

Total Synthesis of (±)-Ginkgolide C and Formal Syntheses of (±)-Ginkgolide A and (±)-Ginkgolide B

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Legend:

Ac: Acetyl

Ac₂O: Acetic anhydride

acac: Acetyl acetate

AcO: Acetate

AcOH: Acetic acid

AD: Alzheimer's disease

ADDP: Azodicarboxylic acid dipiperidide

AIBN: Azobisisobutyronitrile

All: Allyl

anh.: Anhydrous

API-MS: Atmospheric pressure ionization mass spectrometry

aq.: Aqueous

Ar: Aryl

ATP: Adenosine Triphosphate

B: Base

BBB: Blood-brain barrier

Bn: Benzyl

BOX: Bisoxazoline

BPD: 1,2-Bis(diphenylphosphino)benzene

Bu: Butyl

calcd.: Calculated

CBS: Corey-Bakshi-Shibata

CDP: Cytidine diphosphate

CH(OMe)₃: Trimethylorthoformate

CMP: Cytidine monophosphate

CNS: Central nervous system

CoA: Coenzyme A

Cod: 1,5-Cyclooctadiene

conc.: Concentrated

COSY: Correlation Spectroscopy

CSA: Camphorsulfonic acid

CTP: Cytidine triphosphate

CYP450: Cytochrome-P450

d: Day

d: Doublet

DAD: Diode array detection

dba: Dibenzylideneacetone

DBU: 1,8-Diazabicyclo(5.4.0)undec-7-ene

DCE: Dichloroethane

DCM: Dichloromethane

DDQ: 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone

DFT: Density functional theory

DIAD: Diisopropyl azodicarboxylate

DIBALH: Diisobutylaluminium hydride

dig: Digonal

DIPEA: Diisopropylethylamine

DMAP: 4-(Dimethylamino)pyridine

DMAPP: Dimethylallyl pyrophosphate (or Dimethylallyl diphosphate)

DMDO: Dimethyldioxirane

DMF: Dimethylformamide

DMSO: Dimethylsulfoxide

DP: Desired product

dppe: 1,2-Bis(diphenylphosphino)ethane

dr: Diastereomeric ratio

E: Entgegen (Trans-alkene)

ee: Enantiomeric excess

EI: Electron ionization

EI-MS: Electron ionization mass spectrometry

endo: Endocyclic

eq.: Equivalent(s)

ESI: Electrospray ionization

Et: Ethyl

EtCO₂tBu: *tert*-Butyl propionate

Et₂O: Diethyl ether

Et₃N: Triethylamine

EtOAc: Ethyl acetate

EtOH: Ethanol

EVE: Ethyl vinyl ether

exo: Exocyclic

E1: Unimolecular elimination

E2: Bimolecular elimination

FGM: Functional group manipulation

FPP: Farnesyl pyrophosphate (or farnesyl diphosphate)

g: Gram

GA-3P: Glyceraldehyde 3-phosphate

GC: Gas chromatography

GC-MS: Gas chromatography mass spectrometry

GGPP: Geranyl geranyl pyrophosphate (or geranyl geranyl diphosphate)

Gink: Ginkgolide

GPP: Geranyl pyrophosphate (or geranyl diphosphate)

h: Hour

Hex: Hexanes

HIV: Human immunodeficiency virus

HMBC: Heteronuclear Multiple Bond Correlation

HMG-CoA: 3-hydroxy-3-methylglutaryl coenzyme A (β -Hydroxy β -methylglutaryl coenzyme A)

HMPA: Hexamethylphosphoramide

HPLC: High pressure liquid chromatography

HRMS: High resolution mass spectrometry

HSQC: Heteronuclear Single Quantum Coherence

HWE: Horner-Wadsworth-Emmons

h ν : Irradiation

Hz: Hertz

IBX: 2-Iodoxybenzoic acid

IPP: Isopentenyl pyrophosphate (or isopentenyl diphosphate)

*i*Pr: Isopropyl

IPr: 1,3-Bis(2,6-diisopropylphenyl-imidazol-2-ylidene)

IR: Infrared

kg: Kilogram ($\times 10^3$ g)

KHMDS: Potassium bis(trimethylsilyl)amide

L: Ligand

L: Liter

LC: Liquid chromatography

LDA: Lithium diisopropylamide

LDEA: Lithium diethylamide

LiHMDS: Lithium bis(trimethylsilyl)amide

LPS: Levopimaradiene synthase

m: Meta

M: Molarity

m: Multiplet

MCBA: *m*-Chlorobenzoic acid

MCPBA: *m*-Chloroperoxybenzoic acid

Me: Methyl

Me₂S: Dimethylsulfide

MeCN: Acetonitrile

MeOH: Methanol

MEP: Methylerythritol 4-phosphate

mg: Milligram ($\times 10^{-3}$ g)

MHz: Megahertz ($\times 10^6$ Hz)

min: Minute

mL: Milliliter ($\times 10^{-3}$ L)

mmol: Millimol ($\times 10^{-3}$ mol)

MoA: Migraine without aura

MOM: Methoxymethyl

MoOPH: Oxodiperoxymolybdenum(pyridine)-(hexamethylphosphoric triamide)

mp: Melting point

MPLC: Medium pressure liquid chromatography

MPO: 4-Methoxypyridine *N*-oxide

MS: Mass spectrometry

MS: Molecular sieves

MVA: Mevalonate

MVL: Mevalonic acid

MwA: Migraine with aura

N/A: Not applicable

NADPH: Nicotinamide adenine dinucleotide phosphate

NaHMDS: Sodium bis(trimethylsilyl)amide

NBS: *N*-bromosuccinimide

*n*Bu: *n*-Butyl

ND: Not determined

nm: Nanometer ($\times 10^{-9}\text{m}$)

NMO: *N*-methylmorpholine *N*-oxide

NMR: Nuclear magnetic resonance

NOESY: Nuclear Overhauser Effect Spectrometry

o.n.: Overnight

ORD: Optical rotatory dispersion

Ox.: Oxaziridine

P: Partition coefficient

p: Para

PAF: Platelet-activating factor

PAFR: Platelet-activating factor receptor

PBu₃: Tributylphosphine

PCC: Pyridinium chlorochromate

PDC: Pyridinium dichromate

Pet.: Petroleum

PG: Protecting group

pH: Potential of hydrogen (or Power of hydrogen)

Ph: Phenyl

Ph₃COOH: Trityl hydroperoxide

Ph₃P=O: Triphenylphosphine oxide

PHOX: 2-[2-(Diphenylphosphino)phenyl]-2-oxazoline

PIFA: [Bis(trifluoroacetoxy)iodo]benzene

Piv: Pivaloyl

PMB: *p*-Methoxybenzyl
PMHS: Polymethylhydrosiloxane
P(OMe)₃: Trimethylphosphite
PP: Pyrophosphate (or diphosphate)
PPh₃: Triphenylphosphine
ppm: Parts per million
PPTS: Pyridinium *p*-toluenesulfonic acid
PTSA: *p*-Toluenesulfonic acid
pyr: Pyridine
q: Quadruplet
quant.: quantitative
quint: Quintuplet
R: Alkyl or other substituent
R: Rectus
RCM: Ring-closing metathesis
R_f: Retention Factor
rr: Regioisomeric ratio
RT: Room temperature
rxn: Reaction
s: Singlet
S: Sinister
SAM: S-adenosyl methionine
sat.: Saturated
SEM: 2-(Trimethylsilyl)ethoxymethyl
sext.: Sextuplet
SGC: Silica gel chromatography
SM: Starting material

SN1: Unimolecular nucleophilic substitution
SN2: Bimolecular nucleophilic substitution
SP: Side product
SP: Sodium pyruvate
t: Triplet
TBAOH: Tetrabutylammonium hydroxide
TBAF: Tetrabutylammonium fluoride
TBD: Triazabicyclodecene
TBS: *tert*-Butyldimethylsilyl
*t*Bu: *tert*-Butyl
*t*BuOH: *tert*-Butanol
TES: Triethylsilyl
tet: Tetrahedral
Tf: Triflyl
TFA: Trifluoroacetic acid
TFDO: (Trifluoromethyl)methyldioxirane
TfO: Triflate
THF: Tetrahydrofuran
THP: Tetrahydropyranyl
TIPS: Triisopropylsilyl
TLC: Thin layer chromatography
TMAD: *N,N,N',N'*-tetramethylazodicarboxamide
TMEDA: Tetramethylethylenediamine
TMS: Trimethylsilyl
TMS-EBX: 1-[(trimethylsilyl)ethynyl]-1,2-benziodoxol-3(*1H*)-one
trig: Trigonal
TRIS: Tris(hydroxymethyl)aminomethane

Ts: Tosyl

TTL: terpene trilactone

UV: Ultraviolet

w/w: Weight-to-weight ratio

X: Halide or other substituent

xs: Excess

Y: Halide or other substituent

Z: Zusammen (Cis-alkene)

1D: 1-Dimensional

2D: 2-Dimensional

3,5-DMP: 3,5-Dimethylpyrazole

Å: Angstrom ($\times 10^{-10}\text{m}$)

(br): Broad

[H]: Reductant or reduction

[O]: Oxidant or oxidation

δ : Chemical shift

μg : Microgram ($\times 10^{-6}\text{g}$)

μL : Microliter ($\times 10^{-6}\text{L}$)

ρ : Density (g/mL)

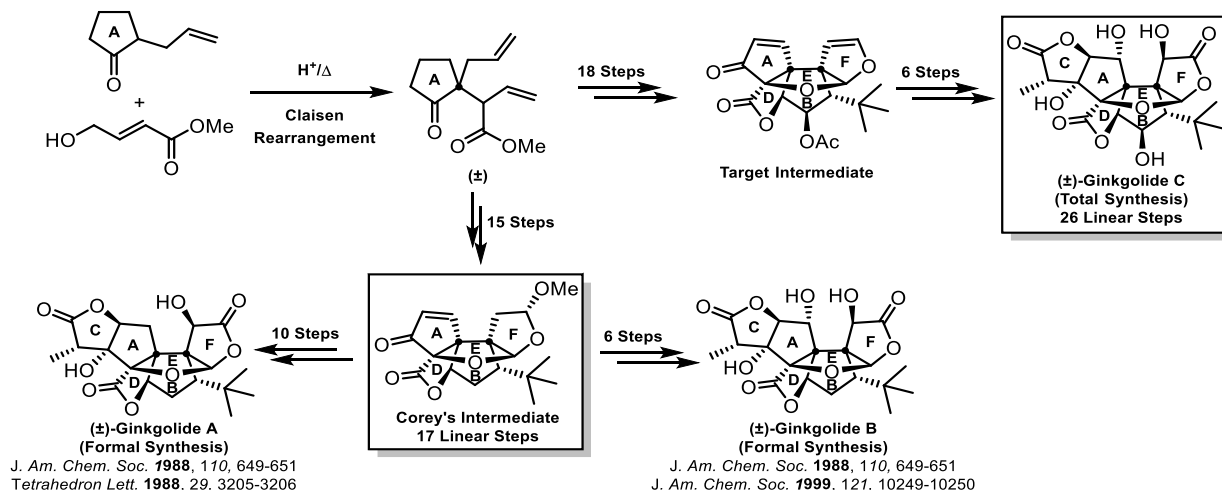
$^{\circ}\text{C}$: Degrees Celsius

%: Percent

Abstract:

Ginkgolides are naturally occurring compounds that can be extracted from the *Ginkgo Biloba* tree. Their synthesis remains a significant challenge for organic chemists given their complex structure and their numerous stereocenters (2 adjacent quaternary carbons and up to 12 stereocenters). Both Corey and Crimmins reported the total synthesis of (±)-ginkgolide B in 1988¹ and 1999² respectively. Corey also published the enantioselective formal synthesis of ginkgolide B³ as well as the total synthesis of (±)-ginkgolide A in 1988.⁴ However, the total synthesis of Ginkgolide C, the most complex (and most hydroxylated) member of the family, has not yet been published.

We report herein the first total synthesis of (±)-ginkgolide C as well as the formal synthesis of (±)-ginkgolide A and (±)-ginkgolide B by intercepting Corey's intermediate (from his total synthesis of (±)-ginkgolide B). The first key step of our syntheses was the Claisen rearrangement which set the first quaternary carbon. The second key step of the syntheses was a kinetic alkylation which sets the second quaternary carbon. The third key step for our syntheses was an enyne epoxidation that enabled the formation of the E-ring. Starting from the Claisen rearrangement adduct, our target intermediate (towards ginkgolide C) was obtained in 18 steps, after which, (±)-ginkgolide C was synthesized in an additional 6 steps (total of 26 linear steps). Starting again from the Claisen rearrangement adduct, Corey's intermediate (from the total synthesis of (±)-ginkgolide B) was obtained in 15 steps which completed the formal syntheses of (±)-ginkgolide A (in an additional 10 steps) and (±)-ginkgolide B (with 6 additional steps).



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1.1 Chapter 1 – The Ginkgo Tree, Ginkgolides and Bilobalide

1.1.1 Introduction:

Ginkgolides and bilobalide (both designated as terpene trilactones or TTLs) are naturally occurring compounds which can be extracted from the ginkgo tree, *Ginkgo biloba*, whose name stems from the Japanese word *ginkyo* which signifies silver apricot. It's also known as the maidenhair tree because its leaves resemble those of the maidenhair fern. Their leaves are fan-shaped, they are green in the summer, then they turn yellow and orange in the fall. The trees can grow up to 35 meters tall with the main stem up to 10 meters in girth.⁵

Ginkgo biloba is also known as the “living fossil” because it's the only surviving member of a family of trees (*Ginkgoaceae*) from the Jurassic period about 170 million years ago. Despite the longevity of this tree, according to recent paleontological findings of a 121-million-year-old fossil, *Ginkgo biloba* has hardly changed.⁶ It's different from all other living plants which is why botanical taxonomists often categorize it in its own division (Ginkgophyta). The ginkgo tree is thought to be the oldest living tree species in the world.⁷ To demonstrate the resilience of the tree, *Ginkgo biloba* can live for over one thousand years (due to their resistance to pollution, pests, disease, etc.), and they were the first plants to regrow after the nuclear bomb detonation in Hiroshima on August 6th, 1945 (with no evidence of genetic mutation).⁸

1.1.2 Biological Activity:

1.1.2.1 Ginkgo Biloba Extracts:

The use of *Ginkgo biloba* for medicinal purposes dates to the Yuan dynasty (1280-1368) in Li Tung-wan's *Shi Wu Ben Cao* (Edible Herbal) and in Wu-rui's *Ri Yong Ben Cao* (Herbal for Daily Usage). In these texts, the fruits, or seeds (named “Bai-guo”) were used to treat illnesses such as asthma, chronic bronchitis, tuberculosis, and enuresis (involuntary urination).⁹ Thereafter, in 1436, Lan Mao describes the use of ginkgo leaves to treat freckles as well as skin and head sores in *Dian Nan Ben Cao*. Some time after, there is mention of the use of ginkgo leaves for internal

use in the medical text *Ben Cao Pin Hue Jing Yaor*. This text as well as other *Chinese Materia Medica* describe the use of the leaves to treat dysentery (gastroenteritis that results in diarrhea with blood), asthma and cardiovascular problems.¹⁰

In 1965, the German company, Dr. Willmar Schwabe, introduced the first ginkgo biloba leaf extract to the market (registered as Tebonin® to improve mental performance and well-being).¹¹ The Dr. Willmar Schwabe Company then collaborated with the Beaufour-IPSEN Group to conduct pharmacological and clinical studies which gave rise to a ginkgo extract trademarked Tanakan® for use in venous pathology in 1974. The extract was brought to the market in France as Tanakan® in 1975 (by IPSEN) and in Germany as Rökan in 1978 (by INTERSAN) as well as Tebonin forte in 1982 (by the Dr. Willmar Schwabe Company). In the early 1980s, the extract became known as EGb 761® which is now used to treat insufficiencies in cerebral and peripheral circulation and neurosensory organs. These symptoms are often related to Alzheimer's disease (AD) and other neurosensory problems.¹²

The extract EGb 761® can be obtained by extraction of the dried green ginkgo leaves with a mixture of acetone/water. This standardized extract contains about 6% TTLs (3.1% ginkgolide and 2.9% Bilobalide), which are unique to the ginkgo tree, and 24% flavonoids (which are almost entirely in the form of flavonol-O-glycosides).¹¹ To illustrate the global interest for Ginkgo biloba extracts, worldwide sales have been estimated at about 500 million USD in the year 2000.¹³ Although the bioavailability of the flavonoids remains controversial, the general consensus is that they do not penetrate the blood-brain barrier (BBB) sufficiently to result in physiological effects on the central nervous system (CNS). To the contrary, the bioavailability of ginkgolides and bilobalides stands at about 70-80% with a dose of 80 mg of EGb 761® with half-lives of 3-5 hours.^{14a} There have been many reviews describing the effects of EGb 761® on the CNS.^{14a-e} Observations of its neuromodulatory effects show improved cognition, antioxidant effects, increased cerebral blood flow and circulation, alteration of neurotransmission as well as mitigation of apoptosis.^{14a} In France and Germany, the *Ginkgo biloba* extract remains one of the preferred prescriptions to treat in dementia-related symptoms.¹⁵

Despite the extract's numeral potential applications mentioned above, most studies involving EGb 761® have been focused on the treatment of Alzheimer's disease (AD).^{16a-c} Two crucial studies involving a total of 549 AD patients assessing the effects of EGb 761® showed a significant decrease in the progression of the cognitive symptoms of dementia. Certain data points indicated symptoms were delayed by 7.8 months, which is comparable to the medication that is available for AD patients (Aricept (donepezil, 9.5 months) and Exelon (rivastigmine, 5.5 months), both of which are acetylcholinesterase inhibitors).^{17ab} A follow-up study showed that the treatment of dementia with the Ginkgo biloba extract was more effective in very mild to mild cases as opposed to severe ones, which would suggest that it can stabilize or delay its symptoms.¹⁸ Studies have shown that EGb 761® can inhibit the formation of β -amyloid aggregation,^{19a-c} which is thought to be crucial in the progression of AD.²⁰ In addition, EGb 761® has shown effects on the modulation of gene expression in the cortex and hippocampus of mice. Among the genes that were affected, some are thought to be related to AD.^{21ab}

1.1.2.2 Isolated Ginkgolides:

Although most of the studies surrounding the beneficial biological effects of *G. biloba* were conducted using the tree's extracts, less focus has been put into studying the extract's individual components, namely the flavonoids and the TTLs, which are believed to be responsible for most of its pharmacological effects. In order to have a deeper understanding of their biological activity, it is essential to study the effects of the extract's individual components. As mentioned previously, in terms of bioavailability, the flavonoids have a very low bioavailability, whereas the ginkgolides (particularly ginkgolides A and B) are almost entirely bioavailable.

Since 1985, the ginkgolides, especially ginkgolide B, have gained much interest for their application as antagonists of the platelet-activating factor (PAF) receptor (PAFR). PAF is an endogenous-synthesized phospholipid which is prepared by the cytomembrane, and it's known as a potent inflammatory factor that plays a role in acute and chronic inflammation. Excess expression of PAF has been linked to various CNS diseases.²² Consequently, researchers believe that PAF inhibitors or PAFR antagonists (such as ginkgolide B) could serve as effective therapies to treat CNS illnesses such as Alzheimer's disease²³, cerebral infarction and ischemia-reperfusion

injury,^{24abcd} spinal cord injury,^{25ab} multiple sclerosis,²⁶ Parkinson's disease,²⁷ epilepsy,²⁸ cerebral malaria²⁹ and HIV-1-associated dementia.³⁰ In addition to PAF inhibitors' and PAFR antagonists' potential in CNS disease treatment, studies have shown they could prove useful in pancreatic (in combination therapy)³¹ and colitis-associated cancers.³² Despite the potential application for ginkgolide B (BN52021) as a PAFR antagonist it was never registered as a drug due to its lack of efficacy.

A migraine without aura (MoA) is described by recurring intense headaches (pulsing or throbbing) on one side of the head. Other symptoms include sensitivity to light, sounds and smells. About 30% of migraine sufferers may also manifest visual symptoms such as getting blurred vision or seeing flashing lights, zig-zag lines, or blind spots. The latter condition is known as a migraine with aura (MwA). More recently, ginkgolide B has been studied for its use as prophylactic or acute medication to treat migraines. Studies conducted on adults suffering from MwA were treated 2x/day with Migrasoll® (60 mg of ginkgolide B, 11 mg of coenzyme Q 10 and 8.7 mg of vitamin B2) and reported a significant decrease in the frequency and duration of migraines. In some cases, a complete disappearance of symptoms was observed.³³ Acute treatment of symptoms with Migrasoll® resulted in a decrease of migraine duration as well as reduced neurological symptoms.³⁴ Furthermore, studies conducted on school-aged children suffering from MoA showed a significant decrease in migraine frequency, duration and intensity.^{35a-d} In addition, they were much less likely to consume analgesics for acute treatment of their symptoms.^{35ab} Moreover, the use of ginkgolide B in the prophylaxis of menstrual migraine was shown to be effective in reducing its severity. Additionally, a significant decrease in its physical and psychological symptoms were observed.³⁶

1.1.3 Isolation:

The ginkgolides were first isolated from the root bark of the ginkgo tree by Furukawa in 1932.³⁷ A few decades later, the structure of ginkgolides A (**1.1A**), B (**1.1B**), C (**1.1C**) and M (**1.1M**) (for minor) were elucidated by Nakanishi and coworkers in 1967.^{38a-e} In an independent study later that year, Okabe et al. published the isolation and structure determination for ginkgolides A-C (with an X-ray structure of the mono-*p*-bromobenzoate of ginkgolide A).^{39ab} A few years later,

bilobalide (**1.2**) was isolated by Weinges in 1969⁴⁰ and its structure was determined by Muetterties in 1971.⁴¹ Thereafter, Weinges was able to isolate and elucidate the structure of ginkgolide J (**1.1J**) in 1987.⁴² It is noteworthy to mention that ginkgolide J can only be extracted from the leaves, and ginkgolide M can only be found in the root bark. Some time later, ginkgolides K (**1.1K**) and L (**1.1L**) were identified as trace constituents of the ginkgo tree using LC/DAD/ESI/MS (Liquid Chromatography/Diode Array Detection/Electrospray Ionization/Mass Spectrometry) in 2001 by Wang.⁴³ Finally, in 2011, Peng and coworkers reported the discovery of two new ginkgolides, P (**1.1P**) and Q (**1.1Q**), found in the ginkgo leaves. The structures of ginkgolides P and Q are identical to those of ginkgolides A and B respectively except that one of the methyls from the *tert*-butyl group is substituted with a hydroxymethyl. The structure for ginkgolide P was confirmed by obtaining the X-ray structure of its dihydrate.⁴⁴

Originally, the ginkgolides were obtained in pure form by methanol extraction from 100 kg of undried chopped root bark followed by concentrating and washing with benzene. Crystals in the aqueous layer were recrystallized from ethanol to give a crude mixture of ginkgolides. The ginkgolides were then purified by column chromatography (using a mixture of ethanol and chloroform) giving a mixture of ginkgolides A and B, followed by a small amount of ginkgolide M and finally ginkgolide C. The separation of ginkgolides A and B was described as being extremely difficult since ginkgolide A can exhibit polymorphism. However, after performing a 10-15 step fractional recrystallization procedure, ginkgolides A and B were eventually separated. From the original 100 kg of Ginkgo biloba tree bark, 10 g of ginkgolide A, 10 g of ginkgolide B, 20 g of ginkgolide C, and 200 mg of ginkgolide M were obtained.^{38a}

In view of the difficulties faced to purify the ginkgolides and bilobalide, van Beek and Lelyveld developed a simpler method to separate the pairs of ginkgolides A/B and J/C as well as bilobalide. The main issue in separating these two pairs of ginkgolides is the fact that ginkgolides B and C both have a hydroxyl on C1. The hydrogen bonding between 1-OH and 10-OH can partially mask the polarity of these functional groups, which causes an overlap (with ginkgolides A and J respectively) in the chromatographic profile. This time starting from either dried ginkgo leaves or the commercial standardised ginkgo extract (EGb 761®), these were boiled in water and filtered (this process was repeated). Salt was added to the water and the aqueous solution was extracted

with EtOAc, dried over Na₂SO₄ and evaporated under reduced pressure. The mixture was then purified by MPLC (Medium Pressure Liquid Chromatography) with silica impregnated with NaOAc (which limits hydrogen bonding between the hydroxyls on C1 and C10) with an eluent gradient of 70% to 80% EtOAc/petroleum ether, followed by 100% EtOAc and 2% MeOH/EtOAc. Finally, the fractions were recrystallized 3-4 times using different mixtures of MeOH/H₂O.⁴⁵

Capitalizing on the thermal and oxidative stability of ginkgolides, Nakanishi and coworkers developed an interesting approach to facilitate the purification and quantification of ginkgolides in 2002. This method involved boiling the ginkgo leaves in dilute hydrogen peroxide for 1 hour (degrades leaf constituents that lead to emulsifications during extractions) followed by extraction with EtOAc. This treatment afforded an off-white powder that contained between 60-70% of TTLs. Interestingly, this method proved to be efficient in removing many compounds that caused troublesome emulsions in the extraction steps. After purification by MPLC (as described by van Beek and Lelyveld)⁴⁵, the ginkgolides were quantitatively analyzed by ¹H NMR comparing the integration of maleic acid (internal standard) with 12-H, which has a different chemical shift in ginkgolides A, B, C, J and bilobalide.⁴⁶

1.1.4 Structure and Physical Properties:

Ginkgolides A (**1.1A**), B (**1.1B**), C (**1.1C**), J (**1.1J**) and M (**1.1M**) all share a very similar molecular formula: C₂₀H₂₄O₍₉₋₁₁₎. These diterpene compounds have a structure that consists of six 5-membered rings including a spiro[4.4]nonane carbocyclic ring, three lactones, a tetrahydrofuran (THF) ring and a *tert*-butyl moiety (which is rarely found in natural products). The ginkgolides have 2 contiguous quaternary carbons (on the THF ring), they have 4 contiguous tetrasubstituted carbons (except for ginkgolide M, which only has 3) and they can have up to 12 stereocenters (varies from 10 to 12).

Their structure is identical except for R₁, R₂ and R₃ being permutations of either H or OH. The simplest one of the family is ginkgolide A with R₁ = R₂ = H and R₃ = OH. In contrast, the most complex of the family is ginkgolide C, which bears hydroxyl groups at all three R positions. Ginkgolides K (**1.1K**) and L (**1.1L**) are analogous to ginkgolides B and A (respectively) except they

have an alkene on the C-ring instead of a methyl and a R_3 group. As for ginkgolides P (**1.1P**) and Q (**1.1Q**), their structures are analogous to ginkgolides A and B (respectively) except that one of the methyls from the *tert*-butyl is hydroxylated (see **Figure 1.1**).

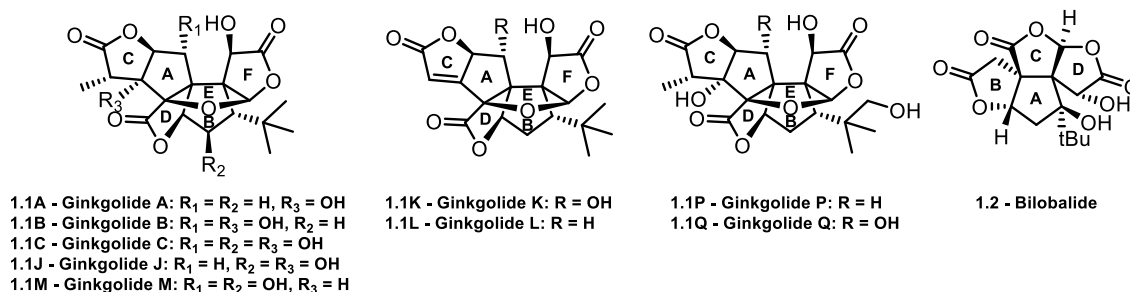


Figure 1.1: Structure of Ginkgolides A, B, C, J, M, K, L, P and Q as well as Bilobalide

As mentioned previously, ginkgolides and bilobalide bear a *tert*-butyl group, which is quite rare to find in naturally occurring compounds. Other examples often contain the non-proteinogenic amino acid *tert*-Leu (for example: hemiasterlin⁴⁷ and hemiasterlin A, criamide A and B,⁴⁸ milnamide A and D,⁴⁹ which have been isolated from the marine sponge *Cymbastela sp.*, as well as discodermin A-C⁵⁰ and E⁵¹ (A and E contain both L- and D-units of *tert*-Leu) which have been isolated in marine sponge *Discodermia kiiensis*). Nonetheless, plinabulin (contains *tert*-butyl on an imidazole ring)⁴⁷, bryostatins 4, 5, 10 and 14 (contain OPiv group)⁵² pranferins I and III (OtBu ethers),⁵³ the *tert*-butyl ketone swietenone,⁵⁴ the triterpenoids I-III,⁵⁵ the sponge sterols 25-methylfucosterol and axinyssasterol⁵⁶ as well as butyrolactol A (terminal *tert*-butyl group)⁵⁷ are a few examples of natural *tert*-butyl containing compounds which do not bear the *tert*-Leu residue.

As mentioned previously, the X-ray structure of the mono-*p*-bromobenzoate ginkgolide A was obtained by Okabe in 1967.^{39b} Some time later, the X-ray structure of ginkgolide B (monohydrate) was obtained in 1986.⁵⁸ Then, X-ray structures for ginkgolide A (monohydrate) and ginkgolide C (ethanol.1•5-hydrate) were obtained in 1987.⁵⁹ Fronczek and coworkers managed to obtain an X-ray structure for ginkgolide J (dihydrate) in addition to ginkgolide A (monohydrate) and ginkgolide C (sesquihydrate) at 120K.⁶⁰ Finally, an X-ray structure of ginkgolide P (dihydrate) was obtained in 2011 by Peng and coworkers.⁴⁴

As for their physical properties, ginkgolides are known to make odorless, bitter tasting white crystals or powders.^{38a} Due to their high number of polar (and/or hydrogen-bonding) functional groups, the ginkgolides all have elevated melting points (mp ~ 300 °C (dec)). When it comes to solubility, they can be dissolved in acetone, ethanol, methanol, ethyl acetate, tetrahydrofuran, dioxane, acetic acid, trifluoroacetic acid, acetonitrile, pyridine, and dimethyl sulfoxide. They are poorly soluble in diethyl ether as well as water, and they are insoluble in hexane, benzene, chloroform, and carbon tetrachloride.⁶¹ These compounds are light- and moisture-stable.⁶² Surprisingly, ginkgolides are also stable in extremely acidic conditions. To illustrate, ginkgolide crystals were recovered unchanged after evaporating to dryness in concentrated nitric acid. They were also dissolved in warm concentrated sulfuric acid and recovered intact after the addition of water. In addition, ginkgolides were dissolved in a dilute alkaline solution (cleavage of lactones to carboxylates) and they were later recovered quantitatively upon acidification of the solution.⁶³ Further details on the physical (taste, appearance, melting points, solubilities, water/*n*-octanol partition coefficient (*P*), ionization constants), chromatographic (TLC on silica gel, reversed-phase HPLC, GC) and spectroscopic properties (specific optical rotation, UV spectra, optical rotatory dispersion (ORD) spectra, IR spectra, EI-MS, API-MS, GC-MS, NMR spectra and X-ray crystallography) of ginkgolides and bilobalide are available in van Beek's review.⁶¹

1.1.5 Biosynthesis:

1.1.5.1 Terpene Biosynthesis:

Terpenoids, also known as isoprenoids, are one of the biggest and most structurally diverse groups of natural products, which account for over 30 000 compounds known to date.⁶⁴ In plants, they represent the largest class of small molecule natural products. The names "terpene" and "terpenoid" stem from the word turpentine, or "terpentin" in German, since some of the first ones were discovered in turpentine. They consist of five-carbon isoprene units (they are called isoprene units because isoprene gas can be released from certain terpenoids in high temperatures). The isoprene units are linked from end to end to make higher order terpenes such as monoterpenes (C₁₀), sesquiterpenes (C₁₅), diterpenes (C₂₀), etc. With the assistance of

multiple enzymes, these higher order terpenes can then be converted into a wide variety of complex natural products.⁶⁵

The biosynthesis of terpenoids (ginkgolides are classified as diterpenoids derived from geranylgeranyl pyrophosphate, C₂₀) are executed in four phases. In phase I, the C₅ isoprene building blocks, known as isopentenyl pyrophosphate (IPP) and dimethylallyl pyrophosphate (DMAPP), are formed in one of two possible pathways. The cytosolic mevalonate (MVA) pathway synthesizes IPP (**1.8**) from acetyl-CoA (**1.3**) using 6 enzymes and it can isomerize IPP into DMAPP (**1.9**) with a 7th enzyme (see **Figure 1.2**).

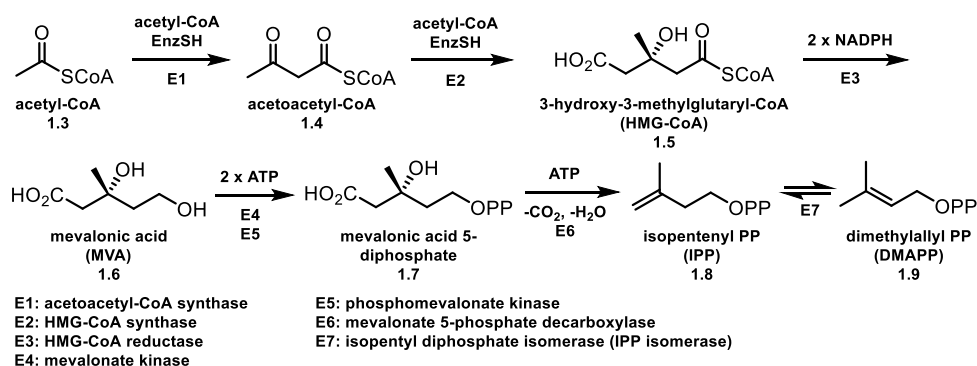


Figure 1.2: IPP and DMAPP Biosynthesis from Acetyl-CoA via the MVA Pathway

On the other hand, the plastidial methylerythritol phosphate (MEP) pathway can synthesize both IPP and DMAPP with the use of 7 enzymes starting from pyruvic acid (**1.10**) and D-glyceraldehyde 3-phosphate (IPP and DMAPP can be interconverted with an 8th enzyme)(see **Figure 1.3**).

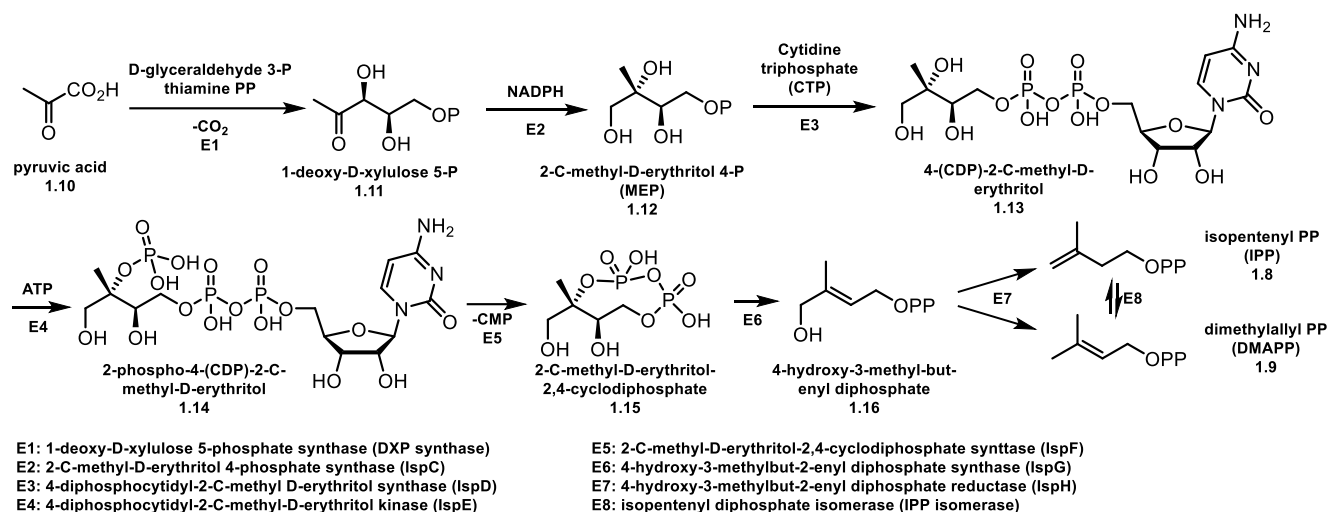


Figure 1.3: IPP and DMAPP Biosynthesis from Pyruvic Acid and D-Glyceraldehyde 3-P via the MEP Pathway

In phase II, the isoprene units IPP and DMAPP (hemiterpenes, C₅) are condensed together to form geranyl pyrophosphate (GPP, monoterpenes, C₁₀)(1.19). Then, subsequent IPP condensations generate farnesyl pyrophosphate (FPP, sesquiterpenes, C₁₅)(1.22), geranylgeranyl pyrophosphate (GGPP, diterpenes, C₂₀)(1.25A), sesterterpenes (C₂₅), triterpenes (C₃₀), tetraterpenes (C₄₀) and so on (see **Figure 1.4**).

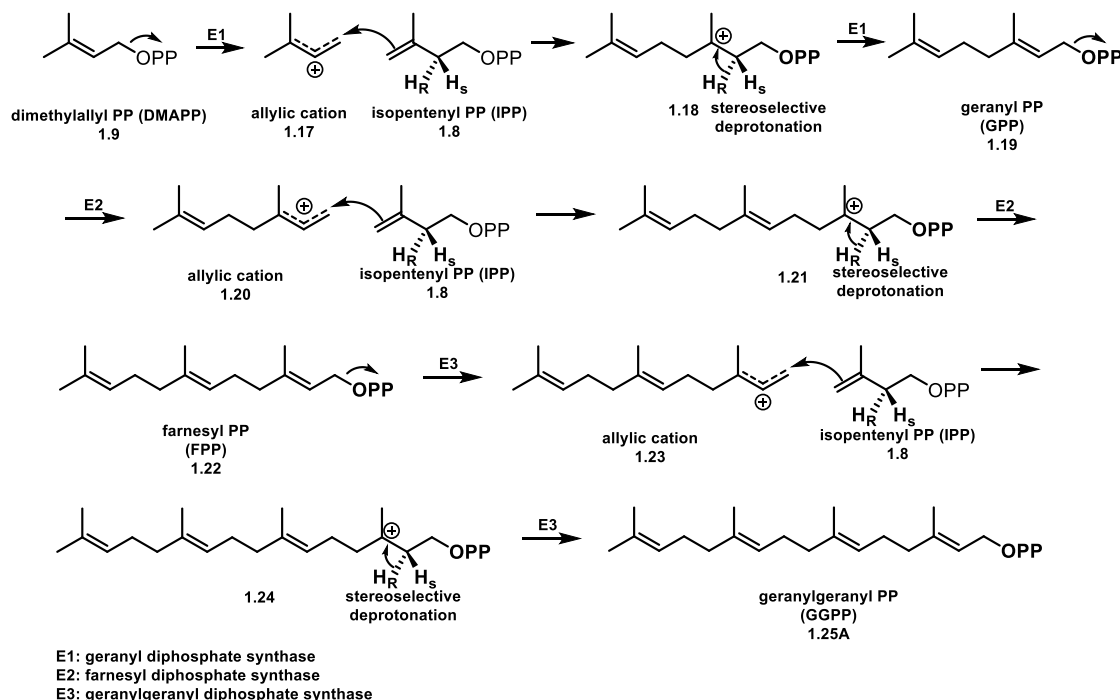


Figure 1.4: Assembly of IPP and DMAPP Units for the Biosynthesis of GGPP

In phase III, the terpenoid (GGPP in the case of ginkgolides) undergoes series of cyclizations and rearrangements which forms the parent skeleton of the molecule. Finally, phase IV includes a series of redox, isomerization, substitution, and conjugation reactions to give the final terpenoid product.⁶⁵⁻⁶⁶

1.1.5.2 Ginkgolide Biosynthesis – Nakanishi's Model:

To this day, the details for the biosynthetic pathway of ginkgolide remain uncertain. The first paper delving into its biosynthesis was published by Nakanishi and coworkers in 1971. In this publication, Nakanishi suggests a mechanism based on conclusions drawn after the incorporation of radioactive precursors in *G. biloba* by feeding with either sodium [2-¹⁴C]acetate (**1.26**), [2-¹⁴C]mevalonate (MVA)(**1.6**) (MVA pathway precursors) or [Me-¹⁴C]methionine using the cotton wick method. In the case of feeding with sodium [2-¹⁴C]acetate (denoted by *), through enzymatic processes, mevalonic acid (**1.6**) is formed and later converted to IPP and DMAPP which should invoke a specific labelling pattern of radioactive carbons (3 locations in both IPP and DMAPP). In the case of feeding with [2-¹⁴C]mevalonate (**1.6**)(denoted by Δ), it's converted to IPP and DMAPP with only one radioactive carbon (see **Figure 1.5**). Finally, feeding with [Me-¹⁴C]methionine (denoted by •) was performed in order to investigate the mechanism in which the *tert*-butyl is formed.

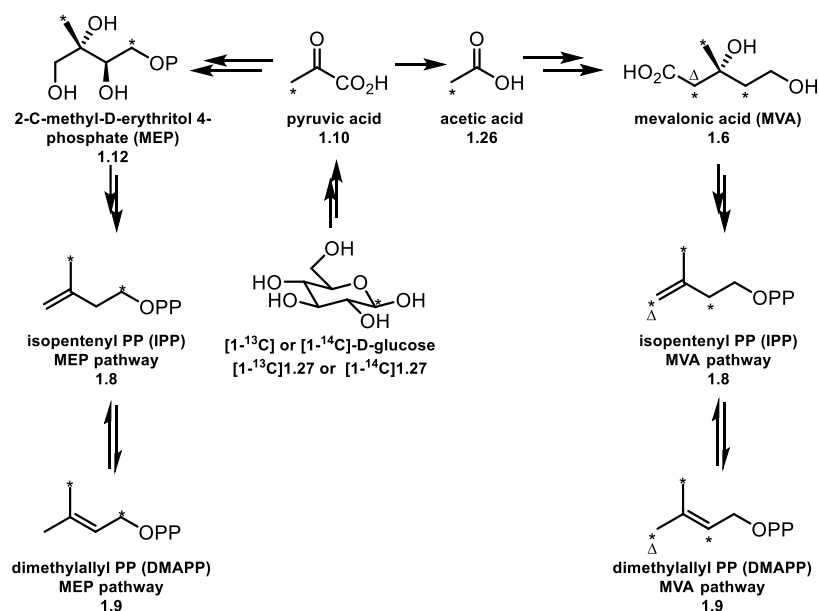


Figure 1.5: Radioactive Carbon Labelling Patterns of IPP and DMAPP Biosynthesis via MVA or MEP Pathway

After the formation of the labelled IPP and DMAPP, the diterpenoid precursor GGPP (**1.25A**) is generated. The authors propose a cyclization cascade with an oxidation which would generate the *ent*-pimaradienone cation (**1.28**). After a 1,2-methyl shift, an oxidation, the loss of a proton, a 1,2-alkyl shift and a Norrish-type-I-like reaction with abstraction of a β -proton (to generate the aldehyde and alkene), a spiro[4.5]decane **1.29** would be formed. After which, a 1,2-alkenyl shift, an alkene isomerization, and a series of oxidations would give rise to spiro[4.4]nonane **1.30**. Methylation of the alkene with the *S*-adenosyl methionine (SAM) and loss of a proton would generate the *tert*-butyl. The authors propose that the C₂₁ compound would undergo a decarboxylation to yield C₂₀ intermediate **1.31** (correct number of carbons for ginkgolides). After a series of oxidations and cyclizations, Nakanishi postulates that ginkgolide (**1.1**) can be obtained with the correct stereochemistry (with inversion of the stereochemistry of the *tert*-butyl) from intermediate **1.32** (see **Figure 1.6**).

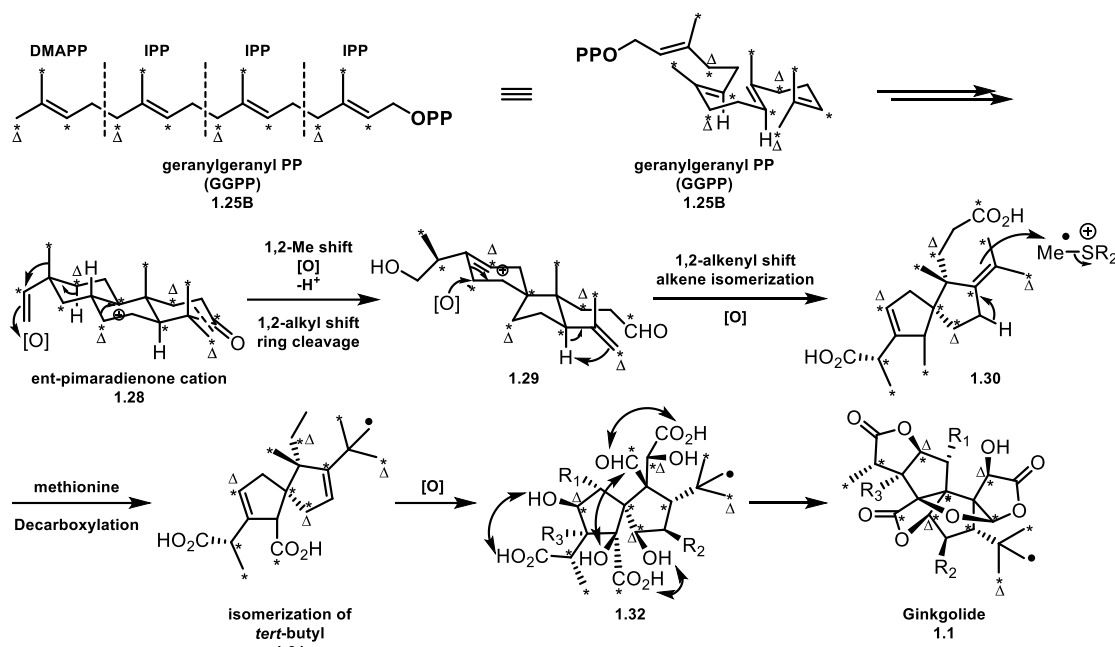


Figure 1.6: Proposed Biosynthetic Pathway for Ginkgolides by Nakanishi in 1971

After performing the Kuhn-Roth oxidation followed by the Schmidt reaction on the obtained ginkgolide B (after incorporation of radioactive precursors), the location of these radioactive carbons was then utilized to draw conclusions on plausible biosynthetic pathways to prepare ginkgolide. Namely, while feeding with sodium [2-¹⁴C]acetate, they observed that the ratio of radioactive methyls on the *tert*-butylamine (**1.34**) was 2.2:1 ¹⁴C/¹²C instead of having all three methyl groups labelled with ¹⁴C (which was inconsistent with a ring cleavage to form the *tert*-butyl (**1.36**), thus eliminating this pathway). In addition, the isolated acetic acid (**1.26**) showed that the methyl and carboxylic acid carbons were marked at a 1.2:1 ratio which would support the 1,2-methyl shift. As for the feeding with [2-¹⁴C]mevalonate, the isolated pivalic acid showed 95% of the expected activity from having one MVA unit assuming that the four isoprene units are distributed evenly. Finally, when feeding with [Me-¹⁴C]methionine, the authors claim the radioactive carbon was exclusively found on one of the methyls from the *tert*-butyl group which would support their proposed mechanism for its formation (see **Figure 1.7**).⁶⁷

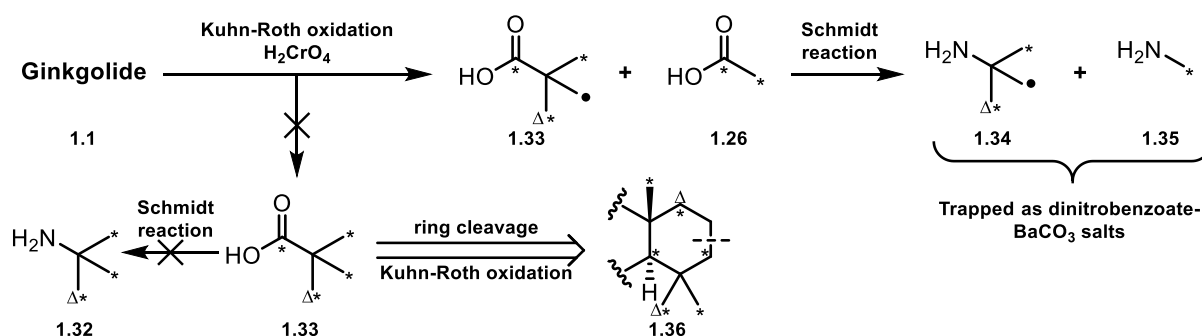


Figure 1.7: Kuhn-Roth Oxidation and Schmidt Reaction on Ginkgolide and Fragment Analysis by Nakanishi in 1971

In summary, radioactive carbon-14 studies seem to show evidence supporting: 1: The formation of the *tert*-butyl via alkylation of an alkene with an activated methionine (as opposed to a ring cleavage); 2: A pathway allowing for inversion of the stereocenter bearing the *tert*-butyl; 3: The 1,2-methyl shift onto the alkene; 4: Ginkgolide can be biosynthesized via the MVA pathway.

However, the mechanism proposed in this paper does have its share of inconsistencies. For instance, it is important to note that at the time this paper was published, the MVA pathway was the only known pathway for the biosynthesis of the IPP and DMAPP isoprene units. It wasn't until 1988 that Rohmer and colleagues discovered that the isoprene units could also be biosynthesized by a MVA-independent pathway known as the MEP pathway.^{68a-d} The current literature states that only about 1-2% of ginkgolides stem from the MVA pathway and that the rest relies on the prevalent MEP pathway (which could explain Nakanishi's very low incorporation rates of the radioactive labels into ginkgolide).

1.1.5.3 Ginkgolide Biosynthesis – Schwarz's Model:

Despite Nakanishi's work in the early 1970s related to the biosynthesis of ginkgolide, the general consensus of the literature leans towards the conclusions drawn by Schwarz described in his doctoral thesis in 1994⁶⁹ and in his work alongside Arigoni in 1999.⁷⁰ Their approach was focused on extensive labelling studies involving the use of a wide range of ^{14}C -, ^{13}C - and/or ^2H -labelled biosynthetic precursors. The *G. biloba* embryos were supplied with radiomarked

biogenetic precursors and incubated for 6 weeks before sitosterol, ginkgolides A and B as well as bilobalide were isolated by reversed phase HPLC followed by analysis via multiple 1D and 2D NMR experiments. A total of 21 feeding experiments were conducted including acetate and methionine (to compare with Nakanishi's results) as well as 7 labelled forms of D-glucose and 12 forms of mevalolactones (lactonized variant of mevalonic acid, also abbreviated as MVL) among which 16 precursors had a ^{13}C - and/or ^2H -label and 5 had a ^{14}C -label.

After conducting experiments with 6 differently labelled forms of glucose, Schwarz noted that the ginkgolides, in addition to bilobalide, had a different labelling pattern than sitosterol (1.37). The labelling pattern for sitosterol was in agreement with the classic MVA pathway, whereas the ginkgolides and bilobalide were consistent with Rohmer's MEP pathway (see **Figure 1.8**). This led to the conclusion that *G. biloba* can form the isoprenoid units (IPP and DMAPP) in two distinct biosynthetic pathways. This kind of mechanistic and structural dichotomy had already been observed in Cartayrade's study of *Salvia miltiorrhiza* (sage species) cell culture lines that produces the diterpene ferruginol.⁷¹

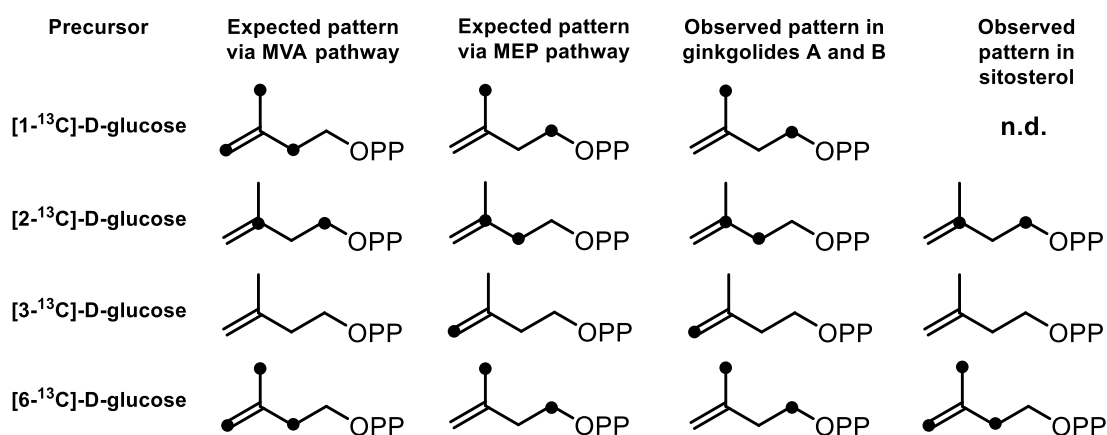


Figure 1.8: Expected and Observed Labelling Patterns of IPP Units of Upon Incorporation of ^{13}C -Labelled D-Glucose in Ginkgolide A, B, and Sitosterol

In terms of labelling patterns of the carbons in the IPP unit (from the metabolism of glucose), there is a symmetry between the upper and lower halves of D-glucose. In other words, the incorporation of either [1- ^{13}C]- or [6- ^{13}C]-D-glucose will give the same substitution pattern on the IPP unit in their respective pathways. This is also true for the [2- ^{13}C]/[5- ^{13}C]-D-glucose and [3- ^{13}C]/[4- ^{13}C]-D-glucose pairs. This stems from the fact that the hexose is split into two trioses that

are then converted to either acetyl-CoA in the MVA pathway (wherein carbons 3 and 4 of glucose are lost in the form of CO₂) or pyruvate in the MEP pathway (see **Figures 1.8** and **1.9**).

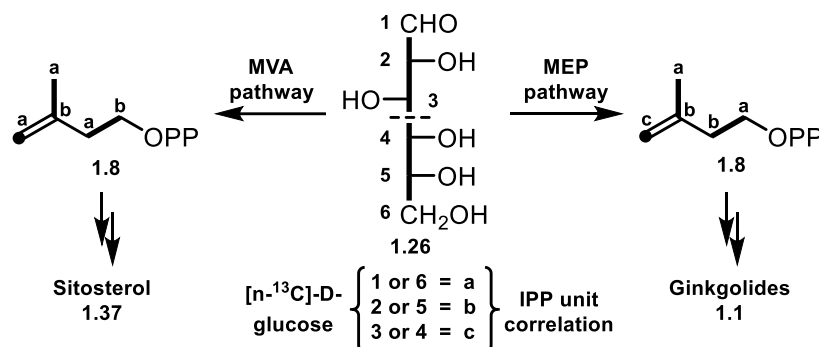


Figure 1.9: Symmetry of D-Glucose Labelling in IPP Units

Contrary to Nakanishi's model suggesting an epoxide opening driven 1,2-methyl shift (via **1.39**), an experiment using a uniformly labelled sample of D-glucose (equally distributed on all six positions), [U-¹³C]-D-glucose, mixed with 9 parts of unlabelled D-glucose revealed that the 1,2-methyl shift occurs after the protonation of the vinyl moiety (via **1.42**)(where the methyl implicated in the 1,2-methyl shift from **1.43** is later oxidized to lactone **1.44** instead of the terminal carbon of the vinyl group) (see **Figure 1.10**).

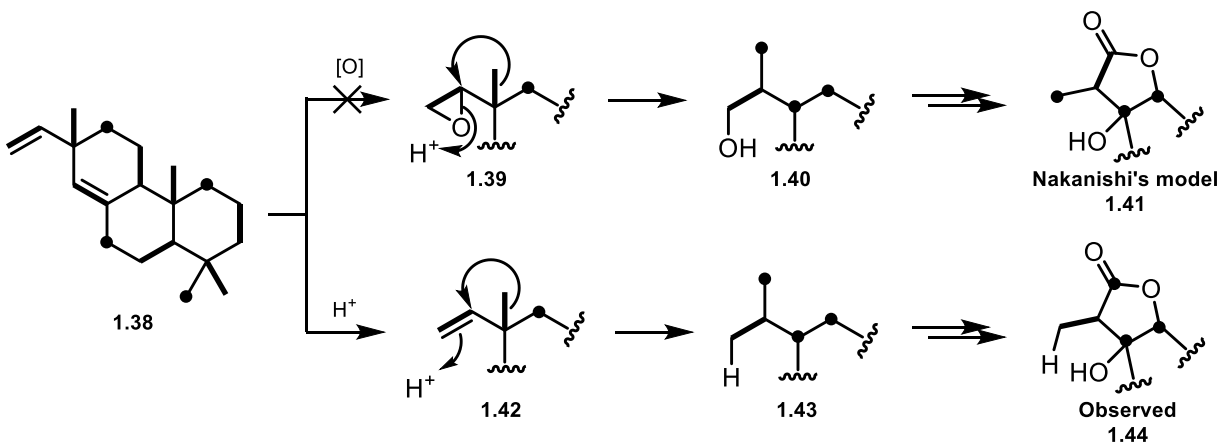


Figure 1.10: Schwarz's Incorporation of [U-¹³C]-D-Glucose for the Determination of the 1,2-Methyl Shift Mechanism

Then, upon incorporation of [6,6,6-²H₃]MVL, which forms [5,5,5-²H₃]IPP followed by the polydeuterated GGPP (**1.25C**), the obtained ²D-labelled ginkgolide (**1.46A**) surprisingly had an

entire equivalent of deuterium on its methyl group. The origin from this deuterium could come from one of the four IPP units. The first IPP unit can be ruled out because it retains its CD₃ group. The second IPP unit was ruled out because of the long distance between the second and fourth IPP units. Finally, the fourth IPP unit was ruled out because it couldn't have transferred a full equivalent of deuterium due to the fact that the fourth IPP unit always shows a diminished ¹³C- and/or ²H-labelling compared to the first three IPP units (between 5-20% of the average values of the first three units). Consequently, it was proposed that the deuterium must originate from the third IPP unit (see **Figure 1.11**).

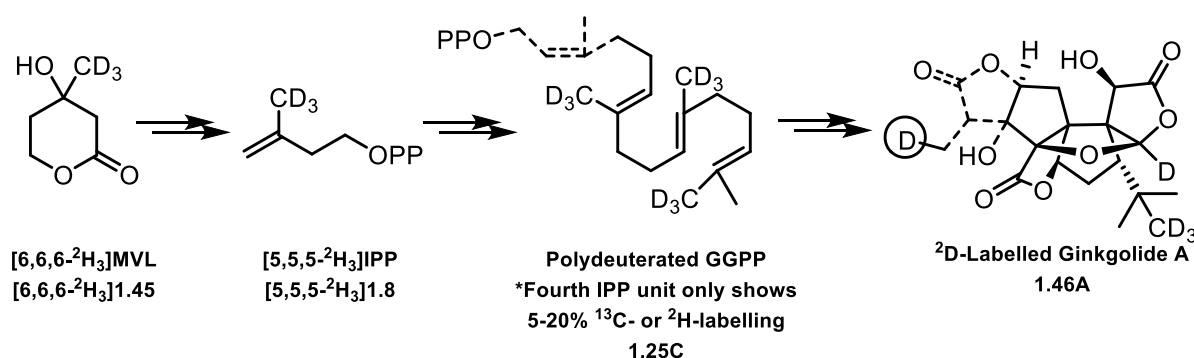


Figure 1.11: Schwarz's Incorporation of [6,6,6-²H₃]MVL for the Elucidation of the 1,2-Methyl Shift Mechanism

From this experiment, four possible pathways were proposed with (+)-copalyl PP (**1.47B**), the sandaracopimarenyl cation (**1.48**) and levopimaradiene (**1.50**) as intermediates. Further evidence of levopimaradiene as a key intermediate in the biosynthesis of ginkgolide has been brought to light by the cloning and characterization of the genes encoding for levopimaradiene synthase (LPS) in *G. biloba*.⁷² Pathway A involves an external base that would capture one of the two deuteriums on C14 to generate **1.49**, after which a protonation of the vinyl followed by a 1,2-methyl shift and an elimination of a proton would generate levopimaradiene **1.50B**. However, in this case, the methyl remains undeuterated, unlike the observed ginkgolide. Pathway B is very similar to pathway A, except that it involves an enzyme-bound base which could act both as a base to capture the deuterium and as an acid to deuterate the vinyl group. This kind of enzyme-bound base mechanism had been previously proposed in the biosynthesis of pentalenene,⁷³ taxadiene⁷⁴ and (-)-abietadiene.⁷⁵ This route allows for deuteration of the methyl group, but this

“sticky enzyme” base mechanism was discarded mainly for energetic reasons. It seemed very unlikely to link an exothermic α -deprotonation of a cation followed by a highly endothermic protonation of a vinyl group. Consequently, pathways C1 and C2 involving an internal base mechanism were proposed to bypass these energy barrier issues. Pathway C1 describes a more stepwise approach involving a 1,4-deuterium shift (from the vinyl group) which generates a double bond and a secondary carbocation (**1.51**). In fact, this type of 1,4-hydrogen shift has been reported in the literature.^{75a} Subsequently, a 1,2-methyl shift followed by proton elimination would yield deuterated levopimaradiene **1.50C**. Similarly, pathway C2 also involves a 1,4-deuterium shift from the vinyl group, but instead of an E1-type elimination (to generate an alkene between carbons C9-C14), the authors propose a simultaneous 1,2-methyl shift and alkene formation between carbons C13-C14 (to **1.52**) in a concerted process. Finally, a conjugated E1 elimination of a proton would generate the deuterated levopimaradiene **1.50C** (see **Figure 1.12**).

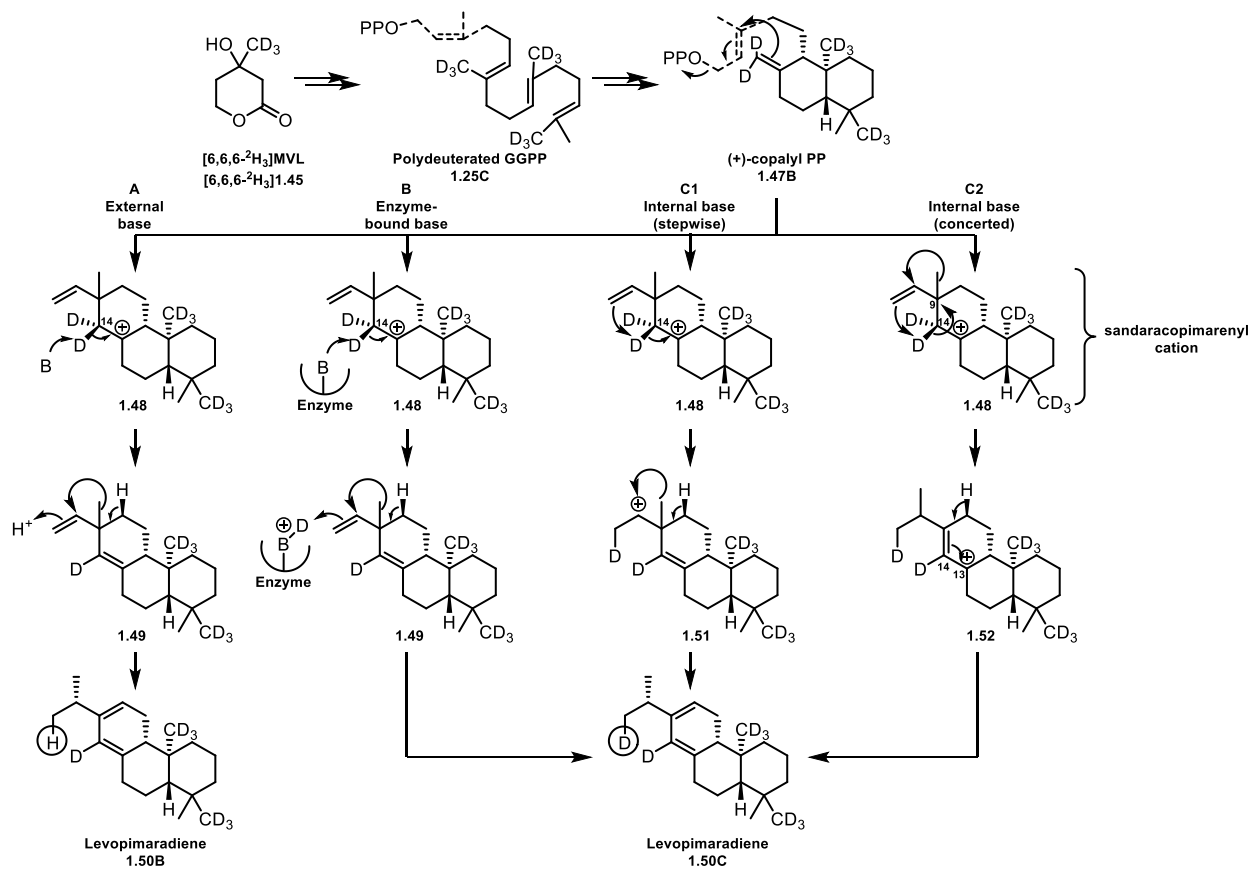


Figure 1.12: Schwarz’s Incorporation of [6,6,6-²H₃]MVL for the Determination of the Mechanism for the Proton Transfer and 1,2-Methyl Shift

In Cartayrade's quest for discovering intermediates in the ginkgolide biosynthesis, he was able to isolate about 50 μg of (+)-dehydroabietane (**1.53**), via GC-MS, from 2 kg of dried *G. biloba* roots.⁷¹ Analysis upon purification by chiral GC revealed it had the same retention time as the dehydroabietane found in a pine specimen that is known to have the "normal" configuration ((10*S*, 5*S*), (+)-rotation) as opposed to the "ent" configuration proposed by Nakanishi. The origin of the aromatic intermediate dehydroabietane (**1.53A**) stems from the oxidation of levopimaradiene (**1.50A**).

In order to determine which proton is lost during the aforementioned oxidation, two experiments using either [6,6-²H₂]-D-glucose or [1-²H]-D-glucose were conducted. In the case of feeding with [6,6-²H₂]-D-glucose, one equivalent of deuterium is lost on C11 during the oxidation of levopimaradiene **1.50D** into dehydroabietane **1.53B** and an equivalent of hydrogen is gained on C11 of **1.46B** (H-11 β). In the case of feeding with [1-²H]-D-glucose, the D-11 α is abstracted to generate dehydroabietane **1.53C** from levopimaradiene **1.50E**. Analogous to the previous experiment, an equivalent of hydrogen is gained on C11 of **1.46C** (H-11 β). From this, the investigators determined that an α -H/D abstraction occurs on C11 when levopimaradiene **1.50D/E** is oxidized to dehydroabietane **1.53B/C**. Subsequently, a β -hydrogenation takes place on C11 which can be observed on ²D-labelled ginkgolide A **1.46B/C** (see **Figure 1.13**).

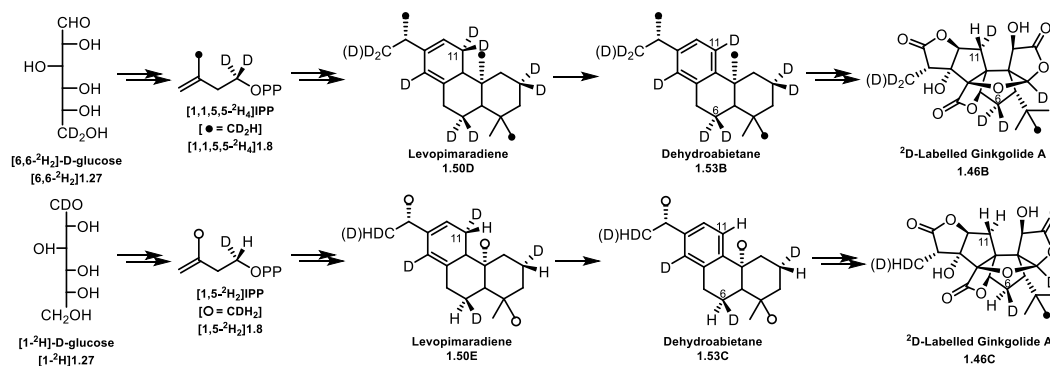


Figure 1.13: Schwarz's Incorporation of [6,6-²H₂]-D-Glucose or [1-²H]-D-Glucose for the Determination of Which C11 Proton is Lost During the Oxidation of Levopimaradiene to Dehydroabietane

Additional evidence to support the involvement of dehydroabietane **1.53A** as a key intermediate in biosynthetic pathway was brought forth by the work of Neau and Walter. While

supplying *G. biloba* with cytochrome-P450 (CYP450) inhibitors, they observed a four-fold increase in production of dehydroabietane **1.53A** as well as a three-fold decrease in production of ginkgolides **1.1**. This study suggests that dehydroabietane **1.53A** might be the last oxygen-free hydrocarbon intermediate before obtaining ginkgolide **1.1** via a series of oxidations led by CYP450 (see **Figure 1.14**).⁷⁶

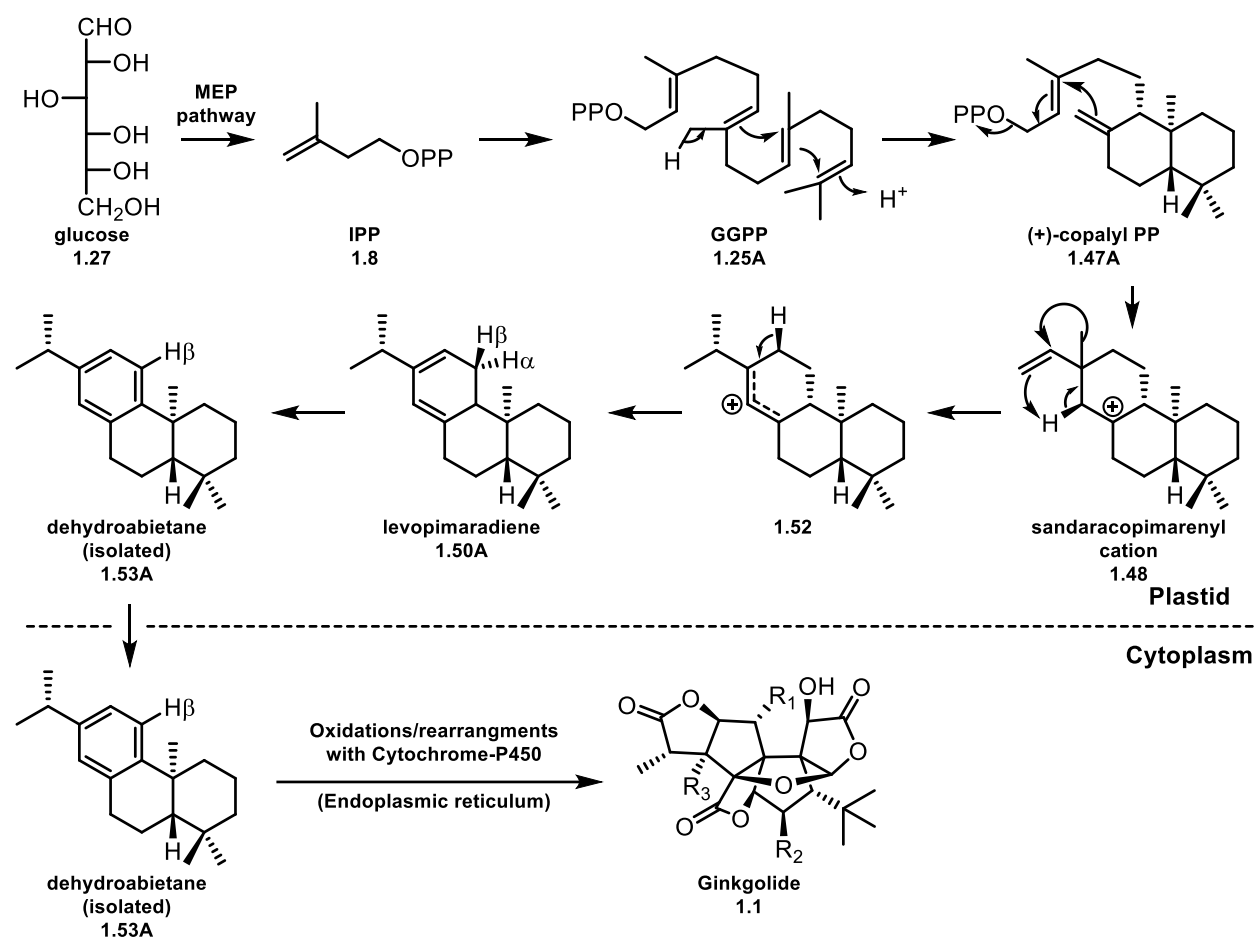


Figure 1.14: Summary of the Biosynthesis of Ginkgolide from Glucose via the Isolated Intermediate Dehydroabietane

One of the most controversial aspects in the biosynthesis of ginkgolide is the formation of the *tert*-butyl moiety. Nakanishi postulated it originated from a SAM-dependant methylation of an alkene (followed by the loss of a carbon via decarboxylation), whereas Schwarz proposes a C-C cleavage between C2 and C3 where C2 is eventually oxidized to the carboxylic function and C3 is reduced to the methyl, thus forming the *tert*-butyl. To prove his claim that the *tert*-butyl

originated from a C2/C3 bond cleavage, Schwarz conducted a few ^{14}C -, ^2H - or ^{13}C -labelled MVL experiments using samples of $[4\text{-}^{14}\text{C}]\text{MVL}$, $[4,4\text{-}^2\text{H}_2]\text{MVL}$, $[4,5\text{-}^{13}\text{C}_2]\text{MVL}$ and $[3,4\text{-}^{13}\text{C}_2]\text{MVL}$. In the first experiment, $[4\text{-}^{14}\text{C}]\text{MVL}$ was incorporated and the labelled ginkgolides A, B and C were isolated. They were then subjected to a Kuhn-Roth degradation that yielded pivalic acid. These ginkgolide fragments represented a molar specific activity of 60-62% in relation to the molar specific activity of ginkgolides A, B and C (**1.54A**). The slight difference from the theoretical value of 67% was justified by the weak but significant labelling of the fourth IPP unit. In the case where the formation of the *tert*-butyl was to include a cleavage between carbons C3 and C4 (as postulated by Nakanishi), the observed molar specific value would be around 46% (corrected from a theoretical value of 50%). Next, the incorporation of $[4,4\text{-}^2\text{H}_2]\text{MVL}$ yielded ginkgolide bearing a single deuterium on carbons C3 and C5 (**1.46D**) which supports the theory that the *tert*-butyl is formed via a cleavage between the C2 and C3 bonds. The justification for carbon C3 only bearing one out of two deuteriums has been attributed to the interconversion of IPP into DMAPP, which would result in the loss of a deuterium. According to Nakanishi's model, featuring a SAM-dependant methylation, neither H3 nor H5 would be conserved in the formation of the *tert*-butyl (which is not the case in this experiment). Then, feeding with $[4,5\text{-}^{13}\text{C}_2]\text{MVL}$ generated samples of ginkgolides A and B (**1.54B**) that determined that the bond between carbons C2 and C3 was indeed cleaved. Finally, the incorporation of an undiluted synthetic sample of $[3,4\text{-}^{13}\text{C}_2]\text{MVL}$ (99% of ^{13}C -labelling per position) was able to show that carbons C3 and C4 remain intact throughout the entire biosynthesis via **1.54C** (see **Figure 1.15**).

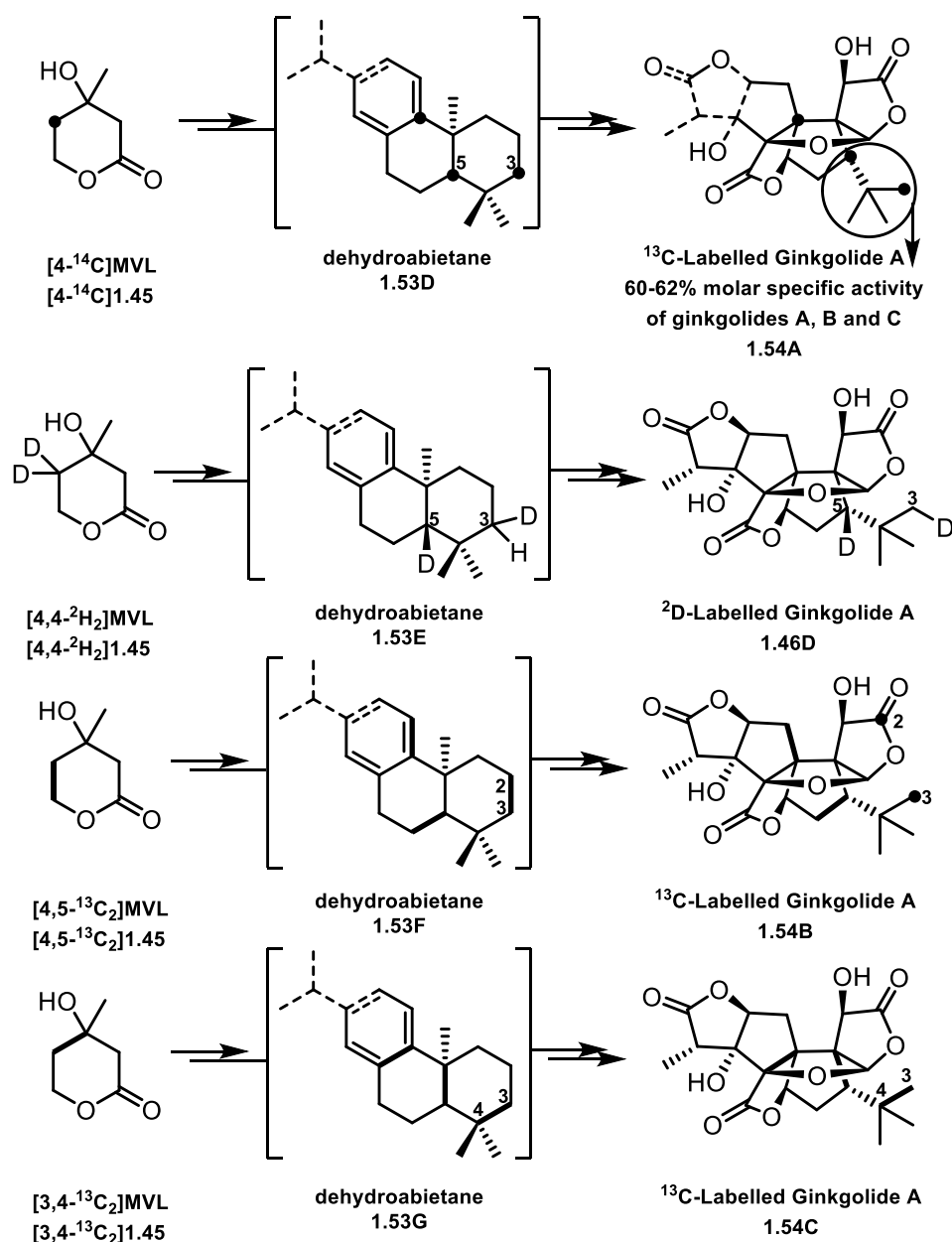


Figure 1.15: Schwarz's Investigation of the Origin of the *tert*-Butyl of Ginkgolide via the Incorporation of $[4-^{14}\text{C}]\text{MVL}$, $[4,4-^2\text{H}_2]\text{MVL}$, $[4,5-^{13}\text{C}_2]\text{MVL}$ and $[3,4-^{13}\text{C}_2]\text{MVL}$

Next, the investigators sought to find evidence (or scars) of the C2/C3 bond cleavage. In the case of C2, it becomes oxidized to the carboxylic function, but C3's scar seems to have disappeared. Schwarz and coworkers propose a CYP450 oxidation of **1.55** yielding hemiacetal **1.56**, which can be further oxidized to its corresponding oxygen-centered radical **1.58** via **1.57**. The highly reactive oxygen-centered radical **1.58** is susceptible to a radical β -cleavage yielding

lactone **1.59** which bears an unstable primary carbon-centered radical at C3 ($\text{BDE}(\bullet\text{CH}_2\text{C}(\text{CH}_3)_3) \sim 422.4 \text{ kJ/mol}$).⁷⁷ An intramolecular H atom transfer from C1 to C3 would generate a more stable secondary carbon-centered radical (**1.60**) which would also be stabilized by resonance with the lactone (thus forming the C3 methyl of the *tert*-butyl) ($\text{BDE}(\bullet\text{CH}_2\text{C}(\text{O})\text{OCH}_3) \sim 412.0 \pm 6 \text{ kJ/mol}$).⁷⁷ The presence of the hydroxyl group on C1 of all five ginkgolides, which could stem from oxidation of the corresponding carbon-centered radical by CYP450 (to **1.61**), displays further evidence of the ring cleavage followed by a hydrogen atom transfer. In other words, it seems C3's C-C bond cleavage scar was transferred to C1 which was later oxidized to its corresponding alcohol (see **Figure 1.16**).

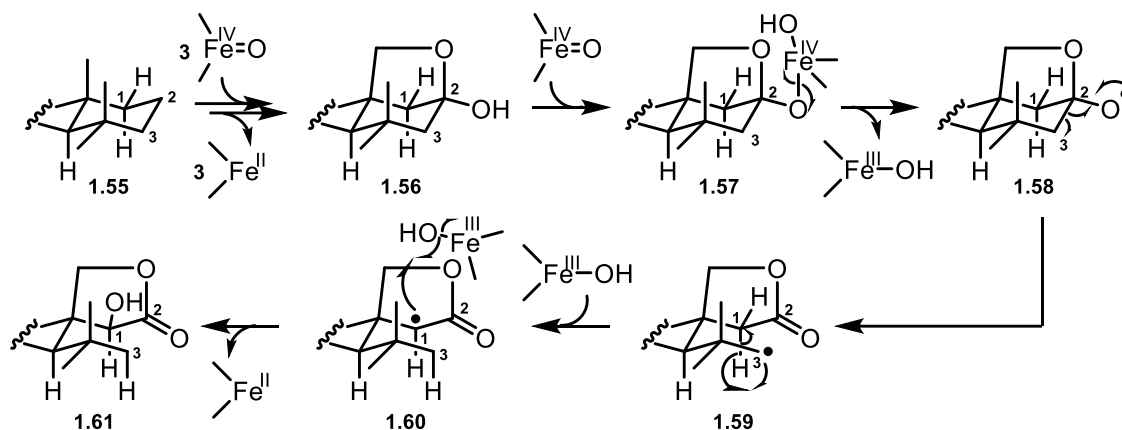


Figure 1.16: Schwarz's Postulated Mechanism for C2-C3 Bond Cleavage, Lactone Formation and Carbon-Centered Radical Oxidation

To verify this hypothesis, the investigators devised an experiment using $[2,2\text{-}^2\text{H}_2]\text{MVL}$. They expected to observe an additional deuterium on the *tert*-butyl (C3) with conservation of the second deuterium on C1 (**1.46E**). Indeed, they observed deuteration on C3, which would confirm the hydrogen transfer hypothesis, but the second deuterium on C1 seems to have been lost at some point in the biosynthesis (**1.46F**)(see **Figure 1.17**).

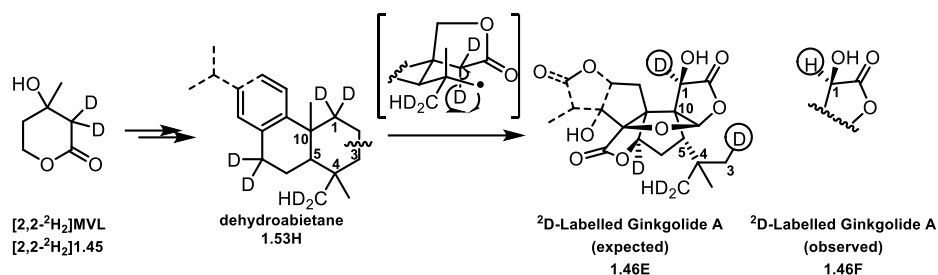


Figure 1.17: Incorporation of $[2,2-^2\text{H}_2]\text{MVL}$ for the Determination of the Mechanism for the Carbon-Centered Radical Hydrogen Transfer

To summarize, these experiments allowed the authors to draw the following conclusions:

1: The bond between C3 and C4 remains untouched throughout the biosynthesis (which rules out a SAM-dependant methylation). 2: The ring cleavage occurs between C2 and C3 which is followed by a hydrogen transfer from C1 to C3 without affecting C5/H5. 3: Feeding with $[4,4-^2\text{H}_2]\text{MVL}$ revealed that H5 remained untouched, meaning that in the “normal” series, C10 must go through an inversion of configuration (as opposed to C5 in Nakanishi’s “ent”-series model).

Gathering all the data collected from the labelling experiments, the following two-part model for the biosynthesis of ginkgolide and bilobalide, starting from the isolated dehydroabietane, was proposed (wherein there is a bifurcation in the biosynthetic pathway, which will determine whether ginkgolide or bilobalide is formed). Part one begins with the oxidation of dehydroabietane (**1.53A**) into ferruginol (**1.62**)(known compound in other plants) which is then further oxidized to ketol **1.63**. In acidic conditions, the dienone can perform a ring contraction, to afford **1.64**, followed by a C-C bond cleavage to restore aromaticity thus forming tertiary carbocation **1.65**. Elimination of H_1 yields **1.66** which is subsequently oxidized to enone **1.67** that can undergo an intramolecular Michael addition to afford **1.68** (inversion of C10 in this step). After protonation on the β -face (H_3) to afford **1.69**, the lactol is oxidized to the oxygen-centered radical which yields the corresponding lactone and primary carbocation **1.70** (upon radical ring cleavage). This highly reactive primary carbon-centered radical scavenges the α -proton (H_2) yielding the more stabilized secondary carbon-centered radical (**1.71**) which is subsequently oxidized to the hydroxyl (**1.72**). An oxidation followed by the formation of a hemiketal generates “Schwarz’s Intermediate” **1.73**, after which a bifurcation in the biosynthetic pathway will occur to produce either ginkgolide **1.1** or bilobalide **1.2** (see **Figure 1.18**).

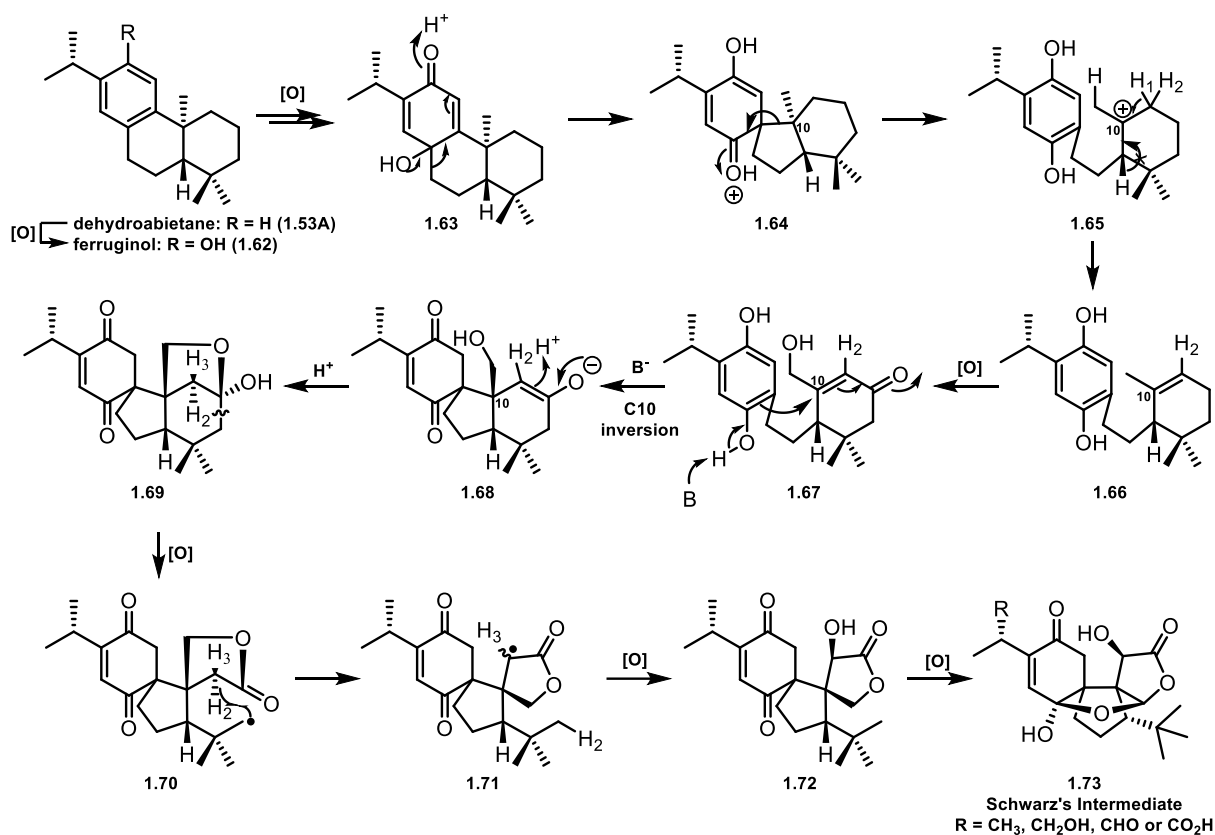


Figure 1.18: Biosynthesis of Schwarz's Intermediate **1.73** from Dehydroabietane **1.53A**

From "Schwarz's Intermediate", a bifurcation in the biosynthetic pathway occurs. In the case where there is an α -hydroxylation on C7 (to afford **1.74**), the formation of lactol **1.75** will prevent the ketone from being reduced and the alkene will be oxidized to **1.76**. Next, a ring opening/lactone formation (yielding **1.77**) followed by another lactone formation (expelling C₅ fragment **1.78**) generates bilobalide (**1.2**). Whereas a β -hydroxylation of C7 (to afford **1.79**) will allow for the ketone to be reduced from the α -face and the alkene will be oxidized to afford **1.80**. Finally, a lactone formation which induces a ring contraction and loss of a molecule of water (in addition to the condensation of the alcohol onto the carboxylic acid) yields ginkgolide A (**1.1A**) (see **Figure 1.19**).

