THE UNIVERSITY OF CHICAGO

THE EVOLUTION OF STRATEGIES FOR THE DEVELOPMENT OF NOVEL ELECTROPHILIC REAGENTS AND THE TOTAL SYNTHESIS OF DIVERSE NATURAL PRODUCTS

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ABSTRACT

The Evolution of Strategies for the Development of Novel Electrophilic Reagents and the Total Synthesis of Diverse Natural Products

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Chemical synthesis of structurally complex and diverse natural products has been explored by synthetic chemists throughout centuries. The scientific essence within inspires and guides relevant fields in society and science, for example, pharmaceutical industry, material science, and agricultural industry. In this vein, people cultivate the toolbox of synthetic chemistry, hoping to invent stronger, cheaper, and more versatile reagents and catalysts to enable shorter pathways toward those "formidable" molecules. The advancement of synthetic methodology and natural product synthesis therefore become two powerful engines, boosting the evolution of organic chemistry and related fields. By this principle, this dissertation describes four components on how strategies are designed and developed toward 1) Halophosphonium pre-reagents for alkene hydro- and deuterio-halogenation; 2) synthesis of diverse bromo-chamigrene natural products; 3) biomimetic and nonbiomimetic synthetic studies of fungal metabolite homodimericin A; and 4) a unified solution toward the *Myrioneuron* alkaloids.

In the first chapter, the discovery of a group of halophosphonium reagents will be discussed starting from their structural precedents, halogenation reagent series XDSX (X = Cl, Br, I). The optimization process and the substrate scope exploration will then be covered. The latter portion of the chapter will be focusing on our attempts to elucidate the structures of these reagents, and the efforts on investigating the active reaction intermediate and related mechanisms. A case of application in isotope incorporation onto alkene substrates is included as well.

Then chapter 2 will detail the evolution of two generations of synthetic strategies toward the bromo-chamigrene natural product aplydactone. The first-generation strategy enabled a highly stereoselective bromo-cyclization key reaction while its product proved unable to proceed to the desired natural product. The second-generation strategy features a Lewis acid promoted Diels-Alder reaction in assembling the core spirocycle structure of bromo-chamigrenes. This ultimately led to the synthesis of three members in the family and a formal synthesis of aplydactone.

As an intermittent part, chapter 3 serves to introduce the story of a hexacyclic fungal metabolite homodimericin A. Failure in discovering a suitable biomimetic condition of dimerization guided us to a non-biomimetic route. Although we reached a key intermediate that can potentially be transformed into a putative biosynthetic intermediate, the project was terminated there since the synthesis of the molecule was reported by other research groups.

Finally, in chapter 4, the evolution of a unified strategy toward the *Myrioneuron* alkaloids will be delineated. The diversity in structures and biological activities of various family members is introduced in the first place, followed by the proposed biosynthetic analysis of the family tree. The currently known synthetic efforts toward these alkaloids will be covered, especially a significant report of a special member, myrioneurinol, from Weinreb. We then explore our 20-step synthesis of this molecule, featuring an *aza*-Michael cyclization reaction as a key step. The application of this type of cyclization will be plotted in the synthesis of two other family members myrioxazine A and schoberine B as well.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF SCHEMES

LIST OF ABBREVIATIONS

BDSB	bromodiethylsulfonium bromopentachloroantimate
BINAP	bis(diphenylphosphino)-1,1′-binaphthalene
CAN	ammonium cerium(IV) nitrate
Cbz	carboxyl benzyl
CDSC	chlorodiethylsulfonium hexachloroantimate
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DDQ	2,3-dicyano-5,6-dichlorobenzoquinone
DEAD	diethyl azodicarboxylate
depe	1,2-bis(diethylphosphino)ethane
DIBAL-H	diisobutylaluminum hydride
DIPEA	*N*,*N*-diisopropylethylamine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
DPPA	diphenylphosphoryl azide
dppe	1,2-bis(diphenylphosphino)ethane
dppp	bis(diphenylphosphino)propane
IBX	2-iodoxybenzoic acid
IDSI	iododiethylsulfonium iodopentachloroantimate
$[Ir(cod)Cl]_2$	bis(1,5-cyclooctadiene)diiridium(I) dichloride

KHMDS	potassium bis(trimethylsilyl)amide
LDA	lithium diisopropylamide
LiHMDS	lithium bis(trimethylsilyl)amide
NBS	*N*-bromosuccinimide
NIS	*N*-iodosuccinimide
$Ni(acac)_2$	nickel(II) acetylacetonate
Pd_2dba_3	tris(dibenzyllideneacetone)dipalladium(0)
$Pd(dppf)Cl_2$	[1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II)
$Rh_2(cap)_4$	dirhodium tetracaprolactamate
$Rh_2(tfa)_4$	rhodium(II) trifluoroacetate dimer
TBAF	tetrabutylammonium fluoride
TBCO	2,4,4,6-tetrabromo-2,5-cyclohexadien-1-one
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMSCl	chlorotrimethylsilane
Triton-B	benzyltrimethylammonium hydroxide

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CHAPTER 1

HALOPHOSPHONIUM PRE-REAGENTS FOR ALKENE HYDRO- AND DEUTERIO-HALOGENATION

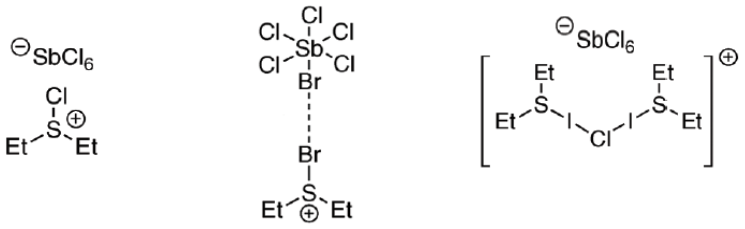
1.1 Introduction

The introductory part of the HX addition reagent chapter is divided into two portions. The first part will focus on the development of XDSX reagents and their applications. The latter one will be on the development history of hydrohalogenation reactions.

1.1.1 Introduction of XDSX reagents

1.1.1.1 Structures and reactivity of XDSX reagents

Among such vast range of natural product molecules, halogenated natural products are of particular interests due to their unique structural properties and biological activities.[1] In 2009, our group devised a group of halogenation reagents, XDSX (X = Cl, Br, I, Figure 1-1),[2,3] which are capable of reacting with alkenes and arenes, incorporating halogen atoms and triggering tandem reactions to construct topologically complex structures found in various natural products.[4-7] The following introductory chapter serves to briefly describe the development of the XDSX reagent series and their applications in the relevant natural product synthesis.

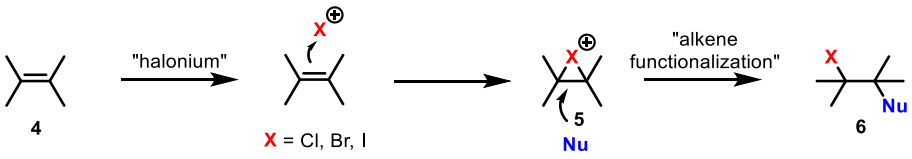


1: CDSC **2**: BDSB **3**: IDSI

Figure 1-1. The crystal structures of XDSX reagent series

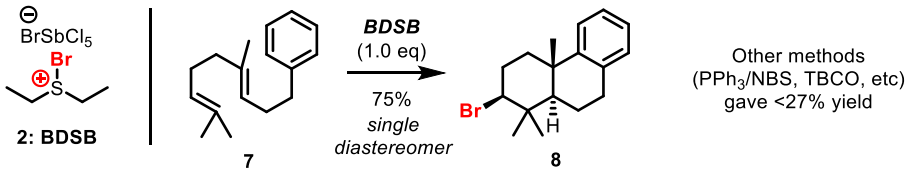
From a mechanistic perspective, CDSC (**1**) and BDSB (**2**) both contain an "exposed" halonium where the Lewis acid part pulled Cl^-/Br^-, rendering the cationic portion of the reagent a strong Cl^+/Br^+ source, as shown in their crystal structure (Figure 1-1). IDSI (**3**) is slightly different in its crystalline structure. Nevertheless, it is still a reactive I^+ reagent. As an example (Scheme 1-

1), these reagents first react with an alkene substrate to form a three-membered cationic intermediate, naming haloranium. Then this high-energy intermediate **5** can be captured by a variety of nucleophiles, including *O*- and *N*- containing moieties, and alkenes or arenes, to form the resultant functionalized product (**6**). In this chapter, important electrophiles are globally marked in red while nucleophiles are in blue, for clarity.



Scheme 1-1. A general illustration of halonium reagent induced alkene functionalization reactions

These reagents showed significant improvement in reactivity compared to the recorded halogenation reagents in literatures.[2] For example, BDSB reacts with homogeranylbenzene (**7**) to afford its π-cationic bromo-cyclized product (**8**) in 75% isolated yield. This level of isolated yield was never achieved with known protocols, such as NBS/PPh_3 or TBCO (Scheme 1-2). Several other geranyl-derivatives were also bromo-cyclized in high and improved yield.



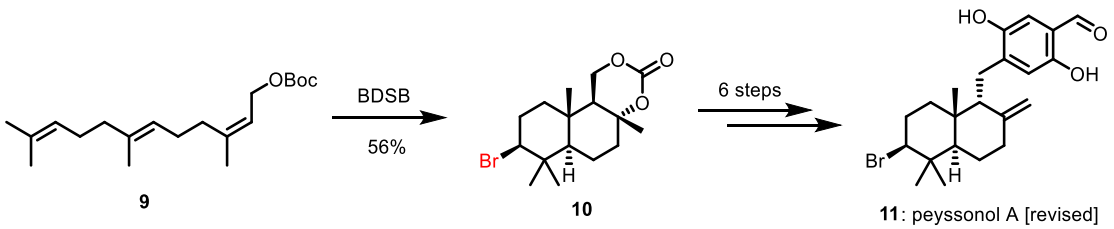
Scheme 1-2. BDSB provided superior yield in the bromo-cyclization reaction than previous methods

Likewise, CDSC reacts with polyene substrates to generate the corresponding cyclization product as well, though giving lower yield than BDSB does. Another deficit of CDSC is that the chloro-cyclization reaction on polyene substrates like homogeranylbenzene (**7**), resulted in a 1:1 diastereomeric mixture at the secondary chloride stereocenter,[3] while BDSB ended in one product as a single diastereomer (Scheme 1-2). The motive to optimize and refine the reactivity of CDSC led to the discovery of a group of hydro-/deuterio-halogenative reagents, which will be covered in

the main body of this chapter. Of note, the iodo-version in the reagent series can afford cyclization on various polyene substrates in generally good yield (45%-90%).[3]

1.1.1.2 Accomplished synthesis of various halogenated natural products using BDSB

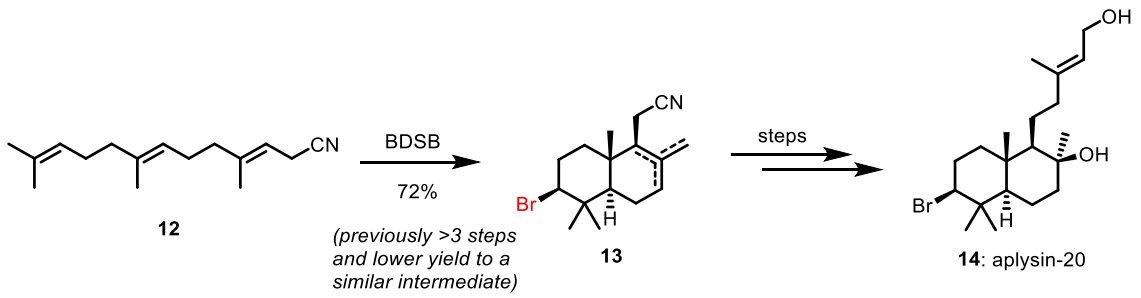
The outstanding reactivity of BDSB in terms of incorporating bromine atoms into organic molecules enabled its employment in the synthesis of complex brominated natural products. Analogous to the bromo-cyclization reaction of homogeranylbenzene (**7**), the polyene substrate **9** was converted to its cyclized counterpart **10** in 56% yield (Scheme 1-3). After another 6 steps of functional group interconversions from the tricycle **10**, the revised structure of natural product peyssonol A (**11**) was reached.[3]



9 **10** **11**: peyssonol A [revised]

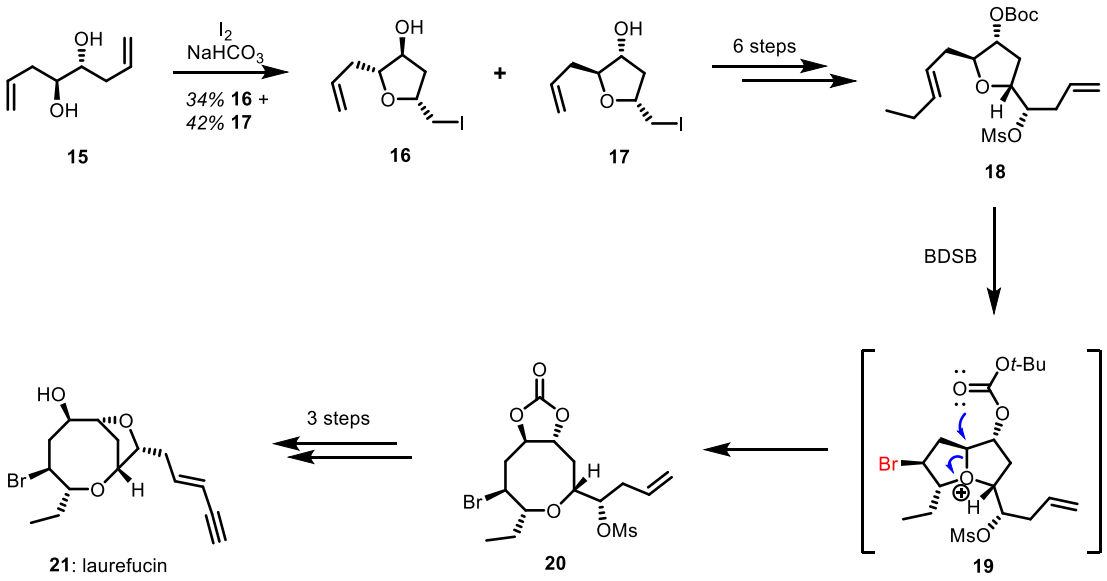
Scheme 1-3. Synthesis of the revised structure of peyssonol A via a key step promoted by BDSB

On the farnesyl nitrile substrate **12**, BDSB was able to render the bromo-cyclized product in good yield (72%).[3] As a comparison, the recorded approach towards an intermediate close to **13** (only different in alkene positions) encountered low yield and the transformation had to be done in 3 steps. Bromo-bicycle intermediate **13** could then be processed to the natural product aplysin-20 (**14**) by the reported route shown in Scheme 1-4.



Scheme 1-4. A formal synthesis of aplysin-20 via a key step promoted by BDSB

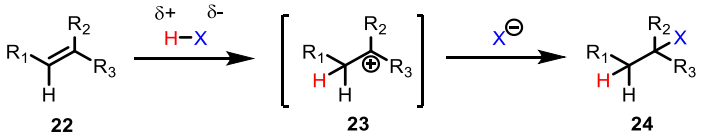
The strength of BDSB in natural product synthesis is not limited to polyene type of substrates. The oxygen atom of ether can serve as nucleophile in the bromination reaction as well. A formal synthesis of the bromo-ether natural product laurefucin (**21**) was achieved through BDSB-mediated key reaction (Scheme 1-5). Staring from the diol **15**, an iodo-cyclization furnished the substituted tetrahydrofuran compounds **16** and **17** as two diastereomers. The major isomer **17** was then converted to the cyclization precursor **18** in 6 steps. Under the treatment of BDSB, **18** initially underwent a *5-exo-trig* cyclization to form the oxonium intermediate **19**. The carbonyl oxygen containing lone pair electrons then acted as nucleophile to attack the oxonium, opening up the fused oxonium to generate the 8-membered ether **20**. With three additional steps (last two steps previously reported), the target molecule laurefucin (**21**) was completed in total 13 steps (previously reported in 19 longest linear steps). This example further demonstrates the efficacy of BDSB in the synthetic campaigns towards different bromine-containing natural products.



Scheme 1-5. A formal synthesis of laurefucin via a key tandem ring closing/expansion step promoted by BDSB

1.1.2 Introduction of hydrohalogenation chemistry on alkenes

The hydrohalogenation reaction of alkenes (HX addition) are among the most historical and widely used reactions in the history of organic chemistry.[8] A typical reaction of this genre is the Markovnikov hydrohalogenation, in which general transformation can be illustrated by Scheme 1-6. Under the treatment of hydrohalogenic acid HX (X = F, Cl, Br, I), the alkene substrate **22** is first protonated to form a carbocation intermediate **23**, where the protonation occurs on the less substituted carbon of the alkene double bond so that the formed carbocation is the most stabilized one due to higher degree of substitution on the positively charged carbon. The final step is a capture by halide anion to forge the corresponding hydrohalogenation product **24**.



Scheme 1-6. A general transformation of the Markovnikov hydrohalogenation of alkenes

Among all four types of regular halide elements, chloride and bromide contribute to the majority of achievements recorded in hydrohalogenation literatures. Conventionally, Markovnikov HCl addition employs dry HCl gas or condensed liquid HCl,[9-17] tools with considerable operational difficulty that a number of alternatives have been advanced. These include the use of phase-transfer conditions employing lipophilic phosphonium catalysts and aqueous HCl solution, the *in situ* generation of HCl from highly reactive inorganic/organic chlorides, as well as solid surface-promoted and metal-mediated hydrochlorinations.[18-27] Several indirect approaches have been developed as well, such as reduction of vinyl halides to alkyl halides, hydrometallation/halogen trap sequence, and C-H halogenation of alkanes (see the published paper and reference there in).[28] Of significance, Carreira[29] in 2008 demonstrated a radical-based process to directly mono-substitute terminal alkenes with acid-sensitive moieties hard to functionalize through cationic processes.[30,31] Nevertheless, limitations still exist with these collated methods, largely due to issues with unwanted leaving group displacements, cyclization reactions, and other polymerization events that can occur inherently because of the reaction conditions, especially when experiments are conducted on small scale.

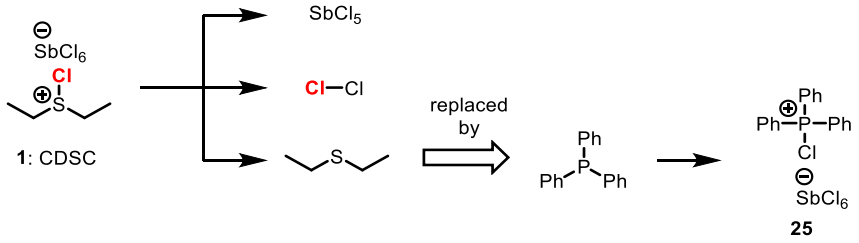
Unlike HCl, solutions of HBr can readily add across alkenes,[32] but typically do so under conditions that are quite harsh, with few alternatives identified for Markovnikov additions outside of surface supported methods (such as PBr_3/SiO_2).[20,23,33] Additionally, anti-Markovnikov side-products are possible, though, if the reaction is not under strict protection from air, light, and/or trace peroxides. Overall, this reaction process is much less developed. And, more globally, few effective and practical methods exist for either DCl or DBr addition, particularly on laboratory scale.[34-38]

It shall be mentioned that after we published our results in this chapter, Xu and Hammond et al reported a versatile hydrohalogenation tool featuring the combination of HX and DMPU.[39,40] Their system has the capability of adding HX, including HF across a variety of alkene substrates including terminal alkenes with high efficacy.[41]

1.2 Reagent development

1.2.1 An entry to hydrohalogenation reagents from modification of CDSC

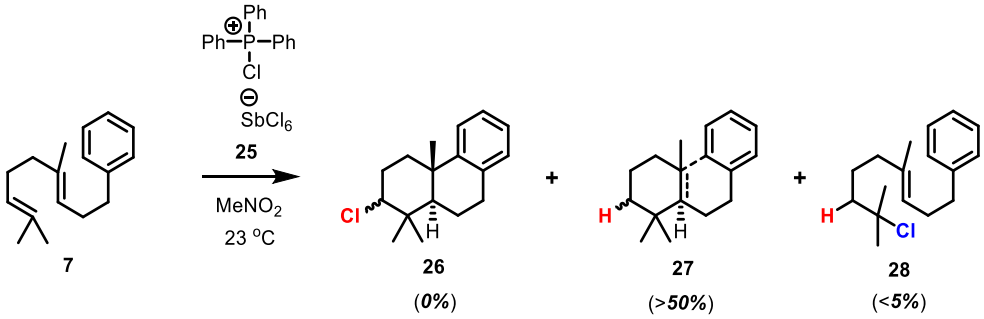
Our initial motivation in the project is to improve the yield and diastereoselectivity of the polyene chlorocyclization reaction induced by CDSC (**1**). As mentioned in the introductory paragraphs, CDSC promoted the cyclization reaction of homogeranylbenzene (**7**) and afforded the product in 41% isolated yield and a 1:1 diastereomeric mixture at the secondary chloride position. In an attempt to gain higher yield and better selectivity on this exact substrate, our group conducted an extensive screening of reaction parameters, including solvent, temperature, concentration, *etc*.[42] One of other directions toward refinement is to modify the structure of CDSC itself, so that the new analogues may exhibit enhanced reactivity. From a structural perspective, CDSC comprises of three part: a Lewis base (diethyl sulfide), a molecular halogen (Cl_2), and a Lewis acid ($SbCl_5$), as shown in Scheme 1-7.



Scheme 1-7. Changing the Lewis base component of CDSC led to a new group of reagents

We first attempted to change the Lewis base part of CDSC and keep the other two parts unchanged. Among the commonly used Lewis base reagents we selected triphenylphosphine (PPh_3)

as an initial attempt. In fact, the complex $[ClPPh_3]^+[SbCl_6]^-$ (**25**) has already been reported in inorganic literatures,[43,44] despite that its reactivity against alkenes was still unknown. We prepared complex **25** through mixing triphenyl phosphine, Cl_2, $SbCl_5$ in 1:1:1 ratio and tested it on homogeranylbenezene **7** (Scheme 1-8). To our surprise, no desired chloro-cyclized product **26** was isolated, with the major product is a mixture of several non-polar compounds that we tentatively assigned as fully or partially proton-cyclizated products (**27**). In addition, we identified 5% of acyclic compound (**28**) where its terminal alkene was hydrochlorinated with Markovnikov regioselectivity.



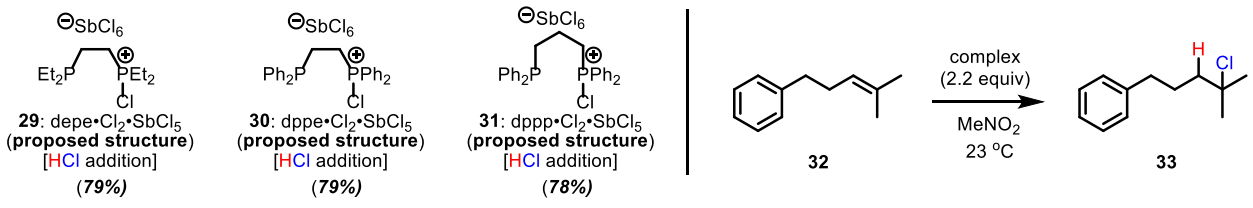
Scheme 1-8. The PPh_3 based complex **25** gave rise to a small amount of HCl addition product **28**

The result clearly indicated that there's no active chloronium (Cl^+) species in the reagent (PPh_3 complex **25**). Even more, the occurrence of proton-cyclized product (**27**) reflected that this reagent could possibly have been hydrolyzed by the adventitious water present in the reaction solvent nitromethane. Nonetheless, the HX addition product **28** was intriguing since the selective hydrochlorination seems to not be the predominant pathway in this transformation, partially owing to the promiscuous nature of the substrate **7** in terms of two reactive C-C double bonds. Eager to command the hydrochlorination pathway, we started to optimize the structure of such phosphine complexes. The potential benefits over the current hydrochlorination methods might reside in: 1) ease to run a hydrochlorination reaction in commercial grade solvents, instead of preparing an anhydrous solution of alkene substrate and dry HCl gas; 2) usage of a stoichiometric amount of

solid reagents that are easy to weigh and handle, instead of bubbling excessive HCl gas into the reaction media; 3) broader substrate scope than conventional HCl addition methodologies with strongly acidic conditions.

1.2.2 Screening of phosphine/Lewis acid combinations for optimal HCl/HBr addition reagents

Initially we used several mono-phosphines to synthesize their relevant complexes. We found out that when alkyl phosphines, such as *n*-Bu_3P were employed, the corresponding complex $[ClPn\text{-}Bu_3]^+[SbCl_6]^-$ was so prone to hydrolysis in air that it could barely be productively isolated through regular lab operations such as filtration. Hybrid phosphines ($MePPh_2$, Me_2PPh) did not show significant improvement in yield of hydrochlorination. However, bis-phosphines, 1,2-bis(diethylphosphino)ethane (depe), 1,2-bis(diphenylphosphino)ethane (dppe) and 1,3-bis(diphenylphosphino)propane (dppp) performed well in the synthesis of their complexes (**29**-**31**) and the following HCl addition reactions (Scheme 1-9). On polyene substrate homogeranylbenzene **7**, they all afforded good yield of a mixture of mono- and di-hydrochlorinated product. To have a fair comparison, we moved onto simpler mono-alkene substrate **32** for further testing. All three reagents gave 78%-79% isolated yield in the hydrochlorination reaction on the test substrate **32** (Scheme 1-9, yield shown in parentheses). Since the depe complex **29** is vulnerable to hydrolysis at a decomposing rate much faster than **30** and **31**, dppe and dppp were chosen as the optimal phosphine backbone for the hydrohalogenation reagents.



Scheme 1-9. Bis-phosphine complexes displayed synthetically improved yield on the test substrate

A variety of Lewis acids were then screened based on the dppe and dppp backbone. The method for efficacy determination follows: 1) visual TLC inspection of the reaction between geranylsulfone and a complex (homogeranylbenzene and its hydrochlorinated product is more UV and stain active while mono alkene test substrate **32** is barely visible on TLC), and if TLC looks promising, then 2) performing a 30-mg scale reaction of the test substrate and the selected complex and measure isolated yield. The result of the screening is given in Table 1-1.

Table 1-1. Testing HCl reagent combinations based on the selected phosphine backbones.

Halide	**Phosphine**	**Lewis Acid**	**TLC screening on geranylsulfone (Success = Yes, Failure = No)**	**Yield on test substrate 32[a]**
Cl_2	dppe	$AlCl_3$	No	\
Cl_2	dppp	$AlCl_3$	No	\
Cl_2	dppe	BCl_3	No	\
Cl_2	dppp	BCl_3	No	\
Cl_2	dppe	$BiCl_3$	No	\
Cl_2	dppp	$BiCl_3$	No	\
Cl_2	dppe	$CeCl_3$	No	\
Cl_2	dppp	$CeCl_3$	No	\
Cl_2	dppe	$CoCl_2$	Yes	78% (+4% of protocyclization)
Cl_2	dppp	$CoCl_2$	No	\
Cl_2	dppe	$CuCl_2$	No	\
Cl_2	dppp	$CuCl_2$	No	\

Table 1-1. (Continued)

Cl_2	dppe	$FeCl_3$	No	\
Cl_2	dppp	$FeCl_3$	No	\
Cl_2	dppe	$GaCl_3$	No	\
Cl_2	dppp	$GaCl_3$	No	\
Cl_2	dppe	$HfCl_4$	No	\
Cl_2	dppp	$HfCl_4$	No	\
Cl_2	dppe	$MnCl_2$	Yes	82% (+3% of protocyclization)
Cl_2	dppp	$MnCl_2$	Yes	78% (+3% of protocyclization)
Cl_2	dppe	$NbCl_5$	No	\
Cl_2	dppp	$NbCl_5$	Yes	77% (traces of protocyclization)
Cl_2	dppe	$NiCl_2$	No	\
Cl_2	dppp	$NiCl_2$	No	\
Cl_2	dppe	$SbCl_3$	No	\
Cl_2	dppp	$SbCl_3$	No	\
Cl_2	dppe	$SbCl_5$	Yes	79% (+2% of protocyclization)
Cl_2	dppp	$SbCl_5$	Yes	78% (+8% of protocyclization)

Table 1-1. (Continued)

Cl_2	dppe	$SnCl_4$	Yes	58% (+14% of protocyclization)
Cl_2	dppp	$SnCl_4$	Yes	42% (+23% of protocyclization)
Cl_2	dppe	$TaCl_5$	No	\
Cl_2	dppp	$TaCl_5$	No	\
Cl_2	dppe	$TiCl_4$	Yes	52% (+2% of protocyclization)
Cl_2	dppp	$TiCl_4$	Yes	79% (+3% of protocyclization)
Cl_2	dppe	VCl_3	No	\
Cl_2	dppp	VCl_3	No	\
Cl_2	dppe	$ZnCl_4$	No	\
Cl_2	dppp	$ZnCl_4$	No	\
Cl_2	dppe	$ZrCl_4$	No	\
Cl_2	dppp	$ZrCl_4$	No	\

[a]Isolated yields. Contaminated by the proton cyclized product, estimated by NMR.

Given the result that no other metal chloride Lewis acids performed better than antimony(V) in the transformation, complex dppe·Cl_2·$SbCl_5$ (**30**) and dppp·Cl_2·$SbCl_5$ (**31**) turned out to be the two optimal reagents for alkene hydrochlorination. The denoted formula expressed composition in a 1:1:1 ratio of each component (phosphine/molecular halogen/metal halide) during preparation

of the complex. At this stage, we did not have a clear observation of the structures for these reagents. The elucidation of structures and reaction mechanism is discussed *vide infra*.

The success in optimization of hydrochlorination reagents prompted us to further explore related reagents for hydrobromination. We conducted a similar screening campaign, attempting to rapidly pick out promising combinations through TLC inspection & 30-mg run sequence. Since we discovered that a hybrid halide species (i.e. using Br_2 together with $SbCl_5$) ended in delivering both chloride and bromide onto C-C double bonds without selectivity, resulting in a mixture of HCl and HBr addition products, only metal bromide salts were employed in HBr reagents screening. Table 1-2 covers the details.

Table 1-2. Testing HBr reagent combinations based on the selected phosphine backbones

Halide	**Phosphine**	**Lewis Acid**	**TLC screening on geranylsulfone (Success = Yes, Failure = No)**	**Yield on test substrate 32[a]**
Br_2	dppe	$AlBr_3$	No	\
Br_2	dppp	$AlBr_3$	No	\
Br_2	dppe	BBr_3	No	\
Br_2	dppp	BBr_3	No	\
Br_2	dppe	$BiBr_3$	No	\
Br_2	dppp	$BiBr_3$	No	\
Br_2	dppe	$CeBr_3$	No	\
Br_2	dppp	$CeBr_3$	No	\
Br_2	dppe	$CoBr_3$	No	\
Br_2	dppp	$CoBr_3$	No	\

Table 1-2. (Continued)

Br_2	dppe	$CuBr_3$	No	\
Br_2	dppp	$CuBr_3$	No	\
Br_2	dppe	$FeBr_3$	Yes	33%
Br_2	dppp	$FeBr_3$	No	\
Br_2	dppe	$GaBr_3$	No	\
Br_2	dppp	$GaBr_3$	No	\
Br_2	dppe	$HfBr_4$	Yes	51%
Br_2	dppp	$HfBr_4$	Yes	28%
Br_2	dppe	$MnBr_2$	No	\
Br_2	dppp	$MnBr_2$	No	\
Br_2	dppe	$NbBr_5$	No	\
Br_2	dppp	$NbBr_5$	No	\
Br_2	dppe	$NiBr_2$	No	\
Br_2	dppp	$NiBr_2$	Yes	39%
Br_2	dppe	$SbBr_3$	No	\
Br_2	dppp	$SbBr_3$	Yes	14%
Br_2	dppe	$SnBr_4$	Yes	traces, mostly protocyclization
Br_2	dppp	$SnBr_4$	No	\
Br_2	dppe	$TaBr_5$	No	\
Br_2	dppp	$TaBr_5$	No	\
Br_2	dppe	$TiBr_4$	Yes	40%

Table 1-2. (Continued)

Br_2	dppp	$TiBr_4$	No	\
Br_2	dppe	VBr_3	No	\
Br_2	dppp	VBr_3	No	\
Br_2	dppe	$ZnBr_2$	Yes	traces, nearly only protocyclization
Br_2	dppp	$ZnBr_2$	No	\
Br_2	dppe	$ZrBr_4$	No	\
Br_2	dppp	$ZrBr_4$	No	\

[a]Isolated yields. Contaminated by the proton cyclized product, estimated by NMR.

$TiBr_4$ and $HfBr_4$ were proven the best metal halide salts to form the complexes dppe·Br_2·$TiBr_4$ (**34**) and dppe·Br_2·$HfBr_4$ (**35**), which gave the highest isolated yield in hydrobromination of the test substrate **32**. The large-scale preparation of the selected hydrochlorination and hydrobromination reagents are operationally friendly. Simply by mixing 1.1 equivalents of phosphine and 1.0 equivalents of molecular halogen (Cl_2 or Br_2) in 1,2-dichloroethane at -30 ^oC, followed by adding metal halide (1.1 equivalents) and slowly warming the reaction mixture to room temperature, we can harvest the reagents in nice powder form by collecting and drying the filter cake after aging the reaction mixture in freezer for a certain time length (typically 16 h).

It was noteworthy that we also attempted to prepare such reagents delivering HF and HI. Some of the fluoride reagents could be synthesized and isolated, but they generally convey only proton-induced cyclization. The cause behind may be that the metal fluoride anions in the complex

coordinate metals much tighter than chloride or bromide do, so the fluoride cannot leave and attack the carbocation intermediate to furnish C-F bond. For hydroiodination, we did capture small amounts of HI addition products in some cases. Unfortunately, we were unable to further improve the yield and; the product in the reaction, a tertiary iodide, was relatively unstable under neutral conditions with even weak light irradiation. Thereon, only HCl and HBr addition reagents were further developed and investigated.

1.3 Substrate scope for HCl and HBr addition

1.3.1 Exploration of substrate scope for HCl addition

The optimal reagents **30** and **31** were selected to react with a wide range of alkene substrates. The overall reaction condition was mild. Alkene substrates were dissolved in a commercial nitromethane ($MeNO_2$) solution; sometimes dichloromethane is required as a co-solvent for extremely non-polar substrates. Without the necessity of strict anhydrous reaction setup, adding 2.2 equivalents of reagents into the reaction mixture, followed by letting the reaction stir for 3 to 16 hours, one can quench the reaction once TLC indicates the completion of reaction. Analytically pure products could then be obtained via regular separation methods such as silica gel flash chromatography.

The hydrochlorination reaction has a broad substrate scope (Figure 1-2). Starting with simple mono-alkenes, hydrocarbon substrates **33**, **39**, **40** were hydrochlorinated in good yield. A sulfide (**36**) and a three-unsubstituted indole compound (**37**) were functionalized uneventfully. High yields were also observed for a series of homoallyl esters and ethers (**41**-**46**). Heterocyclic arenes were tolerated, including a substrate containing a basic pyridine ring (**44**). A series of chemoselectivity-proving substrates were functionalized, for instance, substrate **47** where 1,1-

disubstituted alkene is preferred over the terminal alkyne moiety. Similar unsaturated π-systems that are preserved under the treatment of the HCl addition reagents include internal alkyne, terminal alkene, and *cis*- or *trans*- 1,2-disubstituted alkenes (**48**-**51**). An interesting case happens on substrate **52**, where a less sterically hindered 1,1-disubstituted alkene was hit while the more hindered one remained intact. Both conjugated alkenes (**53**) and partially deactivated alkenes (**54**) endured the reaction conditions. With **55**, we observed less than 10% product whose benzyl bromide was displaced by chloride, while the desired product was still harnessed in 67% yield. Finally, for the geranyl derivative (**56**-**62**),[45] yields were generally ranging from good to excellent. Although in some cases (**59** and **60**) our reagents gave inferior yields compared to those by $TiCl_4$-mediated hydrochlorination conditions,[46] significant improvements were recorded for geranyl benzoate (**62**) and sulfone substrates (**56**-**57**). Terminal styrene substrates generally gave partial conversions under the optimal condition. Yet α-methyl or β-methyl styrene were found unreactive here.

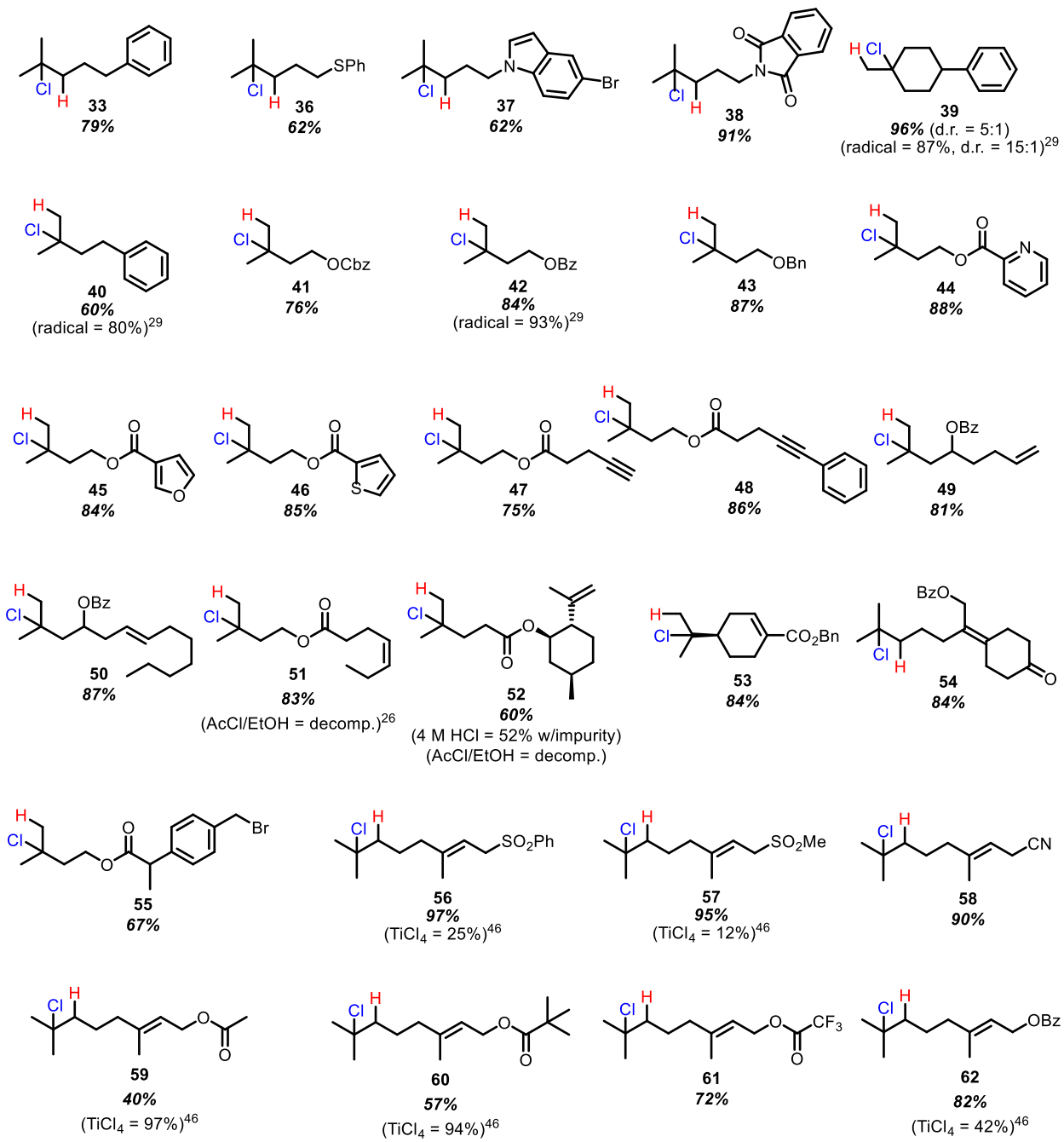


Figure 1-2. HCl addition products generated with reagent **30** or **31** (highest yield shown)

The major functionalities that could not be tolerated by the reagents are free alcohols and silyl ethers. The decomposition pathway plausibly proceeds through the formation of a highly reactive oxophosphonium species, which tend to behave like leaving group. This is a known

reactivity from the structurally similar Hendrickson's reagents.[47] In addition, BINAP-backboned reagents were tested for enatioselective hydrochlorination on unsymmetrical alkene substrates but only racemic products were gained.

1.3.2 Exploration of substrate scope for HBr addition

Several representative substrates were selected to test on our hydrobromination tools. Figure 1-3 presents the analogous results with a smaller number of substrates using HBr sources **34** and **35**, separating the two tools based on some reactivity differences observed with certain substrates. Of note, benzyl ethers (**63**) and basic nitrogen atoms (**64**) were tolerated with the other chemoselectivities as observed above with our hydrochlorination reagents retained, though in some cases, such as with product **69**, yields were reduced. In most cases, though, the throughput was effective, such as the formation of **65** in 91% yield. The main difference between these reagents and their chlorine counterparts, however, was with polyene substrates. Hafnium reagent **35** proved capable of generating mono-hydrobrominated products, such as **68**, in a reasonable yield (61%), while titanium reagent **34** instead afforded full consumption of both distal and internal alkenes, yielding di-hydrobrominated product **70** under the standard reaction conditions. It should be noted that further addition of Hf-reagent **35** to mono-hydrobrominated **68** did not touch the internal alkene. The key point for this chemistry, however, is that controlled monohydrobromination, particularly for polyunsaturated substrates, is much more challenging to achieve with other available approaches. As highlighted by the yields in parentheses, use of HBr/AcOH in our hands proved challenging with several of the selected substrates, either affording decomposition (as with **63**) or full conversion into dihydrobrominated products (as was observed with the substrates leading to **66** and **69**); as evidence that we attempted to use best

practices, we were able to form **65** in 85% yield with HBr/AcOH, noting that a previous literature report with this same combination documented 53% yield on a larger scale.[48]

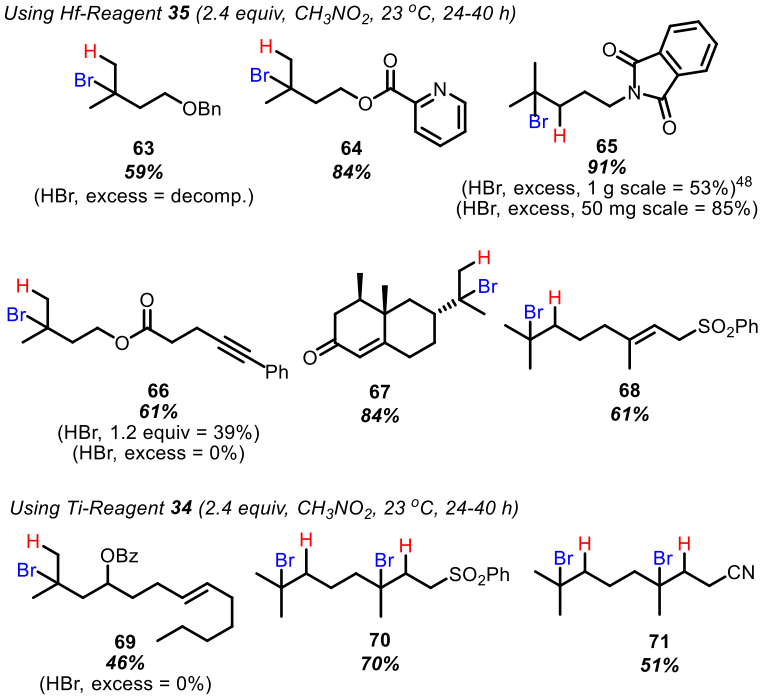


Figure 1-3. HBr addition products generated with reagent **34** or **35**

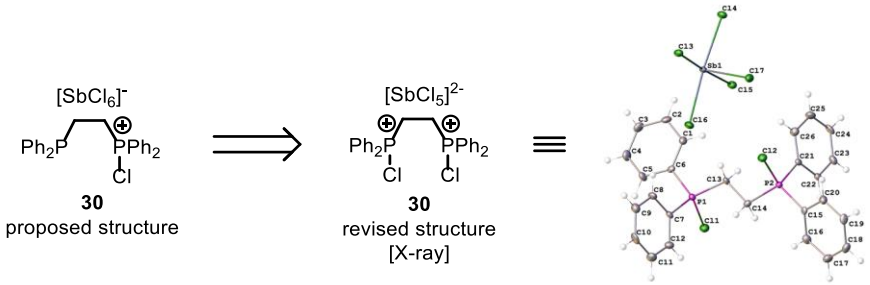
1.4 Structure elucidation of the HCl/HBr addition reagents

Although the substrate scope with HCl addition reagents (**30** and **31**) and HBr addition reagents (**34** and **35**) has been efficiently probed, the structural nature of these reagent remained to be uncovered. It was mentioned that the proposed structures of these reagents were based on the stoichiometry of components during preparation; and several inorganic literatures describing similar complexes adopted similar drawing of structures without robust structural confirmations.[49-51] We therefore felt that a structural investigation is mandatory. Initial attempts of characterization by NMR and mass spectroscopy were fruitless. The ^{31}P NMR data from stored samples of **30** and **31** generally gave single peaks at around δ = 50 ppm, which could possibly correspond to a

phosphine oxide but is not decisive. The HBr counterparts were even harder to pierce due to their low solubility and multiple peaks observed on ^{31}P NMR and ^{1}H NMR. The mass spectroscopy of HCl reagents **30** and **31** displayed peaks from bis(diphenylphosphino)ethane dioxide ($dppeO_2$) and bis(diphenylphosphino)propane dioxide ($dpppO_2$). Molecular ion peaks from dppe, dppeO, and $dppeO_2$ appeared for HBr reagents **34** and **35**. This evidence indicated that hydrolysis might occurred on the halophosphonium species to generate HCl or HBr, thus enabling hydrohalogenation reactions. Nevertheless, a direct observation into these reagents is still coveted to demonstrate their original structures and further illuminate the mechanism in the HCl/HBr addition reactions.

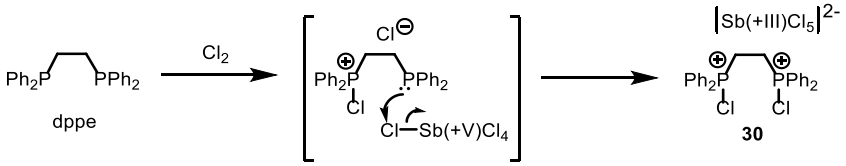
1.4.1 Single crystal of HCl reagents before hydrolysis: a structural revision

For such a *direct* insight of a solid sample, we decide to adopt the most *direct* method in the toolbox, single crystal X-ray diffraction. As mentioned above, the HCl addition reagents showed peaks from hydrolyzed species from mass spectroscopy. Thus, we prepared a dry and diluted solution of phosphine and Cl_2 in 1,2-dichloroethane, then slowly added a solution of $SbCl_5$ in 1,2-DCE at ambient temperature until the mixture turned slightly cloudy. Such a solution was then sealed in the freezer (-20 ^{o}C) for growth of crystals. The single crystal of **30** was also susceptible to hydrolysis so operations were conducted carefully under inert atmosphere (Ar).



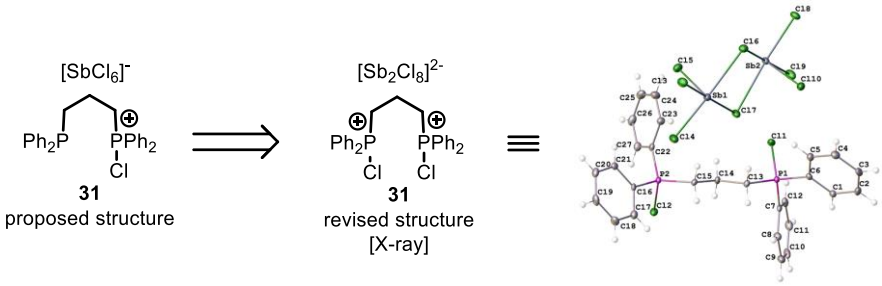
Scheme 1-10. Single crystal reveals the dichlorophosphonium nature of reagent **30**

The so-obtained single crystal revealed that the true natural of reagent **30**'s cationic part is a dichlorophosphonium species instead of the proposed mono-chlorophosphonium (Scheme 1-10). In addition, the oxidation state of antimony in the anionic component turned +III rather than proposed $SbCl_6^-$. A redox process clearly took place during the preparation of the reagent, where Sb(+V) oxidized the other free phosphine into chlorophosphonium, itself reduced to Sb(+III) (Scheme 1-11). This type of dichlorophosphonium was found to be already known in literature. However, it was prepared from phosphine together with PCl_3 and $SbCl_5$.[52]



Scheme 1-11. A plausible redox process leading to dichlorophosphonium and antimony(+III)

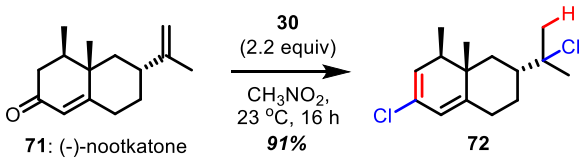
Reagent **31**, which differs from **30** solely from its phosphine backbone by one methylene, underwent the same redox event as well. Its structure was also determined unambiguously by single crystal (Scheme 1-12). Note that the anionic part of **31** shown in the crystal is the dimeric form of Sb(+III)-Cl complex anion ($[Sb_2Cl_8]^{2-}$), indicating that Sb(+III)-Cl bond is weak enough that dissociation, coordination, and dimerization of anions are active.



Scheme 1-12. Single crystal reveals the dichlorophosphonium nature of reagent **31**

A side evidence of the chlorophosphonium came from the reaction between reagent **30** and natural product nootkatone (Scheme 1-13). A dehydrative chlorination took place on the enone

moiety of nootkatone (**71**), in addition to the regular hydrochlorination of distal alkene, forming a cyclic vinyl choride **72**. Such reactivity mirroring PCl_5 or $POCl_3$ reflected the existence of cationic P-Cl species.[53]



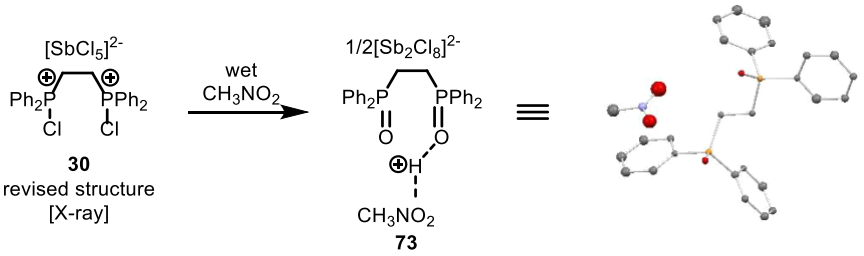
Scheme 1-13. The reaction between reagent **30** and nootkatone

However, the redox process described above requires the participation of Sb (+V), which is absent in reagents with other metal halide Lewis acids (Table 1-1 and 1-2). We attempted to prepare single crystals for other HCl addition reagents and HBr addition reagents, yet no fruitful results were gleaned, owing to the fact that most of the complexes are amorphous and uncrystalizable. Considering that NMR and mass spectroscopy of them mostly gave multiple peaks/signals, the structural nature of HBr addition reagents **34** and **35**, together with other HCl addition reagents, may comprise a complex mixture of various components.

1.4.2 Single crystal of HCl reagents after hydrolysis: breakthrough into the reaction mechanism

Besides growing the crystal of HCl addition reagents **30** and **31** in their original form, we also prepared a solution of stored **30** in commercial nitromethane (containing 2000 ppm water measured by Karl-Fisher titration). By evaporation we gathered crystals belonging to the species of **30** after hydrolysis. X-ray diffraction showed that the hydrolyzed species is a bis(diphenylphosphino)ethane dioxide, with a proton binding to the oxygen atom of P=O double bond (Scheme 1-14).[54] A molecule of nitromethane was also included in the crystal lattice. This observation corresponded with that from mass spectroscopy, where signals from $dppeO_2$ appeared.

The crystal structure of original **30** and its hydrolyzed form **73** paved way for the following mechanism studies. In the next portion, we will discuss what is happening during the hydrochlorination reaction.



Scheme 1-14. Single crystal of hydrolyzed reagent **30** reveals dppeO_2 in a proton-binded form

1.5 Mechanistic studies into the halophosphonium mediated hydrohalogenation of alkenes

The identification of the original form of **30** and **31**, or, the pre-reagent form and the post-hydrolysis active form **73** indicated that hydrolysis plays a vital role in the reaction. From a view of stoichiometry, one equivalent of dichlorophosphonium can be fully hydrolyzed to release 4 equivalents of HCl and 1 equivalent of bisphosphine dioxide. There comes the question: Is the released HCl responsible for the hydrochlorination reaction? Is phosphine oxide merely a spectator? We will try to solve these questions in the following contents.

1.5.1 Capturing phosphine oxide-HCl complexes via NMR studies

To answer the question above, we picked NMR studies of reagent **30** as a breakthrough point. By assuming that dppeO_2 serves as a spectator in the reaction, the ^{31}P NMR spectra of reaction media should show peaks close to the peak belonging to dppeO_2. As is mentioned in chapter 2.4, the ^{31}P NMR chemical shift of a stored **30** has a single peak at around 50 ppm in d^3-acetonitrile (Table 1-3, Entry 4), while ^{31}P NMR shift of dppeO_2 is δ = 36.6 ppm (Entry 1), verifying the absence of free dppeO_2 in the reaction.

Could $dppeO_2$ form a 1:1 complex with proton, just like what was seen in the single crystal of hydrolyzed **73** (Scheme 1-14)? We prepared such complex **74** by mixing $dppeO_2$, HCl, $SbCl_3$ in a 1:1:1 ratio. The solution of $dppeO_2$ and HCl in dichloromethane is clear at ambient temperature. Once antimony trichloride was added, complex $dppeO_2 \cdot HCl \cdot SbCl_3$ ($[dppeO_2H]^+[SbCl_4]^-$) precipitated rapidly, and was isolated in 97% yield after filtration. This complex gave a single peak at δ = 43.3 ppm on ^{31}P NMR (Entry 2), which still has discrepancy from observation of reagent (Entry 4), but is closer to Entry 4 compared to $dppeO_2$.

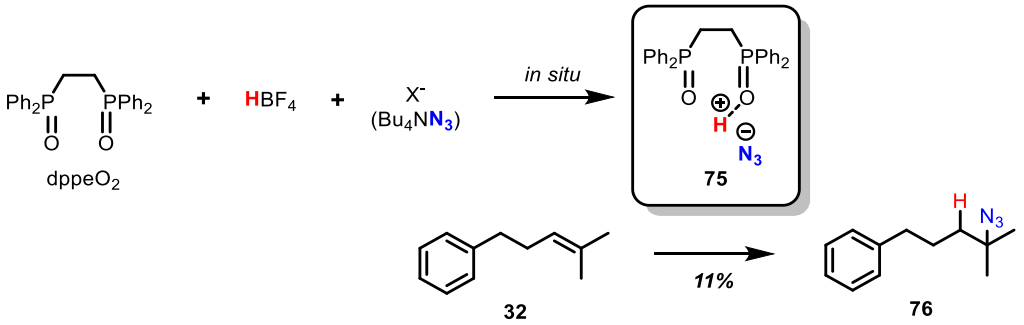
Having one proton binding to the oxygen atom of P=O double bond made the chemical shift closer to the reagent's shift on ^{31}P NMR. We suspected that more than one molecule of HCl can interact with one P=O double bond. The chemical shift recorded for a sample with $dppeO_2 \cdot HCl \cdot SbCl_3$ ($[dppeO_2H]^+[SbCl_4]^-$) plus excessive amount (>10 equivalents) of anhydrous HCl solution appeared at δ = 50.7 ppm on ^{31}P NMR (Entry 3). This data had high resemblance with that for reagent **30**, taking comparison of ^1H NMR chemical shift into consideration. It strongly signified that a complex between one $dppeO_2$ center and multiple coordinating HCl molecules were responsible for major species from reagent **30** in the hydrochlorination reaction. Interestingly, we tried to precipitate such complex (Entry 3), but ended up with $dppeO_2 \cdot HCl \cdot SbCl_3$ ($[dppeO_2H]^+[SbCl_4]^-$), meaning that the $dppeO_2$-multiple HCl(s) complex is likely to be expedient and only capable of survival in solution.

The chemical shift on ^{31}P NMR for the dichlorophosphonium from the original form of **30** was also recorded at δ = 73.9 ppm (Entry 5) by using freshly prepared reagents, as an extra piece of evidence.

Table 1-3. ^{31}P NMR chemical shift of dppeO_2/HCl derivatives and reagent **30** in two forms

Entry	Reagent	^{1}H δ (ppm, m)	^{31}P δ (ppm, m)
1	dppeO_2	--	36.6
2	dppeO_2·HCl·$SbCl_3$ (**74**) ($[dppeO_2H]^+[SbCl_4]^-$)	2.86 (d)	43.3
3	dppeO_2·HCl·$SbCl_3$ (**74**) ($[dppeO_2H]^+[SbCl_4]^-$) + HCl (excess)	3.05 (d)	50.7
4	dppe·Cl_2·$SbCl_5$ (**30**) after hydrolysis	3.04 (d)	48.9-50.4
5	dppe·Cl_2·$SbCl_5$ (**30**) before hydrolysis	--	73.9

Learning from the knowledge that protonated dppeO_2 together with chloride can deliver HCl across alkenes, we attempted to use such backbones to deliver other anions to explore more possible hydrofunctionalization reactions of alkene. We found that by mixing dppeO_2 together with HBF_4 and tetrabutylammonium azide (Bu_4NN_3), followed by the addition of alkene substrate (**32**, 0.1 equivalent compared to dppeO_2), a limited conversion (11% isolated yield) of the desired Markovnikov hydroazidation product **76** arose after long-term heating (40 h) in THF (Scheme 1-15).[55] We examined several other anions such as CN^-, I^-, F^-, but no positive results were obtained.



Scheme 1-15. A proof-of-principle expansion of dppeO_2 complex in delivering alkene hydroazidation

1.5.2 The active role of phosphine oxide-HCl complex in the hydrochlorination reaction

The NMR studies substantiated the dppeO_2-multiple HCl(s) complex as the major component of reagent **30** in hydrochlorination reaction, while a question still remained for whether such complexes contributed to the majority of conversion of alkene substrates. A control experiment survey was therefore conducted (Table 1-4). Anhydrous HCl pushed a limited amount of conversion (23% isolated yield of product, Entry 1), indicating that free HCl itself took responsibility for a small portion of conversion in reagent **30** mediated hydrochlorination. The addition of dppeO_2 dramatically accelerated the conversion rate and in a shorter reaction time (16 hours in Entry 2 compared to 40 hours in Entry 1) the isolated yield of product **33** increased to 64%. This confirmed that dppeO_2-multiple HCl(s) complex was not only the major component, but also being the most active species in the hydrochlorination reaction. Regardless of the anion part, dppeO_2·HCl·$SbCl_3$ (**74**, $[dppeO_2H]^+[SbCl_4]^-$) could push conversion as well (Entry 3). Nevertheless, the dppeO_2-multiple HCl(s) can be spoiled by water in reaction media, losing its ability to add HCl across alkenes. Since such a "mimic" of dppeO_2-multiple HCl(s) complex was only reproducible in anhydrous media, usage of pre-made reagent **30** and **31** was hence indispensable, for operationally simplicity and higher isolated yield (Entry 5).

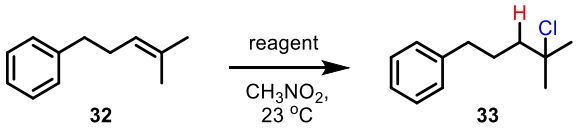


Table 1-4. Control experiment supporting the pivotal role of phosphine-HCl complex

Entry	Reagent	Additive	Solvent	Reaction time	Isolated yield
1	HCl (4.4 equiv)	--	Dry $MeNO_2$	40 h	23%
2	HCl (4.4 equiv)	$dppeO_2$ (2.2 equiv)	Dry $MeNO_2$	16 h	64%
3	HCl (4.4 equiv)	$dppeO_2 \cdot HCl \cdot SbCl_3$ (**74**) ($[dppeO_2H]^+[SbCl_4]^-$) (2.2 equiv)	Dry $MeNO_2$	16 h	68%
4	HCl (4.4 equiv)	$dppeO_2 \cdot HCl \cdot SbCl_3$ (**74**) ($[dppeO_2H]^+[SbCl_4]^-$) (2.2 equiv)	Wet $MeNO_2$	40 h	23%
5	**30** (2.2 equiv)	--	Wet $MeNO_2$	16 h	79%

From the control experiments above one may conclude that water can prevent the formtation of active complexes between phosphine oxides and HCl molecules (Entry 3 and 4). However, the environment (commercial nitromethane) in which reagent 30 and other similar reagents function typically contain excessive amount of water. One of the reasons that the *in situ* formed $dppeO_2$-multiple HCl(s) complex from reagent **30** in commercial, wet nitromethane was not disrupted by water and able to push hydrochlorination to end might be that the hydrolysis of chlorophosphonium species released $dppeO_2$ and HCl locally, so that the complex can be organized before surrounding water involved. A ^{31}PNMR tracking of reaction profile in d^3-

nitromethane provided support. Reagent **30** displayed a chemical shift at δ = 51.2 ppm (Figure 1-4). Once alkene substrate **32** was added, the single peak started to broaden and move upfield. This suggested a gradual loss of coordinating HCl molecules around the dppeO_2 center. Whilst HCl molecules were consumed and dissociated from phosphine oxide center, the complex's ability to attack alkene compromised.

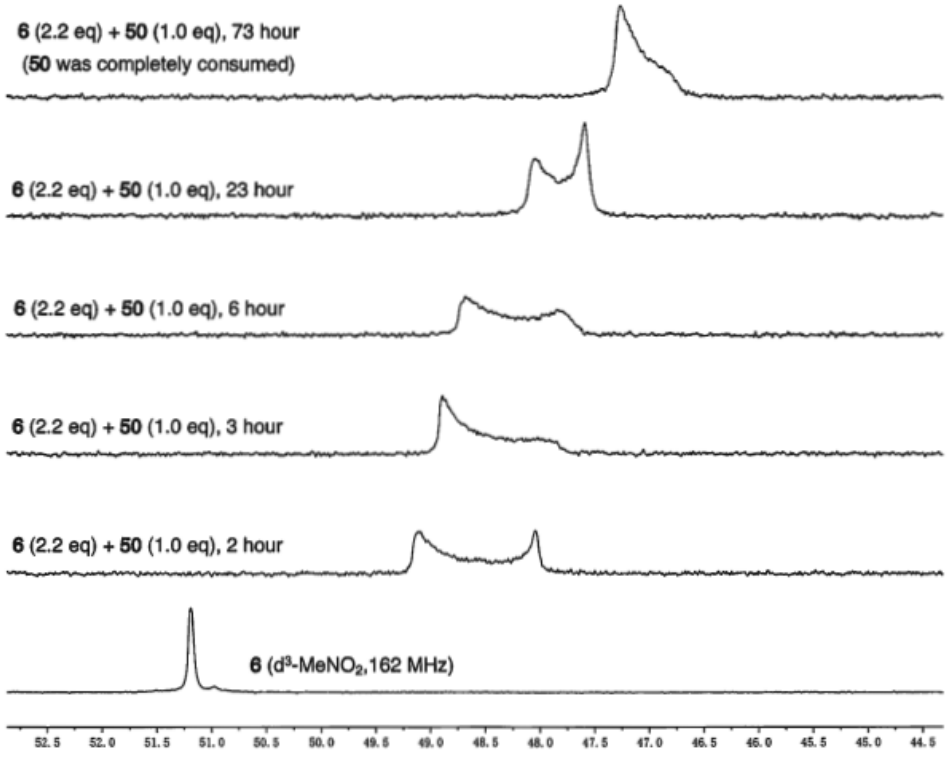


Figure 1-4. Tracking of reaction profile by ^{31}P NMR in d^3-nitromethane ("6": reagent **30**; "50": substrate **32**)

A tracking of remaining starting material over reaction time denoted a fast conversion at the beginning phase (Figure 1-5). The longer the reaction time was, the slower the conversion rate became, reflecting a significant compromising of reactivity when the *in situ* formed active complex loses coordinating HCl molecules. The kinetic study also verified the necessary stoichiometry (2.2 equivalents) of reagents employed in the reaction.

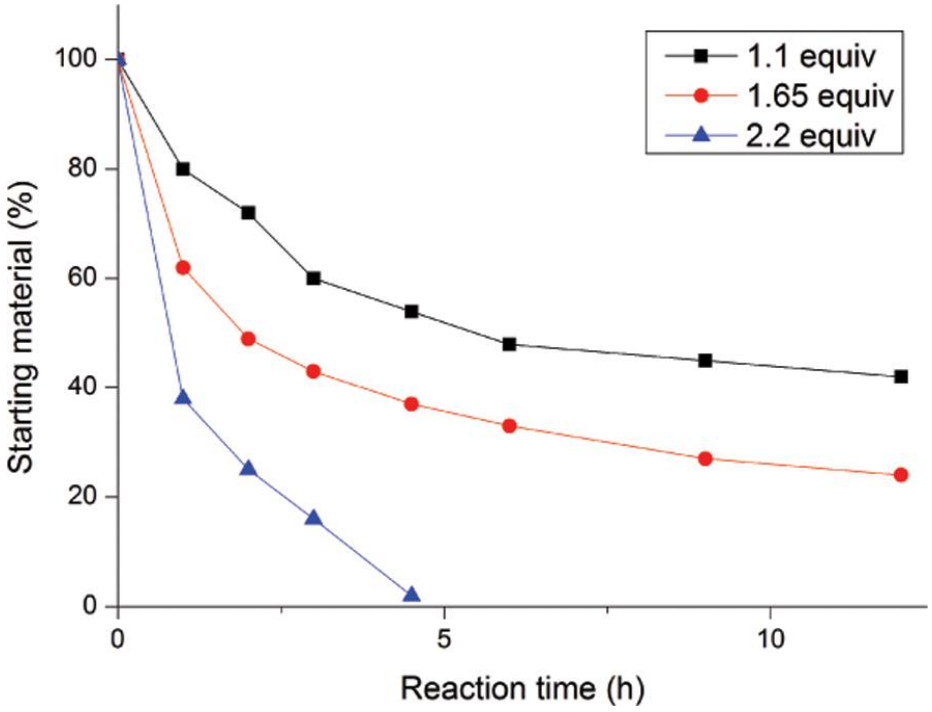


Figure 1-5. Rate of starting material disappearance in the reaction converting **32** into **33** using freshly prepared **30** in varied stoichiometry.

Of note, we screened a variety of solvents (CH_3CN, $CHCl_3$, CCl_4, C_6H_6, C_6H_5Cl, DMSO, DMF, THF, Et_2O, EtOAc, MeOH, EtOH, ethylene glycol, dioxane, and acetone), only to find that nitromethane or nitroethane help promote hydrochlorination with the chlorophosphium reagents (**30** and **31**). Other common solvents, containing water or not, were incapable of playing the role nitromethane can serve. This phenomenon can be explained by the observation that nitromethane is unique in stabilization of certain reactive carbocation intermediates.[56]

One last remaining question reside in the manner of using reagents: why not pre-hydrolyze the reagent if it needs hydrolysis anyway? To answer this question, we investigated the influence that the age of reagents had on yield of reactions. In a water-saturated nitromethane solution where hydrolysis can be complete (Table 1-5), a freshly prepared reagent provided higher yield (65%) than a 1-year-old reagent did (44%). The data in Table 1-5 support that water is the proton source

of HCl based on the phenomena that freshly prepared reagents could barely promote conversion of alkene substrate **32** in hydrochlorination.

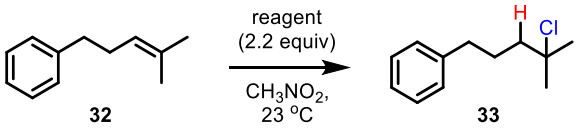


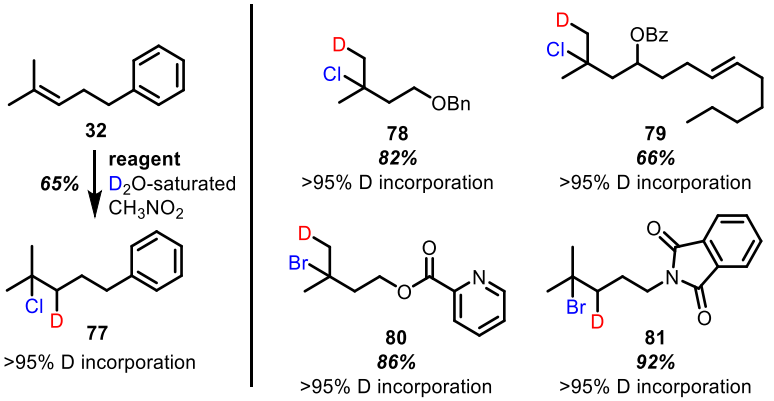
Table 1-5. Further efforts to determine the role of water content and reagent age on the hydrochlorination of **32**

Entry[a]	Reagent age	H_2O content (ppm) (1.5 mL solvent)[b]	Projected SM remaining (%)	Isolated SM remaining (%)	Projected product yield (%)	Isolated product yield (%)
1	1 year	30	97	0	3	57
2	1 year	670	41	0	59	45
3	1 year	>30000	0	0	100	44
4	Fresh	30	97	62	3	11
5	Fresh	670	41	29	59	46
6	Fresh	>30000	0	0	100	65

[a]Reactions were all performed on a 0.215 mmol scale using 2.2 equiv of reagent 5 in CH_3NO_2 at 23 °C, stopping the reaction after 4 h. [b]H_2Ocontent of the CH_3NO_2 solutions was determined by blank parallel experiments.

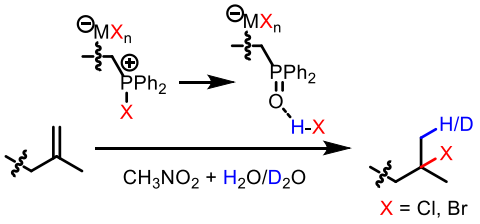
1.5.3 Hydrolysis by D_2O: deuterio-halogenation of alkenes

The mechanism that our reagents reacted with water to generate active hydrohalogenating components enlightened the utilization of heavy water (D_2O) as replacement of regular water for a deuterio-halogenation transformation. Such a hypothesis can be realized by implementing D_2O-saturated nitromethane, a "special" solvent prepared by soaking dry nitromethane with D_2O, as the reaction media. We selected several representative alkene substrates and exercised deuterio-chlorination/bromination on them (Scheme 1-16). For all the cases (**77**-**81**), excellent isotope incorporation and good isolated yield were obtained. One of the advantages for this deuterio-halogenation method is the exploitation of the cheapest deuterium source, D_2O, in isotope labelling, compared to the reported methods using in situ generated and distilled DCl or DBr.[34-38] In that vein, operational simplicity is also greatly improved by the ease of reagent manipulation and reaction setup.



Scheme 1-16. Facile deuterium incorporations by halophosphonium reagents and D_2O

1.6 Summary and outlook



Scheme 1-17. A general transformation of halophosphonium HX addition reagents

In summary, we have developed a group of halophosphonium reagents on the basis of XDSX reagents. These reagents can add HCl and HBr across a variety of alkene substrates facilely. Through a number of mechanistic experiments, we discovered the structural nature of the reagents and some details on how they get hydrolyzed and exert hydrochlorination in the reaction media. Additionally, we expanded the utility of the reagents to deuterio-halogenation and substrates can be functionalized with high isotope incorporation. Another critical value is the sease of use and effectiveness on complex substrates such as geranyl derivatives. Further mechanistic investigations on these reagents and development of other highly reactive cationic reagents are ongoing in our lab.

1.7 Experimental Section

General Procedures. All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Dry tetrahydrofuran (THF), toluene, dimethylformamide (DMF), diethyl ether (Et_2O) and dichloromethane (CH_2Cl_2) were obtained by passing commercially available pre-dried, oxygen-free formulations through activated alumina columns. Yields refer to chromatographically and spectroscopically (^1H and ^{13}C NMR) homogeneous materials, unless otherwise stated. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Reactions were

magnetically stirred and monitored by thin-layer chromatography (TLC) carried out on 0.25 mm Silicycle silica gel plates (60F-254) using UV light as visualizing agent, and an ethanolic solution of phosphomolybdic acid and cerium sulfate, and heat as developing agents. SiliCycle silica gel (60, academic grade, particle size 0.040–0.063 mm) was used for flash column chromatography. Preparative thin-layer chromatography separations were carried out on 0.50 mm Silicycle silica gel plates (60F-254). NMR spectra were recorded on Bruker 400 and 500 MHz instruments and calibrated using residual undeuterated solvent as an internal reference. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, br = broad, app = apparent. IR spectra were recorded on a Perkin-Elmer 1000 series FT-IR spectrometer and a Thermal Nicolett 6700 Mid-FTIR spectrometer. High-resolution mass spectra (HRMS) were recorded on a Waters Synapt G2-Si mass spectrometer using ESI (Electrospray Ionization) at the University of Illinois Urbana–Champaign Mass Spectrometry Laboratory, and Agilent 6244 Tof-MS using ESI (Electrospray Ionization) at the University of Chicago Mass Spectroscopy Core Facility. Melting points were recorded on a Digimelt apparatus (Stanford Research System). Water amounts were determined by Karl-Fischer coulometric titration on Metrohm 756 KF Coulometer.

Abbreviations. BzCl = benzoyl chloride, CbzCl = benzyl chloroformate, DCC = *N*,*N*'-dicyclohexylcarbodiimide, depe = 1,2-bis(diethylphosphino)ethane, DIBAL-H = diisobutylaluminum hydride, DMAP = dimethylaminopyridine, DMSO = dimethyl sulfoxide, dppe = 1,2-bis(diphenylphosphino)ethane, dppeO_2 = 1,2-bis(diphenylphosphino)ethane dioxide, dppp = 1,3-bis(diphenylphosphino)propane, EtOAc = ethyl acetate, LiHMDS = lithium bis(trimethylsilyl)amide, Tf_2O = trifluoromethanesulfonic anhydride.

Preparation of reagents.

Note: Anhydrous CD_3CN for NMR analyses was prepared by distillation of commercial CD_3CN over CaH_2, with the solvent stored over activated 4Å MS; the initial NMR data was taken immediately after sonicating the sample and CD_3CN (either anhydrous or commercial, 0.75 mL) in an NMR tube for 15 min. Subsequent NMR analyses were performed at varied time points indicated by "X d," taken after storing the initial NMR tube sample at 23 °C for X days to allow full hydrolysis. Corresponding ^{1}H NMR and ^{13}C NMR spectra were taken when a clean ^{31}P NMR spectra was observed. Each spectrum is labelled with corresponding assigned structures.

dppe•Cl_2•$SbCl_5$ (30). Chlorine gas was bubbled into 1,2-dichloroethane (10 mL) at –30 °C, with the amount of chlorine added then weighed (0.121 g, 1.70 mmol, 1.0 equiv). The solution was then recooled to –30 °C and dppe (0.745 g, 1.87 mmol, 1.1 equiv) was added. After stirring for 5 min at –30 °C, a solution of $SbCl_5$ (0.24 mL, 1.87 mmol, 1.1 equiv) in CH_2Cl_2 (3.1 mL) was added. The resultant white slurry was then warmed to 23 °C and stirred for an additional 1 h. Upon completion, the reaction mixture was stored at –20 °C for 2 h to maximize precipitation. The precipitate was then collected by filtration, washing the filter cake carefully with cold 1,2-dichloroethane (2 × 10 mL). Drying of the resultant material afforded **30** (1.27 g, 97% yield) as a white solid. **30**: mp = 196–198 °C; ^{31}P NMR (202 MHz, anhydrous CD_3CN) δ 73.9, 49.2, 38.3; ^{31}P NMR (202 MHz, commercial CD_3CN) δ 74.0, 50.3 (major), 37.2; ^{31}P NMR (202 MHz, commercial CD_3CN, 3 d) δ 50.4; ^{1}H NMR (500 MHz, commercial CD_3CN, 3 d) δ 7.87–7.75 (m, 12 H), 7.73–7.63 (m, 8 H), 3.05 (d, J = 9.9 Hz, 4 H); ^{13}C NMR (126 MHz, commercial CD_3CN, 3 d) δ 135.5, 132.3 (t, J = 5.5 Hz), 130.7 (t, J = 5.5 Hz), 22.1 (dt, J = 30.4, 5.2 Hz). Crystals were obtained following the same synthetic procedure at a higher dilution (30 mL of 1,2-dichloroethane).

Stirring was stopped prior to the addition of the $SbCl_5$ solution (in 1,2-dichloroethane) and the reaction was then stored at –18 °C for 40 h.

dppp•Cl_2•$SbCl_5$ (**31**). Chlorine gas was bubbled into 1,2-dichloroethane (10 mL) at –30 °C, with the amount of chlorine added then weighed (1.20 g, 17.0 mmol, 1.0 equiv). The solution was then recooled to –30 °C and dppp (7.71 g, 18.7 mmol, 1.1 equiv) was added. After stirring for 5 min at –30 °C, a solution of $SbCl_5$ (2.4 mL, 18.7 mmol, 1.1 equiv) in CH_2Cl_2 (4.8 mL) was added. The resultant yellow solution with a sticky yellow solid was then warmed to 23 °C and stirred for an additional 3 h until it converted into a white slurry. Upon completion, the reaction mixture was stored at –20 °C for 2 h to maximize precipitation. The precipitate was then collected by filtration, washing the filter cake carefully with cold 1,2-dichloroethane (2 × 10 mL). Drying of the resultant material afforded **31** (10.30 g, 77% yield) as a white solid. **31**: mp = 98–100 °C; ^{31}P NMR (202 MHz, anhydrous CD_3CN) δ 73.6, 51.8, 49.4; ^{31}P NMR (202 MHz, commercial CD_3CN) δ 73.7, 51.7; ^{31}P NMR (202 MHz, commercial CD_3CN, 1 d) δ 52.1; ^{1}H NMR (500 MHz, commercial CD_3CN, 1 d) δ 7.82–7.69 (m, 12 H), 7.66–7.57 (m, 8 H), 2.90 (dt, *J* = 12.5, 6.7 Hz, 4 H), 2.10–1.98 (m, 2 H); ^{13}C NMR (126 MHz, commercial CD_3CN, 1 d) δ 135.1 (d, *J* = 2.9 Hz), 132.0 (d, *J* = 10.7 Hz), 130.6 (d, *J* = 12.8 Hz), 27.5 (dd, *J* = 65.0, 6.0 Hz), 14.5 (t, *J* = 4.8 Hz). Crystals were obtained following the same synthetic procedure at a higher dilution (30 mL of 1,2-dichloroethane). Stirring was stopped prior to the addition of the $SbCl_5$ solution (in 1,2-dichloroethane) and the reaction was then stored at –18 °C for 40 h.

dppe•Br_2•$TiBr_4$ (**34**). To a solution of dppe (2.19 g, 5.50 mmol, 1.0 equiv) in 1,2-dichloroethane (30 mL) at 0 °C was added Br_2 (0.28 mL, 5.50 mmol, 1.0 equiv). After stirring for

15 min at 0 °C, $TiBr_4$ (2.02 g, 5.50 mmol, 1.0 equiv, weighed quickly in an argon-flushed vial) was added. The resultant dark homogeneous solution was then warmed to 23 °C and stirred for an additional 5 h until it turned into a dark red slurry. Upon completion, the reaction mixture was stored at –20 °C for 16 h to maximize precipitation. The precipitate was then collected by filtration, washing the filter cake carefully with cold 1,2-dichloroethane (2 × 10 mL). Drying of the resultant material afforded **34** (3.21 g, 63% yield) as a dark red solid. **34**: mp = 208–210 °C; ^{31}P NMR (202 MHz, anhydrous CD_3CN) δ 60.4, 58.6, 57.7 (major), 37.6, 12.5; ^{31}P NMR (202 MHz, commercial CD_3CN) δ 63.2, 60.7, 57.7 (major), 9.8, 9.1; ^{1}H NMR (500 MHz, commercial CD_3CN) δ 8.19–7.20 (m, 20 H), 3.23 (d, *J* = 11.8 Hz, 4 H); ^{31}P NMR (202 MHz, commercial CD_3CN, 1 d) δ 57.8 (major), 46.7, 45.9.

dppe•Br_2•$HfBr_4$ (**35**). To a solution of dppe (0.797 g, 2.00 mmol, 1.0 equiv) in 1,2-dichloroethane (11 mL) at 0 °C was added Br_2 (0.10 mL, 2.00 mmol, 1.0 equiv). After stirring for 15 min at 0 °C, $HfBr_4$ (0.996 g, 2.00 mmol, 1.0 equiv, weighed quickly in an argon-flushed vial) was added. The resultant ocre slurry was then warmed to 23 °C and stirred for an additional 16 h until it turned into an off-white slurry. Upon completion, the reaction mixture was stored at –20 °C for 16 h to maximize precipitation. The precipitate was then collected by filtration, washing the filter cake carefully with cold 1,2-dichloroethane (2 × 5 mL). Drying of the resultant material afforded **35** (2.02 g, 96% yield) as a white solid.**35**: mp > 260 °C, collapse point at 250 °C; ^{31}P NMR (202 MHz, anhydrous CD_3CN) δ 56.4, 54.3 (d, *J* = 60.8 Hz), 10.0 (d, *J* = 60.5 Hz), 6.9; ^{31}P NMR (202 MHz, commercial CD_3CN) δ 56.4, 54.3 (d, *J* = 62.4 Hz), 10.0 (d, *J* = 64.3 Hz), 6.9; ^{31}P NMR (202 MHz, commercial CD_3CN, 1 d) δ 56.4 (minor), 54.3 (d, *J* = 62.4 Hz), 9.8 (d, *J* = 61.8 Hz).

Please note that attempts to directly crystallize **34**, and **35** from the reaction in a similar fashion to **30** and **31** led only to amorphous powders with 1,2-dichloroethane or 1,1,2,2-tetrachloroethane as solvents. Recrystallizations of the isolated powders of **34** and **35** in an attempt to obtain their hydrolyzed products failed with all tested solvents (CH_3NO_2, CH_3CN, $CHCl_3$, CCl_4, C_6H_6, C_6H_5Cl, DMSO, DMF, THF, Et_2O, EtOAc, MeOH, EtOH, ethylene glycol, dioxane and acetone). No signals were observed by IR (ATR and film) for the five synthesized reagents. MS showed the presence of dppeO_2 for **30** and **31** while a mixture of dppe, dppeO and dppeO_2 was detected for **34** and **35**. NMR studies in $CDCl_3$, CD_2Cl_2 and CD_3NO_2 clearly showed the hydrolyzed species for **30** and **31**. By contrast, **34** and **35** were insoluble in $CDCl_3$.

Preparation of substrates.

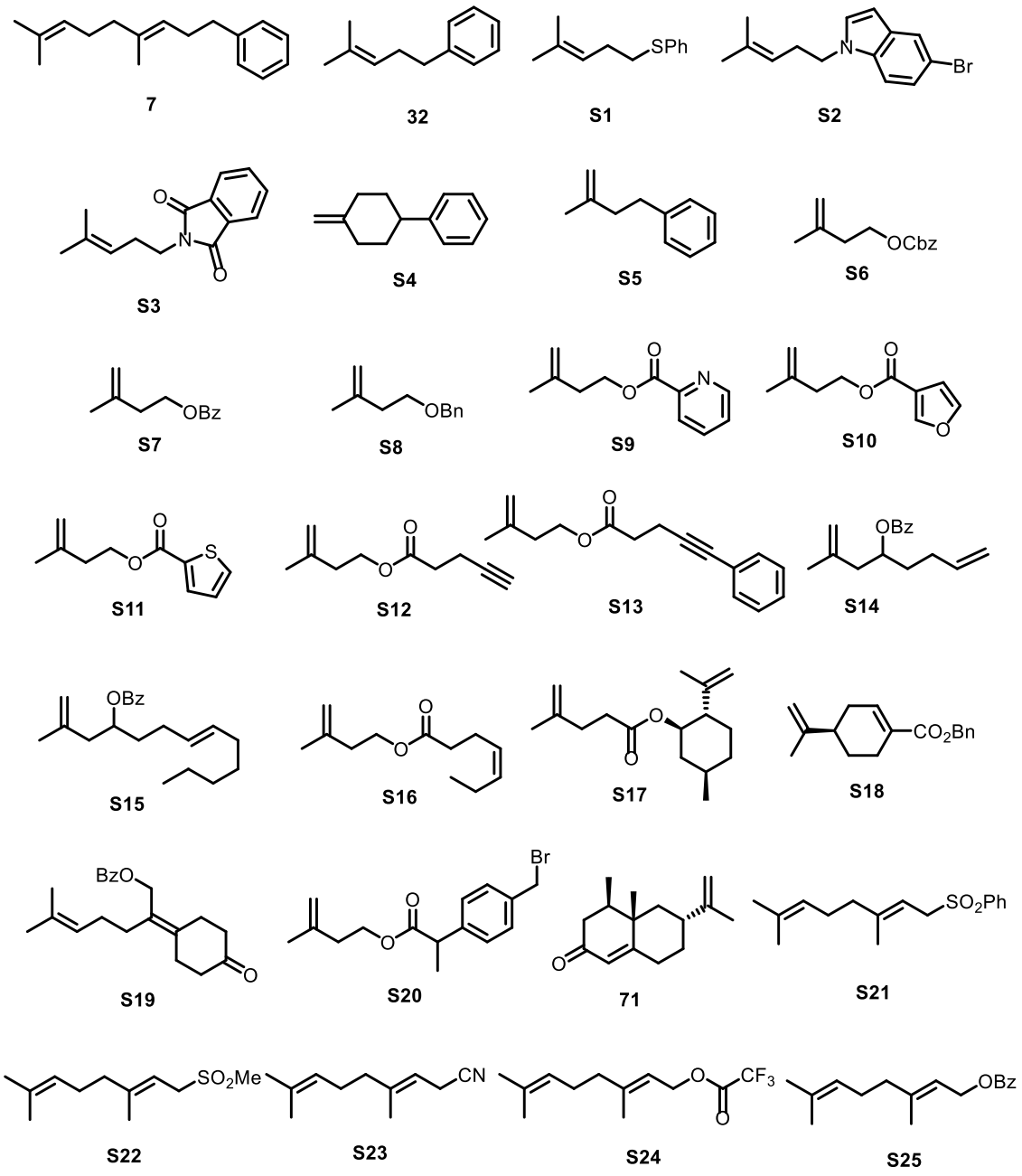


Figure 1-S1. Structures of substrates for exploring scope of hydrohalogenation

7. Prepared according to the method reported by Snyder from geraniol.[2]

32. Prepared according to the method reported by Cravero from 3-phenylpropanal.[57]

S1. Prepared according to the method reported by Nakamura from 1-bromo-4-methyl-3-pentene.[58]

S2. NaH (60% dispersion in mineral oil, 0.168 g, 4.20 mmol, 1.2 equiv) was suspended in DMF (12 mL) and 5-bromoindole (0.686 g, 3.50 mmol, 1.0 equiv) was added portionwise at 23 °C. The resultant slurry was then stirred at 23 °C for 30 min before homoprenyl bromide (0.735 g, 3.50 mmol, 1.0 equiv) was added. The reaction contents were stirred at 23 °C for an additional 1 h. Upon completion, the reaction was diluted with EtOAc (20 mL) and quenched with a half-saturated aqueous NH_4Cl solution (15 mL). The aqueous phase was then extracted with EtOAc (2 × 15 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography (silica gel, hexanes→ hexanes/EtOAc, 100/1) to afford **S2** (0.892 g, 92% yield) as a light yellowish oil. **S2**: R_f = 0.75 (silica gel, hexanes/EtOAc, 4/1); IR (ATR) ν_{max} 2967, 2928, 1510, 1470, 1449, 1397, 1329, 1277, 1195, 1164, 1090, 1053, 897, 867, 790, 750, 714 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.74 (dd, *J* = 1.9, 0.4 Hz, 1 H), 7.29–7.26 (m, 1 H), 7.21 (d, *J* = 8.7 Hz, 1 H), 7.07 (d, *J* = 3.1 Hz, 1 H), 5.14–5.07 (m, 1 H), 4.07 (t, *J* = 7.1 Hz, 2 H), 2.47 (q, *J* = 7.2 Hz, 2 H), 1.66 (d, *J* = 1.0 Hz, 3 H), 1.42 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.1, 134.6, 130.2, 129.0, 124.0, 123.3, 119.8, 112.4, 110.8, 100.4, 46.5, 29.0, 25.7, 17.5; HRMS (AP+) calcd for $C_{14}H_{17}BrN^+$ [M + H^+] 278.0539, found 278.0547.

S3. Prepared according to the method reported by Gong from potassium phthalimide.[48]

S4. Prepared according to the method reported by Renaud from phenylcyclohexanone.[59]

S5. Prepared according to the method reported by Hoffman from benzyl bromide.[60]

S6. To a solution of 3-methyl-3-butenol (0.431 g, 5.00 mmol, 1.0 equiv) in THF (15 mL)

was added LiHMDS (1.0 M in THF, 5.0 mL, 5.0 mmol, 1.0 equiv) dropwise at –55 °C. Then, a solution of CbzCl (1.02 g, 6.00 mmol, 1.2 equiv) in THF (15 mL) was added at –55 °C, and the reaction was kept at that temperature with stirring for 10 min. Upon completion, water (20 mL) was added to quench the reaction contents, and the aqueous phase was extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography (silica gel, hexanes/EtOAc, 30/1) to afford **S6** (1.07 g, 97% yield) as a colorless oil. **S6**: R_f = 0.60 (silica gel, hexanes/EtOAc, 4/1); IR (ATR) ν_{max} 2968, 1740, 1456, 1395, 1241, 950, 894, 790, 753, 738, 695 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.44–7.29 (m, 5 H), 5.17 (s, 2 H), 4.82 (s, 1 H), 4.75 (s, 1 H), 4.26 (t, *J* = 7.0 Hz, 2 H), 2.39 (t, *J* = 6.9 Hz, 2 H), 1.76 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.1, 141.0, 135.3, 128.6, 128.5, 128.3, 112.6, 69.5, 66.2, 36.6, 22.5; HRMS (ESI+) calcd for $C_{13}H_{16}NaO_3^+$ [M + Na^+] 243.0992, found 243.1003.

S7. Prepared according to the method reported by Carreira from 3-methyl-3-butenol.[29]

S8. Prepared according to the method reported by Woerpel from 3-methyl-3-butenol.[61]

General procedure for the preparation of ester substrates from the corresponding acids and alcohols. To a solution of acid (5.00 mmol, 1.0 equiv, variable scale) in CH_2Cl_2 (25 mL) at 23 °C was added the desired alcohol (5.50 mmol, 1.1 equiv), followed by 4-DMAP (0.060 g, 0.050 mmol, 0.1 equiv) and DCC (1.15 g, 5.50 mmol, 1.1 equiv). The resultant reaction mixture was stirred at 23 °C overnight. Upon completion, the reaction mixture was filtered through Celite and the filter cake was washed with EtOAc (3 × 5 mL). The resultant filtrate was concentrated and

purified by flash column chromatography to afford the corresponding esters.

S9. Starting from 2-picolinic acid (0.616 g, 5.00 mmol, 1.0 equiv) and using the procedure for ester preparation described above, **S9** (0.782 g, 82% yield) was obtained as a light yellowish oil. **S9**: R_f = 0.45 (silica gel, hexanes/EtOAc, 1/1); IR (ATR) ν_{max} 3076, 2969, 1740, 1716, 1584, 1438, 1377, 1303, 1292, 1280, 1242, 1127, 1088, 1045, 994, 965, 891, 823, 745, 705 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.76 (dd, *J* = 4.7, 0.7 Hz, 1 H), 8.11 (d, *J* = 7.9 Hz, 1 H), 7.89–7.78 (m, 1 H), 7.52–7.41 (m, 1 H), 4.81 (d, *J* = 12.2 Hz, 2 H), 4.53 (t, *J* = 7.1 Hz, 2 H), 2.53 (t, *J* = 7.1 Hz, 2 H), 1.80 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.0, 149.8, 148.1, 141.4, 137.0, 126.8, 125.1, 112.5, 64.1, 36.7, 22.6; HRMS (AP+) calcd for $C_{11}H_{14}NO_2^+$ [M + H^+] 192.1019, found 192.1027.

S10. Starting from 3-furoic acid (0.560 g, 5.00 mmol, 1.0 equiv) and using the procedure for ester preparation described above, **S10** (0.766 g, 85% yield) was obtained as a colorless oil. **S10**: R_f = 0.63 (silica gel, hexanes/EtOAc, 4/1); IR (ATR) ν_{max} 3153, 2970, 1719, 1579, 1508, 1404, 1305, 1156, 1075, 1007, 978, 893, 873, 829, 758, 740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.99 (dd, *J* = 1.5, 0.7 Hz, 1 H), 7.41 (t, *J* = 1.7 Hz, 1 H), 6.73 (dd, *J* = 1.9, 0.7 Hz, 1 H), 4.84–4.80 (m, 1 H), 4.79–4.76 (m, 1 H), 4.36 (t, *J* = 6.8 Hz, 2 H), 2.42 (t, *J* = 6.8 Hz, 2 H), 1.79 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.0, 147.6, 143.6, 141.6, 119.4, 112.4, 109.8, 62.7, 36.8, 22.5; HRMS (EI+) calcd for $C_{10}H_{12}O_3^+$ [M^+] 180.0781, found 180.0779.

S11. To a solution of 3-methyl-3-butenol (0.474 g, 5.50 mmol, 1.0 equiv), 4-DMAP (0.060 g, 0.50 mmol, 0.09 equiv) and Et_3N (0.840 g, 8.30 mmol, 1.5 equiv) in CH_2Cl_2 (25 mL) at 0 °C was added 2-thiophenecarbonyl chloride (0.967 g, 6.6 mmol, 1.2 equiv) dropwise. The resultant reaction was stirred at 0 °C for 2 h. Upon completion, the reaction contents were quenched with

water (25 mL) and extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were washed with brine (25 mL), dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography to afford **S11** (1.08 g, 99% yield) as a colorless oil. **S11**: R_f = 0.60 (silica gel, hexanes/EtOAc, 4/1); IR (ATR) ν_{max} 2970, 1704, 1526, 1418, 1358, 1254, 1225, 1094, 1071, 1041, 892, 861, 747, 716 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.79 (dd, *J* = 3.7, 1.3 Hz, 1 H), 7.54 (dd, *J* = 5.0, 1.3 Hz, 1 H), 7.09 (dd, *J* = 5.0, 3.7 Hz, 1 H), 4.85–4.82 (m, 1 H), 4.80 (dd, *J* = 1.9, 0.9 Hz, 1 H), 4.40 (t, *J* = 6.8 Hz, 2 H), 2.46 (t, *J* = 6.8 Hz, 2 H), 1.80 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2, 141.6, 133.9, 133.3, 132.3, 127.7, 112.5, 63.4, 36.8, 22.6; HRMS (AP+) calcd for $C_{10}H_{13}O_2S^+$ [M + H^+] 197.0631, found 197.0637.

S12. Starting from 4-pentynoic acid (0.491 g, 5.00 mmol, 1.0 equiv) and using the procedure for ester preparation described above, **S12** (0.751 g, 90% yield) was obtained as a colorless oil. **S12**: R_f = 0.50 (silica gel, hexanes/EtOAc, 4/1); IR (ATR) ν_{max} 3298, 2933, 1733, 1437, 1377, 1358, 1242, 1163, 1044, 977, 892 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.80 (dd, *J* = 1.9, 1.5 Hz, 1 H), 4.73 (dd, *J* = 1.9, 0.9 Hz, 1 H), 4.22 (t, *J* = 6.9 Hz, 2 H), 2.59–2.46 (m, 4 H), 2.34 (t, *J* = 6.8 Hz, 2 H), 1.97 (t, *J* = 2.5 Hz, 1 H), 1.75 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 141.5, 112.3, 82.5, 69.0, 62.8, 36.6, 33.3, 22.4, 14.4; HRMS (AP+) calcd for $C_{10}H_{15}O_2^+$ [M + H^+] 167.1067, found 167.1070.

S13. Starting from 5-phenyl-4-pentynoic acid[62] (0.782 g, 6.10 mmol, 1.0 equiv) and using the procedure for ester preparation described above, **S13** (0.765 g, 64% yield) was obtained as a colorless oil. **S13**: R_f = 0.68 (silica gel, hexanes/EtOAc, 4/1); IR (film) ν_{max} 3078, 2968, 2917, 1736, 1651, 1491, 1442, 1253, 1166, 1030, 893, 757, 692 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.42–7.35 (m, 2 H), 7.31–7.26 (m, 3 H), 4.80 (s, 1 H), 4.74 (s, 1 H), 4.24 (t, *J* = 6.8 Hz, 2 H), 2.73

(t, J = 7.2 Hz, 2 H), 2.67–2.60 (t, J = 7.2 Hz, 2 H), 2.36 (t, J = 6.7 Hz, 2 H), 1.76 (s, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.7, 141.5, 131.5, 128.1, 127.7, 123.5, 112.2, 88.0, 81.2, 62.8, 36.7, 33.6, 22.4, 15.4; HRMS (CI+) calcd for $C_{16}H_{19}O_2^+$ [M + H^+] 243.1380, found 243.1391.

S14. 4-pentenal (0.421 g, 5.00 mmol, 1.0 equiv) was added dropwise to 2-methylallyl magnesium chloride (12.0 mL, 0.5 M in THF, 6.00 mmol, 1.2 equiv) at –78 °C. Next, half-saturated aqueous NH_4Cl (10 mL) was added and the resultant mixture was warmed to 23 °C over 10 min. Upon completion, the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic phase was washed with brine (15 mL), dried ($MgSO_4$), filtered, and concentrated to afford the crude alcohol. Pressing forward without any additional purification, the crude alcohol (at most 5.0 mmol) was dissolved in CH_2Cl_2 (10 mL), and 4-DMAP (0.060 g, 0.05 mmol, 0.1 equiv) and Et_3N (1.26 g, 12.5 mmol, 2.5 equiv) were added sequentially at 23 °C. Next, the reaction was cooled to 0 °C, and BzCl (0.984 g, 7.00 mmol, 1.4 equiv) was then added dropwise. The resultant reaction mixture was allowed to warm to 23 °C and stirred overnight. Upon completion, the reaction contents were quenched by the addition of aqueous saturated $NaHCO_3$ (15 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine (15 mL), dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography (silica gel, hexanes/EtOAc, 25/1) to afford **S14** (0.910 g, 70% yield overall) as a colorless oil. **S14**: R_f = 0.55 (silica gel, hexanes/EtOAc, 4/1); IR (ATR) ν_{max} 3076, 2918, 1715, 1643, 1451, 1314, 1267, 1176, 1110, 1069, 1026, 994, 893, 707, 687, 675 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13–7.99 (m, 2 H), 7.58–7.52 (m, 1 H), 7.48–7.40 (m, 2 H), 5.89–5.75 (m, 1 H), 5.32 (tt, J = 7.4, 5.5 Hz, 1 H), 5.08–4.92 (m, 2 H), 4.81–4.74 (m, 2 H), 2.52–2.30 (m, 2 H), 2.25–2.08 (m, 2 H), 1.88–1.70 (m, 5 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 141.6, 137.7, 132.8, 130.6, 129.5, 128.3, 115.0, 113.6, 72.3, 42.9, 33.3, 29.7, 22.6; HRMS (AP+) calcd for $C_{16}H_{21}O_2^+$ [M + H^+] 245.1536, found 245.1547.

S15. *trans*-4-decenal (0.771 g, 5.00 mmol, 1.0 equiv) was added dropwise to 2-methylallyl magnesium chloride (12.0 mL, 0.5 M in THF, 1.2 equiv) at –78 °C. Then, half-saturated aqueous NH_4Cl (10 mL) was added and the mixture was allowed to warm to 23 °C. The aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (15 mL), dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography (silica gel, hexanes/EtOAc, 6/1) to give the desired intermediate alcohol (0.668 g, 64% yield) as a colorless oil. Next, the purified alcohol (0.668 g, 3.18 mmol) was dissolved in CH_2Cl_2 (10 mL), and pyridine (0.503 g, 6.36 mmol, 2.0 equiv) and BzCl (0.670 g, 4.77 mmol, 1.5 equiv) was then added dropwise sequentially at 23 °C. The reaction mixture was then allowed to stir at 23 °C overnight. Upon completion, saturated aqueous $NaHCO_3$ (15 mL) was added and the reaction contents were extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine (15 mL), dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography (silica gel, hexanes/EtOAc, 25/1) to afford **S15** (0.826 g, 53% yield overall) as a colorless oil. **S15**: R_f = 0.55 (silica gel, hexanes/EtOAc, 4/1); IR (ATR) ν_{max} 2956, 2925, 2855, 1716, 1451, 1314, 1268, 1176, 1111, 1069, 1027, 968, 892, 708, 688 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.07–8.01 (m, 2 H), 7.59–7.51 (m, 1 H), 7.48–7.40 (m, 2 H), 5.46–5.35 (m, 2 H), 5.30 (ddd, *J* = 19.0, 13.9, 6.2 Hz, 1 H), 4.80–4.73 (m, 2 H), 2.39 (ddd, *J* = 12.8, 7.5, 5.5 Hz, 2 H), 2.19–2.03 (m, 2 H), 1.99–1.88 (m, 2 H), 1.79 (s, 3 H), 1.77–1.70 (m, 2 H), 1.32–1.23 (m, 6 H), 0.87 (t, *J* = 6.1 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 141.6, 132.7, 131.3, 130.7, 129.5, 128.8, 128.2, 113.5, 72.5, 42.9, 34.0, 32.5, 31.4, 29.2, 28.5, 22.6, 22.5, 14.0; HRMS (AP+) calcd for $C_{21}H_{31}O_2^+$ [M + H^+] 315.2319, found 315.2329.

S16. Starting from (*Z*)-hept-4-enoic acid[63] (0.782 g, 6.10 mmol, 1.0 equiv) and using the procedure for ester preparation described above, **S16** (0.765 g, 64% yield) was obtained as a

colorless oil. **S16**: R_f = 0.68 (silica gel, hexanes/ EtOAc, 4/1); IR (film) ν_{max} 2965, 2935, 2875, 1738, 1456, 1243, 1165, 893, 734 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.45–5.38 (m, 1 H), 5.34–5.25 (m, 1 H), 4.80 (s, 1 H), 4.73 (s, 1 H), 4.19 (t, *J* = 6.9 Hz, 2 H), 2.37–2.32 (m, 6 H), 2.06 (quintet, *J* = 7.4 Hz, 2 H), 1.76 (s, 3 H), 0.96 (t, *J* = 7.5 Hz, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.1, 141.6, 133.0, 126.8, 112.2, 62.5, 36.7, 34.4, 22.7, 22.4, 20.4, 14.2; HRMS (ESI+) calcd for $C_{12}H_{21}O_2^+$ [M + H^+] 197.1536, found 197.1534.

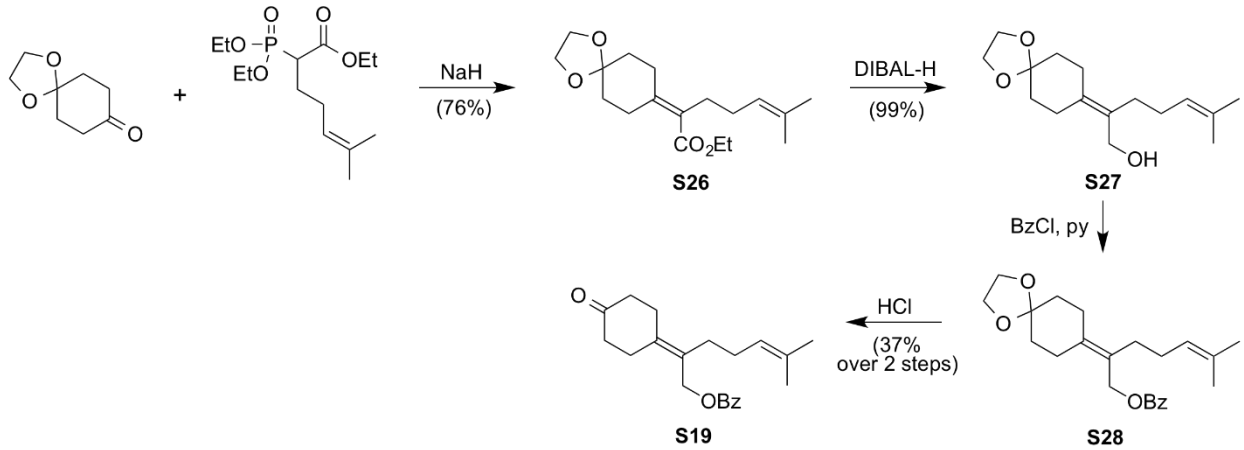
S17. Starting from 4-methylpent-4-enoic acid (0.694 g, 2.66 mmol, 1.0 equiv) and using the procedure for ester preparation described above, **S17** (0.612 g, 92% yield) was obtained as a colorless oil. **S17**: R_f = 0.55 (silica gel, hexanes/EtOAc, 4/1); IR (ATR) ν_{max} 2926, 2871, 1730, 1649, 1452, 1378, 1235, 1159, 1130, 1089, 1050, 983, 888 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.80 (td, *J* = 10.9, 4.4 Hz, 1 H), 4.72 (s, 3H), 4.66 (s, 1 H), 2.43–2.34 (m, 2 H), 2.33–2.25 (m, 2 H), 2.10 (ddd, *J* = 12.5, 10.9, 3.7 Hz, 1 H), 2.03–1.95 (m, 2 H), 1.72 (s, 3 H), 1.71–1.66 (m, 1 H), 1.65 (s, 3 H), 1.61–1.48 (m, 1 H), 1.47–1.31 (m, 1 H), 1.01 (dd, *J* = 23.2, 11.9 Hz, 2 H), 0.92 (d, *J* = 6.6 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 146.2, 144.2, 111.7, 110.2, 73.4, 50.7, 40.4, 34.1, 32.8, 32.7, 31.4, 30.4, 22.5, 22.0, 19.4; HRMS (ESI+) calcd for $C_{16}H_{27}O_2^+$ [M + H^+] 251.2006, found 251.2010.

S18. Starting from *S*-perillic acid (0.250 g, 1.50 mmol, 1.0 equiv) and using the procedure for ester preparation described above, **S18** (0.366 g, 99% yield) was obtained as a colorless oil. **S18**: R_f = 0.55 (silica gel, hexanes/EtOAc, 4/1); IR (ATR) ν_{max} 2931, 1707, 1650, 1453, 1241, 1074, 1044, 1028, 889, 741, 695 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.41–7.28 (m, 5 H), 7.06 (ddd, *J* = 4.8, 2.3, 1.1 Hz, 1 H), 5.18 (s, 2 H), 4.79–4.74 (m, 1 H), 4.74–4.69 (m, 1 H), 2.57–2.46 (m, 1 H), 2.18–2.05 (m, 2 H), 1.96–1.85 (m, 2 H), 1.74 (s, 3 H), 1.62–1.38 (m, 2 H); ^{13}C NMR

(100 MHz, $CDCl_3$) δ 167.1, 148.8, 139.6, 136.4, 129.9, 128.5, 128.0, 128.0, 109.2, 66.0, 40.0, 31.1, 27.0, 24.6, 20.7; HRMS (AP+) calcd for $C_{17}H_{21}O_2^+$ [M + H^+] 257.1536, found 257.1545.

S19. This compound is a synthetic intermediate related to a recently published work from the Snyder group,[6] prepared as described below.

Scheme S1. Synthesis of starting material **S19**.



To a solution of ethyl 2-(diethylphosphono)-6-methyl-5-heptaenoate[64] (6.57 g, 21.4 mmol, 1.2 equiv) in THF (15 mL) at 23 °C was added NaH (60% dispersion in mineral oil, 0.824 g, 20.6 mmol, 1.15 equiv) portionwise over 20 min. The resultant slurry was stirred for 1 h at 23 °C before solid 1,4-dioxaspiro[4.5]decan-8-one (2.79 g, 17.9 mmol, 1.0 equiv) was added portionwise. The reaction contents were then stirred at 23 °C overnight. Upon completion, the reaction contents were quenched by the addition of a half-saturated solution of aqueous NH_4Cl (50 mL) and extracted with EtOAc (3 × 30 mL). The combined organic layers were then dried ($MgSO_4$), filtered, and concentrated. The resultant residue was purified by flash column chromatography (silica gel,

hexanes/EtOAc, 24/1→4/1) to afford **S26** (4.20 g, 76% yield) as a white solid. Pressing forward, to a solution of a portion of this conjugated ester (**S26**, 2.42 g, 7.85 mmol, 1.0 equiv) in CH_2Cl_2 (25 mL) at –78 °C was added DIBAL-H (1.0 M solution in hexanes, 23.5 mL, 23.5 mmol, 3.0 equiv) dropwise. After stirring for 2 h at –78 °C, water (25 mL) was carefully added. The mixture was then allowed to warm to 23 °C and was partitioned between EtOAc (100 mL) and a saturated aqueous solution of Rochelle's salt (100 mL). The resultant biphasic mixture was stirred vigorously until phase separation was observed and the layers were separated. The aqueous phase was extracted with EtOAc (3 × 75 mL) and the combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$), filtered, and concentrated to afford **S27** (2.08 g, 99%) as a white solid. Next, to a solution of a portion of this allylic alcohol (**S27**, 0.259 g, 1.16 mmol, 1.0 equiv) in CH_2Cl_2 (3 mL) was sequentially added pyridine (0.19 mL, 2.32 mmol, 2.0 equiv) and BzCl (0.17 mL, 1.39 mmol, 1.2 equiv) at 0 °C. The reaction contents were then stirred at 23 °C for 1 h. Upon completion, the reaction was quenched by the addition of aqueous saturated $NaHCO_3$ (15 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine (15 mL), dried ($MgSO_4$), filtered, and concentrated to afford **S28** which was taken directly into the next step. Finally, to a solution of the crude allylic benzoate in acetone (3 mL) was added HCl (5% in H_2O, 1.5 mL) at 23 °C and the resultant mixture was stirred at 23 °C overnight. Upon completion, EtOAc (10 mL) was added, followed by saturated aqueous $NaHCO_3$ (10 mL). The layers were separated and the aqueous phase was then extracted with EtOAc (3 × 10 mL). The combined organic layers were then washed with brine (10 mL), dried ($MgSO_4$), and concentrated. The resultant residue was purified by flash column chromatography (silica gel, hexanes/EtOAc, 6/1) to afford **S19** (0.139 g, 37% yield over 2 steps, some contaminated fractions were abandoned) as a colorless oil. **S19**: R_f = 0.30 (silica gel, hexanes/EtOAc, 4/1); IR (film) ν_{max} 2964, 2910, 2848,

1716, 1269, 1108, 1069, 713, 668 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.08–8.00 (m, 2 H), 7.59–7.52 (m, 1 H), 7.48–7.41 (m, 2 H), 5.14 (t, *J* = 6.9 Hz, 1 H), 4.91 (s, 2 H), 2.71 (t, *J* = 6.8 Hz, 2 H), 2.63 (t, *J* = 6.9 Hz, 2 H), 2.47–2.42 (m, 4 H), 2.28 (t, *J* = 7.8 Hz, 2 H), 2.18–2.11 (m, 4 H), 1.67 (s, 3 H), 1.58 (s, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 211.5, 166.6, 135.3, 132.9, 132.2, 130.2, 129.5, 128.6, 128.4, 123.6, 64.0, 40.2, 40.1, 31.2, 27.3, 27.2, 25.7, 17.6; HRMS (ESI+) calcd for $C_{27}H_{26}O_{23}Na^+$ [M + Na^+] 349.1780, found 349.1768.

S20. Starting from 4-(bromomethyl)phenylacetic acid (0.729 g, 3.00 mmol, 1.0 equiv) and using the procedure for ester preparation described above, **S20** (0.809 g, 87% yield) was obtained as a colorless oil. **S20**: R_f = 0.60 (silica gel, hexanes/EtOAc, 4/1); IR (ATR) ν_{max} 2974, 2937, 1729, 1652, 1514, 1454, 1422, 1377, 1322, 1229, 1203, 1160, 1059, 892, 842 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39–7.31 (m, 2 H), 7.30–7.25 (m, 2 H), 4.74 (dd, *J* = 1.9, 1.5 Hz, 1 H), 4.63 (dd, *J* = 1.9, 0.9 Hz, 1 H), 4.48 (s, 2H), 4.24–4.12 (m, 2 H), 3.70 (q, *J* = 7.2 Hz, 1 H), 2.29 (t, *J* = 6.8 Hz, 2 H), 1.69 (s, 3 H), 1.48 (d, *J* = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.2, 141.5, 140.8, 136.6, 129.2, 128.0, 112.3, 63.0, 45.2, 36.6, 33.2, 22.3, 18.4; HRMS (AP+) calcd for $C_{15}H_{20}BrO_2^+$ [M + H^+] 311.0641, found 311.0657.

(–)-Nootkatone (**71**). Commercially available from Alfa Aesar (purity >98%)

S21. Prepared according to the method reported by Davis from geranyl bromide.[65]

S22. To a solution of geranyl bromide (0.770 g, 5.00 mmol, 1.0 equiv) in DMF (3 mL) at 0 °C was added methanesulfinic acid sodium salt ($NaSO_2Me$, 85% purity, 0.918 g, 7.50 mmol, 1.5 equiv). After stirring at 0 °C for 2 h, the reaction mixture was diluted with EtOAc (10 mL) and washed with 0.5 M HCl (5 mL), saturated aqueous $NaHCO_3$ (5 mL), water (5 mL) and brine (5

mL). The resultant organic layer was dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography (silica gel, hexanes/EtOAc, 3/1) to afford **S25** (0.728 g, 67% yield) as a waxy white solid. **S25**: R_f = 0.30 (silica gel, hexanes/EtOAc, 7/3); IR (ATR) ν_{max} 2927, 1448, 1302, 1143, 1125, 968, 902, 737 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.35 (t, *J* = 7.9 Hz, 1 H), 5.10–5.00 (m, 1 H), 3.72 (d, *J* = 7.9 Hz, 2 H), 2.81 (s, 3 H), 2.20–2.09 (m, 4 H), 1.74 (s, 3 H), 1.68 (s, 3 H), 1.60 (s, 3 H), 1.56 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.1, 132.2, 123.3, 110.9, 54.7, 39.6, 38.8, 26.0, 25.7, 17.7, 16.6; HRMS (AP+) calcd for $C_{11}H_{21}O_2S^+$ [M + H^+] 217.1257, found 217.1268.

S23. Prepared according to the method reported by Snyder from geranyl bromide.[2]

S24. Prepared according to the method reported by Snyder from geraniol.[2]

S25. Prepared according to the method reported by Hanson from geraniol.[66]

General procedure for HCl addition using reagents 30 and 31. The alkene substrate (0.25 mmol, 1.0 equiv, variable scale) was dissolved in $MeNO_2$ (2 mL, Alfa Aesar, 98$^+$%) and the solid hydrochlorinating reagent (2.2 equiv unless otherwise mentioned) was added at 23 °C. The reaction mixture was then allowed to stir for 3–16 h at 23 °C, with completion monitored by TLC. Upon completion, a mixed solution of saturated aqueous $NaHCO_3$ (1.5 mL) and 5% aqueous $Na_2S_2O_3$ (1.5 mL) was added slowly, and the mixture was vigorously stirred for another 5 min. The aqueous phase was extracted with CH_2Cl_2 (4 × 2 mL). The combined organic phase was dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography (silica gel) or preparative thin layer chromatography (silica gel) under the conditions indicated to afford the

corresponding product.

General procedure for HCl addition by AcCl/EtOH. This approach is based on the method described by Yadav and Babu.[26] AcCl (8.0 equiv) was added dropwise to a solution of the alkene substrate (1.0 equiv) in dry EtOH (8.0 equiv) at 23 °C. The reaction was stoppered tightly and allowed to stir at 30 °C. After all of the starting material was deemed consumed by TLC, the remaining AcCl and EtOH were removed *in vacuo* and the residue was purified by flash column chromatography (silica gel) or preparative thin layer chromatography (silica gel) under the conditions indicated to afford the corresponding product.

General procedure for HCl addition by HCl solution. In an effort to mimic the reaction temperature, time, and stoichiometry of the method described in this chapter using reagents **4**, **5**, and **6**, a commercial HCl solution was selected to effect hydrochlorination. Thus, HCl solution (4 M in 1,4-dioxane, 2.2 equiv) was added to the alkene substrate (1.0 equiv) at 23 °C. The reaction was then allowed to stir for 16 h at 23 °C. The reaction was then monitored by TLC and another 2.2 equiv of HCl solution was added if starting material still remained. The reaction was allowed to stir for another 16 h at 23 °C. The operations presented above were repeated until all of the starting material was deemed consumed by TLC. Upon completion, the remaining HCl and solvent were removed *in vacuo* and the residue purified by flash column chromatography (silica gel) or preparative thin layer chromatography (silica gel) under the conditions indicated to afford the corresponding product.

Compound 33. Obtained as a colorless oil (40.0 mg, 81% yield) starting from **32** (40.0 mg, 0.250 mmol) and using depe•Cl_2•$SbCl_5$ (0.316 g, 0.550 mmol) or obtained as a colorless oil (39.0 mg, 79% yield) starting from **32** (40.0 mg, 0.250 mmol) and using dppe•Cl_2•$SbCl_5$ (**30**, 0.422 g, 0.550 mmol) or obtained as a colorless oil (42.6 mg, 90% purity, 78% yield) starting from **32** (40.0 mg, 0.250 mmol) and using dppp•Cl_2•$SbCl_5$ (**31**, 0.430 g, 0.550 mmol) or obtained as a colorless oil (31.3 mg, 93% purity, 79% yield) starting from **32** (30.0 mg, 0.187 mmol) and using dppp•Cl_2•$TiCl_4$ (0.277 g, 0.412 mmol). **33**: R_f = 0.64 (silica gel, hexanes/CH_2Cl_2, 10/1); IR (ATR) ν_{max} 2946, 1496, 1454, 1370, 1148, 1113, 839, 749, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32–7.27 (m, 2 H), 7.23–7.17 (m, 3 H), 2.65 (t, *J* = 7.2 Hz, 2 H), 1.89–1.75 (m, 4 H), 1.56 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.0, 128.3, 128.3, 125.8, 70.9, 45.5, 35.8, 32.4, 26.9; HRMS (EI+) calcd for $C_{12}H_{17}Cl^+$ [M^+] 196.1013, found 196.1021.

Compound 36. Obtained as a colorless oil (31.9 mg, 62% yield) starting from **S1** (43.1 mg, 0.224 mmol) and using dppe•Cl_2•$SbCl_5$ (**30**, 0.379 g, 0.493 mmol) or obtained as a colorless oil (33.7 mg, 57% yield) starting from **S1** (49.2 mg, 0.256 mmol) and using dppp•Cl_2•$SbCl_5$ (**31**, 0.441 g, 0.563 mmol). **36**: R_f = 0.40 (silica gel, hexanes/EtOAc, 50/1); IR (ATR) ν_{max} 2923, 1585, 1481, 1439, 1371, 1094, 1026, 735, 689 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36–7.28 (m, 4 H), 7.21–7.15 (m, 1 H), 2.95 (t, *J* = 6.6 Hz, 2 H), 1.93–1.83 (m, 4 H), 1.56 (s, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.5, 129.3, 128.9, 126.0, 70.4, 44.9, 33.9, 32.4, 24.8; HRMS (AP+) calcd for $C_{12}H_{17}ClS^+$ [M^+] 228.0734, found 228.0744.

Compound 37. Obtained as a colorless oil (slowly turning yellow when exposed to air, 24.3 mg, 47% yield) starting from **S2** (45.5 mg, 0.164 mmol) and using dppe•Cl_2•$SbCl_5$ (**30**, 0.276 g, 0.360 mmol) or obtained as a colorless oil (slowly turning yellow when exposed to air, 30.7 mg, 62% yield) starting from **S2** (43.9 mg, 0.158 mmol) and using dppp•Cl_2•$SbCl_5$ (**31**, 0.272 g, 0.347 mmol). **37**: R_f = 0.65 (silica gel, hexanes/EtOAc, 4/1); IR (ATR) ν_{max} 2966, 1510, 1470, 1449, 1398, 1371, 1329, 1273, 1197, 1118, 1053, 898, 869, 792, 754, 718 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 1.8 Hz, 1 H), 7.29 (dd, *J* = 8.7, 1.9 Hz, 1 H), 7.21 (d, *J* = 8.7 Hz, 1 H), 7.10 (t, *J* = 3.4 Hz, 1 H), 6.44 (dd, *J* = 3.1, 0.7 Hz, 1 H), 4.13 (t, *J* = 7.0 Hz, 2 H), 2.12–2.00 (m, 2 H), 1.76–1.67 (m, 2 H), 1.53 (s, 6 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 134.6, 130.2, 128.7, 124.3, 123.4, 112.6, 110.7, 100.8, 70.1, 46.4, 42.9, 32.4, 26.0; HRMS (EI+) calcd for $C_{14}H_{17}BrClN^+$ [M^+] 313.0227, found 313.0237.

Compound 38. Obtained as a white solid (47.2 mg, 91% yield) starting from **S3** (44.7 mg, 0.195 mmol) and using dppe•Cl_2•$SbCl_5$ (**30**, 0.429 g, 0.329 mmol) or obtained as a white solid (52.5 mg, 90% yield) starting from **S3** (49.6 mg, 0.216 mmol) and using dppp•Cl_2•$SbCl_5$ (**31**, 0.373 g, 0.476 mmol). **38**: R_f = 0.35 (silica gel, hexanes/EtOAc, 4/1); IR (ATR) ν_{max} 2974, 1773, 1709, 1468, 1438, 1397, 1373, 1361, 1084, 1032, 720 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.91–7.66 (m, 4 H), 3.72 (t, *J* = 7.0 Hz, 2 H), 1.95–1.74 (m, 4 H), 1.55 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 133.9, 132.0, 123.2, 70.1, 43.0, 37.8, 32.4, 24.5; HRMS (AP+) calcd for $C_{14}H_{16}NO_2^+$ [M – Cl^+] 230.1176, found 230.1184.

Compound 39. Obtained as a light yellow oil (49.2 mg, 96% yield, d.r. = 5:1) starting from **S4** (42.5 mg, 0.247 mmol) and using dppe•Cl_2•$SbCl_5$ (**30**, 0.417 g, 0.543 mmol) or obtained

as a light yellow oil (50.6 mg, 96% yield, d.r. = 4.5:1) starting from **S4** (43.7 mg, 0.254 mmol) and using dppp•Cl_2•$SbCl_5$ (**31**, 0.437 g, 0.558 mmol). **39**: R_f = 0.18 (silica gel, hexanes); IR (ATR) ν_{max} 2931, 2863, 1494, 1440, 1121, 962, 821, 756, 741, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, integrated here as if one compound as most signals overlap except for the one set indicated) δ 7.34–7.26 (m, 3 H), 7.26–7.17 (m, 2 H), 2.62 (tt, *J* = 11.8, 3.9 Hz, 0.16 H, minor diastereomer), 2.47 (tt, *J* = 12.3, 3.6 Hz, 0.81 H, major diastereomer), 2.22–1.94 (m, 4 H), 1.94–1.69 (m, 3 H), 1.67 (s, 3 H), 1.67–1.62 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$, both diastereomers) δ 146.8, 145.8, 128.5, 128.4, 126.9, 126.8, 126.2, 126.1, 71.6, 70.5, 43.5, 42.8, 42.5, 41.6, 34.3, 31.4, 29.9, 28.1; HRMS (EI+) calcd for $C_{13}H_{17}Cl^+$ [M^+] 208.1013, found 208.1016.

Compound 40. Obtained as a colorless oil (30.4 mg, 60% yield) starting from **S5** (40.5 mg, 0.277 mmol) and using dppe•Cl_2•$SbCl_5$ (**30**, 0.468 g, 0.609 mmol) or obtained as a colorless oil (30.6 mg, 57% yield) starting from **S5** (43.2 mg, 0.295 mmol) and using dppp•Cl_2•$SbCl_5$ (**31**, 0.509 g, 0.650 mmol). **40**: R_f = 0.45 (silica gel, hexanes); IR (ATR) ν_{max} 2972, 2932, 1498, 1455, 1388, 1371, 1197, 1112, 1073, 746, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32–7.27 (m, 2 H), 7.24–7.17 (m, 3 H), 2.87–2.78 (m, 2 H), 2.10–1.99 (m, 2 H), 1.65 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.8, 128.4, 128.4, 125.9, 70.5, 48.0, 32.5, 31.7; HRMS (EI+) calcd for $C_{11}H_{15}Cl^+$ [M^+] 182.0857, found 182.0860.

Compound 41. Obtained as a colorless oil (29.7 mg, 60% yield) starting from **S6** (42.6 mg, 0.193 mmol) and using dppe•Cl_2•$SbCl_5$ (**30**, 0.327 g, 0.425 mmol) or obtained as a colorless oil (39.9 mg, 76% yield) starting from **S6** (44.9 mg, 0.204 mmol) and using dppp•Cl_2•$SbCl_5$ (**31**, 0.351 g, 0.448 mmol). **41**: R_f = 0.55 (silica gel, hexanes/EtOAc, 4/1); IR (ATR) ν_{max} 2974, 1741,

1456, 1374, 1247, 1218, 1133, 947, 906, 790, 753, 738, 695 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.30 (m, 5 H), 5.17 (s, 2 H), 4.39 (t, *J* = 7.0 Hz, 2 H), 2.15 (t, *J* = 7.0 Hz, 2 H), 1.61 (s, 6 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.0, 135.2, 128.6, 128.5, 128.3, 69.6, 68.0, 65.1, 43.8, 32.8; HRMS (EI+) calcd for $C_{13}H_{17}ClO_3^+$ [M^+] 256.0861, found 256.0869.

Compound 42. Obtained as a colorless oil (54.5 mg, 80% yield) starting from **S7** (57.0 mg, 0.300 mmol) and using dppe•Cl_2•$SbCl_5$ (**30**, 0.506 g, 0.659 mmol) or obtained as a colorless oil (59.3 mg, 84% yield) starting from **S7** (59.2 mg, 0.311 mmol) and using dppp•Cl_2•$SbCl_5$ (**30**, 0.536 g, 0.685 mmol). **42**: R_f = 0.55 (silica gel, hexanes/EtOAc, 4/1); IR (ATR) ν_{max} 2974, 1716, 1452, 1316, 1270, 1176, 1109, 1070, 1027, 707, 687 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (m, 2 H), 7.60–7.53 (m, 1 H), 7.48–7.40 (m, 2 H), 4.57 (t, *J* = 6.7 Hz, 2 H), 2.26 (t, *J* = 6.7 Hz, 2 H), 1.68 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 133.0, 130.1, 129.5, 128.4, 68.5, 61.0, 44.1, 33.0; HRMS (ESI+) calcd for $C_{12}H_{15}ClNaO_2^+$ [M + Na^+] 249.0653, found 249.0669.

Compound 43. Obtained as a colorless oil (42.6 mg, 84% yield) starting from **S8** (41.8 mg, 0.237 mmol) and using dppe•Cl_2•$SbCl_5$ (**30**, 0.401 g, 0.522 mmol) or obtained as a colorless oil (43.4 mg, 87% yield) starting from **S8** (41.4 mg, 0.235 mmol) and using dppp•Cl_2•$SbCl_5$ (**31**, 0.405 g, 0.517 mmol). **23**: R_f = 0.55 (silica gel, hexanes/EtOAc, 4/1); IR (ATR) ν_{max} 2972, 2927, 2863, 1455, 1370, 1100, 1029, 734, 696 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.27 (m, 5 H), 4.52 (s, 2 H), 3.72 (t, *J* = 6.7 Hz, 2 H), 2.12 (t, *J* = 6.7 Hz, 2 H), 1.62 (s, 6 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.3, 128.4, 127.7, 127.6, 73.0, 69.4, 67.4, 45.2, 33.0; HRMS (EI+) calcd for $C_{12}H_{17}ClO$ [M^+] 212.0962, found 212.0971.

Compound 44. Obtained as a colorless oil (42.1 mg, 88% yield) starting from **S9** (40.2 mg, 0.210 mmol) and using dppe•Cl_2•$SbCl_5$ (**30**, 0.355 g, 0.462 mmol) or obtained as a colorless oil (42.2 mg, 85% yield) starting from **S9** (41.9 mg, 0.219 mmol) and using dppp•Cl_2•$SbCl_5$ (**31**, 0.378 g, 0.482 mmol). **44**: R_f = 0.40 (silica gel, hexanes/EtOAc, 1/1); IR (ATR) ν_{max} 2974, 1741, 1717, 1584, 1438, 1373, 1303, 1291, 1280, 1244, 1126, 1088, 1045, 995, 745, 705 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.77 (ddd, *J* = 4.7, 1.7, 0.9 Hz, 1 H), 8.13 (dt, *J* = 7.9, 1.0 Hz, 1 H), 7.85 (td, *J* = 7.7, 1.8 Hz, 1 H), 7.52–7.45 (m, 1 H), 4.69–4.62 (m, 2 H), 2.31 (t, *J* = 7.2 Hz, 2 H), 1.67 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.0, 149.9, 147.9, 137.1, 127.0, 125.2, 68.1, 63.0, 43.8, 32.9; HRMS (ESI+) calcd for $C_{11}H_{15}ClNO_2^+$ [M + H^+] 228.0786, found 228.0793.

Compound 45. Obtained as a colorless oil (41.3 mg, 80% yield) starting from **S10** (42.7 mg, 0.237 mmol) and using dppe•Cl_2•$SbCl_5$ (**30**, 0.400 g, 0.521 mmol) or obtained as a colorless oil (41.2 mg, 84% yield) starting from **S10** (40.8 mg, 0.226 mmol) and using dppp•Cl_2•$SbCl_5$ (**31**, 0.390 g, 0.498 mmol). **45**: R_f = 0.55 (silica gel, hexanes/EtOAc, 4/1); IR (ATR) ν_{max} 3153, 2975, 1721, 1579, 1507, 1373, 1304, 1157, 1077, 980, 873, 759, 741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.00 (dd, *J* = 1.5, 0.8 Hz, 1 H), 7.43 (t, *J* = 1.7 Hz, 1 H), 6.73 (dd, *J* = 1.9, 0.7 Hz, 1 H), 4.49 (t, *J* = 6.8 Hz, 2 H), 2.20 (t, *J* = 6.8 Hz, 2 H), 1.66 (s, 6 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.8, 147.6, 143.7, 119.3, 109.7, 68.2, 61.5, 44.0, 32.8; HRMS (EI+) calcd for $C_{10}H_{13}ClO_3^+$ [M^+] 216.0548, found 216.0562.

Compound 46. Obtained as a colorless oil (35.1 mg, 80% yield) starting from **S11** (36.8 mg, 0.187 mmol) and using dppe•Cl_2•$SbCl_5$ (**30**, 0.317 g, 0.521 mmol) or obtained as a colorless oil (38.8 mg, 85% yield) starting from **S11** (38.6 mg, 0.197 mmol) and using dppp•Cl_2•$SbCl_5$ (**31**,

0.339 g, 0.498 mmol). **46**: R_f = 0.55 (silica gel, hexanes/EtOAc, 4/1); IR (ATR) ν_{max} 2974, 1705, 1526, 1418, 1360, 1278, 1258, 1222, 1131, 1092, 1076, 1038, 861, 748, 717 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.80 (dd, *J* = 3.7, 1.3 Hz, 1 H), 7.62–7.52 (m, 1 H), 7.10 (dt, *J* = 7.9, 3.9 Hz, 1 H), 4.54 (t, *J* = 6.7 Hz, 2 H), 2.23 (t, *J* = 6.7 Hz, 2 H), 1.67 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.1, 133.7, 133.5, 132.4, 127.8, 68.4, 62.2, 44.0, 32.9; HRMS (AP+) calcd for $C_{10}H_{13}O_2S^+$ [M – Cl^+] 197.0631, found 197.0636.

Compound 47. Obtained as a colorless oil (30.9 mg, 67% yield) starting from **S12** (38.1 mg, 0.229 mmol) and using dppe•Cl_2•$SbCl_5$ (**30**, 0.387 g, 0.504 mmol) or obtained as a colorless oil (39.1 mg, 75% yield) starting from **S12** (43.0 mg, 0.259 mmol) and using dppp•Cl_2•$SbCl_5$ (**31**, 0.446 g, 0.569 mmol). **47**: R_f = 0.60 (silica gel, hexanes/EtOAc, 7/3); IR (ATR) ν_{max} 3299, 2974, 2928, 1733, 1391, 1372, 1163, 1132, 1022, 981, 778 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.38–4.32 (m, 2 H), 2.58–2.47 (m, 4 H), 2.11 (t, *J* = 6.9 Hz, 2 H), 1.98 (t, *J* = 2.5 Hz, 1 H), 1.62 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6, 82.4, 69.1, 68.3, 61.8, 43.9, 33.4, 32.8, 14.3; HRMS (ESI+) calcd for $C_{10}H_{15}ClNaO_2^+$ [M + Na^+] 225.0653, found 225.0654.

Compound 48. Obtained as a colorless oil (41.3 mg, 86% yield) starting from **S13** (41.9 mg, 0.173 mmol) and using dppe•Cl_2•$SbCl_5$ (**30**, 0.292 g, 0.380 mmol). **48**: R_f = 0.58 (silica gel, hexanes/EtOAc, 4/1); IR (film) ν_{max} 2972, 2925, 1735, 1491, 1371, 1255, 1167, 757, 692 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.42–7.35 (m, 2 H), 7.31–7.24 (m, 3 H), 4.36 (t, *J* = 6.9 Hz, 2 H), 2.73 (t, *J* = 7.1 Hz, 2 H), 2.63 (t, *J* = 7.2 Hz, 2 H), 2.12 (t, *J* = 6.9 Hz, 2 H), 1.61 (s, 6 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.7, 131.6, 128.2, 127.8, 123.5, 87.9, 81.3, 68.3, 61.8, 44.0, 33.7, 32.8, 15.4; HRMS (ESI+) calcd for $C_{16}H_{20}ClO_2^+$ [M + H^+] 279.1146, found 279.1147.

Compound 49. Obtained as a colorless oil (39.8 mg, 79% yield) starting from **S14** (44.0 mg, 0.180 mmol) and using dppe•Cl_2•$SbCl_5$ (**30**, 0.304 g, 0.396 mmol) or obtained as a colorless oil (40.3 mg, 81% yield) starting from **S14** (43.2 mg, 0.177 mmol) and using dppp•Cl_2•$SbCl_5$ (**31**, 0.305 g, 0.389 mmol). **49**: R_f = 0.55 (silica gel, hexanes/EtOAc, 4/1); IR (ATR) ν_{max} 2976, 2926, 1713, 1642, 1603, 1451, 1372, 1315, 1267, 1176, 1108, 1070, 1026, 993, 913, 687, 676 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.15–8.00 (m, 2 H), 7.59–7.54 (m, 1 H), 7.50–7.40 (m, 2 H), 5.82 (ddt, *J* = 16.8, 10.2, 6.5 Hz, 1 H), 5.47 (dtd, *J* = 8.5, 6.1, 2.4 Hz, 1 H), 5.04 (ddd, *J* = 17.1, 3.4, 1.6 Hz, 1 H), 4.97 (ddd, *J* = 10.2, 3.0, 1.3 Hz, 1 H), 2.29 (dd, *J* = 15.2, 8.2 Hz, 1 H), 2.21–2.08 (m, 3 H), 1.86–1.78 (m, 2 H), 1.63 (s, 3 H), 1.59 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 137.5, 133.0, 130.4, 129.6, 128.4, 115.2, 71.8, 68.8, 49.6, 34.9, 33.7, 31.9, 29.2; HRMS (AP+) cacld for $C_{16}H_{22}ClO_2^+$ [M + H^+] 281.1303, found 281.1313.

Compound 50. Obtained as a colorless oil (46.6 mg, 80% yield) starting from **S15** (51.4 mg, 0.163 mmol) and using dppe•Cl_2•$SbCl_5$ (**30**, 0.276 g, 0.360 mmol) or obtained as a colorless oil (43.3 mg, 87% yield) starting from **S15** (44.6 mg, 0.142 mmol) and using dppp•Cl_2•$SbCl_5$ (**31**, 0.244 g, 0.312 mmol). **50**: R_f = 0.55 (silica gel, hexanes/EtOAc, 4/1); IR (ATR) ν_{max} 2957, 2925, 2856, 1716, 1451, 1372, 1315, 1268, 1176, 1109, 1070, 1026, 968, 709, 688 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.08–8.01 (m, 2 H), 7.59–7.52 (m, 1 H), 7.49–7.40 (m, 2 H), 5.49-5.33 (m, 3 H), 2.28 (dd, *J* = 15.2, 8.3 Hz, 1 H), 2.12 (ddd, *J* = 21.0, 14.1, 5.2 Hz, 3 H), 1.94 (dd, *J* = 13.5, 6.2 Hz, 2 H), 1.82–1.73 (m, 2 H), 1.62 (s, 3 H), 1.60 (s, 3 H), 1.32–1.22 (m, 6 H), 0.87 (t, *J* = 7.0 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 132.9, 131.4, 130.5, 129.6, 128.6, 128.4, 71.9, 68.9, 49.6,

35.6, 33.6, 32.5, 31.9, 31.4, 29.2, 28.1, 22.5, 14.0; HRMS (AP+) calcd for $C_{21}H_{32}ClO_2^+$ [M + H^+] 351.2085, found 351.2094.

Compound 51. Obtained as a colorless oil (36.6 mg, 83% yield) starting from **S16** (37.3 mg, 0.190 mmol) and using dppe•Cl_2•$SbCl_5$ (**30**, 0.321 g, 0.418 mmol). The use of AcCl/EtOH effected full conversion, but afforded neither desired product, any identifiable side product, or recovered starting material. **51**: R_f = 0.62 (silica gel, hexanes/EtOAc, 4/1); IR (film) ν_{max} 2967, 2933, 2874, 1738, 1452, 1165, 1133 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.53–5.37 (m, 1 H), 5.36–5.22 (m, 1 H), 4.31 (t, *J* = 6.9 Hz, 2 H), 2.37–2.33 (m, 4 H), 2.10 (t, *J* = 7.0 Hz, 2 H), 2.08–2.02 (m, 2 H), 1.62 (s, 6 H), 0.96 (t, *J* = 7.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.0, 133.2, 126.7, 68.3, 61.4, 44.0, 34.4, 32.8, 22.6, 20.5, 14.2; HRMS (ESI+) calcd for $C_{12}H_{22}ClO_2^+$ [M + H^+] 233.1303, found 233.1300.

Compound 52. Obtained as a colorless oil (25.8 mg, 60% yield) starting from **S17** (37.8 mg, 0.151 mmol) and using dppe•Cl_2•$SbCl_5$ (**30**, 0.255 g, 0.332 mmol) or obtained as a colorless oil (31.0 mg, 52% yield, including an unidentified impurity) starting from **S17** (52.0 mg, 0.208 mmol) and using HCl solution (4 M in 1,4-dioxane, 0.46 mL in total, 1.828 mmol). The use of AcCl/EtOH effected full conversion, but afforded neither desired product or recovered starting material, but did generate an unidentified mixture with less than 30% mass recovery. **52**: R_f = 0.58 (silica gel, hexanes/EtOAc, 4/1); IR (ATR) ν_{max} 2926, 2871, 1732, 1648, 1456, 1373, 1179, 1130, 1113, 983, 891 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.81 (td, *J* = 10.9, 4.4 Hz, 1 H), 4.76–4.69 (m, 2 H), 2.50–2.44 (m, 2 H), 2.11 (ddd, *J* = 12.4, 10.6, 3.6 Hz, 1 H), 2.04 (dt, *J* = 2.4, 1.6 Hz, 1 H), 2.02–1.95 (m, 2 H), 1.71 (ddd, *J* = 10.7, 6.0, 3.8 Hz, 2 H), 1.67–1.65 (m, 3 H), 1.63–1.59 (m, 1 H),

1.56 (d, J = 0.7 Hz, 6 H), 1.38 (ddd, J = 12.9, 11.2, 3.8 Hz, 1 H), 1.08–0.95 (m, 2 H), 0.93 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 146.2, 111.8, 73.5, 69.8, 50.7, 40.5, 40.4, 34.1, 32.3, 32.3, 31.4, 30.7, 30.3, 22.0, 19.5; HRMS (ESI+) calcd for $C_{16}H_{28}ClO_2^+$ [M + H^+] 287.1772, found 287.1777.

Compound 53. Obtained as a colorless oil (43.1 mg, 84% yield) starting from **S18** (44.9 mg, 0.175 mmol) and using dppe•Cl_2•$SbCl_5$ (**30**, 0.296 g, 0.385 mmol). **53**: R_f = 0.52 (silica gel, hexanes/EtOAc, 4/1); IR (ATR) ν_{max} 2931, 1707, 1653, 1455, 1389, 1371, 1242, 1216, 1118, 1074, 1029, 740, 711, 695 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.29 (m, 5 H), 7.03 (dt, J = 4.9, 2.3 Hz, 1 H), 5.19 (s, 2H), 2.66–2.55 (m, 1 H), 2.50–2.40 (m, 1 H), 2.30–2.06 (m, 3 H), 1.81–1.71 (m, 1 H), 1.60 (s, 3 H), 1.58 (s, 3 H), 1.45–1.31 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 139.1, 136.3, 130.1, 128.5, 128.1, 128.0, 73.5, 66.0, 45.6, 30.4, 30.2, 28.0, 25.0, 24.0; HRMS (ESI+) calcd for $C_{17}H_{22}ClO_2^+$ [M + H^+] 293.1303, found 293.1316.

Compound 54. Obtained as a colorless oil (29.6 mg, 84% yield) starting from **S19** (31.8 mg, 0.097 mmol) and using dppe•Cl_2•$SbCl_5$ (**30**, 0.165 g, 0.214 mmol). **54**: R_f = 0.25 (silica gel, hexanes/EtOAc, 4/1); IR (ATR) ν_{max} 2970, 1711, 1452, 1371, 1314, 1265, 1175, 1097, 1069, 1026, 939, 710 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08–8.01 (m, 2 H), 7.60–7.54 (m, 1 H), 7.48–7.40 (m, 2 H), 4.92 (s, 2 H), 2.77–2.71 (m, 2 H), 2.63 (t, J = 6.9 Hz, 2 H), 2.47 (t, J = 6.7 Hz, 4 H), 2.31–2.24 (m, 2 H), 1.80–1.73 (m, 2 H), 1.73–1.62 (m, 2 H), 1.54 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.5, 166.6, 135.5, 133.0, 130.1, 129.6, 128.4, 128.4, 70.7, 64.1, 45.8, 40.2, 40.0, 32.4, 31.1, 27.2, 27.1, 24.4; HRMS (ESI+) calcd for $C_{21}H_{27}ClNaO_3^+$ [M + Na^+] 385.1541, found 385.1545.

Compound 55. Obtained as a colorless oil (33.9 mg, 66% yield of the desired product, along with an additional 7% of an inseparable side product identified as the corresponding benzyl chloride) starting from **S20** (42.5 mg, 0.136 mmol) and using dppe•Cl_2•$SbCl_5$ (**30**, 0.231 g, 0.300 mmol) or obtained as a colorless oil (42.4 mg, 67% yield of the desired product, along with an additional 12% of an inseparable side product identified as the corresponding benzyl chloride) starting from **S20** (42.4 mg, 0.136 mmol) and using dppp•Cl_2•$SbCl_5$ (**31**, 0.235 g, 0.300 mmol). **55**: R_f = 0.55 (silica gel, hexanes/EtOAc, 4/1); IR (ATR) ν_{max} 2976, 2935, 1731, 1514, 1456, 1422, 1373, 1323, 1229, 1203, 1161, 1130, 1084, 835 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37–7.33 (m, 2 H), 7.28–7.24 (m, 2 H), 4.48 (s, 2 H), 4.32–4.27 (m, 2 H), 3.77–3.65 (m, 1 H), 2.09–1.99 (m, 2 H), 1.52 (d, *J* = 2.7 Hz, 6 H), 1.49 (d, *J* = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 140.6, 136.6, 129.3, 128.0, 68.4, 62.0, 45.2, 43.8, 33.1, 32.7, 32.7, 18.3; HRMS (AP+) calcd for $C_{15}H_{21}BrClO_2^+$ [M + H^+] 347.0408, found 347.0411.

Compound 56. Obtained as a white solid (79.7 mg, 97% yield) starting from **S21** (72.5 mg, 0.260 mmol) and using dppe•Cl_2•$SbCl_5$ (**30**, 0.440 g, 0.573 mmol) or obtained as a white solid (70.1 mg, 92% yield) starting from **S21** (67.5 mg, 0.242 mmol) and using dppp•Cl_2•$SbCl_5$ (**31**, 0.418 g, 0.533 mmol). **56**: R_f = 0.40 (silica gel, hexanes/EtOAc, 7/3); IR (ATR) ν_{max} 2945, 1663, 1586, 1447, 1388, 1371, 1306, 1238, 1150, 1130, 1086, 772, 741, 689 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.91–7.84 (m, 2 H), 7.69–7.60 (m, 1 H), 7.59–7.51 (m, 2 H), 5.23–5.16 (m, 1 H), 3.82 (d, *J* = 7.8 Hz, 2 H), 2.01 (t, *J* = 7.3 Hz, 2 H), 1.68–1.60 (m, 2 H), 1.56 (s, 6 H), 1.55–1.48 (m, 2 H), 1.33 (s, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.9, 138.6, 133.4, 128.9, 128.3, 110.6, 70.7,

55.9, 45.1, 39.3, 32.3, 22.9, 15.9; HRMS (ESI+) calcd for $C_{16}H_{23}ClNaO_2S^+$ [M + Na^+] 337.0999, found 337.1009.

Compound 57. Obtained as a colorless oil (59.3 mg, 95% yield) starting from **S22** (53.8 mg, 0.249 mmol) and using dppe•Cl_2•$SbCl_5$ (**30**, 0.420 g, 0.547 mmol) or obtained as a colorless oil (71.2 mg, 93% yield) starting from **S22** (68.1 mg, 0.315 mmol) and using dppp•Cl_2•$SbCl_5$ (**31**, 0.542 g, 0.692 mmol). **57**: R_f = 0.25 (silica gel, hexanes/EtOAc, 7/3); IR (ATR) ν_{max} 2974, 2944, 1455, 1388, 1371, 1300, 1244, 1121, 967, 903, 760 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.41–5.33 (m, 1 H), 3.74 (d, *J* = 7.9 Hz, 2 H), 2.84 (s, 3 H), 2.14 (t, *J* = 6.6 Hz, 2 H), 1.75 (s, 3 H), 1.73–1.61 (m, 4 H), 1.56 (s, 6 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.7, 110.8, 70.7, 54.4, 45.1, 39.3, 39.2, 32.3, 22.8, 16.5; HRMS (ESI+) calcd for $C_{11}H_{21}ClNaO_2S^+$ [M + Na^+] 275.0843, found 275.0844.

Compound 58. Obtained as a colorless oil (54.0 mg, 81% yield) starting from **S23** (54.4 mg, 0.333 mmol) and using dppe•Cl_2•$SbCl_5$ (**30**, 0.563 g, 0.733 mmol) or obtained as a colorless oil (59.1 mg, 90% yield) starting from **S23** (53.9 mg, 0.330 mmol) and using dppp•Cl_2•$SbCl_5$ (**31**, 0.569 g, 0.726 mmol). **58**: R_f = 0.60 (silica gel, hexanes/EtOAc, 7/3); IR (ATR) ν_{max} 2974, 2947, 2249, 1457, 1418, 1388, 1371, 1116, 918, 827 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.22–5.16 (m, 1 H), 3.05 (dd, *J* = 6.9, 0.8 Hz, 2 H), 2.06 (t, *J* = 6.8 Hz, 2 H), 1.72–1.69 (m, 1 H), 1.68 (s, 3 H), 1.67–1.58 (m, 3 H), 1.57 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.0, 118.5, 112.0, 70.8, 45.3, 39.0, 32.4, 22.9, 16.2, 16.2; HRMS (AP+) calcd for $C_{11}H_{19}ClN^+$ [M + H^+] 200.1201, found 200.1208.

Compound 59. Obtained as a colorless oil (25.8 mg, 35% yield) starting from geranyl acetate (Sigma-Aldrich, 98%, 63.0 mg, 0.321 mmol) and using dppe•Cl_2•$SbCl_5$ (**30**, 0.518 g, 0.706 mmol) or obtained as a colorless oil (32.9 mg, 40% yield) starting from geranyl acetate (Sigma-Aldrich, 98%, 68.8 mg, 0.350 mmol) and using dppp•Cl_2•$SbCl_5$ (**31**, 0.577 g, 0.771 mmol). **59**: R_f = 0.42 (silica gel, hexanes/EtOAc, 10/1); IR (film) ν_{max} 2972, 2946, 1740, 1456, 1369, 1233, 1024, 955 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.34 (t, *J* = 7.1 Hz, 1 H), 4.57 (d, *J* = 7.1 Hz, 2 H), 2.07–1.98 (m, 2 H), 2.04 (s, 3 H), 1.72 – 1.58 (m, 4 H), 1.69 (s, 3 H), 1.55 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.0, 141.7, 118.7, 70.8, 61.2, 45.4, 39.3, 32.4, 22.9, 21.0, 16.2; HRMS (ESI+) calcd for $C_{12}H_{21}ClO_2^+$ [M^+] 233.1303, found 233.1308.

Compound 60. Obtained as a colorless oil (42.0 mg, 57% yield) starting from geranyl pivalate[16] (64.0 mg, 0.268 mmol) and using dppe•Cl_2•$SbCl_5$ (**30**, 0.434 g, 0.591 mmol) or obtained as a colorless oil (42.0 mg, 57% yield) starting from geranyl pivalate (63.9 mg, 0.268 mmol) and using dppp•Cl_2•$SbCl_5$ (**31**, 0.441 g, 0.591 mmol). **60**: R_f = 0.50 (silica gel, hexanes/EtOAc, 10/1); IR (film) ν_{max} 2972, 2872, 1728, 1480, 1458, 1369, 1282, 1152, 953 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.33 (t, *J* = 6.9 Hz, 1H), 4.56 (d, *J* = 6.9 Hz, 2H), 2.04 (t, *J* = 7.1 Hz, 2H), 1.69 (s, 3H), 1.68 – 1.58 (m, 4H), 1.56 (s, 6H), 1.18 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.5, 141.2, 119.2, 70.8, 61.2, 45.3, 39.2, 38.7, 32.4, 27.2, 22.9, 16.2; HRMS (ESI+) calcd for $C_{15}H_{27}ClO_2^+$ [M^+] 275.1772, found 275.1779.

Compound 61. Obtained as a colorless oil (52.3 mg, 72% yield) starting from **S24** (63.6 mg, 0.254 mmol) and using dppe•Cl_2•$SbCl_5$ (**30**, 0.430 g, 0.559 mmol) or obtained as a colorless oil (42.5 mg, 55% yield) starting from **S24** (68.1 mg, 0.272 mmol) and using dppp•Cl_2•$SbCl_5$ (**31**,

0.469 g, 0.599 mmol). **39c**: R_f = 0.65 (silica gel, hexanes/EtOAc, 7/3); IR (ATR) ν_{max} 2948, 1782, 1389, 1372, 1360, 1328, 1218, 1139, 909, 834, 777, 730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.45–5.38 (m, 1 H), 4.86 (d, *J* = 7.3 Hz, 2 H), 2.09 (t, *J* = 6.6 Hz, 2 H), 1.76 (s, 3 H), 1.72–1.61 (m, 4 H), 1.57 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.5 (q, *J* = 42.1 Hz), 145.4, 116.3, 114.5 (q, *J* = 285.8 Hz), 70.8, 64.7, 45.2, 39.3, 32.4, 22.8, 16.4; HRMS (EI+) calcd for $C_{12}H_{18}ClF_3O_2^+$ [M^+] 286.0942, found 286.0951.

Compound 62. Obtained as a colorless oil (48.0 mg, 71% yield) starting from **S25** (59.7 mg, 0.231 mmol) and using dppe•Cl_2•$SbCl_5$ (**30**, 0.390 g, 0.508 mmol) or obtained as a colorless oil (61.1 mg, 82% yield) starting from **S25** (66.0 mg, 0.255 mmol) and using dppp•Cl_2•$SbCl_5$ (**31**, 0.440 g, 0.562 mmol). **62**: R_f = 0.70 (silica gel, hexanes/EtOAc, 7/3); IR (ATR) ν_{max} 2946, 1715, 1451, 1266, 1176, 1107, 1069, 1026, 935, 708, 688, 677 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.12–7.97 (m, 2 H), 7.61–7.50 (m, 1 H), 7.50–7.37 (m, 2 H), 5.55–5.43 (m, 1 H), 4.85 (d, *J* = 6.6 Hz, 2 H), 2.09 (t, *J* = 6.9 Hz, 2 H), 1.79 (s, 3 H), 1.75–1.62 (m, 4 H), 1.57 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 142.0, 132.8, 130.4, 129.6, 128.3, 118.8, 71.0, 61.8, 45.4, 39.3, 32.4, 22.9, 16.4; HRMS (EI+) calcd for $C_{17}H_{23}ClO_2^+$ [M^+] 294.1381, found 294.1385.

Compound 72. Obtained as a light brown oil (55.0 mg, 91% yield) starting from **71** (46.8 mg, 0.214 mmol) and using dppe•Cl_2•$SbCl_5$ (**30**, 0.362 g, 0.472 mmol). **72**: R_f = 0.70 (silica gel, hexanes/EtOAc, 4/1); IR (ATR) ν_{max} 2972, 2917, 1619, 1456, 1431, 1387, 1371, 1354, 1116, 1024, 900, 886, 823, 801, 713, 668 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.08 (s, 1 H), 5.41 (d, *J* = 4.2 Hz, 1 H), 2.39–2.24 (m, 3 H), 2.05–1.87 (m, 3 H), 1.74–1.64 (m, 1 H), 1.61 (s, 3 H), 1.56 (s, 3 H), 1.16–1.04 (m, 1 H), 0.93 (d, *J* = 6.8 Hz, 3 H), 0.89 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.0,

130.6, 126.4, 123.2, 74.4, 42.3, 39.8, 39.3, 36.3, 35.5, 30.8, 29.9, 27.8, 17.4, 14.4; HRMS (AP+) calcd for $C_{15}H_{21}Cl_2$ [M – H^+] 271.1015, found 271.1020.

General procedure for HBr addition with reagents 34 and 35. The alkene substrate (0.15 mmol, 1.0 equiv, variable scale) was dissolved in $MeNO_2$ (2 mL), and the hydrobromination reagent (2.4 equiv unless otherwise mentioned) was then added as a solid at 23 °C. The reaction mixture was allowed to stir for 16–40 h, with completion monitored by TLC. Upon completion, a mixed solution of saturated aqueous $NaHCO_3$ (1.5 mL) and 5% aqueous $Na_2S_2O_3$ (1.5 mL) was added slowly, the mixture was then vigorously stirred for another 5 min, and the contents were extracted with CH_2Cl_2 (4 × 2 mL). The combined organic layers were dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography (silica gel) under the conditions indicated to afford the corresponding product. Note: when the dppe/dppp ligand was found to be inseparable from the product by TLC analysis, CuBr was added during the drying step to remove the phosphines.

General procedure for HBr addition by HBr solution. HBr solution [commercial, 33% in AcOH, 1.0 equiv or 10.0 equiv (excess)] was added to the alkene substrate (1.0 equiv) at 23 °C. The reaction was then allowed to stir for 30 min at 23 °C. Following TLC analysis, another portion of HBr solution (0.2 equiv) was added if starting material still remained. The reaction was allowed to stir for another 30 min at 23 °C. Upon completion, CH_2Cl_2 was added to dilute the reaction. The organic phase was washed by saturated aqueous $NaHCO_3$ (1.5 mL), dried ($MgSO_4$), filtered,

concentrated, and purified by flash column chromatography (silica gel) under the conditions indicated to afford the corresponding product.

Compound 63. Obtained as a colorless oil (25.3 mg, 59% yield) starting from **S8** (29.6 mg, 0.168 mmol) and using dppe•Br_2•$HfBr_4$ (**35**, 0.426 g, 0.403 mmol). The use of HBr solution (excess) effected complete conversion but afforded neither desired product, any identifiable side product, or recovered starting material. **63**: R_f = 0.50 (silica gel, hexanes/EtOAc, 4/1); IR (ATR) ν_{max} 2925, 2857, 1454, 1370, 1111, 1029, 734, 695 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37–7.28 (m, 5 H), 4.52 (s, 2 H), 3.74 (t, *J* = 6.7 Hz, 2 H), 2.17 (t, *J* = 6.7 Hz, 2 H), 1.80 (s, 6 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.3, 128.4, 127.6, 73.1, 68.5, 65.8, 46.6, 34.8; HRMS (EI+) calcd for $C_{12}H_{17}BrO^+$ [M^+] 256.0457, found 256.0474.

Compound 64. Obtained as a colorless oil (35.6 mg, 84% yield) starting from **S9** (30.0 mg, 0.157 mmol) and using dppe•Br_2•$HfBr_4$ (**35**, 0.398 g, 0.376 mmol). **64**: R_f = 0.40 (silica gel, hexanes/EtOAc, 1/1); IR (ATR) ν_{max} 2969, 1741, 1720, 1584, 1439, 1372, 1305, 1292, 1281, 1245, 1131, 1089, 747, 707 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.77 (ddd, *J* = 4.7, 1.7, 0.9 Hz, 1 H), 8.13 (dt, *J* = 7.9, 1.1 Hz, 1 H), 7.85 (td, *J* = 7.7, 1.8 Hz, 1 H), 7.52–7.45 (m, 1 H), 4.70–4.65 (m, 2 H), 2.39–2.34 (m, 2 H), 1.85 (s, 6 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.0, 149.9, 148.0, 137.0, 126.9, 125.1, 64.0, 63.6, 45.2, 34.6; HRMS (ESI+) calcd for $C_{11}H_{15}BrNO_2^+$ [M + H^+] 272.0281, found 272.0284.

Compound 65. Obtained as a white solid (41.2 mg, 91% yield) starting from **S3** (33.6 mg, 0.146 mmol) and using dppe•Br_2•$HfBr_4$ (**35**, 0.372 g, 0.352 mmol) or obtained as a white solid

(61.0 mg, 85% yield) starting from **S3** (52.3 mg, 0.146 mmol) and using HBr solution (33% in acetic acid, 1.46 mmol, 0.26 mL). **65**: R_f = 0.40 (silica gel, hexanes/EtOAc, 4/1); IR (ATR) ν_{max} 2933, 1773, 1707, 1467, 1437, 1395, 1372, 1360, 1082, 1030, 718 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.88–7.82 (m, 2 H), 7.75–7.69 (m, 2 H), 3.73 (t, *J* = 6.9 Hz, 2 H), 1.99–1.89 (m, 2 H), 1.89–1.80 (m, 2 H), 1.74 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 134.0, 132.1, 123.2, 66.8, 44.4, 37.7, 34.2, 25.7; HRMS (ESI+) calcd for $C_{14}H_{16}NO_2^+$ [M – Br^+] 230.1176, found 230.1190.

Compound 66. Obtained as a colorless oil (24.9 mg, 61% yield) starting from **S13** (30.5 mg, 0.126 mmol) and using dppe•Br_2•$HfBr_4$ (**35**, 0.319 g, 0.302 mmol) or obtained as a colorless oil (24.5 mg, along with an inseparable impurity and trace amount of starting material, 39% yield after recalibration) starting from **S13** (27.6 mg, 0.114 mmol) and using HBr solution (33% in AcOH, 0.137 mmol, 0.04 mL). The use of HBr solution (excess) afforded neither desired product, nor recovered starting material, but did lead to the di-HBr adduct which was obtained in 62% yield. **66**: R_f = 0.57 (silica gel, hexanes/EtOAc, 4/1); IR (film) ν_{max} 2966, 2921, 1738, 1491, 1371, 1166, 1129, 757, 692 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.41–7.36 (m, 2 H), 7.31–7.26 (m, 3 H), 4.39 (t, *J* = 6.9 Hz, 2 H), 2.74 (t, *J* = 7.5 Hz, 2 H), 2.63 (t, *J* = 7.2 Hz, 2 H), 2.17 (t, *J* = 6.9 Hz, 2 H), 1.79 (s, 6 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.7, 131.6, 128.2, 127.8, 123.5, 87.9, 81.3, 64.0, 62.8, 45.4, 34.6, 33.7, 15.4; HRMS (ESI+) calcd for $C_{16}H_{20}BrO_2^+$ [M + H^+] 323.0641, found 323.0640.

Compound 67. Obtained as a white solid (26.6 mg, 84% yield) starting from **71** (23.2 mg, 0.106 mmol) and using dppe•Br_2•$HfBr_4$ (**35**, 0.269 g, 0.255 mmol). **67**: R_f = 0.25 (silica gel, hexanes/EtOAc, 4/1); IR (ATR) ν_{max} 2969, 1669, 1620, 1456, 1372, 1285, 1201, 1097, 737 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.77 (s, 1 H), 2.51 (tdd, *J* = 13.7, 5.1, 2.0 Hz, 1 H), 2.40 (ddd, *J* = 15.2, 4.2, 2.8 Hz, 1 H), 2.31–2.10 (m, 4 H), 2.09–1.98 (m, 1 H), 1.89 (tt, *J* = 12.2, 3.0 Hz, 1 H), 1.79 (s, 3 H), 1.77 (s, 3 H), 1.33 (ddd, *J* = 25.9, 12.5, 4.4 Hz, 1 H), 1.18–1.12 (m, 1 H), 1.10 (s, 3 H), 0.99 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.4, 169.7, 124.6, 72.0, 46.4, 42.0, 41.0, 40.4, 39.2, 32.6, 32.4, 31.9, 28.9, 17.0, 15.0; HRMS (AP+) calcd for $C_{15}H_{23}O^+$ [M^+] 219.1743, found 219.1757.

Compound 68. Obtained as a white solid (21.4 mg, 61% yield) starting from **S21** (27.4 mg, 0.098 mmol) and using dppe•Br_2•$HfBr_4$ (**35**, 0.250 g, 0.236 mmol). **68**: R_f = 0.40 (silica gel, hexanes/EtOAc, 7/3); IR (ATR) ν_{max} 2919, 1447, 1307, 1151, 1086, 740, 690 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90–7.85 (m, 2 H), 7.68–7.61 (m, 1 H), 7.58–7.52 (m, 2 H), 5.24–5.16 (m, 1 H), 3.82 (d, *J* = 7.9 Hz, 2 H), 2.02 (t, *J* = 7.4 Hz, 2 H), 1.74 (s, 6 H), 1.65–1.60 (m, 1 H), 1.54–1.46 (m, 3 H), 1.34 (d, *J* = 1.1 Hz, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 146.0, 138.8, 133.5, 129.0, 128.5, 110.8, 67.8, 56.0, 46.8, 39.4, 34.2, 24.2, 16.0; HRMS (ESI+) calcd for $C_{16}H_{23}BrO_2SNa^+$ [M + Na^+] 381.0494, found 381.0493.

Compound 69. Obtained as a colorless oil (17.3 mg, 39% yield) starting from **S15** (35.7 mg, 0.114 mmol) and using dppe•Br_2•$HfBr_4$ (**35**, 0.288 g, 0.272 mmol) or obtained as a colorless oil (20.2 mg, 46% yield) starting from **S15** (35.3 mg, 0.112 mmol) and using dppe•Br_2•$TiBr_4$ (**34**, 0.249 g, 0.269 mmol). The use of HBr solution (excess) afforded neither desired product or recovered starting material, but did lead to the di-HBr adduct which was obtained in 64% yield. **69**: R_f = 0.55 (silica gel, hexanes/EtOAc, 4/1); IR (ATR) ν_{max} 2957, 2924, 2855, 1717, 1451, 1372, 1314, 1268, 1176, 1108, 1070, 1026, 968, 709, 687 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08–

8.00 (m, 2 H), 7.62–7.51 (m, 1 H), 7.49–7.40 (m, 2 H), 5.49–5.34 (m, 3 H), 2.41–2.25 (m, 2 H), 2.09 (dd, *J* = 13.2, 7.9 Hz, 2 H), 1.94 (dd, *J* = 13.4, 6.2 Hz, 2 H), 1.81 (s, 3 H), 1.80–1.77 (m, 1 H), 1.77 (s, 3 H), 1.32–1.24 (m, 6 H), 0.87 (t, *J* = 7.0 Hz, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.9, 132.9, 131.5, 130.6, 129.6, 128.6, 128.4, 72.7, 64.8, 51.2, 35.6, 35.4, 33.6, 32.5, 31.4, 29.2, 28.1, 22.5, 14.0; HRMS (ESI+) calcd for $C_{21}H_{32}BrO_2^+$ [M + H^+] 395.1580, found 395.1598.

Compound 70. Obtained as a yellow oil (52.3 mg, 70% yield) starting from **S21** (47.0 mg, 0.169 mmol) and using dppe•Br_2•$TiBr_4$ (**34**, 0.377 g, 0.405 mmol). **70**: R_f = 0.45 (silica gel, hexanes/EtOAc, 3/1); IR (ATR) ν_{max} 2924, 1447, 1307, 1150, 1114, 1087, 789, 746, 689 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99–7.90 (m, 2 H), 7.73–7.66 (m, 1 H), 7.65–7.55 (m, 2 H), 3.43–3.28 (m, 2 H), 2.33–2.21 (m, 1 H), 2.21–2.10 (m, 1 H), 1.92–1.77 (m, 2 H), 1.75 (s, 6 H), 1.74–1.70 (m, 2 H), 1.70 (s, 3 H), 1.68–1.54 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.8, 133.9, 129.4, 128.0, 68.4, 67.4, 53.7, 47.0, 45.2, 37.4, 34.3, 34.1, 31.0, 22.5; HRMS (ESI+) calcd for $C_{16}H_{24}BrO_2S^+$ [M – Br^+] 359.0675, found 359.0688.

Compound 71. Obtained as a colorless oil (28.2 mg, 51% yield) starting from **S23** (28.0 mg, 0.172 mmol) and using dppe•Br_2•$TiBr_4$ (**34**, 0.383 g, 0.412 mmol). **71**: R_f = 0.37 (silica gel, hexanes/EtOAc, 5/1); IR (ATR) ν_{max} 2960, 2919, 1445, 1386, 1371, 1120, 1076, 812, 762, 736 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.72–2.54 (m, 2 H), 2.31–2.19 (m, 1 H), 2.15–2.05 (m, 1 H), 1.96–1.85 (m, 1 H), 1.85–1.78 (m, 3 H), 1.77 (s, 6 H), 1.75 (s, 3 H), 1.74–1.65 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 119.3, 69.0, 67.4, 47.0, 45.1, 40.6, 34.3, 34.2, 30.7, 22.6, 14.5; HRMS (EI+) calcd for $C_{11}H_{19}BrN^+$ [M – Br^+] 244.0695, found 244.0701.

General procedure for DCl and DBr addition. All reactions were carried out under the same conditions as their HCl and HBr addition counterparts, but were carried out in D_2O-saturated CH_3NO_2, prepared as described here. First, CH_3NO_2 (10 mL) was added under argon to a flask containing CaH_2 and the resultant slurry was heated at 60 °C for 2 min and then was allowed to cool to 23 °C. It was then distilled, with a total of 5–6 mL of CH_3NO_2 collected. After cooling to 23 °C, the distillate was dried over freshly activated 4 Å molecular sieves (flame-dried under high vacuum). It was then transferred into a flame-dried flask under argon and D_2O (0.2 mL) was added, and the biphasic mixture was stirred for 5 min at 23 °C. At this time, stirring was stopped and the CH_3NO_2 was taken out carefully via syringe so as not to disturb the D_2O droplets in the original flask. It was then added into another flame-dried flask and the same process of D_2O addition and syringe removal was repeated twice to obtain D_2O-saturated CH_3NO_2.

Compound 77. Obtained as a colorless oil (40.0 mg, 65% yield) starting from **32** (50.0 mg, 0.315 mmol) and using dppe•Cl_2•$SbCl_5$ (**30**, 0.527 g, 0.686 mmol). **77**: R_f = 0.64 (silica gel, hexanes/CH_2Cl_2, 10/1); IR (ATR) ν_{max} 2939, 1496, 1454, 1371, 1126, 748, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34–7.28 (m, 2 H), 7.25–7.18 (m, 3 H), 2.66 (t, 2 H), 1.90–1.72 (m, 3 H), 1.57 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.0, 128.4, 128.3, 125.8, 70.9 (t, J = 6.3 Hz), 45.1 (t, J = 19.3 Hz), 35.8, 32.4, 32.3, 26.8; HRMS (EI+) calcd for $C_{12}H_{16}DCl^+$ [M^+] 197.1076, found 197.1082.

Compound 78. Obtained as a colorless oil (30.0 mg, 82% yield) starting from **S8** (30.0 mg, 0.170 mmol) and using dppe•Cl_2•$SbCl_5$ (**30**, 0.288 g, 0.374 mmol). **78**: R_f = 0.55 (silica gel, hexanes/EtOAc, 4/1); IR (ATR) ν_{max} 2928, 2863, 1454, 1366, 1098, 1029, 735, 696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39–7.27 (m, 5 H), 4.52 (s, 2 H), 3.72 (t, *J* = 6.7 Hz, 2 H), 2.12 (t, *J* = 6.7 Hz, 2 H), 1.62 (s, 3 H), 1.61–1.58 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.3, 128.4, 127.6, 127.6, 73.1, 69.4 (t, *J* = 6.0 Hz), 67.4, 45.1, 33.0, 32.7 (t, *J* = 19.8 Hz); HRMS (EI+) calcd for $C_{12}H_{16}DClO^+$ [M^+] 213.1025, found 213.1032.

Compound 79. Obtained as a colorless oil (39.5 mg, 66% yield) starting from **S15** (51.0 mg, 0.162 mmol) and using dppe•Cl_2•$SbCl_5$ (**5**, 0.274 g, 0.357 mmol). **79**: R_f = 0.55 (silica gel, hexanes/EtOAc, 4/1); IR (ATR) ν_{max} 2957, 2926, 2856, 1716, 1451, 1315, 1269, 1176, 1111, 1070, 1027, 969, 910, 734, 709 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.08–8.01 (m, 2 H), 7.60–7.52 (m, 1 H), 7.48–7.40 (m, 2 H), 5.49–5.34 (m, 3 H), 2.33–2.24 (m, 1 H), 2.20–2.04 (m, 3 H), 2.00–1.89 (m, 2 H), 1.85–1.69 (m, 2 H), 1.64–1.56 (m, 5 H), 1.34–1.22 (m, 6 H), 0.87 (t, *J* = 7.0 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 132.9, 131.4, 130.5, 129.5, 128.6, 128.3, 71.9, 68.8 (t, *J* = 6.2 Hz), 49.5, 35.6, 33.3 (t, *J* = 19.5 Hz), 32.4, 31.8, 31.3, 29.1, 28.1, 22.5, 14.0; HRMS (ESI+) calcd for $C_{21}H_{31}DClO_2^+$ [M + H^+] 352.2148, found 352.2159.

Compound 80. Obtained as a colorless oil (40.0 mg, 86% yield) starting from **S9** (33.0 mg, 0.172 mmol) and using dppe•Br_2•$HfBr_4$ (**14**, 0.437 g, 0.414 mmol). **54**: R_f = 0.40 (silica gel, hexanes/EtOAc, 1/1); IR (ATR) ν_{max} 2966, 2921, 1741, 1720, 1438, 1305, 1291, 1281, 1245, 1131, 1089, 1046, 995, 747, 707 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.77 (ddd, *J* = 4.7, 1.7, 0.9 Hz, 1 H), 8.16–8.11 (m, 1 H), 7.85 (tt, *J* = 6.7, 3.3 Hz, 1 H), 7.49 (ddd, *J* = 7.6, 4.7, 1.2 Hz, 1 H), 4.70–

4.65 (t, *J* = 7.2 Hz, 2 H), 2.37 (t, *J* = 7.2 Hz, 2 H), 1.86–1.84 (m, 3H), 1.84–1.82 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.0, 149.9, 147.8, 137.0, 126.9, 125.1, 63.9, 63.6 (t, *J* = 6.2 Hz), 45.1, 34.6, 34.3 (t, *J* = 19.8 Hz); HRMS (ESI+) calcd for $C_{11}H_{14}DBrNO_2^+$ [M + H^+] 273.0343, found 273.0347.

Compound 81. Obtained as a white solid (48.8 mg, 92% yield) starting from **S3** (39.0 mg, 0.170 mmol) and using dppe•Br_2•$HfBr_4$ (**14**, 0.431 g, 0.408 mmol). **55**: R_f = 0.40 (silica gel, hexanes/EtOAc, 4/1). IR (ATR) ν_{max} 2928, 1774, 1706, 1467, 1438, 1395, 1361, 720 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88–7.82 (m, 2 H), 7.75–7.70 (m, 2 H), 3.73 (t, *J* = 7.1 Hz, 2 H), 1.97–1.89 (m, 2 H), 1.86–1.78 (m, 1 H), 1.76–1.70 (m, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 133.9, 132.0, 123.2, 66.7 (t, *J* = 7.2 Hz), 44.0 (t, *J* = 19.7 Hz), 37.6, 34.2, 34.1, 25.6 (t, *J* = 9.7 Hz); HRMS (ESI+) calcd for $C_{14}H_{15}DNO_2^+$ [M + H^+] 311.0500 found 311.0503.

Preparation of complexes for mechanistic studies

dppeO_2. To a solution of dppe (3.98 g, 10.0 mmol, 1.0 equiv) in CH_2Cl_2 (25 mL) at 23 °C was added H_2O_2 (30% aqueous solution, 10 mL) dropwise. The reaction was allowed to stir at 23 °C for 10 min. Upon completion, the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers dried ($MgSO_4$), filtered, and concentrated to afford dppeO_2 (4.29 g, 99% yield) as a white solid.

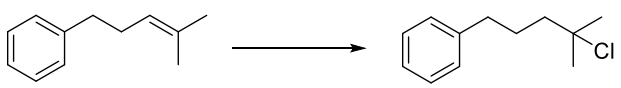
dppeO_2•$SbCl_3$ (I). To a solution of dppeO_2 (0.430 g, 1.0 mmol, 1.0 equiv) in CH_2Cl_2 (5 mL) at 23 °C was added $SbCl_3$ (0.228 g, 1.0 mmol, 1.0 equiv). A white precipitate was generated

1 min after adding the $SbCl_3$. After stirring at 23 °C for 30 min, the reaction was then cooled to –20 °C and stirred at that temperature for 16 h. Upon completion, the precipitate was collected by filtration and the filter cake was carefully washed with CH_2Cl_2 (2 × 2 mL). The precipitate was then dried under vacuum to afford $dppeO_2$•$SbCl_3$ (0.448 g, 68% yield) as a white solid. Alternatively, direct evaporation of the solvent from the reaction mixture instead of cooling and filtration afforded $dppeO_2$•$SbCl_3$ (0.620 g, 99% yield) as a white solid with no significant impurities present according to ^{1}H NMR.

$dppeO_2$•$SbCl_3$•HCl (74). To a solution of $dppeO_2$ (0.430 g, 1.0 mmol, 1.0 equiv) and HCl (1 M in Et_2O, 2.0 mL, 2.0 mmol, 2.0 equiv; note: using less or more HCl gave the same product based on ^{1}H NMR and ^{31}P NMR analysis) in CH_2Cl_2 (5 mL) at 23 °C was added $SbCl_3$ (0.228 g, 1.0 mmol, 1.0 equiv). A white precipitate was generated 1 min after adding the $SbCl_3$. After stirring at 23 °C for 30 min, the reaction was then cooled to –20 °C and stirred at that temperature for 16 h. Upon completion, the precipitate was collected by filtration and the filter cake was carefully washed with CH_2Cl_2 (2 × 2 mL). The precipitate was then dried under vacuum to afford $dppeO_2$•$SbCl_3$•HCl (0.348 g, 51%) as a white solid. Alternatively, direct evaporation of the solvent from the reaction mixture instead of cooling and filtration afforded $dppeO_2$•$SbCl_3$ (0.649 g, 98% yield) as a white solid with no significant impurities present according to ^{1}H NMR.

$dppeO_2$•$SbCl_3$•HCl + HCl (excess) (II). This compound was generated *in situ* by adding HCl (1 M in EtOAc, 0.05 mL, 0.05 mmol, 5.0 equiv) into $dppeO_2$•$SbCl_3$•HCl (**59**, 6.8 mg, 0.01 mmol, 1 equiv) in CD_3CN (1 mL) at 23 °C.

Table 1-S1. Original design of the reagents through varied combinations



Entry	Solvent	Reagent (usually 2.2 equiv)	Outcome
1	$MeNO_2$	dppe•Cl_2•$SbCl_5$	79%[a]
2	$MeNO_2$	dppp•Cl_2•$SbCl_5$	78%[a]
3	$MeNO_2$	dppp•Cl_2•$TiCl_4$	79%[a]
4	CH_2Cl_2	dppe•Cl_2•$SbCl_5$	n.r.
5	1,2-dichloroethane	dppe•Cl_2•$SbCl_5$	n.r.
6	$CHCl_3$	dppe•Cl_2•$SbCl_5$	n.r.
7	$CHCl_3$ (H_2O-sat.)	dppp•Cl_2•$SbCl_5$	n.r.
8	MeOH	dppe•Cl_2•$SbCl_5$	n.r.
9	MeOH/AcOH	dppe•Cl_2•$SbCl_5$	n.r.
10	EtOH	dppe•Cl_2•$SbCl_5$	n.r.
11	*i*-PrOH	dppe•Cl_2•$SbCl_5$	n.r.
12	THF	dppe•Cl_2•$SbCl_5$	n.r.
13	THF (wet)	dppe•Cl_2•$SbCl_5$	n.r.
14	Et_2O	dppe•Cl_2•$SbCl_5$	n.r.
15	Acetone	dppe•Cl_2•$SbCl_5$	n.r.
16	DMSO	dppe•Cl_2•$SbCl_5$	n.r.
17	DMF	dppe•Cl_2•$SbCl_5$	n.r.
18	MeCN	dppe•Cl_2•$SbCl_5$	n.r.
19	Benzene	dppe•Cl_2•$SbCl_5$	n.r.

Table 1-S1. (Continued)

20	1,4-dioxane	dppe•Cl_2•$SbCl_5$	n.r.
21	$PhNO_2$	dppe•Cl_2•$SbCl_5$	n.r. (rapid reagent decomposition)
22	$EtNO_2$	dppe•Cl_2•$SbCl_5$	<50% conversion
23	$MeNO_2$	HCl (aq)	n.r.
24	$MeNO_2$	PCl_3	n.r.
25	$MeNO_2$	PCl_5	n.r.
26	$MeNO_2$	$POCl_3$	n.r.
27	$MeNO_2$	$SbCl_5$ (0.3 equiv)	n.r.
28	$MeNO_2$	Ph_3P•Cl_2•$SbCl_5$	<10% conversion
29	$MeNO_2$	dppe•$SbCl_3$	n.r.
30	$MeNO_2$	dppe•$SbCl_5$	<50% conversion
31	$MeNO_2$	dppe•2$SbCl_5$	50%[a]
32	$MeNO_2$	dppp•Cl_2	n.r.
33	$MeNO_2$	dppp•2Cl_2	<50% conversion
34	$MeNO_2$	dppp•2Cl_2•2$SbCl_5$	protocyclization
35	$MeNO_2$	dppe•Tf_2O (10 equiv) + Bu_4NCl (10 equiv)	<10% conversion
36	$MeNO_2$	dppe•O_2•HBF_4 (10 equiv) + Bu_4NCl (10 equiv)	<10% conversion
37[b]	$MeNO_2$	dppe•O_2•HBF_4 (10 equiv) + Bu_4NCl (10 equiv)	<50% conversion

Table 1-S1. (Continued)

38	$MeNO_2$	dppe•O_2•HBF_4 (2.2 equiv) + Bu_4NCl (2.2 equiv)	<10% conversion
39[b]	$CHCl_3$	dppe•O_2•HBF_4 (10 equiv) + Bu_4NCl (10 equiv)	<10% conversion
40	$MeNO_2$	dppeO_2•$SbCl_5$	n.r.
41	$MeNO_2$	dppe•O_2•Cl_2•$SbCl_5$	n.r.
42	$MeNO_2$	HCl (1 M in EtOAc)	20%
43	$MeNO_2$	dppe•O_2•HCl•$SbCl_3$	23%
44	$MeNO_2$ (dry)	HCl (1 M in EtOAc)	23%
45	$MeNO_2$ (dry)	HCl (1 M in EtOAc) + dppeO_2	64%
46	$MeNO_2$ (dry)	HCl (1 M in EtOAc) + dppe•O_2•HCl•$SbCl_3$	68%

[a]Isolated yield; [b]Reaction carried out at 50 °C. Note that all dppe and dppe•O_2 complexes were prepared by similar methods of preparing the main reagents.

1.8 References

[1] G. W. Gribble, *J. Nat. Prod*. **1992**, *55*, 1353.

[2] S. A. Snyder, D. S. Treitler, *Angew. Chem. Int. Ed*. **2009**, *48*, 7899.

[3] S. A. Snyder, D. S. Treitler, A. P. Brucks, *J. Am. Chem. Soc*. **2010**, *132*, 14303.

[4] S. A. Snyder, D. S. Treitler, A. P. Brucks, W. Sattler, *J. Am. Chem. Soc*. **2011**, *133*, 15898.

[5] S. A. Snyder, A. P. Brucks, D. S. Treitler, I. Moga, *J. Am. Chem. Soc*. **2012**, *134*, 17714.

[6] M. Shen, M. Kretschmer, Z. G. Brill, S. A. Snyder, *Org. Lett*. **2016**, *18*, 5018.

[7] Y. -A. Zhang,

[8] T. W. G. Solomons, C. B. Fryhle, S. A. Snyder, Organic Chemistry, 12th ed,; Wiley 2016; pp 1124.

[9] (a) F. C. Whitmore, F. Johnston, *J. Am. Chem. Soc.* **1933**, *55*, 5020.

[10] L. Schmerling, *J. Am. Chem. Soc.* **1946**, *68*, 195.

[11] M. J. S. Dewar, R. C. Fahey, *J. Am. Chem. Soc.* **1963**, *85*, 2245.

[12] H. C. Brown, M.-H. Rei, *J. Org. Chem.* **1966**, *31*, 1090.

[13] J. K. Stille, F. M. Sonnenberg, T. H. Kinstle, *J. Am. Chem. Soc.* **1966**, *88*, 4922.

[14] R. C. Fahey, C. A. McPherson, *J. Am. Chem. Soc.* **1971**, *93*, 2445

[15] K. B. Becker, C. A. Grob, *Synthesis* **1973**, 789.

[16] K. B. Becker, C. A. Grob, *Helv. Chim. Acta* **1973**, *56*, 2723.

[17] P. Frøyen, J. Skramstad, *Synth. Commun.* **1994**, 24, 1871.

[18] D. Landini, F. Rolla, *J. Org. Chem.* **1973**, *38*, 2262.

[19] D. Landini, F. Rolla, *J. Org. Chem.* **1980**, *45*, 3527.

[19] J. M. Khurana, P. Tetenyi, M. Kodomari, S. Steven, *Ind. J. Chem.* **1988**, *27B*, 1129.

[20] P. J. Kropp, K. A. Daus, S. D. Crawford, M. W. Tubergen, K. D. Kepler, S. L. Craig, V. P. Wilson, *J. Am. Chem. Soc.* **1990**, *112*, 7433.

[21] H. Alper, Y. Huang, *Organometallics* **1991**, *10*, 1665.

[22] L. Delaude, P. Laszlo, *Tetrahedron Lett.* **1991**, *32*, 3705.

[23] P. J. Kropp, K. A. Daus, M. W. Tubergen, K. D. Kepler, V. P. Wilson, S. L. Craig, M. M. Baillargeon, G.W. Breton, *J. Am. Chem. Soc.* **1993**, *115*, 3071.

[24] P. Boudjouk, B.-K. Kim, B.-H. Han, *Synth. Commun.* **1996**, *26*, 3479.

[25] M. C. S. de Mattos, A. M. Sanseverino, *Synth. Commun.* **2000**, *30*, 1975.

[26] V. K. Yadav, K. G. Babu, *Eur. J. Org. Chem.* **2005**, 452.

[27] K. Tanemura, *Tetrahedron Lett.* **2018**, *59*, 4253.

[28] F. T. Schevenels, M. Shen, S. A. Snyder, *J. Am. Chem. Soc.* **2017**, *139*, 6239.

[29] B. Gaspar, E. M. Carreira, *Angew. Chem. Int. Ed.* **2008**, *47*, 5758.

[30] E. K. Leggans, T. J. Barker, K. K. Duncan, D. L. Boger, *Org. Lett.* **2012**, *14*, 1428.

[31] X. Ma, S. B. Herzon, *Chem. Sci.* **2015**, *6*, 6250.

[32] F. R. Mayo, C. Walling, *Chem. Rev.* **1940**, *27*, 351.

[33] A. M. Sanseverino, M. C. S. de Mattos, *J. Braz. Chem. Soc.* **2001**, *12*, 685.

[34] H. C. Brown, C. Groot, *J. Am. Chem. Soc.* **1942**, *64*, 2223.

[35] P. S. Skell, R. G. Allen, *J. Am. Chem. Soc.* **1959**, *81*, 5383.

[36] J. M. S. Dewar, R. C. Fahey, *J. Am. Chem. Soc.* **1963**, *85*, 2245.

[37] H. C. Brown, K. T. Lin, *J. Am. Chem. Soc.* **1975**, *97*, 600.

[38] A. Hassner, R. F. Fibiger, *Synthesis* **1984**, 960.

[39] Z. Li, R. Ebule, J. Kostyo, G. B. Hammond, B. Xu, *Chem. Eur. J.* **2017**, *23*, 12739.

[40] S. Liang, G. B. Hammond, B. Xu, *Green Chem.* **2018**, *20*, 680.

[41] Z. Lu, X. Zeng, G. B. Hammond, B. Xu, *J. Am. Chem. Soc.* **2017**, *139*, 18202.

[42] Unpublished work from Dr. J. Pitzen in our group.

[43] G. A. Wiley, W. R. Stine, *Tetrahedron Lett.* **1967**, *8*, 2321.

[44] J. Hartke, E. Akgün, *Chem. Ber.* **1979**, *112*, 2436.

[45] M. Julia, P. Roy, *Tetrahedron* **1986**, *42*, 4991.

[46] A. Demotie, I. J. S. Fairlamb, S. K. Radford, *Tetrahedron Lett.* **2003**, *44*, 4539.

[47] J. B. Hendrickson, S. M. Schwartzman, *Tetrahedron Lett.* **1975**, *16*, 277.

[48] C. Zhao, X. Jia, X. Wang, H. Gong, *J. Am. Chem. Soc.* **2014**, *136*, 17645.

[49] V. J. Ellermann, M. Z. Theierling, *Anorg. Allg. Chem*. **1975**, *411*, 15.

[50] N. Burford, D. E. Herbert, P. J. Ragogna, R. McDonald, M. J. Ferguson, *J. Am. Chem. Soc*. **2004**, *126*, 17067.

[51] Y. Carpenter, N. Burford, M. D. Lumsden, R. McDonald, *Inorg. Chem*. **2011**, *50*, 3342.

[52] H. L. Byers, K. B. Dillon, A. E. Goeta, *Inorg. Chim. Acta*. **2003**, *344*, 239.

[53] A. S. Banerjee, R. Engel, G. Axelrad, *Phosphorus Sulfur Relat. Elem*. **1983**, *15*, 15.

[54] I. A. Razak, A. Usman, H. -K. Fun, B. M. Yamin, N. A. M. Kasim, *Acta Crystallogr., Sect C: Cryst. Struct. Commun.* **2002**, *58*, m225.

[55] A. Hassner, R. Fibiger, D. Andisik, *J. Org. Chem*. **1984**, *49*, 4237.

[56] M. Dryzhakov, M. Hellal, E. Wolfe, F. C. Falk, J. Moran, *J. Am. Chem. Soc*. **2015**, *137*, 9555.

[57] M. F. Plano, G. R. Labadie, M. R. Jacob, B. L. Tekwani, R. M. Cravero, *Chem. Biodivers.* **2011**, *8*, 1098.

[58] K. Ishizuka, H. Seike, T. Hatakeyama, N. Nakamura, *J. Am. Chem. Soc.* **2010**, *132*, 13117.

[59] G. Villa, G. Povie, P. Renaud, *J. Am. Chem. Soc.* **2011**, *133*, 5913.

[60] R. W. Hoffman, E. Haeberlin, T. Rhode, *Synthesis* **2002**, *2*, 207.

[61] P. A. Cleary, K. A. Woerpel, *Org. Lett.* **2005**, *7*, 5531.

[62] A. Nagendiran, O. Verho, C. Haller, E. V. Johnston, J.-E. Bäckvall, *J. Org. Chem.* **2014**, *79*, 1399.

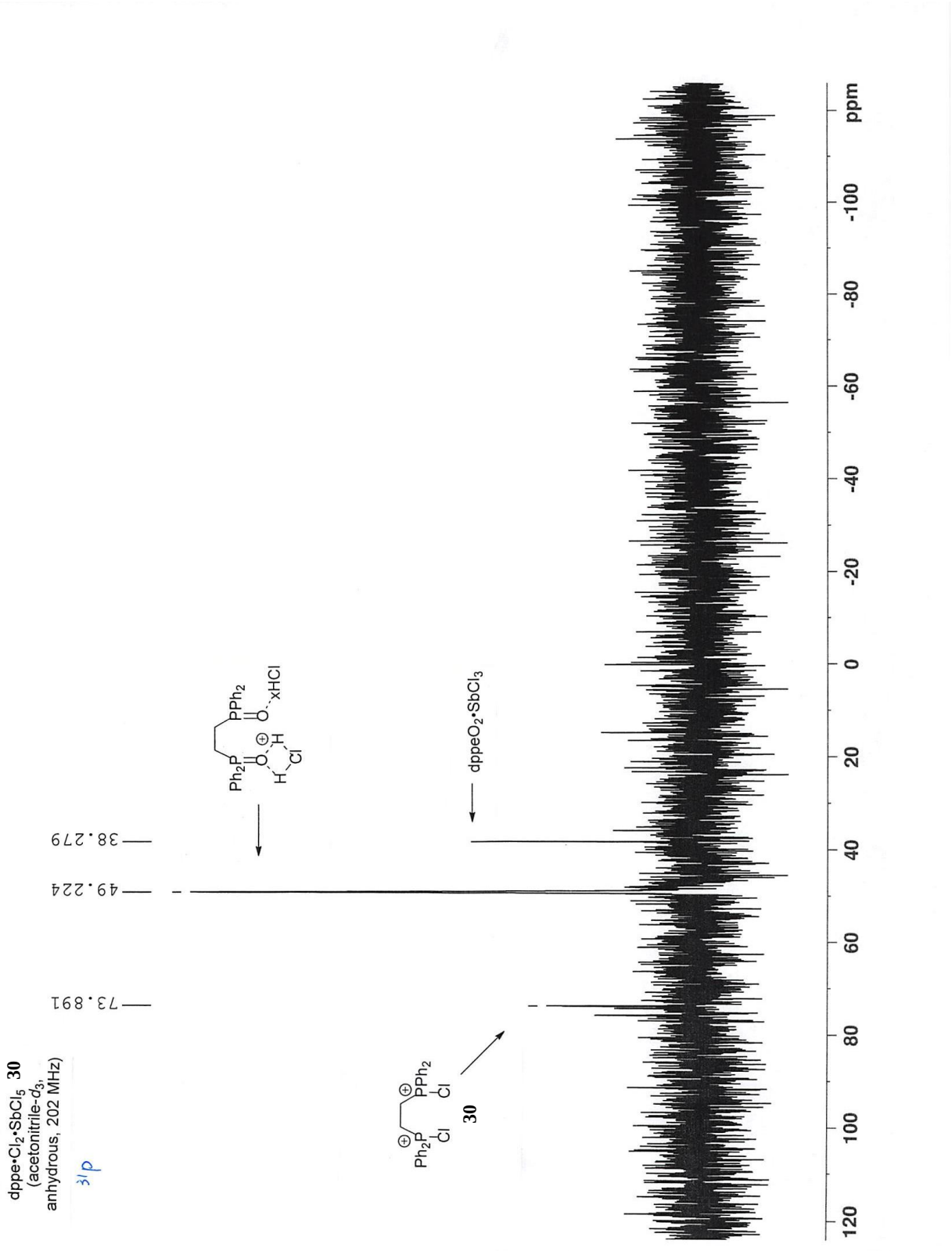
[63] S. Kano, T. Yokomatsu, H. Iwasawa, S. Shibuya, *Heterocycles* **1987**, *26*, 359.

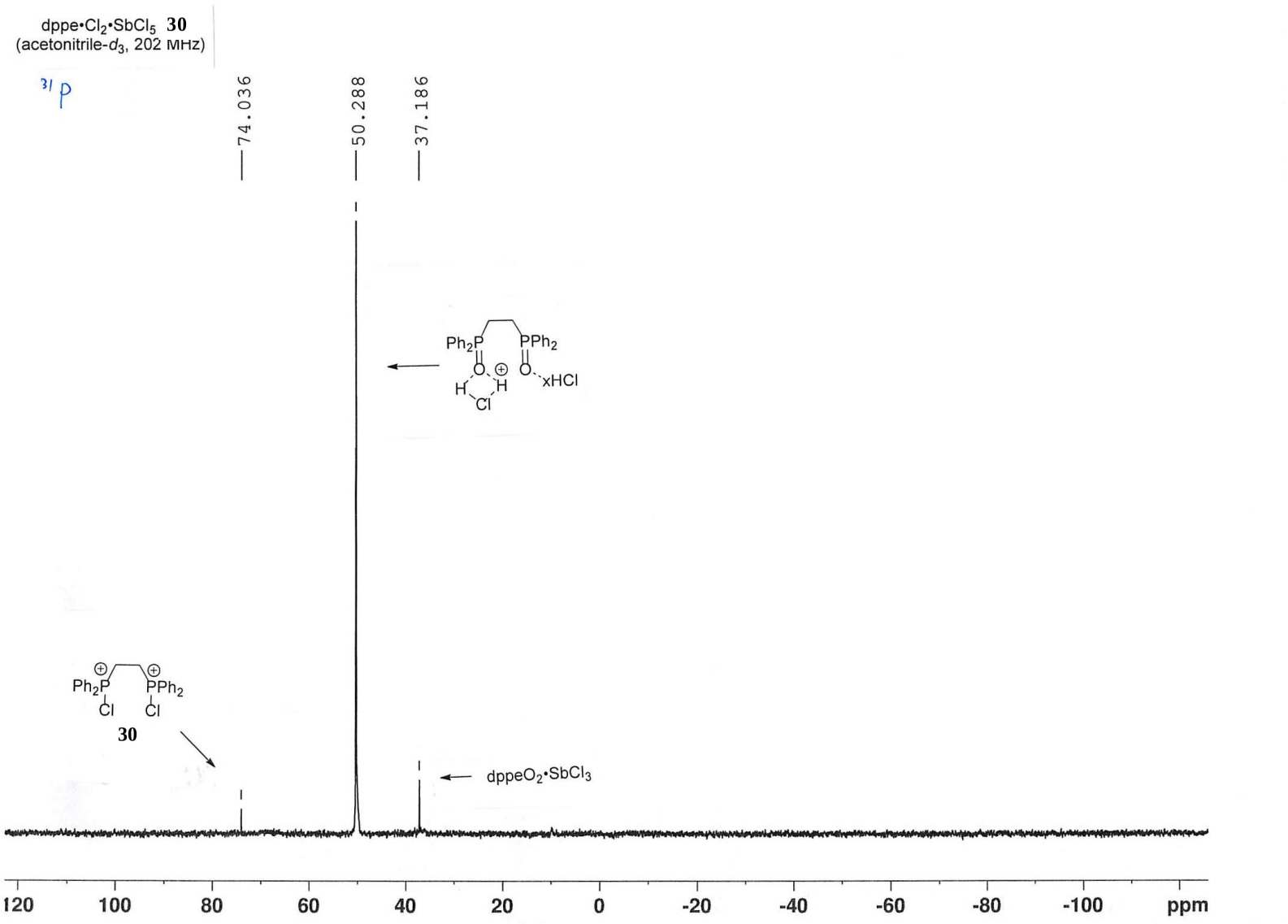
[64] Z. Liu, L. Peng, T. Zhang, Y. Li, *Synth. Commun.* **2001**, *31*, 2549.

[65] F. Liu, B. Vijayakrishnan, A. Faridmoayer, T. A. Taylor, T. B. Parsons, G. J. L. Bernards, M. Kowarik, B. G. Davis, *J. Am. Chem. Soc.* **2014**, *136*, 566.

[66] J. D. Moore, A. M. Harned, J. Henle, D. L. Flynn, P. R. Hanson, *Org. Lett.* **2002**, *4*, 1847.

