## Title

Chemical Investigations into Pyrrole-Containing Secondary Metabolites Isolated From Curvularia Sp. and Bipolaris Maydis



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# Chemical Investigations into Pyrrole-Containing Secondary Metabolites Isolated From *Curvularia* Sp. and *Bipolaris Maydis*

By

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Professor Thomas J. Maimone, Chair
Professor Richmond Sarpong
Professor Roberto Zoncu

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Pyrrole-containing alkaloids have long captured the attention of the synthetic chemistry community due to their intriguing and reactive chemical architectures; such is the case of curvulamine and associated polypyrrole natural products. Curvulamine, curindolizine, and the related bipolamines share a unique compact pentacyclic skeleton flanked by two electron-rich pyrroles and up to seven stereocenters. Synthetic access to these complex alkaloids has previously been limited to curvulamine and bipolamine I. In this work, we aim to chronicle the results of our synthetic investigations into this family of unique alkaloids. In the first chapter, we provide an overview into their isolation and antibiotic properties, and discuss our initial synthesis of curvulamine which frames our studies in subsequent chapters. The second chapter describes the total synthesis of curindolizine and the substrate scope of a microwave-assisted method to access pyrroloazepinones, bicyclic heterocycles used in the synthesis of curvulamine and curindolizine. Finally, in the last chapter we describe the synthetic strategies used to access bipolamine C, D, G, and I and describe the unexpected reactivity of some pyrrole-containing intermediates along this journey.

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**Acknowledgements**

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## List of Abbreviations

| | |
|---|---|
| ABNO | 9-azabicyclo[3.3.1]nonane N-oxyl |
| AIBN | azobisisobutyronitrile |
| Boc | tert-butyloxycarbonyl |
| bpy | 2,2'-bipyridyl |
| CAN | ceric ammonion nitrate |
| CBS | Corey–Bakshi–Shibata |
| CDI | 1,1'-carbonyldiimidazole |
| CuDPP | $Cu^{I}$ diphenylphosphinate |
| dba | dibenzalacetone |
| DBU | 1,8-diazabicyclo(5.4.0)undue-7-ene |
| DCA | 9,10-dicyanoanthracene |
| DCC | N,N'-dicyclohexylcarbodiimide |
| DCE | 1,2-dichloroethane |
| DCM | dichloromethane |
| DIPEA | N,N-diisopropylethylamine |
| DFT | density functional theory |
| DIBAL | diisobutylaluminium hydride |
| DMac | dimethylacetamide |
| DMAP | 4-dimethylaminopyridine |
| DMDO | dimethyldioxirane |
| DMF | dimethylformamide |
| DMS | dimethyl sulfide |
| DMSO | dimethyl sulfoxide |
| dr | diastereomeric ratio |
| dpm | dipivaloylmethanato. |
| dt-Bu | di-tert-butyl |
| dtbpy | 4,4′-di-tert-butyl-2,2′-dipyridyl |
| ee | enantiomeric excess |
| Et | ethyl |
| FVP | flash vacuum pyrolysis |
| HAT | hydrogen atom transfer |
| HFIP | hexafluoroisopropanol |
| HMPA | hexamethylphosphoramide |
| h$\nu$ | photo irradiation |
| KHMDS | potassium bis(trimethylsilyl)amide |
| LDA | lithium diisopropylamide |
| LiHMDS | lithium bis(trimethylsilyl)amide |
| Lg | leaving group |
| Me | methyl |
| MeCN | acetonitrile |

| | |
|---|---|
| Mes | mesitylene |
| $MeO_{bpy}$ | 4,4′-dimethoxy-2,2′-bipyridine |
| Ms | methanesulfonyl |
| MVK | methyl vinyl ketone |
| MWI | microwave irradiation |
| m-CPBA | meta-chloroperoxybenzoic acid |
| NaHMDS | sodium bis(trimethylsilyl)amide |
| NBS | N-bromosuccinimide |
| NIS | N-iodosuccinimide |
| NMI | N-methylimidazole |
| NMR | nuclear magnetic resonance |
| NOE | nuclear Overhauser effect |
| [O] | oxidation |
| OTF | trifluoromethanesulfonate |
| Phen | 1,10-phenanthroline |
| PhMe | toluene |
| PIDA | diacetoxyiodobenzene |
| ppy | 2-phenylpyridinato-$C^2$,N |
| SEM | 2-(trimethylsilyl)ethoxymethyl |
| SET | single electron transfer |
| TBAF | tetra-n-butylammonium fluoride |
| TES | triethylsilyl |
| TFAA | trifluoroacetic anhydride |
| TFP | tri(2-furyl)phosphine |
| TBS | tert-butyldimethylsilyl |
| TEMP | 2,2,6,6-retramethyl-1-piperidinyloxy |
| O THF | tetrahydrofuran |
| TLC | thin layer chromatography |
| t-Bu | tert-butyl |
| TIPS | triisopropoylsilyl |
| TMS | trimethylsilyl |
| OAc | acetate |
| Pin | pinacolato |
| PPTS | pyridinium p-toluenesulfonate |
| PTSA | p-toluenesulfonic acid monohydrate |

*Chapter 1*

# Overview of the Curvulamine-Type Alkaloids

## 1.1 Curvulamine-Type Alkaloids, Isolation and Biosynthesis

The *Pleosporaceae* is the most diverse family of ascomycete in the *Dothideomycetes* class of fungi.[1] Species belonging to this family are reported to be endophytes, epiphytes or parasites and inhabit a broad range of ecosystems.[2] Notable *Pleosporaceae* are found in the genera *Bipolaris* and *Curvularia*, which contain species known to reside in tropical and subtropical environments and have symbiotic relations with plants and marine animals.[3-6] The intimate symbiotic connection of these fungi to other species has driven the interest of the scientific community to investigate the biosynthesis and biological activities of the secondary metabolites produced by organisms in these genera.[7-10]

As part of a campaign to identify novel agents with promising biological activities, Tan and co-workers identified two fungi present in the fish *Argyrosomus argentatus*: *Myrothecium* sp. Z16 and *Curvularia* sp. IFB-Z10. The first fungus was isolated from the spermary glad of the fish and the second was isolated from the intestinal tract.[7,8] The fungal broth obtained from *Myrothecium* sp. Z16 was found to exhibit antimycotic activity against *Candida albicans*, *Trichophyton rubrum,* and *Aspergillus niger*. The broth obtained from *Curvularia* sp. IFB-Z10 was found to have antibiotic activity and shown to inhibit the growth of the following bacterial strains: *Peptostreptococcus* sp., *Veillonella parvula, Bacteroides vulgatus*, and *Streptococcus* sp. with minimum inhibitory concentrations (MICs) in the low micromolar range (0.37 μM).[8] Notably, Tan and co-workers identified a novel bis-pyrrole alkaloid named curvulamine (**1**) as the agent responsible for these antimicrobial activities. The structure of **1** was unequivocally assigned by single crystal X-ray crystallography and confirmed a unique [5,7,6,5]-fused tetracyclic bispyrrole skeleton.

Since the initial discovery of **1**, Tan and co-workers have identified more than 11 nitrogen-containing secondary metabolites with skeletons akin to curvulamine (**1**) (Figure 1.1A).[10] In 2016, as part of an effort to further investigate the biological properties of **1**, an unexpected and novel nitrogenated alkaloid, namely curindolizine (**2**), was discovered when scaling up the cultivation of *Curvularia* sp. IBF-Z10. Single crystal X-ray crystallography was employed to assign the structure of curindolizine (**2**).[9] Due to its structural similarities to curvulamine (**1**), **2** is believed to be a metabolite derived from **1** after a regiospecific Michael addition of the eastern pyrrole of **1** into 3,5-dimethylindolizin-8(5H)-one.[9] Recent studies by the Tan group on the biosynthesis of these nitrogenated metabolites shed light on the biosynthetic gene cluster (BGC) responsible for making curvulamine (**1**).[7] In this work, the *cuaB* gene was identified as being responsible for assembling the $C_{10}N$ indolizine unit, a key component in all curvulamine-type alkaloids. This finding triggered a genome mining campaign to search for homologous fungal biosynthetic gene clusters (BGCs) in genomes catalogued in databases from the Joint Genome Institute (JGI) and the National Center for Biotechnology Information (NCBI). From this study, the fungus *Bipolaris maydis* (ATCC48331) was identified as not only possessing *cuaB*, but also a set of distinctive genes coding for tailoring enzymes predicted to facilitate the synthesis of novel indolizine-type alkaloids. The culture broth of *Bipolaris maydis* failed to produce any detectable quantity of nitrogenated secondary metabolites under laboratory conditions; but fermentation along with the overexpression

of the putative transcription factor *bipF* afforded 9 new nitrogenated alkaloids with indolizine scaffolds similar to curvulamine (**1**). These new nitrogenated metabolites were named bipolamines A-I (**3-11**) and analysis of their structures revealed various oxidation

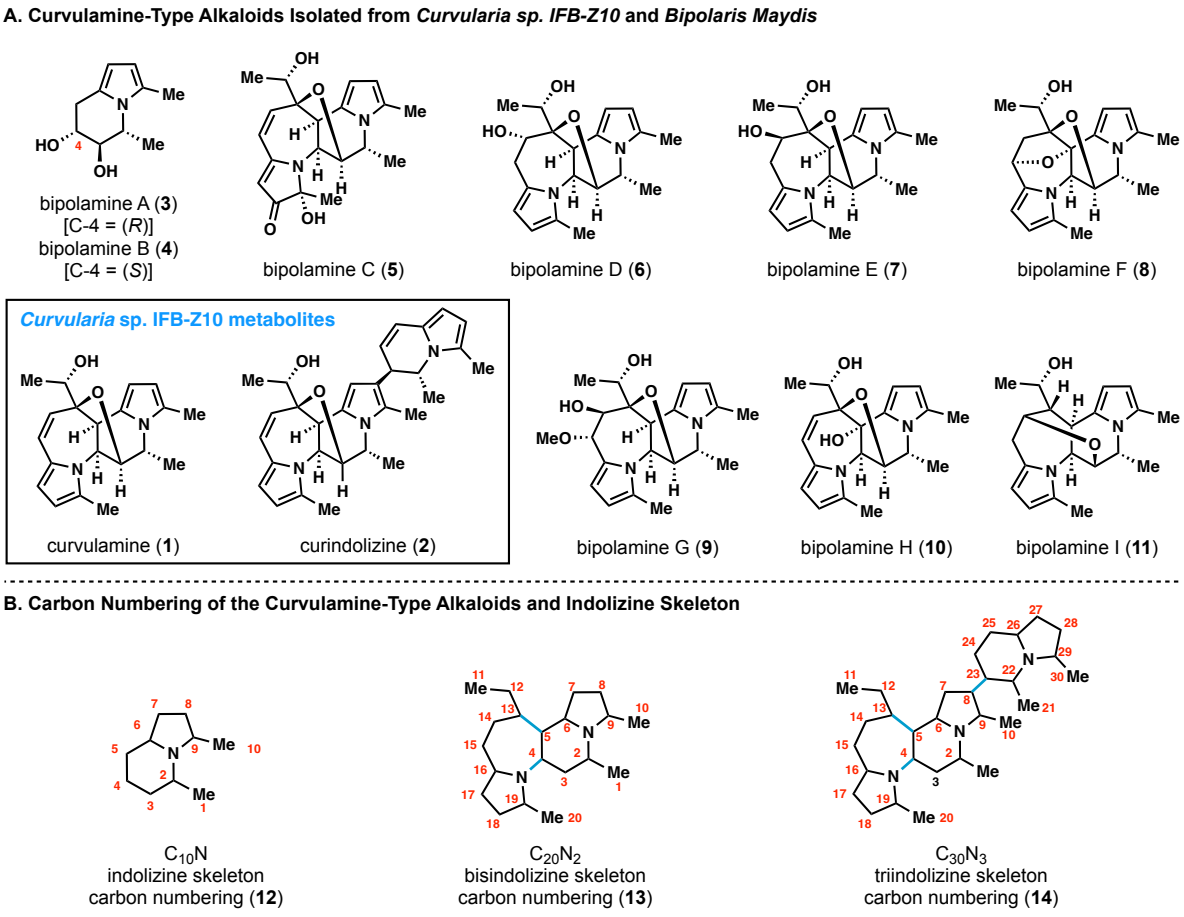


**Figure 1.1** The secondary metabolites isolated from *Curvularia* sp. IFB-Z10 and *Bipolaris maydis*. **A**. The curvulamine alkaloids. **B**. Carbon numbering and skeletal patters of the curvulamine-type alkaloids.

patters that are attributed to the tailoring enzymes cytochrome P450 monooxygenase, cofactor $F_{420}$-depented oxidoreductase, and an α-ketoglutarate-dependent oxygenase.

The $C_{10}N$ indolizine unit (see **12**) is a common element in all curvulamine-type alkaloids (*vide supra*), and their members can be grouped into three different categories based on the number of these indolizine units present in their carbon skeleton (Figure 1.1B).[11] Bipolamine A (**3**) and bipolamine B (**4**) are the simplest congeners with a single methylated tetrahydroindolizine $C_{10}N$ skeleton (**12**). These metabolites are believed to be early biosynthetic building blocks to higher order curvulamine-type alkaloids.[10] The $C_{20}N_2$ group of congeners, is the most diverse and contains the largest number of family members. The tetracyclic $C_{20}N_2$ bisindolizine skeleton (**13**) in these curvulamine type alkaloids is functionalized with different levels of oxidation and hydroxylation patterns. The preserved tetracyclic $C_{20}N_2$ core is believed to be derived from the fusion of a $C_{10}N$ indolizine unit (**12**) to a cleaved indolizine biosynthetic intermediate. The final category of

curvulamine-type alkaloids is the product of enzymatic addition of a $C_{10}N$ unit to the C-8 position of the tetracyclic $C_{20}N_2$ bisindolizine skeleton. To this date, curindolizine (**2**) is the only known higher-order curvulamine alkaloid in this group containing a $C_{30}N_2$ skeleton (**14**).

Two studies by Tan and co-workers has partially elucidated the biosynthesis of the curvulamine alkaloids.[8,10] In the first study, evidence was obtaining for a polyketide origin of curvulamine (**1**) via isotopic labeling experiments. *Curvularia* sp. IFB-Z10 was cultivated in the presence of 1-$^{13}$C or 2-$^{13}$C enriched sodium acetate, and $^{13}$C NMR analysis of the fungal culture extracts revealed a curvulamine skeleton with $^{13}$C enrichment in an alternating fashion, indicative of a polyketide origin of this alkaloid. Notably, no labeling was observed at C-9, C-10, C-19 or C-20 in either of these experiments. This indicated the possible involvement of other carbon sources and enzymes in the biogenesis of the skeleton of **1**. Further $^{13}$C labeling experiments employing [2,3-$^{13}$C] alanine resulted in $^{13}$C enrichment at C-9, C-10, C-19, and C-20 in curvulamine (**1**). In subsequent biochemical experiments, pyridoxal-5'-phosphate(PLP)-dependent oxoamine synthase (AOS) was identified as a key enzyme in the formation of the $C_{10}N$ indolizine unit. As stated, the $C_{10}N$ unit is believed to be an early intermediate in the biosynthesis of all curvulamine alkaloids. This hypothesis was confirmed by cultivating *Curvularia* sp. IFB-Z10 in the presence of a known inhibitor of AOS, which blocked production of **1**. More recently, Tan and co-workers sequenced the genome of *Curvularia* sp. IFB-Z10 and identified the biosynthetic gene cluster and enzymes involved in the synthesis of early precursors en-route to curvulamine (**1**) and seemingly the rest of the curvulamine alkaloids.[10]

It is proposed that the *cuaA* gene encodes the polyketide synthase machinery to condense one acetyl-CoA and three malonyl-CoA into linear β-keto enone **15**. *cuaB* encodes a multipurpose enzyme that first condenses alanine with PLP forming iminium **16**. *cuaB* then triggers a PLP mediated chain release involving a Claisen condensation of **16** with enone **15**. Subsequent decarboxylation, aerobic oxidation, intramolecular condensation and dehydration produces cyclic hemiaminal **17**. Polyene **17** is proposed to be the key synthetic unit in the biogenesis of all the curvulamine alkaloids. Genes *cuaC* and *cuaD* encode the enzymes responsible for converting hemiaminal **17** into indolizine **18** and epoxide **19**. It is postulated the $C_{20}N_2$ skeleton is generated after a coupling event between **18** and **19** and a series of redox reactions, however the precise mechanism of this biosynthetic step remains elusive. The biosynthetic gene cluster of *Bipolaris maydis* indicates that tailoring enzymes such as cytochrome P450 dependent monooxygenases and oxidoreductases could further functionalize the $C_{20}N_2$ skeleton giving rise to the diversity of oxidation patterns found in the curvulamine alkaloids.[10]

In a separate study, during the investigations of curindolizine (**2**), Tan and co-workers isolated procuramine (**20**) from the culture broth of *Curvularia* sp. IFB-Z10.[9] Interestingly, incubation of **20** and curvulamine (**1**) in the presence of *Curvularia* sp. IFB-Z10 protein lysate formed curindolizine (**2**). The individual enzymes involved in this transformation were not identified, but a plausible route to **2** might involve dehydration of **20** to form 3,5-dimethylindolinone (**21**), which can undergo regioselective Michael addition with **1** followed by a reduction and dehydration.

It is worth noting that while these previously described studies provide information about the plausible biosynthetic pathway of the curvulamine alkaloids, a complete biogenesis remains elusive, especially with respect to how the seven-membered ring is formed.

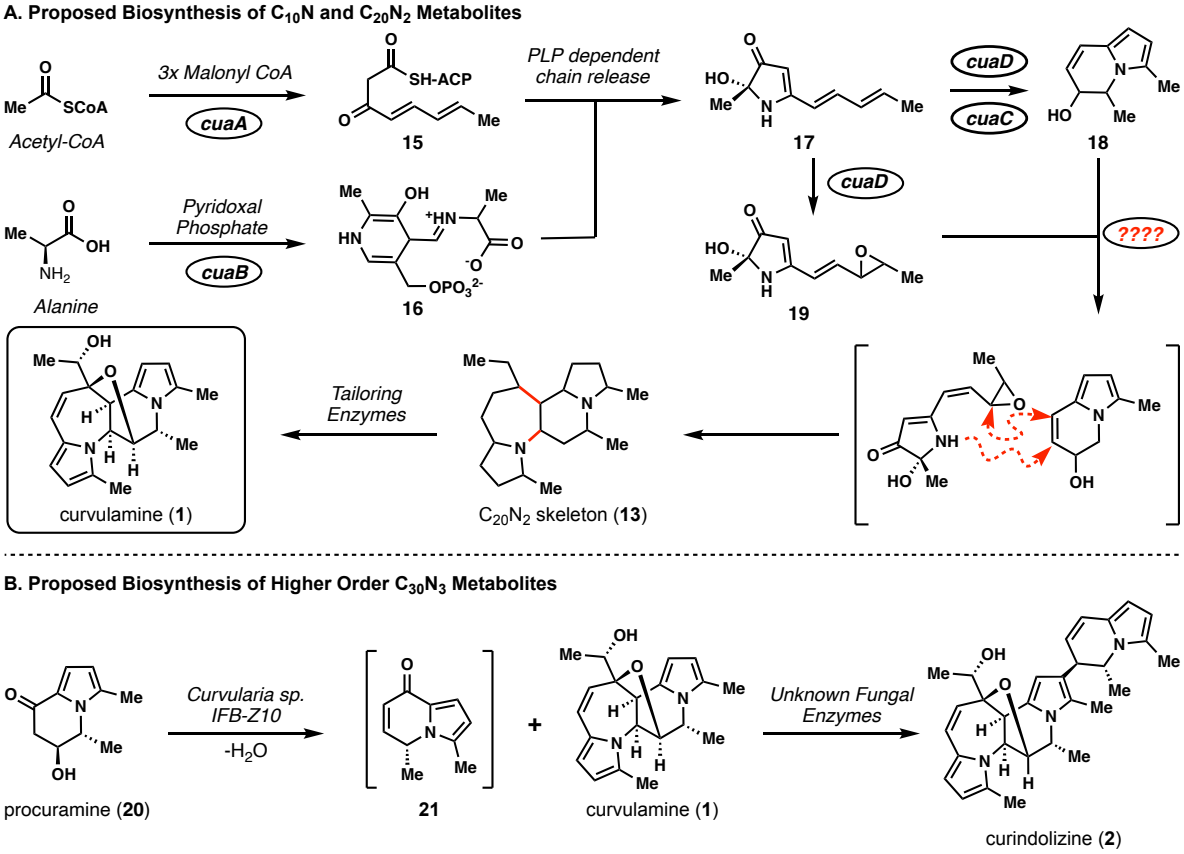


**Figure 1.2** Summary of biosynthetic studies on the curvulamine alkaloids. **1.2A**. Proposed biosynthesis of **1**. **1.2B**. Proposed biosynthesis of **2**.

## 1.2 Biological Activity of the Curvulamine-Type Alkaloids

| Compounds | *Veillonella parvula* | *Streptococcus* sp. | *Bacterioides vulgatus* | *Peptostreptococcus* sp. |
|---|---|---|---|---|
| curvulamine (**1**) | 0.37 | 0.37 | 0.37 | 0.37 |
| bipolamine A (**3**) | 4.20 | 8.40 | 8.40 | >10 |
| bipolamine D (**6**) | 2.87 | >10 | 5.74 | 5.74 |
| bipolamine E (**7**) | 0.73 | 2.92 | 2.92 | 5.85 |
| bipolamine F (**8**) | 3.52 | 3.52 | 3.52 | 3.52 |
| bipolamine G (**9**) | 0.32 | 0.32 | 0.32 | 0.32 |
| bipolamine H (**10**) | 0.35 | 2.94 | 1.47 | 2.94 |
| bipolamine I (**11**) | 1.53 | >10 | >10 | >10 |

**Table 1.1** Antibacterial activity (MICs in μM) of the curvulamine alkaloids.

Natural products have been employed throughout history for the treatment of various ailments and have been a rich source of potential drug candidates.[12-14] Natural products sourced from fungi, such as penicillin, have played an important role in modern medicine.[15] Particular focus has been paid to fungal symbionts because they produce secondary metabolites that promote the proliferation and survival of their hosts.[16-18] In 2014, Tan and co-workers discovered the fungal ectosymbiont *Curvularia* sp. IFB-Z10 in the gut of the white croaker, a marine organism that feeds on carrion. Evaluation of the fungal extracts against a broad range of bacterial strains revealed potent antibiotic activity against Gram-positive and negative bacteria. Upon further examination, the antibacterial activity observed on the crude extracts was attributed to the denitrogenated alkaloid curvulamine (**1**).[8] Isolated **1** was found to exhibit low micromolar minimum inhibitory concentrations (MICs) against *Veillonella parvula*, *Streptococus* sp., *Bacteroides vulgatus*, and *Peptostreptococcus* sp. (Table 1.1). In an antibacterial assay, **1** was shown to be more selective and potent than tinidazole, a prescribed antibiotic and anti-parasitic.[19,20]

Curindolizine (**2**), a metabolite also isolated from *Curvularia* sp. IFB-Z10 was also tested for antibacterial activity, but found to be inactive against the bacterial strains used in the curvulamine studies.[9] In a broader screen for biological properties, **2** was evaluated for anti-inflammatory activity using the Griess method, and gratifyingly displayed anti-inflammatory properties in lipopolyssacharide-induced RAW 264.7 macrophages by inhibiting nitric oxide production.[21] Nitric oxide is a signaling molecule heavily involved in the pathogenesis of inflammation. The antagonistic property of **2** extends to cytokines TNF-α, IL-1β, and IL-6, which are also involved in inflammation pathways in cells. It is worth noting that despite the structural similarities of curindolizine (**2**) with the rest of the curvulamine alkaloids, it is the only congener reported to exhibit anti-inflammatory activity.

To date, the precise mechanism of action of the *Curvularia* sp. IFB-Z10 and *Bipolaris*

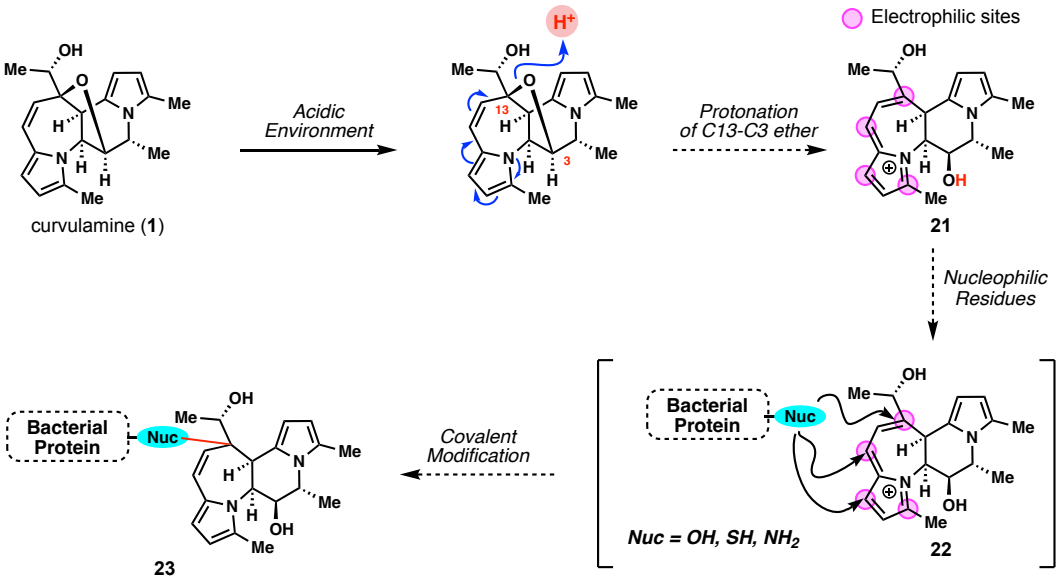


**Figure 1.3** Proposed mechanism of action of the curvulamine alkaloids.

*maydis* bioactive metabolites (**2-11**) is still unknown. It is possible that **1** and its congeners

bind to a protein pocket disrupting bacterial proliferation in a non-covalent mode of action, such is the case for the polyketide antibiotic erythromycin which stops the synthesis of bacterial proteins by blocking the nascent peptide exit tunnel (Figure 1.3).[22,23] Alternatively, one can also envision a covalent mode of action like β-lactams such as the antibiotic penicillin may be operative.[24,25] This mode of action would require reactive sites in **1** that can interact with protein residues. A cursory analysis of the structure of curvulamine (**1**) shows no electrophilic sites, however under conditions where the C13-C3 ether bridge is protonated and ionizes, several electrophilic sites could be unveiled. This newly formed intermediate (see **21**) could act as a covalent inhibitor in the presence of nucleophilic amino acid residues to form bacterial protein-small molecule complex **23** inhibiting bacterial proliferation (Figure 1.3). This hypothesis may explain the lack of bioactivity of bipolamine I (**11**), the only metabolite with a C-14–C-3 ether bridge, which would be unable to form electrophilic intermediate **21**.

Our total synthesis campaign was in part motivated by a desire to develop the tools necessary to carry a proper investigation on the biological targets of the curvulamine alkaloids and it will be discussed in greater detailed later in this chapter.

## 1.3 Distinctive Challenges in the Synthesis of Pyrrole-Containing Natural Products

Pyrroles are electron rich heterocycles with reduced aromatic character compared to benzene.[26-29] A combination of these two features define the pyrrole reactivity. This five-membered heterocycle can undergo oxidation via single electron processes, protonation in mild acidic conditions, facile attack by electrophilic reagents, and extrusion of benzylic leaving groups (Figure 1.4).[26] These processes can produce highly reactive cationic intermediates that readily polymerize or undergo side reactions in solution, greatly limiting the compatibility of many chemical transformations of synthetic targets containing pyrrole fragments. The pyrrole reactivity is increased when electron-donating substituents are present and attenuated with electron-withdrawing groups.

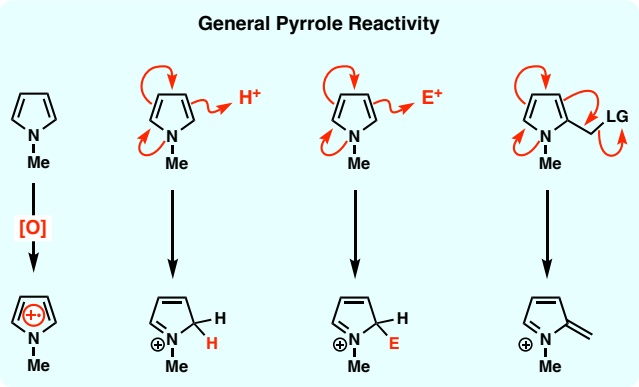


**Figure 1.4** Native pyrrole reactivity.

The curvulamine alkaloids contain a unique [5,7,6,5] tetracyclic core with two electron-rich pyrrole units that are particularly sensitive to oxidative and acidic reaction conditions (Figure 1.5). To overcome this challenge, historically a combination of deactivating groups or pyrrole surrogates are employed when attempting to synthesize this subgroup of alkaloids.[30] In the case of curvulamine (**2**), one of the pyrrole units can be masked as an aromatic 10π heterocycle, an observation which ultimately proved to be critical in the synthesis of this natural product.

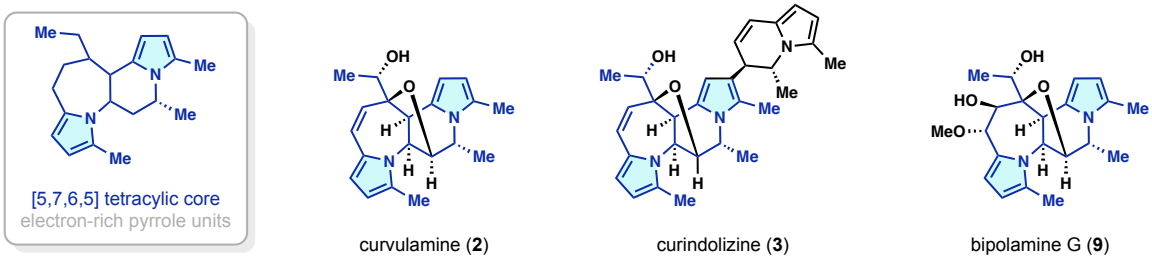


**Figure 1.5** Conserved structural features found in all curvulamine alkaloids.

## 1.4 The Total Synthesis of Curvulamine

The intricate structures and promising biological activities of the curvulamine alkaloids has attracted the attention of the scientific community and they have become appealing targets for synthetic organic chemists.[31-33] Our group has reported pioneering work in this area beginning with the first total synthesis of (–)-curvulamine (**1**)[34], followed by subsequent reports describing the total synthesis of curindolizine (**2**)[11] and four bipolamines.[35] In this chapter, we provide an overview of the synthesis of **1** which is intended to provide context for the subsequent chapters that will describe in detail the synthesis of four *Bipolaris maydis* metabolites (**6**,**7**,**9**,**11**) and curindolizine (**2**).

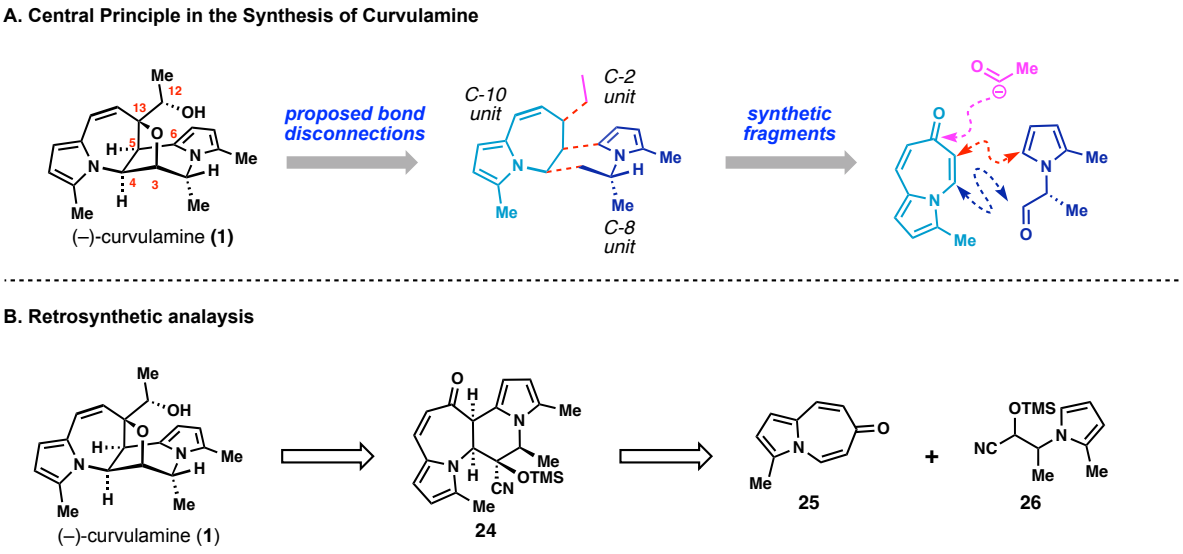


**Figure 1.6** Forays into the development of a strategy toward **1**. **1.6A**. Proposed bond disconnections and synthetic fragments. **1.6B**. Proposed retrosynthesis of **1**.

It was envisioned that **1** could be broken down into three smaller building blocks depicted in Figure 1.6. From the proposed bond disconnections between C-3–C4, C-5–C-6, and C-12–C-13, synthetic fragments that contained functional groups harboring potentially desirable reactivity could be identified. Retrosynthetically, curvulamine (**1**) was traced back to tetracycle **24** after various redox manipulations and removal of a two-

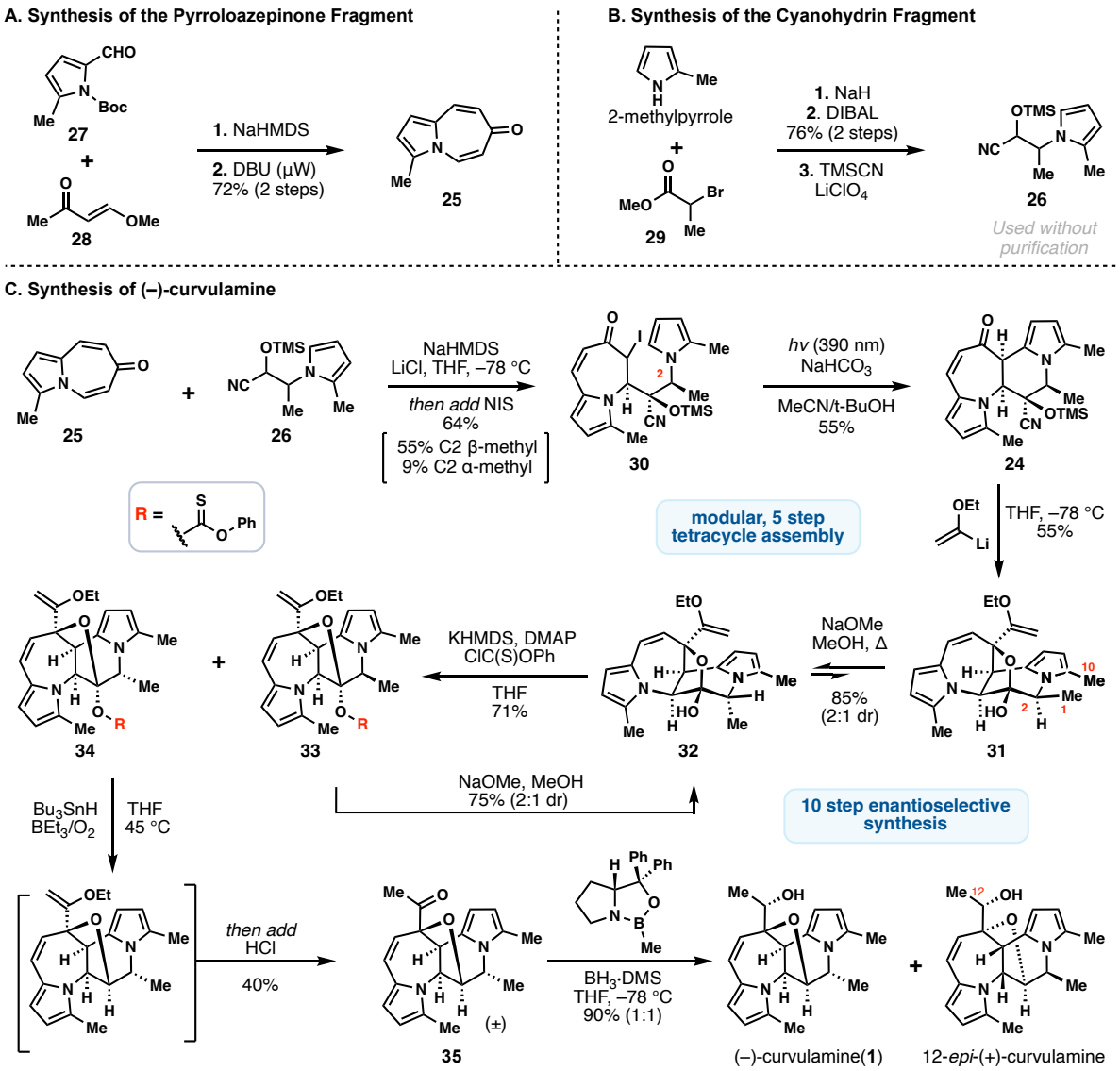


**Figure 1.7** The total synthesis of (–)-curvulamine (**1**). **1.7A**. Synthesis of pyrroloazepinone **25**. **1.7B**. Synthesis of cyanohydrin **26**. **1.7C**. Synthesis of **1**.

carbon unit. Tetracycle **24** in turn, could be disconnected to pyrrolo[1,2-a]azepin-7-one **25** and cyanohydrin **26** via a proposed Michael addition and annulation sequence. This convergent step allowed for an initial foray into the reactivity of nitrogen-containing heterocycle **25**, which will be further discussed in the following chapter.

The synthesis began with the preparation of the pyrrole containing fragments **25** and **26**. The pyrrolo[1,2-a]azepin-7-one **25** fragment was elaborated in two steps. First,

pyrrolecarbaldehyde **27** and (*E*)-4-methoxybut-3-en-2-one (**28**) were joined via an aldol condensation, followed by microwave irradiation of the resulting enone to illicit cyclization. An expedient three-step sequence was developed to synthesize cyanohydrin **26** beginning with nucleophilic substitution of methyl 2-bromopropanoate (**29**) with the metal salt of 2-methyl pyrrole. Then DIBAL reduction of the methyl ester gave an intermediate aldehyde which was reacted with TMSCN in the presence of $LiClO_4$ to give **26**, which was immediately used without further purification. These two fragments were coupled by deprotonation of **26** with NaHMDS to form the sodium anion which, in the presence of LiCl, underwent selective addition to pyrrolo[1,2-a]azepin-7-one **25** aided by lithium chloride. This Michael type addition afforded a product with the desired positional selectivity in moderate yields forging the first C-C bond in the planned annulation strategy. Recognizing that an oxidative process was required to realize the second key bond formation in the annulation, the enolate formed after the 1,4 addition was quenched with NIS to give enone **30** in a combined 64% yield. While this reaction favored the undesired configuration at the C-2 stereocenter, this was addressed later in the synthesis. Simple irradiation of **30** with a 390 nm light source in the presence of a polar protic solvent promoted the cyclization event yielding tetracycle **24**. Treatment of **24** with excess ethyl vinyl ether lithiate produced **31** with the desired formal acyl addition in 55% isolated yield. As previously stated, the methyl bearing stereocenter C-2 needed to be epimerized and lactol **31** offered such opportunity. Conformational analysis suggested that allylic 1,3-strain between the methyl groups at C-1 and C-10 could be minimized with axial positioning of the C-1 methyl group providing the desired configuration. Heating **31** with sodium methoxide in methanol yielded a 2.3:1 thermodynamic mixture of lactols favoring the desired isomer **32** in 85% yield. At this stage, the last hurdle to overcome was the removal of the hydroxyl group at the bridgehead position, which was accomplished in two steps. First, lactols **31** and **32** were deprotonated with KHMDS and subsequent acylation of the resulting anion with ClCSOPh in the presence of DMAP, generated a separable mixture of thiocarbonate epimers **33** and **34**. Then, Barton-McCombie deoxygenation under mild heating with concomitant enol ether hydrolysis during acidic workup afforded methyl ketone **35**. Finally, stereodivergent reduction of the methyl ketone **35** with (*R*)-2-methyl-CBS-oxazaborolidine and $BH_3$•DMS afforded a separable 1:1 mixture of curvulamine (**1**) and epi-curvulamine with 97% yield and 95% ee respectively. In summary, the first total synthesis of (-)-curvulamine (**1**) was accomplished in a total of 10 steps from commercially available materials.

### 1.5 Aims for the Pursuit of the Cuvulamine Alkaloids

Alkaloids have long captured the attention of the synthetic community due to their intriguing chemical architectures and promising biological activities.[13] Pyrrole-containing alkaloids exhibit a broad range of bioactivities, and their structural complexity present a noteworthy challenge for the practitioners of total synthesis.[30] Among the many families of alkaloids, natural products containing electron-rich pyrroles represent an underexplored family for which limited established strategies and methodologies exist. As a result, chemists must often devise novel approaches for the construction of such

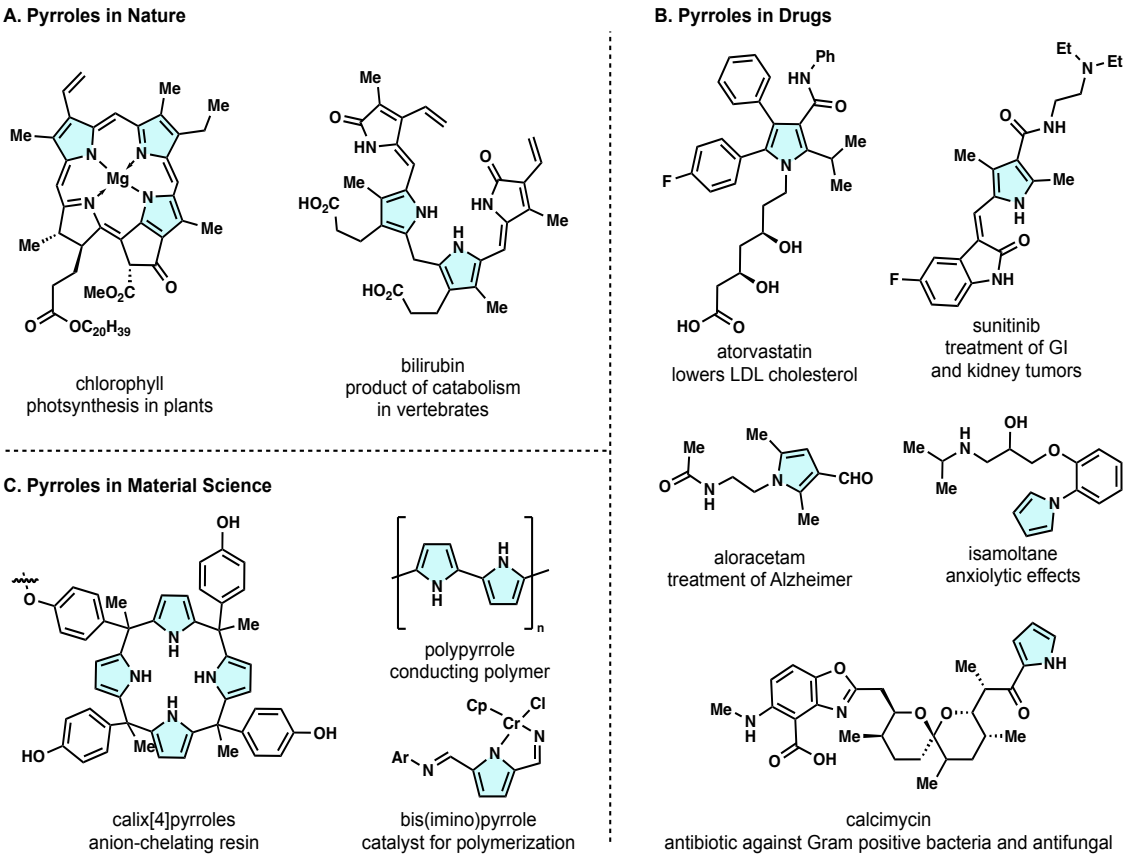


**Figure 1.8** Applications of pyrroles to different scientific areas. **1.8A**. Pyrroles found in nature. **1.8B**. Pyrroles in commercial drugs.**1.8 C**. Applications of pyrroles in material science.

complicated frameworks, triggering the development of new methods and synthetic strategies to access various types of pyrrole scaffolds. Due to the paramount importance of the pyrrole nucleus in multiple chemical applications (Figure 1.8), new synthetic methods to access these nitrogenated heterocycles is essential.[26,27,36,37] We aimed to use our pursuit of the total synthesis of the curvulamine alkaloids as a platform to explore novel chemistries and strategies to access electron rich natural products and functionalized pyrroles.

Preliminary studies on the biological properties of these secondary metabolites have revealed antibiotic or anti-inflammatory properties with MICs in the low micromolar range (*vide supra*). Low isolation yields have so far prevented testing against a wider range of pathogens. Our aim is to improve upon our pioneering synthesis of curvulamine to allow for a scalable and unifying strategy to access all the curvulamine alkaloids, with the end goal of performing a comprehensive evaluation of their biological activities. We also plan in due time, to investigate the antibiotic mode of action of curvulamine (**1**) and bipolamines (**2**-**11**). The synthesis of an alkyne-functionalized curvulamine or bipolamine derivative will enable us to perform isotopic tandem orthogonal proteolysis-activity based protein profiling (isoTOP-ABPP).[38] We predict that advanced proteomics will aid our goal of

gaining a fundamental understanding of the antimicrobial mechanism of action of these interesting metabolites.

## 1.6 Conclusion

The aim of this chapter is to provide a fundamental understanding of the curvulamine alkaloids and a framework of knowledge for subsequent chapters. The following chapters will discuss in greater detail our strategies, obstacles and solutions that ultimately culminated in the syntheses of curindolizine (**2**) and four *Bipolaris maydis* metabolites: bipolamines C,D,G, and I. It is also the goal of this dissertation to document the chemical reactivity and unique findings obtained in our campaign to synthesize these intriguing natural products.

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*Chapter 2*

# The Synthesis of Novel Pyrrolo[1,2-a]azepin-7-ones and the Total Synthesis of (+)-curindolizine

## 2.1 Introduction

The first part of this chapter will elaborate on the background development and the plausible mechanism of a microwave-induced method used to synthesize substituted pyrrolo[1,2-a]azepin-7-ones, an underexplored family of aromatic heterocycles. In addition, a description of the scope of this method will be provided as well as a brief discussion on some of the applications of pyrrolo[1,2-a]azepin-7-ones in the context of drug discovery. The remainder of the chapter will disclose our findings from exploring an initial biomimetic approach toward curindolizine (**2**) and the lessons we learned from this initial approach. Lastly, this chapter will recount the synthetic strategy used to realize the first total synthesis of curindolizine (**2**).

## 2.2 Forays into a Microwave-Induced Synthesis of New Pyrrolo[1,2-a]azepin-7-ones

During our synthetic investigations toward curvulamine (**1**)[1], we were required to synthesize large quantities of pyrrole[1,2-a]azepin-7-one **25**. Initially, a 3-step procedure, inspired from the work of Radley and co-workers, was applied to the synthesis of 5,7-fused bicycle **36** (Figure 2.1A).[2] First, intramolecular conjugate addition of pyrrole-2-carboxaldehyde (**37**) onto methyl vinyl ketone **38** produced Michael addition product **39** in good yield using $K_2CO_3$ in DMF. Then, methyl ketone **39** was heated to reflux under basic conditions (NaOEt, EtOH) to provide a separable mixture of aldol condensation products **36** and **40** in a combined 71% yield. Finally, **41** was obtained after oxidation of

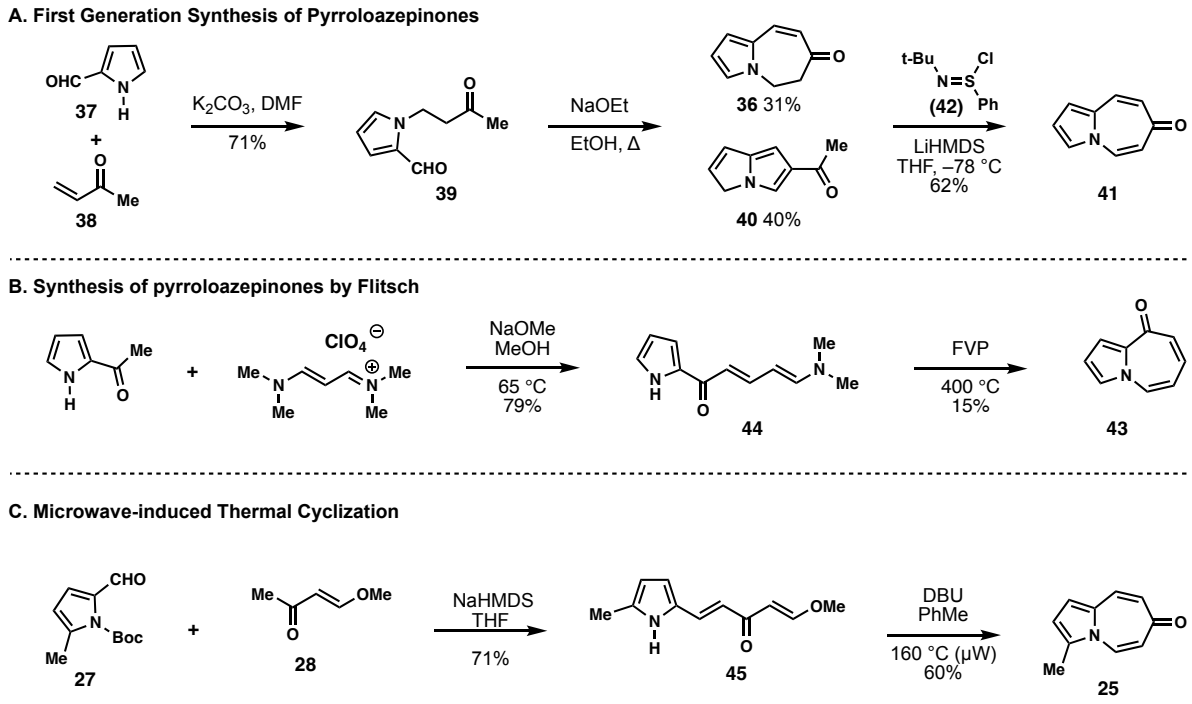



**Figure 2.1** Investigations into the synthesis of pyrrolo[1,2-a]azepin-7-ones. **2.1A** Pioneering studies by Radley and co-workers. **2.2B** Studies by Flitsch and co-workers**. 2.1C** Microwaved-induced synthesis of **25**.

the lithium enolate of **36** with Mukaiyama's reagent (**42**).[3,4] This approach was not implemented during the synthesis of **1** because of the lack of selectivity in the aldol condensation step. In 1988, Flitsch reported the synthesis of analogous pyrroloazepinone **43** from vinylogous amide **44** using flash vacuum pyrolysis (FVP).[5,6] In analogy to the work of Flitsch, a straightforward alternative was developed that used Boc-protected pyrrole-2-carboxaldehyde (**27**) as the starting material (Figure 2.1C). An intermolecular aldol condensation was performed after addition of the sodium enolate of (*E*)-4-methoxybut-3-en-2-one (**28**) to **27** which gave enone **45** in 71% yield (NaHMDS, THF). Notably, concomitant Boc deprotection was observed which presumably occurred via a transesterification-type reaction of the initial aldol addition with the Boc-carbamate group followed by an E1cB reaction to generate enone **45**. Microwave-induced thermal cyclization of **45** in the presence of base proceed to give pyrrolo[1,2-a]azepin-7-one **25** in 60% yield (DBU, PhMe, 160 °C). While several mechanisms could be proposed for this transformation, based on the identification of (*Z*)-**45** during reaction, we hypothesized that this cyclization process could be occurring via two mechanisms. In one possible scenario, **25** could be formed after a conjugate addition of the pyrrole unit into the vinylogous ester followed by extrusion of methoxide via an E1cB reaction. Another possible mechanism

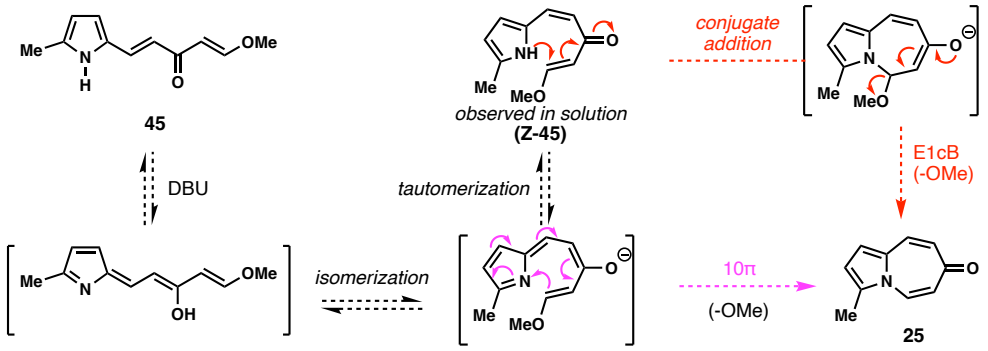



**Figure 2.2** Proposed mechanism for the synthesis of **25** from **45**.

involves a concerted 10π electrocyclic ring closing reaction with concomitant elimination of methoxide to yield cyclized product **25**.

Substituted pyrrolo[1,2-a]azepin-7-ones have been employed in drug discovery, particularly in oncology and neuroleptic research.[7,8] Given the limited number of existing methods to synthesize pyrroloazepinones,[6,9-11] we investigated the application of this microwave-induced cyclization to synthesize novel pyrrolo[1,2-a]azepin-7-ones (Figure 2.3). We initially examined the synthesis of pyrroazepinones bearing different aryl groups (**46**-**48**). Compounds **46**-**48** were prepared in three steps. First. Suzuki coupling ($Pd(dppf)Cl_2$•DCM, $K_2CO_3$) of iodopyrrole **49** with an aryl substituted boronic acid gave the corresponding coupling products **50**-**52** in good yields. Second, the coupling products were subjected to a base-mediated intermolecular aldol condensation (NaHMDS,THF) with vinylogous ester **28** yielding enones **53**-**55**. Third, microwave irradiation (DBU, μW) of **53**-**55** gave monosubstituted pyrroloazepinones **46**-**48** in excellent yields. Encouraged by these initial results, we synthesized disubstituted pyrrole **56** from methyl pyrrole **57** by means of a Vilsmeier-Haack formylation and Boc protection sequence (Oxalyl chloride, DMF *then* $Boc_2O$, THF). Aldol condensation of the sodium enolate of **28** and **56** produced

enone **58** in 73% yield using NaHMDS in THF. Thermal cyclization of **58** proceeded to give the corresponding pyrroloazepinone **59** in 52% yield (DBU, μW). We extended the screening investigations of this method to the synthesis of more complex heterocycles such as **60** and **61**. Cyclization precursor **62** was expediently prepared from tetrahydroindole **63** after formylation (*t*-BuLi, DMF), Boc protection, and addition of the enolate of **28** to intermediate **64** (NaHMDS, THF). Indole **65** was made in two steps: first, regioselective formylation of **66** generated aldehyde **67** ($POCl_3$, DMF), second, an aldol addition of the sodium enolate of **28** to **67** (NaHMDS, THF). Both tetrahydrindole **62** and indole **65** underwent microwave-induced thermal cyclization (DBU, μW) to give **61** and **60**, respectively albeit with diminished yields. Lastly, we sought to demonstrate that

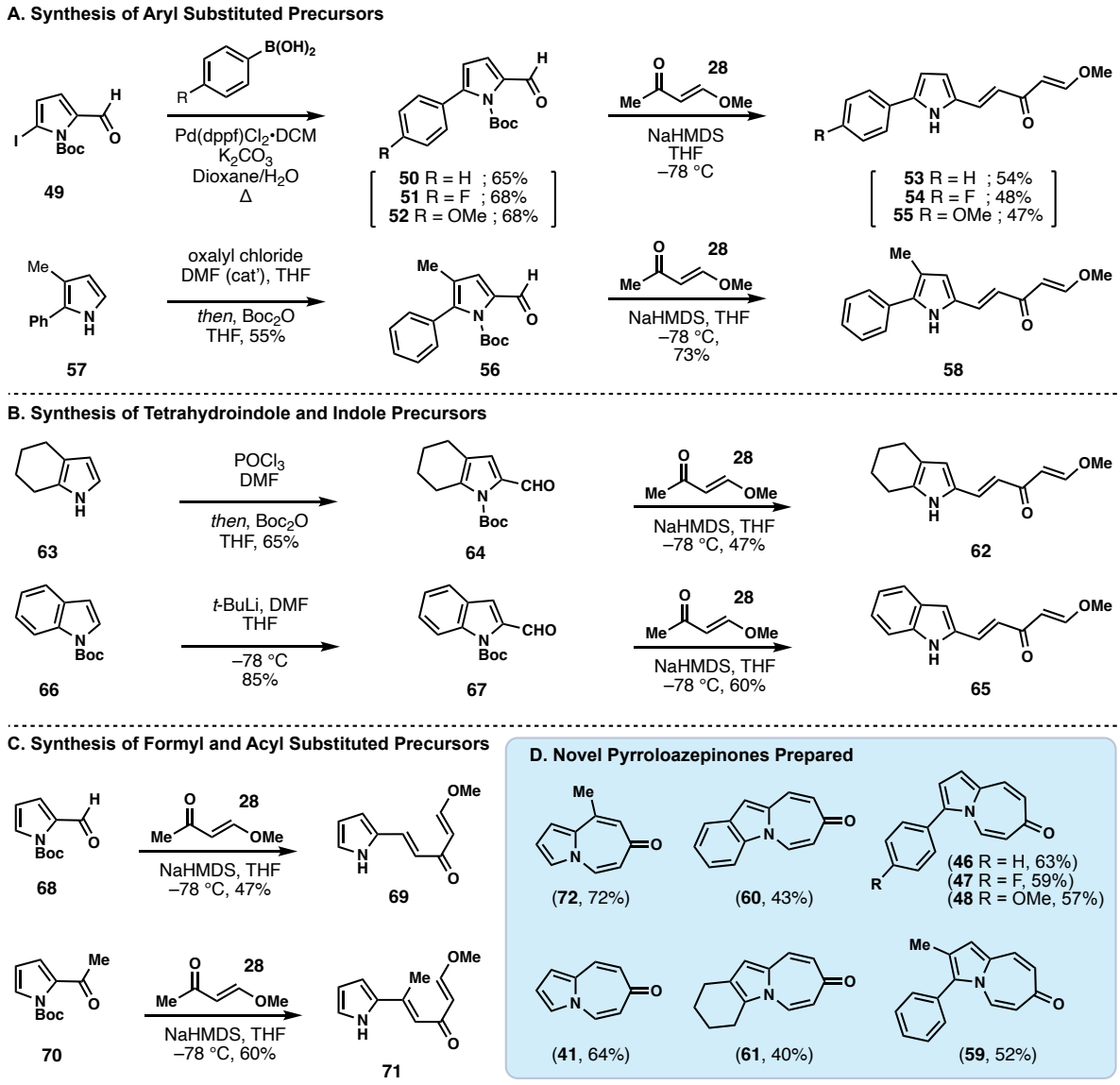



**Figure 2.3** Scope of microwave-assisted cyclization. **2.3A.** Synthesis of aryl substituted pyrroles. **2.3B.** Synthesis of tetrahydroindolizine and indolizine substrates. **2.3C.** Synthesis of simple pyrroles. **2.3D.** Microwave-assisted cyclization products and isolated yields.

pyrroles substituted with aldehydes and ketones were suitable substrates to prepare pyrroloazepinones. Pyrrolecarboxaldehyde **68** was used to make vinylogous ester **69** (NaHMDS, THF), and microwave irradiation of **69** in the presence of DBU yielded pyrroloazepinone **41**. We also observed that methyl ketone **70** could be transformed into intermediate **71**, which underwent smooth cyclization to **72** in 72% yield (DBU, μW). In summary, the broad scope of this methodology illustrates its applicability to synthesize diverse pyrroloazepinones, scaffolds of potential importance in drug discovery.[12-14]

### 2.3 Bioinspired Route Toward Curindolizine

After securing a 10-step route to curvulamine (**1**),[1] we decided to embark on a total synthesis campaign toward curindolizine (**2**), the most complex *Curvularia* sp. IFB-Z10 secondary metabolite. **2** was serendipitously isolated from a large-scale cultivation broth of the *Curvularia* sp. fungus, and surprisingly was observed to be produced by the fungus preferentially over curvulamine (**1**). Motivated by this observation, Tan and co-workers investigated the biosynthetic origin of curindolizine (**2**).[1,15,16] During these investigations procuramine (**72**) was isolated from the fungal cultivation broth, and interestingly, when **1** and **72** were added to the cell lysate containing the fungal proteins, curindolizine (**2**) was subsequently detected. This led to the researchers to concluded that curvulamine (**1**) was a precursor of curindolizine (**2**). The Tan group proposed a biosynthetic process where an enzymatic coupling between **1** and **73** (an intermediate derived from **72**) followed by additional enzymatic transformations ultimately yields curindolizine (**2**) (Figure 2.4).[16] It is worth noting that while enzymes capable of promoting these reactions are suspected to be expressed by the fungus, Tan and co-workers did not perform sequencing experiments to identify the proteins responsible for producing **2**.[17-19]

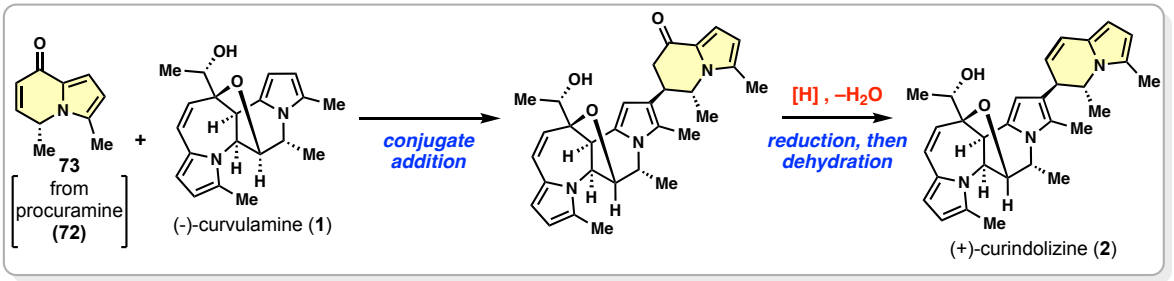
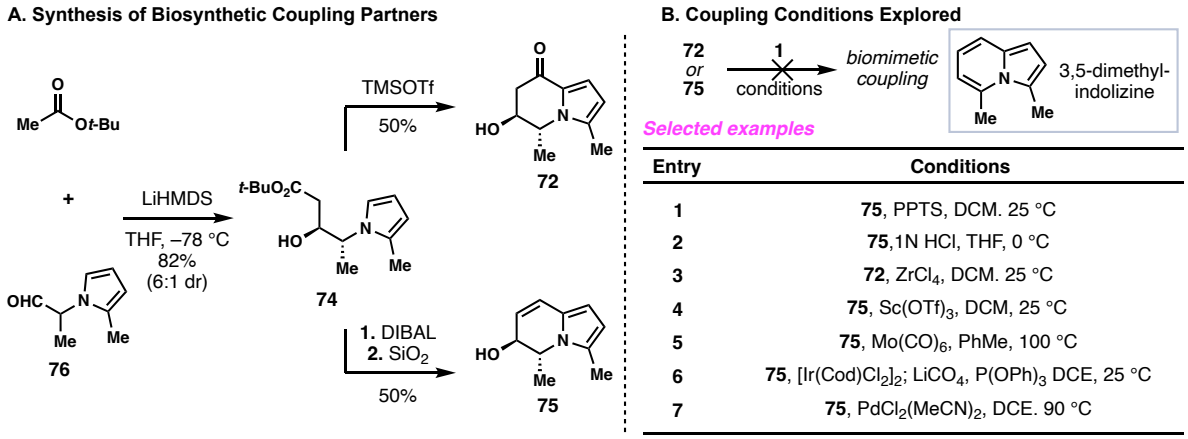



**Figure 2.4** Proposed biosynthesis of curindolizine (**2**).

Inspired by the way nature might synthesize curindolizine (**2**),[16] we aimed to develop a synthetic plan to access electrophilic units analogous to enone **73**, which we would then couple with curvulamine (**1**). To this end we devised simple chemistry to first synthesize *tert*-butyl ester **74** and then transform **74** into ketone **72** and allylic alcohol **75**. A base-catalyzed aldol reaction between the lithium enolate of *tert*-butyl acetate (LiHMDS, THF) and **76** generated ester **74** in a 6:1 diastereomeric ratio and combined 82% yield. Friedel-Craft acylation of **74** under mild conditions (TMSOTf) generated procuramine (**72**) in good yields. Ester **74** underwent DIBAL-mediated reduction to generate an intermediate aldehyde, which cyclized and dehydrated upon treatment with $SiO_2$ to yield allylic alcohol **75**. With synthetic routes to **72** and **75**, we proceeded to screen for conditions to couple

these units to curvulamine (**1**) (Figure 2.5B). Acid-catalyzed allylic substitution of **75** with curvulamine (**1**) in the presence of Brønsted acids PPTS (entry 1) or HCl (entry 2) failed to give curindolizine (**2**); instead, we only observed formation of 3,4-dimethyl-indolizine. Screening different Lewis acids such as $ZrCl_4$ (entry 3), $Sc(OTf)_3$ (entry 4), $Mo(CO)_6$ (entry 5) also failed to give any detectable amount of curindolizine (**2**); under these conditions curvulamine (**1**) and 3,4-dimethyl-indolizine were detected.[20,21] Inspired by the work of Hartwig and co-workers, we attempted an iridium-mediated allylic substitution of **75** with curvulamine (**1**), but only **1** was recovered.[22,23] Lastly, we subjected **75** to Tsuji-Trost conditions in an attempt to form a π-allyl complex which could be intercepted by **1**, but we failed to observe any desired product.[24,25] In the face of these unfortunate results, we moved to explore nonbiomimetic approaches to access the complex alkaloid **2**.




| Entry | Conditions |
|---|---|
| 1 | **75**, PPTS, DCM. 25 °C |
| 2 | **75**,1N HCl, THF, 0 °C |
| 3 | **72**, $ZrCl_4$, DCM. 25 °C |
| 4 | **75**, $Sc(OTf)_3$, DCM, 25 °C |
| 5 | **75**, $Mo(CO)_6$, PhMe, 100 °C |
| 6 | **75**, $[Ir(Cod)Cl_2]_2$; $LiCO_4$, $P(OPh)_3$ DCE, 25 °C |
| 7 | **75**, $PdCl_2(MeCN)_2$, DCE. 90 °C |

**Figure 2.5** Investigations toward a bioinspired synthesis of **2**. **2.5A** Syntheses of coupling partners. **2.5B.** Selected coupling conditions explored.

## 2.4 Revised Approach Toward the Synthesis of Curindolizine

The rational solution to our problem was to install a handle on the eastern pyrrole and then investigate conditions for C-C bond-forming reactions. With that goal in mind, we explored conditions for a regioselective halogenation of **1** and **35**. Halogenation of **1** with NBS in DCM resulted on an intractable mixture of products and halogenation of methyl ketone **35** proceed to give **76** as the single product (NIS, MeOH).

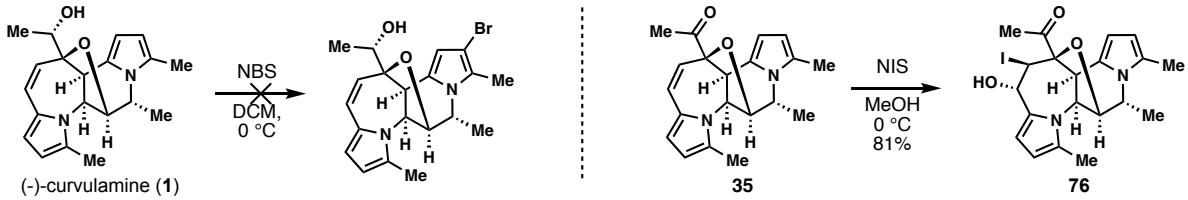



**Figure 2.6** Studies on the halogenation of curvulamine (**1**) and methyl ketone **35**

Computational studies were performed on **35** to further understand the observed regioselectivity during the halogenation reaction. First, a conformational search on

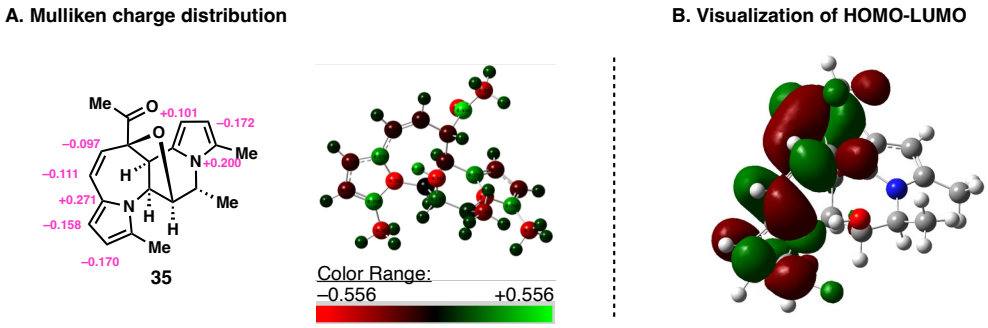
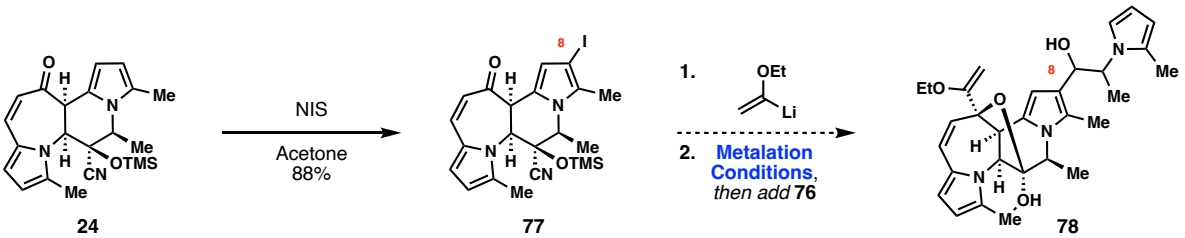



**Figure 2.7** Computational studies on **35**. **2.6A** Mulliken values of **35**. **2.6B** The frontier orbitals of **35**.

Maestro was performed on **35** to find its low-energy conformers. Then, a density functional theory computational analysis was performed on the lowest-energy conformation to calculate the vibrational frequencies in the gas phase at B3LYP/6-31G(d,p) level of theory. A population analysis in Gaussian provided us with the Mulliken values as well as information on the frontier orbitals (HOMO-LUMO) of **35** (Figure 2.7). The Mulliken partial charges (Figure 2.7A) indicates a higher electron density in the western pyrrole compared to the eastern pyrrole; and a visual representation of the frontier molecular orbitals in **35** (Figure 2.7B), shows they are located on the western pyrrole. Therefore, we hypothesize that the observed regioselectivity of the halogenation reaction might be controlled by electronic effects.[26,27]

To overcome this regioselectivity challenge, we hypothesized that an intermediate with a deactivated western pyrrole, might undergo halogenation with the desired regioselectivity. Tetracycle **24** was identified as a suitable candidate to explore this hypothesis. The western pyrrole of **24** is conjugated to an electron-withdrawing group while the eastern pyrrole only has electron-donating substituents. Gratifyingly **24** underwent clean regio- and chemoselective iodination to give **77** in 88% yield (NIS,




| Entry | Metalation Conditions | Product |
|---|---|---|
| 1 | *t*-BuLi, THF, –78 °C | **31** |
| 2 | KHMDS, then t-BuLi, –78 °C | **31** |
| 3 | *i*PrMgCl•LiCl, THF, –78° C | r.s.m. + **31** |
| 4 | *t*-BuLi, then $ZnBr_2$, THF, –78 °C | **31** |
| 5 | $CrCl_2$, $NiCl_2$, DMF, 25 °C | r.s.m. + **31** |

**Figure 2.8** Early investigation of the synthesis of curindolizine(**2**) from iodide **77**

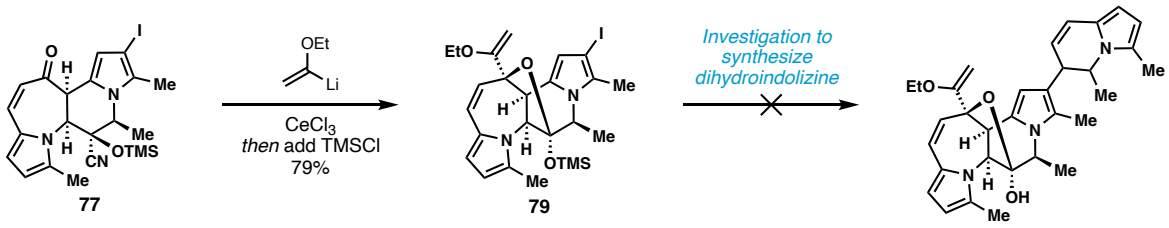



**Figure 2.9** Studies to utilize pentacycle **79** to elaborate curindolizine (**2**).

Acetone). As anticipated, the more electron rich pyrrole preferably reacts with NIS and halogenates the position with the higher electron density on the eastern pyrrole.

Having secured a practical route to iodide **77**, we proceeded to continue our investigations toward the synthesis of curindolizine (**2**). The dihydroindolizine unit at C-8 was envisioned to be derived from **78**, which in turn could be made from iodide **77** in two steps. Addition of ethyl vinyl lithiate gave the corresponding product lactol product, but subsequent lithium-halogen exchange with *t*-BuLi followed by addition of the aldehyde electrophile gave reduction product **31** instead of **78** (entry 1). The observed product **31** was believed to be formed after the protonation of the organolithiate with the lactol proton.

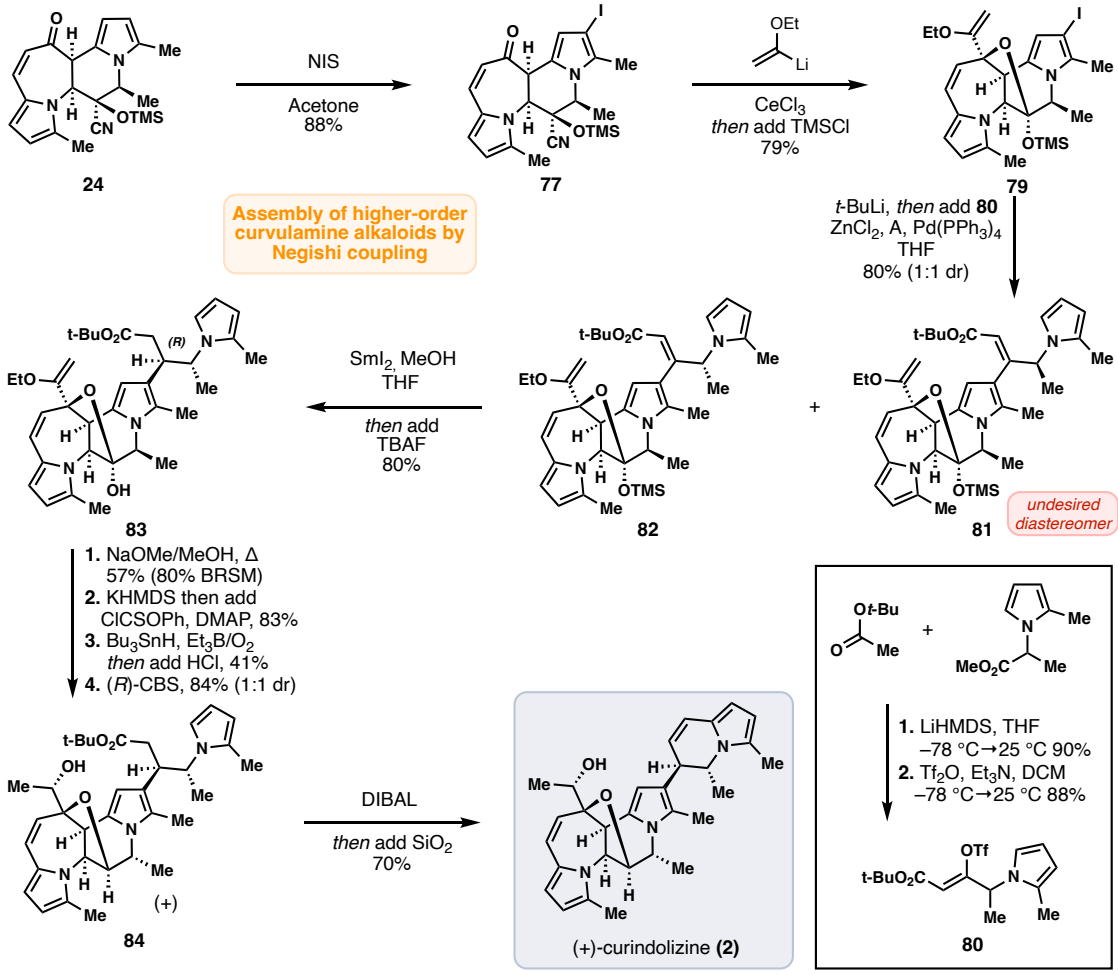



**Figure 2.10** Total synthesis of curindolizine (**2**).

To avoid this, the lactol was deprotonated prior the lithium-halogen exchange (entry 2). Unfortunately, the same reduction product **31** was isolated. Magnesium-halogen exchange using Turbo Grignard at cryogenic temperatures followed by addition of the electrophile gave a mixture of **31** and recovered starting material (entry 3). To explore other organometallic substrates, an organozinc was produced after transmetalation of the organolithiate with $ZnBr_2$; addition of the organozinc reagent to aldehyde (**76**) resulted in the isolation of lactol **31**. We rationalized that even after the deprotonation of the lactol such as in entry 2, the acidic alpha positions of the resulting ketone could still quench the organolithiate. To circumvent this problem, TMS protected lactol **79** was prepared after a $CeCl_3$-assited addition of ethyl vinyl ether lithiate to **77** followed by *in situ* silylation. Lithium-halogen exchange of **79** with *t*-BuLi followed by addition of **76** proceed smoothy to give the desired 1,2 addition product. Unfortunately, all attempts to elaborate this intermediate to the desired indolizine product were met with failure.

Next, we explored palladium-catalyzed reactions to utilize pyrrole **79** to complete the synthesis of curindolizine (**2**). Lithium-halogen exchange of **79** followed by $ZnCl_2$-mediated transmetalation gave the corresponding organozinc reagent, which underwent Pd-catalyzed Negishi coupling with **80** to yield a mixture of diastereomers **81** and **82** in 80% combined yield. The desired diastereomer **82** could be converted to ester **83** after a stereoselective reduction with $SmI_2$ and silyl ether deprotection. NOESY experiments confirmed the desired relative stereochemistry between this newly formed stereocenter and the vicinal methyl group. Racemic **83** was converted to enanotiopure **84** in four steps: first, base mediated thermodynamic isomerization of the C-2 stereocenter (NaOMe, MeOH); second, thiocarbamate formation (KHMDS, ClSOPh, DMAP); third, Barton McCombie deoxygenation ($Bu_3SnH$, $Et_3B$, $O_2$); and fourth, a CBS reduction ($BH_3$•DMS, (*R*)-CBS catalyst). Based on our previous experiments in the preparation of **75**, DIBAL reduction of ester **84** gave an aldehyde which cyclized and dehydrated in the presence of $SiO_2$ to yield (+)-curindolizine (**2**) in 70% yield.

## 2.5 Conclusions

In this chapter, we have documented the result of our investigations on the mechanism and substrate scope of a microwave-induced method to access pyrroloazepinones. We have demonstrated the broad range of substrates that could be used in this transformation with the goal of enabling its implementation in areas such as drug discovery. Lastly, we have chronicled the first total synthesis of curindolizine (**2**), the only trimeric and most structurally complex curvulamine-type alkaloid.

## 2.6 Distribution of Credit and Acknowledgements

Pioneering studies into the microwave-assisted thermal cyclization were performed by Karl Thomas Haelsig and Jun Xuan. The investigation and synthesis **41**-**72** were performed by Paulo Andre Machicao Tello with refinement from Professor Thomas J. Maimone. The synthesis of **2** was spearheaded by Jun Xuan. Characterization of all compounds was completed by Paulo Andre Machicao Tello, Karl Thomas Haelsig, and

Jun Xuan. We thank the NIH NIGMS (R01GM136945 to Thomas J. Maimone, and diversity supplement to Paulo Andre Machicao Tello) for financial support. We thank Dr. Hasan Celik and Dr. Jeffrey G. Pelton for nuclear magnetic resonance spectroscopic assistance (NIH grant GM68933). We also thank QB3/Chemistry Mass Spectrometry Facility scientist Dr. Zhongroui Zhou for mass spectrometry assistance.

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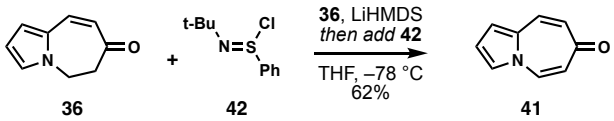
## 2.8 Experimental Procedures and Characterization Data

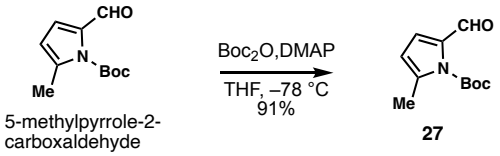
### 2.8.1 General Procedures

All reactions were performed in flame- or oven-dried glassware under a positive pressure of nitrogen or argon, unless otherwise noted. Air-and moisture-sensitive liquids were transferred via syringe. When indicated, solvents or reagents were degassed by sparging with argon for 10 min in an ultrasound bath at 25 °C. Volatile solvents were removed under reduced pressure rotary evaporation below 35 °C. Analytical and preparative thin-layer chromatography (TLC) were performed using glass plates pre-coated with silica gel (0.25-mm, 60-Å pore size, Merck TLC Silicagel 60 $F_{254}$) impregnated with a fluorescent indicator (254 nm). TLC plates were visualized by exposure to ultraviolet light (UV) and then were stained by submersion in an ethanolic anisaldehyde solution or ceric ammonium molybdate solution, followed by brief heating on a hot plate. Flash column chromatography was performed with silica gel purchased from Silicycle (SiliaFlash®, 60 Å, 230-400 mesh, 40-63 µm). Ethyl vinyl ether and 2-bromopropanic acid methyl ester were distilled over calcium hydride prior to use. NaHMDS solutions were purchased from Sigma. All other reagents were used as received from commercial sources, unless stated otherwise. Anhydrous tetrahydrofuran (THF), dichloromethane (DCM), methanol (MeOH), dimethylformamide (DMF), and toluene (PhMe) were obtained by passing these previously degassed solvents through activated alumina columns. Proton nuclear magnetic resonance ($^{1}$H NMR) spectra and carbon nuclear magnetic resonance ($^{13}$C NMR) spectra were recorded on Bruker AV-600 spectrometer at 23 °C. Proton chemical shifts are expressed as parts per million (ppm, δ scale) and are referenced to residual solvent ($CDCl_3$: δ 7.26, $C_6D_6$: δ 7.16), unless stated otherwise. Carbon chemical shifts are expressed as parts per million (ppm, δ scale) and are referenced to the solvent ($CDCl_3$: δ 77.16, $C_6D_6$: δ 128.06), unless stated otherwise. Data is represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, dd = doublet of doublets, ddd, doublet of doublet of doublet, dt = triplet of doublets, t = triplet, q = quartet, m = multiplet, br = broad), coupling constant (*J*) in Hertz (Hz), and integration. Infrared (IR) spectra were recorded on a Bruker Alpha FT-IR spectrometer as thin films and are reported in frequency of absorption ($cm^{-1}$). Only selected resonances are reported. High-resolution mass spectra (HRMS) were obtained by the mass spectrometry facility at the University of California, Berkeley using a Finnigan LTQFT mass spectrometer (Thermo Electron Corporation). X-ray diffraction data was collected at the Small Molecule X-ray Crystallography Facility (CheXray) at University of California, Berkeley using a Rigaku XtaLAB P200 equipped with a MicroMax 007HF rotating anode and Pilatus3 R 200K-A hybrid pixel array detector. Data were collected using CuKα radiation (λ = 1.5418 Å).

### 2.8.2 Experimental Procedures and Tabulated Characterization Data

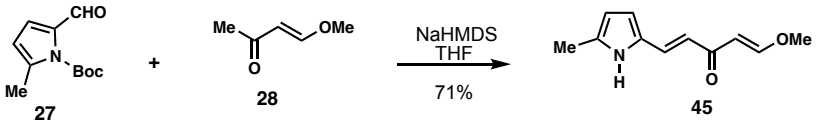



**Pyrroloazepinone 41:** Enone **36** (2.52 g, 17.1 mmol, 1.0 equiv.) was transferred (in benzene) to a 250 mL round bottom flask and was concentrated to dryness *in vacuo*. The 250 mL round bottom flask was then sealed, evacuated, and back filled with nitrogen (3x). The sealed flask was charged with THF (70 mL), and cooled to –78 °C. LiHMDS (1.0 M in THF, 20.4 mL, 20.4 mmol, 1.2 equiv.) was added dropwise, and the resulting suspension was stirred for 30 min at –78 °C. In a separate flask, Mukaiyama's reagent **42** (4.04 g, 18.8 mmol, 1.1 equiv.) was azeotropically dried with benzene (3x) and then dissolved in THF (10 mL) under an atmosphere of nitrogen. The solution was then transferred via cannula to the reaction mixture, with an additional THF (5 mL) rinse ensuring quantitative transfer. Upon completion of the consumption of **36** as indicated by TLC, the reaction was quenched with saturated *aq.* $NaHCO_3$ (50 mL). The solution was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over $Na_2SO_4$, filtered, and concentrated *in vacuo* to afford a brown residue. The resulting crude residue was purified by column chromatography (15% EtOAc in hexanes→ 35% EtOAc in hexanes) to afford **41** (1.53 g, 10.5 mmol, 62%) as a yellow solid. **TLC:** $R_f$ = 0.5 (40% EtOAc in hexanes); **$^1$H NMR** (600 MHz, $C_6D_6$) δ 6.39 (d, *J* = 12.3 Hz, 1H), 6.21 (dd, *J* = 12.3, 2.3 Hz, 1H), 6.13 (t, *J* = 2.3 Hz, 1H), 6.10 (dd, *J* = 3.9, 1.6 Hz, 1H), 6.02 (d, *J* = 10.4 Hz, 1H), 5.98 (t, *J* = 3.3 Hz, 1H), 5.69 (dd, *J* = 10.4, 2.4 Hz, 1H); **$^{13}$C NMR** (151 MHz, $C_6D_6$) δ 186.4, 132.7, 128.7, 127.6, 126.3(2C), 118.1, 115.8, 111.9; **HRMS (m/z):** (ESI) calcd. For $C_9H_8ON$ $[M+H]^+$: 146.0600, found 146.0599.

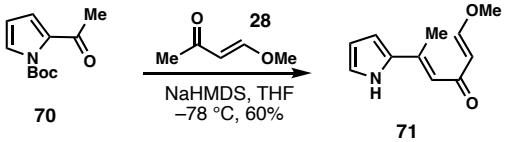



**Aldehyde 27**: To a 1 L round bottom flask containing 5-methylpyrrole-2-carboxaldehyde (32.4 g, 296.9 mmol, 1.0 equiv.) was added THF (590 mL). The vigorously stirring solution was cooled to 0 °C, and DMAP (1.81 g, 14.8 mmol, 0.05 equiv.) and $Boc_2O$ (77.7 g, 356 mmol, 1.2 equiv.) were added in a single portion sequentially. The resulting suspension was removed from the cooling bath and warmed to room temp, at which point the septum was removed allowing for evolved gases to escape. Upon consumption of the starting material as indicated by TLC, the reaction mixture was quenched with saturated *aq.* $NaHCO_3$ (300 mL) and stirred for 30 min. The biphasic reaction mixture was poured into a separatory funnel and extracted with EtOAc (3 x 500 mL). The combined organic layers were washed with brine (100 mL), dried over $Na_2SO_4$, filtered, and concentrated *in vacuo*. The dark brown colored crude product was first filtered through a short silica gel plug (eluting with 50% EtOAc in hexanes), concentrated *in vacuo*, and purified by column chromatography (10% EtOAc in hexanes → 40% EtOAc) to afford

aldehyde **27** (56.5 g, 270 mmol, 91% yield) as a yellow oil. **TLC:** $R_f$ = 0.3 (40% EtOAc in hexanes); **$^1$H NMR** (600 MHz, $C_6D_6$) δ 9.33 (s, 1H), 6.86 (d, *J* = 3.6 Hz, 1H), 5.63 (d, *J* = 3.4 Hz, 1H), 2.13 (s, 3H), 1.28 (s, 9H); **$^{13}$C NMR** (151 MHz, $C_6D_6$) δ 178.3, 148.5, 138.2, 134.4, 120.7, 111.1, 83.9, 26.5, 14.1(3C); **IR** (thin film) $\nu_{max}$ ($cm^{-1}$): 2979, 2932, 1745, 1663, 1485, 1300, 1124, 861, 798, 777; **HRMS (m/z):** (ESI) calcd. for $C_{11}H_{16}NO_3$ $[M+H]^+$: 210.1125, found 210.1126.

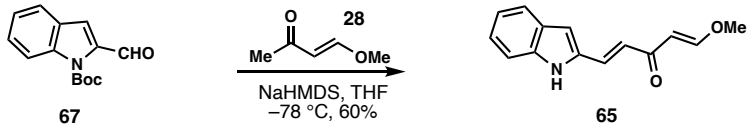



**Compound 45**: To a flame-dried 1L round bottom flask was added (*E*)-4-methoxybut-3-en-2-one (**28**) (8.13 mL, 79.7 mmol, 1.0 equiv.) and THF (478 mL). The resulting solution was cooled to –78 °C and NaHMDS (1.0 M in THF, 104 mL, 104 mmol, 1.3 equiv.) was transferred via cannula to the reaction mixture. The resulting suspension was then stirred for 30 min at –78 °C. In a separate flask, aldehyde **27** (20.0 g, 95.7 mmol, 1.2 equiv.) was azeotropically dried with benzene (3x) and then dissolved in THF (20 mL) under an atmosphere of nitrogen. The aldehyde solution was then transferred via cannula to the reaction mixture, with an additional THF (5 mL) rinse ensuring quantitative transfer. The resulting reaction mixture was then stirred at –78 °C for 1 hour, and upon consumption of the starting material as indicated by TLC, the reaction was then quenched with saturated *aq.* $NH_4Cl$ (200 mL) at –78°C. The mixture was warmed to room temperature and extracted with EtOAc (3 x 400 mL). The combined organic layers were washed with brine (200 mL), dried over $Na_2SO_4$, filtered, and concentrated *in vacuo*. The dark brown colored crude material was purified by column chromatography (10% EtOAc in hexanes → 45 % EtOAc in hexanes) to afford dienone **45** (10.8 g, 56.5 mmol, 71%) as an orange solid. **TLC:** $R_f$ = 0.4 (40% EtOAc in hexanes); **$^1$H NMR** (600 MHz, $CDCl_3$) δ 9.08 (s, 1H), 7.70 (d, *J* = 12.3 Hz, 1H), 7.48 (d, *J* = 15.7 Hz, 1H), 6.50 (br s, 1H), 6.42 (d, *J* = 15.7 Hz, 1H), 5.98 (br s, 1H), 5.86 (d, *J* = 12.4 Hz, 1H), 3.75 (s, 3H), 2.34 (s, 3H); **$^{13}$C NMR** (151 MHz, $CDCl_3$) δ 189.3, 162.6, 135.1, 132.8, 128.1, 118.0, 116.8, 109.8, 104.5, 57.6, 13.4; **IR** (thin film) $\nu_{max}$ ($cm^{-1}$): 3255, 1600, 1546, 1274, 1089, 1035, 778, 618; **HRMS (m/z):** (ESI) calcd. for $C_{11}H_{14}NO_2$ $[M+H]^+$: 192.1019, found 192.1020.

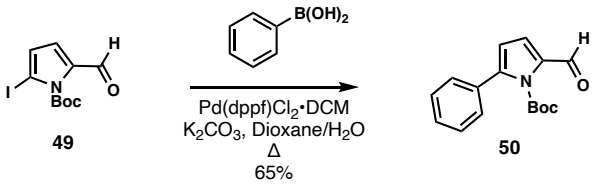



**Compound 71**: To a flame-dried reaction tube was added (*E*)-4-methoxybut-3-en-2-one (**28).** (60 mg, 0.60 mmol, 1.0 equiv.) and THF (3 mL). The resulting solution was cooled to –78 °C and NaHMDS (1.0 M in THF, 0.78 mL, 0.78 mmol, 1.3 equiv.) was added dropwise to the reaction mixture. The resulting suspension was then stirred for 1 hour. In a separate flask 2-Acetyl-1-tert-butoxy carbonyl pyrrole (**70**) (150 mg, 0.72 mmol, 1.2 equiv.) was dissolved in THF under an atmosphere of nitrogen. The ketone solution was then added dropwise to the reaction mixture at –78 °C. The resulting reaction mixture

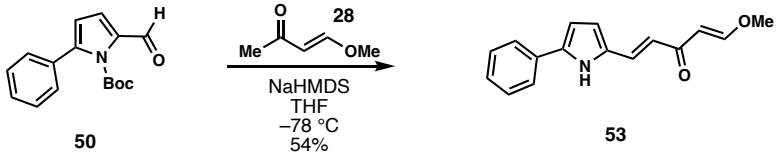
was warmed up to –40 °C and stirred for 2 hours, and upon consumption of the starting material as indicated by TLC, the reaction was then quenched with *aq.* $NH_4Cl$ (1.5 mL). The mixture was warmed to room temperature and extracted with EtOAc (3 x 5 mL). The combined organic layers were dried over $Na_2SO_4$, filtered, and concentrated *in vacuo*. The crude material was purified by column chromatography (0% EtOAc in hexanes → 40% EtOAc in hexanes) to afford dienone **71** (69 mg, 0.36 mmol, 60%). **TLC:** $R_f$ = 0.30 (30% EtOAc in hexanes); **$^1$H NMR** (600 MHz, $C_6D_6$) δ 7.72 (d, *J* = 12.4 Hz, 1H), 7.43 – 7.25 (m, 1H), 6.52 (ddd, *J* = 3.9, 2.7, 1.4 Hz, 1H), 6.32 (td, *J* = 2.7, 1.4 Hz, 1H), 6.20 (dt, *J* = 3.7, 2.5 Hz, 1H), 6.07 (q, *J* = 1.2 Hz, 1H), 5.66 (d, *J* = 12.4 Hz, 1H), 3.00 (s, 3H), 2.60 (d, *J* = 1.1 Hz, 3H); **$^{13}$C NMR** (151 MHz, $C_6D_6$) δ 188.6, 162.3, 143.7, 133.5, 121.3, 117.7, 111.8, 110.7, 108.4, 57.2, 16.6; **IR** (thin film) $\nu_{max}$ ($cm^{-1}$): 1656, 1617,1542, 1422, 1308, 1248, 1207, 1131, 1093, 1044, 858, 738, 737; **HRMS (m/z)**: (ESI) calcd. for $C_{11}H_{14}NO_2$ $[M+H]^+$: 192.1019, found 192.1019.




**Compound 65**: To a flame-dried reaction tube was added (*E*)-4-methoxybut-3-en-2-one (**28**) (25 mg, 0.25 mmol, 1.0 equiv.) and THF (1.5 mL). The resulting solution was cooled to –78 °C and NaHMDS (1.0 M in THF, 0.33 mL, 0.33 mmol, 1.3 equiv.) was added dropwise to the reaction mixture. The resulting suspension was then stirred for 30 min. In a separate flask N-Boc-indole-2-carboxaldehyde **67** (76 mg, 0.31 mmol, 1.2 equiv.) was dissolved in THF under an atmosphere of nitrogen. The aldehyde solution was then added dropwise to the reaction mixture at –78 °C. The resulting reaction stirred for 1 hour at –78 °C, and upon consumption of the starting material as indicated by TLC, the reaction was then quenched with *aq.* $NH_4Cl$ (1.5 mL). The mixture was warmed to room temperature and extracted with EtOAc (3 x 5 mL). The combined organic layers were dried over $Na_2SO_4$, filtered, and concentrated *in vacuo*. The crude material was purified by column chromatography (0% EtOAc in hexanes → 50% EtOAc in hexanes) to afford dienone **65** (33 mg, 0.15 mmol, 60%) as a yellow solid. TLC: Rf = 0.30 (30% EtOAc in hexanes); **$^1$H NMR** (600 MHz, $C_6D_6$) δ 7.76 (d, *J* = 12.4 Hz, 1H), 7.64 (d, *J* = 15.9 Hz, 1H), 7.54 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.37 (s, 1H), 7.21 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H), 7.13 – 7.05 (m, 2H), 6.57 (d, *J* = 2.1 Hz, 1H), 6.33 (d, *J* = 15.9 Hz, 1H), 5.75 (d, *J* = 12.4 Hz, 1H), 2.99 (s, 3H); **$^{13}$C NMR** (151 MHz, $C_6D_6$) δ 186.9, 163.2, 138.2, 134.4, 131.3, 129.3, 124.8, 124.6, 121.9, 120.9, 111.5, 108.5, 105.1, 57.4; **IR** (thin film) $\nu_{max}$ ($cm^{-1}$): 1644, 1605, 1588, 1345, 1307, 1254, 1126, 1068, 752, 738; **HRMS (m/z)**: (ESI) calcd. for $C_{14}H_{14}NO_2$ $[M+H]^+$: 228.1019, found 228.1021.

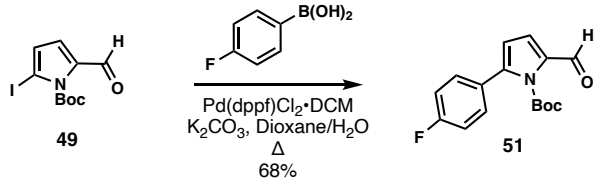



**Compound 50**: To a flame-dried round-bottom flask were added *tert*-butyl-2-formyl-5-iodo-1H-pyrrole-1-carboxylate **49** (100 mg, 0.31 mmol, 1.0 equiv.), phenylboronic acid (46 mg, 0.38 mmol, 1.2 equiv.), Pd(dppf)$Cl_2$•DCM (30 mg, 36 µmol, 0.1 equiv.), $K_3PO_4$ (140 mg, 0.66 mmol, 2.1 equiv.), dioxane (1.5 mL) and $H_2O$ (75 µL). The resulting solution was sparged with argon for 5 min, then the reaction mixture was stirred at 85 °C for 1 hour. Upon consumption of the starting material as indicated by TLC, the reaction was then cooled down to room temperature and diluted with $Et_2O$ (3 mL) and $H_2O$ (3 mL). The biphasic mixture was poured into a separatory funnel and extracted with $Et_2O$ (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over $Na_2SO_4$, filtered, and concentrated *in vacuo*. The crude material was purified by column chromatography (0% EtOAc in hexanes → 30% EtOAc in hexanes) to afford aldehyde **50** (54 mg, 0.20 mmol, 65%). **TLC:** $R_f$ = 0.60 (30% EtOAc in hexanes); **$^1$H NMR** (600 MHz, $C_6D_6$) δ 9.95 (s, 1H), 7.24 – 7.18 (m, 2H), 7.06 – 7.01 (m, 3H), 6.79 (d, *J* = 3.8 Hz, 1H), 5.95 (d, *J* = 3.8 Hz, 1H), 1.15 (s, 9H); **$^{13}$C NMR** (151 MHz, Acetone) δ 180.5, 150.0, 141.9, 135.7, 133.1, 129.4(3C), 129.2(2C), 121.4, 113.1, 86.4, 27.4(3C); **IR** (thin film) $\nu_{max}$ ($cm^{-1}$): 2982, 2935, 1765, 1743, 1663, 1506, 1414, 1396, 1371, 1300, 1285, 1260, 1140, 1075; **HRMS (m/z)**: (ESI) calcd. for $C_{16}H_{17}NO_3Na$ $[M+Na]^+$: 294.1101, found 294.1100.




**Compound 53**: To a flame-dried reaction tube was added (E)-4-methoxybut-3-en-2-one (**28**) (37 mg, 0.37 mmol, 1.0 equiv.) and THF (1.5 mL). The resulting solution was cooled to –78 °C and NaHMDS (1.0 M in THF, 0.48 mL, 0.48 mmol, 1.3 equiv.) was added dropwise to the reaction mixture. The resulting suspension was then stirred for 30 min. In a separate flask aldehyde **50** (133 mg, 0.49 mmol, 1.3 equiv.) was dissolved in THF under an atmosphere of nitrogen. The aldehyde solution was then added dropwise to the reaction mixture at –78 °C. The resulting reaction stirred for 1 hour at –78 °C, and upon consumption of the starting material as indicated by TLC, the reaction was then quenched with *aq.* $NH_4Cl$ (3.0 mL). The mixture was warmed to room temperature and extracted with EtOAc (3 x 5 mL). The combined organic layers were dried over $Na_2SO_4$, filtered, and concentrated *in vacuo*. The crude material was purified by column chromatography (0% EtOAc in hexanes → 30% EtOAc in hexanes) to afford dienone **53** (50 mg, 0.20 mmol, 54%). **TLC:** $R_f$ = 0.30 (40% EtOAc in hexanes); **$^1$H NMR** (600 MHz, $C_6D_6$) δ 9.32

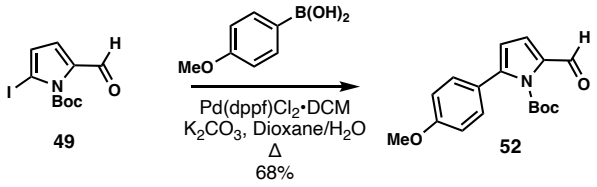
(s, 1H), 7.82 (d, *J* = 15.7 Hz, 1H), 7.73 (d, *J* = 12.3 Hz, 1H), 7.41 (d, *J* = 7.7 Hz, 2H), 7.07 – 7.00 (m, 2H), 6.63 – 6.57 (m, 2H), 6.53 (dd, *J* = 3.8, 2.5 Hz, 1H), 5.74 (d, *J* = 12.4 Hz, 1H), 2.98 (s, 3H); **$^{13}$C NMR** (151 MHz, $C_6D_6$) δ 187.9, 162.9, 137.0, 132.4, 132.0, 130.9, 129.1(2C), 127.3, 125.1(2C), 121.1, 115.6, 109.5, 105.2, 57.3; **IR** (thin film) $\nu_{max}$ ($cm^{-1}$): 1637, 1600, 1549, 1462, 1291, 1258, 1206, 1142, 1090, 1045, 975, 759; **HRMS (m/z)**: (ESI) calcd. for $C_{16}H_{16}NO_2$ $[M+H]^+$: 254.1176, found 254.1176.




**Compound 51**: To a flame-dried round-bottom flask were added *tert*-butyl-2-formyl-5-iodo-1*H*-pyrrole-1-carboxylate **49** (120 mg, 0.37 mmol, 1.0 equiv.), 4-fluorophenylboronic acid (60 mg, 0.43 mmol, 1.2 equiv.), Pd(dppf)$Cl_2$•DCM (30 mg, 36 µmol, 0.1 equiv.), $K_3PO_4$ (130 mg, 0.94 mmol, 2.5 equiv.), dioxane (1.5 mL) and $H_2O$ (75 µL). The resulting solution was sparged with argon for 5 min, then the reaction mixture was stirred at 85 °C for 1 hour. Upon consumption of the starting material as indicated by TLC, the reaction was then cooled down to room temperature and diluted with $Et_2O$ (3 mL) and $H_2O$ (3 mL). The biphasic mixture was poured into a separatory funnel and extracted with $Et_2O$ (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over $Na_2SO_4$, filtered, and concentrated *in vacuo*. The crude material was purified by column chromatography (0% EtOAc in hexanes → 30% EtOAc in hexanes) to afford aldehyde **51** (71 mg, 0.25 mmol, 68%). **TLC:** $R_f$ = 0.65 (30% EtOAc in hexanes); **$^1$H NMR** (600 MHz, $C_6D_6$) δ 9.92 (s, 1H), 7.02 – 6.96 (m, 2H), 6.78 (d, *J* = 3.7 Hz, 1H), 6.73 – 6.66 (m, 2H), 5.86 (d, *J* = 3.7 Hz, 1H), 1.15 (s, 9H); **$^{13}$C NMR** (151 MHz, $C_6D_6$) δ 179.5, 164.0, 162.4, 149.3, 140.0, 135.4, 131.1, 131.0, 120.9, 115.4, 115.2, 112.8, 85.4, 27.1(3C); **IR** (thin film) $\nu_{max}$ ($cm^{-1}$): 2982, 1744, 1663, 1606, 1462, 1422, 1397, 1299, 1260, 1220, 1159, 1139, 840, 802; **HRMS (m/z)**: (ESI) calcd. for $C_{16}H_{17}NFO_3$ $[M+H]^+$: 290.1187, found 290.1189.

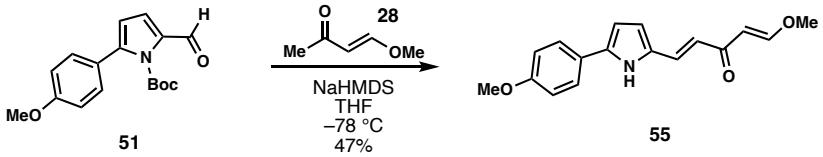

**Compound 54**: To a flame-dried reaction tube was added (*E*)-4-methoxybut-3-en-2-one (**28**) (39 mg, 0.39 mmol, 1.0 equiv.) and THF (3.0 mL). The resulting solution was cooled to –78 °C and NaHMDS (1.0 M in THF, 0.51 mL, 0.51 mmol, 1.3 equiv.) was added dropwise to thereaction mixture. The resulting suspension was then stirred for 1 hour. In a separate flask aldehyde **51** (140 mg, 0.48 mmol, 1.2 equiv.) was dissolved in THF under an atmosphere of nitrogen. The aldehyde solution was then added dropwise to the reaction mixture at –78 °C. The resulting reaction stirred for 1 hour at –78 °C, and upon consumption of the starting material as indicated by TLC, the reaction was then quenched

with *aq.* $NH_4Cl$ (1.5 mL). The mixture was warmed to room temperature and extracted with EtOAc (3 x 5 mL). The combined organic layers were dried over $Na_2SO_4$, filtered, and concentrated *in vacuo*. The crude material was purified by column chromatography (0% EtOAc in hexanes → 40% EtOAc in hexanes) to afford dienone **54** (51 mg, 0.19 mmol, 48%). **TLC:** $R_f$ = 0.65 (30% EtOAc in hexanes); **$^1$H NMR** (600 MHz, $C_6D_6$) δ 9.30 (s, 1H), 7.81 (d, *J* = 15.7 Hz, 1H), 7.68 (d, *J* = 12.4 Hz, 1H), 6.84 – 6.77 (m, 2H), 6.63 (d, *J* = 15.7 Hz, 1H), 6.59 (dd, *J* = 3.8, 2.4 Hz, 1H), 6.39 (dd, *J* = 3.8, 2.5 Hz, 1H), 5.73 (d, *J*= 12.4 Hz, 1H), 2.97 (s, 3H); **$^{13}$C NMR** (151 MHz, $C_6D_6$) δ 188.1, 163.3, 162.9, 161.7, 136.1, 132.0, 130.9, 126.8(2C), 121.2, 116.1, 115.9, 115.5, 109.4, 105.0, 57.3; **IR** (thin film) $\nu_{max}$ ($cm^{-1}$): 1634, 1618, 1599, 1562, 1516, 1467, 1344, 1233, 1211, 851, 834, 781, 684; **HRMS (m/z)**: (ESI) calcd. for $C_{16}H_{15}NFO_2$ $[M+H]^+$: 272.1081, found 272.1082.



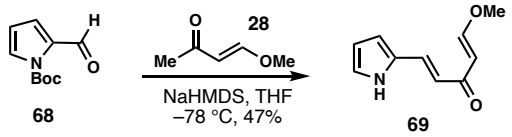
49 52

**Compound 52**: To a flame-dried round-bottom flask were added *tert*-butyl-2-formyl-5-iodo-1*H*-pyrrole-1-carboxylate **49** (110 mg, 0.34 mmol, 1.0 equiv.), 4-methoxyphenylboronic acid (80 mg, 0.53 mmol, 1.6 equiv.), Pd(dppf)$Cl_2$•DCM (25 mg, 31 µmol, 0.09 equiv.), $K_2CO_3$ (120 mg, 0.87 mmol, 2.6 equiv.), dioxane (2.0 mL) and $H_2O$ (0.1 mL). The resulting solution was sparged with argon for 5 min, then the reaction mixture was stirred at 85 °C for 3 hours. Upon consumption of the starting material as indicated by TLC, the reaction was then cooled down to room temperature and diluted with EtOAc (3 mL) and $H_2O$ (3 mL). The biphasic mixture was poured into a separatory funnel and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over $Na_2SO_4$, filtered, and concentrated *in vacuo*. The crude material was purified by column chromatography (0% EtOAc in hexanes → 40% EtOAc in hexanes) to afford aldehyde **52** (70 mg, 0.23 mmol, 68%). **TLC:** $R_f$ = 0.65 (30% EtOAc in hexanes); **$^1$H NMR** (600 MHz, $C_6D_6$) δ 9.86 (s, 1H), 7.26 – 7.20 (m, 2H), 6.77 (d, *J* = 3.8 Hz, 1H), 6.72 – 6.67 (m, 2H), 5.99 (d, *J* = 3.7 Hz, 1H), 3.24 (s, 3H), 1.24 (s, 9H); **$^3$C NMR**(151 MHz, $C_6D_6$) δ 179.0, 160.4, 149.8, 141.5, 135.0(2C), 130.5, 124.9, 121.4(2C), 113.9, 112.1, 85.2, 54.8, 27.2(2C); **IR** (thin film) $\nu_{max}$ ($cm^{-1}$): 1762, 1743, 1660, 1611, 1577, 1463, 1370, 1287, 1250, 1178, 1137, 1075, 1032, 835; **HRMS (m/z)**: (ESI) calcd. For $C_{17}H_{19}NO_4Na$ $[M+Na]^+$: 324.1206, found 324.1207.

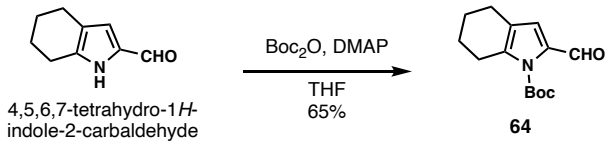


51 55

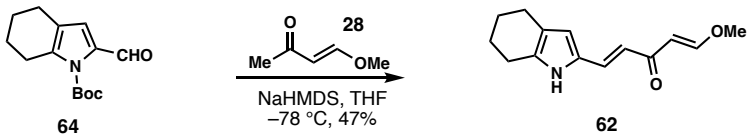
**Compound 55**: To a flame-dried reaction tube was added (*E*)-4-methoxybut-3-en-2-one (**28**) (40 mg, 0.40 mmol, 1.0 equiv.) and THF (3.0 mL). The resulting solution was cooled to –78 °C and NaHMDS (1.0 M in THF, 0.52 mL, 0.52 mmol, 1.3 equiv.) was added dropwise to the reaction mixture. The resulting suspension was then stirred for 1 hour. In a separate flask aldehyde **51** (144 mg, 0.47 mmol, 1.2 equiv.) was dissolved in THF under an atmosphere of nitrogen. The aldehyde solution was then added dropwise to the reaction mixture at –78 °C. The resulting reaction stirred for 1 hour at –78 °C, and upon consumption of the starting material as indicated by TLC, the reaction was then quenched with *aq.* $NH_4Cl$ (3.0 mL). The mixture was warmed to room temperature and extracted with EtOAc (3 x 5 mL). The combined organic layers were dried over $Na_2SO_4$, filtered, and concentrated *in vacuo*. The crude material was purified by column chromatography (0% EtOAc in hexanes → 40% EtOAc in hexanes) to afford dienone **55** (53 mg, 0.19 mmol, 47%). **$^1$H NMR** (600 MHz, Acetone) δ 10.70 (s, 1H), 7.72 – 7.63 (m, 3H), 7.49 (d, *J* = 15.8 Hz, 1H), 7.00 – 6.95 (m, 2H), 6.77 (d, *J* = 15.7 Hz, 1H), 6.66 (dd, *J* = 3.7, 2.4 Hz, 1H), 6.56 (dd, *J* = 3.8, 2.4 Hz, 1H), 5.90 (d, *J* = 12.5 Hz, 1H), 3.83 (s, 3H), 3.78 (s, 3H); **$^{13}$C NMR** (151 MHz, Acetone) δ 187.8, 162.7, 160.1, 137.7, 131.6, 130.9, 126.7(2C), 125.7, 120.4, 117.4, 115.2(2C), 108.5, 105.9, 58.0, 55.7; **IR** (thin film) $\nu_{max}$ ($cm^{-1}$): 1599, 1569, 1549, 1517, 1468, 1439, 1281, 1252, 1206, 1183, 1088, 1075; **HRMS (m/z)**: (ESI) calcd. for $C_{17}H_{18}NO_3$ $[M+H]^+$: 284.1281, found 284.1281.




**Compound 69**: To a flame-dried reaction tube was added (*E*)-4-methoxybut-3-en-2-one (**28**) (60 mg, 0.60 mmol, 1.0 equiv.) and THF (3 mL). The resulting solution was cooled to –78 °C and NaHMDS (1.0 M in THF, 0.78 mL, 0.78 mmol, 1.3 equiv.) was added dropwise to the reaction mixture. The resulting suspension was then stirred for 30 min. In a separate flask N- Boc-pyrrole-2-carboxaldehyde **68** (140 mg, 0.72 mmol, 1.2 equiv.) was dissolved in THF under an atmosphere of nitrogen. The aldehyde solution was then added dropwise to the reaction mixture at –78 °C. The resulting reaction stirred for 1 hour at –78 °C, and upon consumption of the starting material as indicated by TLC, the reaction was then quenched with *aq.* $NH_4Cl$ (3.0 mL). The mixture was warmed to room temperature and extracted with EtOAc (3 x 5 mL). The combined organic layers were dried over $Na_2SO_4$, filtered, and concentrated *in vacuo*. The crude material was purified by column chromatography (0% EtOAc in hexanes → 40% EtOAc in hexanes) to afford dienone **69** (50 mg, 0.28 mmol, 47%). **TLC:** $R_f$ = 0.35 (30% EtOAc in hexanes); **$^1$H NMR** (600 MHz, $C_6D_6$) δ 7.78 (d, *J* = 12.4 Hz, 2H), 7.64 (d, *J* = 15.8 Hz, 1H), 6.57 – 6.39 (m, 1H), 6.37 – 6.24 (m, 2H), 6.18 (dt, *J* = 3.6, 2.5 Hz, 1H), 5.73 (d, *J* = 12.3 Hz, 1H), 2.96 (s, 3H); **$^{13}$C NMR** (151 MHz, $C_6D_6$) δ 187.4, 162.6, 131.6, 129.3, 122.4, 121.0, 114.1, 111.1, 105.0, 57.2; **IR** (thin film) $\nu_{max}$ ($cm^{-1}$): 1734, 1641, 1603, 1568, 1541, 1437, 1414, 1290, 1125, 1088, 1035, 977, 740; **HRMS (m/z)**: (ESI) calcd. for $C_{10}H_{12}NO_2$ $[M+H]^+$: 178.0863, found 178.0861.

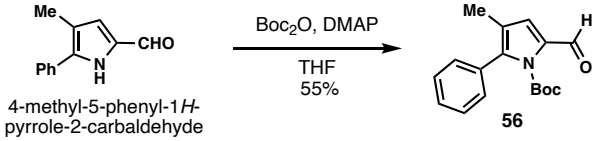



**Compound 64**: To a round bottom flask containing 4,5,6,7-tetrahydro-1*H*-indole-2-carbaldehyde (55 mg, 0.37 mmol, 1.0 equiv.) was added THF (2 mL). To the resulting solution were added DMAP (2 mg, 16.4 µmol, 0.04 equiv.) and $Boc_2O$ (105 mg, 0.48 mmol, 1.3 equiv.) in a single portion sequentially. The reaction mixture was stirred at room temperature for 1 hour, and upon consumption of the starting material as indicated by TLC, the mixture was diluted with EtOAc (3 mL) and quenched with *aq.* $NaHCO_3$ (5 mL). The biphasic reaction mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed were dried over $Na_2SO_4$, filtered, and concentrated *in vacuo*. The crude material was purified by column chromatography (0% EtOAc in hexanes → 40% EtOAc in hexanes) to afford aldehyde **64** (59 mg, 0.24 mmol, 65%). **TLC:** $R_f$ = 0.50 (10% EtOAc in hexanes); **$^1$H NMR** (600 MHz, $C_6D_6$) δ 10.21 (s, 1H), 6.85 (s, 1H), 2.64 (tt, *J* = 6.4, 1.6 Hz, 2H), 2.12 (tt, *J* = 6.1, 1.7 Hz, 2H), 1.41 (pd, *J* = 5.9, 3.3 Hz, 2H), 1.38 – 1.32 (m, 2H), 1.28 (s, 9H); **$^{13}$C NMR** (151 MHz, $C_6D_6$) δ180.1, 149.4, 137.8, 134.6, 122.3, 121.6, 84.4, 27.6(3C), 25.4, 23.1, 22.9, 22.7; **IR** (thin film) $\nu_{max}$ ($cm^{-1}$): 2935, 1739, 1648, 1483, 1462, 1416, 1348, 1333, 1296, 1259, 1144, 1125, 1086, 849; **HRMS (m/z)**: (ESI) calcd. for $C_{14}H_{19}NO_3Na[M+Na]^+$: 272.1257, found 272.1258.

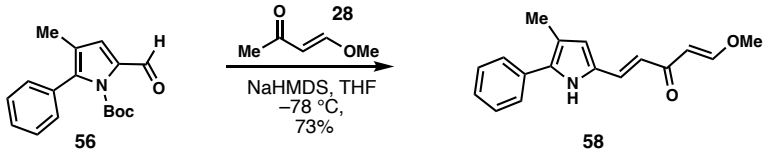



**Compound 62**: To a flame-dried reaction tube was added (*E*)-4-methoxybut-3-en-2-one (**28**) (60 mg, 0.60 mmol, 1.0 equiv.) and THF (3.5 mL). The resulting solution was cooled to –78 °C and NaHMDS (1.0 M in THF, 0.78 mL, 0.78 mmol, 1.3 equiv.) was added dropwise to the reaction mixture. The resulting suspension was then stirred for 1 hour. In a separate flask aldehyde **64** (200 mg, 0.80 mmol, 1.3 equiv.) was dissolved in THF under an atmosphere of nitrogen. The aldehyde solution was then added dropwise to the reaction mixture at –78 °C. The resulting reaction stirred for 1 hour at –78 °C, and upon consumption of the starting material as indicated by TLC, the reaction was then quenched with *aq.* $NH_4Cl$ (3.0 mL). The mixture was warmed to room temperature and extracted with EtOAc (3 x 5 mL). The combined organic layers were dried over $Na_2SO_4$, filtered, and concentrated *in vacuo*. The crude material was purified by column chromatography (0% EtOAc in hexanes → 50% EtOAc in hexanes) to afford dienone **62** (65 mg, 0.28 mmol, 47%). **TLC:** $R_f$ = 0.45 (30% EtOAc in hexanes); **$^1$H NMR** (600 MHz, $C_6D_6$) δ 7.83 (d, *J* = 12.3 Hz, 1H), 7.69 (d, *J* = 15.7 Hz, 1H), 7.38 (s, 1H), 6.32 (d, *J* = 15.7 Hz, 1H), 6.27 (d, *J* = 2.5 Hz, 1H), 5.81 (d, *J* = 12.3 Hz, 1H), 3.01 (s, 3H), 2.40 (tt, *J* = 4.8, 2.0 Hz, 2H), 2.16 (q, *J* = 4.3, 3.2 Hz, 2H), 1.53 (td, *J* = 3.8, 1.9 Hz, 4H); **$^{13}$C NMR** (151

MHz, $C_6D_6$) δ187.2, 162.2, 132.8, 131.9, 127.6, 120.5, 119.1, 114.1, 105.2, 57.1, 23.9, 23.4, 23.2, 23.1; **IR**(thin film) $\nu_{max}$ ($cm^{-1}$): 2932, 1637, 1602, 1570, 1546, 1411, 1362, 1318, 1285, 1198, 1119, 1082, 975; **HRMS (m/z)**: (ESI) calcd. for $C_{14}H_{18}NO_2$ $[M+H]^+$: 232.1332, found 232.1333.




**Compound 56**: To a round bottom flask containing 4-methyl-5-phenyl-1*H*-pyrrole-2-carbaldehyde (155 mg, 0.84 mmol, 1.0 equiv.) was added THF (5 mL). To the resulting solution were added DMAP (4.9 mg, 40 µmol, 0.05 equiv.) and $Boc_2O$ (253 mg, 1.16 mmol, 1.4 equiv.) in a single portion sequentially. The reaction mixture was stirred at room temperature for 1 hour, and upon consumption of the starting material as indicated by TLC, the mixture was diluted with EtOAc (5 mL) and quenched with *aq.* $NaHCO_3$ (5 mL). The biphasic reaction mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed were dried over $Na_2SO_4$, filtered, and concentrated *in vacuo*. The crude material was purified by column chromatography (0% EtOAc in hexanes → 35% EtOAc in hexanes) to afford aldehyde **56** (132 mg, 0.46 mmol, 55%). **TLC:** $R_f$ = 0.60 (10% EtOAc in hexanes); **$^1$H NMR** (600 MHz, $C_6D_6$) δ 10.21 (s, 1H), 7.09 – 7.00 (m, 5H), 6.81 (s, 1H), 1.70 (s, 3H), 1.08 (s, 9H); **$^{13}$C NMR** (151 MHz, Acetone) δ 180.9, 149.8, 138.2, 134.4, 133.1, 130.5(2C), 129.1(2C), 122.2, 121.9, 85.7, 27.3(3C), 11.3; **IR** (thin film) $\nu_{max}$ ($cm^{-1}$): 1739, 1663, 1605, 1508, 1465, 1443, 1415, 1371, 1337, 1300, 1154, 1089, 703; **HRMS (m/z)**: (ESI) calcd. for $C_{17}H_{19}NO_3Na$ $[M+Na]^+$: 308.1257, found 308.1257.

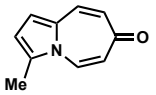



**Compound 58**: To a flame-dried reaction tube was added (*E*)-4-methoxybut-3-en-2-one (**28**) (26 mg, 0.26 mmol, 1.0 equiv.) and THF (1.5 mL). The resulting solution was cooled to –78 °C and NaHMDS (1.0 M in THF, 0.33 mL, 0.33 mmol, 1.3 equiv.) was added dropwise to the reaction mixture. The resulting suspension was then stirred for 1 hour. In a separate flask aldehyde **56** (82 mg, 0.29 mmol, 1.1 equiv.) was dissolved in THF under an atmosphere of nitrogen. The aldehyde solution was then added dropwise to the reaction mixture at –78 °C. The resulting reaction stirred for 1 hour at –78 °C, and upon consumption of the starting material as indicated by TLC, the reaction was then quenched with *aq.* $NH_4Cl$ (1.5 mL). The mixture was warmed to room temperature and extracted with EtOAc (3 x 5 mL). The combined organic layers were dried over $Na_2SO_4$, filtered, and concentrated *in vacuo*. The crude material was purified by column chromatography

(0% EtOAc in hexanes → 50% EtOAc in hexanes) to afford dienone **58** (50 mg, 0.19 mmol, 73%). **TLC:** $R_f$ = 0.35 (30% EtOAc in hexanes); **$^1$H NMR** (600 MHz, Acetone) δ 7.67 (d, *J* = 12.5 Hz, 1H), 7.62 – 7.58 (m, 2H), 7.51 – 7.42 (m, 3H), 7.31 (t, *J* = 7.4 Hz, 1H), 6.81 (d, *J* = 15.7 Hz, 1H), 6.56 (s, 1H), 5.90 (d, *J* = 12.5 Hz, 1H), 3.78 (s, 3H), 2.26 (s, 3H); **$^{13}$C NMR** (151 MHz, Acetone) δ 187.8, 162.8, 133.9, 133.7, 131.6, 129.5(2C), 127.6(3C), 120.7, 119.6, 118.7, 118.6, 106.0, 58.0, 12.9; **IR** (thin film) $\nu_{max}$ ($cm^{-1}$): 1636, 1597, 1550, 1458, 1437, 1410, 1350, 1331, 1291, 1267, 1082, 979, 768; **HRMS (m/z)**: (ESI) calcd. for $C_{17}H_{18}NO_2[M+H]^+$: 268.1332, found 268, 1332.

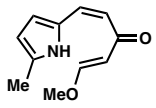
## Standard Procedure for the microwave-assisted synthesis of substituted pyrroloazepinones

To a 5 mL Biotage microwave vial was added dienone (50 mg, 1.0 equiv.), PhMe (2 mL), and DBU (2.0 equiv.). The resulting solution was sealed, placed in a Biotage microwave reactor, and heated at 160 °C for 2-4 hours. Upon cooling, the reaction mixture filtered through a cotton plug (eluting with EtOAc), concentrated in vacuo, and then purified by column chromatography chromatography (0% EtOAc in hexanes → 60% EtOAc in hexanes) to the corresponding pyrroloazepinone.




**25**

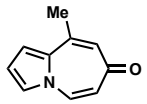
**Compound 25**: The standard procedure was followed with dienone **45** (2.0 g, 10.5 mmol, 1.0 equiv.) and DBU (3.1 mL, 21.0 mmol, 2.0 equiv.) to afford compound **25** (1.0 g, 6.2 mmol, 60% yield) as a yellow solid. **TLC:** $R_f$ = 0.4 (50% EtOAc in hexanes); **$^1$H NMR** (600 MHz, $CDCl_3$) δ 7.28 (d, *J* = 10.6 Hz, 1H), 7.09 (d, *J* = 12.2 Hz, 1H), 6.61 (d, *J* = 3.7 Hz, 1H), 6.27 (d, *J* = 3.3 Hz, 1H), 6.12 (dd, *J* = 12.2, 2.4 Hz, 1H), 5.90 (dd, *J* = 10.6, 2.4 Hz, 1H), 2.40 (s, 3H); **$^{13}$C NMR** (151 MHz, $CDCl_3$) δ 187.6, 134.0, 132.7, 130.1, 130.0, 123.9, 117.8, 114.9, 112.7, 13.1; **IR** (thin film) $\nu_{max}$ ($cm^{-1}$): 3108, 3031, 2980, 2923, 1640, 1610, 1495, 1396, 1347, 1261, 1139, 1027, 844, 763, 660; **HRMS (m/z):** (ESI) calcd. for $C_{10}H_{10}ON$ $[M+H]^+$: 160.0757, found160.0756.