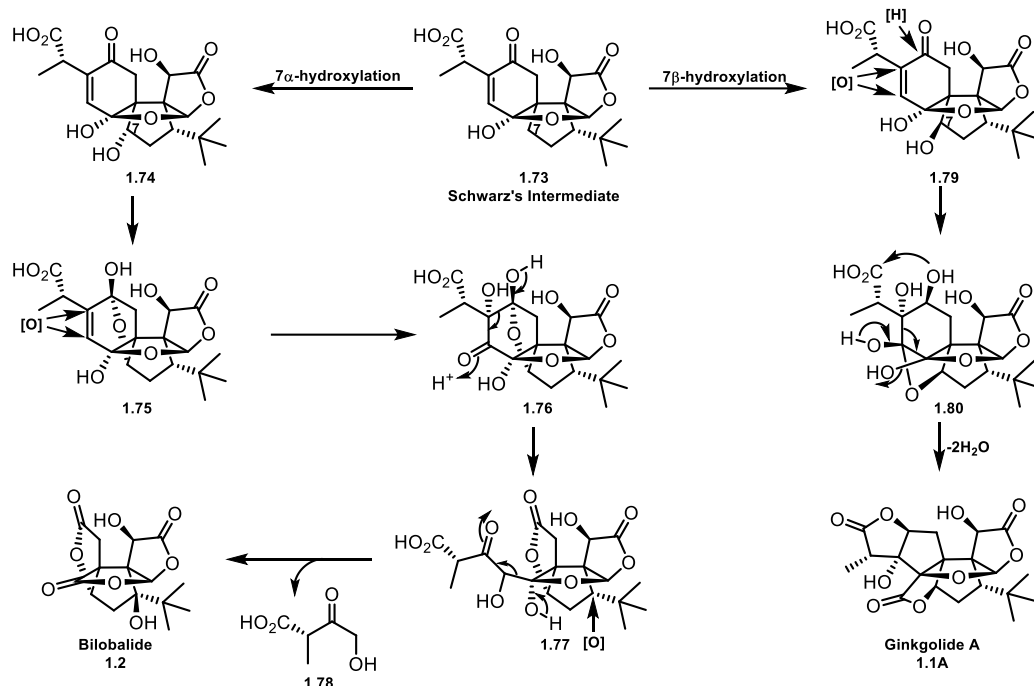


Figure 1.19: Bifurcation of Schwarz's Intermediate Towards the Biosynthesis of Ginkgolide or Bilobalide

1.1.5.4 Addition of Biosynthetic Precursors or Elicitors to Increase Ginkgolide Production:

Some research groups aimed to increase the production of ginkgolides in *G. biloba* by adding biosynthetic precursors as well as fungal or bacterial elicitors. Studies carried out by Kang et al. showed that the total production (in cells and culture medium) of ginkgolide A was most increased by feeding with the MVA pathway precursor HMG-CoA. For ginkgolide B, feeding with more downstream precursors such as IPP, DMAPP and GPP showed most effective compared to the control. As for bilobalide, a large increase in production was observed in feeding with more downstream precursors (especially GPP, but also IPP, GGPP, DMAPP, and FPP) and an increase in production was also observed upon feeding with MEP pathway precursors such as GA-3P (glyceraldehyde 3-phosphate) and SP (sodium pyruvate).⁷⁸ In addition, Kang found that the native *Staphylococcus aureus* KCTC 1916 and *Candida albicans* KCTC 7121 (biotic elicitors) increased the production of ginkgolides A and B.⁷⁹ Studies by Dai and coworkers determined that the mycelium extract of *Rhizopus japonicus* was the most effective to increase production of ginkgolide B out

of the 10 kinds of fungi that were tested. In the same paper, the authors showed that the addition of isoprene could also increase the production of ginkgolide B by up to 69%.⁸⁰

1.1.6 Total Syntheses of Ginkgolide and Bilobalide:

1.1.6.1 Ginkgolide and Bilobalide – Partial Structures:

The first paper pertaining to the total synthesis of ginkgolide, or in this case, its ABE ring system, was published by Weinges and coworkers in 1971. Therein, they described a 3-step process including a 1,2-addition onto ketone **1.81** (with a Grignard reagent) followed by a benzyl deprotection to afford triol **1.82**. Heating to 150 °C in DMSO enabled the formation of the E-ring which afforded the ABE tricyclic core (**1.83**) with omission of the *tert*-butyl group (see **Figure 1.20**).⁸¹

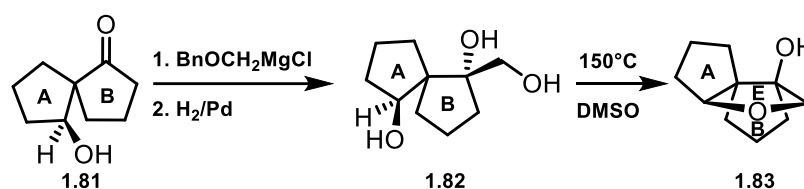


Figure 1.20: Weinges' Formation of the ABE Tricyclic Core of Ginkgolide

Some time later, Villhauer and Anderson focused on building the DEF ring system of ginkgolide. Epoxide opening of **1.84** with dimethyl malonate formed E-ring lactone **1.85**. Krapcho dealcoxycarbonylation followed by a double alkylation of the E-ring lactone with LDA/BnCl, then with LDA/*tert*-butyl bromoacetate yielded intermediate **1.86**. After converting the *tert*-butyl ester to the corresponding carboxylic acid (with TFA), the E-ring lactone was reduced with DIBALH, then treatment with PTSA generated F-ring lactone **1.87**. Benzyl deprotection with H_2 and Pd/C followed by treatment with PTSA generated D-ring acetal **1.88**. Finally, conversion of acetal **1.88** to the lactol (with aqueous HCl) followed by oxidation to the lactone with PCC afforded the DEF tricyclic ring system **1.89** (see **Figure 1.21**).⁸²

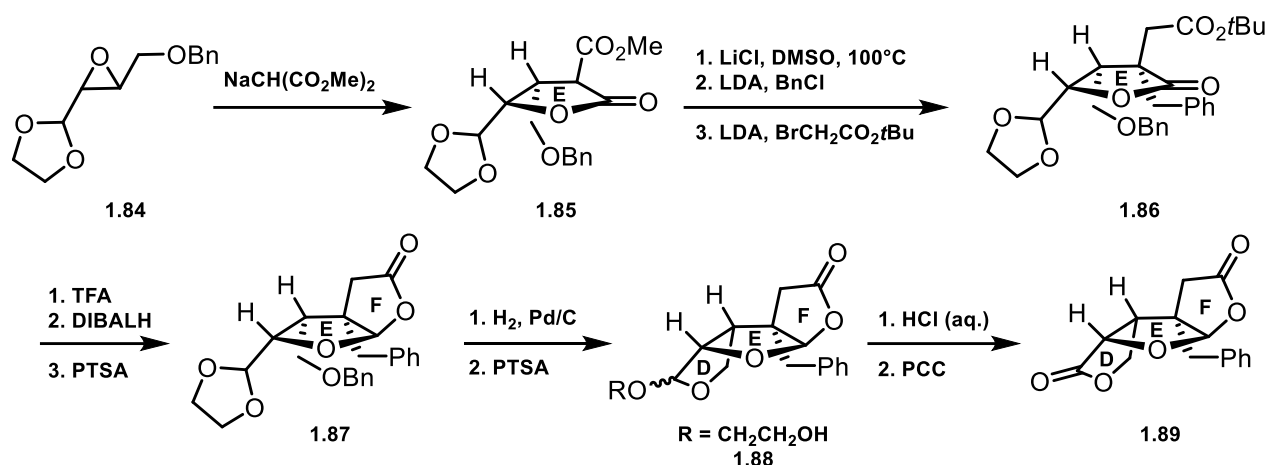


Figure 1.21: Villhauer's and Anderson's Formation of the DEF Ring System of Ginkgolide

Next, Pattenden et al. developed an intramolecular radical cyclization methodology where carbon-centered radicals are generated from alkyl bromides (**1.91**, **1.94**, **1.96** and **1.98**) and are subsequently cyclized onto α,β -unsaturated esters to prepare spiro-fused γ -lactone ring systems (**1.92** and **1.95**) as well as linear-fused γ -lactone ring systems (**1.90** and **1.97**) found in ginkgolide (**1.1**) and bilobalide (**1.2**) (see **Figure 1.22**).^{83ab}

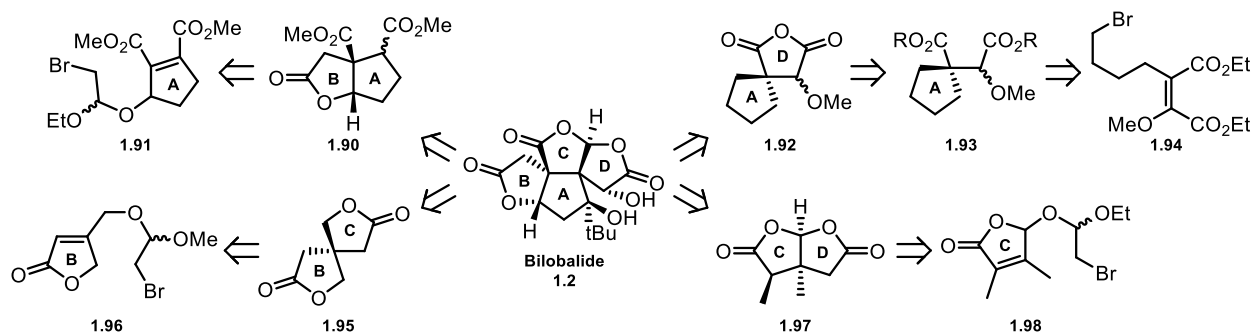


Figure 1.22: Pattenden's Methodology for Intramolecular Radical Cyclizations to Form Spiro- and Linear-Fused γ -Lactone Ring Systems in Ginkgolide and Bilobalide

Finally, in 1991, DeLuca and Magnus published a methodology describing the preparation of the spiro[4.4]nonane scaffold (**1.100**) via a double alkylation (with diiodide **1.101**) of cyclopentadiene **1.102** to **1.103**. Oxidation with singlet oxygen yielded **1.105** (through intermediate **1.104**). The B-ring was formed in slight acidic conditions (via the enol with SiO₂) to afford **1.106**. Oxidation of the allylic alcohol with MnO₂ followed by selective reduction of the ketone (farthest from the *tert*-butyl) with K-Selectride generated compound **1.107**. The alkene

was then reduced with H_2 and PtO_2 to afford intermediate **1.108** which the authors claim could be utilized towards the total synthesis of ginkgolides (see **Figure 1.23**).⁸⁴

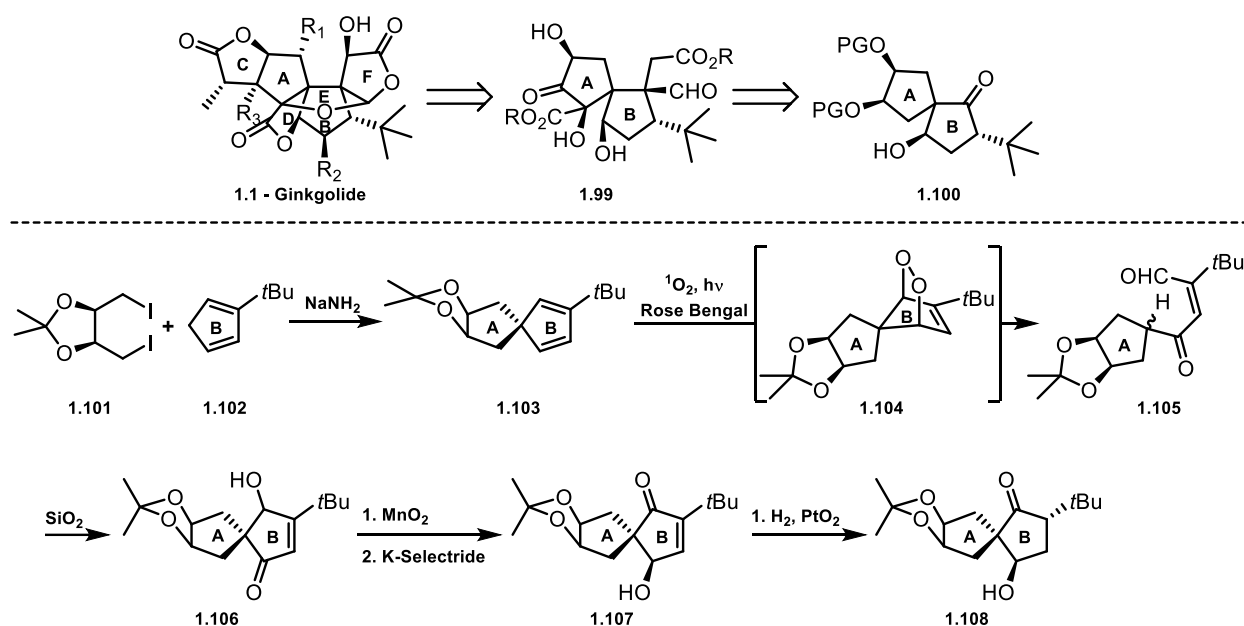


Figure 1.23: DeLuca and Magnus' Preparation of the Spiro[4.4]nonane Followed by Singlet Oxygen Oxidation

1.1.6.2 Total Syntheses of Ginkgolides:

The first racemic total synthesis of ginkgolide B (**1.1B**) was achieved by Corey et al. in 1988 featuring a [2+2] ketene-olefin cycloaddition as a key step.¹ In the same calendar year, Corey's group published an enantioselective formal synthesis of ginkgolide B³ followed by the total synthesis of ginkgolide A⁴ (from either ginkgolide B (**1.1B**) or advanced intermediate **1.122**). In 1989, Crimmins et al. showcased their intramolecular [2+2] photocycloaddition strategy on a model substrate to afford the ABDEF pentacyclic scaffold thus establishing their progress towards the total synthesis of ginkgolides A and B. Although it wasn't until 1999 that Crimmins and coworkers reported their racemic total synthesis of ginkgolide B^{2a} as well as a more detailed full paper in 2000.^{2b} Due to the structural complexity of ginkgolides, they remain a difficult synthetic target for chemists today. Consequently, their total syntheses were highlighted in *Strategies and Tactics in Organic Synthesis*⁸⁵ and *Classics in Total Synthesis*.⁸⁶

Corey's approach for the total synthesis of (±)-ginkgolide B started by the alkylation of 1-morpholinocyclopentene (**1.109**) with 2,2-dimethoxyacetaldehyde to obtain the cyclopentenone **1.110**. Conjugate addition with *tert*-butyl cuprate (and trapping with TMSCl) followed by treatment with trioxane and TiCl₄ formed the F-ring to afford **1.111**. After 4 steps, the stage was set for the key step of their synthesis, a [2+2] ketene-olefin cycloaddition affording the A- and D-rings (**1.113**) via **1.112**. The D-ring underwent a ring expansion via a Baeyer-Villiger oxidation yielding **1.114**. The F-ring was opened to **1.115** via thioacetal formation and the primary alcohol was oxidized to aldehyde **1.116**. Treatment with HIO₄ deprotected the thioacetal, then treatment with CSA in MeOH formed the F-ring (**1.117**). Lactone **1.117** was α-hydroxylated with lithium diethylamide (LDEA) and Davis' oxaziridine to afford **1.118**. Upon treatment with CSA, the E-ring was formed (**1.119**). A-ring enone **1.120** was obtained after allylic oxidation of **1.119** (in 2 steps). The F-ring enol ether was obtained via MeOH elimination (with PPTS and pyridine at 135 °C) and the A-ring enone was epoxidized with [BnNMe₃]O^tPr and trityl hydroperoxide yielding **1.121**. A 1,2-addition onto the A-ring ketone with the *Z*-enolate of *tert*-butyl propionate (formed with LDA in THF/HMPA (4:1)) followed by an acid-catalyzed cyclization (with CSA) formed the C-ring (**1.122**). The secondary A-ring alcohol was then TBS-protected with TBSOTf to afford **1.123**. Finally, an OsO₄ dihydroxylation of the F-ring enol ether followed by lactol oxidation to lactone **1.124** (with I₂/CaCO₃) and a TBS-deprotection with BF₃•OEt₂ gave rise to (±)-ginkgolide B (**1.1B**) in 24 steps (see **Figure 1.24**).¹

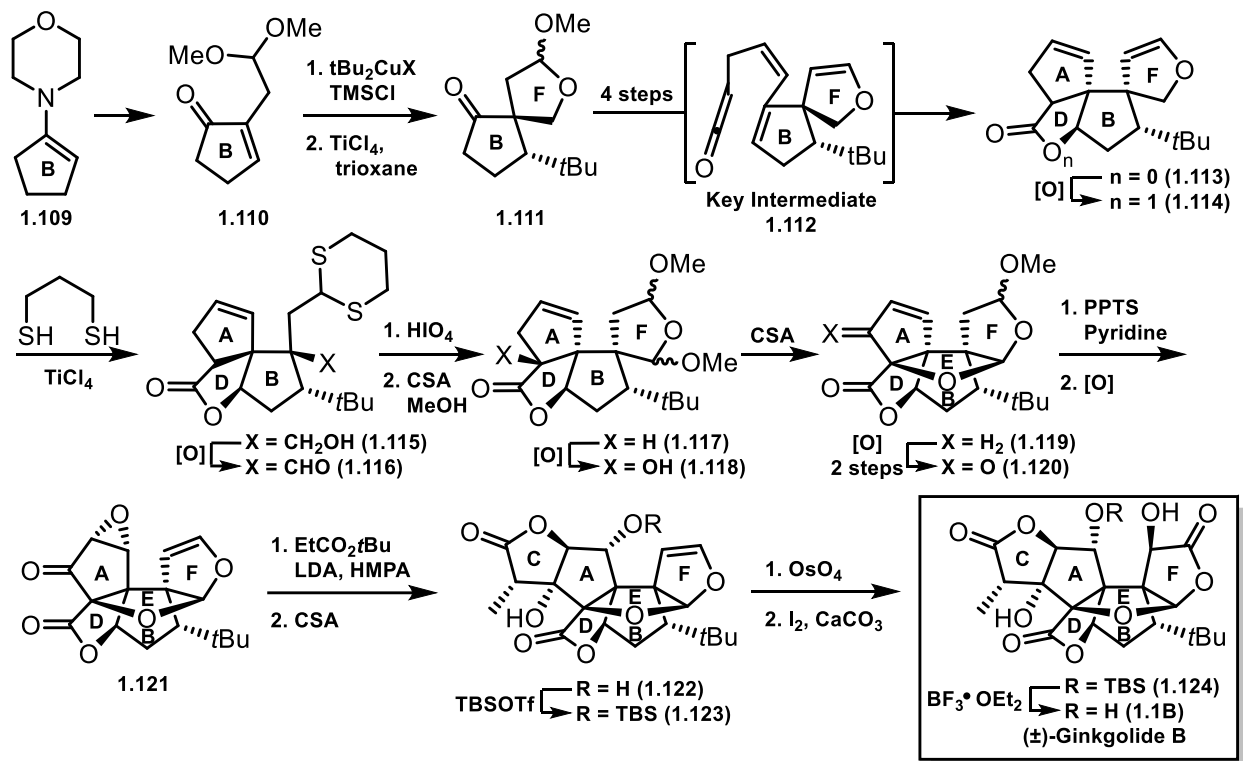


Figure 1.24: Corey's Racemic Synthesis of (±)-Ginkgolide B

In Corey's enantioselective formal synthesis of ginkgolide B, an enantioselective reduction of enone **1.110** using the (*S*)-CBS reagent yielded allylic alcohol **1.125** which was then converted to pivalic ester **1.126**. This laid the groundwork for a stereospecific $\text{S}_{\text{N}}2'$ substitution of the OPiv for a *tert*-butyl group with the use of a *tert*-butyl cuprate (**1.127**). Thereafter, a hydroboration followed by a PCC oxidation generated the corresponding ketone (**1.128**). After the preparation of the TBS enol ether, treatment with TiCl_4 and trioxane formed the F-ring and afforded acetal **1.129**. After 3 steps, compound **1.130** was obtained, after which, the ketene was prepared (via the acyl chloride) which underwent a [2+2] ketene-olefin cycloaddition to form the A- and D-rings. Finally, the enantioselective formal synthesis was completed by performing a Baeyer-Villiger reaction on the cyclobutanone to afford lactone **1.114*** (>98% ee). In sum, the enantioselective formal synthesis of ginkgolide B (**1.1B**) was achieved by preparing lactone **1.114*** enantioselectively with a >98% ee (from which ginkgolide B can be obtained in 16 additional steps) from (1-morpholinocyclopentene) for a total of 29 steps to ginkgolide B (see **Figure 1.25**).^{1,3}

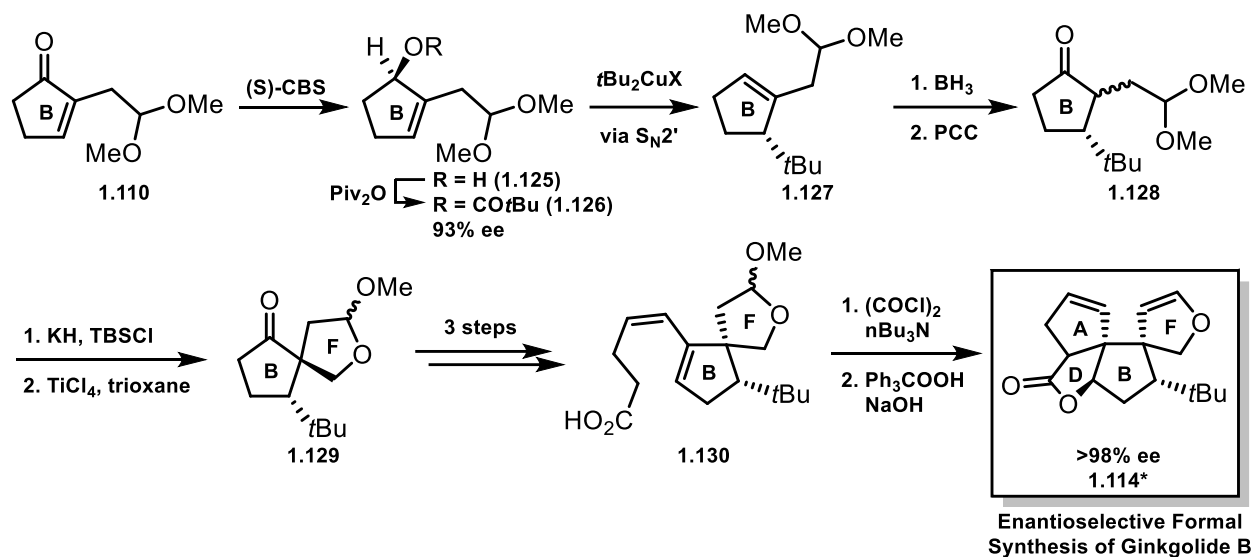


Figure 1.25: Corey's Enantioselective Formal Synthesis of Ginkgolide B

The only difference between ginkgolides A and B is the lack of the secondary alcohol on the A-ring in the case of ginkgolide A. Corey and coworkers obtained ginkgolide A (**1.1A**) starting from either ginkgolide B (**1.1B**) or intermediate **1.122** (from Corey's total synthesis of ginkgolide B). Starting from ginkgolide B (**1.1B**), the F-ring hydroxyl was MOM-protected to **1.131** with MOMCl. Then, the secondary A-ring hydroxyl was converted to the corresponding methyl or benzyl xanthates (**1.132** and **1.133** respectively). Xanthates **1.132** and **1.133** were reduced with tributyltin hydride, then, the MOM was deprotected with $\text{BF}_3 \cdot \text{OEt}_2$ to afford ($\pm$)-ginkgolide A (**1.1A**). Starting from intermediate **1.122**, The secondary A-ring alcohol was converted to the corresponding thiocarbonylimidazole before being reduced to **1.134** with tributyltin hydride. Treatment with OsO_4 yielded undesired 1,2-diol (at C10) and the lactol was subsequently oxidized to lactone **1.135** with I_2/CaCO_3 . The C10 alcohol was oxidized to dihydrofuran-2,3-dione **1.136** using benzeneseleninic anhydride. Finally, the formal synthesis of ($\pm$)-ginkgolide A (**1.1A**) was completed upon reduction of the ketone with NaBH_4 (see **Figure 1.26**).⁴

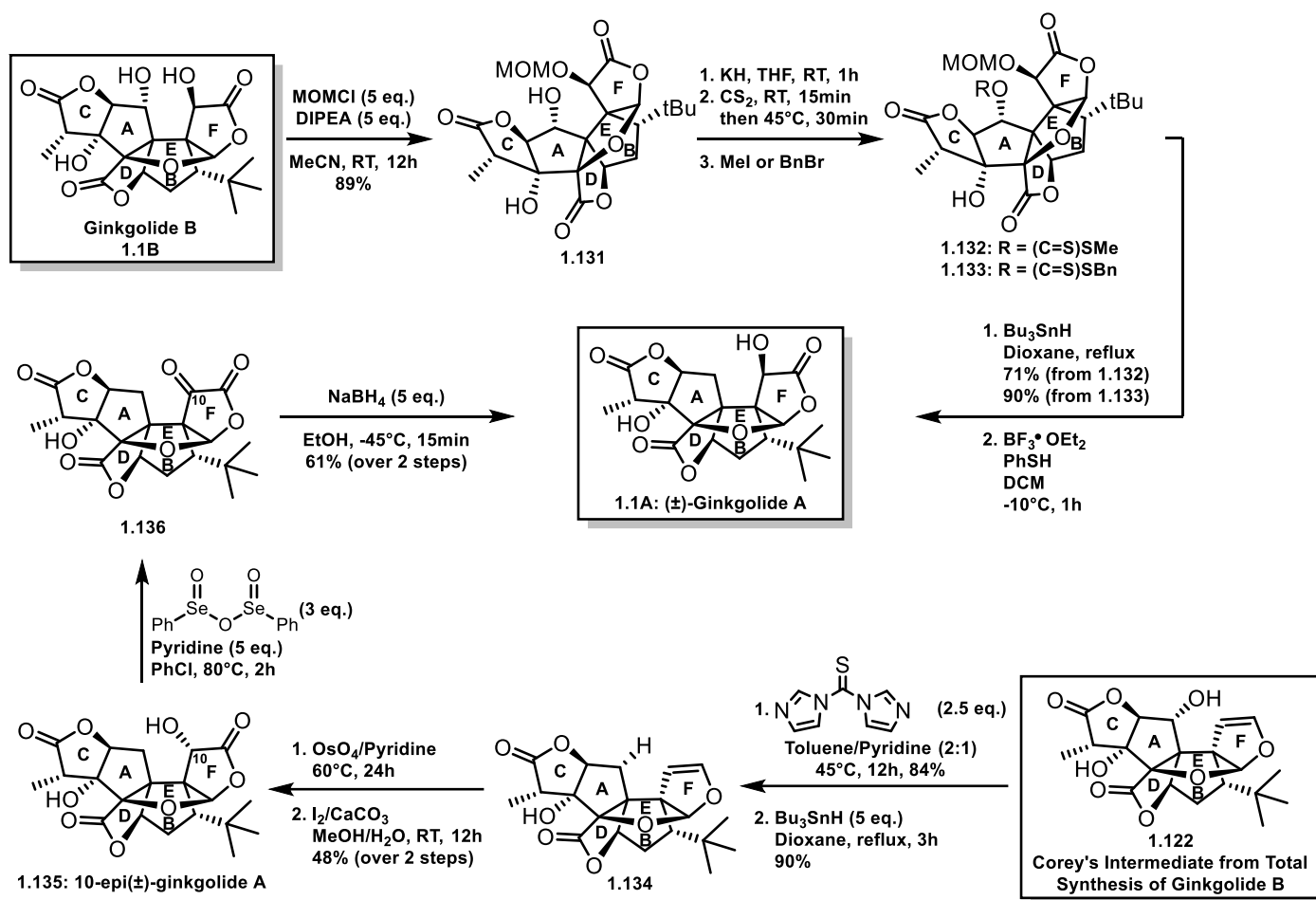


Figure 1.26: Corey's Racemic Formal Synthesis of Ginkgolide A Starting from Ginkgolide B or Advanced Intermediate **1.122** from his Total Synthesis of Ginkgolide B

Crimmins started his total synthesis of (±)-ginkgolide B (**1.1B**) from 3-furaldehyde (**1.137**) by performing a Wittig reaction followed by a conjugate addition (with a *tert*-butyl cuprate) and a DIBALH reduction to obtain aldehyde **1.138**. An additional 5 steps yielded acetylenic ester **1.139**. Compound **1.139** was submitted to a zinc-copper homoenolate that conducted a 1,4-addition followed by a Claisen condensation to generate the A-ring (**1.140**)(key step). Then, upon irradiation, the cyclobutane and B-ring were formed via a [2+2] photocycloaddition to afford **1.141** (second key step of the synthesis). Thereafter, the B-ring alcohol was deprotected (with TBAF) and mesylated (with MsCl) yielding **1.143** in 2 steps. Treatment with PPTS in EtOH enabled the formation of the D-ring lactone. Next, the A-ring ketone was oxidized to the corresponding enone via phenylselenation of the ketone with PhSeCl and HCl (via the enol) followed by

oxidation to the selenoxide (with NaIO_4) which underwent a *syn*-selenoxide elimination to afford enone **1.144**. The cyclobutane was fragmented/oxidized and the F-ring enol ether was oxidized to the corresponding diol with DMDO. Subsequent treatment with PTSA and $\text{CH}(\text{OMe})_3$ in MeOH yielded **1.145**. The F-ring underwent a Barton McCombie deoxygenation (over 2 steps) to afford intermediate **1.147**. Oxidation of the A/D-ring junction with LDEA and Davis' oxaziridine followed by acylation with propionic anhydride and treatment with LDA afforded lactone **1.148**. CSA in MeOH opened lactone **1.148** and enabled the formation of the E-ring. Treatment with PPTS and pyridine in PhCl at 135 °C yielded enol ether **1.149**. Sharpless epoxidation of the allylic alcohol (with $\text{VO}(\text{acac})_2$ and *t*BuOOH) followed by the addition of PTSA formed the C-ring. The F-ring enol ether was epoxidized with DMDO, the epoxide was opened with AcOH/ H_2O and the resulting lactol was oxidized to the lactone with HOBr as the active oxidant (formed via $\text{Br}_2 + \text{H}_2\text{O} \rightarrow \text{HOBr} + \text{HBr}$) and NaOAc as a base to afford ($\pm$)-ginkgolide B (**1.1B**)(see **Figure 1.27**).²

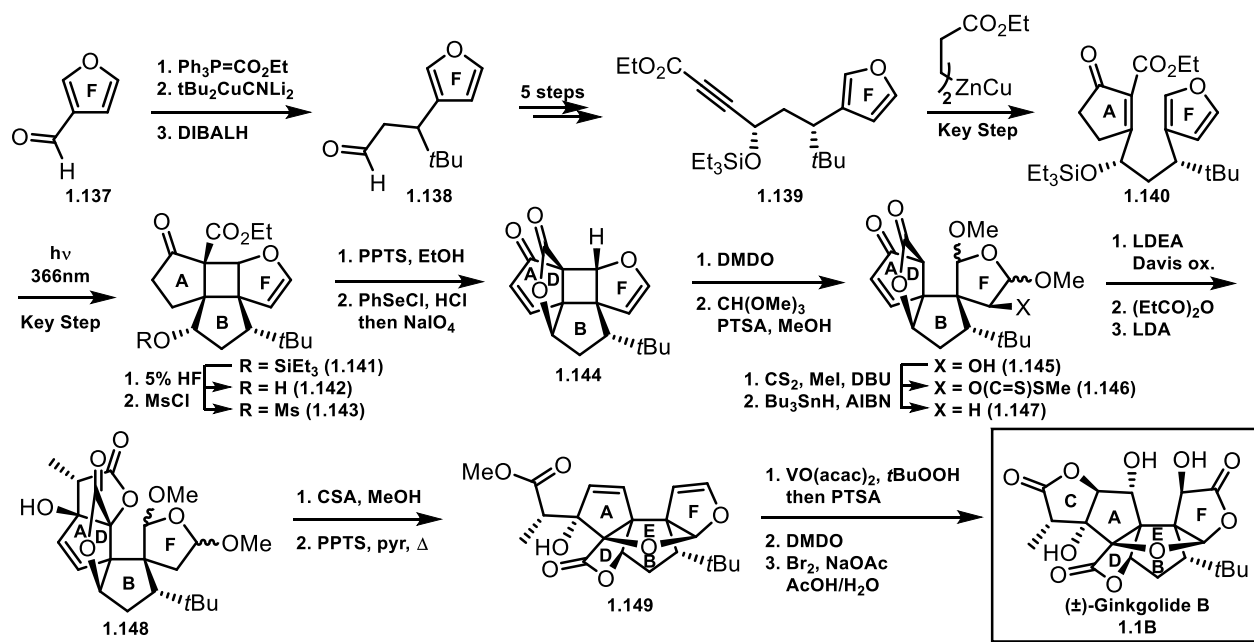


Figure 1.27: Crimmins' Racemic Total Synthesis of ($\pm$)-Ginkgolide B

1.1.6.3 Total Syntheses of Bilobalide:

Weinges and coworkers were the first ones to report their progress towards the total synthesis of bilobalide by degradation of ginkgolide A in 1986.⁸⁷ Corey et al. achieved the first

racemic total synthesis of bilobalide in 22 steps from dimethyl (*cis*)-4-cyclohexen-1,2-dicarboxylate in 1987.⁸⁸ Enone **1.152** was obtained from dimethyl *cis*-4-cyclohexen-1,2-dicarboxylate (**1.150**) and phenyl 3-*tert*-butylpropionate (**1.151**). Enone reduction with NaBH₄ followed by ozonolysis of the cyclohexene yielded **1.153**. Treatment with PTSA and CH(OMe)₃ in MeOH yielded **1.154** which was then reduced to diol **1.155** (with LiAlH₄) and then oxidized to bis-aldehyde **1.156** (via Swern oxidation). Addition of HCl formed the D- and C-rings yielding lactols **1.157A** and **1.157B** in an anomeric mixture which were subsequently oxidized to lactone **1.158** with PCC. Treatment with KOH led to lactol **1.159** which was then converted to chloro ether **1.160** (with MsCl and Et₃N). D-ring enol ether **1.161** was obtained by adding DIPEA. The newly formed D-ring enol, along with the A-ring alkene, were epoxidized with peroxy-3,5-dinitrobenzoic acid to afford diepoxide **1.162**. Opening of the D-ring epoxide with HCl (0.5 M) followed by acetylation with Ac₂O generated compound **1.164**. Treatment with MCPBA and BF₃•OEt₂ converted the B-ring acetal to the corresponding lactone (**1.165**). The D-ring *O*-acetyl lactol was converted to lactol **1.166** (with HCl/AcOH) which was then oxidized to lactone **1.167** with PDC. The A-ring epoxide was deoxygenated to alkene **1.168** with Et₃SiH in toluene at 300 °C. Finally, alkene **1.168** was dihydroxylated to diol **1.169** with OsO₄, then methyl oxalylate **1.170** was obtained using methyl oxalyl chloride (and DIPEA), and treatment with Bu₃SnH and AIBN afforded (±)-bilobalide (**1.2**)(see **Figure 1.28**).

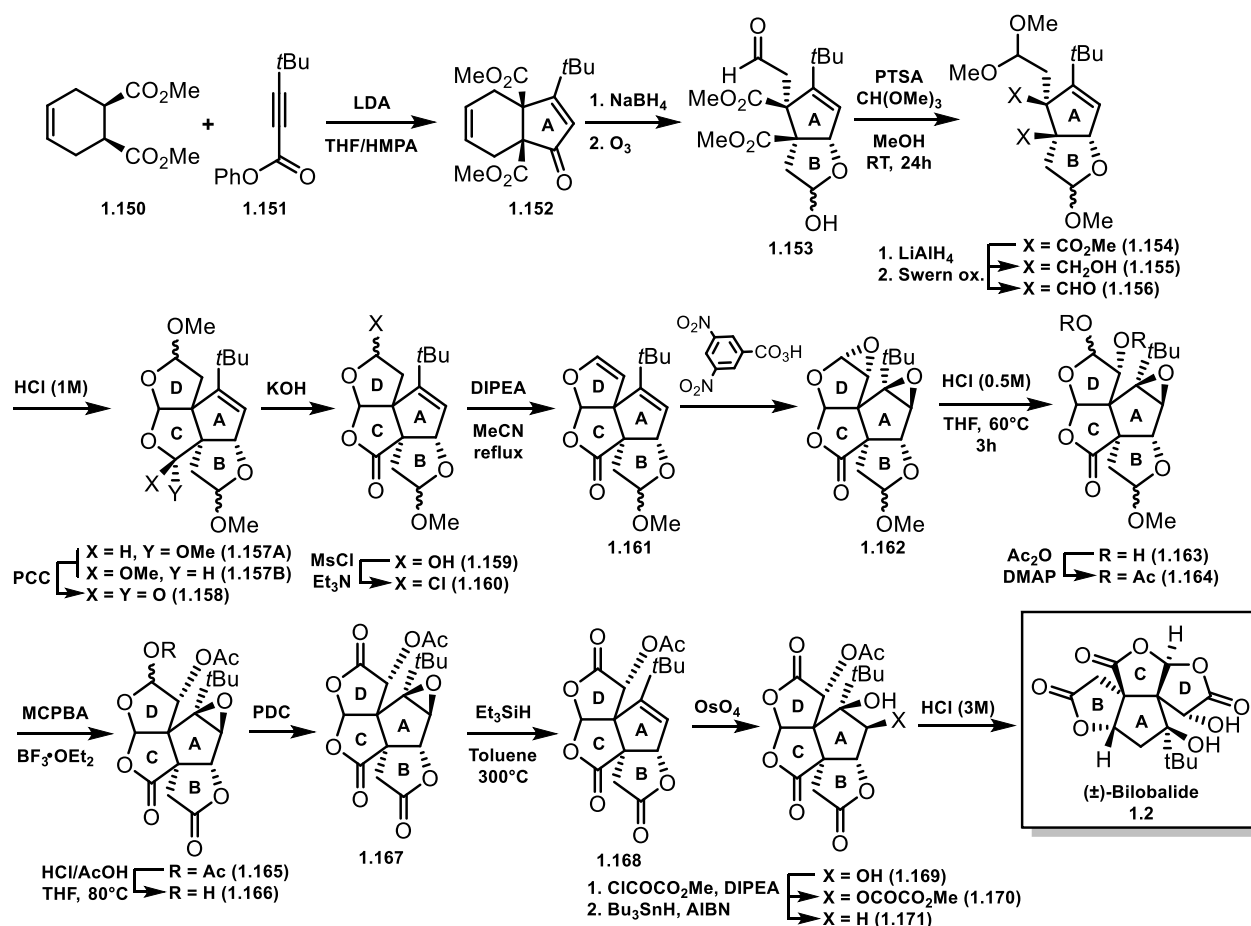


Figure 1.28: Corey's Racemic Total Synthesis of Bilobalide

Corey and coworkers achieved the first enantioselective formal synthesis of (-)-bilobalide in a total of 24 steps by preparing a bis-(+)-menthol ester to induce enantioselectivity.⁸⁹ First, the bis-(+)-menthoxy-(*R,R*)-*trans*-4-cyclohexen-1,2-dicarboxylic acid **1.174** was prepared via an *i*Bu₂AlCl-catalyzed Diels-Alder reaction between butadiene (**1.172**) and the (+)-menthol diester of fumaric acid (**1.173**). Unlike Corey's racemic synthesis, treatment with LDA and **1.151** afforded Claisen product **1.175** instead of Michael adduct **1.176**. Subsequent treatment with KHMDS generated the desired Michael product **1.176**. Enone **1.176** was diastereoselectively reduced with (*R*)-CBS yielding allylic alcohol **1.177**. Ozonolysis followed by treatment with PTSA and trimethyl orthoformate in MeOH afforded compound **1.179**. The (+)-menthol esters were reduced to diol **1.155*** with LiAlH₄ and then oxidized to bis-aldehyde **1.156***. Treatment with HCl formed the D- and C-rings, then oxidation with PDC generated C-ring lactone **1.158***. The D-ring acetal was converted to the corresponding lactol (with KOH) which was then chlorinated (with

MsCl and Et₃N) and eliminated to enol ether **1.161*** with DIPEA. Bis-epoxidation with 3,5-dinitroperbenzoic acid afforded bis-epoxide **1.162***. The formal synthesis of (-)-bilobalide (**1.2**) was completed in 5 steps by intercepting enantiomerically pure (-)-**1.167*** which was identical to a sample prepared from the natural (-)-bilobalide (which could be obtained in an additional 5 steps)(see **Figure 1.29**).

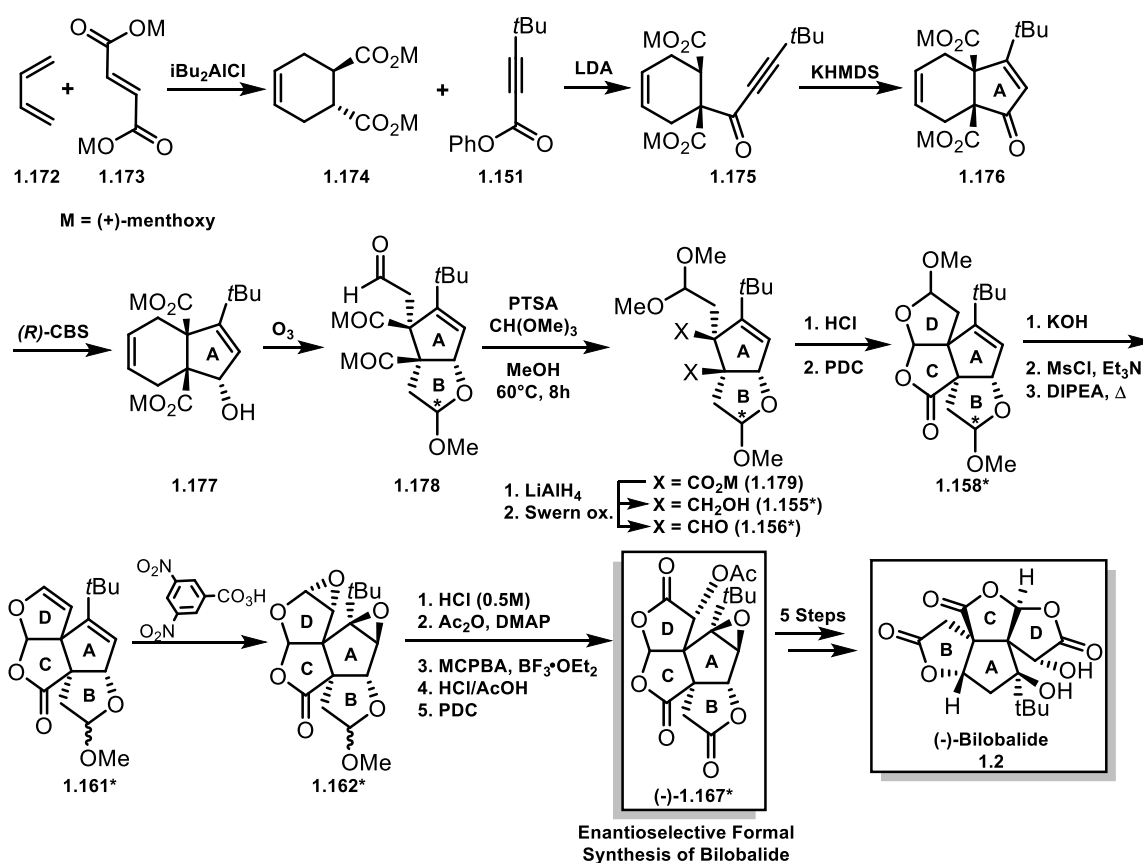


Figure 1.29: Corey's Enantioselective Formal Synthesis of (-)-Bilobalide

As mentioned previously, Pattenden et al. reported their intramolecular radical cyclization strategy towards building multiple ring systems (of ginkgolide and bilobalide) without completing the synthesis (see **Figure 1.22**).^{83ab} In 1992, Crimmins and colleagues published their total synthesis of bilobalide in 17 steps from 3-furaldehyde (**1.137**) as well as a formal synthesis by synthesizing an intermediate in Corey's synthesis.^{90ab} A 1,2-addition of *t*BuLi (with CeCl₃) onto **1.137** yielded the corresponding secondary alcohol which was then oxidized to the ketone (via Swern oxidation) which was later condensed with lithioacetonitrile to afford **1.180**. The nitrile

was reduced to the corresponding aldehyde (with DIBALH followed by quenching with H_3O^+) to which was added enolate **1.181** yielding intermediate **1.182**. The TBS enol ether was deprotected with KF. The more stable tetrasubstituted Piv enol ether was generated with PivCl, after which the secondary alcohol was protected with TMSCl. Compound **1.184** was obtained after a [2+2] photocyclization (key step). The ketone was α -hydroxylated with LDA and MoOPH (oxodiperoxymolybdenum(pyridine)-(hexamethylphosphoric triamide)). The α -hydroxyketone was subjected to $\text{Pb}(\text{OAc})_4$ in MeOH which yielded oxidative cleavage adduct **1.185**. The B-ring acetal was formed with PTSA in MeOH, after which the methyl and pivalic esters were reduced with LiAlH_4 and cyclobutanone **1.186** was obtained following a diol oxidative cleavage with $\text{Pb}(\text{OAc})_4$. Baeyer-Villiger oxidation of cyclobutanone **1.186** with MCPBA followed by treatment with Jones' reagent yielded **1.187**. Finally, oxidation of D-ring enol ether **1.187** with DMDO followed by Jones oxidation afforded ($\pm$)-bilobalide (**1.2**) (see **Figure 1.30**).

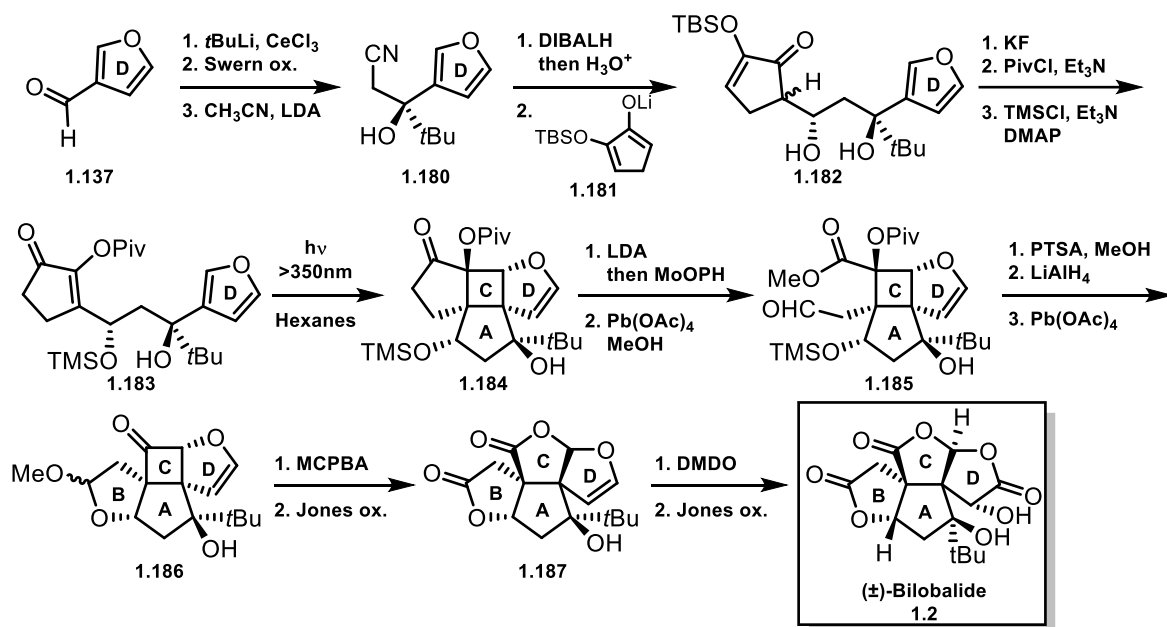


Figure 1.30: Crimmins' Total Synthesis of ($\pm$)-Bilobalide

In 2017, Opatz and Emsermann reported their progress towards the core of bilobalide using a photochemical approach.⁹¹ Finally, Shenvi and colleagues achieved the enantioselective total synthesis of (-)-bilobalide in an impressively short 13 steps from benzyl acetate.⁹² First, Claisen adduct **1.191** was obtained by treating benzyl acetate (**1.189**) with LDA followed by ester

1.190. Next, pinacolone **1.193** was converted to α,β -unsaturated aldehyde **1.194** with DMF and PBr_3 . With these building blocks in hand, Shenvi begins by brominating ylid **1.188** (with NBS), then ketone **1.191** was added which yielded Wittig olefination product **1.192**. An asymmetric Reformatsky reaction between **1.192**, **1.194** and the chiral BOX (bisoxazoline) ligand (-)-**1.195** yielded compound **1.196** with a 94% ee. A Giese-type 5-*exo-trig* cyclization afforded cyclopentenol **1.197** using Bu_3SnH and AIBN. Mukaiyama hydration yielded diol **1.198**, which was then converted to oxetane **1.200** using binolphosphoric acid (-)-**1.199**. Alcohol **1.200** was oxidized to ketone **1.201** with IBX. Then, β -ketoester **1.201** was alkynylated with TMS-EBX (1-[(trimethylsilyl)ethynyl]-1,2-benziodoxol-3(1*H*)-one) **1.202**, then TBAF was added to deprotect the alkyne which yielded intermediate **1.203**. The ketone was stereoselectively reduced to alcohol **1.204** with SmI_2 . Alcohol **1.204** was treated with an excess of LiHMDS and $\text{B}(\text{OMe})_3$ to which was added MCPBA that ultimately yielded lactone **1.205**. Debenzylation with H_2 and Pd/C followed by treatment with HCl (6 M) afforded trilactone **1.206**. Finally, Shenvi completed the enantioselective synthesis of (-)-bilobalide (**1.2**) in 2 additional steps (see **Figure 1.31**).

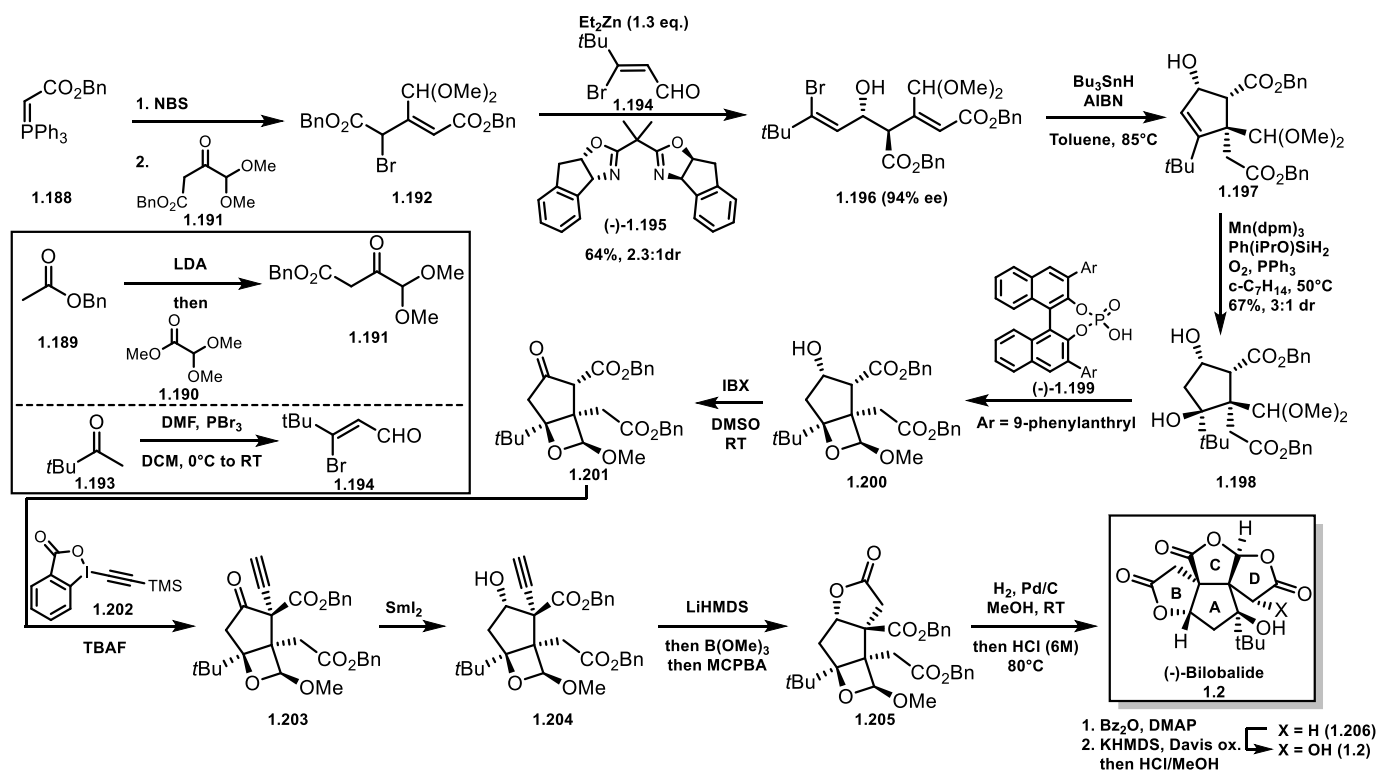


Figure 1.31: Shenvi's Enantioselective Total Synthesis of (-)-Bilobalide

1.1.6.4 General Strategies Adopted in the Total Syntheses of Ginkgolides and Bilobalide:

In each synthesis of ginkgolide or bilobalide by either Corey, Crimmins or Shenvi, the authors share the same strategy of introducing the *tert*-butyl group relatively early in their respective total syntheses. Due to its bulky nature, it can be utilized as a directing group for further functionalization. For example, in Corey's total synthesis of ginkgolide B, the *tert*-butyl directed the alkylation of the TMS enol ether (or TBS enol ether in the case of his enantioselective formal synthesis of ginkgolide B) with trioxane and TiCl_4 . Furthermore, in Crimmins' total synthesis of ginkgolide B and bilobalide, the *tert*-butyl group played a major role in the diastereoselectivity of the [2+2] photocyclization, the key step of the synthesis. Additionally, considering the highly encumbered hexacyclic scaffold of ginkgolide, it would likely be difficult to add the *tert*-butyl group in a later stage of the synthesis.

In both syntheses of ginkgolide B by Corey and Crimmins, they featured a [2+2] cycloaddition. In the case of Corey's synthesis, the [2+2] ketene-olefin cycloaddition was able to construct the A- and D-rings in a single step. As for Crimmins' synthesis, the [2+2] photocycloaddition generated the B-ring and the cyclobutane ring in one step. In both cases, a cyclobutane was formed that either underwent a ring expansion via Baeyer-Villiger oxidation (in Corey's synthesis) or a ring fragmentation/oxidation with DMDO which was later closed to afford the desired 5-membered E-ring (in Crimmins' synthesis). The [2+2] cycloaddition was a clever strategy as it forms two rings at once while ensuring the correct stereochemistry of the three/four newly formed stereocenters.

In Shenvi's enantioselective synthesis of (-)-bilobalide, he noted that both Corey's and Crimmins' syntheses featured many redox reactions (11 and 8 redox reactions respectively). As for his synthesis, he was able to cut down on a significant number of steps by limiting the amount of redox reactions to 3.

2.1 Chapter 2 – The Barriault Lab: Previous Work Towards the Total Synthesis of Ginkgolide C

2.1.1 Part A: Studies Towards the Synthesis of Ginkgolide C Spirocyclic Core by Au(I)-Catalyzed Cyclizations – David Lapointe

2.1.1.1 Preamble – David Lapointe:

David Lapointe was the first Ph.D. student at the University of Ottawa to work towards the total synthesis of ginkgolide C. Although his main objective was the development of Pd-catalyzed C-H bond functionalization methodologies, he also worked on obtaining the spirocyclic core of ginkgolide via Au(I)-catalyzed cyclizations.⁹³

2.1.1.2 Retrosynthetic Analysis:

David Lapointe's retrosynthetic approach shared a similar endgame to Corey's¹ and Crimmins'^{2a} syntheses of ginkgolide B (**2.1B**), namely the oxidation of the F-ring enol ether (in **2.2**) to the corresponding α -hydroxylactone. The C-ring (in **2.1C**) would be generated from enone **2.2** via an aldol reaction followed by an acid-catalyzed epoxide opening (as demonstrated in Corey's synthesis). Enone **2.2** could be obtained upon oxidation of the ketone obtained after the ozonolysis of exocyclic alkene **2.3**. The F-ring enol ether stems from a MeOH elimination of the corresponding acetal (in **2.3**). The D-ring lactone (of **2.2**) can be generated by oxidation of cyanohydrin **2.3**. The E-ring (of **2.2**) could be formed via an acid-catalyzed cyclization of the tertiary alcohol to the F-ring acetal (in **2.3**). The D-ring (of **2.3**) can be formed after a 1,2-addition of a nitrile anion onto the A-ring ketone (of **2.4**). Exocyclic α,β -unsaturated ketone **2.4** can be obtained by an aldol condensation of benzaldehyde with A-ring ketone **2.5**. The F-ring bis-acetal (in **2.5**) could be formed in acidic conditions from bis-aldehyde **2.6**. Next, the B-ring ether (in **2.5**) stems from reduction of B-ring ketone (in **2.6**) followed by an *O*-alkylation. Intermediate **2.6** could be obtained (from **2.7**) by a double ozonolysis and an oxidation of the primary alcohol to the aldehyde. The OBn on the B-ring could be formed via α -hydroxylation (with Davis' oxaziridine) of ketone **2.8** (followed by benzylation). Then, Lapointe proposes a Au(I)-catalyzed *5-exo-dig*

cyclization of TMS enol ether **2.9** onto a terminal alkyne as a key step to afford **2.8** (formation of A-ring and spiro[4.4]nonane core). Lapointe postulated that the cyclization should occur on the top face of the B-ring (of **2.9**) since the bottom face was shielded with the bulky *tert*-butyl. TMS enol ether **2.9** stems from the corresponding ketone **2.10**. Finally, compound **2.10** can be generated upon 1,4-addition (of **2.11**) with a vinylcopper species followed by C-alkylation with the resulting enolate (see **Figure 2.1**).

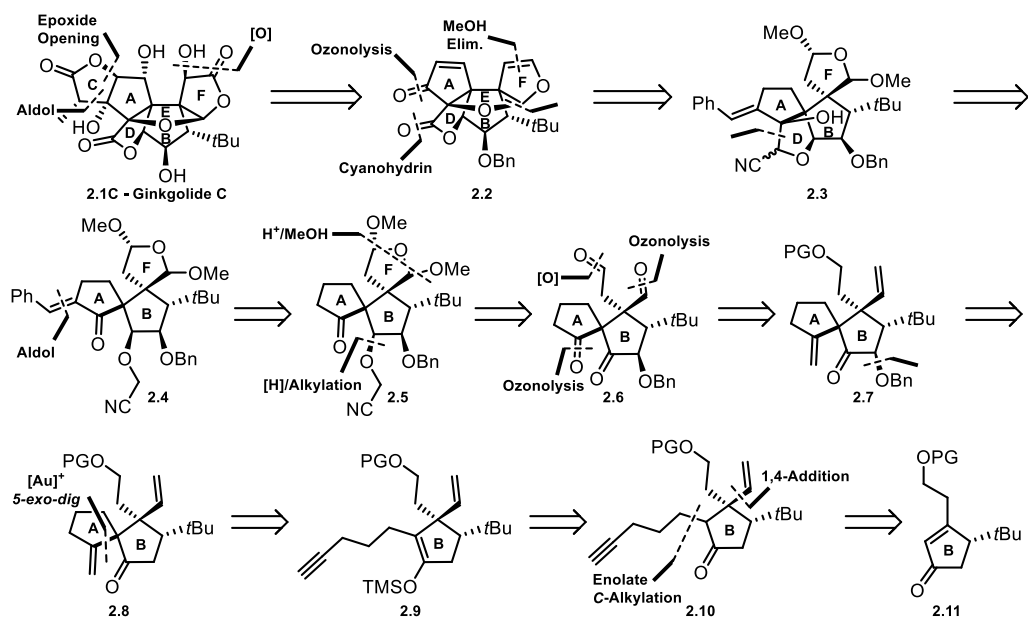


Figure 2.1: David Lapointe's Retrosynthetic Analysis of Ginkgolide C

In order to form the B-ring (**2.11**), Lapointe envisaged a cationic gold(I)-catalyzed Rautenstrauch-type rearrangement starting from **2.12**. Substrate **2.12** could be prepared by opening lactone **2.14** with **2.13** (followed by ketone reduction and alcohol protection with PivCl). Then, α,β -unsaturated ester **2.14** can be obtained by condensation of pivaldehyde onto lactone **2.15** (see **Figure 2.2**).

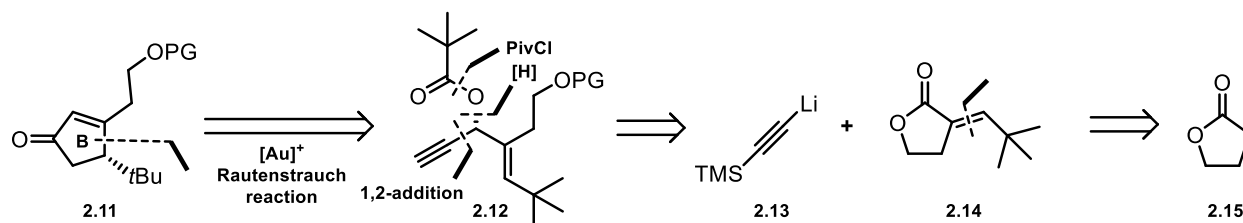


Figure 2.2: Preparation of **2.11** via Au(I)-Catalyzed Rautenstrauch-Like Rearrangement

2.1.1.3 Precedents in Gold(I) Catalysis – Select Examples:

As for the precedents of Rautenstrauch rearrangement as a means to form cyclopentenones, the two main contributors of this reaction were Rautenstrauch and Toste. In 1984, Rautenstrauch reported a Pd(II)-catalyzed methodology which afforded 1,4-cyclopentadienyl acetates (cleaved in situ to cyclopentenone **2.17**) from 1-ethynyl-2-propenyl acetate **2.16** (see **Figure 2.3a**).⁹⁴ Some time later, Toste et al. developed a cationic Au(I)-catalyzed variant that could operate at room temperature (see **Figure 2.3b**). In addition, Toste was able to transfer chiral information (of **2.20** to **2.21**) with 94% efficiency by running the reaction at -20 °C in MeCN with Ph₃PAuSbF₆ as the catalyst (see **Figure 2.3c**).⁹⁵

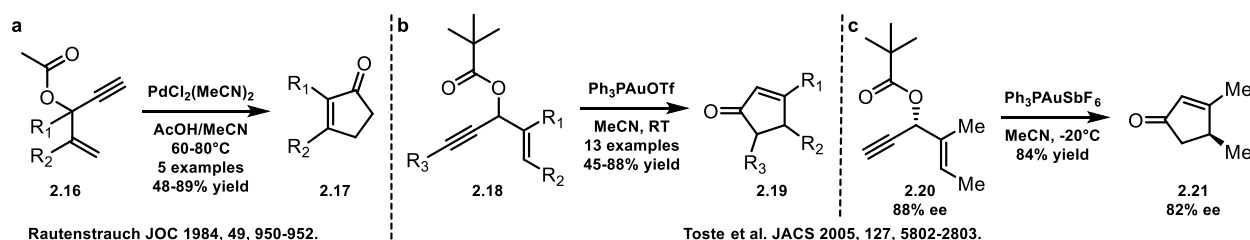


Figure 2.3: Pd(II)-Catalyzed Rautenstrauch Rearrangement and Au(I)-Catalyzed Rautenstrauch-Like Rearrangement Developed by Toste

In this paper, they also propose a possible mechanism for the transformation. First, the cationic Au(I) catalyst binds to alkyne **2.20** (thus forming **2.20i**) which causes the carbonyl oxygen to cyclize onto the alkyne generating vinyl gold species **2.20ii**. According to Toste, the stereoselectivity of the reaction can be attributed by the formation of transition state **2.20iii** where the leaving group is orthogonal to the plane of the olefin. A cyclization occurs thus forming allylic cation **2.20iv**. Thereafter, diene **2.22** is formed upon the elimination of the cationic Au(I) species. Finally, enol ether **2.22** is hydrolyzed to the corresponding ketone functionality to form the desired cyclopentenone **2.21** (see **Figure 2.4**).

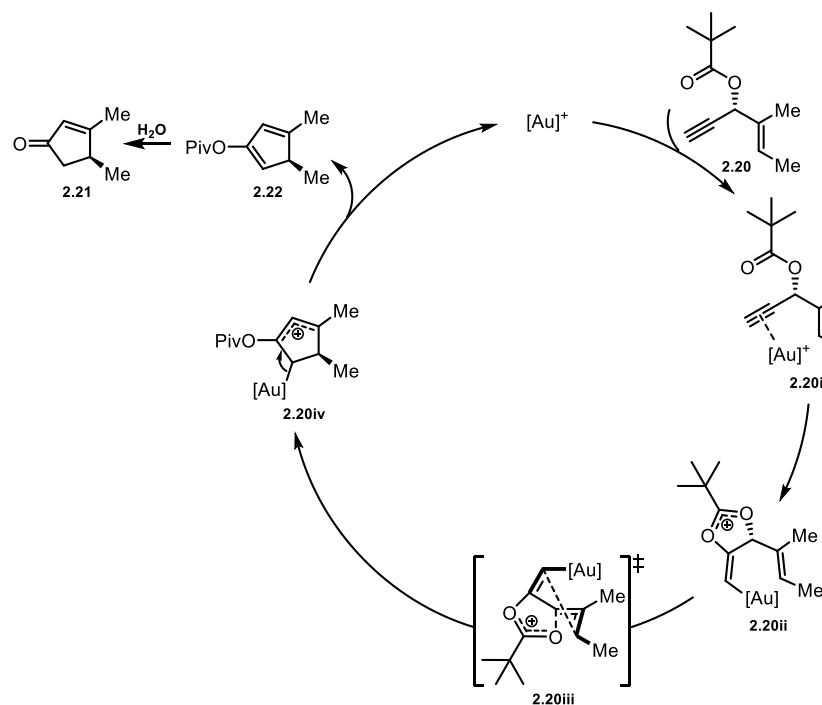


Figure 2.4: Proposed Catalytic Cycle for the Cationic Au(I)-Catalyzed Rautenstrauch-Like Rearrangement by Toste

The following year, de Lera et al. proposed a slight alteration to Toste's mechanism which was supported by DFT calculations. Their findings indicated that the reaction's transition state was in fact an acyclic pentadienyl cation (**2.23iii**) rather than Toste's cationic cyclized OPiv intermediate **2.20iii** (which they include as an intermediate in their mechanism) (see **Figure 2.5**).⁹⁶

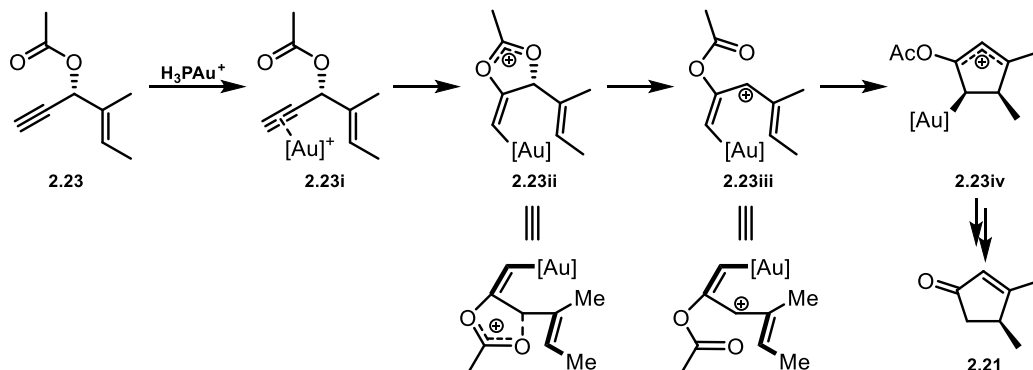


Figure 2.5: Proposed Mechanism of Au(I)-Catalyzed Rautenstrauch-Like Rearrangement According to DFT Calculations by de Lera et al.

Demonstrating the practicality of gold catalysis, Nicolaou and coworkers performed a Au(I)-catalyzed *5-exo-dig* cyclization of silyl enol ether **2.24** onto a terminal alkyne to form [3.1.2]bicyclic intermediate **2.25** in the early stage of their total synthesis of placentin in 2008 (see **Figure 2.6**).⁹⁷

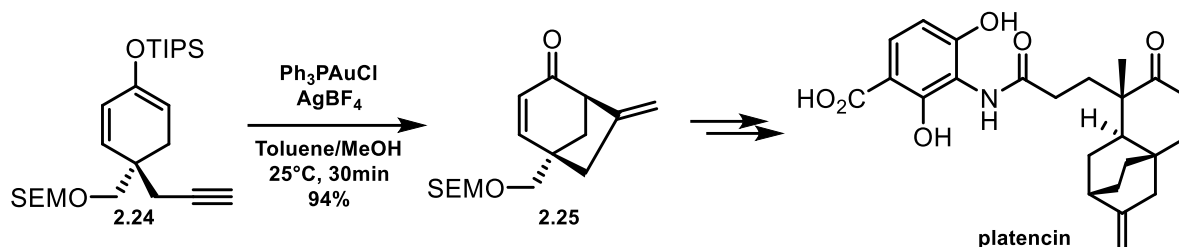


Figure 2.6: Au(I)-Catalyzed *5-exo-dig* Cyclization in the Total Synthesis of Platencin by Nicolaou et al.

Two years later, Davies and coworkers reported a Au(I)-catalyzed methodology that enabled cycloisomerization of enolisable ketones onto alkynes at room temperature. In the case where the alkyl chain containing the alkyne was in the β -position (relative to the ketone), the reaction gave rise to conjugated α,β -unsaturated ketone **2.28** as the major product (see **Figure 2.7**).

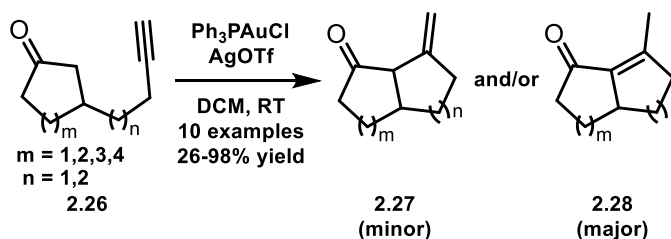


Figure 2.7: Au(I)-Catalyzed *5-exo-dig* or *6-exo-dig* Cyclizations of Enols onto Alkynes

However, when the alkyl chain containing the alkyne was placed α to the ketone, there were no α -protons to afford the α,β -unsaturated ketone after the initial *5-exo-dig* or *6-exo-dig* cyclizations. Consequently, exocyclic alkenes (**2.32**) were obtained initially, but in most cases, isomerization led to the more thermodynamically stable endocyclic trisubstituted alkene (**2.31**) (see **Figure 2.8** – Right-hand side).⁹⁸ The transformation of **2.29** to **2.30** (via **2.29i**) was conducted at extremely high temperatures (up to 350 °C) as demonstrated by Conia and coworkers (see **Figure 2.8** – Left-hand side).^{99a-c} Although this methodology doesn't require the use of a catalyst,

submitting substrates to these elevated temperatures would most likely limit the scope of the reaction as opposed to the cationic Au(I) methodology which operates at room temperature.

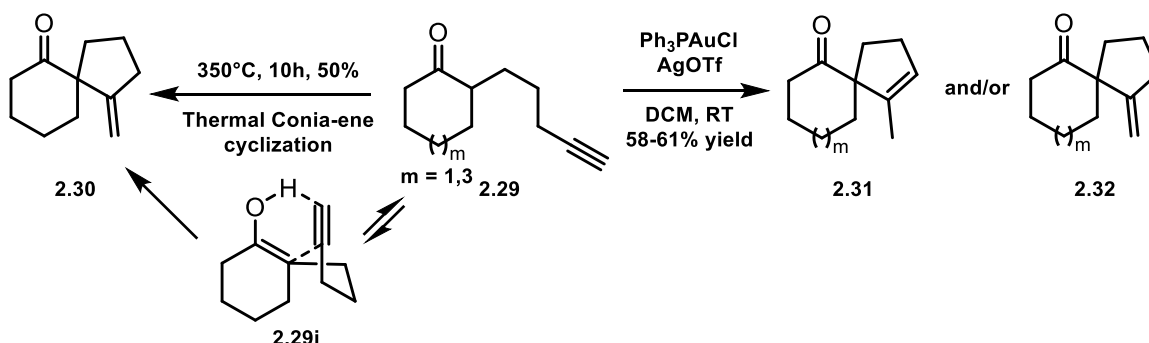


Figure 2.8: Synthesis of Spirocyclic Compounds via Thermal Conia Cyclization or Au(I)-Catalyzed 5-*exo-dig* Cyclization

In 2011, the Barriault group reported a cationic Au(I)-catalyzed cyclization of silyl enol ethers (**2.33**) onto alkynes that operates at room temperature. The methodology made use of the cationic $[\text{Me}_4\text{XPhosAuNCMe}]\text{SbF}_6$ catalyst (**2.34**), which gave rise 6-*endo-dig*/5-*exo-dig* adducts (**2.35** and **2.36**). In most cases, the major product was 6-*endo-dig* adduct **2.35**; however, in cases where R_2 was an aryl group containing an electron withdrawing group (such as COMe, CF_3 or NO_2), the yields of 5-*endo-dig* adducts **2.36** increased (see **Figure 2.9**).¹⁰⁰

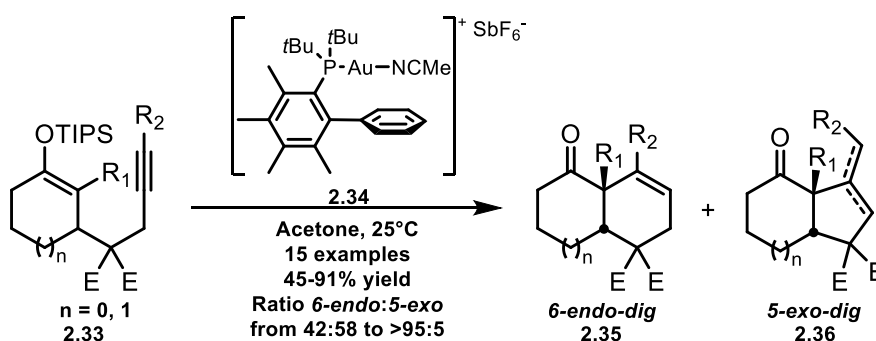


Figure 2.9: Barriault's Au(I)-Catalyzed 6-*endo-dig* or 5-*exo-dig* Cyclization of Silyl Enol Ethers onto Alkynes

2.1.1.4 Efforts Toward the Preparation of the Spirocyclic Core of Ginkgolide C:

In an effort to prepare the spiro[4.4]nonane core found in ginkgolide (**2.1**), Lapointe focused on making α,β -unsaturated ester **2.14**. Attempts to obtain **2.14** from a Wittig reaction

between **2.37** and pivaldehyde failed to give any desired product. The Horner-Wadsworth-Emmons (HWE) reaction between **2.38** and pivaldehyde afforded **2.14** in a 46% yield (1.6:1 E/Z ratio)(see **Figure 2.10a**). Alternatively, an aldol reaction between **2.15** and pivaldehyde followed by dehydration gave a 76% yield of **2.14** as a sole diastereoisomer (see **Figure 2.10b**).

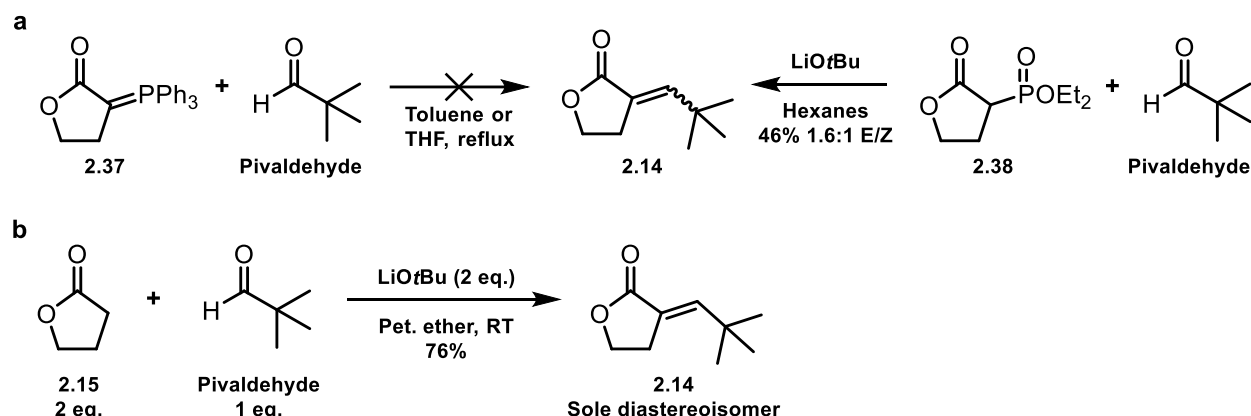


Figure 2.10: Attempts to Prepare α,β -Unsaturated Ester **2.14** via Wittig, HWE or Aldol/Dehydration

Then, the mono-alkylation of lactone **2.14** (to ynone **2.39**) was performed using TMS-protected acetyltrifluoroborate lithium salts using a procedure found in the literature.¹⁰¹ Subsequent TIPS protection of primary alcohol **2.39** gave an 85% yield of **2.40**. Luche reduction of **2.40** followed by a TMS acetylene deprotection with K_2CO_3 in MeOH yielded ynol **2.41**. Finally, protection of alcohol **2.41** with PivCl yielded Rautenstrauch rearrangement precursor **2.42TIPS** (see **Figure 2.11**).

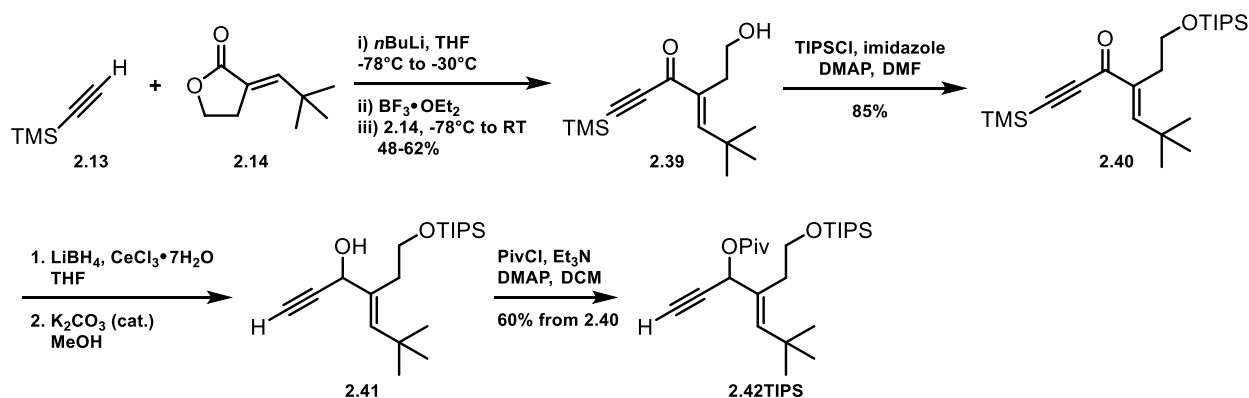


Figure 2.11: Preparation of Rautenstrauch Rearrangement Precursor **2.42TIPS**

The cationic Au(I)-catalyzed Rautenstrauch-like rearrangement was performed on either the TIPS- or TBS-protected alcohols **2.42TIPS**/**2.42TBS**. The TIPS-protected substrate yielded diene **2.43TIPS** as the major product, whereas the TBS-protected substrate afforded enone **2.44TBS** as the major product (see **Figure 2.12a**). The addition of trace HCl and H₂O (to **2.43TBS**) hydrolyzed the Piv enol ether (and TBS) to enone **2.45** in a 59% yield (see **Figure 2.12b**).

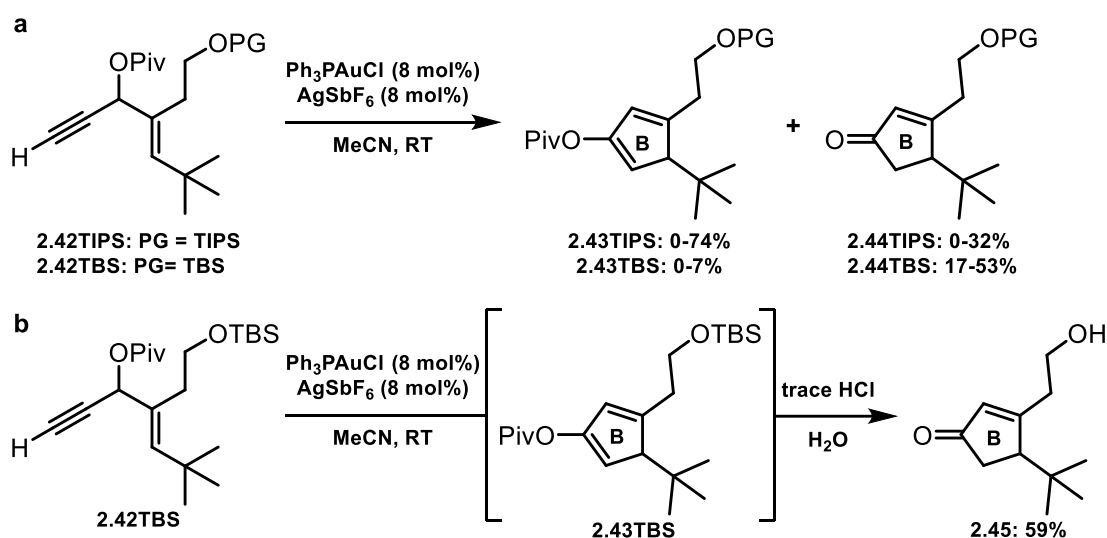


Figure 2.12: Preparation of Enone via Au(I)-Catalyzed Rautenstrauch Rearrangement

Next, Lapointe performed a conjugate addition on a model substrate using vinylmagnesium bromide with CuI trapped as TMS enol ether **2.46i**, after which the TMS enol ether was converted to the lithium enolate **2.46ii** (with MeLi), then MgBr₂•OEt₂ and aldehyde **2.47** were added to afford aldol adduct **2.48** and dehydration product **2.49** in this stepwise sequence (see **Figure 2.13a**). To optimize on efficiency, enolate **2.46ii** (obtained following the conjugate addition) was used directly in the aldol reaction (with **2.47**), after which the dehydration catalyzed by trimethyl orthoformate and PTSA yielded the desired enone **2.49** in a 40-67% yield (1:1.1 ratio cis/trans) from **2.46** (see **Figure 2.13b**).

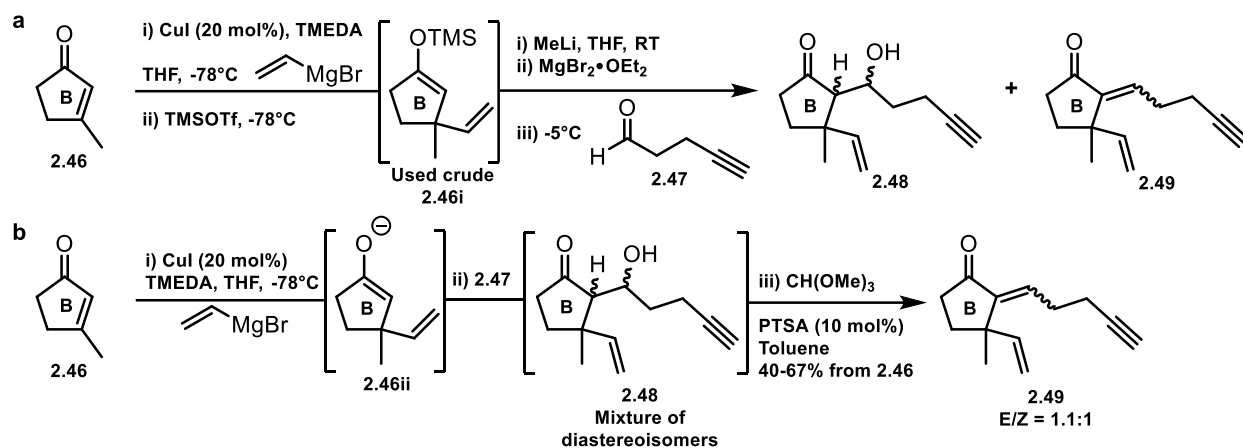


Figure 2.13: Model Studies for the Conjugate Addition and Enolate C-Alkylation

With enone **2.49** in hand, Lapointe proposed a sequence to form the spiro[4.4]nonane core of ginkgolide. First, a hydrosilylation reaction would generate silyl enol ether **2.50**. Next, a Au(I)-catalyzed 5-*exo-dig* cyclization would generate the A-ring of **2.51** (see **Figure 2.14**).

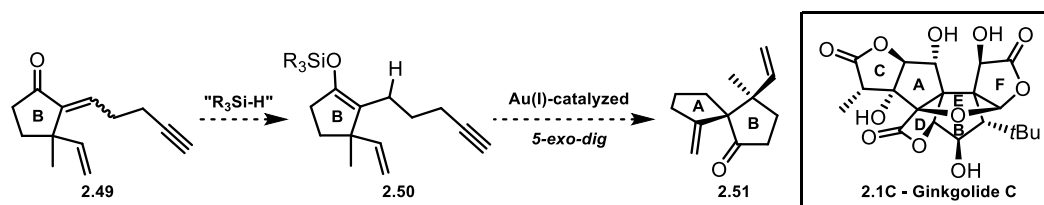


Figure 2.14: Proposed Sequence to Prepare Spiro[4.4]nonane Core of Ginkgolide C from Model Substrate **2.49**

Attempts to perform a 1,4-reduction of *trans*-**2.49** using “Hot” Stryker’s conditions (using $\text{Cu}(\text{OAc})_2$ as a copper source, polymethylhydrosiloxane (PMHS) as a hydride source and 1,2-bis(diphenylphosphino)benzene as a ligand) failed to yield any desired product **2.52** (see **Figure 2.15a**). Then, efforts to obtain the hydrosilylation product **2.53** of the *trans* isomer of enone **2.49** failed to give any conversion using either “Hot” Stryker’s conditions (with TESCl to trap the enolate) or Stryker’s reagent $[\text{Ph}_3\text{PCuH}]_6$. The use of $[\text{RhCodCl}]_2$ gave some conversion, but unfortunately, the alkyne was hydrosilylated (instead of the enone) to generate **2.54** in 52% yield (see **Figure 2.15b**).

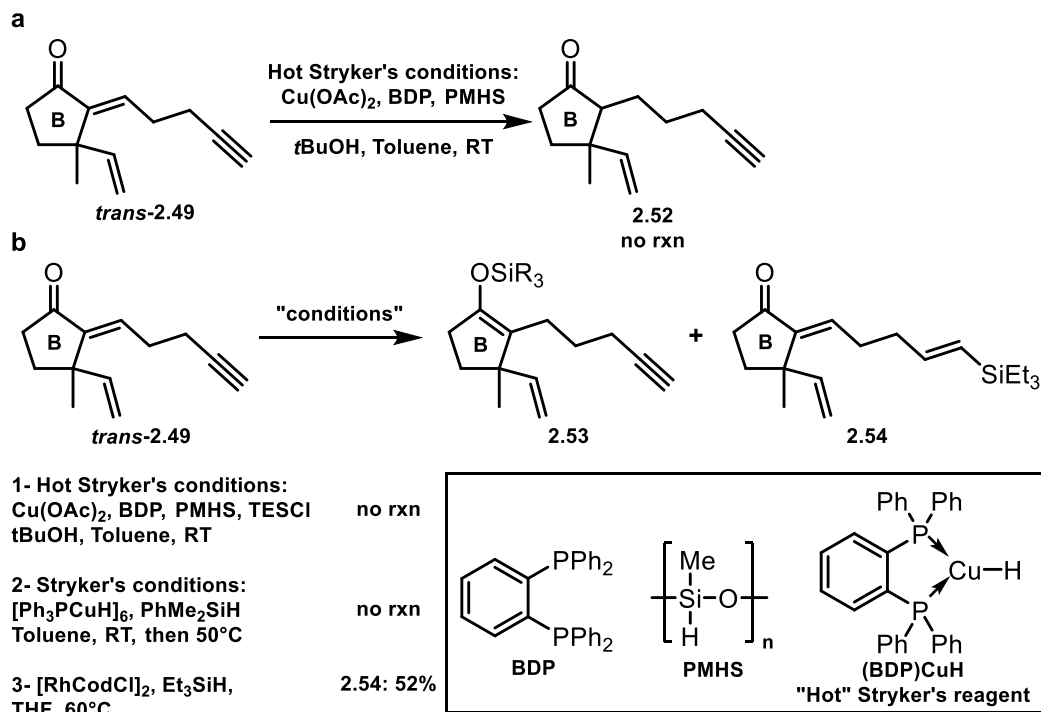


Figure 2.15: Attempts to Perform Hydrosilylation of Enone **2.49**

Another route toward the *5-endo-dig* cyclization was attempted by Lapointe. First, the conjugate addition of **2.46** with vinylcopper was trapped with TMSCl (**2.46i**). Then, a Mannich reaction with Eschenmoser's salt was conducted on TMS enol ether **2.46i** to afford **2.55**. Subsequently, the tertiary amine **2.55** was methylated, and the resulting ammonium was eliminated to generate the corresponding enone **2.56** in 54% yield (from **2.46**). However, attempts to perform a TBSOTf promoted 1,4-addition using allenyltributylstannane failed to give any desired product (**2.57**). In the event where the previous reaction would have been successful, the terminal alkyne would have been TMS protected (**2.58**), after which the Au(I)-catalyzed *5-endo-dig* cyclization would have generated the desired spiro[4.4]nonane core (**2.59**). Subsequently, the formation of a silyl enol ether (**2.60**) followed by a simultaneous Rubottom oxidation and vinyl silane oxidation with MCPBA would yield intermediate **2.61** (see **Figure 2.16**).

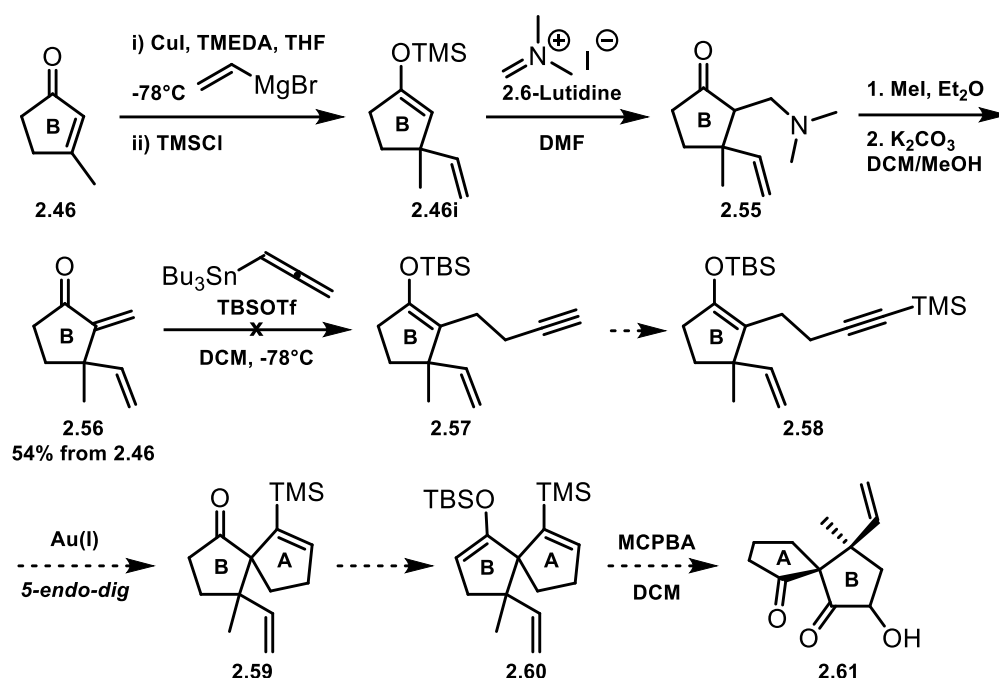


Figure 2.16: Proposed Au(I)-Catalyzed 5-endo-dig Cyclization Approach to Afford Spiro[4.4]nonane Core

Lapointe's final attempt to obtain the spiro[4.4]nonane core featured a Barton-McCombie deoxygenation. First, identically to **Figure 2.13b**, a conjugate addition was performed on enone **2.46**, and the resulting enolate was quenched with ynal **2.47** yielding aldol product **2.48** in a mixture of isomers. Unfortunately, attempts to form xanthate **2.62** failed. Had the reaction been successful, a Barton-McCombie deoxygenation of **2.62** would have afforded **2.52**. Finally, ketone **2.52** would have been submitted to a Au(I)-catalyzed 5-*exo-dig* cyclization (via enol tautomer **2.52i**) to afford the desired spiro[4.4]nonane core (**2.51**)(see **Figure 2.17**).

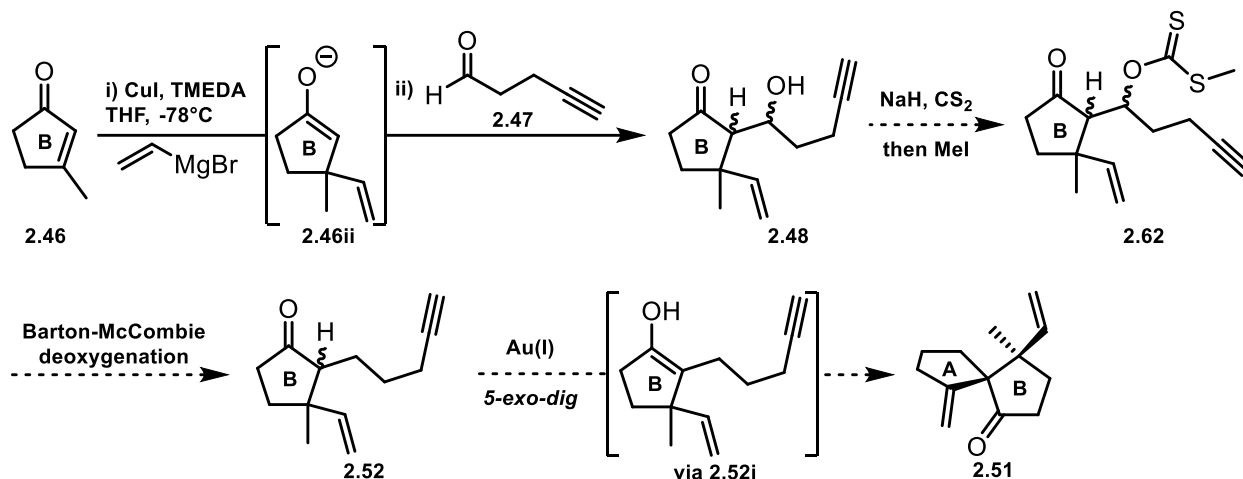


Figure 2.17: Proposed Barton-McCombie Approach to Afford Spiro[4.4]nonane Core

2.1.1.5 Summary – David Lapointe:

Lapointe succeeded in preparing a robust sequence of reactions enabling the cationic Au(I)-catalyzed Rautenstrauch reaction in order to prepare the desired enone **2.45**. The use of 3-methylcyclopent-2-en-1-one (**2.46**) as a model substrate allowed him to investigate many synthetic pathways to obtain the spiro[4.4]nonane core found in ginkgolide. Despite David Lapointe's many attempts to afford the spiro[4.4]nonane core via Au(I)-catalyzed reactions (as key steps), he fell short in achieving his goal.

2.1.2 Part B: Studies Toward the Synthesis of Ginkgolides – Gabriel Bellavance:

2.1.2.1 Preamble – Gabriel Bellavance:

In his time as a Ph.D. student at the University of Ottawa, Gabriel Bellavance's main focus was to develop a modular synthetic approach to polycyclic polyprenylated acylphloroglucinols. Along his studies, he completed the total synthesis of papuaforin A, B, C and hyperforin as well as the formal synthesis of nemorosone. In addition, he also continued David Lapointe's work towards the total synthesis of ginkgolide C featuring a Claisen rearrangement as a key step.¹⁰² In the following sections, Bellavance's progress towards the synthesis of ginkgolides as well as select approaches will be elaborated.

2.1.2.2 Optimization of Reproducibility and Scalability of Rautenstrauch Rearrangement:

Picking up where David Lapointe left off, Gabriel Bellavance realized that the Rautenstrauch reaction had some issues with reproducibility and scalability. In an effort to solve these problems, Bellavance conducted a thorough solvent, ligand and concentration optimization for the transformation. In his studies, acetone stood out as a solvent for faster reaction times for the Rautenstrauch rearrangement. As for the ligands, two of them stood out. JohnPhos (**L**₁) was the faster and MeXPhos (**L**₂) also performed well but with longer reaction times. On a smaller scale, the best conditions to obtain enone **2.44TBS** were: **L**₂AuSbF₆ in acetone (0.1 M) at RT for 72 h with a yield of 73%. On a larger scale (3.5 g), the optimal conditions were: **L**₁AuSbF₆ in chloroform (0.1 M) at RT for the first 20 min, then acetone (0.05 M total) was added and the reaction was stirred at RT for another 20 min for complete conversion of the starting material to obtain a yield of 66% (see **Figure 2.18**).

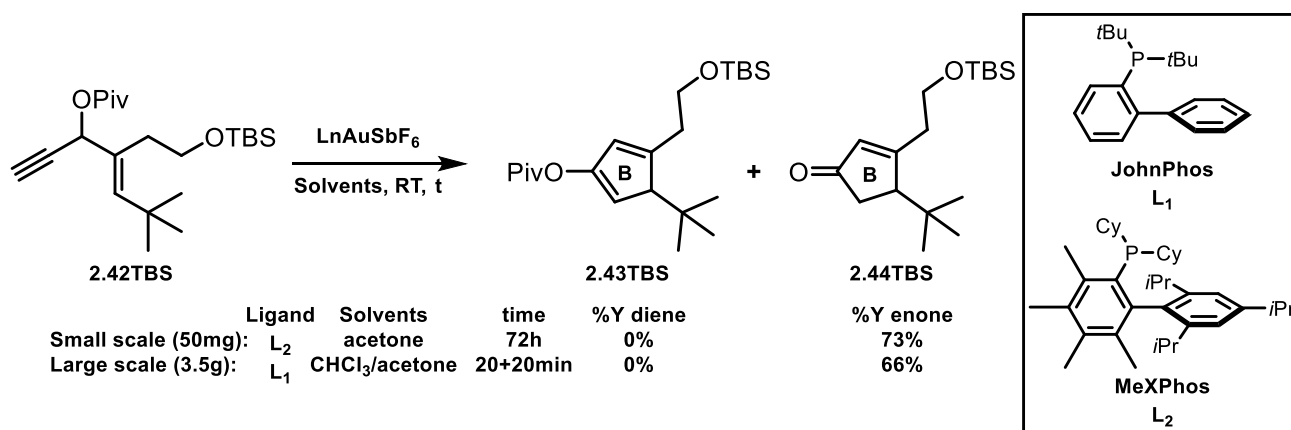


Figure 2.18: Optimization of Reproducibility and Scalability Rautenstrauch Rearrangement by Bellavance

Continuing Lapointe's work on the conjugate addition on his model substrate, 3-methylcyclopent-2-enone (see **Figures 2.13**, **2.14** and **2.17**), Bellavance investigated the feasibility of the 1,4-addition of a vinyl group on a bulkier substrate. Despite multiple attempts to perform this 1,4-addition using a variety of copper catalysts, different vinyl sources and various hydroxyl protecting groups, Bellavance failed to obtain any conjugate addition product (see **Figure 2.19**).

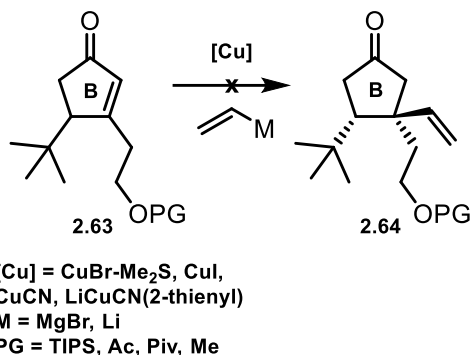


Figure 2.19: Attempts to Perform 1,4-Addition of Vinyl Group onto Enone

2.1.2.3 Oxy-Cope and Tandem Cope/Claisen Rearrangement Approaches:

Following Gabriel Bellavance's optimization of the Au(I)-catalyzed Rautenstrauch rearrangement and the failed attempts at performing conjugate additions, he shifted his focus to [3,3]-sigmatropic rearrangements, namely the oxy-Cope, Cope and Claisen rearrangements. In an attempt to construct the F-ring, Bellavance performed a 1,2-addition with allylmagnesium bromide onto enone **2.65** in order to obtain tertiary alcohol **2.66** that would set the stage for an oxy-cope rearrangement. Unfortunately, after treatment with KH, 18-crown-6 ether and microwave heating (in addition to KH with conventional heating or heating only), the reaction did not proceed as anticipated and no desired product **2.67** was obtained. Surprisingly, only the double elimination adduct **2.69** was obtained (see **Figure 2.20**).

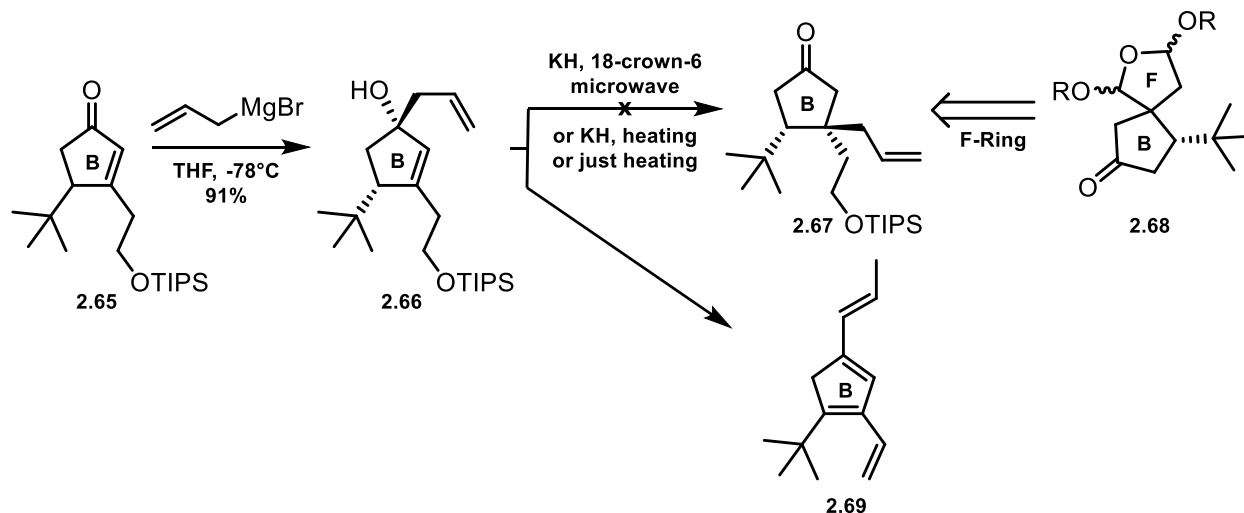


Figure 2.20: Oxy-Cope Rearrangement Attempts to Construct the F-Ring

Next, Bellavance envisaged a tandem Cope/Claisen rearrangement that could lead to the formation of both A- and F-rings (and possibly the E-ring) through subsequent functional group manipulation. The 1,2-addition adduct **2.66** obtained from the oxy-Cope approach was allylated to **2.70** using NaH and allyl bromide. Assuming the reaction was successful, the goal was to heat the substrate which would undergo a Cope rearrangement, thus forming the enol ether **2.71** required for the subsequent Claisen rearrangement (to obtain **2.72**). Unfortunately, this transformation was unsuccessful and only led to decomposition products (see **Figure 2.21**).