1.9 NMR Spectra of Selected Intermediates

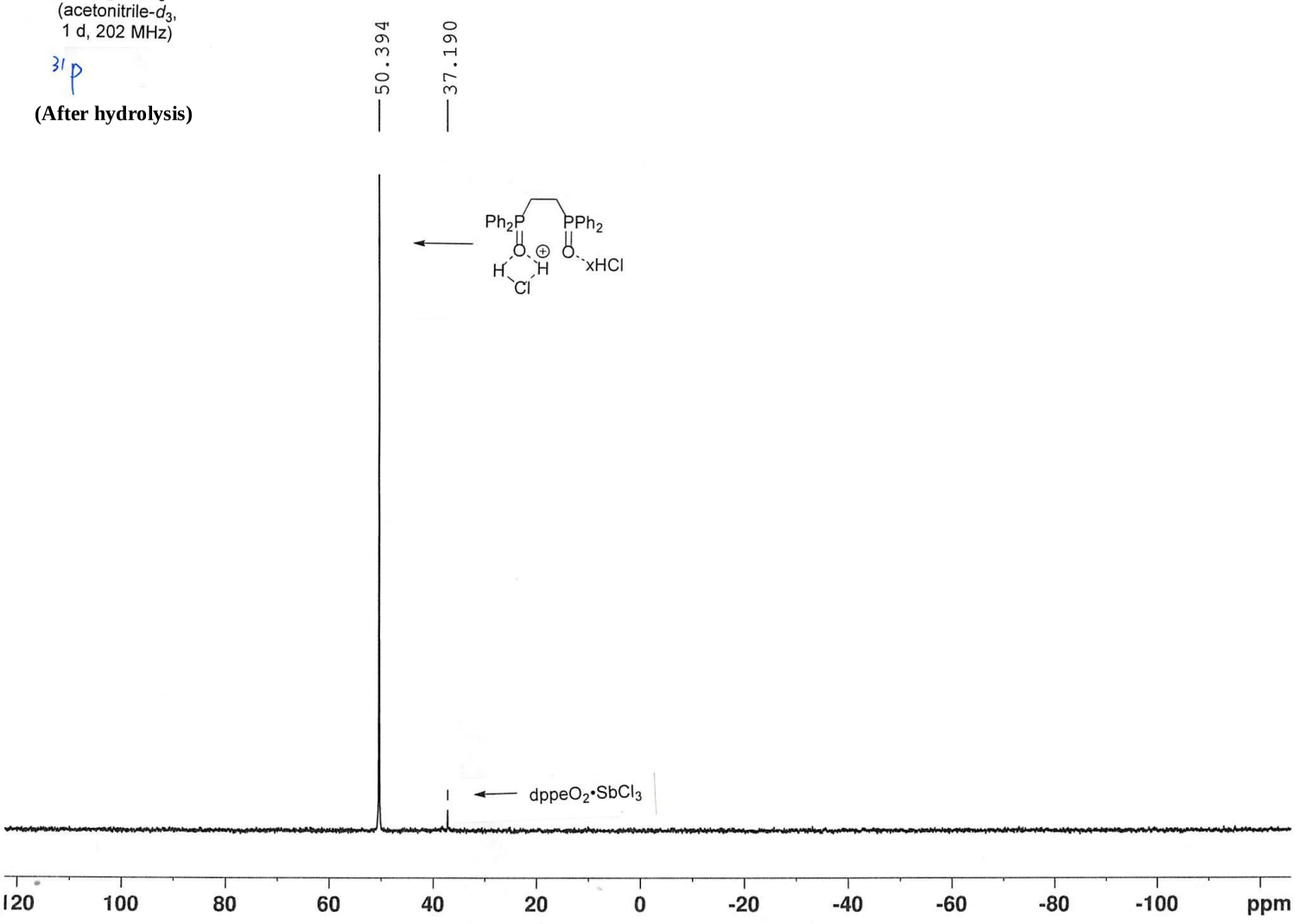



dppe•Cl2•SbCl5 30
(acetonitrile-d3, 202 MHz)
31P
74.036
50.288
37.186
Ph2P
PPh2
O
H
Cl
xHCl
30
dppeO2•SbCl3
120
100
80
60
40
20
0
-20
-40
-60
-80
-100
ppm

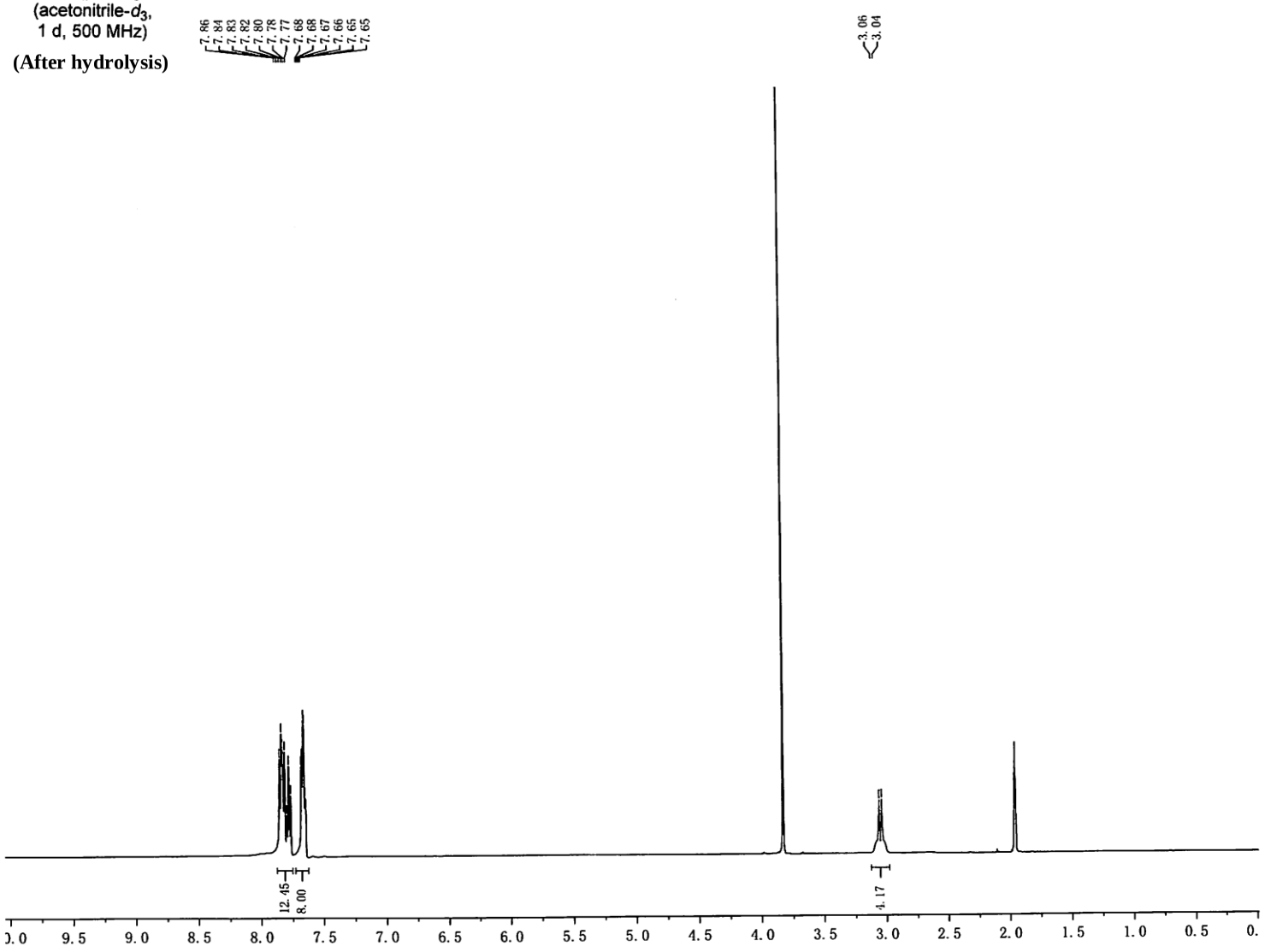
dppe•Cl_2•$SbCl_5$ **30**
(acetonitrile-d_3,
1 d, 202 MHz)

^{31}P

(After hydrolysis)



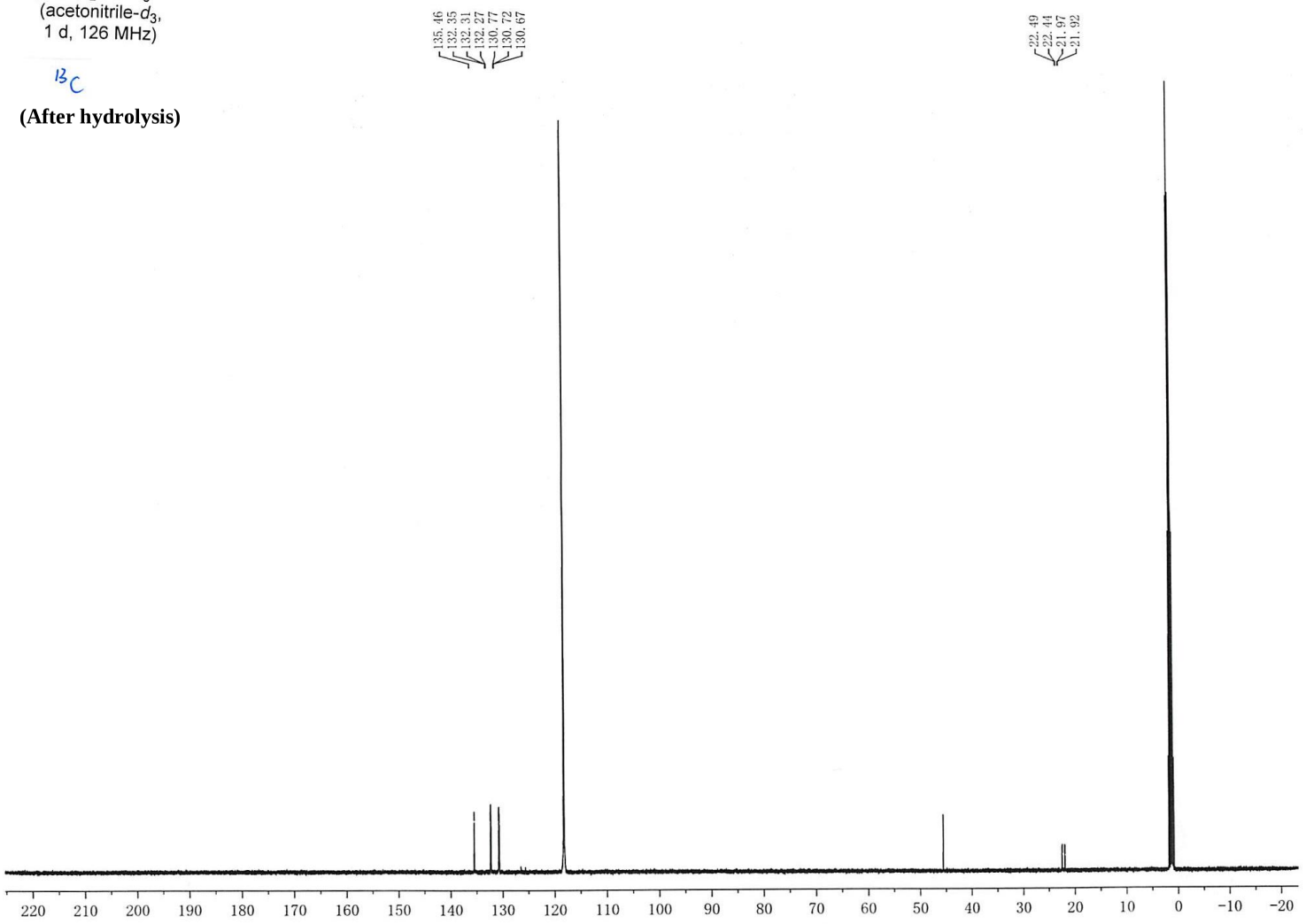
dppe•Cl_2•$SbCl_5$ **30**
(acetonitrile-d_3,
1 d, 500 MHz)
(After hydrolysis)

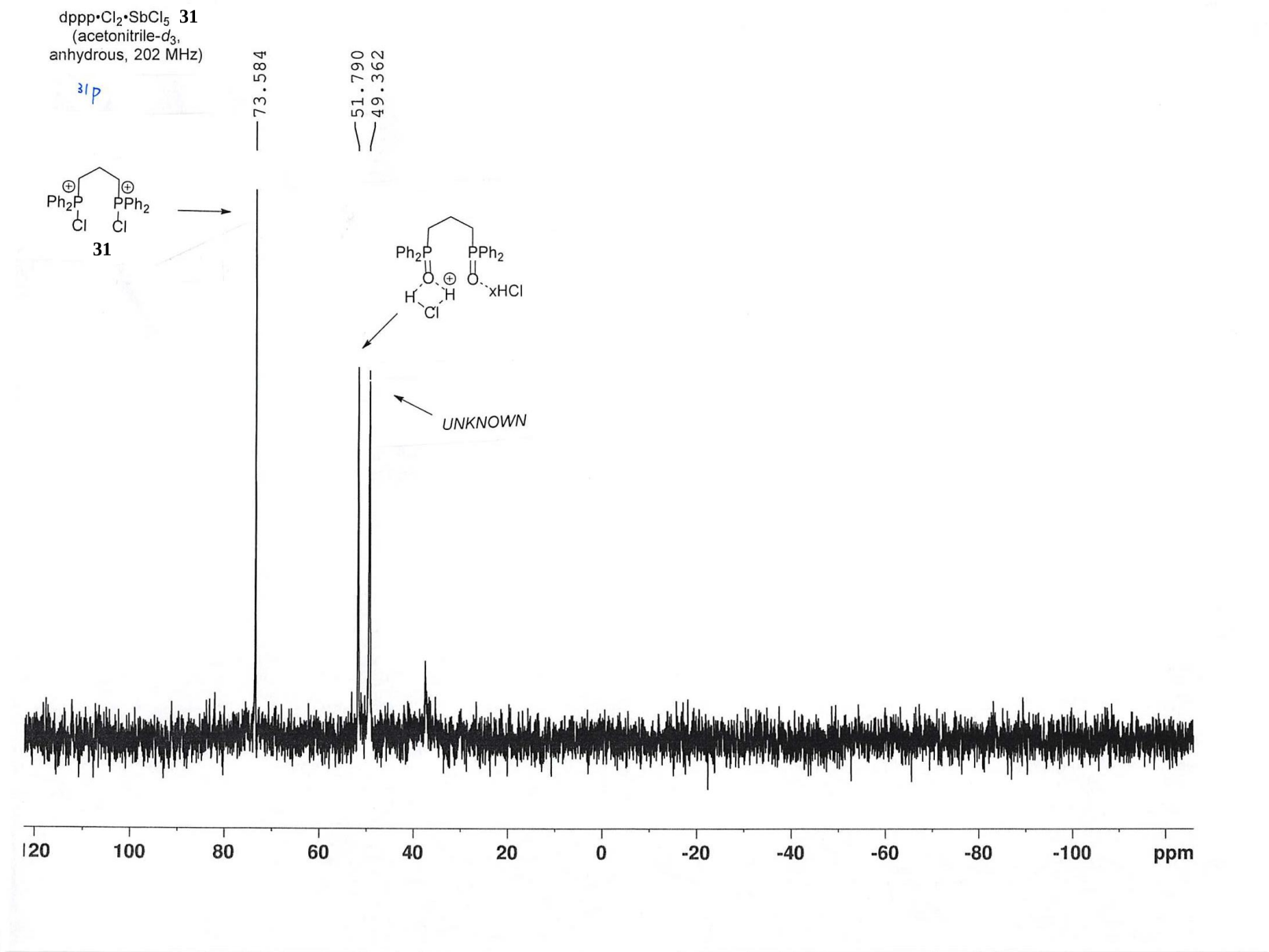


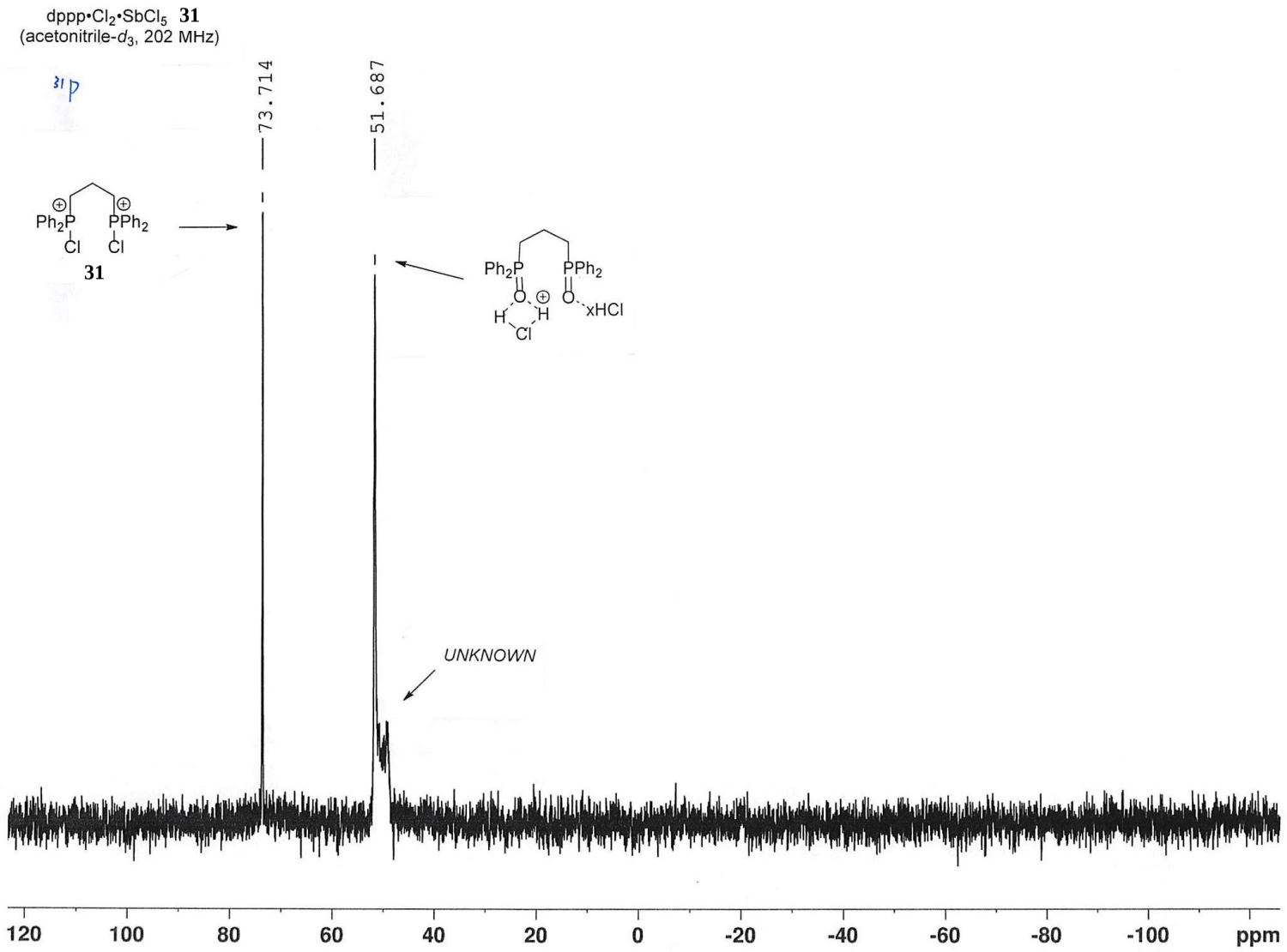
dppe•Cl_2•$SbCl_5$ **30**
(acetonitrile-d_3,
1 d, 126 MHz)

^{13}C

(After hydrolysis)



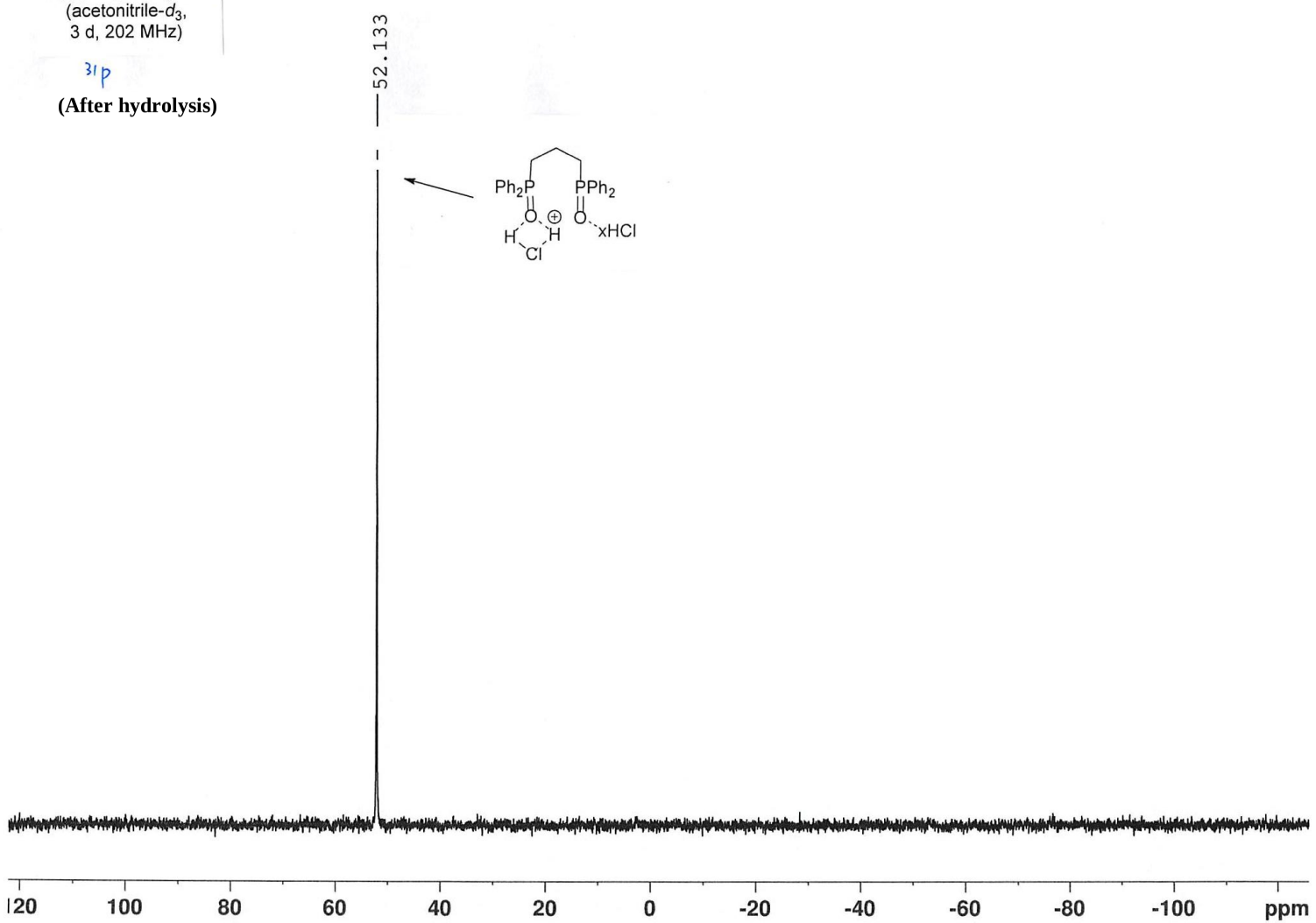

dppp•Cl2•SbCl5 31
(acetonitrile-d3,
anhydrous, 202 MHz)
31P
73.584
51.790
49.362
Ph2P
PPh2
Cl
Cl
31
Ph2P
PPh2
O
O
H
H
Cl
xHCl
UNKNOWN
120
100
80
60
40
20
0
-20
-40
-60
-80
-100
ppm

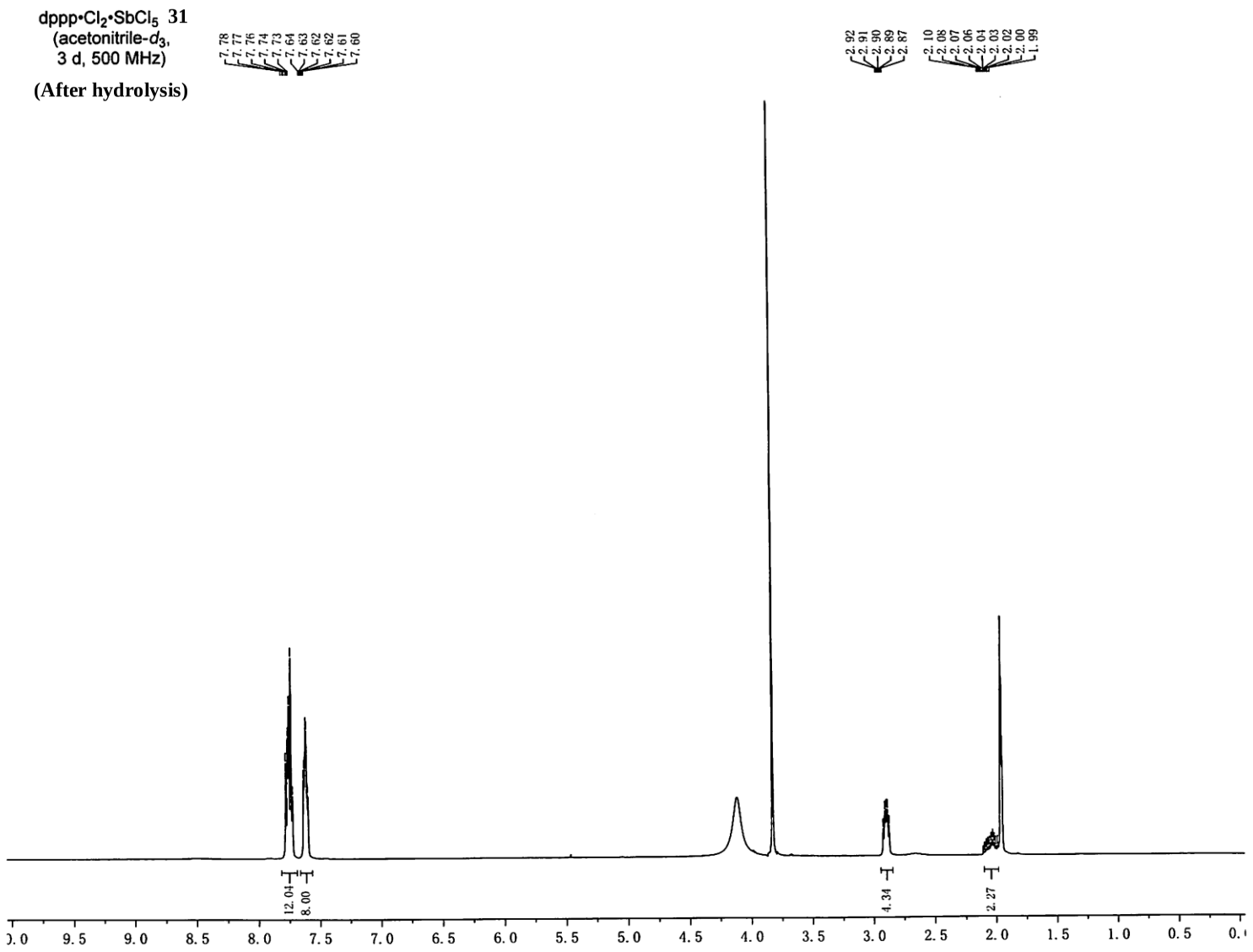

dppp•Cl2•SbCl5 31
(acetonitrile-d3, 202 MHz)
31P
73.714
51.687
Ph2P
PPh2
Cl
Cl
31
Ph2P
PPh2
O
O
H
H
Cl
xHCl
UNKNOWN
120
100
80
60
40
20
0
-20
-40
-60
-80
-100
ppm

dppp•Cl_2•$SbCl_5$ **31**
(acetonitrile-d_3,
3 d, 202 MHz)

^{31}P

(After hydrolysis)

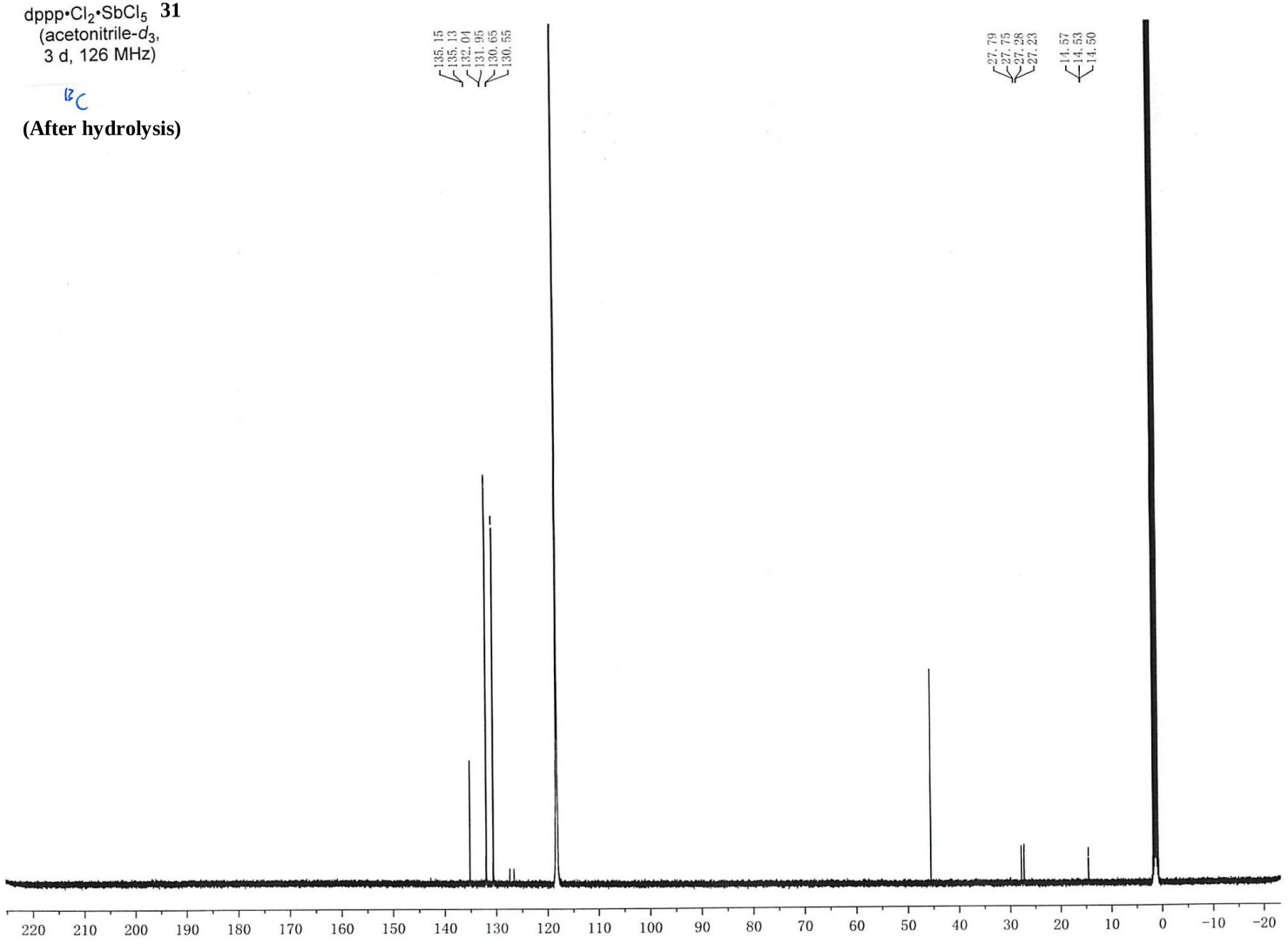


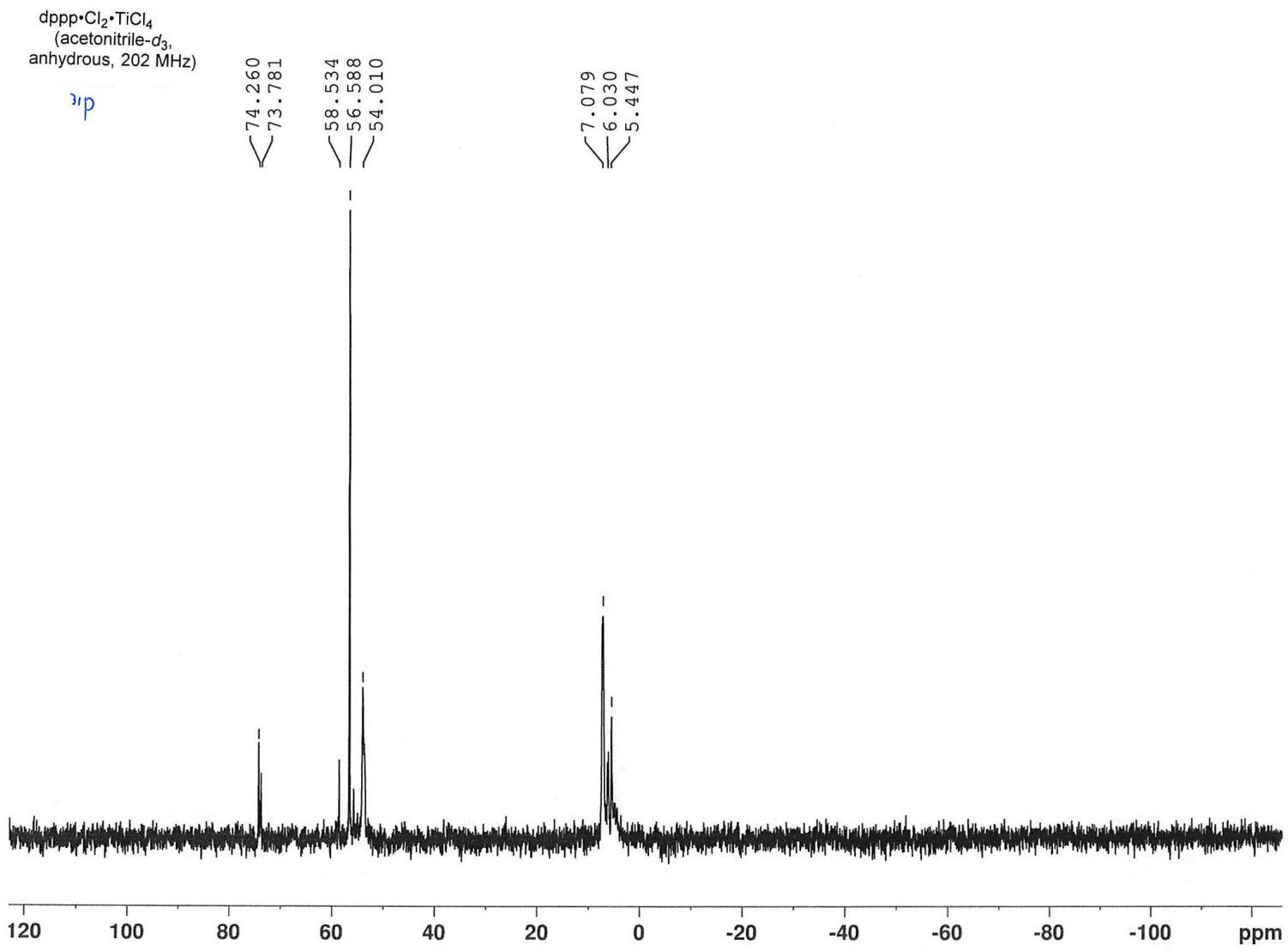

dppp•Cl2•SbCl5 31
(acetonitrile-d3,
3 d, 500 MHz)
(After hydrolysis)
7.78
7.77
7.76
7.74
7.73
7.64
7.63
7.62
7.62
7.61
7.60
2.92
2.91
2.90
2.89
2.87
2.10
2.08
2.07
2.06
2.04
2.03
2.02
2.00
1.99
12.04
8.00
4.34
2.27
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5

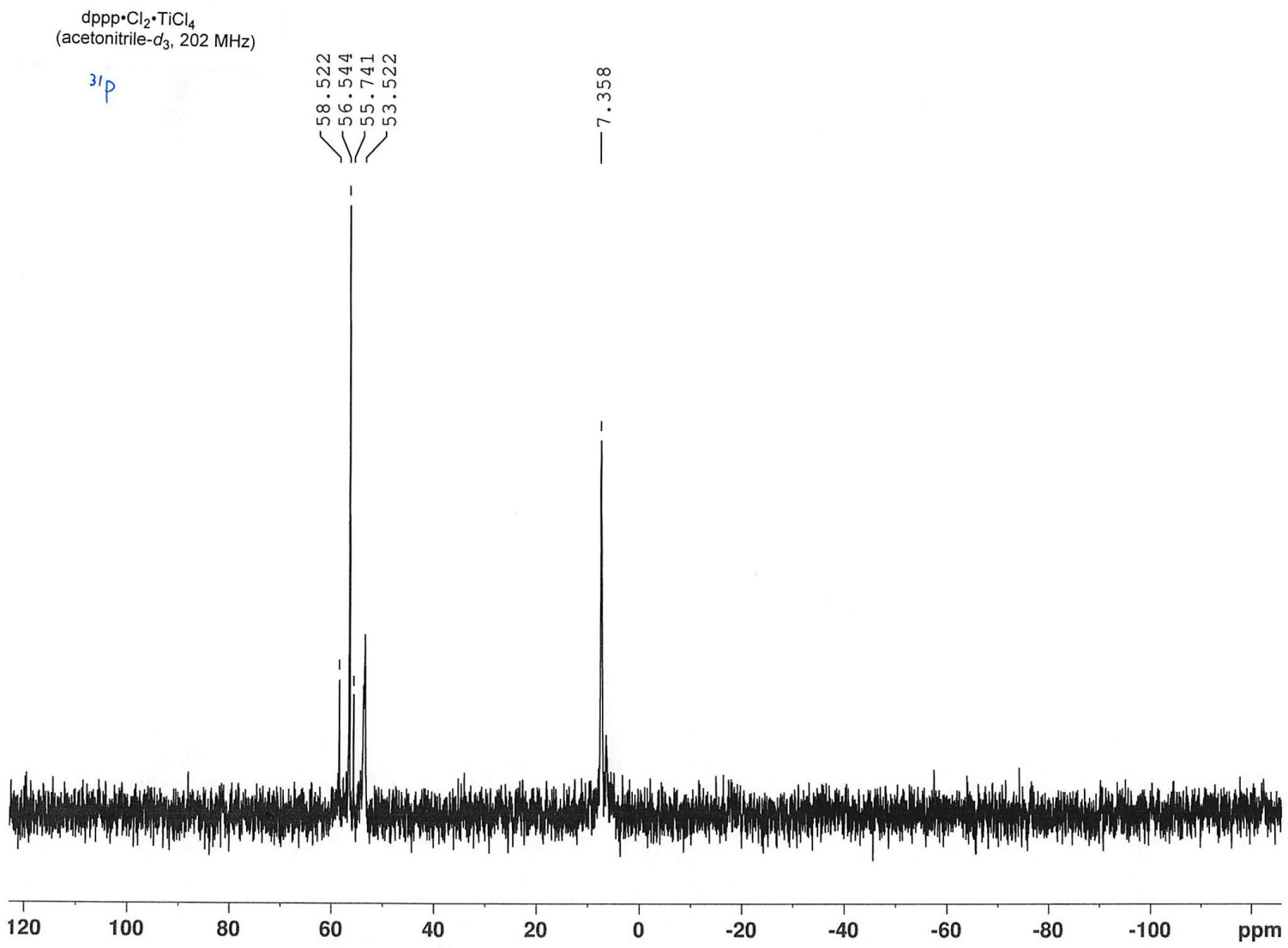
dppp•Cl_2•$SbCl_5$ **31**
(acetonitrile-d_3,
3 d, 126 MHz)

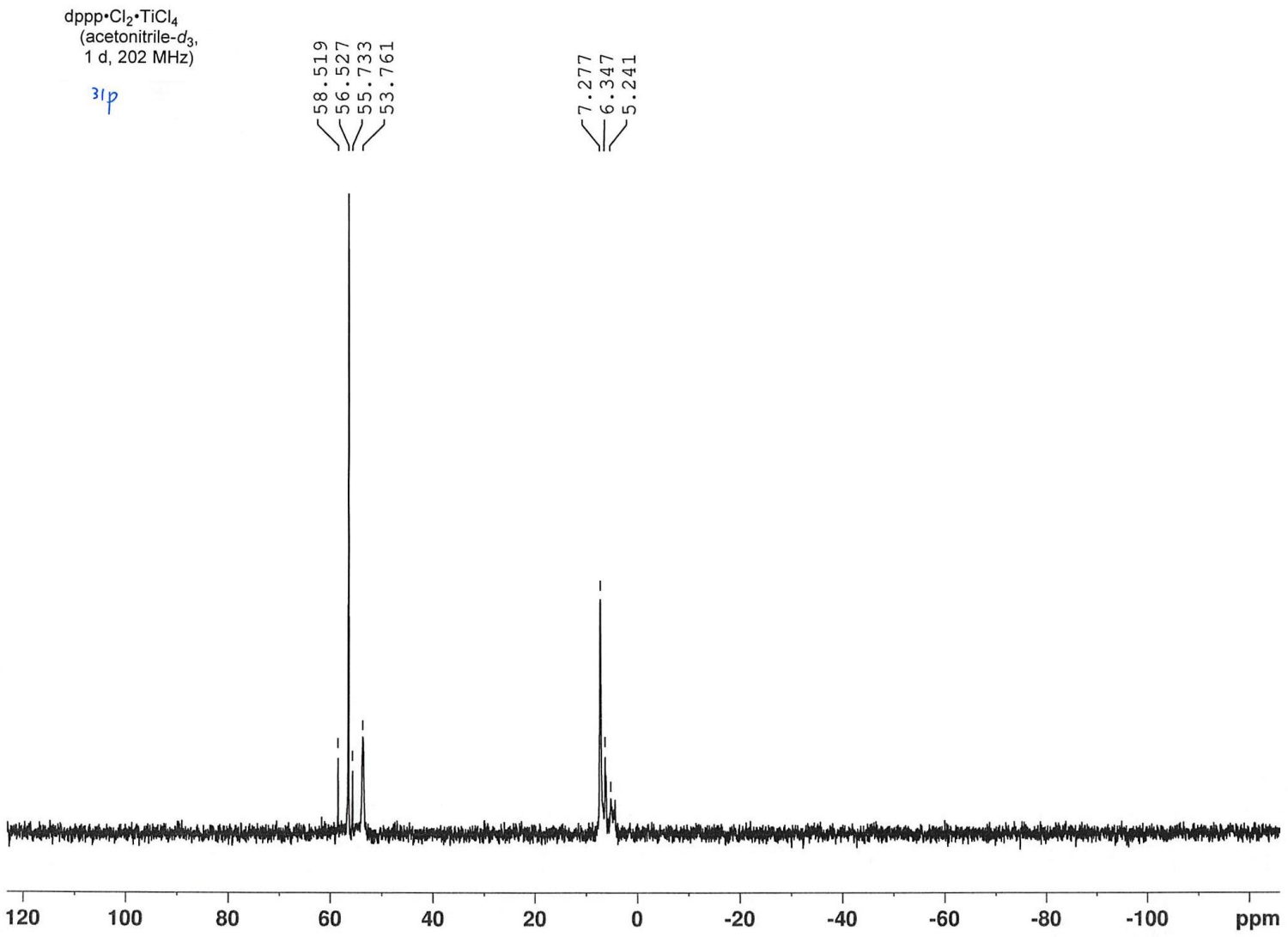
^{13}C

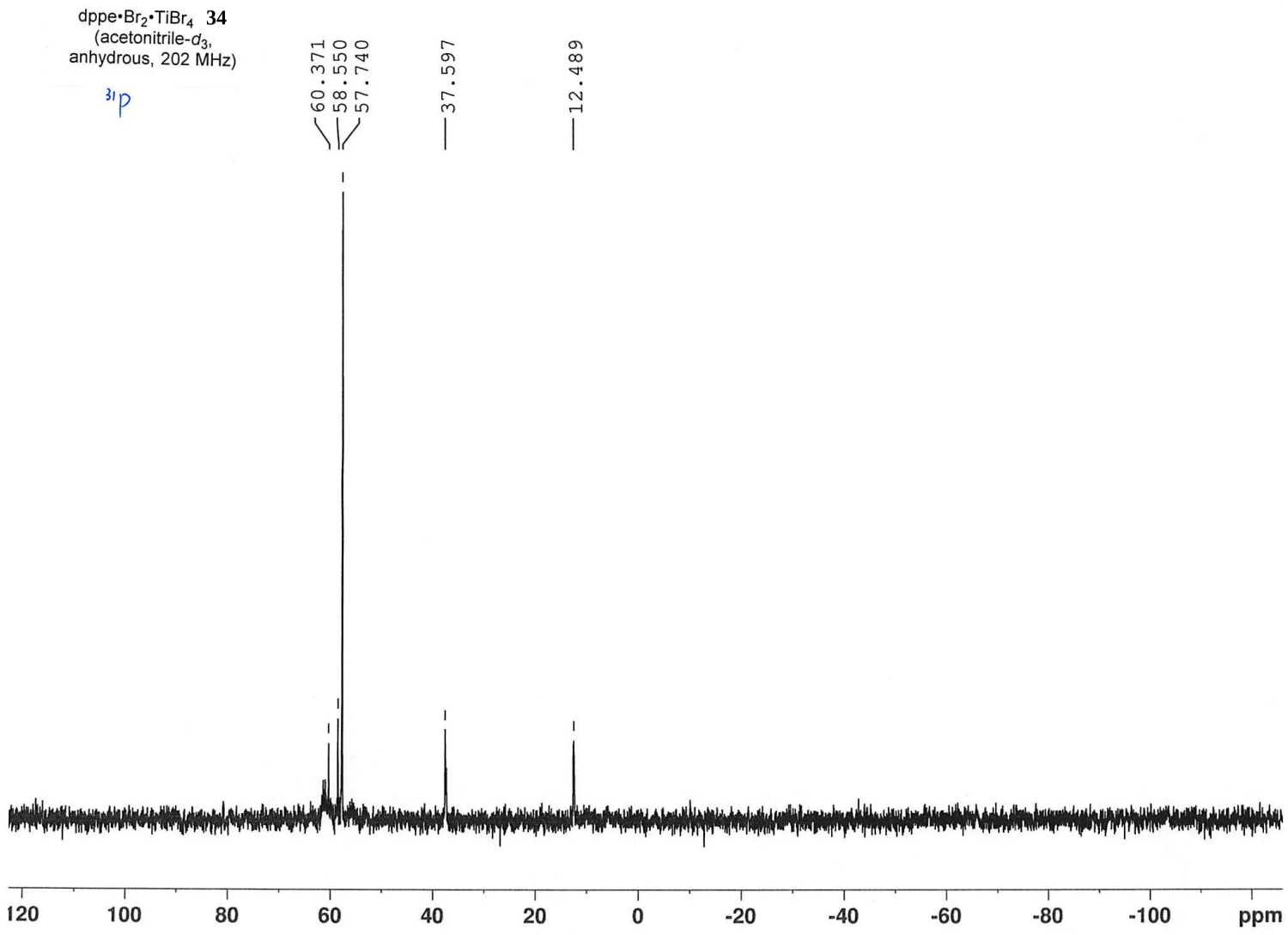
(After hydrolysis)

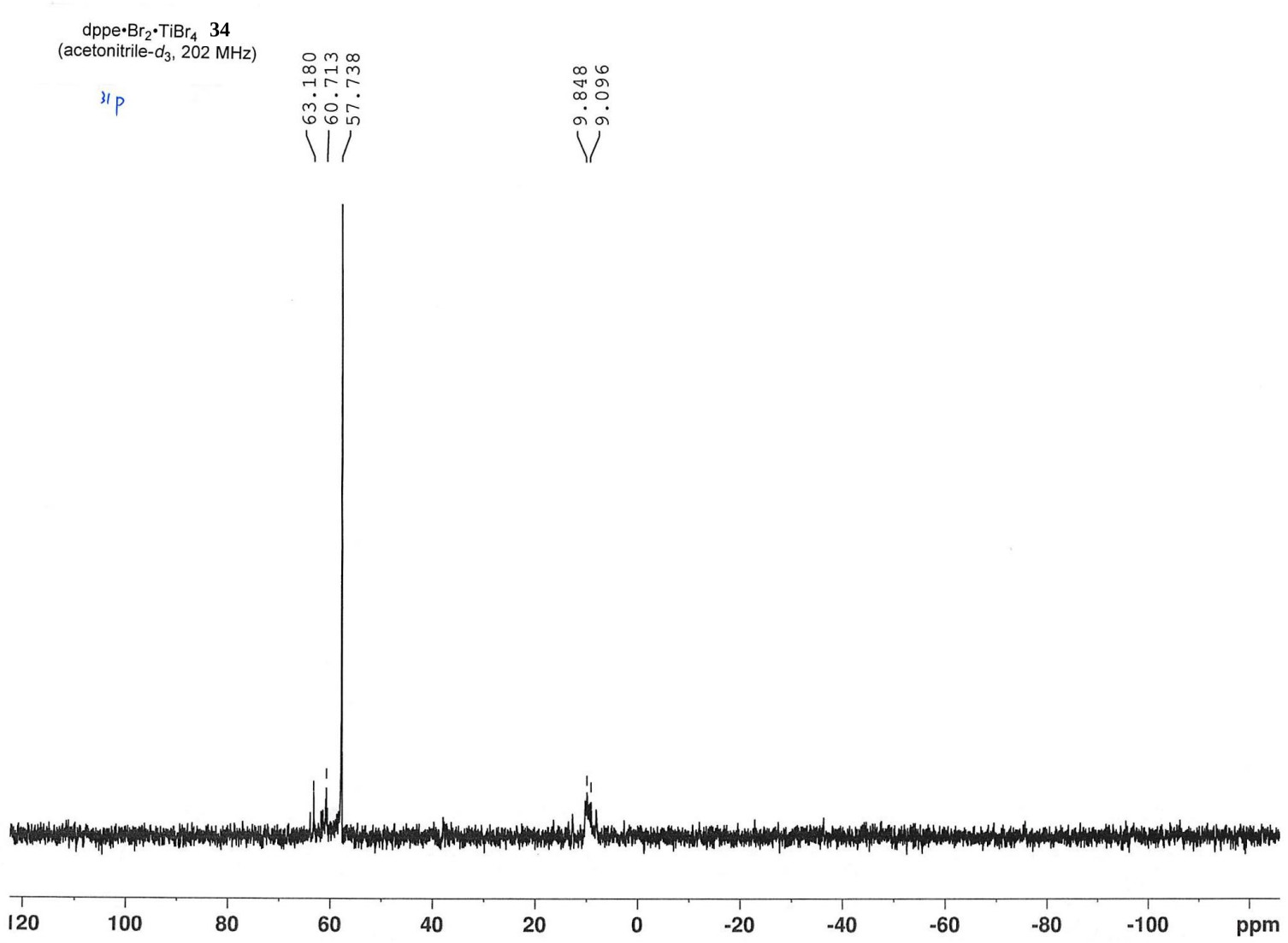


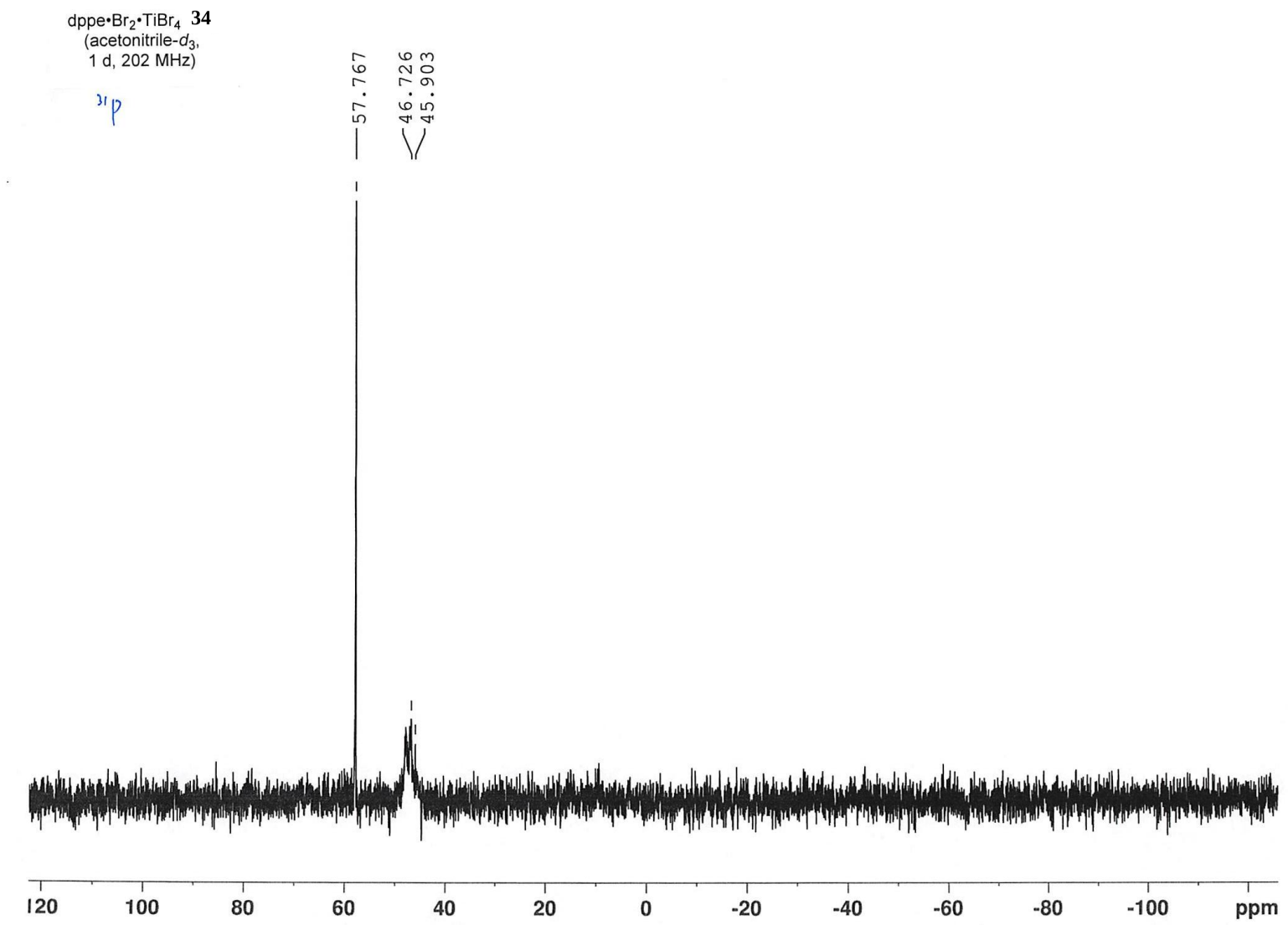

dppp•Cl2•TiCl4
(acetonitrile-d3,
anhydrous, 202 MHz)
31p
74.260
73.781
58.534
56.588
54.010
7.079
6.030
5.447
120
100
80
60
40
20
0
-20
-40
-60
-80
-100
ppm


dppp•Cl2•TiCl4
(acetonitrile-d3, 202 MHz)
31P
58.522
56.544
55.741
53.522
7.358
120
100
80
60
40
20
0
-20
-40
-60
-80
-100
ppm

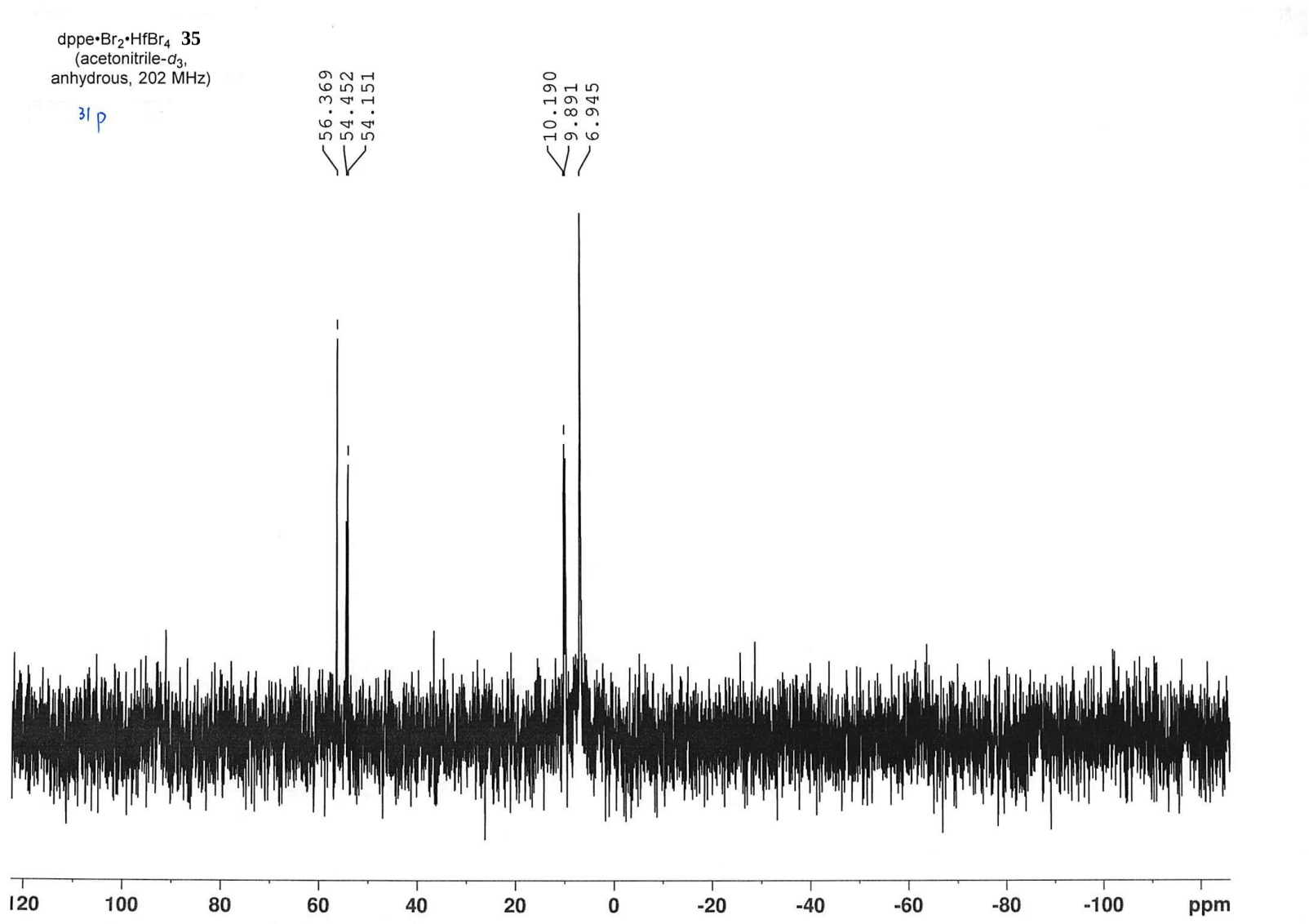

dppp•Cl2•TiCl4
(acetonitrile-d3,
1 d, 202 MHz)
31P
58.519
56.527
55.733
53.761
7.277
6.347
5.241
120
100
80
60
40
20
0
-20
-40
-60
-80
-100
ppm

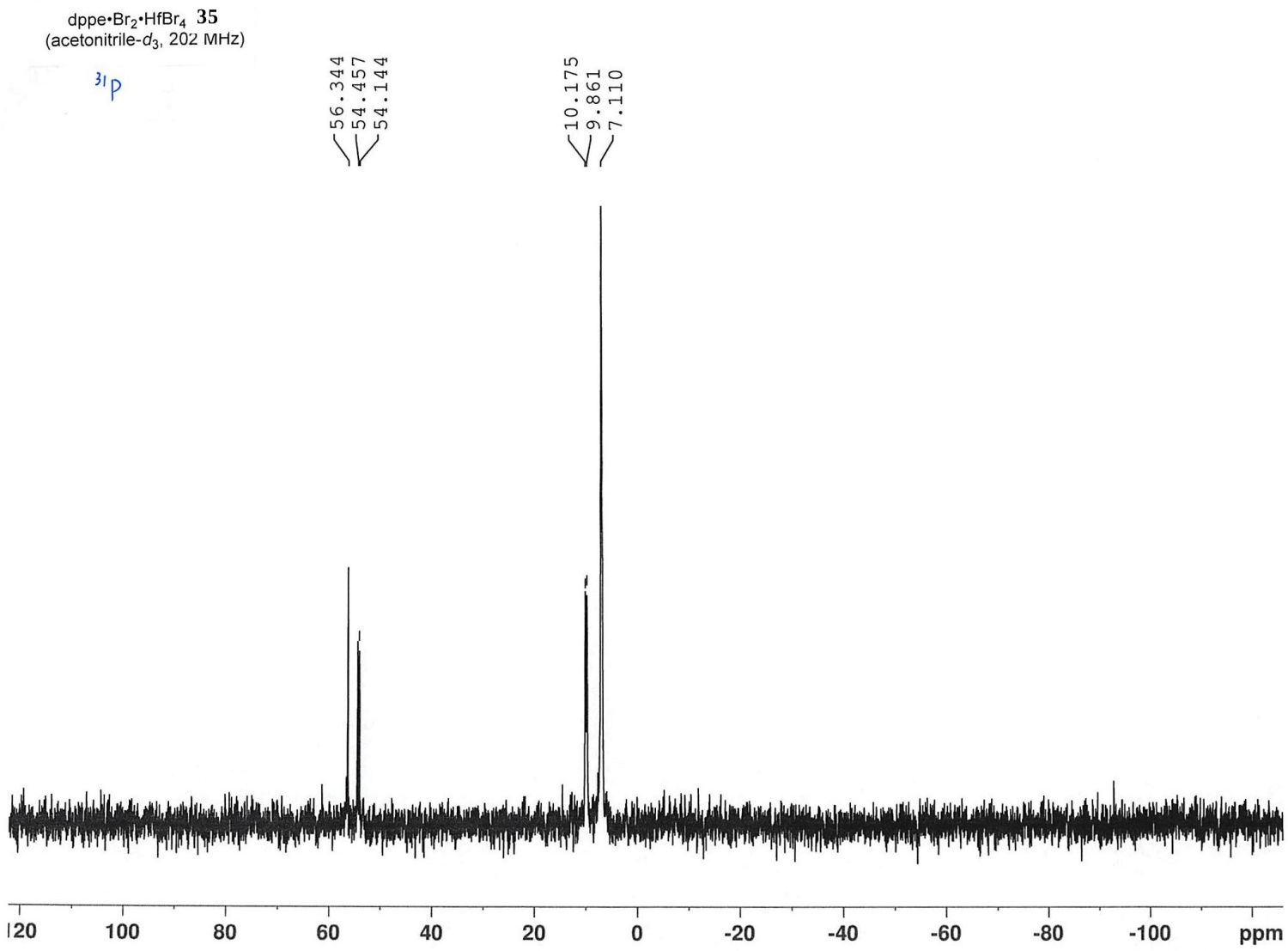

dppe•Br2•TiBr4 34
(acetonitrile-d3,
anhydrous, 202 MHz)
31P
60.371
58.550
57.740
37.597
12.489
120
100
80
60
40
20
0
-20
-40
-60
-80
-100
ppm

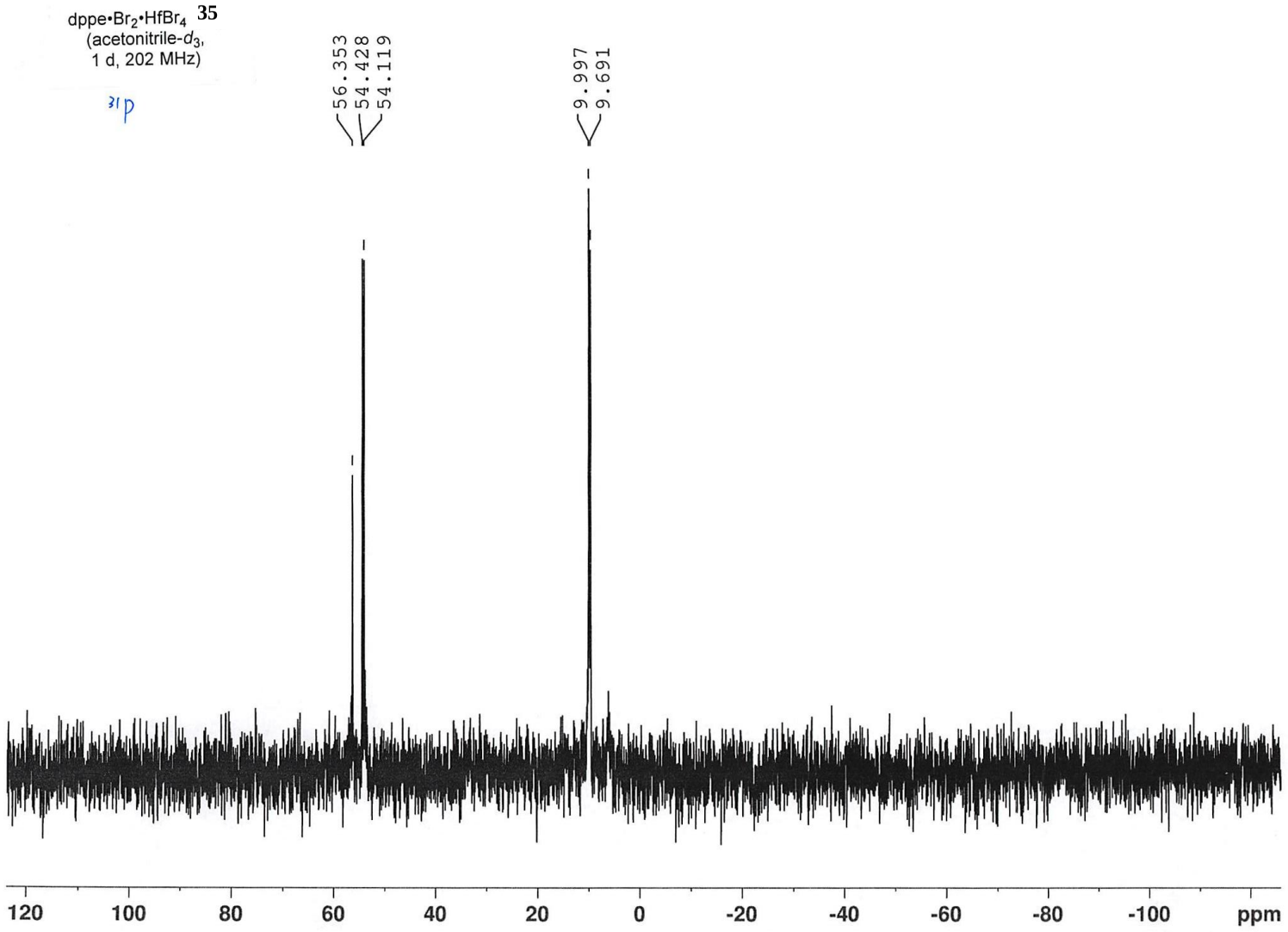

dppe•Br2•TiBr4 34
(acetonitrile-d3, 202 MHz)
31P
63.180
60.713
57.738
9.848
9.096
120
100
80
60
40
20
0
-20
-40
-60
-80
-100
ppm


dppe•Br2•TiBr4 34
(acetonitrile-d3,
1 d, 202 MHz)
31P
57.767
46.726
45.903
120
100
80
60
40
20
0
-20
-40
-60
-80
-100
ppm

dppe•Br2•TiBr4 34
(acetonitrile-d3, 500 MHz)
8.063
8.048
8.038
8.022
7.902
7.886
7.762
7.747
7.733
7.668
7.661
7.653
7.646
3.245
3.221
20.18
4.00
ppm

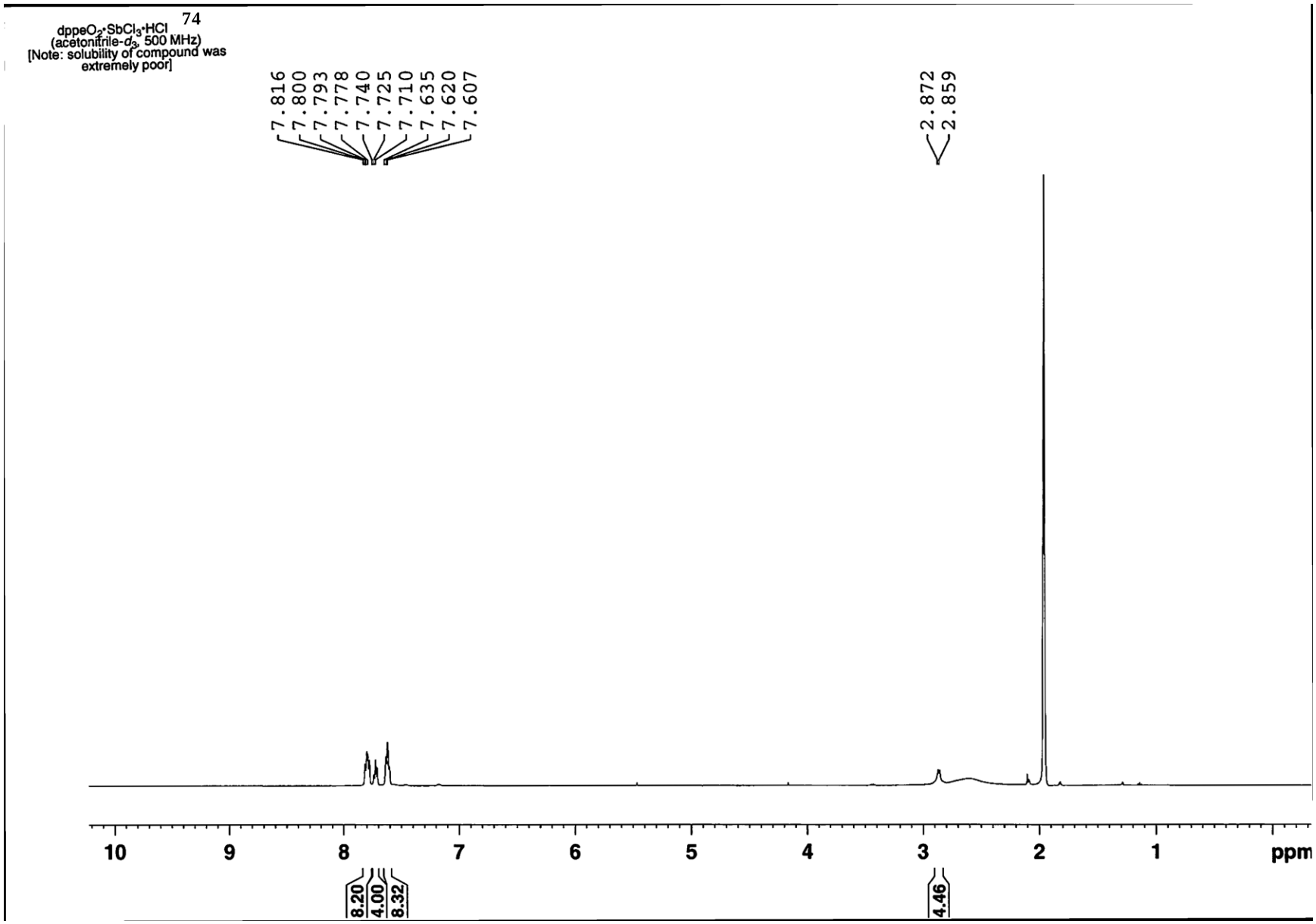

dppe•Br2•HfBr4 35
(acetonitrile-d3,
anhydrous, 202 MHz)
31 P
56.369
54.452
54.151
10.190
9.891
6.945
120
100
80
60
40
20
0
-20
-40
-60
-80
-100
ppm

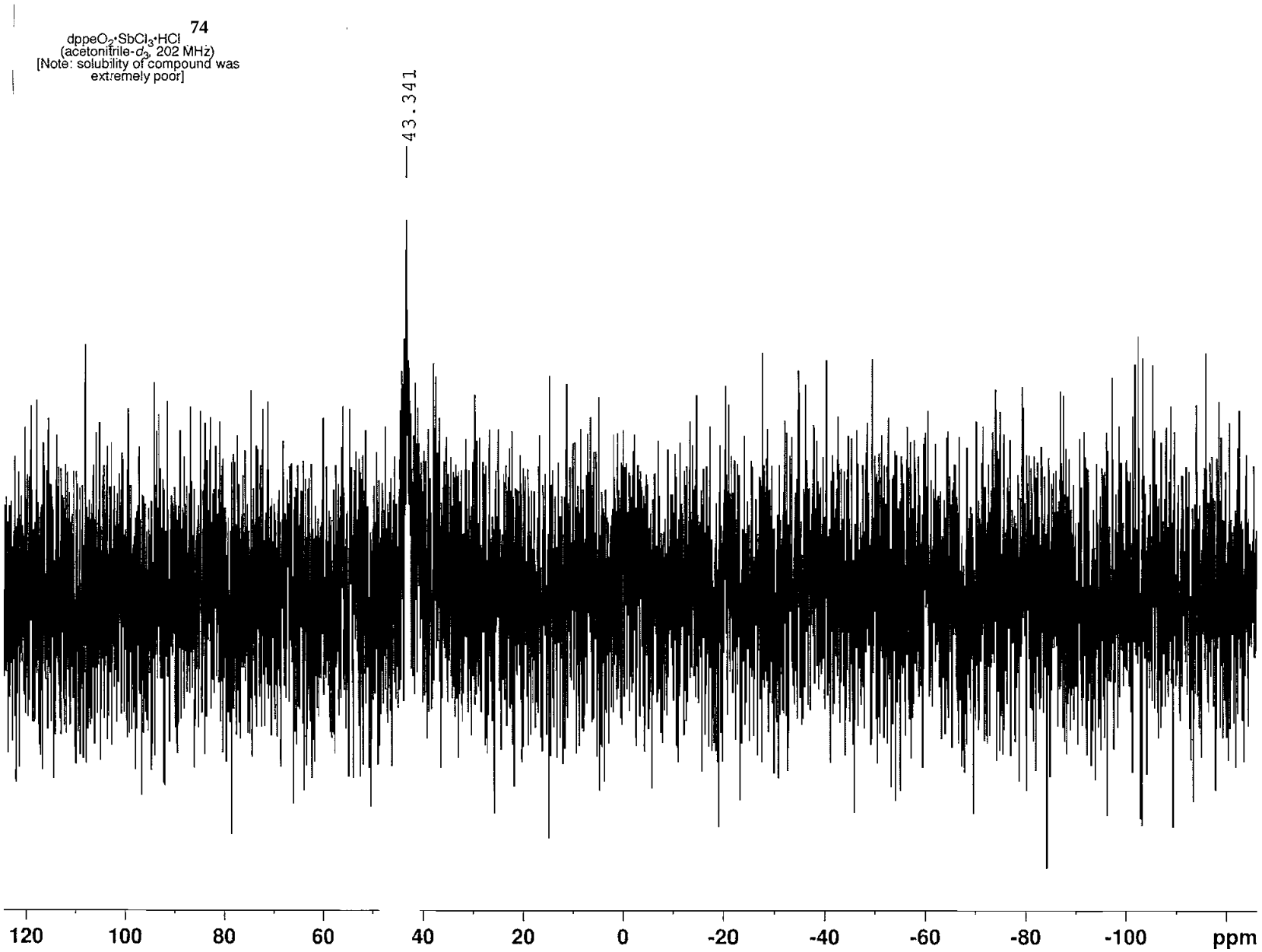

dppe•Br2•HfBr4 35
(acetonitrile-d3, 202 MHz)
31P
56.344
54.457
54.144
10.175
9.861
7.110
120
100
80
60
40
20
0
-20
-40
-60
-80
-100
ppm

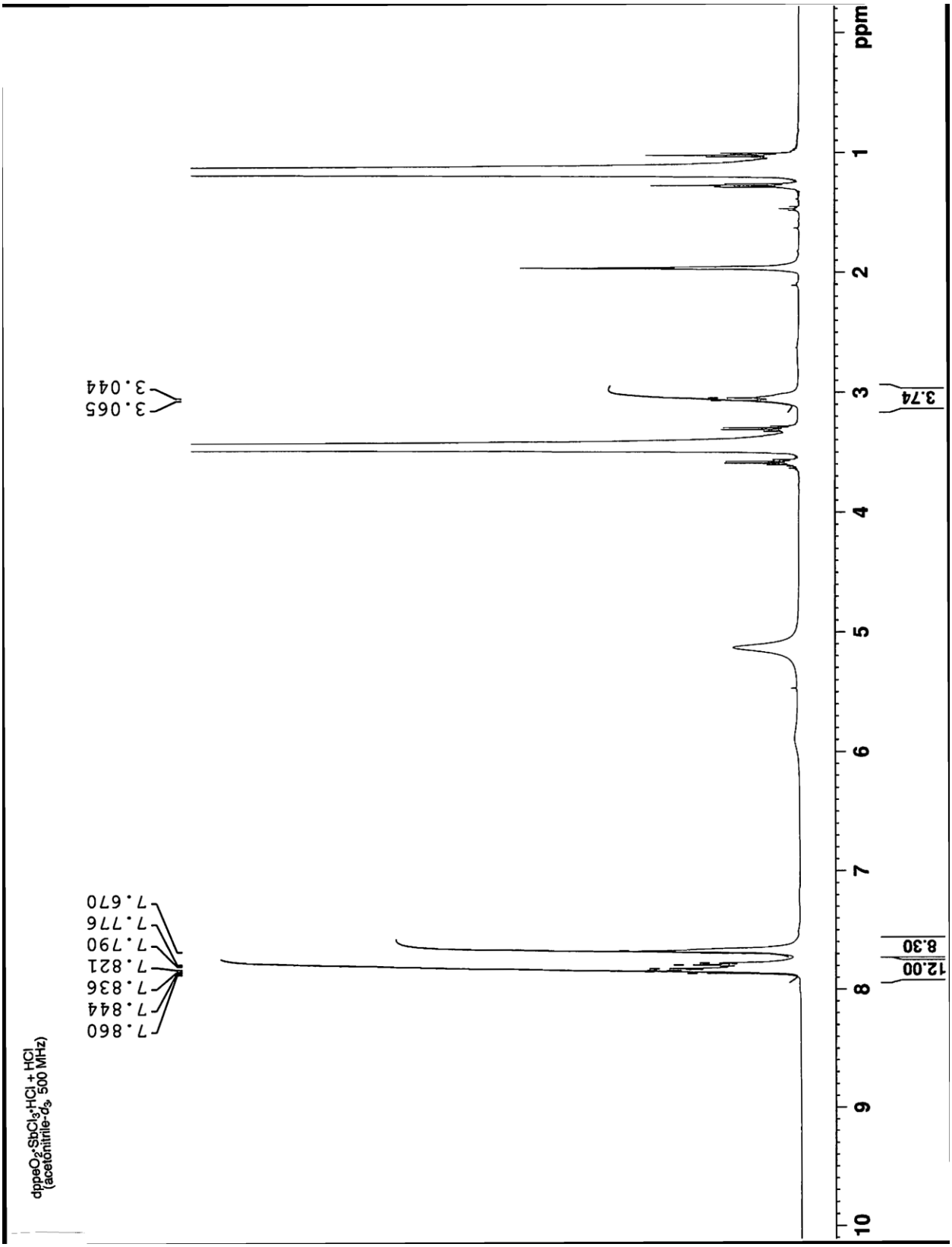

dppe•Br2•HfBr4 35
(acetonitrile-d3,
1 d, 202 MHz)
31P
56.353
54.428
54.119
9.997
9.691
120
100
80
60
40
20
0
-20
-40
-60
-80
-100
ppm

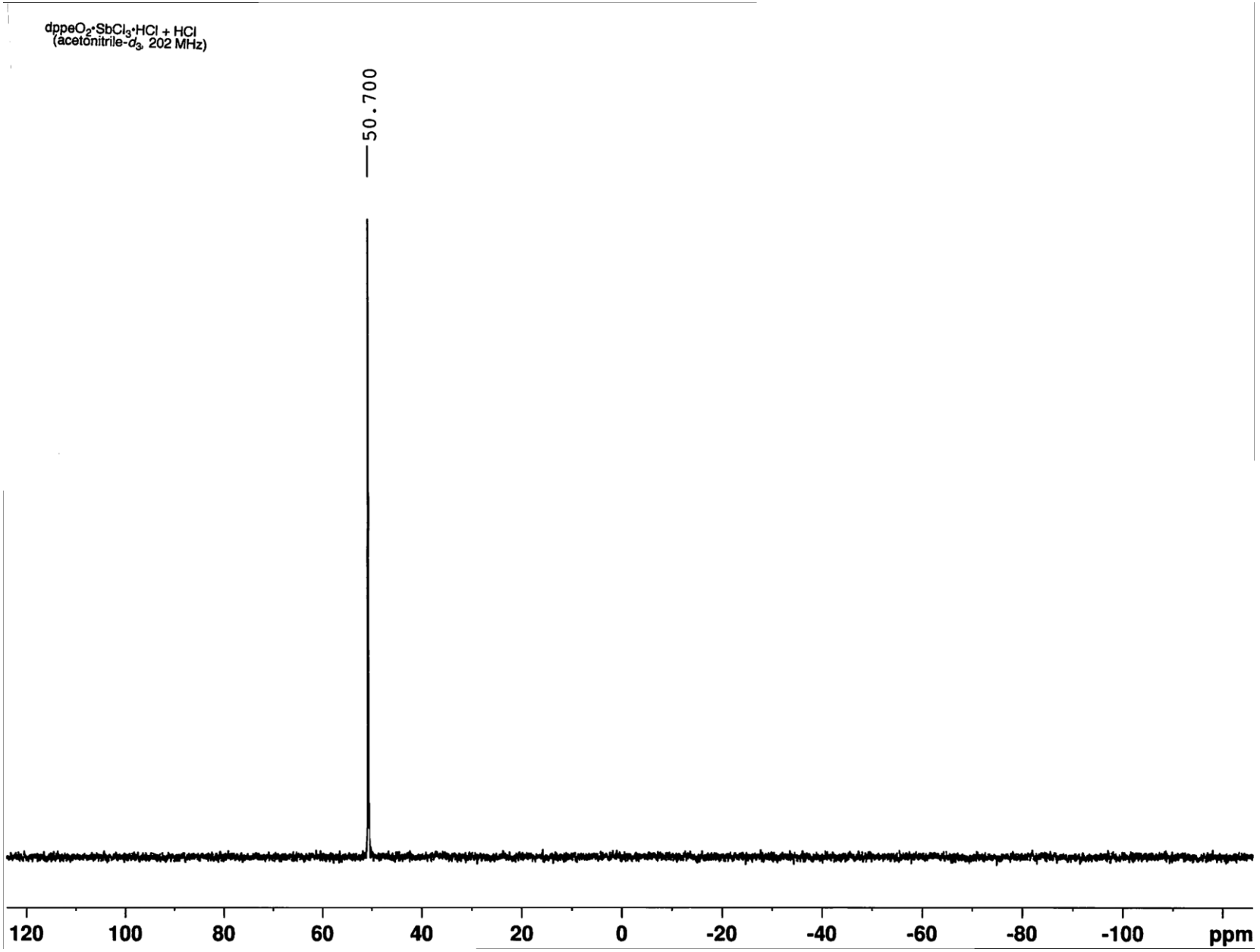
74

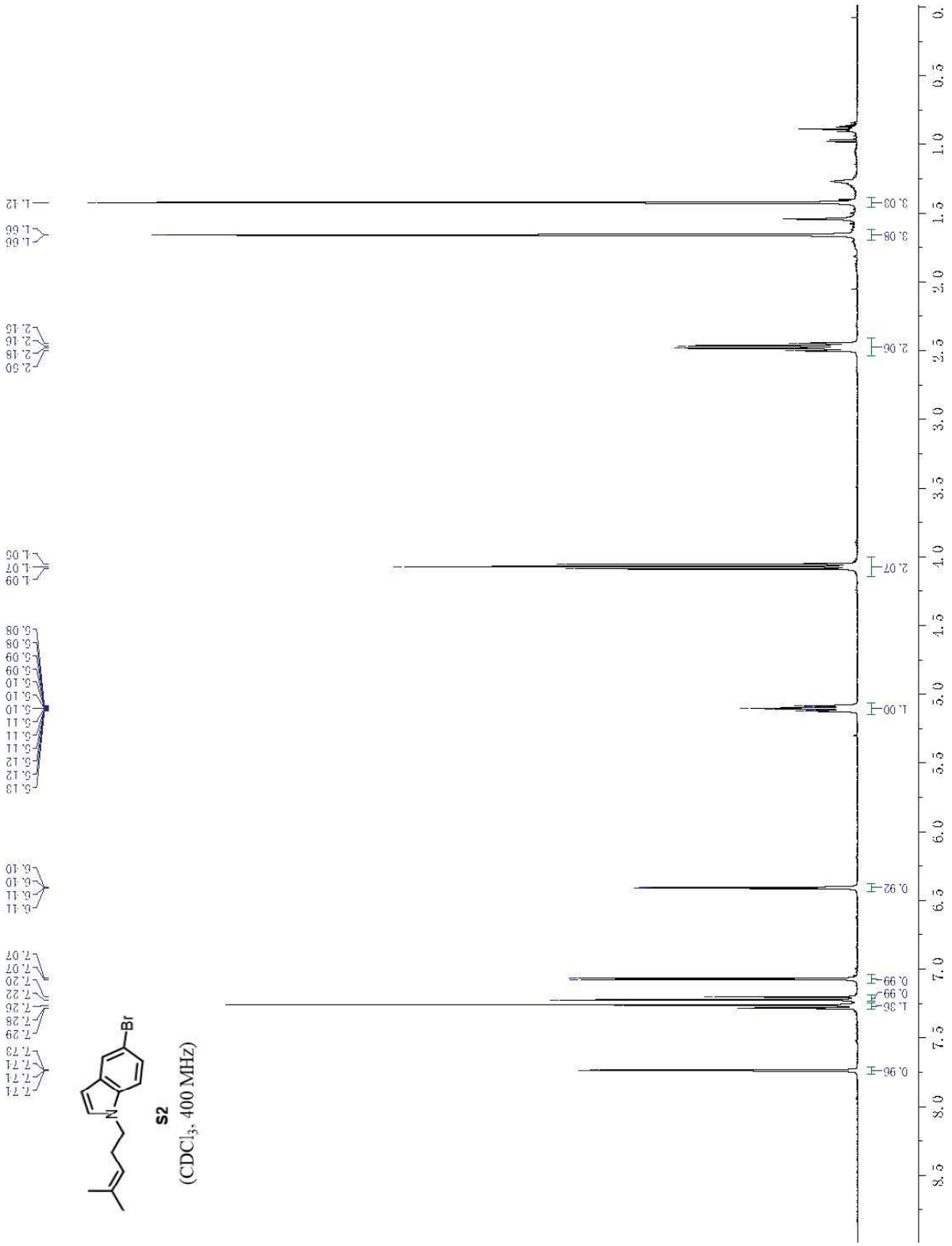
dppeO$_2$·SbCl$_3$·HCl
(acetonitrile-d_3, 500 MHz)
[Note: solubility of compound was extremely poor]

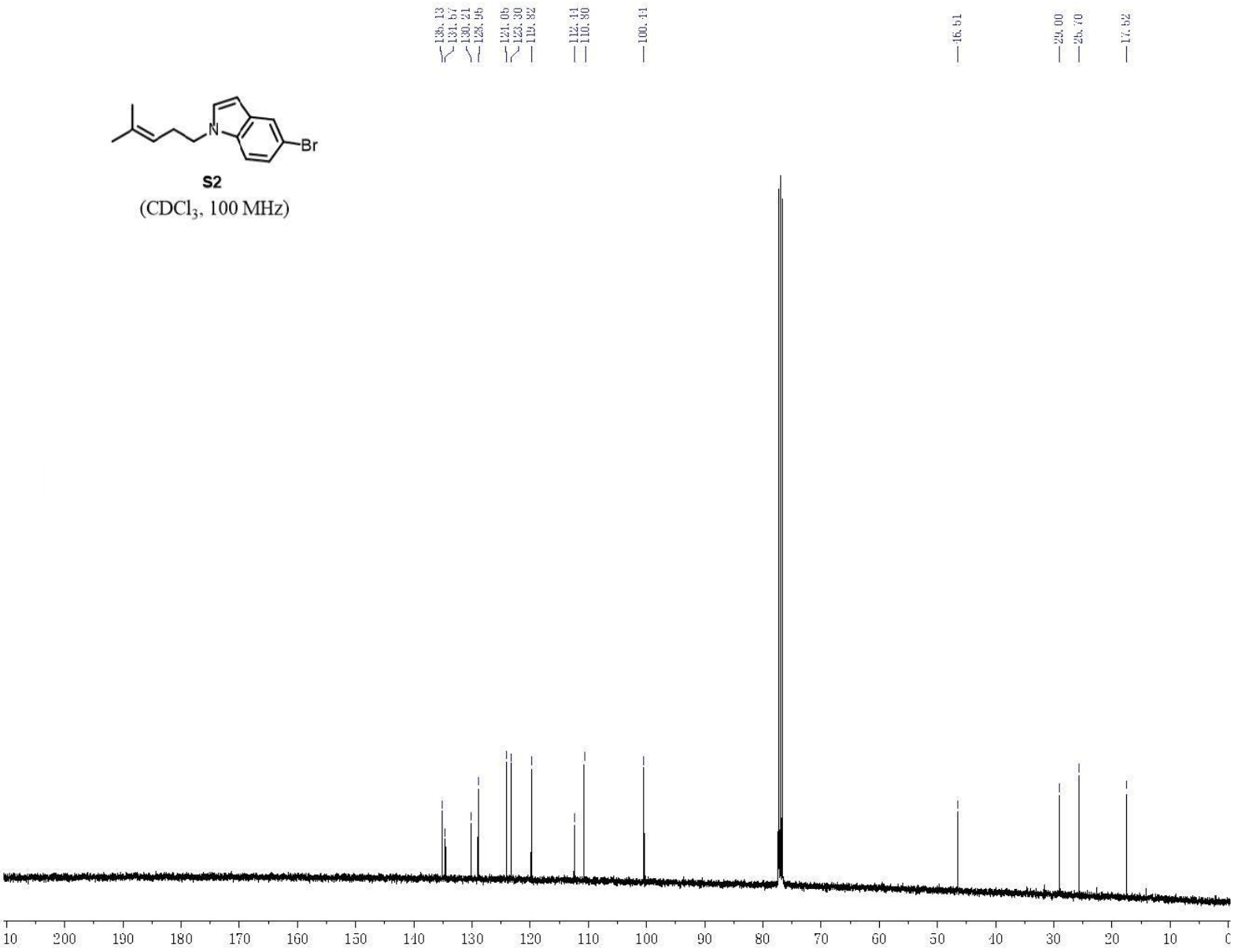


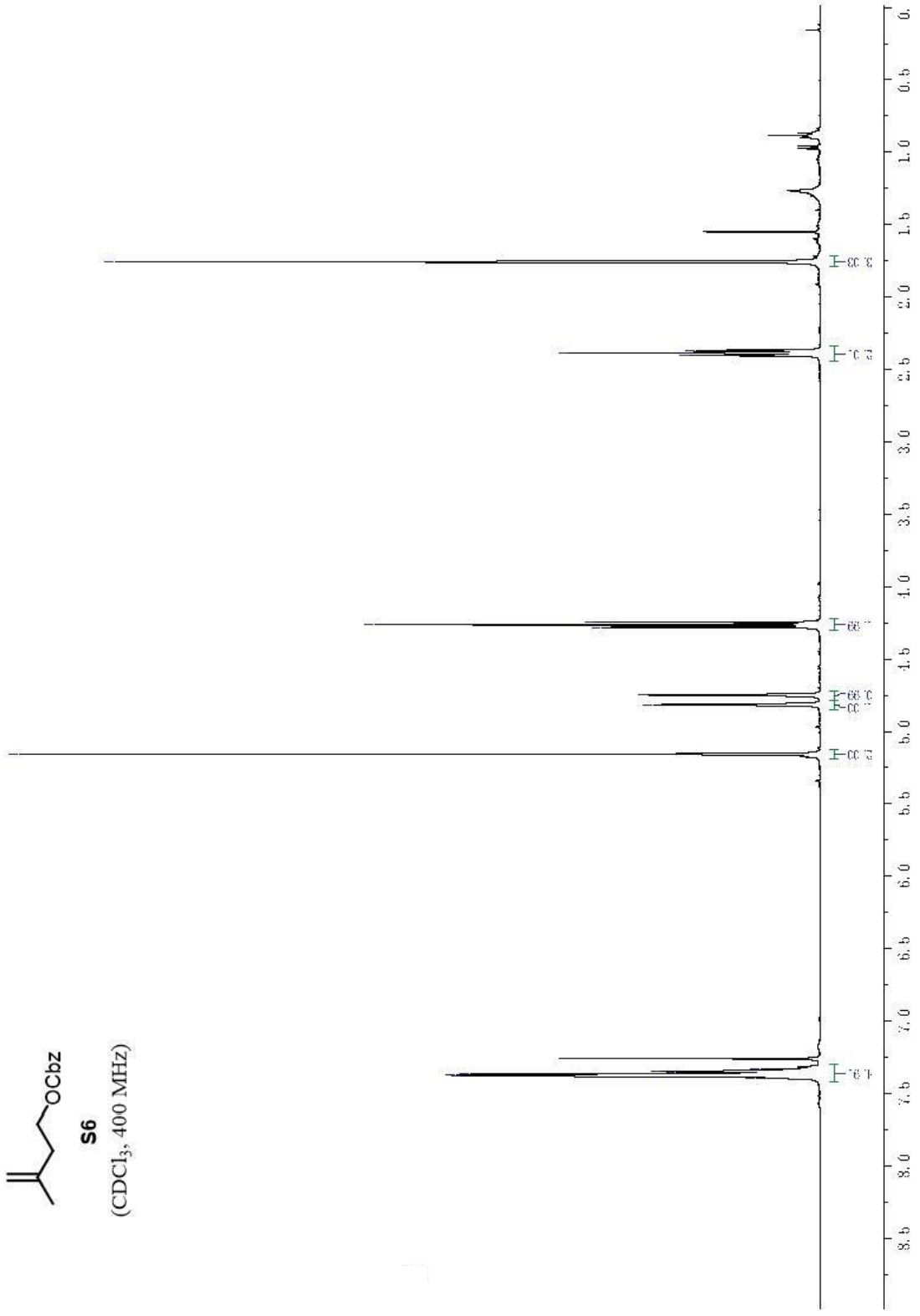

74
dppeO2•SbCl3•HCl
(acetonitrile-d3, 202 MHz)
[Note: solubility of compound was extremely poor]
43.341
120
100
80
60
40
20
0
-20
-40
-60
-80
-100
ppm


dppeO2•SbCl3•HCl + HCl
(acetonitrile-d3, 500 MHz)
7.860
7.844
7.836
7.821
7.790
7.776
7.670
3.065
3.044
ppm
1
2
3
4
5
6
7
8
9
10
3.74
12.00
8.30


dppeO2•SbCl3•HCl + HCl
(acetonitrile-d3, 202 MHz)
50.700
120
100
80
60
40
20
0
-20
-40
-60
-80
-100
ppm

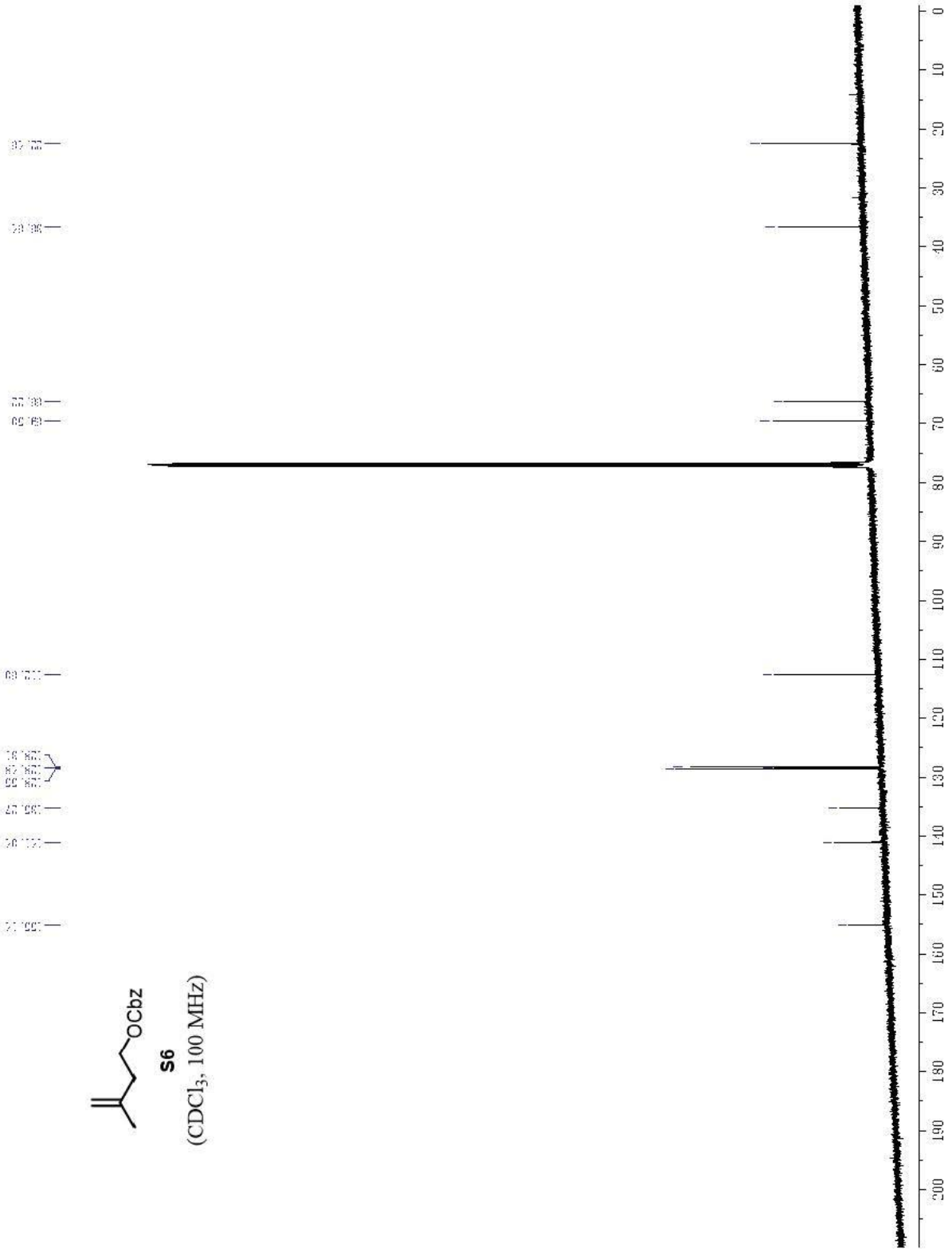

Br
N
S2
(CDCl3, 400 MHz)


138.13
131.67
130.21
128.96
121.05
123.30
119.82
112.41
110.80
100.41
16.61
29.00
25.70
17.82
Br
S2
(CDCl3, 100 MHz)



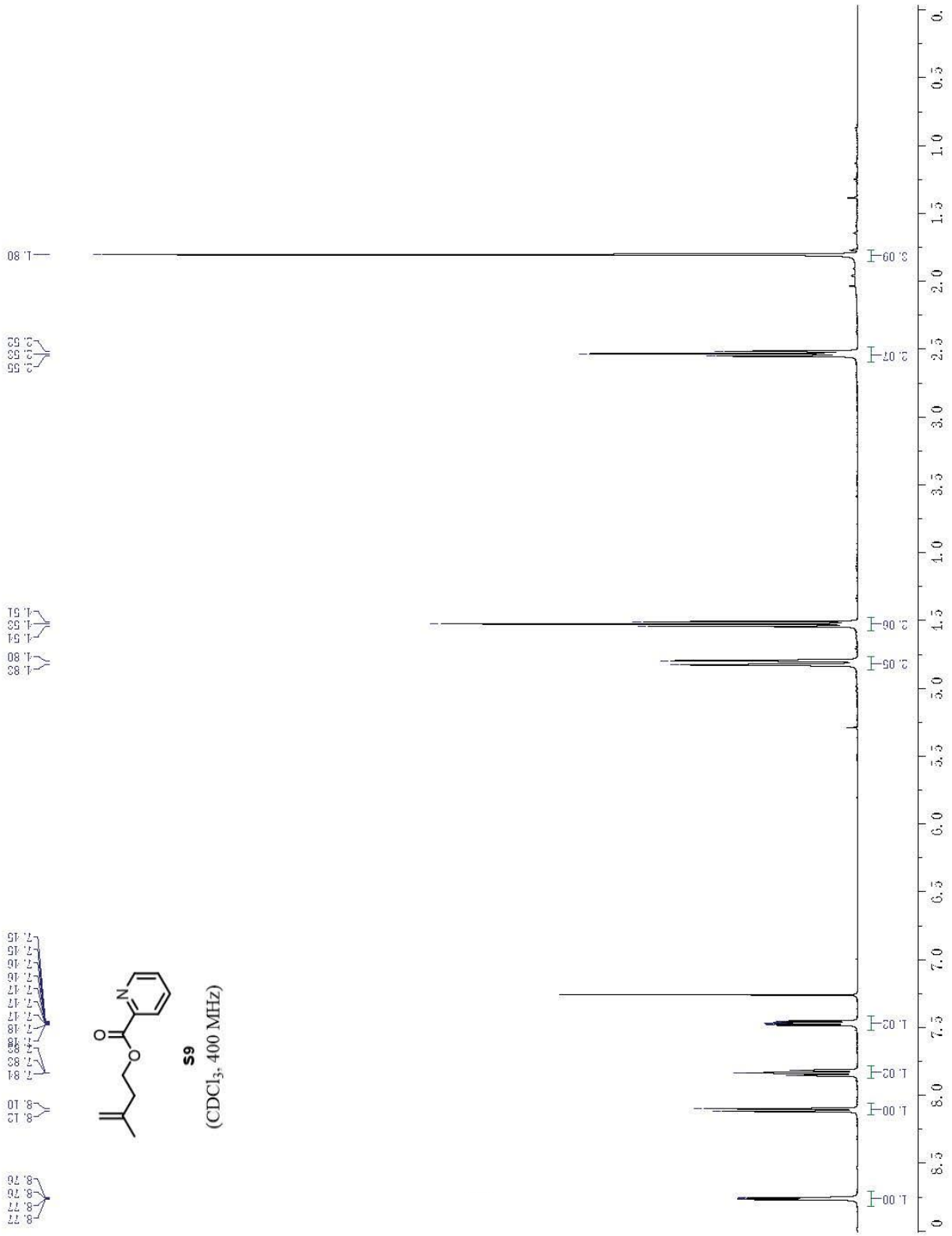
S6

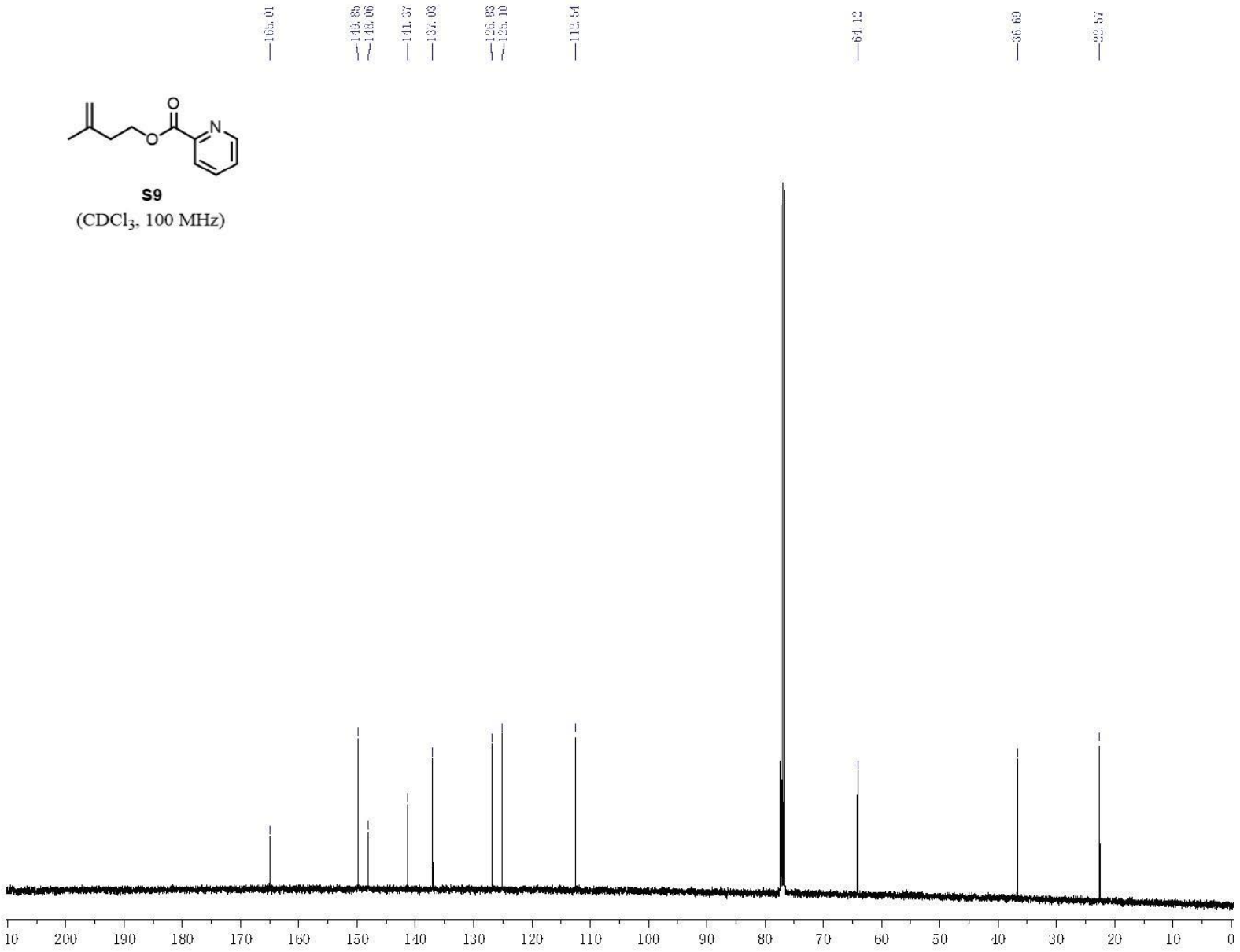
($CDCl_3$, 400 MHz)

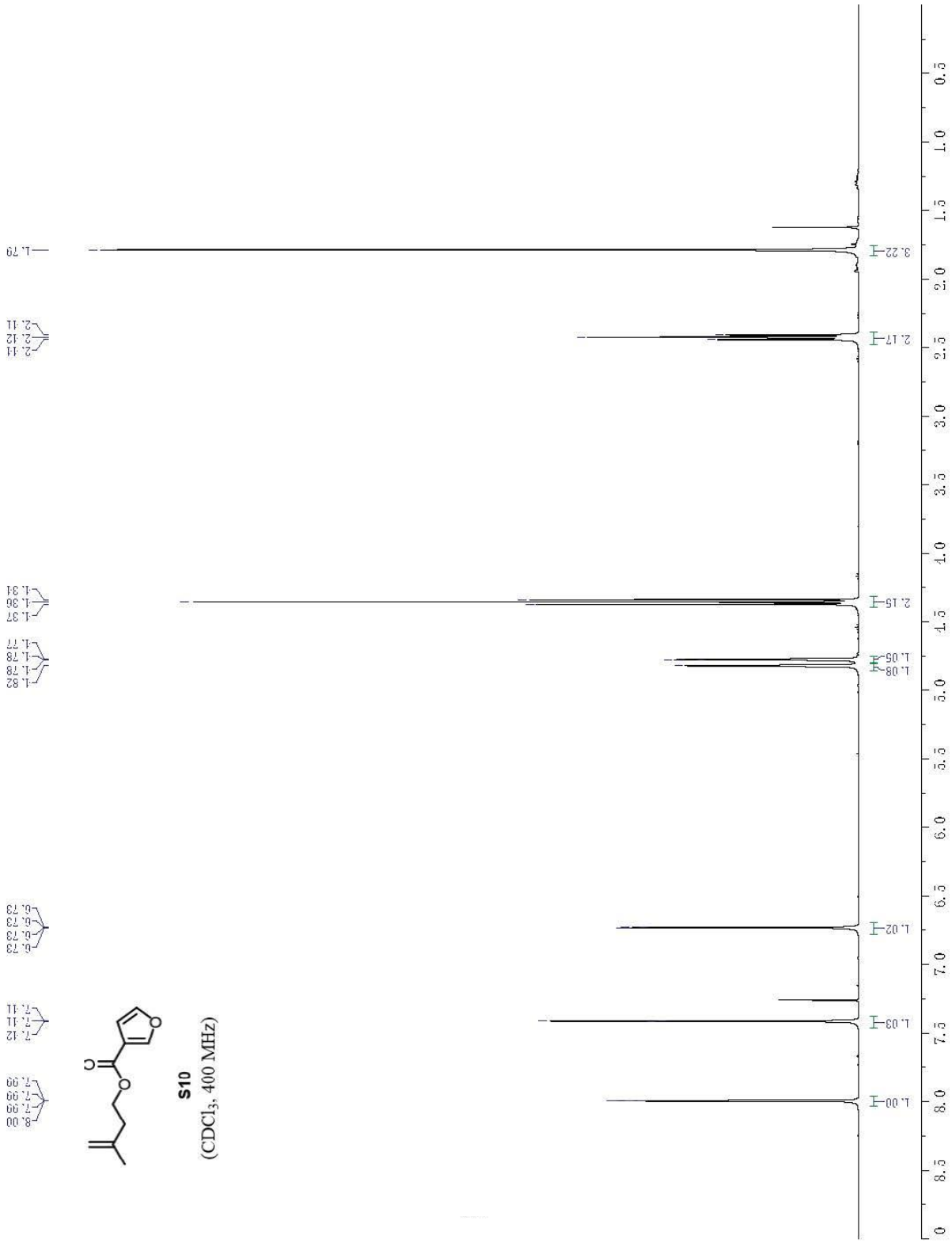


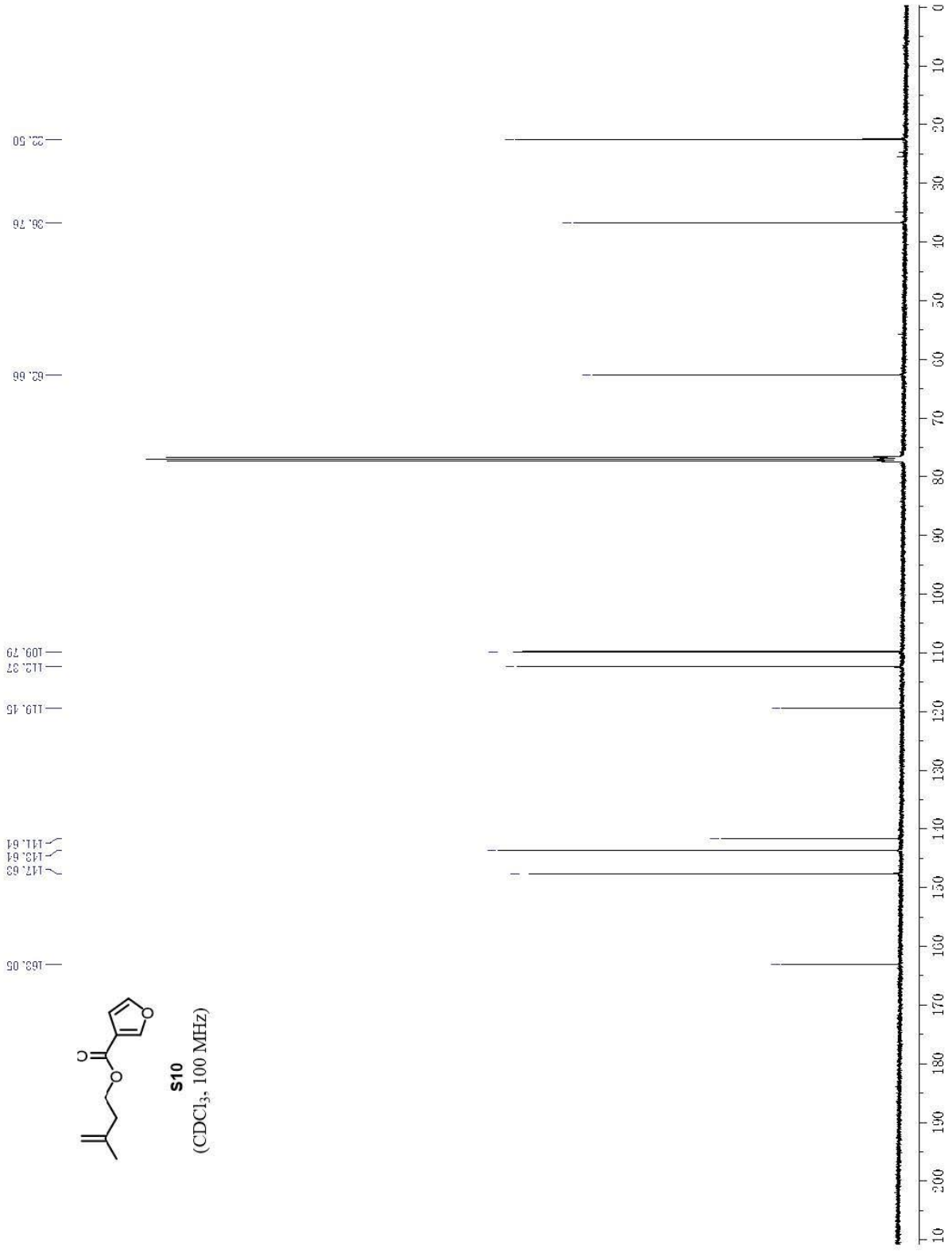
S6

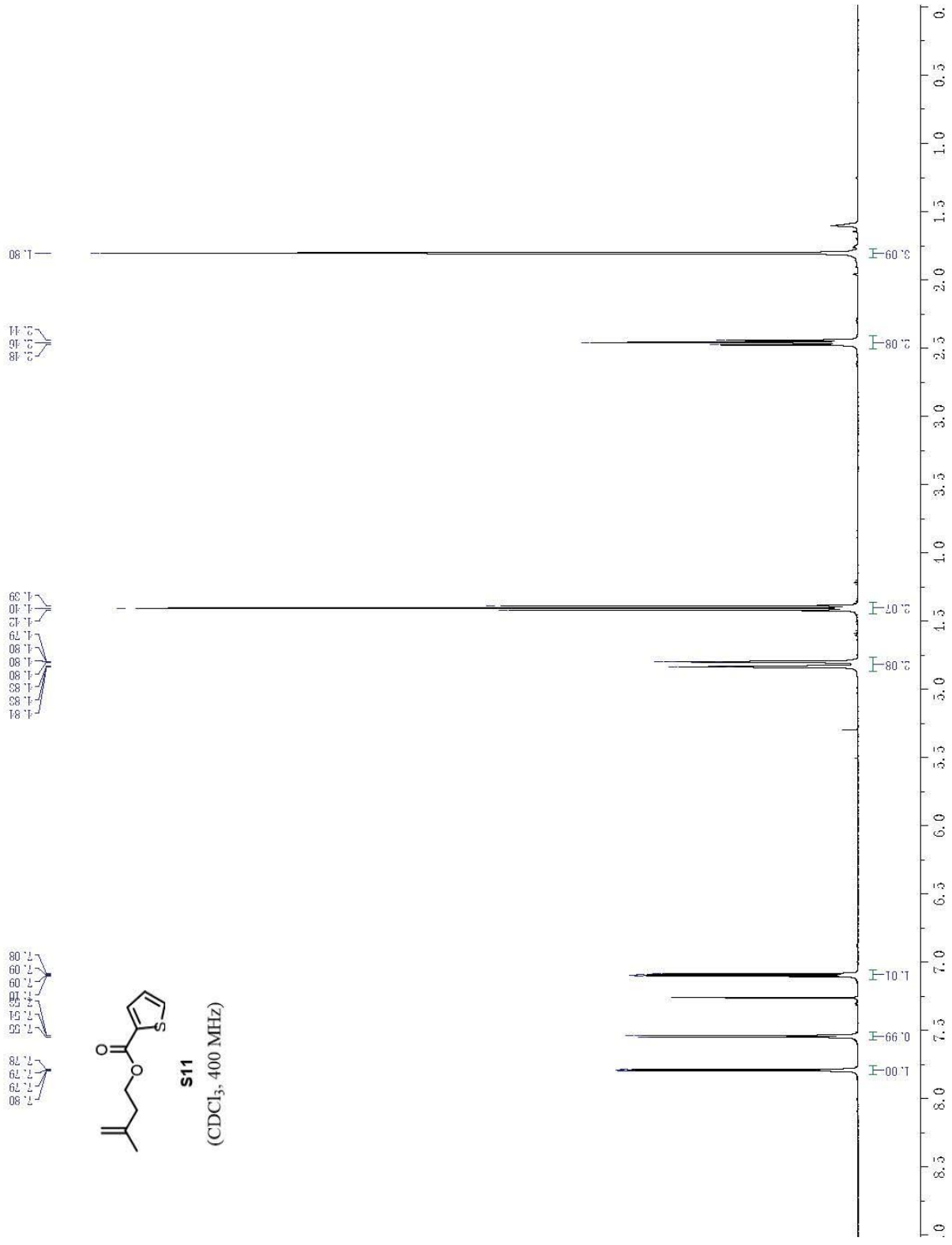
($CDCl_3$, 100 MHz)

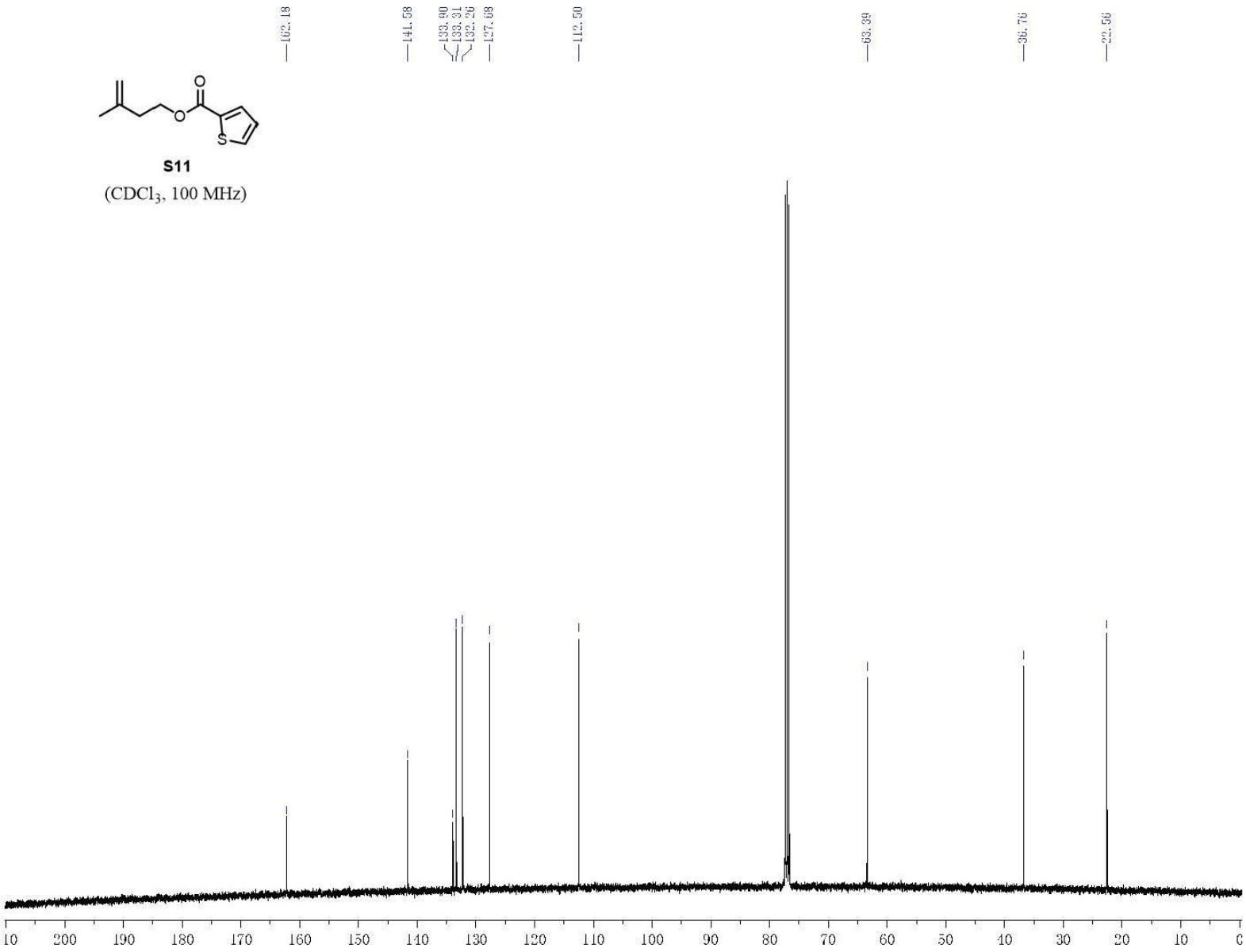

S9
(CDCl3, 400 MHz)

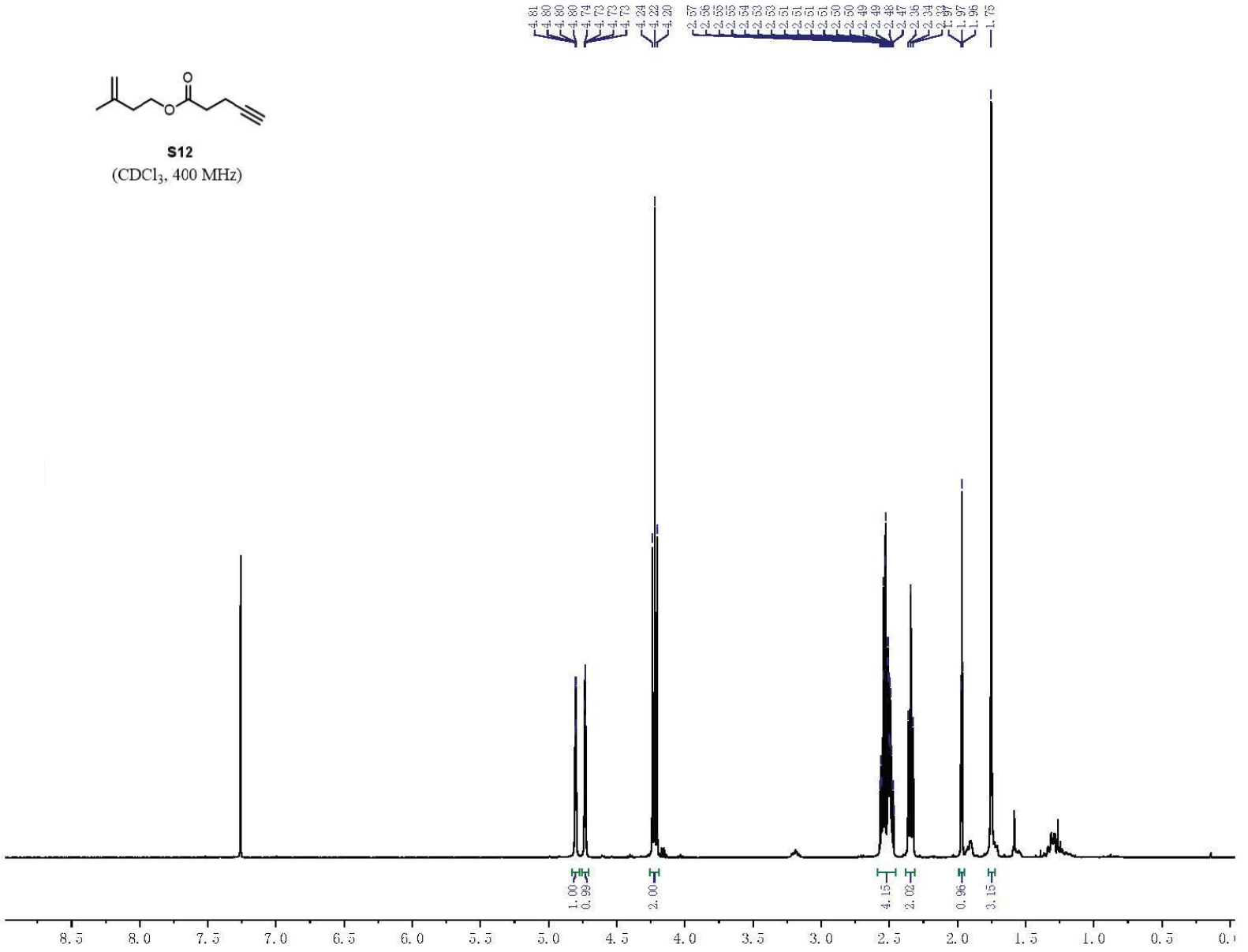

165.01
149.85
148.06
141.37
137.03
126.83
125.10
112.54
64.12
36.69
22.57
O
O
N
S9
(CDCl3, 100 MHz)
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

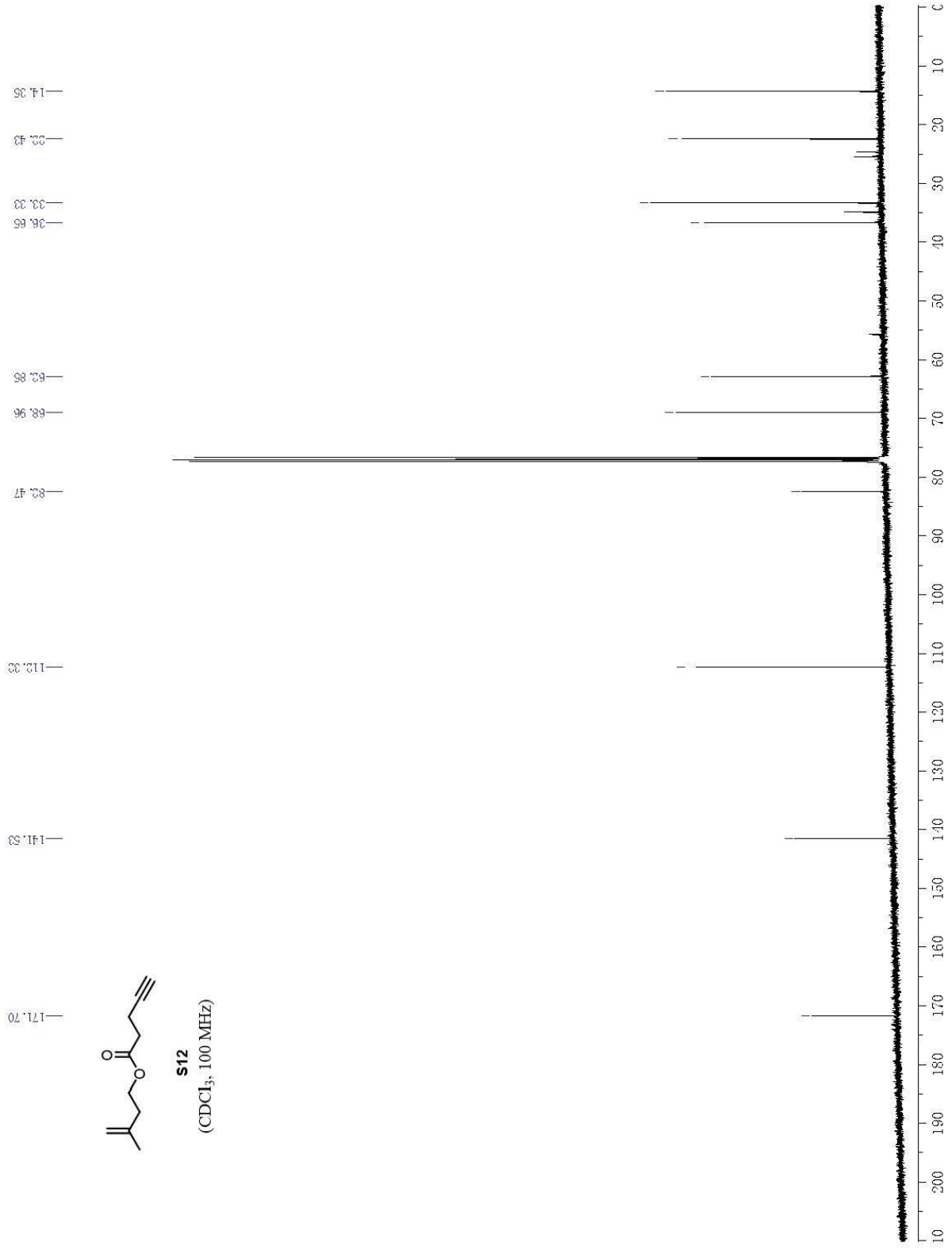

S10
(CDCl3, 400 MHz)


33.50
36.76
62.66
109.79
112.87
119.15
141.61
142.61
147.63
163.05
S10
(CDCl3, 100 MHz)


S11
(CDCl3, 400 MHz)


162.18
141.58
133.90
133.31
132.26
127.68
112.50
63.39
36.76
22.56
O
O
S
S11
(CDCl3, 100 MHz)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


S12
(CDCl3, 400 MHz)



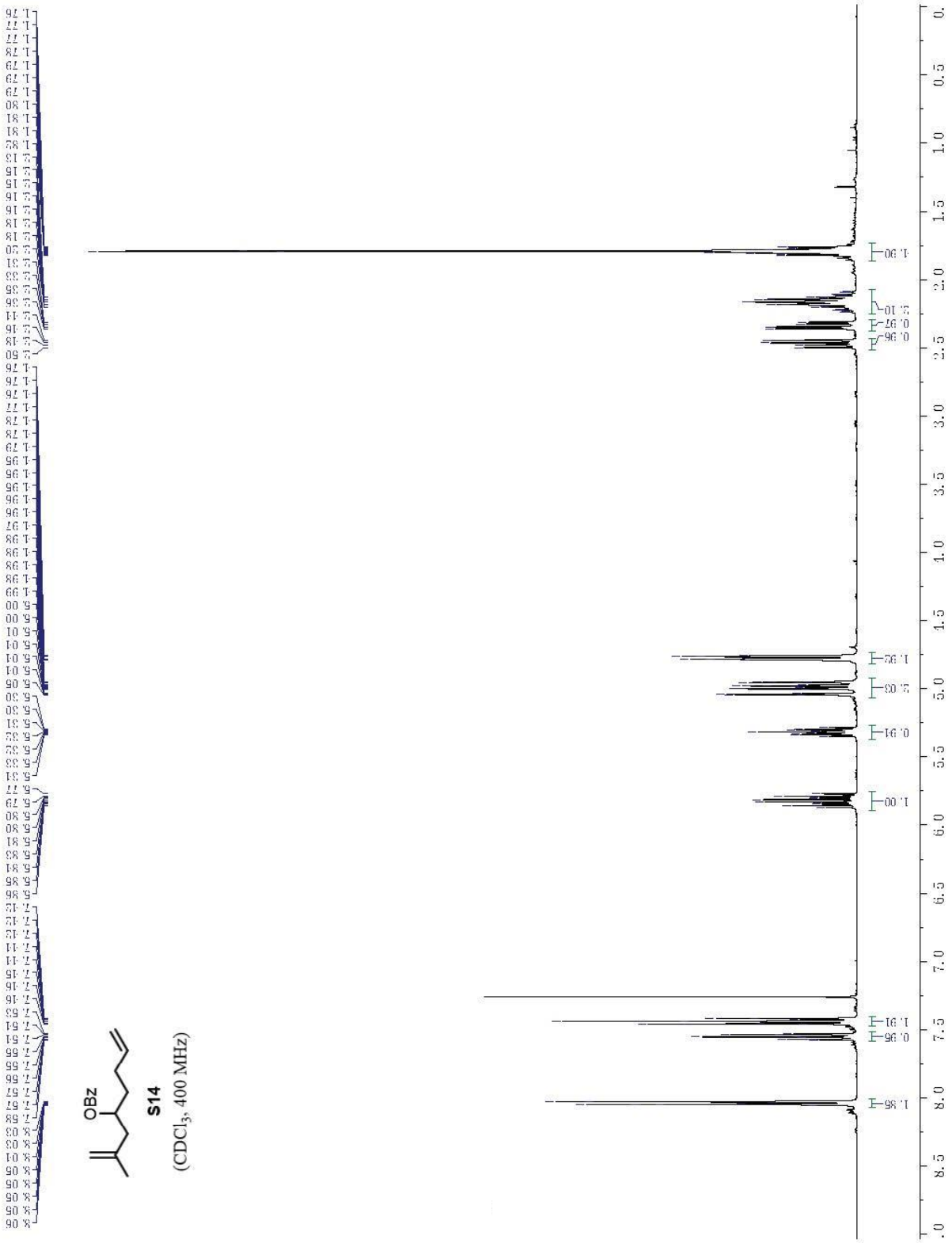
S12

($CDCl_3$, 100 MHz)

S13

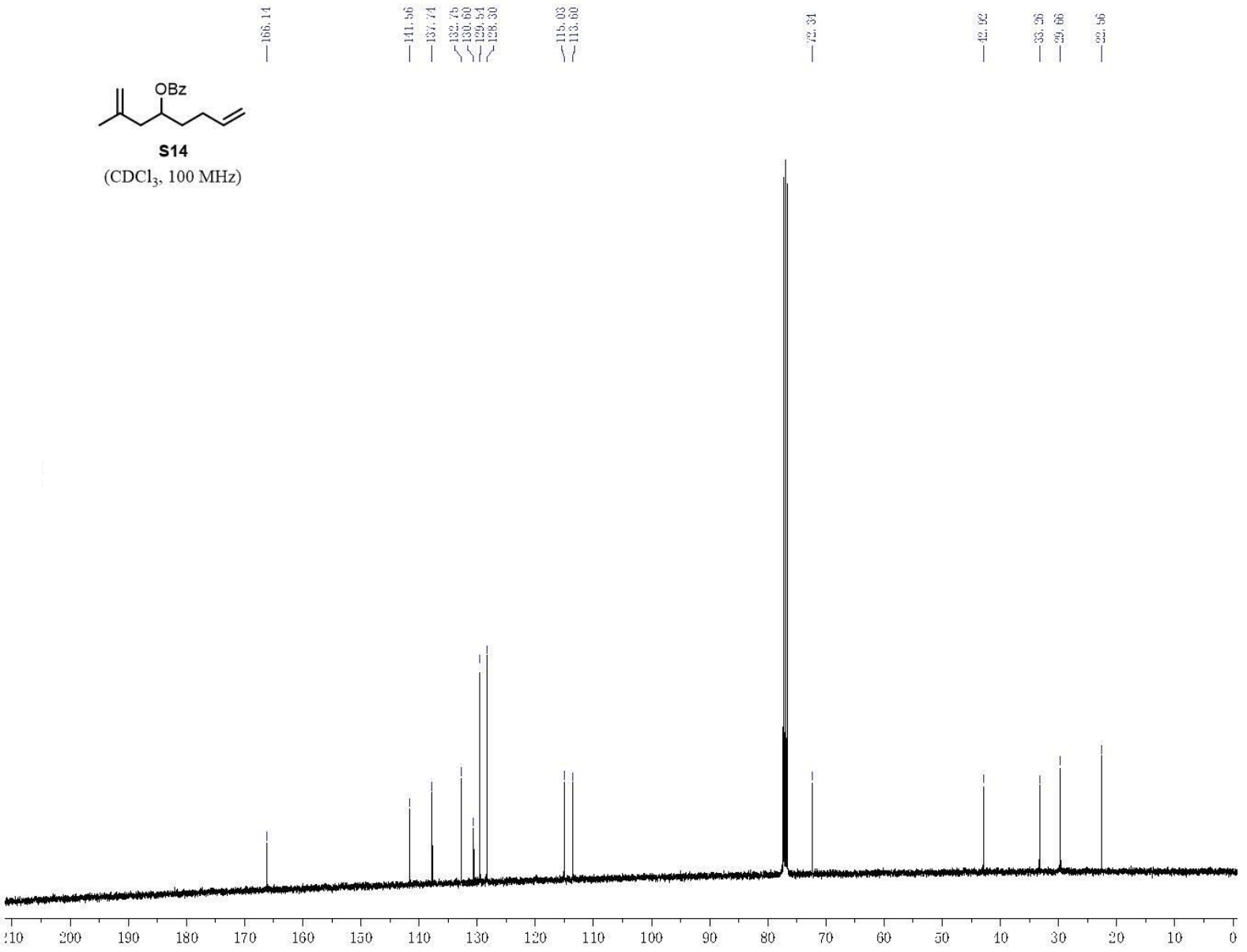
($CDCl_3$, 500 MHz)

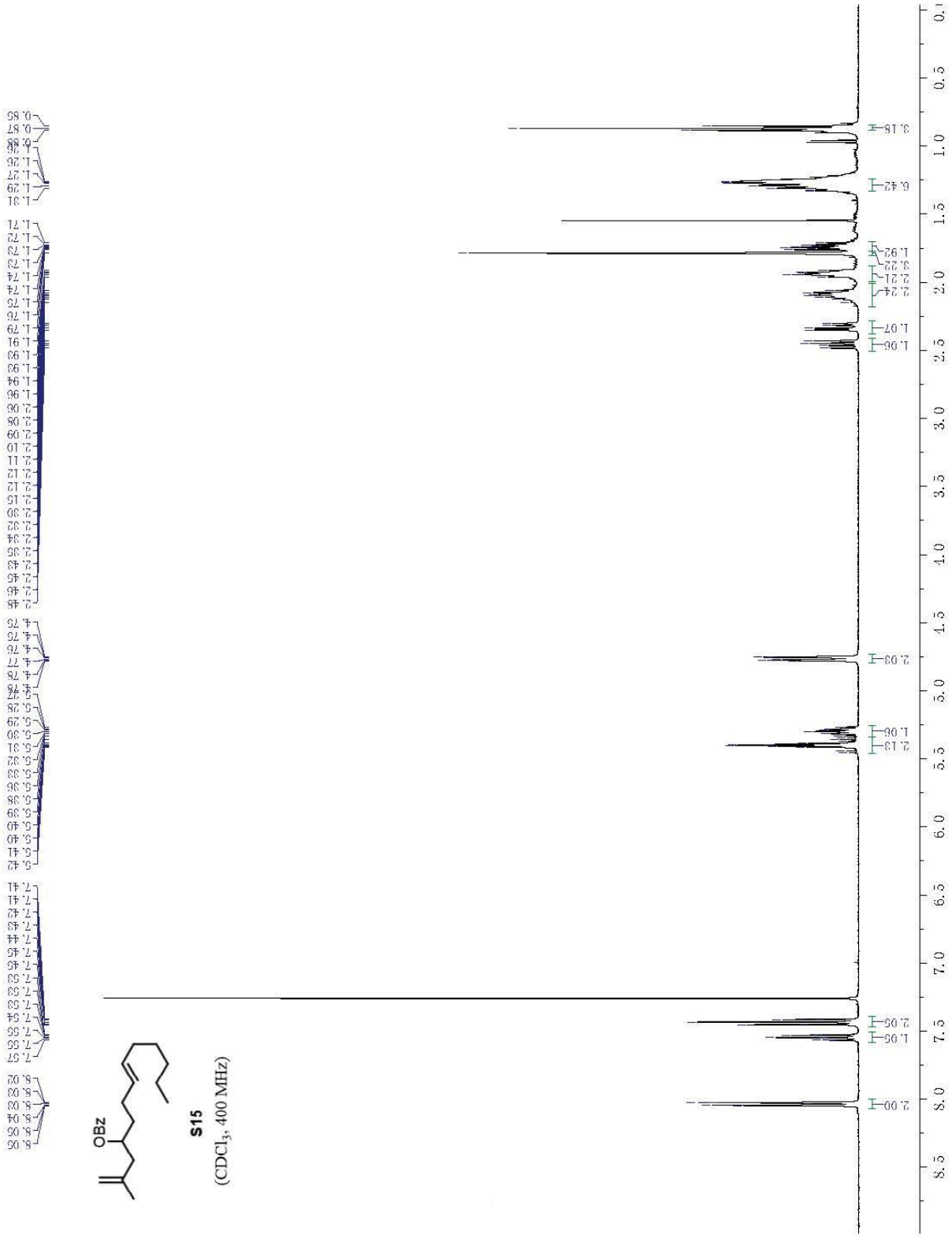
15.35
22.96
33.65
36.67
62.78
81.15
87.96
112.25
123.53
127.69
128.11
131.52
141.51
171.74
S13
(CDCl3, 126 MHz)

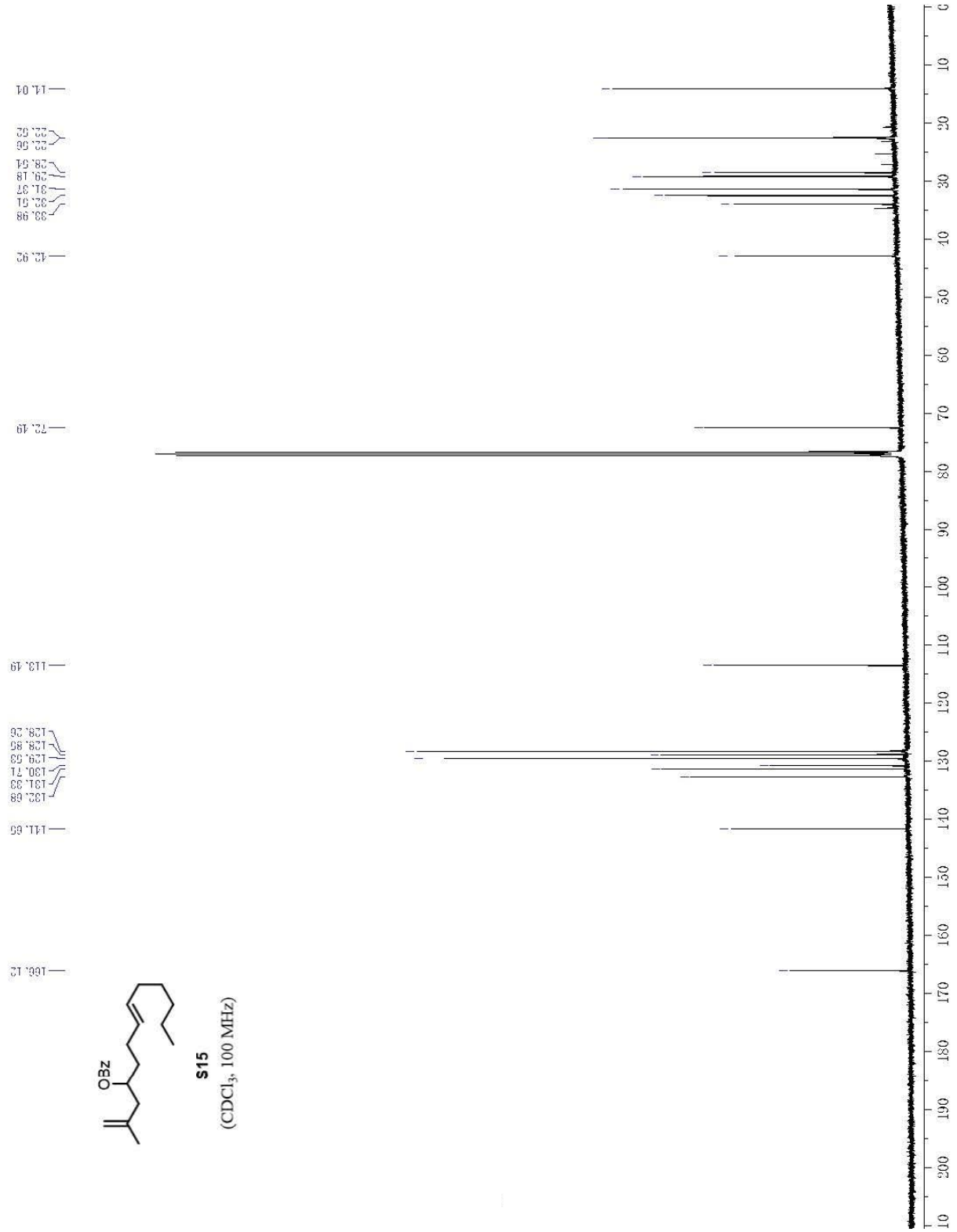


S14

($CDCl_3$, 400 MHz)

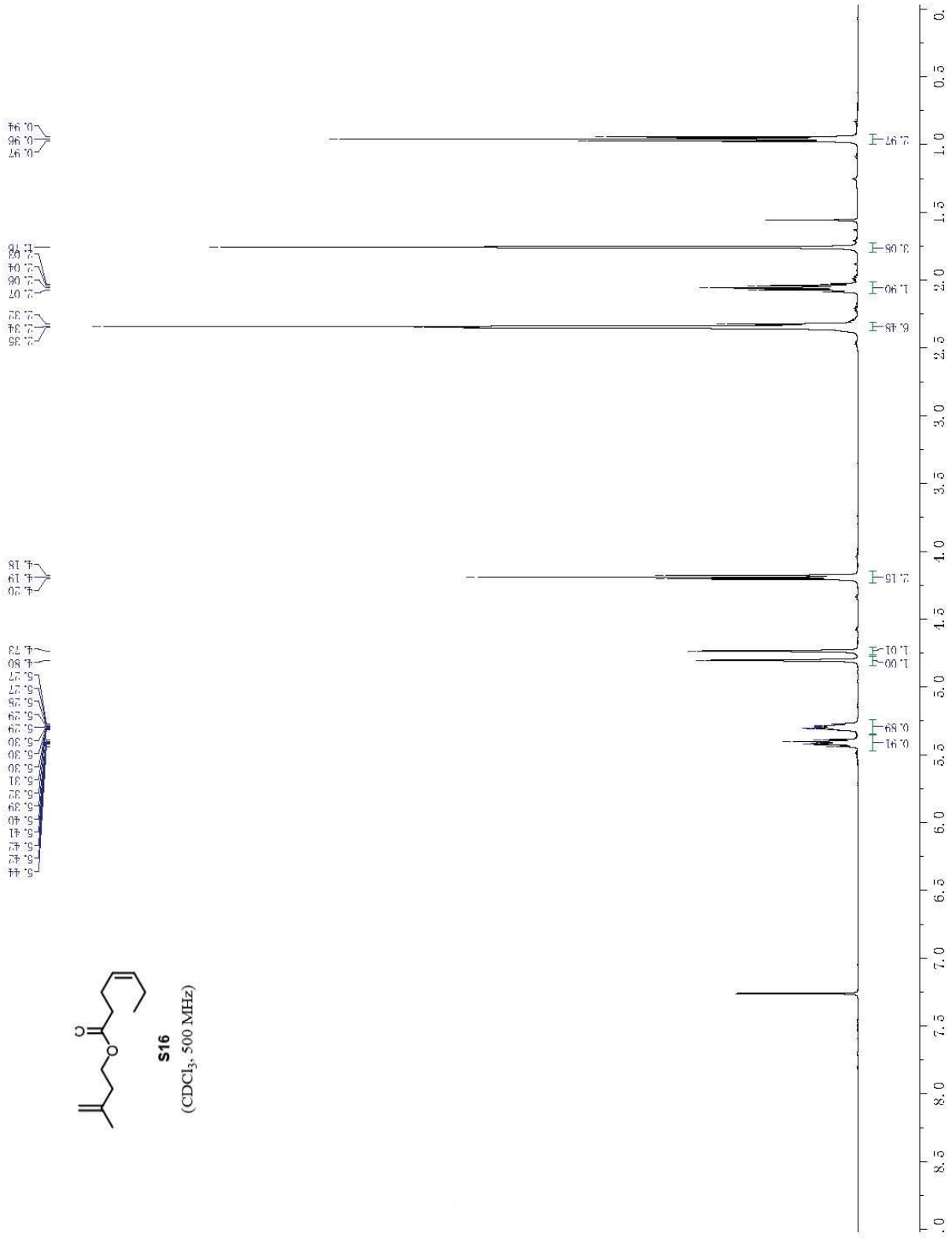

166.14
141.56
137.74
132.75
130.60
129.54
128.30
115.03
113.60
72.34
42.92
33.26
29.66
22.56
OBz
S14
(CDCl3, 100 MHz)
210
200
190
180
170
160
150
110
130
120
110
100
90
80
70
60
50
10
30
20
10
0


OBz
S15
(CDCl3, 400 MHz)



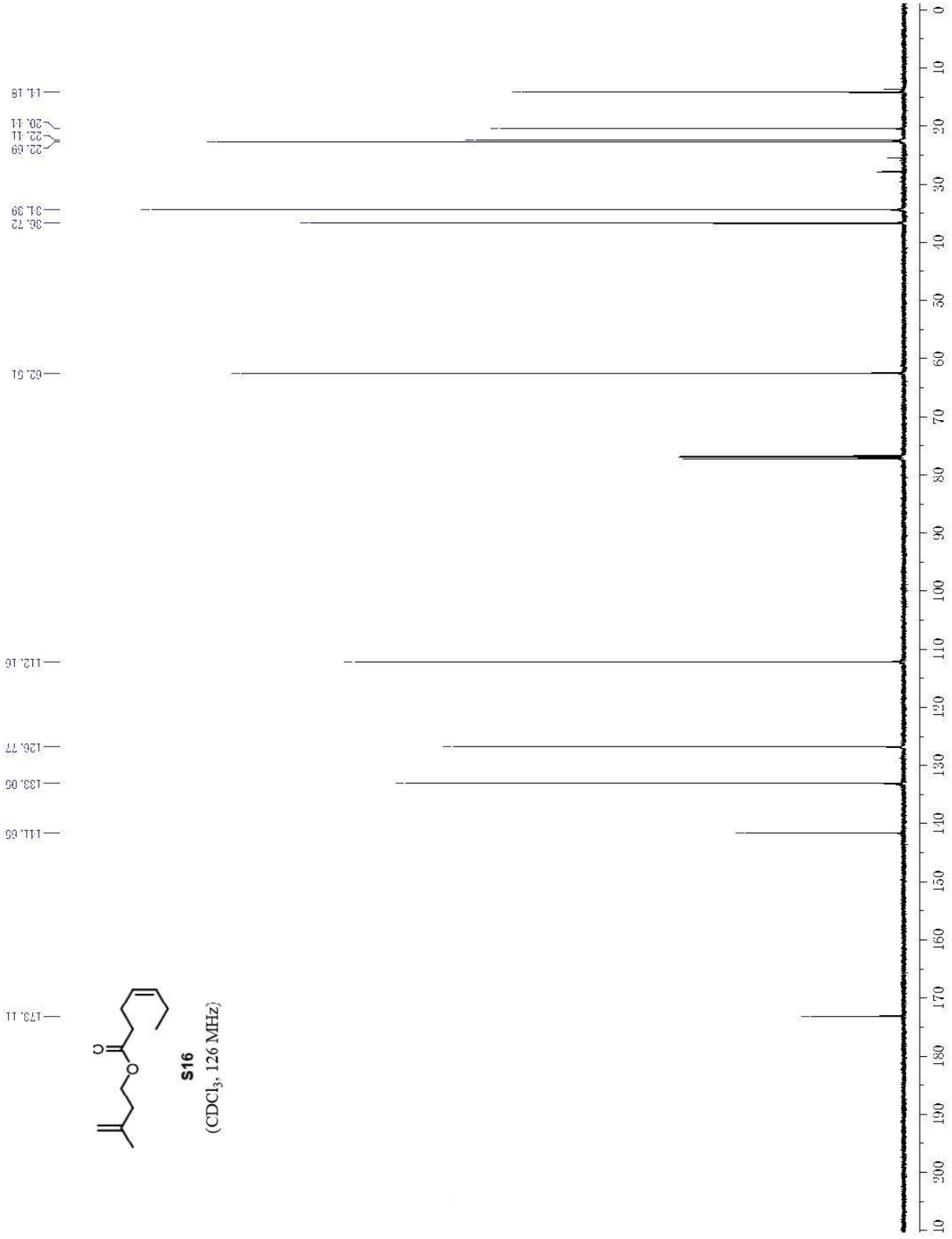
S15

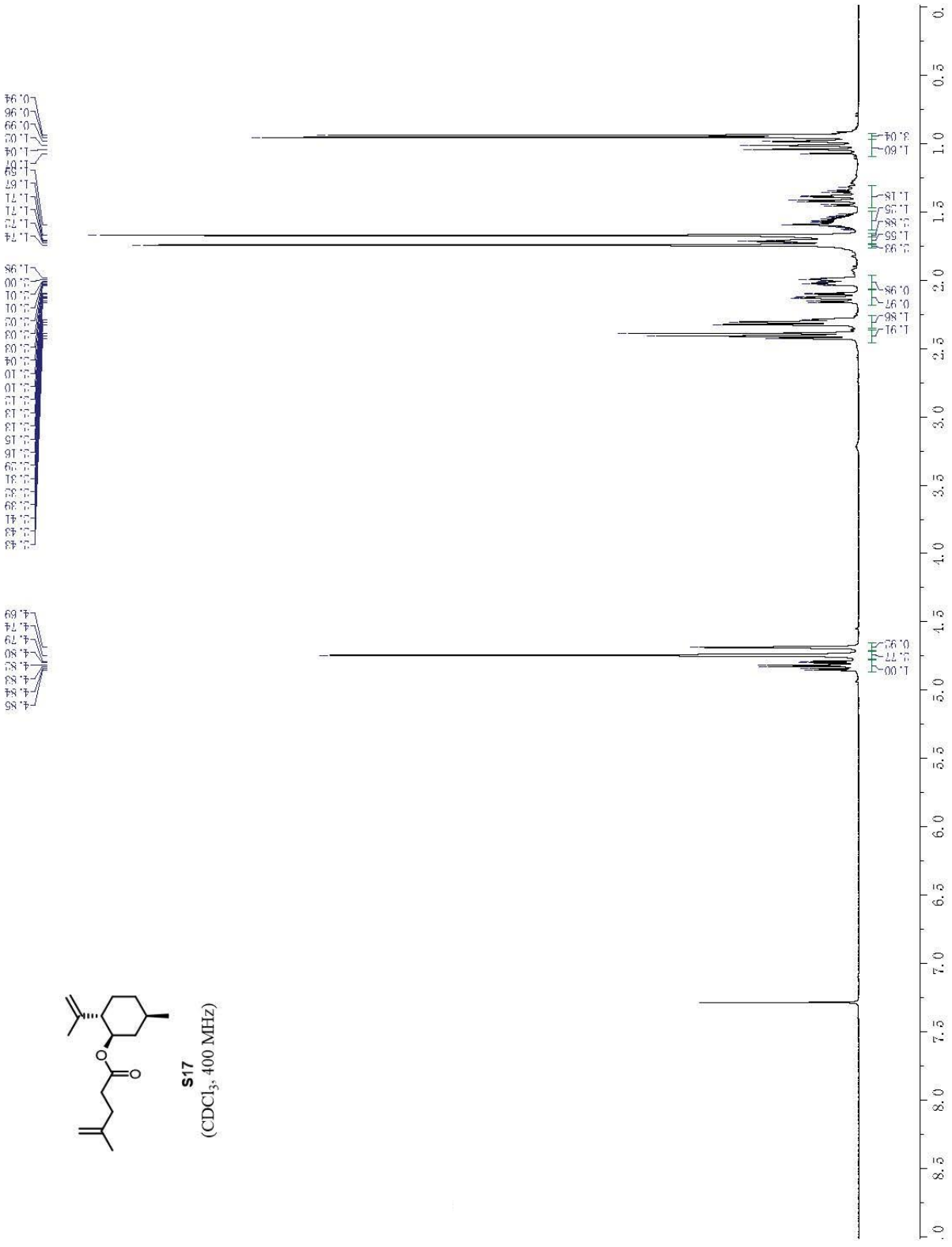
($CDCl_3$, 100 MHz)



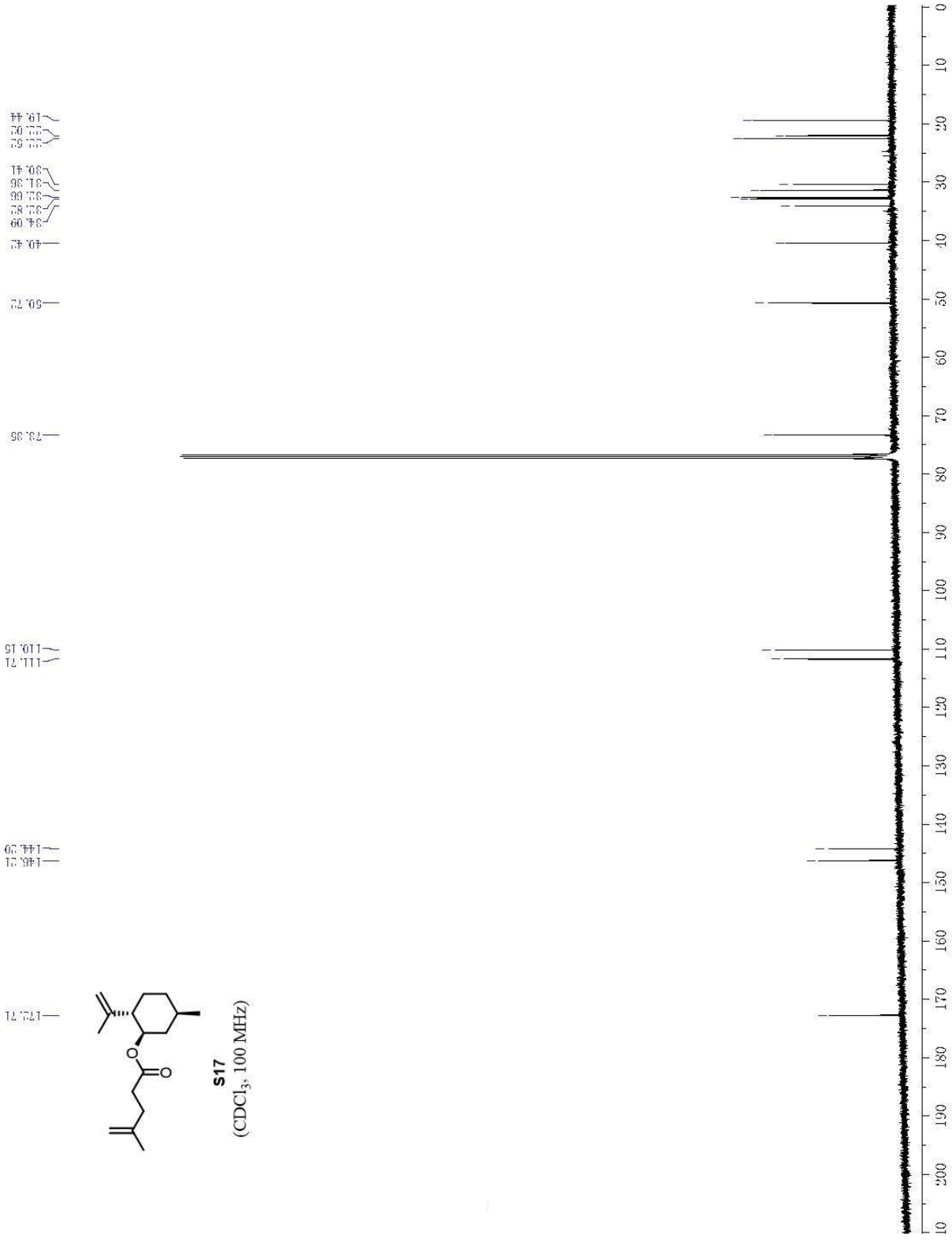
S16

($CDCl_3$, 500 MHz)

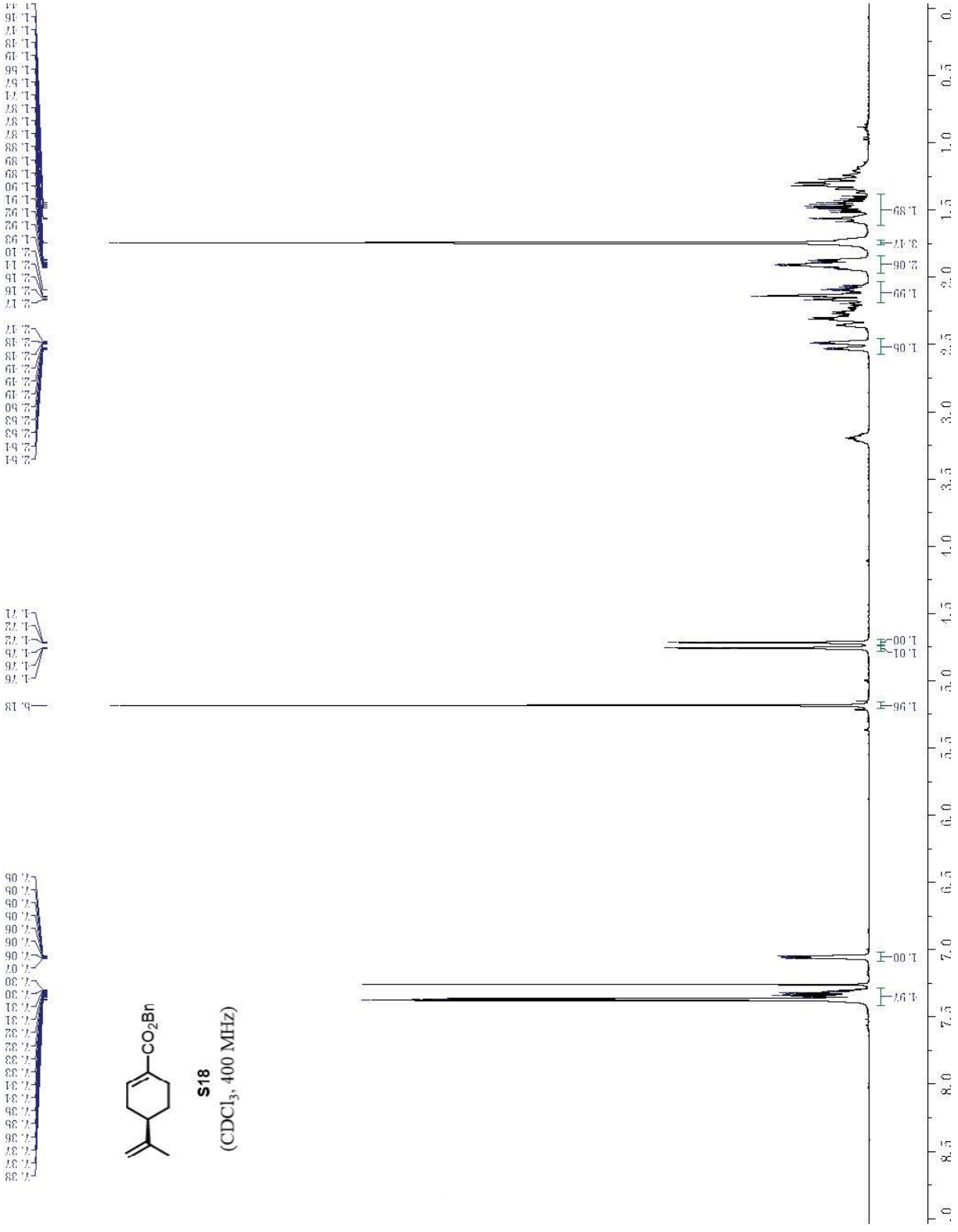

14.18
20.44
22.11
22.69
31.39
36.72
62.61
112.16
126.77
138.06
141.66
173.11
S16
(CDCl3, 126 MHz)



S17
($CDCl_3$, 400 MHz)

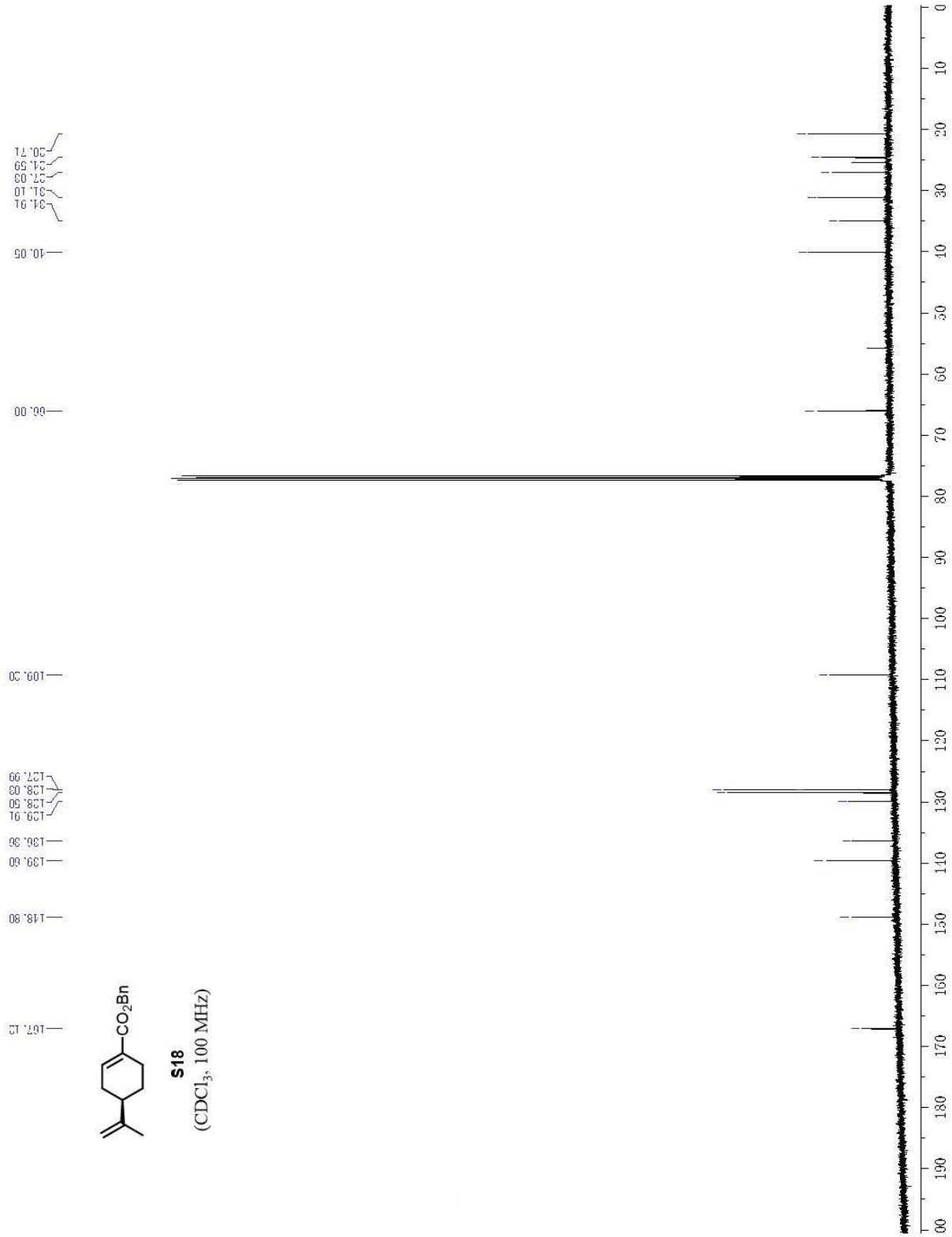


S17
($CDCl_3$, 100 MHz)

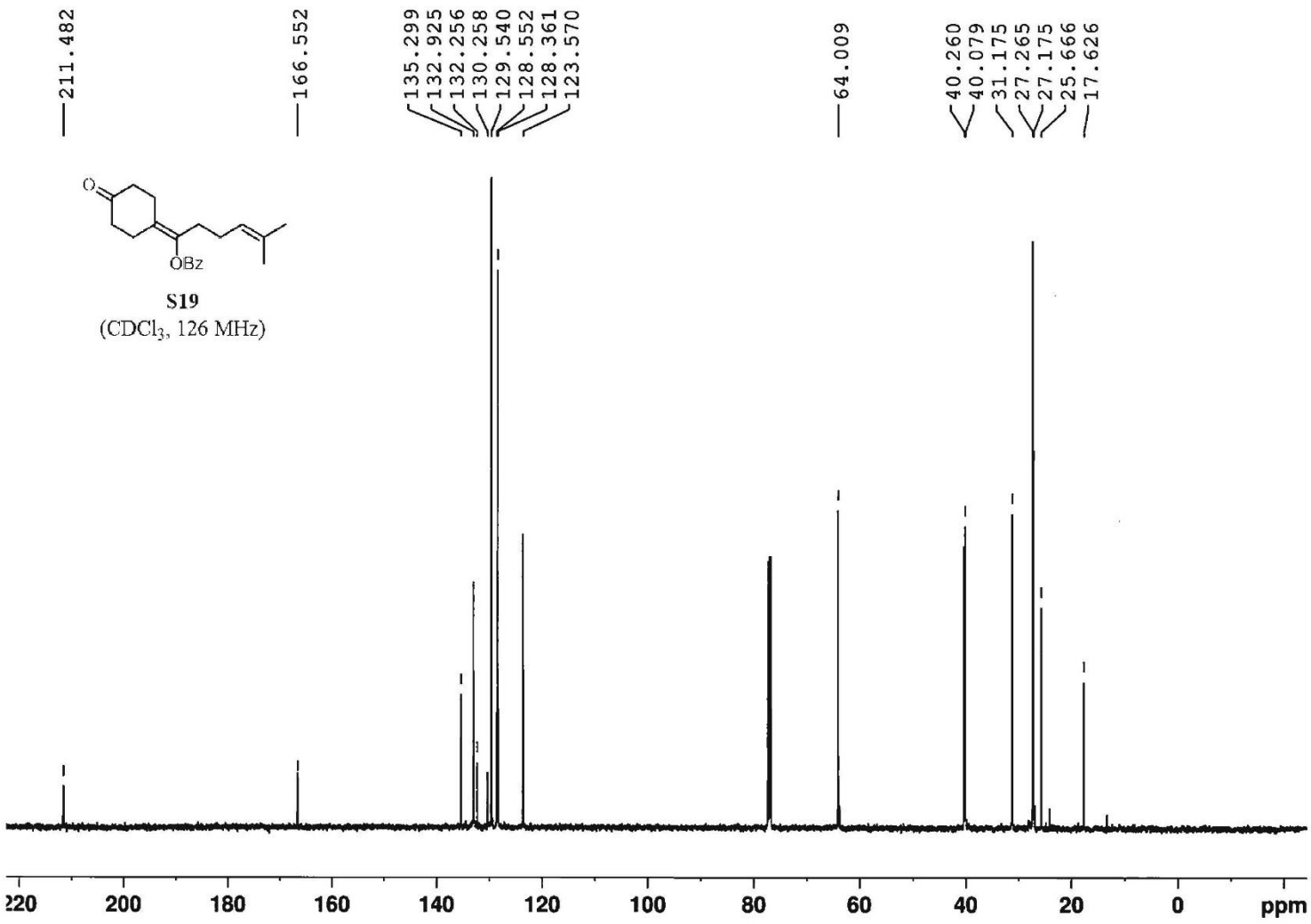


S18

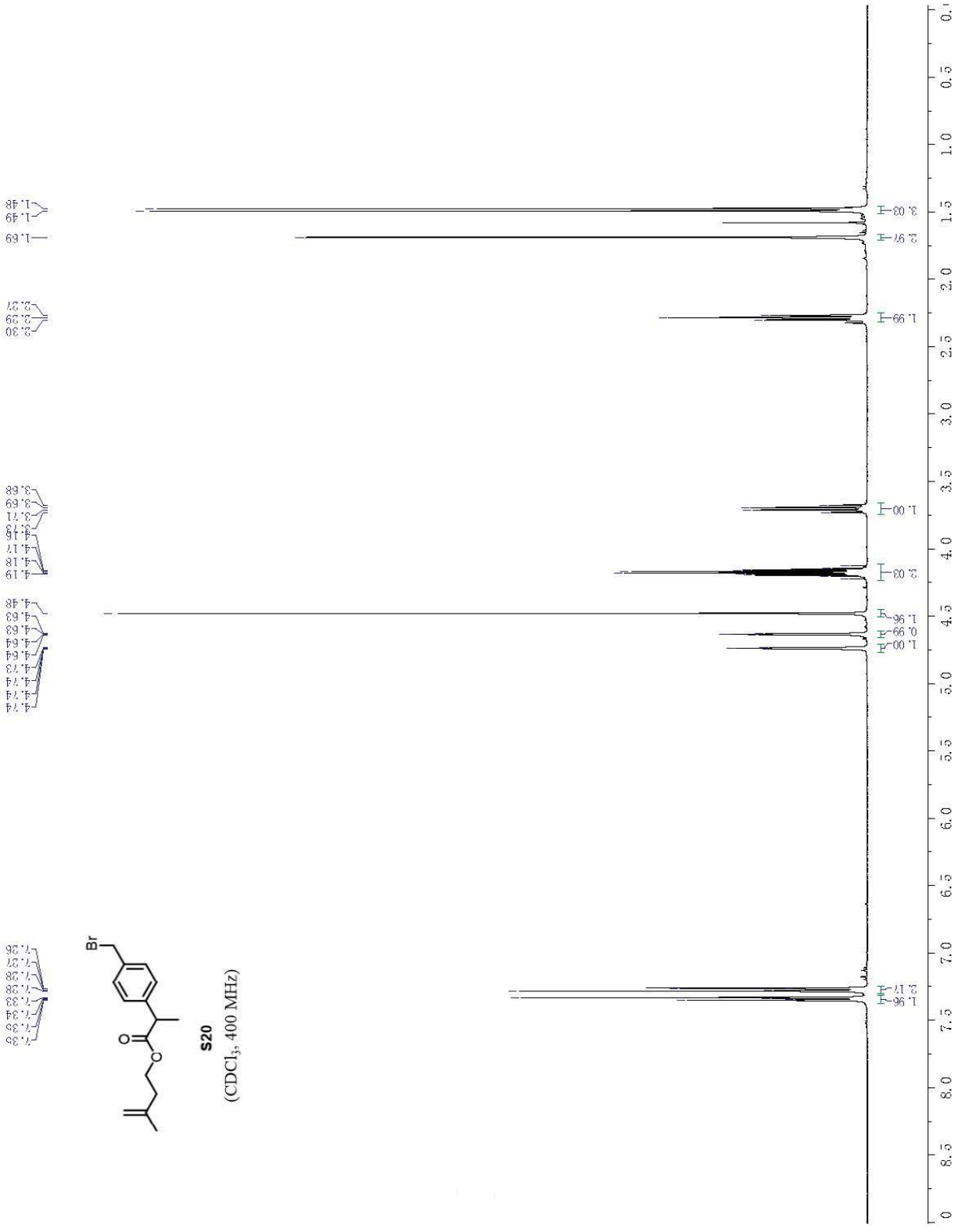
($CDCl_3$, 400 MHz)

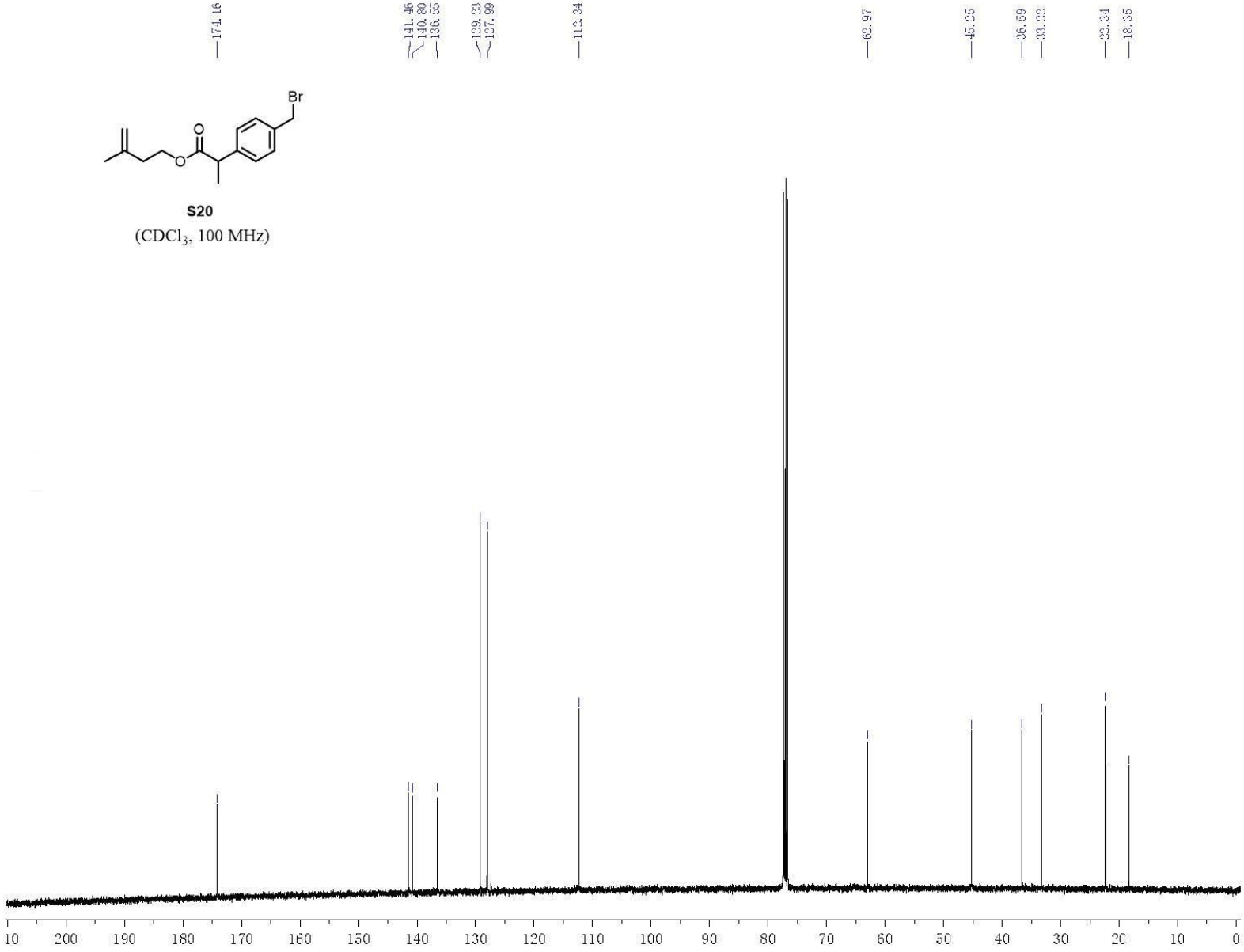

CO2Bn
S18
(CDCl3, 100 MHz)
167.15
148.80
139.60
136.86
129.91
128.50
128.09
127.99
109.30
66.00
40.05
34.91
31.10
27.09
24.59
20.71

8.040
8.024
7.569
7.555
7.540
7.450
7.435
7.419
5.150
5.136
5.123
4.912
2.728
2.714
2.700
2.639
2.626
2.611
2.462
2.458
2.447
2.435
2.431
2.296
2.282
2.265
2.165
2.162
2.160
2.150
2.135
2.120
1.670
1.583
OBz
O
S19
(CDCl3, 500 MHz)
1.92
1.00
2.13
0.94
2.00
2.12
2.10
4.23
2.18
2.12
3.05
2.78
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
ppm



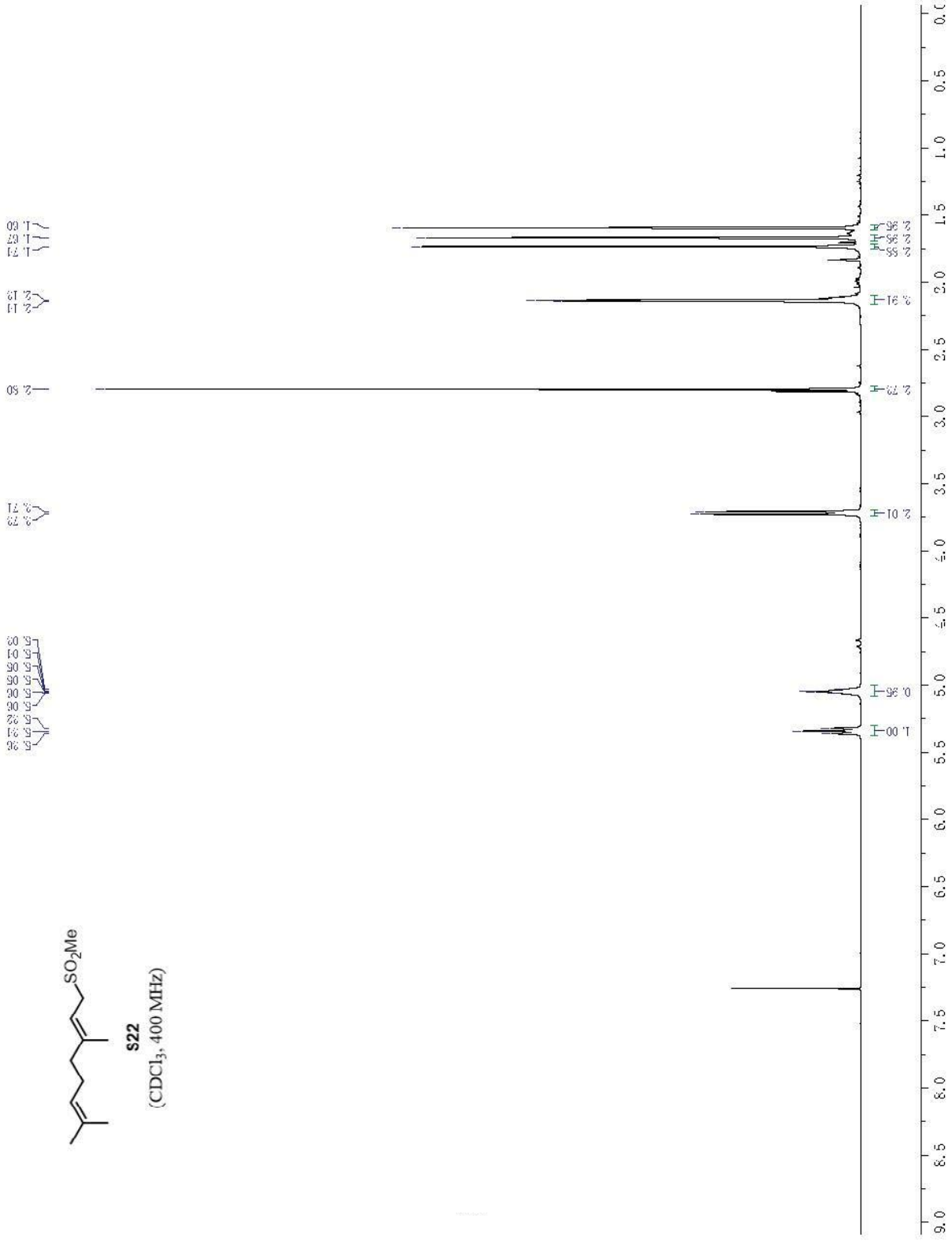
S19
($CDCl_3$, 126 MHz)

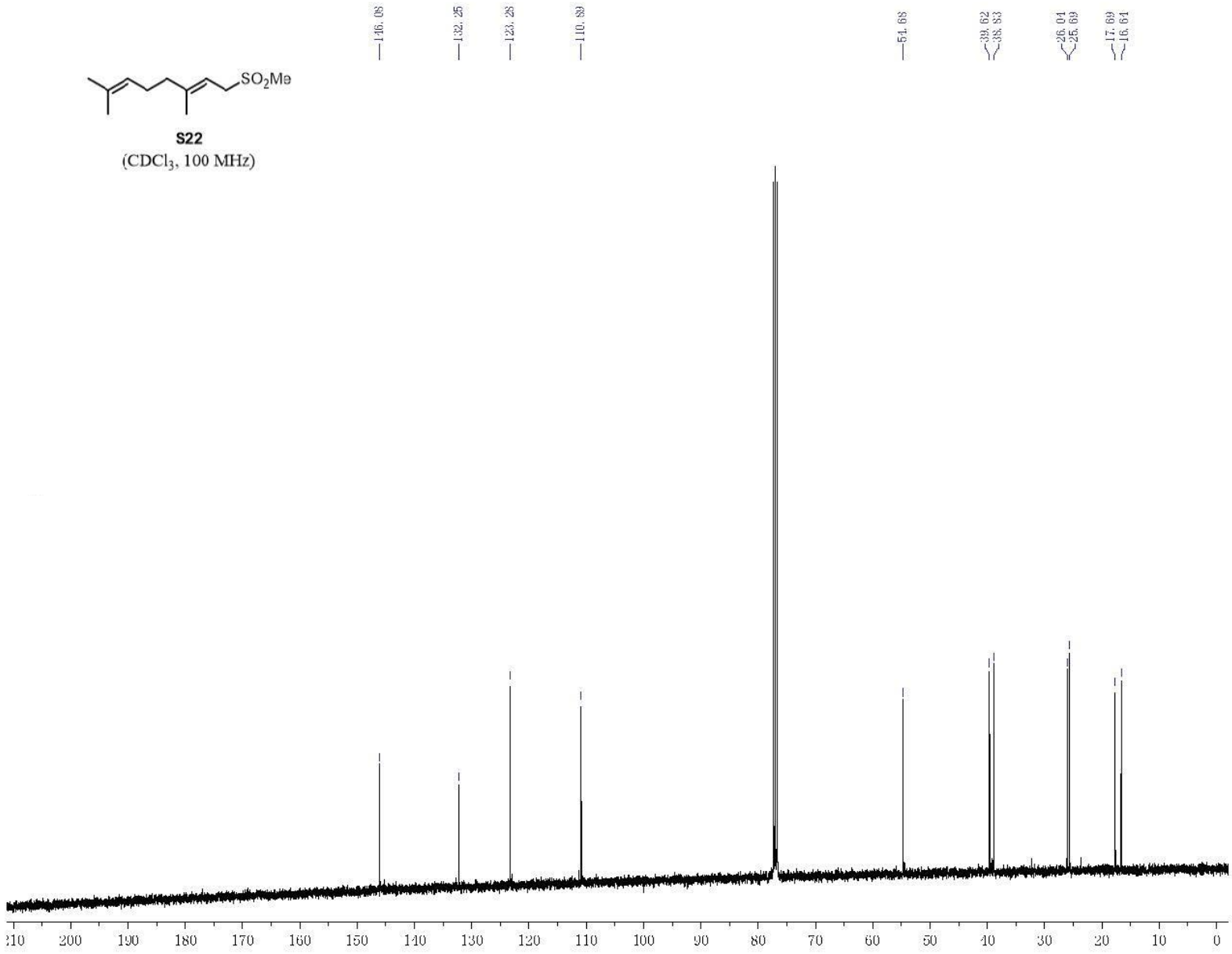

Br
O
O
S20
(CDCl3, 400 MHz)

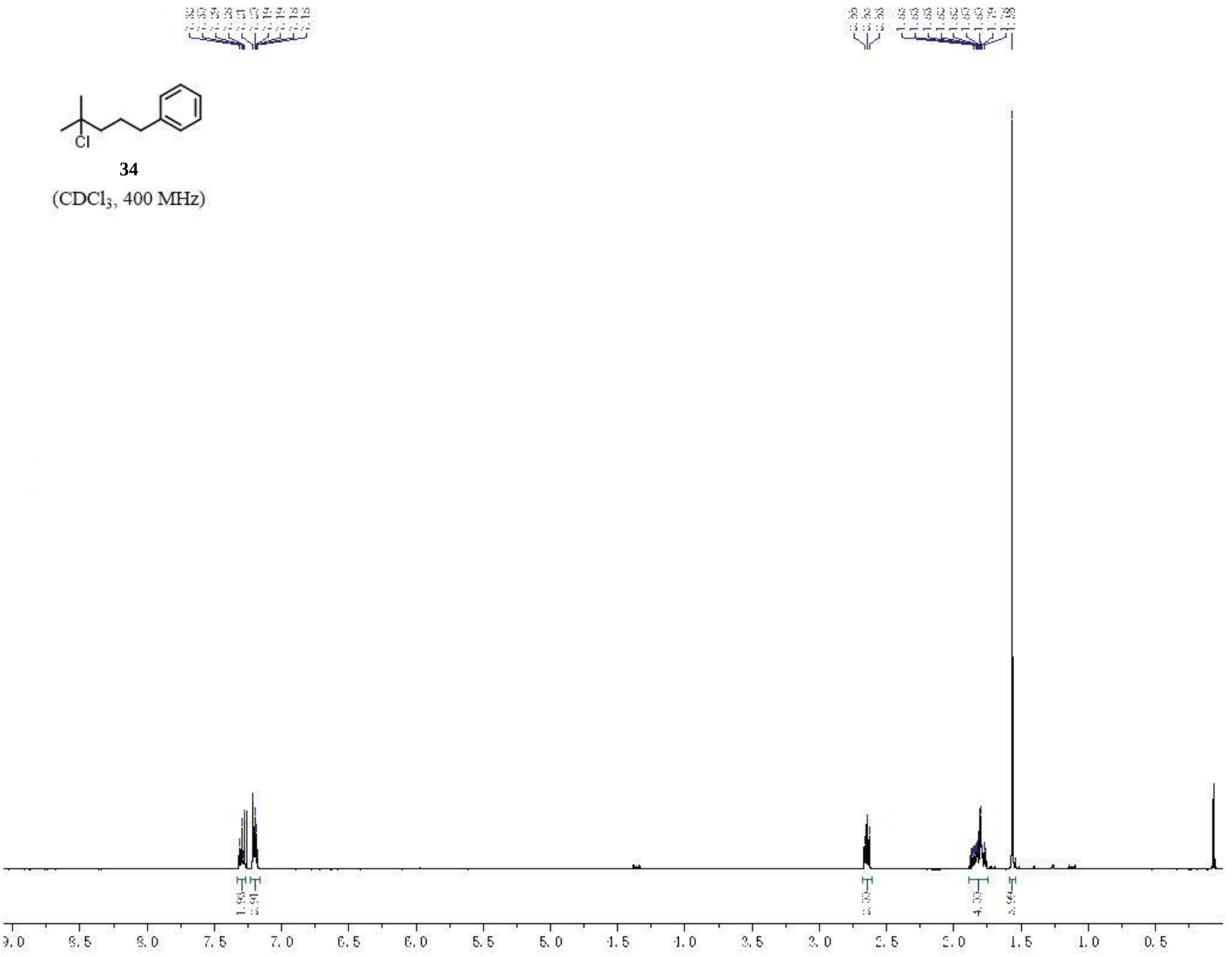


S20

($CDCl_3$, 100 MHz)

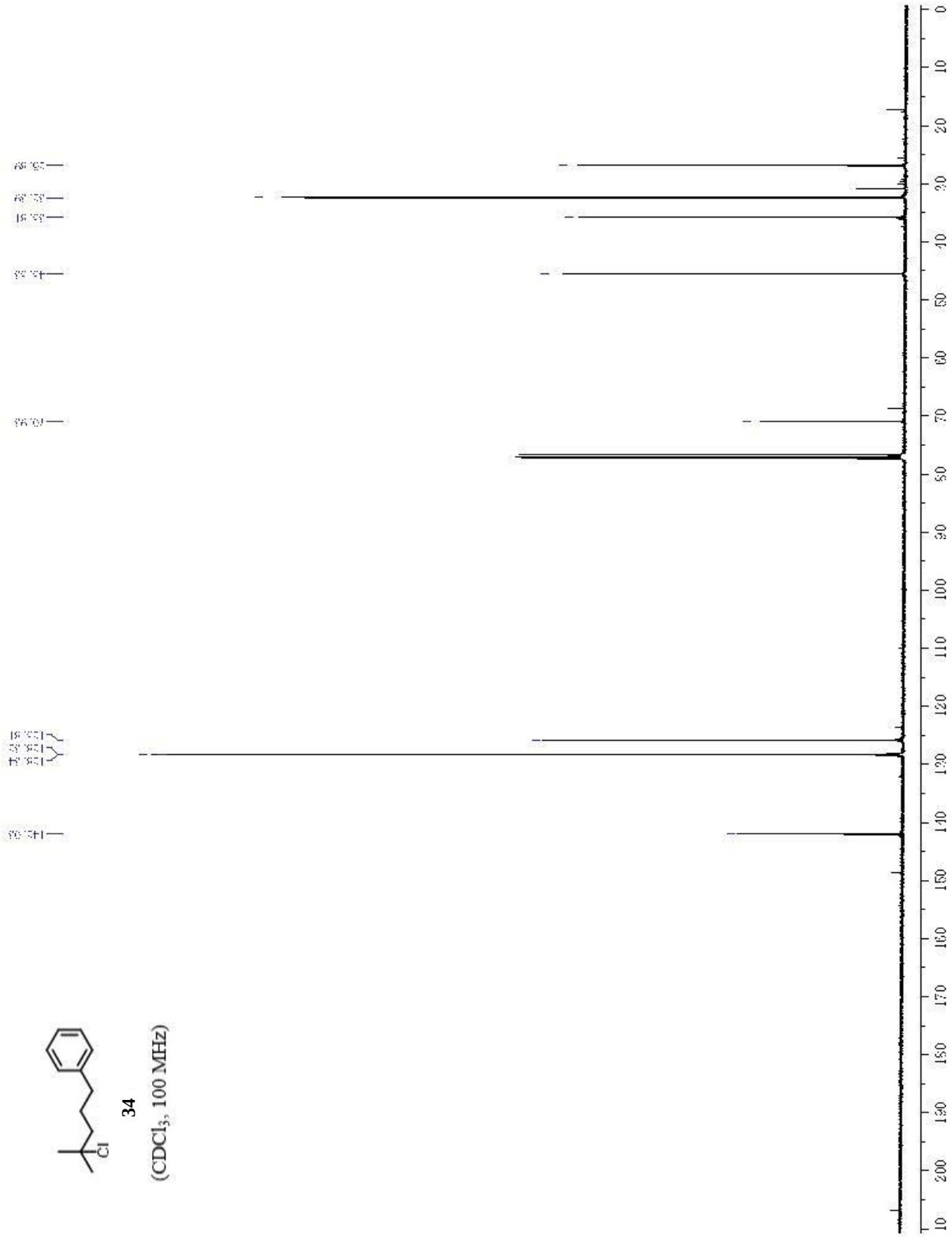

SO2Me
S22
(CDCl3, 400 MHz)


146.08
132.25
123.28
110.89
54.68
39.62
38.53
26.04
25.69
17.69
16.64
SO2Me
S22
(CDCl3, 100 MHz)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0



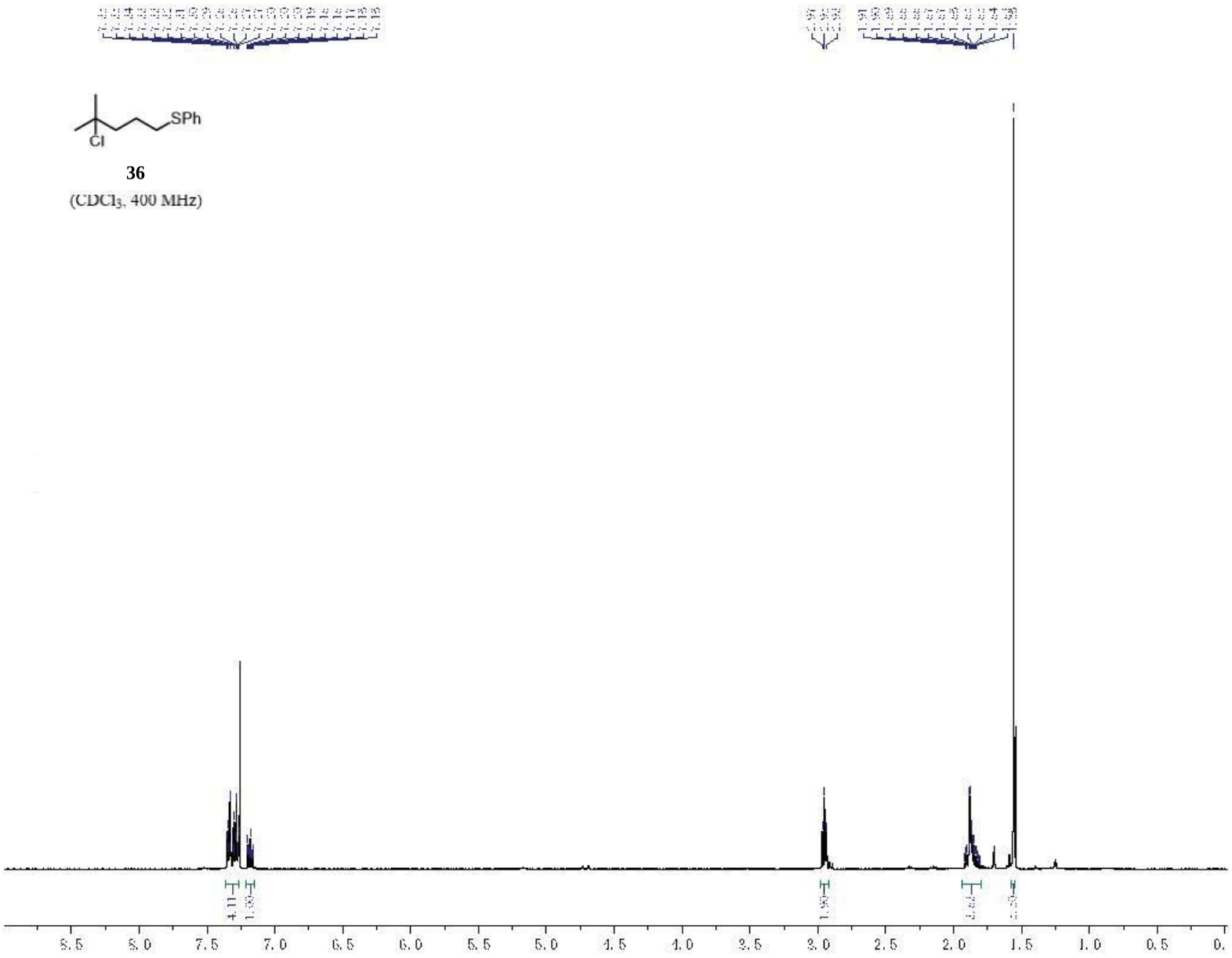
34

($CDCl_3$, 400 MHz)



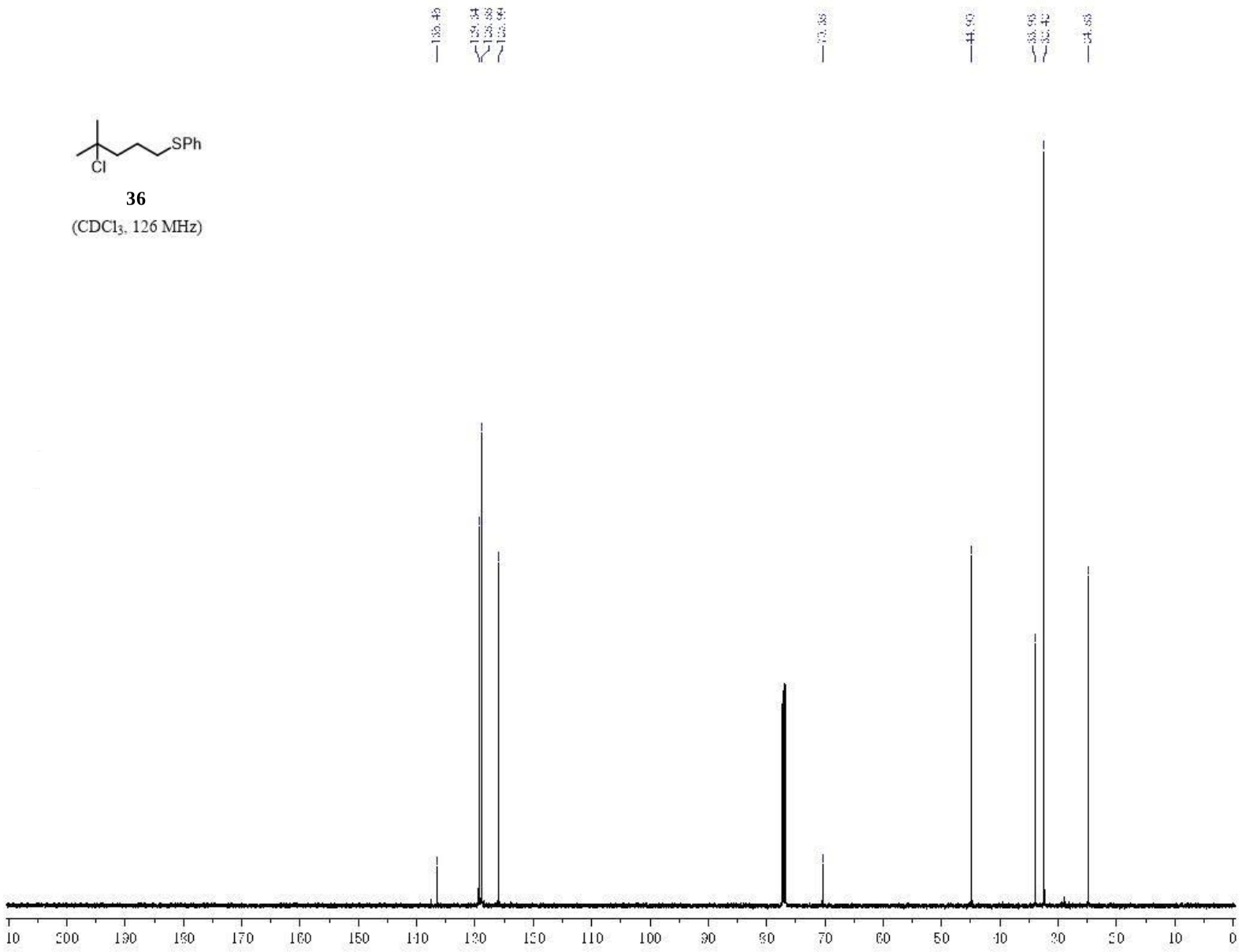
34

($CDCl_3$, 100 MHz)



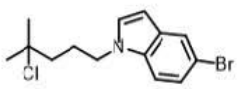
36

($CDCl_3$, 400 MHz)



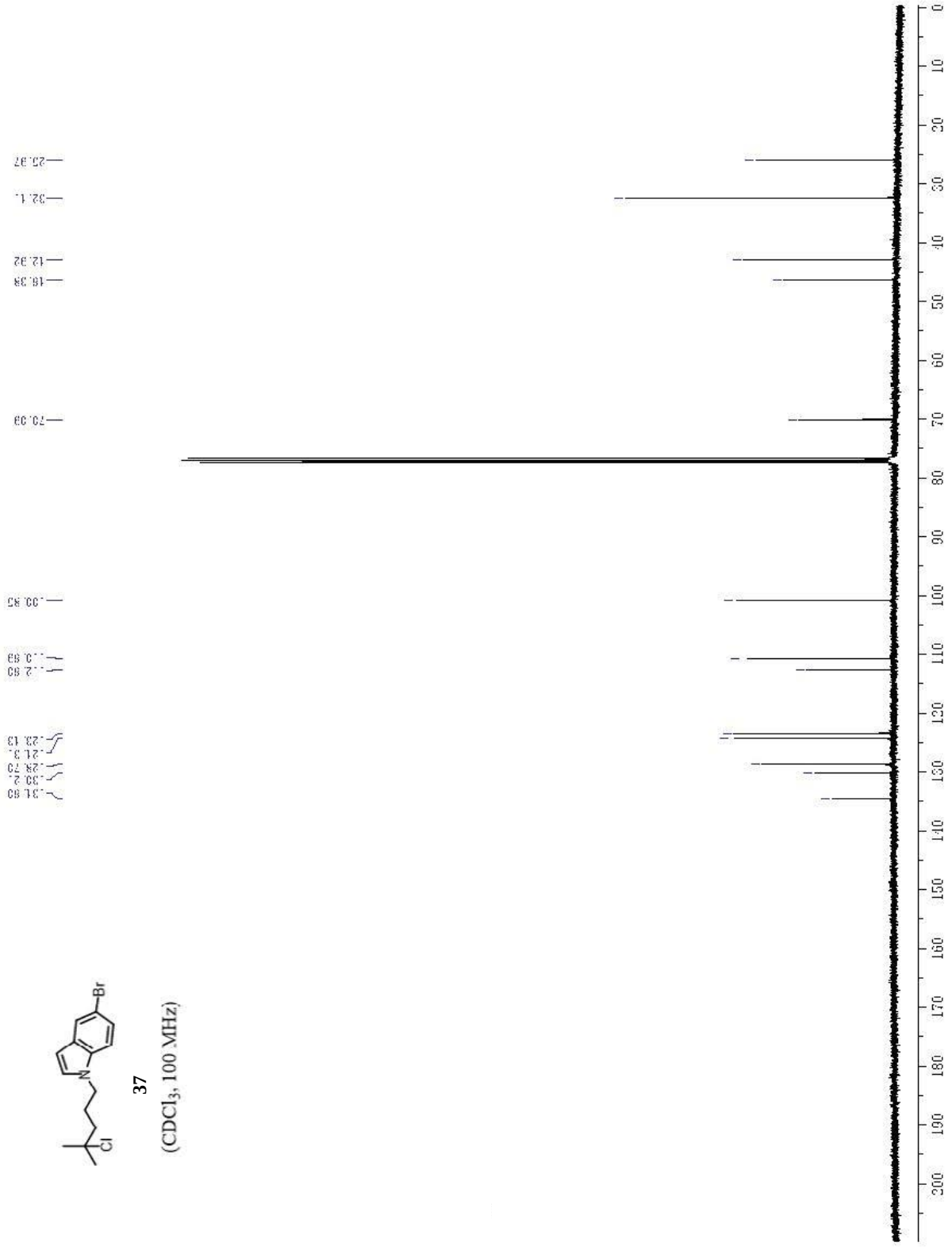
36

($CDCl_3$, 126 MHz)



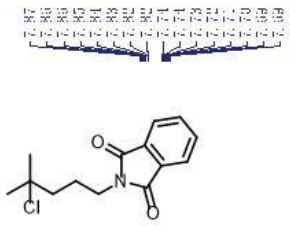
37

($CDCl_3$, 400 MHz)



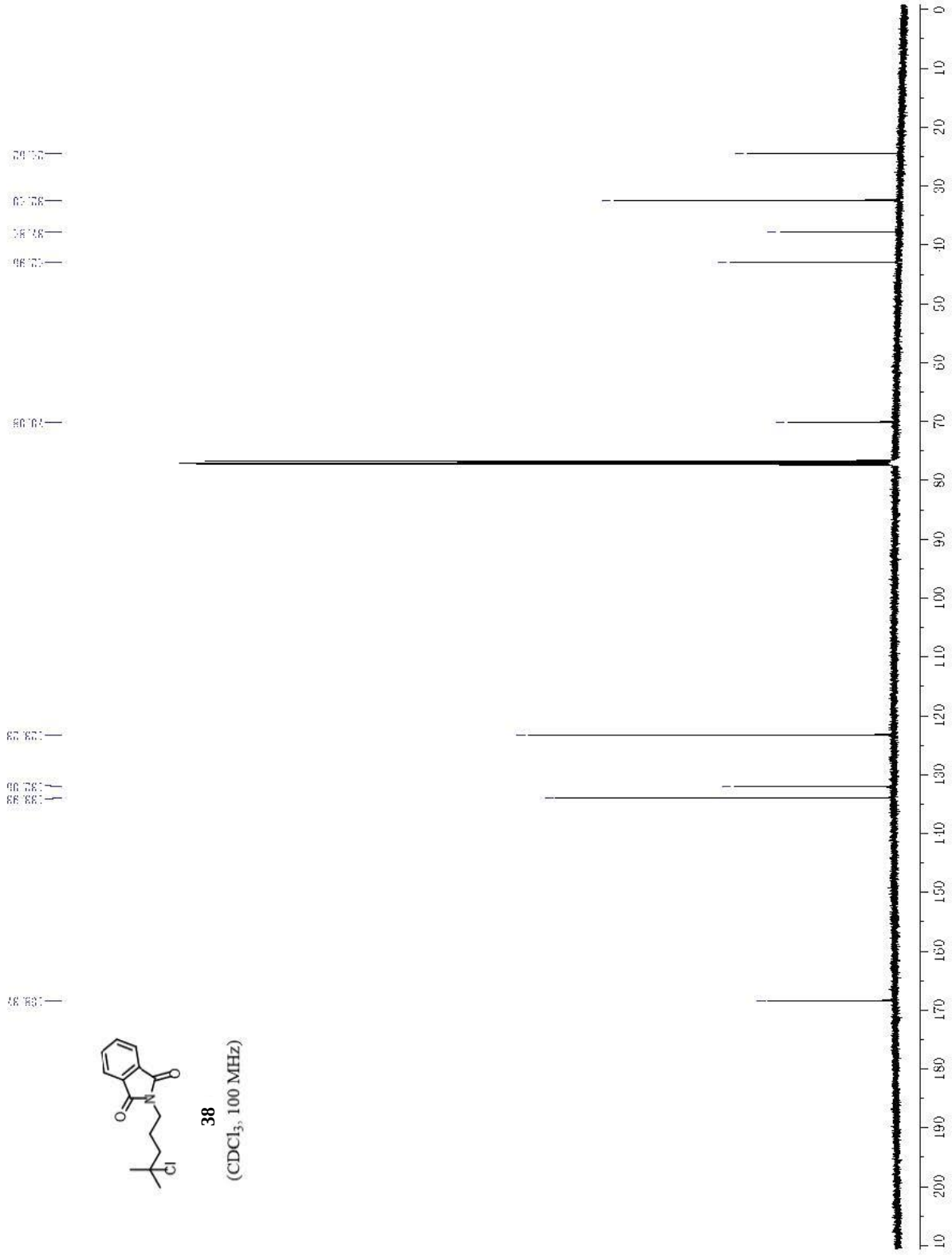
37

($CDCl_3$, 100 MHz)



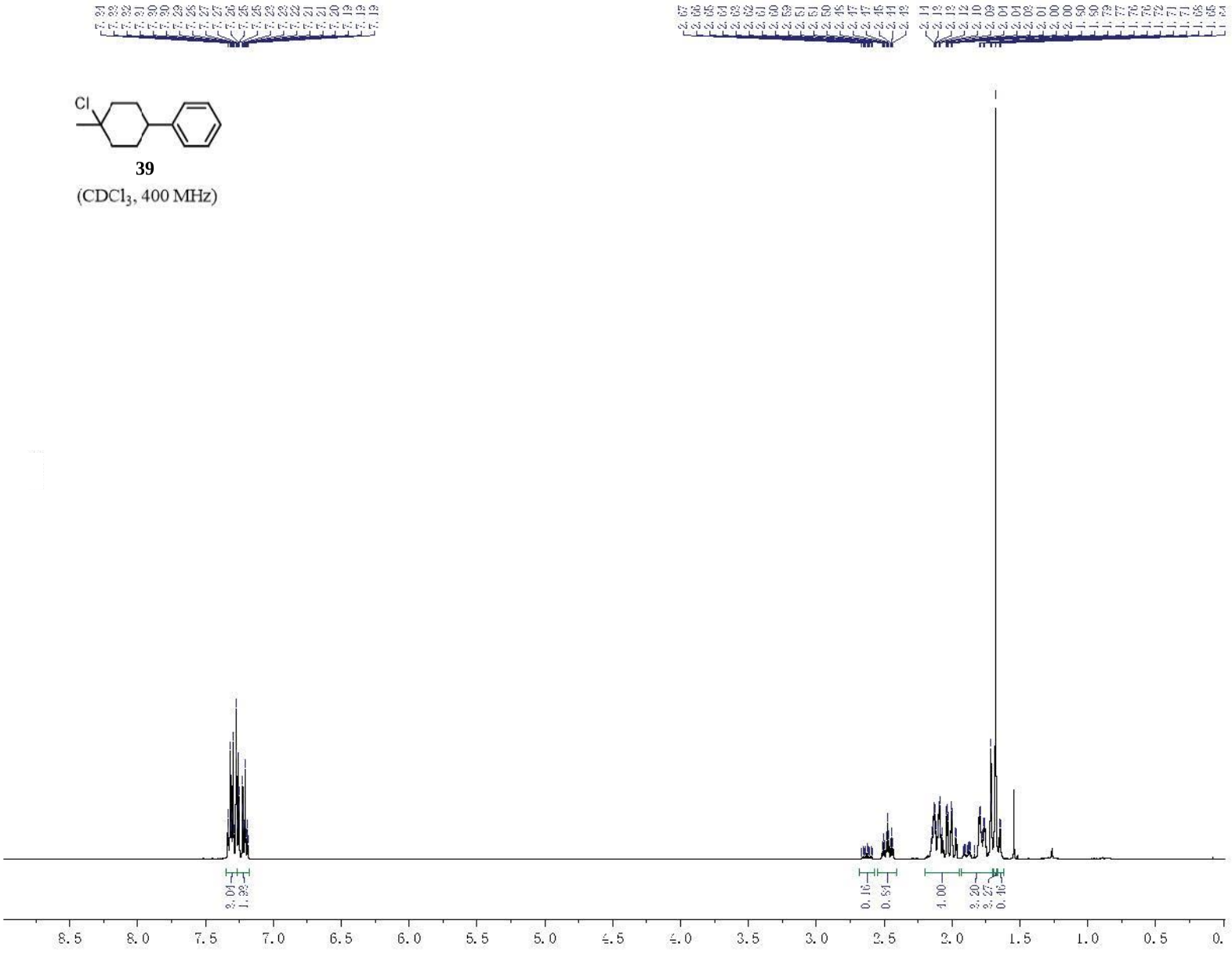
38

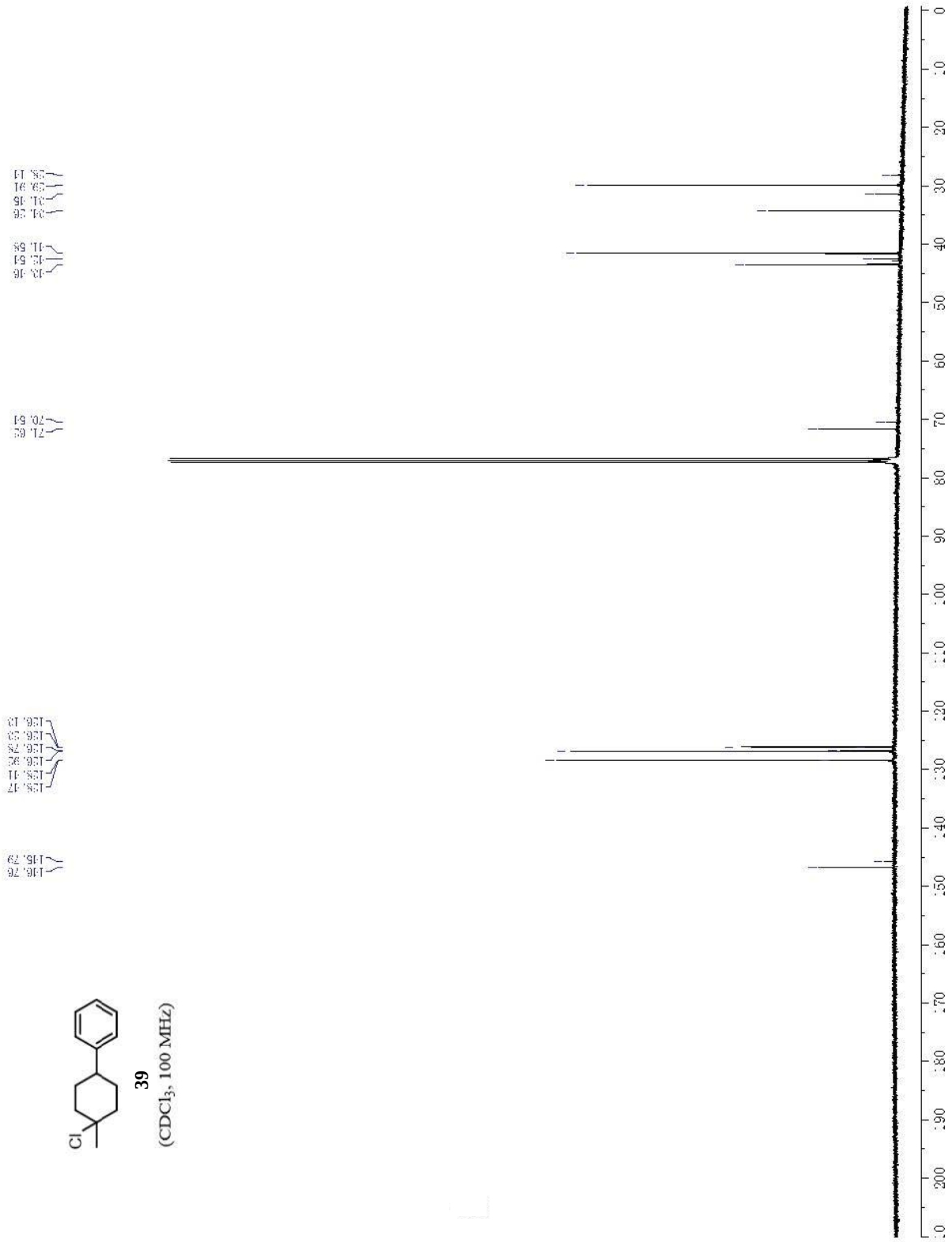
($CDCl_3$, 400 MHz)

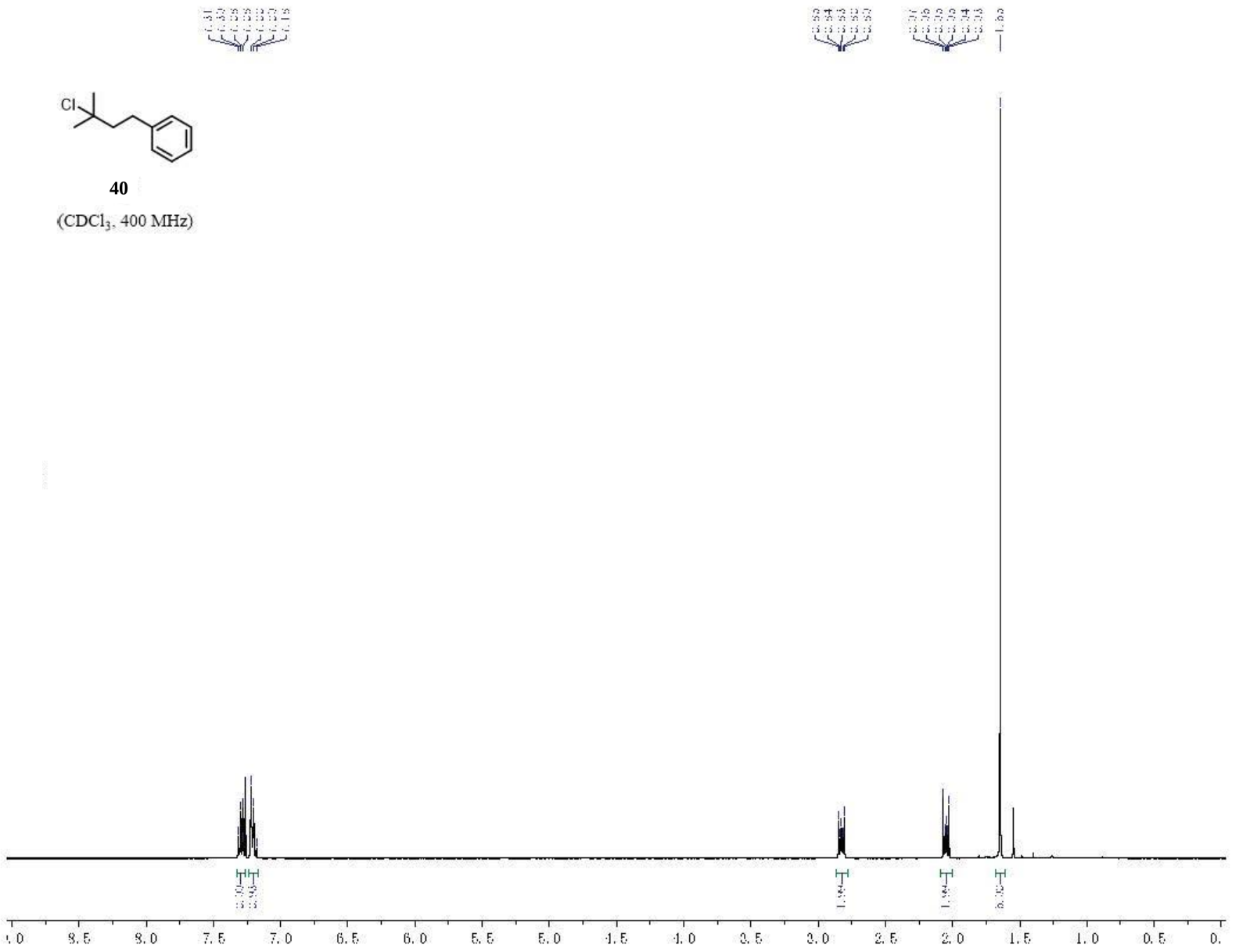


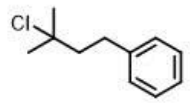
38

($CDCl_3$, 100 MHz)


Cl
39
(CDCl3, 400 MHz)
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.