**(Z-45)**

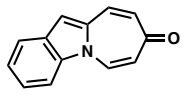
(Observed with decreased reaction times)

**TLC:** $R_f$ = 0.7 (40% EtOAc in hexanes); **$^1$H NMR** (600 MHz, $C_6D_6$) δ 13.64 (bs, 1H), 7.79 (d, *J* = 12.3 Hz, 1H), 6.52 – 6.50 (m, 1H), 6.48 (d, *J* = 12.0 Hz, 1H), 6.02 (t, *J* = 3.1 Hz, 1H), 5.62 (d, *J* = 12.0 Hz, 1H), 5.55 (d, *J* = 12.3 Hz, 1H), 2.96 (s, 3H), 1.95 (s, 3H); **$^{13}$C NMR** (151 MHz, $C_6D_6$) δ 188.8, 162.6, 134.6, 133.7, 130.6, 121.0, 114.8, 111.0, 107.3, 57.0, 13.4; **IR** (thin film) $\nu_{max}$ ($cm^{-1}$): 3260, 1651, 1584, 1529, 1497, 1435, 1406, 1352, 1309, 1245, 1205, 1170, 1079, 1029, 831; **HRMS (m/z):** (ESI) calcd for $C_{11}H_{14}O_2N$ $[M+H]^+$: 192.1019, found 192.1018.



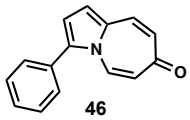

72

**Compound 72**: The standard procedure was followed with dienone **71** (50 mg, 0.26 mmol, 1.0 equiv.) and DBU (77.5 µL, 0.52 mmol, 2.0 equiv.) to afford compound **72** (30 mg, 0.18 mmol, 72%) as a yellow solid. **TLC:** $R_f$ = 0.30 (50% EtOAc in hexanes); **$^1$H NMR** (600 MHz, $CDCl_3$) δ 7.41 (d, *J* = 10.3 Hz, 1H), 7.18 (dd, *J* = 2.9, 1.7 Hz, 1H), 6.78 (dd, *J* = 4.1, 1.6 Hz, 1H), 6.53 (dd, *J* = 3.9, 2.9 Hz, 1H), 6.31 (dd, *J* = 2.5, 1.2 Hz, 1H), 5.92 (dd, *J* = 10.3, 2.4 Hz, 1H), 2.37 (d, *J* = 1.1 Hz, 3H); **$^{13}$C NMR** (151 MHz, $CDCl_3$) δ 187.0, 138.7, 134.3, 133.6, 128.1, 127.0, 116.5, 114.9, 112.4, 24.3; **IR** (thin film) $\nu_{max}$ ($cm^{-1}$): 3105, 3055, 3015, 2983, 1643, 1593, 1576, 1530, 1471, 1374, 896, 764. **HRMS (m/z)**: (ESI) calcd. for $C_{10}H_{10}NO$ $[M+H]^+$ m/z: 160.0757, found 160.0756.



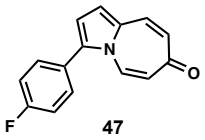

60

**Compound 60**: The standard procedure was followed with dienone **65** (50 mg, 0.22 mmol, 1.0 equiv.) and DBU (65.7 µL, 0.44 mmol, 2.0 equiv.) to afford compound **60** (18.5 mg, 94.7 µmol, 43%) as an orange solid. **TLC:** $R_f$ = 0.55 (50% EtOAc in hexanes); **$^1$H NMR** (600 MHz, $C_6D_6$) δ 7.40 – 7.35 (m, 1H), 7.12 – 7.04 (m, 2H), 6.76 (dd, *J* = 9.3, 4.9 Hz, 2H), 6.43 (d, *J* =12.4 Hz, 1H), 6.30 – 6.24 (m, 2H), 5.73 (dd, *J* = 10.5, 2.3 Hz, 1H); **$^{13}$C NMR** (151 MHz, Acetone) δ 187.8, 138.3, 137.5, 131.6, 130.5, 129.3, 128.6, 126.3, 124.4, 122.7, 113.5, 112.5, 111.7; **IR** (thin film) $\nu_{max}$ ($cm^{-1}$): 1634, 1595, 1523, 1471, 1426, 1409, 1391, 1357, 1315, 878, 850, 781; **HRMS (m/z)**: (ESI) calcd. for $C_{13}H_{10}NO$ $[M+H]^+$ m/z: 196.0757, found 196.0758.



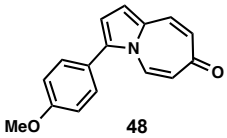

46

**Compound 46**: The standard procedure was followed with dienone **53** (50 mg, 0.20 mmol, 1.0 equiv.) and DBU (58.9 µL, 0.40 mmol, 2.0 equiv.) to afford compound **46** (23 mg, 126 µmol, 63%) as a yellow solid. **TLC:** $R_f$ = 0.50 (45% EtOAc in hexanes); **$^1$H NMR** (600 MHz, $C_6D_6$) δ7.04 (dd, *J* = 5.2, 2.0 Hz, 3H), 6.95 (dt, *J* = 6.7, 2.2 Hz, 2H), 6.92 (d, *J* = 10.7 Hz, 1H), 6.49 (d, *J* = 12.2 Hz, 1H), 6.27 (dd, *J* = 12.3, 2.3 Hz, 1H), 6.19 (d, *J* = 3.8 Hz, 1H), 6.14 (d, *J* = 3.8 Hz, 1H), 5.67 (dd, *J* = 10.7, 2.3 Hz, 1H); **$^{13}$C NMR** (151 MHz, $C_6D_6$) δ 186.8, 138.7, 133.8, 131.3, 130.0,129.8(2C), 129.4, 129.1(2C), 128.8, 126.0, 117.8, 116.0, 113.1; **IR** (thin film) $\nu_{max}$ ($cm^{-1}$): 1637,1613, 1595, 1446, 1435, 1411, 1396, 1346, 1322, 877, 849, 758, 702; **HRMS (m/z)**: (ESI) calcd. for $C_{15}H_{12}NO$ $[M+H]^+$ m/z: 222.0913, found 222.0916.



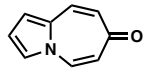
47

**Compound 47**: The standard procedure was followed with dienone **54** (50 mg, 0.18 mmol, 1.0 equiv.) and DBU (55 µL, 0.36 mmol, 2.0 equiv.) to afford compound **47** (26 mg, 108 µmol, 59%) as a yellow oil which slowly solidified. **TLC:** $R_f$ = 0.50 (50% EtOAc in hexanes); **$^1$H NMR** (600 MHz, $C_6D_6$) δ 6.74 (d, *J* = 10.7 Hz, 1H), 6.66 (d, *J* = 6.9 Hz, 4H), 6.49 (d, *J* = 12.3 Hz, 1H), 6.28 (dd, *J* = 12.3, 2.4 Hz, 1H), 6.17 (d, *J* = 3.8 Hz, 1H), 6.04 (d, *J* = 3.8 Hz, 1H), 5.72 (dd, *J* = 10.7, 2.3 Hz, 1H); **$^{13}$C NMR** (151 MHz, $C_6D_6$) δ 186.7, 164.0, 162.4, 137.5, 133.7, 131.7, 131.6, 129.7, 129.3, 126.1, 117.7, 116.2, 116.1, 116.0, 113.1; **IR** (thin film) $\nu_{max}$ ($cm^{-1}$): 1646, 1635, 1615, 1507, 1478, 1417, 1271, 1227, 1159, 1099, 840, 814, 770; **HRMS (m/z)**: (ESI) calcd. for $C_{15}H_{11}NFO$ $[M+H]^+$ m/z: 240.0819, found 240.0820.



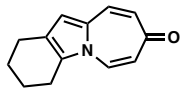
48

**Compound 48**: The standard procedure was followed with dienone **55** (50 mg, 0.18 mmol, 1.0 equiv.) and DBU (52.7 µL, 0.36 mmol, 2.0 equiv.) to afford compound **48** (26 mg, 103 µmol, 57%) as an orange oil which slowly solidified. **TLC:** $R_f$ = 0.35 (50% EtOAc in hexanes); **$^1$H NMR** (600 MHz, $C_6D_6$) δ 7.00 (d, *J* = 10.7 Hz, 1H), 6.92 – 6.87 (m, 2H), 6.69 – 6.63 (m, 2H), 6.53 (d, *J* = 12.3 Hz, 1H), 6.29 (dd, *J* = 12.3, 2.3 Hz, 1H), 6.23 (d, *J* = 3.7 Hz, 1H), 6.16 (d, *J* = 3.8 Hz, 1H), 5.75 (dd, *J* = 10.7, 2.4 Hz, 1H), 3.26 (s, 3H); **$^{13}$C NMR** (151 MHz, $C_6D_6$) δ 186.8,160.5, 138.8, 133.5, 131.2(2C), 130.1, 129.5, 125.7, 123.4, 117.8, 115.8, 114.6(2C), 112.8, 54.9. **IR** (thin film) $\nu_{max}$ ($cm^{-1}$): 1645, 1634, 1608, 1478, 1436, 1406, 1397, 1343, 1287, 1250, 1178, 1087, 877; **HRMS (m/z)**: (ESI) calcd. for $C_{16}H_{14}NO_2$ $[M+H]^+$ m/z: 252.1019, found 252.1021.



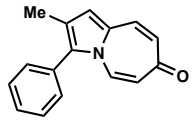
41

**Compound 41**: The standard procedure was followed with dienone **69** (50 mg, 0.28 mmol, 1.0 equiv.) and DBU (83.3 µL, 0.56 mmol, 2.0 equiv.) to afford compound **41** (26 mg, 0.18 mmol, 64%) as a yellow solid. **TLC:** $R_f$ = 0.35 (50% EtOAc in hexanes); **$^1$H NMR** (600 MHz, $CDCl_3$) δ 7.38 (dd, *J* = 10.4, 0.7 Hz, 1H), 7.21 – 7.16 (m, 2H), 6.73 (dd, *J* = 3.4, 1.4 Hz, 1H), 6.52 (dd, *J* = 3.8, 2.9 Hz, 1H), 6.24 (dd, *J* = 12.4, 2.4 Hz, 1H), 5.94 (dd, *J* = 10.4, 2.4 Hz, 1H); **$^{13}$C NMR** (151 MHz, $C_6D_6$) δ 186.5, 132.7, 132.6, 128.8, 126.3, 126.2, 118.2, 115.8, 111.9; **IR** (thin film) $\nu_{max}$ ($cm^{-1}$): 3111, 3091, 1640, 1611, 1589, 1527, 1478, 1432, 1382, 1370, 1291, 868, 846, 749; **HRMS (m/z)**: (ESI) calcd. for $C_9H_8NO$ $[M+H]^+$ m/z: 146.0600, found 146.0600.



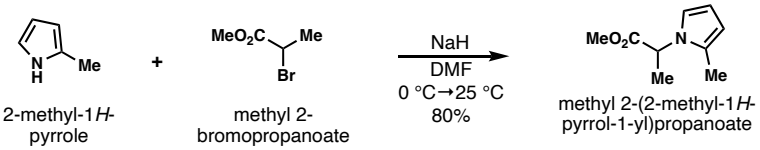
61

**Compound 61**: The standard procedure was followed with dienone **62** (50 mg, 0.22 mmol, 1.0 equiv.) and DBU (65.7 µL, 0.44 mmol, 2.0 equiv.) to afford compound **61** (17.5 mg, 88 µmol, 40%) as a yellow solid. **TLC:** $R_f$ = 0.30 (50% EtOAc in hexanes); **$^1$H NMR** (600 MHz, $C_6D_6$) δ 6.52 (d, *J* = 12.2 Hz, 1H), 6.34 (dd, *J* = 12.2, 2.4 Hz, 1H), 6.28 (d, *J* = 10.5 Hz, 1H), 5.97 (s, 1H), 5.88 (dd, *J* = 10.5, 2.4 Hz, 1H), 2.24 – 2.19 (m, 2H), 1.73 – 1.68 (m, 2H), 1.35 (p, *J* = 3.0 Hz, 4H); **$^{13}$C NMR** (151 MHz, $C_6D_6$) δ 186.7, 132.6, 132.0, 128.8, 128.7, 125.1, 122.4, 117.1, 114.9, 23.0, 22.9, 22.6, 21.8; **IR** (thin film) $\nu_{max}$ ($cm^{-1}$): 2933, 2853, 1636, 1615, 1582, 1497, 1441, 1406, 1356, 1300, 850; **HRMS (m/z)**: (ESI) calcd. for $C_{13}H_{14}NO$ $[M+H]^+$ m/z: 200.1070, found 200.1072.



59

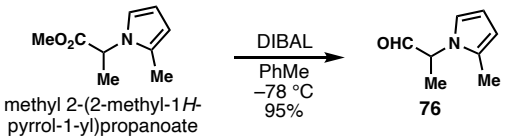
**Compound 59**: The standard procedure was followed with dienone **58** (50 mg, 0.19 mmol, 1.0 equiv.) and DBU (56.9 µL, 0.38 mmol, 2.0 equiv.) to afford compound **58** (23 mg, 97.8 µmol, 52%) as a yellow oil. **TLC:** $R_f$ = 0.38 (50% EtOAc in hexanes); **$^1$H NMR** (600 MHz, $C_6D_6$) δ 7.09 – 7.01 (m, 3H), 6.87 – 6.83 (m, 2H), 6.82 (d, *J* = 10.7 Hz, 1H), 6.54 (d, *J* = 12.2 Hz, 1H), 6.33 (dd, *J* = 12.2, 2.4 Hz, 1H), 6.07 (s, 1H), 5.67 (dd, *J* = 10.7, 2.4 Hz, 1H), 1.80 (s, 3H); **$^{13}$C NMR** (151 MHz, $C_6D_6$) δ 186.7, 135.2, 132.5, 130.9(2C), 130.5, 130.3, 129.1(2C), 128.9, 128.8, 126.1, 121.6, 119.4, 115.3, 11.5; **IR** (thin film) $\nu_{max}$ ($cm^{-1}$): 1636, 1616, 1589, 1480, 1433, 1422, 1302, 1193, 880, 763, 703; **HRMS (m/z)**: (ESI) calcd. for $C_{16}H_{14}NO$ $[M+H]^+$ m/z: 236.1070, found 236.1072.




2-methyl-1*H*-pyrrole | methyl 2-bromopropanoate | methyl 2-(2-methyl-1*H*-pyrrol-1-yl)propanoate

**Methyl 2-(2-methyl-1*H*-pyrrol-1-yl)propanoate**: A dry 100 mL round bottom flask was charged NaH (984 mg (60% dispersion in mineral oil), 24.6 mmol, 2.0 equiv.) and evacuated and backfilled with nitrogen three times. Hexanes (10.0 mL) was added and the suspension was swirled. Upon settling of the suspension, the hexane was carefully removed via syringe under nitrogen. The flask containing the rinsed NaH was then charged with DMF (20.0 mL) and cooled to 0 °C, wherein 2-methyl pyrrole (1.06 mL, 12.3 mmol, 1.0 equiv.) was added, and the resulting mixture was stirred for 30 min at 0 °C. Methyl 2-bromopropionate (2.7 mL, 24.6 mmol, 2.0 equiv.) was added dropwise, and upon completion of the addition, the mixture was warmed to room temperature. Upon completion of the reaction, as indicated by TLC, the reaction was cooled to 0 °C and

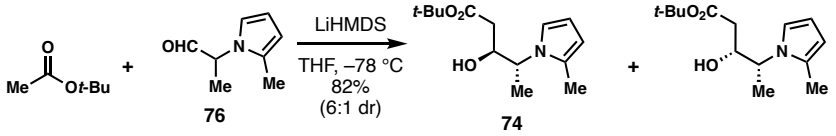
quenched with saturated *aq.* $NH_4Cl$ (100 mL). The mixture was extracted with $Et_2O$ (3 x 100 mL). The combined organic layers were washed with brine (200 mL), dried over $Na_2SO_4$, filtered, and concentrated *in vacuo*. The brown colored crude material was purified by column chromatography (0% EtOAc in hexanes → 15% EtOAc in hexanes) to afford methyl 2-(2-methyl-1*H*-pyrrol-1-yl)propanoate (1.64 g, 9.8 mmol, 80%) as a yellow oil. **TLC:** $R_f$ = 0.4 (10% EtOAc in hexanes); **$^1$H NMR** (600 MHz, $C_6D_6$) δ 6.68 (dd, *J* = 3.0, 1.8 Hz, 1H), 6.28 (t, *J* = 3.2 Hz, 1H), 6.03 (m, 1H), 4.34 (q, *J* = 7.2 Hz, 1H), 3.16 (s, 3H), 2.01 (s, 3H), 1.31 (d, *J* = 7.2 Hz, 3H); **$^{13}$C NMR** (151 MHz, $C_6D_6$) δ 171.4, 128.4, 117.4, 108.4, 107.9, 53.6, 51.8, 17.9, 12.1; **IR** (thin film) $\nu_{max}$ ($cm^{-1}$): 2989, 2950, 1742, 1420, 1296, 1204, 1086, 773, 700; **HRMS (m/z):** (ESI) calcd. for $C_9H_{14}O_2N$ $[M+H]^+$: 168.1019, found 168.1013.



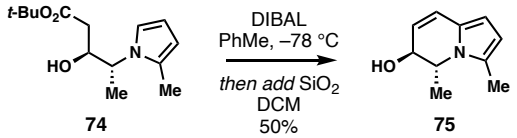
methyl 2-(2-methyl-1*H*-pyrrol-1-yl)propanoate

**76**

**Pyrrole Aldehyde 76**: To a 500 mL round bottom flask was added PhMe (250 mL) and methyl 2-(2-methyl-1*H*-pyrrol-1-yl)propanoate (7.0 g, 41.9 mmol, 1.0 equiv.). The mixture was cooled to –78 °C, and DIBAL (1.0 M in hexanes, 46.1 mL, 46.1 mmol, 1.1 equiv.) was added dropwise over 15 min. Upon completion of the reaction as indicated by TLC, the reaction mixture was quenched with saturated *aq.* Rochelle's salt (50 mL) and warmed to room temperature by removing the vessel from the cooling bath. The resulting biphasic suspension was stirred until the cloudiness dissipated (~2 hours). The mixture was then poured into a separatory funnel and extracted with $Et_2O$ (3 x 300 mL), the combined organics were washed with brine (100 mL), dried over $Na_2SO_4$, filtered, and concentrated *in vacuo*. The resulting crude residue was purified by column chromatography (10% $Et_2O$ in hexanes → 50% $Et_2O$ in hexanes) to afford aldehyde **76** (5.47 g, 40.1 mmol, 95%) as a colorless oil. **TLC:** $R_f$ = 0.4 (40% $Et_2O$ in hexanes); **$^1$H NMR** (600 MHz, $C_6D_6$) δ 9.03 (d, *J* = 0.7 Hz, 1H), 6.28 (dd, *J* = 11.3, 5.2 Hz, 2H), 6.04 (m, 1H), 3.77(q, *J* = 7.2 Hz, 1H), 1.81 (s, 3H), 1.02 (d, *J* = 7.2, 3H); **$^{13}$C NMR** (151 MHz, $C_6D_6$) δ 197.9, 128.0, 117.4, 109.0, 108.6, 59.8, 14.9, 12.0; **IR** (thin film) $\nu_{max}$ ($cm^{-1}$): 2982, 2936, 2826, 1734,1448, 1231, 703; **HRMS (m/z):** (ESI) calcd. for $C_8H_{12}ON$ $[M+H]^+$: 138.0913, found 138.0913.

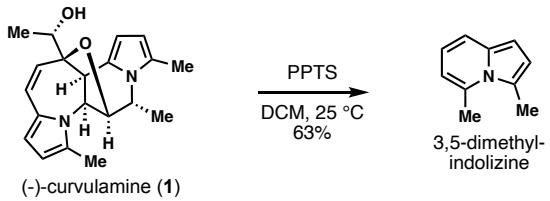



**Alcohol 74**: To a 100 mL round bottom flask containing *t*-BuOAc (450 mg, 3.88 mmol, 1.0 equiv.) was added THF (30 mL). The mixture was cooled to –78 °C before LiHMDS (1.0 M in THF, 4.3 mL, 4.3 mmol, 1.1 equiv.) was added dropwise. The resulting mixture was stirred for 30 min before aldehyde **76** (591 mg, 4.3 mmol, 1.1 equiv.) in THF (5 mL) was added. Upon consumption of the starting material as indicated by TLC, the reaction mixture was quenched with saturated *aq*. $NH_4Cl$ solution (20 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (30 mL), dried over $Na_2SO_4$, filtered, and concentrated *in vacuo*. The resulting crude product was purified by column chromatography (0% EtOAc in hexanes → 20% EtOAc in hexanes) to afford an inseparable mixture of alcohol epimers **74** (809 mg, 3.18 mmol, 82% yield, 6:1 *dr*) as a yellow oil. **TLC**: $R_f$ = 0.4 (50% EtOAc in hexanes); **$^1$H NMR** (600 MHz, $C_6D_6$) δ 6.83 (dd, *J* = 3.0, 1.8 Hz, 0.15H), 6.45 (dd, *J* = 2.9, 1.8 Hz, 0.85H), 6.30 (t, *J* = 3.1 Hz, 0.15H), 6.26 (t, *J* = 3.2 Hz, 0.85H), 6.03 (ddd, *J* = 3.6, 1.9,1.0 Hz, 0.15H), 5.99 (ddd, *J* = 3.7, 1.8, 0.9 Hz, 0.85H), 3.96 (ddd, *J* = 9.0, 7.7, 3.2 Hz, 0.85H), 3.91 (ddd, *J* = 8.8, 5.0, 3.7 Hz, 0.15H), 3.82 (p, *J* = 7.0 Hz, 0.85H), 3.74 – 3.68 (m, 0.15H), 3.31(s, 0.85H), 2.96 (s, 0.15H), 2.13 – 2.01 (m, 2H), 2.00 (s, 0.45H), 1.98 (s, 2.55H), 1.30 (d, *J* = 6.8 Hz, 2.55H), 1.28 (s, 0.45H), 1.24 (s, 2.55H), 1.15 (d, *J* = 7.0 Hz, 0.45H); **$^{13}$C NMR** (151 MHz, $C_6D_6$) δ 172.5, 172.1, 127.8(2C), 117.6, 116.4, 108.5, 108.1, 107.3, 107.1, 81.0, 80.8, 72.5, 71.7, 54.9, 54.4, 39.2, 39.0, 28.0(3C), 27.9(3C), 17.9, 17.6, 12.5, 12.4; **IR** (thin film) $\nu_{max}$ ($cm^{-1}$): 3454, 2978, 2934, 1723, 1486, 1417, 1368, 1287, 1155, 1080, 842, 768, 704; **HRMS** (m/z): (ESI) calcd. for $C_{14}H_{24}NO_3$ $[M+H]^+$: 254.1751, found 254.1751.




**Alcohol 75**: To a 20 mL round bottom flask containing alcohol **74** (90 mg, 0.36 mmol, 1.0 equiv.) was added PhMe (5 mL). The resulting mixture was cooled to –78 °C before DIBAL (1.0 M in hexanes, 1.78 mL, 1.78 mmol, 5.0 equiv.) was added dropwise. Upon consumption of the starting material as indicated by TLC, the reaction mixture was quenched with saturated *aq*. Rochelle's salt (5 mL) and extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine (30 mL), dried over $Na_2SO_4$, filtered, and concentrated *in vacuo*. The resulting crude product was dissolved in DCM (5 mL) followed by the addition of $SiO_2$ (100 mg). Upon consumption of the starting material as indicated by TLC, the reaction mixture was filtered and concentrated *in vacuo*. The resulting crude product was purified by column chromatography (0% EtOAc in hexanes → 30% EtOAc in hexanes) to afford alcohol **75** (25 mg, 0.16 mmol, 50% yield) as a yellow oil. **TLC**: $R_f$ = 0.4 (50% EtOAc in hexanes); **$^1$H NMR** (600 MHz, $C_6D_6$) δ 6.33

(d, *J* = 9.6 Hz, 1H), 6.15 (d, *J* = 3.4 Hz, 1H), 6.00 (d, *J* = 3.3 Hz, 1H), 5.42 (dd, *J* = 9.6, 5.9 Hz, 1H), 4.04 (q, *J* = 6.9 Hz, 1H), 3.73 (t, *J* = 6.6 Hz, 1H), 1.97 (s, 3H), 1.22 (d, *J* = 8.3 Hz, 1H), 0.72 (d, *J* = 6.9 Hz, 3H); **$^{13}$C NMR** (151 MHz, $C_6D_6$) δ 130.4, 126.1, 122.7, 116.0, 108.2, 108.1, 68.4, 54.6, 18.6, 11.2; **IR** (thin film) $\nu_{max}$ ($cm^{-1}$): 3358, 2923, 2852, 1658, 1631, 1464, 1421, 1060, 764; **HRMS** (m/z): (ESI) calcd. for $C_{10}H_{14}NO$ $[M+H]^+$: 164.1070, found 164.1071.



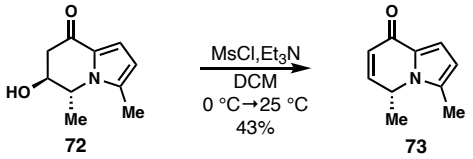
(-)-curvulamine (**1**) 3,5-dimethyl-indolizine

**3,5-dimethyl-indolizine**: To a 10 mL reaction tube containing (–)-curvulamine (**1**) (2.0 mg, 6.2 *μ*mol, 1.0 equiv.) and alcohol 17 (2.0 mg, 12.4 *μ*mol, 2.0 equiv.) was added DCM (1 mL). PPTS (1.6 mg, 0.62 *μ*mol, 0.1 equiv.) was added dropwise. The resulting mixture was warmed to 25°C. Upon consumption of the starting material as indicated by TLC, the reaction mixture was quenched with saturated *aq*. $NaHCO_3$ (2 mL) and extracted with DCM (3 x 3 mL). The combined organic layers were washed with brine (5 mL), dried over $Na_2SO_4$, filtered, and concentrated *in vacuo*. The resulting crude product was purified by preparative TLC (10% EtOAc in hexanes) to afford 3,5-dimethyl-indolizine (0.6 mg, 3.9 *μ*mol, 63% yield) as a yellow oil. **TLC**: $R_f$ = 0.7 (10% EtOAc in hexanes); **$^1$H NMR** (600 MHz, $C_6D_6$) δ 7.13 (d, *J* = 8.9 Hz, 1H), 6.49 (d, *J* = 3.8 Hz, 1H), 6.46 (d, *J* = 3.8 Hz, 1H), 6.30 (dd, *J* = 8.9, 6.4 Hz, 1H), 5.81 (dt, *J* = 6.5, 1.2 Hz, 1H), 2.41 (s, 3H), 2.19 (s, 3H); **$^{13}$C NMR** (151 MHz, $C_6D_6$) δ 135.6, 134.6, 122.0, 118.4, 115.8, 115.8, 111.4, 99.3,1.1, 16.8; **IR** (thin film) $\nu_{max}$ ($cm^{-1}$): 2961, 2922, 1588, 1538, 1456, 1290, 1154, 750; **HRMS** (m/z): (ESI) calcd. for $C_{10}H_{12}N$ $[M+H]^+$: 146.0964, found 146.0964.

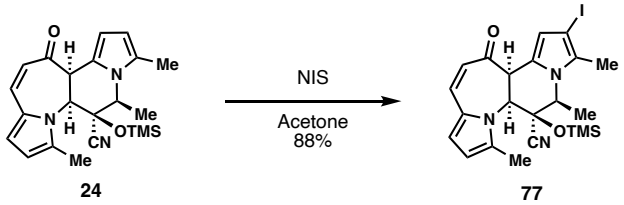
74 72

**Procuramine 72**: To a 20 mL reaction tube containing alcohol **124** (80 mg, 0.32 mmol, 1.0 equiv.) was added DCM (4 mL). The resulting mixture was cooled to 0 °C and TMSOTf (64 *μ*L, 0.35 mmol, 1.1 equiv.) was added dropwise. The resulting mixture was warmed to 25°C. Upon consumption of the starting material as indicated by TLC, the reaction mixture was quenched with saturated *aq*. $NaHCO_3$ (5 mL) and extracted with DCM (3 x 5 mL). The combined organic layers were washed with brine (10 mL), dried over $Na_2SO_4$, filtered, and concentrated *in vacuo*. The resulting crude product was purified by column chromatography (0% EtOAc in hexanes →80% EtOAc in hexanes) to afford procuramine **72** (28 mg, 0.16 mmol, 50% yield) as a yellow oil. **TLC**: $R_f$ = 0.1 (50% EtOAc in hexanes); **$^1$H NMR** (600 MHz, $CDCl_3$) δ 7.01 (d, *J* = 4.0 Hz, 1H), 6.08 (d, *J* = 4.0 Hz, 1H), 4.40 (qd, *J* = 6.8, 1.9 Hz, 1H), 4.35 (s, 1H), 2.87 (dd, *J* = 18.0, 3.2 Hz, 1H), 2.79 (s, 1H), 2.64 (dd,

$J$ = 18.0, 2.7 Hz, 1H), 2.32 (s, 3H), 1.36 (d, $J$ = 6.9 Hz, 3H); **$^{13}$C NMR** (151 MHz, $CDCl_3$) δ 183.7, 135.8, 128.3, 115.1, 111.2, 70.5, 53.6, 39.4, 19.3, 12.0; **IR** (thin film) $\nu_{max}$ ($cm^{-1}$): 3452, 2923, 1739, 1626, 1492, 1462, 1347, 1256, 1177, 1033, 776, 642; **HRMS** (m/z): (ESI) calcd. for $C_{10}H_{14}NO_2$ $[M+H]^+$: 180.1019, found 180.1018.

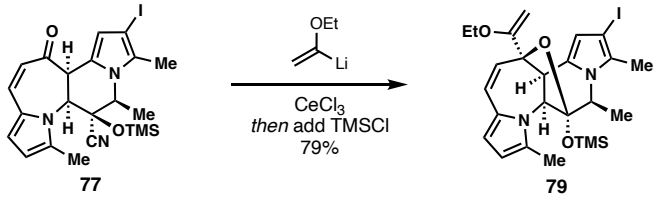



**Enone 73**: To a 10 mL reaction tube containing ketone **72** (10.0 mg, 0.056 mmol, 1.0 equiv.) was added DCM (30 mL). The resulting mixture was cooled to 0 °C, $Et_3N$ (23.0 $\mu$L, 0.17 mmol, 3.0 equiv.) and MsCl (5.1 $\mu$L, 0.067 mmol, 1.2 equiv.) were added dropwise sequentially. The resulting mixture was warmed to room temperature. Upon consumption of the starting material as indicated by TLC, the reaction mixture was quenched with saturated *aq*. $NaHCO_3$ (5 mL) and extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine (5 mL), dried over $Na_2SO_4$, filtered, and concentrated *in vacuo*. The resulting crude product was purified by preparative TLC (50% EtOAc in hexanes) to afford enone **73** (3.9 mg, 0.024 mmol, 43% yield) as a yellow oil. **TLC**: $R_f$ = 0.4 (50% EtOAc in hexanes); **$^1$H NMR** (600 MHz, $C_6D_6$) δ 7.33 (d, $J$ = 3.9 Hz, 1H), 6.19 (dd, $J$ = 10.3, 1.6 Hz, 1H), 5.94 (dd, $J$ = 3.9, 0.8 Hz, 1H), 5.80 (dd, $J$ = 10.4, 4.0 Hz, 1H), 3.67 (tdd, $J$ = 6.7, 5.4, 3.4 Hz, 1H), 1.70 (s, 3H), 0.64 (d, $J$ = 6.8 Hz, 3H); **$^{13}$C NMR** (151 MHz, $C_6D_6$) δ 175.3, 143.1, 133.3, 129.7, 127.7, 112.9, 110.8, 49.3, 21.7, 12.0; **IR** (thin film) $\nu_{max}$ ($cm^{-1}$): 2950, 1733, 1685, 1462, 1342, 1033, 766, 651; **HRMS** (m/z): (ESI) calcd. for $C_{10}H_{12}NO$ $[M+H]^+$: 162.0913, found 162.0913.

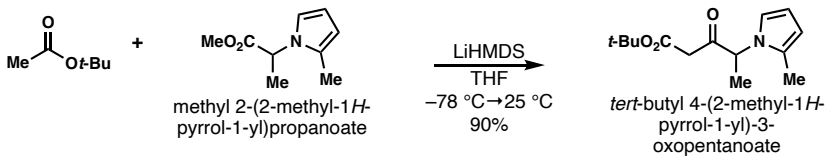



**Iodide 77**: To a 100 mL round bottom flask containing enone **24** (1.10 g, 2.80 mmol, 1.0 equiv.) was added acetone (30 mL). The resulting mixture was cooled to 0 °C and a solution of NIS (0.63 g, 29.4 mmol, 1.05 equiv.) in acetone (10 mL) was added dropwise. Upon consumption of the starting material as indicated by TLC, the reaction mixture was quenched with saturated *aq*. $NH_4Cl$ solution (30 mL) and extracted with EtOAc (3 x 40 mL). The combined organic layers were washed with brine (30 mL), dried over $Na_2SO_4$, filtered, and concentrated *in vacuo*. The resulting crude product was purified by column chromatography (0% EtOAc in hexanes → 10% EtOAc in hexanes) to afford iodide **77** (1.28 g, 2.46 mmol, 88% yield) as a yellow oil. **TLC**: $R_f$ = 0.6 (20% EtOAc in hexanes); **$^1$H NMR** (600 MHz, $C_6D_6$) δ6.28 (dd, $J$ = 12.1, 0.8 Hz, 1H), 6.16 (d, $J$ = 3.7 Hz, 1H), 6.04 (s, 1H), 5.82 (dd, $J$ = 3.8, 0.9 Hz, 1H), 5.69 (d, $J$ = 12.1 Hz,

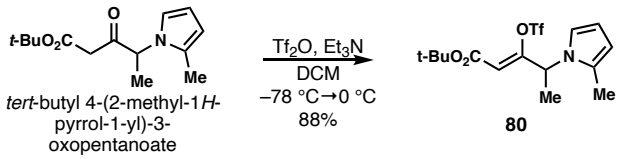
1H), 4.50 (q, *J* = 6.8 Hz, 1H), 4.40 (d, *J* = 3.6 Hz, 1H), 3.32 (dd, *J* =, 1.8 Hz, 1H), 1.94 (s, 3H), 1.89 (s, 3H), 1.07 (d, *J* = 6.8 Hz, 3H), 0.03 (s, 9H); **$^{13}$C NMR**(151 MHz, $C_6D_6$) δ 193.6, 137.9, 132.4, 131.0, 128.6, 128.5, 120.6, 120.4, 120.1, 114.2, 110.9, 73.0, 64.7, 61.6, 60.9, 47.5, 18.4, 13.8, 13.2, 0.8(3C); **IR** (thin film) $\nu_{max}$ ($cm^{-1}$): 2954, 2921, 1654, 1620, 1483, 1422, 1255, 1161, 1068, 851, 765; **HRMS** (m/z): (ESI) calcd. for $C_{22}H_{27}IN_3O_2Si$ $[M+H]^+$: 520.0912, found 520.0920.




**Iodide 79**: To a 20 mL reaction tube containing ethyl vinyl ether (0.20 mL, 2.1 mmol, 5.5 equiv.) was added THF (2 mL). The mixture was cooled to –78 °C and *t*-BuLi (1.6 M in pentane, 1.2 mL, 2.0 mmol, 5.0 equiv.) was added dropwise. Upon completion of the addition, the mixture was warmed to 0 °C and stirred for 30 min followed by the addition of $CeCl_3$ (0.49 g, 2.0 mmol, 5.0 equiv). The mixture was stirred for 1 h at 25 °C. To a 20 mL reaction tube containing iodide **77** (200 mg, 0.39 mmol, 1.0 equiv.) was added THF (5 mL). The mixture was –78 °C and a solution of fresh cerium reagent was added dropwise. The mixture was stirred for 1 h before the addition of TMSCl (0.25 mL, 2.0 mmol, 5.0 equiv.). The resulting mixture was stirred for 30 min before it was quenched with saturated *aq*. $NaHCO_3$ (5 mL) and extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine (5 mL), dried over $Na_2SO_4$, filtered, and concentrated *in vacuo*. The resulting crude product was purified by column chromatography (0% EtOAc in hexanes → 10% EtOAc in hexanes) to afford iodide **79** (171 mg, 0.30 mmol, 79% yield) as a yellow oil. **TLC**: $R_f$ = 0.7 (10% EtOAc in hexanes); **$^1$H NMR** (600 MHz, $C_6D_6$) δ 6.21 (dd, *J* = 11.5, 0.7 Hz, 1H), 6.09 (d, *J* = 3.5 Hz, 1H), 6.01 (s, 1H), 5.90 (d, *J* = 3.5 Hz, 1H), 5.59 (d, *J* = 11.4 Hz, 1H), 4.56 (d, *J* = 1.5 Hz, 1H), 4.24 (s, 1H), 4.00 (q, *J* = 6.3 Hz, 1H), 3.81 (s, 1H), 3.78 (d, *J* = 1.4 Hz, 1H), 3.36 – 3.30 (m, 1H), 3.23 (ddt, *J* = 9.0, 7.6, 6.6 Hz, 1H), 2.03 (s, 3H), 1.88 (s, 3H), 1.48 (d, *J* = 6.3 Hz, 3H), 1.04 (t, *J* = 7.0 Hz, 3H), 0.10 (s, 9H); **$^{13}$C NMR** (151 MHz, $C_6D_6$) δ 164.2, 135.2, 132.3, 130.8, 128.6, 124.3, 123.9, 114.8, 112.1, 111.4, 108.6, 86.7, 80.8, 65.0, 63.6, 63.1, 62.7, 46.1, 14.6(2C), 14.5, 13.1, 1.7(3C); **IR** (thin film) $\nu_{max}$ ($cm^{-1}$): 3269, 2977, 1640, 1491, 1414, 1311, 1250, 1079, 908, 844, 764; **HRMS** (m/z): (ESI) calcd. for $C_{25}H_{34}IN_2O_3Si$ $[M+H]^+$: 565.1378, found 565.1377.



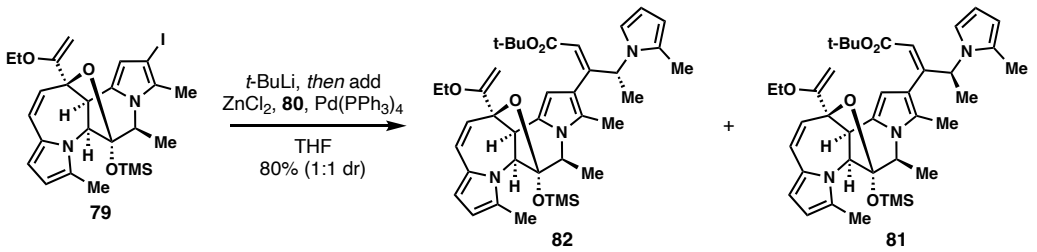
**Ester**: To a 100 mL round bottom flask containing *t*-BuOAc (1.00 g, 8.62 mmol, 1.0 equiv.) was added THF (30 mL). The resulting mixture was cooled to –78 °C before LiHMDS (1.0 M in THF, 9.5 mL, 9.48 mmol, 1.1 equiv.) was added dropwise. The resulting mixture was stirred for 30 min before ester **SI-11** (1.58 g, 9.48 mmol, 1.0 equiv.) in THF (10 mL) was added. The mixture was warmed to 25 °C. Upon consumption of the starting material as indicated by TLC, the reaction mixture was quenched with saturated *aq*. $NH_4Cl$ solution (20 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (30 mL), dried over $Na_2SO_4$, filtered, and concentrated *in vacuo*. The resulting crude product was purified by column chromatography (0% EtOAc in hexanes → 20% EtOAc in hexanes) to afford ester (1.95 g, 7.76 mmol, 90% yield) as a yellow oil. **TLC**: $R_f$ = 0.6 (50% EtOAc in hexanes); **$^1$H NMR** (600 MHz, $C_6D_6$) δ 12.95 (s, 0.24H), 6.57 (dd, *J* = 3.0, 1.8 Hz, 0.24H), 6.28 (dd, *J* = 3.0, 1.8 Hz, 0.76H), 6.24 (t, *J* = 3.2 Hz, 0.24H), 6.20 (t, *J* = 3.2 Hz, 0.76H), 6.00 – 5.98 (m, 0.24H), 5.97 (ddd, *J* = 3.5, 1.8, 0.9 Hz, 0.76H), 4.58 (d, *J* = 0.9 Hz, 0.24H), 4.41 – 4.34 (m,0.24H), 4.30 (q, *J* = 7.1 Hz, 0.76H), 2.89 (d, *J* = 16.2 Hz, 0.76H), 2.84 (d, *J* = 16.2 Hz, 0.76H),1.90 (s, 0.72H), 1.89 (d, *J* = 0.8 Hz, 2.28H), 1.35 (d, *J* = 7.2 Hz, 0.72H), 1.30 (s, 6.84H), 1.25 (s,.16H), 1.22 (d, *J* = 7.1 Hz, 2.28H); **$^{13}$C NMR** (151 MHz, $C_6D_6$) δ 201.2, 178.4, 173.6, 166.4,128.6, 128.3, 117.6, 117.0, 109.3, 108.8, 108.3, 108.0, 89.3, 81.4, 81.3, 59.9, 53.6, 45.8, 28.1(3C), 27.9(3C), 17.9, 16.2, 11.9(2C); **IR** (thin film) $\nu_{max}$ ($cm^{-1}$): 2980, 2935, 1742, 1719,1649, 1325, 1294, 1247, 1153, 1054, 814, 703; **HRMS** (m/z): (ESI) calcd. for $C_{14}H_{21}NNaO_3$ $[M+Na]^+$: 274.1414, found 274.1414.



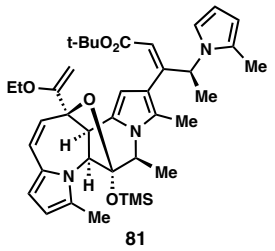
*tert*-butyl 4-(2-methyl-1*H*-pyrrol-1-yl)-3-oxopentanoate

**80**

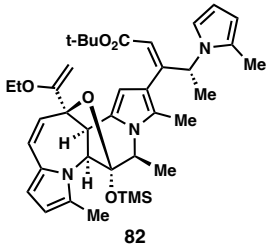
**Triflate 80**: To a 50 mL round bottom flask containing ester (1.00 g, 3.98 mmol, 1.0 equiv.) was added DCM (20 mL). The resulting mixture was cooled to –78 °C, then $Et_3N$ (1.6 mL, 11.94 mmol, 3.0 equiv.) and $Tf_2O$ (0.74 mL, 4.38 mmol, 1.1 equiv.) was added dropwise. The resulting mixture was warmed to 0 °C. Upon consumption of the starting material as indicated by TLC, the). The combined organic layers were washed with brine (30 mL), dried over $Na_2SO_4$, filtered reaction mixture was quenched with saturated *aq*. $NaHCO_3$ (20 mL) and extracted with DCM (3 x 30 mL and concentrated *in vacuo*. The resulting crude product was purified by column chromatography (0% EtOAc in hexanes → 10% EtOAc in hexanes) to afford triflate **80** (1.34 g, 3.51 mmol, 88% yield) as a yellow oil. **TLC**: $R_f$ = 0.5 (10% EtOAc in hexanes); **$^1$H NMR** (600 MHz, $C_6D_6$) δ 6.30 (dd, *J* = 3.0, 1.7 Hz, 1H), 6.18 (t, *J* = 3.2 Hz, 1H), 5.97 – 5.92 (m,1H), 5.01 (d, *J* = 1.5 Hz, 1H), 4.52 (qd, *J* = 7.1, 1.5 Hz, 1H), 1.92 (s, 3H), 1.25 (s, 9H), 1.10 (d, *J* = 7.1 Hz, 3H); **$^{13}$C NMR** (151 MHz, $C_6D_6$) δ 161.6, 157.7, 128.9, 128.5, 116.1, 113.5, 109.3,109.0, 82.6, 52.8, 27.7(3C), 17.1, 11.4; **IR** (thin film) $\nu_{max}$ ($cm^{-1}$): 2982, 2936, 1725, 1673, 1431, 1297, 1209, 1153, 1020, 915, 792, 700, 595; **HRMS** (m/z): (ESI) calcd. for $C_{15}H_{21}F_3NO_5S$ $[M+H]^+$: 384.1087, found 384.1092.




**Negishi coupling of 79 & (±)-80**: To a 20 mL reaction tube containing iodide **79** (130 mg, 0.23 mmol, 1.0 equiv.) was added THF (5 mL) at –78 °C. *t*-BuLi (1.6 M in pentane, 0.36 mL, 0.58 mmol, 2.5 equiv) was added and the resulting mixture was stirred for 30 min. Then a solution of $ZnCl_2$ (94 mg, 0.69 mmol, 3.0 equiv.) in THF (1 mL) was added dropwise. The resulting mixture was stirred for 1 h at –78 °C. Then a solution of triflate (±)**-80** (176 mg, 0.46 mmol, 2.0 equiv.) and $Pd(PPh_3)_4$ (8.0 mg, 0.0069 mmol, 3 mol%.) in THF (3 mL) was added dropwise at –78 °C. The resulting was warmed to 25 °C and stirred for 6 h. Upon completion of the reaction as indicated by TLC, the reaction mixture was quenched with saturated *aq*. $NH_4Cl$ solution (5 mL) and extracted with $Et_2O$ (3 x 10 mL). The combined organic layers were washed with brine (5 mL), dried over $Na_2SO_4$, filtered, and concentrated *in vacuo*. The resulting crude product was purified by column chromatography (0% EtOAc in hexanes → 10% EtOAc in hexanes) to afford **81** (61 mg, 0.092 mmol, 40% yield), **82** (64 mg, 0.092 mmol, 40% yield) and **110** (10 mg, 0.023 mmol, 10% yield) as yellow oils.

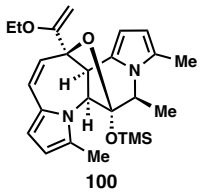



**TLC**: $R_f$ = 0.4 (10% EtOAc in hexanes); **$^1$H NMR** (600 MHz, $C_6D_6$) δ 6.71 (dd, *J* = 3.0, 1.8 Hz, 1H), 6.34 (t, *J* = 3.1 Hz, 1H), 6.27 (d, *J* = 11.5 Hz, 1H), 6.15 – 6.13 (m, 1H), 6.13 (d, *J* = 3.7 Hz,1H), 5.93 (d, *J* = 3.4 Hz, 1H), 5.72 (s, 1H), 5.70 (d, *J* = 11.5 Hz, 1H), 5.46 (d, *J* = 1.1 Hz, 1H), 4.68 (q, *J* = 6.9 Hz, 1H), 4.61 (d, *J* = 1.9 Hz, 1H), 4.39 (s, 1H), 4.13 (q, *J* = 6.3 Hz, 1H), 3.96 (s, 1H), 3.90 (d, *J* = 1.9 Hz, 1H), 3.48 (dq, *J* = 9.4, 7.0 Hz, 1H), 3.40 (dq, *J* = 9.4, 7.1 Hz, 1H), 2.14 (s, 3H), 2.06 (s, 3H), 1.89 (s, 3H), 1.61 (d, *J* = 6.3 Hz, 3H), 1.30 (d, *J* = 7.1 Hz, 3H), 1.25 (s, 9H), 1.13 (t, *J* = 7.0 Hz, 3H), 0.13 (s, 9H); **$^{13}$C NMR** (151 MHz, $C_6D_6$) δ 165.9, 164.2, 152.2, 135.2, 130.9, 129.9, 128.5, 126.0, 124.4, 124.1, 118.7, 118.5, 117.1, 114.8, 111.5, 108.6, 108.2, 107.6, 104.5, 86.9, 81.1, 78.9, 65.3, 63.1, 61.9, 57.6, 46.2, 28.2(3C), 19.4, 14.7(2C), 13.0(2C), 12.4, 1.7(3C); **IR** (thin film) $\nu_{max}$ ($cm^{-1}$): 2977, 2929, 1718, 1699, 1640, 1419, 1307, 1253, 1164, 1143,1080, 910, 845, 764, 698; **HRMS** (m/z): (ESI) calcd. for $C_{39}H_{53}N_3NaO_5Si$ $[M+Na]^+$: 694.3647,found 694.3643.



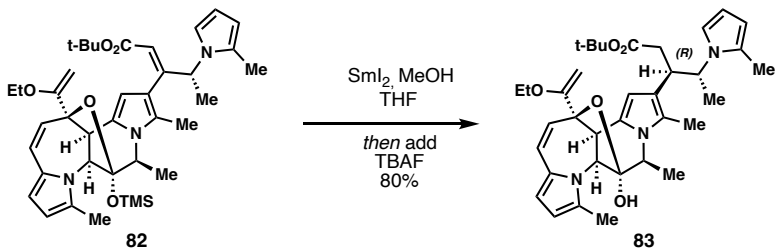

**82**

**TLC**: $R_f$ = 0.3 (10% EtOAc in hexanes); **$^1$H NMR** (600 MHz, $C_6D_6$) δ 6.48 (dd, *J* = 2.9, 1.8 Hz, 1H), 6.30 – 6.23 (m, 2H), 6.13 (d, *J* = 3.6 Hz, 1H), 6.09 – 6.07 (m, 1H), 5.96 – 5.94 (m, 1H), 5.72 – 5.67 (m, 2H), 5.62 (s, 1H), 4.62 (d, *J* = 1.8 Hz, 1H), 4.56 (q, *J* = 7.1 Hz, 1H), 4.39 (s, 1H), 4.05 (q, *J* = 6.3 Hz, 1H), 3.96 (s, 1H), 3.86 (d, *J* = 1.8 Hz, 1H), 3.41 (dq, *J* = 9.6, 7.0 Hz, 1H), 3.31 (dq, *J* = 9.5, 7.0 Hz, 1H), 2.10 (s, 3H), 1.90 (s, 3H), 1.81 (s, 3H), 1.53 (d, *J* = 6.3 Hz, 3H), 1.32 (d, *J* = 7.1 Hz, 3H), 1.20 (s, 9H), 1.11 (t, *J* = 7.0 Hz, 3H), 0.15 (s, 9H); **$^{13}$C NMR** (151 MHz, $C_6D_6$) δ 165.6, 164.5, 152.6, 135.2, 130.8, 129.4, 128.5, 125.9, 124.3, 124.0, 120.2, 117.4, 116.8, 114.7, 111.6, 108.5, 107.8, 107.1, 104.8, 86.9, 80.6, 79.0, 65.2, 63.0, 61.7, 58.4, 46.0, 28.1(3C), 19.2, 14.8, 14.6, 13.0, 12.4, 11.8, 1.7(3C); **IR** (thin film) $\nu_{max}$ ($cm^{-1}$): 2977, 2926, 1699, 1641, 1419, 1307, 1253, 1163, 1081, 910, 845, 763, 698; **HRMS** (m/z): (ESI) calcd. for $C_{39}H_{53}N_3NaO_5Si$ $[M+Na]^+$: 694.3647, found 694.3640.



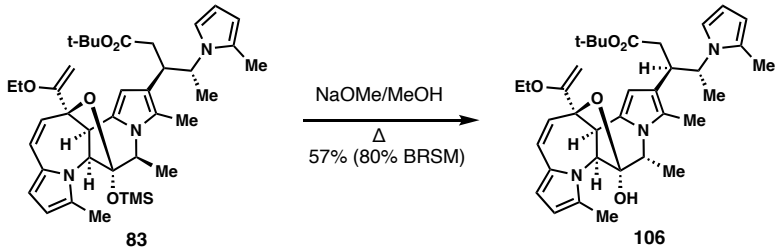

**100**

**TLC**: $R_f$ = 0.6 (10% EtOAc in hexanes); **$^1$H NMR** (600 MHz, $C_6D_6$) δ 6.26 (d, *J* = 11.5 Hz, 1H), 6.11 (d, *J* = 3.6 Hz, 1H), 5.98 (dd, *J* = 3.3, 1.0 Hz, 1H), 5.90 (dd, *J* = 3.6, 0.9 Hz, 1H), 5.86 (d, *J* = 3.3 Hz, 1H), 5.68 (d, *J* = 11.5 Hz, 1H), 4.64 (d, *J* = 1.7 Hz, 1H), 4.35 (s, 1H), 4.12 (q, *J* = 6.3 Hz, 1H), 4.00 (s, 1H), 3.84 (d, *J* = 1.7 Hz, 1H), 3.39 (dq, *J* = 9.3, 7.0 Hz, 1H), 3.29 (dq, *J* = 9.3, 7.0 Hz, 1H), 2.07 (s, 3H), 1.82 (s, 3H), 1.61 (d, *J* = 6.3 Hz, 3H), 1.09 (t, *J* = 7.0 Hz, 3H), 0.14 (s, 9H); **$^{13}$C NMR** (151 MHz, $C_6D_6$) δ 164.7, 135.3, 130.9, 130.4, 127.1, 124.3, 124.2, 114.6, 111.7, 108.4, 108.4, 104.7, 86.9, 80.6, 65.5, 63.0, 61.7, 46.4, 14.8, 14.6, 14.2, 13.0, 1.8(3C); **IR** (thin film) $\nu_{max}$ ($cm^{-1}$): 2977, 2958, 1641, 1416, 1309, 1251, 1080, 909, 845, 762; **HRMS** (m/z): (ESI) calcd. for $C_{25}H_{35}N_2O_3Si$ $[M+H]^+$: 439.2411, found 439.2411.




**82** **83**

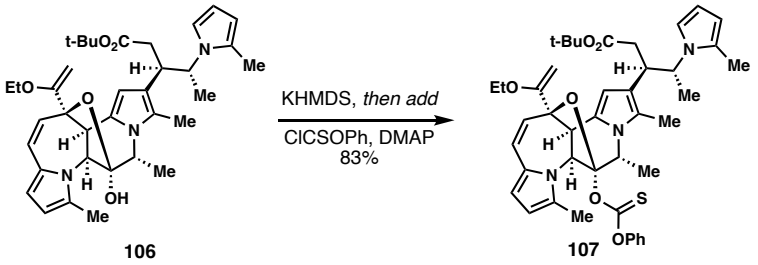
**Lactol 83**: Ester **82** (100 mg, 0.15 mmol, 1.0 equiv.) was dissolved in THF (9 mL) and MeOH (1 mL) at 0 °C, then the solution was degassed by sparging with argon for 5 min. $SmI_2$ (0.1 M in THF, 3.0 mL, 0.30 mmol, 2.0 equiv) was added and the resulting mixture was stirred for 30 min. The mixture was warmed to 25 °C and then TBAF (1.0 M in THF, 0.3 mL, 0.30 mmol, 2.0 equiv.) was added. Upon completion of the reaction as indicated by TLC, the reaction mixture was quenched with saturated *aq*. $NH_4Cl$ solution (5 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over $Na_2SO_4$, filtered, and concentrated *in vacuo*. The resulting crude product was purified by column chromatography (0% EtOAc in hexanes → 10% EtOAc in hexanes) to afford lactol **83** (71.6 mg, 0.12 mmol, 80% yield) as a brown foam. **TLC**: $R_f$ = 0.5 (20% EtOAc in hexanes); **$^1$H NMR** (600 MHz, $C_6D_6$) δ 6.40 (dd, *J* = 2.9, 1.8 Hz, 1H), 6.29 (t, *J* = 3.2 Hz, 1H), 6.27 (d, *J* = 11.6 Hz, 1H), 6.14 (d, *J* = 3.6 Hz, 1H), 6.08 (ddd, *J* = 3.6, 1.8, 0.9 Hz, 1H), 5.92 (dd, *J* = 3.6, 0.9 Hz, 1H), 5.77 (d, *J* = 11.5 Hz, 1H), 5.65 (s, 1H), 4.66 (d, *J* = 1.9 Hz, 1H), 4.31 (d, *J* = 0.9 Hz, 1H), 4.18 – 4.12 (m, 1H), 4.10 (q, *J* = 6.3 Hz, 1H), 3.83 (s, 1H), 3.80 (d, *J* = 1.9 Hz, 1H), 3.43 – 3.35 (m, 2H), 3.29 (dq, *J* = 9.4, 7.0 Hz, 1H), 2.67 (s, 1H), 2.47 (dd, *J* = 14.9, 9.2 Hz, 1H), 2.40 (dd, *J* = 14.9, 6.3 Hz, 1H), 2.24 (s, 2H), 1.81 (s, 3H), 1.80 (s, 3H), 1.61 (d, *J* = 6.2 Hz, 3H), 1.21 (d, *J* = 6.6 Hz, 3H), 1.20 (s, 9H), 1.12 (t, *J* = 7.0 Hz, 3H); **$^{13}$C NMR** (151 MHz, $C_6D_6$) δ 171.6, 164.4, 134.9, 130.3, 129.1, 127.5, 125.9, 125.7, 122.9, 118.5, 116.8, 114.5, 109.4, 109.2, 107.5, 107.0, 103.5, 85.9, 80.7, 79.5, 64.6, 63.0, 59.5, 55.2, 45.6, 40.6, 39.5, 28.0(3C), 17.9, 15.2, 14.6, 12.9, 12.5, 11.0; **IR** (thin film) $\nu_{max}$ ($cm^{-1}$): 2977, 2924, 2361, 1726, 1643, 1424, 1300, 1144, 1081, 951, 767, 702; **HRMS** (m/z): (ESI) calcd. for $C_{36}H_{47}N_3NaO_5$ $[M+Na]^+$: 624.3408, found 624.3408.



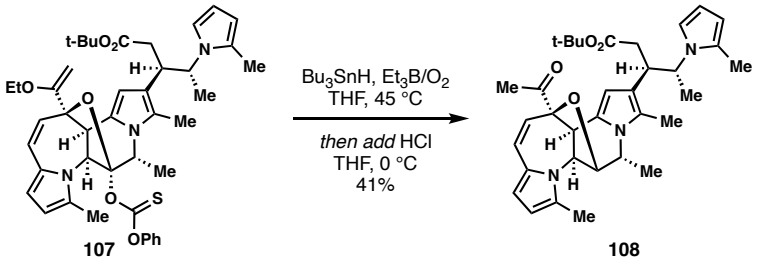

83 106

**Epimerization of 106**: In a nitrogen-filled glovebox, a reaction tube containing lactol **83** (730 mg, 1.21 mmol, 1.0 equiv.) was charged with NaOMe (328 mg, 6.07 mmol, 5.0 equiv.). The reaction tube was sealed, removed from the glovebox, and placed under an atmosphere of nitrogen. Anhydrous MeOH (30 mL) was then added, the $N_2$ balloon was removed, and the sealed reaction vessel was heated at 90 °C for 1 h. The reaction mixture was then cooled to room temperature and quenched with saturated *aq*. $NH_4Cl$ solution (30 mL). The solution was extracted with EtOAc (3 x 40 mL) and the combined organic layers were washed with brine (40 mL), dried over $Na_2SO_4$, filtered and concentrated *in vacuo*. The resulting crude residue was purified by column chromatography (0% EtOAc in hexanes → 10% EtOAc in hexanes) to afford lactol epimers **106** (416 mg, 0.69 mmol, 57%, 80% BRSM) and **83** (211 mg, 0.35 mmol, 29%) as brown foams. **TLC**: $R_f$ = 0.4 (20% EtOAc in hexanes); **$^1$H NMR** (600 MHz, $C_6D_6$) δ 6.65 (t, *J* = 2.2 Hz, 1H), 6.37 (t, *J* = 3.1 Hz, 1H), 6.28 (d, *J* = 11.5 Hz, 1H), 6.16 (d, *J*

= 3.6 Hz, 1H), 6.10 (dd, *J* = 3.4, 1.7 Hz, 1H), 5.94 (d, *J* = 3.5 Hz, 1H), 5.78 (d, *J* = 11.5 Hz, 1H), 5.68 (s, 1H), 4.57 (s, 1H), 4.45 (d, *J* = 1.7 Hz, 1H), 4.16 (q, *J* = 6.4 Hz, 1H), 3.99 (dq, *J* = 9.1, 6.8 Hz, 1H), 3.85 (s, 1H), 3.58 (d, *J* = 1.8 Hz, 1H), 3.42 – 3.34 (m, 2H), 3.29 (dq, *J* = 9.3, 7.1 Hz, 1H), 2.68 (s, 1H), 2.37 (dd, *J* = 14.8, 10.6 Hz, 1H), 2.26 (dd, *J* = 14.8, 4.8 Hz, 1H), 2.18 (s, 3H), 1.93 (s, 3H), 1.88 (s, 3H), 1.30 (d, *J* = 6.5 Hz, 3H), 1.20 (d, *J* = 6.7 Hz, 3H), 1.18 (s, 9H), 1.12 (t, *J* = 7.0 Hz, 3H); **$^{13}$C NMR** (151 MHz, $C_6D_6$) δ 171.6, 163.9, 135.0, 130.6, 128.6, 127.6, 125.1, 125.0, 122.8, 120.2, 116.2, 114.6, 110.3, 109.1, 108.4, 107.0, 103.0, 87.1, 79.4, 79.1, 62.9, 60.5, 60.3, 56.0, 46.4, 41.6, 39.7, 28.0(3C), 19.8, 19.3, 14.7, 13.3, 12.5, 10.2; **IR** (thin film) $\nu_{max}$ ($cm^{-1}$): 2973, 2925, 2853, 2363, 2336, 1727, 1489, 1283, 1192, 1162, 1027, 767; **HRMS** (m/z): (ESI) calcd. for $C_{36}H_{47}N_3NaO_5$ $[M+Na]^+$: 624.3408, found 624.3412.

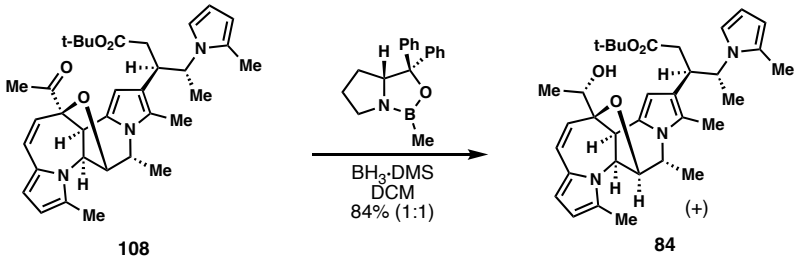



**Thiocarbonate 107**: Lactol **106** (500 mg, 0.83 mmol, 1.0 equiv.) was azeotropically dried with benzene (3x) and then dissolved in THF (50 mL) under an inert atmosphere. The solution was cooled to –78 °C and KHMDS (1.0 M in THF, 1.0 mL, 0.99 mmol, 1.2 equiv.) was added dropwise down the side of the reaction vessel. The reaction was stirred for 30 min and added a solution of DMAP (195 mg, 1.6 mmol, 2.0 equiv.) in THF (5 mL) and followed by O-phenyl chlorothionoformate (75 μL, 1.6 mmol, 2.0 equiv.). The mixture was stirred for 1 h at –78 °C and then quenched by the addition of saturated *aq*. $NaHCO_3$ (10 mL). The solution was extracted with EtOAc (3 x 30 mL) and the combined organics were washed with brine (20 mL), dried over $Na_2SO_4$, filtered and concentrated *in vacuo*. The resulting crude residue was purified by column chromatography (0% EtOAc in hexanes → 10% EtOAc in hexanes) to afford thiocarbonate **107** (509 mg, 0.69 mmol, 83%), as a yellow oil. **TLC**: $R_f$ = 0.5 (20% EtOAc in hexanes); **$^1$H NMR** (600 MHz, $C_6D_6$) δ 6.92 – 6.85 (m, 2H), 6.82 – 6.77 (m, 1H), 6.68 (dd, *J* = 2.9, 1.8 Hz, 1H), 6.64 – 6.60 (m, 2H), 6.37 (t, *J* = 3.1 Hz, 1H), 6.32 (d, *J* = 11.6 Hz, 1H), 6.19 (d, *J* = 3.6 Hz, 1H), 6.14 – 6.07 (m, 1H), 6.00 – 5.94 (m, 2H), 5.72 (t, *J* = 5.7 Hz, 2H), 4.95 (d, *J* = 1.0 Hz, 1H), 4.69 (d, *J* = 2.0 Hz, 1H), 4.00 (dq, *J* = 9.8, 6.7 Hz, 1H), 3.94 (s, 1H), 3.59 (d, *J* = 2.0 Hz, 1H), 3.43 (td, *J* = 10.2, 4.6 Hz, 1H), 3.34 (dq, *J* = 9.4, 7.0 Hz, 1H), 3.28 (dq, *J* = 9.3, 7.1 Hz, 1H), 2.40 (dd, *J* = 14.9, 10.5 Hz, 1H), 2.29 (dd, *J* = 14.9, 4.7 Hz, 1H), 2.19 (s, 3H), 2.02 (s, 3H), 2.00 (s, 3H), 1.47 (d, *J* = 6.5 Hz, 3H), 1.21 (d, *J* = 6.9 Hz, 3H), 1.20 (s, 9H), 1.12 (t, *J* = 7.0 Hz, 3H); **$^{13}$C NMR** (151 MHz, $C_6D_6$) δ 190.3, 171.6, 163.2, 153.6, 135.3, 130.5,129.6, 128.4, 127.6, 126.5, 125.4, 124.3, 122.6, 122.2, 120.7, 116.1, 115.6, 115.3, 109.1, 108.5, 107.1, 103.2, 91.1, 80.2, 79.2, 63.0, 61.7, 57.6, 56.0, 45.4, 41.5, 39.7, 28.0(3C), 19.9, 18.7, 14.7, 13.6, 12.5, 10.4; **IR** (thin film) $\nu_{max}$ ($cm^{-1}$): 2977, 2928, 2361, 1726, 1489, 1300, 1277,1197, 1161, 1077, 1003, 768; **HRMS** (m/z): (ESI) calcd. for $C_{43}H_{51}N_3NaO_6S$ $[M+Na]^+$: 760.3391, found 760.3392.




107 108

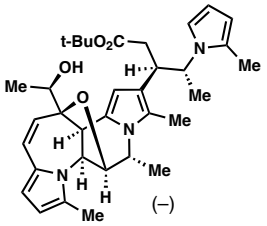
**Ketone 108**: Thiocarbonate **107** (70 mg, 0.095 mmol, 1.0 equiv.) was dissolved in THF (5 mL) and the solution degassed by sparging with argon for 5 min at 45 °C. Tributyltin hydride (51 $\mu$L, 0.19 mmol, 2.0 equiv.) and $BEt_3$ (1.0 M in hexanes, 95 $\mu$L, 0.095 mmol, 1.0 equiv.) were then added to the mixture. A syringe containing 3 mL of air was placed into the reaction solution, and air was bubbled into the mixture at a rate of approximately 1mL/hr. Upon completion of the reaction as indicated by TLC, the mixture was cooled to 0 °C and 1M *aq*. HCl (1 mL) was added dropwise. The resulting solution was vigorously stirred for 30 min, and was quenched with saturated *aq*. $NaHCO_3$ (5 mL). The solution was extracted with EtOAc (3 x 10 mL) and the combined organic layers were washed with brine (10 mL), dried over $Na_2SO_4$, filtered and concentrated *in vacuo*. The resulting crude residue was purified by preparative TLC (10% $Et_2O$ in DCM) to afford ketone **108** (21.7 mg, 0.039 mmol, 41%) as a white solid. **TLC**: $R_f$ = 0.6 (10% $Et_2O$ in DCM); **$^1$H NMR** (600 MHz, $C_6D_6$) δ 6.57 (dd, *J* = 3.0, 1.8 Hz, 1H), 6.31 (t, *J* = 3.1 Hz, 1H), 6.28 (d, *J* = 11.5 Hz, 1H), 6.17 (d, *J* = 3.6 Hz, 1H), 6.09 – 6.05 (m, 1H), 5.95 (dd, *J* = 3.7, 0.9 Hz, 1H), 5.63 (d, *J* = 11.4 Hz, 1H), 5.61 (s, 1H), 4.48 (s, 1H), 4.16 – 4.13 (m, 1H), 4.11 (q, *J* = 7.2 Hz, 1H), 3.75 (s, 1H), 3.72 (qd, *J* = 6.7, 2.2 Hz, 1H), 3.44 – 3.36 (m, 1H), 2.35 – 2.25 (m, 2H), 2.19 (s, 3H), 1.75 (s, 3H), 1.74 (s, 3H), 1.70 (s, 3H), 1.25 (d, *J* = 6.8 Hz, 3H), 1.17 (s, 9H), 0.78 (d, *J* = 6.6 Hz, 3H); **$^{13}$C NMR** (151 MHz, $C_6D_6$) δ 209.3, 171.5, 132.8, 130.6, 127.6, 127.3, 125.7, 124.2, 121.4, 120.1, 116.6, 114.7, 109.1, 107.8, 107.2, 104.8, 94.4, 90.3, 79.2, 60.1, 56.7, 55.0, 46.0, 41.1, 40.0, 28.0(3C), 26.8, 19.3, 18.3, 13.4, 12.5, 9.6; **IR** (thin film) $\nu_{max}$ ($cm^{-1}$): 3481, 2925, 2854, 2364, 1725, 1644, 1449, 1391, 1282, 1165, 1067, 770, 750,702; **HRMS** (m/z): (ESI) calcd. for $C_{34}H_{43}N_3NaO_4$ $[M+Na]^+$: 580.3146, found 580.3140.




108 84

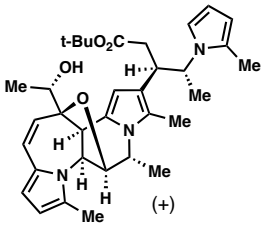
**CBS reduction of 108**: In a $N_2$ filled glovebox, a reaction tube was charged with (*R*)-(+)-2-methyl-CBS-oxazaborolidine (2.0 mg, 9.0 $\mu$mol, 1.0 equiv.). The reaction tube was sealed and brought out of the glovebox under inert atmosphere. DCM (0.2 mL) was

added followed by $BH_3$•DMS (1.1 $\mu$L, 18.0 $\mu$mol, 2.0 equiv.) and the mixture stirred for 15 min. Methyl ketone **108** (5.0 mg, 9.0 $\mu$mol, 1.0 equiv.) was dissolved in DCM (0.2 mL) and added dropwise to the reaction mixture. Additional DCM (0.1 mL) was used to render the transfer quantitative. Upon completion of the reaction as indicated by TLC, the reaction mixture was quenched with saturated *aq*. $NH_4Cl$ solution (1 mL) and the mixture stirred for 5 min. The solution was extracted with DCM (3 x 3 mL). The combined organic layers were washed with brine (5 mL), dried over $Na_2SO_4$, filtered, and concentrated *in vacuo*. The resulting crude residue was purified by preparative TLC (10% $Et_2O$ in DCM) to afford (–)-**109** (2.2 mg, 3.8 $\mu$mol, 42%) and (+)-**84** (2.1 mg, 3.8 $\mu$mol, 42%) both as white solids.




**109**

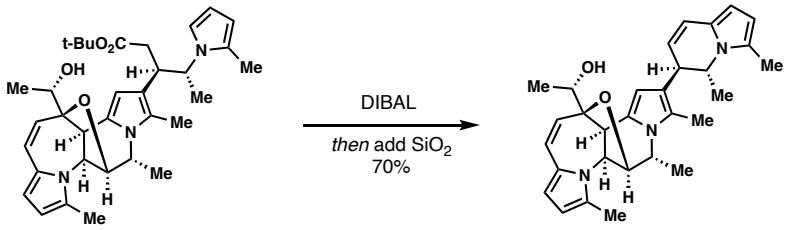
**TLC**: $R_f$ = 0.7 (10% $Et_2O$ in DCM); **$^1$H NMR** (600 MHz, $C_6D_6$) δ 6.54 (t, *J* = 2.3 Hz, 1H), 6.48 (d, *J* = 11.7 Hz, 1H), 6.30 (t, *J* = 3.2 Hz, 1H), 6.23 (d, *J* = 3.3 Hz, 1H), 6.08 (s, 1H), 5.99 (d, *J* = 3.4 Hz, 1H), 5.92 (d, *J* = 11.7 Hz, 1H), 5.47 (s, 1H), 4.54 (s, 1H), 4.17 (p, *J* = 6.9 Hz, 1H), 3.99 (d, *J* = 1.4 Hz, 1H), 3.70 (s, 1H), 3.63 – 3.56 (m, 1H), 3.46 (q, *J* = 7.5 Hz, 1H), 2.86 (d, *J* = 6.8 Hz, 1H), 2.44 – 2.35 (m, 2H), 2.21 (s, 3H), 1.78 (s, 3H), 1.71 (s, 3H), 1.44 (d, *J* = 6.5 Hz, 3H), 1.25 (d, *J* = 6.8 Hz, 3H), 1.22 (s, 9H), 0.74 (d, *J* = 6.6 Hz, 3H); **$^{13}$C NMR** (151 MHz, $C_6D_6$) δ 171.5, 132.2, 131.2, 129.1, 128.0, 126.2, 124.3, 120.8, 119.1, 116.7, 113.7, 108.9, 107.5, 107.1, 103.3, 89.8, 88.8, 79.5, 70.7, 60.6, 57.3, 54.7, 45.3, 40.5, 39.4, 28.0(3C), 19.4, 17.8, 17.7, 13.5, 12.5, 9.6; **IR** (thin film) $\nu_{max}$ ($cm^{-1}$): 3592, 3004, 1709, 1420, 1358, 1220, 1092, 902, 529; **HRMS** (m/z): (ESI) calcd. for $C_{34}H_{45}N_3NaO_4$ $[M+Na]^+$: 582.3302, found 582.3295; $[\alpha]^{25}$ = –15°(c = 0.01, MeOH).




**84**

**TLC**: $R_f$ = 0.4 (10% $Et_2O$ in DCM); **$^1$H NMR** (600 MHz, $C_6D_6$) δ 6.53 (dd, *J* = 3.0, 1.8 Hz, 1H), 6.43 (d, *J* = 11.8 Hz, 1H), 6.34 (t, *J* = 3.1 Hz, 1H), 6.21 (d, *J* = 3.6 Hz, 1H), 6.09 (d, *J* = 2.8 Hz, 1H), 6.04 (d, *J* = 11.7 Hz, 1H), 5.98 (dd, *J* = 3.5, 0.9 Hz, 1H), 5.52 (s, 1H), 4.52 (s, 1H), 4.14 (p, *J* = 7.0 Hz, 1H), 4.02 – 3.99 (m, 1H), 3.61 (qd, *J* = 6.6, 2.1 Hz, 1H), 3.48 – 3.42 (m, 1H), 3.32 (s, 1H), 2.91 (q, *J* = 6.6 Hz, 1H), 2.44 – 2.33 (m, 2H), 2.24 (s, 3H), 2.13 (s, 1H), 1.79 (s, 3H), 1.77 (s, 3H), 1.21 (s, 9H), 1.21 (d, *J* = 6.6

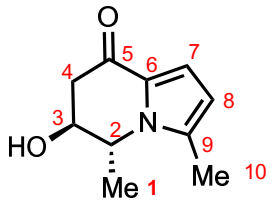
Hz, 3H), 1.19 (d, *J* = 7.0 Hz, 3H), 0.78 (d, *J* = 6.6 Hz, 3H); **$^{13}$C NMR** (151 MHz, $C_6D_6$) δ 171.5, 132.3, 131.1, 128.5, 127.7, 125.9, 124.6, 119.8, 118.9, 116.4, 113.9, 108.9, 107.9, 107.2, 104.2, 91.1, 88.9, 79.4, 72.3, 61.2, 57.6, 55.0, 43.9, 40.8, 39.8, 28.0(3C), 19.3, 18.0, 17.3, 13.5, 12.5, 9.7; **IR** (thin film) $\nu_{max}$ ($cm^{-1}$): 3360, 2922, 2852, 1727, 1646, 1465, 1425, 1280, 1159, 1080, 950, 786, 701; **HRMS** (m/z): (ESI) calcd. for $C_{34}H_{45}N_3NaO_4$ $[M+Na]^+$: 582.3302, found 582.3296; $[\alpha]^{25}$ = +12° (c = 0.01, MeOH).




84 (+)-curindolizine **(2)**

(+)-**Curindolizine (2)**: To a 10 mL reaction tube containing alcohol **84** (1.7 mg, 3.0 μmol, 1.0 equiv.) was added DCM (0.5 mL). The resulting solution was cooled to –78 °C and DIBAL (1.0 M in hexanes, 15.0 μL, 15.0 μmol, 5.0 equiv) was added dropwise. Upon completion of the reaction as indicated by TLC, the reaction mixture was quenched with saturated *aq*. Rochelle's salt (1 mL). The solution was extracted with EtOAc (3 x 5 mL) and the combined organics were washed with brine (5 mL), dried over $Na_2SO_4$, filtered and concentrated *in vacuo*. The resulting crude residue was purified by preparative TLC (10% $Et_2O$ in DCM) to afford (+)-curindolizine (**2**) (1.0 mg, 2.1 μmol, 70%) as a white solid. **TLC**: $R_f$ = 0.8 (10% $Et_2O$ in DCM); **$^1$H NMR** (600 MHz, $CDCl_3$) δ 6.51 (d, *J* = 9.6 Hz, 1H), 6.34 (d, *J* = 11.7 Hz, 1H), 6.03 (d, *J* = 3.5 Hz, 1H), 5.95 (d, *J* = 3.4 Hz, 1H), 5.87 (d, *J* = 3.5 Hz, 1H), 5.83 (d, *J* = 3.3 Hz, 1H), 5.69 (dd, *J* = 9.6, 6.3 Hz, 1H), 5.59 (d, *J* = 11.7 Hz, 1H), 5.25 (s, 1H), 4.86 (s, 1H), 4.40 (dd, *J* = 2.1, 1.1 Hz, 1H), 4.11 (qd, *J* = 6.7, 2.3 Hz, 1H), 4.02 (q, *J* = 6.7 Hz, 1H), 3.69 (s, 1H), 3.39 (d, *J* = 6.3 Hz, 1H), 2.26 (s, 3H), 2.20 (s, 3H), 2.11 (s, 2H), 1.44 (d, *J* = 6.7 Hz, 3H), 1.33 (d, *J* = 6.7 Hz, 3H), 1.12 (d, *J* = 6.4 Hz, 3H); **$^{13}$C NMR** (151 MHz, $CDCl_3$) δ 132.2, 130.4, 128.9, 128.2, 127.4, 124.0, 122.7, 122.5, 120.0, 119.7, 119.3, 113.2, 108.4, 106.5, 105.4, 103.6, 89.7, 88.9, 69.8, 60.0, 57.3, 54.2, 44.7, 38.3, 20.6, 19.6, 17.7, 13.8, 11.2, 10.3; **IR** (thin film) $\nu_{max}$ ($cm^{-1}$): 3359, 2921, 2852, 1658, 1633, 1465, 720; **HRMS** (m/z): (ESI) calcd. for $C_{30}H_{35}N_3NaO_2$ $[M+Na]^+$: 492.2621, found 492.2620; $[\alpha]^{25}$ = +314° (c = 0.01, MeOH).

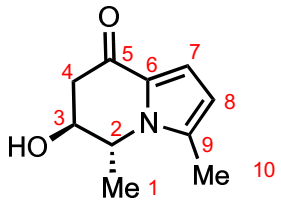
**Procuramine $^{1}$H spectra comparison:**




procuramine

| Position | $^{1}$H NMR (δ)<br>Natural Sample<br>(500 MHz, $CDCl_3$)[9] | $^{1}$H NMR (δ)<br>Synthetic Sample<br>(600 MHz, $CDCl_3$) |
|---|---|---|
| **1** | 1.37 (d, 7.0) | 1.36 (d, 6.9) |
| **2** | 4.40(qd, 7.0, 2.0) | 4.40(qd, 6.8, 1.9) |
| **3** | 4.36 (dt, 3.2, 2.0) | 4.35 (br s) |
| **4** | 2.89 (dd, 18.0, 3.2)<br>2.67 (dd, 18.0, 2.0) | 2.87 (dd, 18.0, 3.2)<br>2.64 (dd, 18.0, 2.7) |
| **5** | | |
| **6** | | |
| **7** | 7.01 (br d, 4.0) | 7.01 (d, 4.0) |
| **8** | 6.08 (br d, 4.0) | 6.08 (d, 4.0) |
| **9** | | |
| **10** | 2.32 (br s) | 2.32 (s) |

**Procuramine $^{13}C$ spectra comparison:**

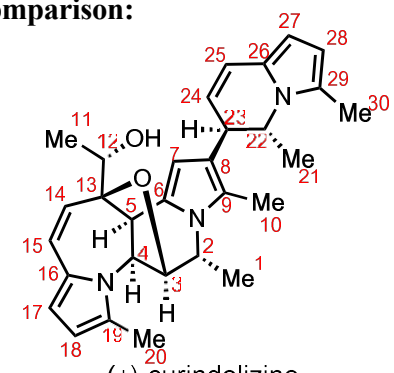



procuramine

| Position | $^{13}C$ NMR (δ) Natural Sample (125 MHz, $CDCl_3$)[9] | $^{13}C$ NMR (δ) Synthetic Sample (151 MHz, $CDCl_3$) |
|---|---|---|
| **1** | 19.3 | 19.3 |
| **2** | 53.7 | 53.6 |
| **3** | 70.5 | 70.5 |
| **4** | 39.5 | 39.4 |
| **5** | 183.5 | 183.7 |
| **6** | 128.3 | 128.3 |
| **7** | 115.1 | 115.1 |
| **8** | 111.2 | 111.2 |
| **9** | 135.7* | 135.8 |
| **10** | 12.0 | 12.0 |

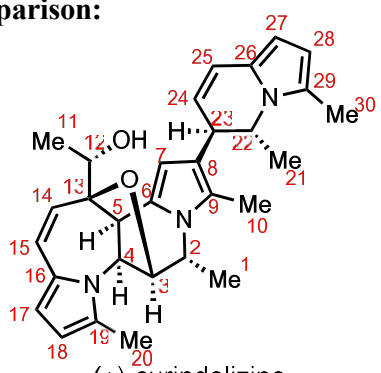
*Revised shift by $^{13}C$ NMR of the isolation paper

**(+)-Curindolizine $^{1}$H spectra comparison:**



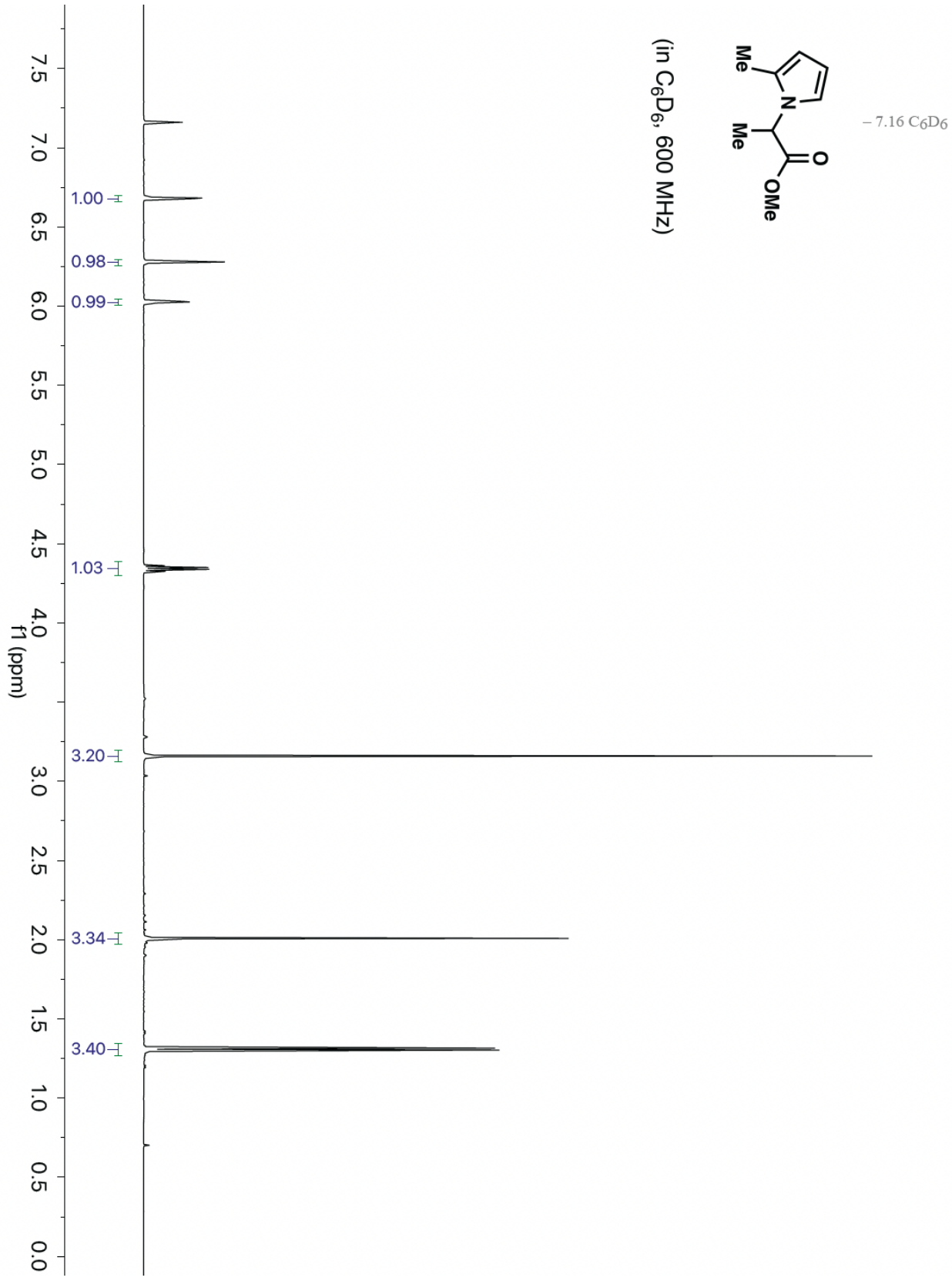

| Position | $^{1}$H NMR (δ) Natural Sample (400 MHz, $CDCl_3$)[9] | $^{1}$H NMR (δ) Synthetic Sample (600 MHz, $CDCl_3$) |
|---|---|---|
| **1** | 1.44 (d, 6.8) | 1.44 (d, 6.7) |
| **2** | 4.11(qd, 6.8, 2.0) | 4.11(qd, 6.7, 2.3) |
| **3** | 4.41 (br s) | 4.40 (dd, 2.1, 1.1) |
| **4** | 4.87 (br s) | 4.86 (s) |
| **5** | 3.70 (br s) | 3.69 (s) |
| **6** | | |
| **7** | 5.25 (br s) | 5.25 (s) |
| **8** | | |
| **9** | | |
| **10** | 2.26 (br s) | 2.26 (s) |
| **11** | 1.13 (d, 6.4) | 1.12 (d, 6.4) |
| **12** | 2.19 (q, 6.4) | 2.20 (s) |
| **13** | | |
| **14** | 5.60 (d, 11.6) | 5.59 (d, 11.7) |
| **15** | 6.35 (d, 11.6) | 6.34 (d, 11.7) |
| **16** | | |
| **17** | 6.06 (d, 3.2) | 6.03 (d, 3.5) |
| **18** | 5.88 (d, 3.2) | 5.87 (d, 3.5) |
| **19** | | |
| **20** | 2.21(br s) | 2.20(s) |
| **21** | 1.33 (d, 6.4) | 1.33 (d, 6.7) |
| **22** | 4.02 (q, 6.8) | 4.02 (q, 6.7) |
| **23** | 3.40 (br d, 6.0) | 3.39 (d, 6.3) |
| **24** | 5.69 (dd, 9.6, 6.4) | 5.69 (dd, 9.6, 6.3) |
| **25** | 6.51 (d, 9.6) | 6.51 (d, 9.6) |
| **26** | | |
| **27** | 5.96 (d, 3.2) | 5.95 (d, 3.4) |
| **28** | 5.83 (d, 3.2) | 5.83 (d, 3.3) |
| **29** | | |
| **30** | 2.12 (br s) | 2.11 (s) |

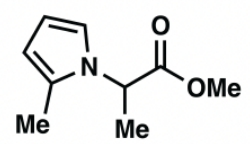
**(+)-Curindolizine $^{13}C$ spectra comparison:**



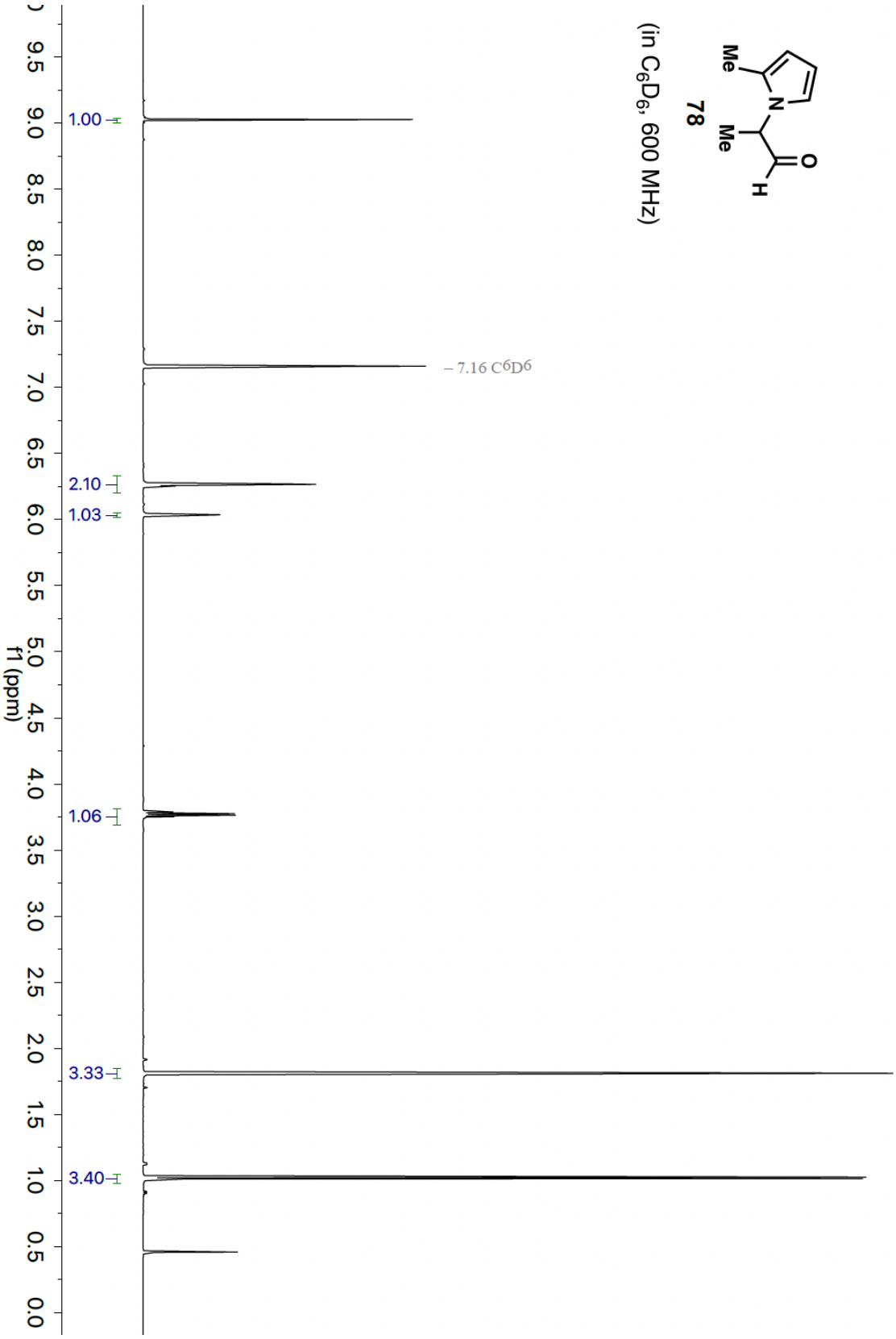
(+)-curindolizine

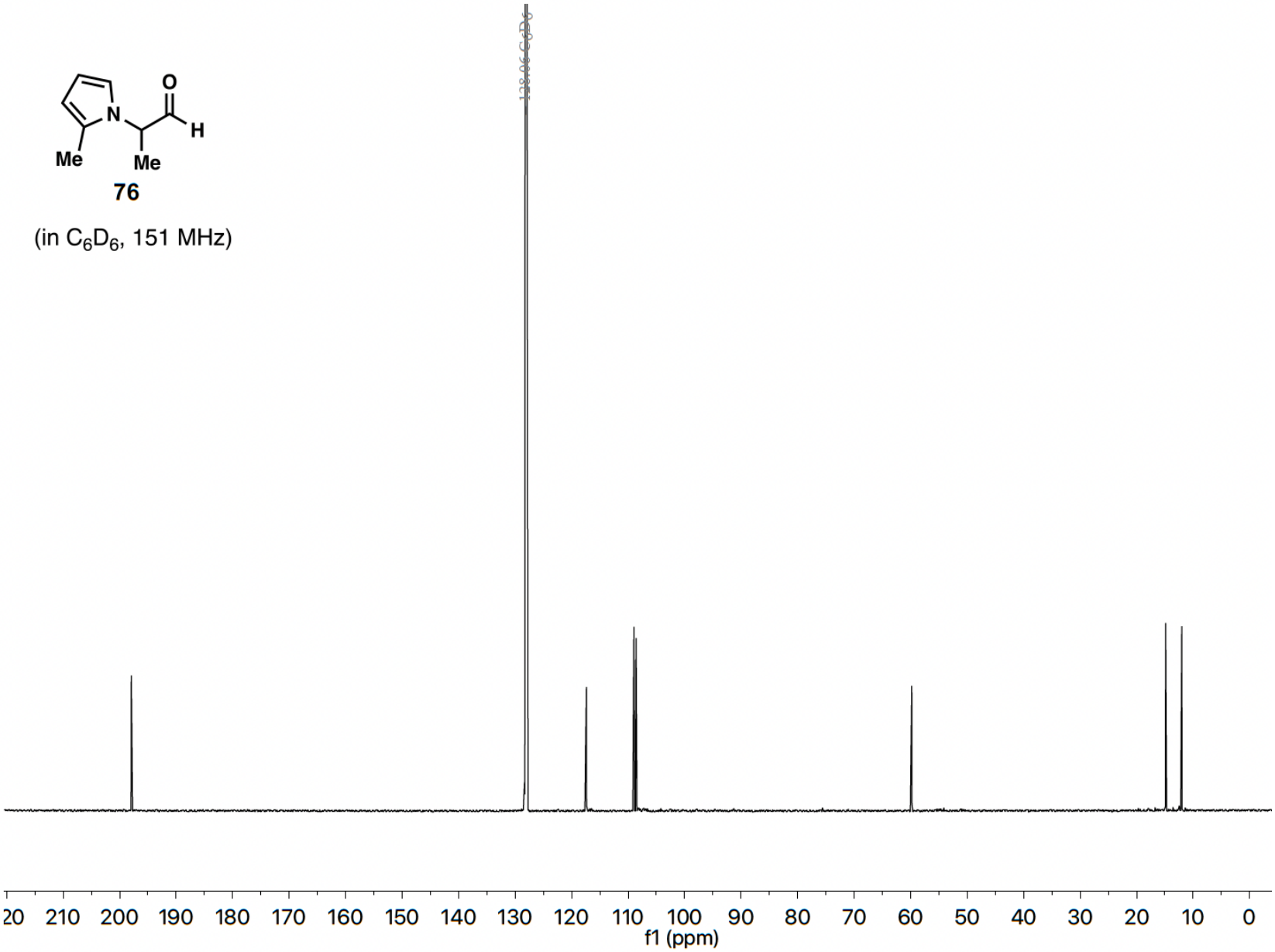
| Position | $^{13}C$ NMR (δ) Natural Sample (101 MHz, $CDCl_3$)[9] | $^{13}C$ NMR (δ) Synthetic Sample (151 MHz, $CDCl_3$) |
|---|---|---|
| **1** | 19.6 | 19.6 |
| **2** | 57.3 | 57.3 |
| **3** | 88.9 | 88.9 |
| **4** | 59.9 | 60.0 |
| **5** | 44.6 | 44.7 |
| **6** | 128.2 | 128.2 |
| **7** | 103.5 | 103.6 |
| **8** | 127.4 | 127.4 |
| **9** | 122.7 | 122.7 |
| **10** | 10.2 | 10.3 |
| **11** | 17.6 | 17.7 |
| **12** | 69.8 | 69.8 |
| **13** | 89.7 | 89.7 |
| **14** | 119.7 | 119.7 |
| **15** | 124.0 | 124.0 |
| **16** | 130.4 | 130.4 |
| **17** | 113.2 | 113.2 |
| **18** | 108.4 | 108.4 |
| **19** | 132.2 | 132.2 |
| **20** | 13.7 | 13.8 |
| **21** | 20.6 | 20.6 |
| **22** | 54.2 | 54.2 |
| **23** | 38.2 | 38.3 |
| **24** | 119.3 | 119.3 |
| **25** | 119.9 | 120.0 |
| **26** | 122.4 | 122.5 |
| **27** | 105.4 | 105.4 |
| **28** | 106.5 | 106.5 |
| **29** | 128.2 | 128.2 |
| **30** | 11.2 | 11.2 |

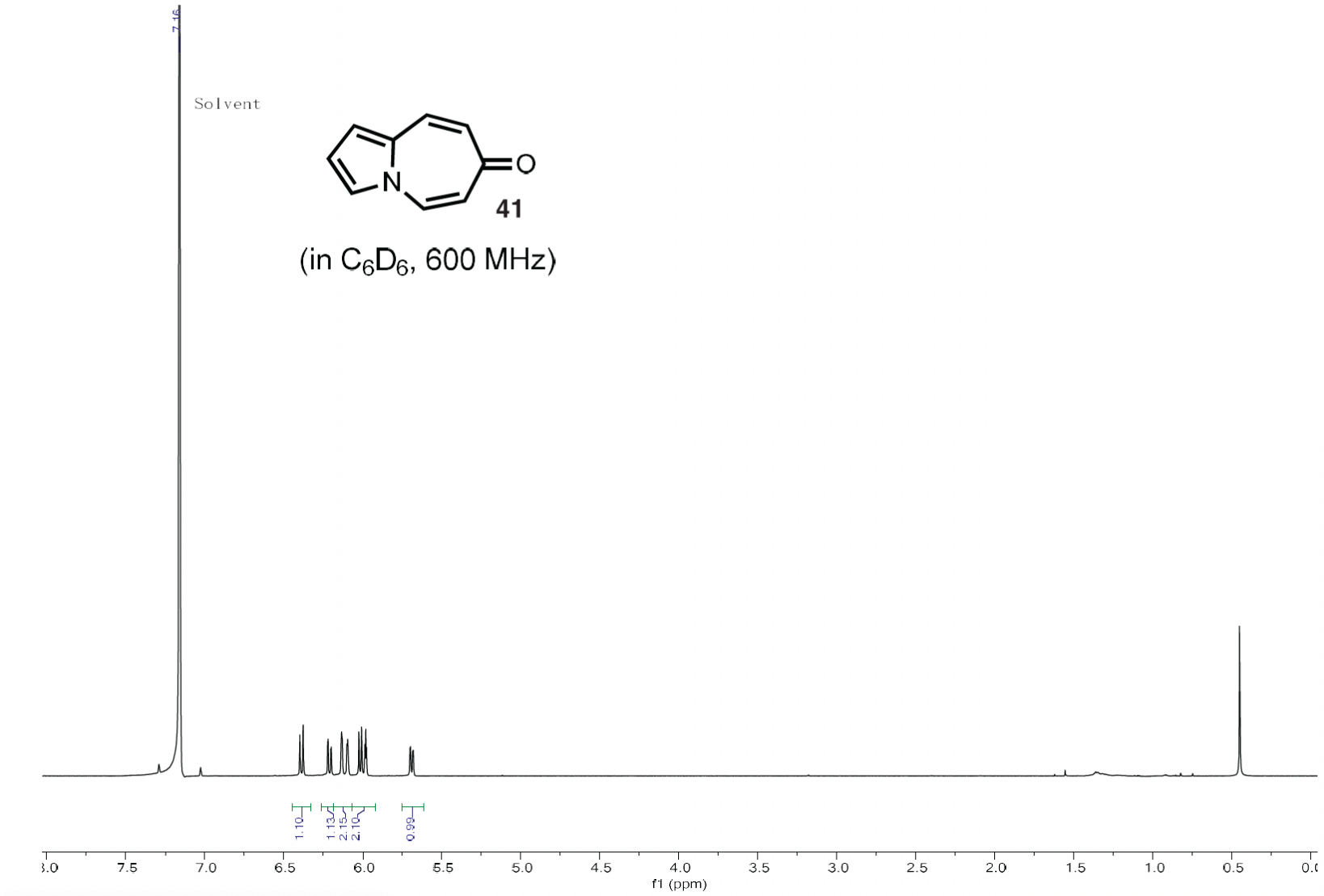

(in C6D6, 600 MHz)
Me
N
Me
O
OMe
– 7.16 C6D6
1.00
0.98
0.99
1.03
3.20
3.34
3.40
f1 (ppm)
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.0
2.5
2.0
1.5
1.0
0.5
0.0

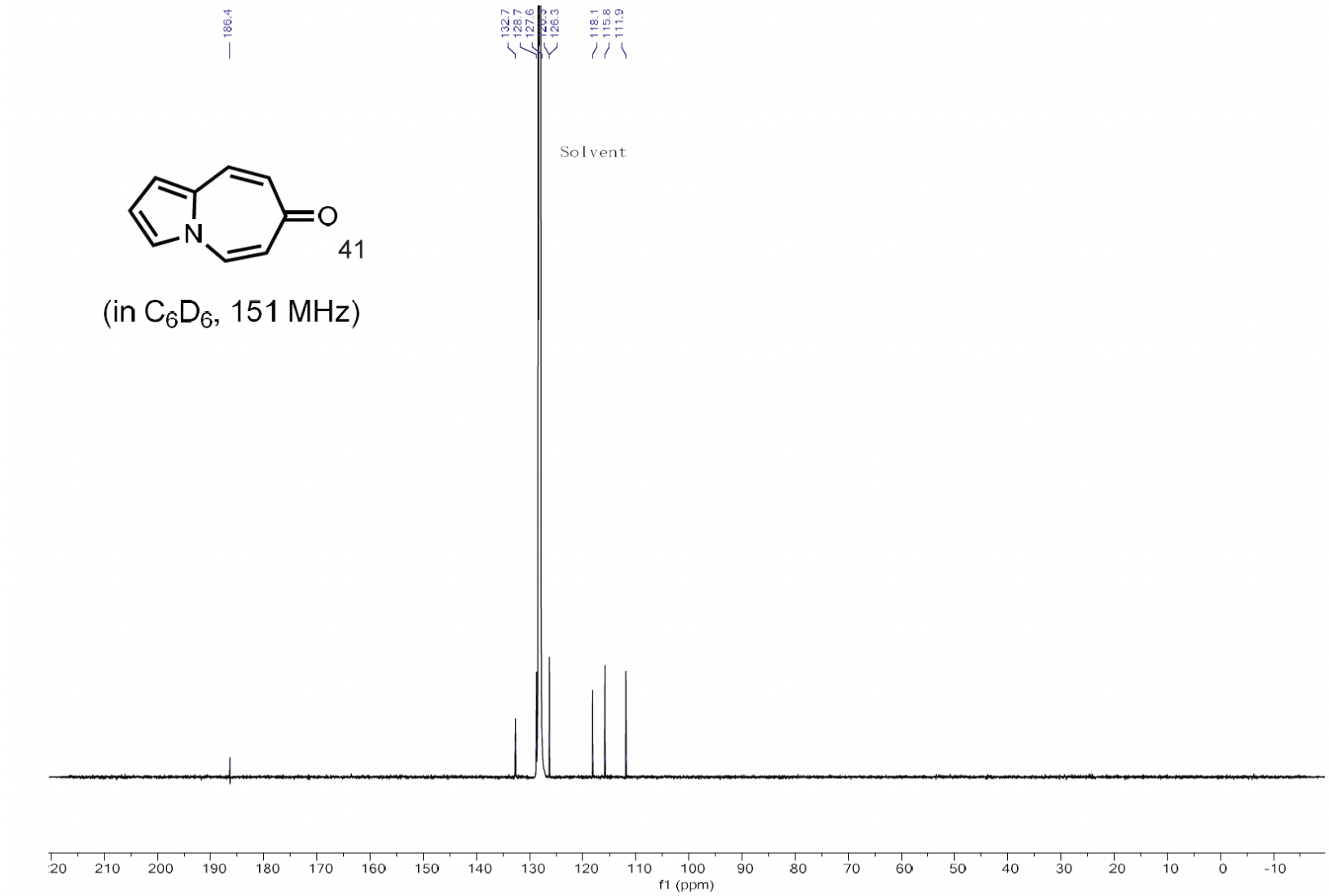


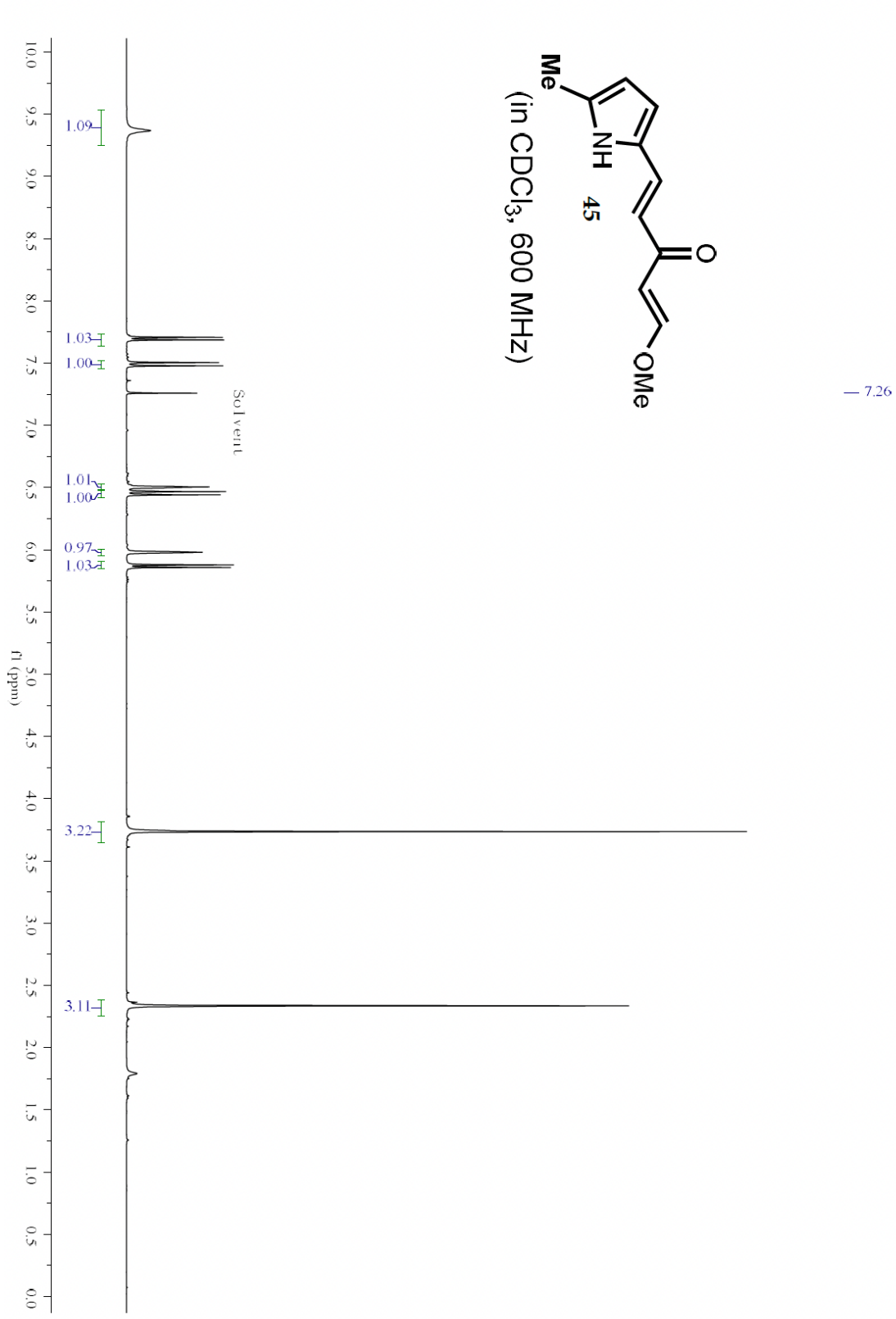

(in $C_6D_6$, 151 MHz)

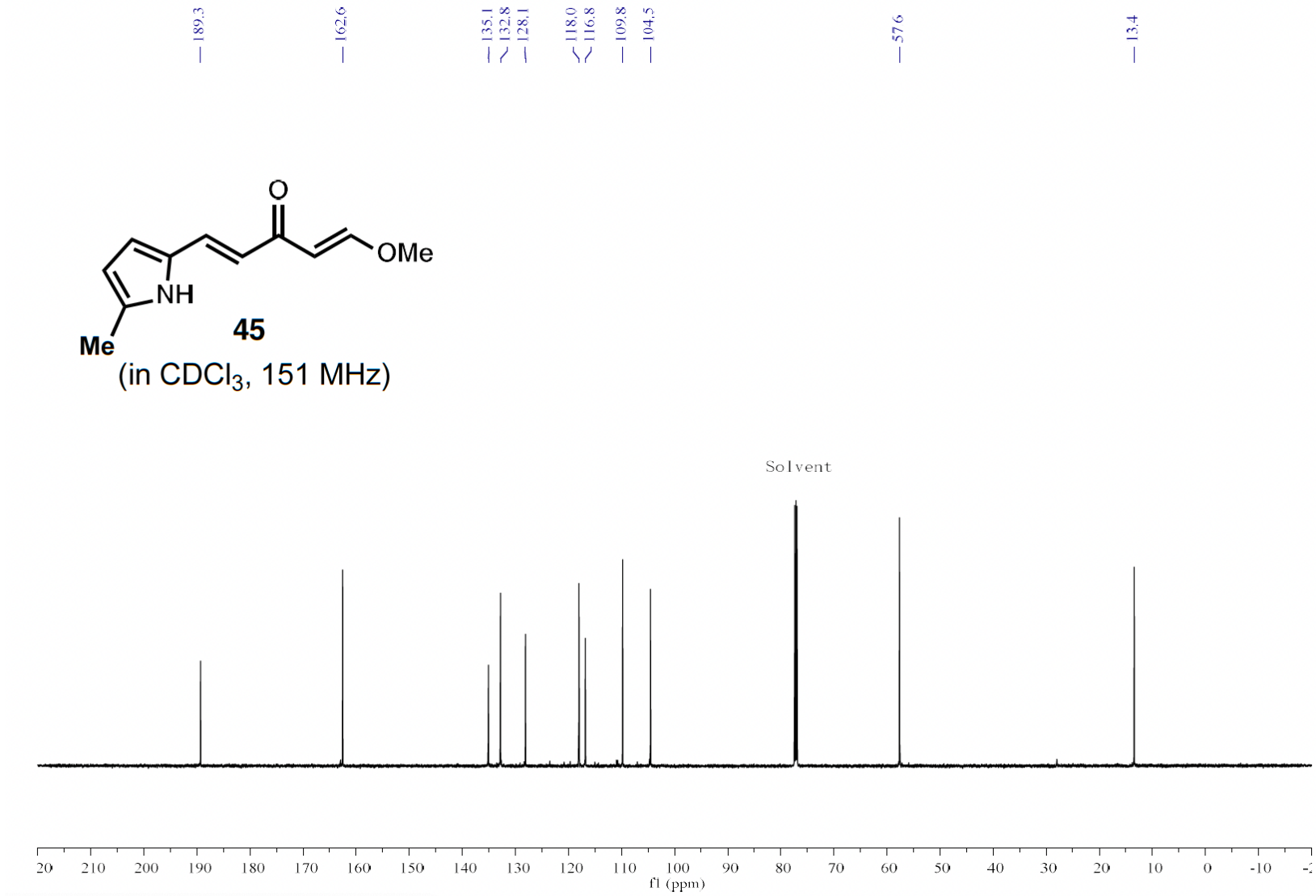

78
(in $C_6D_6$, 600 MHz)
Me
N
Me
O
H
– 7.16 C6D6
1.00
2.10
1.03
1.06
3.33
3.40
f1 (ppm)
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

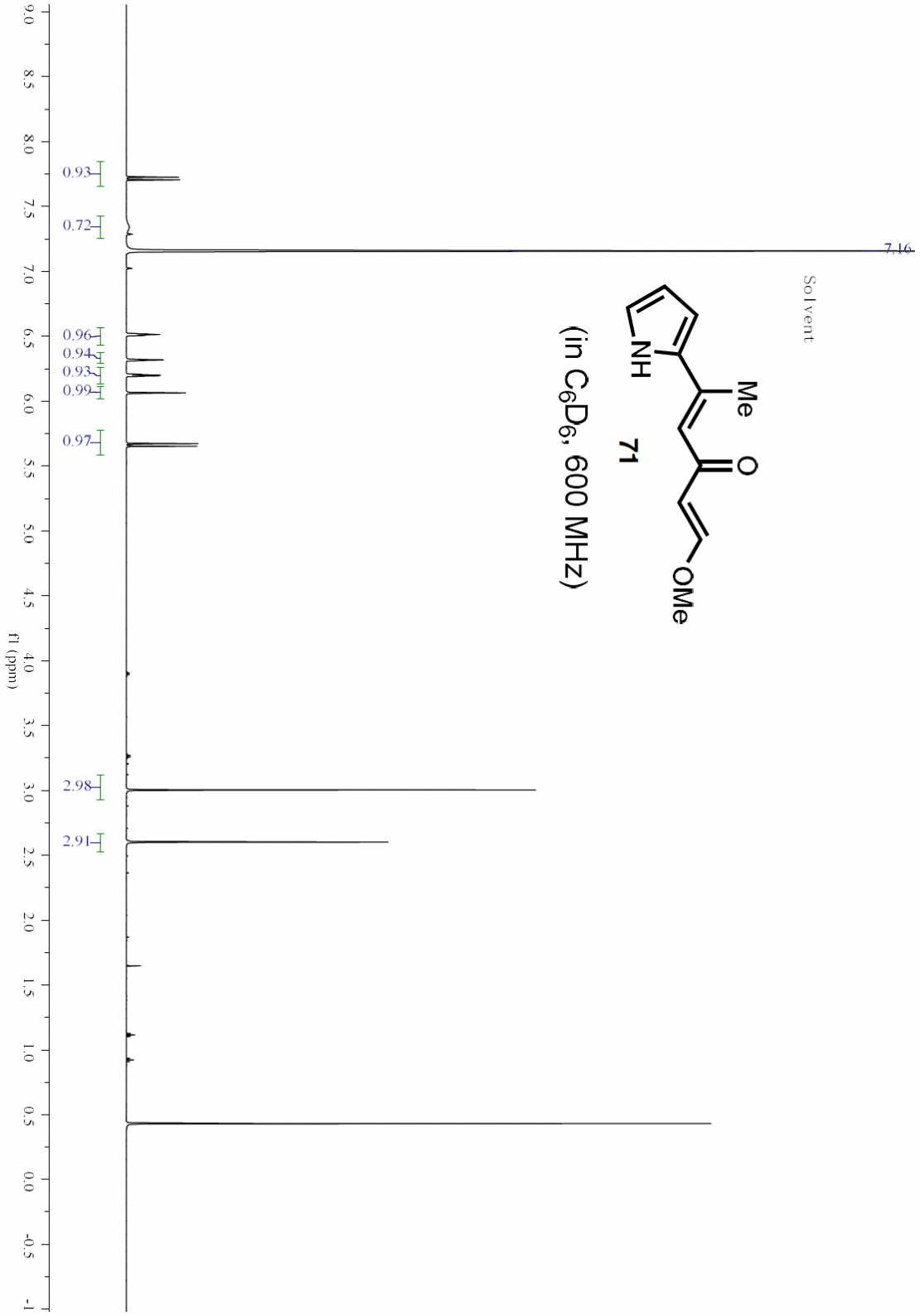

O
N
H
Me
Me
76
(in C6D6, 151 MHz)
128.06 C6D6
20 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

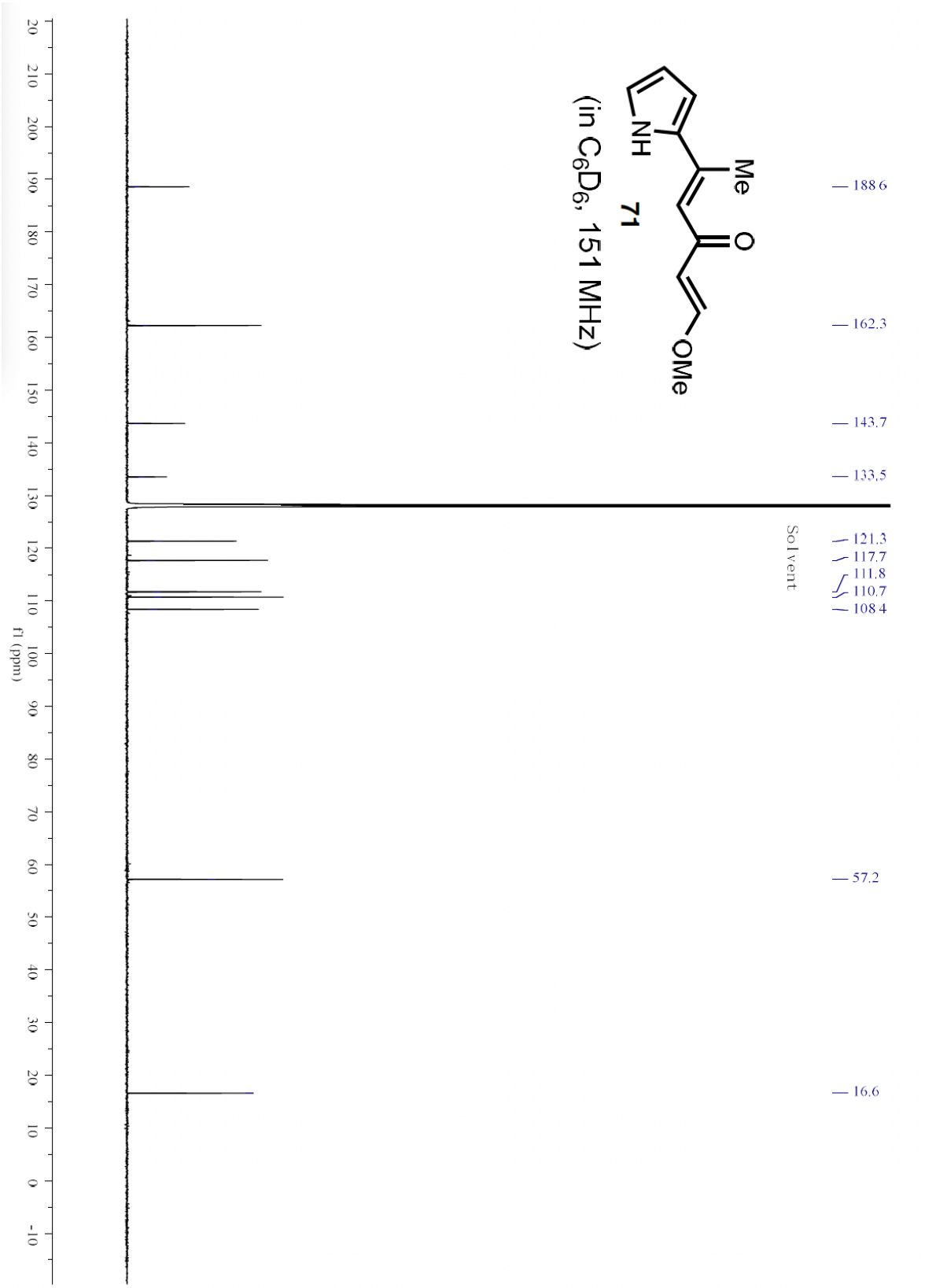

Solvent
O
N
41
(in $C_6D_6$, 600 MHz)
1.10
1.13
2.15
2.10
0.99
f1 (ppm)

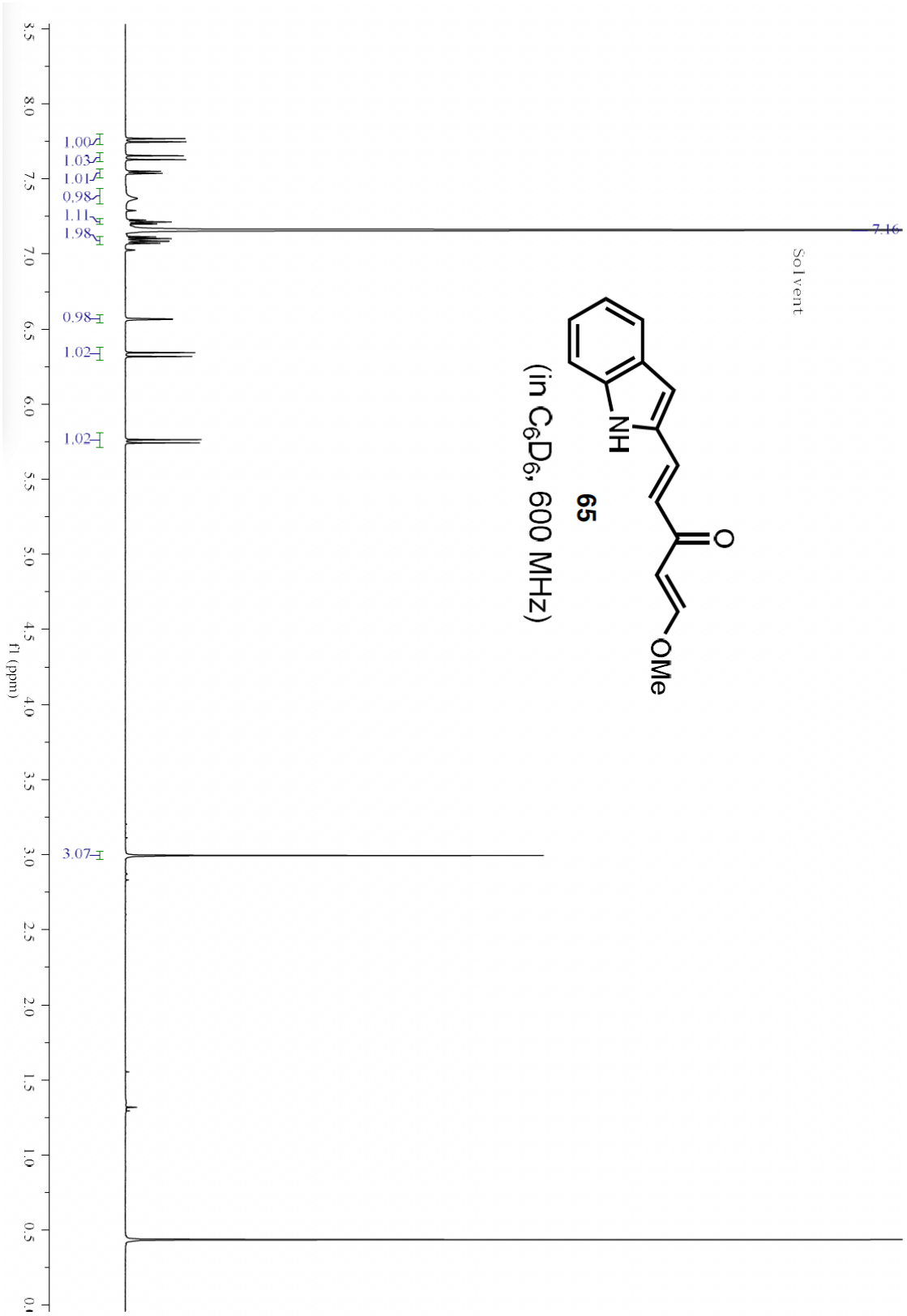

186.4
132.7
128.7
127.6
126.3
118.1
115.8
111.9
Solvent
O
N
41
(in $C_6D_6$, 151 MHz)
f1 (ppm)

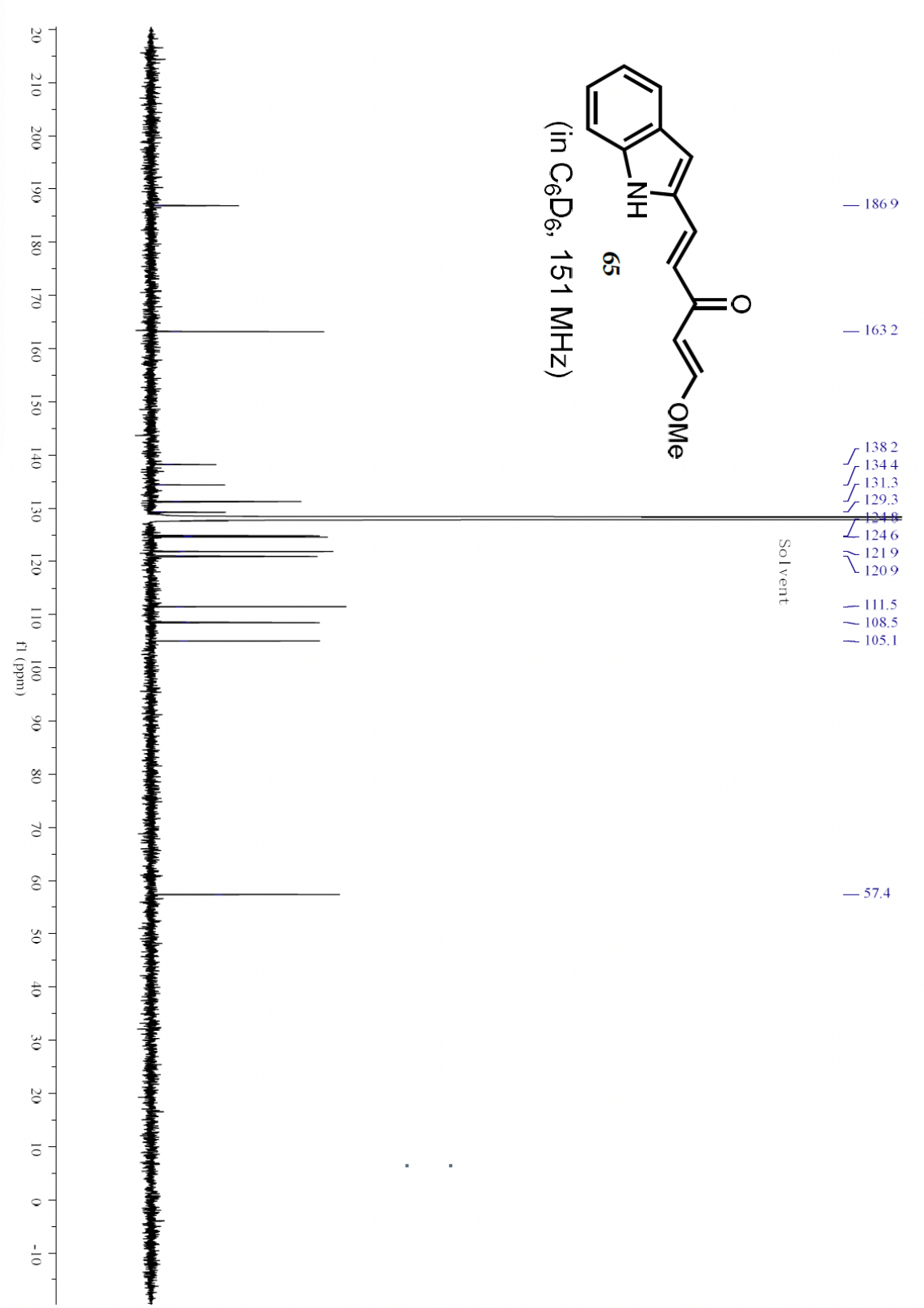

Me
NH
45
O
OMe
(in CDCl3, 600 MHz)
7.26
Solvent
1.09
1.03
1.00
1.01
1.00
0.97
1.03
3.22
3.11
f1 (ppm)