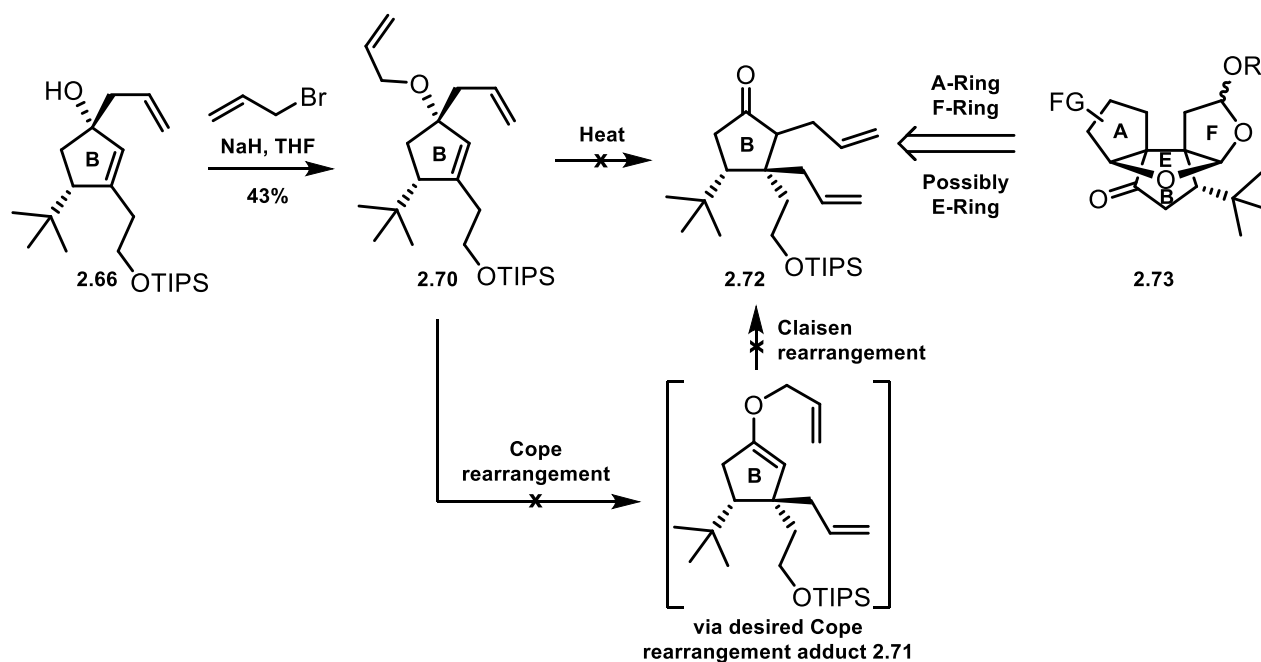


Figure 2.21: Tandem Cope/Claisen Rearrangements Attempt to Construct the A- and F-Rings

2.1.2.4 Bellavance's Au(I)-Catalyzed 5-*exo-dig* Approach Towards the Total Synthesis of Ginkgolide C:

After failing to develop a reliable synthetic route featuring [3,3]-sigmatropic reactions, Bellavance remained motivated to showcase the Au(I)-catalyzed 5-*exo-dig* cyclization to form the A-ring from **2.74** (despite having discarded the Au(I)-catalyzed Rautenstrauch rearrangement approach developed by Lapointe). The F-ring could be constructed from the oxidation of 1,4-diol **2.74**. Diol **2.74** could be obtained via vinyl hydroboration and lactone saponification/decarboxylation of fused bicyclic ketoester **2.75**. The *tert*-butyl could be introduced via a conjugate addition onto enone **2.76** which could be obtained upon oxidation of ketone **2.77**. The vinyl and pentyne fragments could be added to α,β -unsaturated ketoester **2.78** via conjugate addition followed by alkylation with the resulting enolate (see **Figure 2.22**).

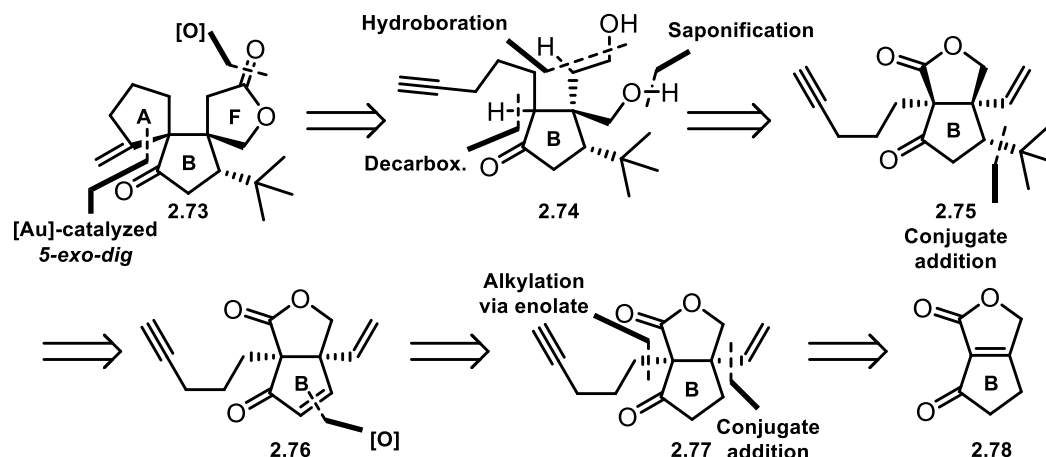


Figure 2.22: Retrosynthetic Analysis for Bellavance's Au(I)-Catalyzed 5-exo-dig Cyclization Approach Towards Ginkgolide C

The preparation of the fused bicyclo β -ketoester began with the double deprotonation of methyl acetoacetate **2.79** followed by alkylation with an alkyl iodide. Diazotransfer onto the β -ketoester **2.80** using tosyl azide enabled the formation of cyclopentanone ring **2.82** via a [Rh(OAc)₂]₂-catalyzed C-H insertion. Treatment with PTSA in MeOH deprotected the THP and subsequent lactonization afforded the corresponding bicyclic lactone **2.83**. Thereafter, a two-step oxidation of the ketoester with PhSeCl followed by treatment with H₂O₂ generated the corresponding α,β -unsaturated ketoester **2.78**. This allowed the formation of the quaternary carbon of **2.84** via conjugate addition with a vinyl cuprate (see Figure 2.23).

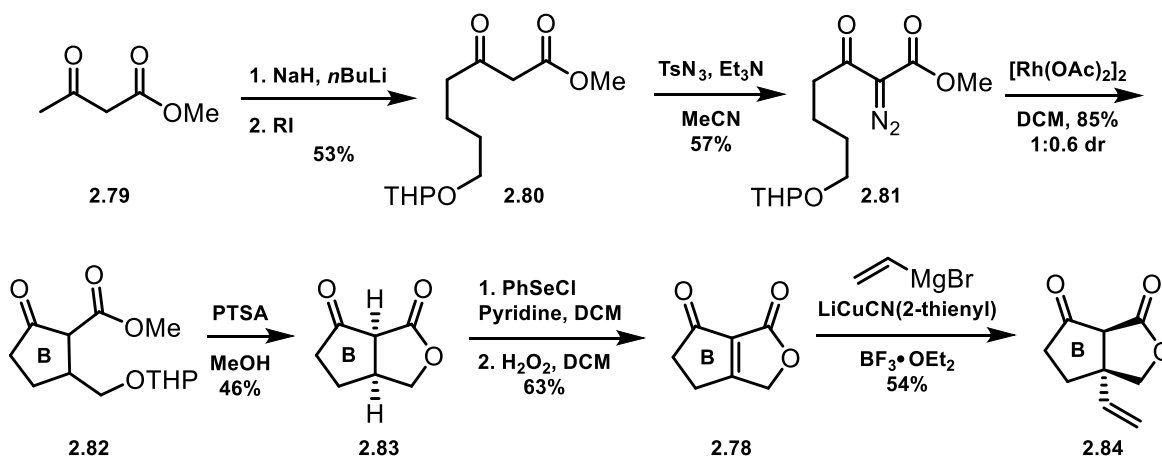


Figure 2.23: Preparation of Fused Bicyclo β -Ketoester Followed by Conjugate Addition

Following the conjugate addition of the vinyl group, Bellavance attempted to perform the C-alkylation of the ketoester to introduce the pentyne fragment. Unfortunately, deprotonation with Cs_2CO_3 in acetone in the presence of an alkyl iodide gave rise to O-alkylation product **2.85** instead of the desired C-alkylation product **2.86** (see **Figure 2.24a**). Next, deprotonation with NaOMe in MeOH with the same alkyl iodide afforded the retro-Dieckmann condensation adduct **2.87** (see **Figure 2.24b**).

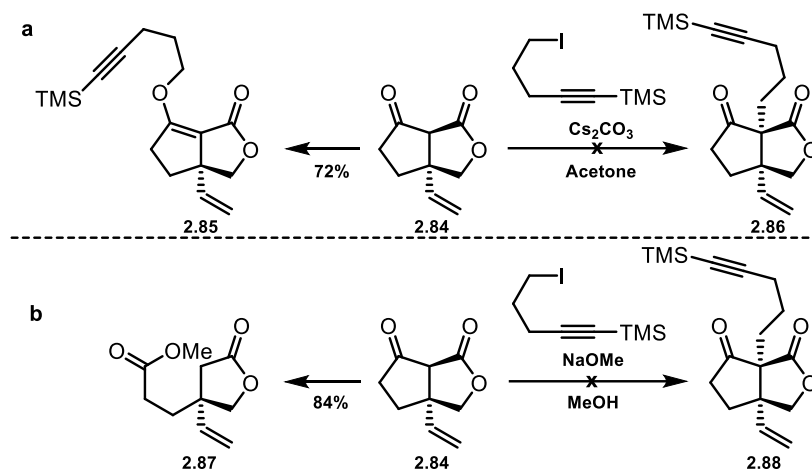


Figure 2.24: Attempts to Introduce Pentyne Chain via C-Alkylation of the β -Ketoester

2.1.2.5 Claisen Rearrangement Methodology Development and Application Towards the Synthesis of Ginkgolide C:

In light of the problems encountered in Bellavance's Au(I)-catalyzed 5-*exo-dig* approach, he postulated that both adjacent quaternary carbons could be obtained in a single step via a Claisen rearrangement. The first stage of the one-pot procedure started by forming ketal **2.90** with triethyl orthoformate in ethanol with a catalytic amount of Amberlyst® 15 (polystyrene based ion exchange resin bearing a sulfonic acid functionality). Next, the formed ethyl formate and ethanol were distilled off. Then, allylic alcohol **2.91** and a catalytic amount of propionic acid were added, and the mixture was distilled at 130-170°C (depending on the substrate). In acidic conditions, the allylic alcohol started to replace the OEt groups (EtOH was distilled off) from ketal **2.90**, and eventually, the corresponding enol **2.92** was generated. Finally, enol ether **2.92** was

geared to undergo a Claisen rearrangement (upon heating) affording the desired product **2.93** (see **Figure 2.25**).

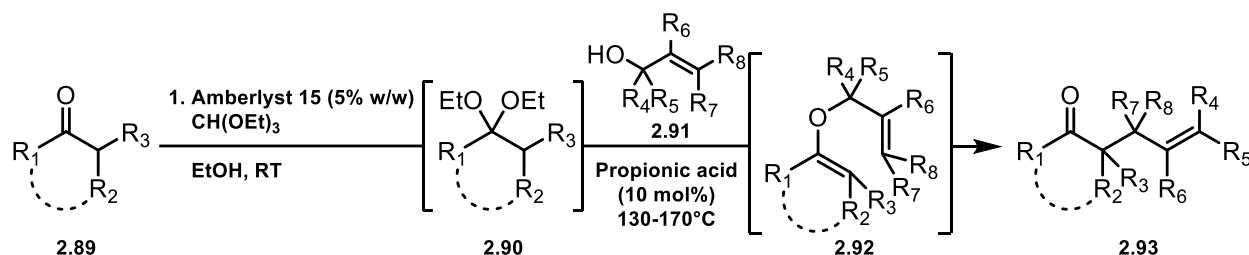


Figure 2.25: Development of a One-Pot Claisen Rearrangement Procedure of Ketones with Allylic Alcohols by Gabriel Bellavance

PMB-protected allylic alcohol **2.100** was prepared from PMBOH (**2.94**) in 6 steps. PMBOH was allylated with NaH and allyl bromide to afford **2.95**. Epoxidation of alkene **2.94** with MCPBA generated epoxide **2.96** which was opened with PMBOH and NaH yielding alcohol **2.97**. Alcohol **2.97** was oxidized to ketone **2.98** with Dess-Martin periodinane which was subsequently submitted to a Horner-Wadsworth-Emmons reaction to afford α,β -unsaturated ester **2.99**. Finally, PMB-protected allylic alcohol **2.100** was prepared after a DIBALH reduction of **2.99** (see **Figure 2.26**).

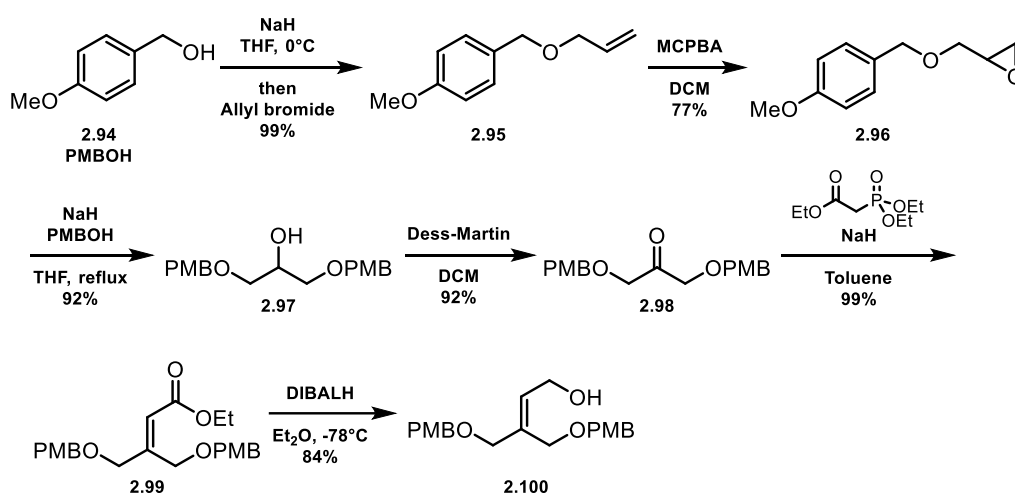


Figure 2.26: Preparation of PMB-Protected Allylic Alcohol **2.100** by Gabriel Bellavance

Making use of the one-pot Claisen rearrangement methodology elaborated in **Figure 2.25**, Bellavance used **2.101** and PMB-protected allyl alcohol **2.100** to form two adjacent quaternary

carbons (**2.102**). Then, a Grubbs II-catalyzed ring closing metathesis (RCM) formed the B-ring (**2.103**). Treatment with TFA in MeOH selectively deprotected a single PMB-protected alcohol which cyclized onto the nearby ketone yielding cyclic methyl ketal **2.104**. The remaining PMB group was removed with DDQ, and the resulting hydroxyl (**2.105**) was subsequently protected with a TBS group (**2.106**) (to avoid benzylic oxidation of the PMB group with CrO_3 in the following step). An allylic oxidation with CrO_3 and 3,5-dimethylpyrazole gave a mixture of two enones (**2.107** and **2.108**). Enone **2.108** was submitted to a 1,4-addition with a *tert*-butyl cuprate which was trapped with TMSCl (**2.109**). Next, the TMS enol ether and the OTBS were deprotected (with TBAF) to afford **2.110**. The primary alcohol was converted to aldehyde **2.111** with Dess-Martin periodinane; however, the aldehyde homologation reaction via Wittig reaction failed to yield any desired product **2.112** (most likely due to steric hindrance from the *tert*-butyl group and/or because of chemoselectivity issues due to the presence of two carbonyl groups on the substrate). Alternatively, homologation of aldehyde **2.113** was successful in affording enol ether **2.114** (see Figure 2.27).

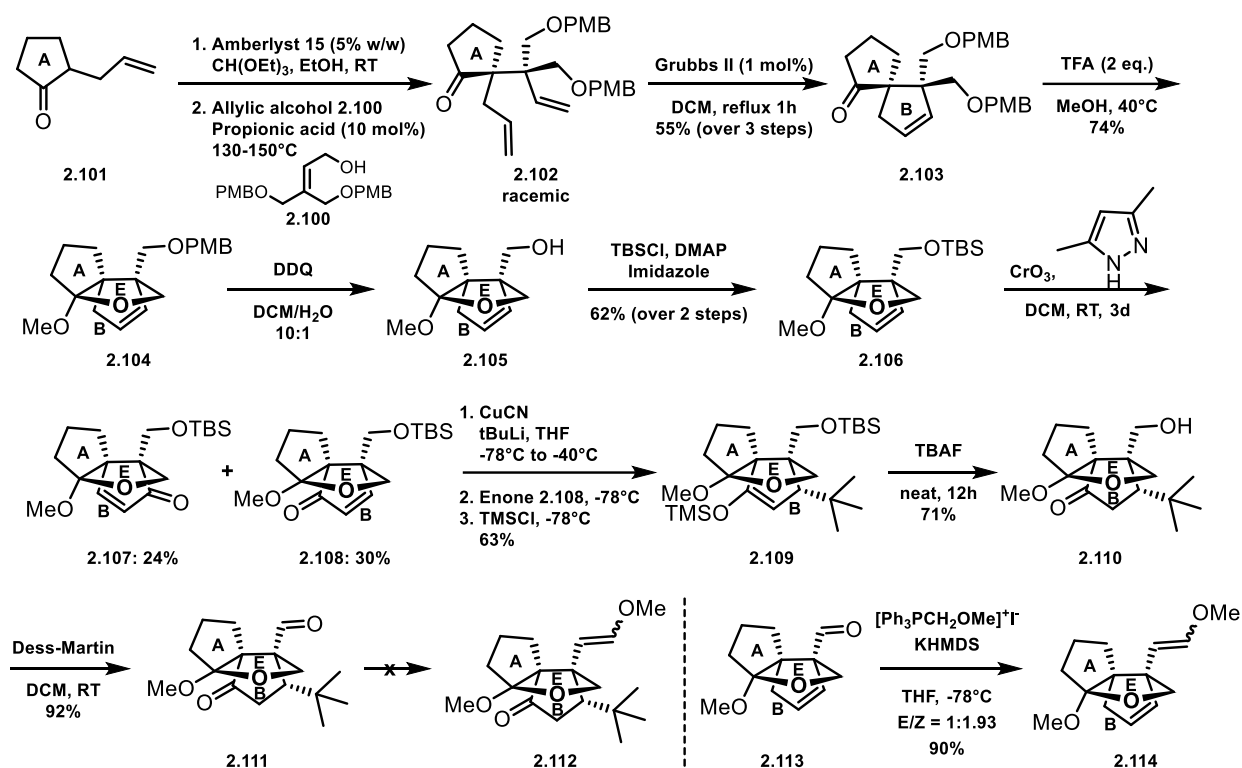


Figure 2.27: Implementation of Claisen Rearrangement with PMB-Protected Allylic Alcohol Towards the Synthesis of Ginkgolide C

In order to cut down on steps, Bellavance thought it was best to employ TBS-protected allylic alcohol **2.118** (prepared in 3 steps) instead of PMB-protected allylic alcohol **2.100** (in 6 steps). An additional 3 steps would be saved by mitigating the PMB deprotection (with DDQ) as well as the TBS protection/deprotection. The preparation of TBS-protected allylic alcohol **2.118** started with the TBS protection of 1,3-dihydroxyaldehyde dimer (**2.115**) to ketone **2.116**. Then, a HWE reaction yielded the corresponding α,β -unsaturated ester **2.117**. Finally, a DIBALH reduction of the ester afforded allylic alcohol **2.118** (see **Figure 2.28**).

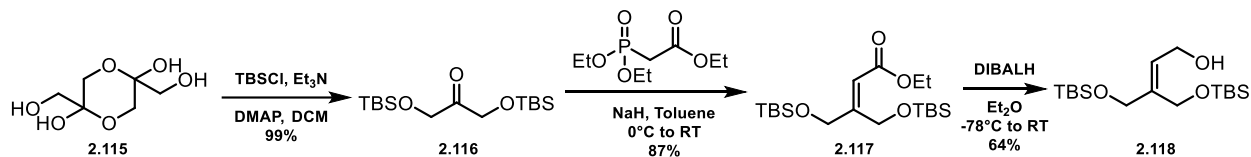


Figure 2.28: Preparation of TBS-Protected Allylic Alcohol by Bellavance

With **2.101** and TBS-protected allylic alcohol **2.118** in hand, Claisen rearrangement adduct **2.119** was obtained and subsequently submitted to a RCM to form the B-ring (**2.120**). Treatment with camphor sulfonic acid (CSA) in MeOH deprotected both TBS groups and formed the corresponding cyclic methyl ketal **2.105** in a single step. The primary alcohol was oxidized to aldehyde **2.113** with Dess-Martin periodinane in a 78% yield. The aldehyde underwent a homologation to enol ether **2.114** via a Wittig reaction. The F-ring was formed with CSA in a mixture of dioxane/MeOH/H₂O (7:2.75:0.25) giving an anomeric mixture of 1.37:1 for **2.121A** and **2.121B**. Thereafter, a CrO₃/3.5-DMP allylic oxidation generated the corresponding enones in a 24% and 30% yield for **2.122A** and **2.122B** respectively. Enone **2.122A** was submitted to a conjugate addition with a *tert*-butyl cuprate, that gave the trapped TMS enol ether **2.123A** (with TMSCl) and the free ketone **2.124A**. A conjugate addition using a *tert*-butyl cuprate was also performed onto enone **2.122B**, although this time, the reaction yielded the desired 1,4-addition adduct trapped as a TMS enol ether **2.123B** in addition to the reduced enone **2.124B** which was also trapped as the TMS enol ether. Both silyl enol ethers were converted to their corresponding ketones (**2.125B** and **2.126B**) with TBAF (see **Figure 2.29**).

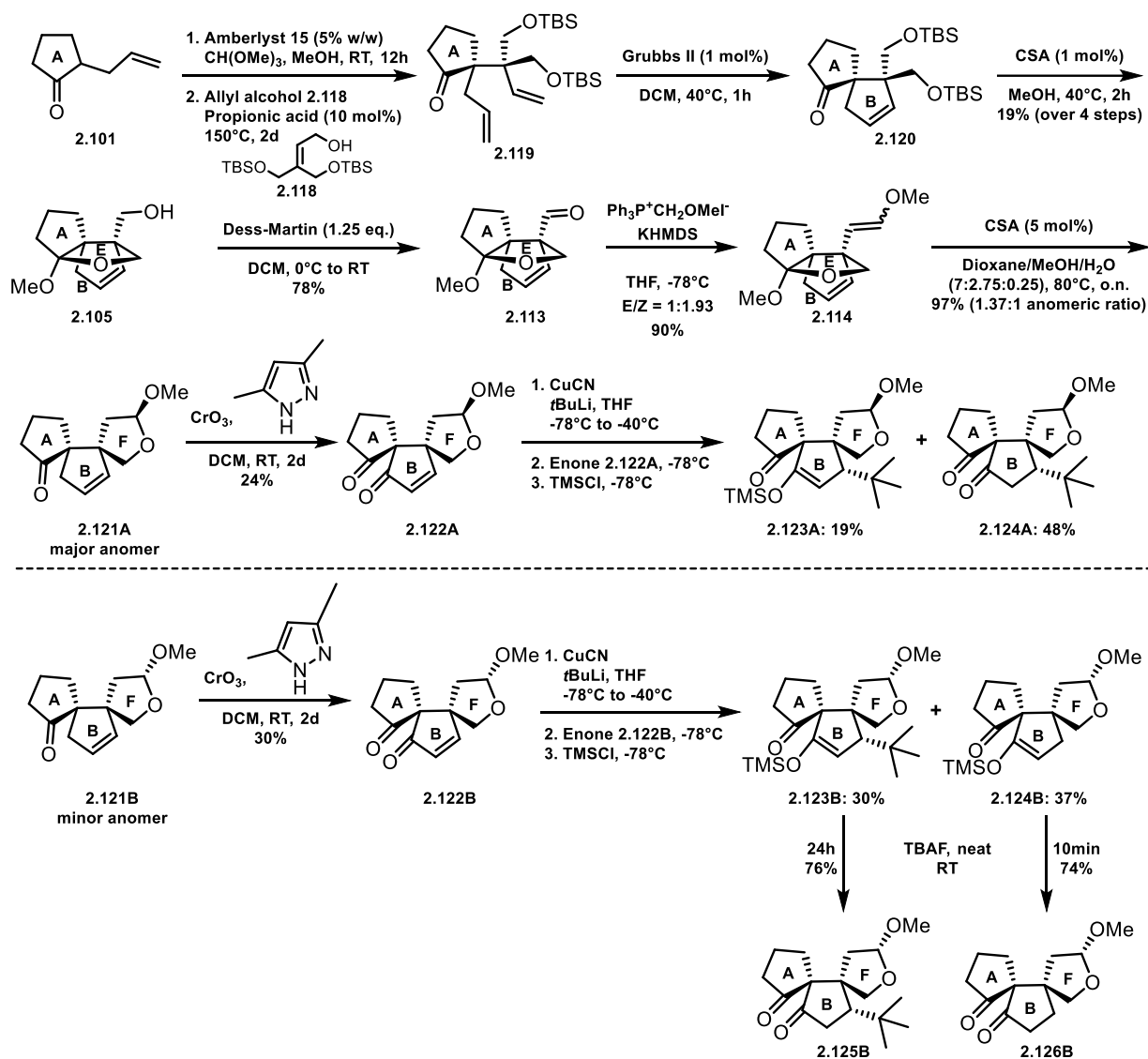


Figure 2.29: Implementation of the Claisen Rearrangement with TBS-Protected Allylic Alcohol **2.118** Towards the Synthesis of Ginkgolide C

The undesired conjugate reduction side-product could stem from the formation of a copper-hydride **2.128** via a β -hydride elimination of one of the *tert*-butyl groups from di-*tert*-butylcuprate **2.127** (see **Figure 2.30**). In fact, Cu(I) hydride has been known since 1844 and is one of the oldest metal-hydride complexes to have been properly characterized.¹⁰³ To support this hypothesis, Whitesides demonstrated that copper-hydrides could be generated via β -hydride elimination through thermal decomposition of alkylcopper species such as *n*BuCu.¹⁰⁴ In addition, there are many examples in the literature of copper hydride species performing conjugate

reductions of unsaturated ketones,¹⁰⁵ esters,^{105a,d} aldehydes,^{105c} nitriles,¹⁰⁶ sulfones and sulfonates^{104e} with Stryker's reagent (also known as the Osborn complex), $[(\text{Ph}_3\text{P})\text{CuH}]_6$.

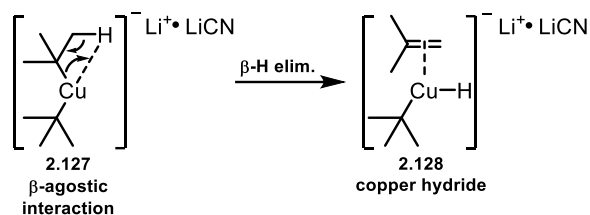


Figure 2.30: Plausible Explanation for Conjugate Reduction of Enone from a Copper-Hydride Obtained from β -Hydride Elimination from a *tert*-Butyl Group

2.1.2.6 Summary – Gabriel Bellavance:

Despite Gabriel Bellavance's optimization of the Rautenstrauch rearrangement and his attempts in incorporating an Oxy-Cope or tandem Cope/Claisen rearrangement, these efforts came short in the development of a robust synthetic route towards ginkgolides.

However, Bellavance's methodology of a one-pot procedure to perform Claisen rearrangements from ketones and substituted allylic alcohols showed potential towards the total synthesis of ginkgolide. This method enabled the formation of two contiguous quaternary carbons in a single step which can be quite tedious using other methodologies due to steric interactions. The B-ring (obtained via RCM) and the F-ring (obtained via acetal formation) were formed through functional group manipulation. Thereafter, an allylic oxidation yielded the corresponding enone which allowed for a conjugate addition of a *tert*-butyl group. Unfortunately, due to the fact that Bellavance was at the end of his doctoral studies, he was unable to complete the total synthesis of ginkgolide C.

3.1 Chapter 3 – Total Synthesis of (±)-Ginkgolide C and Formal Synthesis of (±)-Ginkgolide A and (±)-Ginkgolide B

3.1.1 Preamble – Martin Hébert:

Upon arriving at the University of Ottawa as a new Ph.D. student, my main focus was to complete the total synthesis of ginkgolide C on which David Lapointe and Gabriel Bellavance had devoted efforts during the end of their respective doctoral studies. Completing the formal syntheses of ginkgolide A and ginkgolide B (which had been synthesized by Corey in 1988^{1,3,4} and Crimmins in 1999^{2a}) was set as a side-objective for this project (see **Figure 3.1**).



Figure 3.1: Structure for Ginkgolides A, B, C, J and M

David Lapointe focused on Au(I)-catalyzed reactions such as the Rautenstrauch rearrangement and he also envisaged a Au(I)-catalyzed *5-exo-dig* cyclization of either a ketone/enol/enol ether onto an alkyne as key steps. Although he was successful in performing the Au(I)-catalyzed Rautenstrauch rearrangement, his efforts to showcase the Au(I)-catalyzed *5-exo-dig* cyclization fell short.

As for Gabriel Bellavance, he attempted many approaches including the optimization of Lapointe's Rautenstrauch rearrangement, oxy-Cope or tandem Cope/Claisen rearrangement approaches, a Au(I)-catalyzed *5-exo-dig* approach as well as a one-pot Claisen rearrangement procedure which he developed himself. Remarkably, his Claisen rearrangement methodology enabled the formation of the two adjacent quaternary carbons present in the natural product. After some functional group modification, Bellavance was able to form the ABF ring system of ginkgolide and he was also able to add the bulky *tert*-butyl moiety. Unfortunately, due to the fact

he was nearing the end of his doctoral studies, he was unable to complete the synthesis of the complex natural product.

Despite Bellavance coming short on the total synthesis of ginkgolide C, his synthetic route greatly inspired the pathways explored in our quest towards this complex natural product. In particular, the implementation of his one-pot Claisen rearrangement methodology proved to be quite useful.

3.1.2 Part A: Optimization of Gabriel Bellavance's Route

3.1.2.1 Route 1 – TBS-Protected 1,3-Diol:

Given that Bellavance's one-pot Claisen rearrangement synthetic route proved to be the most successful, this seemed like a good starting point towards the total synthesis of ginkgolide C (**3.1C**). TBS-protected ketone **3.3** was prepared quantitatively from 1,3-dihydroxyacetone dimer **3.2**. It was possible to increase the yield of the Horner-Wadsworth-Emmons adduct **3.4** by 11% by adding more equivalents of the ylid and using dry toluene. The yield of the DIBALH reduction increased 31% by ensuring the complete extraction of the newly formed allyl alcohol **3.5** from the aluminum oxide precipitate formed during the Fieser quench. The precipitate had to be washed thoroughly with Et₂O and filtered multiple times in order to obtain a 95% yield (see **Figure 3.2**).

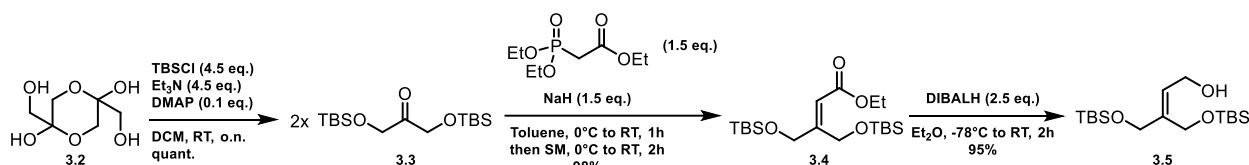


Figure 3.2: Preparation of TBS-Protected Allyl Alcohol

Next came the main route of Bellavance's synthesis. Fortunately, it was possible to optimize a few steps from this pathway. Most importantly, one of the key steps of Bellavance's approach was improved, namely, the Claisen rearrangement.

In order to optimize the Claisen rearrangement, one must first understand every detail of this transformation. First, ketone **3.6** is converted to the dimethyl ketal **3.6iii** with the assistance

of Amberlyst® 15 (sulfonic acid bearing resin) and trimethyl orthoformate ($\text{CH}(\text{OMe})_3$) (which forms methyl formate and 2 equivalents of MeOH). After the first stage of the reaction, the mixture was distilled at 110 °C to remove any remaining MeOH, $\text{CH}(\text{OMe})_3$ and methyl formate. The crude mixture was cooled to RT, then allylic alcohol **3.5** and the propionic acid were added. The reaction was then heated to 150 °C which completed two processes: 1: In acidic conditions, the allyl alcohol replaced the OMe groups of the ketal (after which MeOH was distilled off to favor the equilibrium of the reaction). Eventually, the enol ether containing the allyl alcohol was generated; 2: Upon formation of the enol, the elevated temperature enabled the Claisen rearrangement. Although the reaction was able to generate the desired product, it had three main issues: 1: Dimethyl ketal **3.6iii** formed in the first stage of the reaction was volatile, which would result in a loss of the limiting reagent during the distillation at 110 °C or at 150 °C; 2: While heating to 150°C, the reaction suffered from regioselectivity issues. If the reaction mixture was heated too much too quickly, the two enol ethers would not have time to equilibrate to the most substituted and most thermodynamically stable enol ether **3.6iv** to generate the desired Claisen rearrangement adduct **3.7**; 3: The third issue from this transformation was its long reaction time. In the original protocol, the first stage took 12 hours to convert the ketone to the corresponding dimethyl ketal at RT. As for the second stage, the reaction was distilled at 150 °C for 2 days (distilling off MeOH pushing the equilibrium towards the products) which comes to a total of approximately 3 days for both stages of the reaction.

In order to solve the first issue, 2-allylcyclopentanone **3.6** and $\text{CH}(\text{OMe})_3$ were put in excess to compensate for any losses during the distillation at 110 °C or at 150 °C and allyl alcohol **3.5** (which was not volatile) became the limiting reagent. As for the second issue, in order to reduce the amount of undesired regioisomers, the mixture was heated to 150 °C more gradually. Much better regioselectivities were obtained when the temperature was increased slowly from 85 °C to 150 °C over a period of 1 hour. It was postulated that by heating gradually, the temperature would allow for the two enol ethers to equilibrate to the most thermodynamically stable enol ether **3.7** (but would not bring sufficient energy to enable the Claisen rearrangement to occur). As the heating progressed, the reaction mixture eventually received sufficient energy to perform the sigmatropic rearrangement. Finally, to cut down on reaction times, the majority

of ketone **3.6** was converted to dimethyl ketal **3.6iii** in 30 min by simply heating the reaction to reflux in methanol (instead of stirring at RT for 12 h). In addition, for the second stage of the reaction, it was determined that distilling at 150 °C overnight (instead of 2 days) was sufficient to reach full conversion (see **Figure 3.3**).

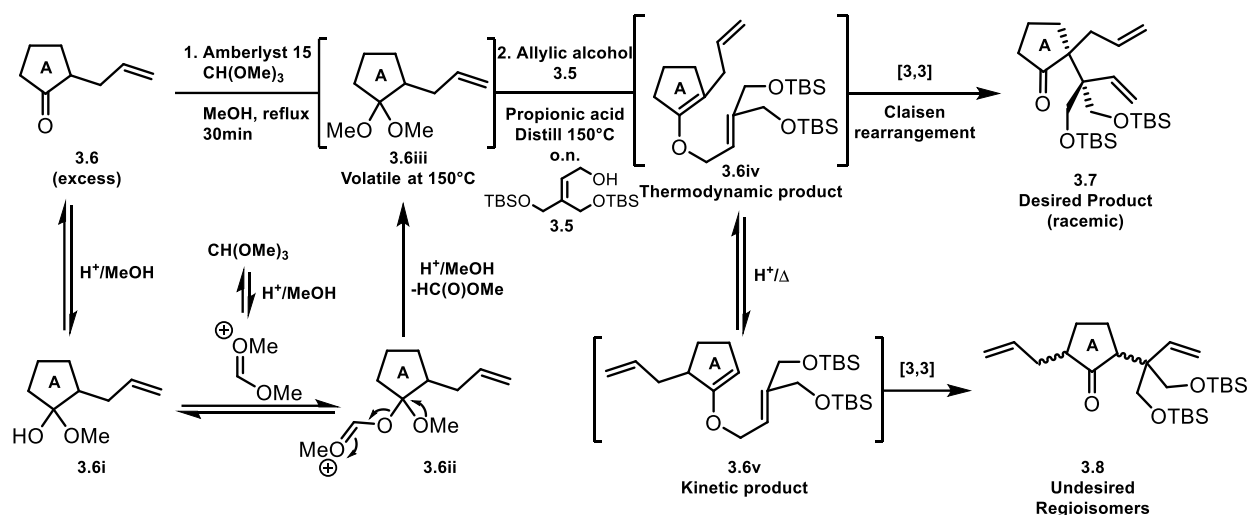


Figure 3.3: Breakdown of Gabriel Bellavance's Claisen Rearrangement

Taking a broader look at Bellavance's synthetic route, 2-allylcyclopentanone **3.6** was prepared in 90% yield (over 2 steps) by allylation of methyl 2-oxocyclopentanecarboxylate **3.9** followed by an acid-catalyzed decarboxylation. Then, the Claisen rearrangement was able to set two adjacent quaternary carbons of **3.7**. Next, the Grubbs II-catalyzed RCM formed the B-ring. Treatment with CSA in MeOH at reflux deprotected both TBS groups and formed cyclic methyl ketal **3.11** in a single step with a 19% yield over 4 steps. The primary alcohol was converted to aldehyde **3.12** with Dess-Martin periodinane. Homologation of aldehyde **3.12** via Wittig reaction generated the corresponding methyl enol ether **3.13**. Thereafter, the F-ring was formed by acidic treatment with CSA at 80 °C overnight in a mixture of dioxane/MeOH/H₂O (7:2.75:0.25) which gave a 90% yield as an anomeric mixture of 1.52:1 for **3.14A** and **3.14B** (the anomers were separated at this stage to simplify further functionalization and purification). As for the allylic oxidation with CrO₃/3,5-DMP, a slight increase in yield for both anomers **3.15A** and **3.15B** was observed. Finally, similar yields were observed for the conjugate addition of the *tert*-butyl group

and the X-ray structures for **3.16A** and **3.16B** were obtained (**3.16AXRay** and **3.16BXRy**)(see **Figure 3.4**).

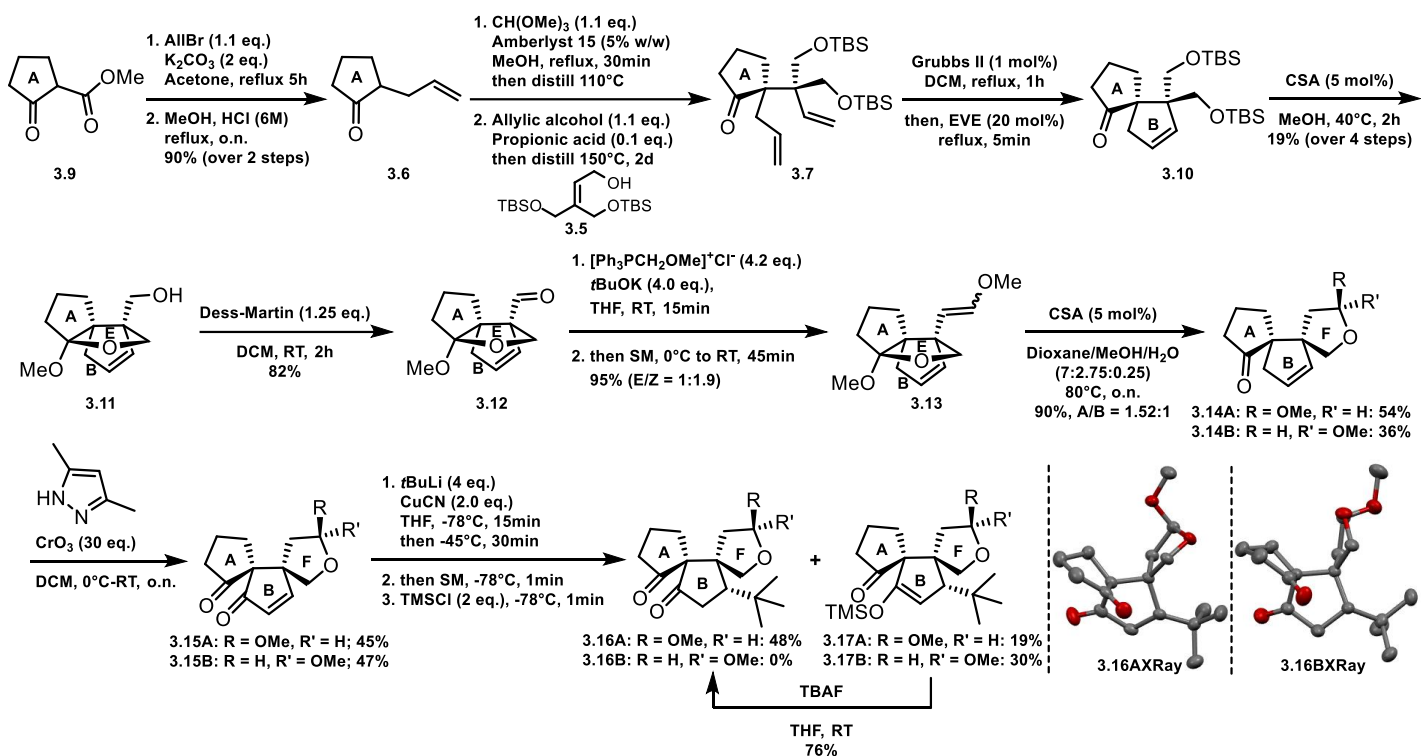


Figure 3.4: Optimization of Gabrielle Bellavance's Route Towards Ginkgolide C

Despite having attained the relatively advanced intermediate **3.18**, it was hypothesized that issues would most likely be encountered in the later stages of the synthesis for the following reasons. First and foremost, the CH₂ adjacent to the F-ring oxygen atom eventually needs to be oxidized to the aldehyde/acetal oxidation state in order to form the E-ring which links the A-, B- and F-rings together. As far as C-H oxidations go, the 2-position of the THF ring would be the easiest position to oxidize. However, performing these types of oxidations at a later stage of the synthesis could indeed be risky. In addition, C-H oxidation reactions are often unreliable and difficult to control. Consequently, it would be likely that a mixture of lactol **3.19**/lactone **3.20** would be obtained. Another issue with advanced intermediate **3.18** is that it bears 2 ketones, which could pose a problem with chemoselectivity (see **Figure 3.5**).

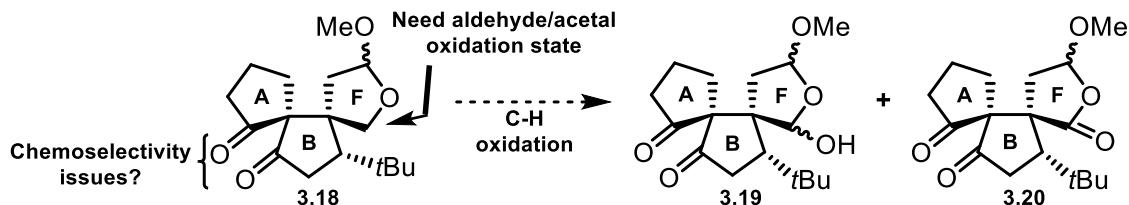


Figure 3.5: Possible Issues with Gabriel Bellavance's Advanced Intermediate

Despite these possible pitfalls, a few C-H oxidation conditions were screened as a means to oxidize the 2-position of the THF ring. First, the Norrish type-II reaction on **3.18** by UV irradiation was attempted. The mechanism involves the formation of a biradical by homolytically breaking the π -bond of carbonyl **3.21**. The highly reactive O-centered radical can subsequently abstract a γ -hydrogen which will in turn form a C-radical (**3.22**). The two C-radicals (1,4-biradical) can then recombine in order to form cyclobutanol ring **3.23** which can later be fragmented (in basic conditions) and oxidized (in the presence of an oxidant) to **3.24**. Unfortunately, the reaction failed to give any conversion (see **Figure 3.6**).

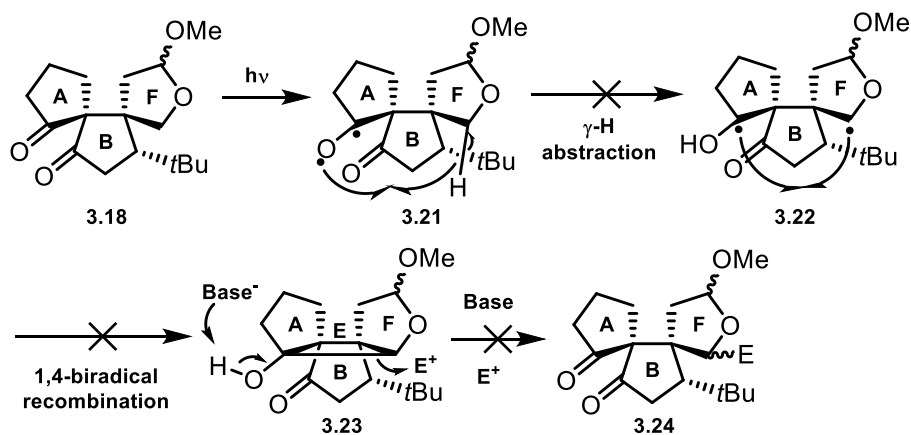


Figure 3.6: Norrish Type-II Attempt on Bellavance's Advanced Intermediate

The next attempt to oxidize the THF-ring was made with RuO_4 (formed *in situ* from $\text{RuCl}_3 \cdot x\text{H}_2\text{O}$ and NaIO_4). Although the reaction conditions were able to form small amounts of lactol **3.19** and lactone **3.20**, the reaction also suffered from poor replicability, therefore, this approach was abandoned (see **Figure 3.7**).

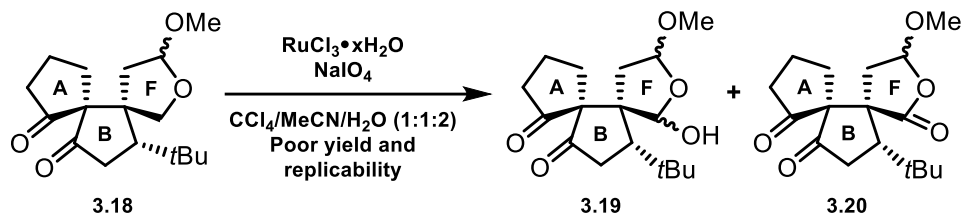


Figure 3.7: C-H Oxidation of THF Ring with RuO_4

After failing to perform the Norrish type-II as well as the C-H oxidation of the THF ring, it was hypothesized that it would be much easier to obtain the aldehyde/acetal oxidation state via oxidation of a primary alcohol. However, starting from **3.10**, upon deprotection of the TBS groups with CSA in MeOH (or H_2O), the formation of ketal **3.11** or hemiketal **3.12** would be unavoidable due to the proximity of the alcohol to the ketone. Conversely, in basic conditions, deprotection with TBAF generated hemiketal **3.13** (see **Figure 3.8**). In short, in order to avoid the cyclization of the alcohol onto the ketone (to be able to oxidize it to the aldehyde), the ketone needs to be protected or functionalized beforehand.

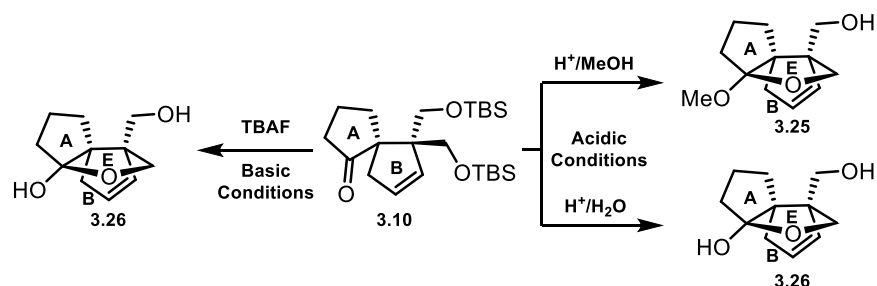


Figure 3.8: Acidic and Basic Deprotection of OTBS Unavoidably Forms the Ketal or Hemiketal

In an effort to functionalize the A-ring ketone, a wide variety of reaction conditions were attempted, including: Wittig, the addition of organolithium and Grignard reagents, cyanosilylation, epoxidation as well as trapping the ketone's enolate with TMSCl or PhNTf_2 . Unfortunately, no conversion was observed in any of the reaction conditions. From these results, it was concluded that ketone **3.10** was likely too shielded by both CH_2OTBS groups to undergo functionalization (see **Figure 3.9**).

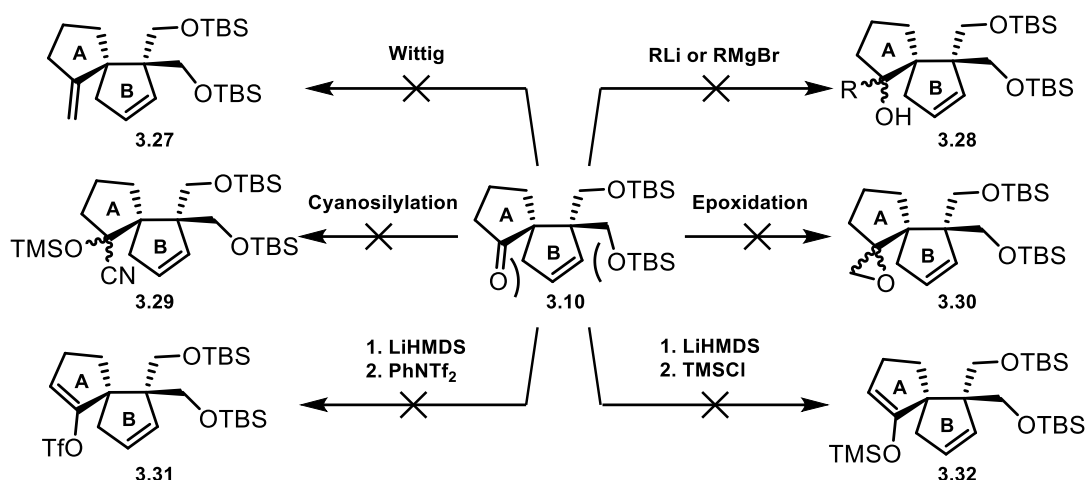


Figure 3.9: Failed Attempts at Ketone Functionalization due to Steric Hindrance

To address this issue, it was hypothesized that the protection of the 1,3-diol with an isopropylidene should reduce the steric hindrance around the ketone for two reasons: 1: The isopropylidene group is relatively small compared to the TBS group; 2: The two hydroxyls would be bound together in a six-membered ring which would restrict their movement (as opposed to having two individually protected alcohols free to move around thus hindering the ketone). This will be further elaborated in Route 2 (following Victor Borba's work).

3.1.3 Part B: Victor Borba's Work:

3.1.3.1 Introduction:

As part of his B.Sc. Honours project, Victor Borba assisted in my research towards the total synthesis of ginkgolide C. His main objectives were: 1: Find a suitable protecting group for the allylic alcohol's 1,3-diol which would reduce steric hindrance (enabling ketone functionalization) and that would also withstand the acidic and thermal conditions of the Claisen rearrangement; 2: Improve the Claisen rearrangement's regioselectivity.

3.1.3.2 Finding a Suitable Protecting Group for the Allylic Alcohol's 1,3-Diol:

As mentioned previously, a few issues were encountered following Bellavance's route. Namely, his most advanced intermediate had 2 ketones, which could be an issue when it comes chemoselectivity. In addition, the THF ring needed to be oxidized to the aldehyde/acetal

oxidation state (see **Figure 3.5**). As previously described, it was postulated that it would be much easier to obtain the aldehyde/acetal oxidation state via oxidation of an alcohol versus performing an unreliable C-H oxidation or a Norrish type-II reaction which failed (see **Figures 3.5** and **3.6**). To do so, the ketone needed to be functionalized or protected, otherwise, the alcohol would quickly form the hemiketal/ketal onto the nearby ketone upon deprotection of the 1,3-diol (see **Figure 3.7**). Ideally, the protecting group should be small in order to reduce steric hindrance, thus enabling ketone functionalization. In addition, the protecting group needed to withstand basic/reductive conditions (Horner-Wadsworth-Emmons reaction and DIBALH reduction) as well as mild acidic and elevated thermal conditions (Claisen rearrangement). With these constraints in mind, Borba investigated the benzylidene and isopropylidene protecting groups for the 1,3-diol. Theoretically, these protecting groups should withstand the reaction conditions stated above. Moreover, having the 1,3-diol protected with a smaller and cyclic protecting group should reduce steric hindrance as opposed to having two CH₂OTBS groups free to move around.

Starting from 1,3-dihydroxyacetone dimer **3.2** (the same starting material as Bellavance's route), Borba attempted to protect the 1,3-diol with either the isopropylidene (**3.33**) or benzylidene (**3.34**) in acidic conditions. Unfortunately, the reaction gave a complex mixture of products in both cases (see **Figure 3.10**).

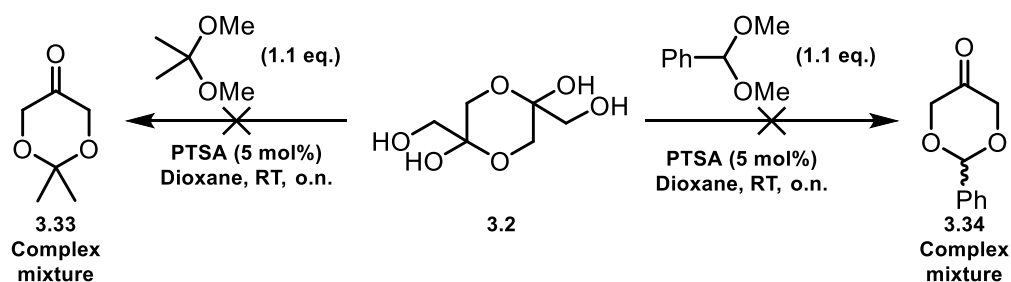


Figure 3.10: Failed Attempts to Protect 1,3-Diol with Isopropylidene or Benzylidene by Borba

Next, Borba attempted to perform the TBS-deprotection of **3.4** (with either TBAF or acidic conditions) to then reprotect 1,3-diol **3.36** with a benzylidene (to **3.37**) in acidic conditions. Unfortunately, both conditions led to lactone **3.35** (see **Figure 3.11**).

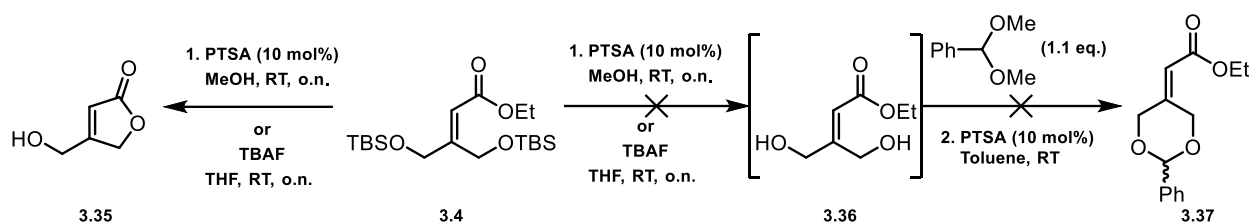


Figure 3.11: Failed Attempt of TBS-Deprotection (on HWE Substrate) and Reprotection with Benzylidene by Borba

Then, Borba was able to deprotect the TBS-protected allylic alcohol **3.5** to triol **3.38** in acidic conditions. However, upon attempting to protect the 1,3-diol with an isopropylidene, it yielded a complex mixture of compounds (mono-, di-, tri-protected triol) (see **Figure 3.12**).

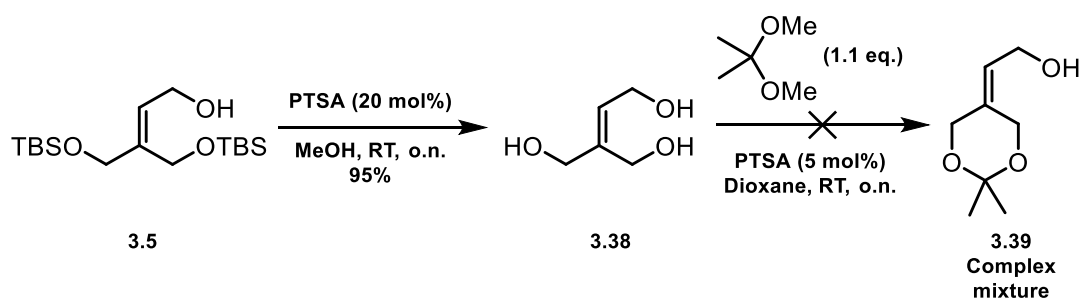


Figure 3.12: TBS-Deprotection (of Allylic Alcohol) and Failed Reprotection with Isopropylidene by Borba

Borba proceeded to attempt the protection of the 1,3-diol of glycerol **3.40** with a benzylidene (to **3.41**) in acidic conditions. If successful, the alcohol on the 2-position of glycerol could be oxidized to ketone **3.34** which could be further functionalized to allylic alcohol **3.42**. Regrettably, the reaction generated a complex mixture of compounds (see **Figure 3.13**).

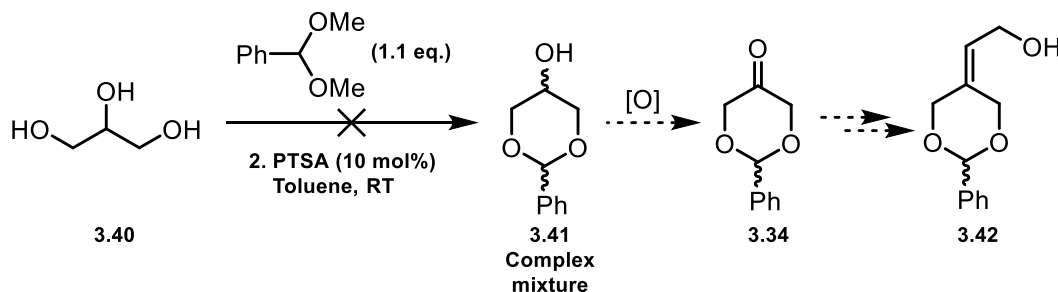


Figure 3.13: Failed Benzylidene Protection of 1,3-Diol of Glycerol by Borba

In his final attempt to protect the 1,3-diol (from hemiketal **3.26** obtained after TBS-deprotection following RCM) to a ketal with either an isopropylidene (**3.44**) or a benzylidene (**3.44**), Borba failed to obtain the desired product. Similarly, trying to perform the MOM-protection of the 1,3-diol (to **3.45**) was also unsuccessful (see **Figure 3.14**).

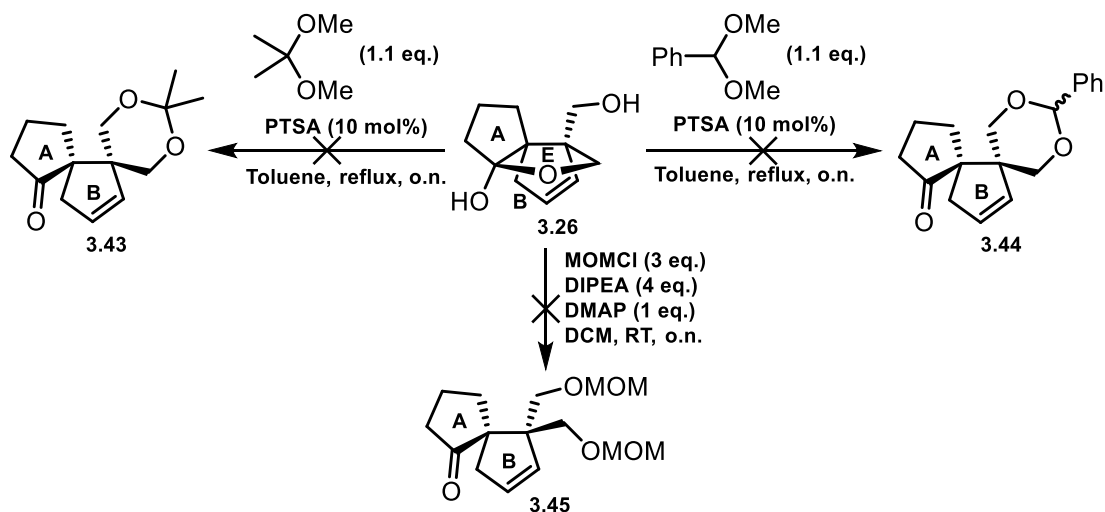


Figure 3.14: Failed Reprotection of 1,3-Diol (of TBS-Deprotection Substrate Following RCM) with Isopropylidene, Benzylidene and MOM by Borba

3.1.3.3 Improve the Claisen Rearrangement's Regioselectivity:

The main issue encountered while performing the Claisen rearrangement was its poor regioselectivity. Particularly when using a bulky allylic alcohol (with large TBS protecting groups), the Claisen rearrangement seems to be under kinetic/steric control. In other words, the reaction occurs on the less hindered/substituted side of the ketone with a 60-65% yield and yields only 30-35% of the desired (and more substituted) product (see **Figure 3.3**). In order to prevent the less substituted side of the ketone to react during the Claisen rearrangement, conversion of ketone **3.6** to the corresponding enone **3.48** was considered. To do so, preparation of α -bromoketone **3.47** from TMS enol ether **3.46** followed by an E2 elimination was considered. Alternatively, phenylselenide **3.49** could be prepared, followed by oxidation to the selenoxide which would undergo *syn*-elimination yielding enone **3.48**. Both the TMS enol ether and the selenoketone were prepared (but not isolated due to purification issues). However, upon addition of NBS to the TMS enol ether, the reaction gave a complex mixture that degraded upon

purification. In the case of the phenylselenide, its preparation led to a complex mixture, therefore, it was never submitted to further oxidation with hydrogen peroxide (see **Figure 3.15**).

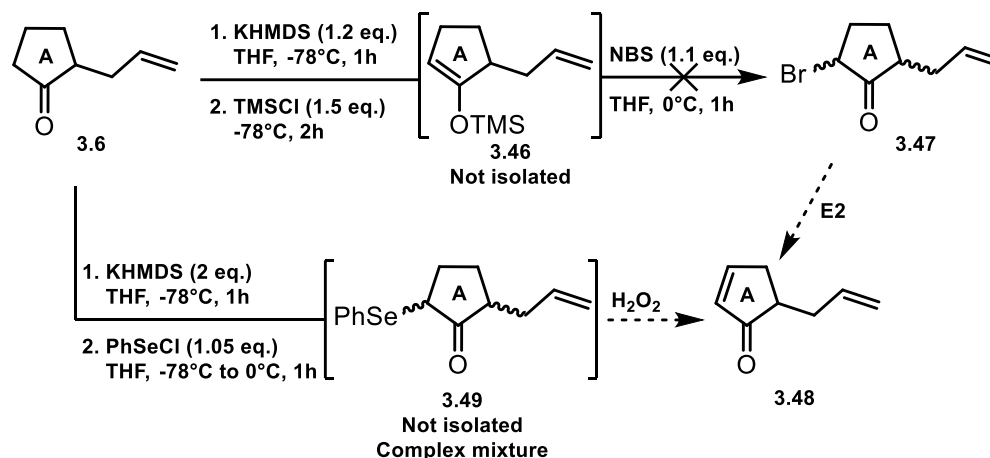


Figure 3.15: Failed Preparation of Enone via α-Bromoketone or α-Selenoketone by Borba

Taking a different approach to address the Claisen rearrangement's regioselectivity issues, Borba started working on the Mitsunobu/Tsuji-Trost allylation route. Interestingly, β-ketoesters (the methyl ester was utilized for this optimization) can be utilized as nucleophiles in the Mitsunobu reaction. First, the mono-TBS-protected 1,4-diol **3.51** was prepared by treating (*Z*)-but-2-en-1,4-diol **3.50** with 1 equivalent of *n*BuLi followed by quenching the alkoxide with TBSCl (see **Figure 3.16**).

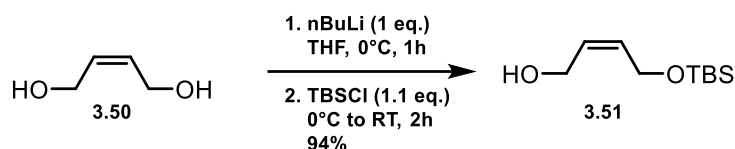


Figure 3.16: Preparation of TBS-Monoprotected (*Z*)-But-2-en-1,4-Diol

Then, a range of catalysts for the Mitsunobu reaction were screened, namely diisopropyl azodicarboxylate (DIAD), *N,N,N',N'*-tetramethylazodicarboxamide (TMAD) and azodicarboxylic acid dipiperidine (ADDP). In addition, a few solvents (THF, benzene and toluene) and phosphines (PPh₃ and PBu₃) were screened. In entries using PPh₃ as a phosphine, the formation of *O*-alkylation (desired product **3.52**) and *C*-alkylation (**3.53**) products was observed (see **Figure 3.17**).

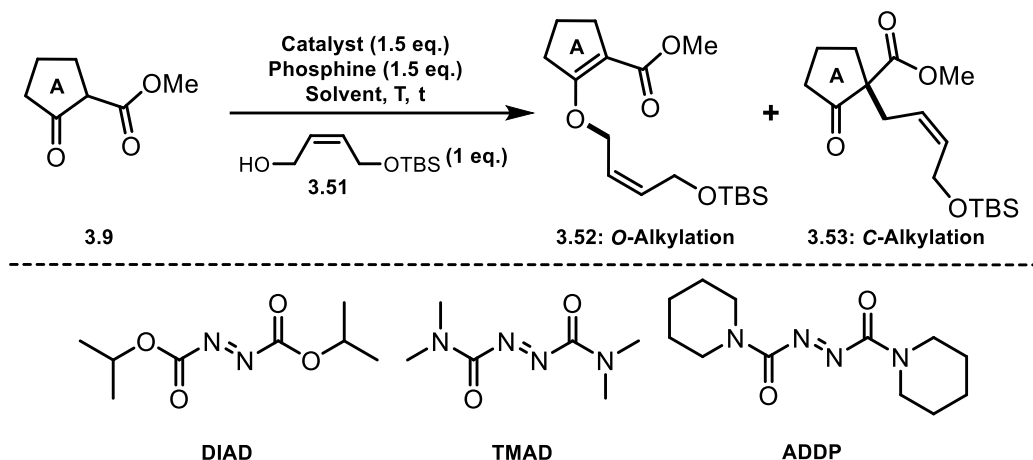


Figure 3.17: Optimization of Mitsunobu Reaction Between a β -Ketoester and the Allylic Alcohol

In both entries with PBU_3 , yields were not determined due to poor conversion. The use of DIAD with PPh_3 in THF gave a moderate yield of 56% and 19% of *O*- and *C*-alkylation respectively. Switching over to ADDP with PPh_3 in toluene, these conditions gave a slightly better yield of 69% and 21% for *O*- and *C*-alkylation respectively (see **Table 3.1**). Having obtained the *O*-alkylation product, it was now geared to undergo the Claisen rearrangement upon heating.

Table 3.1: Mitsunobu Reaction Optimization by Borba

Entry	Azodicarboxylate	Phosphine	Solvent	Temp. (°C)	Time	Yield <i>O</i> -alkylation (%)	Yield <i>C</i> -alkylation (%)
1	DIAD	PBU_3	THF	0°C to RT	o.n.	ND	ND
2	DIAD	PPh_3	THF	0°C to RT	o.n.	56	19
3	TMAD	PBU_3	Benzene	RT	o.n.	ND	ND
4	ADDP	PPh_3	Toluene	RT	o.n.	69	21

Moving forward, allyl ester **3.54** was prepared by transesterification of methyl ester **3.9** in the presence of allyl alcohol and 20 mol% of Zn(0) .¹⁰⁷ Next, the Mitsunobu reaction was carried out using the optimized conditions and the *O*-alkylation product **3.55** was obtained in a 75% yield. Then, the enol ether was heated neat at 140 °C to generate Claisen rearrangement adduct **3.56** in 67% yield (see **Figure 3.18**).

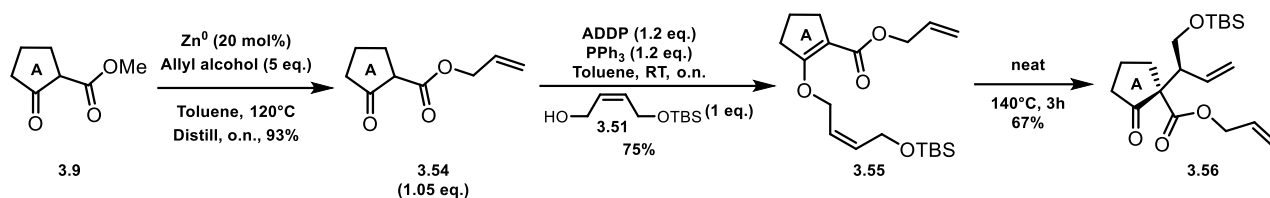


Figure 3.18: Transesterification, Mitsunobu Reaction Followed by the Claisen Rearrangement by Borba

With Claisen rearrangement adduct **3.56** in hand, a variety of reaction conditions were screened for the optimization of the Tsuji-Trost allylation. $\text{Pd}(\text{PPh}_3)_4$ as well as $\text{Pd}(\text{OAc})_2$ (with either PPh_3 or dppe to form $\text{Pd}(0)$ *in situ*) were used as palladium catalysts. Additionally, a range of solvents (DCM, benzene, toluene and MeCN) and temperatures (40 °C to 110 °C) were screened for this transformation. For the most part, the use of $\text{Pd}(\text{PPh}_3)_4$ gave good yields of 61-71% of the desired product (DP) **3.57**. However, when dppe was used as a ligand, the yield dropped to 27% and the β -hydride elimination product **3.58** was also isolated in a 58% yield. In the case of $\text{Pd}(\text{OAc})_2$ with dppe, once again, the yield of DP significantly dropped to 44%. Finally, $\text{Pd}(\text{OAc})_2$ with PPh_3 as a ligand in THF was also attempted, however, the yields weren't determined for this transformation. All things considered, the best conditions for the Tsuji-Trost reaction were: $\text{Pd}(\text{PPh}_3)_4$ (10 mol%) in either benzene (at 80 °C) or toluene (at 110 °C) for 1 hour yielding 71% in both cases. Since toluene is less harmful than benzene, the former was selected as the solvent for this reaction (see **Figure 3.19** and **Table 3.2**).

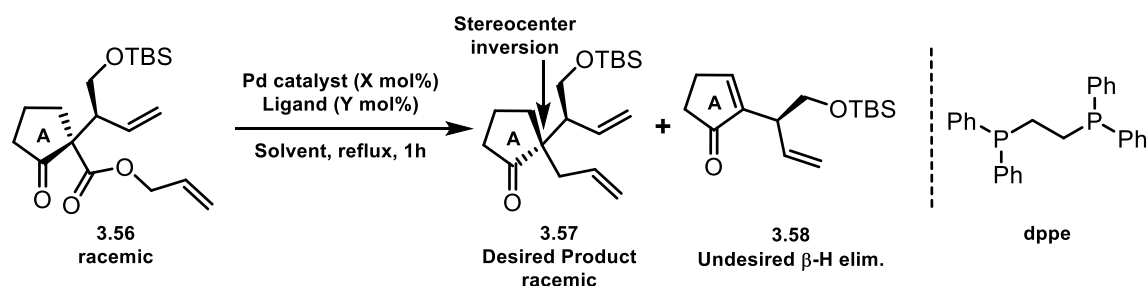


Figure 3.19: Optimization for the $\text{Pd}(0)$ -Catalyzed Tsuji-Trost Allylation of Allyl β -Ketoester by Borba

Table 3.2: Tsuji-Trost Allylation Optimization by Borba

Entry	Catalyst (X mol%)	Ligand (Y mol%)	Solvent (0.1M)	Yield DP (%)	Yield β -H (%)
1	Pd(PPh ₃) ₄ (10 mol%)	N/A	DCM	61	17
2	Pd(PPh ₃) ₄ (10 mol%)	N/A	benzene	71	ND
3	Pd(PPh ₃) ₄ (10 mol%)	N/A	toluene	71	ND
4	Pd(PPh ₃) ₄ (2.5 mol%)	dppe (10 mol%)	MeCN	27	58
5	Pd(OAc) ₂ (2.5 mol%)	dppe (10 mol%)	MeCN	44	ND
6	Pd(OAc) ₂ (2.5 mol%)	PPh ₃ (10 mol%)	THF	ND	ND
7	Pd(OAc) ₂ (5 mol%)	PPh ₃ (20 mol%)	THF	ND	ND

With the Mitsunobu reaction and the Tsuji-Trost allylation optimized, they were incorporated in Borba's synthetic route. As mentioned previously, the methyl ester was transesterified with allyl alcohol with Zn(0) as a catalyst giving a 93% yield of **3.54**. Next, the Mitsunobu reaction (with the mono-TBS-protected (*Z*)-but-2-ene-1,4-diol) yielded 75% of *O*-alkylated product **3.55**. Heating the Mitsunobu adduct neat at 140 °C generated Claisen rearrangement product **3.56** in a 67% yield. Tsuji-Trost allylation of **3.56** gave compound **3.57** in 71% yield. One thing to note from the Tsuji-Trost allylation was that the stereocenter α to the ketone was inverted during this reaction via an η -3 complex (this phenomenon will be discussed in further detail in route 3). Next, the B-ring was formed via a RCM (to **3.59**) with Grubbs II catalyst in 85% yield. Then, the ketone was converted to the corresponding vinyl triflate **3.60** by formation of the enolate with KHMDS followed by the addition of PhNTf₂. The vinyl triflate was submitted to the Sonogashira reaction with phenylacetylene which gave rise to enyne **3.61**. Finally, the TBS group was deprotected (to **3.62**) with TBAF, thus enabling the functionalization of the alcohol (see **Figure 3.20**).

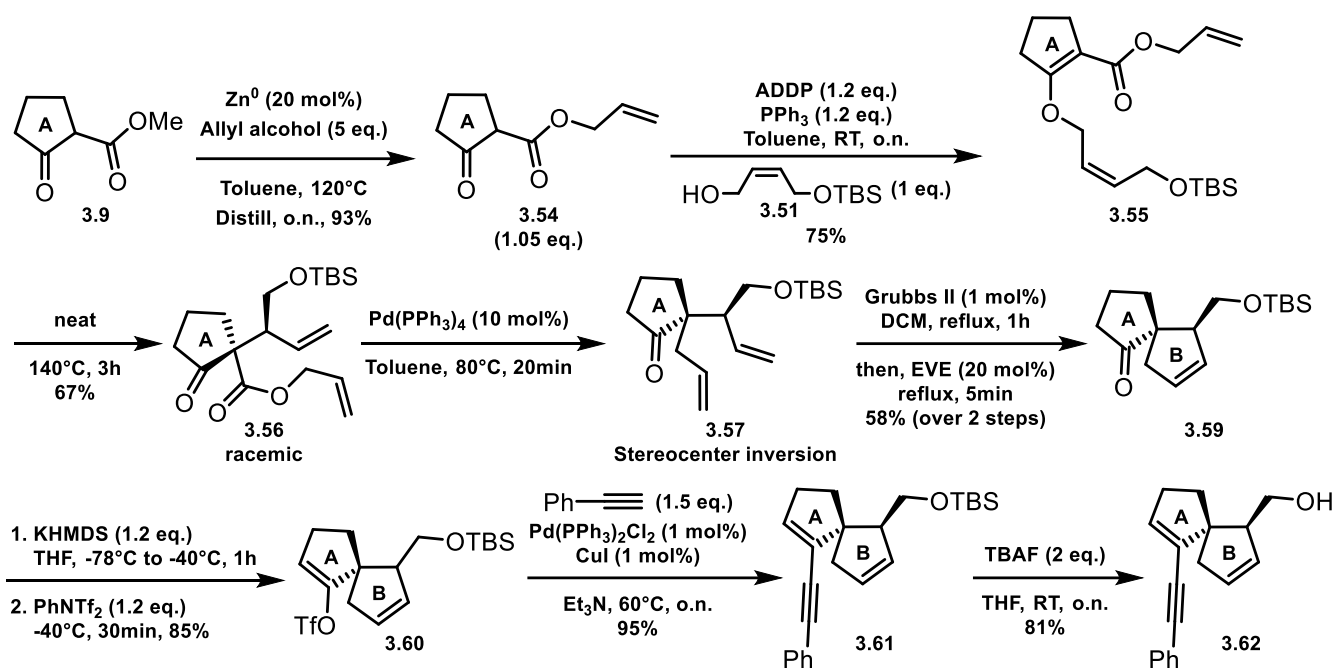


Figure 3.20: Borba's Synthetic Route Featuring Mitsunobu Reaction and Tsuji-Trost Allylation

3.1.4 Part C: Exploration of Viable Routes Towards the Total Synthesis of Ginkgolide C

3.1.4.1 Route 2 – Isopropylidene-Protected 1,3-Diol:

Starting from TRIS-HCl, the 1,3-diol was protected to the corresponding isopropylidene **3.63** with 2,2-dimethoxypropane in acidic conditions. Then, the 1,2-aminoalcohol was submitted to a periodate cleavage to yield ketone **3.33**.¹⁰⁸ The Horner-Wadsworth-Emmons reaction yielded α,β -unsaturated ester **3.64** which was then submitted to a DIBALH reduction, which gave rise to isopropylidene-protected allylic alcohol **3.39**(see **Figure 3.21**).

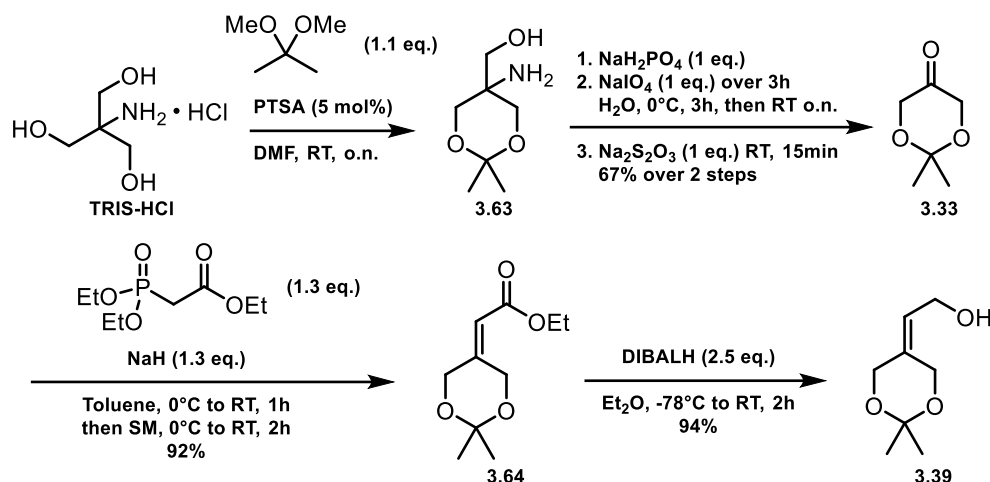


Figure 3.21: Preparation of Isopropylidene-Protected Allylic Alcohol

Isopropylidene-protected allylic alcohol **3.39** was then submitted to the Claisen rearrangement procedure, which yielded **3.65**. Ring-closed adduct **3.43** was then obtained in a 31% yield (over 3 steps) following a Grubbs II-catalyzed RCM (see **Figure 3.22**).

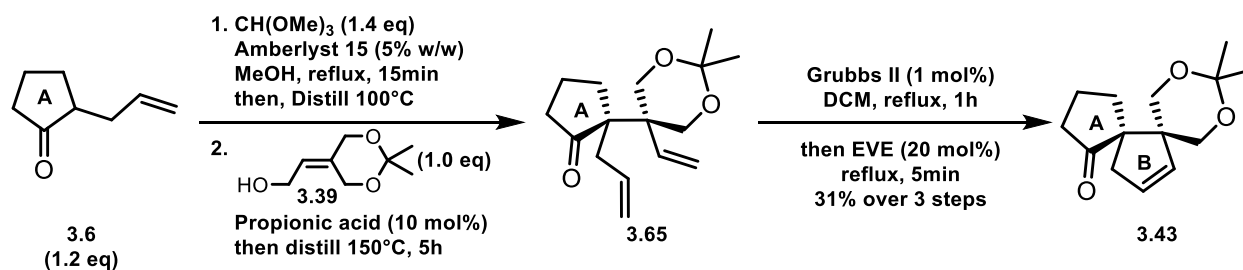


Figure 3.22: Submission of Isopropylidene-Protected Allylic Alcohol to the Claisen Rearrangement and RCM

Fortunately, having the 1,3-diol protected with an isopropylidene enabled the functionalization of the ketone. Cyanosilylation of ketone **3.43** generated the undesired TMS-protected cyanohydrin **3.66** (whose stereochemistry was determined by acidic deprotection of the isopropylidene followed by the lactonization of the hydroxyl onto the nitrile to **3.67**).¹⁰⁹ The addition of an organocerium acetylide to ketone **3.43** gave a diastereomeric mixture of 1,2-addition adducts **3.68** and **3.69** (with the undesired product being the major product).¹¹⁰ Vinyl triflate **3.70** was prepared which allowed for palladium-catalyzed cross-couplings yielding α,β -unsaturated nitrile **3.71**¹¹¹ or enyne **3.74**.¹¹² Unfortunately, epoxidation of the α,β -unsaturated nitrile gave undesired epoxide **3.72** as the major product and epoxide **3.73** as the minor product.

In the case of enyne **3.74**, isopropylidene deprotection yielded 1,3-diol **3.75**. Stereoselective epoxidation of the more electron-rich alkene of the enyne with MCPBA (most likely due to hydrogen bonding of the alcohols with MCPBA) generated the desired epoxide **3.76** in a 58% yield (and 20% yield for the undesired epoxide **3.77**). Upon submission of the 1,3-diol to a double oxidation with Dess-Martin periodinane, the desired bis-aldehyde product **3.78** was observed by ^1H -NMR, however purification by chromatography led to degradation (see **Figure 3.23**).

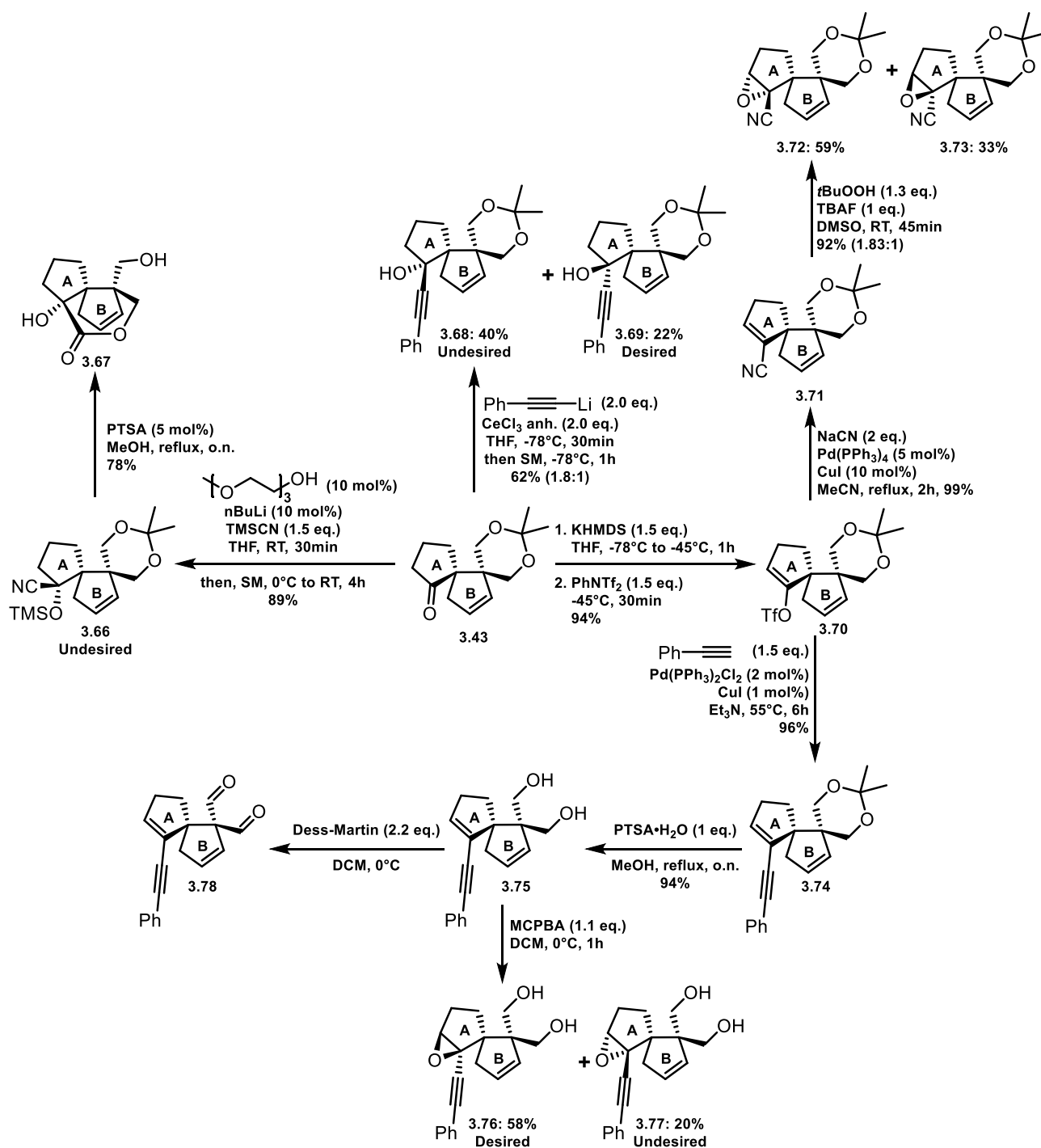


Figure 3.23: Ketone Functionalization of Isopropylidene-Protected 1,3-Diol Intermediate

Out of all the routes involving the functionalization of the ketone, the route with the enyne was definitely the most promising, namely because it would allow for further functionalization of the A-ring via epoxidation of the enyne (which could be directed by hydrogen

bonding). However, epoxide-opening with a carboxylate/hydroxylate/hydroxide would yield a triol/tetraol which would likely lead to chemoselectivity issues for further functionalization. Consequently, this route was abandoned once the iodolactonization was discovered in route 3.

3.1.4.2 Route 3 – Incorporation of the Iodolactonization (with Mono-TBS-Protected Allylic Alcohol):

For route 3, a different approach was explored. Instead of forming the two adjacent quaternary carbons in a single step (via the Claisen rearrangement), the first quaternary carbon would stem from the Claisen rearrangement, and the second would be formed via alkylation of an ester enolate.

The mono-TBS-protected allylic alcohol was submitted to the Claisen rearrangement (to yield **3.79**) followed by a Grubbs II-catalyzed RCM which afforded the desired ring-closed product **3.80** in a 52% yield over 3 steps. The ketone was converted to vinyl triflate **3.81** with KHMDS and PhNTf₂ in a 97% yield, then, the corresponding enyne **3.82** was generated via Sonogashira reaction in a quantitative yield. After TBS deprotection with TBAF (88% yield), alcohol **3.83** was oxidized to aldehyde **3.84** with Dess-Martin periodinane and was then further oxidized to carboxylic acid **3.85** (48% yield over 2 steps) via Pinnick oxidation.¹¹³ The E-ring was formed via a chemoselective iodolactonization (to **3.86**) in a 69% yield.¹¹⁴ The reaction proceeds in a chemoselective fashion because the enyne is electron-rich and more likely to react with the electrophilic I₂ or I₃⁻ (formed by the combination of I₂ and I⁻) than the B-ring alkene. Additionally, 5-membered rings are formed more easily (via *5-exo-tet*) than 4-membered rings (via *4-exo-tet*). However, attempting to perform the α -alkylation of the lactone did not yield the desired alkylation adduct **3.87**, but rather the conjugated α,β -unsaturated ester **3.88** (see **Figure 3.24**).

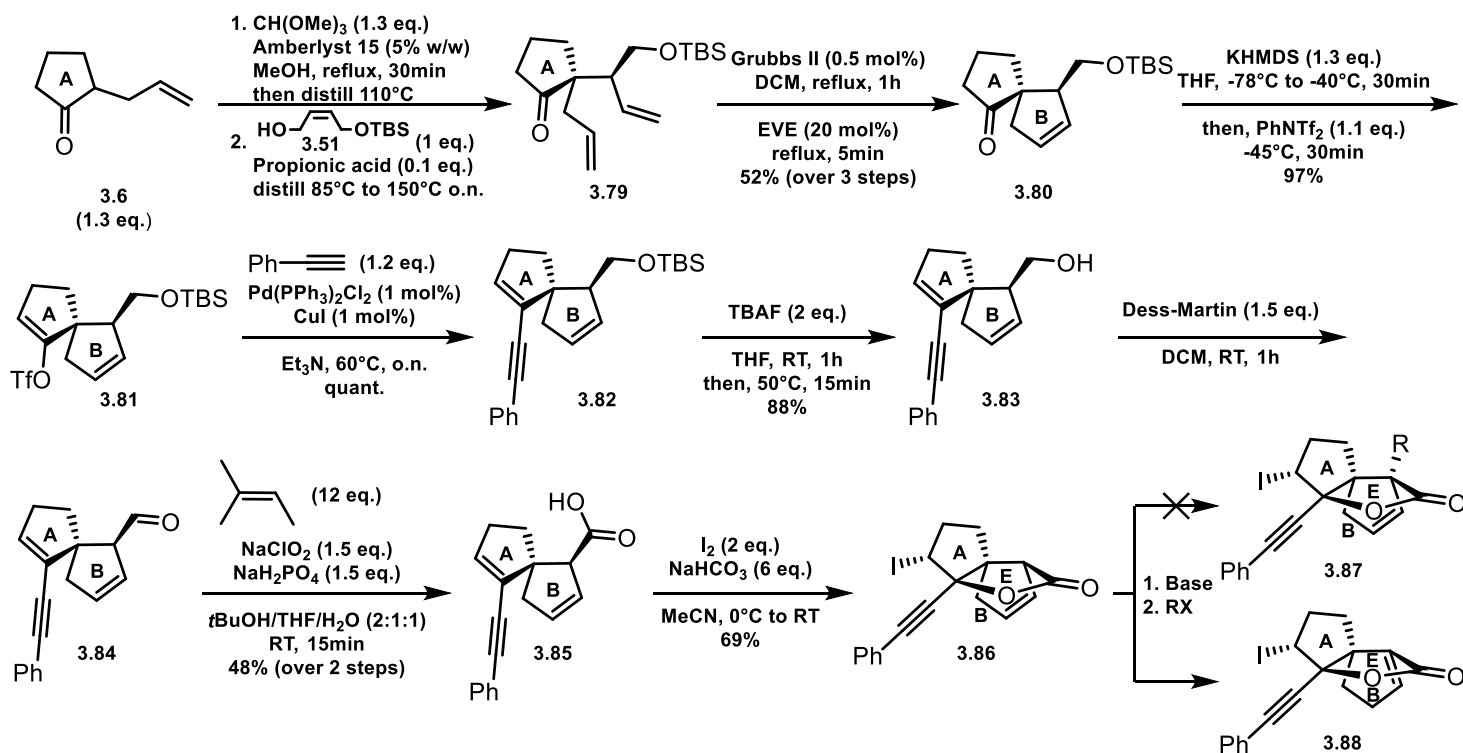


Figure 3.24: Claisen Rearrangement with the Mono-TBS-Protected (*Z*)-But-2-en-1,4-Diol Followed by E-Ring Formation via Iodolactonization

Interestingly, upon comparing the ^1H spectra of enyne **3.83** (prepared by the method illustrated in **Figure 3.24**) and enyne **3.62** (prepared by Victor Borba's method illustrated in **Figure 3.20**), it was determined that these two molecules were in fact distinct from each other. Since the stereocenter bearing the CH_2OTBS was set in the Claisen rearrangement in both cases, it was hypothesized that the difference between the two compounds came from the Tsuji-Trost step in Victor's method as it goes through η -3 enolate intermediates (**3.56ii** and **3.56iii**) following the decarboxylation. Since the palladium was free to roam on the η -3 system, it could eventually equilibrate to the less hindered face (**3.56iii**) after which, allylation would occur α to the ketone on the less hindered face (**3.57**) (see **Figure 3.25**).

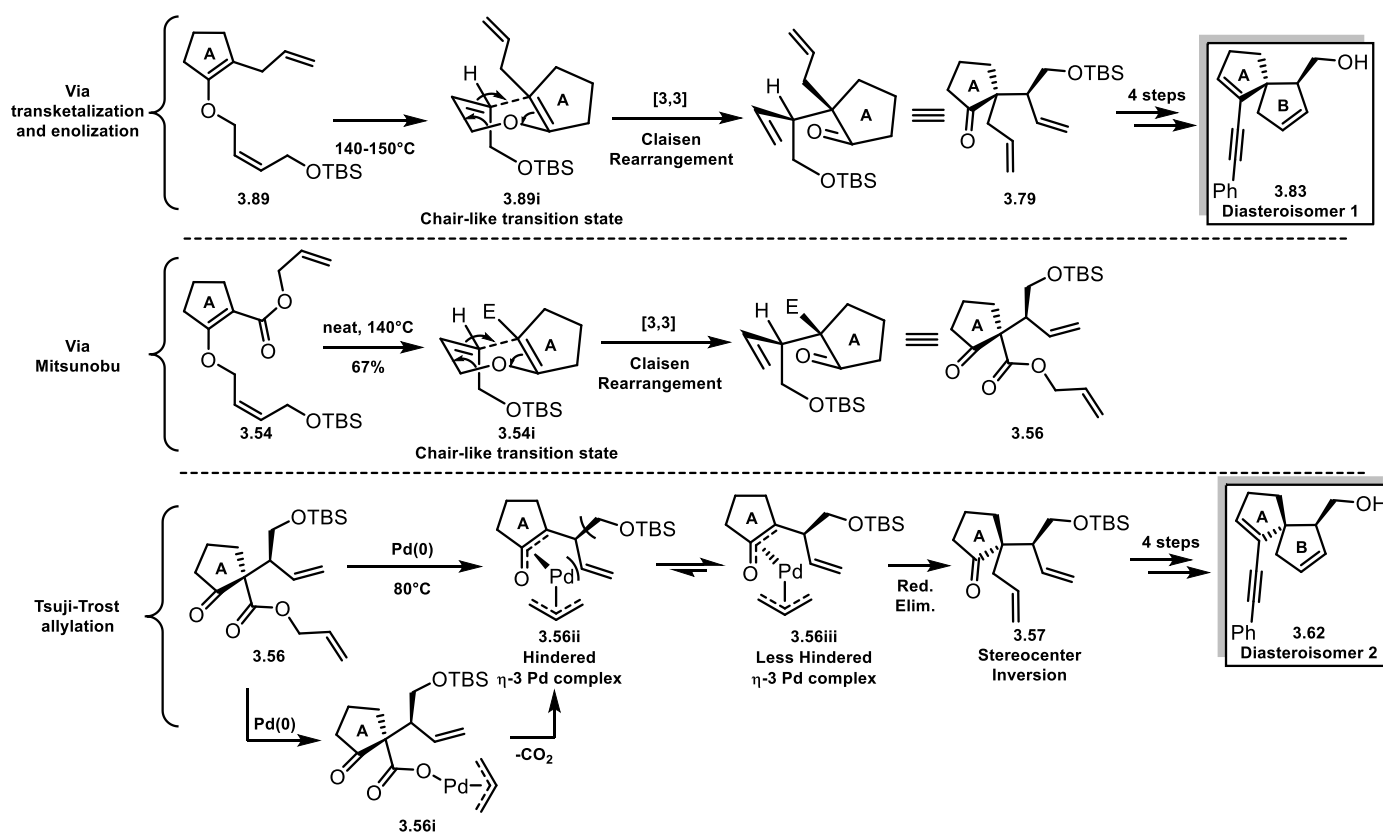


Figure 3.25: Possible Explanation for Obtaining two Distinct Diastereoisomers via the Usual Claisen Rearrangement Procedure or the Mitsunobu/Claisen Rearrangement/Tsuji-Trost Procedure

Although this route enabled the formation of the E-ring, there was a need to cut down on steps (e.g. alcohol deprotection and multiple oxidations necessary to convert the alcohol to the carboxylic acid). To address both these issues, the substitution of the CH₂OTBS with an ester group was proposed (hoping that having an electron-withdrawing group conjugated to the allylic alcohol's alkene would not interfere with the electronics of the Claisen rearrangement). Although, unlike the mono-TBS-protected (*Z*)-but-2-en-1,4-diol, the ester-substituted allylic alcohol would need to have an (*E*)-alkene, otherwise, it would undoubtedly lactonize to afford 2(*5H*)-furanone when submitted to the Claisen rearrangement (acidic and high-temperature) conditions. Another problem that needed to be solved was the α-alkylation of the ester. It was postulated that this reaction could be achieved by vinylogous deprotonation of an α,β-unsaturated ester followed by a low-temperature kinetic alkylation (deconjugation of the α,β-unsaturated system followed by an α-alkylation of the ester).