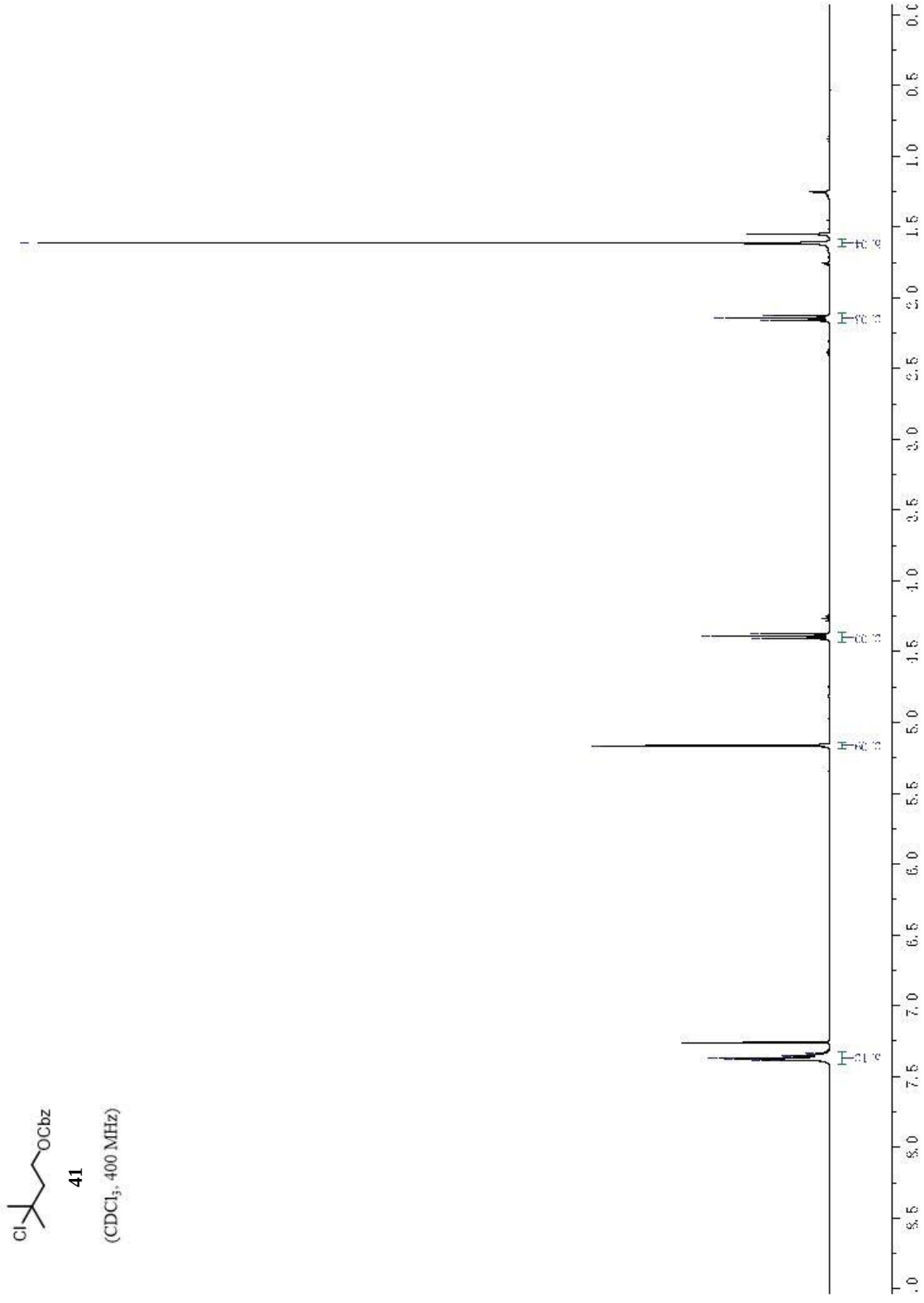

Cl
39
(CDCl3, 100 MHz)


Cl
40
(CDCl3, 400 MHz)



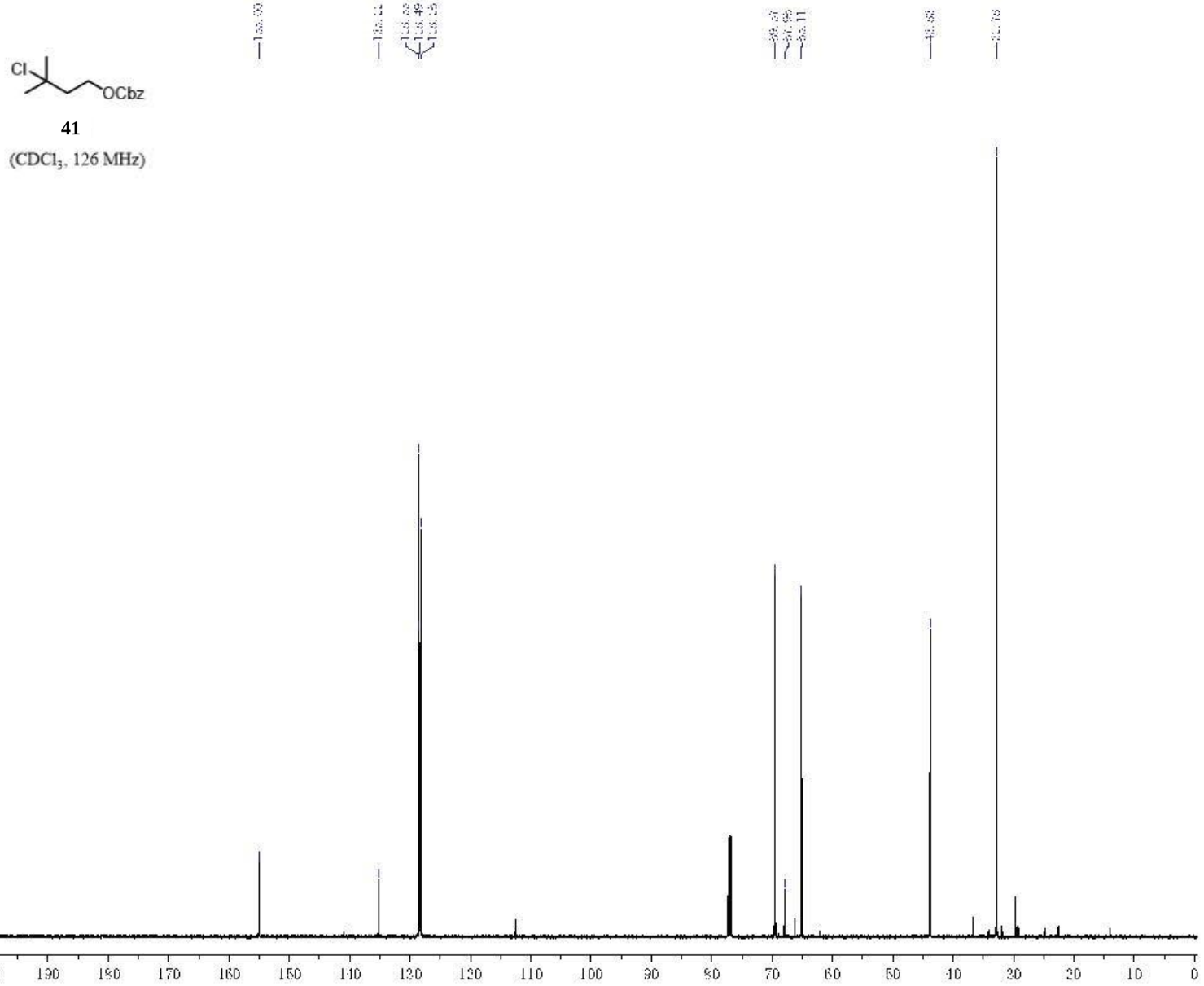
40

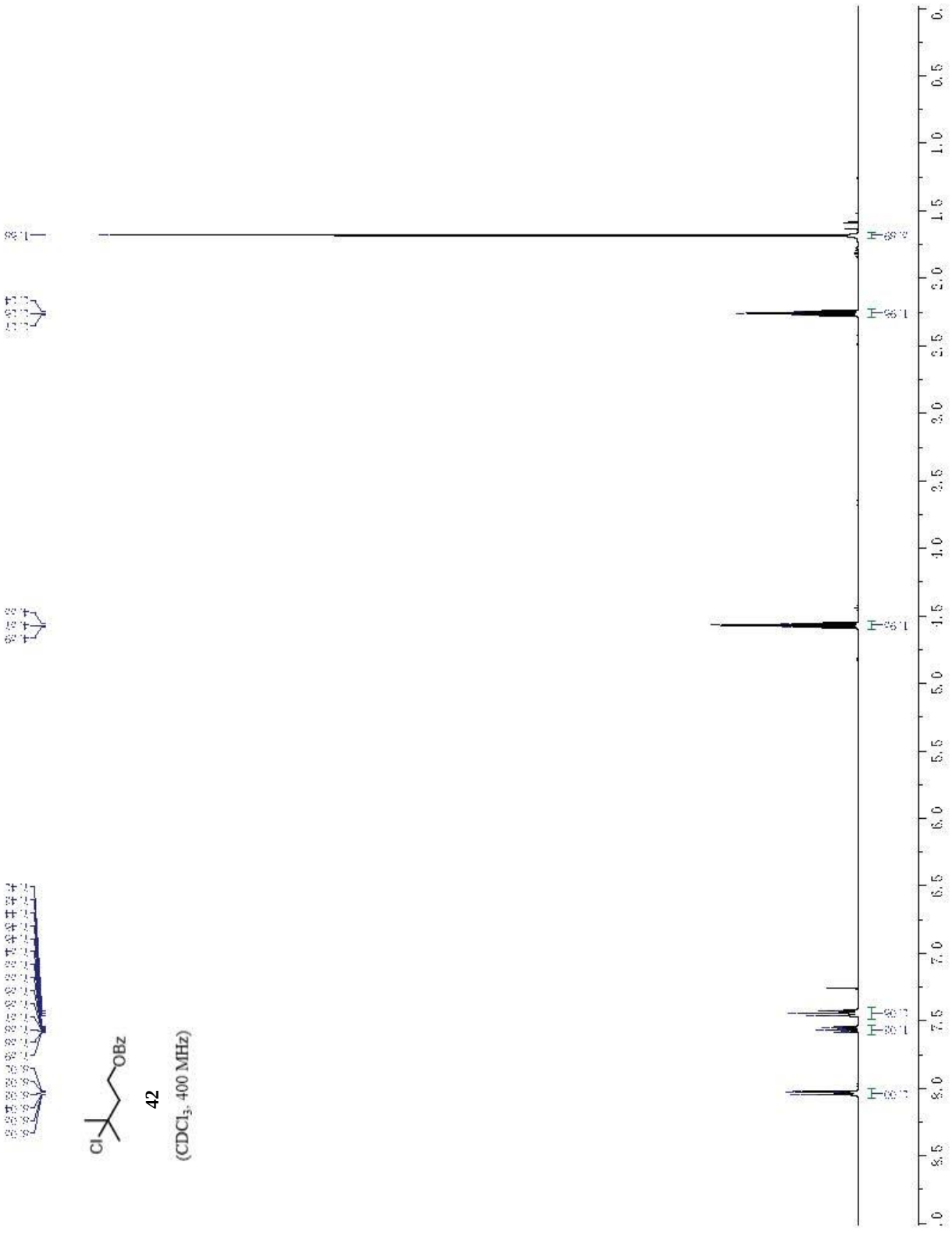
($CDCl_3$, 100 MHz)



41

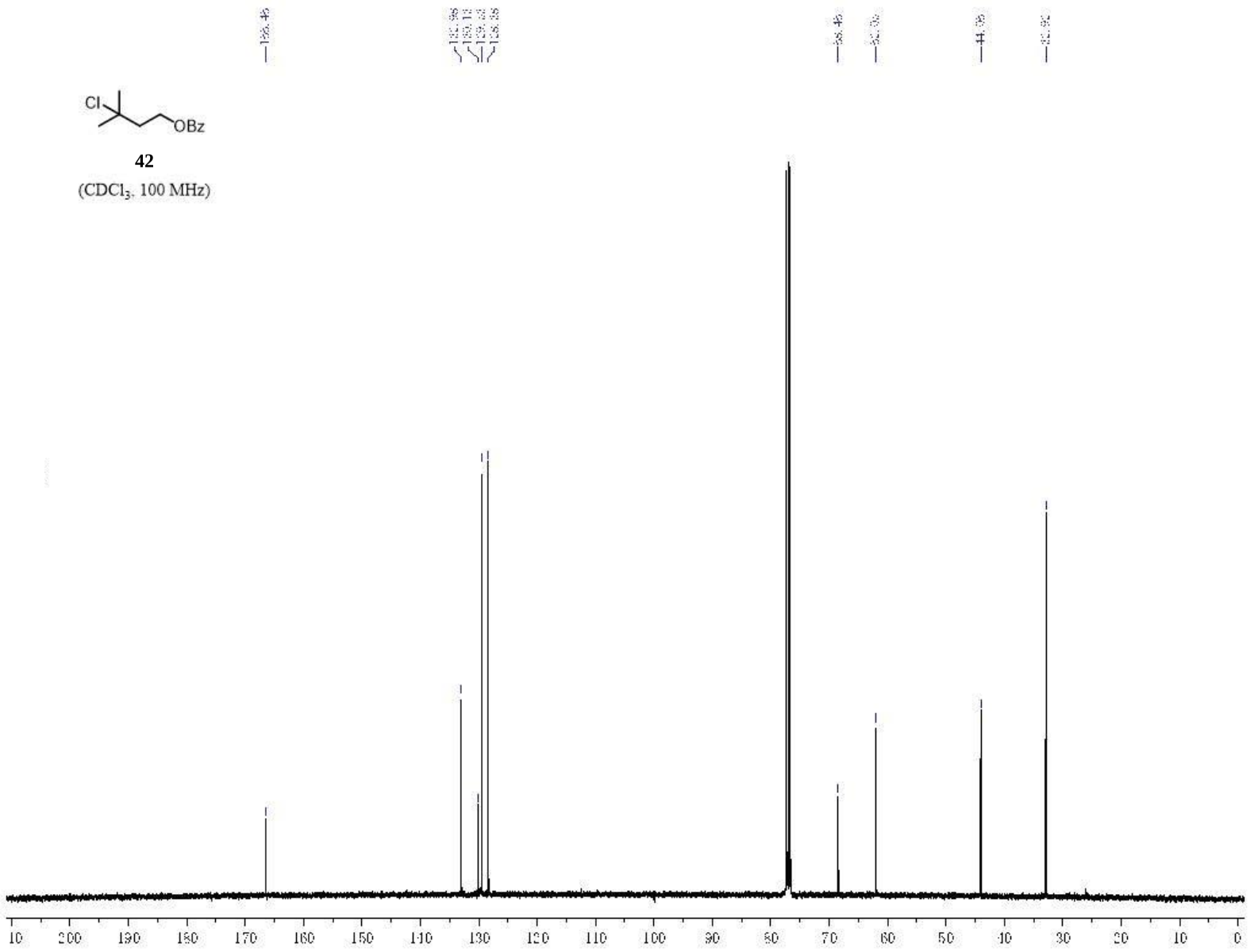
($CDCl_3$, 400 MHz)

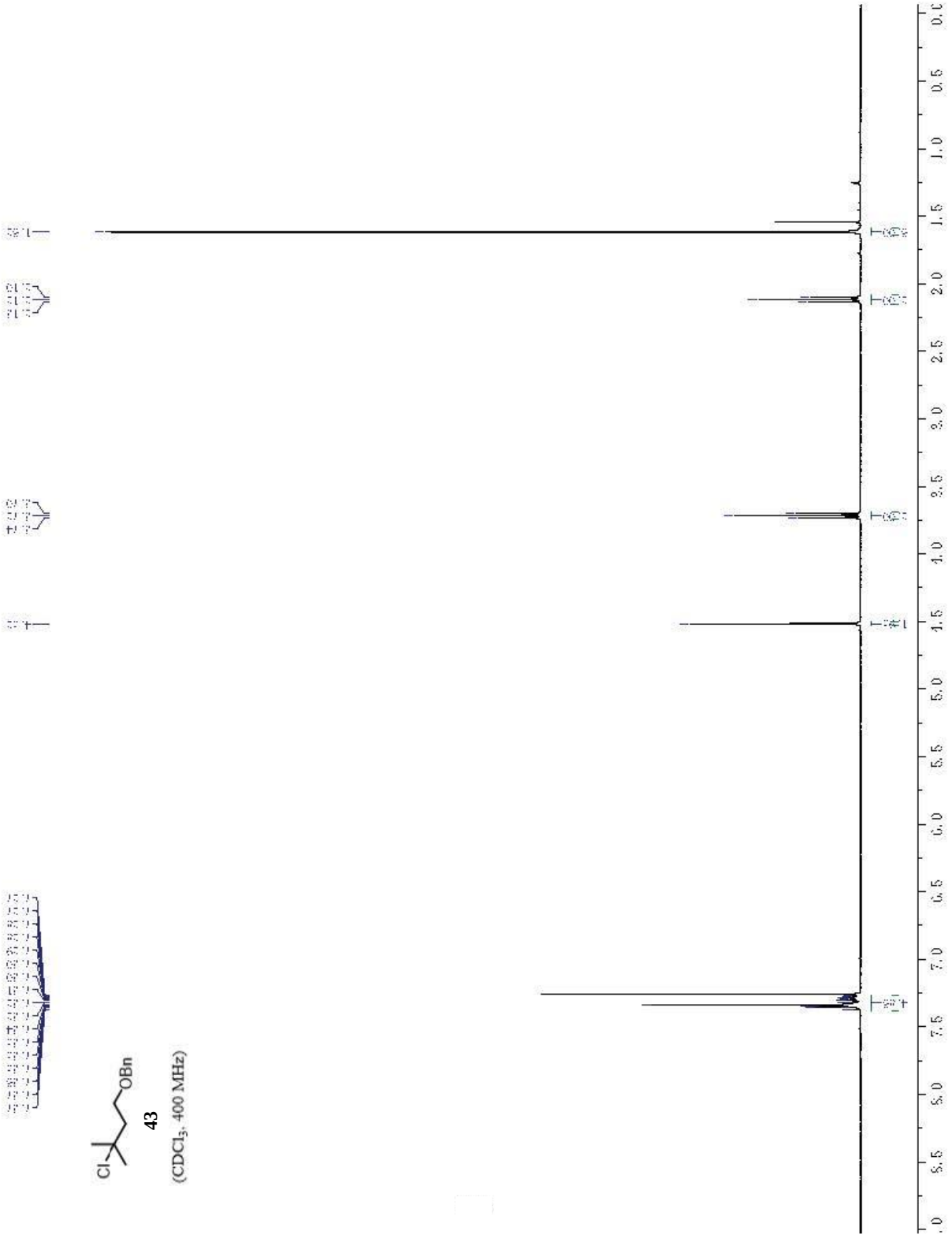

Cl
OCbz
41
(CDCl3, 126 MHz)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

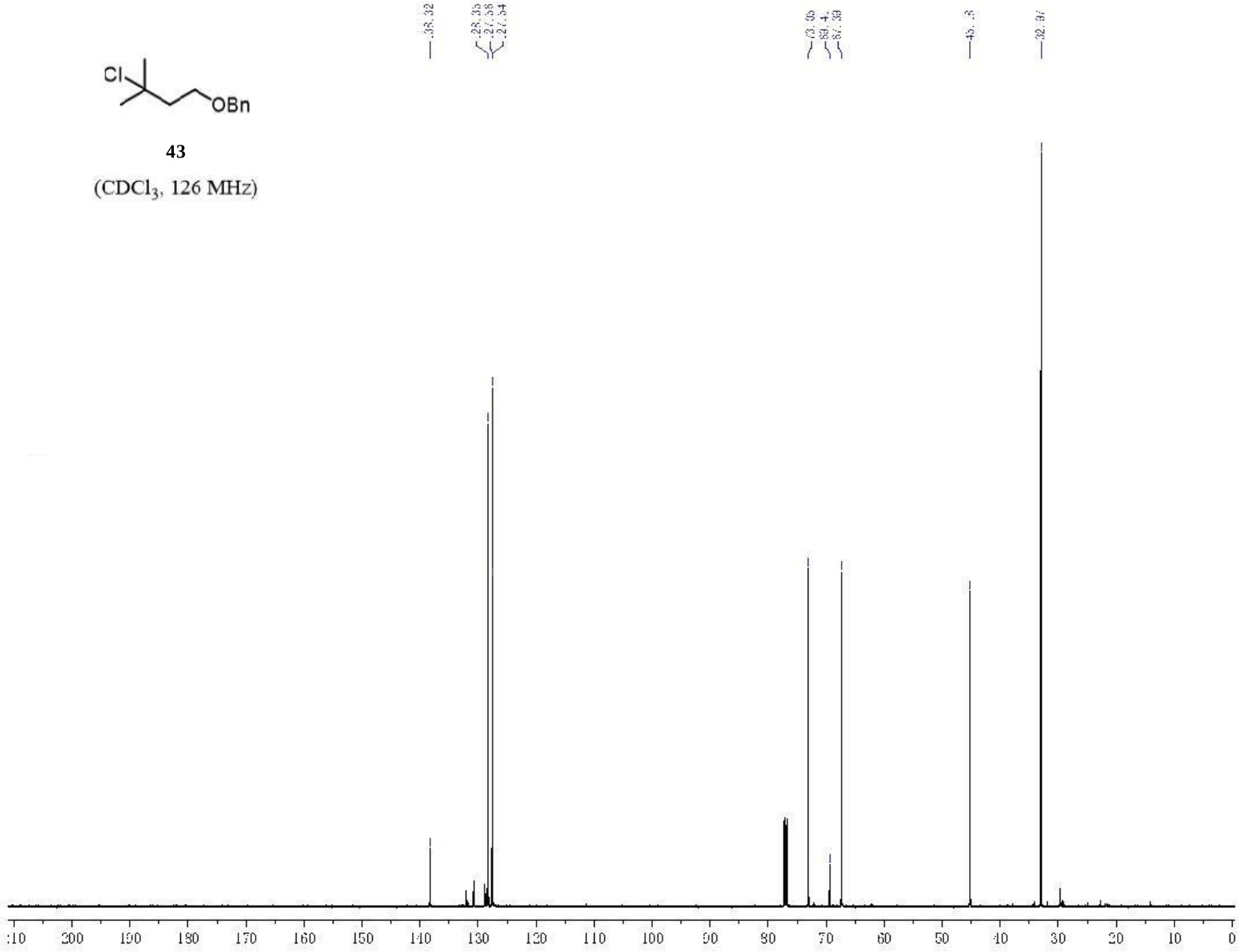


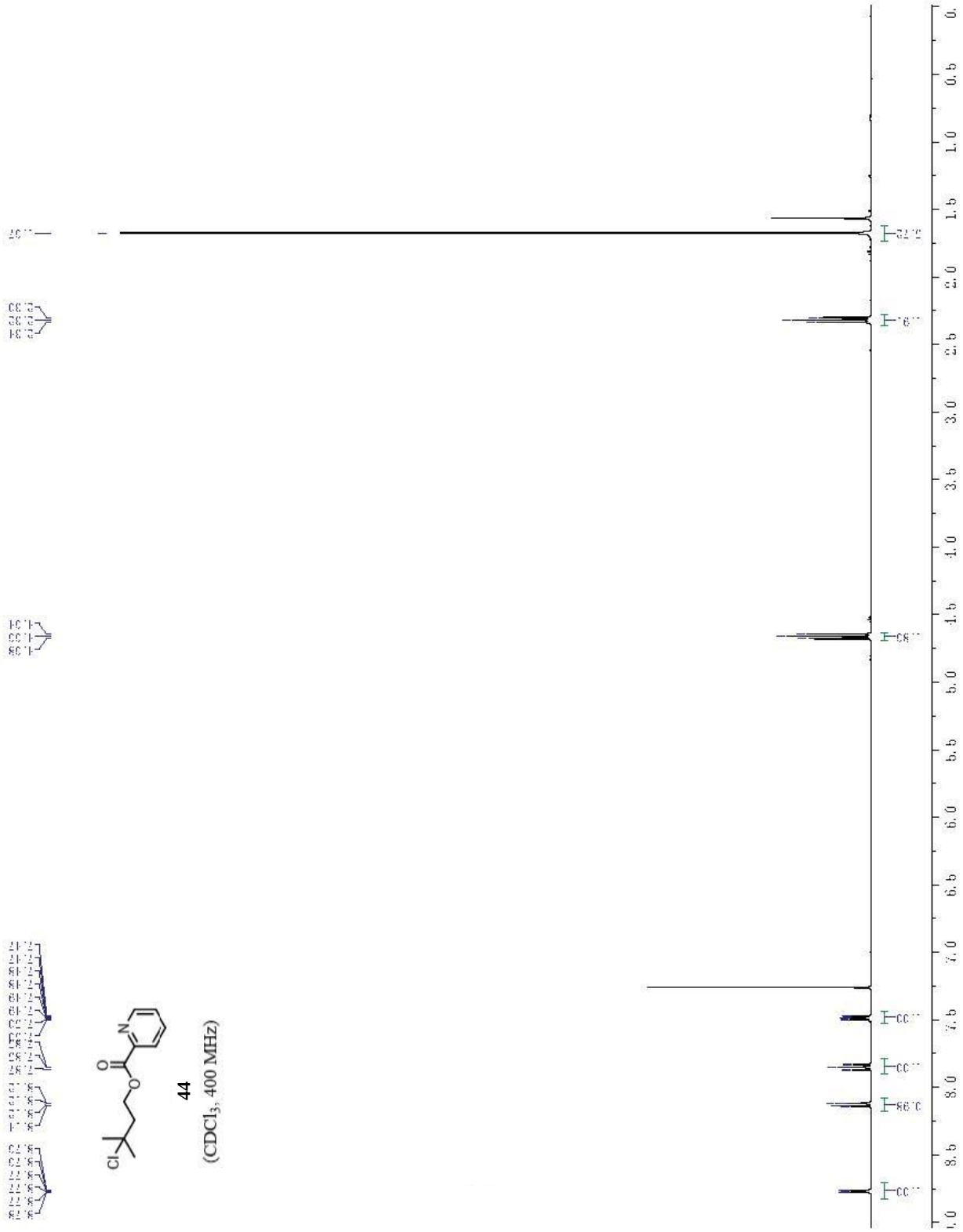
42

($CDCl_3$, 400 MHz)


Cl
OBz
42
(CDCl3, 100 MHz)

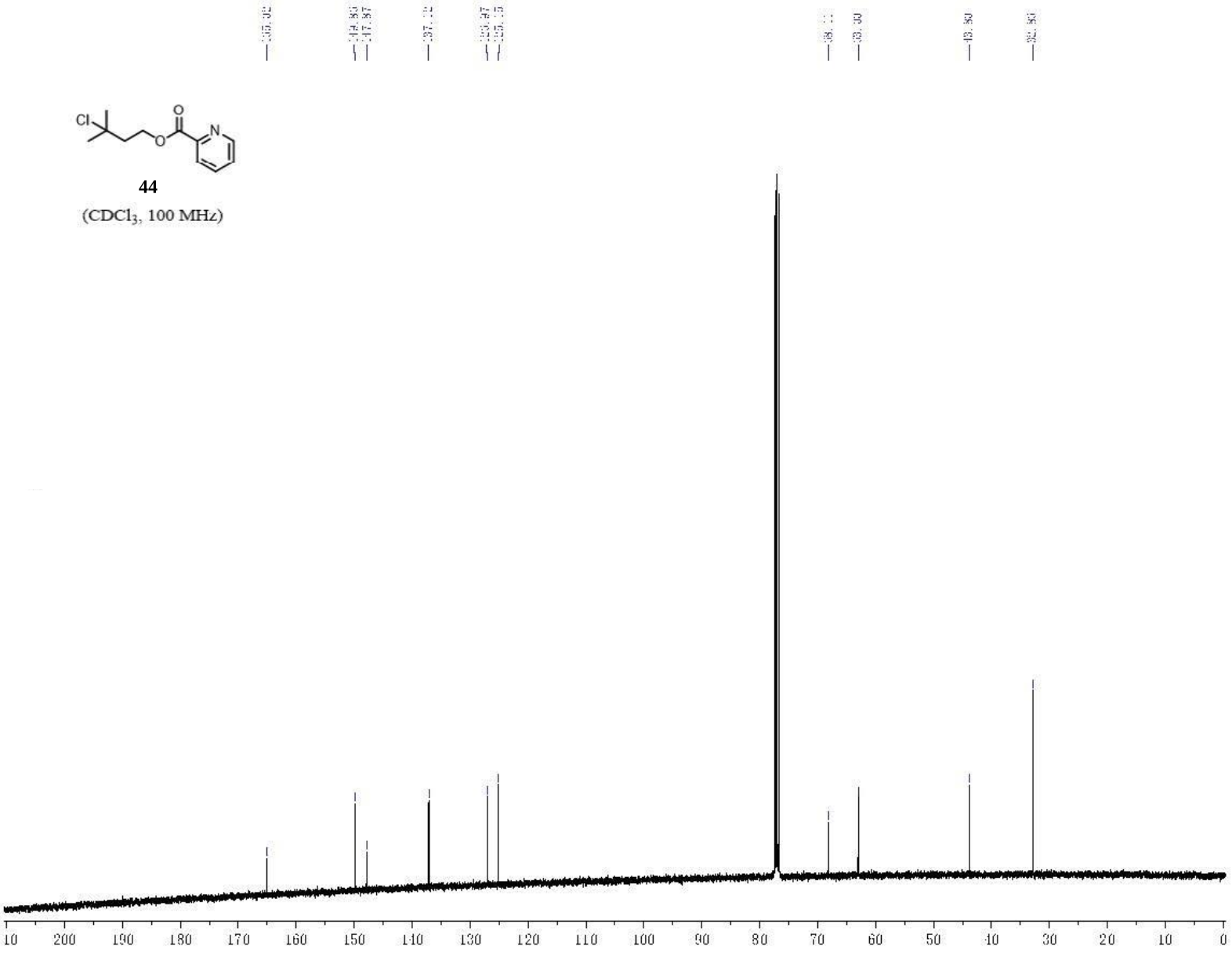

Cl
OBn
43
($CDCl_3$, 400 MHz)

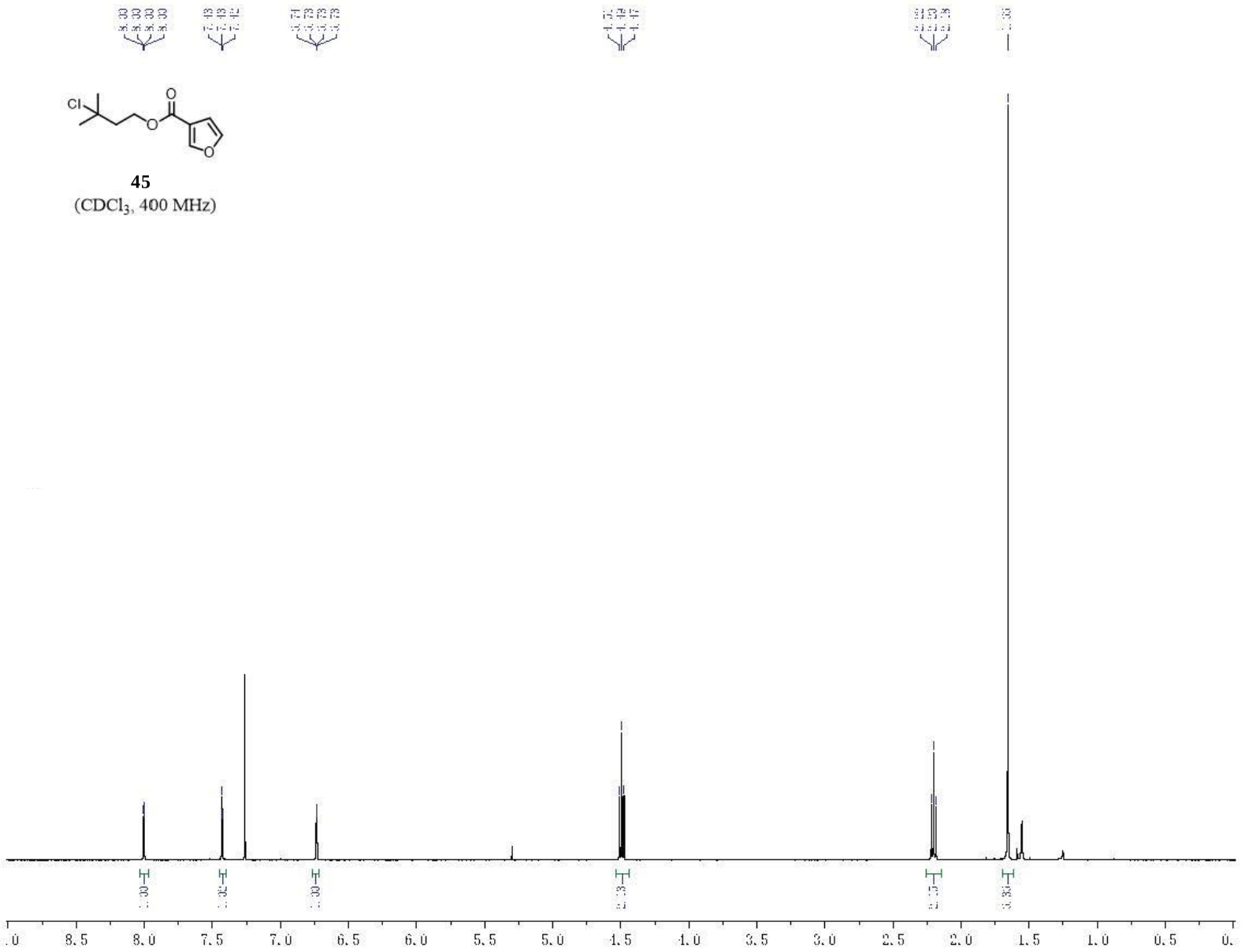

Cl
OBn
43
(CDCl3, 126 MHz)
138.32
128.35
127.58
127.34
73.05
69.47
67.59
43.38
32.87
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0



44

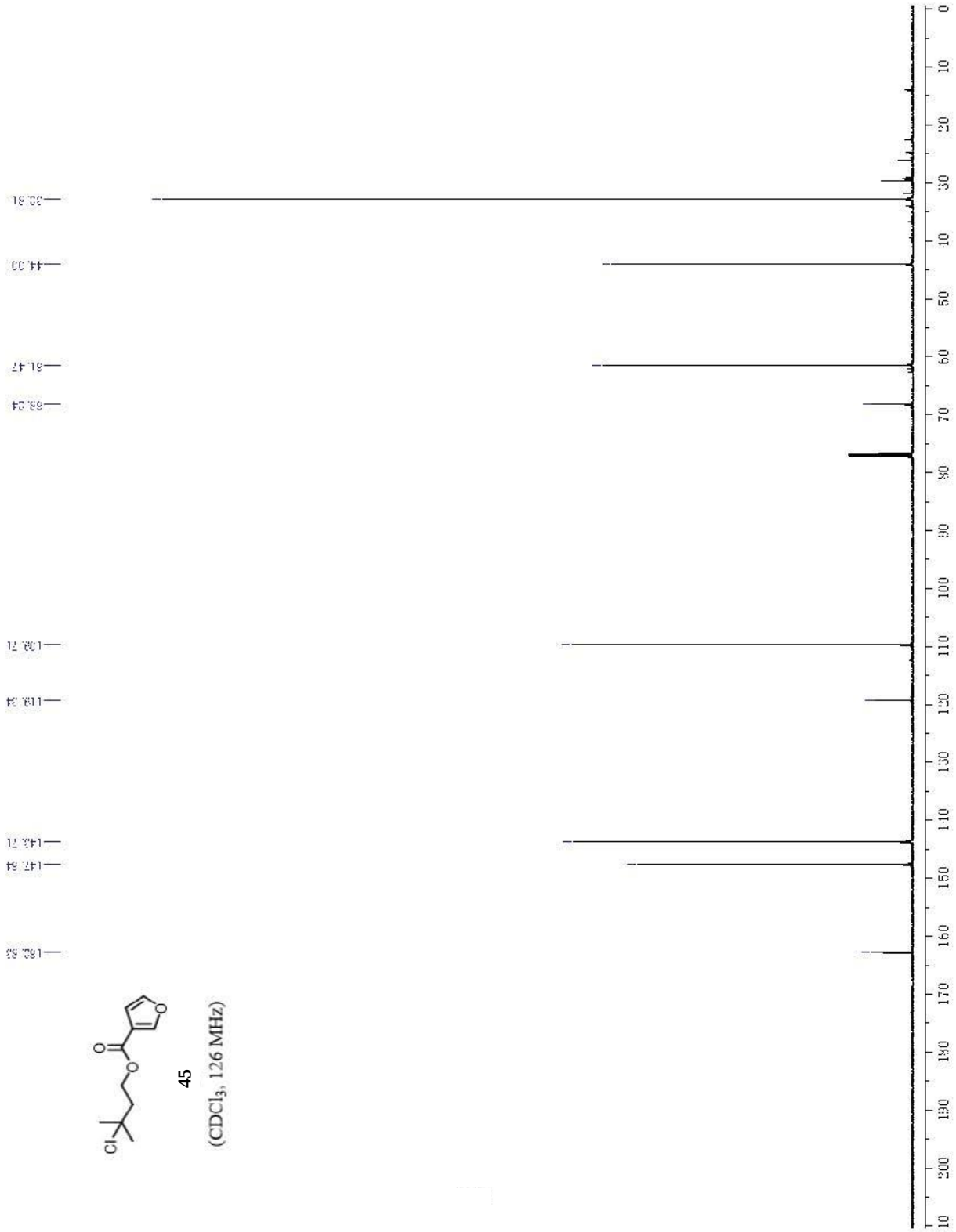
($CDCl_3$, 400 MHz)

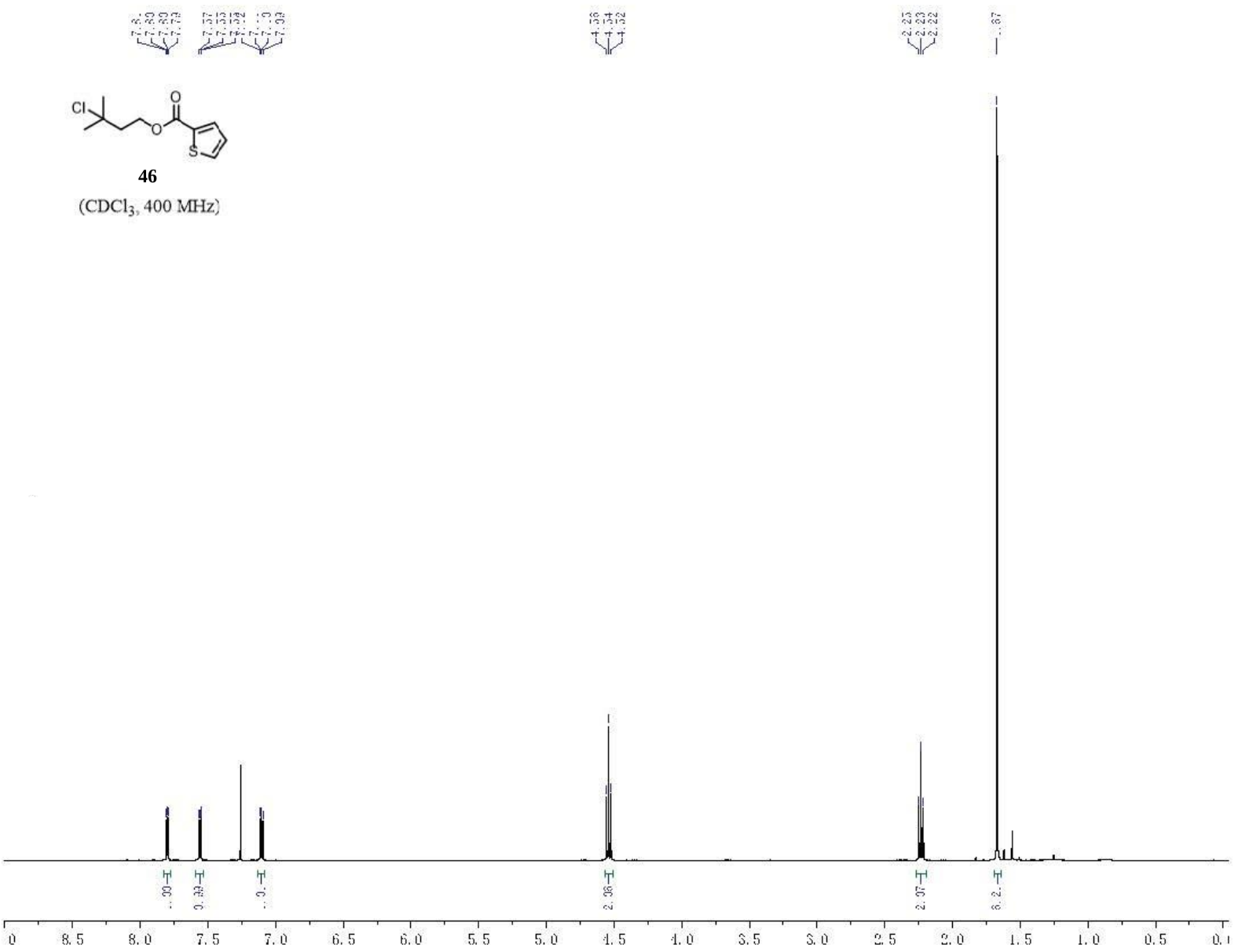

Cl
O
O
N
44
(CDCl3, 100 MHz)
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

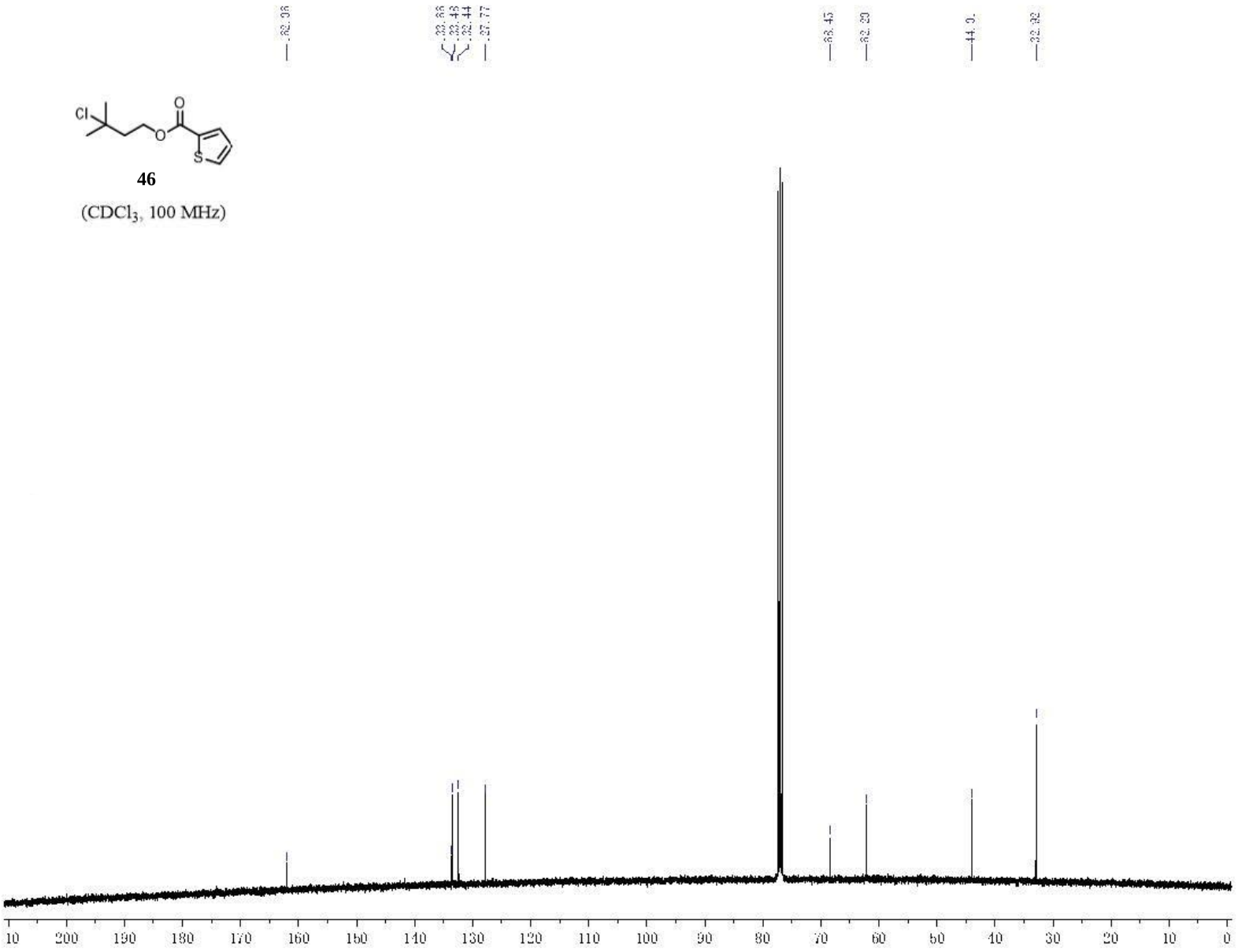


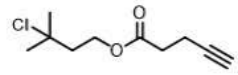
45

($CDCl_3$, 400 MHz)


O
O
O
Cl
45
(CDCl3, 126 MHz)

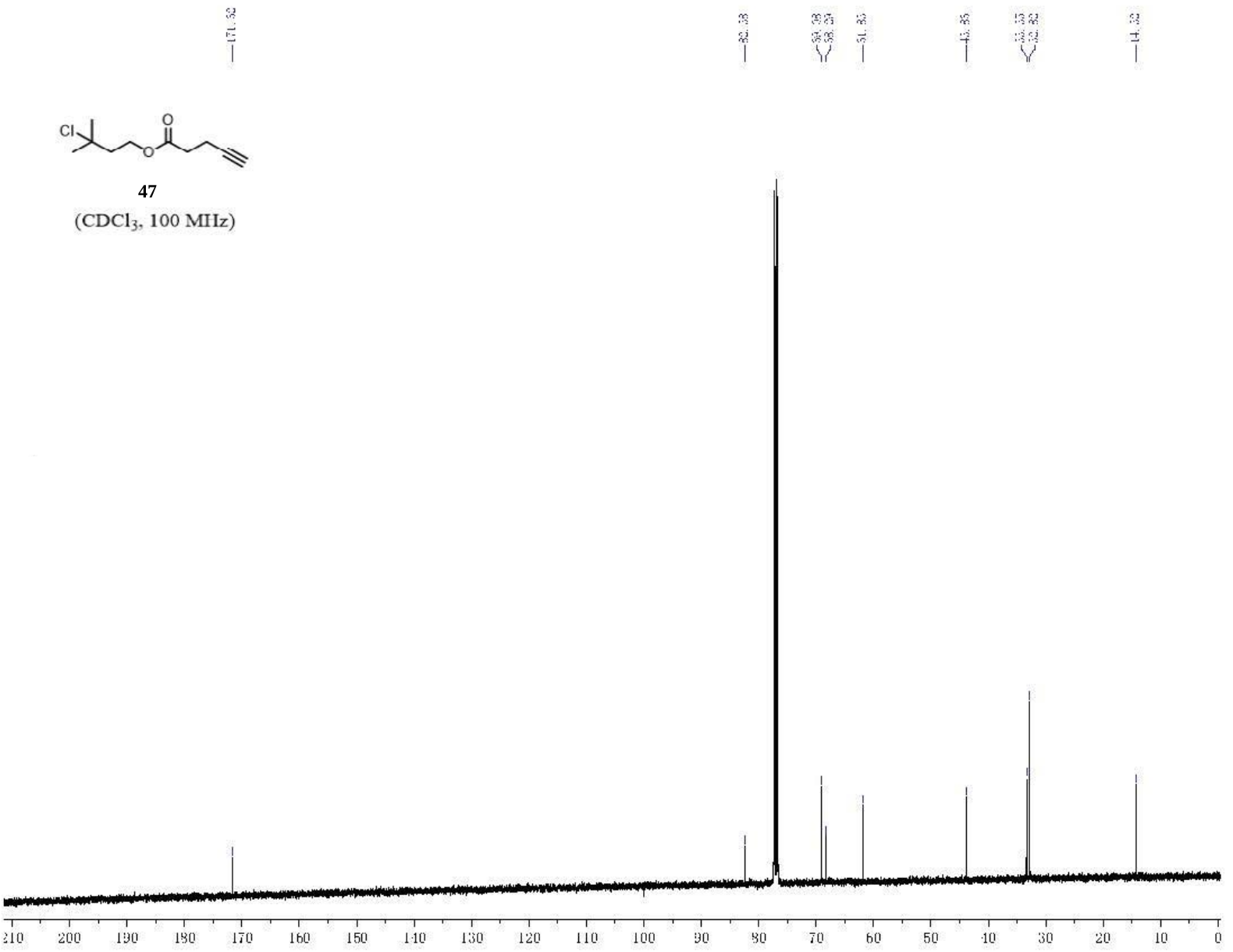

Cl
O
O
S
46
(CDCl3, 400 MHz)

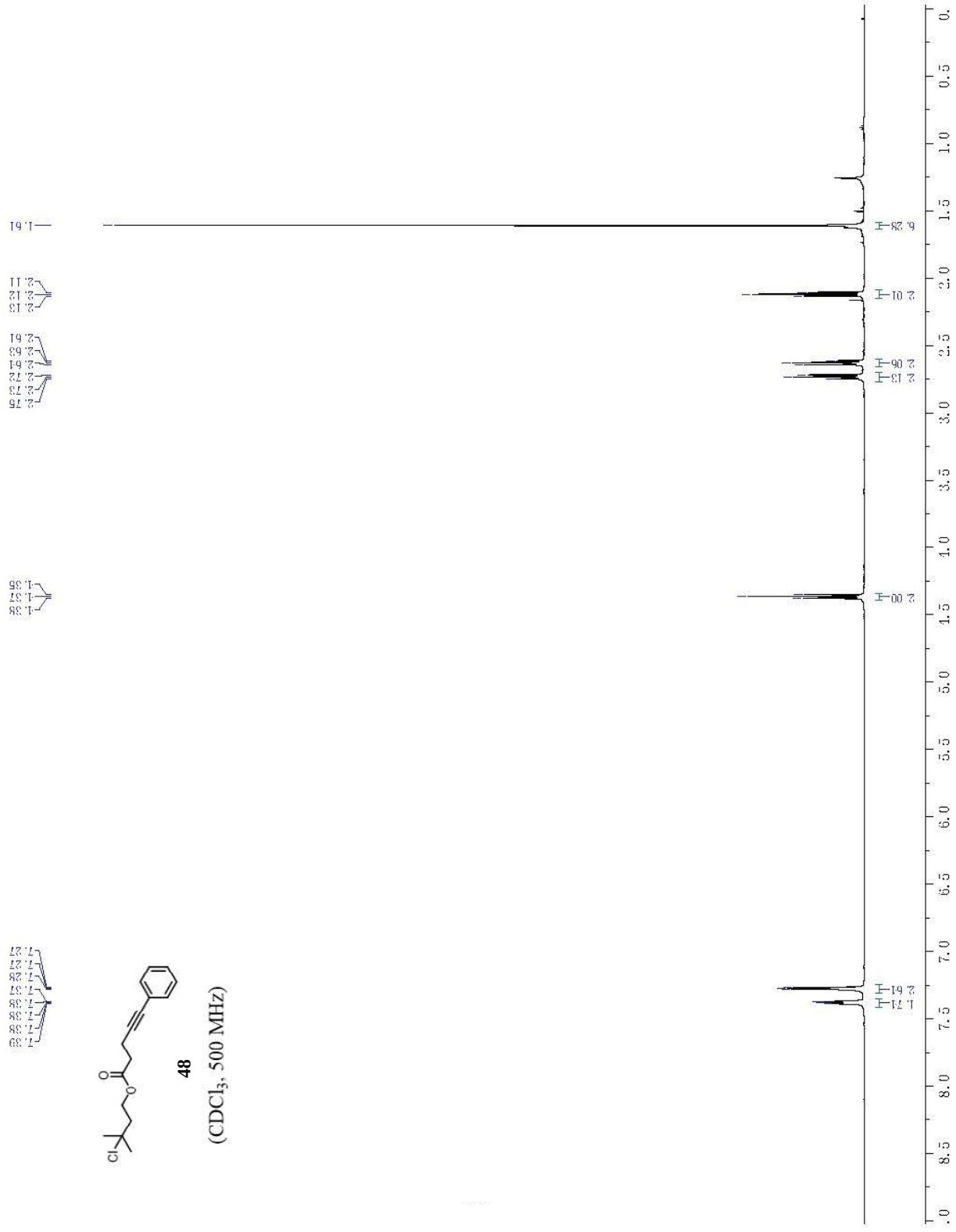

162.36
133.88
133.43
132.44
127.77
83.45
82.29
44.9
32.82
Cl
O
O
S
46
(CDCl3, 100 MHz)
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

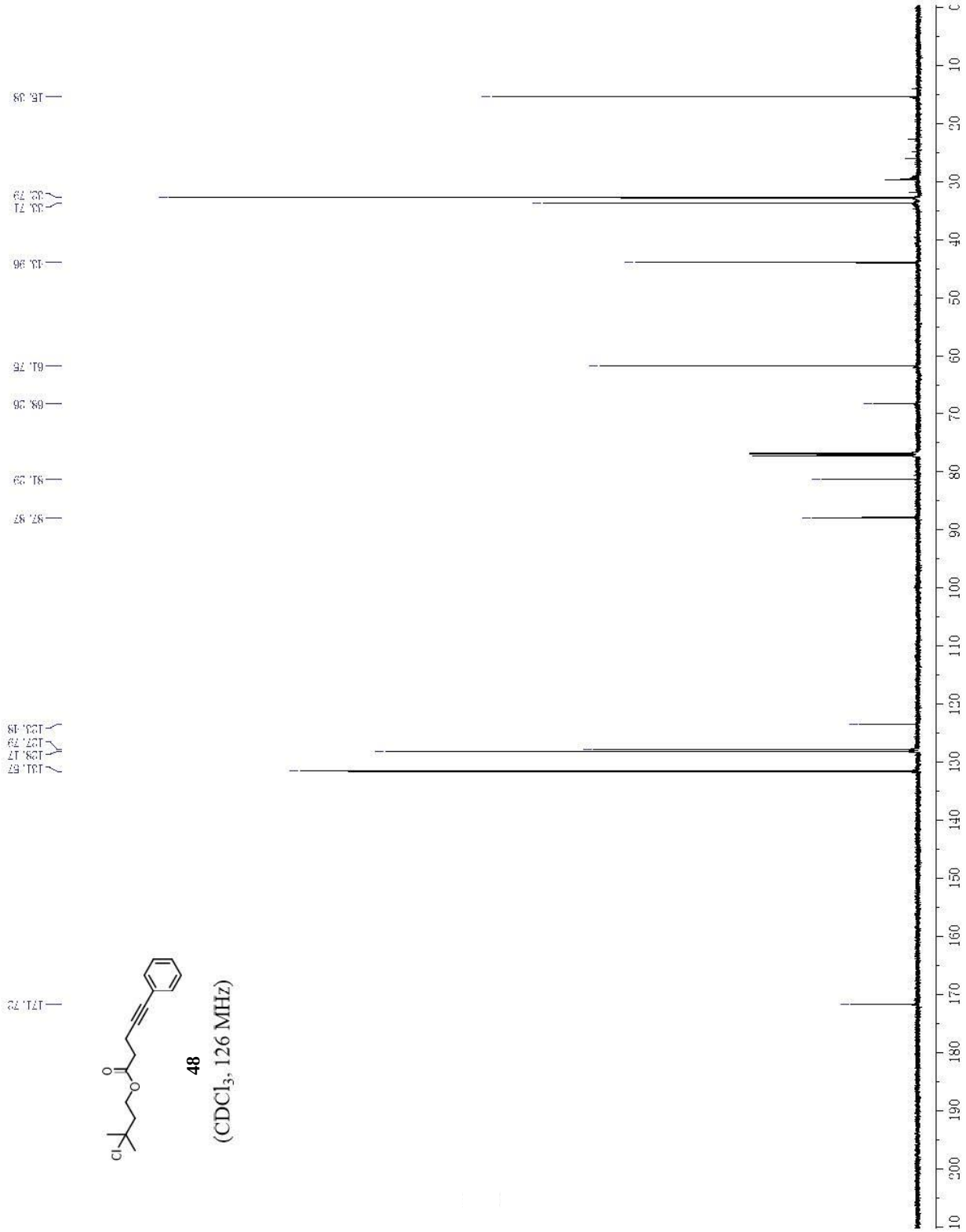


47

($CDCl_3$, 400 MHz)

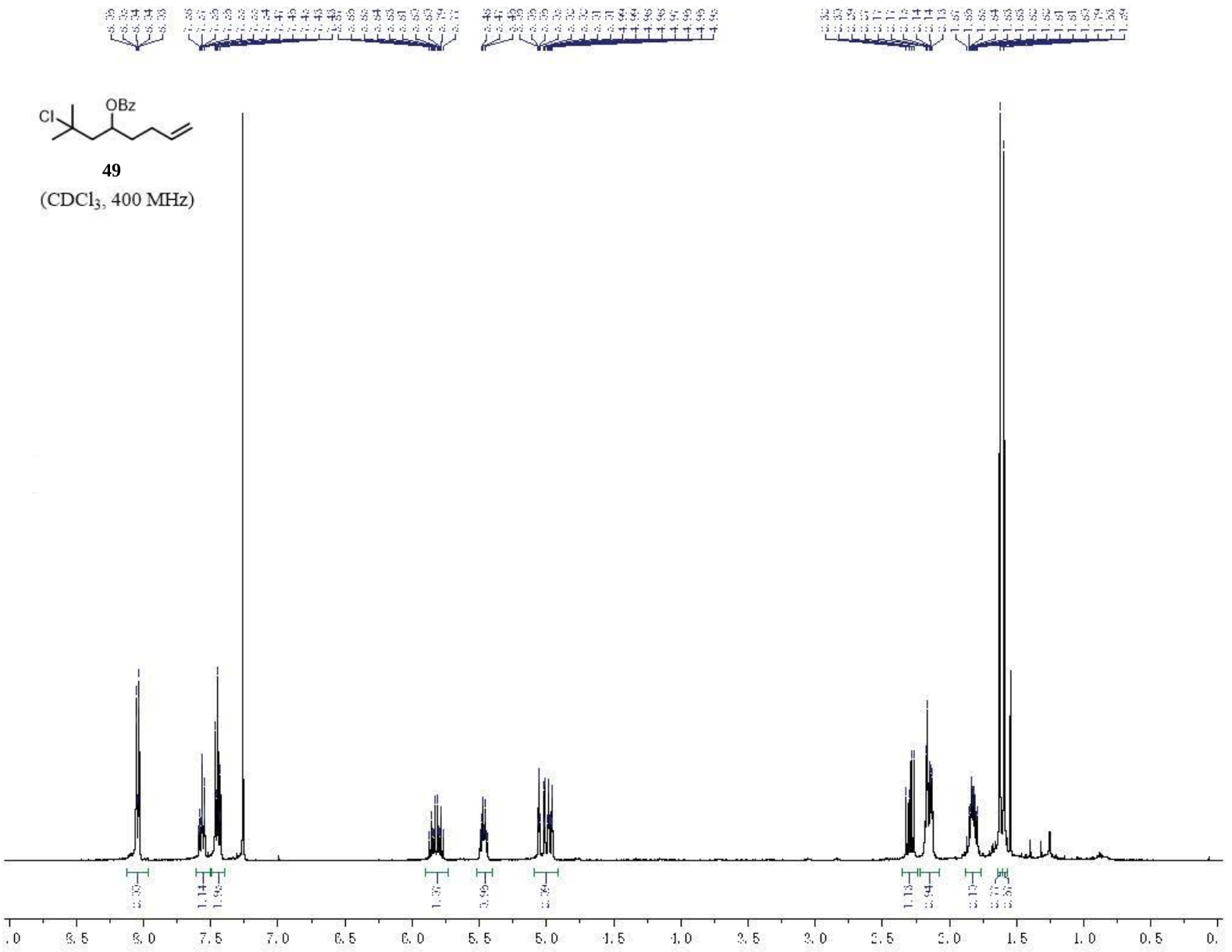

171.52
82.38
69.08
68.24
51.85
43.85
33.13
32.82
14.52
Cl
O
O
47
(CDCl3, 100 MHz)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


48
(CDCl3, 500 MHz)



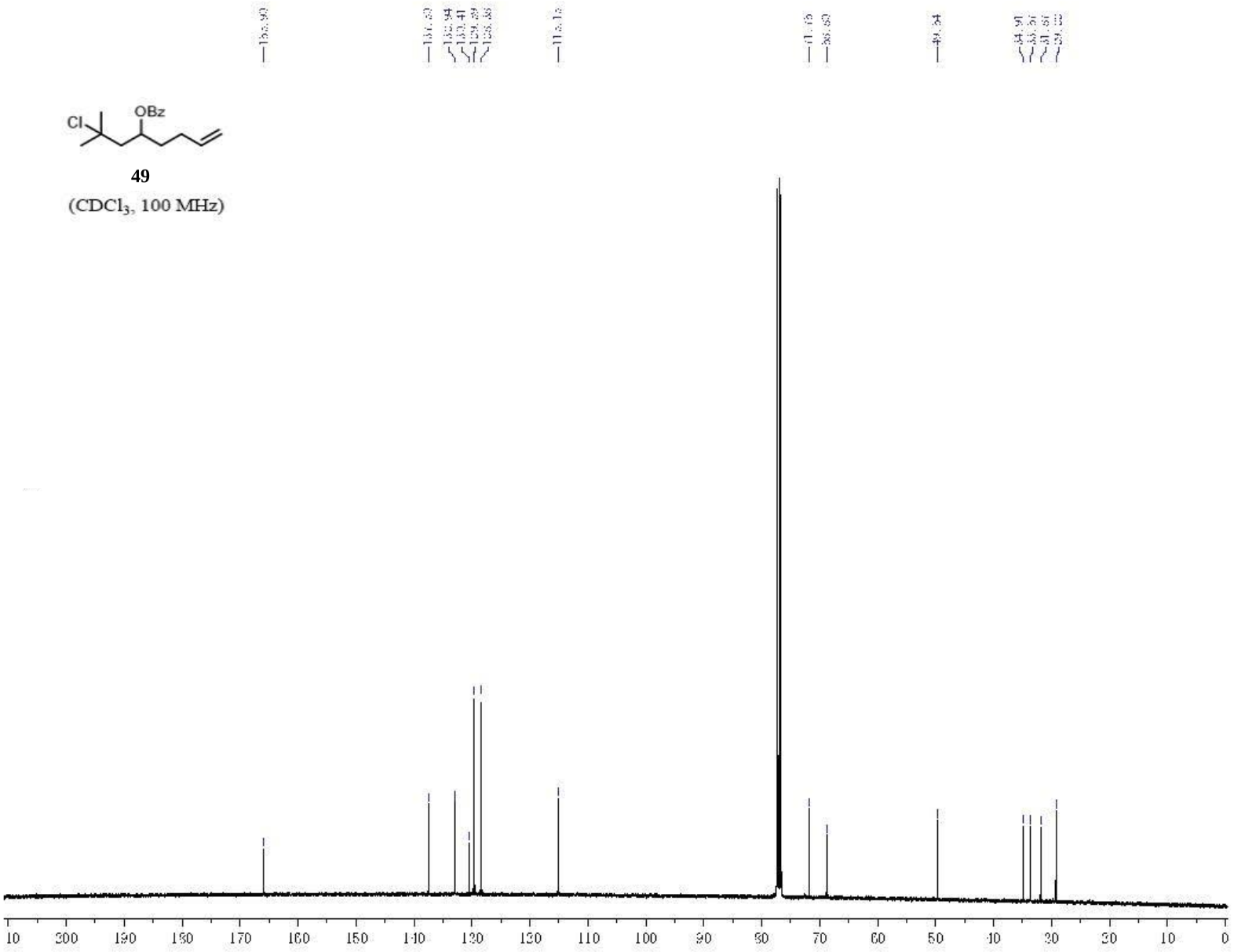
48

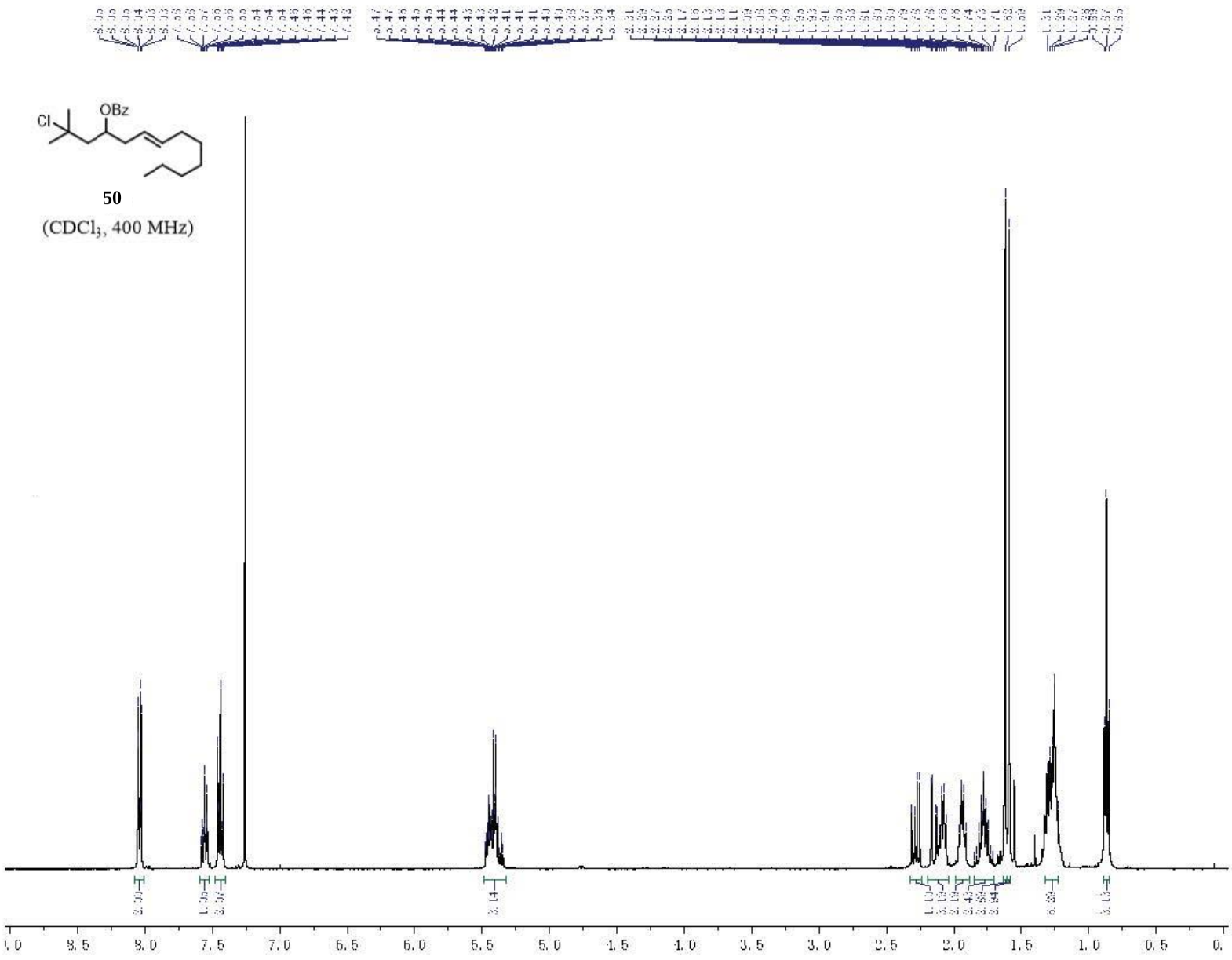
($CDCl_3$, 126 MHz)



49

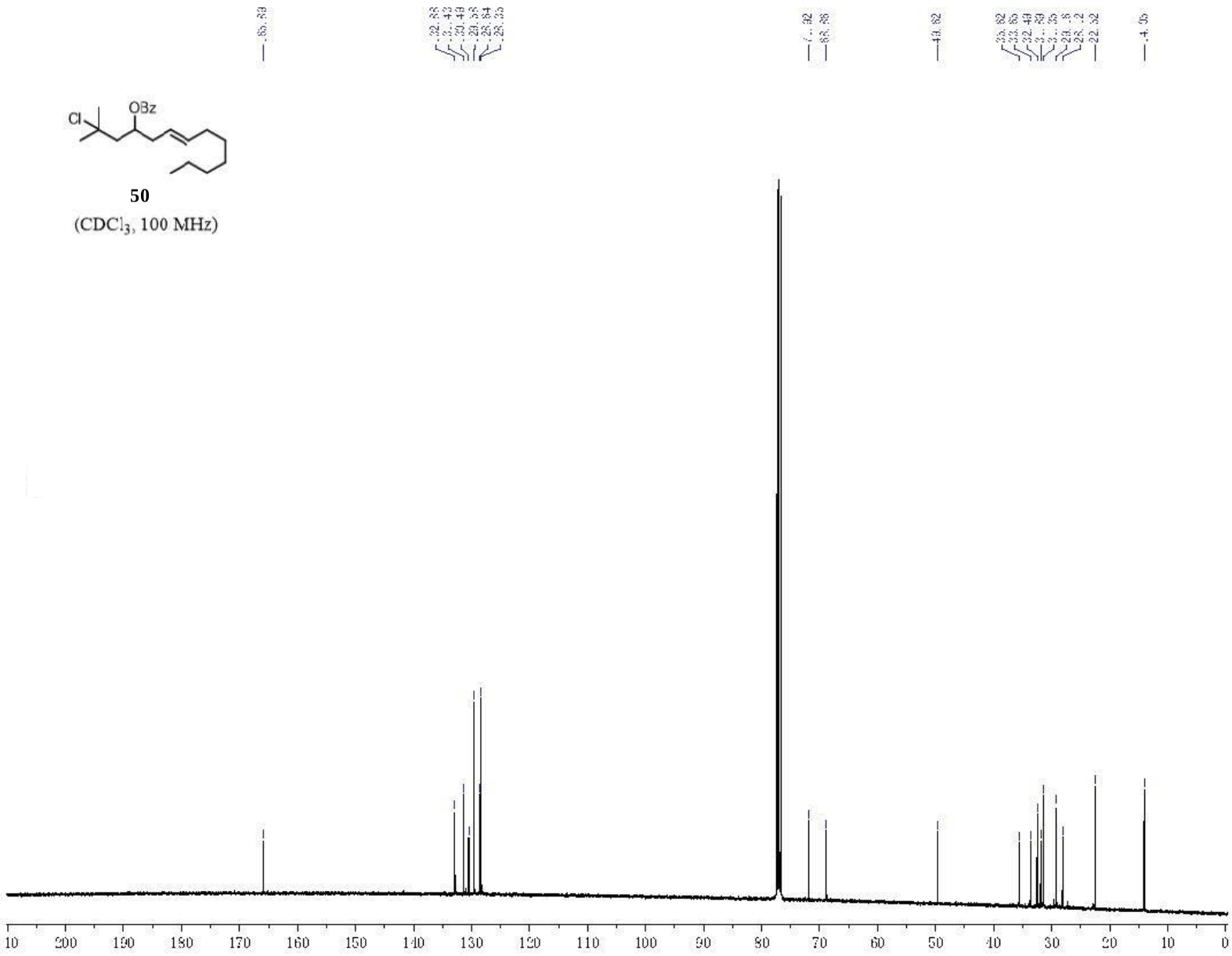
($CDCl_3$, 400 MHz)

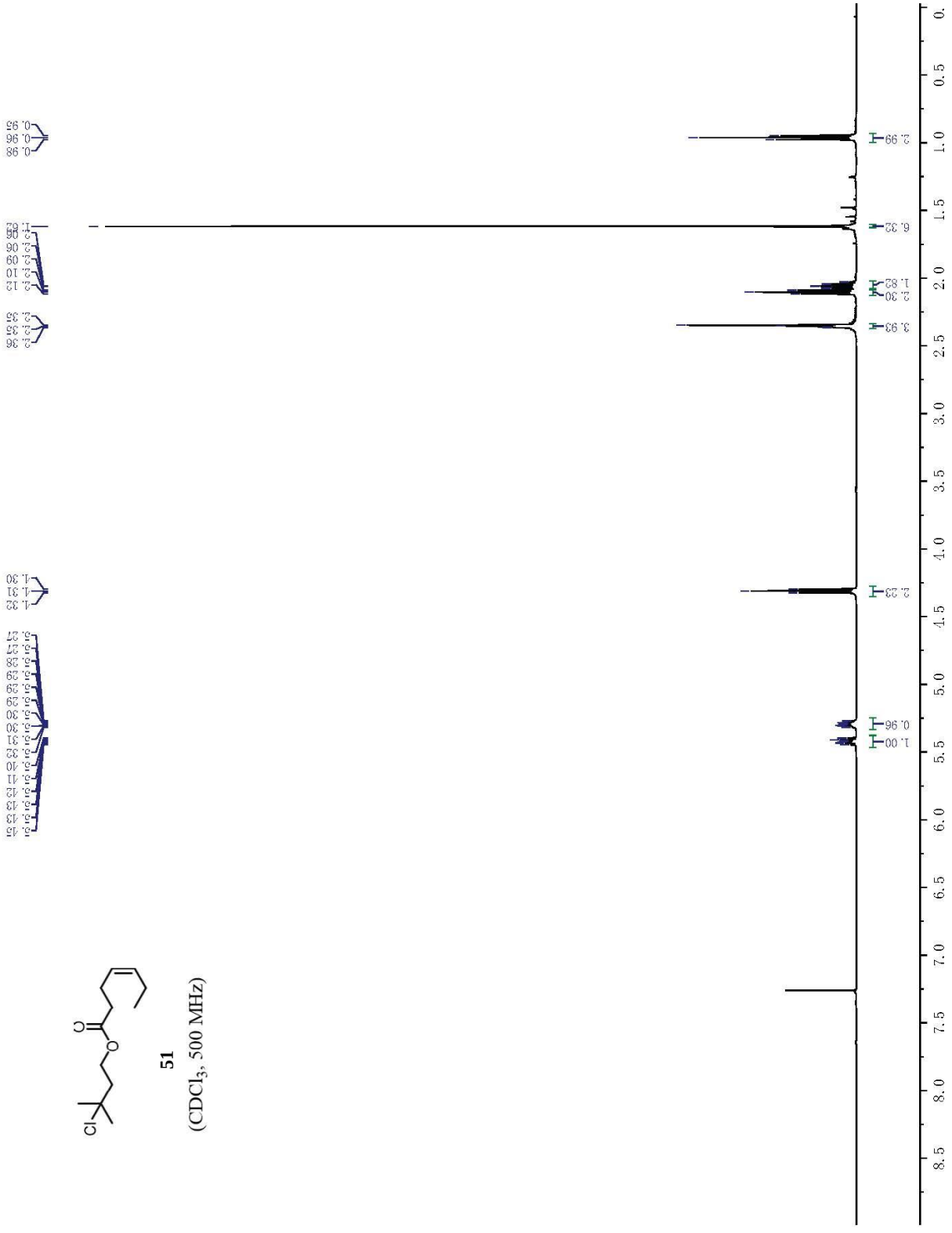

Cl
OBz
49
(CDCl3, 100 MHz)



50

($CDCl_3$, 400 MHz)

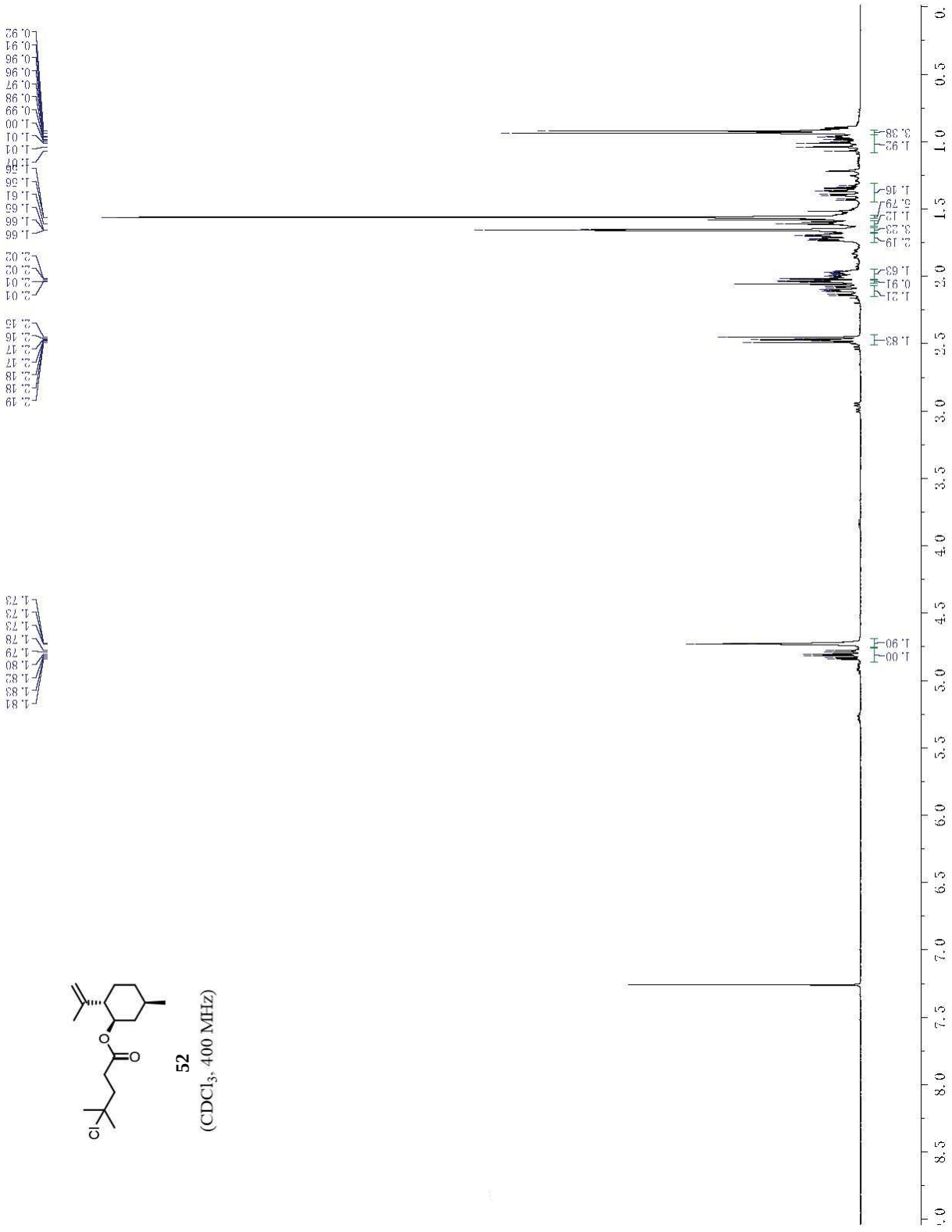

Cl
OBz
50
(CDCl3, 100 MHz)
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0



51

($CDCl_3$, 500 MHz)

14.19
20.17
22.65
31.42
32.80
43.99
61.41
68.28
126.67
133.30
173.03
Cl
O
O
51
(CDCl3, 126 MHz)

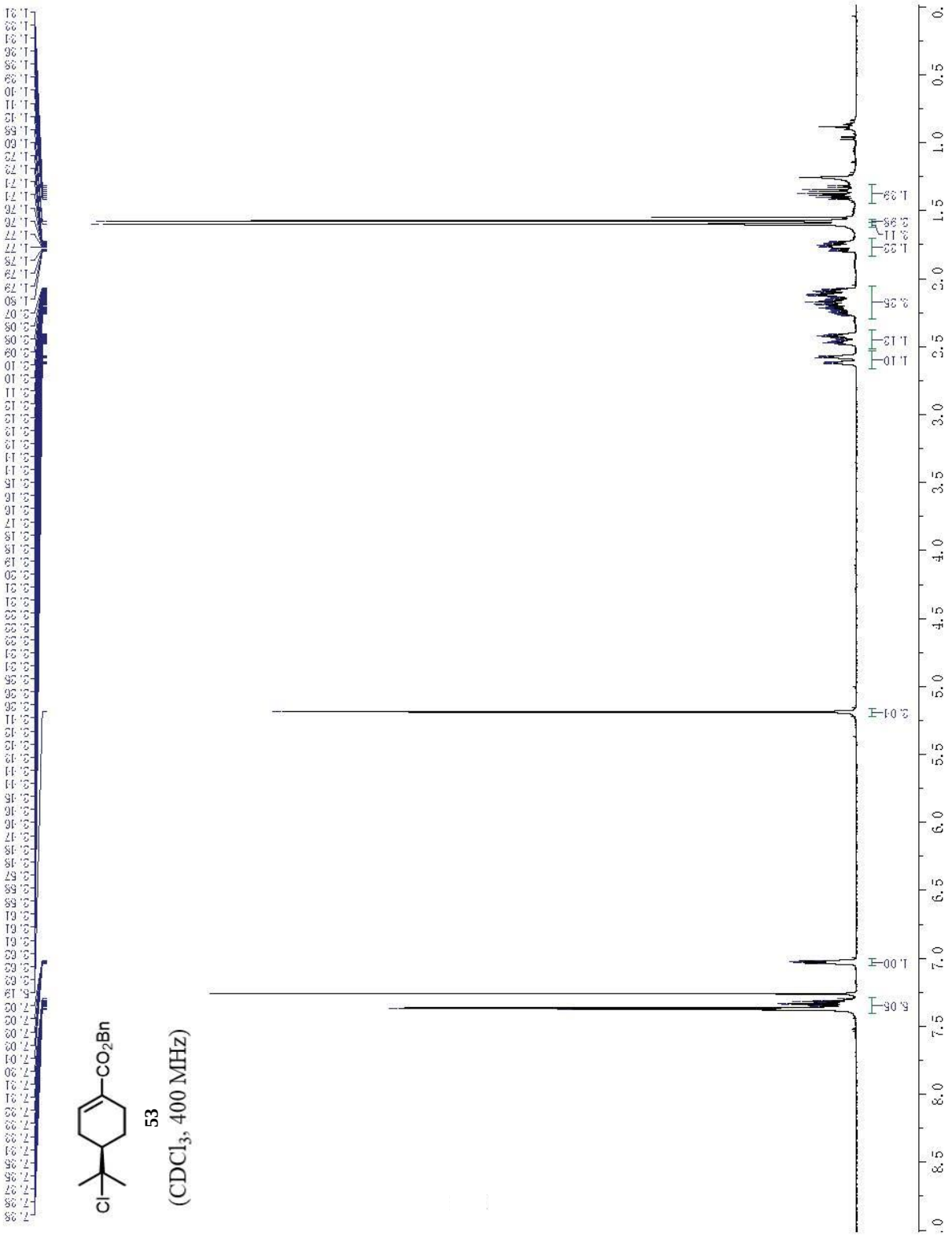


52

($CDCl_3$, 400 MHz)

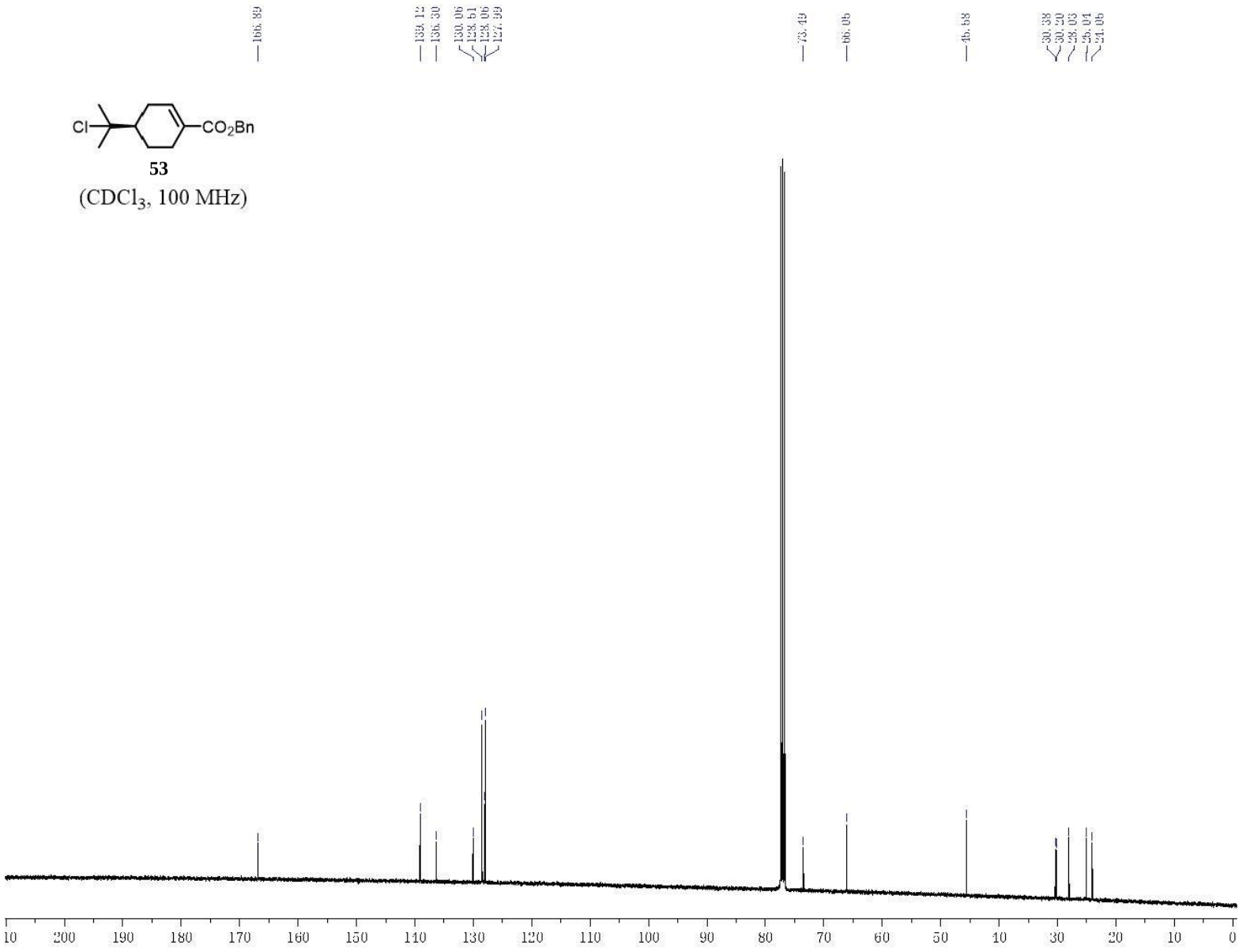
52

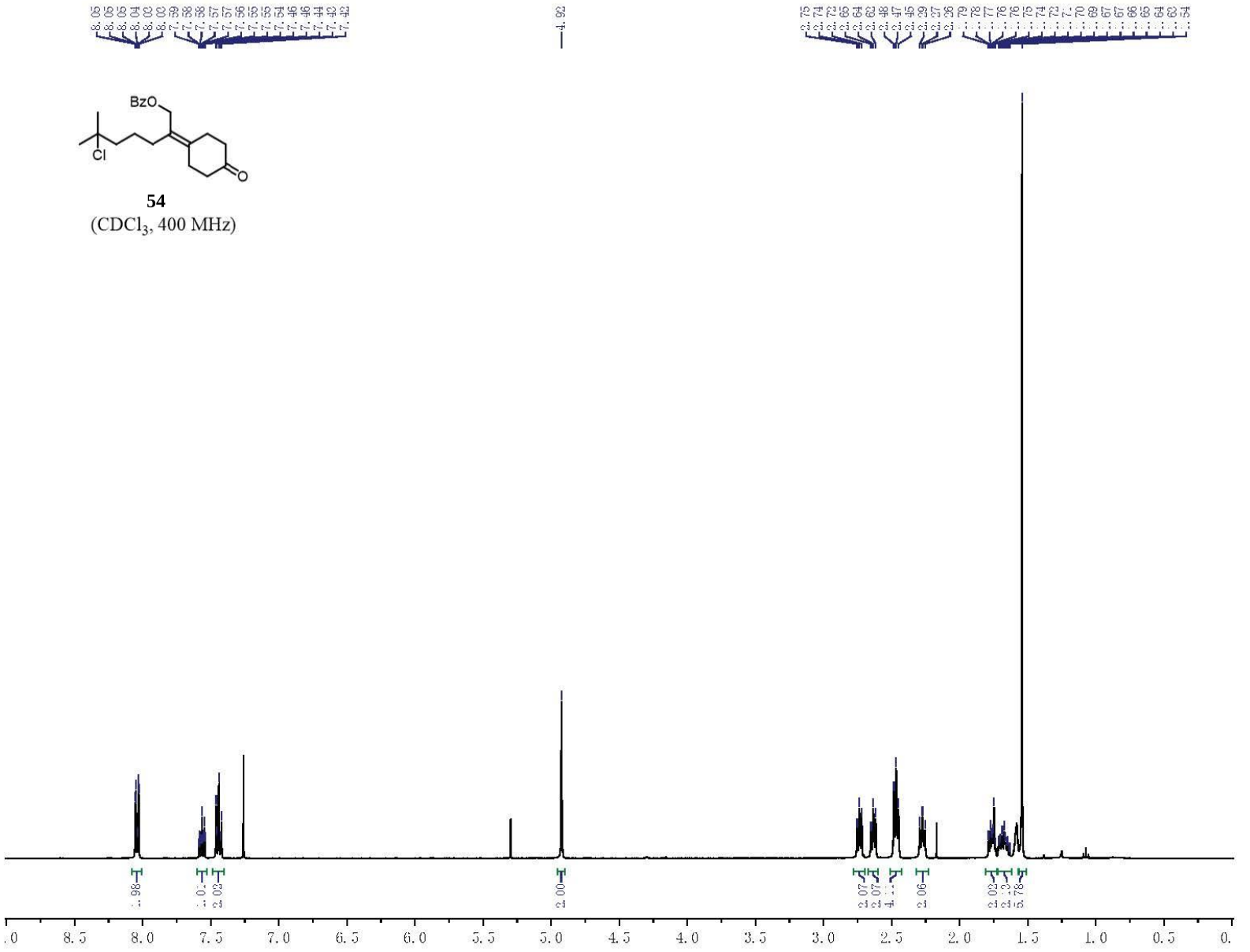
($CDCl_3$, 100 MHz)



53

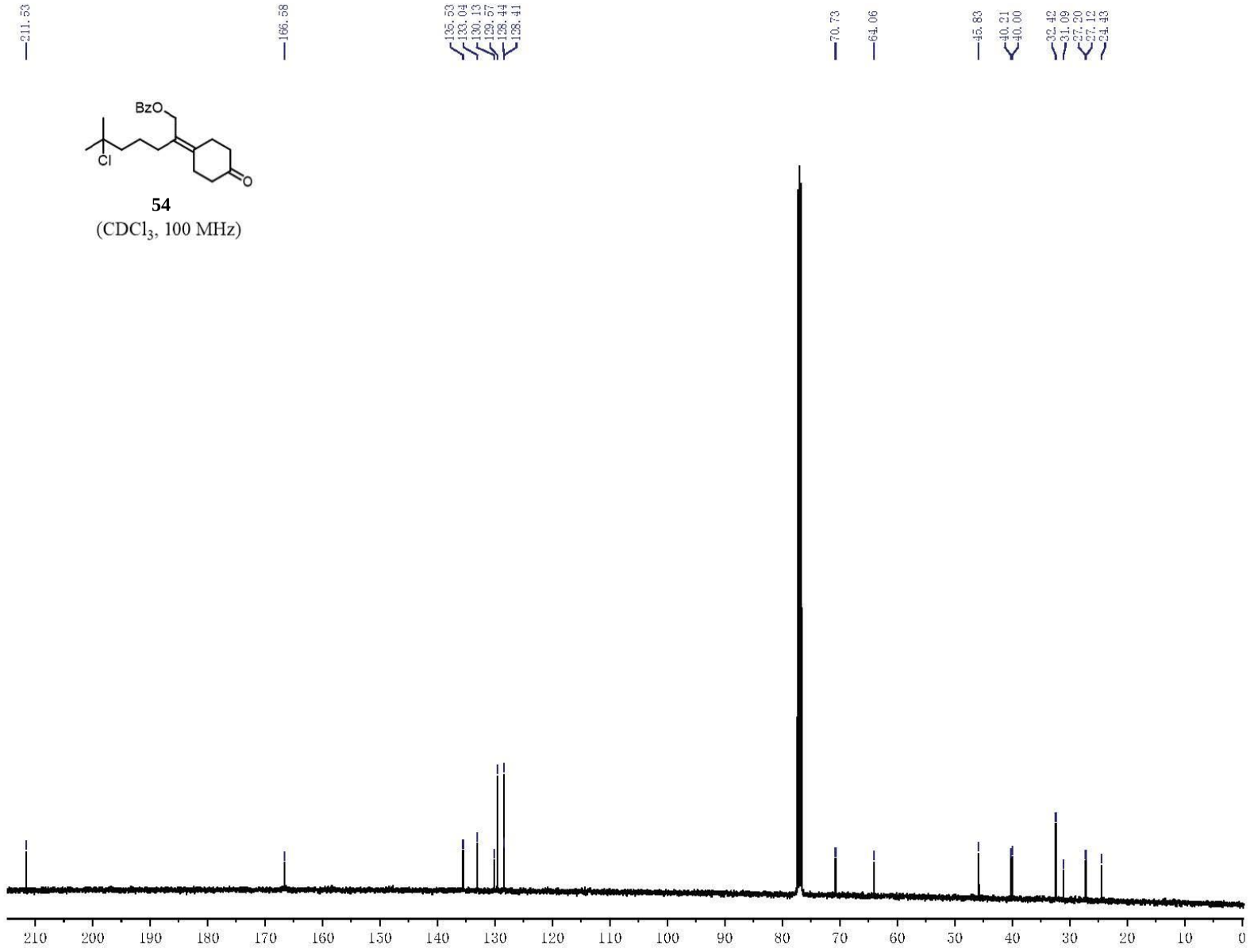
($CDCl_3$, 400 MHz)

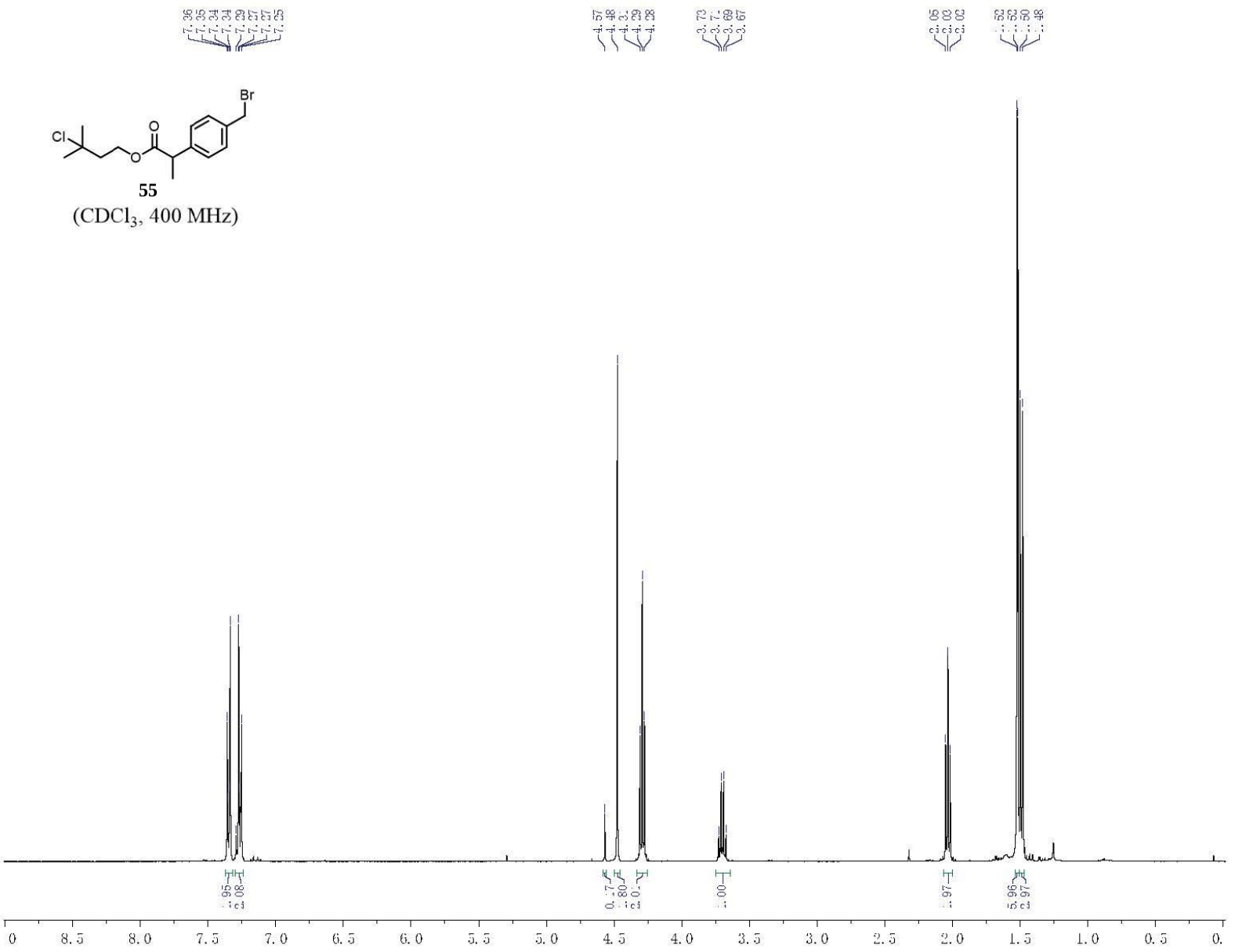

166.89
133.12
130.50
130.06
128.51
128.06
127.99
73.49
66.06
45.68
30.38
30.20
29.03
25.04
24.06
Cl
CO2Bn
53
(CDCl3, 100 MHz)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

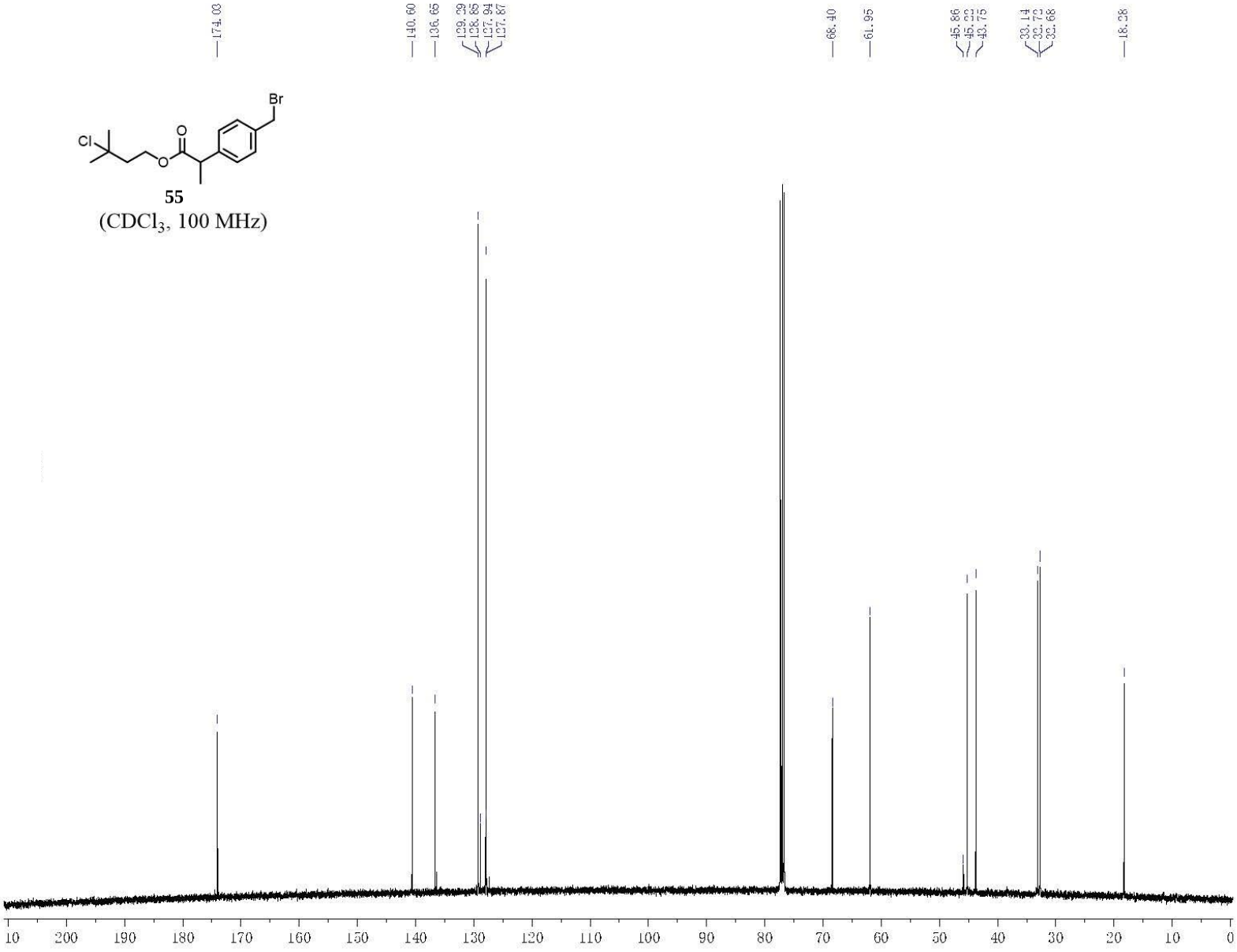


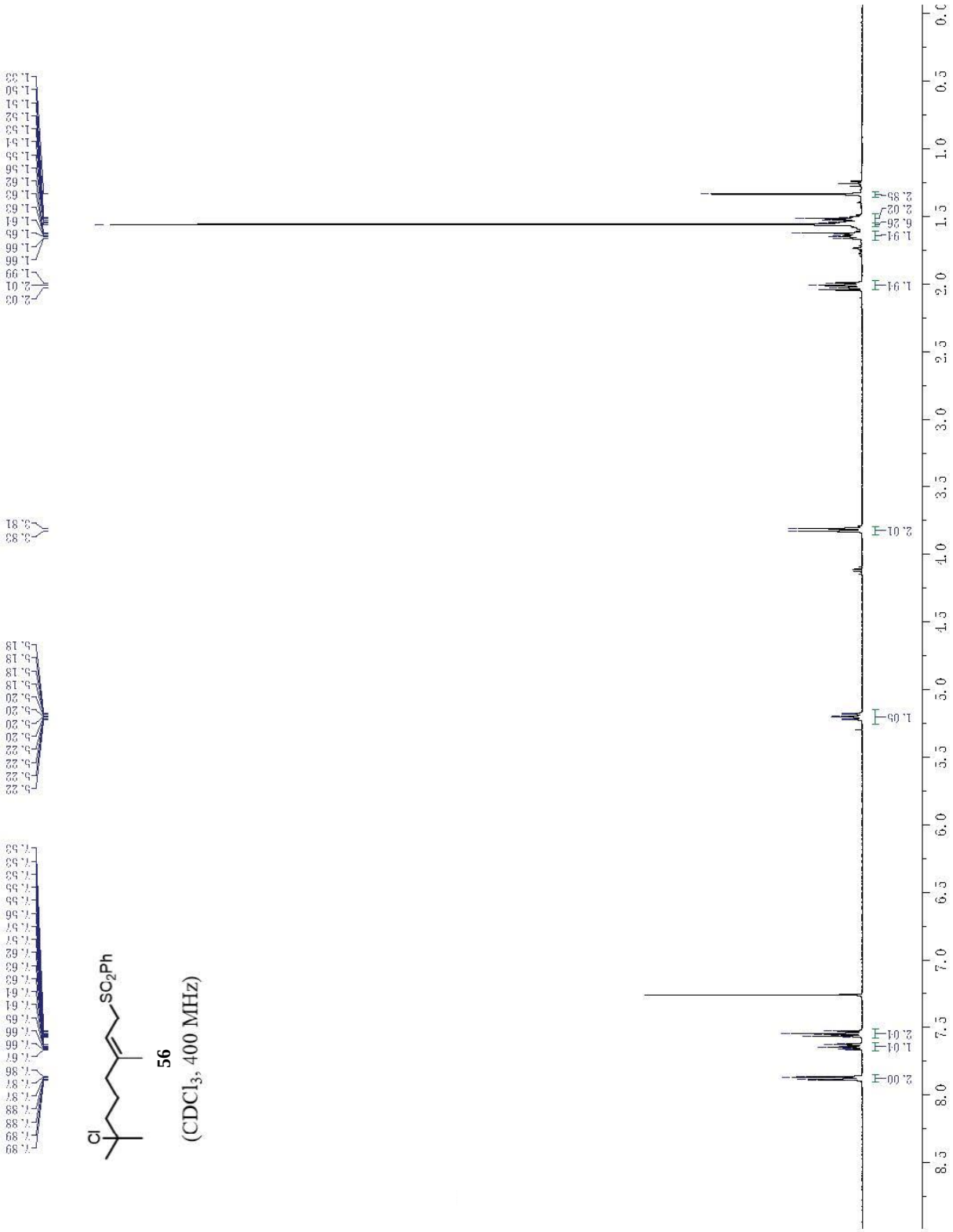
54

($CDCl_3$, 400 MHz)


211.53
166.58
136.53
133.04
130.13
129.57
128.44
128.41
70.73
64.06
45.83
40.21
40.00
32.42
31.09
27.20
27.12
24.43
BzO
Cl
O
54
(CDCl3, 100 MHz)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

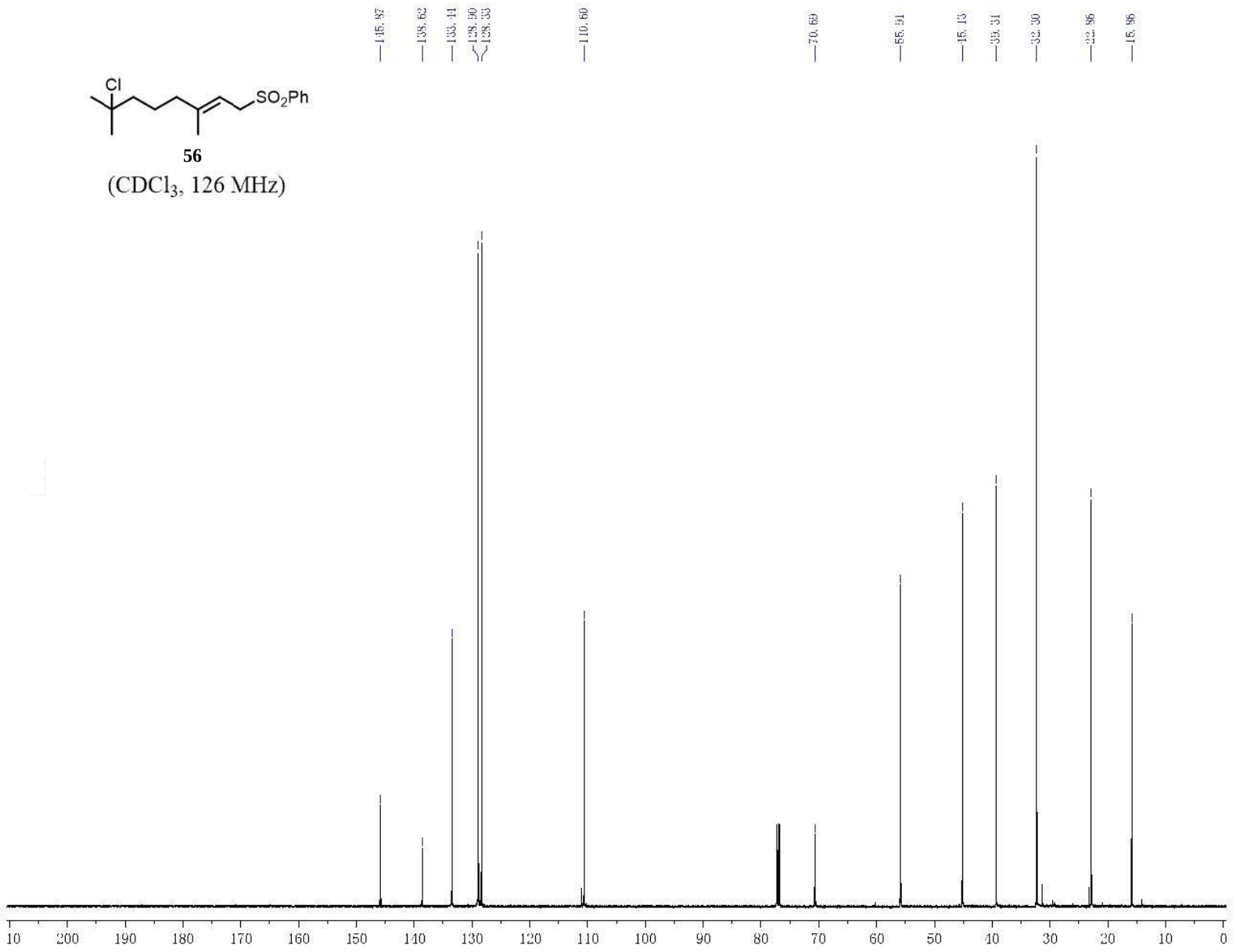

Br
Cl
O
O
55
(CDCl3, 400 MHz)


174.03
140.60
136.65
129.09
128.85
127.94
127.87
68.40
61.95
45.86
45.22
43.75
33.14
32.72
32.68
18.38
Br
Cl
O
O
55
(CDCl3, 100 MHz)
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0



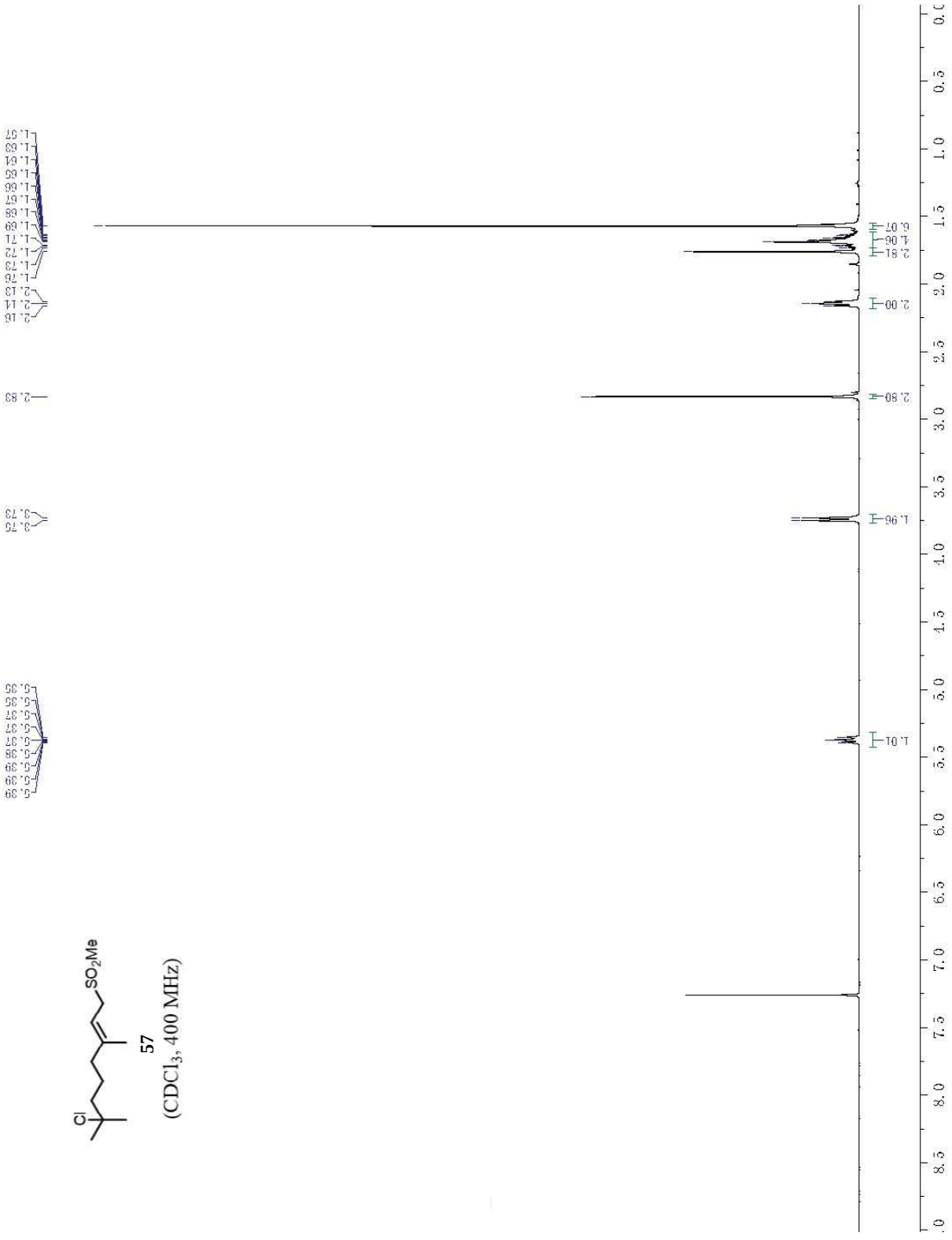
56

($CDCl_3$, 400 MHz)



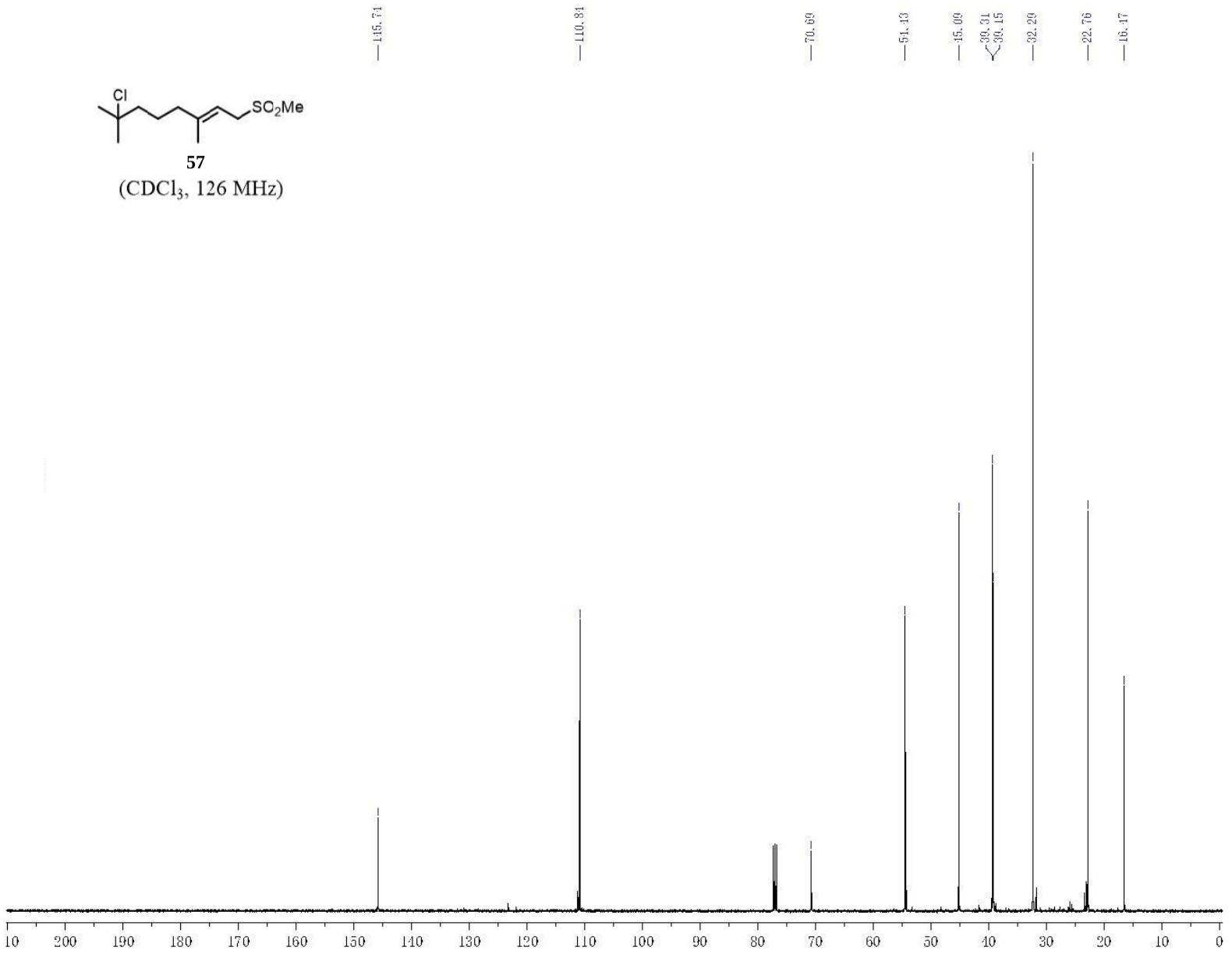
56

($CDCl_3$, 126 MHz)



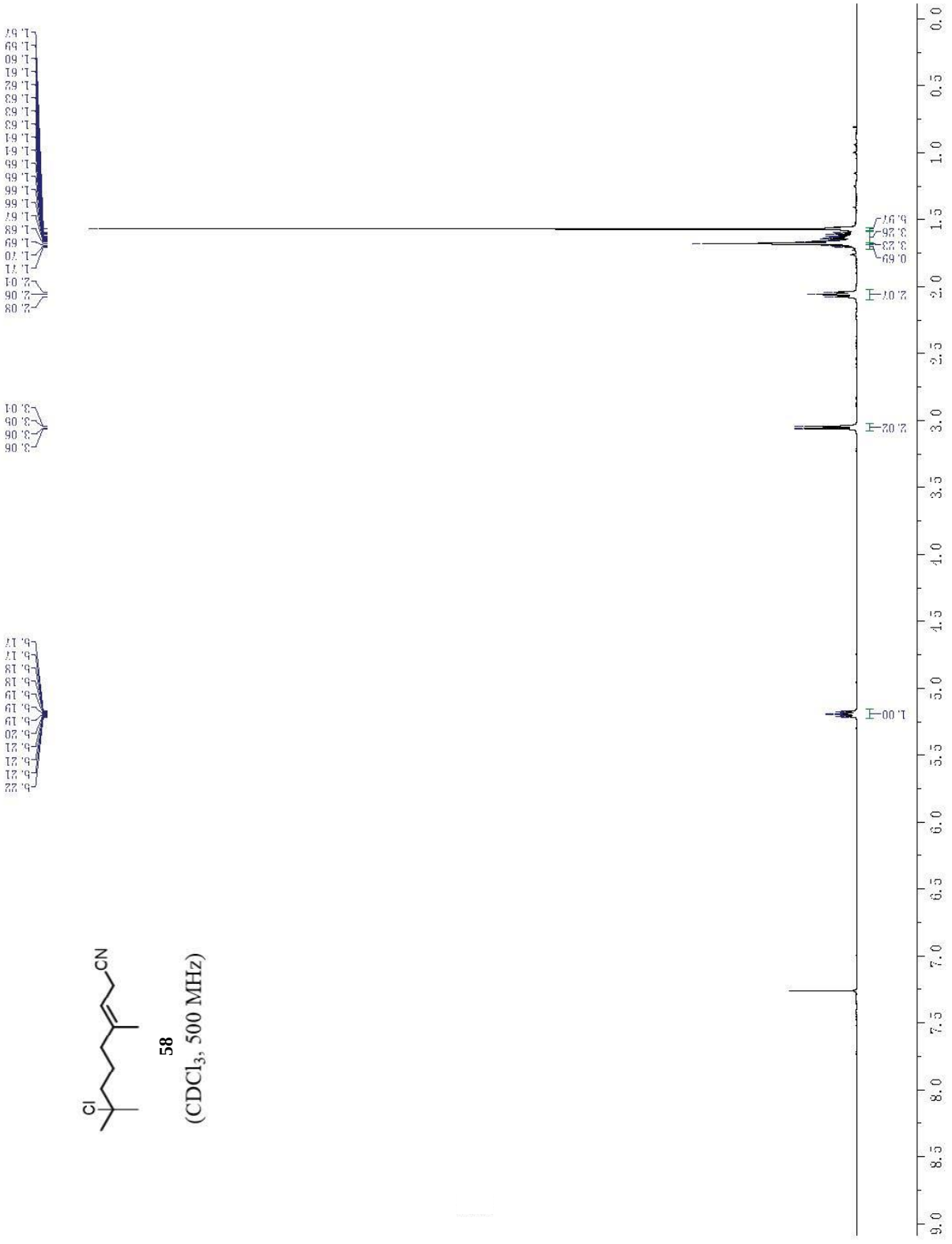
57

($CDCl_3$, 400 MHz)



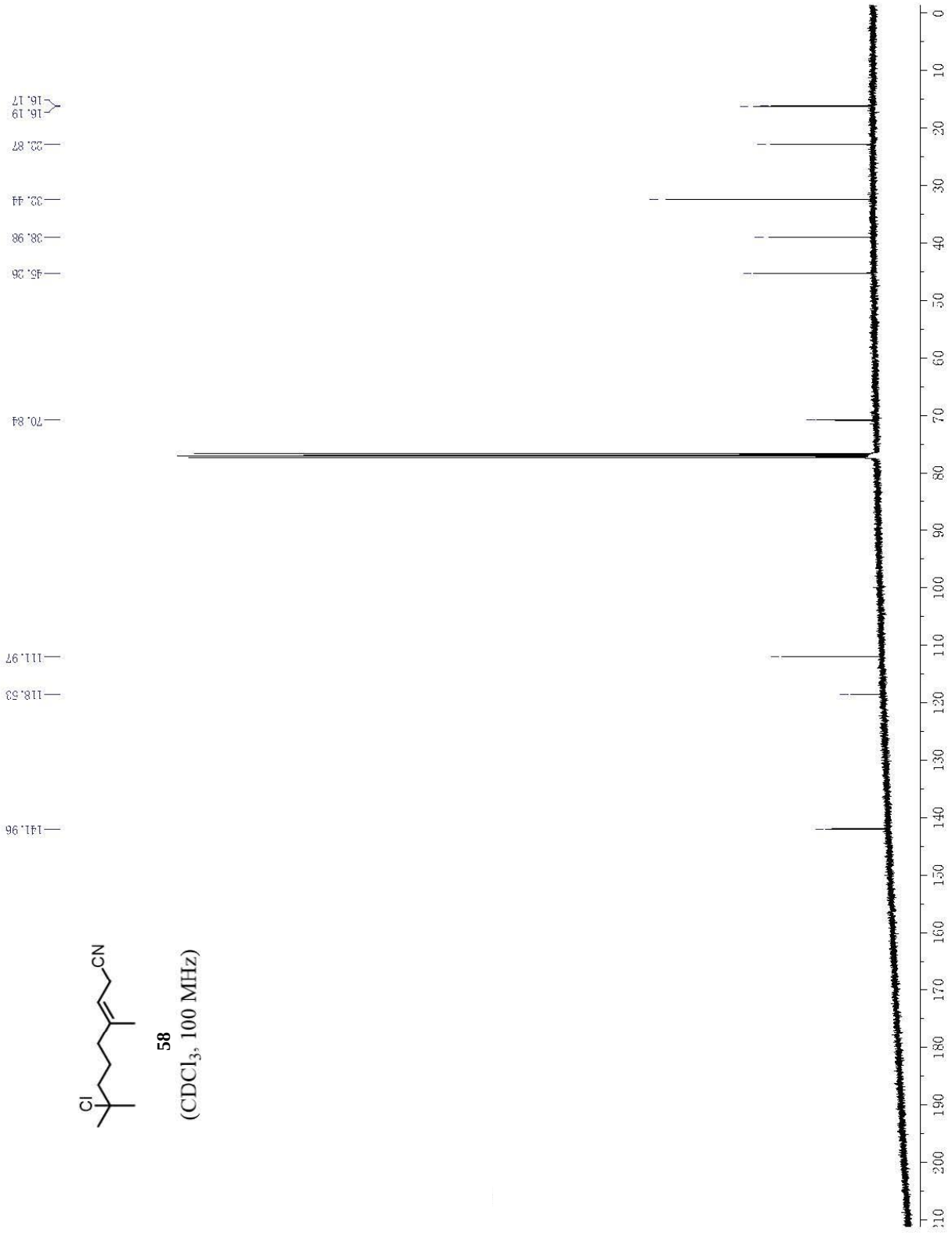
57

($CDCl_3$, 126 MHz)



58

($CDCl_3$, 500 MHz)



58

($CDCl_3$, 100 MHz)

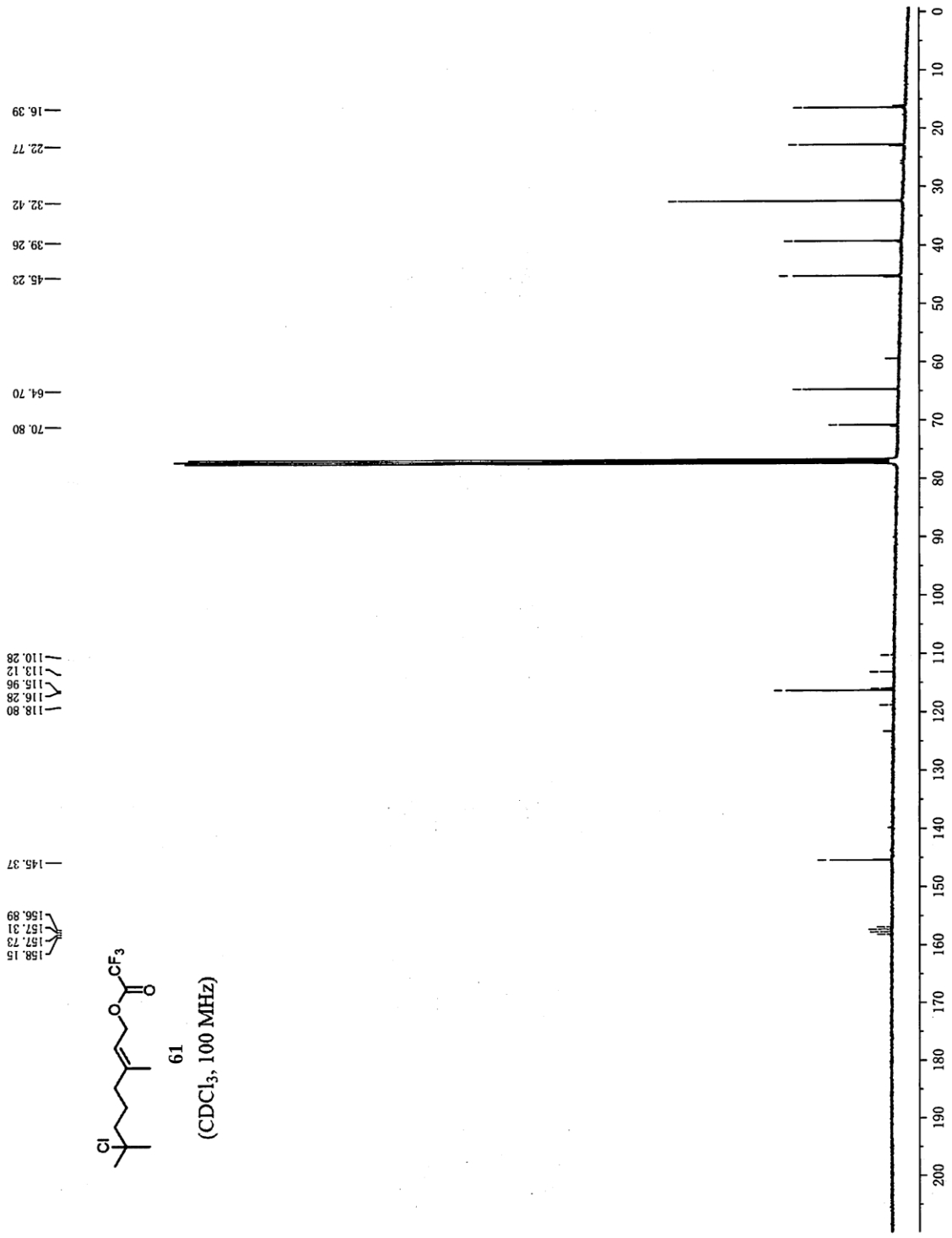
OAc
Cl
59
(CDCl3, 500 MHz)
5.354
5.339
5.325
4.581
4.567
2.053
2.038
2.024
2.013
1.707
1.689
1.663
1.631
1.622
1.618
1.609
1.603
1.593
1.551
0.89
2.00
5.32
2.26
6.22
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

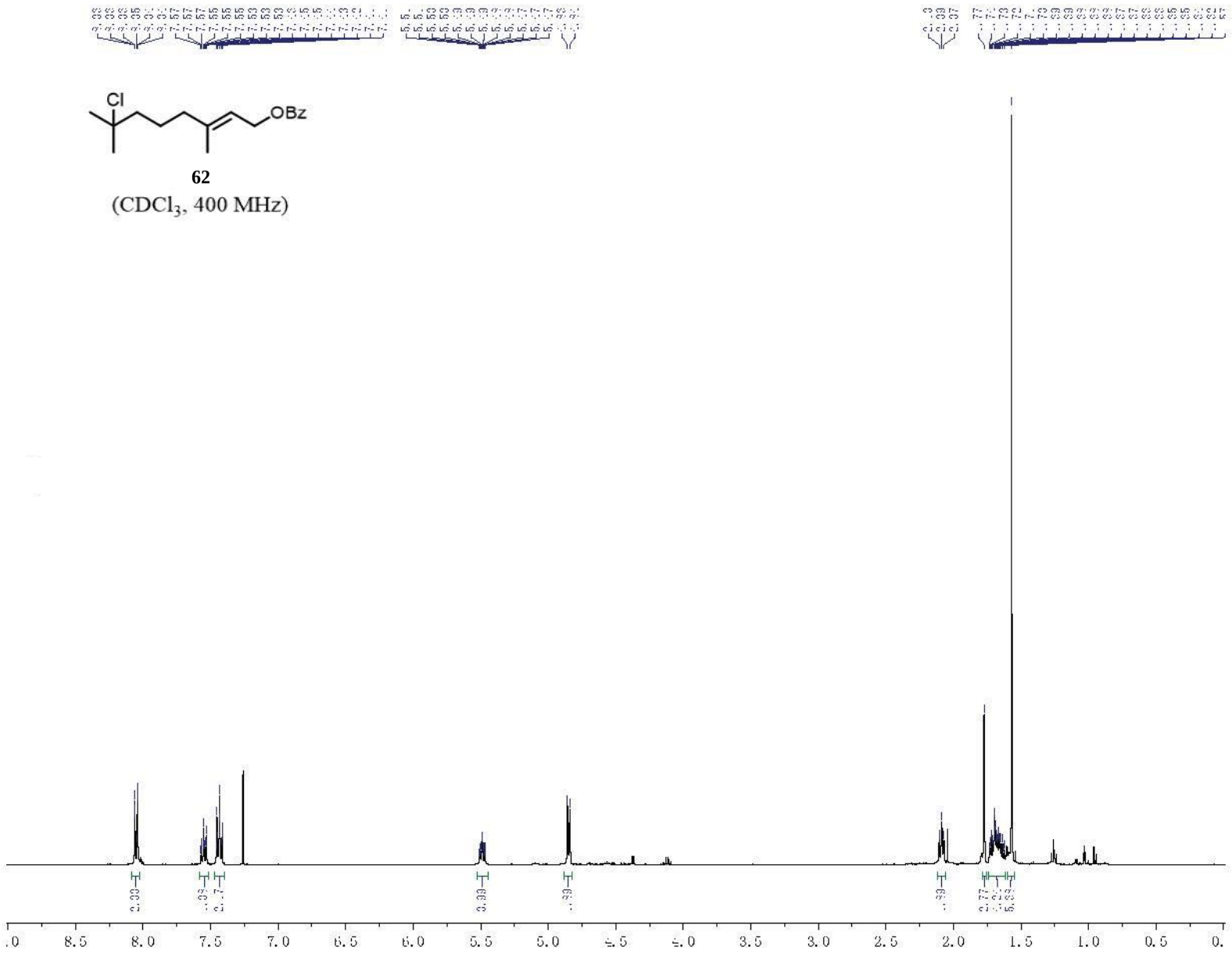
170.991
141.708
118.685
70.824
61.241
45.367
39.268
32.387
22.912
20.970
16.217
OAc
Cl
59
(CDCl3, 125 MHz)
ppm
20
200
180
160
140
120
100
80
60
40
20
0

60
(CDCl3, 500 MHz)
Cl
O
O
9.22
5.71
4.04
3.05
1.99
2.00
0.88
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
5.342
5.328
5.314
4.570
4.556
2.058
2.043
2.030
1.692
1.666
1.661
1.655
1.642
1.639
1.631
1.625
1.619
1.611
1.604
1.590
1.555
1.184

178.491
141.232
119.223
70.856
61.161
45.275
39.234
38.711
32.418
27.189
22.885
16.214
ppm
0
20
40
60
80
100
120
140
160
180
200
220
60
(CDCl3, 125 MHz)
O
O
Cl

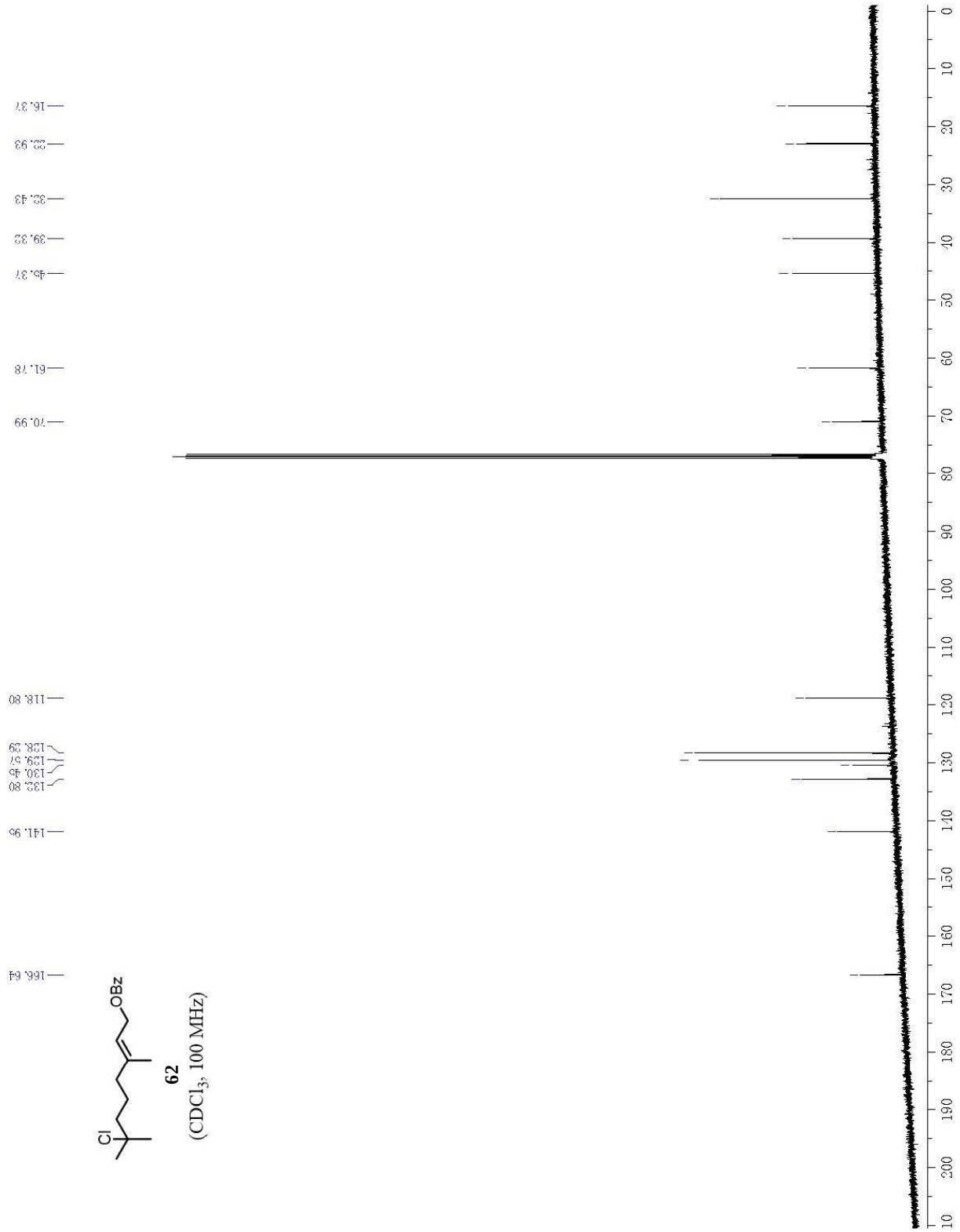
61
(CDCl3, 400 MHz)
Cl
O
CF3
O
1.57
1.62
1.63
1.64
1.64
1.65
1.66
1.67
1.69
1.70
1.71
1.76
2.07
2.09
2.11
4.85
4.87
5.39
5.39
5.39
5.40
5.41
5.41
5.41
5.42
5.43
5.43
6.39
4.46
2.88
2.00
1.94
1.09
0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5


158.15
157.73
157.31
156.89
145.37
118.80
116.28
115.96
113.12
110.28
70.80
64.70
45.23
39.26
32.42
22.77
16.39
Cl
O
O
CF3
61
(CDCl3, 100 MHz)
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200



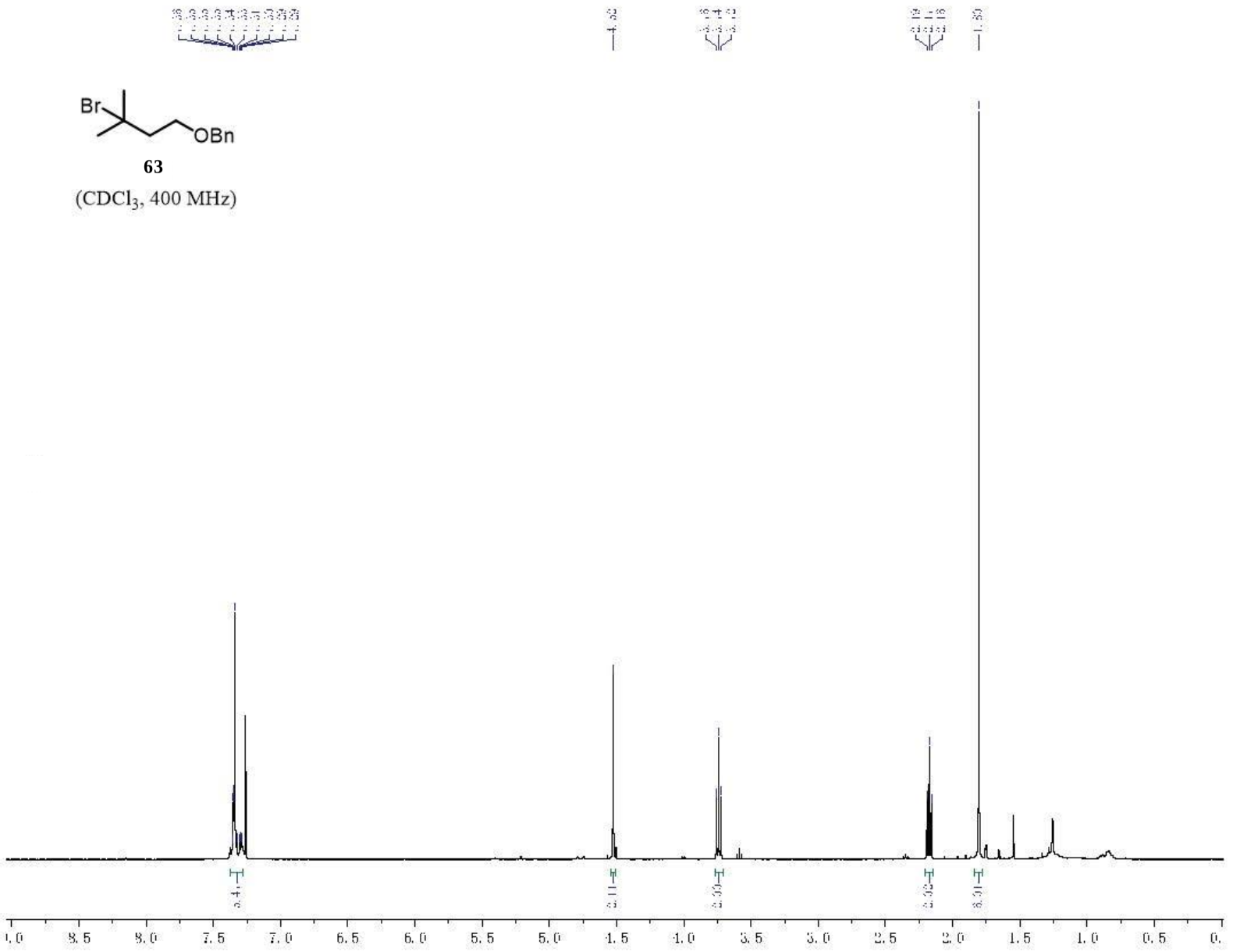
62

($CDCl_3$, 400 MHz)



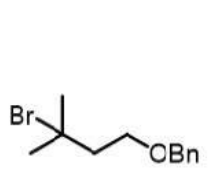
62

($CDCl_3$, 100 MHz)



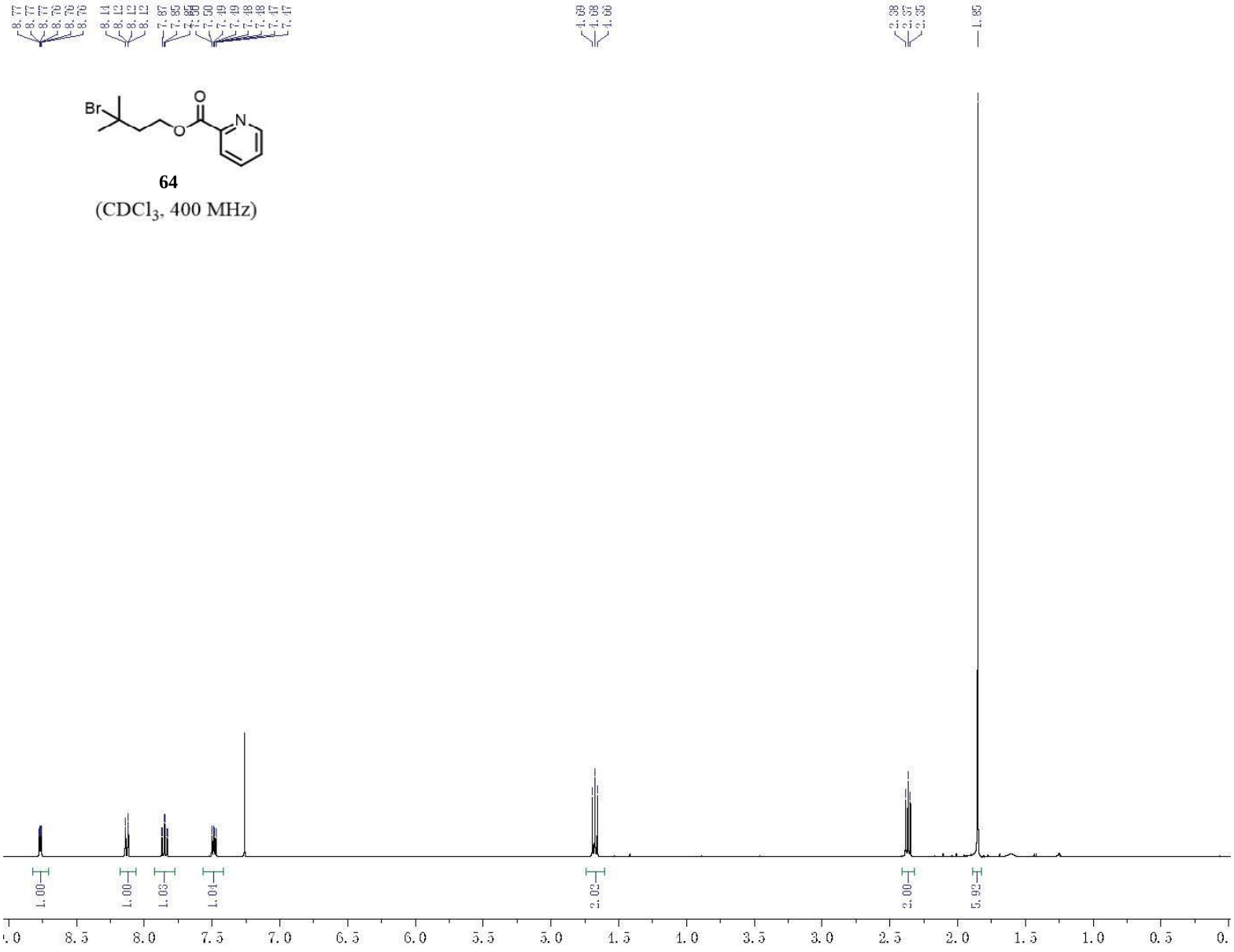
63

($CDCl_3$, 400 MHz)



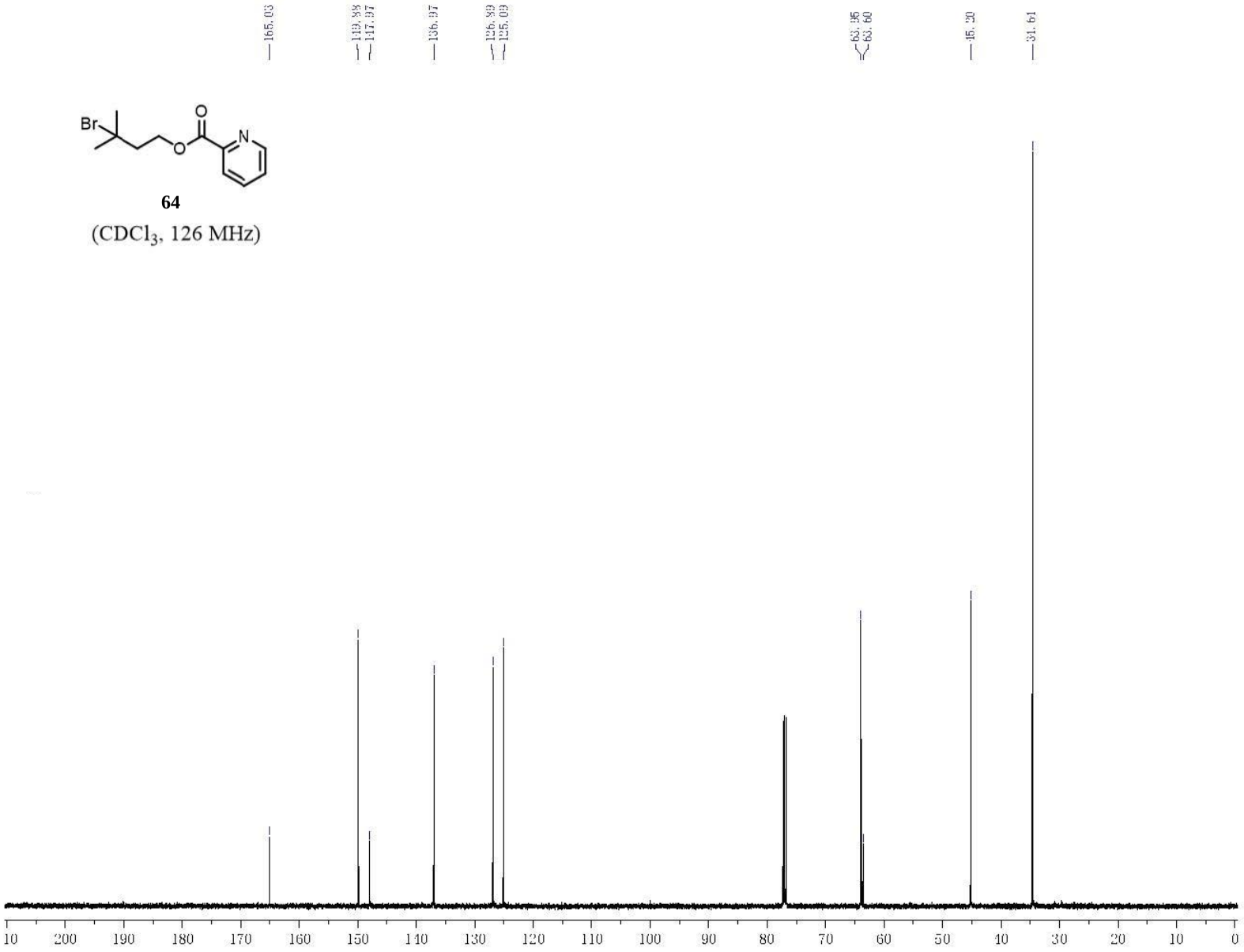
63

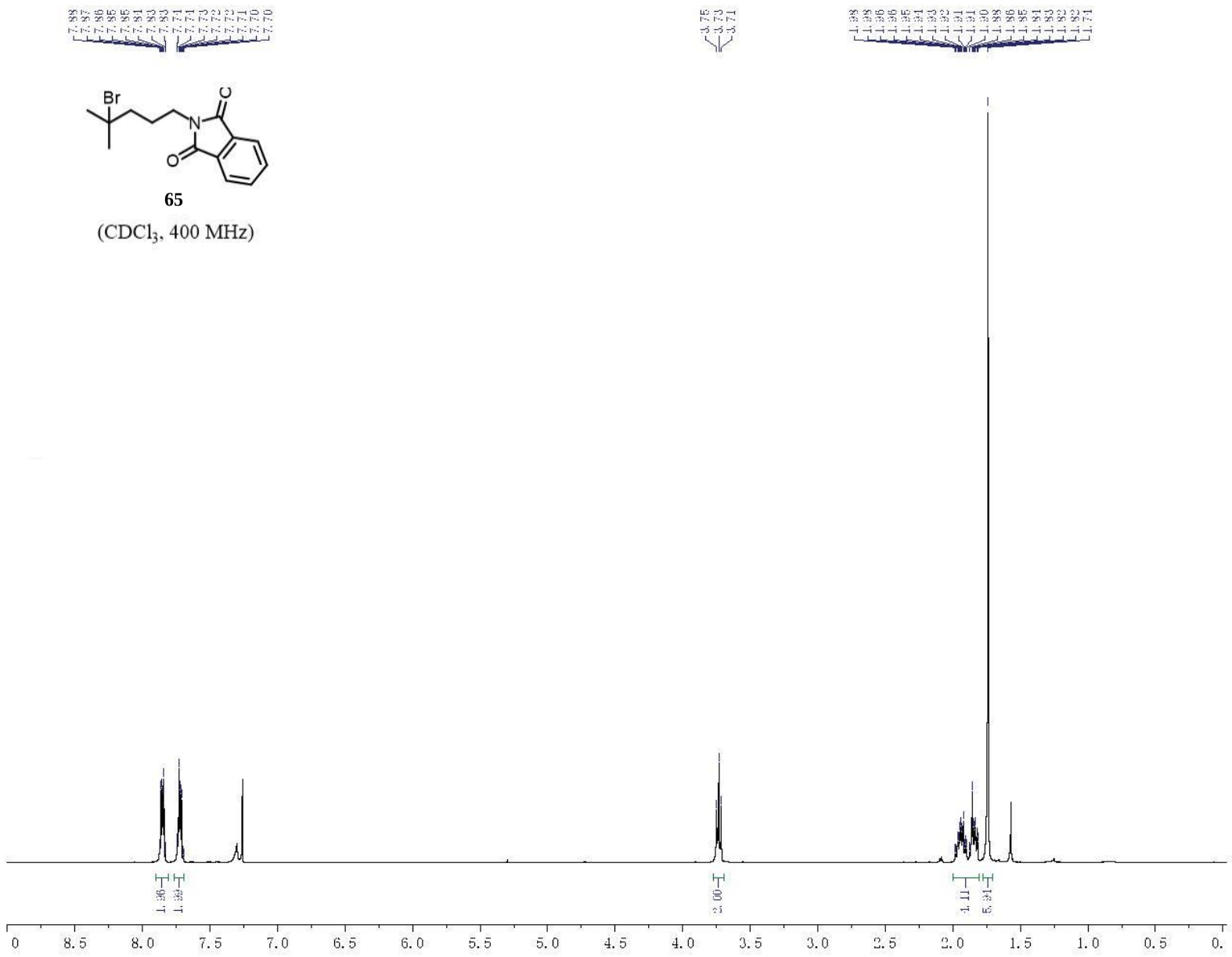
($CDCl_3$, 126 MHz)

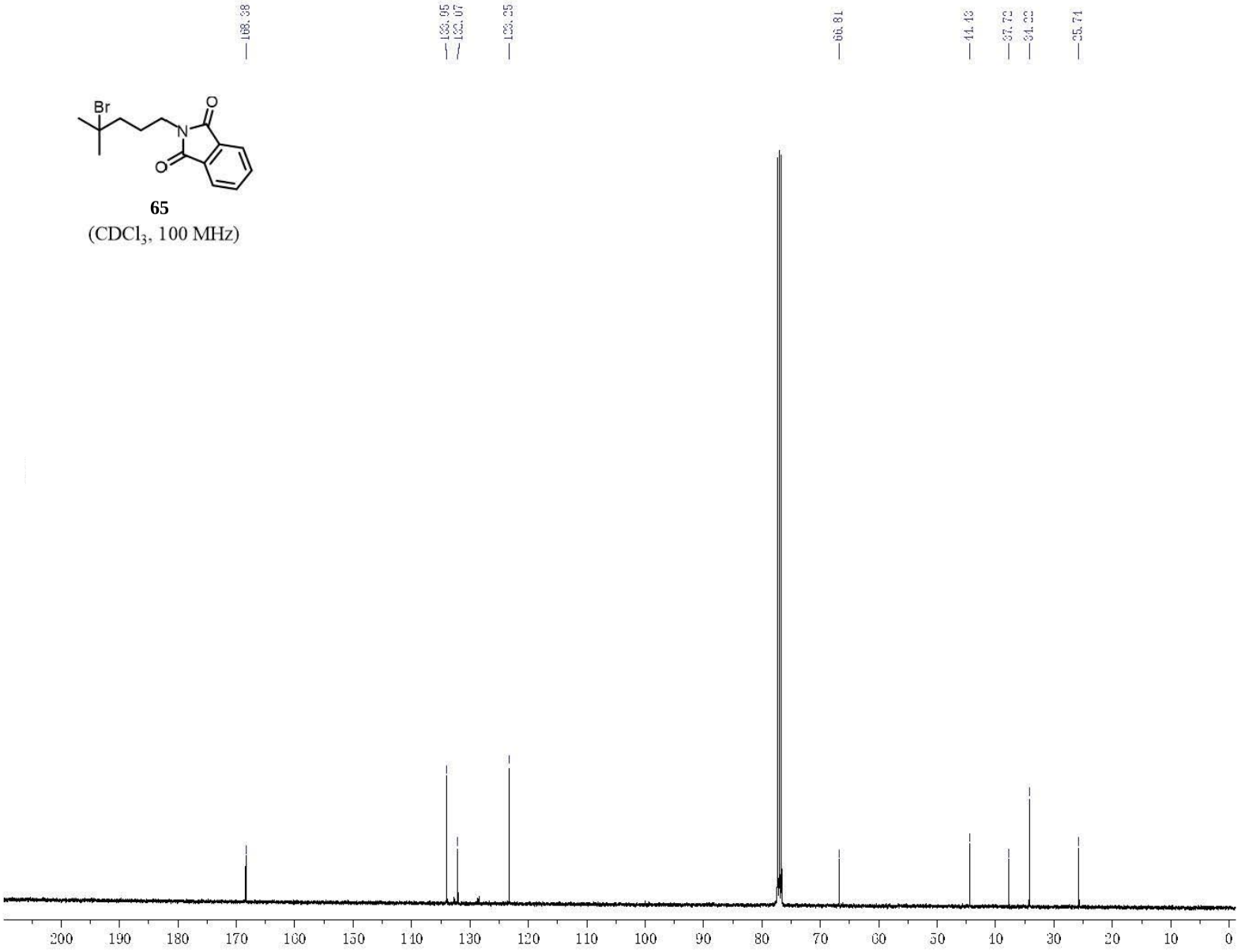


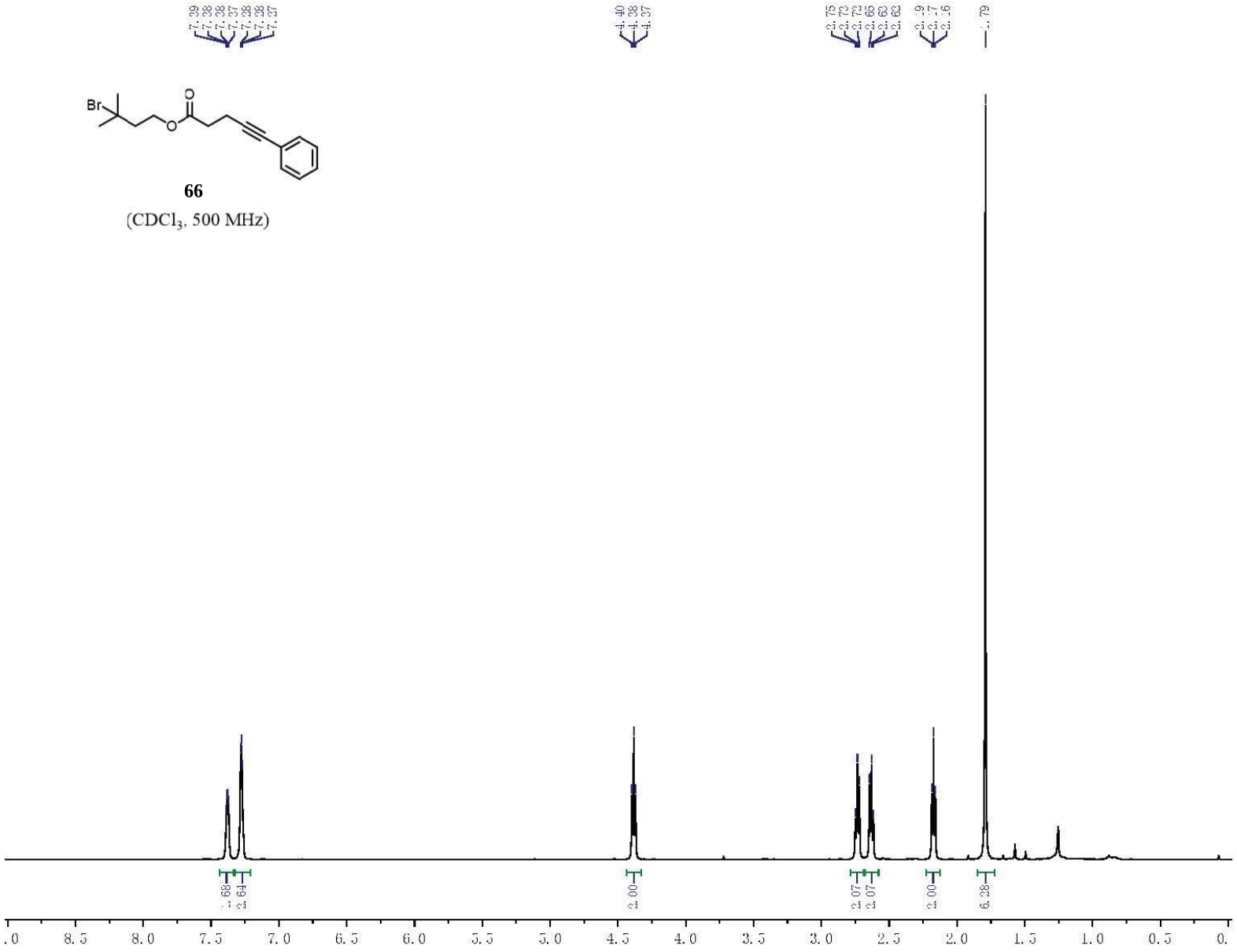
64

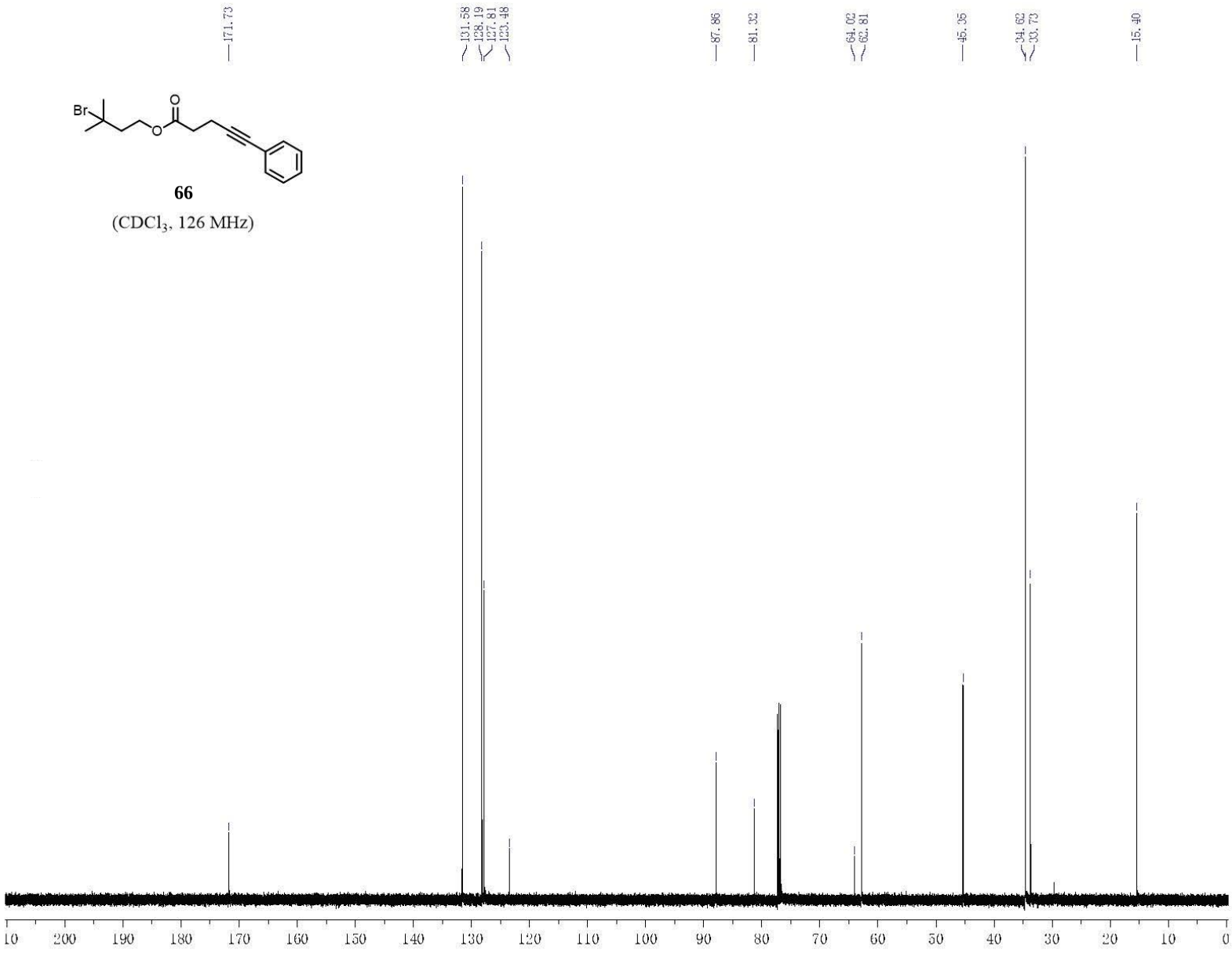
($CDCl_3$, 400 MHz)

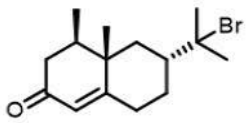

165.03
149.38
147.97
136.97
126.39
125.09
63.95
63.60
45.20
34.61
Br
O
O
N
64
(CDCl3, 126 MHz)
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
10
30
20
10
0


Br
O
N
O
65
(CDCl3, 400 MHz)
1.36
1.39
2.00
1.11
5.41
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.


168.38
133.95
132.07
123.25
66.81
44.43
37.72
34.33
25.74
Br
O
N
O
65
(CDCl3, 100 MHz)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
10
30
20
10
0

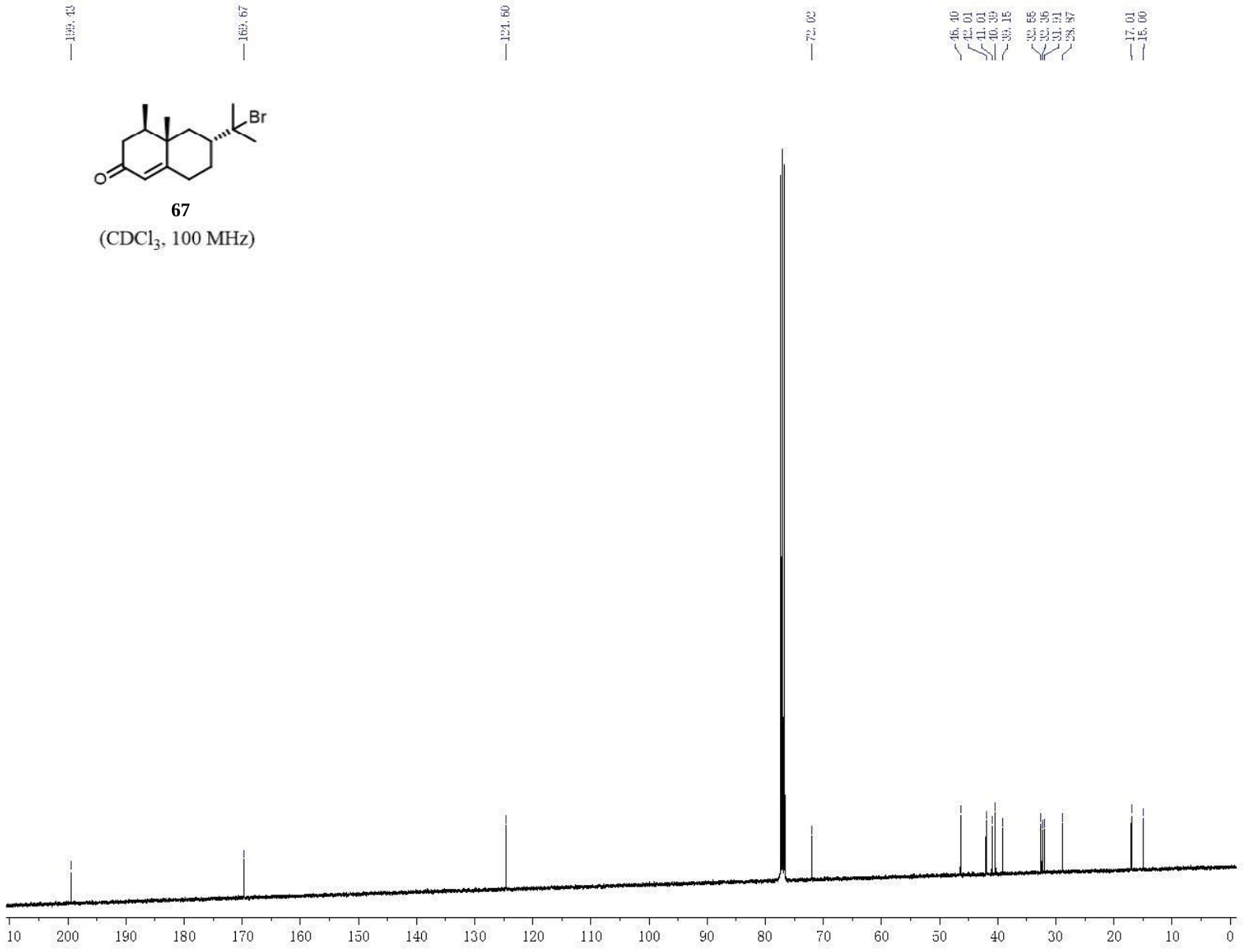

Br
O
O
66
(CDCl3, 500 MHz)

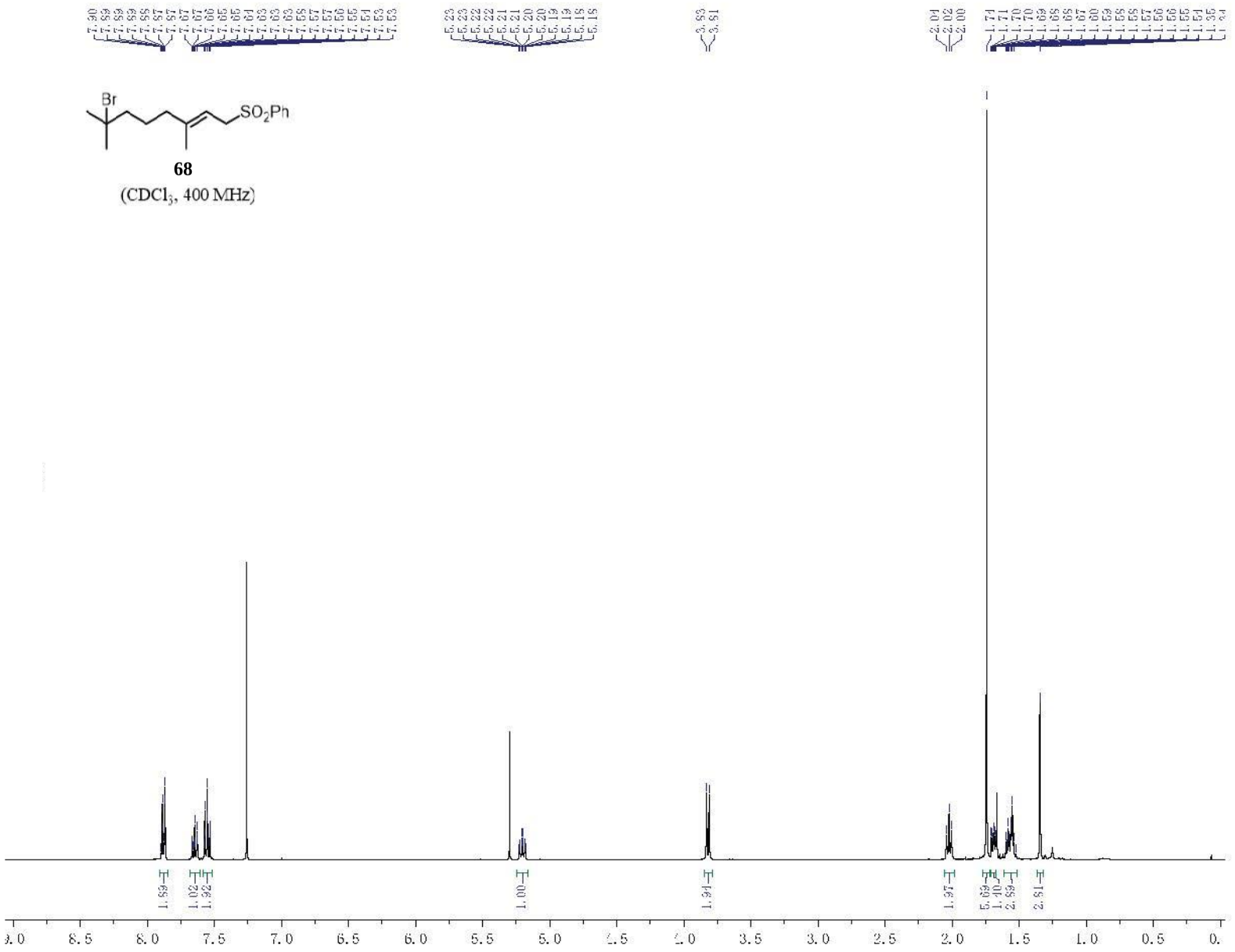

171.73
131.58
128.19
127.81
123.48
87.86
81.32
64.02
62.81
45.35
34.62
33.73
15.40
Br
O
O
66
(CDCl3, 126 MHz)
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0



67

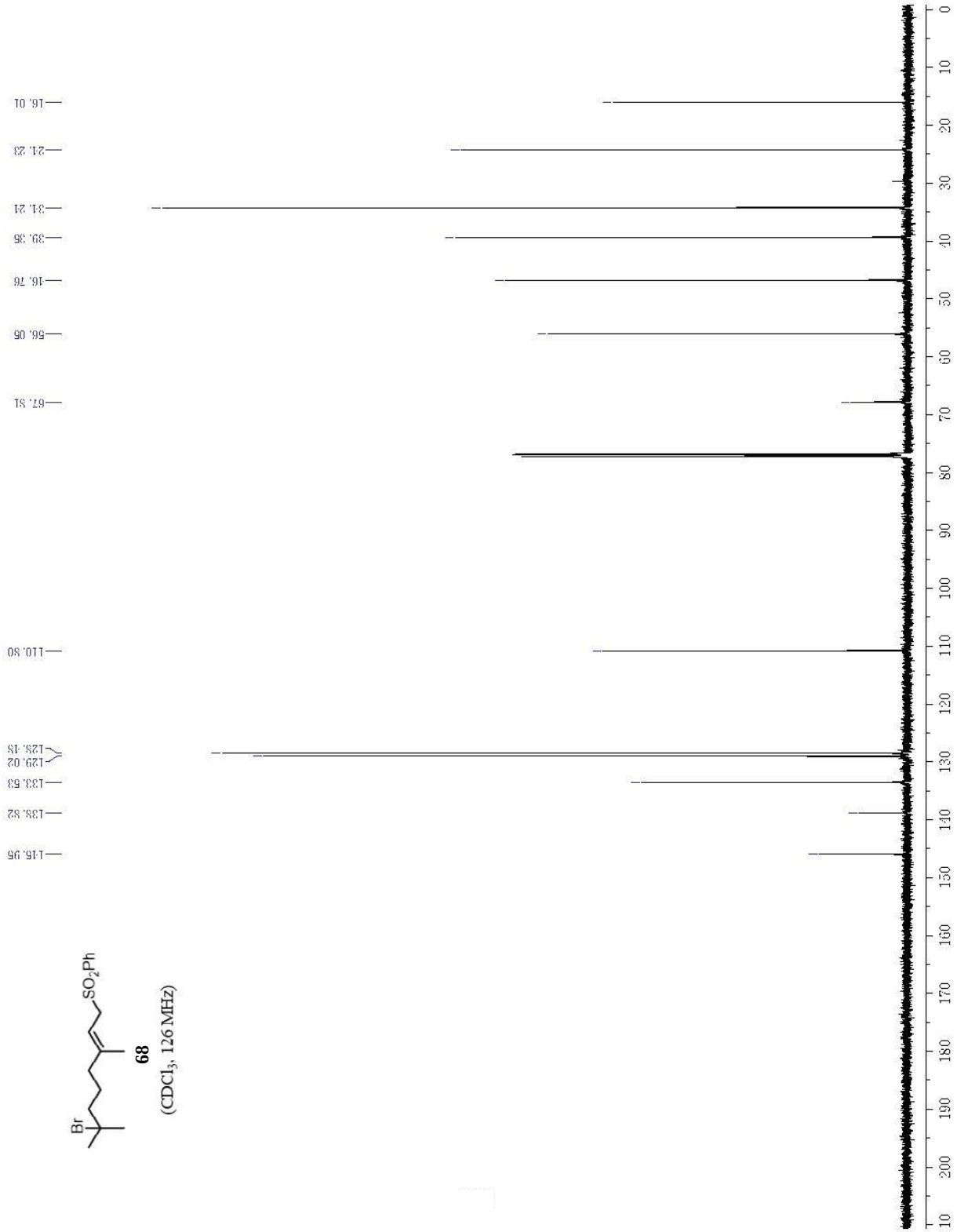
($CDCl_3$, 400 MHz)

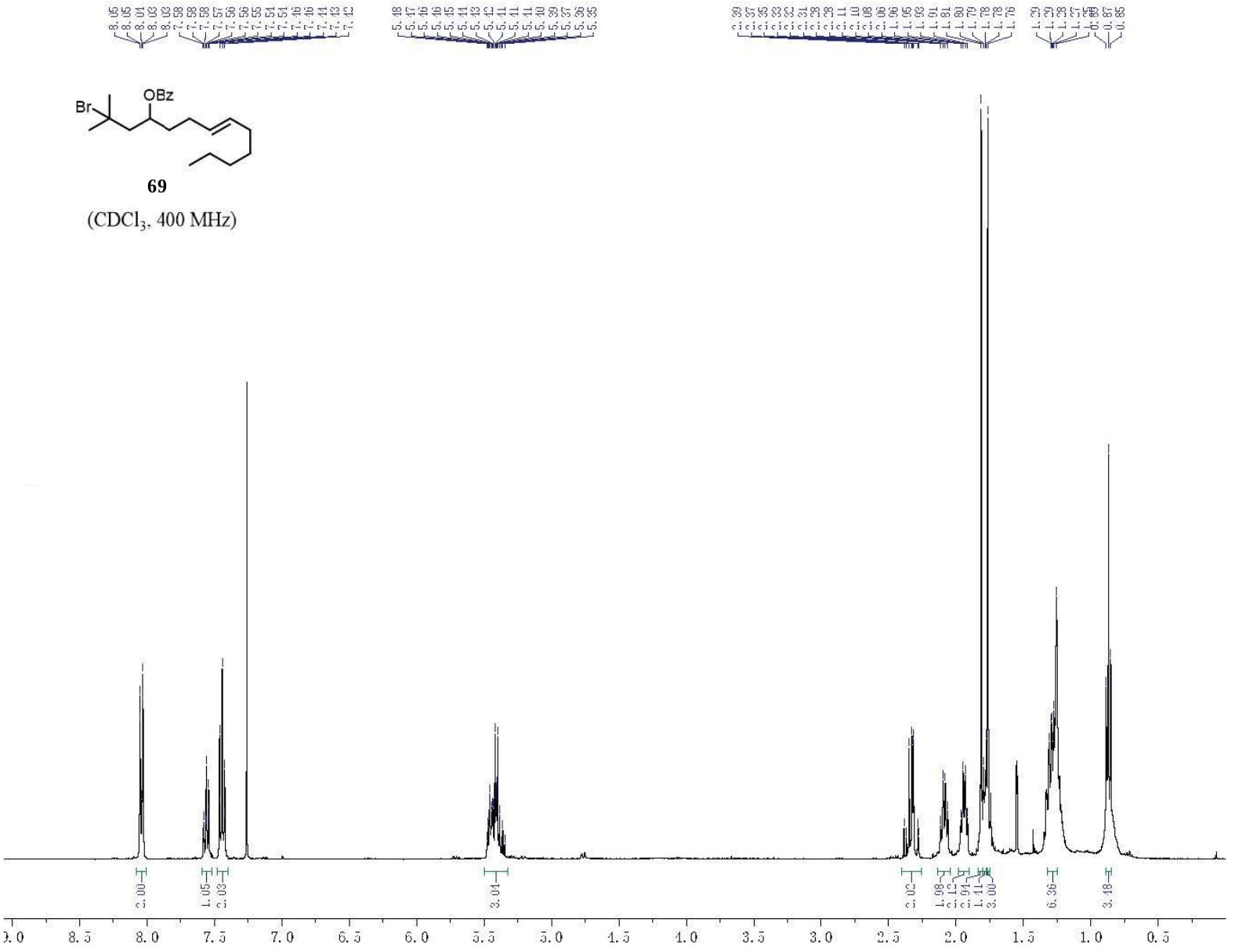

199.43
169.67
124.60
72.02
46.40
42.01
41.01
40.39
33.15
32.55
32.36
31.31
28.87
17.01
15.00
Br
O
67
(CDCl3, 100 MHz)
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0



68

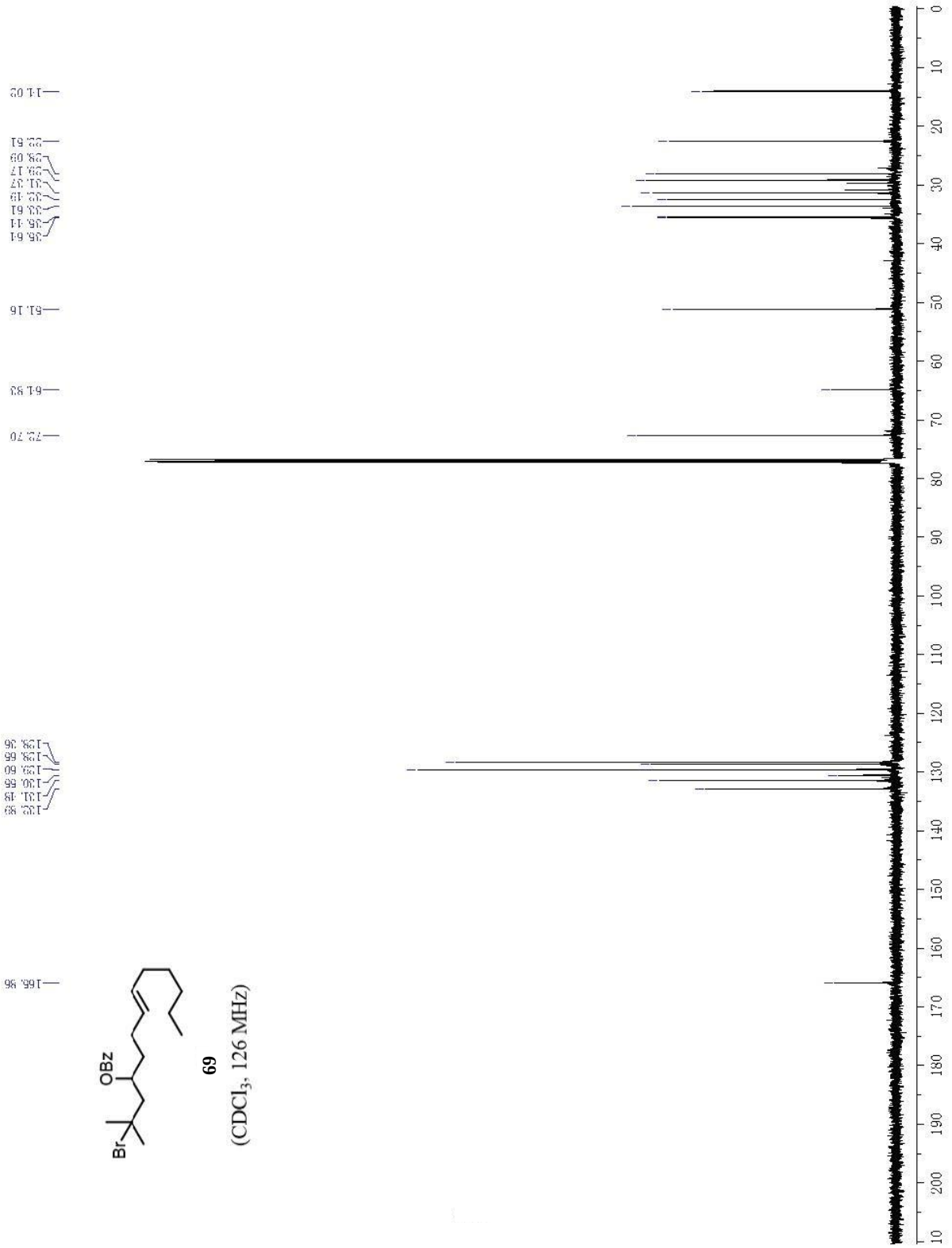
($CDCl_3$, 400 MHz)

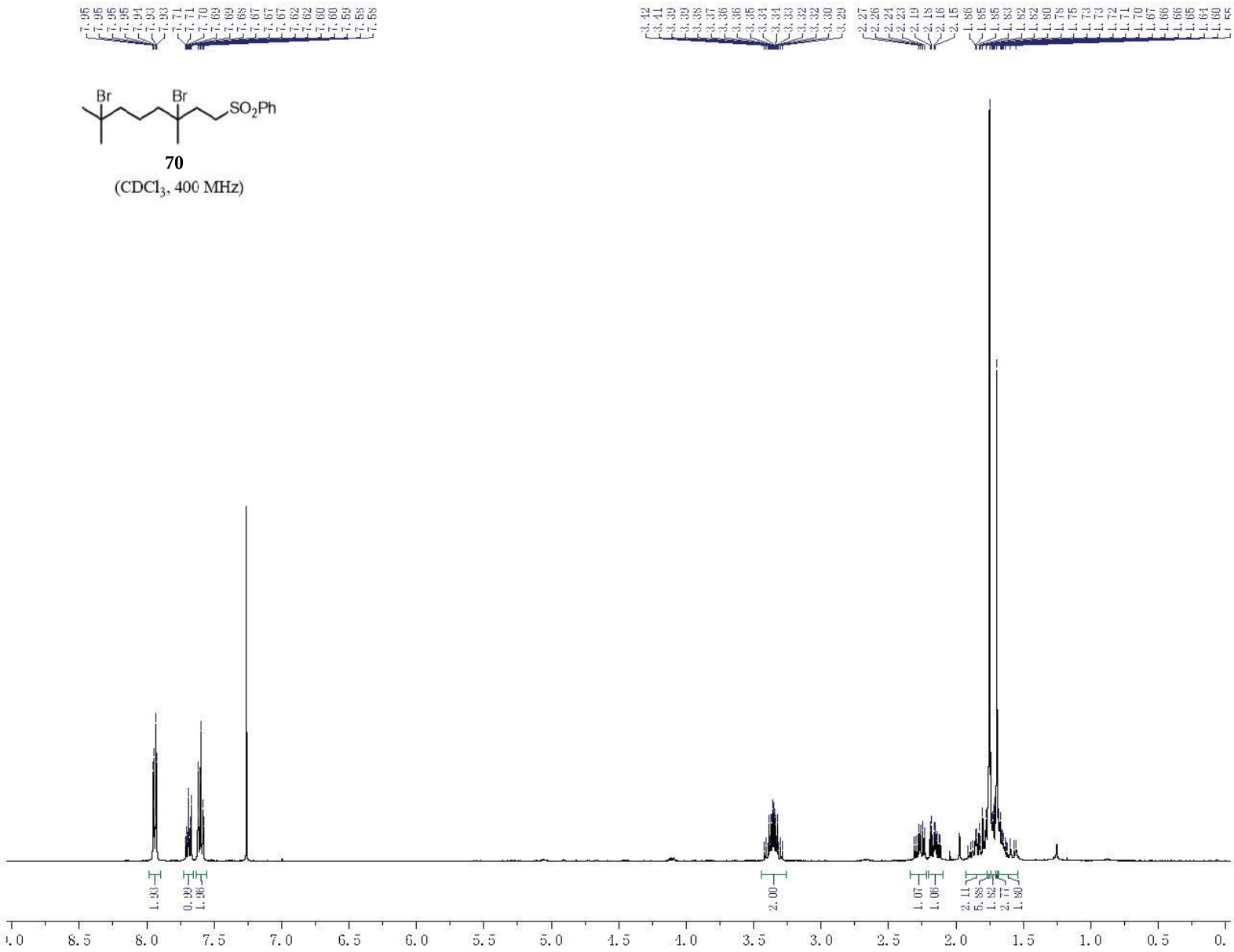

16.01
21.23
31.21
39.36
46.76
56.06
67.81
110.80
128.18
129.02
133.53
138.82
146.96
Br
SO2Ph
68
(CDCl3, 126 MHz)

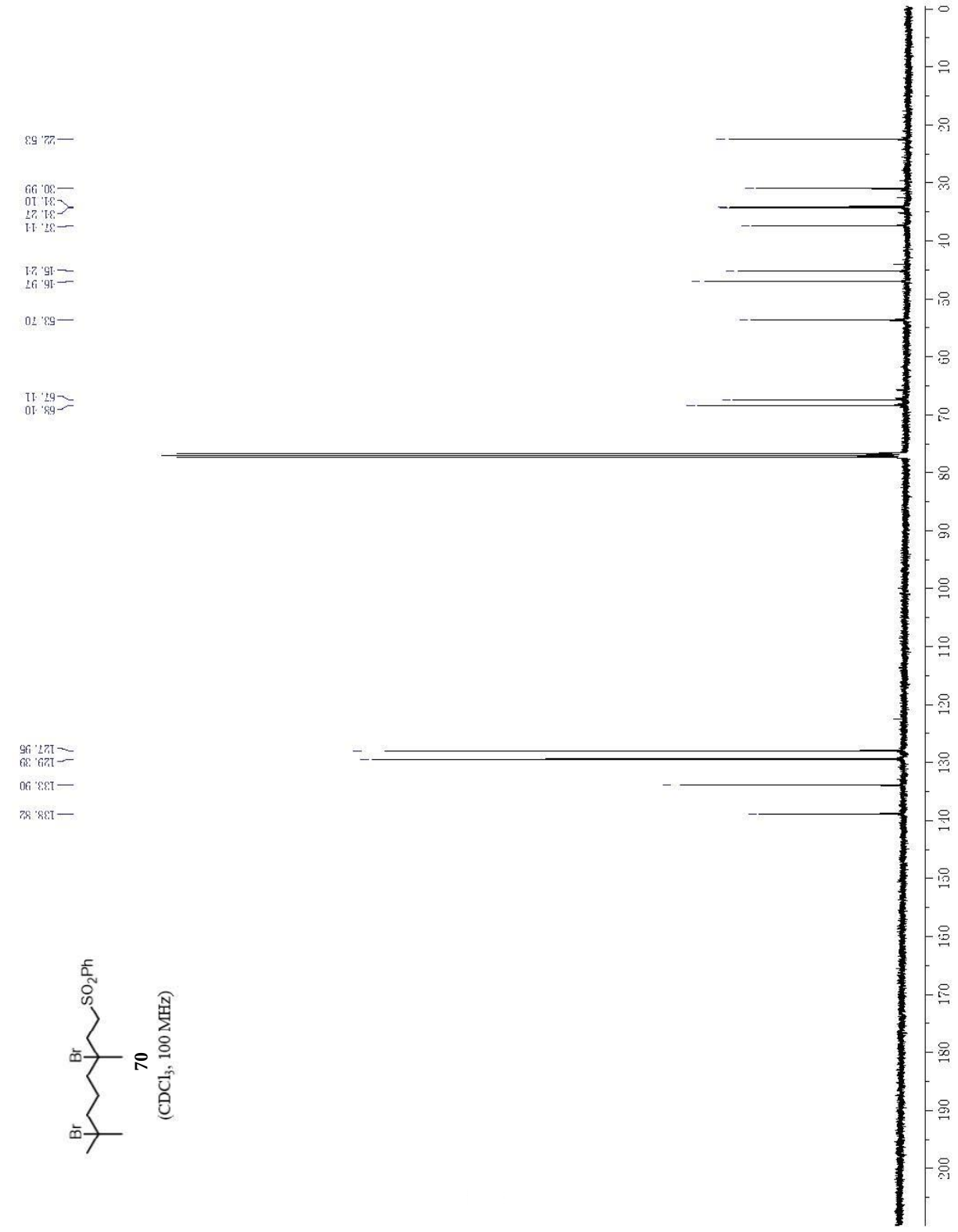


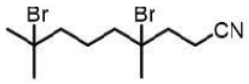
69

($CDCl_3$, 400 MHz)


OBz
Br
69
(CDCl3, 126 MHz)

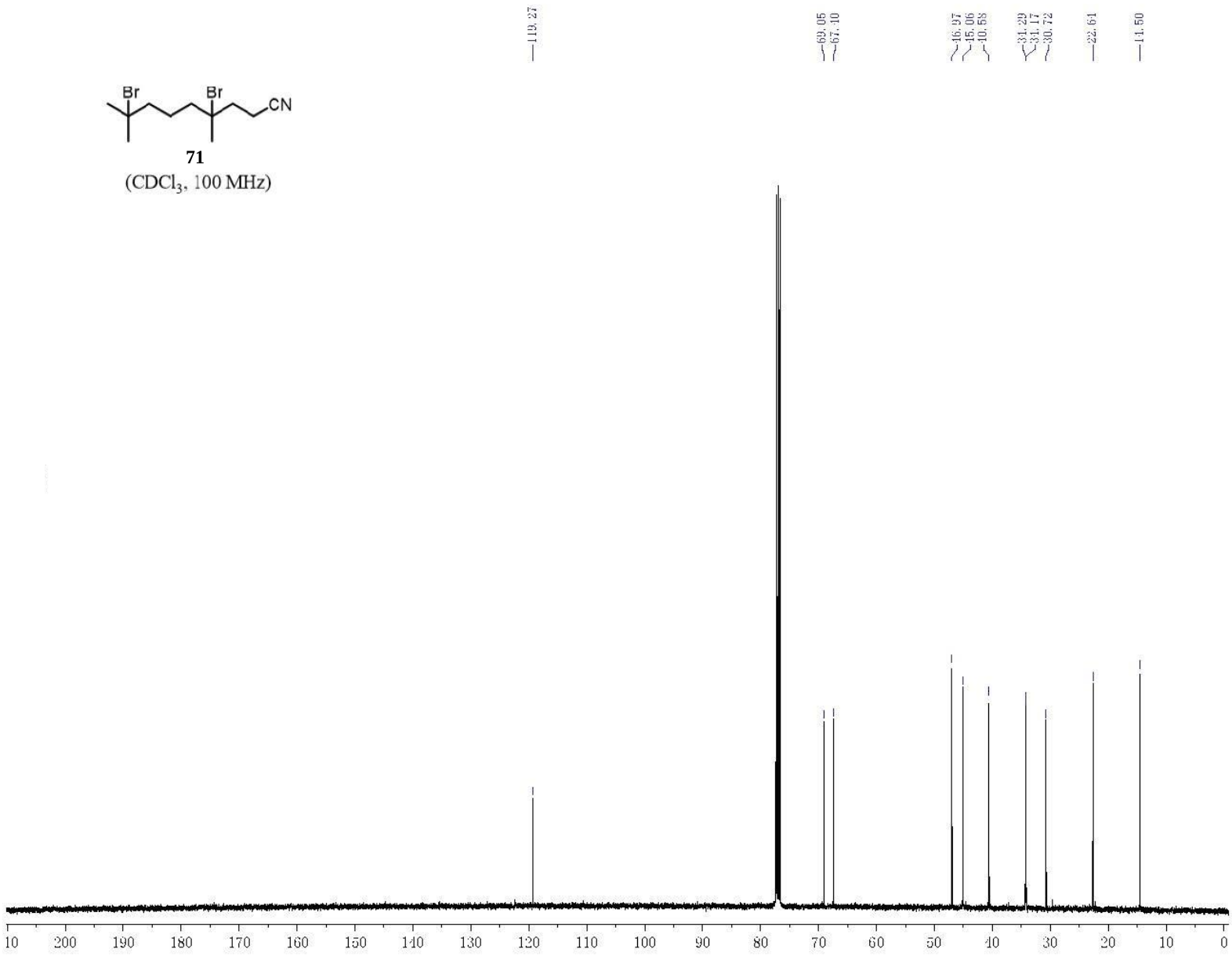

Br
Br
SO2Ph
70
(CDCl3, 400 MHz)

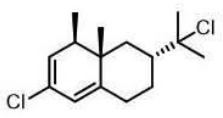

139.82
133.90
129.39
127.96
68.10
67.11
53.70
46.97
46.24
37.44
31.27
31.10
30.99
22.53
Br
Br
SO2Ph
70
(CDCl3, 100 MHz)



71

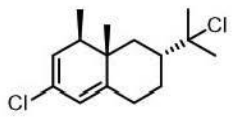
($CDCl_3$, 400 MHz)


Br
Br
CN
71
(CDCl3, 100 MHz)
119.27
69.05
67.10
46.97
45.06
40.58
34.29
31.17
30.72
22.61
14.50
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0



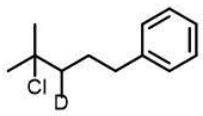
72

($CDCl_3$, 400 MHz)