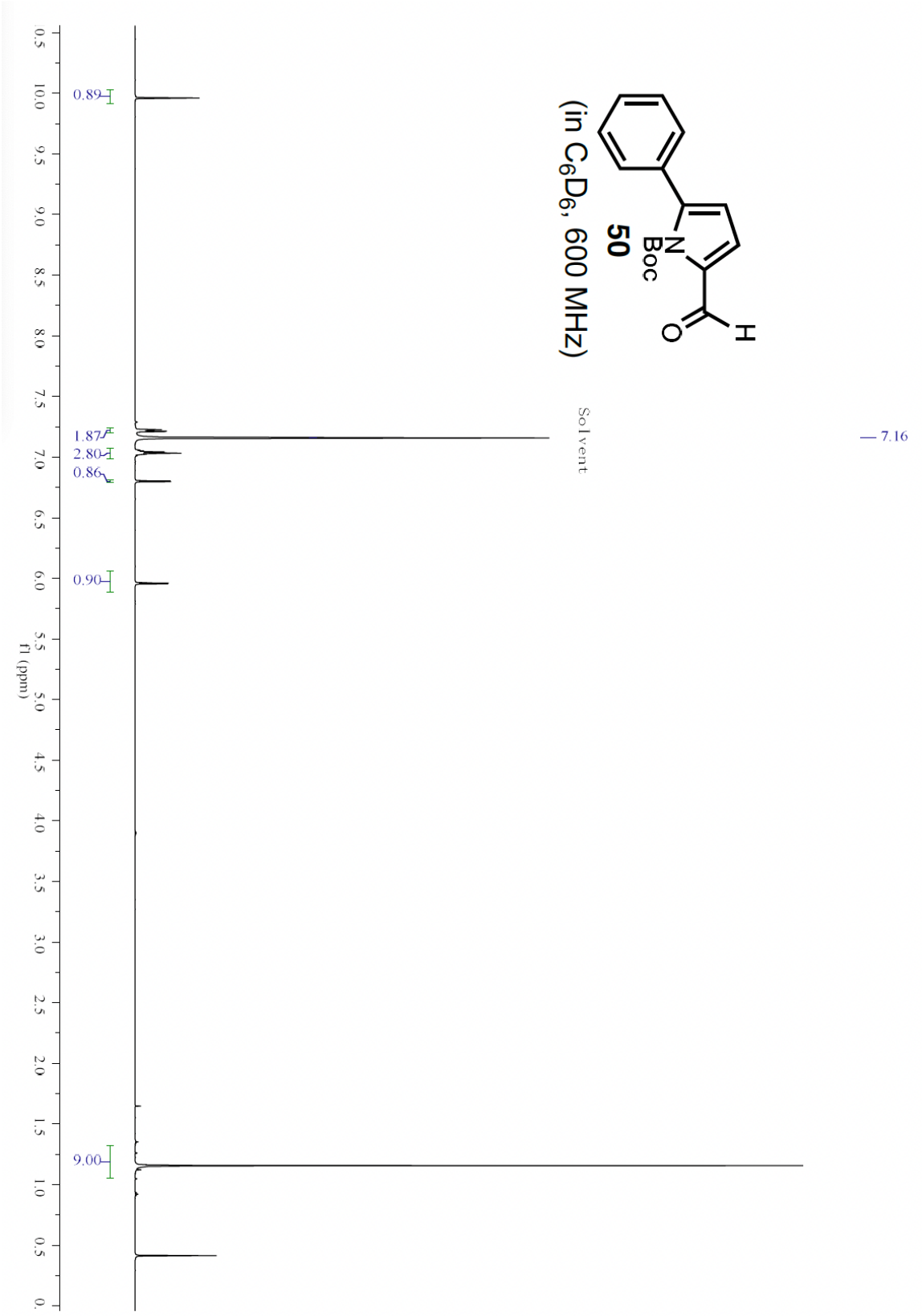

189.3
162.6
135.1
132.8
128.1
118.0
116.8
109.8
104.5
57.6
13.4
O
OMe
NH
Me
45
(in CDCl3, 151 MHz)
Solvent
f1 (ppm)

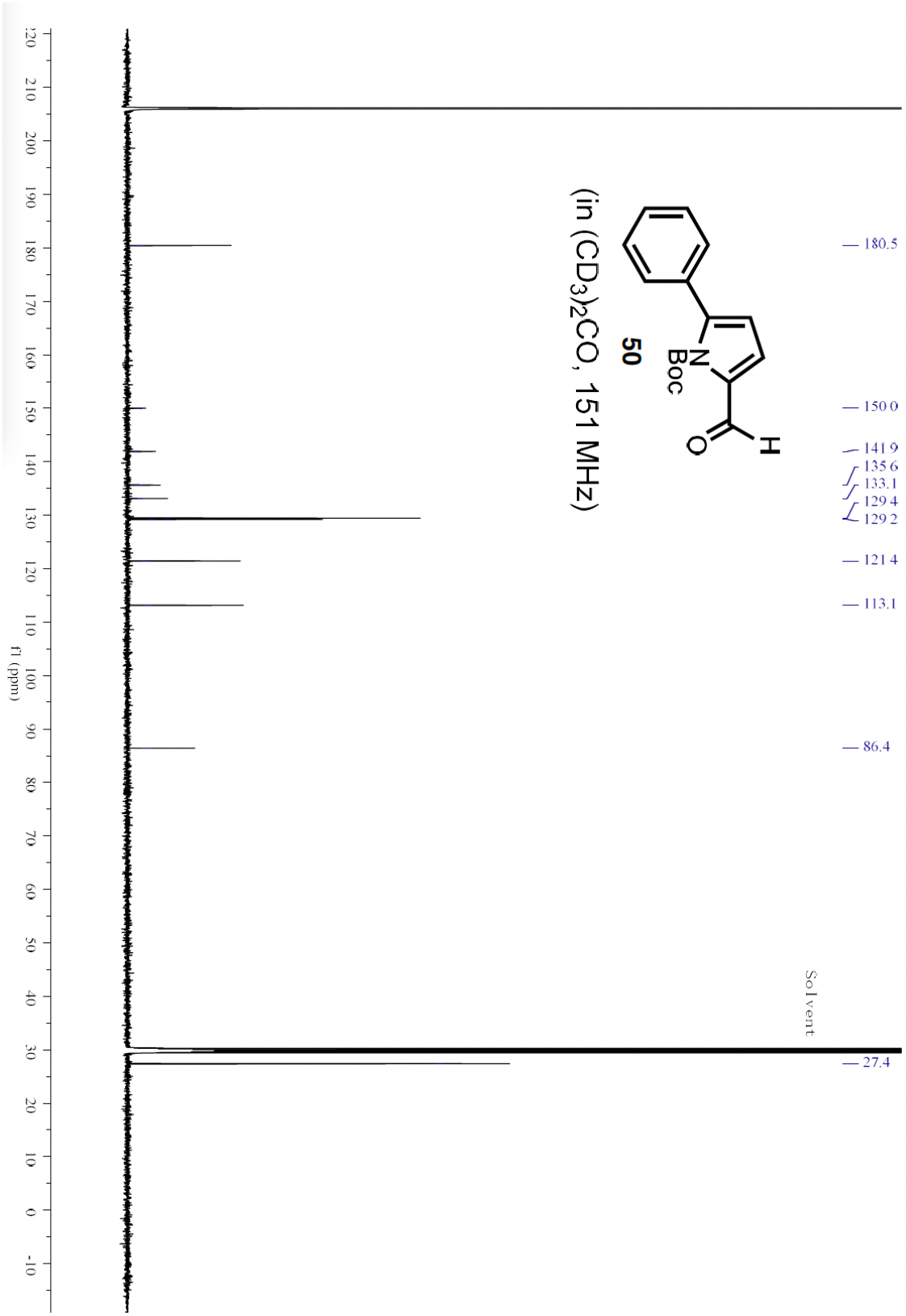

(in $C_6D_6$, 600 MHz)
71
NH
Me
O
OMe
Solvent
7.16
0.93
0.72
0.96
0.94
0.93
0.99
0.97
2.98
2.91
f1 (ppm)

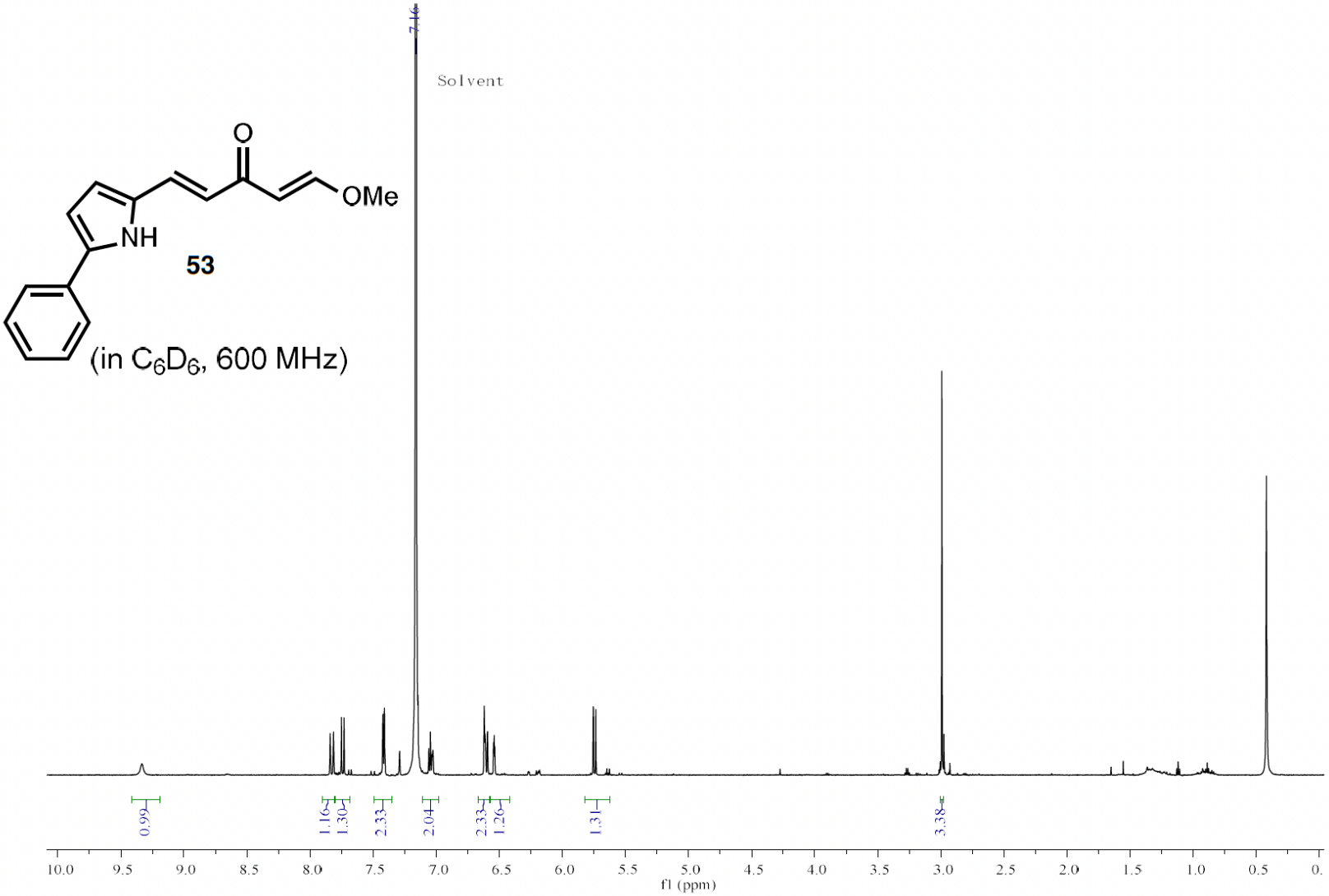

Me
O
NH
OMe
71
(in $C_6D_6$, 151 MHz)
188.6
162.3
143.7
133.5
Solvent
121.3
117.7
111.8
110.7
108.4
57.2
16.6
f1 (ppm)

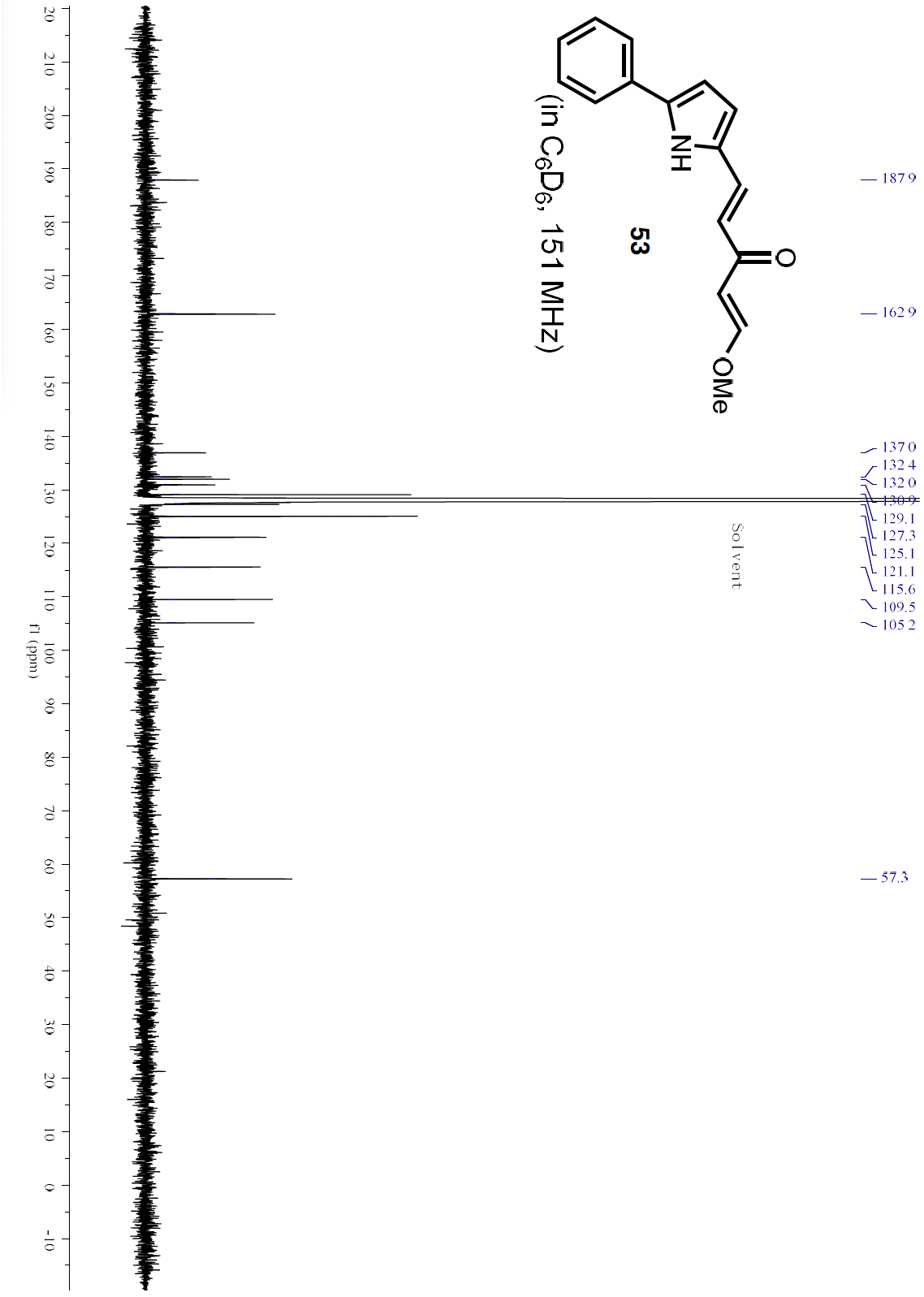

65
(in C6D6, 600 MHz)
NH
O
OMe
Solvent
7.16
1.00
1.03
1.01
0.98
1.11
1.98
0.98
1.02
1.02
3.07
f1 (ppm)

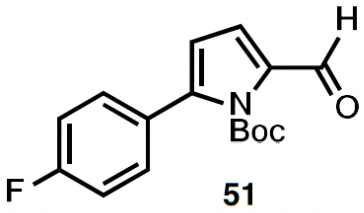

NH
OMe
O
65
(in C6D6, 151 MHz)
186.9
163.2
138.2
134.4
131.3
129.3
124.8
124.6
121.9
120.9
111.5
108.5
105.1
57.4
Solvent
f1 (ppm)


50
(in C6D6, 600 MHz)
Solvent
7.16
0.89
1.87
2.80
0.86
0.90
9.00
f1 (ppm)


50
(in (CD3)2CO, 151 MHz)
N
Boc
O
H
180.5
150.0
141.9
135.6
133.1
129.4
129.2
121.4
113.1
86.4
27.4
Solvent
f1 (ppm)

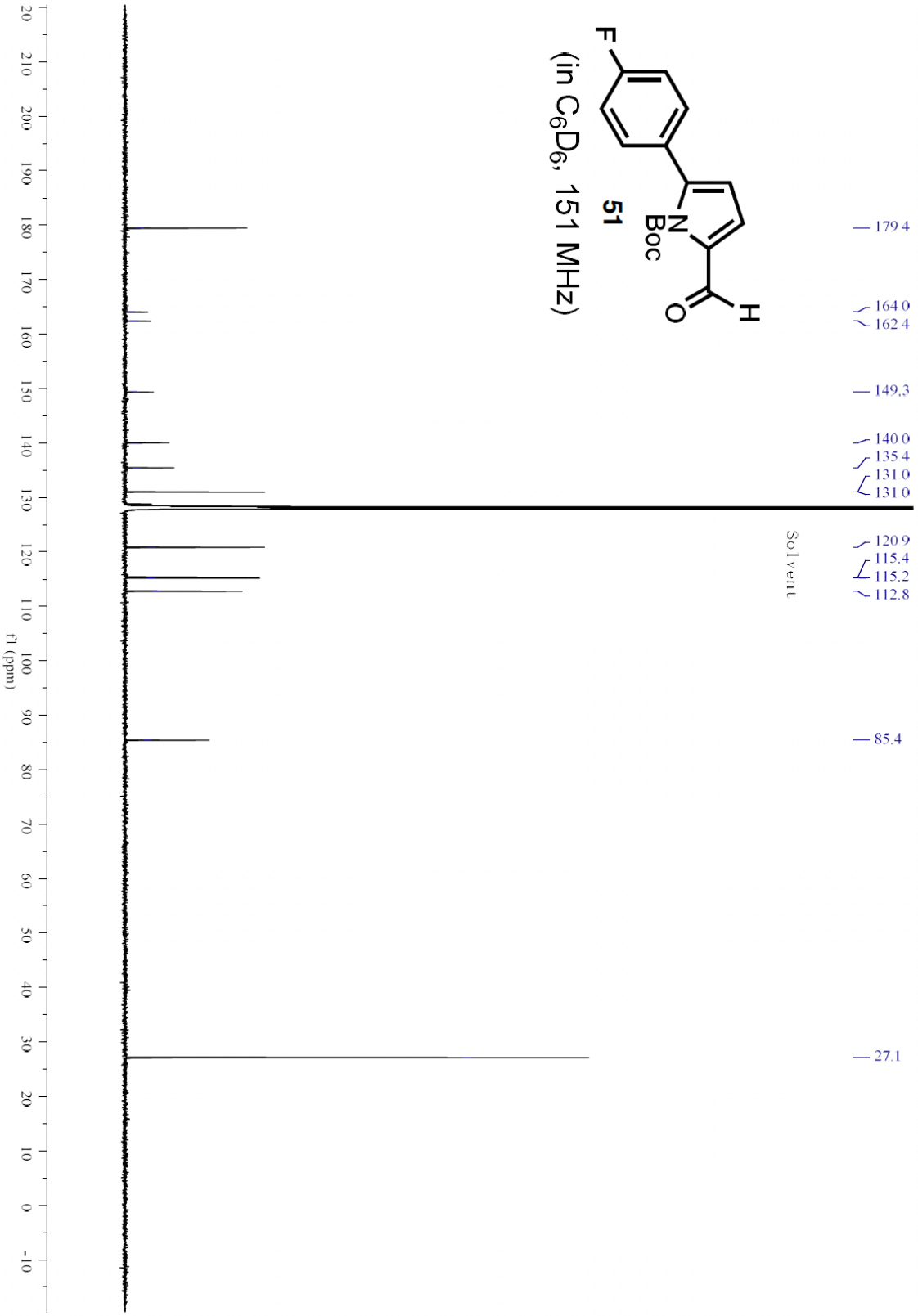

O
OMe
NH
53
(in C6D6, 600 MHz)
7.16
Solvent
0.99
1.16
1.30
2.33
2.04
2.33
1.26
1.31
3.38
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.
f1 (ppm)

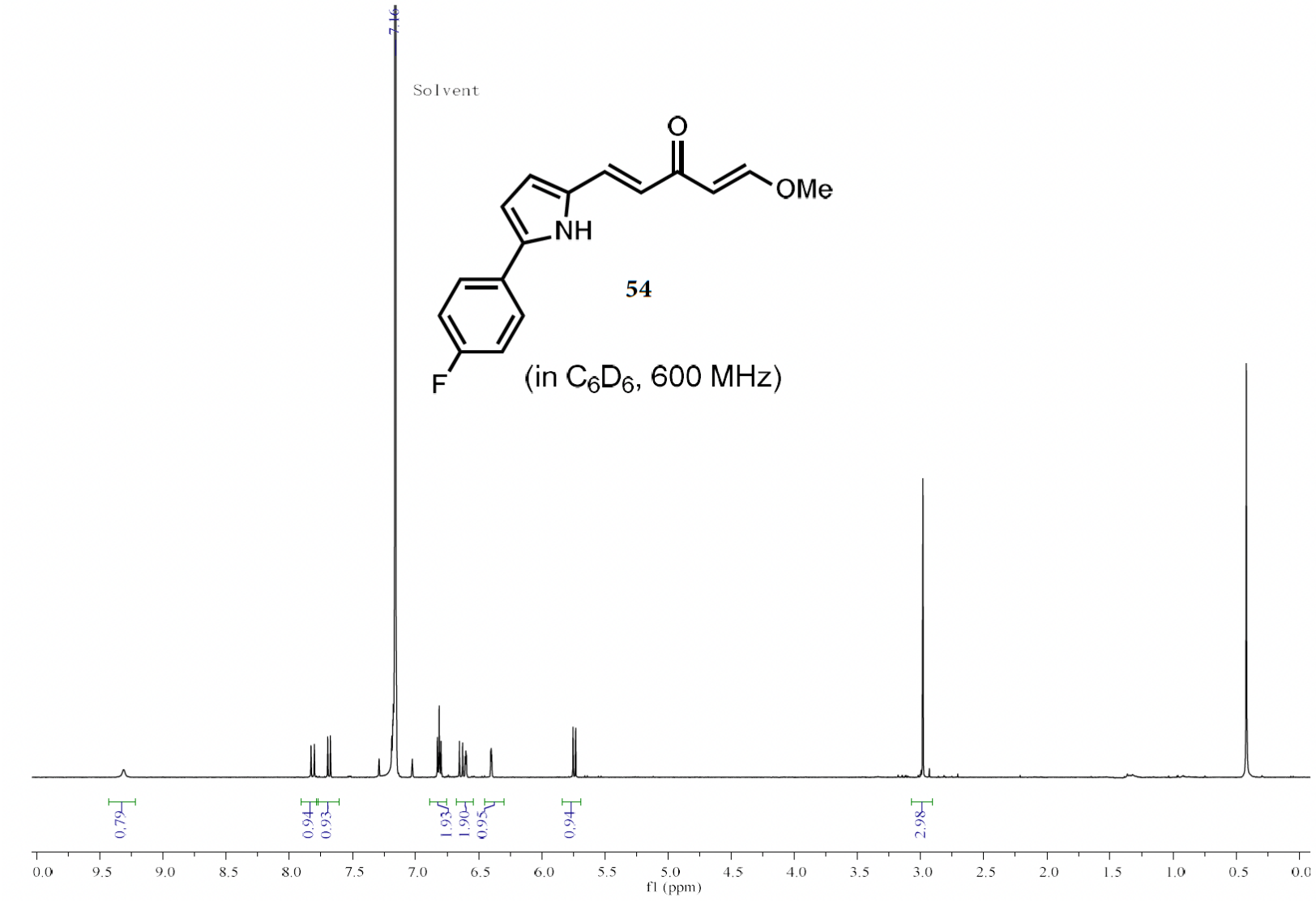

(in $C_6D_6$, 151 MHz)
53
NH
OMe
O
187.9
162.9
137.0
132.4
132.0
130.9
129.1
127.3
125.1
121.1
115.6
109.5
105.2
57.3
Solvent
f1 (ppm)

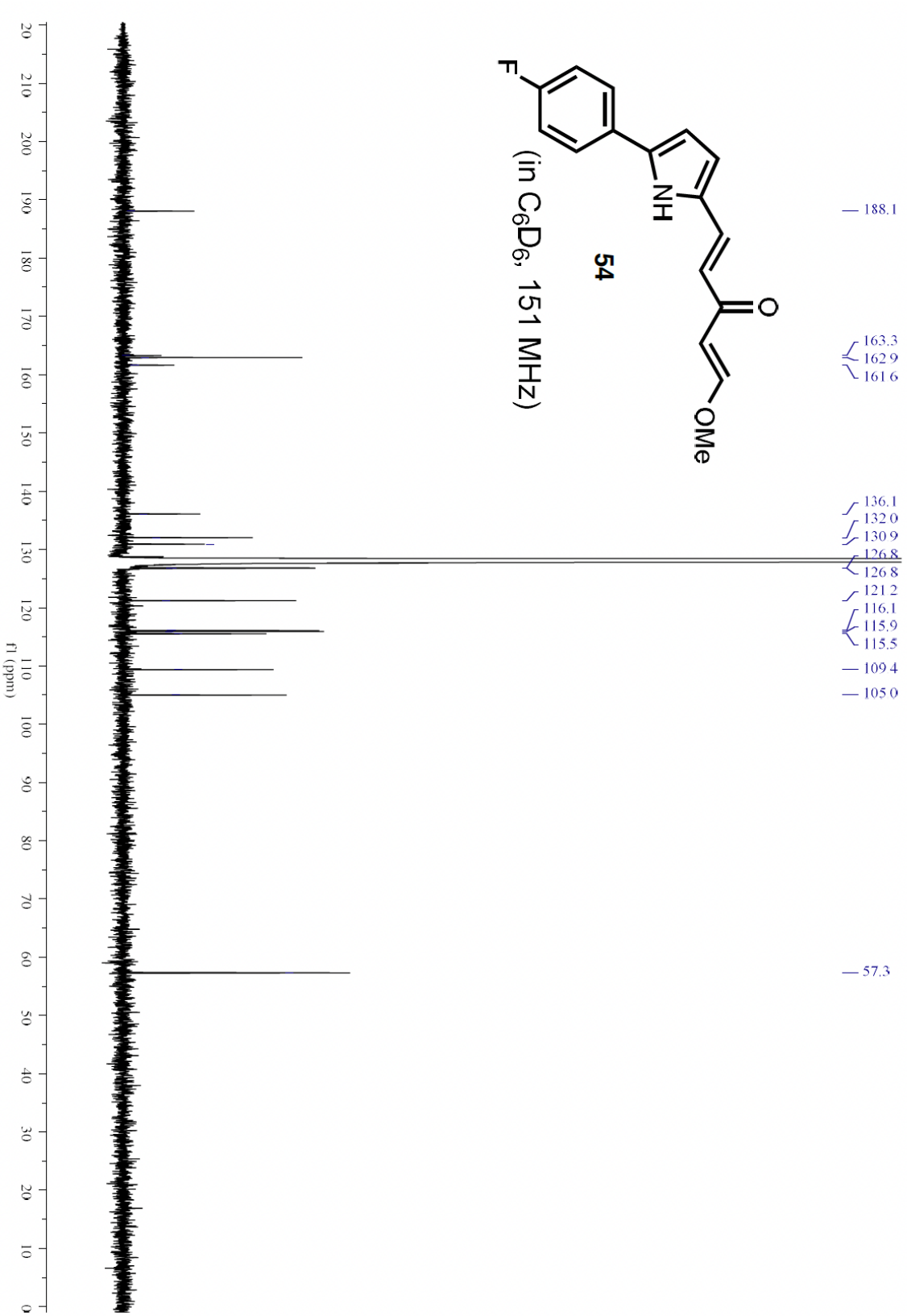



**51**

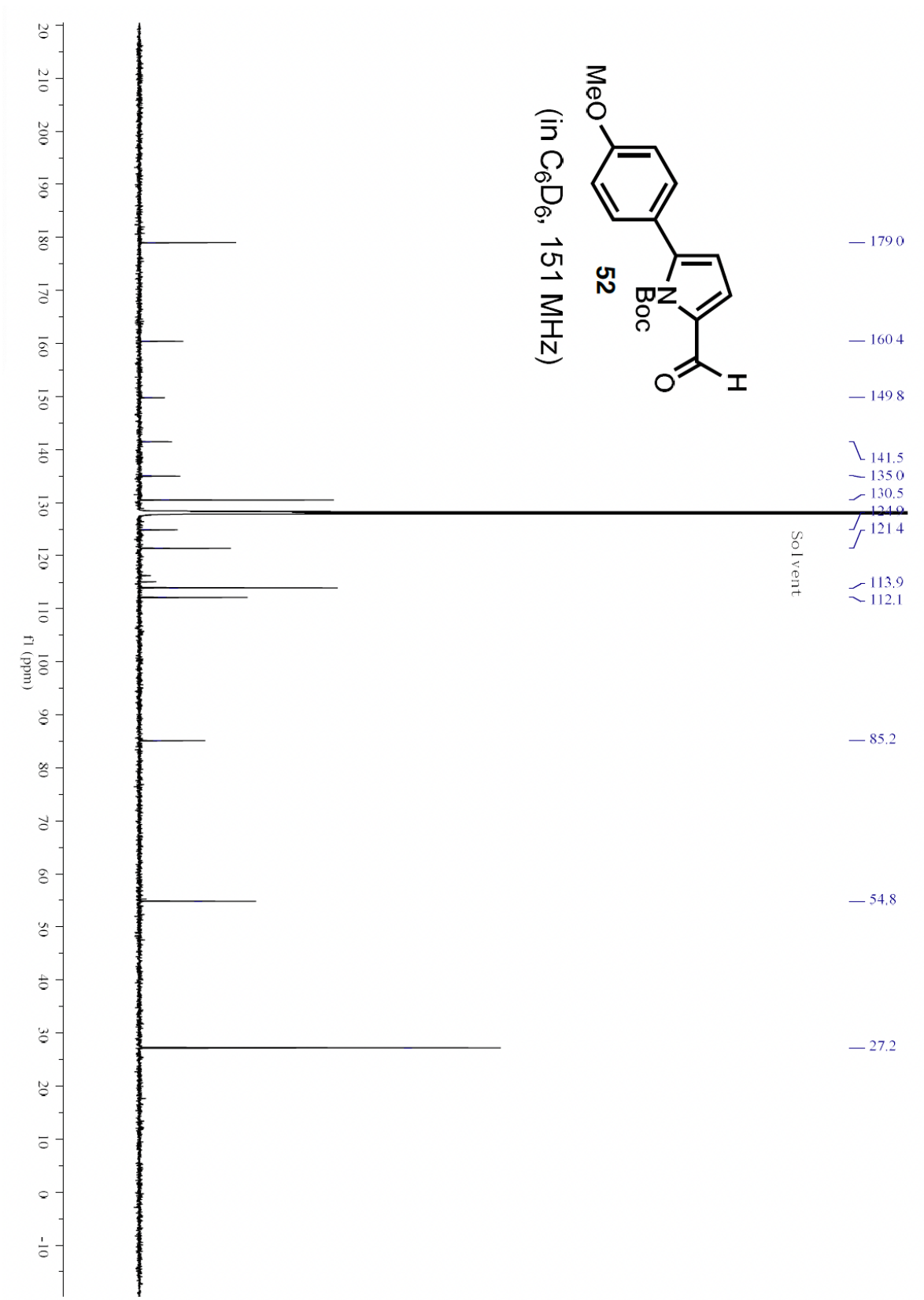
(in $C_6D_6$, 600 MHz)

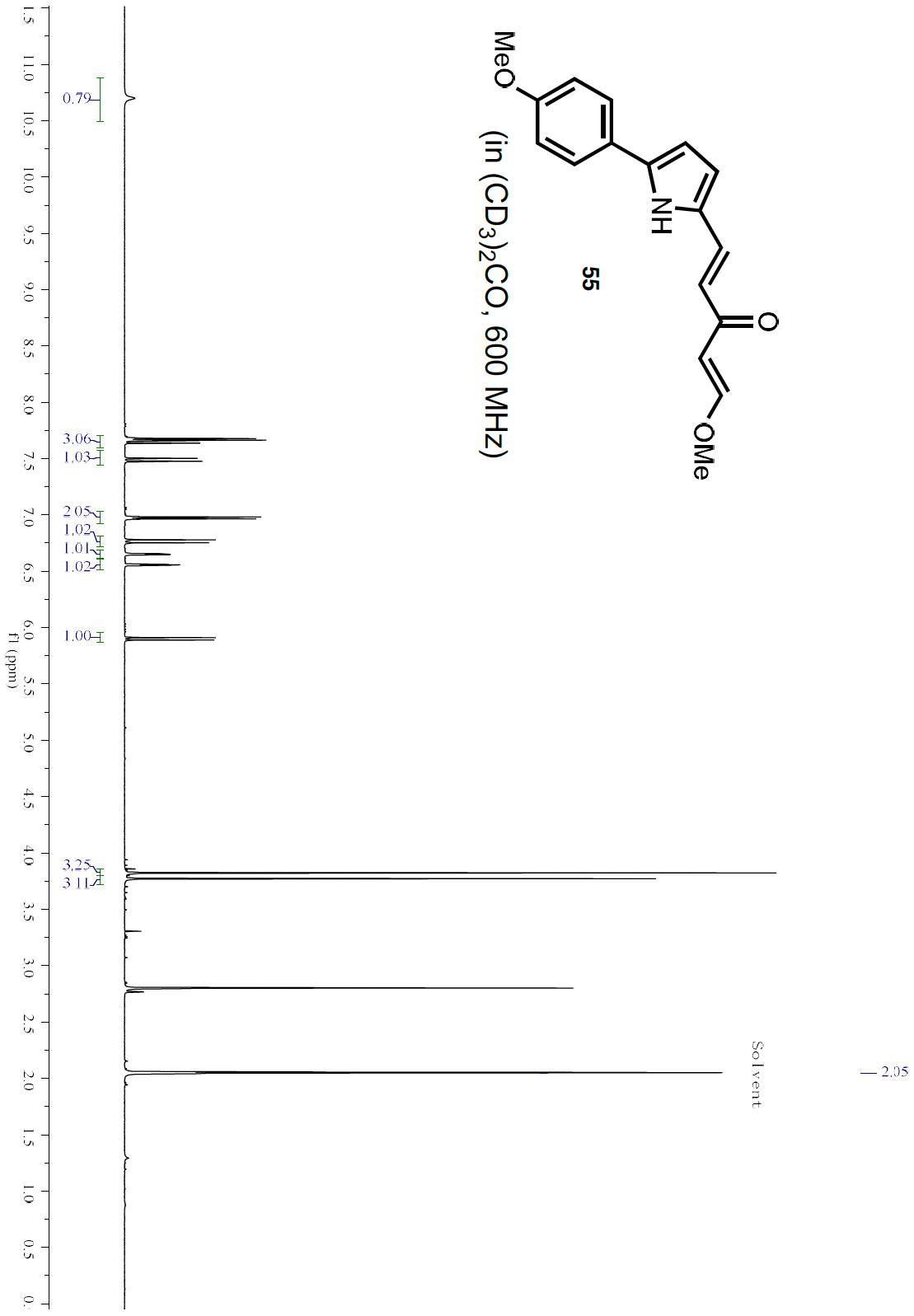

F
N
Boc
O
H
51
(in C6D6, 151 MHz)
179.4
164.0
162.4
149.3
140.0
135.4
131.0
131.0
Solvent
120.9
115.4
115.2
112.8
85.4
27.1
f1 (ppm)

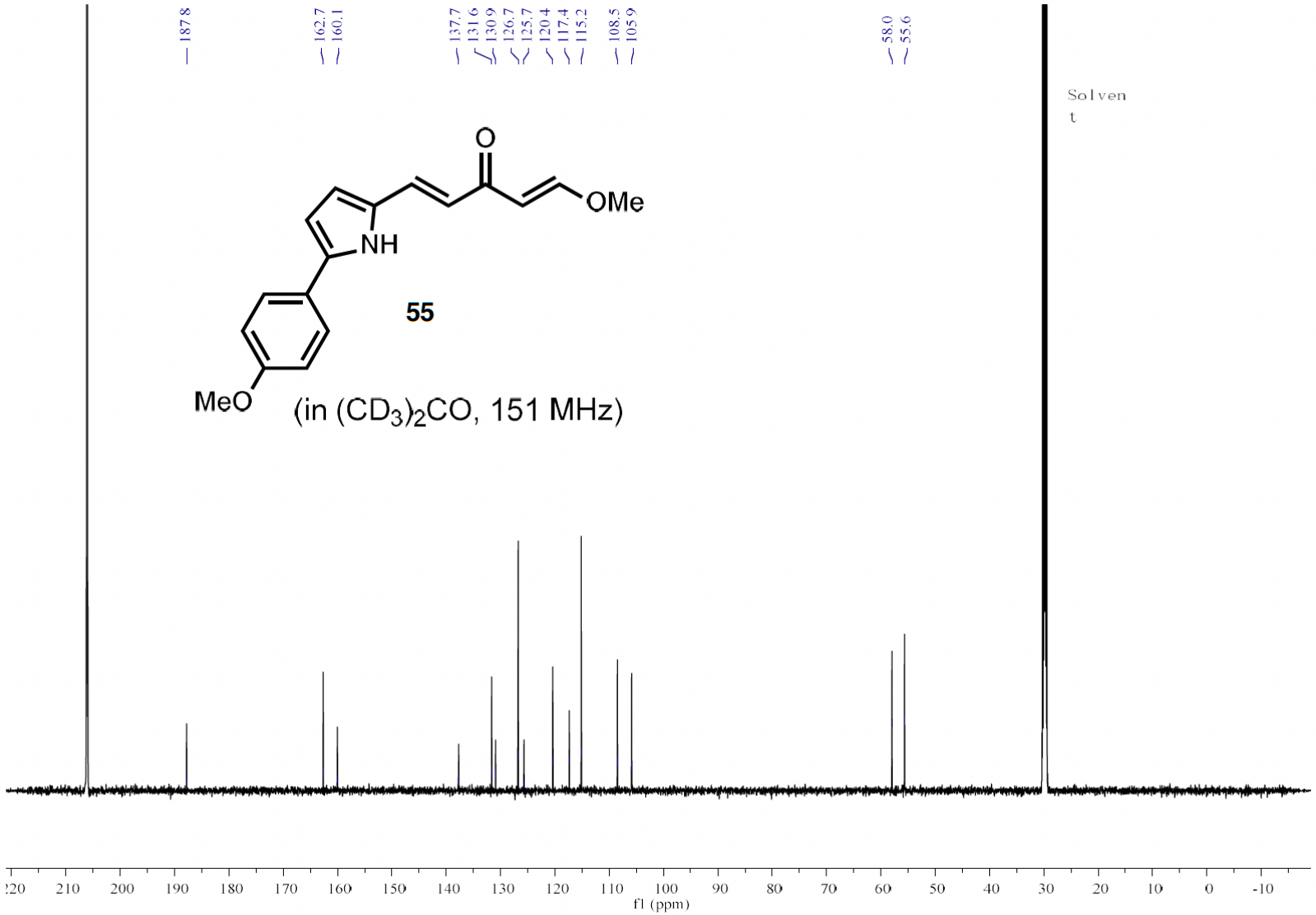

7.16
Solvent
O
OMe
NH
F
54
(in C6D6, 600 MHz)
0.79
0.94
0.93
1.93
1.90
0.95
0.94
2.98
0.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

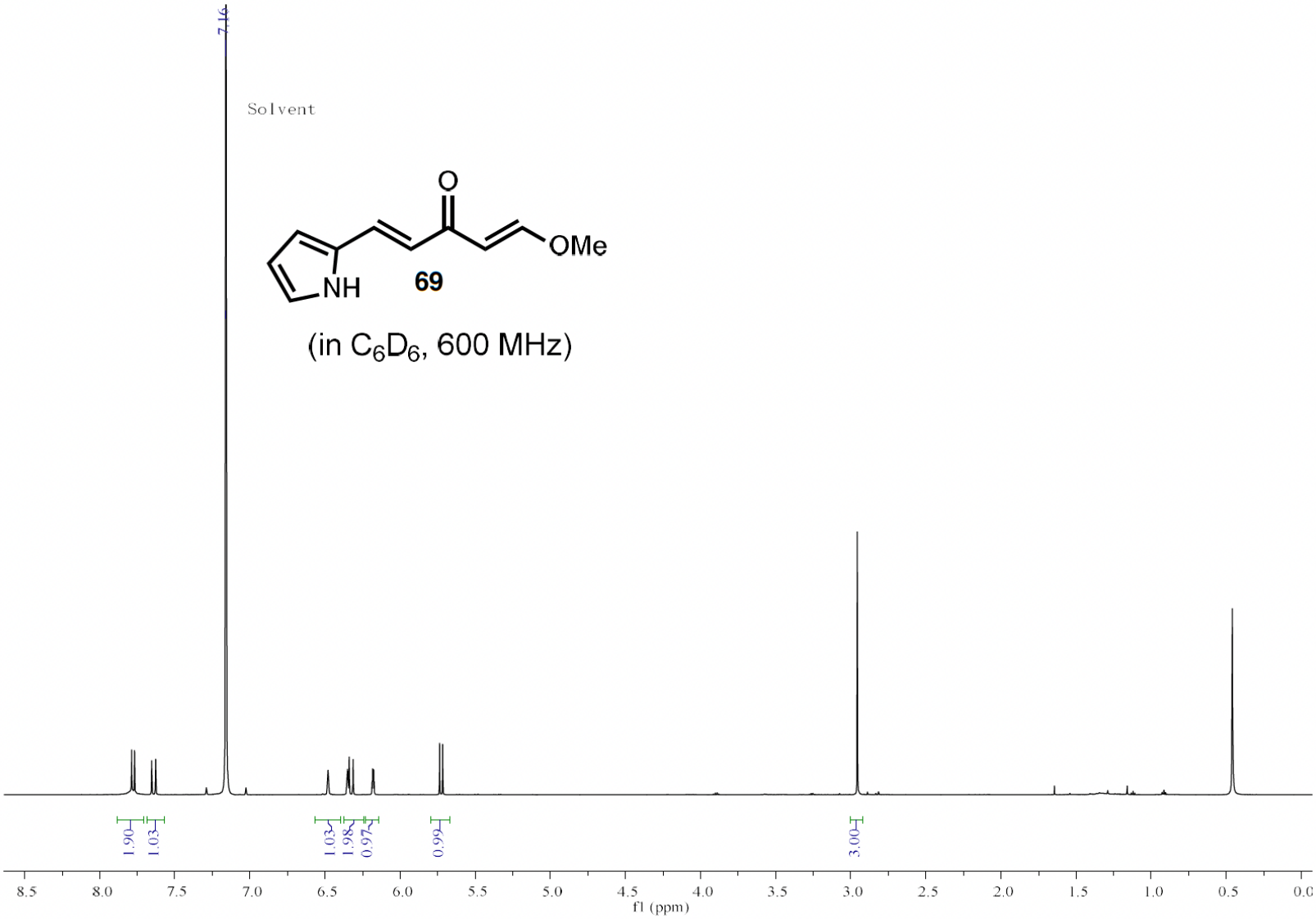

F
NH
O
OMe
54
(in C6D6, 151 MHz)
188.1
163.3
162.9
161.6
136.1
132.0
130.9
126.8
126.8
121.2
116.1
115.9
115.5
109.4
105.0
57.3
f1 (ppm)

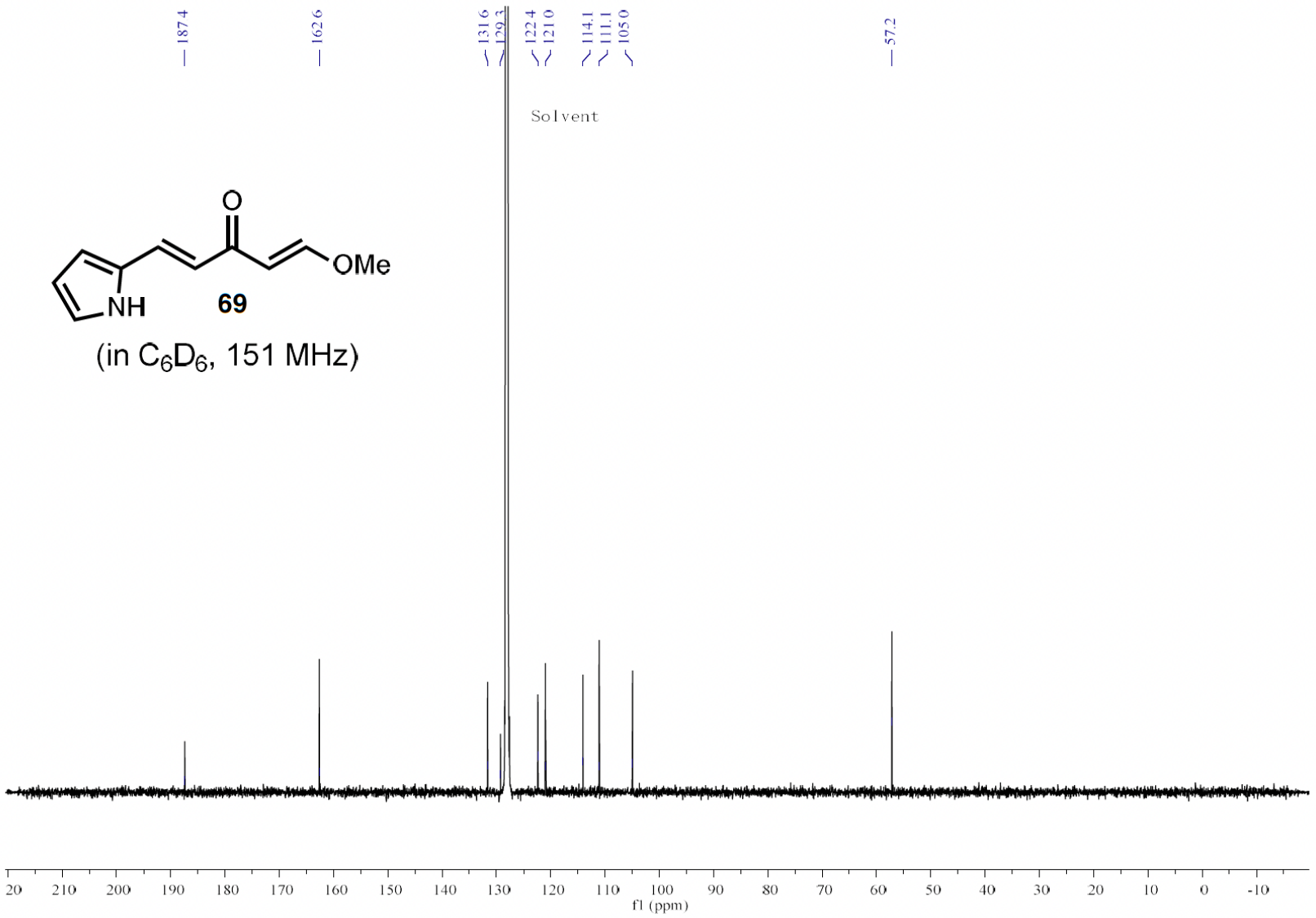
MeO
N
Boc
52
O
H
(in $C_6D_6$, 600 MHz)
Solvent
7.16
0.93
1.93
0.95
2.08
0.96
2.98
9.05
f1 (ppm)

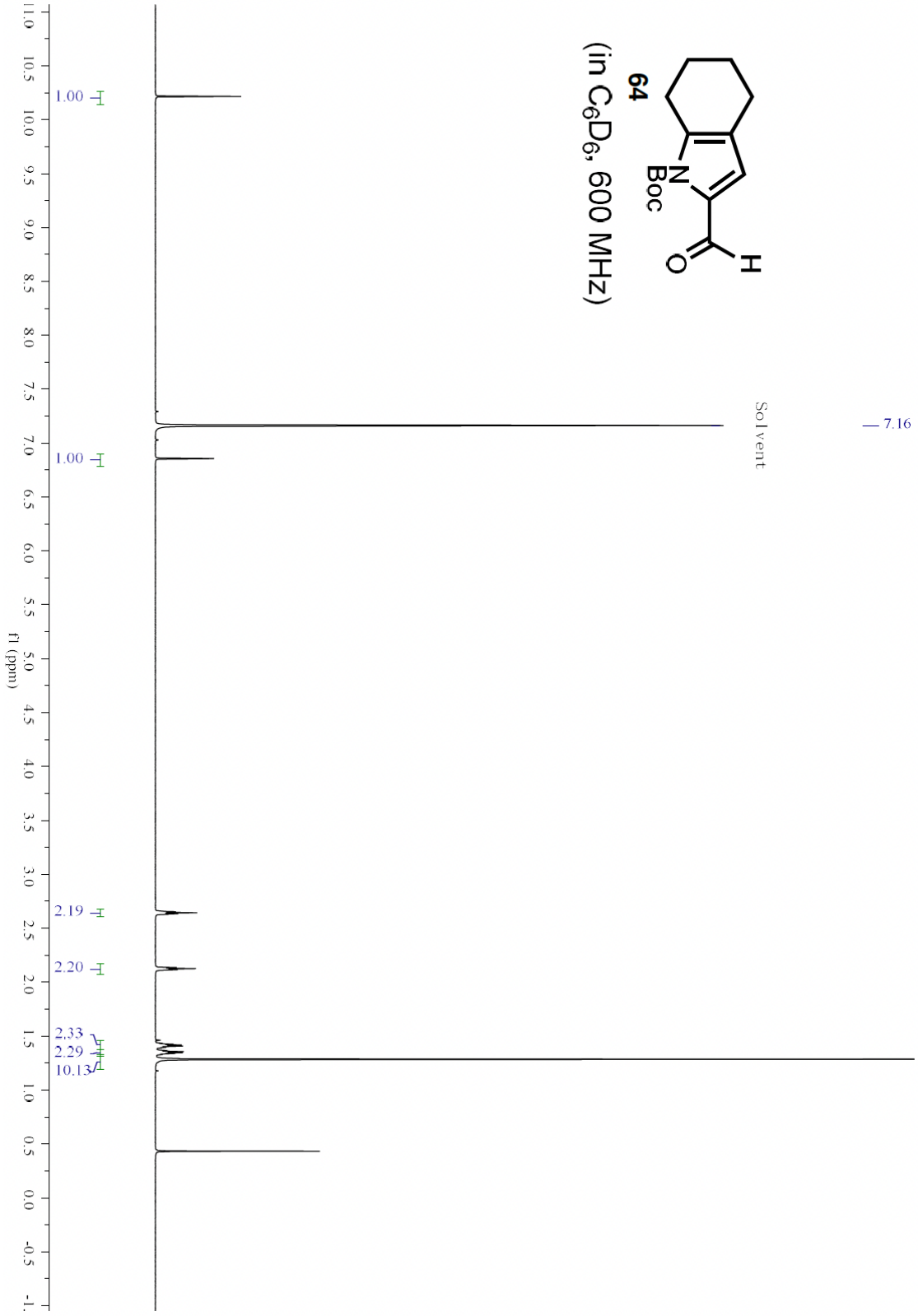

MeO
52
N
Boc
O
H
(in C6D6, 151 MHz)
179.0
160.4
149.8
141.5
135.0
130.5
124.9
121.4
113.9
112.1
85.2
54.8
27.2
Solvent
f1 (ppm)

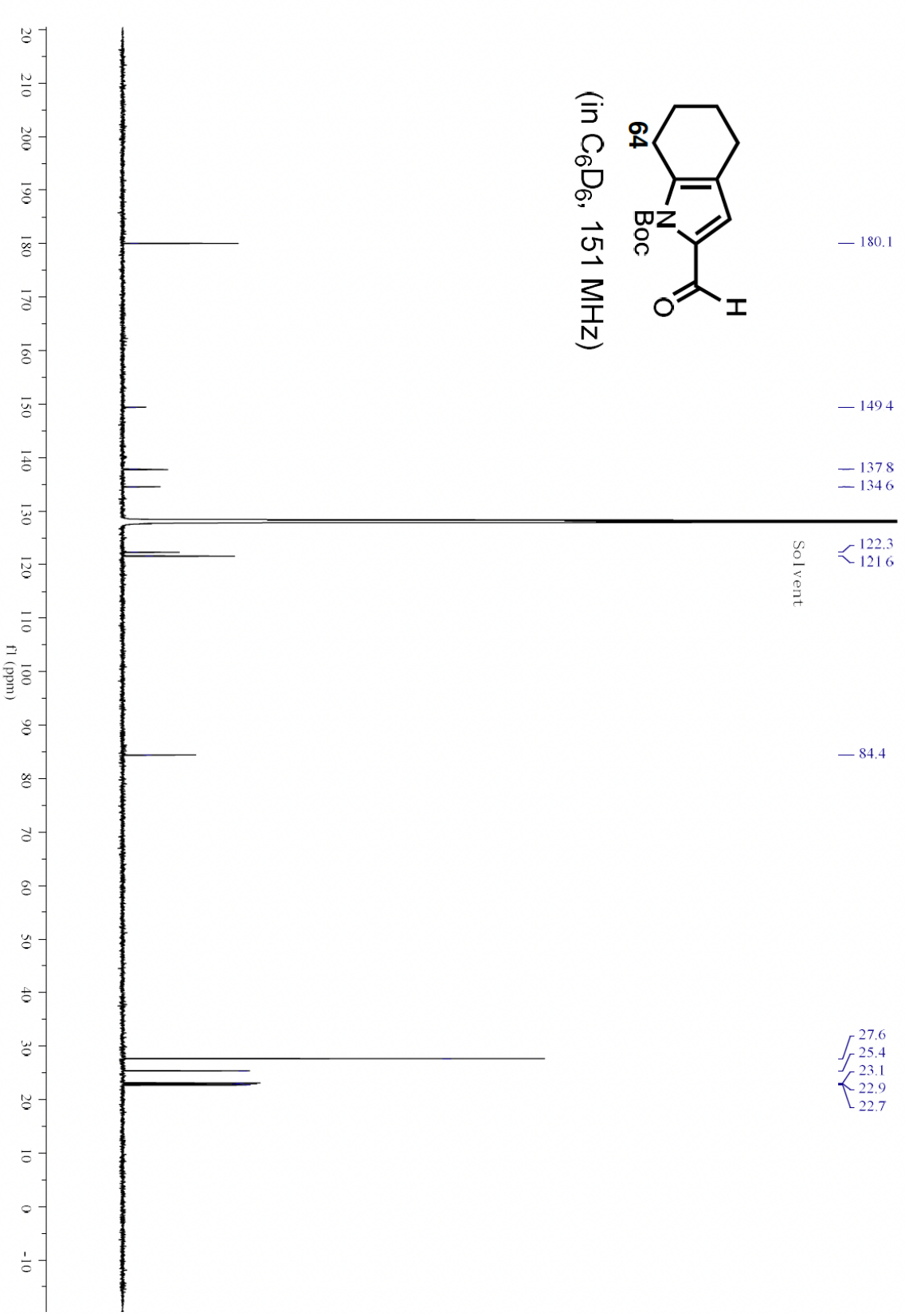

MeO
NH
O
OMe
55
(in (CD3)2CO, 600 MHz)
0.79
3.06
1.03
2.05
1.02
1.01
1.02
1.00
3.25
3.11
Solvent
2.05
f1 (ppm)

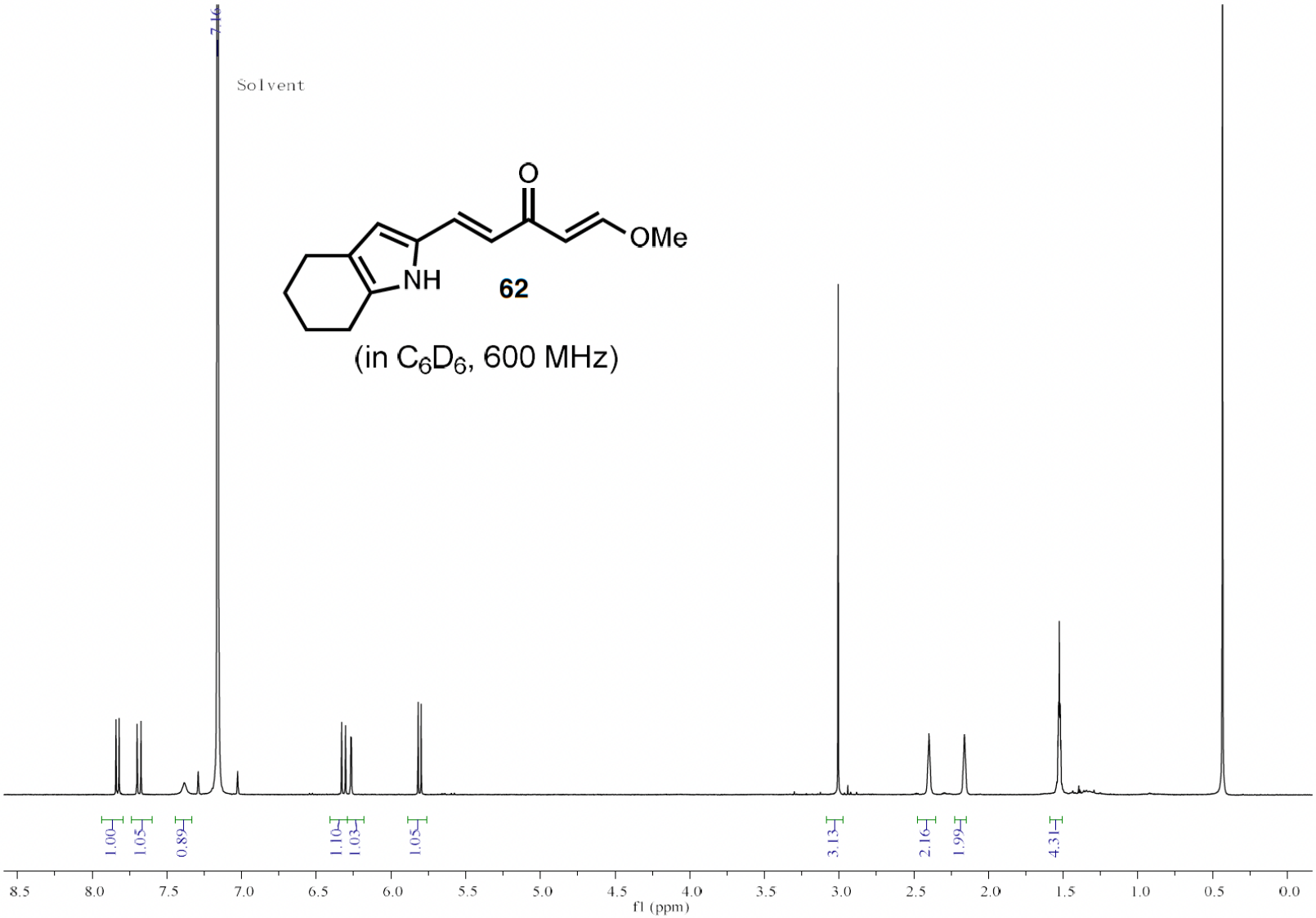

187.8
162.7
160.1
137.7
131.6
130.9
126.7
125.7
120.4
117.4
115.2
108.5
105.9
58.0
55.6
Solvent
O
OMe
NH
MeO
55
(in (CD3)2CO, 151 MHz)
f1 (ppm)

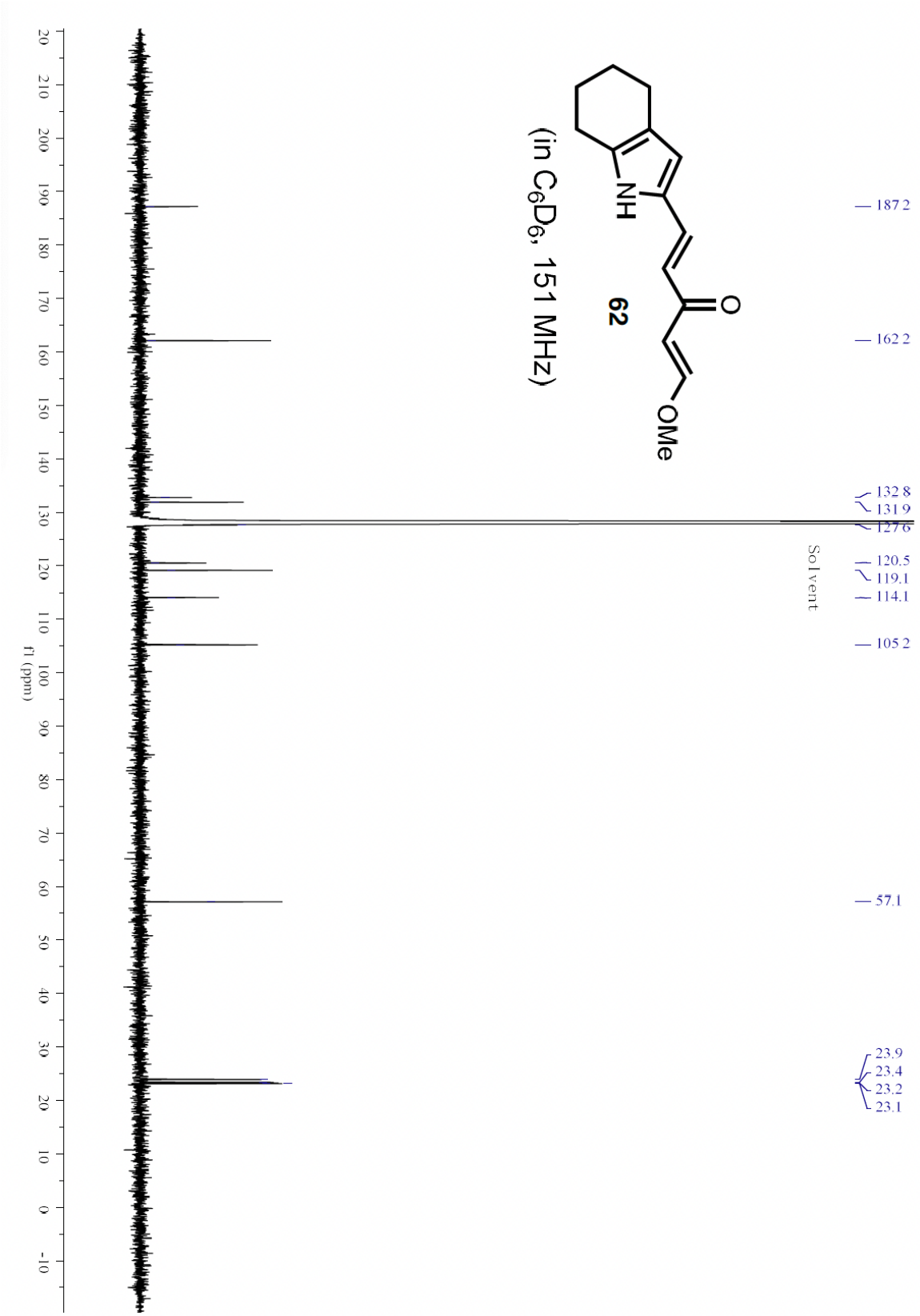

7.16
Solvent
O
OMe
NH
69
(in $C_6D_6$, 600 MHz)
1.90
1.03
1.03
1.98
0.97
0.99
3.00
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

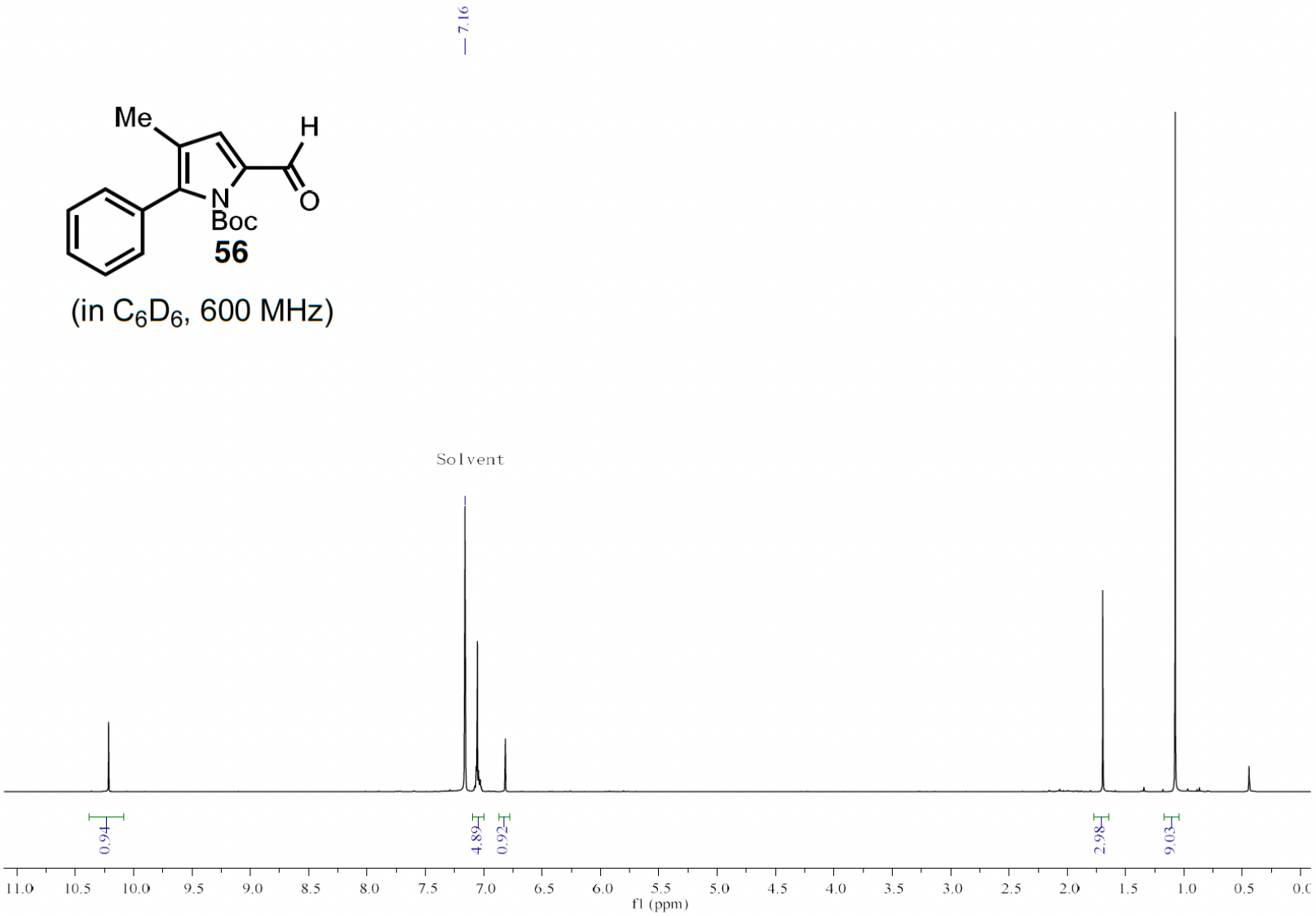

187.4
162.6
131.6
129.3
122.4
121.0
114.1
111.1
105.0
57.2
Solvent
O
OMe
NH
69
(in C6D6, 151 MHz)
f1 (ppm)

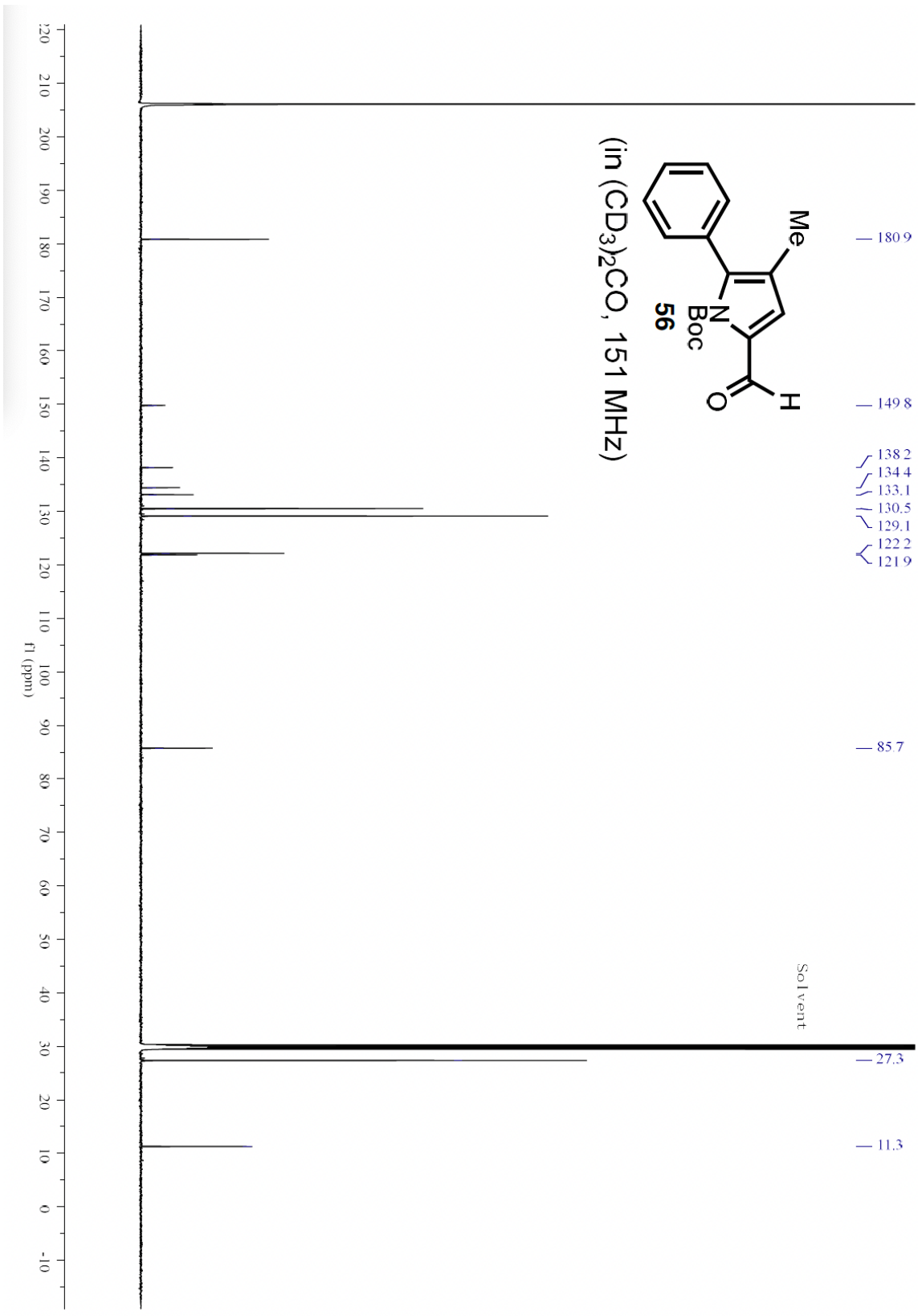

64
(in $C_6D_6$, 600 MHz)
Boc
N
O
H
Solvent
7.16
1.00
1.00
2.19
2.20
2.33
2.29
10.13
f1 (ppm)

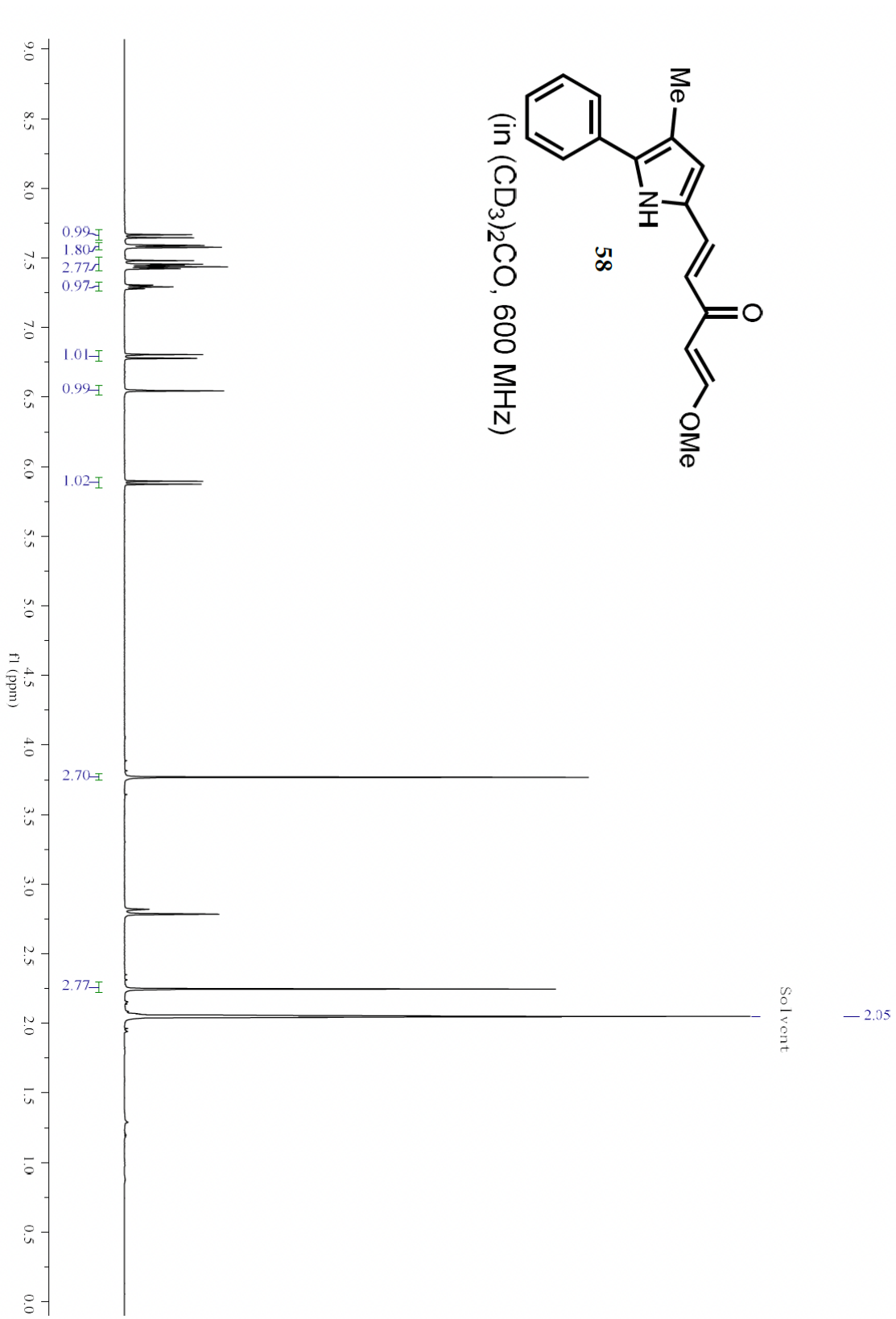

64
(in C6D6, 151 MHz)
Boc
N
O
H
Solvent
180.1
149.4
137.8
134.6
122.3
121.6
84.4
27.6
25.4
23.1
22.9
22.7
f1 (ppm)

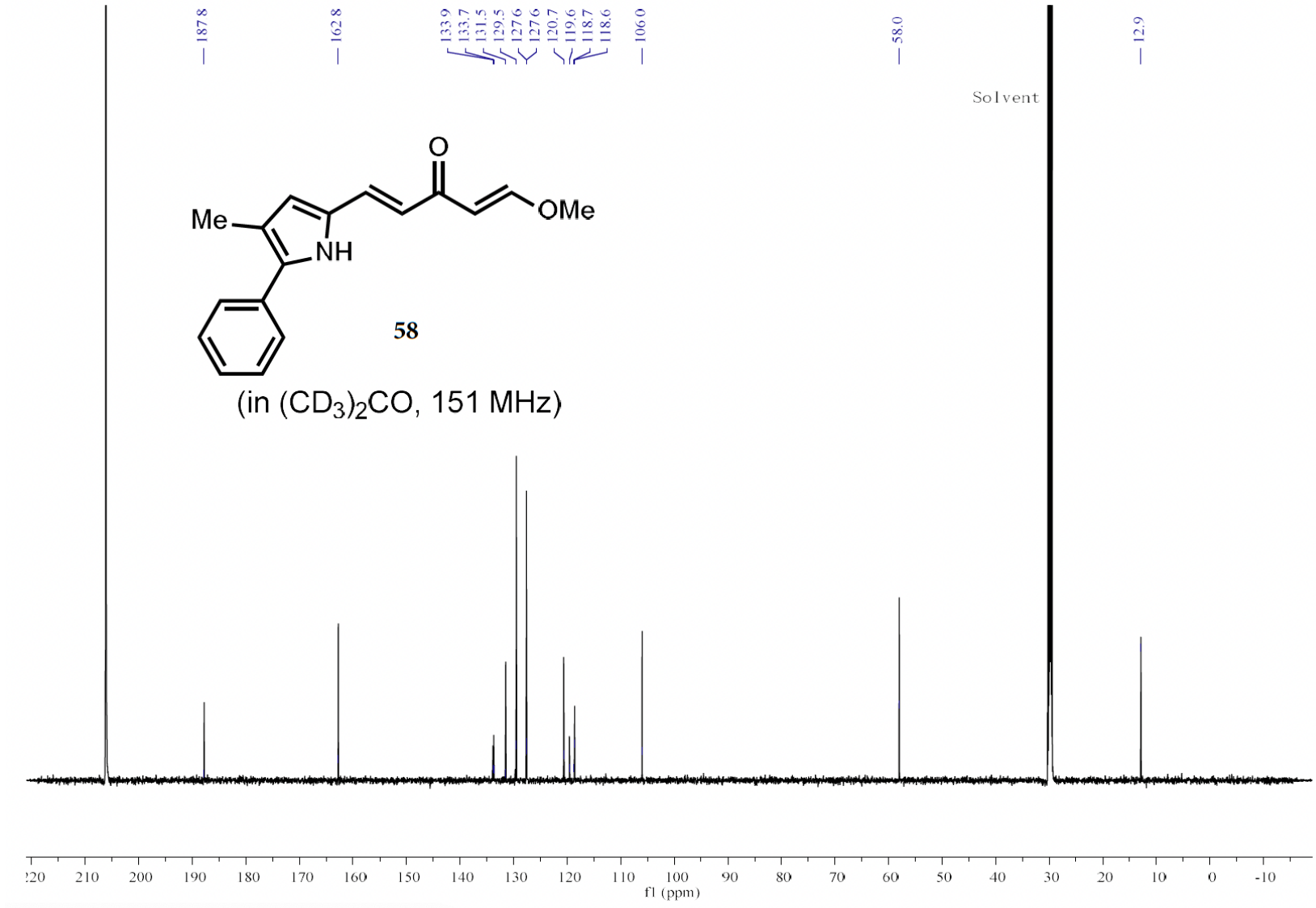

7.16
Solvent
O
OMe
NH
62
(in C6D6, 600 MHz)
1.00
1.05
0.89
1.10
1.03
1.05
3.13
2.16
1.99
4.31
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

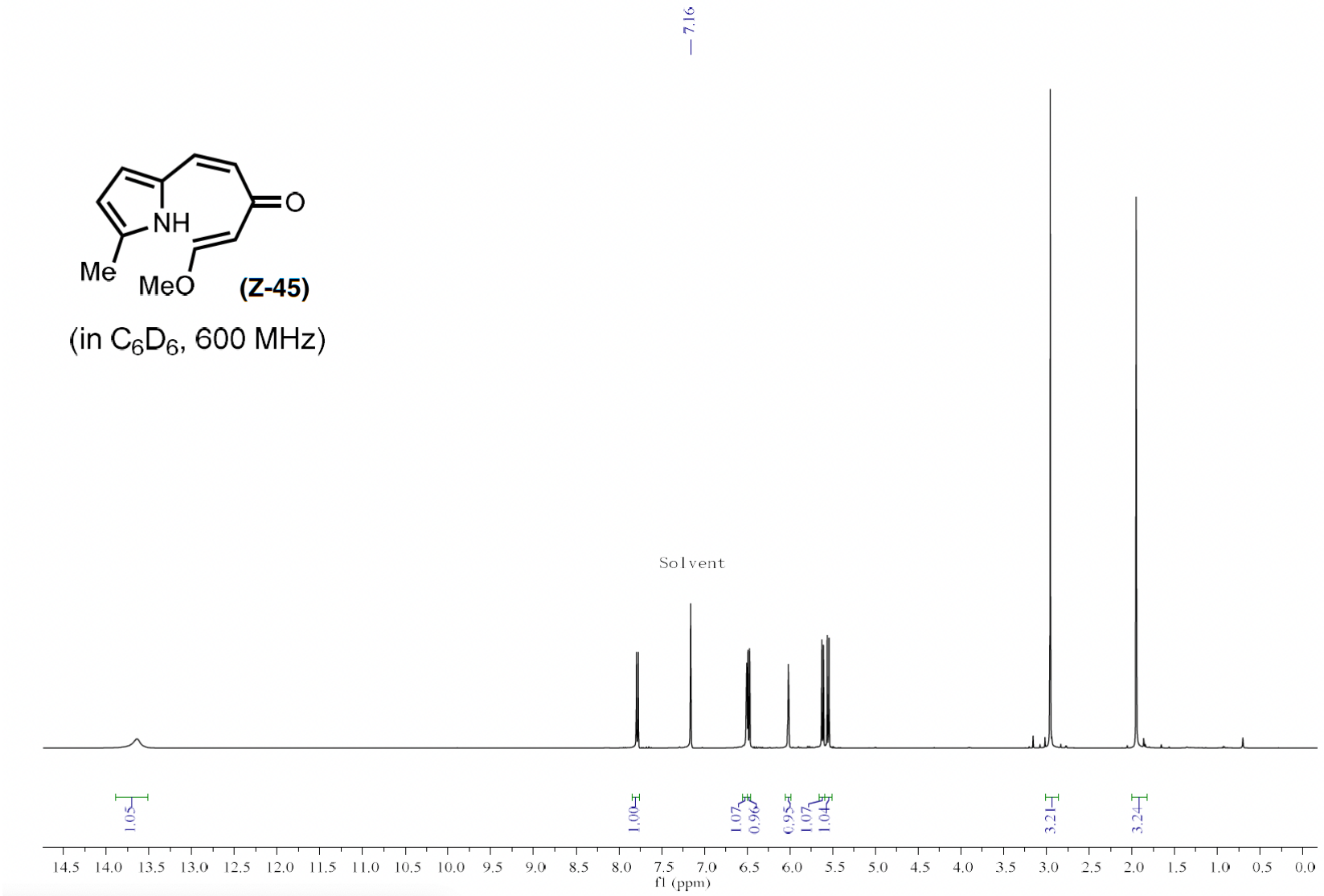

(in $C_6D_6$, 151 MHz)
62
NH
O
OMe
187.2
162.2
132.8
131.9
127.6
120.5
119.1
114.1
105.2
57.1
23.9
23.4
23.2
23.1
Solvent
f1 (ppm)

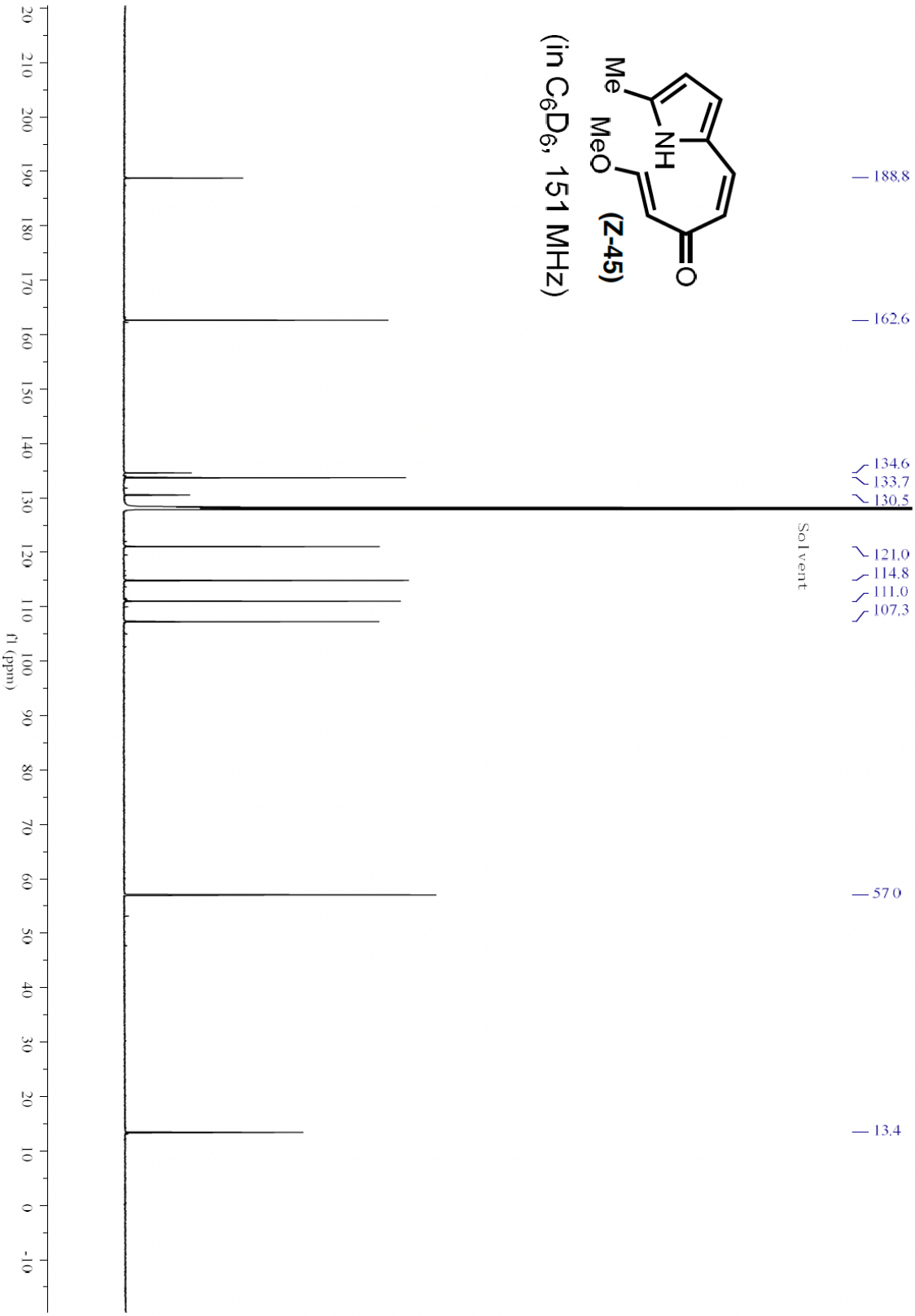

7.16
Me
H
O
N
Boc
56
(in C6D6, 600 MHz)
Solvent
0.94
4.89
0.92
2.98
9.03
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

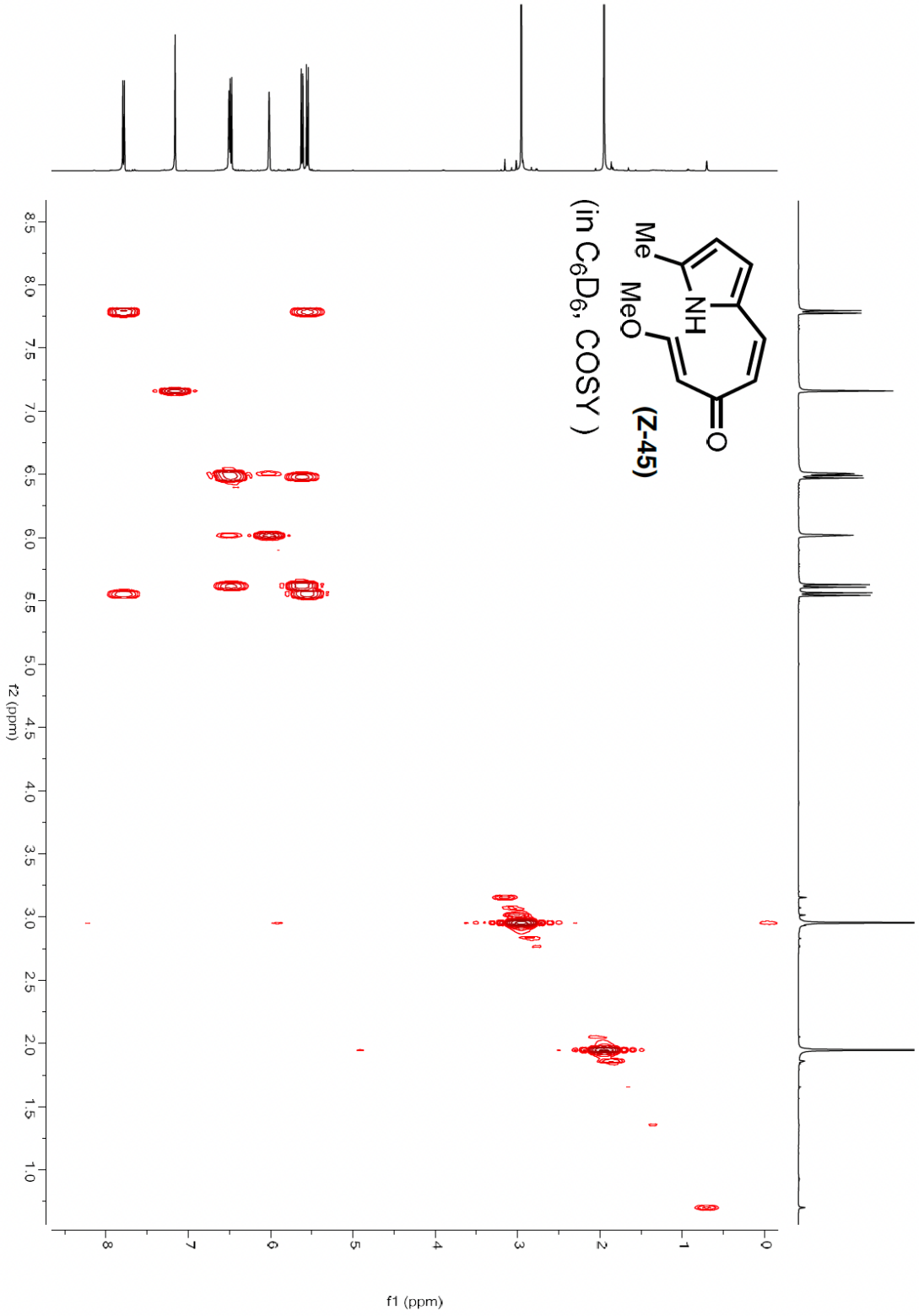

(in (CD3)2CO, 151 MHz)
Me
N
Boc
56
H
O
180.9
149.8
138.2
134.4
133.1
130.5
129.1
122.2
121.9
85.7
Solvent
27.3
11.3
f1 (ppm)

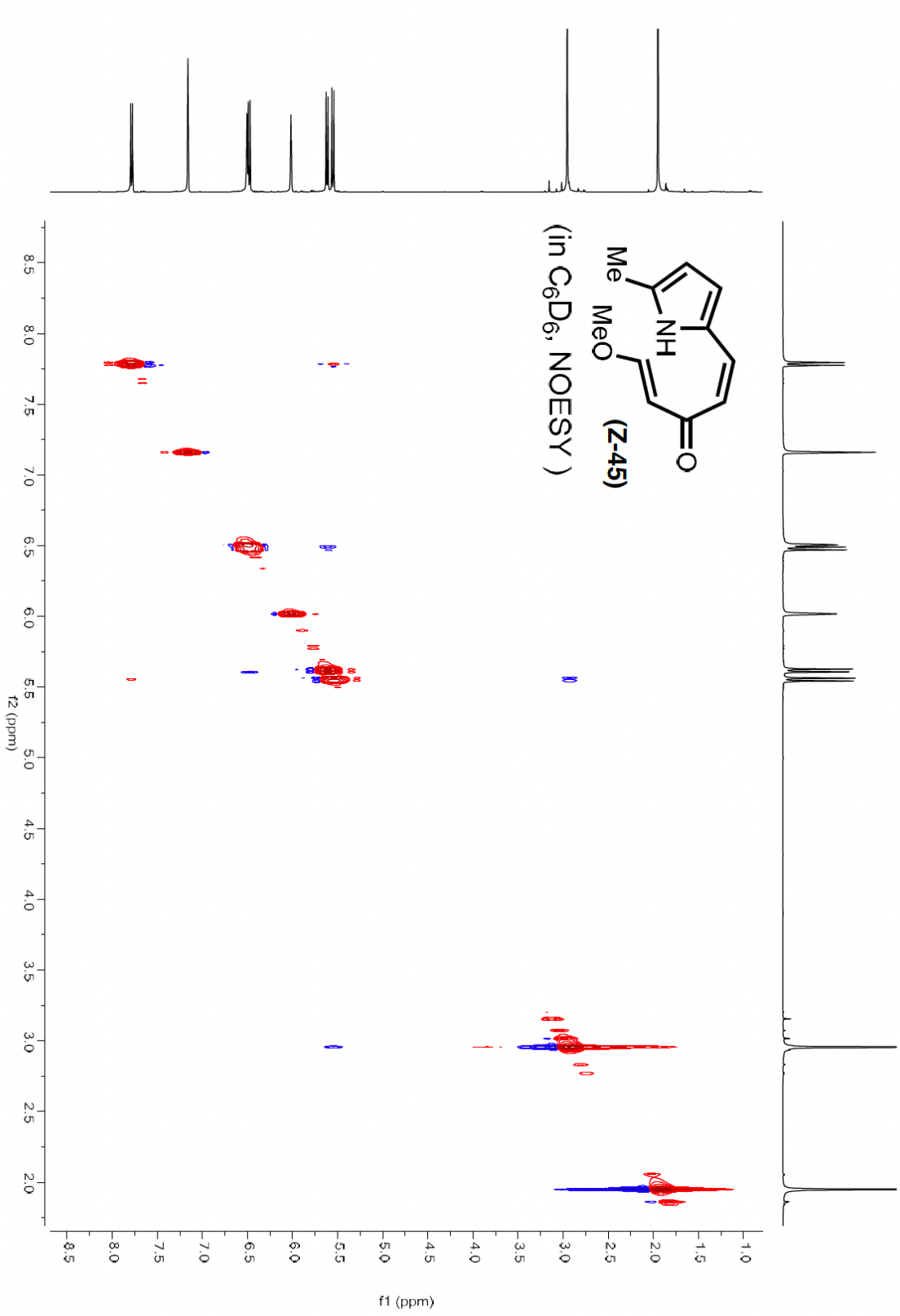

Me
NH
O
OMe
58
(in (CD3)2CO, 600 MHz)
0.99
1.80
2.77
0.97
1.01
0.99
1.02
2.70
2.77
Solvent
2.05
f1 (ppm)

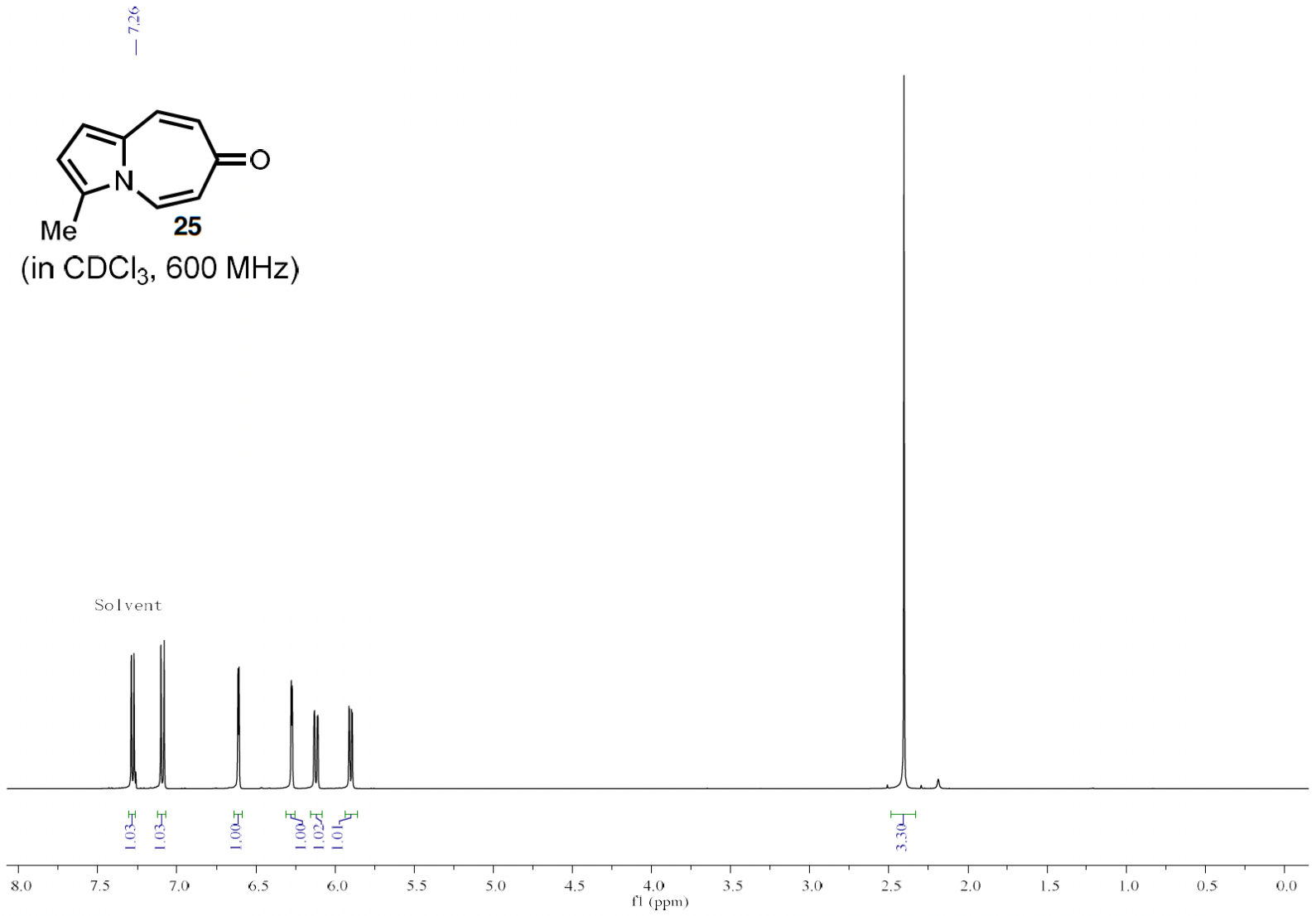

187.8
162.8
133.9
133.7
131.5
129.5
127.6
127.6
120.7
119.6
118.7
118.6
106.0
58.0
12.9
Solvent
O
Me
NH
OMe
58
(in (CD3)2CO, 151 MHz)
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

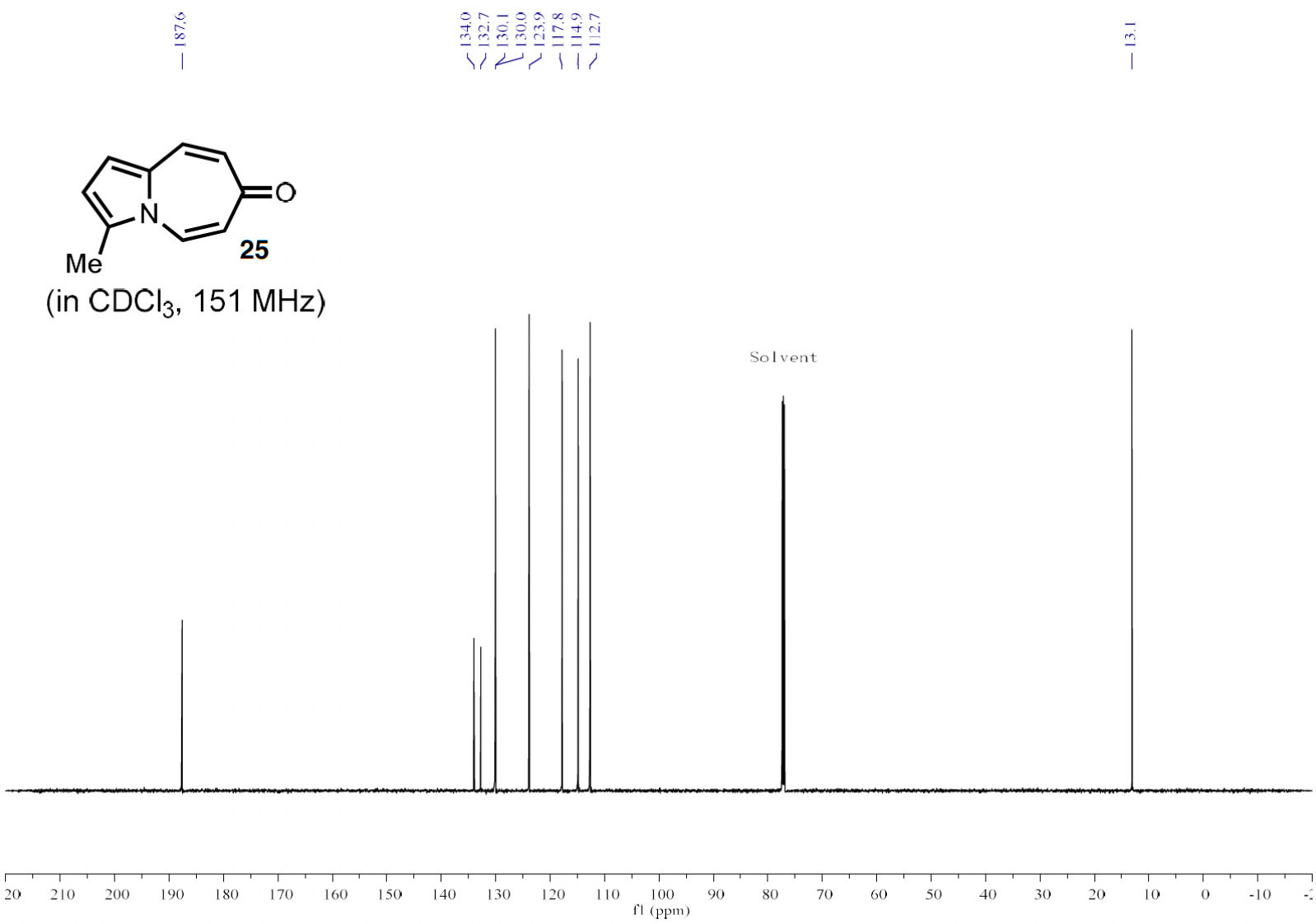

7.16
NH
O
Me
MeO
(Z-45)
(in C6D6, 600 MHz)
Solvent
1.05
1.00
1.07
0.96
0.95
1.07
1.04
3.21
3.24
14.5 14.0 13.5 13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

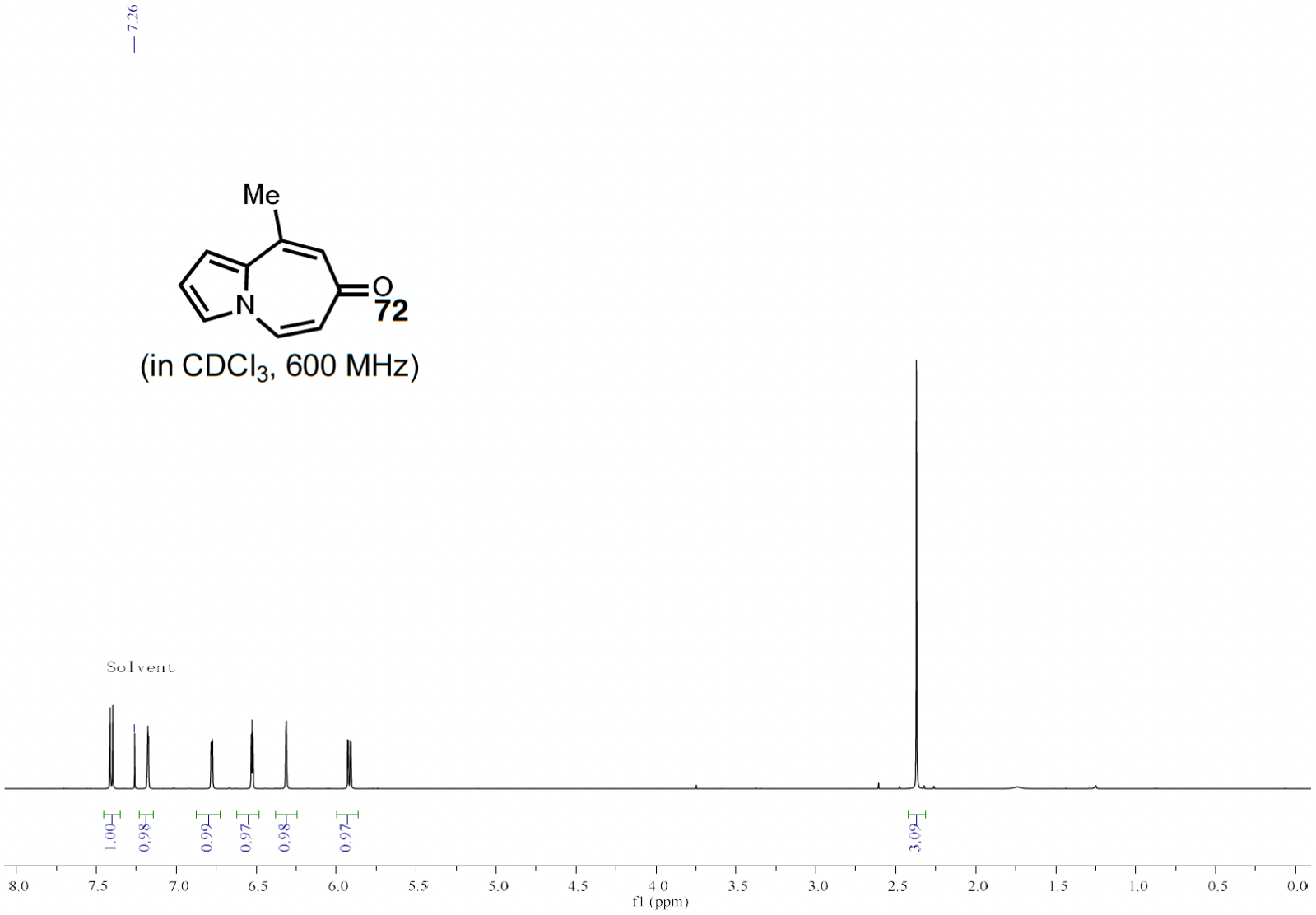

(in $C_6D_6$, 151 MHz)
Me
MeO
NH
O
(Z-45)
188.8
162.6
134.6
133.7
130.5
Solvent
121.0
114.8
111.0
107.3
57.0
13.4
f1 (ppm)

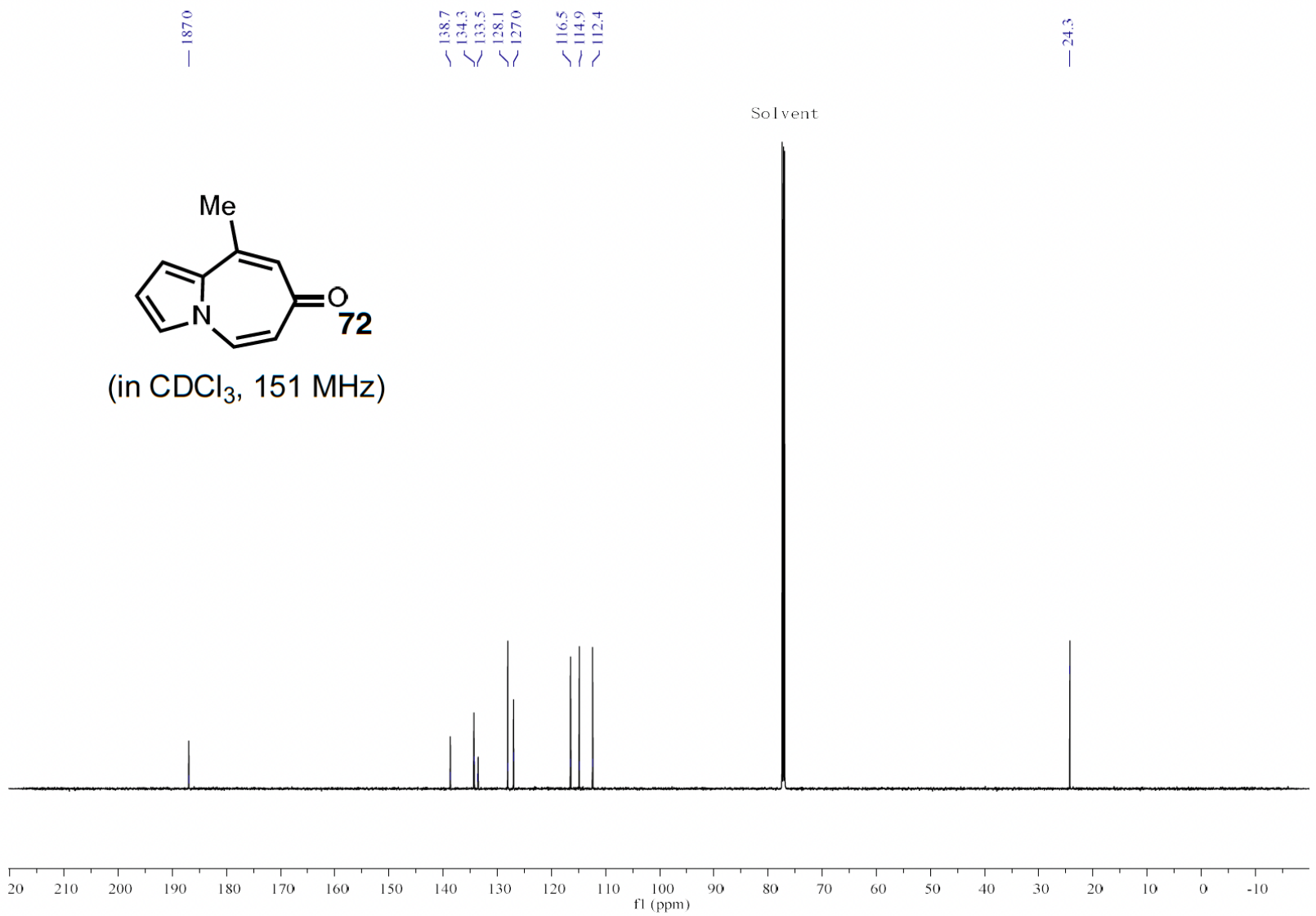

Me
MeO
NH
O
(Z-45)
(in C6D6, COSY )
f2 (ppm)
f1 (ppm)

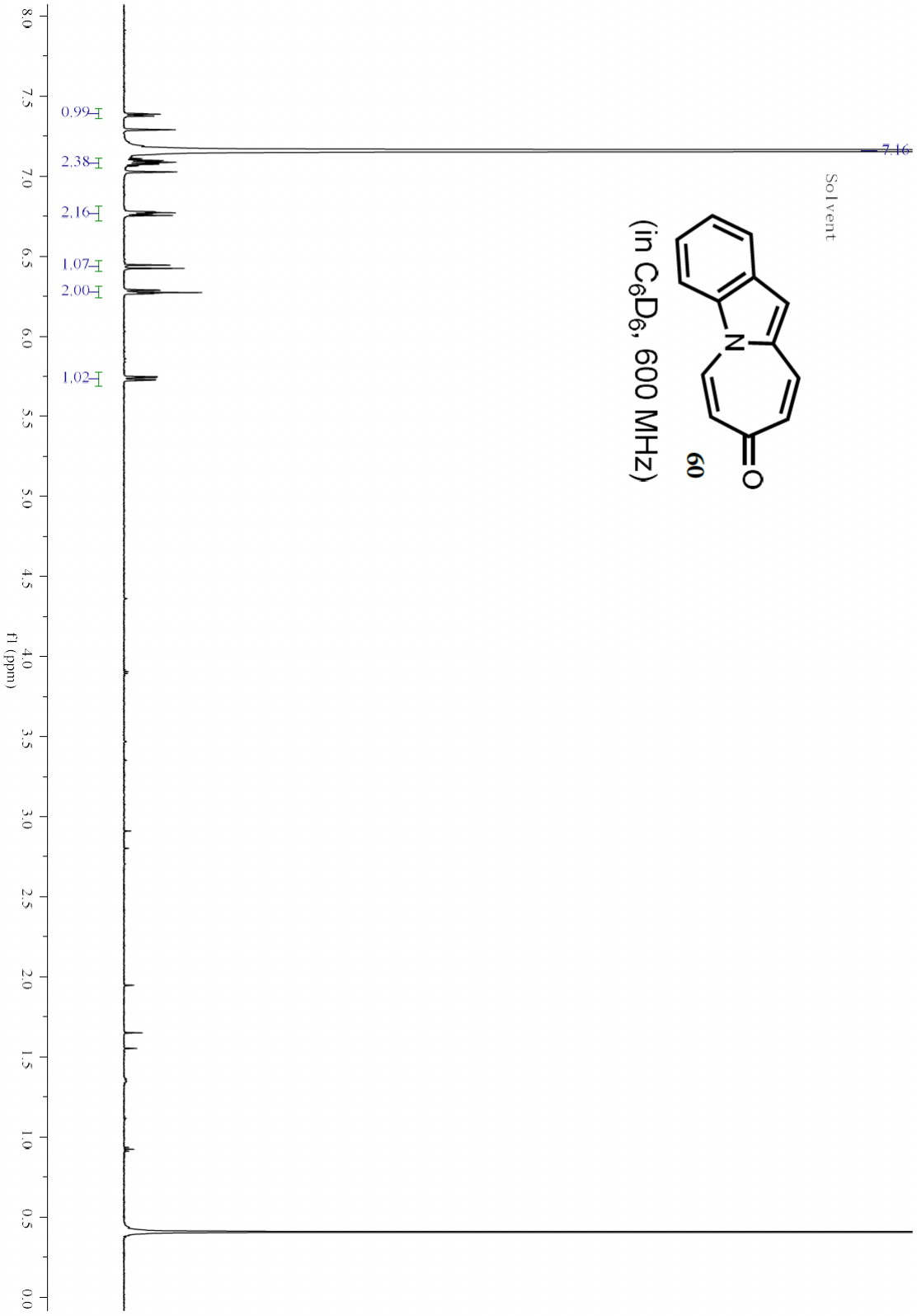

Me
MeO
NH
O
(Z-45)
(in C6D6, NOESY )
f1 (ppm)
f2 (ppm)

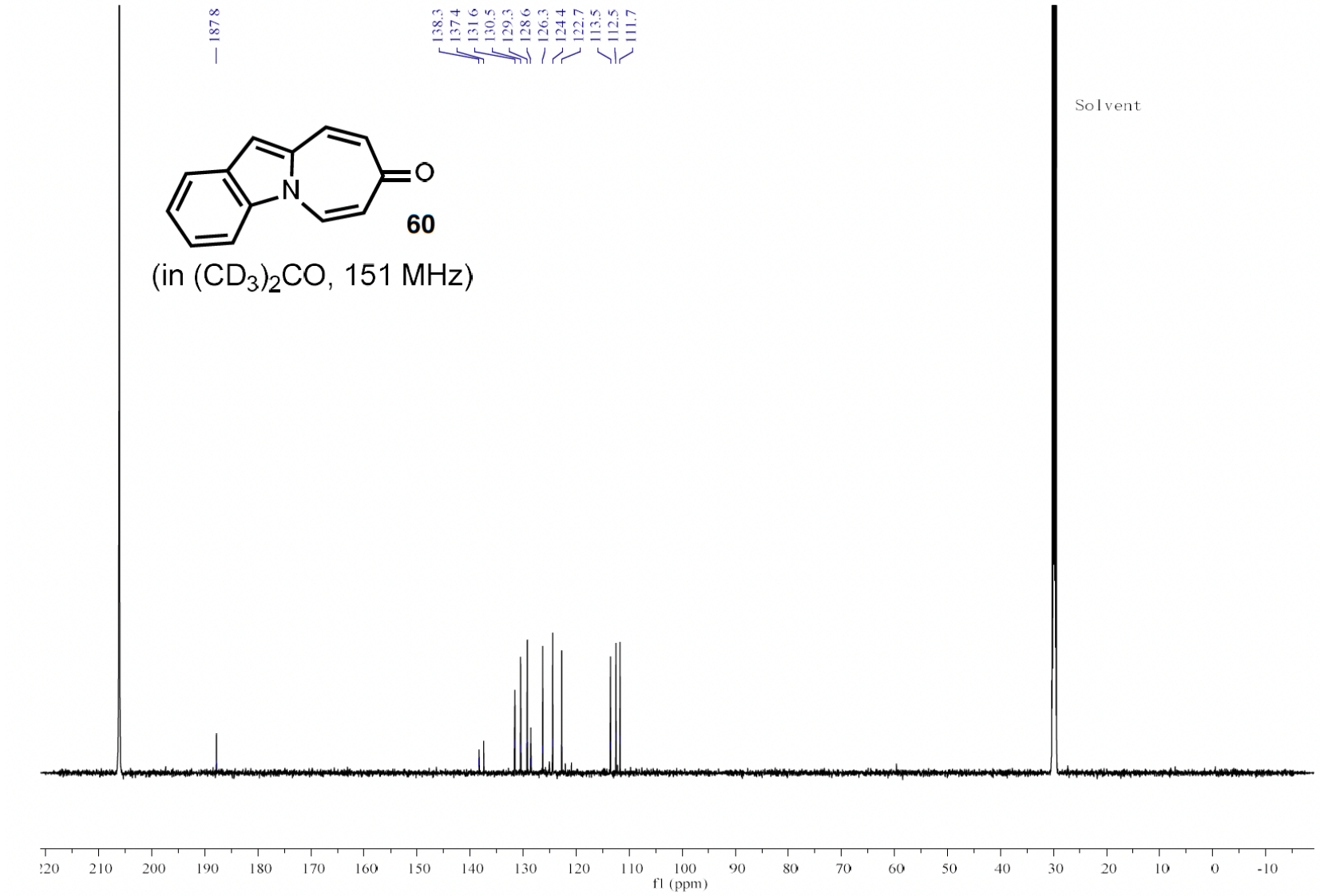

7.26
O
N
Me
25
(in CDCl3, 600 MHz)
Solvent
1.03
1.03
1.00
1.00
1.02
1.01
3.30
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

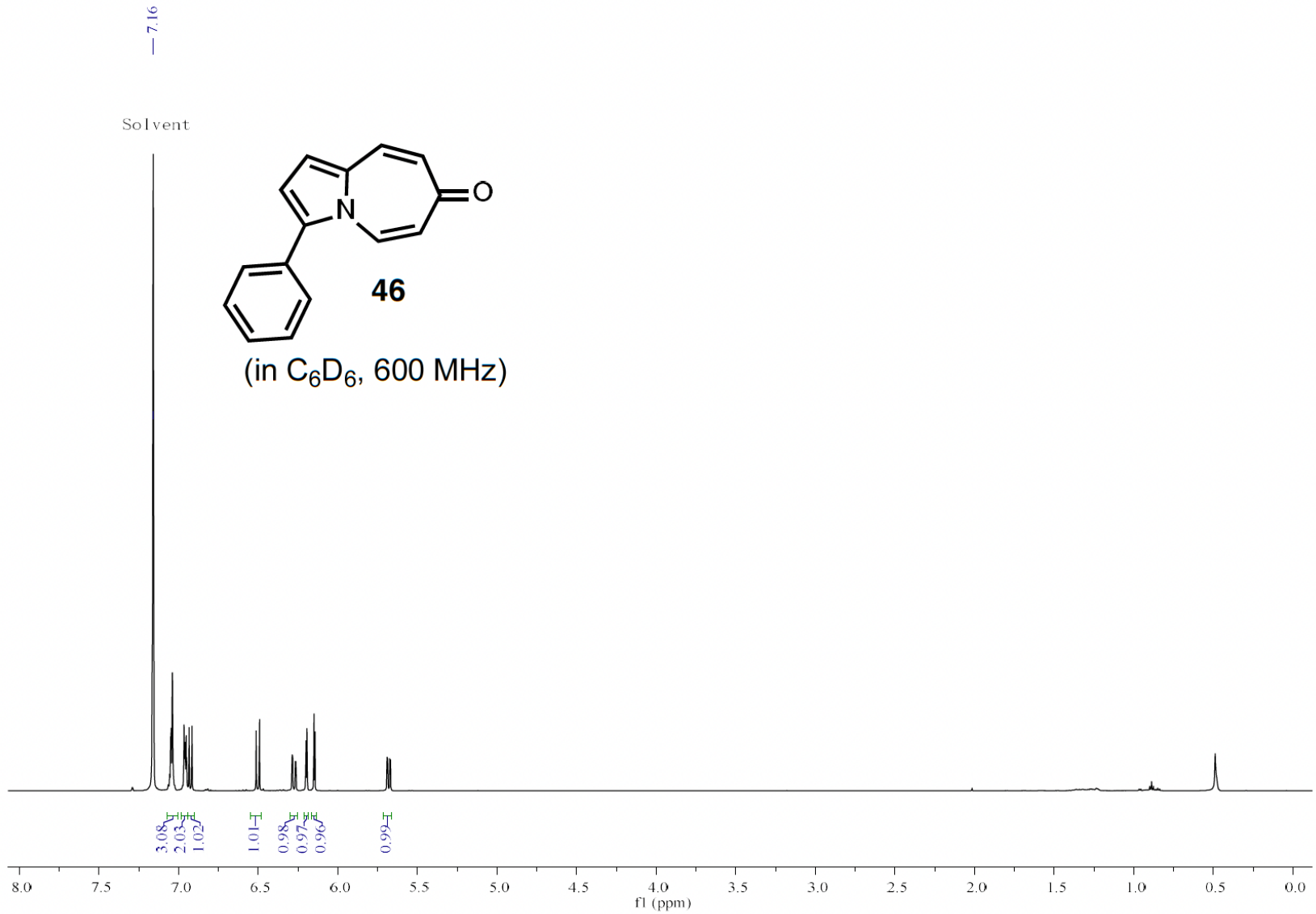

187.6
134.0
132.7
130.1
130.0
123.9
117.8
114.9
112.7
13.1
O
N
Me
25
(in CDCl3, 151 MHz)
Solvent
f1 (ppm)

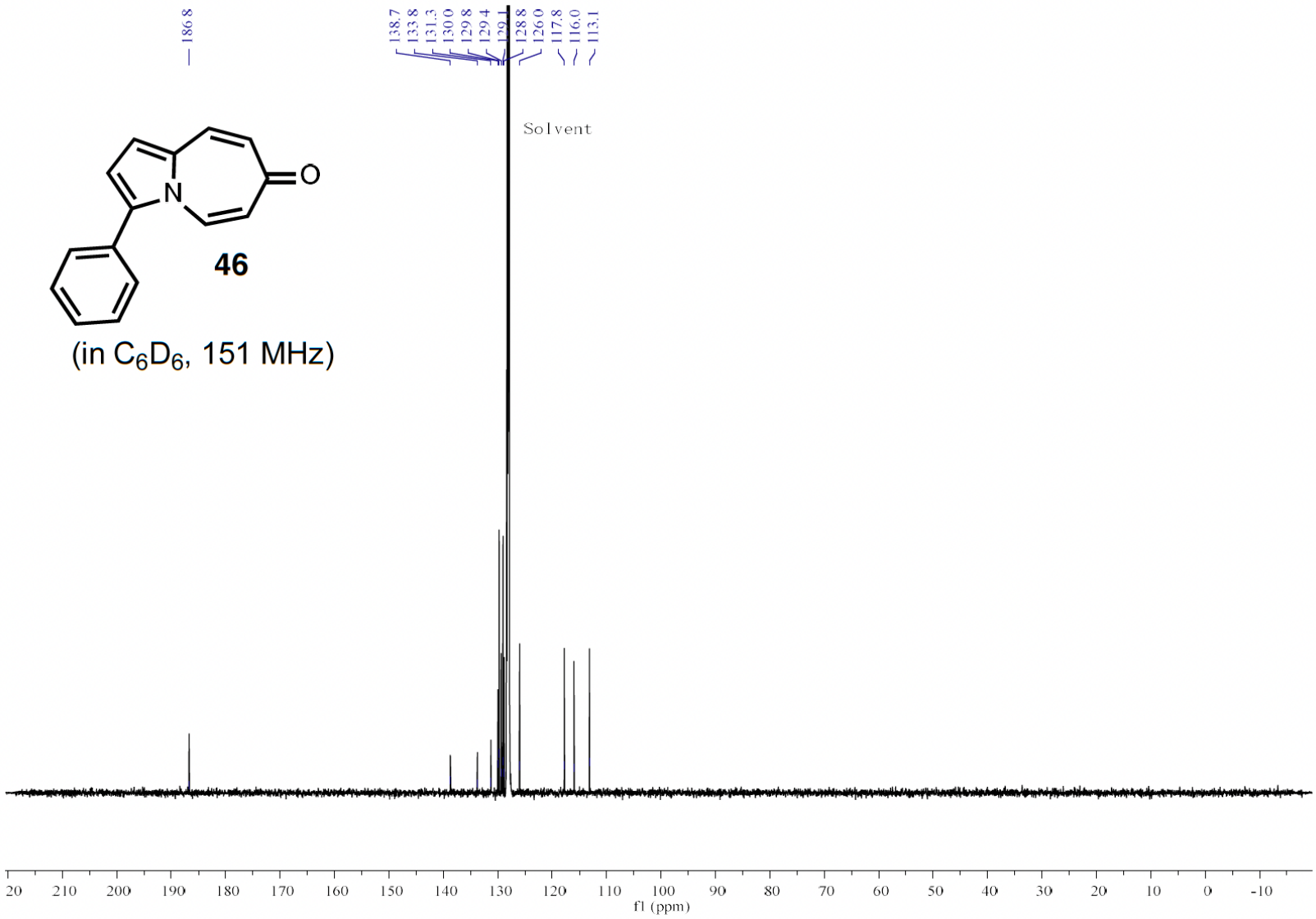

— 7.26
Me
N
O
72
(in CDCl3, 600 MHz)
Solvent
1.00
0.98
0.99
0.97
0.98
0.97
3.09
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