3.1.4.3 Route 4 – Incorporation of (*E*)-Methyl 4-Hydroxybut-2-enoate for Claisen Rearrangement

In order to prepare the (*E*)-methyl 4-hydroxybut-2-enoate **3.91**, a Wittig reaction was performed onto hydroxyacetaldehyde (obtained by heating its dimer **3.90**).¹¹⁵ Alternatively, the (*E*)-methyl 4-hydroxybut-2-enoate can be obtained by reduction of mono-methyl fumarate **3.92** with borane, but a lower yield was obtained for this transformation (see **Figure 3.26**).¹¹⁶ It is to be noted that the borane reduction is very exothermic and needs to be kept at -10 °C during the addition of borane. Consequently, it would have been difficult to scale-up this transformation.

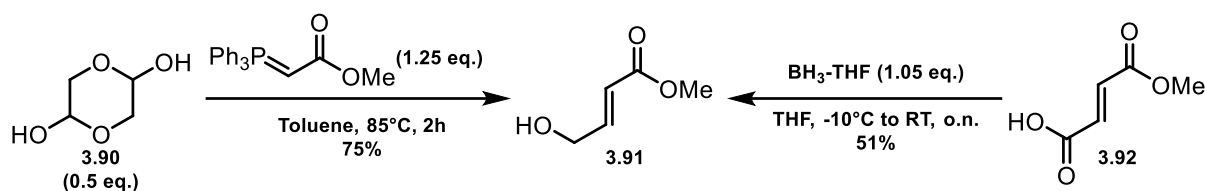


Figure 3.26: Preparation of (*E*)-Methyl 4-Hydroxybut-2-enoate

When comparing the Claisen rearrangement using an allylic alcohol with a (*Z*)- or (*E*)-substituted alkene, it was hypothesized that the lower yield obtained when using (*Z*)-alkene **3.51** (52%) was due to the fact that its substituent (CH₂OTBS) sat in the axial position (more hindered) of the transition state (**3.89i**) (see **Figure 3.27a**), as opposed to the (*E*)-alkene **3.91** (≥78%) whose substituent (CO₂Me) sat in the equatorial position (less hindered) of the transition state (**3.6vi**), thus reducing 1,3-diaxial interactions (see **Figure 3.27b**). A decrease in 1,3-diaxial interactions with the CO₂Me substituent undoubtedly facilitated the equilibration to the most thermodynamically stable (more substituted) enol ether (thereby increasing the reaction's regioselectivity) as opposed to the more kinetically favorable (less substituted) enol ether.

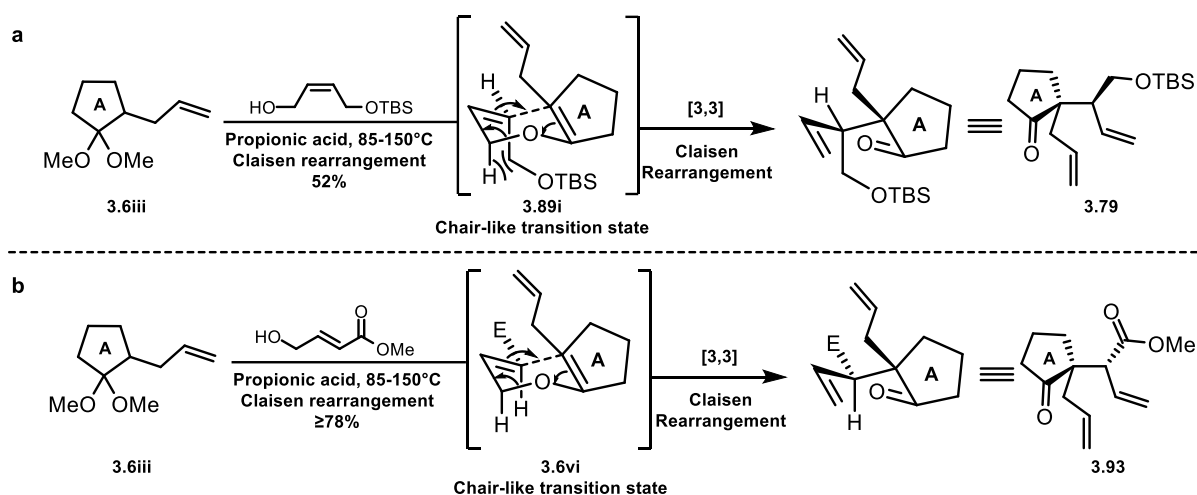


Figure 3.27: Comparison Claisen Rearrangement Using an Allylic Alcohol with a (*Z*)- or (*E*)-Substituted Alkene

Performing the Claisen rearrangement with (*E*)-methyl 4-hydroxybut-2-enoate **3.91** and subsequent formation of the B-ring via RCM with Grubbs II catalyst yielded the ring-closed adduct **3.94** in a 78% yield over 3 steps. Then, the β,γ -unsaturated ester was conjugated to the α,β -unsaturated ester **3.95** by treatment with DBU. In order to convert ketone **3.95** to vinyl triflate **3.96**, the use of LiHMDS as a base was crucial (as opposed to KHMDS, which has a more dissociated cation than its lithium counterpart, or LDA, which has a much higher pK_a of 35), otherwise, deconjugation of the α,β -unsaturated ester was observed. With the vinyl triflate in hand, the corresponding enyne **3.97** was obtained via Sonogashira reaction with phenylacetylene (see **Figure 3.28**).

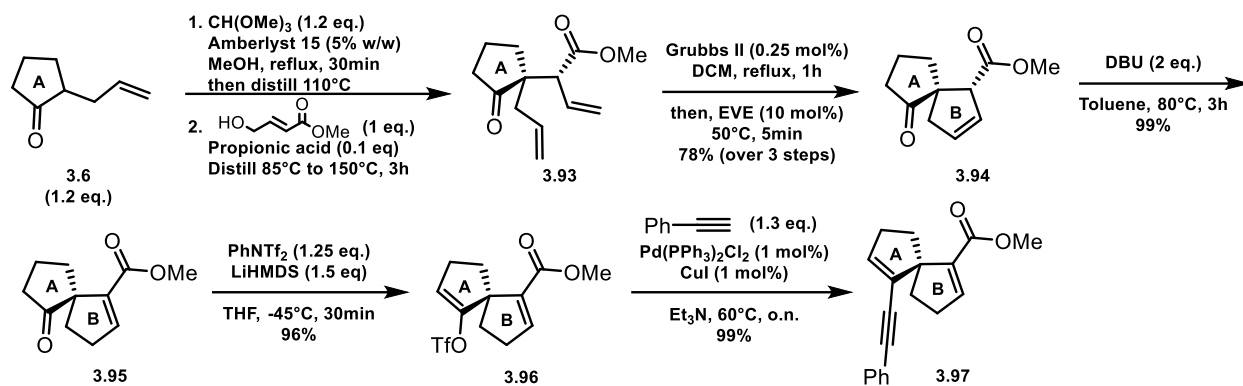


Figure 3.28: Incorporation of (*E*)-Methyl 4-Hydroxybut-2-enoate into the Claisen Rearrangement and Further Functionalization

In order to form the second quaternary carbon, a deconjugative alkylation of α,β -unsaturated ester could be employed to obtain the α -alkylated β,γ -unsaturated ester. To do so, two alkyl iodides, bearing either an ethylene glycol acetal or a TBS-protected alcohol, were prepared. Alkyl bromide **3.98** was converted to the corresponding alkyl iodide **3.99** in a 79% yield via the Finkelstein reaction.¹¹⁷ As for the 2-iodoethanol **3.100**, the alcohol was TBS-protected to **3.101** in a 96% yield (see **Figure 3.29**).

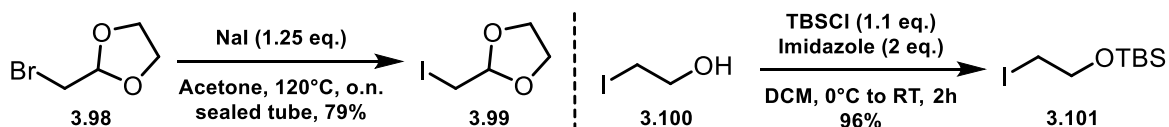


Figure 3.29: Preparation of Alkyl Iodides for the Deconjugative Alkylation of the α,β -Unsaturated Ester

It was hypothesized that a good diastereoselectivity for the kinetic alkylation should be obtained with the phenylacetylene shielding the top face of the molecule. Unfortunately, the kinetic alkylation of **3.97** (to **3.102**) wasn't successful with the ethylene glycol acetal-bearing alkyl halides (only deconjugated starting material was recovered). However, with the TBS-protected iodoethanol, the reaction proceeded well giving **3.103** a 93% yield. As hypothesized, an excellent diastereoselectivity was observed for the alkylation (>20:1 dr). The choice in counter-cation was important for the vinylogous deprotonation. The use of KHMDS (with 18-crown-6 ether) was necessary for the vinylogous deprotonation, whereas LiHMDS (even after the addition of 12-crown-4 ether) was unable to perform the deprotonation (see **Figure 3.30**). It is to be noted that

the enynes prepared in the course of this project are only bench-stable for about a week. Refrigeration was necessary if the compounds needed to be stored for a longer period of time.

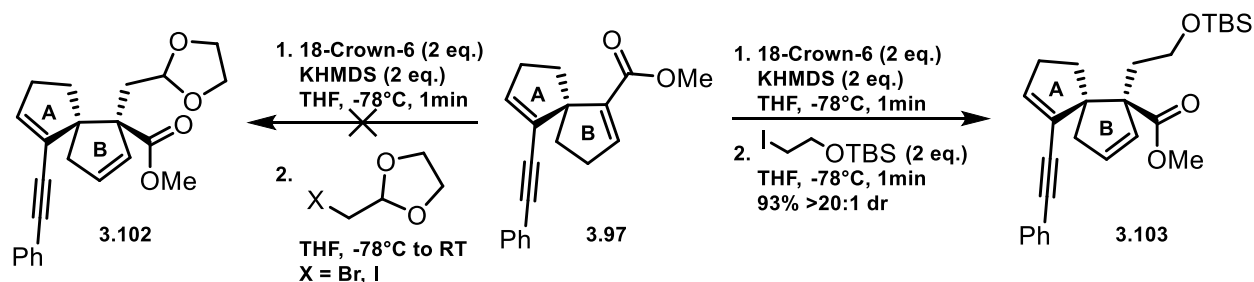


Figure 3.30: Deconjugative Alkylation of α,β -Unsaturated Ester with Functionalized Alkyl Halides

After the deconjugative alkylation, the ester was saponified and the alcohol was deprotected (to **3.104**) by treatment with NaOH (followed by reacidification of the carboxylate with HCl). Then, the E-ring was formed by performing an iodolactonization of the carboxylic acid onto the enyne which generated lactone **3.105** in an 85% yield. Following the iodolactonization, the primary alcohol was oxidized to the aldehyde which was subsequently converted to dimethyl acetal **3.106** with CH(OMe)₃ in acidic conditions in a one-pot fashion. The E-ring lactone was partially reduced to lactols **3.107A/B** (inseparable anomeric mixture) with DIBALH from -78 °C to 0 °C. Thereafter, treatment with anhydrous HCl (4 M in dioxane) enabled the formation of the F-ring methyl acetal. Fortunately, it was possible to separate both anomers (**3.108A** and **3.109B**) which facilitated subsequent steps. Additionally, an X-ray structure for **3.108A** (**3.108AXRay**) was obtained (see **Figure 3.31**).

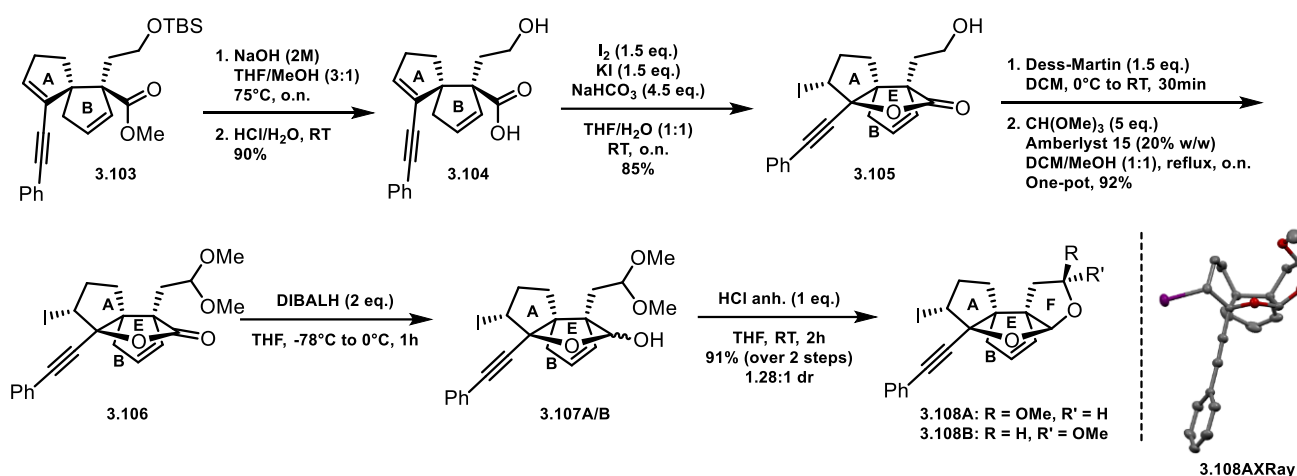


Figure 3.31: E-Ring Formation via Enyne Iodolactonization and F-Ring Formation

To obtain B-ring enone **3.109A** (and **3.109B**), the allylic oxidation of **3.108A** (and **3.108B**) with CrO_3 /3,5-dimethylpyrazole was attempted (conditions used for allylic oxidation in Gabriel Bellavance's route);¹¹⁸ however, these conditions led to degradation of the starting material. To solve this issue, a one-pot procedure, involving a SeO_2 allylic oxidation in dioxane at 110°C for the first stage followed by oxidation of the allylic alcohol to enone **3.109A** (and **3.109B**) with Dess-Martin periodinane in a (1:1) mixture of dioxane/DCM for the second stage of the reaction, was employed (see **Figure 3.32**).¹¹⁹

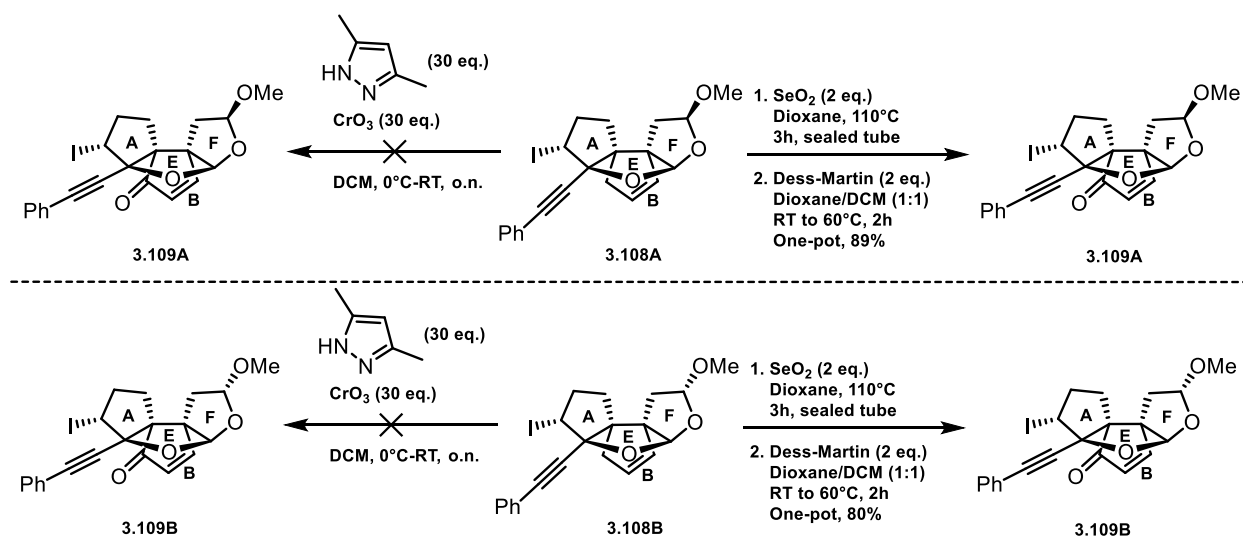


Figure 3.32: One-Pot SeO_2 Allylic Oxidation to the Allylic Alcohol Followed by Dess-Martin Periodinane Oxidation to the Corresponding Enone

Contrary to Corey's and Crimmins' approaches (which both feature the conjugate addition of the *t*Bu group in the second step of their respective syntheses), the *tert*-butyl moiety was installed at a later stage of the synthesis. Performing the *tert*-butyl cuprate addition with activation/trapping with TMSI followed by deprotection of the TMS enol ether with TBAF generated the desired conjugate addition adduct **3.110A** in a 46% yield for this one-pot transformation. Next, the ketone was reduced diastereoselectively to alcohol **3.111A** with LiBH₄ in THF giving a 75% yield. The D-ring was formed by performing a Au(I)-catalyzed 5-*exo-dig* cyclization of the alcohol onto the alkyne (using [IPrAu(MeCN)]SbF₆ as a catalyst), thus generating the corresponding enol ether **3.112A** in a 93% yield. Finally, the D-ring lactone **3.113A** was obtained in a 28% yield via an oxidative cleavage of the exocyclic enol ether by ozonolysis (see Figure 3.33).

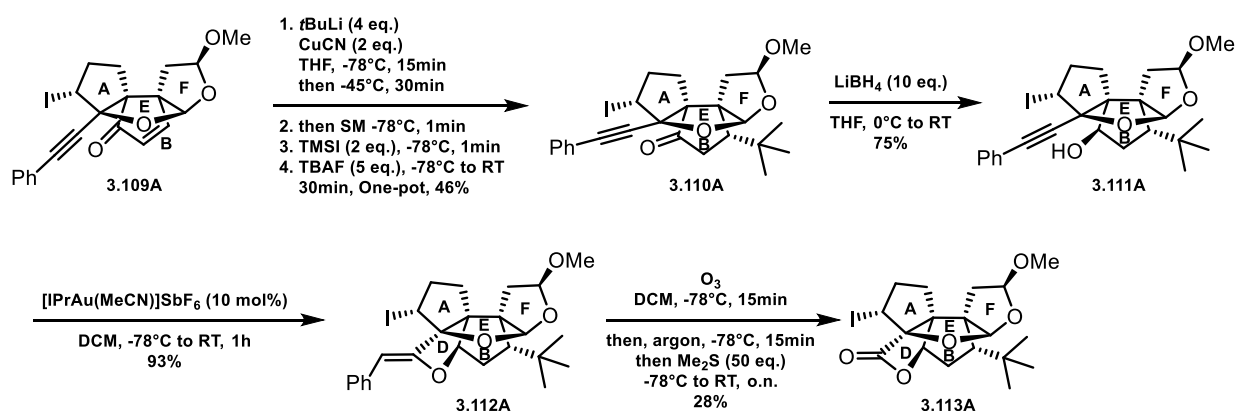


Figure 3.33: Conjugate Addition of *t*Bu Followed by Ketone Reduction, Au(I)-Catalyzed 5-*exo-dig* Cyclization and Oxidative Cleavage

Next, attempts were made to functionalize the A-ring. Alkyl iodide elimination (to **3.114A**), using either *t*BuOK or DBU, gave no conversion of the starting material. Ag(I)-catalyzed iodide substitution with an acetate group gave no conversion to **3.115A**. Then, conditions were screened to convert the B-ring alcohol to the corresponding triflate **3.116A** with Tf₂O in pyridine (to enable an E2 elimination yielding alkene **3.117A**) or to alkene **3.117A** directly with POCl₃ in pyridine; however, no conversion of **3.111A** was observed in both cases (see Figure 3.34).

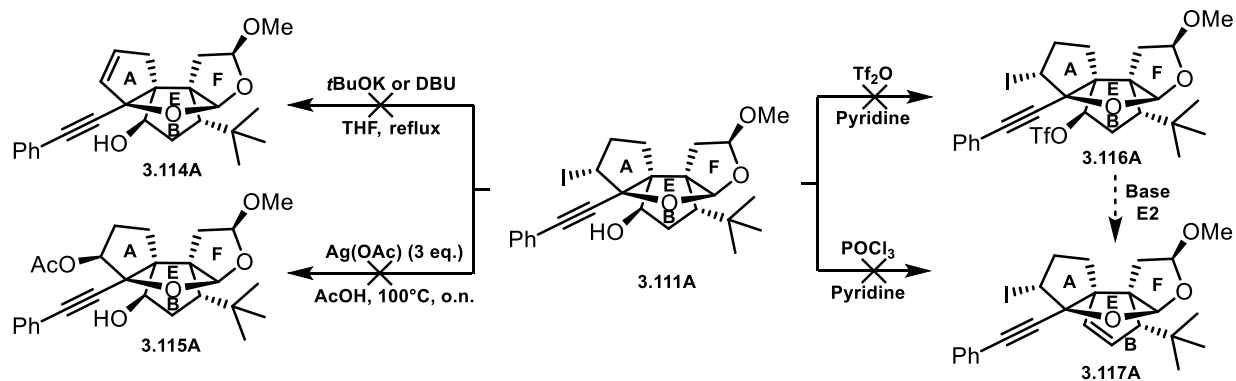


Figure 3.34: Failed Attempts of Alkyl Iodide Elimination/Substitution and B-Ring Alcohol Functionalization

In order to achieve the total synthesis of ginkgolide C, a hydroxyl group needed to be added onto the B-ring. Attempts to perform a Rubottom-type oxidation on TMS enol ether **3.118A** with cyclopropyl malonoyl peroxide (to **3.119A**), MCPBA, peracetic acid or OsO_4 (to **3.120A**) failed to generate any desired product. Next, attempts to perform an α -hydroxylation of ketone **3.110A** to **3.120A** were made with LiHMDS and Davis' oxaziridine; however, no conversion was observed. Efforts to convert ketone **3.110A** to vinyl triflate **3.123A** (to later reduce it to the disubstituted alkene to perform an OsO_4 -catalyzed dihydroxylation) failed to give any conversion. These previous results led to the hypothesis that the TMS enol ether/ketone are most likely too hindered to react (with a phenylacetylene on the top face as well as a *tert*-butyl on the bottom face). To address this issue, attempts were made to perform the oxidative cleavage of the alkyne with either PIFA in MeOH (to **3.121A**), ozonolysis or with RuO_4 (to **3.122A**). Unfortunately, none of these reaction conditions gave any conversion. Treatment with AgNO_3 and KOH in THF yielded bis enol ether **3.124A**. Thinking the exocyclic enol ether would be easier to cleave, this compound was submitted to RuO_4 oxidative cleavage conditions. However, the endocyclic enol ether underwent the oxidative cleavage (to **3.125A**), whereas the exocyclic enol ether remained untouched (see **Figure 3.35**).

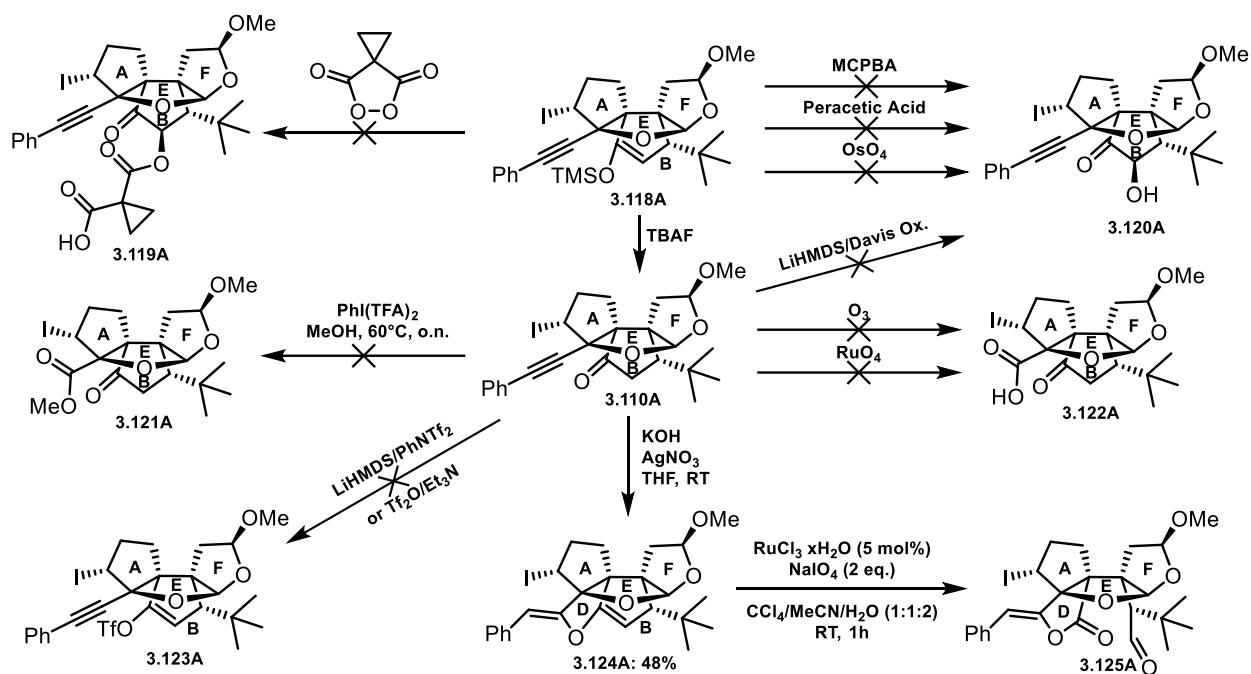


Figure 3.35: Failed Attempts for B-Ring Functionalization and Oxidative Cleavage of the Alkyne

Initially, the idea behind installing the alkyl iodide onto the A-ring was to enable functionalization further down the line in the synthesis either by performing a Kornblum oxidation, a $\text{S}_{\text{N}}2$ reaction (with an acetate for example) or an $\text{E}2$ elimination. The Kornblum oxidation was attempted on intermediate **3.105**. With very little steric hindrance on the molecule, it was hypothesized that the DMSO would have plenty of room to displace the alkyl iodide. In fact, the alkyl iodide was displaced, but it was substituted intramolecularly by the primary alcohol to yield **3.127**. Drawing inspiration from Corey's total synthesis of ginkgolide B, a cyclic enol ether on the F-ring was to be formed in the later stages of the synthesis. The plan was to keep the alkyl iodide until the endgame of the synthesis, then perform the Kornblum oxidation. Consequently, a model substrate bearing a cyclic enol ether on the F-ring was prepared (which would be representative of a late-stage intermediate). Unfortunately, upon submitting the model substrate **3.128** to the Kornblum oxidation conditions, no conversion was observed (see **Figure 3.36**).

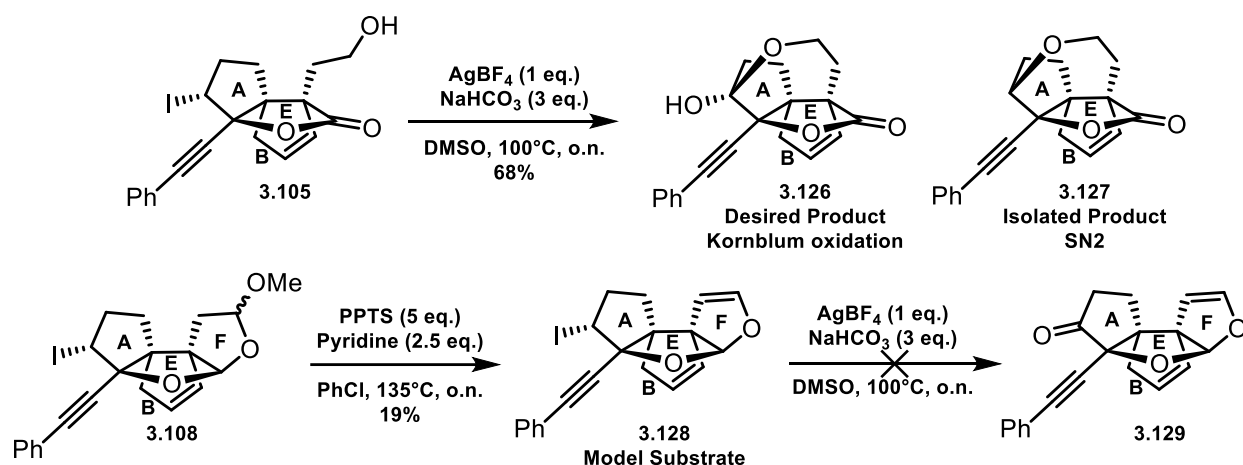


Figure 3.36: Attempts to Perform Kornblum Oxidation on A-Ring Alkyl Iodide

Another strategy that was investigated was the alteration of the alkyne terminal group. After conducting many experiments, it seemed as though the phenylacetylene prevented functionalization of the B-ring (except for reduction of ketone **3.110A** with LiBH_4) most likely due to the fact it overshadowed the B-ring ketone (following the *t*Bu conjugate addition). To remedy this, it was hypothesized that the phenyl could be substituted with a removable alkyne protecting groups such as TMS, TIPS, or $\text{C}(\text{CH}_3)_2\text{OTBS}$. These alkyne protecting groups should be sufficiently bulky to direct the deconjugative alkylation on the desired face, and they should also be easy to remove to clear some space above the B-ring ketone which should enable its functionalization. In the case that the alkyne protecting groups would not survive the reaction conditions the synthetic pathway, “*n*Bu” was also employed as a terminal group. Sterically, the *n*Bu group is smaller than the phenyl group, which means diastereoselectivity would be sacrificed for the deconjugative alkylation in the hopes that the smaller size of the *n*Bu group would facilitate the functionalization of the B-ring. In terms of the Sonogashira coupling, yields ranging from 74-98% were obtained for **3.130TMS**, **3.130TIPS**, **3.130C(CH₃)₂OTBS** and **3.132**. However, upon submitting **3.130TMS**, **3.130TIPS**, **3.130C(CH₃)₂OTBS** to the deconjugative alkylation conditions, the alkylation gave an excellent diastereoselectivity, but the yields were very poor due to alkyne deprotection in these strong nucleophilic/basic conditions. On the other hand, alkylation of **3.132** gave **3.133** in a good yield of 71% with a dr of 2.94:1 (see **Figure 3.37**).

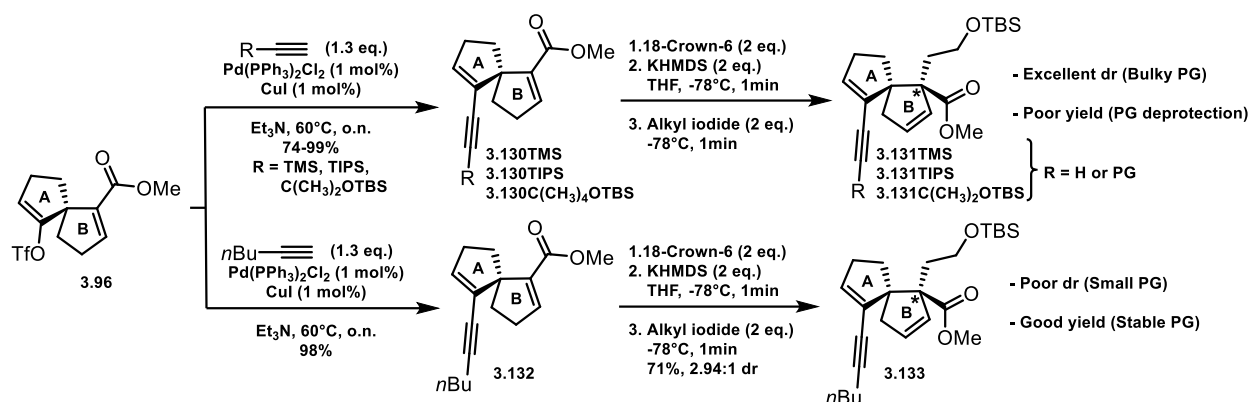


Figure 3.37: Sonogashira Couplings with Different Alkyne Terminal Groups (TMS, TIPS, $C(CH_3)_2OTBS$ and nBu)

Despite the lower diastereoselectivity (compared to the Ph, TMS, TIPS and $C(CH_3)_2OTBS$), the decision was made to pursue the synthesis with **3.133**. The ester was saponified and the TBS was deprotected with NaOH (followed by reacidification of the carboxylate with HCl) to obtain the alcohol bearing carboxylic acid **3.134** in a 73% yield (2.94:1 dr). The substrate underwent an iodolactonization giving **3.135** in a 79% yield (of pure product). The primary alcohol was oxidized to the aldehyde with Dess-Martin periodinane and was then converted to dimethyl acetal **3.136** in a 72% yield (in a one-pot fashion) with $CH(OMe)_3$, Amberlyst® 15 in a DCM/MeOH (1:1) mixture at reflux overnight (see **Figure 3.38**).

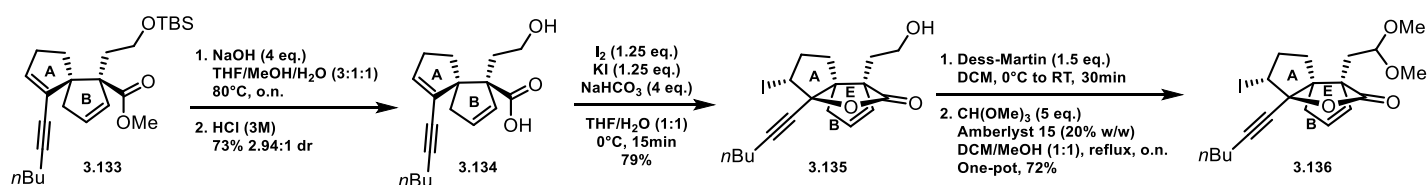


Figure 3.38: Further Functionalization of Intermediate **3.133**

Next, the Kornblum oxidation was attempted on alkyl iodide **3.136**, however, only E2 product **3.137** was obtained in a 98% yield. Despite being able to functionalize the alkyl iodide, the presence of two alkenes on the molecule would most likely lead to chemoselectivity problems for the allylic oxidation (with SeO_2). Then, conditions were screened to obtain the allylic alcohol (or the enone) by submitting **3.136** to SeO_2 in dioxane at reflux overnight. Surprisingly, no allylic oxidation of the B-ring alkene was observed, instead, the corresponding ynone **3.138** was obtained in a 79% yield. This experiment indicated that the nBu alkyne wasn't suitable for

this synthetic route (see **Figure 3.39**). Due to the hardships endured trying to functionalize the alkyl iodide, this strategy was ultimately abandoned.

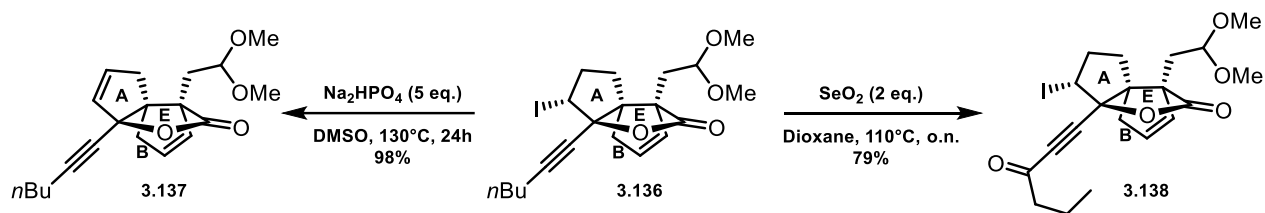


Figure 3.39: Kornblum Oxidation Attempt on the A-Ring Alkyl Iodide and Allylic Oxidation Attempt of the B-Ring Alkene

3.1.4.4 Route 5 – Vinyl Group Installation via Stille Coupling:

Another strategy explored was the replacement of the alkyne group by an alkene. It was postulated that the hybridization of the carbon being sp^2 (instead of sp) would give a better diastereoselectivity for the deconjugative alkylation. In addition, the vinyl group should be easier to oxidatively cleave than the alkyne (which should clear some space around the B-ring ketone thus facilitating its functionalization).

To add the vinyl moiety, a Stille coupling, using tributyl(vinyl)tin as a vinyl source, was performed on vinyl triflate **3.96**.¹²⁰ The reaction proceeded well and yielded diene **3.139** in an 81% yield. It is to be noted that the diene was not bench-stable for more than a few days and had to be stored in the refrigerator (for longer periods of time). Next, the deconjugative alkylation reaction was performed. The reaction achieved full conversion to the desired product **3.140** (which was isolated in small amounts), however, for unknown reasons, a quasi-instant degradation of the desired product was observed at -78°C . Attempts were made to quench the reaction immediately following the addition of the alkyl iodide, but this strategy proved to be ineffective. Lowering the equivalents of KHMDS/18-crown-6 did not solve this issue either. Saponification of methyl ester **3.139** (followed by acidification) was successful in obtaining the corresponding carboxylic acid **3.141** in an 80% yield. Submission to iodolactonization conditions generated the desired product **3.142** in a moderate yield of 62%. Unfortunately, attempts at deconjugative alkylation of **3.142** to **3.143** failed. Epoxidation of diene **3.139** with MCPBA in a (1:1) mixture of DCM/aq. sat. NaHCO_3 gave **3.144** and **3.145** in an 87% yield (6.36:1 dr). This

modification enabled the deconjugative alkylation yielding **3.146** (75% yield as a sole diastereoisomer). Next, it was postulated that an acidic epoxide opening should open the epoxide at the allylic position and the *anti* 1,2-diol should lactonize onto the nearby ester, thus forming the E-ring (the TBS should also deprotect in acidic conditions). Unfortunately, the desired lactone **3.147** was not obtained in this transformation. Rather, acid-activation of the epoxide likely led to an allylic carbocation to which the A-ring alcohol underwent a cyclization to form **3.148** (see **Figure 3.40**). Due to the issues encountered, the decision was made to move on from this approach.

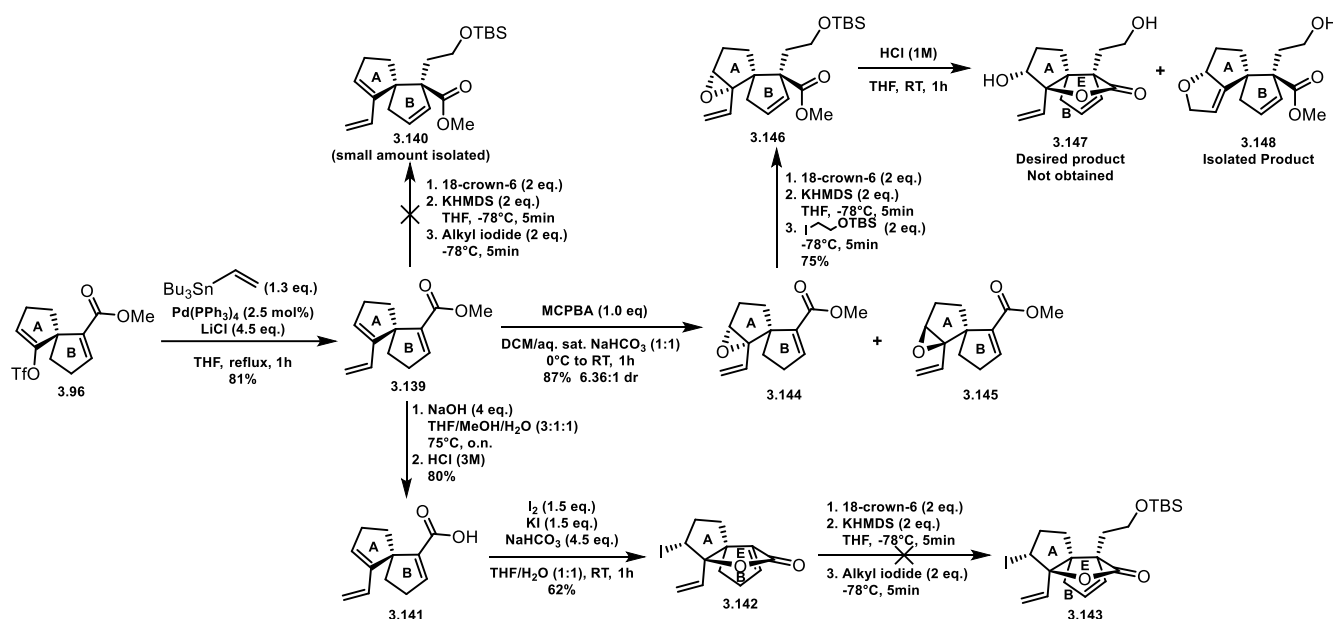


Figure 3.40: Vinyl Installation via Stille Coupling Followed by Further Functionalization

3.1.4.5 Route 6 – Ethylene Glycol Ketal Formation:

Another avenue that was explored was the protection of ketone **3.95** as an ethylene glycol ketal. Ethylene glycol with **3.95** in acidic conditions using a Dean-Stark apparatus yielded ketal **3.149** in an 87% yield.¹²¹ Then, the substrate was submitted to the deconjugative alkylation conditions which gave rise to the desired product **3.150** in a moderate 54% yield (14.2:1 dr) (see **Figure 3.41**). The idea behind this route was to perform the kinetic alkylation, then deprotect the

ketone which would give some creative freedom to the synthetic route (since the ketone is the most versatile functional group). Ultimately, it was decided to abandon this route for three reasons. First, the protection/deprotection of the ketone require one step each. Second, although the diastereoselectivity of the alkylation was excellent, the yield for the transformation was disappointing. Third, upon acidic deprotection of the ethylene glycol ketal, there would be an elevated risk of TBS-deprotection/lactonization of the alcohol onto the ester.

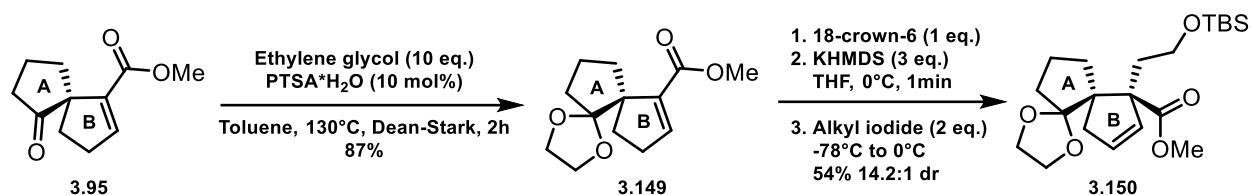


Figure 3.41: Ethylene Glycol Ketal Formation Followed by Deconjugative Alkylation

In summary, due to the hardships endured trying to functionalize the alkyl iodide, the decision was made to abandon this approach. Furthermore, the next strategy aimed at adding oxygen (via enyne epoxidation or dihydroxylation) to the A-ring. This should facilitate functional group manipulation (via alcohol protection/oxidation). Additionally, after extensive experimentation, it was determined that the substitution of the phenylacetylene with a vinyl group or TMS-, TIPS-, TBSO(CH₃)₂C-, and *n*Bu-acetylene (as well as the ethylene glycol protection of the ketone) proved to have their share of issues. Consequently, the decision was made to return to the phenylacetylene and try to find a way to functionalize the B-ring (addition of a hydroxyl group which is found in ginkgolide C).

3.1.4.6 Route 7 – Enyne Epoxidation Followed by Lactonization:

3.1.4.6.1 Preparation of Enones 3.163A and 3.163B from Enyne 3.103

As stated in the previous section, there were some issues with alkyl iodide functionalization. Since ginkgolide has oxygen atoms on both carbons of the enyne's alkene, the retrosynthetic approach was reevaluated, which would feature an enyne epoxidation as a key step. The first disconnections in the retrosynthetic analysis for ginkgolide C (**3.1C**) were inspired

by Corey's and Crimmins' syntheses of ginkgolide B (**3.1B**). The F-ring α -hydroxylactone can be obtained from the corresponding enol ether **3.151**. The C-ring stems from enone **3.152** which can be derived from the alcohol. The D-ring can be formed following an oxidative cleavage of enol ether **3.153** generated from a 5-*endo-dig* cyclization of the A-ring alcohol onto alkyne **3.154**. The *t*Bu and hydroxyl groups of the B-ring would be added via conjugate addition of enone **3.154** followed by a stereoselective α -hydroxylation of the corresponding ketone directed by the *t*Bu group. Enone **3.154** can be obtained by allylic oxidation and the F-ring would be generated via a series of redox transformations from **3.155**. The E-ring lactone stems from epoxidation of enyne **3.103** obtained in Route 4 (see **Figure 3.42**).

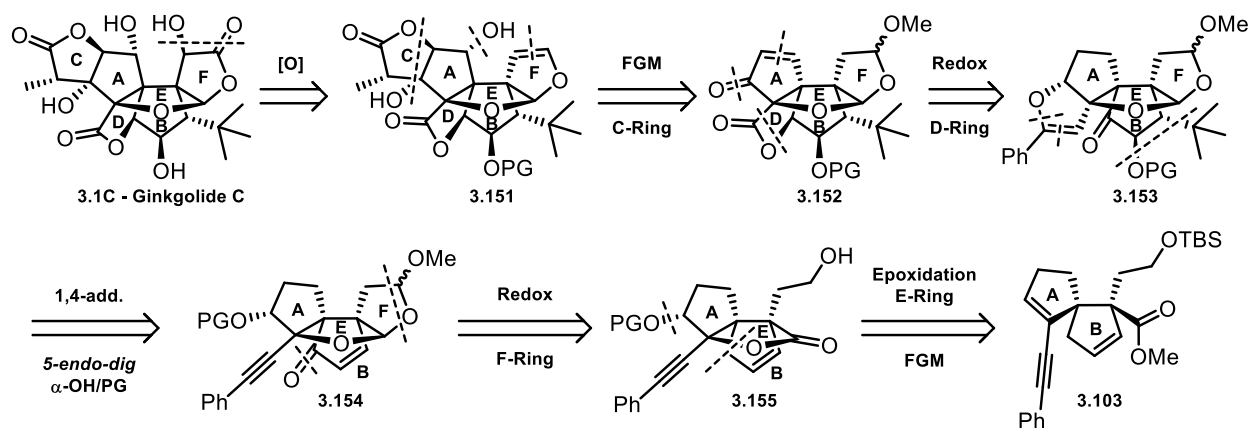


Figure 3.42: Retrosynthetic Analysis Towards Ginkgolide C Featuring the Epoxidation of Enyne **3.103**

The OsO_4 -catalyzed dihydroxylation failed to give any conversion of enyne **3.103**. Fortunately, epoxidation of **3.103** with MCPBA proceeded with excellent chemoselectivity towards the enyne. Strangely, the reaction mostly occurred on the seemingly most hindered face of the enyne (top face) giving a 51% yield of **3.157** (major product). This phenomenon could perhaps be explained by hydrogen bonding between the MCPBA and the methyl ester. Surprisingly, the bottom-face epoxide underwent an intramolecular ring-opening from the nearby ester (35% yield of **3.158**) most likely acid-catalyzed due to the presence of the *m*-chlorobenzoic acid (MCBA) as a by-product of the MCPBA epoxidation. Further evidence for the acid-catalyzed epoxide-opening (via **3.103i**) was provided by performing the reaction in a (1:1) mixture of DCM/aq. sat. NaHCO_3 which gave rise to both epoxides (with no trace of the intramolecular epoxide-opened product). The top-face epoxide **3.157** was opened by addition of

KOAc in DMSO at 145°C (which led to lactonization onto the methyl ester). Despite obtaining a moderate 44% yield (of **3.159**) for the epoxide opening/lactonization, pleasantly, the TBS group was also deprotected due to the relatively harsh reaction conditions. As for the epoxide-opened product **3.158**, the secondary alcohol was acetylated with acetic anhydride (Ac₂O). After full conversion of the starting material, 5 equivalents of MeOH were added to consume any Ac₂O left in the reaction mixture (to avoid acetylation of the primary alcohol following the TBS deprotection with TBAF in this one-pot procedure). After the addition of TBAF (in THF) and heating the reaction mixture to reflux, the desired product **3.159** was obtained in a 78% yield in a one-pot fashion. In total, the primary alcohol was obtained in approximately 50% yield over 2 steps from enyne **3.103** (see Figure 3.43).

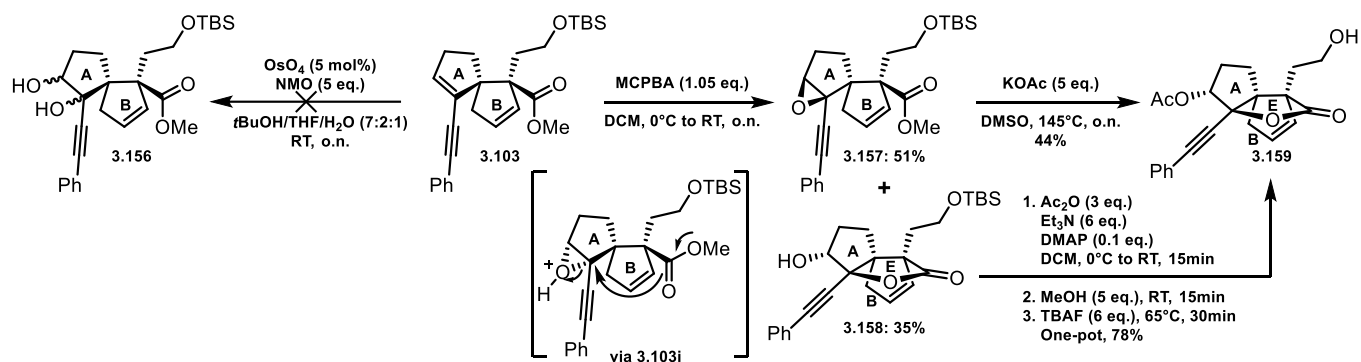


Figure 3.43: Enyne Epoxidation with MCPBA and Epoxide-Opening

The primary alcohol was oxidized to the aldehyde with Dess-Martin periodinane in DCM and was then converted to dimethyl acetal **3.160** with CH(OMe)₃, Amberlyst® 15 in a (1:1) mixture of DCM/MeOH at reflux overnight in a one-pot fashion giving a 75% yield. Next, the substrate was treated with DIBALH from -78 °C to 0 °C, which deprotected the acetate and reduced the lactone to afford lactols **3.161A/3.161B** in a 90% yield (5:1 dr). Upon treatment with anhydrous HCl (4 M in dioxane), the lactols cyclized onto the dimethyl acetal forming the F-ring, then, the secondary alcohol was acetylated with Ac₂O in a one-pot fashion. The reaction yielded separable anomers **3.162A** and **3.162B** in a 96% yield (1.59:1 dr). The two anomers were separated at this stage to facilitate further functionalization and purification. Starting from **3.162A**, allylic oxidation with SeO₂ followed by oxidation of the allylic alcohol with Dess-Martin periodinane yielded enone **3.163A** in an 85% yield in a one-pot fashion (sole regioisomer).

However, in the case of anomer **3.162B**, the allylic oxidation gave a 78% yield as a mixture of regioisomers **3.163B** and **3.163Bregio** (6.43:1 rr) (see **Figure 3.44**).

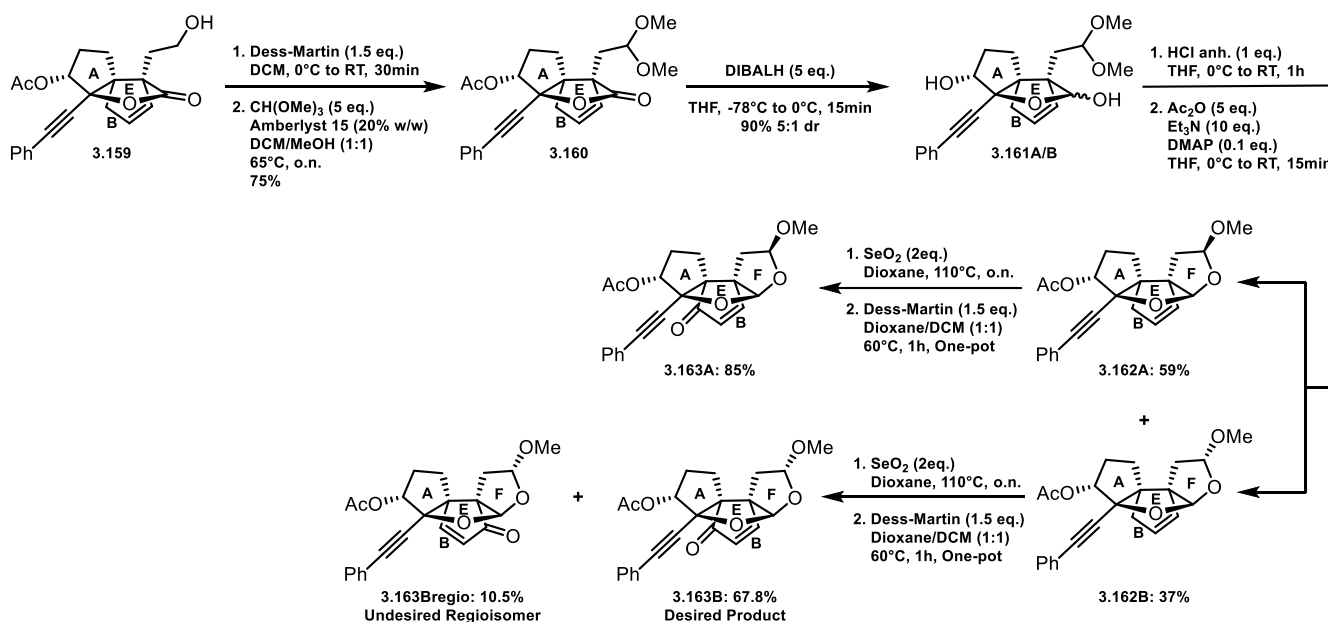


Figure 3.44: F-Ring Formation via Functional Group Manipulation Followed by Allylic Oxidation

To explain this phenomenon, one must first understand the mechanism for the allylic oxidation with SeO₂. First, an ene reaction occurs between the allylic system and the Se=O of SeO₂ in a 6-membered transition state (**3.164**) (the selenium ends up on the allylic carbon, the alkene shifts, and the oxygen picks up the allylic proton thus forming allylic selenic acid **3.165**). In the case of Anomer A, the reaction proceeds normally with a [2,3]-sigmatropic rearrangement, and the Se(IV) is reduced to Se(II) (**3.166**). Finally, in the presence of water, the Se(II) intermediate is hydrolyzed to yield allylic alcohol **3.167**. In the case of Anomer B, the ene reaction begins in the same manner, however, due to the steric hindrance coming from the OMe group on the right-hand side of the molecule, it was postulated that there might be an equilibrium between the two possible regioisomers (**3.165** and **3.168**) of the allylic selenic acid (via some kind of 1,3-Se shift). Then, same as before, a [2,3]-sigmatropic rearrangement occurs to form Se(II) intermediate **3.169**, which gets hydrolyzed to allylic alcohol **3.170**. Although the equilibrium doesn't seem to be severe (observed regioselectivity of 6.43:1), it would explain the presence of the undesired regioisomer (see **Figure 3.45**).

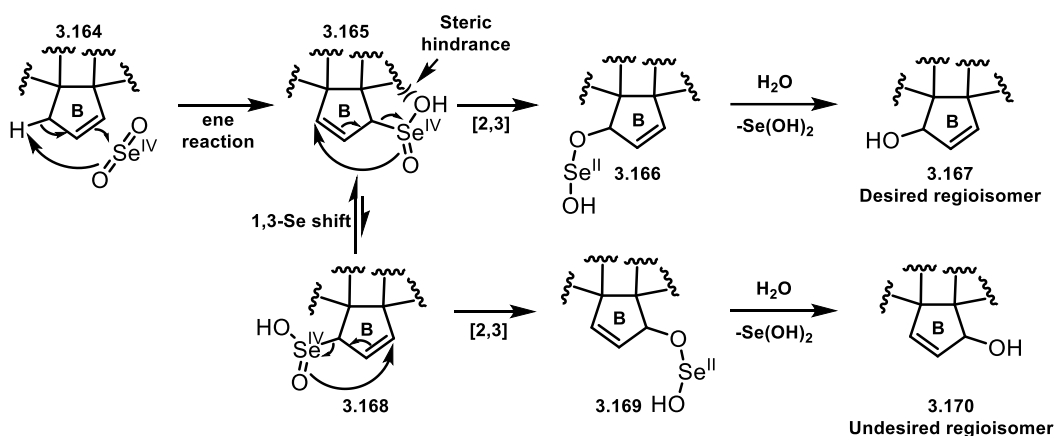


Figure 3.45: Justification for the Regioselectivity Issue in the Allylic Oxidation of Anomer B

3.1.4.6.2 Preparation of Target Intermediate 3.181 from Enone 3.163A:

With both enones **3.163A** and **3.163B** in hand, the next goal was to prepare target intermediate (**3.181**), which was essentially one of Corey's intermediates with a protected alcohol on the B-ring. Since enone **3.163A** was the major anomer, investigations began with this intermediate. First, the Gillman's reagent was prepared by adding *t*BuLi to a suspension of CuCN, then, the enone was added (which turned the solution from clear to red upon coordination of the cuprate with the enone). The addition of TMSI to activate/trap the enone was necessary to observe conversion of the starting material (giving a mixture of the TMS enol ether and the ketone). Finally, TBAF was added to convert the TMS enol ether to the corresponding ketone **3.171A** in an 80% yield for this one-pot transformation. Like the iodolactonization route, α -functionalization the B-ring ketone/TMS enol ether was unsuccessful with the phenylacetylene overshadowing its top face and with the bulky *tert*-butyl hindering the bottom face. It was postulated that the ketone of **3.171A** was too sterically hindered to form the enolate, therefore, making it extremely difficult to functionalize it at the α -position (with Davis' oxaziridine for example). As for the corresponding TMS enol ether, all attempts to perform the Rubottom oxidation (by adding peracids such as peracetic acid or MCPBA) either led to degradation of the starting material or gave no conversion. Solving this issue was crucial to complete the total synthesis of ginkgolide C as it bears a hydroxyl on the B-ring (see **Figure 3.46**).

In order to clear some space around the B-ring ketone, deprotection of the A-ring alcohol was considered. This could enable a Pd-, Au- or base-catalyzed 5-*endo-dig* cyclization of the alcohol onto the phenylacetylene alkyne. Fortunately, it was noted that by simply adding NaOH (1 M), as well as MeOH (to ensure miscibility between the organic and aqueous phases) and heating the reaction mixture to 75 °C overnight, the desired 1,4-addition/5-*endo-dig* product **3.173A** was obtained in an 81% yield for this one-pot transformation. The final stage of the reaction accomplished two tasks. First, the acetylated alcohol was deprotected via saponification. Second, the NaOH was sufficiently basic to generate a fair amount of alkoxide (on the A-ring alcohol) which underwent a 5-*endo-dig* cyclization onto the nearby alkyne. It is to be noted that the conjugate addition/deprotection/cyclization couldn't be scaled-up higher than a 0.5-1 g scale. Any higher than this would result in reduced yield and/or conversion. Having cleared some steric hindrance around the B-ring ketone, the α -hydroxylation with KHMDS and Davis' oxaziridine was performed and the desired α -hydroxyketone **3.174A** was obtained in a 92% yield as the sole diastereoisomer.¹²² The diastereoselectivity of this reaction was undoubtedly due to the bulky *tert*-butyl shielding the bottom face of the B-ring which forced the hydroxylation to occur on the top face. The stereochemistry of the α -hydroxyketone was determined by the relatively large ¹H NMR coupling constant (d, $J = 13.8$ Hz) between the hydrogen α to the ketone and the hydrogen on the *tert*-butyl-bearing carbon which was evidence of an *anti* relationship between the protons. Next, the MOM-protected alcohol **3.175A** was obtained in a quantitative yield with MOMBr (see **Figure 46**). The MOM protecting group was chosen because it would be stable under oxidative cleavage conditions such as O₃, OsO₄/NaIO₄ or RuO₄ (unlike Bn, PMB or All), stable in basic conditions such as NaOH (unlike Ac or Bz), and stable in mild acidic conditions such as AcOH and PPTS (unlike TBS or THP). Also, in Corey's total synthesis of ginkgolide A, the secondary MOM-protected alcohol was deprotected with BF₃•OEt₂ in the last step of their synthesis. That said, it was hypothesized that the MOM-protected B-ring alcohol could be kept until the very end of the synthesis and that ginkgolide C (**3.1C**) could be obtained by deprotection of the MOM with BF₃•OEt₂.

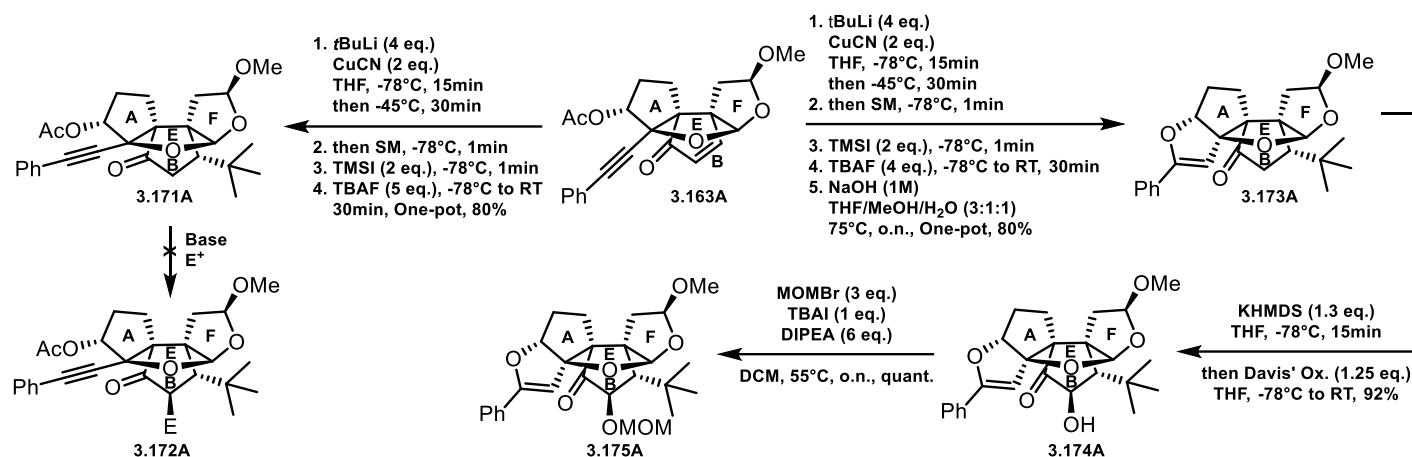


Figure 3.46: Conjugate Addition/*5-endo-dig* Cyclization and α -Hydroxylation of B-Ring Ketone Starting from Enone **3.163A**

Next, efforts were dedicated to form the D-ring lactone. Ozonolysis of enol ether **3.175A**, did not lead to the desired product. Addition of OsO₄ (with either NaIO₄, Oxone or NMO) either gave no conversion or did not lead to the desired product. Pleasantly, treatment with RuO₄ (generated with RuCl₃•xH₂O/NaIO₄) was successful in performing the oxidative cleavage of enol ether **3.175A** yielding lactol **3.176A** and lactone **3.177A**.¹²³ Running the reaction at lower temperatures (0° C to 50 °C or RT to 50 °C) gave lower yields of **3.176A/3.177A**, whereas running the reaction at 75 °C led to a decreased yield of **3.176A** (most likely due to degradation). Adding more NaIO₄ or heating at 50 °C for a longer period of time did not lead to further oxidation of the lactol to the corresponding lactone. This led to the hypothesis that following the oxidative cleavage (to the benzoyl and the aldehyde), only the aldehyde can be oxidized to the carboxylic acid, however, if the aldehyde is hydrated to the *gem*-diol (which cyclizes onto the B-ring ketone to form the bis-hemiacetal), this species cannot undergo further oxidation with RuO₄ (see **Figure 3.47**).

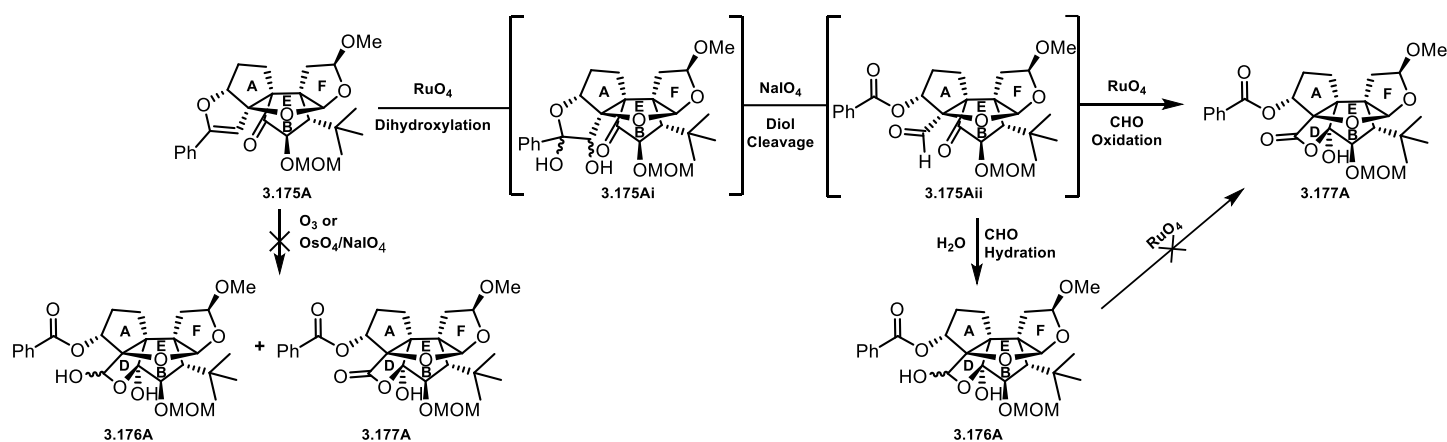


Figure 3.47: $\text{RuO}_4/\text{NaIO}_4$ -Catalyzed Oxidative Cleavage of Cyclic Enol Ether Yielding **3.176A** and **3.177A**

Running the $\text{RuO}_4/\text{NaIO}_4$ oxidative cleavage at 50 °C for 30 minutes turned out to be the best conditions yielding lactol **3.176A** and lactone **3.177A** in an 18% and 73% yield respectively. Fortunately, lactol **3.176A** was successfully oxidized to lactone **3.177A** in a 91% yield with I_2 and ground K_2CO_3 (ground K_2CO_3 was essential to increase its surface area and efficacy in DCM).¹²⁴ With lactone **3.177A** in hand, three tasks needed to be accomplished. First, the benzoyl needed to be deprotected. Second, the lactone had to be opened (to form the carboxylate/ketone), which would enable the reduction of the ketone. Third, following the reduction of the ketone, the D-ring lactone would be obtained via lactonization of the B-ring alcohol onto the nearby carboxylic acid. All these three tasks were accomplished in a one-pot procedure.

The first stage consisted of adding an aqueous solution of NaBH_4 to the starting material (in THF). Having the NaBH_4 dissolved in water greatly increased its solubility in the reaction mixture, enabling the formation of the carboxylate/ketone, and ultimately, the reduction of the ketone to the corresponding alcohol. In the second stage of the reaction, NaOH (1 M) as well as acetone were added to the reaction mixture which was heated to 50 °C overnight. The purpose for adding NaOH was to fully deprotect the benzoyl. Addition of acetone had two purposes in this stage. First, it quenched the majority of the NaBH_4 . Second, it ensured a good miscibility between the organic and aqueous phases. Finally, dilute acetic acid was added to quench any remaining NaBH_4 , NaOH , hydroxylate and carboxylate. Additionally, the acetic acid lowered the pH of the solution sufficiently to enable the intramolecular Fischer esterification of the carboxylic acid with the B-ring alcohol, thus forming D-ring lactone **3.178A** (see **Figure 3.48**).

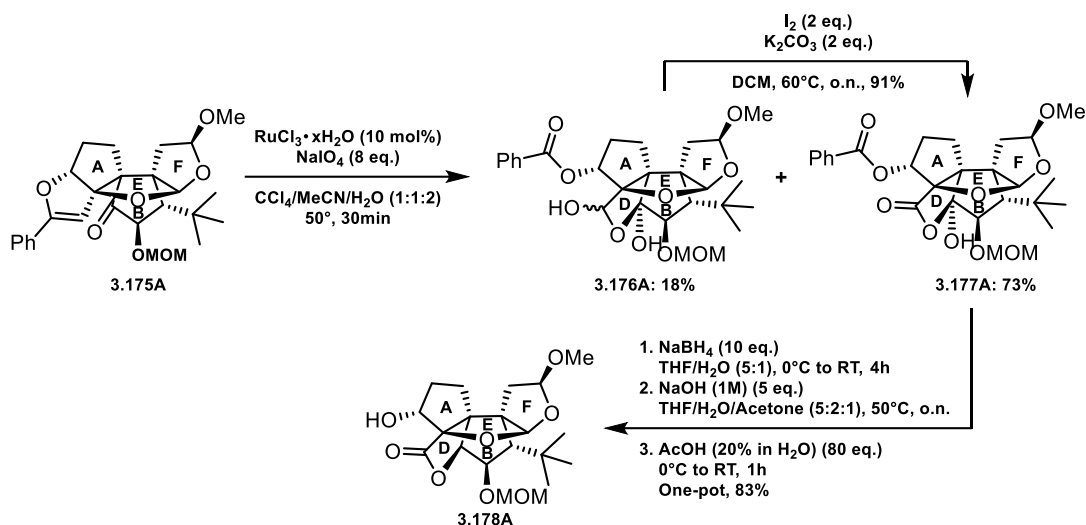


Figure 3.48: D-Ring Formation via Enol Ether Oxidative Cleavage Followed by Ketone Reduction, Benzoyl Deprotection and Fischer Lactonization (Starting from **3.175A**)

After forming the D-ring lactone and deprotecting the benzoyl, A-ring alcohol **3.178A** was oxidized directly to the corresponding enone **2.179A** in a 31% yield with IBX and 4-methoxypyridine *N*-oxide (MPO) using the procedure developed by Baran and Nicolaou.¹²⁵ However, due to the poor yield obtained for this transformation, the same enone was prepared in a higher yielding 3-step procedure. First, the alcohol was oxidized to the ketone with Dess-Martin periodinane. Second, the α -phenylselenide **3.178Ai** (formed via the enol) was prepared with PhSeCl and anhydrous HCl .^{2b} Third, the oxidation of the phenylselenide to the corresponding selenoxide was performed with H_2O_2 and pyridine in a biphasic $\text{DCM}/\text{H}_2\text{O}$ (10:1) mixture, which allowed for the *syn*-selenoxide elimination to occur, and the desired enone **3.179A** was obtained in a 75% yield over 3 steps.¹²⁶ At first, Crimmins' one-pot procedure was attempted to convert the ketone directly to enone **3.179A** (1. PhSeCl/HCl ; 2. $\text{NaHCO}_3/\text{aq. NaIO}_4$); however, the homogenous reaction led to degradation of the desired product. Then, F-ring acetal **3.179A** was submitted to Corey's MeOH elimination conditions ($\text{PPTS}/\text{pyridine}$ in PhCl at 135°C), but unfortunately, the MOM group did not survive the acidity of the PPTS at this elevated temperature. Subsequently, the B-ring alcohol cyclized onto the E-ring which then opened the F-ring yielding the corresponding aldehyde **3.182** (instead of the desired product **3.183**). To remedy this problem, acetic anhydride was added to the reaction mixture so that once the MOM group deprotected with the harsh reaction conditions, the $\text{Ac}_2\text{O}/\text{pyridine}$ quickly acetylated the B-ring

alcohol (which was stable under these reaction conditions). Following the protecting group change, elimination of MeOH (to form the F-ring enol ether) generated the target intermediate **3.181** in a 66% yield along with a 9% yield of acetylated B-ring alcohols **3.180A/B** (4.8:1 anomeric mixture) which did not undergo MeOH elimination (**3.180A/B** were resubmitted to the reaction conditions to yield the target intermediate **3.181** in a 51% yield) (see **Figure 3.49**). It is to be noted that all intermediates between the target intermediate **3.181** and ginkgolide C (**3.1C**) became much less soluble in organic solvents. Consequently, compounds had to be purified over silica gel with EtOAc/DCM and/or MeOH/DCM eluent systems to mitigate losses of product by crystallization onto the column.

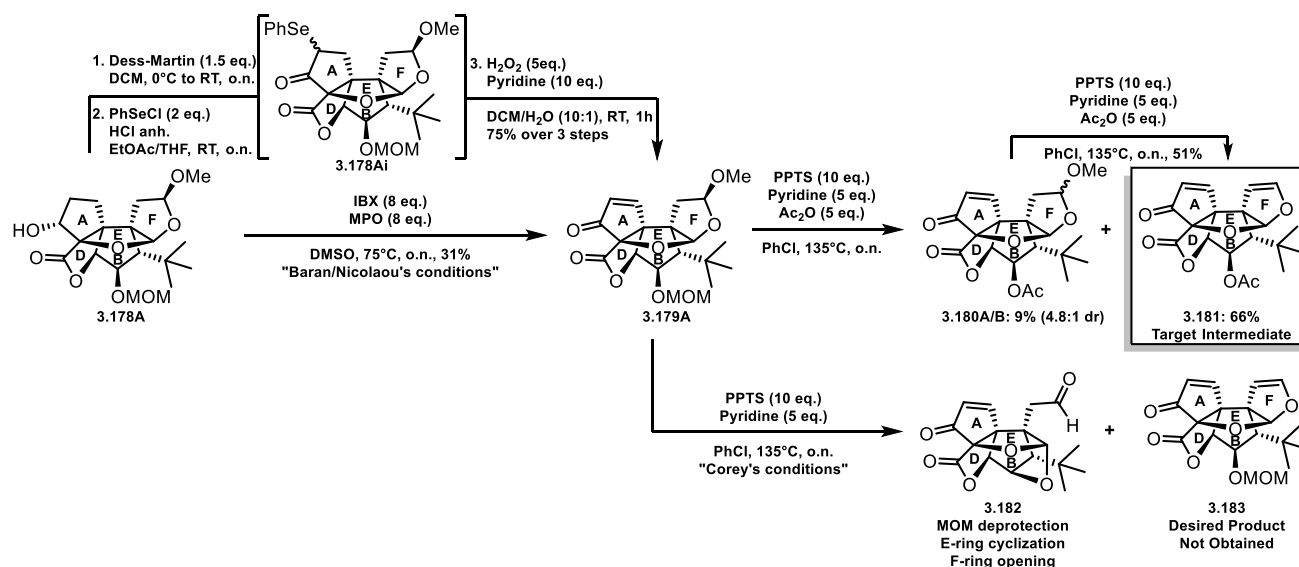


Figure 3.49: Preparation of Target Intermediate **3.181** from **3.178A** via A-Ring Oxidation and MeOH Elimination

3.1.4.6.3 Preparation of Target Intermediate **3.181** from Enone **3.163B**:

Having paved the way to target intermediate **3.181** from enone **3.163B**, the same synthetic route was applied to convert enone **3.163B** to target intermediate **3.181**; however, this task was not as seamless as we had hoped. The *tert*-butyl conjugate addition followed by the 5-*endo-dig* cyclization (to **3.173B**) proceeded well with a 77% yield for this one-pot transformation. Unlike the A anomer, α -hydroxylation of ketone **3.173B** with KHMDS/Davis' oxaziridine gave **3.174B** and **3.174Bdia** in an 88% yield (1.45:1 dr). It was hypothesized that the lack of

stereoselectivity for this transformation was either due to the OMe blocking the top face of the B-ring, or due to an interaction between the OMe and the *tert*-butyl that would lead to a different envelope conformation of the B-ring that would result in a lesser discrimination between the top and bottom faces of the B-ring when it comes to the α -hydroxylation of the B-ring ketone with Davis' oxaziridine. Fortunately, both diastereoisomers were separated and they were subsequently MOM-protected. The desired α -hydroxyketone **3.175B** was protected with MOMCl to afford the desired product in a 91% yield. The undesired α -hydroxyketone was also protected with MOMBr which gave a mixture of the undesired MOM-protected α -hydroxyketone **3.175Bdia** in a 76% yield as well as the desired MOM-protected α -hydroxyketone **3.175B** in a 12% yield. It is to be noted that this reaction had to be run at 70 °C (instead of 60 °C with the desired α -hydroxyketone) which resulted in a slight epimerization of the OMOM-bearing carbon. The ability to convert the undesired MOM-protected alcohol **3.175Bdia** to the desired diastereoisomer **3.175B** was exploited by submitting **3.175Bdia** to *t*BuOK/18-crown-6 in THF/*t*BuOH (70:1) at -78 °C. Surprisingly, an excellent yield of 86% was obtained for this transformation (see **Figure 3.50**).

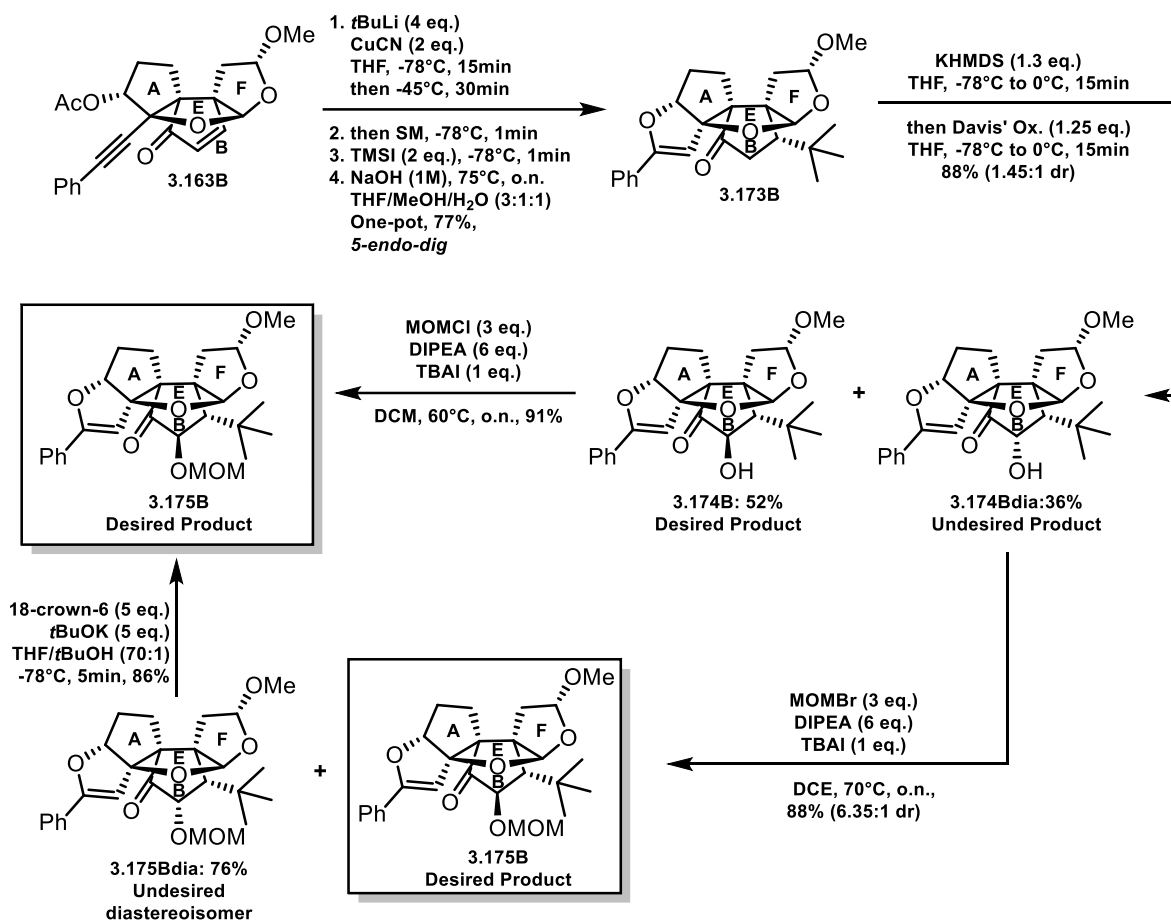


Figure 3.50: Conjugate Addition/5-*endo-dig* Cyclization and α -Hydroxylation/Epimerization of B-Ring Ketone Starting from Enone **3.163B**

The logic behind these reaction conditions was to develop a system that would be sufficiently basic to form the enolate while also ensuring that the reaction is reversible so it can equilibrate to the desired product. Amide bases, such as LDA, LiHMDS, NaHMDS and KHMDS, would be too basic (and irreversible) and would not allow for the formation of an equilibrium between the ketone/enolate. Fortunately, the *t*BuOK/*t*BuOH system (with 18-crown-6 ether coordinating to the potassium cation) was in the appropriate pK_a range to form an equilibrium between the *O*-protected α -hydroxyketone and its corresponding enolate. The equilibrium favoured the formation of the desired thermodynamic product **3.175B** (*anti* relationship between *tert*-butyl and OMOM) which was obtained in an 86% yield. The kinetic product **3.175Bdia** had a more accessible α -hydrogen which made for rapid interconversion between

3.175B and **3.175Bi**. However, once the more thermodynamically stable product **3.175B** was formed, deprotonation of its α -hydrogen was much more difficult due to its proximity to the bulky *tert*-butyl (see **Figure 3.51**).

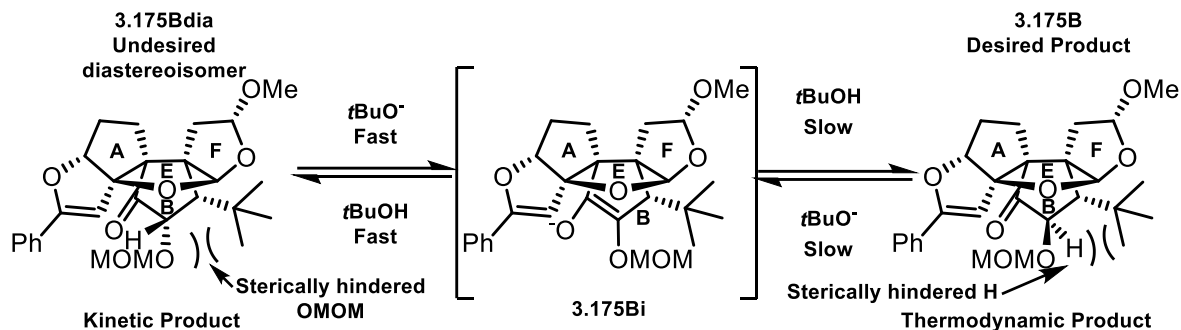


Figure 3.51: Justification for Epimerization with $t\text{BuOK}/t\text{BuOH}$ System

The $\text{RuO}_4/\text{NaIO}_4$ oxidative cleavage of **3.175B** proceeded well, giving lactol **3.176B** and lactone **3.177B** in a 19% and 76% yield respectively. Pleasantly, the reduction/debenzoylation/Fischer lactonization generated alcohol **3.178B** in quantitative yield. An X-ray structure for **3.178B** (dimer with CDCl_3) was obtained (**3.178BXRay**). Enone **3.179B** was obtained in a 28% yield by oxidizing the A-ring alcohol with IBX/MPO. The one-step IBX/MPO procedure was chosen for the B anomer because the usually higher yielding 3-step procedure (for the A anomer) led to some issues. The Dess-Martin oxidation proceeded well, however, since the OMe was facing outwards (away from the A-ring, thus reducing steric hindrance), submitting the ketone to the selenation conditions ($\text{PhSeCl}/\text{anhydrous HCl}$) gave a mixture of the mono- and diselenated ketones. Selenation with $\text{KHMDs}/\text{PhSeCl}$ was also attempted, but this failed to generate the desired product reliably. Finally, target intermediate **3.181** was obtained in a 60% yield following the procedure with PPTS, pyridine and Ac_2O in PhCl at 135°C (see **Figure 3.52**).

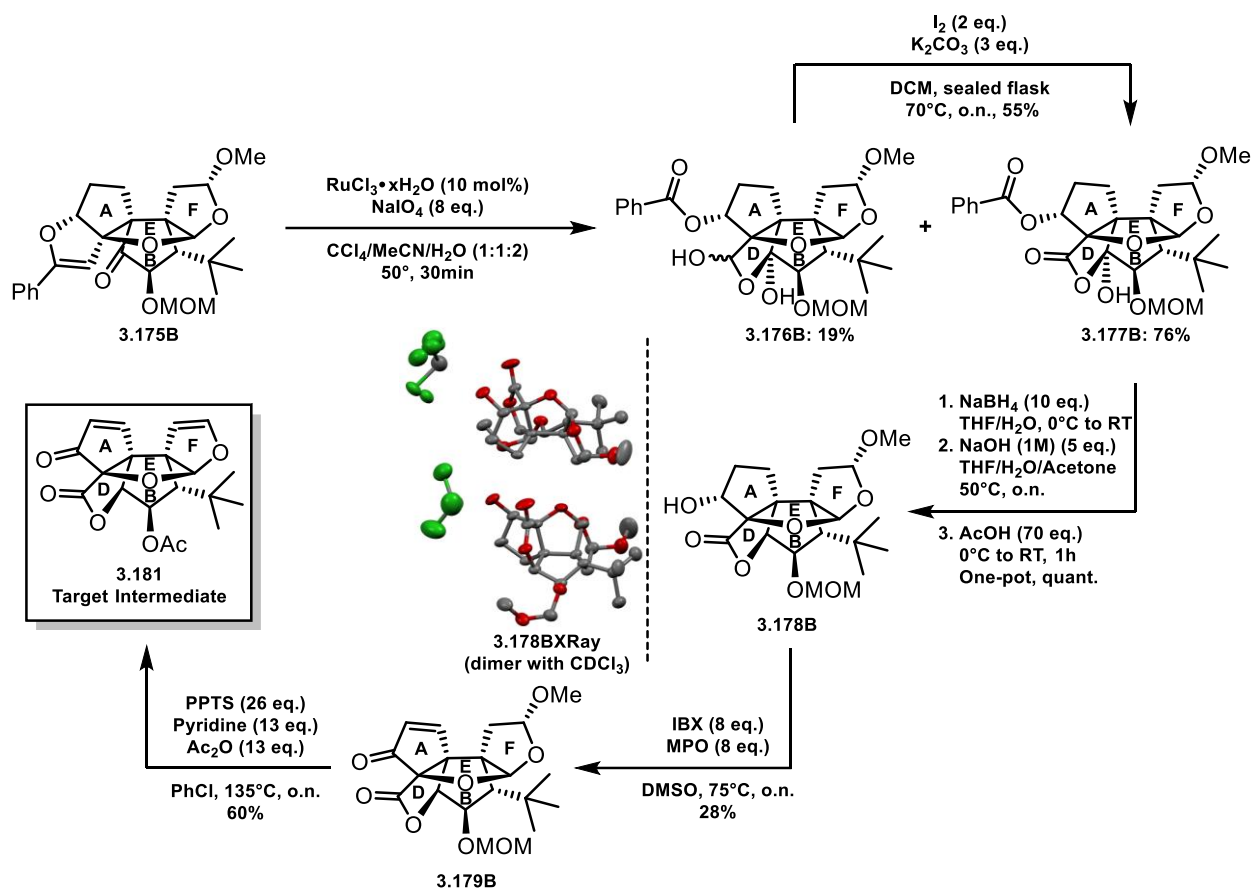


Figure 3.52: Preparation of Target Intermediate **3.181** from **3.175B** via Enol Ether Oxidative Cleavage, Reduction/Benzoyl Cleavage/Fischer Lactonization, A-Ring Oxidation and MeOH Elimination

3.1.4.6.4 Corey- and Crimmins-Inspired Endgame for the Total Synthesis of ($\pm$)-Ginkgolide C from Target Intermediate **3.181**:

With target intermediate **3.181** in hand, we entered the endgame of our synthesis. First, attempts were made to replicate Corey's conditions for epoxidation of the A-ring enone with the bulky trityl hydroperoxide and benzyltrimethylammonium isopropoxide ($[\text{BnNMe}_3]\text{OiPr}$); however, all attempts to synthesize this ammonium base (or to form it *in situ*) failed. Fortunately, it was found that the desired epoxide **3.184** could be obtained in a 57% yield using DBU as a base. Other bases such as *t*BuOK, TBAF, TBAOH and TBD (triazabicyclodecene) were screened; however, they either led to lower yields or no conversion of the starting material. In Corey's synthesis, they used a catalytic amount of base (0.5 eq.) and 5 eq. of trityl hydroperoxide because the trityl hydroxylate formed as a by-product can in turn deprotonate isopropanol/trityl

hydroperoxide. However, when using DBU as a base, in order to achieve full conversion of the starting material, at least 1-1.1 equivalents of DBU was necessary. It was determined that 2-2.4 eq. of trityl hydroperoxide was sufficient for this transformation. The use of 3-5 eq. of hydroperoxide did not lead to higher yields. Next, Corey's conditions were utilized for the 1,2-addition of the *Z*-enolate of *tert*-butyl propionate (formed with LDA in THF/HMPA (4:1)). The reaction gave the desired 1,2-addition adduct **3.185** in a 59% yield as well as the epoxide-opened lactonization product **3.186** in a 4% yield following purification by silica gel chromatography. The lactonized product was not observed upon analysis of the crude by ¹H NMR which led us to believe the cyclization must have occurred during the purification due to the slight acidity of the silica. C-ring lactone **3.186** was obtained in an 89% yield via activation of the epoxide with 5 eq. of CSA in DCM which allowed for the lactonization of the *tert*-butyl ester onto the epoxide (with loss of isobutene)(see Part 1 of **Figure 3.53**).

In Corey's total synthesis of ginkgolide B (**3.1B**), his final 4 steps involve a TBS-protection of the A-ring secondary alcohol, OsO₄ dihydroxylation of the F-ring enol ether, I₂/CaCO₃ oxidation of the lactol to the lactone and TBS-deprotection with BF₃•OEt₂.¹ Nevertheless, all attempts to dihydroxylate the F-ring's enol ether with OsO₄ failed to give any conversion. Attempts of enol ether epoxidation with peracids such as MCPBA, peracetic acid and performic acid also failed to convert the starting material. It is to be noted that Crimmins achieved the total synthesis of ginkgolide B (**3.1B**) in only 2 steps, compared to 4 steps for Corey's synthesis, from intermediate **3.197**. Namely by the epoxidation of enol ether **3.197** (to epoxide **3.203**) with freshly distilled DMDO followed by the addition of Br₂ and NaOAc in a mixture of AcOH and H₂O which yielded (±)-ginkgolide B (**3.1B**)(See **Figure 3.57**).² Attempts to perform the epoxidation using DMDO or TFDO (with acetone/oxone or trifluoroacetone/oxone) formed *in situ* failed to give any conversion. Fortunately, the desired F-ring epoxide **3.187** was obtained by following Crimmins' procedure using freshly distilled DMDO in acetone.¹²⁷ The crude epoxide was submitted to Br₂/NaOAc in AcOH/H₂O which yielded the desired α-hydroxylactone **3.189** (or *O*-acetylginkgolide C) (57% yield over 2 steps) as well as the *O*-acetyl lactol **3.188** as a side product (23% yield over 2 steps). The side product was most likely obtained by AcO⁻/AcOH opening up the epoxide instead of H₂O. Additionally, the stereochemistry of the side product has a *syn*-

relationship between the OH and OAc groups (of the F-ring) because their coupling constant (in ^1H NMR) was only 2.6 Hz which is relatively small (consistent with *syn*-protons). The *O*-acetyl lactol was converted to a mixture of *O*-acetylginkgolide C (**3.189**) and ($\pm$)-ginkgolide C (**3.1C**) (poor yield, 1.5:1 ratio) with $\text{I}_2/\text{K}_2\text{CO}_3$ in $\text{MeOH}/\text{H}_2\text{O}$ at RT overnight. Finally, ($\pm$)-ginkgolide C (**3.1C**) was obtained in a 95% yield from *O*-acetylginkgolide C (**3.189**) with K_2CO_3 in MeOH at RT overnight (see Part 2 of **Figure 3.53**). The synthesis of ($\pm$)-ginkgolide C (**3.1C**) was complete as evidenced by comparison of the synthetic material to an authentic analytical standard of the natural product. The synthetic material provided identical ^1H and ^{13}C spectroscopic data. The final synthetic route required 26 linear steps from 2-allylcyclopentanone **3.6**.