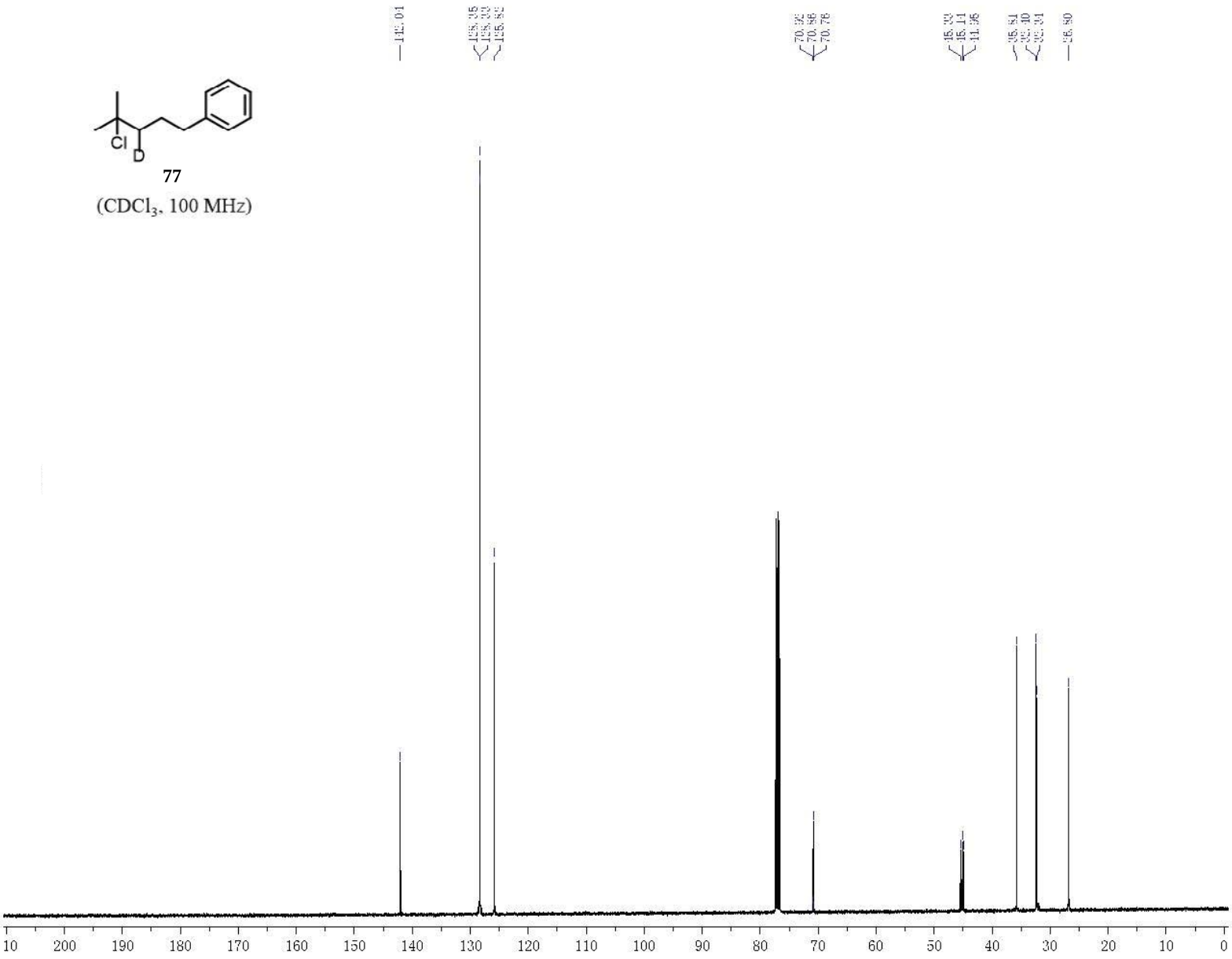
72

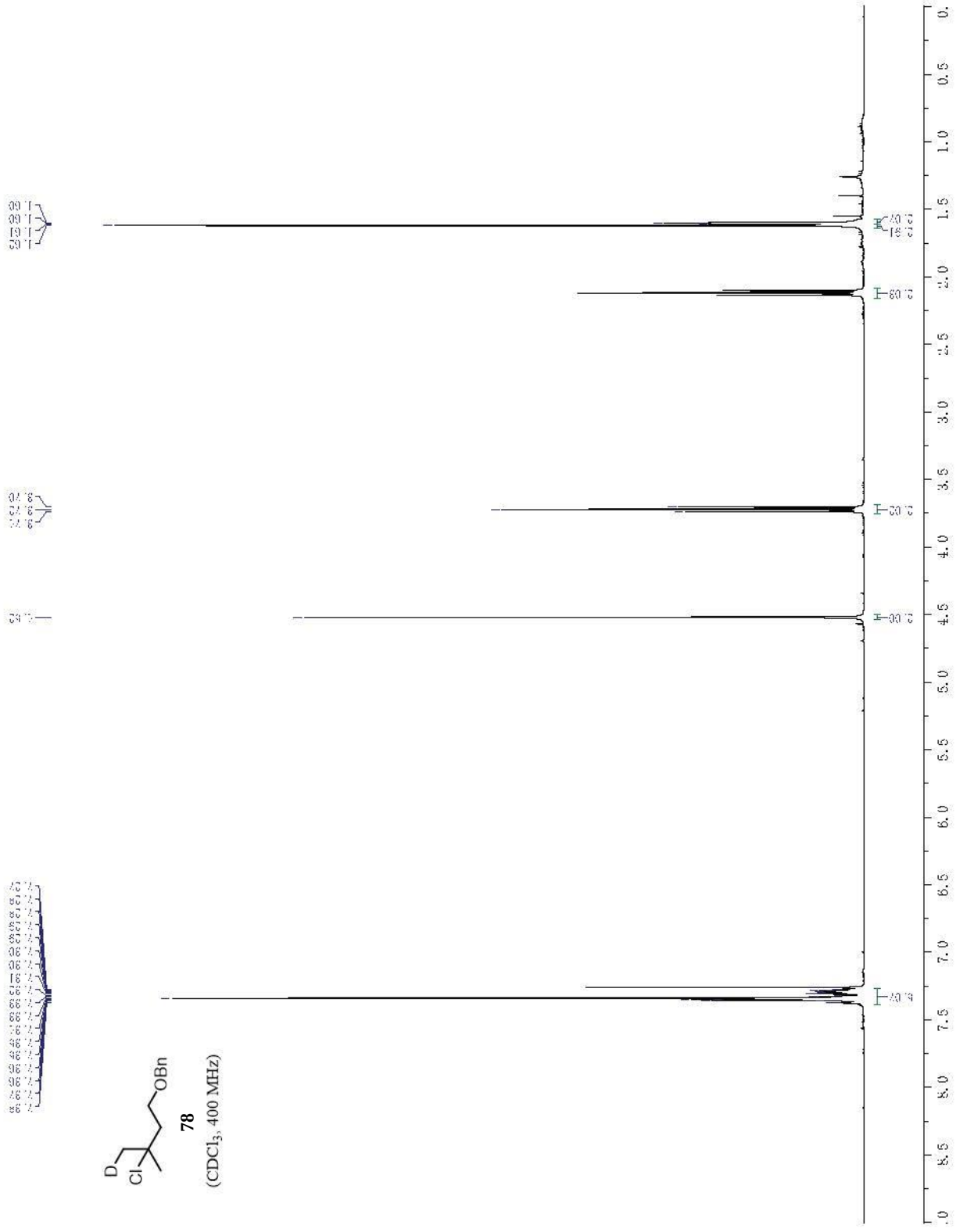
($CDCl_3$, 100 MHz)



77

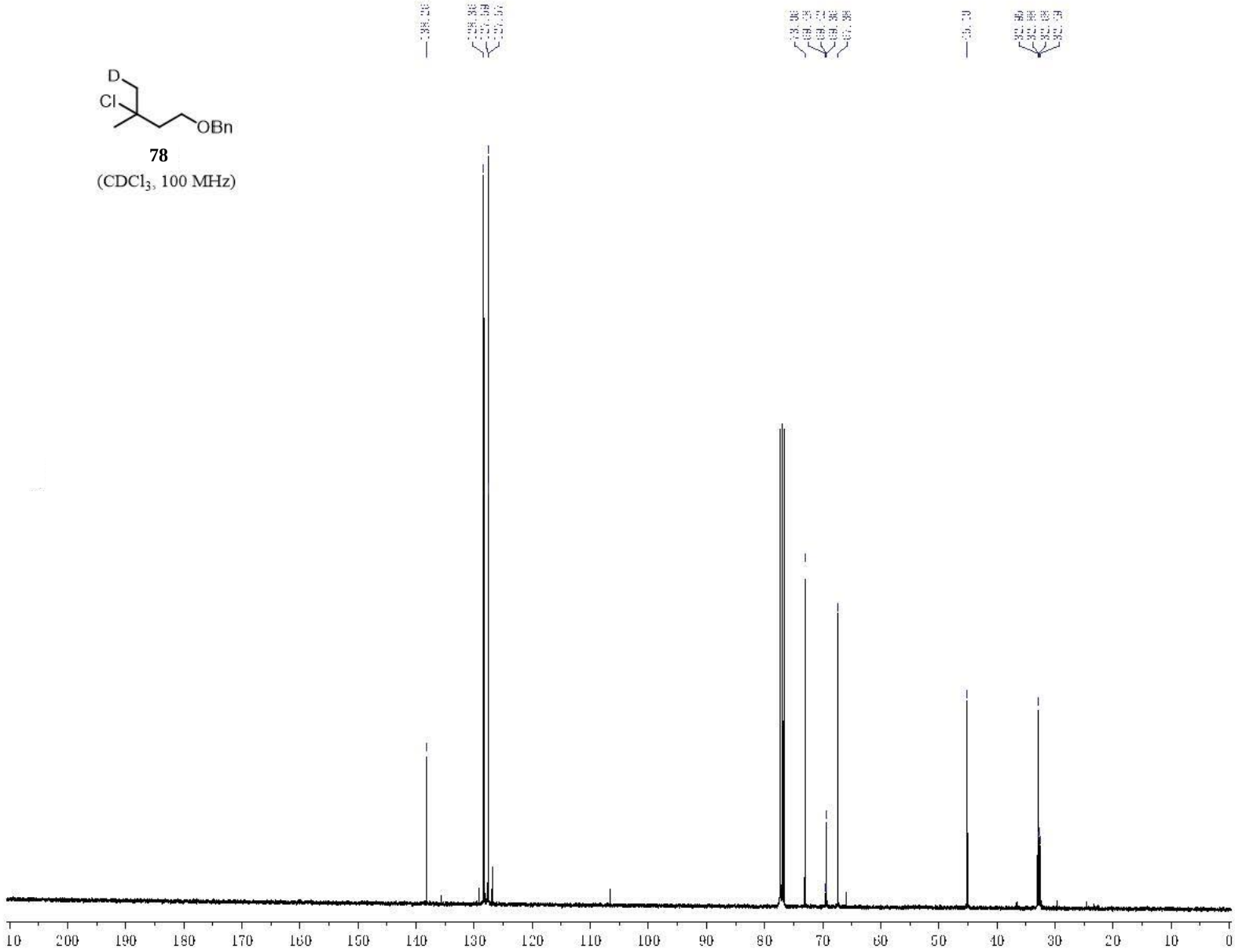
($CDCl_3$, 400 MHz)

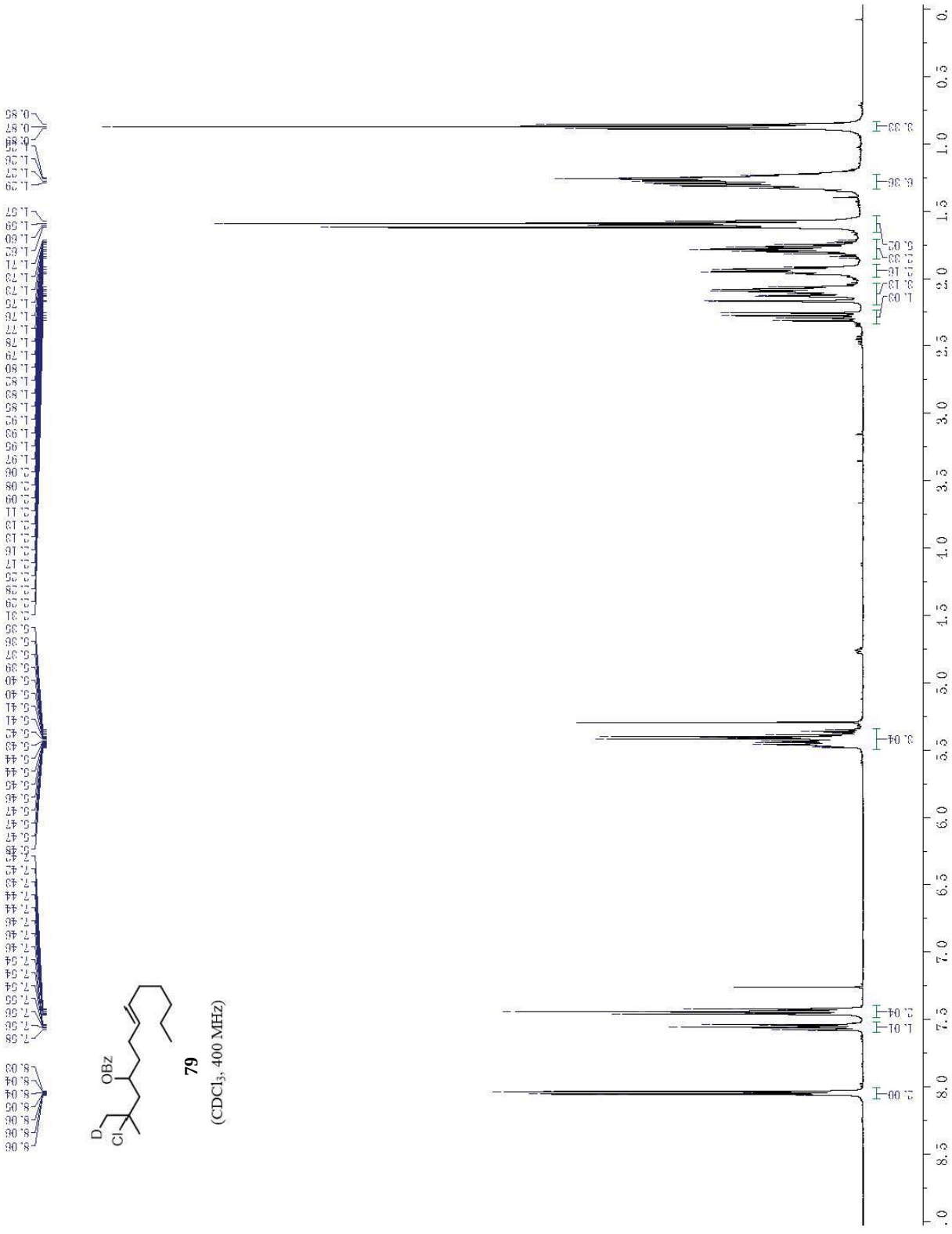

Cl
D
77
(CDCl3, 100 MHz)
142.01
128.35
128.29
125.82
70.92
70.86
70.78
45.29
45.11
44.96
35.84
32.30
32.01
26.80
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0



78

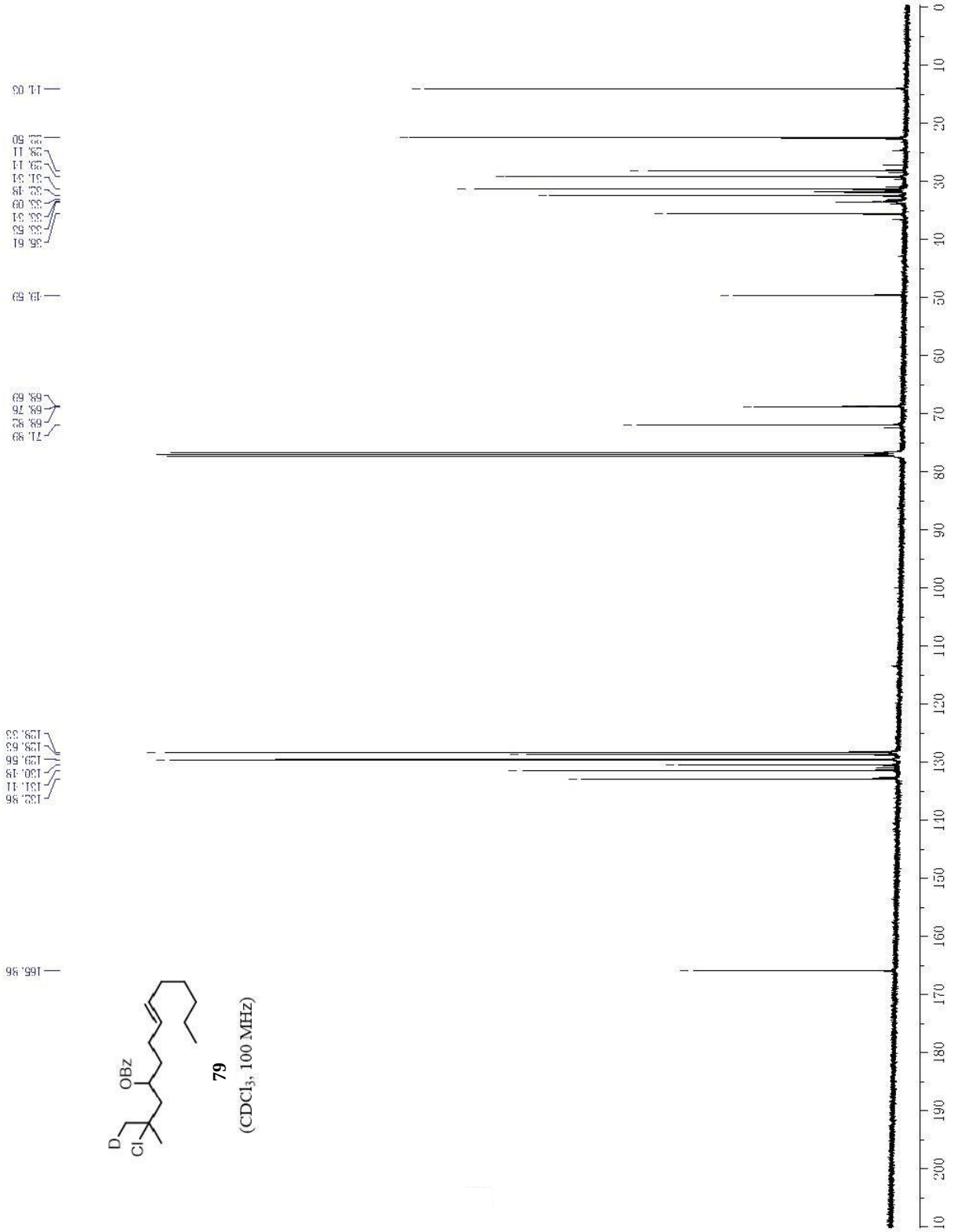
($CDCl_3$, 400 MHz)

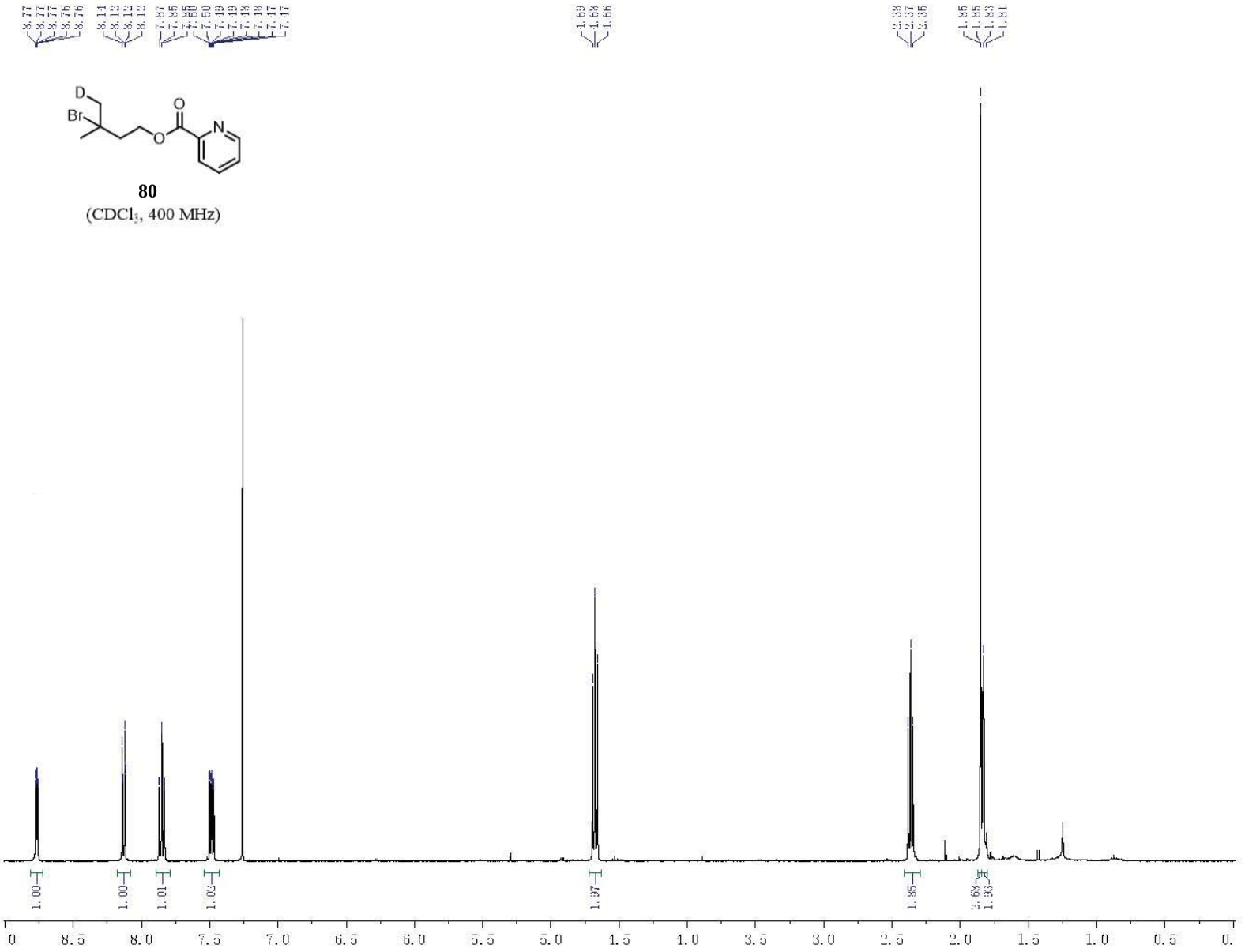

D
Cl
OBn
78
(CDCl3, 100 MHz)
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

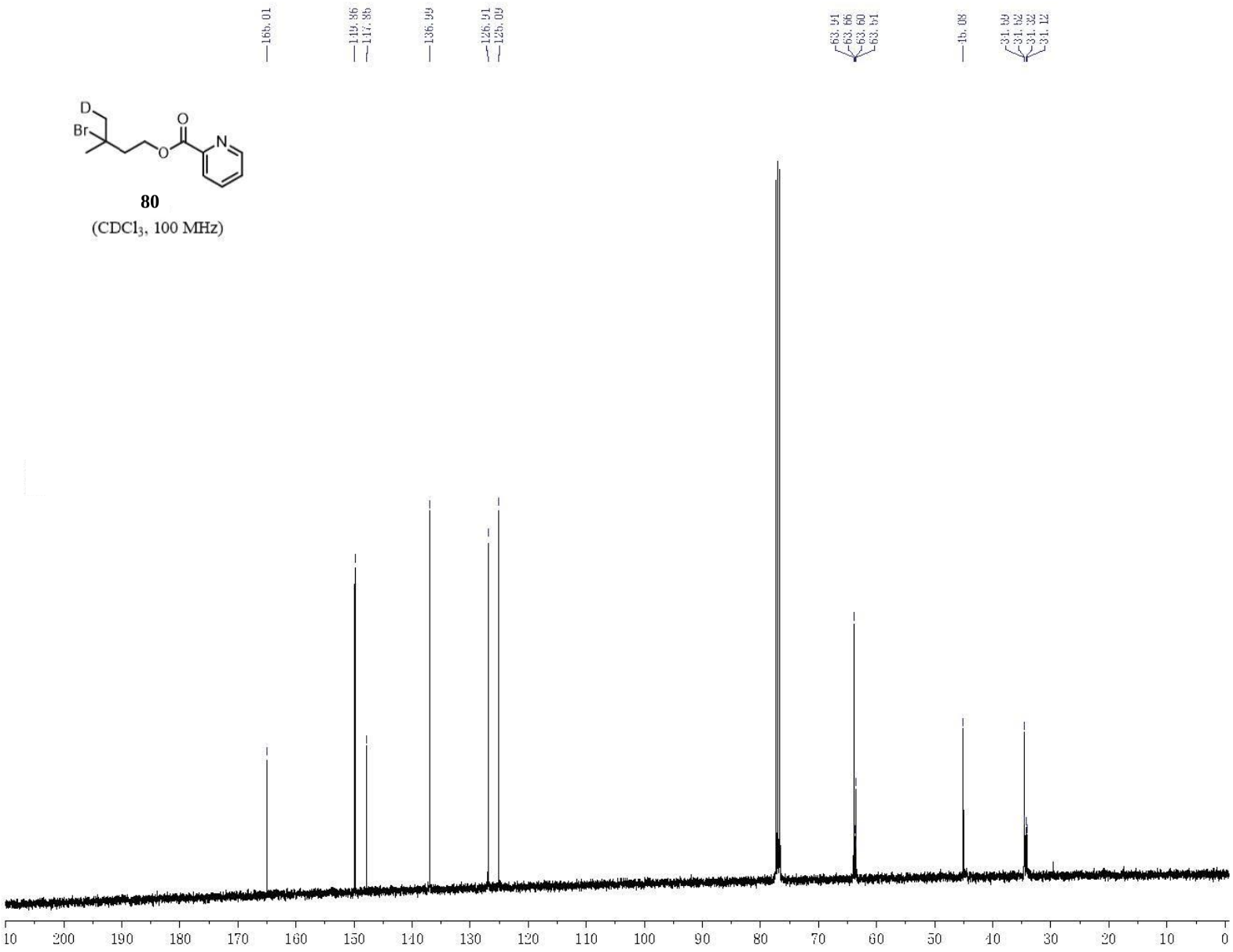


79

($CDCl_3$, 400 MHz)


OBz
D
Cl
79
(CDCl3, 100 MHz)


D
Br
O
O
N
80
(CDCl3, 400 MHz)


D
Br
O
O
N
80
(CDCl3, 100 MHz)
166.01
149.86
147.85
136.99
126.91
125.09
63.91
63.66
63.60
63.34
45.08
31.89
31.82
31.32
31.12
210
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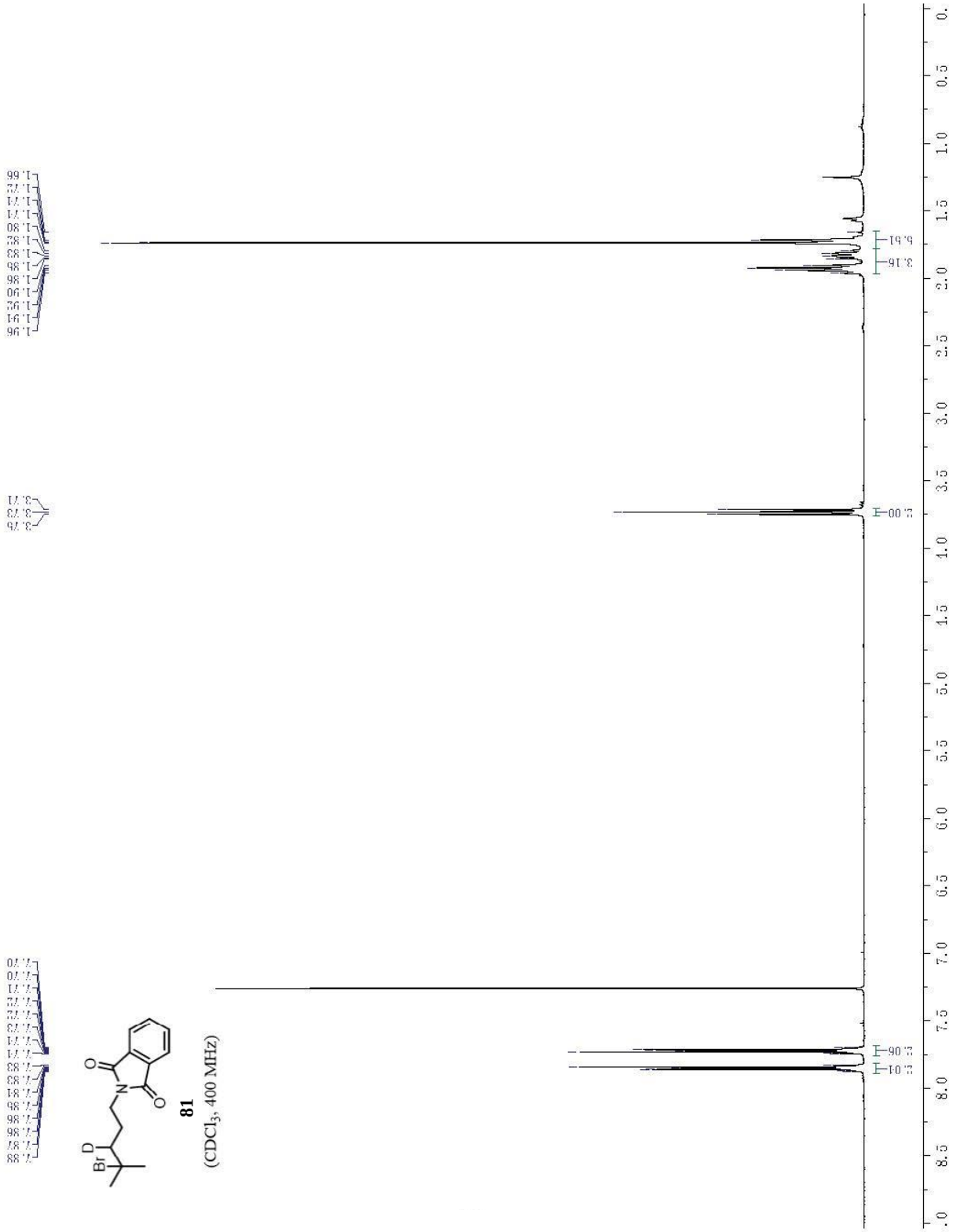
90
80
70
60
50
40
30
20
10
0


81
(CDCl3, 400 MHz)
Br
D
O
N
O

168.51
133.91
132.00
123.19
66.79
66.71
66.65
37.61
34.18
34.10
26.69
14.16
13.97
13.78
81
(CDCl3, 100 MHz)

CHAPTER 2

STRATEGIES FOR THE SYNTHESIS OF DIVERSE BROMO-CHAMIGRENE NATURAL PRODUCTS

2.1 Introduction

Nature produces an array of halogenated natural products, with one particularly extensive class of secondary metabolites being the sesquiterpenes known as the bromo-chamigrenes.[1] Those sesquiterpenoids containing the spiro-[5,5]-undecane skeleton and defining the chamigrane class are the most frequently encountered types of marine natural products from the genus *Laurencia*. The abundancy and diversity of the bromo-chamigrene natural products have drawn attention from many chemical and biological scientists.

2.1.1 Structural features

When bromide is present in such chamigrene-type molecules they are classified as bromo-chamigrenes. Bromo-chamigranes distributed in a wide range of species of the genus, and four species (*L. nidifica*, *L. nipponica*, *L. majuscula*, and *L. obtusa*) are especially abundant sources of this class of compounds. Selected members of this family, a collection which exceeds 50 in number, are shown in Figure 2-1 in 3-D form reflecting their absolute configuration.[2-11] Among them, aplydactone (**10**) is outstanding due to its unique molecular skeleton which contains two four-membered rings fused together, under a decalin frame.[12,13] The molecule has 5 stereocenters, with 3 of them being all-carbon quaternary centers. Such a highly strained structure had soon attracted attention from synthetic chemists. As is introduced in chapter 1, our group has devised a collection of highly reactive halonium source (XDSX series) in 2009.[14] BDSB, which is a representative genre with the widest applications in natural product total synthesis, supplied us with a powerful tool to install the secondary bromide in aplydactone (**10**). In this chapter, we will start with the first-generation strategy based on a BDSB-empowered key transformation; then we discuss other strategies that ultimately led to the total synthesis of diverse bromo-chamigrene natural products, including dactylone (**9**),[15] the putative biosynthetic precursor of aplydactone (**10**).

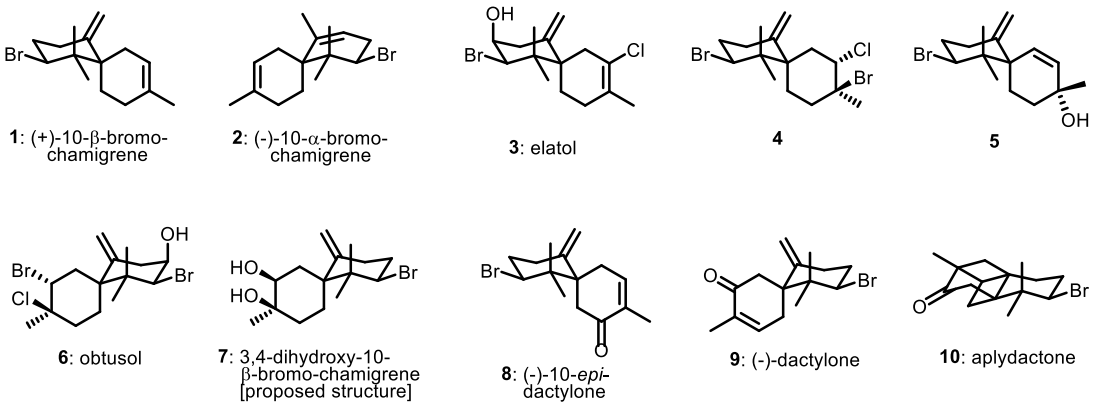


Figure 2-1. Representative bromo-chamigrene type natural products in 3-D expression

2.1.2 Biological activities

Cytotoxicity is a common biological property presented by bromide-containing natural products, with no exceptions for the bromo-chamigrenes. In addition to regular cytotoxicity, other intriguing bio-activities were investigated for various bromo-chamigrenes. For example, elatol (**3**)[16] showed inhibitory effects against six species of human pathogenic bacteria,[17] with particularly promising effects against *Staphylococcus epidermis*, *Klebsiella pneumoniae*, and *Salmonella sp.* The potency observed was as good as or better than six common, commercially available antibiotics (augmentin, latamoxef, ceflaclor, ceftriaxone, kanamycin, and netilmicin). Elatol (**3**) and its de-chlorinated counterpart deschloroelatol also displayed moderate antifungal activity against *Mycotypha microspora* and *Eurotium repens*.[18]

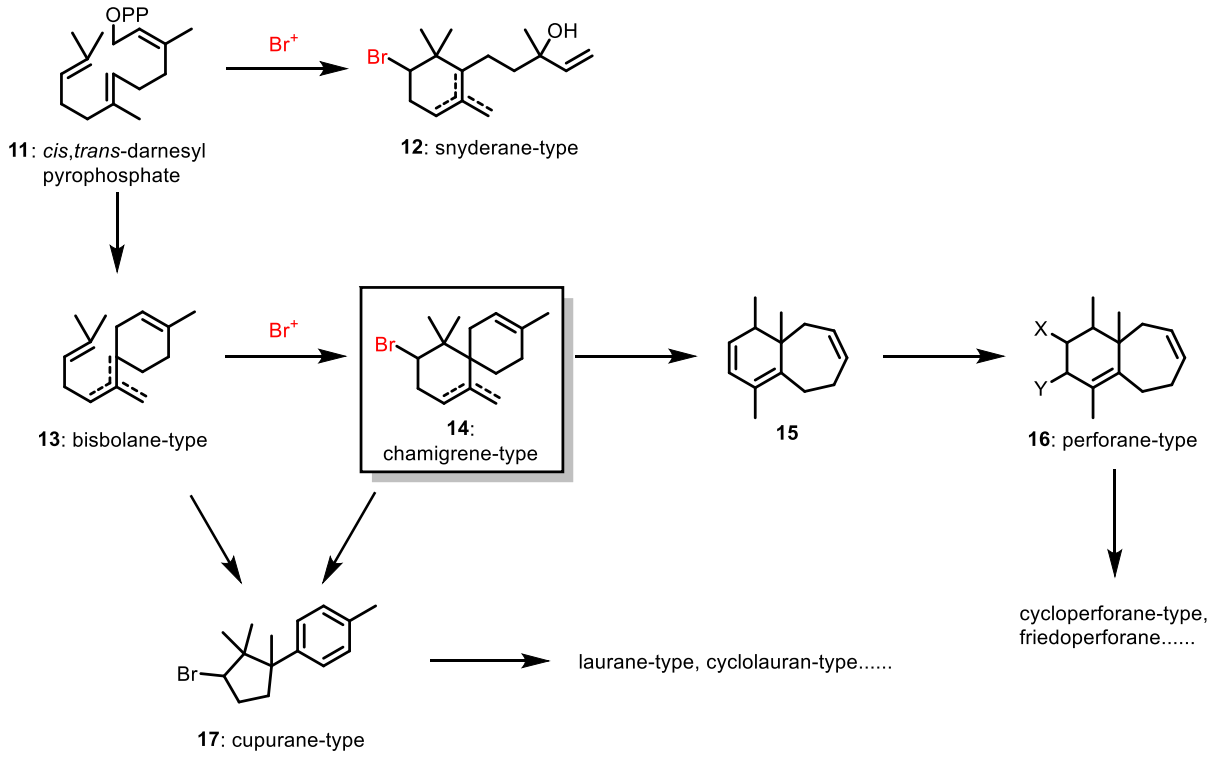
Dactylone(**9**), was found to exhibit anti-cancer properties through inhibiting epidermal growth factor-induced transformation and phenotype expression of several human cancer cells, including lung (H460), colon (HCT-116), and skin melanomas (SK-MEL-5 and SK-MEL-28).[19]

Other biological profiles produced by bromo-chamigrenes were reported but not limited to antiviral, enzyme-inhibitory, antioxidant, antifeedant, insecticidal, antifouling, and allelopathic,

among other miscellaneous activities.[20-28] Nevertheless, biological studies on these bromo-chamigrenes were typically limited to one or two bioassays, lacking systematic investigation such as detailed structure-activity relationship studies. Moreover, many isolation cases of bromo-chamigrenes have been reported without any biological investigations. As such, there's clearly a demand for concise access to such synthetic tartgets, in order to establish a logical and complete biological archive for bromo-chamigrene natural products.

2.1.3 Biogenesis

A broad spectrum of bromo-sesquiterpenoid natural products have their ultimate origin in one single starting material, *cis*, *trans*-farnesyl pyrophosphate (**11**), in a number of plausible biosynthetic pathways (Scheme 2-1).[29]

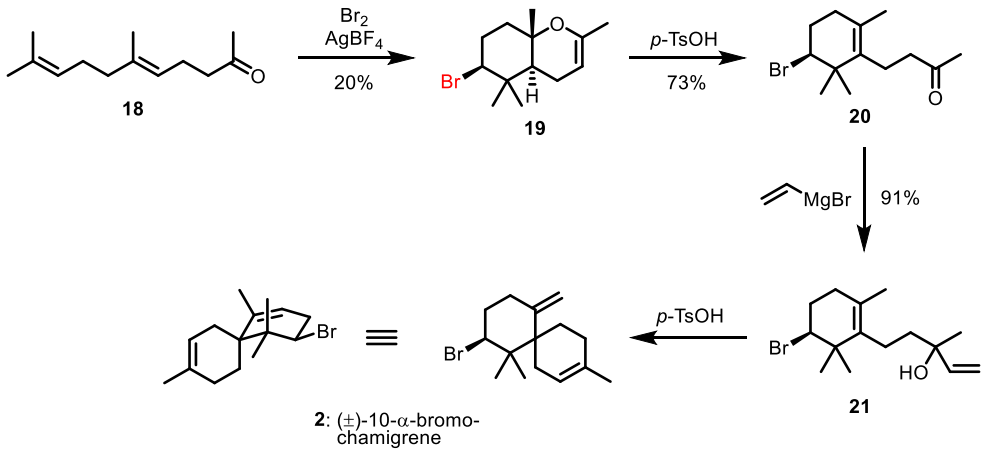


Scheme 2-1. A plausible biogenesis of bromo-chamigrene-type natural products and their related skeleton types

Direct cyclization induced by bromonium (Br^+), which is biosynthetically produced by vanadium bromoperoxidase (V-BrPO),[30] generates the snyderane-type natural products (**12**). Once bisbolanes (**13**) are formed via cyclization of *cis*,*trans*-farnesyl pyrophosphate (**11**), further bromonium-promoted cyclization can afford chamigrene-type bromo-sesquiterpenes, *aka* bromo-chamigrenes. Bromo-chamigrenes serve as a pivotal element in the biogenetic tree of all bromo-sesquiterpenoids (Scheme 2-1). Rearrangement reactions can transform bromo-chamigrenes into many other sub-types like perforane-type (**16**) and cupurane-type (**17**) bromo-sesquiterpenoid natural products.

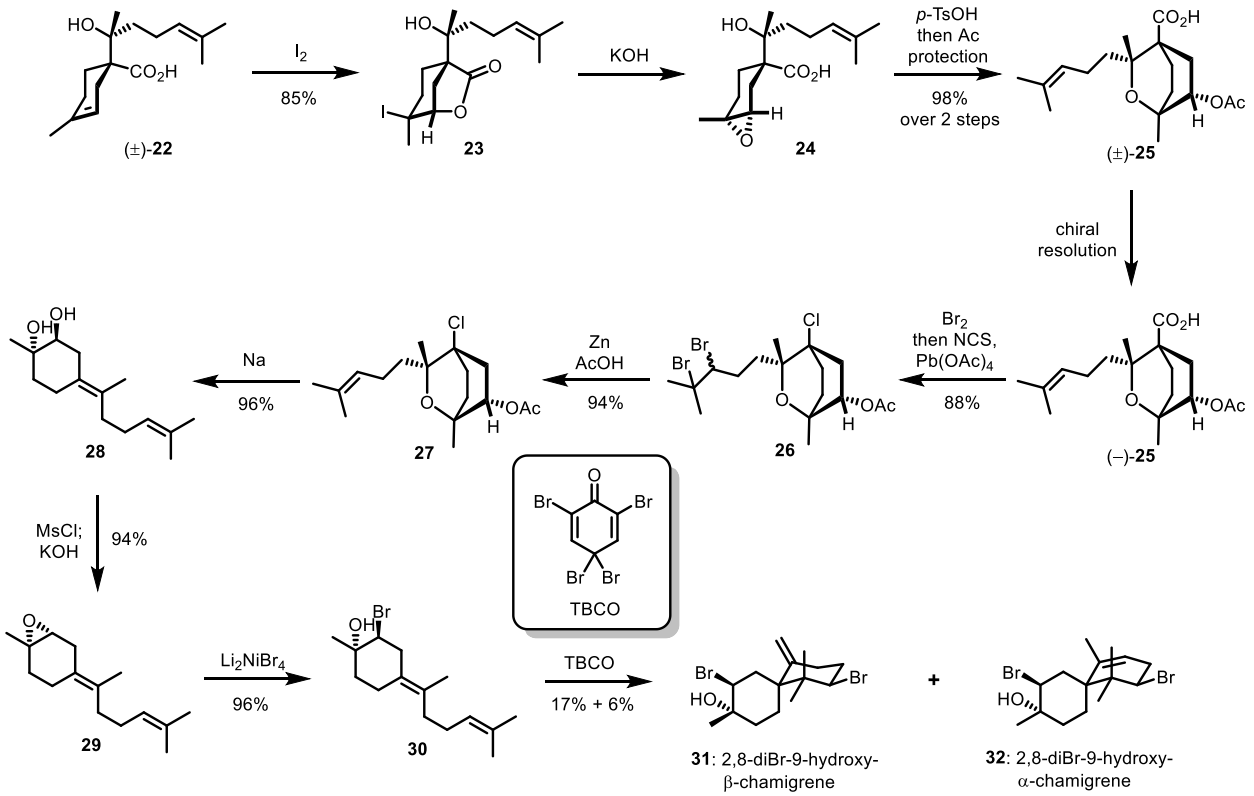
2.1.4 Synthetic studies towards bromo-chamigrenes

The inaugural synthesis of any member in the bromo-chamigrene family was achieved by Faulkner and Wolinsky in 1976.[31] Their synthesis commenced with geranylacetone (Scheme 2-2, **18**). Treatment of **18** with bromine and silver tetrafluoroborate afforded the bromo-cyclized product **19** in 20% yield. The next acid-mediated elimination generated tetrasubstituted alkene **20** in 73% yield. Attachment of a vinyl group followed by a *p*-toluenesulfonic acid promoted cyclization rendered racemic 10-α-bromo-chamigrene ((±)-**2**) as the "major component" in a mixture of brominated hydrocarbon without a marked isolated yield. Later in 1979, Kato and co-workers accomplished a similar synthesis of **2** from a related starting material in higher isolated yield.[32]



Scheme 2-2. The Faulkner&Wolinsky's racemic synthesis of 10-α-bromo-chamigrene

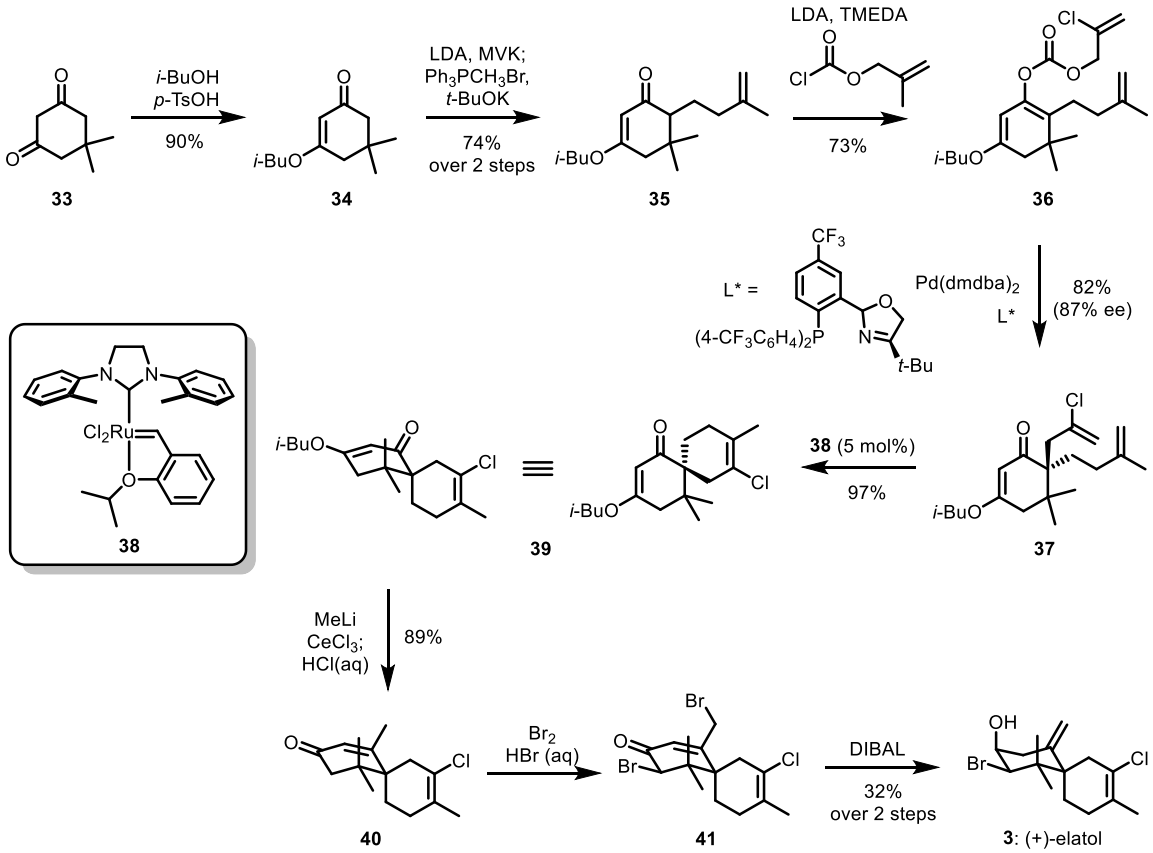
A remarkable enantioselective synthesis of two advanced member of bromo-chamigrenes were achieved by the Martin group in 1986.[33] They started from the iodo-cyclization of the known racemic carboxylic acid **22** (Scheme 2-3). The so-obtained iodoether **23** was subjected to epoxide formation conditions and a subsequent acid-promoted epoxide ring opening to reach racemic **25**. After a chiral resolution event, the enantio-enriched (–)-**25** underwent an alkene bromination/decarboxylative chlorination sequence to yield **26**. Zinc mediated de-bromination and sodium metal initiated radical ring opening afforded polyene compound **28**. Another two steps of manipulation (epoxide formation and re-opening by bromide) provided bromohydrin **30**, which served as the key cyclization precursor. TBCO was selected as the bromonium source in the last cyclization reaction, where the natural product 2,8-dibromo-9-hydroxy-β-chamigrene (**31**) was formed in 17% yield and its regio-isomer 2,8-dibromo-9-hydroxy-α-chamigrene (**32**) in 6% yield.



Scheme 2-3. The Martin's asymmetric synthesis of 2,8-diBr-9-hydroxy-β-chamigrene and 2,8-diBr-9-hydroxy-α-chamigrene

The three syntheses described above were all based on a biomimetic bromonium-induced π-cationic cyclization reaction on polyene substrates. Differentiated from that, the Stoltz and Grubbs synthesis of another important family member, (+)-elatol (**3**), was reported more recently.[34] Their synthesis commenced with cyclohexanedione **33** shown in scheme 2-4. *O*-alkylation and α-alkylation of the ketone afforded racemic **35**, whose chirality was flattened in the next step giving the precursor **36**. Then an asymmetric Tsuji allylation established the second all-carbon quaternary center of intermediate **37** in 87% enantiomeric excess. Ring-closing metathesis with the elaborate ruthenium complex **38** forged the spirocycle **39**, which was then subjected to a methyl addition/elimination sequence to afforded enone **40**. Bromination by bromine in hydrobromic acid occurred on both the α-position of the ketone and distal methyl group. Without any purification the crude material **41** was treated with DIBAL-H to reduce the ketone to an axial secondary alcohol

and the allylic bromide to an exocyclic alkene via S_N2' substitution to access the final target (+)-elatol (**3**).

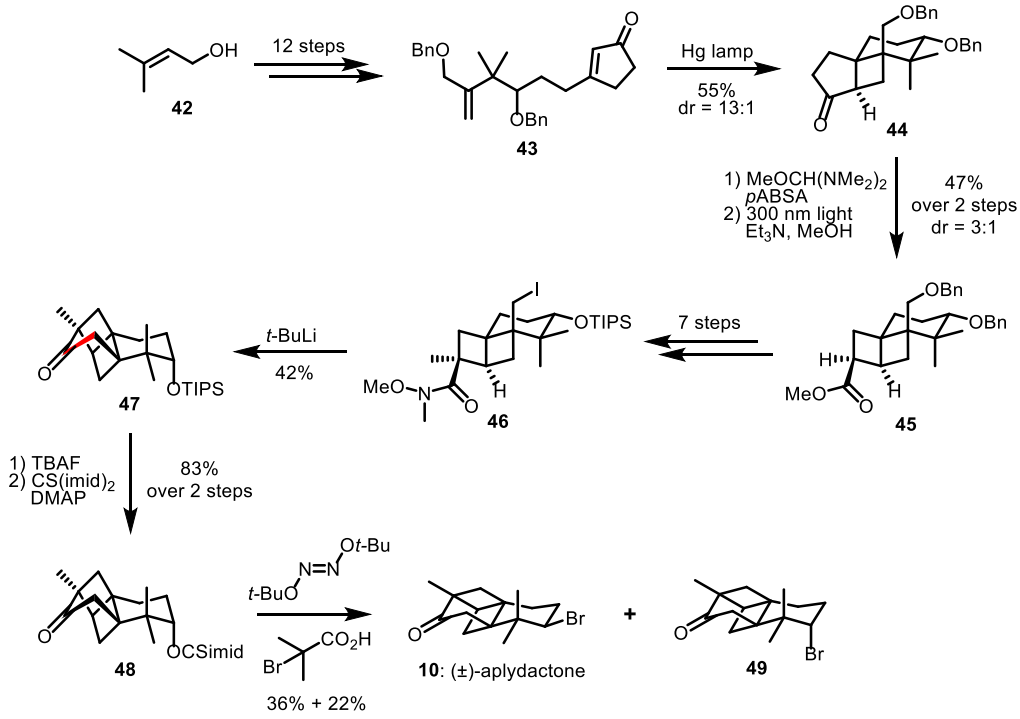


Scheme 2-4. The Stoltz&Grubbs asymmetric synthesis of elatol (**3**) using key allylation and ring-closing metathesis reactions

The last three, most recent synthetic reports are on aplydactone (**10**), the most "special" member in the bromo-chamigrene family owing to its extremely rare structure. It shall be mentioned that our synthetic efforts were finished prior to the publication date (May 2016) of the earliest one among them. Thus, no following chemistry could be referenced during our explorations toward this molecule.

The first is Trauner's synthesis of racemic aplydactone (**10**).[35] They prepared enone **43** starting from prenyl alcohol in 12 steps (Scheme 2-5). A UV light promoted [2+2] cycloaddtion reaction generated **44**, which was subjected to a two-step Wolff rearrangement protocol to give

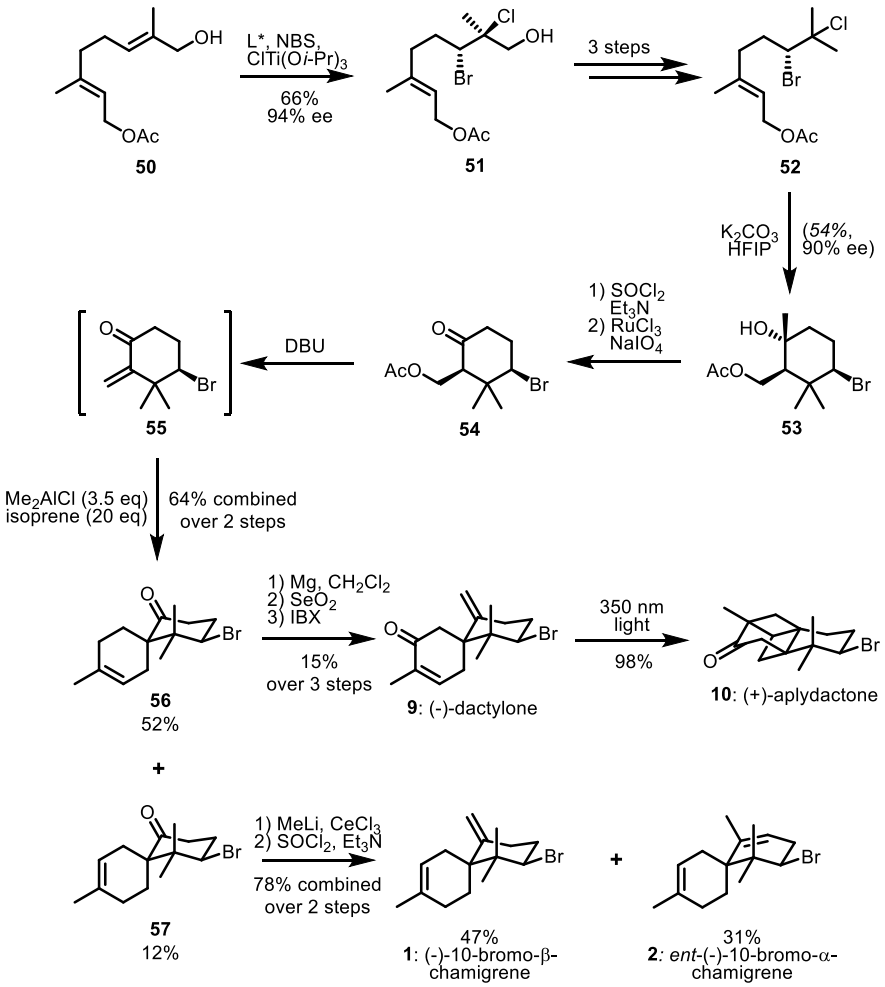
ring-contracted product **45**. Through another several steps they 1) replaced the primary OBn ether with an iodide; 2) changed the secondary OBn ether to an OTIPS ether; 3) transformed the methyl ester to a Weinreb amide. The key intramolecular alkylation event proceeded with a lithium-halogen exchange and then capture by the Weinreb amide, on intermediate **46**. Once the full skeleton of aplydactone was formed, they employed a radical substitution reaction to install the bromide, reaching the final natural product (**10**) in 26 steps (longest linear count), together with the 8-bromo-epimer **49**.



Scheme 2-5. The Trauner synthesis of (±)-aplydactone

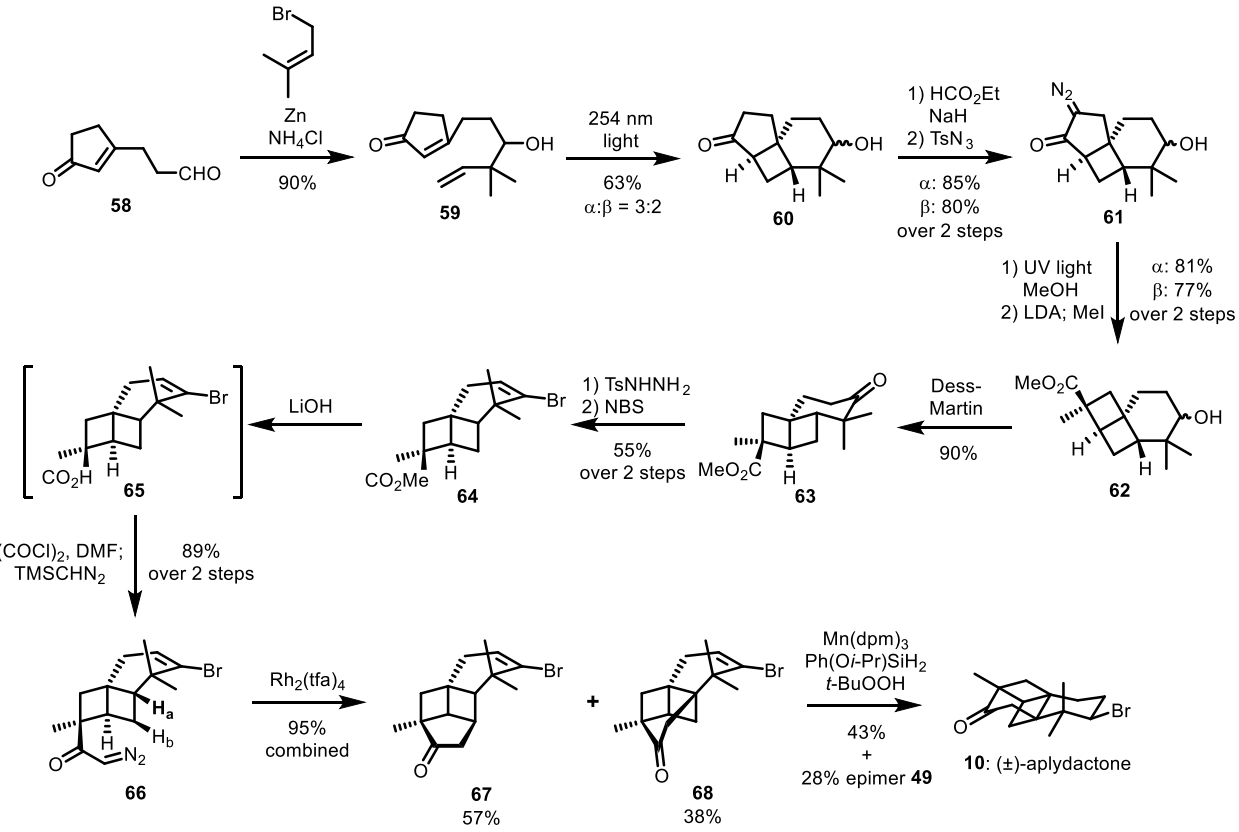
Soon after Trauner's publication, the Burns group reported their concise, asymmetric synthesis featuring higher degrees of biomimicry (Scheme 2-6).[36] Their starting point is the allylic alcohol **50** which was prepared in 1 step from commercially available geranyl acetate. By utilizing their signature asymmetric dihalogenation methodology, the corresponding chloro-brominated product **51** was isolated in 94% ee. A three-step manipulation removed the terminal alcohol to

deliver **52**, a formal chloro-bromination product of geranyl acetate. Treating **52** with anhydrous potassium carbonate in hexafluoroisopropanol promoted the substitution of the tertiary chloride by the secondary bromide, thus rendering a three-membered bromoranium intermediate. This high-energy intermediate was captured by the alkene and a cyclization product arose (**53**, 90% ee) in impressive enantiospecificity, given that bromoranium intermediates were well known to be prone to racemization. The so-obtained cyclization product **53** was subjected to elimination conditions to afford an exocyclic alkene, in which terminal carbon was then pruned by $RuCl_3/NaIO_4$. A DBU-mediated elimination of the terminal acetate provided enone **55**, which was directly used in a Lewis-acid promoted Diels-Alder reaction with isoprene to convey a pair of diastereromers **56** and **57** in 52% and 12% isolated yield respectively. The allylic position of the major isomer (**56**) was oxidized regioselectively to render (–)-dactylone (**9**) in 2 steps. Surprisingly, the proposed biogenetic intramolecular [2+2] cycloaddition reaction on dactylone emerged smoothly under the irradiation by light with 350 nm wavelength, forging (+)-aplydactone (**10**) in excellent yield. Interestingly, the isolated yield significantly diminished when light with shorter wavelength was implemented. In addition to aplydactone, two other natural products, (–)-10-bromo-β-chamigrene (**1**) and *ent*-(–)-10-bromo-α-chamigrene (**2**) were accomplished as well via transformations on the minor isomer product (**57**) from the Diels-Alder reaction.



Scheme 2-6. The Burns asymmetric synthesis of aplydactone and three other bromo-chamigrenes

The most recent synthesis of aplydactone came from the Zhang group in 2017.[37] In their synthesis (Scheme 2-7), the first four-membered ring was formed via a photo [2+2] cycloaddition reaction on precursor **59**, which was prepared from a commercially available compound in 2 steps. Installation of the diazo moiety and the following Wolff rearrangement contracted the five-membered ring to give rise to the second cyclobutane ring in intermediate **62**. Hydrolysis of methyl ester and setting of a terminal diazo functionality paved the way for the key C-H activation reaction. With a rhodium catalyst ($Rh_2(tfa)_4$), two products **67** and **68** appeared, which were spawned from abstracting H_a and H_b of **66**, respectively. The desired product **68** was subjected to a radical reduction protocol to yield the racemic sample of aplydactone (**10**), together with its epimer **49**.



Scheme 2-7. The Zhang synthesis of (±)-aplydactone featuring a key C-H activation reaction

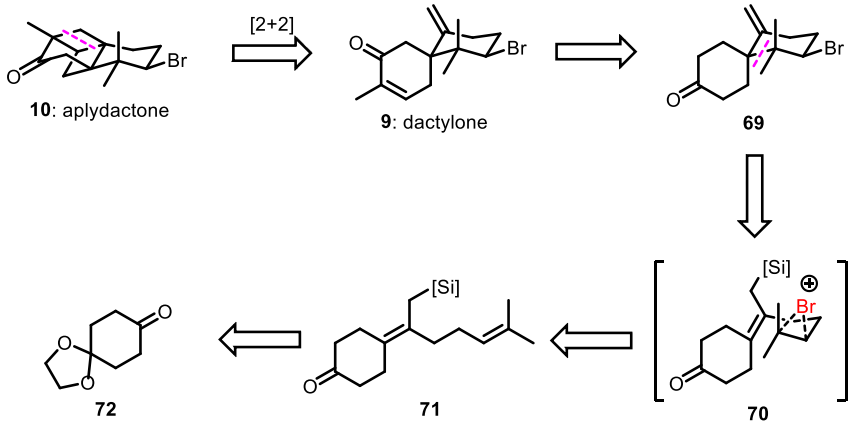
2.2 The first-generation route toward aplydactone: a BDSB-promoted cyclization based strategy

As is analyzed in chapter 1 and the introductory paragraphs in this chapter, BDSB ($[Et_2SBr]^+[SbCl_5Br]^-$), a powerful bromination reagent, can provide us an access to the bromide-containing spirocyclic core of bromo-chamigrene natural products. We designed the first synthetic route toward aplydactone, the star member within the family, based on a BDSB-promoted cyclization reaction.

2.2.1 Retrosynthetic analysis

According to the original isolation paper published in 2001, the putative biosynthetic precursor of aplydactone, dactylone, was "unable" to transform into its intramolecular [2+2]

reaction product aplydactone even under "long-term UV irradiation".[13] This piece of information clearly biased successive synthetic research. In the PhD thesis by Rhode, a model study attempting to construct the frame of aplydactone through an "unnatural" [2+2] cycloaddtion was conducted.[38] Unfortunately, there was no desired product captured but several compounds arising from side reactions. In that vein, we still planned to synthesize dactylone (**9**) or its analogue and extensively test different conditions for the [2+2] cycloaddtion reaction. To reach dactylone, it was proposed in Scheme 2-8 that the western enone moiety could be traced back to a simple cyclohexanone **69** via a series of functional group interconversions (FGIs). Such a spirocycle could be weaved from polyene precursor **71** and BDSB. BDSB would first react with the distal tri-substituted alkene to form the bromoranium intermediate (**70**). The internal alkene then served as a nucleophile to trap it, followed by elimination of the silyl group. So-designed tandem reactions could also be assisted by the β-silicon effect imposed by the silyl group. The multi-substituted polyene precursor **71** would be prepared from monoglycol-protected 1,4-cyclohexanedione (**72**).

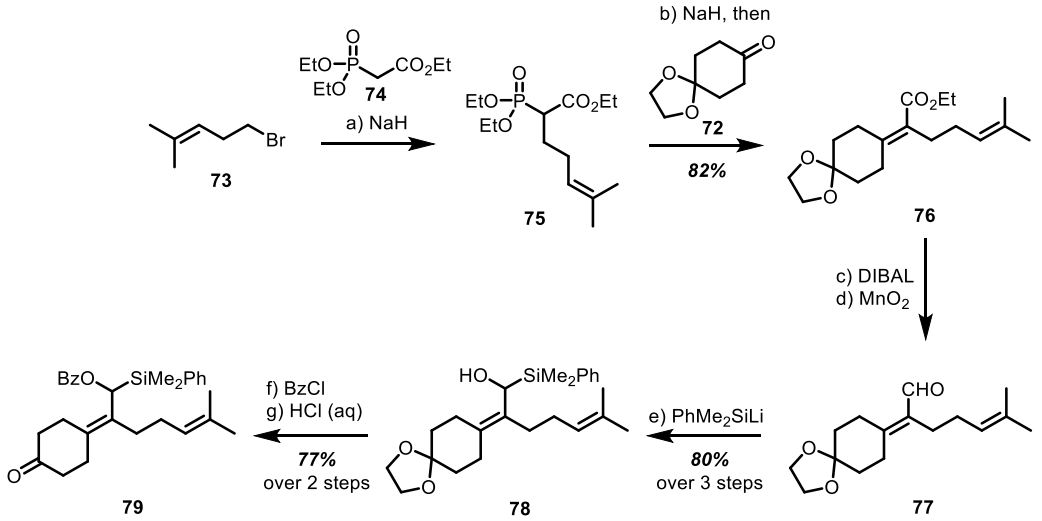


Scheme 2-8. Generation I retrosynthetic analysis of aplydactone based on a BDSB-promoted cyclization

2.2.2 An elaborate precursor and an unexpected cyclization product

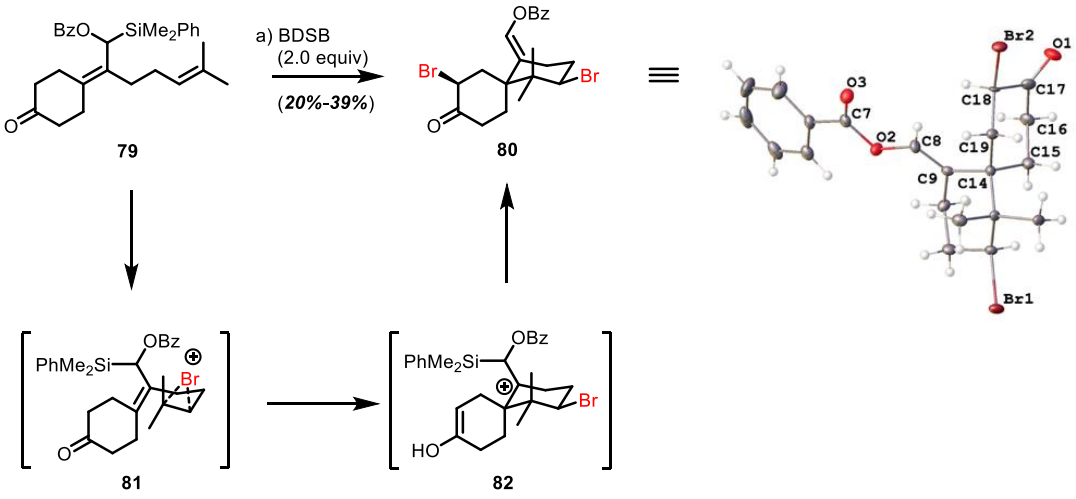
The development of an appropriate cyclization precursor **71** and screening of reaction parameters for cyclization had begun years prior to my admission into the Snyder group. A synthetic route to a highly elaborated precursor was established (Scheme 2-9), though the details of exploration would not be given.

Synthesis of such a polyene precursor began with the alkylation reaction of triethyl acetophosphonate **74** with homoprenyl bromide (**73**). The so-obtained substituted phosphonate **75**[39,40] was deprotonated by NaH and then reacted with ketone **72** to furnish the Horner-Wadsworth-Emmons product **76**. DIBAL-H reduction of the ethyl ester and MnO_2-mediated oxidation of the resultant allylic alcohol forged the α,β-unsaturated aldehyde **77**, which was further treated with phenyldimethylsilyllithium, generating the α-silyl alcohol **78**. Protection of the secondary alcohol with benzoyl chloride and hydrolysis of ethylene glycol ketal revealed the cyclization precursor **79**.



Scheme 2-9. Synthesis of cyclization precursor **79**. *Reagents and conditions*: a) literature reported;[40] b) **74** (1.2 equiv), NaH (60% dispersion in mineral oil, 1.15 equiv),THF, 23 °C, 1 h; then **72** (1.0 equiv), 0 °C to 23 °C, 10 h; c) DIBAL (1.0 M in hexanes, 3.0 equiv), CH_2Cl_2, -78 °C, 2 h; d) MnO_2 (5.0 equiv + 5.0 equiv), CH_2Cl_2, 23 °C, 48 h; e) $PhMe_2SiLi$ (0.75 M in THF, 1.3 equiv), THF, -78 °C, 1 h; f) BzCl (1.2 equiv), pyridine (2.0 equiv), CH_2Cl_2, 23 °C, 8 h; g) HCl (5%, aq), acetone, 23 °C, 8 h

Cyclization of the precursor **79** occurred at ambient temperature (Scheme 2-10). The optimal protocol was to treat a nitromethane solution of **79** (0.01 M) with 2 equivalents of BDSB at ambient temperature. The reaction mixture was allowed to stir for 5 minutes before being quenched by an aqueous mixed solution of $NaHCO_3/Na_2S_2O_3$. The cyclization product **80**, where one additional bromide was installed at the α-position of the ketone, was isolated in up to 39% yield as a single diastereomer. The relative stereochemistry was established unambiguously by X-ray diffraction analysis.



Scheme 2-10. BDSB promoted cyclization of **79**. *Reagents and conditions*: a) BDSB (2.0 equiv), CH_3NO_2, 23 °C, 5 min

The rational for the formation of **80** is included in Scheme 2-10. BDSB first reacted with the terminal alkene of **79**, forming a three-membered bromoranium intermediate **81**. Interception by the internal alkene forged spirocyclic intermediate **82** in which the carbocation was stabilized by the neighboring silyl moiety via the β-silicon effect.[41] A simultaneous stereoselective α-bromination of the ketone which plausibly happened through an enolization/bromination mechanism rendered the final product as a single diastereomer. Employment of less than 2 equivalents of BDSB did not give any isolable mono-brominated product (a spirocycle without the α-brominated ketone). The functionality pattern of precursor **79** was also highly specific. The

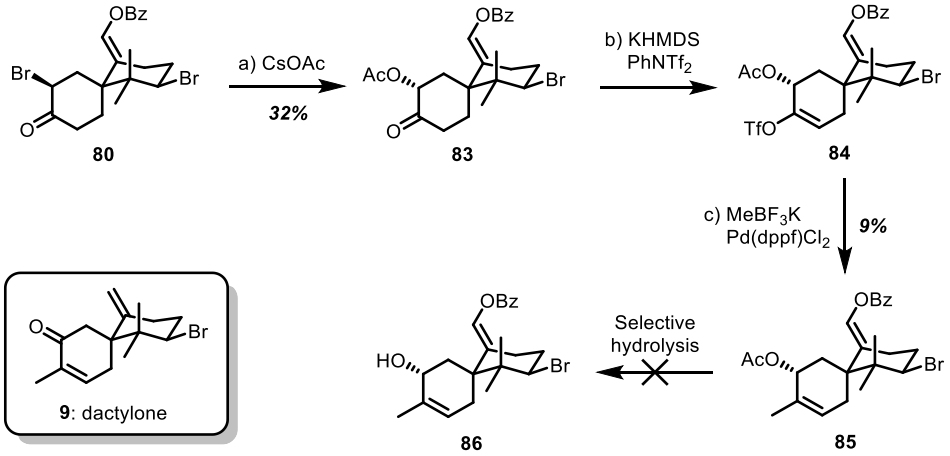
absence of the secondary benzoate made the internal alkene so electron-rich that BDSB would react with it instead of the distal one first, leading to a bromo-desilylation product. Phenyldimethylsily moiety was the only one found to afford any isolable cyclization product, while other silyl groups failed to do so. An unprotected cyclohexanone carbonyl was indispensable as well since its protected form or reduced form (protected secondary alcohol, i.e. OAc) were unable to provide any identifiable cyclization product. Other bromonium sources such as TBCO or $Br(coll)_2PF_6$ under either typically reported or similar reaction conditions as optimized for BDSB did not afford **80**; instead, a complex mixture of products and unreacted **79** resulted. We cannot rule out that bromonium-induced cyclization occurred in these experiments, but there was no single major product generated suggesting that if formed, such reactions proceeded with low efficiency/chemoselectivity. Explorations to understand why the α-bromination occurred with perfect stereoselectivity and regioselectivity are still underway.

2.2.3 Post-BDSB transformations

Significant efforts of substituting the bromide next to the carbonyl in **80** had been made in the early stage. Thiophenol was found to replace the bromide in high yield. But the phenylsulfide turned out to be resistant to oxidation conditions in attempt to transform sulfur to the oxygen atom as in dactylone (**9**). A large number of other unfruitful reactions will not be covered in detail here.

The farthest we can proceed towards dactylone starts with a substitution reaction of the α-bromide by acetate, as shown in Scheme 2-11. Cesium acetate was elected to react with dibromide **80** in anhydrous DMF, with the substituted product **83** isolated in 32% yield. The subsequent kinetic deprotonation and trap by $PhNTf_2$ afforded triflate **84**, again in low yield (29%), with a small amount of starting materials remaining. The methyl coupling ahead turned out to be

extremely challenging. Negishi coupling ($Pd(PPh_3)_4$, Me_2Zn), Kumada coupling ($Ni(acac)_2$, MeMgBr), Stille coupling ($PdCl_2(PhCN)_2$, CuI, $AsPh_3$, Me_4Sn), or other protocols ($Pd(PPh_3)_4$, LiCl, $AlMe_3$) all did not succeed in transferring methyl moiety. These conditions typically gave no conversion or slow consumption of starting material **84** without producing the desired product **85** even at elevated temperature. The only exception was a Suzuki-Miyaura coupling protocol where $Pd(dppf)Cl_2$, $MeBF_3K$ and Cs_2CO_3 were employed in a mixed solvent of THF and water.[42] However, the reaction profile was unsatisfactory, with less than 10% yield of product observed before any further conversion can happen. Strict degassing or higher temperature did not provide any improvement. In fact, prolonged heating resulted in slow decompose of starting material **84**. With the methyl-coupled product **85** in hand, we tried to selectively hydrolyze the secondary acetate to reach allylic alcohol **86** in the presence of the vinyl benzoate moiety, while this task proved to be challenging since it was considerably difficult to differentiate these two ester groups which have very close electronic and steric environments.



Scheme 2-11. Post-BDSB functionalizations of dibromide **80**. *Reagents and conditions*: a) CsOAc, 4 Å MS, DMF, 40 °C, 2 h; b) KHMDS (0.5 M in PhMe, 1.15 equiv), THF, -78 °C, 30 min, then $PhNTf_2$ (1.3 equiv), -78 °C, 3 h; c) $Pd(dppf)Cl_2$ (0.1 equiv), $MeBF_3K$ (1.5 equiv), Cs_2CO_3 (3.0 equiv), THF/H_2O (8:1), 80 °C, 8 h

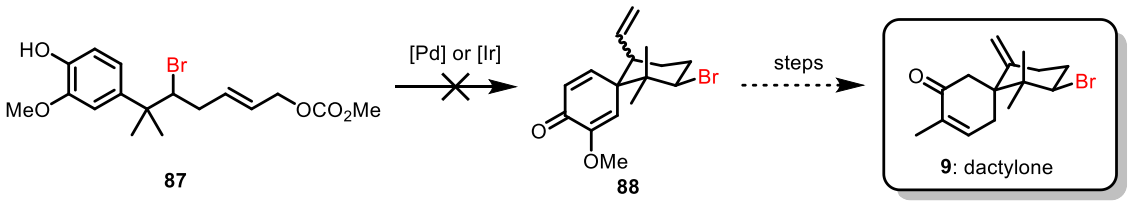
At this stage, a major hurdle arose on the material supply along the synthetic route. Although the polyene compound **79** could be prepared in multi-gram scale, a single setup of

BDSB-mediated cyclization cannot exceed a scale of 300 mg. Together with an average yield of 25% in the cyclization step, less than 300 mg of dibromide **80** could be synthesized in one batch. The following three steps were all low-yielding, despite extensive efforts on optimization. The amount of the most advanced intermediate **85** was obtained in less than 2 mg, which were evaluated sufficient for deeper explorations. A strategic re-design of the synthetic route toward bromo-chamigrenes and aplydactone was hence needed.

2.3 The second-generation route toward aplydactone: a Diels-Alder based strategy

The first-generation route based on a BDSB-promoted cyclization provided an elaborate spirocycle **80** with two bromine atoms implemented stereoselectively. Nevertheless, the yield of several elementary steps significantly restricted the material supply, prompting us to pursue a route toward aplydactone and other bromo-chamigrene natural products in a more efficient manner.

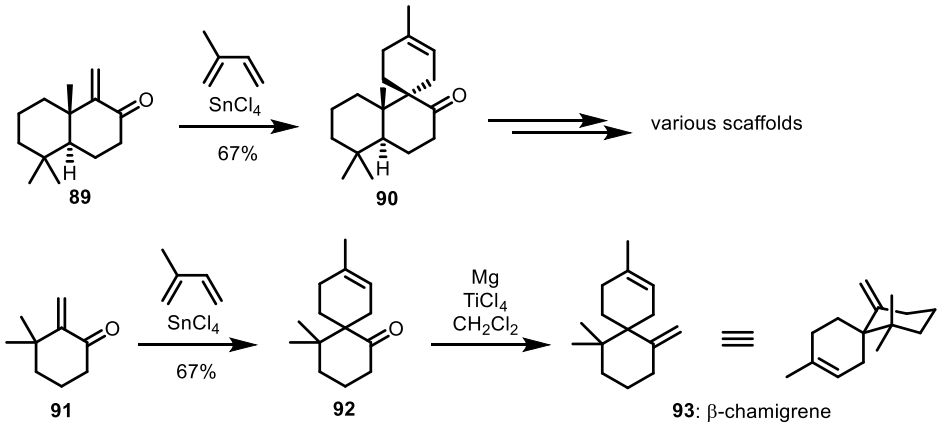
We spared resources to test a metal (palladium[43] or iridium[44])-catalyzed intramolecular dearomatization reaction[45] of phenol substrate **87** to construct the bromo-spirocycle core structure of dactylone (Scheme 2-12). Unfortunately, no desired product **88** was obtained.



Scheme 2-12. An attempted, unsuccessful dearomatization strategy toward the synthesis of the key spirocycle

Inspired by a synthesis of β-chamigrene (**93**, the des-bromo version of 10-β-bromo-chamigrene, which is also a natural isolate),[46] where the spirocycle was rapidly assembled via a Diels-Alder reaction, we then decided to adopt such a Diels-Alder reaction as the key step in the second-generation synthesis. Diels-Alder reactions of this type were applied in the synthesis of

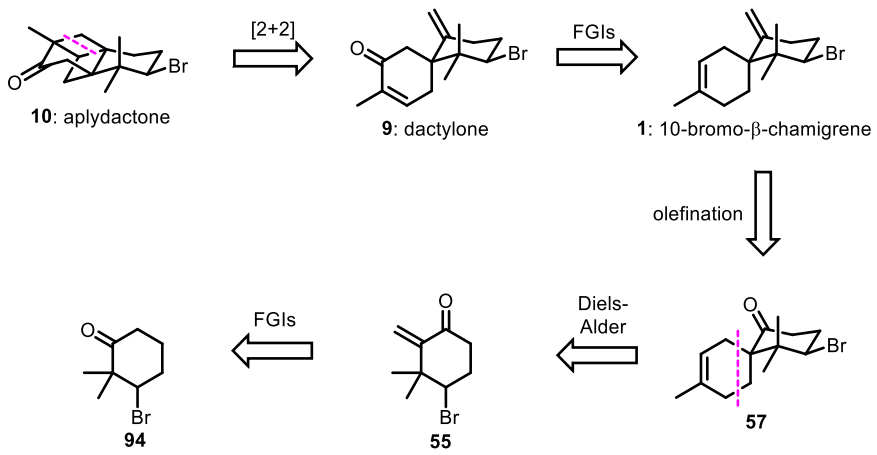
relevant molecular scaffolds,[47-50] particularly [5.5.0] spirocycles with two consecutive all-carbon quaternary centers (Scheme 2-13).



Scheme 2-13. Diels-Alder reactions in constructing two consecutive all-carbon quaternary centers

2.3.1 Retrosynthetic analysis

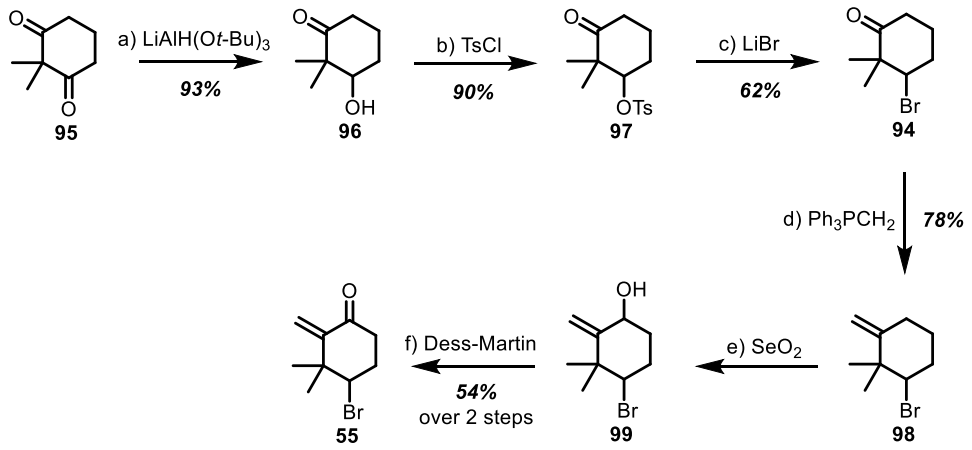
As is in the first-generation retrosynthetic analysis, we devised dactylone (**9**) as the precursor for aplydactone (**10**). In the second-generation retrosynthetic analysis shown in Scheme 2-14, dactylone would be obtained through regioselective manipulations from 10-bromo-β-chamigrene (**1**), one of the least oxidized natural products in the family. The exocyclic alkene of **1** could be furnished from a ketone, tracing back to **57**, a [4+2] adduct of enone **55** and isoprene. Cyclohexanone **94**, which was reported, could serve as the synthetic precursor of enone **55**. Note again that **55** and **57** were not known when we probed this chemistry though later Burns et al published the same intermediates.



Scheme 2-14. Generation II retrosynthetic analysis of aplydactone based on a Diels-Alder cycloaddition

2.3.2 Synthesis of the Diels-Alder precursor

Although the synthesis of ketone **94** was reported,[51] its originally recorded synthetic scale was not ideal to support a synthetic route with more than 10 steps. A modified procedure was then developed to address this problem (Scheme 2-15). 2,2-dimethyl-1,3-cyclohexanedione (**95**) was selectively mono-reduced to **96** in high yield, with other reductants such as $NaBH_4$ giving a significant amount of over-reduction products and remaining starting material. A two-step bromination sequence (tosylation/substitution) reached **94**, which was further subjected to Wittig methylenation condition to yield the volatile alkene **98**. SeO_2-mediated allylic oxidation and Dess-Martin oxidation supplied enone **55** in multi-gram scale. It was worth noting that **55** can be purified and characterized, even though long-term exposure of **55** to vacuum resulted in self-dimerization via a hetero-Diels-Alder pathway, as reported in Burns' aplydactone synthesis.[35]



Scheme 2-15. A scalable synthesis of enone **55.** *Reagents and conditions*: a) $LiAlH(Ot\text{-}Bu)_3$ (0.95 equiv), THF, -78 °C, 30 min; b) TsCl (2.5 equiv), pyridine, 23 °C, 72 h; c) LiBr (8.0 equiv), HMPA, 65 °C, 12 h; d) Ph_3PCH_3Br (2.0 equiv), *t*-BuOK (1.5 equiv), PhH, 80 °C, 1 h, then **94** (1.0 equiv), 80 °C, 10 min; e) SeO_2 (1.0 equiv), *t*-BuOOH (5.5 M in nonane, 3.0 equiv), $CHCl_3$, 55 °C, 11 h; f) Dess-Martin periodinane (1.5 equiv), $NaHCO_3$ (3.0 equiv), CH_2Cl_2, 2 h

*2.3.3 Diels-Alder reaction of **55**: parameters affecting stereoselectivity*

With enone substrate **55** in hand, we proceeded to test the key Diels-Alder cycloaddition reaction. The first attempt gave a cycloaddition product in 60% yield as a single diastereomer when Me_2AlCl was selected as the Lewis acid promoter, with the reaction starting from a relatively high temperature (-30 ^oC) and ending at 0 ^oC (Table 2-1, Entry 1). Soon it was discovered that launching the reaction at a lower temperature (-78 ^oC) gave rise to another diastereomer in the product mixture. The relative stereochemistry of these two diastereomers (**56** and **57**) were determined unambiguously by X-ray diffraction pattern of their single crystal samples. Weight of the minor diastereomer could be amplified in a ratio of 1:3.2 compared to the major isomer (Entry 2). However, keeping the reaction media at -78 ^oC was necessary for achieving this ratio and the requirement caused an incomplete conversion of starting material, plus difficulties in product purification. Therefore, for a full conversion of starting material, a more practical operation was employed, where the reaction mixture was kept at -78 ^oC for 4 h, then allowed to warm to -50 ^oC

and kept at this temperature for one more hour. Hence, a separable mixture arose and the major isomer was isolated in 70% yield whilst the minor in 14% yield (ratio = 4.9:1). Other Lewis acid promoters were tested, for instance, Et_2AlCl and $SnCl_4$. Et_2AlCl can further elevate the content of the minor isomer **57** but both of them failed in providing clean products even after extensive purifications. Thus, Dimethylaluminum chloride (Me_2AlCl) was determined as the optimal promoter.

A series of enone substrate with ester/ether substituents (X group) were studied, in order to comprehend the influence on stereoselectivity exerted by the substituent X. It turned out that whatever oxygen substituents were used (OTBS or OMe or OAc), no significant diastereoselectivity appeared, marking the unique role that the secondary bromide moiety played in generating the obvious stereochemical bias in the reaction. We proposed that the orbital of bromine atom may have stereoelectronic interactions with the metal center of Lewis acids. This effect can be absent in esters/ethers since oxygen only has 2*p* orbitals, so no apparent stereochemical discrimination could come into play (Entry 6-9).

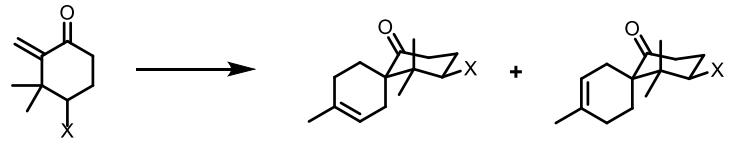


Table 2-1. Exploration of parameters of the key Diels-Alder cycloaddtion reaction

Entry	Substituent X	Lewis acid promoter	Starting temperature (°C)	Ending temperature (°C)	dr[a]	Combined isolated yield (%)
1	Br	Me_2AlCl	-30	0	1.0:0	60

Table 2-1. (Continued)

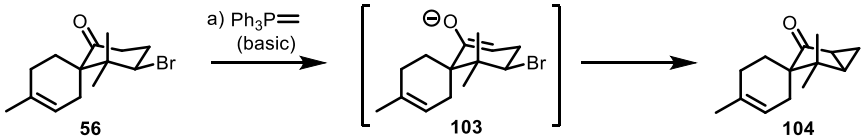
2	Br	Me_2AlCl	-78	-78	3.2:1.0	n.d.[b]
3	Br	Me_2AlCl	-78	-50	4.9:1.0	84
4	Br	Et_2AlCl	-78	-78	1.8:1.0	n.d.[c]
5	Br	$SnCl_4$	-78	-78	5.9:1.0	n.d.[c]
6	OTBS	Me_2AlCl	-78	-50	1.4:1.0	89
7	OTBS	Me_2AlCl	-78	-50	1.0:1.0	66
8	OMe	Me_2AlCl	-78	-50	1.2:1.0	55
9	OAc	Me_2AlCl	-78	-50	1.3:1.0	75

[a]d.r. was determined by ^{1}H NMR of the crude reaction mixture. For X=Br, the ratio refers to **56**:**57**; For other substrates, the ratio refers to the major diastereomer to the minor one, without specific designations. [b]yield was not determined due to incomplete conversion. [c]yield was not determined due to inseparable impurity.

2.3.4 Post Diels-Alder transformations: a formal synthesis of aplydactone

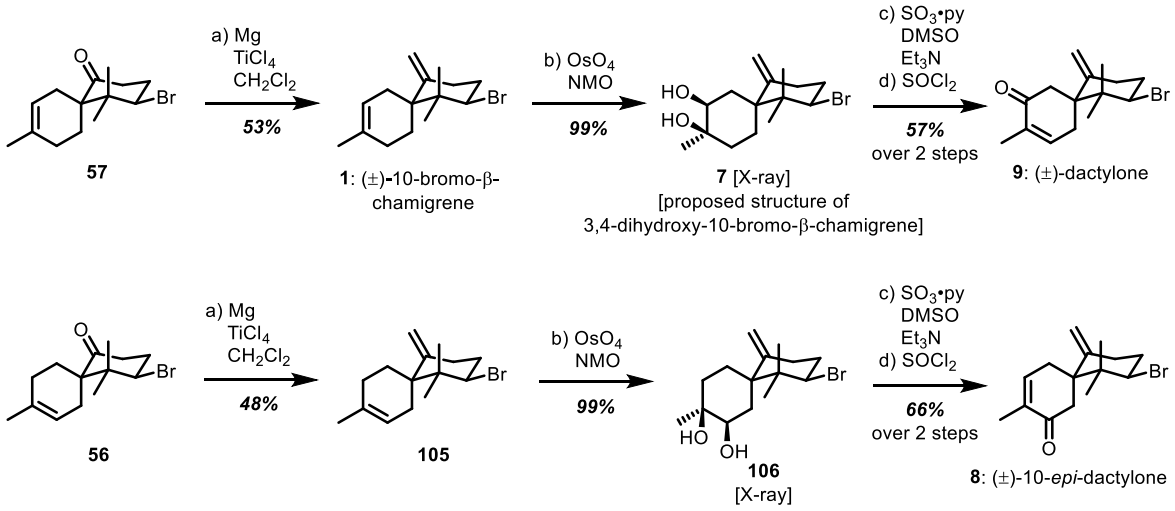
The task forehead from cycloadducts **56** and **57** towards dactylone was 1) methylenation of ketone 2) manipulation of the tertiary alkene into enone. A variety of methylenation conditions were then examined on the major product **56**. The most widely used protocol, Wittig methylenation, resulted in a side reaction. Whichever base were used to generate the methylene ylide, des-bromination product **104** was observed (Scheme 2-16). The rationale was proposed based on the deprotonation of the a-position of the ketone and subsequent intramolecular S_N2 substitution kicked off bromide to form a cyclopropane ring. Indeed, simply treating **56** with strong bases like KHMDS could give rise to the des-bromination compound **104**. Other common methylenation

methods, including Tebbe reagent,[52] Nysted reagent,[53] Petasis reagent,[54] and a Peterson olefination condition,[55] failed to drive any conversion presumably due to the steric hindrance imposed by the adjacent all-carbon quaternary centers.



Scheme 2-16. Wittig methylenation conditions led to des-bromination. *Reagents and conditions*: a) Ph_3PCH_3Br (1.2 equiv), KHMDS (1.0 M in THF, 1.1 equiv), THF, 0 °C, 30 min, then **56**, 0 °C, 1 h

It turned out that a methylenation protocol which worked well on a similar frame provided a breakthrough point. Employment of magnesium powder in the presence of titanium tetrachloride and methylene chloride (CH_2Cl_2) gave rise to an active Mg-CH_2-Ti species, which reacted with the hindered carbonyl of **56** smoothly to give the corresponding alkene product **105** (Scheme 2-17).[56] As the unique method, it turned the minor Diels-Alder product and the major one into (±)-10-bromo-β-chamigrene (**1**) and its isomer (**105**), in 48% and 53% isolated yield, respectively. At this stage, we attempted to directly oxidize the allylic position of the tri-substituted alkene on **105**'s left hand to enone by Salmond oxidation (CrO_3/3,5-dimethylpirazine)[57] and $Rh_2(cap)_4$/*t*-BuOOH.[58] What we encountered was an inseparable mixture of dactylone (**9**) and 10-*epi*-dactylone (**8**), indicating that the oxidation went without regioselectivity. Such a result emphasized the significance of a regioselective/regiospecific route toward dactylone (**9**).

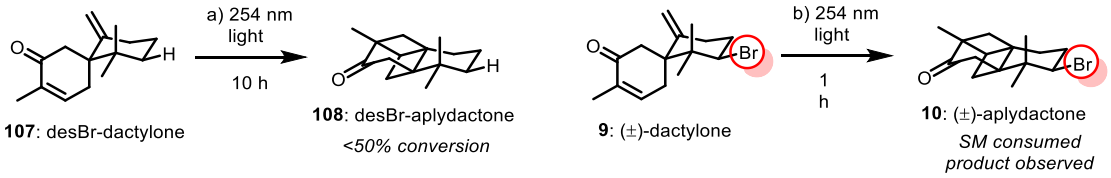


Scheme 2-17. Post-Diels-Alder transformations to various bromo-chamigrenes. *Reagent and conditions*: a) Mg (10.0 equiv), $TiCl_4$ (1.0 M in CH_2Cl_2, 5.0 equiv), 0 °C, 5 min, then **56** or **57**, THF/CH_2Cl_2, 0°C to 23 °C to 33°C, 10 h; b) NMO·H_2O (20.0 equiv), OsO_4 (2.5% in *t*-BuOH, 0.1 equiv), *t*-BuOH/acetone/H_2O, 23 °C, 3 h; c) SO_3·pyridine (3.0 equiv), CH_2Cl_2/DMSO/Et_3N, 0 °C, 1 h; d) $SOCl_2$ (2.0 equiv), pyridine, 0 °C, 20 min

On (±)-10-bromo-β-chamigrene (**1**), osmium tetraoxide (OsO_4) mediated dihydroxylation proceeded stereoselectively and regioselectively, as the configuration of the product **7** was confirmed through X-ray diffraction. Intriguingly, the ^{1}H NMR of the synthetic sample did not show agreement with that of the reported natural isolate **7**,[59] even though the X-ray pattern displayed a structure exactly same as what was drawn in the isolation report. We attribute it to the necessity for a structural revision of the natural isolate. The next task, to oxidize the secondary alcohol, was achieved by a Parikh-Doering condition where SO_3·pyridine/DMSO/Et_3N combination was utilized.[60] Other oxidation methods like Dess-Martin periodinane generally gave incomplete conversions. Eventually, thionyl chloride promoted the elimination of the tertiary alcohol efficiently, in only 20 min reaction time, affording a pure sample of the bromo-chamigrene natural product (±)-dactylone (**9**). In a similar vein, 10-*epi*-dactylone (**8**)[59] was reached from the major Diels-Alder adduct **56** in 4 steps.

Although dactylone had been obtained, we obtained merely 1 mg from the synthesis. We tested the final intramolecular [2+2] cycloaddition reaction on a model compound desbromo-

dactylone **107** where the bromide was removed from dactylone (**107** was made from β-chamigrene). Prolonged (10 h) irradiation of this material resulted in a partial conversion to the intramolecular [2+2] cycloaddition adduct (**108**) which was tentatively assigned by ^{1}H NMR. Guided by this information, we employed the same condition on the real system dactylone (**9**), only finding that the consumption rate of starting material was much more rapid and a messy mixture appeared after irradiation by 254 nm light (Scheme 2-18). We could observe the existence of aplydactone (**10**) in the mixture on ^{1}H NMR by recognizing its characteristic dd peak at δ = 2.90 ppm, but inseparable impuritied and scale (<1 mg) prevented a successful isolation of aplydactone. Apparently, the secondary bromide in dactylone (**9**) played a key role in lowering the energy barrier of the intramolecular [2+2] cycloaddition, levering the appearance of structurally twisted aplydactone in nature.

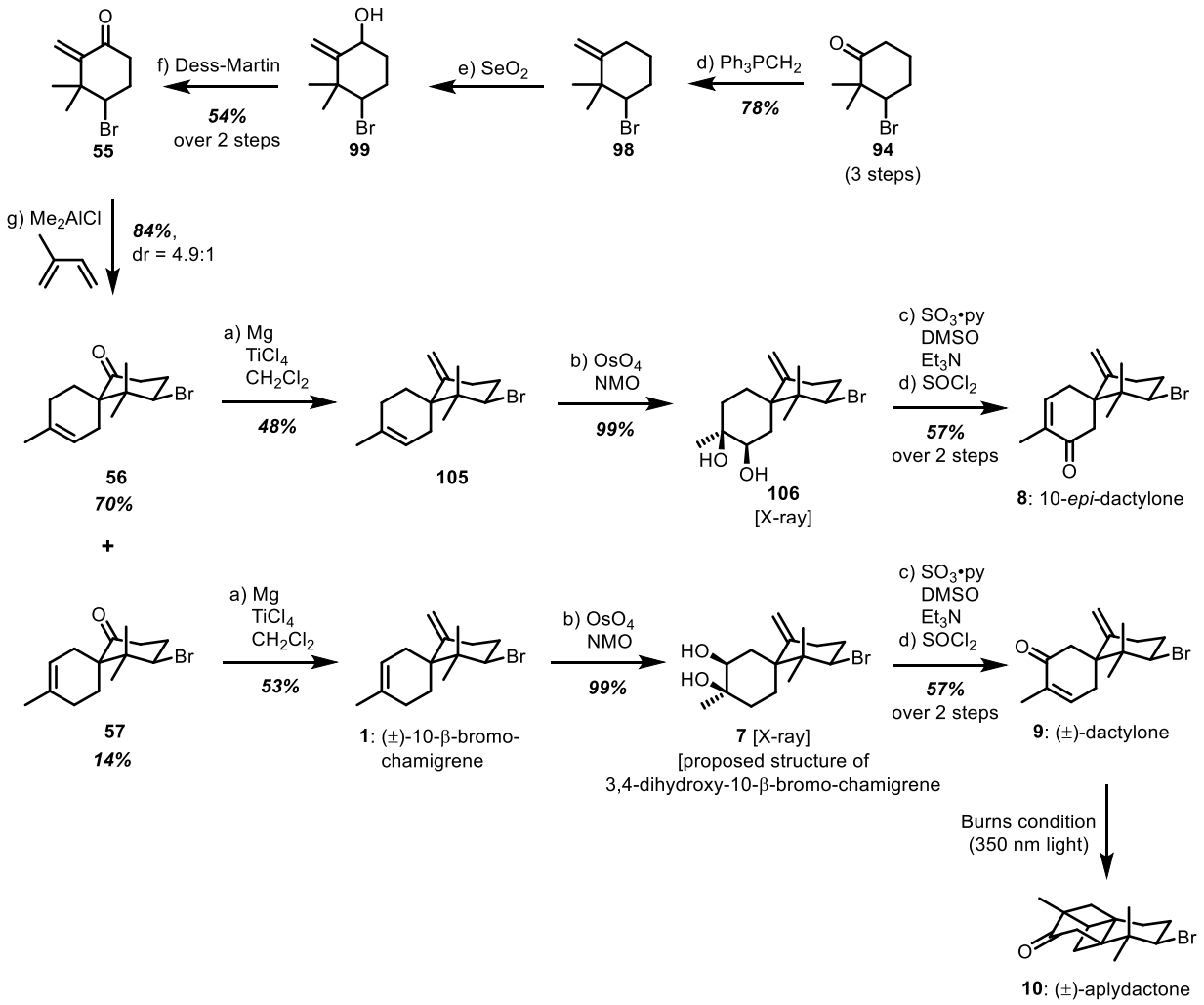


Scheme 2-18. A comparative study of photo [2+2] cycloaddtion reactions. *Reagents and condition*: a) 254 nm light (4 W), decane (0.005 M), 23 °C, 10 h; b) 254 nm light (4 W), decane (0.003 M), 23 °C, 1 h

At this chronological point, the racemic synthesis of aplydactone from the Trauner group[35] and the asymmetric synthesis of aplydactone from the Burns group[36] came out back-to-back. We were surprised to see that the Burns synthesis showed high resemblance to the reactions that we developed in our own second-generation synthesis. Hence, our synthesis constituted a formal synthesis of aplydactone (**10**) according to the optimal [2+2] cycloaddition condition (350 nm light) discovered by the Burns group.

2.4 Conclusions and outlook

Through the explorations of a synthetic route toward the highly congested bromo-chamigrene natural product aplydactone (**10**) we devised two generations of synthetic strategy. The first generation featured an elaborate biomimetic bromo-cyclization reaction in constructing the key bromo-spirocycle in the natural product, while subsequent functional group interconversions did not transform it into the desired natural product.



Scheme 2-19. Summary of the second generation route toward diverse bromo-chamigrenes and a formal synthesis of aplydactone

The second-generation route employed a Diels-Alder reaction as the key spirocycle formation step (Scheme 2-19). A pair of diastereomeric products was formed and they could be

transformed into two natural products, dactylone (**9**) and 10-*epi*-dactylone (**8**), respectively. The synthesis of dactylone thus constituted a formal synthesis of aplydactone (**10**) according to Burns' findings.

Though the Diels-Alder approach won the battle against BDSB-promoted cyclization strategy in the battlefield of bromo-chamigrenes, the vast and diverse brominated sesquiterpenoids provided great opportunities for BDSB-promoted biomimetic cyclization reactions to showcase their utility. Synthetic efforts towards these molecules are ongoing in our lab.

2.5 Experimental section

General Procedures. All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Dry tetrahydrofuran (THF), toluene, dimethylformamide (DMF), diethyl ether (Et_2O) and dichloromethane (CH_2Cl_2) were obtained by passing commercially available pre-dried, oxygen-free formulations through activated alumina columns. Yields refer to chromatographically and spectroscopically (^1H and ^{13}C NMR) homogeneous materials, unless otherwise stated. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Reactions were magnetically stirred and monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent, and an ethanolic solution of phosphomolybdic acid and cerium sulfate, and heat as developing agents. SiliCycle silica gel (60, academic grade, particle size 0.040–0.063 mm) was used for flash column chromatography. Preparative thin-layer chromatography separations were carried out on 0.50 mm E. Merck silica gel plates (60F-254). NMR spectra were recorded on Bruker 400, 500 and 700 MHz instruments and calibrated using residual undeuterated solvent as an internal reference. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet,

br = broad, app = apparent. IR spectra were recorded on a Perkin-Elmer 1000 series FT-IR spectrometer. High-resolution mass spectra (HRMS) were recorded on Agilent 6244 Tof-MS using ESI (Electrospray Ionization), APCI (atmospheric pressure chemical ionization), or Mixed (ionization by both ESI and APCI) at the University of Chicago Mass Spectroscopy Core Facility.

Abbreviations. EtOAc = ethyl acetate, DIBAL-H = diisobuylaluminum hydride, Rochelle's salt = sodium potassium tartrate, BDSB = bromodiethylsulfonium bromopentachloroantimonate, CsOAc = cesium acetate, KHMDS = potassium bis(trimethylsilyl)amide, $Pd(dppf)Cl_2$ = [1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium(II), *t*-BuOK = potassium *tert*-butoxide, *t*-BuOOH = *tert*-butylhydroperoxide, *t*-BuOH = *tert*-butanol, $NMO•H_2O$ = 4-methylmorpholine *N*-oxide monohydrate, SO_3•pyr = sulfur trioxide pyridine complex, DMSO = dimethyl sulfoxide.

Conjugated ester 76. To a solution of ethyl 2-(diethylphosphono)-6-methyl-5-heptaenoate **75** (3.98 g, 13.0 mmol, 1.2 equiv)[40] in THF (6 mL) at 23 °C was added NaH (60% dispersion in mineral oil, 0.497 g, 12.4 mmol, 1.15 equiv) portionwise over the course of 20 min. The resultant mixture was then stirred at 23 °C for 1 h, at which time solid 1,4-cyclohexanedione monoethylene acetal **72** (1.69 g, 10.8 mmol, 1.0 equiv) was added portionwise over the course of 5 min. The reaction contents were then allowed to stir at 23 °C for 10 h. Upon completion, the reaction was quenched by the addition of a half-saturated solution of aqueous NH_4Cl (50 mL), the contents were poured into a separatory funnel, and the layers were separated. The aqueous layer was then extracted with EtOAc (3 × 20 mL) and the combined organic layers were washed with brine (30 mL), dried ($MgSO_4$), filtered, and concentrated. The resultant residue was purified by flash column

chromatography (silica gel, hexanes/EtOAc, 25/1→15/1) to afford **76** (2.73 g, 82% yield) as a white solid. **76**: R_f = 0.51 (silica gel, hexanes/EtOAc, 7/3); IR (film) ν_{max} 2953, 2881, 1712, 1282, 1202, 1161, 1123, 1081, 1035, 945, 916 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.11 (t, *J* = 7.2 Hz, 1 H), 4.19 (q, *J* = 7.1 Hz, 2 H), 3.97 (s, 4 H), 2.54 (t, *J* = 6.4 Hz, 2 H), 2.38 (t, *J* = 6.5 Hz, 2 H), 2.32 (t, *J* = 7.8 Hz, 2 H), 2.06 (dd, *J* = 15.1, 7.4 Hz, 2 H), 1.77–1.70 (m, 4 H), 1.67 (s, 3 H), 1.59 (s, 3 H), 1.29 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.0, 144.4, 132.2, 126.4, 123.4, 114.2, 108.2, 64.3, 60.0, 35.6, 35.6, 29.8, 28.9, 27.9, 27.6, 25.6, 17.5, 14.2; HRMS (Mixed+) calcd for $C_{18}H_{29}O_4^+$ [M + H^+] 309.2060, found 309.2059.

α-silyl alcohol 78. To a solution of ester **76** (2.42 g, 7.85 mmol, 1.0 equiv) in CH_2Cl_2 (25 mL) at –78 °C was added DIBAL-H (1.0 M in hexanes, 23.5 mL, 23.5 mmol, 3.0 equiv) dropwise over the course of 10 min. Once the addition was complete, the reaction contents were stirred at –78 °C for 2 h. Upon completion, the reaction contents were quenched by the slow and careful addition of H_2O (25 mL) and then were warmed to 23 °C, at which time CH_2Cl_2 (25 mL) and saturated aqueous Rochelle's salt (70 mL) were added sequentially. The resultant biphasic mixture was stirred vigorously until clear phase separation was observed. The reaction contents were then poured into a separatory funnel and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic layers were then washed with brine (50 mL), dried ($MgSO_4$), filtered, and concentrated to give the desired crude alcohol as a colorless oil (R_f = 0.29, silica gel, hexanes/EtOAc, 7/3). Pressing forward without any additional purification, the so-formed crude alcohol (7.85 mmol assumed, 1.0 equiv) was dissolved in CH_2Cl_2 (25 mL) and MnO_2 (3.41 g, 39.3 mmol, 5.0 equiv) was added at 23 °C. After stirring the resultant slurry vigorously at 23 °C for 8 h, a second portion of MnO_2 (3.41 g, 39.3 mmol, 5.0 equiv) was added and the reaction

contents were stirred at 23 °C for a further 8 h. Upon completion, the reaction contents were filtered through Celite, with the filter cake washed thoroughly with CH_2Cl_2 (4 × 6 mL). The combined organic filtrate was then concentrated to afford the desired crude aldehyde **77** as a pale yellowish oil (R_f = 0.50, silica gel, hexanes/EtOAc, 7/3). Next, the so-obtained crude aldehyde **77** (7.85 mmol assumed, 1.0 equiv) was dissolved in THF (24 mL), cooled to –78 °C, and a solution of $PhMe_2SiLi$ (0.75 M in THF, 13.6 mL, 10.2 mmol, 1.3 equiv) was added dropwise over the course of 30 min.[61] Once the addition was complete, the reaction was stirred at –78 °C for a further 30 min. Upon completion, the reaction contents were quenched by the addition of a half-saturated aqueous solution of NH_4Cl (50 mL), warmed to 23 °C, and poured into a separatory funnel. The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were then washed with brine (40 mL), dried ($MgSO_4$), filtered, and concentrated. The resultant residue was purified by flash column chromatography (silica gel, hexanes/EtOAc, 15/1) to afford **78** (2.49 g, 6.22 mmol, 80% yield over 3 steps) as a white solid. **78**: R_f = 0.58 (silica gel, hexanes/EtOAc, 7/3); IR (film) ν_{max} 3475, 2960, 2880, 1428, 1247, 1115, 1087, 1034, 916, 834, 818, 782, 736, 701 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.55 (dd, *J* = 7.4, 1.8 Hz, 2 H), 7.40–7.31 (m, 3 H), 5.13 (s, 1 H), 4.63 (s, 1 H), 3.94 (d, *J* = 1.1 Hz, 4 H), 2.38–2.27 (m, 2 H), 2.27–2.18 (m, 1 H), 2.12–1.93 (m, 5 H), 1.68 (s, 3 H), 1.67–1.63 (m, 2 H), 1.57 (s, 3 H), 1.56–1.49 (m, 2 H), 1.42–1.35 (m, 1 H), 0.36 (s, 3 H), 0.30 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.2, 134.1, 132.4, 132.2, 131.1, 129.2, 127.8, 124.5, 108.8, 67.9, 64.2, 64.2, 35.9, 35.6, 29.8, 29.6, 27.6, 27.1, 25.7, 17.7, –4.2, –4.7; HRMS (Mixed+) calcd for $C_{24}H_{36}O_3SiNa^+$ [M + Na^+] 423.2326, found 423.2320.

Polyene 79. To a solution of alcohol **78** (1.39 g, 3.48 mmol, 1.0 equiv) in CH_2Cl_2 (12 mL) at 23 °C was added pyridine (1.65 g, 1.69 mL, 20.9 mmol, 6.0 equiv), and the resultant mixture

was then cooled to 0 °C. Next, benzoyl chloride (1.47 g, 1.21 mL, 10.4 mmol, 3.0 equiv) was added dropwise over the course of 1 min. The reaction contents were then warmed to 23 °C over the course of 30 min and stirred at 23 °C for an additional 8 h. Upon completion, the reaction was quenched with saturated aqueous $NaHCO_3$ (20 mL), poured into a separatory funnel, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic layers were washed sequentially with saturated aqueous $CuSO_4$ (30 mL) and brine (30 mL), dried ($MgSO_4$), filtered, and concentrated. The resultant residue was purified by flash column chromatography (silica gel, hexanes/EtOAc, 12/1) to give an inseparable mixture of the desired benzoate intermediate along with impurities as a pale yellowish oil (R_f = 0.62, silica gel, hexanes/EtOAc, 7/3). Pressing forward, the so-obtained mixture of the desired benzoate intermediate and the associated impurity were dissolved in acetone (60 mL) and 5% aqueous HCl (30 mL) was added dropwise over the course of 5 min at 23 °C. The resultant slightly cloudy solution was then stirred at 23 °C for 8 h. Upon completion, the reaction contents were quenched by the slow addition of saturated aqueous $NaHCO_3$ (40 mL), poured into a separatory funnel, and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 50 mL), and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The resultant residue was purified by flash column chromatography (silica gel, hexanes/EtOAc, 20/1→12/1) to afford polyene **79** (1.27 g, 80% yield over 2 steps) as a white solid. **79**: R_f = 0.60 (silica gel, hexanes/EtOAc, 7/3); IR (film) ν_{max} 2962, 1716, 1271, 1108, 834, 816, 711 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.04 (d, *J* = 7.2 Hz, 2 H), 7.61–7.50 (m, 3 H), 7.45 (t, *J* = 7.7 Hz, 2 H), 7.40–7.30 (m, 3 H), 6.02 (s, 1 H), 5.01 (t, *J* = 7.0 Hz, 1 H), 2.64–2.53 (m, 1 H), 2.49 (t, *J* = 6.7 Hz, 2 H), 2.39–2.30 (m, 1 H), 2.29–2.18 (m, 2 H), 2.13 (t, *J* = 8.3 Hz, 2 H), 2.08–1.83 (m, 4 H), 1.59 (s, 3 H), 1.36 (s, 3 H), 0.46 (s, 3 H), 0.44 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.1, 166.4, 135.7,

134.1, 132.8, 131.8, 131.1, 130.4, 129.7, 129.5, 129.5, 128.4, 127.8, 123.9, 70.6, 40.2, 39.8, 30.9, 28.6, 27.4, 27.4, 25.6, 17.4, –4.2; HRMS (ESI+) calcd for $C_{29}H_{36}O_3SiNa^+$ [M + Na^+] 483.2326, found 483.2321.

Dibromide 80. To a stirred solution of polyene **79** (0.317 g, 0.688 mmol, 1.0 equiv) in CH_3NO_2 (68 mL) at 23 °C was quickly added a solution of BDSB (0.748 g, 1.38 mmol, 2.0 equiv) in CH_3NO_2 (1 mL), and the resultant mixture was stirred for 15 min at 23 °C. Upon completion, the reaction contents were quenched by the sequential addition of 5% aqueous Na_2SO_3 (35 mL) and 5% aqueous $NaHCO_3$ (35 mL) and the resultant mixture was vigorously stirred for additional 30 min at 23 °C before being poured into a separatory funnel and separating the layers. The aqueous layer was then extracted with CH_2Cl_2 (3 × 15 mL) and the combined organic layers were dried ($MgSO_4$), filtered, concentrated. The resultant residue was purified by flash column chromatography (silica gel, hexanes/EtOAc, 10/1) to afford **80** (0.129 g, 39% yield, 6:1 mixture of inseparable diastereomers) as a light yellowish solid. Recrystallization of this material from benzene/$CHCl_3$ afforded crystals of suitable quality for X-ray diffraction, with the resultant crystal structure shown below in Figure S1. [Note: removal of all residual CH_3NO_2 prior to column chromatography is crucial for achieving the desired level of purification]. **80**: R_f = 0.55 (silica gel, hexanes/EtOAc, 7/3); m.p. > 150 °C (decompose); IR (film) ν_{max} 2976, 1730, 1451, 1266, 1134, 1118, 1066, 733, 710 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.13–8.07 (m, 2 H), 7.64 (t, *J* = 7.4 Hz, 1 H), 7.51 (t, *J* = 7.8 Hz, 2 H), 7.39 (s, 1 H), 4.96 (dd, *J* = 12.2, 6.7 Hz, 1 H), 4.52 (dd, *J* = 12.0, 4.5 Hz, 1 H), 3.10–3.00 (m, 1 H), 2.93–2.83 (m, 1 H), 2.57 (dt, *J* = 14.2, 3.3 Hz, 1 H), 2.53–2.45 (m, 1 H), 2.45–2.38 (m, 1 H), 2.38–2.30 (m, 2 H), 2.14–2.02 (m, 3 H), 1.18 (s, 3 H), 1.09 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.8, 163.7, 133.9, 133.0, 129.9, 128.7, 128.7, 123.2, 62.8, 52.2,

48.6, 44.2, 41.7, 36.2, 34.4, 28.8, 23.6, 23.4, 17.9; HRMS (APCI+) calcd for $C_{21}H_{25}Br_2O_3^+$ [M + H^+] 485.0144, found 485.0144.

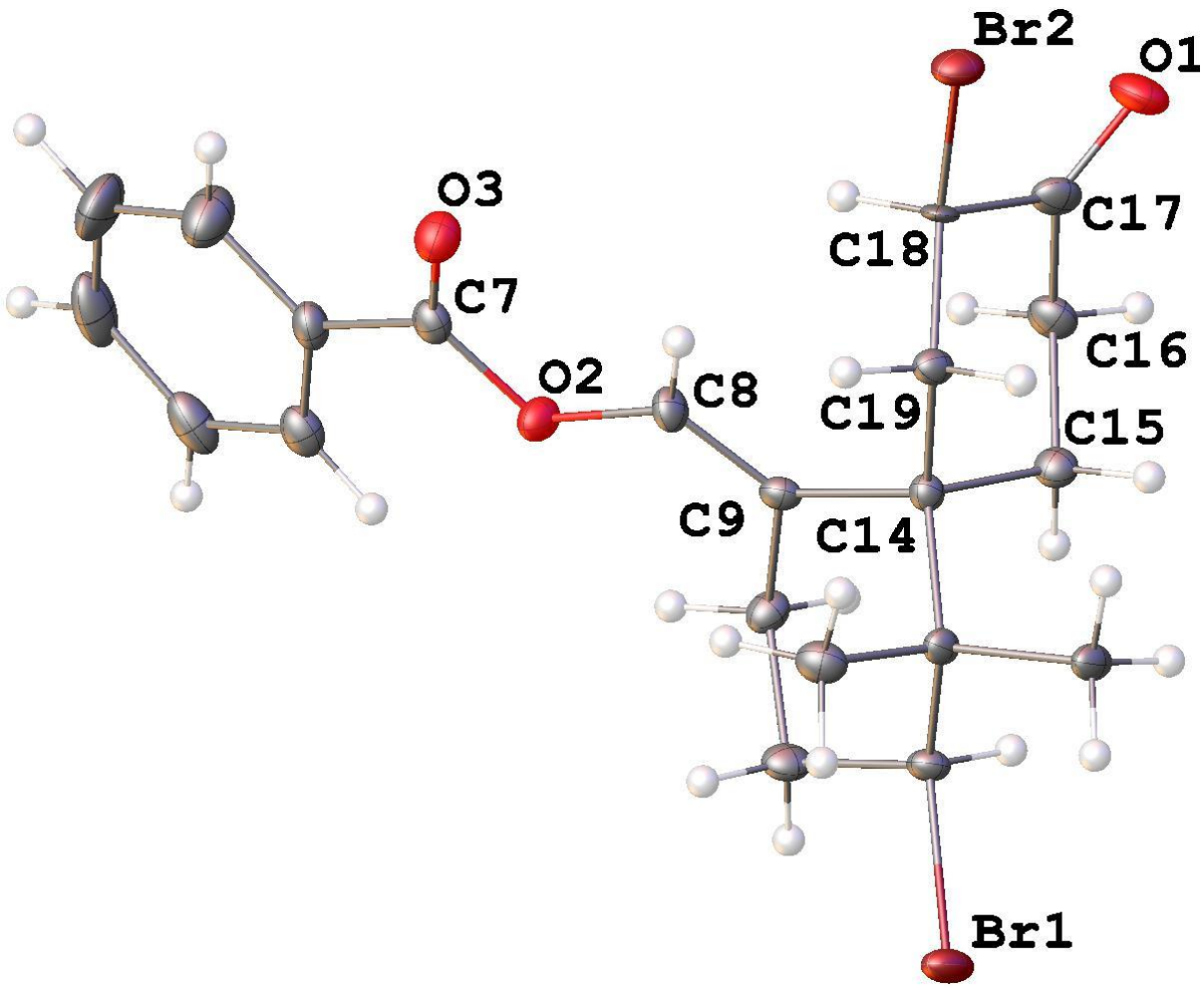


Figure 2-S1. ORTEP representation of Dibromide **80**.

α-acetoxy ketone 83. A flame-dried flask was charged with a solution of compound **80** (55.0 mg, 0.114 mmol, 1.0 equiv) in DMF (1.5 mL), and then activated 4 Å molecular sieves (200 mg) and CsOAc (0.11 g, 0.57 mmol, 5.0 equiv) were added sequentially at 23 °C. The reaction contents were then warmed to 40 °C and stirred at this temperature for 2 h. Upon completion, the

reaction contents were cooled, and H_2O (3 mL) and Et_2O (3 mL) were added. The 4 Å molecular sieves were then removed by filtration, washing with Et_2O (2 × 0.5 mL). The filtrate was then poured into a separatory funnel and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 3 mL) and the combined organic layers were washed with H_2O (2 mL) and brine (3 mL), dried ($MgSO_4$), filtered, and concentrated. The resultant residue was purified by flash column chromatography (silica gel, hexanes/EtOAc, 5/1) to afford **83** (16.6 mg, 32%) as a white solid. **83**: R_f = 0.38 (silica gel, hexanes/EtOAc, 7/3); IR (film) ν_{max} 2977, 1734 (br), 1451, 1375, 1267, 1178, 1119, 1070, 735, 710 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.10–8.01 (m, 2 H), 7.63–7.57 (m, 1 H), 7.51–7.44 (m, 2 H), 7.17 (d, *J* = 1.3 Hz, 1 H), 5.14 (dd, *J* = 12.8, 6.4 Hz, 1 H), 4.59 (dd, *J* = 12.5, 4.4 Hz, 1 H), 3.01–2.91 (m, 1 H), 2.83 (dd, *J* = 14.7, 3.5 Hz, 1 H), 2.63 (d, *J* = 14.7 Hz, 1 H), 2.35–2.25 (m, 2 H), 2.14 (s, 3 H), 2.12–2.06 (m, 1 H), 2.04 (d, *J* = 3.8 Hz, 1 H), 2.02–1.98 (m, 1 H), 1.96 (dd, *J* = 4.9, 1.7 Hz, 1 H), 1.77–1.65 (m, 1 H), 1.24 (s, 3 H), 1.03 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.8, 170.1, 163.3, 134.8, 133.5, 129.9, 129.1, 128.6, 124.4, 75.9, 62.8, 50.8, 44.9, 43.6, 34.0, 26.6, 26.2, 23.9, 23.4, 20.7, 17.8; HRMS (Mixed+) calcd for $C_{23}H_{28}BrO_5^+$ [M + H^+] 463.1115, found 463.1114.

Compound 85. A flame-dried flask was charged with a solution of compound **83** (59.0 mg, 0.127 mmol, 1.0 equiv) in THF (2 mL). After cooling the reaction contents to –78 °C, KHMDS (0.5 M in toluene, 0.29 mL, 0.145 mmol, 1.15 equiv) was added dropwise over the course of 2 min and the resultant mixture was stirred at –78 °C for 30 min. Next, solid $PhNTf_2$ (60.6 mg, 0.166 mmol, 1.3 equiv) was added in a single portion and the reaction contents were stirred at –78 °C for 3 h. Upon completion, the reaction was quenched by the addition of a half-saturated aqueous solution of NH_4Cl (3 mL), poured into a separatory funnel, and the layers were separated. The

aqueous layer was extracted with EtOAc (3 × 3 mL) and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The resultant residue was purified by flash column chromatography (silica gel, hexanes/EtOAc, 8/1) to give the desired vinyl triflate **84** (21.6 mg, 29% yield) as a white gel (R_f = 0.50, silica gel, hexanes/EtOAc, 7/3). Next, the vinyl triflate **84** (21.6 mg, 0.036 mmol, 1.0 equiv) was dissolved in toluene (0.8 mL), H_2O (0.1 mL) was added at 23 °C, and the mixture was degassed for 10 min by bubbling argon directly through the solution. $MeBF_3K$ (6.6 mg, 0.054 mmol, 1.5 equiv), $Pd(dppf)Cl_2$ (3.0 mg, 0.003 mmol, 0.1 equiv), and Cs_2CO_3 (35.5 mg, 0.108 mmol, 3.0 equiv) were then added sequentially at 23 °C. The reaction contents were then warmed to 80 °C and stirred at that temperature for 8 h. Upon completion, the reaction contents were cooled and then quenched by the addition of H_2O (3 mL), poured into a separatory funnel, and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 3 mL), and the combined organic layers were washed by brine (3 mL), dried ($MgSO_4$), filtered, and concentrated. The resultant residue was purified by preparative thin-layer chromatography (silica gel, hexanes/EtOAc, 7/3) to afford **85** (1.5 mg, 9% yield, 2% yield over 2 steps) as a colorless gel along with recovered starting vinyl triflate (11.0 mg, 50% recovery, 18% yield, 4% over 2 steps of **85** based on recovered starting material). **85**: R_f = 0.54 (silica gel, hexanes/EtOAc, 7/3); IR (film) ν_{max} 2923, 2852, 1737, 1730, 1265, 1244, 1119, 1022, 710 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.13–8.05 (m, 2 H), 7.64–7.57 (m, 1 H), 7.51–7.45 (m, 2 H), 7.10 (d, *J* = 1.8 Hz, 1 H), 5.51 (d, *J* = 1.4 Hz, 1 H), 5.28 (dd, *J* = 10.0, 5.6 Hz, 1 H), 4.56 (dd, *J* = 12.2, 4.3 Hz, 1 H), 3.04–2.92 (m, 1 H), 2.29–2.19 (m, 2 H), 2.16–2.09 (m, 2 H), 2.07 (s, 3H), 1.98–1.89 (m, 2 H), 1.86–1.79 (m, 1 H), 1.75 (s, 3 H), 1.12 (s, 3 H), 1.05 (s, 3 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 171.1, 163.6, 137.3, 134.1, 133.5, 129.8, 128.6, 127.6, 125.8, 72.0, 63.4, 49.0, 42.8, 33.0, 25.8, 25.2, 24.6, 23.1, 21.1, 19.5, 18.1; HRMS (ESI+) calcd for $C_{24}H_{29}BrNaO_4^+$ [M + Na^+] 483.1141, found 483.1143.

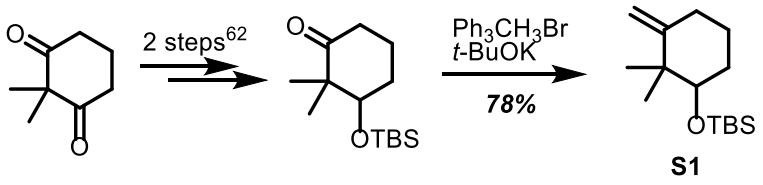
Bromo ketone 94. A small-scale preparation was conducted according to the method reported by Djerassi.[51] Gram-scale synthesis: To a flame-dried flask was added a solution of **95** (3.00 g, 21.4 mmol, 1.0 equiv) in THF (30 mL). The flask was cooled down to -78 °C and $LiAlH(O\textit{t}\text{-}Bu)_3$ (1.0 M in THF, 20.3 mL, 20.3 mmol, 0.95 equiv) was added dropwise over 5 min. After stirring at this temperature for another 30 min, water was added dropwise to quench the remaining reductant, followed by the addition of a saturated aqueous solution of Rochelle salt. The mixture was vigorously stirred at 23 °C for 3 h. The aqueous layer was extracted with EtOAc (3 × 10 mL) and the combined organic layers were washed with brine (10 mL), dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography (silica gel, hexanes/EtOAc, 5/1) to afford **96** (2.83 g, 93% yield) as a colorless oil. Next, to a solution of 96 (2.83 g, 19.9 mmol, 1.0 equiv) in pyridine (12 mL) was added TsCl (9.47 g, 49.8 mmol, 2.5 equiv) as solid at 0 °C. The reaction was then stirred at 23 °C for 72 h. Upon completion, CH_2Cl_2 (50 mL) was added and the organic phase was washed with 1 N HCl (40 mL) and saturated $NaHCO_3$ solution (30 mL) sequentially, dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography (silica gel, hexanes/EtOAc, 10/1) to afford **97** (5.35 g, 90%) as a white solid. Next, to a solution of **97** (5.35 g, 18.0 mmol, 1.0 equiv) in HPMA (36 mL) was added LiBr (12.5 g, 143.8 mmol, 8.0 equiv) as solid. The mixture was vigorously stirred at 65 °C for 4 h before was brought down to 23 °C. EtOAc (100 mL) was added and the organic phase was washed by water (2× 50 mL) and brine (50 mL) sequentially, dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography (silica gel, hexanes/EtOAc, 15/1) to afford **94** (2.28 g, 62%) as a colorless oil. **94**: R_f = 0.46 (silica gel, hexanes/EtOAc, 4/1); IR (film) ν_{max} 2948, 2871, 1712, 1466, 1450, 1385, 1366, 1312, 1260, 1222, 1141, 1104, 990, 936, 916, 841, 805, 728, 563 cm^{-1}; ^1H NMR (500 MHz,

$CDCl_3$) δ 4.15 (dd, *J* = 9.9, 3.7 Hz, 1 H), 2.57–2.46 (m, 1 H), 2.40–2.30 (m, 2 H), 2.29–2.18 (m, 1 H), 2.15–2.03 (m, 1 H), 1.73–1.59 (m, 1 H), 1.22 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.5, 62.9, 51.6, 36.9, 32.2, 24.0, 23.9, 22.5; HRMS (Mixed+) calcd for $C_8H_{13}BrO^+$ [M^+] 205.0223, found 205.0206.

Bromo alkene 98. To a flame-dried flask was added Ph_3PCH_3Br (2.44 g, 6.84 mmol, 2.0 equiv) and benzene (6 mL). Next, solid *t*-BuOK (0.575 g, 5.13 mmol, 1.5 equiv) was added at 23 °C and the resultant mixture was then warmed to 80 °C and stirred at that temperature for 1 h. A solution of ketone **94** (0.702 g, 3.42 mmol, 1.0 equiv) in benzene (2 mL) was then added dropwise over the course of 1 min and the resultant reaction contents were stirred at 80 °C for an additional 10 min. Upon completion, the reaction contents were cooled, diluted with hexanes (20 mL), and filtered. The resultant filtrate was concentrated directly and the resultant residue was purified by flash column chromatography (silica gel, hexanes) to afford alkene **98** (0.540 g, 78% yield) as a colorless oil. [Note: this compound is volatile under long-term exposure to high vacuum]. **98**: R_f = 0.80 (silica gel, hexanes/EtOAc, 4/1); IR (film) ν_{max} 2969, 2942, 2859, 1448, 1380, 1222, 1138, 901, 728, 607 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.79 (s, 1 H), 4.78 (s, 1 H), 4.04 (dd, *J* = 10.3, 4.1 Hz, 1 H), 2.33–2.25 (m, 1 H), 2.25–2.18 (m, 2 H), 2.17–2.08 (m, 1 H), 1.88–1.79 (m, 1 H), 1.48–1.37 (m, 1 H), 1.26 (s, 3 H), 1.19 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.0, 108.7, 66.8, 42.4, 34.0, 32.0, 27.4, 27.1, 23.2; HRMS was attempted but no satisfactory ionization was observed.

Bromo enone 55. To a solution of compound **94** (0.390 g, 1.92 mmol, 1.0 equiv) in $CHCl_3$ (12 mL) at 23 °C was added solid SeO_2 (0.213 g, 1.92 mmol, 1.0 equiv) followed by *t*-BuOOH

(1.04 mL, 5.5 M in nonane, 5.76 mmol, 3.0 equiv). The resultant mixture was then warmed to 55 °C and stirred for 11 h. Upon completion, the reaction was concentrated directly under reduced pressure and the resultant residue was purified by flash column chromatography (silica gel, hexanes/EtOAc, 5/1) to give the desired allylic alcohol **99** (0.295 g, 70% yield) as a light yellowish oil (R_f = 0.24, silica gel, hexanes/EtOAc, 4/1). Next, the newly prepared allylic alcohol **99** (0.295 g, 1.35 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (8 mL) and then $NaHCO_3$ (0.339 g, 4.04 mmol, 3.0 equiv) and Dess–Martin periodinane (0.837 g, 2.02 mmol, 1.5 equiv) were added sequentially at 23 °C. The resultant mixture was stirred at 23 °C for 2 h. Upon completion, the reaction contents were quenched with 10% aqueous $Na_2S_2O_3$ (15 mL), poured into a separatory funnel, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic layers were washed with brine (10 mL), dried ($MgSO_4$), filtered, and concentrated. The resultant residue was purified by flash column chromatography (silica gel, hexanes/EtOAc, 20/1) to afford **55** (0.223 g, 76% yield, 54% yield over 2 steps) as a colorless oil. [Note: this compound could homo-dimerize upon long-term exposure to high vacuum].[35] **55**: IR (film) ν_{max} 2956, 2930, 2886, 2857, 1699, 1472, 1464, 1257, 1092, 836, 775 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.84 (s, 1 H), 5.28 (s, 1 H), 4.31 (dd, *J* = 5.6, 2.9 Hz, 1 H), 2.86–2.75 (m, 1 H), 2.60–2.45 (m, 2 H), 2.39–2.29 (m, 1 H), 1.29 (s, 3 H), 1.26 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.9, 151.8, 119.0, 61.7, 43.2, 37.2, 29.6, 27.8, 26.2; HRMS (Mixed+) calcd for $C_9H_{14}BrO^+$ [M + H^+] 217.0223, found 217.0219.

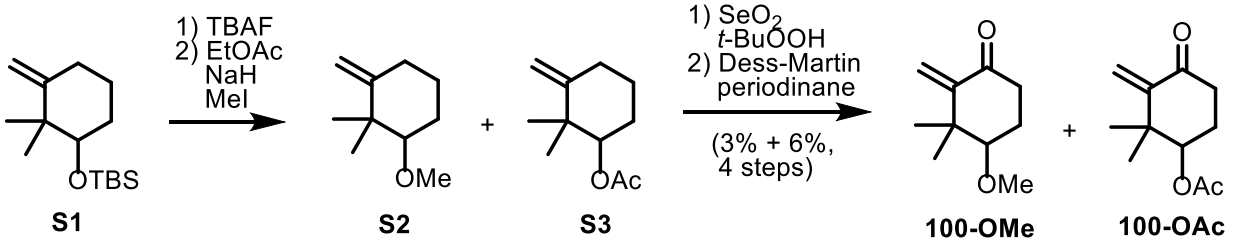


S1

Compound S1. To a flame-dried flask was added Ph_3PCH_3Br (3.43 g, 9.62 mmol, 2.0 equiv) and benzene (24 mL). Next, solid *t*-BuOK (0.808 g, 7.21 mmol, 1.5 equiv) was added at 23 °C and the resultant mixture was then warmed to 80 °C and stirred at that temperature for 1 h. A solution of 3-*tert*-butyldimethylsilyloxy-2,2-dimethylcyclohexaneone[62] (1.23 g, 4.81 mmol, 1.0 equiv) in benzene (2 mL) was then added dropwise over the course of 1 min and the resultant reaction contents were stirred at 80 °C for an additional 10 min. Upon completion, the reaction contents were cooled, diluted with hexanes (40 mL), and filtered. The resultant filtrate was directly concentrated and the crude residue was purified by flash column chromatography (silica gel, hexanes) to afford **S1** (1.02 g, 88% yield) as a colorless oil. **S1**: R_f = 0.84 (silica gel, hexanes/EtOAc, 4/1); IR (film) ν_{max} 2937, 2858, 1472, 1256, 1086, 866, 836, 801, 773 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.69 (s, 2 H), 3.27 (dd, *J* = 9.6, 4.0 Hz, 1 H), 2.25–2.15 (m, 1 H), 2.10 (dt, *J* = 9.0, 4.1 Hz, 1 H), 1.77–1.65 (m, 2H), 1.61–1.51 (m, 1 H), 1.33–1.21 (m, 1 H), 1.08 (s, 3 H), 1.00 (d, *J* = 11.4 Hz, 3 H), 0.89 (s, 9 H), 0.02 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.5, 107.1, 78.0, 42.6, 32.3, 31.1, 25.9, 25.2, 24.3, 20.8, -4.1, -4.9; HRMS (Mixed+) calcd for $C_{15}H_{31}OSi^+$ [M + H^+] 255.2139, found 255.2139.

Enone 100-OTBS. To a solution of compound **S1** (0.112 g, 0.440 mmol, 1.0 equiv) in $CHCl_3$ (6 mL) at 23 °C was added solid SeO_2 (48.8 mg, 0.440 mmol, 1.0 equiv) followed by *t*-BuOOH (0.24 mL, 5.5 M in nonane, 1.32 mmol, 3.0 equiv). The resultant mixture was then stirred at 23 °C for 11 h. Upon completion, the reaction was concentrated directly under reduced pressure and the resultant residue was purified by flash column chromatography (silica gel, hexanes/EtOAc, 10/1) to give the desired allylic alcohol (97.0 mg, 82% yield) as a colorless oil (R_f = 0.24, silica gel, hexanes/EtOAc, 4/1). Next, the newly prepared allylic alcohol (97.0 mg, 0.359 mmol, 1.0

equiv) was dissolved in CH_2Cl_2 (4 mL) and then $NaHCO_3$ (90.4 mg, 1.08 mmol, 3.0 equiv) and Dess–Martin periodinane (0.228 g, 0.538 mmol, 1.5 equiv) were added sequentially at 23 °C. The resultant mixture was stirred at 23 °C for 2 h. Upon completion, the reaction contents were quenched with 10% aqueous $Na_2S_2O_3$ (6 mL), poured into a separatory funnel, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 3 mL) and the combined organic layers were washed with brine (5 mL), dried ($MgSO_4$), filtered, and concentrated. The resultant residue was purified by flash column chromatography (silica gel, hexanes/EtOAc, 25/1) to afford **100-OTBS** (62.5 mg, 65% yield, 53% yield over 2 steps) as a colorless oil. **100-OTBS**: R_f = 0.57 (silica gel, hexanes/EtOAc, 4/1); IR (film) ν_{max} 2970, 1696, 1615, 1407, 1228, 1209, 1179, 1110, 946, 879 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.74 (s, 1 H), 5.17 (s, 1 H), 3.65 (dd, *J* = 6.3, 2.7 Hz, 1 H), 2.64 (ddd, *J* = 16.4, 9.1, 7.0 Hz, 1 H), 2.35 (dt, *J* = 16.9, 6.1 Hz, 1 H), 2.13–2.02 (m, 1 H), 1.88 (td, *J* = 13.0, 6.3 Hz, 1 H), 1.10 (s, 3 H), 1.05 (s, 3 H), 0.87 (s, 9 H), 0.06 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.9, 153.7, 118.0, 75.1, 43.1, 35.7, 27.5, 26.8, 25.7, 23.6, –4.3, –5.0; HRMS (Mixed+) calcd for $C_{15}H_{29}O_2Si^+$ [M + H^+] 269.1931, found 269.1928.



Enone 100-OMe & **enone 100-OAc**. Compound **S1** (0.346 g, 1.36 mmol, 1.0 equiv) was dissolved in THF (6 mL) and then TBAF (1.0 M in THF, 2.72 mL, 2.72 mmol, 2.0 equiv) was added at 23 °C. The resultant solution was then warmed to 45 °C and stirred at this temperature for 12 h. Upon completion, the reaction contents were cooled, quenched by the addition of a half-

saturated aqueous solution of NH_4Cl (10 mL) and poured into a separatory funnel. After separating the layers, the aqueous layer was extracted with EtOAc (3 × 10 mL), and the combined organic layers were washed by brine (15 mL), dried, filtered, and concentrated to give a mixture of the desired crude alcohol (R_f = 0.29, silica gel, hexanes/EtOAc, 4/1) along with some residual EtOAc. Next, the so-obtained mixture of the crude alcohol (1.36 mmol assumed, 1.0 equiv) and residual EtOAc was dissolved in THF (2 mL) and MeI (0.25 mL, 3.92 mmol, 3.0 equiv) and NaH (60% dispersion in mineral oil, 82.0 mg, 2.04 mmol, 1.5 equiv) were added sequentially at 23 °C. The resultant mixture was then warmed to 45 °C and stirred at that temperature for 2 h. Upon completion, the reaction contents were quenched by the addition of a half-saturated aqueous solution of NH_4Cl (10 mL), the contents were poured into a separatory funnel, and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 10 mL), and the combined organic layers were washed with brine (15 mL), dried, filtered, concentrated. The resultant residue was purified by flash column chromatography (silica gel, hexanes/EtOAc, 6/1) to give an inseparable mixture of methyl ether **S2** and acetate **S3** (104 mg, R_f = 0.34, silica gel, hexane/EtOAc, 4/1). Carrying a portion of this mixture forward (60 mg, 0.389 mmol assumed, 1.0 equiv), it was dissolved in $CHCl_3$ (5 mL) and then solid SeO_2 (43 mg, 0.389 mmol, 1.0 equiv) and *t*-BuOOH (5.5 M in nonane, 0.21 mL, 1.17 mmol, 3.0 equiv) were added sequentially at 23 °C. The resultant mixture was stirred at 23 °C for 12 h before the solvent was concentrated directly. The resultant residue was then purified by flash column chromatography (silica gel, hexanes/EtOAc, 3/1) to give an inseparable mixture of the desired allylic alcohols (24.0 mg). Finally, the inseparable mixture of allylic alcohols (24.0 mg, 0.140 mmol assumed, 1.0 equiv) were dissolved in CH_2Cl_2 (3 mL) and solid $NaHCO_3$ (36.0 mg, 0.420 mmol, 3.0 equiv) and Dess–Martin periodinane (89.0 mg, 0.210 mmol, 1.5 equiv) were sequentially added at 23 °C. The resultant reaction mixture was

stirred at 23 °C for 2 h. Upon completion, the reaction contents were quenched by the addition of aqueous $Na_2S_2O_3$ (10%, 3 mL), poured into a separatory funnel, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 2 mL), and the combined organic layers were washed by brine (5 mL), dried ($MgSO_4$), filtered, and concentrated. The resultant residue was purified by preparative thin-layer chromatography (silica gel, hexanes/EtOAc, 3/2) to afford **100-OMe** (3.5 mg, 3% yield over 4 steps) as a colorless oil and **100-OAc** (7.0 mg, 6% yield over 4 steps) as a colorless oil. **100-OMe**: R_f = 0.38 (silica gel, hexanes/EtOAc, 4/1); IR (film) ν_{max} 2970, 1696, 1616, 1457, 1237, 1098, 937 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.79 (s, 1 H), 5.23 (s, 1 H), 3.40 (s, 3 H), 3.16 (t, *J* = 4.1 Hz, 1 H), 2.64–2.54 (m, 1 H), 2.38 (dt, *J* = 16.9, 5.6 Hz, 1 H), 2.12–2.05 (m, 3 H), 1.19 (s, 3 H), 1.10 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.5, 153.3, 118.2, 83.8, 57.3, 42.4, 35.5, 27.3, 23.5, 21.9; HRMS (ESI+) calcd for $C_{10}H_{17}O_2^+$ [M + H^+] 169.1223, found 169.1219. **100-OAc**: R_f = 0.35 (silica gel, hexanes/EtOAc, 4/1); IR (film) ν_{max} 2970, 1739, 1697, 1374, 1239, 1038, 974, 937, 857 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.84 (s, 1 H), 5.27 (s, 1 H), 4.94 (dd, *J* = 6.2, 3.1 Hz, 1 H), 2.58 (ddd, *J* = 16.5, 9.2, 7.1 Hz, 1 H), 2.47 (dt, *J* = 17.2, 6.1 Hz, 1 H), 2.22–2.14 (m, 1 H), 2.08 (s, 3H), 2.07–2.01 (m, 1 H), 1.15 (s, 3 H), 1.13 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.3, 170.4, 152.4, 118.9, 76.0, 41.3, 35.7, 26.8, 24.1, 23.4, 21.0; HRMS (APCI+) calcd for $C_{11}H_{17}O_3^+$ [M + H^+] 197.1172, found 197.1173.

General method for the Diels–Alder Cycloaddition. **Method A**: To a flame-dried flask was charged with a 0.1 M solution of enone **55**, **100-OTBS**, **100-OMe**, or **100-OAc** (1.0 equiv) in CH_2Cl_2 (0.5 M). After the solution was cooled to –78 °C, isoprene (4.0 equiv) was added, followed by the dropwise addition of the Lewis acid promoter (1.2 equiv) over the course of 10 min. The resultant reaction mixture was stirred at –78 °C for 4 h, at which time it was allowed to warm to –

50 °C slowly over the course of 30 min. The reaction contents were then either kept at –50 °C for 1 h. Upon completion, the reaction contents were quenched by the slow addition of aqueous HCl (2 M, equal in volume to that of the original reaction solvent), poured into a separatory funnel, and the layers were separated. The aqueous layer was then extracted with CH_2Cl_2 (3 × 1/3 of volume of reaction). The combined organic layers were washed with brine (equal to volume of reaction), dried ($MgSO_4$), filtered, and concentrated. The resultant residue was purified by flash column chromatography (silica gel) to afford the desired spirocycle products.

Method B: To a flame-dried flask was charged with a 0.1 M solution of enone **55**, **100-OTBS** (1.0 equiv) in CH_2Cl_2 (0.5 M). After the solution was cooled to –30 °C, isoprene (4.0 equiv) was added, followed by the dropwise addition of the Lewis acid promoter (1.2 equiv) over the course of 10 min. The resultant reaction mixture was stirred at –30 °C for 1 h, at which time it was allowed to warm to 0 °C slowly over the course of 15 min. The reaction contents were then either kept at 0 °C for 10 min. Upon completion, the reaction contents were quenched by the slow addition of aqueous HCl (2 M, equal in volume to that of the original reaction solvent), poured into a separatory funnel, and the layers were separated. The aqueous layer was then extracted with CH_2Cl_2 (3 × 1/3 of volume of reaction). The combined organic layers were washed with brine (equal to volume of reaction), dried ($MgSO_4$), filtered, and concentrated. The resultant residue was purified by flash column chromatography (silica gel) to afford the desired spirocycle products.

Spirocyclic ketone 101-OMe & 102-OMe. Enone **100-OMe** (3.2 mg, 0.019 mmol) afforded minor diastereomer **101-OMe or 102-OMe** (minor) (1.3 mg, 29%) as a colorless oil and major diastereomer **101-OMe or 102-OMe** (major) (1.6 mg, 36%) as a colorless oil. **Minor diastereomer**: R_f = 0.50 (silica gel, hexanes/EtOAc, 4/1); IR (film) ν_{max} 2967, 2831, 1710, 1451,

1367, 1231, 1100, 962 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.33 (s, 1 H), 3.38 (s, 3 H), 3.05 (t, *J* = 3.7 Hz, 1 H), 2.82 (td, *J* = 12.4, 6.1 Hz, 1 H), 2.63–2.55 (m, 1 H), 2.24 (d, *J* = 17.2 Hz, 1 H), 2.17 (dt, *J* = 12.6, 4.9 Hz, 1 H), 2.10–2.03 (m, 1 H), 2.01–1.93 (m, 1 H), 1.89 (d, *J* = 17.0 Hz, 1 H), 1.82 (dd, *J* = 17.4, 5.1 Hz, 1 H), 1.71 (t, *J* = 14.5 Hz, 1 H), 1.56 (s, 3 H), 1.03 (s, 3 H), 0.80 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.9, 132.8, 119.5, 85.5, 57.9, 54.8, 45.5, 33.1, 28.1, 27.6, 27.2, 25.8, 23.8, 23.2, 19.4; HRMS (Mixed+) calcd for $C_{15}H_{25}O_2^+$ [M + H^+] 237.1849, found 237.1851. **Major diastereomer** (major): R_f = 0.45 (silica gel, hexanes/EtOAc, 4/1); IR (film) ν_{max} 2967, 1710, 1456, 1436, 1367, 1231, 1100 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.42–5.36 (m, 1 H), 3.56 (dd, *J* = 11.5, 4.6 Hz, 1 H), 3.40 (s, 3 H), 2.69 (td, *J* = 13.9, 6.7 Hz, 1 H), 2.34–2.21 (m, 3H), 2.16–2.09 (m, 1 H), 1.89–1.80 (m, 2 H), 1.75 (td, *J* = 13.1, 4.8 Hz, 1 H), 1.68–1.60 (m, 2 H), 1.58 (s, 3 H), 1.03 (s, 3 H), 0.72 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.2, 131.3, 120.6, 81.5, 58.0, 54.4, 44.6, 34.8, 27.4, 27.2, 26.5, 26.3, 23.2, 21.0, 16.4; HRMS (Mixed+) calcd for $C_{15}H_{25}O_2^+$ [M + H^+] 237.1849, found 237.1850.

Spirocyclic ketone 101-OAc & 102-OAc. Enone **100-OAc** (7.0 mg, 0.036 mmol) afforded an inseparable mixture of diastereomers of **101-OAc** & **102-OAc** (6.6 mg, dr = 1.2/1, 75% yield combined) as a colorless oil. **101-OAc** & **102-OAc**: R_f = 0.41 (silica gel, hexanes/EtOAc, 4/1); IR (film) ν_{max} 2969, 1735, 1711, 1436, 1373, 1243, 1032, 973 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.43–5.36 (m, 2 H), 5.33 (d, *J* = 1.7 Hz, 1 H), 5.01–4.95 (m, 1 H), 2.81 (td, *J* = 14.0, 6.8 Hz, 1 H), 2.69 (ddd, *J* = 13.0, 10.5, 6.2 Hz, 1 H), 2.44 (dd, *J* = 12.9, 2.5 Hz, 1 H), 2.40–2.30 (m, 3 H), 2.30–2.20 (m, 2 H), 2.13 (s, 3 H), 2.17–2.10 (m, 1 H), 2.08 (s, 3 H), 2.03–1.91 (m, 3 H), 1.91–1.81 (m, 4 H), 1.76 (td, *J* = 13.2, 4.8 Hz, 2 H), 1.66–1.60 (m, 2 H), 0.95 (s, 6 H), 0.86 (s, 3 H), 0.81 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.4, 212.0, 170.7, 170.4, 133.1, 131.5, 120.2, 118.8,

76.3, 73.9, 54.6, 54.4, 44.3, 43.2, 34.7, 33.5, 28.1, 28.0, 27.8, 27.3, 27.2, 27.0, 26.3, 26.2, 23.1, 22.8, 21.3, 21.2, 20.8, 18.8, 16.8; HRMS (Mixed+) calcd for $C_{16}H_{25}O_3^+$ [M + H^+] 265.1798, found 265.1799.

Spirocyclic ketone 101-OTBS & 102-OTBS. Enone **100-OTBS** (0.198 g, 0.738 mmol) afforded an inseparable mixture of diastereomers of **101-OTBS** & **102-OTBS** (0.221 g, dr = 1.4/1, 89% yield combined) as a colorless oil. **101-OTBS & 102-OTBS**: R_f = 0.61 (silica gel, hexanes/EtOAc, 4/1); IR (film) ν_{max} 2956, 2930, 1710, 1472, 1257, 1089, 881, 836, 775 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.41 (s, 1 H), 5.36 (s, 1 H), 4.15 (dd, *J* = 11.2, 4.8 Hz, 1 H), 3.63 (t, *J* = 3.7 Hz, 1 H), 2.95 (td, *J* = 12.4, 5.9 Hz, 1 H), 2.82–2.70 (m, 2 H), 2.37–2.13 (m, 7 H), 2.13–2.04 (m, 2 H), 2.03–1.95 (m, 1 H), 1.94–1.83 (m, 7 H), 1.81–1.71 (m, 4 H), 1.70–1.62 (m, 3 H), 1.60 (s, 7 H), 1.01 (s, 4 H), 0.99 (s, 3 H), 0.96 (s, 13 H), 0.92 (s, 9 H), 0.79 (s, 4 H), 0.74 (s, 3 H), 0.13–0.09 (m, 15 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 215.0, 213.2, 132.6, 131.3, 120.6, 119.5, 76.4, 72.5, 54.8, 54.4, 45.7, 44.9, 35.0, 33.0, 31.4, 31.4, 28.1, 27.6, 27.4, 27.1, 26.7, 25.8, 25.8, 23.6, 23.2, 21.7, 20.0, 18.0, 16.0, –4.0, –4.4; HRMS (Mixed+) calcd for $C_{20}H_{37}O_2Si^+$ [M + H^+] 337.2557, found 337.2553.

Siprocyclic bromo ketones 56 & **57**. Enone **55** (0.223 g, 1.03 mmol) afforded **56** (0.206 g, 70% yield) as a white solid and **57** (42.0 mg, 14% yield) as a white solid. Recrystallization of these two materials respectively from hexanes/CH_2Cl_2 afforded crystals of suitable quality for X-ray diffraction, with the resultant crystal structure shown below in Figure S2. **56**: R_f = 0.58 (silica gel, hexanes/EtOAc, 4/1); m.p. = 90–92 ºC; IR (film) ν_{max} 2973, 1708, 1445, 1394, 1374, 1154, 963, 860, 780 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.28 (t, *J* = 10.3 Hz, 1 H), 4.66 (dd, *J* = 11.2,

4.7 Hz, 1 H), 2.81–2.70 (m, 1 H), 2.54–2.39 (m, 2 H), 2.36–2.20 (m, 3 H), 2.29–2.27 (m, 3 H), 2.24–2.18 (m, 1 H), 1.89 (dd, *J* = 16.6, 6.0 Hz, 1 H), 1.56 (s, 3 H), 1.54–1.48 (m, 1 H), 1.10 (s, 3 H), 0.98 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.0, 135.7, 116.6, 61.1, 55.2, 45.6, 37.4, 34.0, 29.2, 28.5, 24.7, 24.2, 23.0, 18.5; HRMS (Mixed+) calcd for $C_{14}H_{21}BrO^+$ [M + H^+] 285.0849, found 285.0844.

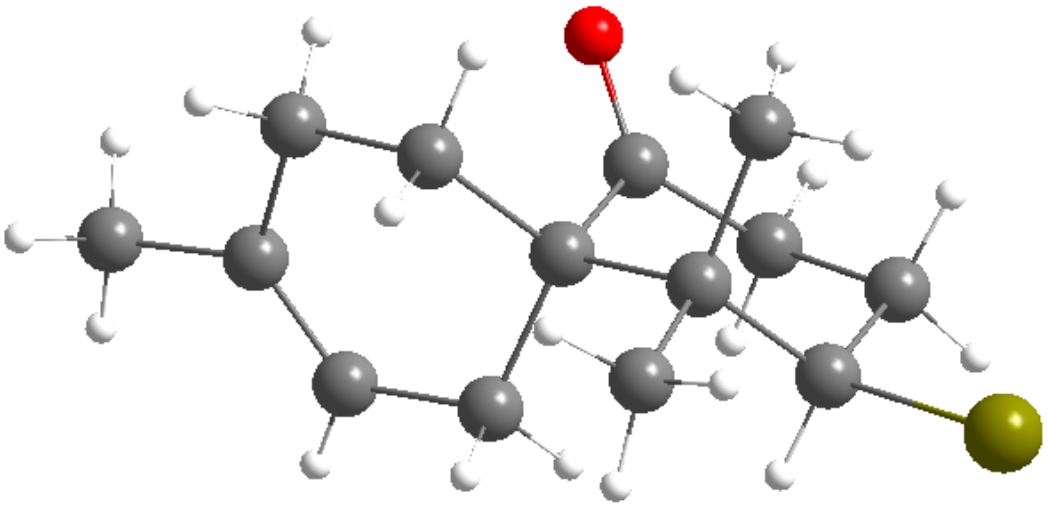


Figure 2-S2. ORTEP representation of **56**

57: R_f = 0.54 (silica gel, hexanes/EtOAc, 4/1); m.p. = 102–103 °C; IR (film) ν_{max} 2949, 1704, 1653, 1559, 1456, 668 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.37 (s, 1 H), 4.80 (dd, *J* = 12.6, 4.7 Hz, 1 H), 2.85–2.75 (m, 1 H), 2.49 (ddd, *J* = 11.4, 7.3, 3.4 Hz, 1 H), 2.37 (d, *J* = 15.9 Hz, 1 H), 2.31–2.22 (m, 2 H), 2.19–2.13 (m, 1 H), 1.90 (dd, *J* = 29.4, 11.8 Hz, 2 H), 1.85–1.77 (m, 1 H), 1.66–1.60 (m, 1 H), 1.59 (s, 3 H), 1.16 (s, 3 H), 0.90 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.7, 131.2, 120.5, 61.1, 56.0, 45.0, 37.7, 33.9, 27.4, 27.2, 27.0, 24.3, 23.1, 17.6; HRMS (Mixed+) calcd for $C_{14}H_{21}BrO^+$ [M + H^+] 285.0849, found 285.0825.

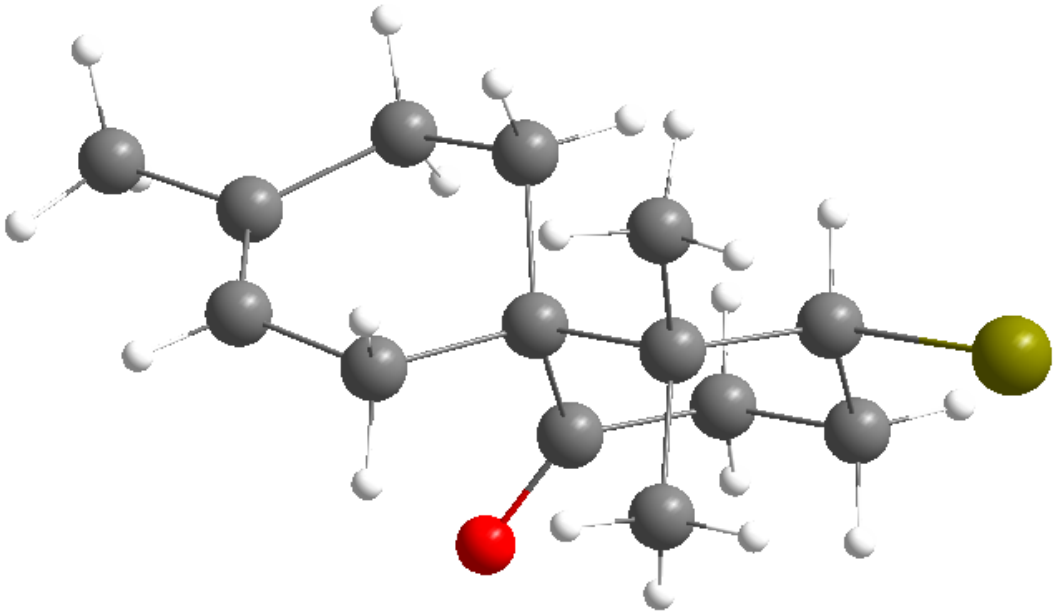


Figure 2-S3. ORTEP representation of **57**

Compound 104. Exposure of **57** to KHMDS, MeLi, $TMSCH_2Li$, PPh_3CH_2 (formed by treatment of PPh_3CH_3Br with *t*BuOK or *n*BuLi) led to rapid formation of **104** (structure tentatively assigned) quantitatively as a colorless oil. **104**: R_f = 0.48 (silica gel, hexanes/EtOAc, 4/1); IR (film) ν_{max} 2964, 2913, 1716, 1463, 1367, 1306, 1242, 1182, 1155, 965, 952, 926, 804 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.38 (s, 1 H), 1.96–1.80 (m, 5 H), 1.76–1.66 (m, 2 H), 1.62 (s, 3 H), 1.56–1.48 (m, 1 H), 1.37 (td, *J* = 4.9, 3.1 Hz, 1 H), 1.07 (s, 6 H), 1.01 (td, *J* = 8.6, 5.5 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 216.8, 132.8, 119.6, 49.3, 40.2, 33.8, 31.0, 29.9, 28.2, 28.1, 27.9, 23.0, 22.6, 14.2; HRMS (Mixed+) calcd for $C_{14}H_{20}O^+$ [M + H^+] 205.1587, found 205.1590.

Bromo spirocyclic alkene 105. To a flame-dried vial was added Mg powder (31.0 mg, 1.26 mmol, 10 equiv) and CH_2Cl_2 (0.2 mL). The resultant suspension was cooled to 0 °C and $TiCl_4$

(1.0 M in CH_2Cl_2, 0.63 mL, 0.63 mmol, 5.0 equiv) was added dropwise over the course of 1 min at 0 °C. After stirring at 0 °C for 5 min, a solution of **56** (36.0 mg, 0.126 mmol, 1.0 equiv) in THF/CH_2Cl_2 (0.3 mL/0.8 mL) was added dropwise over the course of 5 min, resulting in a color change from light yellow to green and then to black to be observed. The resulting mixture was then vigorously stirred at 0 °C for 15 min, at 23 °C for 20 min, and finally at 31 °C for 5 h. Upon completion, the resultant viscous mixture was quenched by being poured into aqueous K_2CO_3 (5%, 5 mL), followed by the addition of saturated aqueous Rochelle's salt (20 mL). The resultant black mixture was stirred vigorously at 23 °C for 16 h until phase separation occurred, was poured into a separatory funnel, and the layers were separated. The aqueous layer was then extracted with CH_2Cl_2 (3 × 2 mL), and the combined organic layers were washed with brine (4 mL), dried ($MgSO_4$), filtered, and concentrated. The resultant residued was purified by flash column chromatography (silica gel, hexanes) to afford **105** (17.0 mg, 48% yield) as a colorless oil. **105**: R_f = 0.80 (silica gel, hexanes/EtOAc, 4/1); IR (film) ν_{max} 2958, 1456, 1389, 1368, 1213, 1156, 1070, 896 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.27 (s, 1 H), 4.97 (s, 1 H), 4.75 (d, *J* = 1.1 Hz, 1 H), 4.46 (dd, *J* = 8.4, 4.1 Hz, 1 H), 2.45–2.38 (m, 1 H), 2.35–2.30 (m, 1 H), 2.29–2.23 (m, 2 H), 2.18–2.09 (m, 3 H), 1.96–1.89 (m, 1 H), 1.85 (dd, *J* = 17.6, 5.7 Hz, 2 H), 1.68 (ddd, *J* = 13.2, 11.6, 6.3 Hz, 1 H), 1.58 (s, 3 H), 1.07 (s, 3 H), 1.04 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.6, 133.2, 118.7, 111.1, 66.1, 46.1, 43.1, 35.5, 31.5, 29.2, 28.2, 26.2, 24.4, 23.1, 21.0; HRMS (APCI+) calcd for $C_{15}H_{23}Br^+$ [M^+] 282.0978, found 282.0982.

(±)-10-β-bromo-chamigrene 1. To a flame-dried vial was added Mg powder (25.6 mg, 1.06 mmol, 10 equiv) and CH_2Cl_2 (0.2 mL). The resultant suspension was cooled to 0 °C and $TiCl_4$ (1.0 M in CH_2Cl_2, 0.53 mL, 0.53 mmol, 5.0 equiv) was added dropwise over the course of 1 min

at 0 °C. After stirring at 0 °C for 5 min, a solution of **57** (30.4 mg, 0.106 mmol, 1.0 equiv) in THF/CH_2Cl_2 (0.3 mL/0.8 mL) was added dropwise over the course of 5 min, resulting in a color change from light yellow to green and then to black to be observed. The resulting mixture was then vigorously stirred at 0 °C for 15 min, at 23 °C for 20 min, and finally at 33 °C for 10 h. Upon completion, the resultant viscous mixture was quenched by being poured into aqueous K_2CO_3 (5%, 5 mL), followed by the addition of saturated aqueous Rochelle's salt (20 mL). The resultant black mixture was stirred vigorously at 23 °C for 16 h until phase separation occurred, was poured into a separatory funnel, and the layers were separated. The aqueous layer was then extracted with CH_2Cl_2 (3 × 2 mL), and the combined organic layers were washed with brine (4 mL), dried ($MgSO_4$), filtered, and concentrated. The resultant residued was purified by flash column chromatography (silica gel, hexanes) to afford **1** (16.0 mg, 53% yield) as a colorless oil. **1**: R_f = 0.80 (silica gel, hexanes/EtOAc, 4/1); IR (film) ν_{max} 2951, 2867, 1456, 1386, 1367, 903, 878, 668 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.28 (s, 1 H), 4.93 (s, 1 H), 4.65 (dd, *J* = 12.9, 4.5 Hz, 1 H), 4.61 (s, 1 H), 2.36 (td, *J* = 13.8, 4.8 Hz, 1 H), 2.27–2.19 (m, 2 H), 2.14 (ddd, *J* = 13.7, 4.8, 2.2 Hz, 1 H), 2.11–2.00 (m, 2 H), 1.90–1.84 (m, 1 H), 1.79–1.73 (m, 1 H), 1.70–1.59 (m, 2 H), 1.57 (s, 3 H), 1.10 (s, 3 H), 0.93 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.6, 132.7, 119.7, 112.6, 66.1, 47.1, 42.7, 35.7, 33.0, 30.3, 27.6, 25.6, 23.8, 23.1, 17.5; HRMS (APCI+) calcd for $C_{15}H_{23}Br^+$ [M^+] 282.0978, found 282.0994.

^1H NMR ($CDCl_3$)			^{13}C NMR ($CDCl_3$)		
Natural 10-β-Br-chamigrene (**1**)[10]	Synthetic 10-β-Br-chamigrene (**1**)	Reported synthetic 10-β-Br-	Natural 10-β-Br-chamigrene (**1**)[10]	Synthetic 10-Br-β-chamigrene (**1**)	Reported synthetic 10-β-Br-chamigrene (**1**)[33]

		chamigrene (**1**)[33]			
5.28 (br s, 1 H)	5.28 (s, 1 H)	5.25 (br s, 1 H)	145.6	145.6	145.8
4.93 (t, *J* = 1.8 Hz, 1H)	4.93 (s, 1 H)	4.91 (s, 1 H)	132.7	132.7	132.9
4.65 (dd, *J* = 12.7, 4.4 Hz, 1H)	4.65 (dd, *J* = 12.9, 4.5 Hz, 1H)	4.61 (dd, *J* = 12, 4 Hz, 1H)	119.7	119.7	119.9
4.61 (br, s, 1 H)	4.61 (s, 1 H)	4.60 (s, 1 H)	112.6	112.6	117.8
2.37 (ddd, *J* = 13.8, 13.8, 5.2 Hz, 1 H)	2.36 (td, *J* = 13.8, 4.8 Hz, 1 H)		66.1	66.1	66.2
2.23 (dddd, *J* = 12.8, 5.2, 4.4, 2.2 Hz, 1 H)	2.27–2.19 (m, 2 H)		47.0	47.1	47.2
2.23 (br, d, *J* = 15.3 Hz, 1 H)			42.7	42.7	42.9

2.14 (ddd, *J* = 13.8, 4.8, 2.2 Hz, 1 H)	2.14 (ddd, *J* = 13.7, 4.8, 2.2 Hz, 1 H)		35.7	35.7	35.9
2.06 (dddd, *J* = 13.8, 12.8, 12.7, 4.8 Hz, 1 H)	2.11–2.00 (m, 2 H)		33.9	33.0	33.2
2.04 (br d, *J* = 15.3 Hz, 1 H)			30.3	30.3	30.5
1.88 (dm, *J* = 10.8 Hz, 1 H)	1.90–1.84 (m, 1 H)		27.5	27.6	27.7
1.76 (m, 1 H)	1.79–1.73 (m, 1 H)		25.6	25.6	25.8
1.62 (m, 1 H)	1.70–1.59 (m, 2 H)		23.9	23.8	24.0
1.58 (m, 1 H)			23.1	23.1	23.3
1.54 (br, s, 3 H)	1.57 (s, 3 H)	1.56 (s, 3 H)	17.5	17.5	17.7
1.10 (s, 3 H)	1.10 (s, 3 H)	1.10 (s, 3 H)			
0.94 (s, 3 H)	0.93 (s, 3 H)	0.94 (s, 3 H)			

Diol 106. Compound **105** (15.0 mg, 0.053 mmol, 1.0 equiv) was dissolved in acetone (1 mL) and *t*-BuOH (0.2 mL), H_2O (0.2 mL), NMO•H_2O (0.143 g, 20 equiv), and OsO_4 (2.5% in *t*-BuOH, 0.06 mL, 0.005 mmol, 0.1 equiv) were added sequentially at 23 °C. The resultant mixture was stirred at 23 °C for 3 h. Upon completion the reaction contents were quenched by the sequential addition of EtOAc (3 mL) and aqueous $Na_2S_2O_3$ (5%, 3 mL), poured into a separatory funnel, and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 2 mL), and the combined organic layers were washed with brine (3 mL), dried ($MgSO_4$), filtered, and concentrated. The resultant residue was purified by flash column chromatography (silica gel, hexanes/EtOAc, 3/1) to afford **106** (16.2 mg, 99%) as a white solid. Recrystallization of this material from hexanes/CH_2Cl_2 afforded crystals of suitable quality for X-ray diffraction, with the resultant crystal structure shown below in Figure S4. **106**: R_f = 0.42 (silica gel, hexanes/EtOAc, 1/1); m.p. = 117–118 °C; IR (film) ν_{max} 3395 (br), 2971, 1456, 1373, 1265, 1058, 1037, 1018, 906, 739 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.08 (d, *J* = 12.1 Hz, 1 H), 4.70 (s, 1 H), 4.59 (dd, *J* = 12.8, 4.7 Hz, 1 H), 3.22 (dd, *J* = 11.7, 3.9 Hz, 1 H), 2.45 (td, *J* = 13.4, 5.3 Hz, 1 H), 2.31–2.24 (m, 1 H), 2.13 (ddd, *J* = 13.3, 5.3, 1.9 Hz, 1 H), 2.05 (td, *J* = 13.0, 5.3 Hz, 1 H), 1.98–1.92 (m, 1 H), 1.87 (d, *J* = 12.2 Hz, 1 H), 1.82 (dd, *J* = 11.6, 2.9 Hz, 1 H), 1.76–1.68 (m, 2 H), 1.66–1.60 (m, 1 H), 1.21 (s, 3 H), 1.15 (s, 3 H), 0.94 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.3, 113.1, 72.2, 71.0, 64.9, 49.2, 43.9, 36.3, 34.2, 33.9, 32.4, 27.1, 23.6, 23.4, 17.2; HRMS (ESI+) calcd for $C_{15}H_{24}BrO^+$ [M – H_2O + H^+] 299.1005, found 299.1002.

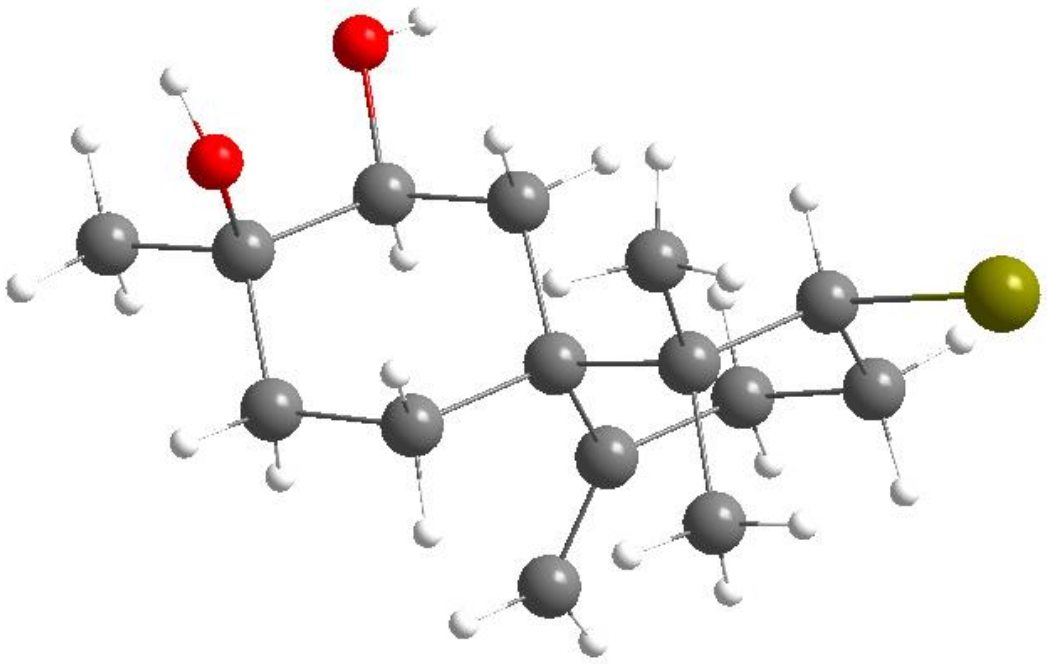


Figure 2-S4. ORTEP representation of **106**

3,4-dihydroxy-10-β-chamigrene [proposed structure] 7. Compound **1** (4.7 mg, 0.016 mmol, 1.0 equiv) was dissolved in acetone (0.8 mL) and *t*-BuOH (0.1 mL), H_2O (0.1 mL), NMO•H_2O (30.0 mg, 20 equiv) and OsO_4 (2.5 w.t.% in *t*-BuOH, 0.02 mL, 0.002 mmol, 0.1 equiv) were added sequentially at 23 °C. The resultant mixture was stirred at 23 °C for 8 h. Upon completion the reaction contents were quenched by the sequential addition of EtOAc (2 mL) and aqueous $Na_2S_2O_3$ (5%, 2 mL), poured into a separatory funnel, and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 2 mL), and the combined organic layers were washed with brine (3 mL), dried ($MgSO_4$), filtered, and concentrated. The resultant residue was purified by flash column chromatography (silica gel, hexanes/EtOAc, 3/1) to afford **7** (4.7 mg, 99% yield) as a white solid. Recrystallization of this material from hexanes/CH_2Cl_2 afforded crystals of suitable quality for X-ray diffraction, with the resultant crystal structure shown below in Figure

S5. **7**: R_f = 0.41 (silica gel, hexanes/EtOAc, 1/1); m.p. = 138–139 °C; IR (film) ν_{max} 3333 (br), 2967, 2926, 1456, 1448, 1060, 1028, 901, 869, 738 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.12 (s, 1 H), 4.85 (s, 1 H), 4.58 (dd, *J* = 12.7, 4.6 Hz, 1 H), 3.74 (dd, *J* = 11.3, 5.0 Hz, 1 H), 2.36–2.22 (m, 2 H), 2.12–1.99 (m, 2 H), 1.96–1.87 (m, 2 H), 1.74–1.70 (m, 1 H), 1.68–1.65 (m, 1 H), 1.60–1.54 (m, 2 H), 1.21 (s, 3 H), 1.16 (s, 3 H), 0.97 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.0, 113.6, 71.8, 70.6, 64.9, 49.8, 43.8, 36.1, 33.8, 33.4, 33.3, 27.3, 23.7, 22.7, 17.5; HRMS (Mixed+) calcd for $C_{15}H_{24}BrO^+$ [M – H_2O + H^+] 299.1005, found 299.0994.

^1H NMR (C_6D_6) (selected peaks)	
Natural "3,4-dihydroxy-10-β- bromo-chamigrane" (**7**)	Synthetic 3,4-dihydroxy-10-β- bromo-chamigrane (**7**)
4.73 (t, *J* = 1.3 Hz)	4.81 (s)
4.46 (br, s)	4.57 (s)
4.12 (dd, *J* = 12.3, 5.1 Hz)	4.24 (dd, *J* = 12.6, 4.9 Hz)
4.12 (dd, *J* = 5.1, 12.3 Hz)	3.45 (dd, *J* = 10.7, 4.8 Hz)
1.05 (s)	1.03 (s)
1.07 (s)	1.14 (s)
0.87 (s)	0.97 (s)

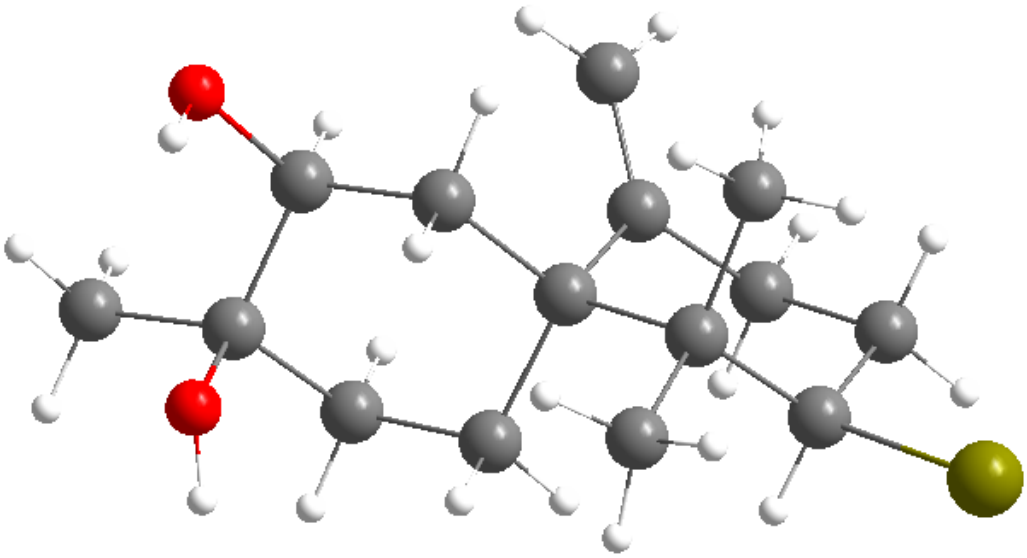


Figure 2-S5. ORTEP representation of **7**

(±)-10-*epi*-dactylone 8. Compound **106** (5.0 mg, 0.016 mmol, 1.0 equiv) was dissolved in a mixture of CH_2Cl_2/DMSO/Et_3N (0.3 mL/0.3 mL/0.05 mL), the solution was cooled to 0 °C, and SO_3•pyr (7.6 mg, 0.048 mmol, 3.0 equiv) was added. The resultant mixture was stirred at 0 °C for 1 h. Upon completion, the reaction contents were quenched by the addition of aqueous HCl (2 M, 3 mL), poured into a separatory funnel, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 2 mL). The combined organic layers were washed with brine (2 mL), dried ($MgSO_4$), filtered, and concentrated to give the crude hydroxyketone (R_f = 0.66, hexanes/EtOAc, 1/1) that was used without any further purification. Next, the crude hydroxyketone (0.016 mmol assumed, 1.0 equiv) was dissolved in pyridine (0.5 mL), the resultant solution was cooled to 0 °C, and $SOCl_2$ (3.0 μL, 0.032 mmol, 2.0 equiv) was added. The reaction mixture was then stirred at 0 °C for 20 min. Upon completion, the reaction contents were quenched by the sequential addition of CH_2Cl_2 (2 mL) and aqueous HCl (2 M, 3 mL), poured into a

separatory funnel, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 2 mL), and then the combined organic layers were washed by brine (2 mL), dried ($MgSO_4$), filtered, and concentrated. Purification of the resultant residue preparative thin-layer chromatography (silica gel, hexanes/EtOAc, 3/1) afforded 10-*epi*-dactylone **8** (3.1 mg, 66% yield over 2 steps) as a white solid. **8**: R_f = 0.49 (silica gel, hexanes/EtOAc, 4/1); IR (film) ν_{max} 2976, 2924, 1675, 1456, 1369, 1213, 907, 795 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.66–6.59 (m, 1 H), 4.98 (s, 1 H), 4.54 (s, 1 H), 4.48 (dd, *J* = 12.6, 4.5 Hz, 1 H), 2.80 (dd, *J* = 14.9, 2.3 Hz, 1 H), 2.71–2.61 (m, 2 H), 2.52 (dd, *J* = 18.3, 5.2 Hz, 1 H), 2.42 (td, *J* = 13.8, 5.0 Hz, 1 H), 2.28–2.21 (m, 1 H), 2.14 (ddd, *J* = 14.1, 4.8, 2.6 Hz, 1 H), 2.04 (ddd, *J* = 26.2, 13.0, 5.0 Hz, 1 H), 1.70 (d, *J* = 1.2 Hz, 3 H), 1.19 (s, 3 H), 0.99 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.4, 144.1, 143.1, 134.5, 114.7, 63.6, 51.7, 43.0 (2 C), 35.2, 32.5, 31.6, 24.7, 17.2, 15.3; HRMS (APCI+) calcd for $C_{15}H_{22}BrO^+$ [M + H^+] 297.0849, found 297.0840.

^1H NMR ($CDCl_3$)		^{13}C NMR ($CDCl_3$)	
Natural 10-*epi*-dacylone (**8**)[59]	Synthetic 10-*epi*-dacylone (**8**)	Natural 10-*epi*-dacylone (**8**)[59]	Synthetic 10-*epi*-dacylone (**8**)
6.63 (m, 1 H)	6.66–6.59 (m, 1H)	198.2	198.4
5.00 (br, s, 1 H)	4.98 (s, 1 H)	144.3	144.1
4.54 (s, 1 H)	4.54 (s, 1 H)	142.9	143.1
4.48 (dd, *J* = 12.4, 4.5 Hz, 1 H)	4.48 (dd, *J* = 12.6, 4.5 Hz, 1 H)	134.6	134.5

2.81 (dd, *J* = 14.9, 2.3 Hz, 1 H)	2.80 (dd, *J* = 14.9, 2.3 Hz, 1 H)	114.6	114.7
2.67 (dm, *J* = 18.9 Hz, 1 H)	2.71–2.61 (m, 2 H)	63.6	63.6
2.65 (d, *J* = 14.9 Hz, 1 H)		51.8	51.7
2.53 (dm, *J* = 18.9 Hz, 1 H)	2.52 (dd, *J* = 18.3, 5.2 Hz, 1 H)	43.15	43.0 (two overlapping signals)
2.42 (m, 1 H)	2.42 (td, *J* = 13.8, 5.0 Hz, 1 H)	43.1	
2.25 (m, 1 H)	2.28 – 2.21 (m, 1 H)	35.4	35.2
2.15 (m, 1 H)	2.14 (ddd, *J* = 14.1, 4.8, 2.6 Hz, 1 H)	32.6	32.5
2.03 (m, 1 H)	2.04 (ddd, *J* = 26.2, 13.0, 5.0 Hz, 1 H)	31.7	31.6
1.71 (dt, *J* = 2.6, 1.4 Hz, 3 H)	1.70 (d, *J* = 1.2 Hz, 3 H)	24.8	24.7
1.20 (s, 3 H)	1.19 (s, 3 H)	17.3	17.2
1.00 (s, 3 H)	0.99 (s, 3 H)	15.2	15.3

(±)-dactylone 9. Compound **7** (1.5 mg, 0.005 mmol, 1.0 equiv) was dissolved in a mixture of CH_2Cl_2/DMSO/Et_3N (0.2 mL/0.2 mL/0.03 mL), the solution was cooled to 0 °C, and SO_3•pyr

(2.4 mg, 0.015 mmol, 3.0 equiv) was added. The resultant mixture was stirred at 0 °C for 1 h. Upon completion, the reaction contents were quenched by the addition of aqueous HCl (2 $_{M}$, 2 mL), poured into a separatory funnel, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 1.5 mL). The combined organic layers were washed with brine (2 mL), dried ($MgSO_4$), filtered, and concentrated to give the crude hydroxyketone (R_f = 0.66, hexanes/EtOAc, 1/1) that was used without any further purification. Next, the crude hydroxyketone (0.005 mmol assumed, 1.0 equiv) was dissolved in pyridine (0.3 mL), the resultant solution was cooled to 0 °C, and $SOCl_2$ (1.6 μL, 0.015 mmol, 3.0 equiv) was added. The reaction mixture was then stirred at 0 °C for 15 min. Upon completion, the reaction contents were quenched by the sequential addition of CH_2Cl_2 (1.5 mL) and aqueous HCl (2 M, 2 mL), poured into a separatory funnel, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 1.5 mL), and then the combined organic layers were washed by brine (2 mL), dried ($MgSO_4$), filtered, and concentrated. Purification of the resultant residue preparative thin-layer chromatography (silica gel, hexanes/EtOAc, 3/1) afforded dactylone **9** (0.8 mg, 57% over 2 steps) as a white solid. **9**: R_f = 0.49 (silica gel, hexanes/EtOAc, 4/1); IR (film) ν_{max} 2924, 1671, 1450, 1371, 1113, 905, 872, 782 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.52–6.48 (m, 1 H), 4.97 (s, 1 H), 4.60 (s, 1 H), 4.53 (dd, *J* = 12.6, 4.5 Hz, 1 H), 2.75 (d, *J* = 16.4 Hz, 1 H), 2.65 (d, *J* = 1.8 Hz, 2 H), 2.56 (dd, *J* = 16.6, 9.0 Hz, 1 H), 2.36 (td, *J* = 13.6, 5.4 Hz, 1 H), 2.30–2.22 (m, 1 H), 2.16 (dd, *J* = 15.0, 6.1 Hz, 1 H), 2.09 (ddd, *J* = 26.2, 12.9, 5.3 Hz, 1 H), 1.73 (d, *J* = 1.4 Hz, 3 H), 1.19 (s, 3 H), 0.99 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.5, 146.0, 141.4, 135.3, 63.1, 51.2, 44.0, 43.1, 35.2, 33.6, 29.7, 25.0, 17.5, 15.3; HRMS (APCI+) calcd for $C_{15}H_{22}BrO^+$ [M + H^+] 297.0849, found 297.0844.

^1H NMR ($CDCl_3$)	^{13}C NMR ($CDCl_3$)

Natural dacylone (**9**)[15]	Synthetic dacylone (**9**)	Natural dacylone (**9**)[15]	Synthetic dacylone (**9**)
6.50 (m, 1 H)	6.52–6.48 (m, 1 H)	198.8	199.5
4.98 (br, d, *J* = 1.5 Hz, 1 H)	4.97 (s, 1 H)	146.1	146.0
4.61 (s, 1 H)	4.60 (s, 1 H)	140.7	141.4
4.52 (dd, *J* = 12.5, 4.5 Hz, 1 H)	4.53 (dd, *J* = 12.6, 4.5 Hz, 1 H)	135.5	135.3
2.74 (br, d, *J* = 16.5 Hz, 1 H)	2.75 (d, *J* = 16.4 Hz, 1 H)	63.0	63.1
2.65 (m, 2 H)	2.65 (d, *J* = 1.8 Hz, 2 H)	51.4	51.2
2.57 (d, *J* = 16.5 Hz, 1 H)	2.56 (dd, *J* = 16.6, 9.0 Hz, 1 H)	44.2	44.0
2.37 (m, 1 H)	2.36 (td, *J* = 13.6, 5.4 Hz, 1 H)	43.2	43.1
2.26 (m, 1 H)	2.30–2.22 (m, 1 H)	35.5	35.2
2.17 (m, 1 H)	2.16 (dd, *J* = 15.0, 6.1 Hz, 1 H)	33.7	33.6
2.11 (m, 1 H)	2.09 (ddd, *J* = 26.2, 12.9, 5.3 Hz, 1 H)	30.0	29.7
1.73 (d, *J* = 1.8 Hz, 3 H)	1.73 (d, *J* = 1.4 Hz, 3 H)	25.1	25.0

1.19 (s, 3 H)	1.19 (s, 3 H)	17.7	17.5
0.99 (s, 3 H)	0.99 (s, 3 H)	15.3	15.3

2.6 References

[1] B. -G. Wang, J. B. Gloer, N. -Y. Ji, J. -C. Zhao, *Chem. Rev*. **2013**, *113*, 3632.

[2] B. M. Howard, W. Fenical, *Tetrahedron Lett.* **1976**, *17*, 2519.

[3] M. Suzuki, A. Furusaki, E. Kurosawa, *Tetrahedron* **1979**, *35*, 823.

[4] G. M. König, A. D. Wright, *J. Nat. Prod.* **1994**, *57*, 477.

[5] G. M. König, A. D. Wright, *J. Nat. Prod.* **1997**, *60*, 967

[6] X. -D. Li, W. Ding, F. -P. Miao, N. -Y. Ji, *Magn. Reson. Chem.* **2012**, *50*, 174

[7] K. Kokkotou, E. Ioannou, M. Nomikou, F. Pitterl, A. Vonaparti, E. Siapi, M. Zervou, V. Roussis, *Phytochemistry* **2014**, *108*, 208.

[8] G. Guella, A. Öztunç, I. Mancini, F. Pietra, *Tetrahedron Lett.* **1997**, *38*, 8261.

[9] R. R. Izac, PhD thesis, University of California, Riverside, CA, **1978**.

[10] G. M. König, A. D. Wright, *Phytochem. Anal.* **1997**, *8*, 167

[11] N. -Y. Ji, X. -M. Li, K. Li, L. -P. Ding, J. B. Gloer, B. -G. Wang, *J. Nat. Prod.* **2007**, *70*, 1901.

[12] S. N. Fedorov, A. P. Reshetnyak, S. G. Il'in, Y. T. Struchkov, V. A. Stonik, G. B. Elyakov, *Dokl. Akad. Nauk. SSSR* **1989**, *305*, 877.

[13] S. N. Fedorov, O. S. Radchenko, L. K. Shubina, A. I. Kalinovsky, A. V. Gerasimenko, D. Y. Popov, V. A. Stonik, *J. Am. Chem. Soc.* **2001**, *123*, 504.

[14] See the introduction part of chapter 1 and references therein.

[15] E. G. Lyakhova, S. N. Fedorov, L. K. Shubina, O. S. Radchenko, A. I. Kalinovsky, A. S. Dvitrenok, V. A. Stonik, *Russ. Chem. Bull.* **2003**, *52*, 1022.

[16] J. J. Sims, G. H. Y. Lin, R. M. Wing, *Tetrahedron Lett.* **1974**, *15*, 3487.

[17] C. S. Vairappan, M. Daitoh, M. Suzuki, T. Abe. M. Masuda, *Phytochemistry* **2001**, *58*, 291.

[18] G. M. König, A. D. Wright, *J. Nat. Prod.* **1997**, *60*, 967.

[19] S. N. Fedorov, L. K. Shubina, A. M. Bode, V. A. Stonik, Z. Dong, *Cancer Res*. **2007**, *67*, 5914.

[20] I. Granado, P. Caballero, *Sci. Mar*. **1995**, *59 (Supl. 1)*, 31.

[21] M. A. Rashid, K. R. Gustafson, J. H. Cardellina, M. R. Boyde, *Nat. Prod. Lett.* **1995**, *6*, 255.

[22] R. de Nys, T. Leya, R. Maximilien, A. Afsar, P. S. R. Nair, P. D. Steinberg, *Biofouling* **1996**, *10*, 213.

[23] E. G. Juagdan, R. Kalidindi, P. Scheuer, *Tetrahedron* **1997**, *53*, 521.

[24] J. Kimura, N. Kamada, Y. Tsujimoto, *Bull. Chem. Soc. Jpn.* **1999**, *72*, 289.

[25] D. Davyt, R. Fernandez, L. Suescun, A. W. Mombrú, J. Saldaña, L. Domínguez, J. Coll, M. T. Fujii, E. Manta, *J. Nat. Prod.* **2001**, *64*, 1552.

[26] C. S. Vairappan, M. Daitoh, M. Suzuki, T. Abe, M. Masuda, *Phytochemistry* **2001**, *58*, 517.

[27] C. S. Vairappan, *Biomol. Eng*. **2003**, *20*, 255.

[28] T. Dias, I. Brito, L. Moujir, N. Paiz, J. Darias, M. Cueto, *J. Nat. Prod*. **2005**, *68*, 1677.

[29] K. L. Erickson, In Marine Natural Products; P. J. Scheuer, Ed.; Academic Press: New York, **1983**; Vol. 5, p 131

[30] J. N. Carter-Franklin, A. Butler, *J. Am. Chem. Soc*. **2004**, *126*, 15060.

[31] L. E. Wolinsky, D. J. Folkner, *J. Org. Chem*. **1976**, *41*, 597.

[32] I. Ichinose, T. Kato, *Chem. Lett.* **1979**, *8*, 61.

[33] J. D. Martin, C. Pérez, J. L. Ravelo, *J. Am. Chem. Soc.* **1986**, *108*, 7801.

[34] D. E. White, I. C. Stewart, R. H. Grubbs, B. M. Stoltz, *J. Am. Chem. Soc.* **2008**, *130*, 810.

[35] R. Meier, D. Trauner, *Angew. Chem. Int. Ed*. **2016**, *55*, 11251.

[36] A. J. Burckle, V. H. Vasilev, N. Z. Burns, *Angew. Chem. Int. Ed*. **2016**, *55*, 11476.

[37] C. Liu, R. Chen, Y. Shen, Z. Liang, Y. Hua, Y. Zhang, *Angew. Chem. Int. Ed*. **2017**, *56*, 8187.

[38] J. M. Rhode, Ph.D. thesis, The Scripps Research Institute, La Jolla, CA, 2005.

[39] M. Kodama, M. Shiobara, H. Sumimoto, K. Fukuzumi, H. Minami, Y. Miyamoto, *Tetrahedron Lett*. **1986**, *27*, 2157.

[40] Z. Liu, L. Peng, T. Zhang, Y. Li, *Synth. Commun*. **2001**, *31*, 2549.

[41] J. B. Lambert, G. T. Wang, R. B. Finzel, D. H. Teramura, *J. Am. Chem. Soc*. **1987**, *109*, 7838.

[42] G. A. Molander, C. -S. Yun, M. Ribagorda, B. Biolatto, *J. Org. Chem*. **2003**, *68*, 5534.

[43] T. Nemoto, Y. Ishige, M. Yoshida, Y. Kohno, M. Kanematsu, Y. Hamada, *Org. Lett.* **2010**, *12*, 5020.

[44] Q.-F. Wu, W.-B. Liu, C.-X. Zhuo, Z.-Q. Rong, K.-Y. Ye, S.-L. You, *Angew. Chem., Int. Ed.* **2011**, *50*, 4455.

[45] W. -T. Wu, L. Zhang, S. -L. You, *Chem. Soc. Rev.* **2016**, *45*, 1570.

[46] S. Antonsen, L. Skattebøl, Y. Stenstrøm, *Molecules*, 2014, 19, 20664.

[47] J. D. White, R. W. Skeean, G. L. Trammell, *J. Org. Chem.* **1985**, *50*, 1939.

[48] J. -L. Gras, A. Guerin, *Tetrahedron Lett.* **1985**, *26*, 1781.

[49] R. E. Ireland, W. C. Dow, J. D. Godfrey, S. Thaisrivongs, *J. Org. Chem.* **1984**, *49*, 1001.

[50] A. Tanaka, H. Uda, A. Yoshikoshi, *Chem. Commun.* **1967**, 188.

[51] L. A. Gorthey, M. Vairamani, C. Djerassi, *J. Org. Chem.* **1985**, *50*, 4173.

[52] F. N. Tebbe, G. W. Parshall, G. S. Reddy, J. Am. Chem. Soc. 1978, 100, 3611.

[53] L. N. Nysted, US Patent, **1975**, 3 865 848.

[54] N. A. Petasis, E. I. Bzowej, J. Am. Chem. Soc. 1990, 112, 6392.

[55] H. Lebel, D. Guay, V. Paquet, K. Huard, *Org. Lett.* **2004**, *6*, 3047.

[56] T. Yan, C. Tsai, C. Chien, C. Cho, P. Huang, *Org. Lett.* **2004**, *6*, 4961.

[57] W. G. Salmond, M. A. Barta, J. L. Havens, J. Org. Chem. 1978, 43, 2057.

[58] H. Choi, M. P. Doyle, Org. Lett. 2007, 9, 5349.

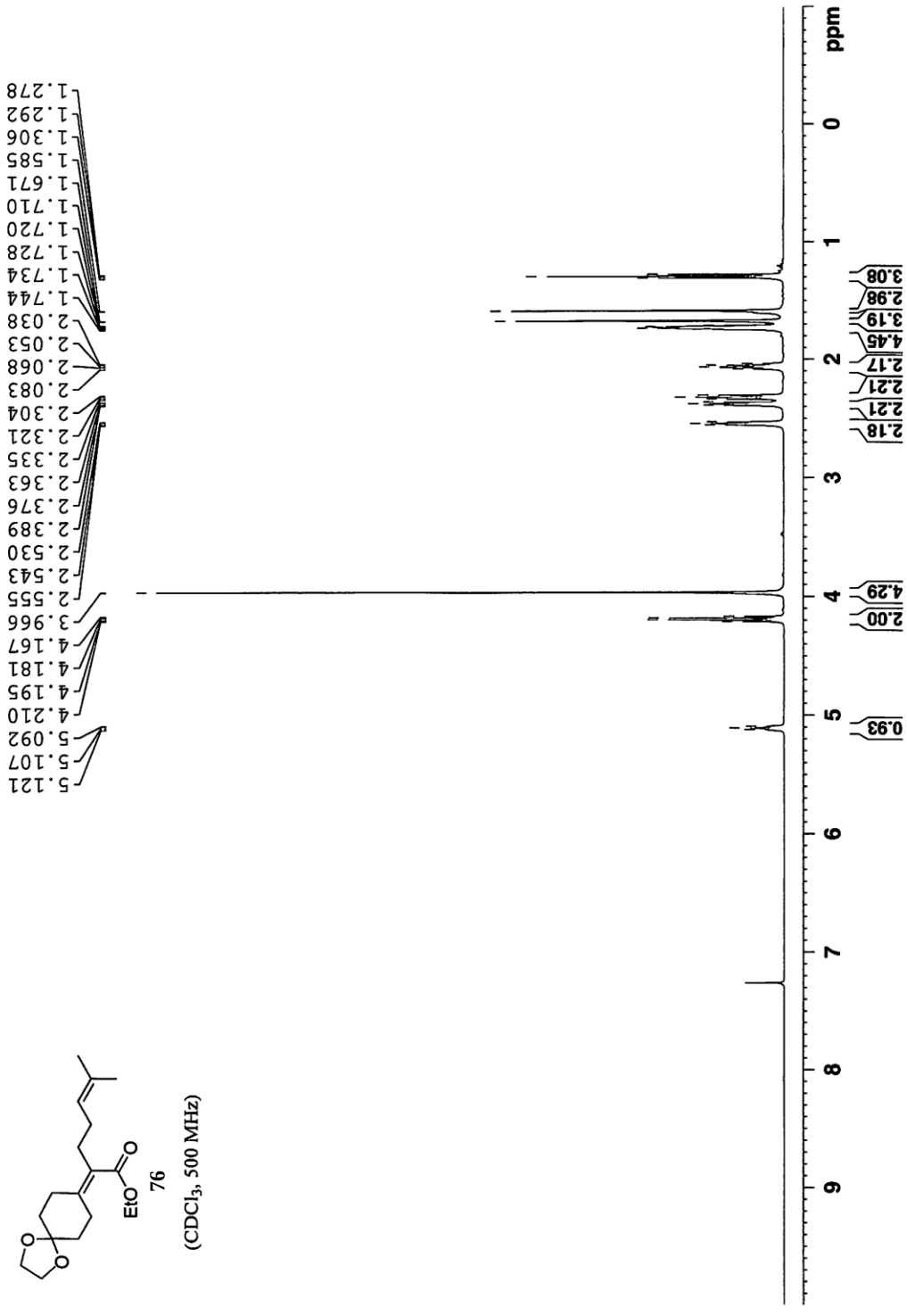
[59] L. K. Shubina, S. N. Fedorov, A. I. Kalinovsky, A. S. Dvitrenok, J. O. Jin, M. G. Song, J. Y. Kwak, V. A. Stonik, *Russ. Chem. Bull.* **2007**, *56*, 2109.

[60] J. R. Parikh, W. E. Doering, *J. Am. Chem. Soc.* **1967**, *89*, 5505.

[61] R. B. Lettan II, B. C. Milgram, K. A. Scheidt, *Org. Synth.* **2007**, *84*, 22.

[62] K. Mori, H. Watanabe, *Tetrahedron* **1986**, *42*, 273.

