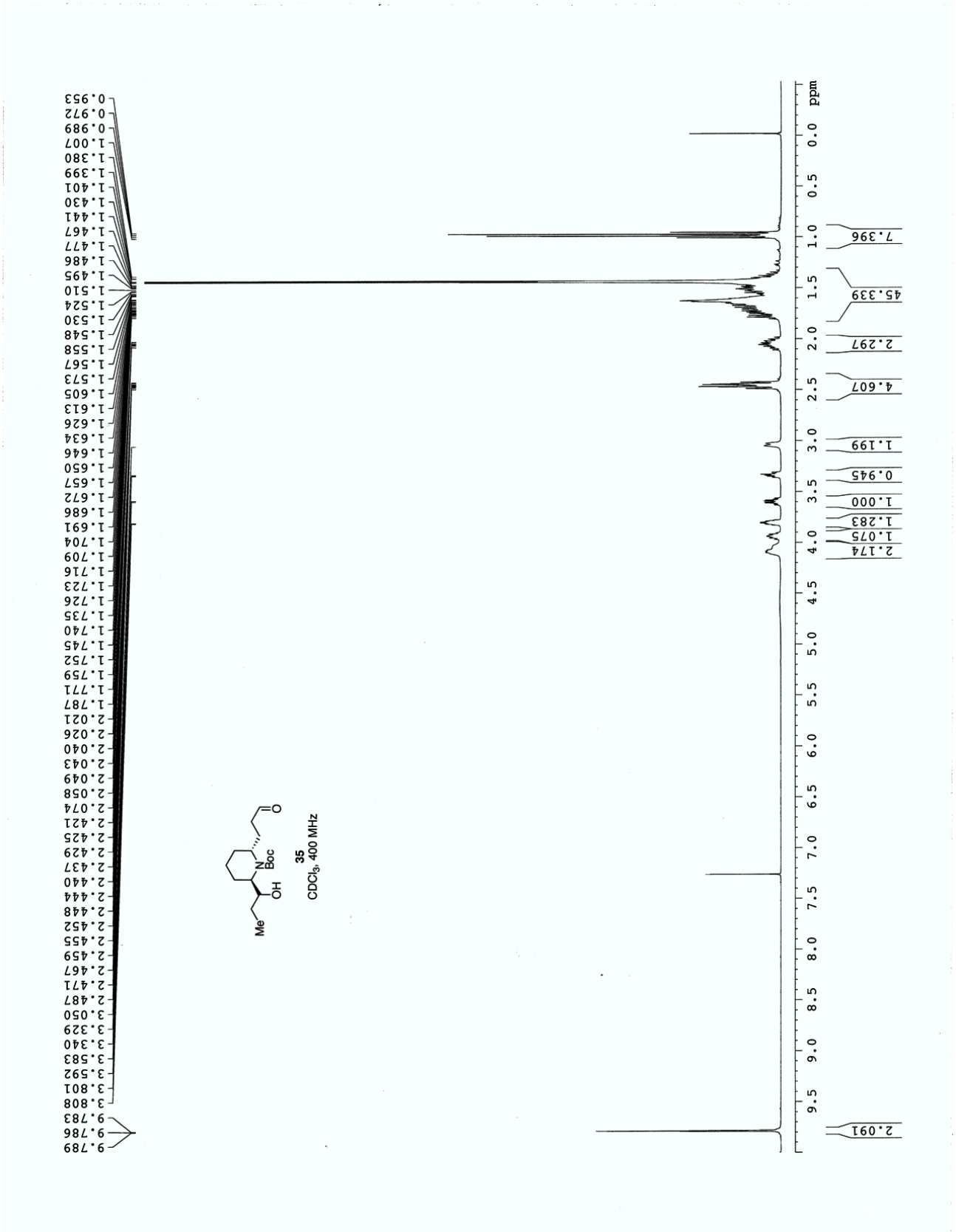
7.237
7.221

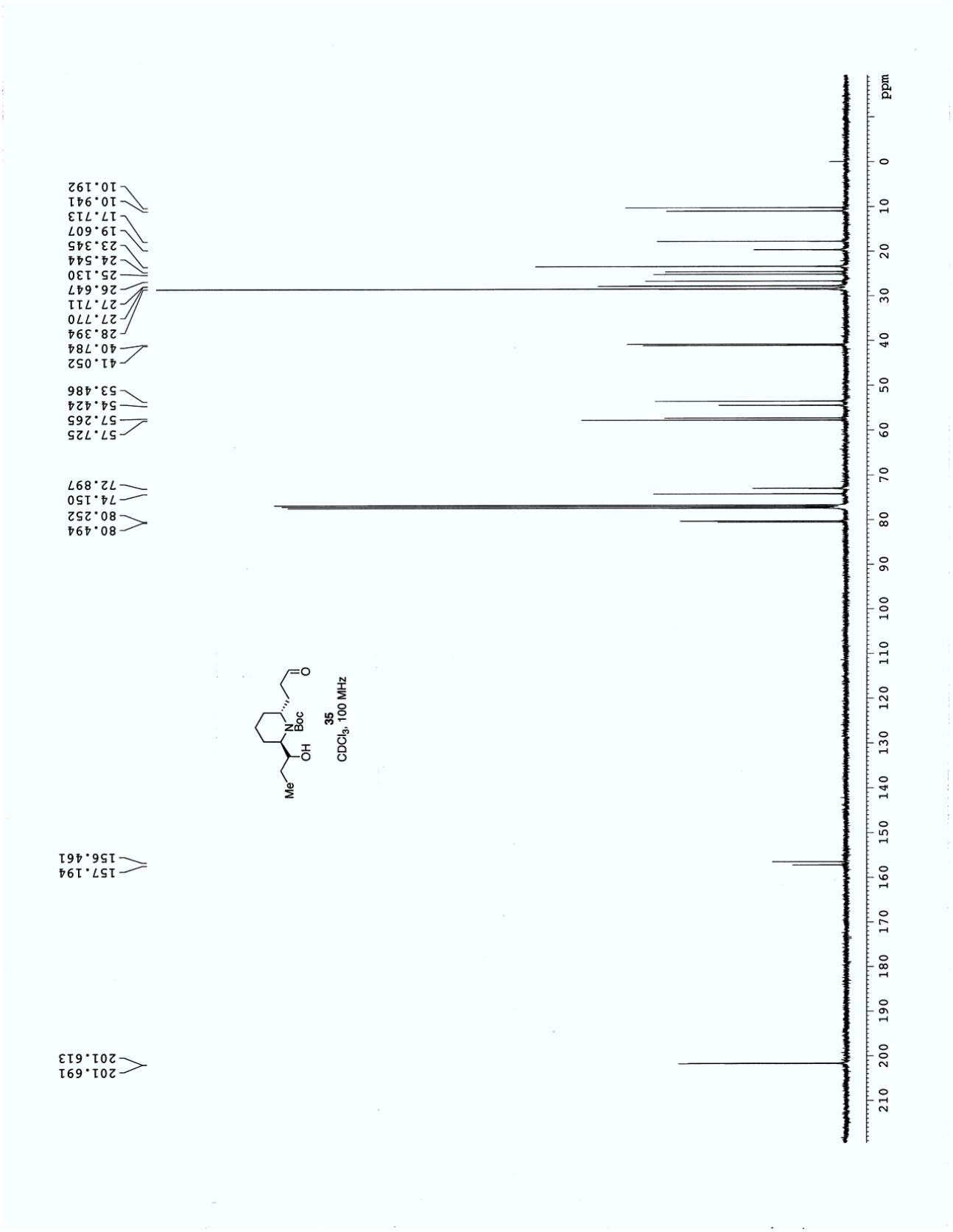

OTBS
N
Boc
33
CDCl3, 400 MHz
ppm
0.033
0.872
0.879
1.408
1.437
1.470
1.529
1.537
1.554
1.578
1.721
2.701
2.731
2.764
3.591
3.604
3.619
3.941
4.182
5.997
9.402
18.662
1.152
0.896
2.000
0.859
0.879

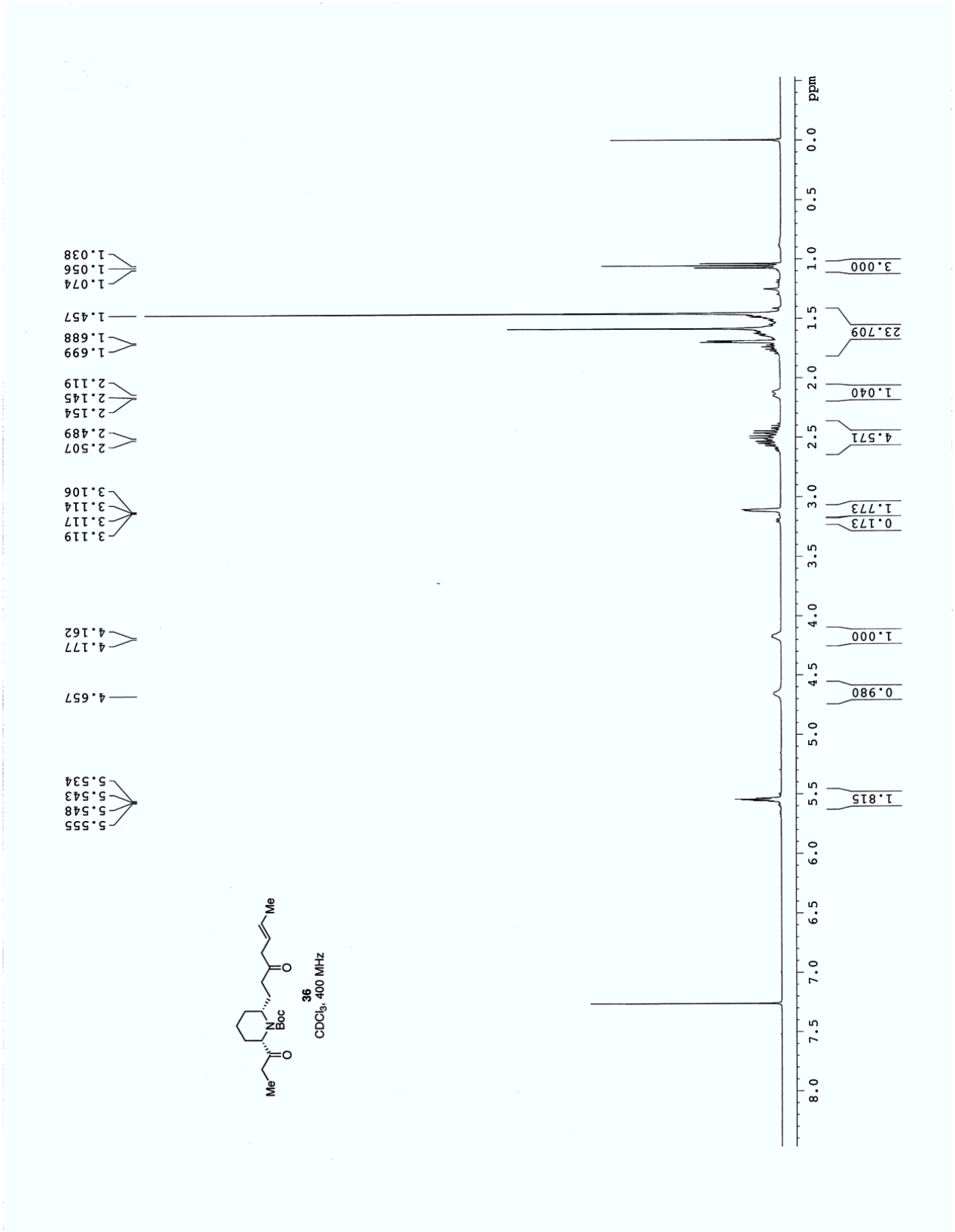

-5.291
18.280
19.002
25.634
25.918
28.463
28.593
29.648
38.517
50.142
62.931
78.957
155.122
OTBS
N
Boc
33
CDCl3, 100 MHz
ppm
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210

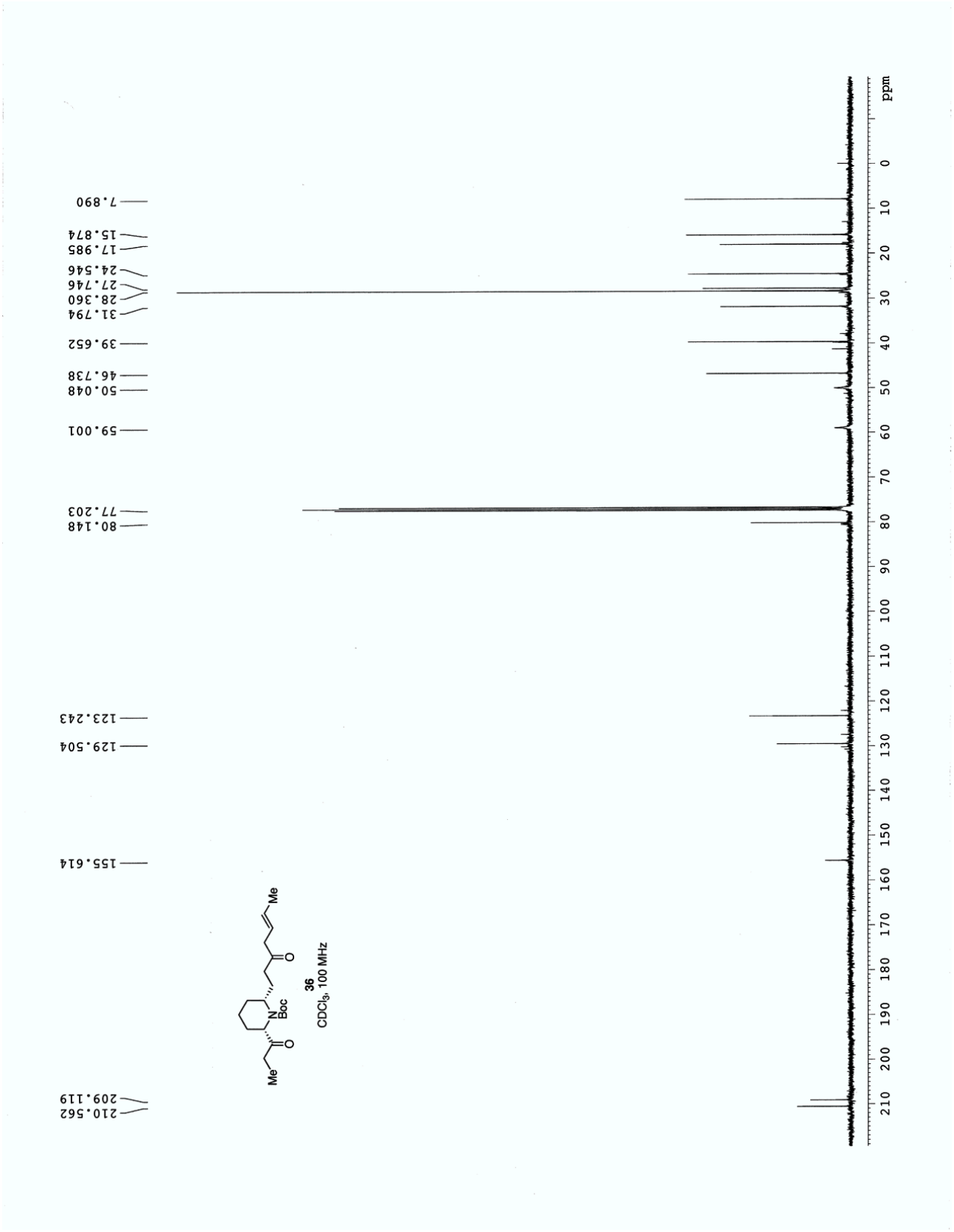

34
CDCl3, 400 MHz
Me
OH
Boc
N
O
ppm
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0
9.5
0.913
3.219
17.825
2.828
1.133
1.120
1.935
1.000
0.978
1.045
9.766
4.178
4.162
4.144
4.015
4.008
3.997
3.991
3.980
3.973
3.597
2.489
2.470
2.453
2.435
2.046
2.038
2.024
2.008
1.962
1.944
1.927
1.907
1.891
1.872
1.793
1.774
1.755
1.738
1.720
1.701
1.689
1.661
1.644
1.636
1.620
1.613
1.601
1.593
1.584
1.577
1.565

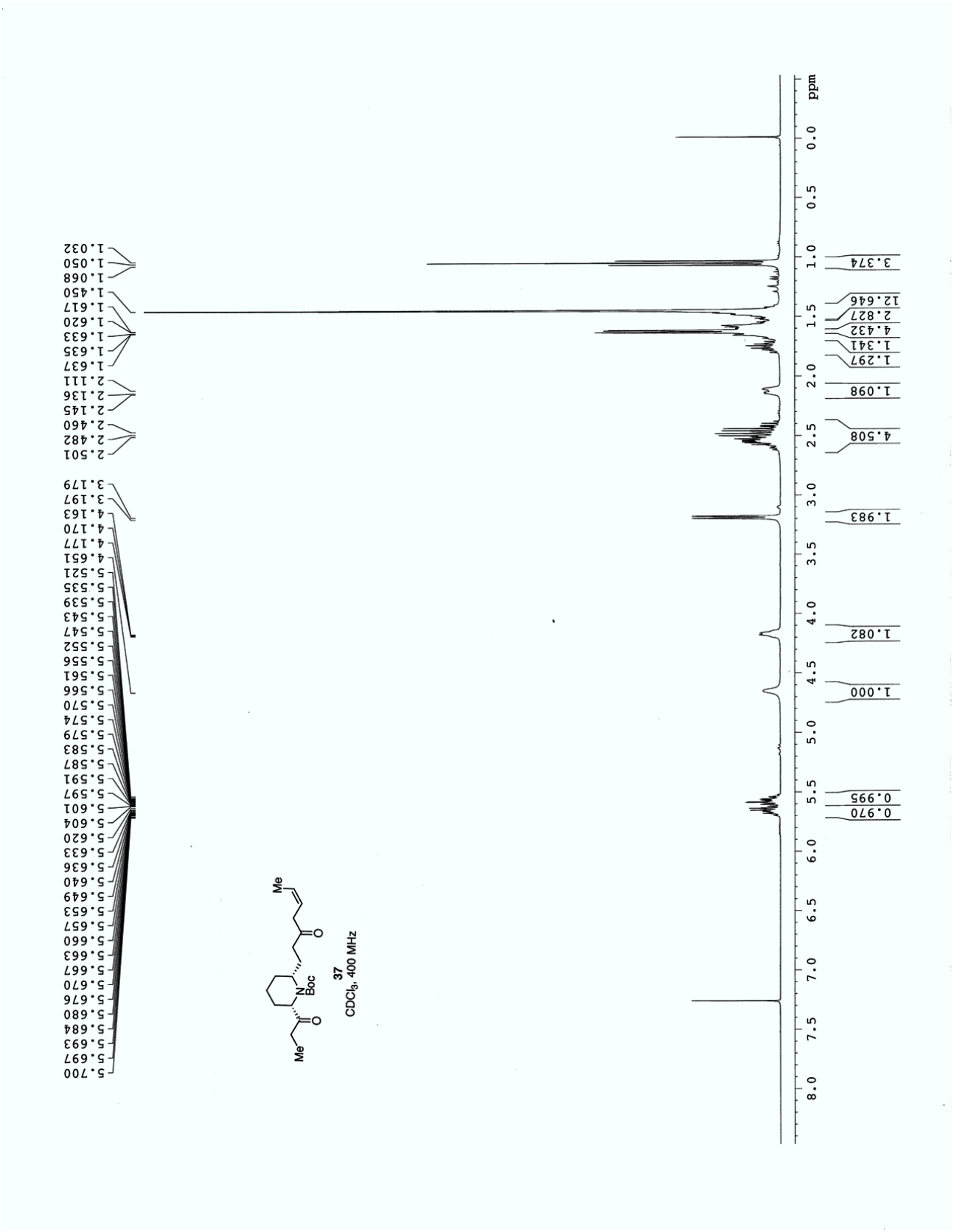

10.615
15.268
23.791
27.025
27.437
28.158
28.367
41.596
49.672
54.687
74.495
79.684
155.840
202.025
Me
OH
N
Boc
O
34
CDCl3, 100 MHz
ppm

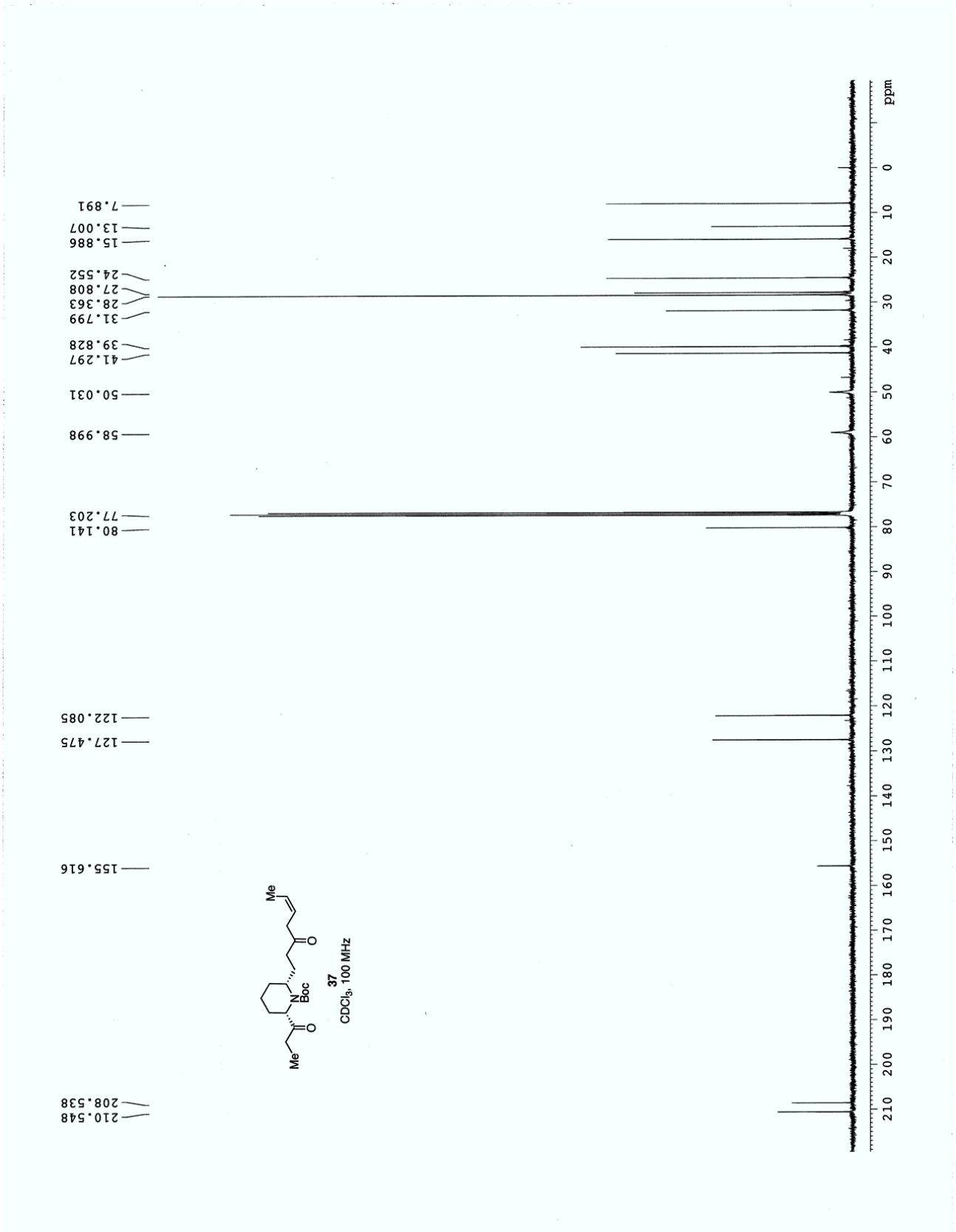

35
CDCl3, 400 MHz
Me
OH
N
Boc
O
ppm
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
2.091
7.396
45.339
2.297
4.607
1.199
0.945
1.000
1.283
1.075
2.174

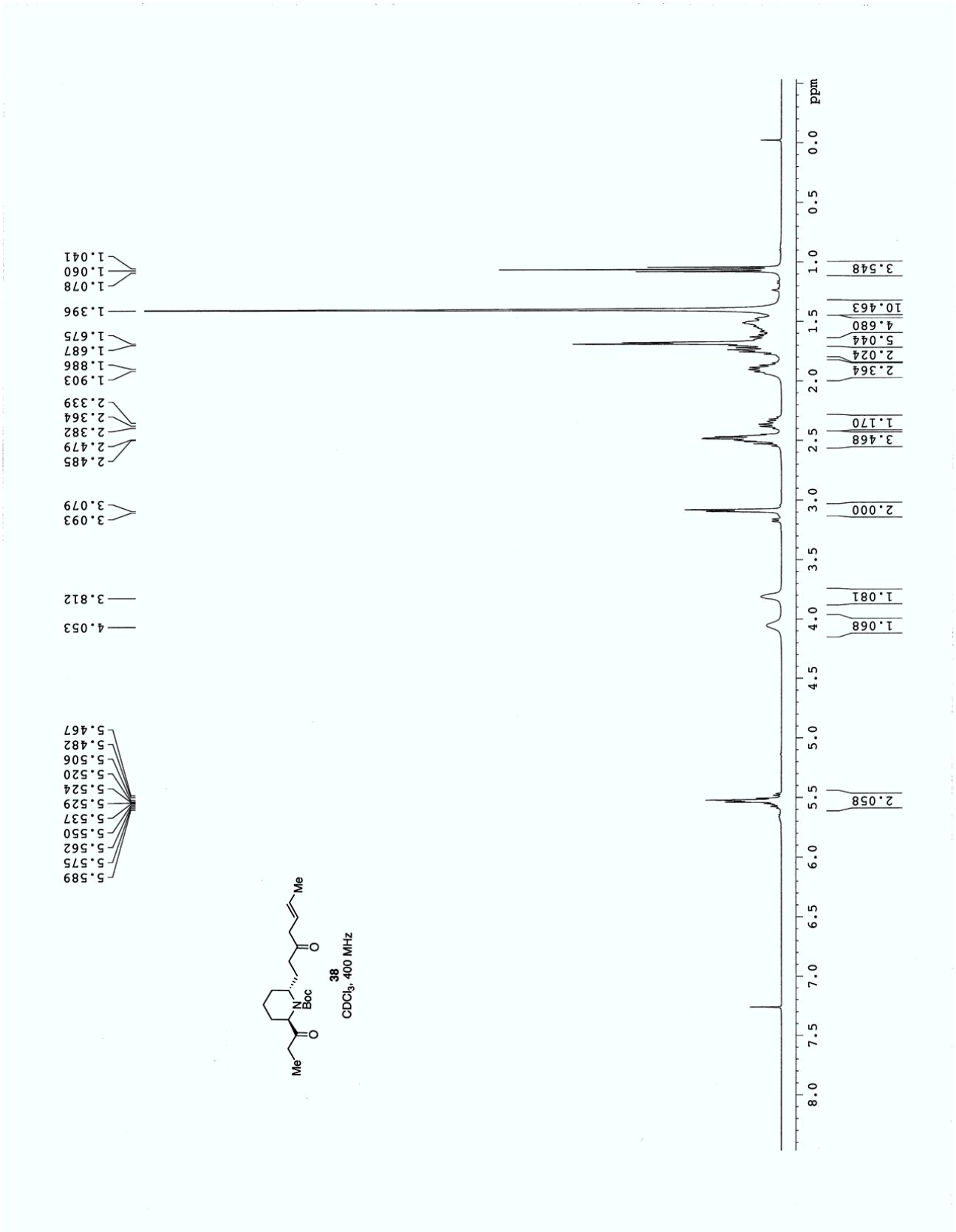

10.192
10.941
17.713
19.607
23.345
24.544
25.130
26.647
27.711
27.770
28.394
40.784
41.052
53.486
54.424
57.265
57.725
72.897
74.150
80.252
80.494
156.461
157.194
201.613
201.691
Me
OH
N
Boc
O
35
CDCl3, 100 MHz
ppm
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210

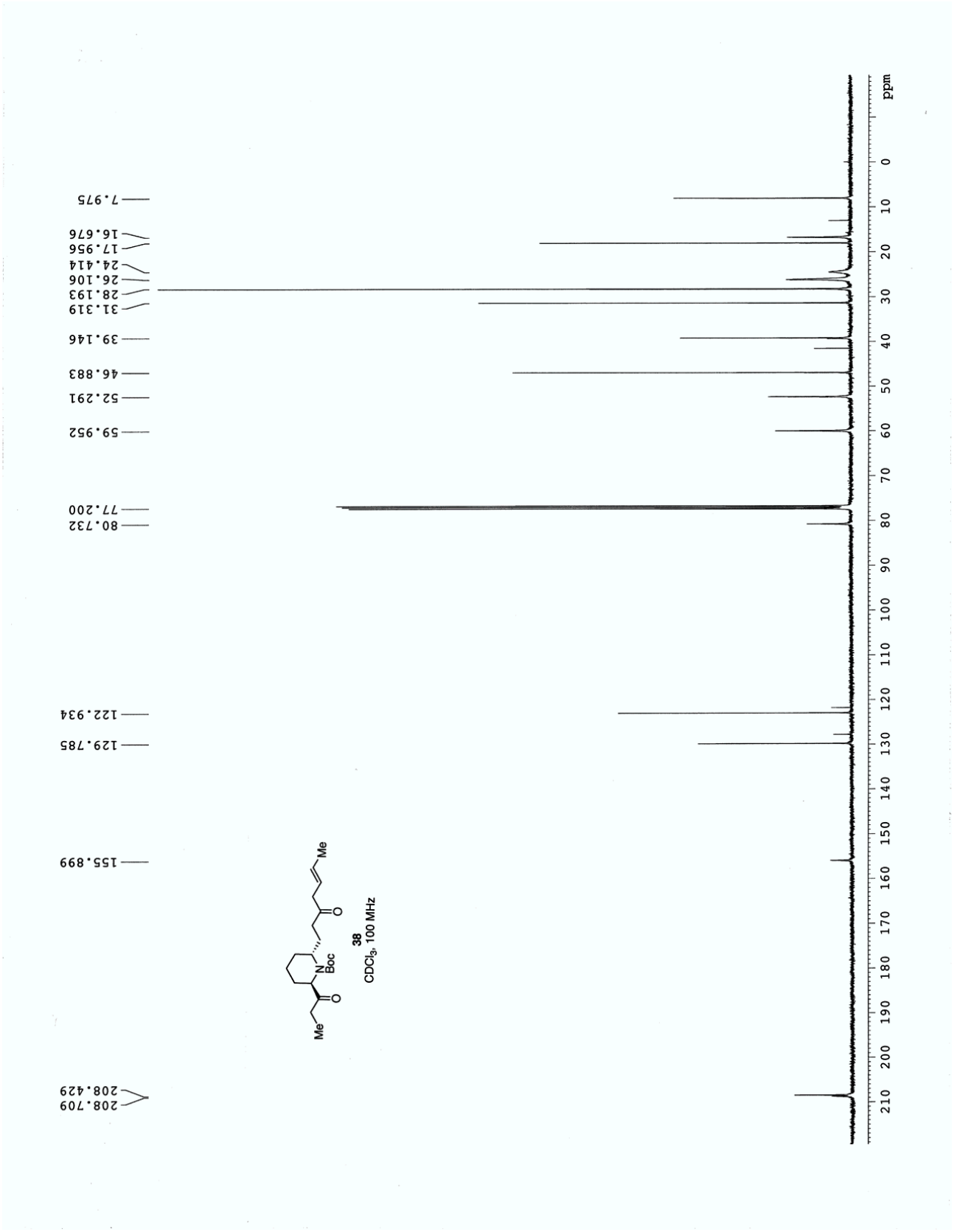

36
CDCl3, 400 MHz
Me
O
N
Boc
O
Me
ppm
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
3.000
23.709
1.040
4.571
0.173
1.773
1.000
0.980
1.815
5.555
5.548
5.543
5.534
4.657
4.177
4.162
3.119
3.117
3.114
3.106
2.507
2.489
2.154
2.145
2.119
1.699
1.688
1.457
1.074
1.056
1.038