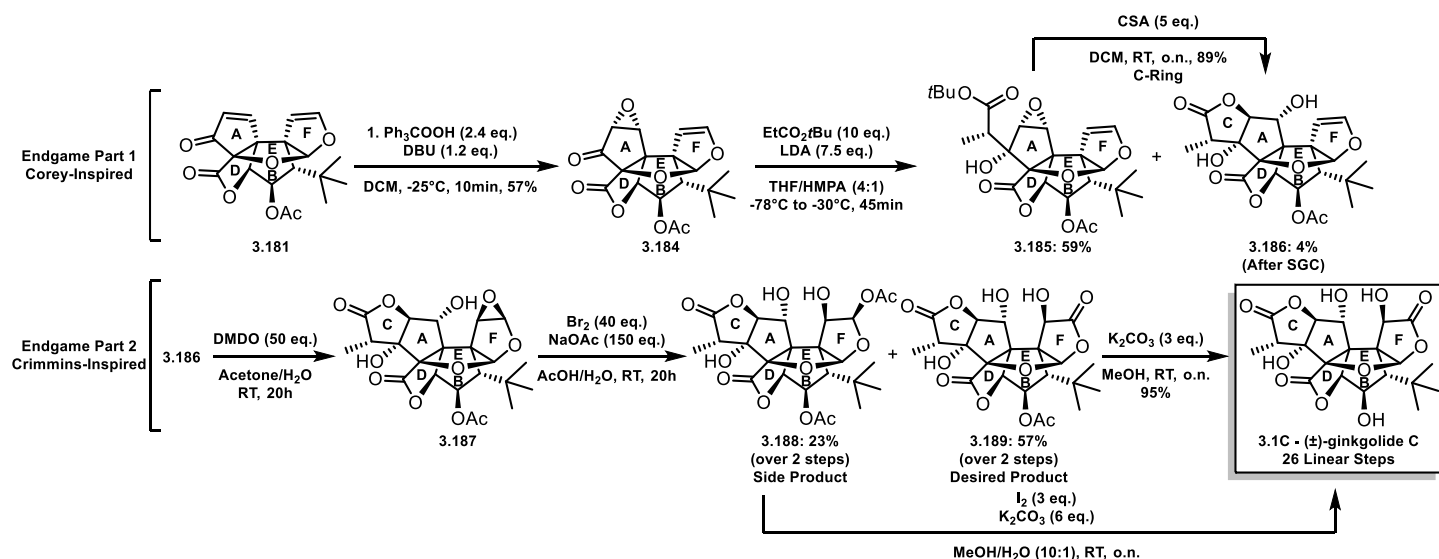


Figure 3.53: Corey- and Crimmins-Inspired Endgame for the Total Synthesis of ($\pm$)-Ginkgolide C via C-Ring Formation and F-Ring Oxidation

3.1.4.6.5 Formal Syntheses of ($\pm$)-Ginkgolide A and ($\pm$)-Ginkgolide B from Enone **3.163B** by Intercepting Corey's Intermediate:

As a side project, the formal syntheses of ($\pm$)-ginkgolide A/B (**3.1A/3.1B**) were achieved by intercepting Corey's intermediate **3.192B**.¹ Following the conjugate addition of the *tert*-butyl onto enone **3.163B**, the reaction was quenched with TBAF to convert the TMS enol ether to ketone **3.171B** in an 81% yield (one-pot). The ketone was reduced with LiBH_4 from 0°C to RT (to ensure a diastereoselective reduction). Then, methanol was added, which reacted with the LiBH_4 (generating methoxide anions), thus promoting the *5-exo-dig* cyclization (formation of the D-

ring). Upon heating the reaction mixture, the OAc was deprotected and the desired product **3.190B** was obtained in a 92% yield for this one-pot procedure. After ozonolysis of the exocyclic enol ether, D-ring lactone **3.191B** was obtained in a 91% yield. Next, the A-ring alcohol was oxidized directly to enone **3.192B** with IBX/MPO (which concluded the formal synthesis of (±)-ginkgolide A (**3.1A**)(obtained in 10 additional steps)⁴ and (±)-ginkgolide B (**3.1B**)(obtained in 6 additional steps)(see **Figure 3.54**).¹

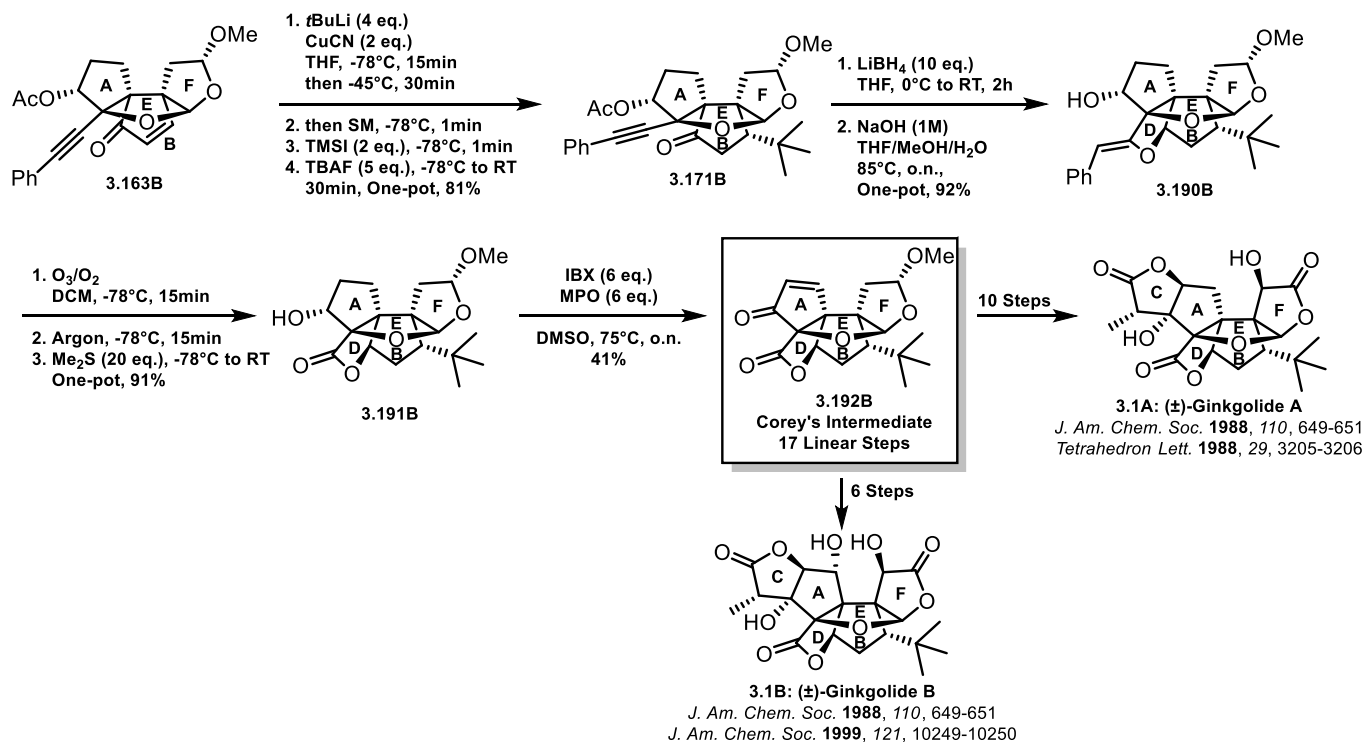


Figure 3.54: Formal Synthesis of (±)-Ginkgolide A and (±)-Ginkgolide B from Enone **3.163B** by Intercepting Corey's Intermediate

Ketone **3.171A** was reduced to the corresponding alcohol with LiBH₄, after which MeOH was added (forming LiOMe) which deprotected the A-ring acetate to afford diol **3.193A** in a 73% yield. Diol **3.193A** was underwent a Au(I)-catalyzed 5-*exo-dig* cyclization (forming the D-ring) with [IPrAu(MeCN)]SbF₆ yielding enol ether **3.190A** in a 50% yield. Ozonolysis of enol ether **3.190A** generated D-ring lactone **3.191A** in an 83% yield. Moreover, X-ray structures for **3.171A** (enantiomer)(**3.171AXRay**), **3.193A** (**3.193AXRay**) and **3.191A** (dimer)(**3.191AXRay**) were obtained (see **Figure 3.55**)

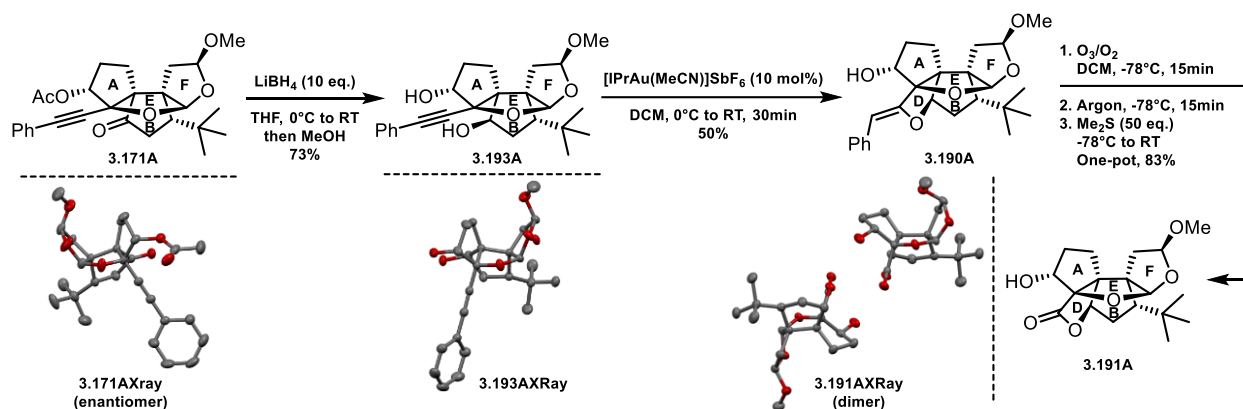


Figure 3.55: Towards the Formal Synthesis of (±)-Ginkgolide A and (±)-Ginkgolide B from Ketone **3.171A**

As previously stated, starting from Corey's intermediate **3.192B** (from his total synthesis of (±)-ginkgolide B), (±)-ginkgolide A was obtained in 10 steps. First, F-ring enol ether **3.194** was obtained by elimination of MeOH with PPTS/pyridine in PhCl at 135 °C. Then, the A-ring enone was epoxidized to **3.195** with trityl hydroperoxide and $[\text{BnNMe}_3]\text{O}i\text{Pr}$. Next, a 1,2-addition onto the ketone was performed with the *Z*-enolate of *tert*-butyl propionate (prepared with LDA in THF/HMPA (4:1)) to afford **3.196**. 1,2-Addition adduct **3.196** underwent an acid-catalyzed lactonization onto the A-ring epoxide to form C-ring lactone **3.197**, thus intercepting a common intermediate in Corey's total syntheses of (±)-ginkgolide A and (±)-ginkgolide B. The secondary alcohol was converted to the corresponding xanthate **3.198** with 1,1'-thiocarbonyldiimidazole. Subsequently, the xanthate was deoxygenated to **3.199** with Bu_3SnH . OsO_4 -mediated dihydroxylation of the F-ring enol ether generated 1,2-diol **3.199** (with the incorrect stereochemistry at C-10 which was inverted over 2 steps following the I_2/CaCO_3 oxidation). Lactol **3.200** was oxidized to the corresponding lactone **3.201** with I_2/CaCO_3 in MeOH/ H_2O (10:1). Next, α-hydroxylactone **3.201** was oxidized to dihydrofuran-2,3-dione **3.202** with benzeneseleninic anhydride. Finally, (±)-ginkgolide A (**3.1A**) was obtained by reduction of the dihydrofuran-2,3-dione **3.202** with NaBH_4 (see **Figure 3.56**).⁴

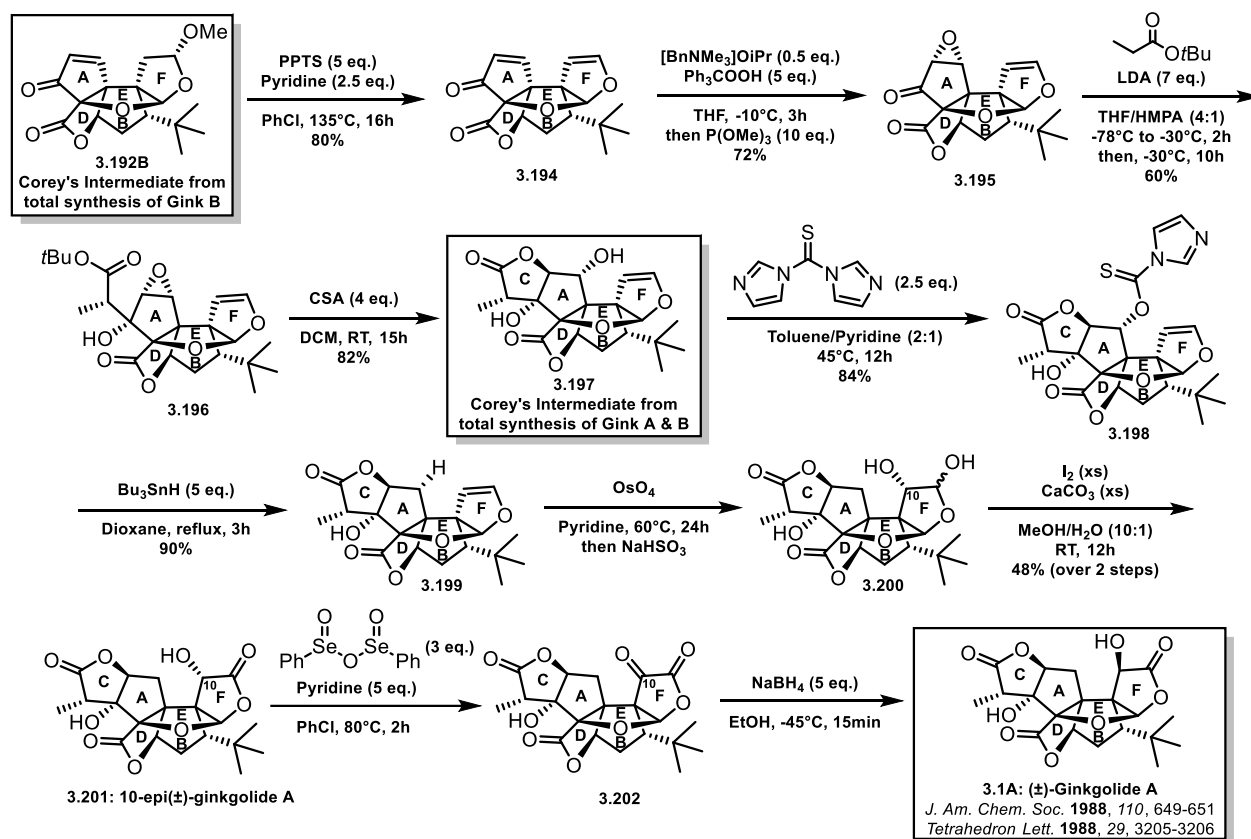


Figure 3.56: Synthetic Pathway for the Formal Synthesis of (±)-Ginkgolide A by Intercepting Corey's Intermediate

As for the formal synthesis of (±)-ginkgolide B (**3.1B**)(from Corey's intermediate **3.192B**), **3.197** (common intermediate in Corey's and Crimmins' syntheses of (±)-ginkgolide B) was obtained with the same 4 steps (1: MeOH elimination with PPTS/pyridine; 2: enone epoxidation; 3: 1,2-addition onto the ketone with *tert*-butyl propionate's Z-enolate; and 4: CSA-catalyzed lactonization/epoxide-opening) from **3.192B**. From common intermediate **3.197**, Corey completed the synthesis in 4 additional steps, although, Crimmins was able to finish the synthesis in only 2 additional steps. Crimmins proceeded to epoxidize enol ether **3.197** (to epoxide **3.203**) with freshly distilled DMDO which was subsequently opened and oxidized to the corresponding α-hydroxylactone with Br₂/NaOAc in AcOH/H₂O to afford (±)-ginkgolide B (**3.1B**)(see **Figure 3.57**).¹

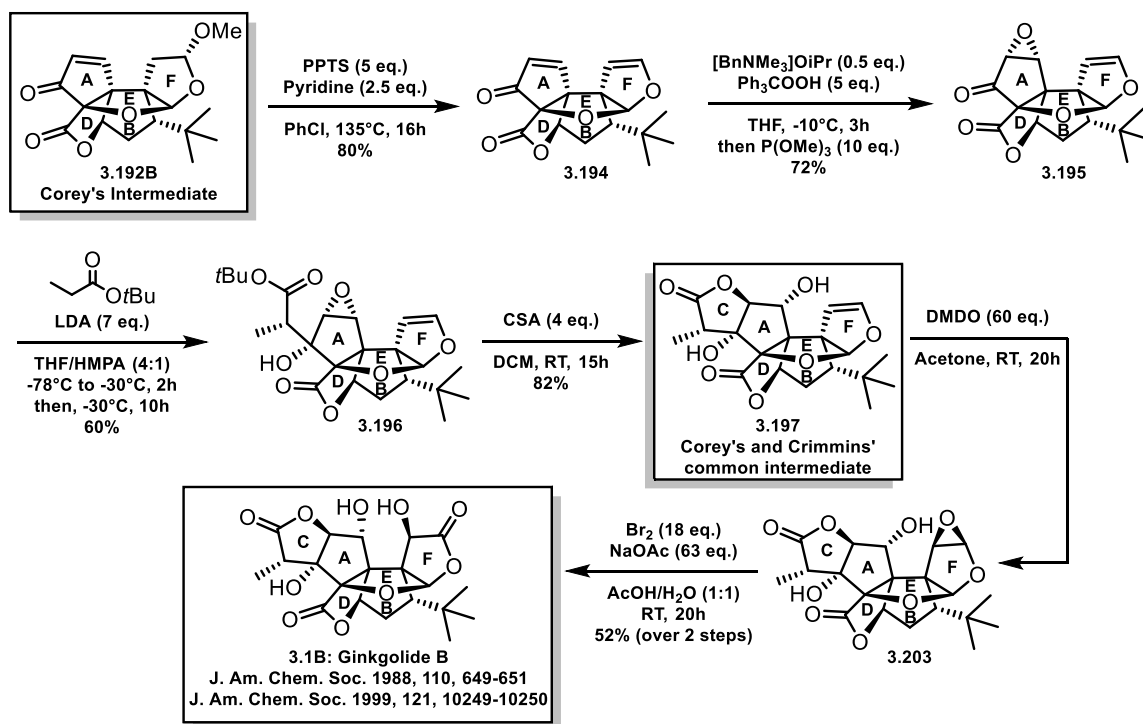


Figure 3.57: Synthetic Pathway for the Formal Synthesis of (±)-Ginkgolide B by Intercepting Corey's Intermediate and Crimmins' Intermediate

3.1.5 Future Work – Total Synthesis of (±)-Ginkgolide J

To further display the versatility of our synthetic sequence, three synthetic pathways to complete the first total synthesis of (±)-ginkgolide J were proposed starting from an advanced intermediate prepared in the total synthesis of (±)-ginkgolide C. The development of robust synthetic sequence leading to 4 out of the 5 main ginkgolides could prove useful for the preparation of fragments and analogues of the natural products which could be investigated for new or improved biological activity. Drawing inspiration from Corey's total synthesis of (±)-ginkgolide A, it was hypothesized that the first total synthesis of (±)-ginkgolide J could be achieved via a Barton-McCombie deoxygenation. Path A would start by preparing xanthate **3.204** (from **3.186**) on the secondary A-ring alcohol with 1,1'-thiocarbonyldiimidazole. Next, a Barton-McCombie deoxygenation would be performed with Bu₃SnH to afford **3.205**. Next, epoxidation of **3.205** with freshly distilled DMDO would lead to epoxide **3.206** (the reaction should occur on the top face of the molecule since the bottom face is shielded by the *tert*-butyl and the top face

is less hindered upon deoxygenation of the secondary alcohol). Epoxide-opening/lactol oxidation of **3.206** with Br_2/NaOAc (in $\text{AcOH}/\text{H}_2\text{O}$) would yield the desired α -hydroxylactone **3.207**. Finally, deprotection of the acetate with K_2CO_3 in MeOH would generate ($\pm$)-ginkgolide J (**3.1J**). Alternatively, paths B and C would rely on an OsO_4 dihydroxylation of the enol ether **3.205**. In Corey's total synthesis of ($\pm$)-ginkgolide A, dihydroxylation occurred on the bottom face of the F-ring giving the undesired stereochemistry on C10 (**3.208**).⁴ Path B would implicate the oxidation of lactol **3.208** to lactone **3.210** with I_2/CaCO_3 in $\text{MeOH}/\text{H}_2\text{O}$. Then, the C10 stereocenter would be inverted in 2 steps via: 1: Oxidation to dihydrofuran-2,3-dione **3.211** with benzeneseleninic anhydride; 2: Reduction of ketone **3.211** to α -hydroxylactone **3.207** with NaBH_4 . Finally, ($\pm$)-ginkgolide J would be obtained after deacetylation of **3.207** with K_2CO_3 in MeOH . Path C assumes the desired stereochemistry would be obtained at C10 after dihydroxylation with OsO_4 , after which, lactol **3.209** would be oxidized to α -hydroxylactone **3.212** with I_2/CaCO_3 in $\text{MeOH}/\text{H}_2\text{O}$ and the B-ring alcohol would be deprotected with K_2CO_3 in MeOH to yield ($\pm$)-ginkgolide J (**3.1J**) (see **Figure 3.58**).

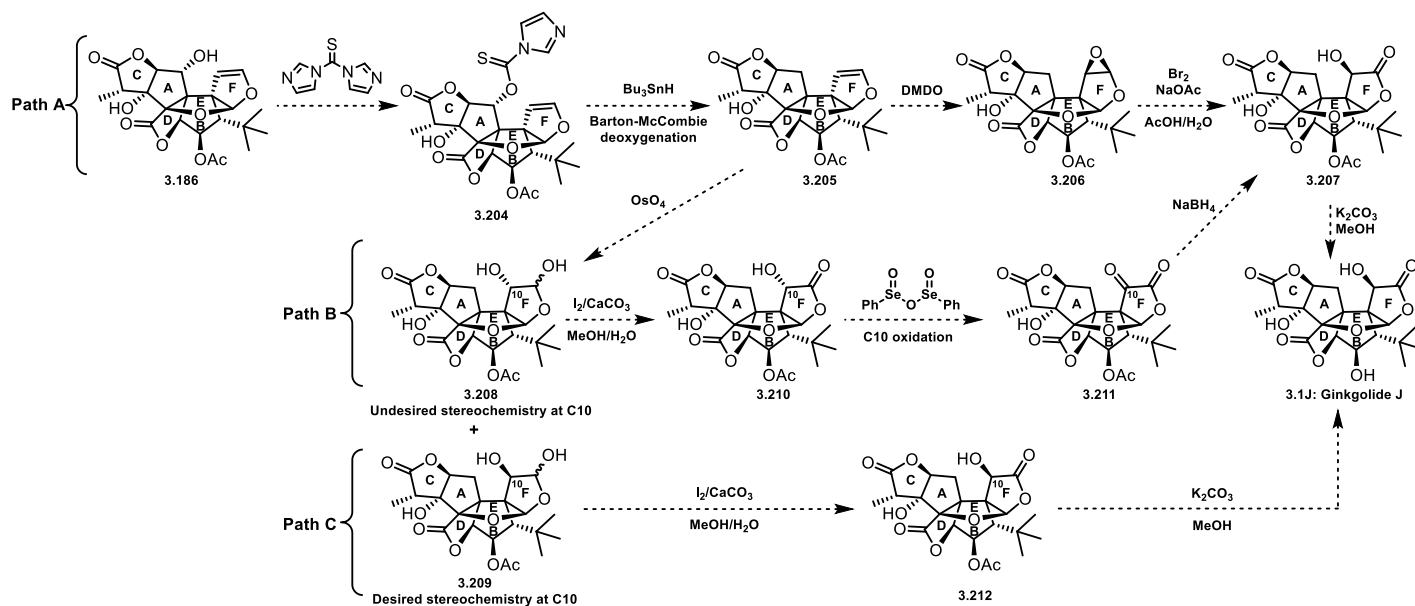


Figure 3.58: Proposed Synthetic Pathways for the Total Synthesis of ($\pm$)-Ginkgolide J

3.1.6 Conclusion:

In conclusion, multiple synthetic pathways were explored in order to synthesize the complex natural product, ginkgolide C (**3.1C**). The first total synthesis of (±)-ginkgolide C (**3.1C**) was completed in 26 linear steps in a 0.19% overall yield from 2-allylcyclopentanone. The synthesis of (±)-ginkgolide C (**3.1C**) was completed as evidenced by comparison of the synthetic material to an authentic analytical standard of the natural product. The synthetic material provided identical ¹H and ¹³C NMR spectroscopic data.

As a side project, the formal synthesis of (±)-ginkgolide A (**3.1A**) was completed by intercepting Corey's intermediate **3.192B** (from which (±)-ginkgolide A (**3.1A**) can be prepared in 10 additional steps) in 17 linear steps from 2-allylcyclopentanone **3.6** (0.11% yield over 27 steps).^{1,4} Finally, the shortest synthesis of (±)-ginkgolide B (**3.1B**) was achieved by intercepting the same intermediate (**3.192B**)(from which (±)-ginkgolide B (**3.1B**) can be obtained in 6 steps) in 17 linear steps from 2-allylcyclopentanone **3.6** (0.22% yield over 23 steps). After 4 steps, Corey's/Crimmins' common intermediate (**3.197**) can be obtained from which Crimmins prepared (±)-ginkgolide B (**3.1B**) in an additional 2 steps.^{1,2} The completion of both formal syntheses was evidenced by comparison of the synthetic material (**3.192B**) with the ¹H NMR and IR spectra of **compound 18** in Corey's total synthesis of (±)-ginkgolide B (**3.1B**).¹ In comparison, Corey completed the first total syntheses of (±)-ginkgolide A (**3.1A**) in 26 steps in a 0.12% yield as well as (±)-ginkgolide B (**3.1B**) in 24 steps in a 0.17% yield (from 1-morpholinocyclopentene). Crimmins managed to synthesize (±)-ginkgolide B (**3.1B**) in a higher yielding 27 step sequence with an overall 2.4% yield (from 3-furaldehyde).

When comparing our synthetic approach to Corey's and Crimmins' respective syntheses of ginkgolides, similar endgames strategies were employed in all syntheses. Namely, formation of the C-ring followed by oxidation of the F-ring. In contrast, Corey and Crimmins both installed the *tert*-butyl group in the second step of their respective syntheses; however, we decided to install the *tert*-butyl in middle of our synthesis (step 14 out of 26) via a conjugate addition of a *tert*-butyl cuprate onto enones **3.163A/B**. This approach enabled the hydroxylation of the B-ring (via α-hydroxylation of ketones **3.173A/B**) which was crucial to complete the total synthesis of

ginkgolide C (**3.1C**). In addition, both Corey and Crimmins employed [2+2] cycloadditions to construct their ring systems; whereas, the synthetic pathway described in this work relied on a RCM as well as redox and acid/base reactions.

The synthetic pathway developed during this work was undoubtedly successful due to four key features. Namely: 1: The Claisen rearrangement/ring-closing metathesis sequence proved to be especially useful to rapidly form quaternary carbons and spirocyclic ring systems; 2: The diastereoselective (due to the phenylacetylene shielding the top face of the B-ring) deconjugative alkylation of α,β -unsaturated ester **3.97** was crucial in order to set the second quaternary carbon of ginkgolide; 3: The development of several one-pot procedures (with careful planning of functional groups compatibility) helped to reduce the amount of steps and purifications required in this synthetic pathway; 4: The one-pot conjugate addition with subsequent *5-endo-dig* cyclization of **3.163A/3.163B** to **3.173A/3.173B** was crucial to complete the total synthesis of ginkgolide C (**3.1C**) as it was necessary to enable the α -hydroxylation of the B-ring ketone.

The contributions to science detailed in this work can be summarized by 2 key achievements. First, this work describes an in-depth exploration of many synthetic pathways in order to achieve the first total synthesis of ginkgolide C (**3.1C**), the most oxygenated and most complex member of the family, in addition to the formal syntheses of ginkgolide A (**3.1A**) and ginkgolide B (**3.1B**) (shortest synthesis of the natural product). The development of total syntheses of natural products can be an effective strategy to synthesize their fragments and analogues which can be used to further understand their metabolism, biological activity, etc. Second, this work provides a testing ground for existing methodologies described in the literature. Especially in the case of the compact and densely functionalized structure of ginkgolide, functional group manipulation was consistently challenging. Consequently, it was often required to screen multiple reaction conditions to achieve the desired transformation.

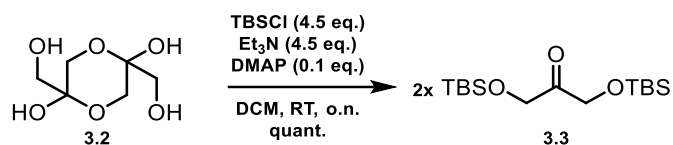
4.1 Chapter 4 – Experimental Section

4.1.1 General Information:

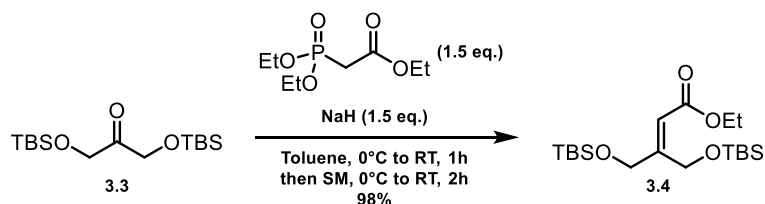
All reactions were performed under nitrogen or argon atmosphere in flame-dried glassware equipped with a magnetic stir bar and a rubber septum, unless otherwise indicated. All commercial reagents were used without further purification, unless otherwise noted. Diisopropylamine (DIPA) as well as hexamethylphosphoramide (HMPA) were distilled over CaH_2 and stored over flame dried 3 Å molecular sieves (1-2 mm beads) under argon atmosphere. Anhydrous tetrahydrofuran (THF), dichloromethane (DCM), toluene and methanol (MeOH) were prepared by storing over flame dried 3 Å molecular sieves (1-2 mm beads) under argon atmosphere. Reactions were monitored by thin layer chromatography (TLC) analysis. TLC plates (SiliaPlate TLC Plates, Aluminium-Backed, Silica, 200 μm , F254)) were viewed under UV light and stained with potassium permanganate or *p*-anisaldehyde staining solution. Column chromatography was carried out with silica gel 60 (230-400 mesh, Silicycle Inc.). Yields refer to products isolated after purification, unless otherwise stated. Proton nuclear magnetic resonance (^1H NMR) spectra were recorded on Bruker Avance 300 MHz, Bruker Avance II 400 MHz, and Bruker Avance III 600 MHz spectrometers. NMR samples were dissolved in deuterated chloroform, benzene, or acetone and chemical shifts are reported in ppm referenced to the solvent residual peak (Chloroform: 7.26 ppm; Benzene: 7.16 ppm; Acetone: 2.05 ppm). Data are reported as follows: chemical shift, multiplicity, coupling, integration. Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on the same Bruker instruments as in proton NMR at 75 MHz, 100 MHz or 150 MHz. Chemical shifts are reported in ppm referenced to the solvent residual peak (Chloroform: 77.16 ppm; Benzene: 128.06 ppm; Acetone: 29.84 ppm). IR spectra were recorded with an Agilent Technologies Cary 630 FTIR Spectrometer equipped with a diamond ATR module. HRMS were obtained on a Kratos Analytical Concept- Magnetic Sector Electron Impact Mass Spectrometer instrument and Micromass Q-TOF I – TOF Electrospray Ionisation mass spectrometer (University of Ottawa Mass Spectrum Centre). Melting points were determined with a Gallenkamp Melting Point Apparatus.

4.1.2 Experimental Procedures:

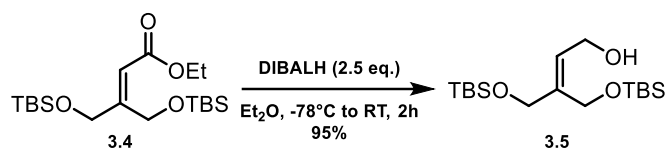
4.1.2.1 Gabriel Bellavance's Route:



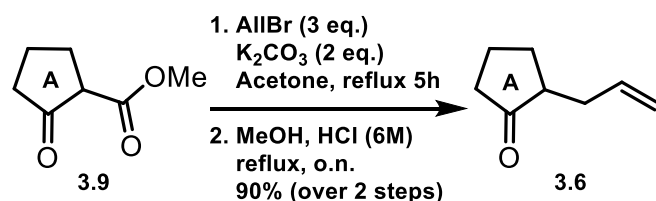
2,2,3,3,9,9,10,10-octamethyl-4,8-dioxo-3,9-disilaundecan-6-one (3.3). To a stirred solution of 1,3-dihydroxyacetone dimer **3.2** (10.0 g, 55.5 mmol dimer/111 mmol monomer) and *tert*-butyldimethylsilyl chloride (37.65 g, 249.8 mmol, 4.5 eq.) in 555 mL DCM were added Et₃N (34.82 mL, 249.8 mmol, 4.5 eq.) as well as DMAP (0.678 g, 5.55 mmol, 0.1 eq.). The reaction mixture was stirred at RT overnight. The reaction mixture was washed with (2 x 300 mL) H₂O, (2 x 300 mL) HCl (1 M), (2 x 300 mL) NaOH (1 M), and (2 x 300 mL) aq. sat. NaCl. The organic layer was dried over Na₂SO₄, filtered, and evaporated under reduced pressure. The crude was purified over silica gel (5-8% EtOAc/Hex) to afford ketone **3.3** as a clear oil (33.85 g, quant.): R_f 0.40 (5% EtOAc/Hex). Spectral data was identical to those found in the literature.¹²⁸



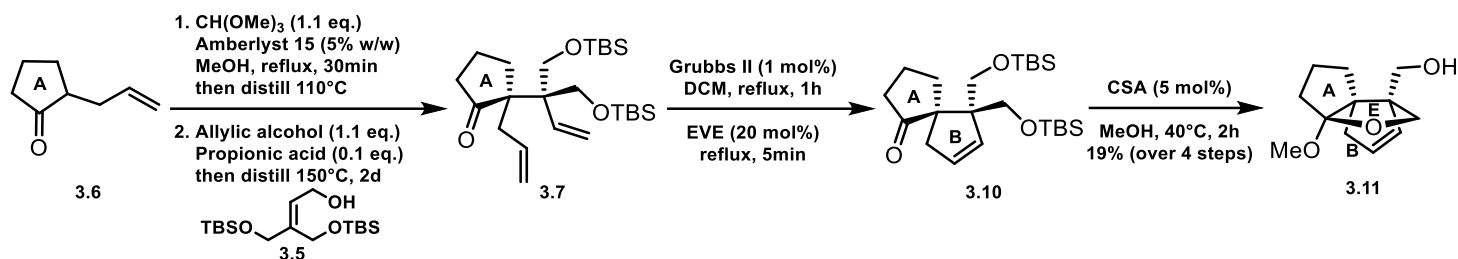
ethyl 4-((*tert*-butyldimethylsilyl)oxy)-3-(((*tert*-butyldimethylsilyl)oxy)methyl)but-2-enoate (3.4). To a suspension of NaH (60% in mineral oil, 14.53 g, 342.5 mmol, 1.5 eq.) in 740 mL toluene at 0 °C was added triethyl phosphonoacetate (66.4 mL, 343 mmol, 1.5 eq.) slowly over 5 min. The reaction mixture was warmed to RT and stirred for 1 h until the full consumption of the NaH. The solution was cooled to 0 °C, and ketone **3.3** (69.75 g, 228.3 mmol) was added and warmed to RT and stirred for 45 min (the solution turned dark red upon adding **3.3**). The reaction mixture was quenched with 500 mL aq. sat. NH₄Cl, extracted with (3 x 300 mL) EtOAc, dried over Na₂SO₄, filtered, and evaporated under reduced pressure. The crude was purified over silica gel (2.5-7.5% EtOAc/Hex) to afford α,β-unsaturated ester **3.4** as a clear oil (86.5 g, 98%): R_f 0.45 (5% EtOAc/Hex). Spectral data was identical to those found in the literature.¹²⁹ (note: if a thick paste forms upon adding ketone **3.3**, add EtOH 99% until it is completely dissolved)



4-((*tert*-butyldimethylsilyl)oxy)-3-(((*tert*-butyldimethylsilyl)oxy)methyl)but-2-en-1-ol (3.5). To a solution of α,β -unsaturated ester **3.4** (86.52 g, 222.6 mmol) in 1.00 L Et₂O at -78°C was added DIBALH (25% in hexane, 340 mL, 521.9 mmol, 2.5 eq.) slowly. The reaction mixture was stirred at -78°C for 30 min, warmed to RT and stirred for 2 h. The reaction mixture was cooled to 0 °C, 21 mL H₂O was added slowly, after which 21 mL NaOH (15%) and 52 mL H₂O were added (formation of a white precipitate). The white precipitate was filtered over a Buchner filter and rinsed thoroughly with (5 x 500 mL) Et₂O until all the desired product was extracted. The organic layer was dried over Na₂SO₄, filtered, and evaporated under reduced pressure. The crude was purified over silica gel (5-25% EtOAc/Hex) to afford allylic alcohol **3.5** as a clear oil (73.36 g, 95%): *R*_f 0.19 (10% EtOAc/Hex). Spectral data was identical to those found in the literature.¹³⁰



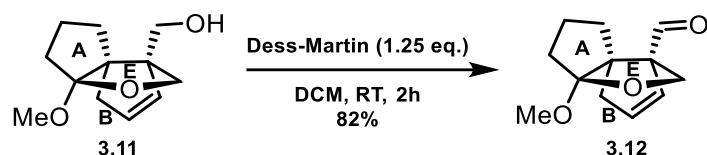
2-allylcyclopentanone (3.6). To a solution of methyl 2-oxocyclopentanecarboxylate **3.9** (20.00 mL, 22.89 g, 161 mmol), ground K₂CO₃ (44.5 g, 322 mmol, 2 eq.) and ground KI (2.67 g, 16.1 mmol, 0.1 eq.) in 350 mL acetone was added allyl bromide (41.81 mL, 58.44 g, 483 mmol, 3 eq.). The reaction mixture was heated to reflux for 5 h. The reaction mixture was filtered and evaporated under reduced pressure. The crude mixture was dissolved in 290 mL MeOH and 160 mL HCl (6 M) then was heated to reflux overnight. The reaction mixture was cooled to RT, extracted with (3 x 500 mL) DCM, dried over Na₂SO₄, filtered, and evaporated under reduced pressure. The crude was purified over silica gel (5-10% EtOAc/Hex) to afford 2-allylcyclopentanone **3.6** as a clear oil (17.93 g, 90%): *R*_f 0.37 (10% EtOAc/Hex). Spectral data was identical to those found in the literature.¹³¹



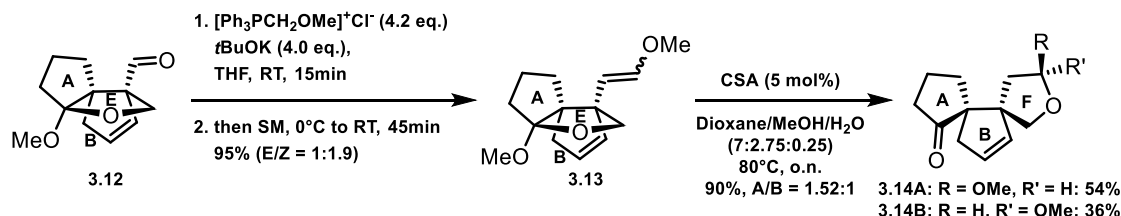
(3a-methoxy-2,3,3a,5,5a,8-hexahydro-1H-dicyclopenta[b,c]furan-5a-yl)methanol (3.11). To solution of α -allyl ketone **3.6** (1.00 g, 8.05 mmol) and Amberlyst® 15 (50 mg, 5% w/w) in 2 mL MeOH heated to reflux was added trimethyl orthoformate (0.969 mL, 8.86 mmol, 1.1 eq.). After 30 min of heating at reflux, the reaction mixture was cooled to RT, filtered over celite, and rinsed with DCM. The filtrate was distilled at 110 °C to remove any residual MeOH, DCM and methyl formate. Thereafter, the solution was cooled to RT and allyl alcohol **3.5** (2.93 g, 8.46 mmol, 1.1 eq.) as well as propionic acid (60 μL , 0.80 mmol, 0.1 eq.) were added. The solution was distilled at 150 °C for 2 days, cooled to RT and purified directly over silica gel (100% Hex then 2-3% EtOAc/Hex) to afford the desired bis α -allylated ketone **3.7** as a clear oil (inseparable mixture): R_f 0.36 (5% EtOAc/Hex). The mixture was used directly in the next step.

A solution of bis α -allylated ketone **3.7** and Grubbs' catalyst 2nd generation (67 mg, 0.081 mmol, 1 mol%) in 81 mL DCM was heated to reflux for 1 h. After the starting material was consumed, ethyl vinyl ether (155 μL , 1.62 mmol, 20 mol%) was added and the solution was refluxed for 5 min. The reaction mixture was cooled to RT and evaporated under reduced pressure. The crude was purified over silica gel (2-3% EtOAc/Hex) to afford the desired ring-closed spiro ketone **3.10** as a clear oil within an inseparable mixture that was used directly in the next step R_f 0.51 (10% EtOAc/Hex).

To a solution of spiro ketone **3.10** in 17mL MeOH was added CSA (40 mg, 0.17 mmol, 5 mol%). The resulting mixture was heated to 40 °C for 2 h, cooled to RT, evaporated under reduced pressure and the crude was purified directly over silica gel (20-30% EtOAc/Hex) to afford alcohol **3.11** as a clear oil (317.8 mg, 19% over 3 steps); R_f 0.42 (40% EtOAc/Hex); $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 5.91 (dt, J = 5.6, 2.3 Hz, 1H), 5.50 (dt, J = 5.8, 2.2 Hz, 1H), 3.76 (d, J = 8.7 Hz, 1H), 3.72 (d, J = 8.7 Hz, 1H), 3.69-3.57 (m, 2H), 3.28 (s, 3H), 2.93 (dt, J = 17.4, 2.2 Hz, 1H), 2.24-2.09 (m, 1H), 2.09-1.97 (m, 2H), 1.75-1.50 (m, 4H), 1.39 (s(br), 1H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 134.0, 132.2, 120.3, 75.1, 65.4, 65.2, 62.8, 51.0, 42.8, 34.5, 33.8, 23.9; IR (neat): 3453(br), 2916, 2354, 1110, 732 (cm^{-1}); HRMS (EI) calcd for $\text{C}_{12}\text{H}_{18}\text{O}_3$ $[\text{M}]^+$: 210.1256, found 210.1240.



3a-methoxy-2,3,3a,5,5a,8-hexahydro-1H-dicyclopenta[b,c]furan-5a-carbaldehyde (3.12). To a solution of alcohol **3.11** (2.72 g, 12.9 mmol) in 130 mL DCM at 0 °C was added Dess-Martin periodinane (6.86 g, 16.2mmol, 1.25 eq.). The solution was warmed to RT and stirred for 2 h. The reaction mixture was quenched with 125 mL 10% Na₂S₂O₃/aq. sat. NaHCO₃ (1:1), extracted with (3 x 100 mL) DCM, dried over Na₂SO₄, filtered, and evaporated under reduced pressure. The crude was purified over silica gel (5-10% EtOAc/Hex) to afford aldehyde **3.12** as a clear oil (2.21 g, 82%): *R_f* 0.55 (20% EtOAc/Hex); ¹H-NMR (400 MHz, CDCl₃) δ 9.57 (s, 1H), 6.03 (dt, *J* = 5.7, 2.3 Hz, 1H), 5.39 (dt, *J* = 5.7, 2.3 Hz, 1H), 4.53 (d, *J* = 9.0 Hz, 1H), 3.62 (d, *J* = 9.0 Hz, 1H), 3.30 (s, 3H), 3.10 (dt, *J* = 17.7, 2.4 Hz, 1H), 2.14 (dt, *J* = 17.6, 2.3 Hz, 1H), 2.10-2.00 (m, 1H), 2.00-1.88 (m, 1H), 1.74-1.51 (m, 4H); ¹³C-NMR (100 MHz, CDCl₃) δ 201.0, 136.8, 127.6, 119.5, 75.2, 71.2, 66.8, 51.1, 42.0, 35.3, 33.2, 23.7; IR (neat): 2936, 1716, 1118, 1047 (cm⁻¹); HRMS (EI) calcd for C₁₂H₁₈O₃ [M]⁺: 208.1099, found 208.1101.



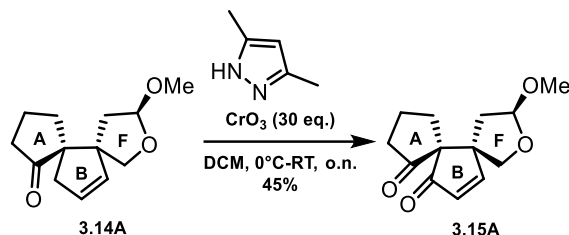
3-methoxy-2-oxadispiro[4.0.4⁶.3⁵]tridec-12-en-7-one (3.14A/3.14B). To a solution of (methoxymethyl)triphenylphosphonium chloride (4.22 g, 12.1 mmol, 4.2 eq.) in 29 mL THF at 0 °C was added *t*BuOK (1.29 g, 11.5 mmol, 4 eq.). The solution was warmed to RT, stirred for 15min (the solution turned deep red) and cooled to 0 °C. A solution of aldehyde **3.12** (600 mg, 2.88 mmol) in 10 mL THF was added to the reaction mixture. The reaction was stirred at 0 °C for 5 min, warmed to RT and stirred for 30 min. The THF was evaporated under reduced pressure and the remaining residue was dissolved in 50 mL Et₂O, washed with 50 mL aq. sat. NaCl, extracted with (3 x 50 mL) Et₂O, dried over Na₂SO₄, filtered, and evaporated under reduced pressure. The crude was purified over silica gel (2.5-10% EtOAc/Hex with 1% Et₃N) to afford an inseparable E/Z mixture of enol ethers **3.13** as a clear oil (644 mg, 95%, 1:1.9 E/Z ratio): *R_f* 0.41 (10% EtOAc/Hex). The impure mixture was used directly in the next step.

To a solution of E/Z enol ethers **3.13** (644 mg, 2.73 mmol) in 27 mL dioxane/MeOH/H₂O (7:2.75:0.25) was added CSA (31.7 mg, 0.136 mmol, 5 mol%). The resulting solution was heated at 80 °C overnight. The

solvent was evaporated under reduced pressure and the crude was purified directly over silica gel (15-25% EtOAc/Hex with 1% Et₃N) to afford alkene **3.14A** as pale white oil (327.2 mg, 54%) and alkene **3.14B** as pale white oil (218.0 mg, 36%) (90% total, 1.52:1 dr).

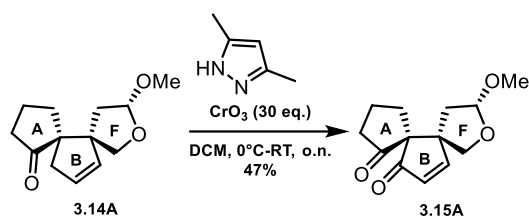
3.14A: *R_f* 0.30 (20% EtOAc/Hex); ¹H-NMR (400 MHz, CDCl₃) δ 5.85 (ddd, *J* = 5.7, 2.2, 1.7 Hz, 1H), 5.58 (dt, *J* = 5.2, 2.3 Hz, 1H), 5.04 (dd, *J* = 5.5, 2.4 Hz, 1H), 3.96 (d, *J* = 9.2 Hz, 1H), 3.54 (d, *J* = 9.2 Hz, 1H), 3.32 (s, 3H), 2.51 (ddd, *J* = 16.5, 2.7, 1.5 Hz, 1H), 2.40 (ddt, *J* = 18.7, 8.2, 2.1 Hz, 1H), 2.22 (dt, *J* = 16.5, 2.2 Hz, 1H), 2.22-1.96 (m, 4H), 1.91 (ddt, *J* = 12.6, 6.1, 2.0 Hz, 1H), 1.84 (dd, *J* = 13.9, 5.6 Hz, 1H), 1.84-1.69 (m, 1H); ¹³C-NMR (100 MHz, CDCl₃) δ 219.2, 139.3, 125.2, 105.0, 72.0, 59.4, 58.4, 54.9, 42.9, 42.8, 37.8, 34.4, 19.5; IR (neat): 2947, 1730, 1097 (cm⁻¹); HRMS (EI) calcd for C₁₂H₁₆O₂ [M-OCH₂]⁺: 192.1150, found 192.1155.

3.14B: *R_f* 0.22 (20% EtOAc/Hex); ¹H-NMR (400 MHz, CDCl₃) δ 5.92 (ddd, *J* = 5.7, 2.2, 1.8 Hz, 1H), 5.59 (dt, *J* = 5.3, 2.4 Hz, 1H), 4.98 (dd, *J* = 5.4, 1.8 Hz, 1H), 3.99 (d, *J* = 9.5 Hz, 1H), 3.71 (d, *J* = 9.5 Hz, 1H), 3.34 (s, 3H), 2.58 (ddd, *J* = 16.5, 2.7, 1.6 Hz, 1H), 2.41 (ddt, *J* = 18.5, 8.5, 2.2 Hz, 1H), 2.30-2.10 (m, 3H), 2.10-1.87 (m, 3H), 1.87-1.77 (m, 1H), 1.74 (dd, *J* = 13.5, 1.8 Hz, 1H); ¹³C-NMR (100 MHz, CDCl₃) δ 219.3, 138.9, 125.8, 105.1, 72.8, 60.3, 58.7, 55.0, 43.0, 42.5, 37.6, 34.3, 19.4; IR (neat): 2927, 1733, 1097, 987 (cm⁻¹); HRMS (EI) calcd for C₁₂H₁₆O₂ [M-OCH₂]⁺: 192.1150, found 192.1146.

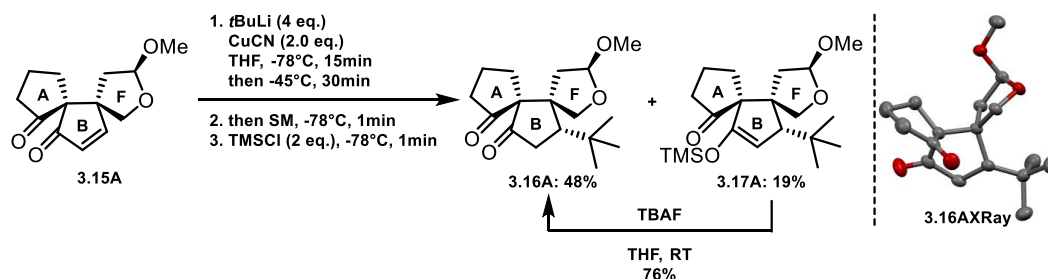


3-methoxy-2-oxadispiro[4.0.4⁶.3⁵]tridec-12-ene-7,11-dione (3.15A). To a solution of 3,5-dimethylpyrazole (14.5 g, 151 mmol, 30 eq.) in 60 mL DCM at 0 °C was added CrO₃ (15.1 g, 151 mmol, 30 eq.) slowly (exothermic). The solution was stirred for 15 min at 0 °C, followed by the addition of a solution of alkene **3.14A** (1.119 g, 5.034 mmol) in 15 mL DCM. The reaction mixture was warmed to RT and stirred for 2 days. The chromium was adsorbed onto silica (about 2 g silica/g CrO₃) and the solvent was evaporated under reduced pressure. The residue was rinsed thoroughly with Et₂O and filtered over celite until all the desired product was extracted from the residue. The filtrate was evaporated under reduced pressure and purified over silica gel (20-40% EtOAc/Hex) to afford enone **3.15A** as a light yellow solid (530 mg, 45%): mp 94-95 °C; *R_f* 0.31 (30% EtOAc/Hex); ¹H-NMR (400 MHz, CDCl₃) δ 7.72 (d, *J* = 5.6 Hz, 1H), 6.06 (d, *J* = 5.6 Hz, 1H), 5.07 (dd, *J* = 5.4, 2.0 Hz, 1H), 4.01 (d, *J* = 9.8 Hz, 1H), 3.48 (d, *J* = 9.7 Hz, 1H), 3.33 (s, 3H), 2.50-2.13 (m, 5H), 2.07-1.93 (m, 1H), 2.01 (dd, *J* = 14.1, 2.0 Hz, 1H), 1.89 (dd, *J* = 14.2, 5.4 Hz, 1H); ¹³C-NMR

(100 MHz, CDCl₃) δ 212.5, 204.1, 169.4, 129.4, 104.4, 70.7, 70.1, 57.0, 55.0, 42.5, 38.6, 30.1, 19.6; IR (neat): 1733, 1707, 1045 (cm⁻¹); HRMS (EI) calcd for C₁₃H₁₆O₄ [M]⁺: 236.1049, found 236.1045.



3-methoxy-2-oxadispiro[4.0.4⁶.3⁵]tridec-12-ene-7,11-dione (3.15B). To a solution of 3,5-dimethylpyrazole (9.55 g, 99.3 mmol, 30 eq.) in 45 mL DCM at 0 °C was added CrO₃ (9.93 g, 99.3 mmol, 30 eq.) slowly (exothermic). The solution was stirred for 15 min at 0 °C, after which was added a solution of alkene **3.14B** (736 mg, 3.31 mmol) in 10 mL DCM. The reaction mixture was warmed to RT and stirred for 2 days. The chromium was adsorbed onto silica (about 2 g silica/g CrO₃) and the solvent was evaporated under reduced pressure. The residue was rinsed thoroughly with Et₂O and filtered over celite until all the desired product was extracted from the residue. The filtrate was evaporated under reduced pressure and the crude was purified over silica gel (20-40% EtOAc/Hex) to afford enone **3.15B** as a light yellow solid (370mg, 47%): R_f 0.32 (30% EtOAc/Hex); ¹H-NMR (400 MHz, CDCl₃) δ 7.92 (d, *J* = 5.7 Hz, 1H), 6.09 (d, *J* = 5.7 Hz, 1H), 5.03 (dd, *J* = 5.2, 1.5 Hz, 1H), 4.07 (d, *J* = 10.0 Hz, 1H), 3.66 (d, *J* = 10.0 Hz, 1H), 3.37 (s, 3H), 2.52-2.22 (m, 4H), 2.19 (dd, *J* = 13.5, 5.3 Hz, 1H), 2.03-1.90 (m, 2H), 1.75 (dd, *J* = 13.6, 1.5 Hz, 1H); ¹³C-NMR (100 MHz, CDCl₃) δ 212.7, 204.1, 169.9, 130.1, 104.6, 72.1, 71.5, 57.3, 55.2, 43.4, 38.5, 29.9, 19.6; IR (neat): 1733, 1695, 1124, 1049, 833 (cm⁻¹); HRMS (EI) calcd for C₁₃H₁₆O₄ [M]⁺: 236.1049, found 236.1055.

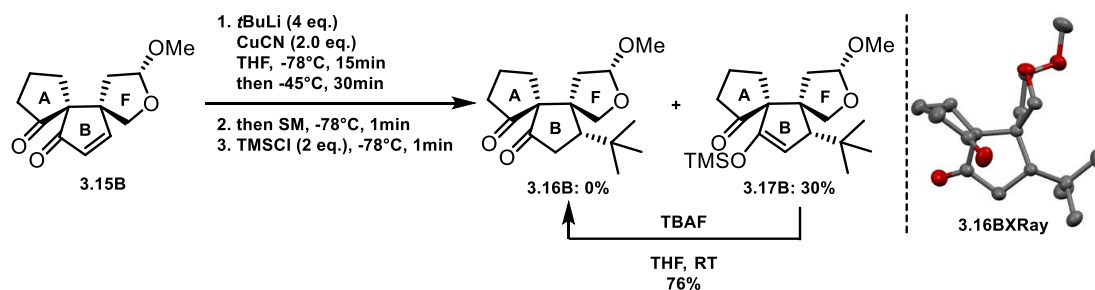


13-(*tert*-butyl)-3-methoxy-2-oxadispiro[4.0.4⁶.3⁵]tridecane-7,11-dione (3.16A). To a suspension of CuCN (37.9 mg, 0.423 mmol, 2 eq.) in 2.5 mL THF at -78 °C was added *t*BuLi (1.7 M in pentane, 498 μ L, 0.846 mmol, 4 eq.) dropwise over 5 min. The solution was stirred at -78 °C for 15 min, then was warmed to -45 °C for 30 min. The resulting mixture was cooled to -78 °C and a solution of enone **3.15A** (50.0 mg, 0.212 mmol) in 7.5 mL THF was added dropwise (solution turned from clear to red). Next, freshly distilled TMSCl

(53.7 μ L, 0.423 mmol, 2 eq.) was added dropwise (solution turned from red to brown). The reaction was quenched with 10 mL aq. sat. NH_4Cl , extracted with (3 x 10 mL) EtOAc, dried over Na_2SO_4 , filtered, and evaporated under reduced pressure. The crude was purified over silica gel (2-7.5% EtOAc/Hex) to afford diketone **3.16A** as a white solid (30.0 mg, 48%) and TMS enol ether **3.17A** (14.7 mg, 19%). TMS enol ether **3.17A** was then converted to diketone **3.16A** with HCl (0.5 M) in THF (9.0 mg, 76%).

3.16A: mp 138-139 $^\circ\text{C}$; R_f 0.49 (20% EtOAc/Hex); ^1H -NMR (400 MHz, CDCl_3) δ 5.10 (dd, J = 5.9, 1.5 Hz, 1H), 4.08 (d, J = 9.6 Hz, 1H), 3.51 (d, J = 9.6 Hz, 1H), 3.32 (s, 3H), 3.16 (dd, J = 14.3, 7.7 Hz, 1H), 2.54-2.32 (m, 3H), 2.32-1.89 (m, 6H), 1.48 (dd, J = 14.8, 1.6 Hz, 1H), 1.05 (s, 9H); ^{13}C -NMR (100 MHz, CDCl_3) δ 213.3, 212.2, 105.7, 74.3, 71.1, 57.8, 54.8, 50.1, 40.5, 40.0, 36.7, 33.5, 30.9, 29.4, 18.8; IR (neat): 2956, 2859, 1743, 1712, 1464, 1364, 1201, 1095, 1042, 984, 937, 870, 819, 746 (cm^{-1}); HRMS (EI) calcd for $\text{C}_{16}\text{H}_{23}\text{O}$ $[\text{M}-\text{OMe}]^+$: 263.1647, found 263.1625.

3.17A: HRMS (EI) calcd for $\text{C}_{16}\text{H}_{25}\text{O}_4\text{Si}$ $[\text{M}-t\text{Bu}]^+$: 309.1522, found 309.1511.

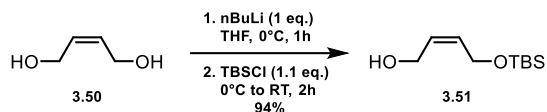


13-(tert-butyl)-3-methoxy-2-oxadispiro[4.0.4⁶.3⁵]tridecane-7,11-dione (3.16B). To a suspension of CuCN (15.3 mg, 0.171 mmol, 2 eq.) in 1 mL THF at -78°C was added $t\text{BuLi}$ (1.7 M in pentane, 201 μL , 0.342 mmol, 4 eq.) dropwise over 5 min. The solution was stirred at -78°C for 15 min, then was warmed to -45°C for 30 min. The resulting mixture was then cooled to -78°C and a solution of enone **3.15B** (50.0 mg, 0.0855 mmol) in 3 mL THF was added dropwise (the solution turned red). Freshly distilled TMSCl (21.7 μL , 0.171 mmol, 2 eq.) was added dropwise (solution turned from red to brown). The reaction was quenched with 10 mL aq. sat. NH_4Cl , extracted with (3 x 10 mL) EtOAc, dried over Na_2SO_4 , filtered, and evaporated under reduced pressure. The crude was purified over silica gel (2-7.5% EtOAc/Hex) to afford TMS enol ether **3.17B** (23.2 mg, 30%) which was subsequently converted to diketone **3.16B** (14.2 mg, 76%) with TBAF (1 M in THF, 69 μL , 0.069 mmol, 1.1 eq.).

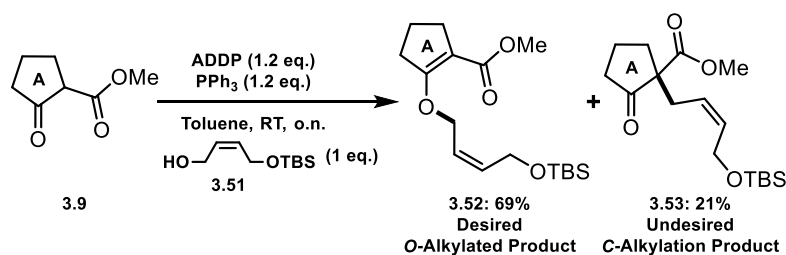
3.16B: R_f 0.42 (20% EtOAc/Hex); ^1H -NMR (400 MHz, CDCl_3) δ 5.02 (dd, J = 6.0, 3.2 Hz, 1H), 4.22 (d, J = 10.0 Hz, 1H), 3.70 (d, J = 9.9 Hz, 1H), 3.35 (s, 3H), 2.97 (dd, J = 11.5, 9.9 Hz, 1H), 2.61 (dd, J = 19.4, 9.9 Hz, 1H),

2.46-2.32 (m, 2H), 2.32-2.14 (m, 3H), 2.13-1.99 (m, 1H), 1.99-1.86 (m, 2H), 1.82 (dd, $J = 14.5, 6.0$ Hz, 1H), 1.08 (s, 9H); ^{13}C -NMR (100 MHz, CDCl_3) δ 214.5, 212.3, 106.2, 76.6, 72.1, 59.0, 55.4, 44.5, 41.0, 39.9, 37.1, 34.1, 30.5, 30.2, 19.1; IR (neat): 1752, 1714, 1049 (cm^{-1}); HRMS (EI) calcd for $\text{C}_{17}\text{H}_{26}\text{O}_4$ $[\text{M}]^+$: 294.1831, found 294.1845.

4.1.2.2 Victor Borba's work:



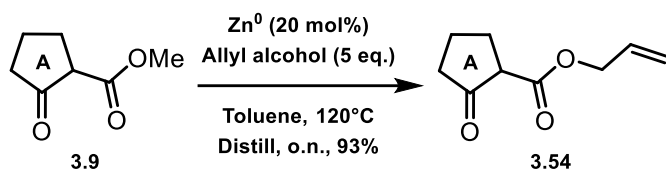
(Z)-4-((tert-butyldimethylsilyl)oxy)but-2-en-1-ol (3.51). To a solution of cis-2-butene-1,4-diol **3.50** (1.000 g, 11.35 mmol) in 40 mL THF at 0 °C was added nBuLi (2.44 M in hexane, 4.65 mL, 11.4 mmol, 1 eq.) and stirred at 0 °C for 1 h. A solution of TBSCl (1.882 g, 12.48 mmol, 1.1 eq.) in 5 mL THF was added dropwise to the reaction mixture at 0 °C. The solution was warmed to RT and stirred for 2 h. The reaction was quenched with 100 mL aq. sat. NaHCO_3 , extracted with (3 x 100 mL) EtOAc, dried over Na_2SO_4 , filtered, and evaporated under reduced pressure. The crude was purified over silica gel (10-20% EtOAc/Hex) to afford allylic alcohol **3.51** as a clear oil (2.17 g, 94%): R_f 0.33 (20% EtOAc/Hex); ^1H -NMR (400 MHz, CDCl_3) δ 5.77-5.60 (m, 1H), 4.26 (dd, $J = 5.1, 0.9$ Hz, 1H), 4.20 (t, $J = 5.4$ Hz, 1H), 2.04 (s(br), 1H), 0.91 (s, 9H), 0.08 (s, 6H). Spectral data was identical to those found in the literature.¹³²



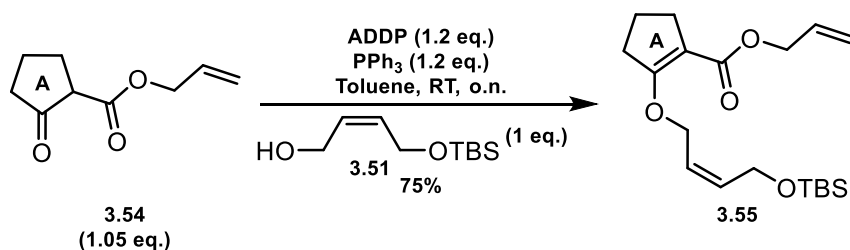
(3.52 and 3.53) To a solution of 1,1'-(Azodicarbonyl)dipiperidine (ADDP) (533 mg, 2.11 mmol, 1.2 eq.) in 18 mL toluene was added PPh_3 (553 mg, 2.11 mmol, 1.2 eq.). The reaction mixture was stirred at RT for 15 min. The reaction mixture was added to a solution of methyl 2-oxocyclopentanecarboxylate **3.9** (250 mg, 1.76 mmol, 1 eq.) and allylic alcohol **3.51** (356 mg, 1.76 mmol, 1 eq.) in 18 mL toluene and the resulting solution was stirred at RT for 24 h. The solution was filtrated (to get rid of some $\text{Ph}_3\text{P}=\text{O}$) and evaporated under reduced pressure. The crude was purified directly over silica gel (7-10% EtOAc/Hex) to afford enol ether **3.52** (396.1 mg, 69%) as a clear oil and **3.53** as a clear oil (120.9 mg, 21%)

3.52: R_f 0.20 (10% EtOAc/Hex); $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 5.76-5.56 (m, 2H), 4.68 (dd, $J = 5.4, 1.1$ Hz, 2H), 4.25 (dd, $J = 5.0, 1.1$ Hz, 2H), 3.69 (s, 3H), 2.70-2.60 (m, 2H), 2.60-2.50 (m, 2H), 1.91-1.78 (m, 2H), 0.89 (s, 9H), 0.07 (s, 6H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 168.4, 165.7, 132.8, 125.9, 104.7, 66.1, 60.0, 51.0, 31.8, 29.5, 26.0, 19.5, 18.4, -5.1; IR (neat): 3393, 3020, 2952, 1725, 1437, 1251, 833, 772, 668 (cm^{-1}); HRMS (ESI) calcd for $[\text{C}_{17}\text{H}_{30}\text{O}_4\text{Si} + \text{Na}]^+$: 349.1811, found 349.1820.

3.53: $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 5.66 (dtt, $J = 11.1, 6.2, 1.5$ Hz, 1H), 5.31 (dtt, $J = 11.1, 7.7, 1.7$ Hz, 1H), 4.21 (ddd, $J = 6.2, 1.7, 0.8$ Hz, 2H), 3.70 (s, 3H), 2.67 (dddt, $J = 14.4, 7.8, 1.5, 0.7$ Hz, 1H), 2.53-2.33 (m, 3H), 2.33-2.16 (m, 1H), 2.10-1.85 (m, 3H), 0.89 (s, 9H), 0.06 (s, 6H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 214.7, 171.5, 133.8, 124.5, 60.1, 59.4, 52.8, 38.3, 32.4, 31.6, 26.1, 19.8, 18.5, -5.0; IR (neat): 3022, 2952, 2855, 1753, 1725, 1462, 1250, 1086, 834, 773 (cm^{-1}); HRMS (ESI) calcd for $[\text{C}_{17}\text{H}_{30}\text{O}_4\text{Si} + \text{Na}]^+$: 349.1811, found 349.1802.

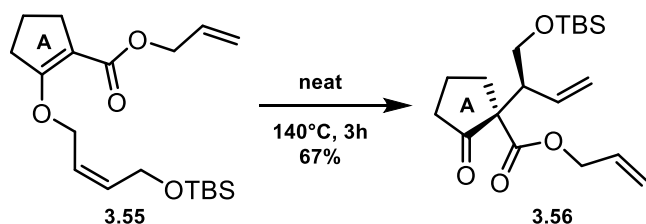


(**3.54**) To a solution of methyl 2-oxocyclopentanecarboxylate **3.9** (40.0 g, 281 mmol) in 281 mL toluene was added zinc powder (3.68 g, 56.3 mmol, 20 mol%). The reaction mixture was distilled at 120°C overnight, cooled to RT, filtrated, evaporated under reduced pressure, and purified over silica gel (5-15% EtOAc/Hex) to afford allyl 2-oxocyclopentanecarboxylate **3.54** (46.06 g, 93%): R_f 0.32 (15% EtOAc/DCM); Spectral data was identical to those found in the literature.¹³³

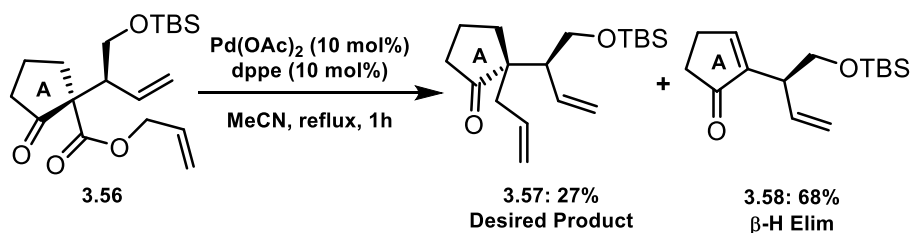


(**3.55**) To a solution of 1,1'-(Azodicarbonyl)dipiperidine (ADDP) (148 mg, 0.586 mmol, 1.2 eq.) in 6 mL toluene was added PPh_3 (154 mg, 0.586 mmol, 1.2 eq.). The reaction mixture was stirred at RT for 15 min. The reaction mixture was added to a solution of allyl 2-oxocyclopentanecarboxylate **3.54** (89.2 mg, 0.530 mmol, 1.1 eq.) and allylic alcohol **3.51** (101 mg, 0.488 mmol, 1 eq.) in 6 mL toluene and the resulting solution was stirred at RT for 24 h. The solution was filtrated (to get rid of some $\text{Ph}_3\text{P}=\text{O}$) and evaporated

under reduced pressure. The crude was purified directly over silica gel (7.5% EtOAc/Hex) to afford enol ether **3.55** (121.1 mg, 70%) as a clear oil: R_f 0.32 (10% EtOAc/DCM); $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 5.95 (ddt, $J = 17.2, 10.5, 5.3$ Hz, 1H), 5.74-5.59 (m, 2H), 5.34 (dq, $J = 17.2, 1.7$ Hz, 1H), 5.18 (dq, $J = 10.5, 1.5$ Hz, 1H), 4.69 (dd, $J = 5.4, 1.0$ Hz, 2H), 4.62 (dt, $J = 5.3, 1.6$ Hz, 2H), 4.24 (dd, $J = 5.0, 1.0$ Hz, 2H), 2.68-2.53 (m, 2H), 1.91-1.80 (m, 2H), 0.89 (s, 9H), 0.06 (s, 6H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 168.8, 164.9, 133.1, 132.8, 125.9, 117.1, 104.6, 67.0, 64.1, 60.0, 31.9, 29.4, 26.0, 19.5, 18.4, -5.1; IR (neat): 3402, 3089, 2955, 2858, 1724, 1464, 1408, 1360, 1251, 1095, 835, 775, 736, 668 (cm^{-1}); HRMS (ESI) calcd for $[\text{C}_{19}\text{H}_{32}\text{O}_4\text{Si} + \text{Na}]^+$: 375.1968, found 375.1966.



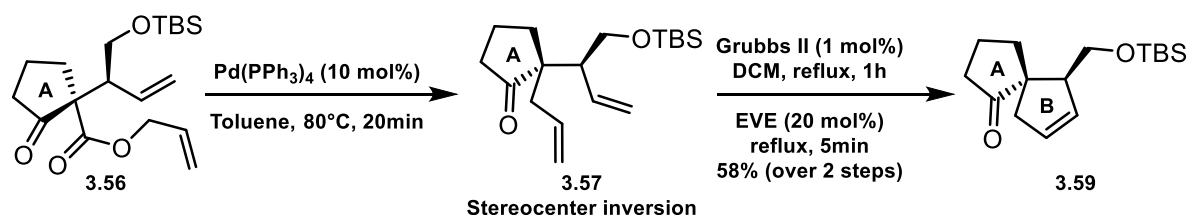
(**3.56**) Enol ether **3.55** was heated neat at 140 °C for 3 h and was then cooled to RT. The crude was purified directly over silica gel (5-10% EtOAc/Hex) to afford Claisen rearrangement adduct **3.56** as a thick white oil (yield not determined for this transformation): R_f 0.31 (10% EtOAc/DCM); $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 5.89 (ddt, $J = 17.2, 10.4, 5.6$ Hz, 1H), 5.73-5.60 (m, 1H), 5.32 (dq, $J = 17.2, 1.5$ Hz, 1H), 5.23 (dq, $J = 10.4, 1.3$ Hz, 1H), 5.18-5.09 (m, 2H), 4.66-4.53 (m, 2H), 3.66 (dd, $J = 6.0, 1.3$ Hz, 2H), 3.20 (dt, $J = 8.9, 5.9$ Hz, 1H), 2.63-2.49 (m, 1H), 2.33 (dddd, $J = 18.6, 7.7, 3.9, 1.7$ Hz, 1H), 2.17-1.99 (m, 2H), 1.99-1.87 (m, 2H), 0.86 (s, 9H), 0.016 (s, 3H), 0.014 (s, 3H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 213.7, 169.3, 134.7, 131.8, 127.9, 119.9, 118.7, 114.1, 66.1, 63.7, 63.4, 49.3, 38.9, 29.1, 26.0, -5.3, -5.4; IR (neat): 3083, 2952, 1751, 1719, 1509, 1461, 1249, 1217, 1101, 1003, 922, 833, 774 (cm^{-1}); HRMS (ESI) calcd for $[\text{C}_{19}\text{H}_{32}\text{O}_4\text{Si} + \text{Na}]^+$: 375.1968, found 375.1975.



(**3.58**) To a solution of Claisen rearrangement adduct **3.56** (50.0 mg, 0.142 mmol) in 1.42 mL MeCN were added $\text{Pd}(\text{OAc})_2$ (3.2 mg, 0.014 mmol, 10 mol%) and dppe (5.7 mg, 0.014 mmol, 10 mol%). The reaction mixture was heated to reflux for 1 h. The solution was cooled to RT, evaporated under reduced pressure,

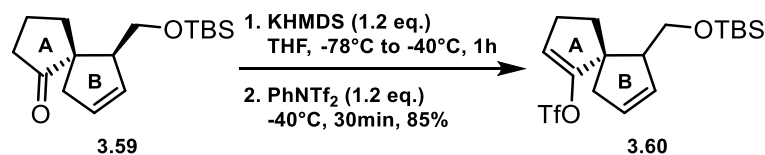
and purified directly over silica gel (1-4% EtOAc/Hex) to afford the desired bis α -allylated ketone **3.57** (11.8 mg, 27%) as well as β -H elimination product **3.58** (25.7 mg, 68%).

(**3.58**) $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.40 (td, $J = 2.8, 0.9$ Hz, 1H), 6.04-5.82 (m, 1H), 5.18-5.07 (m, 1H), 5.07-5.00 (m, 1H), 3.73 (dd, $J = 9.7, 5.6$ Hz, 1H), 3.66 (dd, $J = 9.7, 5.8$ Hz, 1H), 3.38-3.20 (m, 1H), 2.67-2.51 (m, 2H), 2.45-2.28 (m, 2H), 0.84 (s, 9H), 0.00 (s, 3H), -0.02 (s, 3H).



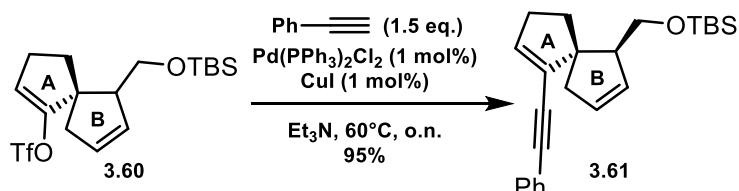
(**3.59**) To a solution of Claisen rearrangement adduct **3.56** (333.5 mg, 0.9460 mmol) in 10 mL toluene was added $\text{Pd}(\text{PPh}_3)_4$ (109.3 mg, 0.09460 mmol, 10 mol%). The reaction mixture was heated to reflux overnight. The solution was cooled to RT, evaporated under reduced pressure, and purified directly over silica gel (1-4% EtOAc/Hex) to afford bis α -allylated ketone **3.57** in an inseparable mixture (208.4 mg, DP/SP = 1:0.23). The mixture was used directly in the next step.

To a solution of impure bis α -allylated ketone **3.57** (208 mg, 0.675 mmol) in 6.8 mL DCM was added Grubbs' catalyst 2nd generation (5.7 mg, 0.0068 mmol, 1 mol%). The reaction mixture was heated to reflux for 1 h. Ethyl vinyl ether (12.8 μL , 0.135 mmol, 20 mol%) was added and the solution was stirred at reflux for 5 min. The reaction mixture was cooled to RT, evaporated under reduced pressure, and purified directly over silica gel (3-4% EtOAc/Hex) to afford the ring-closed adduct **3.59** (153.9 mg, 58% over 2 steps): $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 5.77-5.58 (m, 1H), 5.58-5.45 (m, 1H), 3.66 (dd, $J = 10.3, 5.1$ Hz, 1H), 3.55 (dd, $J = 10.3, 7.8$ Hz, 1H), 3.04 (ddt, $J = 7.5, 5.0, 2.3$ Hz, 1H), 2.43 (dq, $J = 16.2, 2.2$ Hz, 1H), 2.39-2.05 (m, 4H), 2.05-1.90 (m, 1H), 1.90-1.71 (m, 2H), 0.84 (s, 9H), 0.00 (s, 6H).

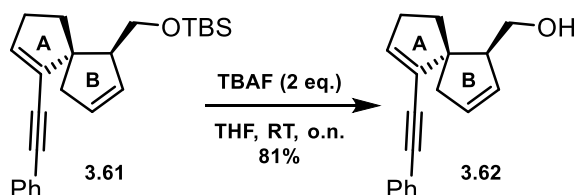


(**3.60**) To a solution of ring-closed adduct **3.59** (130 mg, 0.464 mmol) in 4.6 mL THF at -78°C was added a solution of KHMDS (111 mg, 0.556 mmol, 1.2 eq.) in 3 mL THF. The reaction mixture was stirred at -78°C for 1 h after which the solution was warmed to -45°C . A solution of PhNTf_2 (199 mg, 0.556 mmol, 1.2 eq.) in 3 mL THF was added to the reaction mixture which was stirred at -45°C for 30 min. The reaction was

quenched with 10 mL NaOH (1 M), warmed to RT for 15 min, extracted with (3 x 10 mL) EtOAc, dried over Na₂SO₄, filtered, and evaporated under reduced pressure. The crude was purified over silica gel (1-2% EtOAc/Hex) to afford vinyl triflate **3.60** (163.5 mg, 85%): ¹H-NMR (400 MHz, CDCl₃) δ 5.72 (dq, *J* = 6.7, 2.3 Hz, 1H), 5.63-5.53 (m, 2H), 3.67 (dd, *J* = 10.3, 5.8 Hz, 1H), 3.63 (dd, *J* = 10.3, 6.4 Hz, 1H), 2.91-2.77 (m, 1H), 2.60 (dq, *J* = 16.5, 2.2 Hz, 1H), 2.48-2.26 (m, 4H), 1.81-1.71 (m, 1H), 0.87 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H).

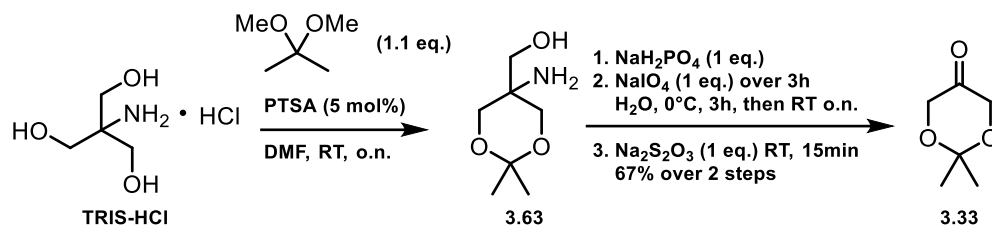


(**3.61**) To a mixture of vinyl triflate **3.60** (164 mg, 0.396 mmol), phenylacetylene (65.3 μL, 0.595 mmol, 1.5 eq.), Pd(PPh₃)₂Cl₂ (2.8 mg, 0.0040 mmol, 1 mol%) and CuI (0.8 mg, 0.004 mmol, 1 mol%) was added 4 mL Et₃N. The flask was sealed and heated to 60 °C overnight. The reaction mixture was cooled to RT, evaporated under reduced pressure, and purified directly over silica gel (5-10% EtOAc/Hex) to afford enyne **3.61** (137.3 mg, 95%): ¹H-NMR (400 MHz, CDCl₃) δ 7.67-7.27 (m, 5H), 6.16-6.06 (m, 1H), 5.88-5.78 (m, 1H), 5.78-5.66 (m, 1H), 3.75-3.60 (m, 2H), 3.07-2.95 (m, 1H), 2.75-2.65 (m, 1H), 2.50-2.15 (m, 4H), 1.77-1.62 (m, 1H), 0.91 (s, 9H), 0.07 (s, 6H).



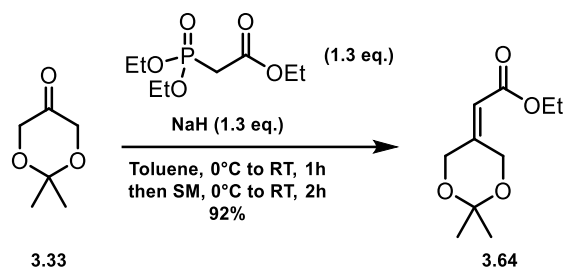
(**3.62**) To a solution of enyne **3.61** (30.6 mg, 0.0839 mmol) in 2 mL THF was added TBAF (1 M in THF, 168 μL, 0.168 mmol, 2 eq.). The reaction was stirred at RT overnight, evaporated under reduced pressure, and purified directly over silica gel (10-20% EtOAc/Hex) to afford alcohol **3.62** (17.0 mg, 81%): ¹H-NMR (400 MHz, CDCl₃) δ 7.66-7.36 (m, 2H), 7.36-7.27 (m, 3H), 6.12 (t, *J* = 2.7 Hz, 1H), 5.89 (dq, *J* = 6.9, 2.3 Hz, 1H), 5.72 (dq, *J* = 6.1, 2.1 Hz, 1H), 3.74 (d, *J* = 5.7 Hz, 2H), 3.09-3.00 (m, 1H), 2.69 (dq, *J* = 16.5, 2.3 Hz, 1H), 2.48-2.33 (m, 3H), 2.25 (ddd, *J* = 12.9, 7.8, 6.3 Hz, 1H), 1.78 (ddd, *J* = 13.3, 7.9, 5.7 Hz, 1H), 1.68 (s(br), 1H).

4.1.2.3 Route 2 – Isopropylidene-Protected 1,3-Diol:

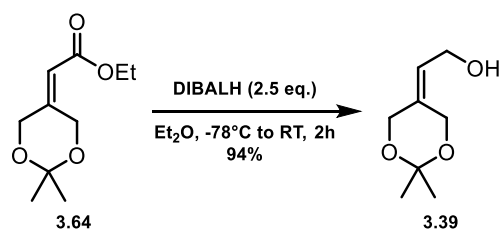


2,2-dimethyl-1,3-dioxan-5-one (3.33). To a solution of TRIS-HCl (44.6 g, 283 mmol) in 314 mL DMF was added PTSA•H₂O (2.69 g, 14.1 mmol, 5 mol%) and 2,2-dimethoxypropane (38.2 mL, 311 mmol, 1.1 eq.). The resulting solution was stirred at RT overnight. Et₃N (2.37 mL, 17.0 mmol, 6 mol%) was added and the solution was stirred at RT for 10 min before being concentrated under reduced pressure. 1.13 L EtOAc and Et₃N (31.54 mL, 226.3 mmol, 80 mol%) were added (which formed a white precipitate), and the solution was filtrated. The filtrate was evaporated under reduced pressure and the DMF was distilled off under high vacuum at 60–85 °C. The crude of aminoalcohol **3.63** was used directly in the next step. Spectral data was identical to those found in the literature.¹³⁴ (note: no aqueous workup was done to remove the DMF because aminoalcohol **3.63** is soluble in water)

The crude from the previous step was dissolved in 943 mL H₂O, NaH₂PO₄ (33.9 g, 283 mmol, 1 eq.) was added and the solution was cooled to 0 °C. A solution of NaIO₄ (60.5 g, 283 mmol, 1 eq.) in 775 mL H₂O was added to the reaction mixture dropwise via an addition funnel at 0 °C over 3 h. The reaction mixture was stirred for 1 h at 0 °C after the addition of the NaIO₄ solution before being warmed to RT and stirred overnight. Thereafter, Na₂S₂O₃ (44.7 g, 283 mmol, 1 eq.) was added and the reaction was stirred at RT for 15 min. The reaction mixture was extracted with (8 x 500 mL) DCM, dried over Na₂SO₄, and evaporated under reduced pressure (at 30 °C because the desired product is volatile) to afford ketone **3.33** (24.81 g, 67% over 2 steps) which was used directly in the next step: R_f 0.30 (10% EtOAc/Hex). Spectral data was identical to those found in the literature.¹³⁵

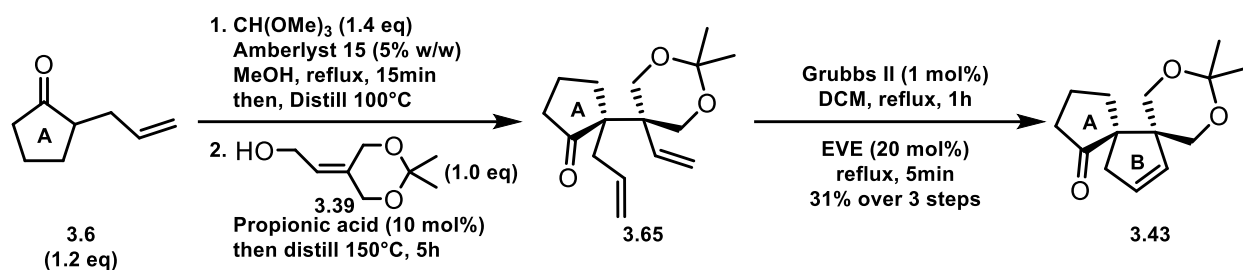


ethyl 2-(2,2-dimethyl-1,3-dioxan-5-ylidene)acetate (3.64). To a suspension of NaH (60% in mineral oil, 9.91 g, 248 mmol, 1.3 eq.) in 635 mL toluene at 0 °C was added triethyl phosphonoacetate (49.4 mL, 248 mmol, 1.3 eq.) over 5 min. The reaction mixture was warmed to RT and stirred for 1 h until the full consumption of the NaH. The solution was cooled to 0 °C, ketone **3.33** (24.81 g, 190.6 mmol) was added, then the solution was warmed to RT (formation of a thick red paste). The thick paste was dissolved after adding 70 mL EtOH 99% and the resulting solution was stirred for 45 min at RT. The reaction mixture was quenched with 500 mL aq. sat. NH₄Cl, extracted with (3 x 500 mL) EtOAc, dried over Na₂SO₄, filtered, and evaporated under reduced pressure. The crude was purified over silica gel (5-10% EtOAc/Hex) to afford α,β -unsaturated ester **3.64** as a clear oil (35.0 g, 92%): *R*_f 0.37 (10% EtOAc/Hex); ¹H-NMR (400 MHz, CDCl₃) δ 5.64-5.56 (m, 1H), 4.90-4.82 (m, 2H), 4.26 (dd, *J* = 2.4, 1.2 Hz, 2H), 4.16 (q, *J* = 7.1 Hz, 2H), 1.40 (s, 6H), 1.27 (t, *J* = 7.1 Hz, 3H).



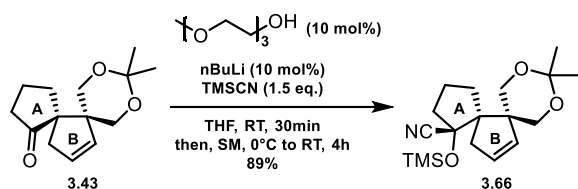
2-(2,2-dimethyl-1,3-dioxan-5-ylidene)ethanol (3.39). To a solution of α,β -unsaturated ester **3.64** (35.0 g, 175 mmol) in 1.00 L Et₂O at -78 °C was added DIBALH (25% in hexane, 285 mL, 437 mmol, 2.5 eq.) slowly. The reaction mixture was stirred at -78 °C for 30 min, warmed to RT and stirred for 2 h before quenching following the Fieser method (formation of a white precipitate). The white precipitate was filtered over a Buchner filter and rinsed thoroughly with (5 x 500 mL) Et₂O until all the desired product was extracted. The organic layer was dried over Na₂SO₄, filtered, and evaporated under reduced pressure. The crude was purified over silica gel (80% EtOAc/Hex) to afford allylic alcohol **3.39** as a clear oil (26.05 g, 94%): *R*_f 0.48 (80% EtOAc/Hex); ¹H-NMR (400 MHz, CDCl₃) δ 5.68-5.59 (m, 1H), 4.33-4.28 (m, 2H), 4.27-4.24 (m, 2H), 4.03 (s, 2H), 1.43 (s, 6H). Fieser method: For a reaction with X mmol of DIBALH, 0.04X mL of H₂O was

added slowly to the reaction mixture cooled in an ice bath followed by 0.04X mL of NaOH (15%) and 0.1X mL H₂O.

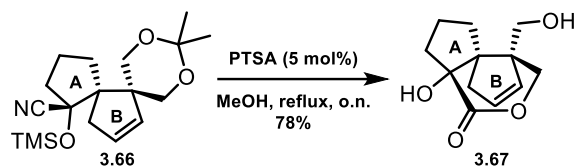


(**3.43**). To a solution of α -allyl ketone **3.6** (8.185 g, 65.92 mmol, 1.2 eq.) and Amberlyst® 15 (409 mg, 5% w/w) in 16.5 mL MeOH heated to reflux was added trimethyl orthoformate (8.43 mL, 79.9 mmol, 1.4 eq.). After 30 min of heating at reflux, the reaction mixture was cooled to RT, filtered over celite, and rinsed with DCM. The filtrate was distilled at 110 °C to remove any residual MeOH, DCM and methyl formate. Thereafter, the solution was cooled to RT, then **3.39** (8.204 g, 51.86 mmol) and propionic acid (389 μ L, 5.19 mmol, 0.1 eq.) were added. The resulting solution was distilled at 150 °C for 2 days. The crude was cooled to RT and purified over silica gel (2.5-10% EtOAc/Hex) to afford bis- α -allylated ketone **3.65** as a clear oil in an inseparable mixture of side products and isomers. The mixture was used directly in the next step.

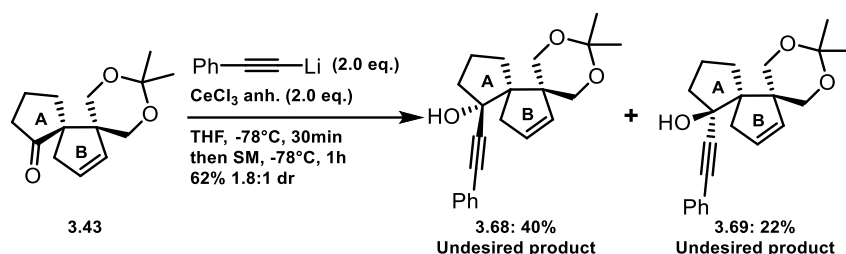
To a solution of bis- α -allylated ketone **3.65** (6.17 g, 23.3 mmol) in 233 mL DCM was added Grubbs' catalyst 2nd generation (198 mg, 0.233 mmol, 1 mol%) and the reaction mixture was heated to reflux for 1 h. After the starting material was consumed, ethyl vinyl ether (447 μ L, 4.67 mmol, 20 mol%) was added and the solution was refluxed for 5 min. The reaction mixture was cooled to RT and evaporated under reduced pressure. The crude was purified over silica gel (5-15% EtOAc/Hex) to afford the desired ring-closed spiro ketone **3.43** as a clear oil (3.768 g, 31% over 3 steps): *R*_f 0.32 (20% EtOAc/Hex); ¹H-NMR (400 MHz, CDCl₃) δ 5.75 (dt, *J* = 5.8, 2.3 Hz, 1H), 5.55 (dt, *J* = 5.8, 2.0 Hz, 1H), 3.94 (dd, *J* = 12.1, 1.5 Hz, 1H), 3.82 (d, *J* = 12.0 Hz, 1H), 3.81 (dd, *J* = 12.1, 1.5 Hz, 1H), 3.69 (d, *J* = 12.1 Hz, 1H), 2.68 (dt, *J* = 16.8, 2.1 Hz, 1H), 2.54 (ddd, *J* = 16.0, 9.3, 6.9 Hz, 1H), 2.36-2.32 (m, 2H), 2.25 (dt, *J* = 16.9, 2.1 Hz, 1H), 2.17-2.04 (m, 1H), 1.88 (m, 1H), 1.77 (m, 1H), 1.42 (s, 3H), 1.37 (s, 3H).



(3.66). To a solution of tri(ethylene glycol) monoethyl ether (34 μ L, 0.21 mmol, 10 mol%) in 4.25 mL THF at RT was added *n*BuLi (2.13 M in hexane, 99 μ L, 0.21 mmol, 10 mol%), TMSCN (397 μ L, 3.17 mmol, 1.5 eq.) and stirred for 30 min. The reaction mixture was cooled to 0 °C, then a solution of spiro ketone **3.43** (500 mg, 2.12 mmol) in 2 mL THF was added dropwise. The reaction was warmed to RT, stirred for 4 h before being quenched with 10 mL 10% Na₂CO₃, extracted with (3 x 10 mL) EtOAc, dried over Na₂SO₄, filtered, and evaporated under reduced pressure. The crude was purified over silica gel (5-10% EtOAc/Hex with 1% Et₃N) to afford cyanohydrin **3.66** (605 mg, 89%): *R*_f 0.43 (10% EtOAc/Hex); ¹H-NMR (400 MHz, CDCl₃) δ 6.31 (m, 1H), 5.72 (m, 1H), 4.47 (d, *J* = 11.7 Hz, 1H), 4.43 (d, *J* = 11.3 Hz, 1H), 3.64 (dd, *J* = 11.6, 2.4 Hz, 1H), 3.44 (dd, *J* = 11.1, 2.4 Hz, 1H), 2.90-2.80 (m, 1H), 2.40-2.26 (m, 1H), 1.99-1.89 (m, 1H), 1.87-1.74 (m, 3H), 1.74-1.61 (m, 1H), 1.56 (s, 3H), 1.55-1.49 (m, 1H), 1.40 (s, 3H), 0.23 (s, 9H).



3a-hydroxy-6a-(hydroxymethyl)-1,2,3,3a,6,6a-hexahydrodicyclopenta[c,d]pyran-4(9H)-one (3.67). To a solution of cyanohydrin **3.66** (50.0 mg, 0.149 mmol) in 3 mL MeOH was added PTSA•H₂O (285 mg, 1.5 mmol, 10 eq.). The resulting solution was heated to reflux overnight. The reaction mixture was cooled to RT, evaporated under reduced pressure, and the crude was purified over silica gel (40-60% EtOAc/Hex) to afford lactone **3.67** (26.1 mg, 78%): *R*_f 0.33 (60% EtOAc/Hex); ¹H-NMR (300 MHz, CDCl₃) δ 5.98-5.94 (m, 1H), 5.46-5.43 (m, 1H), 4.39 (d, *J* = 11.9 Hz, 1H), 4.20 (d, *J* = 11.8 Hz, 1H), 3.83 (s(br), 1H), 3.67 (d, *J* = 10.9 Hz, 1H), 3.56 (d, *J* = 10.9 Hz, 1H), 3.03 (ddd, *J* = 17.6, 2.9, 0.8 Hz, 1H), 2.31-2.15 (m, 1H), 2.30 (ddd, *J* = 17.6, 2.8, 1.9 Hz, 1H), 2.14-2.04 (m, 2H), 2.02-1.92 (m, 2H), 1.91-1.65 (m, 2H); ¹³C-NMR (75 MHz, CDCl₃) δ 178.3, 135.9, 132.4, 78.7, 70.3, 63.3, 60.9, 55.6, 41.2, 39.0, 33.1, 23.6.

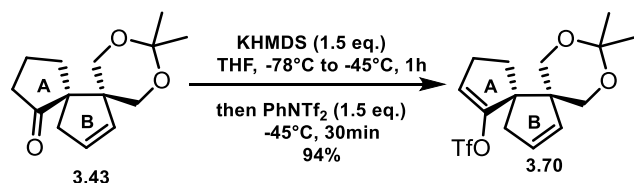


(3.68/3.69). To a suspension of anhydrous CeCl₃ (209 mg, 0.846 mmol, 2 eq.) in 2 mL THF at -78 °C was added lithium phenylacetylide (1 M in THF, 846 μL, 846 mmol, 2 eq.) which was then stirred at -78 °C for 15 min. Thereafter, a solution of spiro ketone **3.43** (100 mg, 0.423 mmol) in 2 mL THF was added dropwise, and the reaction mixture was stirred at -78 °C for 1 h. The reaction was warmed to RT, quenched with 10 mL aq. sat. NaHCO₃, extracted with (3 x 10 mL) EtOAc, dried over Na₂SO₄, filtered, and evaporated under reduced pressure. The crude was purified over silica gel (5-20% EtOAc/Hex) to afford alcohol **3.68** (57 mg, 40%) and alcohol **3.69** (32 mg, 22%) (62% total, 1.8:1 dr).

3.68: R_f 0.76 (40% EtOAc/Hex); ¹H-NMR (400 MHz, CDCl₃) δ 7.48-7.42 (m, 2H), 7.34-7.27 (m, 3H), 6.39-6.29 (m, 1H), 5.80-5.71 (m, 1H), 4.79 (d, *J* = 11.4 Hz, 1H), 4.57 (d, *J* = 11.0 Hz, 1H), 3.74 (dd, *J* = 11.4, 2.3 Hz, 1H), 3.52 (dd, *J* = 10.9, 2.3 Hz, 1H), 3.00-2.91 (m, 1H), 2.37 (s(br), 1H), 2.28-2.18 (m, 1H), 2.03-1.95 (m, 1H), 1.95-1.72 (m, 4H), 1.55-1.47 (m, 1H), 1.43 (s, 3H), 1.38 (s, 3H).

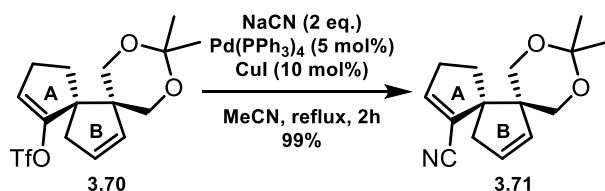
3.69: R_f 0.80 (40% EtOAc/Hex); ¹H-NMR (400 MHz, CDCl₃) δ 7.43-7.36 (m, 2H), 7.31-7.26 (m, 3H), 5.76 (ddd, *J* = 5.7, 2.6, 2.2 Hz, 1H), 5.58-5.48 (m, 1H), 4.85 (dd, *J* = 12.3, 1.4 Hz, 1H), 4.49 (s(br), 1H), 4.09 (dd, *J* = 12.1, 1.2 Hz, 1H), 3.73 (d, *J* = 12.2 Hz, 2H), 2.95-2.84 (m, 1H), 2.32-2.23 (m, 1H), 2.23-2.05 (m, 3H), 1.96-1.82 (m, 1H), 1.78-1.63 (m, 1H), 1.58-1.50 (m, 1H), 1.46 (s, 6H).

*Procedure for drying CeCl₃•7H₂O: Flame dry RBF, weigh CeCl₃•7H₂O, put under high vacuum and heat to 80 °C for 6 h. Thereafter, heat to 140 °C overnight under high vacuum. The RBF was then put under argon and transferred to the glovebox.

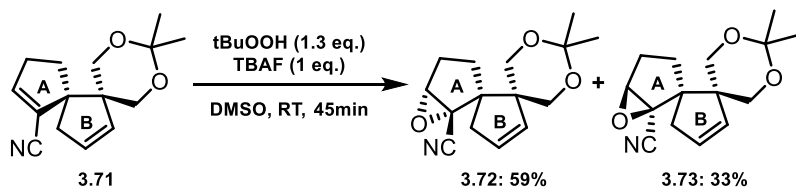


(3.70). To a solution of ketone **3.43** (100 mg, 0.423 mmol) in 2.1 mL THF at -78 °C was added a solution of KHMDS (127 mg, 0.635 mmol, 1.5 eq.) in 1.3 mL THF. The reaction mixture was warmed to -45 °C and stirred for 1 h. Thereafter, a solution of PhNTf₂ (227 mg, 6.35 mmol, 1.5 eq.) in 1.3 mL THF was added to

the reaction mixture which was stirred for 30 min at -45 °C. The reaction was quenched with 10 mL aq. sat. NaHCO₃, extracted with (3 x 10 mL) EtOAc, dried over Na₂SO₄, filtered, and evaporated under reduced pressure. The crude was purified over silica gel (5-10% EtOAc/Hex) to afford the desired vinyl triflate **3.70** as a clear oil (146 mg, 94%): R_f 0.34 (10% EtOAc/Hex); ¹H-NMR (400 MHz, CDCl₃) δ 5.80 (dt, *J* = 6.0, 2.3 Hz, 1H), 5.74 (t, *J* = 2.6 Hz, 1H), 5.51 (dt, *J* = 6.0, 1.9 Hz, 1H), 3.84 (m, 2H), 3.75 (dd, *J* = 12.1, 0.8 Hz, 1H), 3.65 (d, *J* = 12.0 Hz, 1H), 2.80 (ddd, *J* = 13.1, 7.9, 2.4 Hz, 1H), 2.67 (ddd, *J* = 17.0, 2.4, 1.7 Hz, 1H), 2.55 (ddd, *J* = 15.8, 7.8, 2.2 Hz, 1H), 2.49 (dt, *J* = 17.1, 2.3 Hz, 1H), 2.33 (ddt, *J* = 15.9, 8.9, 2.8 Hz, 1H), 1.89 (ddd, *J* = 16.6, 8.7, 7.9 Hz, 1H), 1.44 (s, 3H), 1.39 (s, 3H).