2.7 NMR Spectra of Selected Intermediates



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35.568
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27.928
27.575
25.617
17.492
14.175
EtO
O
O
O
76
(CDCl3, 125 MHz)
ppm
20
0
20
40
60
80
100
120
140
160
180
200
20

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7.553
7.542
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7.362
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0.299
PhMe2Si
OH
78
(CDCl3, 500 MHz)
ppm
0
1
2
3
4
5
6
7
8
9
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3.00
1.31
1.50
3.01
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3.46
5.50
1.37
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2.91

PhMe2Si
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ppm
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1.14
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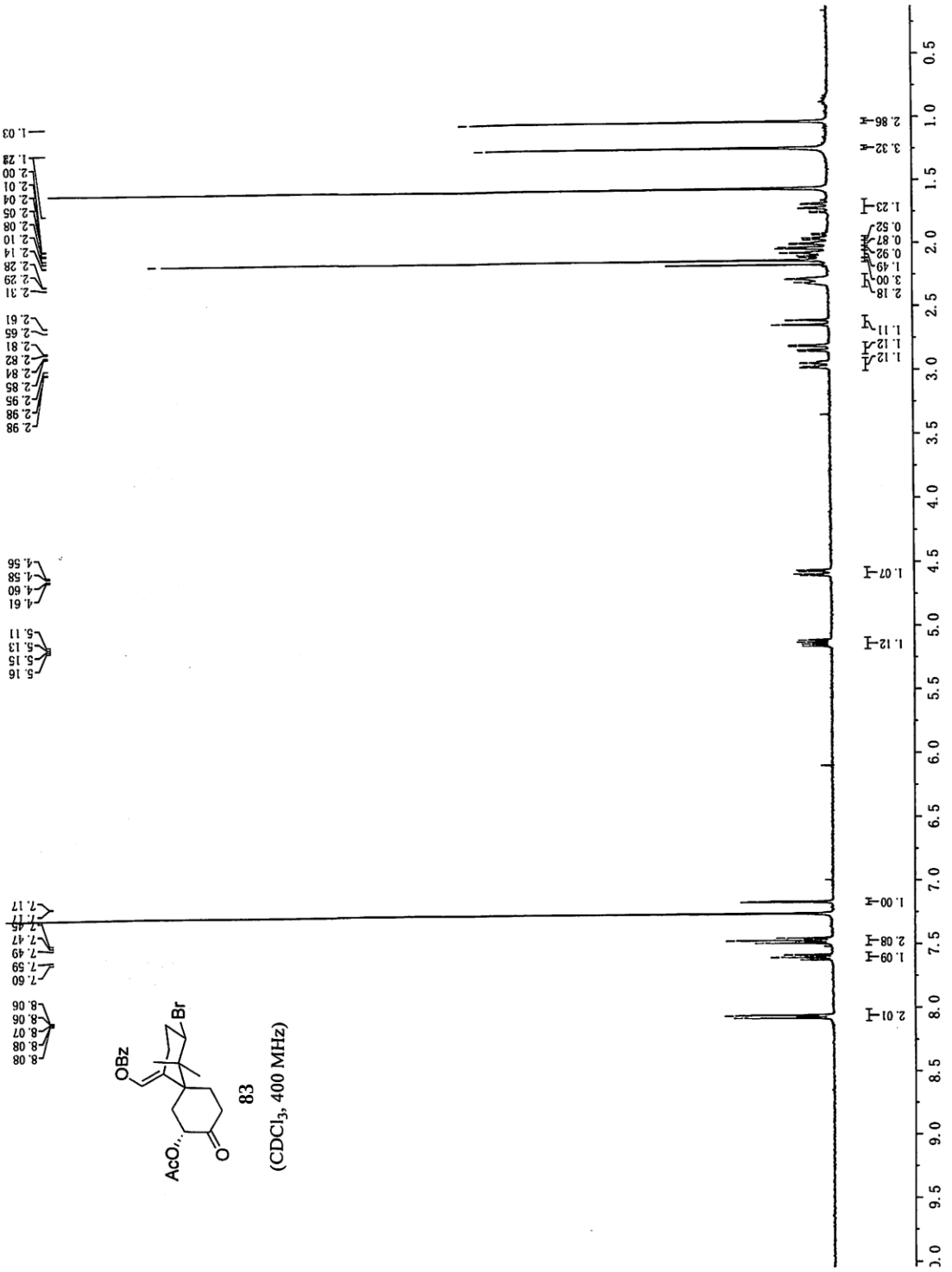
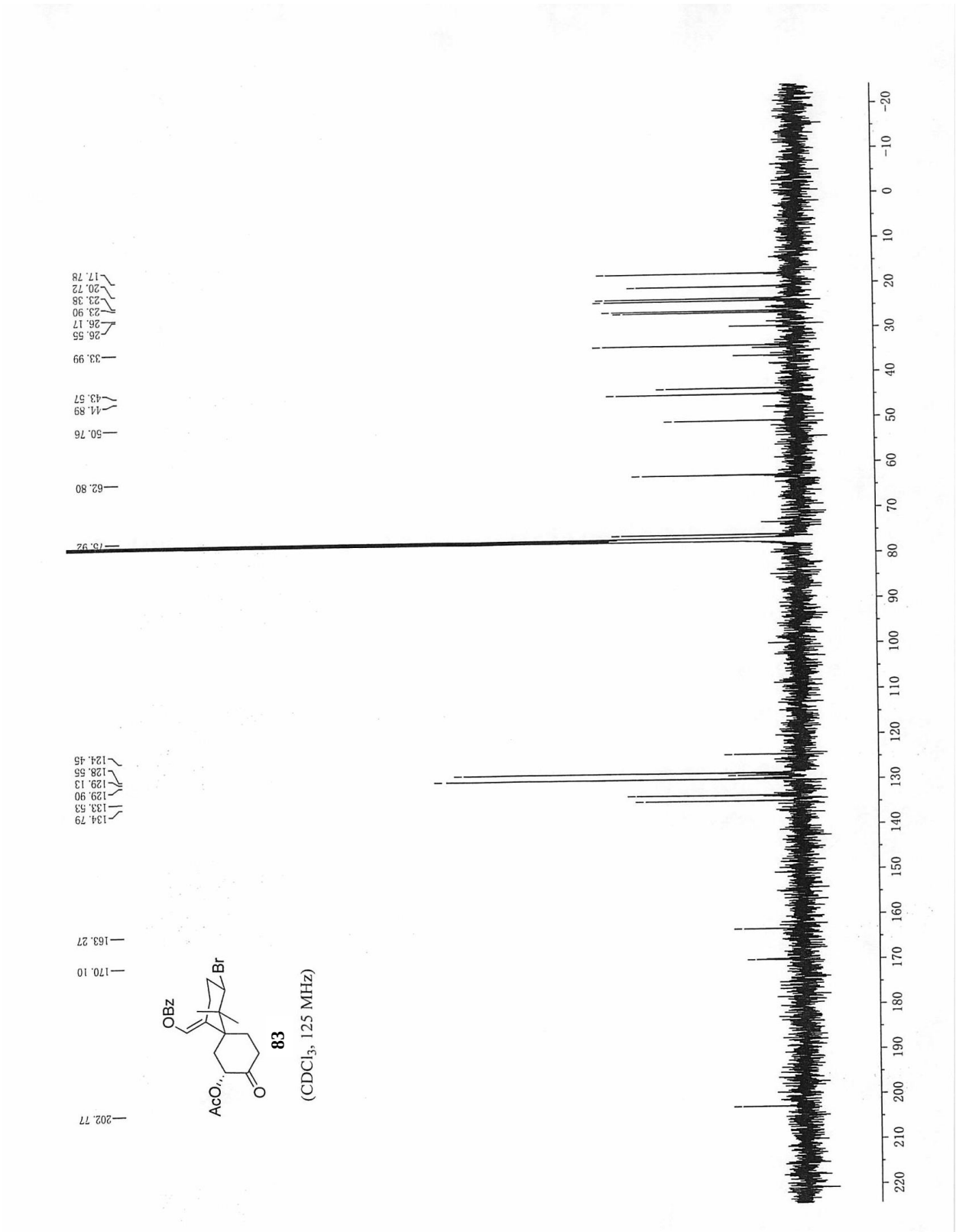
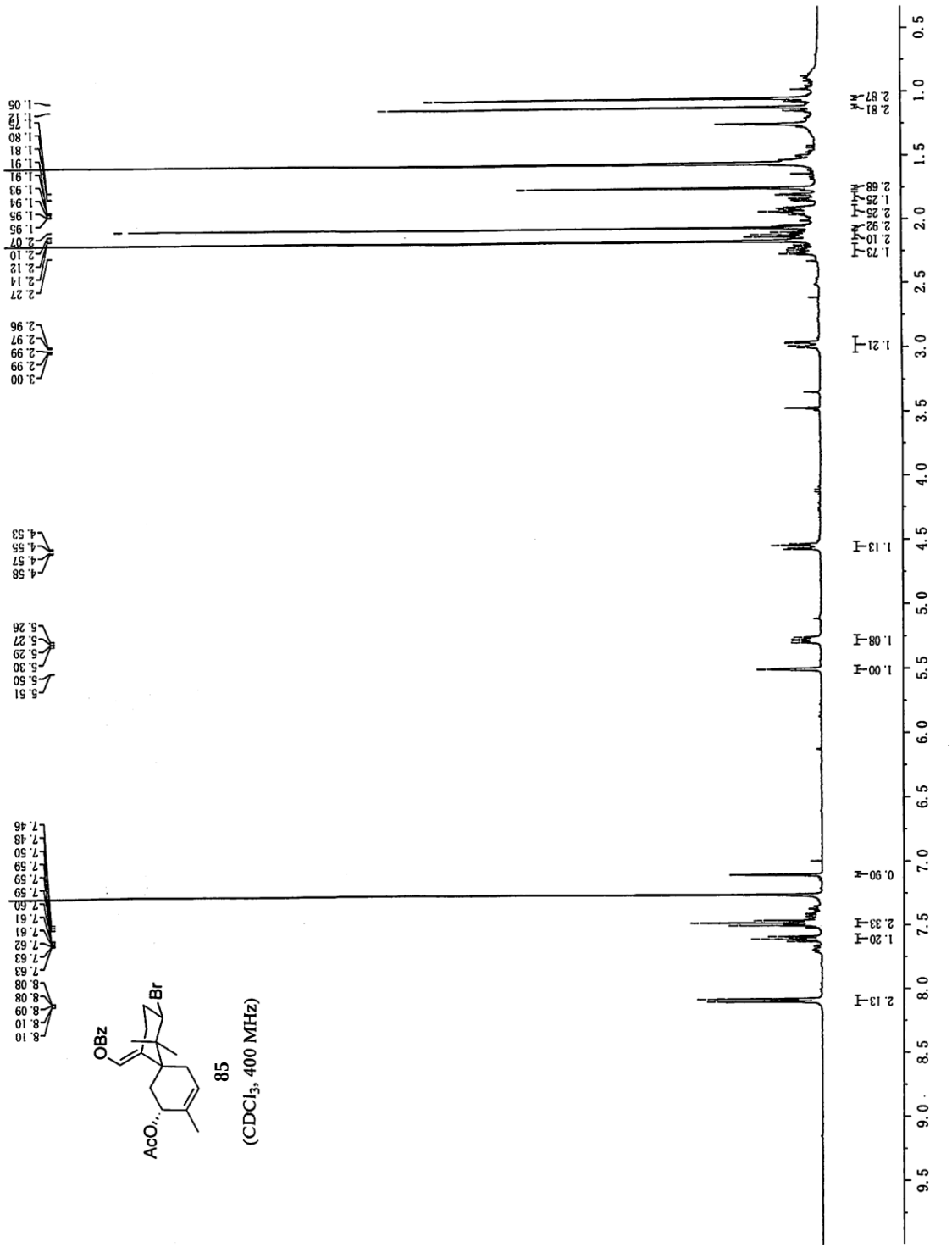
OBz
Br
Br
O
80
(CDCl3, 500 MHz)
ppm
9
8
7
6
5
4
3
2
1
0
1.99
0.99
2.12
1.00
1.06
1.13
1.03
0.97
1.12
1.35
1.30
2.14
3.02
2.95
2.95

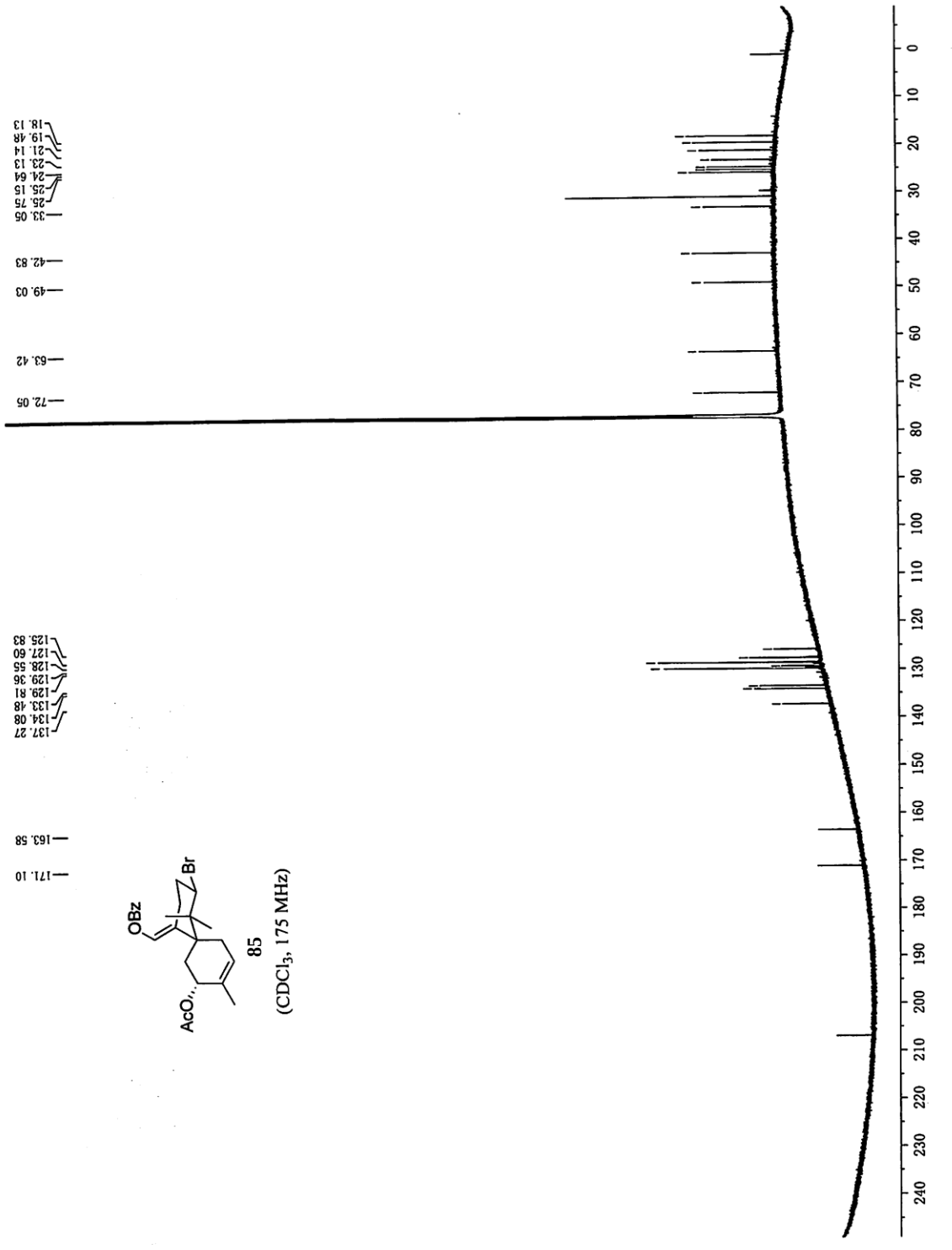
80

($CDCl_3$, 125 MHz)


OBz
Br
AcO
O
83
(CDCl3, 400 MHz)


OBz
Br
AcO
O
83
(CDCl3, 125 MHz)
202.77
170.10
163.27
134.79
133.53
129.90
129.13
128.55
124.45
75.92
62.80
50.76
44.89
43.57
33.99
26.55
26.17
23.90
23.38
20.72
17.78

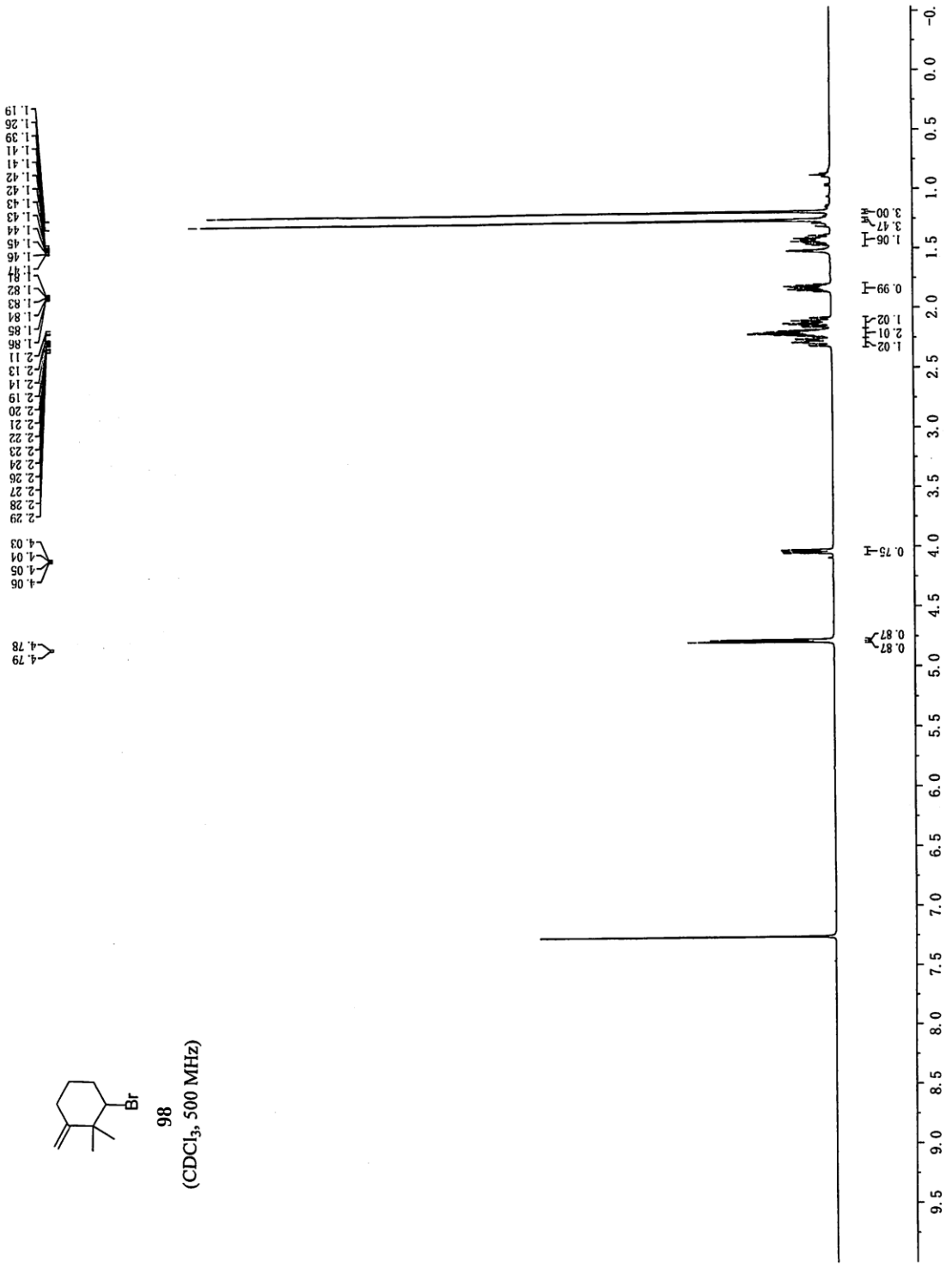

OBz
Br
AcO
85
(CDCl3, 400 MHz)

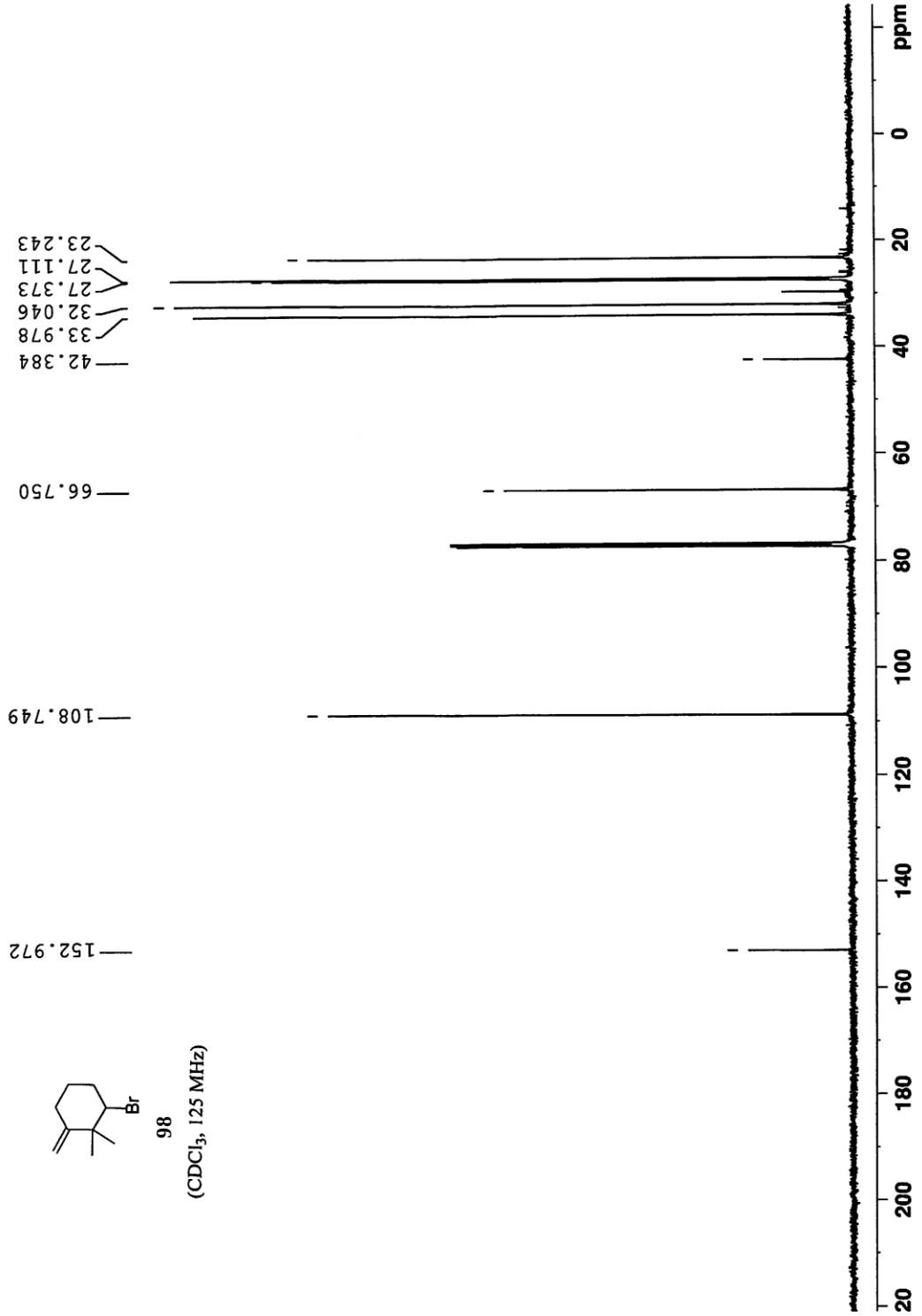

18.13
19.48
21.14
23.13
24.64
25.15
26.75
33.05
42.83
49.03
63.42
72.05
125.83
127.60
128.55
129.36
129.81
133.48
134.08
137.27
163.58
171.10
OBz
Br
AcO
85
(CDCl3, 175 MHz)

94

($CDCl_3$, 500 MHz)

210.509
62.862
51.559
36.899
32.190
24.027
23.953
22.530
ppm
0
20
40
60
80
100
120
140
160
180
200
220
O
Br
94
(CDCl3, 125 MHz)


Br
98
(CDCl3, 500 MHz)


Br
98
(CDCl3, 125 MHz)
152.972
108.749
66.750
42.384
33.978
32.046
27.373
27.111
23.243
ppm

O
Br
55
(CDCl3, 500 MHz)
5.838
5.279
4.319
4.314
4.309
4.302
2.853
2.838
2.829
2.811
2.796
2.779
2.586
2.580
2.574
2.568
2.557
2.550
2.545
2.538
2.529
2.527
2.510
2.499
2.488
2.476
2.371
2.360
2.353
2.348
2.330
1.292
1.255
3.41
3.40
1.10
2.24
1.10
1.05
0.88
1.10
1.00
ppm

200.885
151.785
119.038
61.747
43.249
37.197
29.630
27.801
26.162
O
Br
55
(CDCl3, 125 MHz)
ppm
220
200
180
160
140
120
100
80
60
40
20
0

OTBS
S1
(CDCl3, 500 MHz)
ppm
9
8
7
6
5
4
3
2
1
0
2.00
0.85
1.04
1.03
2.09
1.27
1.08
3.24
3.20
9.41
5.79
4.686
3.279
3.271
3.260
3.252
2.227
2.219
2.201
2.193
2.178
2.169
2.118
2.108
2.100
2.091
2.082
1.755
1.746
1.737
1.729
1.720
1.712
1.704
1.694
1.684
1.676
1.668
1.595
1.589
1.574
1.570
1.566
1.554
1.546
1.543
1.528
1.520
1.304
1.296
1.290
1.280
1.273
1.265
1.256
1.242
1.233
1.075
0.990
0.890
0.022

OTBS
S1
(CDCl3, 125 MHz)
155.466
107.082
77.952
42.563
32.296
31.127
25.892
25.178
24.319
20.791
-4.069
-4.928
ppm
220
200
180
160
140
120
100
80
60
40
20
0

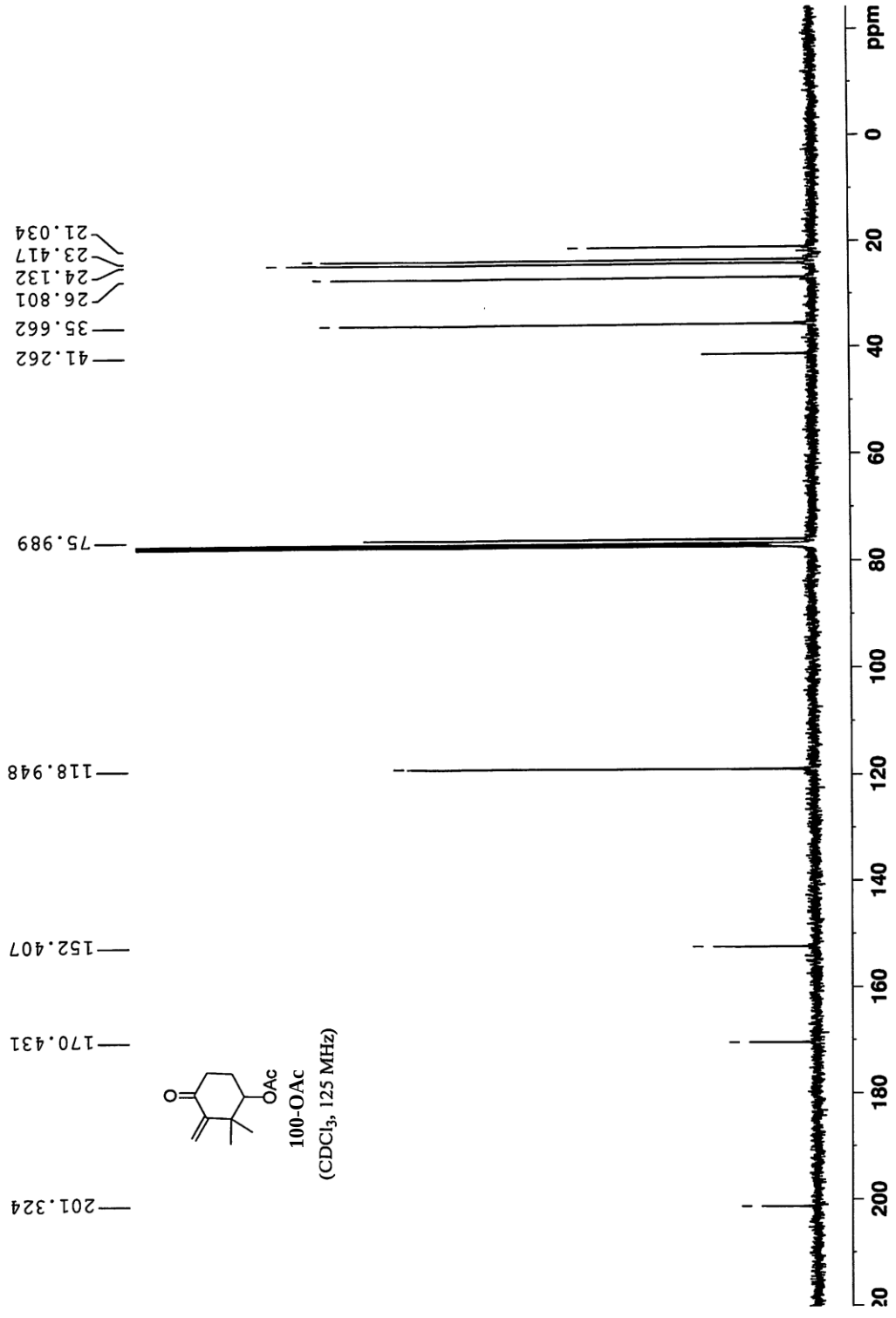
OTBS
O
100-OTBS
(CDCl3, 500 MHz)
5.941
3.131
3.111
9.381
0.971
0.991
1.041
1.011
0.881
1.001
0.921
ppm

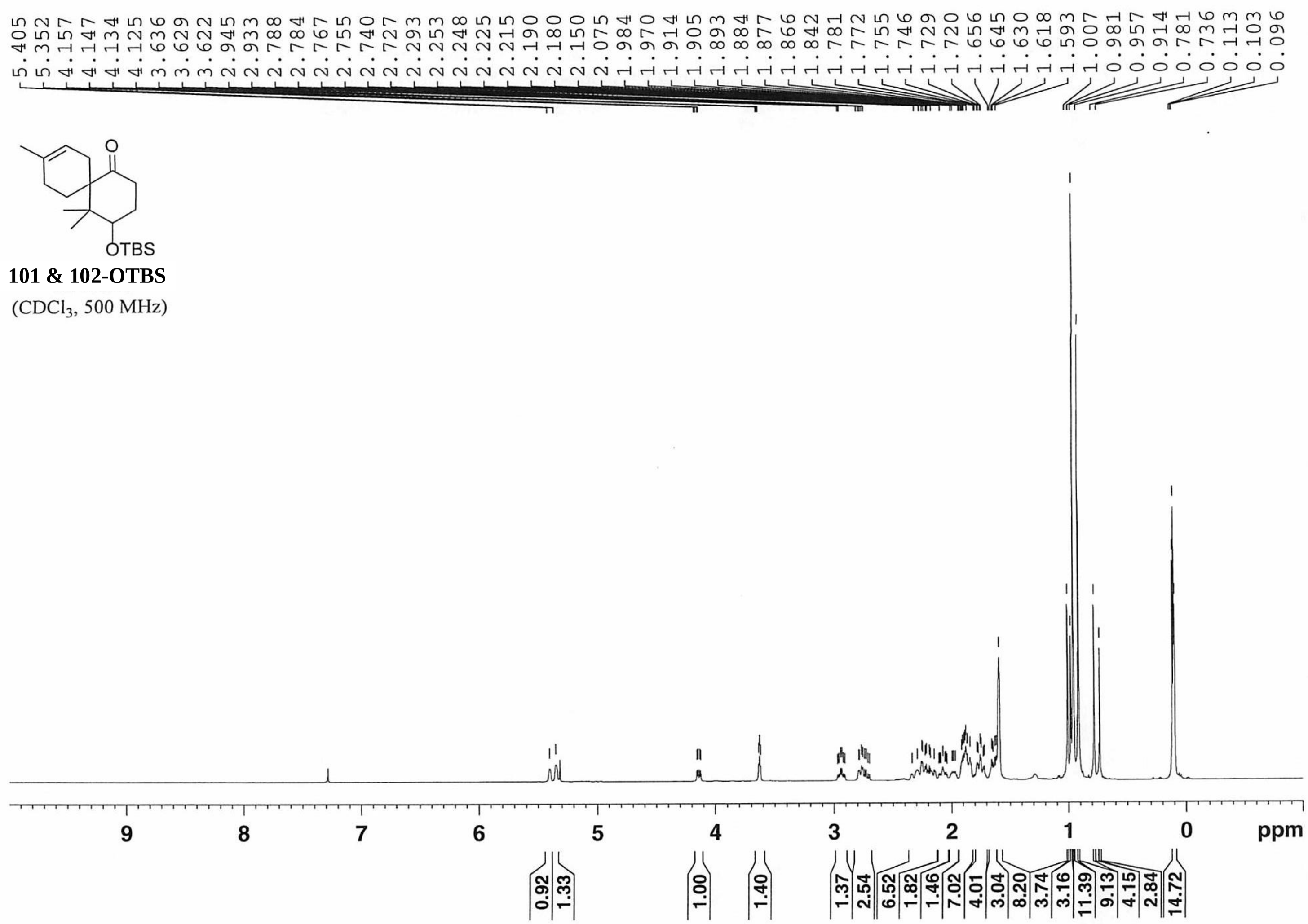
100-OTBS
($CDCl_3$, 125 MHz)

OMe
100-OMe
(CDCl3, 500 MHz)
5.786
5.227
3.402
3.172
3.164
3.156
2.624
2.607
2.590
2.573
2.556
2.408
2.396
2.385
2.374
2.362
2.351
2.103
2.095
2.087
2.084
2.079
2.043
1.191
1.099
0.91
1.00
2.85
0.89
1.10
1.01
2.22
3.33
3.27
ppm

202.520
153.348
118.176
83.840
57.324
42.448
35.476
27.299
23.513
21.868
OMe
O
100-OMe
(CDCl3, 125 MHz)
ppm
20
0
20
40
60
80
100
120
140
160
180
200
20

OAc
O
100-OAc
(CDCl3, 500 MHz)
5.843
5.266
4.945
4.939
4.932
4.926
2.616
2.602
2.597
2.582
2.567
2.563
2.549
2.498
2.486
2.474
2.464
2.451
2.439
2.213
2.207
2.200
2.194
2.188
2.184
2.181
2.178
2.175
2.171
2.165
2.159
2.152
2.146
2.083
2.073
2.059
2.044
2.039
2.030
ppm
9
8
7
6
5
4
3
2
1
0
1.00
1.08
0.90
1.10
1.08
1.16
2.96
1.17
3.35
3.33

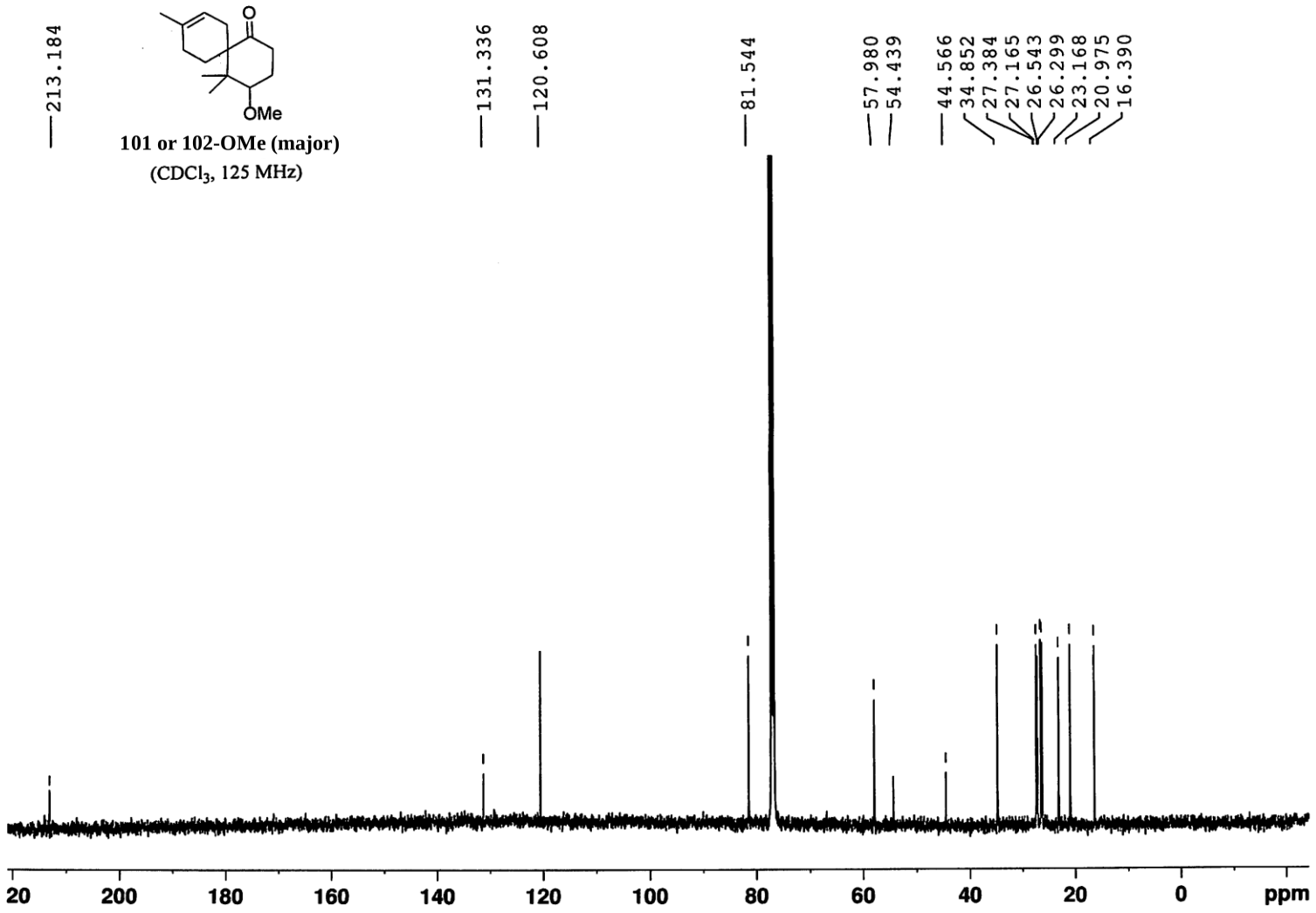

201.324
170.431
152.407
118.948
75.989
41.262
35.662
26.801
24.132
23.417
21.034
OAc
O
100-OAc
(CDCl3, 125 MHz)
ppm
0
20
40
60
80
100
120
140
160
180
200



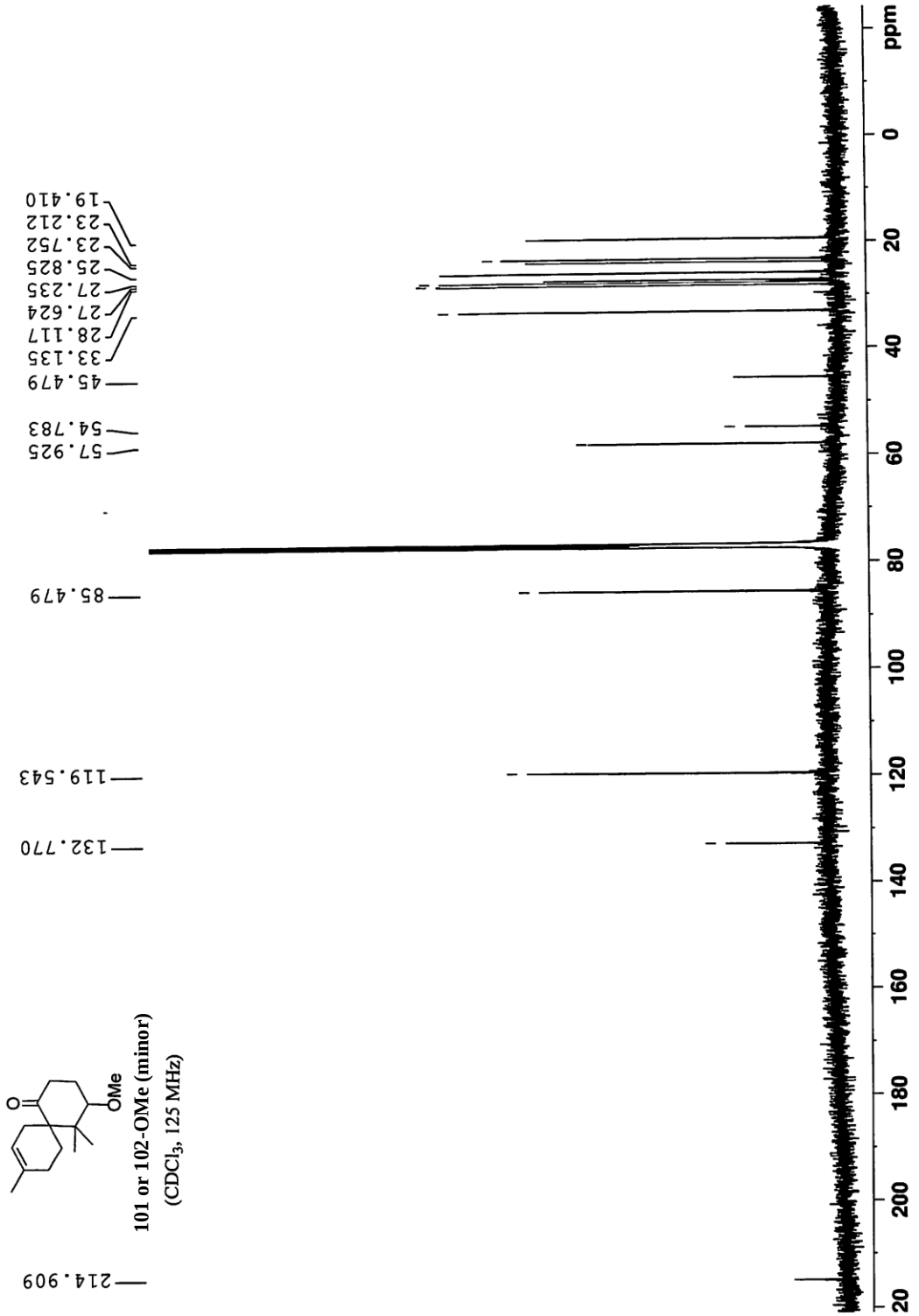
101 & 102-OTBS
($CDCl_3$, 500 MHz)

214.971
213.211
132.626
131.304
120.639
119.529
76.352
72.530
54.823
54.423
45.672
44.919
35.043
32.980
31.410
31.359
28.109
27.630
27.370
27.091
26.682
25.845
25.813
23.656
23.200
21.687
20.048
18.051
15.999
-3.976
-4.421
OTBS
O
101 & 102-OTBS
(CDCl3, 125 MHz)
ppm
20
0
20
40
60
80
100
120
140
160
180
200

OMe
O
101 or 102-OMe (major)
(CDCl3, 500 MHz)
1.00
3.25
3.29
3.67
2.39
1.22
2.48
1.51
3.56
1.14
1.09
3.09
PF
0
1
2
3
4
5
6
7
8
9
1.808
1.618
1.621
1.631
1.637
1.641
1.643
1.721
1.730
1.747
1.756
1.772
1.782
1.830
1.865
2.109
2.114
2.118
2.139
2.238
2.254
2.264
2.277
2.308
2.652
2.666
2.681
2.694
2.708
2.721
3.401
3.548
3.557
3.571
3.580
5.387


213.184
131.336
120.608
81.544
57.980
54.439
44.566
34.852
27.384
27.165
26.543
26.299
23.168
20.975
16.390
OMe
101 or 102-OMe (major)
(CDCl3, 125 MHz)
20
200
180
160
140
120
100
80
60
40
20
0
ppm

O
OMe
101 or 102-OMe (minor)
(CDCl3, 500 MHz)
5.332
3.377
3.060
3.053
3.045
2.854
2.841
2.829
2.817
2.804
2.792
2.608
2.604
2.599
2.582
2.577
2.572
2.261
2.227
2.196
2.186
2.176
2.171
2.161
2.151
2.094
2.084
2.073
2.065
2.056
2.045
2.035
2.002
1.996
1.992
1.986
1.978
1.972
1.968
1.962
1.950
1.944
1.940
ppm
0.89
2.97
1.00
1.04
1.12
1.11
1.12
1.17
1.15
1.18
1.14
1.21
3.63
3.22
3.21


101 or 102-OMe (minor)
(CDCl3, 125 MHz)
OMe
O
214.909
132.770
119.543
85.479
57.925
54.783
45.479
33.135
28.117
27.624
27.235
25.825
23.752
23.212
19.410
ppm

OAc
O
101 & 102-OAc
(CDCl3, 500 MHz)
ppm
9
8
7
6
5
4
3
2
1
0
1.55
1.00
1.07
0.80
1.10
1.24
2.74
2.36
4.11
2.64
2.53
1.84
7.31
6.01
3.76
2.91
5.414
5.404
5.390
5.380
5.329
4.992
4.981
4.973
2.840
2.826
2.812
2.798
2.784
2.770
2.724
2.712
2.699
2.691
2.686
2.678
2.665
2.446
2.420
2.376
2.362
2.350
2.317
2.280
2.247
2.242
2.217
2.212
2.133
2.077
2.011
1.976
1.964
1.952
1.935
1.865
1.792
1.782
1.765

213.456
212.056
170.670
170.371
133.143
131.463
120.228
118.832
76.264
73.944
54.655
54.387
44.308
43.254
34.734
33.498
28.062
27.956
27.851
27.320
27.230
27.059
26.305
26.152
23.129
22.758
21.319
21.166
20.795
18.820
16.848
O
OAc
101 & 102-OAc
(CDCl3, 125 MHz)
ppm
220
200
180
160
140
120
100
80
60
40
20
0

5.263
5.254
4.672
4.663
4.650
4.641
2.768
2.760
2.753
2.739
2.730
2.724
2.718
2.710
2.521
2.515
2.506
2.501
2.497
2.494
2.492
2.488
2.485
2.481
2.471
2.465
2.445
2.436
2.415
2.333
2.312
2.300
2.283
2.278
2.227
2.224
2.213
2.210
2.201
2.187
1.907
1.897
1.875
1.865
1.859
1.570
1.545
1.531
1.524
1.519
1.510
1.505
1.498
1.484
1.095
0.974
Br
O
56
(CDCl3, 500 MHz)
ppm
0
1
2
3
4
5
6
7
8
9
2.97
3.00
1.03
3.02
1.04
1.11
1.03
2.52
2.24
0.95
0.88
0.78

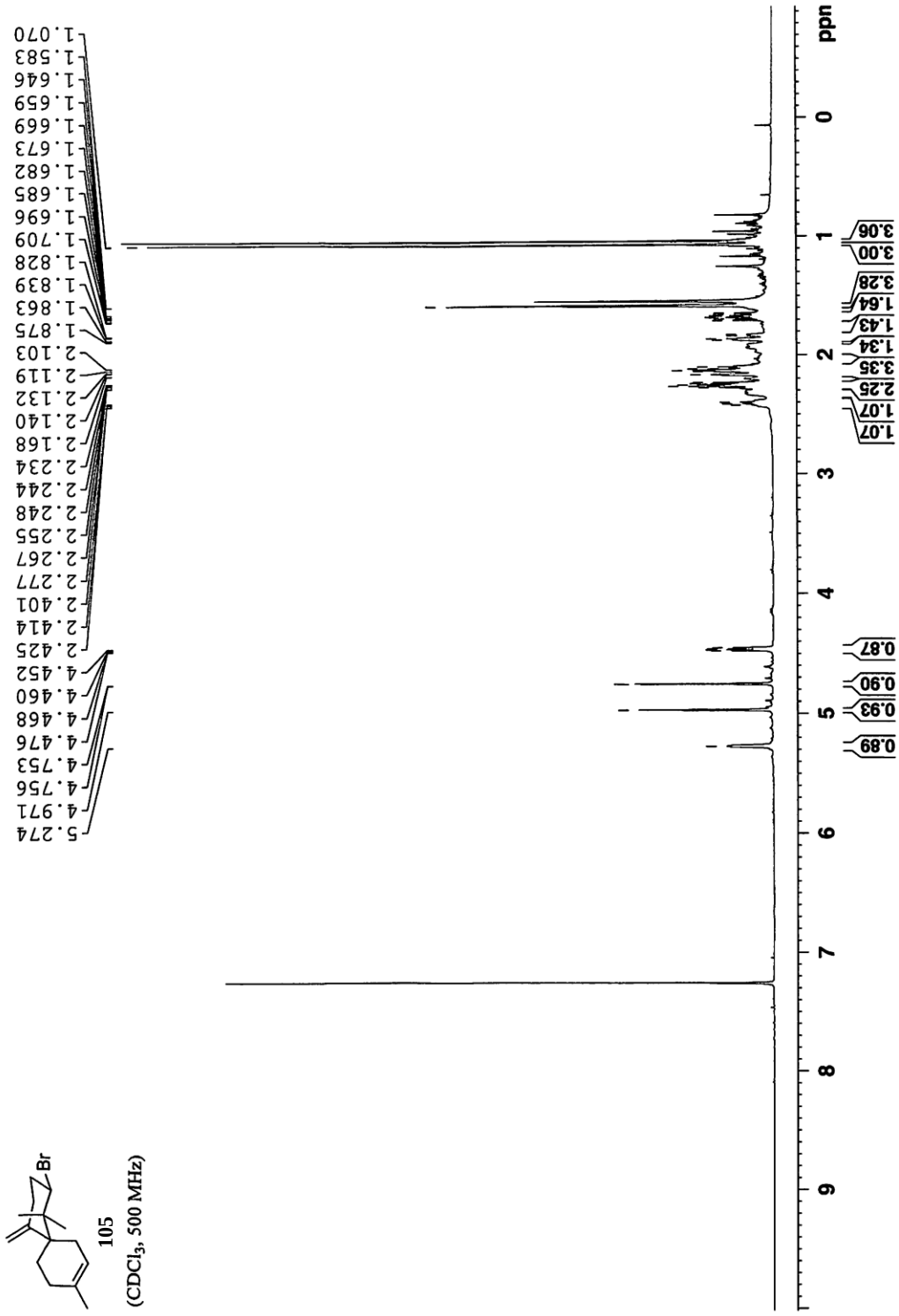
211.989
135.701
116.553
61.149
55.211
45.552
37.383
34.032
29.187
28.475
24.692
24.210
23.021
18.494
Br
O
56
(CDCl3, 125 MHz)
ppm

5.375
4.818
4.809
4.793
4.783
2.838
2.825
2.820
2.808
2.795
2.778
2.768
2.765
2.512
2.506
2.499
2.490
2.486
2.477
2.467
2.386
2.355
2.264
2.245
2.242
2.177
2.173
2.168
2.151
2.147
2.142
1.950
1.913
1.868
1.838
1.828
1.812
1.802
1.785
1.776
1.622
1.587
1.155
0.898
Br
O
57
(CDCl3, 500 MHz)
9
8
7
6
5
4
3
2
1
0
ppm
0.86
0.94
1.09
1.09
1.09
1.19
2.19
1.12
2.26
1.14
0.82
3.35
3.00
3.04

210.704
120.540
131.166
61.085
56.049
45.029
37.701
33.898
27.425
27.257
26.983
24.315
23.078
17.648
Br
O
57
(CDCl3, 125 MHz)
ppm

104
(CDCl3, 500 MHz)
5.380
1.932
1.896
1.891
1.884
1.871
1.866
1.861
1.837
1.830
1.743
1.732
1.723
1.716
1.706
1.697
1.686
1.677
1.618
1.546
1.536
1.527
1.518
1.508
1.500
1.489
1.378
1.368
1.362
1.353
1.074
0.75
4.85
2.11
2.87
1.07
1.00
6.05
1.03
ppm

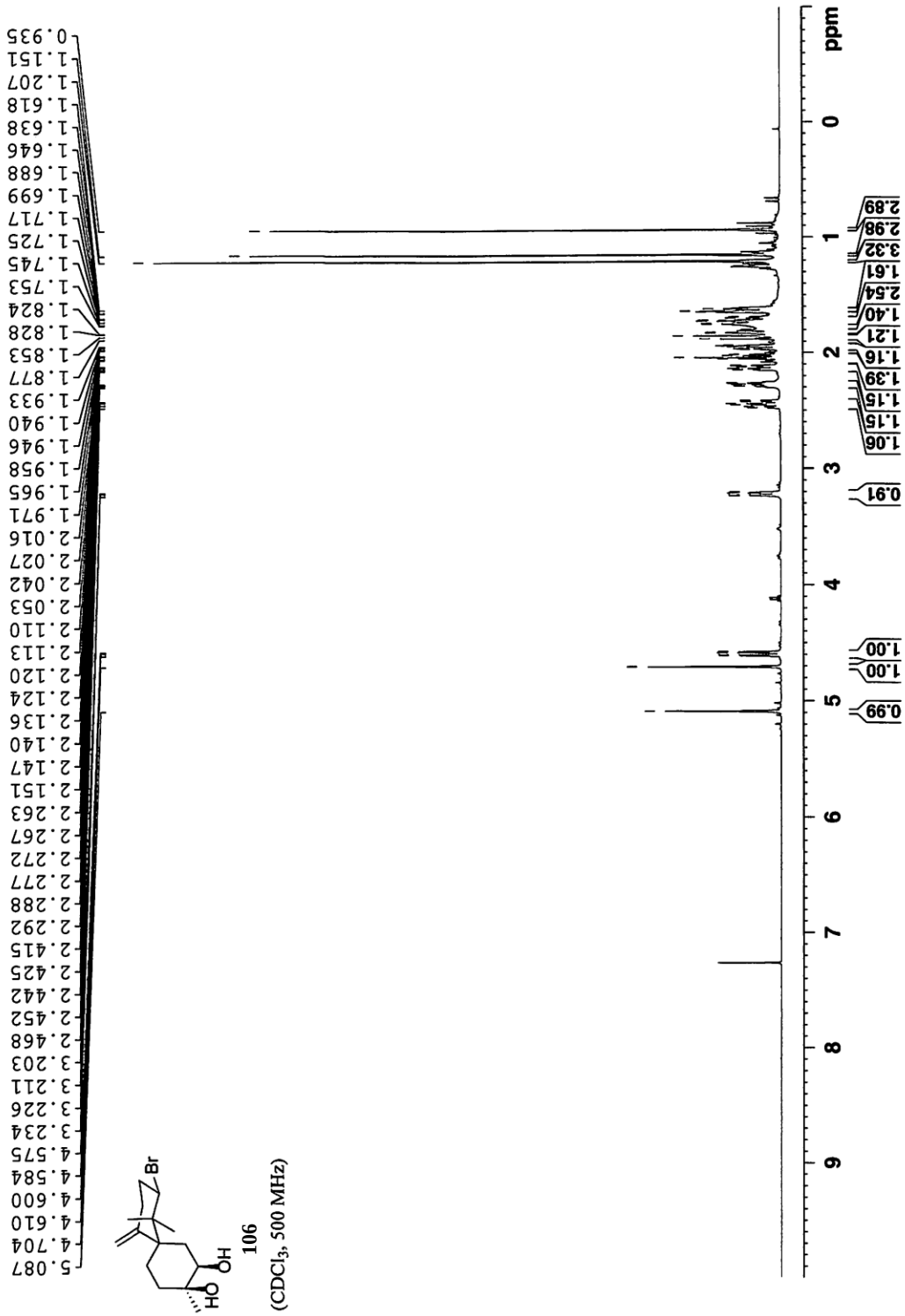
216.829
132.814
119.592
49.260
40.259
33.772
30.964
29.867
28.231
28.082
27.865
23.023
22.626
14.169
104
(CDCl3, 125 MHz)
ppm
220
200
180
160
140
120
100
80
60
40
20
0


Br
105
(CDCl3, 500 MHz)
ppm
0
1
2
3
4
5
6
7
8
9
1.070
1.583
1.646
1.659
1.669
1.673
1.682
1.685
1.696
1.709
1.828
1.839
1.863
1.875
2.103
2.119
2.132
2.140
2.168
2.234
2.244
2.248
2.255
2.267
2.277
2.401
2.414
2.425
4.452
4.460
4.468
4.476
4.753
4.756
4.971
5.274
0.87
0.90
0.93
0.89
1.07
1.07
2.25
3.35
1.34
1.43
1.64
3.28
3.00
3.06

Br
105
(CDCl3, 125 MHz)
147.568
133.226
118.726
111.114
66.135
46.125
43.117
35.479
31.480
29.171
28.239
26.178
24.400
23.086
20.982
ppm

1 : (±)-10-β-bromo-chamigrene
($CDCl_3$, 500 MHz)
Br
5.281
4.932
4.664
4.655
4.638
4.630
4.612
2.395
2.385
2.367
2.358
2.340
2.330
2.248
2.218
2.213
2.209
2.162
2.157
2.152
2.148
2.135
2.130
2.125
2.121
2.071
2.061
2.045
2.034
2.018
1.883
1.863
1.767
1.736
1.623
1.594
1.590
1.569
1.099
0.935
ppm
1.00
1.00
0.94
1.01
1.18
2.30
1.35
2.52
1.35
1.39
2.21
3.46
3.00
3.02

Br
1 : (±)-10-β-bromo-chamigrene
(CDCl3, 125 MHz)
145.645
132.711
119.705
112.623
66.104
47.061
42.745
35.704
33.059
30.348
27.564
25.628
23.845
23.115
17.493
20
200
180
160
140
120
100
80
60
40
20
0
ppm


Br
OH
H
106
(CDCl3, 500 MHz)
ppm
0.99
1.00
1.00
0.91
1.06
1.15
1.15
1.39
1.16
1.21
1.40
2.54
1.61
3.32
2.98
2.89

Br
HO
H
106
(CDCl3, 125 MHz)
146.323
113.117
72.209
71.014
64.946
49.293
43.867
36.286
34.208
33.872
32.373
27.103
23.651
23.412
17.226
ppm
20
0
20
40
60
80
100
120
140
160
180
200

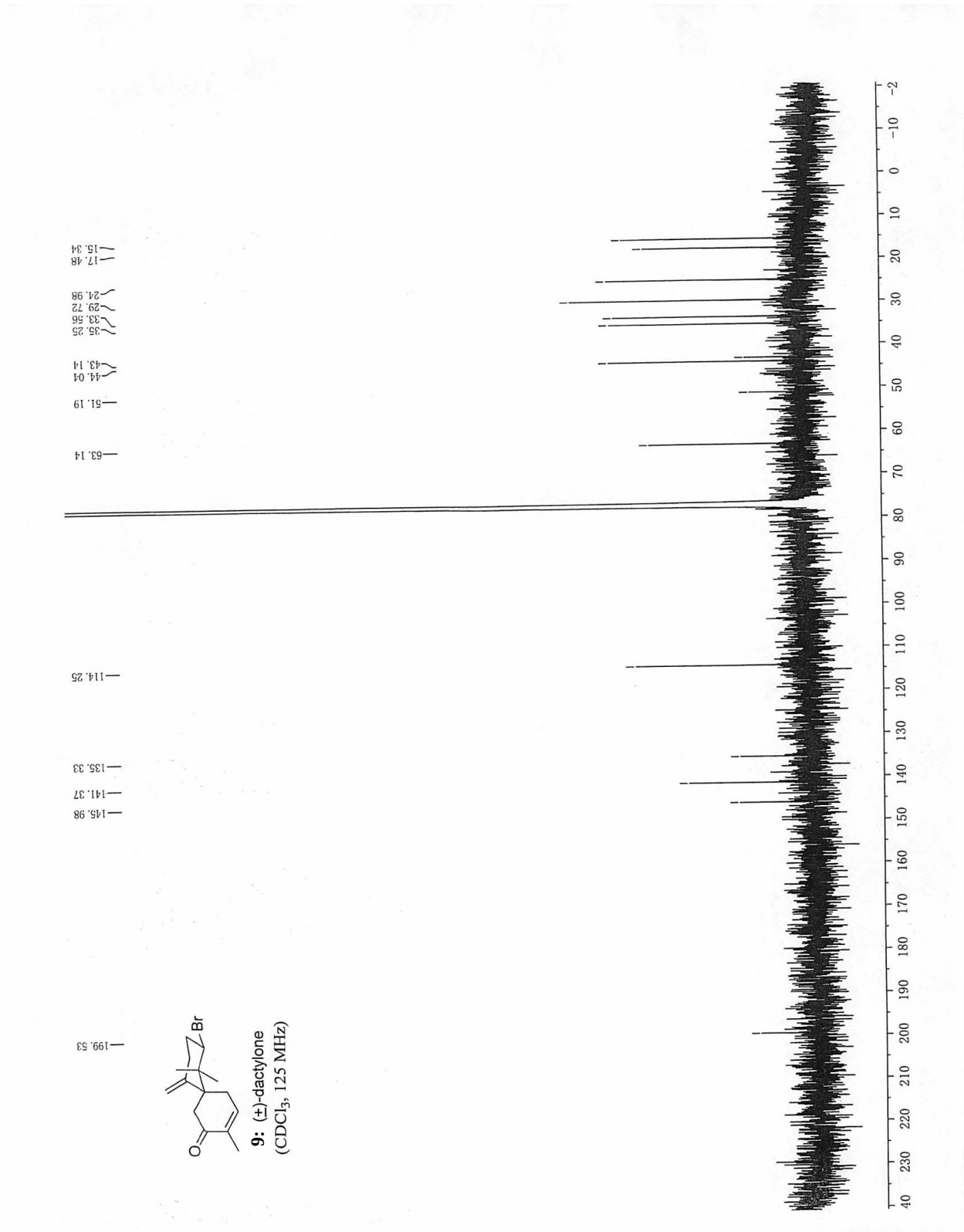
5.124
4.846
4.601
4.591
4.575
4.566
3.755
3.745
3.732
3.722
2.338
2.322
2.312
2.287
2.277
2.270
2.267
2.255
2.245
2.242
2.115
2.102
2.077
2.053
2.043
2.028
2.017
1.937
1.916
1.910
1.889
1.883
1.732
1.726
1.702
1.679
1.653
1.593
1.587
1.580
1.565
1.558
1.552
1.213
1.156
0.968
Br
HO
HO
7
(CDCl3, 500 MHz)
ppm
0
1
2
3
4
5
6
7
8
9
0.96
0.98
0.94
1.00
2.09
2.22
2.20
1.11
1.50
2.42
3.50
3.04
2.81

Br
HO
HO
7
(CDCl3, 125 MHz)
147.032
113.656
71.795
70.616
64.940
49.806
43.784
36.139
33.779
33.374
33.317
27.265
23.706
22.665
17.542
ppm

6.627
6.623
6.620
4.982
4.536
4.494
4.484
4.468
4.459
2.818
2.814
2.789
2.784
2.692
2.687
2.682
2.656
2.650
2.644
2.627
2.542
2.531
2.505
2.494
2.423
2.413
2.396
2.386
2.270
2.265
2.261
2.256
2.245
2.239
2.235
2.230
2.220
2.164
2.159
2.154
2.149
2.135
2.130
2.126
2.121
2.083
2.073
2.057
2.047
2.031
2.021
1.704
1.702
1.194
0.995
Br
O
8: (±)-10-epi-dactylone
(CDCl3, 500 MHz)
ppm
0
1
2
3
4
5
6
7
8
9
0.91
1.00
1.06
0.98
1.04
2.32
1.32
1.29
1.45
1.22
1.40
3.12
3.31
3.12

198.397
144.083
143.089
134.470
114.729
63.636
51.667
43.035
35.258
32.488
31.636
24.745
17.225
15.295
Br
O
8: (±)-10-epi-dactylone
(CDCl3, 125 MHz)
ppm
0
20
40
60
80
100
120
140
160
180
200
220

9: (±)-dactylone
(CDCl3, 500 MHz)
Br
O
ppm
0.90
1.00
0.99
0.96
1.17
2.19
1.15
1.24
1.27
1.37
1.07
3.13
3.18
3.15



9: (±)-dactylone
($CDCl_3$, 125 MHz)

CHAPTER 3

SYNTHETIC STUDIES OF THE FUNGAL METABOLITE

HOMODIMERICIN A

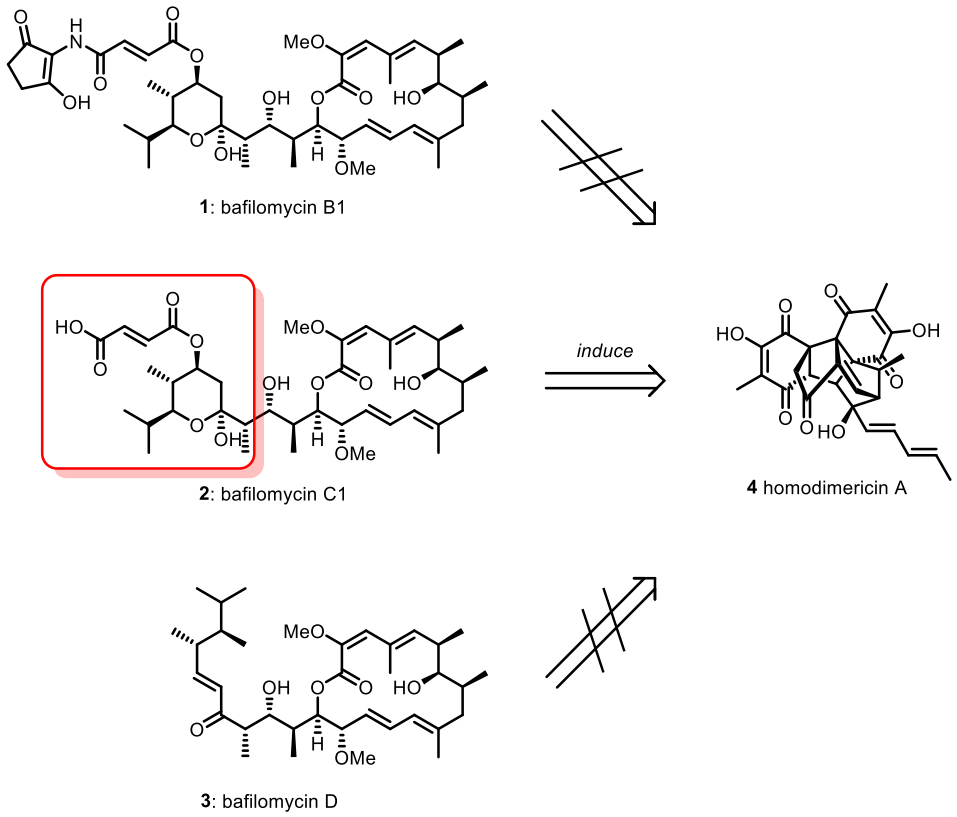
3.1 Introduction

Bacteria and fungi in a confined space often compete for resources through bioactive molecules they secrete. For example, the historical molecule penicillin was generated from fungi *penicillum* to inhibit bacteria's DD-transpeptidase to disrupt cell wall biosynthesis resulting in cell death. On the other hand, bacteria can produce active ingredients to damage fungi. Bafilomycins are a family of macrolide antibiotics produced from a variety of *Streptomycetes* (included in targets of penicillin).[1] These molecules are found to be antifungal, plausibly due to their ability of acting as ionophores in transporting potassium ions across the cell membrane and leading to mitochondria damage and cell death. On the other hand, fungi developed their defense mechanism to protect themselves against these attacks from bacteria. Some of the rebellions are antibacterial, whereas some are produced to attenuate the effect of antifungals, such as homodimericin A.

3.1.1 Origin and structure of homodimericin A

In September 2016, Clardy et al reported that the soil fungus *T. Harzianum* produced a yellow pigment when elicited by bacteria strand *Streptomyces* sp. 4231.[2] This yellow pigment was found to contain the secondary metabolite homodimericin A (Scheme 3-1, **4**), the structure of which was later illuminated by extensive NMR studies coupled with structure-predicting software ACD/Laboratories Computer-Assisted Structure Elucidation (CASE) and other computational tools. The highly congested hexacyclic structure of this molecule looked formidable but the biogenetic analysis *vide infra* degrades its complexity. Further investigation into how it was generated revealed that only bafilomycin C1 (**2**)[3] was capable of inducing generation of homodimericin A (**4**) while other bafilomycins such as bafilomycin B1 (**1**) and D (**3**) failed to do so (Scheme 3-1). Clardy and co-workers did not provide an explanation for this selectivity, but they did suggest homodimericin A is a direct response to "oxidation stress" since the proposed

biosynthesis involve multiple oxidation events. Additionally, the racemic nature of homodimericin A implied that its generation may be nonenzymatic.



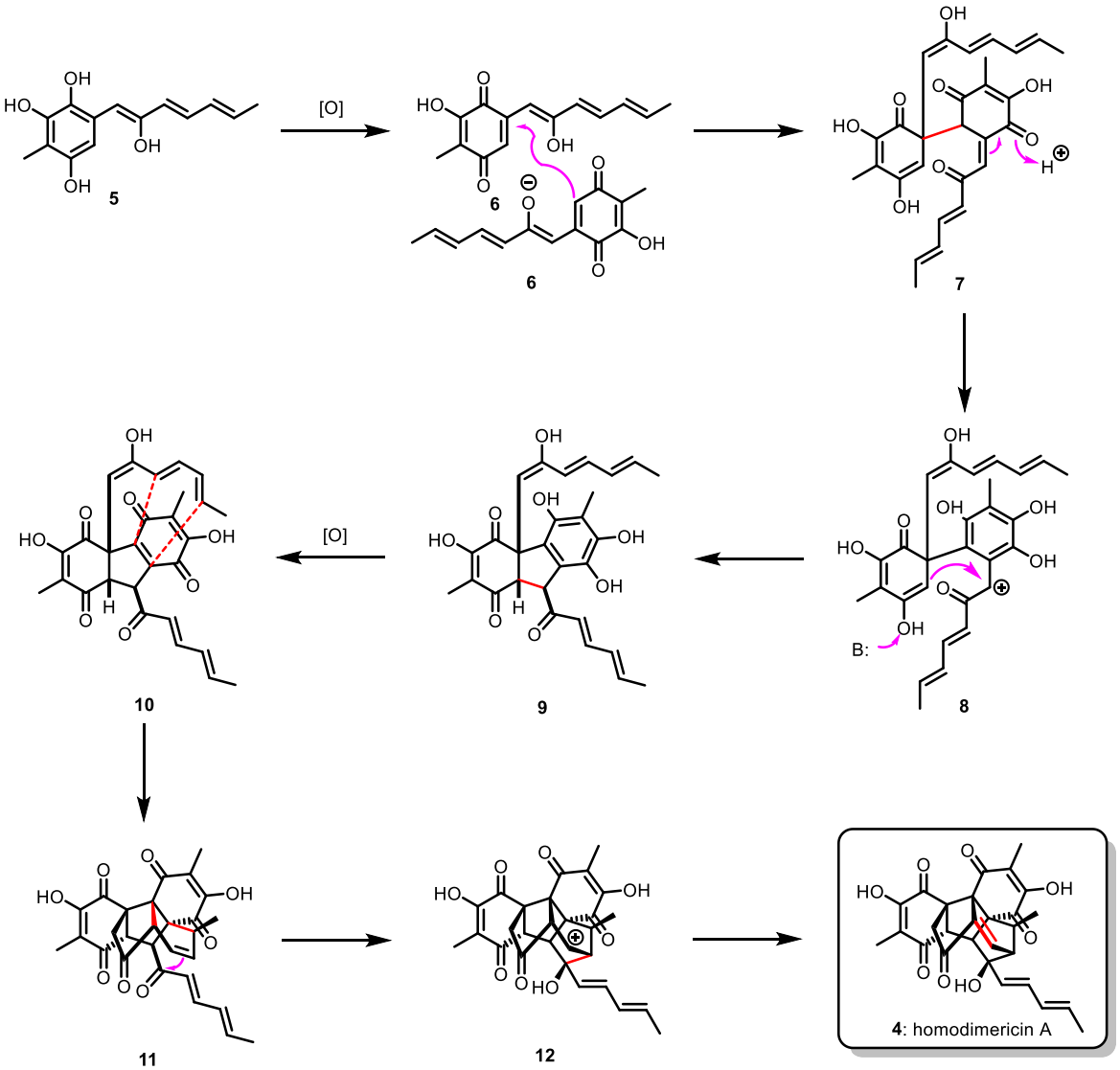
Scheme 3-1. Selective generation of homodimericin A (**4**) induced by bafilomycin C1 (**2**)

Clardy et al also tested homodimericin A in various assays but failed to discover any significant antibacterial or antifungal activities. This phenomenon strongly indicated that homodimericin A is more of a defensive metabolite than offfensive. It is believed that the fungi benefit more from the process of generating homodimericin A to relief oxidative stress, rather than to rely on any potential bioactivity of this molecule.

3.1.2 The proposed biosynthesis of homodimericin A

The proposed biosynthesis of homodimericin A (**4**) from Clardy et al is described in Scheme 3-2. Monomer **5**, consisting of a multi-substituted phenol and a sorbic-like diene-none,

was first oxidized to quinone monomer **6**. Upon deprotonation of one molecule of **6**, the γ-carbon becomes nucleophilic enough to attack the quinone of a second monomer of **6**, thus dimerizing via the red carbon-carbon bond in **7**. Protonation and rearomatization of **7** would then generate the benzylic carbocation intermediate **8**, in which the enol attacks the α-carbocation to close the five-membered ring, forming the stable tricyclic intermediate **9**. The second oxidation event is then proposed to take place on the right-hand phenol ring of **9**. The so-formed quinone can then act as a dienophile to undergo an intramolecular Diels-Alder reaction (IMDA), forming the key cage structure of homodimericin A (**4**). The endocyclic alkene rising from the IMDA is then spacially accessible to the adjacent carbonyl and a subsequent ene reaction can occur forming the last C-C bond formation of homodimericin A.



Scheme 3-2. The biogenesis of homodimericin A (**4**) proposed by Clardy *et al*.

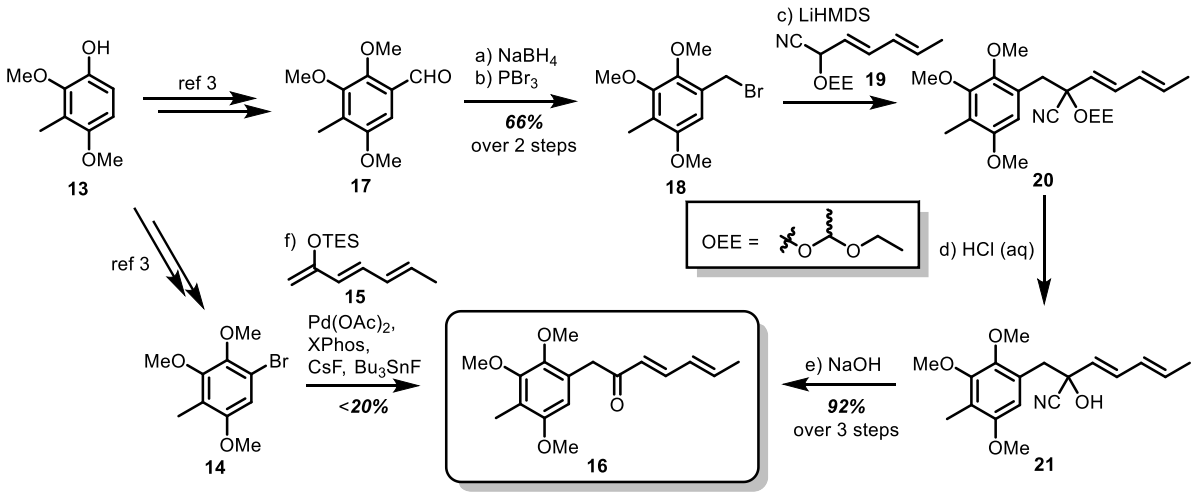
In general, this is a highly detailed and reasonable biosynthetic proposal. The key topological reactions, including dimerization, IMDA, and ene reaction, are almost the only feasible approaches toward this structurally complex molecule. Therefore, we hoped to pursue a biomimetic synthesis of this structurally complex molecule.

3.2. Exploration of a biomimetic approach

The biomimetic synthesis would be divided into two phases. 1) devise a rapid and scalable synthesis of monomer **5** or its protected form; 2) probe dimerization conditions and subsequent decorations that can ultimately shape homodimericin A.

3.2.1 A scalable synthesis of a protected monomer

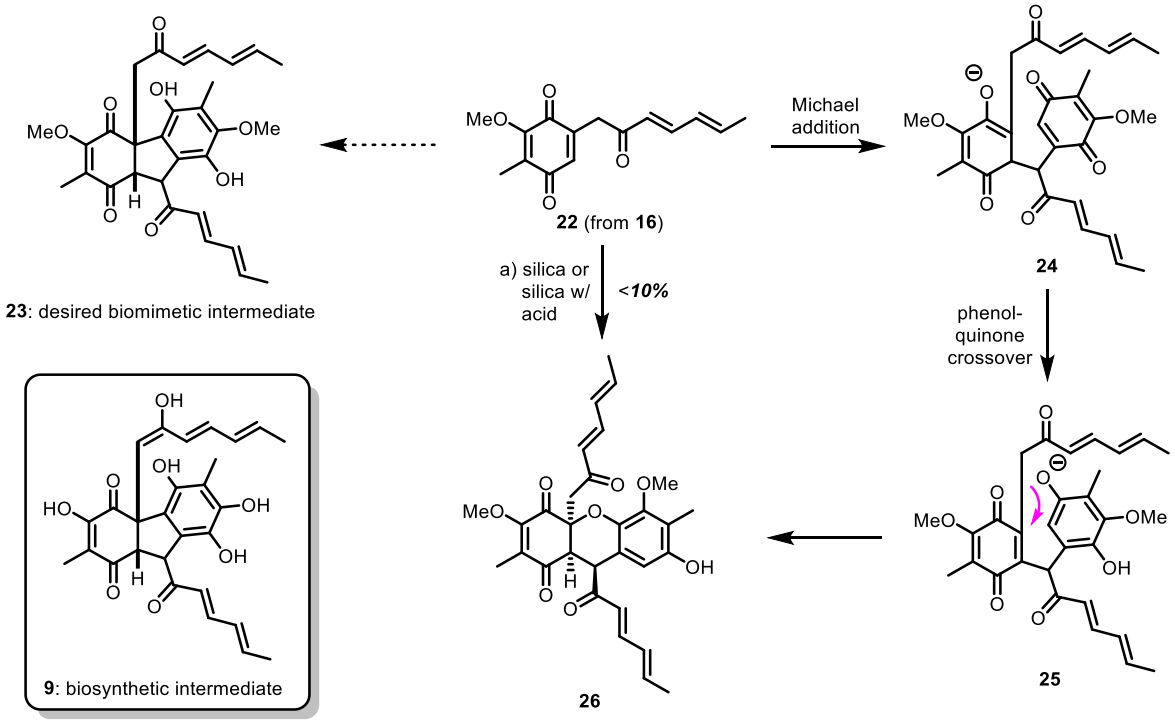
Upon consideration of protecting group selection and the projected ease of various synthetic routes, we decided to pursue a synthesis toward the fully methylated version of biogenetic monomer **5**. To reach the tri-methyl protected monomer **16**, we prepared the known compound **14** and **17** from phenol **13** (Scheme 3-3).[3,4] A Kuwajima-Urabe coupling protocol was attempted on aryl bromide **14**,[5] with conjugated silyl enol ether **15**, but the desired product was isolated in poor yield, along with several inseparable impurities. The scalability of this reaction was unsatisfactory as well, forcing us to seek an alternative solution. One possibility lay in an umpolung substitution between benzyl bromide and a nucleophilic carbonyl surrogate. To probe this route, multi-substituted benzyl bromide **18** was synthesized from known aldehyde **17** in two steps. Upon deprotonation of protected cyanohydrin **19** by LiHMDS at -78 ^{o}C, electrophile **18** was added to capture the carbanion to form coupling product **20**. Two steps of acidic and basic hydrolysis revealed the free carbonyl in the desired monomer **16**. This route allowed for deca-gram scale preparation of materials in which the *E*-isomer was the major component (*E*/*Z* = 5:1).



Scheme 3-3. A scalable synthesis of tri-methyl monomer **16**. Reagents and conditions: a) $NaBH_4$ (0.5 equiv), THF, 0 °C, 30 min; b) PBr_3 (0.5 equiv), Et_2O, 0 °C, 30 min; c) **19** (1.1 equiv), LiHMDS (1.0 M in THF, 1.05 equiv), THF, -78 °C, 15 min, then **18** (1.0 equiv), -78 °C. 30 min; d) HCl (1.5 N), THF/H_2O, 23 °C, 8 h; e) NaOH (1 N), Et_2O/H_2O, 4 h; f) **16** (1.0 equiv), $Pd(OAc)_2$ (0.06 equiv), Xphos (0.11 equiv), CsF (1.4 equiv), Bu_3SnF (1.4 equiv), PhMe, 85 °C, 8 h.

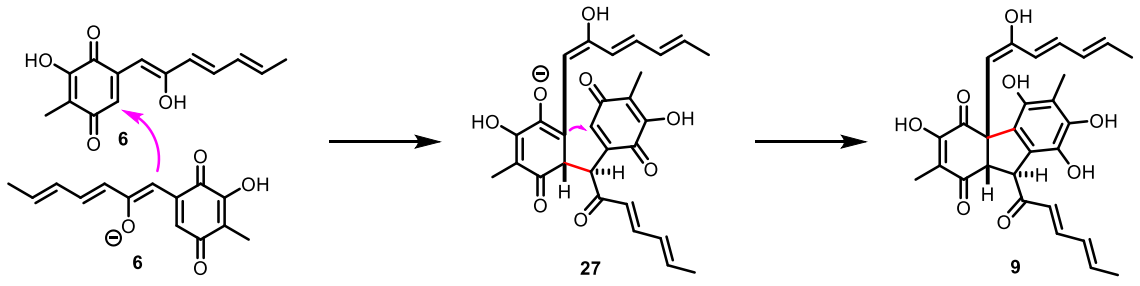
3.2.2 Dimerization trial: a trap of an undesired dimer

Dr. Ming Yang, the collaborator on this project, participated in the dimerization study. He discovered that upon treatment of benzoquinone monomer **22** (obtained by treating **16** with CAN or AgO/HNO_3) by silica gel or silica loaded with acid, dimerization product **26** arose, albeit in low isolated yield (less than 10%, Scheme 3-4). Extensive attempts to elucidate the structure of this compound led to the tentative assignment of a dimer with an embedded six-membered cyclic ether, instead of the desired biomimetic intermediate **23**. A series of transformations were attempted to turn this undesired dimer into **23** but no fruitful results were obtained. From a mechanistic perspective, this undesired dimer may form from the first step in which Michael addition occurred to forge the C-C bond that was proposed to link after the all-carbon quaternary center was constructed. The so formed enolate **24** was in deed a tautomer of phenol. A phenol-quinone crossover would then switch the oxidation state of the two rings, resulting in **25**. The phenoxide then furnished the six-membered ether ring in **26** through an *oxa*-Michael pathway.



Scheme 3-4. Generation of an undesired dimeric compound **26** in the presence of acidic silica. *Reagents and conditions*: a) silica or silica w/acid, neat, 23 °C, 40 h.

Given that the first C-C bond formation could differ from the original biosynthetic proposal, we proposed an alternative biosynthetic pathway of dimerization, as shown in Scheme 3-5. We envisioned that the enolate of one molecule of **6** could attack the less hindered carbon of another molecule of **6**, forming the first C-C bond of intermediate **27** instead of the all-carbon quaternary center proposed by Clardy. The enol generated from this Michael addition would then immediately closes the five-membered ring through a second Michael addition, leading to intermediate **9**.



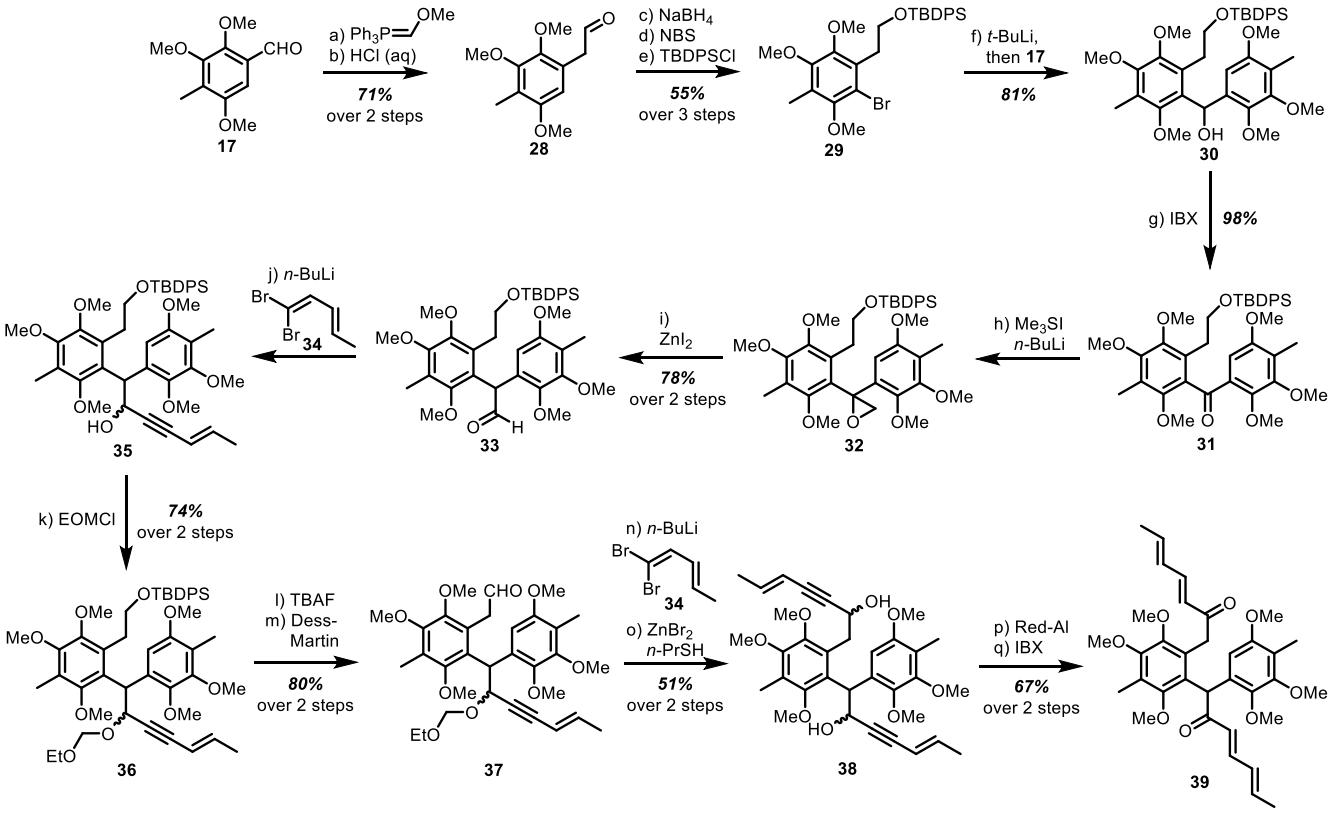
Scheme 3-5. A revised biosynthetic proposal for the dimeric intermediate **9**

The above proposal seems to be more facile, although one forseeable problem is that the final 5-endo-trig cyclization is disfavored according to Baldwin's rules. However, breaking this rule is not impossible, and it can be envisioned that the second cyclization step may proceed through other pathways such as a radical pathway, which is not restricted by Baldwin's rules. From this standing point, we decided to turn to nonbiomimetic synthesis of a protected form of plausible intermediate **27** and then test the second key C-C bond formation to the putative biosynthetic intermediate **9**.

3.3. A nonbiomimetic synthesis of a dimeric intermediate

After extensive probing of various synthetic routes and the screening of parameters of key transformations, we established a robust route toward a protected form of possible biosynthetic intermediate **40** (Scheme 3-6). The synthesis commenced with the substituted benzaldehyde **17** mentioned above. A two-step homologation of **17** afforded aldehyde **28**, which was then reduced by $NaBH_4$, brominated on the aromatic ring and protected with TBDPS to yield elaborate aryl bromide **29**. Lithium-halogen exchange of the aryl bromide **29** with *t*-BuLi generated the corresponding aryllithium anion, which was then quenched by benzaldehyde **17** to yield the coupling product **30**. Using *n*-BuLi in this reaction resulted in incomplete conversion of lithium-halogen exchange. IBX-mediated oxidation of the so-formed secondary alcohol fashioned the diaryl ketone **31**, on which a Corey-Chakovsky reaction and a zinc iodide mediated semi-pinacol rearrangement delivered aldehyde **33**.[6] Installation of the enyne side chain was realized by a nucleophilic addition of *in situ* generated lithium ynoate from gem-dibromide **34**.[7] The same sequence was executed after EOM protection of the propargyl alcohol and transformation of TBDPS ether into aldehyde, on intermediate **37**. The bis-enyne intermediate turned out to be fragile in the presence of aqueous HCl solution when subjected to EOM deprotection. However, a

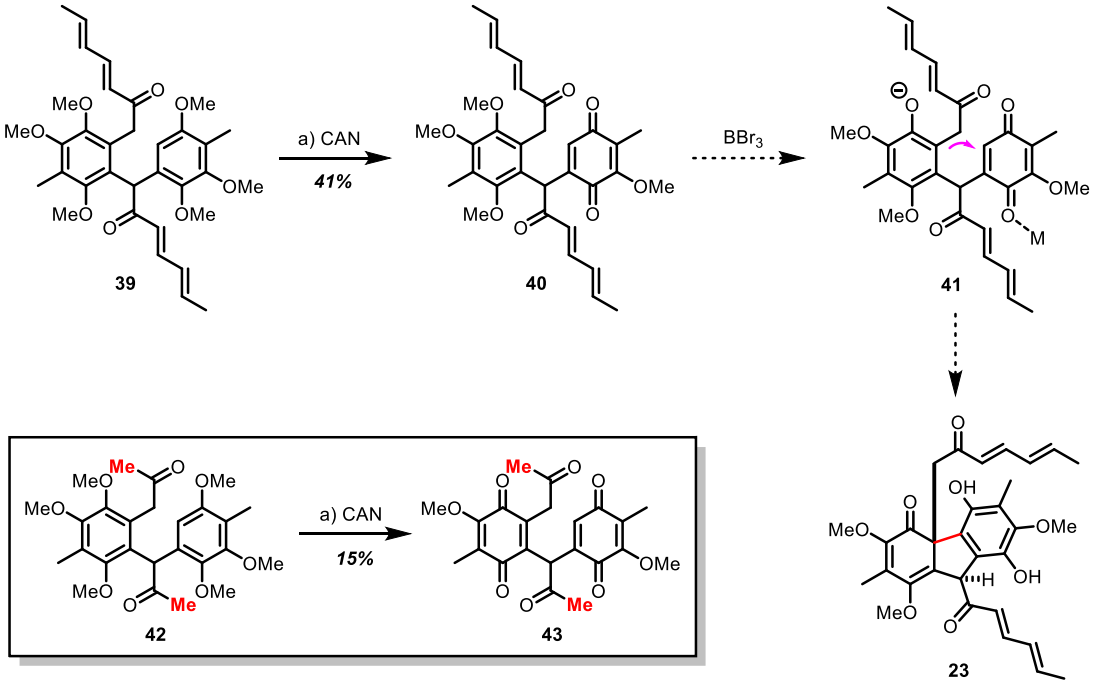
milder protocol using zinc bromide and *n*-propanethiol furnished the desired deprotection product **38**, albeit in moderate yield.[8] Reduction of propargyl alcohol was conducted by using excessive amount of Red-Al and the resultant allylic alcohol was oxidized by IBX to give the full bis-sorbic side chains in compound **39**.



Scheme 3-6. Synthesis of dimeric intermediate **39**. *Reagents and conditions*: a) $MeOCH_2PPh_3$ (1.25 equiv), KHMDS (0.5 M in PhMe, 1.2 equiv), THF, -40 °C, 1 h, then **17** (1.0 equiv), -40 °C, 2 h, slowly to 0 °C, 2 h; b) HCl (2 N), THF/H_2O, 55 °C, 8 h; c) $NaBH_4$ (0.5 equiv), THF/MeOH, 0 °C, 30 min; d) NBS (1.1 equiv), CH_2Cl_2, 23 °C, 10 h; e) TBDPSCl (1.1 equiv), imidazole (2.0 equiv), CH_2Cl_2, 23 °C, 2 h; f) *t*-BuLi (1.7 M in pentane, 2.1 equiv), Et_2O, -78 °C, 5 min, then **17** (1.05 equiv), -78 °C, 15 min; g) IBX (1.2 equiv), DMSO, 23 °C, 16 h; h) Me_3SI (6.0 equiv), *n*-BuLi (2.5 M in hexanes, 5.0 equiv), THF, 0 °C, 15 min, then **31** (1.0 equiv), slowly warm to 23 °C, 30 min; i) ZnI_2 (1.0 equiv), PhH, 23 °C, 15 min; j) **34** (1.8 equiv), *n*-BuLi (2.5 M in hexanes, 3.6 equiv), THF, -78 °C, 45 min, then 23 °C, 25 min, then **33** (1.0 equiv), -78 °C, 30 min, slowly to 23 °C, 8 h; k) EOMCl (3.0 equiv), *i*$PrNEt_2$ (10.0 equiv), CH_2Cl_2, 23 °C, 24 h; l) TBAF (1.0 M in THF, 8.0 equiv), THF, 55 °C, 12 h; m) Dess-Martin periodinane (1.1 equiv), $NaHCO_3$ (3.0 equiv), CH_2Cl_2, 23 °C, 1 h; h) **34** (1.85 equiv), *n*-BuLi (2.5 M in hexanes, 3.7 equiv), THF, -78 °C, 45 min, then 23 °C, 25 min, then **37** (1.0 equiv), -78 °C, 30 min, slowly to 23 °C, 8 h; o) $ZnBr_2$ (1.07 equiv), nPrSH (2.13 equiv), CH_2Cl_2, 0 °C, 1.5 h, slowly warm to 23 °C, 30 min; p) Red-Al (60% in PhMe, 12.0 equiv), THF, 66 °C, 1 h; q) IBX (2.8 equiv), DMSO, 23 °C, 16 h.

The oxidation of **39** by cerium(IV) ammonium nitrate (CAN) proceeded with an unexpected selectivity, as shown in Scheme 3-7. The right-hand aromatic ring was oxidized to the corresponding benzoquinone ring while the left-hand per-methylated arene remained intact in the presence of this strong oxidizer. The presence of sorbic side chains were highly susceptible for the

cause, since the di-methyl analogue **42**, was fully oxidized to bis-benzoquinone within the same environment. Nevertheless, the selectivity helped differentiate the two aromatic rings and provided an opportunity to deprotect the methoxy group, revealing an anion (**41**), and promoting a nucleophilic attack on the right-hand benzoquinone to forge the five-membered core ring of the desired biomimetic dimer **23**. We tried preliminarily deprotection reactions with boron tribromide (BBr_3), but only yielded a messy mixture with no successful product identification.



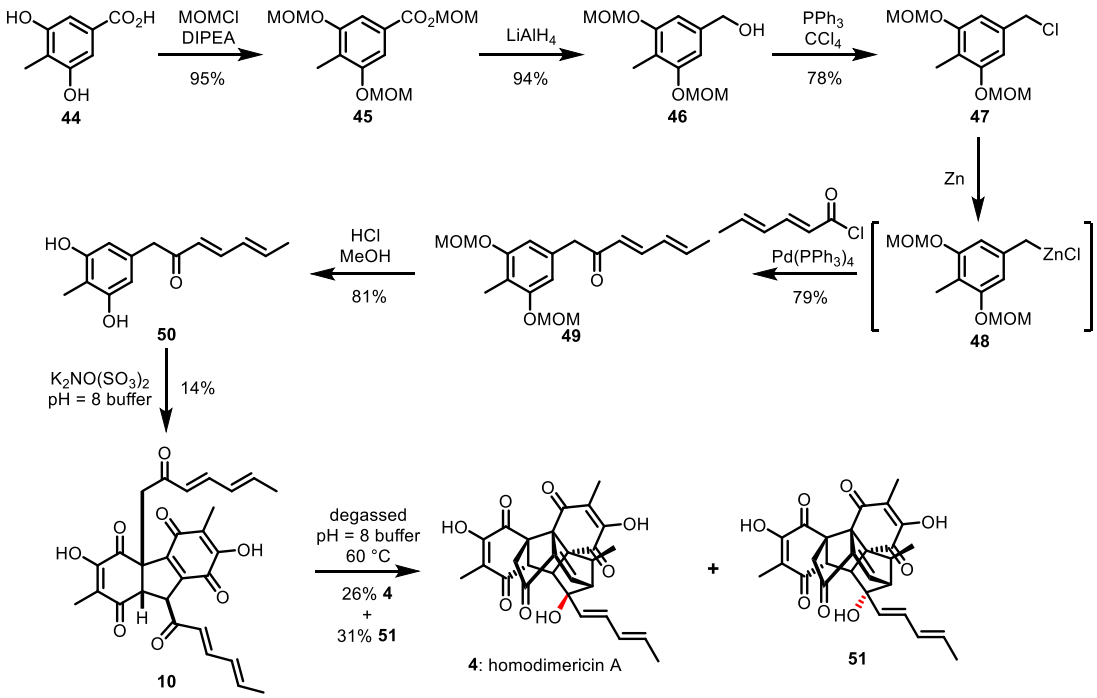
Scheme 3-7. A selective mono-oxidation to benzoquinone **40**. *Reagents and conditions*: a) Cerium (IV) ammonium nitrate (CAN, 3.0 or 6.0 equiv), CH_3CN/H_2O, 0 °C, 15 min.

3.4. Suspension of the project

Like what happened Chapter 2, at this chronological point, three papers of biomimetic synthesis of homodimericin A came out on *Angewandt Chemie* (again), leading to the termination of this project. We use the final space of this chapter to introduce their syntheses and our related results obtained independently.

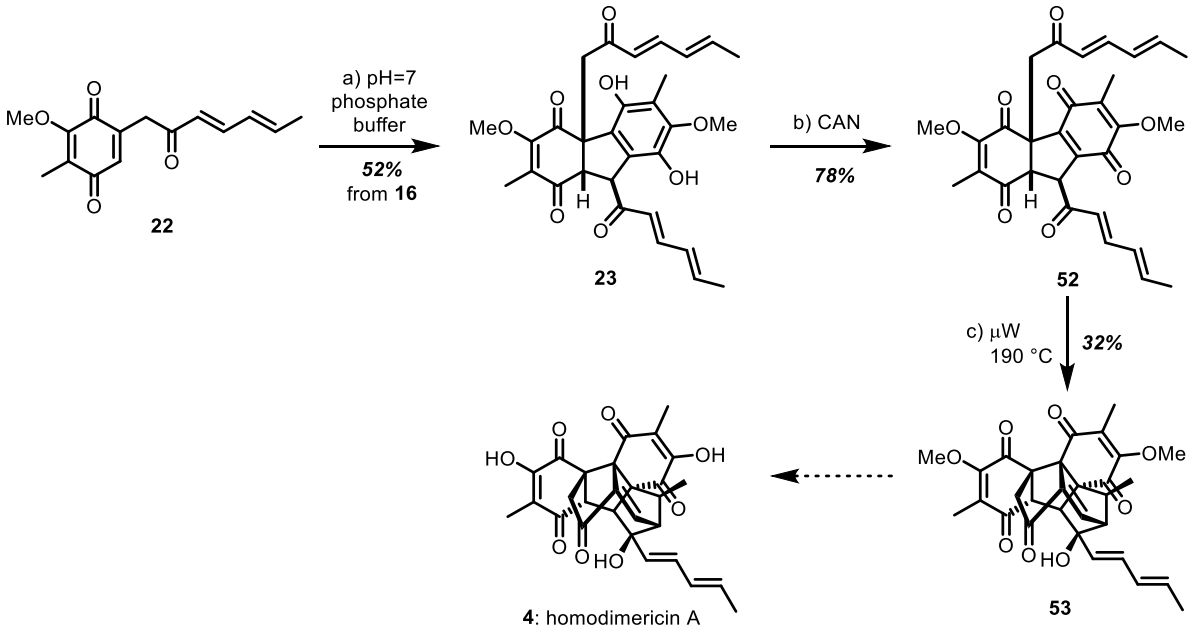
3.4.1 Wang's biomimetic synthesis of homodimericin A and our revisit to dimerization event

The first total synthesis of homodimericin A was reported by Z. Wang on May 11th, 2017 (Scheme 3-8). [9] Their synthesis featured a preparation of protected monomer **49** by Negishi coupling using benzylic zinc reagent **48** and sorbic acid chloride. After removal of two MOM protecting groups, the phenol **50** was exposed to Fremy's salt to give the corresponding benzoquinone monomer, which dimerized smoothly in pH=8 phosphate buffer to yield the proposed biosynthetic intermediate **10**. In a slightly basic media and elevated temperature (60 °C), IMDA and the subsequent ene reaction occurred to afford homodimericin A (**4**) and its 8-epimer **51** in a ratio close to 1:1. It was worth noting that exposure of a solution of benzoquinone monomer in pH=8 buffer to air gave rise to 9% yield of homodimericin A too, accompanied by 8% of 8-epimer. The feasibility of this biomimetic synthesis supported the nonenzymatic hypothesis of homodimericin A's origin, except that 8-*epi*-homodimericin A should then also be present in natural isolates due to the non-selective nature of the ene reaction.



Scheme 3-8. Wang's biomimetic synthesis of homodimericin A with a nonprotected momomer

Inspired by the facile dimerization event reported by Wang, we attempt to use pH=7 buffer on the methyl protected monomer **22**. A different dimer arose this time in moderate isolated yield, as indicated by Scheme 3-9. We tentatively assigned this dimer as the desired dimer and subjected this dimer to CAN-mediated oxidation. The so-obtained benzoquinone intermediate **52** was then exposed to a microwave condition under high temperature (190 ^{o}C). A cycloaddition product with a tertiary alcohol appeared, with several features corresponding to the desired biomimetic intermediate **23**. However, when we obtained **53**, two syntheses from Tang and Yang were published (their routes are descrived *vide infra*). Although we confirmed that we accessed the correct compounds by comparing to the same compounds in their syntheses, our results were too similar to Tang and Yang for publications. Therefore, this project was terminated.

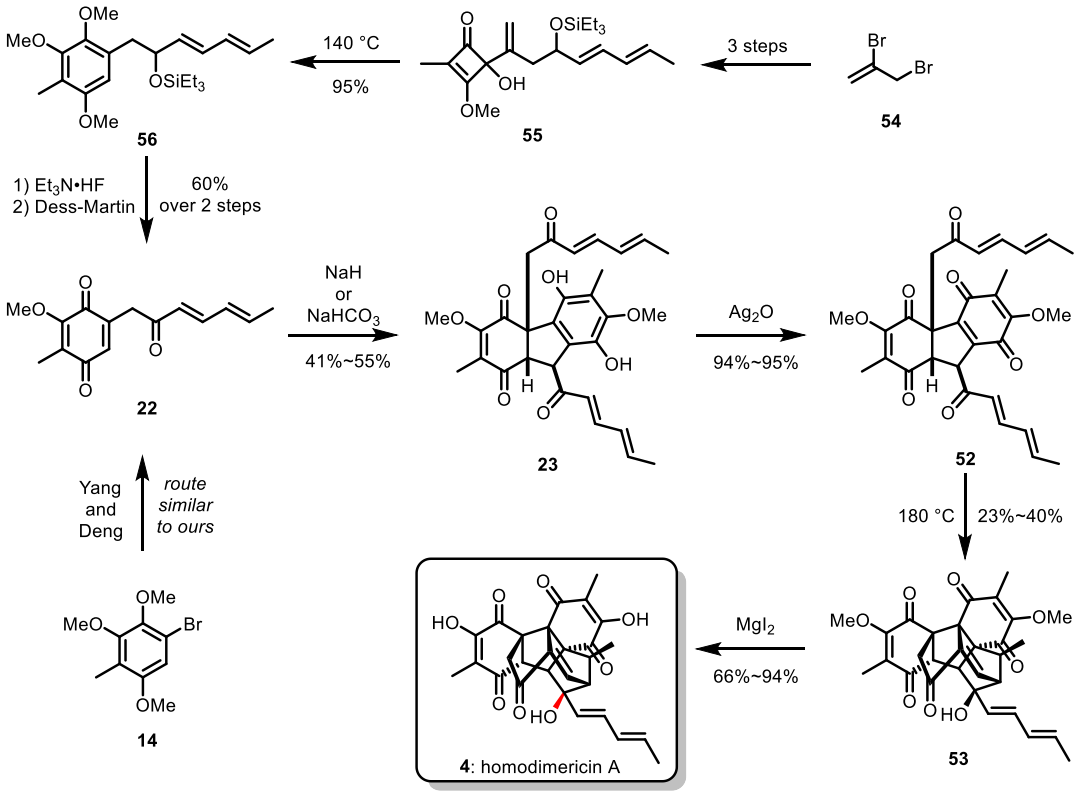


Scheme 3-9. Our biomimetic dimerization and synthesis of a protected form **53** of homodimericin A inspired by Wang's synthesis. *Reagents and conditions*: a) pH=7 phosphate buffer/acetone, 23 °C, 12 h; b) CAN (2.0 equiv), MeCN/H_2O, 0 °C, 1h; c) PhCl, 190 °C, microwave, 30 min.

3.4.2 Tang and Yang's bio-inspired synthesis of homodimercin A with protected monomers

One week after Wang published the first synthesis of homodimericin A, Tang and Yang reported their synthesis featuring the methyl protected monomer **16** (Scheme 3-10).[10,11] While Yang's synthesis of monomer highly resembled our route, Tang employed a thermal Moore rearrangement protocol on cyclobutenenone substrate **55** to harvest the ring-expansion product **56**, which was then transformed into benzoquinone monomer **22** in 2 steps.

The dimerization reaction condition they reported (NaH) was different to what we independently explored (pH=7 buffer). Oxidation of the phenol ring in **23** gave bis-benzoquinone **52**, on which the proposed IMDA and ene reaction took place under heating (180 ^{o}C), with concomitant generation of multiple migration or rearrangement side products. Although the conditions they employed were slightly different, the overall chemical transformations are the same. The last deprotection of OMe was conducted with magnesium iodide in the presence or absence of quinoline to yield homodimericin A (**4**). Deng published a similar synthesis of this molecule later featuring a $NaHCO_3$-promoted dimerization reaction soon after these three papers.[12]



Scheme 3-10. Tang, Yang, and Deng's bioinspired synthesis of homodimericin A employing a monomer **22** that we probed independently

3.5 Summary and outlook

In conclusion, we have developed an efficient synthesis of biomimetic monomer 22. Though initial dimerization attempts led to the undesired dimer, we were able to then develop a chemical synthetic route to access a dimeric intermediate **40** with a single C-C bond constructed. The investigation of transforming **40** to **23** was suspended due to the released publications of homodimericin A.

3.6 Experimental section

General Procedures. All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Dry tetrahydrofuran (THF), toluene,

dimethylformamide (DMF), diethyl ether (Et_2O) and dichloromethane (CH_2Cl_2) were obtained by passing commercially available pre-dried, oxygen-free formulations through activated alumina columns. Yields refer to chromatographically and spectroscopically (^1H and ^{13}C NMR) homogeneous materials, unless otherwise stated. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Reactions were magnetically stirred and monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent, and an ethanolic solution of phosphomolybdic acid and cerium sulfate, and heat as developing agents. SiliCycle silica gel (60, academic grade, particle size 0.040–0.063 mm) was used for flash column chromatography. Preparative thin-layer chromatography separations were carried out on 0.50 mm E. Merck silica gel plates (60F-254). NMR spectra were recorded on Bruker 400, 500 and 700 MHz instruments and calibrated using residual undeuterated solvent as an internal reference. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, br = broad, app = apparent. IR spectra were recorded on a Perkin-Elmer 1000 series FT-IR spectrometer. High-resolution mass spectra (HRMS) were recorded on Agilent 6244 Tof-MS using ESI (Electrospray Ionization), APCI (atmospheric pressure chemical ionization), or Mixed (ionization by both ESI and APCI) at the University of Chicago Mass Spectroscopy Core Facility.

Abbreviations. EtOAc = ethyl acetate, THF = tetrahydrofuran, DMSO = dimethyl sulfoxide, TMSCN = trimethylsilyl cyanide, MeCN = acetonitrile, LiHMDS = lithium bis(trimethylsilyl)amide, KHMDS = potassium bis(trimethylsilyl)amide, NBS = *N*-bromosuccinimide, TBDPSCl = t-butyldiphenylsilyl chloride, IBX = 2-iodoxybenzoic acid, DIPEA = diisopropylethylamine, EOMCl = ethoxymethyl chloride, TBAF = tetrabutylammonium

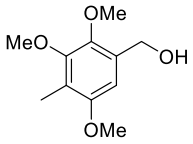
fluoride, Red-Al® = sodium bis(2-methoxyethoxy)aluminum hydride, CAN = ammonium cerium(IV) nitrate.

Protected cyanohydrin 19. Prepared according to the method described by Takahashi, et al.[13] To a flask loaded with sorbic aldehyde (*trans*,*trans*-2,4-hexadienal, 1.09 mL, 10.0 mmol, 1.0 equiv) and TMSCN (1.50 mL, 12.0 mmol, 1.2 equiv) was added K_2CO_3 (42 mg, 0.3 mmol, 0.03 equiv) at 23 °C. The reaction mixture was stirred at 23 °C for 36 h. Upon completion, MeCN (50 mL) was added to dilute the mixture, followed by addition of 1 N HCl (50 mL). The reaction mixture was stirred at 23 °C for 1 h (Caution: HCN generated!). Then the reaction content was poured into a separatory funnel with H_2O (20 mL). The aqueous layer was extracted with EtOAc (20 mL × 2). The combined organic layers were washed sequentially by saturated aqueous $NaHCO_3$ solution (20 mL) and brine (20 mL), dried ($MgSO_4$), filtered, and concentrated to give the crude cyanohydrin as a light yellowish oil. Pressing forward without any purification, the cyanohydrin was dissolved in CH_2Cl_2 (6 mL). Ethyl vinyl ether (1.92 mL, 20.0 mmol, 2.0 equiv) was added and the mixture was cooled to 0 °C. Camphorsulfonic acid (139 mg, 0.6 mmol, 0.06 equiv) was added as solid at this temperature. The reaction was stirred at 23 °C for 1 h. Upon completion, the reaction contents were quenched by the addition of saturated aqueous $NaHCO_3$ solution (10 mL) and extracted with CH_2Cl_2 (10 mL × 2). The combined organic layers were washed by brine (15 mL), dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography (silica gel, hexanes/EtOAc, 40/1) to afford **19** as a light yellowish oil (1.56 g, 80%, dr=1:1). **19**: R_f = 0.52 (silica gel, hexanes/EtOAc, 3/1); IR (film) ν_{max} 3439 (br), 2980, 2917, 1660, 1445, 1140, 1081, 1053, 1025, 988, 931 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.45 (td, *J* = 16.1, 10.5 Hz, 1 H), 6.05 (dd, *J* = 21.6, 11.0 Hz, 1 H), 5.86 (dq, *J* = 13.7, 6.7 Hz, 1 H), 5.58–5.44

(m, 1 H), 4.98 (dd, *J* = 30.5, 5.7 Hz, 1 H), 4.87 (dd, *J* = 15.0, 6.0 Hz, 1 H), 3.73–3.59 (m, 1 H), 3.58–3.44 (m, 1 H), 1.78 (d, *J* = 6.5 Hz, 3 H), 1.37 (dd, *J* = 19.0, 5.4 Hz, 3 H), 1.21 (td, *J* = 7.0, 2.8 Hz, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 135.8, 135.7, 134.0, 133.9, 129.3, 129.3, 121.4, 121.3, 117.9, 117.2, 99.3, 98.7, 63.1, 62.6, 61.0, 60.9, 19.5, 18.1, 15.1, 14.9; HRMS (Mixed+) calcd for $C_{11}H_{17}NO_2^+$ [M + Na^+] 218.1151, found 218.1116.

Compound 16. To a solution of protected cyanohydrin **19** (784 mg, 4.02 mmol, 1.05 equiv) in THF (16 mL) was added LiHMDS (1 M in THF, 4.02 mL, 4.02 mmol, 1.05 equiv) dropwise over 3 min at -78 °C. The reaction mixture was stirred at this temperature for 30 min. Then a solution of substituted benzyl bromide **18** (1052 mg, 3.82 mmol, 1.0 equiv) in THF (3 mL) was added at -78 °C and the reaction was kept at this temperature for a further 15 min. Saturated aqueous NH_4Cl solution (10 mL) was added to quench the reaction and the aqueous layer was extracted with Et_2O (10 mL × 2). The combined organic layers were dried, filtered and concentrated to give the crude coupling product as a yellowish oil. Pressing forward without purification, the crude coupling product was dissolved in THF (12 mL), 1 N HCl (12 mL) was added and the reaction was stirred at 23 °C for 8 h. Upon pouring the reaction contents into a separatory funnel, the aqueous layer was extracted with Et_2O (10 mL × 2). The combined organic layer was dried, filtered, and concentrated to give the crude coupled cyanohydrin as a yellowish oil. Pressing forward without purification, the coupled cyanohydrin was dissolved in Et_2O (12 mL) and 1 N NaOH (12 mL) was added at 0 °C. The reaction mixture was stirred at 23 °C for 3 h. Upon completion, the reaction contents were poured into a separatory funnel, and the aqueous layer was extracted with Et_2O (10 mL × 2). The combined organic layers were washed by brine (15 mL), dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography (silica gel,

hexanes/EtOAc, 20/1 to 15/1) to afford **16** as a light yellowish oil (1.02 g, 92%, dr=9:1). **16**: R_f = 0.40 (silica gel, hexanes/EtOAc, 3/1); IR (film) ν_{max} 2937, 1684, 1637, 1595, 1488, 1465, 1404, 1330, 1242, 1189, 1130, 1088, 1034, 1001 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.25 (dd, *J* = 16.1, 9.2 Hz, 1 H), 6.40 (s, 1 H), 6.18 (dd, *J* = 6.3, 2.1 Hz, 2 H), 6.13 (d, *J* = 15.3 Hz, 1 H), 3.81 (s, 3 H), 3.80 (s, 3 H), 3.77–3.73 (m, 6 H), 2.11 (s, 3 H), 1.85 (d, *J* = 5.0 Hz, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 198.1, 154.0, 151.9, 145.1, 143.5, 140.4, 130.4, 126.7, 125.6, 119.9, 107.4, 60.6, 60.1, 55.7, 42.3, 18.7, 8.8; HRMS (APCI+) calcd for $C_{17}H_{22}O_4^+$ [M + H^+] 291.1591, found 291.1601.



S1

Compound S1. To a solution of the substituted benzaldehyde **17** (1000 mg, 4.76 mmol, 1.0 equiv) in THF (12 mL) and MeOH (3 mL) was added $NaBH_4$ (95 mg, 2.38 mmol, 0.5 equiv) as solid at 0 °C. The reaction mixture was stirred at this temperature for 30 min. Upon completion, the reaction was quenched by the addition of 1 N HCl (20 mL). The aqueous layer was extracted with Et_2O (10 mL × 2). The combined organic layers were washed by saturated aqueous $NaHCO_3$ solution (15 mL), dried ($MgSO_4$), filtered, concentrated to afford **S1** as a colorless oil (996mg, 99%). **S1**: R_f = 0.30 (silica gel, hexanes/EtOAc, 3/1); IR (film) ν_{max} 3406 (br), 2937, 2834, 1588, 1486, 1464, 1406, 1328, 1242, 1189, 1130, 1092, 1033, 1004, 983, 916, 843, 703 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.59 (s, 1 H), 4.66 (s, 2 H), 3.84 (s, 3 H), 3.81 (s, 3 H), 3.79 (s, 4 H), 2.12 (s, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.2, 151.7, 144.8, 131.3, 120.4, 105.4, 61.4, 60.9, 60.2, 55.8, 8.8; HRMS (Mixed+) calcd for $C_{11}H_{16}O_4^+$ [M + Na^+] 235.0941, found 235.0932.

Benzyl bromide 18. To a solution of alcohol **S1** (996 mg, 4.74 mmol, 1.0 equiv) in Et_2O (12 mL) was added PBr_3 (0.22 mL, 2.37 mmol) dropwise over 2 min at 0 °C. The reaction mixture was stirred at this temperature for 30 min. Upon completion, the reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (15 mL). The aqueous layer was extracted with Et_2O (10 mL × 2). The combined organic layers were washed by brine (15 mL), dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography (silica gel, hexanes/EtOAc, 20/1) to afford **18** as a colorless oil (867 mg, 67%). **18**: R_f = 0.56 (silica gel, hexanes/EtOAc, 3/1); IR (film) ν_{max} 2937, 2835, 1486, 1465, 1405, 1335, 1247, 1224, 1132, 1088, 1032 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.58 (s, 1 H), 4.56 (s, 2 H), 3.92 (s, 3 H), 3.82 (s, 3 H), 3.81 (s, 4 H), 2.13 (s, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.1, 152.0, 145.4, 128.4, 122.2, 106.8, 60.8, 60.2, 55.8, 28.8, 8.8; HRMS (Mixed+) calcd for $C_{11}H_{15}BrO_3^+$ [M + H^+] 275.0277, found 275.0285.

Aldehyde 28. To a suspension of methoxymethyltriphenylphosphonium chloride (2.20 g, 6.44 mmol, 1.25 equiv) in THF (20 mL) was added KHMDS (0.5 M in PhMe, 12.4 mL, 6.18 mmol, 1.2 equiv) dropwise over 3 min at -20 °C. The reaction mixture was stirred at this temperature for 30 min. Then the reaction was cooled to -40 °C. A solution of benzaldehyde **17** (1083mg, 5.15 mmol, 1.0 equiv) in THF (4 mL) was added at this temperature and the reaction was allowed to warm to 0 °C over 2 h. After stirring for another 2 h at 0 °C, the reaction was quenched by the addition of saturated aqueous NH_4Cl solution (15 mL). The aqueous layer was extracted with Et_2O (15 mL × 2). The combined organic layers were washed by brine (15 mL), dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography (silica gel, hexanes/EtOAc, 30/1) to afford vinyl methoxy ether as a colorless oil (1020 mg, 83%). The vinyl methoxy ether (1020 mg, 4.28 mmol, 1.0 equiv) was dissolved in THF (15 mL), 2 N HCl (8 mL) was added and the reaction

was stirred at 55 °C for 8 h. Upon completion, the reaction content was poured into a separatory funnel with H_2O (20 mL) and Et_2O (20 mL). The aqueous layer was extracted with Et_2O (15 mL × 2). The combined organic layers were washed by saturated aqueous $NaHCO_3$ solution (20 mL), dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography (silica gel, hexanes/EtOAc, 15/1) to afford aldehyde **28** as a colorless oil (830 mg, 86%). **28**: R_f = 0.50 (silica gel, hexanes/EtOAc, 3/1); IR (film) ν_{max} 2938, 2835, 1725, 1487, 1465, 1405, 1242, 1130, 1088, 1034 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.72 (s, 1 H), 6.38 (s, 1 H), 3.82 (s, 3 H), 3.79 (s, 3 H), 3.78 (s, 3 H), 3.65 (d, *J* = 1.4 Hz, 2 H), 2.12 (s, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 199.6, 154.3, 152.0, 145.6, 122.9, 120.6, 107.4, 60.6, 60.2, 55.8, 45.4, 8.8; HRMS (Mixed+) calcd for $C_{12}H_{16}O_4^+$ [M + H^+] 225.1121, found 225.1127.

Aryl bromide 29. To a solution of aldehyde **28** (830 mg, 3.70 mmol, 1.0 equiv) in THF (6 mL) and MeOH (2 mL) was added $NaBH_4$ (74 mg, 1.85 mmol, 0.5 equiv) at 0 °C. The reaction was stirred at this temperature for 30 min. Upon completion, the reaction was quenched by the addition of 1 N HCl (10 mL). The aqueous layer was extracted by Et_2O (10 mL × 2). The combined organic layers were washed by saturated aqueous $NaHCO_3$ solution (15 mL), dried ($MgSO_4$), filtered, concentrated to afford the alcohol as a colorless oil (770mg, 91%). The alcohol (770 mg, 3.40 mmol, 1.0 equiv) was then dissolved in CH_2Cl_2 (12 mL). NBS (636 mg, 3.57 mmol, 1.05 equiv) was added as solid at 23 °C. The reaction mixture was stirred at this temperature for 10 h. Upon completion, the reaction was quenched by the addition of a mixed aqueous solution of $NaHCO_3$ and $Na_2S_2O_3$ (10 mL). The aqueous layer was extracted with CH_2Cl_2 (10 mL × 2). The combined organic layers were dried ($MgSO_4$), filtered, concentrated to afford the bromo-alcohol as a colorless oil. Pressing forward without purification, the bromo-alcohol was dissolved in

CH_2Cl_2 (12 mL). Imidazole (463 mg, 6.80 mmol, 2.0 equiv) and TBDPSCl (538 mg, 3.57 mmol, 1.05 equiv) were added sequentially at 0 °C. The reaction was stirred at 23 °C for 2 h before quenched by H_2O (15 mL). The aqueous layer was extracted with CH_2Cl_2 (10 mL × 2). The combined organic layers were dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography (silica gel, hexanes/EtOAc, 50/1) to afford **29** as a colorless oil (1070 mg, 55% over 3 steps). **29**: R_f = 0.64 (silica gel, hexanes/EtOAc, 3/1); IR (film) ν_{max} 2933, 2857, 1459, 1428, 1396, 1234, 1110, 1031, 824, 738, 702 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.71–7.66 (m, 4 H), 7.44–7.39 (m, 2 H), 7.37 (t, *J* = 7.1 Hz, 4 H), 3.81 (dd, *J* = 15.1, 7.4 Hz, 2 H), 3.77 (s, 3 H), 3.72 (s, 3 H), 3.71 (s, 3 H), 3.16 (t, *J* = 7.6 Hz, 2 H), 2.22 (s, 3 H), 1.06 (s, 9 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.6, 151.1, 148.8, 135.6, 134.0, 130.2, 129.5, 127.5, 124.9, 114.8, 62.9, 60.7, 60.1, 59.9, 33.6, 26.9, 19.2, 10.0; HRMS (APCI+) calcd for $C_{28}H_{35}BrO_4Si^+$ [M + H^+] 543.1561, found 543.1555.

Compound 30. To a solution of **29** (5.20 g, 9.81 mmol, 1.0 equiv) in Et_2O (20 mL) was added *t*-BuLi (1.7 M in pentane, 12.7 mL, 20.6 mmol, 2.1 equiv) dropwise over 5 min at -78 °C. The mixture was stirred for 5 min at this temperature before a solution of **17** (2.47 g, 11.8 mmol, 1.2 equiv) in THF (5 mL) was added slowly. The reaction was kept at -78 °C for 15 min. Upon completion, the reaction was quenched by the addition of saturated aqueous NH_4Cl solution (15 mL). The aqueous layer was extracted with Et_2O (15 mL × 2). The combined organic layers were washed by brine, dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography (silica gel, hexanes/EtOAc, 25/1 to 15/1) to afford **30** as a light yellowish gum (6.01 g, 93%). **30**: R_f = 0.48 (silica gel, hexanes/EtOAc, 3/1); IR (film) ν_{max} 3411 (br), 2935, 2857, 1588, 1462, 1428, 1403, 1326, 1253, 1190, 1128, 1112, 1096, 1040, 1000, 961, 911, 823, 736, 703

cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68–7.61 (m, 2 H), 7.44 (t, *J* = 7.8 Hz, 2 H), 7.37 (dq, *J* = 14.4, 7.1 Hz, 4 H), 7.27 (t, *J* = 7.1 Hz, 2 H), 7.03 (s, 1 H), 6.32 (d, *J* = 7.9 Hz, 1 H), 4.36 (d, *J* = 7.9 Hz, 1 H), 3.83 (s, 3 H), 3.76 (s, 3 H), 3.74 (s, 3 H), 3.73–3.70 (m, 1 H), 3.60 (s, 3 H), 3.59 (s, 3 H), 3.17 (s, 3 H), 3.11 (dt, *J* = 13.9, 7.8 Hz, 1 H), 2.80 (dt, *J* = 13.3, 4.7 Hz, 1 H), 2.26 (s, 3 H), 2.13 (s, 3 H), 1.03 (s, 9 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.7, 153.3, 151.9, 151.3, 148.5, 143.8, 136.1, 135.6, 133.3, 132.5, 129.6, 129.5, 129.3, 127.6, 127.5, 123.7, 119.0, 104.4, 66.6, 64.8, 61.3, 60.1, 60.0, 59.9, 59.2, 55.9, 29.6, 26.8, 19.0, 9.6, 8.7; HRMS (ESI+) calcd for $C_{39}H_{50}O_8Si^+$ [M + Na^+] 697.3167, found 697.3156.

Compound 31. To a solution of **30** (2.40 g, 3.63 mmol, 1.0 equiv) in DMSO (12 mL) was added IBX (1.22 g, 4.36 mmol, 1.2 equiv) as solid at 23 °C. The reaction was stirred at this temperature for 16 h before quenched by the addition of a mixed aqueous solution of $NaHCO_3$ and $Na_2S_2O_3$. The aqueous layer was extracted by Et_2O (15 mL × 3). The combined organic layers were washed by brine, dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography (silica gel, hexanes/EtOAc, 30/1 to 20/1) to afford **31** as a light yellowish gum (2.34 g, 98%). **31**: R_f = 0.52 (silica gel, hexanes/EtOAc, 3/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67–7.58 (m, 4 H), 7.41–7.27 (m, 6 H), 6.96 (s, 1 H), 3.79 (s, 3 H), 3.78 (s, 3 H), 3.77–3.72 (m, 2 H), 3.68 (s, 3 H), 3.67 (s, 3 H), 3.53 (s, 3 H), 3.38 (s, 3 H), 2.91–2.81 (m, 2 H), 2.17 (s, 3 H), 2.14 (s, 3 H), 0.99 (s, 9 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 195.7, 153.8, 152.4, 152.1, 151.0, 148.4, 147.8, 135.5, 134.2, 133.7, 130.6, 129.3, 127.4, 127.4, 126.6, 123.7, 105.8, 64.0, 61.6, 60.4, 60.2, 60.0, 55.8, 31.2, 26.8, 19.2, 9.5, 9.2.

Compound 33. To a suspension of trimethyl sulfonium iodide (4.16 g, 20.3 mmol, 6.0 equiv) in THF (20 mL) was added *n*-BuLi (2.5 M in hexanes, 6.78 mL, 17.0 mmol, 5.0 equiv) dropwise over 3 min at 0 °C. The mixture was kept at this temperature for 10 min before a solution of **31** (2.28 g, 3.39 mmol, 1.0 equiv) in THF (5 mL) was added at 0 °C. The reaction was stirred at 0 °C for 15 min and was then allowed to warm to 23 °C over 30 min. After another 1 h at this temperature, the reaction was quenched by the addition of saturated aqueous NH_4Cl solution (10 mL). The aqueous layer was extracted by Et_2O (10 mL × 2). The combined organic layers were washed by brine, dried ($MgSO_4$), filtered, concentrated to give the crude epoxide. Pressing forward without purification, the epoxide was dissolved in benzene (12 mL), ZnI_2 (1.08 g, 3.39 mmol, 1.0 equiv) was added as solid at 23 °C. The reaction was stirred at this temperature for 15 min. Upon completion, the reaction was quenched by the addition of saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted by EtOAc (10 mL × 2). The combined organic layers were washed by brine, dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography (silica gel, hexanes/EtOAc, 25/1 to 15/1) to afford **33** as a light yellowish gum (1.82 g, 78% over 2 steps). **33**: R_f = 0.48 (silica gel, hexanes/EtOAc, 3/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.85 (s, 1H), 7.67 (d, *J* = 6.9 Hz, 2 H), 7.61 (d, *J* = 7.0 Hz, 2 H), 7.38–7.35 (m, 10 H), 5.97 (s, 1 H), 5.66 (s, 1 H), 4.77 (d, *J* = 11.2 Hz, 1 H), 4.47 (d, *J* = 11.2 Hz, 1 H), 3.79 (s, 3 H), 3.77 (s, 3 H), 3.74 (s, 3 H), 3.58 (s, 3 H), 3.49 (s, 3 H), 3.48 (s, 3 H), 2.25 (s, 3 H), 2.08 (s, 3 H), 1.55 (s, 9 H), 0.95 (s, 6 H).

Compound 35. To a solution of *gem*-dibromide **34**[7] (1.08 g, 4.61 mmol, 1.8 equiv) in THF (20 mL) was added *n*-BuLi (2.5 M in hexanes, 3.80 mL, 9.22 mmol, 3.6 equiv) dropwise over 5 min at -78 °C. The mixture was stirred at this temperature for 40 min before dry ice bath was

removed and the reaction was stirred at 23 °C for another 25 min. The reaction content was then re-cooled to -78 °C, followed by the addition of **33** (1.82 g, 2.65 mmol, 1.0 equiv) in THF (5 mL) at this temperature. The reaction was allowed to warm to 23 °C slowly over 8 h. Upon completion, the reaction was quenched by the addition of saturated aqueous NH_4Cl solution (15 mL). The aqueous layer was extracted with Et_2O (10 mL × 2). The combined organic layers were washed by brine, dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography (silica gel, hexanes/EtOAc, 20/1 to 12/1) to afford **35** as a light yellowish gum (1.59 g, 79%, dr = 2.5:1). (The ^1H NMR of this compound is hard to interpret due to the nature of diastereomeric mixture.)

Compound 36. The mono-propargyl alcohol **35** (1.59 g, 2.15 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (12 mL). DIPEA (3.74 mL, 21.5 mmol, 10.0 equiv) and EOMCl (0.60 mL, 6.45 mmol, 3.0 equiv) were added sequentially at 23 °C. The reaction was stirred at this temperature for 24 h before the reaction was quenched by the addition of saturated aqueous $NaHCO_3$ solution (15 mL). The aqueous layer was extracted with CH_2Cl_2 (10 mL × 2). The combined organic layers were washed by brine, dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography (silica gel, hexanes/EtOAc, 30/1) to afford **36** as a light yellowish gum (1.63 g, 94%, dr = 2.5:1). (The ^1H NMR of this compound is hard to interpret due to the nature of diastereomeric mixture.)

Compound 37. The EOM-protected mono-propargyl alcohol **36** (1.63 g, 2.00 mmol, 1.0 equiv) was dissolved in THF (12 mL). TBAF (1.0 M in THF, 16.0 mL, 16.0 mmol, 8.0 equiv) was added at 23 °C and the reaction was stirred at 55 °C for 12 h. Upon completion, the reaction was quenched by the addition of saturated aqueous NH_4Cl solution (15 mL). The aqueous layer was

extracted with Et_2O (15 mL × 2). The combined organic layers were washed by brine, dried ($MgSO_4$), filtered, and concentrated to give the crude alcohol as a yellowish oil. Pressing forward without purification, the crude alcohol was dissolved in CH_2Cl_2 (20 mL). $NaHCO_3$ (504 mg, 6.00 mmol, 3.0 equiv) and Dess-Martin periodinane (933 mg, 2.20 mmol, 1.1 equiv) was added sequentially at 23 °C. The reaction was stirred at this temperature for 1 h before it was quenched by the addition of a mixed aqueous solution of $NaHCO_3$ and $Na_2S_2O_3$ (10 mL). The aqueous layer was extracted with CH_2Cl_2 (10 mL × 2). The combined organic layers were dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography (silica gel, hexanes/EtOAc, 15/1) to afford **37** (859 mg, 75% over 2 steps, dr = 2.5:1) as a light yellowish gum. (The ^1H NMR of this compound is hard to interpret due to the nature of diastereomeric mixture.)

Compound 38. To a solution of gem-dibromide **34** (633 mg, 2.80 mmol, 1.85 equiv) in THF (6 mL) was added *n*-BuLi (2.5 M in hexanes, 2.24 mL, 5.60 mmol, 3.7 equiv) dropwise over 5 min at -78 °C. The mixture was stirred at this temperature for 40 min before dry ice bath was removed and the reaction was stirred at 23 °C for another 25 min. The reaction content was then re-cooled to -78 °C, followed by the addition of **37** (859 mg, 1.50 mmol, 1.0 equiv) in THF (3 mL) at this temperature. The reaction was allowed to warm to 23 °C slowly over 8 h. Upon completion, the reaction was quenched by the addition of saturated aqueous NH_4Cl solution (10 mL). The aqueous layer was extracted with Et_2O (8 mL × 2). The combined organic layers were washed by brine, dried ($MgSO_4$), filtered, concentrated to give the alcohol as a light yellowish oil. The crude alcohol was dissolved in CH_2Cl_2 (15 mL). *n*-PrSH (0.29 mL, 3.20 mmol, 2.13 equiv) was added and the reaction was cooled to 0 °C before $ZnBr_2$ (361 mg, 1.60 mmol, 1.07 equiv) was added as solid at this temperature. The reaction was stirred at 0 °C for 1.5 h and was then warmed to 23 °C

slowly over 30 min before it was quenched by the addition of saturated aqueous $NaHCO_3$ solution (10 mL). The aqueous layer was extracted with CH_2Cl_2 (8 mL × 2). The combined organic layers were washed by brine, dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography (silica gel, hexanes/EtOAc, 5/1) to afford **38** as a light yellowish gum (440 mg, 51% over 2 steps, mixtures of multiple diastereomers). (The ^{1}H NMR of this compound is hard to interpret due to the nature of diastereomeric mixture.)

Compound 39. To a solution of **38** (440 mg, 0.76 mmol, 1.0 equiv) in THF (6 mL) was added Red-Al® (60% in PhMe, 2.97 mL, 9.12 mmol, 12.0 equiv). The reaction was stirred at 70 °C for 5 h before it was cooled back to 23 °C. H_2O (2 mL) was added dropwise to quench the extra Red-Al®. 3 N NaOH (15 mL) was then added and the mixture was vigorously stirred for 10 min. The aqueous layer was extracted with Et_2O (8 mL × 2). The combined organic layers were washed by brine, dried ($MgSO_4$), filtered, concentrated to give the bis-allylic alcohol as a light yellowish oil. Pressing forward without purification, the crude bis-allylic alcohol was dissolved in DMSO (6 mL). IBX (596 mg, 2.13 mmol, 2.8 equiv) was added as solid at 23 °C. The reaction was stirred at this temperature for 16 h. Upon completion, the reaction was quenched by the addition of a mixed aqueous solution of $NaHCO_3$ and $Na_2S_2O_3$ (15 mL). The aqueous layer was extracted with Et_2O (10 mL × 3). The combined organic layers were washed by brine, dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography (silica gel, hexanes/EtOAc, 25/1 to 18/1 to 12/1) to afford **39** (349 mg, 79% over 2 steps) as a yellowish gum. **39**: R_f = 0.38 (silica gel, hexanes/EtOAc, 3/1); IR (film) ν_{max} 2938, 1690, 1638, 1597, 1463, 1403, 1328, 1262, 1241, 1190, 1128, 1088, 1067, 1001, 732 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 (ddd, *J* = 19.3, 12.7, 4.9 Hz, 1 H), 7.09 (ddd, *J* = 42.8, 23.2, 13.8 Hz, 1 H), 6.20 (d, *J* = 7.5 Hz, 2 H), 6.18–6.11 (m, 4

H), 5.99 (dd, *J* = 23.2, 11.3 Hz, 1 H), 5.61 (d, *J* = 9.4 Hz, 1 H), 3.97–3.91 (m, 1 H), 3.85 (s, 3 H), 3.81 (s, 3 H), 3.74 (s, 3 H), 3.71 (s, 3 H), 3.64 (d, *J* = 17.3 Hz, 1 H), 3.60 (s, 3 H), 3.53 (s, 3 H), 2.26 (s, 3 H), 2.10 (s, 3 H), 1.86 (d, *J* = 4.8 Hz, 4 H), 1.83 (d, *J* = 4.8 Hz, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 197.3, 197.3, 153.7, 153.6, 151.4, 151.2, 148.3, 145.1, 142.4, 141.9, 139.9, 139.3, 130.7, 130.4, 129.3, 127.9, 127.0, 126.9, 126.9, 124.3, 119.8, 107.1, 60.7, 60.1, 60.0, 60.0, 55.8, 51.6, 39.9, 18.7, 18.6, 10.2, 8.8; HRMS (ESI+) calcd for $C_{34}H_{42}O_8^+$ [M + H^+] 579.2952, found 579.2948.

Compound 40. To a solution of **39** (72 mg, 0.124 mmol, 1.0 equiv) in MeCN (2 mL) and H_2O (0.2 mL) was added a solution of CAN (205 mg, 0.374 mmol, 3.0 equiv) in H_2O (0.8 mL) dropwise over 10 min at 0 °C. After the reaction was stirred at this temperature for another 1 h, H_2O (3 mL) was added. The aqueous layer was extracted by EtOAc (3 mL × 3) and the combined organic layers were washed by brine, dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography (silica gel, hexanes/EtOAc, 10/1) to afford **40** (28 mg, 41%) as yellowish gum. **40**: R_f = 0.21 (silica gel, hexanes/EtOAc, 3/1); IR (film) ν_{max} 2939, 1656, 1637, 1597, 1462, 1404, 1331, 1263, 1230, 1090, 1001, 914, 733 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.15 (ddd, *J* = 18.9, 12.4, 6.7 Hz, 2 H), 6.17 (d, *J* = 1.8 Hz, 1 H), 6.16 (d, *J* = 2.7 Hz, 1 H), 6.13 (d, *J* = 1.6 Hz, 1 H), 6.12 (d, *J* = 2.7 Hz, 1 H), 6.09 (s, 1 H), 6.06 (s, 1 H), 6.04 (s, 1 H), 5.39 (s, 1 H), 4.02 (s, 3 H), 3.90 (dd, *J* = 16.1, 8.3 Hz, 1 H), 3.84 (s, 3 H), 3.73 (s, 3 H), 3.54 (d, *J* = 17.4 Hz, 1 H), 3.51 (d, *J* = 6.2 Hz, 3 H), 2.20 (s, 3 H), 1.90 (s, 3 H), 1.86 (d, *J* = 4.8 Hz, 3 H), 1.80 (d, *J* = 4.8 Hz, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 196.8, 195.5, 187.9, 182.5, 156.9, 153.7, 151.9, 148.4, 146.3, 143.3, 140.7, 140.4, 133.7, 130.5, 130.2, 127.5, 127.2, 126.7, 125.9, 124.9, 123.3, 60.8, 60.7, 60.3, 59.9,

51.2, 39.3, 18.8, 18.7, 10.2, 8.4; HRMS (ESI+) calcd for $C_{32}H_{36}O_8^+$ [M + H^+] 549.2483, found 549.2478.

Compound 43. To a solution of **42** (prepared in a route similar to that for compound **39**, 81 mg, 0.171 mmol, 1.0 equiv) in MeCN (2 mL) and H_2O (0.5 mL) was added a solution of CAN (562 mg, 1.02 mmol, 6.0 equiv) in H_2O (0.8 mL) dropwise over 10 min at 0 °C. After the reaction was stirred at this temperature for another 1.5 h, H_2O (3 mL) was added. The aqueous layer was extracted by EtOAc (3 mL × 3) and the combined organic layers were washed by brine, dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography (silica gel, hexanes/EtOAc, 10/1) to afford **40** (11 mg, 15%) as yellowish gum. **40**: R_f = 0.18 (silica gel, hexanes/EtOAc, 3/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.40 (s, 1 H), 5.80 (s, 1 H), 4.25 (s, 3 H), 3.96 (s, 3 H), 3.41 (d, *J* = 14.0 Hz, 1 H), 2.69 (d, *J* = 14.0 Hz, 1 H), 2.39 (s, 3 H), 2.21 (s, 3 H), 2.20 (s, 3 H), 1.97 (s, 3 H).

Compound 23. To a solution of **16** (115 mg, 0.396 mmol, 1.0 equiv) in CH_3CN (3 mL) and H_2O (0.6 mL) was added CAN (543 mg, 0.99 mmol, 2.5 equiv) as solid at 0 °C. The reaction was allowed to warm to 23 °C over 1 h before H_2O (5 mL) was added. The aqueous layer was extracted by EtOAc (3 mL × 3) and the combined organic layers were washed by brine, dried ($MgSO_4$), filtered, and concentrated to give the crude benzoquinone monomer **22**. To a solution of crude **22** in acetone (3 mL) was added pH=7 phosphate buffer solution until the reaction media turned slightly cloudy (typically 1.5 mL of phosphate buffer solution). The reaction was stirred at this temperature for 12 h before brine (10 mL) was added. The aqueous layer was extracted by Et_2O (5 mL × 3) and the combined organic layers were dried ($MgSO_4$), filtered, concentrated, and

purified by flash column chromatography (silica gel, hexanes/EtOAc, 15/1 to 10/1) to afford **23** (54 mg, 52% over 2 steps) as a light yellowish gum. **23**: R_f = 0.20 (silica gel, hexanes/EtOAc, 3/1); IR (film) ν_{max} 3290 (br), 2939, 1652, 1635, 1592, 1466, 1421, 1375, 1335, 1191, 1125, 1000, 913, 733 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.43 (dd, *J* = 15.3, 9.4 Hz, 1 H), 7.11 (dd, *J* = 15.6, 9.6 Hz, 1 H), 6.45 (d, *J* = 15.4 Hz, 1 H), 6.26–6.22 (m, 2 H), 6.18 (t, *J* = 8.0 Hz, 2 H), 5.97 (d, *J* = 15.6 Hz, 1 H), 5.35 (s, 1 H), 5.10 (s, 1 H), 4.02 (s, 3 H), 3.95 (d, *J* = 18.6 Hz, 1 H), 3.72 (s, 3 H), 3.47 (d, *J* = 18.5 Hz, 1 H), 3.38 (d, *J* = 1.5 Hz, 1 H), 2.14 (s, 3 H), 1.99 (s, 3 H), 1.89–1.83 (m, 6 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 199.6, 198.7, 197.2, 196.7, 159.9, 146.6, 145.9, 145.5, 142.2, 141.6, 138.7, 130.6, 130.2, 126.5, 126.2, 123.6, 120.6, 119.9, 60.8, 60.2, 59.4, 58.1, 54.7, 60.6, 18.9, 18.8, 10.1, 9.6; ; HRMS (Mixed+) calcd for $C_{30}H_{32}O_8^+$ [M + H^+] 521.2170, found 521.2183.

Compound 52. To a solution of **23** (70 mg, 0.134 mmol, 1.0 equiv) in MeCN (2 mL) and H_2O (0.2 mL) was added a solution of CAN (148 mg, 0.268 mmol, 2.0 equiv) in H_2O (0.6 mL) dropwise over 2 min at 0 ºC. After the reaction was stirred at this temperature for another 1 h, H_2O (3 mL) was added. The aqueous layer was extracted by EtOAc (3 mL × 3) and the combined organic layers were washed by brine, dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography (silica gel, hexanes/EtOAc, 10/1) to afford **52** (54 mg, 78%) as yellowish gum. **52**: R_f = 0.24 (silica gel, hexanes/EtOAc, 3/1); ^1H NMR (500 MHz, $CDCl_3$) δ 7.61 (dd, *J* = 15.4, 10.7 Hz, 1 H), 7.07 (dd, *J* = 15.4, 9.2 Hz, 1 H), 6.34 (td, *J* = 13.5, 6.5 Hz, 1 H), 6.28–6.19 (m, 2 H), 6.19–6.13 (m, 2 H), 5.98 (d, *J* = 15.5 Hz, 1 H), 4.01 (s, 3 H), 3.96 (s, 3 H), 3.83–3.73 (m, 2 H), 2.71 (d, *J* = 17.8 Hz, 1 H), 1.92–1.86 (m, 9 H), 1.85 (d, *J* = 4.6 Hz, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 197.5, 196.8, 196.0, 188.4, 184.9, 180.1, 160.6, 156.0, 147.7, 147.4, 146.8, 144.0, 142.9, 141.2, 130.4, 130.1, 129.1, 126.9, 125.5, 61.1, 60.9, 59.8, 57.7, 57.6, 43.7, 18.9, 18.8, 9.5,

8.7; IR (film) ν_{max} 2954, 1701, 1655, 1636, 1596, 1448, 1374, 1331, 1270, 1193, 1161, 1115, 1078, 1002, 909, 734 cm^{-1}; HRMS (ESI+) calcd for $C_{30}H_{30}O_8^+$ [M + H^+] 519.2013, found 519.2022.

Compound 53. To a microwave vial was added a solution of **52** (28 mg, 0.054 mmol, 1.0 equiv) in PhCl (10 mL). The solution was degassed by bubbling with Ar for 10 min before it was subjected to microwave irradiation under 190 °C for 30 min. The reaction was directly concentrated and purified by preparative thin layer chromatography (silica gel, hexanes/EtOAc, 3/1 and 2/1) to afford **53** (9 mg, 32%) as a light yellowish gum. **53**: R_f = 0.28 (silica gel, hexanes/EtOAc, 3/1); IR (film) ν_{max} 3447(br), 2943, 1734, 1668, 1605, 1456, 1374, 1295, 1189, 1139, 1115, 994, 913, 732 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.68 (d, *J* = 5.9 Hz, 1 H), 6.48 (dd, *J* = 15.5, 10.2 Hz, 1 H), 6.11–6.00 (m, 1 H), 5.91–5.82 (m, 2 H), 3.91 (s, 3 H), 3.82 (s, 3 H), 3.73 (d, *J* = 5.5 Hz, 1 H), 3.38 (d, *J* = 5.5 Hz, 1 H), 2.87 (d, *J* = 17.7 Hz, 1 H), 2.67 (dd, *J* = 5.8, 3.3 Hz, 1 H), 2.40 (d, *J* = 17.7 Hz, 1 H), 2.26–2.21 (m, 1 H), 2.21–2.15 (m, 1 H), 2.04 (s, 3 H), 1.89 (s, 3 H), 1.79 (d, *J* = 6.6 Hz, 3 H), 0.88 (d, *J* = 6.9 Hz, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 197.8, 197.1, 195.1, 194.6, 192.0, 159.7, 158.8, 139.7, 137.7, 135.5, 135.3, 134.8, 132.6, 132.1, 130.3, 85.1, 66.0, 64.6, 64.3, 60.1, 60.0, 58.2, 56.0, 52.7, 46.8, 39.6, 18.2, 13.1, 9.8, 9.7; HRMS (ESI+) calcd for $C_{30}H_{30}O_8^+$ [M + Na^+] 541.1833, found 541.1816.

3.7 References

[1] M. E. Papandreou, N. Tavernarakis, *Methods Enzymol*. **2017**, *588*, 429.

[2] E. Mevers, J. Saurí, Y. Liu, A. Moser, T. R. Ramadhar, M. Varlan, R. T. Williamson, G. E. Martin, J. Clardy, *J. Am. Chem. Soc*. **2016**, *138*, 12324.

[3] A. Kubo, Y. Kitahara, S. Nakahara and R. Numata, *Chem. Pharm. Bull*. **1985**, *33*, 2122.

[4] K. B. Bahnck, S. D. Rychnovsky, *Chem. Commun*. **2006**, 2388.

[5] A. P. Kale, G. G. Pawar, M. Kapur, *Org. Lett*. **2012**, *14*, 1808.

[6] N. E. Wright, S. A. Snyder, *Angew. Chem. Int. Ed*. **2014**, *53*, 3409.

[7] H. J. Bestmann, H. Frey, *Liebigs Ann. Chem*. **1980**, 2061.

[8] J. H. Han, Y. E. Kwon, J. -H. Sohn, D. H. Ryu, *Tetrahedron* **2010**, *66*, 1673.

[9] D. Ma, Y. Liu, Z. Wang, *Angew. Chem. Int. Ed*. **2017**, *56*, 7886.

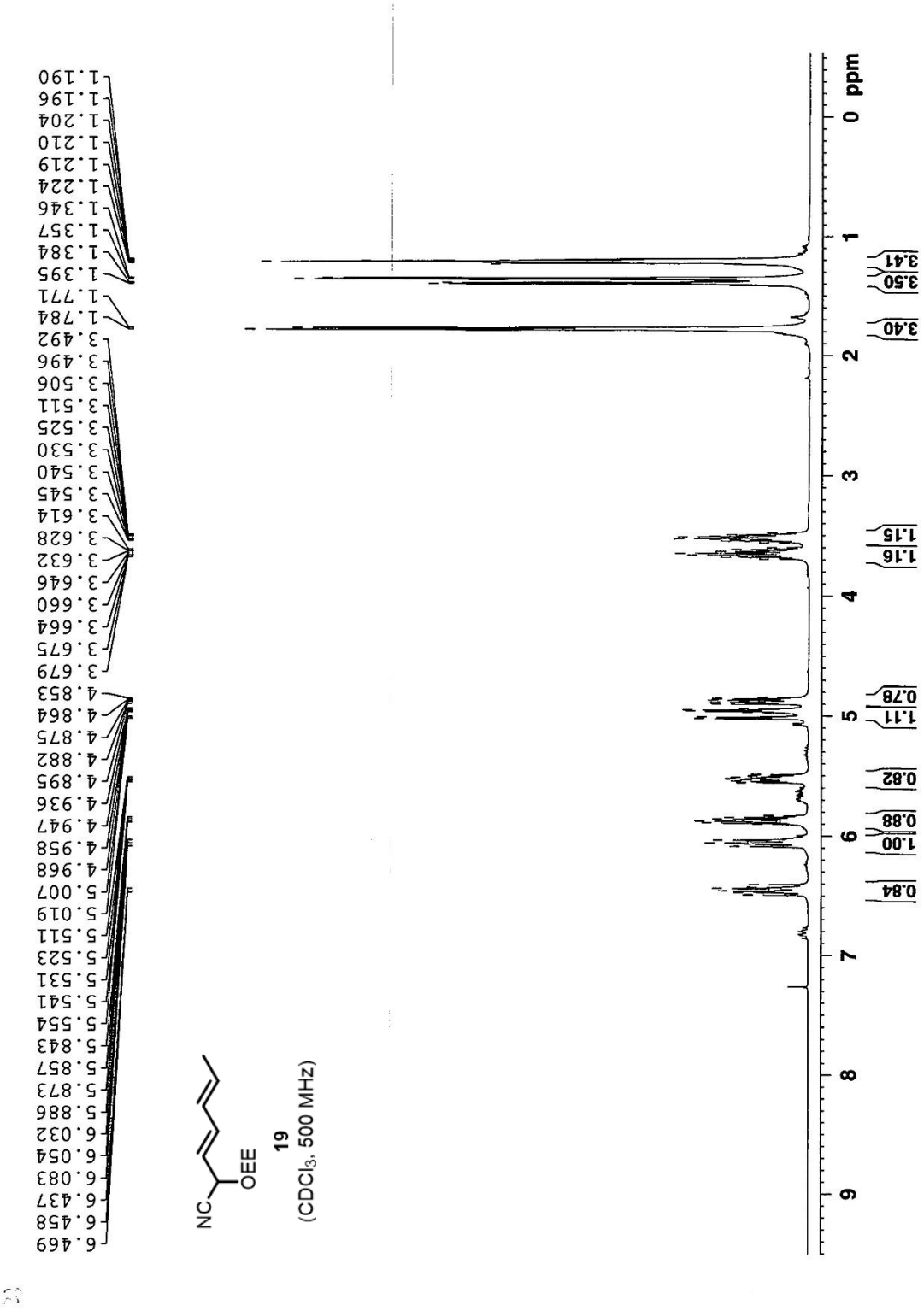
[10] J. Feng, X. Lei, Z. Guo, Y. Tang, *Angew. Chem. Int. Ed*. **2017**, *56*, 7890.

[11] J. Huang, Y. Gu, K. Guo, L. Zhu, Y. Lan, J. Gong, Z. Yang, *Angew. Chem. Int. Ed*. **2017**, *56*, 7895.

[12] X. Long, Y. Huang, Y. Long, J. Deng, *Org. Chem. Front*. **2018**, *5*, 1152.

[13] S. Sugiyama, S. Fuse, T. Takahashi, *Tetrahedron*, **2011**, *67*, 6654.

3.7 NMR Spectra of Selected Intermediates



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60.958
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14.896
NC
OEE
19
(CDCl3, 126 MHz)
ppm

6.587
4.660
3.838
3.810
3.792
2.118
0.93
2.24
3.00
3.02
3.20
3.01
0 ppm
OH
OMe
OMe
MeO
S1
(CDCl3, 500 MHz)

8.798
55.776
60.213
60.932
61.454
105.416
120.384
131.320
144.801
151.684
154.183
ppm
20
40
60
80
100
120
140
160
180
200
OH
OMe
OMe
MeO
S1
(CDCl3, 126 MHz)

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4.561
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3.821
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2.126
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OMe
MeO
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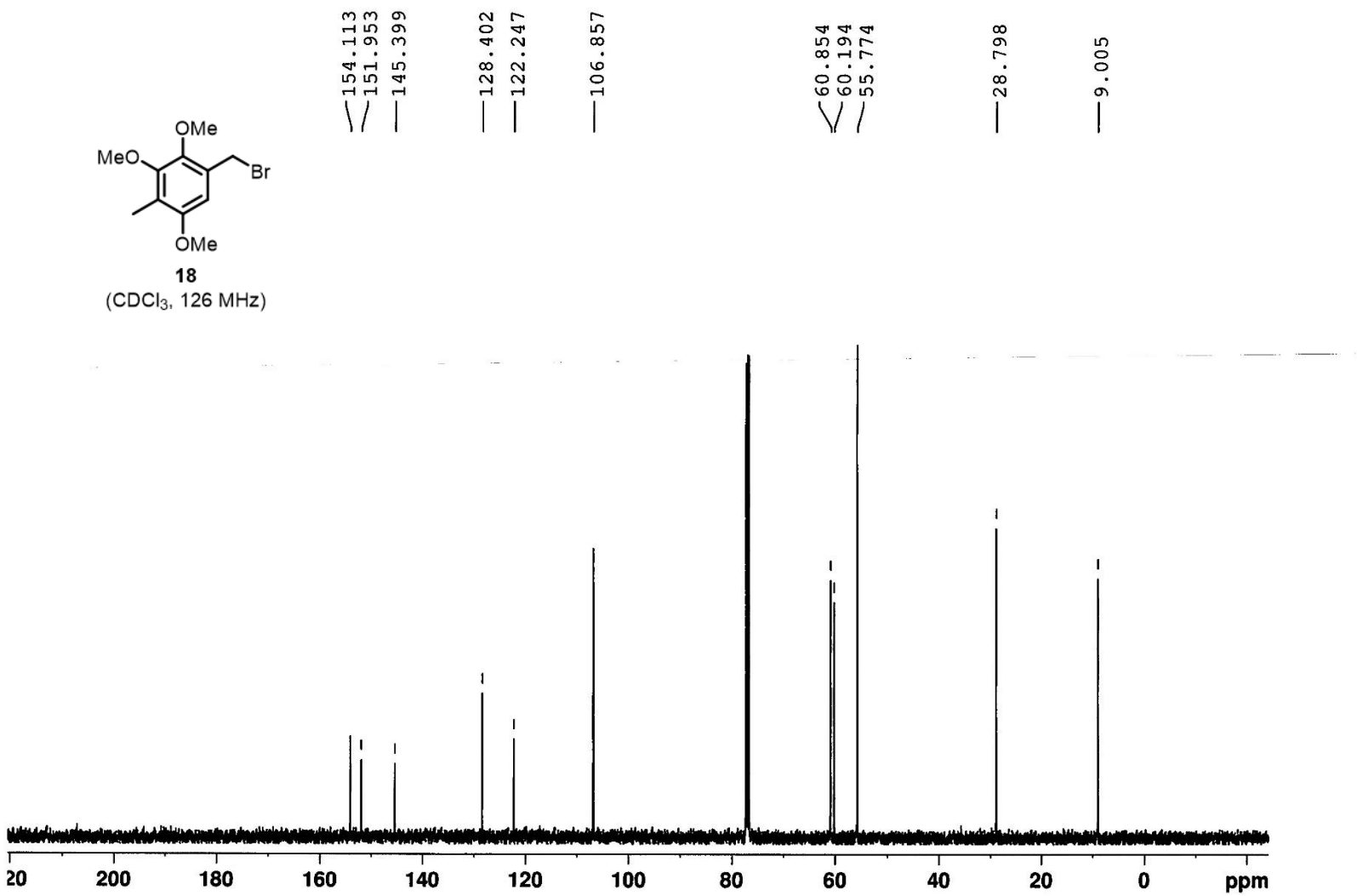
(CDCl3, 500 MHz)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MeO
Br
OMe
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(CDCl3, 126 MHz)
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180
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140
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100
80
60
40
20
0
ppm

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7.260
7.246
7.234
7.227
6.396
6.187
6.183
6.174
6.170
6.144
6.114
3.815
3.802
3.758
3.756
2.107
1.855
1.845
1.00
0.89
1.95
1.08
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3.39
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OMe
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125.574
126.703
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MeO
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O
16
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ppm

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ppm
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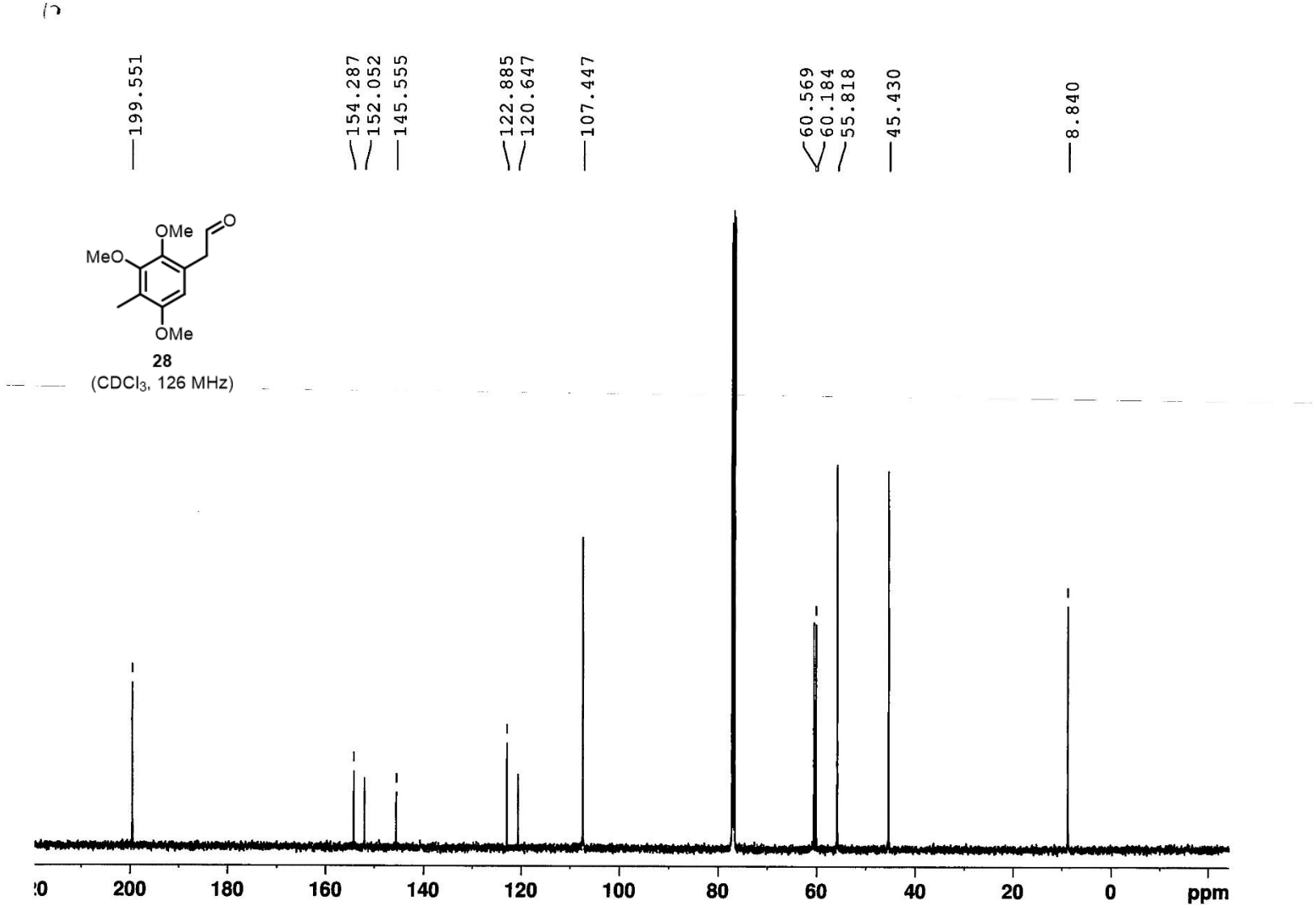
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OMe
O
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(CDCl3, 126 MHz)
200
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80
60
40
20
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ppm

7.695
7.681
7.679
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7.402
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7.370
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3.802
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3.175
3.159
3.144
2.217
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Br
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MeO
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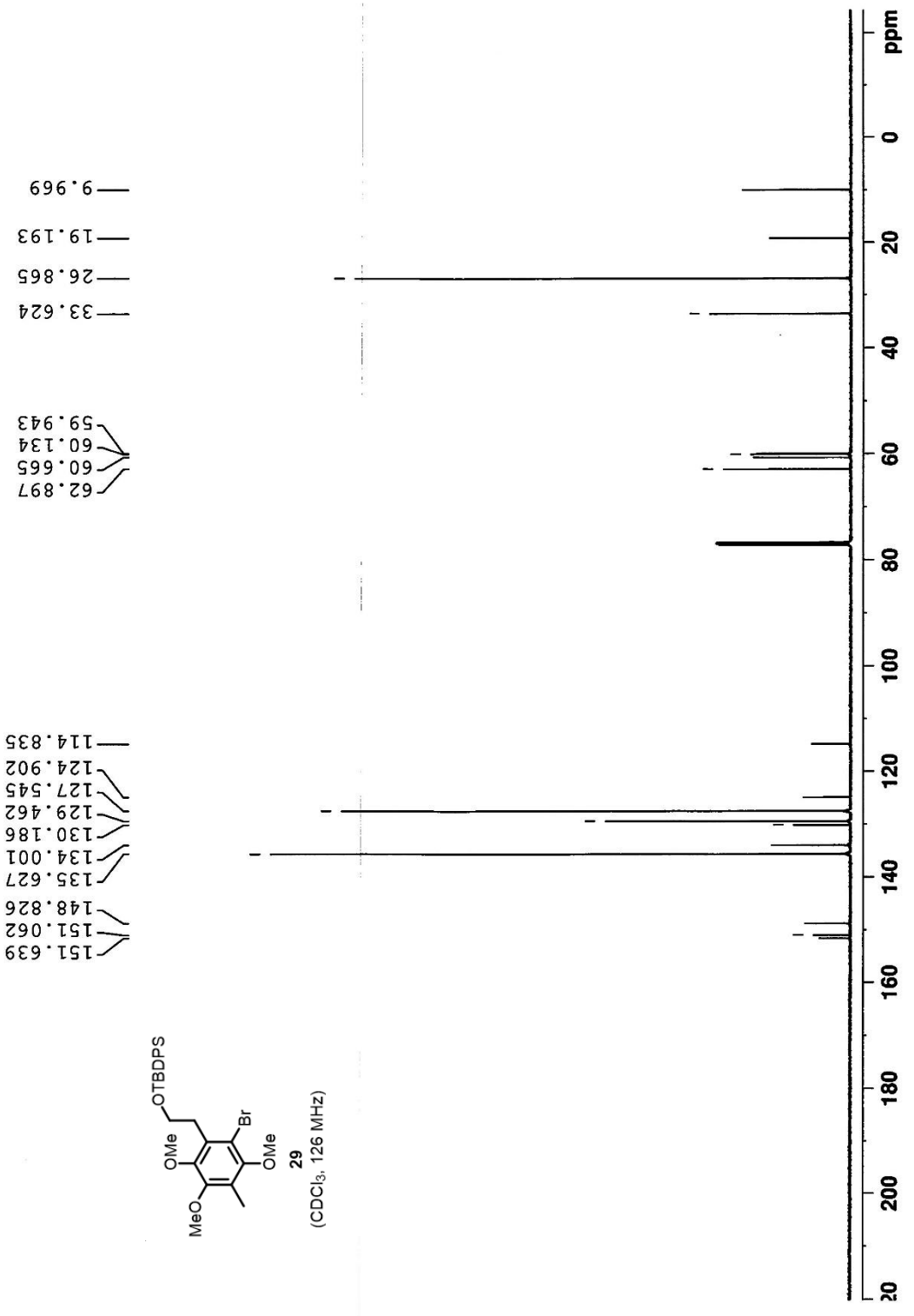
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130.186
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MeO
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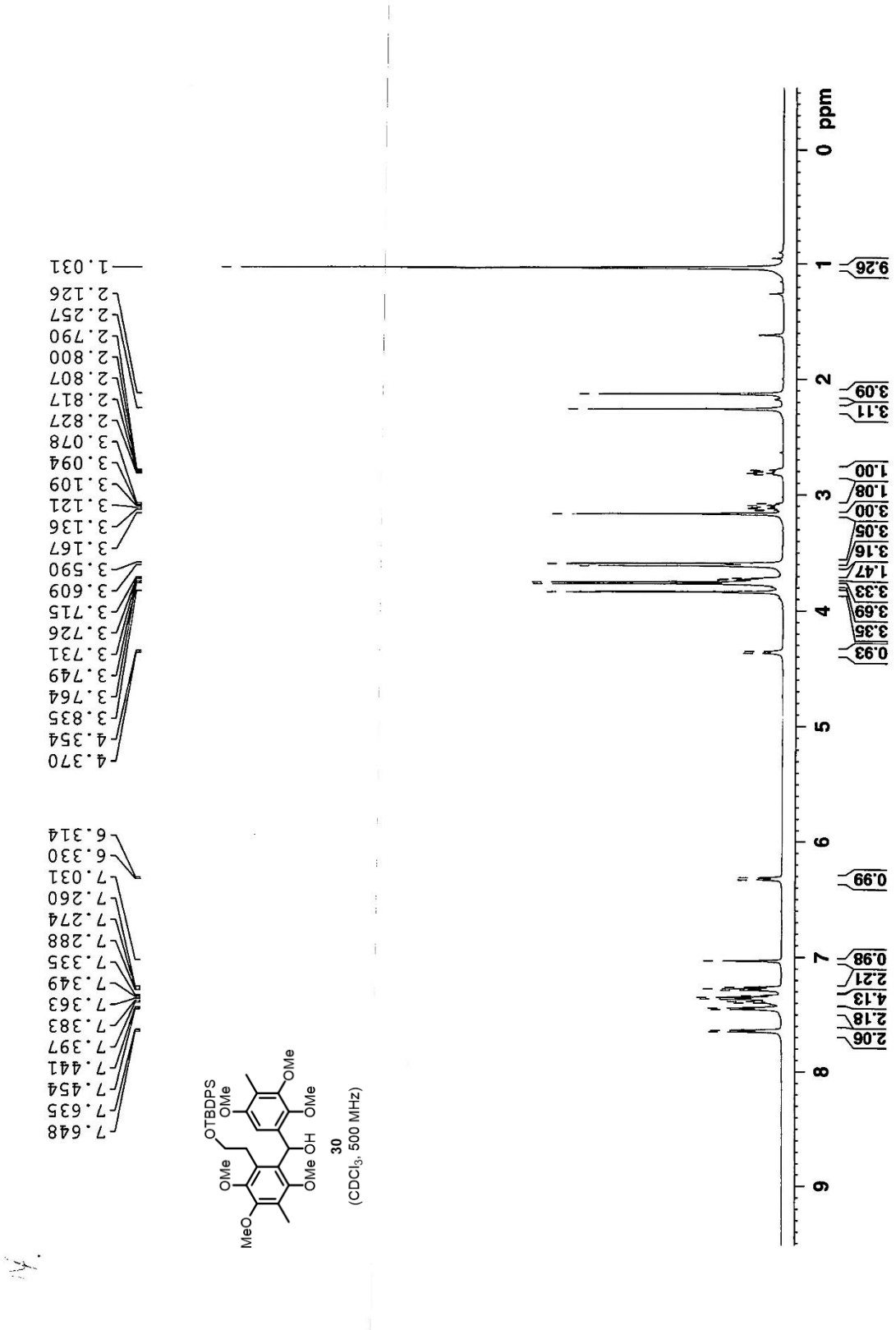
OMe
29
(CDCl3, 126 MHz)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1.00
1.08
3.00
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1.47
3.33
3.69
3.35
0.93
0.99
2.06
2.18
4.13
2.21
0.98
1.031
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2.257
2.790
2.800
2.807
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2.827
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3.109
3.121
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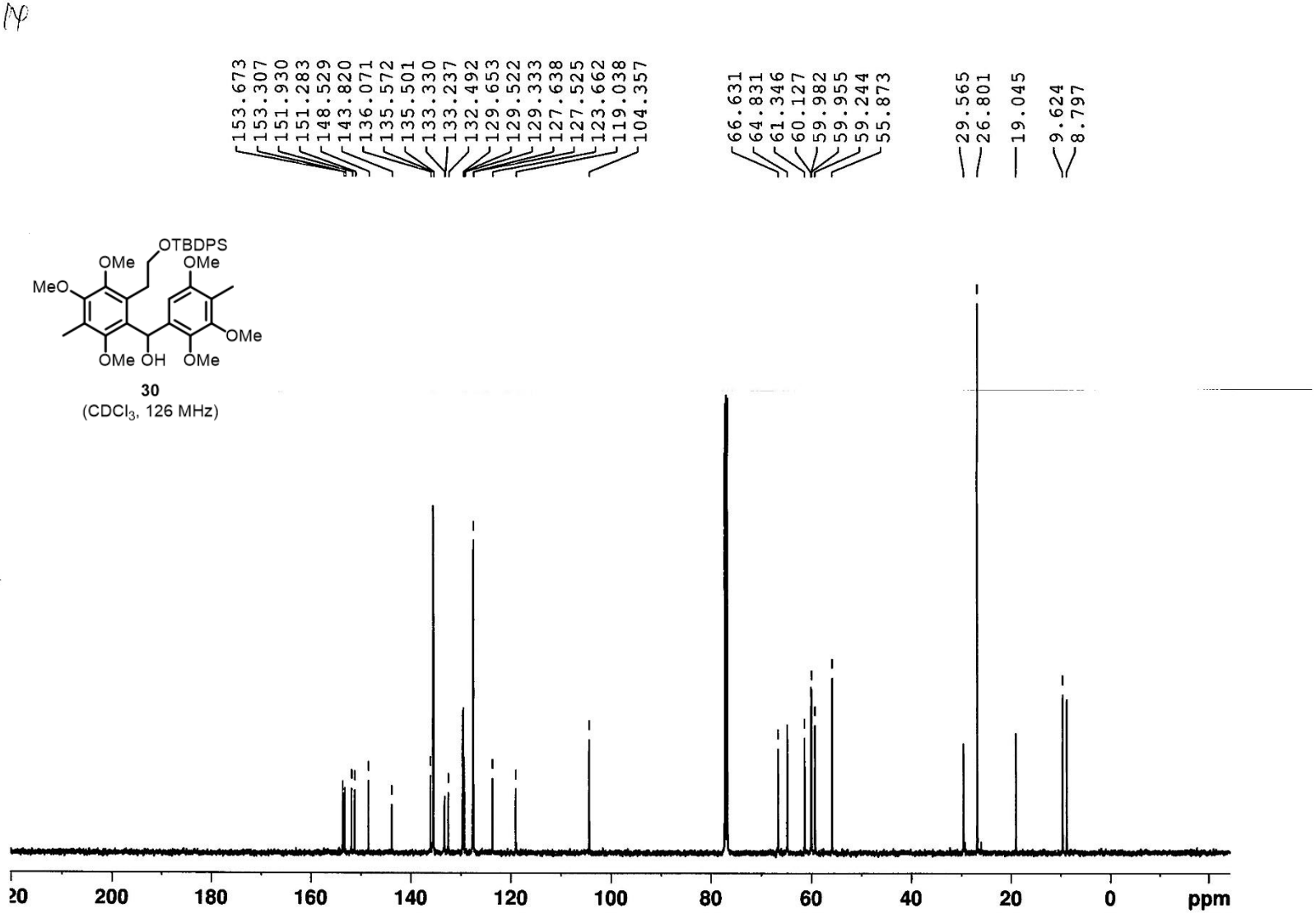
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29.565
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OMe
MeO
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200
180
160
140
120
100
80
60
40
20
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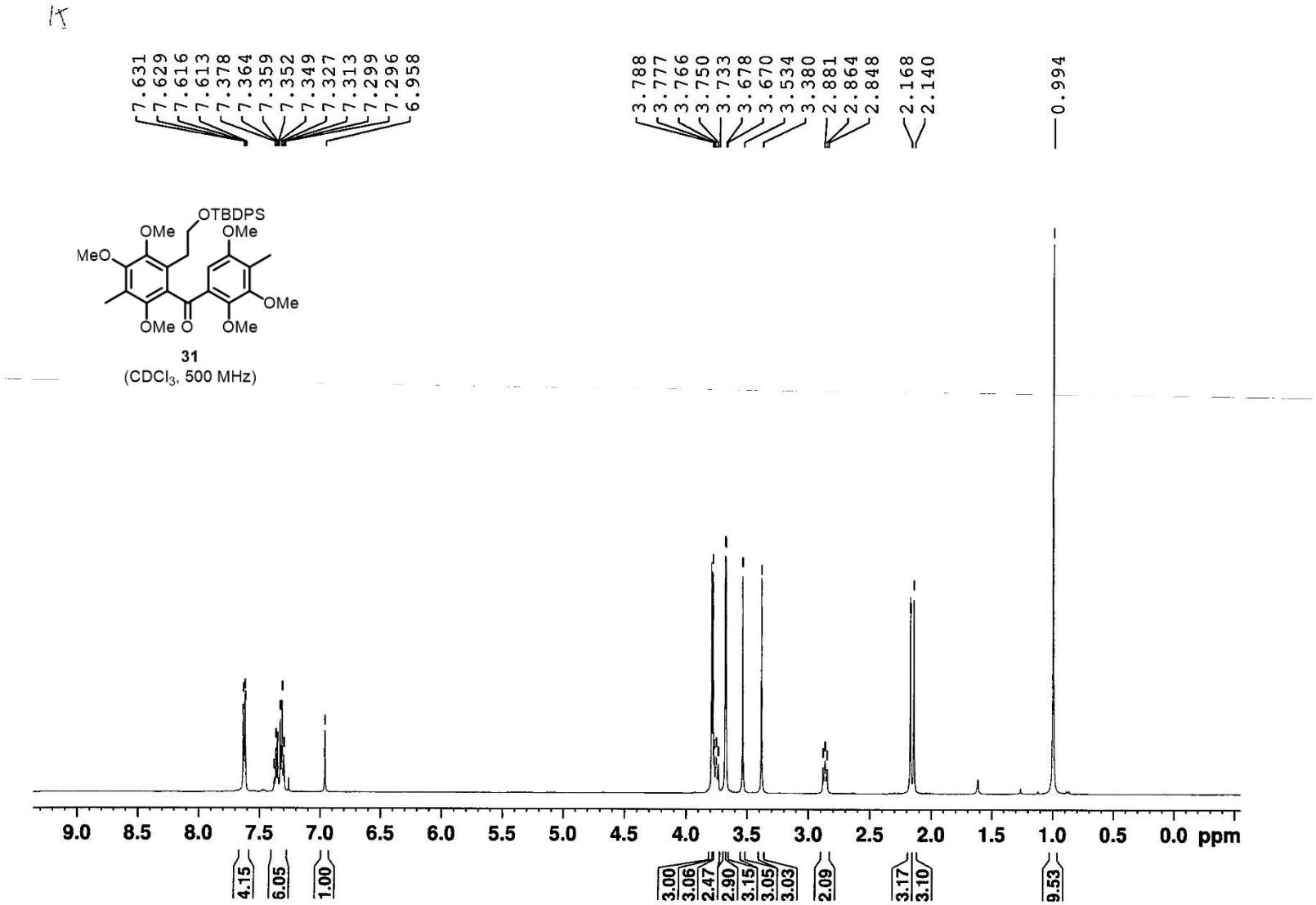
ppm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6.958
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3.777
3.766
3.750
3.733
3.678
3.670
3.534
3.380
2.881
2.864
2.848
2.168
2.140
0.994
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OMe
OMe
MeO
OMe
OMe O
OMe
31
(CDCl3, 500 MHz)
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6.05
1.00
3.00
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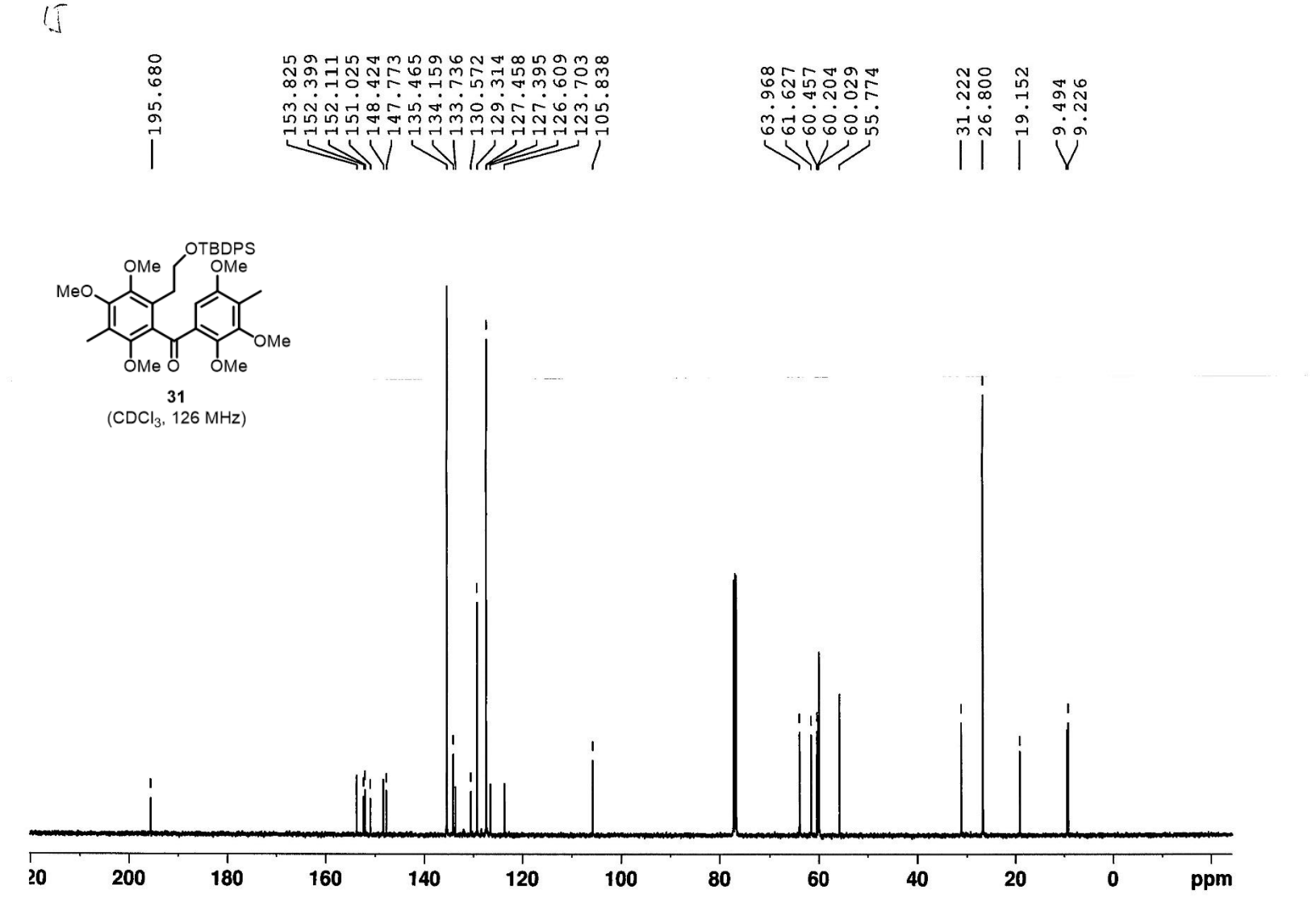
3.05
3.03
2.09
3.17
3.10
9.53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127.395
126.609
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61.627
60.457
60.204
60.029
55.774
31.222
26.800
19.152
9.494
9.226
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OMe
MeO
OMe
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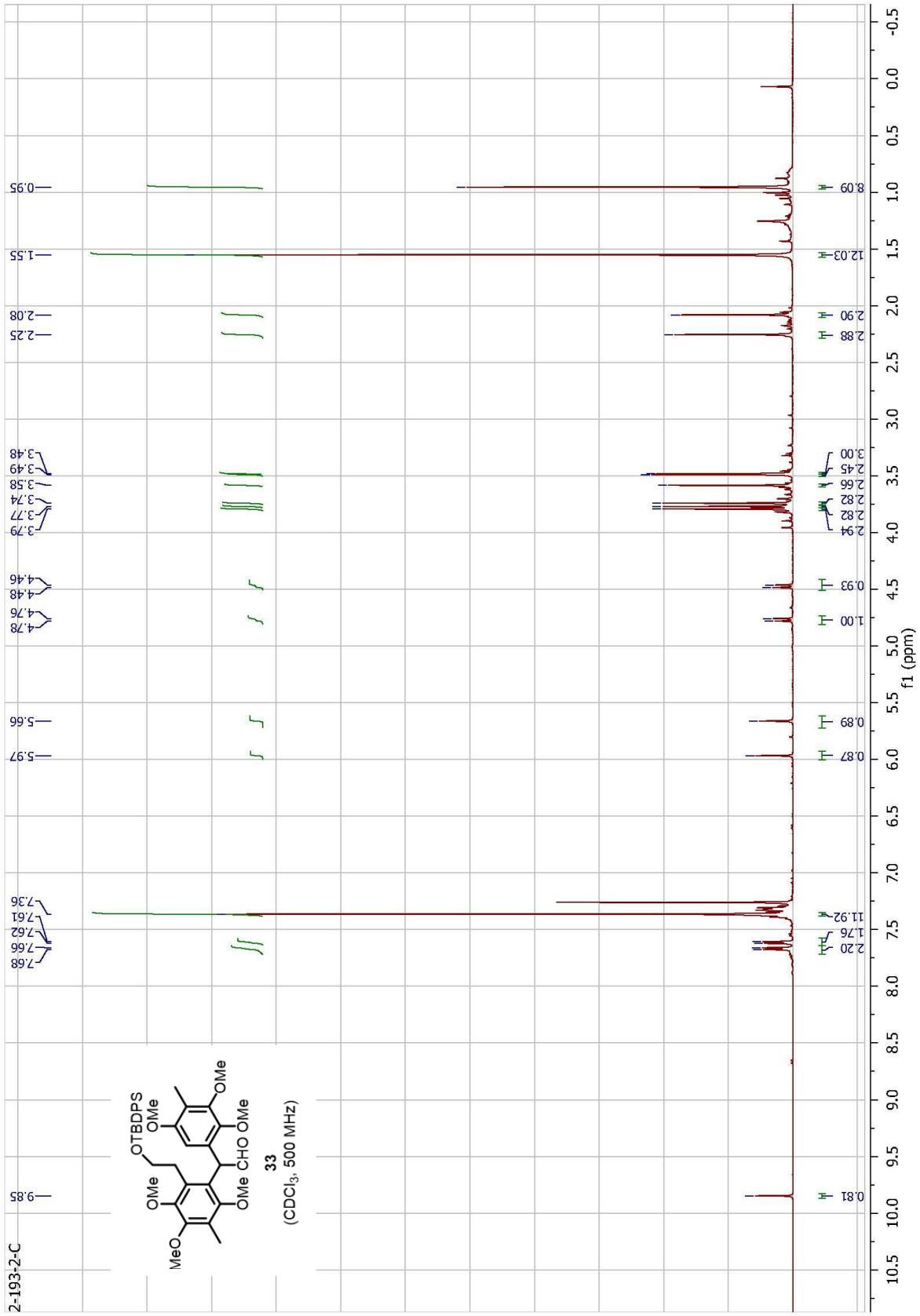
20
0
ppm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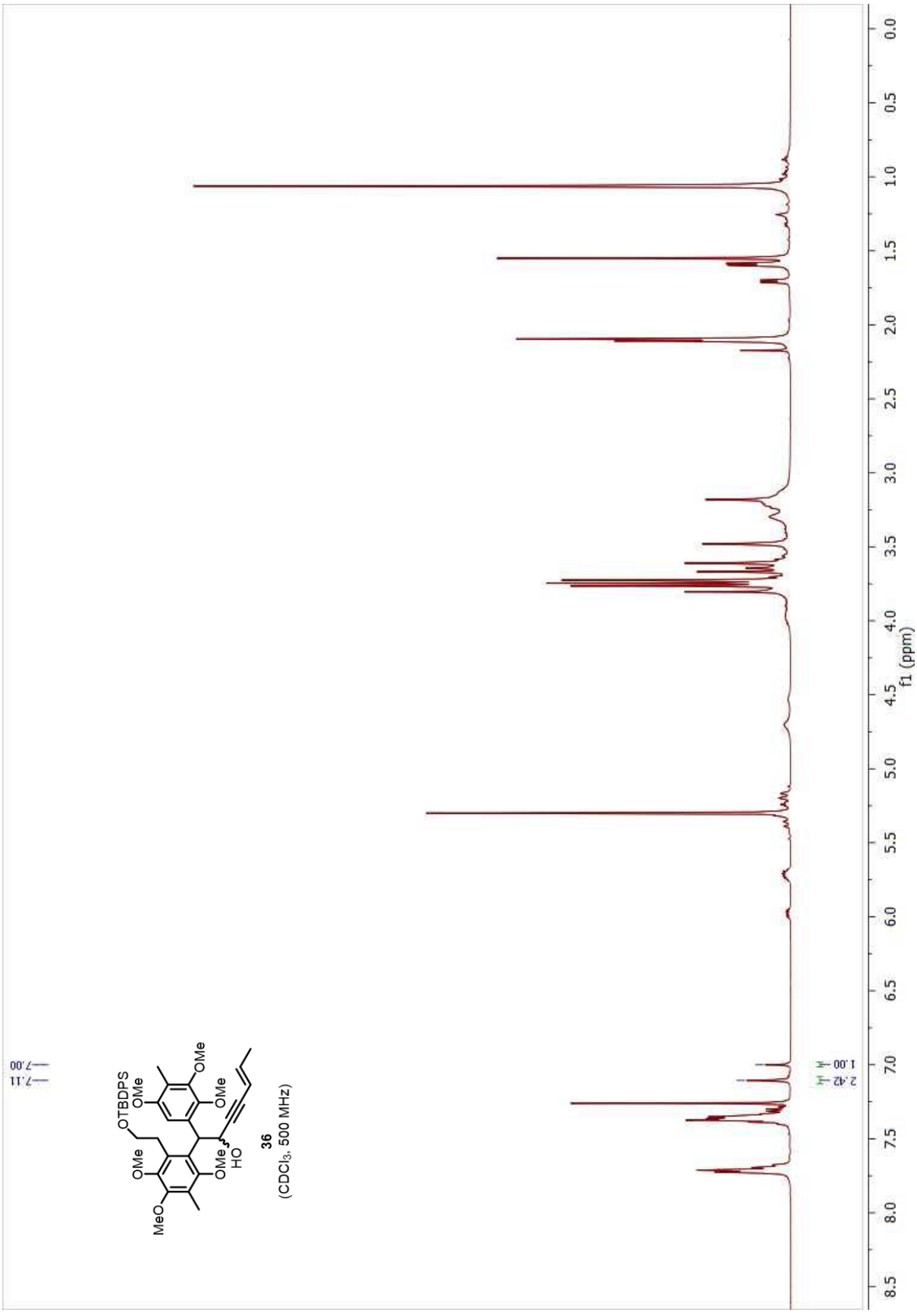
f1 (ppm)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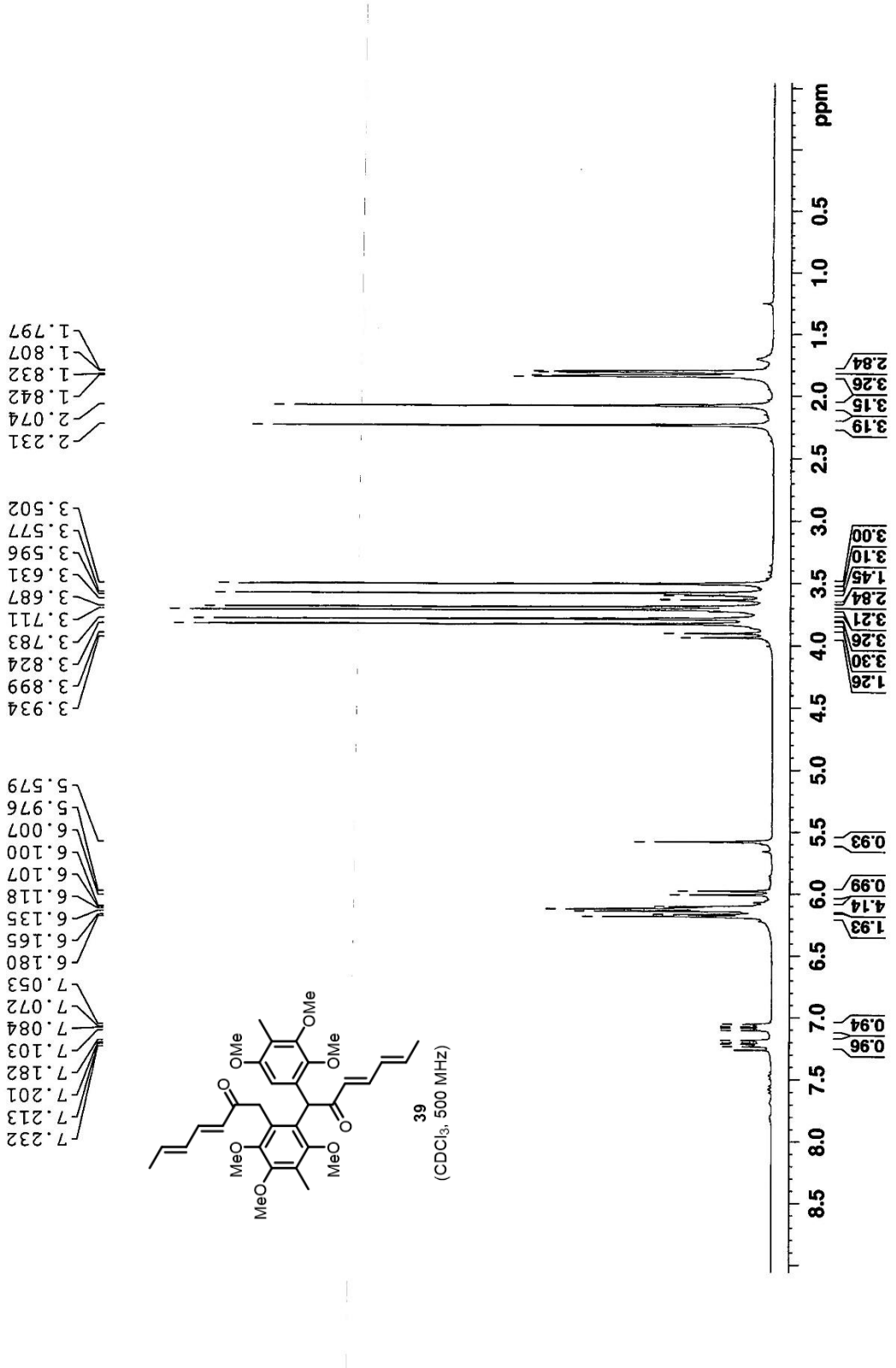
f1 (ppm)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2.5
2.0
1.5
1.0
0.5
0.96
0.94
1.93
4.14
0.99
0.93
1.26
3.30
3.26
3.21
2.84
1.45
3.10
3.00
3.19
3.15
3.26
2.84
OMe
OMe
OMe
MeO
MeO
MeO
O
O
39
(CDCl3, 500 MHz)
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7.182
7.103
7.084
7.072
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6.107
6.100
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1.832
1.807
1.797

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10.162
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18.709
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55.784
59.955
59.983
60.108
60.736
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124.324
126.904
126.939
127.038
127.887
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153.676
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OMe
OMe
MeO
MeO
MeO
O
O
39
(CDCl3, 126 MHz)
ppm

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1.851
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2.12
1.80
1.08
0.94
0.90
0.83
2.93
1.11
3.00
2.93
1.05
2.70
3.01
3.09
2.87
3.00
0 ppm
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MeO
MeO
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127.238
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18.731
10.200
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MeO
MeO
MeO
OMe
O
O
O
O
40
(CDCl3, 126 MHz)
ppm
20
40
60
80
100
120
140
160
180
200
0
20

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6.164
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3.806
3.793
3.768
3.764
3.757
2.730
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1.892
1.872
1.851
1.841
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OH
H
O
O
O
O
MeO
23
(CDCl3, 500 MHz)
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6.5
6.0
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4.0
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1.0
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1.94
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0.86
3.00
3.15
2.13
0.88
9.03
3.03

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ppm
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OH
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MeO
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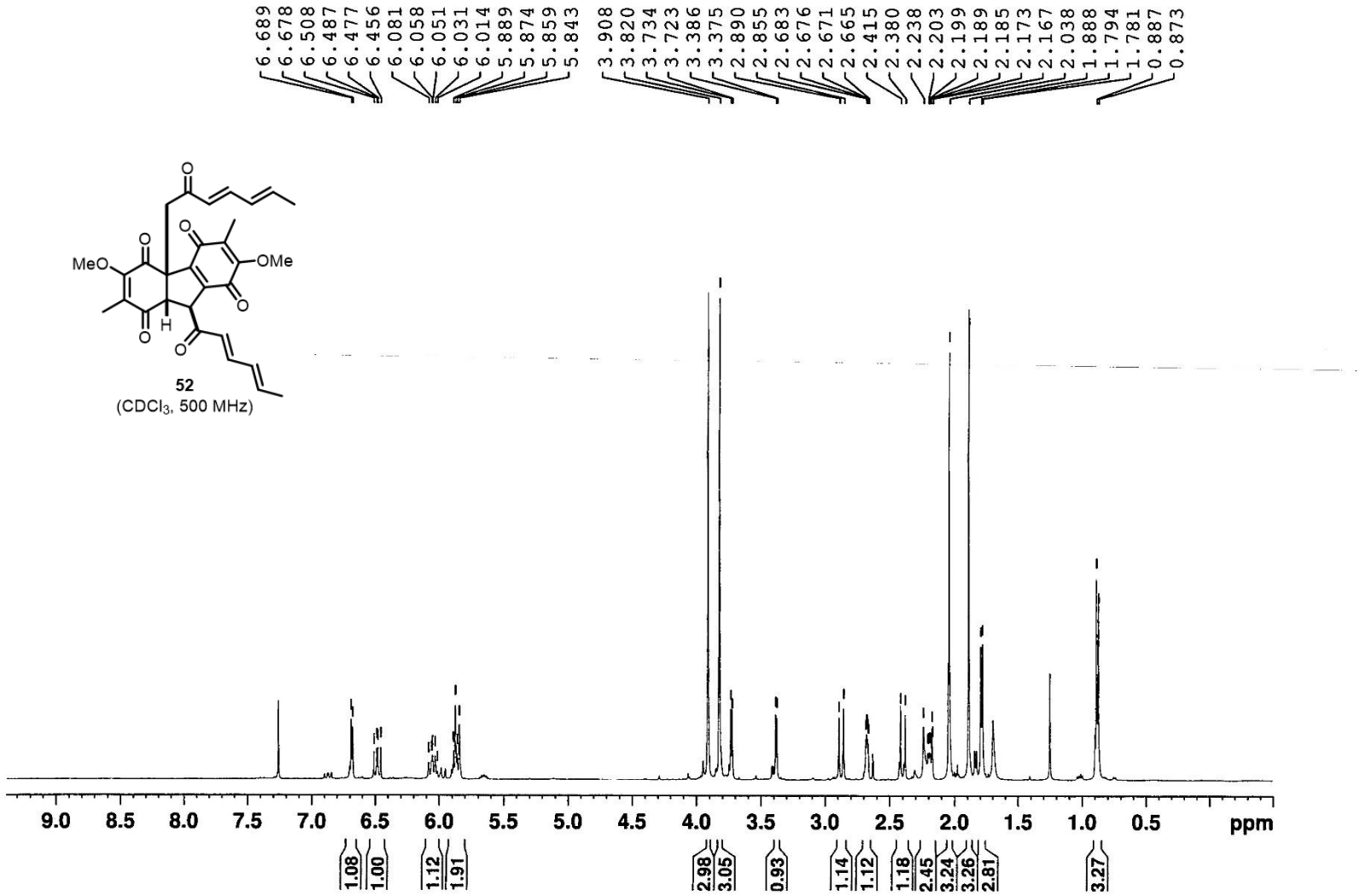
(CDCl3, 126 MHz)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5.859
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3.734
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2.238
2.203
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2.185
2.173
2.167
2.038
1.888
1.794
1.781
0.887
0.873
MeO
OMe
O
H
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(CDCl3, 500 MHz)
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6.0
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3.0
2.5
2.0
1.5
1.0
0.5
ppm
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1.00
1.12
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3.26
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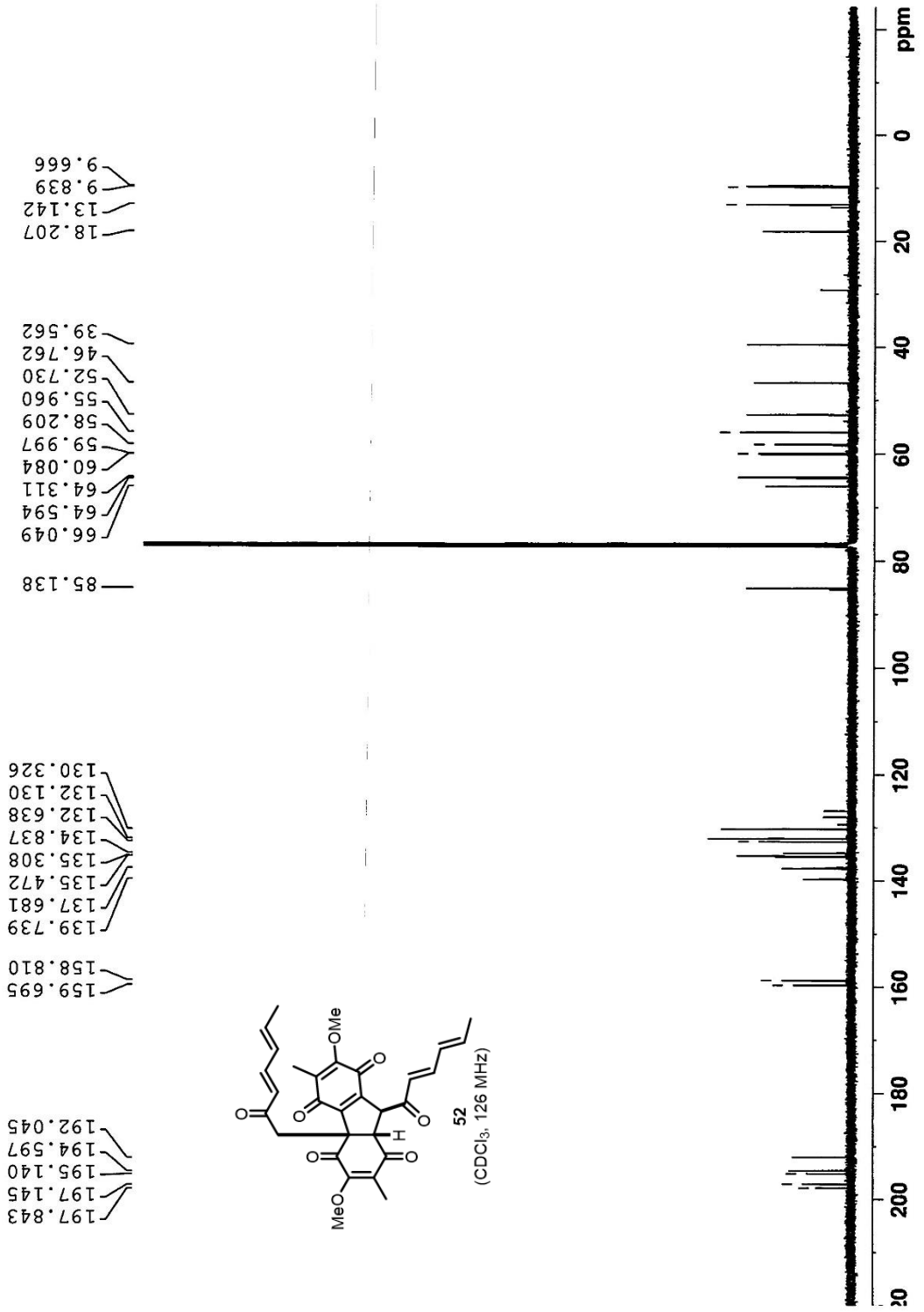
3.27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MeO
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O
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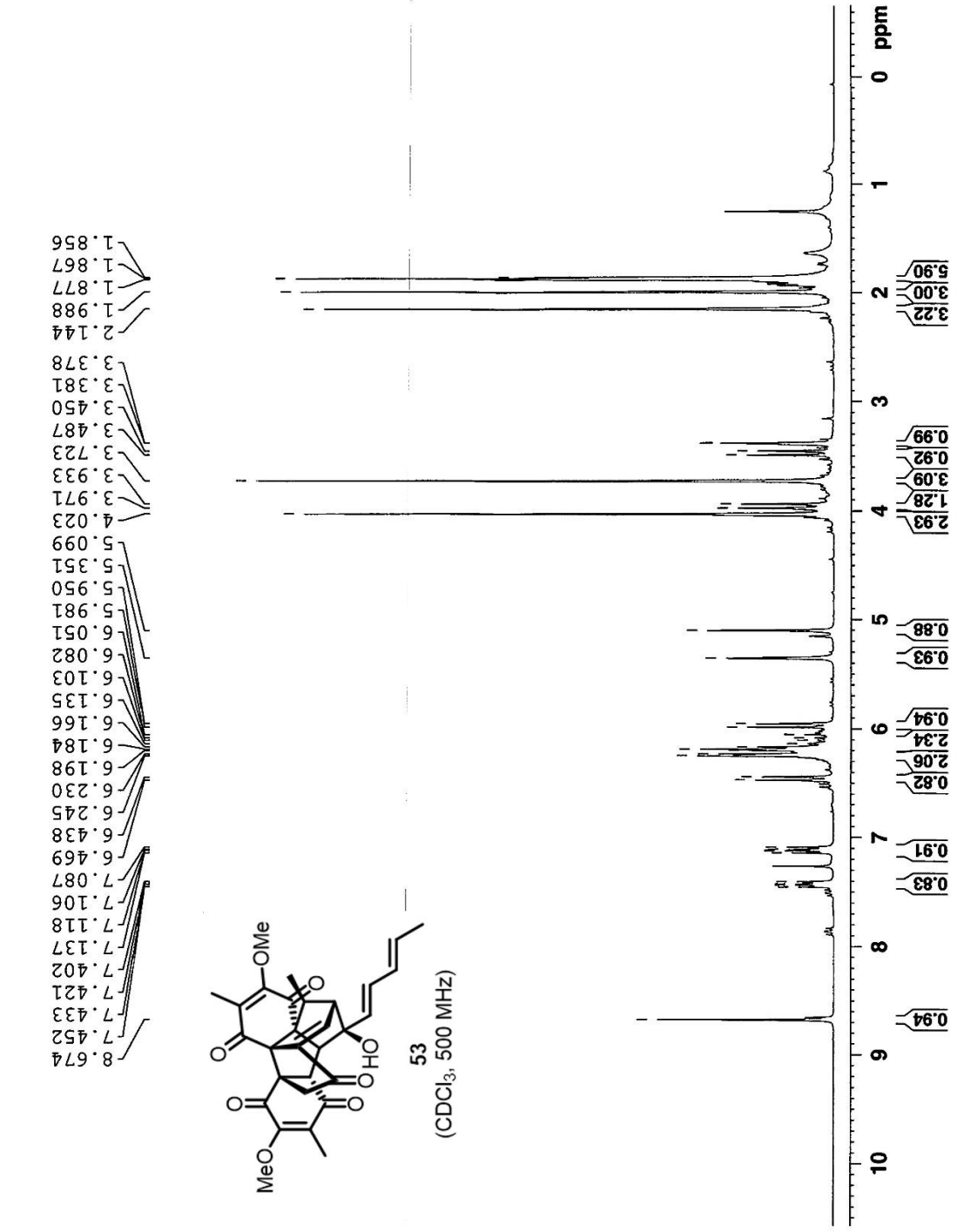
(CDCl3, 126 MHz)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6.082
6.051
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5.950
5.351
5.099
4.023
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3.723
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3.450
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3.378
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(CDCl3, 500 MHz)
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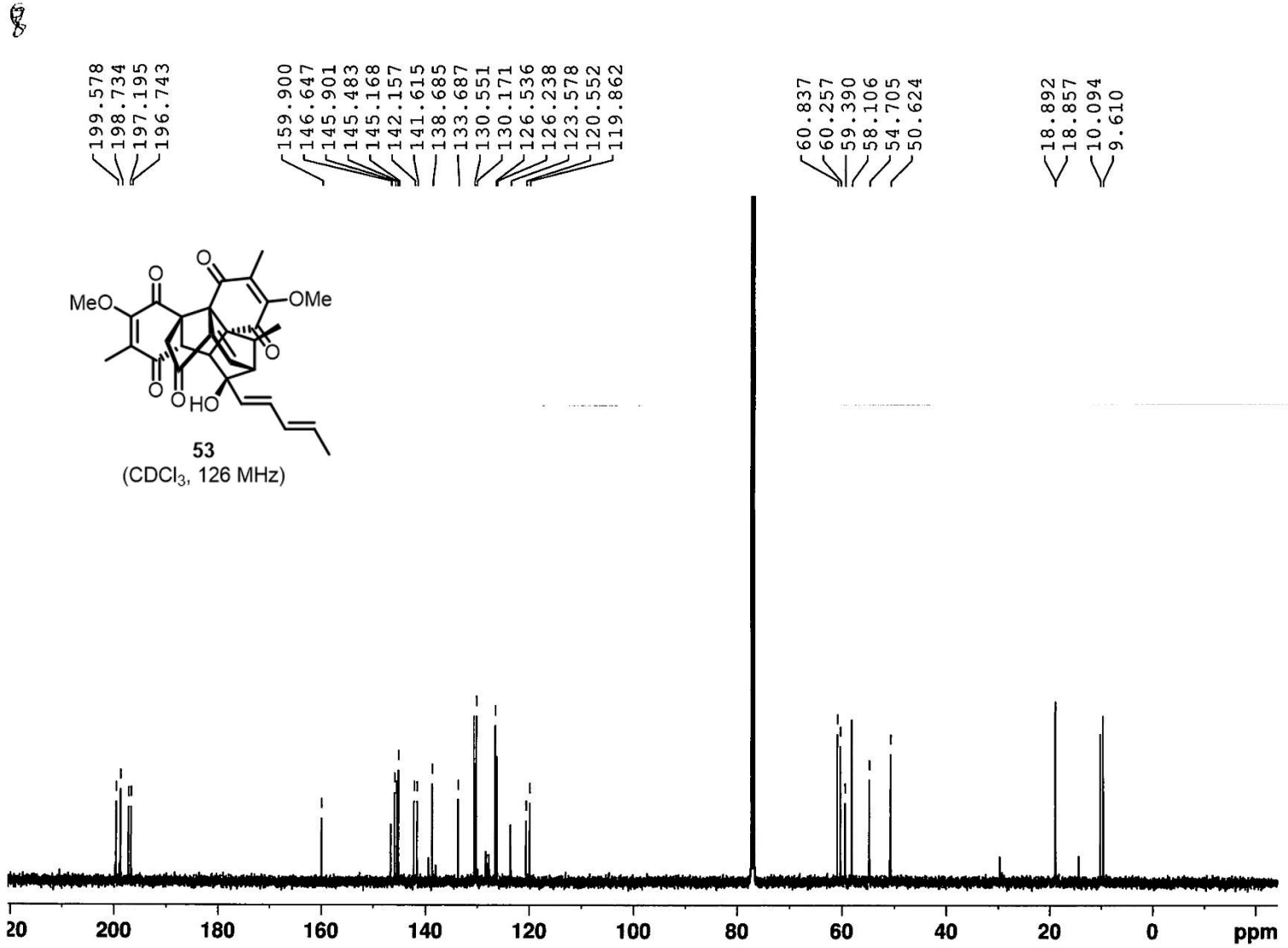
ppm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130.171
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126.238
123.578
120.552
119.862
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59.390
58.106
54.705
50.624
18.892
18.857
10.094
9.610
MeO
OMe
O
HO
53
(CDCl3, 126 MHz)
220
200
180
160
140
120
100
80
60
40
20
0
ppm

CHAPTER 4

DEVELOPING A UNIFIED STRATEGY TOWARD THE MYRIONEURON ALKALOIDS

4.1 Introductions

The *Myrioneuron* alkaloids are a group of natural products isolated from the plant genus *Myrioneuron*, a genus containing 10 specific names of species, with 8 of them are "accepted species names" on "theplantlist" webstie. The genus *Myrioneuron* is in the family *Rubiaceae* of the major group *Angiosperms*. A representative array of the *Myrioneuron* alkaloids were isolated from *Myrioneuron nutans* and *Myrioneuron faberi*, which mostly populate tropical and subtropical areas in Southern Asia, for example, north Vietnam. This is also a related flowering plant recorded in China. The isolation chemistry of the *Myrioneuron* plants have undergone noticeable development in the past 17 years since chemists started to pay attention on these trees, especially the species *Myrioneuron nutans* and *Myrioneuron faberi*. Further isolation of more structurally and biologically intriguing natural products in this family is also expected in the future. From this standpoint, we synthetic chemists wish to employ our tool kit to construct not only as many of the reported *Myrioneuron* alkaloid members as possible, but also to enable the synthesis of analogues of these natural products, to serve the purpose of structure-reactivity relationship (SAR) study and to support other relevant biological research by providing sufficient synthetic material. Hence, we turned our interest to the field of the *Myrioneuron* alkaloids and were eager to solve synthetic problems within.