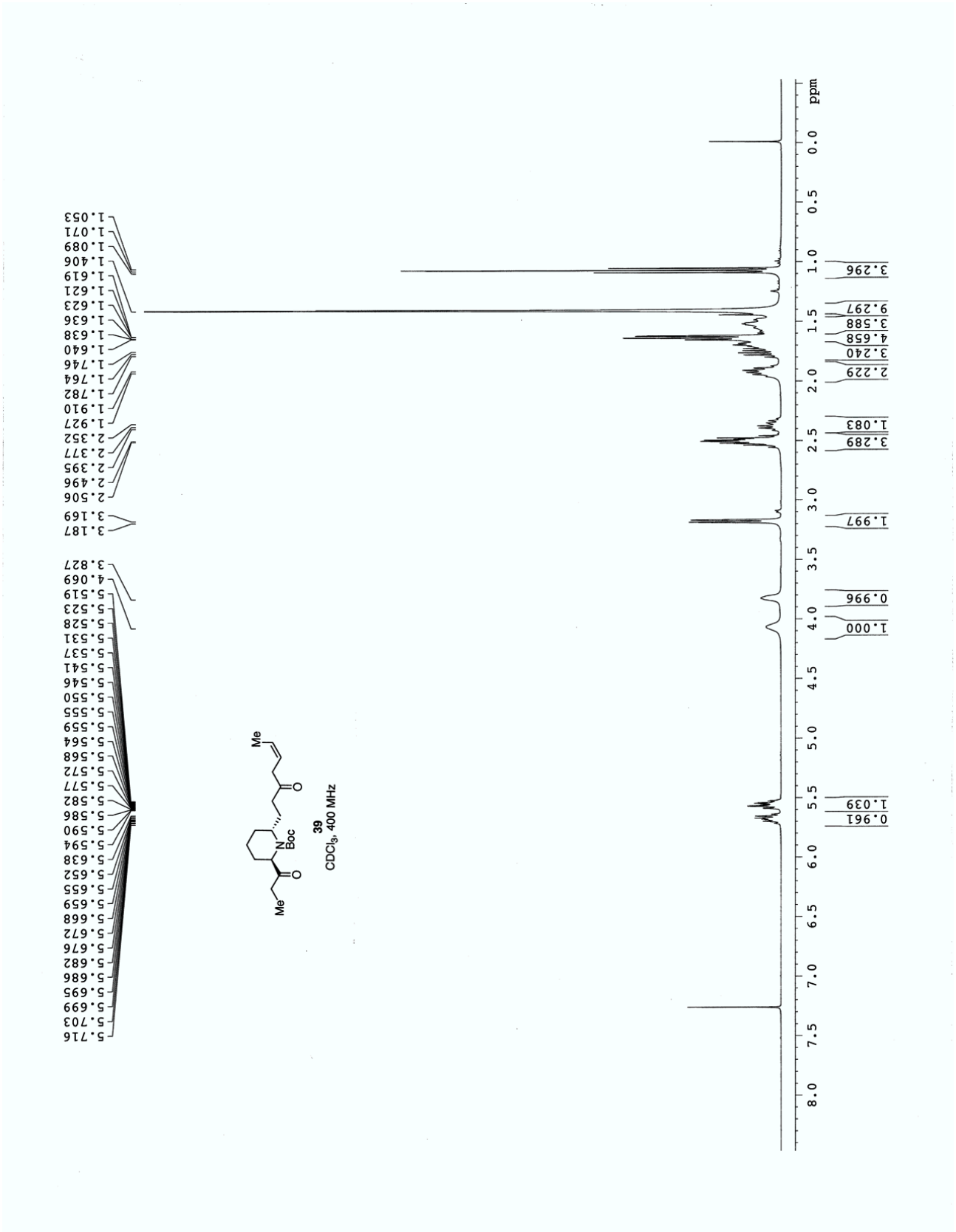

7.890
15.874
17.985
24.546
27.746
28.360
31.794
39.652
46.738
50.048
59.001
77.203
80.148
123.243
129.504
155.614
209.119
210.562
ppm
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
Me
O
N
Boc
O
Me
36
CDCl3, 100 MHz

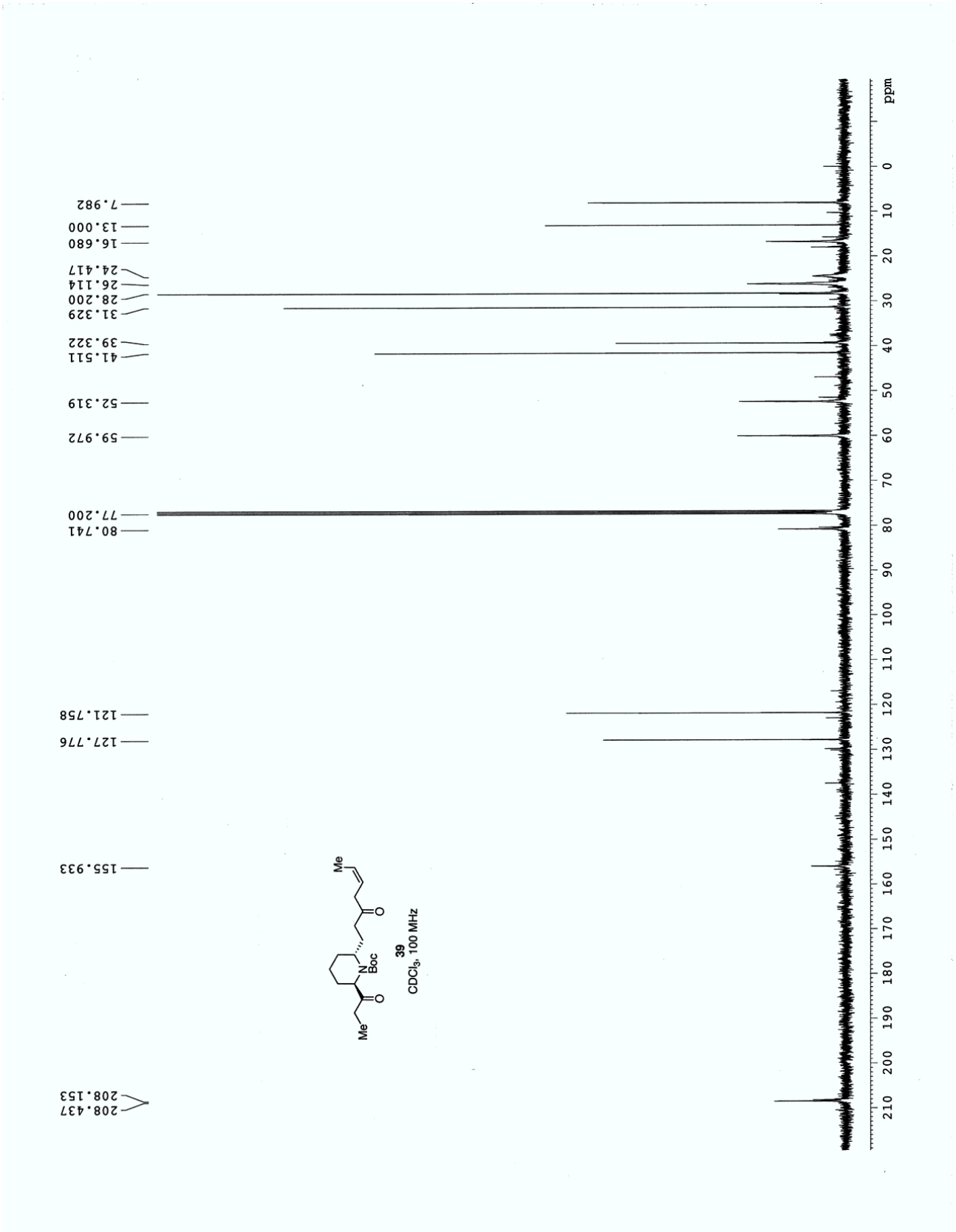

37
CDCl3, 400 MHz
Me
Boc
N
O
O
Me
ppm
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
3.374
12.646
2.827
4.432
1.341
1.297
1.098
4.508
1.983
1.082
1.000
0.995
0.970

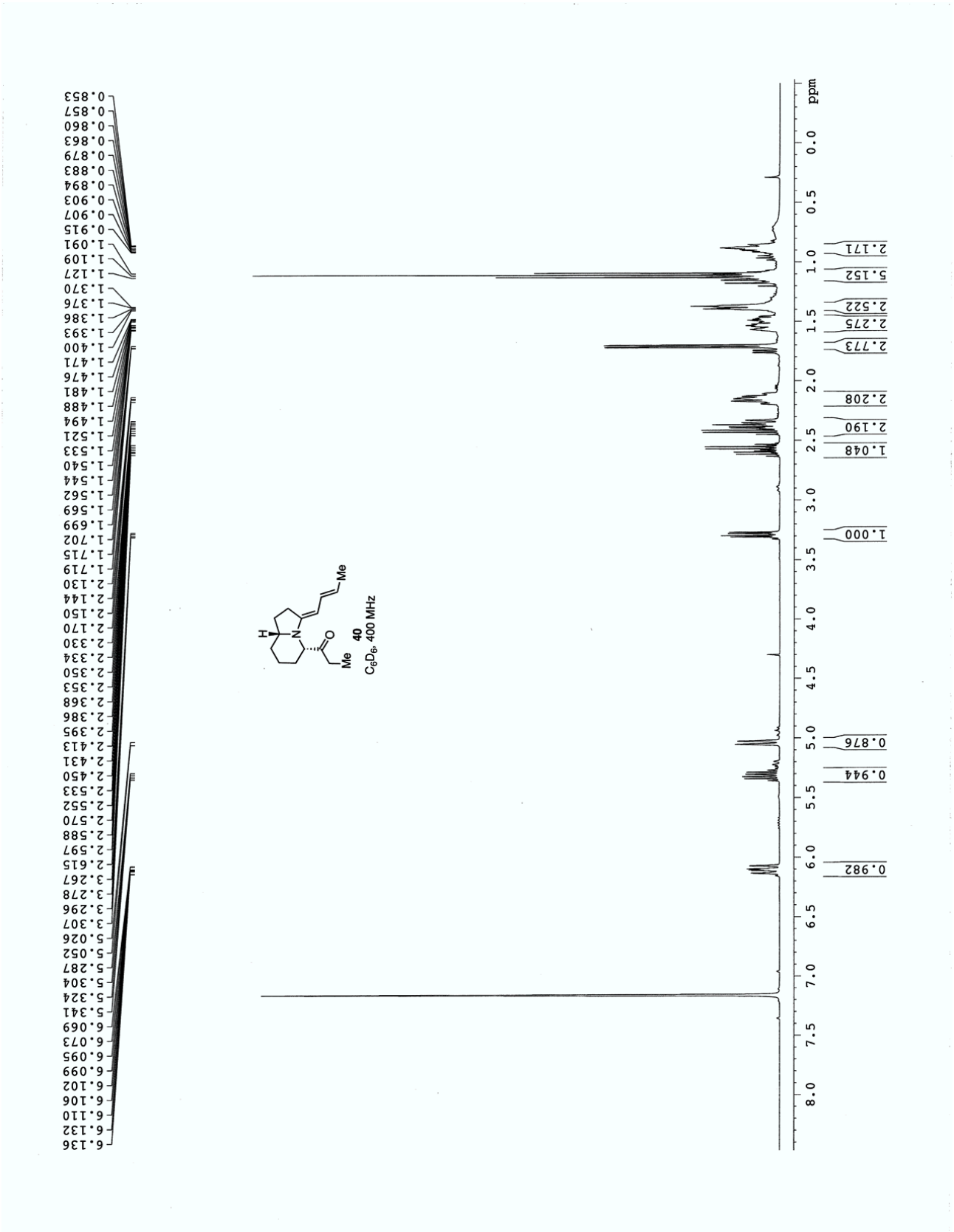

Me
O
N
Boc
O
Me
37
CDCl3, 100 MHz
7.891
13.007
15.886
24.552
27.808
28.363
31.799
39.828
41.297
50.031
58.998
77.203
80.141
122.085
127.475
155.616
208.538
210.548
ppm

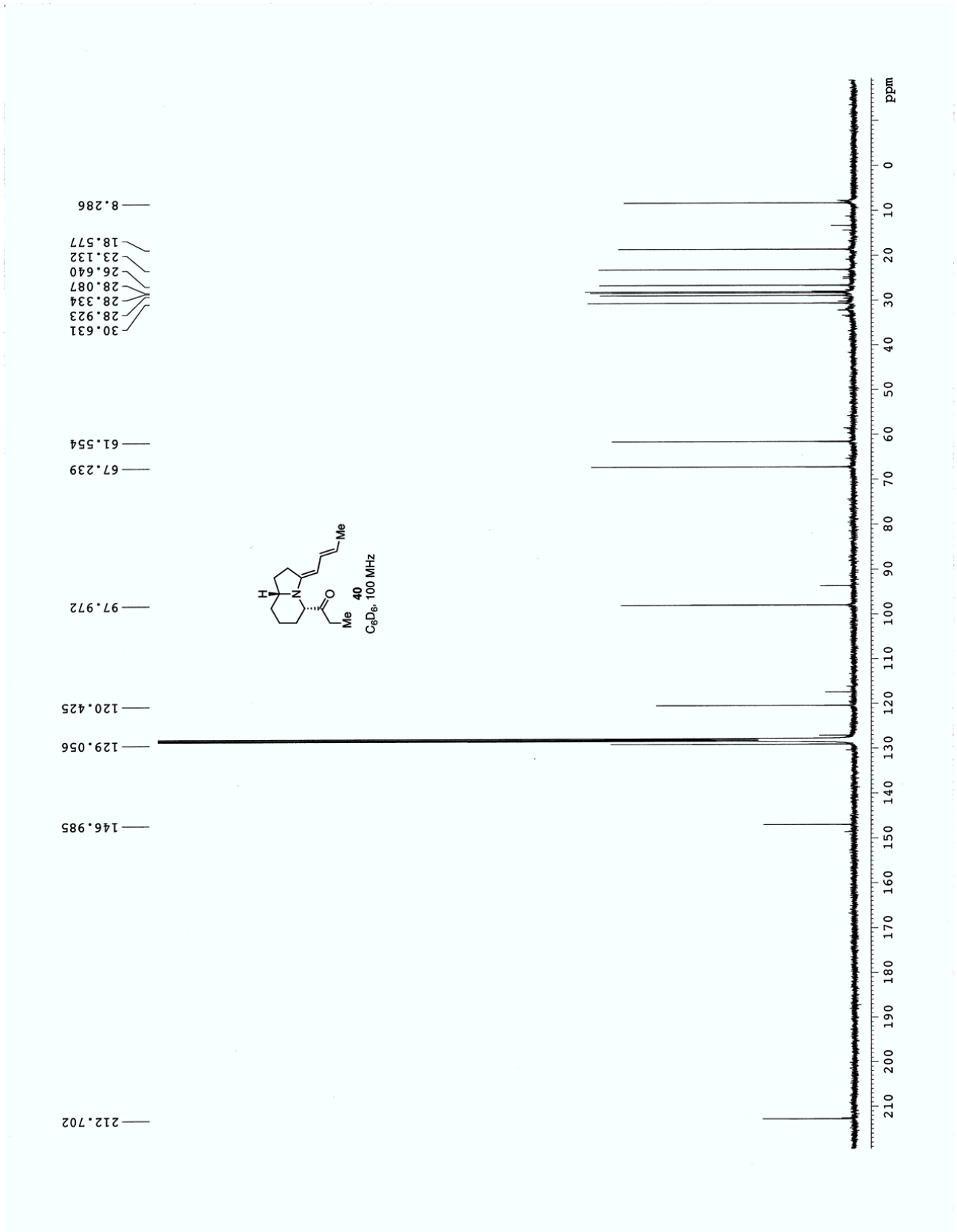

38
CDCl3, 400 MHz
Me
Boc
N
O
O
Me
ppm
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
5.589
5.575
5.562
5.550
5.537
5.529
5.524
5.520
5.506
5.482
5.467
4.053
3.812
3.093
3.079
2.485
2.479
2.382
2.364
2.339
1.903
1.886
1.687
1.675
1.396
1.078
1.060
1.041
2.058
1.068
1.081
3.468
1.170
2.000
2.364
2.024
5.044
4.680
10.463
3.548

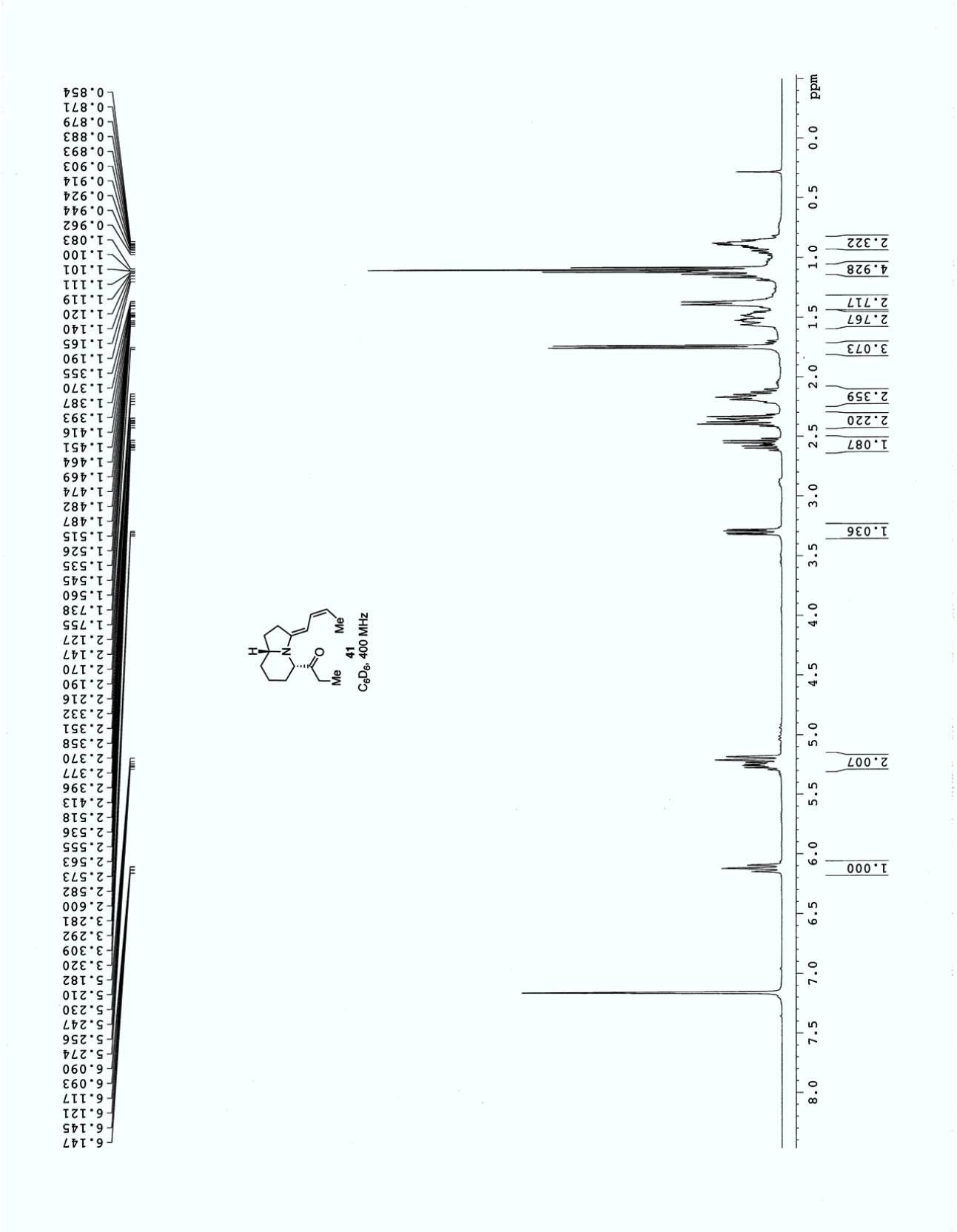

ppm
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
7.975
16.676
17.956
24.414
26.106
28.193
31.319
39.146
46.883
52.291
59.952
77.200
80.732
122.934
129.785
155.899
208.709
208.429
Me
Me
N
Boc
O
O
38
CDCl3, 100 MHz

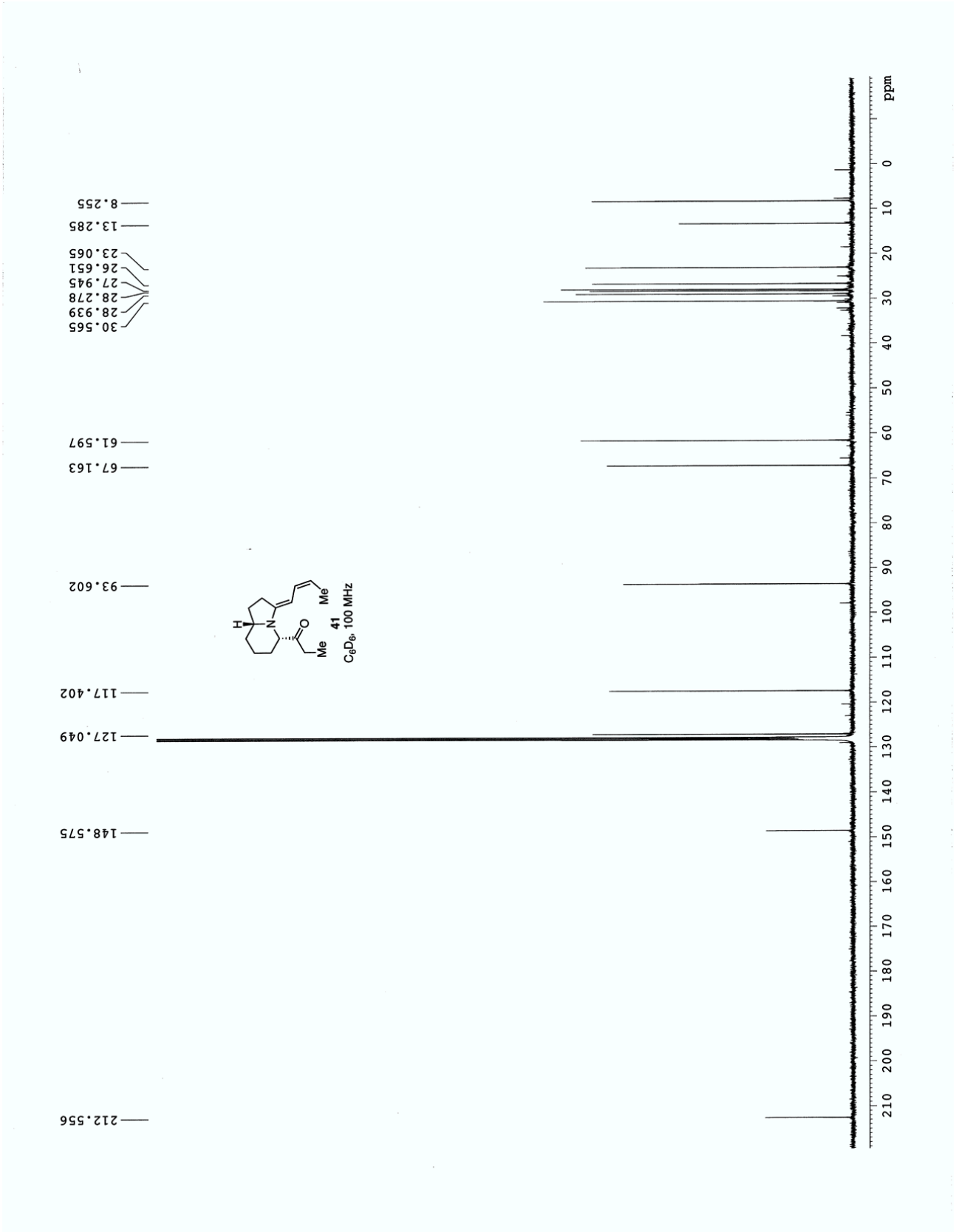

39
CDCl3, 400 MHz
Me
N
Boc
O
O
Me
ppm
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
3.296
9.297
3.588
4.658
3.240
2.229
3.289
1.083
1.997
0.996
1.000
0.961
1.039
1.053
1.071
1.089
1.406
1.619
1.621
1.623
1.636
1.638
1.640
1.746
1.764
1.782
1.910
1.927
2.352
2.377
2.395
2.496
2.506
3.169
3.187
3.827
4.069
5.519
5.523
5.528
5.531
5.537
5.541
5.546
5.550
5.555
5.559
5.564
5.568
5.572
5.577
5.582
5.586
5.590
5.594
5.638
5.652
5.655
5.659
5.668
5.672
5.676
5.682
5.686
5.695
5.699
5.703
5.716

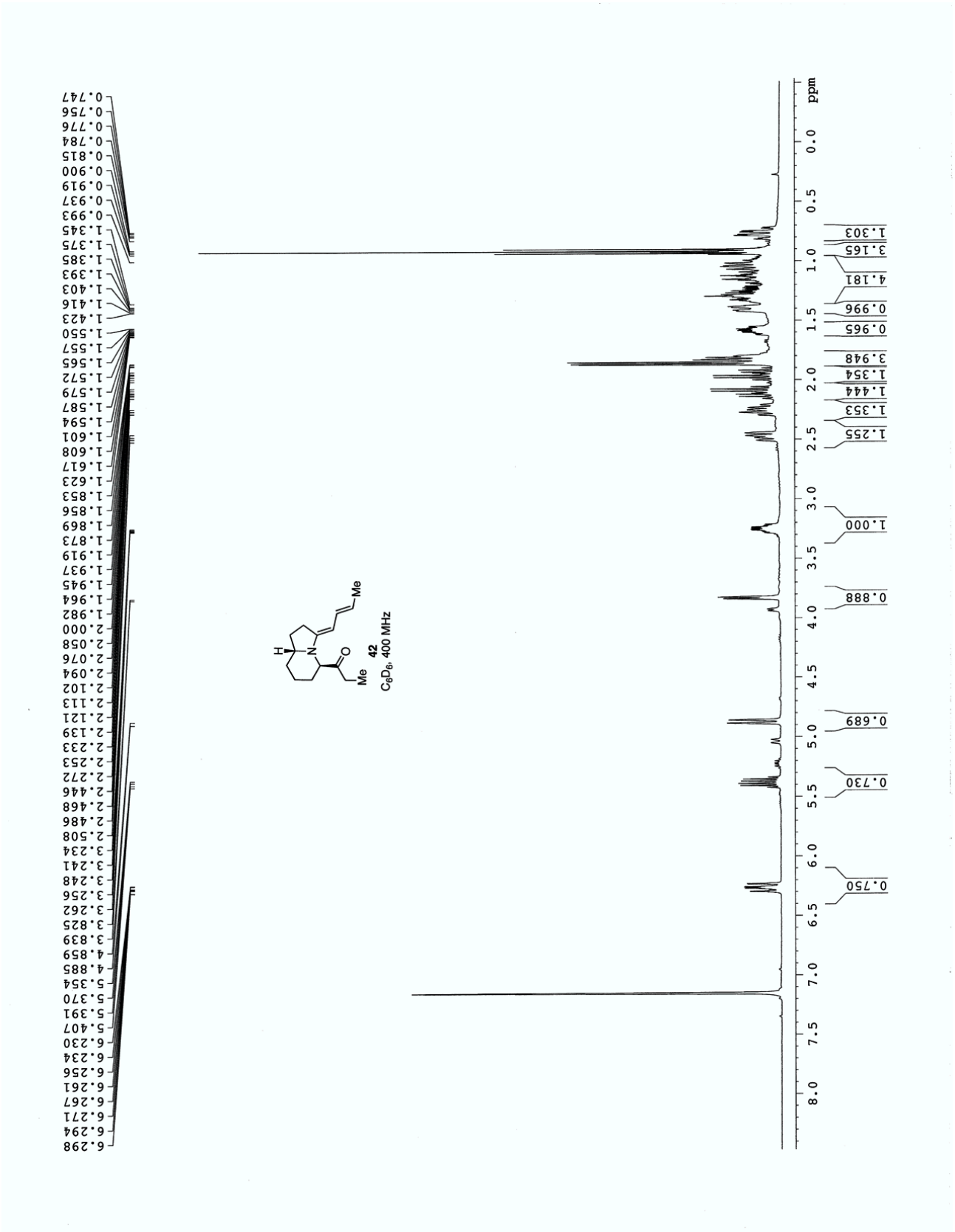

Me
N
Boc
O
O
Me
39
CDCl3, 100 MHz
208.437
208.153
155.933
127.776
121.758
80.741
77.200
59.972
52.319
41.511
39.322
31.329
28.200
26.114
24.417
16.680
13.000
7.982
ppm

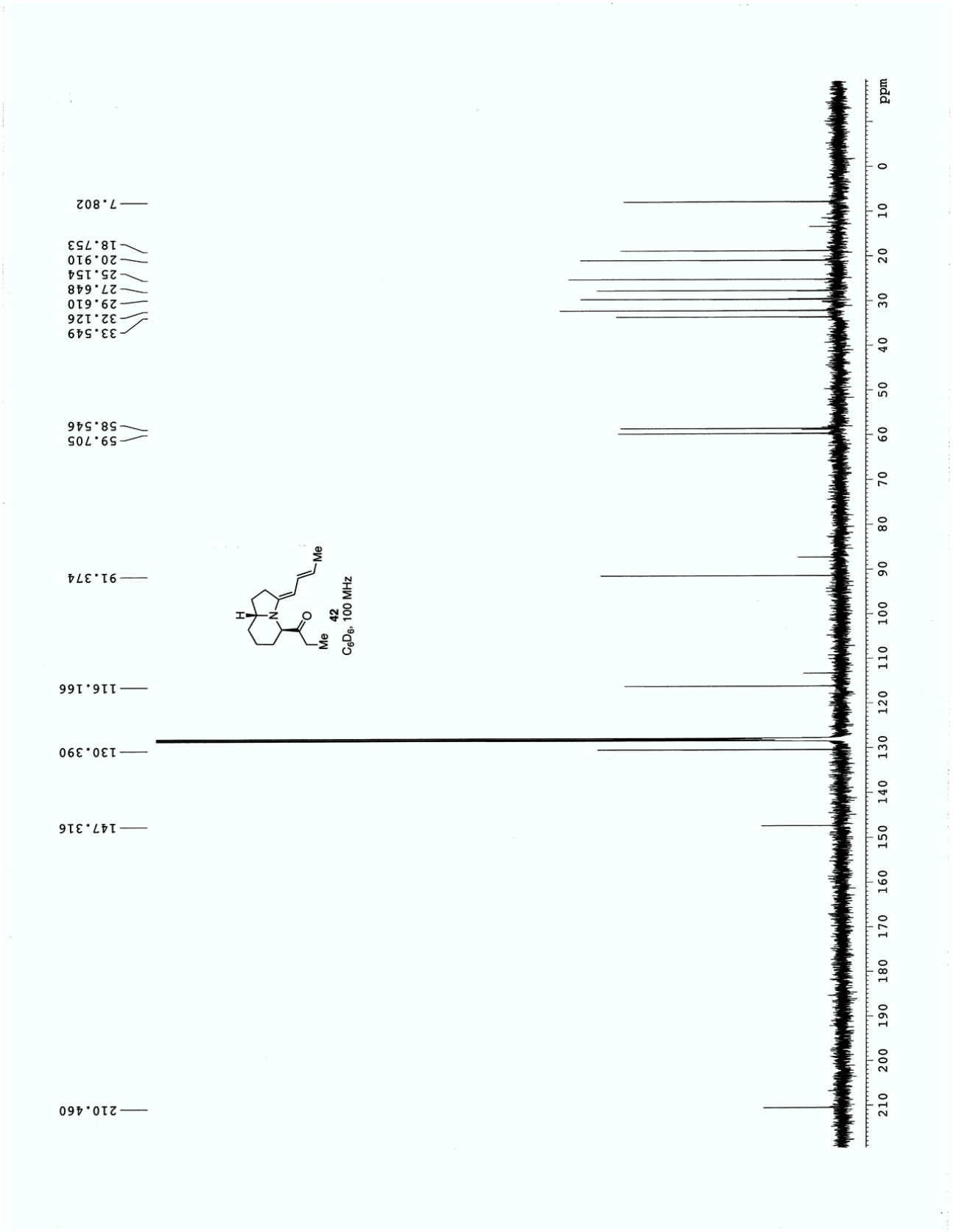

ppm
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
2.171
5.152
2.522
2.275
2.773
2.208
2.190
1.048
1.000
0.876
0.944
0.982
Me
H
N
O
Me
40
C6D6, 400 MHz