(**3.71**) To a solution of **3.70** (960.7 mg, 2.608 mmol) in 10.4 mL MeCN were added NaCN (255.6 mg, 5.216 mmol, 2 eq.), CuI (49.7 mg, 0.261 mmol, 10 mol%), and Pd(PPh₃)₄ (150.7 mg, 0.1304 mmol, 5 mol%). The reaction mixture was heated to reflux for 2 h. The solution was cooled to RT, quenched with 20 mL aq. sat. NaHCO₃, extracted with (3 x 20 mL) EtOAc, dried over Na₂SO₄, filtered, and evaporated under reduced pressure. The crude was purified over silica gel (10-20% EtOAc/Hex) to afford α,β-unsaturated nitrile **3.71** (634.5 mg, 99%): R_f 0.36 (10% EtOAc/Hex); ¹H-NMR (400 MHz, CDCl₃) δ 6.74 (t, *J* = 2.7 Hz, 1H), 5.88 (dt, *J* = 6.0, 2.4 Hz, 1H), 5.52 (dt, *J* = 6.1, 2.0 Hz, 1H), 3.87 (d, *J* = 12.4 Hz, 1H), 3.79 (dd, *J* = 12.4, 1.7 Hz, 1H), 3.72 (dd, *J* = 12.2, 1.7 Hz, 1H), 3.63 (d, *J* = 12.2 Hz, 1H), 2.85 (ddd, *J* = 13.0, 8.1, 2.9 Hz, 1H), 2.73 (dtd, *J* = 18.5, 8.0, 2.3 Hz, 1H), 2.65-2.49 (m, 2H), 2.46 (ddt, *J* = 18.3, 9.0, 3.0 Hz, 1H), 1.81 (dt, *J* = 13.0, 8.4 Hz, 1H), 1.42 (s, 3H), 1.34 (s, 3H).

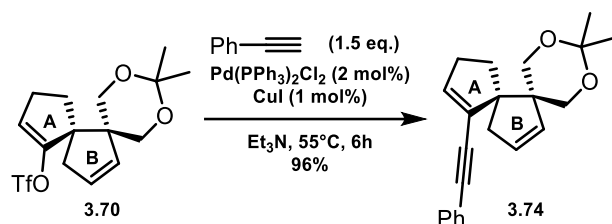


(**3.72/3.73**) To a solution of α,β-unsaturated nitrile **3.71** (20.2 mg, 0.0823 mmol) in 1 mL DMSO were added tBuOOH (5.5 M in decane, 19.2 μL, 0.106 mmol, 1.3 eq.) and TBAF (1 M in THF, 81.5 μL, 0.0815 mmol, 1 eq.). The reaction was stirred at RT for 45 min. The reaction was quenched with 30 mL aq. sat. NaHCO₃, extracted with (3 x 30 mL) EtOAc, dried over Na₂SO₄, filtered, and evaporated under reduced

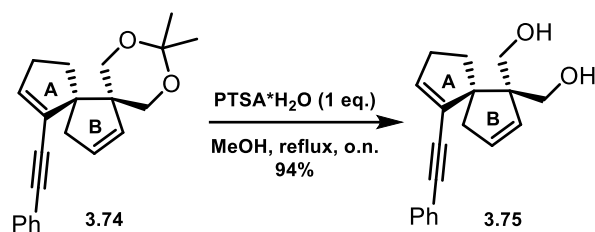
pressure. The crude was purified over silica gel (15-20% EtOAc/Hex) to afford the undesired epoxide **3.72** (12.6 mg, 59%) and the desired epoxide **3.73** (7.1 mg, 33%).

(3.72) R_f 0.24 (20% EtOAc/Hex); $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 5.99 (dt, $J = 6.0, 2.1$ Hz, 1H), 5.86 (dt, $J = 6.0, 2.4$ Hz, 1H), 4.20 (dd, $J = 12.0, 0.8$ Hz, 1H), 3.90 (dd, $J = 12.0, 1.2$ Hz, 1H), 3.85 (s, 1H), 3.82 (dd, $J = 11.7, 0.9$ Hz, 1H), 3.59 (dd, $J = 11.7, 1.3$ Hz, 1H), 2.58 (ddd, $J = 17.0, 2.6, 1.8$ Hz, 1H), 2.38 (dt, $J = 17.0, 2.3$ Hz, 1H), 2.18-2.06 (m, 1H), 1.91-1.70 (m, 2H), 1.46 (s, 3H), 1.44 (s, 3H).

(3.73) R_f = 0.31 (20% EtOAc/Hex); $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 5.95 (ddd, $J = 6.0, 2.9, 1.8$ Hz, 1H), 5.46 (ddd, $J = 6.0, 2.7, 1.1$ Hz, 1H), 4.20-4.13 (m, 2H), 4.05 (s, 1H), 3.63 (d, $J = 12.7$ Hz, 1H), 3.58 (dd, $J = 12.7, 1.4$ Hz, 1H), 2.71 (ddd, $J = 17.4, 2.9, 1.1$ Hz, 1H), 2.36 (dddd, $J = 14.0, 10.9, 8.3, 1.2$ Hz, 1H), 2.05 (ddt, $J = 14.0, 8.0, 0.7$ Hz, 1H), 1.47 (s, 3H), 1.37 (s, 3H).

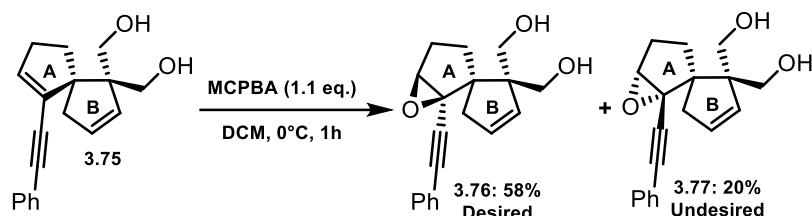


(3.74). In a sealable flask was added vinyl triflate **3.70** (1.00 g, 2.71 mmol), phenylacetylene (447 μL , 4.07 mmol, 1.5 eq.), CuI (5.2 mg, 0.027 mmol, 1 mol%) and $\text{Pd(PPh}_3)_2\text{Cl}_2$ (38 mg, 0.054 mmol, 2 mol%). 10.9 mL Et_3N was added, the flask was sealed and stirred at 55°C overnight. The reaction mixture was evaporated under reduced pressure and the crude was purified directly over silica gel (5-10% EtOAc/Hex) to afford enyne **3.74** as a clear oil (883 mg, 96%): R_f 0.38 (10% EtOAc/Hex); $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.37-7.34 (m, 2H), 7.31-7.26 (m, 3H), 6.23 (t, $J = 1.6$ Hz, 1H), 5.88 (dt, $J = 6.0, 2.2$ Hz, 1H), 5.84 (dt, $J = 6.2, 1.9$ Hz, 1H), 4.00 (d, $J = 11.9$ Hz, 1H), 3.91 (dd, $J = 11.9, 1.0$ Hz, 1H), 3.85 (d, $J = 11.6$ Hz, 1H), 3.63 (dd, $J = 11.6, 0.9$ Hz, 1H), 2.71 (ddd, $J = 16.6, 4.4, 1.5$ Hz, 1H), 2.65-2.47 (m, 3H), 2.39 (dddd, $J = 16.5, 8.7, 3.0, 2.4$ Hz, 1H), 1.79 (ddd, $J = 16.4, 9.5, 7.8$ Hz, 1H), 1.42 (s, 3H), 1.41 (s, 3H).



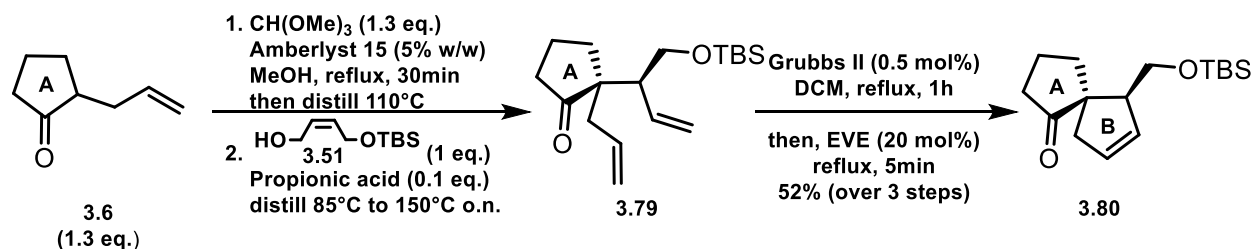
(6-(phenylethynyl)spiro[4.4]nona-2,6-diene-1,1-diyl)dimethanol (3.75). A solution of enyne **3.74** (833 mg, 2.60 mmol) and $\text{PTSA}\cdot\text{H}_2\text{O}$ (494 mg, 2.60 mmol, 1 eq.) in 26 mL MeOH was heated to reflux overnight.

The reaction mixture was cooled to RT, evaporated under reduced pressure and the crude was purified directly over silica gel (30-60% EtOAc/Hex) to afford diol **3.75** (687 mg, 94%): R_f 0.42 (60% EtOAc/Hex); ^1H -NMR (400 MHz, CDCl_3) δ 7.44-7.35 (m, 2H), 7.34-7.27 (m, 3H), 6.23 (t, J = 2.8 Hz, 1H), 5.97 (dt, J = 6.0, 2.3 Hz, 1H), 5.62 (dt, J = 6.0, 1.9 Hz, 1H), 3.99 (d, J = 11.4 Hz, 1H), 3.86 (d, J = 11.4 Hz, 1H), 3.83 (d, J = 11.0 Hz, 1H), 3.80 (d, J = 11.1 Hz, 1H), 2.73 (ddd, J = 16.6, 2.4, 1.8 Hz, 1H), 2.56-2.28 (m, 6H), 1.90-1.78 (m, 1H).



(**3.76/3.77**) To a solution of **3.75** (49.7 mg, 0.177 mmol) in 2 mL DCM at 0 °C was added MCPBA (67.9% w/w, 49.9 mg, 0.196 mmol, 1.1 eq.). The reaction was stirred at 0 °C for 1 h and was then quenched with 10 mL 10% $\text{Na}_2\text{S}_2\text{O}_3$ /aq. sat. NaHCO_3 (1:1), extracted with (3 x 10 mL) DCM, dried over Na_2SO_4 , filtered, and evaporated under reduced pressure. The crude was purified over silica gel (40-60% EtOAc/Hex) to afford epoxide **3.76** (30.6 mg, 58%) and epoxide **3.77** (10.4 mg, 20%) as an inseparable mixture (R_f 0.19 (60% EtOAc/Hex)).

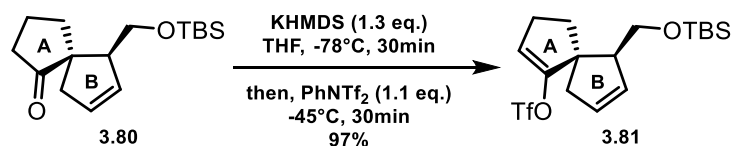
4.1.2.4 Route 3 – Incorporation of the Iodolactonization (with Mono-TBS-Protected Allylic Alcohol):



6-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)spiro[4.4]non-7-en-1-one (3.80). To a solution of α -allyl ketone **3.6** (2.615 g, 21.06 mmol, 1.3 eq.) and Amberlyst® 15 (131 mg, 5% w/w) in 5.23 mL MeOH heated to reflux was added trimethyl orthoformate (2.31 mL, 21.1 mmol, 1.3 eq.). After 30 min of heating to reflux, the reaction mixture was cooled to RT, filtered over celite, and rinsed with DCM. The filtrate was distilled at 110 °C to remove any residual MeOH, DCM and methyl formate. Thereafter, the solution was cooled to RT, then allyl alcohol **3.51** (3.28 g, 16.2 mmol, 1 eq.) and propionic acid (121 μL , 1.62 mmol, 0.1

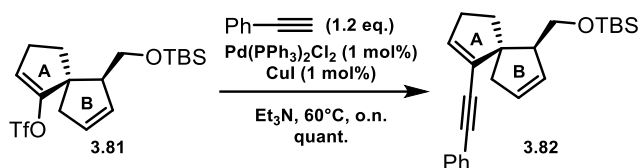
eq.) were added. The resulting solution was distilled from 85 °C to 150 °C gradually (rising the temperature by 15 °C every 15 min), then at 150 °C overnight. The crude was cooled to RT and purified over silica gel (0.5-3% EtOAc/Hex) to afford bis α -allylated ketone **3.79** as a clear oil in an inseparable mixture of side products and isomers: R_f 0.60 (10% EtOAc/Hex). The mixture was used directly in the next step.

To the mixture containing α -allylated ketone **3.79** (≤ 5.00 g, ≤ 16.2 mmol) in 162 mL DCM was added Grubbs' catalyst 2nd generation (68.8 mg, 0.0810 mmol, 0.5 mol%). The reaction mixture was heated to reflux for 1 h. Ethyl vinyl ether (311 μ L, 3.24 mmol, 20 mol%) was added and the solution was stirred at reflux for 5 min. The reaction mixture was cooled to RT, evaporated under reduced pressure and the crude was purified over silica gel (3-4% EtOAc/Hex) to afford ring-closed spiro ketone **3.80** as a clear oil (2.383g, 52% over 2 steps): R_f 0.58 (10% EtOAc/Hex); $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 5.75 (ddt, $J = 5.7, 2.5, 1.9$ Hz, 1H), 5.46-5.27 (m, 1H), 3.42 (dd, $J = 10.0, 4.8$ Hz, 1H), 3.36 (dd, $J = 10.0, 9.3$ Hz, 1H), 2.90 (dq, $J = 17.0, 2.7$ Hz, 1H), 2.82-2.69 (m, 1H), 2.47-2.33 (m, 1H), 2.17-1.92 (m, 4H), 1.92-1.80 (m, 1H), 1.77-1.63 (m, 1H), 0.86 (s, 9H), 0.01 (s, 3H), 0.00 (s, 3H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 221.6, 131.3, 128.1, 62.8, 60.7, 56.3, 43.1, 41.0, 38.6, 26.1, 19.0, 18.5, -5.4, -5.5; IR (neat): 3052, 2952, 2855, 1733, 1463, 1251, 1089, 1059, 1005, 833, 775, 702 (cm^{-1}); HRMS (EI) calcd for $\text{C}_{15}\text{H}_{25}\text{O}_2\text{Si}$ [$\text{M}-\text{CH}_3$] $^+$: 265.1624, found 265.1643.

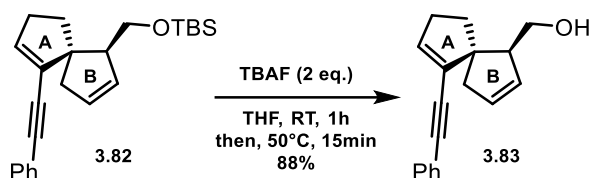


6-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)spiro[4.4]nona-1,7-dien-1-yl trifluoromethanesulfonate (3.81). To a solution of spiro ketone **3.80** (1.4878 g, 5.3046 mmol) in 30 mL THF at -78 °C was added a solution of KHMDS (1.375 g, 6.896 mmol, 1.3 eq.) in 15 mL THF. The reaction mixture was stirred at -78 °C for 30 min and was then warmed to -45 °C. Thereafter, a solution of PhNTf₂ (2.085 g, 5.835 mmol, 1.1 eq.) in 15 mL THF was added to the reaction mixture which was stirred at -45 °C for 30 min. The reaction was quenched with 60 mL aq. sat. NH_4Cl , extracted with (3 x 60 mL) EtOAc, dried over Na_2SO_4 , filtered, and evaporated under reduced pressure. The crude was purified over silica gel (0.5-2% EtOAc/Hex) to afford vinyl triflate **3.81** as a yellow oil (2.1322g, 97%): R_f 0.23 (2% EtOAc/Hex); $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 5.75 (dq, $J = 6.4, 2.2$ Hz, 1H), 5.71-5.58 (m, 2H), 3.61 (dd, $J = 9.9, 7.1$ Hz, 1H), 3.54 (dd, $J = 9.9, 7.7$ Hz, 1H), 2.83 (tt, $J = 7.3, 2.0$ Hz, 1H), 2.73 (dq, $J = 16.7, 2.2$ Hz, 1H), 2.43 (dtd, $J = 15.7, 7.8, 2.3$ Hz, 1H), 2.36-2.23 (m, 2H), 2.18 (ddd, $J = 12.7, 8.0, 2.8$ Hz, 1H), 2.01 (ddd, $J = 12.7, 8.9, 7.5$ Hz, 1H), 0.88 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 152.2, 131.5, 129.8, 118.6 (q, $J_{\text{C-F}} = 320$ Hz, CF_3) 115.7, 63.7, 57.6, 54.9,

43.6, 39.3, 26.0, 25.9, 18.4, -5.37, -5.41; IR (neat): 3055, 2951, 2857, 1648, 1420, 1249, 1206, 1141, 1085, 1015, 832, 774, 702 (cm⁻¹); HRMS (EI) calcd for C₁₃H₁₈F₃O₄SSi [M-tBu]⁺: 355.0647, found 355.0655.

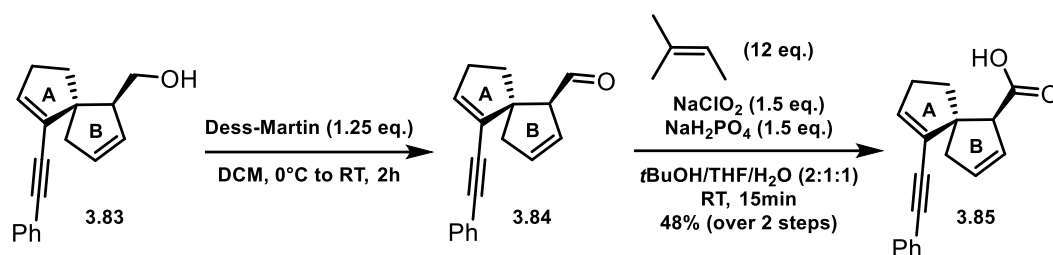


2-((6-(phenylethynyl)spiro[4.4]nona-2,6-dien-1-yl)methoxy)tetrahydro-2H-pyran (3.82). In a sealable flask were added vinyl triflate **3.81** (2.1039 g, 5.0998 mmol), phenylacetylene (672 μ L, 6.12 mmol, 1.2 eq.), CuI (9.7 mg, 0.051 mmol, 1 mol%) and Pd(PPh₃)₂Cl₂ (35.8 mg, 0.0510 mmol, 1 mol%). 10.2 mL Et₃N was added, the flask was sealed and heated to 60 °C overnight. The reaction mixture was evaporated under reduced pressure, and purified directly over silica gel (0.5-2% EtOAc/Hex) to afford enyne **3.82** as an orange oil (1.859 g, quant.): R_f 0.23 (2% EtOAc/Hex); ¹H-NMR (400 MHz, CDCl₃) δ 7.45-7.34 (m, 2H), 7.34-7.27 (m, 3H), 6.17 (t, *J* = 2.8 Hz, 1H), 5.89-5.75 (m, 2H), 3.76 (dd, *J* = 9.7, 6.2 Hz, 1H), 3.71 (t, *J* = 9.5 Hz, 1H), 2.89 (dq, *J* = 16.5, 1.8 Hz, 1H), 2.83 (ddt, *J* = 8.1, 6.1, 1.9 Hz, 1H), 2.51 (dtd, *J* = 17.6, 8.1, 2.4 Hz, 1H), 2.44-2.22 (m, 2H), 2.17 (ddd, *J* = 12.5, 7.8, 2.9 Hz, 1H), 1.93 (dt, *J* = 12.5, 8.6 Hz, 1H), 0.88 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H); ¹³C-NMR (100 MHz, CDCl₃) δ 138.9, 132.5, 131.4, 130.2, 130.0, 128.3, 128.0, 123.9, 92.2, 86.8, 64.9, 59.0, 57.8, 45.8, 41.3, 31.2, 26.1, 18.5, -5.1, -5.2; IR (neat): 3052, 2949, 2853, 1488, 1250, 1077, 832, 752, 689 (cm⁻¹); HRMS (EI) calcd for C₂₄H₃₂OSi [M]⁺: 364.2222, found 364.2216.



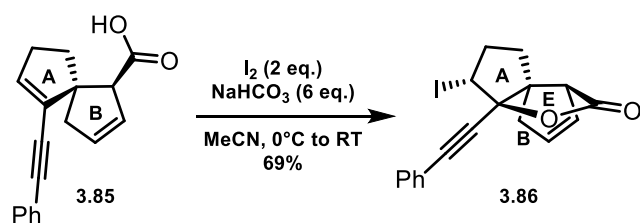
(6-(phenylethynyl)spiro[4.4]nona-2,6-dien-1-yl)methanol (3.83). To a solution of enyne **3.82** (1.7831 g, 4.8905 mmol) in 49 mL THF was added TBAF (1 M in THF, 9.78 mL, 9.78 mmol, 2 eq.). The reaction was stirred at RT for 1 h and was then heated to 50 °C for 15 min. The solution was cooled to RT, evaporated under reduced pressure and the crude was purified directly over silica gel (20-30% EtOAc/Hex) to afford alcohol **3.83** (1.074 g, 88%): R_f 0.31 (20% EtOAc/Hex); ¹H-NMR (400 MHz, CDCl₃) δ 7.50-7.36 (m, 2H), 7.36-7.27 (m, 3H), 6.30 (t, *J* = 2.8 Hz, 1H), 5.90 (dq, *J* = 6.2, 2.1 Hz, 1H), 5.69 (dq, *J* = 11.5, 5.5 Hz, 1H), 3.79 (dd, *J* = 11.5, 6.5 Hz, 1H), 3.69 (dd, *J* = 11.5, 5.5 Hz, 1H), 2.98 (dq, *J* = 16.6, 2.4 Hz, 1H), 2.82-2.76 (ddt, *J* = 6.0, 4.7, 2.3 Hz, 1H), 2.52 (dddd, *J* = 17.8, 8.8, 7.6, 2.4 Hz, 1H), 2.38 (ddt, *J* = 17.8, 8.8, 2.8 Hz, 1H), 2.31-2.20 (m, 1H), 2.14 (ddd, *J* = 12.6, 7.6, 2.6 Hz, 1H), 1.90 (dt, *J* = 12.5, 8.8 Hz, 1H), 1.91 (s(br), 1H); ¹³C-NMR (100 MHz, CDCl₃) δ 140.3, 131.7, 131.5, 130.8, 129.4, 128.44, 128.35, 123.2, 92.5, 86.1, 63.7, 59.1, 57.9, 45.0,

42.4, 30.9; IR (neat): 3325(br), 3050, 2922, 2838, 2201, 1487, 1442, 1322, 1005, 810, 752, 688 (cm^{-1}); HRMS (EI) calcd for $\text{C}_{18}\text{H}_{18}\text{O}$ $[\text{M}]^+$: 250.1358, found 250.1365.



6-(phenylethynyl)spiro[4.4]nona-2,6-diene-1-carboxylic acid (3.85). To a solution of alcohol **3.83** (150 mg, 0.598 mmol) in 6 mL DCM at 0 °C was added Dess-Martin periodinane (318 mg, 0.750 mmol, 1.25 eq.). The solution was warmed to RT and stirred for 2 h. The reaction mixture was quenched with 10 mL aq. sat. NaHCO_3 /5% $\text{Na}_2\text{S}_2\text{O}_3$ (1:1), extracted with (3 x 10 mL) DCM, washed with (3 x 10 mL) NaOH (0.1 M), dried over Na_2SO_4 , filtered, and evaporated under reduced pressure to afford aldehyde **3.84**: R_f 0.64 (20% EtOAc/Hex). The crude was used directly in the next step.

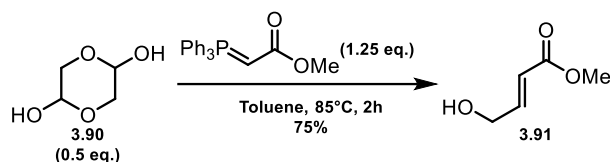
Aldehyde **3.84** (≤ 149 mg, 0.598 mmol) and NaH_2PO_4 (124 mg, 0.898 mmol, 1.5 eq.) were dissolved in 12 mL $t\text{BuOH/THF/H}_2\text{O}$ (2:1:1) at RT. Thereafter, 2-methyl-2-butene (761 μL , 7.18 mmol, 12 eq.) and NaClO_2 (102 mg, 0.898 mmol, 1.5 eq.) were added and the solution was stirred at RT for 30 min. The reaction was quenched with 30 mL aq. sat. NaCl, extracted with (3 x 30 mL) Et_2O , dried over Na_2SO_4 , filtered, and evaporated under reduced pressure. The crude was purified over silica gel (20-30% EtOAc/Hex) to afford carboxylic acid **3.85** (76.2 mg, 48% over 2 steps): R_f 0.16 (20% EtOAc/Hex); $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 11.32 (s(br), 1H), 7.42-7.33 (m, 2H), 7.32-7.22 (m, 3H), 6.15 (t, $J = 2.8$ Hz, 1H), 5.96 (dq, $J = 6.4, 2.3$ Hz, 1H), 5.62 (dq, $J = 6.3, 2.2$ Hz, 1H), 3.37 (quint, $J = 2.0$ Hz, 1H), 2.93 (dq, $J = 16.5, 2.2$ Hz, 1H), 2.53 (dtd, $J = 17.8, 7.7, 2.6$ Hz, 1H), 2.44-2.31 (m, 2H), 2.26 (ddd, $J = 12.1, 8.0, 3.7$ Hz, 1H), 2.07-1.93 (m, 1H).



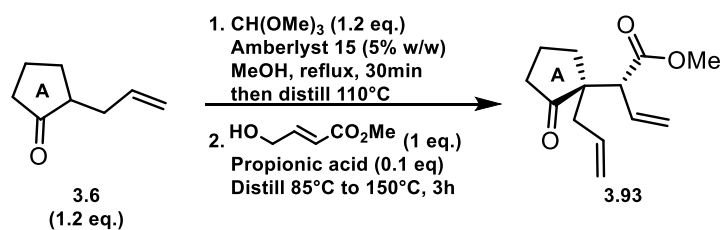
3-iodo-3a-(phenylethynyl)-3,3a,5a,8-tetrahydro-1H-dicyclopenta[b,c]furan-5(2H)-one (3.86). To a solution of carboxylic acid **3.85** (20.4 mg, 0.0771 mmol) in 1 mL MeCN was added NaHCO_3 (38.9 mg, 0.463 mmol, 6 eq.) followed by I_2 (39.2 mg, 0.154 mmol, 2 eq.). The reaction was stirred for 1 h at RT before being quenched with 5 mL 5% $\text{Na}_2\text{S}_2\text{O}_3$, extracted with (3 x 5 mL) Et_2O , dried over Na_2SO_4 , filtered, and

evaporated under reduced pressure. The crude was purified over silica gel (10-20% EtOAc/Hex) to afford lactone **3.86** (20.9 mg, 69%): R_f 0.47 (20% EtOAc/Hex); $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.52-7.39 (m, 2H), 7.39-7.28 (m, 3H), 5.91 (dq, $J = 5.2, 2.5$ Hz, 1H), 5.75-5.64 (m, 1H), 4.79 (q, $J = 2.5$ Hz, 1H), 3.58 (quint, $J = 2.7$ Hz, 1H), 3.44 (dq, $J = 17.7, 2.3$ Hz, 1H), 2.69 (dq, $J = 17.9, 2.5$ Hz, 1H), 2.62 (dt, $J = 13.3, 9.9$ Hz, 1H), 2.22-2.14 (m, 2H), 2.13-2.05 (m, 1H).

4.1.2.5 Route 4 – Incorporation of (*E*)-Methyl 4-Hydroxybut-2-enoate for Claisen Rearrangement:

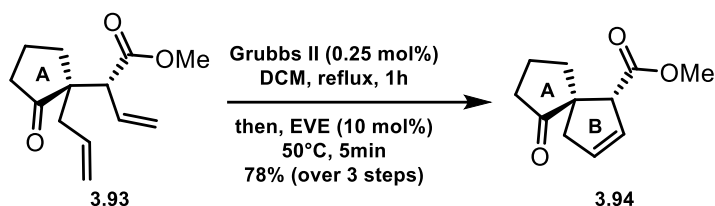


(*E*)-methyl 4-hydroxybut-2-enoate (3.91). A suspension of glycoaldehyde dimer **3.90** (12.5 g, 104 mmol dimer/208 mmol monomer) in toluene (1.04 L) was heated to 85°C for 30 min until the solution turned clear. The reaction mixture was removed from the hot oil bath for 5 min. Thereafter, methyl (triphenylphosphoranylidene)acetate (87.0 g, 260 mmol, 1.25 eq.) was added and the reaction mixture was heated to 85°C for 2 h. The crude was purified over silica gel (40-80% EtOAc/Hex) to afford allyl alcohol **3.91** as a clear oil (18.19 g, 75%): R_f 0.52 (60% EtOAc/Hex). Spectral data was identical to those found in the literature.¹³⁶

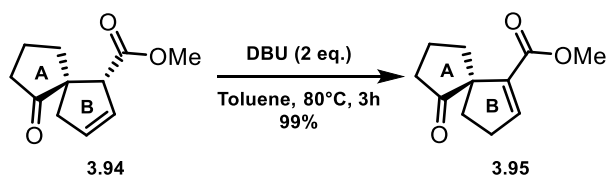


(*R*)-methyl 2-((*R*)-1-allyl-2-oxocyclopentyl)but-3-enoate (3.93). To a solution of α -allyl ketone **3.6** (46.93 g, 377.9 mmol, 1.2 eq.) and Amberlyst® 15 (2.35 g, 5% w/w) in 64 mL MeOH heated to reflux was added trimethyl orthoformate (41.43 mL, 377.9 mmol, 1.2 eq.). After 30 min of heating to reflux, the reaction mixture was cooled to RT, filtered over celite, and rinsed with 20 mL DCM. The filtrate was distilled at 110°C to remove any residual MeOH, DCM and methyl formate. Thereafter, the solution was cooled to RT, then allylic alcohol **3.91** (36.57 g, 314.9 mmol, 1 eq.) and propionic acid (2.35 mL, 31.5 mmol, 0.1 eq.) were added. The resulting solution was distilled at 85°C for 15 min, 100°C for 15 min, 115°C for 15 min, 130°C for 15 min, then 150°C for 2 h. The solution was cooled to RT and evaporated under reduced pressure.

The crude was purified over silica gel (5-12.5% EtOAc/Hex) to afford the bis α -allylated ketone **3.93** as a clear oil in a mixture of isomers which was used directly in the next step: R_f 0.27 (10% EtOAc/Hex); ^1H -NMR (400 MHz, CDCl_3) δ 5.75-5.62 (m, 2H), 5.29 (dd, J = 10.1, 1.5 Hz, 1H), 5.22 (ddd, J = 17.0, 1.5, 0.8 Hz, 1H), 5.12-5.05 (m, 1H), 5.05-4.98 (m, 1H), 3.61 (s, 3H), 3.48 (d, J = 9.6 Hz, 1H), 2.46-2.39 (m, 1H), 2.39-2.31 (m, 1H), 2.31-2.22 (m, 1H), 2.20 (ddt, J = 14.0, 6.7, 1.2 Hz, 1H), 2.11 (ddt, J = 14.0, 8.1, 1.0 Hz, 1H), 2.03-1.91 (m, 1H), 1.91-1.80 (m, 1H), 1.80-1.71 (m, 1H); ^{13}C -NMR (100 MHz, CDCl_3) δ 221.6, 173.0, 132.9, 131.7, 121.0, 119.0, 54.3, 53.0, 52.1, 40.1, 37.9, 31.2, 18.7; IR (neat): 3079, 2955, 1727, 1637, 1435, 1201, 1163, 995, 918 (cm^{-1}); HRMS (EI) calcd for $\text{C}_{11}\text{H}_{14}\text{O}_3$ $[\text{M}]^+$: 222.1256, found 222.1250.

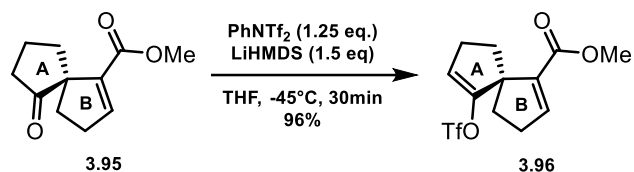


(3.94) A solution of bis α -allylated ketone **3.93** (≤ 70.00 g, ≤ 314.9 mmol) and Grubbs' catalyst 2nd generation (668 mg, 0.787 mmol, 0.25 mol%) in 1.20 L DCM was heated to reflux for 1 h. After the starting material was consumed, ethyl vinyl ether (3.02 mL, 31.5 mmol, 0.1 eq.) was added and the solution was refluxed for 5 min. The reaction mixture was cooled to RT and evaporated under reduced pressure. The crude was purified over silica gel (7.5-15% EtOAc/Hex) to afford the ring-closed spiro ketone **3.94** as a clear oil (47.72 g, 78% over 3 steps): R_f 0.34 (20% EtOAc/Hex); ^1H -NMR (400 MHz, CDCl_3) δ 5.78-5.70 (m, 2H), 3.92 (m, 1H), 3.66 (s, 3H), 2.52 (m, 3H), 2.27-2.15 (m, 1H), 2.04-1.94 (m, 1H), 2.04-1.86 (m, 1H), 1.86-1.71 (m, 2H); ^{13}C -NMR (100 MHz, CDCl_3) δ 219.8, 172.9, 130.1, 128.4, 58.2, 56.2, 51.8, 44.0, 36.7, 33.7, 19.3; IR (neat): 3061, 2954, 1730, 1436, 1317, 1250, 1156, 917, 730 (cm^{-1}); HRMS (EI) calcd for $\text{C}_{11}\text{H}_{14}\text{O}_3$ $[\text{M}]^+$: 194.0943, found 194.0960.

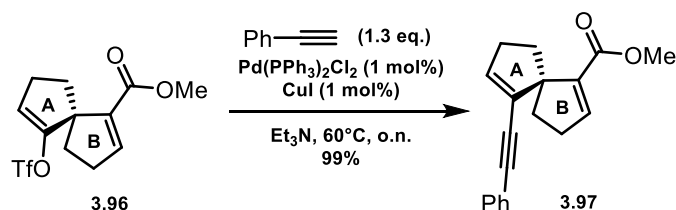


Methyl 6-oxospiro[4.4]non-1-ene-1-carboxylate (3.95). To a solution of ring-closed spiro ketone **3.94** (23.59 g, 121.4 mmol) in 1.21 L toluene was added DBU (36.32 mL, 242.9 mmol, 2 eq.). The reaction mixture was heated to 80 °C for 3 h. The solution was cooled to RT and evaporated under reduced pressure. The crude was purified over silica gel (7.5-15% EtOAc/Hex) to afford α,β -unsaturated ester **3.95**

as a clear oil (23.29 g, 99%): R_f 0.32 (20% EtOAc/Hex); $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 6.92 (t, $J = 2.5$ Hz, 1H), 3.67 (s, 3H), 2.57-2.49 (m, 2H), 2.49-2.38 (m, 1H), 2.36-2.20 (m, 2H), 2.18-2.03 (m, 2H), 1.96-1.68 (m, 3H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 221.7, 164.2, 146.9, 138.8, 61.4, 51.5, 37.8, 36.5, 35.0, 31.5, 20.5; IR (neat): 2954, 1736, 1707, 1625, 1438, 1261, 1156, 1074, 758 (cm^{-1}); HRMS (EI) calcd for $\text{C}_{11}\text{H}_{14}\text{O}_3$ $[\text{M}]^+$: 194.0943, found 194.0917. Spectral data was identical to those found in the literature.¹³⁷

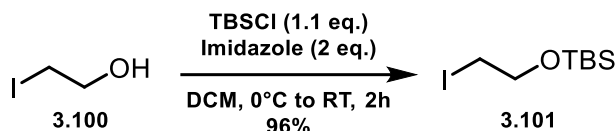


Methyl 6-(((trifluoromethyl)sulfonyl)oxy)spiro[4.4]nona-1,6-diene-1-carboxylate (3.96). To a solution of α,β -unsaturated ester **3.95** (5.00 g, 25.7 mmol) and PhNTf_2 (13.8 g, 38.6 mmol, 1.5 eq.) in 125 mL THF at -45 °C was added a solution of LiHMDS (5.38 g, 32.2 mmol, 1.25 eq.) in 125 mL THF over 5 min. The reaction was stirred at -45 °C for 30 min before being quenched with 250 mL aq. sat $\text{NH}_4\text{Cl}/\text{H}_2\text{O}$ (1:1), extracted with (3 x 200 mL) EtOAc, dried over Na_2SO_4 , filtered, and evaporated under reduced pressure. The crude was purified over silica gel (5% EtOAc/Hex) to afford vinyl triflate **3.96** as a clear oil (8.10 g, 96%): R_f 0.42 (10% EtOAc/Hex); $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 6.94 (t, $J = 2.6$ Hz, 1H), 5.66 (t, $J = 2.6$ Hz, 1H), 3.72 (s, 3H), 2.66-2.55 (m, 1H), 2.55-2.43 (m, 2H), 2.43-2.32 (m, 2H), 2.27 (ddd, $J = 13.4, 8.6, 5.4$ Hz, 1H), 2.03-1.90 (m, 2H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 164.3, 151.2, 147.4, 137.4, 118.6 (q, $J_{\text{C-F}} = 320$ Hz, CF_3), 115.1, 59.3, 51.5, 37.1, 34.6, 30.6, 26.6; IR (neat): 2952, 1718, 1655, 1418, 1203, 1139, 842, 760 (cm^{-1}); HRMS (EI) calcd for $\text{C}_{11}\text{H}_{10}\text{F}_3\text{O}_4\text{S}$ $[\text{M-OMe}]^+$: 295.0258, found 295.0228. Spectral data was identical to those found in the literature.¹³⁷

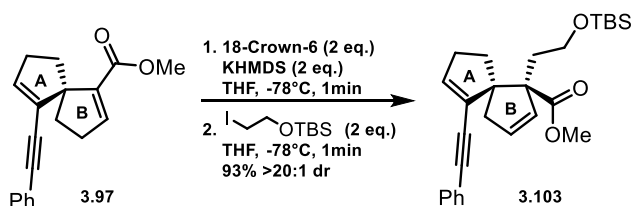


Methyl 6-(phenylethynyl)spiro[4.4]nona-1,6-diene-1-carboxylate (3.97). In a sealable flask were added vinyl triflate **3.96** (5.00 g, 15.3 mmol), phenylacetylene (2.02 mL, 18.4 mmol, 1.2 eq.), CuI (29.2 mg, 0.153 mmol, 1 mol%) and $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (108 mg, 0.153 mmol, 1 mol%). 30.7 mL Et_3N was added, the flask was sealed and heated to 60 °C overnight. The reaction mixture was evaporated under reduced pressure. The crude was purified over silica gel (2.5-5% EtOAc/Hex) to afford enyne **3.97** as a clear oil (4.22 g, 99%): R_f

0.44 (10% EtOAc/Hex); $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.36-7.33 (m, 2H), 7.31-7.24 (m, 3H), 6.93 (t, J = 2.6 Hz, 1H), 6.14 (t, J = 2.8 Hz, 1H), 3.71 (s, 3H), 2.73-2.55 (m, 2H), 2.55-2.39 (m, 2H), 2.39-2.25 (m, 2H), 2.00 (ddd, J = 13.4, 8.6, 5.2 Hz, 1H), 1.93 (ddd, J = 13.0, 8.7, 4.4 Hz, 1H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 165.1, 145.6, 140.0, 137.3, 131.6, 130.6, 128.3, 128.0, 123.8, 90.9, 85.5, 64.0, 51.3, 38.6, 36.0, 32.2, 31.2; IR (neat): 3054, 2936, 2200, 1713, 1619, 1489, 1434, 1247, 1190, 1035, 754, 690 (cm^{-1}); HRMS (EI) calcd for $\text{C}_{19}\text{H}_{18}\text{O}_2$ $[\text{M}]^+$: 278.1307, found 278.1323.

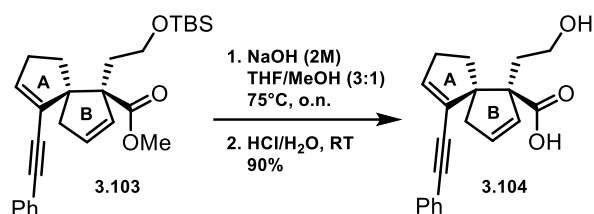


tert-butyl(2-iodoethoxy)dimethylsilane (3.101). To a solution of 2-iodoethanol **3.100** (2.52 g, 14.7 mmol) and imidazole (2.00 g, 29.3 mmol, 2 eq.) in 40 mL DCM at 0 °C was added TBSCl (2.43 g, 16.1 mmol, 1.1 eq.). The reaction mixture was stirred at 0 °C for 30 min, after which the solution was warmed to RT and stirred for 2 h. The reaction was quenched with 50 mL aq. sat. NaHCO_3 , extracted with (3 x 50 mL) DCM, dried over Na_2SO_4 , filtered, and evaporated under reduced pressure. The crude was purified over silica gel (2.5-5% EtOAc/Hex) to afford alkyl iodide **3.101** (4.01 g, 96%) as a clear oil: R_f 0.26 (100% Hex), ρ = 1.306 g/mL. Spectral data was identical to those found in the literature.¹³⁸

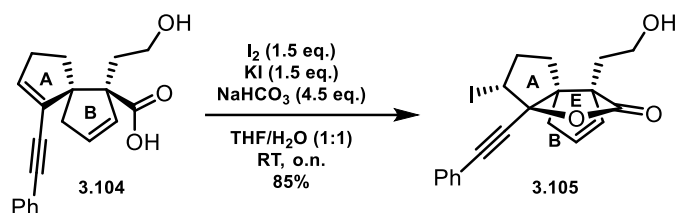


(Methyl 1-(2-((tert-butyl)dimethylsilyl)oxy)ethyl)-6-(phenylethynyl)spiro[4.4]nona-2,6-diene-1-carboxylate (3.103). To a solution of enyne **3.97** (20.00 g, 71.84 mmol) and 18-crown-6 (37.98 g, 143.6 mmol, 2 eq.) in 800 mL THF at -78 °C was added a solution of KHMDS (28.66 g, 143.6 mmol, 2 eq.) in 400 mL THF over 5 min (the solution turns dark red). The reaction mixture was stirred at -78 °C for 1 min before adding alkyl iodide **3.101** (30.51 mL, 41.13 g, 143.6 mmol, 2 eq.). The resulting solution was stirred at -78 °C for 1 min, then the reaction was removed from the cooling bath and was slowly warmed to 0 °C (the solution turns from dark red to brown). The reaction was then quenched with 600 mL aq. sat. NH_4Cl , 600 mL H_2O , extracted with (3 x 600 mL) EtOAc, dried over Na_2SO_4 , filtered, and evaporated under reduced pressure. The crude was purified over silica gel (2.5-4% EtOAc/Hex) to afford α -alkylated ester **3.103** as a clear oil (29.17 g, 93%, >20:1 dr): R_f 0.56 (10% EtOAc/Hex); $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.43-7.34 (m, 2H),

7.32-7.22 (m, 3H), 6.11 (dt, $J = 6.1, 2.0$ Hz, 1H), 6.09 (t, $J = 2.7$ Hz, 1H), 5.82 (dt, $J = 6.0, 2.4$ Hz, 1H), 3.71-3.58 (m, 2H), 3.57 (m, 3H), 2.64-2.57 (m, 1H), 2.57-2.53 (m, 2H), 2.53-2.45 (m, 1H), 2.36 (dddd, $J = 16.9, 7.9, 6.1, 2.7$ Hz, 1H), 2.25 (ddd, $J = 12.6, 8.7, 7.0$ Hz, 1H), 1.89 (ddd, $J = 12.6, 8.3, 4.6$ Hz, 1H), 1.73 (ddd, $J = 12.9, 8.3, 5.0$ Hz, 1H), 0.88 (s, 9H), 0.04 (s, 6H); ^{13}C -NMR (100 MHz, CDCl_3) δ 175.2, 137.9, 133.8, 131.8, 131.3, 129.3, 128.3, 127.8, 124.1, 92.1, 86.0, 65.2, 61.4, 60.4, 51.4, 45.3, 39.2, 32.7, 31.3, 26.1, 18.5, -5.20, -5.23; IR (neat): 3056, 2951, 1727, 1252, 1089, 833 (cm^{-1}); HRMS (EI) calcd for $\text{C}_{27}\text{H}_{36}\text{O}_3\text{Si}$ $[\text{M}]^+$: 436.2434, found 436.2380.

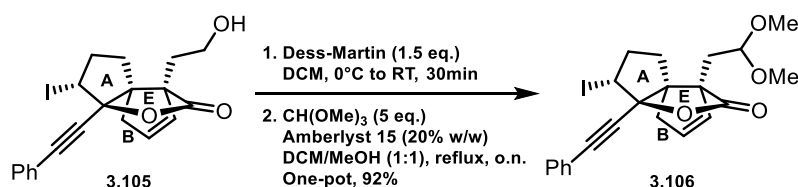


1-(2-hydroxyethyl)-6-(phenylethynyl)spiro[4.4]nona-2,6-diene-1-carboxylic acid (3.104). A solution of α -alkylated ester **3.103** (859 mg, 1.97 mmol) in 20 mL THF/MeOH/NaOH(2 M) (3:1:1) was heated to 75 °C overnight. The reaction mixture was cooled to RT and evaporated under reduced pressure. The residue was diluted with 50 mL H_2O , cooled to 0 °C and acidified to pH 2-3 with HCl (3 M). The solution was warmed to RT, extracted with (3 x 50 mL) EtOAc, dried over Na_2SO_4 , filtered, and evaporated under reduced pressure. The crude was purified over silica gel (60-80% EtOAc/Hex) to afford carboxylic acid **3.104** as a light yellow solid (545 mg, 90%): mp 135-136 °C; R_f 0.24 (80% EtOAc/Hex); ^1H -NMR (400 MHz, CDCl_3) δ 7.41-7.32 (m, 2H), 7.31-7.22 (m, 3H), 6.11 (ddd, $J = 6.0, 2.3, 1.5$ Hz, 1H), 6.07 (t, $J = 2.8$ Hz, 1H), 5.84 (dt, $J = 6.0, 2.4$ Hz, 1H), 3.70-3.62 (m, 2H), 2.60-2.54 (m, 2H), 2.54-2.48 (m, 1H), 2.48-2.39 (m, 1H), 2.38-2.28 (m, 1H), 2.23 (dt, $J = 13.0, 7.6$ Hz, 1H), 1.87 (ddd, $J = 12.4, 9.3, 4.4$ Hz, 1H), 1.75 (ddd, $J = 12.6, 6.6, 5.6$ Hz, 1H); ^{13}C -NMR (100 MHz, CDCl_3) δ 179.3, 138.2, 133.3, 131.4, 131.3, 130.2, 128.3, 127.9, 124.0, 92.7, 86.0, 65.1, 61.2, 60.0, 45.4, 39.1, 32.4, 31.3; IR (neat): 3417(br), 2938, 2840, 1696, 1050, 753 (cm^{-1}); HRMS (ESI) calcd for $[\text{C}_{20}\text{H}_{20}\text{O}_3 + \text{Na}]^+$: 331.1310, found 331.1334.

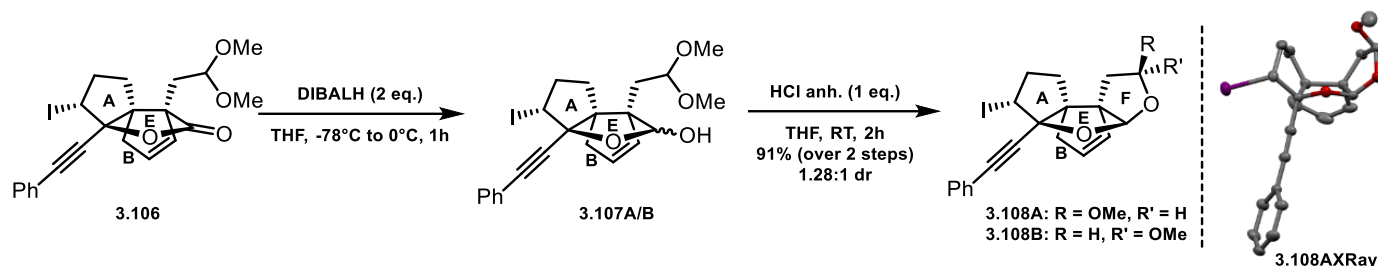


5a-(2-hydroxyethyl)-3-iodo-3a-(phenylethynyl)-3,3a,5a,8-tetrahydro-1H-dicyclopenta[b,c]furan-5(2H)-one (3.105). To a solution of carboxylic acid **3.104** (605 mg, 1.96 mmol), NaHCO_3 (742 mg, 8.83 mmol, 4.5

eq.) and KI (488 mg, 2.94 mmol, 1.5 eq.) in 20 mL THF/H₂O (1:1) was added I₂ (747 mg, 2.94 mmol, 1.5 eq.). The reaction was stirred at RT overnight before being quenched with 20 mL aq. sat. NaHCO₃/5% Na₂S₂O₃ (1:1), extracted with (3 x 20 mL) EtOAc, dried over Na₂SO₄, filtered, and evaporated under reduced pressure. The crude was purified over silica gel (50% EtOAc/Hex) to afford lactone **3.105** as a clear oil (720 mg, 85%): *R*_f 0.51 (60% EtOAc/Hex); ¹H-NMR (400 MHz, CDCl₃) δ 7.47-7.39 (m, 2H), 7.39-7.28 (m, 3H), 6.02 (ddd, *J* = 5.6, 2.5, 1.8 Hz, 1H), 5.73 (m, 1H), 4.76 (d, *J* = 4.6 Hz, 1H), 3.88 (ddd, *J* = 11.2, 7.7, 5.7 Hz, 1H), 3.73 (dt, *J* = 11.7, 6.0 Hz, 1H), 3.32 (ddd, *J* = 17.6, 2.6, 1.1 Hz, 1H), 2.65 (dt, *J* = 17.7, 2.2 Hz, 1H), 2.64 (s(br), 1H), 2.43 (td, *J* = 13.8, 6.2 Hz, 1H), 2.30-2.20 (m, 1H), 2.20-2.08 (m, 2H), 2.08-1.96 (m, 1H), 1.73 (dt, *J* = 14.2, 3.7 Hz, 1H); ¹³C-NMR (100 MHz, CDCl₃) δ 178.7, 134.7, 131.9, 130.6, 129.3, 128.5, 121.7, 94.8, 90.4, 86.6, 63.7, 61.8, 58.6, 45.5, 36.0, 35.6, 35.3, 31.2; IR (neat): 3402(br), 3055, 2965, 2235, 1762, 1442, 1184, 965, 756, 690 (cm⁻¹); HRMS (ESI) calcd for [C₂₀H₁₉IO₃ + Na]⁺: 457.0277, found 457.0257.



5a-(2,2-dimethoxyethyl)-3-iodo-3a-(phenylethynyl)-3,3a,5a,8-tetrahydro-1H-dicyclopenta[b,c]furan-5(2H)-one (3.106). To a solution of lactone **3.105** (720 mg, 1.66 mmol) in 16.5 mL DCM at 0 °C was added Dess-Martin periodinane (1.06 g, 2.49 mmol, 1.5 eq.). The reaction mixture was warmed to RT and stirred for 30 min before adding 16.5 mL MeOH, trimethyl orthoformate (907 μL, 8.29 mmol, 5 eq.) and Amberlyst® 15 (144 mg, 20% w/w). The resulting solution was heated to reflux overnight. The reaction mixture was cooled to RT, filtered, and evaporated under reduced pressure. The crude was purified over silica gel (10-15% EtOAc/Hex with 1% Et₃N) to afford dimethyl acetal **3.106** as a white solid (732 mg, 92%): mp 92-93 °C; *R*_f 0.42 (20% EtOAc/Hex); ¹H-NMR (400 MHz, CDCl₃) δ 7.48-7.38 (m, 2H), 7.38-7.28 (m, 3H), 5.97 (ddd, *J* = 5.6, 2.5, 1.8 Hz, 1H), 5.62 (m, 1H), 4.74 (d, *J* = 4.6 Hz, 1H), 4.52 (dd, *J* = 7.4, 3.6 Hz, 1H), 3.35-3.27 (m, 1H), 3.33 (s, 3H), 3.31 (s, 3H), 2.66 (dt, *J* = 17.5, 2.1 Hz, 1H), 2.41 (m, 2H), 2.31 (dd, *J* = 14.8, 3.6 Hz, 1H), 2.15-2.05 (m, 1H), 2.01-1.90 (m, 1H), 1.89 (dd, *J* = 14.8, 7.4 Hz, 1H); ¹³C-NMR (100 MHz, CDCl₃) δ 177.3, 133.6, 131.8, 130.7, 129.1, 128.4, 121.9, 102.3, 94.3, 90.0, 87.1, 63.3, 61.3, 54.1, 53.0, 46.1, 36.4, 35.8, 35.2, 31.6; IR (neat): 3058, 2992, 1765, 1239, 1045, 903, 767 (cm⁻¹); HRMS (ESI) calcd for [C₂₂H₂₃IO₄ + Na]⁺: 501.0539, found 501.0530.



5-iodo-2-methoxy-4a-(phenylethynyl)-1,2,3a,4a,5,6,7,8-octahydrodicyclopenta[b,c]furo[3,2-d]furan

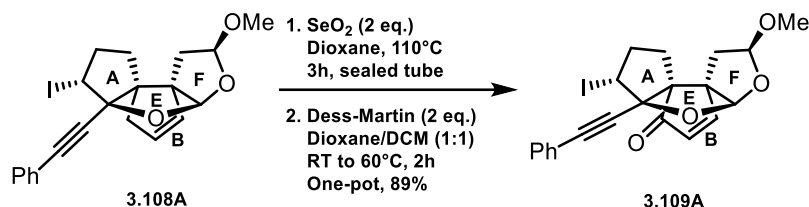
(3.108A/3.108B). To a solution of dimethyl acetal **3.106** (808 mg, 1.69 mmol) in 17 mL THF at -78 °C was added DIBALH (25% in hexane, 2.20 mL, 3.38 mmol, 2 eq.). The reaction was warmed to 0 °C and stirred for 15 min before being quenched with 6.8 mL aq. sat. potassium sodium tartrate and 10 mL NaOH (1 M). The reaction was extracted with (3 x 20 mL) EtOAc, dried over Na₂SO₄, filtered, and evaporated under reduced pressure. The crude was purified over silica gel (20-30% EtOAc/Hex) to afford lactols **3.107A/B** as an inseparable anomeric mixture which was used directly in the next step: *R_f* 0.47 (40% EtOAc/Hex).

To a solution of lactols **3.107A/B** (735 mg, 1.53 mmol) in 15.3 mL THF at 0 °C was added HCl (4 M in dioxane, 383 µL, 1.53 mmol, 1 eq.) dropwise. The reaction mixture was warmed to RT and stirred for 2 h before being quenched with 50 mL aq. sat. NaHCO₃, extracted with (3 x 50 mL) EtOAc, dried over Na₂SO₄, filtered, and evaporated under reduced pressure. The crude was purified over silica gel (5-12.5% EtOAc/Hex) to afford alkene **3.108A** as a white solid (348 mg, 51% over 2 steps) and alkene **3.108B** as a pale-yellow oil (237 mg, 40% over 2 steps) (91% total over 2 steps, 1.28:1 dr).

3.108A: mp 84-85 °C; *R_f* 0.43 (10% EtOAc/Hex); ¹H-NMR (400 MHz, CDCl₃) δ 7.45-7.36 (m, 2H), 7.34-7.27 (m, 3H), 5.75 (dt, *J* = 5.6, 2.2 Hz, 1H), 5.53 (dt, *J* = 5.5, 1.9 Hz, 1H), 5.48 (s, 1H), 5.19 (d, *J* = 5.7 Hz, 1H), 4.67 (d, *J* = 4.8 Hz, 1H), 3.36 (s, 3H), 3.31 (dt, *J* = 17.9, 2.0 Hz, 1H), 2.64 (dddd, *J* = 16.3, 13.6, 7.0, 5.0 Hz, 1H), 2.43 (dt, *J* = 17.9, 2.2 Hz, 1H), 2.31 (dd, *J* = 13.7, 7.2 Hz, 1H), 2.23 (d, *J* = 14.7 Hz, 1H), 2.22-2.11 (m, 1H), 2.09-2.02 (m, 1H), 1.96 (dd, *J* = 14.7, 5.9 Hz, 1H); ¹³C-NMR (100 MHz, CDCl₃) δ 134.2, 131.8, 131.1, 128.5, 128.3, 122.8, 115.4, 108.3, 95.5, 88.5, 88.3, 72.5, 64.8, 55.0, 48.3, 40.5, 38.7, 35.9, 34.5; IR (neat): 3041, 2989, 1017, 912, 776 (cm⁻¹); HRMS (EI) calcd for C₂₁H₂₁IO₃ [M]⁺: 448.0535, found 448.0535.

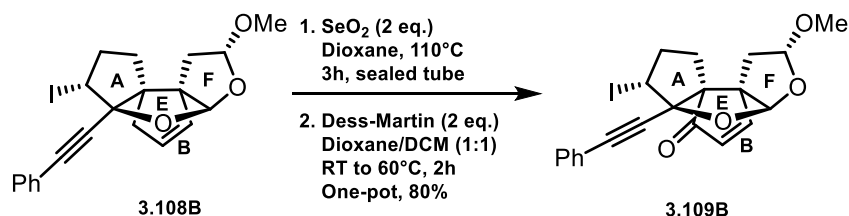
3.108B: *R_f* 0.33 (10% EtOAc/Hex); ¹H-NMR (400 MHz, CDCl₃) δ 7.47-7.38 (m, 2H), 7.35-7.27 (m, 3H), 5.78 (dt, *J* = 5.7, 2.2 Hz, 1H), 5.68 (dt, *J* = 5.6, 1.8 Hz, 1H), 5.53 (s, 1H), 5.14 (t, *J* = 4.9 Hz, 1H), 4.71 (d, *J* = 4.8 Hz, 1H), 3.44 (s, 3H), 3.26 (dt, *J* = 17.6, 2.2, 1.7 Hz, 1H), 2.47 (dt, *J* = 17.6, 2.1 Hz, 1H), 2.47-2.39 (m, 1H), 2.37 (dd, *J* = 14.4, 5.4 Hz, 1H), 2.27 (ddd, *J* = 13.6, 11.9, 6.2 Hz, 1H), 2.10 (ddt, *J* = 13.6, 6.4, 1.6 Hz, 1H), 1.99 (dd, *J* = 13.8, 6.5 Hz, 1H), 1.78 (dd, *J* = 14.3, 4.6 Hz, 1H); ¹³C-NMR (100 MHz, CDCl₃) δ 133.0, 131.8, 131.7,

128.6, 128.3, 122.6, 111.9, 106.6, 97.9, 89.2, 89.0, 71.7, 64.4, 56.2, 46.8, 39.6, 39.0, 36.0, 33.8; IR (neat): 3053, 2952, 966, 757, 691 (cm⁻¹); HRMS (EI) calcd for C₂₁H₂₁IO₃ [M]⁺: 448.0535, found 448.0540.



5-iodo-2-methoxy-4a-(phenylethynyl)-1,2,4a,5,6,7-hexahydrodicyclopenta[b,c]furo[3,2-d]furan-

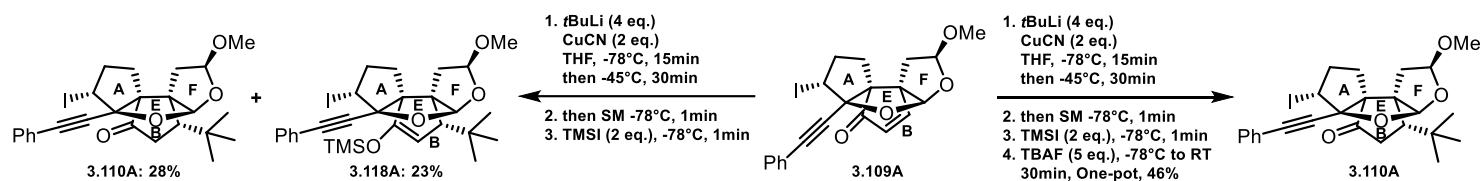
8(3aH)-one (3.109A). In a sealable flask was added alkene **3.108A** (174 mg, 0.388 mmol), 7.8 mL dioxane and SeO₂ (86.0 mg, 0.775 mmol, 2 eq.). The flask was sealed and heated to 110 °C for 3 h, after which the reaction mixture was cooled to RT. 7.8 mL DCM and Dess-Martin periodinane (329 mg, 0.775 mmol, 2 eq.) were added. The flask was sealed and heated to 60 °C for 2 h. The reaction mixture was cooled to RT, a dry pack was prepared and the crude was purified over silica gel (10-40% EtOAc/Hex) to afford enone **3.109A** as a white solid (159 mg, 89%): mp 111-112 °C; R_f 0.42 (40% EtOAc/Hex); ¹H-NMR (400 MHz, CDCl₃) δ 7.42 (d, *J* = 5.7 Hz, 1H), 7.41-7.36 (m, 2H), 7.33-7.26 (m, 3H), 6.20 (d, *J* = 5.7 Hz, 1H), 5.68 (s, 1H), 5.27 (dd, *J* = 5.6, 0.8 Hz, 1H), 4.61 (t, *J* = 4.8 Hz, 1H), 3.41 (s, 3H), 2.80 (dddd, *J* = 13.4, 9.3, 6.7, 5.6 Hz, 1H), 2.56 (ddd, *J* = 13.5, 9.3, 6.9 Hz, 1H), 2.37 (ddt, *J* = 13.5, 6.9, 4.0 Hz, 1H), 2.26 (d, *J* = 14.6 Hz, 1H), 2.19 (dd, *J* = 14.7, 5.6 Hz, 1H), 2.08 (ddd, *J* = 13.4, 6.7, 4.0 Hz, 1H); ¹³C-NMR (100 MHz, CDCl₃) δ 205.1, 162.6, 131.9, 131.8, 128.9, 128.3, 121.9, 112.6, 107.8, 94.1, 91.1, 87.0, 69.9, 69.3, 55.3, 39.7, 37.2, 35.0, 29.8; IR (neat): 2924, 2362, 1717, 1019, 758 (cm⁻¹); HRMS (EI) calcd for C₂₁H₁₉IO₄ [M]⁺: 462.0328, found 462.0319.



5-iodo-2-methoxy-4a-(phenylethynyl)-1,2,4a,5,6,7-hexahydrodicyclopenta[b,c]furo[3,2-d]furan-

8(3aH)-one (3.109B). In a sealable flask was added alkene **3.108B** (479 mg, 1.07 mmol), 21 mL dioxane and SeO₂ (237 mg, 2.14 mmol, 2 eq.). The flask was sealed and heated to 110 °C for 3 h, after which the reaction mixture was cooled to RT. 21 mL DCM and Dess-Martin periodinane (906 mg, 2.14 mmol, 2 eq.) were added and the reaction was stirred at RT for 2 h. A dry pack was prepared and the crude was purified over silica gel (10-40% EtOAc/Hex) to afford enone **3.109B** as a white solid (396 mg, 80%): mp 114-115 °C; R_f 0.44 (40% EtOAc/Hex); ¹H-NMR (400 MHz, CDCl₃) δ 7.60 (d, *J* = 5.8 Hz, 1H), 7.44-7.38 (m, 2H), 7.35-7.27

(m, 3H), 6.23 (d, $J = 5.8$ Hz, 1H), 5.69 (s, 1H), 5.26 (dd, $J = 5.4, 3.0$ Hz, 1H), 4.61 (dd, $J = 6.5, 5.0$ Hz, 1H), 3.45 (s, 3H), 2.57-2.45 (m, 2H), 2.45-2.35 (m, 2H), 1.98 (dd, $J = 14.4, 3.0$ Hz, 1H), 1.74-1.67 (m, 1H); ^{13}C -NMR (100 MHz, CDCl_3) δ 205.0, 162.1, 132.7, 131.9, 129.0, 128.3, 121.8, 110.4, 106.1, 95.9, 91.8, 87.0, 68.8, 68.5, 56.0, 38.1, 37.5, 35.1, 30.6; IR (neat): 2953, 2360, 1717, 1490, 1443, 1214, 1053, 961, 759, 692 (cm^{-1}); HRMS (ESI) calcd for $[\text{C}_{21}\text{H}_{19}\text{IO}_4 + \text{Na}]^+$: 485.0226, found 485.0227.

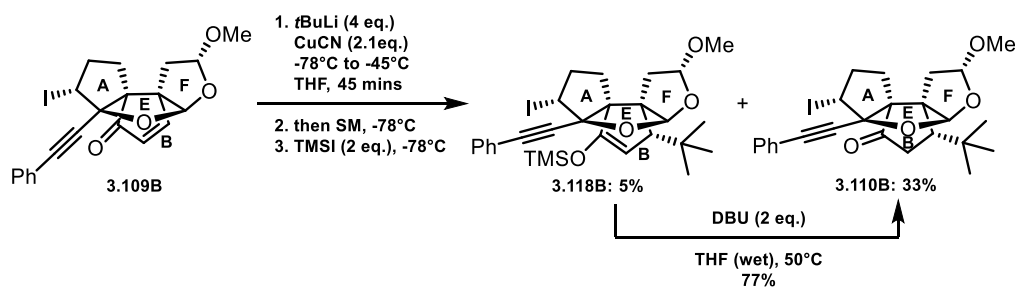


(3.110A/3.118A). (One-pot procedure without TBAF) To a suspension of CuCN (29.1 mg, 0.325 mmol, 2 eq.) in 3.25 mL THF at -78°C was added $t\text{BuLi}$ (1.51 M in pentane, 430 μL , 649 mmol, 4 eq.) dropwise over 5 min (the solution turned from clear to light yellow). The reaction mixture was stirred at -78°C for 15 min before being warmed to -45°C and stirred for 30 min (the solution turned from light yellow to clear). The reaction mixture was cooled to -78°C and a solution of **3.109A** (75.0 mg, 0.162 mmol) in 3.25 mL THF was added dropwise (the solution turned from clear to red). The solution was stirred at -78°C for 1 min before adding TMSI (46.2 μL , 0.325 mmol, 2 eq.) dropwise (solution turned from red to brown). The reaction mixture was quenched with 10 mL aq. sat. NH_4Cl , extracted with (3 x 10 mL) EtOAc, dried over Na_2SO_4 , filtered, and evaporated under reduced pressure. The crude was purified over silica gel (5-15% EtOAc/Hex) to afford ketone **3.110A** as a white solid (23.6 mg, 28%) and TMS enol ether **3.118A** (22.6 mg, 23%).

(One-pot procedure with TBAF) To a suspension of CuCN (58.1 mg, 0.649 mmol, 2 eq.) in 5 mL THF at -78°C was added $t\text{BuLi}$ (1.7 M in pentane, 763 μL , 1.30 mmol, 4 eq.) dropwise over 5 min (the solution turned from clear to light yellow). The reaction mixture was stirred at -78°C for 15 min before being warmed to -45°C and stirred for 30 min (the solution turned from light yellow to clear). The reaction mixture was cooled to -78°C and a solution of **3.109A** (150 mg, 0.324 mmol) in 2 mL THF was added dropwise (the solution turned from clear to red). The solution was stirred at -78°C for 1 min before adding TMSI (92.4 μL , 0.649 mmol, 2 eq.) dropwise (solution turned from red to brown). The reaction mixture was stirred at -78°C for 1 min, then TBAF (1 M in THF, 1.62 mL, 1.62 mmol, 5 eq.) was added and the solution was stirred at -78°C for 5 min after which the reaction quenched with 10 mL aq. sat. NH_4Cl , extracted with (3 x 10 mL) EtOAc, dried over Na_2SO_4 , filtered, and evaporated under reduced pressure. The crude was purified over silica gel (5-15% EtOAc/Hex) to afford ketone **3.110A** as a white solid (78.1 mg, 46%).

3.110A: mp 142-143 °C; R_f 0.49 (20% EtOAc/Hex); $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.49-7.36 (m, 2H), 7.39-7.27 (m, 3H), 5.77 (s, 1H), 5.25 (dd, J = 6.9, 2.7 Hz, 1H), 4.71-4.55 (m, 1H), 3.42 (s, 3H), 2.75 (dd, J = 14.9, 6.9 Hz, 1H), 2.75-2.50 (m, 4H), 2.36 (dd, J = 18.0, 10.9 Hz, 1H), 2.36-2.28 (m, 1H), 2.19 (ddd, J = 13.3, 6.0, 3.8 Hz, 1H), 1.94 (dd, J = 14.8, 2.7 Hz, 1H), 1.06 (s, 9H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 213.4, 131.7, 129.1, 128.4, 121.8, 116.5, 107.8, 96.4, 90.9, 88.0, 75.6, 67.7, 56.5, 47.8, 41.1, 37.6, 36.3, 34.3, 33.4, 31.3, 29.4; IR (neat): 2964, 2362, 1737, 1438, 1103, 964, 757, 694 (cm^{-1}); HRMS (EI) calcd for $\text{C}_{25}\text{H}_{29}\text{IO}_4$ $[\text{M}]^+$: 520.1111, found 520.1094.

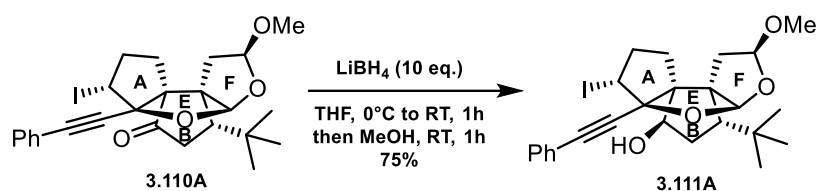
3.118A: R_f 0.67 (20% EtOAc/Hex); $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.49-7.39 (m, 2H), 7.33-7.27 (m, 3H), 5.34 (t, J = 5.7 Hz, 1H), 5.27 (s, 1H), 4.66 (t, J = 4.8 Hz, 1H), 4.58 (d, J = 2.4 Hz, 1H), 3.46 (s, 3H), 2.65 (dd, J = 14.7, 6.0 Hz, 1H), 2.60-2.48 (m, 1H), 2.48-2.36 (m, 1H), 2.35 (d, J = 2.5 Hz, 1H), 2.33-2.22 (m, 1H), 2.04 (dd, J = 14.7, 5.5 Hz, 1H), 1.62 (ddd, J = 13.3, 6.0, 4.0 Hz, 1H), 0.95 (s, 9H), 0.20 (s, 9H).



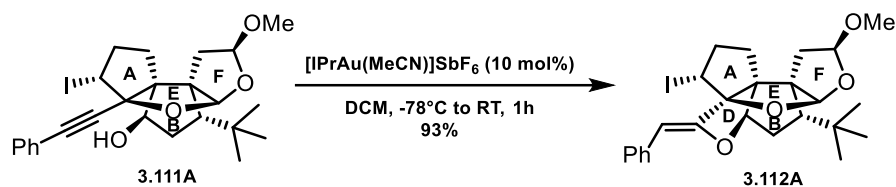
10-(*tert*-butyl)-5-iodo-2-methoxy-4a-(phenylethynyl)octahydrodicyclopenta[b,c]furo[3,2-d]furan-8(3aH)-one (3.110B) and **((10-(*tert*-butyl)-5-iodo-2-methoxy-4a-(phenylethynyl)-1,2,3a,4a,5,6,7,10-octahydrodicyclopenta[b,c]furo[3,2-d]furan-8-yl)oxy)trimethylsilane (3.118B)**. To a suspension of CuCN (81.4 mg, 0.908 mmol, 2.1 eq.) in 8.6 mL THF at -78°C was added $t\text{BuLi}$ (1.41 M in pentane, 1.22 mL, 1.73 mmol, 4 eq.) dropwise over 5 min (the solution turned from clear to light yellow). The reaction mixture was stirred at -78°C for 30 min before being warmed to -45°C and stirred for 30 min (the solution turned from light yellow to clear). The reaction mixture was cooled to -78°C and a solution of **3.109A** (200 mg, 0.433 mmol) in 4 mL THF was added dropwise (the solution turned from clear to red). The solution was stirred at -78°C for 1 min before adding TMSI (123 μL , 0.865 mmol, 2 eq.) dropwise (solution turned from red to brown). The reaction mixture was stirred at -78°C for 1 min, quenched with 25 mL aq. sat. NH_4Cl , extracted with (3 x 25 mL) EtOAc, dried over Na_2SO_4 , filtered, and evaporated under reduced pressure. The crude was purified over silica gel (5-10% EtOAc/Hex with 1% Et_3N) to afford ketone **3.110B** as a white solid (75.0 mg, 33%) and TMS enol ether **3.118B** (13.1 mg, 5%) (which was converted to **3.110B** in a 77% yield with DBU in wet THF at 50°C).

3.110B: R_f 0.42 (20% EtOAc/Hex); $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.44-7.39 (m, 2H), 7.36-7.28 (m, 3H), 5.87 (s, 1H), 5.07 (dd, $J = 6.0, 3.8$ Hz, 1H), 4.61 (t, $J = 5.5$ Hz, 1H), 3.41 (s, 3H), 2.76-2.55 (m, 4H), 2.42 (dd, $J = 14.6, 3.8$ Hz, 1H), 2.38-2.25 (m, 3H), 2.16 (dd, $J = 14.6, 6.2$ Hz, 1H), 1.10 (s, 9H); IR (neat): 2964, 2361, 1737, 1103, 1056, 757, 694 (cm^{-1}).

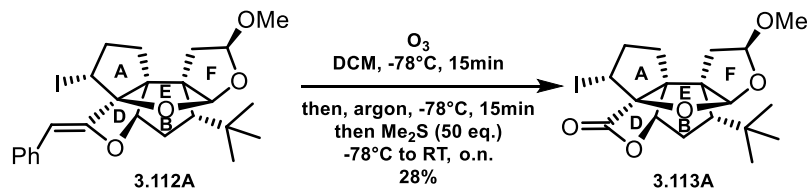
3.118B: R_f 0.62 (20% EtOAc/Hex); $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.48-7.37 (m, 2H), 7.37-7.27 (m, 3H), 6.32 (t, $J = 2.8$ Hz, 1H), 5.65 (s, 1H), 4.99 (t, $J = 5.7$ Hz, 1H), 3.41 (s, 3H), 2.98 (dd, $J = 11.5, 6.5$ Hz, 1H), 2.81 (dd, $J = 18.8, 11.6$ Hz, 1H), 2.62-2.49 (dddd, $J = 17.2, 8.5, 5.4, 3.0$ Hz, 1H), 2.48 (dd, $J = 14.0, 5.3$ Hz, 1H), 2.39 (dd, $J = 18.7, 6.5$ Hz, 1H), 2.38-2.29 (m, 1H), 2.06 (dd, $J = 14.1, 6.0$ Hz, 1H), 1.91 (ddd, $J = 13.8, 8.5, 5.3$ Hz, 1H), 1.05 (s, 9H), 0.12 (s, 9H).



(3.111A). To a solution of **3.110A** (31.7 mg, 0.0609 mmol) in 3 mL THF at 0 °C was added a solution of LiBH_4 (2.0 M in THF, 345 μL 0.609 mmol, 10 eq.). The reaction mixture was stirred from 0 °C to RT for 1 h, after which was added 3 mL MeOH. The reaction was stirred at RT for 1 h, diluted with 20 mL EtOAc, quenched with 20 mL aq. sat. NaCl /aq. sat. NaHCO_3 (1:1), extracted with (3 x 20 mL) EtOAc, dried over Na_2SO_4 , filtered, and evaporated under reduced pressure. The crude was purified over silica gel (5-15% EtOAc/Hex) to afford ketone **3.111A** as a white solid (23.9 mg, 75%): mp 158-159 °C; R_f 0.61 (20% EtOAc/Hex); $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.58-7.45 (m, 2H), 7.42-7.29 (m, 3H), 5.75 (s, 1H), 5.29 (dd, $J = 6.9, 2.9$ Hz, 1H), 5.23 (dd, $J = 10.9, 6.7$ Hz, 1H), 4.15-3.97 (m, 1H), 3.75-3.53 (m, 1H), 3.45 (s, 3H), 2.95 (dd, $J = 15.6, 6.9$ Hz, 1H), 2.56-2.42 (m, 1H), 2.43 (dd, $J = 11.3, 7.3$ Hz, 1H), 2.38-2.24 (m, 1H), 2.12-1.88 (m, 3H), 1.83-1.66 (m 2H), 0.98 (s, 9H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 131.9, 129.3, 128.6, 121.54, 121.51, 108.2, 92.6, 90.0, 89.4, 78.9, 72.1, 65.7, 55.8, 54.3, 37.6, 36.7, 36.3, 36.1, 32.53, 32.51, 29.4; IR (neat): 3550(br), 2960, 2358, 1490, 1374, 1129, 1088, 1032, 956, 757, 690 (cm^{-1}); HRMS (ESI) calcd for $[\text{C}_{25}\text{H}_{31}\text{IO}_4 + \text{Na}]^+$: 545.1165, found 545.1151.

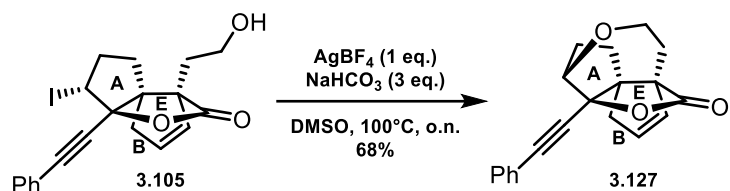


(3.112A). To a solution of **3.111A** (15.0 mg, 0.0287 mmol) in 10 mL DCM at -78 °C was added a solution of [IPrAu(MeCN)]SbF₆ (2.5 mg, 0.0029 mmol, 10 mol%) in 1 mL DCM. The reaction mixture was stirred from -78 °C to RT for 1 h. The reaction mixture was evaporated under reduced pressure and the crude was purified via silica prep TLC plate (15% EtOAc/Hex) to afford enol ether **3.112A** as a white solid (14.0 mg, 93%): mp 57-58 °C; *R*_f 0.28 (10% EtOAc/Hex); ¹H-NMR (400 MHz, CDCl₃) δ 7.59 (d, *J* = 7.7 Hz, 2H), 7.30 (t, *J* = 7.7 Hz, 2H), 7.12 (t, *J* = 7.4 Hz, 1H), 5.60 (s, 1H), 5.45 (s, 1H), 5.23 (d, *J* = 6.3 Hz, 1H), 4.73-4.48 (m, 2H), 3.40 (s, 3H), 2.77 (dq, *J* = 12.1, 5.9 Hz, 1H), 2.60 (dd, *J* = 14.6, 6.4 Hz, 1H), 2.48 (dt, *J* = 13.4, 7.0 Hz, 1H), 2.39-2.10 (m, 3H), 1.95 (d, *J* = 14.6 Hz, 1H), 1.90-1.70 (m, 2H), 0.97 (s, 9H); ¹³C-NMR (100 MHz, CDCl₃) δ 159.1, 136.2, 128.3, 128.1, 125.5, 120.8, 108.8, 105.8, 100.9, 92.5, 72.7, 66.9, 55.3, 53.5, 41.3, 37.9, 35.0, 34.9, 32.8, 32.3, 29.3; IR (neat): 3049, 2944, 1669, 1448, 1368, 1082, 973, 818, 733, 693 (cm⁻¹); HRMS (ESI) calcd for [C₂₅H₃₁O₄ + Na]⁺: 545.1165, found 545.1177. (note: The [IPrAu(MeCN)]SbF₆ catalyst was prepared following the literature procedure by Nolan et al.)¹³⁹

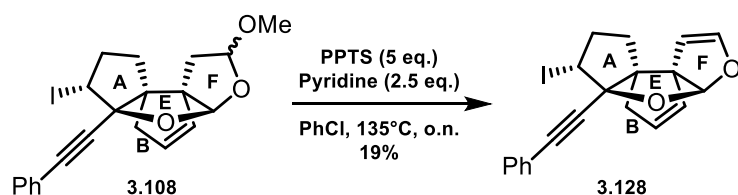


(3.113A). To a solution of **3.112A** (23.7 mg, 0.0454 mmol) in 20 mL DCM at -78 °C was bubbled a stream of O₃/O₂ for 15 min (solution became blue). The solution was then bubbled with argon for 15 min at -78 °C after which Me₂S (167 μL, 2.27 mmol, 50 eq.) was added. The reaction mixture was stirred from -78 °C to RT for 1 h and was then evaporated under reduced pressure. The residue was dissolved in 50 mL EtOAc, washed with 80 mL (1:1) H₂O/aq. sat. NaCl, extracted with (3 x 50 mL) EtOAc, dried over Na₂SO₄, filtered, and evaporated under reduced pressure. The crude was purified over silica gel (5-15% EtOAc/Hex) to afford lactone **3.113A** as a white solid (5.6 mg, 28%): mp 199-200 °C; *R*_f 0.36 (20% EtOAc/Hex); ¹H-NMR (400 MHz, CDCl₃) δ 5.66 (s, 1H), 5.17 (d, *J* = 6.7 Hz, 1H), 4.47 (d, *J* = 4.1 Hz, 1H), 4.37 (dd, *J* = 7.7, 6.6 Hz, 1H), 3.39 (s, 3H), 2.95-2.71 (m, 1H), 2.71-2.48 (m, 2H), 2.42-2.15 (m, 2H), 2.10 (dd, *J* = 14.0, 4.6 Hz, 1H), 1.96 (d, *J* = 14.8 Hz, 1H), 1.85 (dt, *J* = 12.9, 6.2 Hz, 1H), 1.77 (td, *J* = 10.9, 4.1 Hz, 1H), 1.01 (s, 9H); ¹³C-NMR (150 MHz, CDCl₃) δ 173.7, 120.2, 107.6, 101.7, 87.7, 71.6, 67.1, 55.9, 52.7, 40.9, 36.1, 34.5, 33.9, 32.4,

29.3, 26.8; IR (neat): 2943, 2854, 1768, 1442, 1350, 1219, 1126, 1004, 890, 791, 735, 704 (cm^{-1}); HRMS (ESI) calcd for $[\text{C}_{18}\text{H}_{25}\text{IO}_5 + \text{Na}]^+$: 471.0644, found 471.0623.

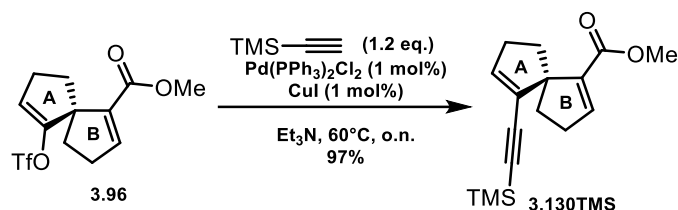


3-hydroxy-3a-(phenylethynyl)-1,2,3a-tetrahydro-3,5a-(epoxyethano)dicyclopenta[b,c]furan-5(8H)-one (3.127). In a sealable flask were added lactone **3.105** (50.0 mg, 0.115 mmol), 1 mL DMSO, NaHCO_3 (29.0 mg, 0.345 mmol, 3 eq.) and a solution of AgBF_4 (22.4 mg, 0.115 mmol, 1 eq.) in 1.3 mL DMSO. The flask was sealed and heated to 100 °C overnight. The reaction was cooled to RT, diluted with 20 mL H_2O , extracted with (3 x 20 mL) EtOAc, washed with 20 mL H_2O , dried over Na_2SO_4 , filtered, and evaporated under reduced pressure. The crude was purified over silica gel (10-40% EtOAc/Hex) to afford ether **3.127** as a thick clear paste (25.2 mg, 68%): R_f 0.58 (40% EtOAc/Hex); $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.58-7.47 (m, 2H), 7.33-7.22 (m, 3H), 6.06 (ddd, J = 5.7, 2.6, 2.2 Hz, 1H), 5.60 (ddd, J = 5.8, 2.4, 1.3 Hz, 1H), 4.53 (ddd, J = 9.8, 8.9, 6.3 Hz, 1H), 4.30 (td, J = 8.6, 2.7 Hz, 1H), 3.76 (s, 3H), 3.08 (dq, J = 15.8, 2.0 Hz, 1H), 2.51 (ddd, J = 13.5, 6.3, 2.7 Hz, 1H), 2.30 (ddd, J = 13.4, 9.8, 8.6 Hz, 1H), 2.24-2.15 (m, 1H), 2.06 (dd, J = 14.1, 7.7 Hz, 1H), 1.84 (dddd, J = 14.1, 10.3, 8.0, 1.1 Hz, 1H), 1.73-1.62 (m, 1H), 1.48 (dd, J = 12.5, 7.9 Hz, 1H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 176.7, 134.3, 133.3, 132.3, 128.6, 128.2, 122.3, 86.9, 83.0, 66.0, 65.7, 58.9, 58.21, 58.17, 41.0, 30.8, 29.4, 25.0; IR (neat): 3057, 2963, 1757, 1490, 1441, 1155, 1066, 872, 757, 693 (cm^{-1}); HRMS (ESI) calcd for $[\text{C}_{20}\text{H}_{18}\text{O}_3 + \text{Na}]^+$: 329.1154, found 329.1130.

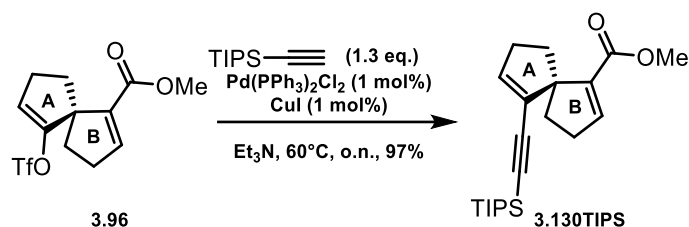


5-iodo-4a-(phenylethynyl)-3a,4a,5,6,7,8-hexahydrodicyclopenta[b,c]furo[3,2-d]furan (3.128). In a sealable flask were added alkenes **3.108** (172.1 mg, 0.3838 mmol), 7.7 mL chlorobenzene, PPTS (482.3 mg, 1.919 mmol, 5 eq.) and pyridine (77.6 μL , 0.960 mmol, 2.5 eq.). The flask was sealed and heated to reflux at 135 °C overnight. The reaction mixture was cooled to RT and evaporated under reduced pressure and the crude was purified over silica gel (2.5% EtOAc/Hex) to afford enol ether **3.128** as a clear oil (29.9 mg, 19%): R_f 0.47 (10% EtOAc/Hex); $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.49-7.39 (m, 2H), 7.37-7.27 (m, 3H), 6.38

(d, $J = 2.8$ Hz, 1H), 5.79 (dt, $J = 5.8, 2.3$ Hz, 1H), 5.64 (s, 1H), 5.49 (dt, $J = 5.8, 2.2$ Hz, 1H), 4.87 (d, $J = 2.8$ Hz, 1H), 4.71-4.63 (m, 1H), 3.37 (dt, $J = 18.1, 2.3$ Hz, 1H), 2.52 (dt, $J = 18.1, 2.3$ Hz, 1H), 2.24-1.97 (m, 4H); ^{13}C -NMR (100 MHz, CDCl_3) δ 145.4, 132.1, 131.9, 131.4, 128.8, 128.4, 122.5, 114.0, 104.3, 96.7, 89.4, 88.1, 77.7, 65.5, 47.5, 38.5, 35.7, 35.5; IR (neat): 3053, 2959, 2364, 1608, 1489, 1145, 1046, 756, 689 (cm^{-1}); HRMS (EI) calcd for $\text{C}_{20}\text{H}_{17}\text{IO}_2$ $[\text{M}]^+$: 416.0273, found 416.0265.

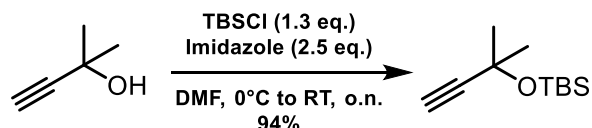


methyl 6-((trimethylsilyl)ethynyl)spiro[4.4]nona-1,6-diene-1-carboxylate (3.130TMS). In a sealable flask were added vinyl triflate **3.96** (8.10 g, 24.8 mmol), trimethylsilylacetylene (4.13 mL, 29.8 mmol, 1.2 eq.), CuI (47.3 mg, 0.248 mmol, 1 mol%) and Pd(PPh₃)₂Cl₂ (174 mg, 0.248 mmol, 1 mol%). 50 mL Et₃N was added, the flask was sealed and stirred at 60 °C overnight. The reaction mixture was evaporated under reduced pressure and the crude was purified directly over silica gel (2.5-5% EtOAc/Hex) to afford enyne **3.130TMS** as a clear oil (6.59 g, 97%): R_f 0.56 (10% EtOAc/Hex); ^1H -NMR (400 MHz, CDCl_3) δ 6.89 (t, $J = 2.6$ Hz, 1H), 6.07 (t, $J = 2.7$ Hz, 1H), 3.70 (s, 3H), 2.66-2.48 (m, 2H), 2.43-2.33 (m, 2H), 2.32-2.18 (m, 2H), 1.93 (ddd, $J = 13.1, 8.6, 5.4$ Hz, 1H), 1.86 (ddd, $J = 13.1, 8.7, 4.5$ Hz, 1H), 0.13 (s, 9H); ^{13}C -NMR (100 MHz, CDCl_3) δ 165.0, 145.6, 139.8, 137.9, 130.7, 101.3, 95.9, 64.0, 51.2, 38.5, 36.0, 32.0, 31.1, 0.1; IR (neat): 2952, 2141, 1717, 1435, 1248, 1053, 839, 758 (cm^{-1}); HRMS (ESI) calcd for $[\text{C}_{16}\text{H}_{22}\text{O}_2\text{Si} + \text{Na}]^+$: 297.1287, found 297.1274.

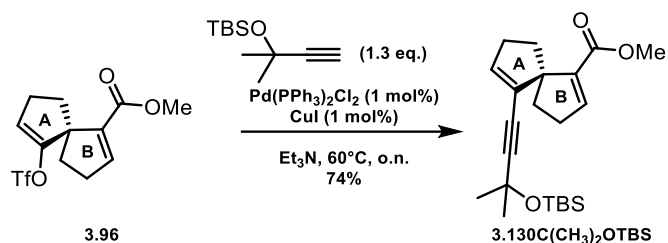


methyl 6-((triisopropylsilyl)ethynyl)spiro[4.4]nona-1,6-diene-1-carboxylate (3.130TIPS). In a sealable flask were added vinyl triflate **3.96** (100 mg, 0.307 mmol), triisopropylsilylacetylene (89 μL , 0.40 mmol, 1.3 eq.), CuI (0.6 mg, 0.003 mmol, 1 mol%) and Pd(PPh₃)₂Cl₂ (2.2 mg, 0.0031 mmol, 1 mol%). 50 mL Et₃N was added, the flask was sealed and stirred at 60 °C overnight. The reaction mixture was evaporated under reduced pressure, and the crude was purified directly over silica gel (2.5-5% EtOAc/Hex) to afford enyne

3.130TIPS as a clear oil (109 mg, 97%): R_f 0.36 (5% EtOAc/Hex); $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 6.84 (t, J = 2.6 Hz, 1H), 6.05 (t, J = 2.7 Hz, 1H), 3.66 (s, 3H), 2.62-2.32 (m, 4H), 2.32-2.12 (m, 2H), 1.94 (ddd, J = 12.9, 8.4, 4.4 Hz, 1H), 1.86 (ddd, J = 12.5, 8.4, 3.7 Hz, 1H), 1.05-0.97 (m, 21H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 164.8, 145.4, 139.9, 137.0, 131.2, 103.1, 92.2, 64.0, 51.1, 37.9, 35.8, 31.7, 31.0, 18.7, 11.3; IR (neat): 2943, 2157, 1721, 1464, 1001 (cm^{-1}); HRMS (EI) calcd for $\text{C}_{22}\text{H}_{34}\text{O}_2\text{Si}$ $[\text{M}]^+$: 358.2328, found 358.2312.

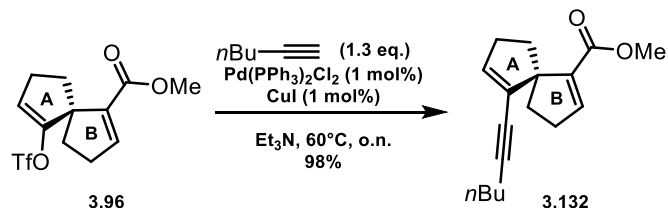


***tert*-butyldimethyl((2-methylbut-3-yn-2-yl)oxy)silane.** To a solution of 2-methyl-3-butyn-2-ol (550 μL , 5.68 mmol) in 5.7 mL DMF at 0 °C was added imidazole (697 mg, 14.2 mmol, 2.5 eq.) followed by TBSCl (1.11 g, 7.39 mmol, 1.3 eq.). The reaction mixture was warmed to RT and stirred overnight. The reaction was quenched with 50 mL H_2O , extracted with (3 x 50 mL) Et_2O , dried over Na_2SO_4 , filtered, and evaporated carefully under reduced pressure (the rotavap bath was kept at 30 °C because the desired product is volatile). The crude was purified over silica gel (100% Hex to 1% Et_2O /Hex) to afford ***tert*-butyldimethyl((2-methylbut-3-yn-2-yl)oxy)silane** as a clear oil (1.054 g, 94%): R_f 0.66 (100% Hex). Spectral data was identical to those found in the literature.¹⁴⁰

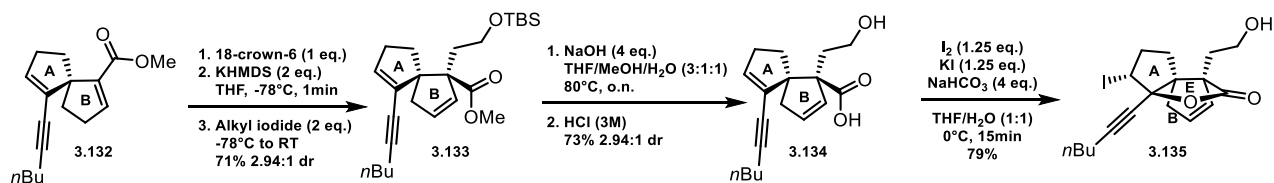


methyl 6-(3-((*tert*-butyldimethylsilyl)oxy)-3-methylbut-1-yn-1-yl)spiro[4.4]nona-1,6-diene-1-carboxylate (3.130C(CH₃)₂OTBS**).** In a sealable flask were added vinyl triflate **3.96** (1.00 g, 3.06 mmol), *tert*-butyldimethyl((2-methylbut-3-yn-2-yl)oxy)silane (666 mg, 3.37 mmol, 1.3 eq.), CuI (5.8 mg, 0.0305 mmol, 1 mol%) and $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (21.5 mg, 0.0306 mmol, 1 mol%). 6.1 mL Et_3N was added, the flask was sealed and stirred at 60 °C overnight. The reaction mixture was evaporated under reduced pressure, and the crude was purified directly over silica gel (1-3% EtOAc/Hex) to afford enyne **3.130C(CH₃)₂OTBS** as a clear oil (853 mg, 74%): R_f 0.36 (3% EtOAc/Hex); $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 6.86 (t, J = 2.6 Hz, 1H), 5.99 (t, J = 2.7 Hz, 1H), 3.68 (s, 3H), 2.63-2.46 (m, 2H), 2.46-2.35 (m, 2H), 2.26 (ddd, J = 12.9, 9.4, 6.2 Hz, 1H), 2.19 (ddd, J = 13.0, 9.0, 6.2 Hz, 1H), 1.93 (ddd, J = 13.4, 8.6, 5.0 Hz, 1H), 1.87 (ddd, J = 12.9, 8.8, 4.3 Hz, 1H), 1.41 (s, 6H), 0.83 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 164.9, 145.5, 140.0,

136.6, 130.4, 96.2, 78.6, 66.7, 63.8, 51.2, 38.3, 36.0, 33.20, 33.18, 31.9, 31.0, 25.8, 18.0, -3.1; IR (neat): 2930, 1720, 1435, 1249, 1158, 1034, 831, 776, 697 (cm⁻¹); HRMS (EI) calcd for C₂₁H₃₁O₃Si [M-Me]⁺: 359.2048, found 359.2046.



methyl 6-(hex-1-yn-1-yl)spiro[4.4]nona-1,6-diene-1-carboxylate (3.132). In a sealable flask was added vinyl triflate **3.96** (2.00 g, 6.13 mmol), 1-hexyne (916 μ L, 7.97 mmol, 1.3 eq.), CuI (11.6 mg, 0.0609 mmol, 1 mol%) and Pd(PPh₃)₂Cl₂ (43.0 mg, 0.00313 mmol, 1 mol%). 12 mL Et₃N was added, the flask was sealed and stirred at 60 °C overnight. The reaction mixture was evaporated under reduced pressure, and the crude was purified directly over silica gel (2.5-5% EtOAc/Hex) to afford enyne **3.132** as a clear oil (1.56 g, 98%); R_f 0.39 (5% EtOAc/Hex); ¹H-NMR (400 MHz, CDCl₃) δ 6.86 (t, *J* = 2.6 Hz, 1H), 5.91 (t, *J* = 2.5 Hz, 1H), 3.69 (s, 3H), 2.61-2.44 (m, 2H), 2.44-2.31 (m, 2H), 2.29-2.11 (m, 2H), 2.25 (t, *J* = 6.9 Hz, 2H), 1.91 (ddd, *J* = 12.5, 8.2, 4.5 Hz, 1H), 1.85 (ddd, *J* = 12.8, 8.4, 4.0 Hz, 1H), 1.48-1.30 (m, 4H), 0.87 (t, *J* = 7.3 Hz, 3H); ¹³C-NMR (100 MHz, CDCl₃) δ 165.1, 145.4, 140.1, 134.9, 131.1, 91.8, 76.2, 63.8, 51.2, 38.1, 35.8, 31.6, 31.01, 30.97, 21.9, 19.2, 13.7; IR (neat): 3056, 2931, 1717, 1622, 1433, 1247, 1120, 1034, 760 (cm⁻¹); HRMS (EI) calcd for C₁₇H₂₂O₂ [M]⁺: 258.1620, found 258.1645.