4.1.1 Structural and biological activities of the Myrioneuron alkaloids

A representative array of the *Myrioneuron* alkaloids isolated from the species *Myrioneuron nutans* is shown in Figure 4-1. A common structural feature for these alkaloid natural products is a *cis*-decahydroquinoline (*cis*-DHQ) core. Outside the *cis*-DHQ core, diverse carbocycles, heterocycles, and carbon chains of different length can arise and contribute to the complexity and diversity of the *Myrioneuron* alkaloid family. The simplest *Myrioneuron* alkaloids, as can be

named based on number of cycles and ease of synthesis, are myrioxazine A (**1**) and myrioxazine B (**2**) discovered and synthesized by the Bodo group (its synthesis will be covered *vide infra*) in 2002.[1] They are both tri-cyclic compounds with one aminal (-NCH_2O-) containing ring fused with the commonly shared *cis*-DHQ motif. For more complex cases, schoberine (**3**)[2] incorporates the fourth ring, a piperidine moiety (It is noteworthy that the isolation of schoberine has been reported in several papers focusing on the *Nitraria* species, and the samples obtained there were not in pure form).[3-5] A long carbon side chain with a terminal primary alcohol was found to be in a structurally similar family member, schoberine B (**4**).[6] A higher oxidation state appears in myrionamide (**5**)[2,7] where the methylene next to nitrogen atom is oxidized to a carbonyl, forging an amide functionality. Two of the most complicated examples are myrioneurinol (**6**)[8] and myrobotinol (**7**).[9] Of them, myrioneuronol (**6**) is a tetracyclic compound containing an all-carbon quaternary center, making itself unique among all *Myrioneuron* alkaloids. Myrobotinol (**7**) is a "dimeric" member comprising two units of *cis*-DHQ motifs. The intriguing biogenesis and synthetic efforts of these molecules are discussed *vide infra*. It is noteworthy that all the *Myrioneuron* alkaloid members described above were isolated from the species *Myrioneuron nutans*, where most of the contributions came from the Bodo group in France and the Hao group in China.

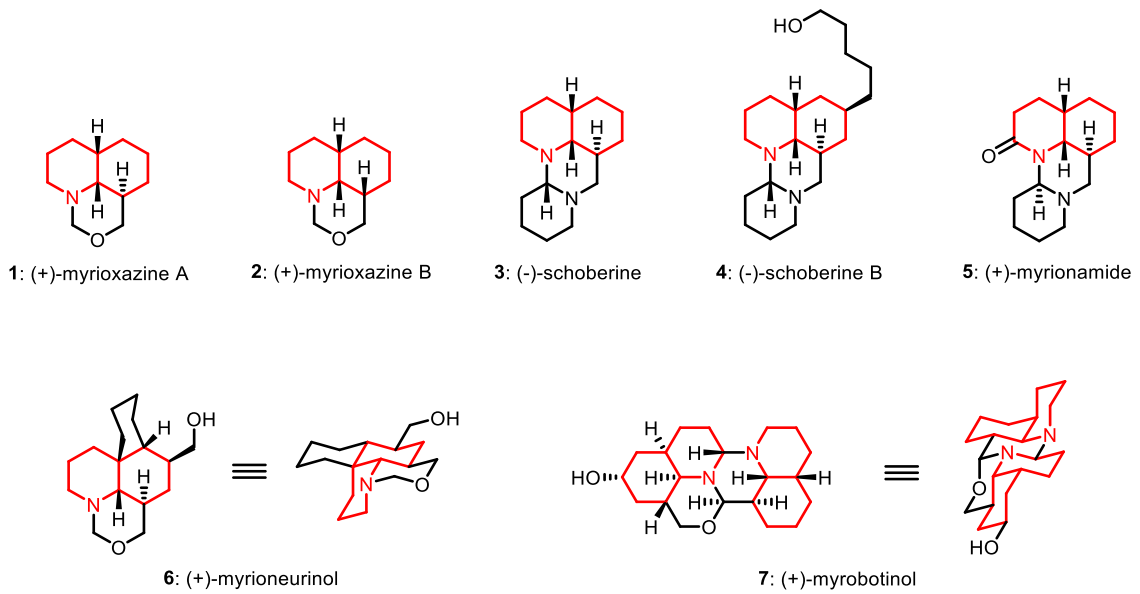


Figure 4-1. Representative *Myrioneuron* alkaloids isolated from species *Myrioneuron nutans*

The *Myrioneuron* alkaloids isolated from the species *Myrioneuron faberi* display many similar structural features, while unusual bond connections and stereochemistry are observed (Figure 4-2). Myrifamine A (**8**) and B (**9**) have similar *cis*-DHQ core structure,[10] however, with a conjugated exocyclic aldehyde incorporated on the β–carbon of the DHQ ring. Myriberine A (**10**)[11], together with myrionamide (Figure 4-1, **5**) has one stereocenter (marked in blue) disparate from structurally analogous schoberine (**3**) in Figure 4-1. Such stereochemistry presents in myrifamine C (**11**) as well.[10] The two halves in this molecule share high structural resemblance with myrionamide (**5**), while two pieces are joined together via a methylene bridge. A heterodimeric natural product myrifabine (**12**) was identified,[12] which consists of two pieces where the right hand one holds a *cis*-DHQ core. The left hand piece however, contains a *trans*-decahydroquinoline (*trans*-DHQ) core. The *trans*-DHQ units are witnessed in molecules from another sister species *Myrioneuron tonkinensis* (Figure 4-4).[13] In addition to DHQ-type members, molecules with varied topology such as β-myrifabral (**13**) was reported as well.[14-15]

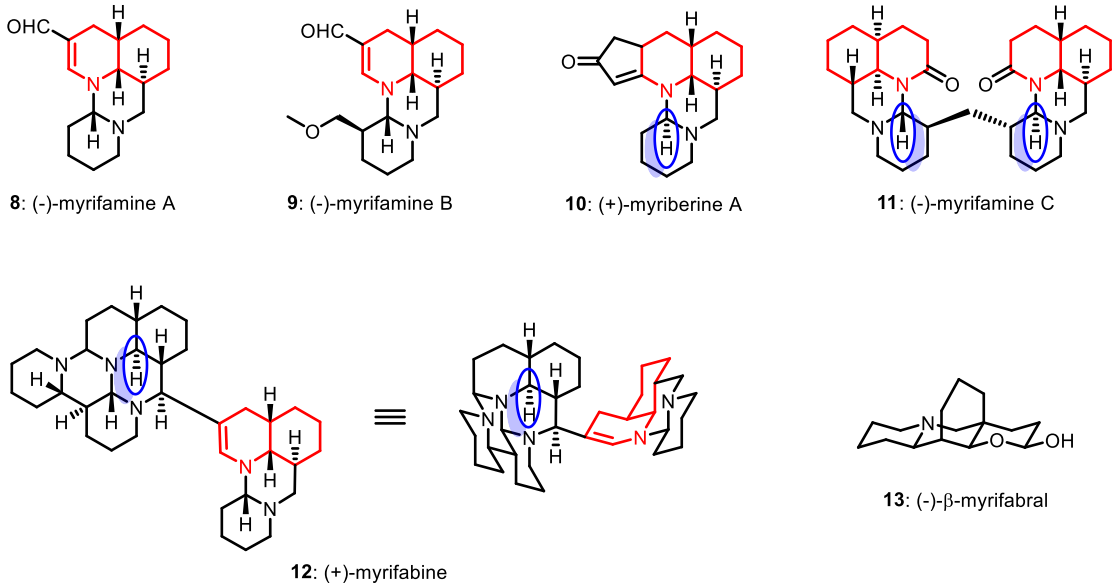


Figure 4-2. Representative *Myrioneuron* alkaloids isolated from *Myrioneuron faberi*

More intriguing *Myrioneuron* alkaloids with various oxidation patterns were isolated from another species *Myrioneuron effusum* as well (Figure 4-3).[16] Unlike myrionamide (**5**) and myrifamine C (**11**) which had their amide moiety appearing at C-2 position, mysumamide A (**14**) has its oxidation occurring on C-17, forming a "regio" isomer of myrionamide (**5**). Mysumamide B (**15**) and C (**16**) had their tertiary amine nitrogen oxidized to *N*-oxide at different positions. A structural diversification was also observed with mysumamide D (**17**) which plausibly experienced a condensation event with formaldehyde to own one additional hydroxymethyl group.

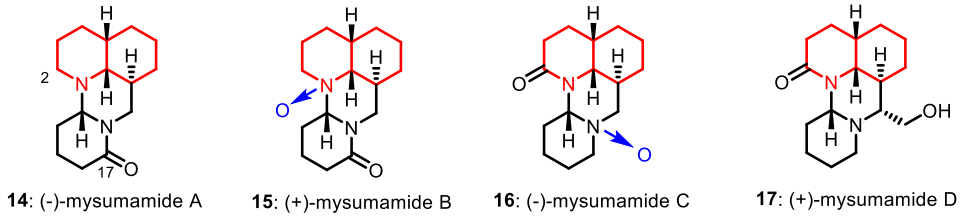
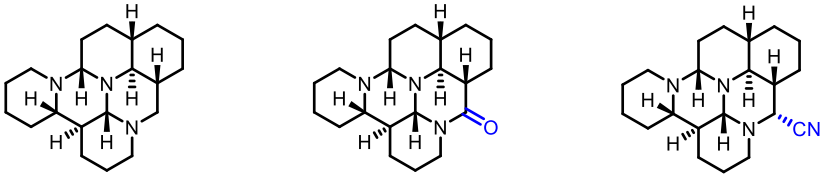


Figure 4-3. Representative *Myrioneuron* alkaloids isolated from *Myrioneuron effusum*

For molecules isolated from *Myrioneuron tonkinensis* (Figure 4-4),[13] they display not only the *trans*-DHQ cores, but also various oxidation states and other features (for example a nitrile in myritonine C **20**) in their hexacyclic sturctures.



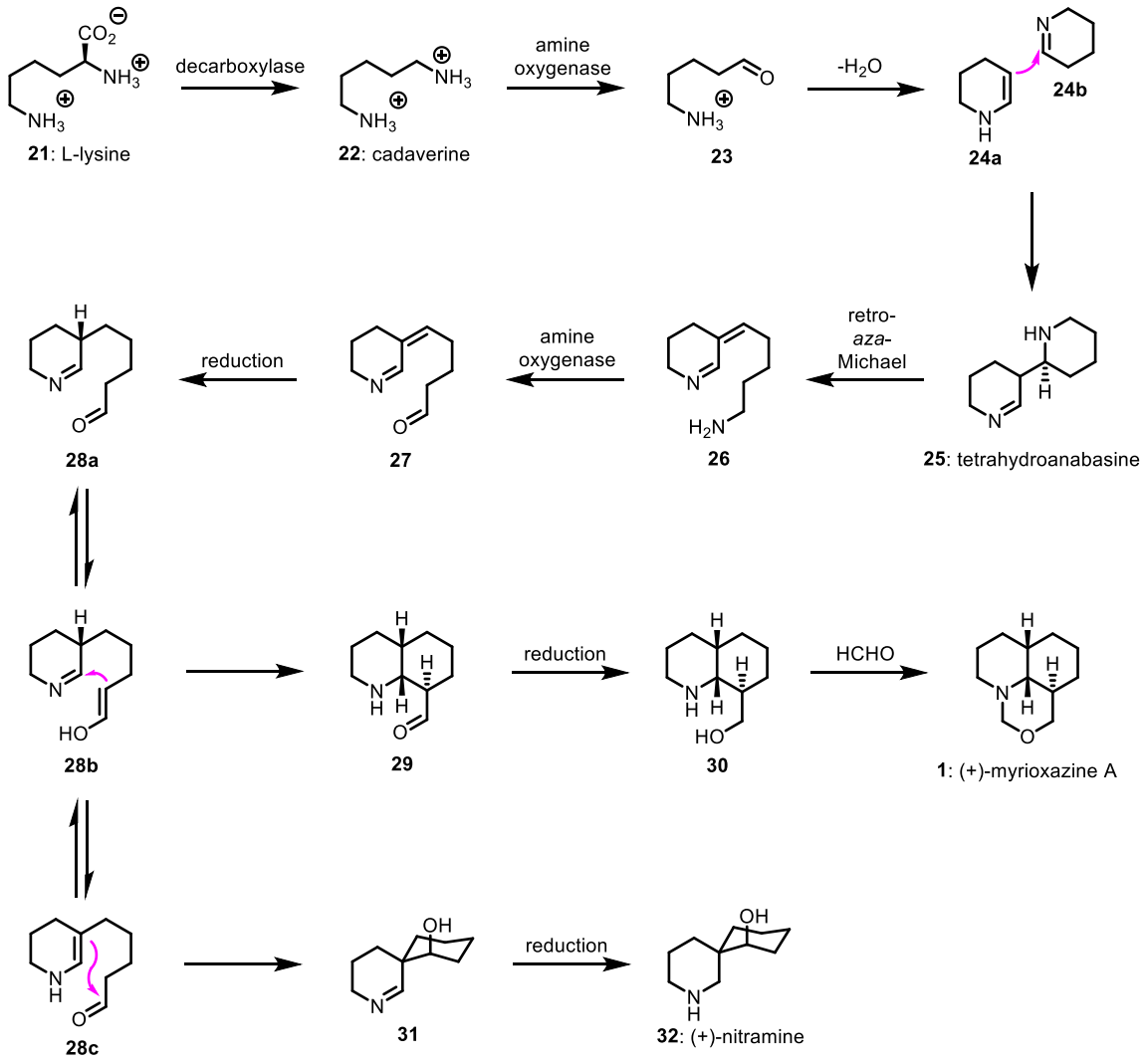
18: (-)-myritonine A **19**: (-)-myritonine B **20**: (-)-myritonine C

Figure 4-4. Representative *Myrioneuron* alkaloids isolated from *Myrioneuron tonkinensis*

The huge structural diversity grants the *Myrioneuron* alkaloids broad biological profiles. Anti-hepatitis C virus (anti-HCV) activities were recorded for schoberine B (**4**, Figure 4-1), myrifamine A-C (**8**, **9**, **11**, Figure 4-2), and myritonine A-C (**18**~**20**, Figure 4-4). Myrobotinol (**7**) and myrifabine (**12**) showed moderate antimicrobial activities. Myrioneurinol (**6**) displayed moderate anti-proliferative acitivity against κB cells but stronger antimalarial activity. Nevertheless, the biological studies related to these alkaloids were typically conducted as experiments complementary to isolation campaigns. Up to date, no systematic and comprehensive research projects have been targeting the structure-reactivity relationship (SAR) of the *Myrioneuron* alkaloids and the biochemical mechanisms within.

4.1.2 Biogenesis

Although many factors may come into play in the biosynthesis of different *Myrioneuron* alkaloids, they share a common ultimate precursor, L-lysine (**21**). Myrioxazine A (**1**) and nitramine (**32**) are selected as examples to demonstrate the biogenetic route of the *Myrioneuron* alkaloids and a closely related family, the *Nitraria* alkaloids, in Scheme 4-1.[17-18]



Scheme 4-1. A general biosynthetic origin of the *Myrioneuron* alkaloids and the *Nitraria* alkaloids exemplifying myroxazine A and nitramine

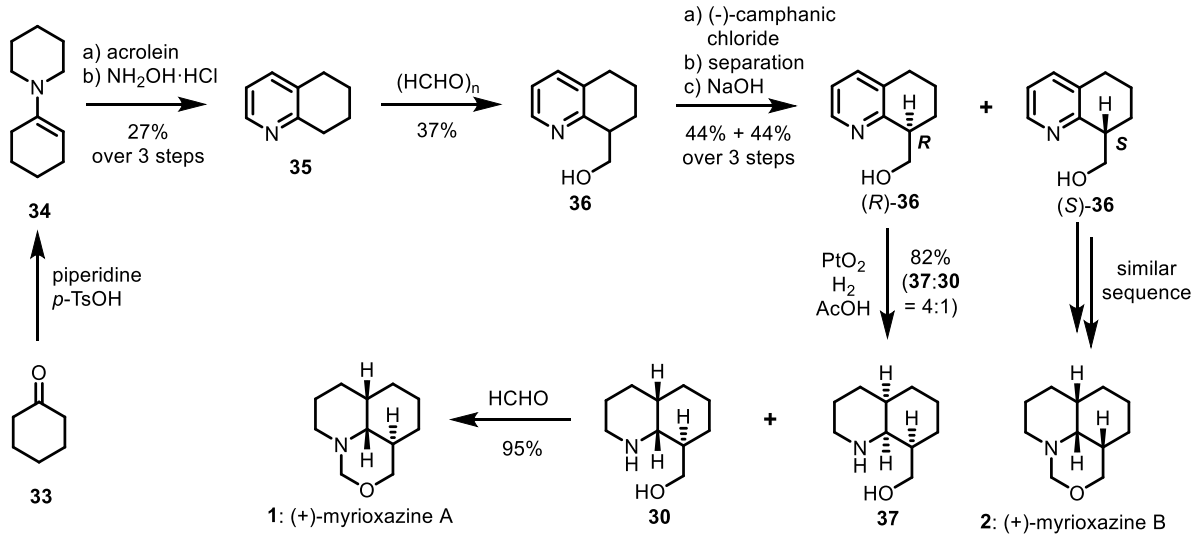
The biosynthetic map commenced with L-lysine (**21**). L-lysine (**21**) can undergo enzyme-mediated decarboxylation to give 1,5-diaminopentane, *aka* cadaverine (**22**). This material can be oxidized to aldehyde **23** by amine oxygenase. The following condensation provides imine **24** which is in an equilibrium of two forms. The nucleophilic attack of one molecule of the enamine form (**24a**) onto one molecule of the imine form (**24b**) results in the homo-dimerization product tetrahydroanabasine (**25**), on which a retro-*aza*-Michael reaction disassembles the piperidine ring and releases a primary amine in intermediate **26**. The primary amine moiety is again oxidized to an aldehyde. A conjugate reduction then reduced the tricyclic alkene of **27**. The so-obtained

intermediate **28** has two functionalities that are able to tautomerize, imine and aldehyde. In tautomer **28b**, the enol moiety attacks the imine to form the *cis*-DHQ in **29**, which was further reduced and cyclized by formaldehyde to form myrioxazine A (**1**). The other active tautomer **28c** results in a spirocycle **31** through the nucleophilic addition of the enamine form onto the pendant aldehyde which ultimately leads to nitramine (**32**), a representative member of the *Nitraria* alkaloid family.[19]

Note that other reactive molecules may intercept the elementary steps described above and further yield various natural products. The biosynthetic pathways of each specific molecules that we pursue synthesis will be discussed below.

4.1.3 Reported syntheses and synthetic studies of the Myrioneuron alkaloids

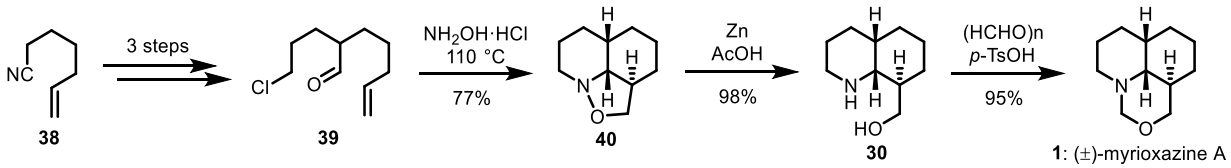
The earliest isolation report of any *Myrioneuron* alkaloids was the isolation of myrioxazine A (**1**) and B (**2**) in 2002 by the Bodo group. In the same research paper they reported the asymmetric synthesis of these two molecules as well (Scheme 4-2).[1] Starting from a three-step sequence, they prepared the substituted pyridine **35** from cyclohexanone (**33**). After a hydroxymethylation reaction, the racemic alcohol product **36** was subjected to chiral resolution protocol, yielding two enantiomers (*R*)-**36** and (*S*)-**36**. (*R*)-**36** was further hydrogenated with Adam's catalyst (PtO_2) in acetic acid to yield a pair of diastereomeric amino alcohols **30** and **37** in 4:1 ratio. The minor diastereomer **30** was treated with 30% formaldehyde solution to reach (+)-myrioxazine A (**1**). (+)-myrioxazine B (**2**) was obtained through the same sequence (hydrogenation/HCHO treatment) from (*S*)-**36**.



Scheme 4-2. Bodo's asymmetric synthesis of myrioxazine A and myrioxazine B

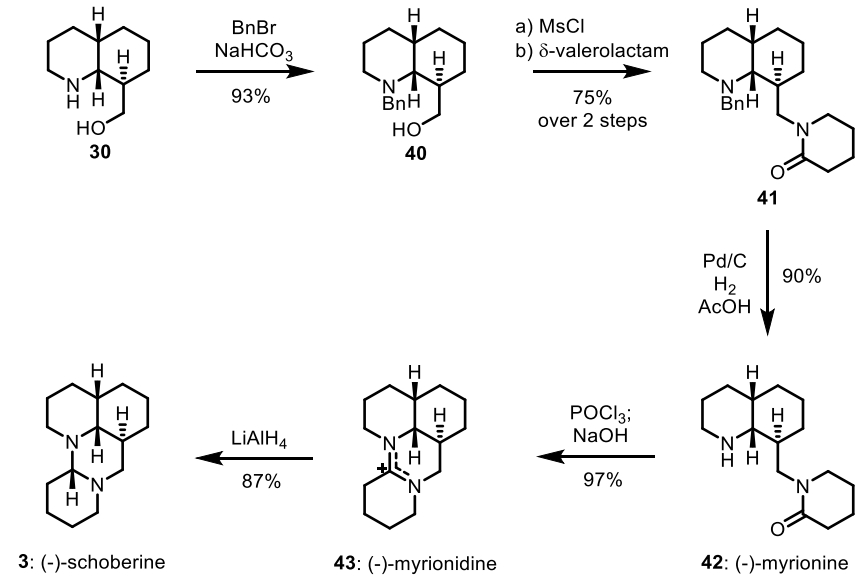
Interestingly, a research article interrogating conformation energy of tricyclic compounds reported the racemic synthesis of myrioxazine A (**1**) and B (**2**) in 1980,[20] 22 years prior to Bodo's isolation from the plant species *Myrioneuron nutan*! The two synthetic routes were almost identical, except for the chiral resolution part. The author at that time, however, merely synthesized these two compounds for their physical chemistry studies. This means that it is just a coincidence that they synthesized something hidden deep in the tropical forests in Vietnam.

The simple structure of myrioxazines attracted attentions from other synthetic chemists to showcase their inventions of new synthetic tools. The Burrell group developed a tandem reaction in achieving a concise synthesis of (±)-myrioxazine A (Scheme 4-3).[21] On a multi-functionalized aldehyde **39** which was prepared from simple nitrile **38** in 3 steps, condensation reaction first happened with hydroxyamine to afford hydroxy imine. The following *N*-alkylation and [3+2] cycloaddition reaction generated tricycle **40**. Zinc promoted reductive cleavage of N-O bond and formaldehyde mediated hemiaminal formation rendered the target molecule **1** in a total of 6 steps.



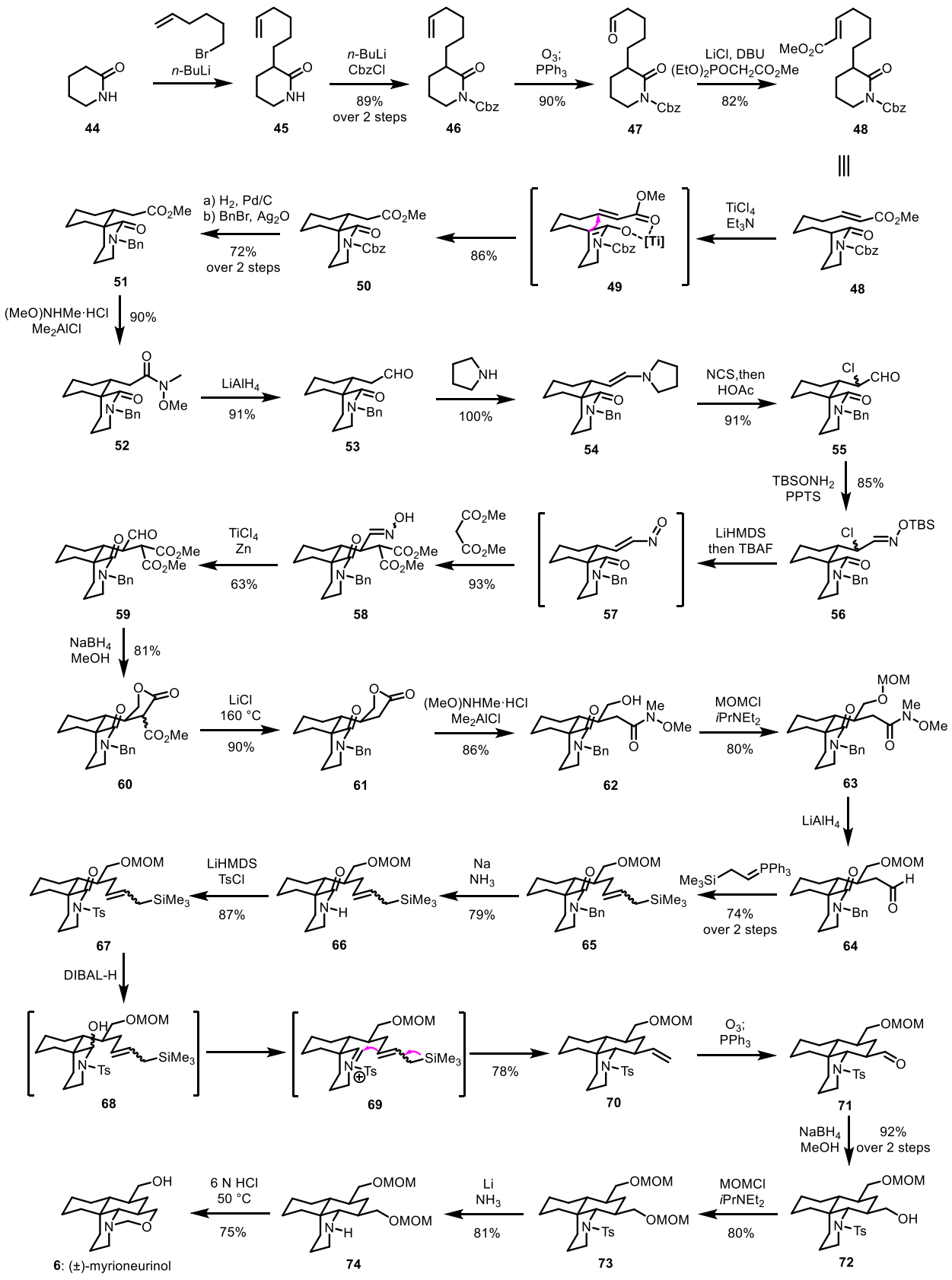
Scheme 4-3. Burrel's racemic synthesis of myrioxazine A featuring a tandem condesation/cyclization/cycloaddtion reaction

Besides the simple myrioxazines, the Bodo group also isolated and synthesized structurally more complex (–)-schoberine (**3**) and its putative biosynthetic precursors, among which two were identified as natural isolates.[2] Taking advantage of the intermediate amino alcohol in the synthesis of myrioxazines (Scheme 4-2), they selectively protected the secondary amine and then mesylated the primary alcohol. This mesylate served as an alkylation reagent in the alkylation reaction of δ-valerolactam, in delivering the tertiary amide **41**. Removal of the *N*-benzyl protecting group under an acidic hydrogenation condition revealed the bicyclic natural product (–)-myrionine (**42**). Upon treatment of dehydration reagent oxyphosphorus trichloride ($POCl_3$), the carbonyl of amide condensed with the secondary amine to form iminium, which is the key portion of the ionic natural product myrionidine (**43**). Further stereoselective reduction of the iminium moiety by $LiAlH_4$ yielded the tetracyclic *Myrioneuron* alkaloid (–)-schoberine (**3**) in high yield (87%). Although the reagents employed in this synthesis may not be perfectly biomimetic, the redox manipulations streamlining three natural products supported their relationship in biogenesis.



Scheme 4-4. Bodo's asymmetric synthesis of schoberine and related *Myrioneuron* alkaloids

The last but most recent synthesis of myrioneurinol, one of the most structurally complex members in the *Myrioneuron* alkaloid family, was published by the Weinreb group in 2014.[22-23] As was mentioned in the introduction section, the unique all-carbon quaternary center in the core of myrioneurinol imposed considerable hurdles toward its chemical synthesis. In order to address the problem, they developed a highly stereoselective enolate Michael addition reaction (Scheme 4-5). Beginning with an α-alkylation of δ-valerolactam (**44**), the following Cbz-protection of the amide generated **46**, which was then oxidatively cleaved at the terminal alkene position to give aldehyde **47**. A Masamune-Roush protocol of the Horner-Wadsworth-Emmons olefination installed the α,β-unsaturated ester in **48**. Treating **48** with $TiCl_4$ and Et_3N resulted in coordination between Ti(IV) and two oxygen atoms from carbonyl. This facilitated an intramolecular Michael addition of enolate onto the electron-withdrawing alkene within intermediate **49**, in a highly stereoselective manner, to give spirocycle **50**. Protecting group exchange from *N*-Cbz to *N*-benzyl, followed by formation of Weinreb amide culminated **52**, followed by a $LiAlH_4$-mediated reduction to yield aldehyde **53**.



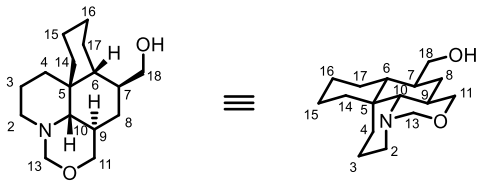
Scheme 4-5. Weinreb's racemic synthesis of myrioneurinol featuring an enolate-Michael addition and an *aza*-Sakurai cyclization

Next, a two-step α-chlorination of the aldehyde **53** and the condensation with TBS-hydroxyamine generated the precursor **56**, which was turned into a nitroso alkene upon treatment of base (LiHMDS) and TBAF. The active Michael acceptor **57** was attacked by the enolate of dimethyl malonate to afford compound **58**. The subsequent reductive removal of oxime and reduction of the resultant aldehyde **59** ended up in lactone **60**. Another four steps, including decarboxylation, opening the lactone ring with Weinreb amide, *O*-MOM protection of the primary alcohol, and reduction of the Weinreb amide revealed the aldehyde **64**. Wittig olefination of this aldehyde and protecting group manipulations from *N*-Bn to *N*-Ts set the stage for the *aza*-Sakurai reaction. The key cyclization was then triggered by DIBAL-mediated reduction of amide to hemiaminal intermediate **68**, followed by a spontaneous dehydration to form iminium **69**. The nucleophilic trapping of this iminium by allyl TMS group rendered the *cis*-DHQ core of the product **70** as a single diastereomer. The final functional group decoration proceeding through ozonolysis, *N*-Ts deprotection, aminal ring formation, and *O*-MOM deprotection generated racemic myrioneurinol (**6**) in a total of 28 steps.

The Weinreb synthesis of myrioneurinol set a high standard for following efforts toward the *Myrioneuron* alkaloid synthesis. Therefore, the representative and challenging molecule, myrioneurinol, was elected for synthetic analysis in the first place.

4.2 Structural and biogenetic properties of myrioneurinol

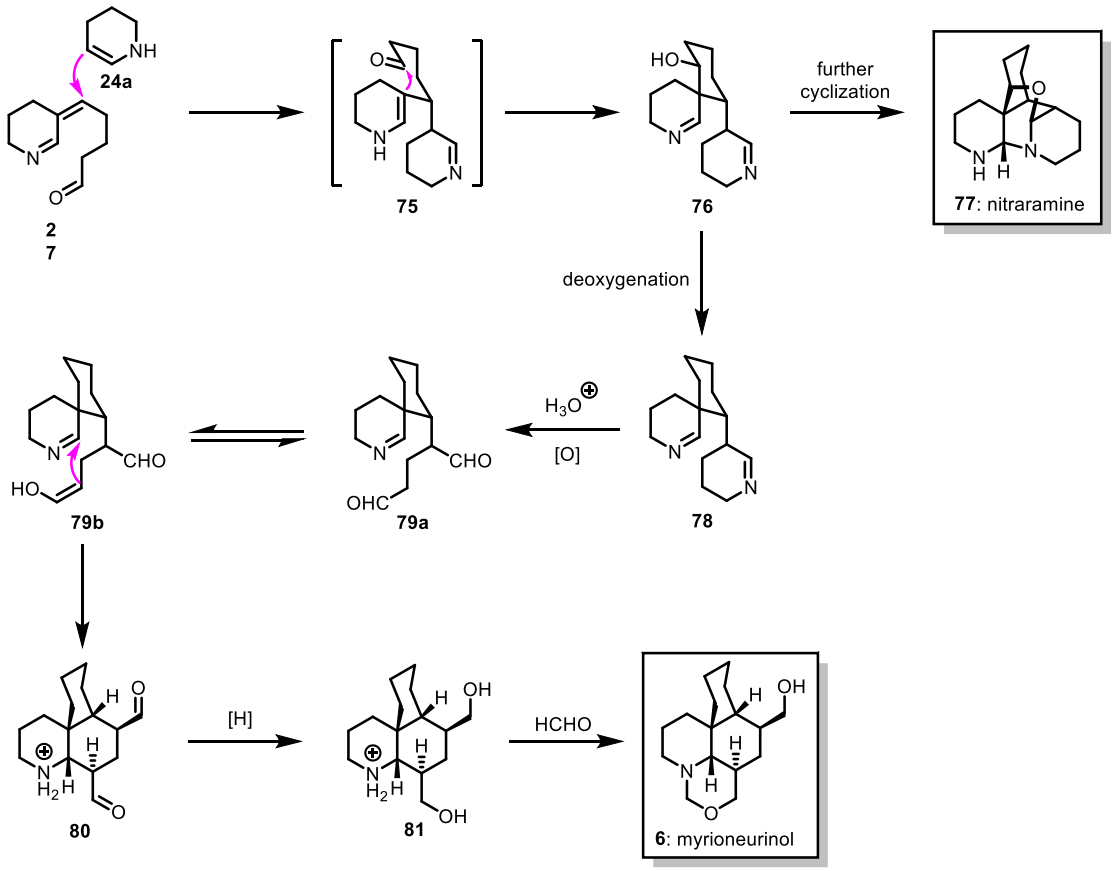
Myrioneurinol (**6**) was isolated from leaves of the plant species *Myrioneuron nutans* collected in North Vietnam. 32 mg of the pure natural product were isolated from 5 kg of biomass. The bond connections and relative stereochemistry were determined through a combination of mass spectroscopy, IR, and a full set of 1D/2D NMR spectra (Figure 4-5).[8]



6: (+)-myrioneurinol

Figure 4-5. Flat and 3-D structure of myrioneurinol

The biosynthetic origin of myrioneurinol (Scheme 4-6) was also proposed to be L-lysine, the same precursor of all other *Myrioneuron* alkaloids. The conjugated imine intermediate **27**, whose biogenesis was described in Scheme 4-1, was intercepted by the six-membered cyclic enamine **24a**, followed by an intramolecular cyclization between the enamine group and the aldehyde group in intermediate **75**, to generate a tricyclic compound **76**. At this point, a ring flip and further cyclization events triggered by the nucleophilic addition of alcohol onto the right-hand imine in intermediate **76** could lead to the *Nitraria* alkaloid nitraramine (**77**),[24] indicating again that the *Nitraria* alkaloids and the *Myrioneuron* alkaloids share the common biosynthetic precursors and part of the biosynthetic conduits. On the other hand, if a deoxygenation event removing the secondary alcohol occurred on **76**, the right-hand cyclic imine could then be hydrolyzed and oxidized to give dialdehyde **79a**, where one of the aldehydes was tautomerized to enol form **79b**. The nucleophilicity of the enol form empowered its attack onto imine (or iminium in vivo), shaping the *cis*-DHQ core (**80**). Reduction of aldehyde to primary alcohol and aminal formation revealed myrioneurinol (**6**) in this biosynthetic proposal.

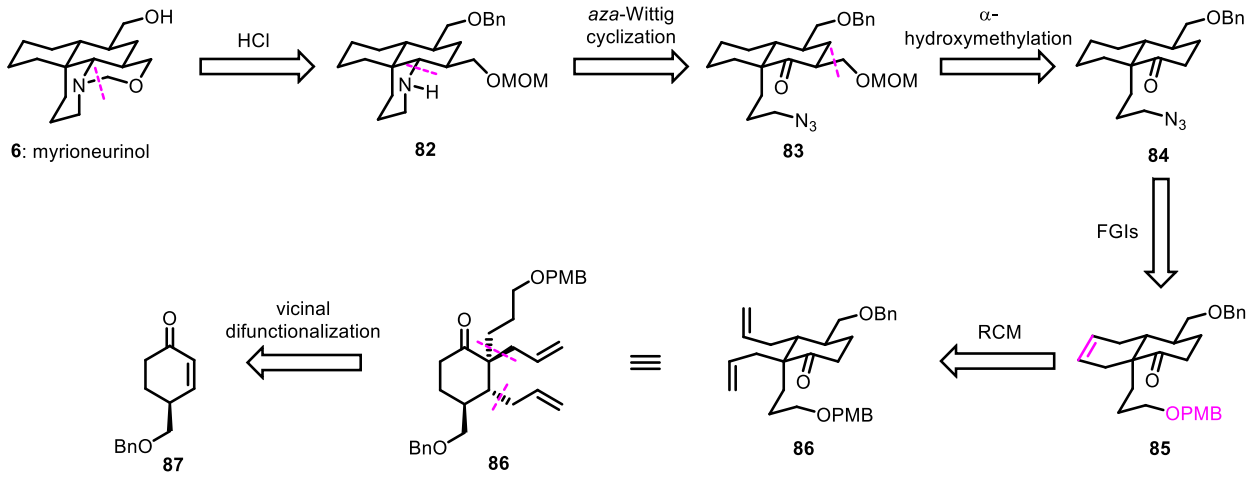


Scheme 4-6. Bodo's proposed biosynthetic pathway to myrioneurinol and a related *Nitraria* alkaloid nitraramine

4.3 Retrosynthetic analysis of myrioneurinol

The unique structure with an all-carbon quaternary center and suitable molecular size for synthetic exploration, together with our passion to achieve a more concise and potentially enantioselective synthesis given the high benchmark that the Weinreb synthesis set, prompted us to select myrioneurinol as the primary synthetic target among the *Myrioneuron* alkaloids. Moreover, an efficacious solution for the *cis*-DHQ core of myrioneurinol that are differentiated from the precious synthesis may serve as a global strategy that can ultimately lead to more *Myrioneuron* alkaloids with *cis*-DHQ features. In that vein, the studies and explorations toward myrioneurinol itself are expected to enlighten a unified strategy toward the chemical synthesis of the *Myrioneuron* alkaloid family.

The retrosynthetic analysis of myrioneurinol began with a disconnection at aminal ring (Scheme 4-7). Its precursor, the *O*-MOM protected amino alcohol **82** can be organized via a cyclization reaction exploiting the reactivity between the carbonyl on the bicycle and the functionality on the side chain, for instance, an *aza*-Wittig cyclization reaction on azide **83**. From there, the protected hydroxymethyl moiety would be installed through an α-functionalization reaction of the ketone carbonyl in **84**. For intermediate **84**, adding one degree of unsaturation to the saturated *trans*-decalin enabled a disconnection of the double bond in **85**, via a ring-closing metathesis (RCM) reaction. In addition, the azide moiety in **84** could be traced back to a protected primary alcohol in monocyclic intermediate **85**. Such a multi-substituted cyclohexanone **86** could be synthesized by installing the 4-benzyloxymethyl cyclohexanone **87** with three three-carbon side chains (3C-unit), with two of which are allyl side chains serving as precursors for RCM. The last side chain containing a primary alcohol would act as a surrogate of azide. Finally, the synthesis of enone **87** has already been reported in both racemic and asymmetric manners.[25]

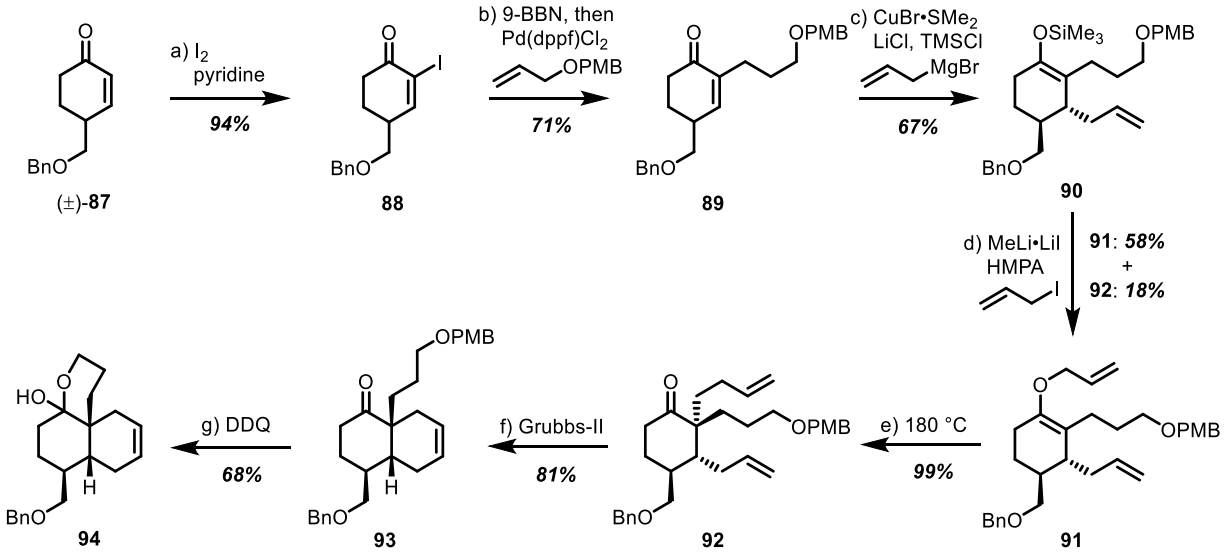


Scheme 4-7. Retrosynthetic analysis of myrioneurinol centered on an *aza*-Wittig cyclization

4.4 Synthetic explorations toward myrioneurinol

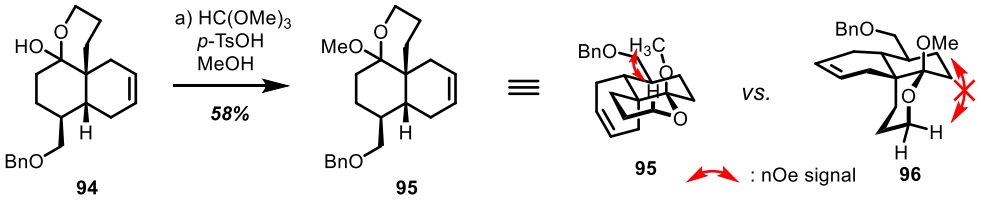
4.4.1 Encountering a wrong decalin configuration

Our journey commenced with racemic enone **87**, which could be prepared in deca-gram scale via a modified procedure (Scheme 4-8). Iodination of α-position of enone, followed by a Suzuki-Miyaura coupling reaction afforded the advanced enone **89** with the first three-carbon unit (3C-unit) implemented. To install the two allyl side chains, an allyl cuprate reagent mediated Michael addition reaction was performed on enone **89**, with the resultant enolate trapped by TMSCl to generate silyl enol ether **90**. Methyllithium-lithium iodide complex or methyllithium desilylated **90** to regenerate lithium enolate, which was then captured by allyl iodide to form a 3:1 mixture of *O*-allylation/*C*-allylation product. Soon we found that the *O*-allylation product **91** can be turned into a *C*-allylation product **92** which was exactly same as the one from direct allylation, as a single isomer under thermal conditions (180 ^{o}C, neat) via a Claisen rearrangement. At this stage we attempted to designate the relative stereochemistry of the *C*-allylation product and its post-RCM derivative **93**, while overlapping of key peaks in ^{1}H NMR spectra prevented us from making a decisive designation. To address the problem, we carried on synthesis and deprotected the *O*-PMB group on the distal primary alcohol of **93** by 2,3-dicyano-5,6-dichlorobenzoquinone (DDQ). The so-exposed free alcohol spontaneously formed hemiketal **94** with the carbonyl on the decalin ring. We tried again to determine whether the desired *trans*-decalin was in hemiketal **94** but correlation NMR data was still unsatisfactory for a clear reading due to impurities and overlapping of proton signals.



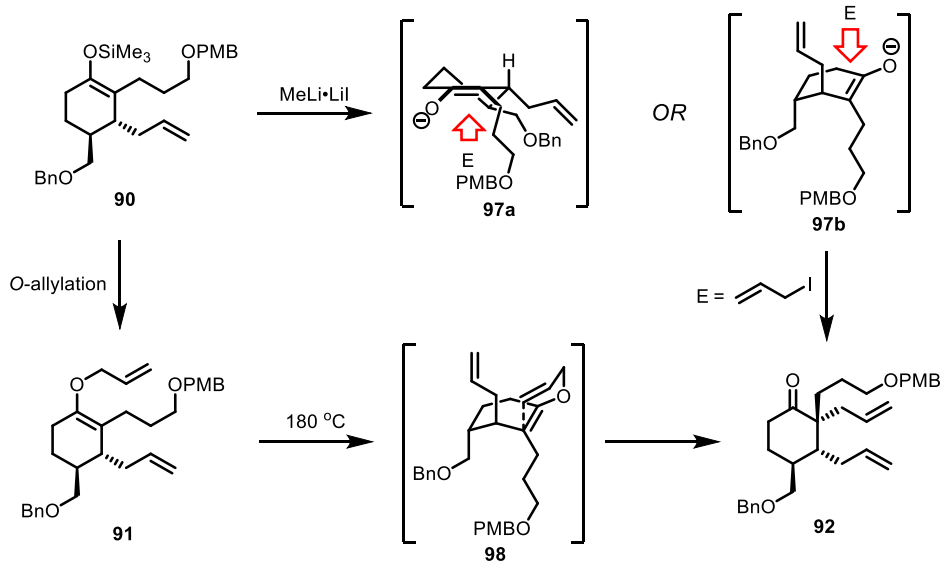
Scheme 4-8. Synthesis of hemiketal **94**. *Reagents and conditions*: (a) I_2 (1.2 equiv), CH_2Cl_2/pyridine, 23 °C, 16 h, 2 cycles; (b) allylOPMB (2.0 equiv), 9-BBN (0.5 M in THF, 1.95 equiv), THF, 70 °C, 6 h, then **88** (1.0 equiv), $Pd(dppf)Cl_2$ (0.075 equiv), $AsPh_3$ (0.08 equiv), Cs_2CO_3 (1.5 equiv), THF/H_2O (10:1), 70 °C, 12 h; (c) CuBr•SMe_2 (1.2 equiv), LiCl (2.4 equiv), THF, 23 °C, 5 min, then allylmagnesium bromide (1.0 M in ether, 3.5 equiv), -78 °C, 30 min, then TMSCl (2.0 equiv) and **89** (1.0 equiv), -78 °C, 2 h, slowly to 23 °C, 8 h; (d) MeLi•LiI (1.0 M in ether, 1.3 equiv), THF, 0 °C, 1 h, then HMPA (6.0 equiv), then allyl iodide (3.0 equiv), -78 °C, 2 h, slowly to 23 °C, 8 h; (e) neat, 180 °C, 6 h; (f) Grubbs-II catalyst (0.15 equiv), CH_2Cl_2, 23 °C, 16 h; (g) DDQ (1.3 equiv), CH_2Cl_2, 23 °C, 30 min

We carried on the synthesis with hemiketal **94** (Scheme 4-9), hoping that we could find a suitable derivative to determine relative stereochemistry. The methyl protection of ketal under an acidic condition (*p*-TsOH) furnished the tricycle **95**. This material is not only sufficiently clean on ^{1}H NMR due to high purity, but also has a strong nOe correlation signal between the proton of methoxy on ketal and that from the axial proton on side chain, indicated by red arrows in Scheme 4-9. As a comparison, such correlation could never appear in a *trans*-decalin system **96** since these two protons are too distant to substantiate any observable correlations. Thence, the relative stereochemistry of the decalin that we made was determined to be a *cis*-decalin, meaning that we needed to adjust our synthetic design to reach the *trans*-decalin core of target molecule myrioneurinol.



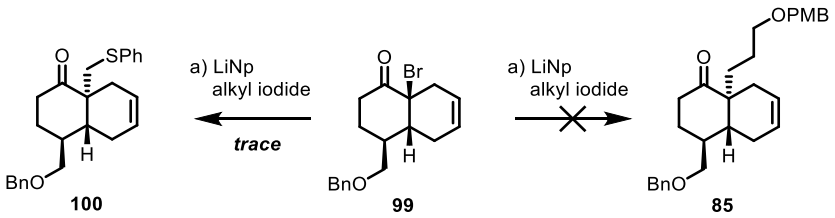
Scheme 4-9. Confirmation of the *cis*-decalin structure. *Reagents and conditions*: (a) $HC(OMe)_3$ (10.0 equiv), *p*-TsOH (0.1 equiv), MeOH, 50 °C, 2 h.

The rationale behind the stereochemical outcome of such an allylation reaction could be referenced from Danishefsky's work (Scheme 4-10).[26] According to their findings, the lithium enolate generated from **90** can adopt two conformations that were ready for electrophilic attack. In the twist-boat conformer **97a**, electrophiles approache from bottom face to form a stable chair-like conformer of products, resulting in *cis*-diallyl relation. The boat-like conformation (**97b**) have two side chains pointing toward opposite directions to avoid steric encumberance. Thus, the favored boat-like conformer **97b** welcomed allyl iodide from top face to form the *cis*-stereochemistry in product **92**. The Claisen rearrangement of *O*-allylation product **91** likely proceeded through a transition state (**98**) in which the six-membered ring resided in a boat-like conformation to avoid steric clash, resulting in the same *C*-allylation product **92**.



Scheme 4-10. A rational for the stereochemical outcome of the *C*-allylation and the Claisen rearrangement

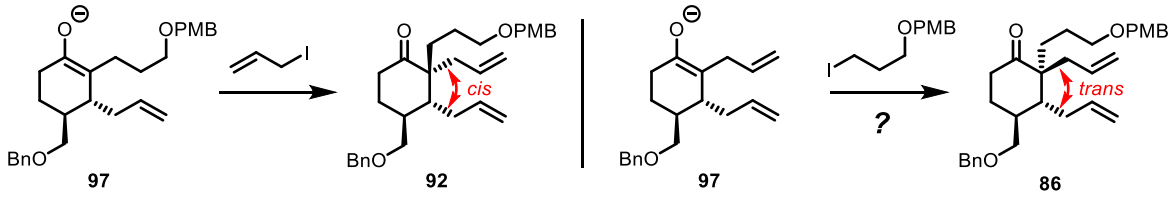
We also tried the radical alkylation method able to generate *trans*-decalin products. This method was reported by Danishefsky as well.[27] Nevertheless, these methods proved unsuccessful (Scheme 4-11) in constructing either designed trans-decalin **85** or a compound (**100**) similar to that described in their paper, presumably due to the intolerance of *O*-Bn groups under lithium naphthalide (LiNp) conditions and low reactivity of regular alkyl iodides.



Scheme 4-11. Attempted Danishefsky radical alkylation reactions to construct *trans*-decalin structures. *Reagents and conditions*: a) Lithium Naphthalene (3.5 equiv), -50 °C to -20 °C, then HMPA (20.0 equiv), alkyl iodide (5.0 equiv), -78 °C to 23°C

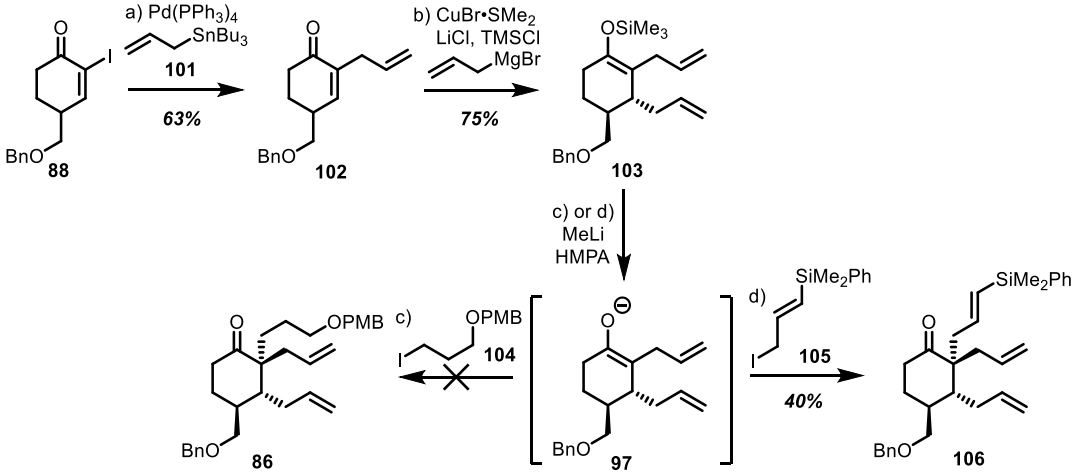
4.4.2 Construction of a trans-diallyl precursor enabled by a substituted allyl iodide

To obtain the desired *trans*-stereochemistry of two allyl side chains, we planned to adopt a direct and feasible method to change the installation order of two side chains on the all-carbon quaternary center, illustrated in Scheme 4-12. We then moved on to prepare the precursors of such an enolate **97**.



Scheme 4-12. Adjusting the order of side chain installation could potentially generate the desired *trans*-decalin frame

Starting from the iodo-enone **88** (Scheme 4-13), we employed a Stille coupling protocol to attach an allyl side chain to the α-position of enone. Of note, a variety of other coupling conditions were attempted, including palladium catalyzed Suzuki-Miyaura reactions. However, they generally gave incomplete conversions. A Stille coupling condition ($Pd(PPh_3)_4$, allyltributyltin, THF, 70 °C) afforded the optimal yield (63%) of desired product **102**. Adding LiCl or application of tetraallyltin both had a deleterious effect on isolated yield. Although an unknown yellowish impurity typically accompanied the product, it could be fully separated by chromatography after the next step, the allylcuprate Michael addition/TMSCl trap sequence, which proceeded smoothly to give chromatographically purifiable product **103** in good yield.



Scheme 4-13. Allylation with a substituted allyl iodide to set up *trans*-diallyl relationship. *Reagents and conditions*: a) $Pd(PPh_3)_4$ (0.1 equiv), allyltributyltin (2.0 equiv), THF, 70 °C; b) $CuBr•SMe_2$ (1.0 equiv), LiCl (2.0 equiv), THF, 23°C, 5 min, then allylmagnesium bromide (1.0 M in ether, 2.0 equiv), -78 °C, 30 min, then TMSCl (1.5 equiv) and **102** (1.0 equiv), -78 °C, 2 h, slowly to 5 °C, 6 h; c) MeLi (1.6 M in ether, 1.2 equiv), THF, 0 °C, 1 h, then HMPA (6.0 equiv), then alkyl iodide **104** (1.3 equiv), -78 °C, 2 h, slowly to 5 °C, 6 h; d) MeLi (1.6 M in ether, 1.2 equiv), THF, 0 °C, 1 h, then HMPA (6.0 equiv), then allyl iodide **105** (1.3 equiv), -78 °C, 2 h, slowly to 5 °C, 6 h

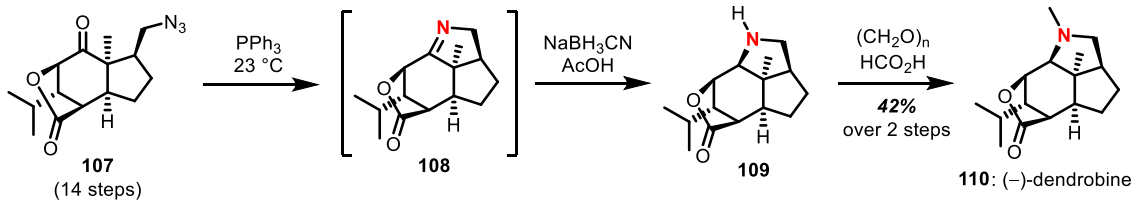
The so-obtained silyl enol ether **102** was subjected to desilylation conditions (MeLi·LiI or MeLi) to generate the corresponding lithium enolate **97**, followed by addition of electrophiles. Unfortunately, a regular alkyl iodide **104** was not able to couple with lithium enolate **97** even upon heating (70 °C), presumably due to insufficient reactivity. After work-up with aqueous NH_4Cl

solution, only protonation product was obtained, instead of any desired alkylation product **86** with an all-carbon quaternary center. We anticipated that a more reactive substituted allyl iodide **105** might be effective in alkylation, similar to what allyl iodide did (Scheme 4-8). This allyl iodide (**105**) could be prepared from the corresponding alcohol precursor in a multi-gram scale.[28] We then tried the substituted allyl iodide **105** in the alkylation reaction. To our delight, the desired product **106** was isolated in 40% yield as a major product. Other identifiable side products, in a chromatographic order (nonpolar to polar), include recovered starting material (~10%), *O*-allylation product (~20%), diastereomer of alkylation (*cis*-relationship of two allyl side chains, ~10%), another unidentified isomer of possible alkylation product (<5%), and finally the protonated product (~10%). We studied various parameters, including temperature, equivalents of different components, time length, etc, trying to suppress the amount of *O*-allylation but these efforts proved fruitless. For example, the starting temperature had little influence on the yield of product when it ranged from -78 ^{o}C to -25 ^{o}C. In addition, when the substituted allyl iodide was added at 0 ^{o}C, no desired product could be obtained.

4.4.3 An aza-Wittig crisis

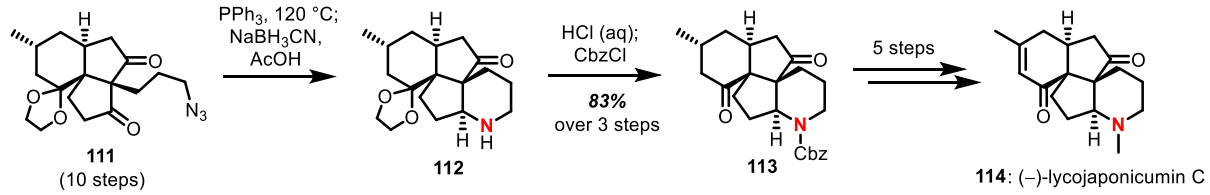
With the correct stereochemistry set up on multi-substituted cyclohexanone **106**, we carried on the synthesis toward construction of *cis*-DHQ by the designed *aza*-Wittig reaction. *Aza*-Wittig reaction served as key cyclization steps in many reports of natural product synthesis.[29-31] For instance, in Sha's synthesis of (–)-dendrobine (Scheme 4-14),[32] azide **107** was treated with triphenylphosphine (PPh_3) at ambient temperature to form *aza*-ylide, which then attacked the carbonyl intramolecularly in a transannular fashion to forge imine intermediate **108**. A facile reduction mediated by sodium cyanoborohydride ($NaBH_3CN$) and the following methylation of

the secondary amine **109** furnished the target molecule dendrobine (**110**), in an overall 42% yield from **107**.



Scheme 4-14. Sha's asymmetric synthesis of dendrobine featuring a key *aza*-Wittig cyclization

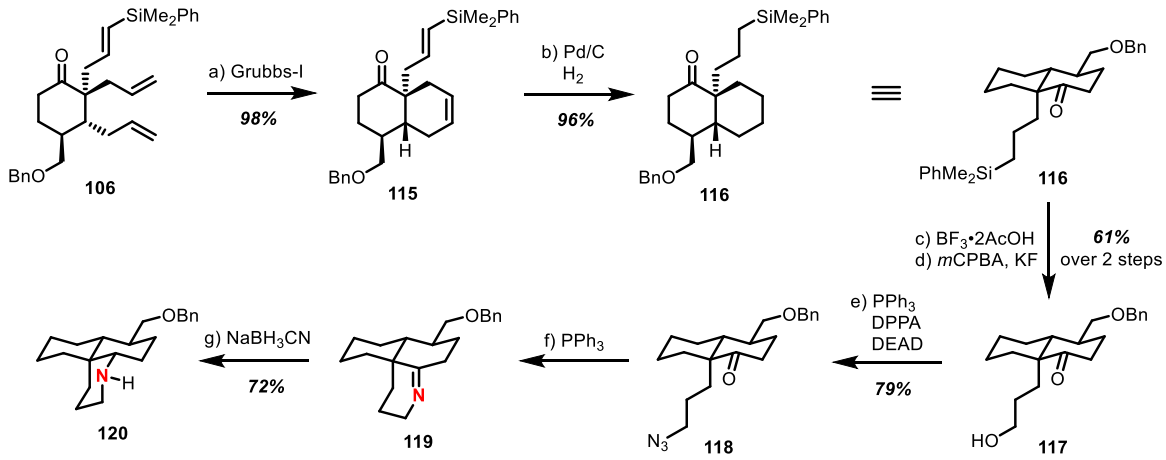
Another case where *aza*-Wittig reactions were employed was the synthesis of lycojaponicumin C from the Tu group.[33] In their route (Scheme 4-15), the advanced azide **111** was reacted with PPh_3 at elevated temperature (120 ^oC) to yield the imine intermediate, which was then reduced to the secondary amine **112**. This cyclization implemented the last piperidine ring of the molecule and five steps of functional group manipulations from **113** were taken to reach the target lycojaponicumin C. A similar *aza*-Wittig reaction was selected as the key cyclization step by the Yang group in the synthesis of same natural product molecule **114** later in 2017.[34]



Scheme 4-15. Tu's asymmetric synthesis of lycojaponicumin C featuring a key *aza*-Wittig cyclization

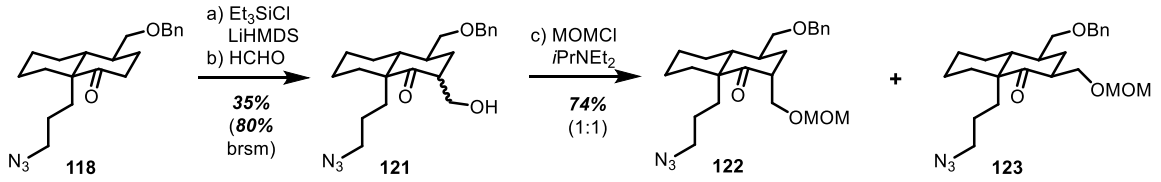
For our efforts toward myrioneurinol (Scheme 4-16), ring-closing metathesis on **106** forged the six-membered ring to render the desired *trans*-decalin core frame in **115**. Selective hydrogenation of two carbon-carbon double bonds without touching neither *O*-Bn moiety nor silyl group took place when 40% mass equivalents of 5% palladium on carbon were utilized in ethyl acetate, furnishing product **116** in 96% yield. Of note, there were in total four possible sites that are reactive on **115** in the hydrogenation condition. The alkene adjacent to the silyl group reacted

first, followed by the endocyclic alkene. When an excess of palladium on carbon or 10% Pd/C were catalyzing the hydrogenation, the benzyl moiety and the phenylsilane became labile sequentially. Longer reaction time could result in over-hydrogenation as well. 40% mass equivalent of 5% Pd/C was therefore selected as an appropriate amount according to experimental screenings. The next task, transforming silyl group of **116** into a primary alcohol was achieved through a two-step sequence. First, $BF_3 \cdot 2AcOH$ complex replaced the phenyl group on silicon with a fluoride,[35] while treating **116** with HBF_4 resulted in full decomposition. Next, *m*CPBA oxidized the fluorosilyl entity to the hydroxy group in product **117**. The installation of azide proceeded smoothly under Mitsunobu conditions utilizing the combination of PPh_3, diphenylphosphoryl azide (DPPA), and diethyl azodicarboxylate (DEAD) in THF.[36] With the desired azide **118** isolated in 79% yield, we set the stage for a model *aza*-Wittig reaction. Although **118** was one hydroxymethyl side chain away from the real system, it served as a model system to probe the reactivity and the *aza*-Wittig cyclization worked pleasingly. Heating azide **118** together with PPh_3 in refluxing toluene afforded the cyclic imine **119**, which was sufficiently stable upon isolation and characterization (δ = 180.2 ppm on ^{13}C NMR spectrum). The subsequent reduction by $NaBH_3CN$ in acetic acid and methanol successfully furnished the tricycle **120** containing the desired *cis*-DHQ core.



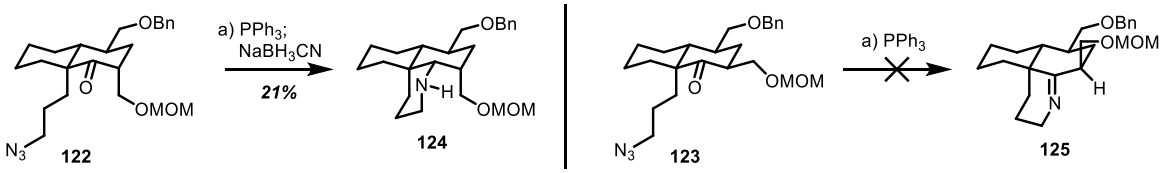
Scheme 4-16. Testing the model *aza*-Wittig cyclization. *Reagents and conditions*: a) Grubbs-I (0.15 equiv), CH_2Cl_2, 23 °C, 16 h; b) Pd/C (5%, 40% mass equiv), H_2 (1 atm), EtOAc, 23 °C, 12 h; c) BF_3•2AcOH (2.0 equiv), CH_2Cl_2, 23 °C, 8 h; d) KF (2.0 equiv), *m*CPBA (2.0 equiv), DMF, 23 °C, 10 h; e) PPh_3 (1.2 equiv), DPPA (1.2 equiv), DEAD (1.2 equiv), THF, 23 °C, 10 h; f) PPh_3 (1.5 equiv), PhMe, 110 °C, 30 min; g) $NaBH_3CN$ (2.0 equiv), AcOH (10.0 equiv), MeOH, 23 °C, 1 h

We then turned to the real system of this *aza*-Wittig cyclization. In order to install the equatorial hydroxymethyl side chain, we tried to deprotonate the α-position of the carbonyl in azide **118**. However, upon treatment with various base such as LDA or LiHMDS, the solution of **118** turned dark rapidly and TLC implied decompostion of starting material. To address this problem, Et_3SiCl was pre-mixed with **118**, followed by addition of base to form the silyl enol ether first (Scheme 4-17). The mixed solution of silyl enol ether and freshly distilled THF solution of formaldehyde was then treated with TBAF,[37] resulting in a mixture of the desired hydroxymethylation product (**121**) and hydrolysis product. Due to the inseparable nature of this hydroxymethylation product in 1:1 ratio, MOM protection was performed and a pair of diastereomeric products **122** and **123** became then separable by chromatography.



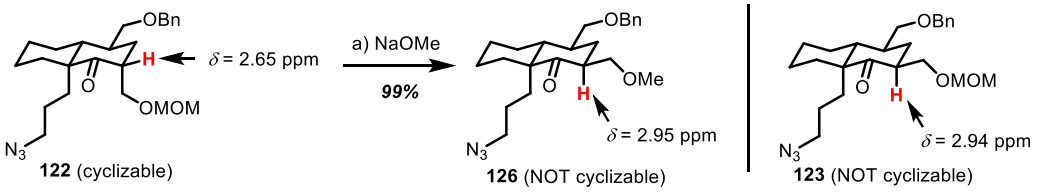
Scheme 4-17. Synthesis of *aza*-Wittig precursors with hydroxymethyl side chain. *Reagents and conditions*: a) Et_3SiCl (1.5 equiv), **118** (1.0 equiv), THF, then LiHMDS (1.0 M in THF, 1.5 equiv), 23 °C, 30 min; b) HCHO (anhydrous in THF, excessive), TBAF (1.5 equiv), THF, -20 °C, 1 h; c) MOMCl (10.0 equiv), *i*PrNEt$_2$ (20.0 equiv), 23 °C, 16 h

Although at this point the exact relative stereochemistry of **122** and **123** cannot be unambiguously determined, we subjected both to the *aza*-Wittig conditions, respectively (Scheme 4-18). We were surprised to discover that only one of them was able to cyclize, while the other did not form the cyclic imine even in refluxing toluene. Even so, the cyclization/reduction sequence proceeded in low yield (21%) and the resultant product **124** was unable to form the final hemiaminal ring upon treatment with aqueous hydrochloric acid (HCl). Deprotection of *O*-MOM on **124** also proved to be infeasible. According to these results, we assign the cyclized product to be from the undesired diastereomer **122**.



Scheme 4-18. The failure of the correct diastereomer **123** in *aza*-Wittig cyclization. *Reagent and conditions*: a) PPh_3 (1.5 equiv), PhMe, 110 °C; removal of PhMe, $NaBH_3CN$ (2.0 equiv), AcOH (10.0 equiv), MeOH, 23 °C

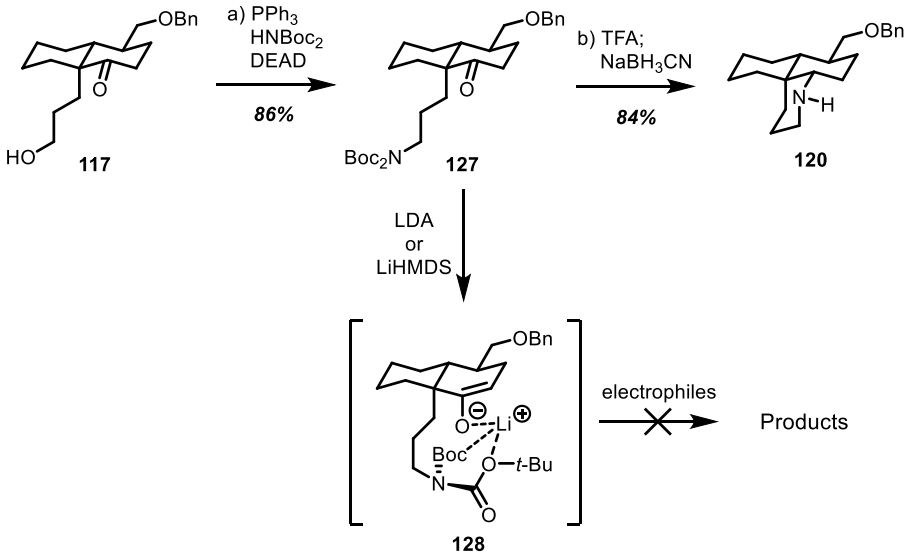
Several other pieces of evidence supported this assignment (Scheme 4-19). The cyclizable diastereomer **122** has its proton α to the carbonyl positioned at δ = 2.65 ppm on ^{1}H NMR. Upon treatment in epimerization conditions (sodium methoxide in methanol), it turned into a more thermodynamically stable compound with an equatorial methoxymethyl substituent (**126**). This compound displayed a chemical shift of the key α-proton at δ = 2.89 ppm, a value that is very close to what uncyclizable, equatorial -CH_2OMOM isomer **123** had (δ = 2.90 ppm). Preliminary computational studies were conducted to help understand the experimental results. However, the DFT calculation indicated a minute difference between the energy barrier of two reaction pathways (**122** and **123** to their cyclic imine, respectively). We are still proactively seeking other tools to investigate this phenomenon. We also attempted to synthesize other *aza*-Wittig precursor derivatives with transformable one-carbon side chains, but most of them were unsuccessful.



Scheme 4-19. Epimerization of cyclizable isomer **122** ended in a diastereomer that cannot cyclize under *aza*-Wittig conditions. *Reagents and condition*: a) NaOMe (0.5 M in MeOH, 20.0 equiv), MeOH, 23 °C, 10 h

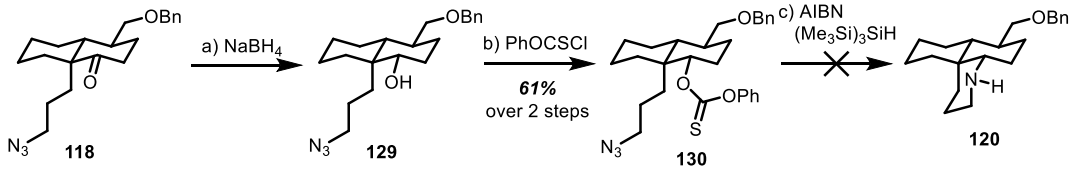
4.4.4 Miscellaneous attempts to form the cis-DHQ core

Given the unsuccessful *aza*-Wittig cyclization in the real system, we moved on to test other reactivities in hope of forging the *cis*-DHQ core in myrioneurinol. As shown in Scheme 4-20, a Mitsunobu reaction transformed the primary alcohol to a bis-Boc protected compound **127**. Intriguingly, when TFA-promoted Boc deprotection was attempted on this compound, cyclization occurred, leaving highly pure product **120** after reduction by $NaBH_3CN$. However, derivatization of **127** proved burdensome. Hard bases such as LDA and LiHMDS deprotonated the α-position of the ketone carbonyl, while the addition of various electrophiles, especially HCHO, failed to provide any coupling product. The reason behind could be that enolate **128** has a strongly chelated lithium cation, thus preventing incoming electrophilic reagents from breaking up this highly stable chelation.



Scheme 4-20. TFA-promoted cyclization and difficulties in functionalizing the $NBoc_2$ substrate. *Reagents and conditions*: a) PPh_3 (1.2 equiv), $HNBoc_2$ (1.2 equiv), DEAD (1.2 equiv), THF, 23 °C, 12 h; b) TFA, 12 h; $NaBH_3CN$ (2.0 equiv), AcOH, MeOH, 2 h.

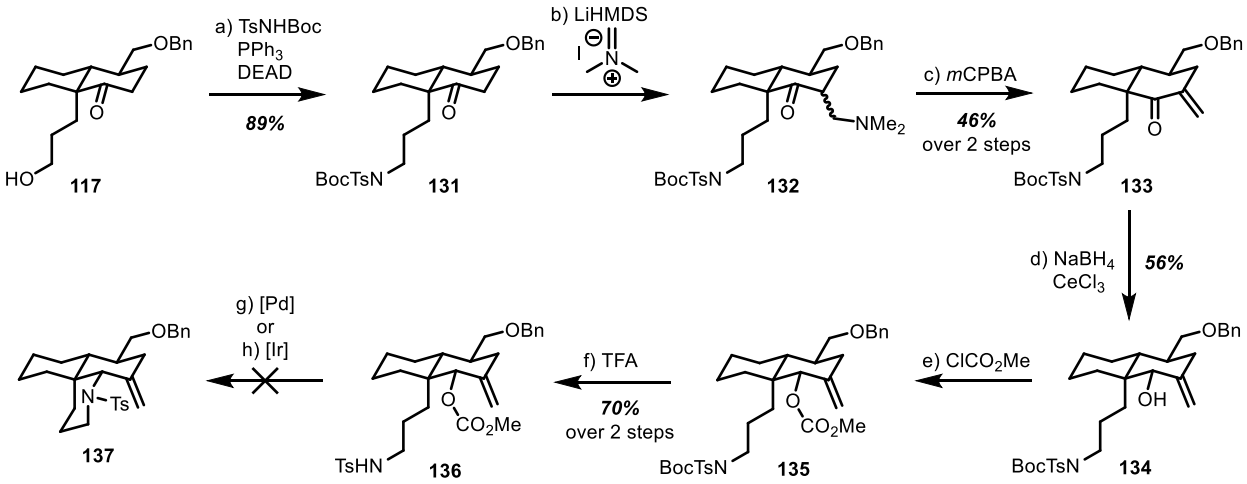
We then turned to other opportunities. Reduction of ketone in azide **118** exclusively generated equatorial alcohol **129** (Scheme 4-21). Esterification with the xanthate provide the precursor **130** for the radical cyclization. However, under thermal radical initiation conditions (AIBN in refluxing toluene, $(TMS)_3SiH$ as the hydride source),[38] **130** suffered from decomposition without forming any desired product **120**.



Scheme 4-21. An attempted radical cyclization to construct the *cis*-DHQ core. *Reagents and conditions*: a) $NaBH_4$ (2.0 equiv), MeOH/THF, 23 °C, 1 h; b) PhOCSCl (1.2 equiv), Et_3N (2.0 equiv), DMAP (1.0 equiv), CH_2Cl_2, 23 °C, 12 h; c) AIBN (0.1 equiv), TTMSS (1.1 equiv), PhMe, 110 °C

The next reaction we tried was metal-mediated Tsuji type allylation.[39-40] Precursor synthesis began from free alcohol **117** in Scheme 4-22. A Mitsunobu reaction installed a fully protected sulfonamide **131**. A two-step α-methylenation protocol was exercised by reacting first with Eschenmoser's salt.[41] The following oxidation of tertiary amine to *N*-oxide and Hoffman

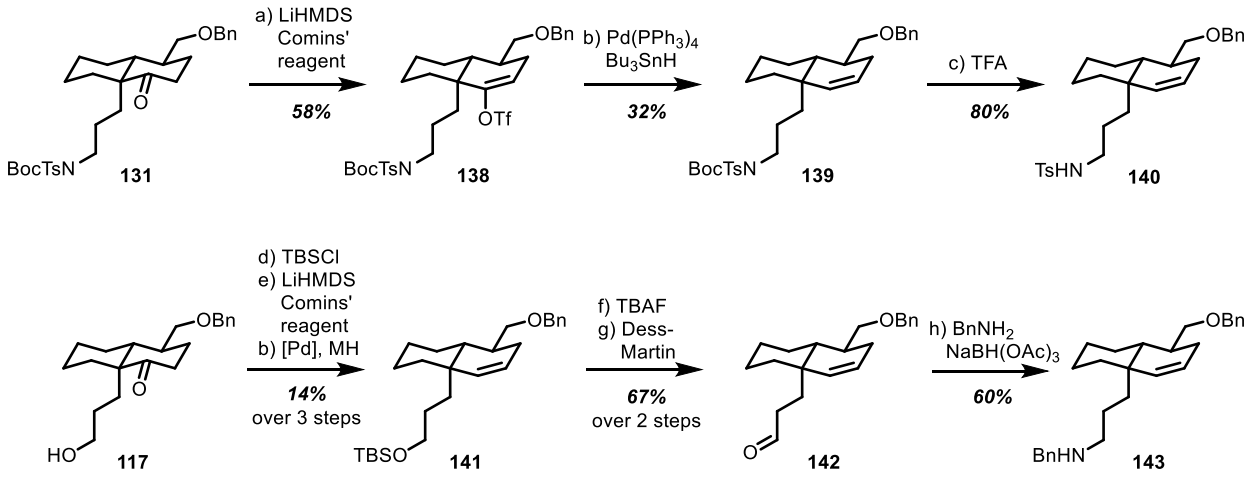
elimination afforded enone **133**. The following Luche reduction of **133** provided allylic alcohol **134** as a single diastereomer similar to **129** (Scheme 4-21) due to a predominant approach of hydride from the top face. Subsequent alcohol protection and *N*-Boc deprotection set the precursor **136** ready for testing the key cyclization. Unfortunately, neither palladium catalysts ($Pd(PPh_3)_4$ or Pd_2dba_3) nor iridium catalyst ($[Ir(cod)Cl]_2$) shed light on any cyclization product. Slow decomposition of starting material was observed upon prolonged heating.



Scheme 4-22. An attempted Tsuji *N*-allylation to construct the *cis*-DHQ core. *Reagents and conditions*: a) TsNHBoc (1.2 equiv), PPh_3 (1.2 equiv), DEAD (40% in PhMe, 1.2 equiv), THF, 23 °C, 12 h; b) Eschenmoser's salt (2.0 equiv), then LiHMDS (1.0 M in THF, 2.0 equiv), 23 °C, 30 min; c) *m*CPBA (2.0 equiv), $NaHCO_3$ (8.0 equiv), CH_2Cl_2, 23 °C, 2 h; d) $CeCl_3 \cdot 7H_2O$ (1.2 equiv), $NaBH_4$ (1.2 equiv), MeOH, 23 °C, 2 h; e) NaH (5.0 equiv), $ClCO_2Me$ (10.0 equiv), THF, 23 °C, 12 h; f) TFA/CH_2Cl_2, 23 °C, 12 h; g) $Pd(PPh_3)_4$ or Pd_2dba_3 (0.1 equiv), MeCN, up to 80 °C; h) $[Ir(cod)Cl]_2$ (0.1 equiv), ligand (0.2 equiv), THF, up to 80 °C

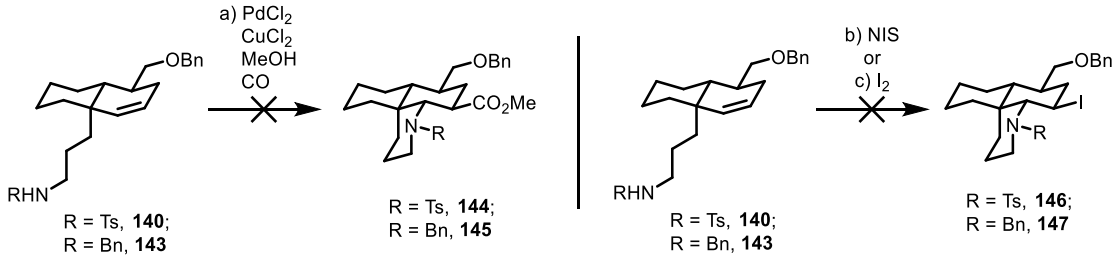
Palladium-catalyzed aminocarbonylation of alkenes and iodocyclization of alkenes were examined as well. Their precursor was synthesized in the route described by Scheme 4-23. The synthesis of *N*-Ts precursor started from compound **131** described in Scheme 4-22. *O*-triflation and palladium-catalyzed deoxygenation afforded alkene **139**, albeit in low yield due to certain degrees of decomposition. Trifluoroacetic acid removed *N*-Boc protecting group to afford sulfonamide **140**. On the other side, *N*-Bn precursor came from alcohol **117**. TBS protection of the primary alcohol, and a similar triflation/reduction sequence cultivated alkene **141**, followed by

deprotection and oxidation to generate aldehyde **142**. The final reductive amination formed the *N*-benzyl amine precursor **143**.



Scheme 4-23. Synthesis of miscellaneous cyclization precursors. *Reagents and conditions*: a) LiHMDS (2.0 equiv), Comins' reagent (1.5 equiv), THF, 23 °C, 1 h; b) $Pd(PPh_3)_4$ (0.1 equiv), LiCl (1.0 equiv), Bu_3SnH (2.0 equiv), THF, 55 °C, 12 h; c) TFA/CH_2Cl_2, 23 °C, 12 h; d) TBSCl (1.1 equiv), imidazole (2.0 equiv), CH_2Cl_2, 23 °C, 1 h; e) LiHMDS (1.2 equiv), Comins' reagent (1.2 equiv), THF, 23 °C, 1 h; f) TBAF (10.0 equiv), THF, 50 °C, 12 h; g) Dess-Martin periodinane (1.5 equiv), $NaHCO_3$ (8.0 equiv), CH_2Cl_2, 23 °C, 30 min; h) $BnNH_2$ (3.0 equiv), CH_2Cl_2, 23 °C, 1 h, then $NaBH(OAc)_3$ (3.0 equiv), CH_2Cl_2, 23 °C, 8 h

Both **140** and **143** were tested in palladium mediated alkene aminocarbonylation reactions (Scheme 4-24).[42] Although such reactions were reported to work in the synthesis of several simple alkaloid natural products,[43-45] the condition used here could barely promote conversion of starting materials, implying that this reaction might be considerably sensitive to steric factors. We attempted *N*-iodosuccinimide (NIS) and I_2 as electrophilic reagents to promote iodocyclization of **140** and **143**, but unfortunately in both cases the starting materials rapidly decomposed.



Scheme 4-24. Unsuccessful aminocarbonylation reactions and iodocyclization reactions in constructing the *cis*-DHQ core. *Reagents and conditions*: a) $PdCl_2$ (0.1 equiv), $CuCl_2$ (3.0 equiv), CO (1 atm), MeOH, up to 60 °C; b) NIS (1.2 equiv), MeCN, 23 °C; c) I_2 (1.2 equiv), $NaHCO_3$ (8.0 equiv), CH_2Cl_2, 23 °C

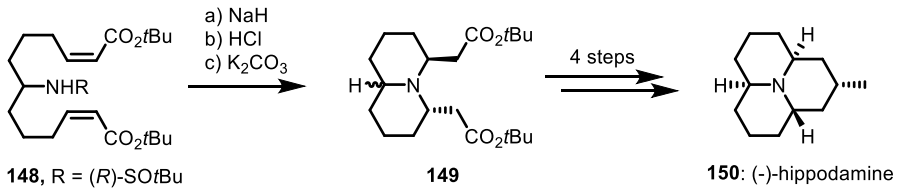
All the unsuccessful trials described in this part were due to no conversion or decomposition. For those reactions without consumption of starting materials, a possible hint may be that the nitrogen-containing side chain in stable conformers are swinging outward, thus being far away from most of the desired reaction sites. Therefore, attempting more reaction types where starting materials can tolerate high temperature and harsh reagents would be appreciated. On the other hand, we have learnt from lessons of *aza*-Wittig transformations that the α-positioned functional groups next to the ketone carbonyl can be problematic in cyclization events. In that sense, it is desirable to design a cyclization pathway that tolerates, or even utilizes the α-substituent.

4.4.5 Aza-Michael reaction: a revival

4.4.5.1 Background

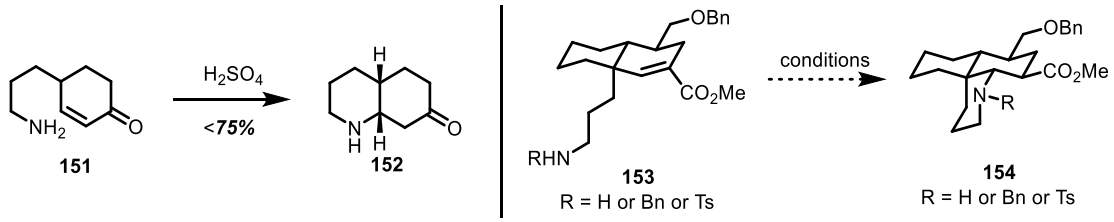
Given that *aza*-Wittig and many other reactions were not capable of delivering the *cis*-DHQ core of myrioneurinol, we moved on to the next station of our screening journey, trying to seek out a robust transformation that can lead to the construction of the key C-N bond. The *aza*-Michael reaction is a historical reaction that may serve the purpose. As a heteroatom-version of Michael addition reaction, nitrogen-containing functionalities such as amine and amide are able to act as nucleophiles and participate in conjugate additions. Although methodology development on asymmetric intramolecular and intermolecular *aza*-Michael reactions utilizing various metal catalysts, acid catalysts, and organocatalysts, on extensively expanded substrate scope such as conjugated aldehydes, conjugated ketone, conjugated esters, and even nitroalkenes have been studied extensively over the past decades,[46-50] its applications in total synthesis of complex natural products are not widely reported.[51-53] One recent example came from Fustero's synthesis of hippodamine in 2015 (Scheme 4-25).[54] They employed a double intramolecular *aza*-Michael

reaction on substrate **148** with a chiral auxiliary. A successful desymmetrization reaction yield bicycle **149**, which was then transformed to (–)-hippodamine (**150**) in another 4 steps.



Scheme 4-25. Fustero's synthesis of (-)-hippodamine featuring an asymmetric intramolecular *aza*-Michael cyclization

Aza-Michael reactions are well precedented in the construction of *cis*-DHQ motifs with various substitution patterns as well. For example, enone **151** in Scheme 4-26 with a pendant primary amine at 4-position underwent an intramolecular *aza*-Michael cyclization under acidic conditions, in forming the *cis*-DHQ ketone **152**.[55] In this vein, a similar *aza*-Michael reaction was designed for the advanced intermediate **153** in our myrioneurinol synthesis (Scheme 4-26). Note that the flexible R group in **153** may be an unprotected primary amine, a secondary amine, or an amide. One of the most important features in this design, however, resided in the methyl ester, which can be easily converted to a hydroxymethyl group required for the final aminal ring formation.

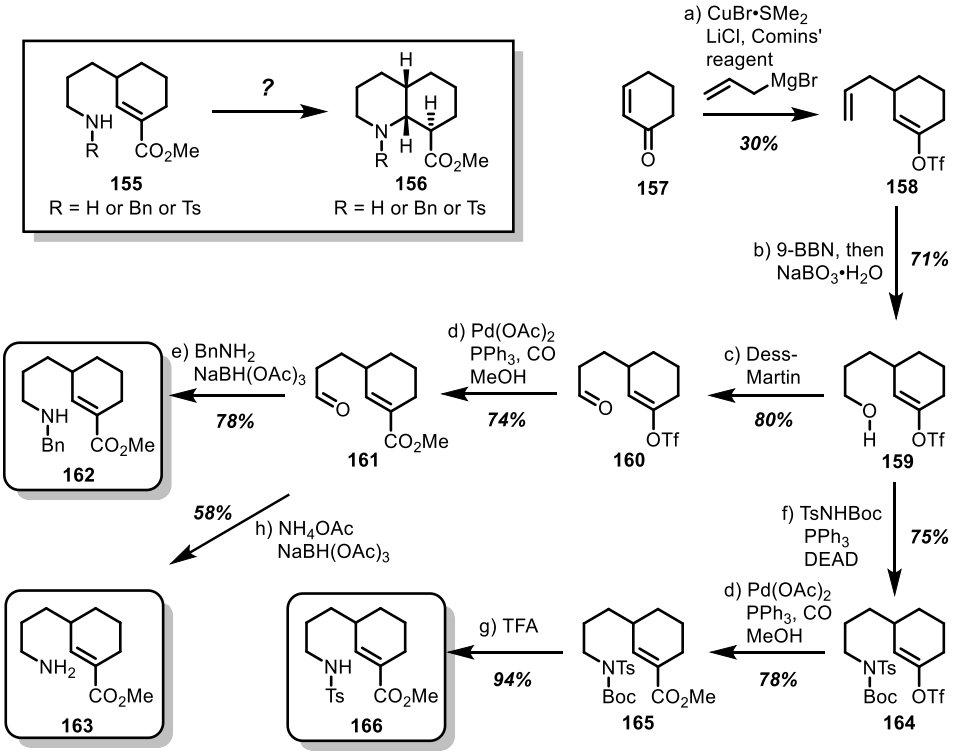


Scheme 4-26. An example of *aza*-Michael reaction building *cis*-DHQ and the blueprint for applications in myrioneurinol synthesis

4.4.5.2 A model study: synthesis of myrioxazine A

The design for a reaction modeling the *aza*-Michael cyclization is shown in the box in Scheme 4-27. We proceed to the synthesis of three types of precursors (**155**) with different

protecting group patterns. A Michael addition/triflation tandem reaction on 2-cyclohexen-1-one (**157**) produced vinyl triflate **158**, whose terminal alkene was hydroborated and oxidized to primary alcohol **159**. This alcohol was bifurcated to two *aza*-Michael precursors. One of them went through a Mitsunobu reaction to generate intermediate **164**, which was further coupled with a methyl ester and deprotected in TFA to afford sulfonamide precursor **166**. The other route utilized a Dess-Martin oxidation to generate aldehyde **161**. This aldehyde was versatile in transforming into both unprotected primary amine **163** and benzyl protected secondary amine **162** via reductive amination reactions with NH_4OAc and $BnNH_2$, respectively.

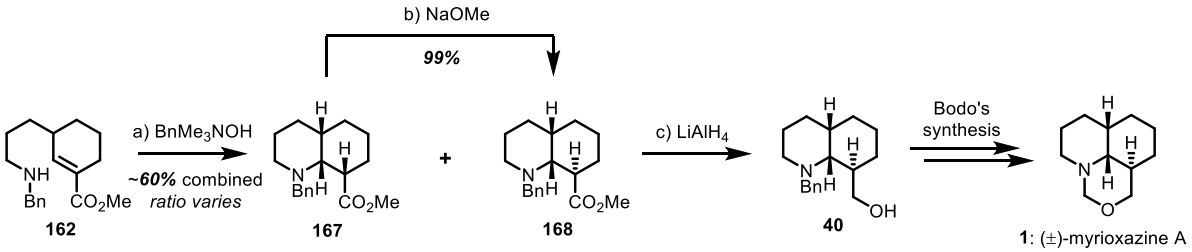


Scheme 4-27. A design of model study for *aza*-Michael cyclization precursors and their synthesis. *Reagents and conditions*: a) $CuBr•SMe_2$ (1.0 equiv), LiCl (2.0 equiv), THF, 23 °C, 5 min, then allylmagnesium bromide (2.0 equiv), -78 °C, 30 min, then **157** (1.0 equiv), -78 °C, 1 h, then Comins' reagent (1.2 equiv), -78 °C, 2 h, slowly to 23 °C, 8 h; b) 9-BBN (0.5 M in THF, 1.05 equiv), THF, 23 °C, 12 h, then $NaBO_3•H_2O$ (3.0 equiv), 23 °C, 24 h; c) Dess-Martin periodinane (1.2 equiv), $NaHCO_3$ (8.0 equiv), 23 °C, 1 h; d) $Pd(OAc)_2$ (0.09 equiv), PPh_3 (0.18 equiv), Et_3N (4.0 equiv), CO (1 atm), MeOH, 23 °C, 8 h; e) $BnNH_2$ (1.3 equiv), CH_2Cl_2, 23 °C, 1h, then $NaBH(OAc)_3$ (1.5 equiv), 23 °C, 8 h; f) TsNHBoc (1.1 equiv), PPh_3 (1.1 equiv), DIAD (1.2 equiv), THF, 23 °C, 12 h; g) TFA/CH_2Cl_2, 23 °C, 12 h; h) NH_4OAc (2.0 equiv), CH_2Cl_2, 23 °C, 1h, then $NaBH(OAc)_3$ (1.5 equiv), 23 °C, 8 h

With these three precursors in hand, we tested their performance in the proposed *aza*-Michael cyclization reaction. The unprotected primary amine **163** was found to partially convert to a cyclization product upon long-term heating with DBU in refluxing MeCN. Nonetheless, both product and starting material were extremely polar that the attempts to isolate the product proved challenging. Addiitonally, we observed a significant amount of decomposition. The sulfonamide precursor **166** was subjected to a variety of basic conditions, including hard bases (NaH, LiHMDS) and soft bases (NaOMe).[54,56] Discouragingly, none of these bases promoted conversion of the starting material to the corresponding cyclization products.

We had to move to our last resort, *N*-benzyl secondary amine **162**. Enlightened by a reported *aza*-Michael reaction on *N*-benzyl substrates where $[BnMe_3N]^+[OH]^-$ (Triton-B) functioned as promoter,[57] we attempted mixing this base it with starting material **162** in methanol (Scheme 4-28). Gratifyingly, two new nonpolar spots close on TLC appeared and they were later identified as a pair of separable diastereomers of cyclization product (**167** and **168**). When 3 equivalents of Triton-B were used and lower temperature (23 ^oC) was set for reaction, up to 35% isolated yield of the diastereomer **167** and same amount of the isomer **168** can be observed after a reaction time of 6 hours. Less base (1.5 equivalents) generated **167** as the major product (47% yield) and **168** as the minor product (7%), with the overall yield (54% compared to 70%) compromised slightly. When the reaction was exposed to higher temperature, more equivalents of base, or longer reaction time, the content of the major isomer **168** increased and ultimately **168** became the sole product from the reaction, in around 60% yield. These phenomena strongly indicated that **168** is the more thermodynamically stable diastereomer rather than **167**, which is the kinetic product from the reaction. An epimerization experiment further substantiated this conclusion by turning the minor isomer **167** exclusively into the major one (**168**) under sodium

methoxide in methanol. The relative stereochemistry of **168** was confirmed after $LiAlH_4$-mediated reduction to amino alcohol **40**, a reported compound in Bodo's synthesis of schoberine.[2] A formal synthesis of (±)-myrioxazine A was then achieved by *N*-Bn deprotection on **40** and final hemiaminal formation; both steps were reported by Bodo.[1]

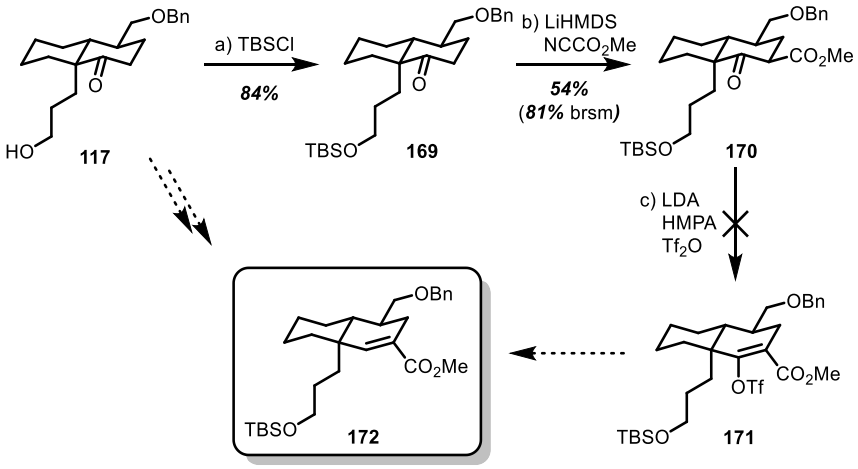


Scheme 4-28. A successful *aza*-Michael cyclization on benzyl amine **162** and a formal synthesis of myrioxazine A. *Reagents and conditions*: a) $BnMe_3NOH$ (Triton-B, 2.0 equiv), MeOH, 23 °C, 6 h; b) NaOMe (0.5 M in MeOH, 10.0 equiv), MeOH, 23 °C, 12 h; c) $LiAlH_4$ (1.0 M in THF, 1.0 equiv), Et_2O, 23 °C, 1 h

4.4.5.3 Synthesis of aza-Michael precursor for myrioneurinol synthesis: A reduction hurdle and an unexpected rearrangement

Given the success of the *6-exo-trig aza*-Michael cyclization on model study and a formal synthesis of a simple *Myrioneuron* alkaloid myrioxazine A, we decided to move back to our myrioneurinol synthesis and revisit the key *cis*-DHQ construction with this new promising tool. To approach the precursor **172** (Scheme 4-29) for *aza*-Michael cyclization, alcohol protection of **117** by TBS was chosen as the starting point. In order to build up the α,β-unsaturated ester moiety in **172**, the carbonyl in **169** was deprotonated by LiHMDS and treated then with Mander's reagent ($NCCO_2Me$) to install an ester adjacent to the carbonyl. The ketoester **170** was then subjected to triflation conditions. Unfortunately, various combinations of bases (LiHMDS, LDA, DIPEA) and triflating reagents ($PhNTf_2$, Comins' reagent, Tf_2O) failed to give any triflation product. As a comparison, the ketone without ester (**169**) was smoothly triflated and reduced to afford alkene **141** (Scheme 4-23). The inaccessibility of triflate source at the carbonyl oxygen atom was hence

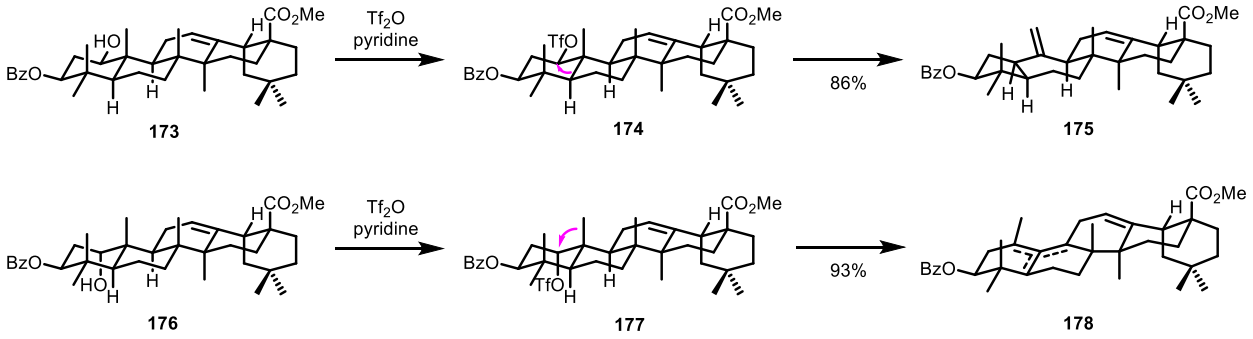
attributed to the joint steric effect from both methyl ester and the adjacent all-carbon quaternary center when a flat conformer of the enolate had to be adopted.



Scheme 4-29. An unsuccessful triflation of ketoester **170**. *Reagents and conditions*: a) TBSCl (1.1 equiv), imidazole (2.0 equiv), CH_2Cl_2, 23 °C, 30 min; b) LiHMDS (2.0 equiv + 1.0 equiv), Mander's reagent (2.0 equiv), THF, 23 °C; c) LDA (2.0 equiv), Et_2O, 23 °C, then HMPA (3.0 equiv), Tf_2O (2.0 equiv), 23 °C

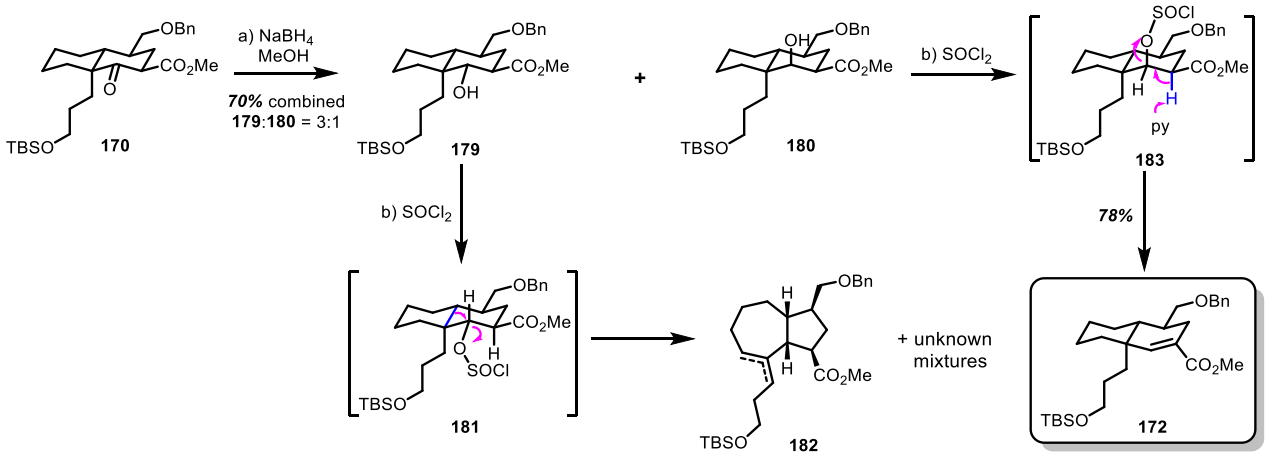
The dead-end on the triflation/reduction pathway guided us to another possibility. Reduction of the carbonyl in ketoester **170** and elimination of the resultant alcohol might be a viable path. To test the hypothesis, we subjected ketoester **170** to sodium borohydride in methanol (Scheme 4-31). To our delight, selective reduction of the carbonyl in the presence of the ester occurred and two products were obtained. The major product (**179**), which was generated by hydride approaching from the sterically more accessible top face and rendered hydroxyl group pointing equatorial, however, went through an unexpected rearrangement reaction when subjected to elimination conditions. When thionyl chloride reacted with alcohol **179** to form a leaving group, the perfectly aligned central C-C bond of *trans*-decalin rapidly migrated and eliminated the leaving moiety, shaping a mixture of nonpolar products in which one was tentatively assigned as a fused five/seven membered ring system **182** evidenced by a triplet at δ = 5.06 ppm on the proton spectrum. The simultaneous generation of inseparable impurities along with this rearranged product prevented us from purifying this interesting side product **182** and further studying it.

Similar rearrangement reactions were reported several terpenoid syntheses. In a research studying the cationic rearrangement reaction in the synthesis of justicane triterpenoids,[58] the divergence of ring rearrangement/methyl migration occurred on *trans*-decalin systems (**173** and **176**, Scheme 4-30). Likewise, construction of fused five/seven membered ring system could be realized by semi-pinalcol rearrangement reactions.[59]



Scheme 4-30. Cationic rearrangement reactions on equatorial/axial secondary alcohol isomers in justicoside E aglycone synthesis

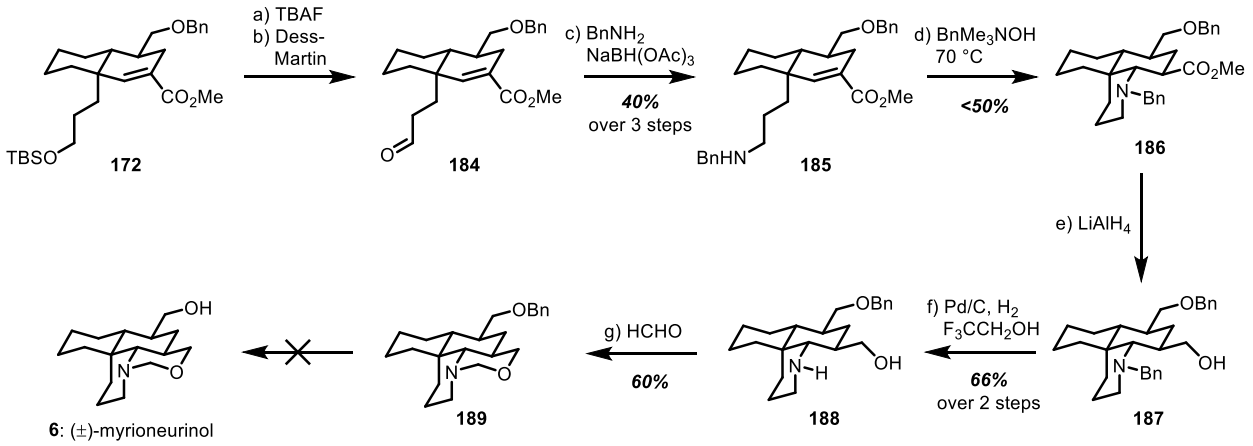
On the other hand, in Scheme 4-31, the minor product **180** with its secondary alcohol pointing axial experienced the desired β-elimination process through intermediate **183** and furnished the α,β-unsaturated ester **172**. The axial proton adjacent to the ester aligned antiperiplanar to the leaving group, leading the occurrence of elimination.



Scheme 4-31. Reduction of ketoester and an unexpected rearrangement of the major alcohol **179**. *Reagents and conditions*: a) $NaBH_4$ (3.0 equiv), MeOH, 23 °C, 8 h; b) $SOCl_2$ (10.0 equiv), pyridine, 23 °C, 10 h

4.4.5.4 Aza-Michael cyclization and a benzyl deprotection dilemma

Although the reduction step significantly limited material supply, as only the minor product **180** led to the desired elimination product and the ratio was 1:3 compared to the undesired isomer **179**), we carried on the synthesis with the obtained conjugated ester **172**. A three-step deprotection/oxidation/reductive amination manipulation placed the key secondary benzyl amine in **185** (Scheme 4-32). Upon heating with excess (10 equiv) of Triton-B, the cyclization product **186** formed smoothly. Reaction temperature lower than 60 ºC could not give rise to any product. Of note, only one stereoisomer was obtained, most likely due to the facile epimerization of the axial ester to the thermodynamically more stable isomer **186**.



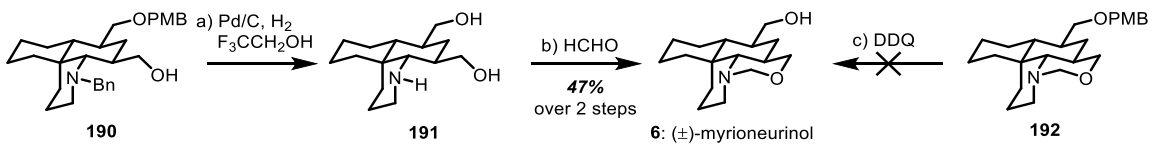
Scheme 4-32. An *aza*-Michael cyclization reaction established the core frame of myrioneurinol. *Reagents and conditions*: a) TBAF (10.0 equiv), THF, 50 °C, 12 h; b) Dess-Martin periodinane (2.0 equiv), $NaHCO_3$ (10.0 equiv), CH_2Cl_2, 23 °C, 20 min; c) $BnNH_2$ (1.3 equiv), CH_2Cl_2, 23 °C, 1h, then $NaBH(OAc)_3$ (1.5 equiv), 23 °C, 8 h; d) $BnMe_3NOH$ (10.0 equiv), MeOH, 70 °C, 40 h, 2 cycles; e) $LiAlH_4$ (1.0 M in THF, 1.0 equiv), Et_2O, 23 °C, 1 h; f) Pd/C (10%, 5.0 mass equiv), H_2 (1 atm), F_3CCH_2OH, 23 °C; g) formalin (excessive), THF, 23 °C, 8 h

To approach myrioneurinol, ester group of cyclization product **186** was reduced to a primary alcohol by lithium aluminum hydride ($LiAlH_4$). The reduction product **187** had two benzyl protecting groups that need removal, one on primary alcohol and the other on secondary amine. We tried several hydrogenative conditions, including adding acid to protonate the amine, in order to remove two benzyl protecting groups in one pot. However, in most cases slow decomposition of the starting material was encountered. A protocol reported for selective *N*-benzyl deprotection

gave clean product **188** with *O*-benzyl retained.[60] Adding up to 50 mass equivalents of palladium on carbon did not succeeded in removing the benzyl protecting group, only resulting in more impurities. The final hemiaminal ring formation on **188** proceeded smoothly in a mixed solution of THF and formalin (37% formaldehyde aqueous solution). The *O*-debenzylation proved challenging yet again on *O*-benzyl protected myrioneurinol **189**. Regular hydrogenations did not touch this compound, while adding acid made the aminal labile. Lewis acid mediated procedures, single electron reduction or photochemical conditions did not promote any conversion or resulted in decomposition of **189**. Extremely limited material supply (<2 mg) of **189** stopped us from extensive screening of debenzylation conditions as well. From a strategic perspective, we decided to run a synthesis with alternative *O*-protecting groups, for example, *O*-PMB group, from the very beginning. We hope this change could provide for a feasible late-stage deprotection.

4.4.6 Completion of myrioneurinol

Through a synthetic route akin to that was described *vide supra*, the *O*-PMB version of amino alcohol **188**, compound **190** was prepared (its detailed synthesis will be described in the summary part 4.4.7 and modification section 4.4.8). When large excess of palladium on carbon (10%, 20 mass equivalents) were applied for hydrogenation on **190** (Scheme 4-33), a simultaneous deprotection of *N*-benzyl and *O*-PMB occurred, affording free amino alcohol **190** which was then treated with formalin to yield myrioneurinol (**6**). The ^{1}H and ^{13}C NMR spectra fully matched those found in Weinreb's synthesis.[22,23]

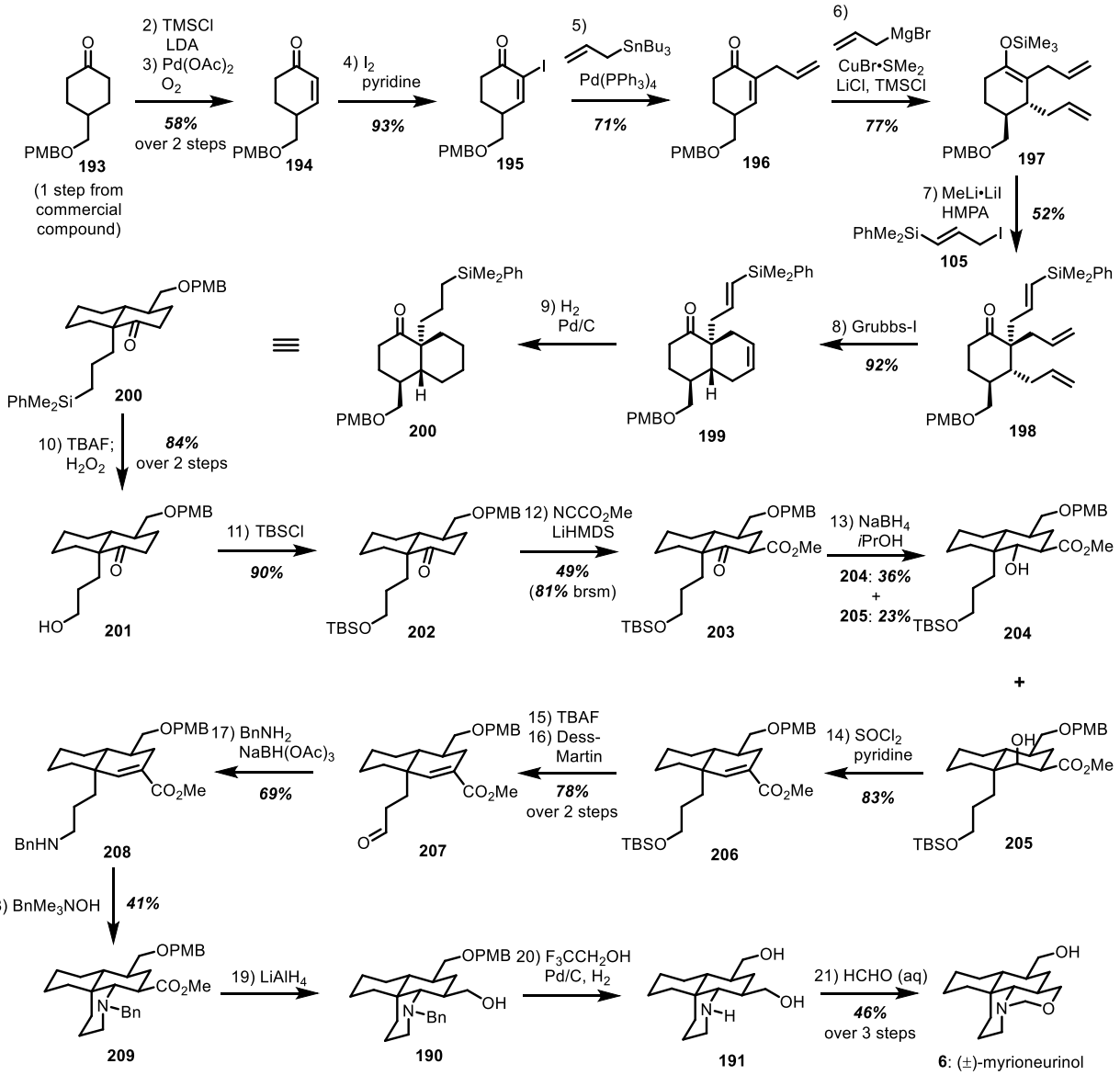


Scheme 4-33. Completion of myrioneurinol. *Reagents and conditions*: a) Pd/C (10%, 20.0 mass equiv), H_2 (1 atm), F_3CCH_2OH, 23 °C; b) formalin (excessive), THF, 23 °C, 8 h; c) DDQ (1.2 eq), CH_2Cl_2/pH=7 phosphate buffer, 23 °C

It is noteworthy that the hydrogenation conditions for **190** were found to have reproducibility issues. The amount of incompletely hydrogenated product with *O*-PMB moiety intact varied from batch to batch. The *O*-PMB protected myrioneurinol **192** underwent an unexpected decomposition in the presence of DDQ in CH_2Cl_2/phosphate buffer system. Note that the *O*-Bn protected myrioneurinol (**189**) was found to be stable upon exposure to DDQ. Therefore, excess of palladium on carbon and prolonged reaction time were necessary in hydrogenation of **190** to ensure full conversion to product **191**.

4.4.7 The full synthetic route of (±)-myrioneurinol

Our synthesis of myrioneurinol started from *O*-PMB protected cyclohexanone **193** (Scheme 4-34). A desaturation and a two-step α-allylation rendered enone **196**, which was further transformed into the *trans*-decalin **199** through a Michael addition/allylation vicinal bisfunctionalization sequence and an RCM reaction. After hydrogenation of two alkenes and a Fleming-Tamao oxidation, the so-exposed alcohol **201** was protected and treated with Mander's reagent to give β-ketoester **203**. Here a chemoselective reduction afforded the desired axial alcohol **205** in up to 22% yield (relevant screenings are covered *vide infra*). This alcohol was subjected to elimination and functional group interconversions to reach the *aza*-Michael precursor **208**. The key cyclization occurred smoothly under basic conditions at elevated temperature (70 ^{o}C). The final reduction/hydrogenation/aminal formation sequence successfully generated the target natural product myrioneurinol, in a total of 21 steps. Currently with step 8 and 9 being telescoped in one pot, the step count dropped to 20. With other ongoing optimization attempts, step counts could be further cut.



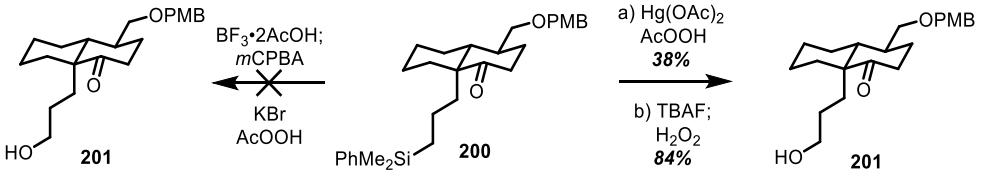
Scheme 4-34. Summary of our 21-step synthesis of (±)-myrioneurinol featuring a *trans*-decalin construction via a Michael addition/alkylation sequence and an *aza*-Michael cyclization leading to the *cis*-DHQ core

4.4.8 Optimization of synthetic steps of myrioneurinol

With the final target, myrioneurinol (**6**) successfully reached, we then turned back and inspected several synthetic steps on the route that were low-yielding or difficult to scale up, hoping to streamline the whole synthesis, cut steps, and elevate the overall yield. The whole synthetic route containing these steps has been described in the summary part 4.4.7.

*4.4.8.1 The Fleming-Tamao oxidation of silane **200***

In the initial synthetic route featuring *O*-benzyl protecting groups, the Fleming-Tamao oxidation to turn the phenyldimethylsilyl group in **116** into the hydroxyl group in **117** was realized by a two-step procedure (Scheme 4-16). BF_3·2AcOH complex served in that case as the fluorination reagent in the first step. However, on our *O*-PMB substrate in the successful route to myrioneurinol, treating silane **200** with BF_3·2AcOH resulted in rapid decomposition, largely due to the incompatibility between electron-rich PMB moiety and the strong Lewis acidity of BF_3·2AcOH complex. To address this problem, we examined several other Fleming-Tamao oxidation protocols, as shown in Scheme 4-35. Of them, the combination of potassium bromide (KBr) and peracetic acid (AcOOH) caused the starting material **200** to decompose.[55] Although a method using mercury acetate ($Hg(OAc)_2$) and AcOOH delivered the desired alcohol product **201** in moderate yield (38%),[61] we were frustrated by the fact that this method was not compatible with large scale setups. In addition, the usage of stoichiometric amount of mercury salt $Hg(OAc)_2$ was not considered environmentally friendly. Fortunately, a one-pot procedure utilizing TBAF as the fluorination reagent and H_2O_2 as the oxidant generated alcohol **201** in 84% isolated yield.[62] The reaction setup can be scaled up to 3 mmol, providing more than 800 mg of **201** in one batch.



Scheme 4-35. Optimization of the Fleming-Tamao oxidation step. *Reagents and conditions*: a) $Hg(OAc)_2$ (1.5 equiv), AcOH/AcOOH, 0 °C, 1 h; b) TBAF (4.0 equiv), 4 Å MS, THF, 70 °C; then KF (4.0 equiv), $NaHCO_3$ (1.0 equiv), MeOH, H_2O_2 (30%, 10.0 equiv), 70 °C, 1h

*4.4.8.2 The reduction of ketoester **203***

In part 4.4.5.3, it was mentioned in Scheme 4-31 that the reduction of ketoester **170** to secondary alcohol imposed a significant challenge to material supply. The desired isomer **180** made up merely 25% in the mixture of diastereomers after reduction by $NaBH_4$ in methanol. This ratio was unchanged when we exercised the synthetic route with the *O*-PMB protecting group. The observed phenomena prompted us to expand entry for the desired alcohol **205**.

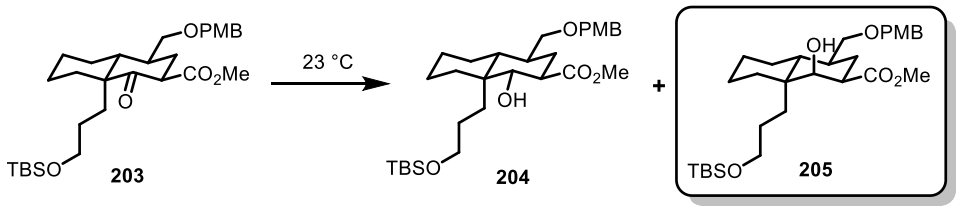


Table 4-1. Selected conditions and results for reduction of ketoester **203**

Entry	Reductant	Solvent	Yield **204** (undesired)	Yield **205** (desired)	Ratio (desired/ undesired)
1	$NaBH_4$	MeOH	45%	15%	1:3
2	$NaBH_4$	EtOH	41%	15%	1:2.7
3	$NaBH_4$	*n*-PrOH	40%	19%	1:2.1
4	**$NaBH_4$**	***i*-PrOH**	**36%**	**23%**	**1:1.6**
5	$NaBH_4$	*i*-BuOH	38%	19%	1:2.0
6	$NaBH_4$	*t*-BuOH	39%	9%	1:4.3
7	$NaBH_4$	THF	59%	<5%	<1:10
8	$Zn(BH_4)_2$	THF	n.d.[a]	n.d.[a]	<1:10
9	Bu_4NBH_4	MeOH	47%	12%	1:3.9

Table 4-1. (Continued)

10	Et_2AlCl/Bu_3SnH	THF	n.d.[a]	n.d.[a]	<1:10
11	DIBAL-H	CH_2Cl_2	n.d.[a]	n.d.[a]	<1:10

a. Not determined

We attempted to invert the equatorial alcohol of **204** to axial position by Mitsunobu conditions but encountered no conversion. We then focused on screening the parameters of reduction, with results displayed in Table 4-1. Borohydride (BH_4^-) was the only reductant here that achieved selective ketone reduction since other common reductants resulted in either no conversion or over-reduction. Sodium turned out to be the optimal countercation for the reductant, as shown in Entry 9 that tetrabutylammonium borohydride provided inferior ratio. $LiBH_4$ proved prone to generate over-reduced product and TLC showed no promising results for an improved ratio of desired isomer **205**. We were surprised to discover that etheric solvents such as THF resulted in exclusive formation of the undesired diastereomer **204** (Entry 7). The indication that alcoholic solvents gave rise to the desired diastereomer might be explained by the larger steric repulsion between the methoxyborohydride species formed in situ and the methyl ester group of **203**, thus allowing some of the hydride to approach from the bottom face. This explanation was partly supported by the fact that ethanol, *n*-propanol and *i*-propanol provided higher ratios of the desired alcohol **205** (up to 1:1.6 by isopropanol, Entry 2-5). However, when *t*-butanol was employed, the ratio dropped to 1:4.3, presumably due to a reluctant formation of alkoxyborohydride species. "Super hydride" ($LiEt_3BH$) resulted in an unidentifiable nonpolar side product and other impurities, though $[Et_3BH]^-$ is considered a bulky anion. We also tried a directed reduction protocol but ended up in only the undesired isomer (Entry 10). DIBAL-H at -78 ^oC led to a complex mixture, in which the ketone reduction product was identified as a pure undesired

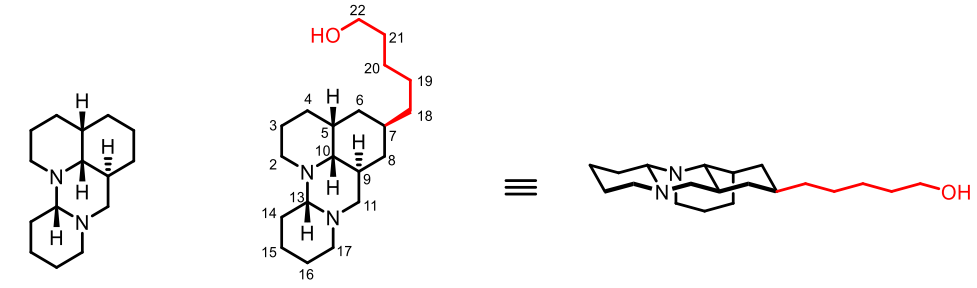
isomer **204**. Therefore, the current optimal output of the desired isomer in this reaction was 23% isolated yield in pure form.[63]

4.5 Application of aza-Michael cyclization I: synthesis of schoberine B

As is described in the previous paragraphs, *aza*-Michael cyclization reactions culminated in synthesis of both simple *Myrioneuron* alkaloid myrioxazine A (Scheme 4-28) and a more complex member myrioneurionol (Scheme 4-34). We were eager to expand the scope of such an *aza*-Michael reaction and utilize them to construct *cis*-DHQ cores of more *Myrioneuron* alkaloids. Schoberine B (**4**) was selected as a target for showcasing our general solution for this natural product family.

4.5.1 Structure and biogenesis of schoberine B

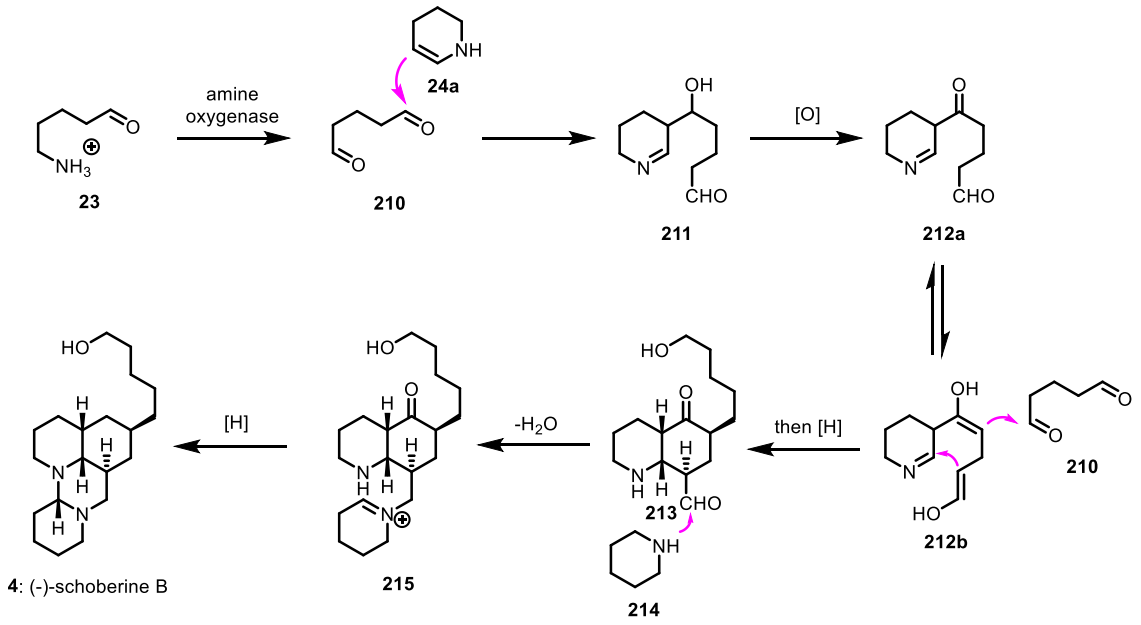
Schoberine B (**4**, Figure 4-1 and 4-6), a *Myrioneuron* alkaloid isolated from the aerial parts of *Myrioneuron faberi* in Sichuan province, China.[6] Merely 2 mg of pure sample was obtained from 30 kg of dry biomass. Its structure was determined by mass spectroscopy and extensive NMR studies. Interestingly, the name schoberine B designated by the isolation chemists is likely to be derived from its structural similarity with schoberine (**3**), which shares the exact same tetracyclic core frame with schoberine B. The five-carbon linear side chain on C-7 distinguished schoberine B from other *Myrioneuron* family members.



3: (-)-schoberine **4**: (-)-schoberine B

Figure 4-6. Flat and 3-D structures of schoberine and schoberine B

The proposed biosynthesis followed the proposals described above for known *Myrioneuron* alkaloids, as shown in Scheme 4-36. Five-carbon aldehyde **23**, derived from L-lysine, is further oxidized to dialdehyde **210**. One of the carbonyl groups is attacked by cyclic enamine **24a**, which also stems from L-lysine as analyzed in Scheme 4-1. After oxidation of **211** to **212**, tautomeric isomer **212b** underwent an intramolecular cyclization to forge *cis*-DHQ **213**. The five-carbon side chain is installed at this stage by an aldol reaction between **212b** and dialdehyde **210**. The secondary alcohol from the aldol reaction was deoxygenated and the terminal aldehyde was reduced to a primary alcohol in **213**. Then the exocyclic aldehyde on the *cis*-DHQ ring condensed with one molecule of piperidine (biogenetically from reduction of cyclic imine **24**). A migration of iminium occurred to give **215** prior to the final ring closure and deoxygenation of the remaining carbonyl leading to schoberine B (**4**).



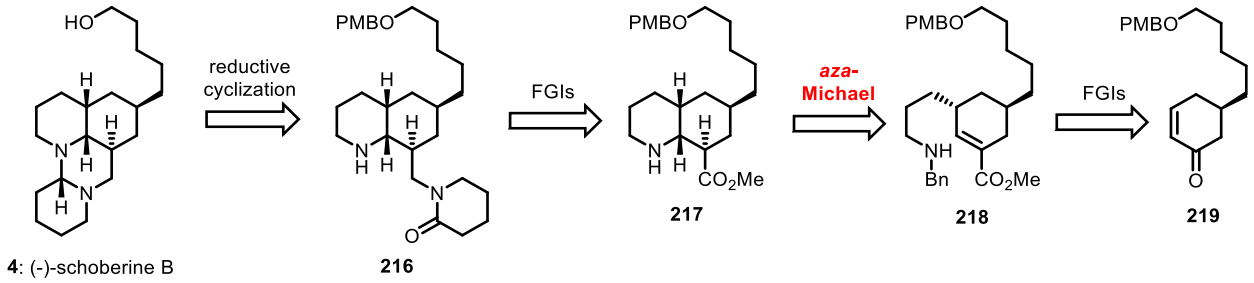
Scheme 4-36. The proposed biosynthesis of schoberine B

The biological profiles of schoberine B were also briefly investigated. It showed moderate *in vitro* inhibitory activity against hepatitis C virus and a therapeutics index of 36.2. Interest on this molecule for further biological inspections and the low availability from isolation of plants stimulated us to probe its chemical synthesis.

4.5.2 Retrosynthetic analysis

The retrosynthetic analysis of schoberine B (Scheme 4-37) starts from the last reductive ring formation in an analogous vein of the proposed biosynthesis in Scheme 4-36. A reductant in this step first reduces the lactam **216** to hemiaminal, which is then dehydrated to form iminium. Capture by the secondary amine on *cis*-DHQ will forge the target molecule **4**. The pendant lactam can be traced back to a methyl ester group in **217**. This becomes a pattern of an *aza*-Michael cyclization reaction. The *aza*-Michael precursor **218** can be synthesized stereoselectively from chiral enone **219** taking advantage of the pre-installed chiral center. We selected *O*-PMB here as the protecting group to proceed through the whole synthetic sequence based on our knowledge

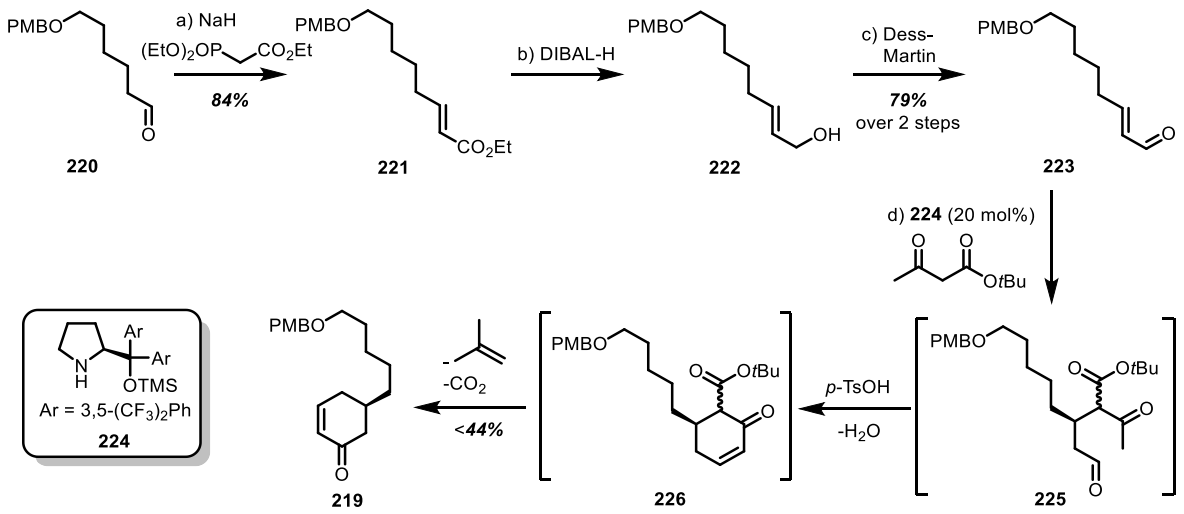
learned in the myrioneurinol synthesis that PMB might be more beneficial in a late-stage deprotection sequence.



Scheme 4-37. Retrosynthetic analysis of schoberine B based on a key *aza*-Michael cyclization reaction

*4.5.3 Synthesis of aza-Michael cyclization precursor **218***

The synthesis of schoberine B commenced with known aldehyde **220**,[64] which could be prepared in deca-gram scale in two steps from commercially available 1,6-hexanediol (Scheme 4-38). HWE olefination installed the α,β-unsaturated ester in **221**, which was transformed into enal **223** in 2 steps with satisfactory isolated yield. With multiple grams of enal **223** in hand, we applied a reported methodology in synthesis of chiral 3-substituted enones.[65] Hayashi-Jørgensen-type proline catalyst **224** condensed with enal **223** to form a conjugated iminium in the first place. Chiral induction occurred when the enolate of *t*-butyl acetoacetate attacked the conjugated iminium in a 1,4-addition manner. The so-formed intermediate **225** then underwent annulation, dehydration, and decarboxylation to ultimately yield chiral enone **219**. However, we encountered not only low yield of product, but also considerable amount of inseparable impurity along with product. To optimize the isolated yield of this step, we conducted a brief investigation of reaction parameters.



Scheme 4-38. Synthesis of chiral enone **219** *via* Michael-addition/condensation/decarboxylation sequence catalyzed by an organocatalyst **224**. *Reagents and condition*: a) triethyl acetophosphonate (1.2 equiv), NaH (60% dispersion in mineral oil, 1.1 equiv), THF, 23 °C, 30 min, then **220** (1.0 equiv), 23 °C, 8 h; b) DIBAL-H (1.0 M in CH_2Cl_2, 2.3 equiv), CH_2Cl_2, -78 °C, 2 h; c) Dess-Martin periodinane (1.2 equiv), $NaHCO_3$ (8.0 equiv), CH_2Cl_2, 23 °C, 1 h; d) **224** (0.20 equiv), *t*-butyl acetoacetate (2.0 equiv), neat, 23 °C, 18 h; *p*-TsOH (0.2 equiv), PhMe, 80 °C, 16 h

We first tried the optimal condition described in the literature (Table 4-2, Entry 1). To our frustration, only trace of the desired product **219** was obtained. By increasing the equivalent of *t*-butyl acetoacetate the isolated yield of product increased to 16% when 2 equivalents of *t*-butyl acetoacetate were employed (Entry 2-4). Higher catalyst loading elevated the isolated yield of product as well. 20 mol% catalyst loading gave the optimal yield of 44% (Entry 6), while further increasing catalyst loading gave rise to more impurities in the product without significantly improving the isolated yield. We inspected the role of solvent in this reaction and were surprised to find that the optimal reaction media, water, in the original literature completely shut down the generation of any desired product **219** (Entry 7). As a comparison, the synthesis of 5-*n*-butyl cyclohexen-1-one was achieved in high yield and enantioselectivity in Jørgensen's report.[65] Such tremendous difference might be attributed to the interactions between *O*-PMB group and the organocatalyst **224**. Detailed studies looking into this phenomenon are still ongoing.

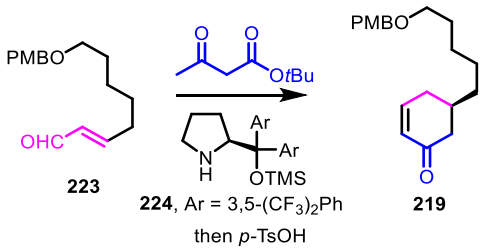


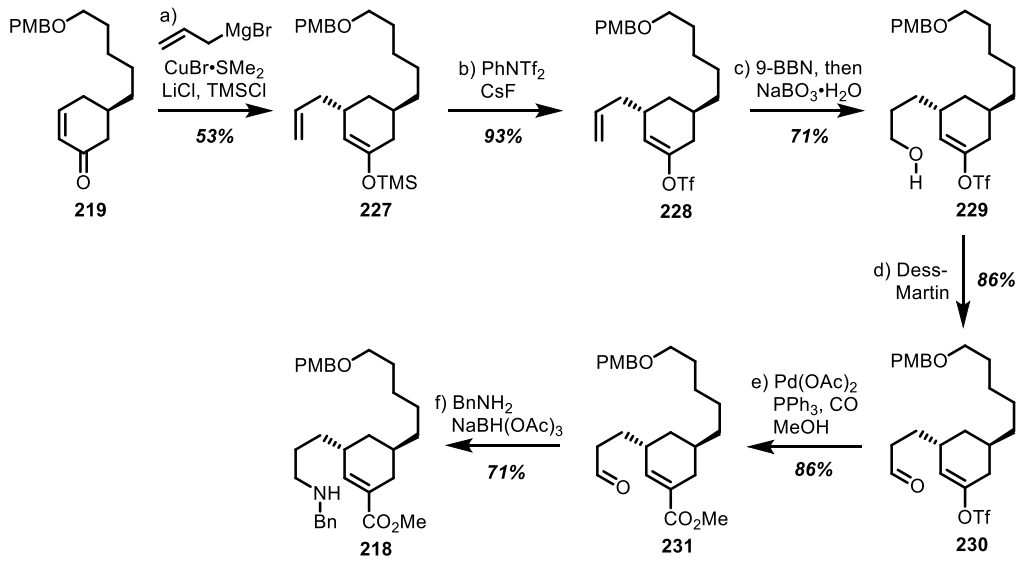
Table 4-2. Selected conditions and results for preparation of enone **219**

Entry	Solvent	Ketoster loading	Catalyst loading	Isolated yield[a]	Ee value[b]
1	neat	0.67 equiv	10 mol%	<5%	n.d.[c]
2	neat	1.0 equiv	10 mol%	<5%	n.d. [c]
3	neat	1.5 equiv	10 mol%	10%	n.d. [c]
4	neat	2.0 equiv	10 mol%	16%	n.d. [c]
5	neat	2.0 equiv	15 mol%	22%	88%
6	**neat**	**2.0 equiv**	**20 mol%**	**44%**	**94%**
7	H_2O or PhMe	2.0 equiv	20 mol%	<5%	n.d. [c]
8[d]	H_2O	0.67 equiv	10 mol%	69%	92%

a. **219** was obtained with inseparable impurities; b. Measured by chiral HPLC on derivative **228**; c. Not determined; d. Literature (ref 65); substituent on enone was *n*-butyl instead of -$(CH_2)_5$OPMB in our case.

Although enone **219** was obtained together with inseparable impurities, flash chromatography could remove all the impurities after the Michael addition/TMS trap sequence (Scheme 4-39). The pure TMS enol ether **227** was desilylated and triflated by the combination of

anhydrous CsF and $PhNTf_2$ to afford vinyl triflate **228**.[66] Subsequent hydroboration and oxidation on this compound generated alcohol **229**, which was then oxidized by Dess-Martin periodinane to aldehyde **230**. The palladium catalyzed carbonylation gave conjugated ester **231**. Reductive amination with benzylamine afforded the *aza*-Michael cyclization precursor **218**.

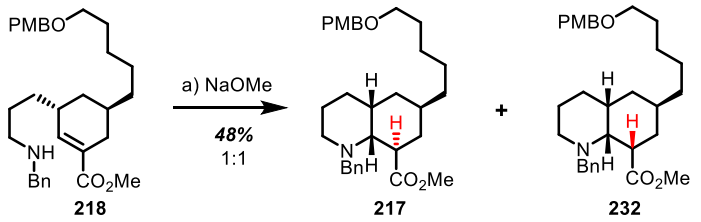


Scheme 4-39. Synthesis of the *aza*-Michael cyclization precursor **218**. *Reagents and condition*: a) $CuBr•SMe_2$ (1.0 equiv), LiCl (2.0 equiv), THF, 23 °C, 5 min, then allylmagnesium bromide (1.0 M in Et_2O, 2.0 equiv), -78 °C, 30 min, then **219** (1.0 equiv), TMSCl (1.5 equiv), -78 °C, 2 h, slowly to 23 °C, 8 h; b) $PhNTf_2$ (1.5 equiv), CsF (3.0 equiv), DME, 23 °C, 12 h; c) 9-BBN (0.5 M in THF, 1.05 equiv), THF, 23 °C, 8 h, then $NaBO_3•H_2O$ (2.5 equiv), THF/H_2O, 23 °C, 12 h; d) Dess-Martin periodinane (1.15 equiv), $NaHCO_3$ (3.0 equiv), CH_2Cl_2, 23 °C, 1 h; e) $Pd(OAc)_2$ (0.1 equiv), PPh_3 (0.2 equiv), Et_3N (4.0 equiv), CO (1 atm), MeOH, 8 h; f) $BnNH_2$ (1.5 equiv), CH_2Cl_2, 23 °C, 1h, then $NaBH(OAc)_3$ (1.3 equiv), 23 °C, 8 h

*4.5.4 aza-Michael cyclization of **218***

Having the precursor **218** with the 5-C side chain which presents in the target molecule schoberine B in hand, we moved to the test ground of the *aza*-Michael cyclization (Scheme 4-40). Initial attempts by exposing **218** to 3 equivalents of Triton-B in methanol at ambient temperature resulted in a conversion slower than that of the model study (Scheme 4-28). We quenched the reaction and analyzed the one new spot appearing on TLC. It turned out to be a mixture of two diastereomers (**217** and **232**) that were inseparable by column chromatography or preparative TLC, as shown in Scheme 4-40. The ratio of these two compounds by quenching the reaction media at

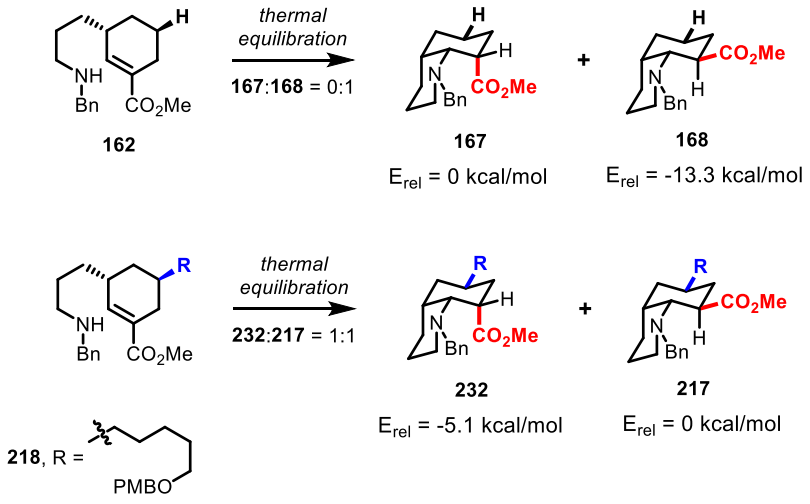
half conversion was close to 2:1, favoring **217**. This ratio varied batch to batch while early interception of the reaction always ended up in **217** as the major product. Increasing the stoichiometry of base surprisingly did not converge to one single product. When 5 equivalents of Triton-B or NaOMe and elongated reaction length (40 hours) were set as the reaction parameters, a 1:1 mixture of diastereomers **217** and **232** arose. This result implied that the energy profiles of the two diastereomers are possibly so close that it wass reflected by the ratio of 1:1 after a prolonged equilibrating process. Later we discovered that employment of large excess of Triton-B could cause significant amount of product to be trapped in aqueous phase due to the phase-transfer nature of Triton-B. Sodium methoxide (NaOMe) was eventually selected as the alternative promoter in this *aza*-Michael reaction.



Scheme 4-40. *Aza*-Michael cyclization of **218** ended in a pair of inseparable diastereomers. *Reagents and conditions*: a) NaOMe (0.5 M in MeOH, 5.0 equiv), MeOH, 50 °C, 40 h

To gain further insights into this transformation, we conducted a preliminary computational study. The results from DFT calculation showed that the conformer with the lowest energy of **232** was 5.1 kcal/mol lower than the most stable conformer of diastereomer **217** (Scheme 4-41). This value did not explain the 1:1 ratio of **217** and **232** from experiments with prolonged equilibration conditions. Nevertheless, the opposite trend of thermodynamically more stable diastereomer in this case emphasized the significance of the side chain, compared to the calculated energy difference (13.3 kcal/mol) between the two diastereomers **167** and **168** from the model study. In this case **168** turned out to be the sole product upon prolonged exposure to excess amount of base

and heating. The reason behind might be from the difference of substituent patterns. In the pair of diastereomers from the schoberine B synthesis, the existence of $-(CH_2)_5OPMB$ side chain introduced additional steric repulsion with the ester group, though they can be in equatorial positions simultaneously, while **167** and **168** from the model study did not have such interactions. Further detailed studies are underway to solve this anomality.

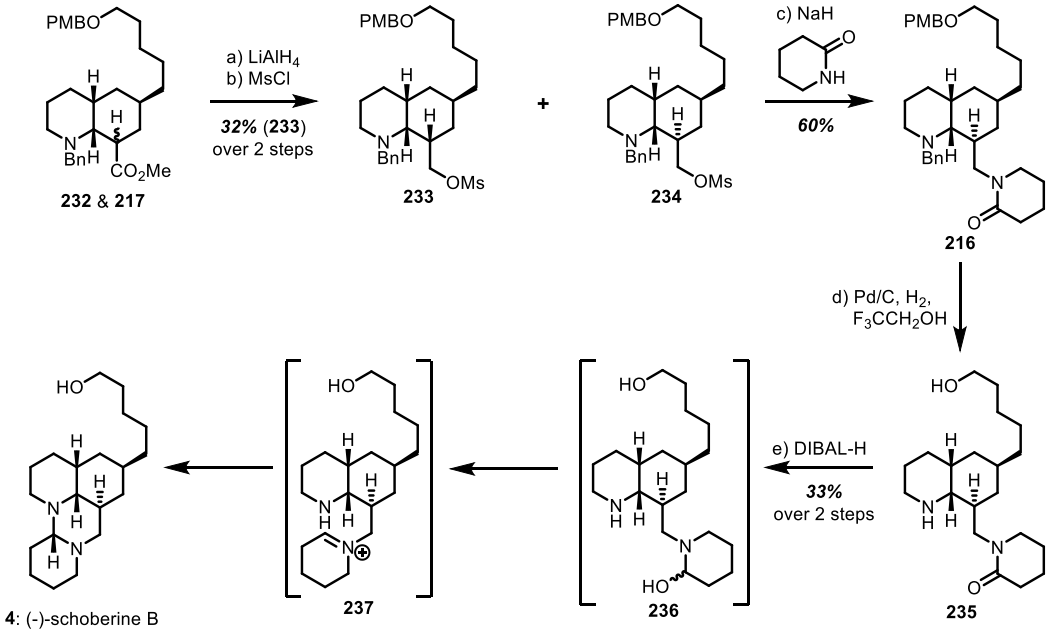


Scheme 4-41. Preliminary computational studies reveal thermodynamically favored products from *aza*-Michael cyclization reactions

4.5.5 Post aza-Michael transformations and completion of schoberine B

To continue the synthesis towards schoberine B, the inseparable mixture of *aza*-Michael cyclization products **217** and **232** were subjected to $LiAlH_4$-mediated reduction and mesylation of so-obtained primary alcohols (Scheme 4-42). We were pleased to see that two diastereomers of mesylate can be readily separated by preparative TLC. The desired isomer **234**, which was slightly less polar than the undesired one (**233**) on silica, was subjected to a substitution reaction by the anion of δ-valerolactam. The *N*-alkylation product **216**, facing the deprotection of *O*-PMB and *N*-Bn moieties, was exposed to atmospheric hydrogenation with large excess of palladium (5 mass

equivalents) on carbon as catalyst. The condition which worked well for the double deprotection in the synthesis of myrioneurionol succeeded again in this case, generating fully deprotected compound **235**. Of note, when analogue of **216** with *O*-Bn protecting group was tested, the benzyl proved again stable under various hydrogenation conditions. The last cyclization reaction was triggered by DIBAL-H, whose hydride attacked lactam to form hemiaminal intermediate **236**. Upon dehydration, the iminium intermediate **237** akin to that was proposed by the biosynthetic hypothesis of schoberine B (Scheme 4-36) was formed. A spontaneous ring closure occurred with excellent selectivity of face projection to deliver (–)-schoberine B (**4**), albeit in moderate yield (33%) over 2 steps from fully protected lactam **235**. Proton and carbon NMR spectra in d^5-pyridine at 313 K had full agreement with the isolation report.[6]

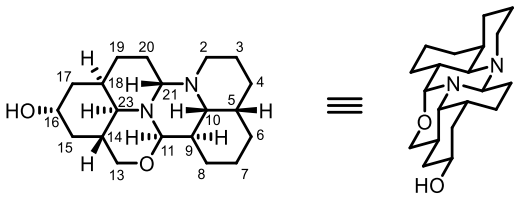


Scheme 4-42. Completion of asymmetric synthesis of (-)-schoberine B by a reductive cyclization. *Reagents and conditions*: a) $LiAlH_4$ (1.0 M in THF, 1.0 equiv), Et_2O, 23 °C, 2 h; b) MsCl (1.2 equiv), Et_3N (2.0 equiv), CH_2Cl_2, 23 °C, 2 h; c) NaH (60% dispersion in mineral oil, 5.0 equiv), δ-valerolactam (3.0 equiv), DMSO, 45 °C, 12 h; d) Pd/C (10%, 5.0 mass equiv), H_2 (1 atm), trifluoroethanol, 23 °C, 40 h; e) DIBAL-H (1.0 M in THF, 2.0 equiv), THF, 23 °C, 8 h.

4.6 Application of aza-Michael cyclization II: Synthetic studies toward myrobotinol

4.6.1 Structure and proposed biosynthesis of myrobotinol

Myrobotinol (**7**, Figure 4-1 and 4-7) is another *Myrioneuron* alkaloid isolated by the Bodo group, from the plant species *Myrioneuron nutans*. With its structure determined by extensive NMR studies and absolute stereochemistry probed by Mosher's methods, its complex skeleton marked itself one of the most structurally intriguing family members owing to the highly fused hexacycle.

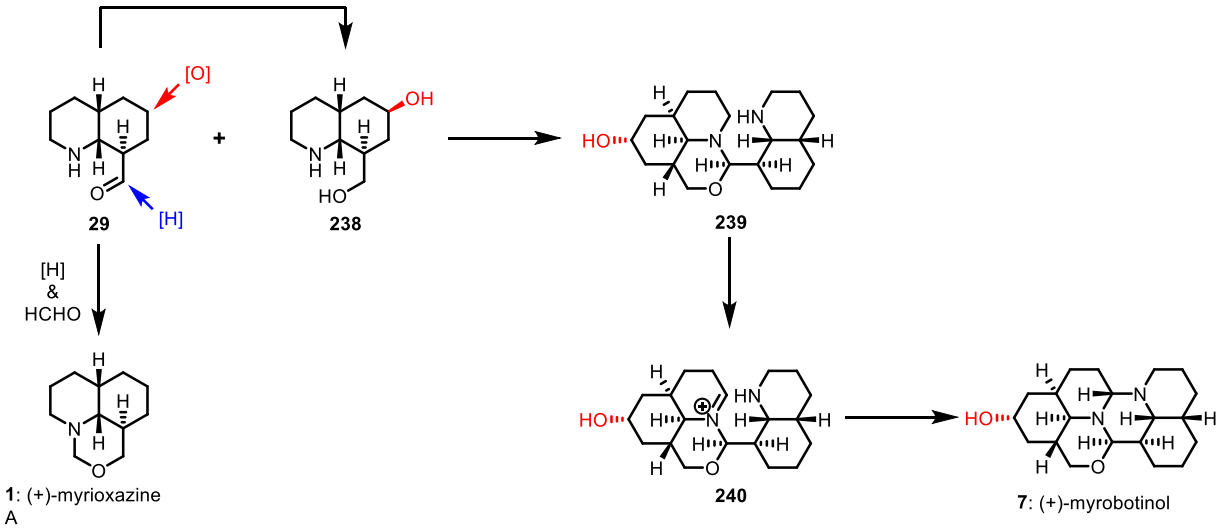


7: (+)-myrobotinol

Figure 4-7. Flat and 3-D structures of myrobotinol

Nonetheless, it is apparent that myrobotinol is likely to be a heterodimeric molecule consisting of two *cis*-DHQ units, and the biosynthesis proposed by the isolation chemists was based on this observation. In their proposal shown in Scheme 4-43, the advanced aldehyde **29**, which is the biosynthetic precursor of myrioxazine A (Scheme 4-1) had its carbonyl reduced to alcohol and a methylene (CH_2) oxidized to a secondary alcohol marked in red, to generate diol **238**. The two pieces were joined together to form **239** via an aminal formation event between the aldehyde carbonyl of **29** and the secondary amine and the primary alcohol in the other piece **238**. The methylene adjacent to the tertiary amine in **239** became the most vulnerable position in terms of enzymatic oxidation. Therefore, the oxidation of this methylene delivered iminium in intermediate **240**. The secondary amine served as the nucleophile to attack the iminium and furnished the final ring. The proposal did not exclude the possibility that the secondary alcohol

was oxidized after the dimerization event happened. Nevertheless, neither oxy-myrioxazines nor deoxy-myrobotinol were isolated, indicating that the oxidation reactions during the biosynthesis of myrobotinol might be highly specific to enzyme-substrate recognition.

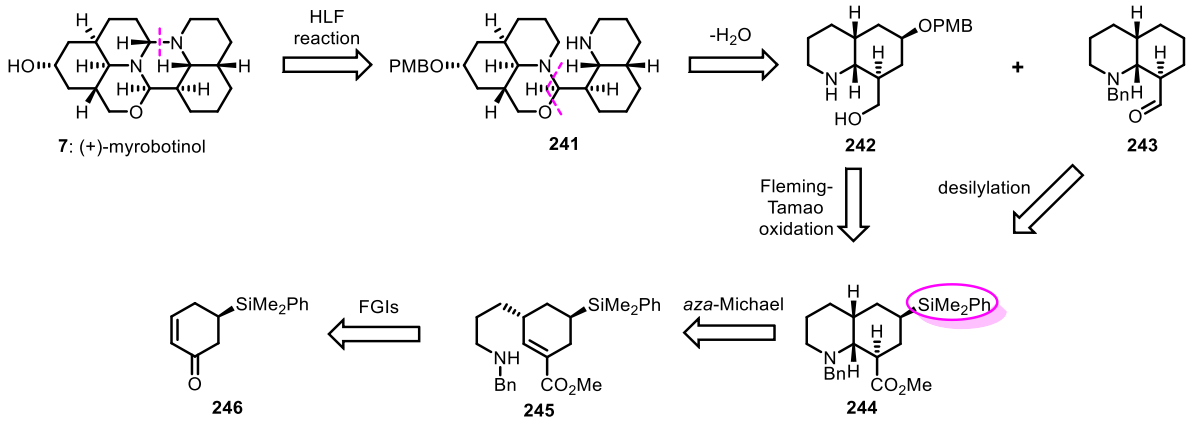


Scheme 4-43. Proposed biosynthesis of myrobotinol via a "dimerization" process and a C-H oxidation step

4.6.2 Retrosynthetic analysis of myrobotinol

The synthetic plan of myrobotinol (Scheme 4-44) is based on the last step in the proposed biosynthesis. A Hofmann-Löffler-Freytag reaction or other oxidation protocols can generate an *N*-baseradical on the secondary amine of **241** and a subsequent 1,6-hydrogen abstraction activates and forms the desired iminium to close the final ring. The 1,6-hydrogen abstraction is considered favored here due to the absence of a 1,5-hydrogen.[67] The disconnection of the heterodimer **241** back to two monomers is realized by a dehydrative aminal formation reaction. The two pieces **242** and **243** are then traced back to a common intermediate **244**, whose silyl moiety serves the surrogate for hydroxy (**242**) and proton (**243**). The *cis*-DHQ intermediate **244**, can then be readily

prepared via an *aza*-Michael cyclization with relative stereochemistry set up thanks to the chiral center in the chiral starting material enone **246**.[68]

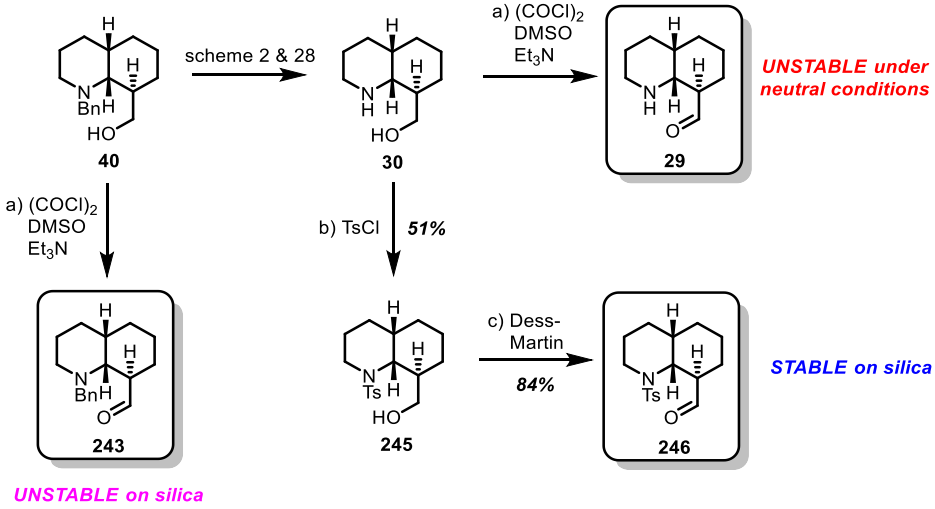


Scheme 4-44. Retrosynthetic analysis of myrobotinol based on an enatioselective synthesis of two pieces utilizing *aza*-Michael cyclization reactions

4.6.3 A model study on dimerization

In order to probe the feasibility of the key dimerization and C-H amination reactions, we initiate a model study using available racemic materials. We attempted first to oxidize the unprotected amino alcohol **30** (Scheme 4-45), but only to find that trace amount of aldehyde was formed according to crude NMR, along with a messy unidentifiable mixture. It shall be noted that **30** serves as a key intermediate in biosynthetic proposals (Scheme 4-1 and 4-43), whereas its stability is questioned given out failure to synthesize it. Then we took the *N*-benzyl alcohol **40** and performed a Swern oxidation on it (Dess-Martin oxidation resulted in decomposition). The crude NMR showed an aldehyde **243** as the major product, together with minor impurities. However, our attempts to purify this compound on either regular or deactivated silica resulted in loss of this compound, indicating its fragility on silica. With secondary and tertiary amine potentially setting aldehydes unstable, we turned to more electron-withdrawing protecting groups on nitrogen. Amino alcohol **40** was subjected to tosyl protection condition (TsCl and NaOH in CH_2Cl_2/H_2O) and the resultant sulfonamide was isolated in 51% yield. It was noteworthy that significant amount of bis-

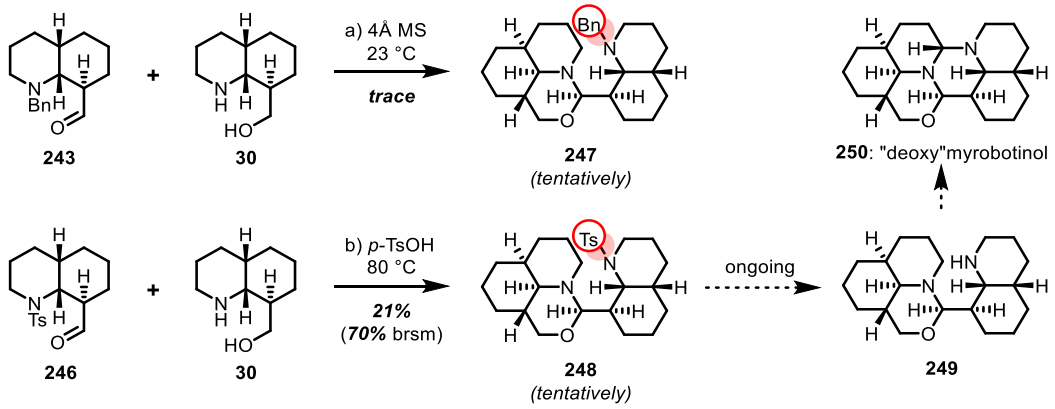
Ts protection product arose, with lowering the loading of TsCl to 1.05 equivalent did not suppress this side product, if Et_3N was employed as base and pure CH_2Cl_2 as solvent. Other protecting reagents, including the structurally similar *p*-NsCl, could not deliver the desired mono *N*-protected product. Oxidation by Dess-Martin periodinane afforded the aldehyde substrate **246** in high yield. This *N*-Ts aldehyde **246** was stable on silica and can readily be purified.



Scheme 4-45. Synthesis of aldehyde pieces with different *N*-protection patterns. *Reagents and conditions*: a) $(COCl)_2$ (1.3 equiv), DMSO (1.5 equiv), CH_2Cl_2, -78 °C, 5 min, then **40** or **30** (1.0 equiv), -78 °C, 30 min, then Et_3N (2.0 equiv), slowly to 23 °C, 1 h; b) TsCl (1.2 equiv), NaOH (6 N, 3.0 equiv), CH_2Cl_2/H_2O, 23 °C, 12 h; c) Dess-Martin periodinane (1.2 equiv), $NaHCO_3$ (8.0 equiv), CH_2Cl_2, 23 °C, 1 h

Next, we tested the dimerization reaction between aldehydes **243** and **246** and amino alcohol **30**. We found that mixing the crude *N*-Bn aldehyde **243** and amino alcohol **30** in anhydrous benzene along with activated molecular sieves produced trace amount of a tentatively assigned dimerization product **247** (Scheme 4-46). Unfortunately, the separation process was extremely challenging because the unreacted aldehyde decomposed and significantly contaminated preparative TLCs. Unlike *N*-Bn aldehyde **243**, *N*-Ts aldehyde **246** was stable on silica so it could be effectively recovered since similar conditions (4Å MS in benzene) stalled at 10% conversion of aldehyde **246**. We later found that *p*-TsOH was able to elevate conversion and to provide the heterodimerization product **248** in 29% isolated yield, as a single isomer on ^1H NMR. Although at

this stage we don't have any insight of its stereochemistry, the spontaneous formation of a single product may mirror the biogenesis of myrobotinol, rendering the model dimer **248** the same relative stereochemistry as that in myrobotinol.



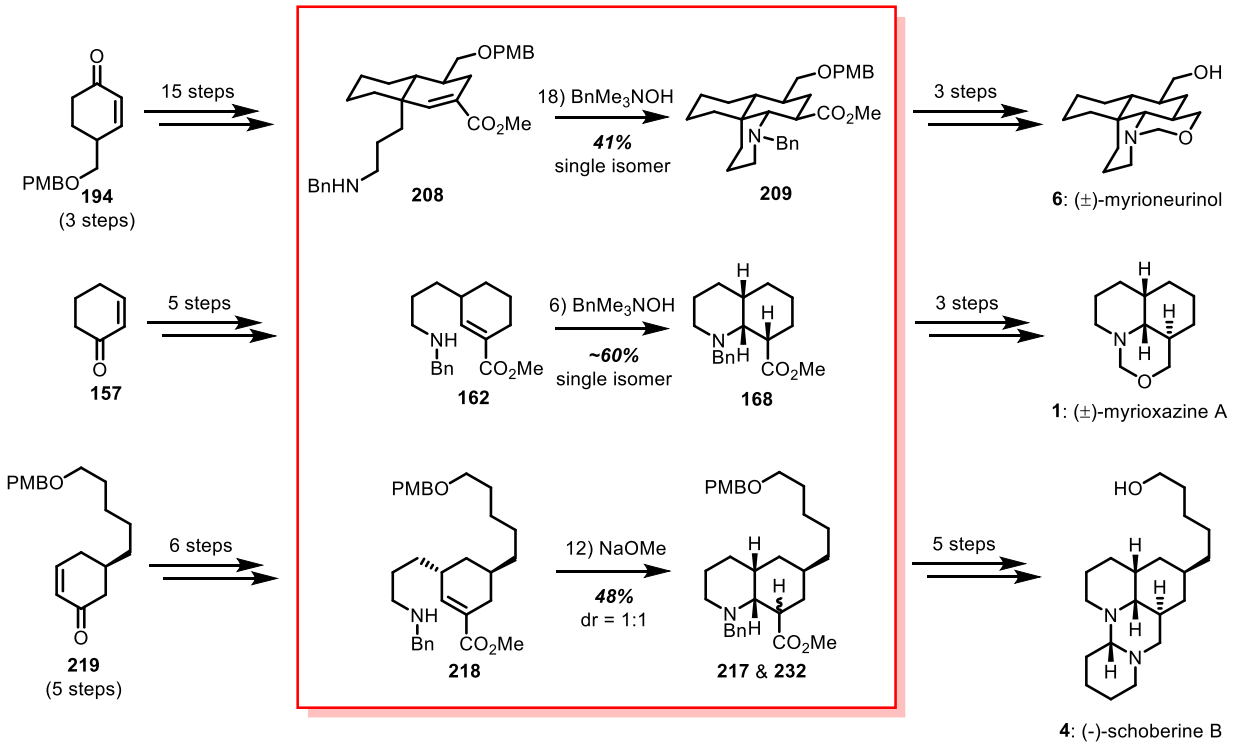
Scheme 4-46. Dimerization of model pieces and future plans. *Reagents and conditions*: a) 4Å MS, PhH, 23 °C, 40 h; b) *p*-TsOH (0.5 equiv), PhMe, 80 °C, 40 h

The task on model study was then two steps from completion: a *N*-Ts deprotection and a Hofmann-Löffler-Freytag reaction. However, we tried several common *N*-Ts deprotection protocols, including Na/Hg, Mg/NH_4Cl, and TBAF under heating. None of these conditions gave the desired deprotection product. We are currently investigating more deprotection conditions, hoping to reach the "deoxy"myrobotinol (**250**) as a mark of success for the model study.

4.7 Conclusions and outlook

Our journey toward the total synthesis of the *Myrioneuron* alkaloids commenced with the explorations targeting myrioneurinol. We encountered several problems in terms of key bond constructions. The first one came when we tried to build the *trans*-decalin core of the myrioneurinol and we solved the problem by an elaborate Michael addition/alkylation sequence (Scheme 4-13). The second was the dilemma of *cis*-DHQ moiety establishment. An array of methods on different substrates was attempted, all of which unfortunately failed to deliver the

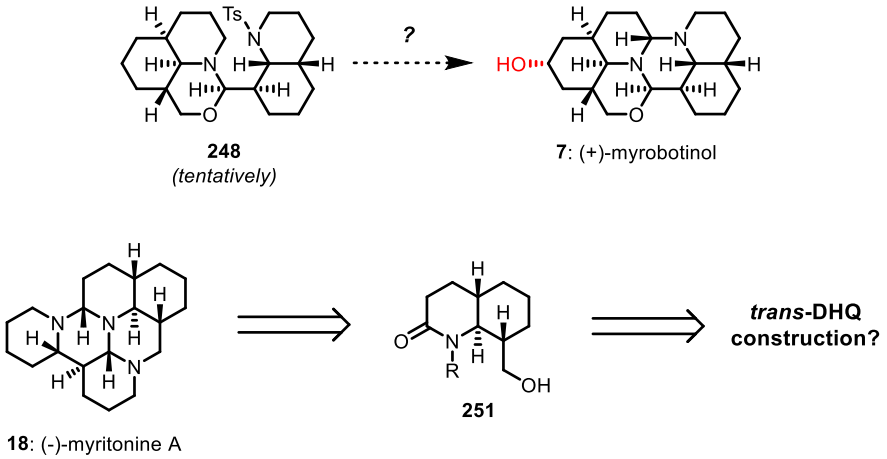
desired tricyclic intermediates (Scheme 4-18, 4-21, 4-22, and 4-23). The solution to this challenge was an *aza*-Michael reaction. This cyclization strategy ultimately constructed the desired tricycle in the core of myrioneurinol, rendering the racemic synthesis of this molecule in a total of 20 step. A potential enatioselective synthesis of myrioneurinol would be realized if the synthesis of enone **194** could be rendered asymmetric. Such a problem is considered technically solvable granted that similar compounds have been reported.[25,69]



Scheme 4-47. Summary of the synthesis of (±)-myrioneurinol, (±)-myrioxazine A, and (–)-schoberine B featuring a unified *aza*-Michael cyclization strategy

With the success of *cis*-DHQ construction in our myrioneurinol synthesis, we expanded this method to the synthesis of other *Myrioneuron* alkaloids. A racemic synthesis of myrioxazine A (**1**) was achieved in 9 steps employing a key *aza*-Michael cyclization (Scheme 4-28). Furthermore, the first asymmetric total synthesis of schoberine B (**4**) was accomplished featuring such an *aza*-Michael cyclization reaction, in a total of 17 steps (Scheme 4-42 and 4-47).

Our explorations will not stop here. The ongoing model study on myrobotinol is expected to answer the question about how to effect a successful heterodimerization and to construct the final C-N bond (Scheme 46). By exercising the *aza*-Michael cyclization strategy as a powerful tool to synthesize two monomer units, we hope to illuminate the late-stage synthetic challenge of myrobotinol and complete the asymmetric total synthesis of myrobotinol (**7**).



Scheme 4-48. Future targets and thinkings of the *Myrioneuron* alkaloids

Moving beyond out current target molecules, we can see more *Myrioneuron* alkaloids with diverse structural and topological challenges awaiting us. For example, the member myritonine A (Figure 4-4 and Scheme 4-48) possesses a *trans*-DHQ core, which is a synthetic hurdle that the current *aza*-Michael cyclization strategy cannot solve. A disparate solution is called for this new challenege.

4.8 Experimental section

General Procedures. All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Dry tetrahydrofuran (THF), toluene, dimethylformamide (DMF), diethyl ether (Et_2O) and dichloromethane (CH_2Cl_2) were obtained by passing commercially available pre-dried, oxygen-free formulations through activated alumina

columns. Yields refer to chromatographically and spectroscopically (^{1}H and ^{13}C NMR) homogeneous materials, unless otherwise stated. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Reactions were magnetically stirred and monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent, and an ethanolic solution of phosphomolybdic acid and cerium sulfate, and heat as developing agents. SiliCycle silica gel (60, academic grade, particle size 0.040–0.063 mm) was used for flash column chromatography. Preparative thin-layer chromatography separations were carried out on 0.50 mm E. Merck silica gel plates (60F-254). NMR spectra were recorded on Bruker 400, 500 and 700 MHz instruments and calibrated using residual undeuterated solvent as an internal reference. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, br = broad, app = apparent. Optical rotations were recorded on a Jasco DIP-1000 polarimeter. IR spectra were recorded on a Nicolet iS5 FT-IR spectrometer. High-resolution mass spectra (HRMS) were recorded on Agilent 6244 Tof-MS using ESI (Electrospray Ionization), APCI (atmospheric pressure chemical ionization), or Mixed (ionization by both ESI and APCI) at the University of Chicago Mass Spectroscopy Core Facility. Chiral high-performance liquid chromatography (HPLC) analysis was performed using a Shimadzu Prominence analytical chromatograph with commercial ChiralPak columns (OJ-H).

Abbreviations. EtOAc = ethyl acetate, 9-BBN = 9-borabicyclo[3.3.1]nonane, dppf = (diphenylphosphinyl)ferrocene, HMPA = hexamethylphosphoramide, DDQ = 2,3-dicyano-5,6-dichlorobenzoquinone, DMF = *N*,*N*-dimethylformamide, DPPA = diphenyl phosphoryl azide, DEAD = diethyl azodicarboxylate, TESCl = chlorotriethylsilane, TBAF = tetrabutylammonium

fluoride, MOMCl = chloromethyl methyl ether, DIPEA = diisopropylethylamine, DIAD = diisopropyl azodicarboxylate, DIPA = diisopropylamine, DIBAL-H = diisobutylaluminum hydride, MsCl = methanesulfonyl chloride,

Synthesis of myrioneurinol

Iodoenone 88. To a solution of **87** (3.80 g, 17.6 mmol, 1.0 equiv) in CH_2Cl_2 (17 mL) and pyridine (17 mL) was added I_2 (5.35 g, 21.1 mmol, 1.2 equiv) portionwise. The reaction was stirred at 23 °C in dark for 12 h before CH_2Cl_2 (20 mL) was added. The solution was washed sequentially by aqueous $NaHCO_3$ (20 mL) and aqueous $Na_2S_2O_3$ (30 mL). After dried ($MgSO_4$), filtered, and concentrated, the crude mixture was dissolved in CH_2Cl_2 (12 mL) and pyridine (12 mL). I_2 (5.35 g, 21.1 mmol, 1.2 equiv) was added portionwise. The mixture was stirred at 23 °C in dark for another 12 h before a mixed aqueous solution of $NaHCO_3$ and $Na_2S_2O_3$ was added to quench the reaction. The aqueous layer was extracted with CH_2Cl_2 (10 mL × 3). The combined organic layers were dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography (silica gel, hexanes/acetone, 20/1) to afford **88** (5.65 g, 94%) as a light yellowish oil (turning yellow upon exposure to light). **88**: R_f = 0.44 (silica gel, hexanes/EtOAc, 3/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (d, *J* = 2.1 Hz, 1 H), 7.41–7.28 (m, 5 H), 4.55 (d, *J* = 2.1 Hz, 2 H), 3.54–3.41 (m, 2 H), 2.88–2.82 (m, 1 H), 2.79 (dt, *J* = 16.7, 4.5 Hz, 1 H), 2.60–2.49 (m, 1 H), 2.15 (ddd, *J* = 13.7, 9.0, 4.4 Hz, 1 H), 1.92–1.81 (m, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 192.0, 160.4, 137.6, 128.4, 127.8, 127.6, 104.5, 73.2, 71.5, 41.3, 35.6, 25.8. HRMS (ESI+) calcd for $C_{14}H_{16}IO_2^+$ [M + H^+] 343.0189, found 343.0191.

Enone 89. To a solution of allyl PMB ether (1.20 g, 6.72 mmol, 1.0 equiv) in THF (6 mL) was added 9-BBN (0.5 M in THF, 13.4 mL, 6.70 mmol, 1.95 equiv) at 23 °C. The mixture was

stirred at 70 °C for 6 h before cooled down to 23 °C. To a flask loaded with **88** (1.15g, 3.36 mmol, 1.0 equiv) was added $AsPh_3$ (82 mg, 0.27 mmol, 0.08 equiv) and THF (10 mL). The solution was degassed by bubbling Ar through for 10 min. Cs_2CO_3 (1.64 g, 5.04 mmol, 1.5 equiv), degassed H_2O (2.5 mL), freshly prepared allyl boron reagent (described above), and $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (206 mg, 0.25 mmol, 0.075 equiv) were then added sequentially. The resulting mixture was then stirred at 70 °C for 12 h. Upon completion, half saturated aqueous NH_4Cl solution (20 mL) was added to quench the reaction. The aqueous layer was extracted with Et_2O (10 mL × 2). The combined organic layers were dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography (silica gel, hexanes/acetone, 40/1 to 30/1 to 20/1) to afford **89** (940 mg, 71%) as a colorless oil. **89**: R_f = 0.36 (silica gel, hexanes/EtOAc, 3/1); IR (film) ν_{max} 2933, 2860, 1675, 1513, 1247, 1100, 1034, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.40–7.28 (m, 5 H), 7.25 (d, *J* = 8.4 Hz, 2 H), 6.87 (d, *J* = 8.5 Hz, 2 H), 6.64 (s, 1 H), 4.54 (d, *J* = 1.2 Hz, 2 H), 4.41 (s, 2 H), 3.79 (s, 3 H), 3.46–3.39 (m, 4 H), 2.71 (d, *J* = 1.7 Hz, 1 H), 2.51 (dt, *J* = 16.6, 4.5 Hz, 1 H), 2.35 (qd, *J* = 12.8, 6.4 Hz, 1 H), 2.27 (t, *J* = 7.6 Hz, 2 H), 2.08 (dq, *J* = 13.5, 4.5 Hz, 1 H), 1.79–1.66 (m, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 199.2, 159.0, 146.2, 139.4, 138.0, 130.7, 129.2, 128.4, 127.7, 127.6, 113.7, 73.2, 72.8, 72.4, 69.4, 55.2, 37.2, 37.0, 28.4, 26.2, 26.1.

Compound 91. To a flame-dried flask was added $CuBr \cdot SMe_2$ (586 mg, 2.86 mmol, 1.2 equiv) and LiCl (246 mg, 5.72 mmol, 2.4 equiv), followed by THF (12 mL). The mixture was stirred at 23 °C for 5 min before the suspension turned homogeneous. The flask was then cooled down to -78 °C and allylmagnesium bromide (1.0 M in Et_2O, 8.34 mL, 8.34 mmol, 3.5 equiv) was added dropwise over 10 min. The resultant dark brownish suspension was then stirred at -78 °C for 30 min. A pre-mixed solution of **89** (940 mg, 2.38 mmol, 1.0 equiv) and TMSCl (0.60 mL,

4.76 mmol, 2.0 equiv) in THF (3 mL) was then added at this temperature. The reaction was kept at -78 °C for 2 h, then allowed to slowly warm up to 23 °C over 8 h before a mixed solution of half-saturated aqueous NH_4Cl solution (50 mL) and 3 N NaOH (30 mL) was added to quench the reaction. The biphasic mixture was vigorously stirred for 30 min before the aqueous layer was extracted with Et_2O (15 mL × 2). The combined organic layers were dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography (silica gel, hexanes/EtOAc, 50/1) to afford TMS silyl enol ether **90** (808 mg, 67%) as a colorless oil. Next, to a solution of TMS silyl enol ether **90** (808 mg, 1.59 mmol, 1.0 equiv) in THF (10 mL) was added MeLi·LiI (1.0 M in Et_2O, 2.08 mL, 2.08 mmol, 1.3 equiv) dropwise over 10 min at 0 °C. The reaction was stirred at this temperature for 1 h before HMPA (1.66 mL, 9.54 mmol, 6.0 equiv) was added. Then the flask was cooled down to -78 °C, followed by the addition of allyl iodide (0.44 mL, 7.15 mmol, 3.0 equiv). The reaction was kept at this temperature for 2 h before allowed to slowly warm to 23 °C over 8 h. The reaction was quenched by the addition of half-saturated aqueous NH_4Cl solution (15 mL) and the aqueous layer was extracted with Et_2O (10 mL × 2). The combined organic layers were washed by half-saturated aqueous $Na_2S_2O_3$ solution, dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography (silica gel, hexanes/EtOAc, 30/1) to afford **91** (440 mg, 58%) as a colorless oil, then (hexanes/acetone, 40/1) to afford **92** (146 mg, 18%) as a colorless oil. **91**: R_f = 0.60 (silica gel, hexanes/EtOAc, 3/1); IR (film) ν_{max} 2930, 2855, 1710, 1612, 1513, 1454, 1363, 1248, 1098, 1036 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35–7.30 (m, 4 H), 7.29–7.26 (m, 1 H), 7.25 (d, *J* = 6.6 Hz, 2 H), 6.87 (d, *J* = 8.5 Hz, 2 H), 5.89 (ddd, *J* = 22.4, 10.6, 5.4 Hz, 1 H), 5.73 (dq, *J* = 10.6, 6.6 Hz, 1 H), 5.26 (dd, *J* = 17.2, 1.1 Hz, 1 H), 5.13 (d, *J* = 10.4 Hz, 1 H), 5.04–4.97 (m, 2 H), 4.50 (d, *J* = 12.0 Hz, 1 H), 4.43 (d, *J* = 11.7 Hz, 1 H), 4.42 (s, 2 H), 4.18–4.08 (m, 1 H), 3.80 (s, 3 H), 3.45–3.39 (m, 2 H), 3.32 (dd, *J* = 7.1, 2.5 Hz, 2 H), 2.51 (ddd, *J* = 12.9, 9.6,

6.4 Hz, 1 H), 2.36–2.28 (m, 1 H), 2.05–1.98 (m, 5 H), 1.84–1.74 (m, 2 H), 1.73–1.65 (m, 2 H), 1.62–1.58 (m, 2 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.0, 147.2, 138.7, 137.5, 134.8, 130.8, 129.2, 128.3, 127.6, 127.4, 119.4, 116.4, 116.0, 113.7, 73.0, 72.4, 72.0, 70.3, 68.8, 55.2, 37.9, 37.4, 34.1, 28.5, 24.3, 21.7, 20.4; HRMS (ESI+) calcd for $C_{31}H_{40}NaO_4^+$ [M + Na^+] 499.2819, found 499.2868.

Compound 92. A solution of **91** (66 mg, 0.138 mmol, 1.0 equiv) in xylenes (6 mL) in a microwave vial was stirred at 180 °C for 6 h. Upon completion, the solution was directly concentrated to give **92** (66 mg, 99%) as a colorless oil. Compound **92** can also be obtained from direct allylation as a minor product as described above. **92**: R_f = 0.50 (silica gel, hexanes/EtOAc, 3/1); IR (film) ν_{max} 2933, 2856, 1704, 1612, 1513, 1454, 1362, 1302, 1246, 1173, 1098, 1036, 914, 821, 735, 699 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38–7.21 (m, 7 H), 6.87 (d, *J* = 8.4 Hz, 2 H), 5.87–5.76 (m, 1 H), 5.57–5.46 (m, 1 H), 5.07–4.90 (m, 4 H), 4.46 (q, *J* = 12.0 Hz, 2 H), 4.42 (s, 2 H), 3.80 (s, 3 H), 3.63 (dd, *J* = 9.1, 2.7 Hz, 1 H), 3.49 (dt, *J* = 12.8, 6.5 Hz, 1 H), 3.41 (dd, *J* = 14.8, 7.6 Hz, 1 H), 3.38–3.32 (m, 1 H), 2.52 (dd, *J* = 14.1, 7.6 Hz, 1 H), 2.42 (dd, *J* = 14.3, 5.8 Hz, 1 H), 2.37–2.28 (m, 2 H), 2.21–2.09 (m, 4 H), 2.05–1.96 (m, 1 H), 1.94–1.87 (m, 1 H), 1.58 (dd, *J* = 13.2, 3.6 Hz, 1 H), 1.49 (dt, *J* = 13.8, 7.0 Hz, 2 H), 1.34–1.24 (m, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 212.4, 159.0, 138.5, 138.4, 132.9, 130.8, 129.2, 129.1, 128.3, 128.3, 127.6, 127.5, 127.5, 117.9, 115.3, 113.7, 73.0, 72.7, 72.2, 70.5, 55.8, 55.2, 42.3, 38.7, 38.5, 38.4, 33.4, 28.9, 28.6, 24.6; HRMS (ESI+) calcd for $C_{32}H_{42}O_4^+$ [M^+] 490.3078, found 490.3022.

Compound 93. To a solution of **92** (60 mg, 0.126 mmol, 1.0 equiv) in CH_2Cl_2 (3 mL) was added Grubbs-II catalyst (22 mg, 0.025 mmol, 0.2 equiv) at 23 °C. The reaction was stirred at this temperature for 16 h. Upon completion, the reaction content was directly concentrated and purified

by flash column chromatography (silica gel, hexanes/EtOAc, 25/1 to 15/1) to afford **93** (46 mg, 81%) as a light yellowish oil. **93**: R_f = 0.46 (silica gel, hexanes/EtOAc, 3/1); IR (film) ν_{max} 2931, 2854, 1703, 1513, 1454, 1248, 1176, 1099, 1035 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.38–7.28 (m, 5 H), 7.25 (d, *J* = 8.0 Hz, 2 H), 6.87 (d, *J* = 8.5 Hz, 2 H), 5.69–5.54 (m, 2 H), 4.52 (d, *J* = 12.1 Hz, 1 H), 4.48 (d, *J* = 12.1 Hz, 1 H), 4.42 (s, 2 H), 3.80 (s, 3 H), 3.52 (dd, *J* = 9.3, 3.1 Hz, 1 H), 3.50–3.45 (m, 1 H), 3.43–3.38 (m, 2 H), 2.61 (ddd, *J* = 15.8, 12.6, 6.1 Hz, 1 H), 2.34 (dd, *J* = 16.1, 4.0 Hz, 2 H), 2.13–2.01 (m, 4 H), 1.97 (d, *J* = 10.9 Hz, 1 H), 1.87–1.78 (m, 1 H), 1.71–1.62 (m, 2 H), 1.62–1.46 (m, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 214.1, 159.0, 138.4, 130.8, 129.2, 129.1, 128.4, 127.6, 127.5, 124.3, 123.6, 113.7, 73.2, 73.2, 72.3, 70.7, 55.2, 49.9, 37.2, 36.2, 34.5, 32.7, 29.0, 28.2, 24.4, 23.1; HRMS (Mixed+) calcd for $C_{29}H_{37}O_4^+$ [M + H^+] 449.2686, found 449.2680.

Ketal 94. To a solution of **93** (46 mg, 0.102 mmol, 1.0 equiv) in CH_2Cl_2 (1 mL) was added DDQ (30 mg, 0.133 mmol, 1.3 equiv) at 23 °C. The reaction was stirred at this temperature for 30 min before it was directly concentrated and purified by flash column chromatography (silica gel, hexanes/acetone, 35/1 to 25/1) to afford **94** (23 mg, 68%) as a colorless oil. **94**: R_f = 0.28 (silica gel, hexanes/EtOAc, 3/1); IR (film) ν_{max} 3404 (br), 2926, 2860, 1453, 1084, 1065, 735, 697, 656 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37–7.30 (m, 4 H), 7.30–7.26 (m, 1 H), 5.56 (s, 1 H), 5.50 (s, 1 H), 4.51 (d, *J* = 12.2 Hz, 1 H), 4.46 (d, *J* = 12.2 Hz, 1 H), 4.06–3.97 (m, 1 H), 3.67 (dd, *J* = 10.9, 5.2 Hz, 1 H), 3.48 (dd, *J* = 9.2, 3.6 Hz, 1 H), 3.32 (dd, *J* = 9.2, 6.1 Hz, 1 H), 2.31 (d, *J* = 18.4 Hz, 1 H), 2.13–2.00 (m, 3 H), 1.95 (dd, *J* = 13.9, 5.3 Hz, 1 H), 1.89–1.84 (m, 1 H), 1.79–1.74 (m, 2 H), 1.67 (dd, *J* = 14.0, 4.0 Hz, 1 H), 1.59–1.52 (m, 2 H), 1.51–1.47 (m, 1 H), 1.30 (dd, *J* = 13.3, 2.9 Hz, 1 H), 1.26 (s, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.8, 128.3, 127.5, 127.4, 124.8, 123.2,

97.9, 74.2, 73.1, 60.8, 38.2, 35.7, 35.0, 33.9, 32.2, 27.0, 26.6, 22.8, 20.8; HRMS (APCI+) calcd for $C_{21}H_{29}O_3^+$ [M + H^+] 329.2111, found 329.2112.

Protected ketal 95. To a solution of **94** (23 mg, 0.070 mmol, 1.0 equiv) in MeOH (0.5 mL) and $HC(OMe)_3$ (0.2 mL) was added *p*-TsOH (3 mg, 0.014 mmol, 0.2 equiv). The mixture was stirred at 50 °C for 4 h. After cooling down to 23 °C, half saturated aqueous $NaHCO_3$ solution (3 mL) was added. The aqueous layer was extracted with Et_2O (2 mL × 3). The combined organic layers were washed by brine, dried (MgSO4), filtered, concentrated, and purified by flash column chromatography (silica gel, hexanes/EtOAc, 25/1) and then preparative thin layer chromatography (silica gel, hexanes/EtOAc, 4/1) to afford **95** (14 mg, 58%) as a colorless oil. **95**: R_f = 0.56 (silica gel, hexanes/EtOAc, 3/1); IR (film) ν_{max} 2947, 2866, 1454, 1094, 1064, 900, 698, 656 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37–7.30 (m, 4 H), 7.30–7.25 (m, 1 H), 5.55 (d, *J* = 10.0 Hz, 1 H), 5.48 (d, *J* = 9.3 Hz, 1 H), 4.49 (q, *J* = 12.2 Hz, 2 H), 3.67–3.61 (m, 2 H), 3.49 (dd, *J* = 9.2, 3.9 Hz, 1 H), 3.31 (dd, *J* = 9.1, 6.2 Hz, 1 H), 3.19 (s, 3 H), 2.23 (dd, *J* = 18.6, 1.4 Hz, 1 H), 2.12–1.98 (m, 3 H), 1.88–1.82 (m, 2 H), 1.81–1.75 (m, 1 H), 1.75–1.66 (m, 4 H), 1.63 (dd, *J* = 13.6, 4.7 Hz, 1 H), 1.41 (qd, *J* = 13.0, 4.4 Hz, 1 H), 1.27 (d, *J* = 11.4 Hz, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.8, 128.3, 127.5, 127.4, 125.1, 123.0, 100.2, 74.3, 73.0, 60.9, 47.0, 38.6, 34.8, 34.1, 32.1, 28.9, 26.6, 26.3, 23.0, 20.7; HRMS (ESI+) calcd for $C_{22}H_{31}O_3^+$ [M + H^+] 343.2268, found 343.2261.

Enone 102. To a solution of **88** (5.21 g, 15.2 mmol, 1.0 equiv) in THF (15 mL) was added allyltributyltin (9.38 mL, 30.4 mmol, 2.0 equiv). The resulting solution was degassed by bubbling Ar through for 5 min. $Pd(PPh_3)_4$ (1.76 g, 1.52 mmol, 0.1 equiv) was added and the reaction was stirred at 70 °C for 12 h. Upon completion, the reaction was directly concentrated and purified by

flash column chromatography (silica gel, hexanes/EtOAc, 30/1 to 20/1) to afford **102** (2.45 g, 63%) as a colorless oil. (Note: The product is typically contaminated by pigment, but it does not affect the next step). **102**: R_f = 0.48 (silica gel, hexanes/EtOAc, 3/1); IR (film) ν_{max} 2928, 2861, 1675, 1454, 1364, 1100, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.40–7.27 (m, 5 H), 6.66 (s, 1 H), 5.87–5.75 (m, 1 H), 5.05 (d, *J* = 6.3 Hz, 1 H), 5.05–5.01 (m, 1 H), 4.55 (s, 2 H), 3.46 (d, *J* = 6.7 Hz, 2 H), 3.01–2.90 (m, 2 H), 2.79–2.71 (m, 1 H), 2.54 (dt, *J* = 16.7, 4.6 Hz, 1 H), 2.42–2.32 (m, 1 H), 2.11 (dq, *J* = 13.5, 4.5 Hz, 1 H), 1.82–1.71 (m, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 198.7, 146.6, 138.3, 138.0, 135.6, 128.4, 127.7, 127.6, 116.4, 73.2, 72.7, 37.2, 37.0, 33.4, 26.1; HRMS (ESI+) calcd for $C_{17}H_{21}O_2^+$ [M + H^+] 257.1536, found 257.1541.

Silyl enol ether 103. To a flame-dried flask was added CuBr·SMe_2 (1.03 g, 5.02 mmol, 1.0 equiv) and LiCl (432 mg, 10.0 mmol, 2.0 equiv), followed by THF (20 mL). The mixture was stirred at 23 °C for 5 min before the suspension turned homogeneous. The flask was then cooled down to -78 °C and allylmagnesium bromide (1.0 M in Et_2O, 10.0 mL, 10.0 mmol, 2.0 equiv) was added dropwise over 10 min. The resultant dark brownish suspension was then stirred at -78 °C for 30 min. A pre-mixed solution of **102** (1.29 g, 5.02 mmol, 1.0 equiv) and TMSCl (0.95 mL, 7.53 mmol, 1.5 equiv) in THF (3 mL) was then added at this temperature. The reaction was kept at -78 °C for 2 h, then allowed to slowly warm up to 23 °C over 8 h before a mixed solution of half-saturated aqueous NH_4Cl solution (20 mL) and 3 N NaOH (10 mL) was added to quench the reaction. The biphasic mixture was vigorously stirred for 30 min before the aqueous layer was extracted with Et_2O (10 mL × 2). The combined organic layers were dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography (silica gel, hexanes/EtOAc, 60/1) to afford TMS silyl enol ether **103** (1.39 g, 75%) as a colorless oil. **103**: R_f = 0.70 (silica gel,

hexanes/EtOAc, 3/1); IR (film) ν_{max} 2926, 2855, 1355, 1252, 1206, 1098, 843 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37–7.30 (m, 4 H), 7.30–7.25 (m, 1 H), 5.79–5.61 (m, 2 H), 5.06–4.93 (m, 4 H), 4.49 (q, *J* = 12.1 Hz, 2 H), 3.39–3.30 (m, 2 H), 3.13 (dd, *J* = 14.6, 5.7 Hz, 1 H), 2.50 (dd, *J* = 14.5, 7.8 Hz, 1 H), 2.33 (dd, *J* = 12.0, 5.7 Hz, 1 H), 2.09–1.90 (m, 5 H), 1.88–1.77 (m, 1 H), 1.71–1.61 (m, 1 H), 0.14 (s, 9 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.3, 138.8, 137.6, 137.1, 128.3, 127.6, 127.5, 116.0, 115.2, 114.9, 73.0, 72.1, 37.6, 37.2, 34.5, 32.8, 26.7, 20.7, 0.7.

Compound 106. To a solution of **103** (1.39 g, 3.75 mmol, 1.0 equiv) in THF (15 mL) was added MeLi (1.6 M in Et_2O, 2.81 mL, 4.50 mmol, 1.2 equiv) dropwise over 15 min at 0 °C. The resulting solution was stirred at this temperature for 1 h before HMPA (2.5 mL) was added. The reaction was then cooled down to -78 °C. A solution of the substituted allyl iodide **105** (1.47 g, 4.88 mmol, 1.3 equiv) was then added. The mixture was kept at -78 °C for 3 h, then allowed to slowly warm up to 23 °C over 8 h before half-saturated aqueous NH_4Cl solution (20 mL) was added to quench the reaction. The aqueous layer was extracted with Et_2O (10 mL × 2). The combined organic layers were washed by brine, dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography (silica gel, hexanes/EtOAc, 80/1 to 70/1 to 65/1) to afford **106** (708 mg, 40%) as a colorless oil. **106**: R_f = 0.66 (silica gel, hexanes/EtOAc, 3/1); IR (film) ν_{max} 2923, 1706, 1427, 1248, 1112, 821, 732, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.53–7.44 (m, 2 H), 7.40–7.23 (m, 8 H), 5.85–5.66 (m, 4 H), 5.02 (dd, *J* = 26.4, 11.9 Hz, 3 H), 4.93 (d, *J* = 10.1 Hz, 1 H), 4.45 (d, *J* = 4.7 Hz, 2 H), 3.62 (dd, *J* = 9.1, 3.0 Hz, 1 H), 3.29 (dd, *J* = 8.9, 7.1 Hz, 1 H), 2.94–2.87 (m, 1 H), 2.63 (dd, *J* = 13.7, 4.8 Hz, 1 H), 2.44 (td, *J* = 14.2, 6.0 Hz, 1 H), 2.39–2.25 (m, 3 H), 2.21–2.15 (m, 2 H), 2.15–2.03 (m, 2 H), 1.98 (dd, *J* = 14.2, 9.7 Hz, 1 H), 1.93–1.86 (m, 1 H), 1.62–1.51 (m, 1 H), 0.29 (d, *J* = 4.7 Hz, 6 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 212.1, 142.6,

138.6, 138.4, 135.4, 133.8, 132.6, 128.9, 128.3, 127.7, 127.5, 117.7, 115.1, 72.9, 72.6, 56.2, 42.8, 41.3, 38.8, 38.7, 37.4, 33.4, 29.1, -2.6, -2.7; HRMS (Mixed+) calcd for $C_{31}H_{40}O_2Si^+$ [M^+] 472.2762, found 472.2784.

Compound 115. To a solution of **106** (820 mg, 1.74 mmol, 1.0 equiv) in CH_2Cl_2 (17 mL) was added Grubbs-I catalyst (214 mg, 0.260 mmol, 0.15 equiv) at 23 °C. The reaction was stirred at this temperature for 16 h. Upon completion, the mixture was directly concentrated and purified by flash column chromatography (silica gel, hexanes/EtOAc, 30/1 to 25/1) to afford **115** (754 mg, 98%) as a colorless oil. **115**: R_f = 0.58 (silica gel, hexanes/EtOAc, 3/1); IR (film) ν_{max} 2954, 1708, 1454, 1427, 1248, 1112, 823, 733, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.50–7.45 (m, 2 H), 7.38–7.27 (m, 8 H), 5.84–5.77 (m, 2 H), 5.67–5.56 (m, 2 H), 4.50 (q, *J* = 12.0 Hz, 2 H), 3.54 (dd, *J* = 9.1, 3.4 Hz, 1 H), 3.35 (dd, *J* = 9.0, 6.3 Hz, 1 H), 2.59 (td, *J* = 14.3, 6.2 Hz, 1 H), 2.55–2.45 (m, 2 H), 2.33 (ddd, *J* = 13.8, 3.9, 2.4 Hz, 1 H), 2.25–2.12 (m, 4 H), 2.04 (tdt, *J* = 10.0, 6.6, 3.5 Hz, 1 H), 1.96–1.86 (m, 1 H), 1.83 (td, *J* = 11.1, 4.7 Hz, 1 H), 1.65 (ddd, *J* = 18.6, 14.9, 5.2 Hz, 1 H), 0.28 (d, *J* = 3.3 Hz, 6 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 213.8, 142.6, 138.7, 138.3, 133.8, 132.4, 128.9, 128.4, 127.7, 127.6, 127.5, 125.0, 124.8, 73.3, 72.1, 49.9, 43.4, 38.6, 37.2, 36.0, 30.5, 29.6, 27.0, -2.6, -2.6; HRMS (APCI+) calcd for $C_{29}H_{37}O_2Si^+$ [M + H^+] 445.2557, found 445.2552.

Alcohol 117. To a flask loaded with **115** (928 mg, 2.09 mmol, 1.0 equiv) was added Pd/C (5%, 371 mg, 40% mass equiv). The flask was back-filled with H_2 twice. EtOAc (10 mL) was added and H_2 was bubbled through solution for 3 min. The reaction was then stirred at 23 °C under 1 atm H_2 atmosphere for 12 h. Upon completion, the reaction was filtered through Celite and the filtrate was concentrated to give the crude hydrogenated product **116**. The so-obtained product was

dissolved in CH_2Cl_2 (12 mL). $BF_3 \cdot 2AcOH$ (0.58 mL, 4.18 mmol, 2.0 equiv) was added at 23 °C and the reaction was stirred at this temperature for 8 h before half-saturated aqueous $NaHCO_3$ solution (15 mL) was carefully added to quench the reaction. The aqueous layer was extracted with CH_2Cl_2 (10 mL × 2). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to yield the crude fluorosilane. Next, the crude fluorosilane was dissolved in DMF (5 mL). KF (364 mg, 6.27 mmol, 3.0 equiv) and *m*CPBA (<72%, 998 mg, 4.18 mmol, 2.0 equiv) was added sequentially at 0 °C. The mixture was then stirred at 23 °C for 14 h before a mixed aqueous solution of $NaHCO_3$ and $Na_2S_2O_3$ was added to quench the reaction. The aqueous layer was extracted with Et_2O (10 mL × 3). The combined organic layers were washed sequentially by H_2O and brine, dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography (silica gel, hexanes/acetone, 30/1 to 10/1 to 5/1) to afford **117** (390 mg, 55% over 3 steps) as a colorless oil. **117**: R_f = 0.07 (silica gel, hexanes/EtOAc, 3/1); IR (film) ν_{max} 3441 (br), 2928, 2863, 1702, 1454, 1098, 1066, 737, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.38–7.27 (m, 5 H), 4.47 (dd, *J* = 27.3, 12.0 Hz, 2 H), 3.66–3.56 (m, 2 H), 3.49 (dt, *J* = 8.2, 4.1 Hz, 1 H), 3.32 (dd, *J* = 9.0, 6.2 Hz, 1 H), 2.63 (td, *J* = 14.1, 6.7 Hz, 1 H), 2.27 (ddd, *J* = 14.1, 4.8, 2.3 Hz, 1 H), 2.21–2.14 (m, 1 H), 2.09 (ddd, *J* = 14.7, 11.3, 5.1 Hz, 1 H), 1.96–1.85 (m, 2 H), 1.84–1.75 (m, 1 H), 1.71 (d, *J* = 12.1 Hz, 1 H), 1.66–1.58 (m, 2 H), 1.58–1.52 (m, 1 H), 1.50 (dd, *J* = 11.7, 3.0 Hz, 1 H), 1.44 (td, *J* = 12.9, 6.1 Hz, 1 H), 1.37 (dd, *J* = 13.0, 4.0 Hz, 1 H), 1.35–1.30 (m, 1 H), 1.30–1.23 (m, 1 H), 1.16 (dt, *J* = 13.0, 4.2 Hz, 1 H), 1.12–1.01 (m, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 216.0, 138.4, 128.3, 127.5, 127.5, 73.2, 72.4, 63.1, 50.8, 48.2, 37.7, 35.8, 30.8, 28.5, 26.4, 25.9, 24.2, 24.0, 20.5; HRMS (APCI+) calcd for $C_{21}H_{31}O_3^+$ [M + H^+] 331.2268, found 331.2279.

Azide 118. To a solution of **117** (222 mg, 0.673 mmol, 1.0 equiv) in THF (3 mL) was added PPh_3 (212 mg, 0.808 mmol, 1.2 equiv), DPPA (0.17 mL, 0.808 mmol, 1.2 equiv), and DEAD (40% in PhMe, 0.16 mL, 0.808 mmol, 1.2 equiv) sequentially at 23 °C. The mixture was stirred at this temperature for 12 h. Upon completion, the reaction was directly concentrated and purified by flash column chromatography (silica gel, hexanes/EtOAc, 20/1 to 15/1) to afford **118** (189 mg, 79%) as a colorless oil. **118**: R_f = 0.46 (silica gel, hexanes/EtOAc, 3/1); IR (film) ν_{max} 2930, 2863, 2096, 1704, 1454, 1098, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.39–7.26 (m, 5 H), 4.54–4.42 (m, 2 H), 3.50 (dd, *J* = 9.1, 3.5 Hz, 1 H), 3.33 (dd, *J* = 9.0, 6.2 Hz, 1 H), 3.31–3.21 (m, 2 H), 2.60 (td, *J* = 14.1, 6.7 Hz, 1 H), 2.29 (ddd, *J* = 14.2, 4.7, 2.3 Hz, 1 H), 2.23–2.14 (m, 1 H), 2.11–2.01 (m, 1 H), 1.89 (dt, *J* = 12.9, 6.9 Hz, 2 H), 1.77 (dd, *J* = 13.1, 3.6 Hz, 1 H), 1.74–1.69 (m, 1 H), 1.66–1.61 (m, 1 H), 1.58 (t, *J* = 8.2 Hz, 2 H), 1.55–1.48 (m, 1 H), 1.48–1.41 (m, 1 H), 1.39–1.30 (m, 1 H), 1.27 (t, *J* = 9.7 Hz, 2 H), 1.22–1.14 (m, 1 H), 1.14–1.04 (m, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 215.5, 138.4, 128.4, 127.6, 127.5, 73.2, 72.3, 51.8, 50.8, 48.1, 37.7, 35.8, 30.7, 28.5, 25.8, 24.9, 24.1, 22.8, 20.4; HRMS (ESI+) calcd for $C_{21}H_{30}N_3O_2^+$ [M + H^+] 356.2333, found 356.2340.