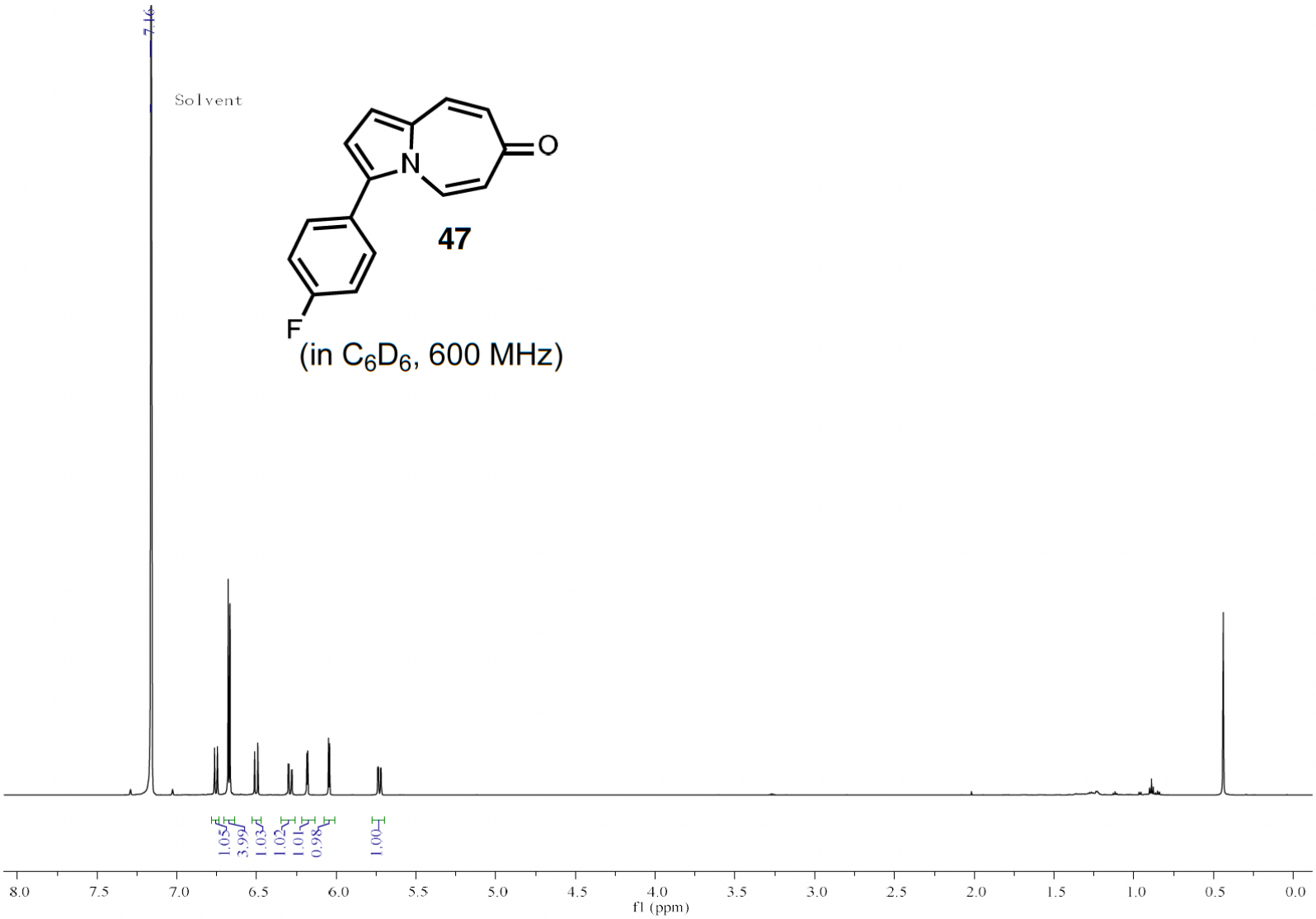

187.0
138.7
134.3
133.5
128.1
127.0
116.5
114.9
112.4
24.3
Solvent
Me
N
O
72
(in CDCl3, 151 MHz)
f1 (ppm)

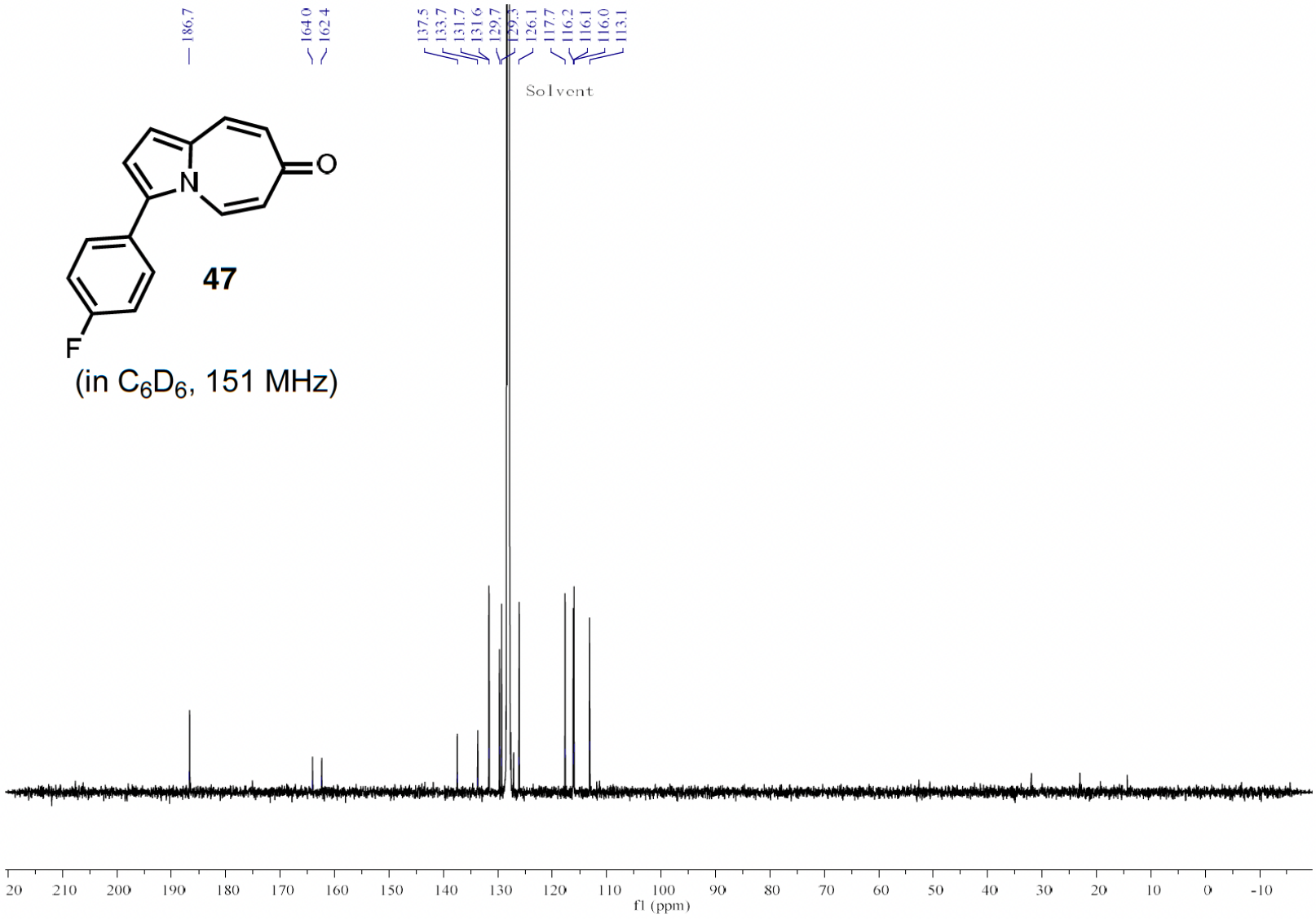

(in $C_6D_6$, 600 MHz)
60
Solvent
7.16
0.99
2.38
2.16
1.07
2.00
1.02
f1 (ppm)

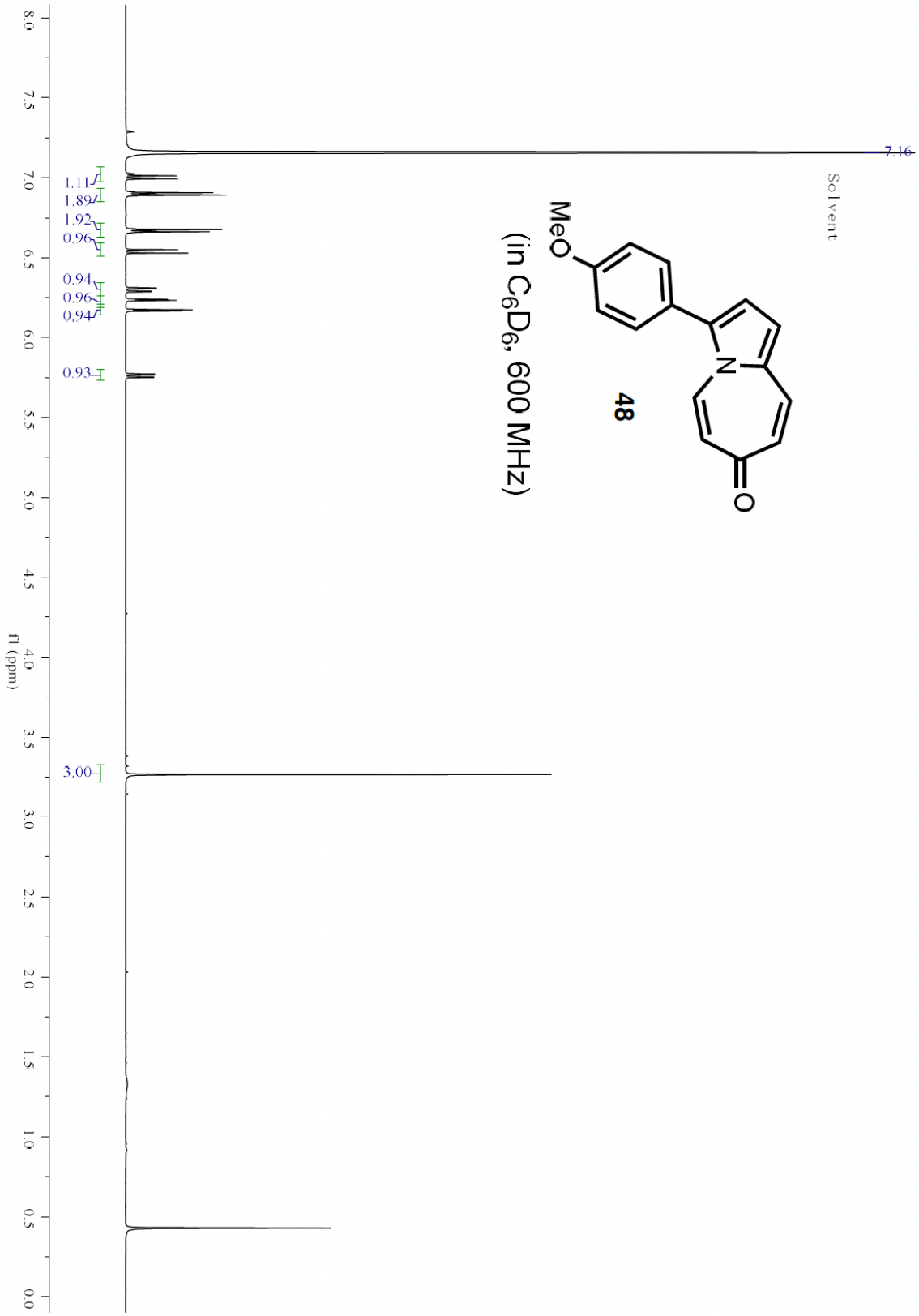

187.8
138.3
137.4
131.6
130.5
129.3
128.6
126.3
124.4
122.7
113.5
112.5
111.7
Solvent
O
N
60
(in (CD3)2CO, 151 MHz)
f1 (ppm)

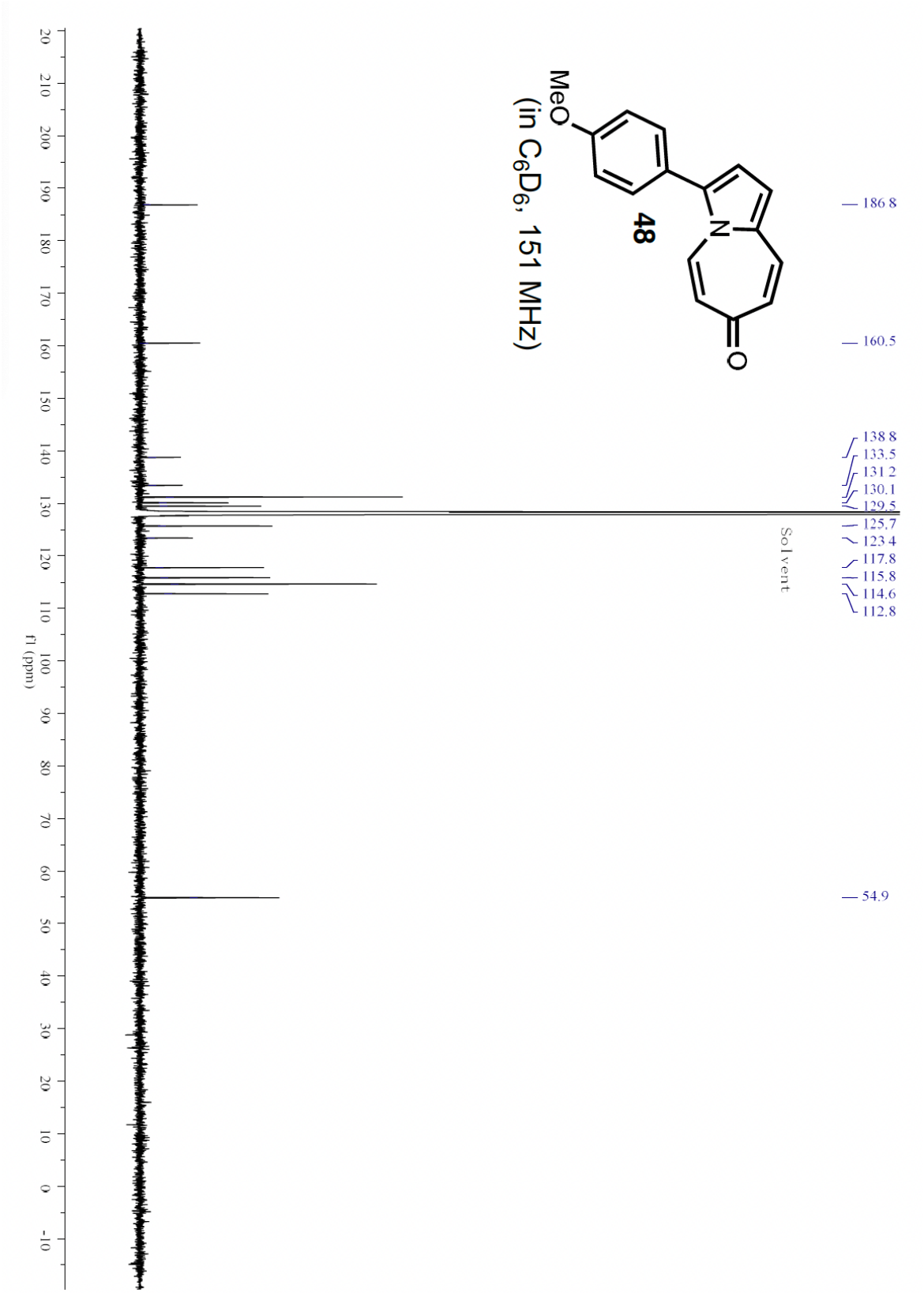

7.16
Solvent
O
N
46
(in C6D6, 600 MHz)
3.08
2.03
1.02
1.01
0.98
0.97
0.96
0.99
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

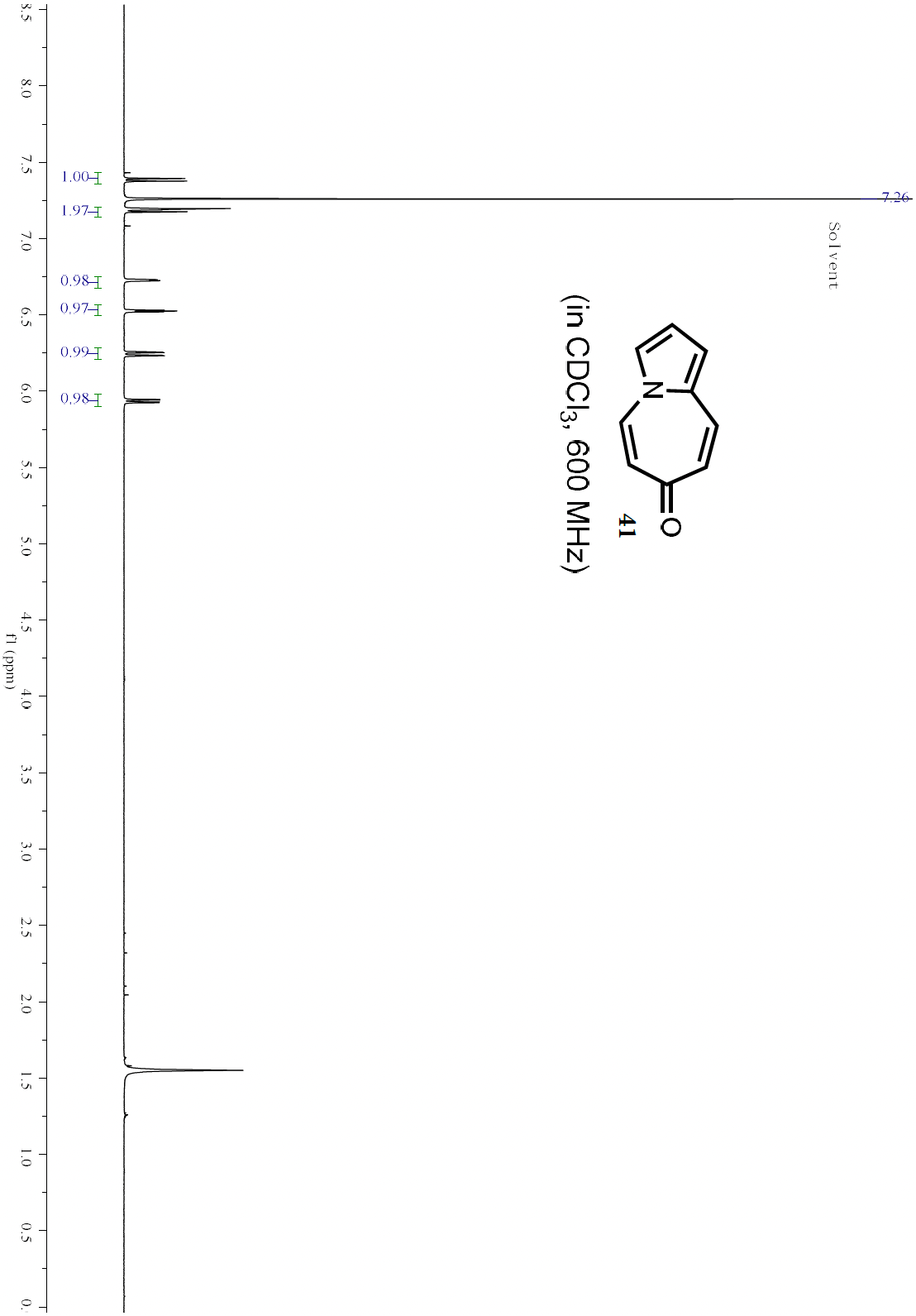

186.8
138.7
133.8
131.3
130.0
129.8
129.4
129.1
128.8
126.0
117.8
116.0
113.1
Solvent
O
N
46
(in C6D6, 151 MHz)
20 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

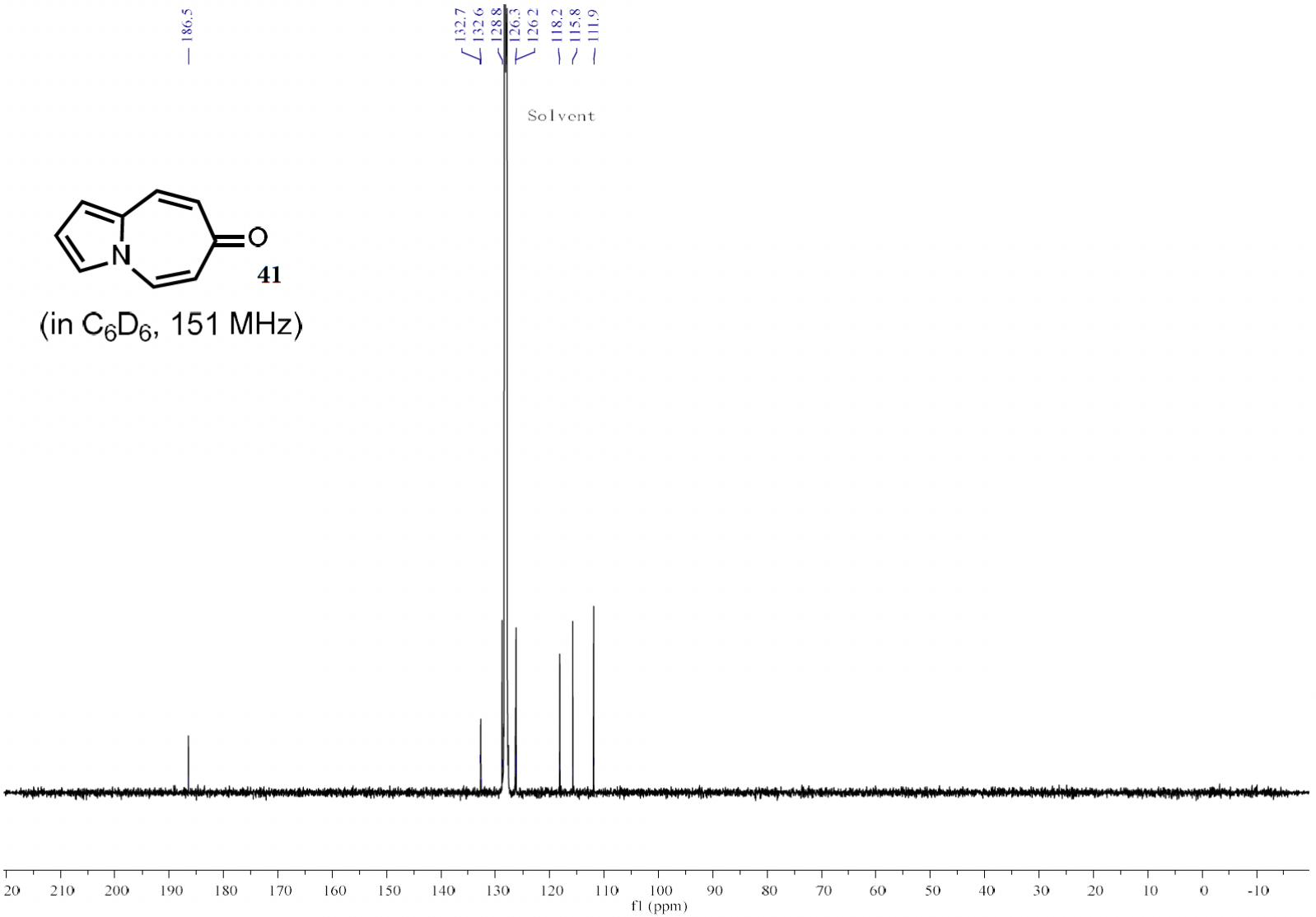

7.16
Solvent
O
N
47
F
(in C6D6, 600 MHz)
1.05
3.99
1.03
1.02
1.01
0.98
1.00
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

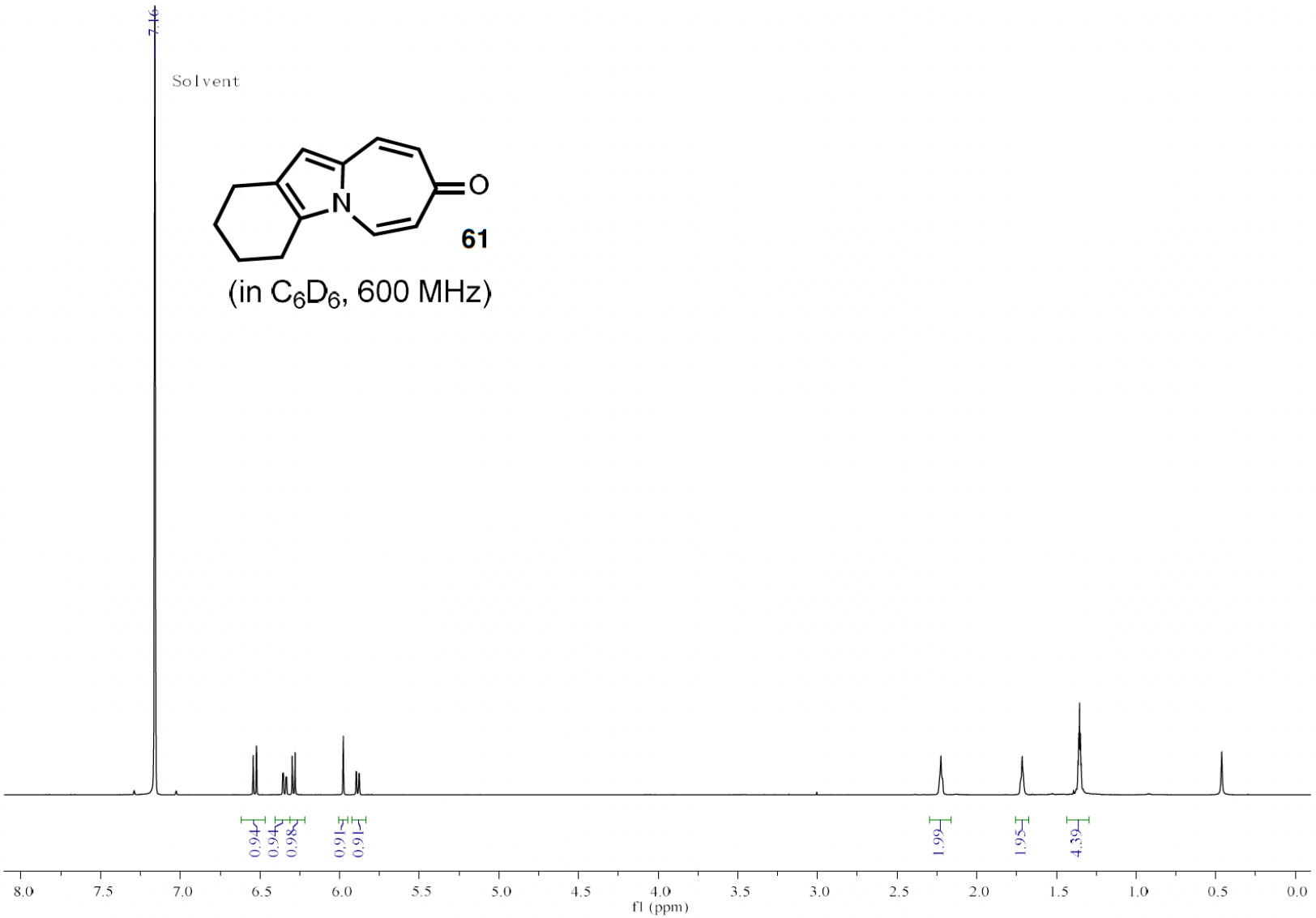

186.7
164.0
162.4
137.5
133.7
131.7
131.6
129.7
129.3
126.1
117.7
116.2
116.1
116.0
113.1
Solvent
O
N
F
47
(in C6D6, 151 MHz)
f1 (ppm)

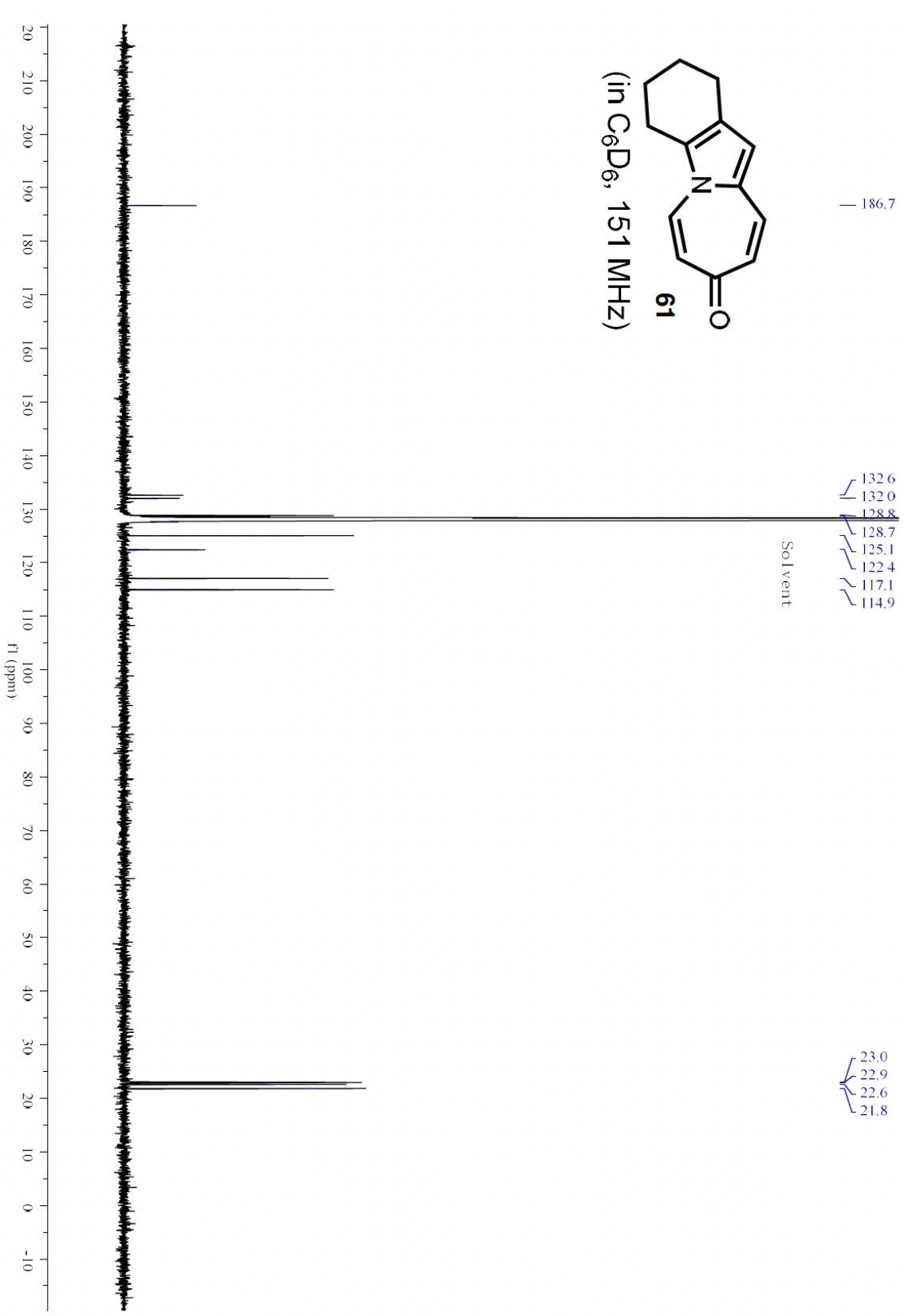

MeO
N
O
48
(in C6D6, 600 MHz)
Solvent
7.16
1.11
1.89
1.92
0.96
0.94
0.96
0.94
0.93
3.00
f1 (ppm)

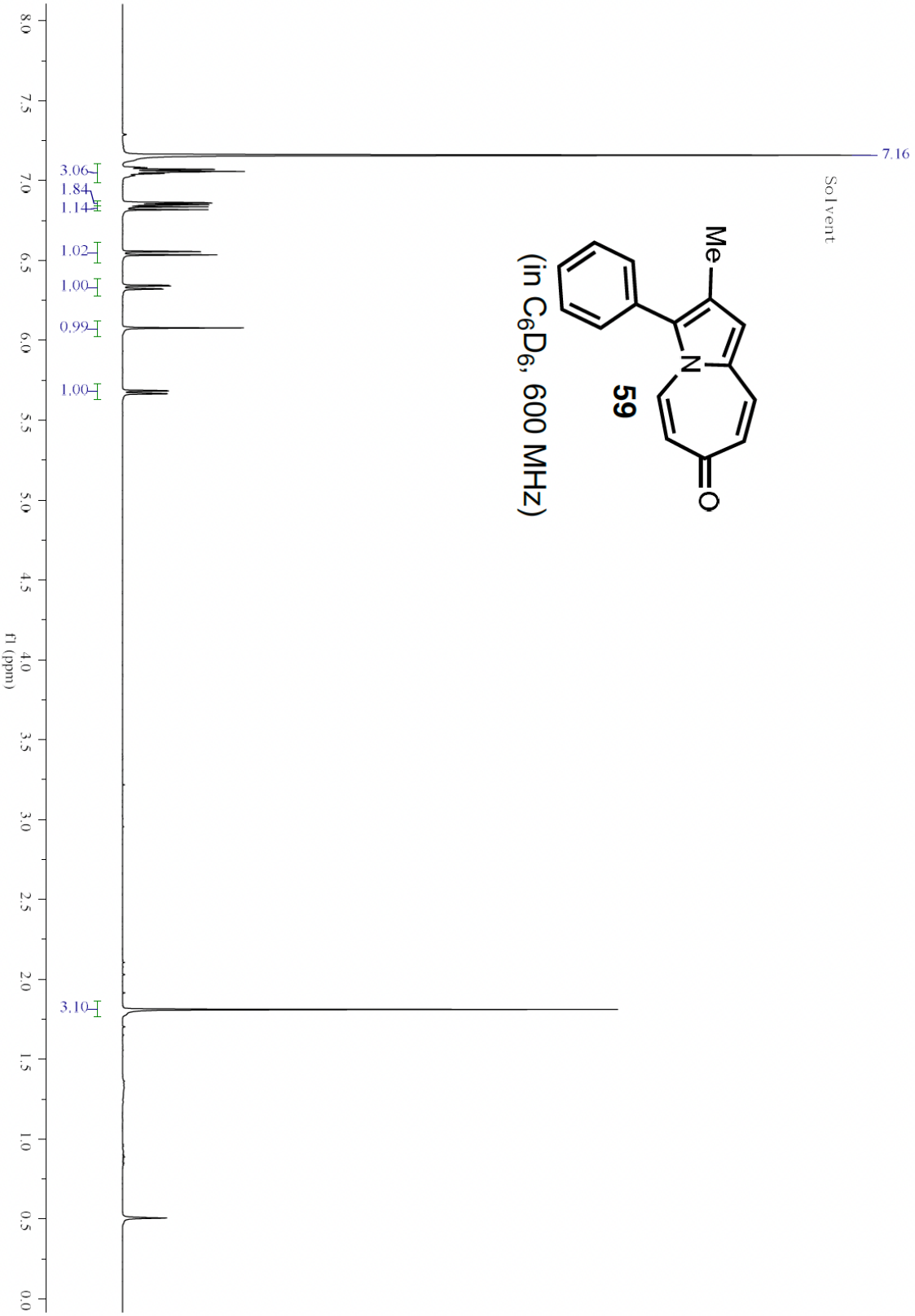

MeO
(in $C_6D_6$, 151 MHz)
48
N
O
186.8
160.5
138.8
133.5
131.2
130.1
129.5
125.7
123.4
117.8
115.8
114.6
112.8
54.9
Solvent
f1 (ppm)

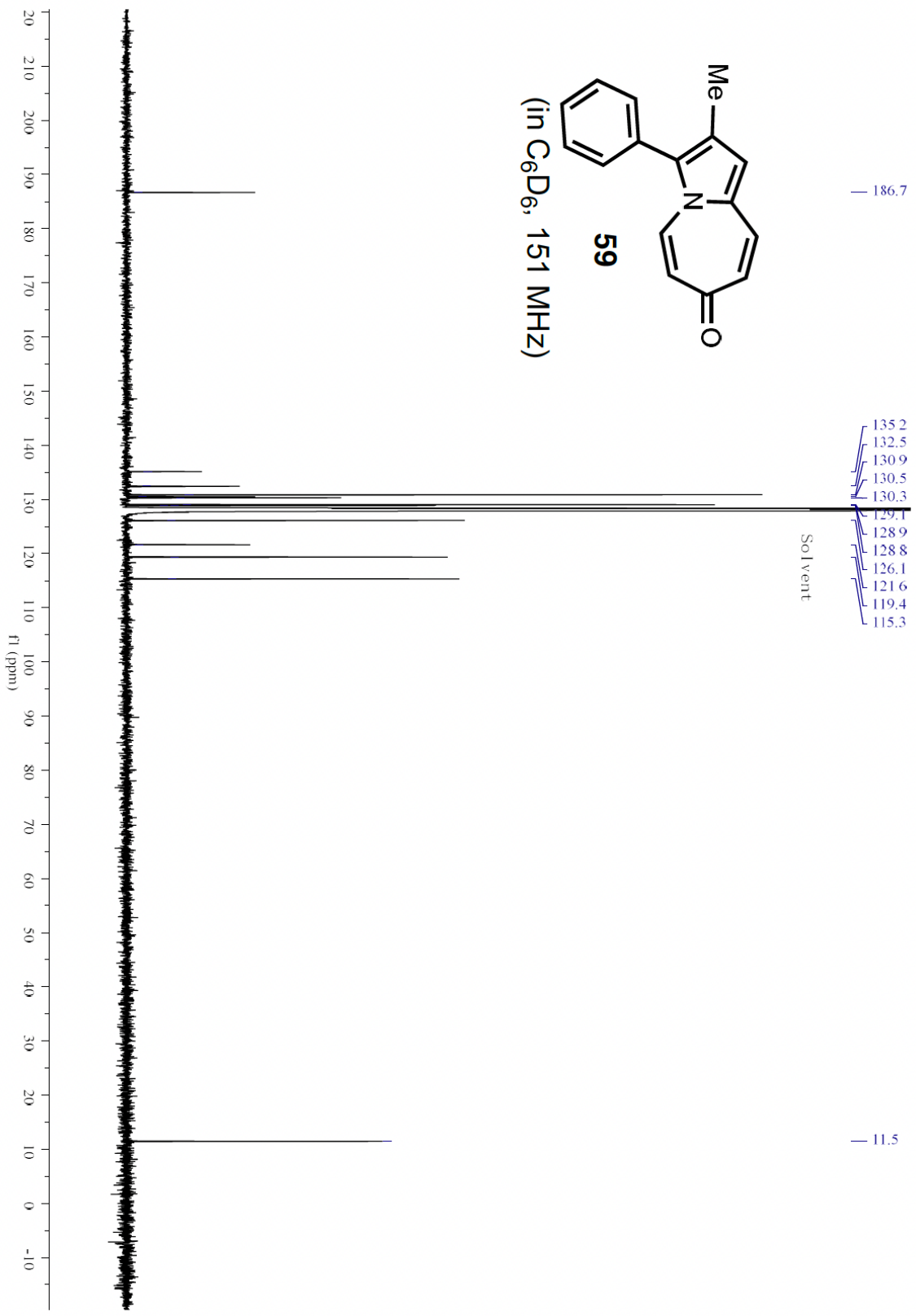

41
(in CDCl3, 600 MHz)
Solvent
7.26
1.00
1.97
0.98
0.97
0.99
0.98
f1 (ppm)

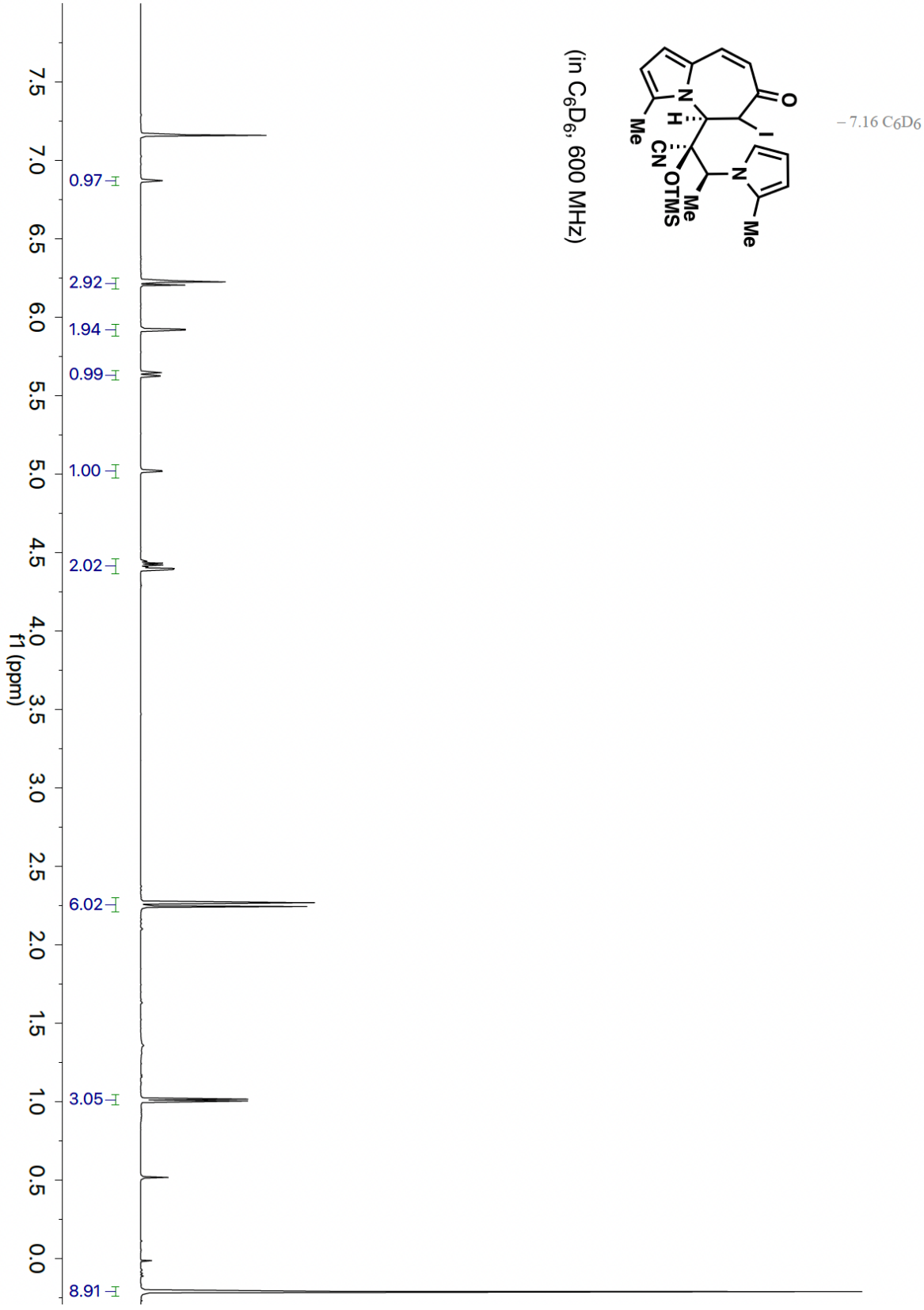

186.5
132.7
132.6
128.8
126.3
126.2
118.2
115.8
111.9
Solvent
O
N
41
(in C6D6, 151 MHz)
f1 (ppm)

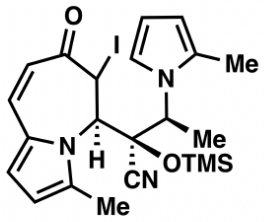

7.16
Solvent
O
N
61
(in $C_6D_6$, 600 MHz)
0.94
0.94
0.98
0.91
0.91
1.99
1.95
4.39
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


61
(in $C_6D_6$, 151 MHz)
186.7
132.6
132.0
128.8
128.7
125.1
122.4
117.1
114.9
Solvent
23.0
22.9
22.6
21.8
f1 (ppm)

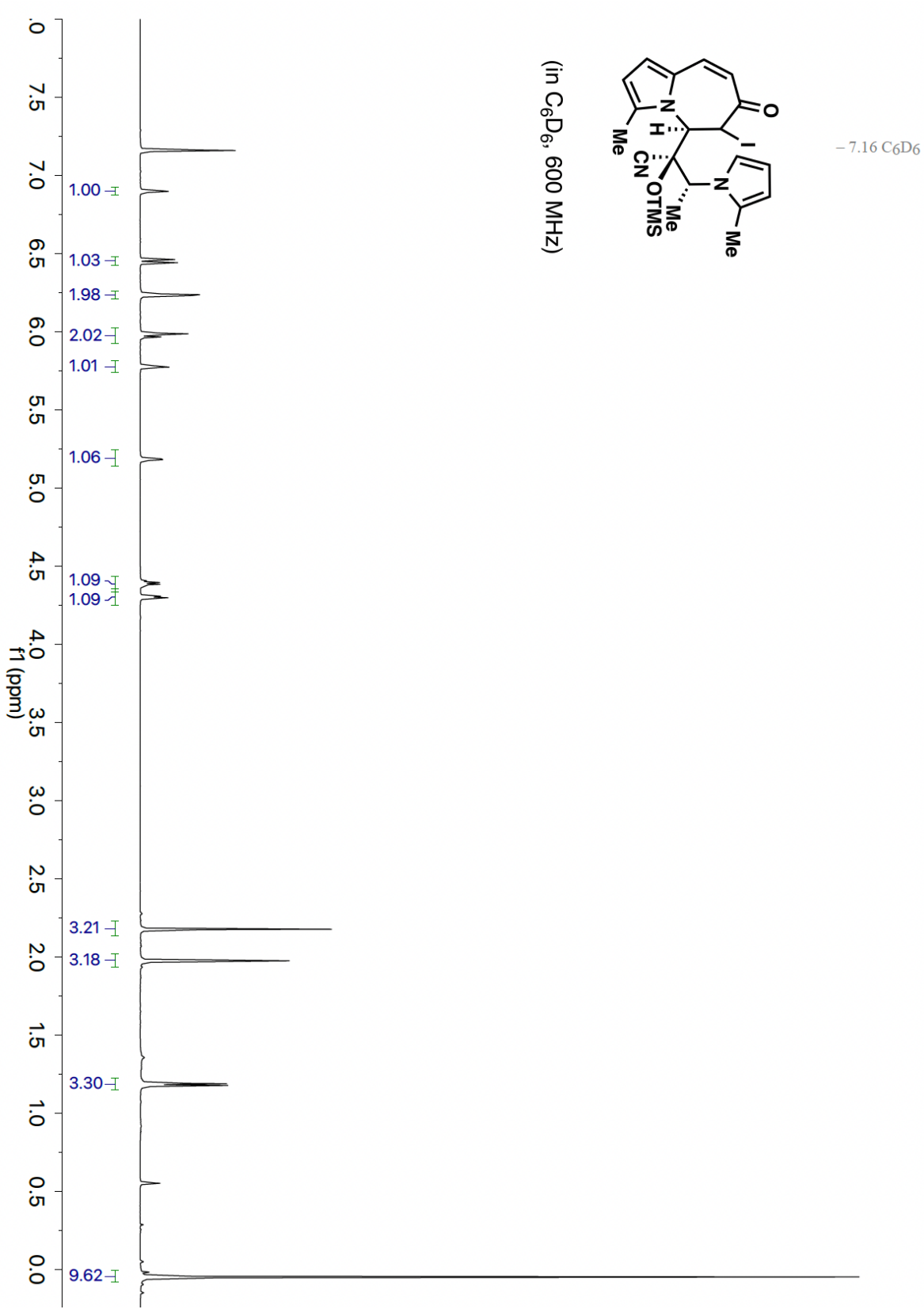

7.16
Solvent
3.06
1.84
1.14
1.02
1.00
0.99
1.00
3.10
f1 (ppm)
(in C6D6, 600 MHz)
59
Me
N
O

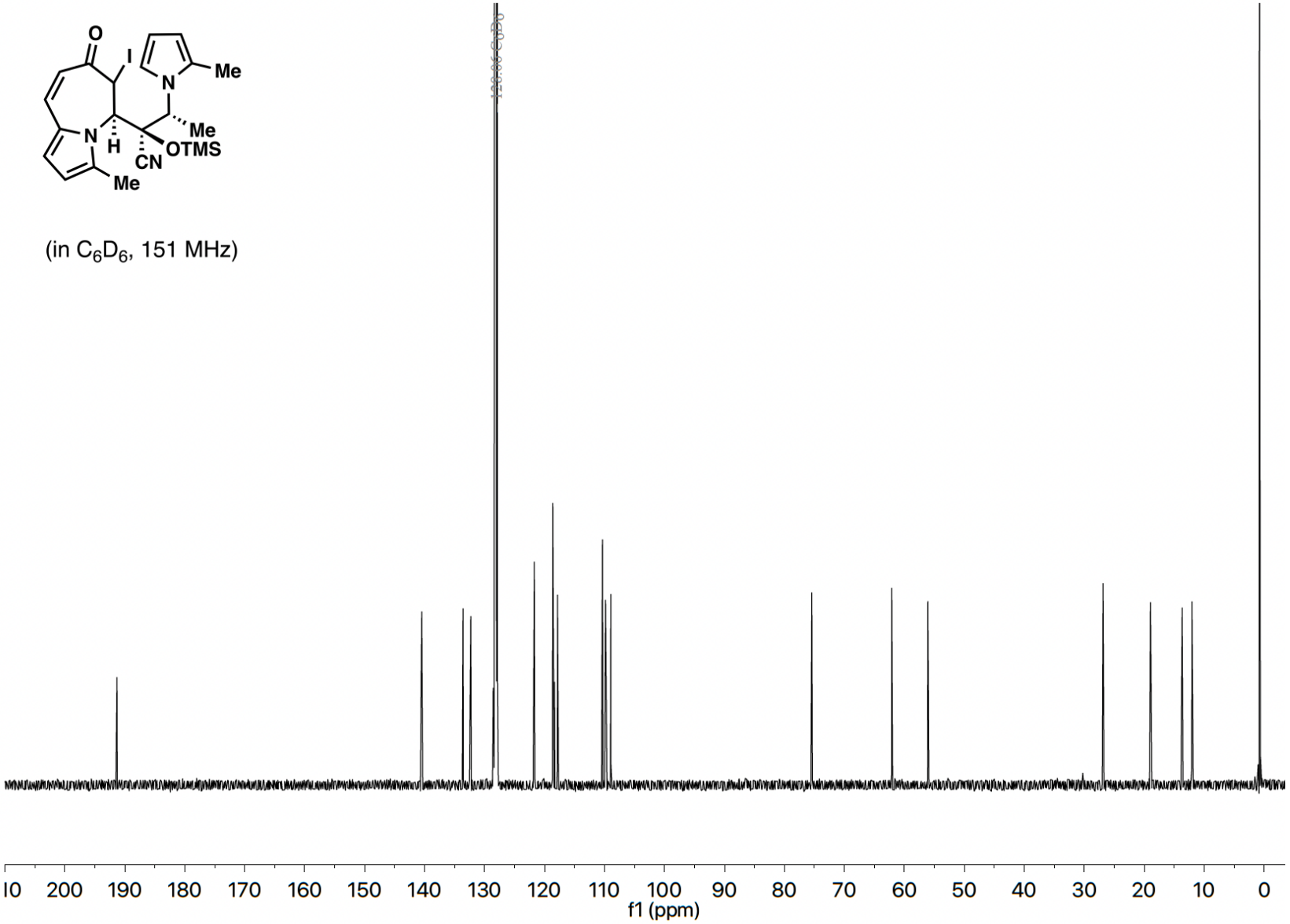

Me
N
O
59
(in C6D6, 151 MHz)
186.7
135.2
132.5
130.9
130.5
130.3
129.1
128.9
128.8
126.1
121.6
119.4
115.3
Solvent
11.5
f1 (ppm)

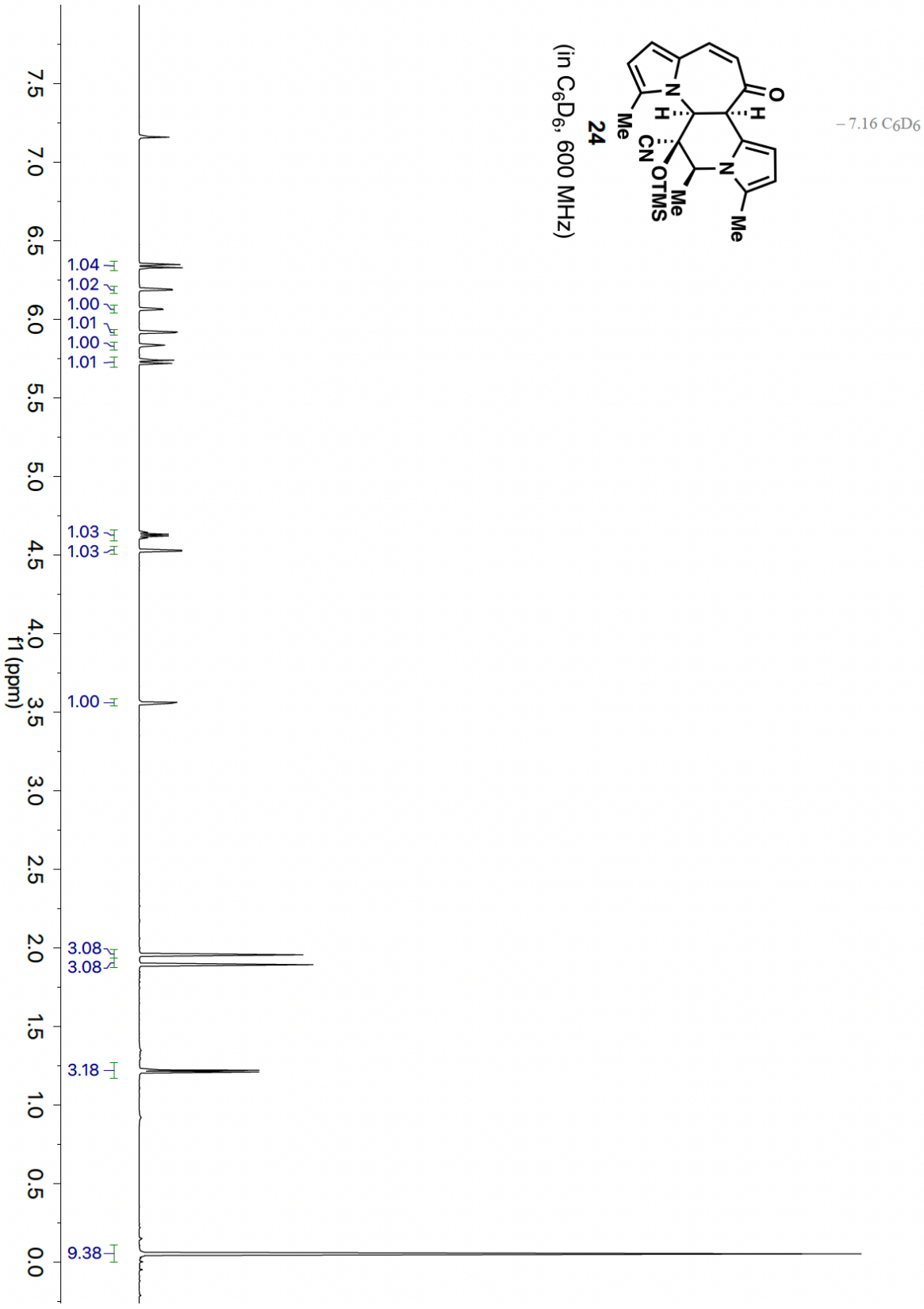

(in C6D6, 600 MHz)
– 7.16 C6D6
f1 (ppm)
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
0.97
2.92
1.94
0.99
1.00
2.02
6.02
3.05
8.91

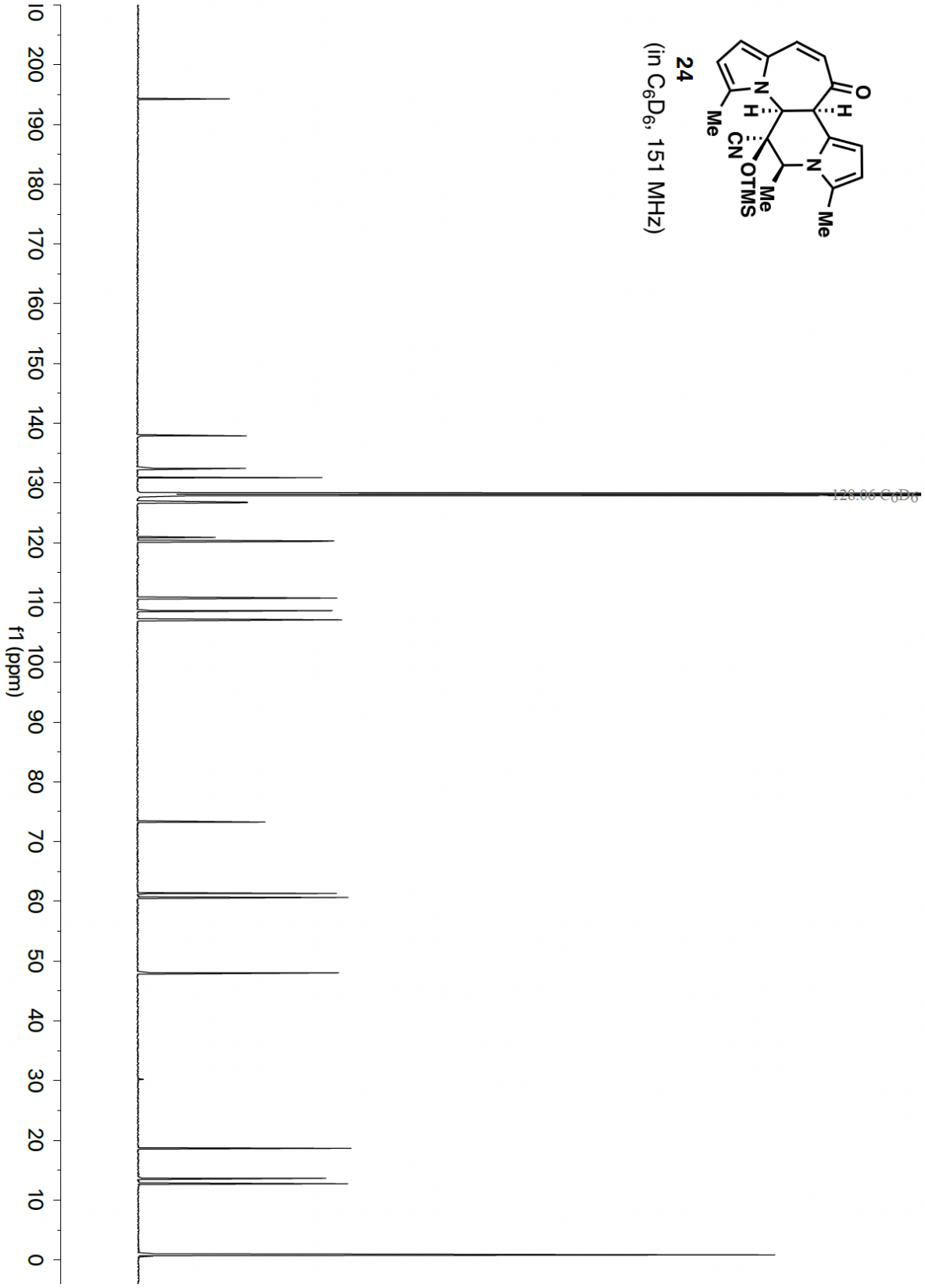


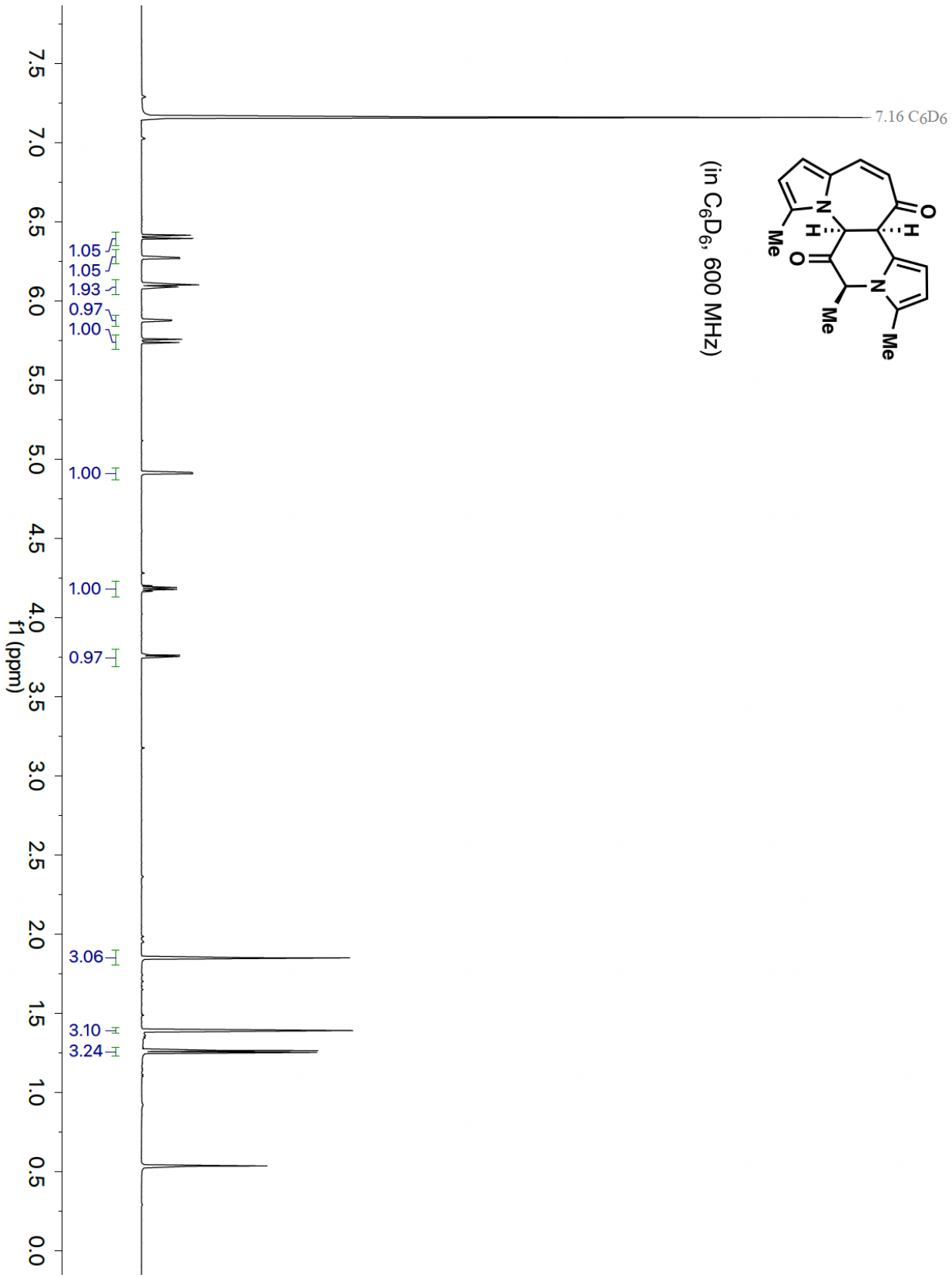

(in $C_6D_6$, 151 MHz)

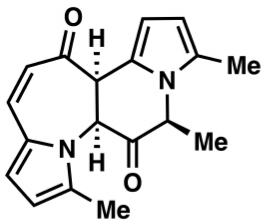

(in C6D6, 600 MHz)
Me
N
H
CN
OTMS
Me
O
I
N
Me
– 7.16 C6D6
1.00
1.03
1.98
2.02
1.01
1.06
1.09
1.09
3.21
3.18
3.30
9.62
f1 (ppm)


O
I
N
Me
Me
N
H
OTMS
CN
Me
(in C6D6, 151 MHz)
f1 (ppm)

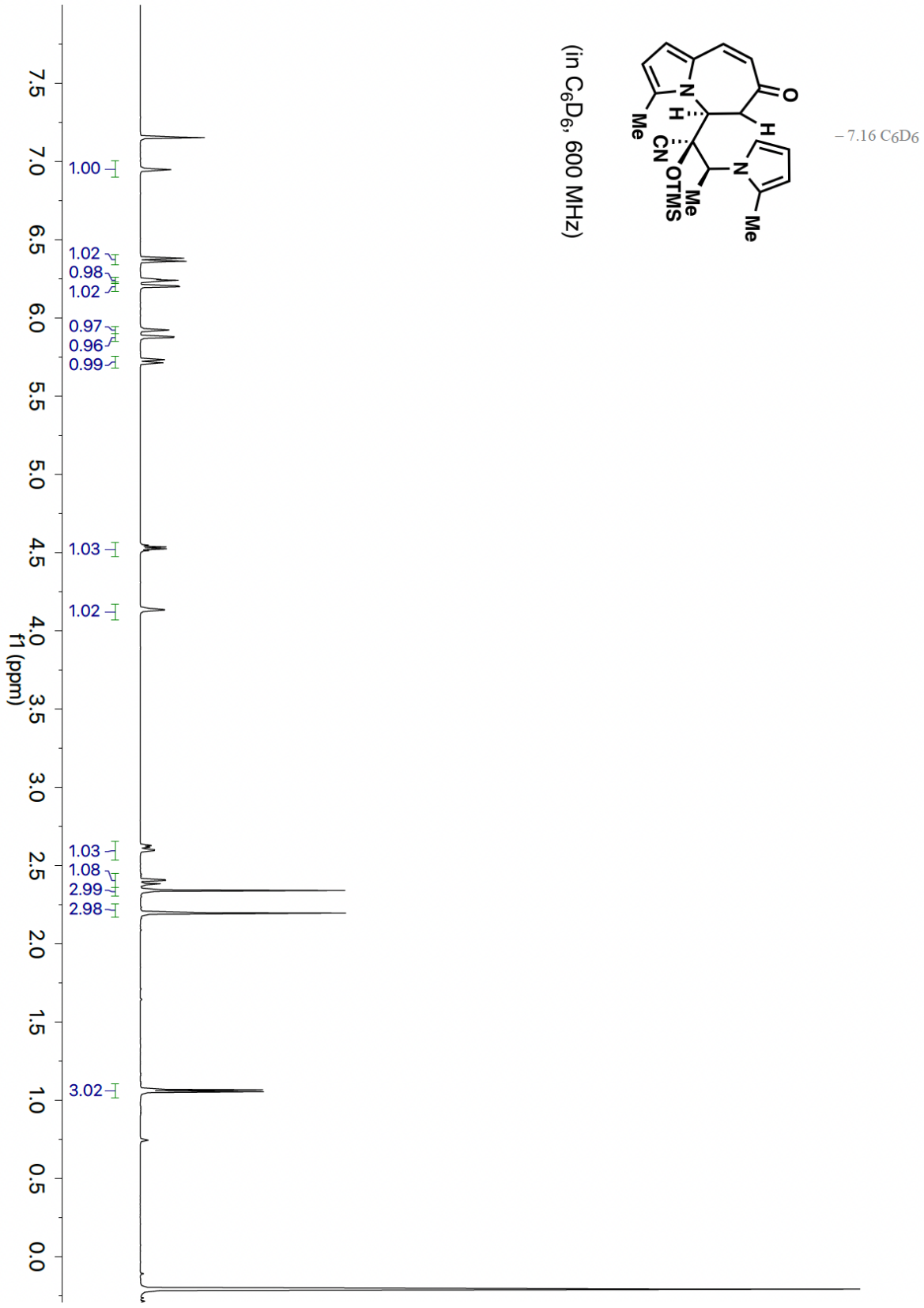

24
(in C6D6, 600 MHz)
– 7.16 C6D6
1.04
1.02
1.00
1.01
1.00
1.01
1.03
1.03
1.00
3.08
3.08
3.18
9.38
f1 (ppm)

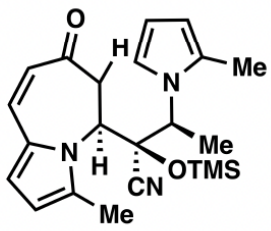

24
(in C6D6, 151 MHz)
128.06 C6D6
f1 (ppm)
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210


7.16 C6D6
(in C6D6, 600 MHz)
Me
Me
Me
N
H
O
H
O
N
1.05
1.05
1.93
0.97
1.00
1.00
1.00
0.97
3.06
3.10
3.24
f1 (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

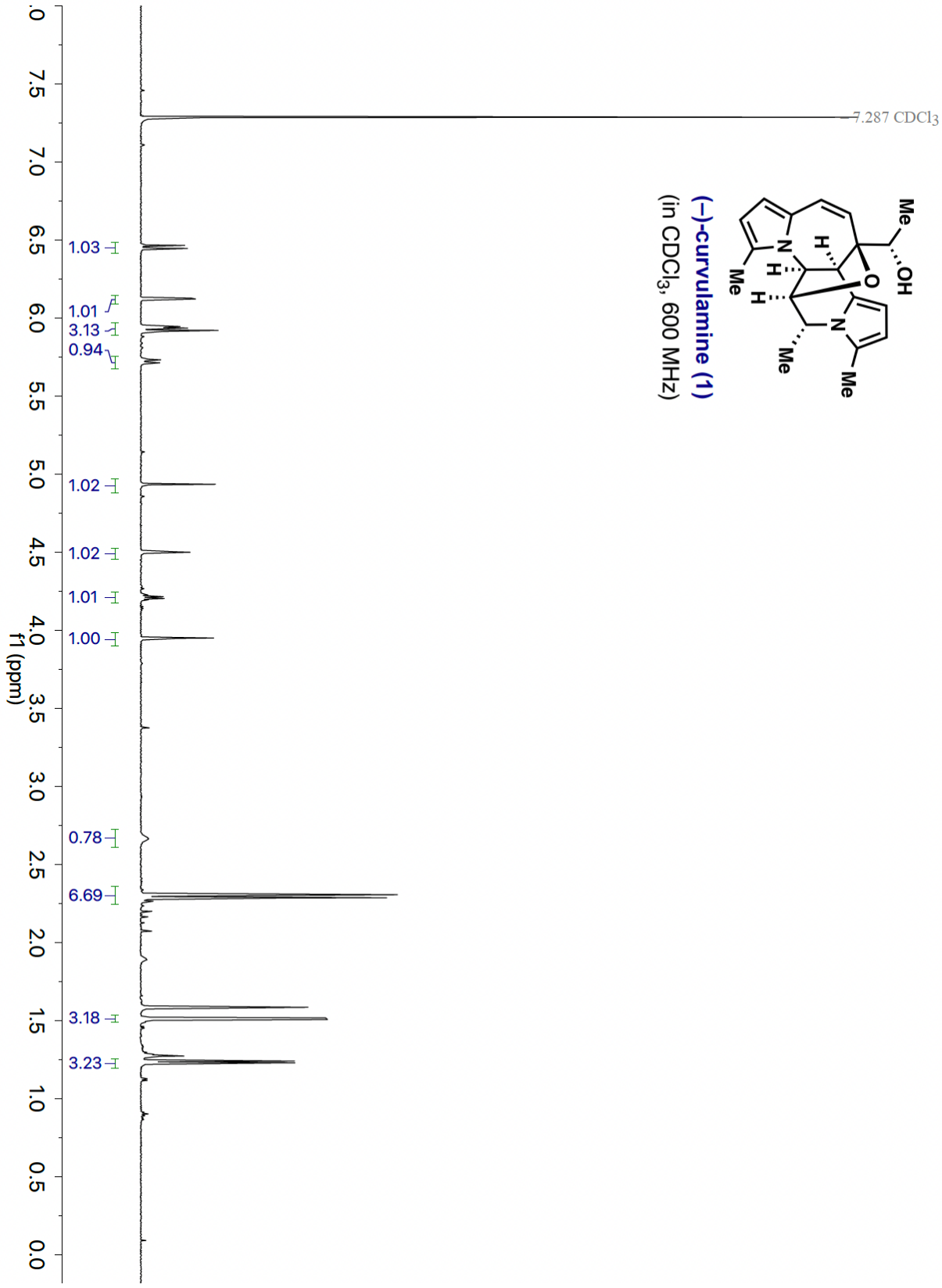


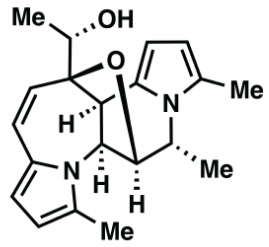

(in $C_6D_6$, 151 MHz)


(in C6D6, 600 MHz)
– 7.16 C6D6
f1 (ppm)
1.00
1.02
0.98
1.02
0.97
0.96
0.99
1.03
1.02
1.03
1.08
2.99
2.98
3.02



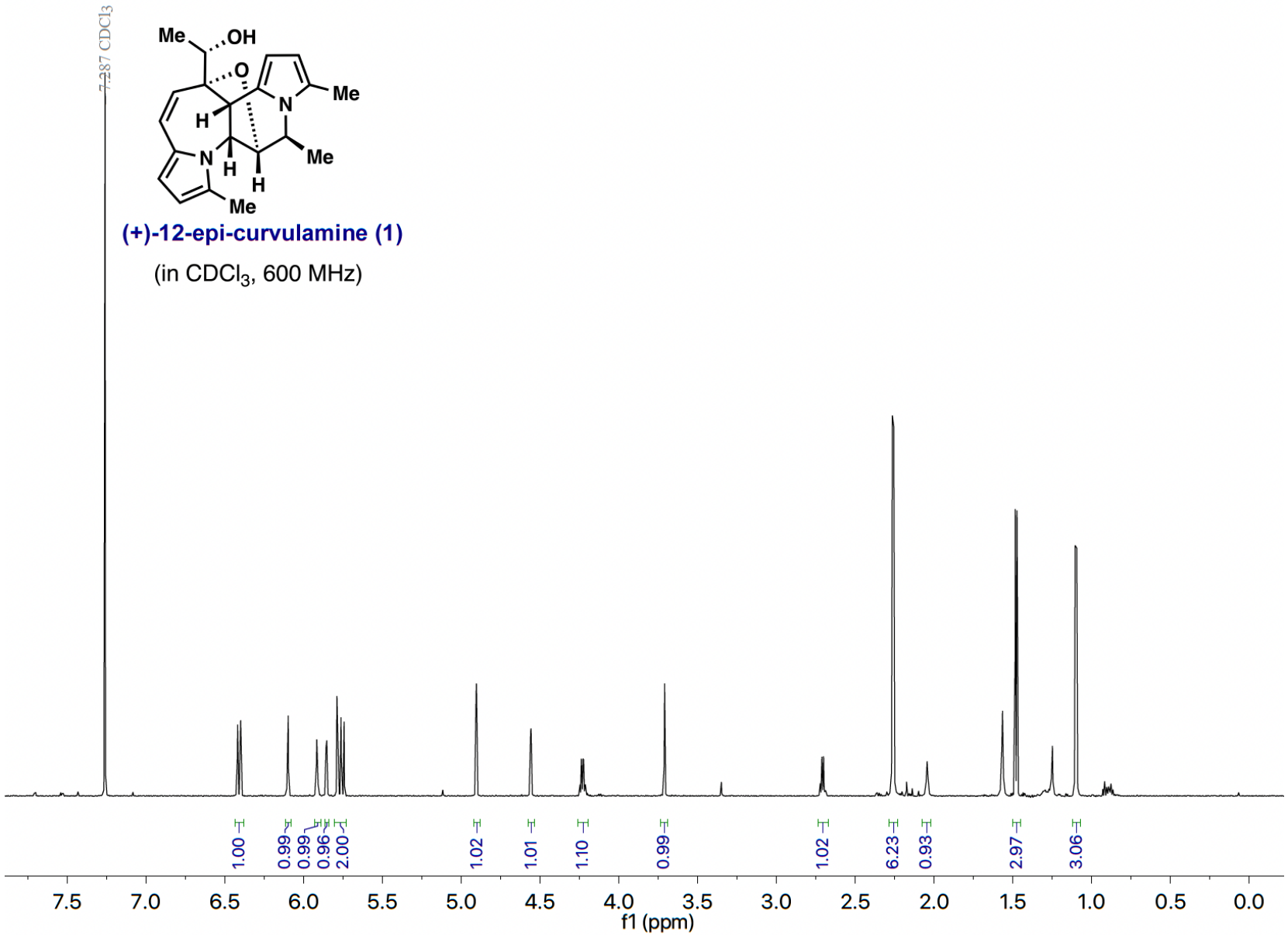

(in $C_6D_6$, 151 MHz)

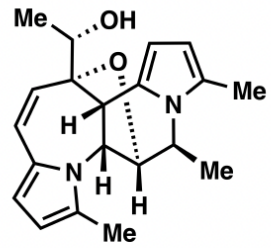

7.287 CDCl3
(–)-curvulamine (1)
(in CDCl3, 600 MHz)
Me
OH
H
N
H
H
O
N
Me
Me
Me
1.03
1.01
3.13
0.94
1.02
1.02
1.01
1.00
0.78
6.69
3.18
3.23
f1 (ppm)
.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0




**(–)-curvulamine (1)**

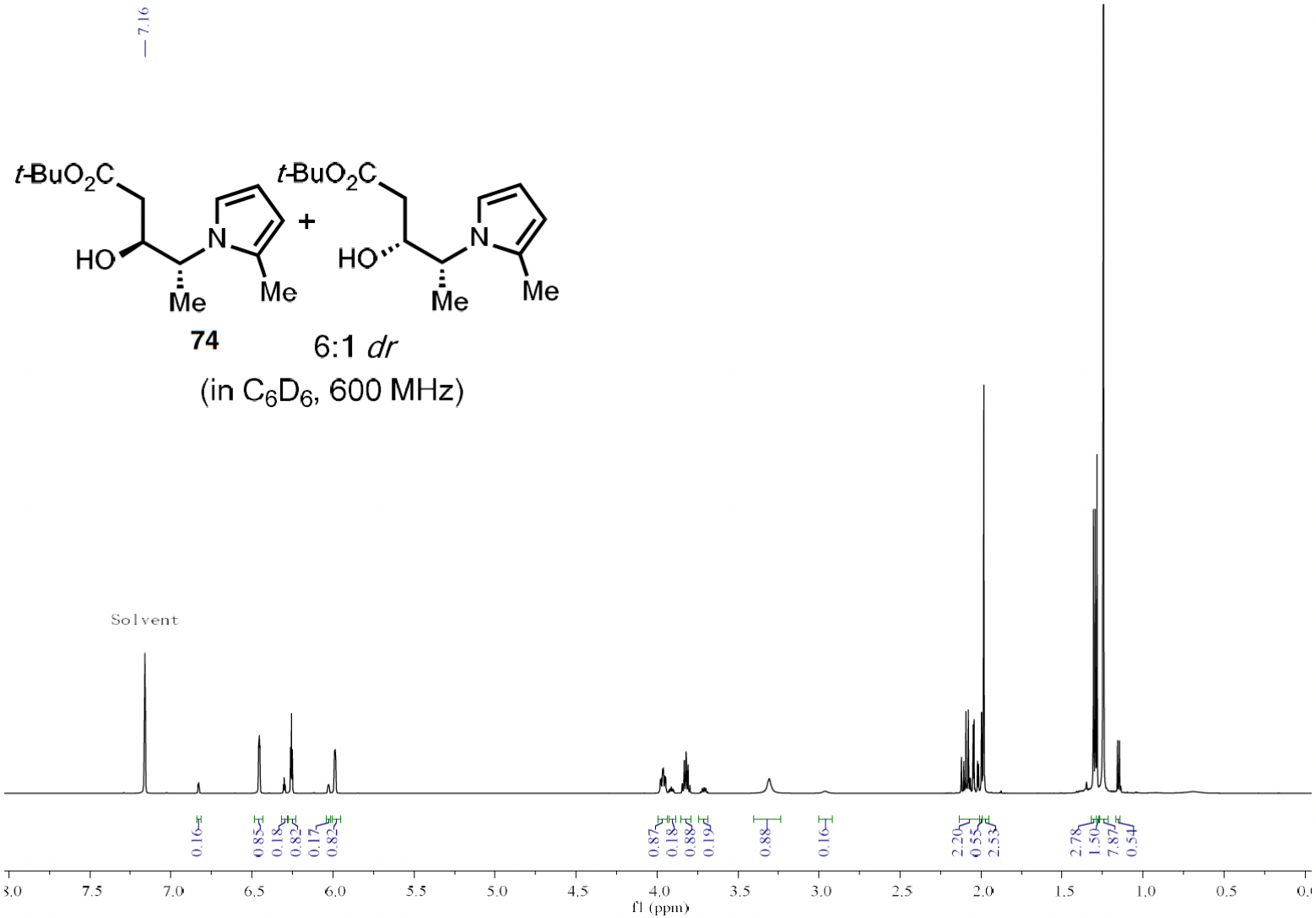
(in $CDCl_3$, 600 MHz)

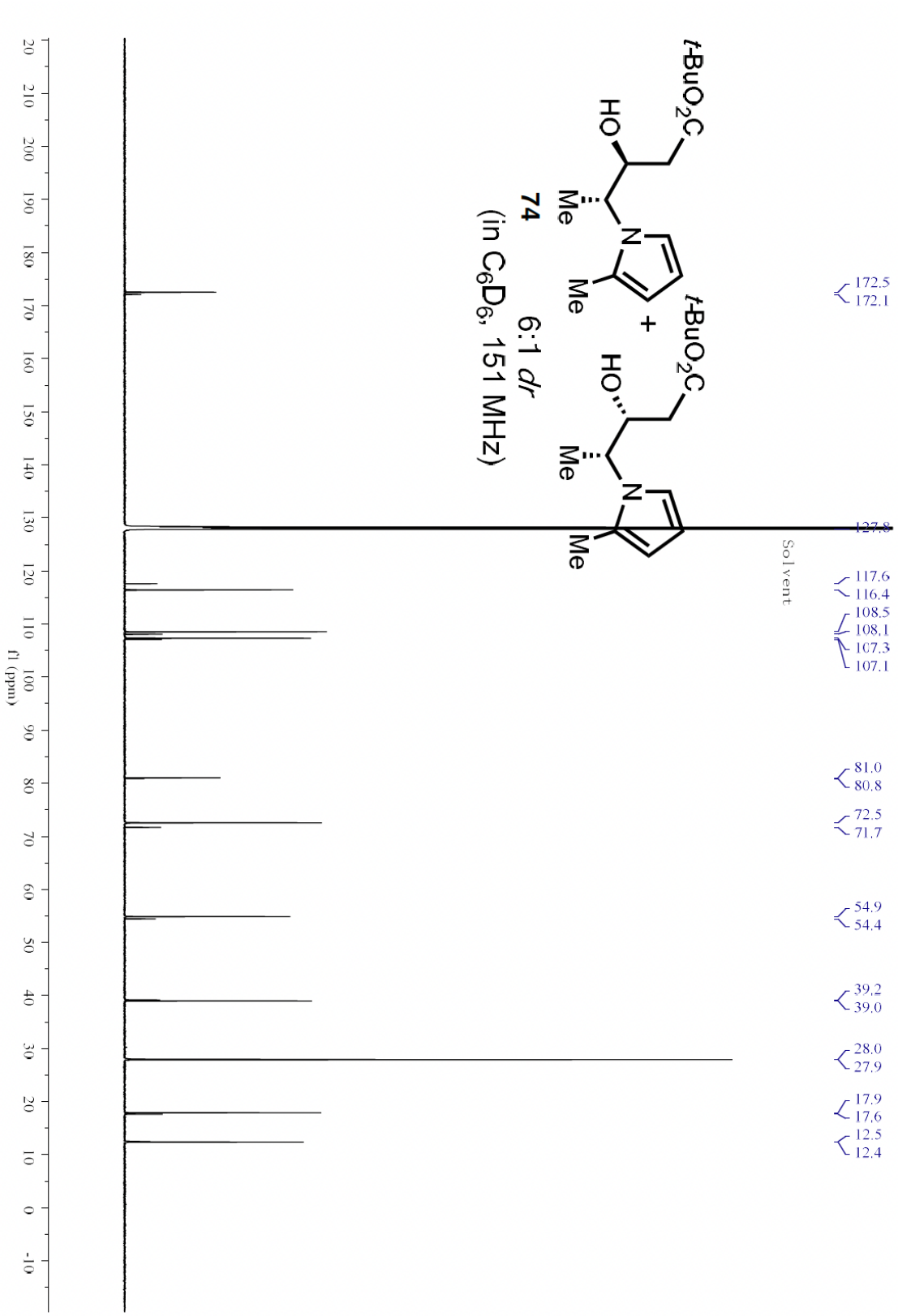

7.287 CDCl3
Me
OH
O
Me
H
N
N
H
Me
H
Me
(+)-12-epi-curvulamine (1)
(in CDCl3, 600 MHz)
1.00
0.99
0.99
0.96
2.00
1.02
1.01
1.10
0.99
1.02
6.23
0.93
2.97
3.06
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

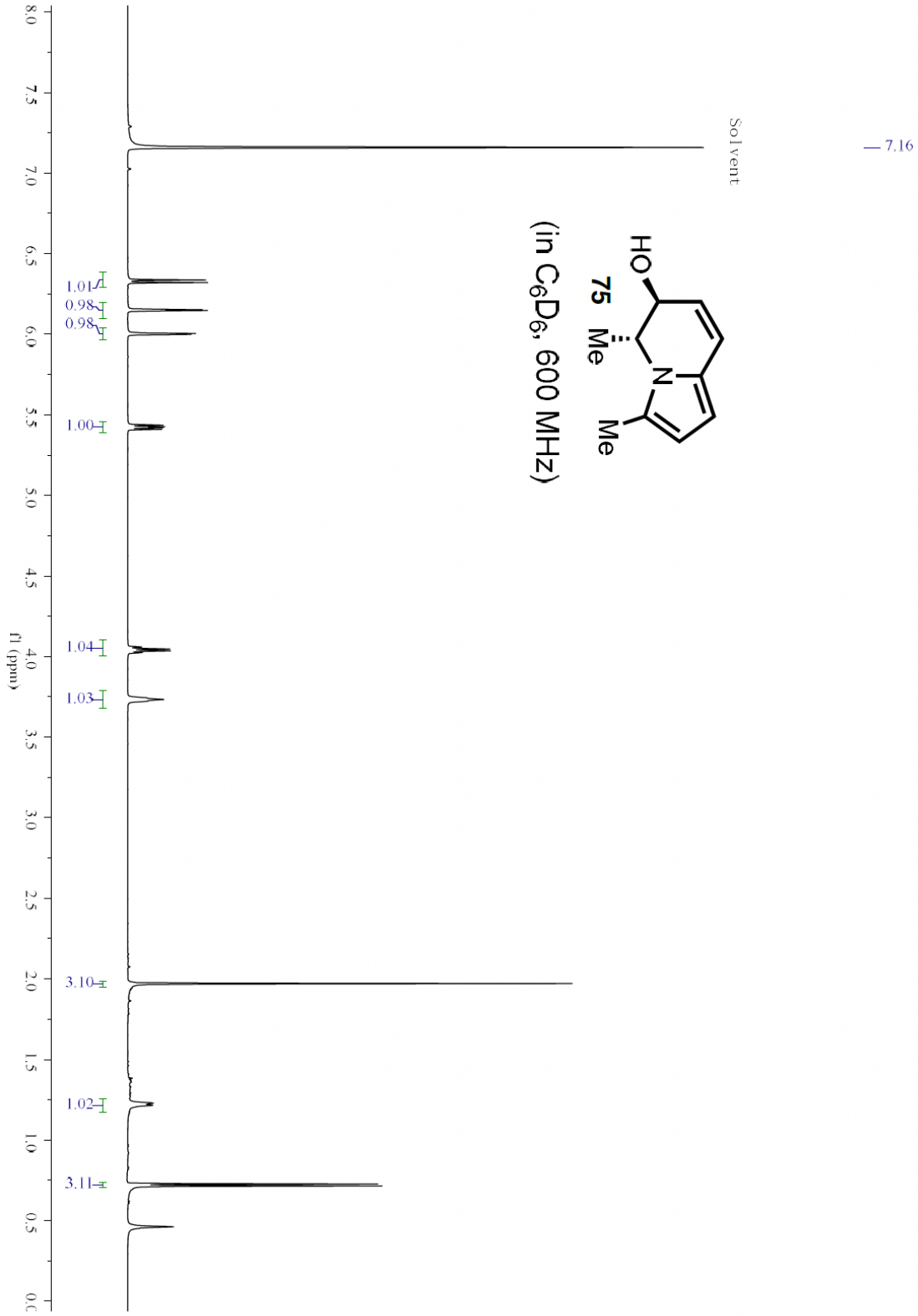


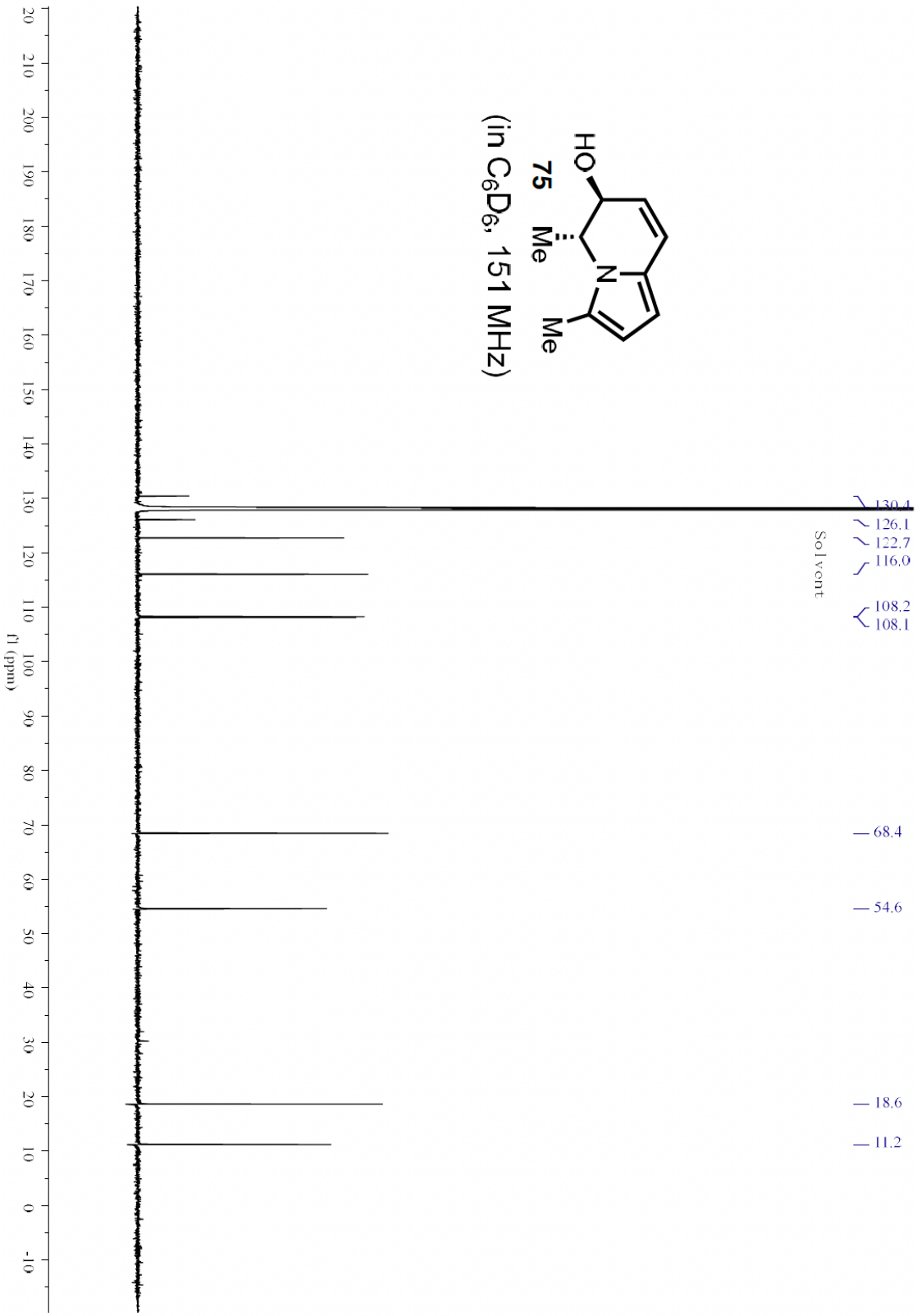

**(+)-12-epi-curvulamine (1)**

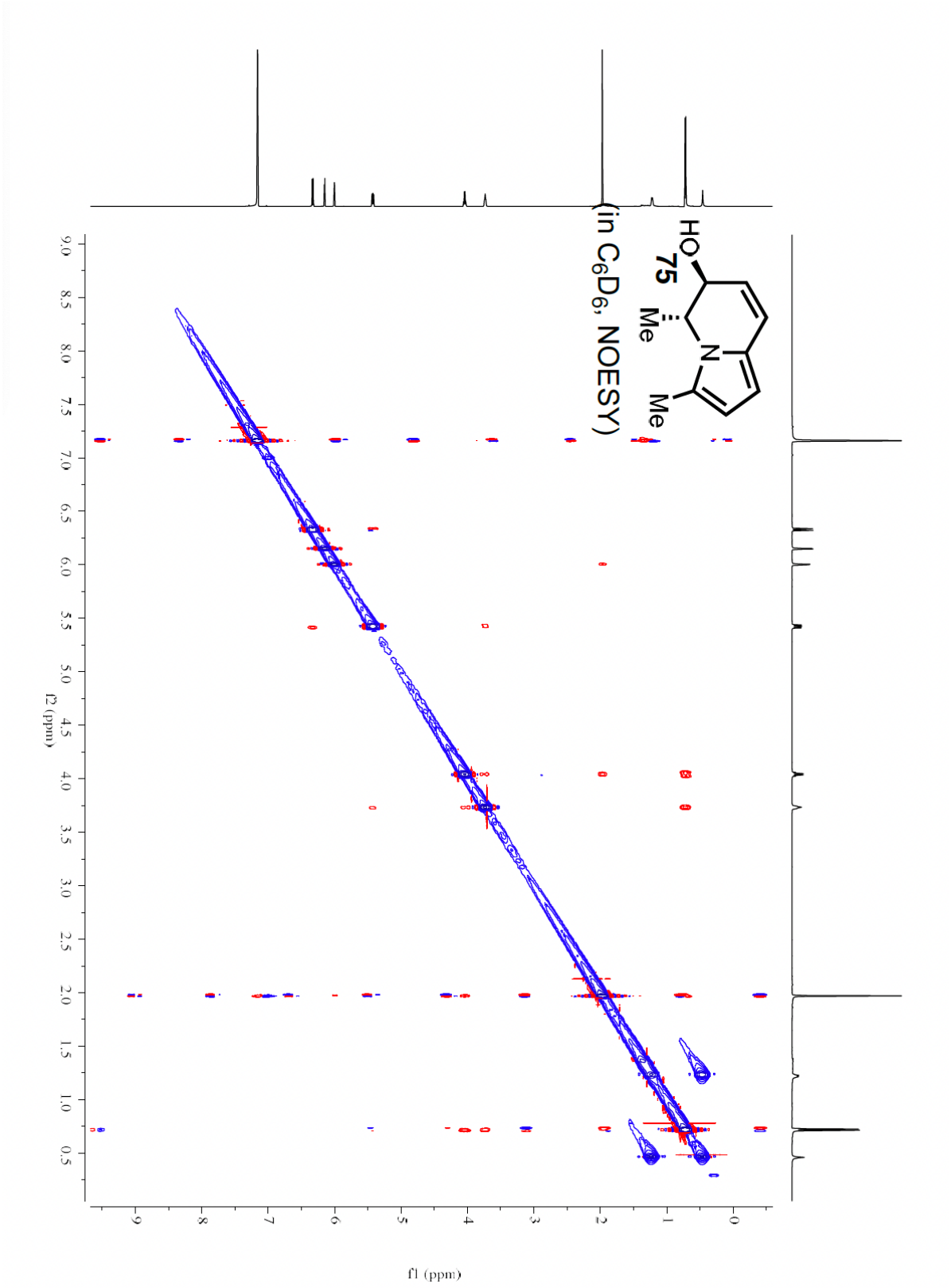
(in $CDCl_3$, 151 MHz)

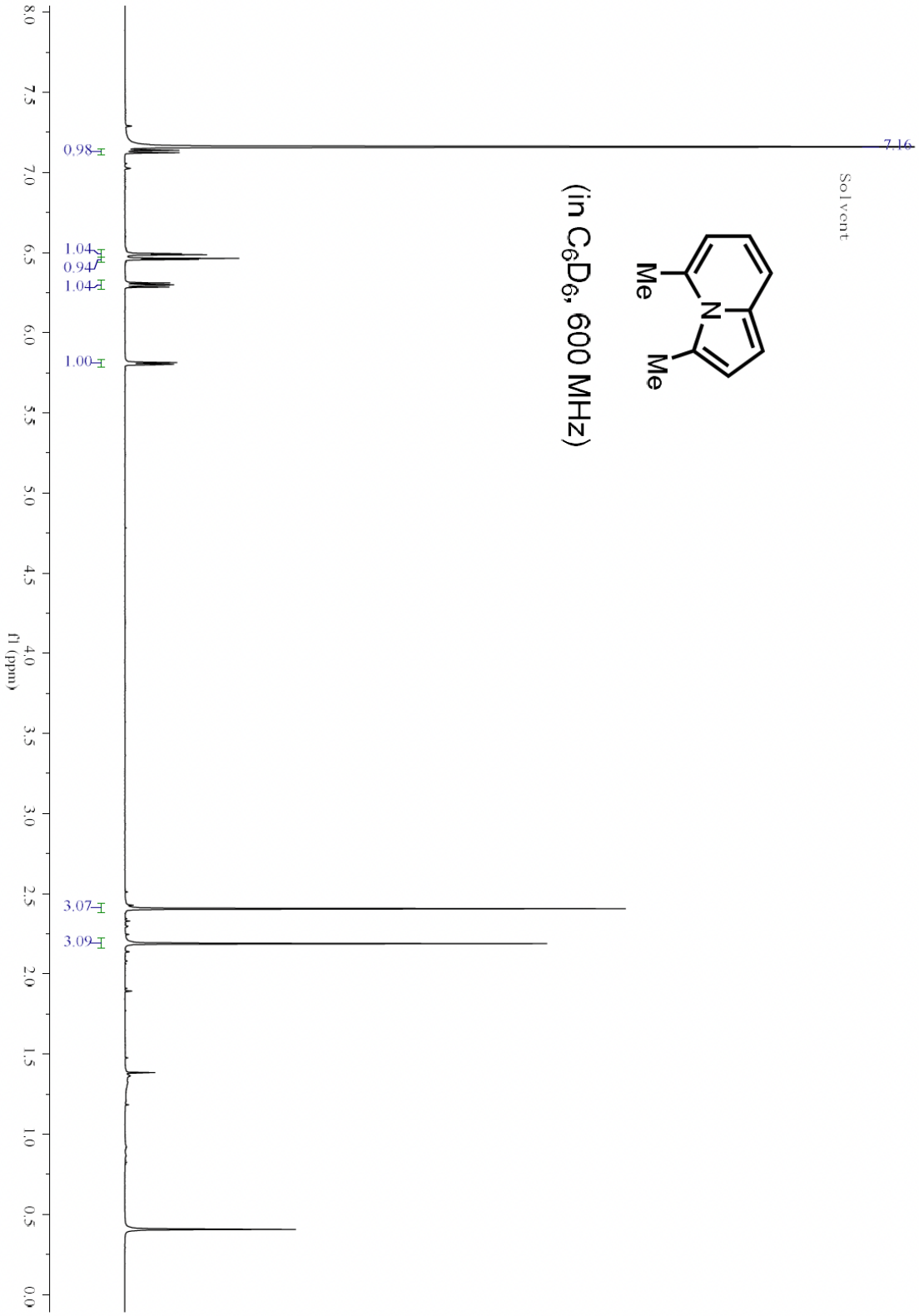

7.16
t-BuO2C
HO
Me
N
Me
+
t-BuO2C
HO
Me
N
Me
74
6:1 dr
(in C6D6, 600 MHz)
Solvent
0.16
0.85
0.18
0.82
0.17
0.82
0.87
0.18
0.88
0.19
0.88
0.16
2.20
0.55
2.53
2.78
1.50
7.87
0.54
3.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

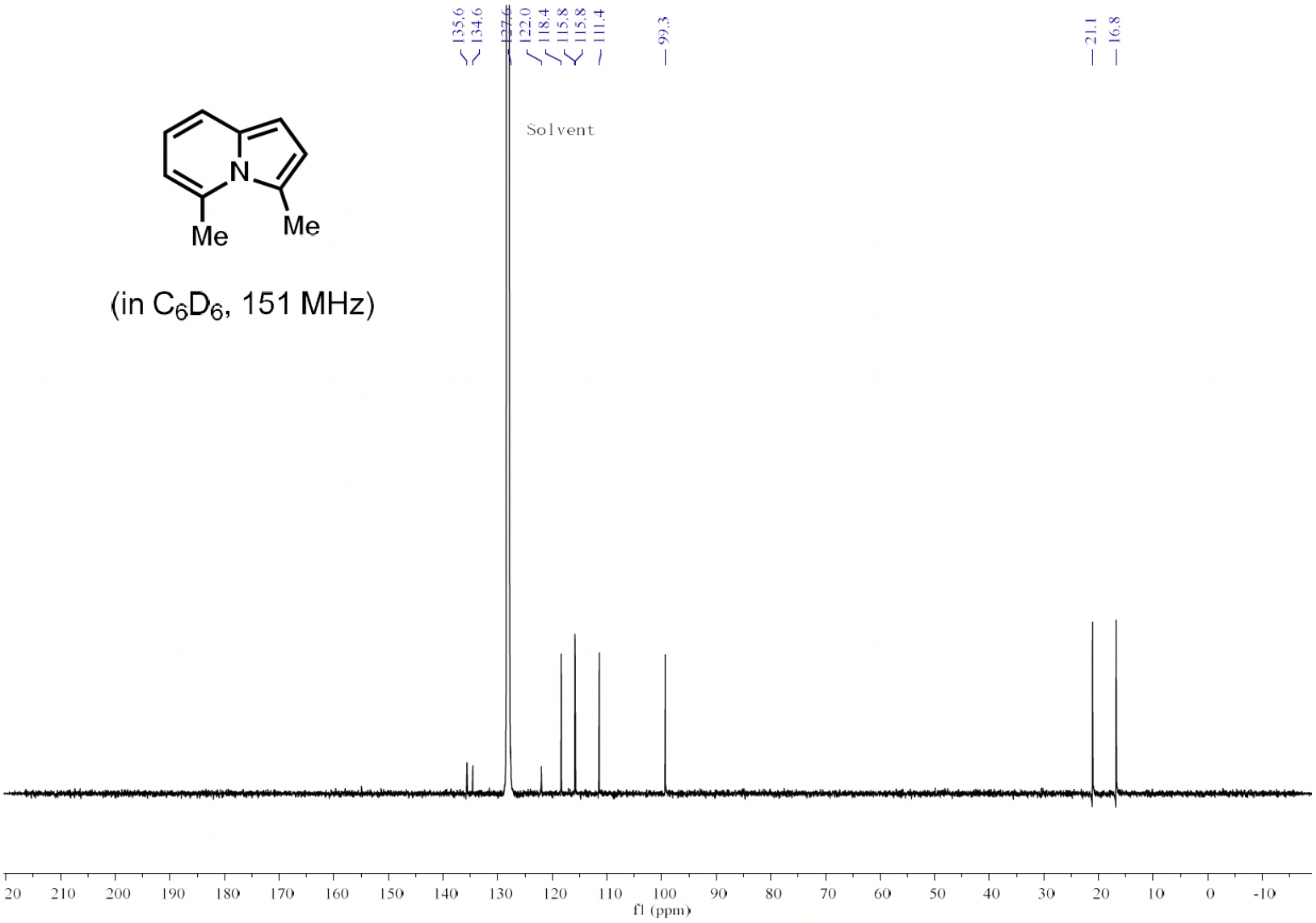

t-BuO2C
HO
Me
N
Me
+
t-BuO2C
HO
Me
N
Me
74
6:1 dr
(in C6D6; 151 MHz)
Solvent
172.5
172.1
127.8
117.6
116.4
108.5
108.1
107.3
107.1
81.0
80.8
72.5
71.7
54.9
54.4
39.2
39.0
28.0
27.9
17.9
17.6
12.5
12.4
f1 (ppm)

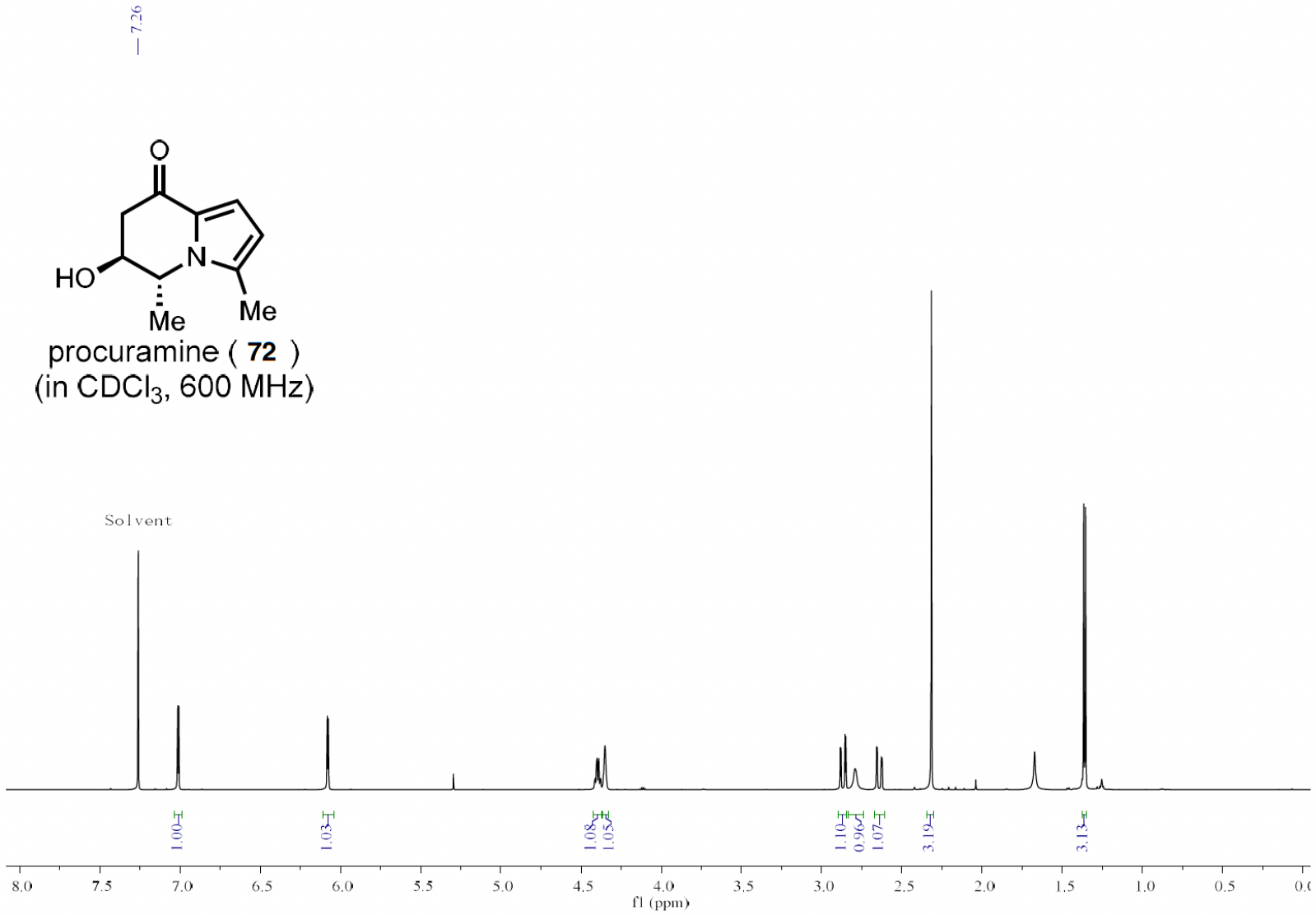

Solvent
7.16
HO
75
Me
N
Me
(in C6D6, 600 MHz)
1.01
0.98
0.98
1.00
1.04
1.03
3.10
1.02
3.11
f1 (ppm)

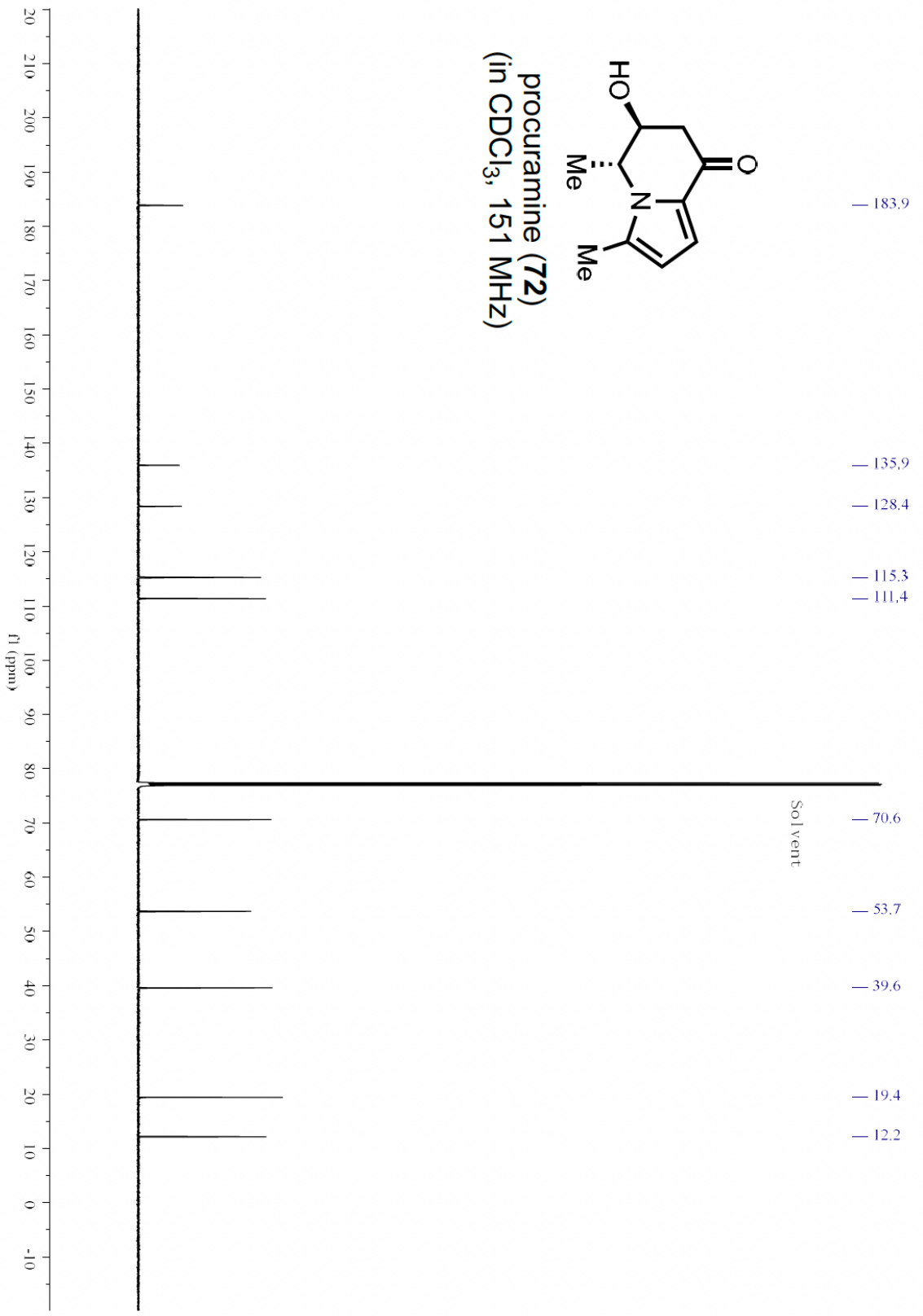

(in $C_6D_6$, 151 MHz)
75
HO
Me
N
Me
130.4
126.1
122.7
116.0
108.2
108.1
Solvent
68.4
54.6
18.6
11.2
f1 (ppm)

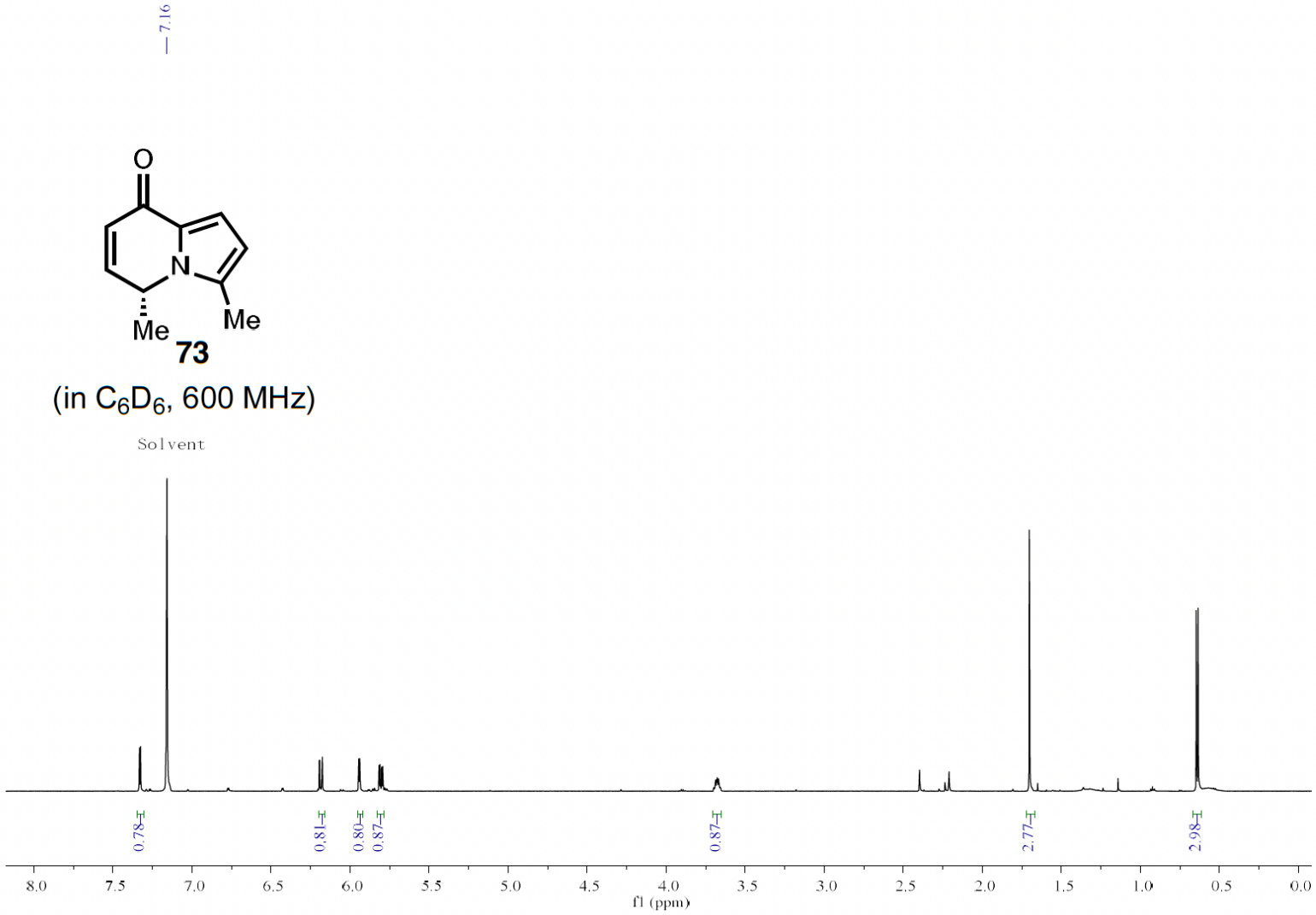

75
(in C6D6, NOESY)
HO
Me
Me
N
f2 (ppm)
f1 (ppm)

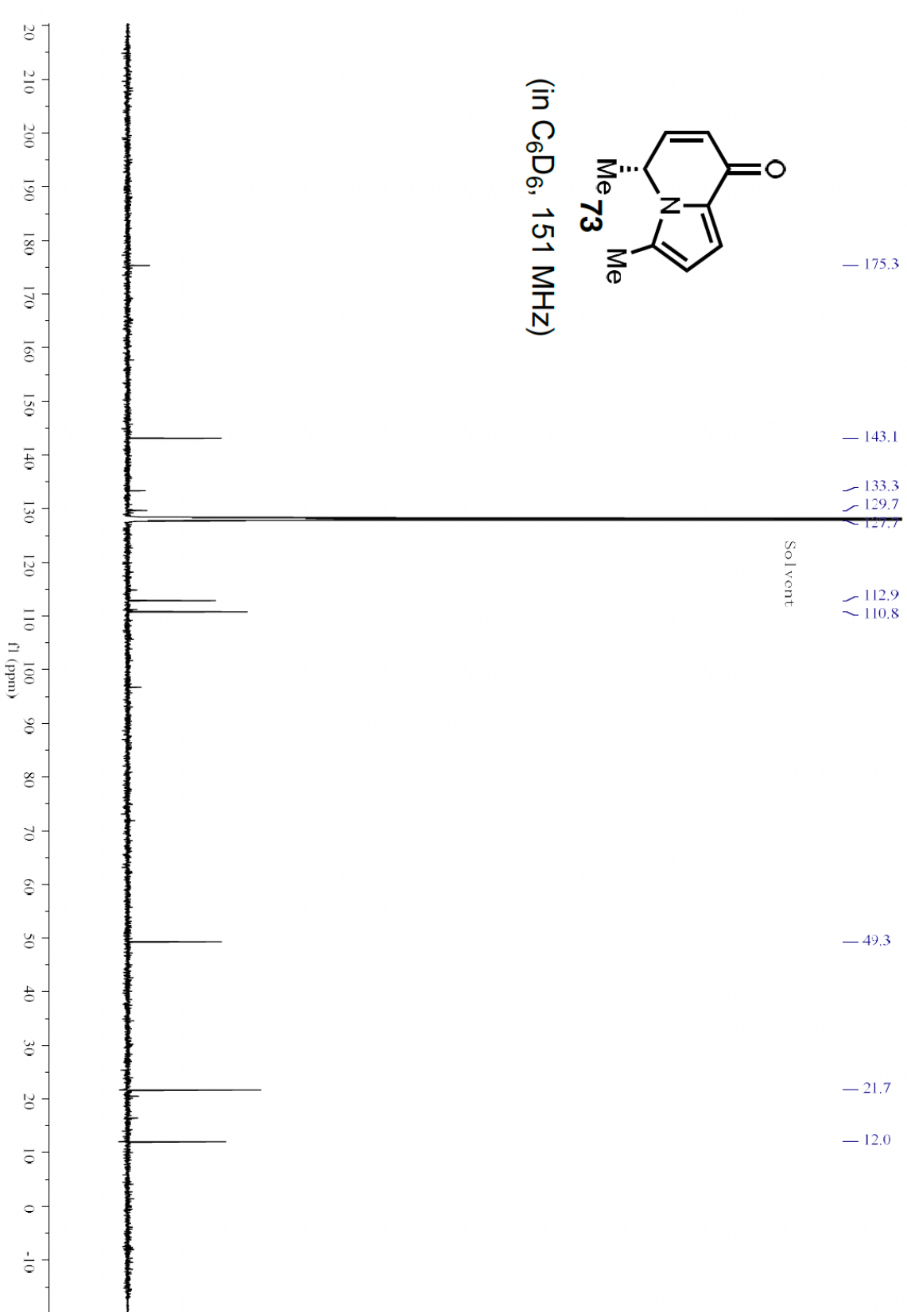

(in $C_6D_6$, 600 MHz)
Me
Me
N
Solvent
7.16
0.98
1.04
0.94
1.04
1.00
3.07
3.09
f1 (ppm)

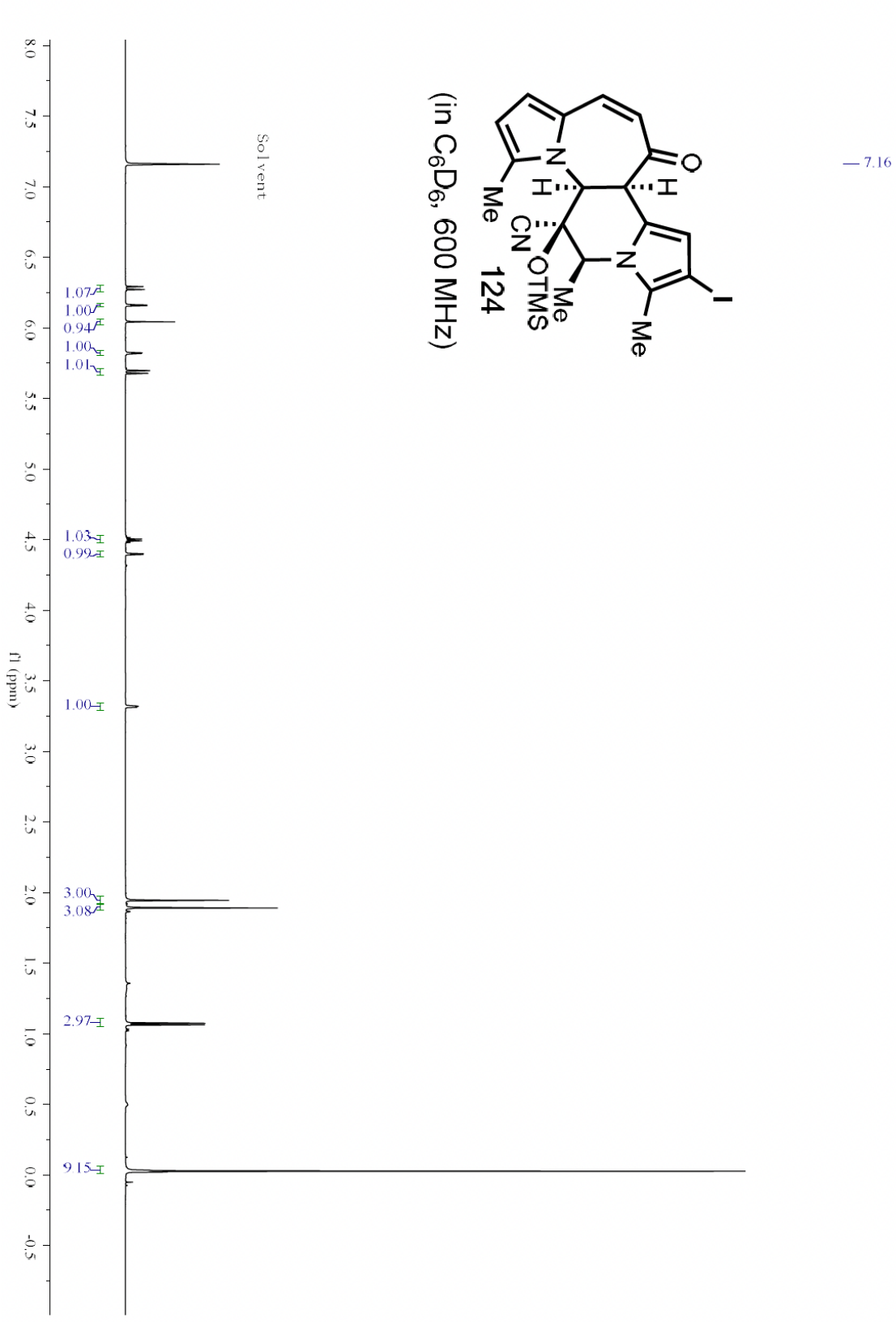

135.6
134.6
127.6
122.0
118.4
115.8
115.8
111.4
99.3
21.1
16.8
Solvent
N
Me
Me
(in C6D6, 151 MHz)
20 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

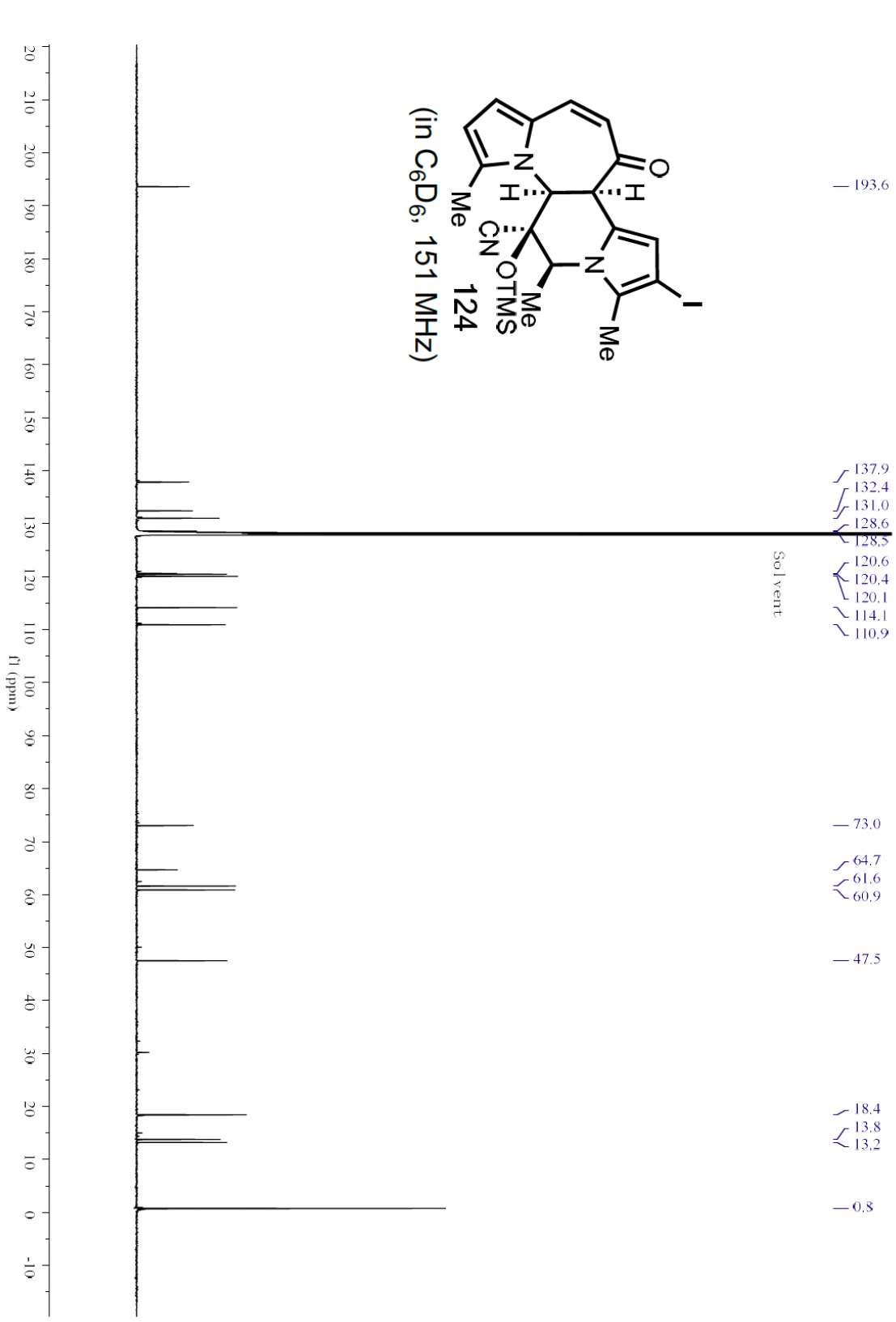

7.26
O
HO
N
Me
Me
procuramine ( 72 )
(in CDCl3, 600 MHz)
Solvent
1.00
1.03
1.08
1.05
1.10
0.96
1.07
3.19
3.13
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