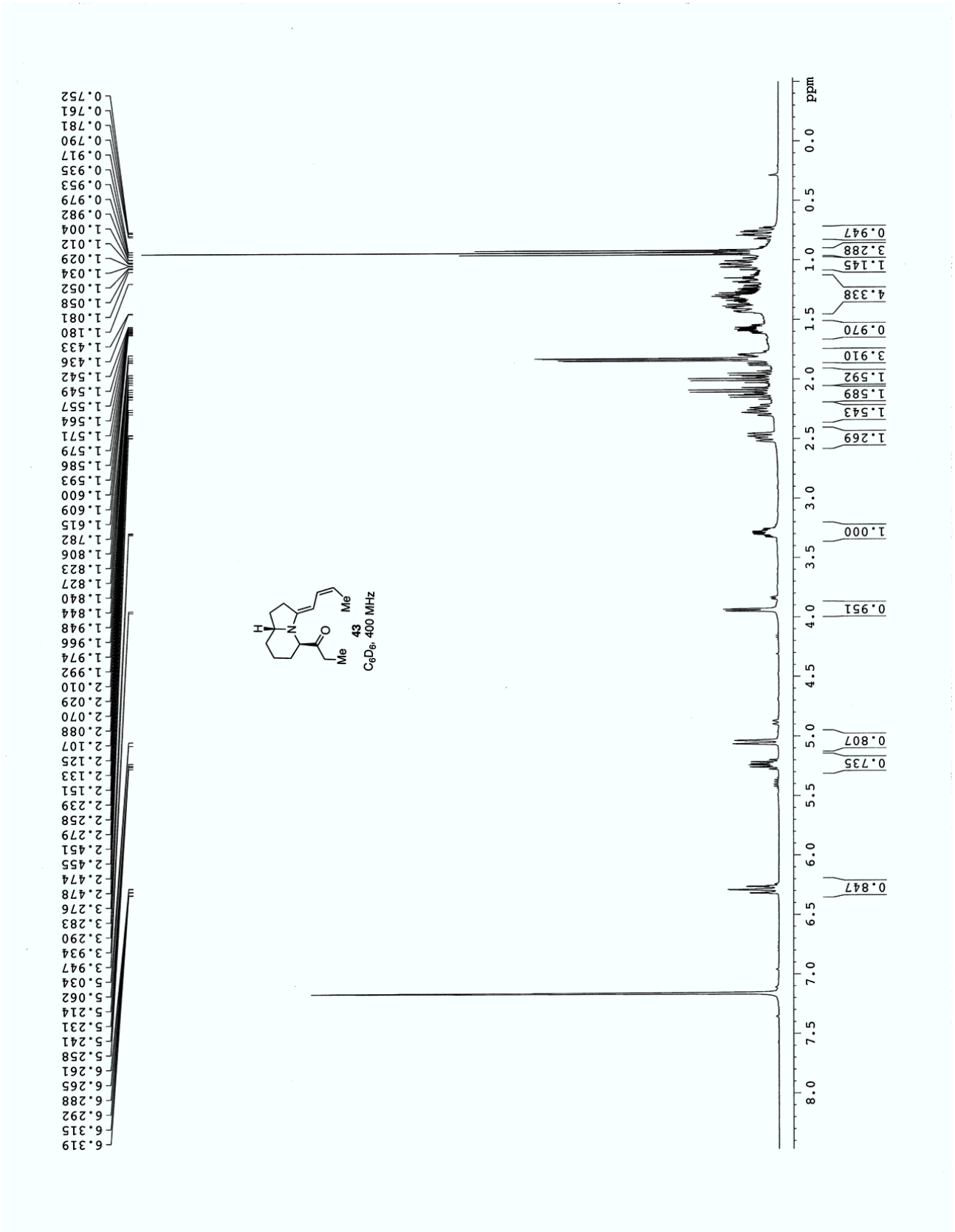

8.286
18.577
23.132
26.640
28.087
28.334
28.923
30.631
61.554
67.239
97.972
120.425
129.056
146.985
212.702
Me
H
N
O
Me
40
C6D6, 100 MHz
ppm
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210

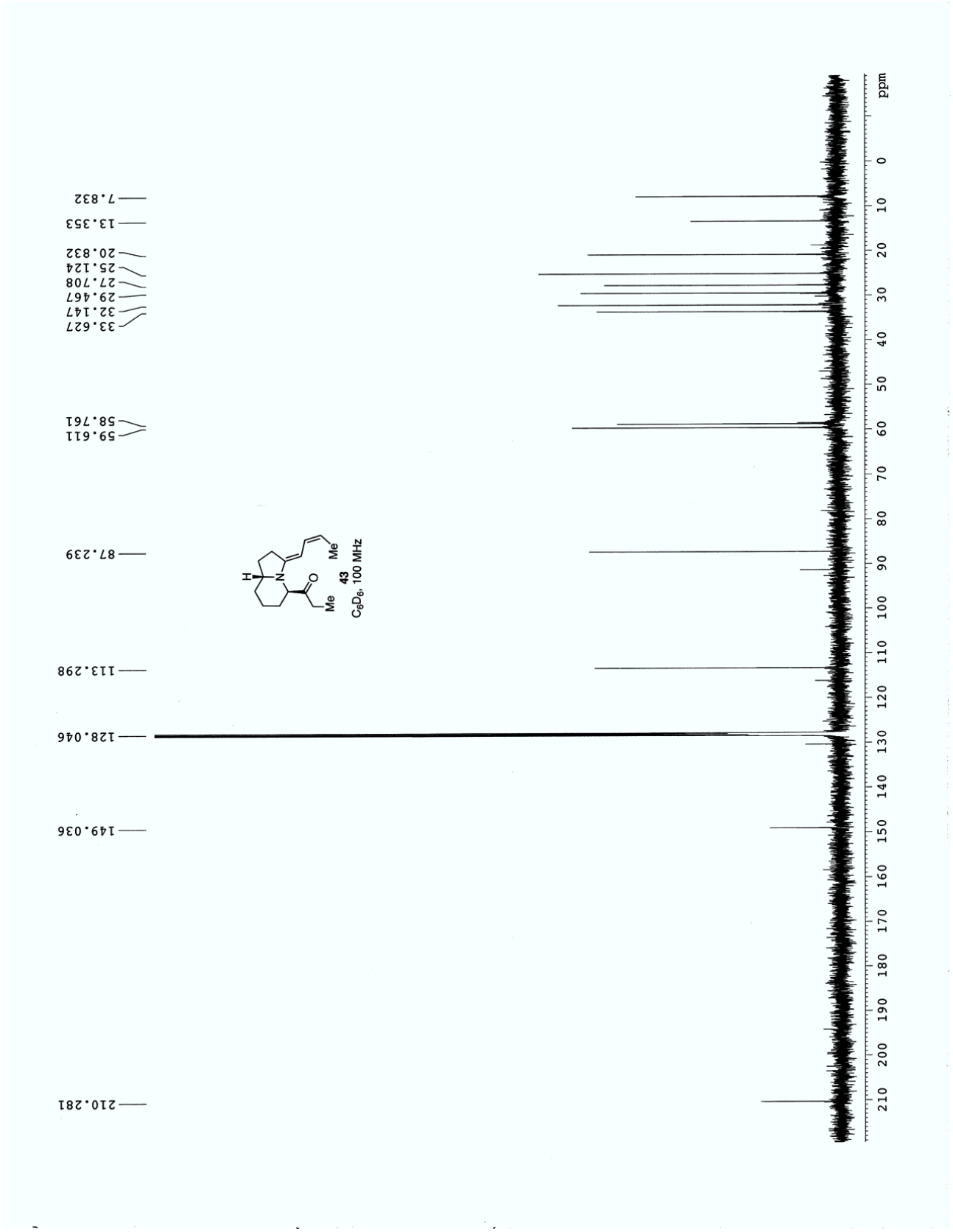

41
C_6D_6, 400 MHz
Me
Me
H
N
O
ppm
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
1.000
2.007
1.036
1.087
2.220
2.359
3.073
2.767
2.717
4.928
2.322

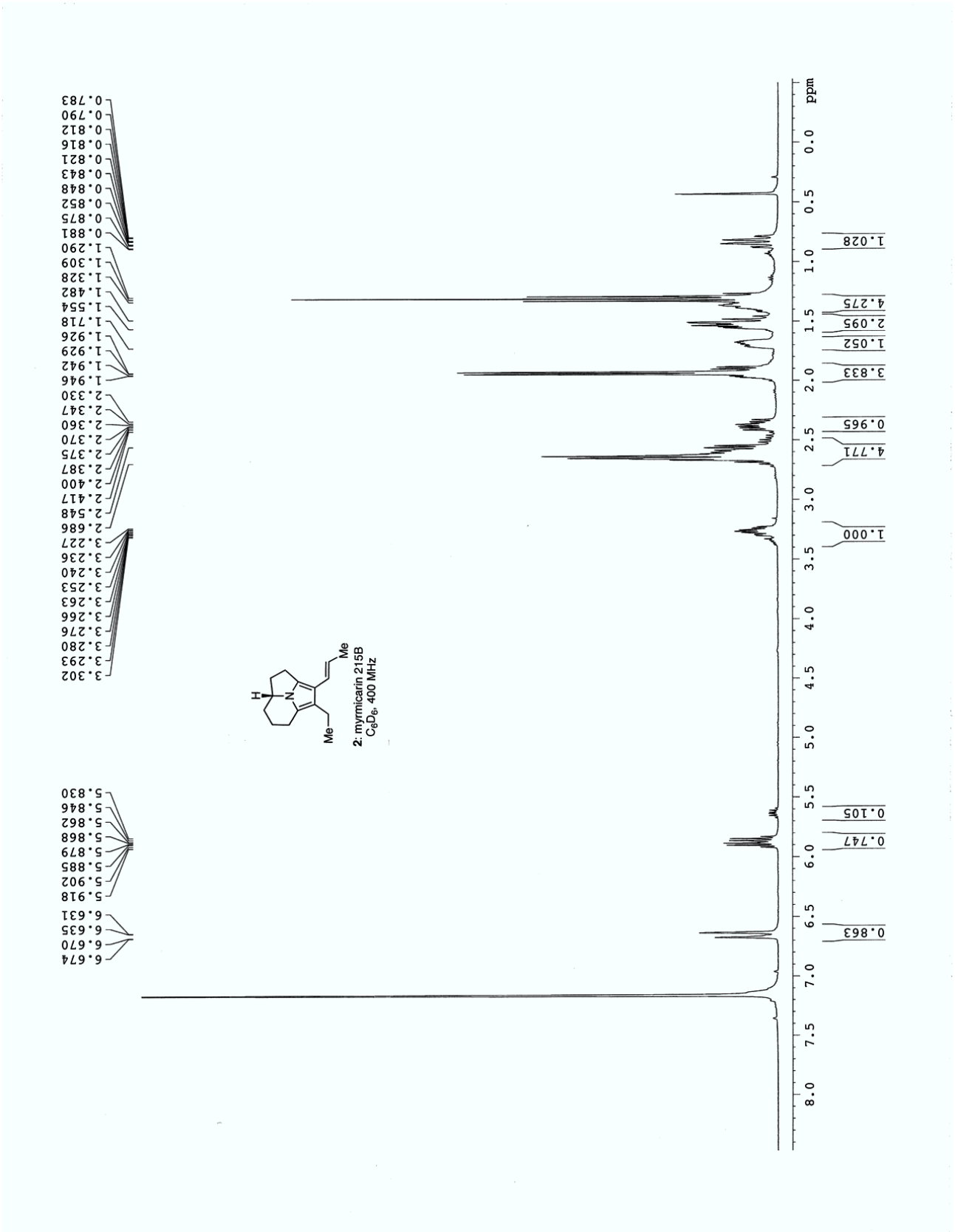

8.255
13.285
23.065
26.651
27.945
28.278
28.939
30.565
61.597
67.163
93.602
117.402
127.049
148.575
212.556
ppm
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
H
N
O
Me
Me
Me
41
C6D6, 100 MHz

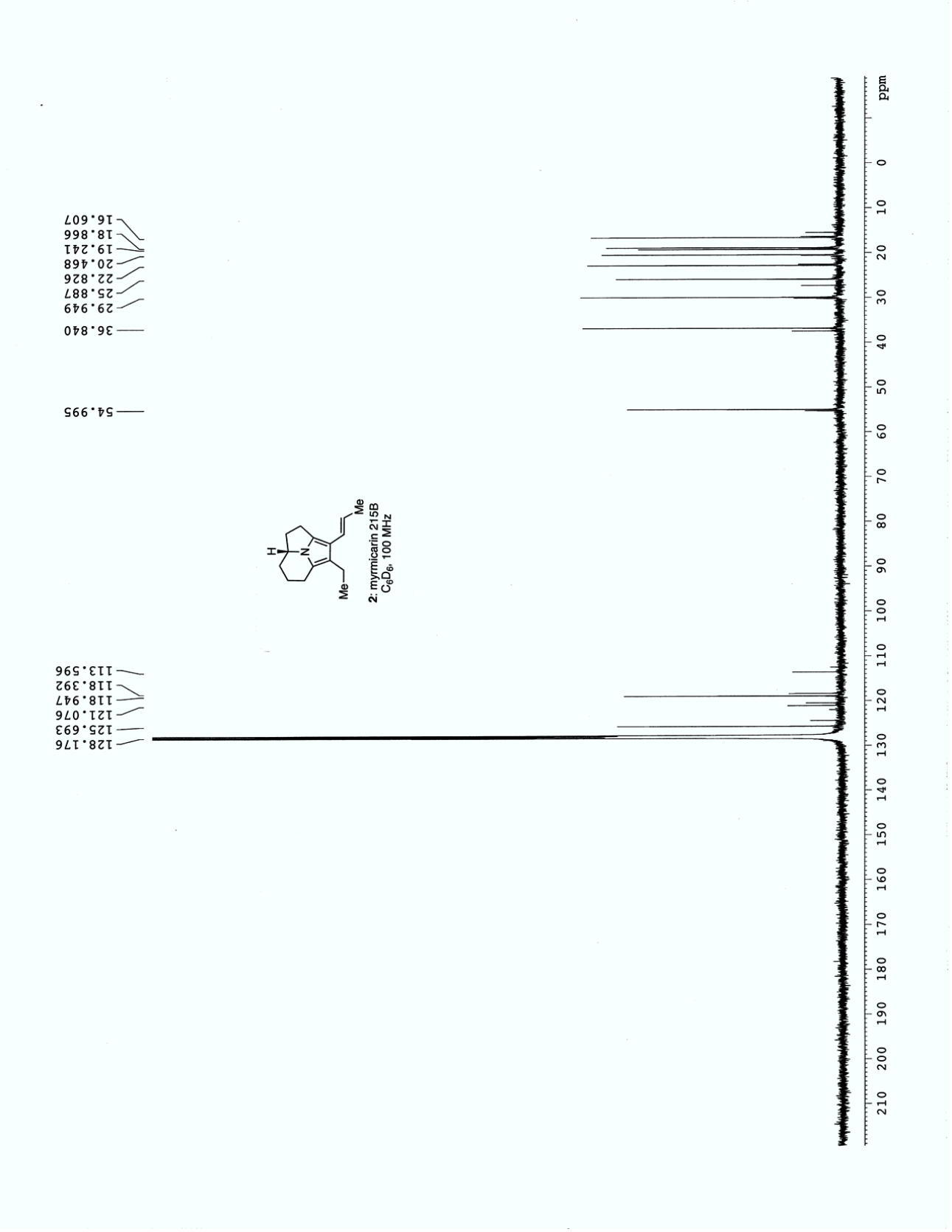

Me
H
N
O
Me
42
C_6D_6, 400 MHz
ppm
0.747
0.756
0.776
0.784
0.815
0.900
0.919
0.937
0.993
1.345
1.375
1.385
1.393
1.403
1.416
1.423
1.550
1.557
1.565
1.572
1.579
1.587
1.594
1.601
1.608
1.617
1.623
1.853
1.856
1.869
1.873
1.919
1.937
1.945
1.964
1.982
2.000
2.058
2.076
2.094
2.102
2.113
2.121
2.139
2.233
2.253
2.272
2.446
2.468
2.486
2.508
3.234
3.241
3.248
3.256
3.262
3.825
3.839
4.859
4.885
5.354
5.370
5.391
5.407
6.230
6.234
6.256
6.261
6.267
6.271
6.294
6.298
1.303
3.165
4.181
0.996
0.965
3.948
1.354
1.444
1.353
1.255
1.000
0.888
0.689
0.730
0.750

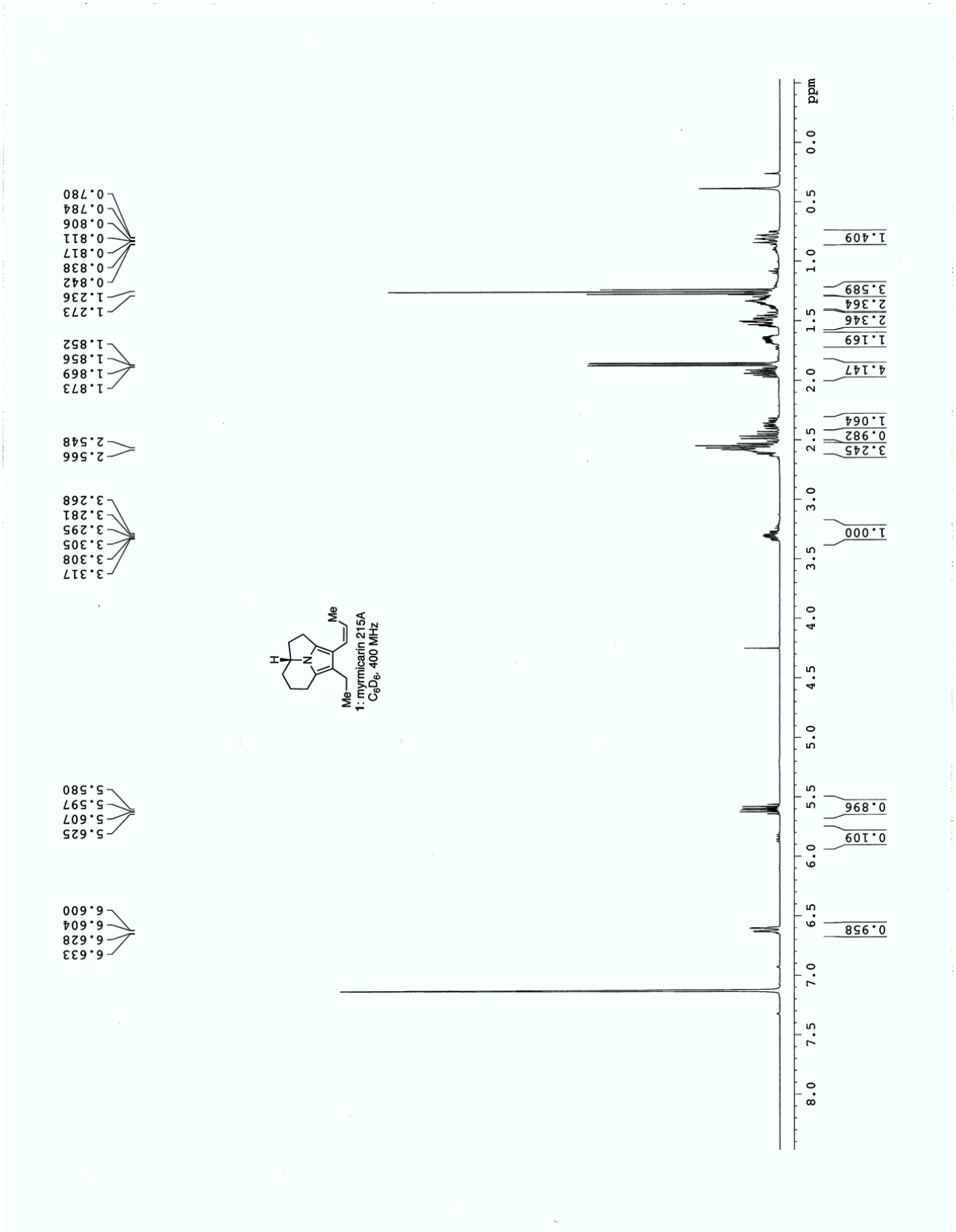

7.802
18.753
20.910
25.154
27.648
29.610
32.126
33.549
58.546
59.705
91.374
116.166
130.390
147.316
210.460
Me
H
N
O
Me
42
C_6D_6, 100 MHz
ppm
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210

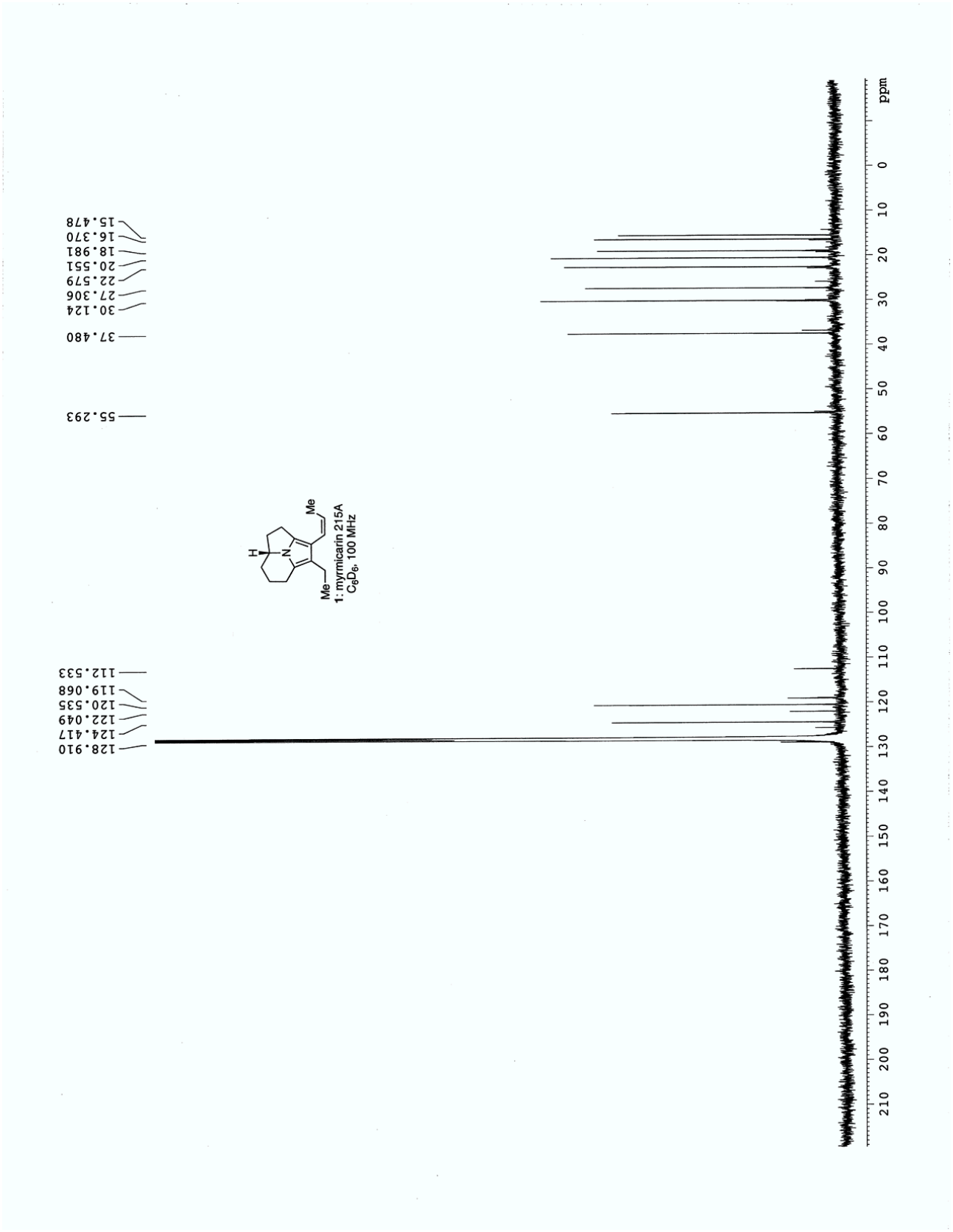

43
C_6D_6, 400 MHz
Me
Me
H
N
O
ppm
0.847
0.735
0.807
0.951
1.000
1.269
1.543
1.589
1.592
3.910
0.970
4.338
1.145
3.288
0.947

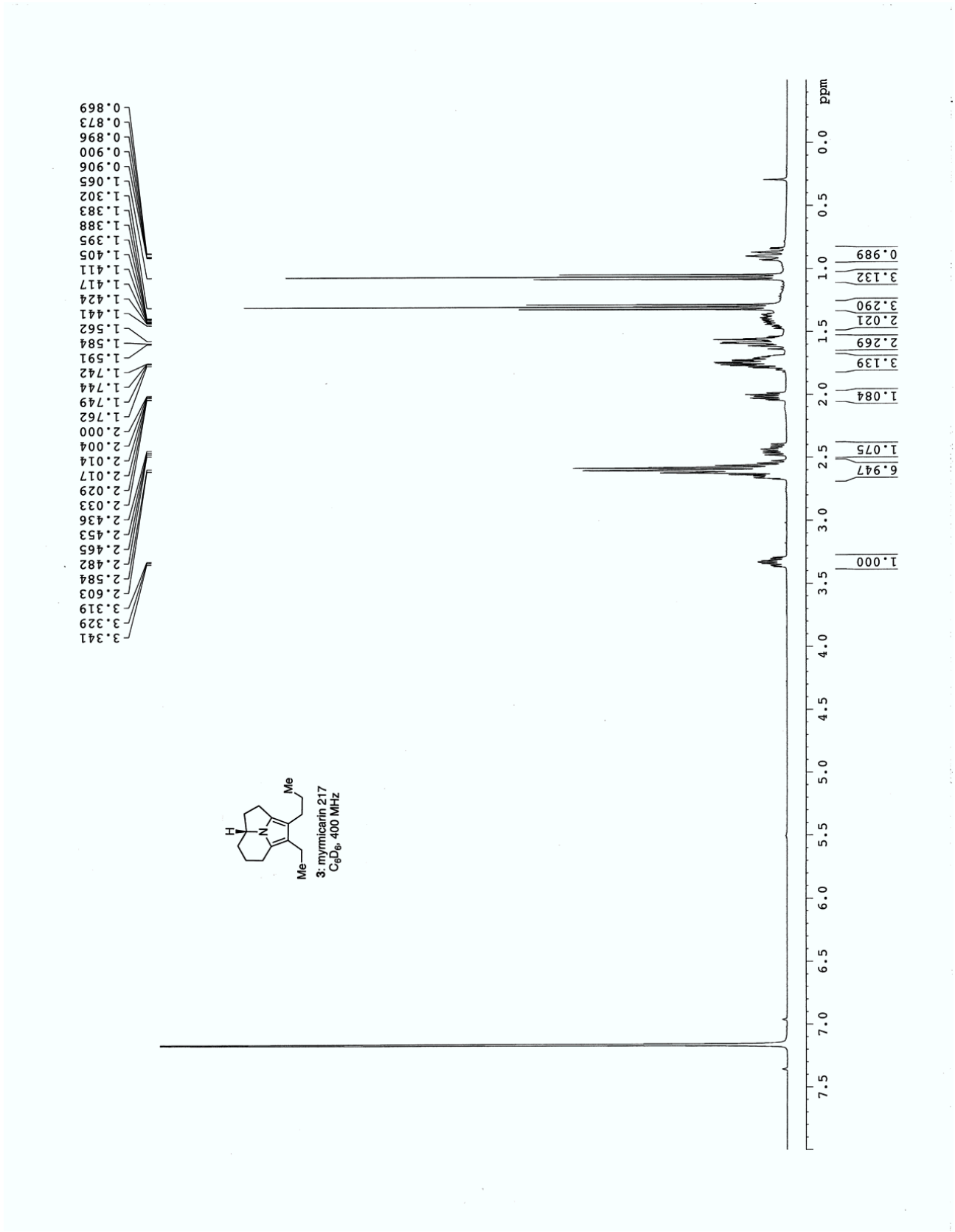

7.832
13.353
20.832
25.124
27.708
29.467
32.147
33.627
58.761
59.611
87.239
113.298
128.046
149.036
210.281
ppm
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
H
N
O
Me
Me
43
C6D6, 100 MHz

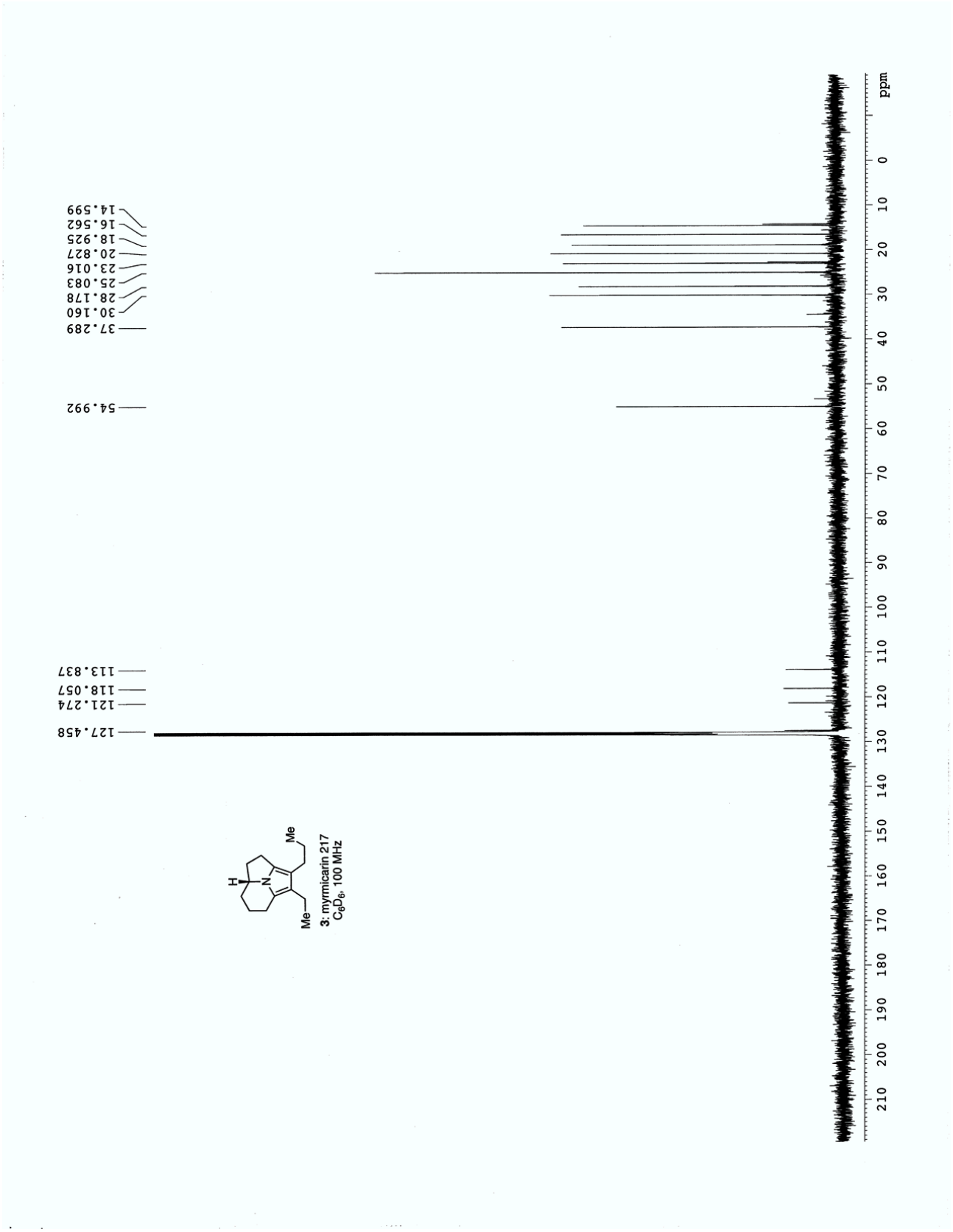

2: myrmicarin 215B
C6D6, 400 MHz
Me
Me
H
N
ppm
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
1.028
4.275
2.095
1.052
3.833
0.965
4.771
1.000
0.105
0.747
0.863
0.783
0.790
0.812
0.816
0.821
0.843
0.848
0.852
0.875
0.881
1.290
1.309
1.328
1.482
1.554
1.718
1.926
1.929
1.942
1.946
2.330
2.347
2.360
2.370
2.375
2.387
2.400
2.417
2.548
2.686
3.227
3.236
3.240
3.253
3.263
3.266
3.276
3.280
3.293
3.302
5.830
5.846
5.862
5.868
5.879
5.885
5.902
5.918
6.631
6.635
6.670
6.674