Compound 120. From **118**: to a solution of **118** (17 mg, 0.048 mmol, 1.0 equiv) in PhMe (1 mL) was added PPh_3 (15 mg, 0.057 mmol, 1.2 equiv) at 23 °C. The mixture was then stirred at 110 °C for 30 min. After cooling to 23 °C, PhMe was removed by evaporation and MeOH (1 mL) was added, followed by AcOH (0.02 mL) and $NaBH_3CN$ (6 mg, 0.095 mmol, 2.0 equiv). After stirring at 23 °C for 2 h, half-saturated aqueous $NaHCO_3$ solution (3 mL) and Et_2O (2 mL) were added. The aqueous layer was extracted with Et_2O (1 mL × 2). The combined organic layers were washed by brine, dried ($MgSO_4$), filtered, concentrated, and purified by preparative thin layer

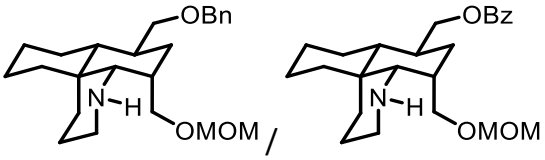
chromatography (silica gel, hexanes/EtOAc/CH_2Cl_2/acetone/Et_3N, 1/1/1/1/0.01) to afford **120** (10 mg, 72%) as a colorless oil. From **127**: to a solution of **127** (8 mg, 0.015 mmol, 1.0 equiv) in CH_2Cl_2 (0.5 mL) was added TFA (0.2 mL). The mixture was stirred at 23 °C for 12 h before half-saturated aqueous $NaHCO_3$ solution (4 mL) was carefully added to quench the reaction. The aqueous layer was extracted with CH_2Cl_2 (1 mL × 2). The combined organic layers were washed dried ($MgSO_4$), filtered, and concentrated to afford crude imine. To a solution of the crude imine in MeOH (1 mL) was added AcOH (0.02 mL) and $NaBH_3CN$ (2 mg, 0.030 mmol, 2.0 equiv). After stirring at 23 °C for 2 h, half-saturated aqueous $NaHCO_3$ solution (3 mL) and Et_2O (2 mL) were added. The aqueous layer was extracted with Et_2O (1 mL × 2). The combined organic layers were washed by brine, dried ($MgSO_4$), filtered, and concentrated to afford crude **120** (4 mg, 84%). **120**: R_f = 0.18, tailing (silica gel, CH_2Cl_2/acetone, 1/1); IR (film) ν_{max} 2926, 2856, 1453, 1403, 1306, 1101, 735, 697 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37–7.30 (m, 4 H), 7.29–7.27 (m, 1 H), 4.50 (d, *J* = 12.1 Hz, 1 H), 4.43 (d, *J* = 12.1 Hz, 1 H), 3.42 (dd, *J* = 9.0, 3.7 Hz, 1 H), 3.24 (dd, *J* = 8.9, 6.3 Hz, 1 H), 2.89 (td, *J* = 13.0, 3.6 Hz, 1 H), 2.75 (dd, *J* = 12.6, 3.6 Hz, 1 H), 2.49 (d, *J* = 13.0 Hz, 1 H), 2.35 (dd, *J* = 12.4, 3.9 Hz, 1 H), 2.18 (ddd, *J* = 26.1, 13.2, 4.1 Hz, 1 H), 2.00–1.91 (m, 1 H), 1.84 (s, 2 H), 1.70 (dd, *J* = 24.2, 12.0 Hz, 2 H), 1.65–1.60 (m, 1 H), 1.56 (d, *J* = 15.5 Hz, 2 H), 1.54–1.45 (m, 2 H), 1.44–1.35 (m, 2 H), 1.29 (dd, *J* = 13.1, 3.9 Hz, 1 H), 1.26–1.19 (m, 1 H), 1.13 (dd, *J* = 12.4, 3.4 Hz, 1 H), 1.10–1.03 (m, 1 H), 0.86 (td, *J* = 13.3, 3.7 Hz, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.8, 128.3, 127.5, 127.4, 73.7, 73.1, 61.0, 48.0, 40.0, 36.0, 34.2, 30.0, 26.7, 25.5, 22.9, 21.4, 20.7, 19.7; HRMS (ESI+) calcd for $C_{21}H_{32}NO^+$ [M + H^+] 314.2478, found 314.2455.

Compound 122. To a solution of **118** (120 mg, 0.337 mmol, 1.0 equiv) and TESCl (0.07 mL, 0.404 mmol, 1.2 equiv) in THF (2 mL) was added LiHMDS (1.0 M in THF, 0.40 mL, 0.404

mmol, 1.2 equiv) dropwise over 2 min at 23 °C. The reaction was stirred at this temperature for 30 min before half-saturated aqueous $NaHCO_3$ solution (3 mL) was added to quench the reaction. The aqueous layer was extracted with Et_2O (1 mL × 2). The combined organic layers were dried ($MgSO_4$), filtered, concentrated, and purified by column chromatography (silica gel, hexanes/EtOAc, 50/1) to give the TES silyl enol ether. Next, the TES silyl enol ether was dissolved in THF (1 mL), followed by the addition of freshly distilled HCHO in THF (1 mL). The solution was then cooled to -20 °C. TBAF (1.0 M in THF, 0.51 mL, 0.505 mmol, 1.5 equiv) was added dropwise over 1 min. The reaction was kept at this temperature for 1 h before half-saturated NH_4Cl solution (3 mL) was added to quench the reaction. The aqueous layer was extracted with Et_2O (1 mL × 2). The combined organic layers were dried ($MgSO_4$), filtered, concentrated, and purified by column chromatography (silica gel, hexanes/acetone, 30/1) to yield hydrolysis product **118** (54 mg, 45%), then (hexanes/acetone, 8/1) to yield aldol adduct **121** (45 mg, 35%, 1:1 inseparable mixture of diastereomers) as a colorless oil. Next, the so-obtained aldol adduct **121** (45 mg, 0.118 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (1.5 mL). DIPEA (0.41 mL, 2.36 mmol, 20.0 equiv) and MOMCl (0.09 mL, 1.18 mmol, 10.0 equiv) were added sequentially at 23 °C. The reaction was stirred at this temperature for 16 h before half-saturared aqueous $NaHCO_3$ (4 mL) was added to quench the reaction. The aqueous layer was extracted with CH_2Cl_2 (1 mL × 2). The combined organic layers were dried ($MgSO_4$), filtered, concentrated, and purified by preparative thin layer chromatography (silica gel, hexanes/EtOAc, 3/1) to afford **122** (19 mg, 37%) as a colorless gum and **123** (19 mg, 37%) as a colorless gum. **122**: R_f = 0.38 (silica gel, hexanes/EtOAc, 3/1); IR (film) ν_{max} 2929, 2861, 2095, 1702, 1454, 1150, 1110, 1052, 738, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.41–7.30 (m, 5 H), 4.61 (dd, *J* = 10.3, 6.4 Hz, 2 H), 4.55 (dd, *J* = 23.6, 12.0 Hz, 2 H), 3.89 (dd, *J* = 9.4, 5.0 Hz, 1 H), 3.63 (dd, *J* = 9.4, 3.6 Hz, 1 H), 3.58–3.49 (m, 2 H), 3.36 (s, 3 H),

3.32–3.19 (m, 2 H), 2.68–2.61 (m, 1 H), 2.23–2.10 (m, 2 H), 2.02 (dd, *J* = 14.2, 5.6 Hz, 1 H), 1.95–1.83 (m, 2 H), 1.73 (d, *J* = 10.1 Hz, 2 H), 1.68–1.57 (m, 3 H), 1.56–1.50 (m, 1 H), 1.48–1.41 (m, 1 H), 1.40–1.27 (m, 2 H), 1.23–1.13 (m, 1 H), 1.06 (td, *J* = 13.8, 3.0 Hz, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 215.3, 138.5, 128.4, 127.6, 127.5, 96.6, 73.2, 73.0, 67.0, 55.2, 52.0, 48.7, 45.0, 40.3, 34.8, 30.1, 26.3, 25.8, 25.5, 23.8, 22.9, 20.9; HRMS (ESI+) calcd for $C_{24}H_{36}N_3O_4^+$ [M + H^+] 430.2700, found 430.2709.

Compound 123. 123: R_f = 0.36 (silica gel, hexanes/EtOAc, 3/1); IR (film) ν_{max} 2930, 2855, 1096, 1702, 1454, 1111, 1051, 917, 699 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39–7.30 (m, 5 H), 4.65 (dd, *J* = 19.3, 6.4 Hz, 2 H), 4.50 (dd, *J* = 31.6, 11.9 Hz, 2 H), 3.86 (dd, *J* = 9.8, 5.5 Hz, 1 H), 3.52 (dd, *J* = 8.8, 3.5 Hz, 1 H), 3.47 (dd, *J* = 9.8, 6.3 Hz, 1 H), 3.39 (s, 3 H), 3.38–3.35 (m, 1 H), 3.32–3.26 (m, 2 H), 2.94 (dq, *J* = 12.0, 5.9 Hz, 1 H), 2.37 (ddd, *J* = 13.0, 5.6, 4.0 Hz, 1 H), 2.21–2.09 (m, 1 H), 1.98–1.89 (m, 1 H), 1.88 (d, *J* = 10.6 Hz, 1 H), 1.85–1.78 (m, 1 H), 1.74 (d, *J* = 10.9 Hz, 1 H), 1.68–1.58 (m, 2 H), 1.57–1.50 (m, 1 H), 1.50–1.46 (m, 1 H), 1.44 (d, *J* = 13.0 Hz, 1 H), 1.38–1.30 (m, 3 H), 1.23–1.09 (m, 2 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 214.5, 138.4, 128.3, 127.6, 127.5, 96.8, 73.2, 72.0, 67.2, 55.2, 51.8, 48.9, 45.7, 36.0, 35.4, 28.4, 25.8, 25.1, 24.1, 22.7, 20.4; HRMS (ESI+) calcd for $C_{24}H_{35}N_3NaO_4^+$ [M + Na^+] 452.2520, found 452.2518.



Compound 124/124-Bz. To a solution of **122** (13 mg, 0.030 mmol, 1.0 equiv) in PhMe (1 mL) was added PPh_3 (10 mg, 0.036 mmol, 1.2 equiv) at 23 °C. The mixture was then stirred at 110 °C for 30 min. After cooling to 23 °C, PhMe was removed by evaporation and MeOH (0.5 mL)

was added, followed by AcOH (0.02 mL) and $NaBH_3CN$ (4 mg, 0.060 mmol, 2.0 equiv). After stirring at 23 °C for 2 h, half-saturated aqueous $NaHCO_3$ solution (3 mL) and Et_2O (2 mL) were added. The aqueous layer was extracted with Et_2O (1 mL × 2). The combined organic layers were washed by brine, dried ($MgSO_4$), filtered, concentrated, and purified by preparative thin layer chromatography (silica gel, hexanes/EtOAc/CH_2Cl_2/acetone/Et_3N, 1/1/1/1/0.01) to afford **124** (3 mg, 21%) as a colorless oil along with inseparable impurity. The ^{1}H NMR of **124** was never clean due to impurities and remaining triphenylphosphine oxide. However, a clean set of NMR data can be recorded on its *O*-Bz derivative **124-Bz**. **124-Bz**: R_f = 0.16 (silica gel, hexanes/acetone, 1/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (d, *J* = 7.3 Hz, 2 H), 7.56 (t, *J* = 7.4 Hz, 1 H), 7.44 (t, *J* = 7.7 Hz, 2 H), 4.62 (q, *J* = 6.5 Hz, 2 H), 4.34 (dd, *J* = 10.8, 3.5 Hz, 1 H), 4.16 (dd, *J* = 10.8, 7.2 Hz, 1 H), 3.71 (dd, *J* = 9.2, 8.1 Hz, 1 H), 3.54 (dd, *J* = 9.3, 7.6 Hz, 1 H), 3.34 (s, 3 H), 2.87–2.74 (m, 2 H), 2.64 (d, *J* = 6.6 Hz, 1 H), 2.31–2.19 (m, 2 H), 2.02–1.92 (m, 1 H), 1.92–1.81 (m, 2 H), 1.75 (d, *J* = 12.5 Hz, 1 H), 1.58 (d, *J* = 5.8 Hz, 2 H), 1.53–1.39 (m, 4 H), 1.36–1.17 (m, 4 H), 0.99 (td, *J* = 13.1, 4.3 Hz, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.9, 132.8, 130.5, 129.5, 128.4, 96.7, 69.5, 67.8, 60.5, 55.3, 42.8, 42.1, 37.4, 36.5, 35.8, 34.0, 26.7, 26.6, 25.3, 21.5, 20.9, 20.2.

Compound 126. To a solution of **122** (6 mg, 0.015 mmol, 1.0 equiv) in MeOH (0.2 mL) was added NaOMe (0.5 M in MeOH, 0.6 mL, 0.30 mmol, 20.0 equiv). The reaction was stirred at this temperature for 10 h before solvent was removed by evaporation. Et_2O (1 mL) and half-saturated aqueous NH_4Cl solution were then added. The aqueous layer was extracted with Et_2O (1 mL × 2). The combined organic layers were washed by brine, dried ($MgSO_4$), filtered, and concentrated to afford crude **126** (6 mg, 99%) as a colorless gum. **126**: R_f = 0.38 (silica gel, hexanes/EtOAc, 3/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36–7.27 (m, 5 H), 4.45 (dd, *J* = 32.4, 12.0

Hz, 2 H), 3.78–3.68 (m, 2 H), 3.46 (dd, *J* = 8.8, 2.7 Hz, 1 H), 3.35 (s, 3 H), 3.27–3.21 (m, 1 H), 3.10 (dtd, *J* = 20.3, 13.4, 6.5 Hz, 2 H), 2.95 (dd, *J* = 12.5, 6.1 Hz, 1 H), 2.31–2.22 (m, 1 H), 2.08 (s, 1 H), 1.91–1.79 (m, 3 H), 1.69 (d, *J* = 13.2 Hz, 1 H), 1.66–1.58 (m, 1 H), 1.56 (d, *J* = 12.1 Hz, 1 H), 1.51–1.44 (m, 1 H), 1.39–1.26 (m, 5 H), 1.00–0.91 (m, 1 H), 0.90–0.85 (m, 1 H).

Compound 127. To a solution of **117** (164 mg, 0.496 mmol, 1.0 equiv) in THF (5 mL) was added PPh_3 (156 mg, 0.595 mmol, 1.2 equiv), Boc_2NH (129 mg, 0.595 mmol, 1.2 equiv), and DEAD (40% in PhMe, 0.11 mL, 0.595 mmol, 1.2 equiv) sequentially at 23 °C. The mixture was stirred at this temperature for 12 h. Upon completion, the reaction was directly concentrated and purified by flash column chromatography (silica gel, hexanes/EtOAc, 20/1 to 15/1) to afford **127** (227 mg, 86%) as a colorless solid. **127**: R_f = 0.48 (silica gel, hexanes/EtOAc, 3/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37–7.27 (m, 5 H), 4.47 (dd, *J* = 27.6, 12.1 Hz, 2 H), 3.51 (t, *J* = 7.2 Hz, 2 H), 3.48 (dd, *J* = 9.2, 3.5 Hz, 1 H), 3.32 (dd, *J* = 9.0, 6.1 Hz, 1 H), 2.57 (td, *J* = 14.1, 6.6 Hz, 1 H), 2.30–2.23 (m, 1 H), 2.19–2.11 (m, 1 H), 2.03 (d, *J* = 5.9 Hz, 1 H), 1.89 (d, *J* = 12.4 Hz, 1 H), 1.79 (td, *J* = 13.5, 4.5 Hz, 1 H), 1.73–1.58 (m, 4 H), 1.51–1.46 (m, 2 H), 1.48 (s, 18 H), 1.29 (dt, *J* = 28.4, 17.4 Hz, 4 H), 1.20–1.12 (m, 1 H), 1.11–1.02 (m, 1 H).

Compound 130. To a solution of **118** (39 mg, 0.110 mmol, 1.0 equiv) in MeOH (0.5 mL) and THF (0.5 mL) was added $NaBH_4$ (9 mg, 0.220 mmol, 2.0 equiv) at 23 °C. The mixture was stirred at this temperature for 1 h before 0.5 N HCl (3 mL) was added to quench the reaction. The aqueous layer was extracted with Et_2O (1 mL × 2). The combined organic layers were washed by half-saturated aqueous $NaHCO_3$ solution, dried ($MgSO_4$), filtered, and concentrated to give the crude alcohol **129**. Next, the crude alcohol **129** was dissolved in CH_2Cl_2 (1 mL). Et_3N (0.03 mL,

0.220 mmol, 2.0 equiv), DMAP (13 mg, 0.110 mmol, 1.0 equiv), and PhOCSCl (23 mg, 0.132 mmol, 1.2 equiv) were added sequentially at 23 °C. The reaction was then stirred at this temperature for 12 h. Upon completion, half-saturated aqueous $NaHCO_3$ solution was added to quench the reaction. The aqueous layer was extracted with CH_2Cl_2 (1 mL × 2). The combined organic layers were dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography (silica gel, hexanes/EtOAc, 40/1 to 25/1) to afford **130** (33 mg, 61% over 2 steps) as a colorless oil. **130**: R_f = 0.54 (silica gel, hexanes/EtOAc, 3/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51–7.19 (m, 8 H), 7.08 (d, *J* = 7.7 Hz, 2 H), 5.10 (dd, *J* = 11.9, 4.2 Hz, 1 H), 4.46 (dd, *J* = 27.9, 12.1 Hz, 2 H), 3.40 (dd, *J* = 9.0, 3.4 Hz, 1 H), 3.26 (dd, *J* = 9.0, 6.0 Hz, 1 H), 3.24–3.15 (m, 2 H), 2.17–2.07 (m, 1 H), 1.97 (t, *J* = 12.8 Hz, 2 H), 1.85–1.72 (m, 2 H), 1.71–1.50 (m, 6 H), 1.50–1.37 (m, 2 H), 1.35–1.16 (m, 4 H), 1.11–1.00 (m, 1 H).

Compound 134. To a solution of **117** (189 mg, 0.572 mmol, 1.0 equiv) in THF (6 mL) was added PPh_3 (180 mg, 0.686 mmol, 1.2 equiv), BocNHTs (186 mg, 0.686 mmol, 1.2 equiv), and DEAD (40% in PhMe, 0.13 mL, 0.686 mmol, 1.2 equiv) sequentially at 23 °C. The mixture was stirred at this temperature for 12 h. Upon completion, the reaction was directly concentrated and purified by flash column chromatography (silica gel, hexanes/EtOAc, 20/1 to 15/1) to afford **131** (298 mg, 89%) as a colorless gum. Next, to a solution of **131** (121 mg, 0.208 mmol, 1.0 equiv) in THF (3 mL) was added Eschenmoser's salt (77 mg, 0.416 mmol, 2.0 equiv) as solid. LiHMDS (1.0 M in THF, 0.42 mL, 0.416 mmol, 2.0 equiv) was then added dropwise over 2 min at 23 °C. The reaction was stirred at this temperature for 30 min. Further LiHMDS may be needed to push the reaction to full conversion. Upon completion, the reaction was quenched by the addition of half-saturated aqueous NH_4Cl solution. The aqueous layer was extracted with Et_2O (3 mL × 2).

The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to give the crude tertiary amine **132** as a light yellowish oil. The crude amine **132** was immediately dissolved in CH_2Cl_2 (4 mL). $NaHCO_3$ (140 mg, 1.66 mmol, 8.0 equiv) and *m*CPBA (<72%, 99 mg, 0.416 mmol, 2.0 equiv) were added sequentially at 0 °C. The reaction was stirred at 23 °C for 2 h before a mixed aqueous solution of $NaHCO_3$ and $Na_2S_2O_3$ was added to quench the reaction. The aqueous layer was extracted with CH_2Cl_2 (3 mL × 2). The combined organic layers were dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography (silica gel, hexanes/EtOAc, 40/1 to 25/1) to yield enone **133** (57 mg, 46% over 2 steps) as a colorless oil. Next, enone **133** (57 mg, 0.096 mmol, 1.0 equiv) was dissolved in MeOH (0.5 mL). $CeCl_3 \cdot 7H_2O$ (43 mg, 0.115 mmol, 1.2 equiv) was added and the resulting solution was stirred at 23 °C for 5 min before $NaBH_4$ (5 mg, 0.115 mmol, 1.2 equiv) was added as solid at this temperature. The reaction was further stirred at 23 °C for 2 h. 0.5 N HCl was added to quench the reaction. The aqueous layer was extracted with Et_2O (3 mL × 2). The combined organic layers were dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography (silica gel, hexanes/acetone, 30/1) to afford **134** (32 mg, 56%) as a colorless gum. **134**: R_f = 0.32 (silica gel, hexanes/EtOAc, 3/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.3 Hz, 2 H), 7.37–7.24 (m, 7 H), 4.97 (d, *J* = 1.3 Hz, 1 H), 4.87 (d, *J* = 1.2 Hz, 1 H), 4.47 (dd, *J* = 27.7, 12.1 Hz, 2 H), 3.82 (s, 1 H), 3.76–3.66 (m, 2 H), 3.38 (dd, *J* = 9.1, 3.2 Hz, 1 H), 3.30 (dd, *J* = 9.0, 5.9 Hz, 1 H), 2.49 (dd, *J* = 13.6, 4.2 Hz, 1 H), 2.42 (s, 3 H), 2.24 (d, *J* = 13.6 Hz, 1 H), 2.12–2.00 (m, 2 H), 1.74 (d, *J* = 11.4 Hz, 1 H), 1.70–1.51 (m, 5 H), 1.39–1.28 (m, 4H), 1.34 (s, 9 H), 1.24–1.10 (m, 2 H), 1.02 (td, *J* = 13.2, 3.0 Hz, 1 H).

Compound 136. To a solution of **134** (32 mg, 0.054 mmol, 1.0 equiv) in THF (1 mL) was added $ClCO_2Me$ (0.04 mL, 0.535 mmol, 10.0 equiv). NaH (11 mg, 0.268 mmol, 5.0 equiv) was

then added as solid at 23 °C. The reaction was stirred at this temperature for 12 h. Upon completion, half-saturated aqueous NH_4Cl solution was added carefully to quench the reaction. The aqueous layer was extracted with Et_2O (2 mL × 2). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to give the crude carbonate **135** as a yellowish oil. Next, the crude **135** was dissolved in CH_2Cl_2 (1 mL). TFA (0.2 mL) was added at 23 °C. The reaction was then stirred at this temperature for 12 h. Upon completion, half-saturated aqueous $NaHCO_3$ solution was added carefully to quench the reaction. The aqueous layer was extracted with CH_2Cl_2 (2 mL × 2). The combined organic layers were dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography (silica gel, hexanes/acetone, 30/1 to 15/1) to afford **136** (21 mg, 70% over 2 steps) as colorless gum. **136**: R_f = 0.36 (silica gel, hexanes/EtOAc, 3/1); IR (film) ν_{max} 2927, 2857, 1749, 1442, 1328, 1269, 1161, 1096, 736, 663 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.1 Hz, 2 H), 7.38–7.24 (m, 8 H), 4.83 (s, 2 H), 4.71 (s, 1 H), 4.46 (q, *J* = 12.1 Hz, 2 H), 4.22 (t, *J* = 5.7 Hz, 1 H), 3.77 (s, 3 H), 3.36 (dd, *J* = 9.1, 3.1 Hz, 1 H), 3.28 (dd, *J* = 9.1, 5.7 Hz, 1 H), 2.87 (q, *J* = 6.3 Hz, 2 H), 2.48 (dd, *J* = 13.9, 4.3 Hz, 1 H), 2.41 (s, 3 H), 2.20–2.09 (m, 1 H), 1.87 (d, *J* = 13.1 Hz, 1 H), 1.74–1.65 (m, 2 H), 1.55–1.44 (m, 3 H), 1.42 (dd, *J* = 11.7, 3.1 Hz, 1 H), 1.40–1.35 (m, 1 H), 1.35–1.28 (m, 2 H), 1.22–1.17 (m, 1 H), 1.12–0.99 (m, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.5, 143.6, 143.2, 138.5, 137.0, 129.6, 128.3, 127.6, 127.5, 127.1, 106.5, 87.6, 73.2, 72.0, 54.8, 46.5, 44.4, 41.2, 38.0, 37.3, 32.3, 25.8, 23.9, 23.3, 21.5, 21.0; HRMS (Mixed+) calcd for $C_{31}H_{42}NO_6S^+$ [M + H^+] 556.2727, found 556.2719.

Compound 139. To a solution of **131** (52 mg, 0.089 mmol, 1.0 equiv) in THF (1 mL) was added Comins' reagent (52 mg, 0.134 mmol, 1.5 equiv). LiHMDS (1.0 M in THF, 0.18 mL, 0.178 mmol, 2.0 equiv) was then added dropwise over 2 min at 23 °C. The reaction was stirred at this

temperature for 1 h before half-saturated aqueous NH_4Cl solution was added to quench the reaction. The aqueous layer was extracted with Et_2O (2 mL × 2). The combined organic layers were dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography (silica gel, hexanes/EtOAc, 40/1 to 30/1) to afford vinyl triflate **138** (37 mg, 58%) as a colorless gum. Next, the vinyl triflate **138** (37 mg, 0.052 mmol, 1.0 equiv) was dissolved in THF (1 mL), followed by the addition of Bu_3SnH (0.03 mL, 0.104 mmol, 2.0 equiv). The resulting solution was degassed by bubbling Ar through for 10 min. Then LiCl (2 mg, 0.052 mmol, 1.0 equiv) and $Pd(PPh_3)_4$ (12 mg,, 0.01 mmol, 0.2 equiv) were added and the mixture was stirred at 55 °C for 12 h. Upon completion, the reaction was directly concentrated and purified by flash column chromatography to afford **139** (9 mg, 31%) as a colorless oil. **139**: R_f = 0.42 (silica gel, hexanes/EtOAc, 3/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.3 Hz, 2 H), 7.40–7.25 (m, 8 H), 5.60–5.45 (m, 2 H), 4.48 (dd, *J* = 26.5, 12.1 Hz, 2 H), 3.82–3.74 (m, 2 H), 3.45 (dd, *J* = 9.0, 3.9 Hz, 1 H), 3.32 (dd, *J* = 8.9, 6.0 Hz, 1 H), 2.43 (s, 3 H), 2.18 (dt, *J* = 9.0, 4.1 Hz, 1 H), 2.03–1.93 (m, 1 H), 1.92–1.85 (m, 1 H), 1.82–1.73 (m, 2 H), 1.70–1.64 (m, 1 H), 1.62–1.53 (m, 1 H), 1.50–1.43 (m, 2 H), 1.42–1.35 (m, 1 H), 1.34 (s, 9 H), 1.28–1.16 (m, 3 H), 1.05 (td, *J* = 13.2, 3.8 Hz, 1 H), 0.96 (t, *J* = 7.4 Hz, 1 H).

Compound 140. To a solution of **139** (9 mg, 0.016 mmol, 1.0 equiv) in CH_2Cl_2 (1 mL) was added TFA (0.2 mL) at 23 °C. The reaction was then stirred at this temperature for 12 h. Upon completion, half-saturated aqueous $NaHCO_3$ solution was added carefully to quench the reaction. The aqueous layer was extracted with CH_2Cl_2 (2 mL × 2). The combined organic layers were dried ($MgSO_4$), filtered, concentrated, and purified by preparative thin layer chromatography (silica gel, hexanes/EtOAc, 21) to afford **140** (6 mg, 80%) as a colorless gum. **140**: R_f = 0.34 (silica gel, hexanes/EtOAc, 3/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.0 Hz, 2 H), 7.38–7.27 (m, 7 H),

5.54–5.46 (m, 1 H), 5.38 (d, *J* = 9.9 Hz, 1 H), 4.47 (q, *J* = 12.1 Hz, 2 H), 4.30 (s, 1 H), 3.42 (dd, *J* = 8.9, 4.1 Hz, 1 H), 3.29 (dd, *J* = 8.9, 6.1 Hz, 1 H), 2.91 (dd, *J* = 13.4, 6.8 Hz, 2 H), 2.41 (s, 3 H), 2.14 (dt, *J* = 18.1, 4.1 Hz, 1 H), 1.98–1.89 (m, 1 H), 1.84–1.76 (m, 1 H), 1.72 (d, *J* = 10.5 Hz, 1 H), 1.64–1.51 (m, 4 H), 1.48 (dd, *J* = 14.6, 7.3 Hz, 1 H), 1.42 (d, *J* = 11.1 Hz, 2 H), 1.39–1.32 (m, 4 H), 1.15–1.02 (m, 3 H).

Compound 141. To a solution of **117** (276 mg, 0.834 mmol, 1.0 equiv) in CH_2Cl_2 (6 mL) was added imidazole (114 mg, 1.67 mmol, 2.0 equiv) and TBSCl (138 mg, 0.917 mmol, 1.1 equiv) sequentially at 0 ^oC. The reaction was stirred at this temperature for 1 h before half-saturated aqueous $NaHCO_3$ solution was added to quench the reaction. The aqueous layer was extracted with CH_2Cl_2 (1 mL × 2). The combined organic layers were dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography (silica gel, hexanes/EtOAc, 35/1 to 25/1) to afford TBS ether (*aka* **169**, 305 mg, 82%) as a colorless oil. Next, to a solution of TBS ether **169** (126 mg, 0.283 mmol, 1.0 equiv) in THF (2 mL) was added Comins' reagent (134 mg, 0.340 mmol, 1.2 equiv). The solution was cooled down to 0 ^oC and LiHMDS (1.0 M in THF, 0.34 mL, 0.340 mmol, 1.2 equiv) dropwise over 2 min. The reaction was stirred at 23 ^oC for 1h (More LiHMDS may be needed to push to full conversion) before half-saturated aqueous NH_4Cl solution was added to quench the reaction. The aqueous layer was extracted with Et_2O (2 mL × 2). The combined organic layers were dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography (silica gel, hexanes/EtOAc, 50/1 to 40/1) to afford vinyl triflate (80 mg, 49%) as a colorless oil. Next, the vinyl triflate (80 mg, 0.139 mmol, 1.0 equiv) was dissolved in THF (2 mL), followed by the addition of Bu_3SnH (0.07 mL, 0.277 mmol, 2.0 equiv). The resulting solution was degassed by bubbling Ar through for 10 min. Then LiCl (6 mg, 0.139 mmol, 1.0 equiv) and $Pd(PPh_3)_4$ (32 mg,,

0.03 mmol, 0.2 equiv) were added and the mixture was stirred at 55 °C for 12 h. Upon completion, the reaction was directly concentrated and purified by flash column chromatography to afford **141** (21 mg, 35%, 14% over 3 steps) as a colorless oil. **141**: R_f = 0.58 (silica gel, hexanes/EtOAc, 3/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37–7.30 (m, 4 H), 7.30–7.27 (m, 1 H), 5.57–5.48 (m, 2 H), 4.48 (dd, *J* = 27.7, 12.1 Hz, 2 H), 3.62–3.52 (m, 2 H), 3.46 (dd, *J* = 9.0, 3.6 Hz, 1 H), 3.32 (dd, *J* = 8.9, 5.8 Hz, 1 H), 2.18 (dd, *J* = 12.5, 2.9 Hz, 1 H), 2.02–1.89 (m, 2 H), 1.80–1.66 (m, 3 H), 1.62–1.52 (m, 2 H), 1.51–1.40 (m, 3 H), 1.38–1.32 (m, 2 H), 1.30–1.19 (m, 3 H), 1.18–1.10 (m, 1 H), 1.02 (td, *J* = 12.8, 4.5 Hz, 1 H), 0.89 (s, 9 H), 0.05 (s, 6 H).

Compound 143. To a solution of **141** (21 mg, 0.049 mmol, 1.0 equiv) in THF (1 mL) was added TBAF (1.0 M in THF, 0.49 mL, 0.490 mmol, 10.0 equiv). The resulting solution was stirred at 50 °C for 12 h before half-saturated aqueous NH_4Cl solution was added to quench the reaction. The aqueous layer was extracted with Et_2O (2 mL × 2). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to give the crude alcohol as a light brownish oil. Next, to a solution of crude alcohol in CH_2Cl_2 (1 mL) was added $NaHCO_3$ (33 mg, 0.391 mmol, 8.0 equiv) and Dess-Martin periodinane (31 mg, 0.073 mmol, 1.5 equiv) sequentially at 23 °C. The mixture was stirred at this temperature for 30 min before a mixed aqueous solution of $NaHCO_3$ and $Na_2S_2O_3$ was added to quench the reaction. The aqueous layer was extracted with CH_2Cl_2 (2 mL × 2). The combined organic layers were dried ($MgSO_4$), filtered, concentrated, and purified by preparative thin layer chromatography (silica gel, hexanes/EtOAc, 3/1) to yield the aldehyde **142** (10 mg, 67% over 2 steps) as a colorless oil. Next, to a solution of this aldehyde **142** (10 mg, 0.033 mmol, 1.0 equiv) in CH_2Cl_2 (1 mL) was added $BnNH_2$ (0.01 mL, 0.098 mmol, 3.0 equiv). The mixture was stirred at 23 °C for 1 h before $NaBH(OAc)_3$ (2 mg, 0.098 mmol, 3.0 equiv) was added

as solid. The reaction was further stirred at 23 °C for 8 h before half-saturated aqueous $NaHCO_3$ solution was added to quench the reaction. The aqueous layer was extracted with CH_2Cl_2 (1 mL × 2). The combined organic layers were dried ($MgSO_4$), filtered, concentrated, and purified by preparative thin layer chromatography (silica gel, CH_2Cl_2/acetone/Et_3N, 1/1/0.01) to afford **143** (8 mg, 60%) as a colorless oil. **143**: R_f = 0.18 (silica gel, hexanes/acetone, 1/1, tailing); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 – 7.24 (m, 10 H), 5.54 (s, 2 H), 4.50 (dd, *J* = 26.8, 12.1 Hz, 2 H), 3.82 (s, 2 H), 3.48 (d, *J* = 6.3 Hz, 1 H), 3.34 (dd, *J* = 8.3, 5.6 Hz, 1 H), 2.62 (t, *J* = 7.2 Hz, 2 H), 2.20 (d, *J* = 14.1 Hz, 1 H), 2.01–1.90 (m, 1 H), 1.82–1.65 (m, 5 H), 1.58 (d, *J* = 8.0 Hz, 1 H), 1.53–1.44 (m, 3 H), 1.41–1.33 (m, 2 H), 1.30–1.16 (m, 5 H), 1.05 (td, *J* = 13.2, 3.7 Hz, 1 H).

Aza-Michael cyclization model study and synthesis of myrioxazine A&B

Compound 158. *One-step procedure*: To a flamed dried flask was added CuBr·SMe_2 (4.10 g, 20.0 mmol, 0.67 equiv) and LiCl (1.72 g, 40.0 mmol, 1.33 equiv), followed by THF (60 mL). The mixture was stirred at 23 °C for 5 min before the suspension turned homogeneous. The flask was then cooled down to -78 °C and allylmagnesium bromide (1.0 M in Et_2O, 40.0 mL, 40.0 mmol, 1.33 equiv) was added dropwise over 10 min. The resultant dark brownish suspension was then stirred at -78 °C for 30 min. 2-cyclohexen-1-one **157** (2.90 mL, 30.0 mmol, 1.0 equiv) was then added at this temperature. The reaction was kept at -78 °C for 2 h before a solution of Comins' reagent (11.8 g, 30.0 mmol, 1.0 equiv) in THF (20 mL) was added. The reaction was then allowed to slowly warm up to 23 °C over 8 h before a mixed solution of half-saturated aqueous NH_4Cl solution (50 mL) and 3 N NaOH (30 mL) was added to quench the reaction. The biphasic mixture was vigorously stirred for 30 min before the aqueous layer was extracted with Et_2O (20 mL × 2). The combined organic layers were dried ($MgSO_4$), filtered, concentrated, and purified by flash

column chromatography (silica gel, hexanes/EtOAc, 60/1) to afford **158** (2.42 g, 30%) as a colorless oil. *Two-step procedure*: To a flamed dried flask was added $CuBr{\cdot}SMe_2$ (4.10 g, 20.0 mmol, 0.67 equiv) and LiCl (1.72 g, 40.0 mmol, 1.33 equiv), followed by THF (60 mL). The mixture was stirred at 23 °C for 5 min before the suspension turned homogeneous. The flask was then cooled down to -78 °C and allylmagnesium bromide (1.0 M in Et_2O, 40.0 mL, 40.0 mmol, 1.33 equiv) was added dropwise over 10 min. The resultant dark brownish suspension was then stirred at -78 °C for 30 min. A pre-mixed solution of 2-cyclohexen-1-one **157** (2.90 mL, 30.0 mmol, 1.0 equiv) and TMSCl (5.07 mL, 40.0 mmol, 1.33 equiv) was then added at this temperature. The reaction was then allowed to slowly warm up to 23 °C over 8 h before a mixed solution of half-saturated aqueous NH_4Cl solution (50 mL) and 3 N NaOH (30 mL) was added to quench the reaction. The biphasic mixture was vigorously stirred for 30 min before the aqueous layer was extracted with Et_2O (20 mL × 2). The combined organic layers were dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography (silica gel, hexanes/EtOAc, 70/1) to afford TMS silyl enol ether (3.66 g, 58%) as a colorless oil. To a flame-dried flask was added CsF (5.29 g, 34.8 mmol, 2.0 equiv) and $PhNTf_2$ (7.15 g, 20.0 mmol, 1.15 equiv). A solution of TMS silyl enol ether (3.66 g, 17.4 mmol, 1.0 equiv) in 1,2-dimethoxyethane (20 mL) was added at 23 °C. The reaction was stirred at this temperature for 16 h. Upon completion, the reaction was quenched by the addition of half-saturated aqueous $NaHCO_3$ solution (40 mL). The aqueous layer was extracted with Et_2O (20 mL × 2). The combined organic layers were dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography (silica gel, hexanes/EtOAc, 70/1 to 60/1) to afford **158** (3.86 g, 82%, 48% over 2 steps) as a colorless oil. **158**: R_f = 0.68 (silica gel, hexanes/EtOAc, 3/1); IR (film) ν_{max} 2942, 2866, 1418, 1210, 1144, 1074, 1011, 943, 905, 877, 826, 609 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.74 (ddt, *J* = 16.2, 11.0, 7.1 Hz, 1 H), 5.68 (s, 1 H),

5.08 (s, 1 H), 5.05 (d, J = 6.1 Hz, 1 H), 2.46–2.34 (m, 1 H), 2.34–2.23 (m, 2 H), 2.19–2.05 (m, 2 H), 1.94–1.85 (m, 1 H), 1.81–1.73 (m, 1 H), 1.68 (qdd, J = 11.5, 6.1, 2.9 Hz, 1 H), 1.31–1.19 (m, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.6, 135.5, 122.1, 118.5 (q, J = 320.1 Hz), 117.1, 39.6, 34.7, 27.6, 27.3, 21.4; HRMS (ESI+) calcd for $C_{10}H_{13}F_3NaO_3S^+$ [M + Na^+] 293.0430, found 293.0392.

Alcohol 159. To a solution of **158** (3.15 g, 11.6 mmol, 1.0 equiv) in THF (23 mL) was added 9-BBN (0.5 M in THF, 24.5 mL, 12.2 mmol, 1.05 equiv) at 23 °C. The reaction was stirred at this temperature for 12 h. Then H_2O (2.3 mL) was added and the reaction was cooled down to 0 °C before $NaBO_3 \cdot H_2O$ (3.46 g, 34.9 mmol, 3.0 equiv) was added as solid. The reaction was then stirred at 23 °C for 24 h. Upon completion, H_2O (20 mL) was added and the aqueous layer was extracted with Et_2O (20 mL × 2). The combined organic layers were washed by brine, dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography (silica gel, hexanes/acetone, 30/1 to 15/1 to 8/1) to afford **159** (2.38 g, 71%) as a colorless oil. **159**: R_f = 0.22 (silica gel, hexanes/EtOAc, 3/1); IR (film) ν_{max} 3341(br), 2940, 2864, 1416, 1245, 1143, 1058, 1014, 899, 823, 612 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.65 (s, 1 H), 3.61 (t, J = 6.4 Hz, 2 H), 2.36–2.22 (m, 3 H), 1.96–1.82 (m, 2 H), 1.81–1.72 (m, 1 H), 1.71–1.62 (m, 1 H), 1.58 (dq, J = 13.4, 6.9 Hz, 2 H), 1.49–1.35 (m, 2 H), 1.26–1.16 (m, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.4, 122.5, 118.5 (q, J = 320.2 Hz), 62.6, 34.7, 31.5, 29.8, 27.6, 27.4, 21.3; HRMS (ESI+) calcd for $C_{10}H_{15}F_3NaO_4S^+$ [M + Na^+] 311.0535, found 311.0541.

Aldehyde 160. To a solution of **159** (1.98 g, 6.86 mmol, 1.0 equiv) in CH_2Cl_2 (70 mL) was added $NaHCO_3$ (4.61 g, 54.9 mmol, 8.0 equiv). Dess-Martin periodinane (3.50 g, 8.2 mmol,

1.2 equiv) was added as solid at 0 °C. The reaction was then stirred at 23 °C for 1 h. Upon completion, a mixed solution of aqueous $NaHCO_3$ and $Na_2S_2O_3$ (50 mL) was added to quench the reaction. The biphasic mixture was vigorously stirred for 30 min before the aqueous layer was extracted with CH_2Cl_2 (20 mL × 2). The combined organic layers were dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography (silica gel, hexanes/acetone, 30/1) to afford **160** (1.57 g, 80%) as a colorless oil. **160**: R_f = 0.48 (silica gel, hexanes/EtOAc, 3/1); IR (film) ν_{max} 2942, 2867, 1727, 1416, 1245, 1209, 1143, 896, 610 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.77 (d, *J* = 1.1 Hz, 1 H), 5.62 (s, 1 H), 2.49 (t, *J* = 7.6 Hz, 2 H), 2.39–2.22 (m, 3 H), 1.93–1.84 (m, 1 H), 1.82–1.73 (m, 1 H), 1.73–1.62 (m, 3 H), 1.20 (tdd, *J* = 11.2, 8.3, 2.7 Hz, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 201.4, 149.9, 121.7, 118.5 (q, *J* = 320.2 Hz), 40.9, 34.2, 27.5, 27.2, 27.1, 21.2; HRMS (ESI+) calcd for $C_{10}H_{13}F_3NaO_4S^+$ [M + Na^+] 309.0379, found 309.0371.

Compound 161. To a solution of **160** (1.57 g, 5.49 mmol, 1.0 equiv) in MeOH (12 mL) was added Et_3N (2.96 mL, 22.0 mmol, 4.0 equiv) and PPh_3(259 mg, 0.99 mmol, 0.18 equiv) at room temperature. The mixture was stirred until PPh_3 fully dissolved. CO gas was then bubbled through the solution for 3 min. $Pd(OAc)_2$ (111 mg, 0.49 mmol, 0.09 equiv) was added as solid and the reaction was stirred under 1 atm CO atmosphere for 8 h at 23 °C. Upon completion, MeOH was removed by evaporation. Half-saturated NH_4Cl solution (15 mL) and Et_2O (10 mL) was then added. The aqueous layer was extracted with Et_2O (10 mL × 2). The combined organic layers were dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography (silica gel, hexanes/acetone, 30/1 to 20/1) to afford **161** (803 mg, 74%) as a colorless oil. **161**: R_f = 0.44 (silica gel, hexanes/EtOAc, 3/1); IR (film) ν_{max} 2934, 2860, 1714, 1640, 1435, 1268, 1244, 1085, 748 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.78 (d, *J* = 1.4 Hz, 1 H), 6.80 (s, 1 H), 3.71 (s, 3 H), 2.55–

2.49 (m, 2 H), 2.34–2.19 (m, 2 H), 2.19–2.09 (m, 1 H), 1.82–1.72 (m, 3 H), 1.70–1.61 (m, 1 H), 1.55–1.44 (m, 1 H), 1.24–1.12 (m, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 201.9, 167.8, 142.1, 130.7, 51.5, 41.2, 35.2, 27.6, 27.2, 24.3, 20.9; HRMS (ESI+) calcd for $C_{11}H_{17}O_3^+$ [M + H^+] 219.0992, found 219.0992.

Compound 162. To a solution of **161** (503 mg, 2.56 mmol, 1.0 equiv) in CH_2Cl_2 (6 mL) was added $BnNH_2$ (0.36 mL, 3.07 mmol, 1.3 equiv). The mixture was stirred at 23 °C for 30 min before $NaBH(OAc)_3$ (760 mg, 3.59 mmol, 1.4 equiv) was added as solid. The reaction was then stirred at 23 °C for 8 h before half-saturated $NaHCO_3$ solution (10 mL) was added to quench the reaction. The aqueous layer was extracted with CH_2Cl_2 (10 mL × 2). The combined organic layers were dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography (silica gel, hexanes/acetone, 10/1 to 5/1 to 2/1) to afford **163** (573 mg, 78%) as a light yellowish oil. **163**: R_f = 0.32, tailing (silica gel, hexanes/acetone, 1/1); IR (film) ν_{max} 2932, 2856, 1713, 1266, 1242, 1089, 698 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35–7.28 (m, 4 H), 7.28–7.21 (m, 1 H), 6.87 (s, 1 H), 3.79 (s, 2 H), 3.72 (s, 3 H), 2.64 (t, *J* = 7.2 Hz, 2 H), 2.30 (d, *J* = 17.4 Hz, 1 H), 2.24–2.10 (m, 2 H), 1.78 (dd, *J* = 10.1, 4.7 Hz, 2 H), 1.64–1.55 (m, 2 H), 1.55–1.41 (m, 2 H), 1.36 (dt, *J* = 15.7, 7.6 Hz, 1 H), 1.23–1.14 (m, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.1, 143.6, 140.4, 129.8, 128.3, 128.0, 126.8, 54.0, 51.4, 49.5, 35.8, 33.0, 27.9, 27.5, 24.4, 21.1; HRMS (ESI+) calcd for $C_{18}H_{25}NNaO_2^+$ [M + Na^+] 310.1778, found 310.1778.

Compound 163. To a solution of **161** (51 mg, 0.234 mmol, 1.0 equiv) in CH_2Cl_2 (1 mL) was added NH_4OAc (36 mg, 0.468 mmol, 2.0 equiv). The mixture was stirred at 23 °C for 30 min before $NaBH(OAc)_3$ (74 mg, 0.351 mmol, 1.5 equiv) was added as solid. The reaction was then

stirred at 23 °C for 8 h before half-saturated $NaHCO_3$ solution (10 mL) was added to quench the reaction. The aqueous layer was extracted with CH_2Cl_2 (10 mL × 2). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to afford the crude **163**. **163**: R_f = 0.10, tailing (silica gel, acetone); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.84 (s, 1 H), 3.72 (s, 3 H), 2.76 (t, *J* = 7.1 Hz, 2 H), 2.31 (d, *J* = 17.1 Hz, 1 H), 2.23–2.11 (m, 2 H), 1.82–1.75 (m, 2 H), 1.63–1.54 (m, 2 H), 1.54–1.42 (m, 2 H), 1.37–1.32 (m, 1 H), 1.22–1.17 (m, 1 H).

Compound 166. To a solution of **159** (798 mg, 2.77 mmol, 1.0 equiv) in THF (12 mL) was added TsNHBoc (826 mg, 3.04 mmol, 1.1 equiv), PPh_3 (798 mg, 3.04 mmol, 1.1 equiv), and DIAD (0.57 mL, 3.04 mmol, 1.1 equiv) sequentially at 23 °C. The reaction was then stirred at this temperature for 12 h before it was directly concentrated and purified by flash column chromatography (silica gel, hexanes/EtOAc, 20/1) to yield **164** (1.24 g, 75%) as a colorless gum. Next, to a solution of **164** (1.24 g, 2.08 mmol, 1.0 equiv) in MeOH (6 mL) was added Et_3N (1.12 mL, 8.30 mmol, 4.0 equiv) and PPh_3(97 mg, 0.332 mmol, 0.16 equiv) at room temperature. The mixture was stirred until PPh_3 fully dissolved. CO gas was then bubbled through the solution for 3 min. $Pd(OAc)_2$ (37 mg, 0.166 mmol, 0.08 equiv) was added as solid and the reaction was stirred under 1 atm CO atmosphere for 8 h at 23 °C. Upon completion, MeOH was removed by evaporation. Half-saturated NH_4Cl solution (15 mL) and Et_2O (10 mL) was then added. The aqueous layer was extracted with Et_2O (10 mL × 2). The combined organic layers were dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography (silica gel, hexanes/acetone, 30/1) to afford **165** (729 mg, 78%) as a light yellowish oil. Next, to a solution of **165** (729 mg, 1.61 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL) was added TFA (3 mL). The reaction was stirred at 23 °C for 12 h. Upon completion, half-saturated aqueous $NaHCO_3$ solution was

added carefully to quench the reaction. The aqueous layer was extracted with CH_2Cl_2 (3 mL × 2). The combined organic layers were dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography (silica gel, hexanes/acetone, 30/1 to 15/1) to afford **166** (532 mg, 94%) as light yellowish gum. **166**: R_f = 0.44 (silica gel, hexanes/EtOAc, 3/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.1 Hz, 2 H), 7.31 (d, *J* = 8.0 Hz, 2 H), 6.76 (s, 1 H), 4.31 (s, 1 H), 3.72 (s, 3 H), 2.95 (d, *J* = 4.2 Hz, 2 H), 2.43 (s, 3 H), 2.29 (d, *J* = 15.3 Hz, 1 H), 2.20–2.07 (m, 2 H), 1.87–1.65 (m, 3 H), 1.54 (dt, *J* = 14.8, 7.4 Hz, 1 H), 1.48 (dd, *J* = 16.0, 11.0 Hz, 1 H), 1.38 (dt, *J* = 15.4, 7.2 Hz, 1 H), 1.29 (ddd, *J* = 15.7, 11.2, 4.9 Hz, 1 H), 1.12 (dd, *J* = 20.6, 9.5 Hz, 1 H).

Compound 167. To a solution of **162** (148 mg, 0.52 mmol, 1.0 equiv) in MeOH (5 mL) was added Triton-B ($BnMe_3NOH$, 40% in MeOH, 0.44 mL, 1.04 mmol, 2.0 equiv). The reaction was stirred at 23 °C for 6 h before solvent was removed by evaporation. Half-saturated NH_4Cl solution (10 mL) was added to quench the reaction. The aqueous layer was extracted with Et_2O (6 mL × 3). The combined organic layers were washed by brine, dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography (silica gel, hexanes/EtOAc, 25/1) to afford **167** (52 mg, 35%) as a light yellowish oil, then (hexanes/acetone, 30/1) to afford **168** (52 mg, 35%) as a light yellowish oil, and then (hexanes/acetone, 2/1) to afford starting material **162** (30 mg, 20%) with inseparable impurity. (Note: *The diastereomeric ratio of this reaction is varied upon slight changes of conditions.*) **167**: R_f = 0.56 (silica gel, hexanes/EtOAc, 3/1); IR (film) ν_{max} 2932, 2853, 1731, 1443, 1298, 1204, 1160, 1034, 698 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33–7.25 (m, 4 H), 7.24–7.19 (m, 1 H), 3.69 (s, 3 H), 3.09 (s, 1 H), 2.79 (d, *J* = 12.4 Hz, 1 H), 2.73–2.64 (m, 1 H), 2.38 (d, *J* = 12.3 Hz, 1 H), 2.26 (qd, *J* = 12.8, 4.2 Hz, 1 H), 2.02–1.90 (m, 2 H), 1.90–1.79 (m, 2 H), 1.72 (d, *J* = 12.3 Hz, 1 H), 1.66–1.52 (m, 3 H), 1.37 (qt, *J* = 12.6, 4.1 Hz, 1

H), 1.24 (dd, *J* = 10.2, 4.9 Hz, 2 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.8, 140.6, 128.5, 128.1, 126.6, 63.2, 57.0, 53.2, 51.5, 48.9, 36.7, 31.0, 26.4, 25.6, 21.3, 21.2; HRMS (Mixed+) calcd for $C_{18}H_{26}NO_2^+$ [M + H^+] 288.1958, found 288.1973.

Compound 168. To a solution of diastereomer **167** (35 mg, 0.12 mmol, 1.0 equiv) in MeOH (0.5 mL) was added NaOMe (0.5 M in MeOH, 0.73 mL, 0.36 mmol, 3.0 equiv). The mixture was stirred at 23 °C for 8 h before before half-saturated NH_4Cl solution (6 mL) was added to quench the reaction. The aqueous layer was extracted with Et_2O (4 mL × 3). The combined organic layers were washed by brine, dried ($MgSO_4$), filtered, concentrated to give **168** (30 mg, 99%) as a light yellowish oil. This compound can also be obtained directly from *aza*-Michael cyclization as described above. **168**: R_f = 0.50 (silica gel, hexanes/EtOAc, 3/1); IR (film) ν_{max} 2926, 2864, 1736, 1451, 1364, 1262, 1191, 1172, 1149, 738, 699 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31–7.23 (m, 4 H), 7.23–7.19 (m, 1 H), 3.84 (s, 1 H), 3.72 (d, *J* = 13.6 Hz, 1 H), 3.66 (s, 3 H), 3.05 (td, *J* = 11.1, 3.3 Hz, 1 H), 2.96 (dd, *J* = 11.0, 4.2 Hz, 1 H), 2.84 (t, *J* = 11.6 Hz, 1 H), 2.45 (d, *J* = 13.1 Hz, 1 H), 2.15 (s, 1 H), 1.91–1.82 (m, 1 H), 1.76–1.63 (m, 2 H), 1.62–1.50 (m, 2 H), 1.50–1.38 (m, 4 H), 1.35 (d, *J* = 7.9 Hz, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.3, 140.7, 128.5, 128.0, 126.6, 62.7, 57.8, 51.4, 43.7, 42.3, 31.0, 30.6, 29.4, 25.5, 21.0, 20.0; HRMS (ESI+) calcd for $C_{18}H_{26}NO_2^+$ [M + H^+] 288.1958, found 288.1971.

(±)-myrioxazine A (1). To a solution of **168** (319 mg, 1.11 mmol, 1.0 equiv) in Et_2O (5 mL) was added $LiAlH_4$ (1.0 M in THF, 1.11 mL, 1.11 mmol, 1.0 equiv) dropwise over 1 min at 0 °C. The reaction was stirred at 23 °C for 1 h before H_2O (0.5 mL) was added carefully to quench the reaction. 2 N NaOH (5 mL) was added and the biphasic mixture was stirred vigorously for 10

min. The aqueous layer was extracted with Et_2O (4 mL × 2). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to give the primary alcohol **40** as a colorless oil. The NMR data of **40** matched the previously reported literature.[2] To a flask with crude **40** was added Pd/C (10 %, 300 mg, ~100% mass equiv). The flask was back-filled with H_2 twice. 1,1,1-trifluoroethanol (6 mL) was added and H_2 was bubbled through the solution for 8 min. The suspension was then vigorously stirred under 1 atm H_2 atmosphere for 24 h. Upon completion, the mixture was filtered through Celite and the filtrate was concentrated to give the crude amino alcohol **30** as a colorless oil. To a solution of amino alcohol **30** in THF (5 mL) was added HCHO (37% in H_2O, 2.5 mL). The reaction was stirred at 23 °C for 10 h before half-saturated aqueous NH_4Cl solution (5 mL) was added to quench the reaction. The aqueous layer was extracted with Et_2O (3 mL × 2). The combined organic layers were dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography (silica gel, hexanes/acetone, 20/1 to 10/1 to 3/1) to afford (±)-myrioxazine A (**1**, 132 mg, 66% over 3 steps) as a colorless oil. **1**: R_f = 0.28, (silica gel, hexanes/acetone, 1/1); IR (film) ν_{max} 2923, 2849, 1177, 1153, 1121, 1045, 1023, 995, 893, 697 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.46 (d, *J* = 10.4 Hz, 1 H), 4.41 (d, *J* = 10.4 Hz, 1 H), 3.85 (dd, *J* = 10.8, 4.2 Hz, 1 H), 3.22–3.09 (m, 2 H), 2.77 (dd, *J* = 11.0, 4.7 Hz, 1 H), 2.60 (d, *J* = 11.4 Hz, 1 H), 2.23–2.11 (m, 1 H), 1.89–1.79 (m, 1 H), 1.79–1.72 (m, 1 H), 1.62–1.49 (m, 4 H), 1.47–1.40 (m, 1 H), 1.40–1.34 (m, 2 H), 1.32–1.25 (m, 1 H), 0.75 (qd, *J* = 12.8, 3.7 Hz, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 86.4, 73.3, 62.5, 44.9, 34.9, 31.1, 27.9, 27.6, 26.1, 23.8, 20.3; HRMS (APCI+) calcd for $C_{11}H_{19}NO^+$ [M^+] 181.1461, found 181.1465.

(±)-myrioxazine B (2). Obtained through a sequence similar to myrioxazine A (**1**) from **167** (103 mg, 0.359 mmol, 1.0 equiv), as a colorless oil (34 mg, 52% over 3 steps). **2**: R_f = 0.26,

(silica gel, hexanes/EtOAc, 2/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.29 (d, *J* = 7.6 Hz, 1 H), 3.74 (d, *J* = 11.1 Hz, 1 H), 3.60 (dd, *J* = 11.1, 2.3 Hz, 1 H), 3.41 (d, *J* = 7.6 Hz, 1 H), 2.60 (d, *J* = 9.9 Hz, 1 H), 2.16 (d, *J* = 14.6 Hz, 1 H), 1.96 (ddd, *J* = 13.6, 13.4, 3.2 Hz, 1 H), 1.88–1.78 (m, 3 H), 1.78–1.70 (m, 1 H), 1.59–1.46 (m, 3 H), 1.45–1.33 (m, 3 H), 1.30 (dt, *J* = 13.4, 3.4 Hz, 1 H), 1.24–1.16 (m, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 87.8, 73.5, 63.4, 50.1, 37.1, 36.3, 30.2, 26.1, 25.6, 25.3, 20.4; HRMS (APCI+) calcd for $C_{11}H_{20}NO^+$ [M + H^+] 182.1539, found 182.1544.

Continuation of myrioneurinol synthesis

(Experimental procedures and data of compound **169** ~ **186** will not be covered; instead, their *O*-PMB variants from the final synthetic route are reported below.)

Compound 189. Obtained in a similar manner to that of compound **192** (described *vide infra*). **189**: R_f = 0.46, (silica gel, hexanes/acetone, 1/1); Selected peaks: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.49 (d, *J* = 12.1 Hz, 1 H), 4.46 (d, *J* = 10.1 Hz, 1 H), 4.43 (d, *J* = 8.7 Hz, 1 H), 4.40 (d, *J* = 6.6 Hz, 1 H), 3.89 (dd, *J* = 10.7, 4.0 Hz, 1 H), 3.42 (dd, *J* = 9.0, 3.4 Hz, 1 H), 3.24 (dd, *J* = 9.0, 6.1 Hz, 1 H), 3.19 (t, *J* = 10.6 Hz, 1 H), 2.65 (d, *J* = 8.1 Hz, 1 H), 2.47 (d, *J* = 14.1 Hz, 1 H), 2.43–2.38 (m, 1 H), 2.37–2.33 (m, 1 H), 2.27 (d, *J* = 10.3 Hz, 1 H).

Enone 194. To a flame-dried flask was added DIPA (5.13 mL, 36.6 mmol, 1.32 equiv) and THF (50 mL), followed by the addition of *n*-BuLi (2.5 M in hexanes, 14.2 mL, 35.5 mmol, 1.28 equiv) in a dropwise manner over 3 min at -40 °C. The resulting solution was allowed to warm to -25 °C over 20 min. The flask was then cooled down to -78 °C. TMSCl (4.20 mL, 33.2 mmol, 1.2 equiv) was added, followed by the slow addition of a solution of **193** (6.88 g, 27.7 mmol,

1.0 equiv) in THF (10 mL). The reaction was stirred at -78 °C for 30 min. Dry ice bath was then removed and the reaction was stirred for a further 30 min. The reaction was quenched by the addition of half-saturated aqueous $NaHCO_3$ solution (100 mL). The aqueous layer was extracted with Et_2O (20 mL × 3). The combined organic layers were dried ($MgSO_4$), filtered, concentrated, and purified by a short column (silica gel, hexanes/EtOAc, 50/1) to yield the TMS silyl enol ether. The so-obtained TMS silyl enol ether was immediately dissolved in DMSO (45 mL). O_2 gas was bubbled through the solution for 10 min. $Pd(OAc)_2$ (623 mg, 2.77 mmol, 0.1 equiv) was then added as solid at 23 °C. The mixture was stirred at this temperature under 1 atm O_2 atmosphere for 16 h. Upon completion, half-saturated aqueous NH_4Cl solution (80 mL) and Et_2O (80 mL) were added and the biphasic mixture was vigorously stirred for 3 min. The aqueous layer was extracted with Et_2O (20 mL × 2). The combined organic layers were washed by brine, dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography (silica gel, hexanes/acetone, 40/1 to 30/1 to 10/1) to afford **194** (4.50 g, 66% over 2 steps) as a light yellowish oil. **194**: R_f = 0.32 (silica gel, hexanes/EtOAc, 3/1); IR (film) ν_{max} 2859, 1680, 1612, 1514, 1247, 1108, 1034, 820 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.4 Hz, 2 H), 6.93 (d, *J* = 10.2 Hz, 1 H), 6.89 (d, *J* = 8.5 Hz, 2 H), 6.03 (dd, *J* = 10.2, 2.3 Hz, 1 H), 4.48 (s, 2 H), 3.81 (s, 3 H), 3.45 (dt, *J* = 15.8, 9.0 Hz, 2 H), 2.77–2.67 (m, 1 H), 2.51 (dt, *J* = 16.8, 4.6 Hz, 1 H), 2.43–2.32 (m, 1 H), 2.11 (dq, *J* = 13.6, 4.6 Hz, 1 H), 1.85–1.74 (m, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 199.6, 159.3, 151.6, 130.0, 129.3, 113.9, 72.9, 72.1, 55.3, 37.0, 36.7, 25.9; HRMS (APCI+) calcd for $C_{15}H_{19}O_3^+$ [M + H^+] 247.1329, found 247.1325.

Iodoenone 195. To a solution of **194** (3.40 g, 13.8 mmol, 1.0 equiv) in CH_2Cl_2 (14 mL) and pyridine (14 mL) was added I_2 (4.20 g, 16.6 mmol, 1.2 equiv) portionwise. The reaction was

stirred at 23 °C in dark for 12 h before CH_2Cl_2 (20 mL) was added. The solution was washed sequentially by aqueous $NaHCO_3$ (20 mL) and aqueous $Na_2S_2O_3$ (30 mL). After dried ($MgSO_4$), filtered, and concentrated, the crude mixture was dissolved in CH_2Cl_2 (12 mL) and pyridine (12 mL). I_2 (5.35 g, 21.1 mmol, 1.2 equiv) was added portionwise. The mixture was stirred at 23 °C in dark for another 12 h before a mixed aqueous solution of $NaHCO_3$ and $Na_2S_2O_3$ was added to quench the reaction. The aqueous layer was extracted with CH_2Cl_2 (10 mL × 3). The combined organic layers were dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography (silica gel, hexanes/acetone, 20/1) to afford **195** (4.80 g, 94%) as a light yellowish oil (turning yellow upon exposure to light). **195**: R_f = 0.38 (silica gel, hexanes/EtOAc, 3/1); IR (film) ν_{max} 2933, 2860, 1687, 1612, 1585, 1303, 1248, 1174, 1097, 1033, 819 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, *J* = 1.9 Hz, 1 H), 7.25 (d, *J* = 8.3 Hz, 2 H), 6.90 (d, *J* = 8.5 Hz, 2 H), 4.47 (d, *J* = 2.1 Hz, 1 H), 3.81 (s, 3 H), 3.44 (dt, *J* = 16.2, 9.1 Hz, 1 H), 2.85–2.74 (m, 1 H), 2.58–2.49 (m, 1 H), 2.18–2.11 (m, 1 H), 1.90–1.80 (m, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 192.1, 160.5, 159.4, 129.7, 129.3, 113.9, 104.5, 73.0, 71.2, 55.3, 41.4, 35.7, 25.8; HRMS (ESI+) calcd for $C_{15}H_{18}IO_3^+$ [M + H^+] 373.0295, found 373.0295.

Advanced enone 196. To a solution of **195** (4.72 g, 12.7 mmol, 1.0 equiv) in THF (14 mL) was added allyltributyltin (7.93 mL, 25.4 mmol, 2.0 equiv). The resulting solution was degassed by bubbling Ar through for 5 min. $Pd(PPh_3)_4$ (1.47 g, 0.127 mmol, 0.1 equiv) was added and the reaction was stirred at 70 °C for 12 h. Upon completion, the reaction was directly concentrated and purified by flash column chromatography (silica gel, hexanes/EtOAc, 25/1 to 18/1) to afford **196** (2.38 g, 66%) as a colorless oil. (Note: The product is typically contaminated by pigment, but it does not affect the next step). **196**: R_f = 0.48 (silica gel, hexanes/EtOAc, 3/1);

IR (film) ν_{max} 2934, 2859, 1675, 1612, 1513, 1363, 1302, 1248, 1173, 1093, 1035, 820 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.5 Hz, 2 H), 6.89 (d, *J* = 8.6 Hz, 2 H), 6.64 (d, *J* = 1.0 Hz, 1 H), 5.80 (ddt, *J* = 19.3, 9.4, 6.8 Hz, 1 H), 5.08–5.00 (m, 2 H), 4.48 (s, 2 H), 3.81 (s, 3 H), 3.42 (d, *J* = 6.7 Hz, 2 H), 2.99–2.90 (m, 2 H), 2.76–2.68 (m, 1 H), 2.53 (dt, *J* = 16.7, 4.6 Hz, 1 H), 2.41–2.32 (m, 1 H), 2.13–2.05 (m, 1 H), 1.80–1.69 (m, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 198.8, 159.3, 146.7, 138.3, 135.7, 130.1, 129.2, 116.4, 113.8, 72.9, 72.4, 55.3, 37.3, 37.0, 33.4, 26.1; HRMS (ESI+) calcd for $C_{18}H_{23}O_3^+$ [M + H^+] 287.1642, found 287.1643.

Compound 198. To a flame-dried flask was added $CuBr{\cdot}SMe_2$ (3.44 g, 16.8 mmol, 1.0 equiv) and LiCl (1.46 g, 33.6 mmol, 2.0 equiv), followed by THF (70 mL). The mixture was stirred at 23 °C for 5 min before the suspension turned homogeneous. The flask was then cooled down to -78 °C and allylmagnesium bromide (1.0 M in Et_2O, 33.6 mL, 33.6 mmol, 2.0 equiv) was added dropwise over 10 min. The resultant dark brownish suspension was then stirred at -78 °C for 30 min. A pre-mixed solution of **196** (4.80 g, 16.8 mmol, 1.0 equiv) and TMSCl (3.17 mL, 25.1 mmol, 1.5 equiv) in THF (6 mL) was then added at this temperature. The reaction was kept at -78 °C for 2 h, then allowed to slowly warm up to 23 °C over 8 h before a mixed solution of half-saturated aqueous NH_4Cl solution (20 mL) and 3 N NaOH (10 mL) was added to quench the reaction. The biphasic mixture was vigorously stirred for 30 min before the aqueous layer was extracted with Et_2O (12 mL × 2). The combined organic layers were dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography (silica gel, hexanes/EtOAc, 50/1) to afford TMS silyl enol ether **197** (4.16 g, 61%) as a colorless oil. Next, to a solution of **197** (4.16 g, 10.4 mmol, 1.0 equiv) in THF (40 mL) was added MeLi (1.6 M in Et_2O, 7.78 mL, 12.5 mmol, 1.2 equiv) dropwise over 15 min at 0 °C. The resulting solution was stirred at this temperature for 1 h before HMPA

(8.7 mL, 51.9 mmol, 5.0 equiv) was added. The reaction was then cooled down to -78 °C. A solution of the substituted allyl iodide **105** (3.92 g, 13.0 mmol, 1.25 equiv) was then added. The mixture was kept at -78 °C for 3 h, then allowed to slowly warm up to 23 °C over 8 h before half-saturated aqueous NH_4Cl solution (20 mL) was added to quench the reaction. The aqueous layer was extracted with Et_2O (10 mL × 2). The combined organic layers were washed by brine, dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography (silica gel, hexanes/EtOAc, 70/1 to 60/1) to afford **198** (2.66 g, 51%) as a colorless oil. **198**: R_f = 0.58 (silica gel, hexanes/EtOAc, 3/1); IR (film) ν_{max} 2954, 1706, 1613, 1513, 1248, 1112, 1036, 912, 821, 732, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.51–7.44 (m, 2 H), 7.37–7.31 (m, 3 H), 7.22 (d, *J* = 8.5 Hz, 2 H), 6.87 (d, *J* = 8.5 Hz, 2 H), 5.82–5.66 (m, 4 H), 5.03 (dd, *J* = 9.2, 7.3 Hz, 2 H), 4.98 (d, *J* = 9.6 Hz, 1 H), 4.93 (d, *J* = 10.1 Hz, 1 H), 4.38 (d, *J* = 2.7 Hz, 2 H), 3.81 (s, 3 H), 3.59 (dd, *J* = 9.2, 3.1 Hz, 1 H), 3.24 (dd, *J* = 9.0, 7.2 Hz, 1 H), 2.90 (dd, *J* = 14.3, 4.5 Hz, 1 H), 2.62 (dd, *J* = 14.1, 4.4 Hz, 1 H), 2.42 (td, *J* = 13.8, 5.6 Hz, 1 H), 2.38–2.23 (m, 3 H), 2.20–2.13 (m, 1 H), 2.13–2.02 (m, 2 H), 1.97 (dd, *J* = 14.2, 9.7 Hz, 1 H), 1.91–1.83 (m, 1 H), 1.58–1.47 (m, 1 H), 0.28 (d, *J* = 4.3 Hz, 6 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 212.1, 159.1, 142.6, 138.6, 135.5, 133.8, 132.6, 130.5, 129.1, 128.9, 127.7, 117.7, 115.1, 113.7, 72.6, 72.4, 56.2, 55.3, 42.9, 41.3, 38.8, 38.7, 37.4, 33.3, 29.1, -2.6, -2.7; HRMS (Mixed+) calcd for $C_{32}H_{43}O_3Si^+$ [M + H^+] 503.2976, found 503.2977.

Compound 199. To a solution of **198** (989 mg, 1.97 mmol, 1.0 equiv) in CH_2Cl_2 (20 mL) was added Grubbs-I catalyst (243 mg, 0.296 mmol, 0.15 equiv) at 23 °C. The reaction was stirred at this temperature for 16 h. Upon completion, the mixture was directly concentrated and purified by flash column chromatography (silica gel, hexanes/EtOAc, 30/1 to 20/1) to afford **199** (861 mg, 92%) as a colorless oil. **199**: R_f = 0.54 (silica gel, hexanes/EtOAc, 3/1); IR (film) ν_{max} 2954, 2854,

1707, 1612, 1513, 1427, 1248, 1172, 1112, 1036, 822, 732, 700 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50–7.43 (m, 2 H), 7.38–7.30 (m, 3 H), 7.23 (d, *J* = 8.4 Hz, 2 H), 6.88 (d, *J* = 8.5 Hz, 2 H), 5.85–5.77 (m, 2 H), 5.66–5.55 (m, 2 H), 4.42 (dd, *J* = 26.1, 11.6 Hz, 2 H), 3.81 (s, 3 H), 3.50 (dd, *J* = 9.1, 3.3 Hz, 1 H), 3.31 (dd, *J* = 9.0, 6.4 Hz, 1 H), 2.57 (td, *J* = 14.4, 6.3 Hz, 1 H), 2.49 (ddd, *J* = 18.9, 15.0, 6.0 Hz, 1 H) 2.34–2.27 (m, 1 H), 2.22–2.12 (m, 4 H), 2.06–1.97 (m, 1 H), 1.94–1.84 (m, 1 H), 1.80 (td, *J* = 11.2, 4.8 Hz, 1 H), 1.67–1.56 (m, 2 H), 0.27 (d, *J* = 3.3 Hz, 6 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 213.8, 159.2, 142.6, 138.7, 133.8, 132.4, 130.4, 129.1, 128.9, 127.7, 125.0, 124.8, 113.8, 72.9, 71.8, 55.3, 49.9, 43.4, 38.7, 37.2, 36.0, 30.5, 29.6, 27.0, -2.6; HRMS (APCI+) calcd for $C_{30}H_{39}O_3Si^+$ [M + H^+] 475.2663, found 475.2661.

Compound 200. To a flask loaded with **199** (928 mg, 2.09 mmol, 1.0 equiv) was added Pd/C (5%, 371 mg, 40% mass equiv). The flask was back-filled with H_2 twice. EtOAc (10 mL) was added and H_2 was bubbled through solution for 3 min. The reaction was then stirred at 23 °C under 1 atm H_2 atmosphere for 12 h. Upon completion, the reaction was filtered through Celite and the filtrate was concentrated to give the crude hydrogenated product **200**. One-pot procedure from **198**: To a solution of **198** (227 mg, 0.452 mmol, 1.0 equiv) in CH_2Cl_2 (5 mL) was added Grubbs-I catalyst (56 mg, 0.068 mmol, 0.15 equiv) at 23 °C. The reaction was stirred at this temperature for 16 h. Then the solvent was removed by evaporation and Pd/C (5%, 125 mg, 55% mass equiv). The flask was back-filled with H_2 twice. EtOAc (10 mL) was added and H_2 was bubbled through solution for 5 min. The reaction was then stirred at 23 °C under 1 atm H_2 atmosphere for 12 h. Upon completion, the reaction was filtered through Celite and the filtrate was concentrated and purified by flash column chromatography (silica gel, hexanes/EtOAc, 30/1 to 25/1) to afford **200** (177 mg, 82%) as a colorless oil. **200**: R_f = 0.54 (silica gel, hexanes/EtOAc,

3/1); IR (film) ν_{max} 2931, 2862, 1704, 1513, 1247, 1113, 1036, 821, 701 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52–7.44 (m, 2 H), 7.37–7.30 (m, 3 H), 7.22 (d, *J* = 8.4 Hz, 2 H), 6.87 (d, *J* = 8.4 Hz, 2 H), 4.39 (dd, *J* = 29.6, 11.6 Hz, 2 H), 3.81 (s, 3 H), 3.44 (dd, *J* = 9.1, 3.4 Hz, 1 H), 3.24 (dd, *J* = 8.9, 6.4 Hz, 1 H), 2.47 (td, *J* = 14.0, 6.7 Hz, 1H), 2.22–2.15 (m, 1 H), 2.14–2.07 (m, 1 H), 2.01–1.91 (m, 1 H), 1.86 (d, *J* = 12.2 Hz, 1 H), 1.78 (td, *J* = 13.5, 4.6 Hz, 1 H), 1.66 (d, *J* = 12.6 Hz, 1 H), 1.61 (dd, *J* = 19.2, 6.4 Hz, 1 H), 1.51 (dd, *J* = 15.5, 10.5 Hz, 2 H), 1.39 (td, *J* = 11.8, 2.7 Hz, 1 H), 1.30–1.19 (m, 4 H), 1.18–1.07 (m, 2 H), 0.90–0.78 (m, 1 H), 0.73–0.67 (m, 2 H), 0.23 (d, *J* = 3.4 Hz, 6 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 216.1, 159.1, 139.3, 133.5, 130.6, 129.1, 128.8, 127.7, 113.7, 72.8, 72.2, 55.3, 51.4, 48.4, 37.7, 35.6, 31.8, 30.9, 28.5, 25.9, 24.1, 20.5, 17.4, 16.7, -3.0; HRMS (Mixed+) calcd for $C_{30}H_{42}NaO_3Si^+$ [M + Na^+] 501.2795, found 501.2787.

Alcohol 201. To a flame-dried flask was added activated 4 Å molecular sieves (1.80 g), followed by a solution of **200** (1.30 g, 2.70 mmol, 1.0 equiv) in THF (8 mL). TBAF (1.0 M in THF, 10.8 mL, 10.8 mmol, 4.0 equiv) was added at 23 °C and the mixture was stirred at 70 °C for 4 h. After the flask was cooled down to 23 °C, KF (648 mg, 10.8 mmol, 4.0 equiv), $NaHCO_3$ (243 mg, 2.70 mmol, 1.0 equiv), and MeOH (6 mL) were added sequentially, followed by the addition of H_2O_2 (30% in H_2O, 5.20 mL) in a careful manner. The mixture was then stirred at 70 °C for 1.5 h. Upon completion, the reaction was cooled back to 23 °C and filtered through Celite. Et_2O (40 mL) was added to the filtrate and the organic phase was washed sequentially by half-saturated aqueous $Na_2S_2O_3$ solution and brine, dried ($MgSO_4$), concentrated, and purified by flash column chromatography (silica gel, hexanes/acetone, 15/1 to 6/1) to afford **201** (815 mg, 84%). **201**: R_f = 0.06 (silica gel, hexanes/EtOAc, 3/1); IR (film) ν_{max} 3444 (br), 2930, 2862, 1702, 1612, 1513, 1454, 1302, 1247, 1173, 1094, 1035, 819 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.4 Hz,

2 H), 6.87 (d, *J* = 8.5 Hz, 2 H), 4.40 (dd, *J* = 28.1, 11.6 Hz, 2 H), 3.81 (s, 3 H), 3.60 (d, *J* = 6.4 Hz, 2 H), 3.46 (dd, *J* = 9.1, 3.5 Hz, 1 H), 3.28 (dd, *J* = 9.0, 6.3 Hz, 1 H), 2.61 (td, *J* = 14.1, 6.8 Hz, 1 H), 2.26 (ddd, *J* = 14.1, 4.7, 2.2 Hz, 1 H), 2.21–2.11 (m, 1 H), 2.11–2.01 (m, 1 H), 1.95–1.84 (m, 2 H), 1.82–1.74 (m, 1 H), 1.71 (d, *J* = 12.9 Hz, 1 H), 1.66–1.58 (m, 2 H), 1.56–1.51 (m, 1 H), 1.49–1.39 (m, 1 H), 1.38–1.29 (m, 2 H), 1.29–1.20 (m, 2 H), 1.16 (dt, *J* = 12.9, 4.1 Hz, 1 H), 1.06 (qd, *J* = 12.6, 6.0 Hz, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 216.0, 159.1, 130.5, 129.1, 113.8, 113.7, 72.8, 72.1, 63.1, 55.3, 50.8, 48.2, 37.7, 35.7, 30.8, 28.5, 26.4, 25.9, 24.2, 24.0, 20.5; HRMS (Mixed+) calcd for $C_{22}H_{32}NaO_4^+$ [M + Na^+] 383.2193, found 383.2203.

Compound 202. To a solution of **201** (294 mg, 0.816 mmol, 1.0 equiv) in CH_2Cl_2 (6 mL) was added imidazole (111 mg, 1.63 mmol, 2.0 equiv) and TBSCl (135 mg, 0.897 mmol, 1.1 equiv) sequentially at 0 °C. The reaction was stirred at this temperature for 1 h before half-saturated aqueous $NaHCO_3$ solution was added to quench the reaction. The aqueous layer was extracted with CH_2Cl_2 (1 mL × 2). The combined organic layers were dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography (silica gel, hexanes/EtOAc, 35/1 to 25/1) to afford **202** (359 mg, 90%) as a colorless oil. **202**: R_f = 0.52 (silica gel, hexanes/EtOAc, 3/1); IR (film) ν_{max} 2929, 2857, 1706, 1612, 1514, 1462, 1361, 1302, 1248, 1180, 1094, 1038, 834, 777 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.4 Hz, 2 H), 6.87 (d, *J* = 8.5 Hz, 2 H), 4.40 (dd, *J* = 30.5, 11.6 Hz, 2 H), 3.80 (s, 3 H), 3.60–3.50 (m, 2 H), 3.46 (dd, *J* = 9.1, 3.4 Hz, 1 H), 3.28 (dd, *J* = 9.0, 6.3 Hz, 1 H), 2.62 (td, *J* = 14.1, 6.7 Hz, 1 H), 2.28–2.19 (m, 1 H), 2.19–2.11 (m, 1 H), 2.10–2.00 (m, 1 H), 1.94–1.81 (m, 2 H), 1.81–1.73 (m, 1 H), 1.70 (d, *J* = 12.7 Hz, 1 H), 1.62 (dd, *J* = 12.9, 4.3 Hz, 1 H), 1.60–1.57 (m, 1 H), 1.56–1.51 (m, 1 H), 1.47 (td, *J* = 11.8, 2.7 Hz, 1 H), 1.42–1.32 (m, 2 H), 1.30 (dd, *J* = 12.9, 3.2 Hz, 1 H), 1.27–1.21 (m, 1 H), 1.15 (dt, *J* = 13.0, 4.0 Hz, 1 H),

0.99 (qd, *J* = 12.5, 5.6 Hz, 1 H), 0.88 (s, 9 H), 0.03 (d, *J* = 1.8 Hz, 6 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 216.1, 159.1, 130.5, 129.1, 113.7, 72.8, 72.1, 63.0, 55.3, 50.8, 48.2, 37.7, 35.7, 30.9, 28.5, 26.4, 25.9, 25.9, 24.2, 24.0, 20.4, 18.2, -5.3; HRMS (Mixed+) calcd for $C_{28}H_{47}O_4Si^+$ [M + H^+] 475.3238, found 475.3241.

Equatorial alcohol 204. To flame-dried flask was added DIPA (0.37 mL, 2.64 mmol, 2.1 equiv) and THF (2 mL). The resulting solution was cooled down to 0 °C and *n*-BuLi (2.5 M in hexanes, 1.03 mL, 2.58 mmol, 2.05 equiv) was added dropwise over 1 min. The mixture was stirred at this temperature before **202** (597 mg, 1.26 mmol, 1.0 equiv) in THF (1 mL) was added. Then the reaction was stirred at 23 °C for 1 h. HMPA (1.09 mL, 6.29 mmol, 5.0 equiv) was added before Mander's reagent ($NCCO_2Me$, 0.21 mL, 2.52 mmol, 2.0 equiv) was added dropwise over 20 s at 10 °C. After stirring for another 30 min at 23 °C, half-saturated aqueous NH_4Cl solution (3 mL) was added to quench the reaction. The aqueous layer was extracted with Et_2O (3 mL × 2). The combined organic layers were washed by brine, dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography (silica gel, hexanes/acetone, 40/1) to afford ketoester **203** (550 mg, 82%). Ketoester **203** tended to display an unstable ratio of ketone/enol form in $CDCl_3$, which prevented the collection of a readable data. Next, to a solution of **203** (48 mg, 0.09 mmol, 1.0 equiv) in *i*-PrOH (1 mL) was added $NaBH_4$ (18 mg, 0.450 mmol, 5.0 equiv) as solid at 23 °C. The mixture was stirred at this temperature for 2 h. Upon completion, half-saturated aqueous NH_4Cl solution (3 mL) was added to quench the reaction. The aqueous layer was extracted with Et_2O (3 mL × 2). The combined organic layers were washed by brine, dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography (silica gel, hexanes/acetone, 40/1) to give an inseparable mixture of diastereomers **204** and **205**. Further iterative preparative thin layer

chromatography (silica gel, hexanes/EtOAc, 3/1) afforded **204** (17 mg, 36%) as a colorless gum and **205** (11 mg, 23%) as a colorless gum. **204**: R_f = 0.40 (silica gel, hexanes/EtOAc, 3/1); IR (film) ν_{max} 3521(br), 2928, 2856, 1734, 1613, 1514, 1462, 1248, 1172, 1097, 1037, 836, 778 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.22 (d, *J* = 8.5 Hz, 2 H), 6.87 (d, *J* = 8.5 Hz, 2 H), 4.40 (d, *J* = 11.6 Hz, 1 H), 4.34 (d, *J* = 11.7 Hz, 1 H), 3.80 (s, 3 H), 3.69 (s, 2 H), 3.63–3.57 (m, 1 H), 3.57–3.52 (m, 1 H), 3.49 (dd, *J* = 10.7, 4.3 Hz, 1 H), 3.36 (dd, *J* = 9.2, 3.4 Hz, 1 H), 3.19 (dd, *J* = 9.0, 6.4 Hz, 1 H), 2.77 (td, *J* = 13.0, 4.5 Hz, 1 H), 2.46 (d, *J* = 4.6 Hz, 1 H), 2.27 (d, *J* = 13.4 Hz, 1 H), 2.09 (dt, *J* = 13.1, 4.0 Hz, 1 H), 1.96–1.82 (m, 1 H), 1.77–1.66 (m, 2 H), 1.66–1.57 (m, 2 H), 1.55–1.46 (m, 2 H), 1.43–1.34 (m, 2 H), 1.34–1.24 (m, 1 H), 1.22–1.09 (m, 3 H), 0.90 (s, 9 H), 0.05 (s, 6 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.1, 159.1, 130.7, 129.1, 113.7, 81.9, 72.6, 72.0, 64.4, 55.2, 52.0, 46.9, 42.6, 41.2, 33.6, 32.8, 30.2, 27.7, 26.2, 26.0, 23.4, 22.5, 20.2, 18.4, -5.2, -5.3; HRMS (ESI+) calcd for $C_{30}H_{51}O_6Si^+$ [M + H^+] 535.3449, found 535.3447.

Axial alcohol 205. **205**: R_f = 0.38 (silica gel, hexanes/EtOAc, 3/1); IR (film) ν_{max} 3492 (br), 2928, 2856, 1701, 1513, 1249, 1096, 835, 776 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.5 Hz, 2 H), 6.88 (d, *J* = 8.5 Hz, 2 H), 4.43 (d, *J* = 11.7 Hz, 1 H), 4.36 (d, *J* = 11.7 Hz, 1 H), 4.01 (d, *J* = 9.1 Hz, 1 H), 3.81 (s, 3 H), 3.74 (s, 3 H), 3.60–3.53 (m, 1 H), 3.48 (dd, *J* = 8.9, 6.4 Hz, 1 H), 3.39 (dt, *J* = 9.7, 6.7 Hz, 1 H), 3.34 (dd, *J* = 9.3, 3.2 Hz, 1 H), 3.27 (dd, *J* = 9.2, 5.4 Hz, 1 H), 2.94 (t, *J* = 5.0 Hz, 1 H), 2.37–2.27 (m, 2 H), 1.71 (d, *J* = 11.6 Hz, 1 H), 1.67–1.56 (m, 4 H), 1.53–1.40 (m, 3 H), 1.34–1.23 (m, 2 H), 1.23–1.08 (m, 3 H), 0.89 (s, 9 H), 0.04 (s, 6 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.1, 159.1, 130.7, 129.1, 113.7, 81.9, 72.6, 72.0, 64.4, 55.2, 52.0, 46.9, 42.6, 41.2, 33.6, 32.8, 30.2, 27.7, 26.2, 26.0, 23.4, 22.5, 20.2, 18.4, -5.2, -5.3; HRMS (ESI+) calcd for $C_{30}H_{50}NaO_6Si^+$ [M + Na^+] 557.3269, found 557.3262.

Compound 206. To a solution of **205** (22 mg, 0.041 mmol, 1.0 equiv) in pyridine (1 mL) was added $SOCl_2$ (0.03 mL, 0.411 mmol, 10.0 equiv) at 23 °C. The resulting solution was stirred at this temperature for 12 h before half-saturated aqueous $NaHCO_3$ solution was added to quench the reaction. The aqueous layer was extracted with CH_2Cl_2 (1 mL × 3). The combined organic layers were dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography (silica gel, hexanes/EtOAc, 30/1) to afford **206** (17 mg, 80%) as a colorless gum. **206**: R_f = 0.64 (silica gel, hexanes/EtOAc, 3/1); IR (film) ν_{max} 2928, 2856, 1716, 1514, 1248, 1101, 836, 776 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.25 (d, *J* = 9.1 Hz, 2 H), 6.88 (d, *J* = 8.4 Hz, 2 H), 6.79 (s, 1 H), 4.45 (d, *J* = 11.6 Hz, 1 H), 4.39 (d, *J* = 11.7 Hz, 1 H), 3.81 (s, 3 H), 3.71 (s, 3 H), 3.58 (dt, *J* = 12.3, 6.2 Hz, 1 H), 3.51 (dt, *J* = 9.9, 6.7 Hz, 1 H), 3.44 (dd, *J* = 9.1, 3.8 Hz, 1 H), 3.35 (dd, *J* = 8.9, 5.7 Hz, 1 H), 2.48 (dd, *J* = 18.4, 5.9 Hz, 1 H), 2.16 (ddd, *J* = 18.4, 10.5, 1.6 Hz, 1 H), 1.89 (ddd, *J* = 15.3, 10.4, 5.2 Hz, 1 H), 1.85–1.79 (m, 2 H), 1.79–1.73 (m, 1 H), 1.57 (dd, *J* = 16.1, 10.4 Hz, 1 H), 1.54–1.47 (m, 2 H), 1.47–1.37 (m, 2 H), 1.30 (t, *J* = 10.6 Hz, 1 H), 1.27–1.19 (m, 2 H), 1.18–1.04 (m, 2 H), 0.88 (s, 9 H), 0.03 (s, 6 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.2, 159.1, 149.0, 130.7, 129.1, 127.6, 113.7, 72.8, 72.2, 63.8, 55.3, 51.5, 45.1, 37.8, 34.3, 33.1, 29.4, 27.8, 26.7, 26.4, 25.9, 23.2, 20.8, 18.3, -5.2, -5.3; HRMS (ESI+) calcd for $C_{30}H_{49}O_5Si^+$ [M + H^+] 517.3344, found 517.3337.

Compound 208. To a solution of **206** (48 mg, 0.093 mmol, 1.0 equiv) in THF (1 mL) was added TBAF (1.0 M in THF, 0.93 mL, 0.929 mmol, 10.0 equiv) at 23 °C. The reaction was then stirred at 50 °C for 12 h. Upon, completion, half-saturated aqueous NH_4Cl solution was added to quench the reaction. The aqueous layer was extracted with Et_2O (2 mL × 2). The combined organic

layers were dried ($MgSO_4$), filtered, and concentrated to give the crude alcohol as a light brownish oil. Next, to a solution of crude alcohol in CH_2Cl_2 (1.5 mL) was added $NaHCO_3$ (62 mg, 0.744 mmol, 8.0 equiv) and Dess-Martin periodinane (79 mg, 0.186 mmol, 2.0 equiv) sequentially at 23 °C. The mixture was stirred at this temperature for 30 min before a mixed aqueous solution of $NaHCO_3$ and $Na_2S_2O_3$ was added to quench the reaction. The aqueous layer was extracted with CH_2Cl_2 (2 mL × 2). The combined organic layers were dried ($MgSO_4$), filtered, concentrated, and purified by preparative thin layer chromatography (silica gel, hexanes/EtOAc, 3/1) to yield the aldehyde **207** (27 mg, 73% over 2 steps) as a colorless oil. Next, to a solution of this aldehyde **207** (27 mg, 0.067 mmol, 1.0 equiv) in CH_2Cl_2 (1 mL) was added $BnNH_2$ (0.03 mL, 0.270 mmol, 4.0 equiv). The mixture was stirred at 23 °C for 1 h before $NaBH(OAc)_3$ (29 mg, 0.135 mmol, 2.0 equiv) was added as solid. The reaction was further stirred at 23 °C for 8 h before half-saturated aqueous $NaHCO_3$ solution was added to quench the reaction. The aqueous layer was extracted with CH_2Cl_2 (1 mL × 2). The combined organic layers were dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography (silica gel, CH_2Cl_2/acetone, 5/1 to 1/1) to afford **208** (23 mg, 69%) as a colorless oil. **208**: R_f = 0.22, tailing (silica gel, hexanes/acetone, 1/1); IR (film) ν_{max} 2927, 2854, 1712, 1513, 1453, 1247, 1105, 1036, 750, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35–7.28 (m, 4 H), 7.28–7.21 (m, 4 H), 6.88 (d, *J* = 8.5 Hz, 2 H), 6.79 (s, 1 H), 4.44 (d, *J* = 11.6 Hz, 1 H), 4.39 (d, *J* = 11.6 Hz, 1 H), 3.81 (s, 3 H), 3.77 (s, 2 H), 3.71 (s, 3 H), 3.43 (dd, *J* = 9.0, 3.9 Hz, 1 H), 2.57 (t, *J* = 7.2 Hz, 2 H), 2.47 (dd, *J* = 18.4, 5.8 Hz, 1 H), 2.14 (ddd, *J* = 18.5, 10.6, 1.9 Hz, 1 H), 1.90–1.71 (m, 4 H), 1.58 (d, *J* = 7.9 Hz, 2 H), 1.54–1.47 (m, 2 H), 1.46–1.37 (m, 2 H), 1.32–1.19 (m, 3 H), 1.19–1.04 (m, 2 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.2, 159.1, 148.9, 130.7, 129.1, 128.4, 128.2, 127.7, 126.9, 113.7, 72.9, 72.3, 55.3, 54.1, 50.4, 45.2, 37.9, 34.3, 33.1,

29.4, 26.4, 23.9, 23.2, 20.9; HRMS (Mixed+) calcd for $C_{31}H_{42}NO_4^+$ [M + H^+] 492.3108, found 492.3111.

Compound 209. To a solution of **208** (23mg, 0.047 mmol, 1.0 equiv) in MeOH (1 mL) was added Triton-B (40% in MeOH, 0.11 mL, 0.234 mmol, 5.0 equiv). The reaction was then stirred at 70 °C for 40 h. After the flask was cooled down to 23 °C, the solvent was removed by evaporation and half-saturated aqueous NH_4Cl solution (3 mL) and Et_2O (2 mL) were added. The aqueous layer was extracted with Et_2O (2 mL × 2). The combined organic layers were dried ($MgSO_4$), filtered, concentrated, and purified by thin layer chromatography (silica gel, hexanes/EtOAc, 3/1) to afford product **209** (9.5 mg, 41%) and recovered starting material **208** (4 mg, 17%) along with inseparable impurities. **209**: R_f = 0.54 (silica gel, hexanes/EtOAc, 3/1); IR (film) ν_{max} 2924, 2856, 1732, 1612, 1513, 1454, 1368, 1301, 1247, 1176, 1116, 1035, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.30–7.16 (m, 8 H), 6.87 (d, *J* = 8.5 Hz, 2 H), 4.42 (d, *J* = 11.6 Hz, 1 H), 4.35 (d, *J* = 11.6 Hz, 1 H), 3.84–3.78 (m, 4 H), 3.70 (s, 3 H), 3.46–3.40 (m, 2 H), 3.32 (td, *J* = 12.7, 3.9 Hz, 1 H), 3.19 (dd, *J* = 8.9, 6.7 Hz, 1 H), 2.81 (d, *J* = 13.5 Hz, 1 H), 2.75 (d, *J* = 10.7 Hz, 1 H), 2.72 (dt, *J* = 12.1, 3.5 Hz, 1 H), 2.41 (dd, *J* = 12.2, 4.6 Hz, 1 H), 2.03 (dt, *J* = 12.8, 3.3 Hz, 1 H), 1.70 (d, *J* = 12.9 Hz, 2 H), 1.63 (ddd, *J* = 16.8, 13.6, 7.2 Hz, 2 H), 1.53–1.46 (m, 2 H), 1.45–1.37 (m, 2 H), 1.33–1.18 (m, 4 H), 1.17–1.10 (m, 1 H), 1.00 (td, *J* = 13.5, 3.1 Hz, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.1, 159.1, 141.6, 130.7, 129.1, 128.0, 128.0, 126.5, 113.7, 72.8, 69.8, 60.0, 55.3, 51.6, 47.9, 43.0, 39.4, 38.4, 35.1, 34.9, 34.0, 26.5, 23.2, 20.9, 20.2, 19.8; HRMS (APCI+) calcd for $C_{31}H_{42}NO_4^+$ [M + H^+] 492.3108, found 492.3108.

Compound 192. Incomplete hydrogenation of **190** can generate selective *N*-Bn deprotected product. Treatment of this product with formalin afforded **192** as a colorless gum. **192**: R_f = 0.50 (silica gel, CH_2Cl_2/acetone, 3/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.4 Hz, 2 H), 6.90 (d, *J* = 8.5 Hz, 2 H), 4.48 (d, *J* = 10.4 Hz, 1 H), 4.46–4.41 (m, 2 H), 4.38 (d, *J* = 11.7 Hz, 1 H), 3.91 (dd, *J* = 10.7, 3.8 Hz, 1 H), 3.83 (s, 3 H), 3.41 (dd, *J* = 9.0, 3.3 Hz, 1 H), 3.32–3.22 (m, 2 H), 3.20 (t, *J* = 8.5 Hz, 1 H), 2.67 (dd, *J* = 11.4, 4.2 Hz, 1 H), 2.49 (d, *J* = 12.9 Hz, 1 H), 2.46–2.39 (m, 1 H), 2.29 (d, *J* = 11.0 Hz, 1 H), 1.84–1.72 (m, 2 H), 1.68 (d, *J* = 13.8 Hz, 1 H), 1.64–1.60 (m, 2 H), 1.55–1.46 (m, 2 H), 1.45–1.34 (m, 2 H), 1.32–1.22 (m, 2 H), 1.20–1.12 (m, 2 H), 0.92–0.84 (m, 1 H), 0.81 (dd, *J* = 25.6, 12.8 Hz, 1 H).

(±)-myrioneurinol (6). To a solution of **209** (9.5 mg, 0.019 mmol, 1.0 equiv) in Et_2O (1 mL) was added $LiAlH_4$ (1.0 M in THF, 0.04 mL, 0.038 mmol, 2.0 equiv) dropwise over 1 min at 23 °C. The mixture was then stirred at this temperature for 1 h before water was added carefully to quench the reaction. 2 N NaOH (2 mL) was added and the biphasic mixture was vigorously stirred for 5 min. The aqueous layer was extracted with Et_2O (2 mL × 2). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to give the crude alcohol **190**. Pressing forward without purification, the crude alcohol **190** was loaded in a flask, followed by the addition of Pd/C (10%, 95 mg, 10.0 mass equiv). The flask was back-filled with H_2 twice. 1,1,1-trifluoroethanol (1 mL) was added and the mixture was bubbled with H_2 for 10 min. The reaction was then stirred under 1 atm H_2 atmosphere at 23 °C for 40 h. Upon completion, the reaction was filtered through Celite and the filtrate was concentrated to give the crude deprotected amino alcohol **191**, which was immediately dissolved in THF (1 mL). Formalin (37% HCHO in H_2O, 0.4 mL) was added and the reaction was stirred at 23 °C for 6 h before half-saturated aqueous

$NaHCO_3$ solution was added. The aqueous layer was extracted with Et_2O (2 mL × 2). The combined organic layers were dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography (silica gel, hexanes/acetone, 8/1) and preparative thin layer chromatography (silica gel, CH_2Cl_2/acetone, 1/1) to afford myrioneurinol **6** (2.5 mg, 49% over 3 steps) as a colorless gum. Myrioneurinol **6**: R_f = 0.46 (silica gel, CH_2Cl_2/acetone, 1/1); IR (film) ν_{max} 3420 (br), 2923, 2853, 1597, 1563, 1464, 1386, 1163, 1130, 1031 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.46 (d, *J* = 10.3 Hz, 1 H), 4.41 (d, *J* = 10.3 Hz, 1 H), 3.90 (dd, *J* = 10.7, 4.0 Hz, 1 H), 3.65 (dd, *J* = 10.6, 3.3 Hz, 1 H), 3.49 (dd, *J* = 10.6, 6.0 Hz, 1 H), 3.27 (td, *J* = 13.2, 3.5 Hz,1 H), 3.20 (t, *J* = 10.7 Hz, 1 H), 2.66 (d, *J* = 7.2 Hz, 1 H), 2.49 (d, *J* = 13.0 Hz, 1 H), 2.47–2.41 (m, 1 H), 2.27 (d, *J* = 10.8 Hz, 1 H), 1.82–1.73 (m, 2 H), 1.68 (d, *J* = 13.9 Hz, 1 H), 1.63–1.53 (m, 4 H), 1.52–1.45 (m, 2 H), 1.45–1.33 (m, 2 H), 1.32–1.26 (m, 1 H), 1.20 (dd, *J* = 12.2, 3.3 Hz, 1 H), 1.14 (dd, *J* = 20.0, 8.0 Hz, 1 H), 0.85 (dd, *J* = 14.2, 10.9 Hz, 1 H), 0.79 (q, *J* = 12.2 Hz, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 86.8, 73.6, 69.6, 65.5, 47.8, 45.0, 37.1, 36.4, 34.4, 31.1, 27.3, 26.7, 23.1, 20.4, 20.4, 19.8; (Note: a singlet peak at δ = 3.34 on ^1H NMR and a peak at δ = 29.7 on ^{13}C NMR appeared both in our and Weinreb's spectra, though the two samples came from different synthetic routes. However, both peaks don't belong to myrioneurinol (**6**); HRMS (APCI+) calcd for $C_{16}H_{28}NO_2^+$ $[M + H^+]$ 266.2115, found 266.2113.

Table 4-S1. ^1H NMR Spectral Data Comparison of Myrioneurinol (**6**) From This Work, Weinreb's synthesis, and the Natural sample Reported by Bodo in $CDCl_3$.

Natural **6** ($CDCl_3$, 400 MHz)	Synthetic **6** (this work) ($CDCl_3$, 500 MHz)	Synthetic **6** (Weinreb) ($CDCl_3$, 850 MHz)
4.41 (dd, *J* = 10.3, 1.0 Hz, 1 H)	4.46 (d, *J* = 10.3 Hz, 1 H)	4.47 (d, *J* = 10.2 Hz, 1 H)

Table 4-S1. (Continued)

4.36 (d, *J* = 10.3 Hz, 1 H)	4.41 (d, *J* = 10.3 Hz, 1 H)	4.42 (d, *J* = 10.2 Hz, 1 H)
3.86 (dd, *J* = 10.8, 4.2, 1.0 Hz, 1 H)	3.90 (dd, *J* = 10.7, 4.0 Hz, 1 H)	3.91 (dd, *J* = 11.1, 4.3 Hz, 1 H)
3.59 (dd, *J* = 10.6, 3.5 Hz, 1 H)	3.65 (dd, *J* = 10.6, 3.3 Hz, 1 H)	3.64 (dd, *J* = 11.1, 4.3 Hz, 1 H)
3.42 (dd, *J* = 10.6, 6.0 Hz, 1 H)	3.49 (dd, *J* = 10.6, 6.0 Hz, 1 H)	3.48 (dd, *J* = 10.2, 6.0 Hz, 1 H)
3.27 (dd, *J* = 12.2, 11.0, 4.0 Hz,1 H)	3.27 (td, *J* = 13.2, 3.5 Hz,1 H)	3.28 (td, *J* = 13.6, 4.3 Hz, 1 H)
3.15 (dd, *J* = 10.8, 10.6 Hz, 1 H)	3.20 (t, *J* = 10.7 Hz, 1 H)	3.21 (t, *J* = 11.1 Hz, 1 H)
2.61 (ddd, *J* = 11.0, 4.8, 0.5 Hz, 1 H)	2.66 (d, *J* = 7.2 Hz, 1 H)	2.67 (dd, *J* = 11.9, 5.1 Hz, 1 H)
2.44 (d, *J* = 13.2 Hz, 1 H)	2.49 (d, *J* = 13.0 Hz, 1 H)	2.49 (br d, *J* = 12.8 Hz, 1 H)
2.40 (ddddd, *J* = 12.0, 11.0, 10.6, 4.2, 4.0 Hz, 1 H)	2.47–2.41 (m, 1 H)	2.46 (qt, *J* = 12.8, 4.3 Hz, 1 H)
2.22 (d, *J* = 11.0 Hz, 1 H)	2.27 (d, *J* = 10.8 Hz, 1 H)	2.28 (d, *J* = 11.1 Hz, 1 H)
1.72 (m, 2 H)	1.82–1.73 (m, 2 H)	1.80−1.74 (m, 2 H)
1.63 (ddd, *J* = 13.3, 13.3, 3.0 Hz, 1 H)	1.68 (d, *J* = 13.9 Hz, 1 H)	1.68 (br d, *J* = 13.6 Hz, 1 H)
1.55 (m, 1 H)	1.63–1.53 (m, 4 H)	1.59 (dd, *J* = 12.8, 2.6 Hz, 1 H)
1.50 (m, 2 H)		1.56 (dt, J = 12.8, 3.4 Hz, 2 H)
1.45 (m, 2 H)	1.52–1.45 (m, 2 H)	1.53−1.48 (m, 2 H)
1.32 (m&d, *J* = 13.3 Hz, 2 H)	1.45–1.33 (m, 2 H)	1.45−1.35 (m, 2 H)
1.20 (m, 1 H)	1.32–1.26 (m, 1 H)	1.30−1.24 (m, 2 H)
1.12 (dddd, *J* = 10.5, 10.4, 9.8, 3.5 Hz, 1 H)	1.20 (dd, *J* = 12.2, 3.3 Hz, 1 H)	1.20 (qd, *J* = 12.8, 3.4 Hz, 1 H)

Table 4-S1. (Continued)

1.11 (ddd, *J* = 10.5, 10.5, 3.0 Hz, 1 H)	1.14 (dd, *J* = 20.0, 8.0 Hz, 1 H)	1.14 (td, *J* = 11.1, 2.6 Hz, 1 H)
0.80 (dddd, *J* = 13.2, 13.2, 4.1, 1.0 Hz, 1 H)	0.85 (dd, *J* = 14.2, 10.9 Hz, 1 H)	0.87 (td, *J* = 14.5, 3.4 Hz, 1 H)
0.74 (ddd, *J* = 12.1, 12.0, 12.0 Hz, 1 H)	0.79 (q, *J* = 12.2 Hz, 1 H)	0.80 (q, *J* = 11.9 Hz, 1 H)

Table 4-S2. ^{13}C NMR Spectral Data Comparison of Myrioneurinol (**6**) From This Work, Weinreb's synthesis, and the Natural sample Reported by Bodo in $CDCl_3$.

Natural **6** ($CDCl_3$, 100 MHz)	Synthetic **6** (this work) ($CDCl_3$, 126 MHz)	Synthetic **6** (Weinreb) ($CDCl_3$, 150 MHz)
86.7	86.8	86.8
73.4	73.6	73.6
69.5	69.6	69.6
65.1	65.5	65.4
47.6	47.8	47.7
44.9	45.0	45.0
37.0	37.1	37.1
36.2	36.3	36.3
34.2	34.4	34.4
31.0	31.1	31.1
27.1	27.3	27.2
26.6	26.7	26.7

Table 4-S2. (Continued)

23.0	23.1	23.1
20.4	20.4	20.5
20.4	20.4	20.5
19.7	19.8	19.8

Synthesis of schoberine B

Compound 221. To a flamed-dried flask was added NaH (60% dispersion in mineral oil, 2.49 g, 62.3 mmol, 1.1 equiv). THF (100 mL) was added, followed by the addition of triethyl phosphonoacetate (13.5 mL, 67.9 mmol, 1.2 equiv) in a dropwise manner over 5 min at 0 °C. After the mixture was stirred at 23 °C for 30 min, aldehyde **220** (13.3 g, 56.6 mmol, 1.0 equiv) in THF (20 mL) was added dropwise over 2 min at 0 °C. The reaction was then stirred at 23 °C for 12 h before half-saturated aqueous NH_4Cl solution (100 mL) was added to quench the reaction. The aqueous layer was extracted with Et_2O (30 mL × 2). The combined organic layers were dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography (silica gel, hexanes/acetone, 40/1) to afford **221** (14.5 g, 84%) as a colorless oil. **221**: R_f = 0.50 (silica gel, hexanes/EtOAc, 3/1); IR (film) ν_{max} 2935, 2857, 1718, 1513, 1247, 1173, 1098, 1037, 820 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.4 Hz, 2 H), 6.99–6.90 (m, 1 H), 6.86 (d, *J* = 8.5 Hz, 2 H), 5.80 (d, *J* = 15.6 Hz, 1 H), 4.41 (s, 2 H), 4.17 (q, *J* = 7.1 Hz, 2 H), 3.78 (s, 3 H), 3.42 (t, *J* = 6.5 Hz, 2 H), 2.18 (q, *J* = 7.1 Hz, 2 H), 1.64–1.56 (m, 2 H), 1.46 (dt, *J* = 14.5, 7.1 Hz, 2 H), 1.39 (dd, *J* = 14.9, 8.3 Hz, 2 H), 1.27 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.6, 159.0, 149.0, 130.6, 129.1, 121.3, 113.6, 72.4, 69.7, 60.0, 55.1, 32.0, 29.4, 27.7, 25.7, 14.2; HRMS (ESI+) calcd for $C_{18}H_{26}O_4^+$ [M^+] 306.1826, found 306.1832.

Enal 223. To a solution of **221** (4.00 g, 13.3 mmol, 1.0 equiv) in CH_2Cl_2 (40 mL) was added DIBAL-H (1.0 M in hexanes, 30.5 mL, 30.5 mmol, 2.3 equiv) dropwise over 5 min at -78 °C. The reaction stirred at this temperature for 2 h before MeOH (1.5 mL) was carefully added to quench the reaction. Half saturated aqueous Rochelle salt solution (80 mL) was added and the resulting mixture was vigorously stirred at 23 °C for 12 h. The aqueous layer was extracted with CH_2Cl_2 (20 mL × 3). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to give the allylic alcohol **222** as a colorless oil. Next, the crude alcohol **222** was dissolved in CH_2Cl_2 (100 mL). $NaHCO_3$ (5.57 g, 66.3 mmol, 5.0 equiv) was added, followed by Dess-Martin periodinane (6.75 g, 15.9 mmol, 1.2 equiv) at 0 °C. The reaction was then stirred at 23 °C for 1 h before a mixed aqueous solution of $NaHCO_3$ and $Na_2S_2O_3$ (100 mL) was added to quench the reaction. The aqueous layer was extracted with CH_2Cl_2 (20 mL × 2). The combined organic layers were dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography (silica gel, hexanes/acetone, 20/1) to afford **223** (2.75 g, 79% over 2 steps) as a colorless oil. **223**: R_f = 0.44 (silica gel, hexanes/EtOAc, 3/1); IR (film) ν_{max} 2935, 2858, 1693, 1513, 1248, 1100, 1035, 820 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.50 (d, *J* = 7.9 Hz, 1 H), 7.25 (d, *J* = 8.6 Hz, 2 H), 6.87 (d, *J* = 8.6 Hz, 2 H), 6.86–6.80 (m, 1 H), 6.11 (dd, *J* = 15.6, 7.9 Hz, 1 H), 4.43 (s, 2 H), 3.80 (s, 3 H), 3.44 (t, *J* = 6.4 Hz, 2 H), 2.33 (q, *J* = 6.8 Hz, 2 H), 1.69–1.57 (m, 2 H), 1.52 (dt, *J* = 14.8, 7.3 Hz, 2 H), 1.47–1.37 (m, 2 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 194.0, 159.1, 158.6, 133.0, 130.6, 129.2, 113.7, 72.6, 69.7, 55.2, 32.6, 29.4, 27.6, 25.8; HRMS (Mixed+) calcd for $C_{16}H_{23}O_3^+$ [M + H^+] 263.1642, found 263.1636.

Chiral enone 219. To a flask loaded with **223** (2.75 g, 10.5 mmol, 1.0 equiv) was added *t*-butyl acetoacetate (3.48 mL, 21.0 mmol, 2.0 equiv). Catalyst **224** (1.25 g, 2.10 mmol, 0.2 equiv) was added and the reaction was stirred at 23 °C for 18 h. PhMe (50 mL) and *p*-TsOH·H_2O (599 mg, 3.14 mmol, 0.3 equiv) were then added. The mixture was stirred at 80 °C for 16 h. After cooling to 23 °C, half-saturated aqueous $NaHCO_3$ solution (30 mL) was added. The aqueous layer was extracted with EtOAc (10 mL × 2). The combined organic layers were dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography (silica gel, hexanes/acetone, 30/1 to 20/1) to afford **219** (1.39 g, 44%, with inseparable impurity) as a yellowish oil. **219**: R_f = 0.38 (silica gel, hexanes/EtOAc, 3/1); Selected identifiable peaks from ^{1}H NMR spectra: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.6 Hz, 2 H), 6.96 (ddd, *J* = 9.9, 5.6, 2.2 Hz, 1 H), 6.88 (d, *J* = 8.6 Hz, 2 H), 6.01 (d, *J* = 9.2 Hz, 1 H), 4.43 (s, 2 H), 3.80 (s, 3 H), 3.43 (t, *J* = 6.5 Hz, 2 H), 2.51 (d, *J* = 12.8 Hz, 1 H), 2.43 (dd, *J* = 15.8, 4.7 Hz, 1 H); HRMS (APCI+) calcd for $C_{19}H_{26}NaO_3^+$ [M + Na^+] 325.1774, found 325.1774. Enantiomeric excess value was measured on derivative **228**.

Compound 228. To a flamed dried flask was added CuBr·SMe_2 (946 mg, 4.62 mmol, 1.0 equiv) and LiCl (198 mg, 40.0 mmol, 2.0 equiv), followed by THF (12 mL). The mixture was stirred at 23 °C for 5 min before the suspension turned homogeneous. The flask was then cooled down to -78 °C and allylmagnesium bromide (1.0 M in Et_2O, 9.2 mL, 9.24 mmol, 2.0 equiv) was added dropwise over 3 min. The resultant dark brownish suspension was then stirred at -78 °C for 30 min. A pre-mixed solution of **219** (1.40 g, 4.62 mmol, 1.0 equiv) and TMSCl (0.87 mL, 6.92 mmol, 1.5 equiv) in THF (3 mL) was then added at this temperature. The reaction was then allowed to slowly warm up to 23 °C over 8 h before a mixed solution of half-saturated aqueous NH_4Cl solution (15 mL) and 3 N NaOH (8 mL) was added to quench the reaction. The biphasic mixture was vigorously stirred for 30 min before the aqueous layer was extracted with Et_2O (10 mL × 2).

The combined organic layers were dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography (silica gel, hexanes/EtOAc, 60/1) to afford TMS silyl enol ether **227** (1.02 g, 53%) as a colorless oil. Next, to a flame-dried flask was added CsF (1.08 g, 7.31 mmol, 3.0 equiv) and $PhNTf_2$ (1.28 g, 3.65 mmol, 1.5 equiv). A solution of TMS silyl enol ether **227** (1.02 g, 2.44 mmol, 1.0 equiv) in 1,2-dimethoxyethane (5 mL) was added at 23 °C. The reaction was stirred at this temperature for 16 h. Upon completion, the reaction was quenched by the addition of half-saturated aqueous $NaHCO_3$ solution (10 mL). The aqueous layer was extracted with Et_2O (8 mL × 2). The combined organic layers were dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography (silica gel, hexanes/EtOAc, 60/1 to 50/1) to afford **228** (1.07 g, 93%, 22% over 3 steps) as a colorless oil. **228**: R_f = 0.66 (silica gel, hexanes/EtOAc, 3/1); $[\alpha]_D^{25}$ = +25 (*c* = 0.4, $CHCl_3$); IR (film) ν_{max} 2931, 2856, 1739, 1688, 1614, 1514, 1404, 1218, 1142, 1036, 913 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.5 Hz, 2 H), 6.88 (d, *J* = 8.6 Hz, 2 H), 5.80–5.68 (m, 2 H), 5.10–5.01 (m, 2 H), 4.43 (s, 2 H), 3.80 (s, 3 H), 3.44 (t, *J* = 6.5 Hz, 2 H), 2.44–2.34 (m, 2 H), 2.19–2.06 (m, 2 H), 1.99 (dd, *J* = 17.0, 7.6 Hz, 1 H), 1.87 (s, 1 H), 1.65–1.56 (m, 2 H), 1.55–1.48 (m, 1 H), 1.44–1.30 (m, 7 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.1, 148.9, 135.8, 130.8, 129.2, 121.5, 118.5 (q, *J* = 320.2 Hz), 117.0, 113.7, 72.0, 70.0, 55.2, 39.5, 34.6, 33.8, 32.8, 32.0, 30.7, 29.6, 26.8, 26.3; HRMS (ESI+) calcd for $C_{23}H_{31}F_3NaO_5S^+$ [M + Na^+] 499.1735, found 499.1726. The enantiomeric excess value was determined using chiral HPLC (OJ-H column, 99.5:0.5 hexanes/*i*-PrOH, 1 mL/min, UV detector at 254 nm) R_T = 29.8 min (major), R_T = 42.4 min (major), ee = 94%.

Aldehyde 230. To a solution of **228** (1.07 g, 2.26 mmol, 1.0 equiv) in THF (6 mL) was added 9-BBN (0.5 M in THF, 4.73 mL, 4.73 mmol, 1.05 equiv) at 23 °C. The reaction was stirred

at this temperature for 12 h. Then H_2O (2.3 mL) was added and the reaction was cooled down to 0 °C before $NaBO_3 \cdot H_2O$ (558 mg, 5.64 mmol, 2.5 equiv) was added as solid. The reaction was then stirred at 23 °C for 24 h. Upon completion, H_2O (10 mL) was added and the aqueous layer was extracted with Et_2O (8 mL × 2). The combined organic layers were washed by brine, dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography (silica gel, hexanes/acetone, 30/1 to 15/1 to 8/1) to afford **229** (790 mg, 71%) as a colorless oil. Next, to a solution of **229** (790 mg, 1.60 mmol, 1.0 equiv) in CH_2Cl_2 (16 mL) was added $NaHCO_3$ (1.07 g, 12.8 mmol, 8.0 equiv). Dess-Martin periodinane (779 mg, 1.84 mmol, 1.15 equiv) was added as solid at 0 °C. The reaction was then stirred at 23 °C for 1 h. Upon completion, a mixed solution of aqueous $NaHCO_3$ and $Na_2S_2O_3$ (15 mL) was added to quench the reaction. The biphasic mixture was vigorously stirred for 30 min before the aqueous layer was extracted with CH_2Cl_2 (8 mL × 2). The combined organic layers were dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography (silica gel, hexanes/acetone, 30/1) to afford **230** (674 mg, 86%) as a colorless oil. **230**: R_f = 0.46 (silica gel, hexanes/EtOAc, 3/1); $[\alpha]_D^{25}$ = +30 (*c* = 0.3, $CHCl_3$); IR (film) ν_{max} 2932, 2857, 1726, 1613, 1514, 1414, 1246, 1213, 1143, 1098, 1036, 906, 612 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.78 (s, 1 H), 7.26 (d, *J* = 5.4 Hz, 2 H), 6.87 (d, *J* = 7.7 Hz, 2 H), 5.67 (s, 1 H), 4.43 (s, 2 H), 3.80 (s, 3 H), 3.43 (t, *J* = 6.3 Hz, 2 H), 2.50 (t, *J* = 7.4 Hz, 2 H), 2.37 (dd, *J* = 17.2, 4.6 Hz, 2 H), 1.99 (dd, *J* = 16.8, 7.4 Hz, 1 H), 1.86 (s, 1 H), 1.78–1.64 (m, 2 H), 1.63–1.56 (m, 2 H), 1.49–1.41 (m, 2 H), 1.38–1.29 (m, 6 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 201.3, 159.2, 149.4, 130.8, 129.2, 120.9, 118.5 (q, *J* = 320.6 Hz), 113.8, 72.6, 70.0, 55.3, 41.5, 34.7, 33.8, 32.4, 32.2, 30.7, 29.7, 27.1, 26.7, 26.3; HRMS (APCI+) calcd for $C_{23}H_{31}F_3NaO_6S^+$ [M + Na^+] 515.1686, found 515.1684.

Compound 231. To a solution of **230** (674 mg, 1.37 mmol, 1.0 equiv) in MeOH (6 mL) was added Et_3N (0.74 mL, 5.47 mmol, 4.0 equiv) and PPh_3 (72 mg, 0.274 mmol, 0.2 equiv) at room temperature. The mixture was stirred until PPh_3 fully dissolved. CO gas was then bubbled through the solution for 3 min. $Pd(OAc)_2$ (31 mg, 0.137 mmol, 0.09 equiv) was added as solid and the reaction was stirred under 1 atm CO atmosphere for 8 h at 23 °C. Upon completion, MeOH was removed by evaporation. Half-saturated NH_4Cl solution (10 mL) and Et_2O (8 mL) was then added. The aqueous layer was extracted with Et_2O (8 mL × 2). The combined organic layers were dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography (silica gel, hexanes/acetone, 30/1 to 20/1) to afford **231** (455 mg, 83%) as a colorless oil. **231**: R_f = 0.44 (silica gel, hexanes/EtOAc, 3/1); $[\alpha]_D^{25}$ = +56 (*c* = 0.8, $CHCl_3$); IR (film) ν_{max} 2930, 2855, 1714, 1612, 1513, 1435, 1248, 1173, 1098, 1035, 821, 744 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.79 (t, *J* = 1.4 Hz, 1 H), 7.26 (d, *J* = 8.5 Hz, 2 H), 6.86 (dd, *J* = 13.9, 7.4 Hz, 3 H), 4.43 (s, 2 H), 3.80 (s, 3 H), 3.73 (s, 3 H), 3.43 (t, *J* = 6.6 Hz, 2 H), 2.53 (td, *J* = 7.6, 1.2 Hz, 2 H), 2.42 (dd, *J* = 17.7, 4.6 Hz, 1 H), 2.29 (d, *J* = 2.1 Hz, 1 H), 1.89–1.80 (m, 1 H), 1.76 (td, *J* = 14.5, 7.4 Hz, 1 H), 1.66 (dt, *J* = 20.8, 7.2 Hz, 2 H), 1.60 (dd, *J* = 12.2, 5.2 Hz, 2 H), 1.46 (dt, *J* = 12.9, 3.3 Hz, 1 H), 1.43–1.37 (m, 1 H), 1.37–1.30 (m, 3 H), 1.30–1.23 (m, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 201.8, 167.9, 159.1, 141.5, 130.8, 130.1, 129.2, 113.7, 72.5, 70.1, 55.2, 51.6, 41.7, 35.2, 33.5, 32.7, 30.6, 29.7, 29.5, 27.1, 26.8, 26.4; HRMS (ESI+) calcd for $C_{24}H_{34}NaO_5^+$ [M + Na^+] 425.2298, found 425.2294.

Compound 218. To a solution of **231** (455 mg, 1.12 mmol, 1.0 equiv) in CH_2Cl_2 (6 mL) was added $BnNH_2$ (0.18 mL, 1.69 mmol, 1.5 equiv). The mixture was stirred at 23 °C for 1 h before $NaBH(OAc)_3$ (310 mg, 1.46 mmol, 1.3 equiv) was added as solid. The reaction was then stirred at 23 °C for 8 h before half-saturated $NaHCO_3$ solution (10 mL) was added to quench the reaction.

The aqueous layer was extracted with CH_2Cl_2 (5 mL × 2). The combined organic layers were dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography (silica gel, hexanes/acetone, 10/1 to 5/1 to 2/1) to afford **218** (395 mg, 71%) as a light yellowish oil. **218**: R_f = 0.14, tailing (silica gel, hexanes/acetone, 1/1); $[\alpha]_D^{25}$ = +53 (*c* = 0.8, $CHCl_3$); IR (film) ν_{max} 2930, 2854, 1713, 1612, 1513, 1454, 1435, 1248, 1173, 1099, 1036, 821, 743, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37–7.28 (m, 5 H), 7.26 (d, *J* = 8.4 Hz, 2 H), 6.94–6.89 (m, 1 H), 6.87 (d, *J* = 8.6 Hz, 2 H), 4.43 (s, 2 H), 3.80 (s, 3 H), 3.79 (s, 2 H), 3.72 (s, 3 H), 3.43 (t, *J* = 6.6 Hz, 2 H), 2.64 (t, *J* = 7.1 Hz, 2 H), 2.41 (dd, *J* = 17.6, 4.5 Hz, 1 H), 2.26 (s, 1 H), 1.82 (dd, *J* = 17.6, 8.1 Hz, 1 H), 1.67–1.53 (m, 6 H), 1.51–1.44 (m, 2 H), 1.41–1.30 (m, 6 H), 1.29–1.22 (m, 2 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.2, 159.1, 143.0, 140.4, 130.8, 129.2, 129.2, 128.4, 128.1, 126.9, 113.7, 72.5, 70.1, 55.2, 54.0, 51.5, 49.5, 35.4, 34.2, 32.9, 32.8, 30.7, 29.7, 29.6, 28.0, 26.9, 26.4; HRMS (APCI+) calcd for $C_{31}H_{44}NO_4^+$ [M + H^+] 494.3265, found 494.3264.

Mesylate 234. To a solution of **218** (395 mg, 0.80 mmol, 1.0 equiv) in MeOH (2 mL) was added NaOMe (0.5 M in MeOH, 8.00 mL, 4.00 mmol, 5.0 equiv). The reaction was stirred at 50 °C for 40 h before solvent was removed by evaporation. Half-saturated NH_4Cl solution (10 mL) was added to quench the reaction. The aqueous layer was extracted with Et_2O (6 mL × 3). The combined organic layers were washed by brine, dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography (silica gel, hexanes/EtOAc, 25/1) to afford an inseparable mixture of **232** and **217** (186 mg, 48% combined) as a light yellowish oil. Next, to a solution of **232** and **217** (186 mg, 0.377 mmol, 1.0 equiv) in Et_2O (3 mL) was added $LiAlH_4$ (1.0 M in THF, 0.38 mL, 0.377 mmol, 1.0 equiv) dropwise at 23 °C. The reaction was then stirred at this temperature for 2 h before water was added carefully to quench the reaction. 2 N NaOH (3 mL)

was added and the biphasic mixture was vigorously stirred for 5 min. The aqueous layer was extracted with Et_2O (3 mL × 3). The combined organic layers were washed by brine, dried ($MgSO_4$), filtered, and concentrated to give the crude diastereomeric mixture of alcohols. Next, to a solution of alcohol in CH_2Cl_2 (3 mL) was added Et_3N (0.10 mL, 0.75 mmol, 2.0 equiv) and MsCl (0.04 mL, 0.452 mmol, 1.2 equiv) sequentially at 23 °C. The reaction was stirred at this temperature for 2 h before half-saturated $NaHCO_3$ solution (5 mL) was added to quench the reaction. The aqueous layer was extracted with CH_2Cl_2 (3 mL × 2). The combined organic layers were dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography (silica gel, hexanes/acetone, 25/1 to 15/1) to afford **234** (67 mg, 32% over 2 steps) as a colorless gum, then **233** (64 mg, 31% over 2 steps) as a colorless gum. Analytically pure samples of **234** and **233** were obtained by further purification from preparative thin layer chromatography (silica gel, hexanes/EtOAc, 2/1). **234**: R_f = 0.28 (silica gel, hexanes/EtOAc, 3/1); $[\alpha]_D^{25}$ = –26 (*c* = 0.1, $CHCl_3$); IR (film) ν_{max} 2927, 2855, 1513, 1356, 1247, 1175, 1098, 1035, 951, 820, 743, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34–7.28 (m, 5 H), 7.26 (d, *J* = 8.5 Hz, 2 H), 6.88 (d, *J* = 8.6 Hz, 2 H), 4.53 (dd, *J* = 9.2, 2.9 Hz, 1 H), 4.43 (s, 2 H), 4.06 (dd, *J* = 9.1, 6.8 Hz, 1 H), 3.90 (d, *J* = 13.5 Hz, 1 H), 3.80 (s, 3 H), 3.77 (d, *J* = 13.5 Hz, 1 H), 3.42 (t, *J* = 6.6 Hz, 2 H), 2.92 (s, 3 H), 2.83–2.73 (m, 1 H), 2.58 (d, *J* = 14.4 Hz, 1 H), 2.44–2.31 (m, 2 H), 2.21 (d, *J* = 10.8 Hz, 1 H), 1.90 (dd, *J* = 12.8, 2.4 Hz, 1 H), 1.83–1.73 (m, 1 H), 1.72–1.64 (m, 1 H), 1.63–1.50 (m, 4 H), 1.49–1.41 (m, 1 H), 1.35–1.23 (m, 6 H), 1.15–1.10 (m, 1 H), 1.06 (td, *J* = 13.0, 4.8 Hz, 1 H), 0.70 (dd, *J* = 24.1, 12.1 Hz, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.1, 140.4, 130.8, 129.2, 128.7, 128.2, 126.9, 113.7, 73.4, 72.5, 70.1, 60.4, 57.6, 55.3, 44.3, 38.5, 37.0, 37.0, 35.8, 33.7, 30.9, 29.7, 28.8, 26.8, 26.4, 26.2, 20.2; HRMS (Mixed+) calcd for $C_{31}H_{46}NO_5S^+$ [M + H^+] 544.3091, found 544.3083.

Mesylate 233. **233**: R_f = 0.26 (silica gel, hexanes/EtOAc, 3/1); $[\alpha]_D^{25}$ = +28 (*c* = 0.1, $CHCl_3$); IR (film) ν_{max} 2927, 2854, 1513, 1454, 1355, 1247, 1175, 1100, 1034, 953, 928, 819, 742, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35–7.28 (m, 4 H), 7.27 (d, *J* = 8.5 Hz, 2 H), 7.25–7.21 (m, 1 H), 6.88 (d, *J* = 8.6 Hz, 2 H), 4.44 (s, 2 H), 4.39 (dd, *J* = 9.6, 2.7 Hz, 1 H), 4.23 (dd, *J* = 9.6, 6.9 Hz, 1 H), 3.80 (s, 3 H), 3.75 (d, *J* = 14.0 Hz, 1 H), 3.71 (d, *J* = 13.9 Hz, 1 H), 3.45 (t, *J* = 6.6 Hz, 2 H), 2.93 (s, 3 H), 2.84 (d, *J* = 13.8 Hz, 1 H), 2.52 (t, *J* = 12.7 Hz, 1 H), 2.35 (t, *J* = 10.9 Hz, 1 H), 2.18–2.08 (m, 1 H), 1.86 (d, *J* = 13.2 Hz, 2 H), 1.74 (d, *J* = 10.6 Hz, 3 H), 1.66–1.58 (m, 2 H), 1.57– 1.52 (m, 2 H), 1.46 (td, *J* = 12.9, 4.4 Hz, 1 H), 1.41–1.34 (m, 3 H), 1.34–1.27 (m, 2 H), 1.19–1.07 (m, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.1, 139.9, 130.8, 129.2, 128.4, 128.3, 113.8, 72.8, 72.6, 70.2, 66.5, 55.3, 50.2, 47.8, 37.0, 36.7, 33.8, 33.2, 32.8, 31.6, 29.8, 27.8, 27.2, 26.4, 18.6; HRMS (APCI+) calcd for $C_{31}H_{46}NO_5S^+$ [M + H^+] 544.3091, found 544.3083.

Lactam 216. To a solution of **234** (67 mg, 0.123 mmol, 1.0 equiv) in DMSO (1 mL) was added δ-valerolactam (37 mg, 0.370 mmol, 3.0 equiv) and NaH (60% dispersion in mineral oil, 25 mg, 0.615 mmol, 5.0 equiv) sequentially at 23 °C. The reaction was then stirred at 45 °C for 12 h before half-saturated NH_4Cl solution (3 mL) was added to quench the reaction. The aqueous layer was extracted with Et_2O (2 mL × 3). The combined organic layers were washed by brine, dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography (silica gel, hexanes/acetone, 10/1 to 0/1) to afford **216** (40 mg, 60%) as a colorless gum. **216**: R_f = 0.16, tailing (silica gel, acetone); $[\alpha]_D^{25}$ = –14 (*c* = 0.5, $CHCl_3$); IR (film) ν_{max} 2928, 2856, 1641, 1613, 1513, 1493, 1464, 1451, 1353, 1247, 1172, 1098, 1036, 743, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34–7.27 (m, 4 H), 7.26 (d, *J* = 8.5 Hz, 2 H), 7.24–7.19 (m, 1H), 6.87 (d, *J* = 8.6 Hz, 2 H), 4.42 (s, 2 H), 3.91 (d, *J* = 13.6 Hz, 1 H), 3.80 (s, 3 H), 3.77 (d, *J* = 13.6 Hz, 1 H), 3.68 (dd, *J* = 13.4,

3.3 Hz, 1 H), 3.42 (t, *J* = 6.7 Hz, 2 H), 3.35–3.28 (m, 1 H), 3.22 (dd, *J* = 13.4, 10.3 Hz, 1 H), 3.18 (d, *J* = 12.1 Hz, 1 H), 2.87 (t, *J* = 13.4 Hz, 1 H), 2.54 (d, *J* = 14.3 Hz, 1 H), 2.38 (s, 2 H), 2.35–2.26 (m, 1 H), 2.22–2.12 (m, 1 H), 1.84–1.75 (m, 5 H), 1.73 (dd, *J* = 13.1, 3.2 Hz, 1 H), 1.67 (dd, *J* = 13.0, 2.1 Hz, 1 H), 1.61–1.54 (m, 2 H), 1.51 (d, *J* = 12.2 Hz, 1 H), 1.45–1.34 (m, 2 H), 1.32–1.20 (m, 6 H), 1.17–1.04 (m, 2 H), 1.01 (dd, *J* = 12.8, 4.6 Hz, 1 H), 0.57 (q, *J* = 12.1 Hz, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.9, 159.1, 140.8, 130.8, 129.2, 128.7, 128.1, 126.7, 113.7, 72.5, 70.2, 63.4, 57.6, 55.3, 51.1, 48.9, 44.0, 38.5, 37.2, 36.9, 32.4, 31.8, 31.2, 29.8, 29.0, 26.8, 26.4, 23.4, 21.5, 20.1; HRMS (ESI+) calcd for $C_{35}H_{51}N_2O_3^+$ [M + H^+] 547.3894, found 547.3896.

(–)-schoberine B (7). To a flask loaded with 235 (28 mg, 0.051 mmol, 1.0 equiv) was added Pd/C (10%, 140 mg, 5.0 mass equiv). The flask was back-filled with H_2 twice. 1,1,1-trifluroethanol (1.5 mL) was added and the mixture was bubbled through H_2 for 10 min. The reaction was then stirred at 23 °C for 40 h (Cease of reaction for NMR analysis to determine completion may be needed). Upon completion, the reaction was filtered through Celite and the filtrate was concentrated to give the crude deprotected product **235**, which was immediately dissolved in THF (1 mL). DIBAL-H (1.0 in THF, 0.10 mL, 0.10 mmol, 2.0 equiv) was added and the reaction was stirred at 23 °C for 8 h before half-saturated NH_4Cl solution (3 mL) was added to quench the reaction. The aqueous layer was extracted with Et_2O (2 mL × 3). The combined organic layers were washed by brine, dried ($MgSO_4$), filtered, concentrated, and purified by preparative thin layer chromatography (silica gel, CH_2Cl_2/acetone, 1/1) to afford schoberine B **4** (5 mg, 33% over 2 steps) as a colorless gum. Schoberine B (**4**): R_f = 0.34 (silica gel, CH_2Cl_2/acetone, 1/1); $[\alpha]_D^{25}$ = –10 (*c* = 0.2, MeOH) (reported: $[\alpha]_D^{24}$ = –12 (*c* = 0.3, MeOH)); IR (film) ν_{max} 3354 (br), 2926, 2853, 2750, 1452, 1392, 1377, 1359, 1183, 1129, 1088, 1047, 735 cm^{-1}; ^{1}H NMR (500 MHz, Pyr)

δ 3.92 (t, *J* = 6.4 Hz, 2 H), 2.97–2.85 (m, 3 H), 2.80 (d, *J* = 10.5 Hz, 1 H), 2.75 (d, *J* = 11.2 Hz, 1 H), 2.51 (dd, *J* = 10.7, 4.0 Hz, 1 H), 2.26–2.13 (m, 1 H), 2.02–1.92 (m, 1 H), 1.88–1.76 (m, 3 H), 1.76–1.58 (m, 6 H), 1.57–1.45 (m, 7 H), 1.44–1.33 (m, 3 H), 1.32–1.21 (m, 2 H), 1.18–1.10 (m, 3 H), 0.47 (dd, *J* = 23.9, 12.0 Hz, 1 H). ^{13}C NMR (126 MHz, Pyr) δ 83.3, 66.1, 64.7, 62.6, 56.8, 40.7, 39.4, 38.1, 37.7, 36.4, 34.2, 31.9, 30.6, 27.7, 27.3, 27.3, 27.2, 26.4, 26.4, 25.6; HRMS (APCI+) calcd for $C_{20}H_{37}N_2O^+$ [M + H^+] 321.2900, found 321.2902.

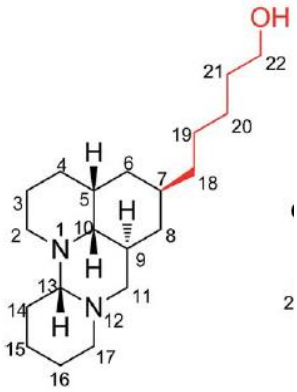


Table 4-S3. ^{1}H and ^{13}C NMR Spectral Data Comparison of Schoberine B (**4**) From This Work and the Natural sample Reported by Hao in d_5-pyridine at 313 K.

H/C #	Natural **4** (^{1}H NMR, d_5-pyridine, 600 MHz)	Synthetic **4** (^{1}H NMR, d_5-pyridine, 500 MHz)	Natural **4** (^{13}C NMR, d_5-pyridine, 150 MHz)	Synthetic **4** (^{13}C NMR, d_5-pyridine, 126 MHz)
2	2.92 (m)	2.97–2.85 (m, 3 H), 2.97–2.85 (m, 3 H)	40.7	40.7
3	1.69 (m), 1.58 (m)	1.76–1.58 (m, 6 H), 1.57–1.45 (m, 7 H),	27.2	27.3

Table 4-S3. (Continued)

4	1.69 (m), 1.28 (m)	1.76–1.58 (m, 6 H), 1.32–1.21 (m, 2 H)	26.3	26.4
5	1.97 (m)	2.02–1.92 (m, 1 H)	36.4	36.4
6	1.55 (m), 1.13 (m)	1.57–1.45 (m, 7 H), 1.18–1.10 (m, 3 H)	39.3	39.4
7	1.40 (m)	1.44–1.33 (m, 3 H)	31.8	31.9
8	1.47 (m), 0.46 (q, 12.0)	1.57–1.45 (m, 7 H), 0.47 (dd, *J* = 23.9, 12.0 Hz, 1 H)	37.6	37.7
9	2.19 (m)	2.26–2.13 (m, 1 H)	27.1	27.2
10	2.52 (dd, 10.8, 4.8)	2.51 (dd, *J* = 10.7, 4.0 Hz, 1 H)	66.0	66.1
11	2.81 (dd, 10.8, 3.6), 1.68 (m)	2.80 (d, *J* = 10.5 Hz, 1 H), 1.76–1.58 (m, 6 H)	64.6	64.7
13	2.92 (m)	2.97–2.85 (m, 3 H)	83.3	83.3

Table 4-S3. (Continued)

14	1.75 (m), 1.68 (m)	1.76–1.58 (m, 6 H), 1.76–1.58 (m, 6 H)	30.5	30.6
15	1.70 (m), 1.25 (m)	1.76–1.58 (m, 6 H), 1.32–1.21 (m, 2 H)	25.5	25.6
16	1.52 (m), 1.46 (m)	1.57–1.45 (m, 7 H), 1.57–1.45 (m, 7 H)	26.3	26.4
17	2.78 (d, 11.4), 1.86 (td, 12.0, 2.4)	2.75 (d, *J* = 11.2 Hz, 1 H), 1.88–1.76 (m, 3 H)	56.8	56.8
18	1.13 (m)	1.18–1.10 (m, 3 H), 1.18–1.10 (m, 3 H)	38.1	38.1
19	1.35 (m)	1.44–1.33 (m, 3 H), 1.44–1.33 (m, 3 H)	27.7	27.7
20	1.52 (m)	1.57–1.45 (m, 7 H), 1.57–1.45 (m, 7 H)	27.3	27.3
21	1.80 (m)	1.88–1.76 (m, 3 H), 1.88–1.76 (m, 3 H)	34.2	34.2

Table 4-S3. (Continued)

22	3.92 (t, 6.0)	3.92 (t, 6.4)	62.6	62.6

Synthetic studies toward myrobotinol (model study)

Alcohol 245. To a solution of **30** (101 mg, 0.596 mmol, 1.0 equiv) in CH_2Cl_2 (2 mL) was added 6 N NaOH (0.30 mL, 1.79 mmol, 3.0 equiv) at 23 °C, followed by TsCl (136 mg, 0.715 mmol, 1.2 equiv) as solid. The biphasic mixture was then vigorously stirred at 23 °C for 12 h. Upon completion, H_2O (2 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (2 mL × 2). The combined organic layers were dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography (silica gel, hexanes/acetone, 20/1 to 10/1) to afford **245** (99 mg, 51%) as a colorless solid. **245**: R_f = 0.18 (silica gel, hexanes/EtOAc, 3/1); IR (film) ν_{max} 3528 (br), 2931, 2869, 1598, 1449, 1395, 1324, 1304, 1190, 1147, 1090, 975, 745, 660, 588 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.1 Hz, 2 H), 7.28 (d, *J* = 8.0 Hz, 2 H), 3.96–3.85 (m, 2 H), 3.82 (dd, *J* = 11.6, 4.7 Hz, 1 H), 3.42–3.34 (m, 1 H), 2.99–2.89 (m, 2 H), 2.40 (s, 3 H), 1.84 (td, *J* = 11.9, 2.4 Hz, 1 H), 1.70 (d, *J* = 13.4 Hz, 1 H), 1.60 (qd, *J* = 13.2, 3.5 Hz, 1 H), 1.50 (qd, *J* = 12.8, 2.9 Hz, 1 H), 1.47–1.38 (m, 4 H), 1.37–1.29 (m, 2 H), 1.22–1.16 (m, 1 H), 1.08 (qt, *J* = 13.2, 4.1 Hz, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.1, 138.8, 129.8, 126.6, 63.1, 55.8, 40.8, 35.7, 33.9, 31.4, 28.6, 24.3, 24.0, 21.4, 20.1; HRMS (APCI+) calcd for $C_{17}H_{26}NO_3S^+$ [M + H^+] 324.1628, found 324.1633.

Aldehyde 246. To a solution of **245** (95 mg, 0.294 mmol, 1.0 equiv) in CH_2Cl_2 (3 mL) was added $NaHCO_3$ (197 mg, 2.35 mmol, 8.0 equiv) and Dess-Martin periodinane (150 mg, 0.353 mmol, 1.2 equiv) sequentially at 23 °C. The mixture was stirred at this temperature for 1 h before

a mixed aqueous solution of $NaHCO_3$ and $Na_2S_2O_3$ was added to quench the reaction. The aqueous layer was extracted with CH_2Cl_2 (2 mL × 2). The combined organic layers were dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography (silica gel, hexanes/acetone, 30/1 to 15/1) to afford **246** (79 mg, 84%) as a white solid. **246**: R_f = 0.28 (silica gel, hexanes/EtOAc, 3/1); IR (film) ν_{max} 2928, 2862, 1725, 1598, 1335, 1166, 1150, 1091, 975, 744, 659 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.53 (d, *J* = 4.1 Hz, 1 H), 7.69 (d, *J* = 8.2 Hz, 2 H), 7.28 (d, *J* = 8.0 Hz, 2 H), 4.28 (dd, *J* = 11.8, 4.4 Hz, 1 H), 3.77 (dd, *J* = 14.9, 3.3 Hz, 1 H), 3.00–2.91 (m, 1 H), 2.68 (tt, *J* = 11.9, 3.9 Hz, 1 H), 2.40 (s, 3 H), 1.84–1.76 (m, 1 H), 1.70–1.62 (m, 1 H), 1.59 (dd, *J* = 13.0, 3.6 Hz, 1 H), 1.56–1.45 (m, 4 H), 1.41 (dd, *J* = 12.6, 2.9 Hz, 1 H), 1.38–1.33 (m, 1 H), 1.33 – 1.27 (m, 1 H), 1.22 (qd, *J* = 13.2, 4.2 Hz, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 203.5, 143.3, 138.4, 129.7, 127.0, 54.8, 46.8, 40.7, 33.5, 30.8, 26.4, 24.1, 23.8, 21.4, 18.6; HRMS (ESI+) calcd for $C_{17}H_{23}NNaO_3S^+$ [M + Na^+] 344.1291, found 344.1289.

Dimer 248. To a solution of **246** (39 mg, 0.121 mmol, 1.0 equiv) and **30** (31 mg, 0.182 mmol, 1.5 equiv) in PhMe (1.5 mL) was added *p*-TsOH·H_2O (3 mg, 0.018 mmol, 0.15 equiv) at 23 °C. The mixture was then stirred at 80 °C for 20 h. Upon cooled down to 23 °C, half-saturated aqueous $NaHCO_3$ solution was added to quench the reaction. The aqueous layer was extracted with EtOAc (2 mL × 2). The combined organic layers were dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography (silica gel, hexanes/acetone, 25/1) to afford recovered starting material **246** (19 mg, 49%) and then (hexanes/acetone, 10/1) to afford dimer **248** (12 mg, 21%) as a white solid. Furthur removal of impurities in **248** was realized by iterative thin layer chromatography (silica gel, hexanes/EtOAc, 1/1) to yield a cleaner sample of **248**. **248**: R_f = 0.14, tailing (silica gel, hexanes/EtOAc, 3/1); IR (film) ν_{max} 2925, 2862, 1598, 1448, 1381,

1335, 1303, 1175, 1152, 1124, 1091, 1026, 975, 745, 659 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.2 Hz, 2 H), 7.28 (d, *J* = 8.0 Hz, 2 H), 4.42 (s, 1 H), 3.92–3.75 (m, 3 H), 3.11 (t, *J* = 10.8 Hz, 1 H), 3.03 (t, *J* = 13.1 Hz, 1 H), 2.78 (t, *J* = 10.6 Hz, 1 H), 2.68 (td, *J* = 11.5, 3.5 Hz, 2 H), 2.41 (s, 3 H), 2.11–2.00 (m, 2 H), 1.91 (d, *J* = 8.1 Hz, 1 H), 1.80 (d, *J* = 9.1 Hz, 1 H), 1.76–1.68 (m, 4 H), 1.62–1.50 (m, 4 H), 1.49–1.42 (m, 2 H), 1.42–1.27 (m, 7 H), 1.21 (d, *J* = 10.8 Hz, 2 H), 0.71 (qd, *J* = 12.3, 3.0 Hz, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.6, 139.8, 129.6, 126.9, 91.4, 73.4, 64.5, 58.4, 41.0, 40.1, 36.9, 35.0, 34.9, 31.7, 31.3, 29.3, 27.6, 27.3, 27.3, 26.1, 24.6, 24.3, 21.5, 20.4, 20.2; HRMS (ESI+) calcd for $C_{27}H_{23}N_2NaO_3S^+$ [M + Na^+] 495.2652, found 495.2662.

4.9 Reference

[1] V. C. Pham, A. Jossang, A. Chiaroni, T. Sévenet, B. Bodo, *Tetrahedron Lett*. **2002**, *43*, 7565.

[2] V. C. Pham, A. Jossang, P. Grellier, T. Sévenet, V. H. Nguyen, B. Bodo, *J. Org. Chem.* **2008**, *73*, 7565.

[3] B. Tashkhodzhaev, A. A. Ibragimov, B. T. Ibragimov, S. Y. Yunusov, *Khim. Prir. Soedin*. **1989**, *32*, 30.

[4] T. S. Tulyagalov, *Chem. Nat. Compd*. **1993**, *29*, 31 Engl. transl. of Khim. Prir. Soedin. 1993, 1, 39.

[5] M. Y. Shen, J. A. Zuanazzi, C. Kan, J. C. Quirion, H. P. Husson, I. R. C. Bick, *Nat. Prod. Lett*. **1995**, *6*, 119.

[6] M. -M. Cao, Y. Zhang, Z. -G. Peng, J. -D. Jiang, Y. -J. Gao, X. -J. Hao, *RSC Adv*. **2016**, *6*, 10180.

[7] V. C. Pham, A. Jossang, A. Chiaroni, T. Sévenet, V. H. Nguyen, B. Bodo, *Org. Lett*. **2007**, *9*, 3531.

[8] V. C. Pham, A. Jossang, T. Sévenet, V. H. Nguyen, B. Bodo, *Tetrahedron* **2007**, *63*, 11244.

[9] V. C. Pham, A. Jossang, T. Sévenet, V. H. Nguyen, B. Bodo, *J. Org. Chem*. **2007**, *72*, 9826.

[10] M. -M. Cao, Y. Zhang, S. -D. Huang, Y. -T. Di, Z. -G. Peng, J. -D. Jiang, C. -M. Yuan, D. -Z. Chen, S. -L. Li, H. -P. He, X. -J. Hao, *J. Nat. Prod.* **2015**, *78*, 2609.

[11] S. -D. Huang, Y. Zhang, M. -M. Cao, Y. -T. Di, G. -H. Tang, Z. -G. Peng, J. -D. Jiang, H. -P. He and X. -J. Hao, *Org. Lett*. **2013**, *15*, 590.

[12] M. -M. Cao, S. -D. Huang, Y. -T. Di, C. -M. Yuan, G. -Y. Zuo, Y. -C. Gu, Y. Zhang and X. -J. Hao, *Org. Lett*. **2014**, *16*, 528.

[13] X. -H. Li, Y. Zhang, J. -H. Zhang, X. -N. Li, M. -M. Cao, Y. -T. Di, Z. -G. Peng, J. -D. Jiang, X. -J. Hao, *J. Nat. Prod*. **2016**, *79*, 1203.

[14] M. -M. Cao, Y. Zhang, X. -H. Li, Z. -G. Peng, J. -D. Jiang, Y. -C. Gu, Y. -T. Di, X. -N. Li, D. -Z. Chen, C. -F. Xia, H. -P. He, S. -L. Li, X. -J. Hao, *J. Org. Chem*. **2014**, *79*, 7945.

[15] D. Song, Z. Wang, R. Mei, W. Zhang, D. Ma, D. Xu, X. Xie, X. She, *Org. Lett*. **2016**, *18*, 669.

[16] J. -H. Zhang, J. -J. Guo, Y. -X. Yuan, Y. -C. Gu, Y. Zhang, D. -Z. Chen, S. -L. Li, Y. -T. Di, X. -J. Hao, *Fitoterapia*, **2016**, *112*, 217.

[17] E. Gravel, E. Poupon, *Nat. Prod. Rep*. **2010**, *27*, 32.

[18] E. Poupon, E. Gravel, *Chem. Eur. J.* **2015**, *21*, 10604.

[19] N. Y. Novgorodova, S. K. Maekh, S. Y. Yunusov, *Khim. Prir. Soedin*. **1973**, *2*, 196.

[20] T. A. Crabb, C. H. Turner, *J. Chem. Soc., Perkin Trans. 2* **1980**, 1778.

[21] A. J. M. Burrell, I. Coldham, N. Oram, *Org. Lett*. **2009**, *11*, 1515.

[22] A. J. Nocket, S. M. Weinreb, *Angew. Chem. Int. Ed*. **2014**, *53*, 14162.

[23] A. J. Nocket, Y. Feng, S. M. Weinreb, *J. Org. Chem*. **2015**, *80*, 1116.

[24] N. Y. Novgorodova, S. K. Maekh, S. Y. Yunusov, *Chem. Nat. Compd*. **1975**, *11*, 455.

[25] A. B. Smith, III, E. G. Nolen, Jr., R. Shirai, F. R. Blase, M. Ohta, N. Chida, R. A. Hartz, D. M. Fitch, W. M. Clark, P. A. Sprengeler, *J. Org. Chem*. **1995**, *60*, 7837.

[26] F. Peng, R. E. Grote, R. M. Wilson, S. J. Danishefsky, *Proc. Natl. Acad. Sci*. **2013**, *110*, 10904.

[27] J. H. Lee, Y. Zhang, S. J. Danishefsky, *J. Am. Chem. Soc*. **2012**, *132*, 14330.

[28] M. A. Kacprzynski, T. L. May, S. A. Kazane, A. H. Hoveyda, *Angew. Chem. Int. Ed*. **2007**, *46*, 4554.

[29] F. Palacios, C. Alonso, D. Aparicio, G. Rubiales, J. M. de los Santos, *Tetrahedron*, **2007**, *63*, 523.

[30] F. Palacios, D. Aparicio, G. Rubiales, C. Alonso, J. M. de los Santos, *Curr. Org. Chem*. **2009**, *13*, 810.

[31] Z. Lao, P. H. Toy, *Beilstein. J. Org. Chem*. **2016**, *12*, 2577.

[32] C. -K. Sha, R. -T. Chiu, C. -F. Yang, N. -T. Yao, W. -H. Tseng, F. -L. Liao, S. -L. Wang, *J. Am. Chem. Soc.* **1997**, *119*, 4130.

[33] S. -H. Hou, Y. -Q. Tu, L. Liu, F. -M. Zhang, S. -H. Wang, X. -M. Zhang, Angew. Chem. Int. Ed. 2013, 52, 11373.

[34] N. Zheng, L. Zhang, J. Gong, Z. Yang, *Org. Lett.* **2017**, *19*, 2921.

[35] I. Fleming, R. Henning, D. C. Parker, H. E. Plaut, P. E. J. Sanderson, *J. Chem. Soc., Perkin Trans. 1* **1995**, 317.

[36] O. Mitsunobu, Y. Yamada, *Bull. Chem. Soc. Jpn*. **1967**, *40*, 2380.

[37] N. Ozasa, M. Wadamoto, K. Ishihara, H. Yamamoto, *Synlett* **2003**, *14*, 2219.

[38] S. Kim, J. H. Joe, J. Y. Do, *J. Am. Chem. Soc*. **1994**, *116*, 5521.

[39] M. Johannsen, K. A. Jørgensen, *Chem. Rev*. **1998**, *98*, 1689.

[40] R. L. Grange, E. A. Clizbe, P. A. Evans, *Synthesis* **2016**, *48*, 2911.

[41] J. Schreiber, H. Maag, N. Hashimoto, A. Eschenmoser, *Angew. Chem. Int. Ed.* **1971**, *10*, 330.

[42] Y. Tamaru, M. Hojo, H. Higashimura, Z. Yoshida, *J. Am. Chem. Soc.* **1988**, *110*, 3994.

[43] C. -Y. Oh, K. -S. Kim, W. -H. Ham, *Tetrahedron Lett.* **1998**, *39*, 2133.

[44] K. Csatayová, I. Špánik, V. Ďurišová, P. Szolcsányi, *Tetrahedron Lett.* **2010**, *51*, 6611.

[45] P. Kubizna, I. Špánik, J. Kožíšek, P. Szolcsányi, *Tetrahedron* **2010**, *66*, 2351.

[46] J. L. Vicario, D. Badiá, L. Carrillo, J. Etxebarria, E. Reyes, N. Ruiz, *Org. Prep. Proced. Int*. **2005**, *37*, 513.

[47] L.-W. Xu, C.-G. Xia, *Eur. J. Org. Chem*. **2005**, 633.

[48] D. Enders, C. Wang, J. X. Liebich, *Chem. Eur. J*. **2009**, *15*, 11058.

[49] S. G. Davies, A. M. Fletcher, P. M. Roberts, J. E. Thomson, *Synlett* **2017**, *28*, 2697.

[50] K. Zheng, X. Liu, X. Feng, *Chem. Rev*. **2018**, *118*, 7586.

[51] Z. Amara, J. Caron, D. Joseph, *Nat. Prod. Rep*. **2013**, 30, 1211.

[52] M. Sánchez-Roselló, J. L. Aceña, A. Simón-Fuentes, C. del Pozo, *Chem. Soc. Rev*. **2014**, 43, 7430.

[53] V. Barát, D. Csókás, R. W. Bates, *J. Org. Chem*. **2018**, *83*, 9088.

[54] M. Guerola, M. Sánchez-Roselló, C. Mulet, C. del Pozo, S. Fustero, *Org. Lett*. **2015**, *17*, 960.

[55] T. Momose, S. Uchida, N. Yamaashi, T. Imanishi, *Heterocycles* **1975**, *3*, 713.

[56] G. Qian, M. Bai, S. Gao, H. Chen, S. Zhou, H. -G. Cheng, W. Yan, Q. Zhou, *Angew. Chem. Int. Ed*. **2018**, *57*, 10980.

[57] C. Schneider, C. Börner, *Synlett*, **1998**, 652.

[58] M. Elkin, A. C. Scruse, A. Turlik, T. R. Newhouse, *Angew. Chem. Int. Ed*. **2019**, *58*, 1025.

[59] C. He, J. Xuan, P. Rao, P. -P. Xie, X. Hong, X. Lin, H. Ding, *Angew. Chem. Int. Ed*. **2019**, *58*, 5100.

[60] P. D. Bailey, M. A. Beard, H. P. T. Dang, T. R. Phillips, R. A. Price, J. H. Whittaker, *Tetrahedron Lett*. **2008**, *49*, 2150.

[61] I. Fleming, P. E. J. Sanderson, *Tetrahedron Lett*. **1987**, *28*, 4229.

[62] H. -J. Knölker, G. Wanzl, *Synlett* **1995**, 378.

[63] J. A. Pigza, J. -S. Han, A. Chandra, D. Mutnick, M. Pink, J. N. Johnston, *J. Org. Chem*. **2013**, *78*, 822.

[64] S. Y. Mhaskar, G. Lakshminarayana, *Tetrahedron Lett*. **1990**, *31*, 7227.

[65] A. Carlone, M. Marigo, C. North, A. Landa, K. A. Jørgensen, *Chem. Commun*. **2006**, 4928.

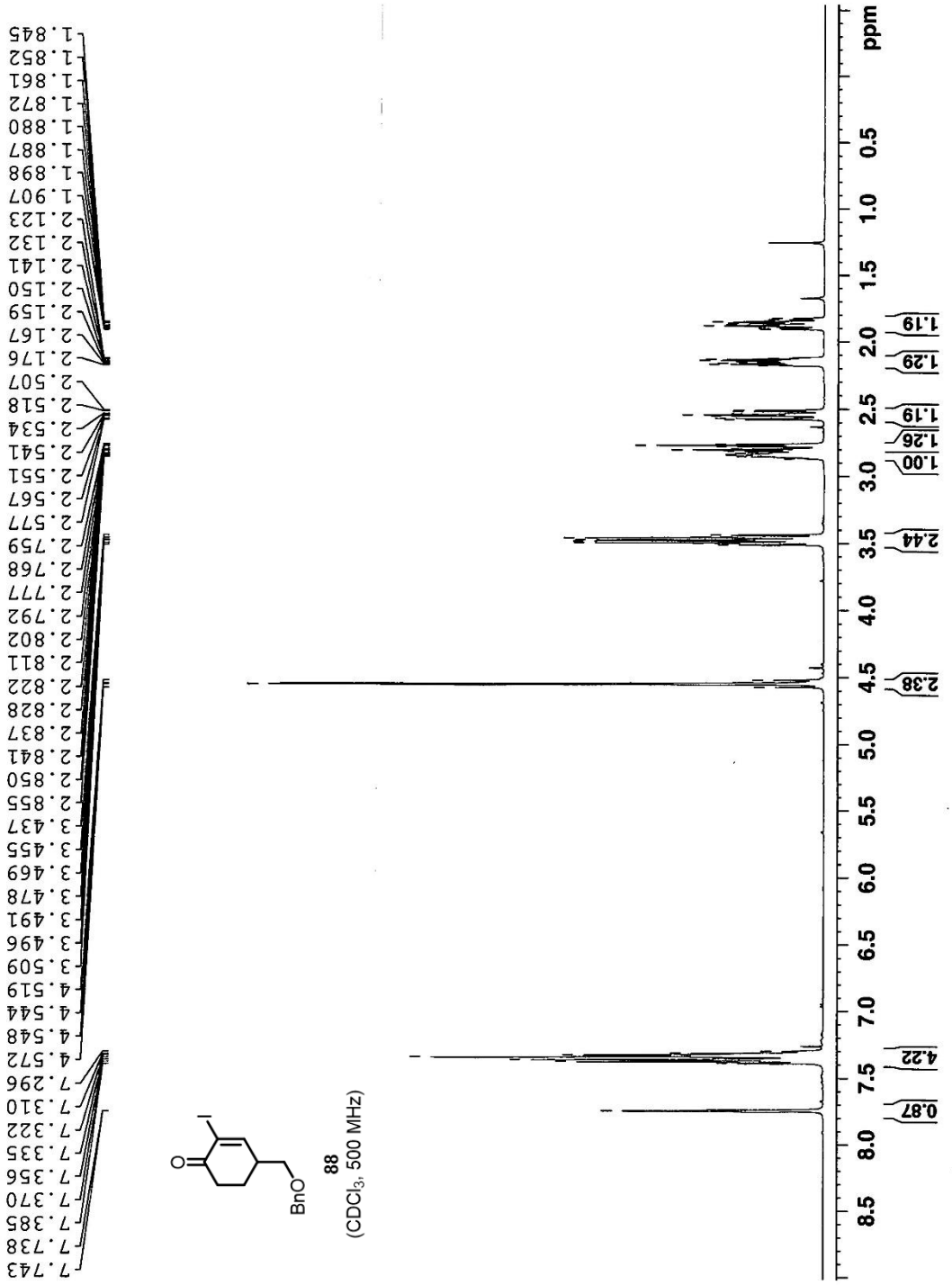
[66] Y. Mi, J. V. Shreiber, E. J. Corey, *J. Am. Chem. Soc*. **2002**, *124*, 11290.

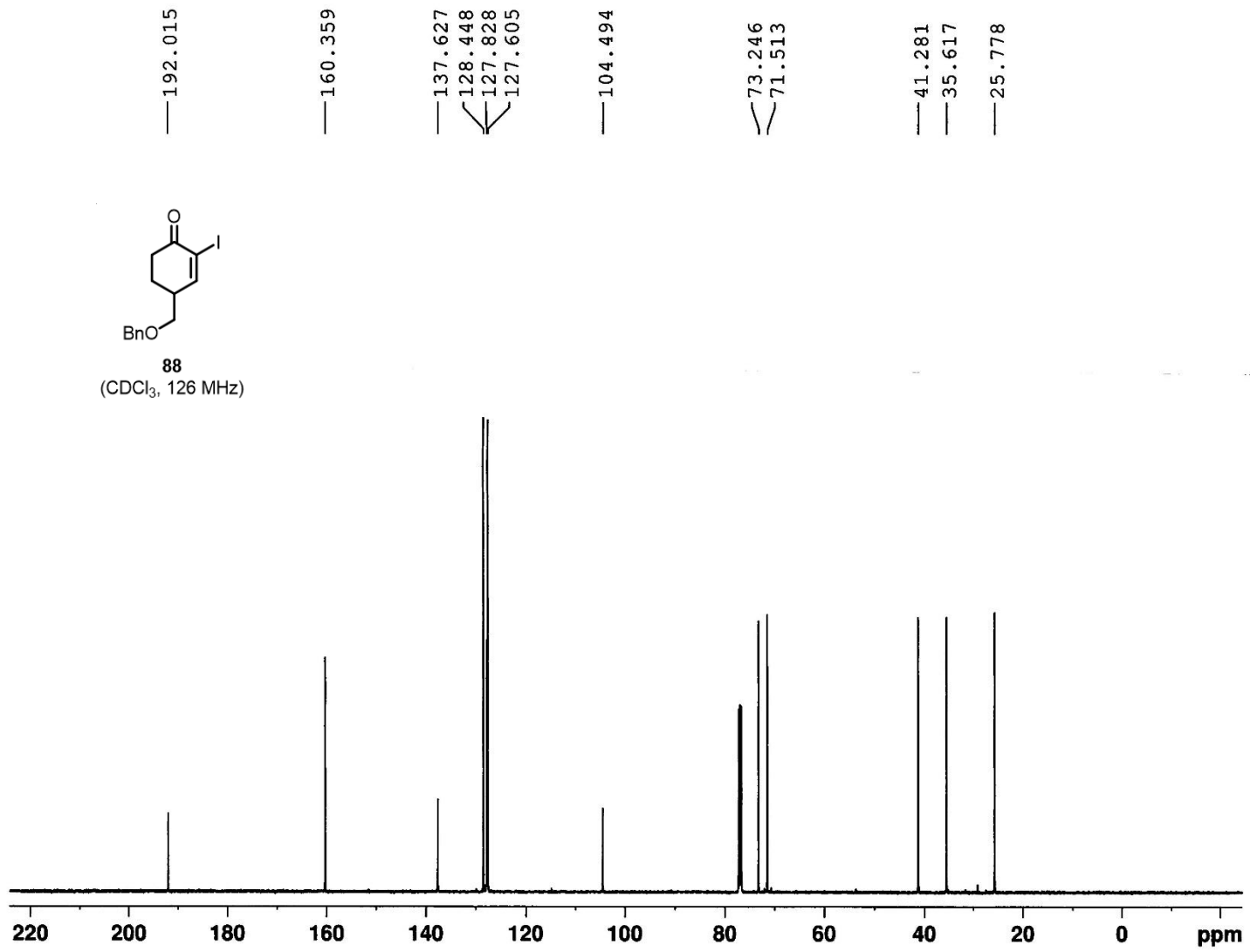
[67] P. Merlin, J. C. Braekman, D. Daloze, *Tetrahedron Lett.* **1988**, *29*, 1691.

[68] P. Bolze, G. Dickmeiss, K. A. Jørgensen, *Org. Lett*. **2008**, *10*, 3753.

[69] V. Rodeschini, P. Van de Weghe, E. Salomon, C. Tarnus, J. Eustache, *J. Org. Chem*. **2005**, *70*, 2409.

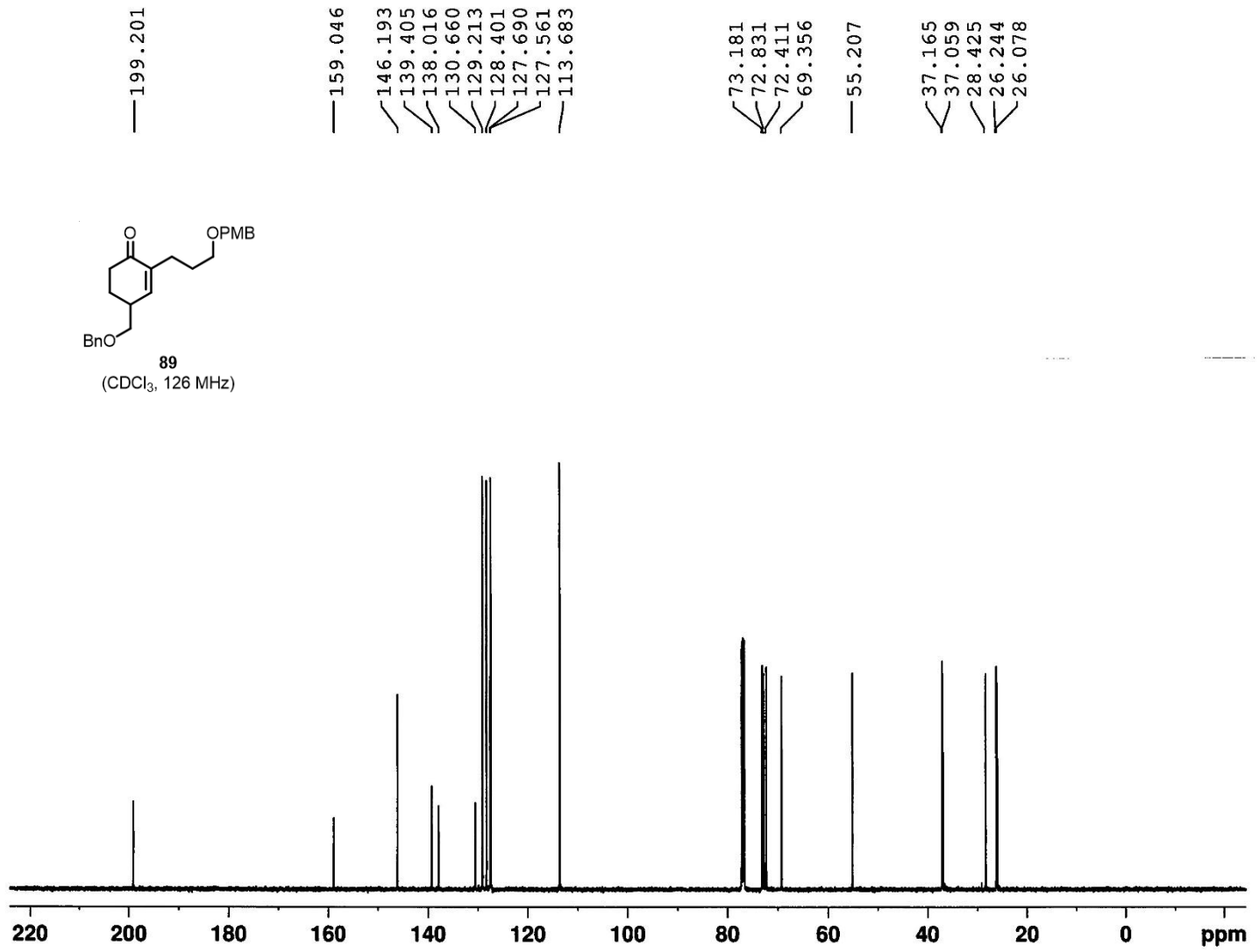
4.10 NMR Spectra of Selected Intermediates and HPLC Information





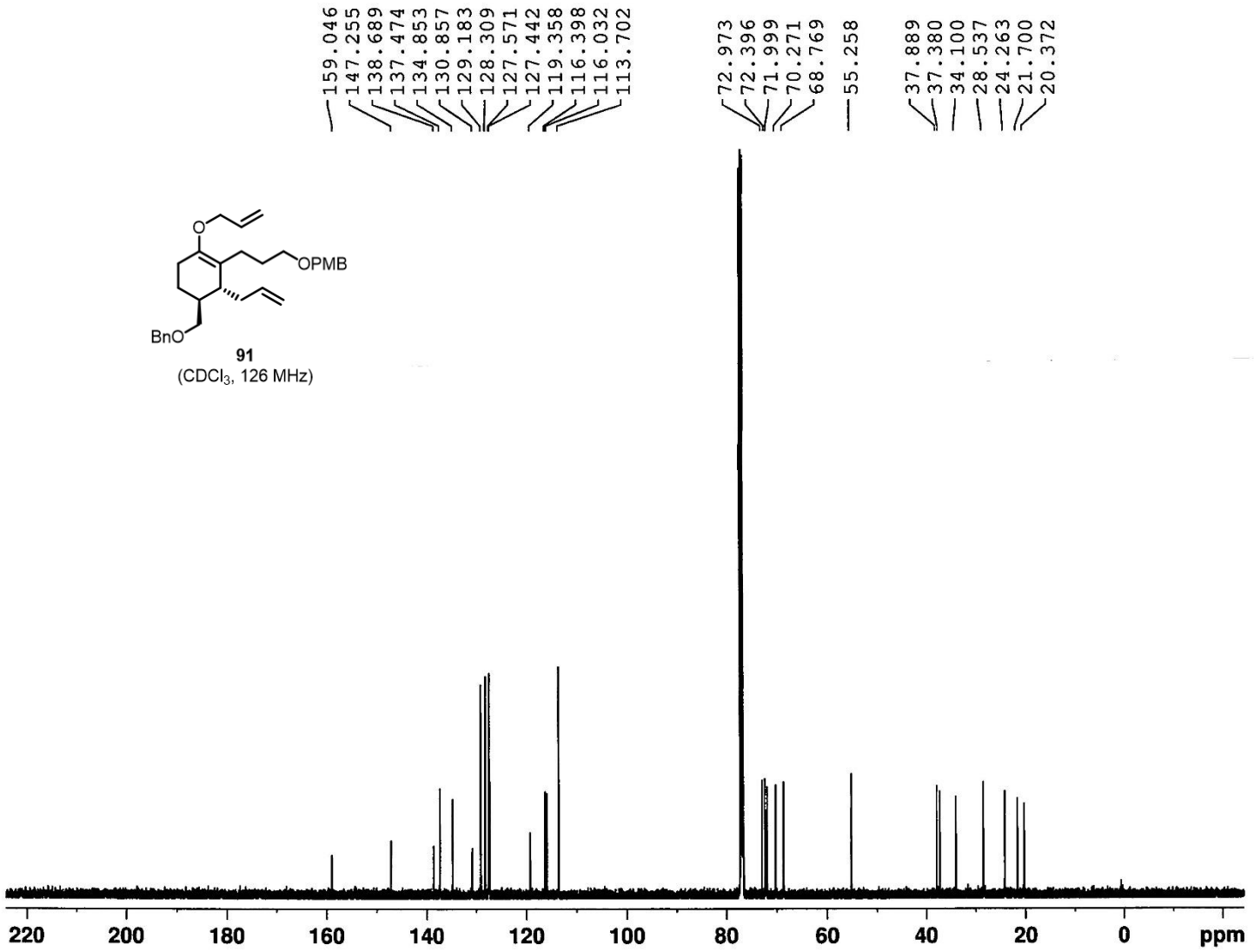
88
($CDCl_3$, 126 MHz)

OPMB
O
BnO
89
(CDCl3, 500 MHz)
ppm
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
3.88
1.69
1.64
0.93
2.00
1.97
2.83
4.00
0.95
0.99
1.04
1.93
0.98
3.10
7.376
7.360
7.346
7.342
7.329
7.312
7.299
7.263
7.246
6.876
6.859
6.643
4.568
4.543
4.540
4.516
4.431
4.407
4.383
3.794
3.440
3.430
3.422
3.418
2.711
2.537
2.528
2.518
2.503
2.494
2.485
2.376
2.366
2.350
2.341
2.333
2.317
2.307
2.286
2.271
2.256
2.095
2.085
2.068
2.059
1.772
1.764
1.747
1.735
1.720
1.706



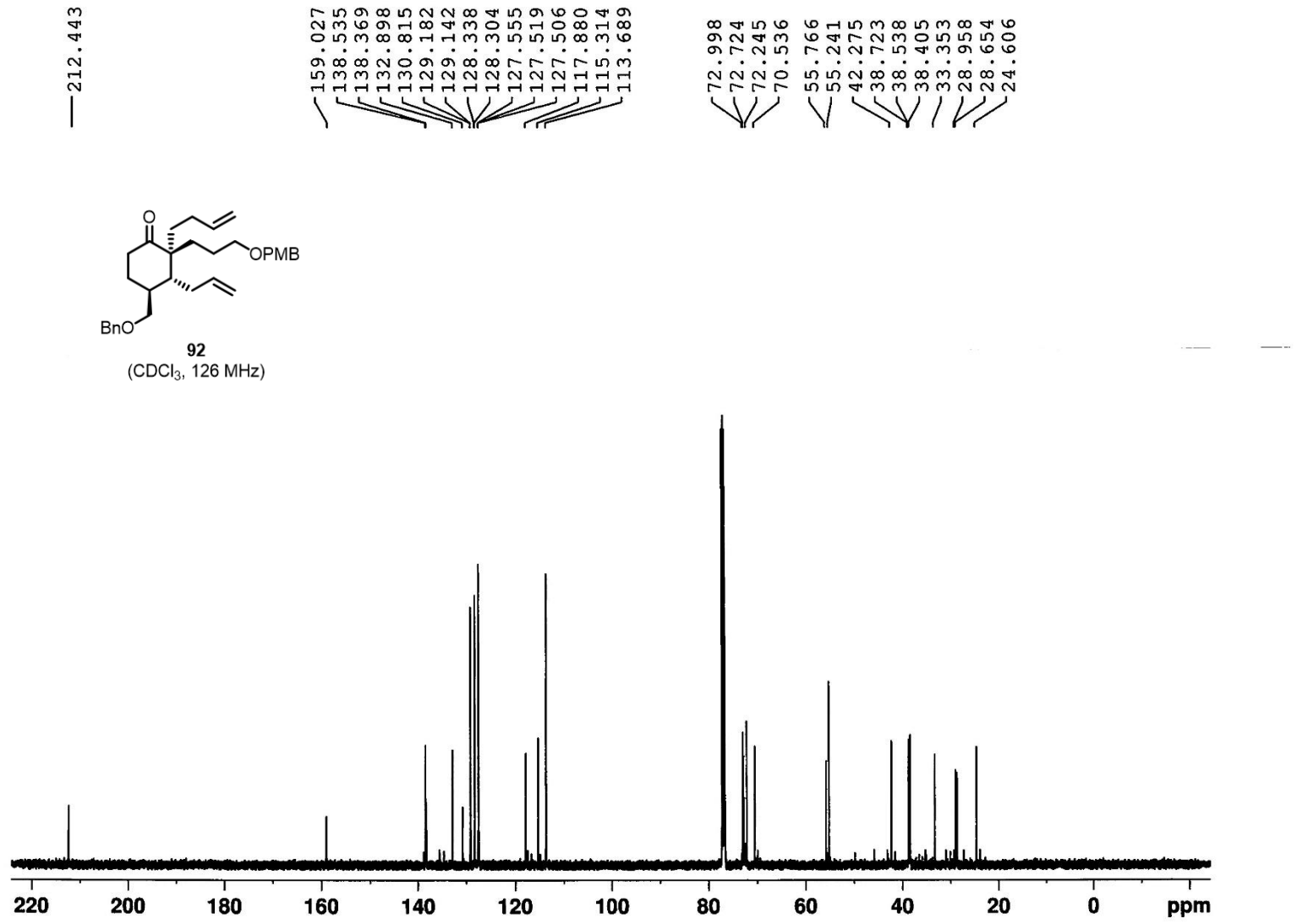
89
($CDCl_3$, 126 MHz)

OPMB
BnO
91
(CDCl3, 500 MHz)
ppm
3.48
3.01
1.78
0.63
0.90
0.77
0.80
2.02
2.24
2.00
1.85
3.02
2.20
2.08
0.97
1.14
5.10
2.22
1.99
1.83



91
($CDCl_3$, 126 MHz)

7.362
7.347
7.333
7.317
7.302
7.265
7.248
6.875
6.859
5.028
5.010
4.986
4.958
4.938
4.495
4.471
4.457
4.433
4.421
3.799
3.638
3.633
3.620
3.615
3.495
3.489
3.477
3.422
3.408
3.389
3.368
3.354
3.350
3.336
2.515
2.500
2.415
2.403
2.374
2.328
2.175
2.160
2.148
2.134
2.120
2.015
2.001
1.913
1.898
1.620
1.594
1.503
1.487
1.473
OPMB
O
BnO
92
(CDCl3, 500 MHz)
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
6.32
1.75
1.10
0.69
4.08
2.16
1.77
3.00
0.82
0.87
2.42
0.83
0.84
2.11
3.66
1.09
1.19
1.59
2.03
0.93



92
($CDCl_3$, 126 MHz)

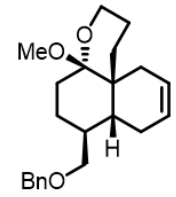
7.365
7.351
7.336
7.320
7.305
7.287
7.263
7.247
6.876
6.859
5.618
5.604
4.530
4.506
4.489
4.465
4.420
3.800
3.528
3.522
3.509
3.503
3.488
3.482
3.471
3.424
3.413
3.406
3.394
2.624
2.616
2.611
2.592
2.579
2.358
2.325
2.318
2.077
2.050
2.040
1.982
1.960
1.827
1.821
1.796
1.677
1.645
1.600
1.583
1.561
1.540
1.533
1.522
1.504
1.494
OPMB
H
O
BnO
93
(CDCl3, 500 MHz)
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
ppm
6.02
1.71
1.90
2.00
1.80
2.94
1.03
0.86
1.88
1.00
1.90
3.77
0.97
1.02
2.04
3.36

214.134
159.041
138.417
130.796
129.210
129.145
128.354
127.552
127.493
124.314
123.552
113.704
73.215
73.176
72.347
70.683
55.253
49.917
37.239
36.256
34.467
32.691
28.998
28.222
24.373
23.079
OPMB
BnO
O
H
93
(CDCl3, 126 MHz)
ppm
0
20
40
60
80
100
120
140
160
180
200
220

7.339
7.327
7.288
7.284
7.276
7.271
5.559
5.503
4.527
4.502
4.474
4.450
4.015
3.994
3.988
3.683
3.673
3.662
3.651
3.497
3.490
3.478
3.471
3.330
3.318
3.312
3.300
2.332
2.295
2.103
2.094
2.071
1.966
1.957
1.876
1.850
1.840
1.805
1.766
1.757
1.716
1.693
1.685
1.665
1.657
1.557
1.537
1.514
1.492
1.484
1.316
1.310
1.289
1.284
HO
O
H
BnO
94
(CDCl3, 500 MHz)
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0 ppm
4.65
1.11
1.02
2.33
1.00
1.18
1.14
1.20
1.33
3.90
1.08
1.02
2.13
1.58
3.90
1.40
1.03

138.759
128.288
127.491
127.395
124.831
123.155
97.874
74.201
73.085
60.845
38.169
35.749
34.979
33.887
32.172
26.975
26.550
22.854
20.750
HO
O
H
BnO
94
(CDCl3, 126 MHz)
220
200
180
160
140
120
100
80
60
40
20
0
ppm

7.338
7.328
7.287
7.281
5.543
5.491
4.527
4.502
4.478
4.453
3.661
3.655
3.647
3.634
3.500
3.492
3.481
3.474
3.329
3.317
3.311
3.299
3.189
2.251
2.214
2.097
2.087
2.064
2.038
1.866
1.857
1.853
1.839
1.833
1.804
1.796
1.771
1.765
1.728
1.700
1.693
1.673
1.643
1.634
1.616
1.607
1.451
1.442
1.425
1.417
1.399
1.391
1.280
1.257
MeO
BnO
H
95
(CDCl3, 500 MHz)
ppm
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
3.92
0.88
0.87
1.95
1.98
1.00
1.01
2.89
0.98
2.78
1.88
1.16
4.21
1.04
1.03
1.15



95
($CDCl_3$, 126 MHz)

138.791
128.265
127.467
127.358
125.123
123.029
100.200
74.316
73.048
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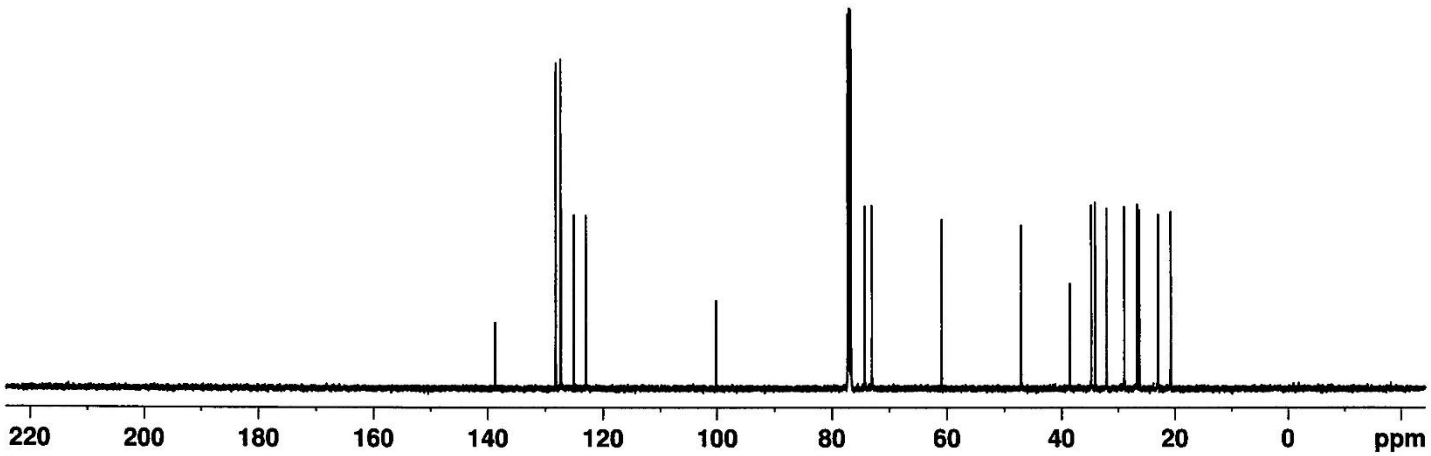
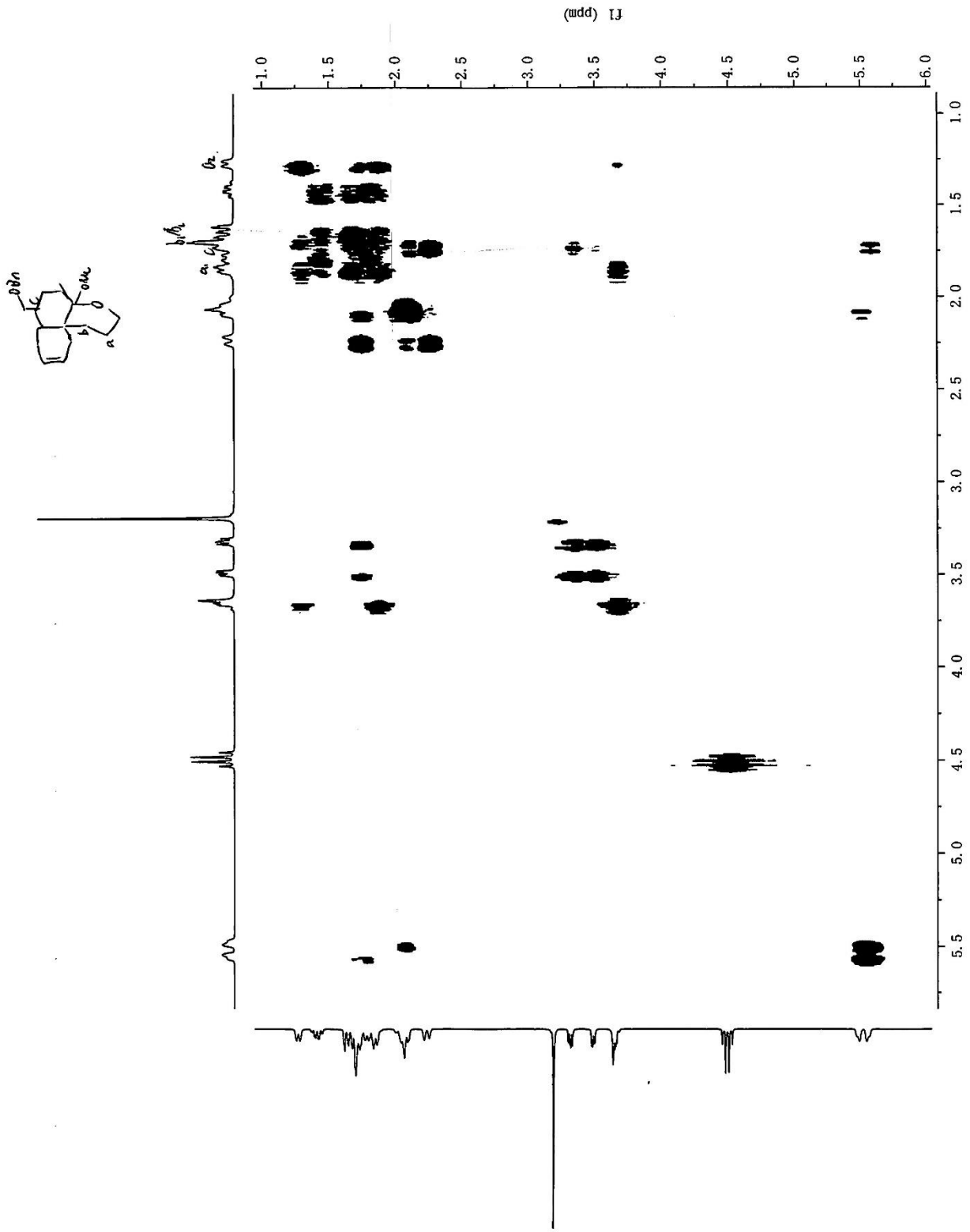
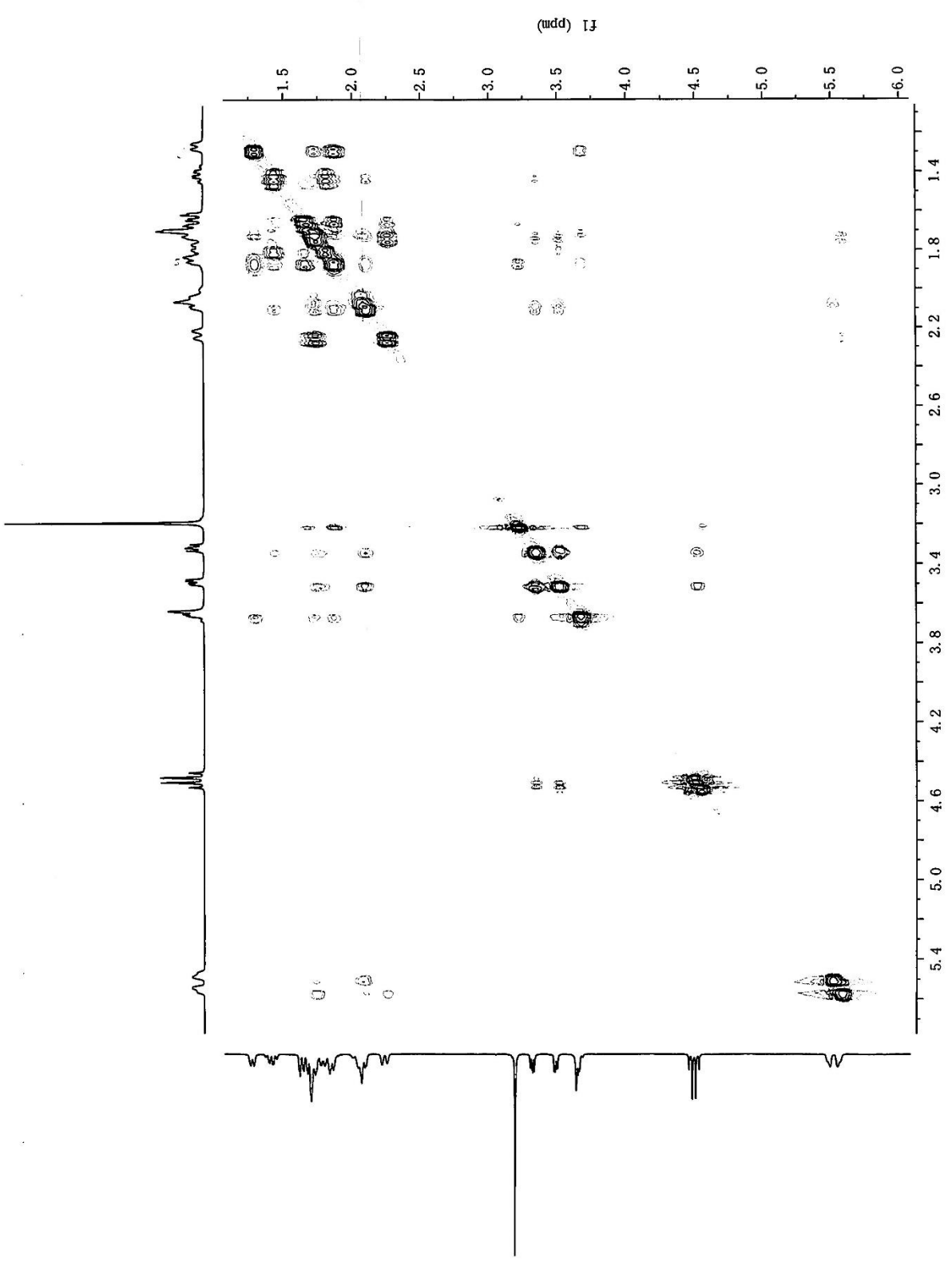
47.043
38.593
34.855
34.126
32.070
28.939
26.631
26.293
22.969
20.711



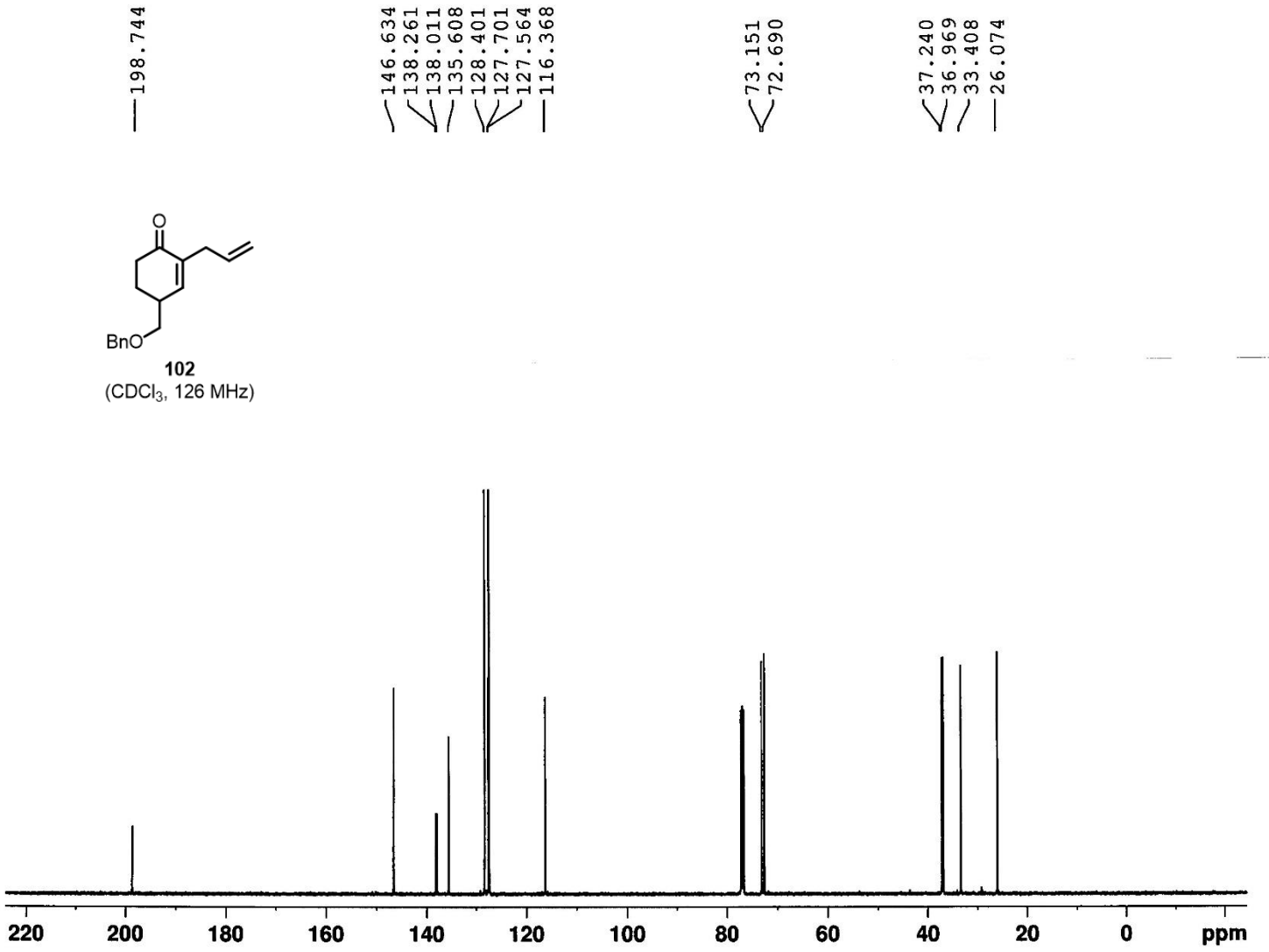
COSY



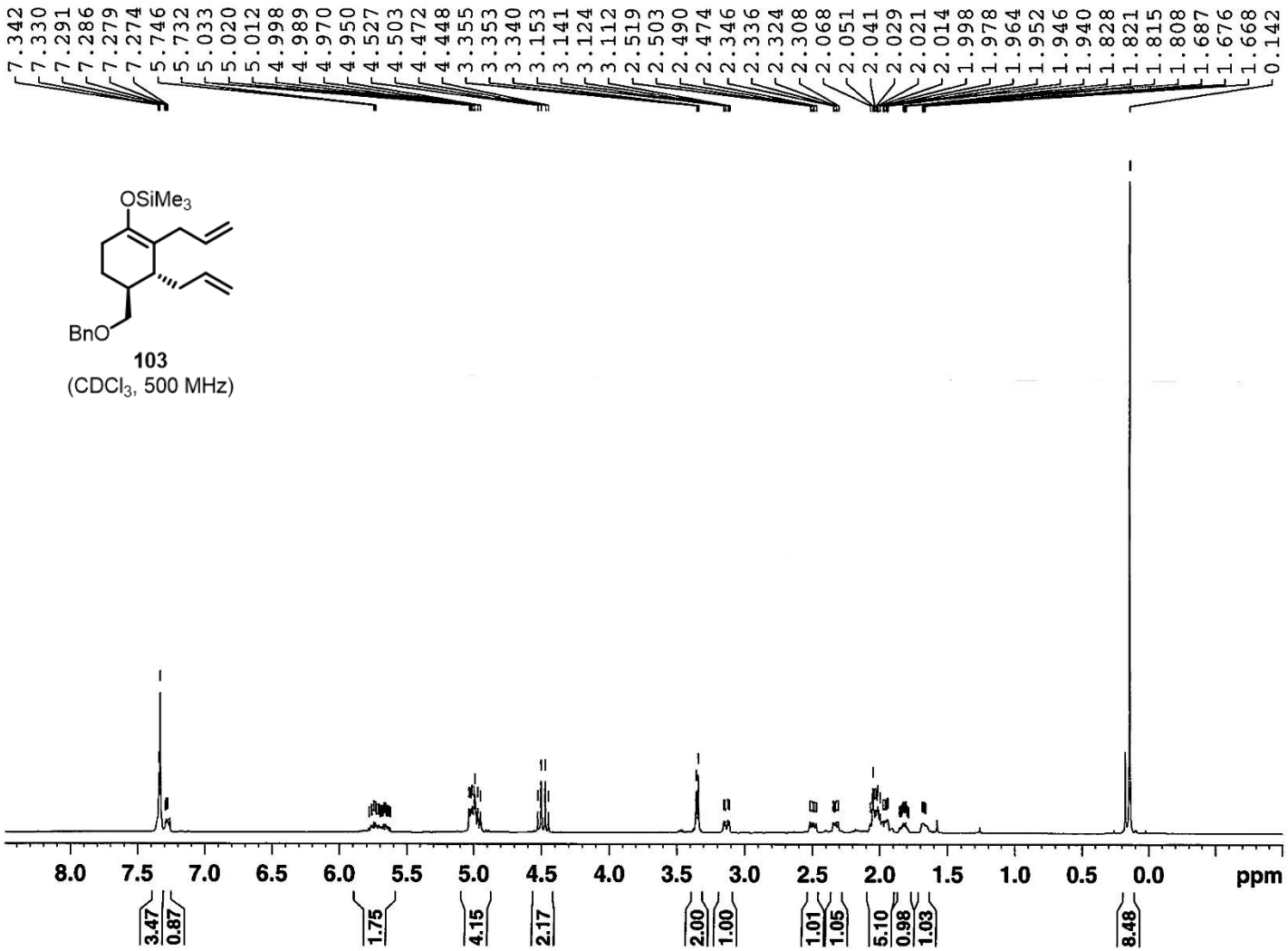
NOESY



7.377
7.362
7.347
7.342
7.329
7.315
7.301
6.662
5.832
5.819
5.813
5.805
5.797
5.791
5.778
5.060
5.036
5.032
4.552
3.466
3.453
2.960
2.948
2.749
2.745
2.736
2.570
2.561
2.551
2.536
2.527
2.518
2.409
2.399
2.383
2.374
2.365
2.350
2.340
2.123
2.113
2.105
2.096
2.087
1.806
1.798
1.786
1.780
1.772
1.761
1.752
1.746
1.734
1.726
BnO
O
102
(CDCl3, 500 MHz)
ppm
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
4.14
0.91
0.70
2.09
0.88
0.81
2.24
2.00
0.99
1.08
1.10
1.11
1.19



102
($CDCl_3$, 126 MHz)

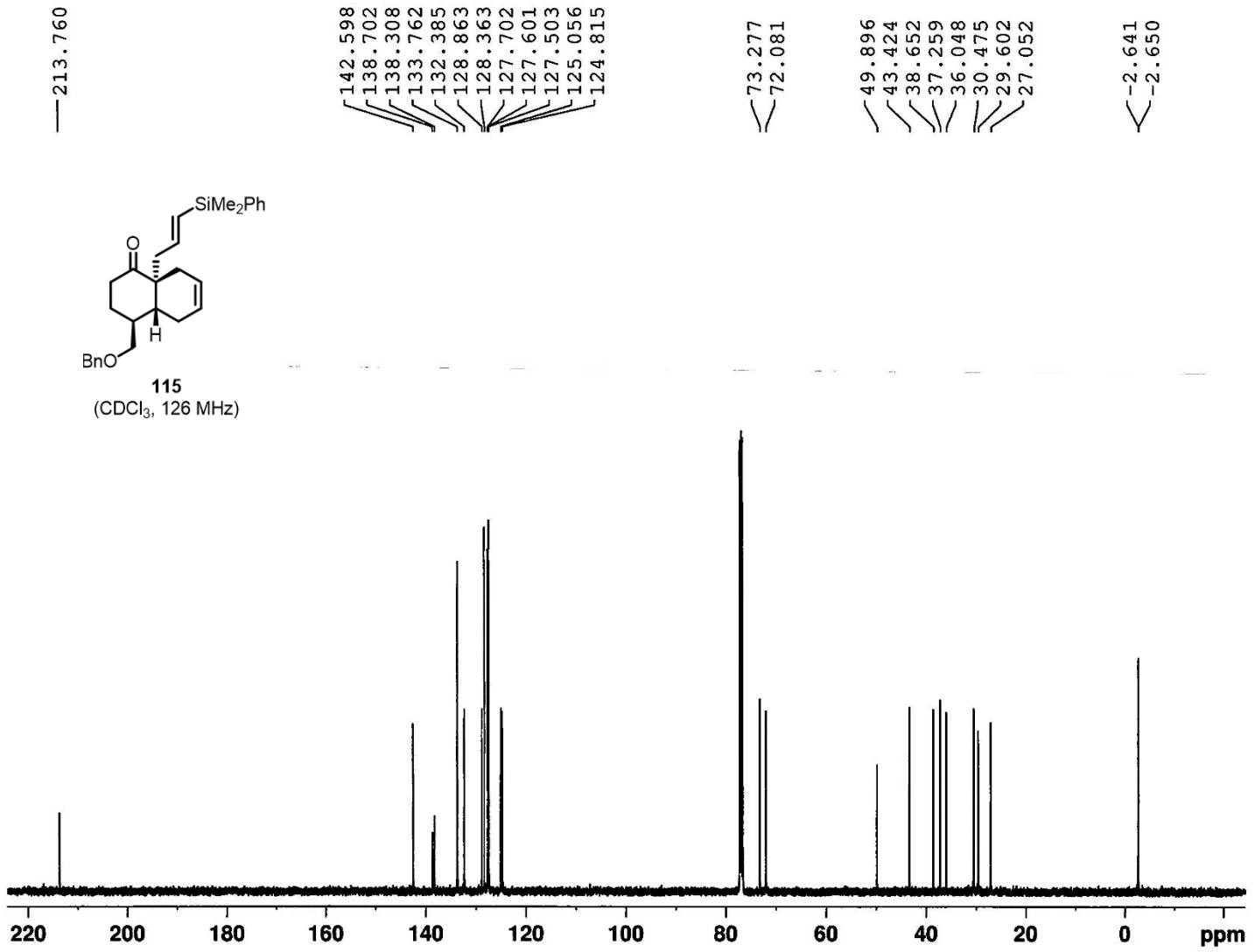

7.342
7.330
7.291
7.286
7.279
7.274
5.746
5.732
5.033
5.020
5.012
4.998
4.989
4.970
4.950
4.527
4.503
4.472
4.448
3.355
3.353
3.340
3.153
3.141
3.124
3.112
2.519
2.503
2.490
2.474
2.346
2.336
2.324
2.308
2.068
2.051
2.041
2.029
2.021
2.014
1.998
1.978
1.964
1.952
1.946
1.940
1.828
1.821
1.815
1.808
1.687
1.676
1.668
0.142
OSiMe3
BnO
103
(CDCl3, 500 MHz)
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
3.47
0.87
1.75
4.15
2.17
2.00
1.00
1.01
1.05
5.10
0.98
1.03
8.48

0.736
20.689
26.743
32.815
34.465
37.236
37.607
72.108
73.025
114.933
115.253
115.989
127.479
127.606
128.343
137.085
137.570
138.765
144.328
OSiMe3
BnO
103
(CDCl3, 126 MHz)
ppm
0
20
40
60
80
100
120
140
160
180
200
220