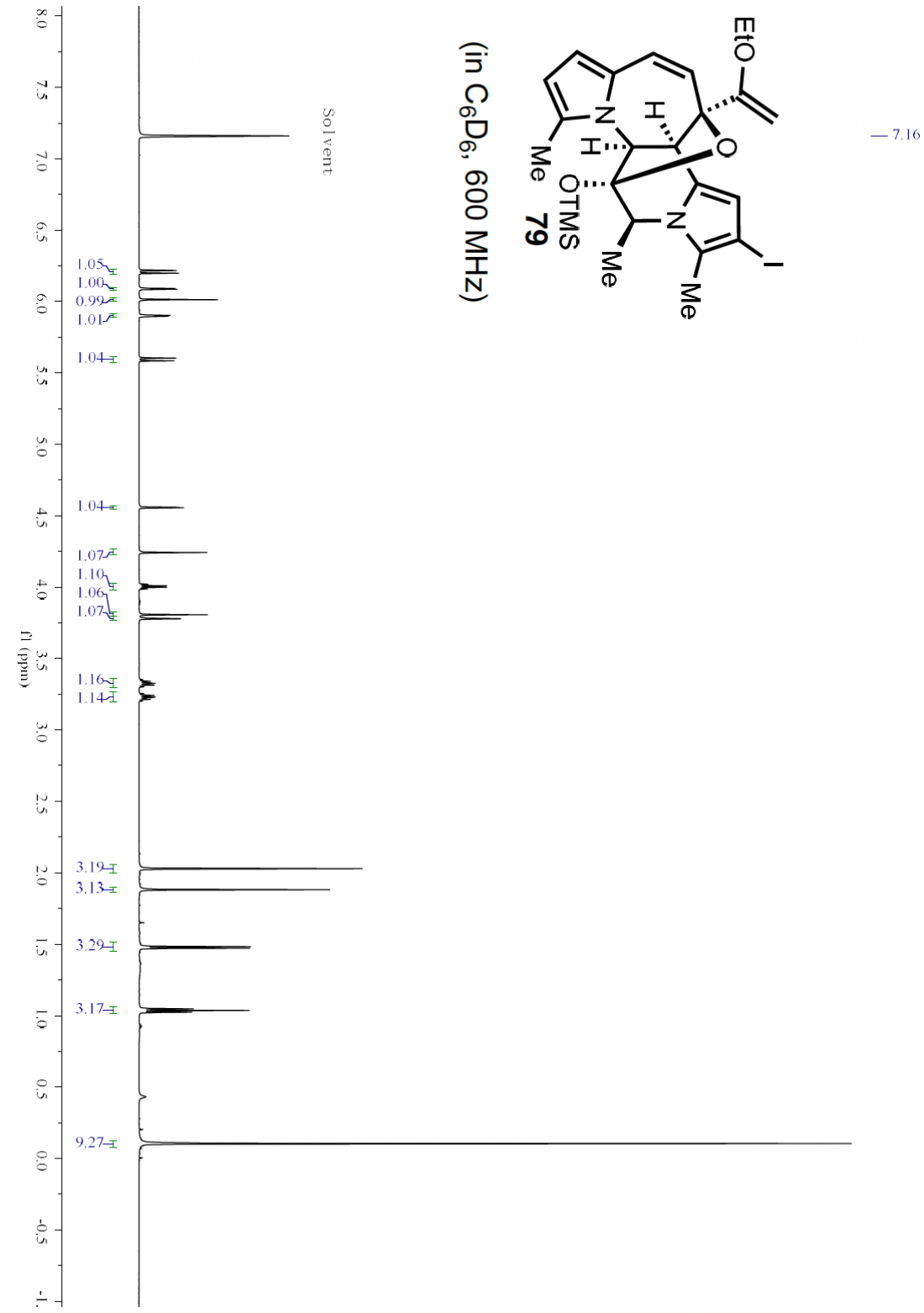

procuramine (72)
(in CDCl3, 151 MHz)
HO
Me
N
Me
O
183.9
135.9
128.4
115.3
111.4
Solvent
70.6
53.7
39.6
19.4
12.2
f1 (ppm)

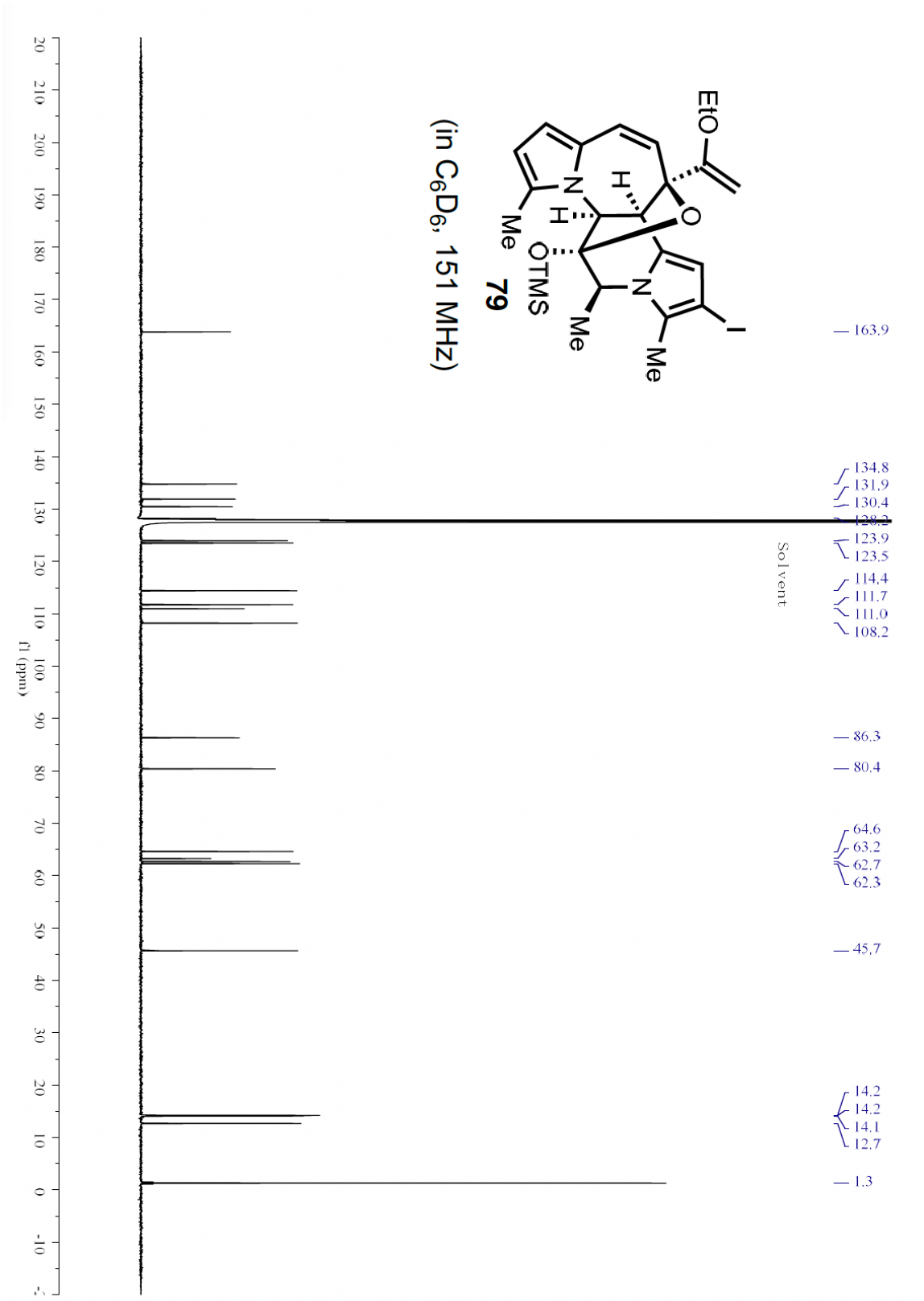

7.16
O
N
Me
Me
73
(in C6D6, 600 MHz)
Solvent
0.78
0.81
0.80
0.87
0.87
2.77
2.98
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

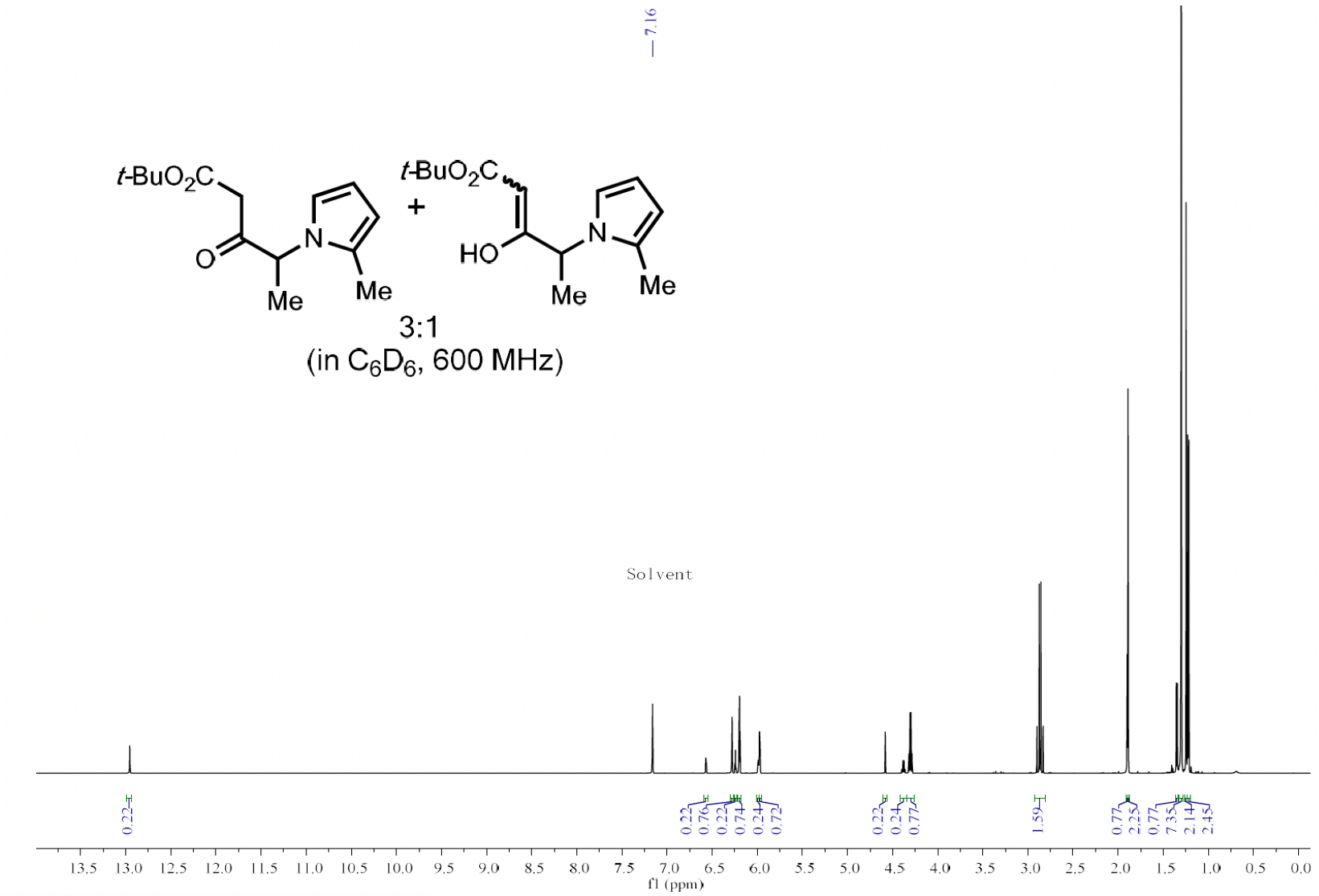

(in C6D6, 151 MHz)
Me
73
Me
N
O
175.3
143.1
133.3
129.7
127.7
Solvent
112.9
110.8
49.3
21.7
12.0
f1 (ppm)
20
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

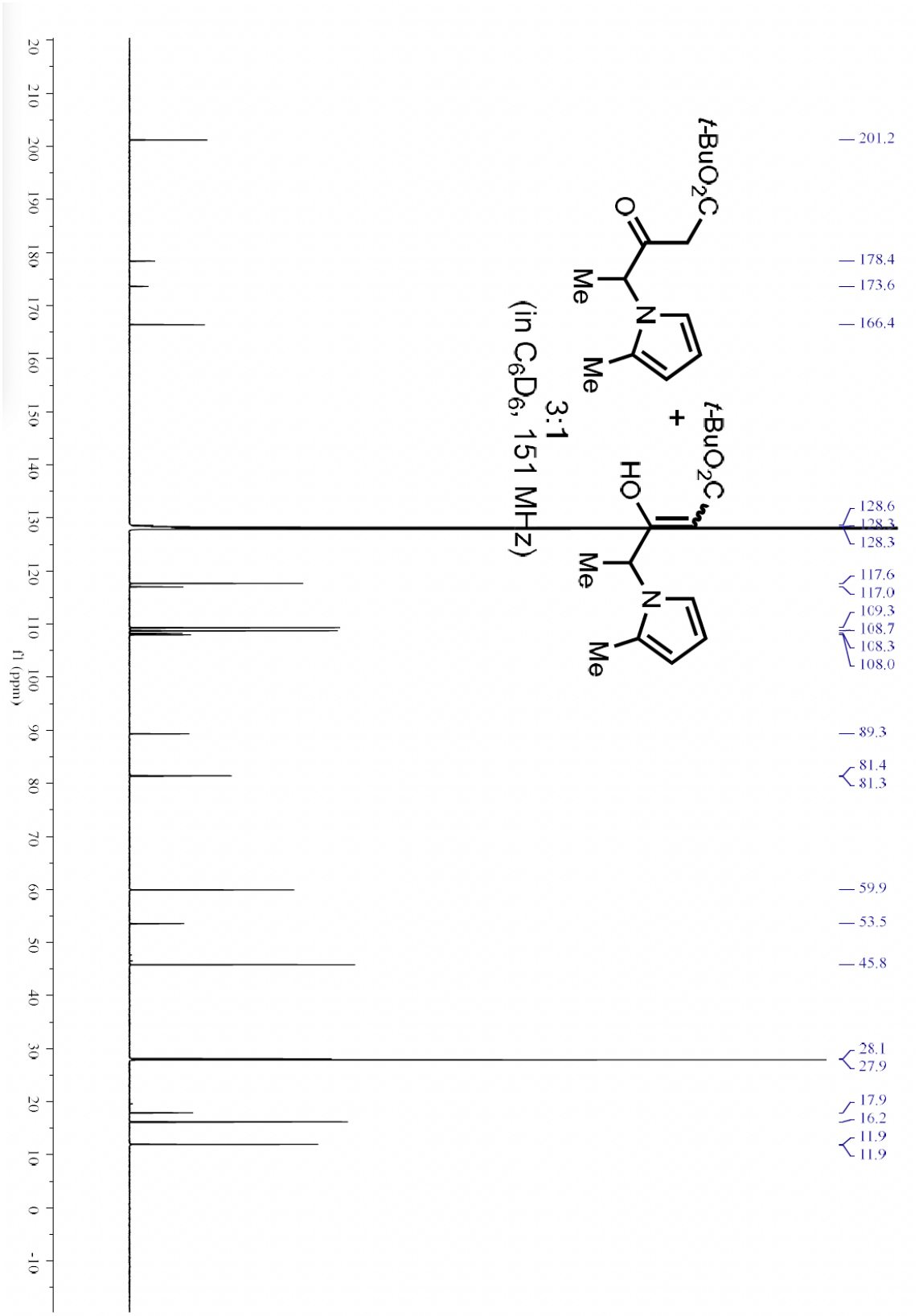

(in $C_6D_6$, 600 MHz)
124
Me
OTMS
CN
Me
Me
I
O
H
H
N
N
Solvent
7.16
1.07
1.00
0.94
1.00
1.01
1.03
0.99
1.00
3.00
3.08
2.97
9.15
f1 (ppm)
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5

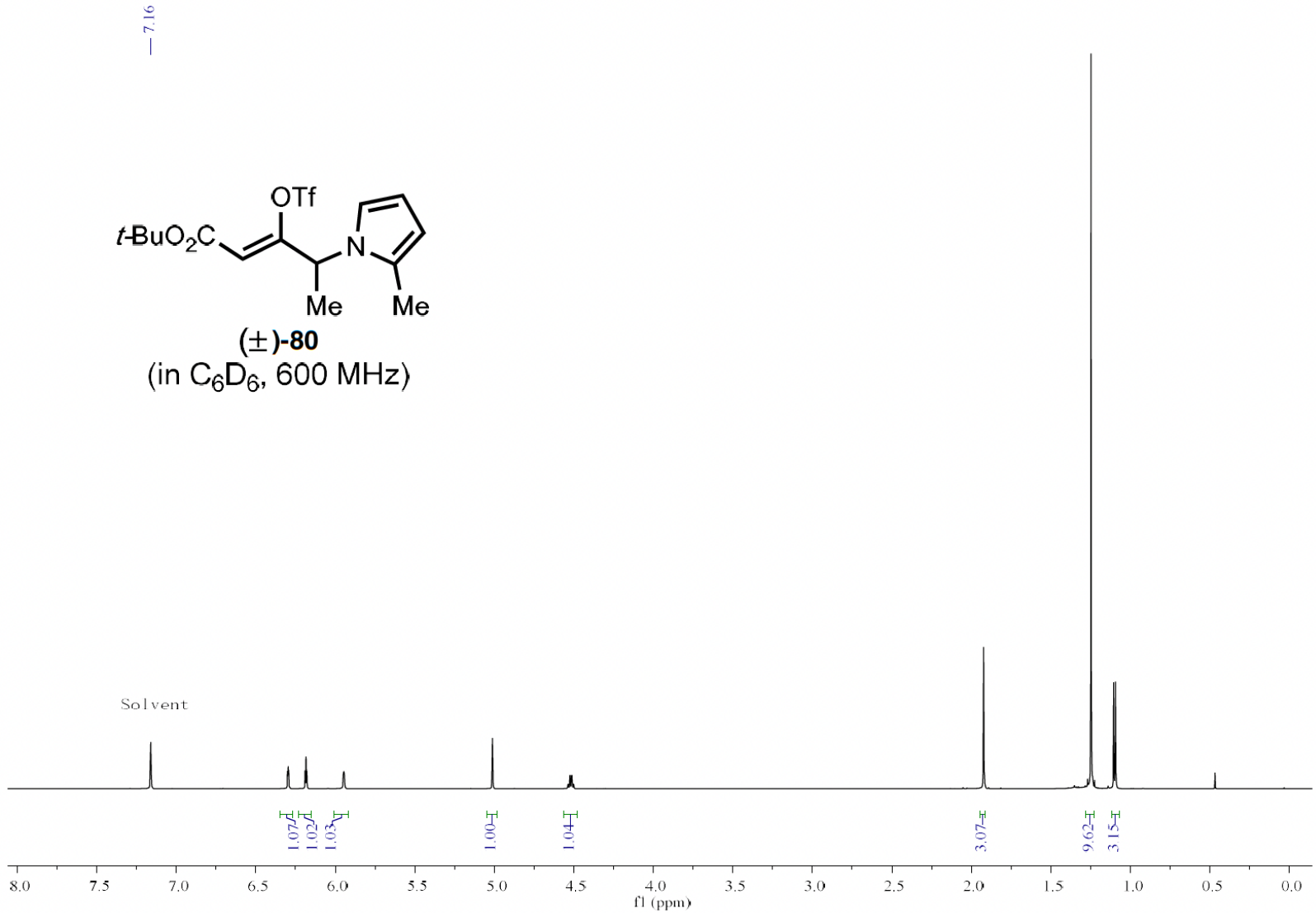

124
(in C6D6, 151 MHz)
Me
CN
OTMS
Me
Me
I
O
H
N
H
N
193.6
137.9
132.4
131.0
128.6
128.5
120.6
120.4
120.1
114.1
110.9
Solvent
73.0
64.7
61.6
60.9
47.5
18.4
13.8
13.2
0.8
f1 (ppm)

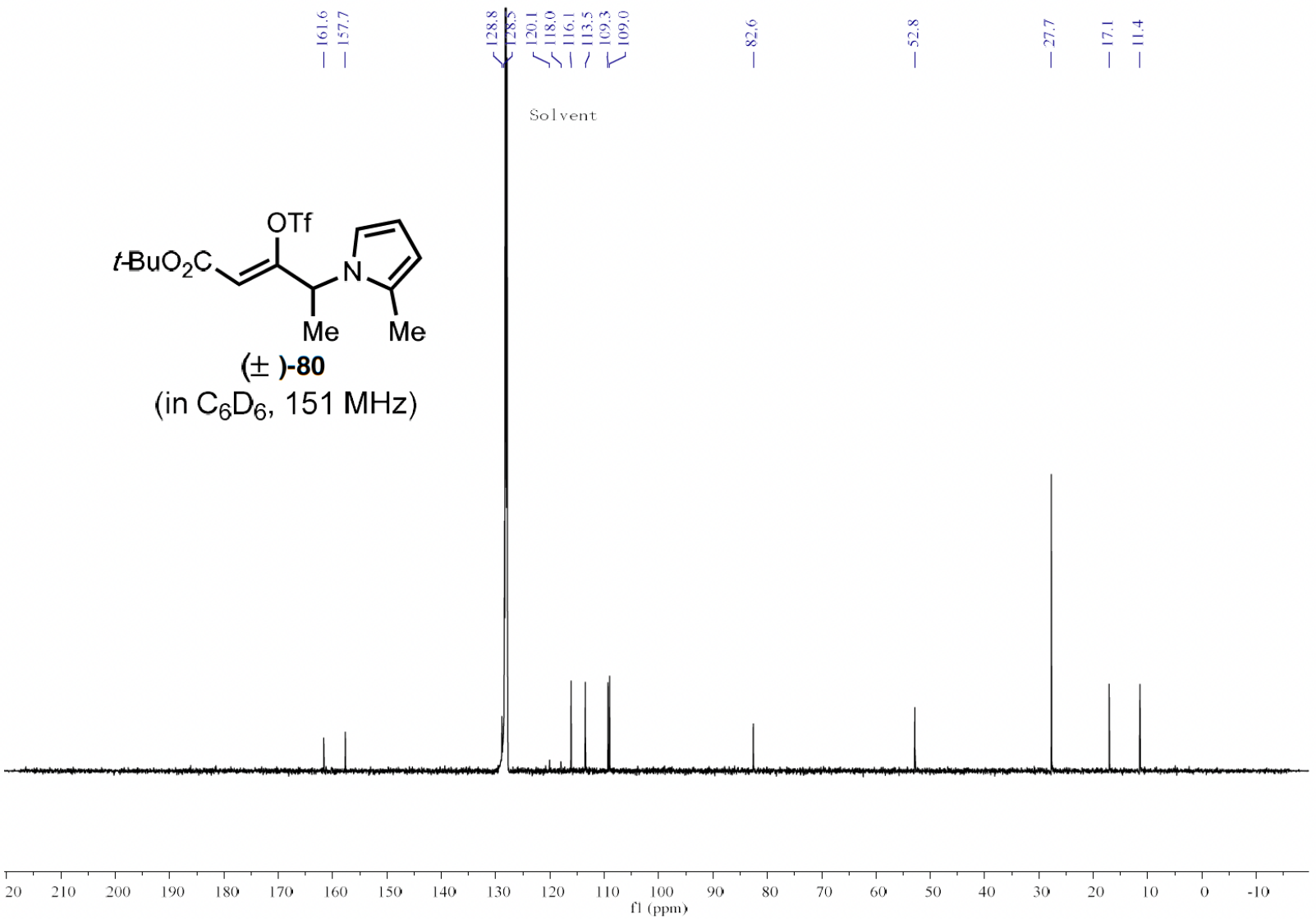

EtO
H
O
N
H
OTMS
Me
79
N
Me
I
Me
(in C6D6, 600 MHz)
Solvent
7.16
1.05
1.00
0.99
1.01
1.04
1.04
1.07
1.10
1.06
1.07
1.16
1.14
3.19
3.13
3.29
3.17
9.27
f1 (ppm)

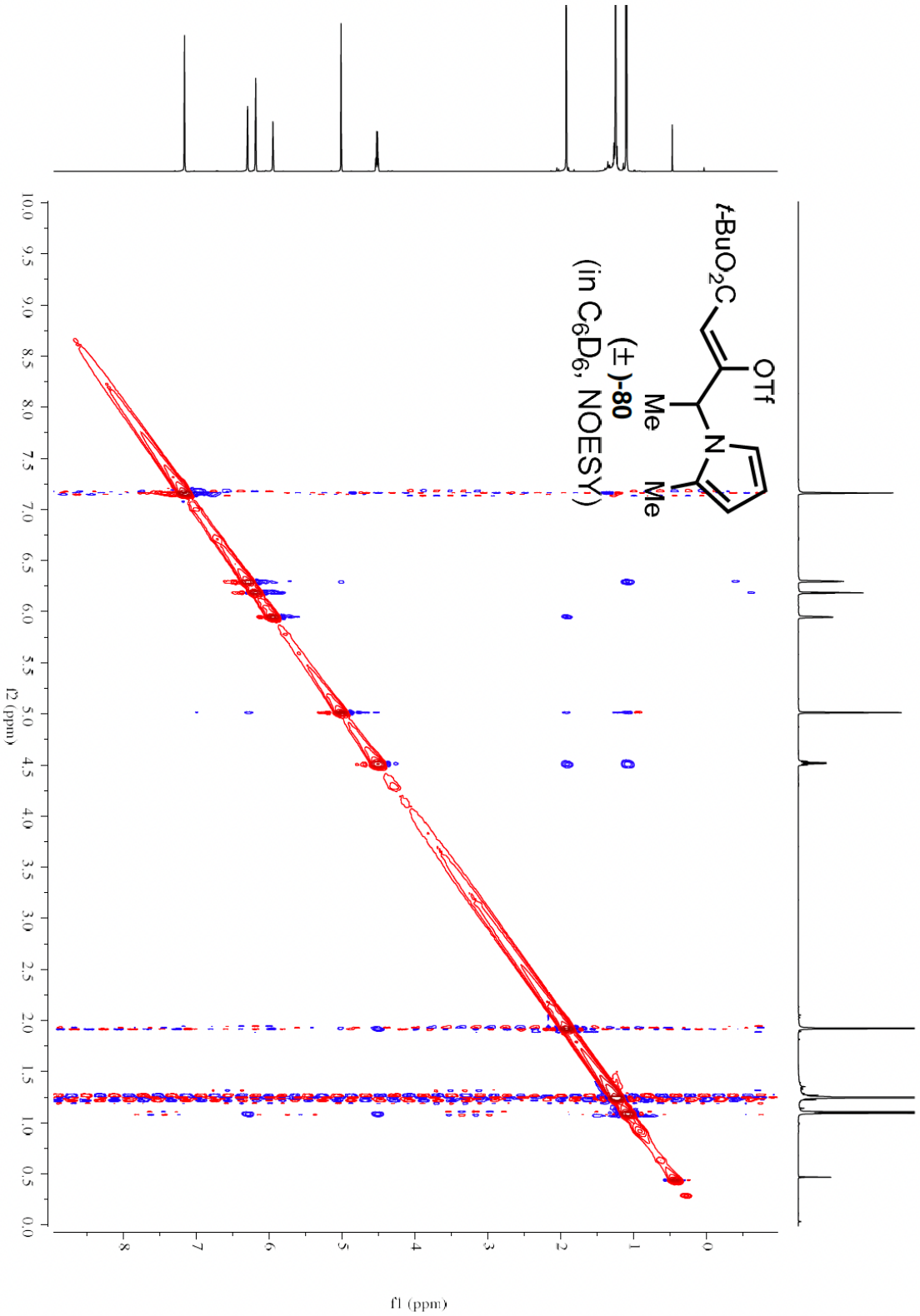

EtO
O
H
N
H
OTMS
Me
79
Me
N
Me
I
(in C6D6, 151 MHz)
163.9
134.8
131.9
130.4
128.2
123.9
123.5
114.4
111.7
111.0
108.2
Solvent
86.3
80.4
64.6
63.2
62.7
62.3
45.7
14.2
14.2
14.1
12.7
1.3
f1 (ppm)

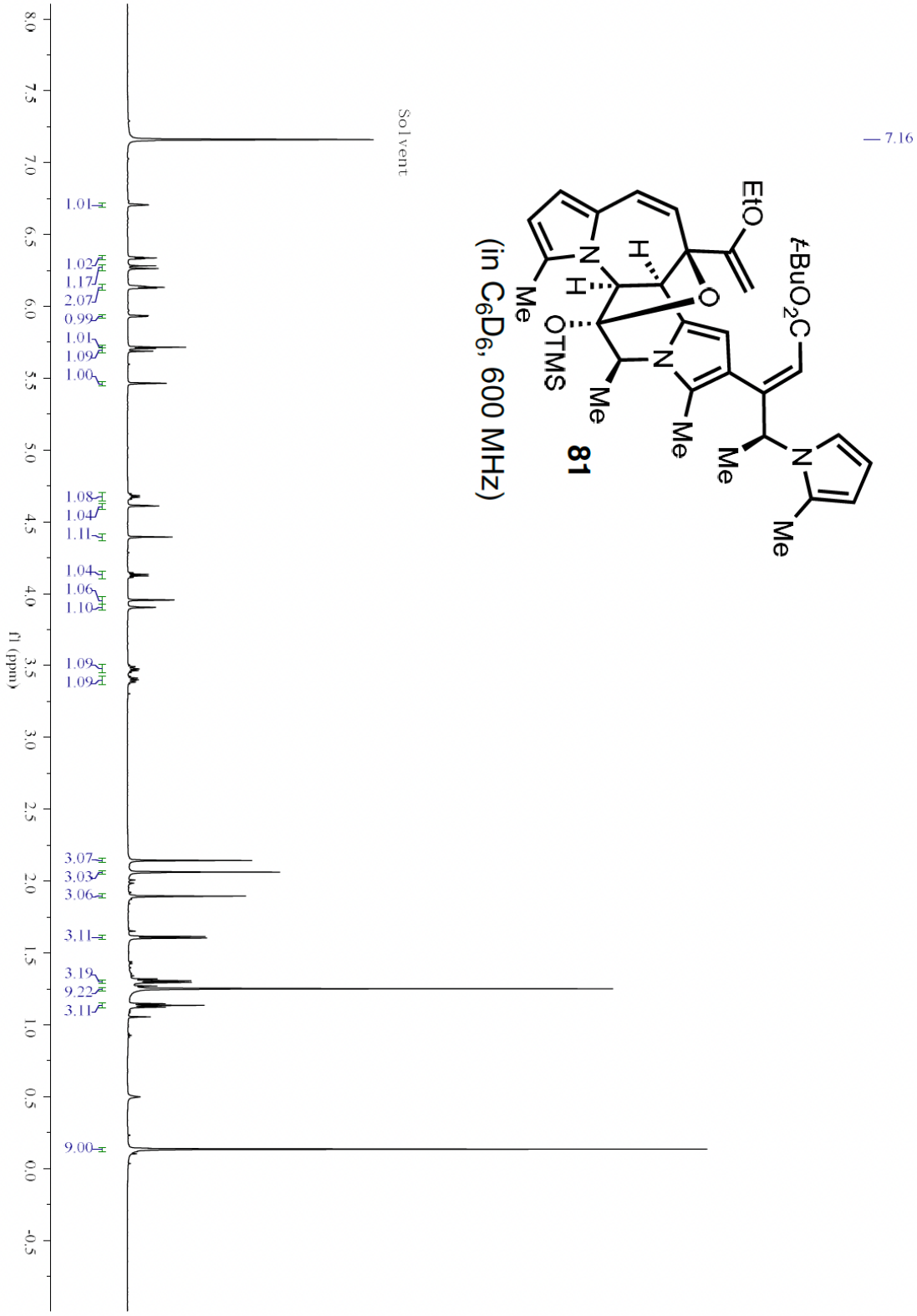

t-BuO2C
O
N
Me
Me
+
t-BuO2C
HO
N
Me
Me
3:1
(in C6D6, 600 MHz)
7.16
Solvent
0.22
0.76
0.22
0.74
0.24
0.72
0.22
0.24
0.77
1.59
0.77
2.25
0.77
7.35
2.14
2.45
13.5 13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

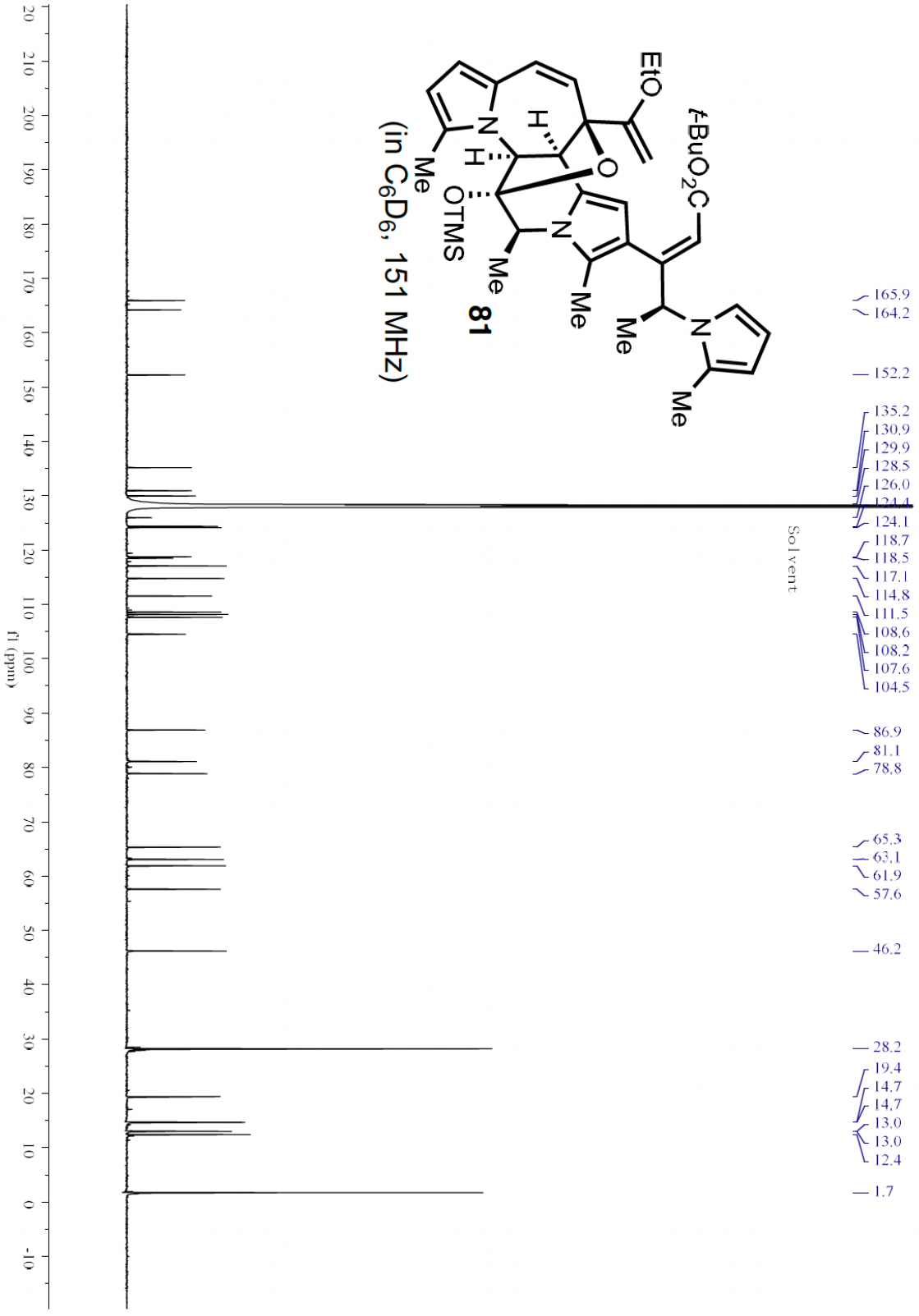

t-BuO2C
O
Me
N
Me
+
t-BuO2C
HO
Me
N
Me
3:1
(in C6D6, 151 MHz)
201.2
178.4
173.6
166.4
128.6
128.3
128.3
117.6
117.0
109.3
108.7
108.3
108.0
89.3
81.4
81.3
59.9
53.5
45.8
28.1
27.9
17.9
16.2
11.9
11.9
f1 (ppm)

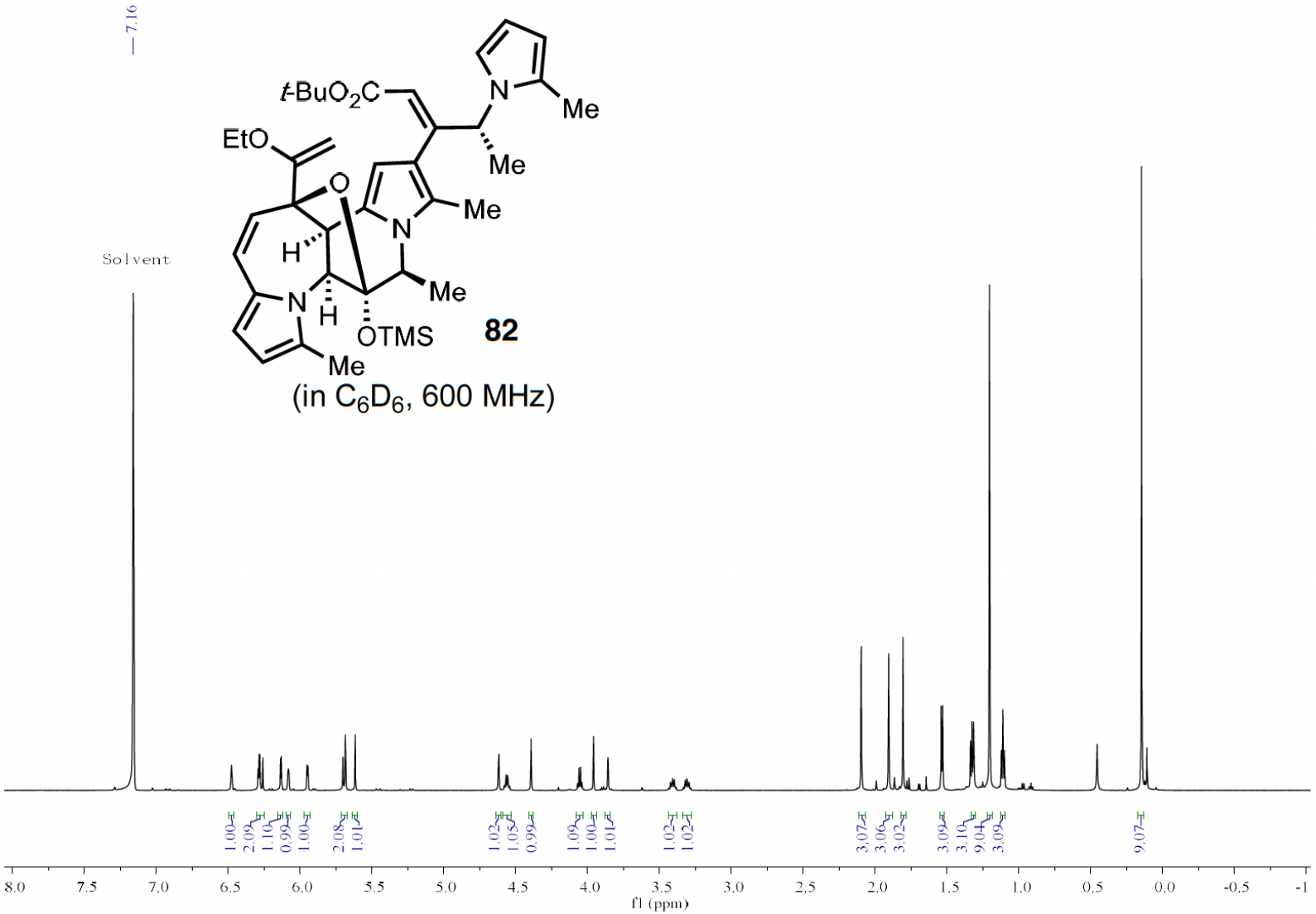

7.16
OTf
t-BuO2C
N
Me
Me
(±)-80
(in C6D6, 600 MHz)
Solvent
1.07
1.02
1.03
1.00
1.04
3.07
9.62
3.15
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

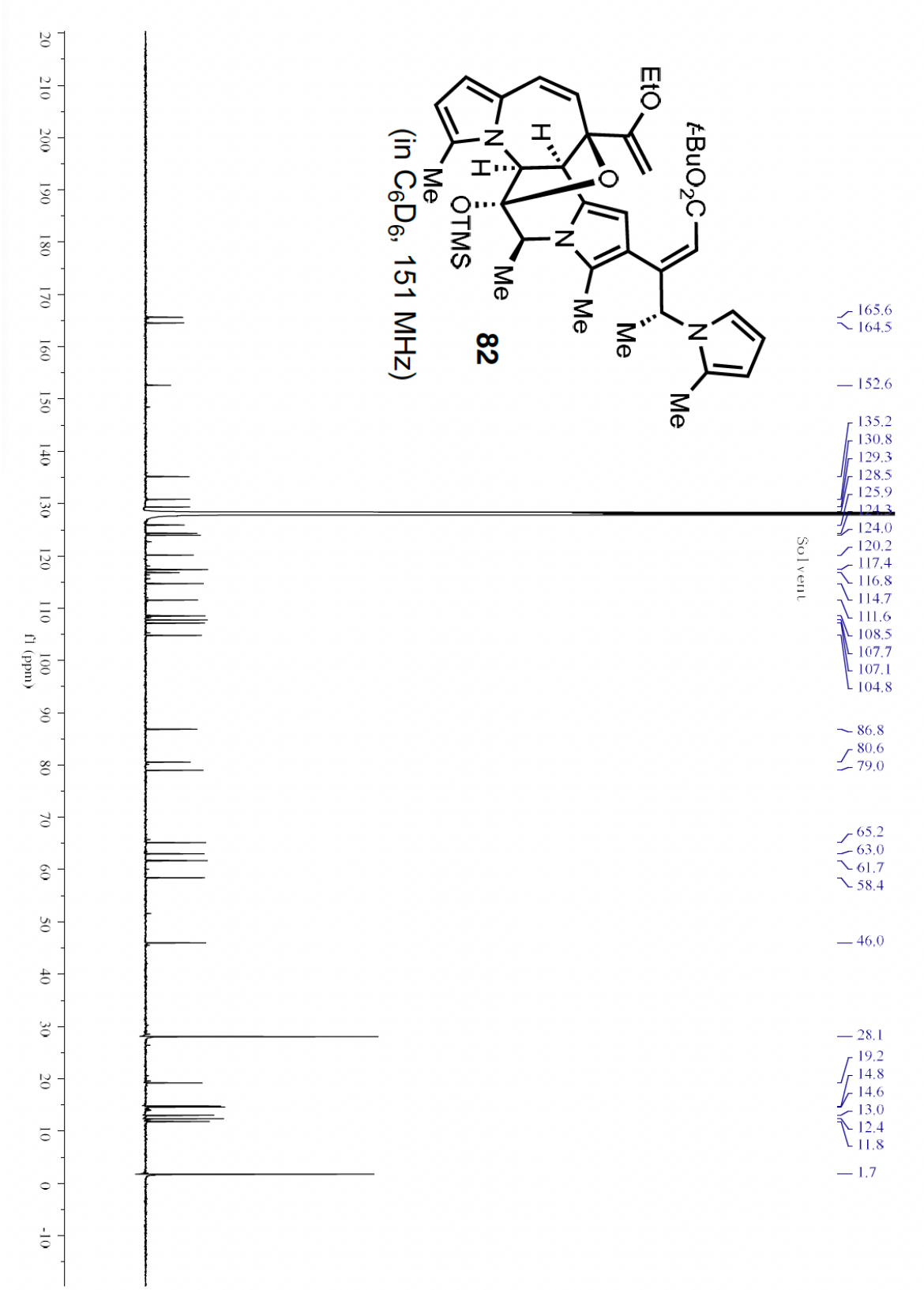

161.6
157.7
128.8
128.5
120.1
118.0
116.1
113.5
109.3
109.0
82.6
52.8
27.7
17.1
11.4
Solvent
OTf
t-BuO2C
N
Me
Me
(± )-80
(in C6D6, 151 MHz)
f1 (ppm)

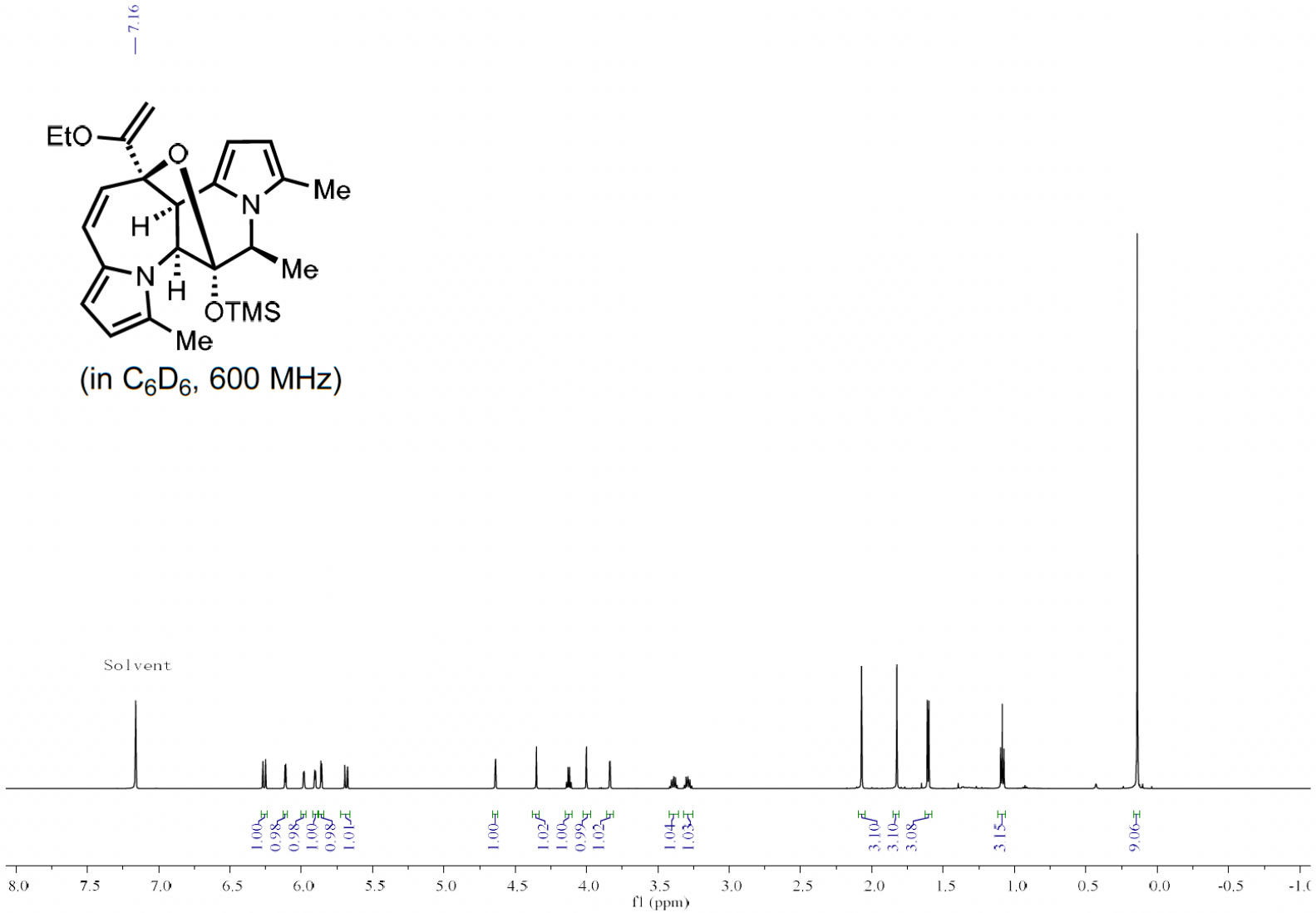

t-BuO2C
OTf
N
Me
Me
(±)-80
(in C6D6, NOESY)
f2 (ppm)
f1 (ppm)

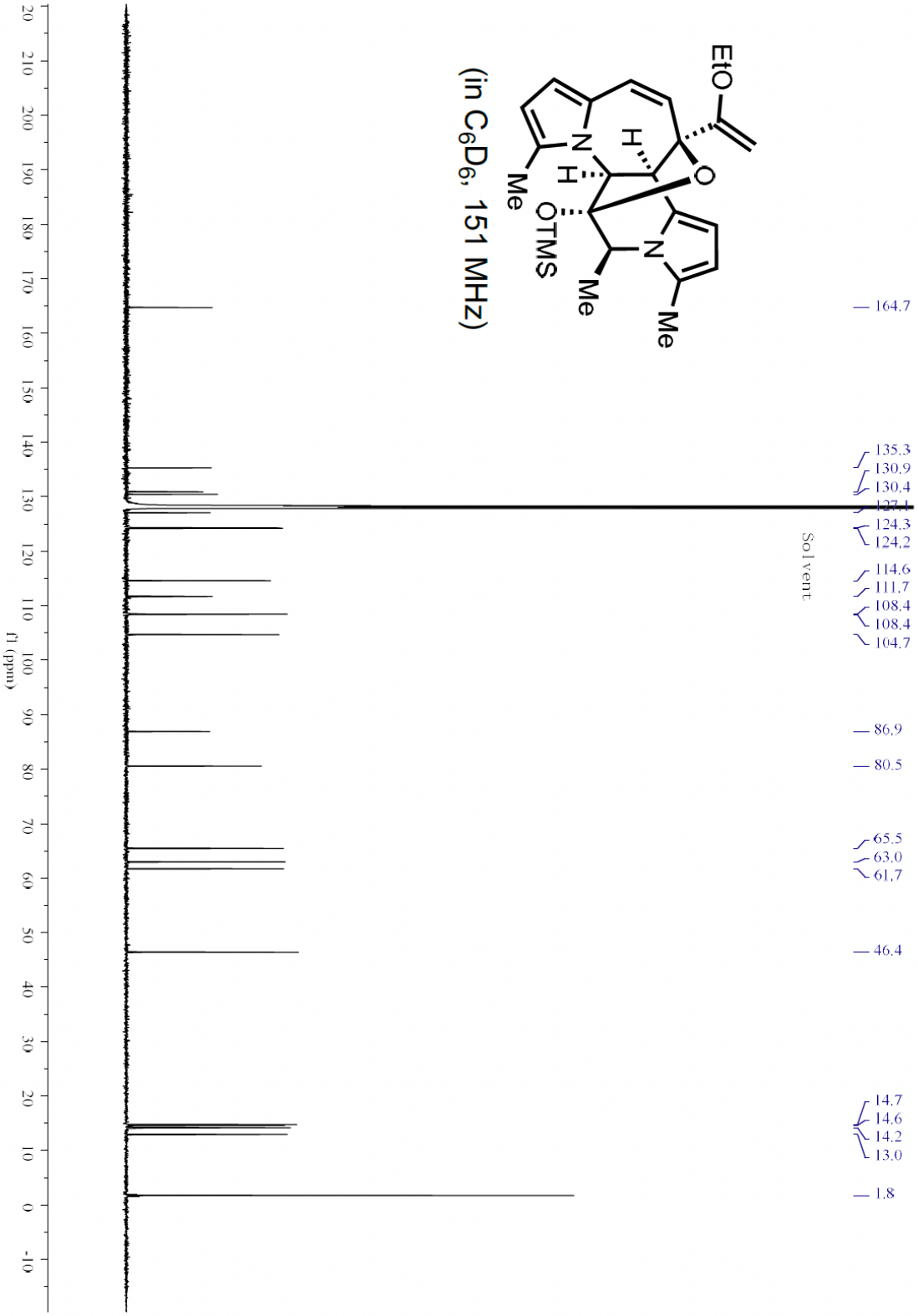

Solvent
— 7.16
EtO
t-BuO2C
H
O
N
H
OTMS
Me
Me
Me
Me
Me
N
Me
81
(in C6D6, 600 MHz)
f1 (ppm)
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
1.01
1.02
1.17
2.07
0.99
1.01
1.09
1.00
1.08
1.04
1.11
1.04
1.06
1.10
1.09
1.09
3.07
3.03
3.06
3.11
3.19
9.22
3.11
9.00

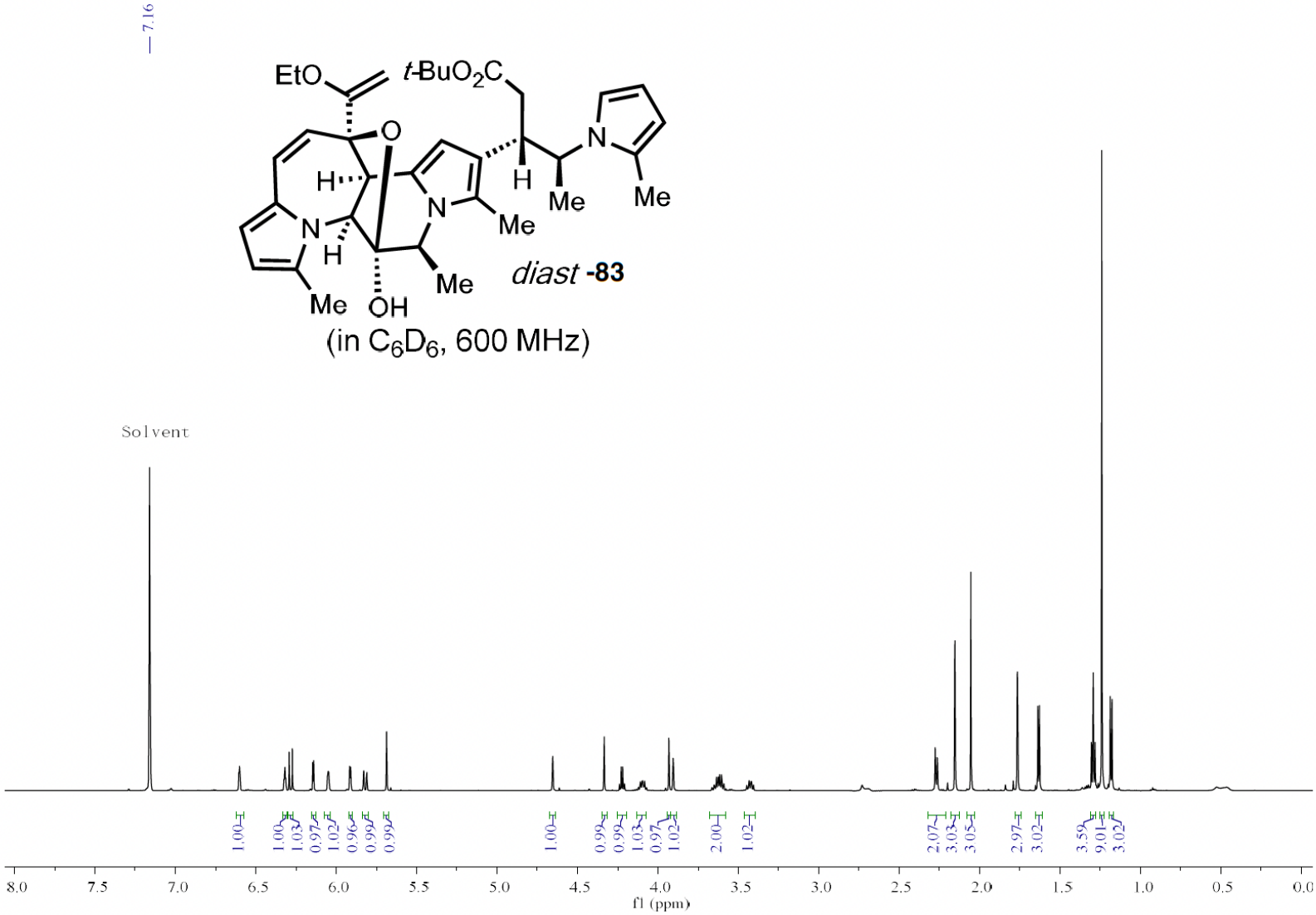

81
(in C6D6, 151 MHz)
Solvent
165.9
164.2
152.2
135.2
130.9
129.9
128.5
126.0
124.4
124.1
118.7
118.5
117.1
114.8
111.5
108.6
108.2
107.6
104.5
86.9
81.1
78.8
65.3
63.1
61.9
57.6
46.2
28.2
19.4
14.7
14.7
13.0
13.0
12.4
1.7
f1 (ppm)

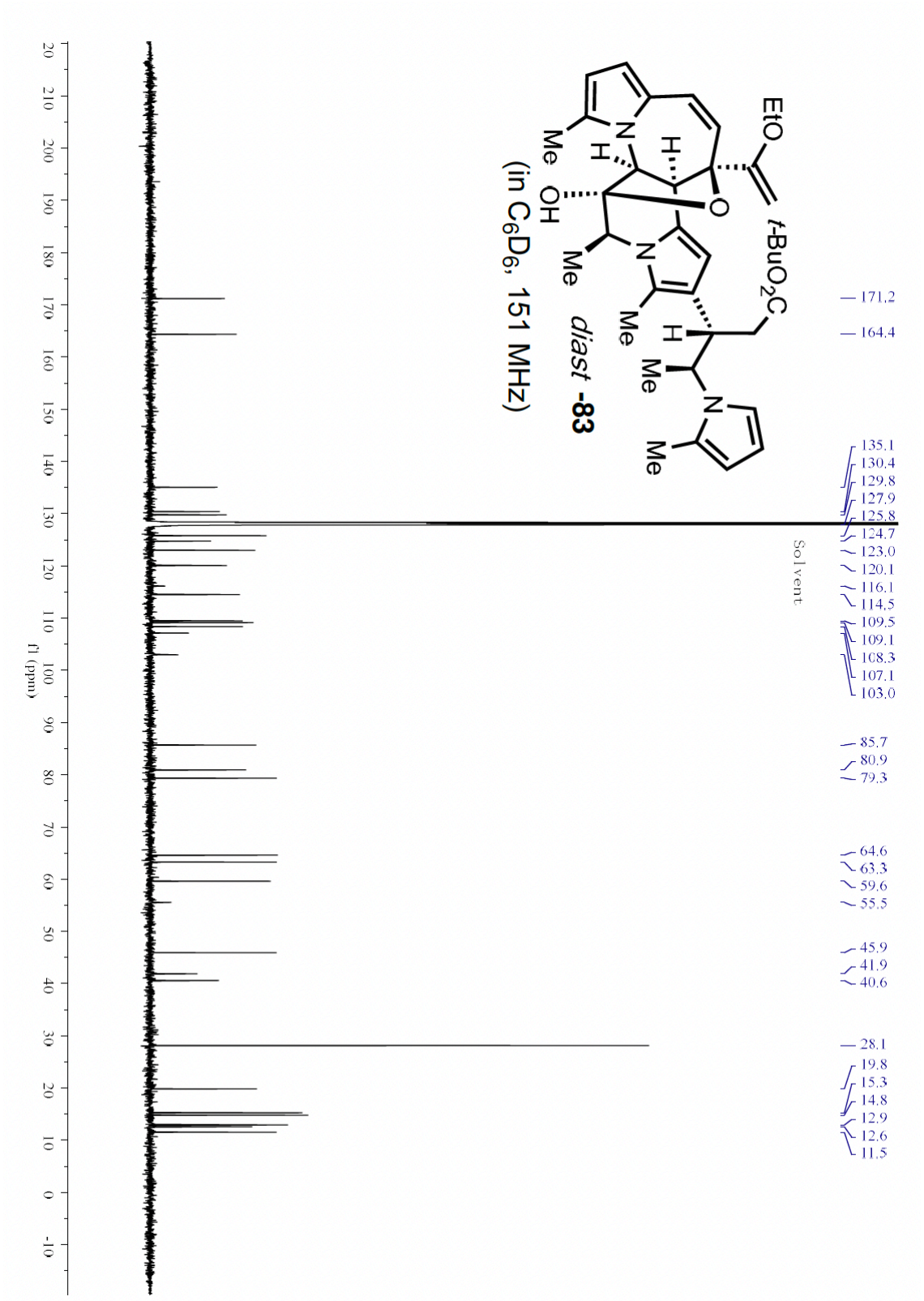

7.16
Solvent
t-BuO2C
EtO
O
N
Me
Me
Me
H
N
H
Me
OTMS
Me
82
(in C6D6, 600 MHz)
1.00
2.09
1.10
0.99
1.00
2.08
1.01
1.02
1.05
0.99
1.09
1.00
1.01
1.02
1.02
3.07
3.06
3.02
3.09
3.10
9.04
3.09
9.07
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1
f1 (ppm)

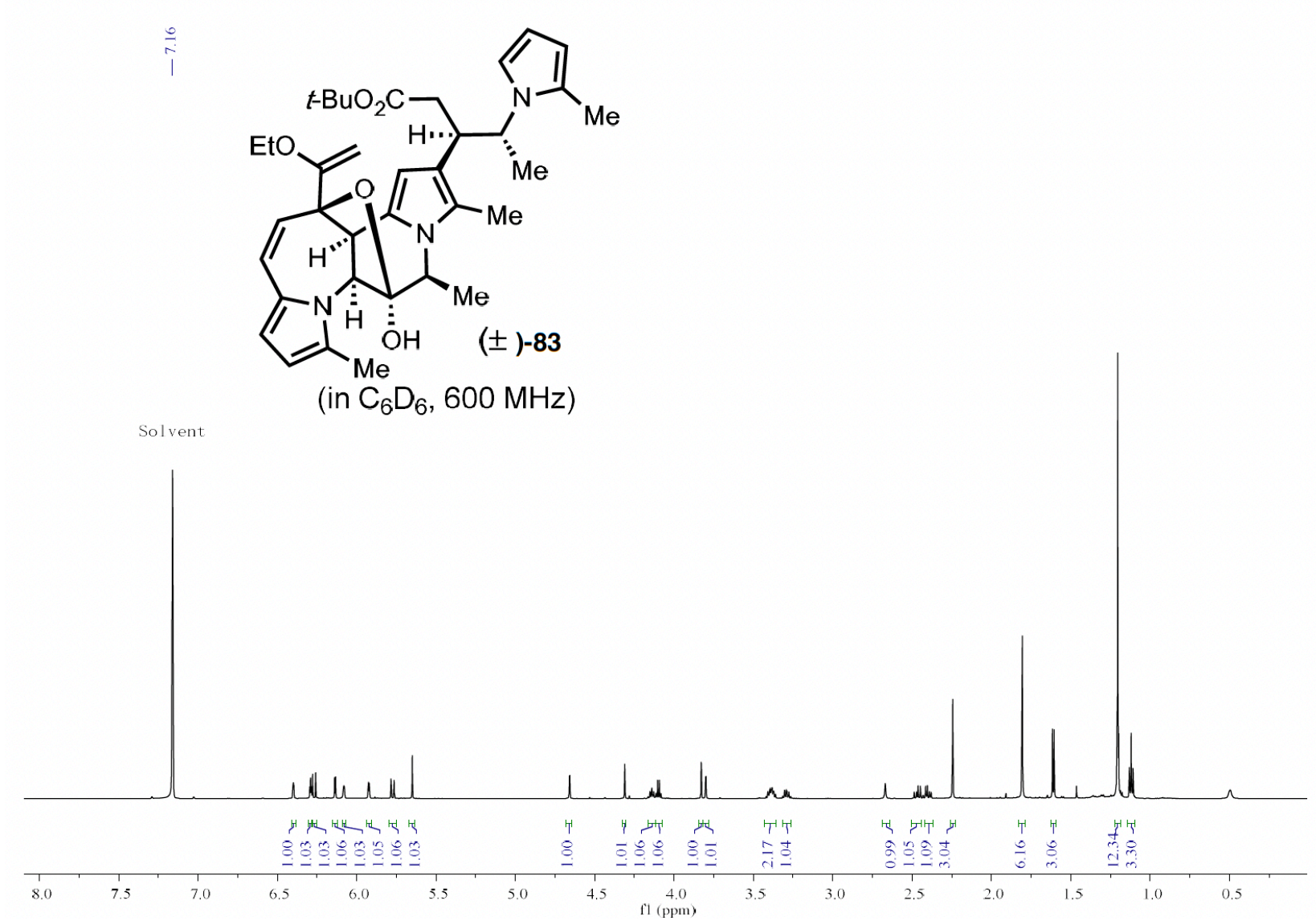

82
(in C6D6, 151 MHz)
Solvent
165.6
164.5
152.6
135.2
130.8
129.3
128.5
125.9
124.3
124.0
120.2
117.4
116.8
114.7
111.6
108.5
107.7
107.1
104.8
86.8
80.6
79.0
65.2
63.0
61.7
58.4
46.0
28.1
19.2
14.8
14.6
13.0
12.4
11.8
1.7
f1 (ppm)

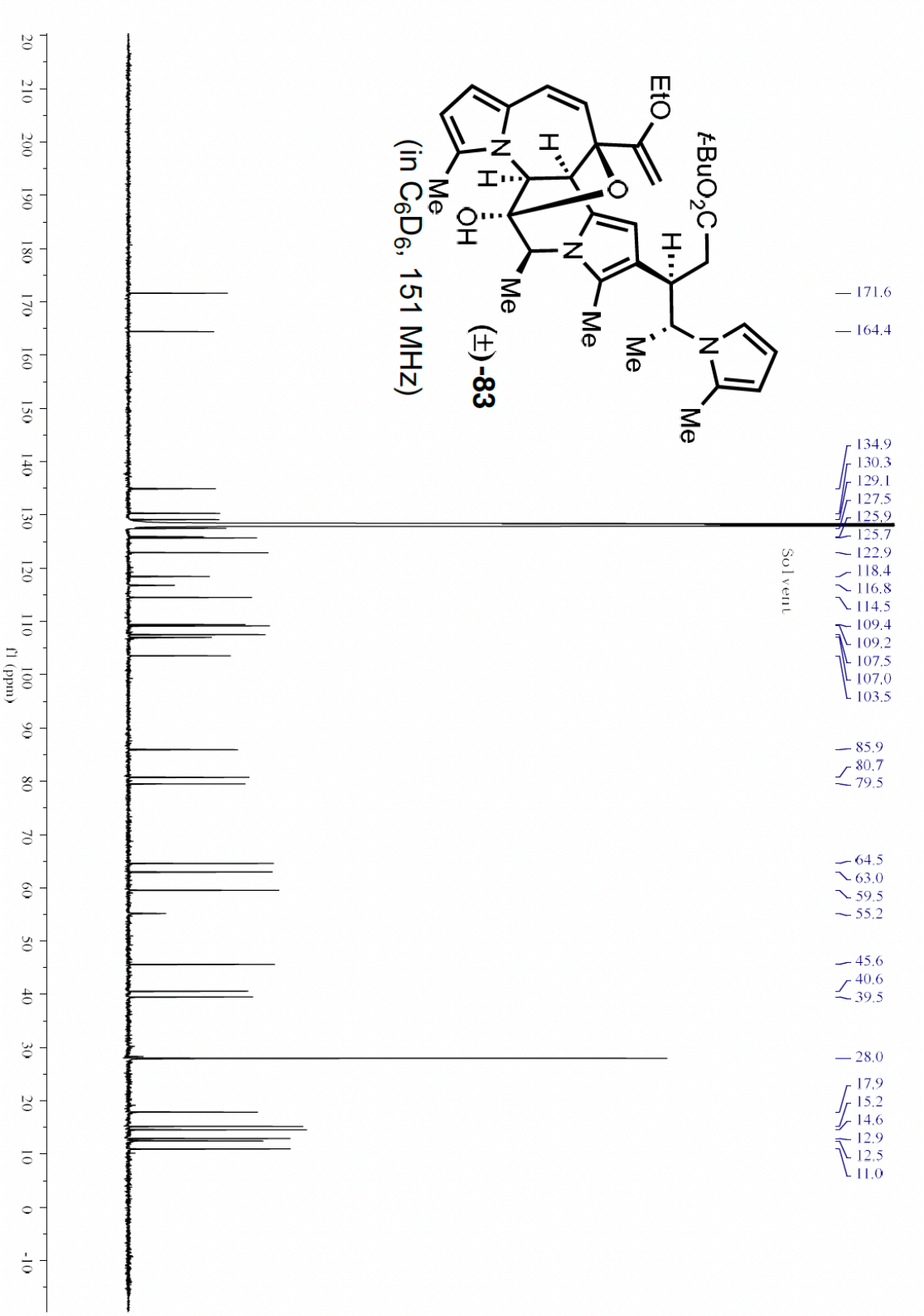

7.16
EtO
O
Me
N
H
Me
N
H
OTMS
Me
(in C6D6, 600 MHz)
Solvent
1.00
0.98
0.98
1.00
0.98
1.01
1.00
1.02
1.00
0.99
1.03
1.04
1.03
3.10
3.10
3.08
3.15
9.06
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)

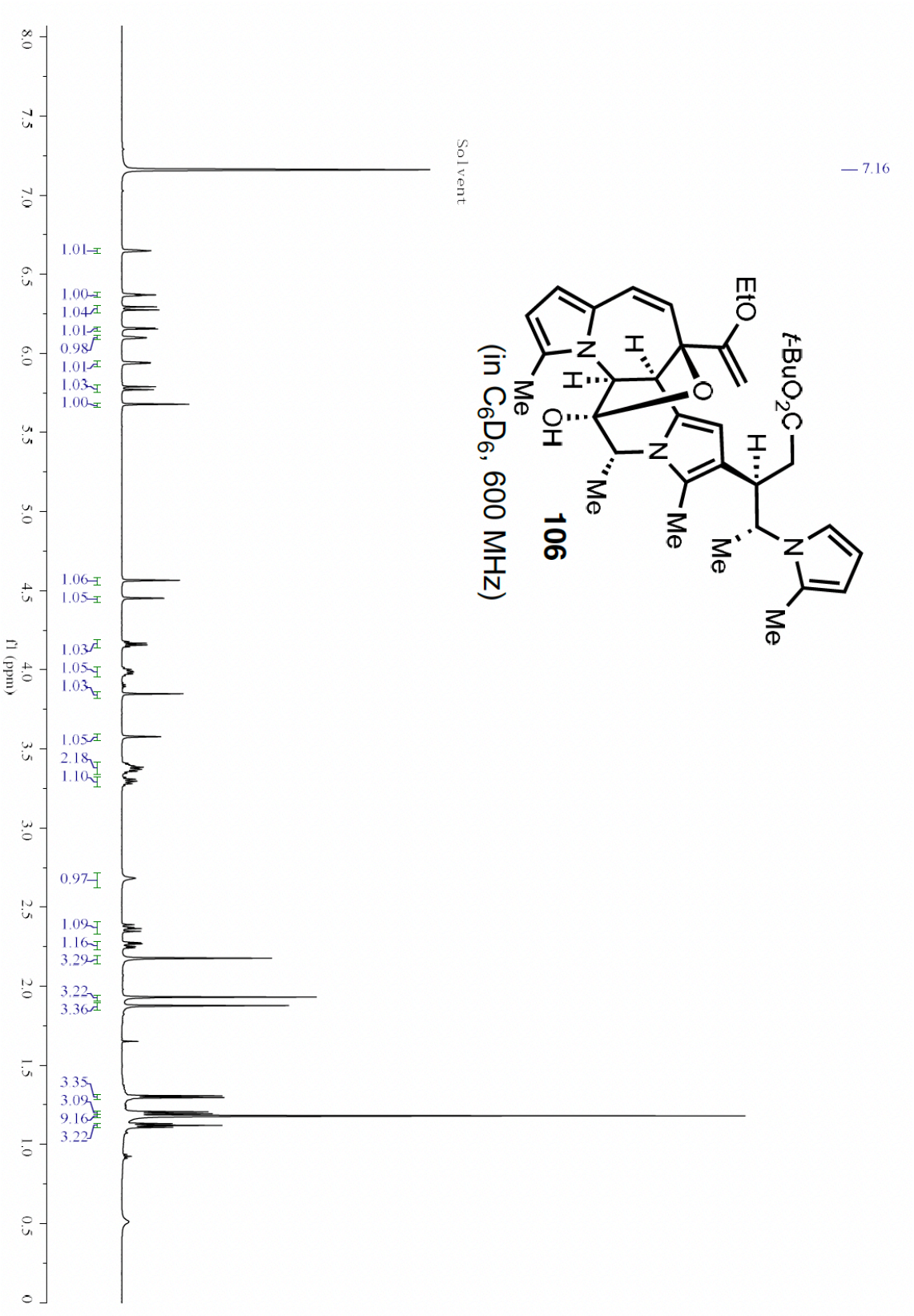

EtO
H
O
N
H
OTMS
Me
Me
N
Me
(in C6D6, 151 MHz)
164.7
135.3
130.9
130.4
127.1
124.3
124.2
114.6
111.7
108.4
108.4
104.7
86.9
80.5
65.5
63.0
61.7
46.4
14.7
14.6
14.2
13.0
1.8
Solvent
f1 (ppm)

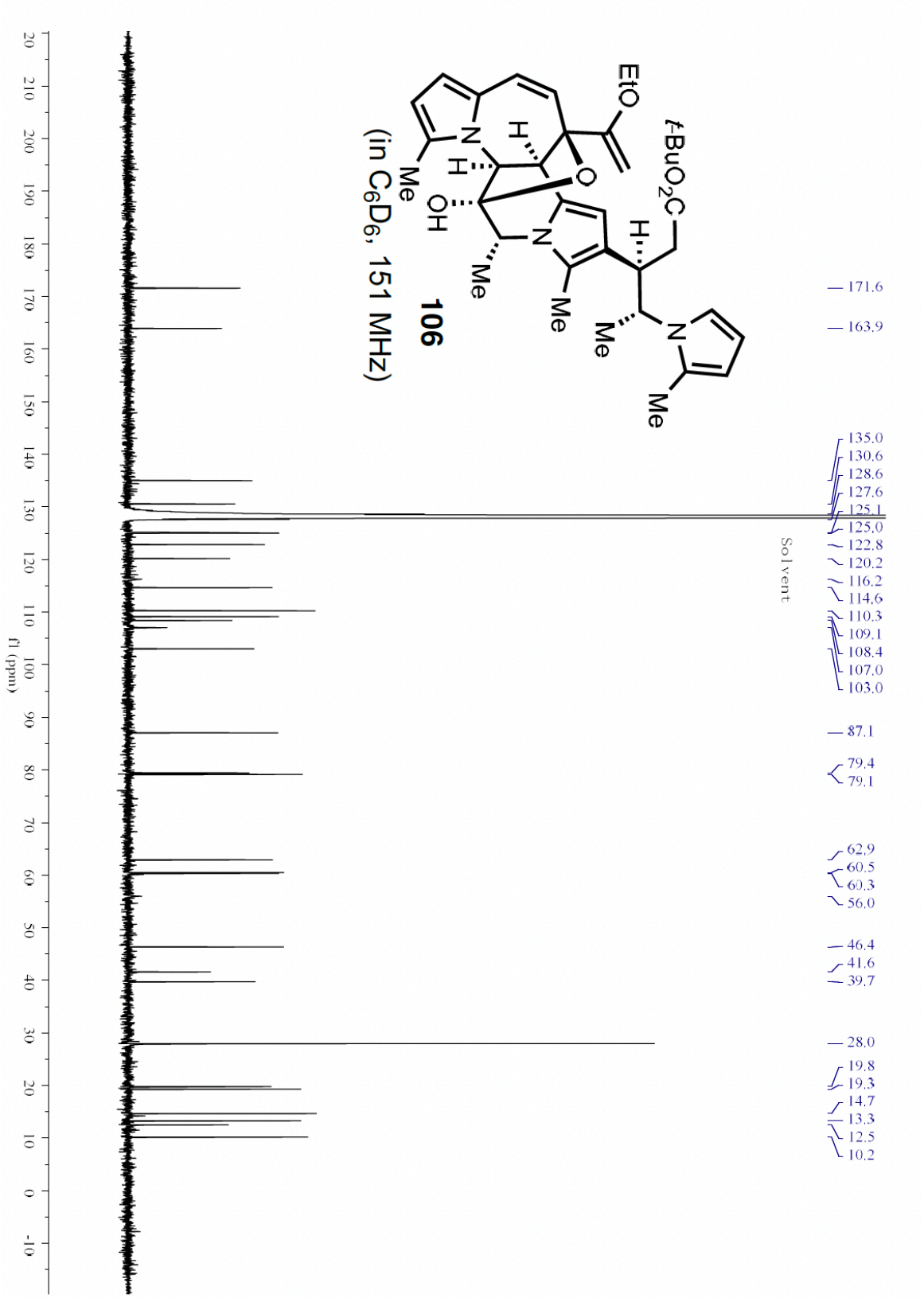

7.16
EtO
t-BuO2C
O
H
N
H
N
H
Me
Me
N
Me
Me
Me
OH
diast -83
(in C6D6, 600 MHz)
Solvent
1.00
1.00
1.03
0.97
1.02
0.96
0.99
0.99
1.00
0.99
0.99
1.03
0.97
1.02
2.00
1.02
2.07
3.03
3.05
2.97
3.02
3.59
9.01
3.02
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

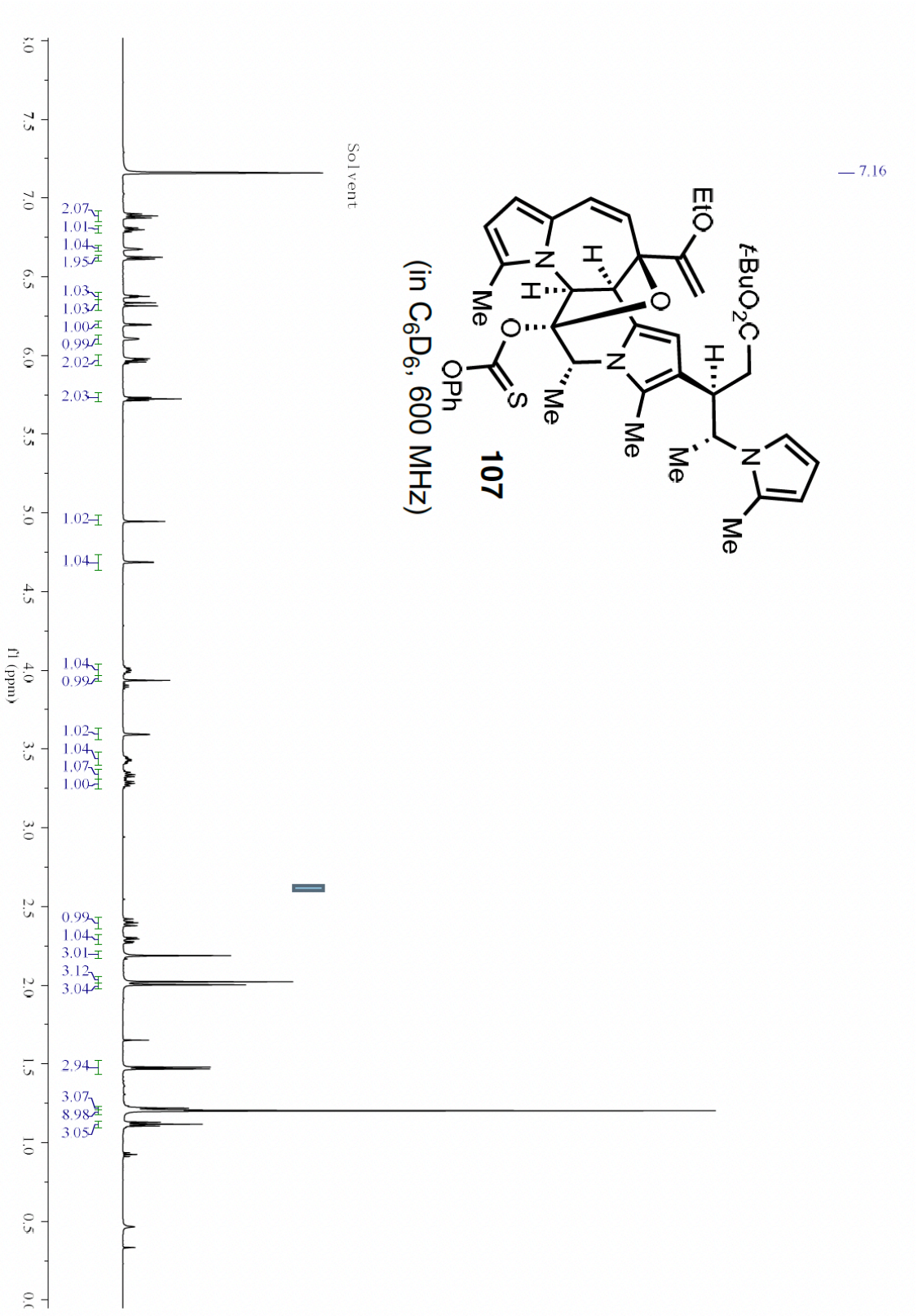

EtO
t-BuO2C
Me
OH
Me
Me
Me
Me
Me
H
H
N
N
N
O
diast -83
(in C6D6, 151 MHz)
171.2
164.4
135.1
130.4
129.8
127.9
125.8
124.7
123.0
120.1
116.1
114.5
109.5
109.1
108.3
107.1
103.0
85.7
80.9
79.3
64.6
63.3
59.6
55.5
45.9
41.9
40.6
28.1
19.8
15.3
14.8
12.9
12.6
11.5
Solvent
f1 (ppm)

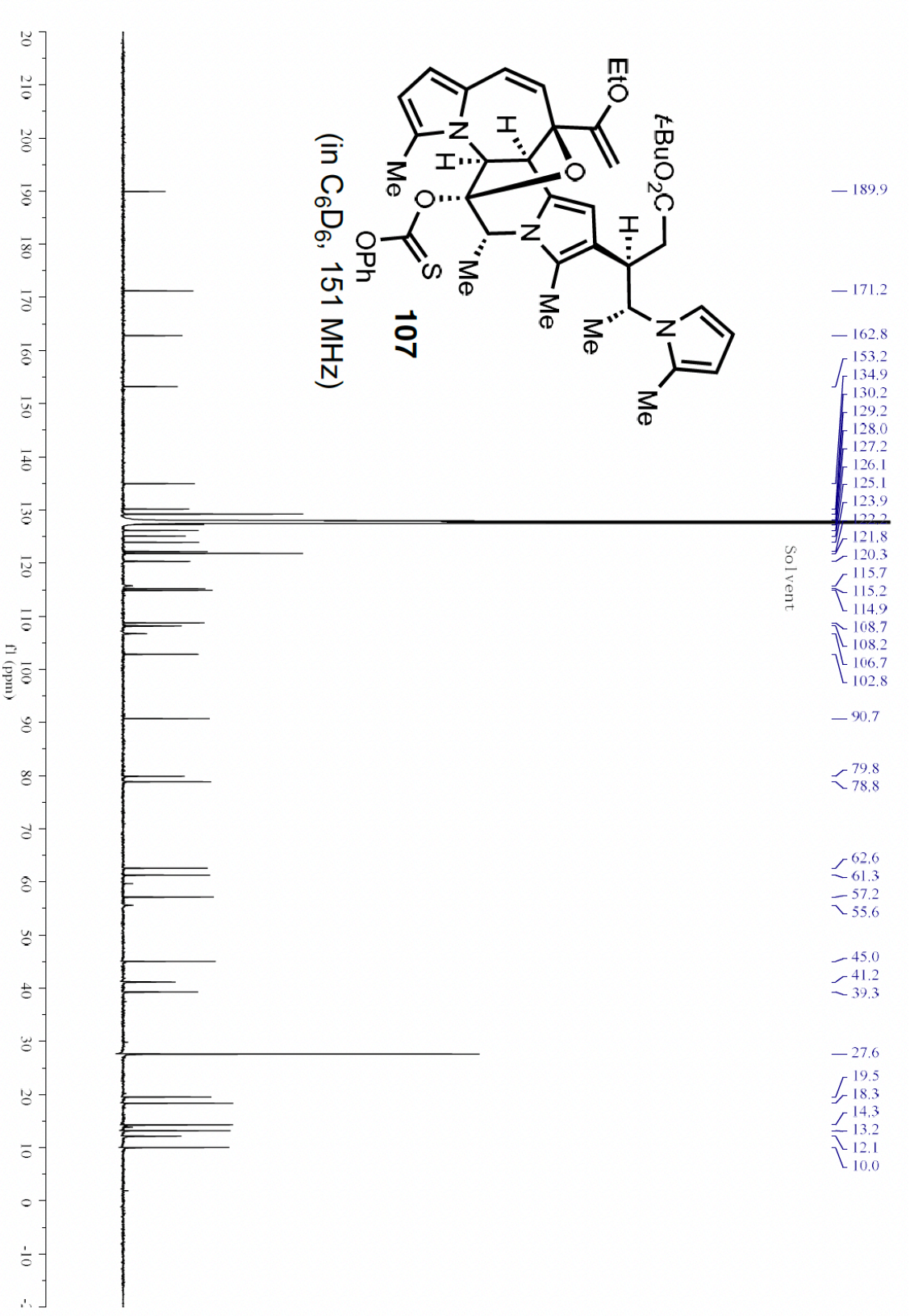

7.16
t-BuO2C
EtO
H
N
Me
Me
O
Me
N
H
Me
N
H
OH
(± )-83
Me
(in C6D6, 600 MHz)
Solvent
1.00
1.03
1.03
1.06
1.03
1.05
1.06
1.03
1.00
1.01
1.06
1.06
1.00
1.01
2.17
1.04
0.99
1.05
1.09
3.04
6.16
3.06
12.34
3.30
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

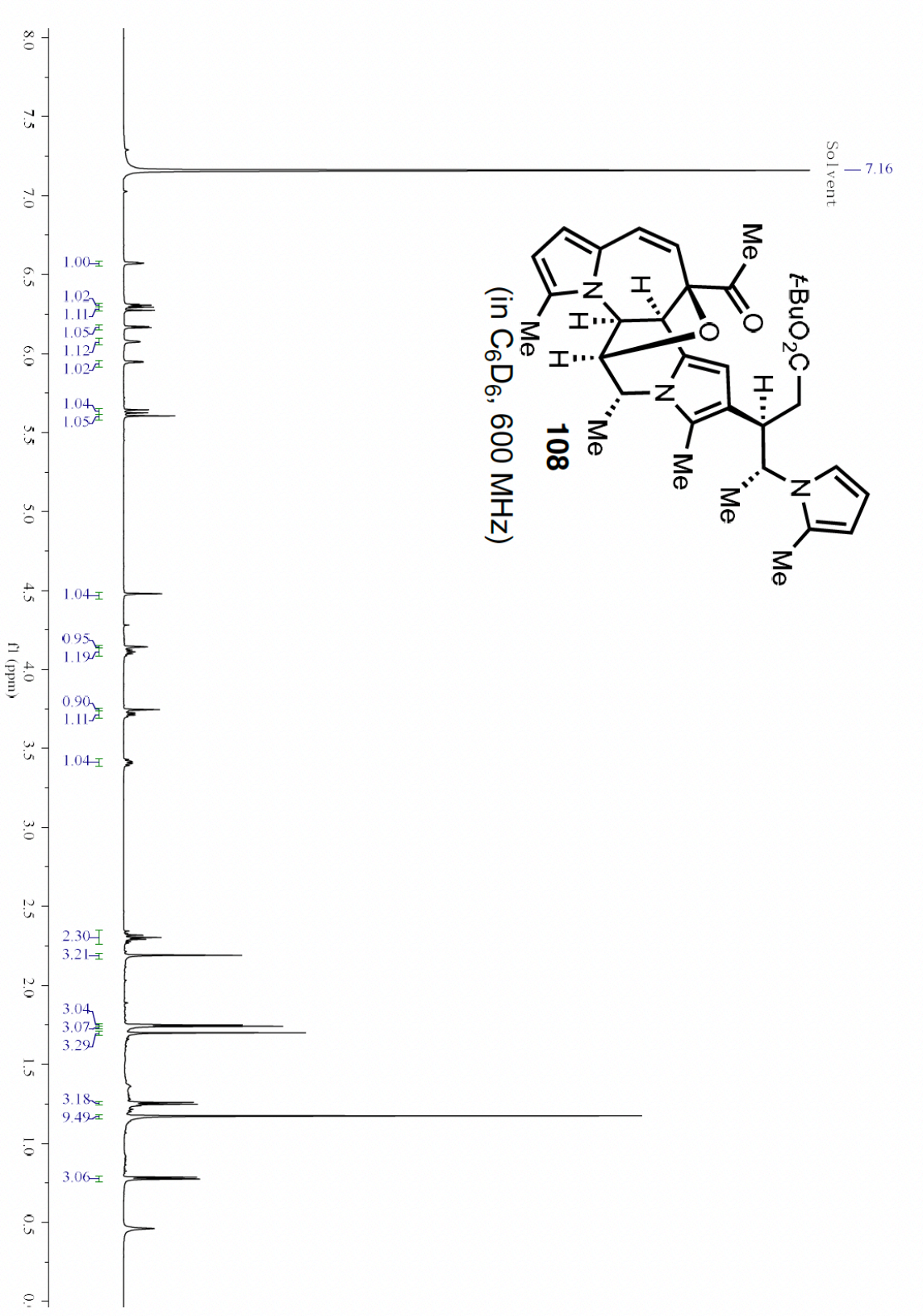

(±)-83
(in C6D6, 151 MHz)
Solvent
171.6
164.4
134.9
130.3
129.1
127.5
125.9
125.7
122.9
118.4
116.8
114.5
109.4
109.2
107.5
107.0
103.5
85.9
80.7
79.5
64.5
63.0
59.5
55.2
45.6
40.6
39.5
28.0
17.9
15.2
14.6
12.9
12.5
11.0
f1 (ppm)

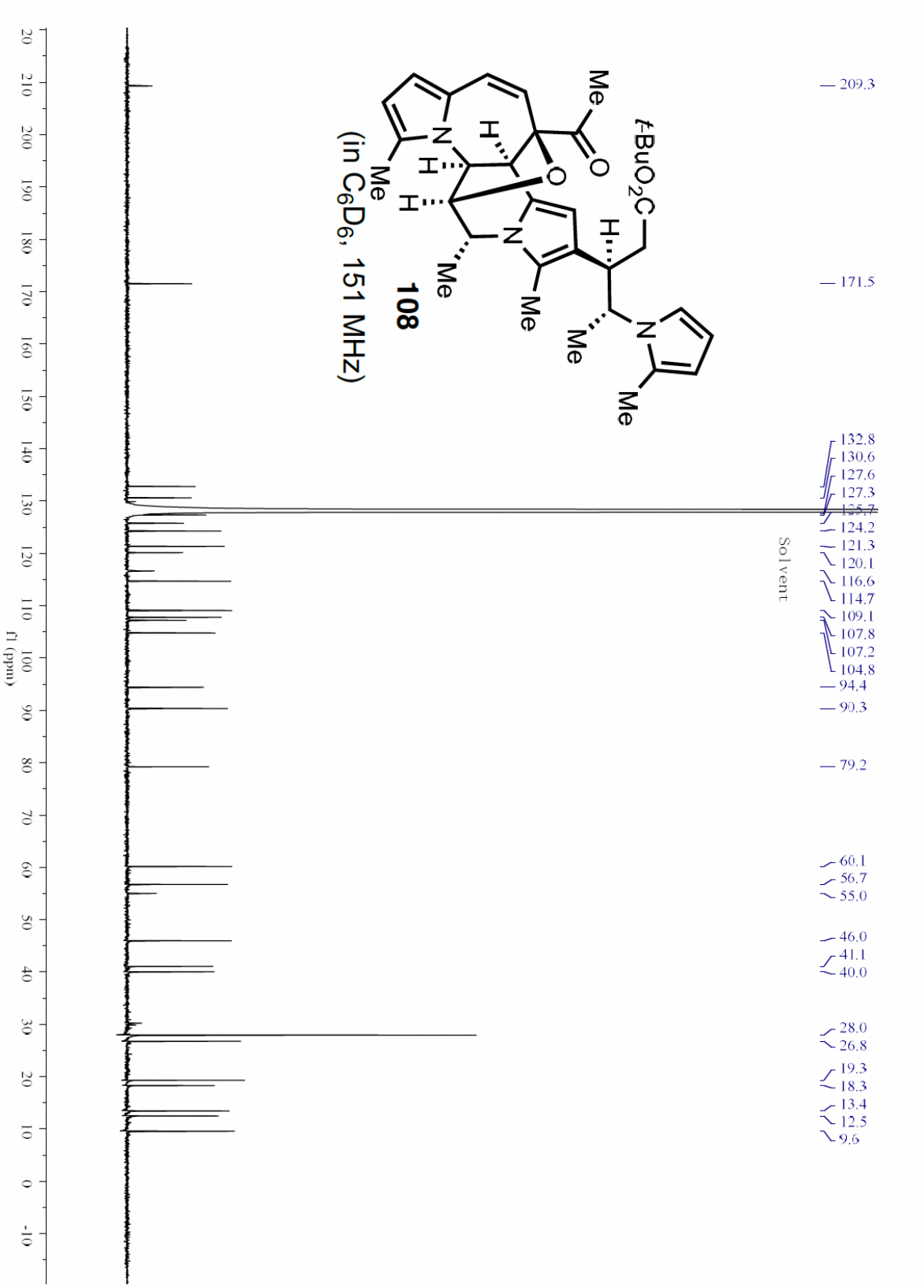

Solvent
7.16
106
(in C6D6, 600 MHz)
f1 (ppm)

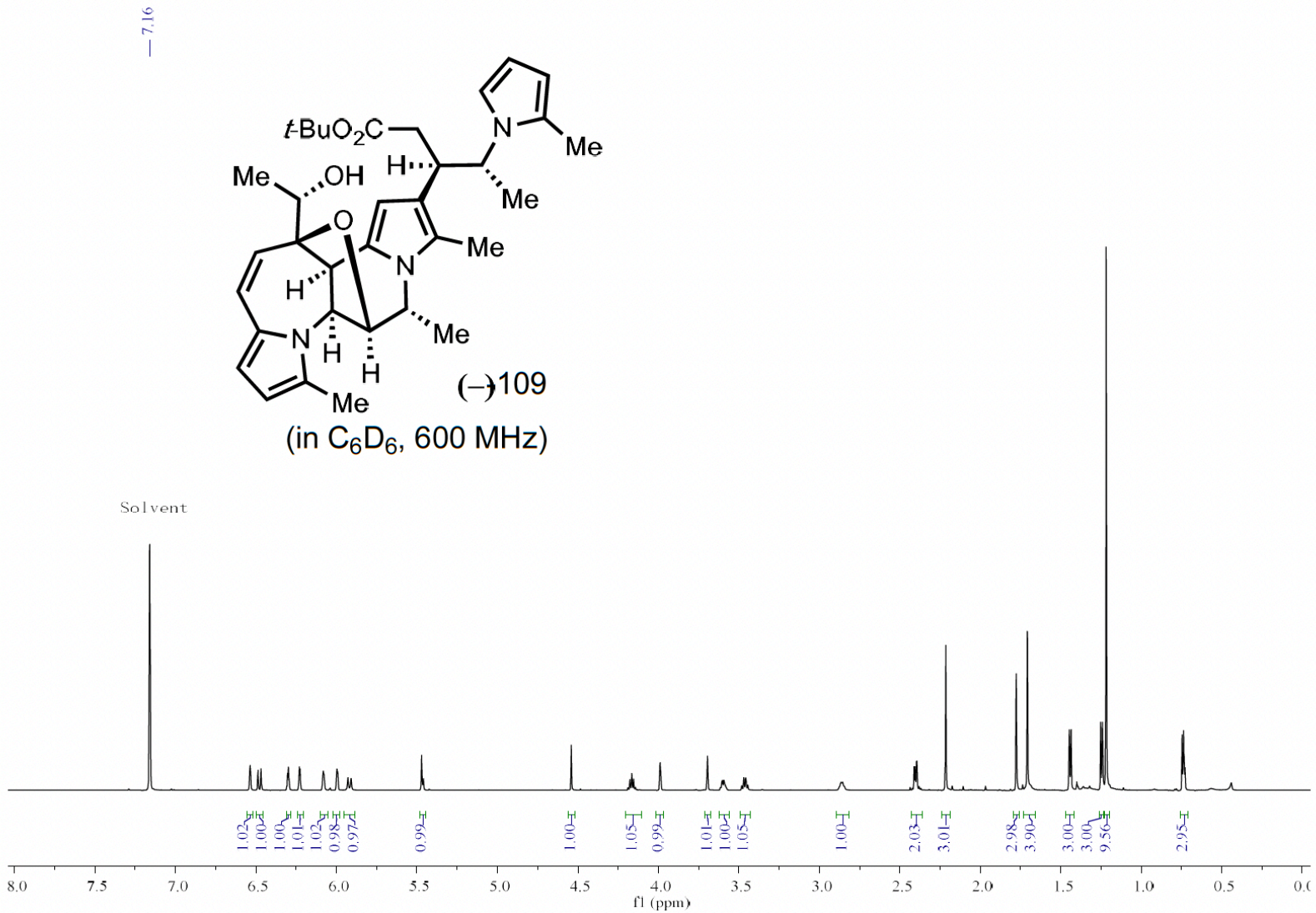

106
(in C6D6, 151 MHz)
EtO
t-BuO2C
Me
OH
Solvent
171.6
163.9
135.0
130.6
128.6
127.6
125.1
125.0
122.8
120.2
116.2
114.6
110.3
109.1
108.4
107.0
103.0
87.1
79.4
79.1
62.9
60.5
60.3
56.0
46.4
41.6
39.7
28.0
19.8
19.3
14.7
13.3
12.5
10.2
f1 (ppm)

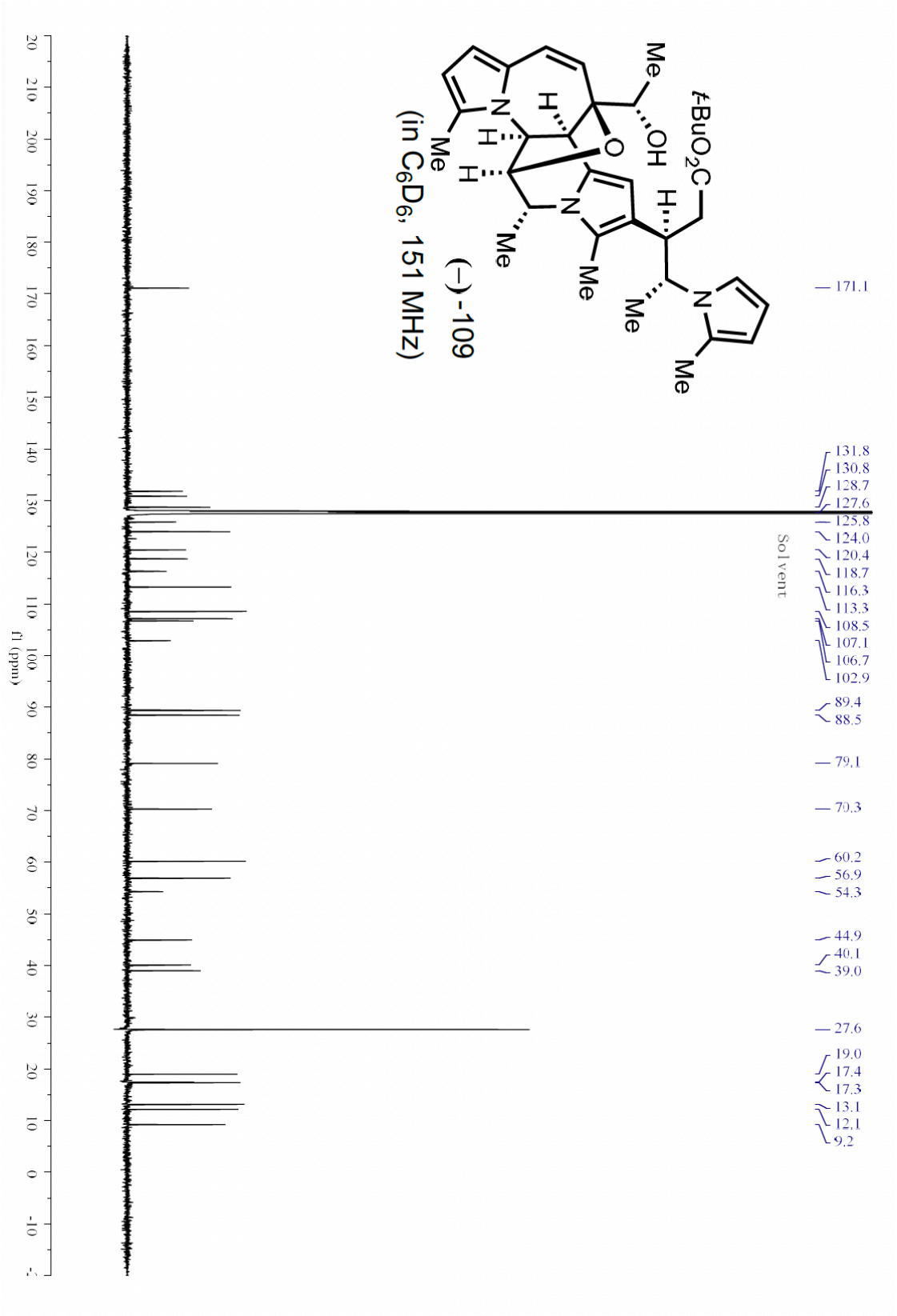

Solvent
7.16
EtO
t-BuO2C
Me
Me
Me
Me
Me
OPh
107
(in C6D6, 600 MHz)
2.07
1.01
1.04
1.95
1.03
1.03
1.00
0.99
2.02
2.03
1.02
1.04
1.04
0.99
1.02
1.04
1.07
1.00
0.99
1.04
3.01
3.12
3.04
2.94
3.07
8.98
3.05
f1 (ppm)

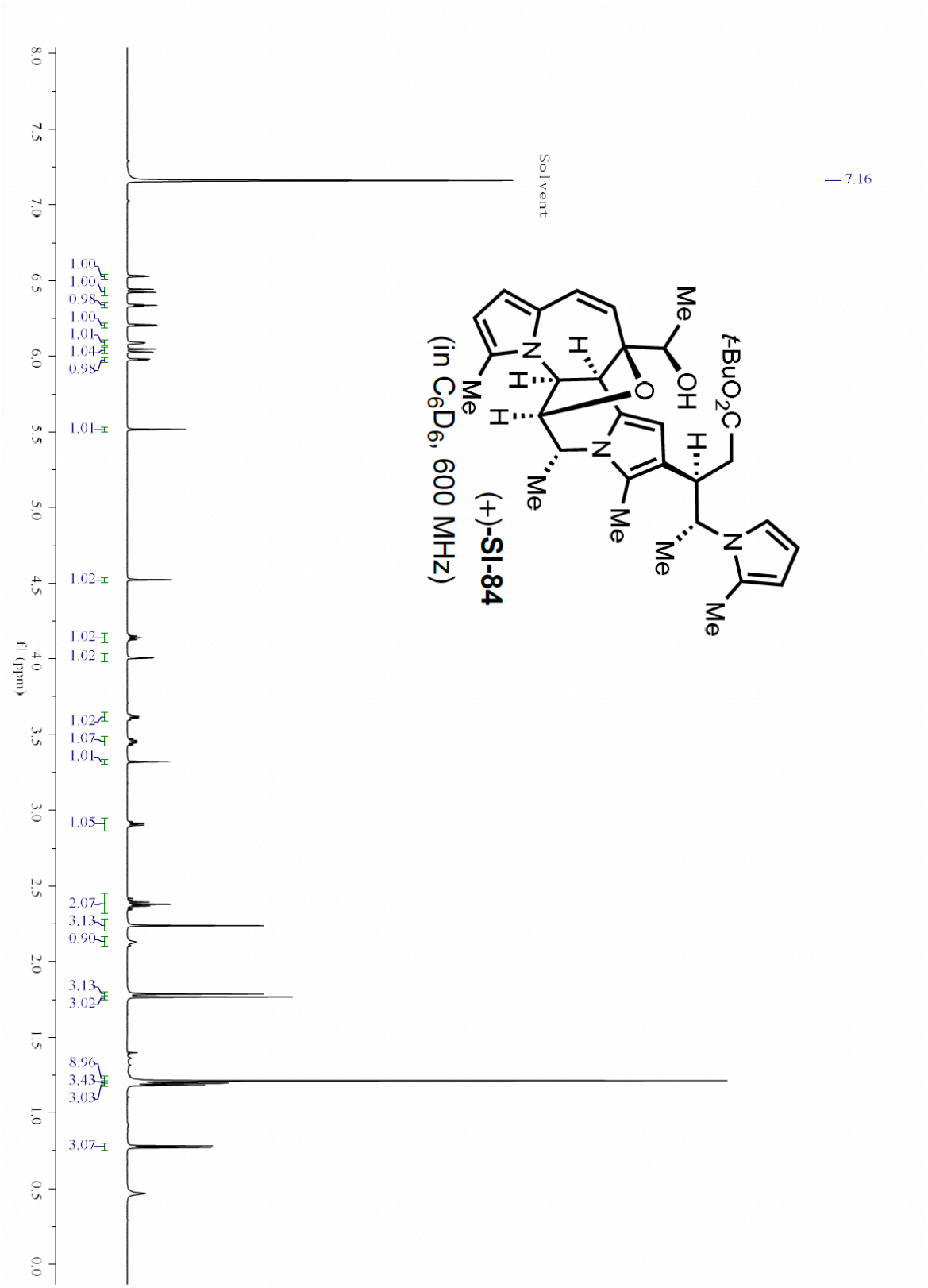

EtO
t-BuO2C
Me
Me
Me
Me
Me
N
H
H
O
O
S
OPh
107
(in C6D6, 151 MHz)
189.9
171.2
162.8
153.2
134.9
130.2
129.2
128.0
127.2
126.1
125.1
123.9
122.2
121.8
120.3
115.7
115.2
114.9
108.7
108.2
106.7
102.8
90.7
79.8
78.8
62.6
61.3
57.2
55.6
45.0
41.2
39.3
27.6
19.5
18.3
14.3
13.2
12.1
10.0
Solvent
f1 (ppm)

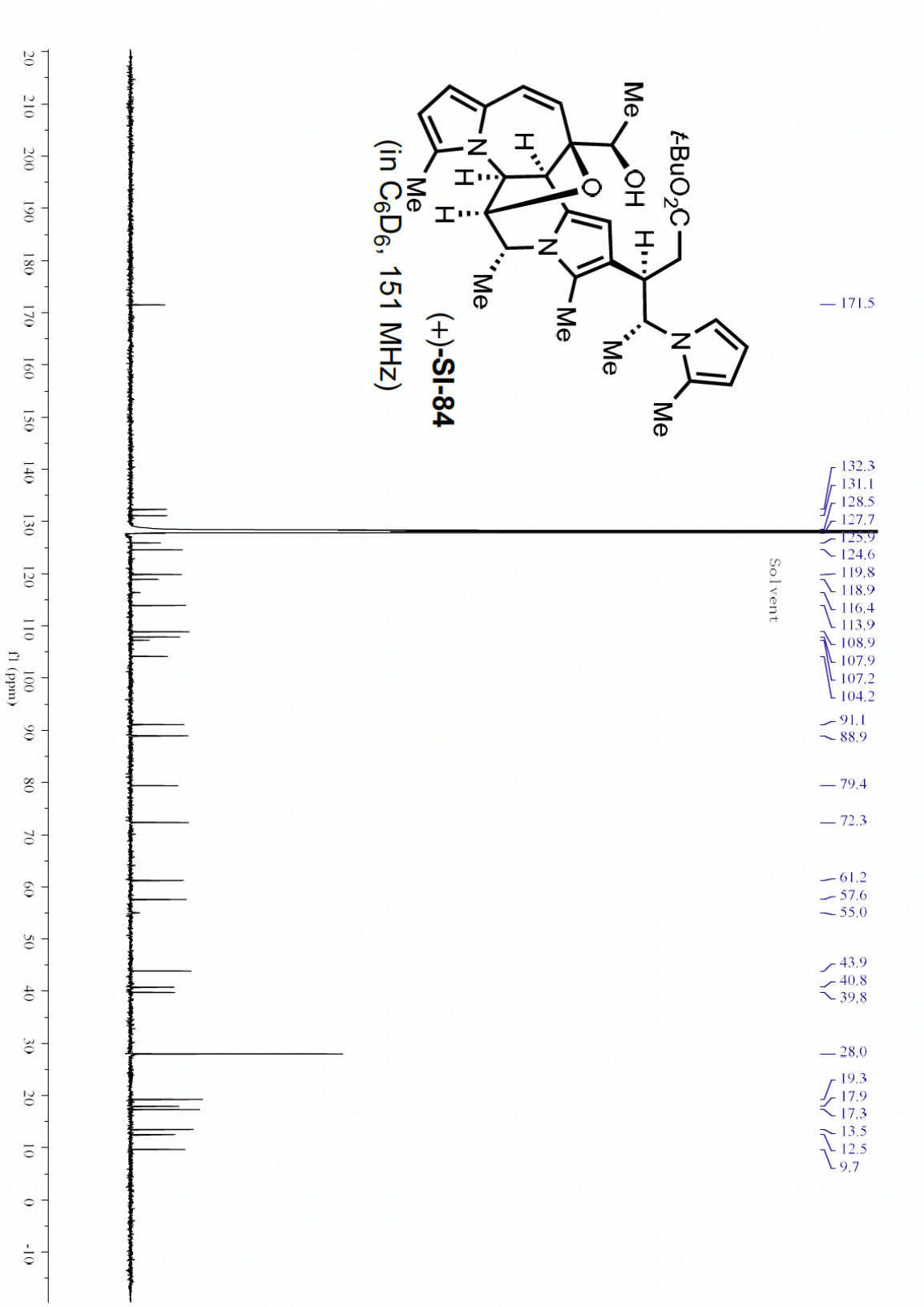

Solvent
7.16
tBuO2C
Me
O
H
N
H
H
O
N
Me
Me
Me
Me
Me
108
(in C6D6, 600 MHz)
1.00
1.02
1.11
1.05
1.12
1.02
1.04
1.05
1.04
0.95
1.19
0.90
1.11
1.04
2.30
3.21
3.04
3.07
3.29
3.18
9.49
3.06
f1 (ppm)

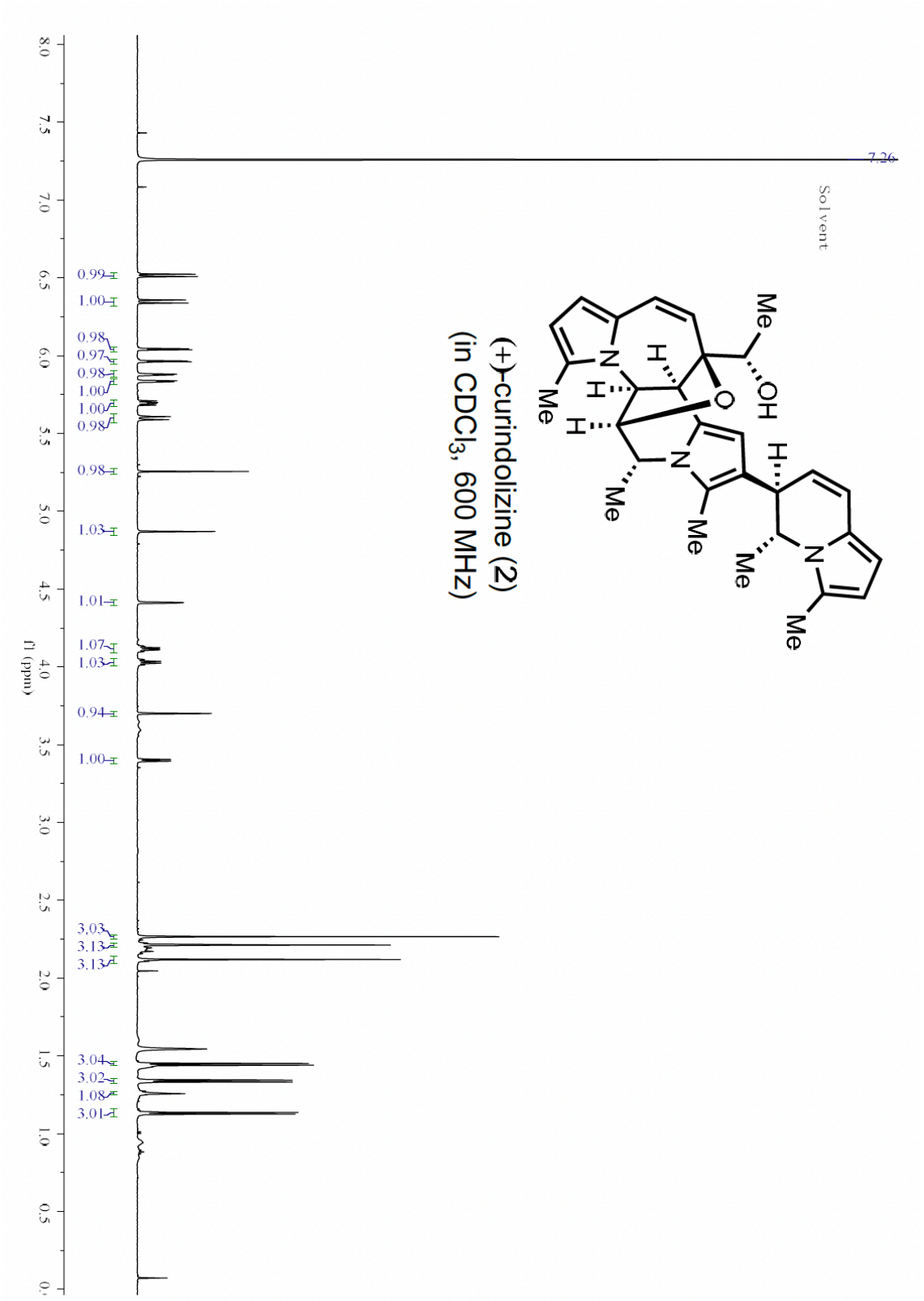

108
(in C6D6, 151 MHz)
Solvent
209.3
171.5
132.8
130.6
127.6
127.3
125.7
124.2
121.3
120.1
116.6
114.7
109.1
107.8
107.2
104.8
94.4
90.3
79.2
60.1
56.7
55.0
46.0
41.1
40.0
28.0
26.8
19.3
18.3
13.4
12.5
9.6
f1 (ppm)

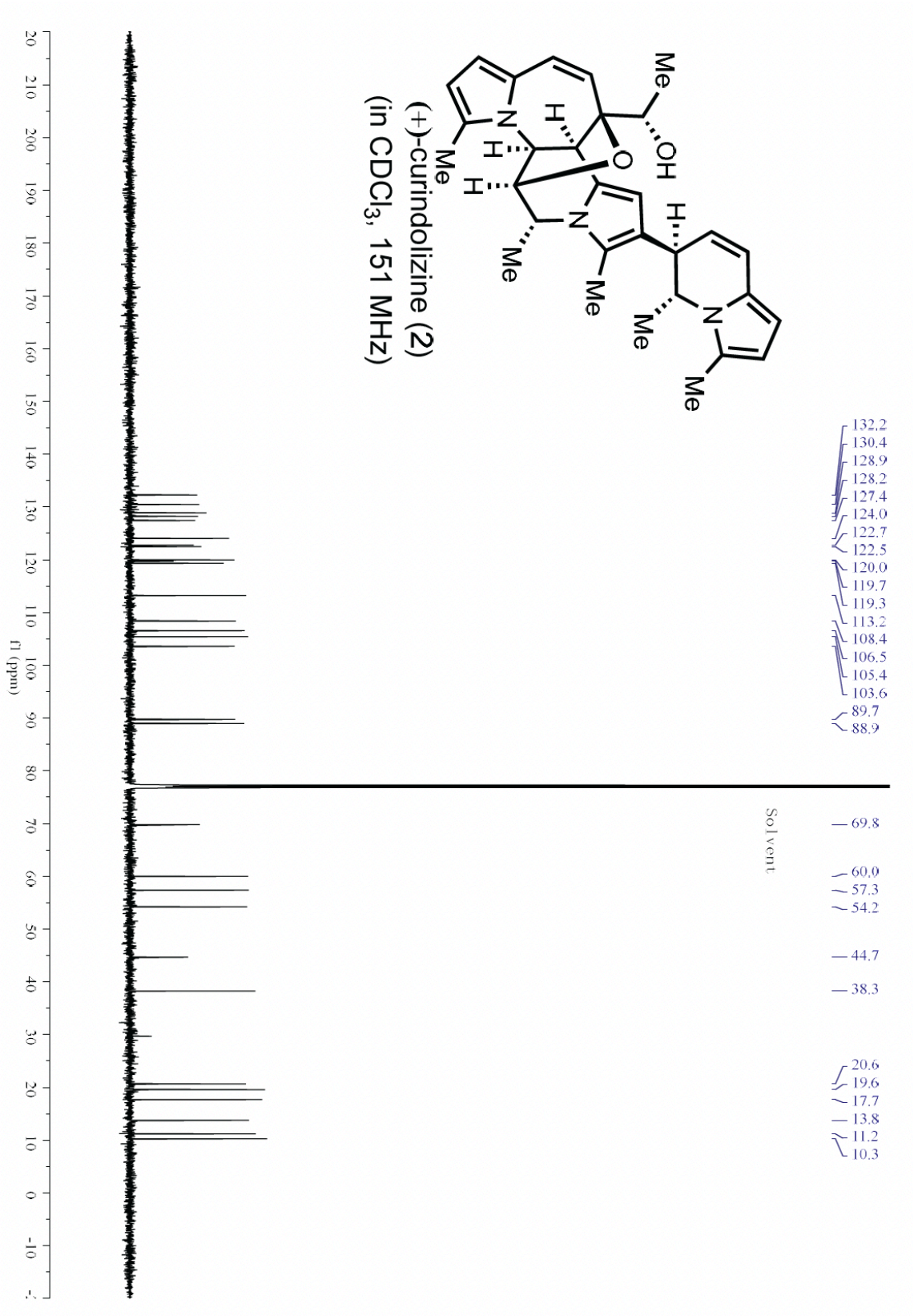

7.16
t-BuO2C
Me
OH
H
Me
O
Me
N
H
N
H
H
Me
Me
(–)109
(in C6D6, 600 MHz)
Solvent
1.02
1.00
1.00
1.01
1.02
0.98
0.97
0.99
1.00
1.05
0.99
1.01
1.00
1.05
1.00
2.03
3.01
2.98
3.90
3.00
3.00
9.56
2.95
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

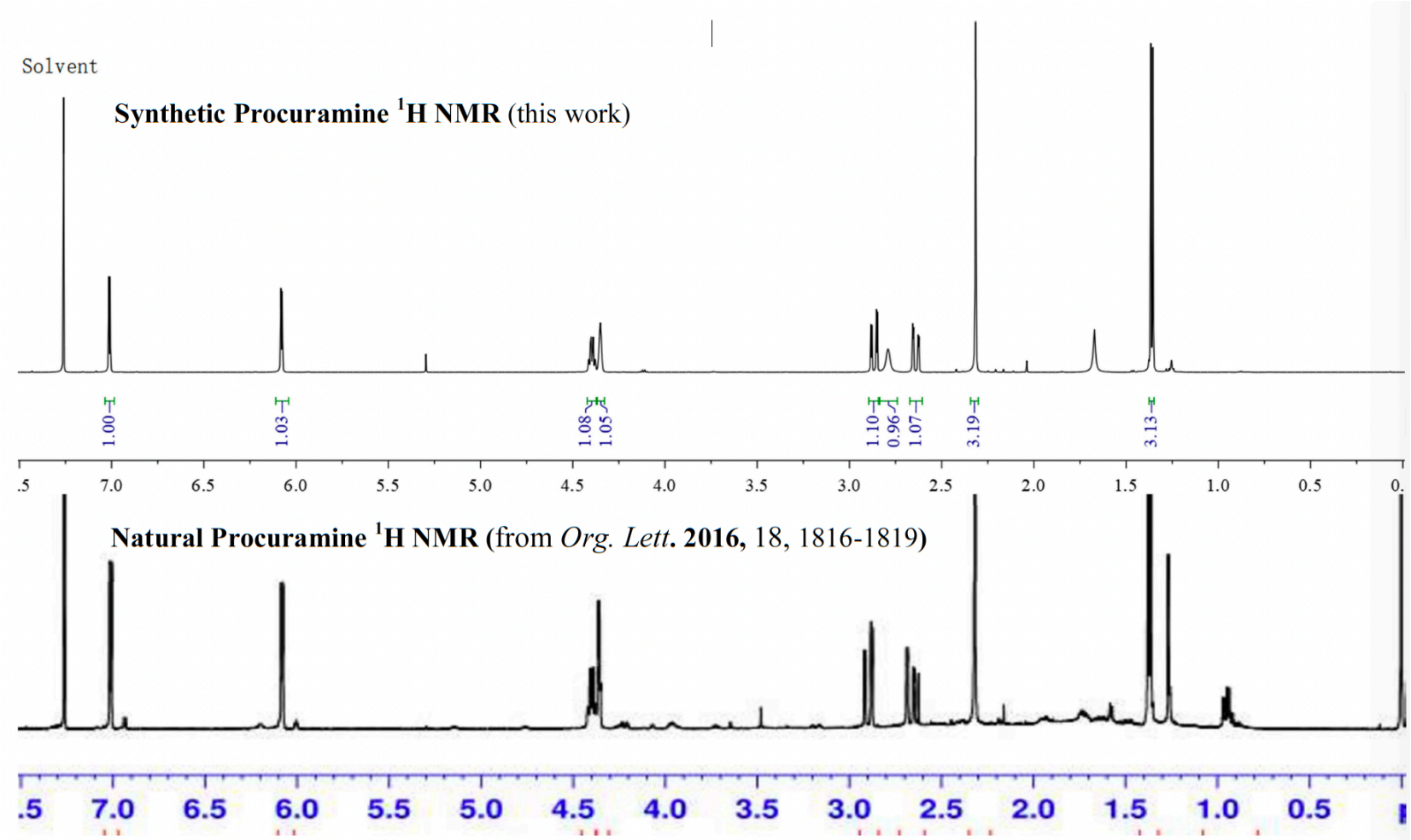

(–)-109
(in $C_6D_6$, 151 MHz)
Solvent
f1 (ppm)

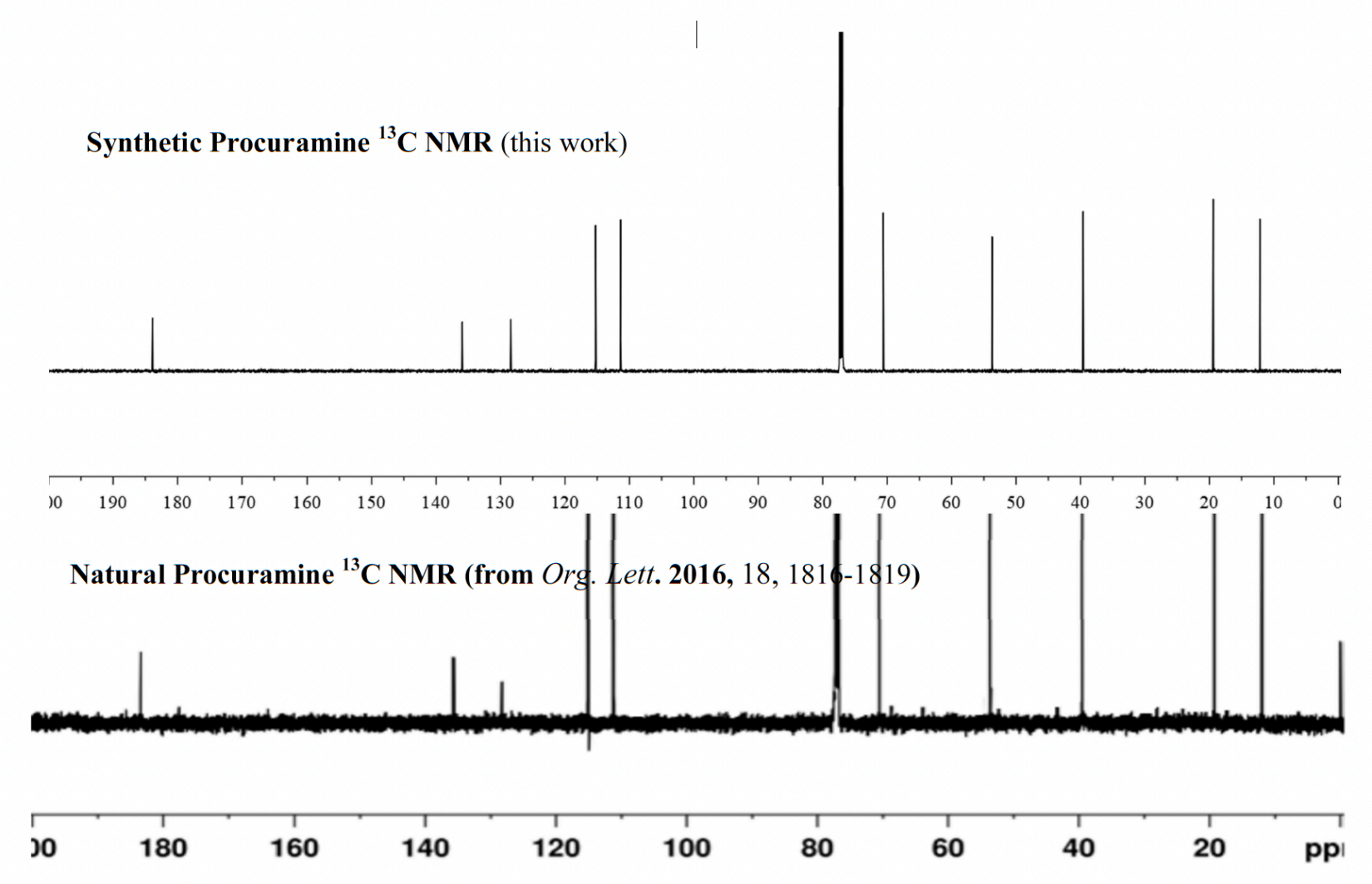

(+)-SI-84
(in $C_6D_6$, 600 MHz)
Solvent
7.16
f1 (ppm)

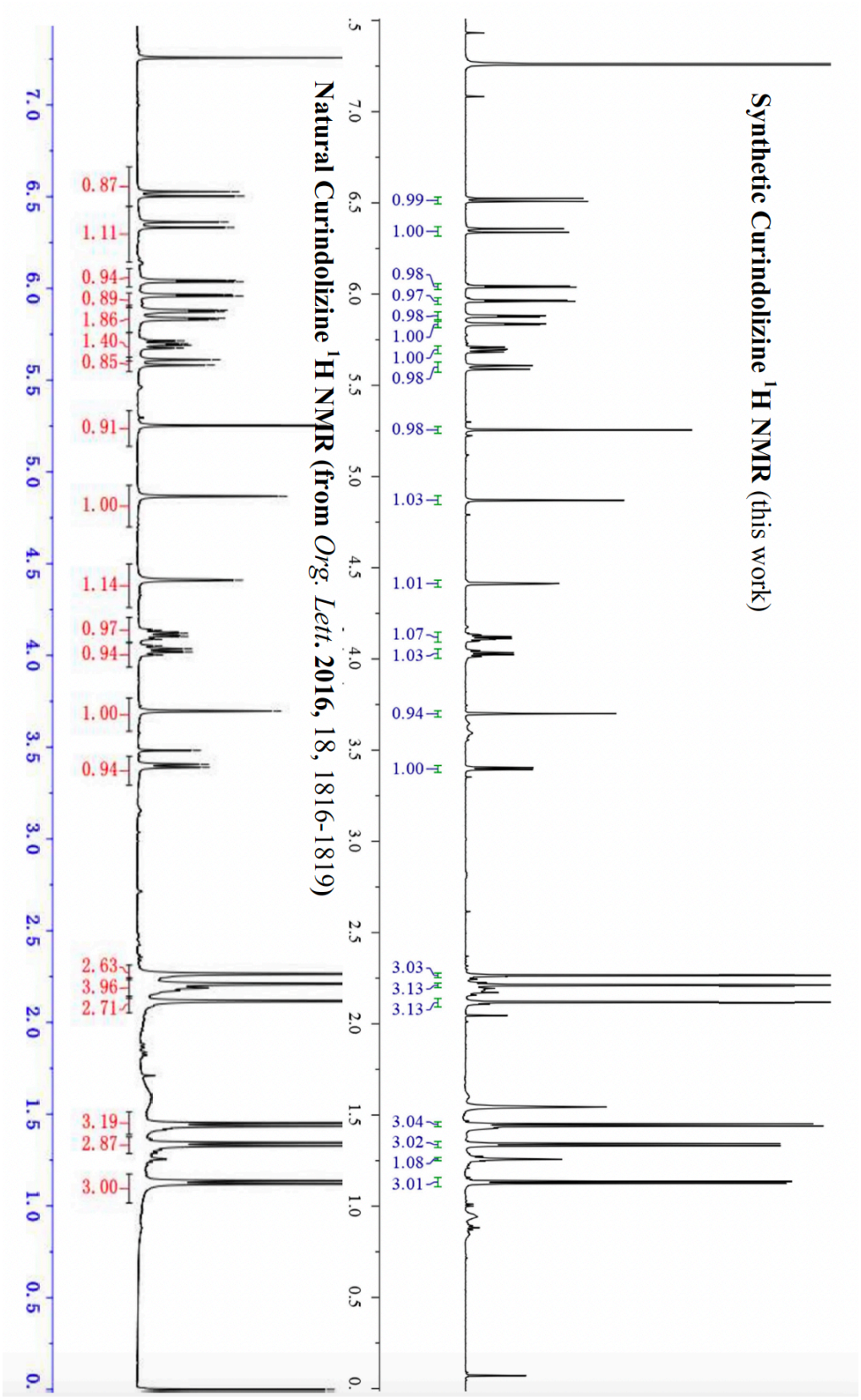

(+)-SI-84
(in $C_6D_6$, 151 MHz)
Solvent
171.5
132.3
131.1
128.5
127.7
125.9
124.6
119.8
118.9
116.4
113.9
108.9
107.9
107.2
104.2
91.1
88.9
79.4
72.3
61.2
57.6
55.0
43.9
40.8
39.8
28.0
19.3
17.9
17.3
13.5
12.5
9.7
f1 (ppm)

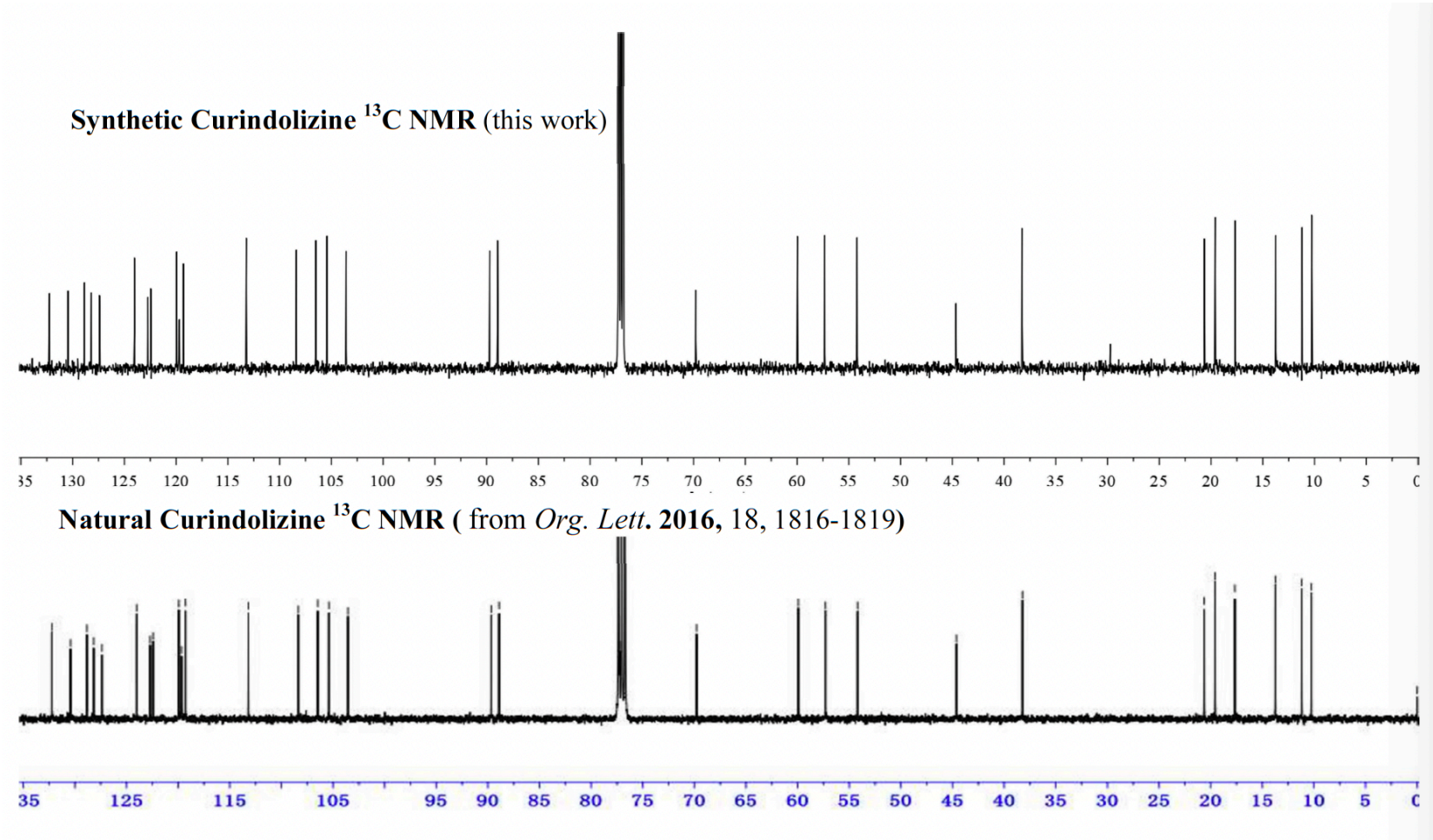

(+)-curindolizine (2)
(in CDCl3, 600 MHz)
Solvent
7.26
Me
OH
H
N
H
H
O
N
Me
Me
Me
Me
N
Me
0.99
1.00
0.98
0.97
0.98
1.00
1.00
0.98
0.98
1.03
1.01
1.07
1.03
0.94
1.00
3.03
3.13
3.13
3.04
3.02
1.08
3.01
f1 (ppm)


(+)-curindolizine (2)
(in CDCl3, 151 MHz)
Me
OH
H
O
N
H
H
Me
Me
Me
Me
N
132.2
130.4
128.9
128.2
127.4
124.0
122.7
122.5
120.0
119.7
119.3
113.2
108.4
106.5
105.4
103.6
89.7
88.9
Solvent
69.8
60.0
57.3
54.2
44.7
38.3
20.6
19.6
17.7
13.8
11.2
10.3
f1 (ppm)


Solvent
Synthetic Procuramine ¹H NMR (this work)
1.00
1.03
1.08
1.05
1.10
0.96
1.07
3.19
3.13
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
Natural Procuramine ¹H NMR (from Org. Lett. 2016, 18, 1816-1819)


Synthetic Procuramine 13C NMR (this work)
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
Natural Procuramine 13C NMR (from Org. Lett. 2016, 18, 1816-1819)
180 160 140 120 100 80 60 40 20


Synthetic Curindolizine ¹H NMR (this work)
Natural Curindolizine ¹H NMR (from *Org. Lett.* **2016**, 18, 1816-1819)


Synthetic Curindolizine $^{13}$C NMR (this work)
35 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10 5 0
Natural Curindolizine $^{13}$C NMR ( from *Org. Lett*. 2016, 18, 1816-1819)
35 125 115 105 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10 5 0

*Chapter 3*

# The Syntheses of Bipolamines D, E, G, and I

## 3.1 Introduction

This chapter chronicles our chemical investigations of bispyrrole metabolites derived from *Bipolaris maydis*. A total of 9 pyrrole-containing secondary metabolites were identified in 2020 from this source.[1] Apart from simpler bipolamine A (**3**) and bipolamine (**4**), the other congeners are differentially oxidized variants of curvulamine (**1**) (Figure 3.1).[2,3] In the case of bipolamine C (**5**), the vinyl pyrrole has undergone oxidation at C-18 and C-19 to yield a hydroxypyrrolone structure. Bipolamines D (**6**) and E (**7**) are C-14 epimers wherein a hydroxyl group at C-14 replaces the $\Delta_{14\text{-}15}$ olefin, and in bipolamine G (**9**) further oxidation of the alkene to a monomethylatated trans diol has occurred. Bipolamine H (**10**) and bipolamine F (**8**) contain oxidation at C-5, in the form of a hydroxyl group in **10** and a THF ring in the case of **8**. Lastly, bipolamine I (**11**) is structurally distinct with its congeners in that is the only isolated metabolite with an ether bridge between C-14 and C-3. Driven to further explore the chemical reactivity of these pyrrole-containing natural products and investigate the superior reported bioactivity of certain bipolamines relative to curvulamine (**1**) (*see* Chapter 1), we aimed to develop a unifying strategy toward these novel bispyrrole alkaloids from a common intermediate.[4,5]

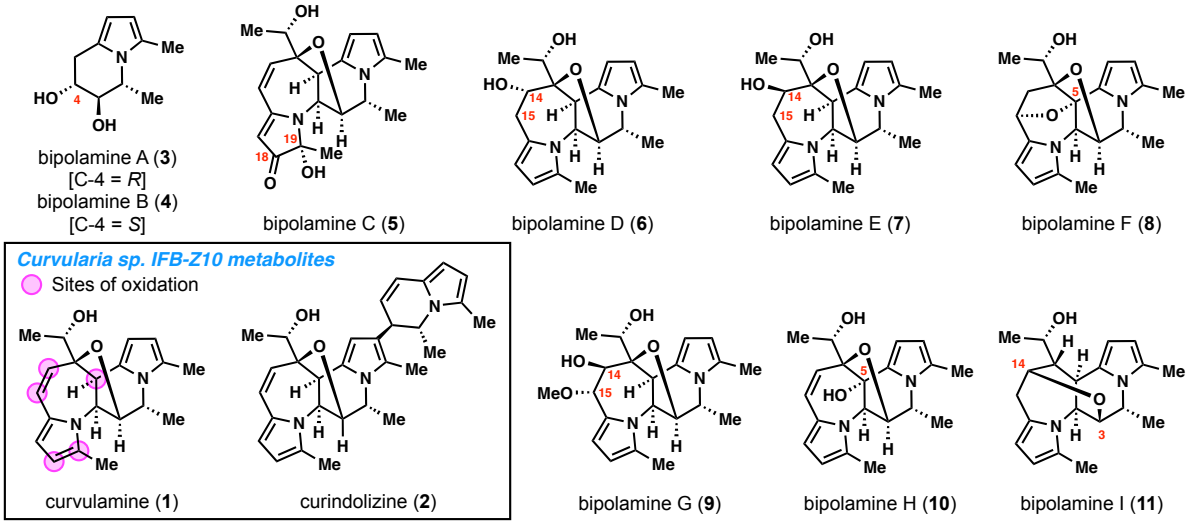



**Figure 3.1** Curvulamine-type alkaloids isolated from *Curvularia* sp. *and Bipolaris maydis*.

## 3.2 Pierce's Total Synthesis of Bipolamine I

In 2022, the Pierce group at North Carolina State University reported the synthesis of bipolamine I (**11**) from mono-ethyl malonate and 2-methylpyrrole.[6] Their 15-step synthesis of **11** featured a two-component ruthenium-catalyzed transfer hydrogenative coupling that yielded most of the carbon skeleton of **11** (Figure 3.2).[7] One of the components, alkyne **85** was made in a few steps from mono-ethyl malonate. First, activation of levulinic acid by CDI, followed by Claisen reaction of the malonte and the levulinic-CDI complex with concomitant decarboxylation proceed to give ester **86** ($Mg(OEt)_2$, CDI). A subsequent Paal-Knorr pyrrole synthesis using propargyl amine then gave **87** in 84% yield (AcOH, PhMe, Δ). DIBAL-mediated reduction of the ethyl ester **87**

to the corresponding aldehyde followed by 1,2 addition of vinyl Grignard to the aldehyde intermediate gave a secondary alcohol that was immediately protected with TBSCl to afford **85** (Figure 3.2A). The other pyrrole-containing component **88** was made from methyl pyrrole in two steps: intermolecular substitution reaction between 2-methyl pyrrole and **29** (NaH, DMF) followed by $LiAlH_4$ reduction to alcohol **88**. Base mediated isomerization of alkyne **85** (*t*-BuOK, *t*-BuOH) and subsequent ruthenium-catalyzed transfer hydrogenative coupling with alcohol **88** gave bispyrrole **89** in a 3.7:1 mixture of diastereomers with a combined 68% yield ($HClRu(CO)(PPh_3)_3$, dippf, 1M dioxane). This intermediate was transformed into **90** after a ring closing metathesis event (Grubbs II, PhMe) and TBAF deprotection sequence. In an unexpected event, exposure of **90** to

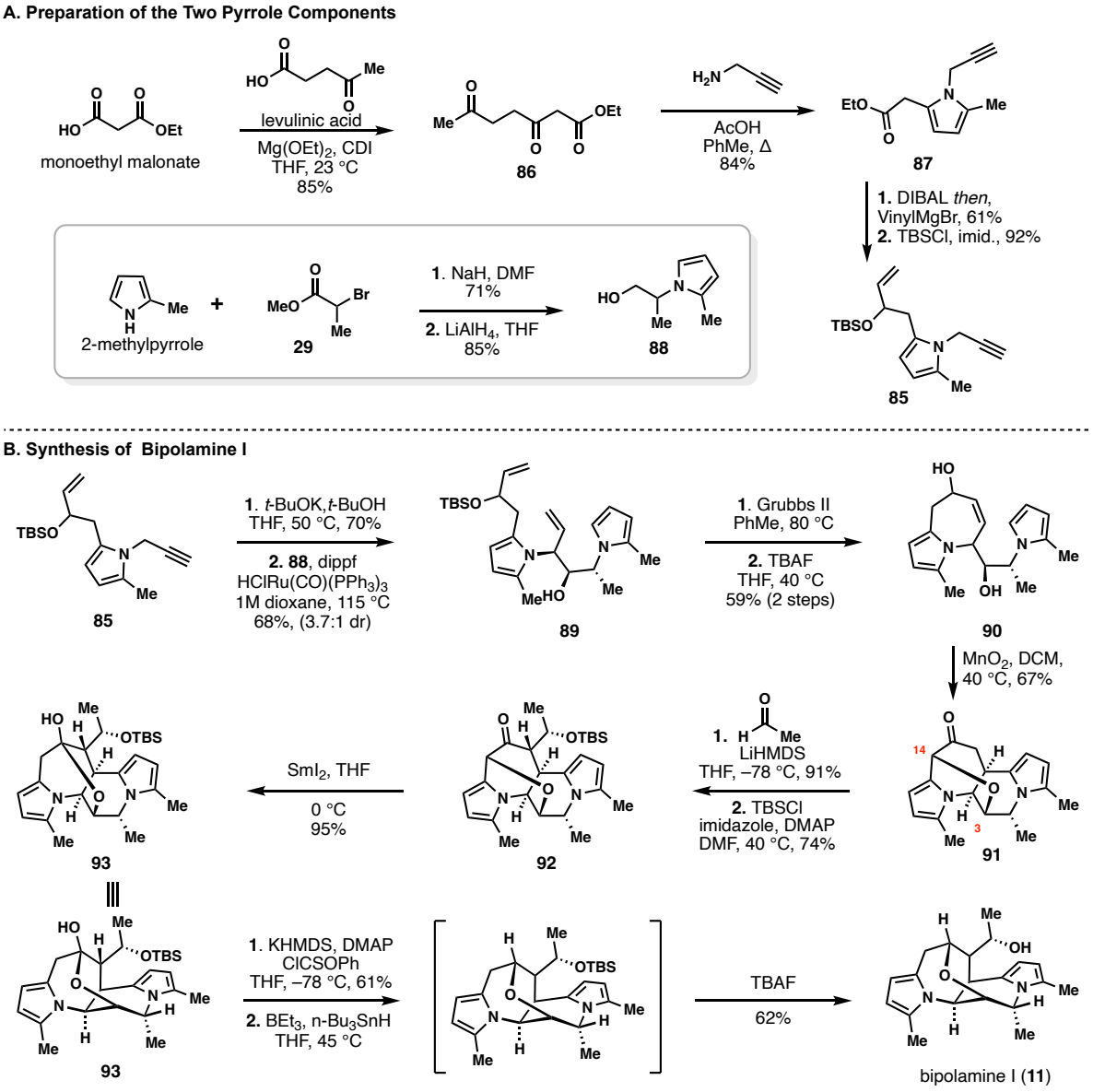



**Figure 3.2** Pierce's total synthesis of bipolamine I. **3.2A** Synthesis of pyrrole-containing coupling fragments. **3.2B** Completion of the synthesis of **11**

$MnO_2$ not only resulted in oxidation of the allylic alcohol to an enone that reacted with the neighboring pyrrole, but also resulted in the formation of the ether bridge between C-14 and C-3 ultimately yielding **91**. An aldol reaction between the kinetic enolate of **91** (LiHMDS, THF) and acetaldehyde gave a secondary alcohol which was protected (TBSCl, imidazole, DMAP) to generate ketone **92**. Exposure of **92** to reductive conditions gave hemiacetal **93** in 95% yield ($SmI_2$, THF). Finally, **93** was converted to a thiocarbonate (KHMDS, ClCOSPh), which underwent smooth radical deoxygenation ($BEt_3$, n-$Bu_3SnH$) and TBAF mediated deprotection completing the synthesis of bipolamine I (**11**).