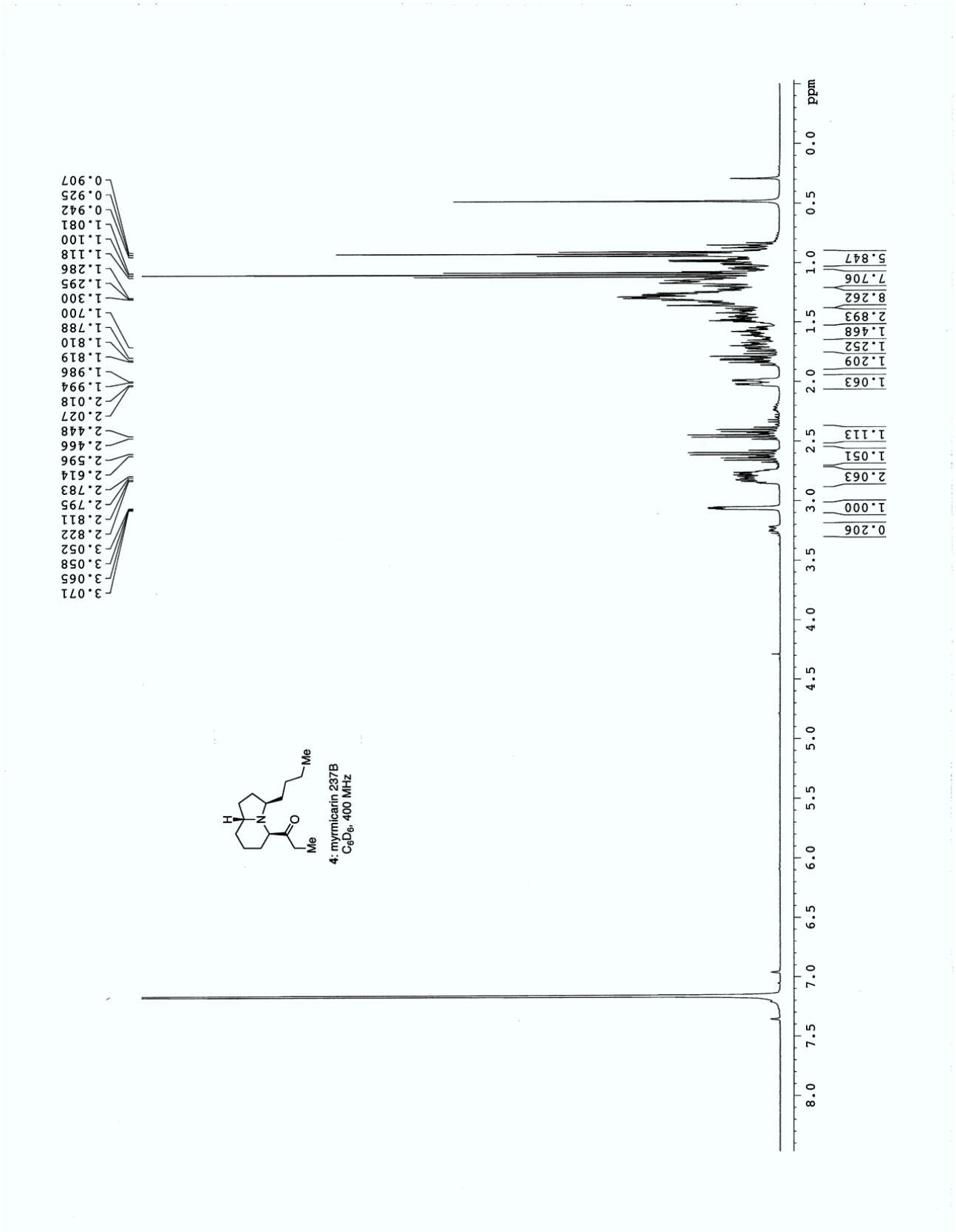

128.176
125.693
121.076
118.947
118.392
113.596
54.995
36.840
29.949
25.887
22.826
20.468
19.241
18.866
16.607
Me
Me
H
N
2: myrmicarin 215B
C6D6, 100 MHz
ppm
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210

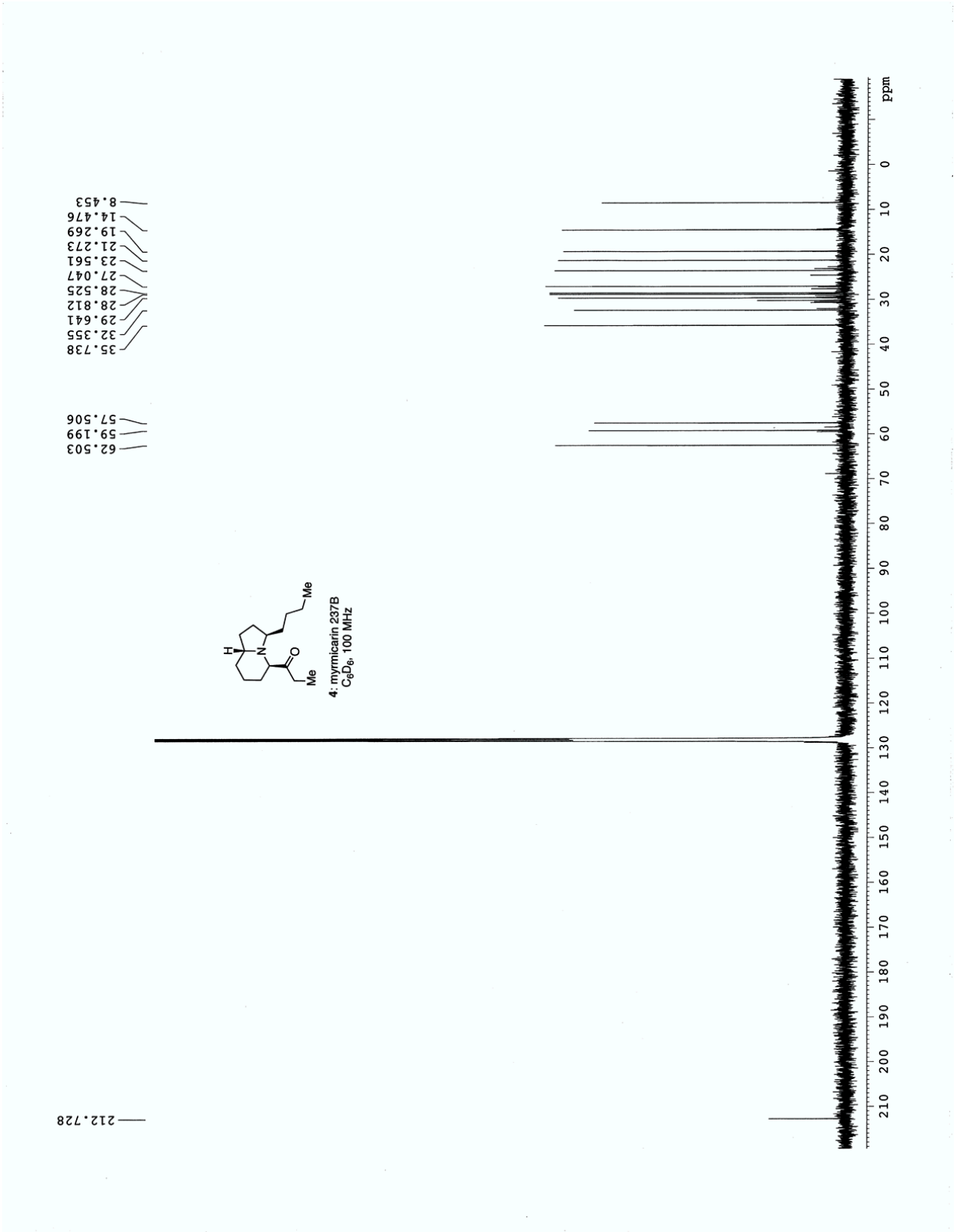

1: myrmicarin 215A
C6D6, 400 MHz
Me
Me
H
N
ppm
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
1.409
3.589
2.364
2.346
1.169
4.147
1.064
0.982
3.245
1.000
0.896
0.109
0.958
0.780
0.784
0.806
0.811
0.817
0.838
0.842
1.236
1.273
1.852
1.856
1.869
1.873
2.548
2.566
3.268
3.281
3.295
3.305
3.308
3.317
5.580
5.597
5.607
5.625
6.600
6.604
6.628
6.633

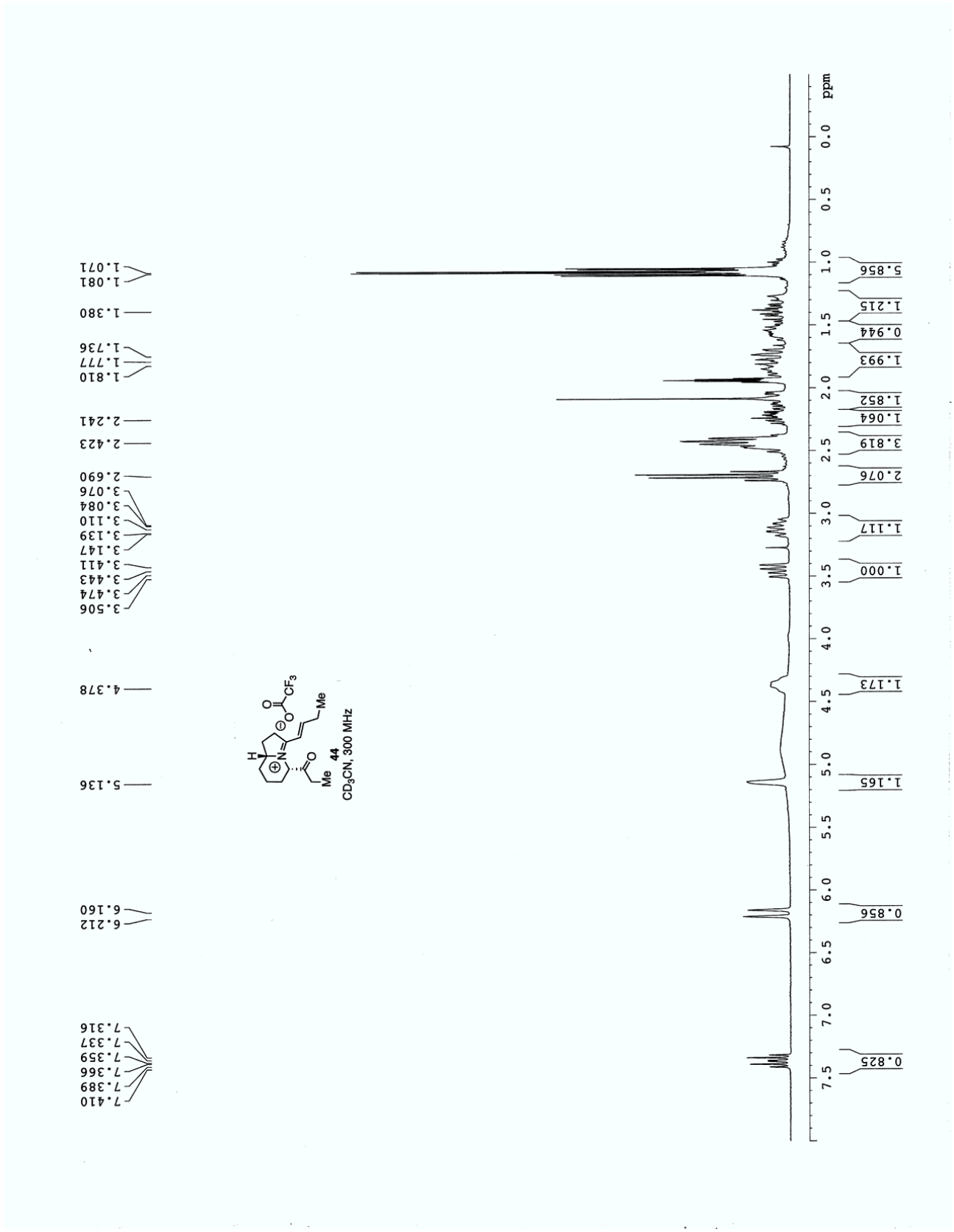

ppm
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
128.910
124.417
122.049
120.535
119.068
112.533
55.293
37.480
30.124
27.306
22.579
20.551
18.981
16.370
15.478
Me
Me
H
N
1: myrmicarin 215A
C6D6, 100 MHz

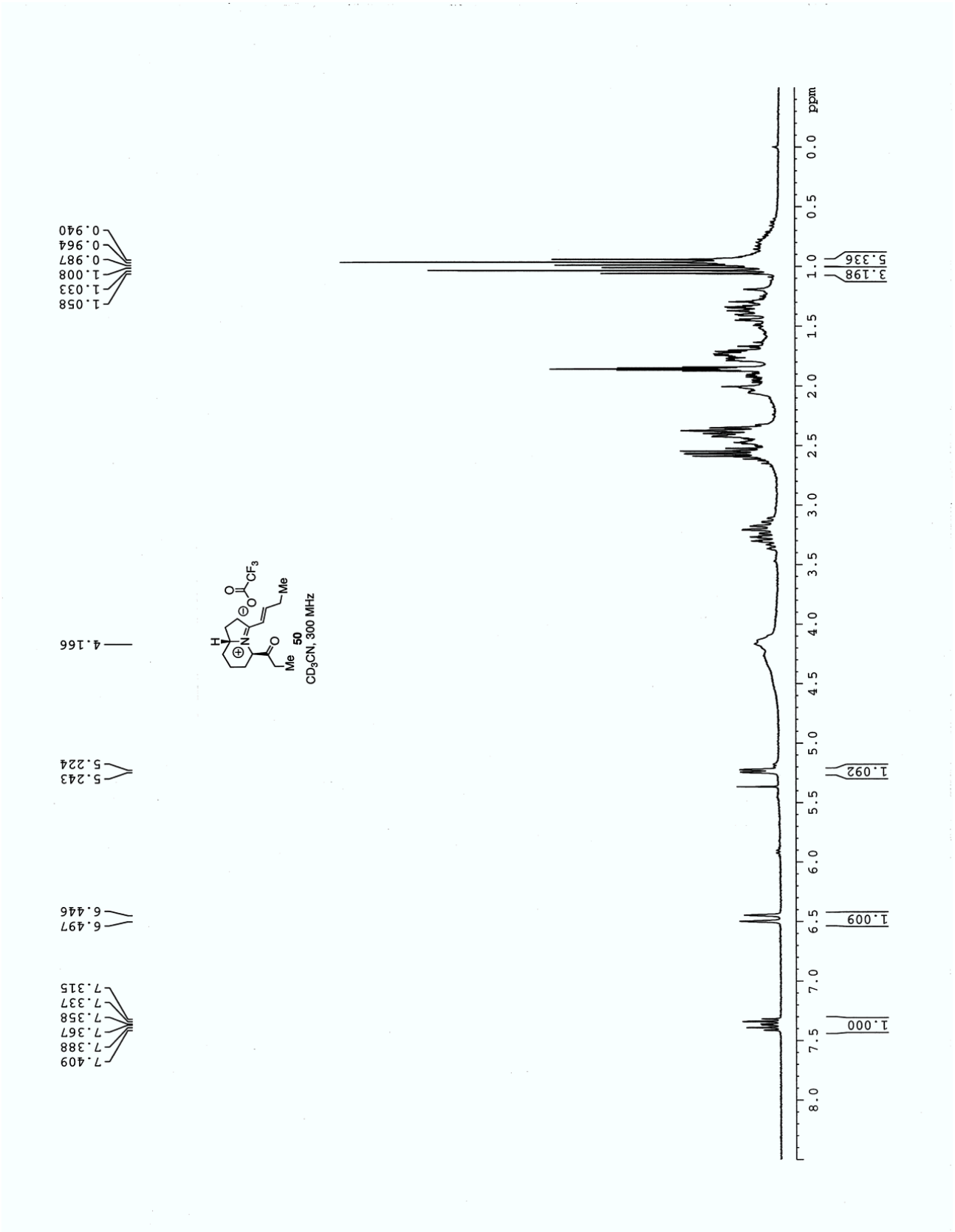

3: myrmicarin 217
C6D6, 400 MHz
Me
Me
H
N
ppm
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
1.000
6.947
1.075
1.084
3.139
2.269
2.021
3.290
3.132
0.989
3.341
3.329
3.319
2.603
2.584
2.482
2.465
2.453
2.436
2.033
2.029
2.017
2.014
2.004
2.000
1.762
1.749
1.744
1.742
1.591
1.584
1.562
1.441
1.424
1.417
1.411
1.405
1.395
1.388
1.383
1.302
1.065
0.906
0.900
0.896
0.873
0.869

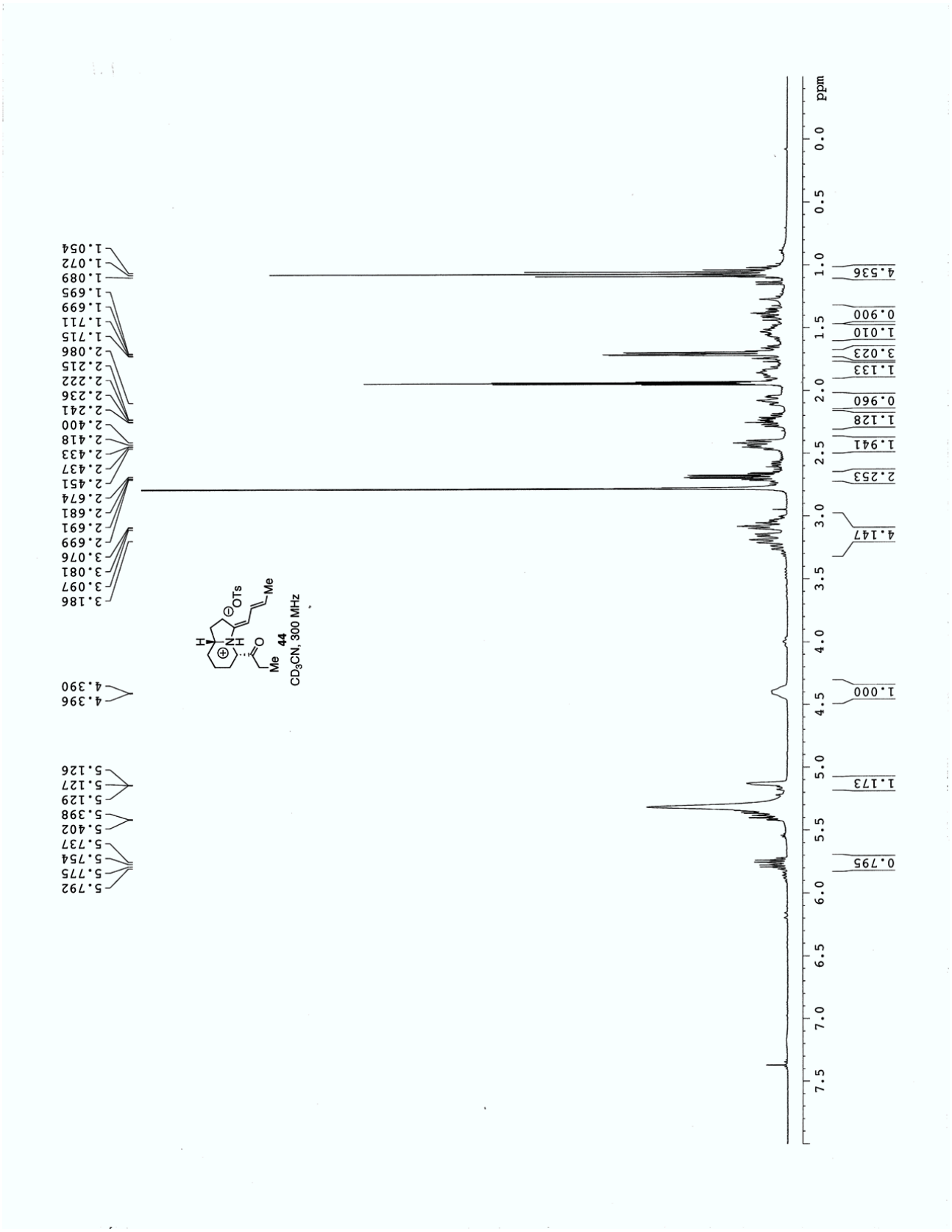

127.458
121.274
118.057
113.837
54.992
37.289
30.160
28.178
25.083
23.016
20.827
18.925
16.562
14.599
Me
Me
H
N
3: myrmicarin 217
C6D6, 100 MHz
ppm

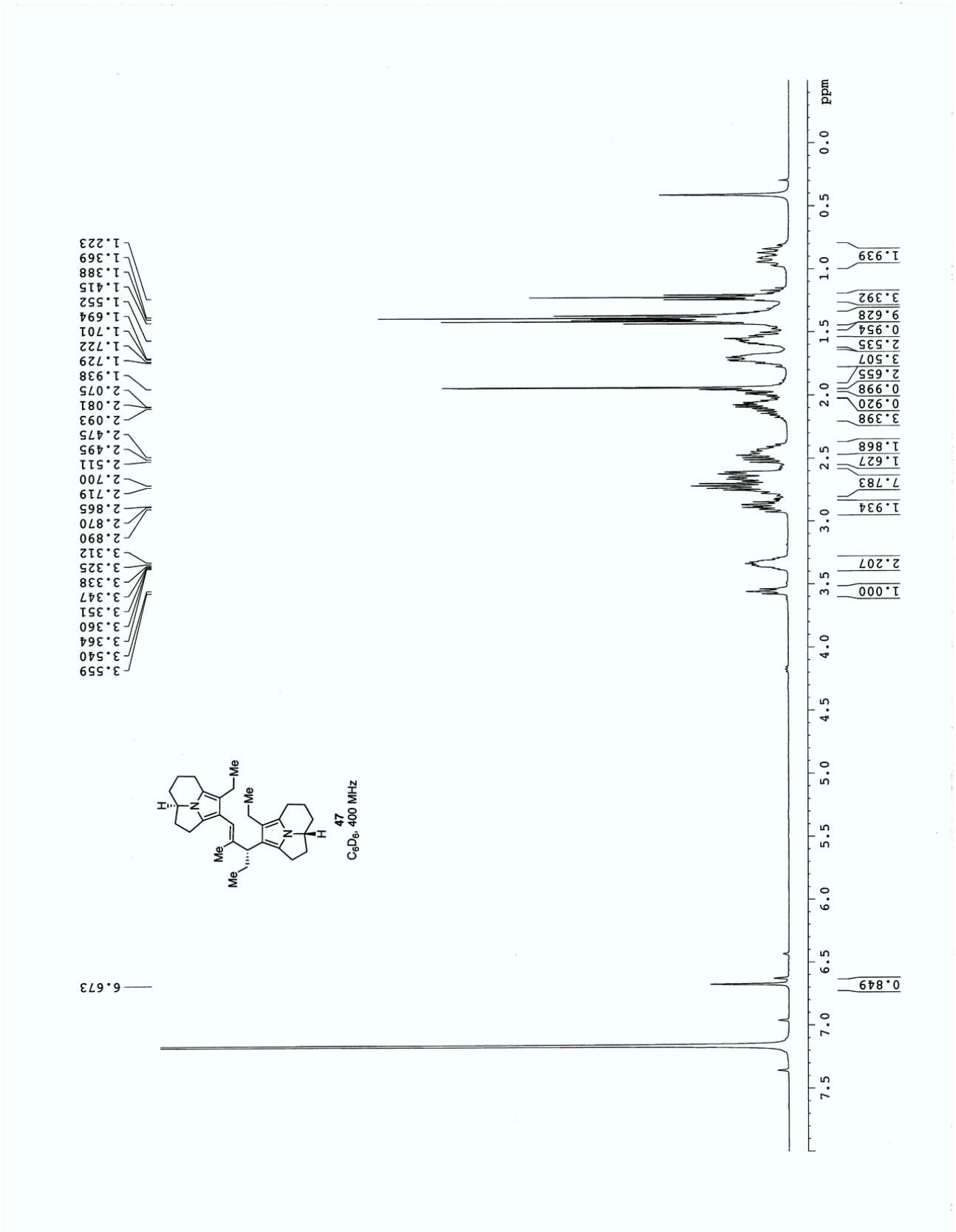

4: myrmicarin 237B
C6D6, 400 MHz
Me
Me
H
N
O
ppm
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
0.206
1.000
2.063
1.051
1.113
1.063
1.209
1.252
1.468
2.893
8.262
7.706
5.847
3.071
3.065
3.058
3.052
2.822
2.811
2.795
2.783
2.614
2.596
2.466
2.448
2.027
2.018
1.994
1.986
1.819
1.810
1.788
1.700
1.300
1.295
1.286
1.118
1.100
1.081
0.942
0.925
0.907

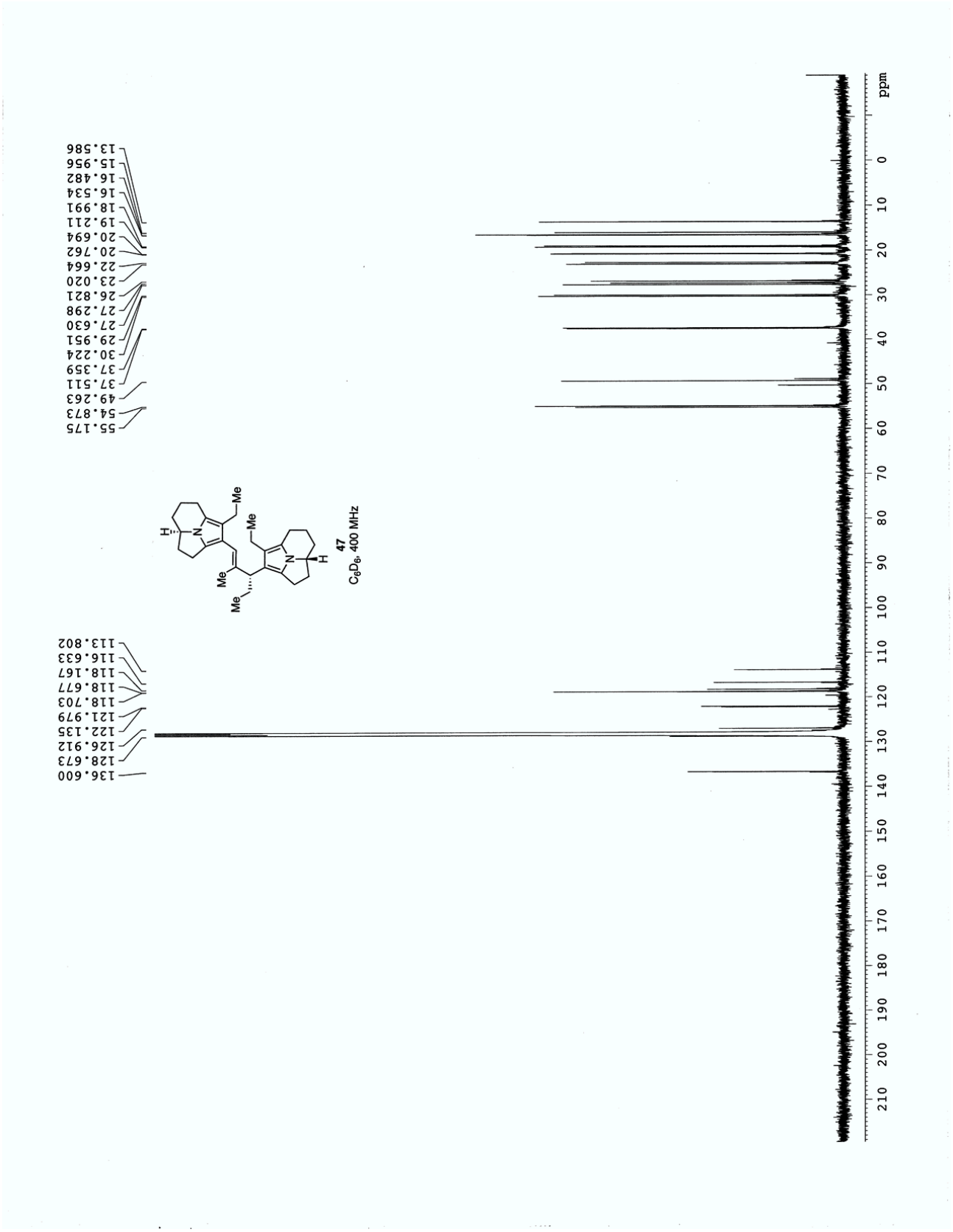

212.728
62.503
59.199
57.506
35.738
32.355
29.641
28.812
28.525
27.047
23.561
21.273
19.269
14.476
8.453
4: myrmicarin 237B
C6D6, 100 MHz
Me
Me
H
N
O
ppm
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210