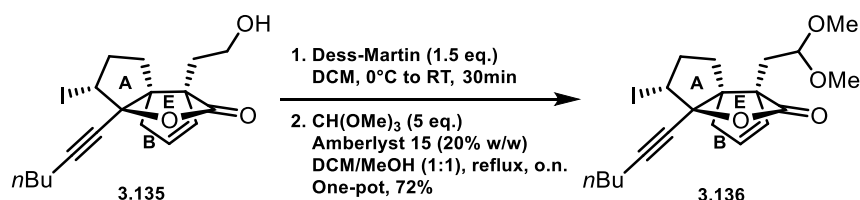


3a-(hex-1-yn-1-yl)-5a-(2-hydroxyethyl)-3-iodo-3,3a,5a,8-tetrahydro-1H-dicyclopenta[b,c]furan-5(2H)-one (3.135). To a solution of enyne **3.132** (4.144 g, 15.66 mmol) and 18-crown-6 (4.138 g, 15.66 mmol, 1 eq.) in 150 mL THF at -78 °C was added a solution of KHMDS (6.246 g, 31.31 mmol, 2 eq.) in 150 mL THF over 5 min. The reaction mixture was stirred at -78 °C for 1 min before adding alkyl iodide **3.101** (8.962 g, 31.31 mmol, 2 eq.). The resulting solution was stirred at -78 °C for 1 min, then the reaction was removed from the cooling bath and was slowly warmed to 0 °C (solution turns from dark red to brown). The reaction was then quenched with 300 mL aq. sat. NH₄Cl, extracted with (3 x 200 mL) EtOAc, dried over Na₂SO₄, filtered, and evaporated under reduced pressure. The crude was purified over silica gel (2.5-6%

EtOAc/Hex) to afford the desired α -alkylated ester **3.133** and the undesired α -alkylated ester diastereoisomer **3.133dia** (4.778 g, 71% 2.94:1 dr) as an inseparable mixture: R_f 0.62 (10% EtOAc/Hex).

The diastereomeric mixture of the α -alkylated ester **3.133** (4.778 g, 11.47 mmol, 2.94:1 dr) from the last step was dissolved in a solution of 200 mL THF/MeOH/NaOH(2 M) (3:1:1). The reaction mixture was heated to reflux for 24 h. The solution was cooled to RT, evaporated under reduced pressure. The residue was diluted with 100 mL H₂O, cooled to 0 °C, and acidified to pH 2-3 with HCl (3 M). The solution was warmed to RT, extracted with (3 x 100 mL) EtOAc, dried over Na₂SO₄, filtered, and evaporated under reduced pressure. The crude was purified over silica gel (40-80% EtOAc/Hex) to afford the desired carboxylic acid **3.134** and the undesired carboxylic acid diastereoisomer **3.134dia** (2.4095 g, 73%, 2.94:1 dr) as an inseparable mixture: R_f 0.41 (80% EtOAc/Hex).

To a solution of the diastereomeric mixture of carboxylic acid **3.134** (2.410 g, 8.354 mmol, 2.94:1 dr) in 170 mL THF/H₂O (1:1) at 0 °C were added NaHCO₃ (2.807g, 33.42 mmol, 4 eq.), KI (1.733 g, 10.44 mmol, 1.25 eq.), and I₂ (2.566 g, 10.44 mmol, 1.25 eq.). The reaction mixture was warmed to RT and stirred for 15 min before being quenched with 200 mL aq. sat. NaHCO₃/5% Na₂S₂O₃ (1:1), extracted with (3 x 200 mL) EtOAc, dried over Na₂SO₄, filtered, and evaporated under reduced pressure. The crude was purified over silica gel (30-50% EtOAc/Hex) to afford lactone **3.135** as a clear oil (2.05 g, 79% relative to carboxylic acid **3.134**): R_f 0.42 (50% EtOAc/Hex); ¹H-NMR (400 MHz, CDCl₃) δ 5.94 (ddd, J = 5.8, 2.8, 1.7 Hz, 1H), 5.68 (ddd, J = 5.8, 2.8, 1.2 Hz, 1H), 4.65 (d, J = 4.5 Hz, 1H), 3.85 (ddd, J = 11.3, 8.0, 5.5 Hz, 1H), 3.70 (ddd, J = 11.5, 6.2, 5.5 Hz, 1H), 3.22 (ddd, J = 17.6, 2.8, 1.3 Hz, 1H), 2.71 (s(br), 1H), 2.57 (ddd, J = 17.6, 2.7, 1.8 Hz, 1H), 2.36 (td, J = 13.8, 6.8 Hz, 1H), 2.25 (td, J = 6.8, 3.5 Hz, 2H), 2.17 (ddt, J = 14.2, 6.1, 1.4 Hz, 1H), 2.13-2.03 (m, 2H), 1.67 (dt, J = 14.4, 5.5 Hz, 1H), 1.54-1.34 (m, 4H), 0.90 (t, J = 7.2 Hz, 3H); ¹³C-NMR (100 MHz, CDCl₃) δ 178.9, 134.6, 130.4, 95.0, 92.0, 77.7, 63.1, 61.8, 58.6, 45.4, 36.6, 35.6, 35.2, 31.2, 30.3, 22.1, 18.5, 13.7; IR (neat): 3419(br), 2955, 2241, 1765, 1438, 1239, 1188, 1037, 966, 703 (cm⁻¹); HRMS (EI) calcd for C₁₈H₂₂IO₂ [M-OH]⁺: 397.0659, found 397.0677.



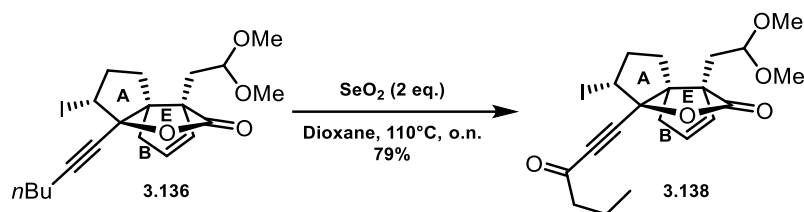
5a-(2,2-dimethoxyethyl)-3a-(hex-1-yn-1-yl)-3-iodo-3,3a,5a,8-tetrahydro-1H-dicyclopenta[b,c]furan-5(2H)-one (3.136). To a solution of lactone **3.135** (373 mg, 0.900 mmol) in 4.5 mL DCM at 0 °C was added

Dess-Martin periodinane (573 mg, 1.35 mmol, 1.5 eq.). The reaction mixture was warmed to RT and stirred for 30 min. Thereafter, 4.5 mL MeOH, trimethyl orthoformate (493 μ L, 4.50 mmol, 5 eq.) as well as Amberlyst® 15 (75 mg, 5% w/w) were added and the reaction was heated to reflux for 2 h. The reaction was cooled to RT, filtered, evaporated under reduced pressure, and the crude was purified directly over silica gel (10-15% EtOAc/Hex with 1% Et₃N) to afford dimethyl acetal **3.136** as an orange-yellow oil (297 mg, 72%): *R*_f 0.29 (20% EtOAc/Hex); ¹H-NMR (400 MHz, CDCl₃) δ 5.88 (ddd, *J* = 5.6, 2.6, 1.8 Hz, 1H), 5.62-5.51 (m, 1H), 4.64 (d, *J* = 4.8 Hz, 1H), 4.49 (dd, *J* = 7.3, 3.6 Hz, 1H), 3.31 (s, 3H), 3.29 (s, 3H), 3.20 (ddd, *J* = 17.3, 2.7, 1.3 Hz, 1H), 2.56 (dt, *J* = 17.4, 2.1 Hz, 1H), 2.38-2.30 (m, 2H), 2.30-2.18 (m, 3H), 2.09-2.01 (m, 1H), 1.94-1.82 (m, 1H), 1.84 (dd, *J* = 14.8, 7.4 Hz, 1H), 1.54-1.35 (m, 4H), 0.90 (t, *J* = 7.2 Hz, 3H); IR (neat): 3058, 2932, 2244, 1764, 1430, 1238, 1188, 1119, 1049, 965, 705 (cm⁻¹); HRMS (EI) calcd for C₁₉H₂₄IO₃ [M-OCH₃]⁺: 427.0765, found 427.0771.



5a-(2,2-dimethoxyethyl)-3a-(hex-1-yn-1-yl)-5a,8-dihydro-1*H*-dicyclopenta[b,c]furan-5(3a*H*)-one

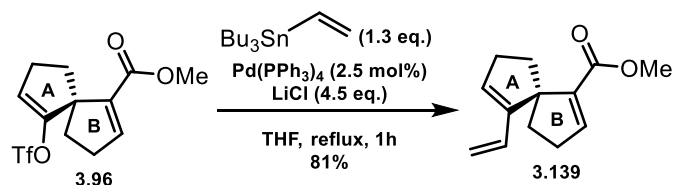
(3.137). In a sealable flask were added dimethyl acetal **3.136** (50.0 mg, 0.109 mmol), Na₂HPO₄ (77.5 mg, 0.546 mmol, 5 eq.) and 2 mL DMSO. The flask was sealed and heated to 130 °C for 24 h. The reaction was cooled to RT, quenched with 25 mL H₂O, extracted with (3 x 25 mL) EtOAc, washed with 50 mL aq. sat. NaCl/H₂O (1:1), dried over Na₂SO₄, filtered, and evaporated under reduced pressure. The crude was purified over silica gel (10-20% EtOAc/Hex) to afford diene **3.137** (35.4 mg, 98%): *R*_f 0.51 (30% EtOAc/Hex); ¹H-NMR (400 MHz, CDCl₃) δ 6.00 (dt, *J* = 5.7, 2.4 Hz, 1H), 5.89 (ddd, *J* = 5.5, 2.4, 2.1 Hz, 1H), 5.74 (dt, *J* = 5.7, 2.2 Hz, 1H), 5.57 (ddd, *J* = 5.9, 2.8, 1.7 Hz, 1H), 4.47 (dd, *J* = 7.5, 3.6 Hz, 1H), 3.29 (s, 3H), 3.28 (s, 3H), 3.23 (ddd, *J* = 17.2, 2.5, 1.4 Hz, 1H), 2.98 (dt, *J* = 18.8, 2.4 Hz, 1H), 2.52 (dt, *J* = 17.2, 2.1 Hz, 1H), 2.46 (dt, *J* = 18.9, 2.0 Hz, 1H), 2.31 (dd, *J* = 14.9, 3.6 Hz, 1H), 2.22 (t, *J* = 6.8 Hz, 2H), 1.88 (dd, *J* = 14.9, 7.5 Hz, 1H), 1.51-1.41 (m, 2H), 1.41-1.29 (m, 2H), 0.89 (t, *J* = 7.3 Hz, 3H); ¹³C-NMR (100 MHz, CDCl₃) δ 177.7, 136.3, 132.9, 131.5, 131.1, 102.6, 94.5, 90.7, 76.6, 62.0, 60.2, 54.1, 52.8, 46.0, 40.6, 36.0, 30.5, 22.0, 18.6, 13.7.



5a-(2,2-dimethoxyethyl)-3-iodo-3a-(3-oxohex-1-yn-1-yl)-3,3a,5a,8-tetrahydro-1H-

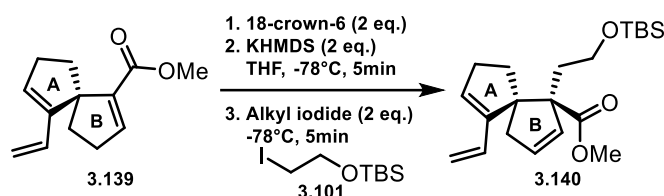
dicyclopenta[b,c]furan-5(2H)-one (3.138). In a sealable flask was added dimethyl acetal **3.136** (50.0 mg, 0.109 mmol), 2 mL dioxane and SeO_2 (24.2 mg, 0.218 mmol, 2 eq.). The flask was sealed and heated to 110°C overnight. A dry pack was prepared and the crude was purified over silica gel (10-30% EtOAc/Hex) to afford the undesired ynone **3.138** (40.5 mg, 79%): R_f 0.50 (50% EtOAc/Hex); $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 5.94 (ddd, $J = 5.5, 2.4, 2.0$ Hz, 1H), 5.68-5.53 (m, 1H), 4.61 (d, $J = 4.8$ Hz, 1H), 4.46 (dd, $J = 7.6, 3.5$ Hz, 1H), 3.31 (s, 3H), 3.28 (s, 3H), 3.17 (ddd, $J = 17.6, 2.6, 1.1$ Hz, 1H), 2.67 (dt, $J = 17.6, 2.1$ Hz, 1H), 2.53 (t, $J = 7.3$ Hz, 2H), 2.47-2.32 (m, 2H), 2.27 (dd, $J = 14.9, 3.5$ Hz, 1H), 2.16-2.04 (m, 1H), 2.01-1.90 (m, 1H), 1.86 (dd, $J = 14.9, 7.6$ Hz, 1H), 1.69 (sext, $J = 7.4$ Hz, 2H), 0.93 (t, $J = 7.4$ Hz, 3H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 187.0, 176.6, 133.8, 130.7, 102.2, 93.0, 87.8, 87.2, 64.1, 61.0, 54.2, 53.0, 47.4, 46.0, 35.6, 35.2, 34.0, 31.4, 17.5, 13.6.

4.1.2.6 Route 5 – Vinyl Group Installation via Stille Coupling:



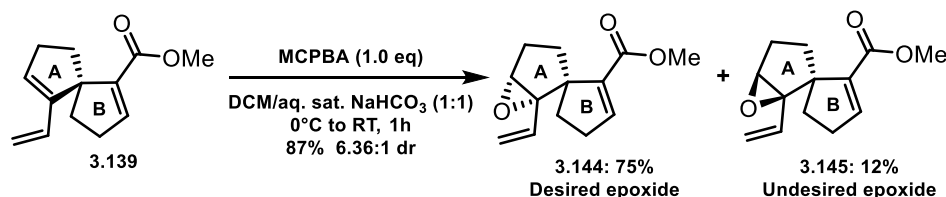
methyl 6-vinylspiro[4.4]nona-1,6-diene-1-carboxylate (3.139). In a sealable flask were added vinyl triflate **3.96** (1.606 g, 4.921 mmol), 49 mL THF, tributyl(vinyl)stannane (1.86 mL, 6.36 mmol, 1.3 eq.), anhydrous LiCl (934 mg, 22.0 mmol, 4.5 eq.) and $\text{Pd(PPh}_3)_4$ (141 mg, 122 mmol, 2.5 mol%). The flask was sealed, and the reaction mixture was stirred at 75°C overnight. The reaction was cooled to RT and evaporated under reduced pressure. The crude was purified over silica gel (2.5-5% EtOAc/Hex) to afford triene **3.139** as a yellow oil (877 mg, 81%): R_f 0.54 (10% EtOAc/Hex); $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 6.82 (t, $J = 2.6$ Hz, 1H), 6.31 (dd, $J = 17.9, 11.3$ Hz, 1H), 5.79 (t, $J = 2.7$ Hz, 1H), 5.14 (d, $J = 17.9$ Hz, 1H), 4.90 (d, $J = 11.3$ Hz, 1H), 3.67 (s, 3H), 2.56-2.44 (m, 2H), 2.44-2.31 (m, 2H), 2.23-2.07 (m, 2H), 2.00-1.85 (m, 2H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 165.1, 145.8, 144.2, 141.6, 132.3, 131.4, 113.4, 61.3, 51.3, 37.4, 35.5, 30.7, 30.3;

IR (neat): 3039, 2931, 1717, 1622, 1248, 1116, 994, 900, 758 (cm⁻¹); HRMS (EI) calcd for C₁₃H₁₆O₂ [M]⁺: 204.1150, found 204.1158.



Methyl 1-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-6-vinylspiro[4.4]nona-2,6-diene-1-carboxylate (3.140).

To a solution of triene **3.139** (51.4 mg, 0.252 mmol) and 18-crown-6 (133 mg, 0.503 mmol, 2 eq.) in 2.5 mL THF at -78 °C was added a solution of KHMDS (100 mg, 0.503 mmol, 2 eq.) in 2.5 mL THF. The reaction mixture was stirred at -78 °C for 5 min before adding alkyl iodide **3.101** (144 mg, 0.503 mmol, 2 eq.). The resulting solution was stirred at -78 °C for 1 min, then the reaction was quenched with 20 mL aq. sat. NH₄Cl, warmed to RT, extracted with (3 x 20 mL) EtOAc, dried over Na₂SO₄, filtered, and evaporated under reduced pressure. The crude was purified over silica gel (1-3% EtOAc/Hex) to afford α-alkylated ester **3.140**; ¹H-NMR (400 MHz, CDCl₃) δ 6.16 (ddq, *J* = 17.3, 10.8, 1.2 Hz, 1H), 6.01 (ddd, *J* = 6.0, 2.7, 0.9 Hz, 1H), 5.85-5.73 (m, 2H), 5.25 (dd, *J* = 17.3, 2.2 Hz, 1H), 4.85 (dd, *J* = 10.8, 2.3 Hz, 1H), 3.61 (ddd, *J* = 10.1, 8.3, 4.6 Hz, 1H), 3.53 (dt, *J* = 10.1, 7.6 Hz, 1H), 3.52 (s, 3H), 2.54 (ddd, *J* = 12.8, 8.2, 4.4 Hz, 1H), 2.49 (ddd, *J* = 16.6, 2.6, 2.0 Hz, 1H), 2.43-2.26 (m, 3H), 2.24-2.12 (m, 1H), 1.83 (ddd, *J* = 13.0, 8.5, 6.4 Hz, 1H), 1.64 (ddd, *J* = 12.4, 7.5, 4.6 Hz, 1H), 0.87 (s, 9H), 0.02 (s, 6H). Note: The majority of the desired product degraded instantly upon alkylation, however, a small amount of desired product was isolated via flash chromatography.

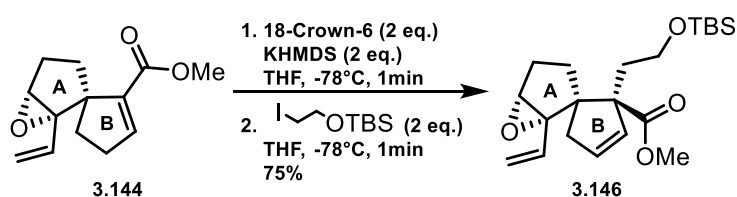


methyl 1-vinyl-6-oxaspiro[bicyclo[3.1.0]hexane-2,1'-cyclopent[2]ene]-2'-carboxylate (3.144/3.145).

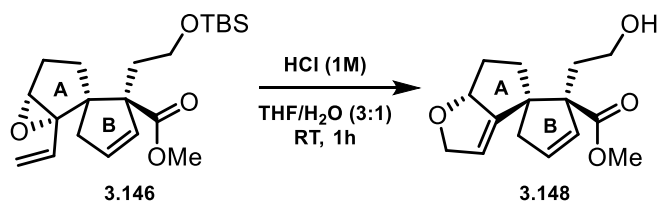
To a solution of triene **3.141** (100 mg, 0.490 mmol) in 3 mL DCM and 5 mL aq. sat. NaHCO₃ at 0 °C was added a solution of MCPBA (68% w/w, 124 mg, 0.490 mmol, 1.0 eq.) in 2 mL DCM. The reaction was warmed to RT and stirred for 1 h. The reaction was extracted with (3 x 5 mL) DCM, dried over Na₂SO₄, filtered, and evaporated under reduced pressure. The crude was purified over silica gel (5-15% EtOAc/Hex) to afford the desired epoxide **3.144** (80.8 mg, 75%) and the undesired epoxide **3.145** (12.7 mg, 12%).

3.144: R_f 0.47 (20% EtOAc/Hex); $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 6.81 (t, J = 2.6 Hz, 1H), 5.94 (dd, J = 17.1, 10.8 Hz, 1H), 5.34 (dd, J = 17.1, 1.8 Hz, 1H), 5.17 (dd, J = 10.8, 1.8 Hz, 1H), 3.68 (s, 3H), 3.33 (s, 1H), 2.51-2.35 (m, 2H), 2.22-1.96 (m, 3H), 1.77 (ddd, J = 13.8, 8.3, 6.0 Hz, 1H), 1.64 (dddd, J = 13.4, 10.4, 7.3, 1.0 Hz, 1H), 1.28 (dd, J = 12.0, 7.7 Hz, 1H).

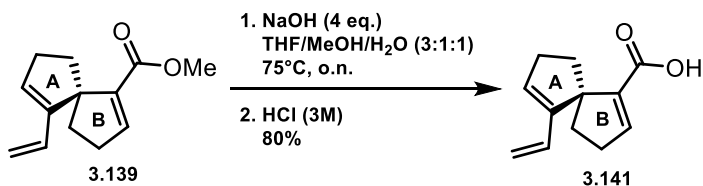
3.145: R_f 0.60 (20% EtOAc/Hex); $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 6.85 (t, J = 2.5 Hz, 1H), 5.91 (dd, J = 17.1, 10.8 Hz, 1H), 5.37 (dd, J = 17.1, 2.0 Hz, 1H), 5.14 (dd, J = 10.8, 2.0 Hz, 1H), 3.73 (s, 3H), 3.52 (s, 1H), 2.50-2.32 (m, 3H), 2.19 (dtd, J = 13.8, 9.5, 1.4 Hz, 1H), 1.94 (dd, J = 13.7, 8.6 Hz, 1H), 1.91-1.78 (m, 2H), 1.69 (dt, J = 13.4, 9.1 Hz, 1H).



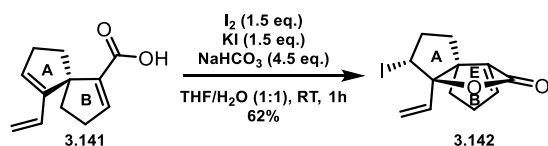
methyl 2'--(2-((tert-butyldimethylsilyl)oxy)ethyl)-1-vinyl-6-oxaspiro[bicyclo[3.1.0]hexane-2,1'-cyclopent[3]ene]-2'-carboxylate (3.146). To a solution of triene **3.144** (80.8 mg, 0.367 mmol) and 18-crown-6 (194 mg, 0.734 mmol, 2 eq.) in 3.6 mL THF at -78°C was added a solution of KHMDS (146 mg, 0.734 mmol, 2 eq.) in 3.6 mL THF. The reaction mixture was stirred at -78°C for 5 min before adding alkyl iodide **3.101** (210 mg, 0.734 mmol, 2 eq.). The resulting solution was stirred at -78°C for 5 min before removing the flask from the cooling bath. The reaction was slowly warmed to 0°C before being quenched with 25 mL aq. sat. NH_4Cl , warmed to RT, extracted with (3 x 25 mL) EtOAc, dried over Na_2SO_4 , filtered, and evaporated under reduced pressure. The crude was purified over silica gel (2.5-10% EtOAc/Hex) to afford α -alkylated ester **3.146** (104 mg, 75%): R_f 0.77 (20% EtOAc/Hex); $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 6.06 (dd, J = 17.0, 10.6 Hz, 1H), 6.01 (ddd, J = 6.0, 2.5, 1.3 Hz, 1H), 5.75 (ddd, J = 5.8, 2.6, 2.0 Hz, 1H), 5.11 (dd, J = 17.0, 2.1 Hz, 1H), 4.96 (dd, J = 10.7, 2.1 Hz, 1H), 3.64 (s, 3H), 3.58-3.45 (m, 2H), 3.12 (s, 1H), 2.43 (ddd, J = 16.6, 2.8, 1.3 Hz, 1H), 2.36 (dt, J = 16.7, 2.2 Hz, 1H), 2.29 (dt, J = 12.7, 7.7 Hz, 1H), 2.05 (m, 2H), 1.64-1.54 (m, 1H), 1.54-1.44 (m, 2H), 0.84 (s, 9H), -0.01 (s, 6H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 173.6, 135.7, 132.0, 129.3, 114.7, 69.0, 64.9, 60.1, 59.0, 58.0, 51.4, 41.5, 37.7, 28.1, 26.0, 25.8, 18.4, -5.36 , -5.38 .



methyl 2-(2-hydroxyethyl)-2',5',6',6a'-tetrahydrospiro[cyclopent[3]ene-1,4'-cyclopenta[b]furan]-2-carboxylate (3.148). To a solution of α -alkylated ester **3.146** (10.0 mg, 0.0264 mmol) in 1 mL THF was added 333 μ L HCl (1 M). The reaction mixture was stirred at RT for 1 h before being quenched with 10 mL aq. sat. NaHCO_3 , extracted with (3 x 10 mL) EtOAc, dried over Na_2SO_4 , filtered, and evaporated under reduced pressure. The crude was purified over silica gel (40-60% EtOAc/Hex) to afford the undesired alcohol **3.148**: R_f 0.23 (60% EtOAc/Hex); $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 6.17 (ddd, J = 6.1, 2.9, 1.3 Hz, 1H), 5.88 (td, J = 8.0, 1.4 Hz, 1H), 5.86 (ddd, J = 6.0, 3.0, 2.0 Hz, 1H), 4.68 (d, J = 3.6 Hz, 1H), 4.14 (d, J = 3.0 Hz, 1H), 4.12 (d, J = 2.7 Hz, 1H), 3.76-3.68 (m, 1H), 3.66 (s, 3H), 3.66-3.56 (m, 1H), 2.63-2.46 (m, 3H), 2.42 (ddd, J = 16.3, 2.7, 2.0 Hz, 1H), 2.27 (dt, J = 13.1, 7.7 Hz, 1H), 1.99-1.89 (m, 1H), 1.78-1.62 (m, 3H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 177.7, 157.1, 134.2, 130.9, 120.2, 71.8, 63.9, 59.7, 58.0, 52.2, 47.8, 41.7, 40.1, 33.6, 32.7.

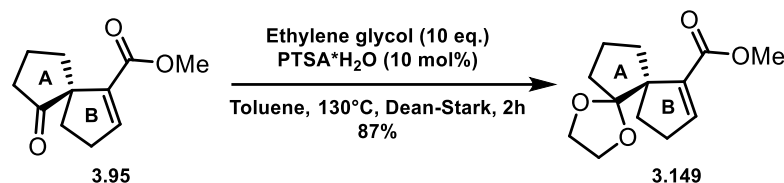


6-vinylspiro[4.4]nona-1,6-diene-1-carboxylic acid (3.141). To a solution of triene **3.139** (599 mg, 2.93 mmol) in 20 mL THF/MeOH (3:1) was added NaOH (2.5 M, 4.70 mL, 11.7 mmol, 4 eq.) before being heated to 75 °C overnight. The reaction mixture was cooled to RT and evaporated under reduced pressure. The residue was diluted in 50 mL H_2O , cooled to 0 °C and acidified with HCl (3 M) to pH 2-3. The solution was warmed to RT, extracted with (3 x 50 mL) EtOAc, dried over Na_2SO_4 , filtered, and evaporated under reduced pressure. The crude was purified over silica gel to afford carboxylic acid **3.141** (446 mg, 80%): $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 11.39 (s(br), 1H), 6.98 (t, J = 2.6 Hz, 1H), 6.32 (dd, J = 17.9, 11.3 Hz, 1H), 5.78 (t, J = 2.5 Hz, 1H), 5.16 (d, J = 17.9 Hz, 1H), 4.93 (d, J = 11.3 Hz, 1H), 2.59-2.46 (m, 2H), 2.46-2.28 (m, 2H), 2.24-2.08 (m, 2H), 1.97 (ddd, J = 13.0, 6.7, 4.2 Hz, 1H), 1.90 (ddd, J = 12.3, 7.0, 2.7 Hz, 1H).

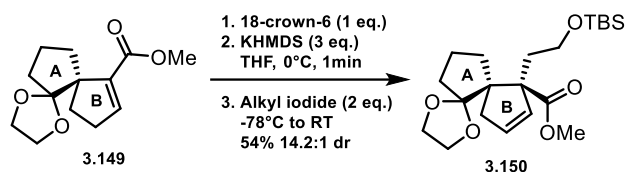


3-iodo-3a-vinyl-3,3a,7,8-tetrahydro-1H-dicyclopenta[b,c]furan-5(2H)-one (3.142). To a solution of carboxylic acid **3.141** (433 mg, 2.28 mmol), NaHCO₃ (861 mg, 10.25 mmol, 4.5 eq.) and KI (567 mg, 3.42 mmol, 1.5 eq.) in 45 mL THF/H₂O (1:1) was added I₂ (867 mg, 3.42 mmol, 1.5 eq.). The reaction mixture was stirred at RT for 1 h before being quenched with 100 mL aq. sat. NaHCO₃/5% Na₂S₂O₃ (1:1), extracted with (3 x 100 mL) EtOAc, dried over Na₂SO₄, filtered, and evaporated under reduced pressure. The crude was purified over silica gel (5-15% EtOAc/Hex) to afford lactone **3.142** (447 mg, 62%): R_f 0.34 (10% EtOAc/Hex); ¹H-NMR (400 MHz, CDCl₃) δ 6.62 (dd, *J* = 3.6, 2.0 Hz, 1H), 6.36 (dd, *J* = 17.0, 11.0 Hz, 1H), 5.35 (dd, *J* = 17.0, 1.3 Hz, 1H), 5.29 (dd, *J* = 11.0, 1.2 Hz, 1H), 4.54-4.41 (m, 1H), 2.98 (dddd, *J* = 17.8, 10.6, 6.2, 2.0 Hz, 1H), 2.71 (dddd, *J* = 17.8, 8.6, 3.6, 0.7 Hz, 1H), 2.54 (dt, *J* = 12.6, 6.9 Hz, 1H), 2.47-2.34 (m, 2H), 2.24-2.14 (m, 1H), 2.13 (dd, *J* = 13.2, 7.0 Hz, 1H), 2.05 (dd, *J* = 12.5, 6.1 Hz, 1H); ¹³C-NMR (100 MHz, CDCl₃) δ 164.7, 141.7, 138.8, 136.6, 118.0, 96.3, 64.4, 40.0, 37.8, 37.7, 36.7, 36.0.

4.1.2.7 Route 6 – Ethylene Glycol Ketal Formation:



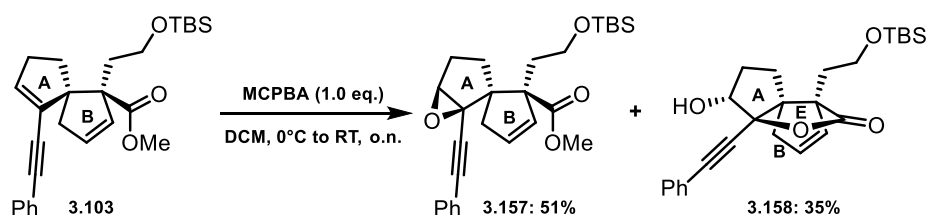
(3.149). To a solution of α,β-unsaturated ester **3.95** (500 mg, 2.57mmol) in 60 mL toluene were added PTSA•H₂O (49.0 mg, 0.257 mmol, 0.1 eq.) and ethylene glycol (1.44 mL, 25.7 mmol, 10 eq.). The reaction was heated to 130 °C using a Dean-Stark apparatus for 2 h. The reaction mixture was cooled to RT and evaporated under reduced pressure. The crude was purified over silica gel (5-15% EtOAc/Hex with 1% Et₃N) to afford ketal **3.149** as a clear oil (536 mg, 87%): R_f 0.47 (20% EtOAc/Hex); ¹H-NMR (400 MHz, Benzene-D₆) δ 6.67 (t, *J* = 2.6 Hz, 1H), 3.49 (s, 3H), 3.49-3.35 (m, 4H), 3.17-3.05 (m, 1H), 2.48 (ddd, *J* = 12.5, 8.2, 2.6 Hz, 1H), 2.38 (dddd, *J* = 17.4, 8.2, 7.4, 2.2 Hz, 1H), 2.03 (ddt, *J* = 17.3, 8.8, 2.5 Hz, 1H), 1.98-1.79 (m, 3H), 1.64-1.48 (m, 3H).



(3.150). To a solution of 18-crown-6 (55.5 mg, 0.210 mmol, 1 eq.) in 2.1 mL THF at 0 °C was added a solution of KHMDS (126 mg, 0.630 mmol, 3 eq.) dropwise and stirred for 1 min. Then, a solution of ketal **3.149** (49.9 mg, 0.210 mmol) in 2.1 mL THF was added at 0 °C and stirred for 1 min. The reaction mixture was cooled to -78 °C before adding alkyl iodide **3.101** (120 mg, 0.42 mmol, 2 eq.) and stirred for 5 min. The reaction was warmed to RT to complete the reaction before being quenched with 10 mL aq. sat. NaHCO₃, extracted with (3 x 10 mL) EtOAc, dried over Na₂SO₄, filtered, and evaporated under reduced pressure. The crude was purified over silica gel (5-10% EtOAc/Hex with 1% Et₃N) to afford α-alkylated ester **3.150** (44.7 mg, 54% 14.2:1 dr): *R_f* 0.58 (20% EtOAc/Hex); ¹H-NMR (400 MHz, Benzene-D₆) δ 6.20 (ddd, *J* = 6.0, 2.6, 1.2 Hz, 1H), 5.72 (ddd, *J* = 5.3, 2.8, 2.1 Hz, 1H), 3.74 (t, *J* = 7.4 Hz, 2H), 3.66 (dt, *J* = 8.0, 6.6 Hz, 1H), 3.58 (dd, *J* = 6.6, 3.0 Hz, 1H), 3.49 (s, 3H), 3.39 (td, *J* = 6.8, 3.4 Hz, 1H), 3.33 (dt, *J* = 7.7, 6.6 Hz, 1H), 2.74 (ddd, *J* = 15.6, 3.0, 1.1 Hz, 1H), 2.53-2.33 (m, 2H), 1.98 (dt, *J* = 15.6, 2.2 Hz, 1H), 1.90-1.75 (m, 2H), 1.72-1.63 (m, 1H), 1.62-1.48 (m, 2H), 1.45-1.33 (m, 1H), 0.98 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H).

4.1.2.8 Route 7 – Enyne Epoxidation Followed by Lactonization:

4.1.2.8.1 Total Synthesis of (±)-Ginkgolide C from Enyne 3.103

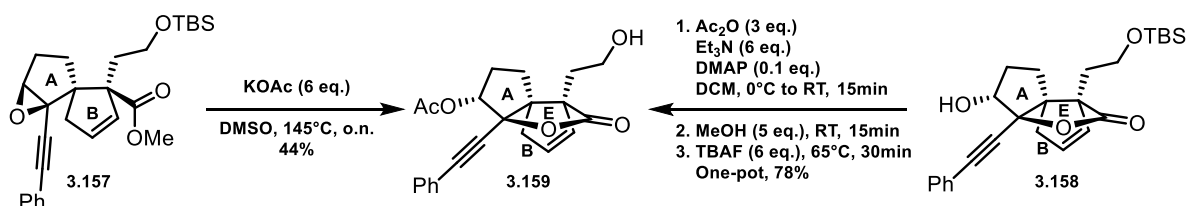


(3.157/3.158). To a solution of α-alkylated ester **3.103** (44.79 g, 0.1026 mmol) in 1.00 L DCM at 0°C was added a solution of MCPBA (68% w/w, 26.03 g, 0.1026 mmol, 1.0 eq.) in 200 mL DCM. The reaction was warmed to RT and stirred overnight before being quenched with 500 mL aq. sat. NaHCO₃ and 500 mL 10% Na₂S₂O₃, extracted with (3 x 300 mL) DCM, dried over Na₂SO₄, filtered, and evaporated under reduced pressure. The crude was purified over silica gel (5-20% EtOAc/Hex) to afford epoxide **3.157** as a pale-yellow oil (23.60 g, 51%) and lactone **3.158** as an orange yellow oil (15.68 g, 35%).

3.157: *R_f* 0.56 (20% EtOAc/Hex); ¹H-NMR (400 MHz, CDCl₃) δ 7.45-7.35 (m, 2H), 7.35-7.26 (m, 3H), 6.06 (ddd, *J* = 6.0, 2.6, 1.1 Hz, 1H), 5.83 (ddd, *J* = 5.8, 2.8, 1.8 Hz, 1H), 3.75 (s, 3H), 3.65-3.52 (m, 3H), 2.64 (ddd,

$J = 16.4, 2.9, 1.2$ Hz, 1H), 2.39 (dt, $J = 16.4, 2.1$ Hz, 1H), 2.33 (ddd, $J = 12.6, 8.3, 7.1$ Hz, 1H), 2.07 (dd, $J = 13.6, 7.7$ Hz, 1H), 1.95 (ddd, $J = 11.8, 11.2, 7.9$ Hz, 1H), 1.72 (dddd, $J = 13.6, 10.7, 7.8, 0.9$ Hz, 1H), 1.58 (dd, $J = 7.8, 5.4$ Hz, 1H), 1.53 (dd, $J = 11.8, 7.6$ Hz, 1H), 0.88 (s, 9H), 0.037 (s, 3H), 0.036 (s, 3H); ^{13}C -NMR (100 MHz, CDCl_3) δ 173.8, 134.4, 131.9, 129.2, 128.4, 128.3, 122.9, 85.4, 84.1, 64.1, 60.3, 60.1, 59.6, 59.4, 51.9, 41.8, 37.8, 27.3, 26.1, 26.0, 18.5, -5.24, -5.27; IR (neat): 2950, 1730, 1471, 1254, 1153, 853, 754, 690 (cm^{-1}); HRMS (EI) calcd for $\text{C}_{26}\text{H}_{34}\text{O}_4\text{Si}$ $[\text{M}]^+$: 475.2281, found 475.2257.

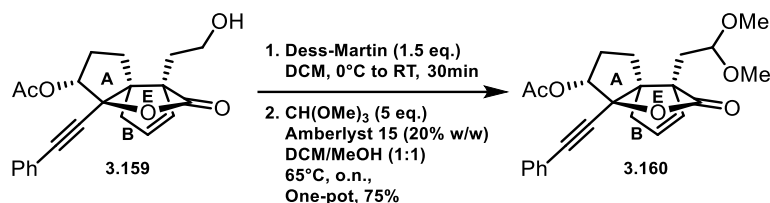
3.158: R_f 0.47 (20% EtOAc/Hex); ^1H -NMR (400 MHz, CDCl_3) δ 7.48-7.39 (m, 2H), 7.39-7.27 (m, 3H), 5.97 (ddd, $J = 5.6, 2.5, 1.8$ Hz, 1H), 5.59-5.51 (m, 1H), 4.26 (d, $J = 3.4$ Hz, 1H), 3.81 (ddd, $J = 10.2, 8.2, 4.9$ Hz, 1H), 3.75-3.56 (m, 2H), 3.09 (ddd, $J = 17.5, 2.6, 1.1$ Hz, 1H), 2.61 (dt, $J = 17.5, 2.1$ Hz, 1H), 2.36 (s(br), 1H), 2.27-2.10 (m, 3H), 1.97-1.88 (m, 2H), 1.79 (dt, $J = 14.3, 7.7$ Hz, 1H), 1.75-1.65 (m, 1H), 0.88 (s, 9H), 0.044 (s, 3H), 0.040 (s, 3H); ^{13}C -NMR (100 MHz, CDCl_3) δ 177.9, 134.0, 132.0, 131.0, 129.4, 128.6, 121.5, 93.4, 91.0, 83.5, 78.2, 62.2, 61.3, 59.1, 45.2, 35.0, 30.6, 30.3, 26.1, 18.4, -5.17, -5.22; IR (neat): 3473(br), 3054, 2949, 2360, 1766, 1443, 1190, 1010, 835, 756, 691 (cm^{-1}); HRMS (ESI) calcd for $[\text{C}_{26}\text{H}_{34}\text{O}_4\text{Si} + \text{Na}]^+$: 461.2124, found 461.2130.



5a-(2-hydroxyethyl)-5-oxo-3a-(phenylethynyl)-2,3,3a,5,5a,8-hexahydro-1H-dicyclopenta[b,c]furan-3-yl acetate (3.159). (From **3.157**) To a solution of **3.157** (16.09 g, 41.37 mmol) in 1.24 L DMSO was added KOAc (24.36 g, 248.2 mmol, 6 eq.). The reaction mixture was heated to 145 °C overnight. The solution was cooled down to RT, partitioned into 4x300 mL fractions, diluted with 500 mL, 1.00 L aq. sat. NaCl and extracted with (7 x 1.00 L) EtOAc. The organic phase was evaporated under reduced pressure (and the EtOAc was recycled). The combined organic phases were washed with (3 x 500 mL) H_2O , (3 x 500 mL) aq. sat. NaCl, dried over Na_2SO_4 , filtered, evaporated under reduced pressure, and purified directly over silica gel (40-75% EtOAc/Hex) to afford alcohol **3.159** as a white solid (5.675 g, 44%).

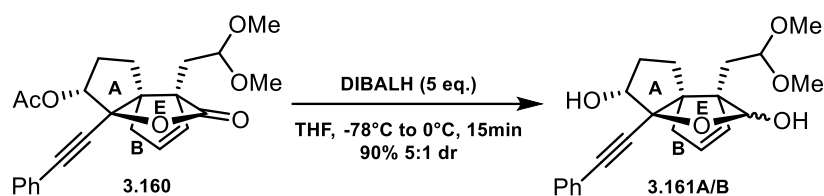
(From **3.158**) To a solution of lactone **3.158** (15.68mg, 35.75mmol) in 357mL DCM at 0°C were added acetic anhydride (10.14mL, 107.2mmol, 3 eq.), Et_3N (29.89mL, 214.5mmol, 6 eq.) and DMAP (436.8mg, 3.575 mmol, 0.1 eq.). The reaction mixture was warmed to RT and stirred for 15 min. Thereafter, MeOH (7.24 mL, 179 mmol, 5 eq.) was added and the reaction mixture was stirred for 15 min before adding TBAF

(1.0 M in THF, 35.75 mL, 35.75 mmol, 6 eq.). The reaction mixture was heated to 65 °C for 30 min. The reaction was cooled to RT, evaporated under reduced pressure, and purified directly over silica gel (40-75% EtOAc/Hex) to afford alcohol **3.159** as a white solid (10.28 g, 78%): mp 158-159 °C; R_f 0.43 (60% EtOAc/Hex); $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.57-7.27 (m, 5H), 6.15-5.93 (m, 1H), 5.83-5.62 (m, 1H), 5.57-5.36 (m, 1H), 3.86 (ddd, J = 13.2, 7.4, 6.1 Hz, 1H), 3.71 (dt, J = 11.2, 6.1 Hz, 1H), 3.25-3.05 (m, 1H), 2.95 (s(br), 1H), 2.56 (dt, J = 17.6, 1.8 Hz, 1H), 2.25-2.00 (m, 3H), 2.08 (s, 3H), 1.98-1.79 (m, 2H), 1.71 (dt, J = 14.2, 5.8 Hz, 1H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 178.7, 169.5, 134.5, 131.8, 130.7, 129.2, 128.5, 121.7, 92.5, 90.0, 82.8, 79.1, 63.0, 61.3, 58.5, 44.3, 35.1, 30.0, 29.7, 21.2; IR (neat): 3458(br), 3062, 2928, 2239, 1776, 1737, 1439, 1235, 1194, 1098, 1041, 988, 768, 697 (cm^{-1}); HRMS (EI) calcd for $\text{C}_{22}\text{H}_{22}\text{O}_5$ $[\text{M}]^+$: 366.1467, found 366.1465.

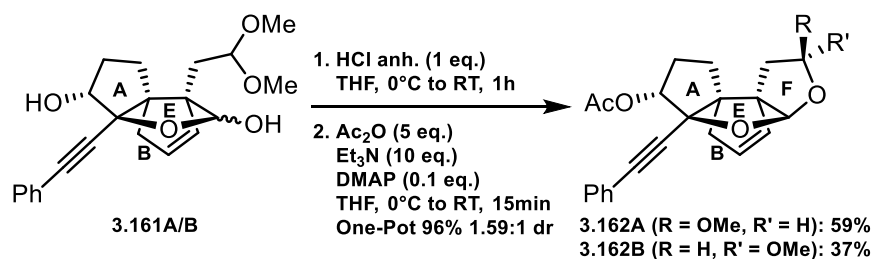


5a-(2,2-dimethoxyethyl)-5-oxo-3a-(phenylethynyl)-2,3,3a,5,5a,8-hexahydro-1H-

dicyclopenta[b,c]furan-3-yl acetate (3.160). In a sealable flask, a solution of alcohol **3.159** (10.27 g, 28.04 mmol) in 147 mL DCM was cooled to 0 °C before adding Dess-Martin periodinane (17.84 g, 42.06 mmol, 1.5 eq.). The reaction mixture was warmed to RT and stirred for 30 min. Thereafter, 147 mL MeOH, trimethyl orthoformate (16.11 mL, 147.0 mmol, 5 eq.) as well as Amberlyst® 15 (2.154 g, 20% w/w) were added. The flask was sealed and heated to 65 °C overnight. The reaction mixture was cooled to RT, filtered and evaporated under reduced pressure and purified directly over silica gel (15-25% EtOAc/Hex with 1% Et_3N) to afford dimethyl acetal **3.160** as a light yellow solid (8.63 g, 75%): mp 103-104 °C; R_f 0.30 (30% EtOAc/Hex); $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.43-7.27 (m, 5H), 5.97 (ddd, J = 5.6, 2.5, 1.8 Hz, 1H), 5.69-5.57 (m, 1H), 5.51-5.38 (m, 1H), 4.52 (dd, J = 7.3, 3.7 Hz, 1H), 3.33 (s, 3H), 3.30 (s, 3H), 3.12 (ddd, J = 17.3, 2.6, 1.2 Hz, 1H), 2.56 (dt, J = 17.3, 2.1 Hz, 1H), 2.40-2.30 (m, 1H), 2.30 (dd, J = 14.8, 3.8 Hz, 1H), 2.12-1.99 (m, 1H), 2.08 (s, 3H), 1.93-1.75 (m, 3H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 177.4, 169.5, 133.4, 131.8, 131.0, 129.1, 128.5, 121.9, 102.4, 92.1, 89.8, 83.3, 79.3, 62.8, 60.7, 54.0, 53.0, 44.9, 35.5, 30.4, 29.6, 21.3; IR (neat): 2915, 2230, 1761, 1736, 1491, 1432, 1370, 1240, 1192, 988, 761, 697 (cm^{-1}); HRMS (EI) calcd for $\text{C}_{24}\text{H}_{26}\text{O}_6$ $[\text{M-OMe}]^+$: 379.1540, found 379.1539.



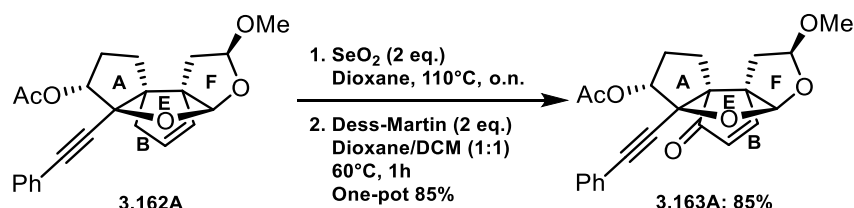
5a-(2,2-dimethoxyethyl)-3a-(phenylethynyl)-2,3,3a,5,5a,8-hexahydro-1H-dicyclopenta[b,c]furan-3,5-diol (3.161A/B). To a solution of dimethyl acetal **3.160** (13.51 g, 32.92 mmol) in 330 mL THF at -78 °C was added DIBALH (25% in hexane, 107.2 mL, 164.6 mmol, 5 eq.) dropwise. The reaction was warmed to 0 °C and stirred for 15 min. The reaction mixture was quenched with 250 mL EtOAc, 660 mL aq. sat. sodium potassium tartrate, 660 mL NaOH (1 M) and warmed to RT. The solution was extracted with (3 x 250 mL) EtOAc, dried over Na₂SO₄, filtered, and evaporated under reduced pressure. The crude was purified over silica gel (40-60% EtOAc/Hex with 1% Et₃N) to afford lactols **3.161A/B** (10.95 g, 90%, 5:1 dr) as an inseparable anomeric mixture which was used directly in the next step: *R_f* 0.45 (60% EtOAc/Hex); IR (neat): 3375(br), 3045, 2937, 1597, 1234, 1107, 1054, 993, 890, 773 (cm⁻¹); HRMS (EI) calcd for C₂₂H₂₆O₅ [M]⁺: 370.1780, found 370.1810.



2-methoxy-4a-(phenylethynyl)-1,2,3a,4a,5,6,7,8-octahydrodicyclopenta[b,c]furo[3,2-d]furan-5-yl acetate (3.162A/B). To a solution of lactols **3.161A/B** (10.95 g, 29.56 mmol, 5:1 dr) in 295 mL THF at 0 °C was added HCl (4 M in dioxane, 7.39 mL, 29.56 mmol, 1 eq.). The solution was warmed to RT and stirred for 1 h before cooling to 0 °C. Thereafter, Et₃N (32.96 mL, 236.4 mmol, 8 eq.), DMAP (361.1 mg, 2.956 mmol, 0.1 eq.) as well as Ac₂O (13.97 mL, 147.8 mmol, 3 eq.) were added to the reaction mixture which was then warmed to RT for 15 min. MeOH (11.96 mL, 295.6 mmol, 10 eq.) was added, the reaction was stirred at RT for 15 min before being quenched with 500 mL aq. sat. NH₄Cl/H₂O (1:1), extracted with (3 x 300 mL) EtOAc, dried over Na₂SO₄, filtered, and evaporated under reduced pressure. The crude was purified over silica gel (5-20% EtOAc/Hex) to afford alkene **3.162A** as a white solid (6.66 g, 59%) and alkene **3.162B** as a white solid (4.18 g, 37%).

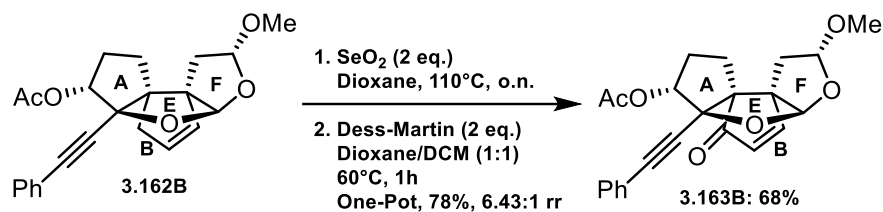
3.162A: mp 117-118 °C; R_f 0.38 (15% EtOAc/Hex); $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.37-7.31 (m, 2H), 7.31-7.21 (m, 3H), 5.77 (dt, J = 5.7, 2.2 Hz, 1H), 5.60 (s, 1H), 5.54 (ddd, J = 5.6, 2.2, 1.7 Hz, 1H), 5.45-5.38 (m, 1H), 5.21 (d, J = 5.8 Hz, 1H), 3.37 (s, 3H), 3.08 (ddd, J = 17.7, 2.3, 1.8 Hz, 1H), 2.47-2.27 (m, 3H), 2.19 (d, J = 14.6 Hz, 1H), 2.06 (s, 3H), 1.97 (dd, J = 14.6, 5.8 Hz, 1H), 1.92-1.81 (m, 1H), 1.81-1.72 (m, 1H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 170.0, 134.3, 131.8, 130.9, 128.5, 128.4, 122.9, 115.0, 108.4, 93.5, 88.1, 85.6, 80.5, 71.6, 64.7, 55.0, 46.1, 40.5, 33.2, 30.4, 21.3; IR (neat): 3060, 2924, 1738, 1437, 1372, 1234, 1024, 936, 767 (cm^{-1}); HRMS (EI) calcd for $\text{C}_{23}\text{H}_{24}\text{O}_5$ $[\text{M}]^+$: 380.1624, found 380.1602.

3.162B: mp 102-103 °C; R_f 0.23 (15% EtOAc/Hex); $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.46-7.33 (m, 2H), 7.33-7.26 (m, 3H), 5.79 (dt, J = 5.7, 2.2 Hz, 1H), 5.68 (ddd, J = 5.6, 2.1, 1.6 Hz, 1H), 5.64 (s, 1H), 5.44 (dd, J = 4.5, 2.3 Hz, 1H), 5.13 (t, J = 5.0 Hz, 1H), 3.44 (s, 3H), 3.09 (dt, J = 17.5, 2.0 Hz, 1H), 2.45-2.30 (m, 2H), 2.30-2.15 (m, 1H), 2.06 (s, 3H), 2.03-1.94 (m, 2H), 1.88-1.79 (m, 1H), 1.78 (dd, J = 14.3, 4.7 Hz, 1H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 169.9, 133.2, 131.8, 131.5, 128.6, 128.4, 122.7, 111.7, 106.5, 95.9, 88.9, 85.9, 80.7, 70.8, 64.4, 56.3, 45.0, 39.5, 32.4, 30.5, 21.4; IR (neat): 3065, 2935, 1736, 1438, 1230, 1096, 958, 766 (cm^{-1}); HRMS (EI) calcd for $\text{C}_{23}\text{H}_{24}\text{O}_5$ $[\text{M}]^+$: 380.1624, found 380.1648.



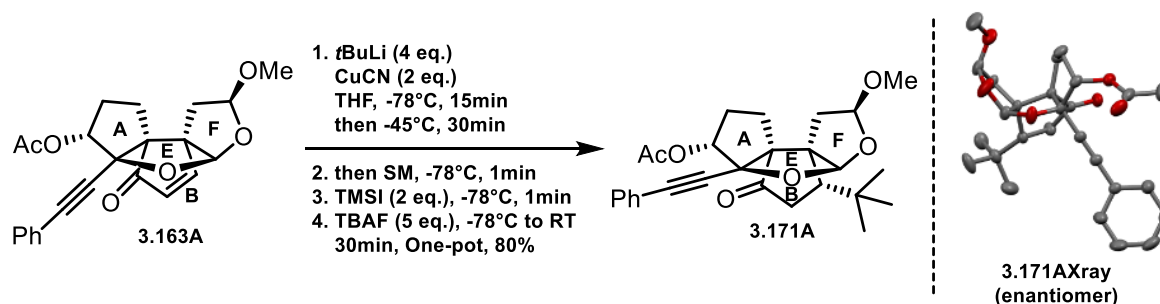
2-methoxy-8-oxo-4a-(phenylethynyl)-1,2,3a,4a,5,6,7,8-octahydrodicyclopenta[b,c]furo[3,2-d]furan-5-yl acetate (3.163A). In a sealable flask were added alkene **3.162A** (6.66 g, 17.5 mmol), 175 mL dioxane and SeO_2 (3.884 g, 35.0 mmol, 2 eq.). The flask was sealed and heated to 110 °C for overnight, after which the reaction mixture was cooled to RT. 175 mL DCM and Dess-Martin periodinane (11.14 g, 26.26 mmol, 1.5 eq.) were added. The flask was sealed and heated to 60 °C for 1 h. The reaction mixture was cooled to RT, a dry pack was prepared and the crude was purified over silica gel (20-30% EtOAc/Hex) to afford enone **3.163A** as a white solid (5.835 g, 85%): mp 109-110 °C; R_f 0.44 (40% EtOAc/Hex); $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.42 (d, J = 5.7 Hz, 1H), 7.34-7.19 (m, 5H), 6.16 (d, J = 5.7 Hz, 1H), 5.73 (s, 1H), 5.34 (dd, J = 3.7, 2.5 Hz, 1H), 5.26 (d, J = 5.4 Hz, 1H), 3.38 (s, 3H), 2.56-2.41 (m, 2H), 2.21 (d, J = 14.5 Hz, 1H), 2.13 (dd, J = 14.5, 5.4 Hz, 1H), 2.10-1.94 (m, 2H), 2.05 (s, 3H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 205.4, 170.3, 162.9, 131.8, 131.6, 128.8, 128.3, 122.0, 111.8, 108.0, 91.3, 89.9, 83.9, 79.4, 70.3, 69.2, 55.0, 39.8, 30.7, 27.8, 21.2; IR (neat):

2945, 1736, 1719, 1370, 1226, 1098, 1028, 762 (cm^{-1}); HRMS (EI) calcd for $\text{C}_{23}\text{H}_{22}\text{O}_6$ $[\text{M}]^+$: 394.1416, found 394.1403.



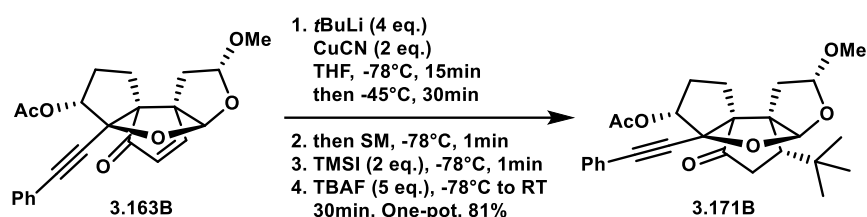
2-methoxy-8-oxo-4a-(phenylethynyl)-1,2,3a,4a,5,6,7,8-octahydrodicyclopenta[b,c]furo[3,2-d]furan-5-yl acetate (3.163B). In a sealable flask were added alkene **3.162B** (4.180 g, 10.99 mmol), 110 mL dioxane, and SeO_2 (2.439 g, 21.98 mmol, 2 eq.). The flask was sealed and heated to 110°C overnight, after which the reaction mixture was cooled to RT. 110 mL DCM and Dess-Martin periodinane (9.323 g, 21.98 mmol, 2 eq.) were added. The flask was sealed and heated to 60°C for 30 min. The reaction mixture was cooled to RT, a dry pack was prepared, and the crude was purified over silica gel (20-30% EtOAc/Hex) to afford enone **3.163B** as an amorphous white solid (3.393 g, 78%, 6.43:1 rr).

3.163B: R_f 0.43 (40% EtOAc/Hex); $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.63 (d, $J = 5.7$ Hz, 1H), 7.41-7.32 (m, 2H), 7.32-7.24 (m, 3H), 6.20 (d, $J = 5.7$ Hz, 1H), 5.73 (s, 1H), 5.38 (dd, $J = 4.8, 2.8$ Hz, 1H), 5.29 (dd, $J = 5.2, 3.0$ Hz, 1H), 3.45 (s, 3H), 2.54 (ddd, $J = 13.7, 11.5, 7.1$ Hz, 1H), 2.36 (dd, $J = 14.1, 5.2$ Hz, 1H), 2.24 (dddd, $J = 13.5, 11.6, 6.9, 4.8$ Hz, 1H), 2.14-2.00 (m, 1H), 2.09 (s, 3H) 1.94 (dd, $J = 14.1, 3.0$ Hz, 1H), 1.72 (ddd, $J = 13.7, 6.9, 3.1$ Hz, 1H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 205.2, 170.2, 162.6, 132.5, 131.8, 128.9, 128.4, 122.0, 110.0, 107.0, 93.3, 90.9, 83.6, 79.6, 69.6, 68.4, 56.1, 37.8, 31.0, 28.4, 21.3; IR (neat): 3080, 2920, 1742, 1716, 1459, 1444, 1370, 1224, 1010, 962, 847, 758, 692 (cm^{-1}); HRMS (EI) calcd for $\text{C}_{23}\text{H}_{22}\text{O}_6$ $[\text{M}]^+$: 394.1416, found 394.1416.



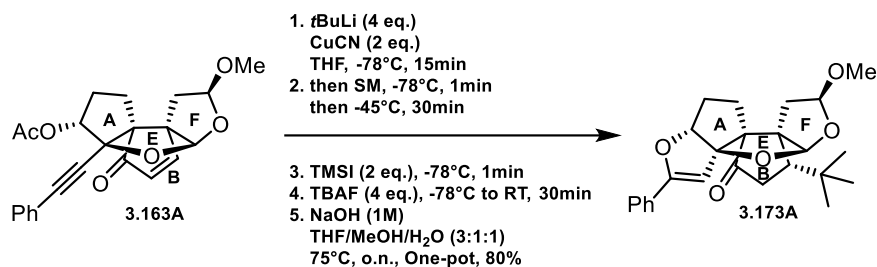
10-(tert-butyl)-2-methoxy-8-oxo-4a-(phenylethynyl)decahydrodicyclopenta[b,c]furo[3,2-d]furan-5-yl acetate (3.171A) To a suspension of CuCN (227 mg, 2.54 mmol, 2 eq.) in 16 mL THF at -78°C was added $t\text{BuLi}$ (1.60 M in pentane, 3.17 mL, 5.07 mmol, 4 eq.) dropwise over 5 min (the solution turned from clear

to light yellow). The reaction mixture was stirred at -78 °C for 15 min before being warmed to -45 °C and stirred for 30 min (the solution turned from light yellow to clear). The reaction mixture was cooled to -78 °C and a solution of **3.163A** (500.0 mg, 1.268 mmol) in 4 mL THF was added dropwise (the solution turned from clear to red). The solution was stirred at -78 °C for 1 min before adding TMSI (361 µL, 2.54 mmol, 2 eq.) dropwise (solution turned from red to brown). The reaction mixture was stirred at -78 °C for 1 min, then TBAF (1 M in THF, 6.34 mL, 6.34 mmol, 5 eq.) was added and the solution was stirred at -78 °C for 5 min after which the reaction quenched with 30 mL aq. sat. NH₄Cl, extracted with (3 x 30 mL) EtOAc, dried over Na₂SO₄, filtered, and evaporated under reduced pressure. The crude was purified over silica gel (10-20% EtOAc/Hex) to afford ketone **3.171A** as a white solid (458.7 mg, 80%): mp 152-153 °C; R_f 0.31 (20% EtOAc/Hex); ¹H-NMR (400 MHz, CDCl₃) δ 7.36-7.26 (m, 5H), 5.88 (s, 1H), 5.39 (dd, *J* = 4.3, 2.8 Hz, 1H), 5.28 (dd, *J* = 6.7, 2.1 Hz, 1H), 3.42 (s, 3H), 2.80-2.61 (m, 3H), 2.50-2.29 (m, 3H), 2.29-2.19 (m, 1H), 2.07 (s, 3H), 2.03-1.94 (m, 1H), 1.95 (dd, *J* = 14.8, 1.8 Hz, 1H), 1.06 (s, 9H); ¹³C-NMR (100 MHz, CDCl₃) δ 213.8, 170.1, 131.5, 128.8, 128.3, 121.8, 117.3, 108.3, 93.7, 89.6, 84.6, 80.0, 75.9, 67.5, 67.5, 56.0, 48.4, 41.5, 34.2, 33.1, 30.9, 29.5, 29.2, 21.2; IR (neat): 2948, 1733, 1731, 1441, 1371, 1234, 1005, 936, 753, 690 (cm⁻¹); HRMS (ESI) calcd for [C₂₇H₃₂O₆ + Na]⁺: 475.2097, found 475.2089.



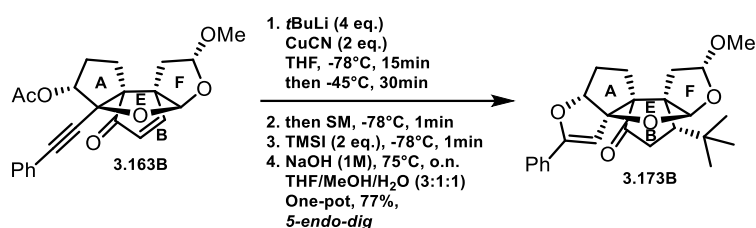
10-(*tert*-butyl)-2-methoxy-8-oxo-4a-(phenylethynyl)decahydrocyclopenta[b,c]furo[3,2-d]furan-5-yl acetate (3.171B**).** To a suspension of CuCN (438.0 mg, 4.89 mmol, 2 eq.) in 30 mL THF at -78 °C was added *t*BuLi (1.67 M in pentane, 5.86 mL, 9.78 mmol, 4 eq.) dropwise over 5 min (the solution turned from clear to light yellow). The reaction mixture was stirred at -78 °C for 15 min before being warmed to -45 °C and stirred for 30 min (the solution turned from light yellow to clear). The reaction mixture was cooled to -78 °C and a solution of **3.163B** (964.6 mg, 2.445 mmol, 3.84:1 rr) in 10 mL THF was added dropwise (the solution turned from clear to red). The solution was stirred at -78 °C for 1 min before adding TMSI (978.6 µL, 4.89 mmol, 2 eq.) dropwise (solution turned from red to brown). The reaction mixture was stirred at -78 °C for 1 min, then TBAF (1 M in THF, 12.23 mL, 12.23 mmol, 5 eq.) was added and the solution was stirred at -78 °C for 5 min after which the reaction quenched with 50 mL aq. sat. NH₄Cl, extracted with (3 x 50 mL) EtOAc, dried over Na₂SO₄, filtered, and evaporated under reduced pressure. The crude was purified over silica gel (10-20% EtOAc/Hex) to afford ketone **3.171B** as a white solid (690.6 mg, 81%). mp

174-175 °C; R_f 0.28 (20% EtOAc/Hex); $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.38-7.27 (m, 5H), 5.96 (s, 1H), 5.39 (dd, $J = 4.7, 3.0$ Hz, 1H), 5.06 (dd, $J = 6.0, 4.0$ Hz, 1H), 3.41 (s, 3H), 2.76 (dd, $J = 12.3, 8.7$ Hz, 1H), 2.69 (dd, $J = 18.3, 8.6$ Hz, 1H), 2.57 (ddd, $J = 13.6, 10.7, 7.3$ Hz, 1H), 2.47-2.35 (m, 2H), 2.29 (dd, $J = 18.3, 12.3$ Hz, 1H), 2.17 (dd, $J = 14.6, 6.0$ Hz, 1H), 2.05 (s, 3H), 1.95 (ddt, $J = 13.6, 7.1, 3.3$ Hz, 1H), 1.56 (ddd, $J = 13.6, 7.4, 3.5$ Hz, 1H), 1.10 (s, 9H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 213.1, 170.1, 131.6, 129.1, 128.5, 121.9, 113.6, 105.6, 95.3, 90.1, 84.8, 81.0, 76.8, 68.1, 56.1, 45.9, 40.7, 34.7, 33.3, 30.7, 29.2, 28.5, 21.3; IR (neat): 2951, 2144, 1742, 1371, 1226, 1048, 978, 759, 719, 707, 688 (cm^{-1}); HRMS (ESI) calcd for $[\text{C}_{27}\text{H}_{32}\text{O}_6 + \text{Na}]^+$: 475.2097, found 475.2104.

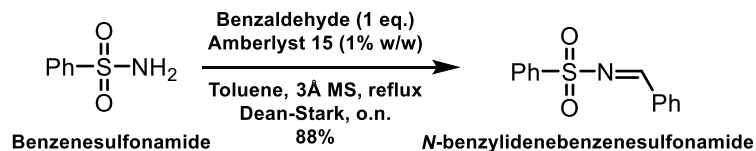


(3.173A) To a suspension of CuCN (227.0 mg, 2.535 mmol, 2 eq.) in 16 mL THF at -78°C was added $t\text{BuLi}$ (1.60 M in pentane, 3.17 mL, 5.07 mmol, 4 eq.) dropwise over 5 min (the solution turned from clear to light yellow). The reaction mixture was stirred at -78°C for 15 min before being warmed to -45°C and stirred for 30 min (the solution turned from light yellow to clear). The reaction mixture was cooled to -78°C and a solution of **3.163A** (500 mg, 1.268 mmol) in 4 mL THF was added dropwise (the solution turned from clear to red). The solution was stirred at -78°C for 1 min before adding TMSI (360.8 μL , 2.254 mmol, 2 eq.) dropwise (solution turned from red to brown). The reaction mixture was stirred at -78°C for 1 min, then TBAF (1 M in THF, 5.07 mL, 5.07 mmol, 4 eq.) was added and the solution was stirred at -78°C to RT for 30 min after which NaOH (1 M, 5.07 mL, 4eq.) and 5.07 mL MeOH were added, the flask was sealed and heated to 75°C overnight. The reaction mixture was cooled to RT and quenched with 25 mL aq. sat. NH_4Cl , extracted with (3 x 25 mL) EtOAc, dried over Na_2SO_4 , filtered, and evaporated under reduced pressure. The crude was purified over silica gel (10-20% EtOAc/Hex) to afford ketone **3.173A** as a white solid (418.7 mg, 80%): mp 166-167 °C; R_f 0.36 (20% EtOAc/Hex); $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.65-7.53 (m, 2H), 7.37-7.28 (m, 3H), 5.67 (s, 1H), 5.13 (dd, $J = 7.2, 3.5$ Hz, 1H), 5.07 (s, 1H), 4.95 (dd, $J = 8.9, 7.3$ Hz, 1H), 3.47 (s, 3H), 2.55 (dtd, $J = 14.0, 7.0, 2.1$ Hz, 1H), 2.51 (dd, $J = 18.3, 8.2$ Hz, 1H), 2.44-2.28 (m, 2H), 2.17-1.98 (m, 2H), 1.93 (dd, $J = 14.7, 3.5$ Hz, 1H), 1.83 (ddd, $J = 12.7, 7.4, 1.8$ Hz, 1H), 1.07 (s, 9H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 216.5, 159.5, 130.5, 129.5, 128.3, 126.3, 113.9, 111.3, 104.6, 95.0, 91.6, 72.7, 64.9, 56.9, 47.9,

41.5, 34.4, 33.6, 33.3, 31.2, 29.5; IR (neat): 3036, 2951, 1724, 1447, 1147, 1070, 964, 751, 698 (cm⁻¹); HRMS (ESI) calcd for [C₂₅H₃₀O₅ + Na]⁺: 433.1991, found 433.1978.

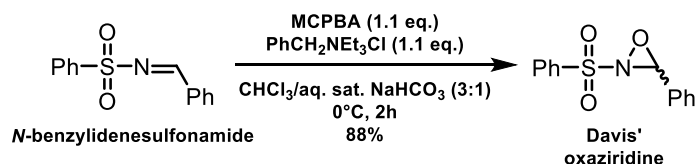


(3.173B) To a suspension of CuCN (269.8 mg, 3.013 mmol, 2 eq.) in 19 mL THF at -78 °C was added *t*BuLi (1.6 M in pentane, 3.77 mL, 6.026 mmol, 4 eq.) dropwise over 5 min (the solution turned from clear to light yellow). The reaction mixture was stirred at -78 °C for 15 min before being warmed to -45 °C and stirred for 30 min (the solution turned from light yellow to clear). The reaction mixture was cooled to -78 °C and a solution of **3.163B** (594.2 mg, 1.506 mmol) in 4 mL THF was added dropwise (the solution turned from clear to red). The solution was stirred at -78 °C for 1 min before adding TMSI (429 µL, 3.013 mmol, 2 eq.) dropwise (solution turned from red to brown). The reaction mixture was stirred at -78 °C for 1 min, then TBAF (1 M in THF, 7.53 mL, 7.53 mmol, 5 eq.) was added and the solution was stirred at -78 °C for 5 min. The solution was warmed to RT, NaOH (1 M, 6.02 mL, 6.02 mmol, 4 eq.) and 6.02 mL MeOH were added. The solution was heated to 75 °C overnight and was then cooled to RT. The reaction was quenched with 20 mL aq. sat. NH₄Cl, warmed to RT, extracted with (3 x 30 mL) EtOAc, dried over Na₂SO₄, filtered, and evaporated under reduced pressure. The crude was purified over silica gel (10-20% EtOAc/Hex) to afford ketone **3.173B** as a white solid (473.6 mg, 77%): mp 203-204 °C; *R*_f 0.30 (20% EtOAc/Hex); ¹H-NMR (400 MHz, Benzene-D₆) δ 7.73-7.57 (m, 2H), 7.12-6.96 (m, 3H), 5.97 (s, 1H), 5.25 (s, 1H), 5.18 (dd, *J* = 9.1, 7.5 Hz, 1H), 4.70 (dd, *J* = 6.3, 2.7 Hz, 1H), 3.21 (s, 3H), 2.47-2.22 (m, 4H), 2.18-1.95 (m, 2H), 1.83 (ddd, *J* = 12.3, 6.6, 2.1 Hz, 1H), 1.76 (dd, *J* = 14.5, 6.3 Hz, 1H), 1.32 (td, *J* = 12.4, 7.1 Hz, 1H), 0.85 (s, 9H); ¹³C-NMR (100 MHz, Benzene-D₆) δ 214.4, 159.8, 131.0, 129.6, 128.6, 126.6, 112.7, 110.8, 104.4, 95.9, 92.2, 72.9, 66.5, 55.3, 46.6, 41.2, 34.8, 34.0, 33.1, 31.9, 28.9; IR (neat): 2995, 2949, 1728, 1635, 1452, 1365, 1148, 1099, 963, 878, 754, 694 (cm⁻¹); HRMS (ESI) calcd for [C₂₅H₃₀O₅ + Na]⁺: 433.1991, found 433.1971.

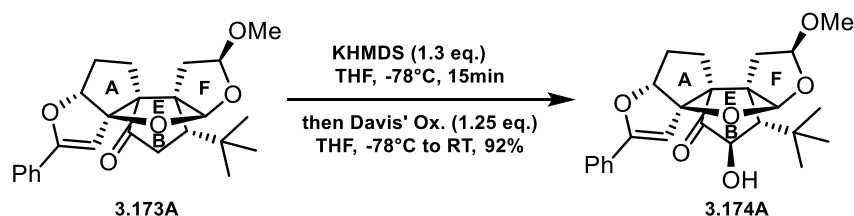


N-benzylidenebenzenesulfonamide. To a solution of benzenesulfonamide (3.20 g, 20.4 mmol) in 32 mL toluene were added benzaldehyde (2.09 mL, 20.6 mmol, 1 eq.), Amberlyst® 15 (32 mg, 1% w/w) and 3 Å

MS (3.2 g). The reaction mixture was heated to reflux overnight using a Dean-Stark apparatus. The solution was cooled to RT, filtered, and evaporated under reduced pressure to give a thick residue that solidifies on standing. The residue was triturated with pentane, filtered, washed with pentane, and evaporated under reduced pressure to afford the desired sulfonamide as a white solid (4.15 g, 88%): R_f 0.32 (20% EtOAc/Hex). Spectral data was identical to those found in the literature.¹⁴¹

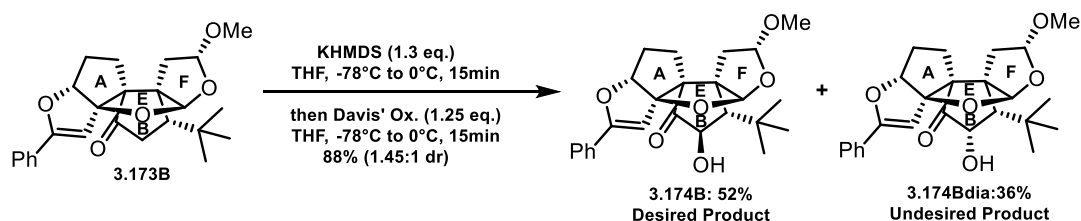


3-phenyl-2-(phenylsulfonyl)-1,2-oxaziridine (Davis' oxaziridine). To a solution of *N*-benzylidenebenzenesulfonamide (4.15 g, 16.9 mmol) in 20 mL CHCl_3 at 0°C was added 20 mL aq. sat. NaHCO_3 and benzyltrimethylammonium chloride (4.24 g, 18.6 mmol, 1.1 eq.). Thereafter, a solution of MCPBA (68% w/w, 4.28 g, 18.6 mmol, 1.1 eq.) in 40 mL CHCl_3 was added to the reaction mixture via an addition funnel over 1 h at 0°C , after which the reaction was stirred at 0°C for 1 h. The organic layer was separated from the aqueous layer using a separation funnel before being washed with 60 mL 5% $\text{Na}_2\text{S}_2\text{O}_3$ and (2 x 60 mL) aq. sat. NaCl . The organic layer was dried over Na_2SO_4 , filtered, and evaporated under reduced pressure while keeping the rotavap bath was kept under 40°C . The residue was suspended in pentane and dissolved in the minimum amount of EtOAc needed. The solution was filtered, diluted with pentane, and placed in the refrigerator to recrystallize overnight. The recrystallized product was filtered, washed with pentane and was air dried. The mother liqueur was evaporated under reduced pressure and the residue was triturated with Et_2O /pentane (1:1). These fractions were combined to afford Davis' oxaziridine as a white solid (3.89 g, 88%): R_f 0.47 (20% EtOAc/Hex). Spectral data was identical to those found in the literature.¹⁴²



(3.174A). To a solution of ketone **3.173A** (661.4 mg, 1.611 mmol) in 20 mL THF at -78°C was added a solution of KHMDS (417.8 mg, 2.094 mmol, 1.3 eq.) in 5 mL THF dropwise. The reaction mixture was warmed to 0°C and stirred for 15 min. The reaction mixture was cooled to -78°C before adding a solution

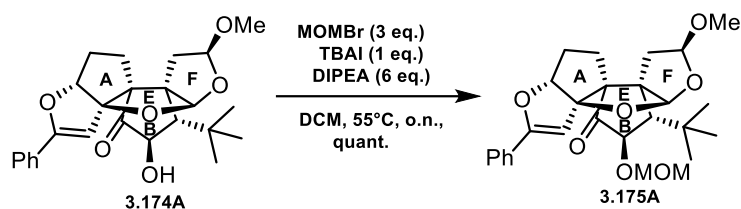
of Davis' oxaziridine (526.3 mg, 2.014 mmol, 1.25 eq.) in 5 mL THF. The solution was warmed to 0 °C and stirred for 15 min. The reaction was quenched with 30 mL aq. sat NH₄Cl, extracted with (3 x 30 mL) EtOAc, dried over Na₂SO₄, filtered, and evaporated under reduced pressure. The crude was purified over silica gel (10-20% EtOAc/Hex) to afford α-hydroxy ketone **3.174A** as a white solid (558.9 mg, 92%): mp 153-154 °C; R_f 0.23 (20% EtOAc/Hex); ¹H-NMR (400 MHz, CDCl₃) δ 7.65-7.56 (m, 2H), 7.37-7.31 (m, 3H), 5.78 (s, 1H), 5.17 (dd, *J* = 7.1, 3.1 Hz, 1H), 5.02 (s, 1H), 4.94 (dd, *J* = 8.6, 6.2 Hz, 1H), 4.13 (d, *J* = 13.8 Hz, 1H), 3.47 (s, 3H), 2.83 (s(br), 1H), 2.76 (dd, *J* = 14.8, 7.1 Hz, 1H), 2.61-2.48 (m, 2H), 2.15-2.06 (m, 1H), 1.93 (dd, *J* = 14.7, 3.0 Hz, 1H), 1.81 (d, *J* = 13.8 Hz, 1H), 1.76-1.69 (m, 1H), 1.20 (s, 9H); ¹³C-NMR (100 MHz, CDCl₃) δ 215.6, 159.1, 130.5, 129.5, 128.3, 126.3, 113.5, 110.9, 104.9, 95.7, 91.0, 77.6, 68.6, 60.1, 56.6, 53.6, 34.1, 33.8, 32.9, 32.3, 29.6; IR (neat): 3463(br), 2963, 1743, 1448, 1071, 967, 761, 690 (cm⁻¹); HRMS (ESI) calcd for [C₂₅H₃₀O₆ + Na]⁺: 449.1940, found 449.1956.



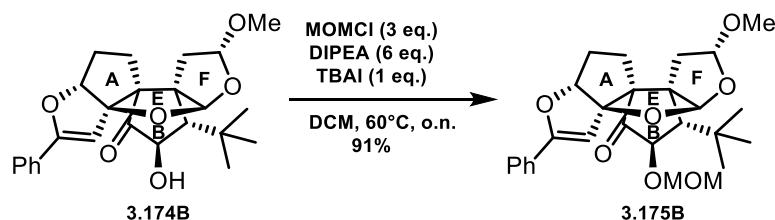
(3.174B/3.174Bdia). To a solution of ketone **3.173B** (661.4 mg, 1.611 mmol) in 20 mL THF at -78 °C was added a solution of KHMDS (417.8 mg, 2.094 mmol, 1.3 eq.) in 5 mL THF dropwise. The reaction mixture was warmed to 0 °C and stirred for 15 min. The reaction mixture was cooled to -78 °C before adding a solution of Davis' oxaziridine (526.3 mg, 2.014 mmol, 1.25 eq.) in 5 mL THF. The solution was warmed to 0 °C and stirred for 15 min. The reaction was quenched with 30 mL aq. sat NH₄Cl, extracted with (3 x 30 mL) EtOAc, dried over Na₂SO₄, filtered, and evaporated under reduced pressure. The crude was purified over silica gel (10-20% EtOAc/Hex) to afford the desired α-hydroxy ketone **3.174B** as a white solid (205.0 mg, 52%) and the undesired α-hydroxy ketone **3.174Bdia** as a white solid (141.0 mg, 36%). The undesired α-hydroxy ketone **3.174Bdia** converted to the desired MOM-protected α-hydroxy ketone **3.175B** after MOM-protection and epimerization.

3.174B: mp 140-141 °C; R_f 0.41 (30% EtOAc/Hex); ¹H-NMR (400 MHz, Benzene-D₆) δ 7.70-7.55 (m, 2H), 7.08-6.96 (m, 3H), 6.06 (s, 1H), 5.22 (s, 1H), 5.15 (dd, *J* = 8.7, 7.4 Hz, 1H), 4.65 (dd, *J* = 6.4, 2.7 Hz, 1H), 3.69 (d, *J* = 13.5 Hz, 1H), 3.19 (s, 3H), 2.86 (s(br), 1H), 2.34-2.20 (m, 3H), 1.95 (d, *J* = 13.5 Hz, 1H), 1.66 (dd, *J* = 14.6, 6.4 Hz, 1H), 1.61-1.51 (m, 1H), 1.40-1.24 (m, 2H), 1.15 (s, 9H); ¹³C-NMR (100 MHz, Benzene-D₆) δ 215.2, 159.4, 130.9, 129.5, 128.5, 126.6, 111.6, 111.2, 104.1, 96.7, 91.7, 77.8, 68.8, 61.7, 55.4, 52.2, 34.5,

34.1, 33.1, 32.5, 29.4; IR (neat): 3440(br), 2963, 2360, 1741, 1636, 1449, 1235, 1142, 1098, 964, 859, 740, 694 (cm⁻¹); HRMS (ESI) calcd for [C₂₅H₃₀O₆ + Na]⁺: 449.1940, found 449.1932.

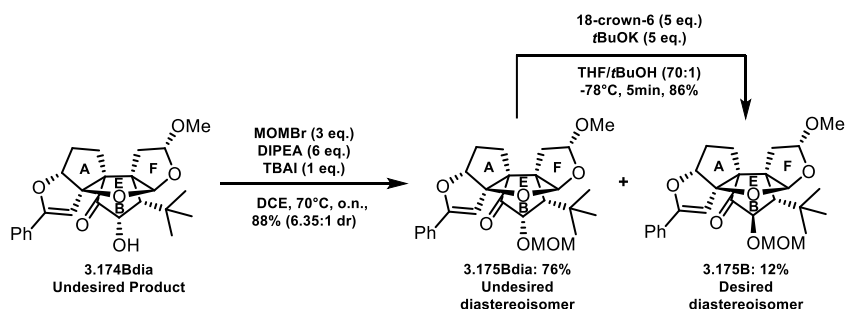


(3.175A) In a sealable flask, **3.174A** (4.735 g, 11.10 mmol) was dissolved in 111 mL DCM after which were added TBAI (4.100 g, 11.10 mmol, 1 eq.), DIPEA (11.6 mL, 66.6 mmol, 6 eq.) and MOMBr (2.72 mL, 33.3 mmol, 3 eq.). The flask was sealed and heated to 55 °C overnight. The reaction mixture was cooled to RT, quenched with 100 mL aq. sat. NaHCO₃, stirred at RT for 15 min, extracted with (3 x 100 mL) DCM, dried over Na₂SO₄, filtered, and evaporated under reduced pressure. The crude was purified over silica gel (10-20% EtOAc/Hex) to afford MOM-protected α-hydroxyketone **3.175A** as a white solid (5.224 g, quant.): mp 63-64 °C; R_f 0.38 (20% EtOAc/Hex); ¹H-NMR (400 MHz, CDCl₃) δ 7.66-7.54 (m, 2H), 7.36-7.28 (m, 3H), 5.77 (s, 1H), 5.15 (dd, *J* = 7.2, 3.4 Hz, 1H), 5.13 (d, *J* = 7.1 Hz, 1H), 5.12 (s, 1H), 4.91 (dd, *J* = 8.7, 6.9 Hz, 1H), 4.75 (d, *J* = 7.1 Hz, 1H), 4.21 (d, *J* = 13.3 Hz, 1H), 3.47 (s, 3H), 3.46 (s, 3H), 2.58-2.48 (m, 1H), 2.45 (dd, *J* = 12.6, 6.3 Hz, 1H), 2.12-2.02 (m, 1H), 2.00 (d, *J* = 13.3 Hz, 1H), 1.91 (dd, *J* = 14.7, 3.3 Hz, 1H), 1.71 (ddd, *J* = 11.4, 7.1, 1.7 Hz, 1H), 1.19 (s, 9H); ¹³C-NMR (100 MHz, CDCl₃) δ 214.1, 159.1, 130.6, 129.4, 128.3, 126.3, 113.5, 111.2, 104.8, 96.6, 95.8, 91.0, 80.5, 68.7, 60.0, 57.2, 56.7, 51.4, 34.1, 33.8, 33.0, 32.3, 29.7; IR (neat): 2950, 1742, 1448, 1117, 966, 736, 691 (cm⁻¹); HRMS (ESI) calcd for [C₂₇H₃₄O₇ + Na]⁺: 493.2202, found 493.2177.

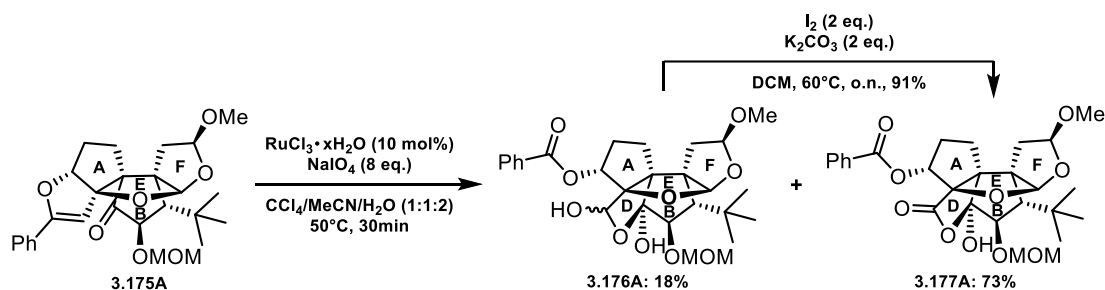


(3.175B) In a sealable flask, **3.174B** (205.0 mg, 0.4806 mmol) was dissolved in 4.8 mL DCM after which were added TBAI (177.5 mg, 0.4806 mmol, 1 eq.), DIPEA (502 μL, 2.88 mmol, 6 eq.) and MOMCl (110 μL, 1.44 mmol, 3 eq.). The flask was sealed and heated to 60 °C overnight. The reaction mixture was cooled to RT, diluted with 30 mL DCM, quenched with 30 mL aq. sat. NaHCO₃, stirred at RT for 15 min, extracted with (3 x 100 mL) DCM, dried over Na₂SO₄, filtered, and evaporated under reduced pressure. The crude was purified over silica gel (10-25% EtOAc/Hex) to afford MOM-protected α-hydroxyketone **3.175B** as a

white solid (205.9 mg, 91%): mp 66-67 °C; R_f 0.28 (20% EtOAc/Hex); $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.69-7.53 (m, 2H), 7.42-7.28 (m, 3H), 5.89 (s, 1H), 5.17 (d, J = 7.0 Hz, 1H), 5.11 (s, 1H), 5.03 (dd, J = 6.4, 2.7 Hz, 1H), 4.92 (dd, J = 9.5, 7.1 Hz, 1H), 4.76 (d, J = 7.0 Hz, 1H), 4.17 (d, J = 12.9 Hz, 1H), 3.47 (s, 3H), 3.40 (s, 3H), 2.55-2.43 (m, 1H), 2.44 (dd, J = 14.6, 2.6 Hz, 1H), 2.18 (dd, J = 14.5, 6.4 Hz, 1H), 2.12-1.97 (m, 1H), 2.05 (d, J = 12.9 Hz, 1H), 1.84 (ddt, J = 12.6, 6.9, 1.2 Hz, 1H), 1.56 (td, J = 13.0, 6.3 Hz, 1H), 1.22 (s, 9H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 214.5, 159.3, 130.5, 129.5, 128.3, 126.3, 111.6, 110.1, 104.1, 96.7, 95.6, 91.3, 80.3, 68.9, 61.6, 57.3, 55.7, 50.3, 34.3, 34.2, 33.1, 32.4, 29.5; IR (neat): 2960, 1743, 1637, 1449, 1372, 1233, 1147, 1099, 1066, 963, 737, 692 (cm^{-1}); HRMS (ESI) calcd for $[\text{C}_{27}\text{H}_{34}\text{O}_7 + \text{Na}]^+$: 493.2202, found 493.2209.



(Preparation of **3.175B** from **3.174Bdia**) In a sealable flask, the undesired α -hydroxy ketone **3.174Bdia** (683.2 mg, 1.602 mmol) was dissolved in 23 mL DCE after which were added TBAI (591.7 mg, 1.602 mmol, 1 eq.), DIPEA (1.67 mL, 9.61 mmol, 6 eq.) and MOMBr (392 μL , 4.81 mmol, 3 eq.). The flask was sealed and heated to 70 °C overnight. The reaction mixture was cooled to RT, diluted with 100 mL DCM, quenched with 100 mL aq. sat. NaHCO_3 , stirred at RT for 15 min, extracted with (3 x 100 mL) DCM, dried over Na_2SO_4 , filtered, and evaporated under reduced pressure. The crude was purified over silica gel (10-30% EtOAc/Hex) to afford the undesired MOM-protected α -hydroxyketone **3.175Bdia** as a white solid (571.1 mg, 76%) and the desired MOM-protected α -hydroxyketone **3.175B** (90.0 mg, 12%). To a solution of the undesired α -hydroxyketone **3.175Bdia** (571.1 mg, 1.213 mmol) and 18-crown-6 (1.603 g, 6.065 mmol, 5 eq.) in 20 mL THF at -78 °C was added a solution of *t*BuOK (680.6 mg, 6.065 mmol, 5 eq.) in 8 mL THF. The reaction was stirred at -78 °C for 5 min before quenching with 25 mL aq. sat. NH_4Cl . The reaction mixture was warmed to RT, extracted with (3 x 25 mL) EtOAc, dried over Na_2SO_4 , filtered, and evaporated under reduced pressure. The crude was purified over silica gel (10-25% EtOAc/Hex) to afford the desired MOM-protected α -hydroxyketone **3.175B** (491.5 mg, 86%).



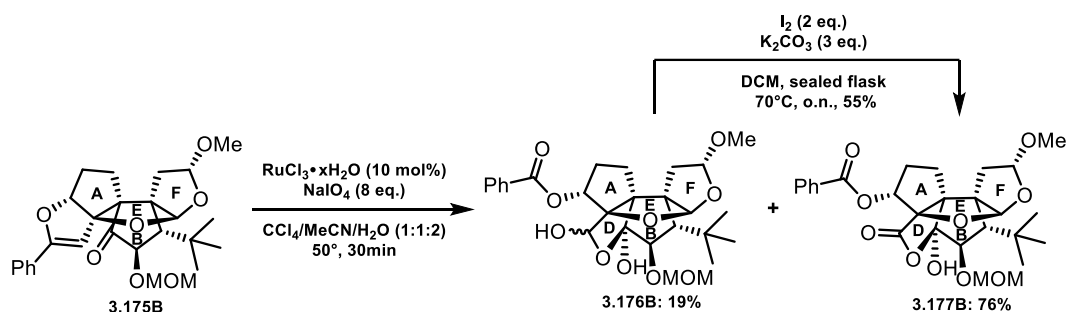
(3.176A/3.177A) A solution of RuO_4 was prepared by dissolving NaIO_4 (1.808 g, 8.452 mmol, 8 eq.) in 10 mL H_2O after which were added 5 mL MeCN, 5 mL CCl_4 and $\text{RuCl}_3 \cdot x\text{H}_2\text{O}$ (21.9 mg, 0.1056 mmol, 10 mol%). The RuO_4 solution was stirred (high stirring) at RT for 5 min and was then added to a solution of **3.175A** (497.2 mg, 1.056 mmol) in 20 mL of $\text{CCl}_4/\text{MeCN}/\text{H}_2\text{O}$ (1:1:2) at 50 °C. The reaction mixture was stirred at 50 °C for 30 min with high stirring. The reaction was cooled to RT, quenched with 30 mL 10% $\text{Na}_2\text{S}_2\text{O}_3$ extracted with (3 x 30 mL) EtOAc, dried over Na_2SO_4 , filtered, and evaporated under reduced pressure. The crude was purified over silica gel (15-30% EtOAc/Hex, then 2% MeOH/DCM) to afford lactol **3.176A** as a white solid (100.1 mg, 18%) and lactone **3.177A** as a white solid (397.7 mg, 73%).

Conversion of 3.176A to 3.177A: In a sealable flask, **3.176A** (100.1 mg, 0.2042 mmol) was dissolved in 4 mL DCM after which were added I_2 (103.6 mg, 0.408 mmol, 2 eq.) and ground K_2CO_3 (56.4 mg, 0.408 mmol, 2 eq.). The flask was sealed and heated to 60 °C overnight. The reaction mixture was cooled to RT, quenched with 10 mL 10% $\text{Na}_2\text{S}_2\text{O}_3$, extracted with (3 x 10 mL) DCM, dried over Na_2SO_4 , filtered, and evaporated under reduced pressure. The crude was purified over silica gel (20-25% EtOAc/Hex, then 2% MeOH/DCM) to afford lactone **3.177A** as a white solid (90.9 mg, 91%).

(3.176A): mp 110-111 °C; R_f 0.32 (40% EtOAc/Hex); $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 8.09-8.03 (m, 2H), 7.53 (ddt, J = 8.0, 6.9, 1.4 Hz, 1H), 7.45-7.36 (m, 2H), 5.90 (s, 1H), 5.82 (s, 1H), 5.78 (d, J = 12.6 Hz, 1H), 5.42 (dd, J = 11.4, 6.6 Hz, 1H), 5.17 (dd, J = 6.6, 1.3 Hz, 1H), 4.75 (d, J = 7.1 Hz, 1H), 4.72 (d, J = 7.2 Hz, 1H), 4.04 (d, J = 12.6 Hz, 1H), 3.56 (s, 3H), 3.50 (s, 3H), 3.46 (d, J = 11.9 Hz, 1H), 2.69 (dd, J = 14.8, 6.6 Hz, 1H), 2.5-2.42 (m, 1H), 2.38 (dd, J = 12.3, 6.7 Hz, 1H), 2.30 (d, J = 11.9 Hz, 1H), 2.05 (d, J = 13.7 Hz, 1H), 2.05-1.94 (m, 1H), 1.89 (dd, J = 11.9, 6.9 Hz, 1H), 1.05 (s, 9H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 166.1, 133.1, 130.2, 129.9, 128.5, 122.8, 107.0, 104.4, 103.5, 98.8, 98.0, 89.2, 79.4, 70.0, 61.4, 56.5, 55.7, 52.7, 35.2, 32.4, 32.2, 29.7, 24.6; IR (neat): 3366(br), 2955, 1719, 1461, 1274, 1071, 956, 880, 713 (cm^{-1}); HRMS (ESI) calcd for $[\text{C}_{27}\text{H}_{36}\text{O}_{10} + \text{Na}]^+$: 543.2206, found 543.2224.

(3.177A): mp 184-185 °C; R_f 0.38 (20-25% EtOAc/Hex then 2% MeOH/DCM); $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 8.13-8.05 (m, 2H), 7.53 (ddt, J = 8.7, 6.9, 1.4 Hz, 1H), 7.47-7.36 (m, 2H), 7.08 (s(br), 1H), 5.73 (s, 1H), 5.50

(dd, $J = 6.9, 5.8$ Hz, 1H), 5.18 (dd, $J = 7.0, 2.2$ Hz, 1H), 4.80 (d, $J = 7.3$ Hz, 1H), 4.78 (d, $J = 7.4$ Hz, 1H), 3.61 (s, 3H), 3.59 (d, $J = 12.5$ Hz, 1H), 3.45 (s, 3H), 2.70 (dd, $J = 14.8, 7.0$ Hz, 1H), 2.60 (dq, $J = 12.5, 6.2$ Hz, 1H), 2.38 (ddd, $J = 8.1, 6.4, 2.4$ Hz, 1H), 2.39 (dd, $J = 6.8, 3.2$ Hz, 1H), 2.37 (dd, $J = 6.6, 1.7$ Hz, 1H), 2.14 (ddt, $J = 13.2, 8.1, 6.9$ Hz, 1H), 2.00 (d, $J = 12.5$ Hz, 1H), 1.98 (dd, $J = 14.8, 2.3$ Hz, 1H) 1.08 (s, 9H); ^{13}C -NMR (100 MHz, CDCl_3) δ 171.2, 165.5, 133.1, 130.1, 130.0, 128.4, 118.9, 107.1, 106.6, 101.2, 97.9, 89.6, 80.4, 67.2, 61.7, 56.8, 56.3, 51.2, 34.4, 33.3, 32.3, 29.6, 26.2; IR (neat): 3400(br), 2970, 1733, 1718, 1273, 1098, 973, 715 (cm^{-1}); HRMS (ESI) calcd for $[\text{C}_{27}\text{H}_{34}\text{O}_{10} + \text{Na}]^+$: 541.2050, found 541.2021.