### 3.3 Unifying Strategy Toward the Synthesis of the Bipolamine Alkaloids

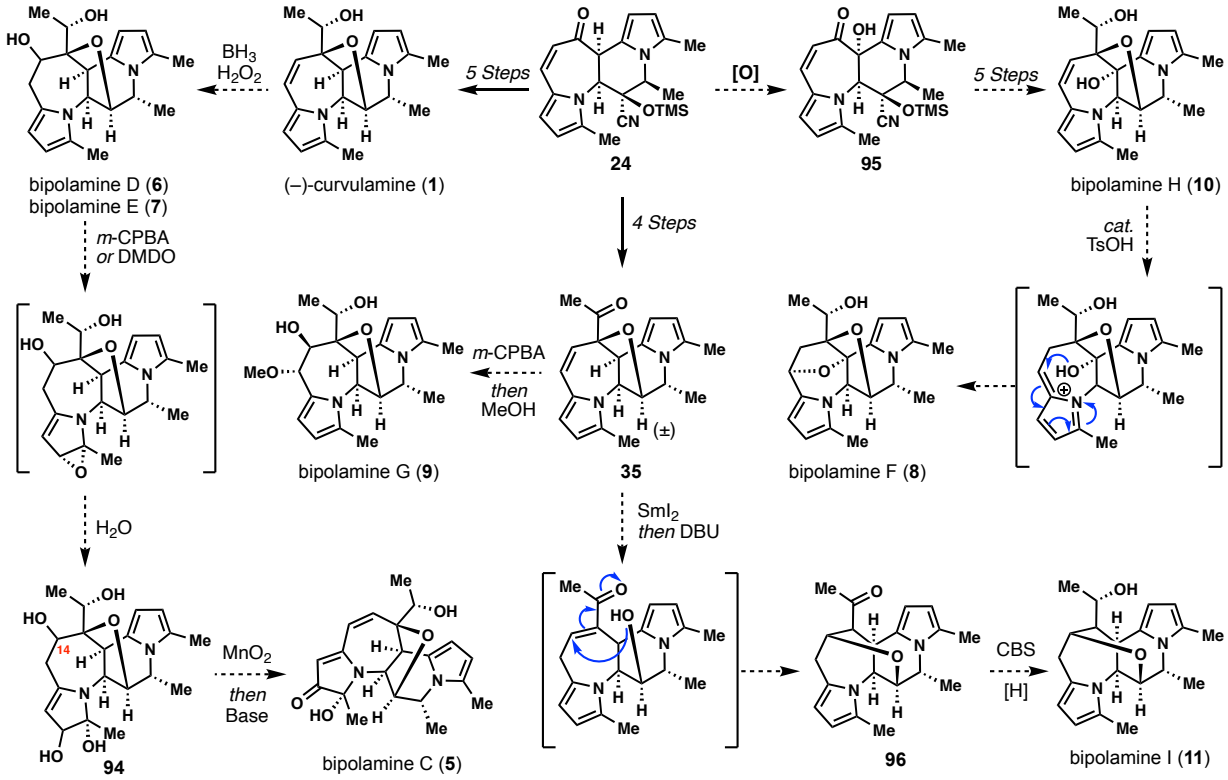



**Figure 3.3** Proposed strategy to access all *Bipolaris maydis* metabolites.

During our synthetic planning, we aimed to develop an approach that targets all the bipolamines from a common intermediate (Figure 3.3). While this strategy might sound routine within a family of natural products,[8] we anticipated significant challenges due to the notorious sensitivity of these pyrrole-containing compounds to acidic and oxidative conditions.[9] As discussed in previous chapters, these properties of electron-rich pyrrole units, such as the ones found in the bipolamine alkaloids, greatly limits the chemical reactions that can be used with these natural products, especially in an oxidative context.[10,11]

In our strategy, we anticipated that bipolamines D (**6**) and E (**7**) could be obtained from curvulamine (**1**) after hydroboration and oxidation.[12] Previously prepared methyl ketone **35** could be elaborated into bipolamine G (**9**) in two steps: an electrophilic epoxidation (*m*-CPBA) followed by an epoxide ring opening reaction with methanol.[13,14] Recognizing that bipolamine C (**5**) has an oxidized pyrrole unit, we envisioned a series of oxidation reactions could furnish this congener. Starting from **5**, *m*-CPBA mediated oxidation of the western pyrrole followed by hydrolysis of the newly formed epoxide ring, could produce allylic alcohol intermediate **94**. A chemoselective oxidation of **94** with $MnO_2$ and subsequent base-mediated elimination of the hydroxyl group at C-14 could produce bipolamine C (**5**).[15] To elaborate bipolamine E (**7**), we proposed a regioselective *α*-hydroxylation of **24** to make **95** followed by an analogous sequence of reactions as the one used to make **1**.[16] We anticipate that bipolamine F (**8**) could be obtained from bipolamine E (**7**) after an acid-catalyzed cyclization. Lastly, we designed a strategy to synthesize bipolamine I (**11**) from methyl ketone **35** in 3 steps: samarium diiodide mediated reduction of **35**, then a base-catalyzed intramolecular conjugate addition, and finally a stereodivergent reduction of ketone **96**.[17] Our proposal employs methyl ketone (**35**) as a key common synthetic intermediate thus we first investigated synthetic routes to produce large quantities of **35**.[18,19]

### 3.4 Scalable Synthetic Plan to Access Intermediate 35

During our campaigns toward curvulamine (**1**) and curindolizine (**2**),[19] we observed inconsistent results in the Barton-McCombie deoxygenation step. We noticed that the yield of the radical deoxygenation oscillated between 40% to 10% depending on the scale. Presumably, the substrate or the reaction conditions are very sensitive to the amount of oxygen used during the radical initiation step ($O_2$, $Et_3B$), which is hard to control accurately.[15] While one could have assumed that this accuracy problem could have been less chronic in larger scales, the issue still persisted. These results prompt us to look for a more robust and scalable strategy to access methyl ketone **35** from pentacycle **31**.

Beginning with pentacycle **31**, thermodynamic isomerization of the C-2 stereocenter proceeded to give an inseparable mixture of diastereomers **31** and **32** (NaOMe, MeOH). This diasteoromeric mixture was acetylated ($Ac_2O$, $Et_3N$, 4-DMAP) to yield **97** and the corresponding C-2 epimer. These diastereomers could be easily separated and heating 2-*epi*-**97** in sodium methoxide afforded a mixture containing **31** and **32**. Global reduction ($LiAlH_4$, THF) of pure **97** gave diol **98** in 85% yield. Additionally, we found that this transformation could be carried out in gram scale without any decrease in yield. Mesylation (MsCl, DMAP, $Et_3N$) of the more accessible secondary alcohol gave **99,** and intramolecular displacement of the activated alcohol by the tertiary alcohol in **99** (DBU, PhMe, Δ) followed by hydrolysis of the ethyl vinyl ether during the acidic work-up afforded methyl ketone **35**. Even though, this new synthetic route to **35** is one step longer compared to the previous Barton-McCombie deoxygenation sequence, we were able to more than double the overall yield and more easily obtain large quantities of **35** in a short amount of time. In addition, as we will discuss later, some of the lessons learned during this optimization campaign proved critical in the synthesis of bipolamine I (**11**).

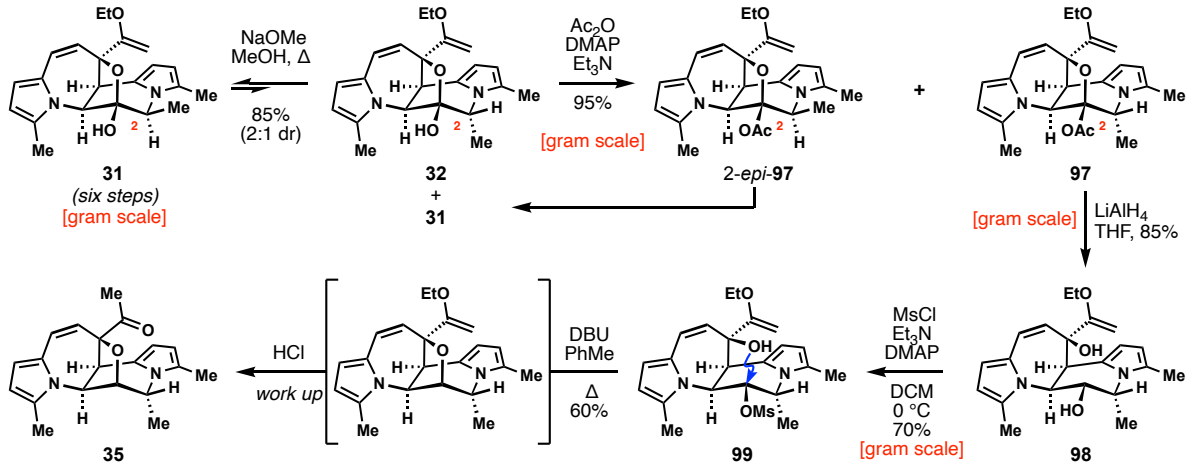



**Figure 3.3** Scalable route toward intermediate **35**.

## 3.5 The Total Syntheses of Bipolamines D and E

Having secured a scalable procedure to access methyl ketone **35** we then set our sights on the synthesis of bipolamine D (**6**) and bipolamine E (**7**). Stereodivergent reduction of **35** under previously discussed conditions ((*R*)-CBS, $BH_3$·THF) proceed to give **1** and 12-*epi*-**1** in a combined 90% yield.[18] Brown hydroboration-oxidation of **1** ($BH_3$•DMS *then* NaOH, $H_2O_2$) generated **5** and **6** in almost equimolar quantities. To rationalize the regioselectivity of this reaction, we analyzed the Muliken charge distribution of **35** (Chapter 2, section 1.4), but these data did not provide evidence of an electronic basis for the selectivity.[20,21] Perturbations of hydroboration regioselectivity and stereoselectivity by oxygen-containing substituents are well reported in the literature, however, and a mechanism that involves the hydroxyl group at C-12 directing the reaction could be operating, which would explain the observed regioselectivity.[22,23]

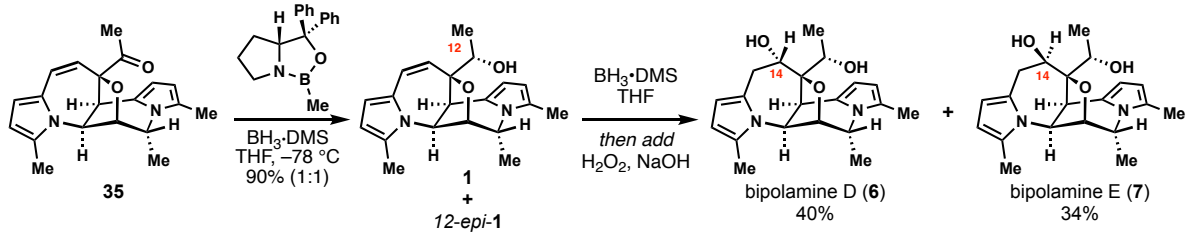



**Figure 3.4** Syntheses of bipolamines D and E.

## 3.6 The Total Synthesis of Bipolamine G

During our synthetic planning to access bipolamine G (**9**) (Figure 3.3), we proposed to transform **35** into **9** via an electrophilic epoxidation of the $\Delta_{14\text{-}15}$ alkene followed by opening of the oxirane ring with MeOH.[15] When we subjected **35** to *m*-CPBA at –35° C, we observed formation of methyl ether compound **100**, likely via a mechanism that involves oxidation of the eastern pyrrole (**101**). This formal benzylic oxidation product was

unexpected because during previous studies on **35** and its derivatives, we only observed reactivity at the western pyrrole unit.[18,19] For instance, during our synthetic studies of curindolizine (**2**), treatment of **35** with NIS in methanol at low temperatures gave **76** as the only product. While trying to further investigate the unexpected oxidation of **35**, we quickly recognized that **76** could be elaborated into bipolamine G (**9**) via solvolysis of the iodide atom at C-14. Methyl ether **76** was treated with silver (I) salts in a nitromethane-water mixture, which we hoped would generate a carbocation that could be intercepted by water.[24] Under these conditions however, instead of forming bipolamine G (**9**), we observed exclusive formation of aldehyde **102**, presumably formed via a semi pinacol-type rearrangement aided by the neighboring pyrrole. We then evaluated a one-electron approach to this transformation, but subjecting **76** to radical conditions ($Bu_3SnH$, $O_2$, AIBN) only afforded the reduction product. In a revised approach, dihydroxylation of **35** ($OsO_4$, NMO) was found to be productive, albeit with poor conversion due to decomposition upon prolongation of reaction time. Diol **103** proceeded to give substitution product **104** in 85% yield (MeOH, HCl), possibly via the initial formation of an azafulvenium ion, which is then trapped by methanol.[25] DIBAL reduction of **104** yielded nearly identical quantities of bipolamine G (**9**) and its C-12 epimer. Notably, during the synthesis of curvulamine (**1**), when compound **35** is treated to the same reduction conditions (DIBAL, DCM), primarily the C-12 epimer of the corresponding product is obtained.[18]

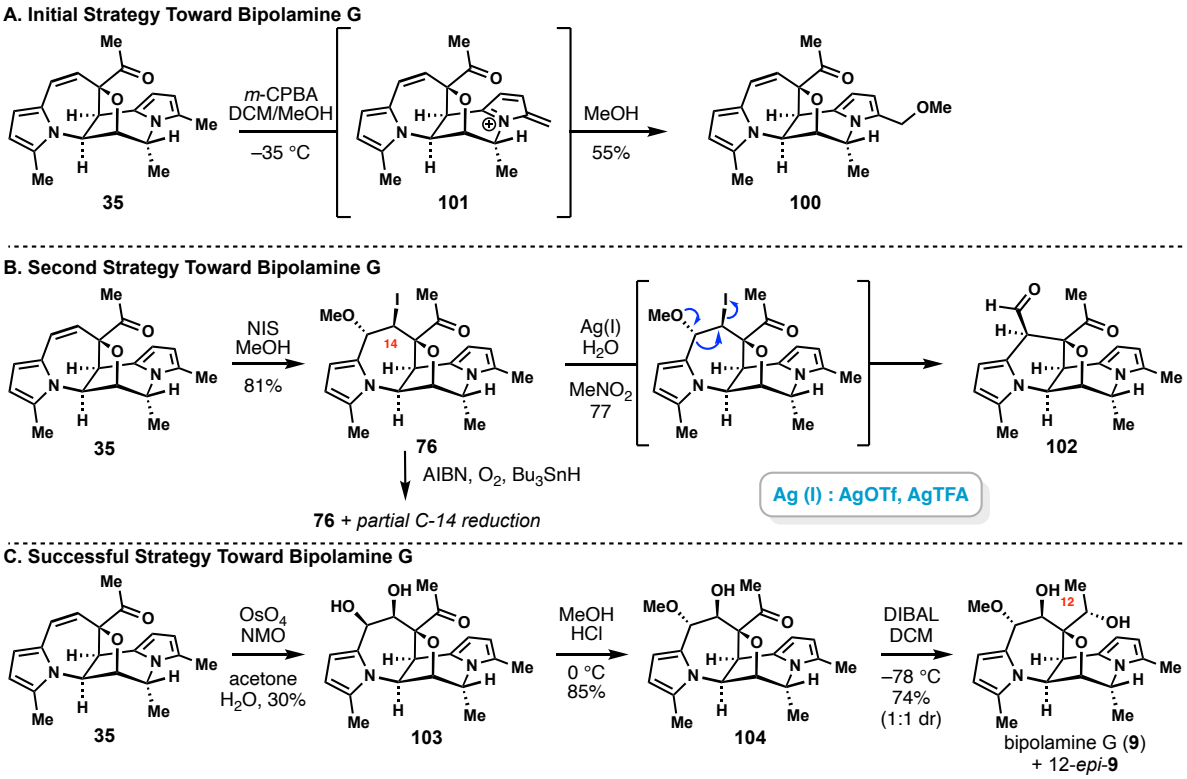



**Figure 3.5** Synthesis of bipolamine G. **3.5A.** Initial strategy toward **9** **3.5B** Second generation route toward **9** **3.5C** Successful synthesis of **9**

## 3.7 The Total Synthesis of Bipolamine I

After completing the synthesis of **9**, we directed our efforts toward bipolamine I (**11**), a topologically distinct molecule relative to its congeners. We rationalized that **11** could be elaborated from enone **105** via an intramolecular Michael addition and ketone reduction sequence. Enone intermediate **105** could be prepared from methyl ketone **35** via a reductive ring cleavage (Figure 3.6).[17]

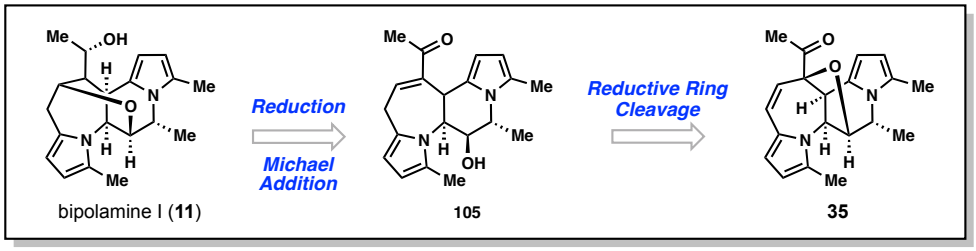
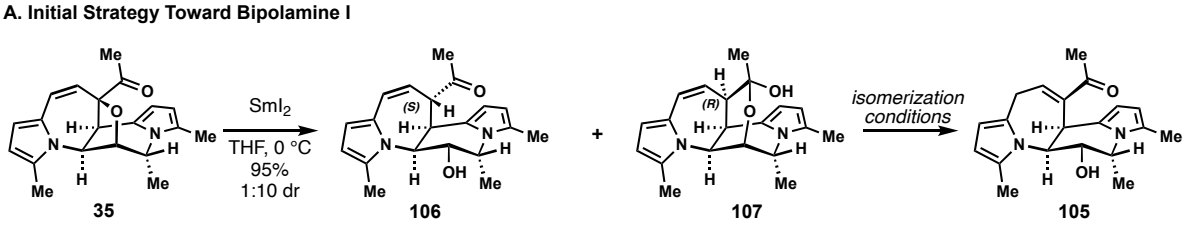



**Figure 3.6** Bipolamine I retrosynthetic analysis.

Exposing **35** to reductive conditions ($SmI_2$, THF) proceeded to smoothly cleave the C-O bond, but upon work-up, the extended samarium enolate yielded a 10:1 mixture of alkene **106** and hemiacetal **107** instead of the desired enone **105**. Different conditions were explored to isomerize the double bond into conjugation with the carbonyl group to obtain **105**. Ketone **106** was heated with *t*-BuOK in THF and at temperatures below 60




| Entry | Isomerization Conditions | Product |
|---|---|---|
| 1 | *t*-BuOK, THF, 25 °C → 60 °C | **106** |
| 2 | *t*-BuOK, THF, 60 °C → 100 °C | decomp. |
| 3 | DBU, PhMe, 130 °C | **106 + 107** |
| 4 | $RhCl_3 \cdot 6H_2O$, EtOH, 70 °C | decomp. |
| 5 | $PdCl_2(MeCN)_2$, DCM, 25 °C | decomp. |

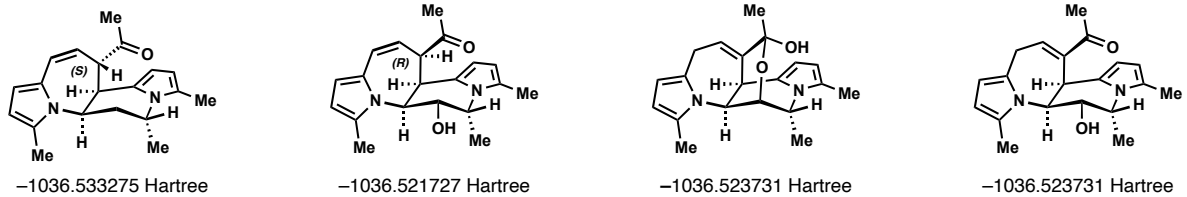



**Figure 3.7** Bipolamine I synthetic investigations. **3.7A** First generation strategy toward bipolamine I. **3.7B** DFT calculations of isomerization intermediates.

°C, only unreacted starting material was recovered (entry 1) while decomposition products were observed at elevated temperatures (entry 2). Heating **106** in the presence of DBU at refluxing temperatures resulted in isomers **106** and **107** (3:1 ratio). This result indicated that deprotonation is possible, but isomerization is unfavorable. Attempts to perform a metal-catalyzed isomerization with $RhCl_3 \cdot 6H_2O$ or $PdCl_2(MeCN)_2$ resulted in mixture of decomposition products (entry 4 and entry 5).[26-28] DFT calculations of the ground state energies of the optimized structures of **105** and **106** at the B3LYP/6-31 G (d,p) level of theory, informed us that alkene **106** is 5.98 kcal/mol lower in energy compared to enone **105**, supporting our results at attempting to carry out a thermodynamic isomerization.

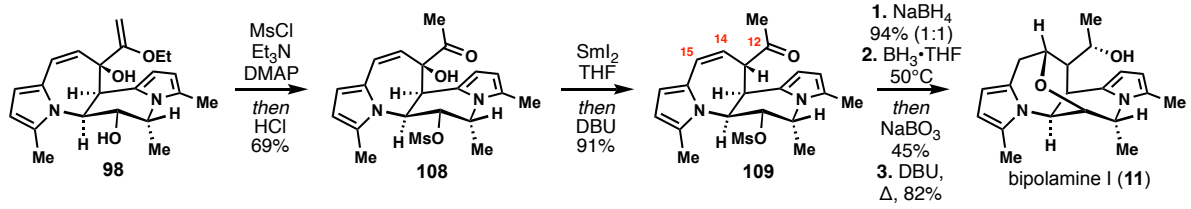



**Figure 3.8** Synthesis of bipolamine I.

Recognizing the smooth hydroboration of the $\Delta_{14\text{-}15}$ olefin during the synthesis of **5** and **6**, a revised strategy was devised (Figure 3.8). Starting from **98**, regioselective mesylation (MsCl, $Et_3N$, DMAP) with concomitant acidic hydrolysis of the enol ether afforded ketone **108**. Subsequent $SmI_2$ mediated single-electron reduction of **108** furnished the corresponding ketone product which was equilibrated to a single diastereomer (**109**) after addition of DBU. Methyl ketone **109** was transformed into bipolamine I (**11**) in three steps. First, **109** was reduced ($NaBH_4$, MeOH) to a separable mixture of C-12 epimers in a 1:1 ratio. Second, regioselective hydroboration oxidation ($BH_3 \cdot$THF *then* $NaBO_3$) of the $\Delta_{14\text{-}15}$ alkene yielded the desired isomer in good yields. Finally, DBU mediated intramolecular $SN_2$ at elevated temperatures proceeded to give bipolamine I (**11**).

## 3.8 Future Directions

Through our investigations, we have established efficient synthetic routes to several curvulamine type alkaloids. We are currently still investigating the synthesis of the syntheses of bipolamines C, E and F (Figure 3.3). So far, during our studies on the synthesis of bipolamine C (**5**) and E (**7**) we haven't observed oxidation of curvulamine (**1**) at C-5 or C-18/19 π-bond and selective oxidation at these positions is required for the synthesis of the remaining bipolamine congeners. Recently, we discovery conditions to selectively oxidize **24** at C-5, and we are investigating conditions to transform this intermediate into bipolamines E and F. We are concurrently investigating different strategies to synthesize bipolamine C from methyl ketone **35**.

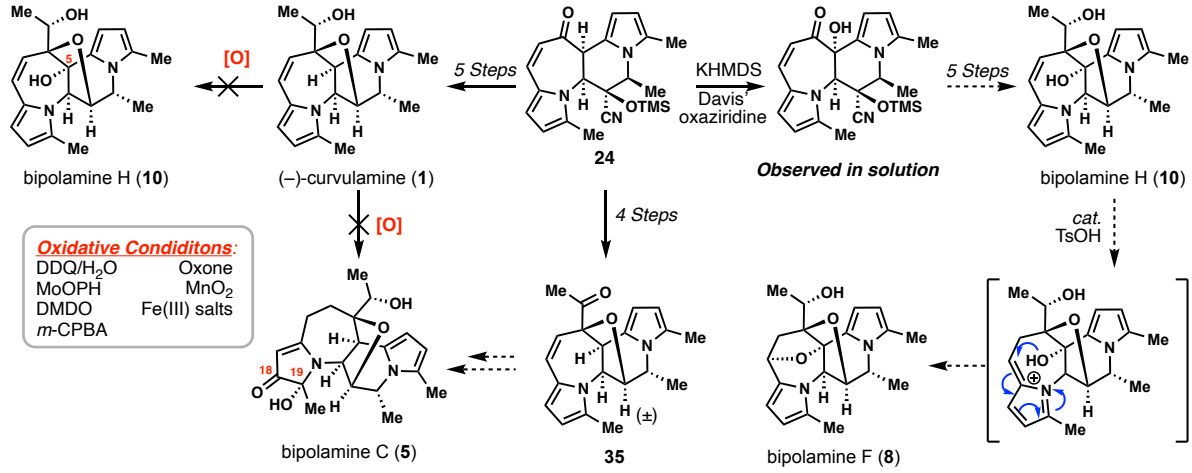



**Figure 3.9** Possible future synthetic strategies to access bipolamines C, H, and F.

## 3.9 Conclusion

This chapter has chronicled the chemistry of the electron-rich pyrrole natural products observed while investigating the synthesis of several curvulamine derivatives. Several novel bipolamine alkaloids have been synthesized, including **9** the most potent antibiotic in the family. This work lays the foundation for future mechanism of action studies of these molecules.

## 3.10 Distribution of Credit

Second-generation synthesis of methyl ketone **35** was performed by Jun Xuan and Paulo Andre Machicao Tello. The investigation and synthesis **5** and **6** were performed by Paulo Andre Machicao Tello with refinement from Professor Thomas J. Maimone. The synthesis of **9** and **11** were performed by Jun Xuan. Preliminary studies on the synthesis of **7** and **8** were performed by Paulo Andre Machicao Tello. Characterization of all compounds was completed by Paulo Andre Machicao Tello and Jun Xuan. We thank the NIH NIGMS (R01GM136945 to Thomas J. Maimone, and diversity supplement to Paulo Andre Machicao Tello) for financial support. We thank Dr. Hasan Celik and Dr. Jeffrey G. Pelton for nuclear magnetic resonance spectroscopic assistance (NIH grant GM68933). We also thank QB3/Chemistry Mass Spectrometry Facility scientist Dr. Zhongroui Zhou for mass spectrometry assistance.

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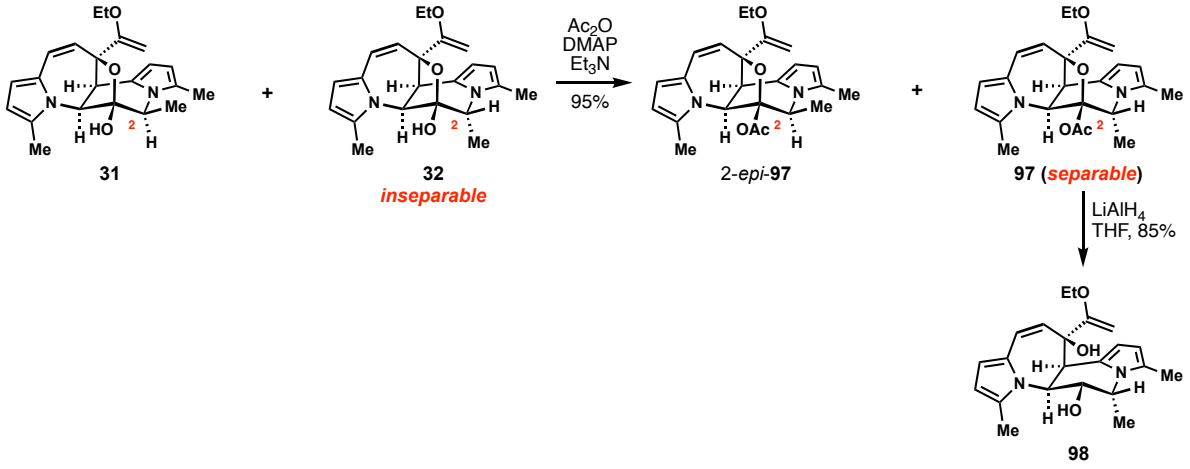
## 3.12 Experimental Procedures and Characterization Data

### 3.12.1 General Procedures

All reactions were performed in flame- or oven-dried glassware under a positive pressure of nitrogen or argon, unless otherwise noted. Air-and moisture-sensitive liquids were transferred via syringe. When indicated, solvents or reagents were degassed by sparging with argon for 10 min in an ultrasound bath at 25 °C. Volatile solvents were removed under reduced pressure rotary evaporation below 35 °C. Analytical and preparative thin-layer chromatography (TLC) were performed using glass plates pre-coated with silica gel (0.25-mm, 60-Å pore size, Merck TLC Silicagel 60 $F_{254}$) impregnated with a fluorescent indicator (254 nm). TLC plates were visualized by exposure to ultraviolet light (UV) and then were stained by submersion in an ethanolic anisaldehyde solution or ceric ammonium molybdate solution, followed by brief heating on a hot plate. Flash column chromatography was performed with silica gel purchased from Silicycle (SiliaFlash®, 60 Å, 230-400 mesh, 40-63 μm). Ethyl vinyl ether and 2-bromopropanic acid methyl ester were distilled over calcium hydride prior to use. NaHMDS solutions were purchased from Sigma. All other reagents were used as received from commercial sources, unless stated otherwise. Anhydrous tetrahydrofuran (THF), dichloromethane (DCM), methanol (MeOH), dimethylformamide (DMF), and toluene (PhMe) were obtained by passing these previously degassed solvents through activated alumina columns. Proton nuclear magnetic resonance ($^1$H NMR) spectra and carbon nuclear magnetic resonance ($^{13}$C NMR) spectra were recorded on Bruker AV-600 spectrometer at 23 °C. Proton chemical shifts are expressed as parts per million (ppm, δ scale) and are referenced to residual solvent ($CDCl_3$: δ 7.26, $C_6D_6$: δ 7.16), unless stated otherwise. Carbon chemical shifts are expressed as parts per million (ppm, δ scale) and are referenced to the solvent ($CDCl_3$: δ 77.16, $C_6D_6$: δ 128.06), unless stated otherwise. Data is represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, dd = doublet of doublets, ddd, doublet of doublet of doublet, dt = triplet of doublets, t = triplet, q = quartet, m = multiplet, br = broad), coupling constant (*J*) in Hertz (Hz), and integration. Infrared (IR) spectra were recorded on a Bruker Alpha FT- IR spectrometer as thin films and are reported in frequency of absorption ($cm^{-1}$). Only selected resonances are reported. High-resolution mass spectra (HRMS) were obtained by the mass spectrometry facility at the University of California, Berkeley using a Finnigan LTQFT mass spectrometer (Thermo Electron Corporation). X-ray diffraction data was collected at the Small Molecule X-ray Crystallography Facility (CheXray) at University of California, Berkeley using a Rigaku XtaLAB P200 equipped with a MicroMax 007HF rotating anode and Pilatus3 R 200K-A hybrid pixel array detector. Data were collected using CuKα radiation (λ = 1.5418 Å).

### 3.12.2 Experimental Procedures and Tabulated Characterization Data

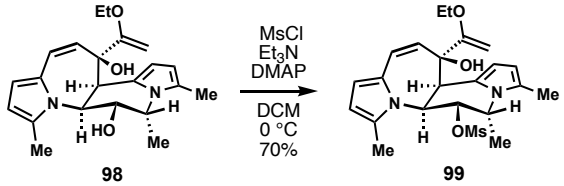



**Tetracyclic diol 13**: To a 100 mL round bottom flask containing pentacyclic bispyrrole **31** and **32** (1.5 g, 4.10 mmol, 1.0 equiv.) was added $CH_2Cl_2$ (30 mL). To the stirring solution was added $Ac_2O$ (577 $\mu$L , 6.15 mmol, 1.5 equiv.), DMAP (500 mg, 4.10 mmol, 1.0 equiv.) and $Et_3N$ (1.71 ml, 12.3 mmol, 3.0 equiv.). Upon consumption of the starting material as indicated by TLC, the reaction mixture was quenched with saturated *aq*. $NaHCO_3$ (50 mL) and extracted with $CH_2Cl_2$ (3 x 50 mL). The combined organic layers were washed with brine (20 mL), dried over $Na_2SO_4$, and concentrated *in vacuo*. The resulting crude residue was purified by column chromatography (5% EtOAc in hexanes) to afford **97** (1.12 g, 2.73 mmol) and 2-*epi*-**97** (477 mg,1.17 mmol).

To a reaction tube containing 2-*epi*-**12** (477 mg, 1.17 mmol, 1.0 equiv.) was added NaOMe (317 mg, 5.85 mmol, 5.0 equiv.). The reaction tube was sealed and anhydrous MeOH (20 mL) was then added, the sealed reaction vessel was heated at 90 °C for 4 hours. The reaction mixture was then cooled to room temperature quenched with saturated. *aq*. $NH_4Cl$ solution (50 mL). The solution was extracted with EtOAc (3 x 30 mL) and the combined organic layers were washed with brine (50 mL), dried over $Na_2SO_4$, filtered, and concentrated *in vacuo*. The resulting crude residue was purified by column chromatography (0% EtOAc in hexanes → 20% EtOAc in hexanes) to afford an inseparable mixture of pentacyclic bispyrrole **11** and 2-*epi*-**11** (2.3:1 ratio) (367 mg, 0.99 mmol, 85%) as a brown foam. To a 100 mL round bottom flask containing **97** (1.12 g, 2.73 mmol, 1.0 equiv.) was added THF (30 mL). To the vigorously stirring solution was added $LiAlH_4$ (1.0 M in THF, 8.19 mL, 8.19 mmol, 3.0 equiv.) dropwise. Upon consumption of the starting material as indicated by TLC, the reaction mixture was cooled to 0 °C and quenched with saturated *aq*. Rochelle salt (30 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (20 mL), dried over $Na_2SO_4$, and concentrated *in vacuo*. The resulting crude residue was purified by column chromatography (10% EtOAc in hexanes) to afford tetracyclic diol **98** (854 mg, 2.32 mmol, 85%) as a yellow oil.

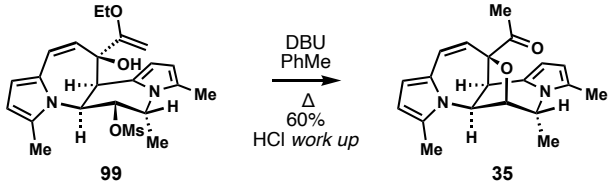
**TLC:** $R_f$ = 0.5 (30% EtOAc in hexanes).**$^1$H NMR** (600 MHz, Benzene-$d_6$) δ 6.34 ( d, $J$ = 12.5 Hz, 1H), 6.15 (d, $J$ = 3.5 Hz, 1H), 6.03 –5.99 (m, 2H), 5.93 (dd, $J$ = 3.5, 0.9 Hz,

1H), 5.51 (d, *J* = 12.4 Hz, 1H), 5.44 (ddd, *J* = 11.4, 6.1, 3.5 Hz, 1H), 4.85 (dd, *J* = 11.4, 3.8 Hz, 1H), 4.69 (d, *J* = 3.7 Hz, 1H), 4.45 (d, *J* = 2.4 Hz, 1H), 4.36 (p, *J* = 6.4 Hz, 1H), 3.95 (d, *J* = 2.4 Hz, 1H), 3.48 – 3.37 (m, 2H), 2.00 (s, 3H), 1.97 (s, 3H),1.70 (s, 1H), 1.64 (d, *J* = 2.5 Hz, 1H), 1.21 (d, *J* = 6.5 Hz, 3H), 0.92 (t, *J* = 7.0 Hz, 3H) **$^{13}$C NMR** (151 MHz, $C_6D_6$) δ 167.1, 134.8, 129.4, 128.4, 126.2, 124.9, 120.5, 112.9, 108.4, 108.2, 106.8, 81.4, 79.9, 64.9, 63.8, 55.8, 54.0, 45.4, 15.4, 14.3, 13.6, 12.3. **IR** (thin film) $\nu_{max}$ ($cm^{-1}$): 3451, 2977, 2924, 1710, 1616, 1415, 1239, 1016, 871, 773. 748. **HRMS** (m/z): (ESI) calcd. for $C_{22}H_{29}N_2O_3$ $[M+H]^+$ m/z: 369.2173, found 369.2174.



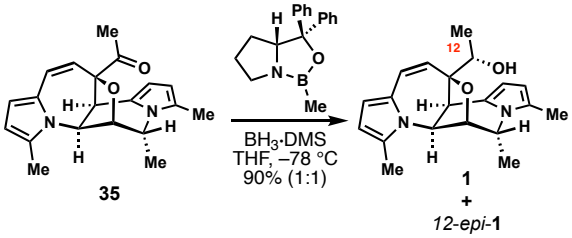

**Mesylate 99**: To a 100 mL round bottom flask containing tetracyclic diol **98** (500 mg, 1.36 mmol, 1.0 equiv.) was added $CH_2Cl_2$ (30 mL). The resulting mixture was cooled to 0 °C, $Et_3N$ (567 µL,4.08 mmol, 3.0 equiv.), MsCl (116 µL, 1.5 mmol, 1.1 equiv.) and DMAP (166 mg, 1.36 mmol,1.0 equiv.) were added dropwise sequentially. The resulting mixture was warmed to room temperature. Upon consumption of the starting material as indicated by TLC, the reaction mixture was quenched with saturated aq. $NaHCO_3$ (30 mL) and extracted with EtOAc (3 x 30mL). The combined organic layers were washed with brine (20 mL), dried over Na2SO4, and concentrated in vacuo. The resulting crude product was purified by column chromatography (10% EtOAc in hexanes) to afford mesylate **99** (443 mg, 0.95 mmol, 70%) as a white solid.

**TLC:** $R_f$ = 0.6 (30% EtOAc in hexanes). **$^1$H NMR** (600 MHz, Chloroform-*d*) δ 6.30 (d *J* = 12.5 Hz, 1H), 6.17 (dd, *J* = 11.8, 6.3 Hz, 1H), 6.09 (d, *J* = 3.6 Hz, 1H), 5.94 (d, *J* = 3.5 Hz, 1H), 5.89 (d, *J* = 3.4 Hz, 1H), 5.70 (d, *J* = 3.4 Hz, 1H), 5.26 (d, *J* = 12.4 Hz, 1H), 5.04 (dd, *J* = 11.8, 3.7 Hz, 1H), 4.82 (p, *J* = 6.5 Hz, 1H), 4.44 (d, *J* = 3.7 Hz, 1H), 4.19 (d, *J* = 2.8 Hz, 1H), 4.01 (d, *J* = 2.8 Hz, 1H), 3.84 – 3.70 (m, 2H), 2.44 (s, 3H), 2.29 (s, 3H), 2.28 (s, 3H), 1.51 (s, 1H), 1.50 (d, *J* = 6.9 Hz, 3H), 1.30 (t, *J* = 7.0 Hz, 3H). **$^{13}$C NMR** (151 MHz, $CDCl_3$) δ 165.9, 134.8, 129.1, 128.8, 125.1, 124.4, 120.0, 113.0, 108.5, 108.2, 106.7, 81.4, 79.7, 74.5, 63.8, 53.4, 53.0, 44.2, 36.6, 16.6, 14.5, 13.7, 12.6. **IR** (thin film) $\nu_{max}$ ($cm^{-1}$): 3441, 2924, 2854, 1665, 1607, 1362, 1299, 1179, 885, 758, 406. **HRMS** (m/z): (ESI) calcd. for $C_{23}H_{31}N_2O_5S$ $[M+H]^+$ m/z: 447.1948, found 447.1947.




**Ketone 35**: To a reaction tube containing mesylate **99** (300 mg, 0.67 mmol, 1.0 equiv.) was added PhMe (20 mL) and DBU (100 µL, 0.67 mmol, 1.0 equiv.). The resulting mixture was heated up to 120 °C. Upon consumption of the starting material as indicated by TLC, the reaction mixture was cooled to 25 °C followed by the addition of aq. 1 M HCl (5 mL).

Upon consumption of the starting material as indicated by TLC, the reaction mixture was quenched with saturated aq. $NH_4Cl$ (10 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over $Na_2SO_4$, and concentrated in vacuo. The resulting crude residue was purified by column chromatography (20% EtOAc in hexanes) to afford ketone **35** (186 mg, 0.57 mmol, 86%) as a white solid. **TLC**: $R_f$ = 0.5 (40% EtOAc in hexanes). **$^1$H NMR** (600 MHz, Benzene-*$d_6$*) δ 6.28 (d *J* = 11.5 Hz, 1H), 6.15 (d, *J* = 3.6 Hz, 1H), 5.94 (dd, *J* = 3.5, 0.9 Hz, 1H), 5.87 (dd, *J* = 3.4, 1.0 Hz, 1H), 5.77 (d, *J* = 3.4 Hz, 1H), 5.74 (d, *J* = 11.5 Hz, 1H), 4.46 (br s, 1H), 4.14 (br s, 1H), 3.72 (br s, 1H), 3.69 (dq, *J* = 6.7, 2.1 Hz, 1H), 1.83 (d, *J* = 0.9 Hz, 3H), 1.73 (s, 3H), 1.53 (s, 3H), 0.73 (d, *J* = 6.7 Hz, 3H). **$^{13}$C NMR** (150.9 MHz, $C_6D_6$) δ 209.7, 132.8, 130.6, 128.6, 127.4, 124.0. 121.6, 114.5, 109.0. 108.9, 106.3, 94.0, 90.5, 60.0, 56.7, 46.1, 25.2, 19.1, 13.4, 12.3. **IR** (thin film) $\nu_{max}$ ($cm^{-1}$): 2972, 2932, 1741, 1682, 1640, 1456, 1378, 1214, 1071, 786, 734. **HRMS** (m/z): (ESI) calcd. for $C_{20}H_{23}O_2N_2$ $[M+H]^+$: 323.1754, found 323.1756.

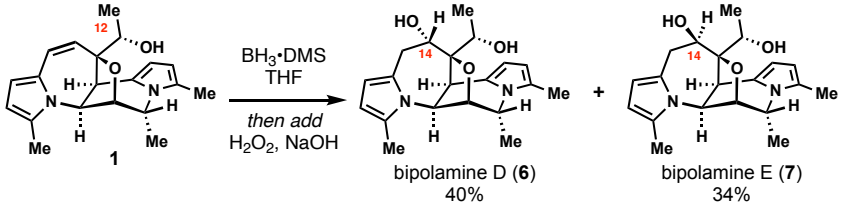



**Curvulamine (1)**: In a $N_2$ filled glovebox, a reaction tube was charged with (*R*)-(+)-2-methyl-CBS-oxazaborolidine (86 mg, 0.31 mmol, 1.0 equiv.). The reaction tube was sealed and brought out of the glovebox under inert atmosphere. $CH_2Cl_2$ (2.0 mL) was added followed by $BH_3$•DMS (60 µL, 0.62 mmol, 2.0 equiv.) and the mixture stirred for 15 minutes. Ketone **35** (100 mg, 0.31 mmol, 1.0 equiv.) was dissolved in $CH_2Cl_2$ (2.0 mL) and added dropwise to the reaction mixture. Additional $CH_2Cl_2$ (1.5 mL) was used to render the transfer quantitative. Upon completion of the reaction as indicated by TLC, saturated aq. $NH_4Cl$ solution (5 mL) was added, and the mixture stirred for 5 minutes. The biphasic mixture was poured into a separatory funnel and the organic layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over $Na_2SO_4$, filtered, and concentrated in vacuo. The resulting crude residue was purified by preparative TLC (50% Et2O in hexanes) to afford curvulamine **1** (46 mg, 0.14 mmol, 45%) and 12-*epi*-**1** (44 mg, 0.14 mmol, 45%) both as white solids.

curvulamine **(1)**:
**TLC**: $R_f$ = 0.4 (40% EtOAc in hexanes). **$^1$H NMR** (600 MHz, $CDCl_3$) δ 6.45 (d, *J* =11.6 Hz, 1H), 6.13 (d, *J* = 3.6 Hz, 1H), 5.94 (br d, *J* = 3.6 Hz, 1H), 5.93 (d, *J* = 3.4 Hz, 1H), 5.92 (d, *J* = 3.4 Hz, 1H), 5.72 (d, *J* = 11.6 Hz, 1H), 4.94 (br, s, 1H), 4.50 (br, s, 1H), 4.21 (qd, *J* = 6.7, 1.9 Hz, 1H), 3.95 (br, s, 1H), 2.67 (br s, 1H), 2.31 (br s, 3H), 2.29 (br s, 3H), 1.51 (d, *J* = 6.7 Hz, 3H), 1.24 (d, *J* = 6.4 Hz, 3H). **$^{13}$C NMR** (151 MHz, $CDCl_3$) δ 132.4,129.8, 128.5, 124.2, 119.7, 113.4, 108.5 103.5, 89.4, 89.0, 70.2, 60.3, 57.4, 44.9, 19.5, 17.3, 13.8, 12.8. **IR** (thin film) $\nu_{max}$ ($cm^{-1}$): 3466, 2972, 2925, 3852, 1643, 1425, 1393, 1322,

1301, 1044, 1011, 763. **HRMS** (m/z): (ESI) calcd. for $C_{20}H_{24}O_2N_2Na$ $[M+Na]^+$: 347.1730, found 347.1731.

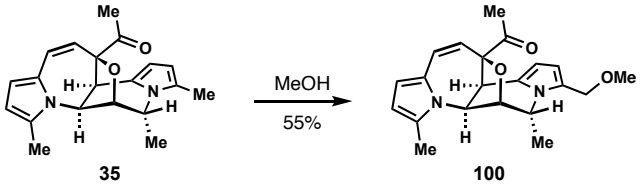
12-epi-**1** :
TLC: $R_f$ = 0.2 (40% EtOAc in hexanes). **$^1$H NMR** (600 MHz, $CDCl_3$) δ 6.41(d, *J* =11.7 Hz, 1H), 6.10 (d, *J* = 3.6 Hz, 1H), 5.91 (dd, *J* = 3.6, 0.9 Hz, 1H), 5.86 (dd, *J* = 3.4, 1.0 Hz, 1H), 5.79 (d, *J* = 3.4 Hz, 1H), 5.75 (d, *J* = 11.7 Hz 1H), 4.90 (br, s, 1H), 4.56 (br, s, 1H), 4.23 (qd, *J* = 6.7, 2.1 Hz, 1H), 3.71 (br, s, 1H), 2.71 (q, *J* = 6.3 Hz, 1H), 2.27 (br s, 3H), 2.26 (br s, 3H), 2.05 (d, *J* = 2.2 Hz, 3H), 1.48 (d, *J* = 6.7 Hz, 3H), 1.10 (d, *J* = 6.3 Hz, 3H). 13C NMR (151 MHz, $CDCl_3$) δ 132.6; 130.3, 128.4, 128.0, 124.1, 118.9, 113.5, 108.5, 107.2, 105.0, 90.6, 89.4, 89.1, 72.0, 61.0, 57.6, 43.7, 19.4, 16.9, 13.8, 12.8. **IR** (thin film) $\nu_{max}$ ($cm^{-1}$): 3468, 2925, 1644, 1415, 1299, 1077, 776, 670. HRMS (m/z): (ESI) calcd. for $C_{20}H_{24}O_2N_2Na$ $[M+Na]^+$: 347.1730, found 347.1731.



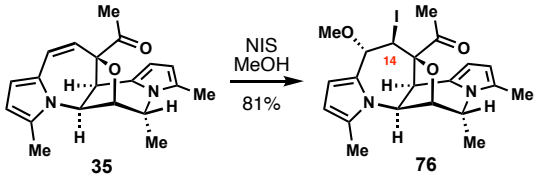

**Bipolamine D (6) and bipolamine E (7)**: To a reaction tube containing curvulamine **(1)** (5.0 mg, 0.015 mmol, 1.0 equiv.) and THF (0.8 mL) was added $BH_3$•DMS (10.0 µL, 0.020 mmol, 1.3 equiv.) at 25 °C. The resulting mixture was stirred at 25 °C for 3 hours and then cooled down to 0 °C. At this point, aq. 1 M NaOH ( 23.1 µL, 0.023 mmol, 1.5 equiv.) and 50% $H_2O_2$ (4.4 µL, 0.077 mmol, 5 equiv.) were added to the reaction mixture. Upon consumption of the starting material as indicated by TLC, the reaction mixture was quenched with saturated aq. $NaHCO_3$ (3 mL) and extracted with $CH_2Cl_2$ (3 x 5 mL). The combined organic layers were washed with brine (5 mL), dried over $Na_2SO_4$, and concentrated in vacuo. The resulting crude residue was purified by preparative TLC (50% EtOAc in hexanes) to afford bipolamine D **(6)** (2.1 mg, 0.0061 mmol, 40%) as a white solid and bipolamine E **(7)** (1.8 mg, 0.0053 mmol, 34%) as a white solid.

Bipolamine D:
TLC: $R_f$ = 0.35 (50% EtOAc in hexanes). **$^1$H NMR** (600 MHz, Acetone-*d*$_6$) δ 5.82 (d *J* = 3.3 Hz, 1H), 5.75 (br d, *J* = 3.3 Hz, 1H), 5.70 (br d, *J* = 3.3 Hz, 1H), 5.67 (br d, *J* = 3.3 Hz, 1H), 4.84 (s, 1H), 4.38 (s, 1H), 4.36 (s, 1H) , 4.32 (qd, *J* = 6.6, 2.3 Hz, 1H), 4.04 (d, *J* = 4.3 Hz, 1H), 3.91 (s, 1H), 3.73 (d, *J* = 1.9 Hz, 1H), 3.09 (d, *J* = 15.6 Hz, 1H), 2.93 (qd, *J* = 6.4, 4.5 Hz, 1H), 2.87 (dd, *J* = 15.6, 5.0 Hz, 1H), 2.24 (s, 3H), 2.21 (s, 3H), 1.48 (d, *J* = 6.6 Hz, 3H), 1.12 (d, *J* = 6.4 Hz, 3H). **$^{13}$C NMR** (151 MHz, Acetone) δ 131.5, 128.8, 128.6, 128.3, 108.8, 107.8, 107.0, 105.5, 91.8, 85.6, 72.3, 68.3, 59.6, 59.0, 43.7, 31.4, 19.2, 18.8, 13.5, 12.8. IR (thin film) $\nu_{max}$ ($cm^{-1}$): 3520, 2925, 2855, 2150, 1465, 1298, 1022, 755, 619, 429. HRMS (m/z): (ESI) calcd. for $C_{20}H_{27}N_2O_3$ $[M+H]^+$ m/z: 343.2016, found 343.2016.

Bipolamine E:
TLC: $R_f$ = 0.32 (50% EtOAc in hexanes). **$^1$H NMR** (600 MHz, Acetone-*d*$_6$) δ 5.92 (d, *J* = 3.4 Hz, 1H), 5.78 (d, *J* = 3.4 Hz, 1H), 5.74 (d, *J* = 3.3 Hz, 1H), 5.67 (d, *J* = 3.3 Hz, 1H), 4.91 (s, 1H), 4.35 – 4.32 (m, 1H), 4.30 (br s, 1H), 4.30 – 4.29 (m, 1H), 4.22 (br s, 1H), 3.07 (d, *J* = 15.7 Hz, 1H), 3.03 (d, *J* = 4.2 Hz, 1H), 2.95 (d, *J* = 9.8 Hz, 1H), 2.82 (d, *J* = 4.0 Hz, 1H), 2.53 (q, *J* = 6.5 Hz, 1H), 2.26 (s, 3H), 2.26 (s, 3H), 1.55 (d, *J* = 6.7 Hz, 3H), 1.08 (d, *J* = 6.5 Hz, 3H). **$^{13}$C NMR** (151 MHz Acetone) δ 131.4, 128.7, 128.6, 128.2, 108.7, 107.7, 107.0, 105.5, 91.7, 85.5, 72.2, 68.2, 59.5, 59.0, 43.6, 31.3, 19.1, 18.7, 13.4, 12.8. (IR thin film) $\nu_{max}$ ($cm^{-1}$): 3575, 2925, 2854, 2106, 1445, 1296, 1048, 802, 760, 621, 429. HRMS (m/z): (ESI) calcd. for $C_{20}H_{27}N_2O_3$ $[M+H]^+$ m/z: 343.2016, found 343.2015.

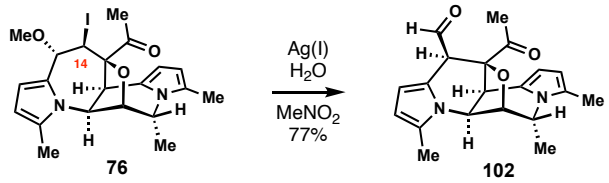



**Formal benzylic oxidation product 100**: To a reaction tube containing ketone **35** (5.0 mg, 0.016 mmol, 1.0 equiv.) was added $CH_2Cl_2$/MeOH (1:1, 1 mL). The resulting mixture was cooled to –35 °C followed by the addition of *m*-CPBA (purified1, 2.8 mg, 0.016 mmol, 1.0 equiv.). Upon consumption of the starting material as indicated by TLC, the reaction mixture was quenched with saturated aq. $Na_2SO_3$ (2 mL) and extracted with EtOAc (3 x 3 mL). The combined organic layers were washed with brine (3 mL), dried over $Na_2SO_4$, and concentrated in vacuo. The resulting crude residue was purified by column chromatography (30% EtOAc in hexanes) to afford ketone formal benzylic oxidation product **100** (3.0 mg, 0.0088 mmol, 55%) as a yellow oil.
**TLC**: $R_f$ = 0.3 (40% EtOAc in hexanes). **$^1$H NMR** (600 MHz, Benzene-*d*$_6$) δ 6.28 (d *J* = 11.5 Hz, 1H), 6.15 (d, *J* = 3.6 Hz, 1H), 6.03 (d, *J* = 3.5 Hz, 1H), 5.92 (dd, *J* = 3.6, 0.9 Hz, 1H), 5.77 (d, *J* = 3.5 Hz, 1H), 5.71 (d, *J* = 11.5 Hz, 1H), 4.48 (s, 1H), 4.23 (qd, *J* = 6.7, 2.0 Hz, 1H), 4.18 (d, *J* = 12.8 Hz, 1H), 4.16 (dd, *J* = 2.0, 1.1 Hz, 1H), 3.95 (d, *J* = 12.8 Hz, 1H), 3.72 (s, 1H), 3.01 (s, 3H), 1.69 (s, 3H), 1.62 (s, 3H), 0.99 (d, *J* = 6.7 Hz, 3H). **$^{13}$C NMR** (151 MHz, $C_6D_6$) δ 209.9, 132.9, 130.7, 130.5, 128.3, 124.1, 121.5, 114.5, 112.5, 109.0, 106.2, 94.2, 90.6, 66.4, 59.9, 57.6, 56.7, 46.1, 25.6, 19.2, 13.4. **IR** (thin film) $\nu_{max}$ ($cm^{-1}$): 3495, 3286, 2953, 2870, 1702, 1471, 1169, 901, 726. **HRMS** (m/z): (ESI) calcd. for $C_{21}H_{25}N_2O_3$ $[M+H]^+$ m/z: 353.1860, found 353.1861.

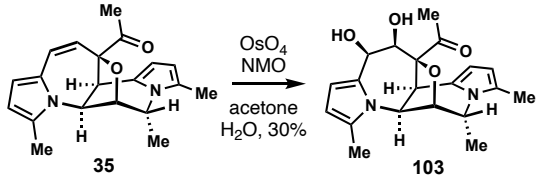



**Iodohydrin 76**: To a reaction tube containing ketone **35** (10.0 mg, 0.032 mmol, 1.0 equiv.) was added MeOH (2 mL). The resulting mixture was cooled to 0 °C followed by the slow addition of NIS (7.2 mg, 0.032 mmol, 1.0 equiv.) in THF (0.5 mL). Upon consumption of

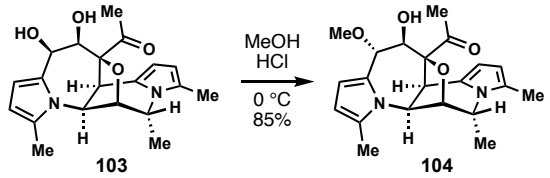
the starting material as indicated by TLC, the reaction mixture was quenched with saturated aq. $NaHCO_3$ (3 mL) and extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine (3 mL), dried over $Na_2SO_4$, and concentrated in vacuo. The resulting crude residue was purified by column chromatography (10% EtOAc in hexanes) to afford iodohydrin **76** (12.5 mg, 0.026 mmol, 81%) as a yellow oil.
**TLC**: $R_f$ = 0.6 (40% EtOAc in hexanes). **$^1$H NMR** (700 MHz, Benzene-*d*$_6$) δ 6.18 (d, *J* = 3.4 Hz, 1H), 6.00 (d, *J* = 3.3 Hz, 1H), 5.80 (t, *J* = 3.3 Hz, 3H), 5.24 (s, 1H), 4.66 (d, *J* = 2.3 Hz, 1H), 4.44 (s, 1H), 3.76 (s, 1H), 3.65 (q, *J* = 6.9 Hz, 1H), 2.93 (s, 3H), 1.78 (s, 3H), 1.73 (s, 3H), 1.58 (s, 3H), 0.67 (d, *J* = 6.7 Hz, 3H). **$^{13}$C NMR** (151 MHz, $C_6D_6$) δ 209.5*, 131.2, 127.4, 127.1, 125.5, 114.4, 109.3, 108.2, 107.1, 96.0, 88.2, 83.8, 59.9, 56.1, 55.4, 44.5, 38.2, 24.9, 18.8, 13.4, 12.2. *see HSQC **IR** (thin film) $\nu_{max}$ ($cm^{-1}$): 3444, 2922, 2851, 1713, 1414, 1351, 1301, 1219, 1040, 765, 597. HRMS (m/z): (ESI) calcd. for $C_{21}H_{25}N_2O_3INa$ $[M+Na]^+$ m/z: 503.0802, found 503.0803.



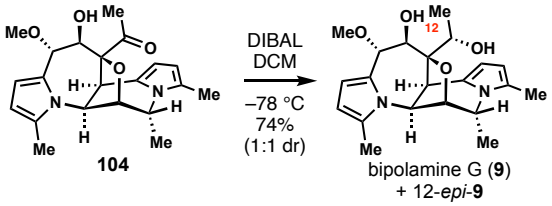

**Aldehyde 102**: To a reaction tube containing iodohydrin **76** (10.0 mg, 0.021 mmol, 1.0 equiv.) was added $MeNO_2$ (2 mL). The resulting mixture was cooled to 0 °C followed by the addition of $H_2O$ (3.8 µL, 0.21 mmol, 10 equiv.) and AgTFA (7.0 mg, 0.032 mmol, 1.5 equiv.). Silver iodide began to precipitate immediately. Upon consumption of the starting material as indicated by TLC, the reaction mixture was quenched with saturated aq. $NaHCO_3$ (3 mL) and extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine (3 mL), dried over $Na_2SO_4$, and concentrated in vacuo. The resulting crude residue was purified by column chromatography (30% EtOAc in hexanes) to afford aldehyde **102** (5.5 mg, 0.016 mmol, 77%) as a yellow solid.
**TLC**: $R_f$ = 0.3 (40% EtOAc in hexanes). **$^1$H NMR** (600 MHz, Benzene-*d*$_6$) δ 9.52 (s, 1H), 6.04 – 6.01 (m, 2H), 5.87 (dd, *J* = 3.4, 1.0 Hz, 1H), 5.80 (d, *J* = 3.5 Hz, 1H), 4.50 (s, 1H), 4.04 (d, *J* = 1.4 Hz, 1H), 3.64 (qd, *J* = 6.7, 2.6 Hz, 1H), 3.51 (d, *J* = 2.7 Hz, 1H), 2.87 (s, 1H), 1.87 (s, 3H), 1.81 (d, *J* = 0.9 Hz, 3H), 1.72 (s, 3H), 0.59 (d, *J* = 6.7 Hz, 3H). **$^{13}$C NMR** (151 MHz, $C_6D_6$) δ 208.9, 197.1, 127.4, 126.0, 125.1, 120.7, 108.6, 108.0, 106.6, 106.5, 92.4, 86.2, 56.4, 54.6, 53.4, 45.7, 26.3, 18.3, 11.9, 11.5. **IR** (thin film) $\nu_{max}$ ($cm^{-1}$): 3479, 2924, 2159, 1725, 1635, 1222, 773, 558, 512. **HRMS** (m/z): (ESI) calcd. for $C_{20}H_{23}N_2O_3$ $[M+H]^+$ m/z: 339.1703, found 339.1708.



**Diol 103**: To a reaction tube containing ketone **35** (30.0 mg, 0.093 mmol, 1.0 equiv.) and $H_2O$/acetone (1/4, 5 mL) was added $OsO_4$ (2.5 wt% in *t*-BuOH, 95.2 mg, 0.0093 mmol, 10 mol%) and NMO (50 wt% in H2O, 22.0 mg, 0.093 mmol, 1.0 equiv.). The resulting mixture was stirred at 25 °C for 4 hours and quenched with saturated aq. $Na_2SO_3$ (3 mL) and extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine (5 mL), dried over $Na_2SO_4$ and concentrated in vacuo. The resulting crude product was purified by column chromatography (100% EtOAc in hexanes) to afford ketone **35** (16.0 mg, 0.050 mmol) as a white solid and diol **103** (10.1 mg, 0.028 mmol, 30% yield, 65% brsm) as a yellow oil.
**TLC**: $R_f$ = 0.2 (100% EtOAc in hexanes). **$^1$H NMR** (600 MHz, Benzene-*d*$_6$) δ 6.30 (d, *J* = 3.5 Hz, 1H), 5.93 (dd, *J* = 3.4, 0.9 Hz, 1H), 5.84 (dd, *J* = 3.4, 1.0 Hz, 1H), 5.67 (d, *J* = 3.5 Hz, 1H), 4.84 (dd, *J* = 8.8, 3.9 Hz, 1H), 4.34 (s, 1H), 4.26 (dt, *J* = 8.7, 3.4 Hz, 1H), 3.75 (q, *J* = 5.8, 5.2 Hz, 1H), 3.67 (s, 1H), 3.46 (d, *J* = 9.7 Hz, 1H), 3.26 (d, *J* = 9.2 Hz, 1H), 2.81 (s, 1H), 1.82 (s, 3H), 1.79 (s, 3H), 1.65 (s, 3H), 0.72 (d, *J* = 6.6 Hz, 3H). **$^{13}$C NMR** (151 MHz, $C_6D_6$) δ 205.3*, 130.5, 129.7, 127.6, 127.4, 113.1, 108.6, 107.9, 106.6, 101.1, 85.8, 73.4, 70.2, 58.2, 56.2, 46.5, 26.7, 18.6, 13.2, 12.3. *see HSQC **IR** (thin film) $\nu_{max}$ ($cm^{-1}$): 3667, 3146, 2889, 2474, 1728, 1437, 1275, 1047, 950, 920, 868. **HRMS** (m/z): (ESI) calcd. for $C_{20}H_{24}N_2O_4Na$ $[M+Na]^+$ m/z: 379.1628, found 379.1626.



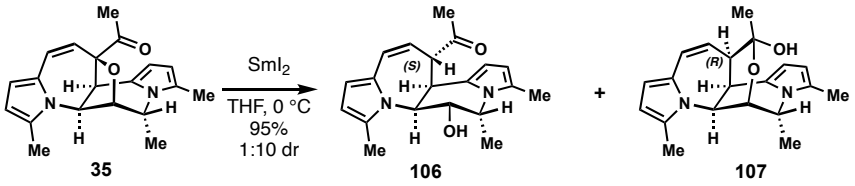

**Ketone 104**: To a reaction tube containing diol **103** (10.0 mg, 0.028 mmol, 1.0 equiv.) was added MeOH (1.5 mL). The resulting mixture was cooled to 0 °C followed by the addition of aq. 1 M HCl (56.0 µL, 0.056 mmol, 2.0 equiv.). The resulting mixture was stirred for 10 minutes and quenched with saturated aq. $NaHCO_3$ (3 mL) and extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine (5 mL), dried over $Na_2SO_4$, and concentrated in vacuo. The resulting crude product was purified by preparative TLC (50% EtOAc in hexanes) to afford ketone **104** (8.9 mg, 0.024 mmol, 85% yield) as a yellow oil.
**TLC**: $R_f$ = 0.4 (50% EtOAc in hexanes).**$^1$H NMR** (600 MHz, Chloroform-*d*) δ 6.16 (d, *J* = 3.4 Hz, 1H), 5.94 (dd, *J* = 3.4, 1.0 Hz, 1H), 5.82 (dd, *J* = 3.5, 1.0 Hz, 1H), 5.71 (d, *J* = 3.4 Hz, 1H), 4.88 (s, 1H), 4.51 (s, 0H), 4.49 (td, *J* = 6.7, 2.1 Hz, 1H), 4.41 (dd, *J* = 2.2, 1.0 Hz, 1H), 4.37 (dd, *J* = 8.5, 4.8 Hz, 1H), 4.28 (d, *J* = 4.7 Hz, 1H), 3.34 (s, 3H), 2.87 (d, *J* = 8.5 Hz, 1H), 2.27 (d, *J* = 0.9 Hz, 3H), 2.23 (d, *J* = 0.9 Hz, 3H), 1.69 (s, 3H), 1.56 (s, 3H), 1.55 (d, *J* = 6.8 Hz, 3H).**$^{13}$C NMR** (151 MHz, $CDCl_3$) δ 209.0, 131.2, 128.1, 127.0, 126.5, 112.6, 108.5, 107.9, 106.5, 96.6, 87.6, 80.4, 74. 5, 59.4, 57.4, 56.2, 43.9, 26.3, 19.4, 13.6, 12.7. **IR** (thin film) $\nu_{max}$ ($cm^{-1}$): 3536, 3253, 2953, 2616, 2396, 1721, 1234, 945, 713. **HRMS** (m/z): (ESI) calcd. for $C_{20}H_{24}N_2O_4Na$ $[M+Na]^+$ m/z: 393.1785, found 393.1783.




**Bipolamine G (9)**: To a reaction tube containing ketone **104** (8.0 mg, 0.022 mmol, 1.0 equiv.) was added $CH_2Cl_2$ (1.5 mL). The resulting mixture was cooled to –78 °C followed by the addition of DIBAL (1.0 M in hexanes, 44.0 µL 0.044 mmol, 2.0 equiv.). Upon consumption of the starting material as indicated by TLC, the reaction mixture was quenched with saturated aq. Rochelle salt (3 mL) and extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine (20 mL), dried over $Na_2SO_4$, and concentrated in vacuo. The resulting crude residue was purified by preparative TLC (50% EtOAc in hexanes) to afford bipolamine G **(9)** (3.0 mg, 0.0080 mmol, 36%) and 12-*epi*-**9** (3.1 mg, 0.0084 mmol, 38%) both as white solids.

Bipolamine G **(9)**:
**TLC**: $R_f$ = 0.4 (50% EtOAc in hexanes).**$^1$H NMR** (600 MHz, Acetone-$d_6$) δ 6.04 (d, *J* = 3.4 Hz, 1H), 5.91 (d, *J* = 3.3 Hz, 1H), 5.84 (dd, *J* = 3.3, 1.0 Hz, 1H), 5.78 (dd, *J* = 3.4, 1.0 Hz, 1H), 4.89 (d, *J* = 1.0 Hz, 1H), 4.86 (s, 1H), 4.36 (dd, *J* = 10.0, 3.6 Hz, 1H), 4.32 (qd, *J* = 6.7, 1.9 Hz, 1H), 4.29 (br s, 1H), 4.13 (d, *J* = 3.6 Hz, 1H), 3.16 (s, 3H), 3.02 (d, *J* = 10.0 Hz, 1H), 2.92 (s, 1H), 2.47 (td, *J* = 6.6, 4.4 Hz, 1H), 2.31 (d, *J* = 0.9 Hz, 3H), 2.26 (d, *J* = 0.9 Hz, 3H), 1.56 (d, *J* = 6.7 Hz, 3H), 1.07 (d, *J* = 6.6 Hz, 3H). **$^{13}$C NMR** (151 MHz Acetone) δ 131.5, 130.9, 128.4, 127.4, 114.1, 108.2, 108.1, 105.2, 91.5, 87.5, 81.4, 70.4, 69.2, 60.8, 57.6, 55.8, 42.6, 19.5, 18.7, 13.7, 12.8. **IR** (thin film) $\nu_{max}$ ($cm^{-1}$): 3480, 3108, 3071, 3041, 2507, 2105, 1431, 1148. **HRMS** (m/z): (ESI) calcd. for $C_{21}H_{28}N_2O_4Na$ $[M+Na]^+$ m/z: 395.1941, found 395.1939.

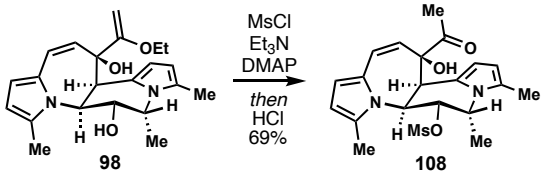
12-*epi*-**9**:
**TLC**: $R_f$ = 0.2 (50% EtOAc in hexanes). **$^1$H NMR** (600 MHz, Acetone-$d_6$) δ 6.04 (d, *J* = 3.3 Hz, 1H), 5.84 (dd, *J* = 3.4, 1.0 Hz, 1H), 5.75 (dd, *J* = 3.4, 1.0 Hz, 1H), 5.72 (d, *J* = 3.4 Hz, 1H), 4.84 (d, *J* = 1.0 Hz, 1H), 4.55 (s, 1H), 4.36 (qd, *J* = 6.7, 2.0 Hz, 1H), 4.31 (t, *J* = 1.5 Hz, 1H), 4.28 (d, *J* = 3.7 Hz, 1H), 4.15 (d, *J* = 3.7 Hz, 1H), 3.45 (s, 1H), 3.18 (s, 3H), 2.71 (q, *J* = 6.3 Hz, 1H), 2.30 (d, *J* = 0.9 Hz, 3H), 2.25 (d, *J* = 0.8 Hz, 3H), 1.54 (d, *J* = 6.7 Hz, 3H), 1.05 (d, *J* = 6.3 Hz, 3H). **$^{13}$C NMR** (151 MHz Acetone ) δ 131.5, 129.7, 128.2, 127.4, 114.0, 108.0, 107.8, 106.0, 92.1, 87.3, 80.7, 73.9, 71.0, 61.3, 57.6, 56.0, 42.3, 19.4, 18.9, 13.7, 12.8. **IR** (thin film) $\nu_{max}$ ($cm^{-1}$): 3285, 3192, 2706, 2415, 1487, 1328, 1191, 1021, 811. **HRMS** (m/z): (ESI) calcd. for $C_{21}H_{28}N_2O_4Na$ $[M+Na]^+$ m/z: 395.1941, found 395.1937.




**Ketone 106 and hemiacetal 107**: To a reaction tube containing ketone **35** (20.0 mg, 0.062 mmol, 1.0 equiv.) was added THF (3 mL). The resulting mixture was cooled to 0 °C, $SmI_2$ (0.1 M in THF, 0.930 mL, 0.093 mmol, 1.5 equiv.) was added dropwise. The resulting mixture was warmed to room temperature. Upon consumption of the starting material as indicated by TLC, the reaction mixture was quenched with saturated aq. $NH_4Cl$ (5 mL) and extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine (5 mL), dried over $Na_2SO_4$, and concentrated in vacuo. The resulting crude product was purified by preparative TLC (20%
EtOAc in hexanes) to afford ketone **106** (17.2 mg, 0.053 mmol, 86%) and hemiacetal **107** (2.0 mg, 0.006 mmol, 9%) as light yellow oils.

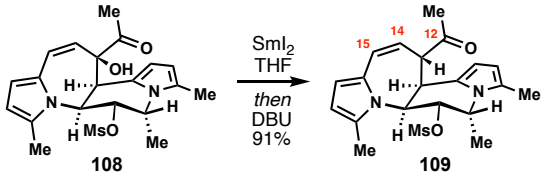
Ketone **106**:
**TLC**: $R_f$ = 0.5 (40% EtOAc in hexanes). **$^1$H NMR** (600 MHz, Benzene-*d*$_6$) δ 6.19 (dd *J* = 11.7, 1.8 Hz, 1H), 6.11 (d, *J* = 3.5 Hz, 1H), 6.01 (td, *J* = 2.9, 2.5, 1.6 Hz, 2H), 5.97 (d, *J* = 3.4 Hz, 1H), 5.14 (dd, *J* = 11.7, 5.1 Hz, 1H), 4.68 (dd, *J* = 6.6, 2.3 Hz, 1H), 4.65 (t, *J* = 7.2 Hz, 1H), 3.99 (ddd, *J* = 7.4, 5.1, 1.7 Hz, 1H), 3.95 (qd, *J* = 6.9, 1.8 Hz, 1H), 3.47 (dt, *J* = 4.3, 2.0 Hz, 1H), 1.95 (s, 3H), 1.89 (d, *J* = 4.6 Hz, 1H), 1.83 (s, 3H), 1.73 (s, 3H), 0.78 (d, J = 6.9 Hz, 3H). **$^{13}$C NMR** (151 MHz, $C_6D_6$) δ 206.8, 131.7, 131.5, 130.4, 127.6, 122.6, 119.5, 112.6, 109.5, 108.2, 105.2, 75.7, 60.2, 55.0, 54.6, 37.2, 29.5, 19.9, 13.3, 12.0. **IR** (thin film) $\nu_{max}$ ($cm^{-1}$): 3345, 2853, 2409, 1725, 1377, 1301, 1221, 1042, 940, 758. **HRMS** (m/z): (ESI) calcd. for $C_{20}H_{25}N_2O_2$ $[M+H]^+$ m/z: 325.1911, found 325.1910.

Hemiacetal **107**:
**TLC**: $R_f$ = 0.4 (40% EtOAc in hexanes). **$^1$H NMR** (600 MHz, Benzene-*d*$_6$) δ 6.33 (d, *J* = 11.7 Hz, 1H), 6.23 (d, *J* = 3.6 Hz, 1H), 6.07 (dd, *J* = 3.6, 1.0 Hz, 1H), 5.98 (dd, *J* = 3.5, 1.0 Hz, 1H), 5.82 (d, *J* = 3.4 Hz, 1H), 5.26 (dd, *J* = 11.7, 8.4 Hz, 1H), 4.40 – 4.32 (m, 2H), 3.88 (d, *J* = 1.5 Hz, 1H), 3.47 (q, *J* = 2.4 Hz, 1H), 2.53 (dd, *J* = 8.4, 2.3 Hz, 1H), 2.03 (s, 1H), 1.93 (d, *J* = 0.9 Hz, 3H), 1.83 (s, 3H), 1.48 (s, 3H), 0.85 (d, *J* = 6.9 Hz, 3H). **$^{13}$C NMR** (151 MHz, $C_6D_6$) 132.8, 132.1, 131.3, 127.3, 122.4, 120.1, 112.7, 109.1, 108.9, 104.2, 98.2, 77.0, 55.8, 51.1, 49.2, 32.9, 29.6, 20.5, 13.9, 12.4. **IR** (thin film) $\nu_{max}$ ($cm^{-1}$): 3455, 2925, 2162, 2143, 1429, 1377, 1042, 940, 780, 668. **HRMS** (m/z): (ESI) calcd. for $C_{20}H_{25}N_2O_2$ $[M+H]^+$ m/z: 325.1911, found 325.1912.



**Ketone 108**: To a reaction tube containing diol **98** (30.0 mg, 0.081 mmol, 1.0 equiv.) was added $CH_2Cl_2$ (5 mL). The resulting mixture was cooled to 0 °C, $Et_3N$ (33.7 µL, 0.24 mmol, 3.0 equiv.), MsCl (6.9 µL, 0.089 mmol, 1.1 equiv.) and DMAP (9.9 mg, 0.081 mmol, 1.0 equiv.) were added dropwise sequentially. The resulting mixture was warmed to room temperature. Upon consumption of the starting material as indicated by TLC, the reaction mixture was cooled to 0 °C followed by the addition of aq. 1 M HCl (2 mL). Upon consumption of the starting material as indicated by TLC, the reaction mixture was quenched with saturated aq. $NaHCO_3$ (3 mL) and extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine (20 mL), dried over $Na_2SO_4$, and concentrated in vacuo. The resulting crude product was purified by preparative TLC (10% EtOAc in hexanes) to afford ketone **108** (23.5 mg, 0.056 mmol, 69% yield) as a white solid.

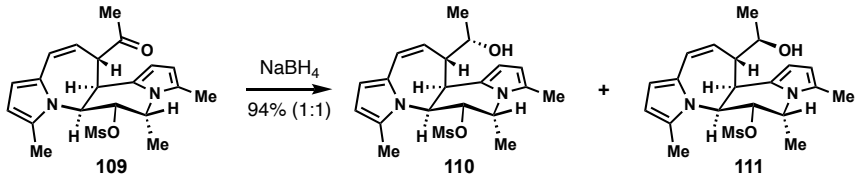
**TLC**: $R_f$ = 0.4 (30% EtOAc in hexanes). **$^1$H NMR** (600 MHz, Benzene-*d*$_6$) δ 6.36 (dd, *J* = 11.8, 6.3 Hz, 1H), 6.02 (d, *J* = 12.2 Hz, 1H), 5.93 (d, *J* = 3.6 Hz, 1H), 5.88 (d, *J* = 3.3 Hz, 1H), 5.80 (d, *J* = 3.6 Hz, 1H), 5.54 (d, *J* = 3.5 Hz, 1H), 4.86 (dd, *J* = 11.9, 3.8 Hz, 1H), 4.82 (p, J = 6.5 Hz, 1H), 4.77 (d, J = 12.1 Hz, 1H), 4.03 (d, J = 3.8 Hz, 1H), 3.70 (s, 1H), 2.00 (s, 3H), 1.96 (s, 3H), 1.80 (s, 3H), 1.80 (s, 3H), 1.23 (d, *J* = 6.6 Hz, 3H). **$^{13}$C NMR** (151 MHz, $C_6D_6$) δ 206.0, 135.8, 129.1, 128.7, 124.4, 122.7, 120.0, 114.5, 109.1, 108.5, 105.5, 84.5, 75.0, 53.9, 53.6, 44.0, 36.2, 23.6, 16.7, 13.3, 12.2. **IR** (thin film) $\nu_{max}$ ($cm^{-1}$): 3430, 2926, 2855, 1715, 1360, 1179, 1003, 972, 635, 465. **HRMS** (m/z): (ESI) calcd. for $C_{21}H_{27}N_2O_5S$ $[M+H]^+$ m/z: 419.1635, found 419.1635.




**Ketone 109**: To a reaction tube containing ketone **108** (20.0 mg, 0.048 mmol, 1.0 equiv.) was added THF (4 mL). The resulting mixture was cooled to 0 °C, $SmI_2$ (0.1 M in THF, 0.72 mL, 0.072 mmol, 1.5 equiv.) were added dropwise. The resulting mixture was warmed to room temperature. Upon consumption of the starting material as indicated by TLC, the reaction mixture was quenched with air followed by the addition of DBU (36.0 µL, 0.24 mmol, 5.0 equiv.). Upon consumption of the starting material as indicated by TLC, the reaction mixture was quenched with saturated aq. $NH_4Cl$ (3 mL) and extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine (5 mL), dried over $Na_2SO_4$, and concentrated in vacuo. The resulting crude product was purified by preparative TLC (20% EtOAc in hexanes) to afford ketone **109** (17.6 mg, 0.044 mmol, 91% yield) as a white solid.

**TLC**: $R_f$ = 0.5 (30% EtOAc in hexanes). **$^1$H NMR** (600 MHz, Benzene-*d*$_6$) δ 6.02 (d, *J* = 3.5, 1.0 Hz, 1H), 6.01 (d, *J* = 10.7 Hz, 1H), 5.85 (dd, *J* = 3.5, 1.2 Hz, 1H), 5.74 (d, *J* = 3.5 Hz, 1H), 5.66 (dd, *J* = 3.5, 0.9 Hz, 1H), 5.53 (dd, *J* = 10.4, 8.7 Hz, 1H), 5.14 (dd, *J* = 11.3, 5.2 Hz, 1H), 5.06 (dd, *J* = 9.9, 3.3 Hz, 1H), 4.72 (dd, *J* = 11.3, 9.8 Hz, 1H), 4.60 (qd, *J* =

6.6, 5.1 Hz, 1H), 3.08 (dd, *J* = 8.7, 3.3 Hz, 1H), 2.02 (s, 3H), 1.91 (s, 3H), 1.83 (s, 3H), 1.63 (s, 3H), 1.10 (d, *J* = 6.7 Hz, 3H). **$^{13}$C NMR** (151 MHz, $C_6D_6$) δ 205.4, 134.7, 129.7, 126.7, 126.2, 125.0, 124.9, 111.3, 108.4, 108.0, 104.6, 80.2, 57.3, 51.4, 51.0, 42.4, 37.0, 27.7, 15.3, 12.9, 11.2. **IR** (thin film) $\nu_{max}$ ($cm^{-1}$): 3381, 2924, 2853, 1707, 1358, 1290, 1176, 969, 872, 772. **HRMS** (m/z): (ESI) calcd. for $C_{21}H_{26}N_2O_4SNa$ $[M+Na]^+$ m/z: 425.1506, found 425.1509.

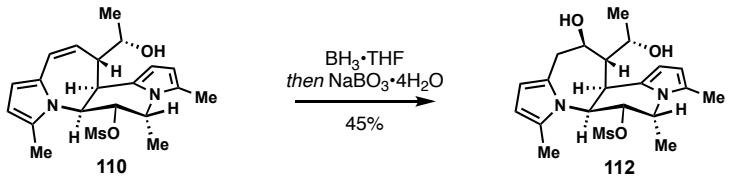



**Alcohol 110 and 111**: To a reaction tube containing ketone **109** (10.0 mg, 0.025 mmol, 1.0 equiv.) and MeOH (2 mL) was added $NaBH_4$ (1.0 mg, 0.025 mmol, 1.0 equiv.). The resulting mixture was stirred at 25 °C. Upon consumption of the starting material as indicated by TLC, the reaction mixture was cooled to 0 °C and quenched with saturated aq. $NH_4Cl$ (3 mL) and extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine (5 mL), dried over $Na_2SO_4$, and concentrated in vacuo. The resulting crude residue was purified by preparative TLC (50% EtOAc in hexanes) to afford alcohol **110** (4.8 mg, 0.012 mmol, 47%) and alcohol **111** (4.7 mg, 0.012 mmol, 47%) as white solids.

**Alcohol 110** (desired):
**TLC**: $R_f$ = 0.5 (50% EtOAc in hexanes).**$^1$H NMR** (600 MHz, Benzene-*$d_6$*) δ 6.18 (d, *J* = 11.9 Hz, 1H), 5.98 – 5.92 (m, 2H), 5.87 (d, *J* = 3.5 Hz, 1H), 5.78 (d, *J* = 3.4 Hz, 1H), 5.60 (dd, *J* = 11.5, 5.9 Hz, 1H), 5.14 (dd, *J* = 12.0, 6.0 Hz,1H), 4.72 – 4.64 (m, 2H), 3.90 (t, *J* = 5.9 Hz, 1H), 3.86 (s, 1H), 2.29 (q, *J* = 5.9 Hz, 1H), 2.03 (s, 3H), 1.84 (s, 3H), 1.82 (s, 3H), 1.17 (d, *J* = 6.5 Hz, 3H), 1.05 (s, 1H) 0.94 (d, *J* = 6.4 Hz, 3H). **$^{13}$C NMR** (151 MHz, $C_6D_6$) δ 133.4, 131.1, 130.1, 128.0, 123.8, 121.6, 111.6, 109.1, 108.3, 105.6, 76.1, 68.7, 54.0, 52.8, 52.5, 41.9, 37.3, 21.8, 16.1, 12.7, 11.8. **IR** (thin film) $\nu_{max}$ ($cm^{-1}$): 3435, 2926, 2857, 1660, 1557, 1359, 1177, 972, 959, 744, 483. **HRMS** (m/z): (ESI) calcd. for $C_{21}H_{29}N_2O_4S$ $[M+H]^+$ m/z: 405.1843, found 405.1844.

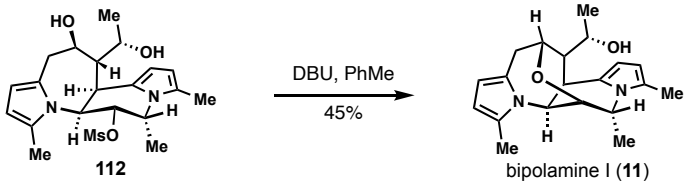
**Alcohol 111**:
**TLC**: $R_f$ = 0.3 (50% EtOAc in hexanes). **$^1$H NMR** (600 MHz, Benzene-*$d_6$*) δ 6.14 (d, *J* = 11.3 Hz, 1H), 6.05 (dd, *J* = 3.4, 1.0 Hz, 1H), 6.02 (dd, *J* = 3.4, 0.9 Hz, 1H), 5.81 (d, *J* = 3.5 Hz, 1H), 5.75 (dd, *J* = 3.4, 0.9 Hz, 1H), 5.60 (dd, *J* = 11.5, 5.6 Hz, 1H), 5.55 (dd, *J* = 11.3, 7.6 Hz, 1H), 4.72 – 4.63 (m, 2H), 4.33 (dd, *J* = 8.1, 3.9 Hz, 1H), 3.43 (dt, *J* = 12.1, 6.1 Hz, 1H), 2.47 (td, *J* = 8.0, 3.9 Hz, 1H), 2.01 (s, 3H), 1.95 (s, 3H), 1.84 (s, 3H), 1.17 (d, *J* = 6.5 Hz, 3H), 0.86 (d, *J* = 6.1 Hz, 3H), 0.61 (s, 1H). **$^{13}$C NMR** (151 MHz, $C_6D_6$) δ 133.4, 131.1, 129.8, 126.5, 126.3, 123.3, 110.7, 108.9, 107.9, 105.6, 77.8, 68.4, 55.1, 51.9, 51.8, 41.4, 37.3, 22.1, 15.8, 12.8, 11.5. **IR** (thin film) $\nu_{max}$ ($cm^{-1}$): 3687, 2929, 2178, 1602, 1357,

1177, 962, 611, 407. **HRMS** (m/z): (ESI) calcd. for $C_{21}H_{29}N_2O_4S$ $[M+H]^+$ m/z: 405.1843, found 405.1844.




**Diol 112** To a reaction tube containing alcohol **110** (10.0 mg, 0.025 mmol, 1.0 equiv.) and THF (1.5 mL) was added $BH_3$·THF (6.4 mg, 0.075 mmol, 3.0 equiv.). The resulting mixture was stirred at 50 °C. Upon consumption of the starting material as indicated by TLC, the reaction mixture was cooled to 0 °C followed by the addition of $NaBO_3$·$4H_2O$ (38.5 mg, 0.25 mmol, 10 equiv.). The reaction mixture was quenched with saturated aq. $NH_4Cl$ (5 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (5 mL), dried over $Na_2SO_4$, and concentrated in vacuo. The resulting crude residue was purified by preparative TLC (100% EtOAc in hexanes) to afford diol **112** (4.7 mg, 0.011 mmol, 45%) as a white solid.

**TLC**: $R_f$ = 0.3 (100% EtOAc in hexanes). **$^1$H NMR** (600 MHz, Chloroform-*d*) δ 6.17 (dd, *J* = 3.6, 1.4 Hz, 1H), 5.93 (dd, *J* = 3.5, 1.0 Hz, 1H), 5.86 (d, *J* = 3.4 Hz, 1H), 5.78 (d, *J* = 3.1 Hz, 1H), 4.95 (dd, *J* = 10.5, 4.9 Hz, 1H), 4.69 (t, *J* = 11.0 Hz, 1H), 4.60 (qd, *J* = 6.8, 4.8 Hz, 1H), 4.10 (s, 1H), 4.02 (dd, *J* = 11.5, 2.8 Hz, 1H), 3.08 (dd, *J* = 14.2, 5.7 Hz, 1H), 2.62 (dd, *J* = 14.2, 11.0 Hz, 1H), 2.56 (dd, *J* = 9.3, 3.8 Hz, 1H), 2.41 – 2.32 (m, 2H), 2.26 (s, 3H), 2.26 (s, 3H), 2.24 (s, 3H), 1.43 (d, *J* = 6.8 Hz, 3H), 1.38 (s, 1H), 1.18 (d, *J* = 6.2 Hz, 3H). **$^{13}$C NMR** (151 MHz, $CDCl_3$) δ 129.6, 127.7, 126.8, 126.5, 108.3, 107.7, 107.6, 105.5, 82.8, 72.0, 68.3, 54.9, 50.5, 50.2, 35.7, 34.0, 33.8, 23.1, 14.4, 12.7, 11.7. **IR** (thin film) $\nu_{max}$ ($cm^{-1}$): 3394, 2925, 2853, 1634, 1401, 1360, 1299, 1177, 1080, 970, 770, 649. **HRMS** (m/z): (ESI) calcd. for $C_{21}H_{31}N_2O_5S$ $[M+H]^+$ m/z: 423.1948, found 423.1950.

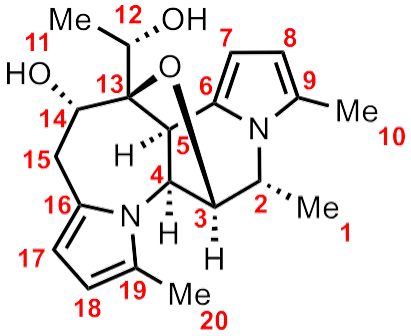



**Bipolamine I** (**11**): To a reaction tube containing diol **112** (2.4 mg, 0.0056 mmol, 1.0 equiv.) and PhMe (1 mL) was added DBU (8.5 µL, 0.056 mmol, 10.0 equiv.). The resulting mixture was heated up to 120 °C. Upon consumption of the starting material as indicated by TLC, the reaction mixture was cooled to 25 °C. The organic layers were concentrated in vacuo. The resulting crude residue was purified by column chromatography (40% EtOAc in hexanes) to afford bipolamine I (**11**) (1.5 mg, 0.0046 mmol, 82%) as a white solid.

**TLC**: $R_f$ = 0.4 (50% EtOAc in hexanes). **$^1$H NMR** (600 MHz, Acetone-*d*$_6$) δ 5.76 (dd, *J* = 3.4, 1.0 Hz, 1H), 5.75 (dd, *J* = 3.4, 1.0 Hz, 1H), 5.65 (br d, *J* = 3.1 Hz, 1H), 5.60 (d, *J* = 3.4 Hz, 1H), 4.56 (br d, *J* = 3.6 Hz, 1H), 4.40 – 4.33 (m, 3H), 3.52 (dd, *J* = 17.3, 4.8 Hz, 1H), 3.26 (dq, *J* = 11.1, 5.5 Hz, 1H), 3.13 (br d, *J* = 17.3 Hz, 1H), 2.97 (br t, *J* = 1.8 Hz, 1H), 2.22 (br d, *J* = 0.9 Hz, 3H), 2.19 (s, 3H), 2.16 (br dd, *J* = 11.0, 7.1 Hz, 1H), 1.42 (d, *J* = 6.6 Hz, 3H), 1.21 (d, *J* = 6.0 Hz, 3H). **$^{13}$C NMR** (151 MHz, Acetone) δ 134.9, 128.8, 126.3 (2C), 108.1, 108.0, 105.2, 102.4, 76.9, 71.2, 68.2, 56.5, 55.7, 49.6, 36.4, 31.2, 22.7, 19.1, 12.3, 12.2. **IR** (thin film) $\nu_{max}$ ($cm^{-1}$): 3558, 2922, 2164, 1726, 1588, 1446, 1304, 1067, 562. **HRMS** (m/z): (ESI) calcd. for $C_{20}H_{27}N_2O_2$ $[M+H]^+$ m/z: 327.2067, found 327.206.