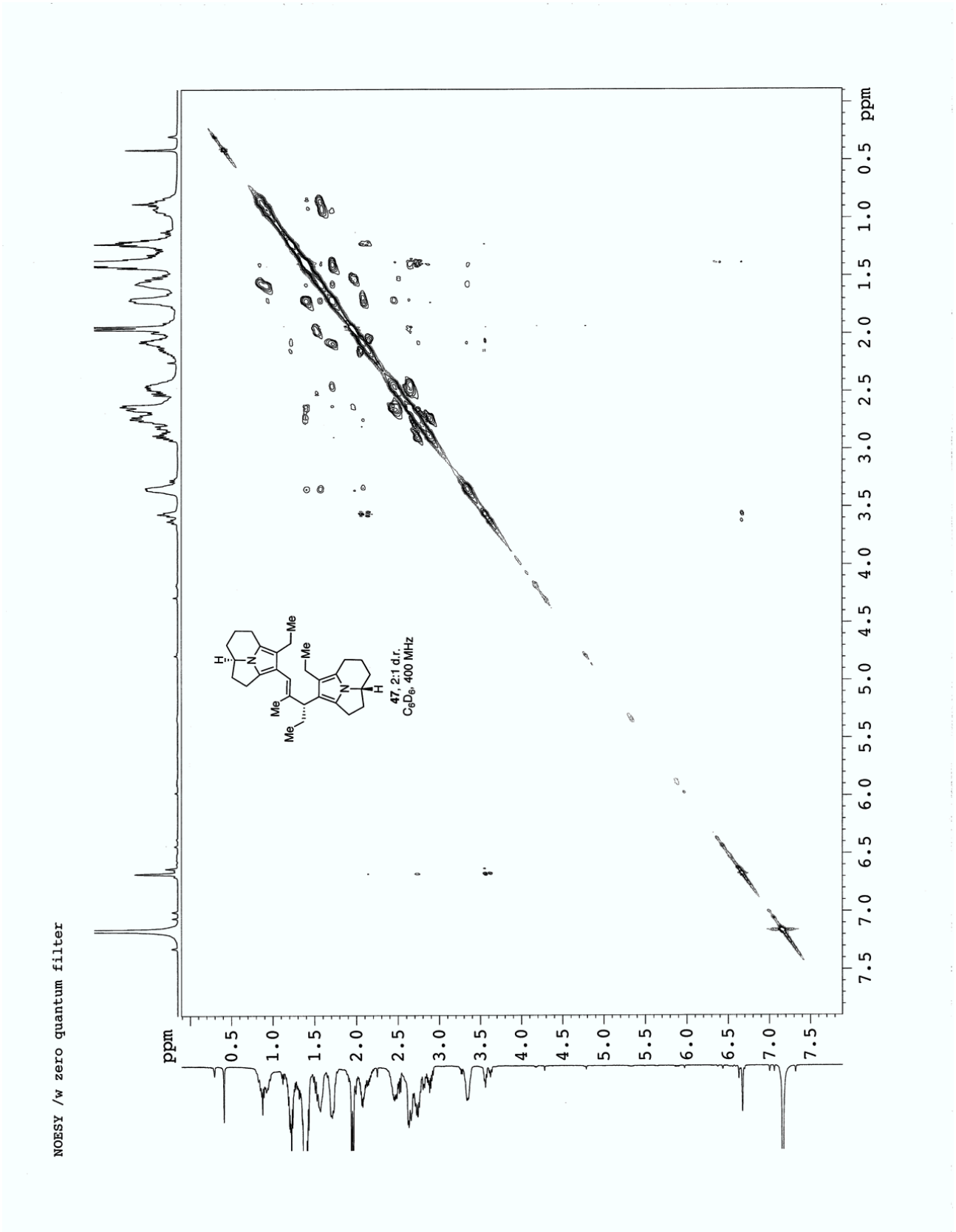

Me 44
CD3CN, 300 MHz
ppm

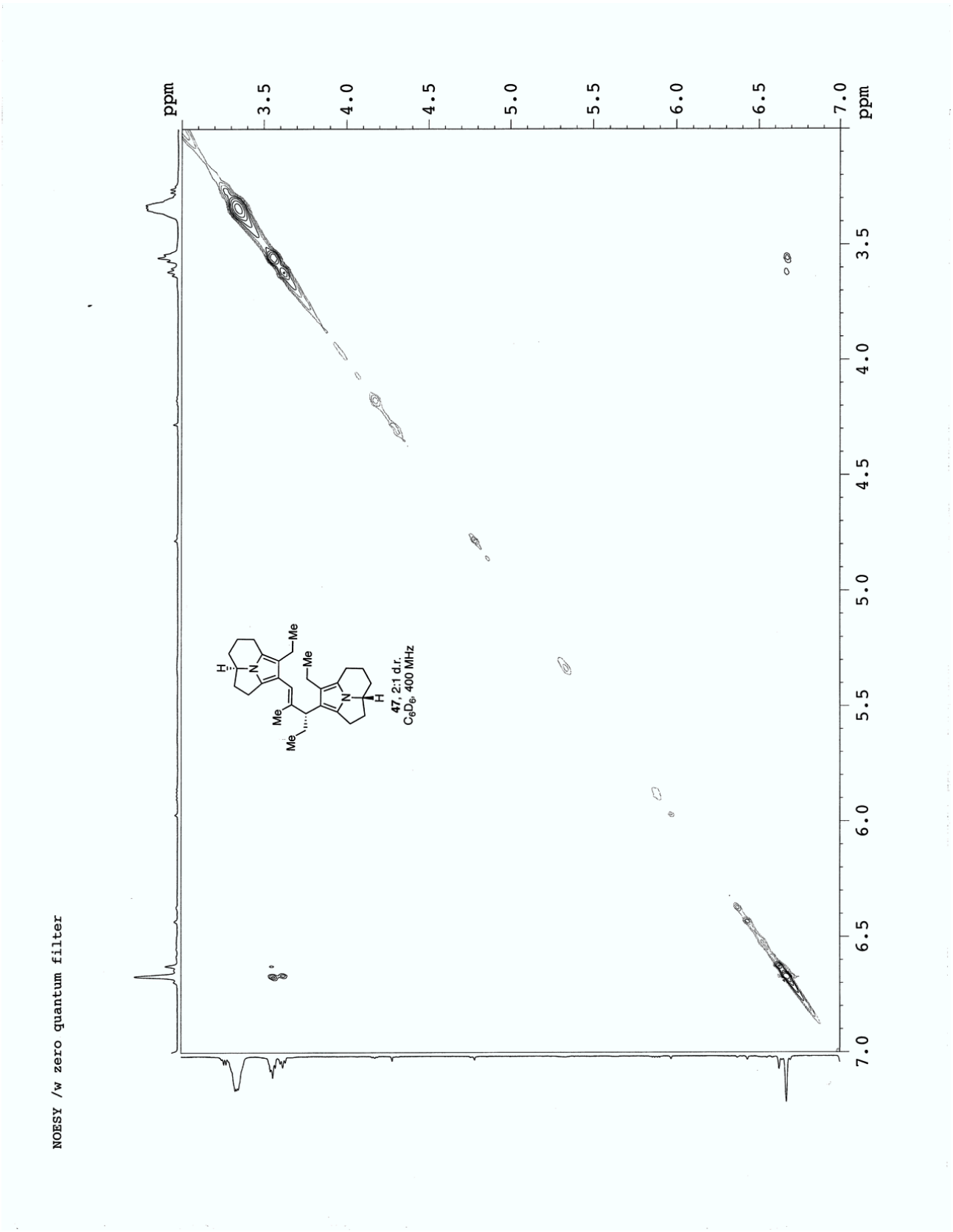

7.409
7.388
7.367
7.358
7.337
7.315
6.497
6.446
5.243
5.224
4.166
1.058
1.033
1.008
0.987
0.964
0.940
50
CD3CN, 300 MHz
1.000
1.009
1.092
5.336
3.198
ppm

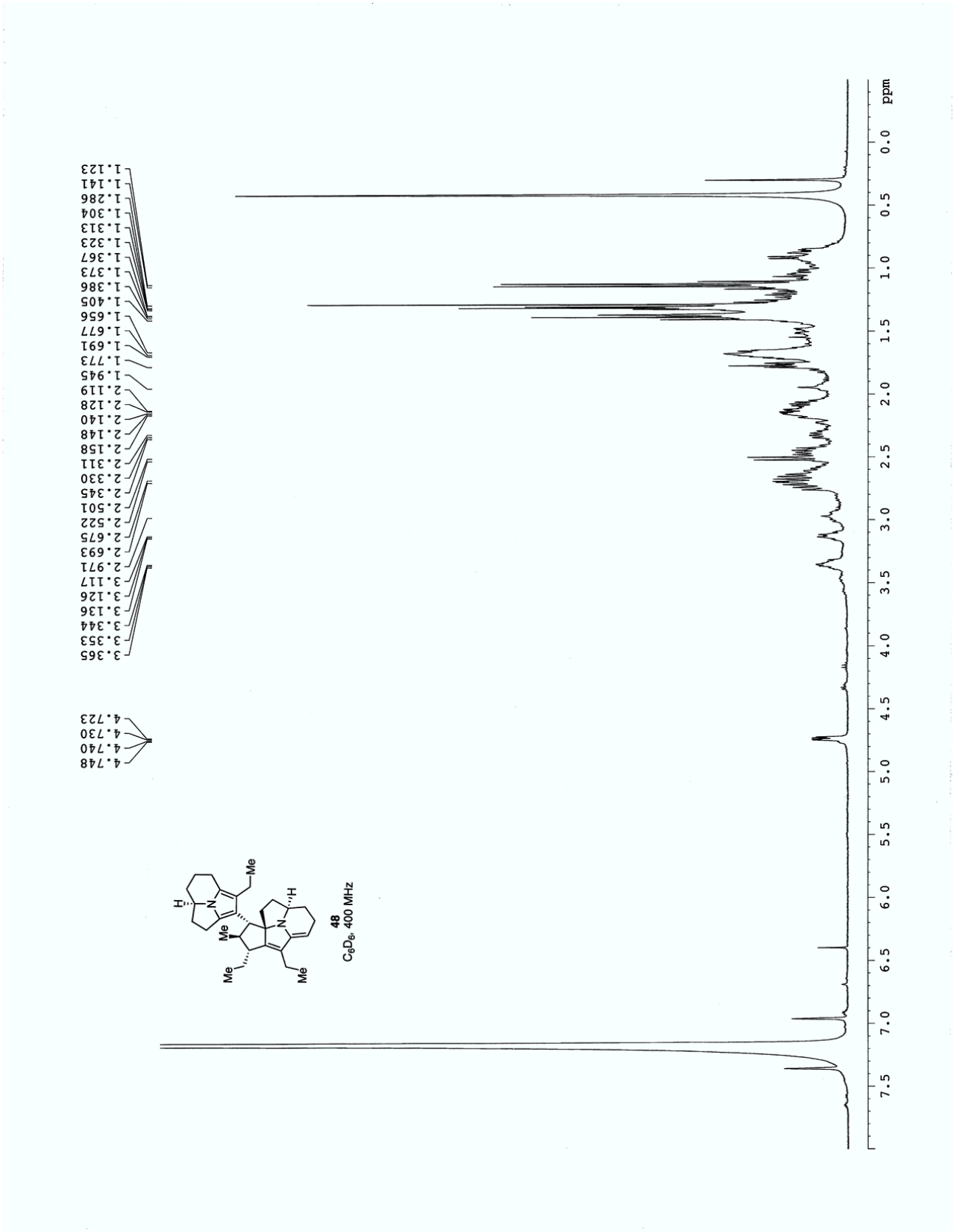

ppm
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
4.536
0.900
1.010
3.023
1.133
0.960
1.128
1.941
2.253
4.147
1.000
1.173
0.795
1.054
1.072
1.089
1.695
1.699
1.711
1.715
2.086
2.215
2.222
2.236
2.241
2.400
2.418
2.433
2.437
2.451
2.674
2.681
2.691
2.699
3.076
3.081
3.097
3.186
4.390
4.396
5.126
5.127
5.129
5.398
5.402
5.737
5.754
5.775
5.792
OTs
Me
Me
44
CD3CN, 300 MHz

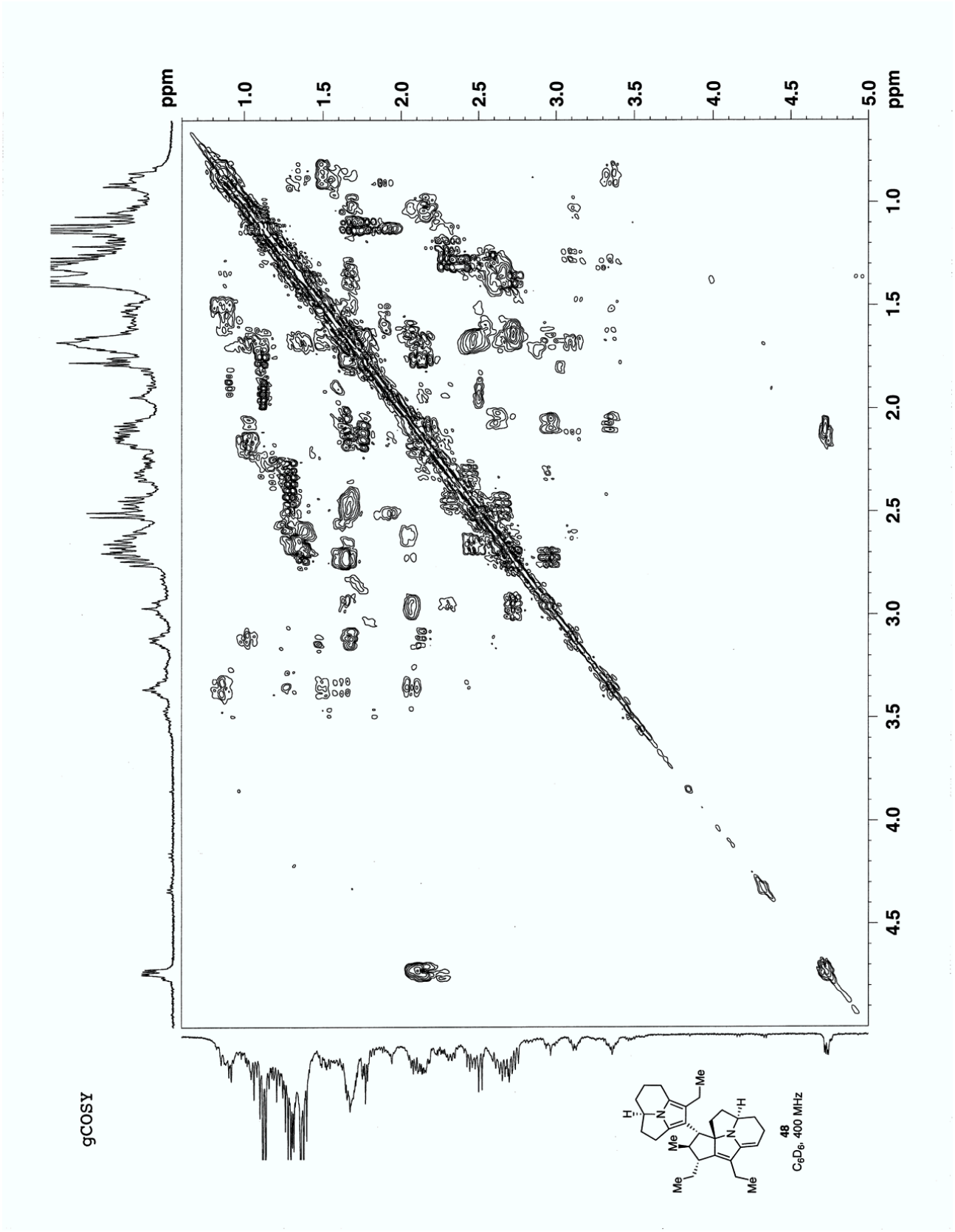

47
C6D6, 400 MHz
Me
Me
Me
Me
H
H
N
N
6.673
3.559
3.540
3.364
3.360
3.351
3.347
3.338
3.325
3.312
2.890
2.870
2.865
2.719
2.700
2.511
2.495
2.475
2.093
2.081
2.075
1.938
1.729
1.722
1.701
1.694
1.552
1.415
1.388
1.369
1.223
0.849
1.000
2.207
1.934
7.783
1.627
1.868
3.398
0.920
0.998
2.655
3.507
2.535
0.954
9.628
3.392
1.939
ppm

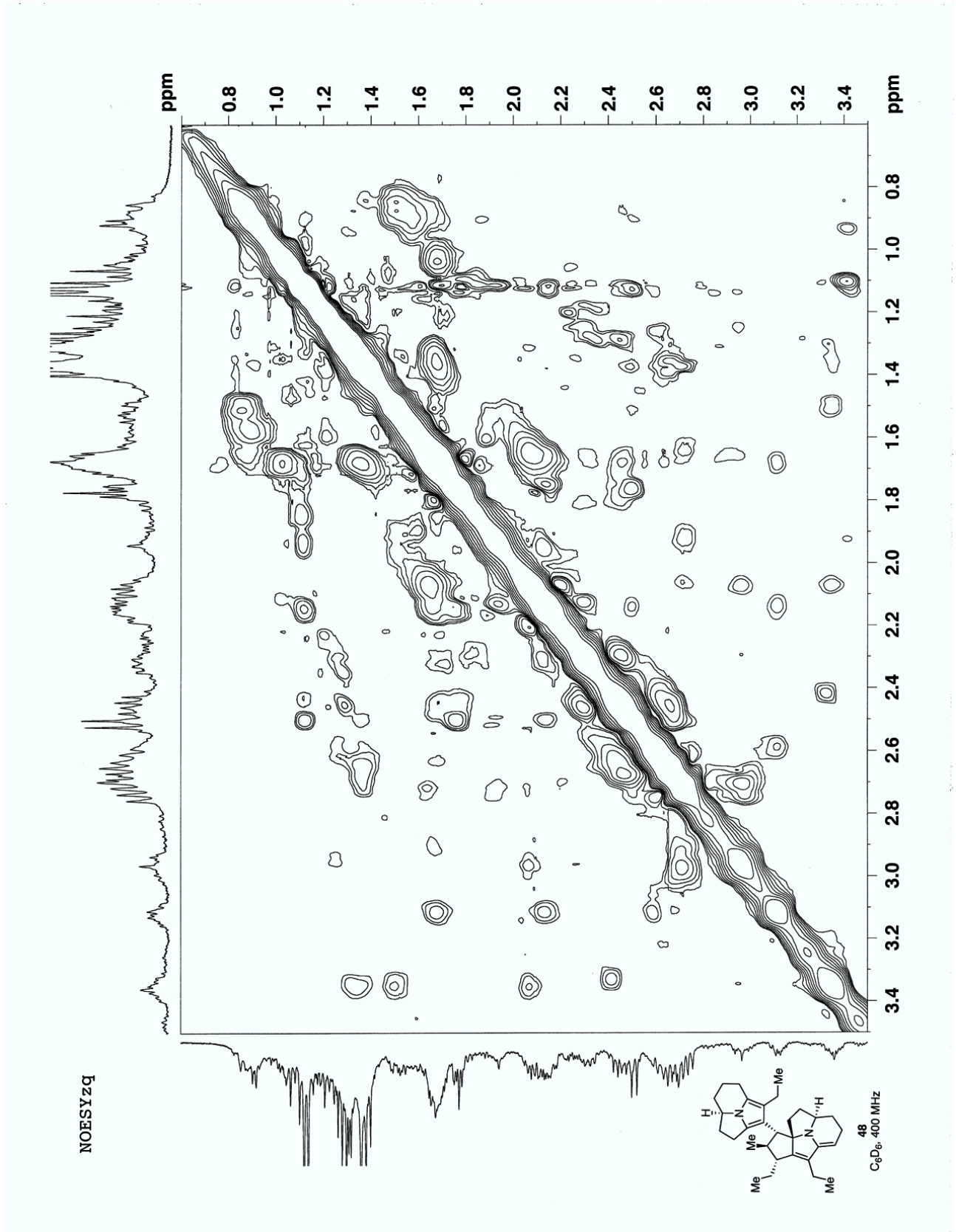

13.586
15.956
16.482
16.534
18.991
19.211
20.694
20.762
22.664
23.020
26.821
27.298
27.630
29.951
30.224
37.359
37.511
49.263
54.873
55.175
113.802
116.633
118.167
118.677
118.703
121.979
122.135
126.912
128.673
136.600
Me
Me
Me
Me
H
N
N
H
47
C6D6, 400 MHz
ppm
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210

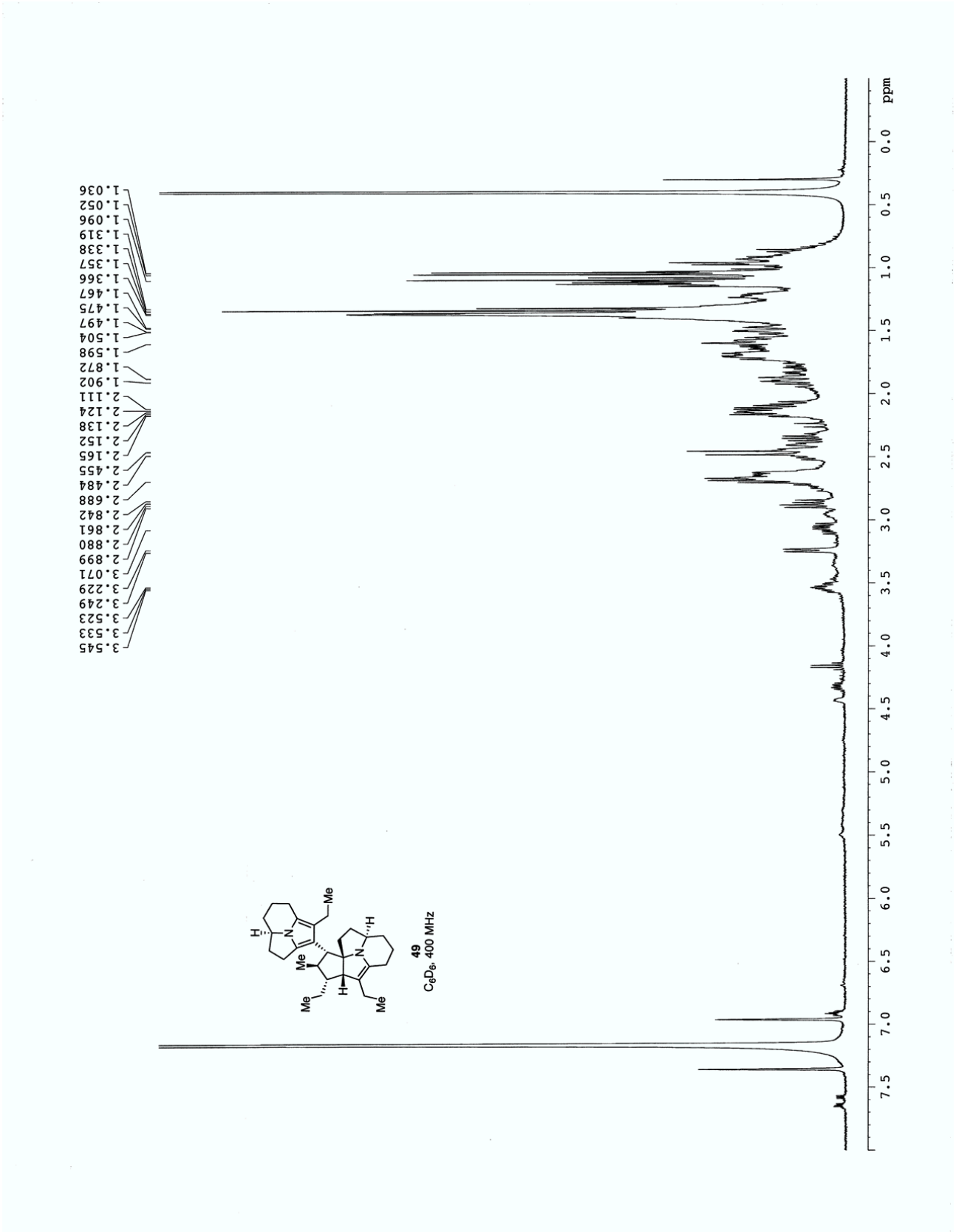

NOESY /w zero quantum filter
ppm
47, 2:1 d.r.
C6D6, 400 MHz
Me
Me
Me
Me
H
H
N
N
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

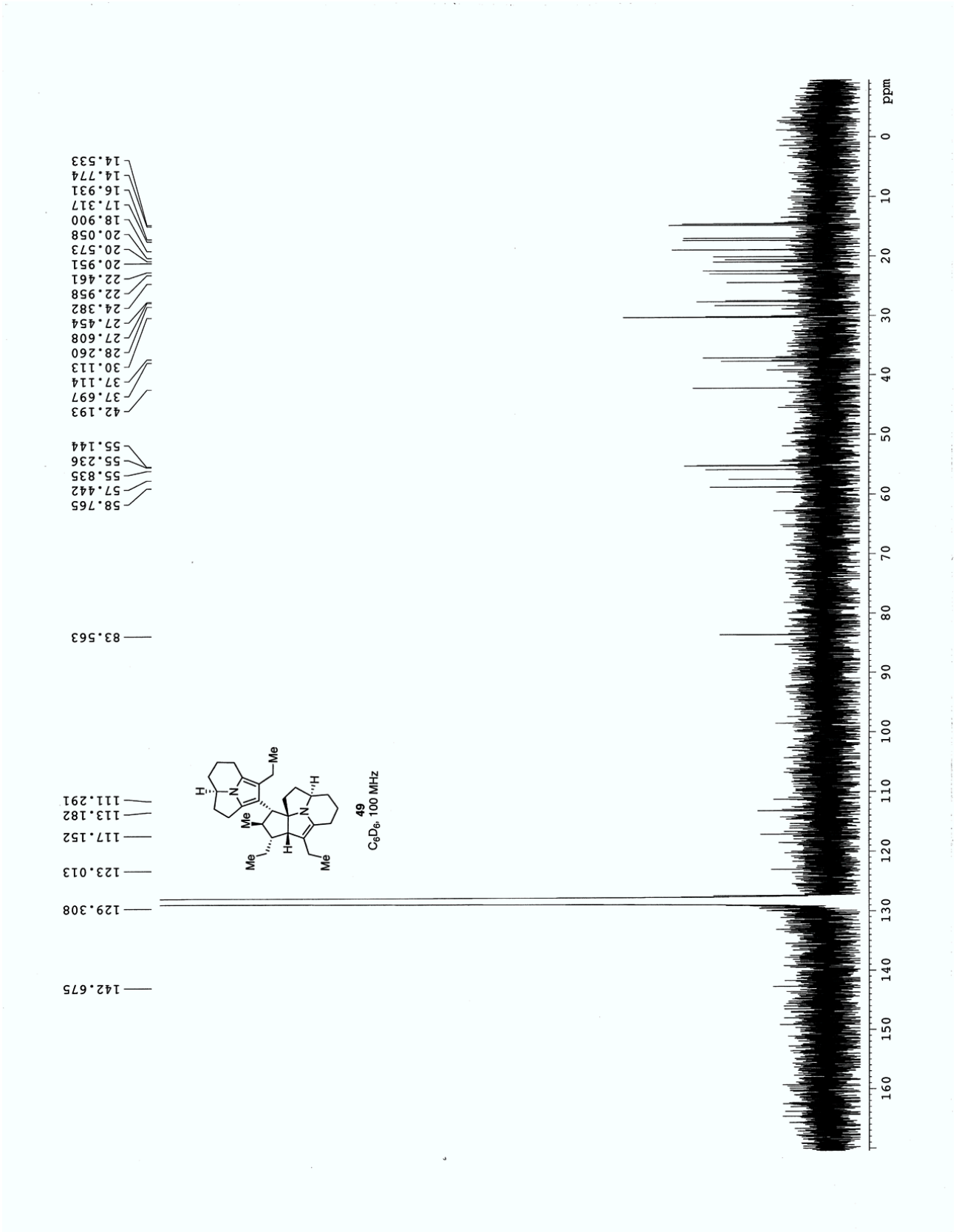

NOESY /w zero quantum filter
ppm
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
Me
Me
Me
Me
N
N
H
H
47, 2:1 d.r.
C6D6, 400 MHz

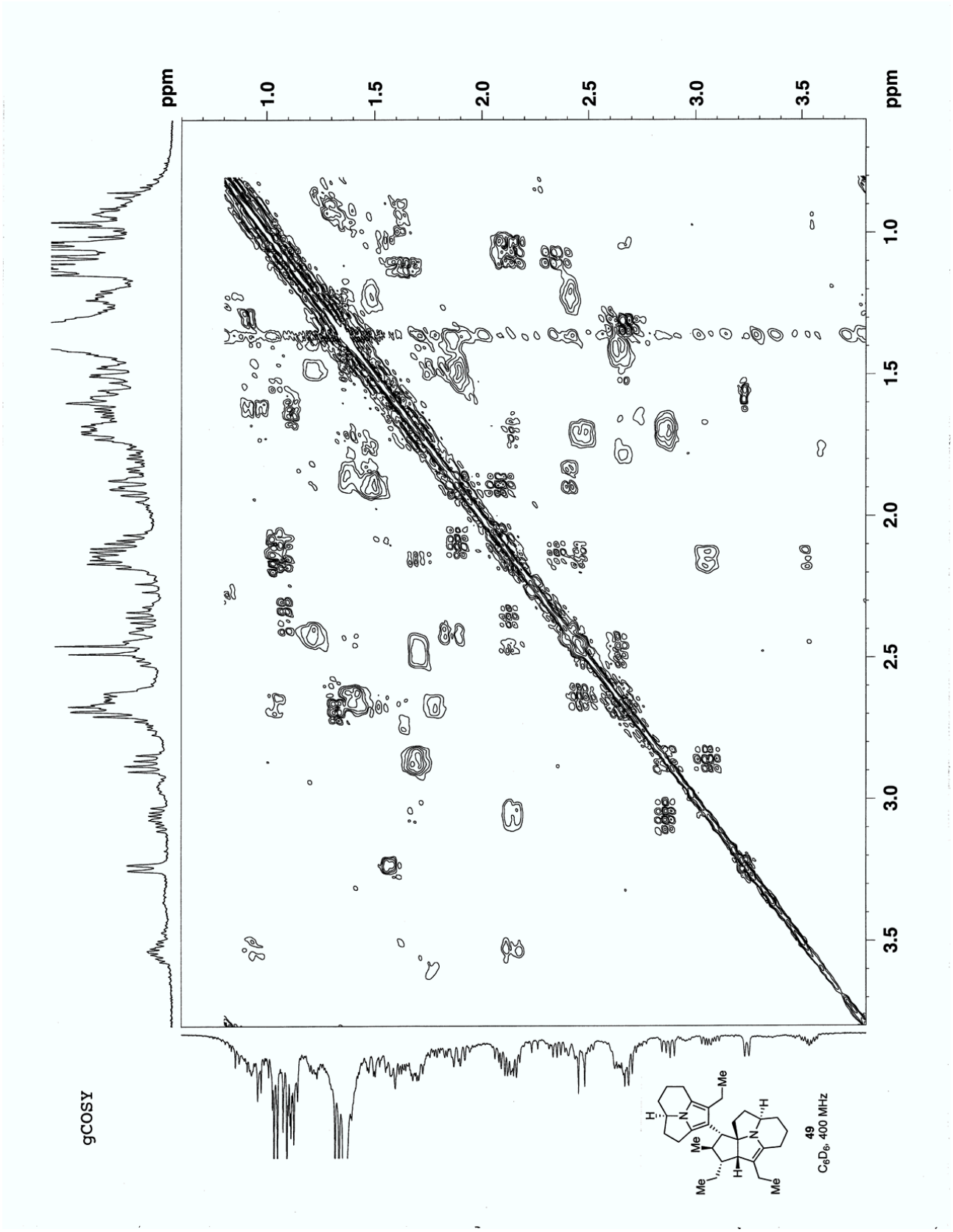

48
C6D6, 400 MHz
ppm
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
4.748
4.740
4.730
4.723
3.365
3.353
3.344
3.136
3.126
3.117
2.971
2.693
2.675
2.522
2.501
2.345
2.330
2.311
2.158
2.148
2.140
2.128
2.119
1.945
1.773
1.691
1.677
1.656
1.405
1.386
1.373
1.367
1.323
1.313
1.304
1.286
1.141
1.123