SiMe2Ph
O
BnO
106
(CDCl3, 500 MHz)
ppm
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
6.25
1.51
1.04
1.07
2.05
1.48
3.22
1.07
1.06
0.99
1.00
1.00
2.10
1.02
3.21
3.97
1.75
6.99
7.485
7.480
7.476
7.467
7.350
7.344
7.338
7.330
7.311
7.298
7.284
5.812
5.796
5.760
5.740
5.051
5.035
5.006
4.974
4.939
4.918
4.456
4.447
3.634
3.628
3.616
3.610
3.310
3.296
3.292
3.278
2.639
2.622
2.611
2.443
2.431
2.356
2.347
2.341
2.332
2.311
2.302
2.293
2.273
2.263
2.162
2.086
2.001
1.981
1.972
1.953
1.897
0.296
0.288

212.065
142.560
138.585
138.448
135.444
133.774
132.607
128.911
128.322
127.731
127.509
117.690
115.132
72.902
72.598
56.165
42.787
41.328
38.774
38.718
37.434
33.358
29.074
-2.651
-2.669
SiMe2Ph
O
BnO
106
(CDCl3, 126 MHz)
ppm
0
20
40
60
80
100
120
140
160
180
200
220

7.479
7.473
7.469
7.466
7.460
7.369
7.350
7.344
7.341
7.322
7.308
7.293
5.819
5.808
5.801
5.620
5.604
4.532
4.508
4.482
4.458
3.550
3.544
3.532
3.526
3.367
3.355
3.349
3.337
2.598
2.585
2.569
2.557
2.523
2.512
2.502
2.494
2.346
2.341
2.338
2.333
2.313
2.201
2.195
2.177
1.852
1.843
1.830
1.821
1.660
1.639
1.634
1.602
0.286
0.280
SiMe2Ph
H
O
BnO
115
(CDCl3, 500 MHz)
ppm
0
1
2
3
4
5
6
7
8
5.71
1.37
1.04
1.06
1.12
4.28
1.09
1.00
0.99
1.06
1.02
1.00
2.09
1.79
1.96
1.69
6.69

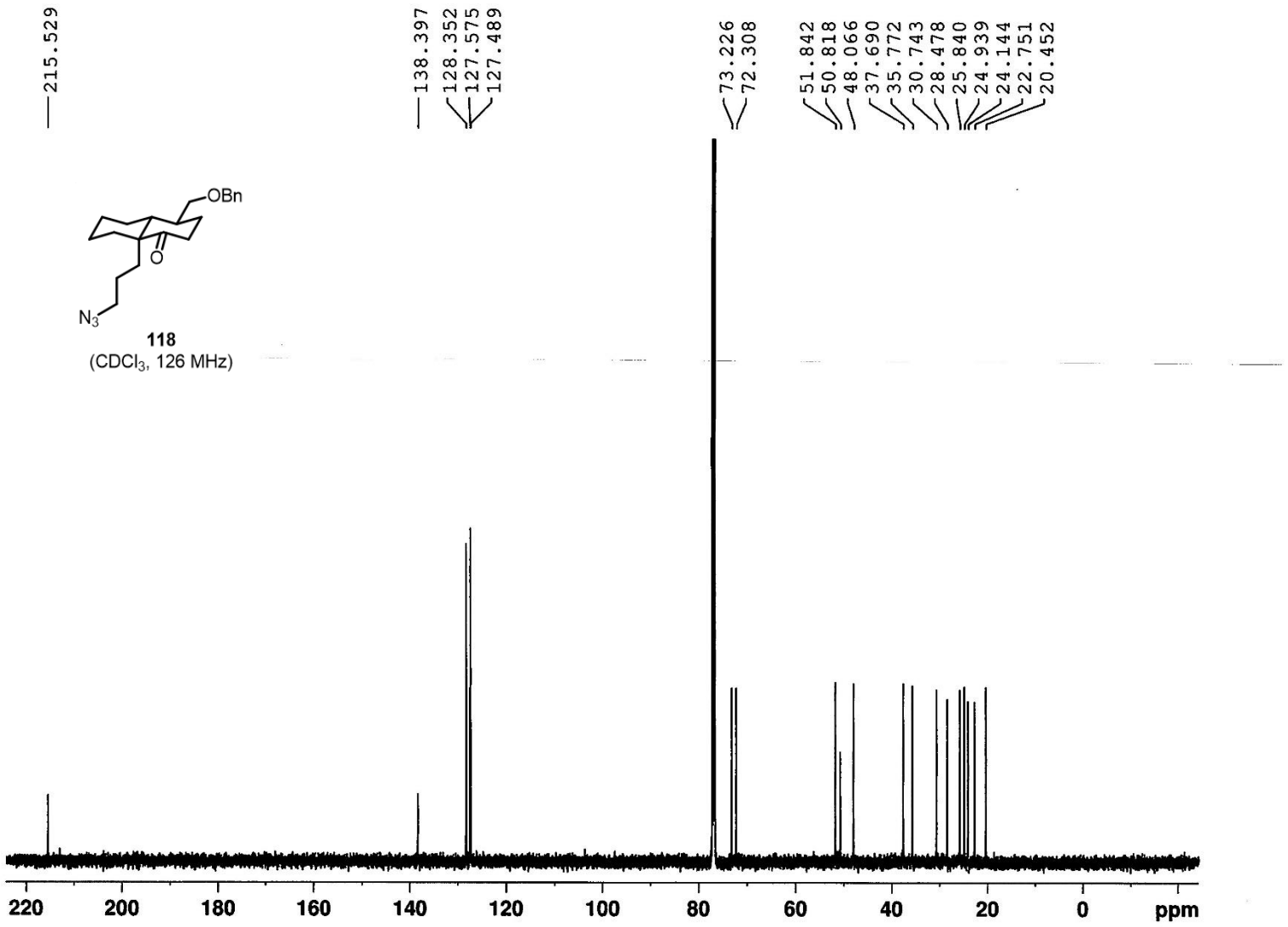


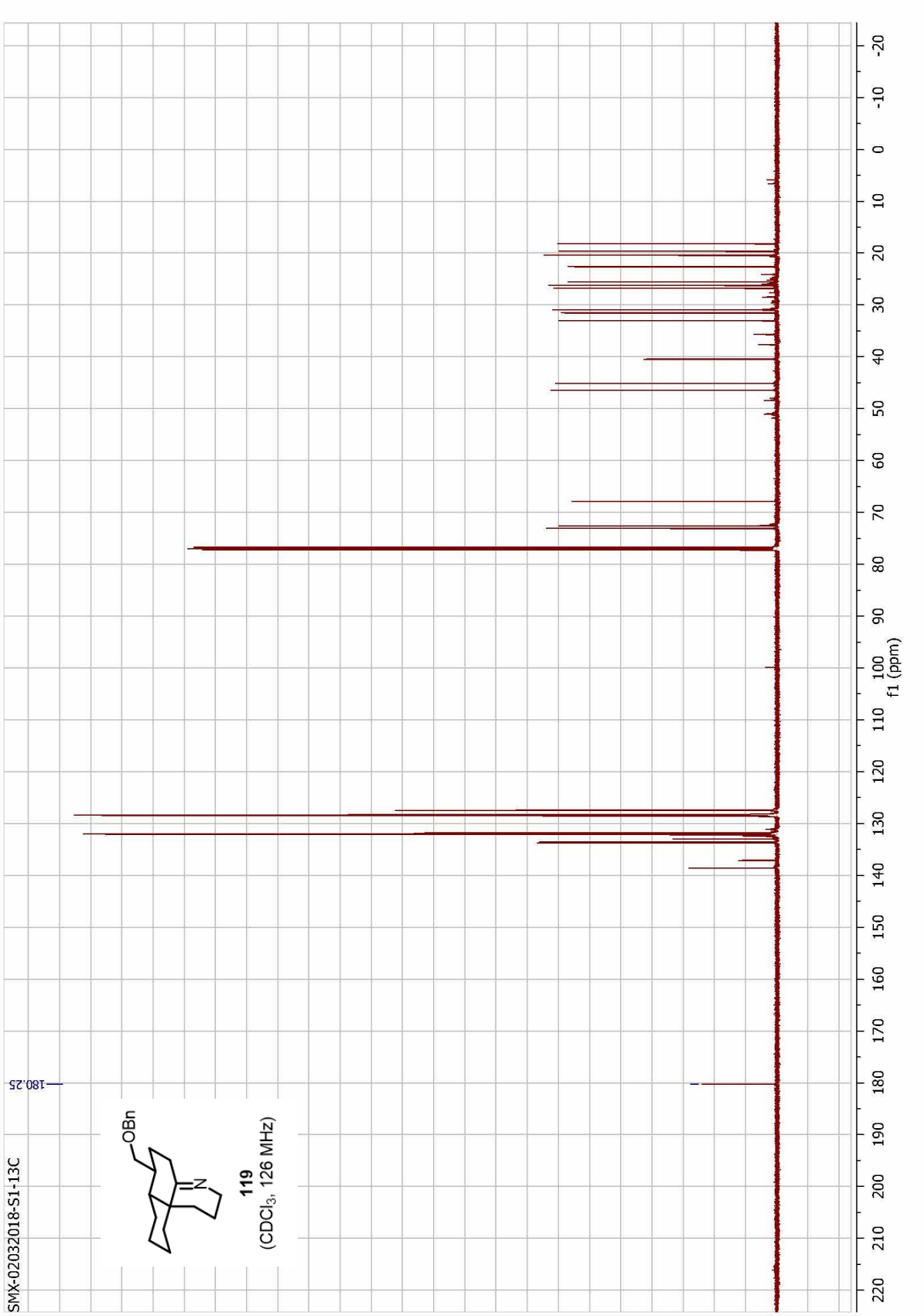
115
($CDCl_3$, 126 MHz)

117
(CDCl3, 500 MHz)
OBn
HO
O
ppm
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
4.70
2.19
1.95
1.04
1.00
0.95
0.98
1.04
1.07
2.23
1.14
1.18
2.99
1.60
1.00
1.18
4.41
1.59
1.09
7.357
7.342
7.328
7.321
7.308
7.294
7.280
4.511
4.487
4.456
4.432
3.624
3.613
3.595
3.583
3.504
3.497
3.486
3.478
3.339
3.327
3.321
3.309
2.632
2.618
2.291
2.286
2.281
2.277
2.258
2.172
2.159
1.923
1.905
1.897
1.881
1.790
1.785
1.722
1.698
1.636
1.611
1.594
1.537
1.513
1.508
1.490
1.430
1.365
1.358
1.339
1.309
1.274
1.254
1.176

215.956
138.453
128.342
127.549
127.466
73.185
72.383
63.068
50.846
48.155
37.724
35.756
30.838
28.506
26.353
25.900
24.161
23.977
20.464
OBn
O
HO
117
(CDCl3, 126 MHz)
ppm
220
200
180
160
140
120
100
80
60
40
20
0

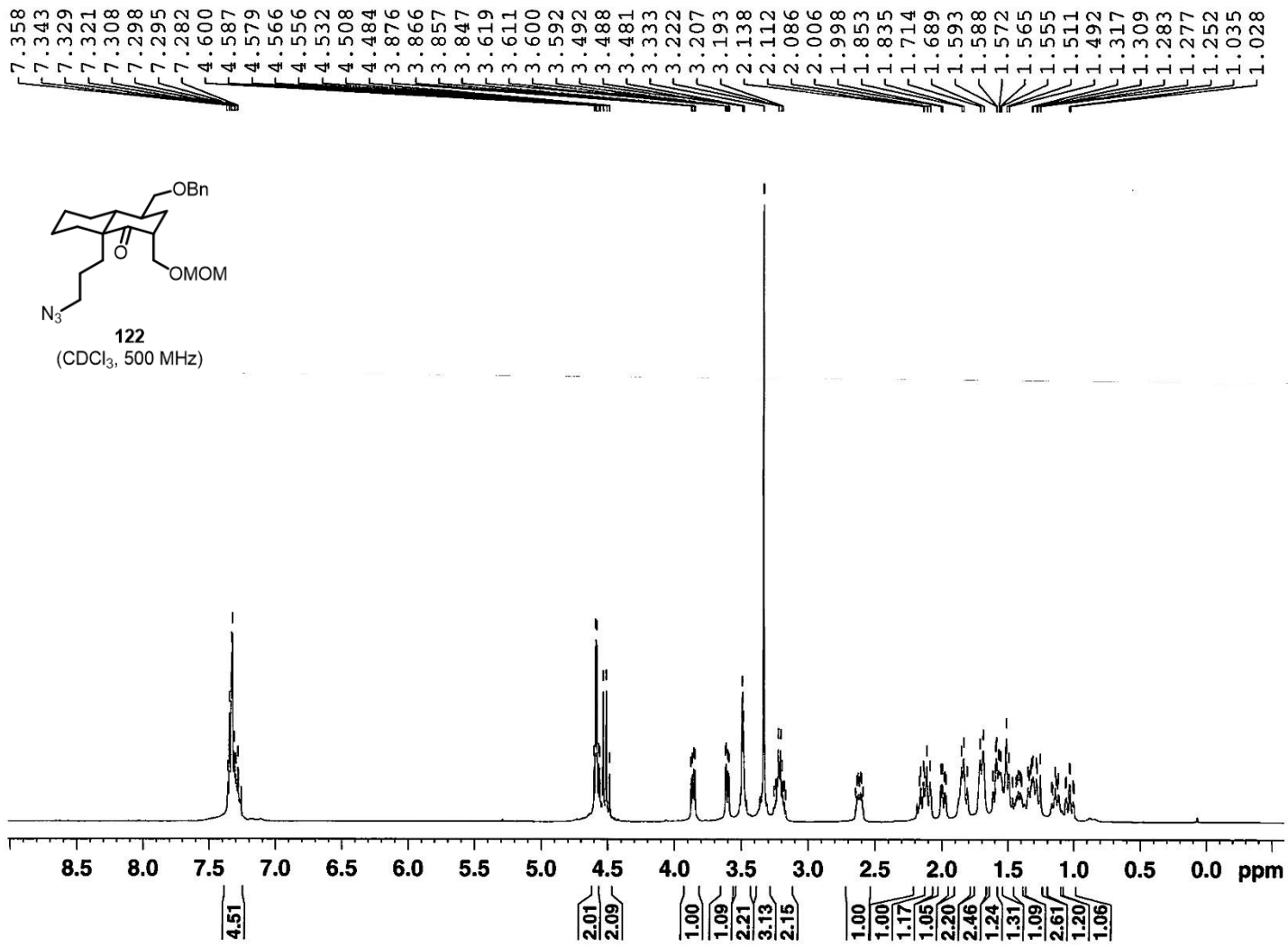
7.360
7.346
7.331
7.310
7.297
7.283
4.514
4.490
4.460
4.436
3.508
3.501
3.490
3.483
3.346
3.333
3.328
3.315
3.288
3.276
3.268
3.264
3.256
3.243
2.603
2.589
2.308
2.304
2.299
2.169
1.904
1.896
1.884
1.869
1.749
1.730
1.722
1.709
1.654
1.645
1.620
1.576
1.559
1.520
1.514
1.497
1.350
1.342
1.323
1.317
1.291
1.271
1.252
1.179
OBn
O
N3
118
(CDCl3, 500 MHz)
ppm
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
4.30
2.05
1.00
1.09
1.99
0.99
1.02
1.11
1.06
2.03
2.12
1.97
1.89
1.90
1.27
2.03
2.32


215.529
138.397
128.352
127.575
127.489
73.226
72.308
51.842
50.818
48.066
37.690
35.772
30.743
28.478
25.840
24.939
24.144
22.751
20.452
OBn
O
N3
118
(CDCl3, 126 MHz)
220
200
180
160
140
120
100
80
60
40
20
0
ppm


SMX-02032018-S1-13C
180.25
OBn
N
119
(CDCl3, 126 MHz)
f1 (ppm)

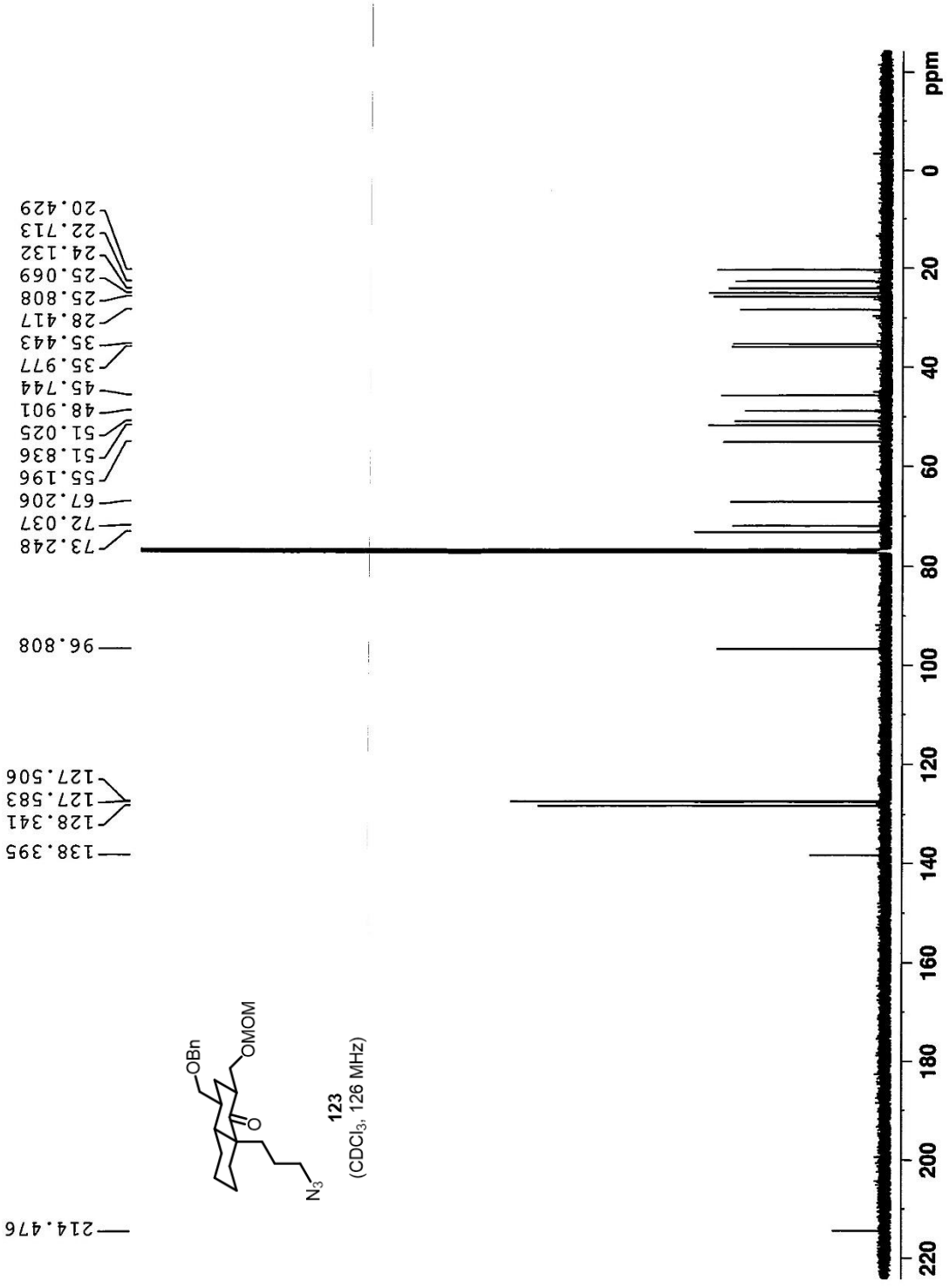
7.338
7.324
7.307
7.283
7.270
4.508
4.484
4.442
4.418
3.431
3.424
3.413
3.406
3.250
3.238
3.233
3.220
2.890
2.884
2.769
2.763
2.504
2.478
2.344
2.336
2.195
2.187
1.955
1.949
1.929
1.923
1.739
1.714
1.690
1.666
1.580
1.549
1.485
1.424
1.391
1.363
1.278
1.271
1.253
1.228
1.222
1.214
1.146
1.139
1.121
1.114
1.088
1.063
0.860
0.853
OBn
H-N
120
(CDCl3, 500 MHz)
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
2.00
1.00
1.02
0.95
0.99
1.01
1.04
1.16
1.43
2.09
2.80
0.98
1.87
3.86
2.28
2.97
1.06
1.29
1.33

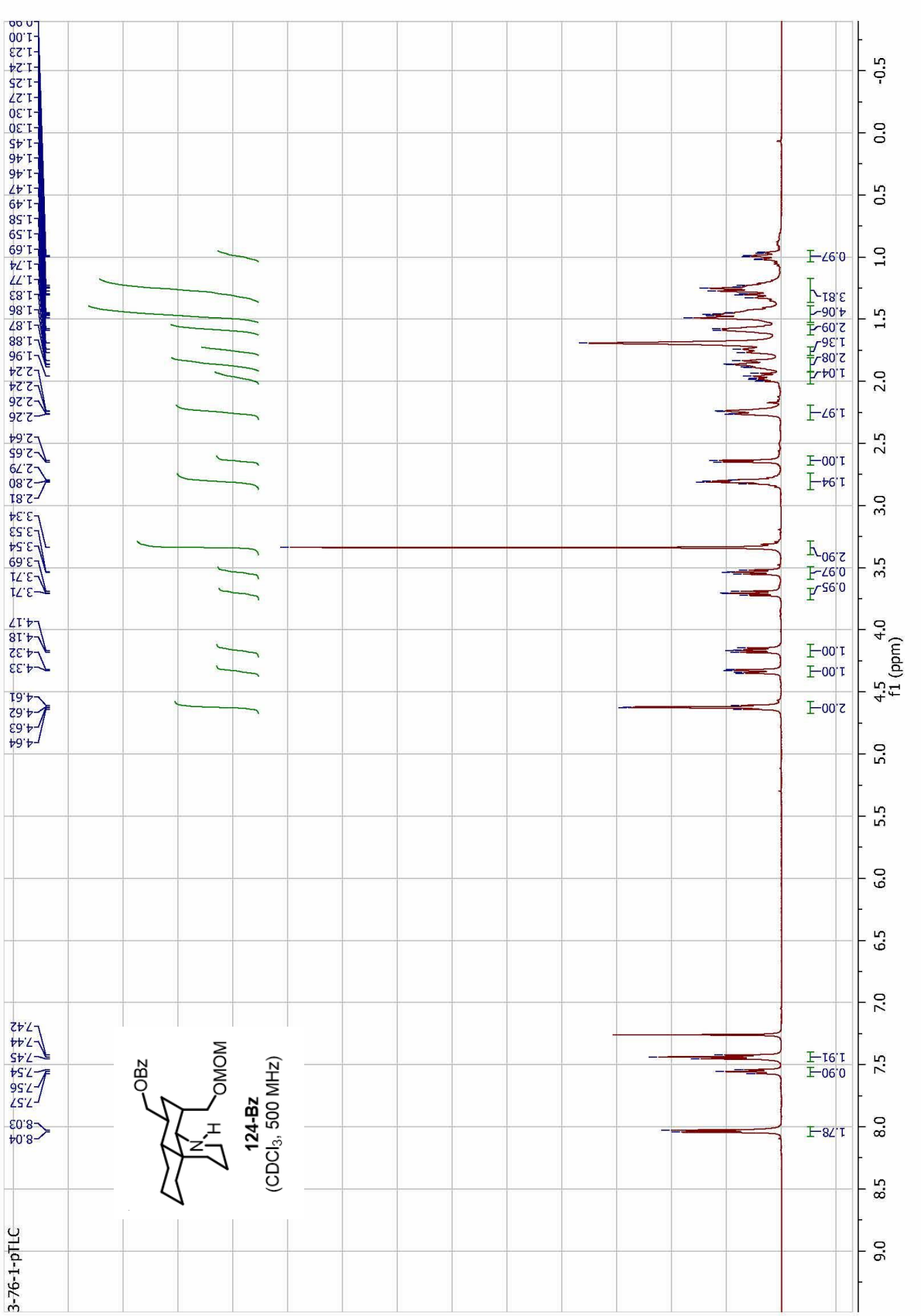
OBn
H
N
120
(CDCl3, 126 MHz)
138.787
128.285
127.492
127.410
73.666
73.095
61.048
47.997
39.994
35.971
34.227
30.035
26.692
25.503
22.935
21.428
20.745
19.673
ppm
220
200
180
160
140
120
100
80
60
40
20
0

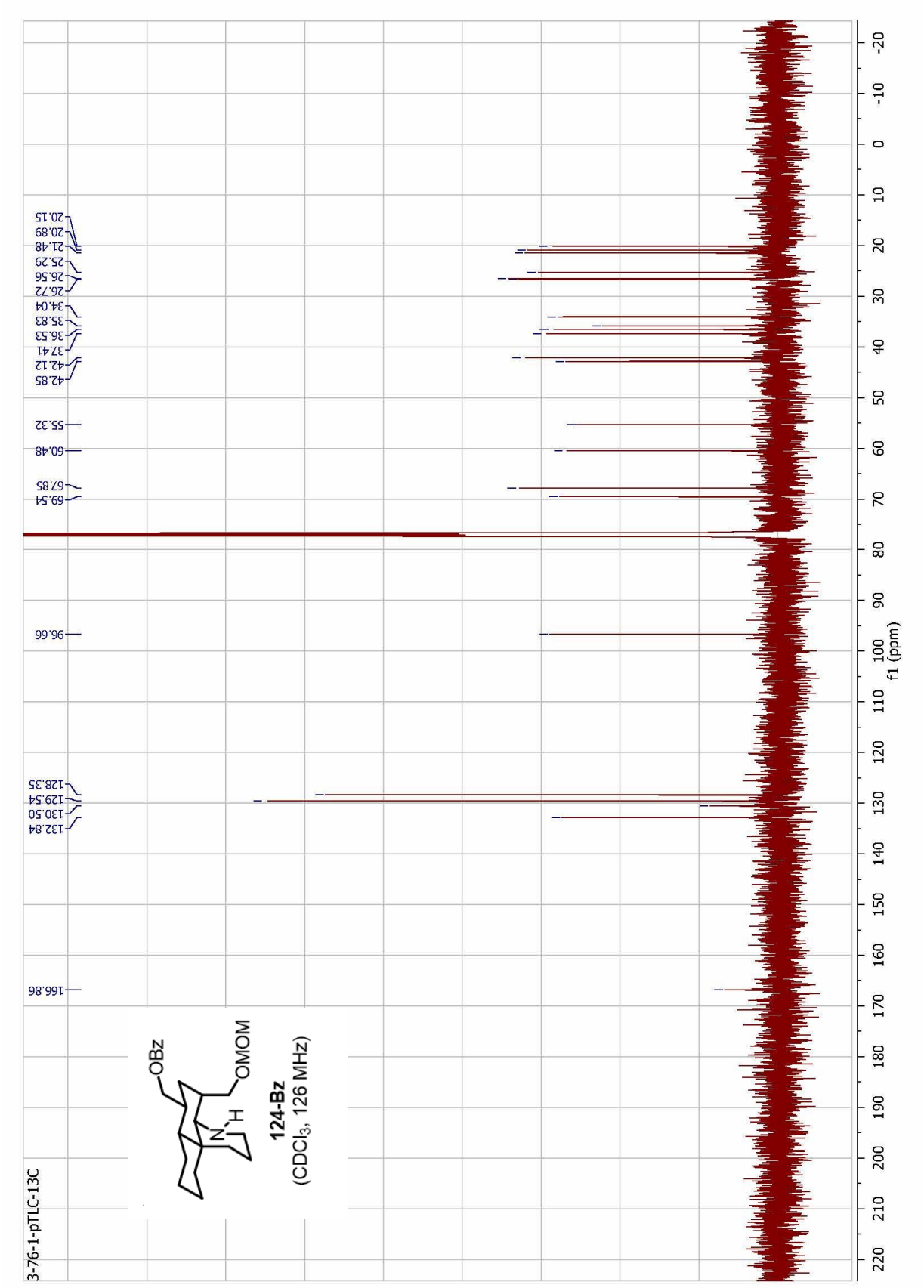

7.358
7.343
7.329
7.321
7.308
7.298
7.295
7.282
4.600
4.587
4.579
4.566
4.556
4.532
4.508
4.484
3.876
3.866
3.857
3.847
3.619
3.611
3.600
3.592
3.492
3.488
3.481
3.333
3.222
3.207
3.193
2.138
2.112
2.086
2.006
1.998
1.853
1.835
1.714
1.689
1.593
1.588
1.572
1.565
1.555
1.511
1.492
1.317
1.309
1.283
1.277
1.252
1.035
1.028
OBn
O
OMOM
N3
122
(CDCl3, 500 MHz)
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
4.51
2.01
2.09
1.00
1.09
2.21
3.13
2.15
1.00
1.00
1.17
1.05
2.20
2.46
1.24
1.31
1.09
2.61
1.20
1.06

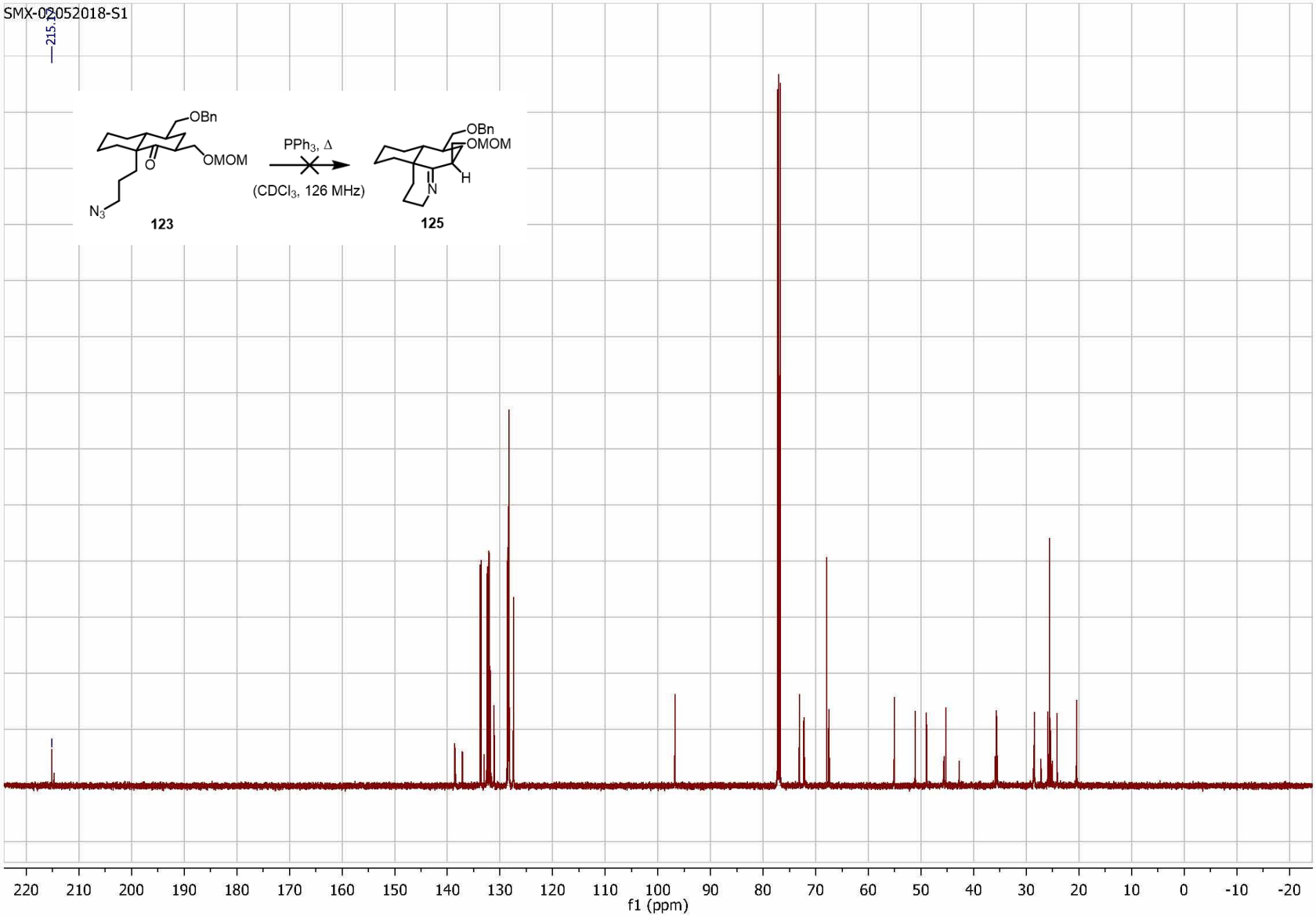
215.320
138.469
128.375
127.585
127.484
96.625
73.164
72.994
67.028
55.162
52.002
48.693
44.974
40.304
34.818
30.105
26.331
25.820
25.516
23.791
22.947
20.900
OBn
OMOM
O
N3
122
(CDCl3, 126 MHz)
ppm
220
200
180
160
140
120
100
80
60
40
20
0

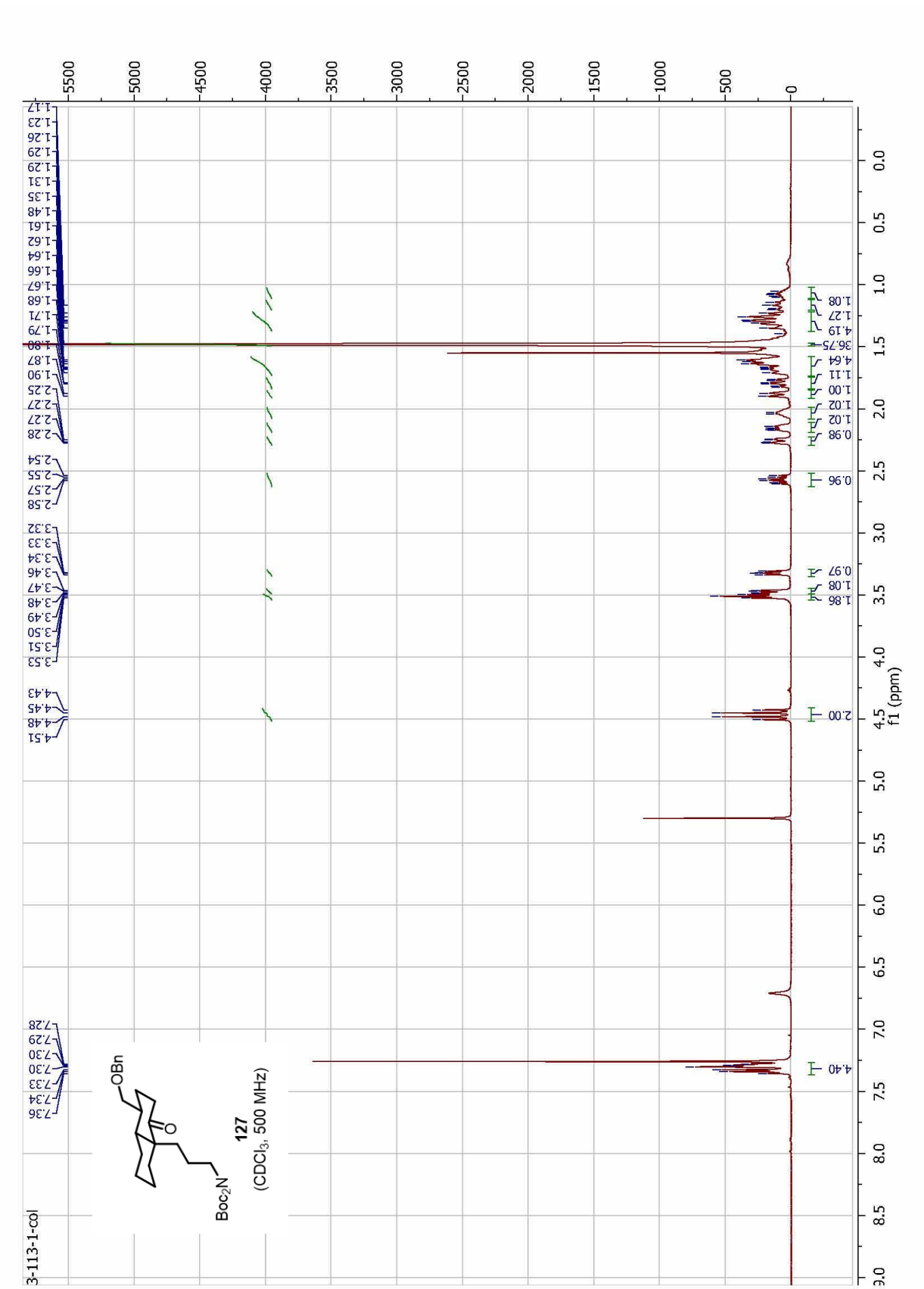
OBn
OMOM
O
N3
123
(CDCl3, 500 MHz)
ppm

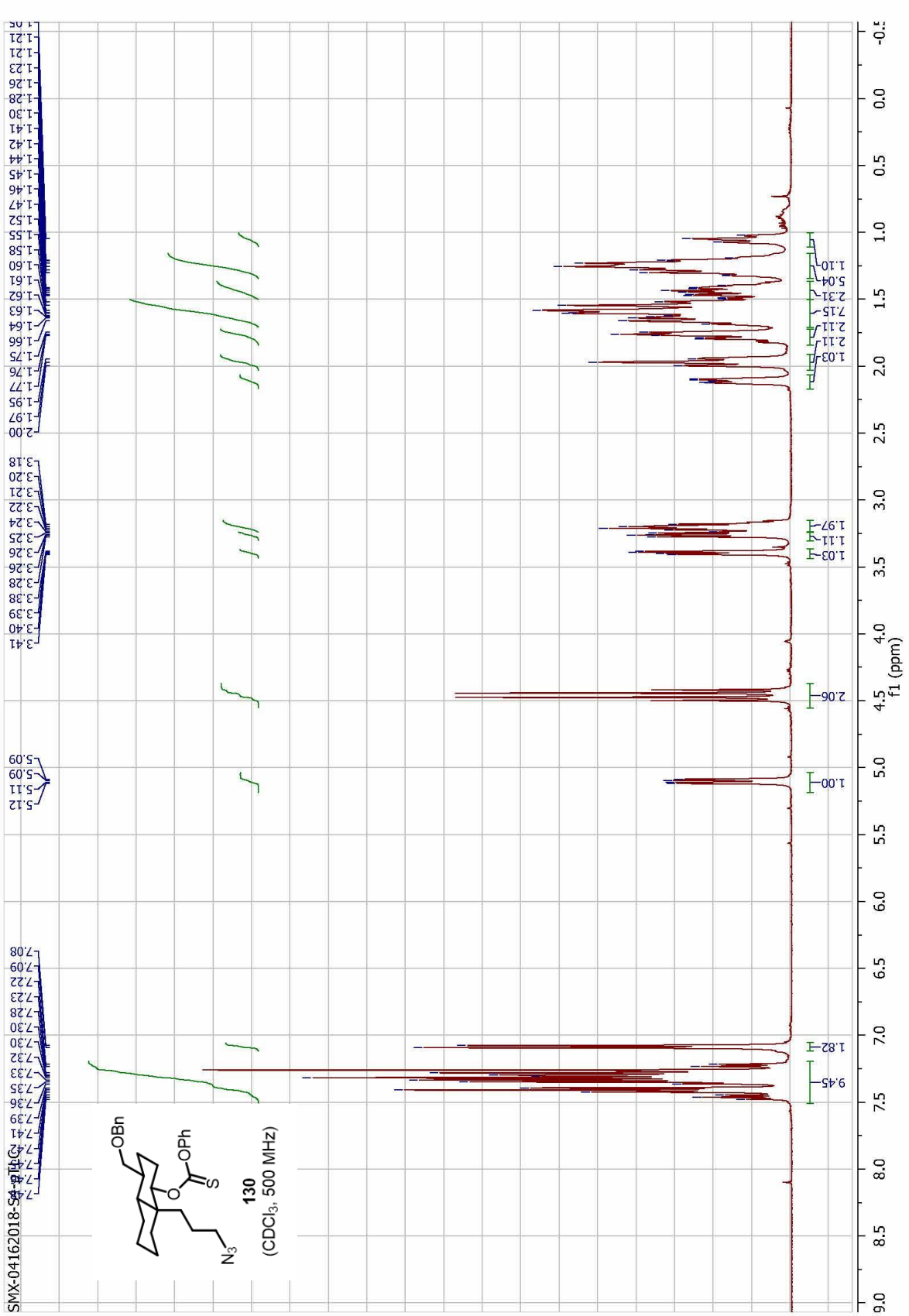

214.476
138.395
128.341
127.583
127.506
96.808
73.248
72.037
67.206
55.196
51.836
51.025
48.901
45.744
35.977
35.443
28.417
25.808
25.069
24.132
22.713
20.429
OBn
OMOM
O
N3
123
(CDCl3, 126 MHz)
ppm
0
20
40
60
80
100
120
140
160
180
200
220

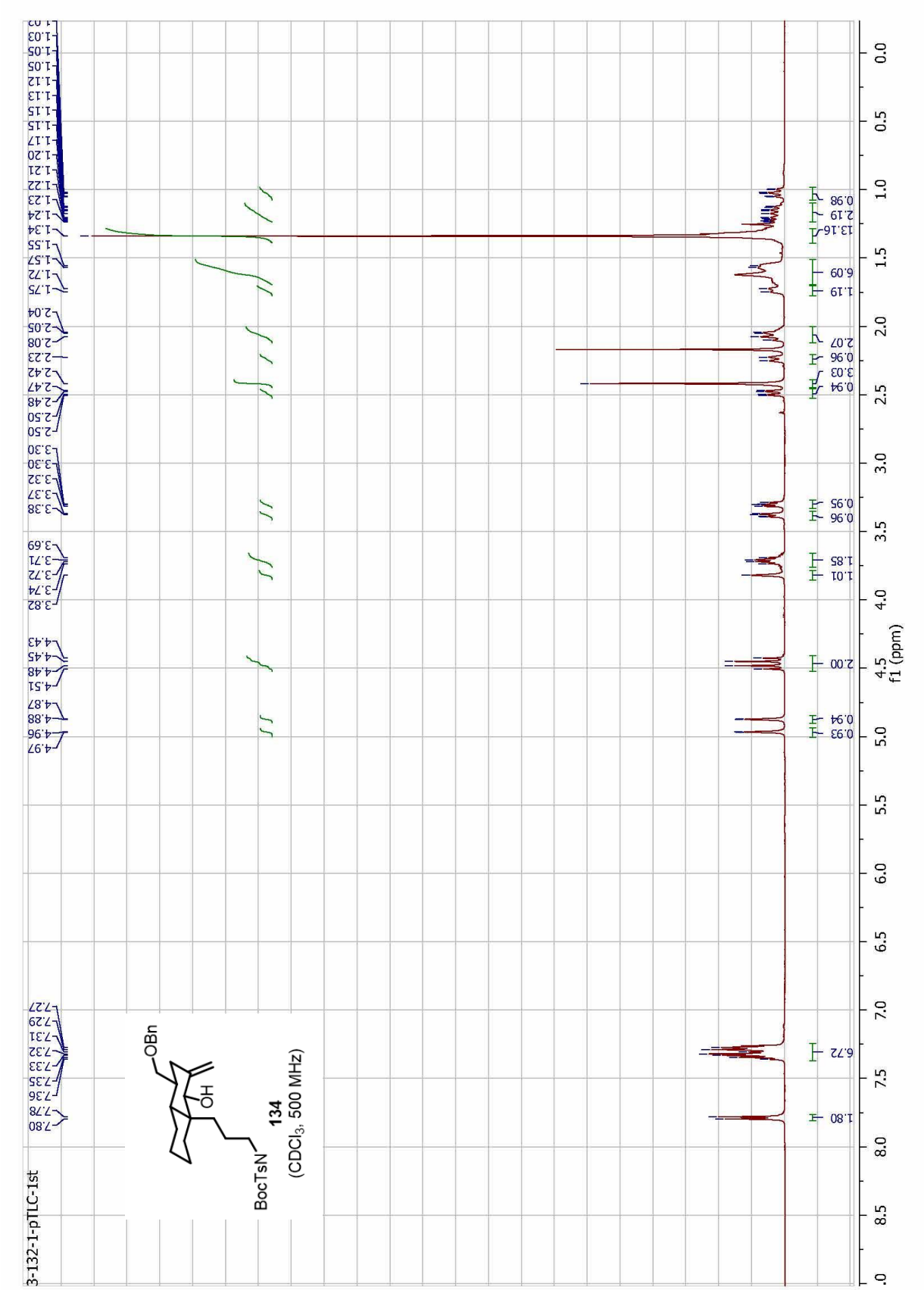

3-76-1-pTLC
OBz
OMOM
H
N
124-Bz
(CDCl3, 500 MHz)
f1 (ppm)

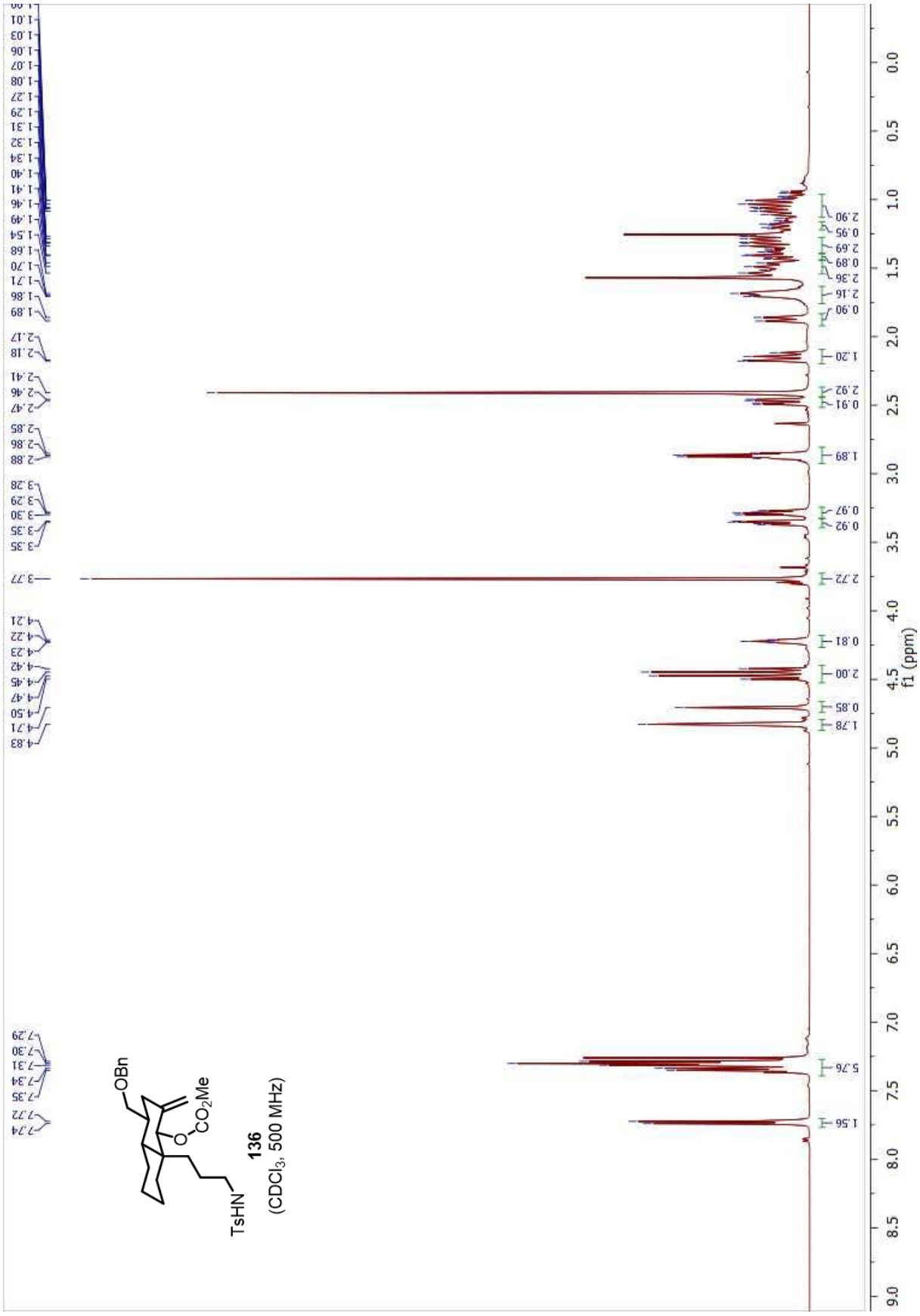

3-76-1-pTLC-13C
OBz
OMOM
N
H
124-Bz
(CDCl3, 126 MHz)
166.86
132.84
130.50
129.54
128.35
96.66
69.54
67.85
60.48
55.32
42.85
42.12
37.41
36.53
35.83
34.04
26.72
26.56
25.29
21.48
20.89
20.15
f1 (ppm)

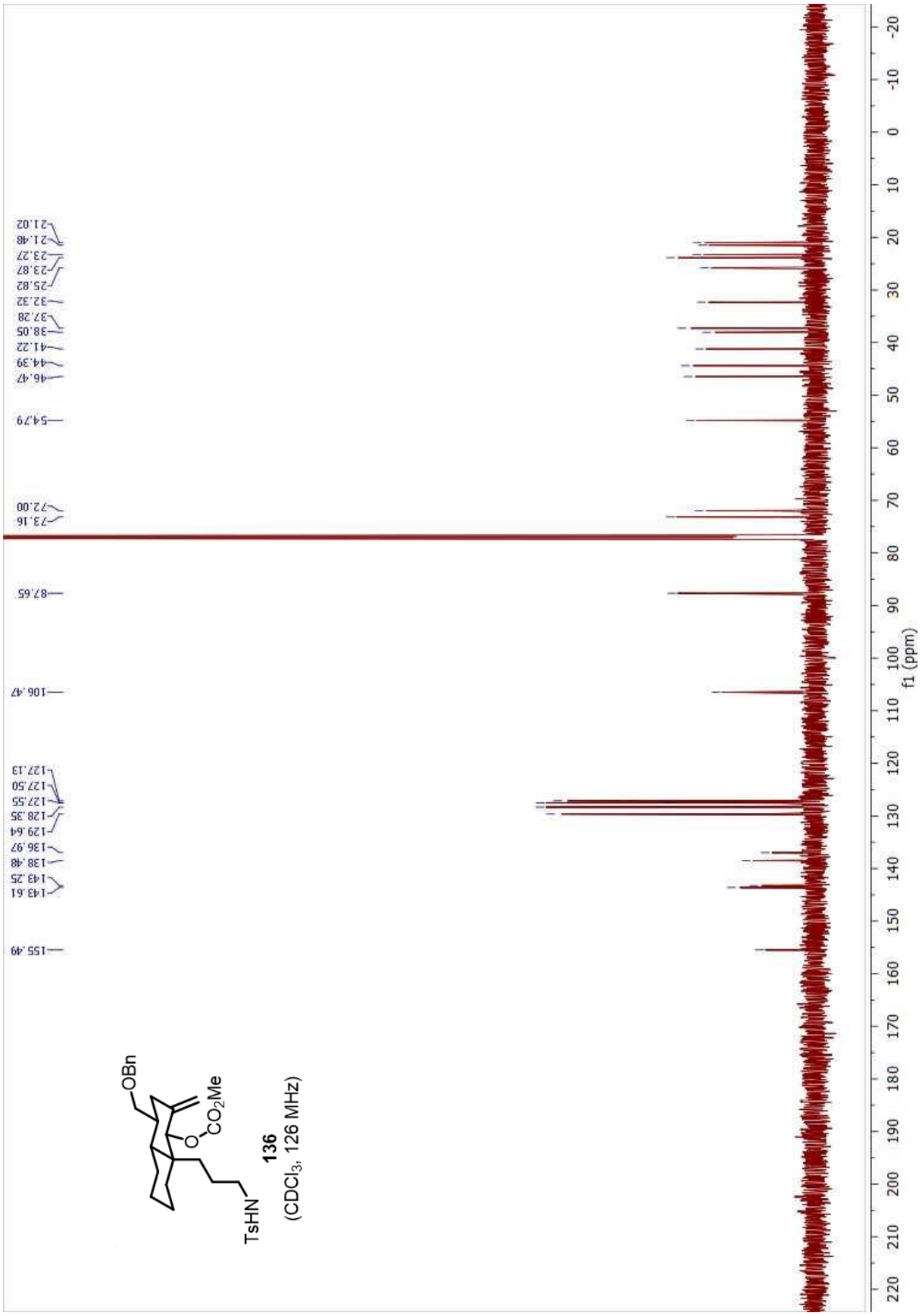

SMX-02052018-S1
215.20
OBn
OMOM
O
N3
123
PPh3, Δ
(CDCl3, 126 MHz)
OBn
OMOM
H
N
125
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)

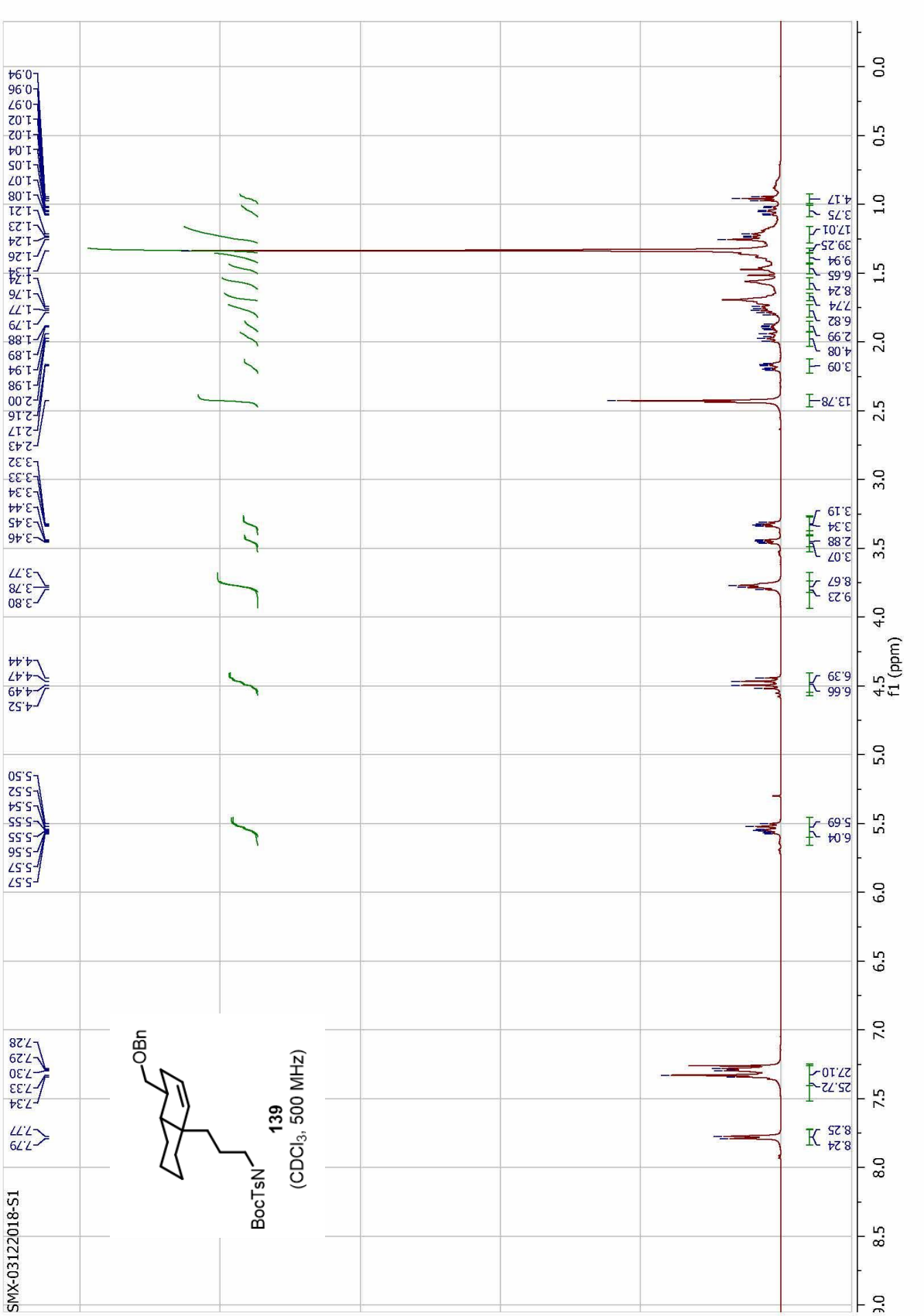

OBn
O
Boc2N
127
(CDCl3, 500 MHz)
f1 (ppm)

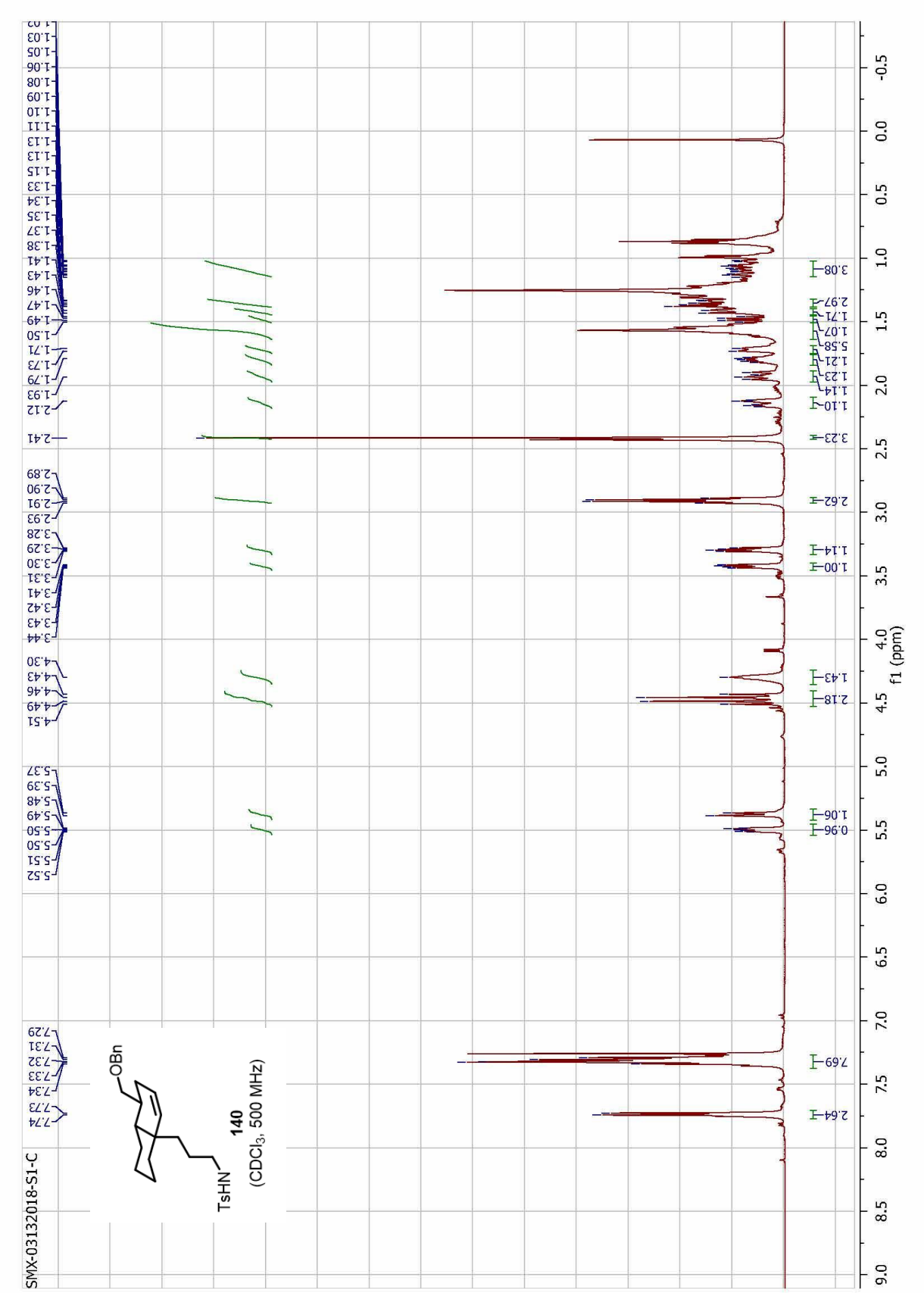

SMX-04162018-S4-1H-CDCl3
OBn
OPh
S
O
N3
130
(CDCl3, 500 MHz)
f1 (ppm)

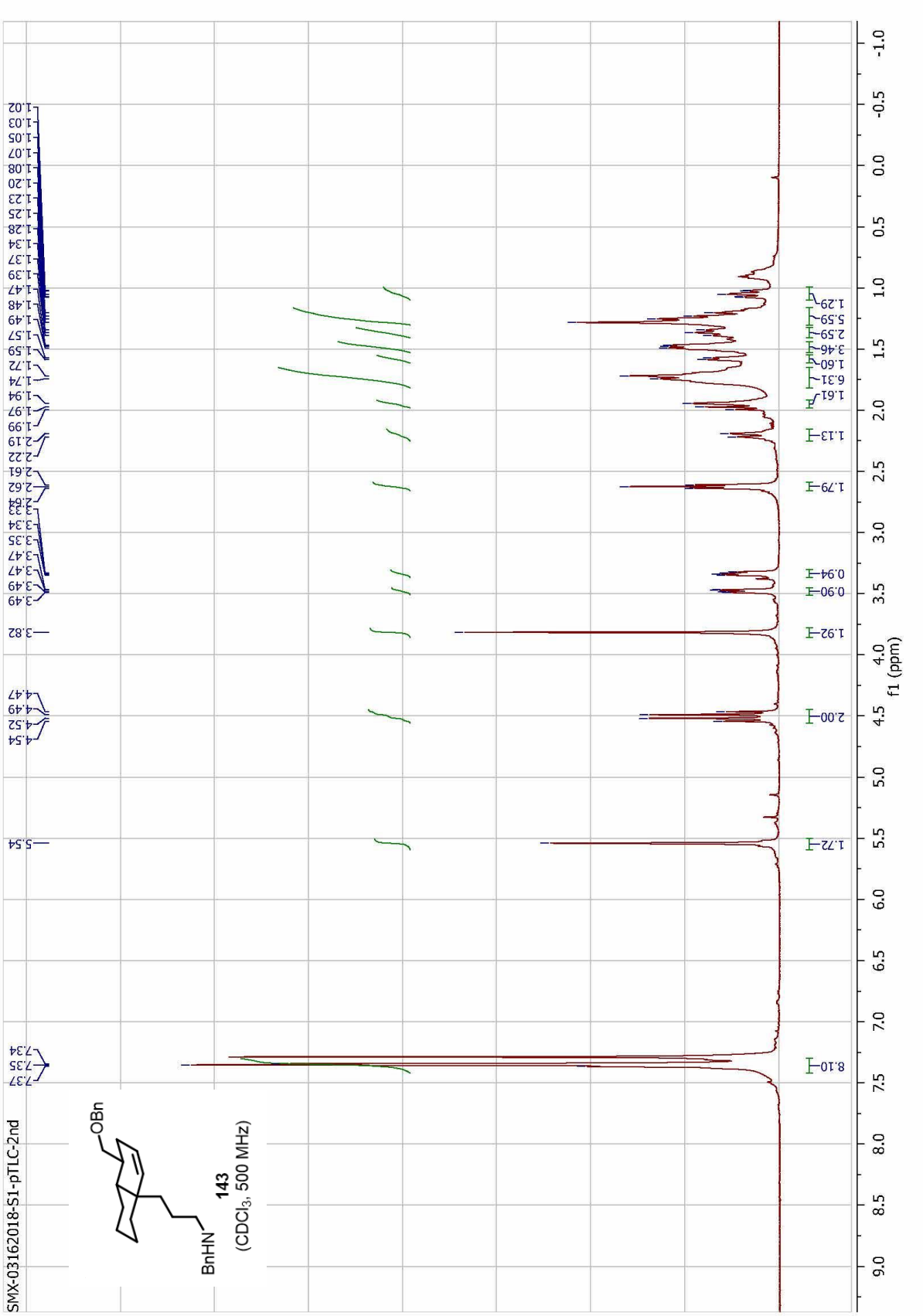

3-132-1-pTLC-1st
OBn
OH
BocTsN
134
(CDCl3, 500 MHz)
f1 (ppm)


OBn
CO2Me
TsHN
136
(CDCl3, 500 MHz)
f1 (ppm)

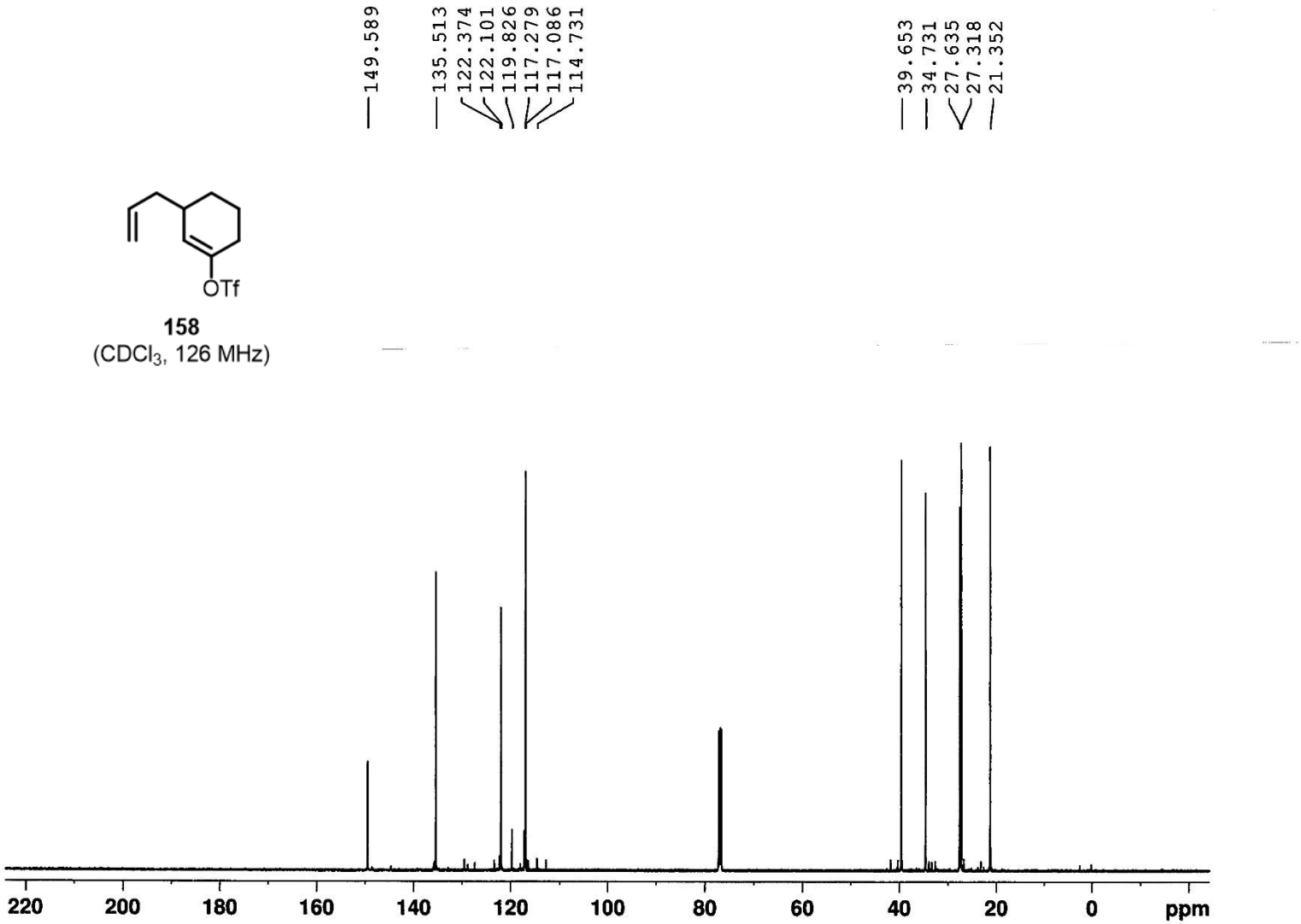

OBn
CO2Me
TsHN
136
(CDCl3, 126 MHz)
21.02
21.48
23.27
23.87
25.82
32.32
37.28
38.05
41.22
44.39
46.47
54.79
72.00
73.16
87.65
106.47
127.13
127.50
127.55
128.35
129.64
136.97
138.48
143.25
143.61
155.49
f1 (ppm)


SMX-03122018-S1
OBn
BocTsN
139
(CDCl3, 500 MHz)
f1 (ppm)


SMX-03132018-S1-C
OBn
TsHN
140
(CDCl3, 500 MHz)
f1 (ppm)

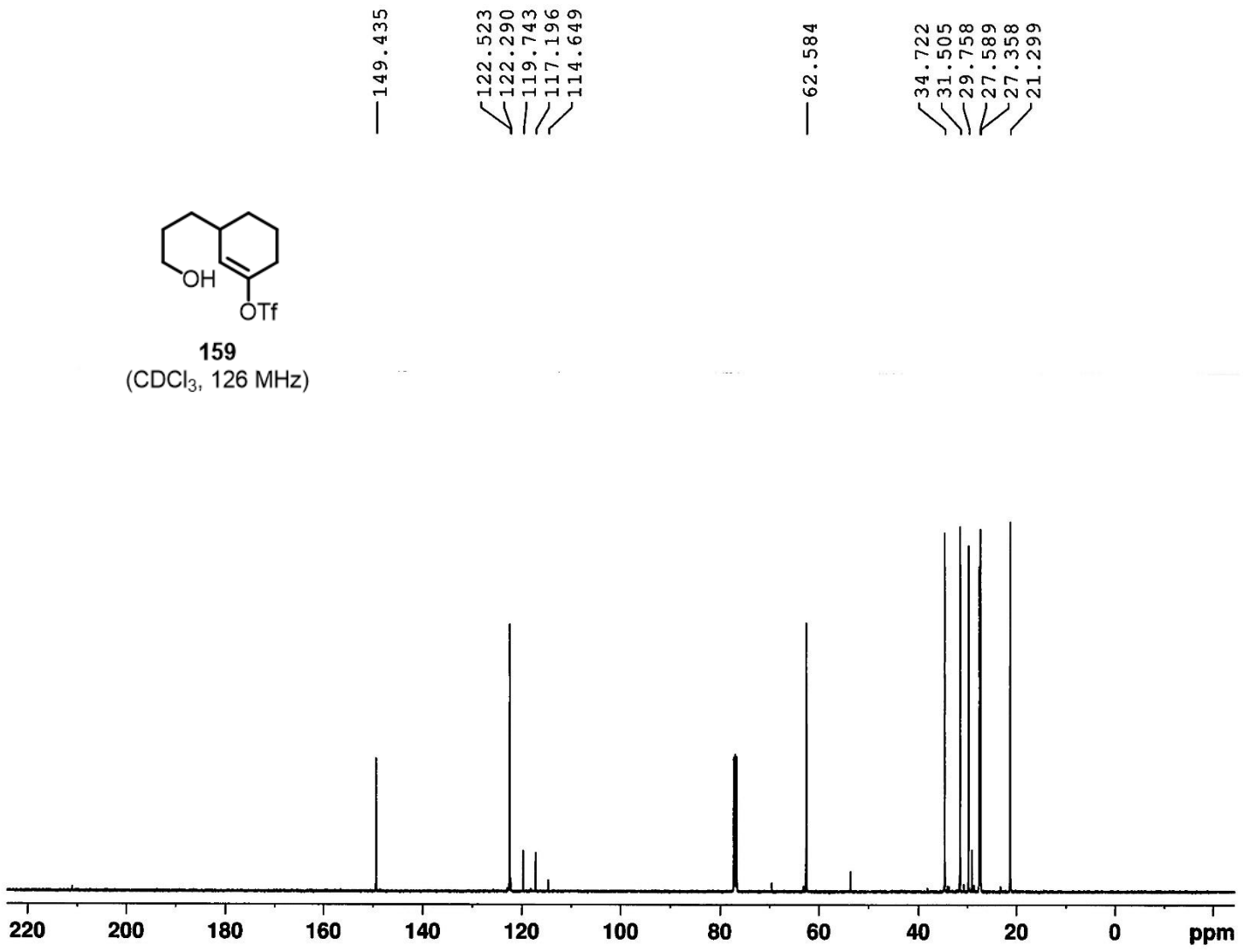

SMX-03162018-S1-pTLC-2nd
OBn
BnHN
143
(CDCl3, 500 MHz)
f1 (ppm)

OTf
158
(CDCl3, 500 MHz)
ppm
0 1 2 3 4 5 6 7 8
0.88
0.88
1.00
0.97
3.39
2.49
1.21
1.26
1.20
1.27
5.785
5.770
5.763
5.756
5.752
5.749
5.738
5.734
5.731
5.724
5.716
5.702
5.681
5.075
5.054
5.042
2.377
2.372
2.367
2.363
2.315
2.311
2.303
2.293
2.179
2.165
2.151
2.137
2.123
2.108
2.094
2.080
2.066
1.898
1.891
1.885
1.878
1.777
1.766
1.750
1.684
1.679
1.674
1.284
1.278
1.267
1.261
1.256



158
($CDCl_3$, 126 MHz)

OTf
OH
159
(CDCl3, 500 MHz)
5.647
3.625
3.612
3.599
2.299
2.284
2.270
1.877
1.864
1.778
1.766
1.752
1.661
1.656
1.651
1.592
1.578
1.575
1.562
1.437
1.422
1.416
1.401
1.244
1.202
1.198
1.175
0.90
2.00
3.23
2.05
1.17
1.09
2.25
2.25
1.56
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

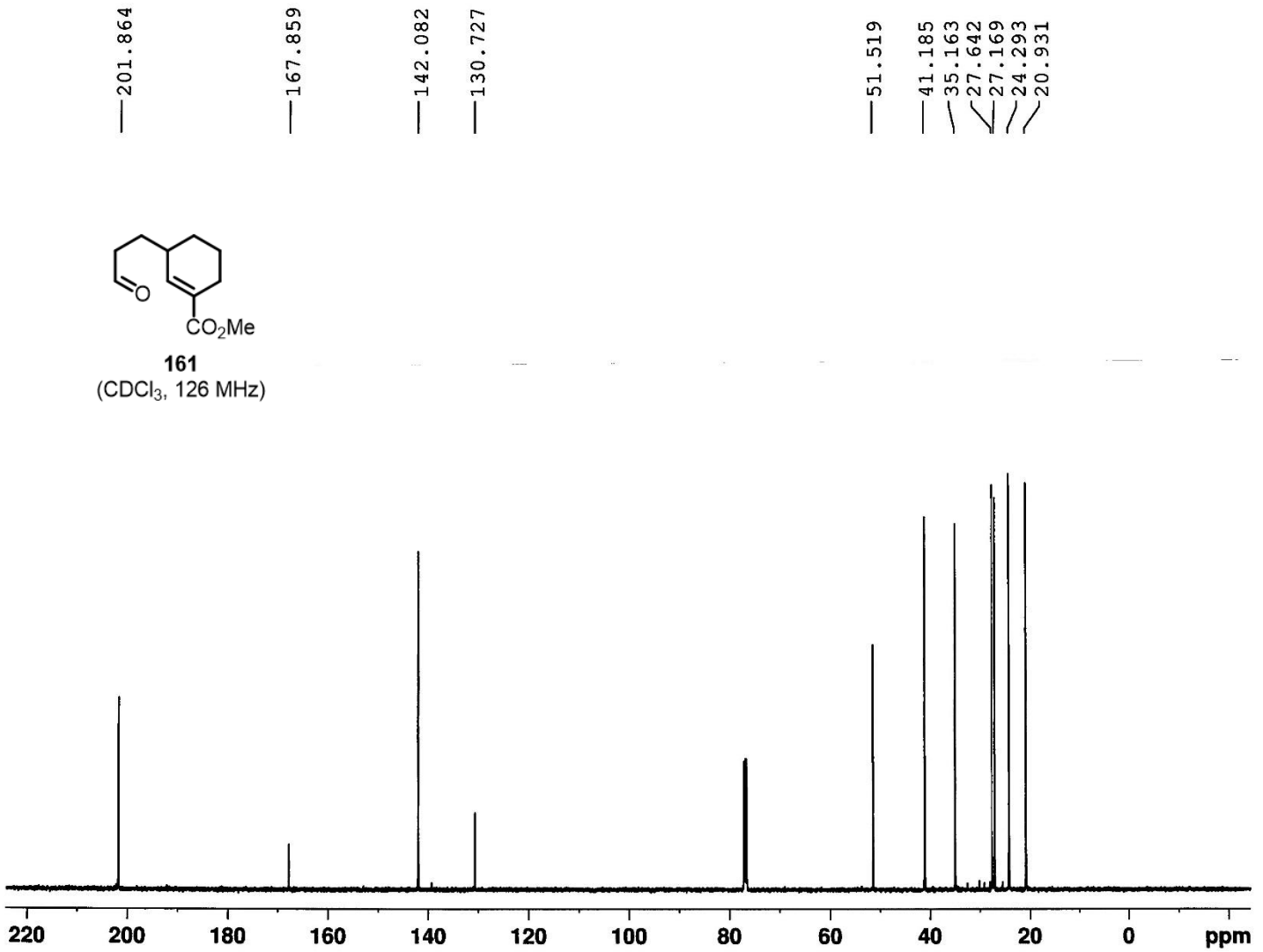


159
($CDCl_3$, 126 MHz)

9.774
5.620
2.503
2.488
2.473
2.335
2.279
1.895
1.882
1.875
1.780
1.768
1.753
1.740
1.725
1.711
1.701
1.686
1.672
1.658
1.643
1.240
1.234
1.218
1.213
OTf
O
160
(CDCl3, 500 MHz)
ppm
0.66
0.82
2.00
3.14
1.06
4.44
1.14

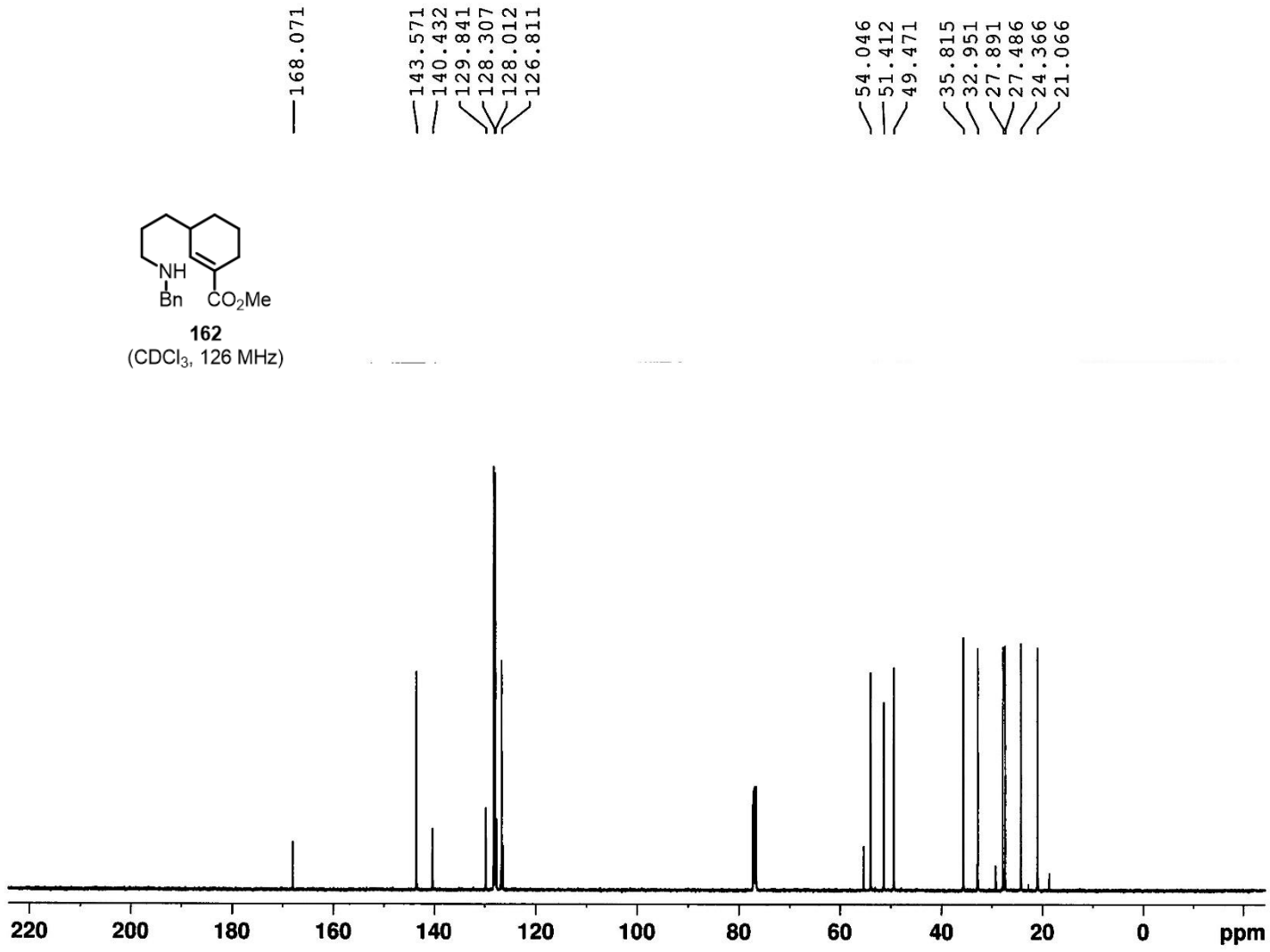
201.436
149.894
122.294
121.698
119.747
117.200
114.652
40.905
34.194
27.537
27.150
27.083
21.173
OTf
O
160
(CDCl3, 126 MHz)
ppm
220
200
180
160
140
120
100
80
60
40
20
0

9.778
9.776
6.798
3.708
3.706
2.532
2.529
2.515
2.501
2.313
2.277
2.238
2.155
1.791
1.776
1.772
1.761
1.747
1.733
1.720
1.694
1.678
1.663
1.649
1.635
1.621
1.539
1.525
1.516
1.506
1.496
CO2Me
O
161
(CDCl3, 500 MHz)
ppm
10
9
8
7
6
5
4
3
2
1
0.69
3.00
0.85
2.04
2.10
1.12
3.47
1.16
1.11
1.19

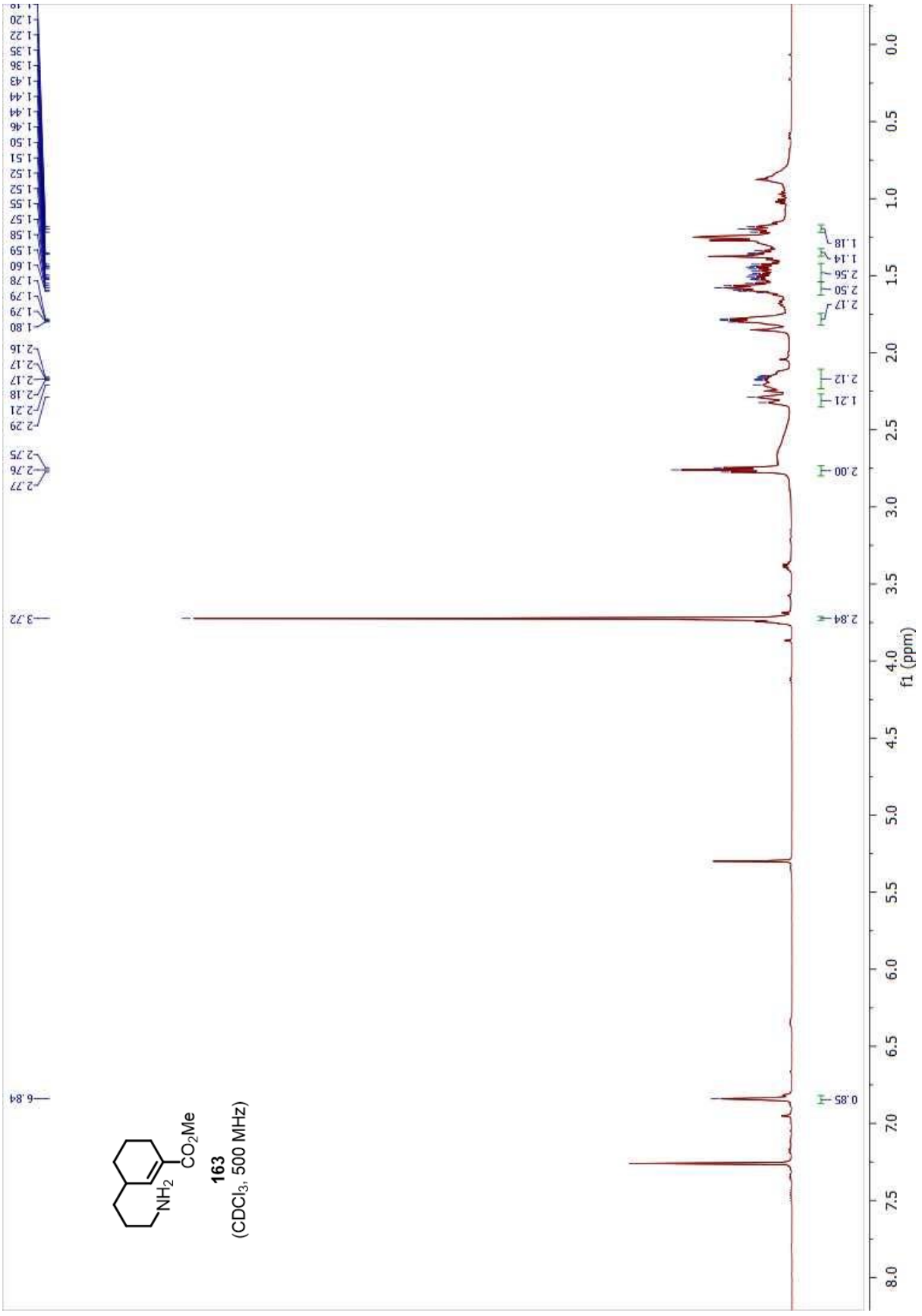


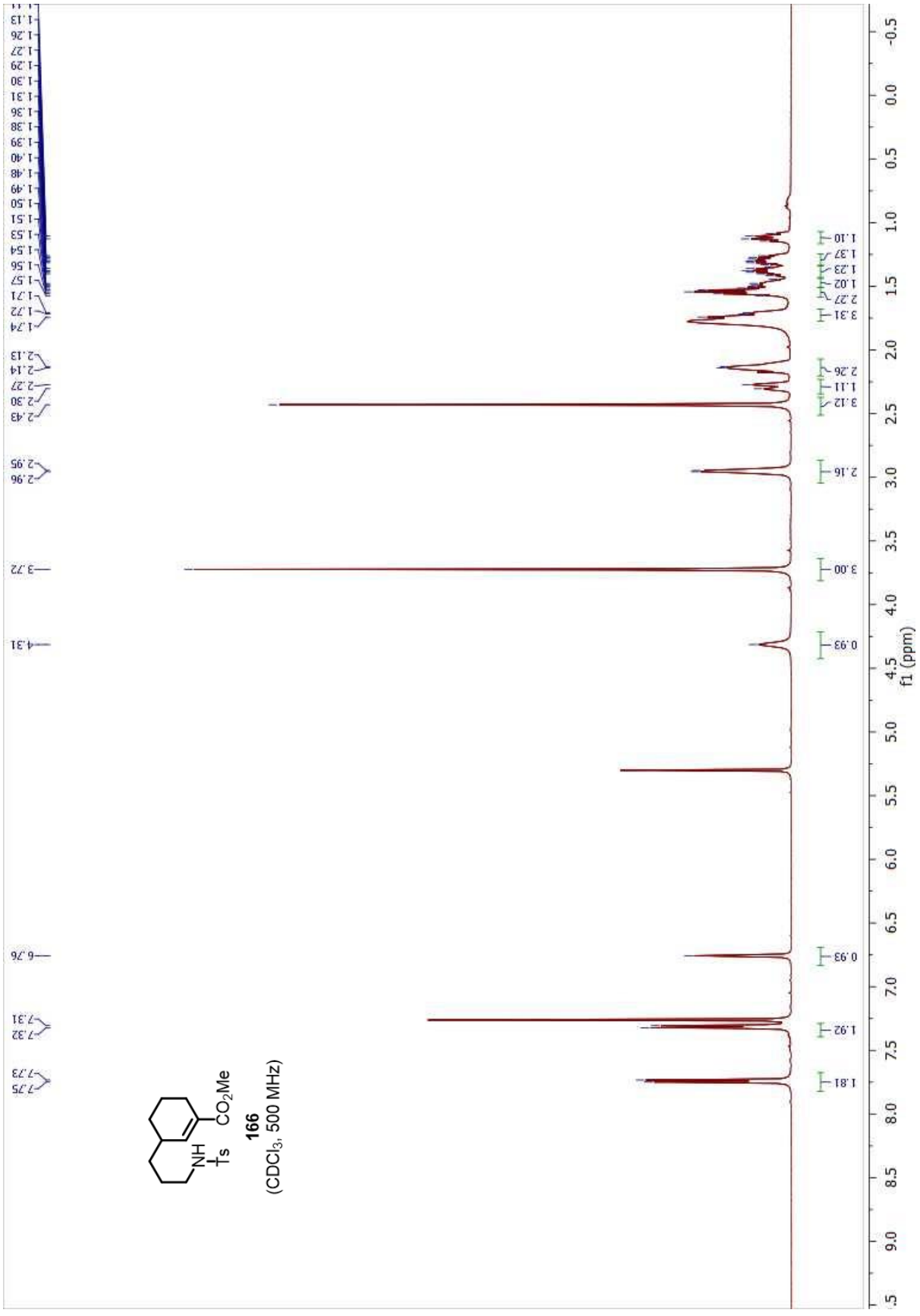
161
($CDCl_3$, 126 MHz)

7.311
7.242
6.865
3.785
3.716
2.651
2.637
2.623
2.318
2.284
2.183
1.796
1.786
1.775
1.626
1.610
1.595
1.580
1.566
1.519
1.508
1.499
1.490
1.478
1.465
1.451
1.436
1.399
1.384
1.367
1.357
1.341
1.325
NH
Bn
CO2Me
162
(CDCl3, 500 MHz)
ppm
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
4.02
0.98
0.91
2.10
3.00
2.11
1.07
2.13
2.17
2.17
2.38
1.38
1.20

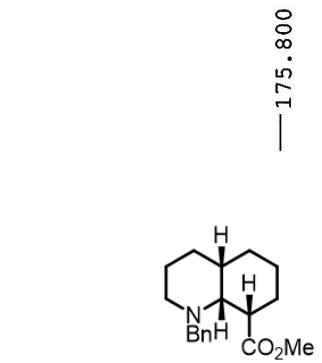


162
($CDCl_3$, 126 MHz)

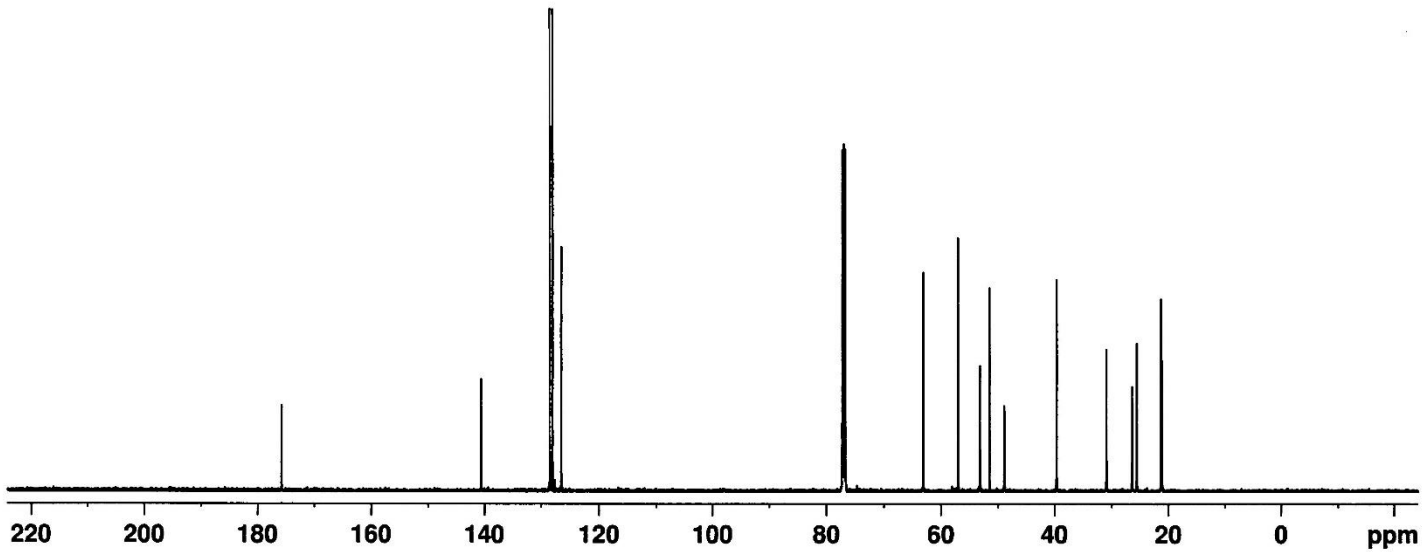

NH2
CO2Me
163
(CDCl3, 500 MHz)
f1 (ppm)

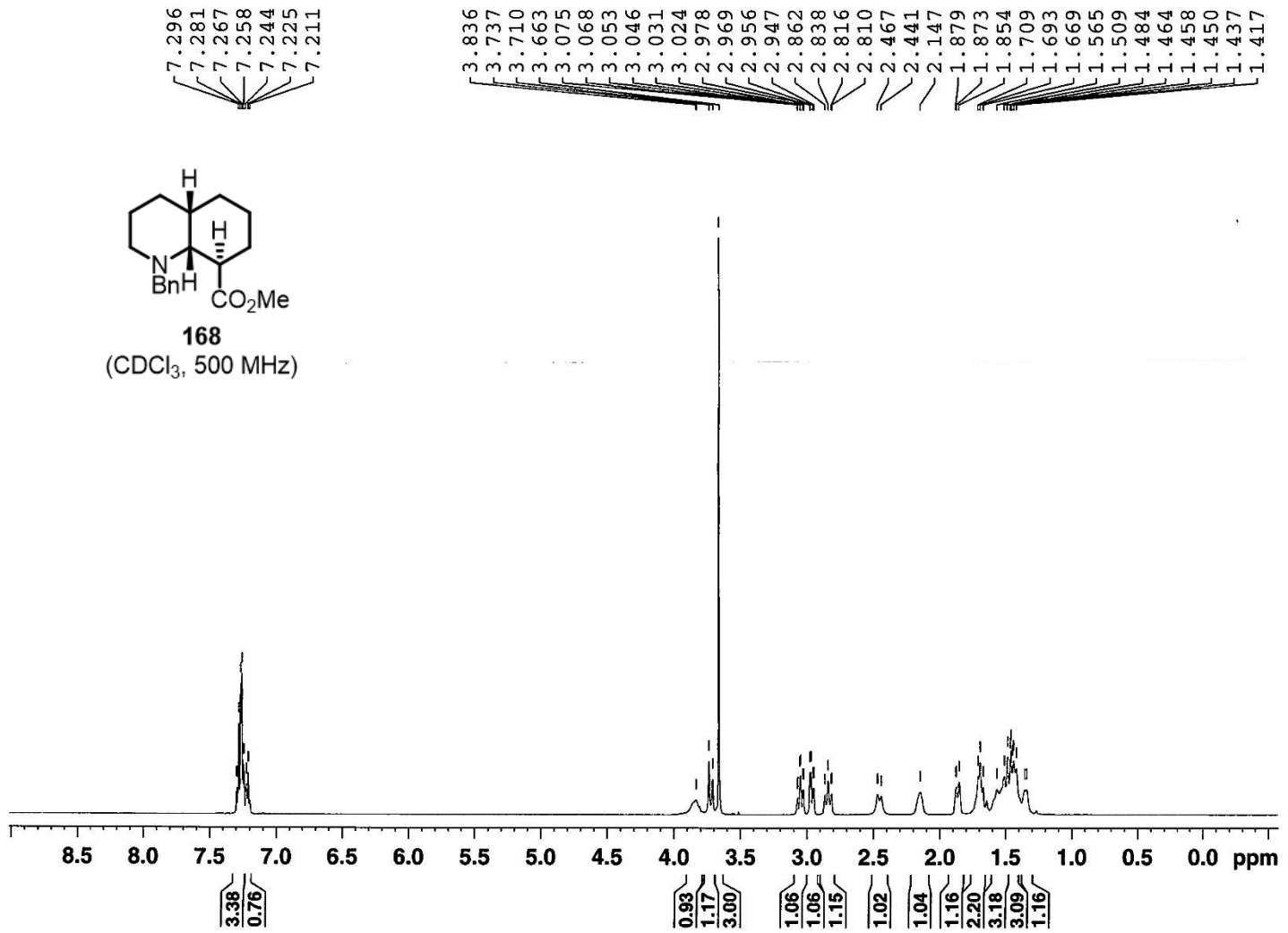

NH
Ts
CO2Me
166
(CDCl3, 500 MHz)
f1 (ppm)

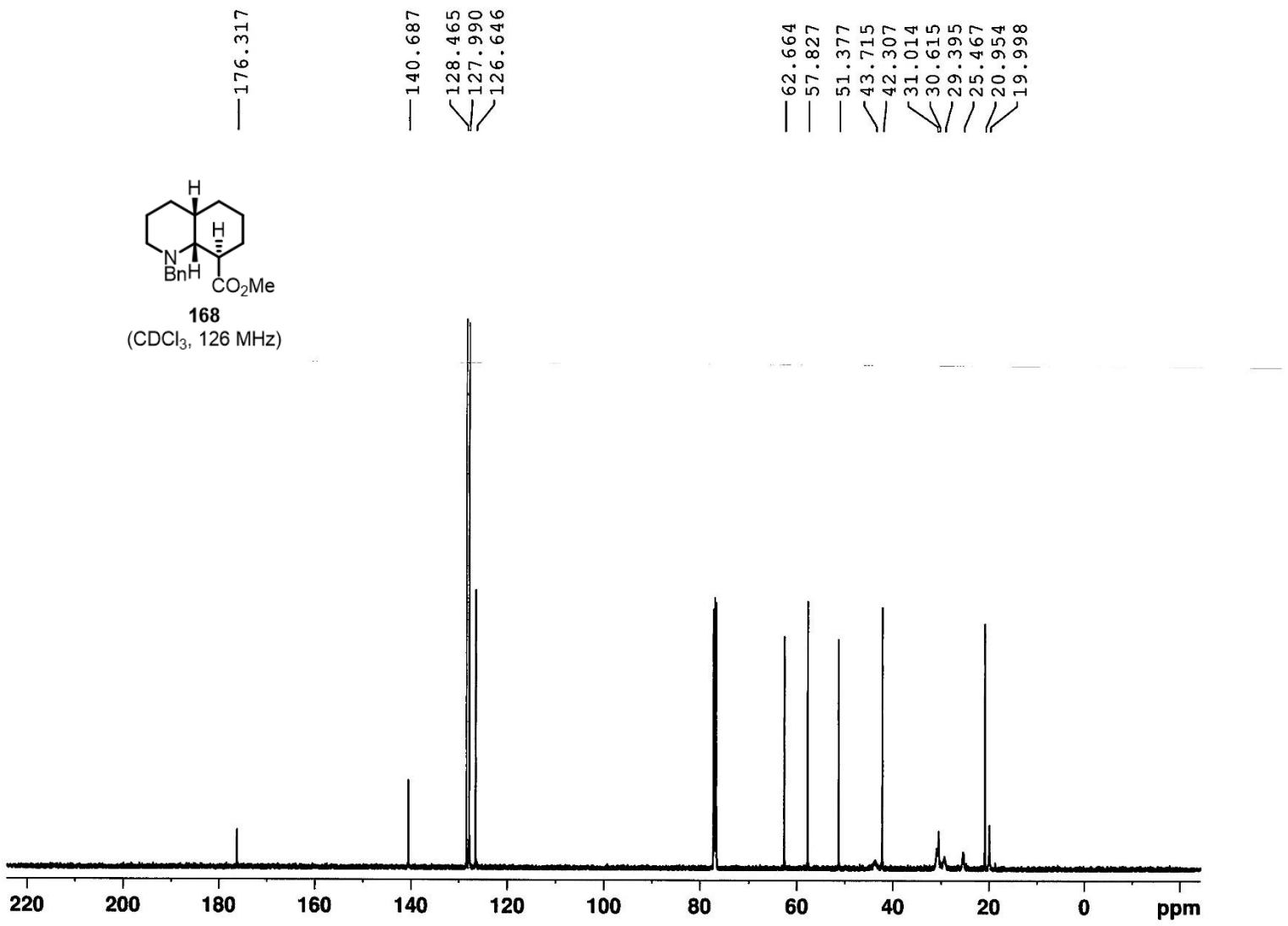
7.300
7.287
7.228
7.215
3.693
3.087
2.799
2.774
2.704
2.678
2.388
2.363
2.297
2.289
2.272
2.264
2.247
2.238
2.221
2.212
1.982
1.955
1.949
1.915
1.866
1.858
1.849
1.841
1.833
1.729
1.704
1.621
1.604
1.596
1.570
1.564
1.413
1.395
1.387
H
H
N
BnH
CO2Me
167
(CDCl3, 500 MHz)
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0 ppm
3.70
0.78
3.28
0.96
1.00
1.00
0.97
1.02
2.07
2.08
1.05
3.17
1.12
2.15



167
($CDCl_3$, 126 MHz)

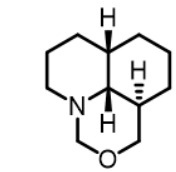



7.296
7.281
7.267
7.258
7.244
7.225
7.211
3.836
3.737
3.710
3.663
3.075
3.068
3.053
3.046
3.031
3.024
2.978
2.969
2.956
2.947
2.862
2.838
2.816
2.810
2.467
2.441
2.147
1.879
1.873
1.854
1.709
1.693
1.669
1.565
1.509
1.484
1.464
1.458
1.450
1.437
1.417
H
H
N
BnH
CO2Me
168
(CDCl3, 500 MHz)
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
3.38
0.76
0.93
1.17
3.00
1.06
1.06
1.15
1.02
1.04
1.16
2.20
3.18
3.09
1.16



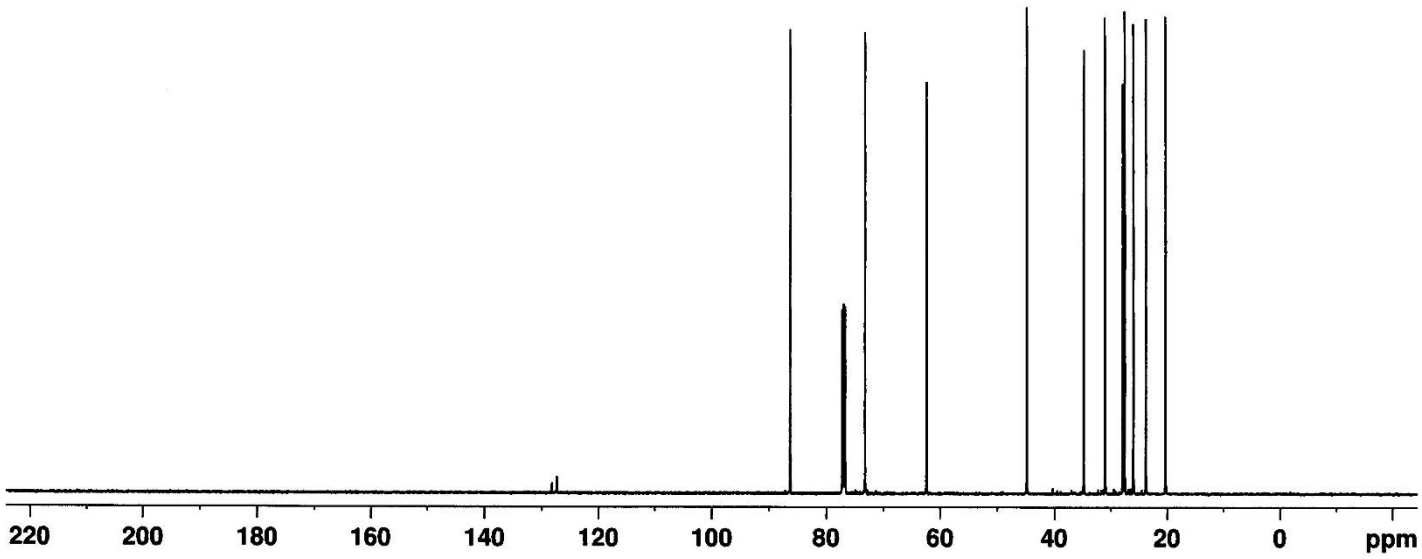
168
($CDCl_3$, 126 MHz)

1: (±)-myrioxazine A
(CDCl3, 500 MHz)
ppm
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
1.09
0.96
1.00
2.10
0.90
1.04
0.95
0.95
1.08
4.19
1.25
1.90
1.11
1.04
4.472 4.452 4.417 4.396 3.861 3.853 3.840 3.831 3.194 3.172 3.151 3.131 3.112 3.107 2.784 2.774 2.762 2.752 2.613 2.590 2.206 2.198 2.183 2.176 2.167 2.160 2.153 2.146 2.138 1.834 1.825 1.819 1.758 1.745 1.741 1.560 1.552 1.548 1.538 1.529 1.425 1.417 1.411 1.381 1.370 1.359 1.305 0.795 0.789 0.770 0.762 0.745 0.737 0.720 0.711

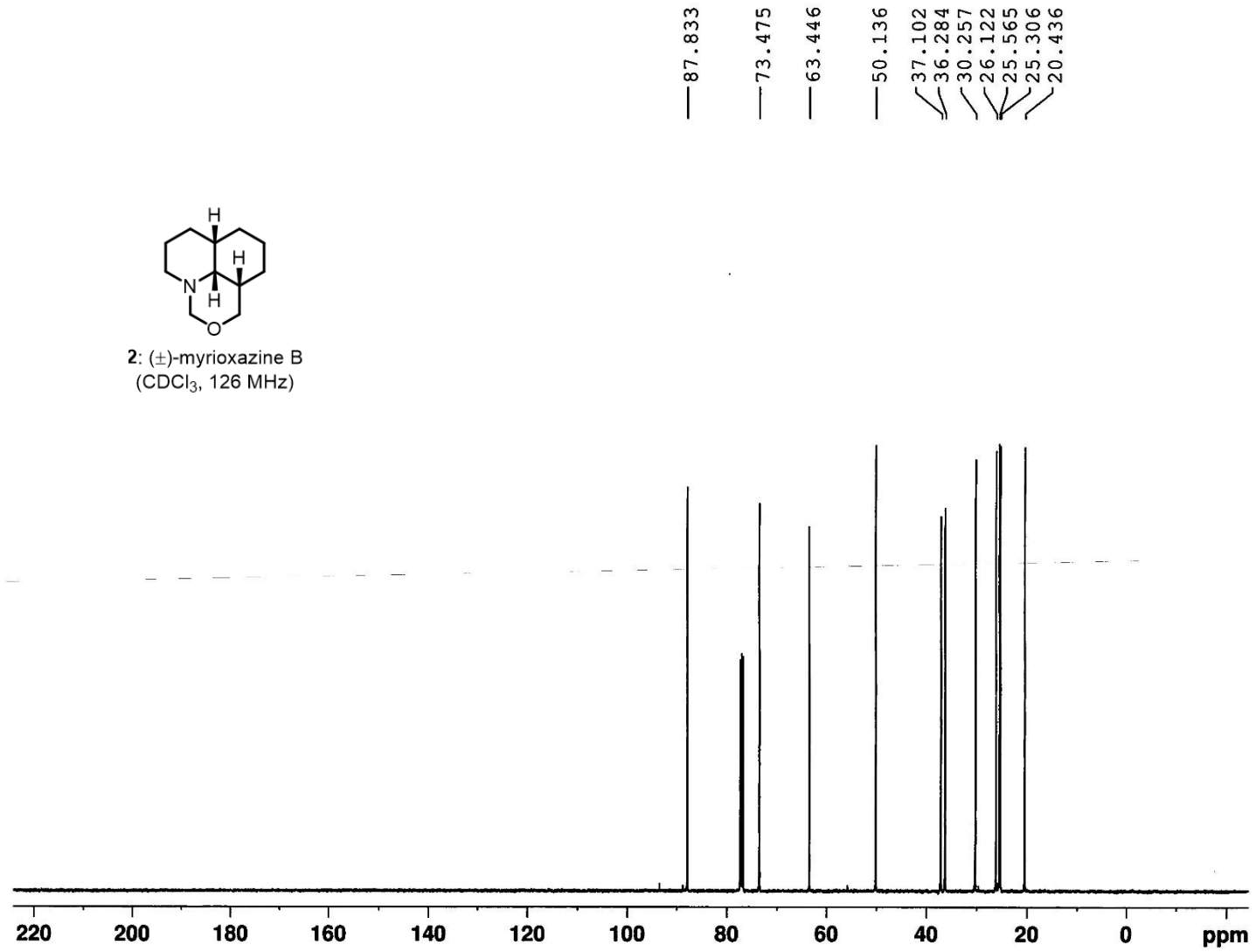


1: (±)-myrioxazine A
($CDCl_3$, 126 MHz)

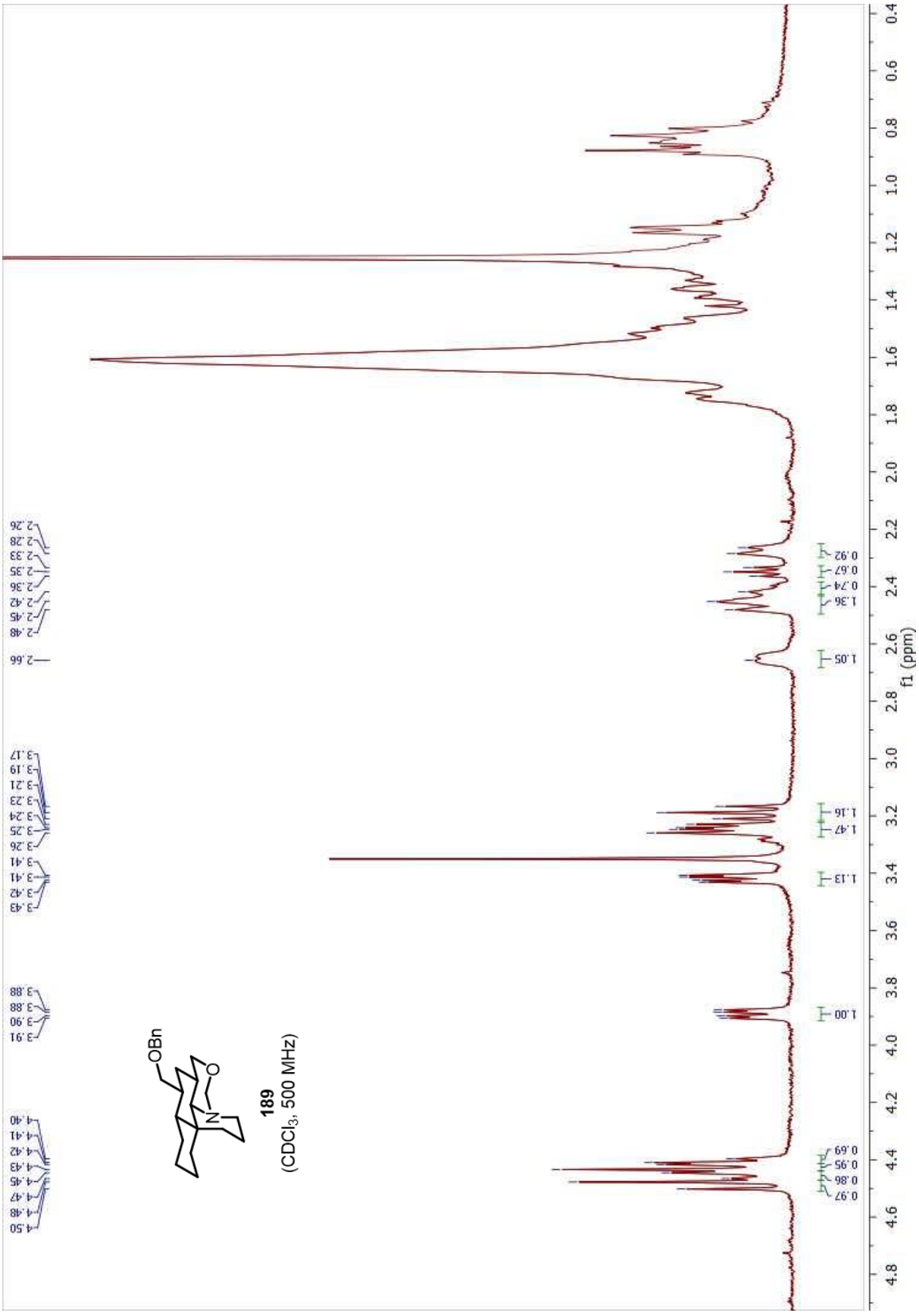
86.359
73.280
62.472
44.894
34.923
31.082
27.940
27.582
26.069
23.852
20.335



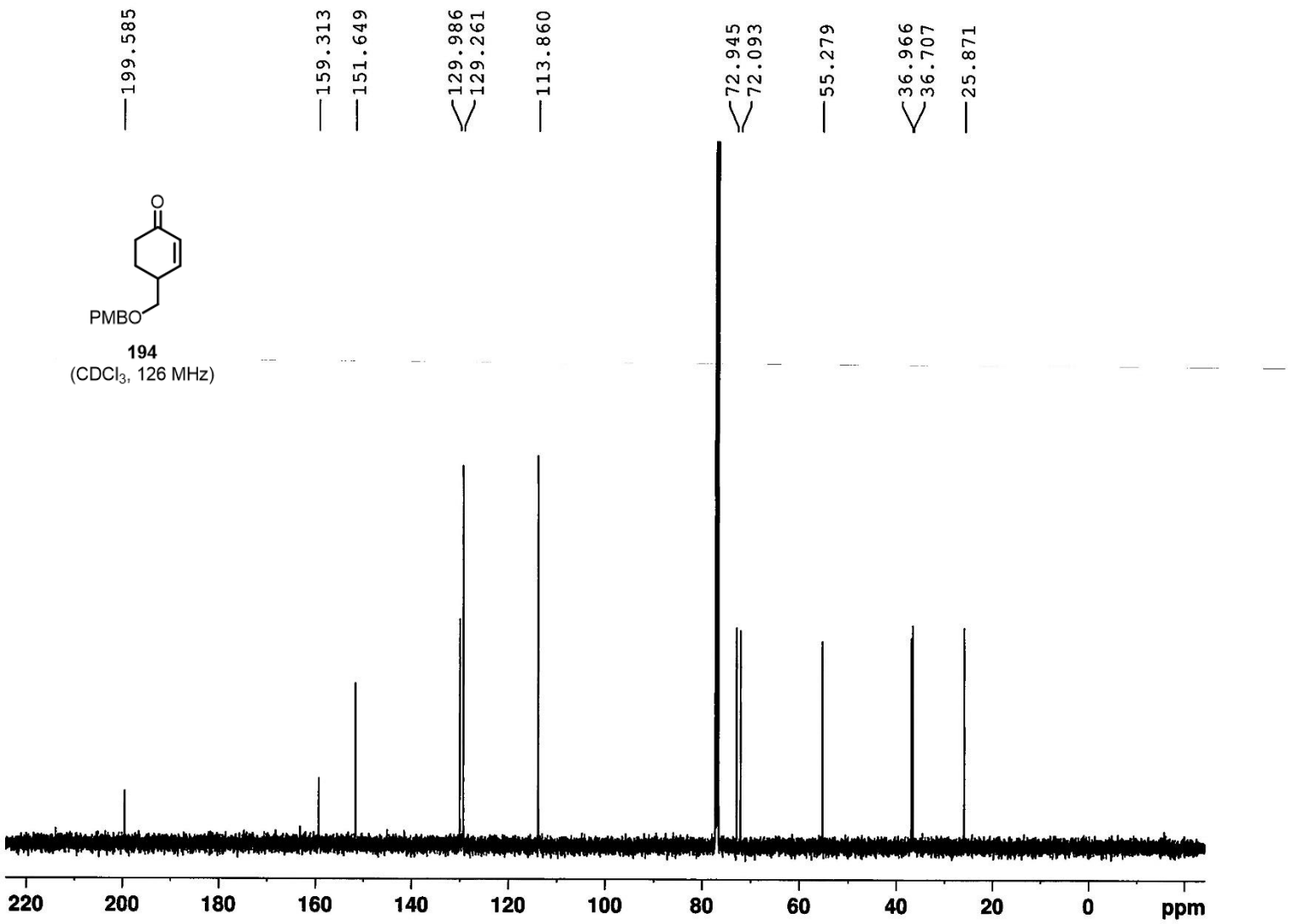
2: (±)-myrioxazine B
($CDCl_3$, 500 MHz)



2: (±)-myrioxazine B
($CDCl_3$, 126 MHz)


OBn
N
O
189
(CDCl3, 500 MHz)
f1 (ppm)

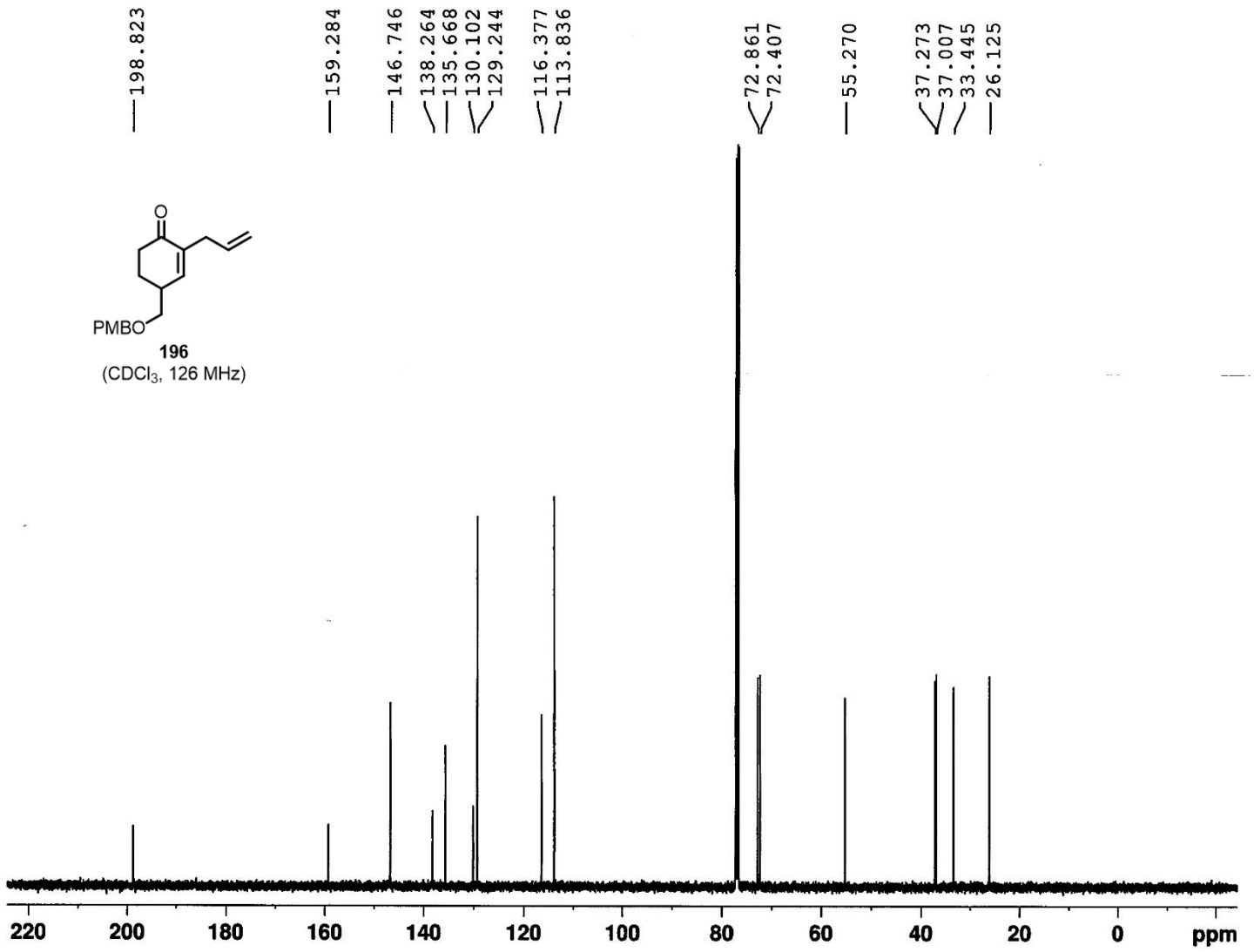
7.266
7.250
6.942
6.922
6.900
6.883
6.042
6.038
6.022
6.017
4.480
3.811
3.486
3.468
3.455
3.444
3.430
3.412
2.732
2.723
2.718
2.713
2.704
2.538
2.529
2.520
2.505
2.495
2.486
2.406
2.396
2.381
2.372
2.363
2.347
2.337
2.137
2.128
2.119
2.110
2.102
2.092
2.083
1.835
1.826
1.815
1.809
PMBO
O
194
(CDCl3, 500 MHz)
ppm
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
2.16
0.93
1.68
0.75
2.11
3.00
2.13
0.91
1.04
1.07
1.04
1.09
1.04


199.585
159.313
151.649
129.986
129.261
113.860
72.945
72.093
55.279
36.966
36.707
25.871
O
PMBO
194
(CDCl3, 126 MHz)
220
200
180
160
140
120
100
80
60
40
20
0
ppm

7.724
7.720
7.261
7.245
6.907
6.890
4.500
4.476
4.472
4.449
3.814
3.475
3.462
3.457
3.445
3.434
3.420
3.416
3.402
2.832
2.827
2.818
2.807
2.798
2.789
2.773
2.764
2.755
2.572
2.562
2.546
2.537
2.529
2.513
2.503
2.169
2.157
2.148
2.139
2.130
2.121
2.112
1.890
1.881
I
O
PMBO
195
(CDCl3, 500 MHz)
0 ppm
1
2
3
4
5
6
7
8
9
0.78
1.98
1.74
2.13
3.00
2.10
1.99
1.01
1.12
1.03

192.110
160.489
159.388
129.733
129.340
113.910
104.495
72.996
71.250
55.289
41.362
35.676
25.857
PMBO
195
(CDCl3, 126 MHz)
ppm

7.268
7.250
6.899
6.881
6.644
6.642
5.824
5.805
5.789
5.784
5.770
5.055
5.053
5.030
5.024
4.478
3.812
3.429
3.416
2.951
2.948
2.945
2.942
2.938
2.734
2.729
2.724
2.720
2.715
2.711
2.559
2.550
2.541
2.526
2.517
2.508
2.399
2.389
2.373
2.364
2.356
2.340
2.330
2.108
2.099
2.089
2.082
2.072
1.784
1.775
1.764
1.757
1.749
1.738
1.729
PMBO
196
(CDCl3, 500 MHz)
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
ppm
1.99
1.74
0.92
0.67
1.66
2.15
3.00
2.18
1.99
0.97
1.07
1.06
1.08
1.06


198.823
159.284
146.746
138.264
135.668
130.102
129.244
116.377
113.836
72.861
72.407
55.270
37.273
37.007
33.445
26.125
O
PMBO
196
(CDCl3, 126 MHz)
220
200
180
160
140
120
100
80
60
40
20
0
ppm

7.474
7.467
7.460
7.345
7.339
7.333
7.233
7.216
6.881
6.864
5.801
5.790
5.785
5.749
5.042
5.027
5.023
5.009
4.994
4.975
4.941
4.920
4.378
4.373
3.806
3.606
3.599
3.587
3.581
3.261
3.246
3.243
3.228
2.609
2.598
2.426
2.414
2.385
2.339
2.331
2.323
2.291
2.263
2.252
2.091
2.076
1.992
1.972
1.963
1.944
1.866
0.289
0.280
SiMe2Ph
O
PMBO
198
(CDCl3, 500 MHz)
ppm
8
7
6
5
4
3
2
1
0
1.73
2.51
1.91
1.88
4.01
3.25
1.05
2.10
3.09
1.00
1.00
1.02
1.02
1.00
4.33
3.32
1.11
1.07
1.10
6.40

212.092
159.129
142.577
138.615
135.466
133.782
132.595
130.539
129.134
128.915
127.737
117.683
115.131
113.731
72.596
72.365
56.177
55.270
42.866
41.323
38.772
38.689
37.427
33.339
29.085
-2.647
-2.665
SiMe2Ph
O
PMBO
198
(CDCl3, 126 MHz)
ppm
220
200
180
160
140
120
100
80
60
40
20
0

7.468
7.463
7.458
7.450
7.342
7.336
7.330
7.242
7.225
6.888
6.871
5.806
5.794
5.786
5.608
5.593
4.454
4.431
4.402
4.378
3.808
3.511
3.505
3.493
3.486
3.321
3.308
3.303
3.290
2.579
2.567
2.538
2.507
2.496
2.486
2.478
2.321
2.314
2.294
2.180
2.174
2.161
2.016
2.010
1.825
1.816
1.803
1.794
1.631
1.625
1.606
1.598
1.579
0.275
0.269
SiMe2Ph
O
H
PMBO
199
(CDCl3, 500 MHz)
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
1.61
2.42
1.84
1.81
1.75
1.95
2.13
3.08
1.00
1.03
0.94
2.03
1.10
4.18
1.15
1.07
1.02
1.62
5.63

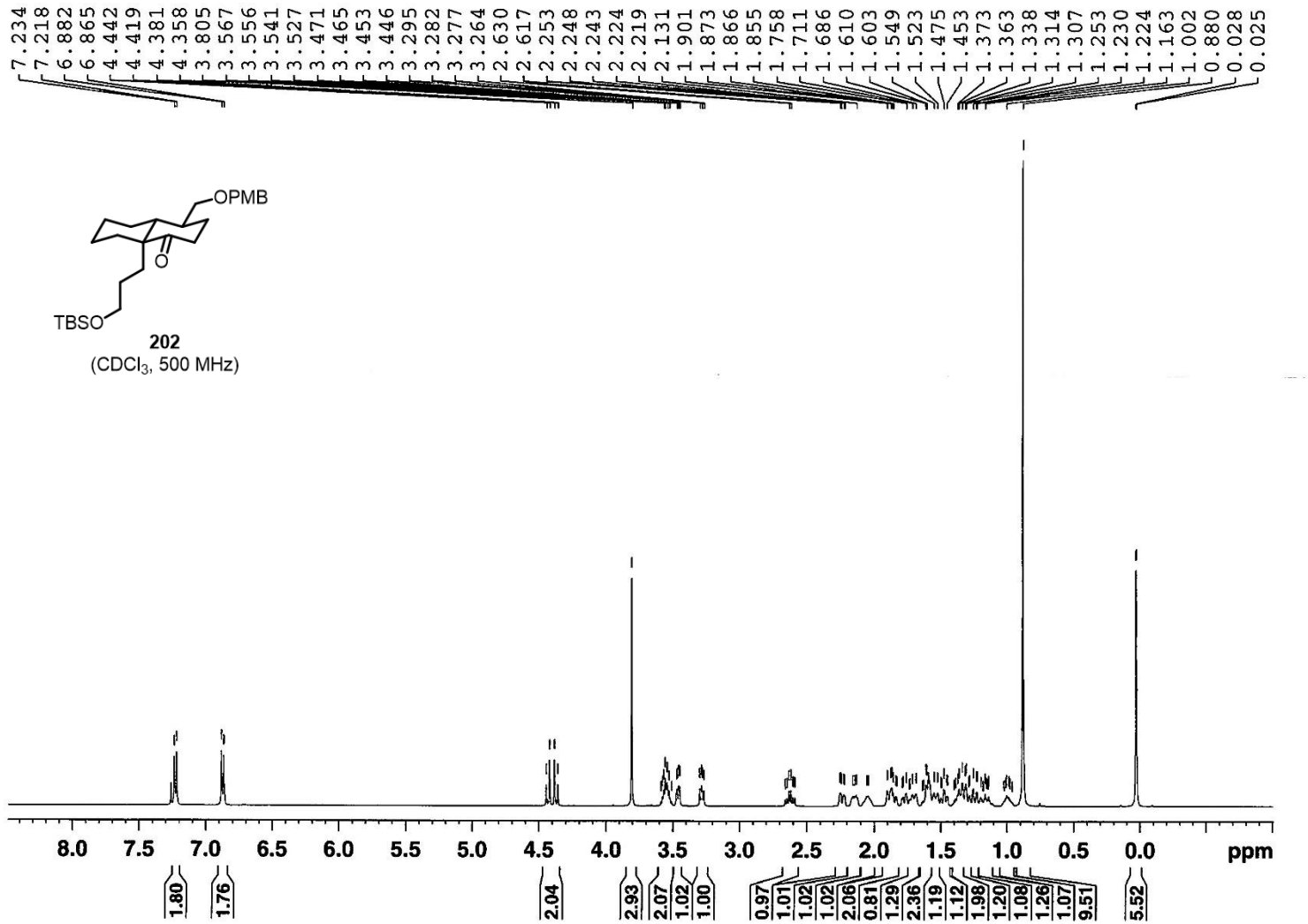
213.799
159.180
142.624
138.721
133.772
132.375
130.397
129.140
128.869
127.709
125.053
124.842
113.771
72.943
71.780
55.268
49.905
43.456
38.663
37.238
36.058
30.501
29.606
27.054
-2.636
ppm
0
20
40
60
80
100
120
140
160
180
200
220
SiMe2Ph
H
O
PMBO
199
(CDCl3, 126 MHz)

OPMB
O
PhMe2Si
200
(CDCl3, 500 MHz)
ppm
0
1
2
3
4
5
6
7
8
5.99
2.11
1.40
6.19
1.21
2.30
1.02
1.08
1.10
1.02
1.00
1.05
1.05
0.94
1.00
0.99
3.07
2.13
1.84
1.87
2.39
1.67
7.463
7.337
7.332
7.231
7.215
6.883
6.866
4.432
4.409
4.373
4.350
3.806
3.447
3.441
3.429
3.422
3.258
3.245
3.240
3.227
2.473
2.459
2.204
2.199
2.194
2.176
1.869
1.845
1.786
1.777
1.676
1.651
1.598
1.537
1.511
1.501
1.485
1.396
1.391
1.254
1.236
1.227
1.217
1.196
1.170
1.126
0.712
0.703
0.698
0.692
0.685
0.679
0.229
0.222

OPMB
O
PhMe2Si
200
(CDCl3, 126 MHz)
216.088
159.128
139.316
133.472
130.560
129.067
128.839
127.744
113.735
72.826
72.156
55.271
51.360
48.388
37.704
35.656
31.851
30.947
28.463
25.923
24.140
20.537
17.371
16.718
-2.964
ppm
220
200
180
160
140
120
100
80
60
40
20
0

OPMB
O
HO
201
(CDCl3, 500 MHz)
ppm
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
1.95
1.91
2.27
3.35
2.03
1.14
0.99
1.00
0.99
1.16
1.18
2.27
1.15
1.25
2.14
3.51
2.48
2.87
0.92
1.12

215.954
159.143
130.543
129.089
113.751
113.702
72.848
72.075
63.086
55.276
50.848
48.179
37.733
35.737
30.858
28.510
26.361
25.910
24.156
23.982
20.475
OPMB
O
HO
201
(CDCl3, 126 MHz)
220
200
180
160
140
120
100
80
60
40
20
0
ppm

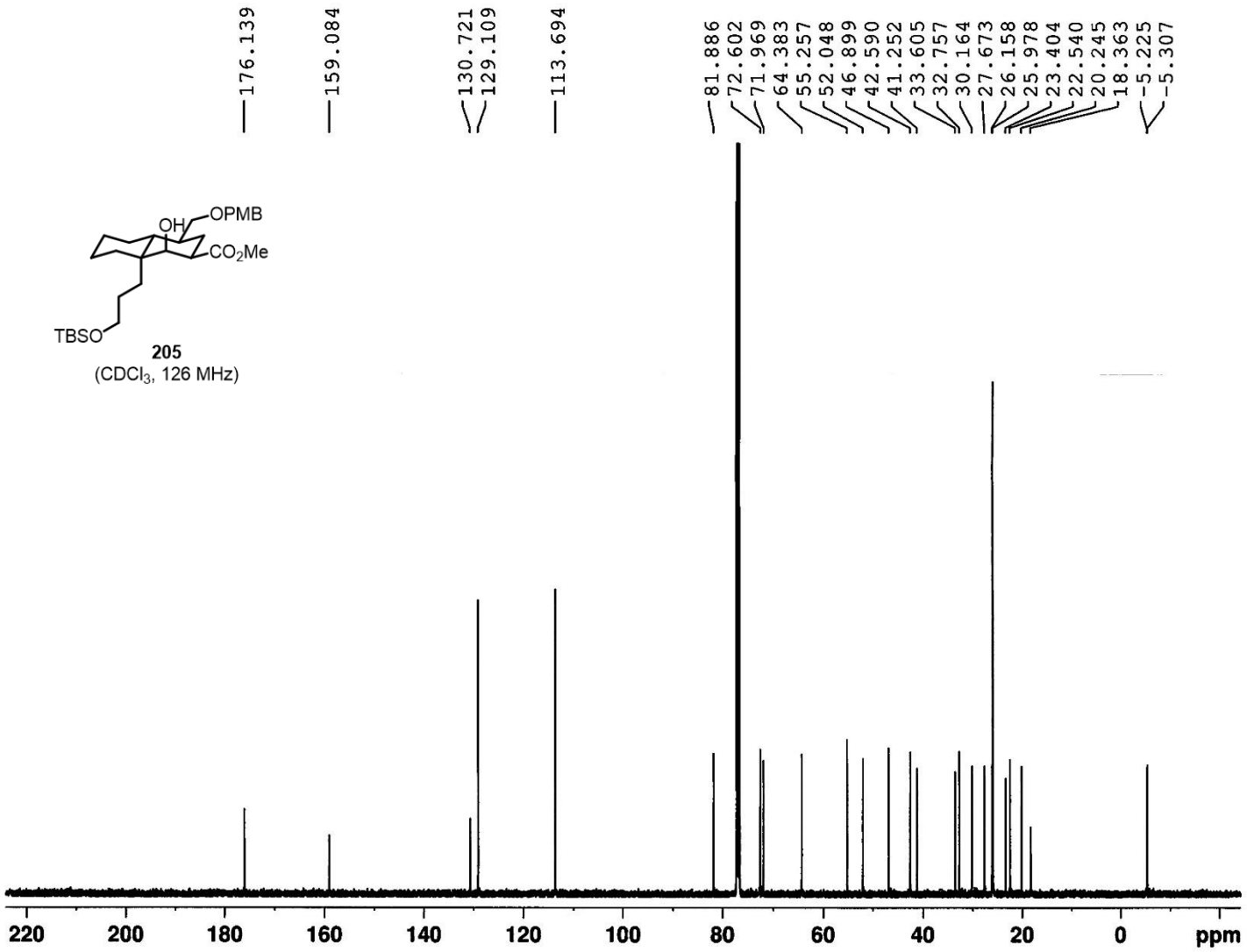

7.234
7.218
6.882
6.865
4.442
4.419
4.381
4.358
3.805
3.567
3.556
3.541
3.527
3.471
3.465
3.453
3.446
3.295
3.282
3.277
3.264
2.630
2.617
2.253
2.248
2.243
2.224
2.219
2.131
1.901
1.873
1.866
1.855
1.758
1.711
1.686
1.610
1.603
1.549
1.523
1.475
1.453
1.373
1.363
1.338
1.314
1.307
1.253
1.230
1.224
1.163
1.002
0.880
0.028
0.025
OPMB
O
TBSO
202
(CDCl3, 500 MHz)
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
1.80
1.76
2.04
2.93
2.07
1.02
1.00
0.97
1.01
1.02
1.02
2.06
0.81
1.29
2.36
1.19
1.12
1.98
1.20
1.08
1.26
1.07
9.51
5.52

-5.310
18.255
20.451
23.978
24.205
25.907
25.944
26.394
28.525
30.895
35.741
37.671
48.259
50.846
55.260
63.014
72.110
72.811
113.733
129.084
130.538
159.129
216.115
OPMB
O
TBSO
202
(CDCl3, 126 MHz)
ppm
0
20
40
60
80
100
120
140
160
180
200
220

OPMB
CO2Me
OH
TBSO
204
(CDCl3, 500 MHz)
ppm

OPMB
CO2Me
OH
TBSO
204
(CDCl3, 126 MHz)
176.134
159.096
130.593
129.095
129.062
113.709
113.681
81.172
72.814
72.206
64.275
55.258
51.723
46.275
45.837
39.653
35.030
33.525
32.298
27.463
26.078
25.984
23.622
22.544
20.819
18.332
-5.241
-5.276
ppm
220
200
180
160
140
120
100
80
60
40
20
0

OPMB
OH
CO2Me
TBSO
205
(CDCl3, 500 MHz)
ppm



205
($CDCl_3$, 126 MHz)

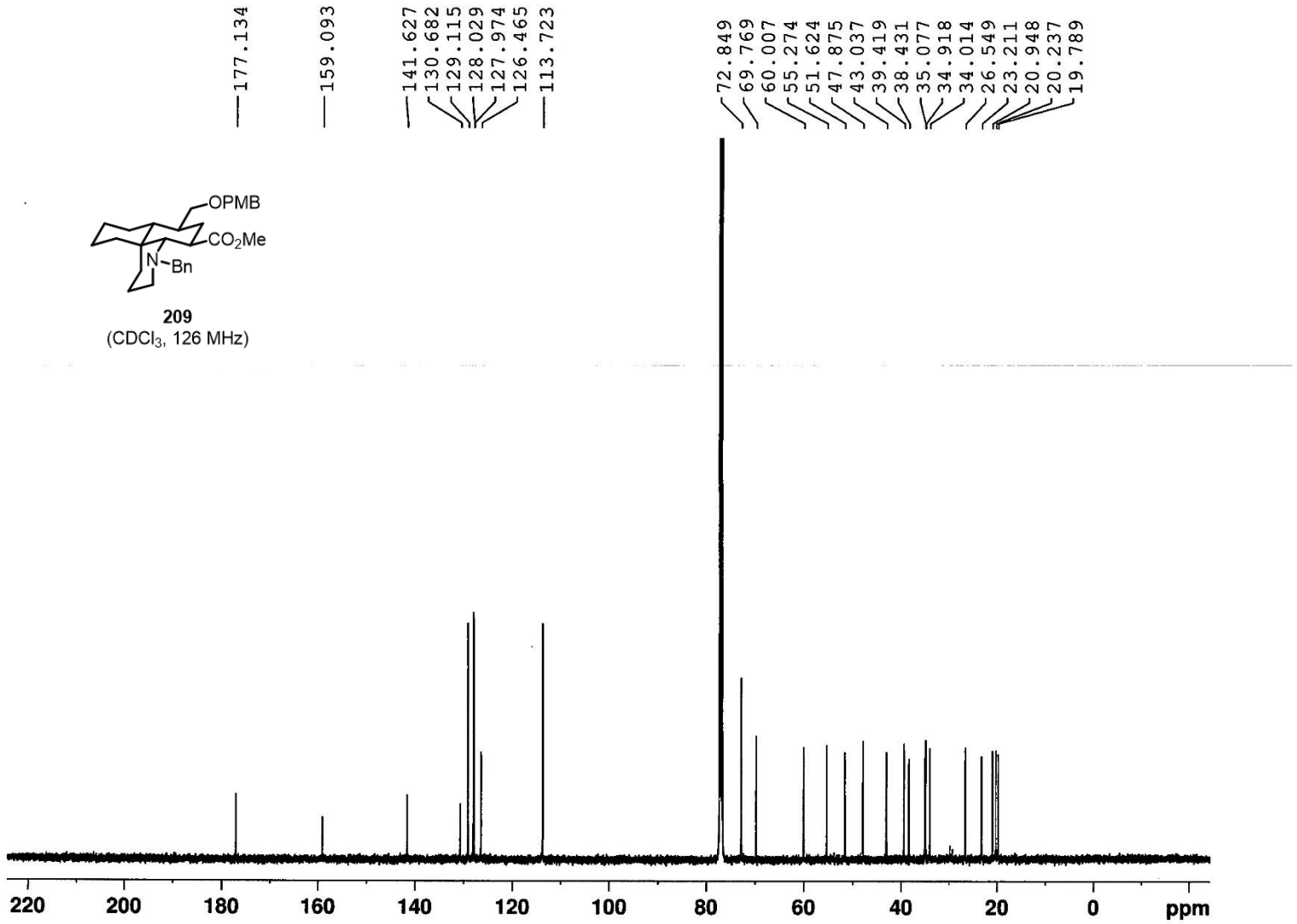
OPMB
CO2Me
TBSO
206
(CDCl3, 500 MHz)
ppm

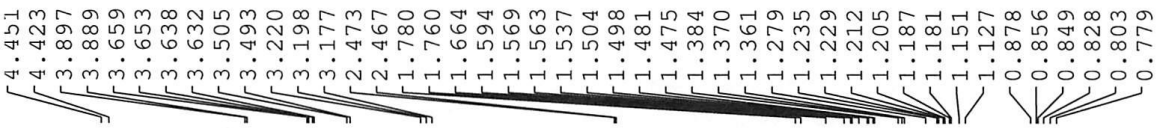
168.238
159.064
149.015
130.731
129.115
127.652
113.702
72.835
72.239
63.846
55.264
51.482
45.102
37.755
34.346
33.104
29.377
27.839
26.698
26.430
25.927
23.220
20.835
18.298
-5.245
-5.285
OPMB
CO2Me
TBSO
206
(CDCl3, 126 MHz)
ppm

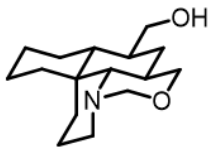
OPMB
CO2Me
BnHN
208
(CDCl3, 500 MHz)
ppm
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
7.47
1.78
0.85
2.00
3.08
1.94
2.63
0.91
1.07
1.83
0.91
1.15
4.13
1.91
2.16
2.23
3.72
2.31

168.207
159.076
148.906
130.705
129.130
128.394
128.179
127.743
126.934
113.710
72.872
72.289
55.268
54.070
51.504
50.397
45.181
37.928
34.337
33.110
29.425
26.419
23.946
23.211
20.915
OPMB
CO2Me
BnHN
208
(CDCl3, 126 MHz)
220
200
180
160
140
120
100
80
60
40
20
0
ppm

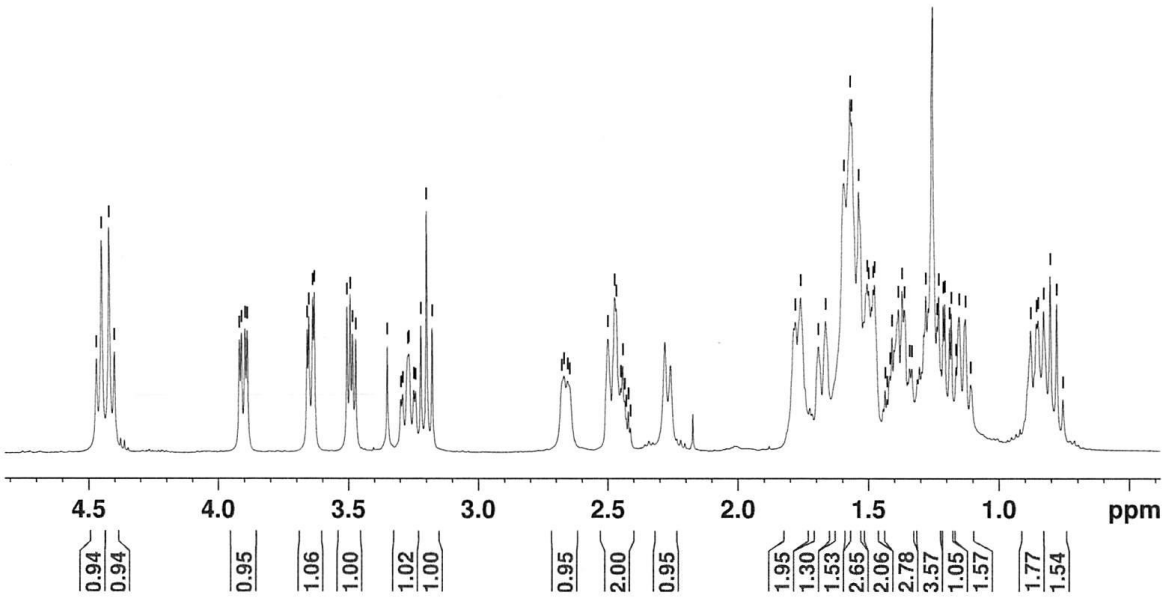
7.281
7.266
7.252
7.245
7.238
7.221
7.201
7.187
6.881
6.864
4.428
4.404
4.359
4.336
3.821
3.807
3.793
3.697
3.447
3.433
3.426
3.418
3.408
3.320
3.315
3.205
3.192
3.188
3.174
2.799
2.760
2.739
2.723
2.717
2.046
2.020
1.716
1.690
1.631
1.621
1.615
1.606
1.519
1.494
1.469
1.442
1.413
1.405
1.386
1.304
1.274
1.222
1.204
0.998
OPMB
CO2Me
N
Bn
209
(CDCl3, 500 MHz)
ppm
0
1
2
3
4
5
6
7
8
7.85
1.71
1.98
3.91
2.89
2.00
1.10
1.00
0.98
2.00
0.99
1.04
2.18
1.95
5.08
2.28
4.58
1.05
1.06


177.134
159.093
141.627
130.682
129.115
128.029
127.974
126.465
113.723
72.849
69.769
60.007
55.274
51.624
47.875
43.037
39.419
38.431
35.077
34.918
34.014
26.549
23.211
20.948
20.237
19.789
OPMB
CO2Me
N
Bn
209
(CDCl3, 126 MHz)
220
200
180
160
140
120
100
80
60
40
20
0
ppm





6: (±)-myrioneurinol
($CDCl_3$, 500 MHz)

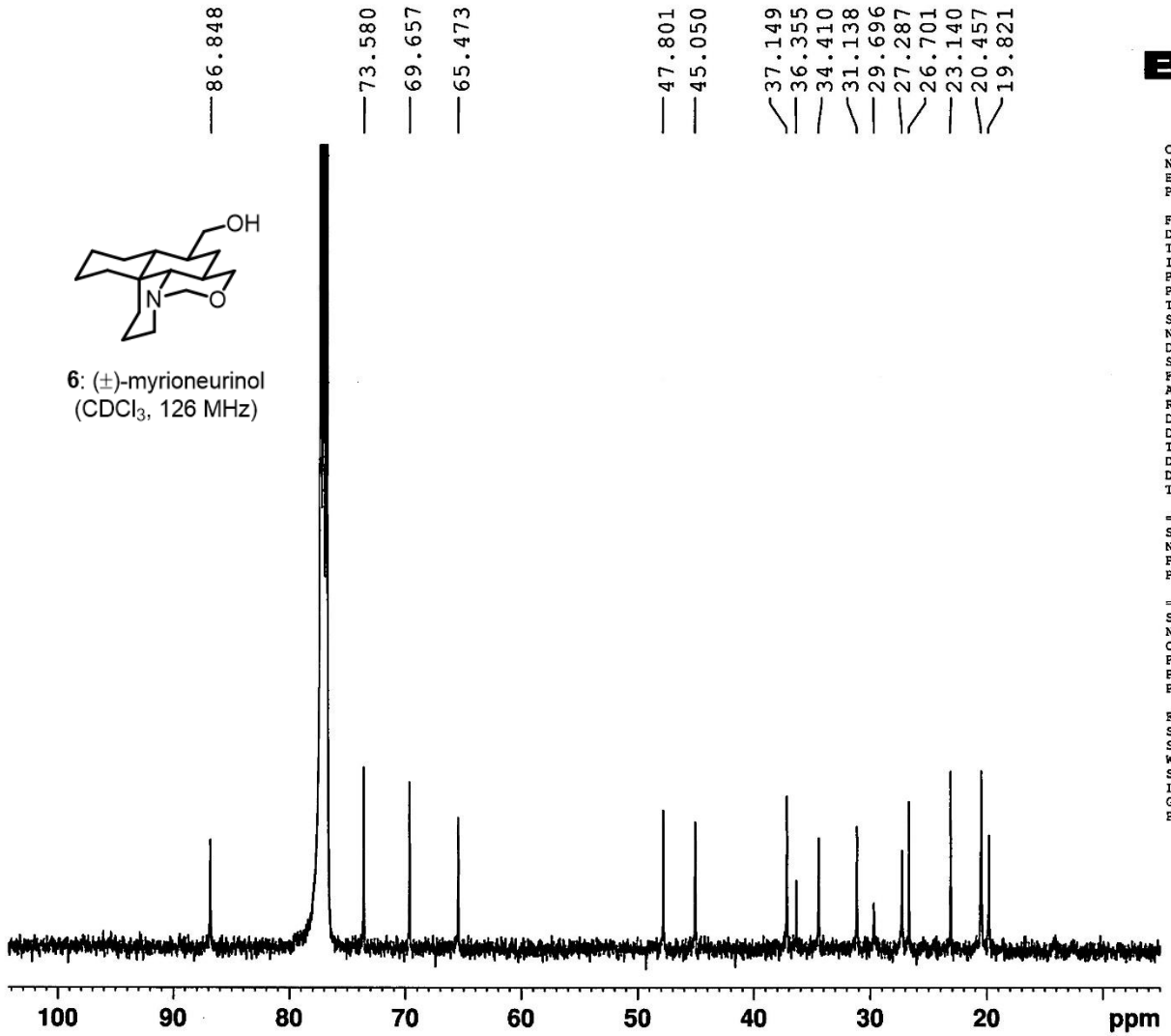



```
Current Data Parameters
NAME      SMX-myol-myrioneurinol
EXPNO                          3
PROCNO                         1

F2 - Acquisition Parameters
Date_              20190424
Time                 20.57
INSTRUM              spect
PROBHD    5 mm PATXI 1H/
PULPROG                 zg
TD                   59998
SOLVENT              CDCl3
NS                      80
DS                       0
SWH             10000.000 Hz
FIDRES              0.166672 Hz
AQ                2.9999001 sec
RG                   196.79
DW                   50.000 usec
DE                   10.00 usec
TE                   295.2 K
D1              2.00000000 sec
TD0                      1

======== CHANNEL f1 ========
SFO1          500.1330885 MHz
NUC1                    1H
P1                    9.90 usec
PLW1         12.19999981 W

F2 - Processing parameters
SI                    65536
SF            500.1300136 MHz
WDW                     EM
SSB         0
LB                    0.30 Hz
GB          0
PC                    1.00
```



BRUKER

```
Current Data Parameters
NAME      SMX-myol-myrioneurinol-13C
EXPNO                 1
PROCNO                1

F2 - Acquisition Parameters
Date_          20190425
Time               9.53
INSTRUM           spect
PROBHD   5 mm PABBO BB/
PULPROG           zgdc
TD               62496
SOLVENT          CDCl3
NS               36585
DS                   0
SWH          31250.000 Hz
FIDRES        0.500032 Hz
AQ           0.9999360 sec
RG                2050
DW              16.000 usec
DE               6.50 usec
TE              299.1 K
D1           0.20000000 sec
D11          0.03000000 sec
TD0                  1

======== CHANNEL f1 ========
SFO1        125.7049802 MHz
NUC1              13C
P1               3.00 usec
PLW1        72.83999634 W

======== CHANNEL f2 ========
SFO2        499.8724993 MHz
NUC2              1H
CPDPRG[2        waltz16
PCPD2            80.00 usec
PLW2        19.00000000 W
PLW12        0.29688001 W

F2 - Processing parameters
SI               1048576
SF          125.6924106 MHz
WDW                 EM
SSB       0
LB               2.00 Hz
GB        0
PC               1.40
```

7.252
7.235
6.972
6.958
6.942
6.927
6.913
6.873
6.856
5.813
5.782
4.412
4.191
4.176
4.162
4.148
3.783
3.432
3.419
3.406
2.203
2.189
2.175
2.160
1.623
1.609
1.595
1.581
1.567
1.485
1.471
1.456
1.441
1.427
1.409
1.393
1.380
1.362
1.287
1.272
1.258
PMBO
CO2Et
221
(CDCl3, 500 MHz)
ppm
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
1.74
0.75
1.82
0.73
2.08
1.81
3.00
2.07
2.01
2.17
2.11
2.10
2.99

166.563
159.019
149.018
130.573
129.092
121.266
113.633
72.428
69.722
59.978
55.108
31.995
29.413
27.729
25.665
14.163
PMBO
CO2Et
221
(CDCl3, 126 MHz)
ppm
0
20
40
60
80
100
120
140
160
180
200
220

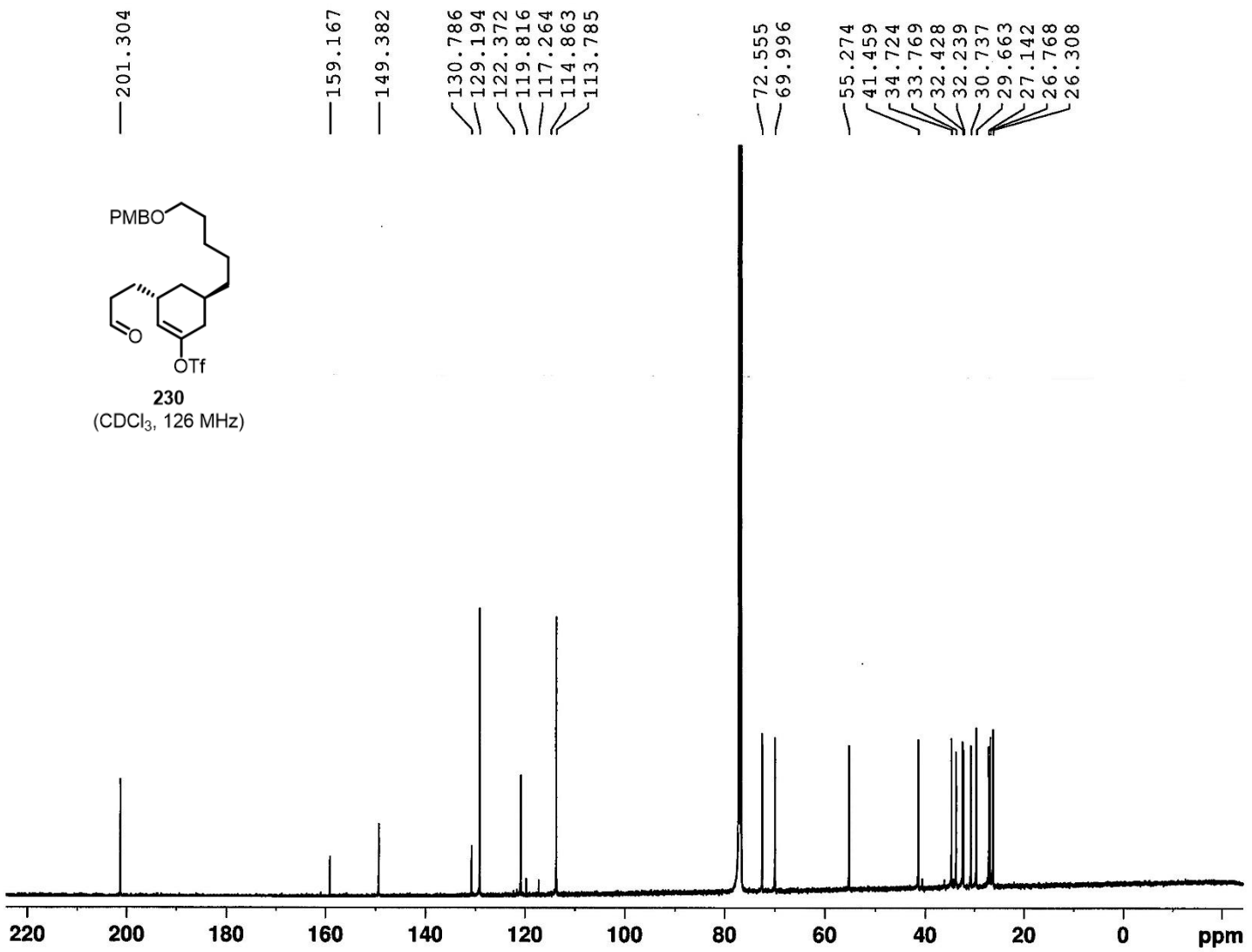
9.504
9.489
7.260
7.243
6.883
6.866
6.848
6.835
6.831
6.817
6.804
6.131
6.115
6.100
6.084
4.425
3.800
3.450
3.438
3.425
2.354
2.341
2.327
2.314
1.647
1.633
1.619
1.604
1.591
1.550
1.536
1.520
1.505
1.491
1.448
1.438
1.432
1.425
PMBO
CHO
223
(CDCl3, 500 MHz)
ppm
0.74
1.79
1.73
0.82
0.65
2.13
3.00
2.16
2.03
2.30
2.17
2.19

194.051
159.116
158.656
133.012
130.590
129.200
113.731
72.553
69.719
55.234
32.613
29.455
27.628
25.785
PMBO
CHO
223
(CDCl3, 126 MHz)
ppm
220
200
180
160
140
120
100
80
60
40
20
0

PMBO
OTf
228
(CDCl3, 500 MHz)
ppm
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
1.78
1.73
1.93
2.16
2.00
3.02
2.03
2.20
2.26
1.13
1.07
2.36
1.17
8.07

159.131
148.943
135.810
130.758
129.156
122.364
121.488
119.815
117.267
116.969
114.721
113.738
72.510
69.984
55.210
39.471
34.652
33.799
32.837
31.953
30.723
29.653
26.751
26.261
PMBO
OTf
228
(CDCl3, 126 MHz)
ppm
220
200
180
160
140
120
100
80
60
40
20
0

9.784
7.264
7.250
6.882
6.867
5.673
4.427
3.445
3.432
3.420
2.510
2.496
2.481
2.393
2.383
2.358
2.350
2.012
1.997
1.979
1.964
1.857
1.756
1.742
1.728
1.714
1.705
1.690
1.675
1.662
1.611
PMBO
OTf
O
230
(CDCl3, 500 MHz)
ppm
0.64
2.11
1.67
0.83
2.00
2.89
2.02
1.99
2.01
1.00
0.99
2.19
2.94
2.06
4.46

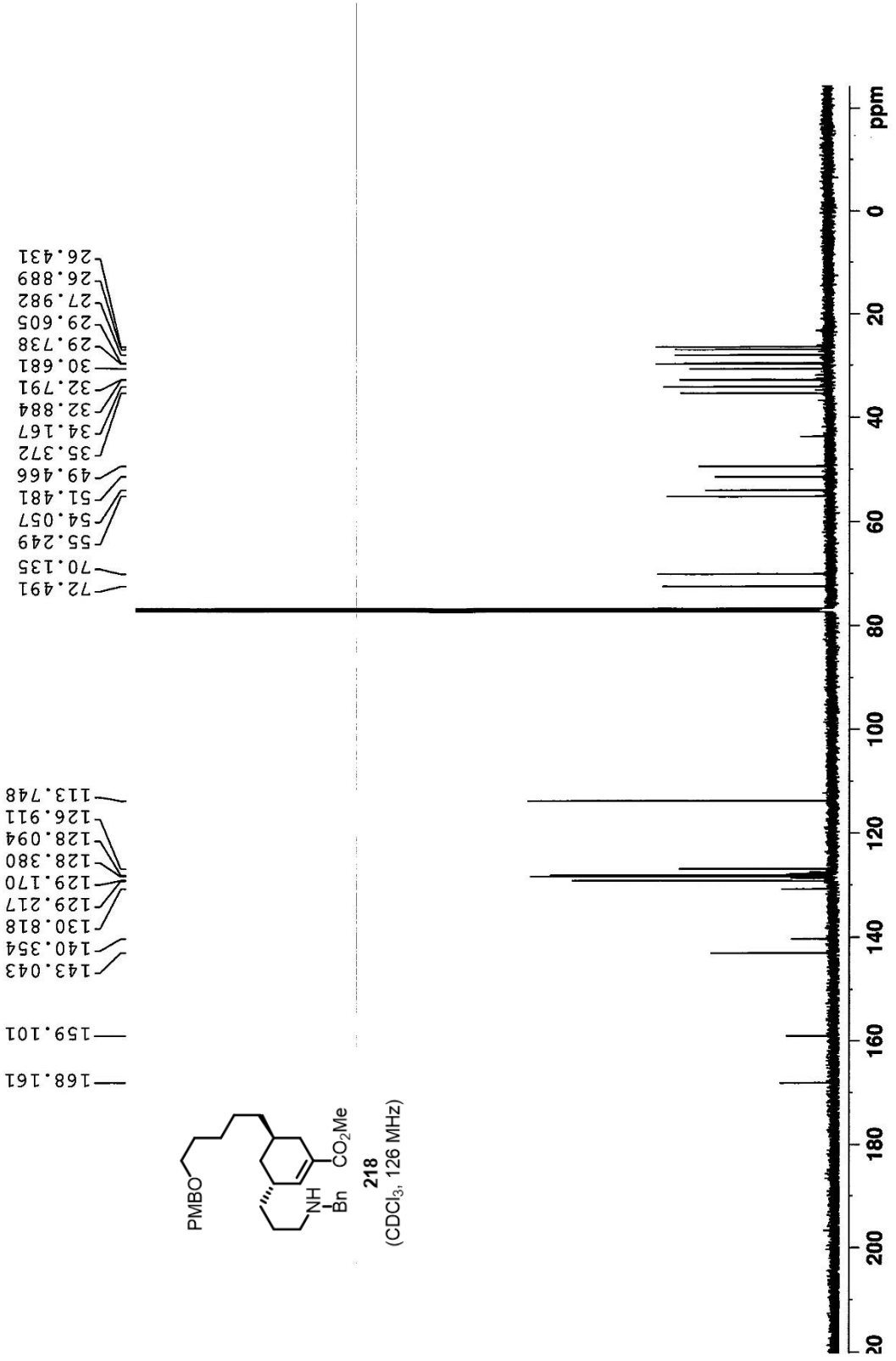


230
($CDCl_3$, 126 MHz)

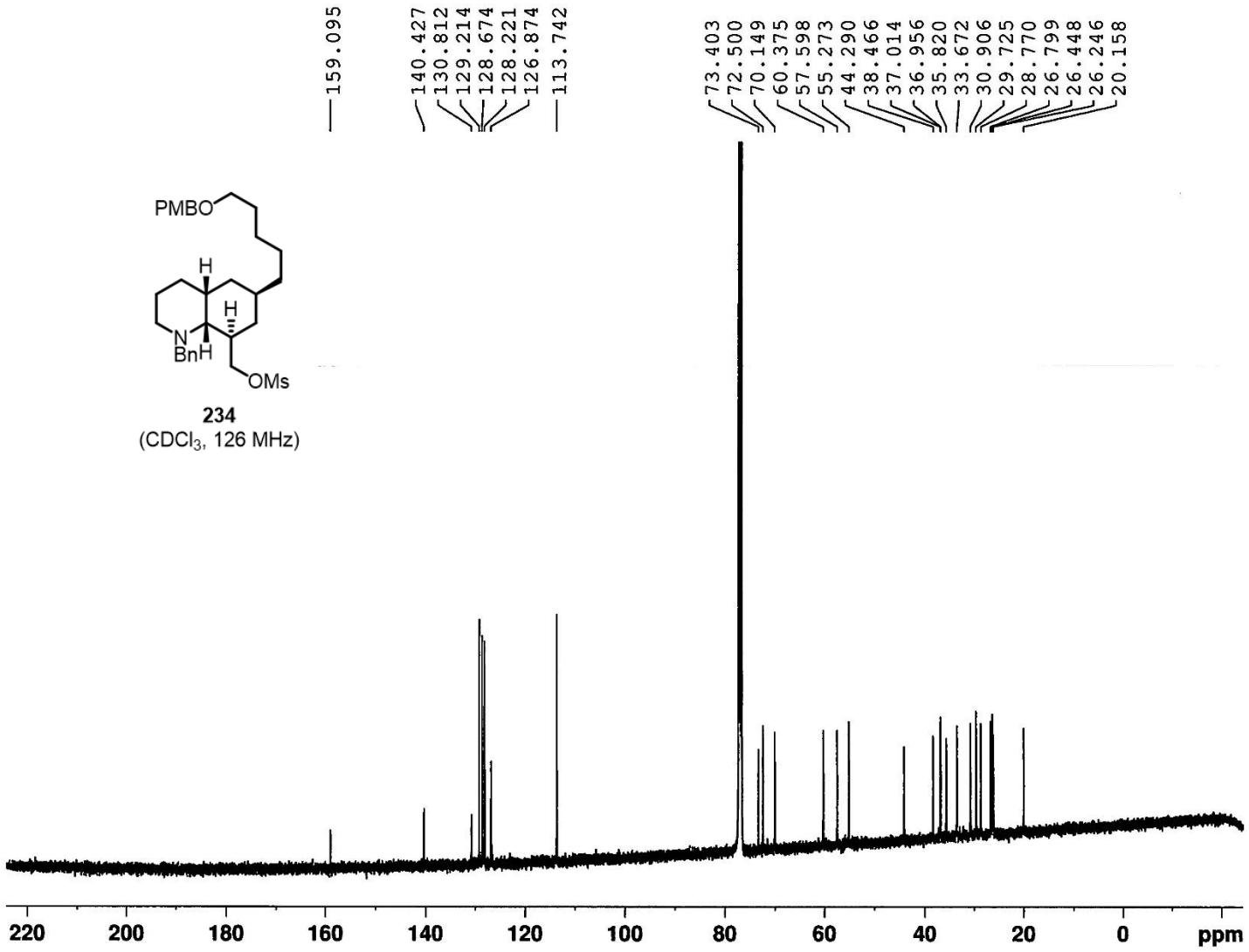
PMBO
CO2Me
O
231
(CDCl3, 500 MHz)
ppm
0.72
2.06
3.04
3.00
2.08
2.23
1.07
1.13
1.17
1.24
2.45
2.27
1.10
1.28
4.17
2.33
1.86
2.71

201.776
167.929
159.107
141.482
130.803
130.147
129.171
113.746
72.500
70.090
55.249
51.573
41.696
35.237
33.510
32.673
30.619
29.717
29.521
27.079
26.846
26.399
PMBO
O
CO2Me
231
(CDCl3, 126 MHz)
ppm
220
200
180
160
140
120
100
80
60
40
20
0

7.326
7.320
7.315
7.268
7.251
6.911
6.907
6.883
6.866
6.852
4.427
3.798
3.790
3.719
3.444
3.430
3.417
2.650
2.636
2.622
2.427
2.418
2.392
2.383
2.257
1.845
1.829
1.810
1.794
1.599
1.488
1.481
1.467
1.461
1.454
1.440
1.435
1.345
1.335
1.264
1.254
PMBO
NH
Bn
CO2Me
218
(CDCl3, 500 MHz)
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0 ppm
4.30
2.84
0.93
1.68
2.32
3.07
2.12
2.86
2.00
2.24
1.00
1.08
1.12
6.95
2.40
6.45
2.44

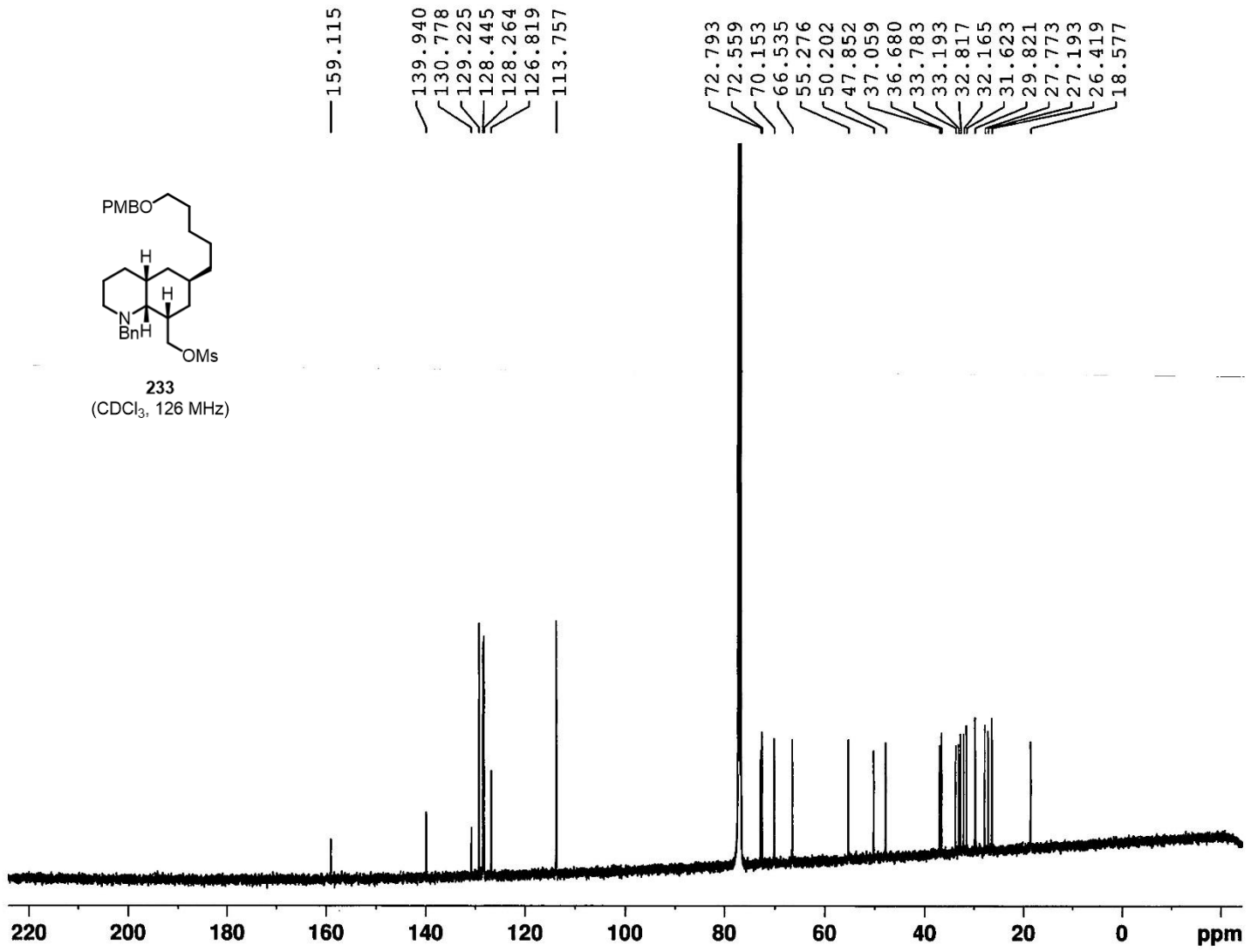

26.431
26.889
27.982
29.605
29.738
30.681
32.791
32.884
34.167
35.372
49.466
51.481
54.057
55.249
70.135
72.491
113.748
126.911
128.094
128.380
129.170
129.217
130.818
140.354
143.043
159.101
168.161
PMBO
NH
Bn
CO2Me
218
(CDCl3, 126 MHz)
ppm

7.306
7.301
7.295
7.269
7.252
6.884
6.867
4.544
4.538
4.426
4.080
4.067
4.062
4.049
3.911
3.884
3.803
3.784
3.757
3.438
3.425
3.412
2.921
2.776
2.590
2.561
2.397
2.389
2.363
1.915
1.910
1.889
1.884
1.766
1.758
1.711
1.704
1.685
1.678
1.596
1.583
1.567
1.522
1.471
1.447
1.284
1.254
1.129
1.086
1.076
1.060
1.051
0.715
0.691
PMBO
H
H
N
BnH
OMs
234
(CDCl3, 500 MHz)
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
ppm
4.34
4.56
1.89
1.00
2.32
1.02
1.03
3.14
1.23
2.27
3.00
1.13
1.07
2.29
1.12
1.14
0.93
0.95
4.55
2.27
5.54
2.18
1.23
1.09



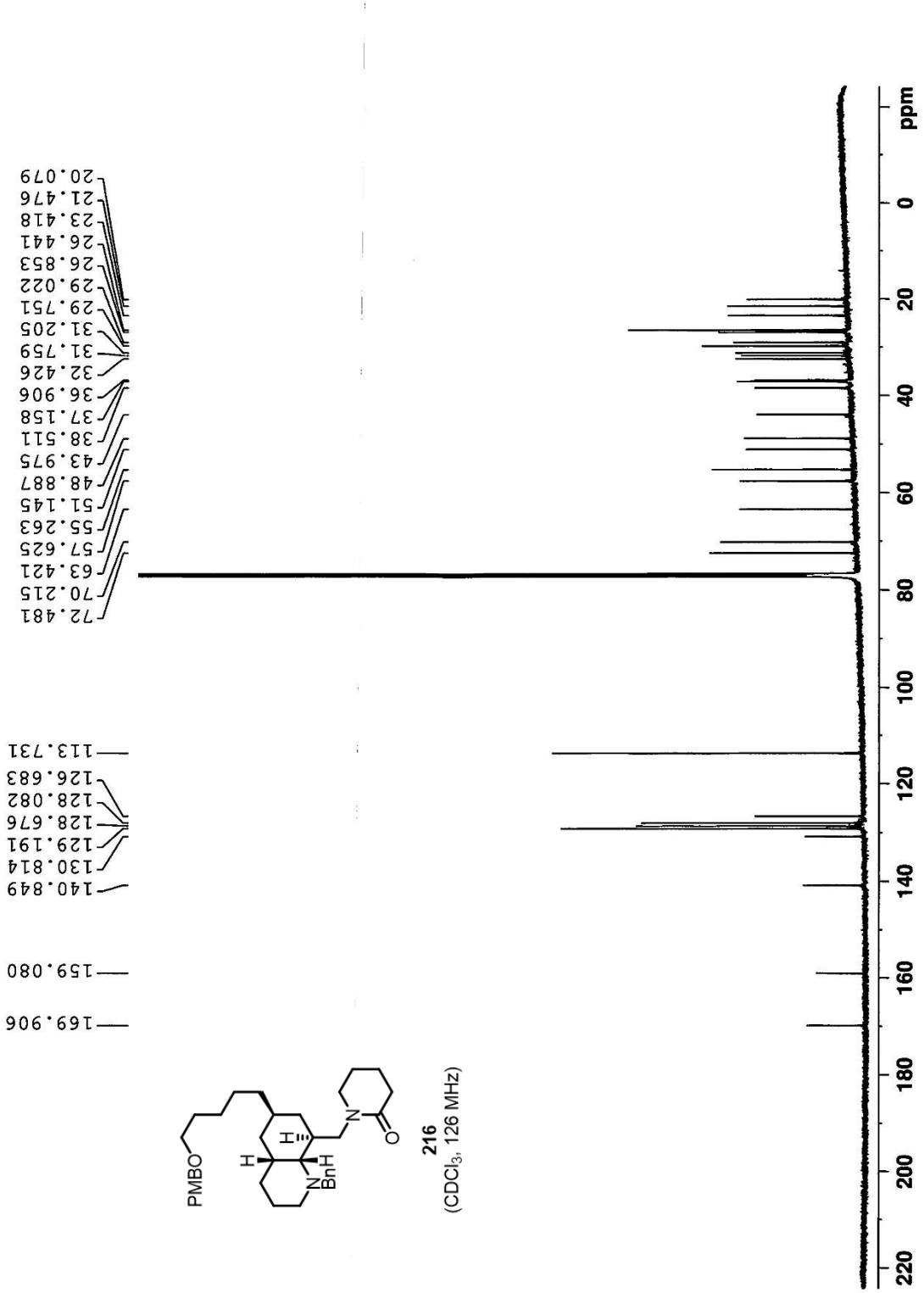
234
($CDCl_3$, 126 MHz)

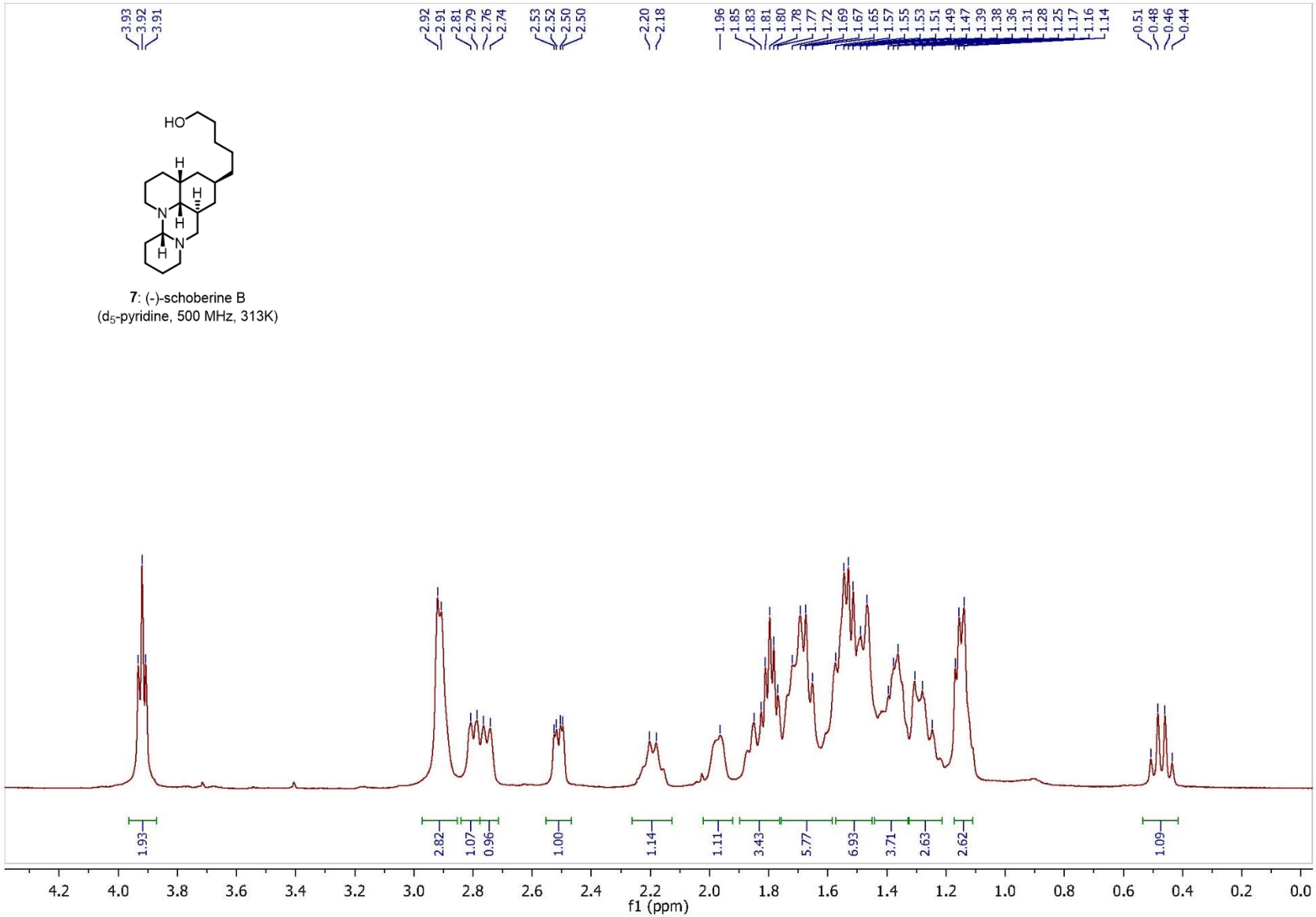
7.324
7.318
7.314
7.275
7.258
7.235
7.230
7.224
6.886
6.869
4.438
4.404
4.399
4.385
4.379
4.246
4.232
4.227
4.213
3.800
3.768
3.740
3.721
3.694
3.460
3.447
3.434
2.925
2.853
2.825
2.521
2.371
2.349
2.327
1.870
1.844
1.748
1.727
1.635
1.621
1.605
1.592
1.535
1.468
1.460
1.370
1.356
1.322
1.310
1.296
1.254
1.167
1.140
1.117
1.091
PMBO
H
H
N
BnH
OMs
233
(CDCl3, 500 MHz)
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
3.90
2.08
0.95
1.68
2.08
1.02
1.00
2.95
2.07
2.09
3.00
1.01
1.02
1.05
1.01
2.06
3.19
2.27
0.81
1.20
4.14
2.56
3.20

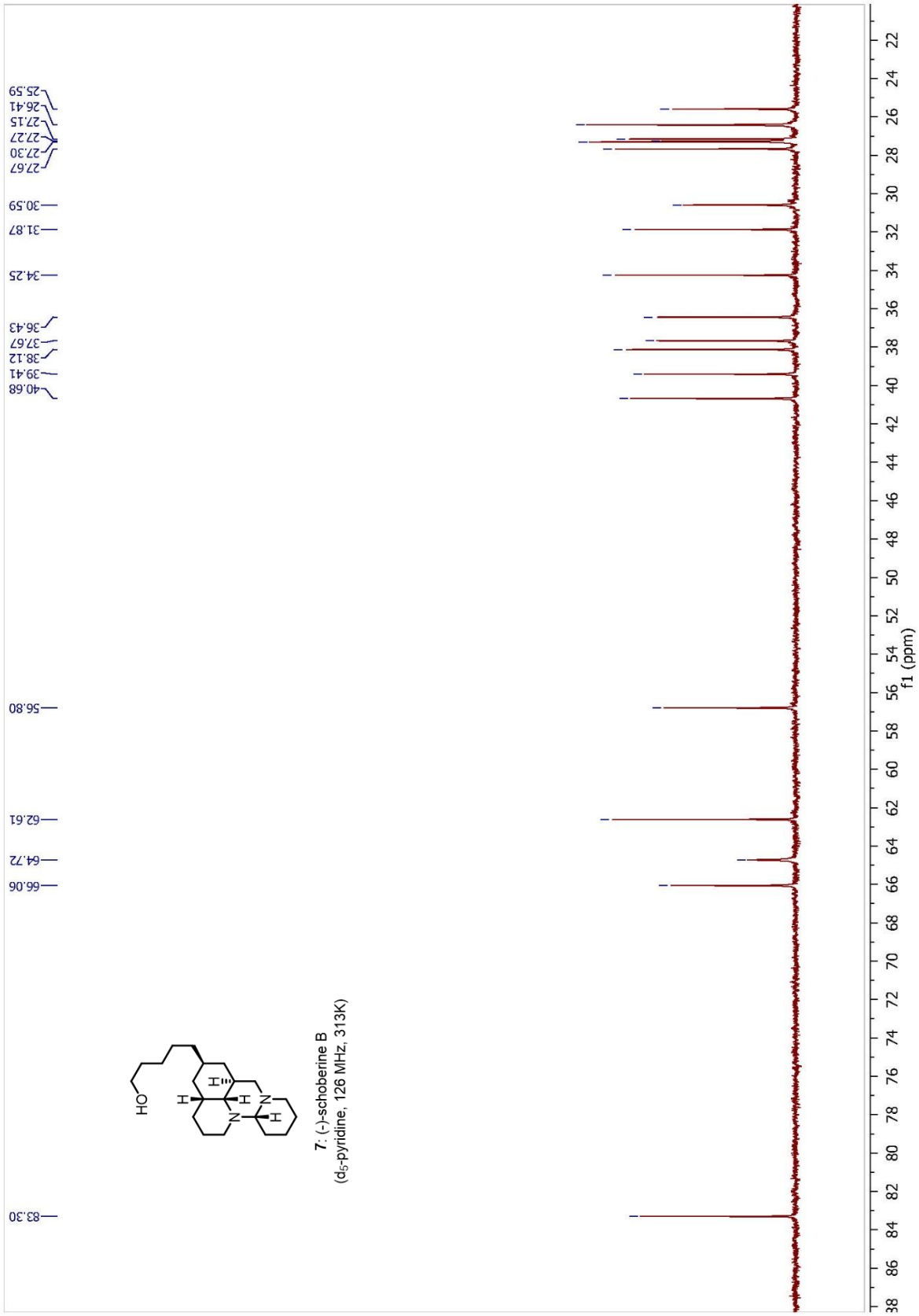


233
($CDCl_3$, 126 MHz)

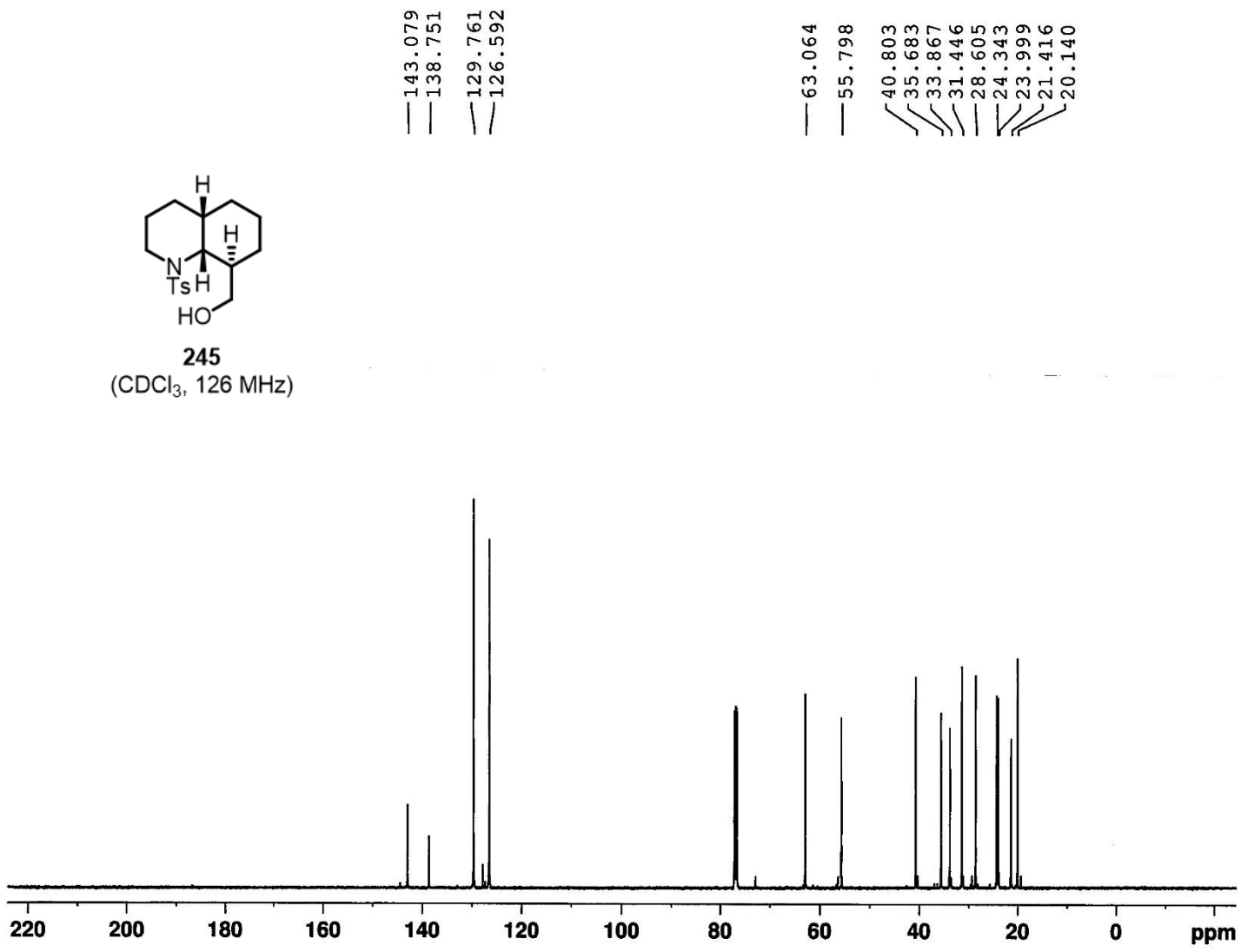
7.313
7.296
7.281
7.266
7.250
7.225
7.211
6.883
6.865
4.423
3.924
3.897
3.802
3.757
3.689
3.669
3.662
3.430
3.417
3.404
3.300
3.246
3.225
3.219
3.199
3.189
2.868
2.551
2.384
2.312
2.304
2.172
1.777
1.742
1.681
1.651
1.587
1.573
1.558
1.522
1.498
1.424
1.398
1.371
1.290
1.254
1.121
1.081
1.066
1.054
1.028
1.019
0.585
0.561
PMBO
H
H
N
Bn
H
N
O
216
(CDCl3, 500 MHz)
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
6.57
0.91
1.76
2.13
1.05
3.00
1.08
0.95
2.17
1.21
1.14
0.80
0.90
1.03
2.34
1.20
1.20
6.25
1.54
2.52
1.24
1.42
6.68
2.05
1.36
0.93


169.906
159.080
140.849
130.814
129.191
128.676
128.082
126.683
113.731
72.481
70.215
63.421
57.625
55.263
51.145
48.887
43.975
38.511
37.158
36.906
32.426
31.759
31.205
29.751
29.022
26.853
26.441
23.418
21.476
20.079
PMBO
BnH
O
N
H
H
216
(CDCl3, 126 MHz)
ppm
220
200
180
160
140
120
100
80
60
40
20
0


3.93
3.92
3.91
2.92
2.91
2.81
2.79
2.76
2.74
2.53
2.52
2.50
2.50
2.20
2.18
1.96
1.85
1.83
1.81
1.80
1.78
1.77
1.72
1.69
1.67
1.65
1.57
1.55
1.53
1.51
1.49
1.47
1.39
1.38
1.36
1.31
1.28
1.25
1.17
1.16
1.14
0.51
0.48
0.46
0.44
HO
H
H
N
H
H
N
7: (-)-schoberine B
(d5-pyridine, 500 MHz, 313K)
1.93
2.82
1.07
0.96
1.00
1.14
1.11
3.43
5.77
6.93
3.71
2.63
2.62
1.09
4.2
4.0
3.8
3.6
3.4
3.2
3.0
2.8
2.6
2.4
2.2
2.0
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
f1 (ppm)

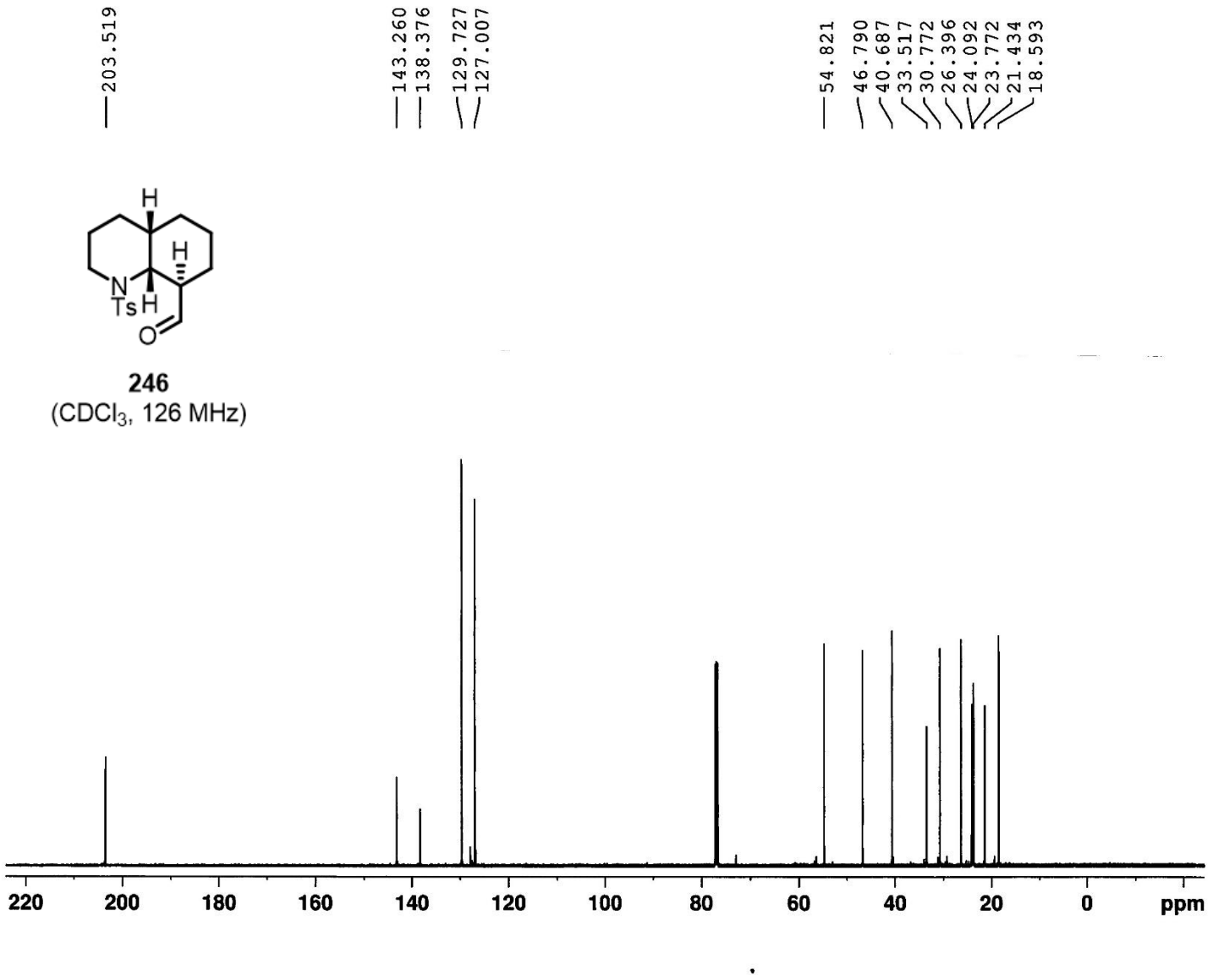

7: (-)-schoberine B
(d_5-pyridine, 126 MHz, 313K)
HO
H
H
H
N
N
H
83.30
66.06
64.72
62.61
56.80
40.68
39.41
38.12
37.67
36.43
34.25
31.87
30.59
27.67
27.30
27.27
27.15
26.41
25.59
f1 (ppm)

7.723
7.707
7.284
7.268
3.926
3.896
3.860
3.835
3.825
3.812
3.802
3.399
3.381
3.362
2.972
2.967
2.940
2.916
2.403
1.865
1.847
1.842
1.823
1.818
1.718
1.691
1.640
1.621
1.614
1.595
1.588
1.568
1.562
1.541
1.520
1.515
1.495
1.489
1.426
1.397
1.350
1.339
1.330
1.324
1.227
1.202
1.179
1.123
1.115
1.105
1.097
1.089
1.079
1.070
1.062
H
H
N
Ts
H
HO
245
(CDCl3, 500 MHz)
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0 ppm
1.83
1.97
2.01
1.04
1.00
1.94
3.43
1.07
1.04
1.21
1.11
4.64
2.20
1.37
1.12



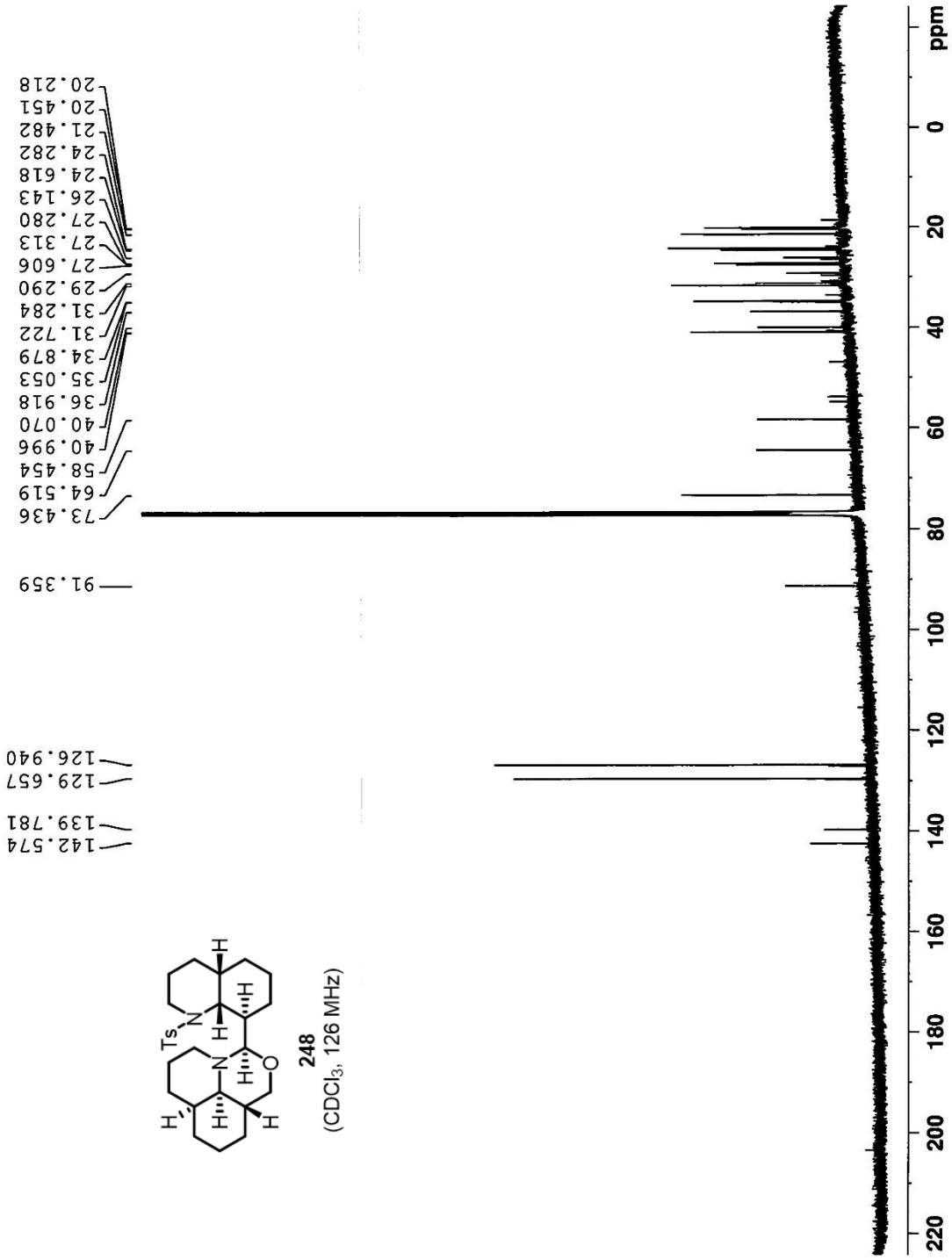
245
($CDCl_3$, 126 MHz)

9.530
9.521
7.703
7.687
7.284
7.268
4.294
4.285
4.271
4.262
3.788
3.785
3.781
3.757
3.754
3.751
2.987
2.981
2.955
2.930
2.925
2.714
2.707
2.699
2.691
2.683
2.675
2.667
2.659
2.651
2.403
1.812
1.785
1.645
1.609
1.602
1.583
1.576
1.509
1.424
1.418
1.399
246
(CDCl3, 500 MHz)
ppm
0.77
2.03
2.14
1.00
1.09
1.05
1.00
3.53
1.10
1.35
0.91
4.60
1.06
2.51
1.41



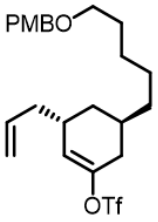
246
($CDCl_3$, 126 MHz)

7.769
7.752
7.287
7.271
4.415
3.865
3.841
3.834
3.827
3.818
3.803
3.133
3.111
3.090
3.052
3.026
2.999
2.804
2.783
2.761
2.715
2.700
2.677
2.414
2.062
2.045
1.921
1.905
1.808
1.745
1.698
1.690
1.585
1.558
1.389
1.364
1.340
1.317
1.224
Ts
N
H
O
248
(CDCl3, 500 MHz)
ppm
1.00
2.01
7.14
3.18
1.74
4.33
1.12
0.97
1.83
3.00
1.85
0.93
0.92
0.88
2.96
0.84
1.69
1.72


142.574
139.781
129.657
126.940
91.359
73.436
64.519
58.454
40.996
40.070
36.918
35.053
34.879
31.722
31.284
29.290
27.606
27.313
27.280
26.143
24.618
24.282
21.482
20.451
20.218
ppm
0
20
40
60
80
100
120
140
160
180
200
220
Ts
N
H
O
248
(CDCl3, 126 MHz)

SHIMADZU LabSolutions

Analysis Report

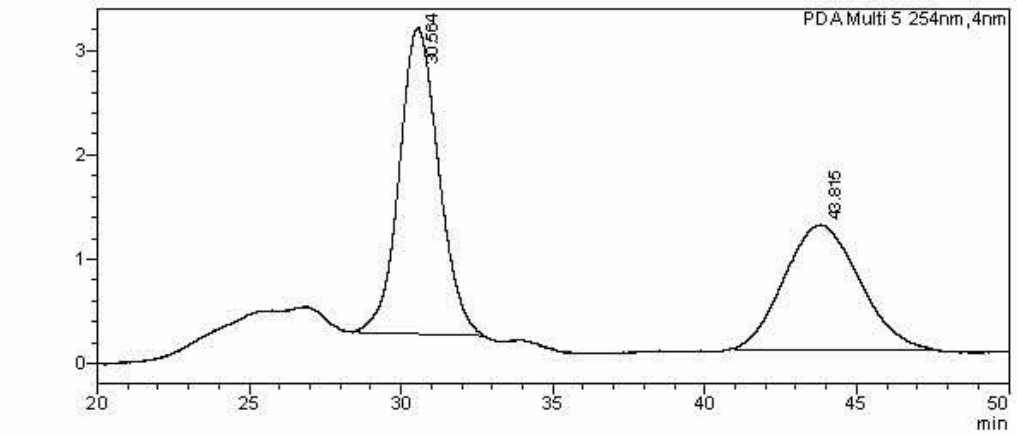


rac-**228**

<Sample Information>

Sample Name	: SMX-schoberineB-OTfalkene-0406-rac1		
Sample ID	: SMX-schoberineB-OTfalkene-46rac		
Data Filename	: SMX-schoberineB-OTfalkene-0406-rac1.lcd		
Method Filename	: Default Method.lcm		
Batch Filename	:		
Vial #	: -1	Sample Type	: Unknown
Injection Volume	: 20 uL		
Date Acquired	: 4/6/2019 6:04:45 PM	Acquired by	: Snyder Group
Date Processed	: 4/6/2019 8:24:45 PM	Processed by	: Snyder Group

<Chromatogram>

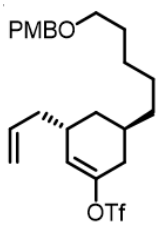


<Peak Table>

PDA Ch5 254nm

Peak#	Ret. Time	Area	Height	Area%
1	30.564	265610	2936	56.420
2	43.815	205162	1195	43.580
Total		470773	4132	100.000

SHIMADZU LabSolutions **Analysis Report**

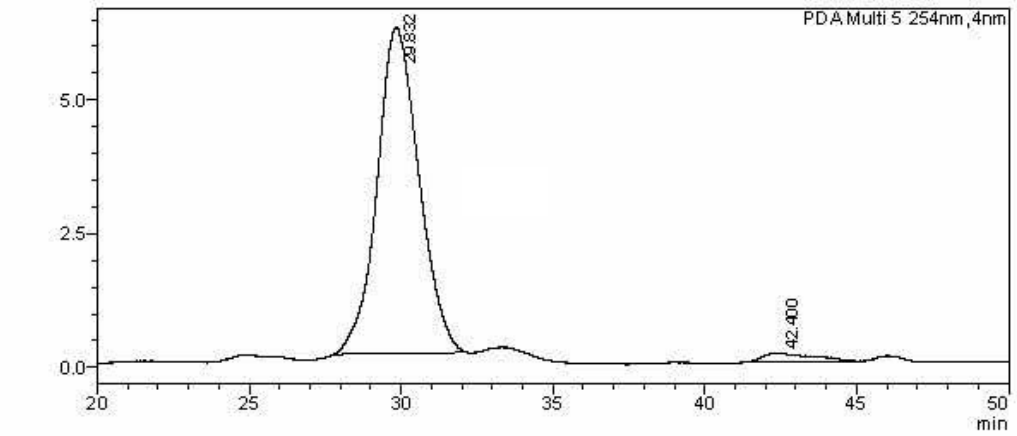


chiral-**228**

<Sample Information>

Sample Name	: SMX-schoberineB-OTfalkene-0406-ent1		
Sample ID	: SMX-schoberineB-OTfalkene-46ent		
Data Filename	: SMX-schoberineB-OTfalkene-0406-ent1.lcd		
Method Filename	: Default Method.lcm		
Batch Filename	:		
Vial #	: -1	Sample Type	: Unknown
Injection Volume	: 20 uL		
Date Acquired	: 4/6/2019 7:06:05 PM	Acquired by	: Snyder Group
Date Processed	: 4/6/2019 8:37:43 PM	Processed by	: Snyder Group

<Chromatogram>



<Peak Table>

PDA Ch5 254nm

Peak#	Ret. Time	Area	Height	Area%
1	29.832	585071	6090	96.901
2	42.400	18708	169	3.099
Total		603779	6259	100.000