# Natural Product Spectral Comparisons

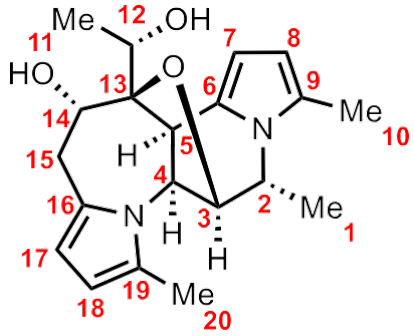
**Bipolamine D (6) $^1$H spectra comparison:**



bipolamine D (**6**)

| Position | $^1$H NMR δ) Natural Sample (500 MHz, $CDCl_3$)[2] | $^1$H NMR δ) Synthetic Sample (600 MHz, $CDCl_3$) |
|---|---|---|
| **1** | 1.49 (d, 6.3) | 1.48 (d, 6.6) |
| **2** | 4.32 (qd, 6.3, 2.1) | 4.32 (qd, 6.6, 2.3) |
| **3** | 4.35 (br s) | 4.36 (s) |
| **4** | 4.85 (br s) | 4.84 (s) |
| **5** | 3.92 (br s) | 3.91 (s) |
| **6** | | |
| **7** | 5.83 (d, 3.0) | 5.82 (d, 3.3) |
| **8** | 5.76 (br d, 3.0) | 5.75 (br d, 3.3) |
| **9** | | |
| **10** | 2.25 (br s) | 2.24 (s) |
| **11** | 1.13 (d, 6.6) | 1.12 (d, 6.4) |
| **12** | 2.93 (q, 6.6) | 2.93 (qd, 6.4, 4.5) |
| **13** | | |
| **14** | 4.38 (br s) | 4.38 (s) |
| **15** | 3.11 (br d, 15.6), 2.88 (dd, 15.6, 5.1) | 3.09 (d, 15.6), 2.87 (dd, 15.6, 5.0) |
| **16** | | |
| **17** | 5.71 (s) | 5.70 (br d, 3.3) |
| **18** | 5.69 (br s) | 5.67 (br d, 3.3) |
| **19** | | |
| **20** | 2.22 (br s) | 2.21 (s) |

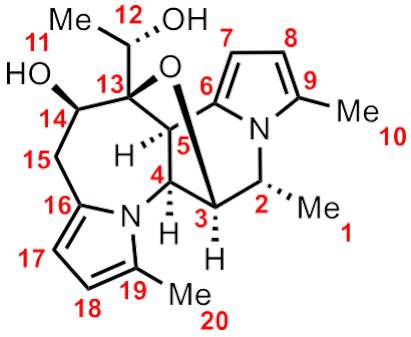
**Bipolamine D (6) $^{13}C$ spectra comparison:**



bipolamine D (**6**)

| Position | $^{13}C$ NMR δ) Natural Sample (125 MHz, $CDCl_3$)[2] | $^{13}C$ NMR δ) Synthetic Sample (151 MHz, $CDCl_3$) |
|---|---|---|
| **1** | 19.2 | 19.2 |
| **2** | 59.0 | 59.0 |
| **3** | 85.6 | 85.6 |
| **4** | 59.6 | 59.6 |
| **5** | 43.7 | 43.7 |
| **6** | 131.5 | 131.5 |
| **7** | 105.5 | 105.5 |
| **8** | 107.8 | 107.8 |
| **9** | 128.2 | 128.3 |
| **10** | 12.8 | 12.8 |
| **11** | 18.7 | 18.8 |
| **12** | 72.3 | 72.3 |
| **13** | 91.8 | 91.8 |
| **14** | 68.3 | 68.3 |
| **15** | 31.4 | 31.4 |
| **16** | 128.6 | 128.6 |
| **17** | 108.8 | 108.8 |
| **18** | 107.0 | 107.0 |
| **19** | 128.8 | 128.8 |
| **20** | 13.5 | 13.5 |

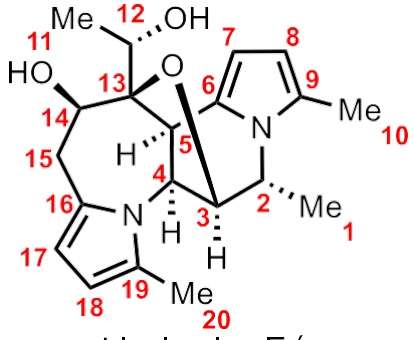
**Bipolamine E (7) $^{1}$H spectra comparison:**



bipolamine E ( 7)

| Position | $^{1}$H NMR δ)<br>Natural Sample<br>(500 MHz, $CDCl_3$)[2] | $^{1}$H NMR δ)<br>Synthetic Sample<br>(600 MHz, $CDCl_3$) |
|---|---|---|
| **1** | 1.54 (d, 6.5) | 1.55 (d, 6.7) |
| **2** | 4.32 (qd, 6.5, 1.6) | 4.32 (m) |
| **3** | 4.26 (br s) | 4.29 (m) |
| **4** | 4.89 (br s) | 4.91 (s) |
| **5** | 4.21 (br s) | 4.22 (br s) |
| **6** | | |
| **7** | 5.92 (d, 3.0) | 5.92 (d, 3.4) |
| **8** | 5.78 (br d, 3.0) | 5.78 (d, 3.4) |
| **9** | | |
| **10** | 2.25 (br s) | 2.26 (s) |
| **11** | 1.08 (d, 6.5) | 1.08 (d, 6.5) |
| **12** | 2.53 (q, 6.5) | 2.53 (q, 6.5) |
| **13** | | |
| **14** | 4.29 (br s) | 4.30 (br s) |
| **15** | 3.06<br>2.81 (dd, 15.5, 4.0) | 3.07<br>2.82 (dd, 15.7, 4.0) |
| **16** | | |
| **17** | 5.68 (br d, 2.8) | 5.67 (d, 3.3) |
| **18** | 5.75 (br d, 2.8) | 5.74 (d, 3.3) |
| **19** | | |
| **20** | 2.26 (br s) | 2.26 (s) |

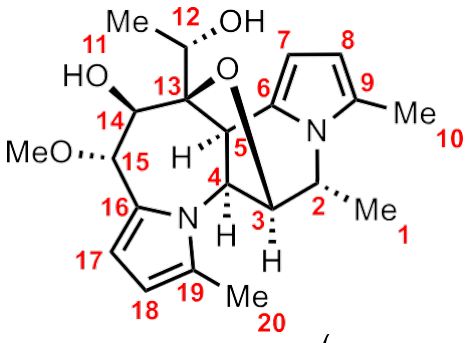
**Bipolamine E (7) $^{13}C$ spectra comparison:**



bipolamine E ( 7)

| Position | $^{13}C$ NMR δ) Natural Sample (125 MHz, $CDCl_3$)[2] | $^{13}C$ NMR δ) Synthetic Sample (151 MHz, $CDCl_3$) |
|---|---|---|
| **1** | 19.4 | 19.3 |
| **2** | 57.5 | 57.5 |
| **3** | 87.4 | 87.4 |
| **4** | 61.0 | 61.0 |
| **5** | 44.1 | 44.0 |
| **6** | 130.5 | 130.5 |
| **7** | 105.3 | 105.2 |
| **8** | 108.0 | 108.0 |
| **9** | 128.3 | 128.3 |
| **10** | 12.7 | 12.7 |
| **11** | 18.5 | 18.5 |
| **12** | 70.2 | 70.3 |
| **13** | 92.0 | 91.9 |
| **14** | 67.3 | 67.3 |
| **15** | 34.3 | 34.3 |
| **16** | 128.9 | 128.8 |
| **17** | 108.7 | 108.7 |
| **18** | 107.8 | 107.8 |
| **19** | 128.8 | 128.7 |
| **20** | 13.5 | 13.5 |

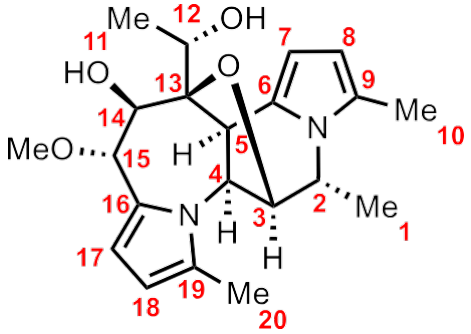
**Bipolamine G (9) $^1$H spectra comparison:**




bipolamine G **9)**

| Position | $^1$H NMR δ) Natural Sample (500 MHz, Acetone-$d_6$)[2] | $^1$H NMR δ) Synthetic Sample (600 MHz, Acetone-$d_6$) |
|---|---|---|
| **1** | 1.55 (d, 7.0) | 1.56 (d, 6.7) |
| **2** | 4.31 (qd, 7.0, 2.0) | 4.32 (qd, 6.7, 1.9) |
| **3** | 4.26 (br s) | 4.29 (br s) |
| **4** | 4.88 (br s) | 4.89 (d, 1.0) |
| **5** | 4.85 (br s) | 4.86 (d, 1.0) |
| **6** | | |
| **7** | 5.92 (br d, 3.0) | 5.91 (d, 3.3) |
| **8** | 5.79 (br d, 3.0) | 5.78 (dd, 3.4, 1.0) |
| **9** | | |
| **10** | 2.26 (br s) | 2.26 (d, 0.9) |
| **11** | 1.08 (d, 7.0) | 1.07 (d, 6.6) |
| **12** | 2.47 (q, 7.0) | 2.47 (td, 6.6, 4.4) |
| **13** | | |
| **14** | 4.36 (d, 3.5) | 4.36 (dd, 10.0, 3.6) |
| **15** | 4.15 (d, 3.5) | 4.13 (d, 3.6) |
| **16** | | |
| **17** | 6.07 (br d, 3.0) | 6.05 (d, 3.4) |
| **18** | 5.86 (br d, 3.0) | 5.84 (d, 3.3) |
| **19** | | |
| **20** | 2.31 (br s) | 2.31 (d, 0.9) |
| **15-OMe** | 3.17 (s) | 3.16 (s) |

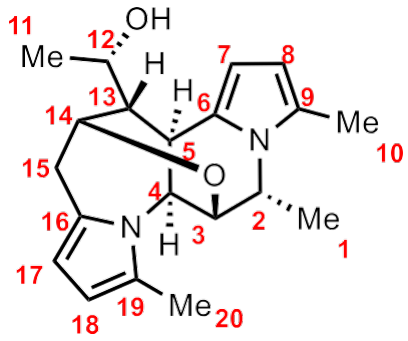
**Bipolamine G (9) $^{13}C$ spectra comparison:**



bipolamine G ( **9**)

| Position | $^{13}C$ NMR δ) Natural Sample (125 MHz, Acetone-$d_6$)[2] | $^{13}C$ NMR δ) Synthetic Sample (151 MHz, Acetone-$d_6$) |
|---|---|---|
| **1** | 19.5 | 19.4 |
| **2** | 57.5 | 57.5 |
| **3** | 87.4 | 87.4 |
| **4** | 60.7 | 60.7 |
| **5** | 42.6 | 42.5 |
| **6** | 130.7 | 130.8 |
| **7** | 105.2 | 105.1 |
| **8** | 108.1 | 108.1 |
| **9** | 128.3 | 128.3 |
| **10** | 12.8 | 12.8 |
| **11** | 18.6 | 18.6 |
| **12** | 70.2 | 70.3 |
| **13** | 91.4 | 91.4 |
| **14** | 69.1 | 69.1 |
| **15** | 81.3 | 81.3 |
| **16** | 127.3 | 127.3 |
| **17** | 114.1 | 114.1 |
| **18** | 108.0 | 108.0 |
| **19** | 131.5 | 131.4 |
| **20** | 13.6 | 13.6 |
| **15-OMe** | 55.8 | 55.8 |

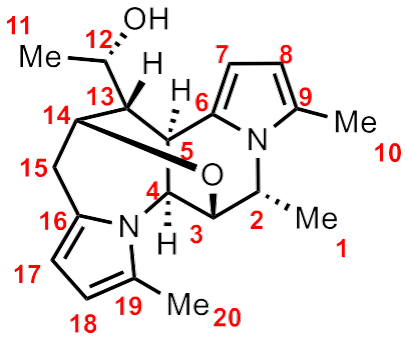
**Bipolamine I (11) $^{1}$H spectra comparison:**




bipolamine I (**10**)

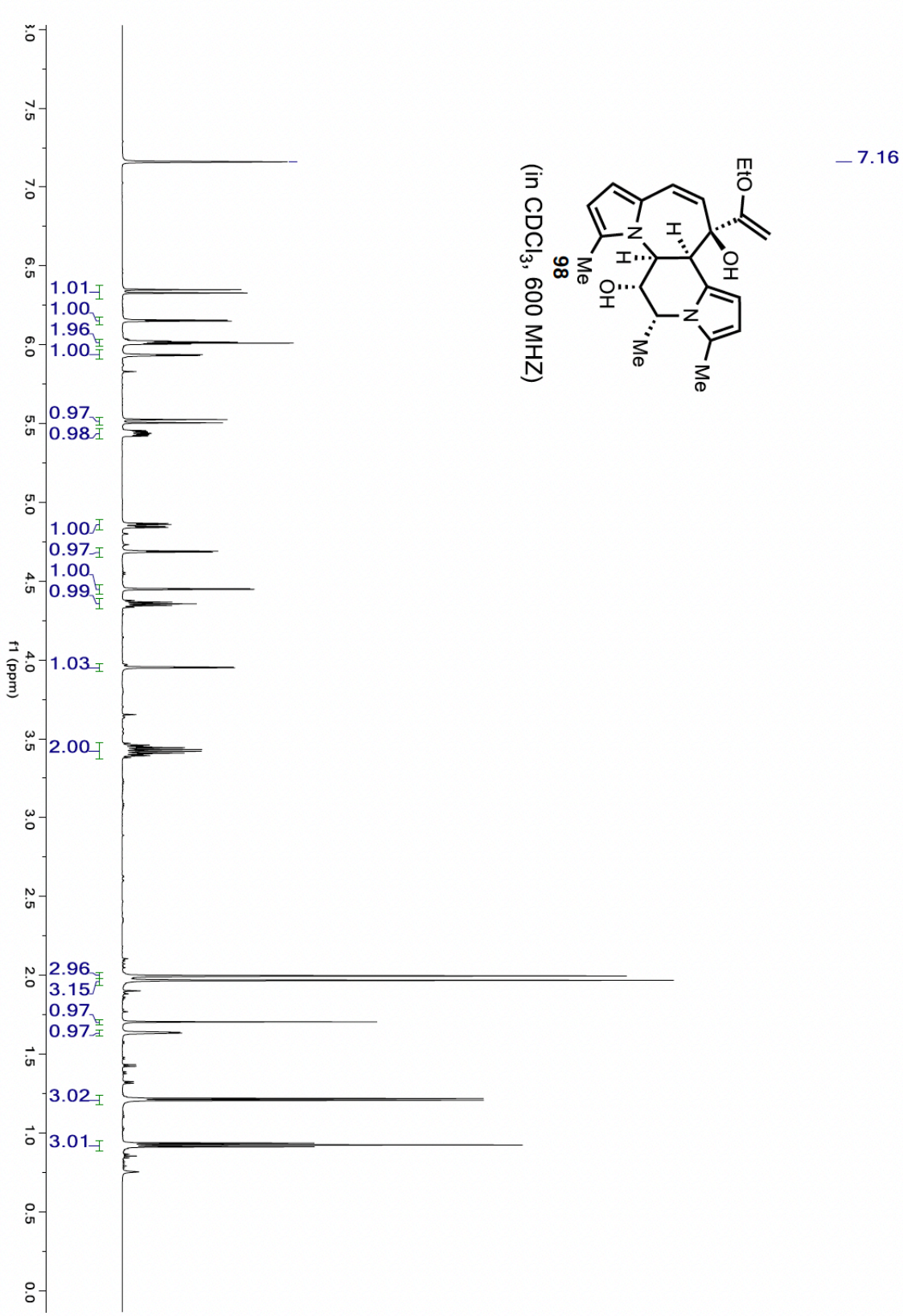
| Position | $^{1}$H NMR δ)<br>Natural Sample<br>(500 MHz, Acetone-$d_6$)[2] | $^{1}$H NMR δ)<br>Synthetic Sample<br>(600 MHz, Acetone-$d_6$) |
|---|---|---|
| **1** | 1.42 (d, 6.6) | 1.42 (d, 6.6) |
| **2** | 4.37 (overlapped) | 4.37 (overlapped) |
| **3** | 4.36 ( overlapped ) | 4.36 (overlapped) |
| **4** | 4.56 (br d, 3.6) | 4.56 (br d, 3.6) |
| **5** | 2.97 (br t, 1.8) | 2.97 (br t, 1.8) |
| **6** | | |
| **7** | 5.61 (d, 3.4) | 5.60 (d, 3.4) |
| **8** | 5.77 (dd, 3.4, 0.8) | 5.76 (dd, 3.4, 1.0) |
| **9** | | |
| **10** | 2.23 (br d, 0.8) | 2.22 (br d, 0.9) |
| **11** | 1.22 (d, 6.0) | 1.21 (d, 6.0) |
| **12** | 3.26 (dq, 11.5, 6.0) | 3.26 (dq, 11.1, 5.5) |
| **13** | 2.16 (br dd, 11.5, 8.0) | 2.16 ( br dd, 11.0, 7.1) |
| **14** | 4.39 (dd, 8.0, 4.8) | 4.38 (overlapped) |
| **15** | 3.52 (dd, 17.0, 4.8)<br>3.14 (br d, 17.0) | 3.52 (dd, 17.3, 4.8)<br>3.13 (br d, 17.3) |
| **16** | | |
| **17** | 5.65 (br d, 3.3) | 5.65 (br d, 3.1) |
| **18** | no data | 5.75 (dd, 3.4, 1.0) |
| **19** | | |
| **20** | no data | 2.19 (s) |

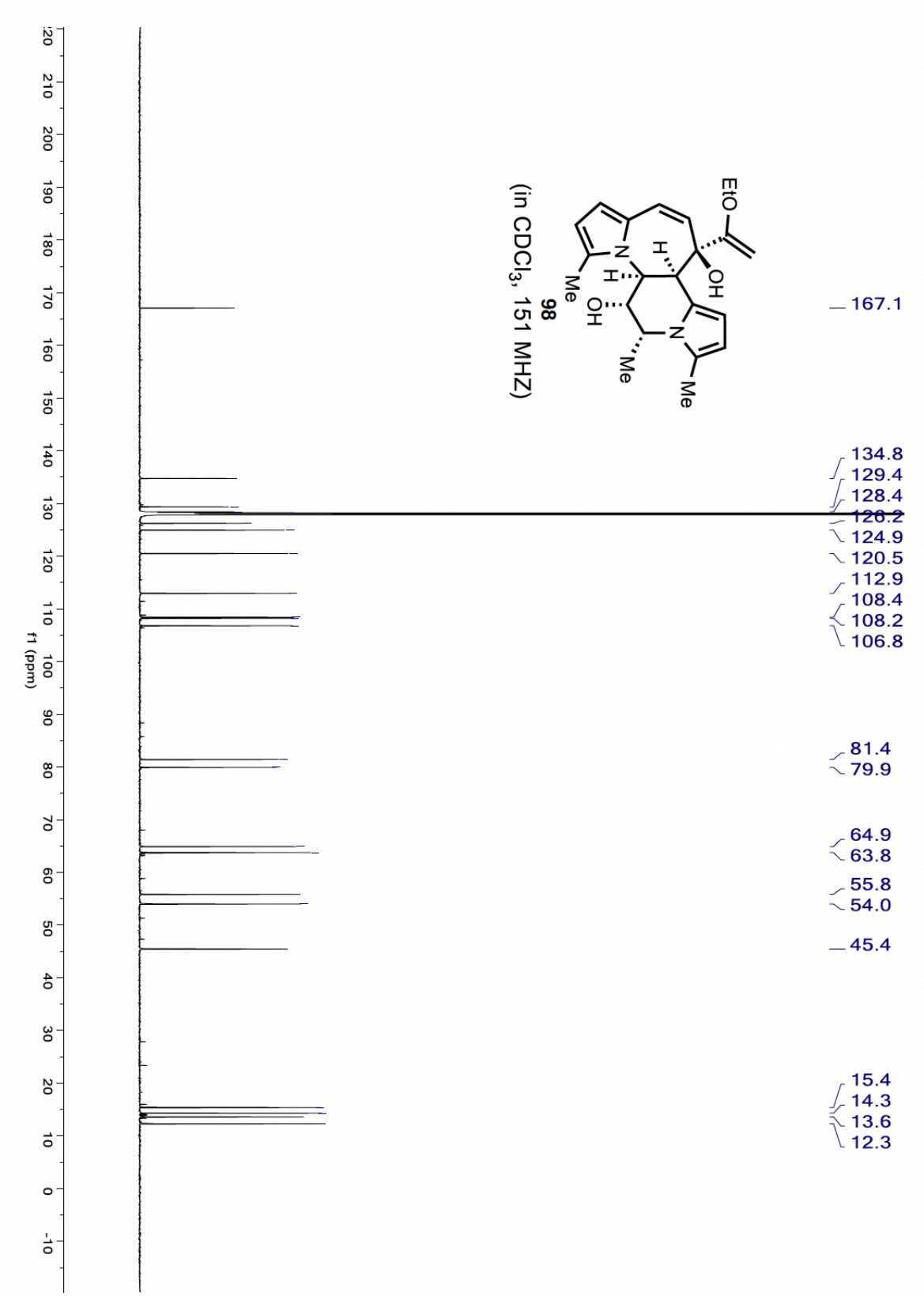
**Bipolamine I (11) $^{13}C$ spectra comparison:**

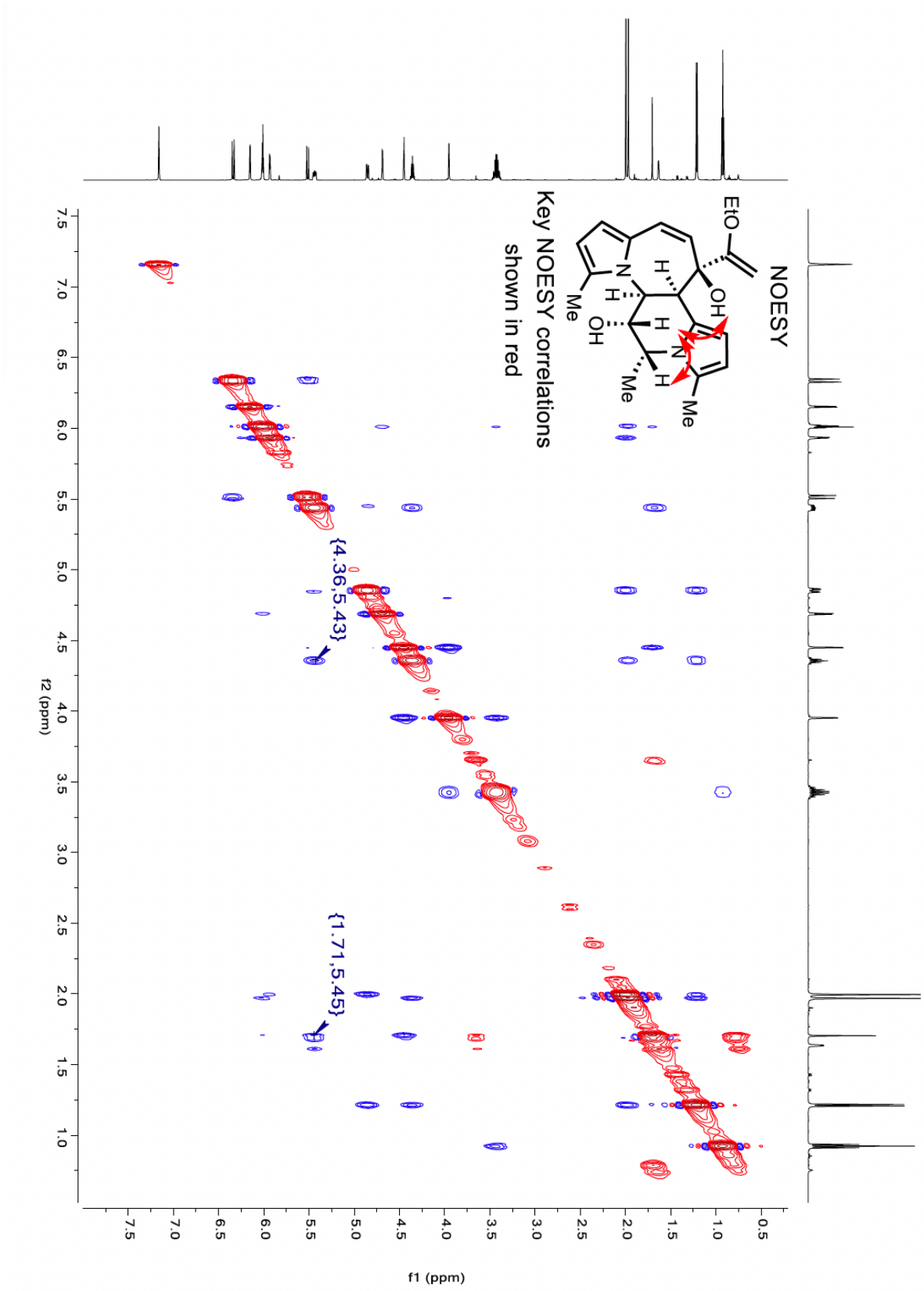


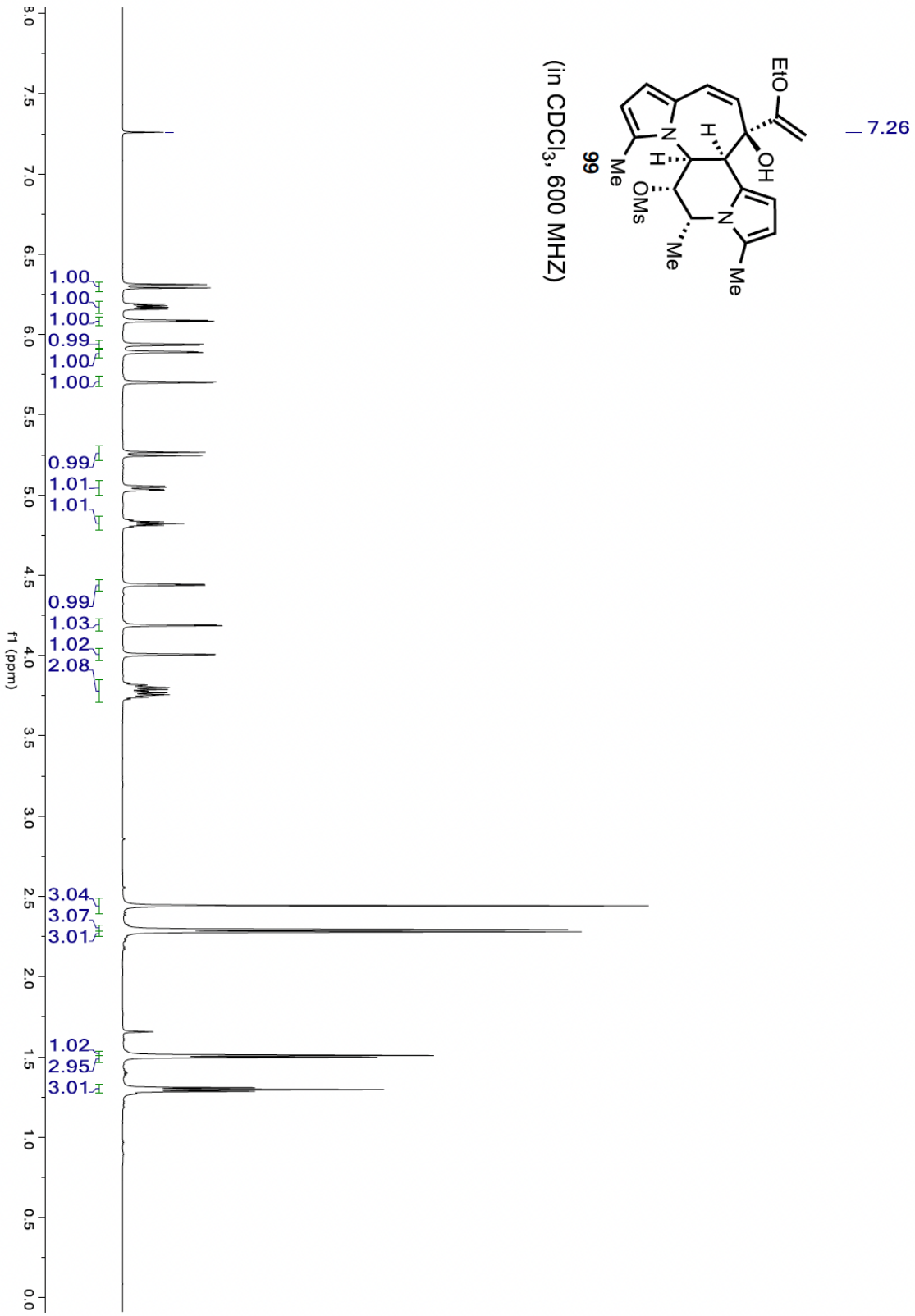

bipolamine I ( **11)**

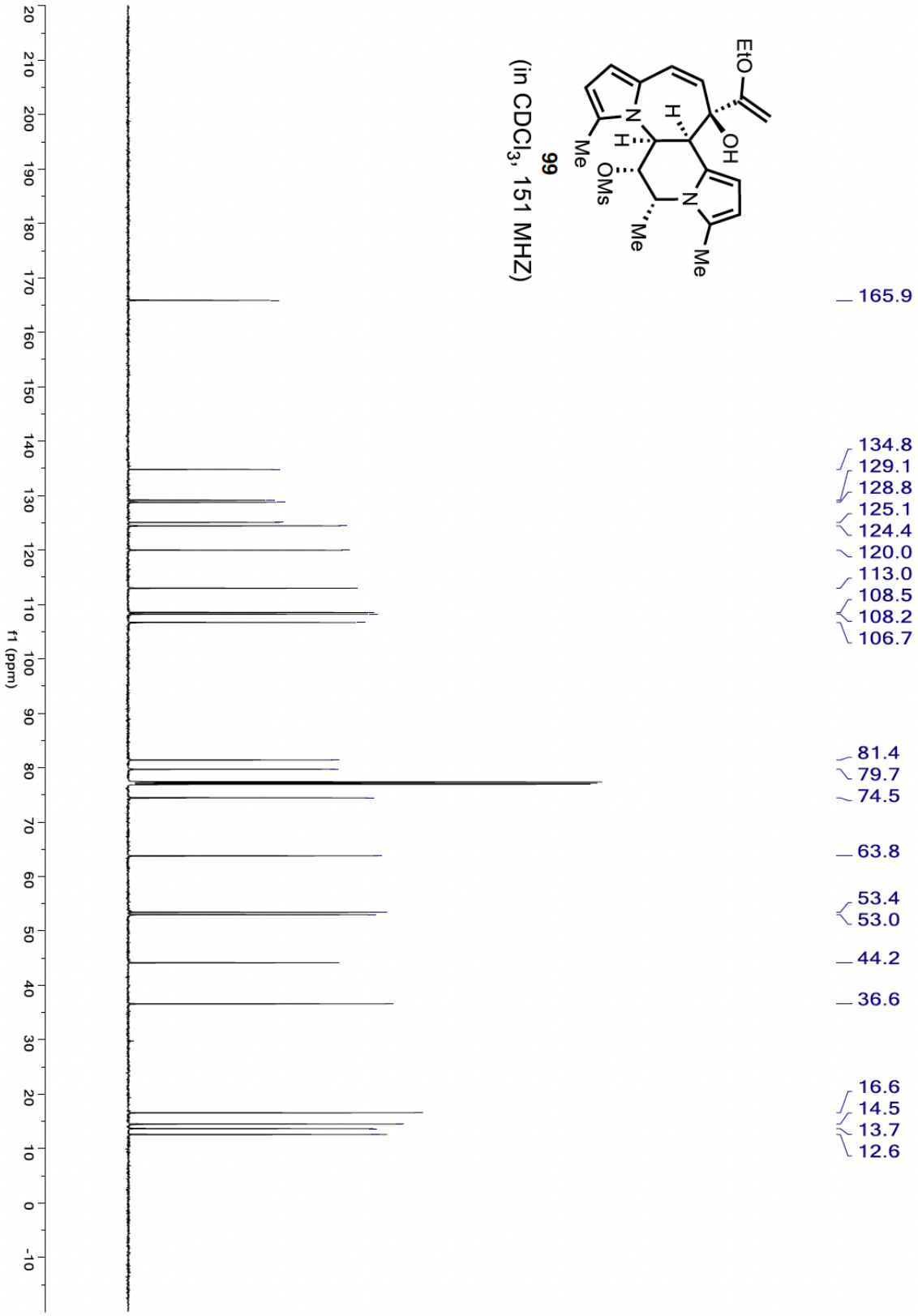
| Position | $^{13}C$ NMR δ) Natural Sample (125 MHz, Acetone-$d_6$)[2] | $^{13}C$ NMR δ) Synthetic Sample (151 MHz, Acetone-$d_6$) |
|---|---|---|
| **1** | 19.1 | 19.1 |
| **2** | 56.5 | 56.5 |
| **3** | 76.9 | 76.9 |
| **4** | 49.6 | 49.6 |
| **5** | 36.4 | 36.4 |
| **6** | 134.9 | 134.9 |
| **7** | 102.4 | 102.4 |
| **8** | 108.1 | 108.1 |
| **9** | 126.4 | 126.3 |
| **10** | 12.1 | 12.2 |
| **11** | 22.6 | 22.7 |
| **12** | 68.1 | 68.2 |
| **13** | 55.7 | 55.7 |
| **14** | 71.2 | 71.2 |
| **15** | 31.2 | 31.2 |
| **16** | 128.8 | 128.8 |
| **17** | 105.2 | 105.2 |
| **18** | 108.0 from $^{13}C$ NMR | 108.0 |
| **19** | 126.3 from $^{13}C$ NMR | 126.3 |
| **20** | 12.3 from $^{13}C$ NMR | 12.3 |

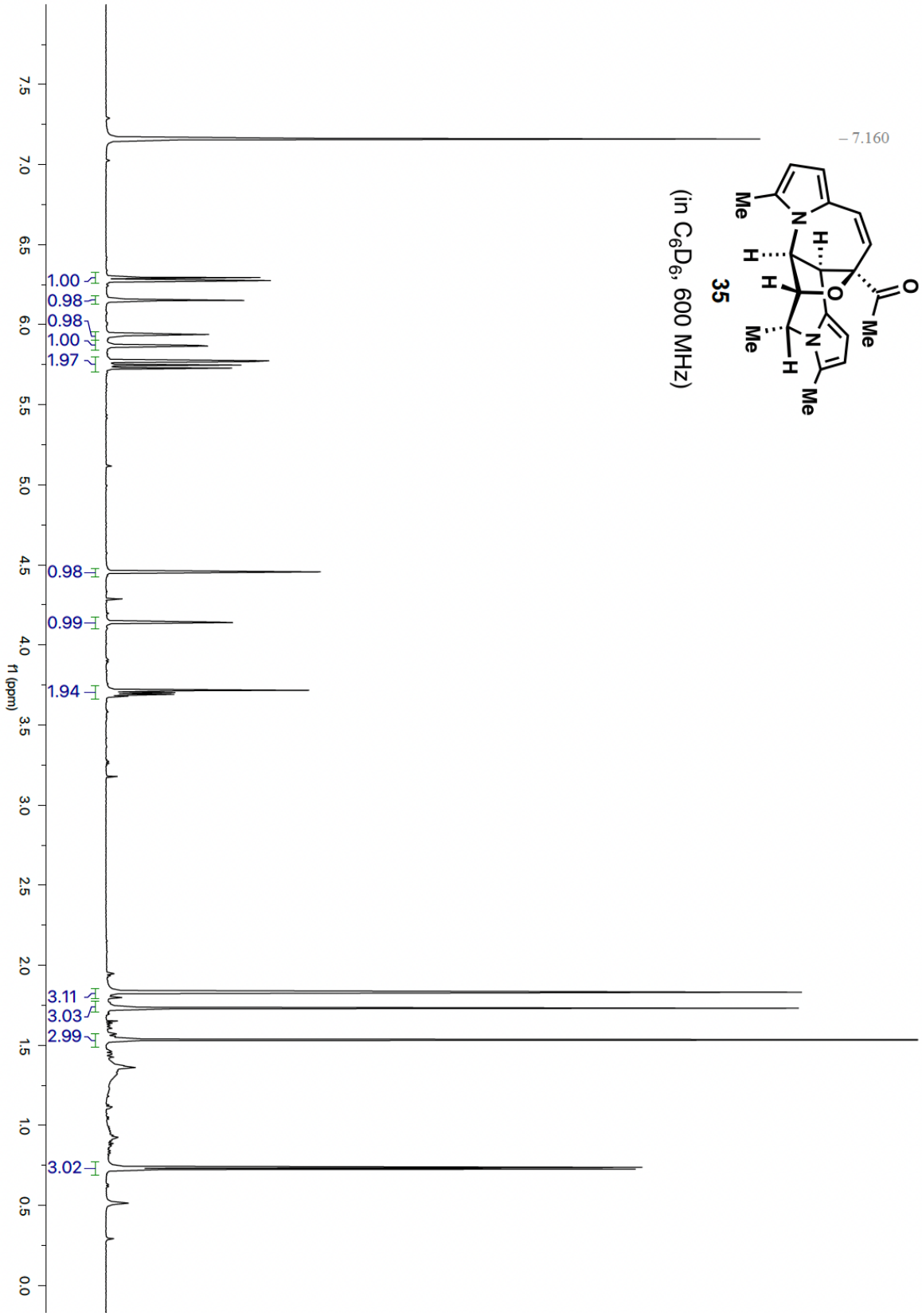

7.16
EtO
OH
H
N
H
OH
Me
Me
Me
N
98
(in CDCl3, 600 MHZ)
1.01
1.00
1.96
1.00
0.97
0.98
1.00
0.97
1.00
0.99
1.03
2.00
2.96
3.15
0.97
0.97
3.02
3.01
f1 (ppm)

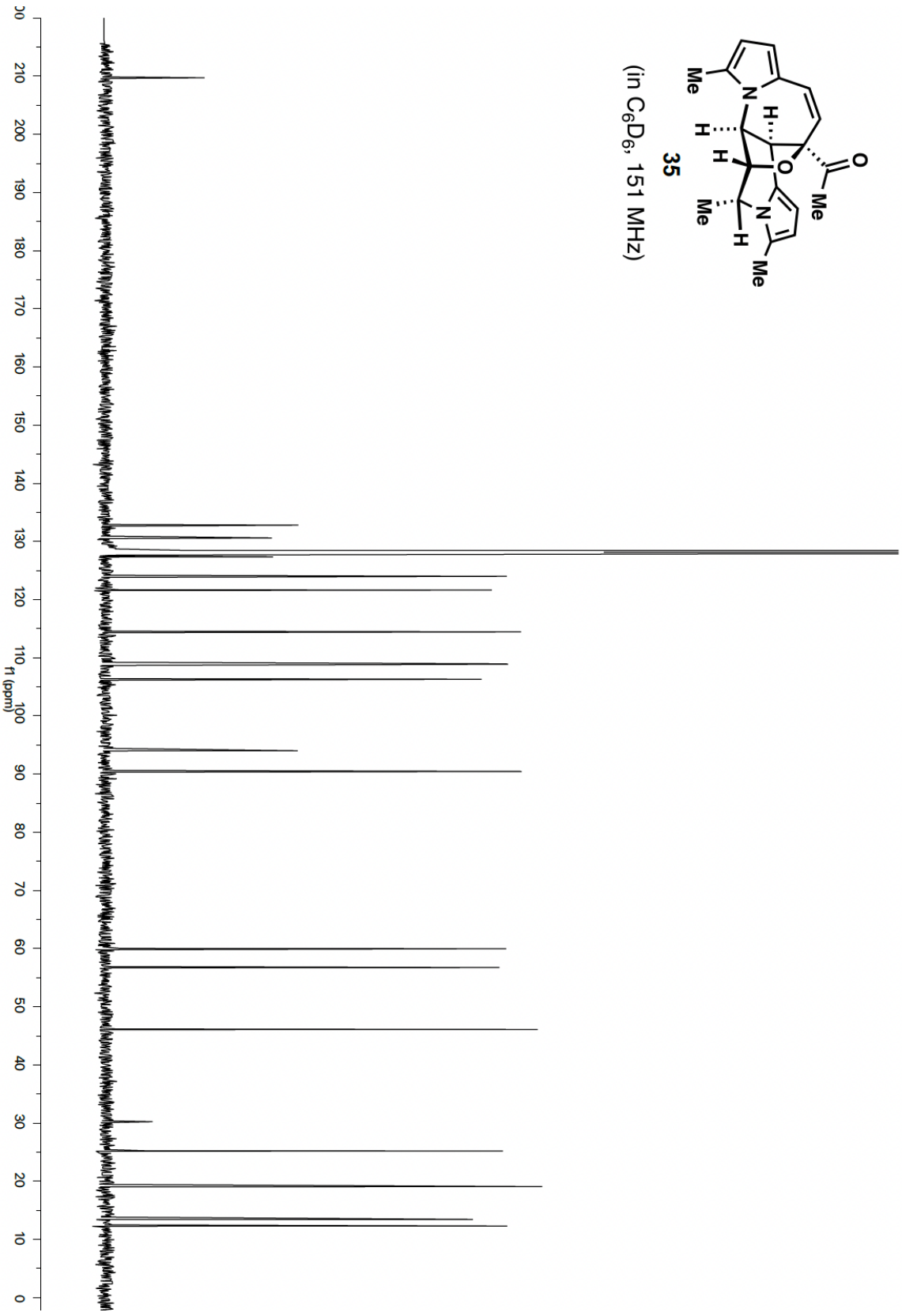

98
(in CDCl3, 151 MHZ)
EtO
OH
H
N
H
OH
Me
Me
N
Me
167.1
134.8
129.4
128.4
126.2
124.9
120.5
112.9
108.4
108.2
106.8
81.4
79.9
64.9
63.8
55.8
54.0
45.4
15.4
14.3
13.6
12.3
f1 (ppm)

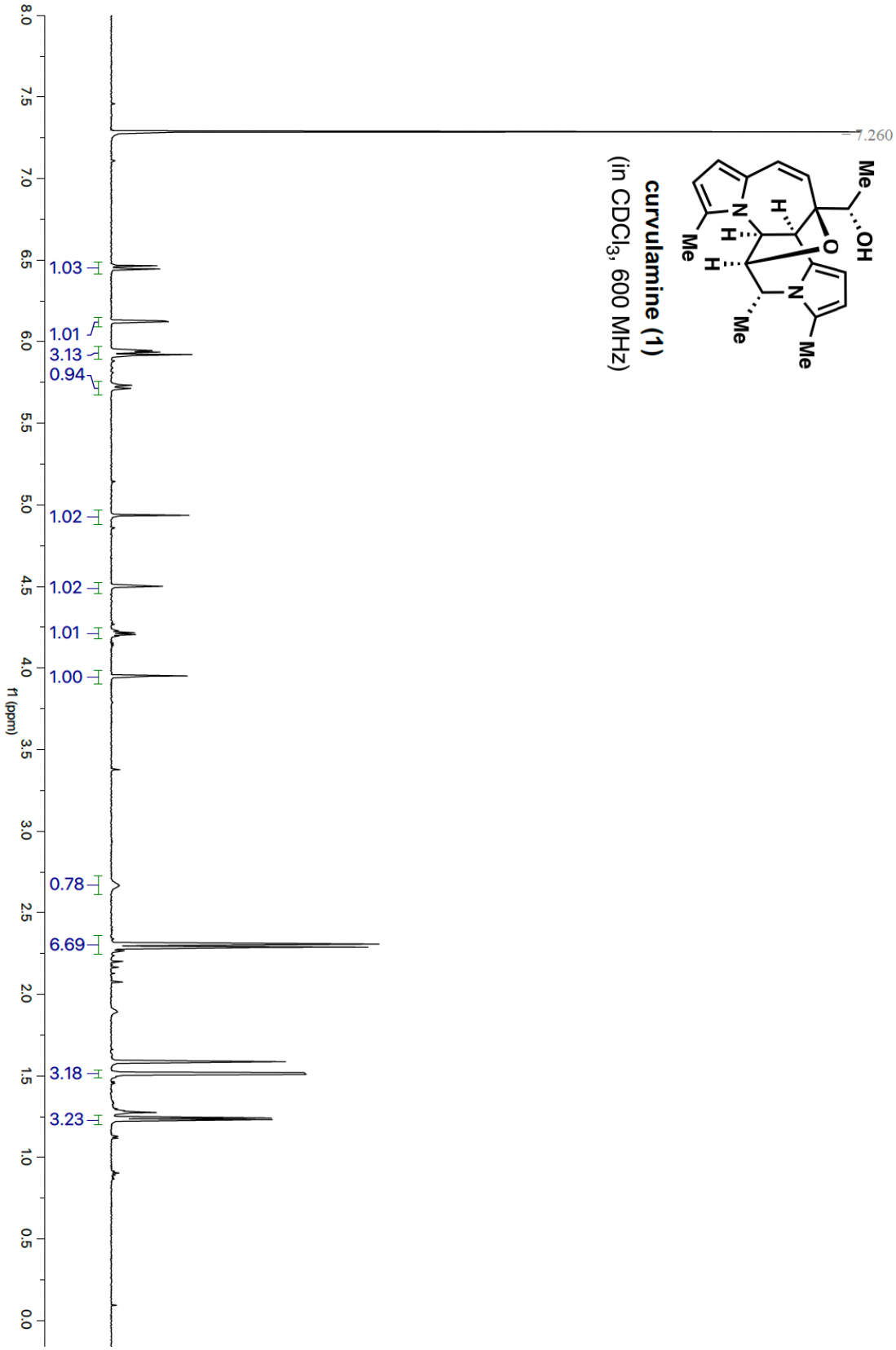

NOESY
Key NOESY correlations
shown in red
{4.36,5.43}
{1.71,5.45}
f2 (ppm)
f1 (ppm)

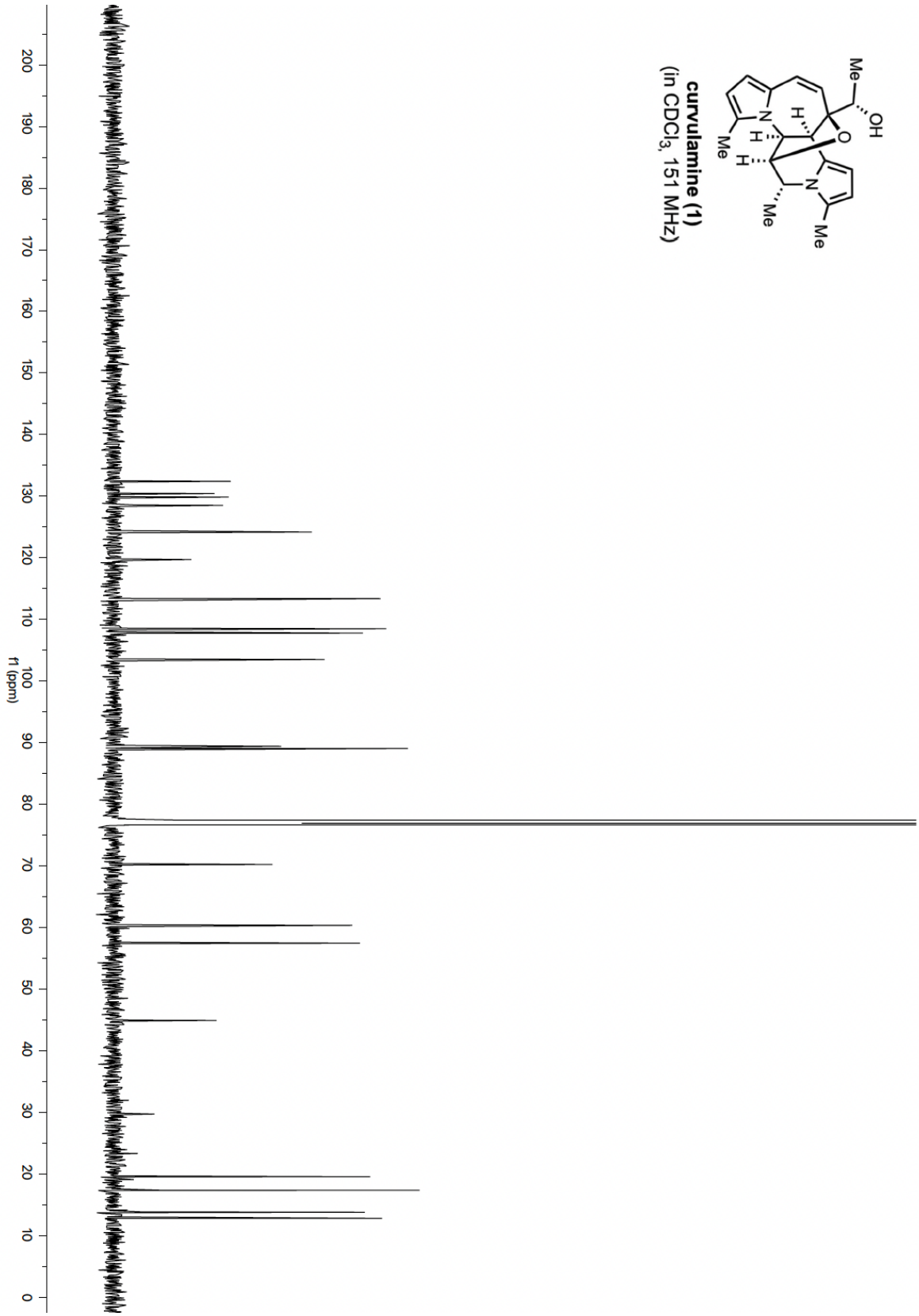

(in $CDCl_3$, 600 MHZ)
99
EtO
OH
Me
OMs
Me
Me
7.26
f1 (ppm)
1.00
1.00
1.00
0.99
1.00
1.00
0.99
1.01
1.01
0.99
1.03
1.02
2.08
3.04
3.07
3.01
1.02
2.95
3.01

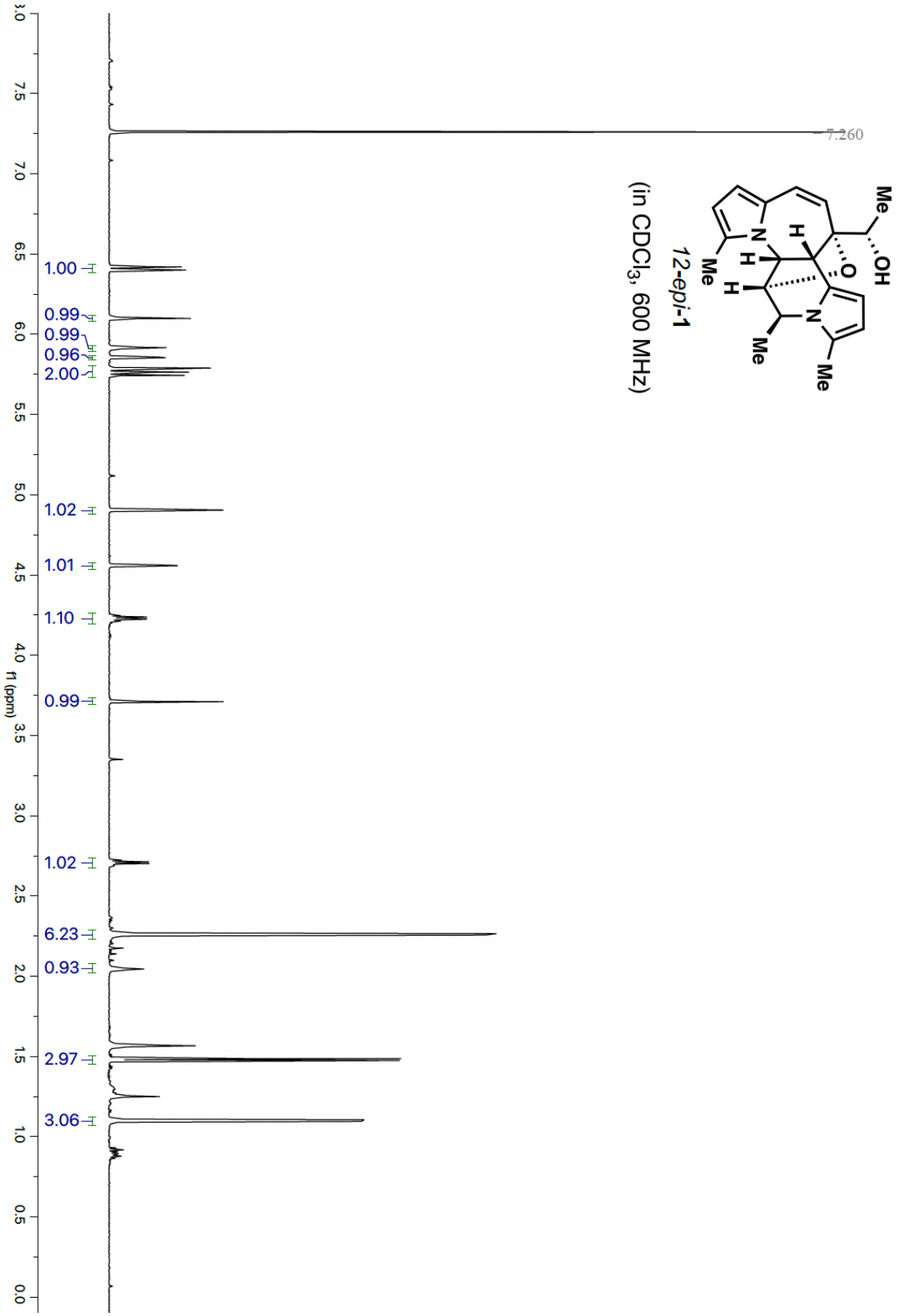

99
(in CDCl3, 151 MHZ)
EtO
OH
H
N
H
OMs
Me
Me
N
Me
165.9
134.8
129.1
128.8
125.1
124.4
120.0
113.0
108.5
108.2
106.7
81.4
79.7
74.5
63.8
53.4
53.0
44.2
36.6
16.6
14.5
13.7
12.6
f1 (ppm)

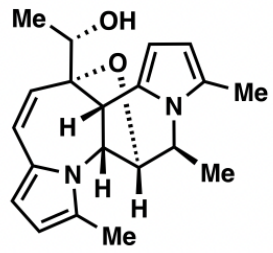

– 7.160
Me
N
H
H
O
Me
N
H
Me
O
Me
35
(in $C_6D_6$, 600 MHz)
1.00
0.98
0.98
1.00
1.97
0.98
0.99
1.94
3.11
3.03
2.99
3.02
f1 (ppm)


35
(in $C_6D_6$, 151 MHz)
f1 (ppm)


curvulamine (1)
(in CDCl3, 600 MHz)
7.260
1.03
1.01
3.13
0.94
1.02
1.02
1.01
1.00
0.78
6.69
3.18
3.23
f1 (ppm)

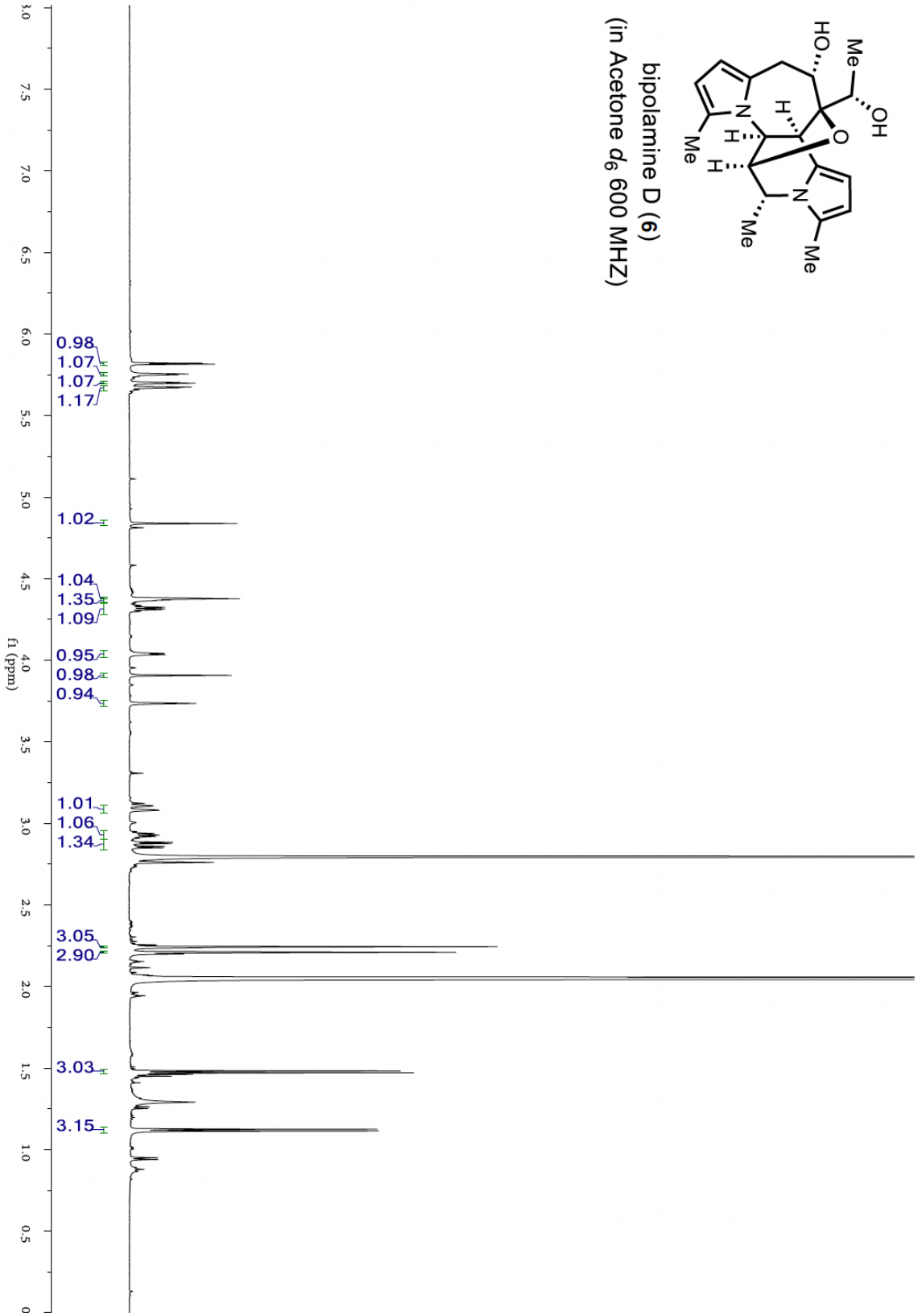

curvulamine (1)
(in CDCl3, 151 MHz)
Me
OH
H
O
N
H
H
Me
Me
N
Me
f1 (ppm)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

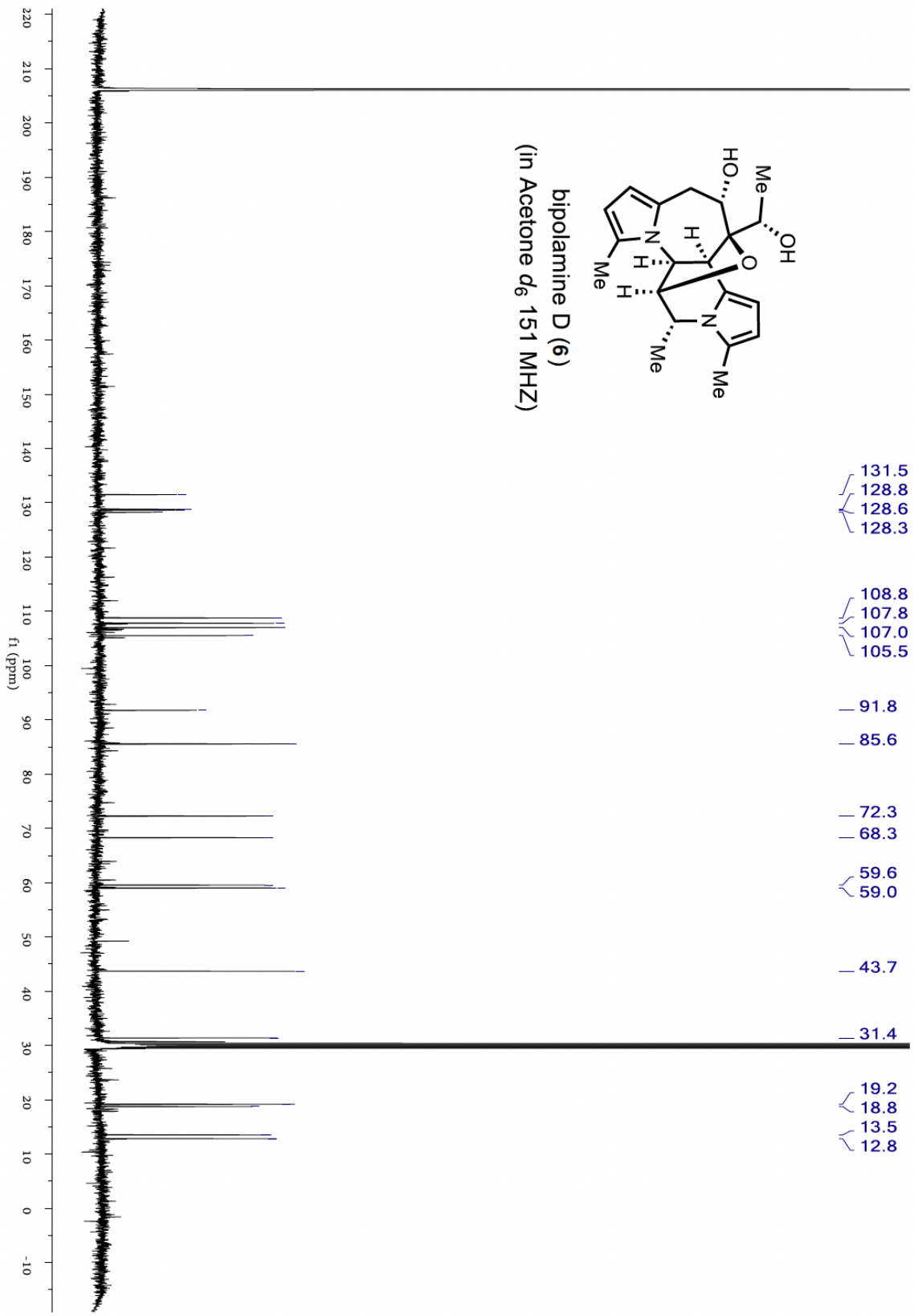

7.260
1.00
0.99
0.99
0.96
2.00
1.02
1.01
1.10
0.99
1.02
6.23
0.93
2.97
3.06
f1 (ppm)
12-epi-1
(in CDCl3, 600 MHz)
Me
OH
H
O
N
H
H
Me
Me
N
Me

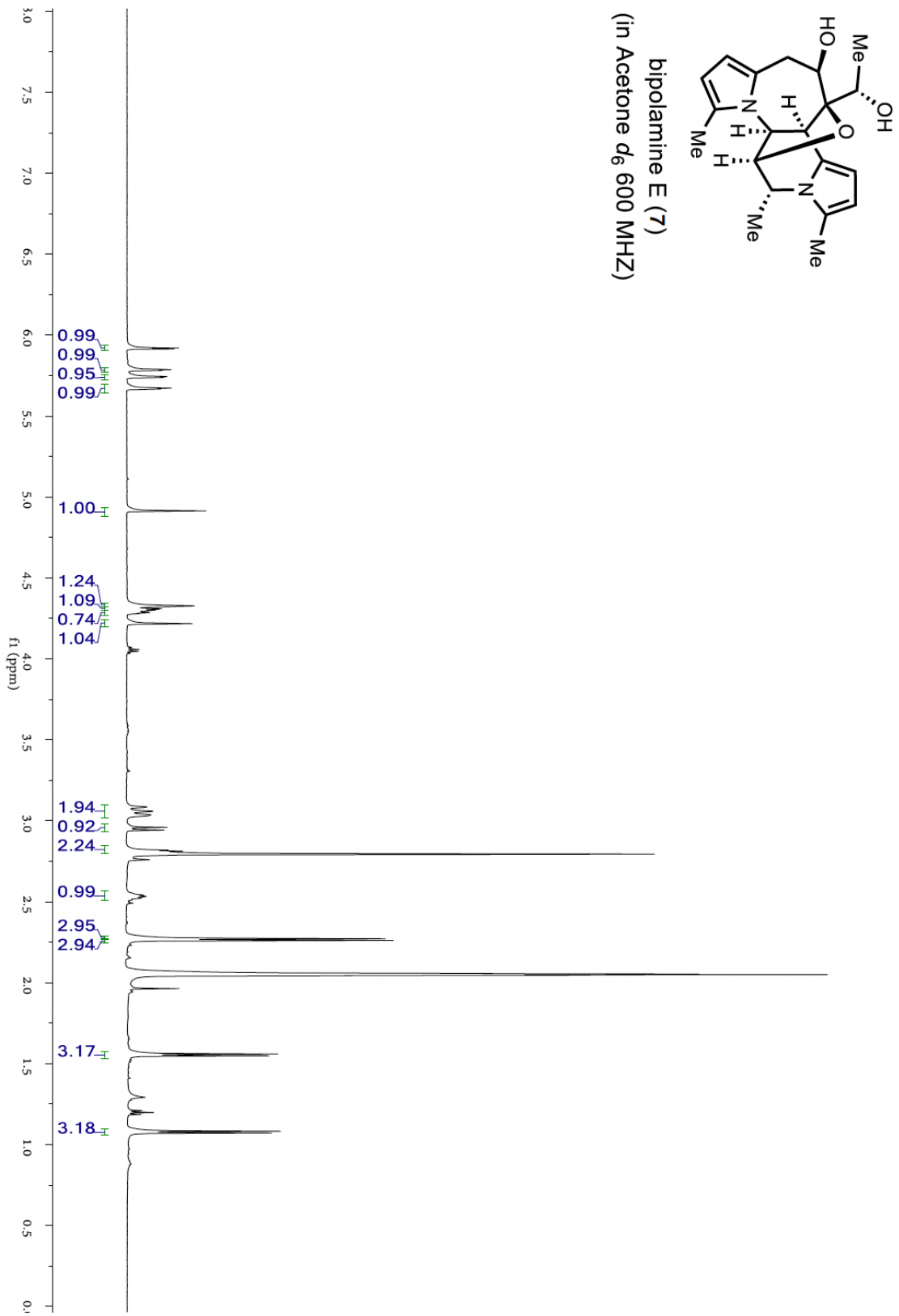


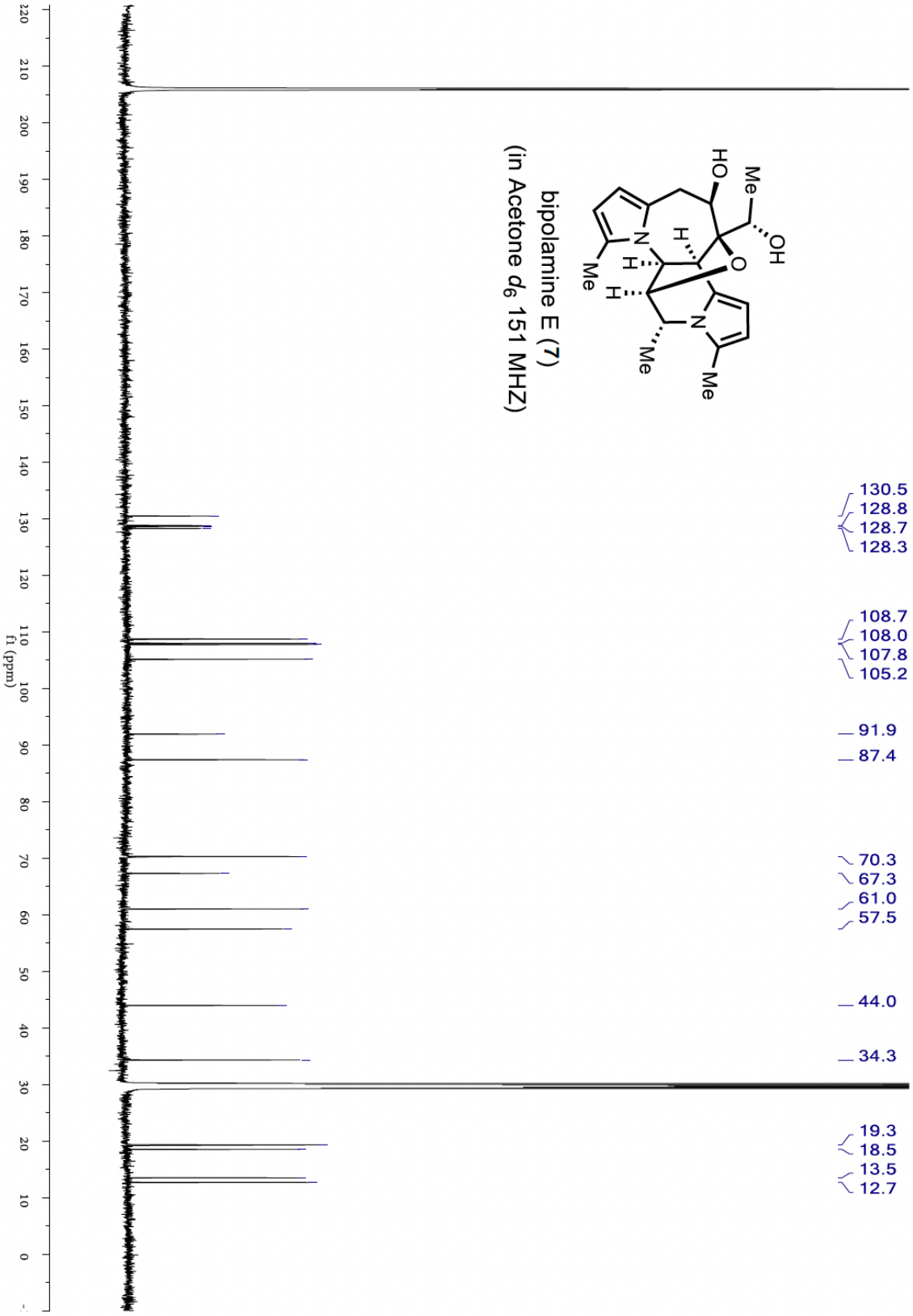

*12-epi-***1**

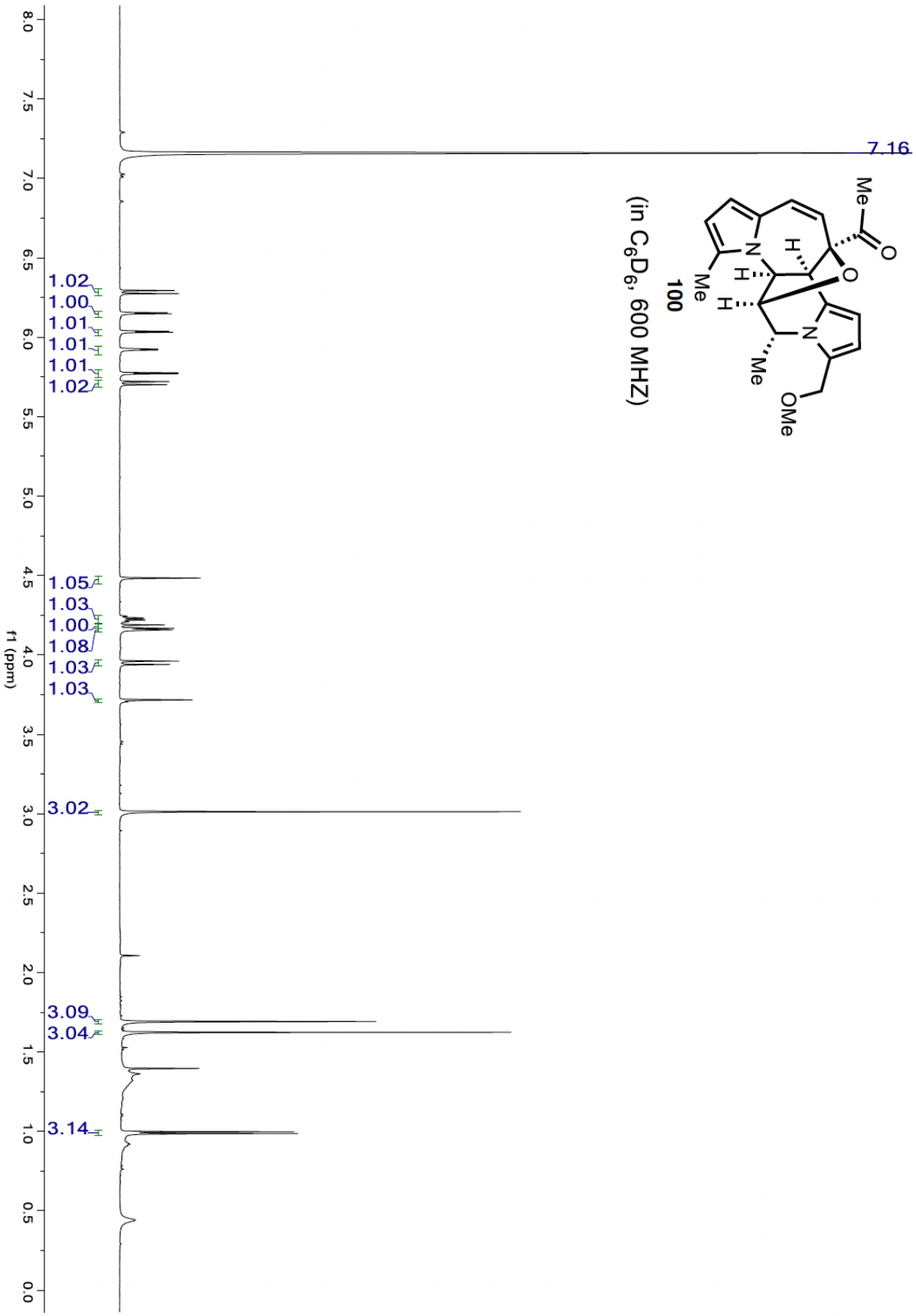
(in $CDCl_3$, 151 MHz)

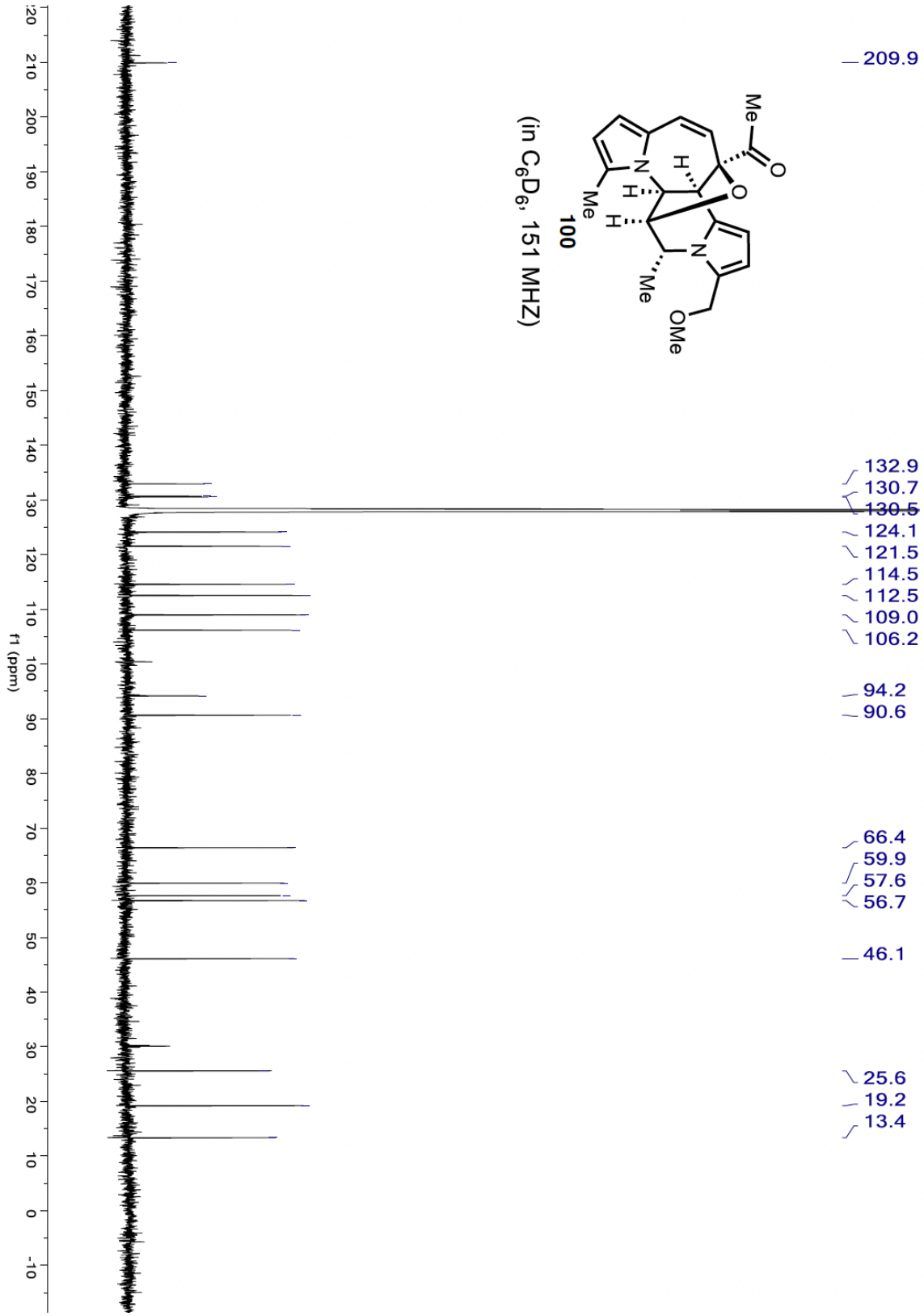

bipolamine D (6)
(in Acetone $d_6$ 600 MHZ)
HO
Me
OH
H
O
N
H
H
Me
N
Me
Me
0.98
1.07
1.07
1.17
1.02
1.04
1.35
1.09
0.95
0.98
0.94
1.01
1.06
1.34
3.05
2.90
3.03
3.15
f1 (ppm)

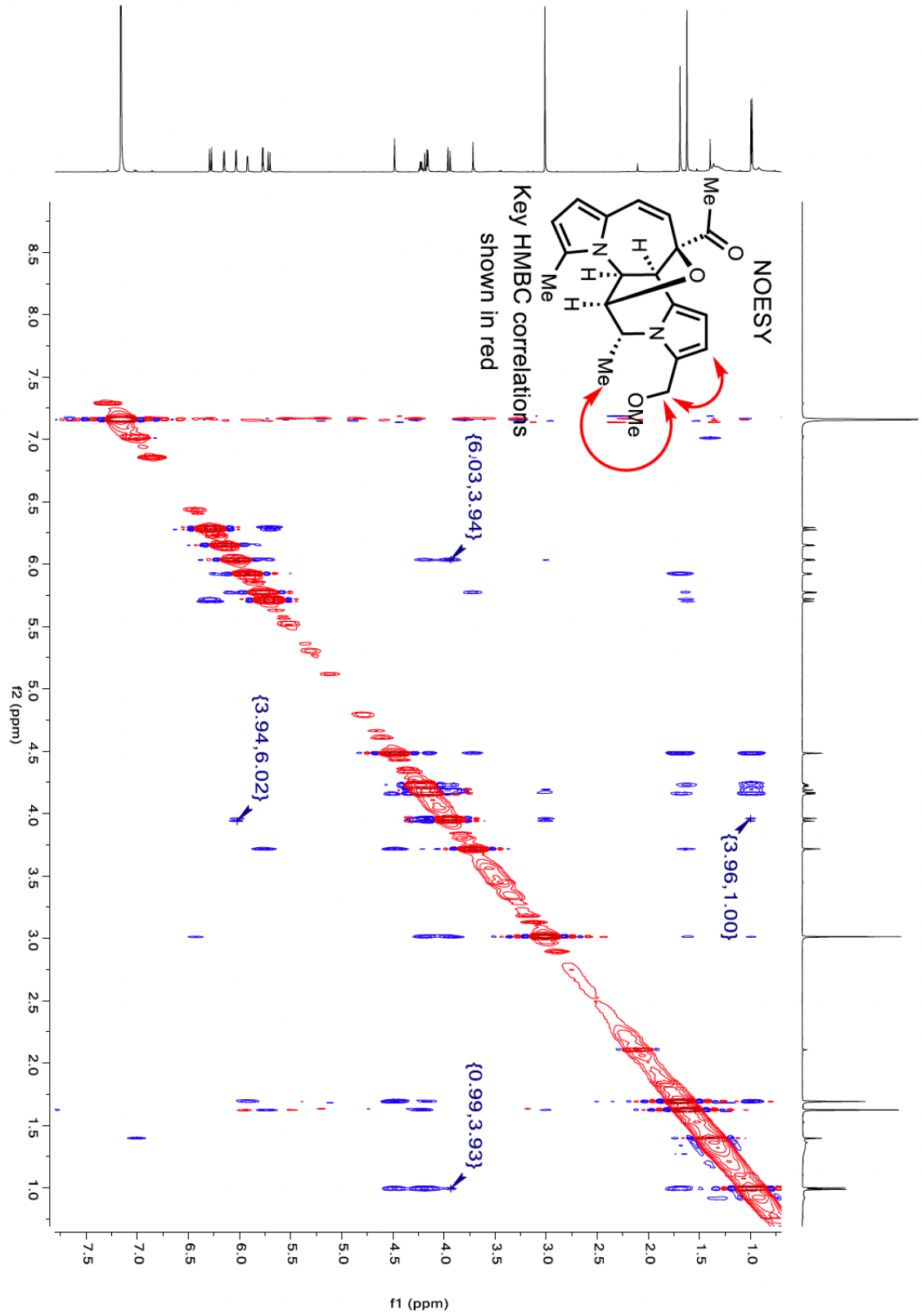

bipolamine D (6)
(in Acetone $d_6$ 151 MHZ)
HO
Me
OH
H
N
H
Me
O
H
N
Me
Me
131.5
128.8
128.6
128.3
108.8
107.8
107.0
105.5
91.8
85.6
72.3
68.3
59.6
59.0
43.7
31.4
19.2
18.8
13.5
12.8
f1 (ppm)

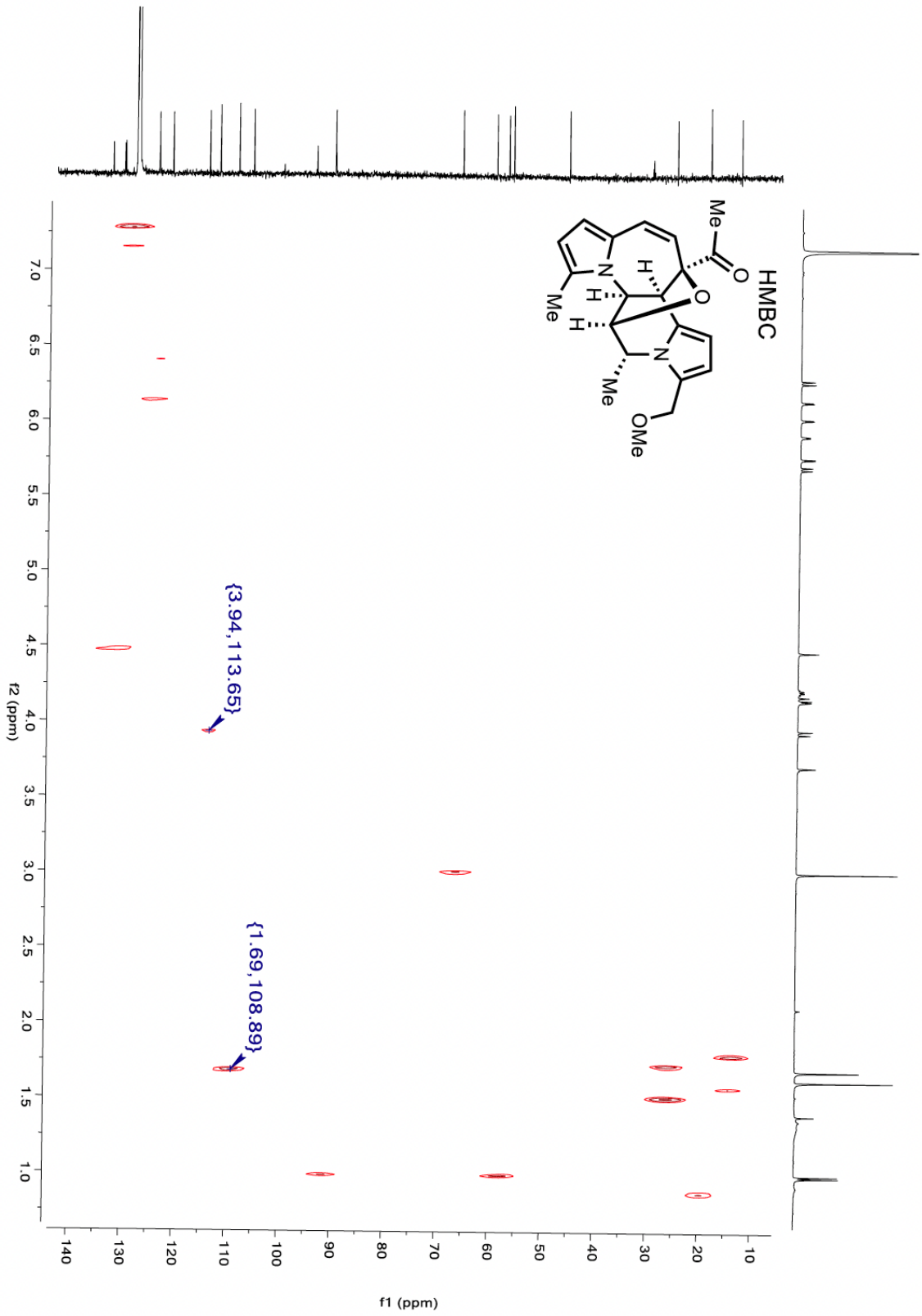

bipolamine E (7)
(in Acetone $d_6$ 600 MHZ)
HO
Me
OH
H
N
H
O
Me
H
N
Me
Me
f1 (ppm)
0.99
0.99
0.95
0.99
1.00
1.24
1.09
0.74
1.04
1.94
0.92
2.24
0.99
2.95
2.94
3.17
3.18

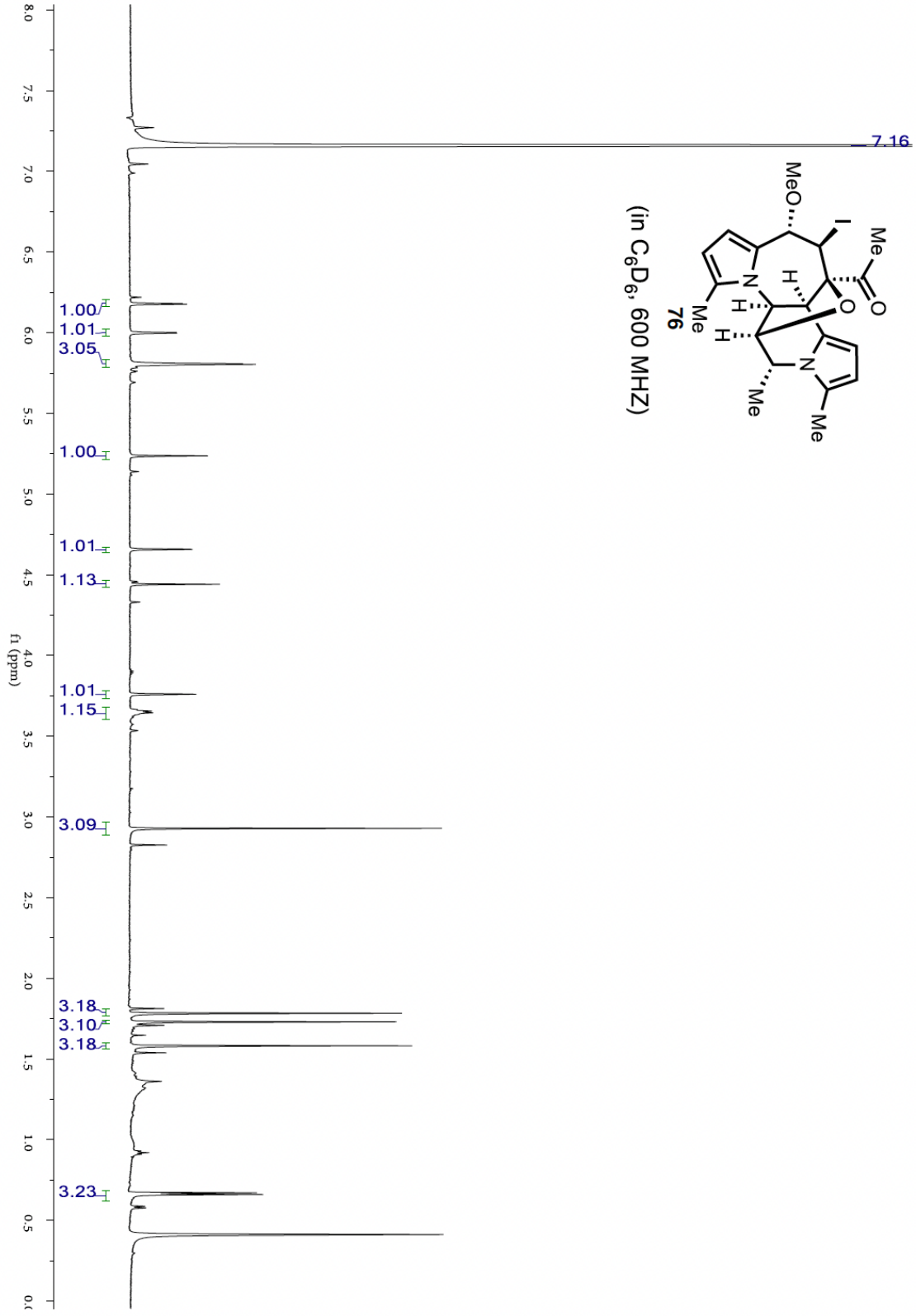

bipolamine E (7)
(in Acetone $d_6$ 151 MHZ)
HO
Me
OH
H
N
H
O
H
N
Me
Me
Me
130.5
128.8
128.7
128.3
108.7
108.0
107.8
105.2
91.9
87.4
70.3
67.3
61.0
57.5
44.0
34.3
19.3
18.5
13.5
12.7
f1 (ppm)

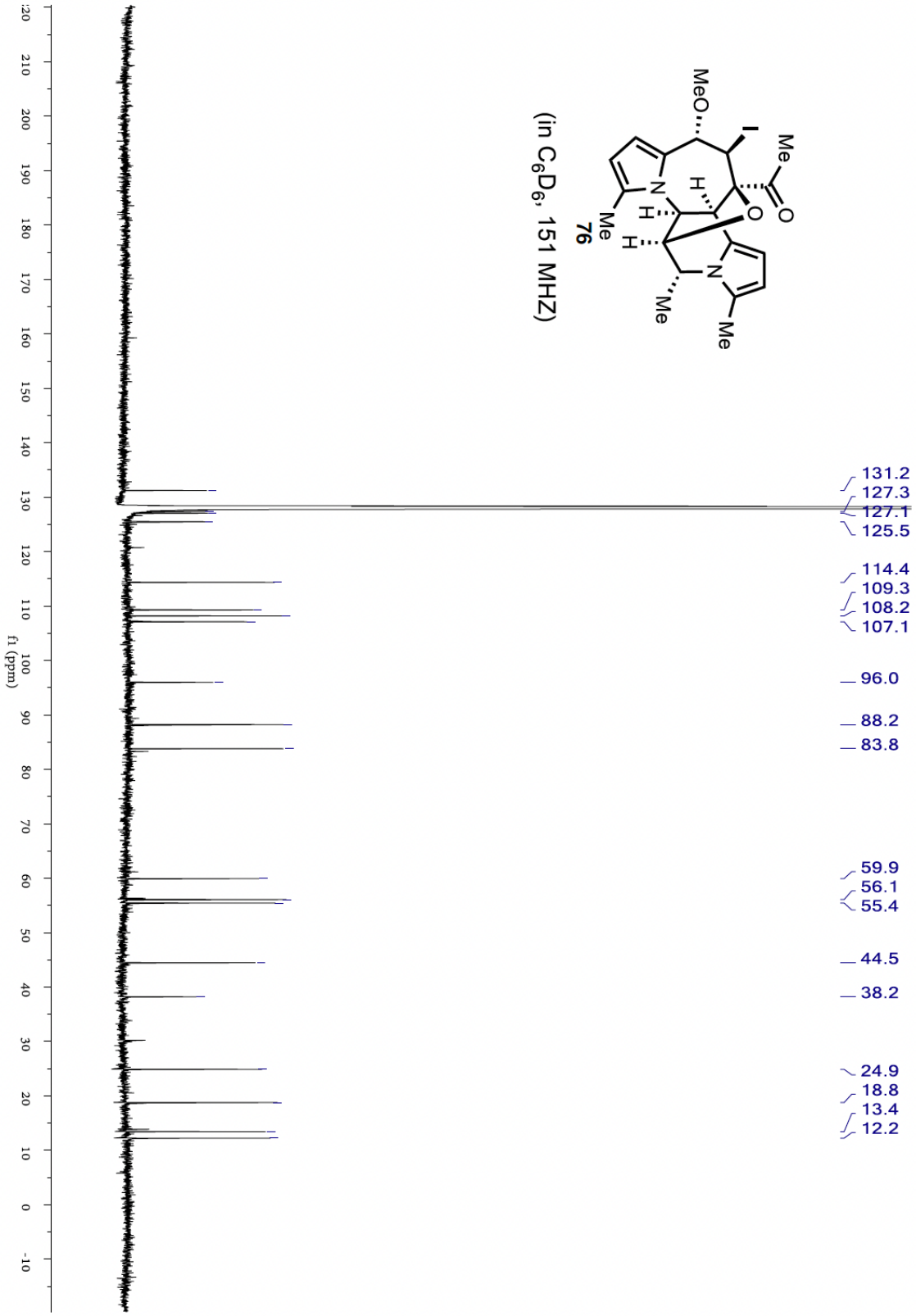

7.16
1.02
1.00
1.01
1.01
1.01
1.02
1.05
1.03
1.00
1.08
1.03
1.03
3.02
3.09
3.04
3.14
f1 (ppm)
(in $C_6D_6$, 600 MHZ)
100
Me
O
H
N
H
Me
O
N
Me
OMe

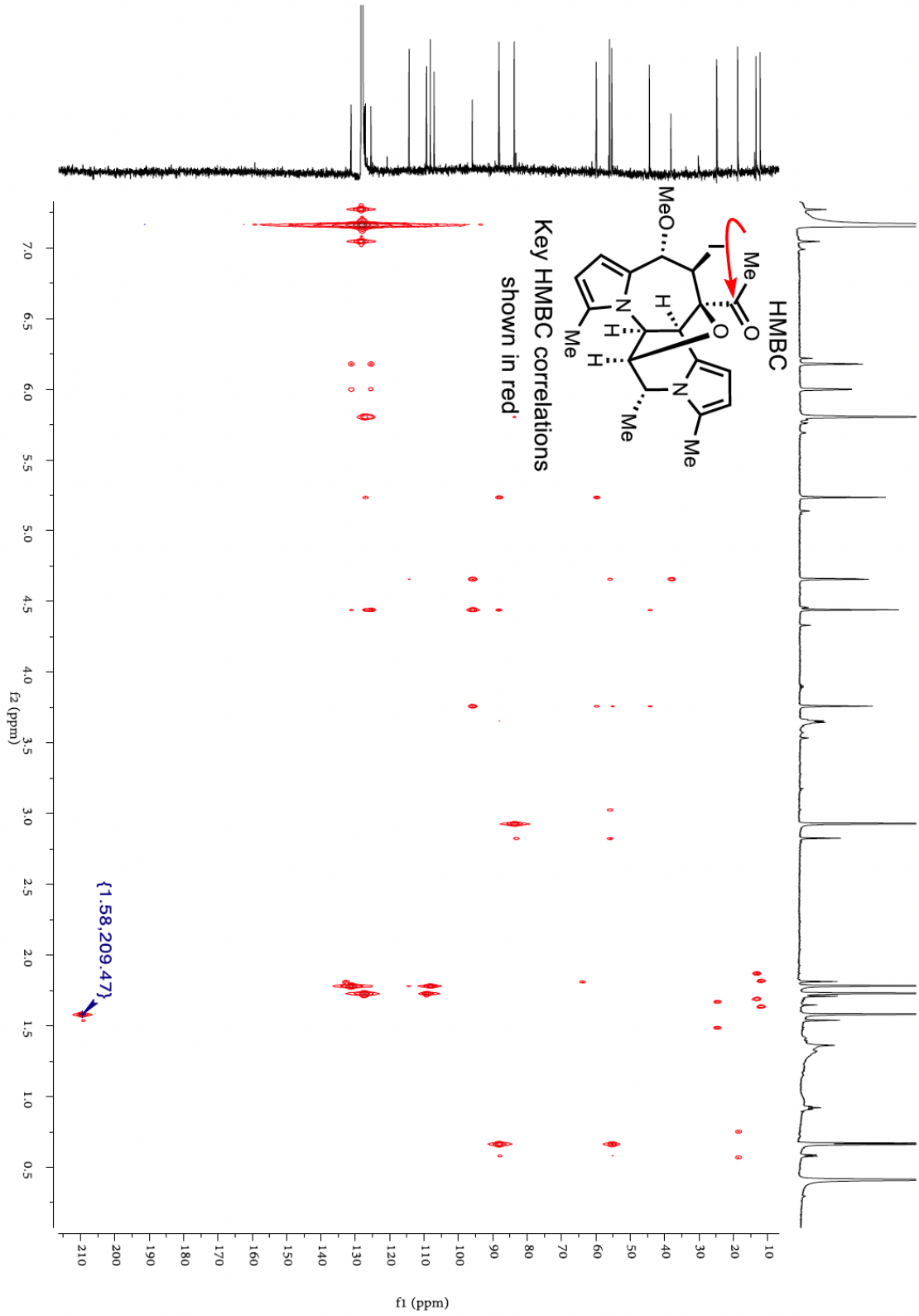

209.9
132.9
130.7
130.5
124.1
121.5
114.5
112.5
109.0
106.2
94.2
90.6
66.4
59.9
57.6
56.7
46.1
25.6
19.2
13.4
f1 (ppm)
(in C6D6, 151 MHZ)
100
Me
O
H
N
H
H
Me
N
Me
OMe

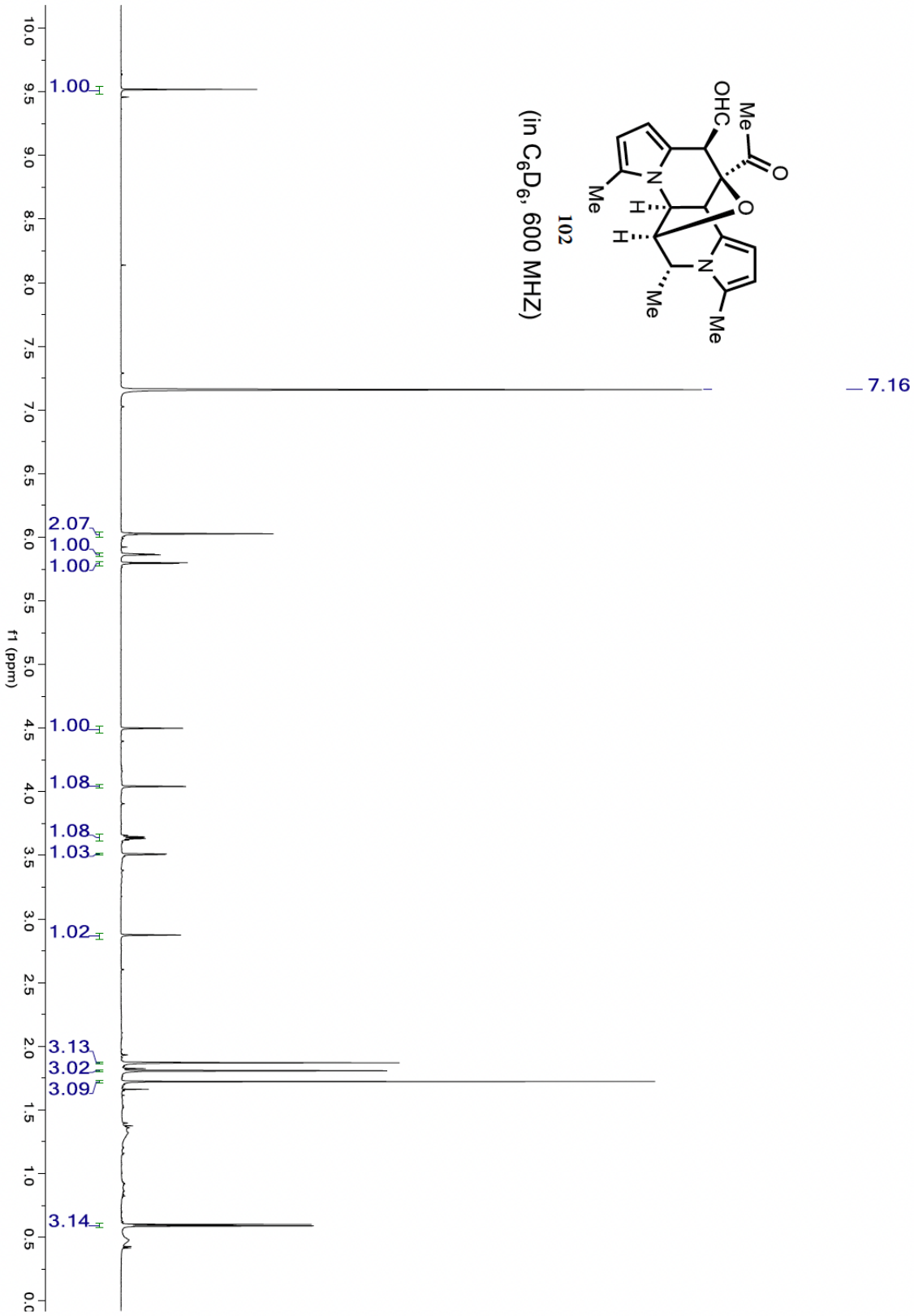

Key HMBC correlations
shown in red
NOESY
{6.03,3.94}
{3.94,6.02}
{3.96,1.00}
{0.99,3.93}
f1 (ppm)
f2 (ppm)

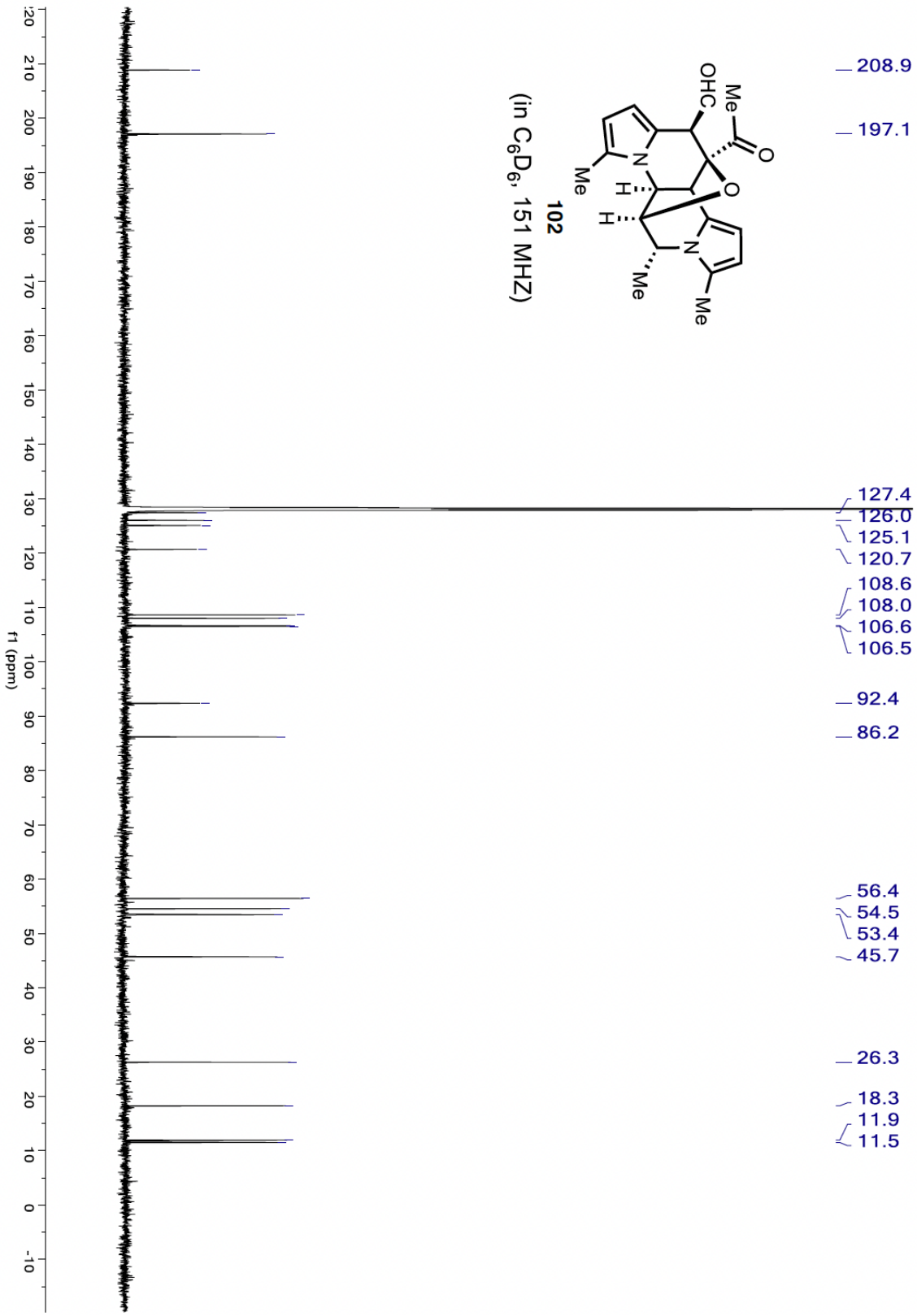

HMBC
Me
O
H
N
H
H
Me
O
N
Me
OMe
{3.94,113.65}
{1.69,108.89}
f2 (ppm)
f1 (ppm)

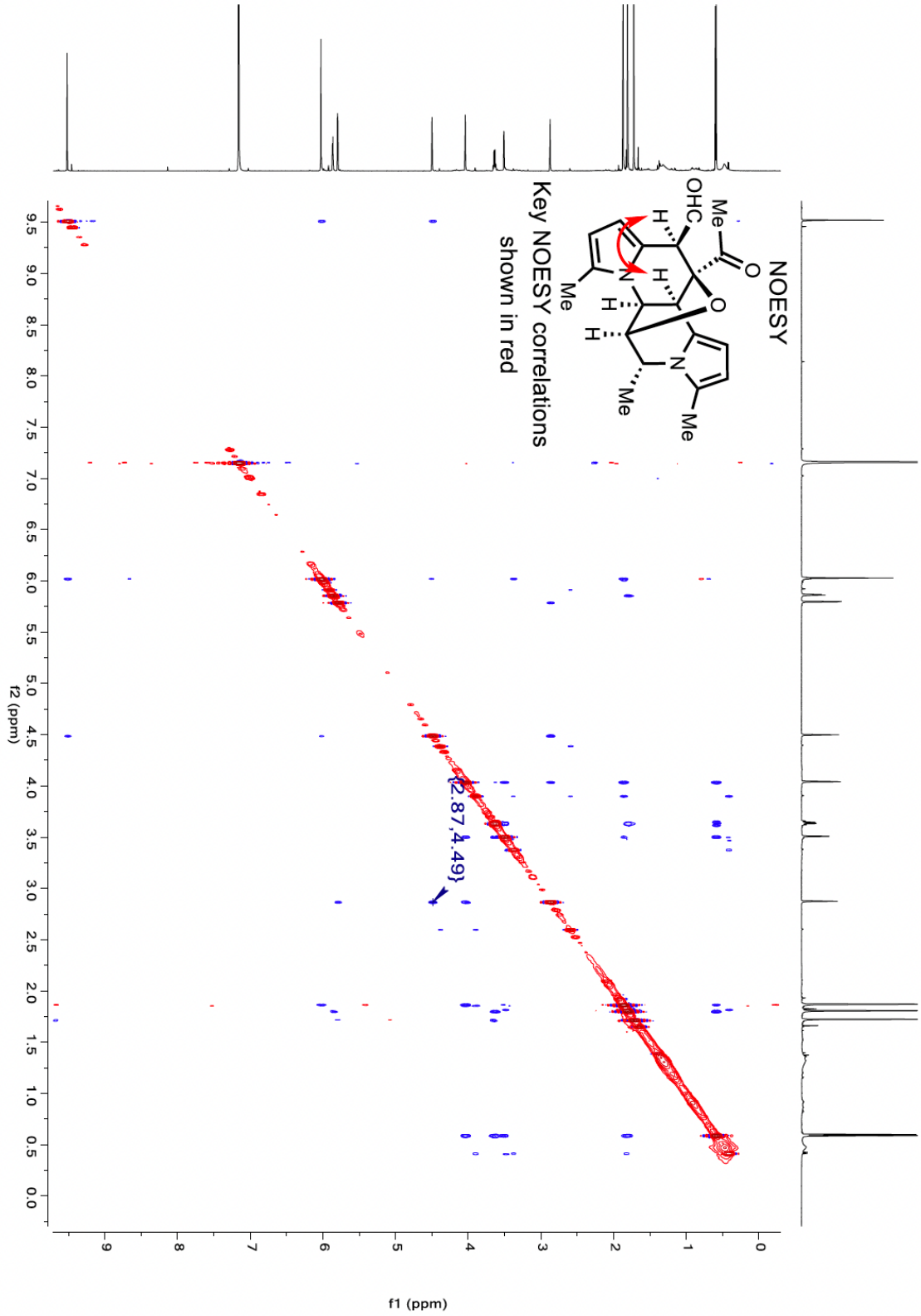

7.16
1.00
1.01
3.05
1.00
1.01
1.13
1.01
1.15
3.09
3.18
3.10
3.18
3.23
f1 (ppm)
(in $C_6D_6$, 600 MHZ)
76
MeO
I
Me
O
O
N
H
H
H
Me
N
Me
Me

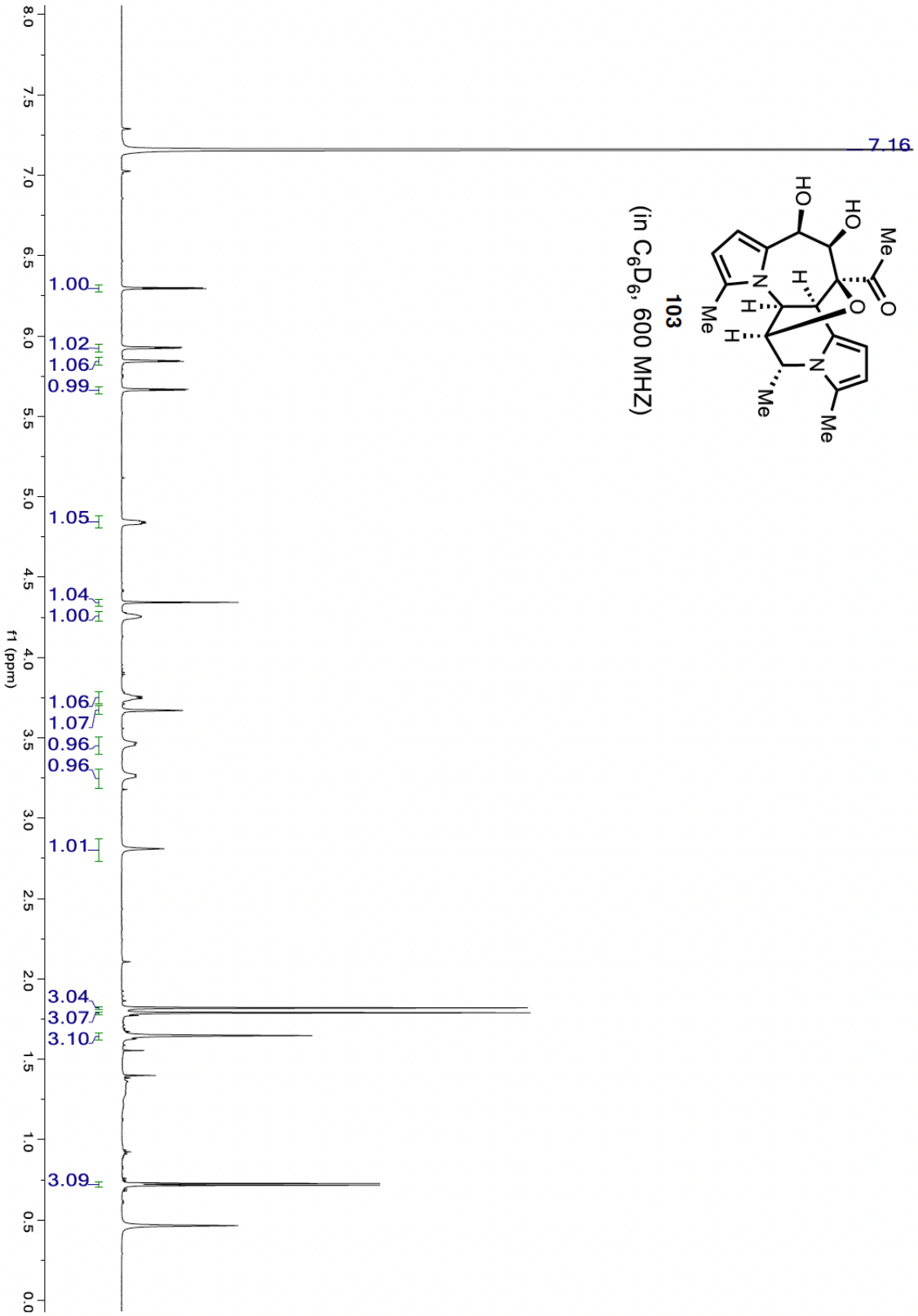

(in $C_6D_6$, 151 MHZ)
76
MeO
Me
O
H
N
H
H
Me
Me
Me
O
N
Me
131.2
127.3
127.1
125.5
114.4
109.3
108.2
107.1
96.0
88.2
83.8
59.9
56.1
55.4
44.5
38.2
24.9
18.8
13.4
12.2
f1 (ppm)

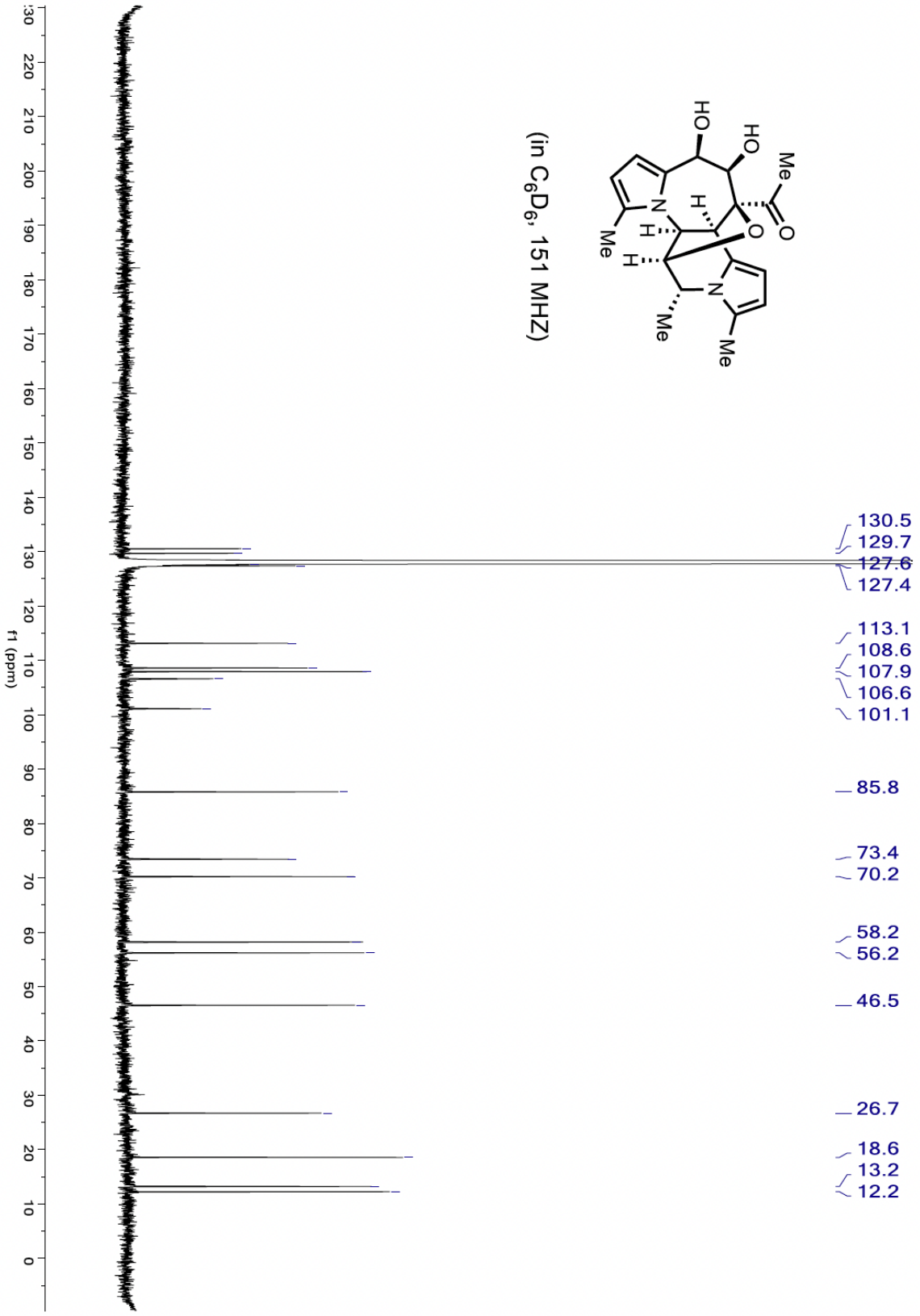

HMBC
Key HMBC correlations
shown in red
MeO
Me
O
H
N
H
H
Me
Me
Me
N
Me
{1.58,209.47}
f2 (ppm)
f1 (ppm)

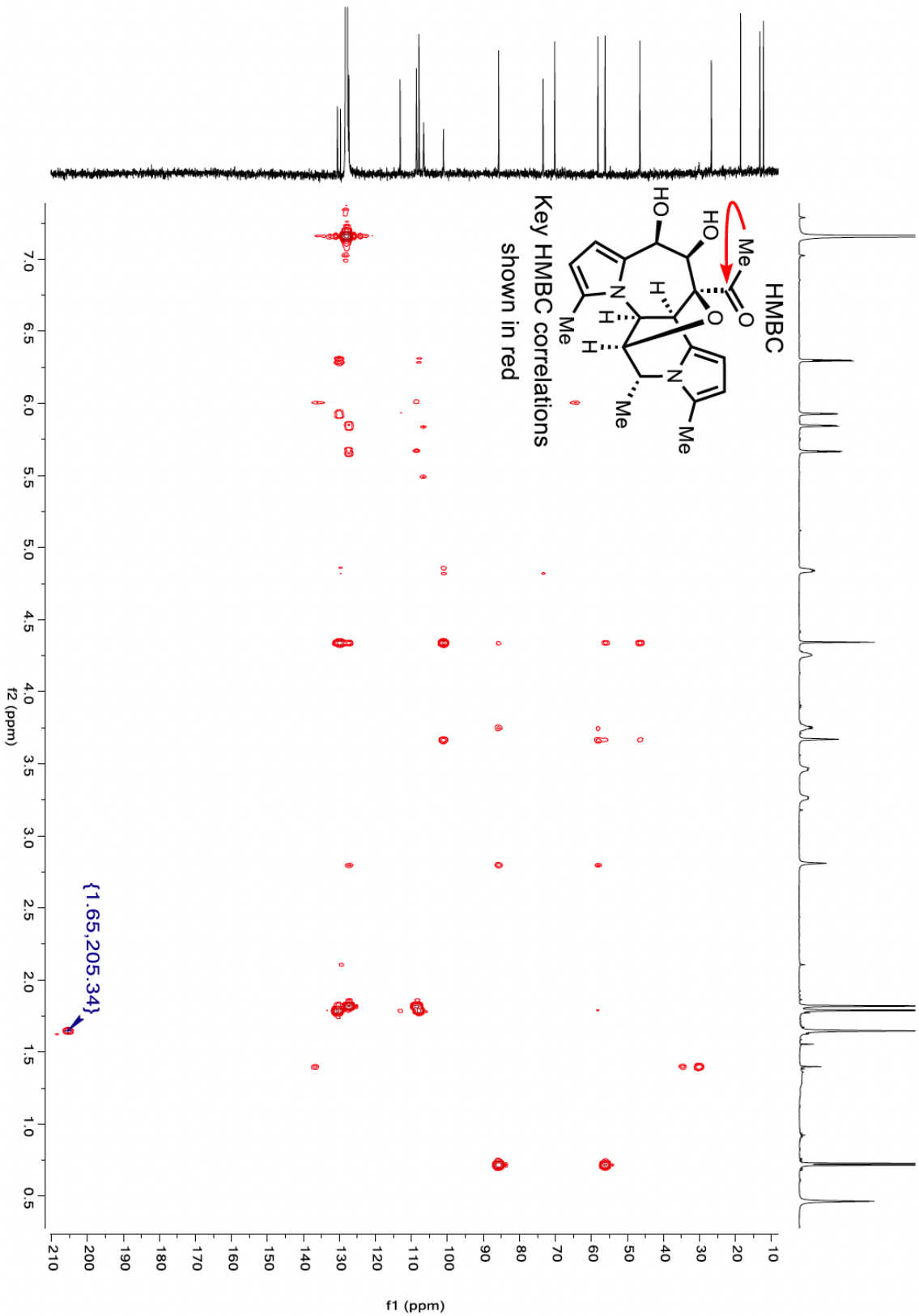

102
(in $C_6D_6$, 600 MHZ)
Me
OHC
O
N
H
H
O
Me
N
Me
Me
7.16
1.00
2.07
1.00
1.00
1.00
1.08
1.08
1.03
1.02
3.13
3.02
3.09
3.14
f1 (ppm)

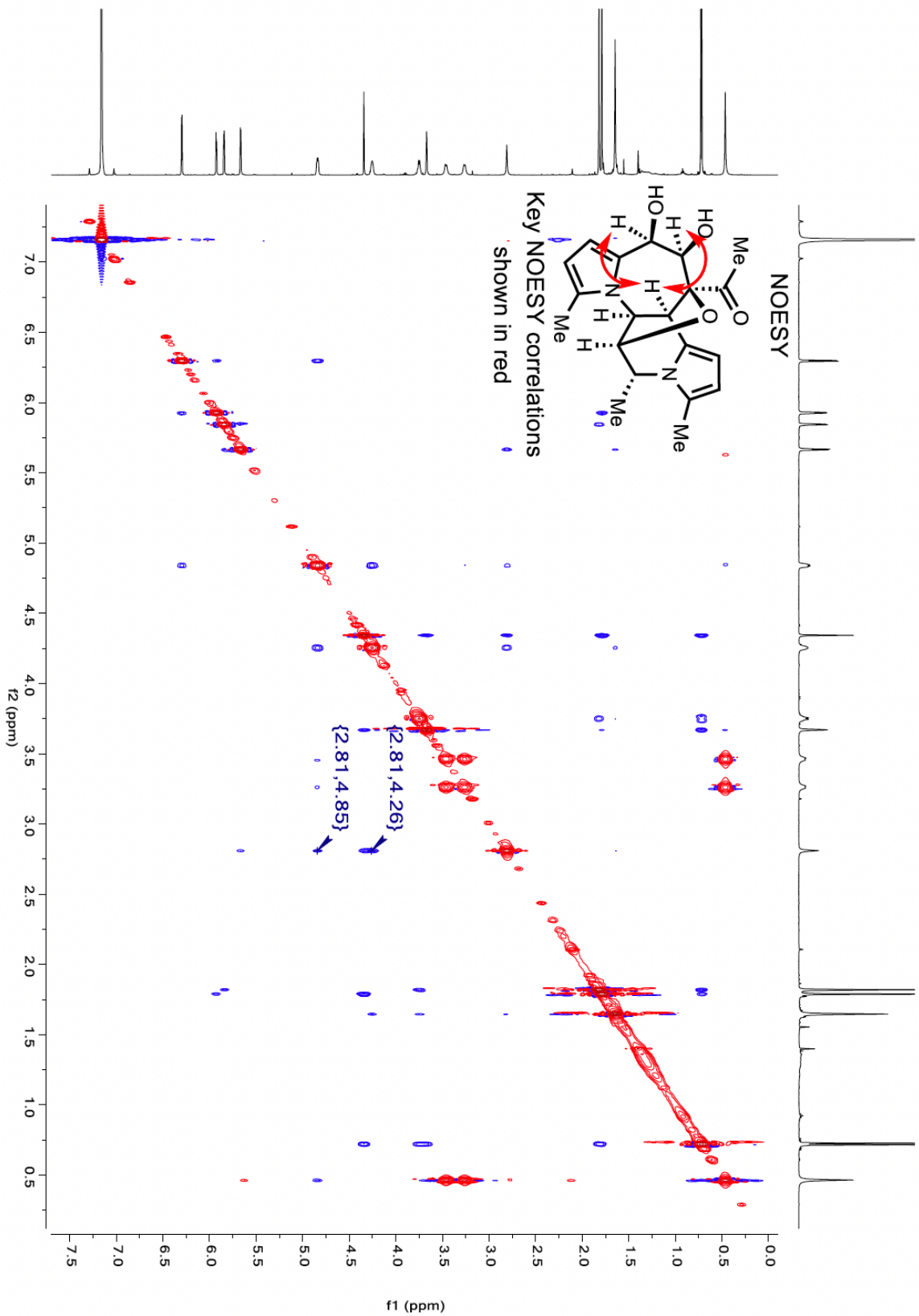

208.9
197.1
127.4
126.0
125.1
120.7
108.6
108.0
106.6
106.5
92.4
86.2
56.4
54.5
53.4
45.7
26.3
18.3
11.9
11.5
f1 (ppm)
102
(in C6D6, 151 MHZ)
OHC
Me
O
N
H
H
Me
Me
N
Me

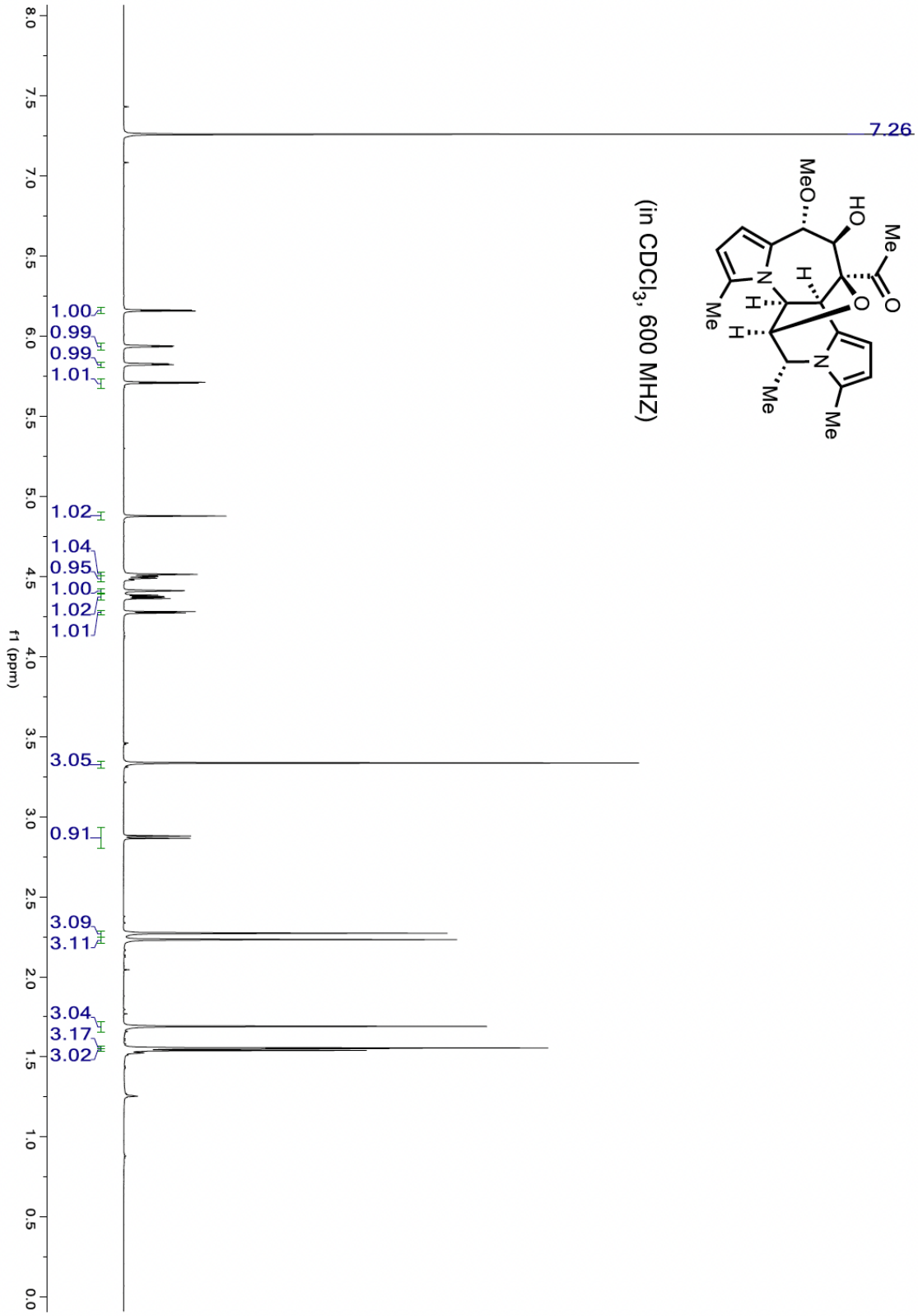

NOESY
Key NOESY correlations
shown in red
Me
OHC
O
H
H
N
H
H
O
N
Me
Me
{2.87, 4.49}
f2 (ppm)
f1 (ppm)

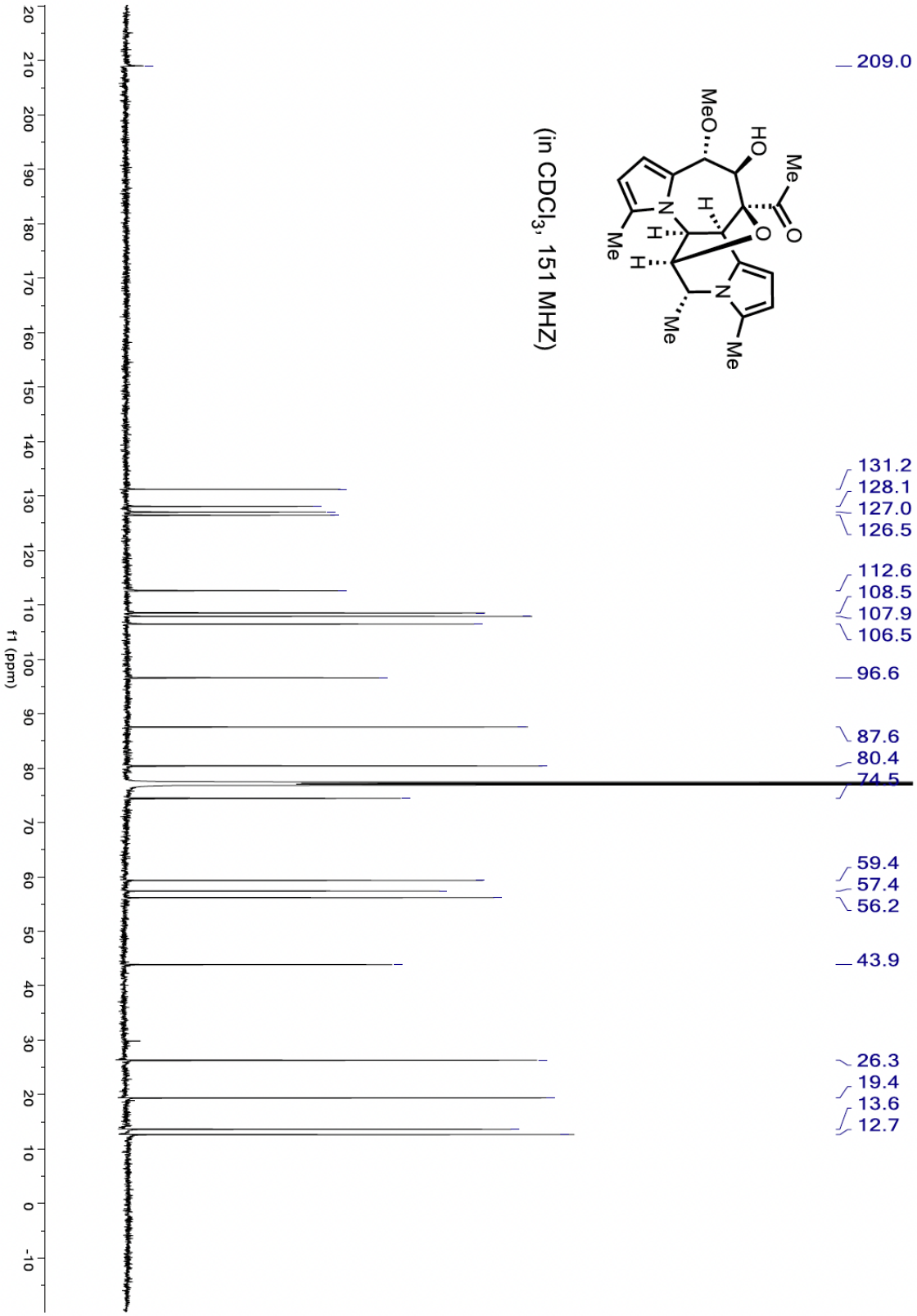

7.16
1.00
1.02
1.06
0.99
1.05
1.04
1.00
1.06
1.07
0.96
0.96
1.01
3.04
3.07
3.10
3.09
f1 (ppm)
103
(in C6D6, 600 MHZ)
HO
HO
Me
O
H
N
H
H
Me
Me
Me
N

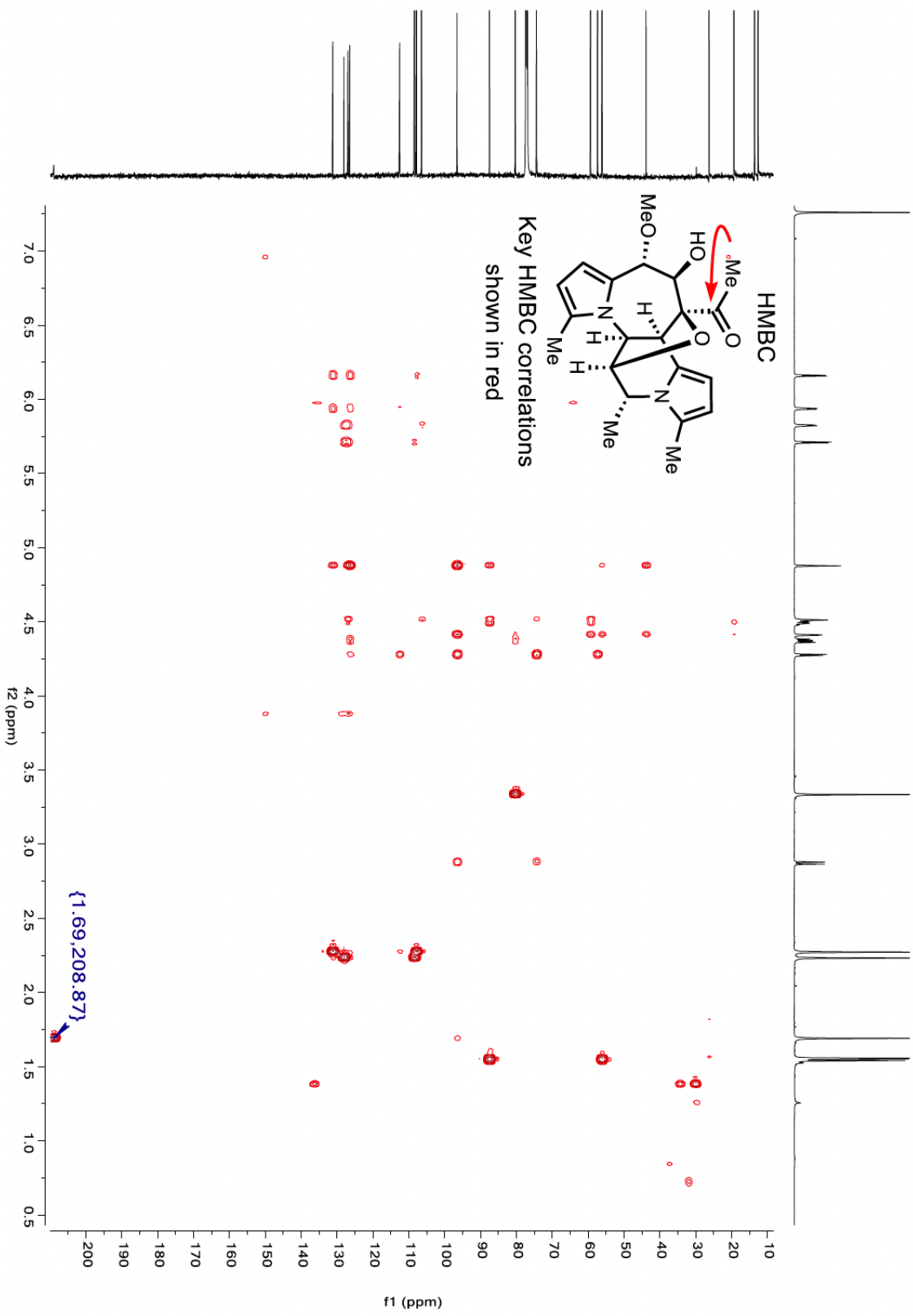

(in $C_6D_6$, 151 MHZ)
HO
HO
Me
O
H
N
H
H
Me
N
Me
Me
f1 (ppm)
130.5
129.7
127.6
127.4
113.1
108.6
107.9
106.6
101.1
85.8
73.4
70.2
58.2
56.2
46.5
26.7
18.6
13.2
12.2

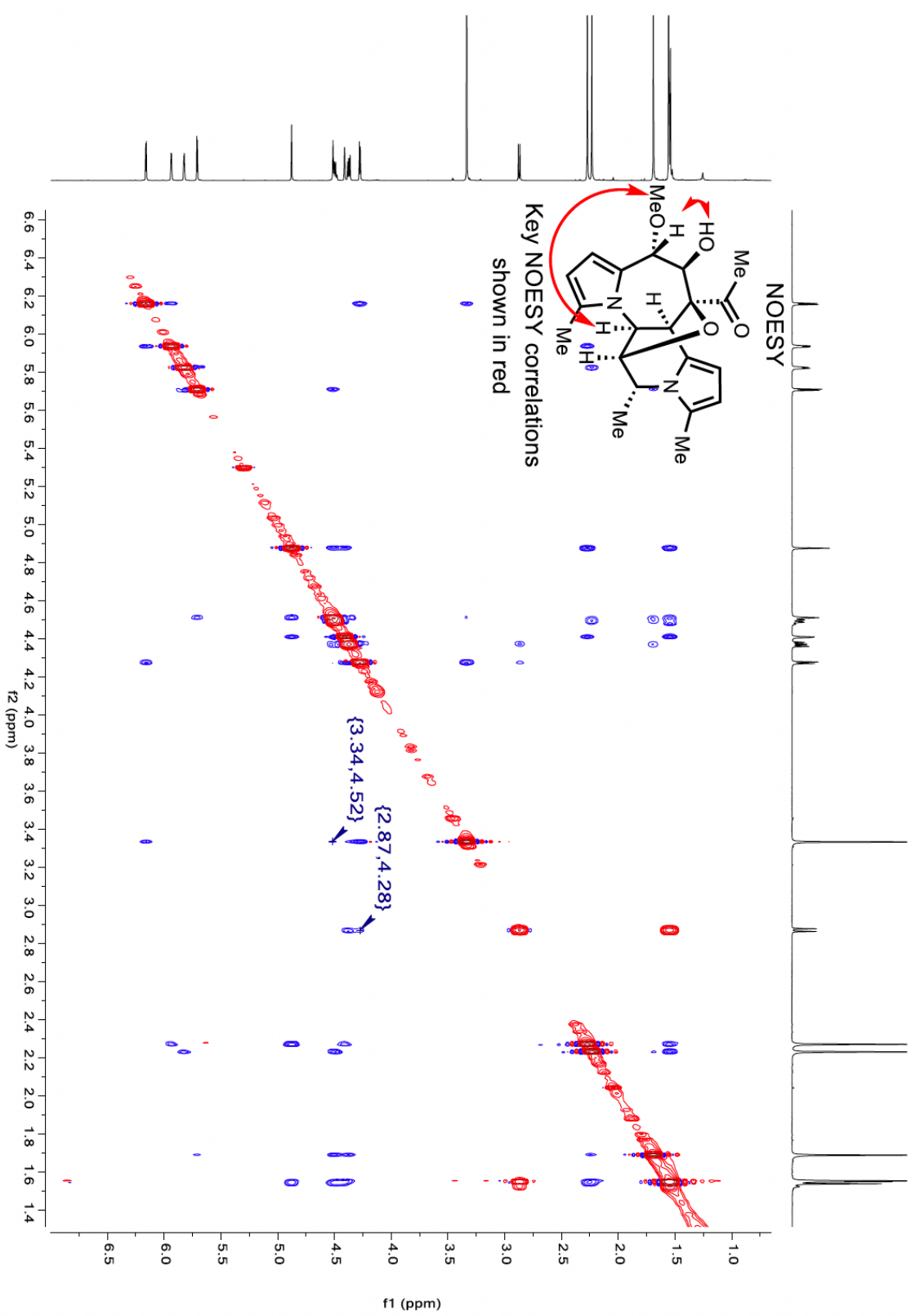

HMBC
Key HMBC correlations
shown in red
HO
HO
Me
O
H
N
H
H
Me
N
Me
Me
{1.65,205.34}
f1 (ppm)
f2 (ppm)

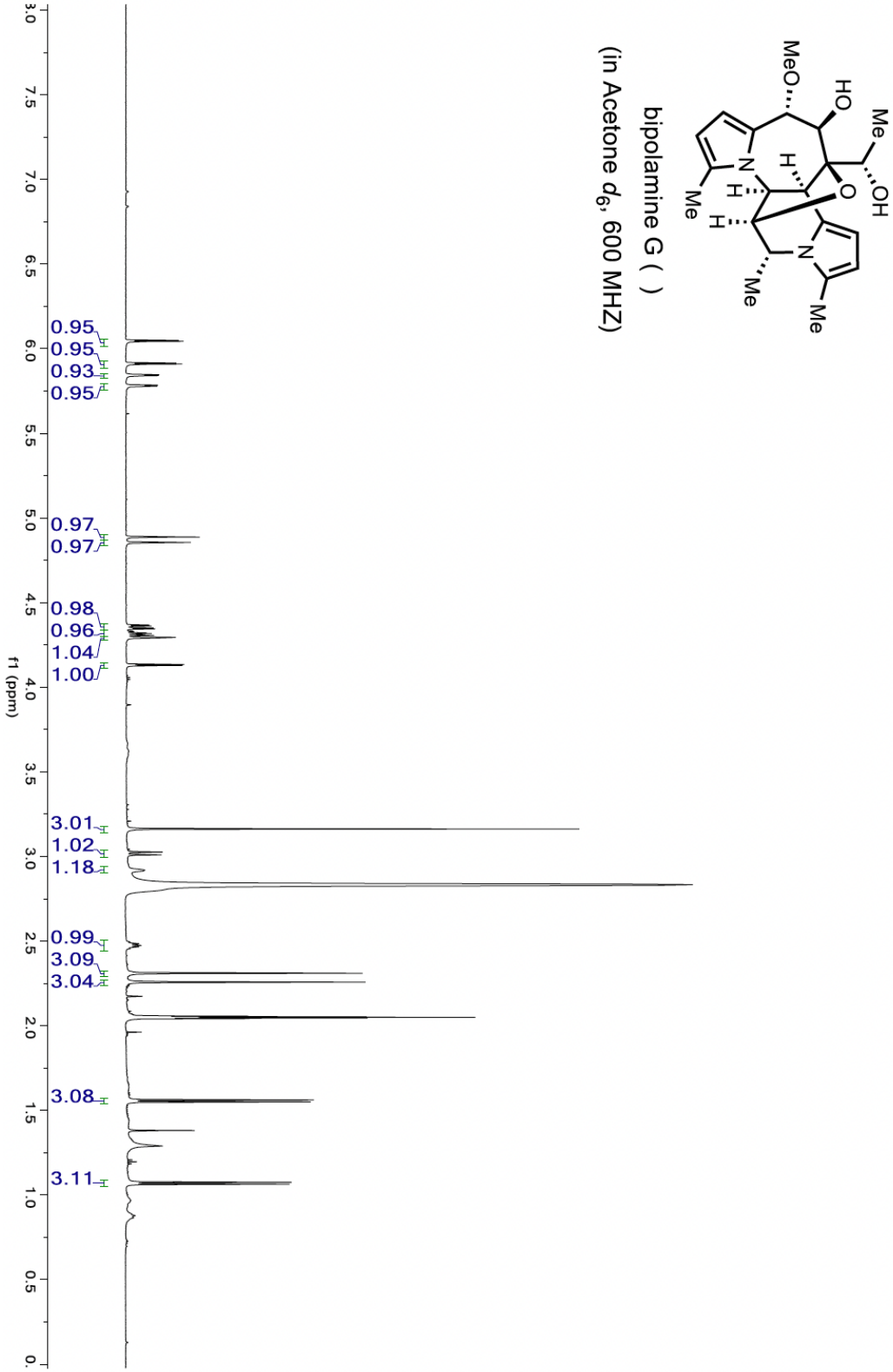

NOESY
Key NOESY correlations
shown in red
{2.81,4.85}
{2.81,4.26}
f1 (ppm)
f2 (ppm)