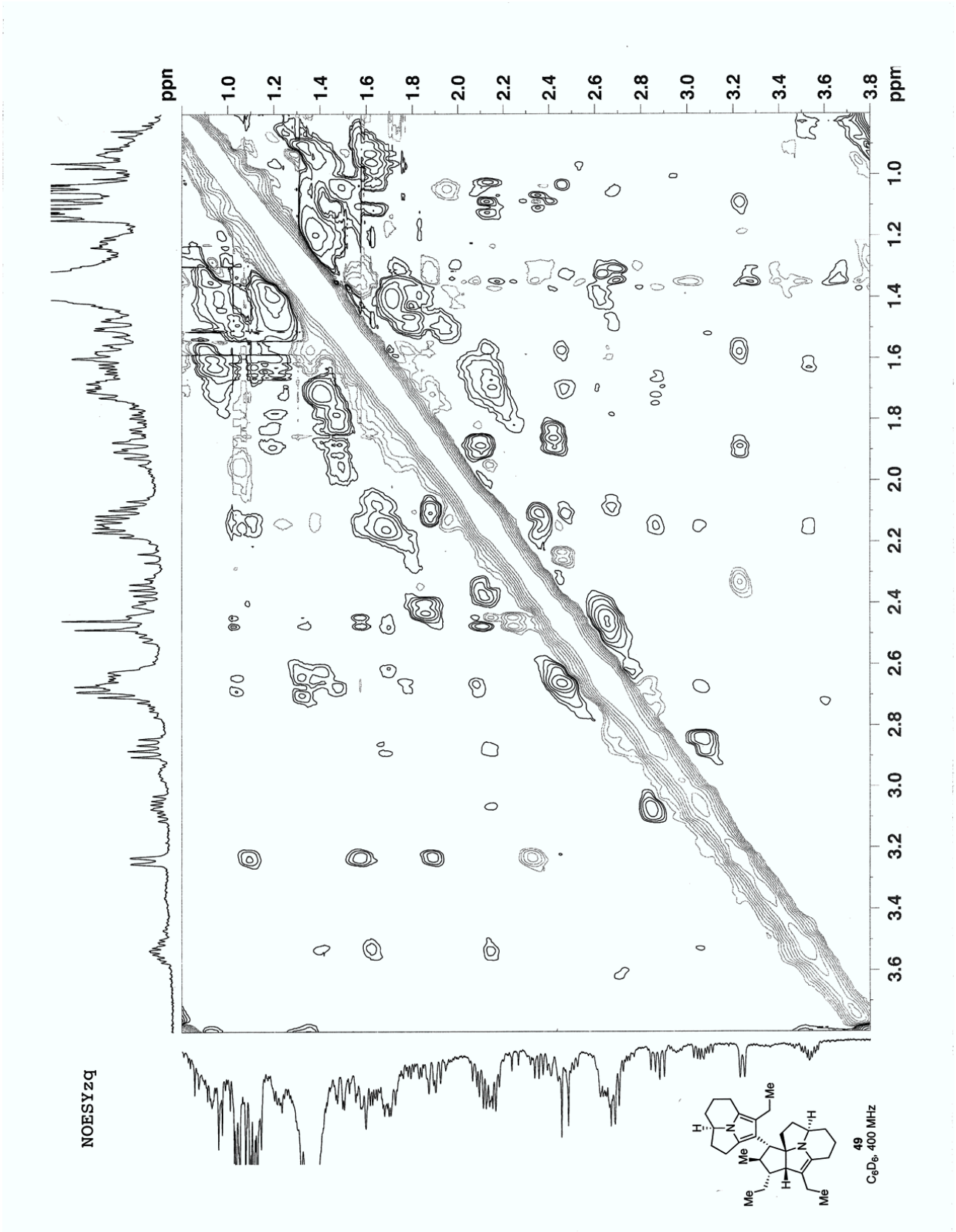

gCOSY
ppm
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
Me
Me
Me
Me
H
H
N
N
48
C6D6, 400 MHz

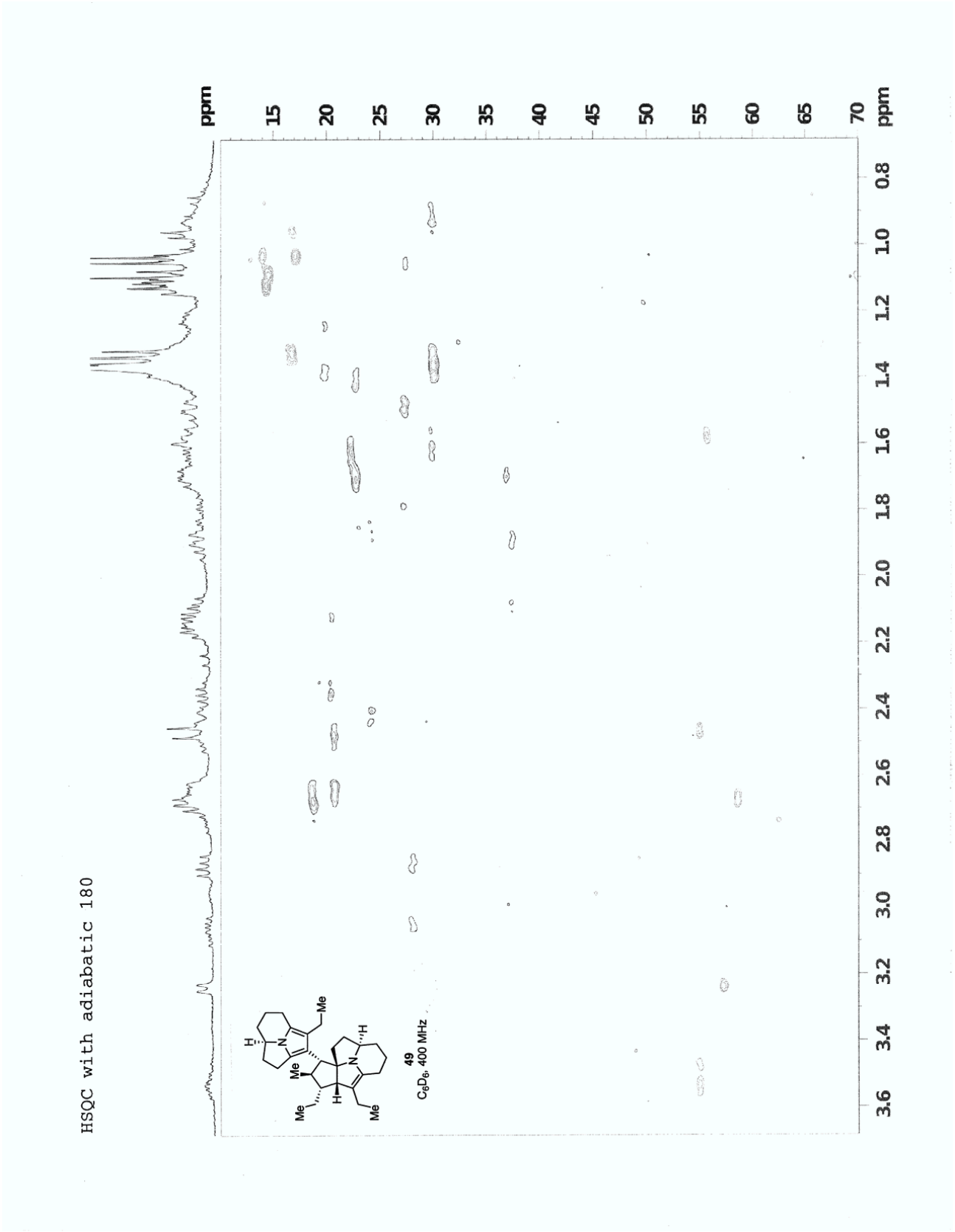

NOESYzq
ppm
0.8
1.0
1.2
1.4
1.6
1.8
2.0
2.2
2.4
2.6
2.8
3.0
3.2
3.4
Me
Me
Me
Me
H
H
N
N
48
C6D6, 400 MHz


3.545
3.533
3.523
3.249
3.229
3.071
2.899
2.880
2.861
2.842
2.688
2.484
2.455
2.165
2.152
2.138
2.124
2.111
1.902
1.872
1.598
1.504
1.497
1.475
1.467
1.366
1.357
1.338
1.319
1.096
1.052
1.036
Me
Me
Me
Me
H
H
N
N
49
C6D6, 400 MHz
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm


49
C6D6, 100 MHz
Me
Me
Me
Me
H
H
N
N
ppm
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
14.533
14.774
16.931
17.317
18.900
20.058
20.573
20.951
22.461
22.958
24.382
27.454
27.608
28.260
30.113
37.114
37.697
42.193
55.144
55.236
55.835
57.442
58.765
83.563
111.291
113.182
117.152
123.013
129.308
142.675


gCOSY
ppm
1.0
1.5
2.0
2.5
3.0
3.5
Me
Me
Me
Me
H
H
N
N
49
C6D6, 400 MHz


NOESYzq
ppm
1.0
1.2
1.4
1.6
1.8
2.0
2.2
2.4
2.6
2.8
3.0
3.2
3.4
3.6
3.8
Me
H
N
49
C6D6, 400 MHz


HSQC with adiabatic 180
ppm
15
20
25
30
35
40
45
50
55
60
65
70
ppm
3.6
3.4
3.2
3.0
2.8
2.6
2.4
2.2
2.0
1.8
1.6
1.4
1.2
1.0
0.8
Me
Me
Me
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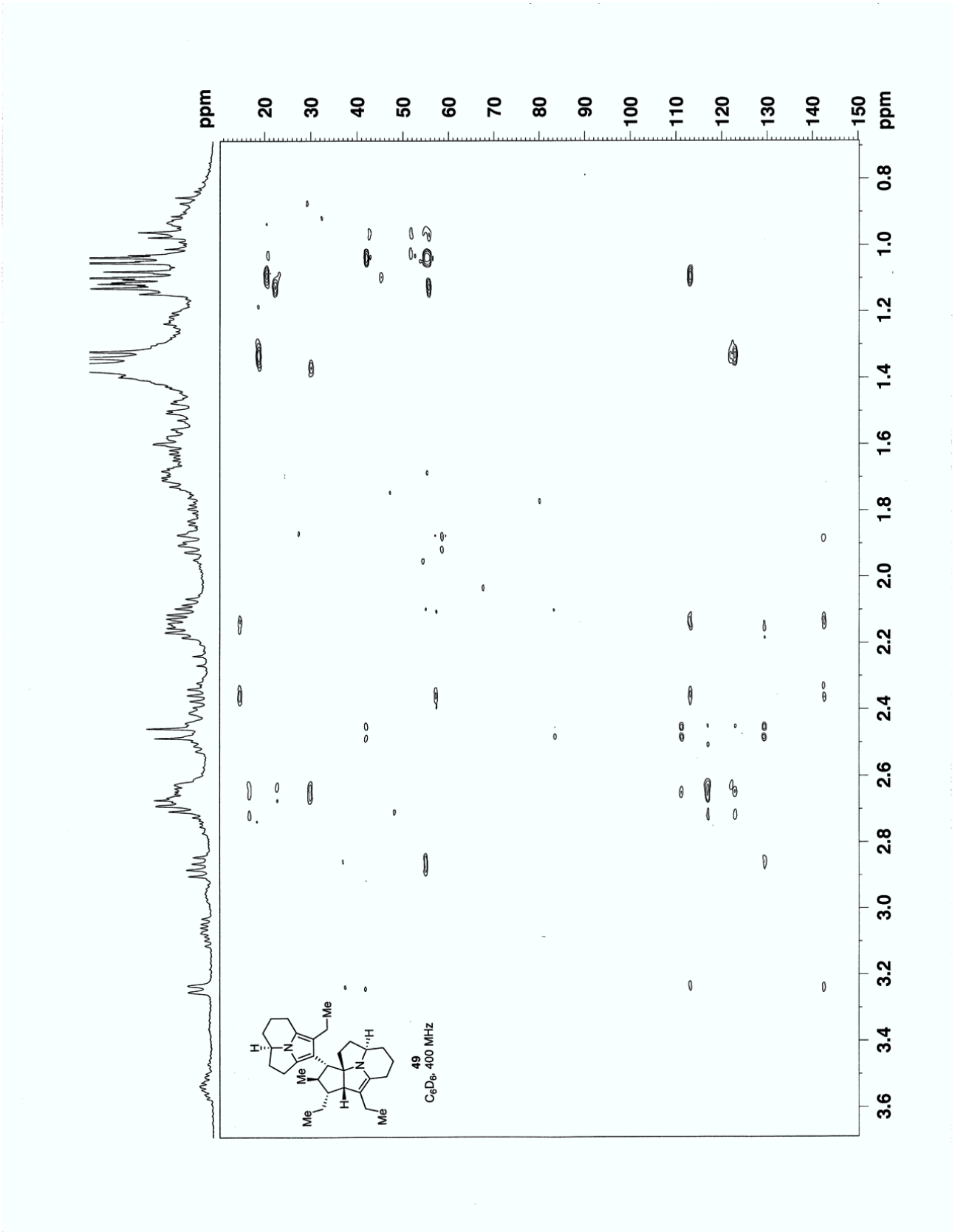
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CHAPTER 5

Studies On The Mechanism of the Knorr Pyrrole Cyclization

5.1 Introduction

The pyrrole heterocycle is a prominent motif in natural products, pharmaceutically active compounds, and useful synthetic materials (Figure 1).[1] These molecules often contain highly substituted pyrroles, as shown by the examples given in Figure 1 (**1**–**6**), and this ring system often presents a unique challenge to synthetic chemists.[2] As a result many different methods exist for the preparation of this heterocycle, most of which involve condensation reactions from acyclic starting materials.[3] One of the earliest of these condensation methods is the Knorr pyrrole synthesis, first described in 1884 (Scheme 1).[4]

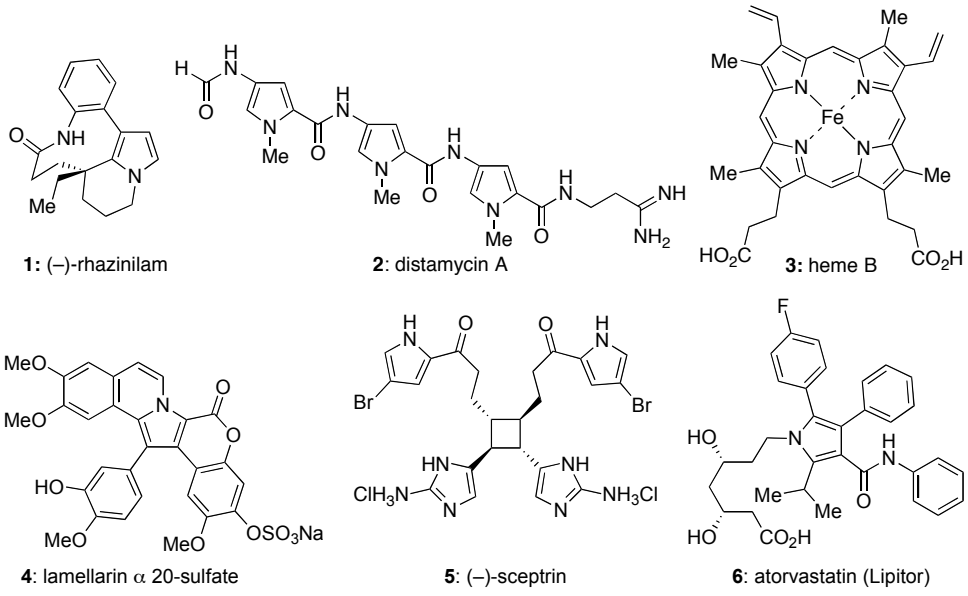
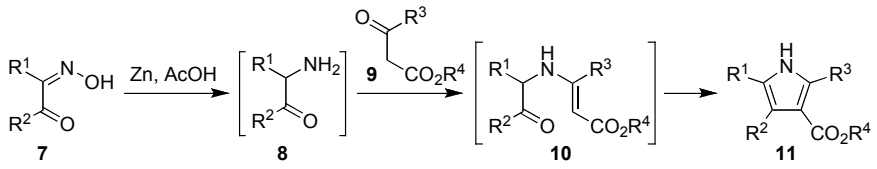
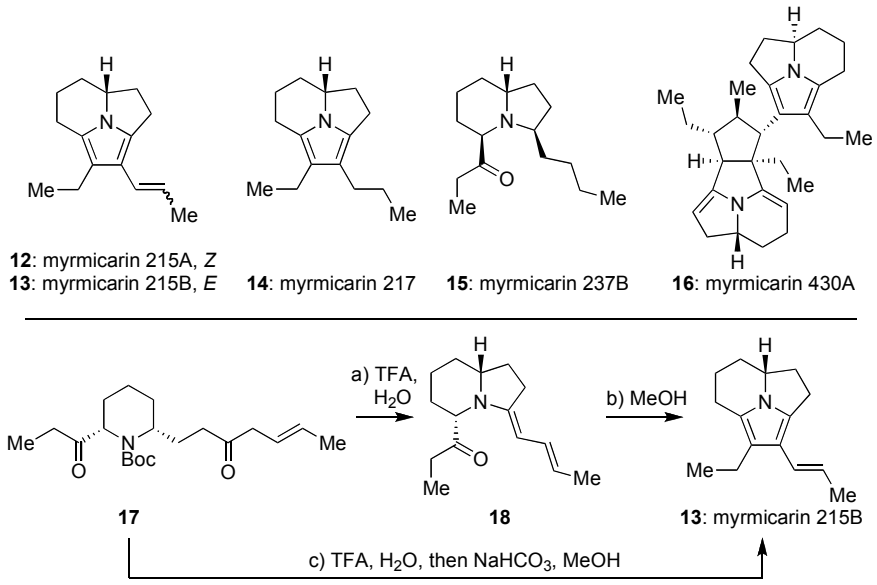


Figure 1. Selected examples of natural and synthetic products containing the pyrrole heterocycle.



Scheme 1. The Knorr pyrrole synthesis.

This reaction occurs via the condensation of an α-aminoketone (**8**) with a β-ketoester (**9**) or a related molecule to form an α-enamino ketone intermediate (**10**). That intermediate then sponaneously cyclizes under the reaction conditions to form a pyrrole (**11**). The α-aminoketone component (**8**) has a propensity to undergo self-condensation so it is generally prepared *in situ* by, for example, the reduction of a hydroxime (**7**).[2]



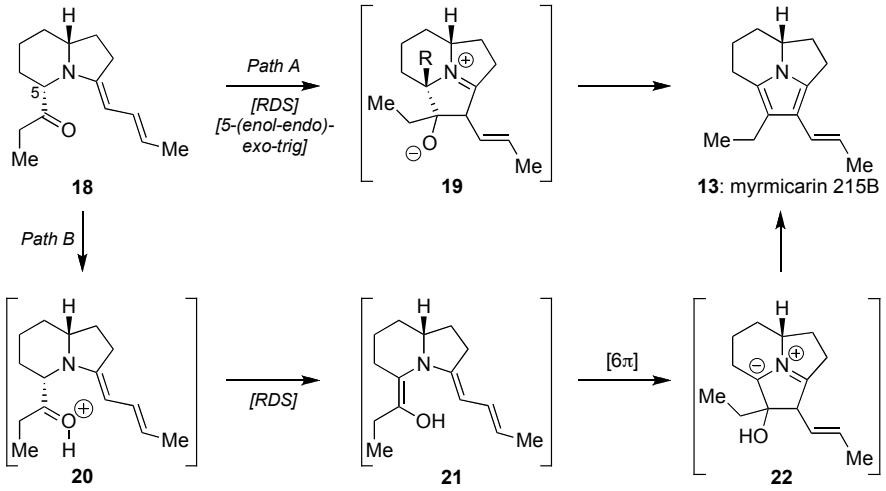
Scheme 2. Structures of selected members of the myrmicarin alkaloids (**12**–**16**) and Knorr pyrrole synthesis of myrmicarin 215B (**13**): (a) TFA/CH_2Cl_2/H_2O (4:4:1), 0 °C, 1 h, then NaOH (1.0 M in H_2O), 0 °C, 99%; (b) MeOH, 23 °C, 1 h, 99%; (c) TFA/CH_2Cl_2/H_2O (4:4:1), 0 °C, 1 h, then sat. aq. $NaHCO_3$/MeOH (1:2), 23 °C, 2 h, 71%. TFA = trifluoroacetic acid

We recently employed an intramolecular variant of the Knorr pyrrole synthesis in a total synthesis of the monomeric pyrroloindolizidine myrmicarin alkaloids (**12**–**15**, Scheme 2, see Chapter 4 for more details).[5,6] In this work, disubstituted piperidine derivative **17** was prepared in eight steps from pyridine. Following *N*-Boc deprotection and basic workup, the secondary amine underwent an intramolecular condensation to quantitatively generate dienamine **18**. In contrast with reports on related monoenamine compounds,[7] **18** showed remarkable configurational and chemical stability in aprotic solvents; however, upon dissolution in a protic solvent the dienamine underwent a quatitative cyclodehydration to afford myrmicarin 215B (**13**). The ability to arrest the sequence after enamine condensation and then promote the cyclodehydration at will by switching solvent was critical in the synthesis of the all-*trans* upper half of the cyclopentane core of myrmicarin 430A (**16**). Additionally, the unexpected stability and isolability of **18** provided the opportunity to explore the mechanism of the cyclodehydration step of the Knorr pyrrole synthesis in this unique molecular framework. This chapter details our mechanistic work, which has led us to a revised mechanistic proposal for the Knorr cyclization of **18**.[8]

5.2 The Mechanism of the Knorr Pyrrole Cyclization

The generally accepted mechanism of the cyclization step of the Knorr pyrrole synthesis, as applied to the myrmicarin alkaloids, involves an initial 5-(enol-*endo*)-*exo*-trig cyclization of **18** to form **19** (Scheme 3, *Path A*).[9] Intriguingly, this initial step is disfavored by Baldwin's rules.[10] Furthermore, despite the fact that the intermediate

enamine has been observed previously in other systems,[11] only a limited number of mechanistic studies have been performed, and no conclusive evidence has been posited regarding the mechanism of the cyclodehydration step.[12]



Scheme 3. Plausible mechanistic pathways for the cyclization of dienamine **18**.

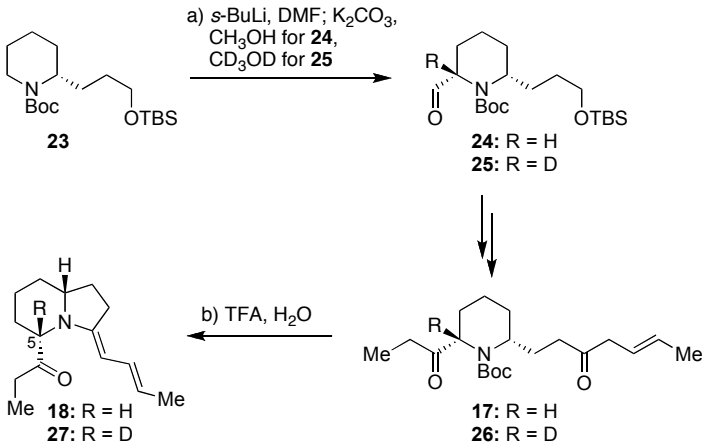
Inspired by literature reports of related systems undergoing 6π-electrocyclization reactions,[13] an alternative mechanistic pathway for this reaction was envisioned during the course of our studies. *Path B* in Scheme 3 outlines this hypothesis in the context of the myrmicarin alkaloids. Instead of the stereoelectronically disfavored direct attack depicted in *Path A*, **18** could tautomerize to its enol form and undergo a 6π-electrocyclization to generate azomethine ylide **22**. A final loss of a water molecule would then generate the pyrrole.

Control experiments demonstrated that the starting dienamine (**18**) undergoes neither exchange nor epimerization at C-5 in deuterated protic solvents, and, as such, deuterium labeling at that position would allow us to measure a β-kinetic isotope effect (KIE) during the cyclodehydration reaction. If *Path A* were operative, an inverse

secondary KIE would be expected consistently with a decrease in hyperconjugation in the transition state and a consequent strengthening of the C-5 C–H(D) bond.[14] On the other hand, if *Path B* were operative, a primary normal KIE would be expected. Since we observed no exchange at C-5 in deuterated protic solvents and the deprotonation at the α-position of a ketone is typically the slow step during acid-catalyzed enol formation,[15] deprotonation at the C-5 position of **20** would be rate limiting leading to a large isotope effect.

5.3 Preparation of C-5 Deuterated Dienamine

In order to probe these mechanistic possibilities, the C-5 deuterated variant **27** was prepared by implementing a slight modification to the route that had been previously developed for the synthesis of such dienamines (see Chapter 4).[6] The formylation reaction of piperidine derivative **23** was quenched with K_2CO_3 and methanol–d_4, which introduced the deuterium label during the epimerization of the initial *trans*-piperidine product[16] to *cis*-piperidine derivative (Scheme 4). Deuterium incorporation during this reaction was greater than 20:1 to afford aldehyde **25**. This intermediate was then elaborated according to the previously developed route to the desired deuterated dienamine (**27**).



Scheme 4. Preparation of deuterated dienamine **27**: (a) *s*-BuLi (1.8 equiv), TMEDA (2.2 equiv), Et_2O, –78→40 °C, 1 h; DMF (10 equiv), –78→40 °C, 1.5 h; K_2CO_3/MeOH, 23 °C, 3 h for **24**; K_2CO_3/CD_3OD, 23 °C, 3 h for **25**; 80–90%; (b) (a) TFA/CH_2Cl_2/H_2O (4:4:1), 0 °C, 1 h, then NaOH (1.0 M in H_2O), 0 °C, 99%. DMF = *N*,*N*-dimethylformamide, TMEDA = *N*,*N*,*N*',*N*'-tetramethylethylenediamine, TFA = trifluoroacetic acid

5.4 Kinetic Experiments

With starting materials **18** and **27** in hand, a series of rate measurements using ^{1}H NMR were performed. Initial experiments in isopropanol-d_8, in which the cyclization was sufficiently slow for us to obtain reliable kinetic data, exhibited excellent fits to simple first order rate equations, and a normal secondary β KIE was measured (k_H/k_D = 1.23, Figure 1). Intriguingly, this result was inconsistent with our expectations based on the proposed mechanistic pathways outlined above and in Scheme 3. Thus, we became interested in further investigating the role of the polar protic solvent in order to gain additional insight into the mechanism of the cyclization. Specifically, we sought to determine the order of the polar protic solvent in the rate equation.

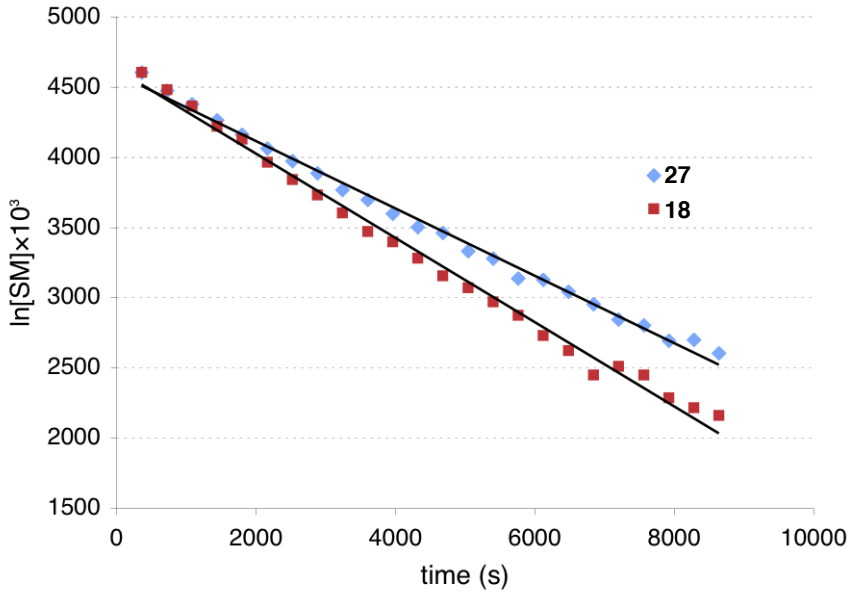


Figure 2. Observed first-order plots for the disappearance of **18** and **27** in isopropanol-d_8.

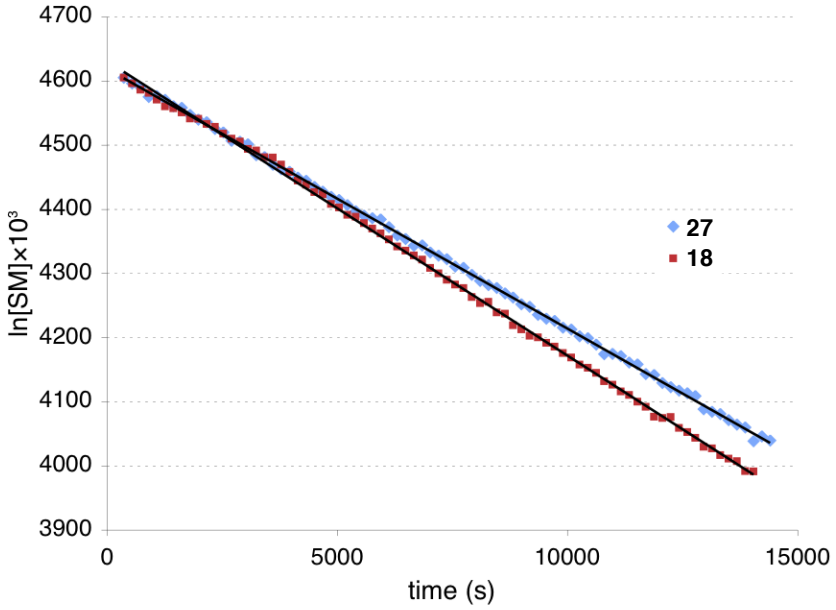


Figure 2. Selected example of observed first-order plots for the disappearance of **18** and **27** in DMSO-d_6/D_2O.

A series of rate measurements in DMSO-d_6/D_2O were undertaken. This solvent combination has previously been used to analyze the effect of the concentration of water on the observed rate in other pseudo-first order processes.[17] The use of this solvent combination also resulted in a normal secondary β kinetic isotope effect, albeit of a smaller magnitude (k_H/k_D = 1.11±0.05, n = 3, Figure 2), which suggests that the cyclization was occurring via the same mechanism as in isopropanol. Additionally, the pseudo-first order rate constant (k_{obs}) of the cyclization of **18** was determined at various concentrations of D_2O in DMSO-d_6. The rate of cyclization of **18** increased with increasing [D_2O], and a plot of k_{obs} *vs.* [D_2O] (Figure 3a) displayed significant polynomial character. A plot of k_{obs}/[D_2O] *vs.* [D_2O] (Figure 3b), on the other hand, was linear with a non-zero slope indicating that the rate-determining protonation step is second-order in water; that is, two water molecules in addition to those involved in solvation are required in the course of this cyclization.

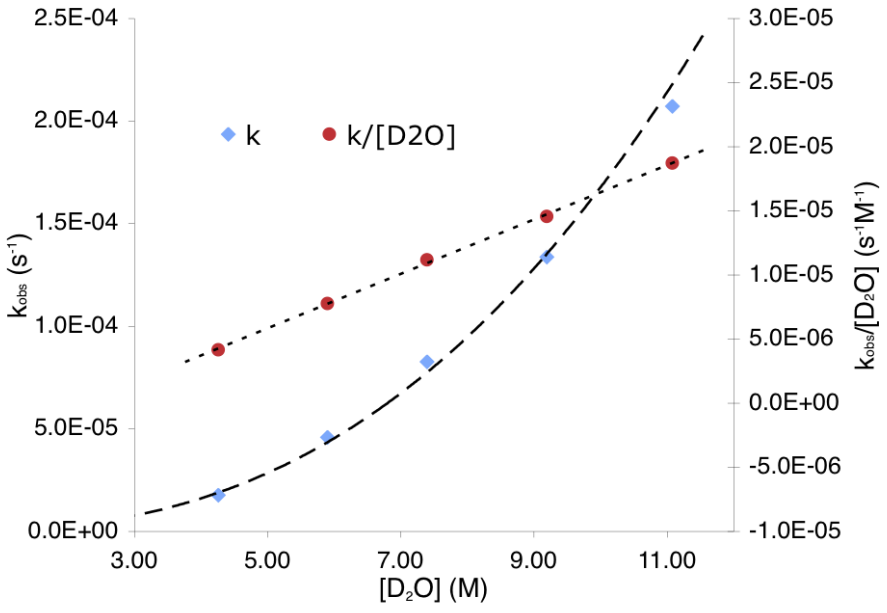


Figure 4. Plots of (a) k_{obs} vs. [D_2O] and (b) k_{obs}/[D_2O] vs. [D_2O] for the cyclization of **18** in DMSO-d_6/D_2O.

5.5 Discussion

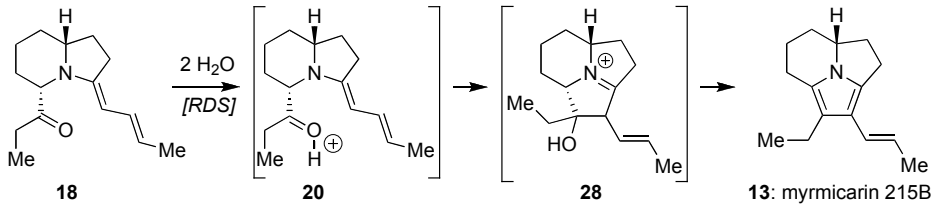
The observation of a normal secondary KIE in both solvent systems is consistent with a weakening of the C–H(D) bond in the transition state due to increased hyperconjugation with an increasingly electron deficient sp^2 carbonyl carbon atom,[18] which is consistent with a rate determining step that involves protonation of the ketone to form an oxocarbenium ion. Direct attack of the enamine on an unprotonated ketone (Scheme 3, *Path A*) is unlikely, as that event would lead to a strengthening of the C–H(D) bond from a decrease in hyperconjugation and, therefore, an inverse secondary kinetic isotope effect would result.[14] Overall, this hypothesis is also consistent with the experimental observation that the cyclization of **18** does not readily occur in aprotic solvents. The zwitterionic intermediate **19** that would result from direct attack of the enamine β-carbon on the unprotonated ketone is likely an unstable intermediate, especially in a non-polar medium. This statement is supported by semi-empirical (PM3[19]) calculations in which we were unable to locate **19** as a stationary point on the potential energy surface. Secondly, without an excess of the proton source in a polar environment (i.e. a protic solvent), a stablilized oxocarbenium likely cannot form. Furthermore, the basicity of the enamine precludes the use of acids to promote this cyclization, a finding that was confirmed by our own experiments showing that **18** does not cyclize cleanly under acidic conditions[6] as well as a previous study that has determined the optimal pH for cyclization to be near neutrality (pH = 6.9).[20]

Nonetheless, our experimental results cannot rule out a 6π-electrocyclization mechanism (Scheme 3, *Path B*) in which the rate-determining step is protonation of the

ketone prior to enol formation. However, the protonation of the ketone in acid-catalyzed enol formation is not typically rate-determining.[15] Moreover, our semi-empirical (PM3) calculations indicate that the proposed enol tautomer **21** is a prohibitively high-energy intermediate, due most likely to the placement of five contiguous sp^2 atoms in a highly rigid and constrained ring system.

5.6 A Revised Mechanistic Proposal

Collectively, our experimental and theoretical findings lead us to propose the revised mechanism for the cyclization of **18** shown in Scheme 5. In this sequence, two water molecules participate in a slow protonation of its ketone to afford intermediate **20**, which then undergoes a fast cyclization to afford iminium **28** followed by a fast tautomerization and loss of a molecule of water to afford myrmicarin 215B (**13**).



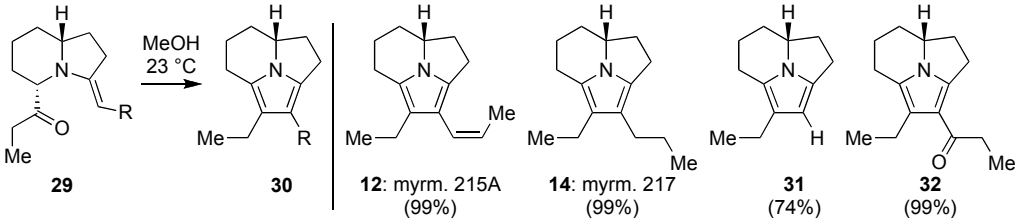
Scheme 5. Revised mechanistic proposal for the cyclization of dienamine **18**.

It is important to note that although this revised mechanism is consistent with the experimental observations outlined above, further experimentation is required to firmly establish its validity. If protonation is truly rate limiting, the reaction should be pH dependent, proceeding faster at lower and slower at higher pH values. However, such

experiments have not been performed in a systematic way, in part because data-analysis would be complicated by the basicity of the dienamine and the acidity of the C-5 position. Indeed, as some experiments have shown, protonation of the dienamine, alkene isomerization and general decomposition starts to appear when the cyclization is performed in an acidic buffer (acetate, pH = 5), and epimerization at C-5 starts to occur when the cyclization is performed in basic buffer (phosphate, pH = 8.4).[6] Furthermore, it is also important to note that no conclusions can be drawn regarding the generality of this mechanism to the Knorr pyrrole synthesis. Substrate **18** has a unique and highly rigid structure, and other slow steps or other overall mechanisms may occur within different architectures.

5.7 Scope of the Reaction

Finally, the scope of this cyclization reaction to produce various pyrrolo[2,1,5-*cd*]indolizidines was examined in Scheme 6. Enamines, dienamines and a vinylogous amide readily cyclized to afford products **12**, **14**, **31** and **32** in good to quantitative yields and short reaction times in MeOH at ambient temperature. Furthermore, it was also possible to effect *N*-Boc deprotection and double cyclization of piperidine derivative **17** in one pot to afford the pyrroloindolizidine **13** by simply quenching the *N*-Boc deprotection reaction with basic MeOH, albeit in somewhat reduced yield (71%, Scheme 2, bottom portion).



Scheme 6. Examining the scope of pyrroloindolizidine formation.

5.8 Conclusion

In summary, we have completed a mechanistic study of the Knorr pyrrole cyclization of indolizidine-based dienamine **18**. Based on the results of kinetic experiments, we have proposed a revised mechanism for this cyclization in which a slow ketone protonation step precedes the 5-(enol-*endo*)-*exo*-trig cyclization and dehydration steps. We have also determined that this protonation only occurs in polar protic solvents and that under aqueous conditions, two water molecules participate in this event.

As in the work described in Chapter 4, this work was also a collaborative undertaking with fellow graduate student Adel M. ElSohly. Many of the synthetic methods needed to access the molecules described in this chapter were originally developed, and the results from kinetic experiments discussed, jointly. Adel is also acknowledged for performing the computational analysis. In addition, Professors Ronald Breslow and Jack R. Norton are thanked for helpful discussions.

5.9 References

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5.10 Experimental Section

General Procedures. All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Dry benzene and methylene chloride (CH_2Cl_2) were obtained by passing commercially available pre-dried, oxygen-free formulations through activated alumina columns. Yields refer to chromatographically and spectroscopically (^{1}H and ^{13}C NMR) homogeneous materials, unless otherwise stated. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Reactions were magnetically stirred and monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent and cerium sulfate (CAM) or aqueous $KMnO_4$, and heat as developing agents. SiliCycle silica gel (60, academic grade, particle size 0.040–0.063 mm) or Aldrich neutral alumina was used for flash chromatography. NMR spectra were recorded on a DMX 500 instrument and calibrated using residual undeuterated solvent as an internal reference.

Abbreviations. Boc = *tert*-butyloxycarbonyl, Cbz = carboxybenzyl, DMF = *N,N*-dimethylformamide, TBS = *tert*-butyldimethylsilyl, TFA = trifluoroacetic acid.

***Cis*-Piperidine-Derived Aldehyde 24.** TBS-protected piperidine derivative **23** (2.64 g, 7.37 mmol, 1.0 equiv) was dissolved in Et_2O (40 mL) and then TMEDA (2.43 mL, 16.2 mmol, 2.2 equiv) was added at 23 °C. The reaction contents were then cooled to –78 °C and *s*-BuLi (1.4 M in cyclohexane, 9.5 mL, 1.8 equiv) was added dropwise. The

resultant pale yellow solution was allowed to warm to –40 °C over 1 h, then stirred at that temperature for an additional 1 h before cooling back to –78 °C. DMF (5.7 mL, 73.7 mmol, 10.0 equiv) was then added quickly in a single portion and the resultant solution was slowly warmed to –40 °C. After stirring for an additional 1.5 h at –40 °C, the reaction contents were quenched by the addition of MeOH (50 mL) and warmed to 23 °C. Excess K_2CO_3 was then added, and the reaction was stirred at 23 °C for 2 h. Upon completion, the reaction contents were poured into saturated aqueous NH_4Cl (100 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated to afford a crude yellow oil. This material was purified by flash column chromatography (silica gel, hexanes/EtOAc, 19:1) to afford the desired *cis*-piperidine aldehyde **24** (2.31 g, 81% yield) as a colorless oil along with some mixed *cis*- and *trans*-piperidine material (0.270 g, 10% yield). The mixed fractions were recycled by resubjecting to K_2CO_3 (excess) in MeOH (6 mL) for 2 h at 23 °C. Work-up and purification as above afforded a second batch of *cis*-piperidine product (0.246 g, 91% yield for this step), which was combined with the product from above (2.56 g overall, 90% yield). [Note: careful control of reaction temperature is essential, as reaction temperatures above –40 °C led to large amounts of cyclization of the resultant alkoxide onto the neighboring Boc group.] **24:** R_f = 0.58 (silica gel, hexanes/EtOAc, 4:1, $KMnO_4$ stain); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.61 (d, J = 0.9 Hz, 1 H), 6.64 (br s, 1 H), 4.21 (br s, 1 H), 3.60 (td, J = 1.1 Hz, 1 H), 2.32 (d, J = 12.6 Hz, 1 H), 1.70–1.30 [m, 19 H, including 1.48 (s, 9 H)], 0.88 (s, 9 H), 0.03 (s, 6 H).

***Cis*-Piperidine-Derived C-5-Deuterated Aldehyde 25.** This aldehyde was

prepared as described for **24**, except that upon completion of the formylation, the reaction was quenched with K_2CO_3 in CD_3OD to afford deuterated variant **25** with >20:1 D-incorporation. Alternatively, pure **24** was exposed to K_2CO_3 in CD_3OD for 2 h at 23 °C to afford **25** with >20:1 D-incorporation. **25:** R_f = 0.53 (silica gel, hexanes/EtOAc, 4:1, $KMnO_4$ stain); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.61 (d, *J* = 0.9 Hz, 1 H), 4.21 (br s, 1 H), 3.60 (td, *J* = 6.4, 1.1 Hz, 1 H), 2.32 (d, *J* = 12.6 Hz, 1 H), 1.70–1.30 [m, 19 H, including 1.48 (s, 9 H)], 0.88 (s, 9 H), 0.03 (s, 6 H).

β,γ-Unsaturated Ketone (17 and 26). *Cis*-piperidine-derived aldehyde (**24** and **25**) was converted to β,γ-unsaturated ketone (**17** and **26**) in four steps according the published procedure. **17:** R_f = 0.21 (silica gel, hexanes/EtOAc, 4:1, $KMnO_4$ stain); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.59–5.48 (m, 2 H), 4.65 (br s, 1 H), 4.16 (m, 1 H), 3.10 (d, 2.8 Hz, 2 H), 2.61–2.38 (m, 4 H), 2.16–2.08 (m, 1 H), 1.74 (dtd, *J* = 14.4, 8.8, 6.0 Hz, 1 H), 1.68 (dd, *J* = 3.6, 1.2 Hz, 3 H), 1.67–1.42 (m, 6 H), 1.45 (s, 9 H), 1.05 (t, 7.2 Hz, 3 H).

26: R_f = 0.21 (silica gel, hexanes/EtOAc, 4:1, $KMnO_4$ stain); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.59–5.48 (m, 2 H), 4.17 (m, 1 H), 3.11 (d, 2.8 Hz, 2 H), 2.61–2.38 (m, 4 H), 2.16–2.08 (m, 1 H), 1.80–1.72 (m, 1 H), 1.69 (dd, *J* = 3.6, 1.2 Hz, 3 H), 1.67–1.42 (m, 6 H), 1.45 (s, 9 H), 1.06 (t, 7.2 Hz, 3 H).

General Procedure for *N*-Boc Deprotection (18, 27 and 29). To a solution of the *N*-Boc piperidine derivative starting material (**17**, **26** and precursor to **29**) in CH_2Cl_2 (10 mL/mmol) was added water (2.5 mL/mmol) at 0 °C and the resultant biphasic

mixture was stirred vigorously for 5 min before TFA (10 mL/mmol) was added dropwise. The resultant mixture was stirred vigorously at 0 °C for 1 h and then was diluted with CH_2Cl_2. The reaction contents were then poured into a separatory funnel containing an ice-cold 1 M NaOH / 0.5 M K_2CO_3 solution and was shaken vigorously for 20 sec. The resultant layers were separated and the aqueous layer was extracted with CH_2Cl_2 twice. The combined organic layers were then dried (Na_2SO_4), filtered, and concentrated. This material was taken up in benzene at 23 °C for 1 h (to ensure complete cyclization) then concentrated to afford the desired enamine (**18**, **27** and **29**) as light yellow to orange oils. All spectroscopic data for these materials matches those previously reported.[4,15] [Note: vigorous shaking of the separatory funnel is necessary to ensure complete deprotonation of the amine. When not shaken vigorously enough, the resultant products exhibit reduced *E*/*Z* ratios. The use of saturated $NaHCO_3$ in this operation led to poor mass recoveries, even following multiple extractions. These compounds were found to be unstable to isolation on neutral or basic alumina or Et_3N-deactivated silica gel.]

18: ^{1}H NMR (500 MHz, 4:1 DMSO-d_6/D_2O) δ 5.89 (ddq, J = 14.6, 12.4, 1.1 Hz, 1 H), 5.02 (dq, J = 14.8 Hz, 6.4 Hz, 1 H), 4.35 (d, J = 10.6 Hz, 1 H), 3.25 (dd, J = 11.6, 4.3 Hz, 1 H), 2.62 (m, 1 H), 2.29 (m, 1 H), 1.91 (m, 1 H), 1.83–1.65 (m, 4 H), 1.62 (d, J = 6.6 Hz, 3 H), 1.40–1.28 (m, 4 H), 1.15 (m, 1 H), 0.93–0.85 [m, 4 H, including 0.89 (t, J = 7.2 Hz, 3 H)].

27: ^{1}H NMR (500 MHz, 4:1 DMSO-d_6/D_2O) δ 5.89 (ddq, J = 14.6, 12.4, 1.1 Hz, 1 H), 5.02 (dq, J = 14.8 Hz, 6.4 Hz, 1 H), 4.35 (d, J = 10.6 Hz, 1 H), 2.62 (m, 1 H), 2.29 (m, 1 H), 1.91 (m, 1 H), 1.83–1.65 (m, 4 H), 1.62 (d, J = 6.6 Hz, 3 H), 1.40–1.28 (m, 4 H), 1.15 (m, 1 H), 0.93–0.85 [m, 4 H, including 0.89 (t, J = 7.2 Hz, 3 H)].

General Procedure for Knorr Pyrrole Cyclization (12–14, 31 and 32). Freshly prepared enamine (**18**, **27** or **29**) was dissolved in degassed MeOH (0.1 M, sparged with Ar for at least 20 min) at 23 °C, and after standing for 1 h, the solvent was removed to afford the crude pyrrole. Pure material was obtained by purification on a short plug of neutral alumina (Et_2O/pentane, 1:9). All spectroscopic data for these materials (**12**–**14**, **31** and **32**) match those previously reported.[1]

12: ^{1}H NMR (400 MHz, C_6D_6) δ 6.65 (dd, *J* = 11.2, 1.6 Hz, 1 H), 5.63 (dq, *J* = 11.2, 6.8 Hz, 1 H), 3.33 (tdd, *J* = 10.4, 5.2, 3.6 Hz, 1 H), 2.68–2.54 (m, 3 H), 2.49 (dd, *J* = 14.8, 8.0 Hz, 1 H), 2.39 (ddd, *J* = 18.8, 12.0, 7.2 Hz, 1 H), 1.97 (dt, *J* = 12.0, 6.0 Hz, 1 H), 1.89 (dd, *J* = 7.2, 1.6 Hz, 3 H), 1.73–1.65 (m, 1 H), 1.58–1.47 (m, 2 H), 1.43–1.31 (m, 2 H), 1.29 (t, *J* = 7.6 Hz, 3 H), 0.83 (tdd, *J* = 13.6, 10.8, 3.2 Hz, 1 H).

13: ^{1}H NMR (400 MHz, C_6D_6) δ 6.65 (dd, *J* = 15.6, 1.6 Hz, 1 H), 5.88 (dq, *J* = 15.6, 6.4 Hz, 1 H), 3.26 (tdd, *J* = 10.4, 5.2, 3.6 Hz, 1 H), 2.70–2.51 (m, 4 H), 2.37 (ddd, *J* = 16.0, 12.0, 6.8 Hz, 1 H), 1.99–1.91 (m, 1 H), 1.93 (dd, *J* = 6.8, 1.6 Hz, 3 H), 1.73–1.65 (m, 1 H), 1.57–1.45 (m, 2 H), 1.42–1.27 (m, 1 H), 1.31 (t, *J* = 7.6 Hz, 3 H), 0.83 (tdd, *J* = 13.2, 10.8, 2.4 Hz, 1 H).

14: ^{1}H NMR (400 MHz, C_6D_6) δ 3.33 (tdd, *J* = 10.8, 5.2, 3.6 Hz, 1 H), 2.67–2.53 (m, 7 H), 2.44 (ddd, *J* = 16.0, 11.6, 6.4 Hz, 1 H), 2.01 (dtd, *J* = 11.6, 5.2, 1.6 Hz, 1 H), 1.82–1.69 (m, 3 H), 1.64–1.53 (m, 2 H), 1.48–1.35 (m, 1 H), 1.30 (t, *J* = 7.6 Hz, 3 H), 1.07 (t, *J* = 7.2 Hz, 3 H), 0.88 (tdd, *J* = 13.6, 11.2, 2.8 Hz, 1 H).

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[1] a) F. Schröder, S. Franke, W. Francke, H. Baumann, M. Kaib, J. M. Pasteels, D. Daloze, *Tetrahedron* **1996**, *52*, 13539–13546; b) B. Sayah, N. Pelloux-Leon, Y. Vallée, *J. Org. Chem.* **2000**, *65*, 2824–2826.

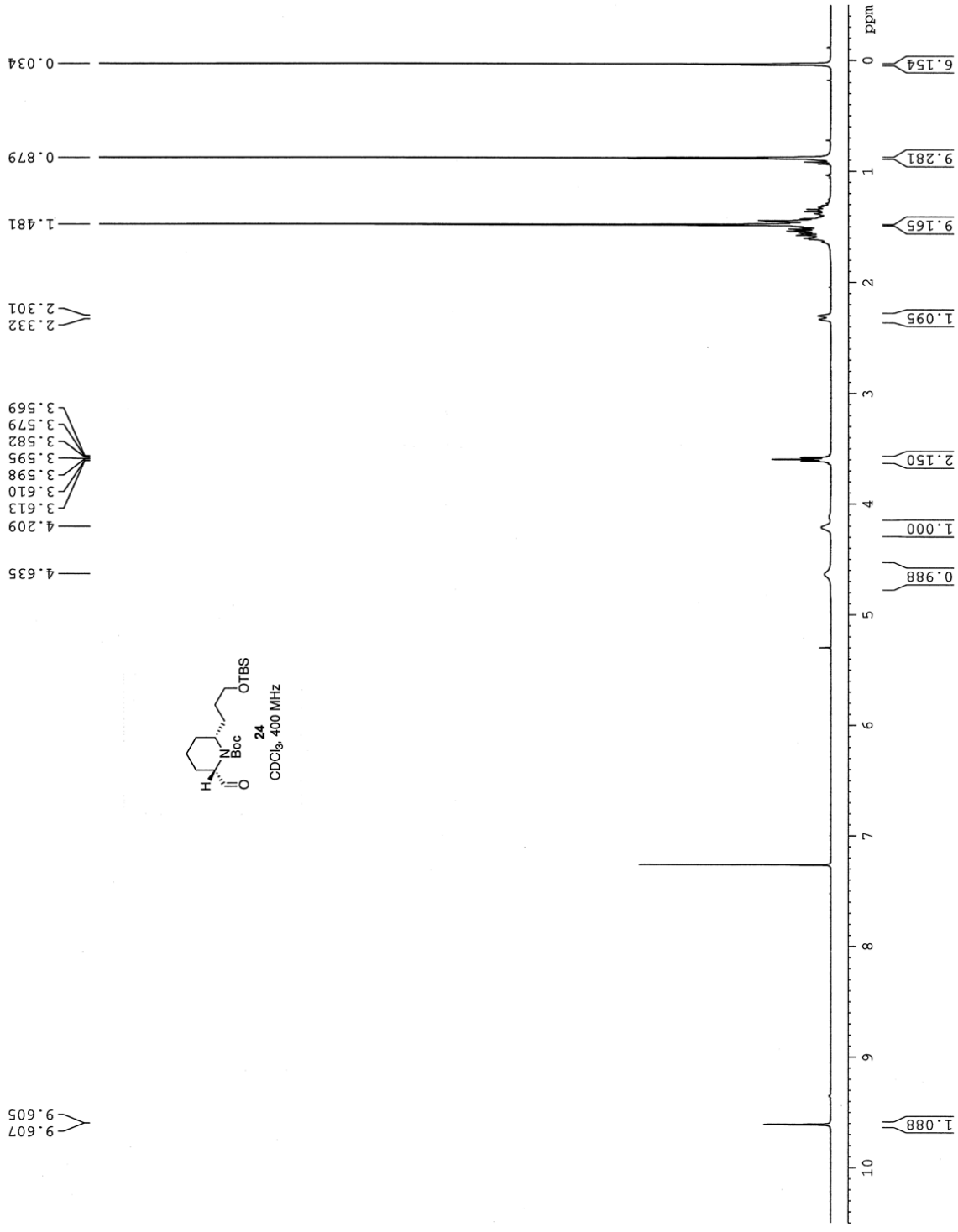
31: R_f = 0.61 (silica gel, hexanes/EtOAc, 4:1, CAM stain); ^{1}H NMR (300 MHz, C_6D_6) δ 5.98 (s, 1 H), 3.30 (m, 1 H), 2.68–2.54 (m, 4 H), 2.47–1.35 (m, 1 H), 2.02–1.94 (m, 1 H), 1.75–1.51 (m, 4 H), 1.35 (t, *J* = 7.6 Hz, 3 H), 0.92–0.79 (m, 2 H).

32: R_f = 0.27 (silica gel, hexanes/EtOAc, 4:1, CAM stain); ^{1}H NMR (500 MHz, C_6D_6) δ 3.14 (dq, *J* = 13.4, 7.0 Hz, 1 H), 3.09–3.02 (m, 2 H), 2.58 (q, *J* = 7.4 Hz, 2 H), 2.52–2.38 (m, 3 H), 2.22–2.15 (m, 1 H), 1.82–1.77 (m, 1 H), 1.57 (m, 1 H), 1.51 (t, *J* = 1.51, 3 H), 1.44 (dq, *J* = 12.5, 3.4 Hz, 1 H), 1.38 (dd, *J* = 11.1, 2.7 Hz, 1 H), 1.33 (t, *J* = 7.4 Hz, 3 H), 1.26–1.16 (m, 1 H), 0.77–0.69 (m, 1 H).

General Kinetic Procedures and Analysis. Kinetic measurements were made using ^{1}H NMR spectroscopy on a Bruker DMX 500 MHz spectrometer at 35 °C. DMSO-d_6/D_2O solutions of known concentration were prepared using a Hamilton Co. microliter syringe and a 2 mL volumetric flask. To obtain k_{obs} for the cyclization, freshly prepared dienamine **18** or **27** was taken up in a solution of isopropanol-d_8 or DMSO-d_6/D_2O and immediately transferred to an NMR tube. Following temperature equilibration to 35 °C, the instrument was locked, tuned and shimmed. A ^{1}H NMR spectrum was then obtained every 3 or 6 minutes using the *kineticzg* program, and the disappearance of starting material was measured by monitoring the integration of the peak corresponding to the dienamine β-CH relative to residual benzene as internal standard. A plot of ln [SM] *vs.* time (s) allowed a fit of a line with slope k_{obs}. To obtain k_H/k_D, this procedure was repeated with both **18** and **27** using isopropanol-d_8 or the same solution of DMSO-d_6/D_2O. To calculate the order of water in the cyclization, the above procedure

was repeated at various concentrations of D_2O in DMSO-d_6. A plot of k_{obs} *vs.* [D_2O] then showed an excellent fit to an exponential curve ($y=ax^b$), whereas a plot of k_{obs}/[D_2O] *vs.* [D_2O] showed a linear relationship.