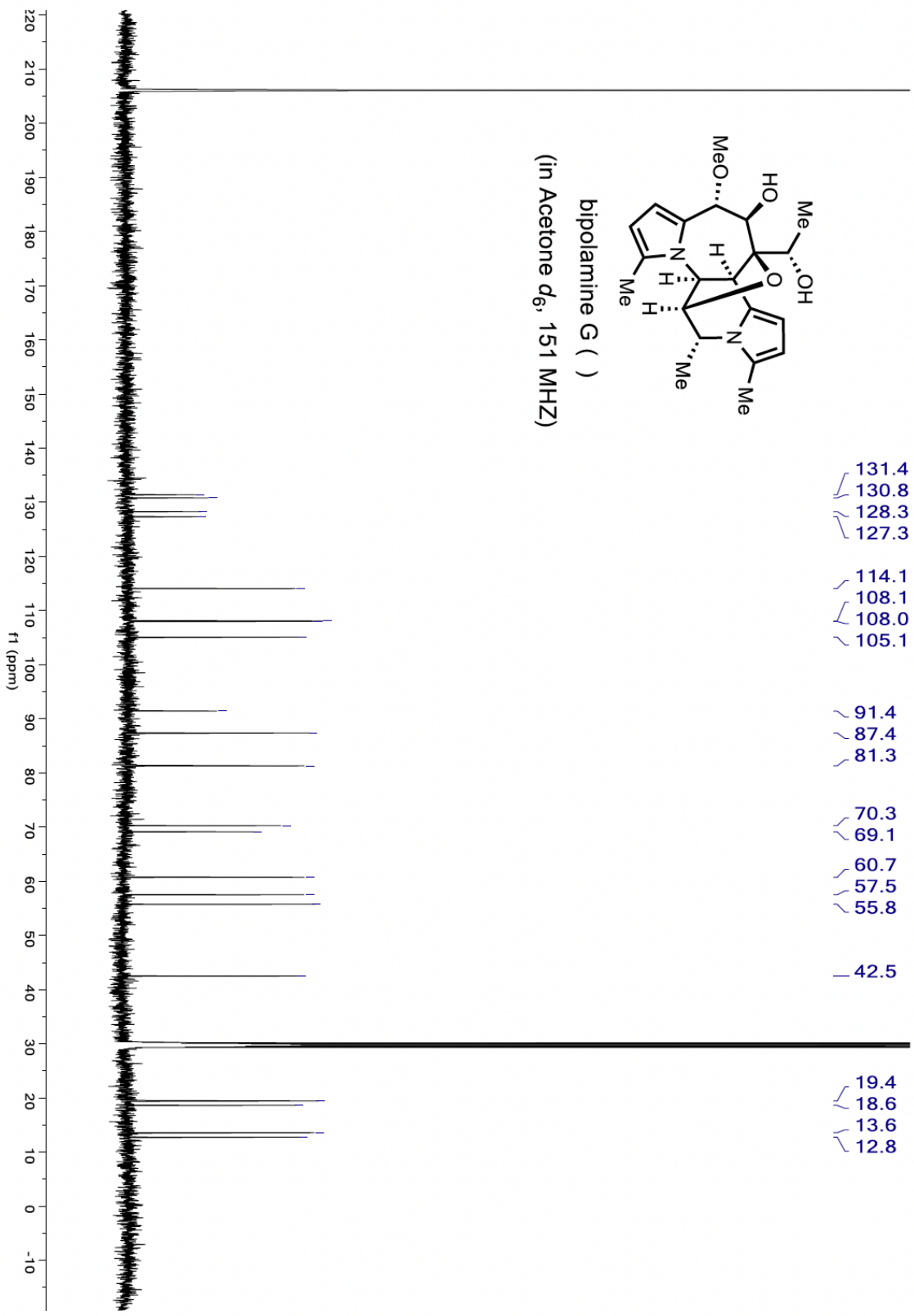

(in $CDCl_3$, 600 MHZ)
7.26
1.00
0.99
0.99
1.01
1.02
1.04
0.95
1.00
1.02
1.01
3.05
0.91
3.09
3.11
3.04
3.17
3.02
f1 (ppm)
MeO
HO
Me
O
N
H
H
Me
Me
Me
N

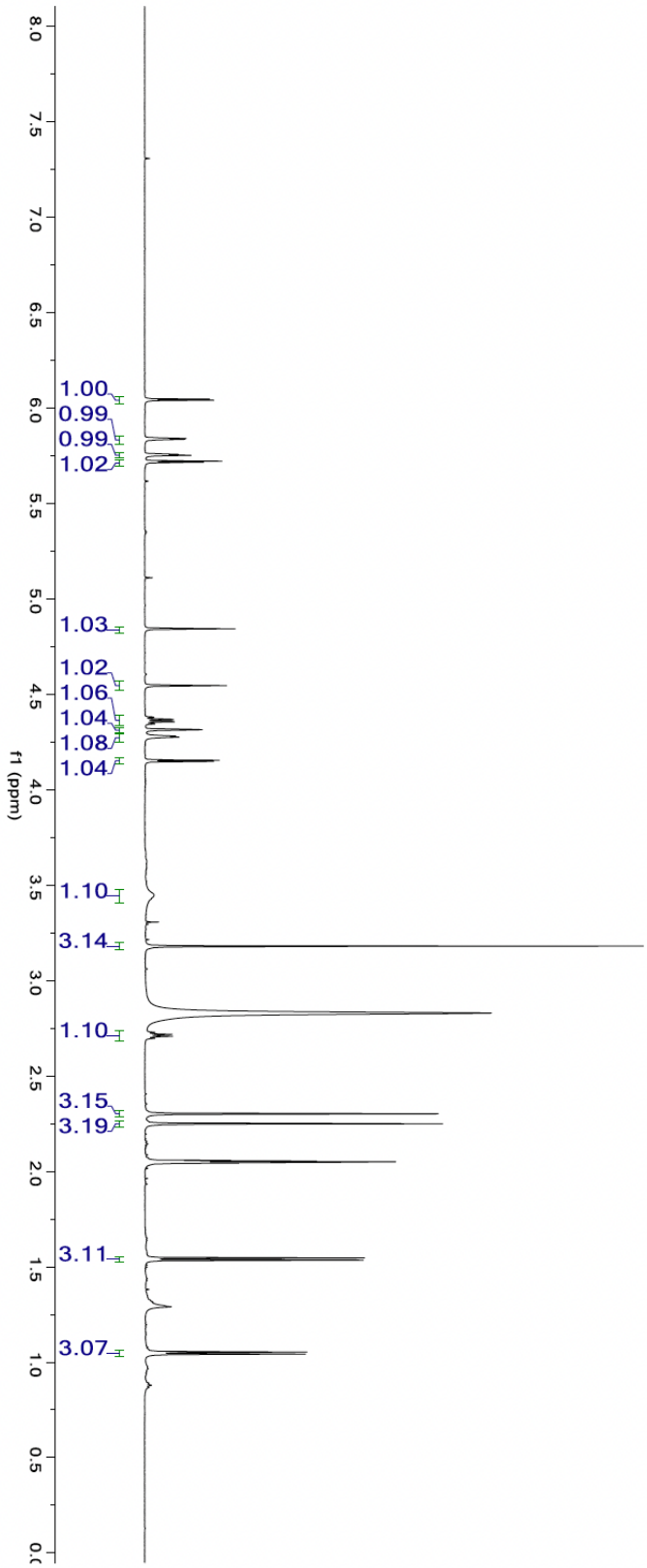

(in CDCl3, 151 MHZ)
209.0
131.2
128.1
127.0
126.5
112.6
108.5
107.9
106.5
96.6
87.6
80.4
74.5
59.4
57.4
56.2
43.9
26.3
19.4
13.6
12.7
f1 (ppm)


HMBC
Key HMBC correlations
shown in red
MeO
HO
Me
O
H
N
H
Me
Me
Me
N
Me
{1.69,208.87}
f1 (ppm)
f2 (ppm)


NOESY
Key NOESY correlations
shown in red
{3.34,4.52}
{2.87,4.28}
f1 (ppm)
f2 (ppm)

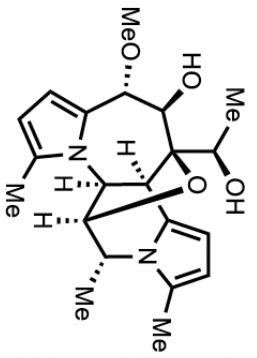

bipolamine G ( )
(in Acetone $d_6$, 600 MHZ)
MeO
HO
Me
OH
H
N
H
H
O
N
Me
Me
Me
f1 (ppm)
0.95
0.95
0.93
0.95
0.97
0.97
0.98
0.96
1.04
1.00
3.01
1.02
1.18
0.99
3.09
3.04
3.08
3.11

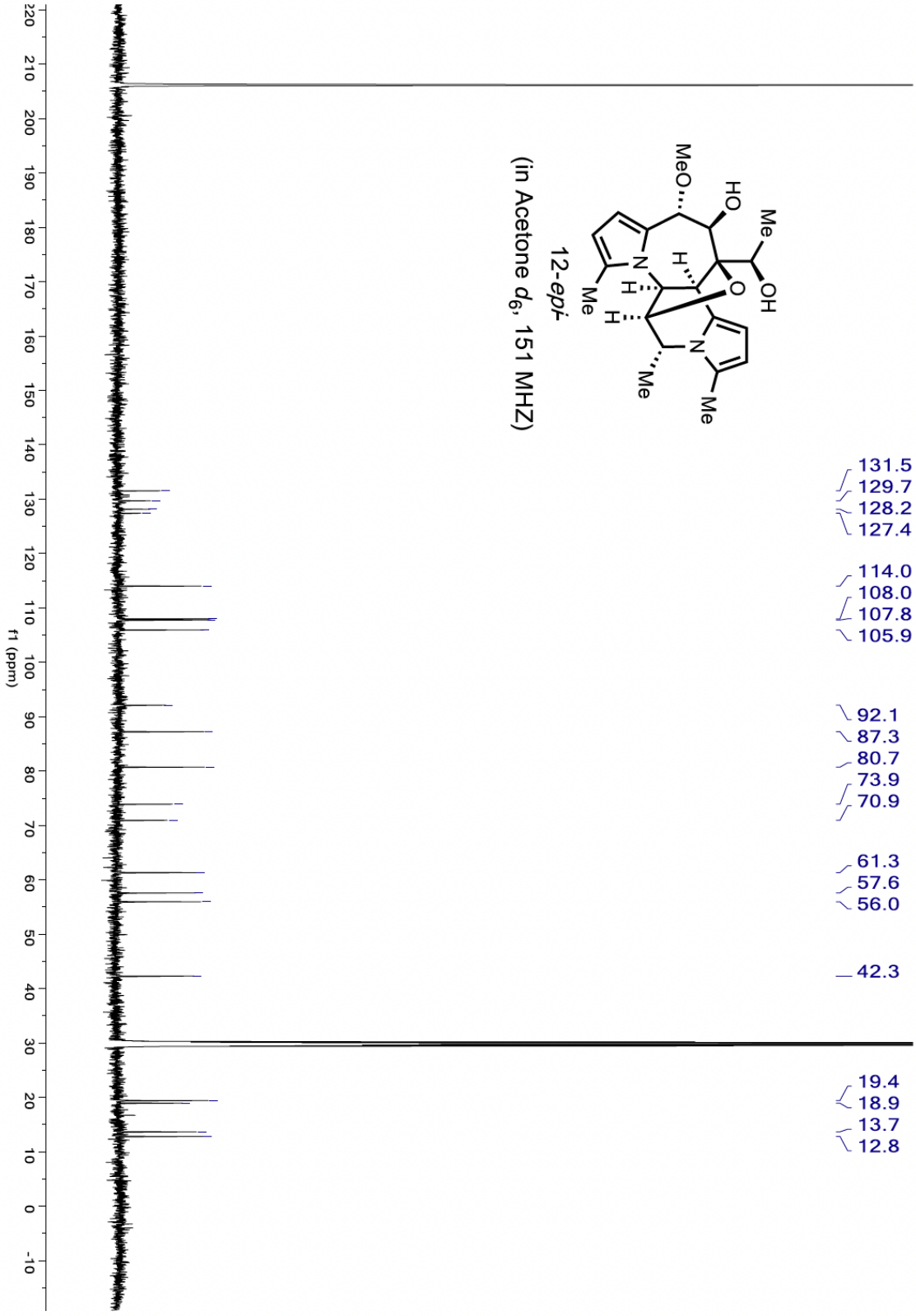

bipolamine G ( )
(in Acetone $d_6$, 151 MHZ)
MeO
HO
Me
OH
N
H
H
O
N
Me
Me
Me
131.4
130.8
128.3
127.3
114.1
108.1
108.0
105.1
91.4
87.4
81.3
70.3
69.1
60.7
57.5
55.8
42.5
19.4
18.6
13.6
12.8
f1 (ppm)

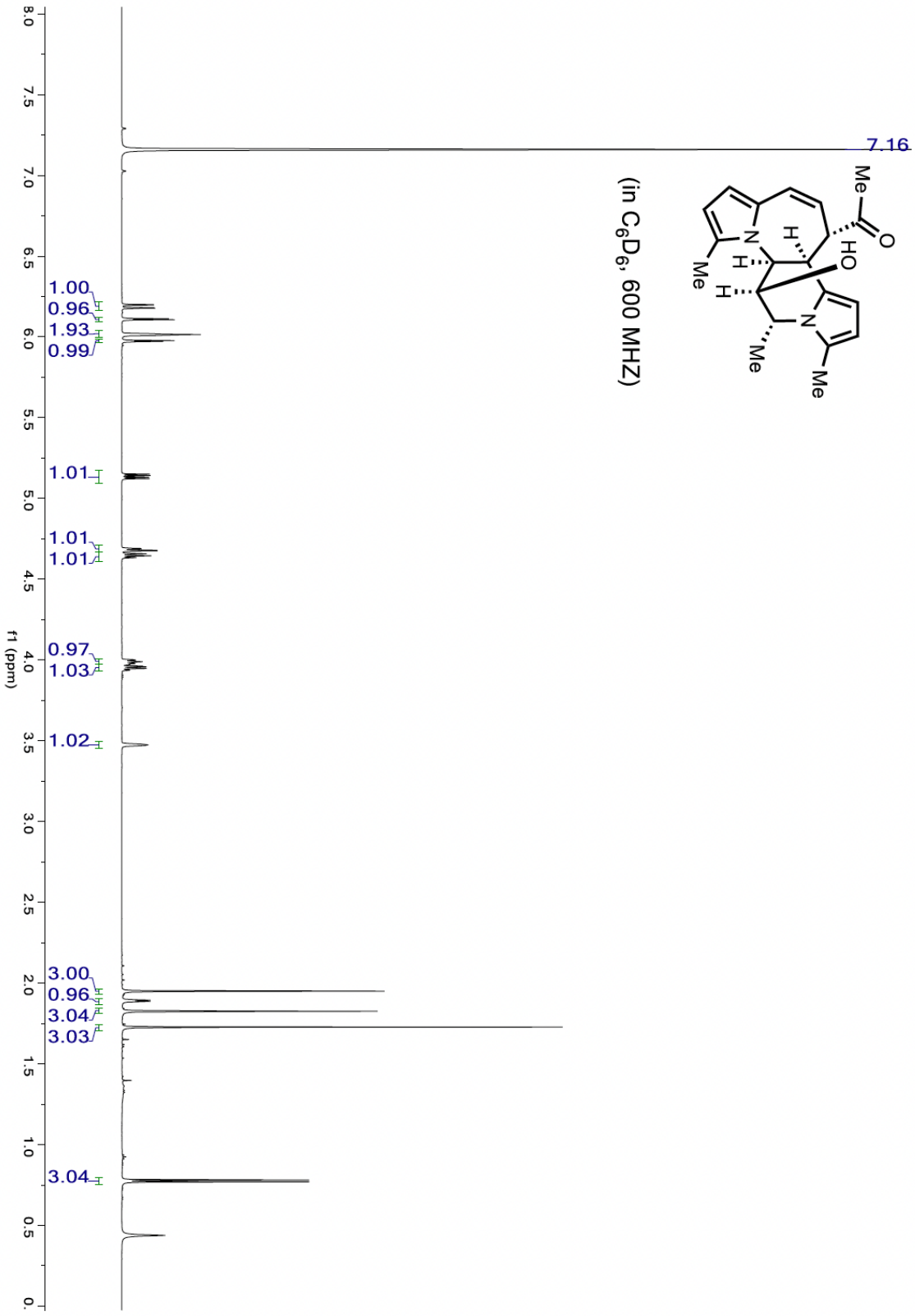


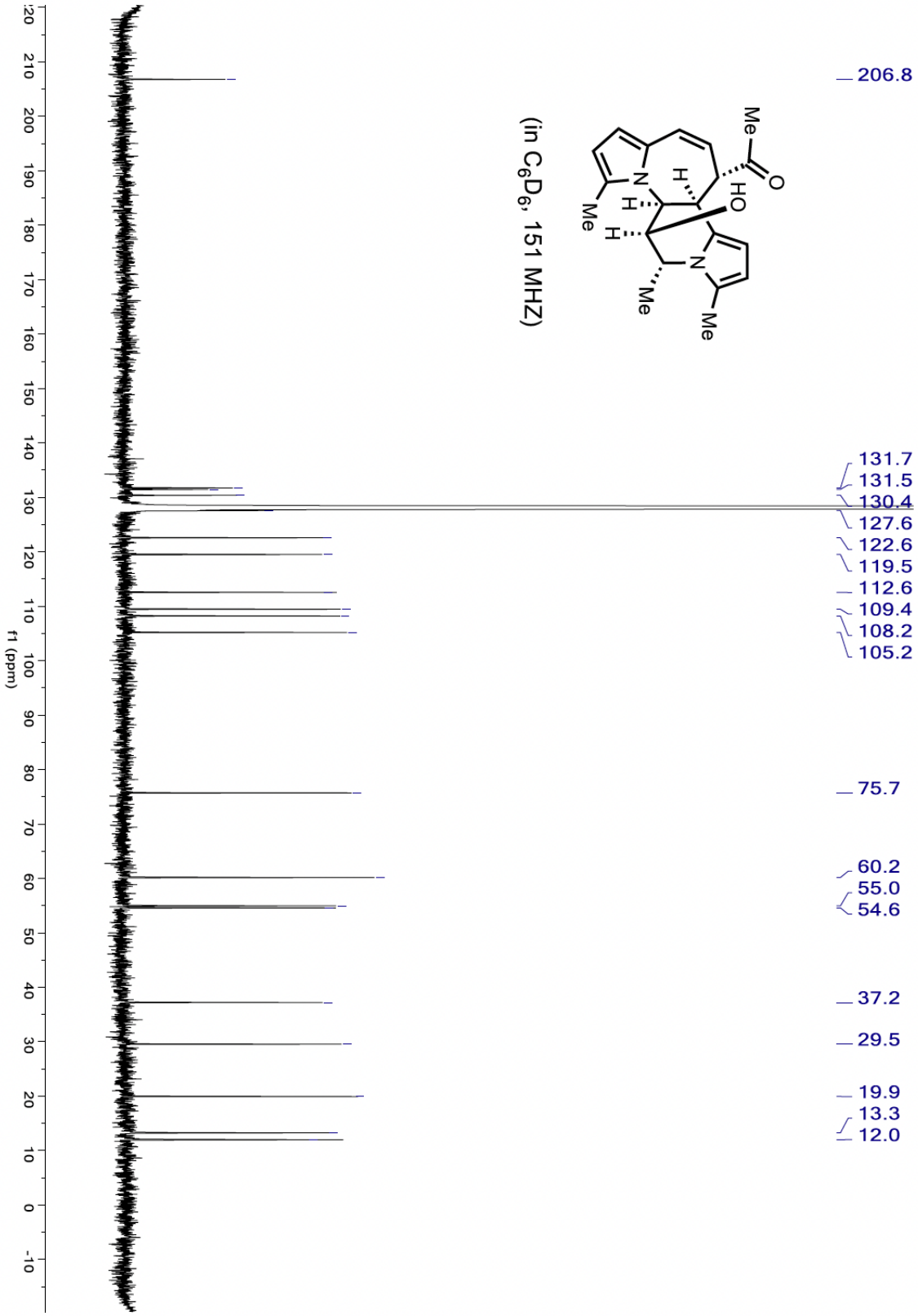

12-*epi*-

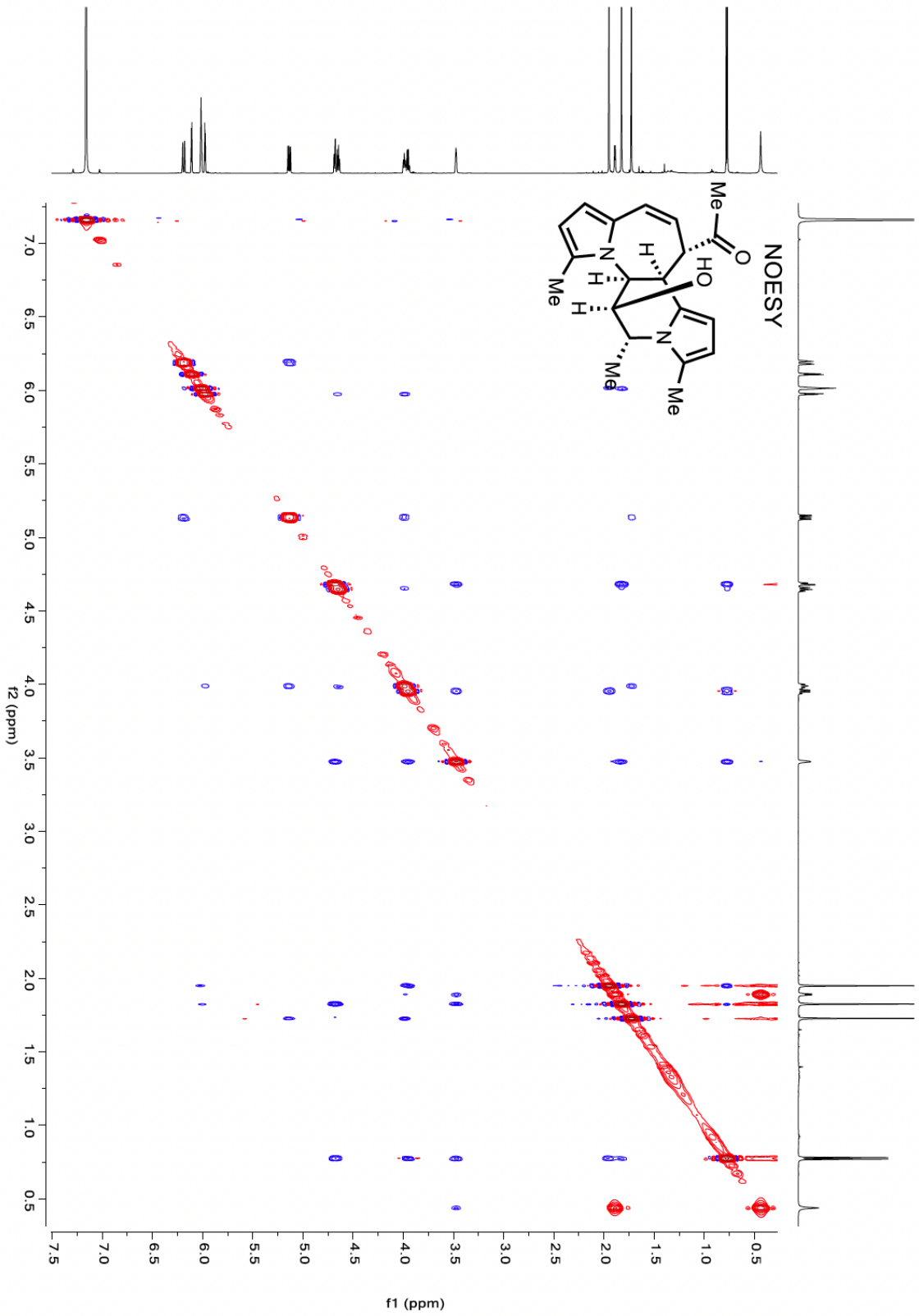
(in Acetone $d_6$, 600 MHZ)

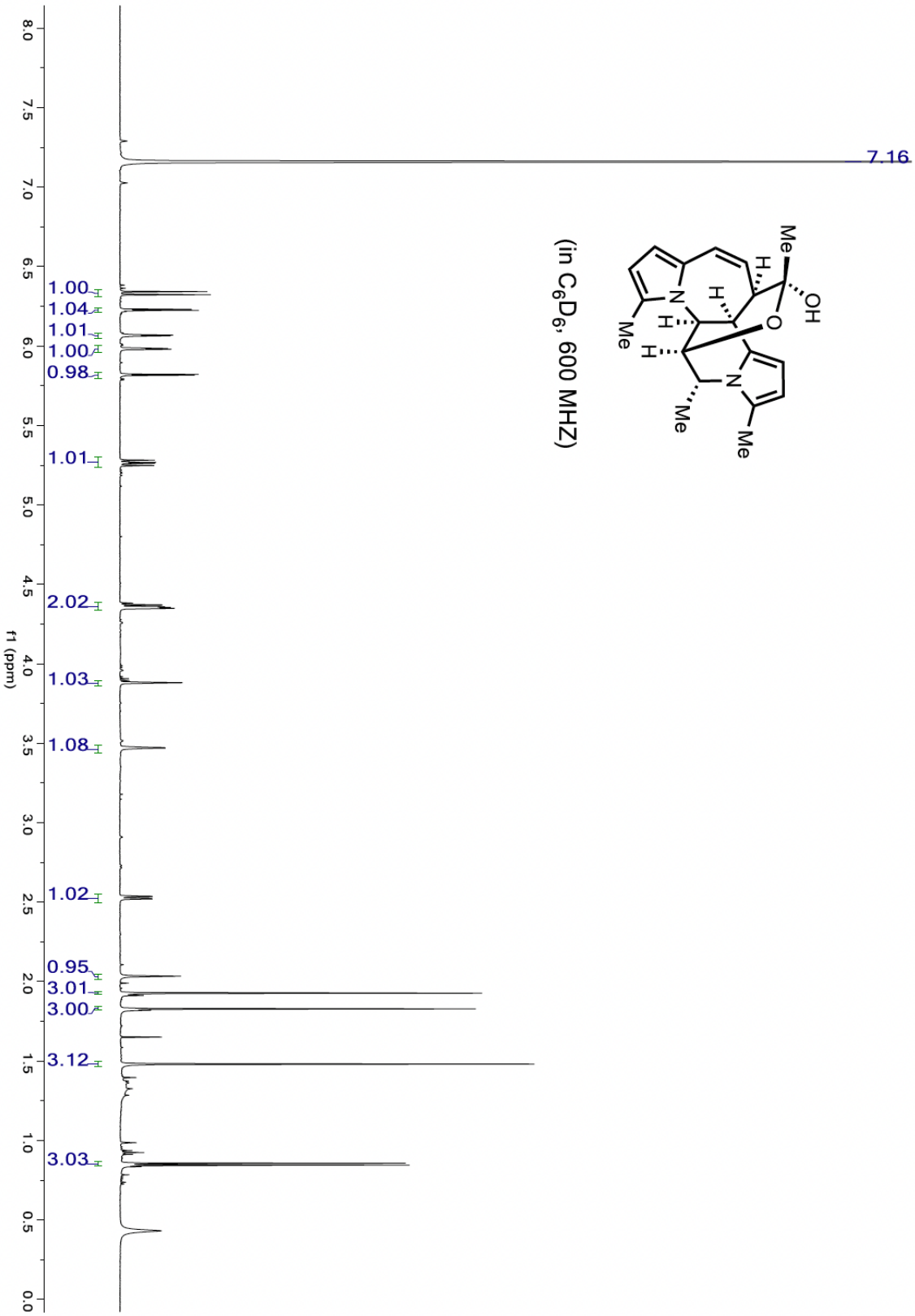


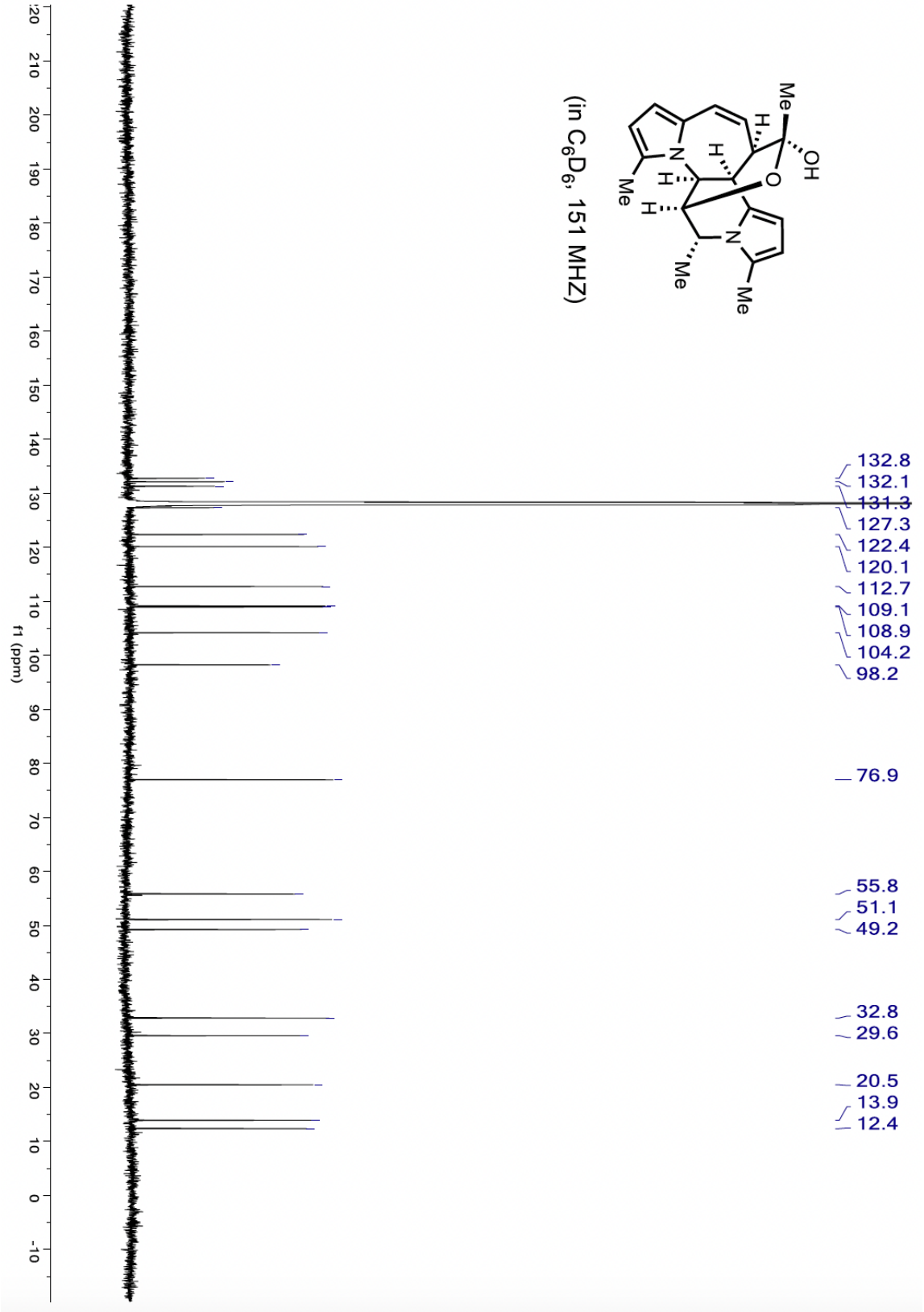

12-epi-
(in Acetone $d_6$, 151 MHZ)
MeO
HO
Me
OH
N
H
H
O
N
Me
Me
Me
131.5
129.7
128.2
127.4
114.0
108.0
107.8
105.9
92.1
87.3
80.7
73.9
70.9
61.3
57.6
56.0
42.3
19.4
18.9
13.7
12.8
f1 (ppm)

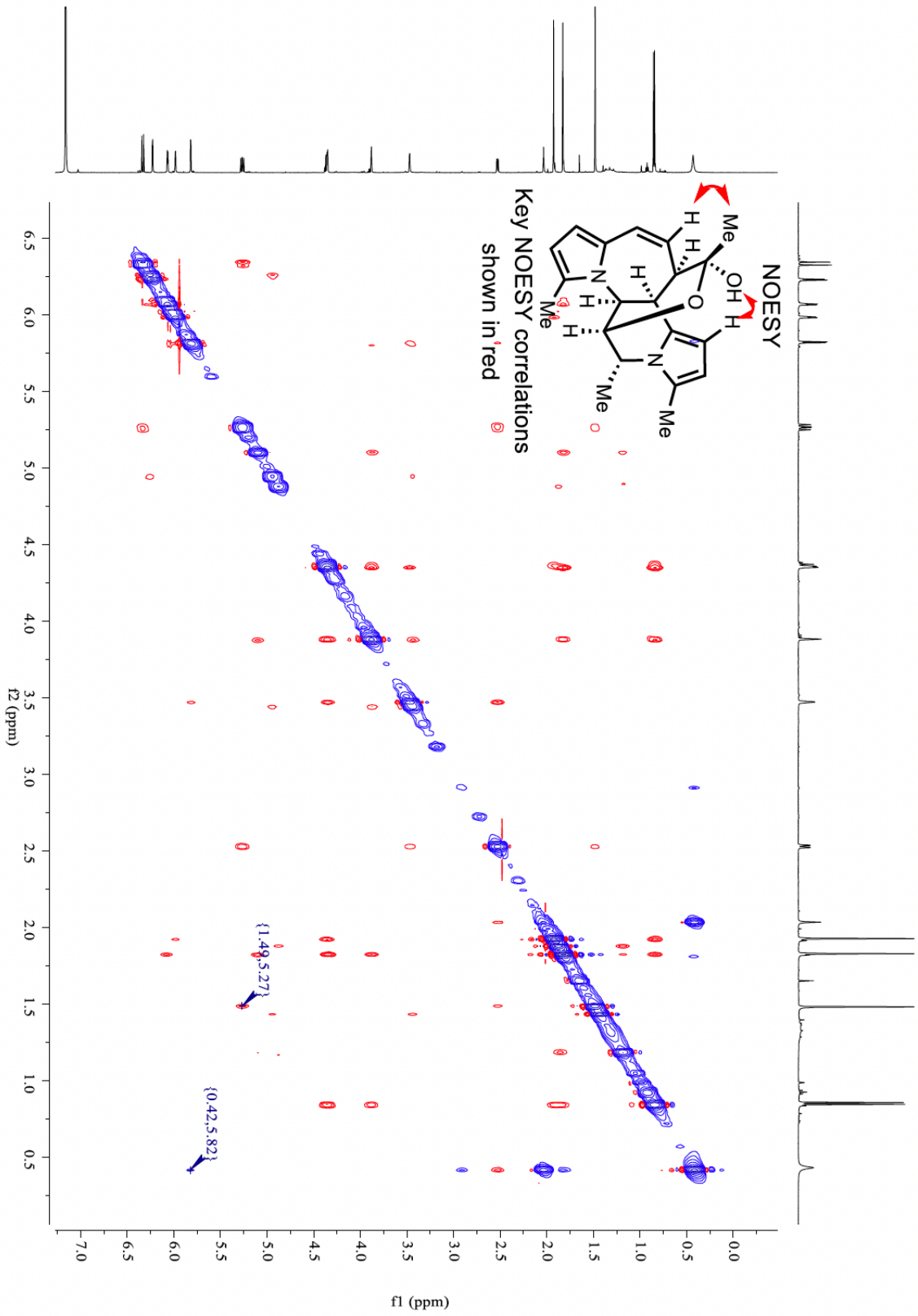

7.16
1.00
0.96
1.93
0.99
1.01
1.01
1.01
0.97
1.03
1.02
3.00
0.96
3.04
3.03
3.04
f1 (ppm)
(in C6D6, 600 MHZ)
Me
O
HO
H
H
H
N
N
Me
Me
Me

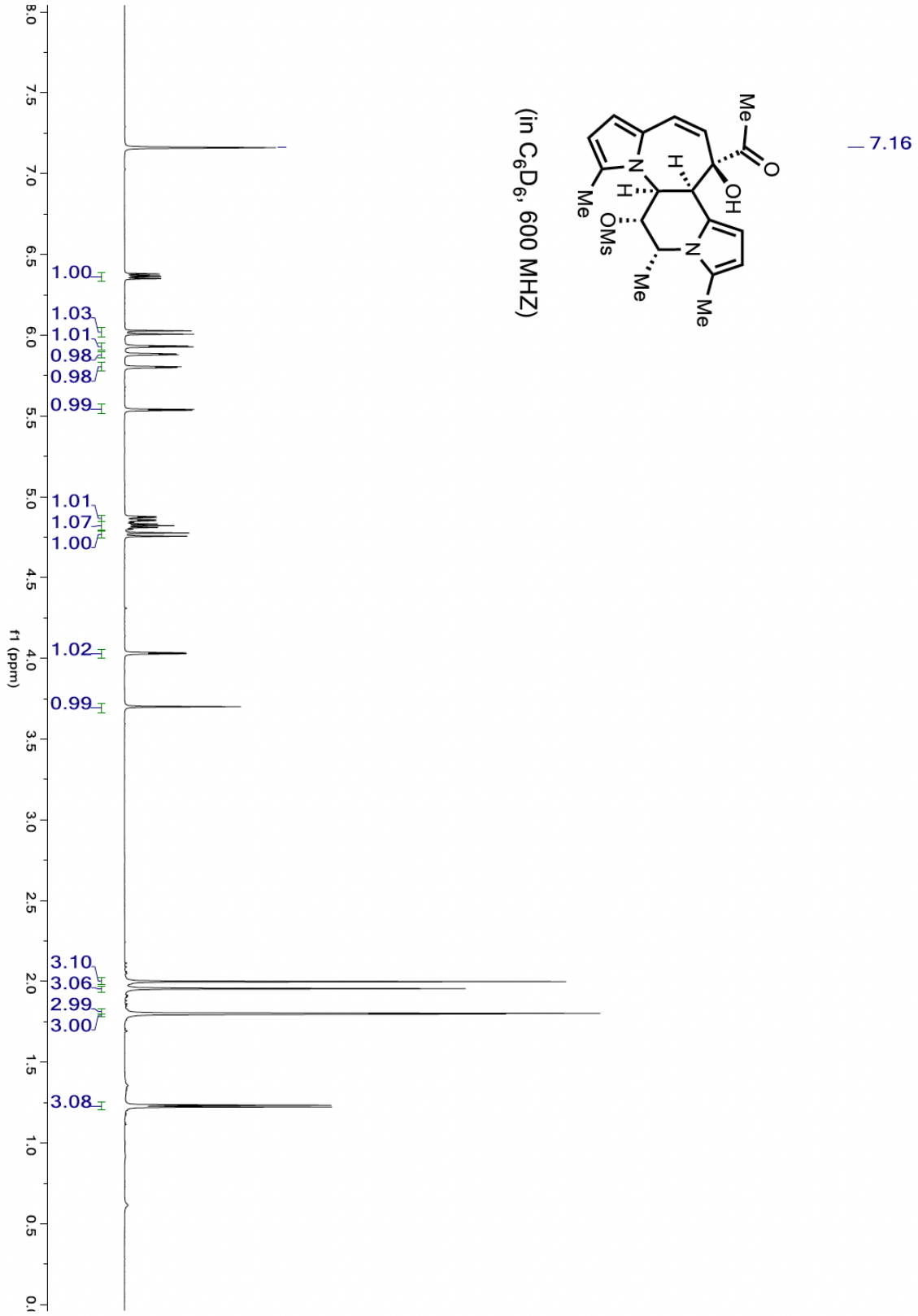

206.8
131.7
131.5
130.4
127.6
122.6
119.5
112.6
109.4
108.2
105.2
75.7
60.2
55.0
54.6
37.2
29.5
19.9
13.3
12.0
(in C6D6, 151 MHZ)
f1 (ppm)

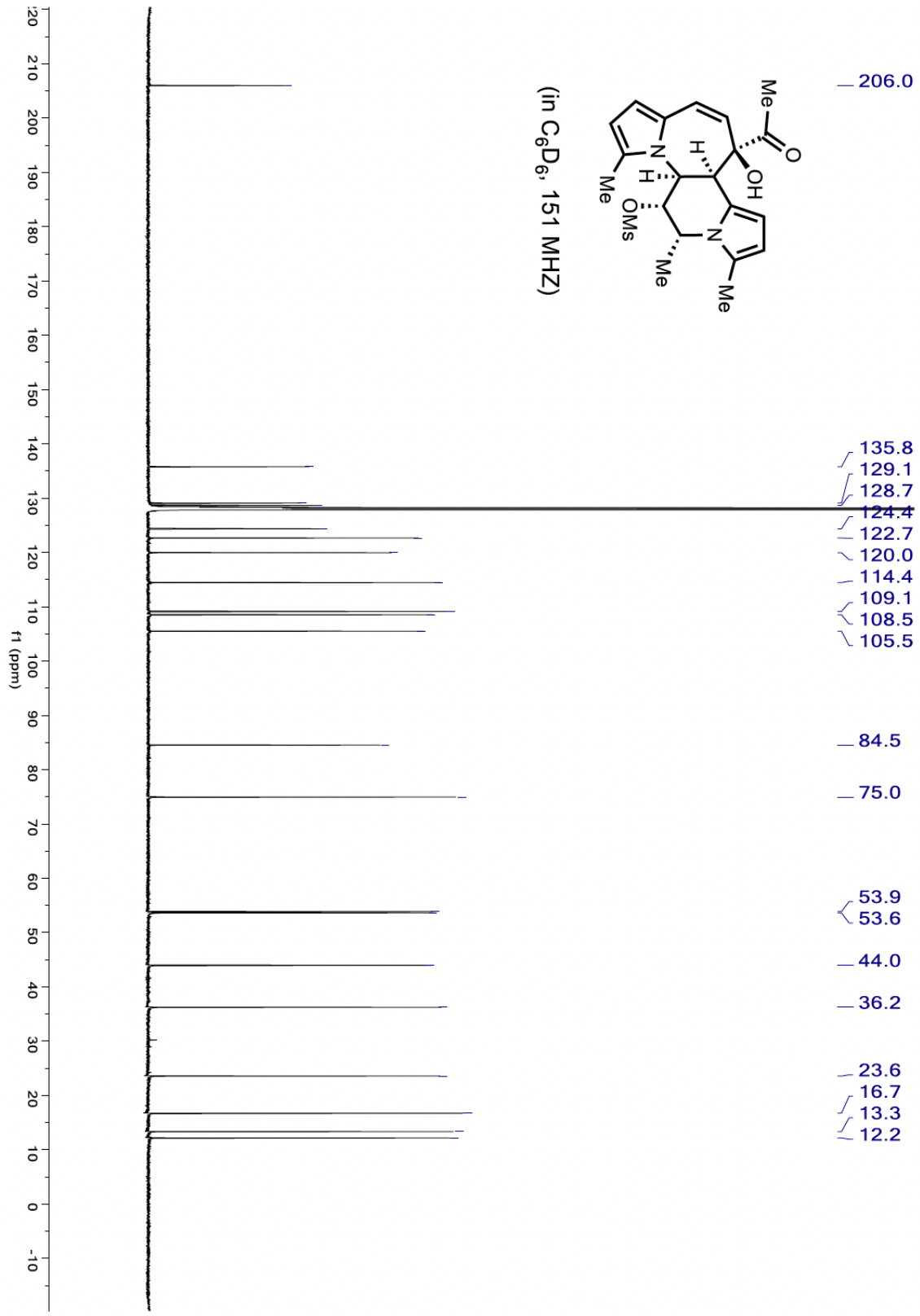

NOESY
Me
O
HO
H
N
H
H
Me
N
Me
Me
f2 (ppm)
f1 (ppm)
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5

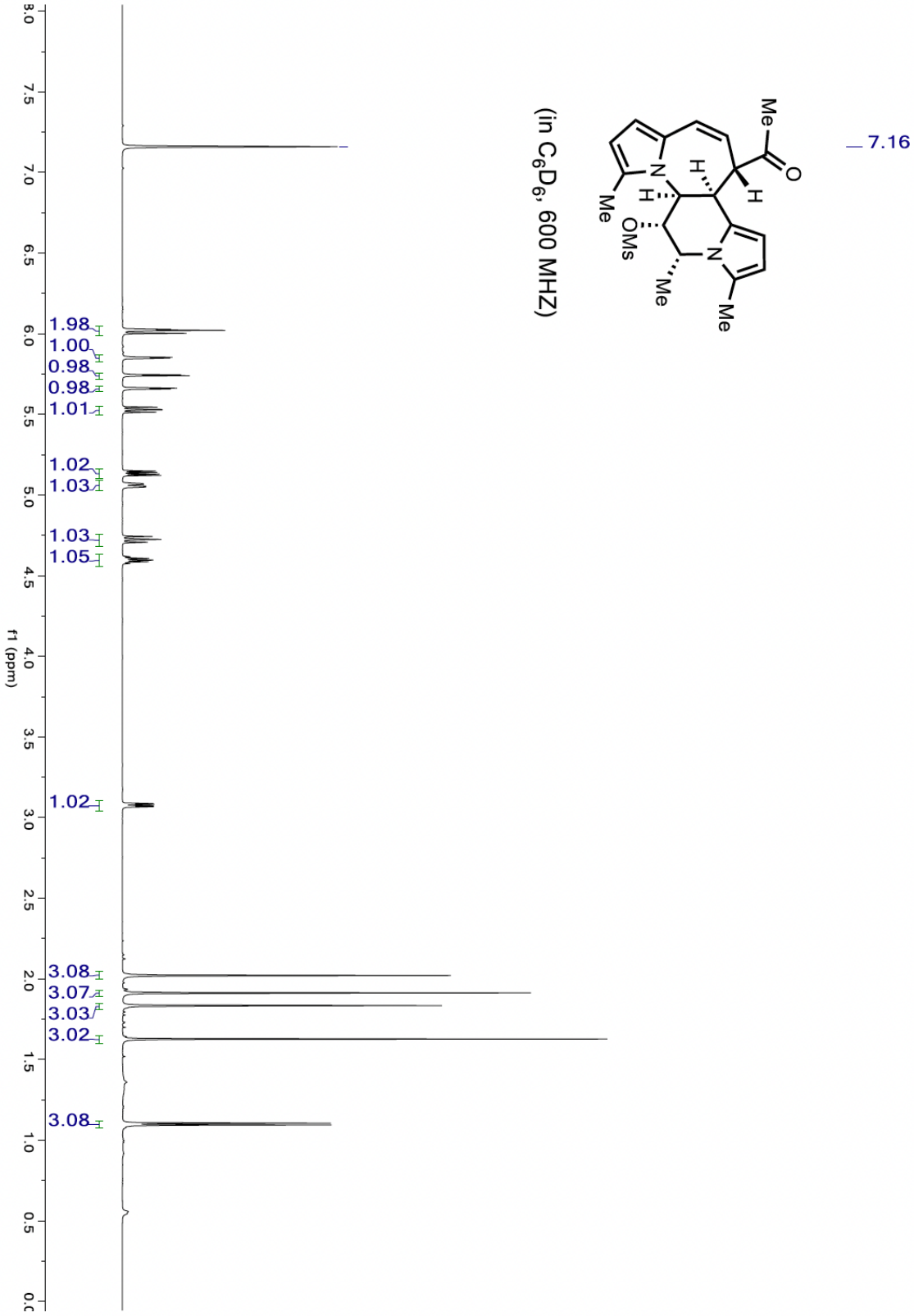

(in $C_6D_6$, 600 MHZ)
Me
OH
H
H
O
N
H
H
Me
Me
N
Me
7.16
1.00
1.04
1.01
1.00
0.98
1.01
2.02
1.03
1.08
1.02
0.95
3.01
3.00
3.12
3.03
f1 (ppm)
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

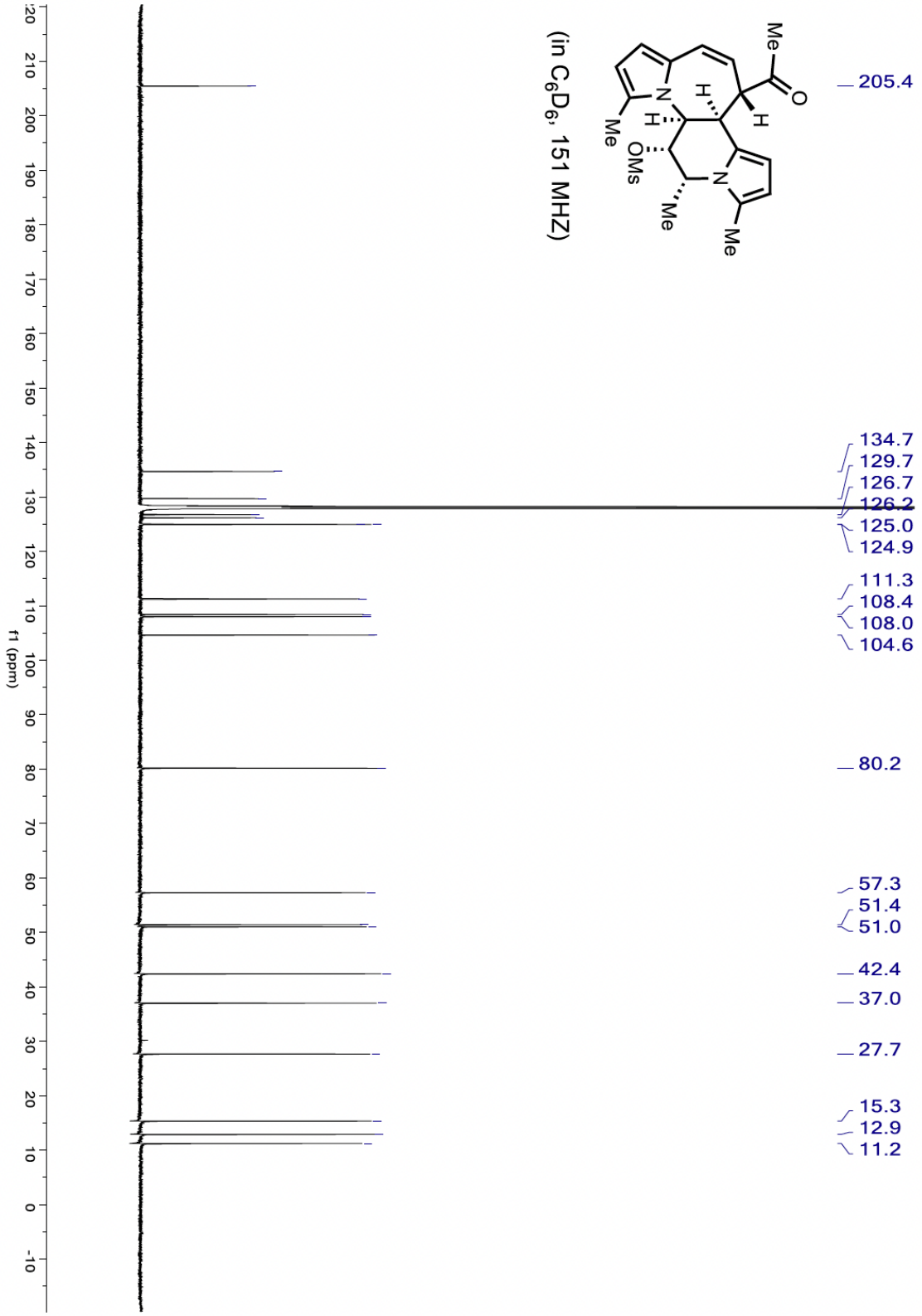

(in $C_6D_6$, 151 MHZ)
Me
OH
H
H
N
H
H
Me
O
N
Me
Me
132.8
132.1
131.3
127.3
122.4
120.1
112.7
109.1
108.9
104.2
98.2
76.9
55.8
51.1
49.2
32.8
29.6
20.5
13.9
12.4
f1 (ppm)

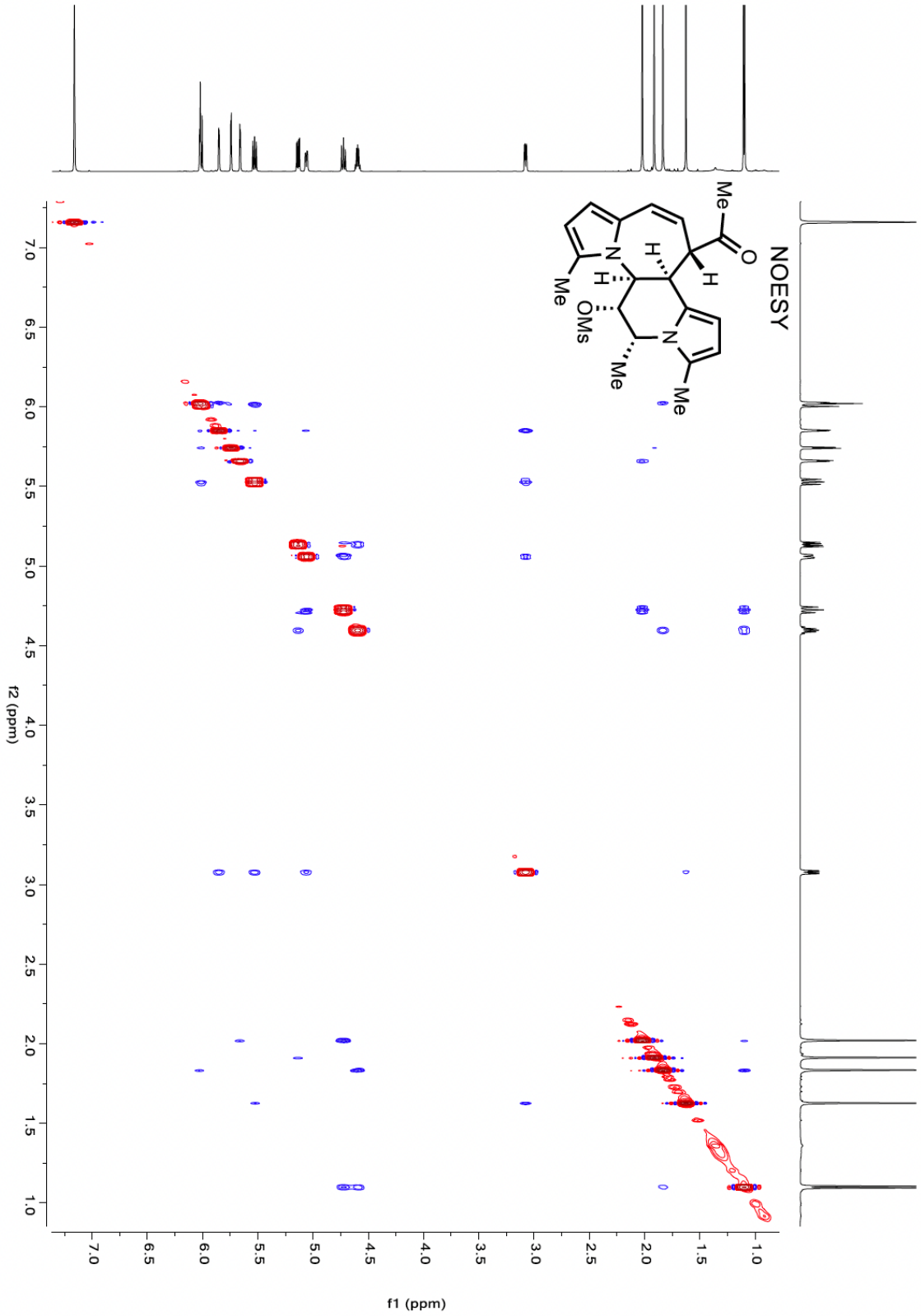

NOESY
Key NOESY correlations
shown in red
Me
OH
H
N
O
Me
Me
{1.49,5.27}
{0.42,5.82}
f2 (ppm)
f1 (ppm)

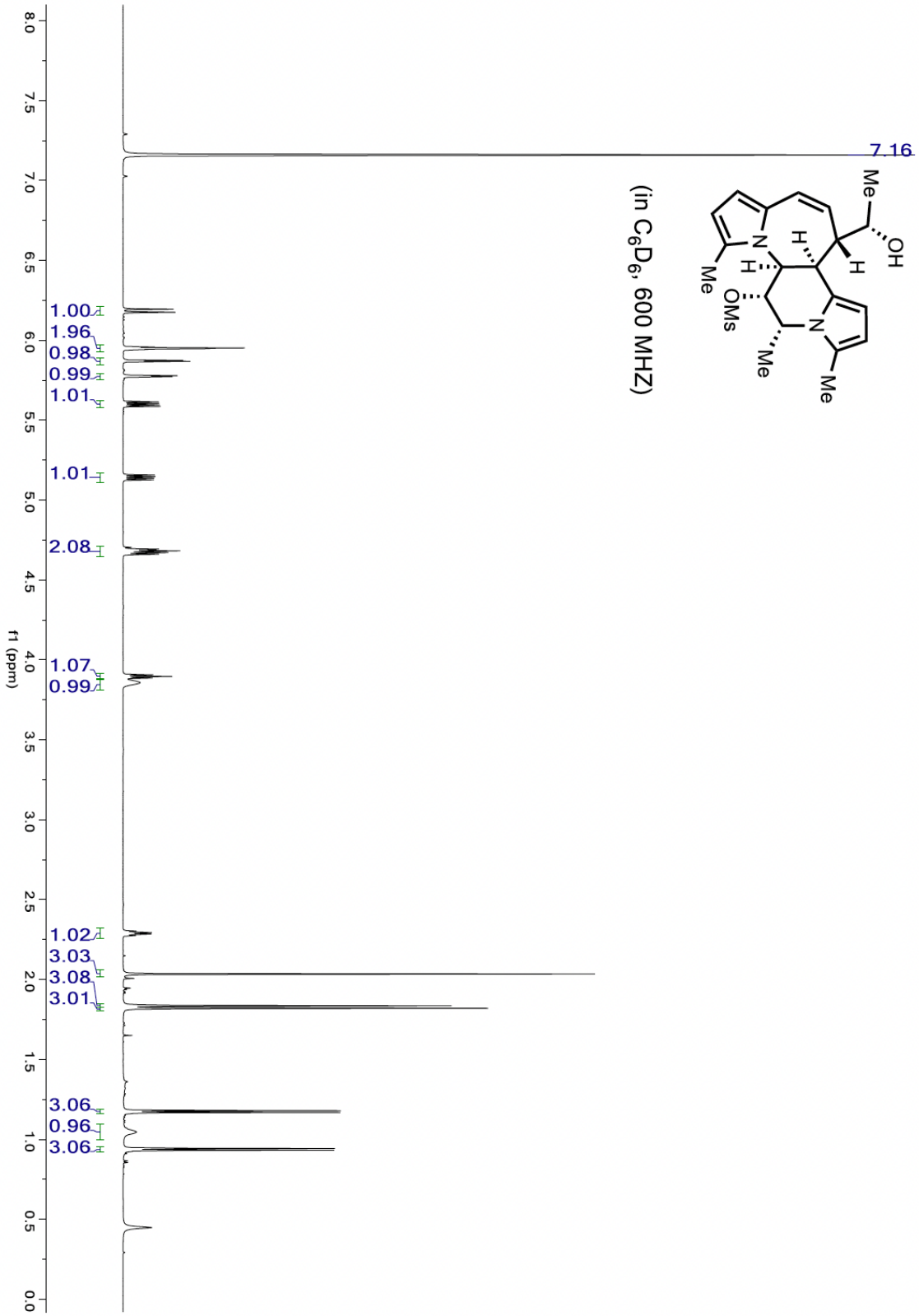

(in $C_6D_6$, 600 MHZ)
7.16
1.00
1.03
1.01
0.98
0.98
0.99
1.01
1.07
1.00
1.02
0.99
3.10
3.06
2.99
3.00
3.08
f1 (ppm)

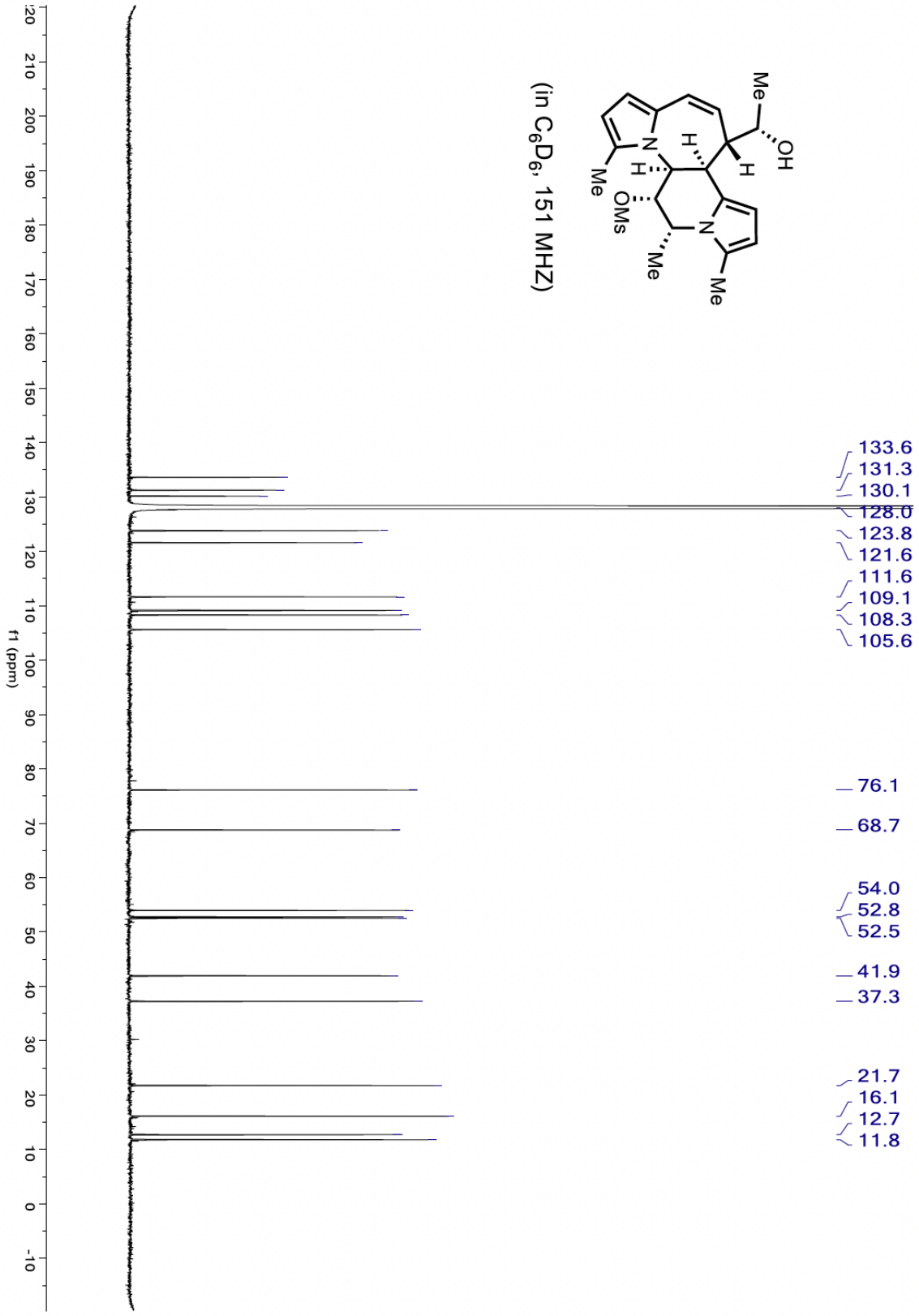

(in $C_6D_6$, 151 MHZ)
206.0
135.8
129.1
128.7
124.4
122.7
120.0
114.4
109.1
108.5
105.5
84.5
75.0
53.9
53.6
44.0
36.2
23.6
16.7
13.3
12.2
f1 (ppm)

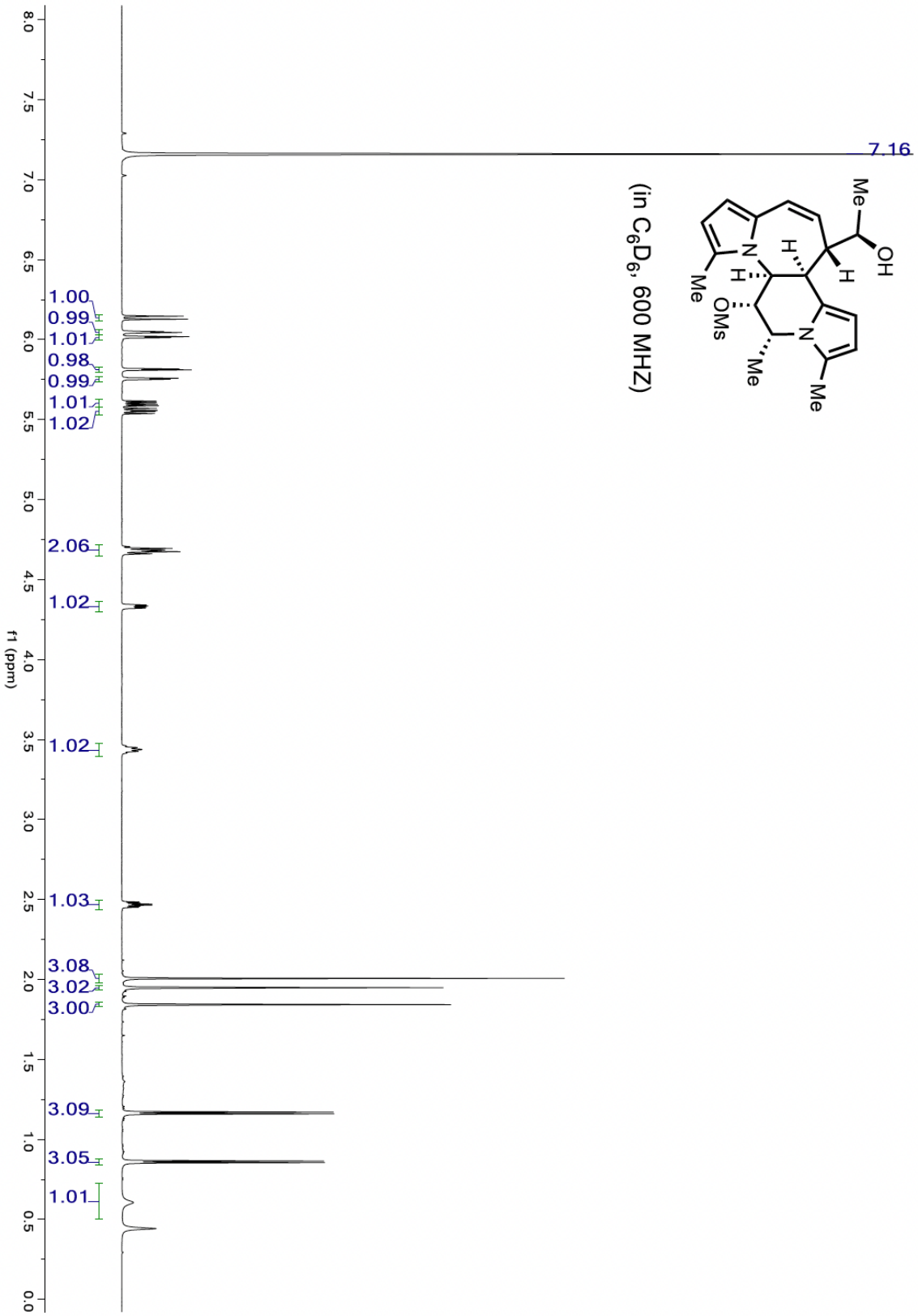

(in $C_6D_6$, 600 MHZ)
7.16
1.98
1.00
0.98
0.98
1.01
1.02
1.03
1.03
1.05
1.02
3.08
3.07
3.03
3.02
3.08
f1 (ppm)

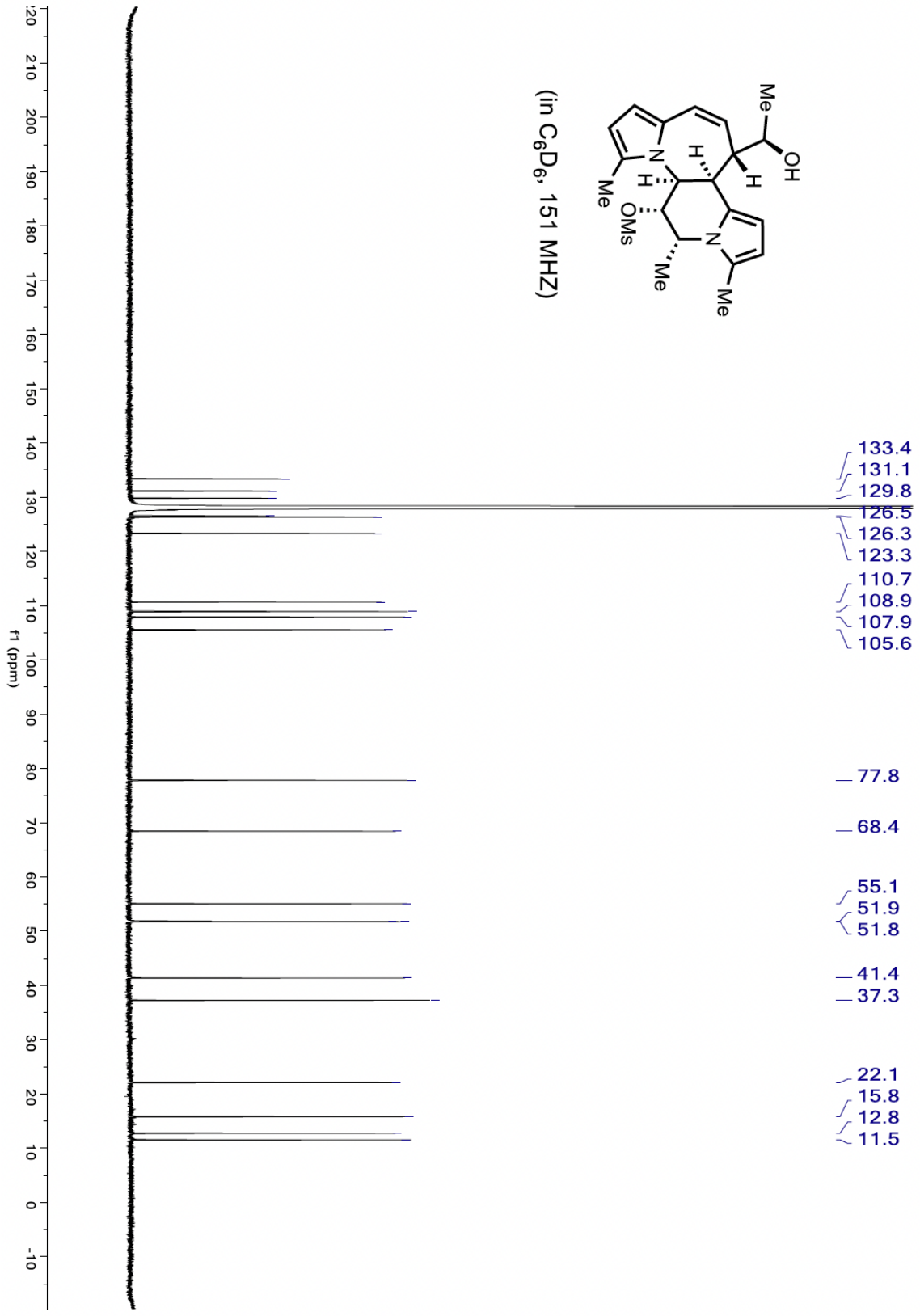

(in $C_6D_6$, 151 MHZ)
205.4
134.7
129.7
126.7
126.2
125.0
124.9
111.3
108.4
108.0
104.6
80.2
57.3
51.4
51.0
42.4
37.0
27.7
15.3
12.9
11.2
f1 (ppm)

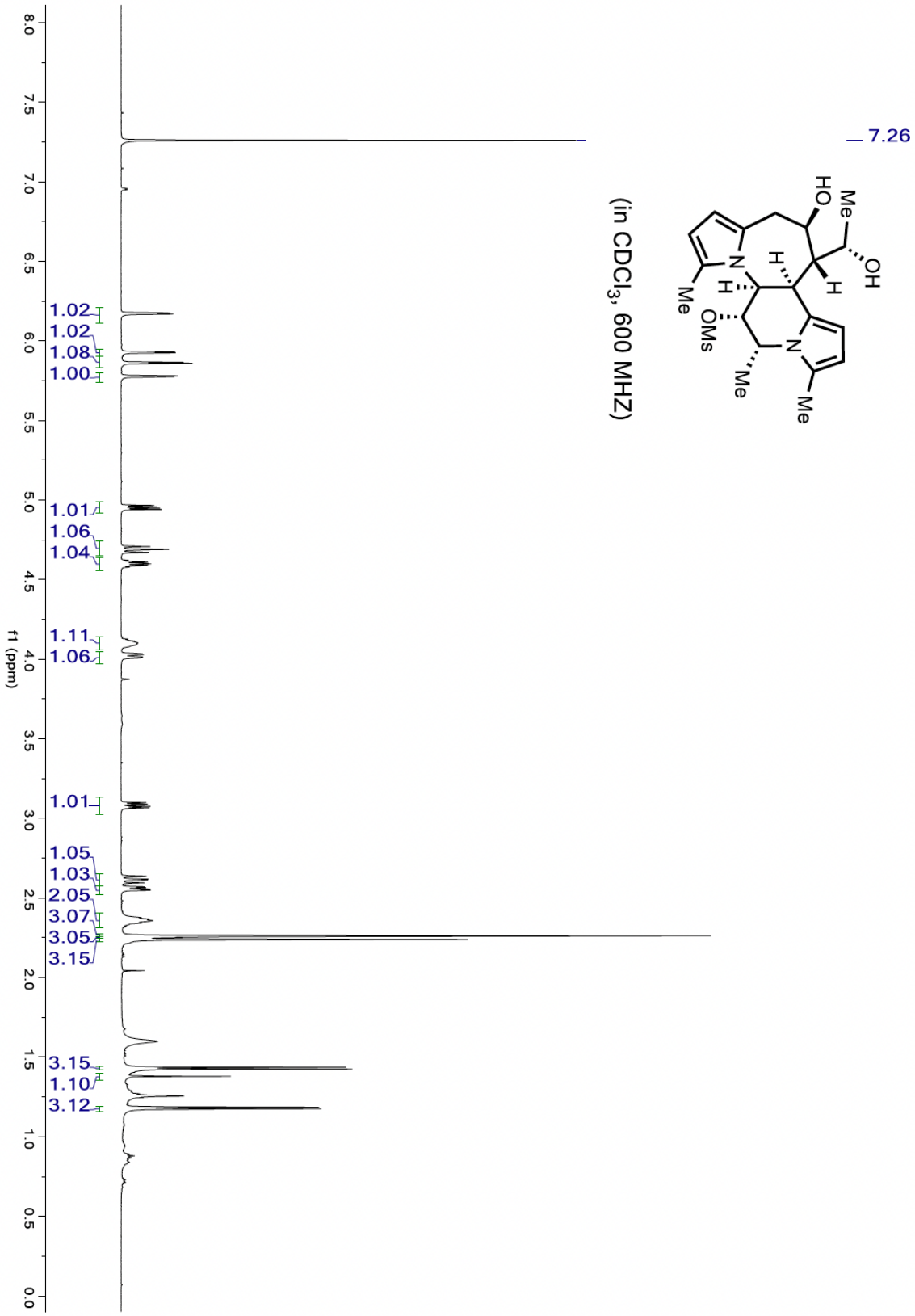

NOESY
Me
O
H
H
N
H
Me
OMs
Me
N
Me
f2 (ppm)
f1 (ppm)
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0

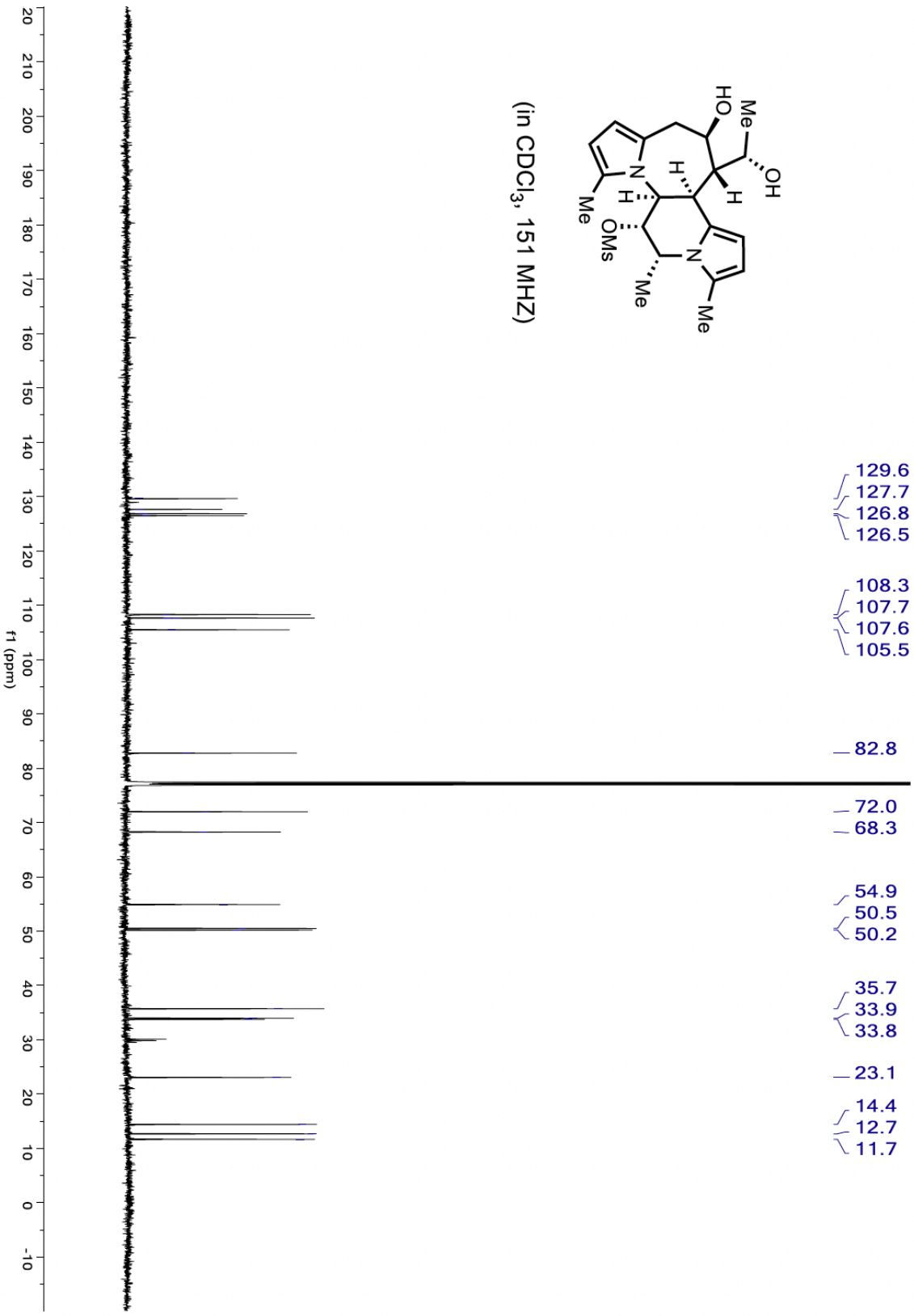

(in $C_6D_6$, 600 MHZ)
7.16
1.00
1.96
0.98
0.99
1.01
1.01
2.08
1.07
0.99
1.02
3.03
3.08
3.01
3.06
0.96
3.06
f1 (ppm)
Me
OH
H
N
H
Me
OMs
Me
N
Me

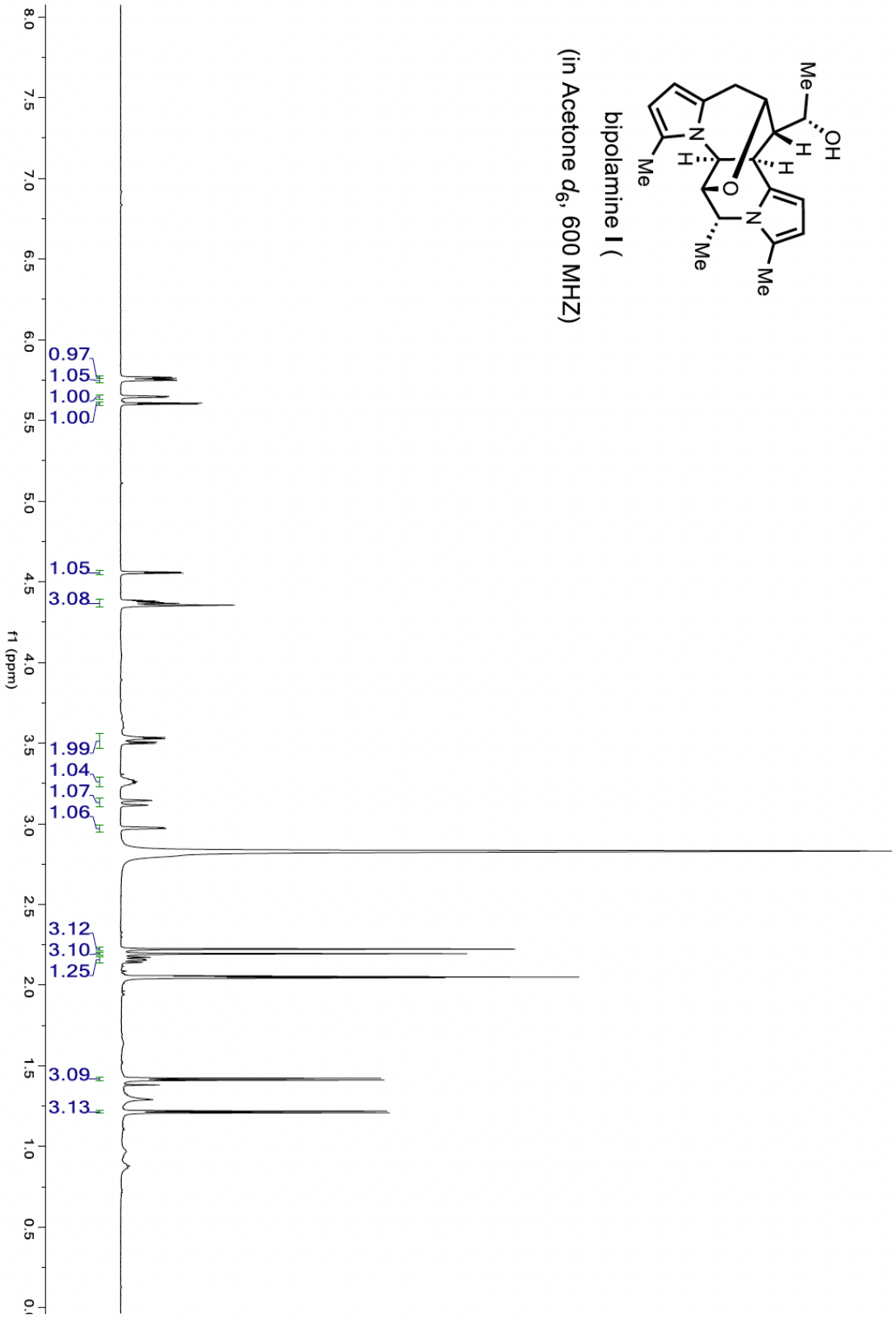

(in C6D6, 151 MHZ)
Me
OH
H
H
N
Me
OMs
Me
N
Me
133.6
131.3
130.1
128.0
123.8
121.6
111.6
109.1
108.3
105.6
76.1
68.7
54.0
52.8
52.5
41.9
37.3
21.7
16.1
12.7
11.8
f1 (ppm)

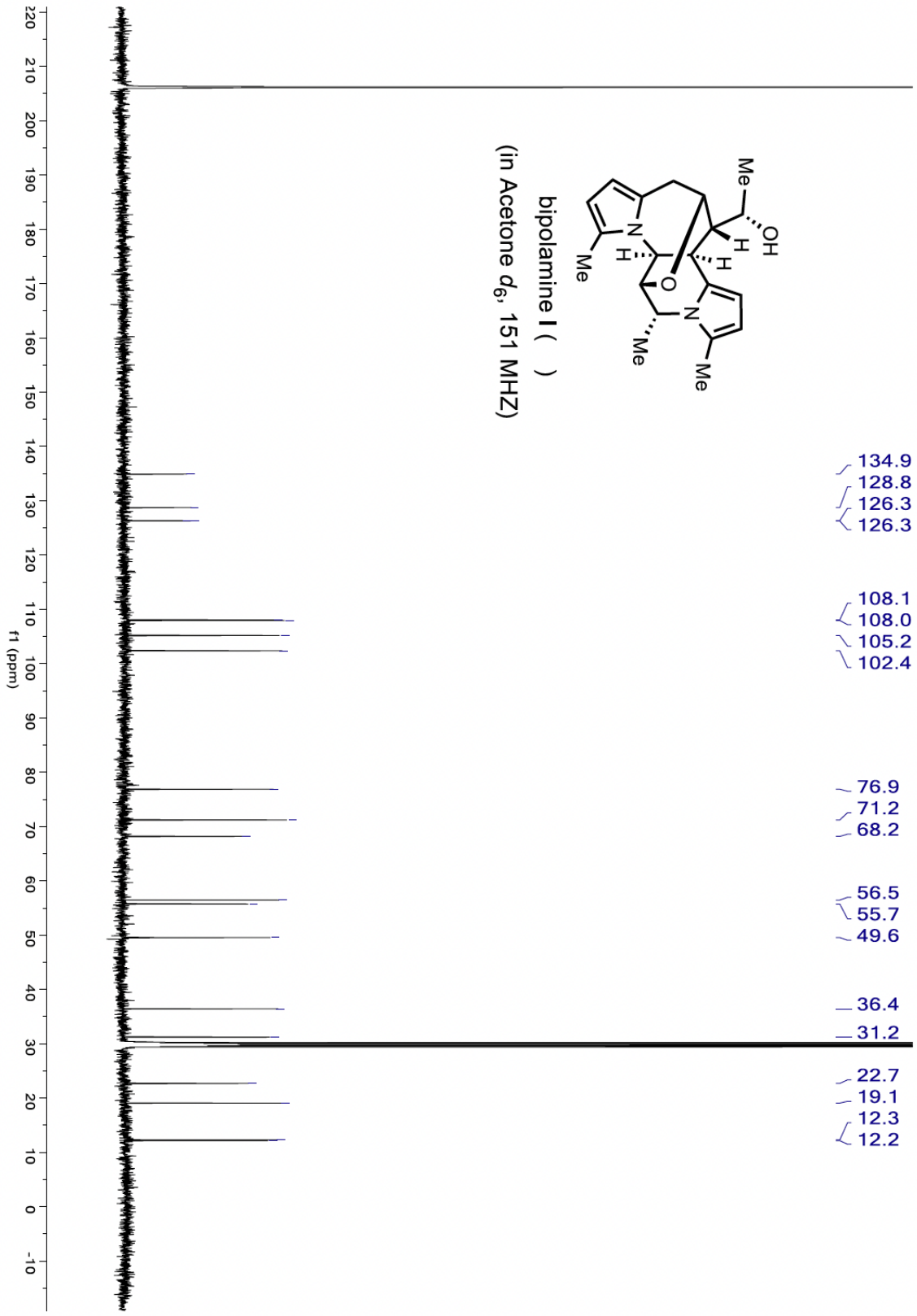

7.16
(in $C_6D_6$, 600 MHZ)
Me
OH
H
N
H
Me
OMs
Me
N
Me
1.00
0.99
1.01
0.98
0.99
1.01
1.02
2.06
1.02
1.02
1.03
3.08
3.02
3.00
3.09
3.05
1.01
f1 (ppm)

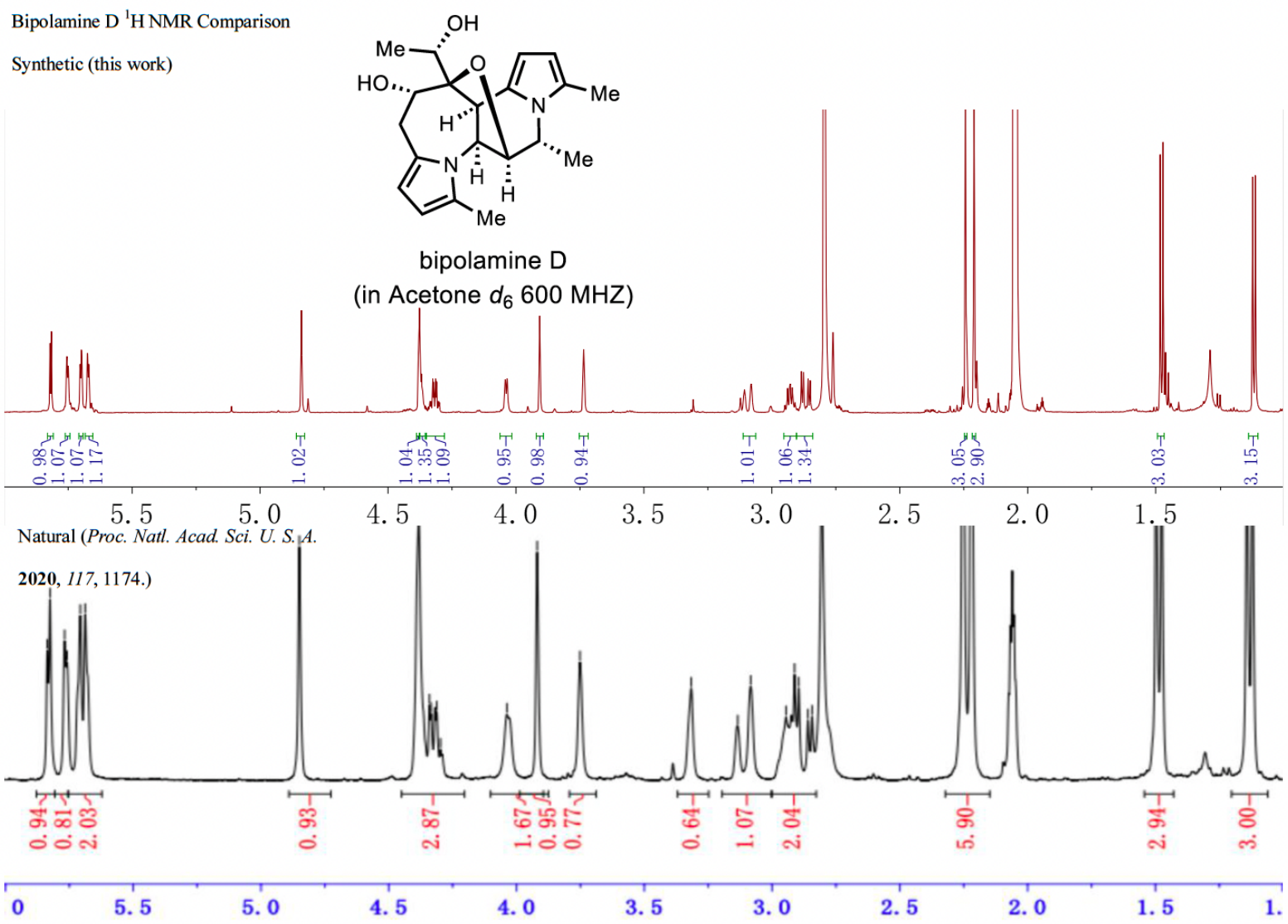

(in $C_6D_6$, 151 MHZ)
Me
OH
H
H
N
H
Me
OMs
Me
N
Me
133.4
131.1
129.8
126.5
126.3
123.3
110.7
108.9
107.9
105.6
77.8
68.4
55.1
51.9
51.8
41.4
37.3
22.1
15.8
12.8
11.5
f1 (ppm)


7.26
(in CDCl3, 600 MHZ)
HO
Me
OH
H
N
H
OMs
Me
Me
N
Me
1.02
1.02
1.08
1.00
1.01
1.06
1.04
1.11
1.06
1.01
1.05
1.03
2.05
3.07
3.05
3.15
3.15
1.10
3.12
f1 (ppm)


(in CDCl3, 151 MHZ)
Me
HO
OH
H
H
N
H
Me
OMs
Me
N
Me
129.6
127.7
126.8
126.5
108.3
107.7
107.6
105.5
82.8
72.0
68.3
54.9
50.5
50.2
35.7
33.9
33.8
23.1
14.4
12.7
11.7
f1 (ppm)

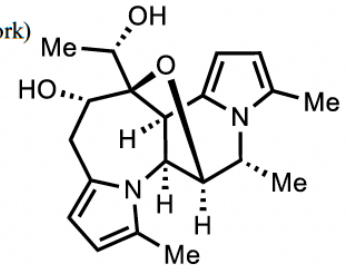

bipolamine I (
(in Acetone $d_6$, 600 MHZ)
Me
OH
H
H
N
H
Me
O
N
Me
Me
f1 (ppm)
0.97
1.05
1.00
1.00
1.05
3.08
1.99
1.04
1.07
1.06
3.12
3.10
1.25
3.09
3.13


bipolamine I ( )
(in Acetone $d_6$, 151 MHZ)
Me
OH
H
H
N
H
Me
O
N
Me
Me
134.9
128.8
126.3
126.3
108.1
108.0
105.2
102.4
76.9
71.2
68.2
56.5
55.7
49.6
36.4
31.2
22.7
19.1
12.3
12.2
f1 (ppm)
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10


Bipolamine D $^1$H NMR Comparison
Synthetic (this work)
OH
Me
HO
O
H
N
Me
N
H
Me
H
H
Me
bipolamine D
(in Acetone $d_6$ 600 MHZ)
0.98
1.07
1.07
1.17
1.02
1.04
1.35
1.09
0.95
0.98
0.94
1.01
1.06
1.34
3.05
2.90
3.03
3.15
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
Natural (*Proc. Natl. Acad. Sci. U. S. A.*
**2020**, *117*, 1174.)
0.94
0.81
2.03
0.93
2.87
1.67
0.95
0.77
0.64
1.07
2.04
5.90
2.94
3.00
0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.

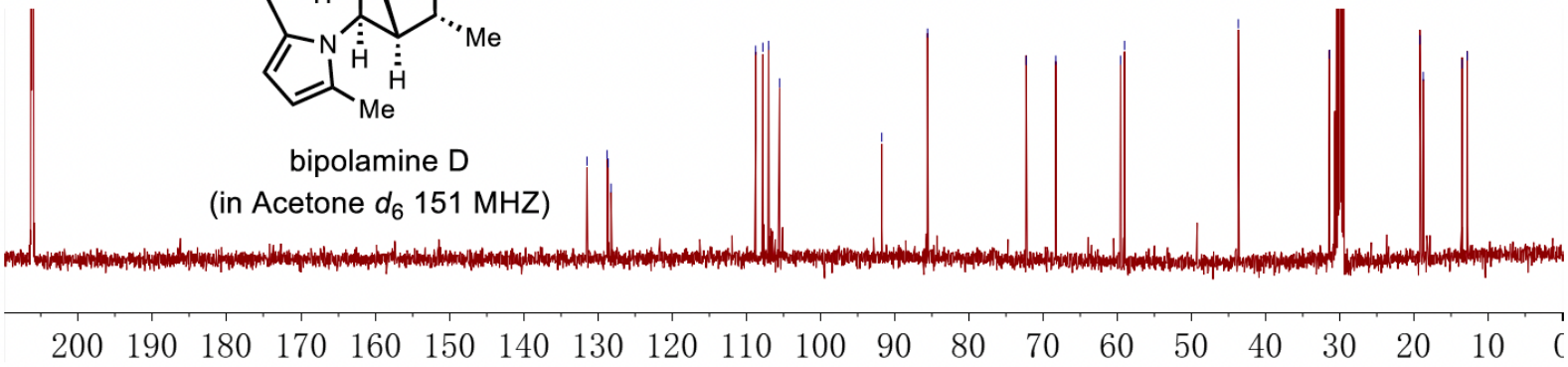
Bipolamine D $^{13}$C NMR Comparison

Synthetic (this work)



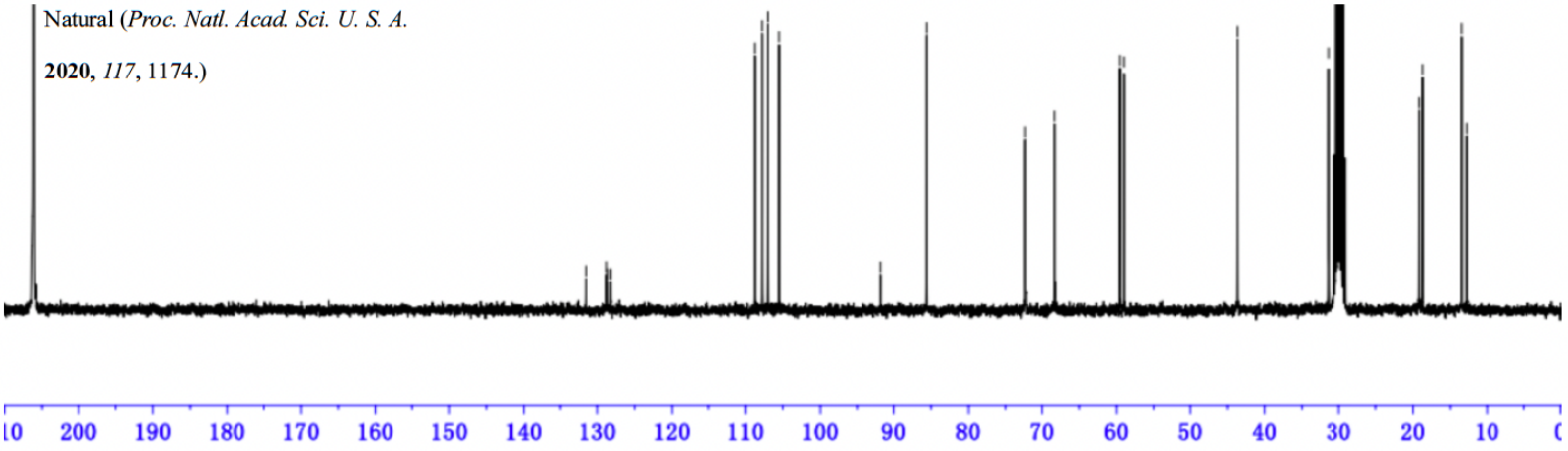

bipolamine D

(in Acetone $d_6$ 151 MHZ)



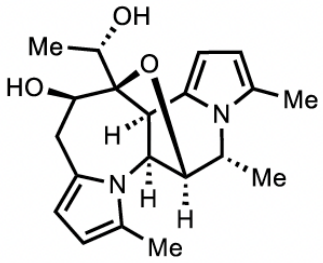

Natural (*Proc. Natl. Acad. Sci. U. S. A.*

**2020**, *117*, 1174.)

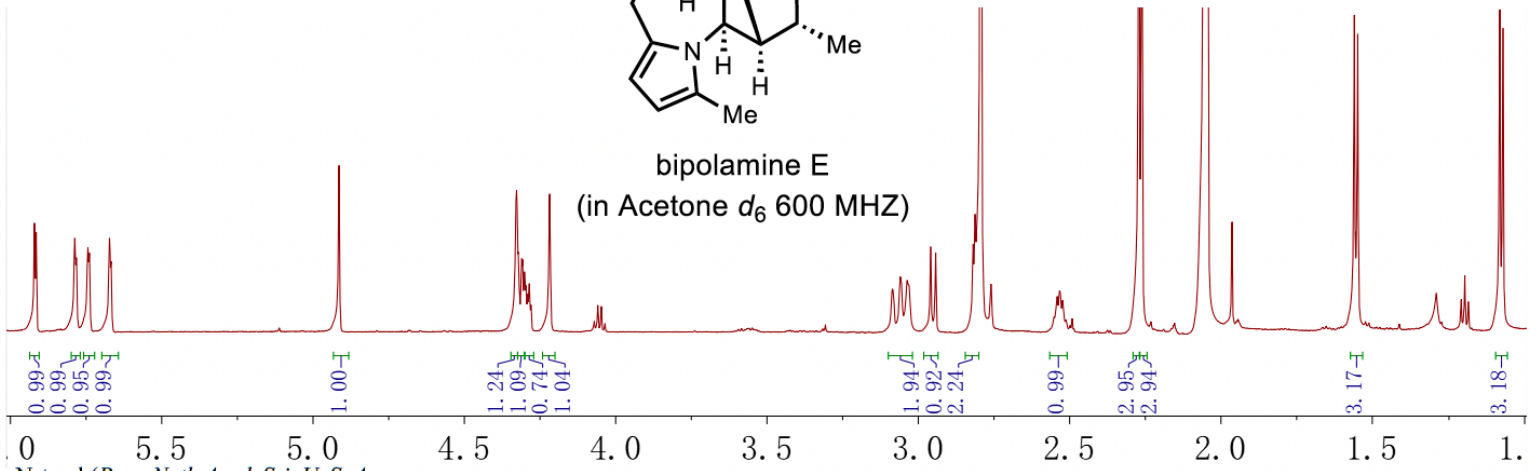


Bipolamine E $^{1}$H NMR Comparison

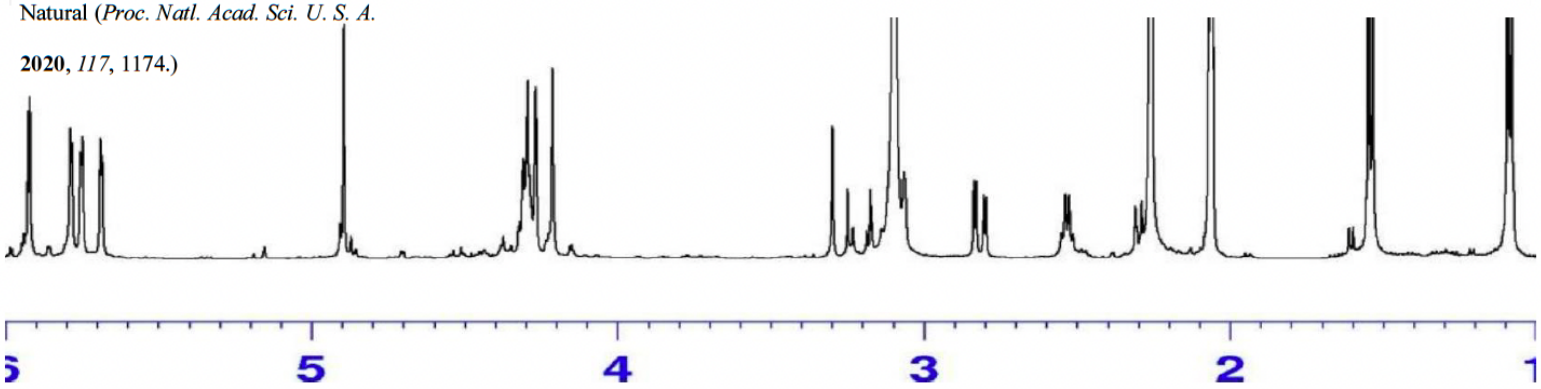
Synthetic (this work)




bipolamine E
(in Acetone $d_6$ 600 MHZ)

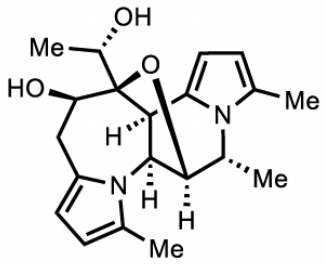



Natural (*Proc. Natl. Acad. Sci. U. S. A.* **2020**, *117*, 1174.)

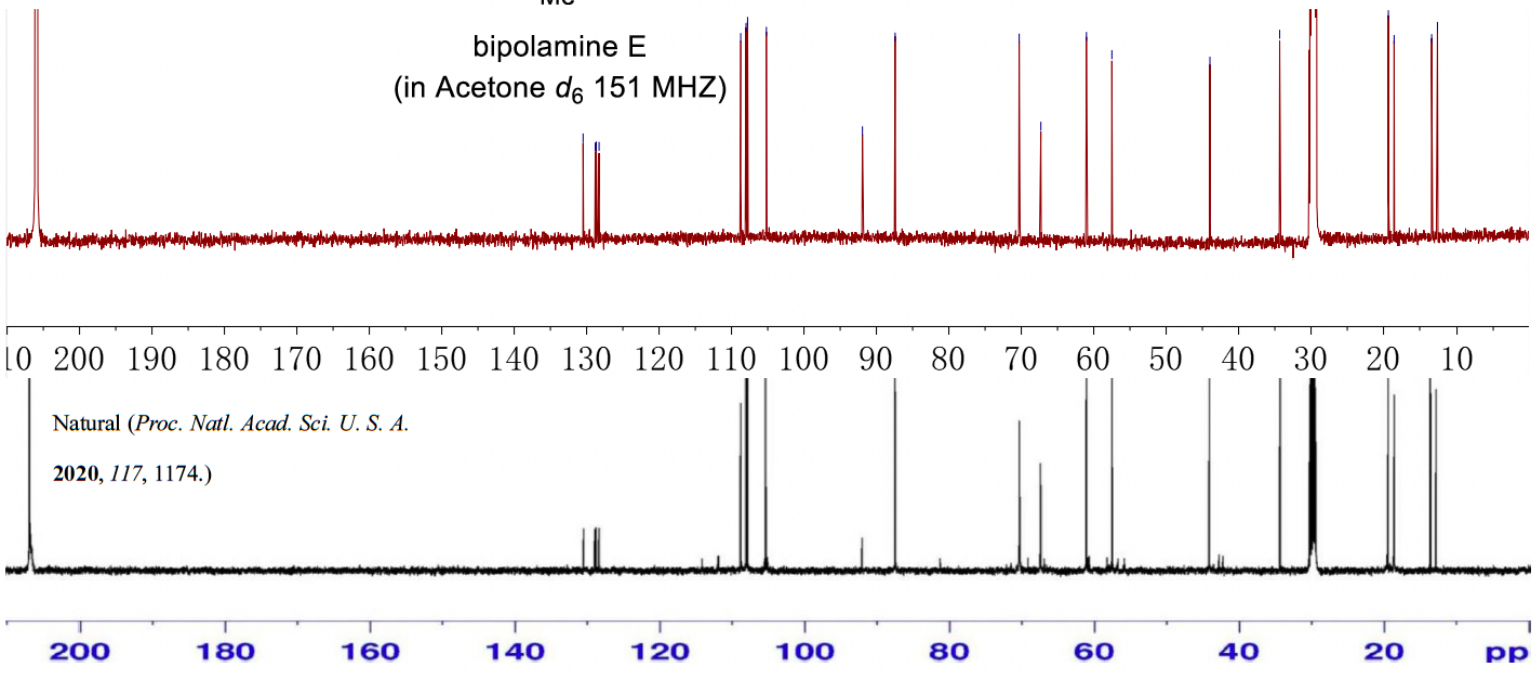


Bipolamine E $^{1}$H NMR Comparison

Synthetic (this work)

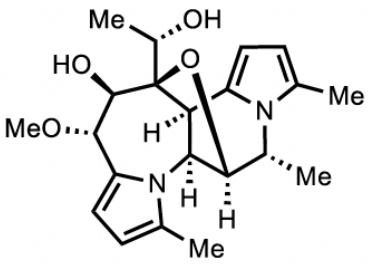



bipolamine E
(in Acetone $d_6$ 151 MHZ)

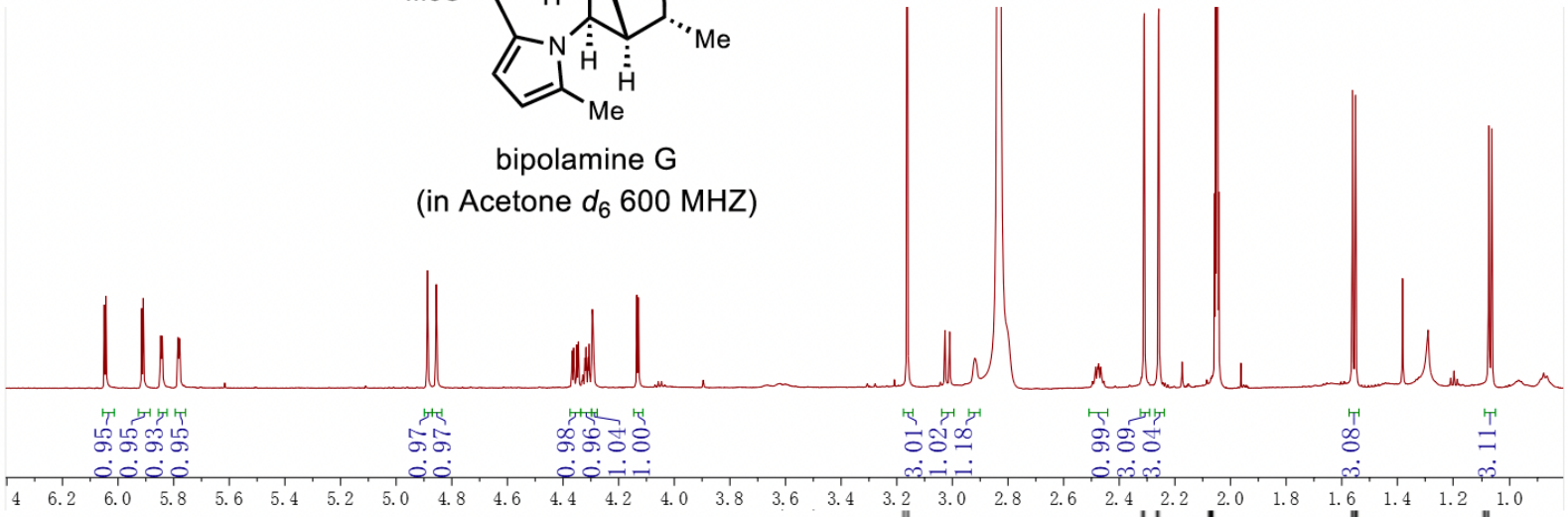


Bipolamine G $^{1}$H NMR Comparison

Synthetic (this work)

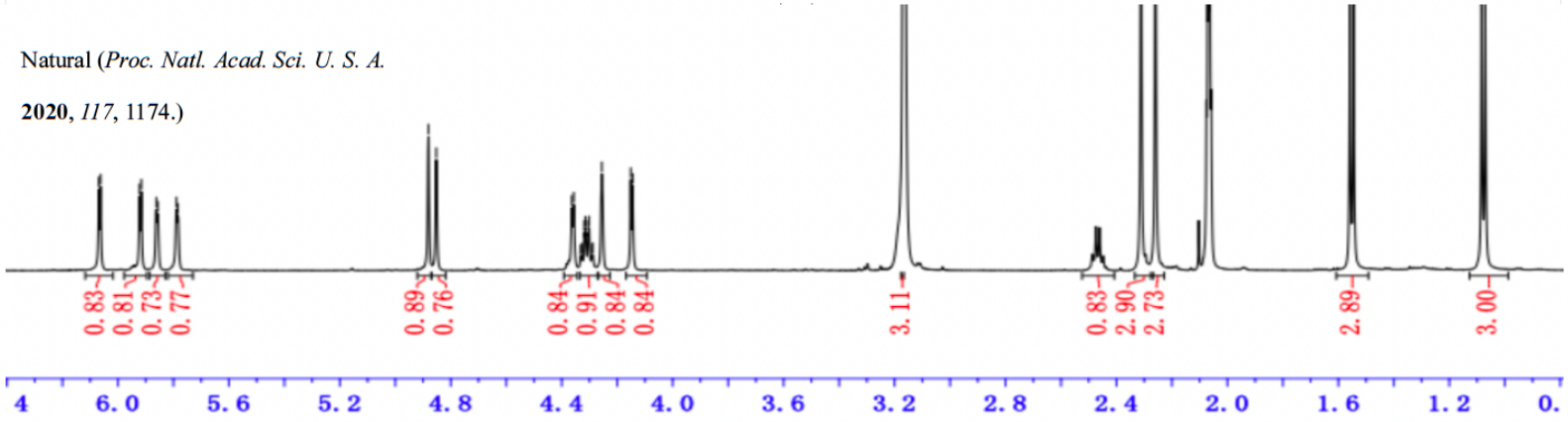



bipolamine G
(in Acetone $d_6$ 600 MHZ)



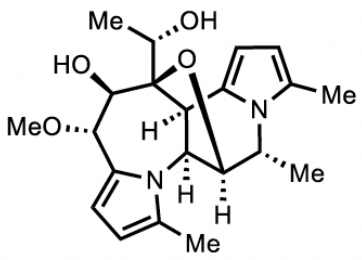

Natural (*Proc. Natl. Acad. Sci. U. S. A.*

**2020**, *117*, 1174.)

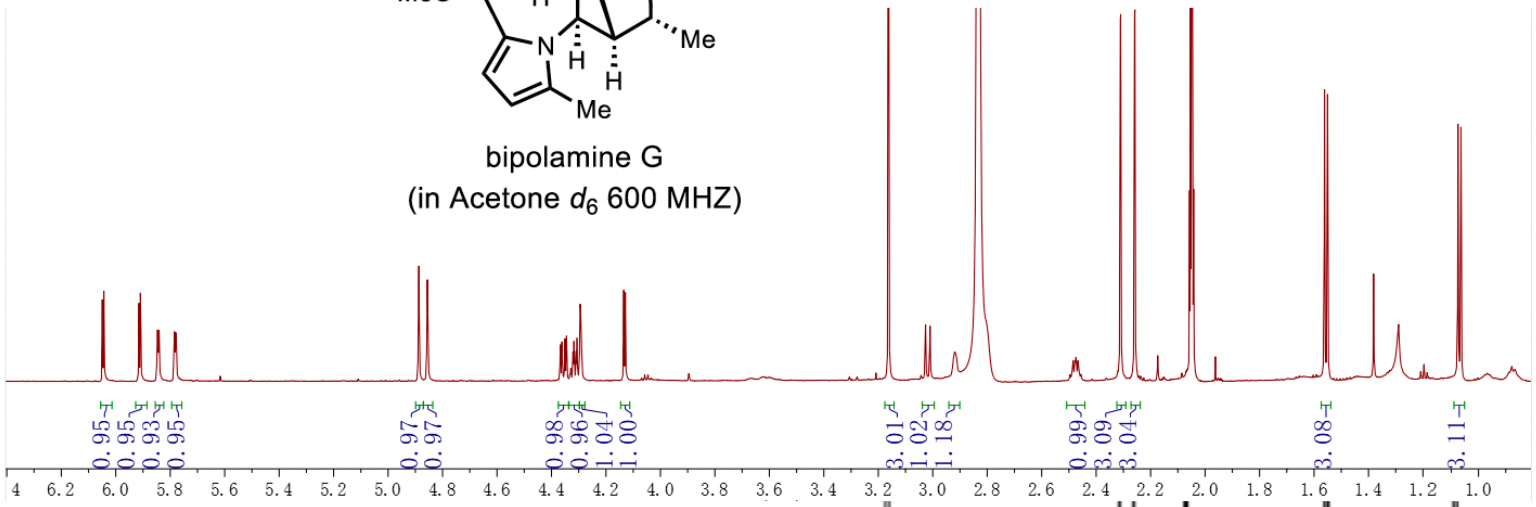


Bipolamine G $^{1}$H NMR Comparison

Synthetic (this work)

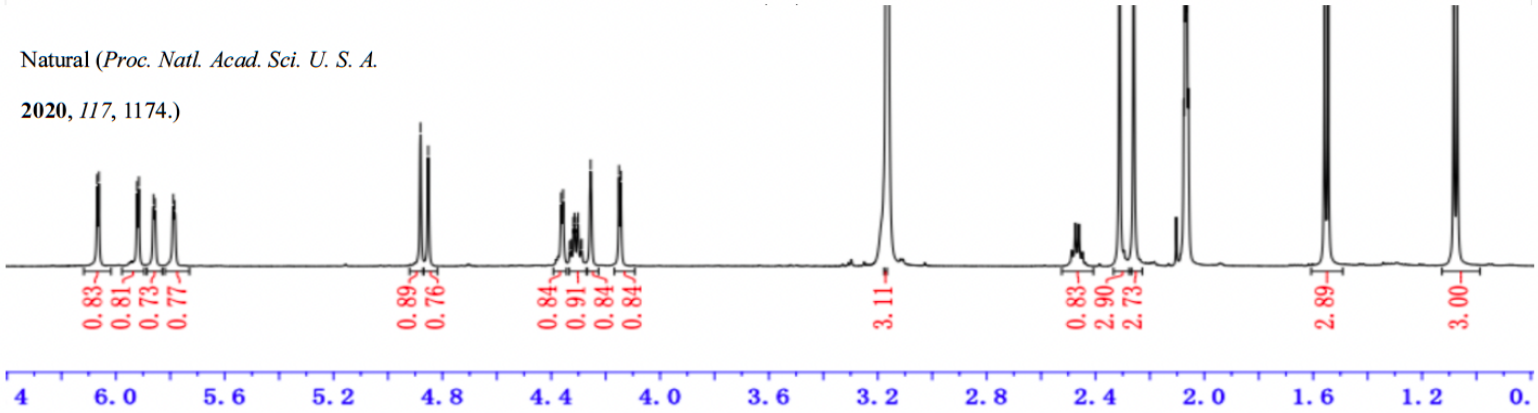


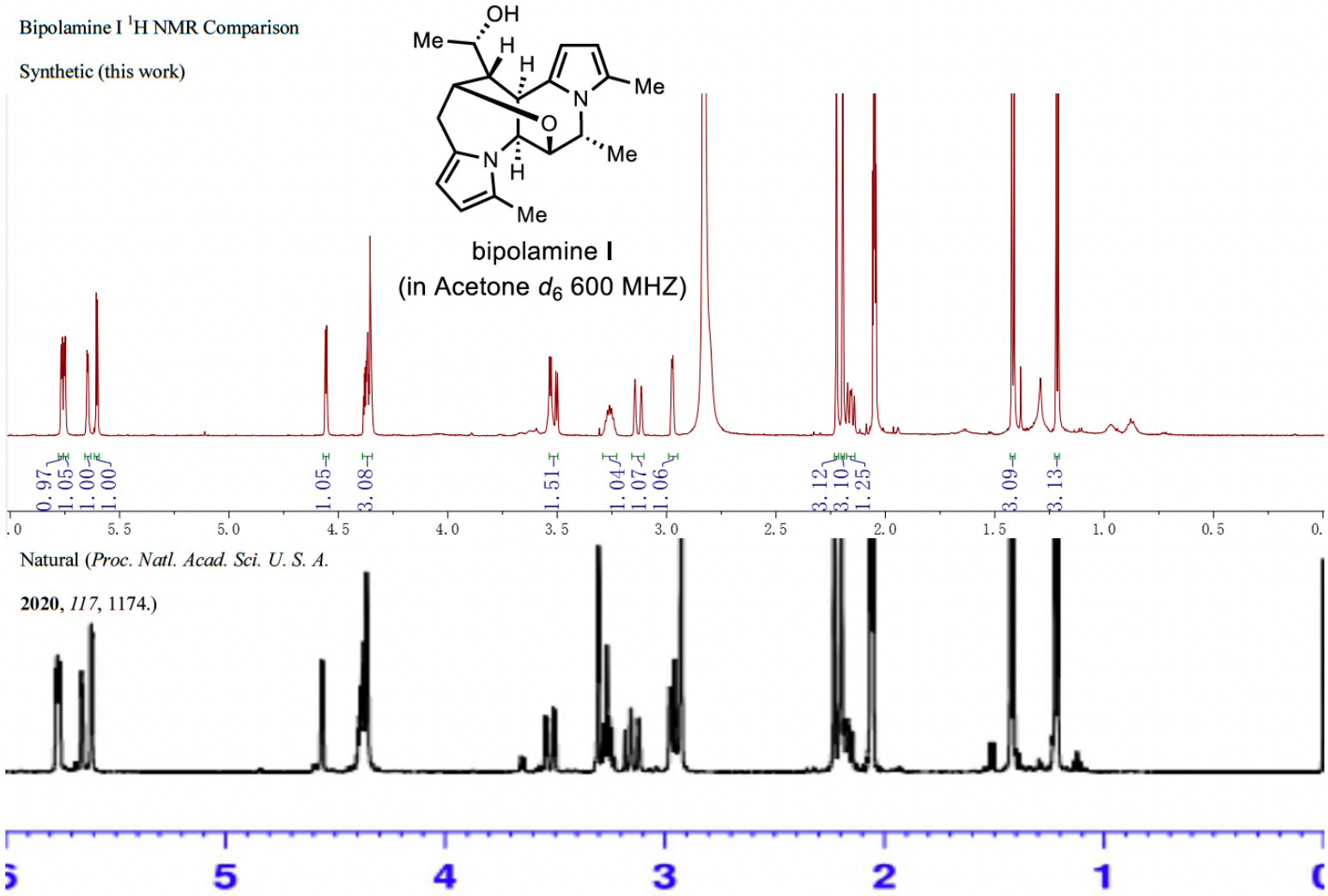

bipolamine G
(in Acetone $d_6$ 600 MHZ)

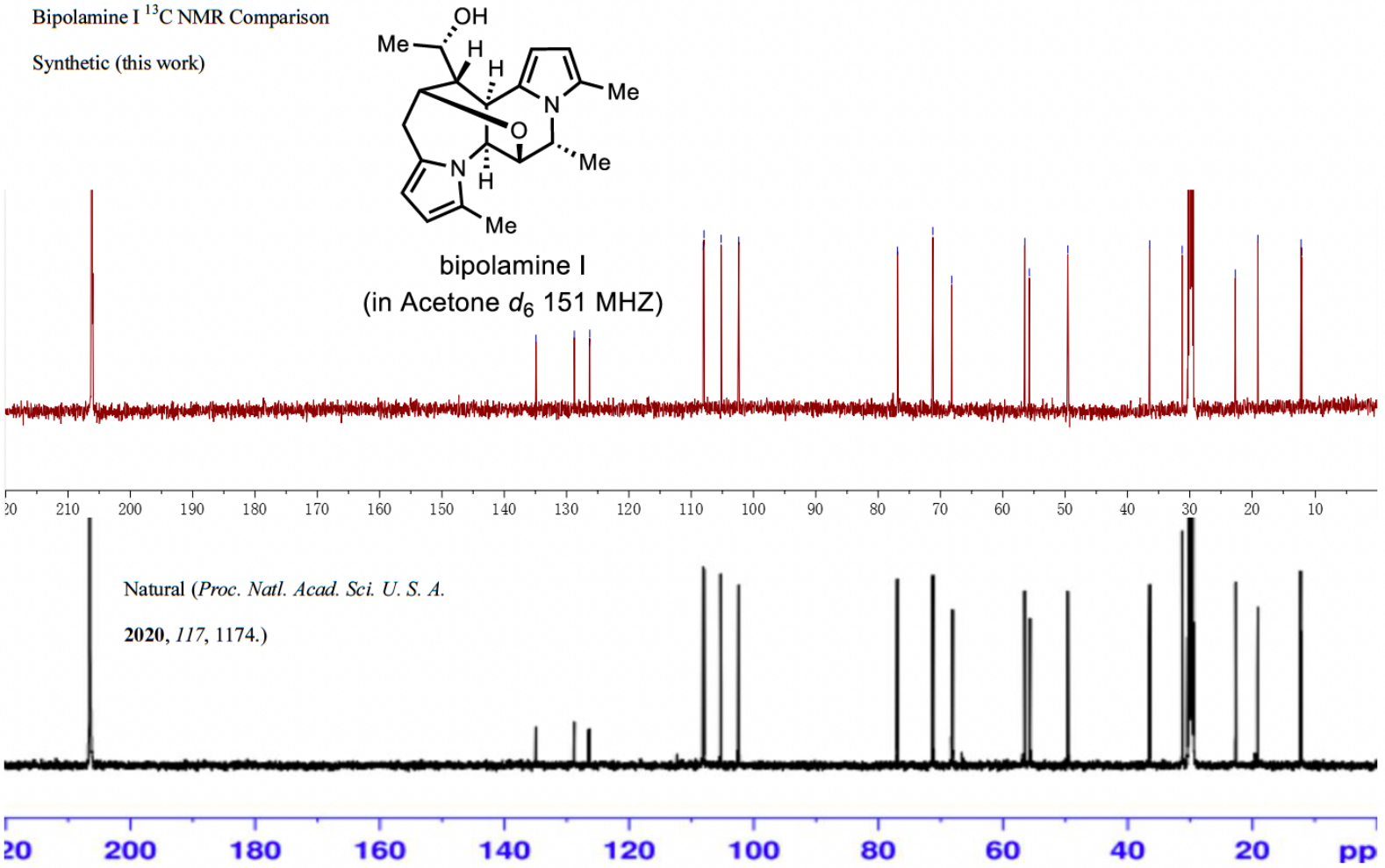



Natural (*Proc. Natl. Acad. Sci. U. S. A.*

**2020**, *117*, 1174.)




Bipolamine I $^1$H NMR Comparison
Synthetic (this work)
OH
Me
H
H
N
Me
O
Me
N
H
Me
bipolamine I
(in Acetone $d_6$ 600 MHZ)
0.97
1.05
1.00
1.00
1.05
3.08
1.51
1.04
1.07
1.06
3.12
3.10
1.25
3.09
3.13
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
Natural (*Proc. Natl. Acad. Sci. U. S. A.*
**2020**, *117*, 1174.)
5
4
3
2
1


Bipolamine I $^{13}$C NMR Comparison
Synthetic (this work)
OH
Me
H
H
Me
N
O
Me
N
H
Me
bipolamine I
(in Acetone $d_6$ 151 MHZ)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
Natural (*Proc. Natl. Acad. Sci. U. S. A.*
**2020**, *117*, 1174.)
200 180 160 140 120 100 80 60 40 20 ppm