General Procedure for One-Pot Deprotection-Knorr Pyrrole Synthesis. To a solution of the alkene starting material **17** (7 mg, 0.02 mmol) in CH_2Cl_2 (0.2 mL) was added water (0.05 mL) at 0 °C and the resultant biphasic mixture was stirred vigorously for 5 min before TFA (0.2 mL) was added dropwise. The resultant mixture was stirred vigorously at 0 °C for 1 h. The deprotection was then was quenched by addition of saturated aq. $NaHCO_3$ (2.5 mL) and MeOH (5.0 mL), and the reaction was stirred at 23 °C for 2 h. The reaction contents were then poured into a separatory funnel containing 1 M NaOH (10 mL) and extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were then dried (Na_2SO_4), filtered, and concentrated to a crude orange solid. This crude material was purified on a short plug of neutral alumina (Et_2O/pentane, 1:9) to afford myrmicarin 215B (**13**) as a white crystalline solid (3 mg, 71% yield).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Boc
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O
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3
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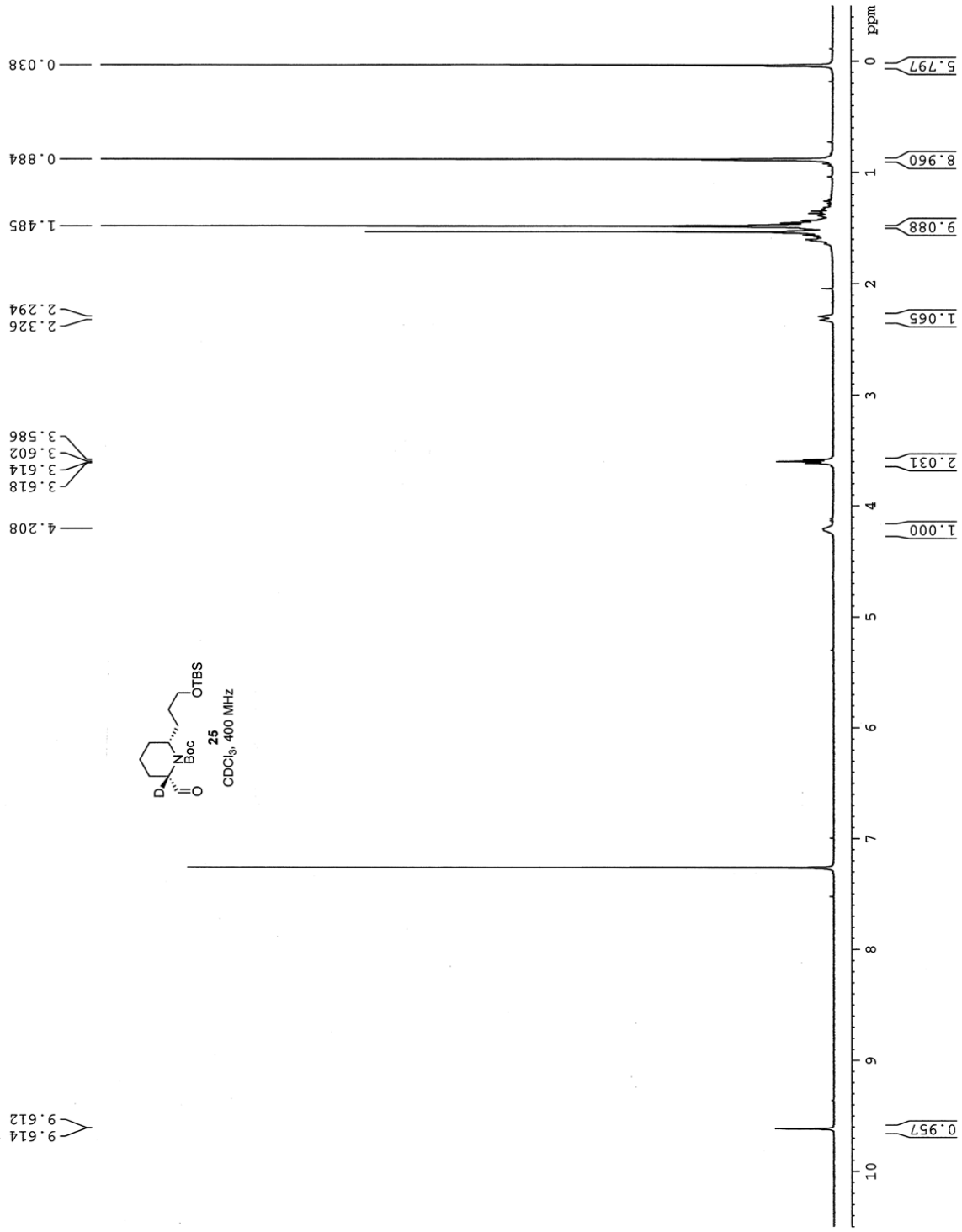
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Boc
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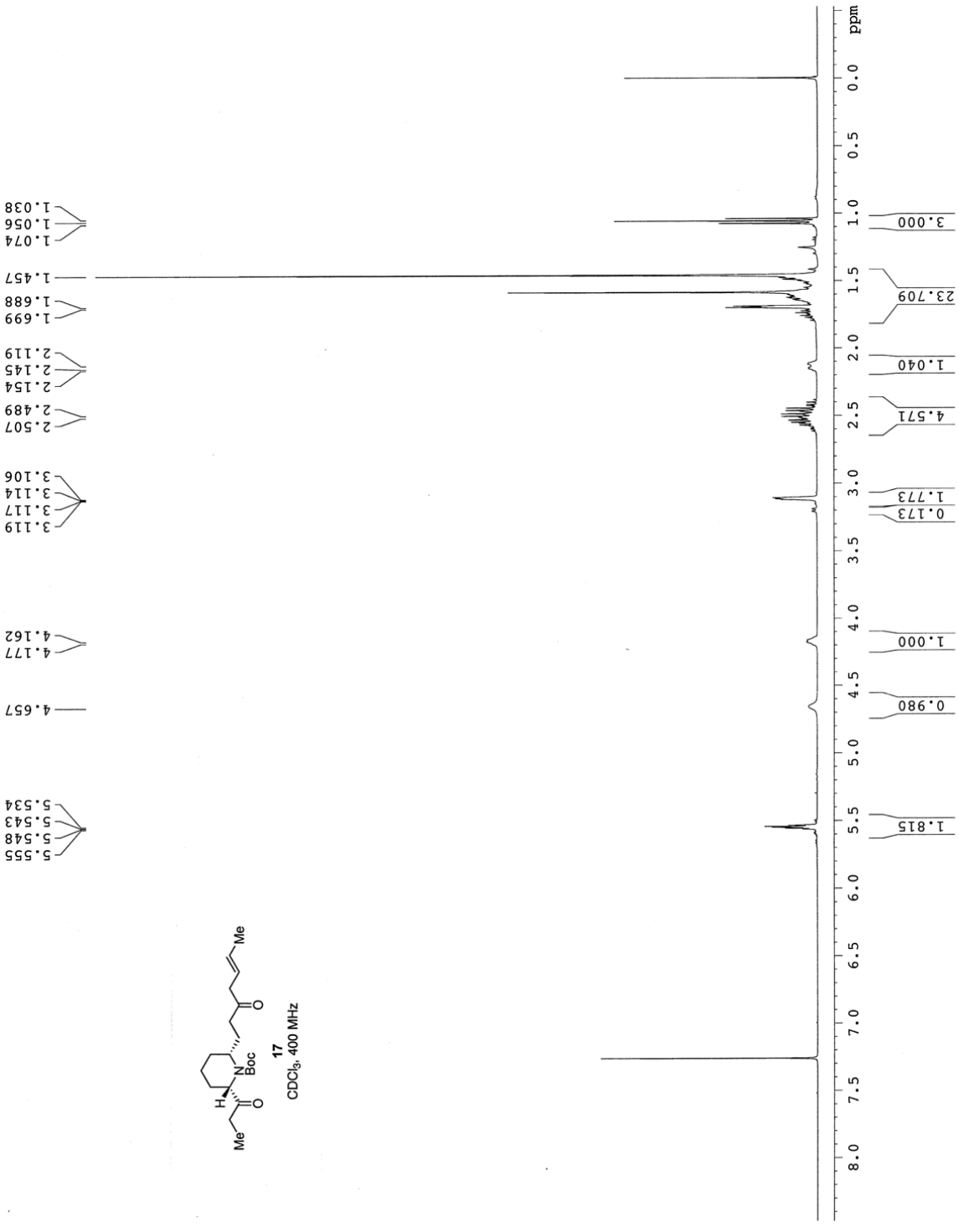
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H
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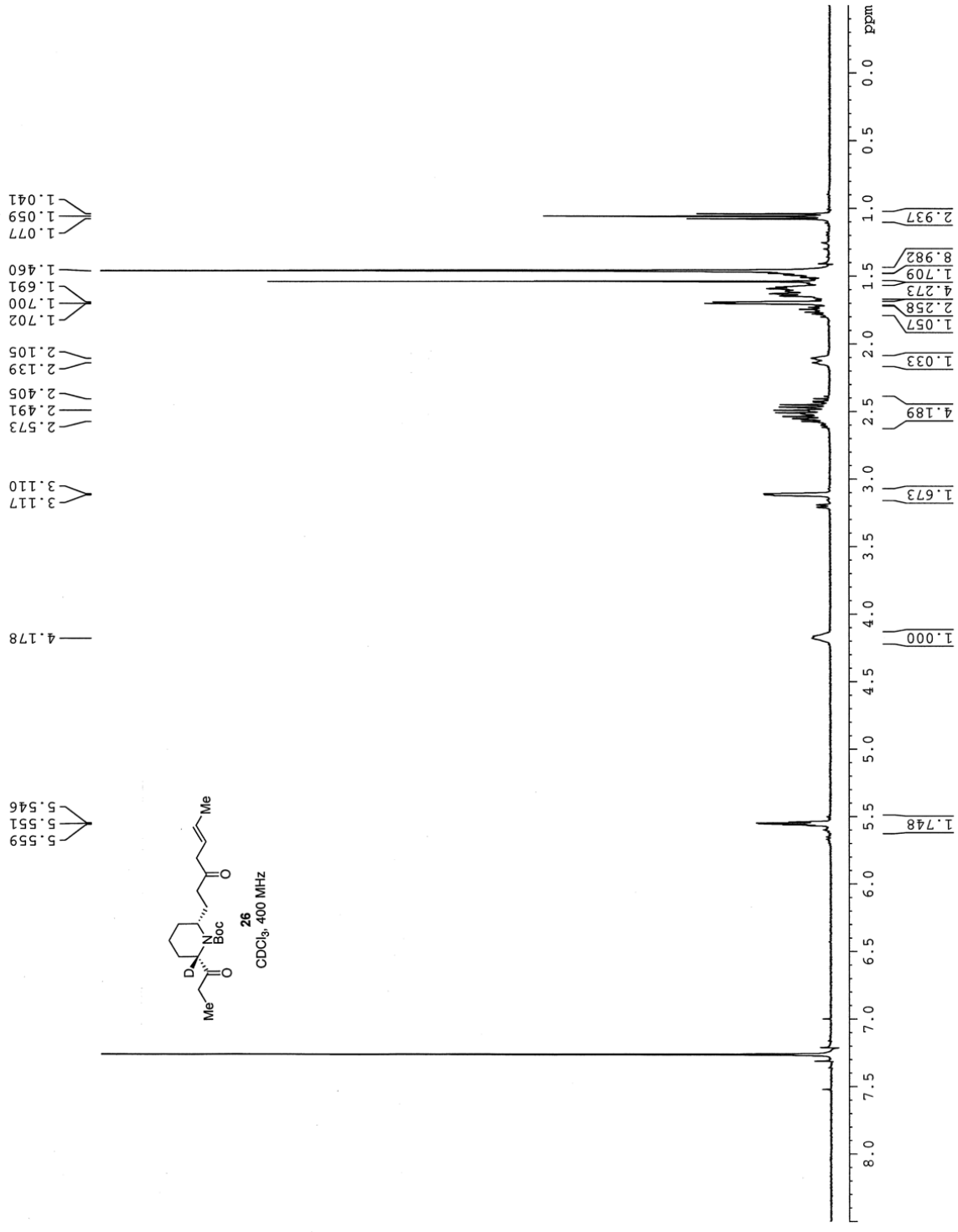
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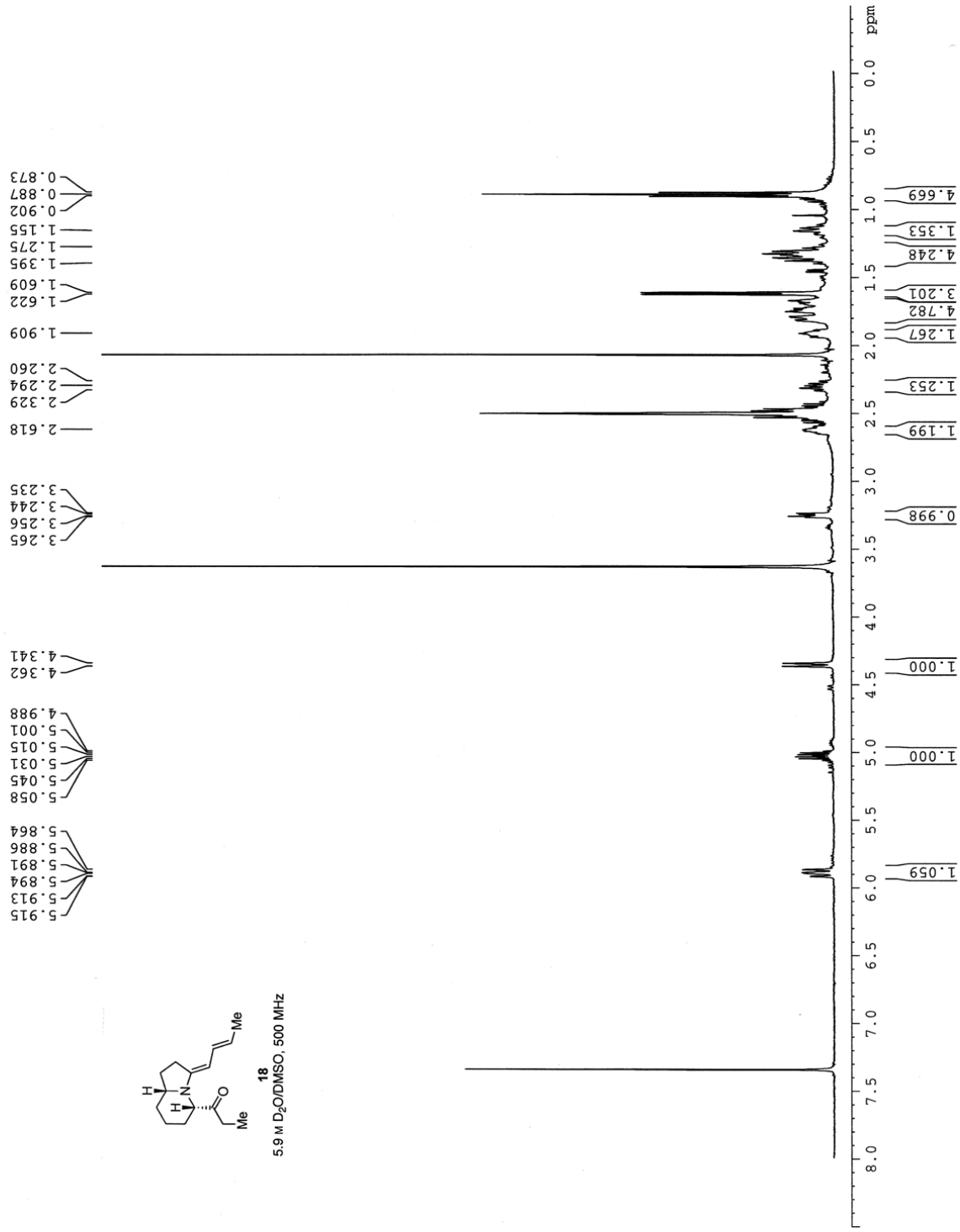
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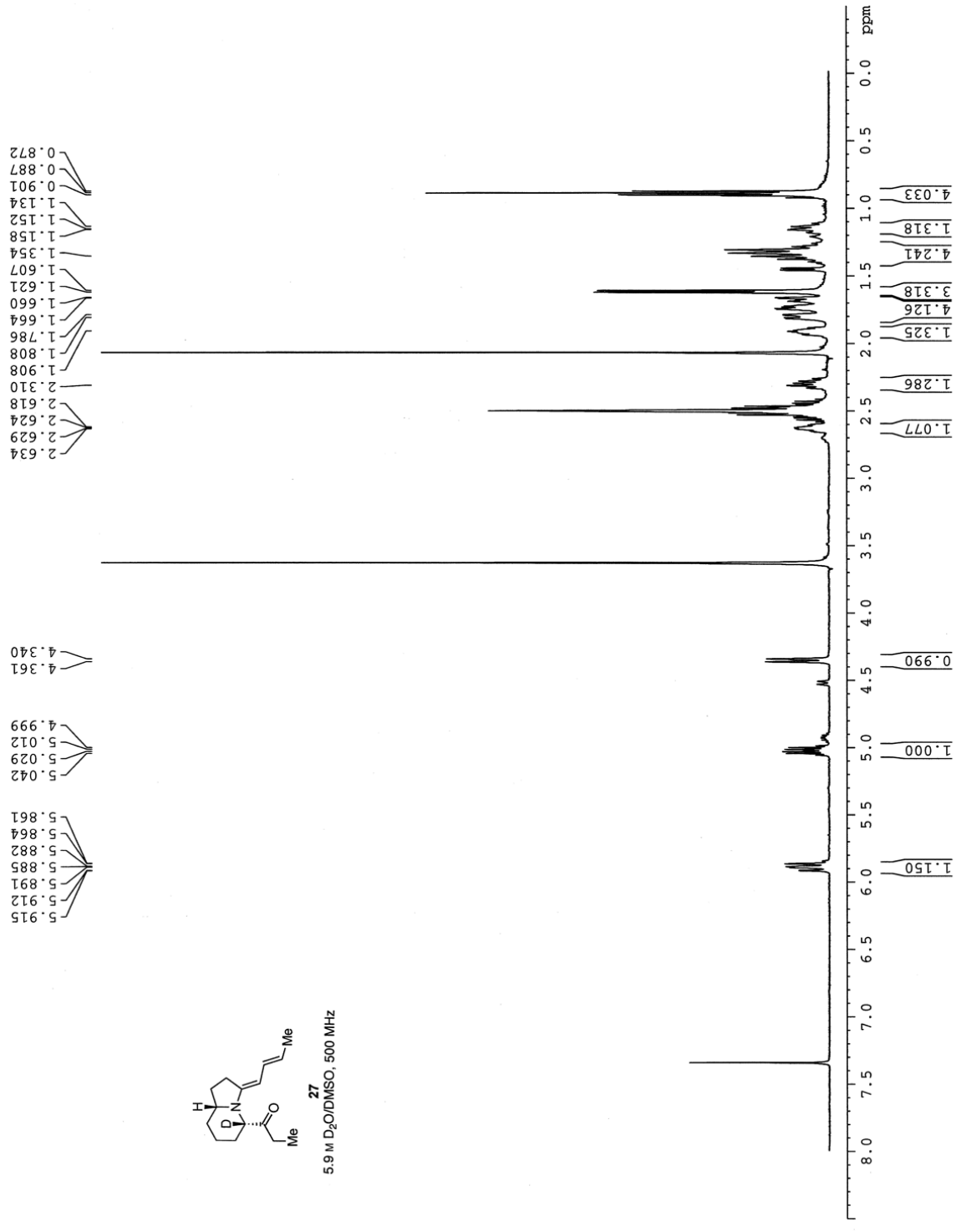
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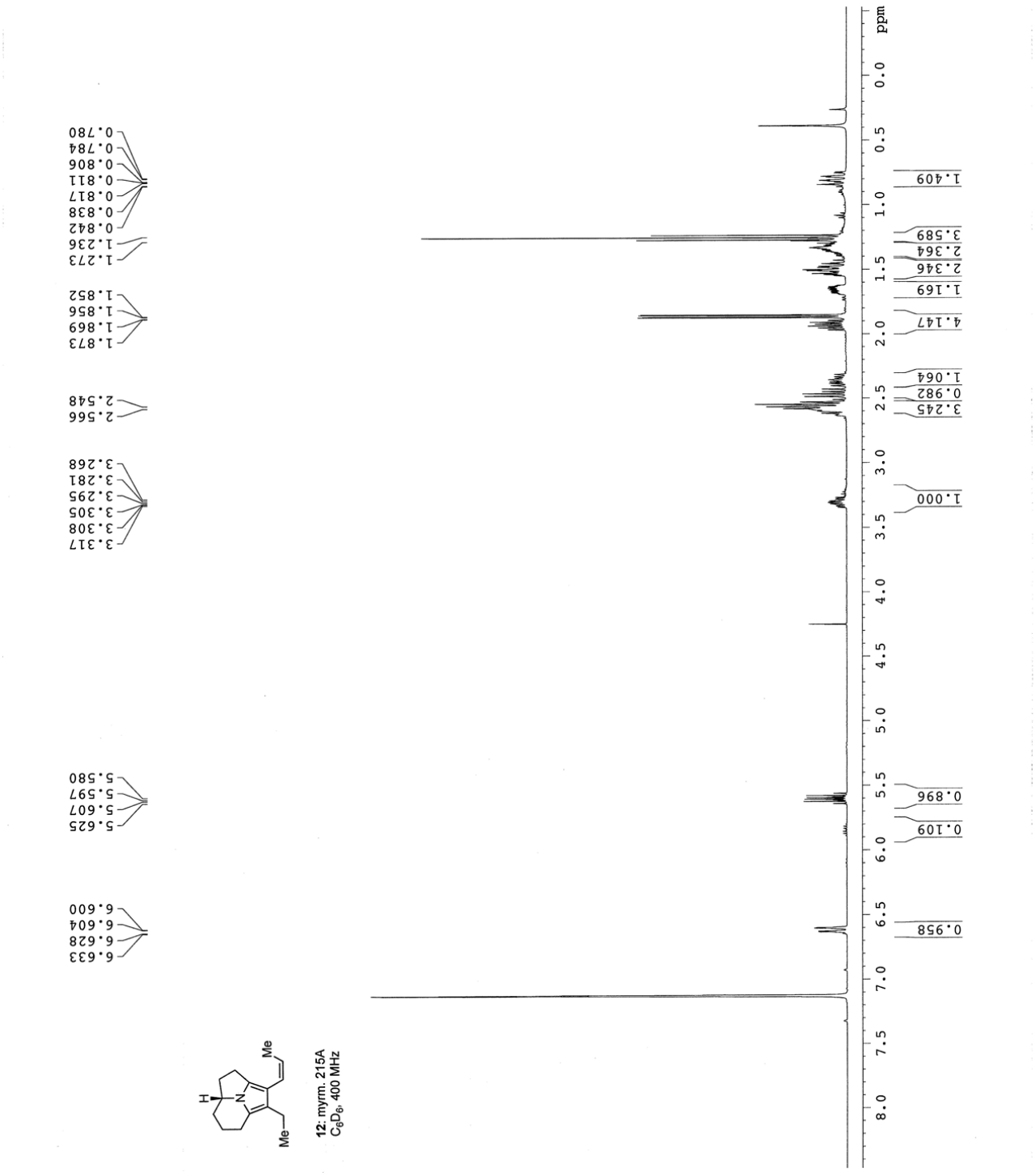
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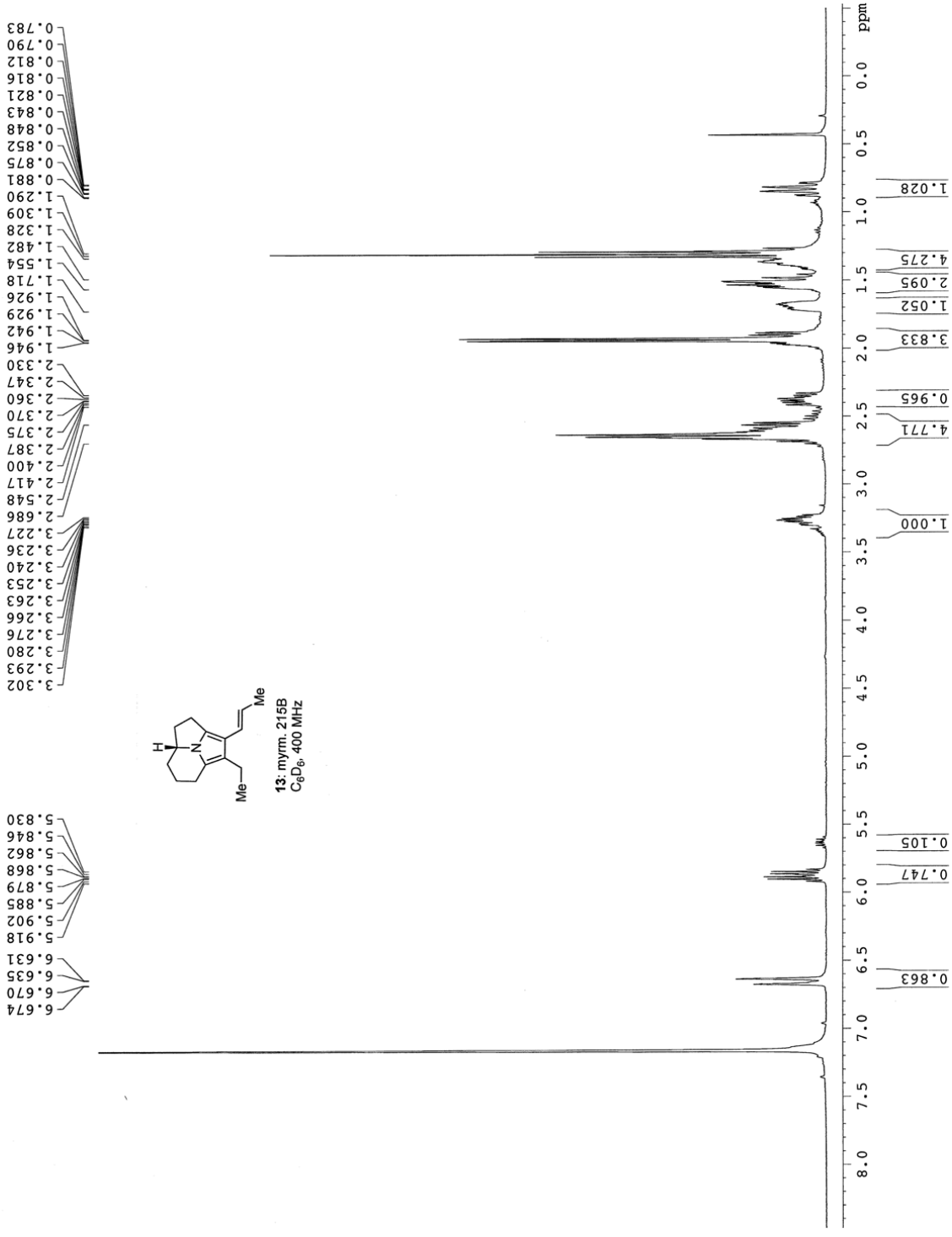
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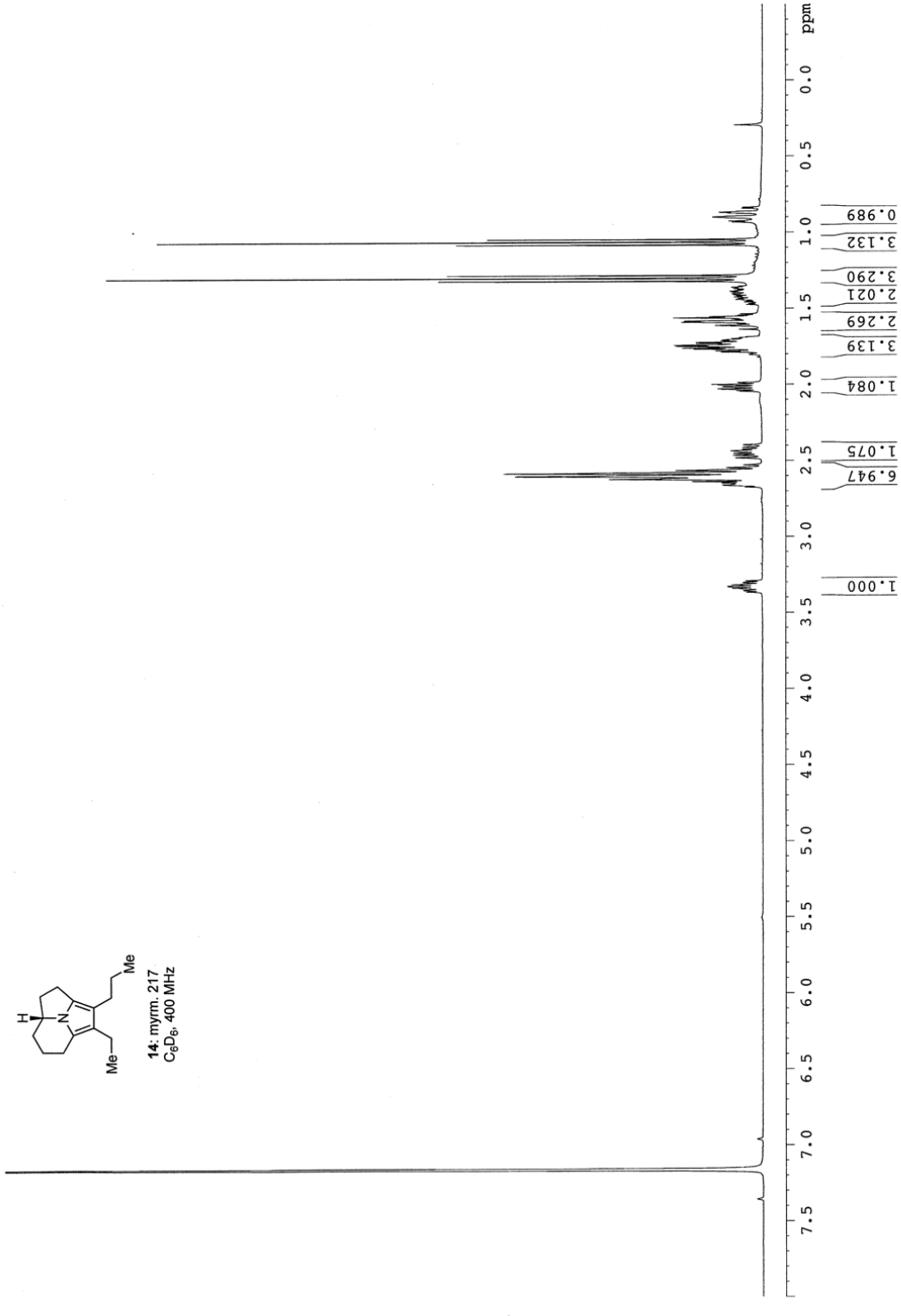
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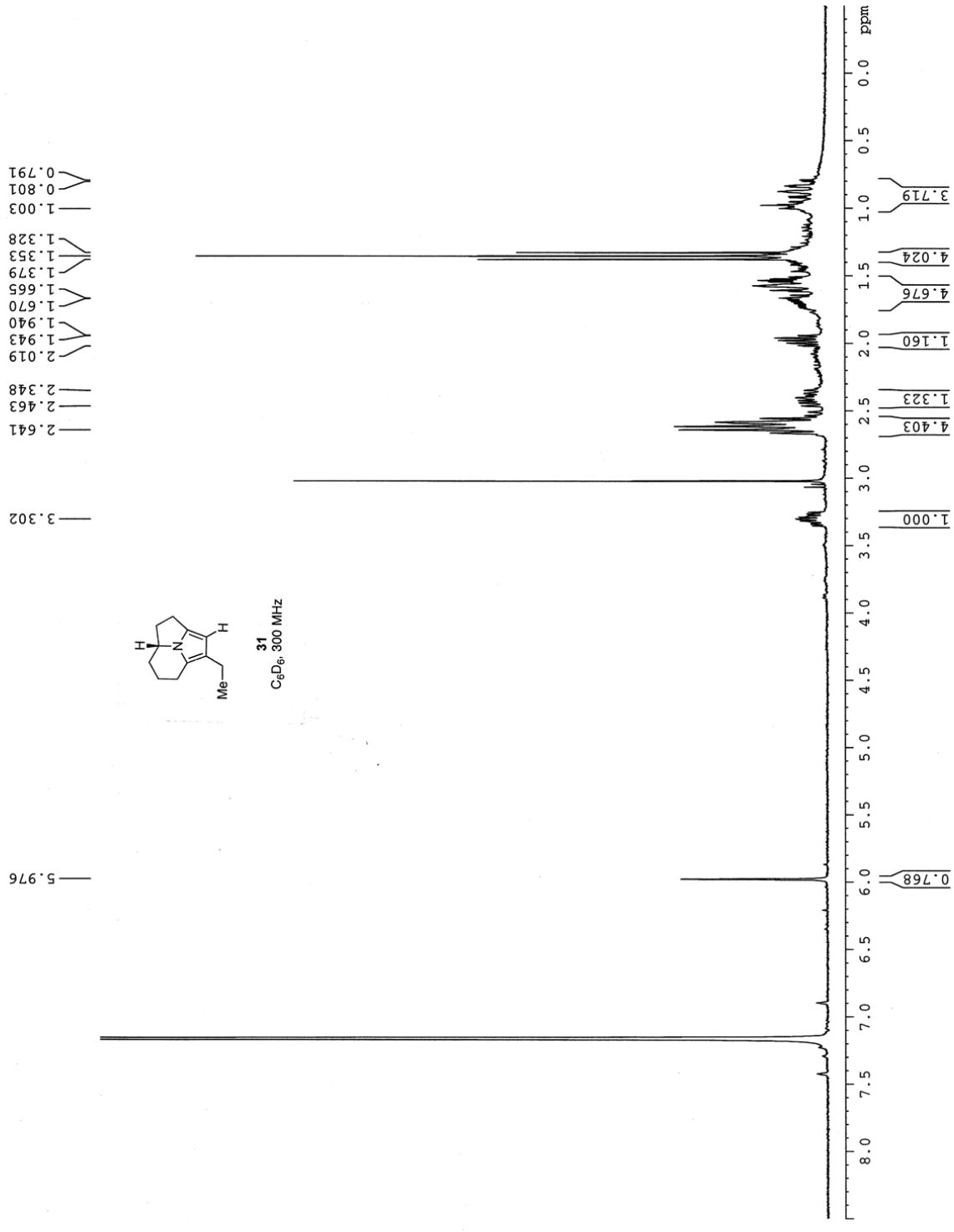
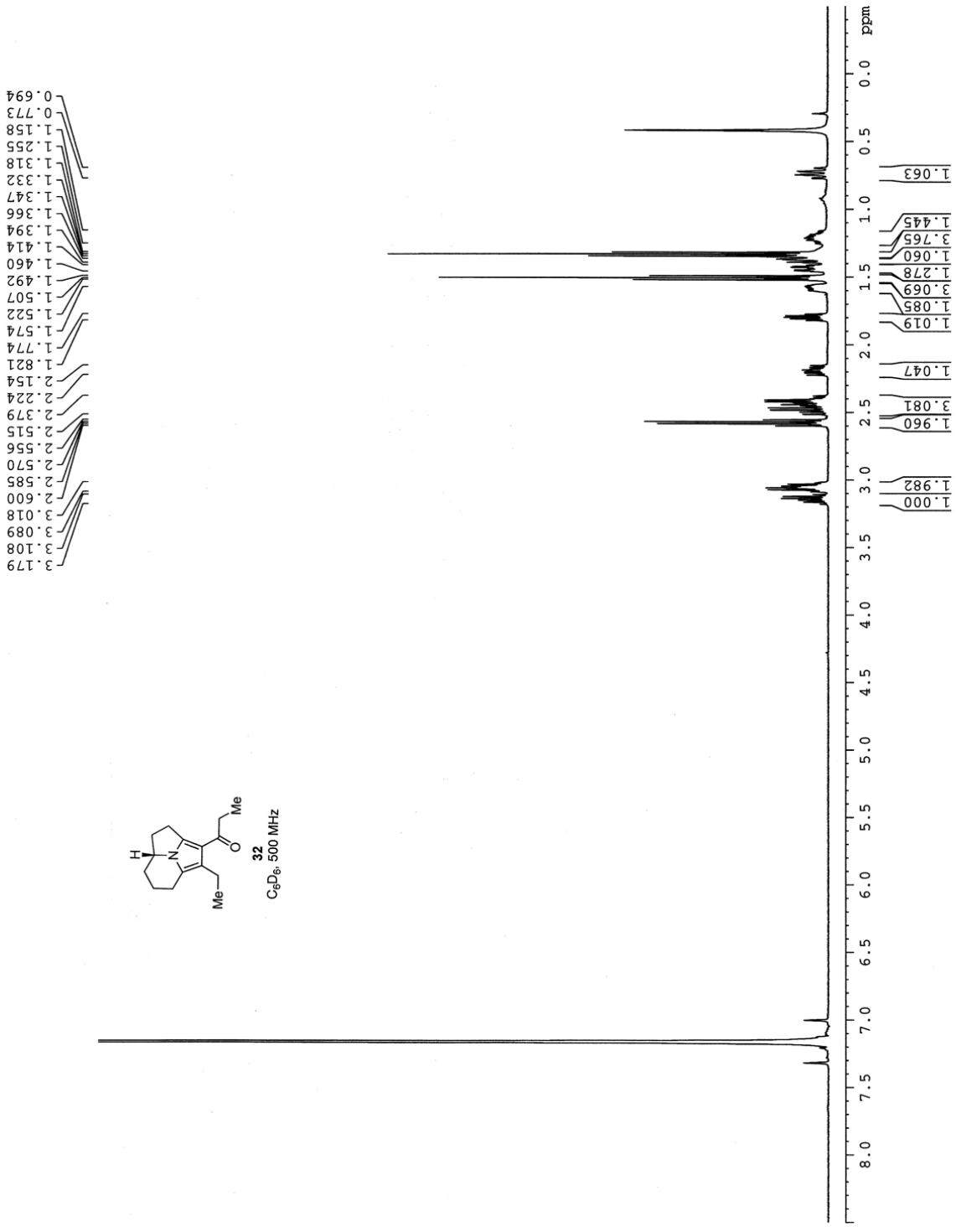
2.004
2.000
1.762
1.749
1.744
1.742
1.591
1.584
1.562
1.441
1.424
1.417
1.411
1.405
1.395
1.388
1.383
1.302
1.065
0.906
0.900
0.896
0.873
0.869


31
C6D6, 300 MHz
Me
H
H
N
5.976
3.302
2.641
2.463
2.348
2.019
1.943
1.940
1.670
1.665
1.379
1.353
1.328
1.003
0.801
0.791
0.768
1.000
4.403
1.323
1.160
4.676
4.024
3.719
ppm


32
C_6D_6, 500 MHz
Me
Me
O
N
H
ppm
0.694
0.773
1.158
1.255
1.318
1.332
1.347
1.366
1.394
1.414
1.460
1.492
1.507
1.522
1.574
1.774
1.821
2.154
2.224
2.379
2.515
2.556
2.570
2.585
2.600
3.018
3.089
3.108
3.179
1.063
1.445
3.765
1.060
1.278
3.069
1.085
1.019
1.047
3.081
1.960
1.982
1.000