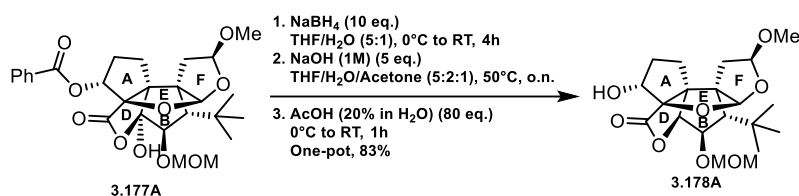
(3.176B/3.177B) A solution of RuO_4 was prepared by dissolving NaIO_4 (2.900 g, 13.56 mmol, 8 eq.) in 17 mL H_2O after which were added 8.5 mL MeCN , 8.5 mL CCl_4 and $\text{RuCl}_3 \cdot x\text{H}_2\text{O}$ (35.2 mg, 0.170 mmol, 10 mol%). The RuO_4 solution was stirred (high stirring) at RT for 5 min and was then added to a solution of **3.175B** (798.0 mg, 1.696 mmol) in 34 mL of $\text{CCl}_4/\text{MeCN}/\text{H}_2\text{O}$ (1:1:2) at 50 °C. The reaction was stirred at 50 °C for 30 min with high stirring. The reaction was cooled to RT, quenched with 50 mL 10% $\text{Na}_2\text{S}_2\text{O}_3$ extracted with (3 x 50 mL) EtOAc , dried over Na_2SO_4 , filtered, and evaporated under reduced pressure. The crude was purified over silica gel (20-25% EtOAc/Hex , then 2% MeOH/DCM) to afford lactol **3.176B** as a white solid (169.8 mg, 19%) and lactone **3.177B** as a white solid (672.4 mg, 76%).

Conversion of **3.176B** to **3.177B**: In a sealable flask, **3.176B** (198.7 mg, 0.3816 mmol) was dissolved in 12.5 mL DCM after which were added I_2 (193.7 mg, 0.7631 mmol, 2 eq.) and ground K_2CO_3 (158.2 mg, 1.145 mmol, 3 eq.). The flask was sealed and heated to 70 °C overnight. The reaction mixture was cooled to RT, quenched with 10 mL 10% $\text{Na}_2\text{S}_2\text{O}_3$, extracted with (3 x 10 mL) DCM , dried over Na_2SO_4 , filtered, and evaporated under reduced pressure. The crude was purified over silica gel (20-25% EtOAc/Hex , then 2% MeOH/DCM) to afford lactone **3.177B** as a white solid (84.3 mg, 55%).

(3.176B): mp 139-140 °C; R_f 0.60 (40% EtOAc/Hex); ^1H -NMR (400 MHz, CDCl_3) δ 8.13-7.99 (m, 2H), 7.60-7.49 (m, 1H), 7.49-7.35 (m, 2H), 5.94 (s, 1H), 5.81 (d, $J = 11.5$ Hz, 1H), 5.78 (s, 1H), 5.39 (dd, $J = 11.7, 6.5$ Hz, 1H), 5.09 (dd, $J = 6.3, 3.4$ Hz, 1H), 4.76 (d, $J = 7.1$ Hz, 1H), 4.72 (d, $J = 7.1$ Hz, 1H), 3.93 (d, $J = 12.8$ Hz, 1H), 3.55 (s, 3H), 3.41 (d, $J = 12.8$ Hz, 1H), 3.39 (s, 3H), 2.55-2.35 (m, 2H), 2.22 (dd, $J = 14.7, 6.3$ Hz, 1H),

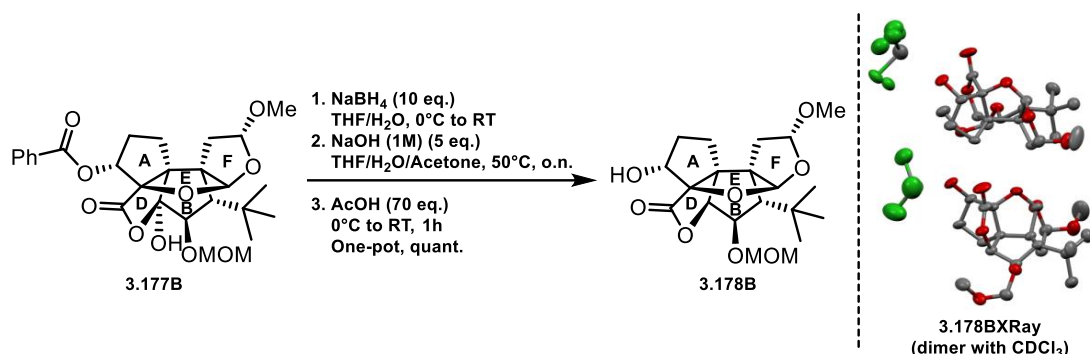
2.14 (d, $J = 12.0$ Hz, 1H), 2.12 (dd, $J = 12.8, 6.6$ Hz, 1H), 1.93 (dtd, $J = 13.3, 12.0, 6.8$ Hz, 1H), 1.34 (td, $J = 13.0, 6.4$ Hz, 1H), 1.10 (s, 9H); ^{13}C -NMR (100 MHz, CDCl_3) δ 166.1, 133.2, 130.1, 130.0, 128.5, 115.8, 104.8, 104.0, 102.6, 98.6, 98.0, 89.5, 80.4, 69.1, 62.0, 56.5, 56.0, 49.4, 34.9, 32.3, 31.4, 29.6, 25.4; IR (neat): 3400(br), 2970, 1733, 1718, 1273, 1098, 974, 715 (cm^{-1}); HRMS (ESI) calcd for $[\text{C}_{27}\text{H}_{36}\text{O}_{10} + \text{Na}]^+$: 543.2206, found 543.2213.

(**3.177B**): mp 178-179 °C; R_f 0.51 (40% EtOAc/Hex); ^1H -NMR (400 MHz, CDCl_3) δ 8.18-8.03 (m, 2H), 7.60-7.48 (m, 1H), 7.48-7.35 (m, 2H), 7.01 (s, 1H), 5.81 (s, 1H), 5.52 (dd, $J = 8.5, 5.7$ Hz, 1H), 5.07 (dd, $J = 6.2, 3.3$ Hz, 1H), 4.80 (d, $J = 7.4$ Hz, 1H), 4.77 (d, $J = 7.4$ Hz, 1H), 3.60 (s, 3H), 3.58 (d, $J = 12.6$ Hz, 1H), 3.39 (s, 3H), 2.60-2.43 (m, 2H), 2.39 (dd, $J = 14.6, 3.3$ Hz, 1H), 2.24 (dd, $J = 14.6, 6.2$ Hz, 1H), 2.14-2.00 (m, 1H), 1.92 (d, $J = 12.5$ Hz, 1H), 1.61-1.51 (m, 1H), 1.11 (s, 9H); ^{13}C -NMR (100 MHz, CDCl_3) δ 170.3, 165.6, 133.2, 130.2, 129.9, 128.4, 115.1, 106.3, 104.9, 100.4, 98.1, 89.6, 80.8, 67.4, 62.7, 56.9, 56.0, 48.8, 34.5, 32.8, 32.4, 29.5, 26.5; IR (neat): 3285(br), 2959, 1782, 1730, 1452, 1268, 1100, 1017, 958, 891, 717 (cm^{-1}); HRMS (ESI) calcd for $[\text{C}_{27}\text{H}_{34}\text{O}_{10} + \text{Na}]^+$: 541.2050, found 541.2025.

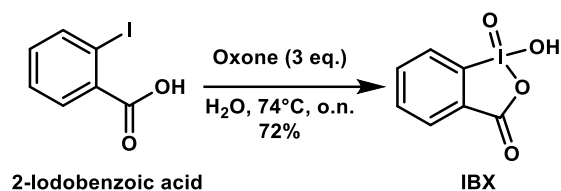


(**3.178A**) To a solution of **3.177A** (347.2 mg, 0.6695 mmol) in 25 mL THF at 0 °C was added a solution of NaBH_4 (259.3 mg, 6.695 mmol, 10 eq.) in 5 mL H_2O . The reaction was warmed to RT and stirred for 4 h. NaOH (1 M, 3.35 mL, 3.35 mmol, 5 eq.) and 3.35 mL acetone were added, and the reaction mixture was heated to 50 °C overnight. The reaction was cooled to 0 °C and dilute AcOH (20% in H_2O , 15.32 mL, 53.56 mmol, 80 eq.) was added slowly after which the solution was warmed to RT and stirred for 1 h. The reaction mixture was quenched with 50 mL aq. sat. NaHCO_3 and extracted with (3 x 50 mL) DCM, dried over Na_2SO_4 , filtered, and evaporated under reduced pressure. The crude was purified over silica gel (0.5-2% MeOH/DCM) to afford lactone **3.178A** as a white solid (278.3 mg, 83%): mp 180-181 °C; R_f 0.33 (50% EtOAc/Hex); ^1H -NMR (400 MHz, CDCl_3) δ 5.69 (s, 1H), 5.16 (dd, $J = 6.8, 1.7$ Hz, 1H), 4.77 (d, $J = 7.1$ Hz, 1H), 4.71 (d, $J = 7.1$ Hz, 1H), 4.55 (d, $J = 4.0$ Hz, 1H), 4.45 (t, $J = 6.0$ Hz, 1H), 3.77 (dd, $J = 12.4, 4.0$ Hz, 1H), 3.45 (s, 3H), 3.38 (s, 3H), 2.66 (dd, $J = 15.0, 7.0$ Hz, 1H), 2.63-2.51 (m, 1H), 2.43 (ddt, $J = 13.3, 7.4, 5.3$ Hz, 1H), 2.08 (d, $J = 12.4$ Hz, 1H), 1.91 (dd, $J = 14.8, 1.6$ Hz, 1H), 1.88-1.80 (m, 1H), 1.80-1.72 (m, 1H), 1.07 (s, 9H); ^{13}C -NMR (100 MHz, CDCl_3) δ 174.7, 119.9, 107.6, 101.1, 96.5, 86.2, 80.9, 79.0, 65.9, 62.2, 56.6, 55.9, 52.7,

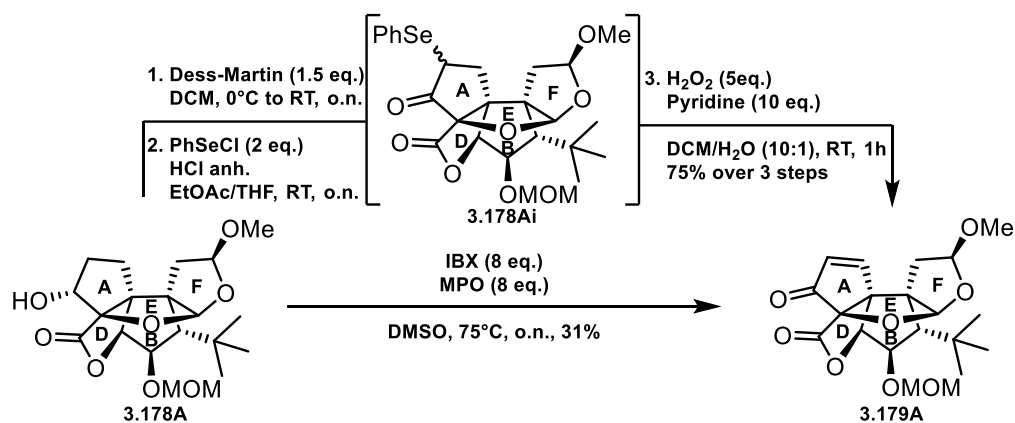
35.0, 34.6, 32.2, 30.4, 29.5; IR (neat): 3431(br), 2909, 1770, 1229, 1121, 1008, 851, 696 (cm⁻¹); HRMS (ESI) calcd for [C₂₀H₃₀O₈ + Na]⁺: 421.1838, found 421.1841.



(3.178B) To a solution of **3.177B** (1.064 g, 2.051 mmol) in 20.5 mL THF at 0 °C was added a solution of NaBH₄ (776.0 mg, 20.51 mmol, 10 eq.) in 4 mL H₂O. The reaction was warmed to RT and stirred for 4 h. NaOH (1 M, 10.25 mL, 10.25 mmol, 5 eq.) and 10.25 mL acetone were added, and the reaction mixture was heated to 50 °C overnight. The reaction was cooled to 0 °C and 41 mL dilute AcOH (20% in H₂O, 8.21 mL, 144 mmol, 70 eq.) was added slowly after which the solution was warmed to RT and stirred for 1 h. The reaction mixture was quenched with 200 mL aq. sat. NaHCO₃ and extracted with (3 x 100 mL) DCM, dried over Na₂SO₄, filtered, and evaporated under reduced pressure. The crude was purified over silica gel (0.75-1.5% MeOH/DCM) to afford lactone **3.178B** as a white solid (817.4 mg, quant.): mp 147-148 °C; R_f 0.26 (60% EtOAc/Hex); ¹H-NMR (400 MHz, CDCl₃) δ 5.78 (s, 1H), 5.02 (dd, *J* = 6.2, 3.5 Hz, 1H), 4.77 (d, *J* = 7.1 Hz, 1H), 4.72 (d, *J* = 7.1 Hz, 1H), 4.53 (d, *J* = 4.3 Hz, 1H), 4.51 (td, *J* = 7.8, 2.6 Hz, 1H), 3.77 (dd, *J* = 12.6, 4.3 Hz, 1H), 3.46 (s, 3H), 3.38 (s, 3H), 2.47 (d, *J* = 3.3 Hz, 1H), 2.41-2.30 (m, 1H), 2.37 (dd, *J* = 14.9, 3.3 Hz, 1H), 2.19 (dd, *J* = 14.7 Hz, 1H), 1.98 (d, *J* = 12.5 Hz, 1H), 1.96-1.72 (m, 3H), 1.11 (s, 9H); ¹³C-NMR (100 MHz, CDCl₃) δ 173.6, 115.2, 104.9, 101.1, 96.7, 86.1, 80.8, 79.6, 66.5, 63.2, 56.7, 56.1, 49.8, 34.6 (2 carbons: verified by HSQC), 32.3, 30.9, 29.4; IR (neat): 3451(br), 2954, 1773, 1466, 1371, 1228, 1130, 1055, 971, 733 (cm⁻¹); HRMS (ESI) calcd for [C₂₀H₃₀O₈ + Na]⁺: 421.1838, found 421.1821. Note: HSQC analysis of **3.178B** revealed that the ¹³C signal at 34.6ppm represents the overlapping of 2 distinct carbons because it correlated with at least 3 ¹H signals (2.35ppm, 2.16ppm, and 1.82ppm).



2-Iodoxybenzoic acid (IBX): In a sealable flask, was added 2-iodobenzoic acid (2.000 g, 8.064 mmol). A solution of Oxone® (7.436 g, 24.19 mmol, 3 eq.) in 30 mL H₂O was added and the reaction was stirred at RT for 5 min. The flask was sealed and heated to 74 °C overnight. The reaction mixture was cooled to RT and filtrated over filter paper. The residue was washed with 20 mL of cold water and rinsed with 10mL of cold acetone. The residue was collected and dried over high vacuum to afford IBX as a white solid (1.631 g, 72%).^{143a} Spectral data was identical to those found in the literature.^{143b}



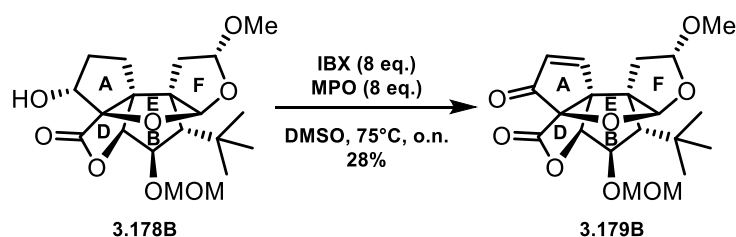
(3.179A) In a sealable flask, **3.178A** (63.6 mg, 0.160 mmol) was dissolved in 12 mL DMSO after which were added IBX (357.5 mg, 1.277 mmol, 8 eq.) and 4-methoxypyridine *N*-oxide (MPO) (182.8 mg, 1.277 mmol, 8 eq.). The flask was sealed and heated to 75 °C overnight. The reaction mixture was cooled to RT, quenched with 100 mL 10% Na₂S₂O₃/aq. sat. NaHCO₃ (1:1) and stirred at RT for 30 min. The mixture was extracted with (3 x 50 mL) EtOAc, washed with (2 x 100 mL) aq. sat. NaHCO₃ and 100 mL aq. sat. NaCl, dried over Na₂SO₄, filtered, and evaporated under reduced pressure. The crude was purified over silica gel (30-50%EtOAc/Hex) to afford enone **3.179A** as a white solid (19.2 mg, 31%).

(3-step procedure) To a solution of **3.178A** (282.7 mg, 0.7094 mmol) in 14 mL DCM at 0 °C was added Dess-Martin periodinane (451.3 mg, 1.064 mmol, 1.5 eq.). The reaction mixture was stirred at 0 °C for 1 h, after which the solution was warmed to RT and stirred for 2 h. The reaction was diluted with 50 mL DCM, quenched with 60 mL 10% Na₂S₂O₃/aq. sat. NaHCO₃ (1:1) and stirred at RT for 30 min. The mixture

was extracted with (3 x 50 mL) DCM, dried over Na₂SO₄, filtered, and evaporated under reduced pressure to afford the corresponding ketone. The crude was used directly in the next step.

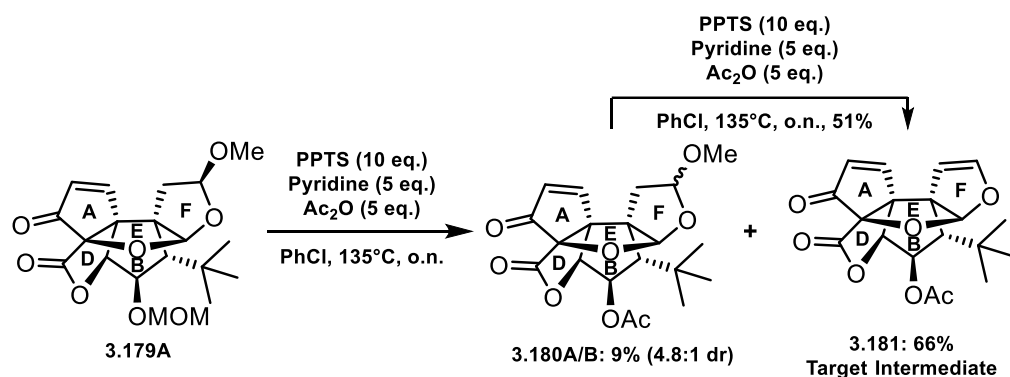
In a sealable flask, the corresponding ketone (≤ 281.3 mg, ≤ 0.7094 mmol) was dissolved in 15 mL THF. A solution of PhSeCl (271.7 mg, 1.419 mmol, 2 eq.) and 1.25 mL HCl (4 M in dioxane) in 10 mL EtOAc was added, the flask was sealed and stirred at RT for 18 h. The reaction mixture was quenched with 100 mL aq. sat. NaHCO₃, extracted (3 x 50 mL) EtOAc, dried over Na₂SO₄, filtered, and evaporated under reduced pressure to afford the corresponding α -phenylselenide **3.178Ai**. The crude was used directly in the next step.

To a solution of α -phenylselenide **3.178Ai** (≤ 391.3 mg, ≤ 0.7094 mmol) in 36 mL DCM were added pyridine (574 μ L, 7.09 mmol, 10 eq.) and H₂O₂ (30% in H₂O, 362 μ L, 3.55 mmol, 5 eq.). The reaction mixture was stirred (on high stirring) at RT for 1 h. The solution was diluted with 30 mL DCM and 50 mL aq. sat. NaHCO₃. The mixture was extracted (3 x 50 mL) DCM, dried over Na₂SO₄, filtered, and evaporated under reduced pressure. The crude was purified over silica gel (30-50% EtOAc/Hex) to afford enone **3.179A** as a white solid (209.8 mg, 75% over 3 steps): mp 239-240 °C; R_f 0.47 (50% EtOAc/Hex); ¹H-NMR (400 MHz, CDCl₃) δ 7.47 (d, *J* = 5.9 Hz, 1H), 6.26 (d, *J* = 5.8 Hz, 1H), 6.21 (s, 1H), 5.06 (d, *J* = 5.5 Hz, 1H), 4.80 (d, *J* = 5.1 Hz, 1H), 4.72 (d, *J* = 6.9 Hz, 1H), 4.67 (d, *J* = 6.9 Hz, 1H), 4.43 (dd, *J* = 5.1, 3.4 Hz, 1H), 3.41 (s, 3H), 3.15 (s, 3H), 2.61 (dd, *J* = 13.9, 5.6 Hz, 1H), 2.33 (d, *J* = 3.4 Hz, 1H), 1.97 (d, *J* = 13.8 Hz, 1H), 1.13 (s, 9H); ¹³C-NMR (150 MHz, CDCl₃) δ 196.9, 169.4, 156.2, 135.3, 125.4, 105.9, 96.5, 91.8, 84.5, 78.4, 69.6, 64.2, 61.6, 56.3, 54.6, 36.8, 33.4, 31.0; IR (neat): 2957, 1776, 1714, 1205, 1083, 1009, 836 (cm⁻¹); HRMS (ESI) calcd for [C₂₀H₂₆O₈ + Na]⁺: 417.1525, found 417.1550.

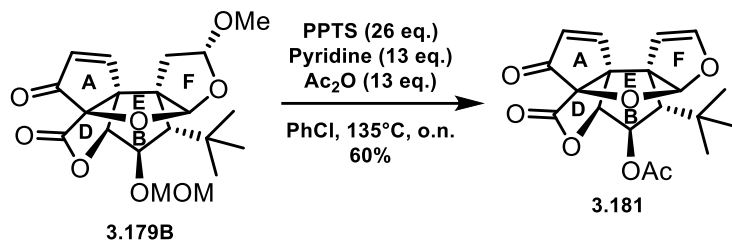


(3.179B) In a sealable flask, **3.178B** (39.4 mg, 0.0989 mmol) was dissolved in 3 mL DMSO after which were added IBX (221.5 mg, 0.7910 mmol, 8 eq.) and 4-methoxypyridine *N*-oxide (MPO) (113.2 mg, 0.7910 mmol, 8 eq.). The flask was sealed and heated to 75 °C overnight. The reaction mixture was cooled to RT, quenched with 20 mL 10% Na₂S₂O₃/aq. sat. NaHCO₃ (1:1) and stirred at RT for 30 min. The mixture was extracted with (3 x 20 mL) EtOAc, washed with (2 x 20 mL) aq. sat. NaHCO₃ and 20 mL aq. sat. NaCl, dried over Na₂SO₄, filtered, and evaporated under reduced pressure. The crude was purified over silica gel (1-

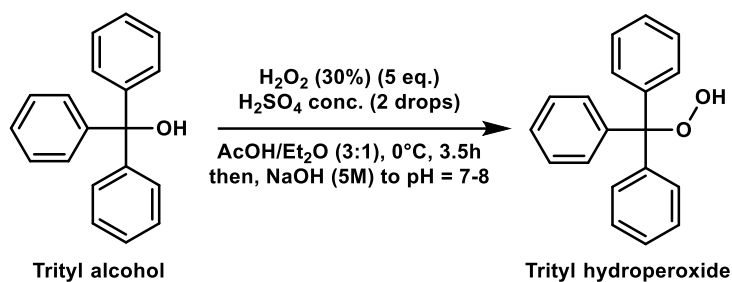
1.5%MeOH/DCM) to afford enone **3.179B** as a white solid (10.9 mg, 28%): mp 245-246 °C; R_f 0.33 (60% EtOAc/Hex); $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.63 (d, J = 5.8 Hz, 1H), 6.29 (d, J = 5.8 Hz, 1H), 5.86 (s, 1H), 4.77 (d, J = 7.2 Hz, 1H), 4.74 (d, J = 7.2 Hz, 1H), 4.77-4.73 (m, 1H), 4.71 (d, J = 4.9 Hz, 1H), 3.45 (s, 3H), 3.32 (s, 3H), 2.42 (dd, J = 14.6, 4.2 Hz, 1H), 2.27 (dd, J = 14.6, 6.0 Hz, 1H), 2.15 (d, J = 12.6 Hz, 1H), 1.13 (s, 9H); $^{13}\text{C-NMR}$ (150 MHz, CDCl_3) δ 195.7, 167.5, 157.3, 134.4, 115.7, 104.4, 96.9, 90.0, 81.9, 80.8, 68.4, 63.4, 56.8, 56.4, 50.1, 34.4, 32.4, 29.3; IR (neat): 3069, 2956, 1782, 1726, 1472, 1372, 1214, 1114, 1056, 987, 834, 736 (cm^{-1}); HRMS (ESI) calcd for $[\text{C}_{20}\text{H}_{26}\text{O}_8 + \text{Na}]^+$: 417.1525, found 417.1502.



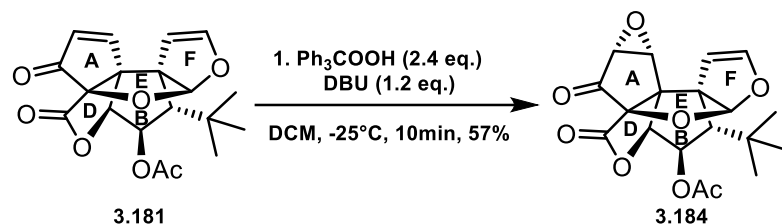
(3.181) To a solution of **3.179A** (1.626 g, 4.122 mmol) in 250 mL PhCl were added PPTS (10.36 g, 41.22 mmol, 10 eq.), pyridine (1.67 mL, 20.6 mmol, 5 eq.) and Ac_2O (1.95 mL, 20.6 mmol, 5 eq.). The reaction mixture was heated to reflux at 135 °C overnight. The solution was cooled to RT, quenched with 250 mL aq. sat. NaHCO_3 , extracted with (3 x 250 mL) DCM, dried over Na_2SO_4 , filtered, and evaporated under reduced pressure. The crude was purified over silica gel (40-60% EtOAc/Hex, then 2-5% MeOH/DCM) to afford and acetylated acetals **3.180A/B** as a white solid (169 mg, 9%, 4.8:1 dr) (which was resubmitted to the reaction conditions to obtain **3.181** in a 51% yield) and acetylated enol ether **3.181** as a white solid (1.184 g, 66%): mp 265-266 °C; R_f 0.59 (60% EtOAc/Hex); $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.53 (d, J = 5.8 Hz, 1H), 6.30 (s, 1H), 6.28 (d, J = 3.1 Hz, 1H), 6.16 (d, J = 5.8 Hz, 1H), 5.29 (dd, J = 10.7, 5.1 Hz, 1H), 5.25 (d, J = 3.1 Hz, 1H), 4.84 (d, J = 5.1 Hz, 1H), 2.23 (d, J = 10.7 Hz, 1H), 2.14 (s, 3H), 1.07 (s, 9H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 195.1, 170.0, 167.8, 157.7, 146.3, 132.8, 122.3, 101.7, 90.4, 80.4, 75.1, 71.2, 66.9, 54.4, 33.0, 29.5, 21.0; IR (neat): 3074, 2960, 2873, 1787, 1727, 1612, 1373, 1233, 1046, 1002, 759 (cm^{-1}); HRMS (ESI) calcd for $[\text{C}_{19}\text{H}_{20}\text{O}_7 + \text{Na}]^+$: 383.1107, found 383.1098.



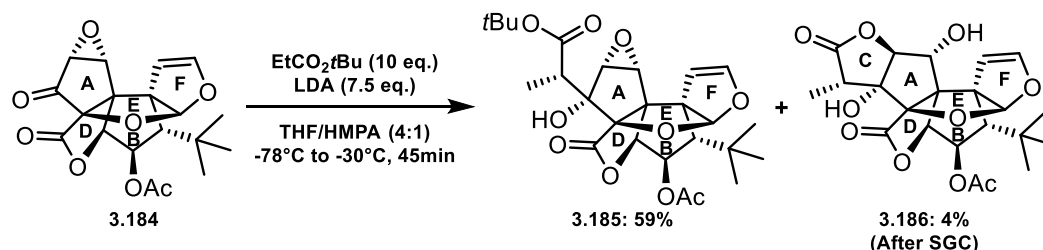
(3.181) To a solution of **3.179B** (10.9 mg, 0.0276 mmol) in 5 mL PhCl were added PPTS (180 mg, 0.716 mmol, 26 eq.), pyridine (29 μ L, 0.36 mmol, 13 eq.) and Ac₂O (20.5 μ L, 0.358 mmol, 13 eq.). The reaction mixture was heated to reflux at 135 °C overnight. The solution was cooled to RT, quenched with 10 mL aq. sat. NaHCO₃, extracted with (3 x 10 mL) DCM, dried over Na₂SO₄, filtered, and evaporated under reduced pressure. The crude was purified over silica gel (40-60% EtOAc/Hex, then 2-5% MeOH/DCM) to afford acetylated enol ether **3.181** as a white solid (6.0 mg, 60%).



(Trityl hydroperoxide): To a solution of trityl alcohol (2.000 g, 7.682 mmol) in 7.7 mL Et₂O and 23.1 mL AcOH at 0 °C were added 2 drops of H₂SO₄ (conc.) and H₂O₂ (30% in H₂O, 3.92 mL, 38.4 mmol, 5 eq.). The reaction mixture was stirred at 0 °C for 3.5 h. The solution was neutralized to pH 7-8 with $\geq$ 81 mL NaOH (5 M) (and adjusted with NaOH (1 M) or HCl (1 M)), extracted with (2 x 100 mL) Et₂O, washed with 100 mL aq. sat. NaHCO₃, then 100 mL aq. sat. NaCl, dried over Na₂SO₄, filtered, and evaporated under reduced pressure to obtain a white residue. The white residue was recrystallized in pentane, filtered, and evaporated under reduced pressure to afford trityl hydroperoxide as a white solid (2.0335 g, 96%): mp 84-85°C; R_f 0.25 (10% EtOAc/Hex) ¹H-NMR (400 MHz, CDCl₃) δ 7.47-7.39 (m, 6H), 7.39-7.27 (m, 9H); ¹³C-NMR (100 MHz, CDCl₃) δ 142.4, 129.0, 128.1, 127.8, 94.0.



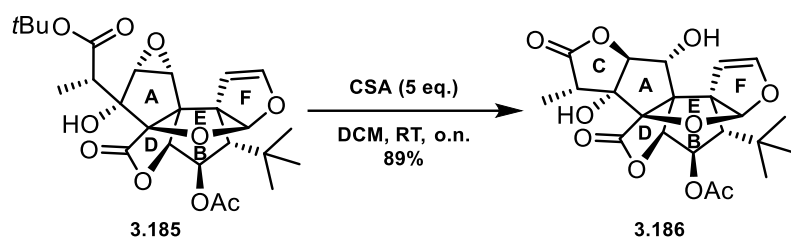
(3.184) A solution of trityl hydroperoxide (184 mg, 0.666 mmol, 2.4 eq.) with DBU (49.8 μL , 0.333 mmol, 1.2 eq.) in 3 mL was prepared and stirred at RT for 10 min. To a solution of **3.181** (100 mg, 0.278 mmol) in 10 mL DCM at -25°C was added the solution of trityl hydroperoxide/DBU. The reaction mixture was stirred at -25°C for 10 min. The reaction was quenched with 15 mL 10% $\text{Na}_2\text{S}_2\text{O}_5$ and stirred from -25°C to RT for 15 min. The solution was extracted with (3 x 15 mL) DCM, dried over Na_2SO_4 , filtered, and evaporated under reduced pressure. The crude was purified over silica gel (5-10% EtOAc/Hex, then 5% MeOH/DCM) to afford epoxide **3.184** as a white solid (59.9 mg, 57%): mp $183\text{--}184^\circ\text{C}$; R_f 0.56 (60% EtOAc/Hex); $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 6.40 (d, $J = 3.1$ Hz, 1H), 6.26 (s, 1H), 5.45 (dd, $J = 7.9, 5.6$ Hz, 1H), 5.33 (d, $J = 3.1$ Hz, 1H), 5.24 (dd, $J = 5.5, 0.5$ Hz, 1H), 3.96 (d, $J = 2.2$ Hz, 1H), 3.74 (d, $J = 2.2$ Hz, 1H), 2.24 (d, $J = 7.9$ Hz, 1H), 2.11 (s, 3H), 1.09 (s, 9H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 193.6, 169.7, 166.6, 146.5, 122.8, 101.6, 92.9, 80.6, 74.5, 67.3, 67.1, 58.3, 57.8, 57.2, 33.2, 29.7, 20.8; IR (neat): 3064, 2956, 1793, 1743, 1621, 1371, 1212, 1042, 856, 737 (cm^{-1}); HRMS (ESI) calcd for $[\text{C}_{19}\text{H}_{20}\text{O}_8 + \text{Na}]^+$: 399.1056, found 399.1063.



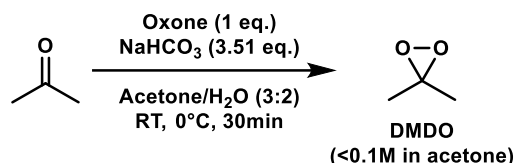
(3.185) To a solution of 10 mL THF and diisopropylamine (DIPA) (310 μL , 2.22 mmol, 10 eq.) at 0°C was added $n\text{BuLi}$ (2.5 M in hexane, 664 μL , 1.66 mmol, 7.5 eq.) slowly. The reaction mixture was stirred at 0°C for 30 min, then cooled to -78°C . 2.5 mL HMPA was added slowly (solidifies upon addition), then the flask was removed from the -78°C bath until the HMPA fully dissolved after which the flask was cooled to -78°C and stirred for 5 min. A solution of *tert*-butyl propionate (310 μL , 2.06 mmol, 10 eq.) in 1.25 mL THF/HMPA (4:1) was added to the reaction mixture and stirred at -78°C for 15 min. A solution of **3.184** (83.4 mg, 0.222 mmol) in 7.5 mL THF/HMPA (4:1) was added to the reaction mixture and stirred at -78°C for 15 min. The solution was warmed to -30°C and stirred for 30 min. The reaction was quenched with 12 mL aq. sat. NH_4Cl , warmed to RT. The reaction mixture was diluted with 150 mL EtOAc and washed with

(4 x 200 mL) aq. sat. NaCl/H₂O (1:1), dried over Na₂SO₄, filtered, and evaporated under reduced pressure. The crude was purified over silica gel (2.5-30% EtOAc/Hex, 5% MeOH/DCM) to afford 1,2-addition adduct **3.185** as a white solid (61.2 mg, 59%) and lactone **3.186** as a white solid (3.4 mg, 4% after SGC).

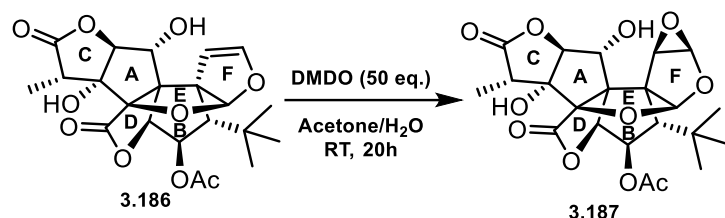
3.185: mp 175-176 °C; *R*_f 0.65 (10% EtOAc/DCM); ¹H-NMR (400 MHz, acetone-D₆) δ 6.51 (d, *J* = 2.9 Hz, 1H), 6.07 (s, 1H), 5.73 (d, *J* = 2.9 Hz, 1H), 5.34 (dd, *J* = 12.4, 4.3 Hz, 1H), 5.02 (d, *J* = 4.2 Hz, 1H), 4.20 (s, 1H), 3.93 (d, *J* = 2.4 Hz, 1H), 3.87 (d, *J* = 2.4 Hz, 1H), 2.85 (q, *J* = 7.1 Hz, 1H), 2.20 (d, *J* = 12.4 Hz, 1H), 2.09 (s, 3H), 1.47 (s, 9H), 1.40 (d, *J* = 7.1 Hz, 3H), 1.04 (s, 9H); ¹³C-NMR (100 MHz, acetone-D₆) δ 174.7, 171.3, 170.2, 146.4, 119.4, 106.4, 103.6, 81.6, 81.2, 78.8, 75.8, 68.4, 67.8, 67.3, 61.4, 55.1, 44.4, 33.2, 29.2, 28.2, 20.9, 13.7; IR (neat): 3481(br), 3062, 2978, 2875, 1788, 1728, 1614, 1457, 1357, 1234, 1141, 1008, 734 (cm⁻¹); HRMS (ESI) calcd for [C₂₆H₃₄O₁₀ + Na]⁺: 529.2050, found 529.2043.



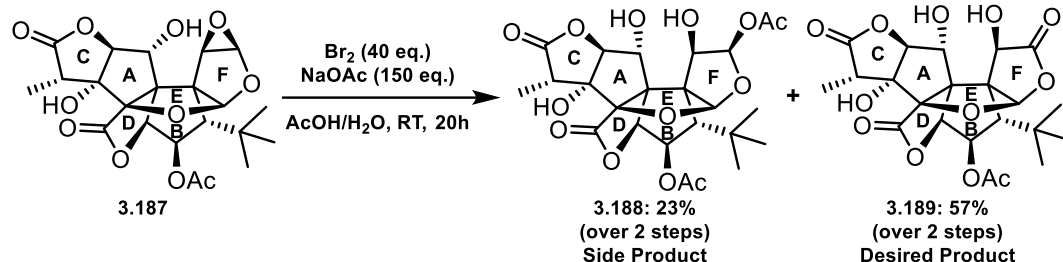
(3.186)(from **3.185**) To a solution of alcohol **3.185** (60.5 mg, 0.119 mmol) in 12 mL DCM was added CSA (138.7 mg, 0.5971 mmol, 5 eq.). The reaction mixture was stirred at RT overnight. The solution was diluted with 50 mL DCM and quenched with 50 mL aq. sat. NaHCO₃. The solution was extracted with (3 x 50 mL) DCM, dried over Na₂SO₄, filtered, and evaporated under reduced pressure. The crude was purified over silica gel (10-30% EtOAc/DCM, then 5% MeOH/DCM) to afford lactone **3.186** as a white solid (47.8 mg, 89%): mp 245-246 °C; *R*_f 0.24 (20% EtOAc/DCM); ¹H-NMR (400 MHz, CDCl₃) δ 6.44 (d, *J* = 2.9 Hz, 1H), 6.07 (s, 1H), 5.30 (d, *J* = 4.0 Hz, 1H), 5.25 (d, *J* = 3.0 Hz, 1H), 5.06 (dd, *J* = 12.6, 4.1 Hz, 1H), 4.66 (d, *J* = 8.0 Hz, 1H), 4.08 (dd, *J* = 8.0 Hz, 1H), 3.32 (s(br), 1H), 3.04 (s(br), 1H), 2.95 (q, *J* = 7.1 Hz, 1H), 2.14 (s, 3H), 2.08 (d, *J* = 12.6 Hz, 1H), 1.26 (d, *J* = 7.2 Hz, 3H), 1.00 (s, 9H); ¹³C-NMR (100 MHz, CDCl₃) δ 177.2, 172.5, 170.4, 146.7, 120.2, 102.5, 94.5, 92.6, 83.7, 77.6, 75.7, 74.5, 68.2, 66.9, 52.5, 41.5, 32.7, 29.2, 21.2, 7.5; IR (neat): 3394(br), 3065, 2955, 1769, 1726, 1612, 1364, 1230, 1005, 732 (cm⁻¹); HRMS (ESI) calcd for [C₂₂H₂₆O₁₀ + Na]⁺: 473.1424, found 473.1413.



DMDO ($<0.1\text{M}$ in acetone): To a solution of NaHCO_3 (24.00 g, 285.7 mmol, 3.51 eq.) in 20 mL H_2O and 30 mL acetone at 0°C was added Oxone® (25.00 g, 81.33 mmol, 1 eq.) in small portions over 1 min. The reaction mixture was stirred at 0°C for 30 min. The stir bar was rinsed with some H_2O . The DMDO was distilled in a rotavap (vacuum set to 150 Torr) into a 250 mL bump trap (cooled to -78°C) with the water bath from RT to 40°C . Following the distillation, the distillate was cooled at -78°C , dried over Na_2SO_4 , and filtered to afford a DMDO solution ($\leq 0.1\text{ M}$ in acetone).



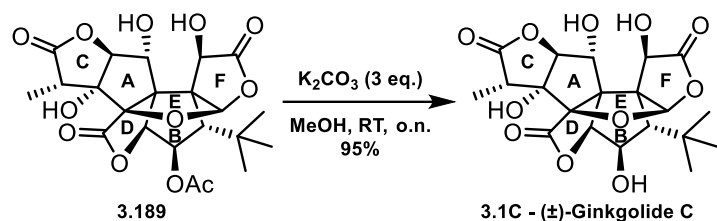
(3.187) In a sealable flask, enol ether **3.186** (44.9 mg, 0.0997 mmol) was dissolved in 5 mL acetone was added 50 mL DMDO ($<0.1\text{ M}$ in acetone, $<5.0\text{ mmol}$, $<54.8\text{ eq.}$) was added. The flask was sealed and stirred at RT for 20 h. The reaction mixture was evaporated under reduced pressure. The residue was dissolved in 50 mL EtOAc, dried over Na_2SO_4 , filtered, and evaporated under reduced pressure to afford epoxide **3.187** as an impure mixture. The crude was used in the next step without any further purification: R_f 0.47 (30% EtOAc/DCM); $^1\text{H-NMR}$ (400 MHz, acetone- D_6) δ 5.85 (s, 1H), 5.77 (d, $J = 1.0\text{ Hz}$, 1H), 5.66 (d, $J = 4.8\text{ Hz}$, 1H), 5.39 (dd, $J = 12.3, 4.0\text{ Hz}$, 1H), 5.26 (d, $J = 4.0\text{ Hz}$, 1H), 5.04 (dd, $J = 7.1, 4.6\text{ Hz}$, 1H), 4.76 (d, $J = 7.5\text{ Hz}$, 1H), 4.27 (d, $J = 1.2\text{ Hz}$, 1H), 3.18 (q, $J = 7.2\text{ Hz}$, 1H), 2.43 (d, $J = 12.3\text{ Hz}$, 1H), 2.10 (s, 3H), 1.19 (d, $J = 7.2\text{ Hz}$, 3H), 1.10 (s, 9H); $^{13}\text{C-NMR}$ (100 MHz, acetone- D_6) δ 177.3, 172.0, 170.0, 123.7, 94.8, 93.7, 88.1, 83.7, 78.8, 77.1, 73.5, 66.9, 62.1, 59.2, 56.1, 42.7, 32.7, 30.0, 20.9, 8.1; IR (neat): 3452(br), 3055, 2962, 1773, 1752, 1740, 1374, 1228, 1052, 895, 837, 733 (cm^{-1}); HRMS (ESI) calcd for $[\text{C}_{22}\text{H}_{26}\text{O}_{11} + \text{Na}]^+$: 489.1373, found 489.1353.



(3.188/3.189) A solution of Br_2 (204 μL , 3.99 mmol, 40 eq.) and NaOAc (1.23 g, 15.0 mmol, 150 eq.) in 10 mL H_2O was stirred at RT for 5 min after which was added 10 mL AcOH . The resulting solution was added to epoxide **3.187** (≤ 46.5 mg, ≤ 0.0997 mmol). The reaction mixture was stirred at RT overnight. The solution was diluted with 125 mL EtOAc and quenched with 40 mL 10% $\text{Na}_2\text{S}_2\text{O}_3$ and 200 mL aq. sat. NaHCO_3 . The solution was stirred at RT for 15 min, extracted with (3 x 100 mL) EtOAc , washed with 300 mL H_2O and 300 mL aq. sat. NaCl , dried over Na_2SO_4 , filtered, and evaporated under reduced pressure. The crude was purified over silica gel (10-25% EtOAc/DCM , then 5% MeOH/DCM) to afford (*O*-acetyl)-lactol **3.188** as a white solid (11.9 mg, 23% over 2 steps) as well as (*O*-acetyl)-ginkgolide C **3.189** as a white solid (27.4 mg, 57% over 2 steps).

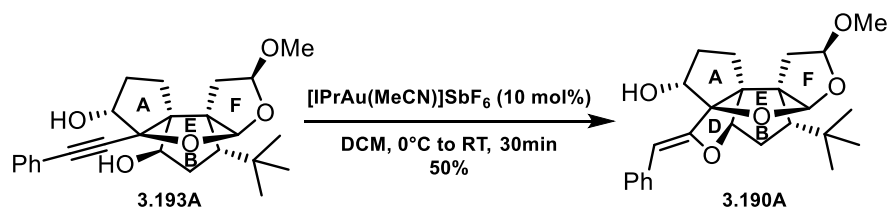
3.188: R_f 0.28 (30% EtOAc/DCM); ^1H -NMR (400 MHz, acetone- D_6) δ 6.35 (d, $J = 2.6$ Hz, 1H), 5.97 (s, 1H), 5.34 (d, $J = 4.4$ Hz, 1H), 5.26 (s(br), 1H), 5.17 (d, $J = 2.6$ Hz, 1H), 5.10 (dd, $J = 13.0, 4.3$ Hz, 1H), 4.61 (d, $J = 8.1$ Hz, 1H), 4.56 (d, $J = 8.1$ Hz, 1H), 4.44 (s(br), 1H), 3.50 (q, $J = 7.1$ Hz, 1H), 2.14 (s, 3H), 2.06 (s, 3H), 1.99 (d, $J = 13.0$ Hz, 1H), 1.23 (d, $J = 7.1$ Hz, 3H), 1.19 (s, 9H); ^{13}C -NMR (150 MHz, acetone- D_6) δ 177.2, 171.5, 170.0, 169.9, 115.9, 102.1, 99.2, 92.0, 84.7, 77.5, 76.3, 76.01, 75.96, 68.4, 68.2, 48.5, 42.4, 32.7, 20.9, 8.1; IR (neat): 3456(br), 3342(br), 2918, 2850, 1796, 1770, 1739, 1558, 1366, 1223, 1058, 998, 901 (cm^{-1}); HRMS (ESI) calcd for $[\text{C}_{24}\text{H}_{30}\text{O}_{13} + \text{Na}]^+$: 549.1584, found 549.1561. Note: The ^{13}C signal at 162.1 ppm was attributed to an impurity by HMBC analysis.

3.189: mp 295-296 $^\circ\text{C}$; R_f 0.44 (30% EtOAc/DCM); ^1H -NMR (600 MHz, acetone- D_6) δ 6.23 (s, 1H), 5.46 (s(br), 1H), 5.40 (d, $J = 4.3$ Hz, 1H), 5.37 (s, 1H), 5.21 (dd, $J = 12.9, 4.3$ Hz, 1H), 4.68 (d, $J = 7.8$ Hz, 1H), 4.24 (d, $J = 7.8$ Hz, 1H), 3.03 (q, $J = 7.1$ Hz, 1H), 2.15 (s, 3H), 2.14 (d, $J = 12.8$ Hz, 1H), 1.27 (d, $J = 7.1$ Hz, 3H), 1.22 (s, 9H); ^{13}C -NMR (150 MHz, acetone- D_6) δ 176.5, 173.5, 170.7, 170.0, 110.9, 99.2, 92.1, 84.4, 76.3, 75.5, 74.9, 70.3, 68.4, 64.7, 49.1, 42.8, 32.9, 29.4, 20.9, 8.1; IR (neat): 3304(br), 2920, 2852, 1791, 1758, 1375, 1217, 1083, 949, 885, 803, 731 (cm^{-1}); HRMS (ESI) calcd for $[\text{C}_{22}\text{H}_{26}\text{O}_{12} + \text{Na}]^+$: 505.1322, found 505.1300.



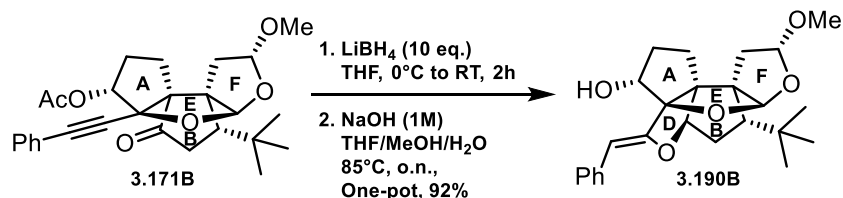
(±)-Ginkgolide C (3.1C) To a solution of (*O*-acetyl)-ginkgolide C **3.189** (16.2 mg, 0.0336 mmol) in 10 mL MeOH was added K_2CO_3 (13.9 mg, 0.101 mmol, 3 eq.). The reaction mixture was diluted with 30 mL EtOAc and quenched with 30 mL aq. sat. NaHCO_3 /aq. sat. NaCl (1:1). The solution was extracted with (3 x 30 mL) EtOAc, dried over Na_2SO_4 , filtered, and evaporated under reduced pressure. The crude was purified over silica gel (40-60% EtOAc/DCM) to afford (±)-ginkgolide C (**3.1C**) as a white solid (14.1 mg, 95%): mp >300 °C; R_f 0.44 (60% EtOAc/DCM); $^1\text{H-NMR}$ (600 MHz, acetone- D_6 /D $_2\text{O}$) δ 6.13 (s, 1H), 5.25 (s, 1H), 5.11 (d, J = 4.3 Hz, 1H), 4.64 (d, J = 7.8 Hz, 1H), 4.29 (dd, J = 12.4, 4.3 Hz, 1H), 4.15 (d, J = 7.8 Hz, 1H), 2.99 (q, J = 7.0 Hz, 1H), 1.79 (d, J = 12.4 Hz, 1H), 1.29 (d, J = 7.1 Hz, 3H), 1.23 (s, 9H); $^1\text{H-NMR}$ (600 MHz, acetone- D_6) δ 6.15 (s, 1H), 5.40 (s(br), 1H), 5.32 (s, 1H), 5.12 (d, J = 4.3 Hz, 1H), 4.71 (s(br), 1H), 4.66 (d, J = 7.8 Hz, 1H), 4.33 (dd, J = 12.4, 4.3 Hz, 1H), 4.19 (d, J = 7.8 Hz, 1H), 3.02 (q, J = 7.1 Hz, 1H), 1.82 (d, J = 12.2 Hz, 1H), 1.27 (d, J = 7.1 Hz, 3H), 1.26 (s, 9H); $^{13}\text{C-NMR}$ (150 MHz, acetone- D_6) δ 176.6, 173.9, 171.0, 111.1, 99.1, 92.2, 84.4, 79.9, 76.0, 74.9, 70.4, 67.8, 65.0, 50.6, 42.8, 33.0, 29.4, 8.1; IR (neat): 3448(br), 3356, 2952, 2922, 2851, 1782, 1653, 1259, 1168, 1089, 950, 801 (cm^{-1}); HRMS (ESI) calcd for $[\text{C}_{20}\text{H}_{24}\text{O}_{11} + \text{Na}]^+$: 463.1216, found 463.1216. The synthetic material provided identical ^1H and ^{13}C NMR spectroscopic data with the natural product. Evidence for the ^{13}C signal at 29.4ppm (overlapped with the acetone- D_6 residual peak at 29.84ppm) was provided by the HSQC spectrum of the analytical standard of ginkgolide C in acetone- D_6 showing a correlation with the ^1H signal at 1.26 ppm (s, 9H) which corresponds to the *tert*-butyl (3 x CH_3).

4.1.2.8.2 Formal Synthesis of (±)-Ginkgolide A and (±)-Ginkgolide B:

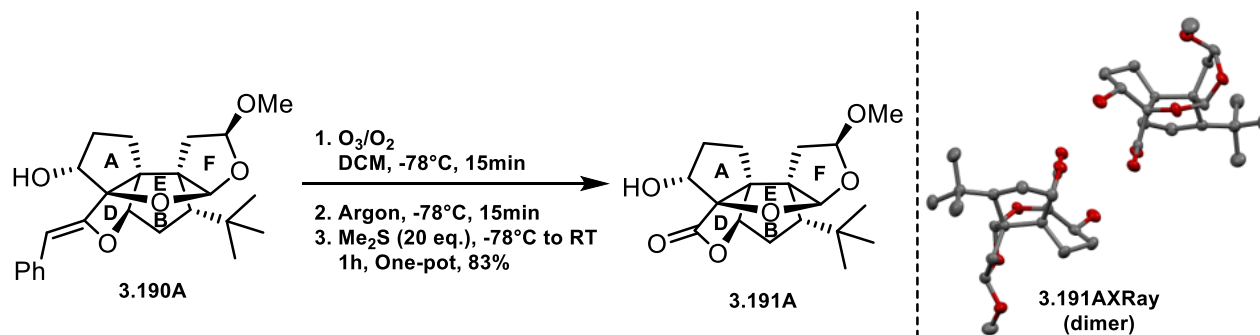


(3.190A) To a solution of **3.193A** (36.9 mg, 0.0894 mmol) in 1.5 mL DCM at 0 °C was added $[\text{IPrAu}(\text{MeCN})]\text{SbF}_6$ (7.7 mg, 0.0089 mmol, 10 mol%). The reaction mixture was warmed to RT and stirred for 30 min. The reaction mixture was evaporated under reduced pressure and was purified directly over

silica gel (0.5-1% MeOH/DCM) to afford enol ether **3.190A** as a white solid (18.3 mg, 50%): R_f 0.34 (2% MeOH/DCM); $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.65-7.53 (m, 2H), 7.35-7.27 (m, 2H), 7.19-7.09 (m, 1H), 5.68 (s, 1H), 5.44 (s, 1H), 5.22 (dd, $J = 6.4, 1.1$ Hz, 1H), 4.57 (d, $J = 3.8$ Hz, 1H), 4.23 (t, $J = 5.5$ Hz, 1H), 3.41 (s, 3H), 2.60 (dd, $J = 14.6, 6.5$ Hz, 1H), 2.52-2.37 (m, 2H), 2.31-2.15 (m, 2H), 1.90 (s(br), 1H), 1.97 (d, $J = 14.7$ Hz, 1H), 1.87-1.70 (m, 3H), 0.99 (s, 9H).

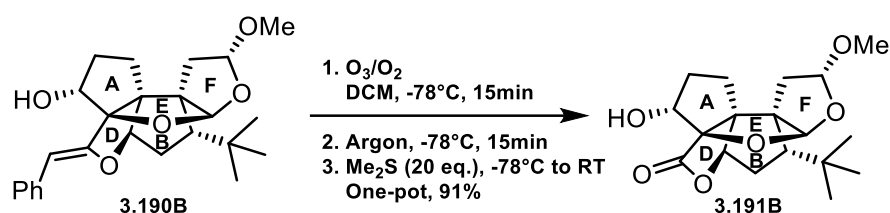


(**3.190B**). To a solution of **3.171B** (95.6 mg, 0.211 mmol) in 7 mL THF at 0 °C was added a solution of LiBH_4 (2.0 M in THF, 1.056 mL, 2.112 mmol, 10 eq.). The reaction mixture was stirred from 0 °C to RT for 2 h after which were added NaOH (1 M, 2.11 mL, 2.11 mmol, 1 eq.) and 2 mL MeOH. The flask was then sealed and heated to 85 °C overnight. The reaction mixture was cooled to RT, quenched with 20 mL aq. sat. NaHCO_3 , extracted with (3 x 30 mL) EtOAc, dried over Na_2SO_4 , filtered, and evaporated under reduced pressure. The crude was purified over silica gel (0.5-1% MeOH/DCM) to afford enol ether **3.190B** as a white solid (80.2 mg, 92%): mp 163-164 °C; R_f 0.23 (2% MeOH/DCM); $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.65-7.55 (m, 2H), 7.33-7.27 (m, 2H), 7.14 (m, 1H), 5.80 (s, 1H), 5.41 (s, 1H), 5.06 (dd, $J = 5.9, 4.2$ Hz, 1H), 4.57 (d, $J = 4.4$ Hz, 1H), 4.31 (dd, $J = 11.4, 5.9$ Hz, 1H), 3.41 (s, 3H), 2.35-2.08 (m, 5H), 2.00 (m, 2H), 1.85-1.71 (m, 3H), 1.03 (s, 9H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 156.7, 136.1, 128.3, 128.2, 125.8, 115.7, 107.4, 104.9, 100.3, 93.5, 80.1, 73.1, 67.5, 56.0, 49.9, 37.3, 35.2, 34.5, 32.4, 30.1, 29.3; IR (neat): 3466(br), 2955, 1665, 1449, 1370, 1238, 1100, 1048, 968, 887, 753 695 (cm^{-1}); HRMS (EI) calcd for $\text{C}_{25}\text{H}_{32}\text{O}_5$ $[\text{M}]^+$: 412.2250, found 412.2271.

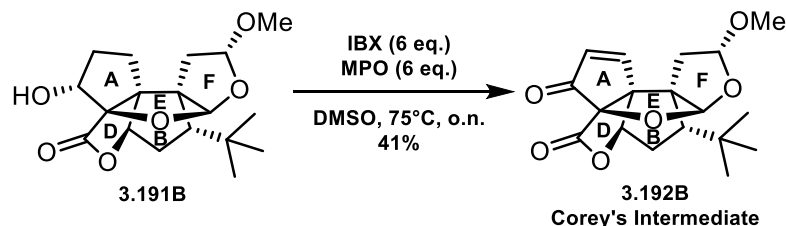


(**3.191A**) A solution of enol ether **3.190A** (41.6 mg, 0.101 mmol) in 10 mL at -78 °C was bubbled a stream of O_3/O_2 for 15 min before being bubbled with argon for 5 min. Thereafter, Me_2S (370 μL , 5.04 mmol, 50

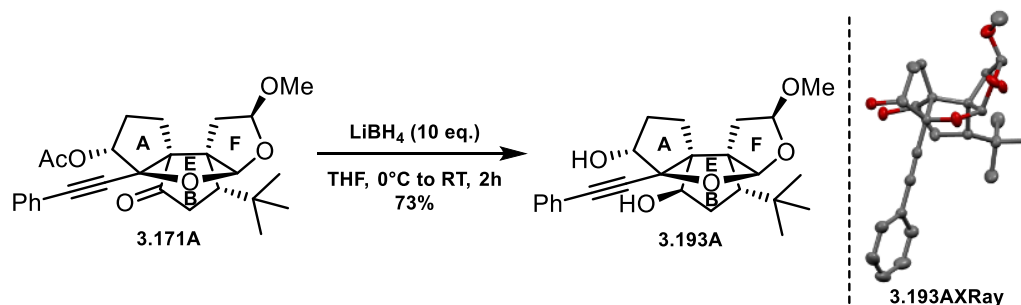
eq.) was added, after which the reaction mixture was warmed to RT and stirred at this temperature for 1 h. The mixture was evaporated under reduced pressure and purified directly over silica gel (30-50% EtOAc/Hex) to afford lactone **3.191A** as a white solid (28.2 mg, 83%): mp 87-88 °C; R_f 0.38 (50% EtOAc/Hex); $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 5.69 (s, 1H), 5.17 (dd, J = 6.7, 1.3 Hz, 1H), 4.53 (d, J = 4.1 Hz, 1H), 4.45 (dd, J = 7.5, 5.7 Hz, 1H), 3.39 (s, 3H), 2.71-2.55 (m, 2H), 2.53 (s(br), 1H), 2.45 (dddd, J = 12.6, 6.7, 5.7, 4.6 Hz, 1H), 2.20 (dd, J = 13.6, 4.9 Hz, 1H), 2.10 (dd, J = 14.1, 4.9 Hz, 1H), 1.94 (dd, J = 14.6, 1.3 Hz, 1H), 1.91-1.82 (m, 1H), 1.82-1.68 (m, 2H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 175.1, 120.6, 107.7, 101.0, 88.5, 79.3, 71.3, 66.8, 55.7, 52.8, 36.0, 35.2, 34.3, 32.4, 30.1, 29.3; IR (neat): 3470, 2959, 1778, 1466, 1236, 1077, 1008, 762 (cm^{-1}); HRMS (EI) calcd for $\text{C}_{18}\text{H}_{24}\text{O}_5$ $[\text{M}-\text{H}_2\text{O}]^+$: 320.1624, found 320.1616.



(3.191B). A solution of **3.190B** (72.0 mg, 0.175 mmol) in 6 mL DCM at -78°C was bubbled with a stream of O_3/O_2 for 15 min before being bubbled with argon for 5 min. Thereafter, Me_2S (256 μL , 3.49 mmol, 20 eq.) was added, after which the reaction mixture was warmed to RT and stirred at this temperature for 1 h. The mixture was evaporated under reduced pressure, the crude was diluted with 30 mL aq. sat. NaCl, extracted with (3 x 30 mL) EtOAc, washed with 100 mL H_2O , dried over Na_2SO_4 , filtered, and evaporated under reduced pressure. The crude was purified over silica gel (30-50% EtOAc/Hex) to afford lactone **3.191B** as a white solid (50.7 mg, 91%): mp 199-200 °C; R_f 0.22 (50% EtOAc/Hex); $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 5.75 (s, 1H), 5.03 (dd, J = 6.0, 3.9 Hz, 1H), 4.53 (d, J = 4.5 Hz, 1H), 4.50 (dd, J = 7.5, 5.5 Hz, 1H), 3.39 (s, 3H), 2.44 (s(br), 1H), 2.41-2.31 (m, 1H), 2.32 (dd, J = 14.6, 4.0 Hz, 1H), 2.22 (dd, J = 14.6, 5.9 Hz, 1H), 2.17 (dd, J = 13.6, 4.7 Hz, 1H), 2.04-1.91 (m, 2H), 1.91-1.71 (m, 2H), 1.79 (dd, J = 13.9, 4.7 Hz, 1H), 1.04 (s, 9H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 174.0, 115.4, 104.9, 101.5, 88.4, 79.5, 71.3, 68.1, 56.0, 49.6, 36.0, 34.7, 34.2, 32.4, 30.8, 29.2; IR (neat): 3430(br), 2963, 1775, 1099, 973 (cm^{-1}); HRMS (ESI) calcd for $[\text{C}_{18}\text{H}_{26}\text{O}_6 + \text{Na}]^+$: 361.1650, found 361.1627.



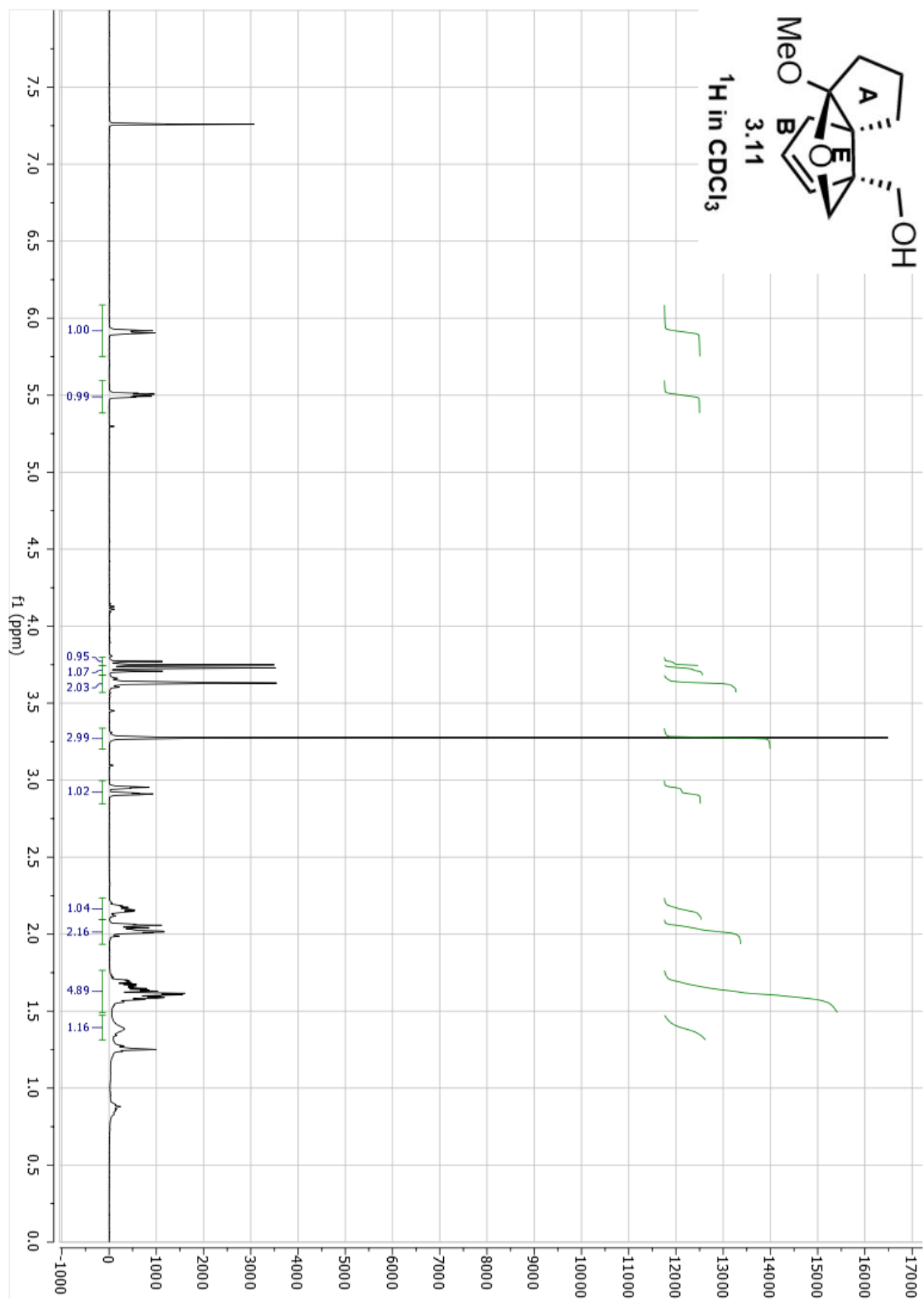
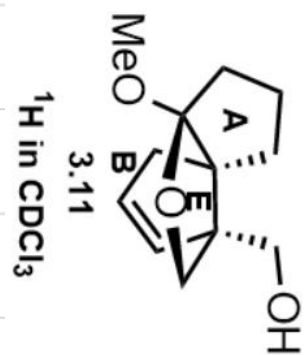
(3.192B). To a solution of **3.191B** (5.5 mg, 0.016 mmol) in 2.5 mL DMSO, IBX (27.5 mg, 0.0982 mmol, 6 eq.), and 4-methoxypyridine *N*-oxide (MPO) (14.1 mg, 0.0982 mmol, 6 eq.). The flask was sealed and heated to 75 °C overnight. The reaction mixture was cooled to RT, quenched with 30 mL 10% Na₂S₂O₃ and stirred at RT for 30 min. The mixture was extracted with (3 x 30 mL) EtOAc, washed with (2 x 100 mL) aq. sat. NaHCO₃ and 100 mL aq. sat. NaCl, dried over Na₂SO₄, filtered, and evaporated under reduced pressure. The crude was purified over silica gel (60-70% EtOAc/Hex) to afford enone **3.192B** as a white solid (2.7 mg, 41%): mp 284-285 °C; *R*_f 0.26 (60% EtOAc/Hex); ¹H-NMR (400 MHz, CDCl₃) δ 7.66 (d, *J* = 5.9 Hz, 1H), 6.28 (d, *J* = 5.8 Hz, 1H), 5.82 (s, 1H), 4.75 (dd, *J* = 5.8, 4.7 Hz, 1H), 4.71 (d, *J* = 5.4 Hz, 1H), 3.33 (s, 3H), 2.43-2.25 (m, 3H), 2.19 (d, *J* = 14.3, 5.3 Hz, 1H), 1.99 (td, *J* = 14.2, 5.4 Hz, 1H), 1.07 (s, 9H); ¹³C-NMR (100 MHz, CDCl₃) δ 165.9, 167.7, 157.5, 134.3, 116.1, 104.4, 90.4, 84.0, 73.0, 68.4, 56.4, 49.7, 36.2, 34.0, 32.6, 29.1; IR (neat): 3053, 2965, 1771, 1717, 1040, 967, 836 (cm⁻¹); HRMS (ESI) calcd for [C₁₈H₂₂O₆ + Na]⁺: 357.1314, found 357.1340. ¹H NMR and IR spectroscopic data of **3.192B** was identical to **Compound 18** reported by Corey's total synthesis of (±)-ginkgolide B.¹

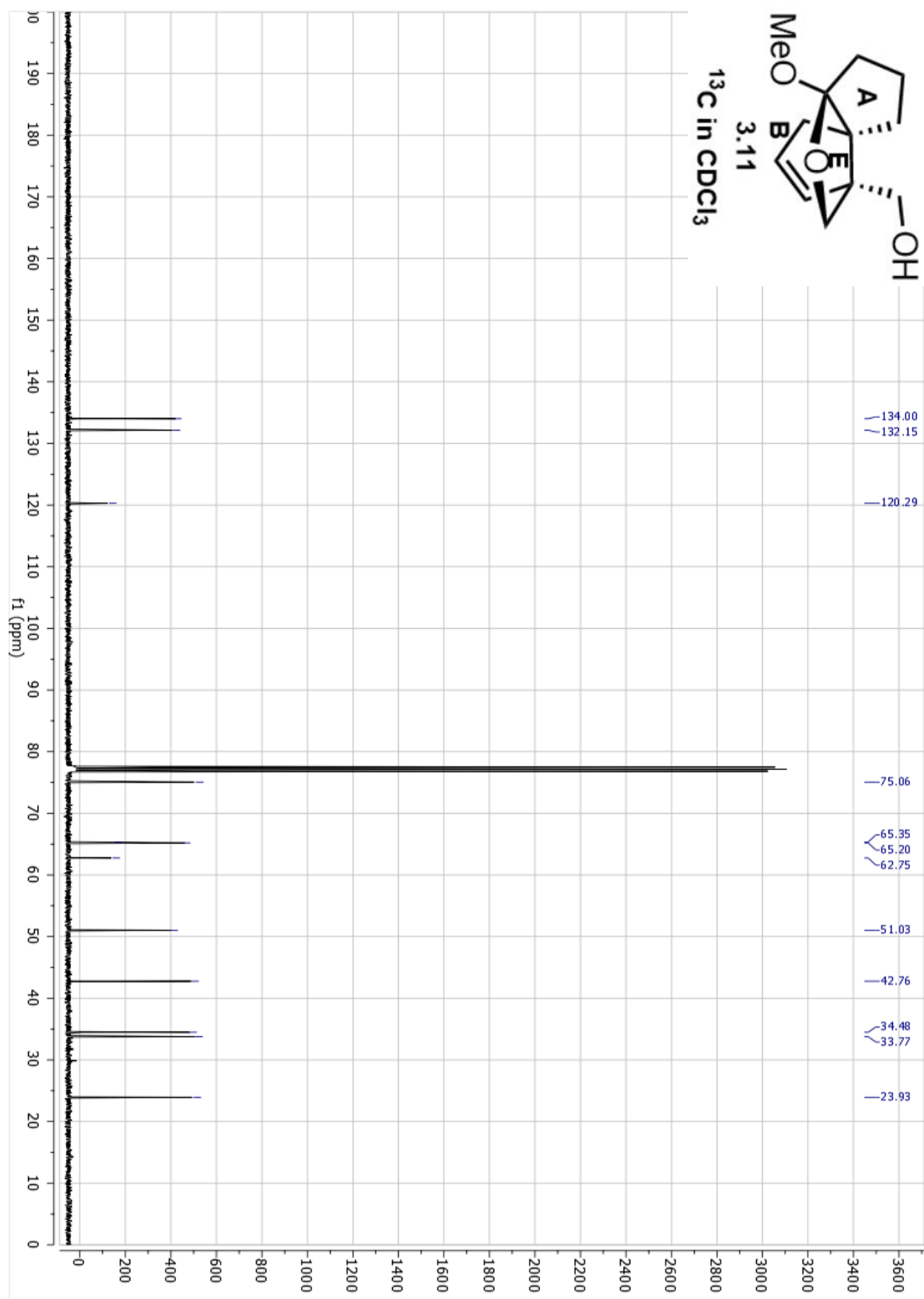
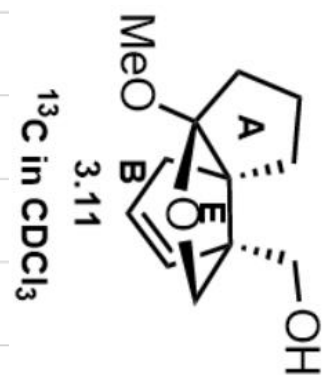


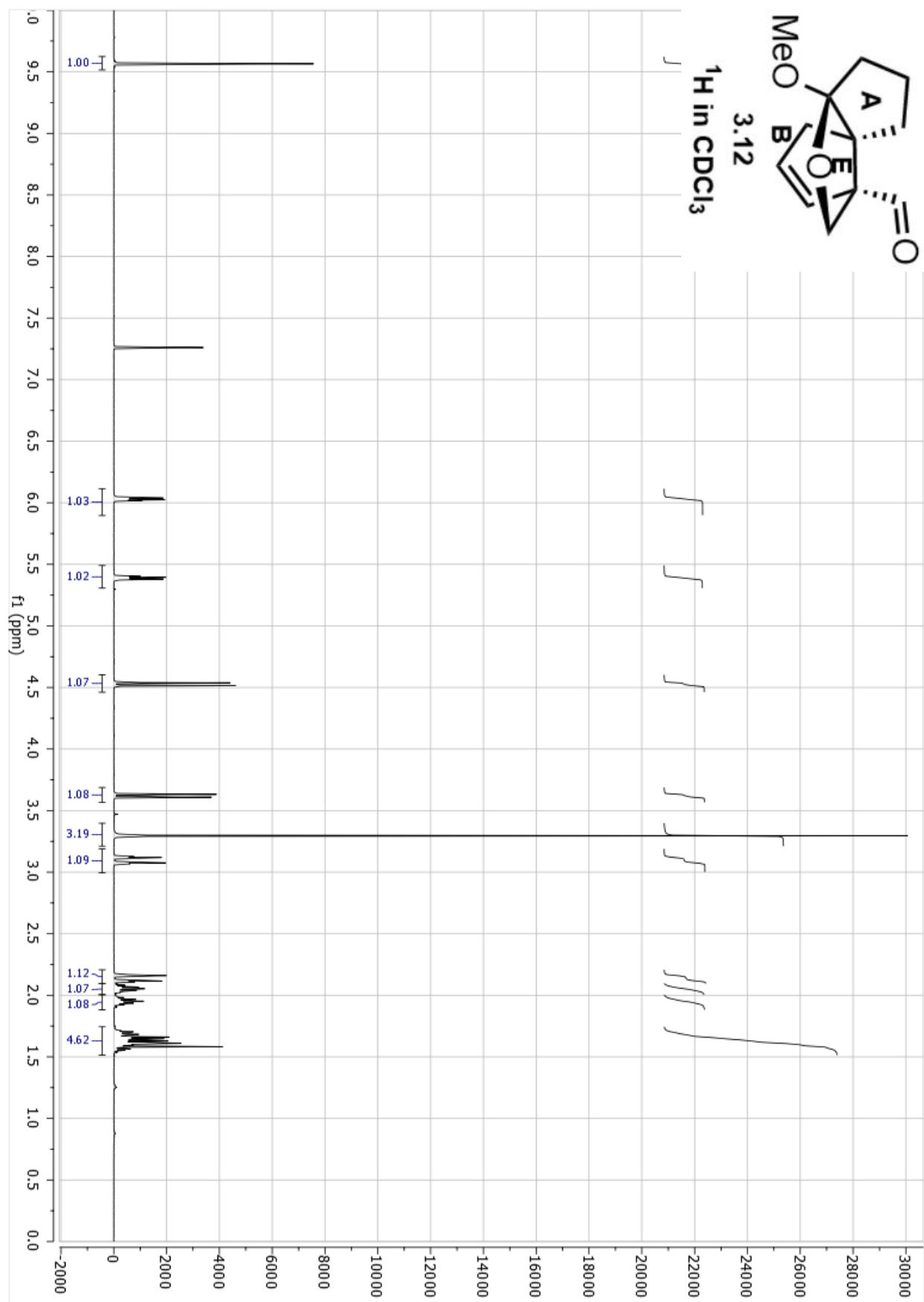
(3.193A). To a solution of **3.171A** (54.1 mg, 0.120 mmol) in 2.4 mL THF at 0 °C was added a solution of LiBH₄ (2.0 M in THF, 598 μL, 1.20 mmol, 10 eq.). The reaction mixture was stirred from 0 °C to RT for 2 h. The solution was diluted with 10 mL EtOAc and quenched with 10 mL aq. sat. NaHCO₃, extracted with (3 x 10 mL) EtOAc, dried over Na₂SO₄, filtered, and evaporated under reduced pressure. The crude was purified over silica gel (10-30% EtOAc/Hex) to afford ketone **3.193A** as a white solid (35.8 mg, 73%): mp 175-176 °C; *R*_f 0.33 (40% EtOAc/Hex); ¹H-NMR (400 MHz, CDCl₃) δ 7.55-7.41 (m, 2H), 7.42-7.29 (m, 3H), 5.64 (s, 1H), 5.23 (dd, *J* = 6.9, 3.2 Hz, 1H), 4.33 (dd, *J* = 4.0, 2.7 Hz, 1H), 3.99 (t, *J* = 8.3 Hz, 1H), 3.43 (s, 3H),

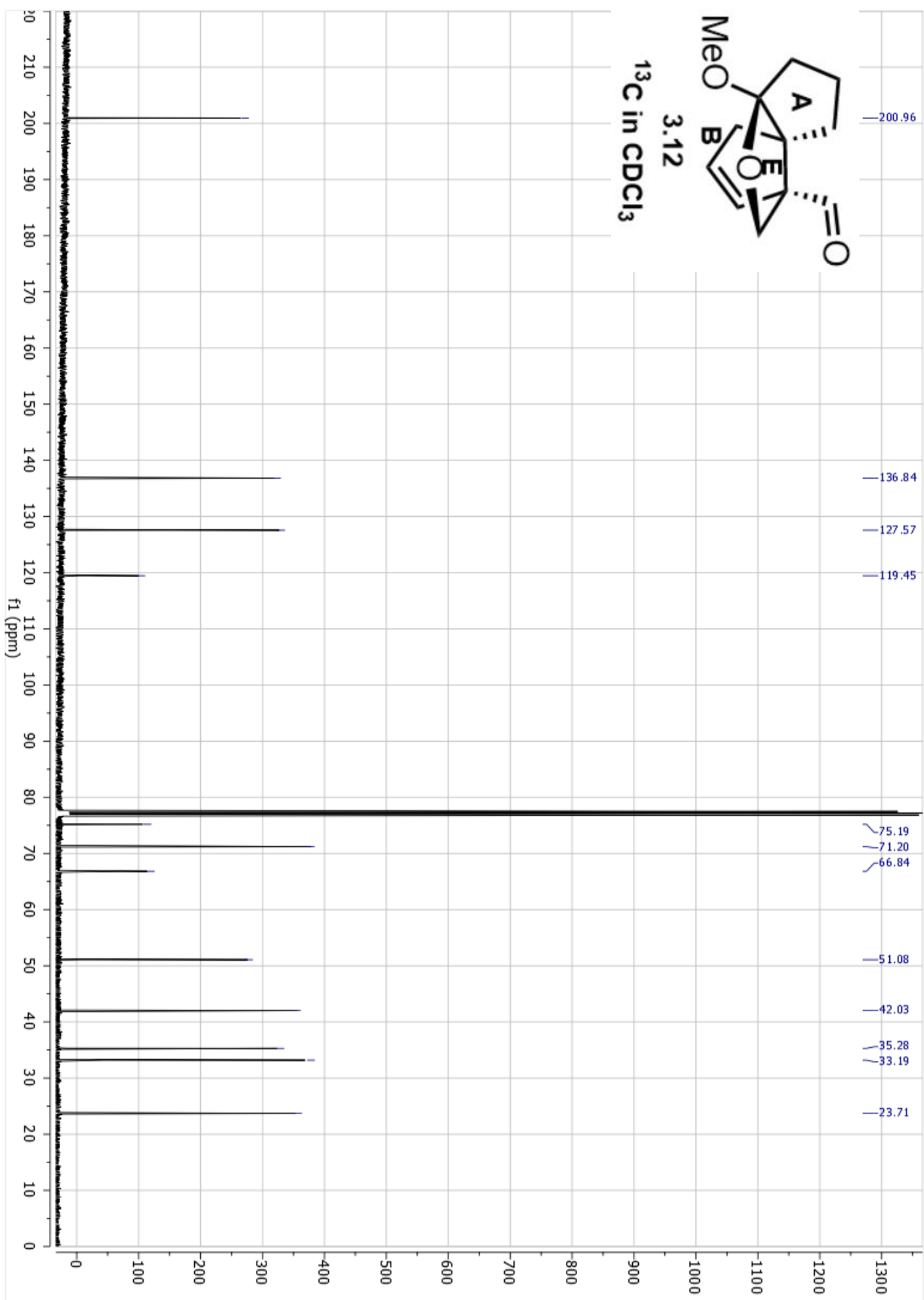
3.03 (s(br), 1H), 2.74 (dd, $J = 15.0, 7.0$ Hz, 1H), 2.62 (s(br), 1H), 2.53 (dd, $J = 10.5, 7.9$ Hz, 1H), 2.39-2.27 (m, 1H), 2.27-2.15 (m, 2H), 2.11-1.95 (m, 2H), 1.87 (dd, $J = 15.0, 3.3$ Hz, 1H), 1.84-1.75 (m, 1H), 1.01 (s, 9H).

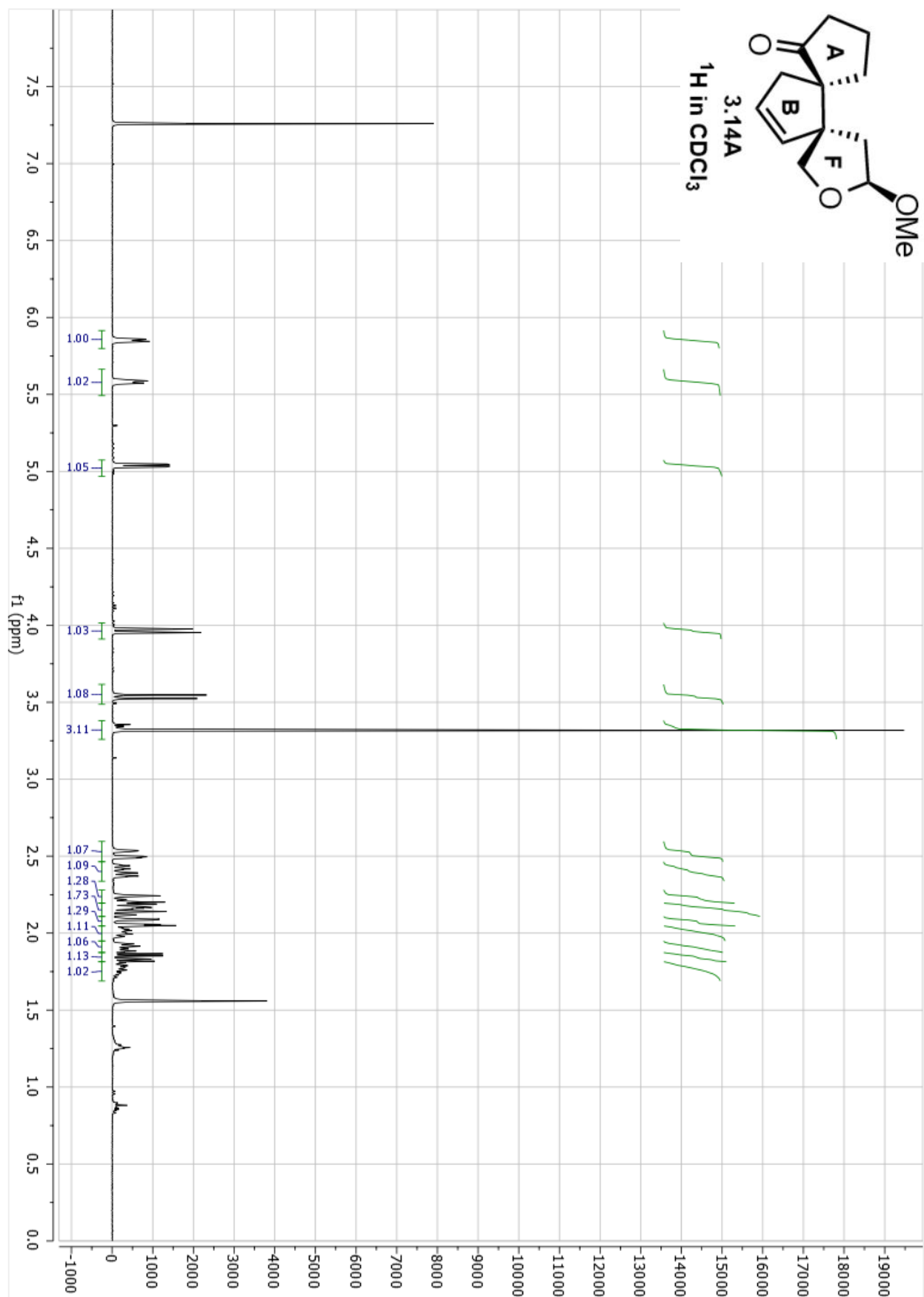
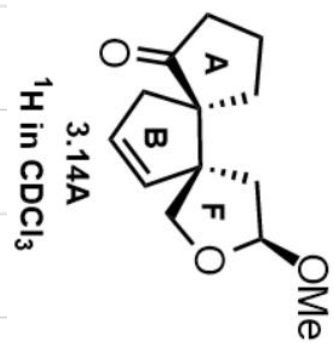
4.1.3 ^1H , ^{13}C , HSQC and HMBC NMR Spectra:

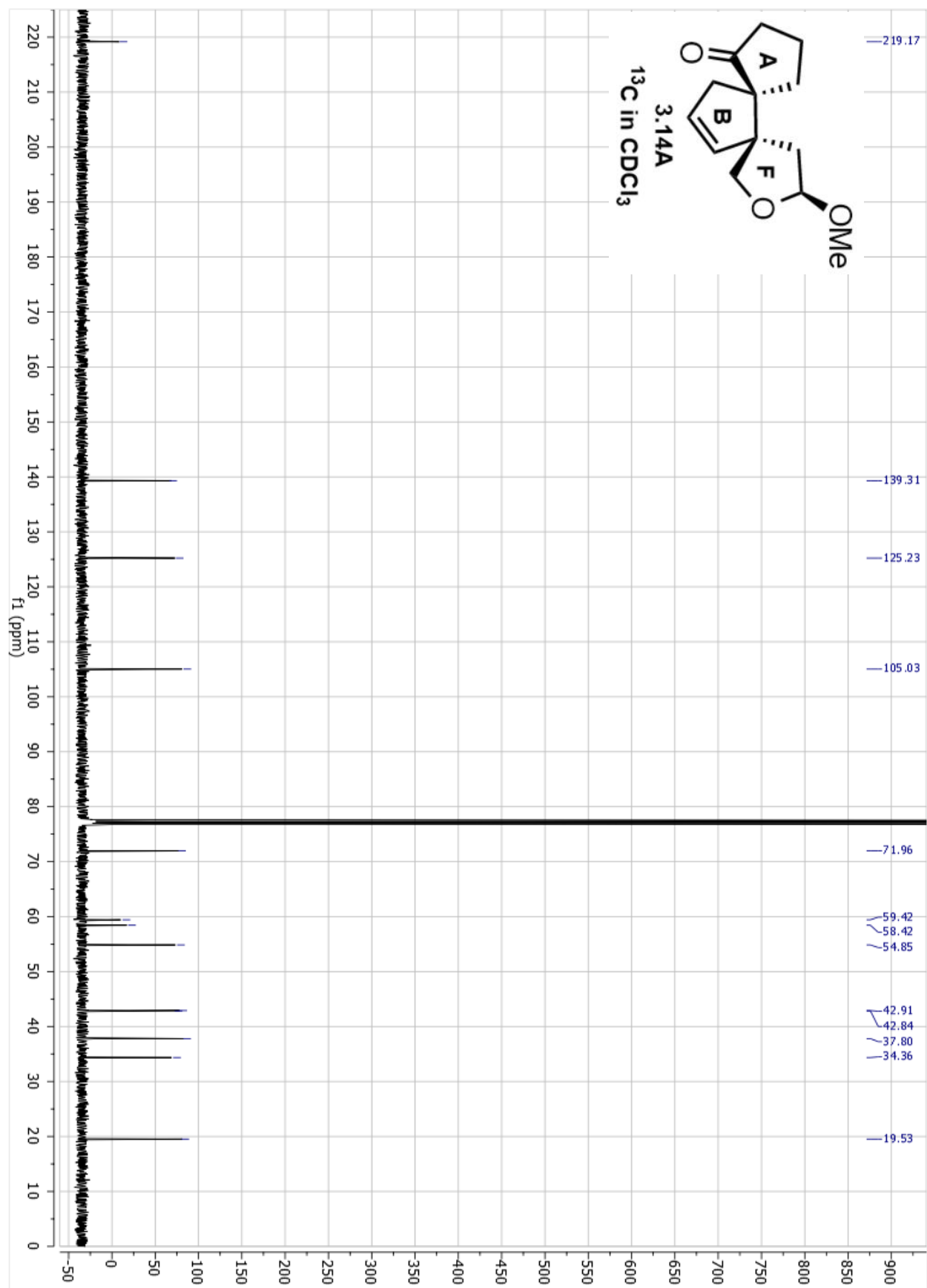


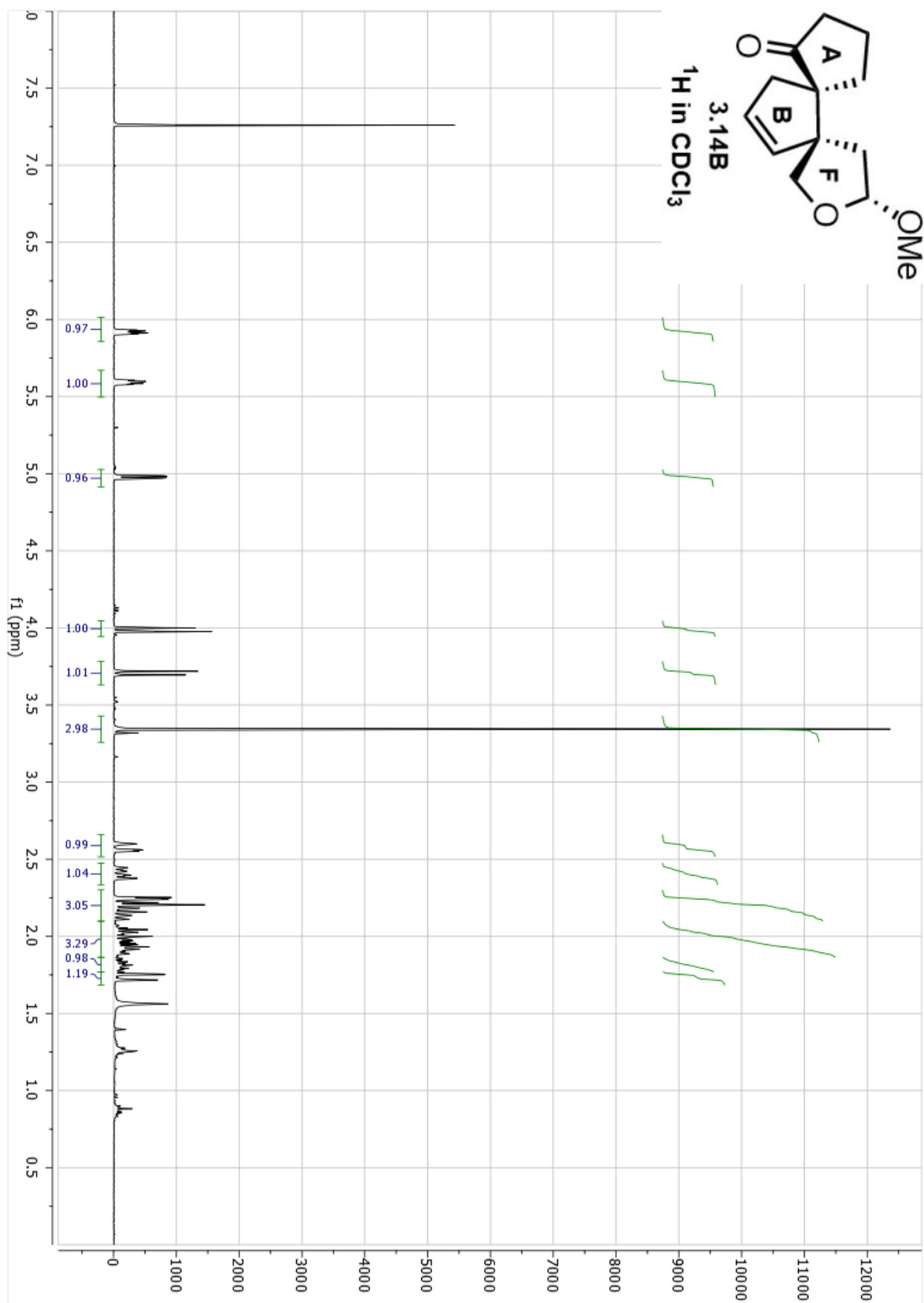


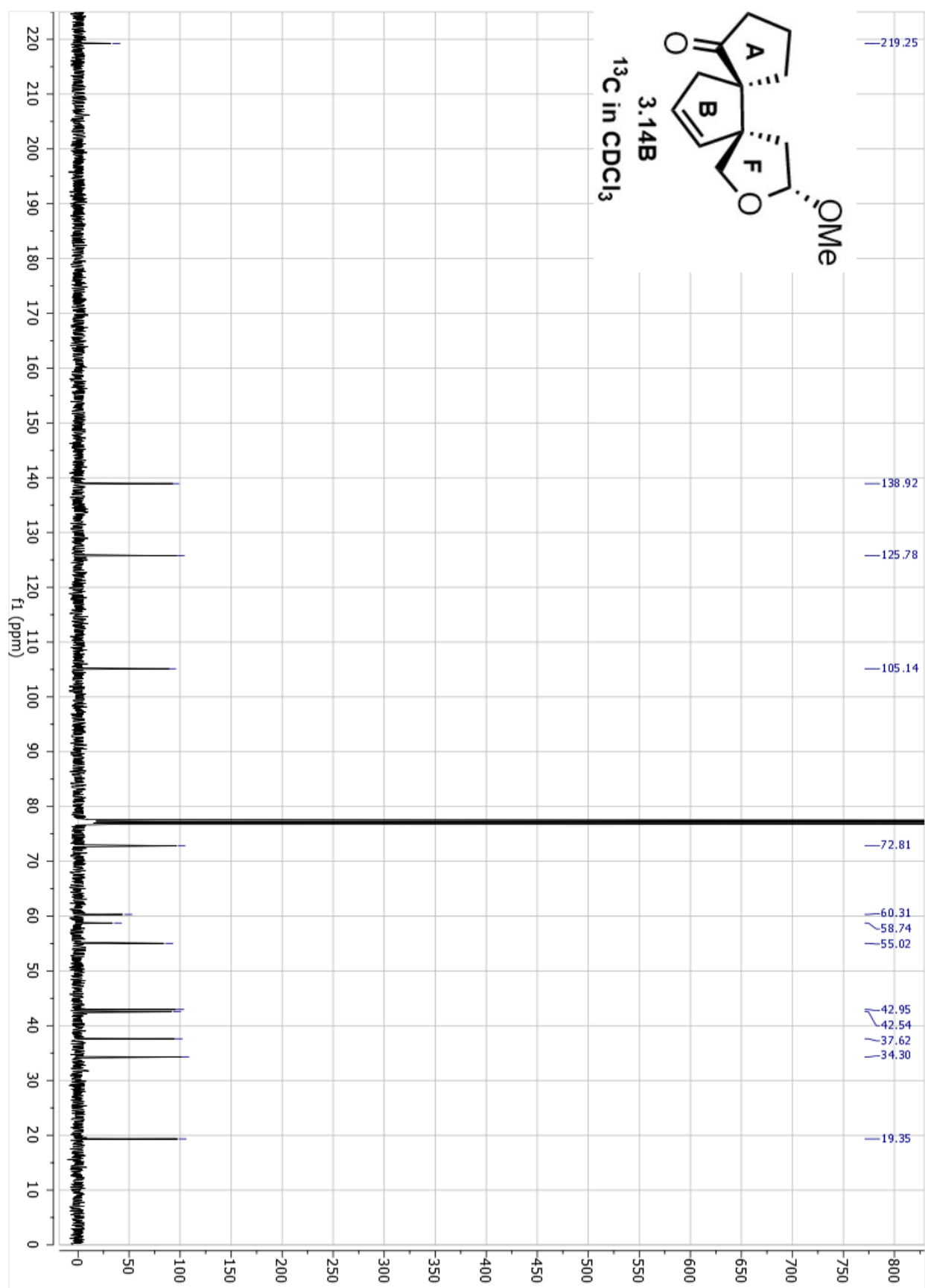


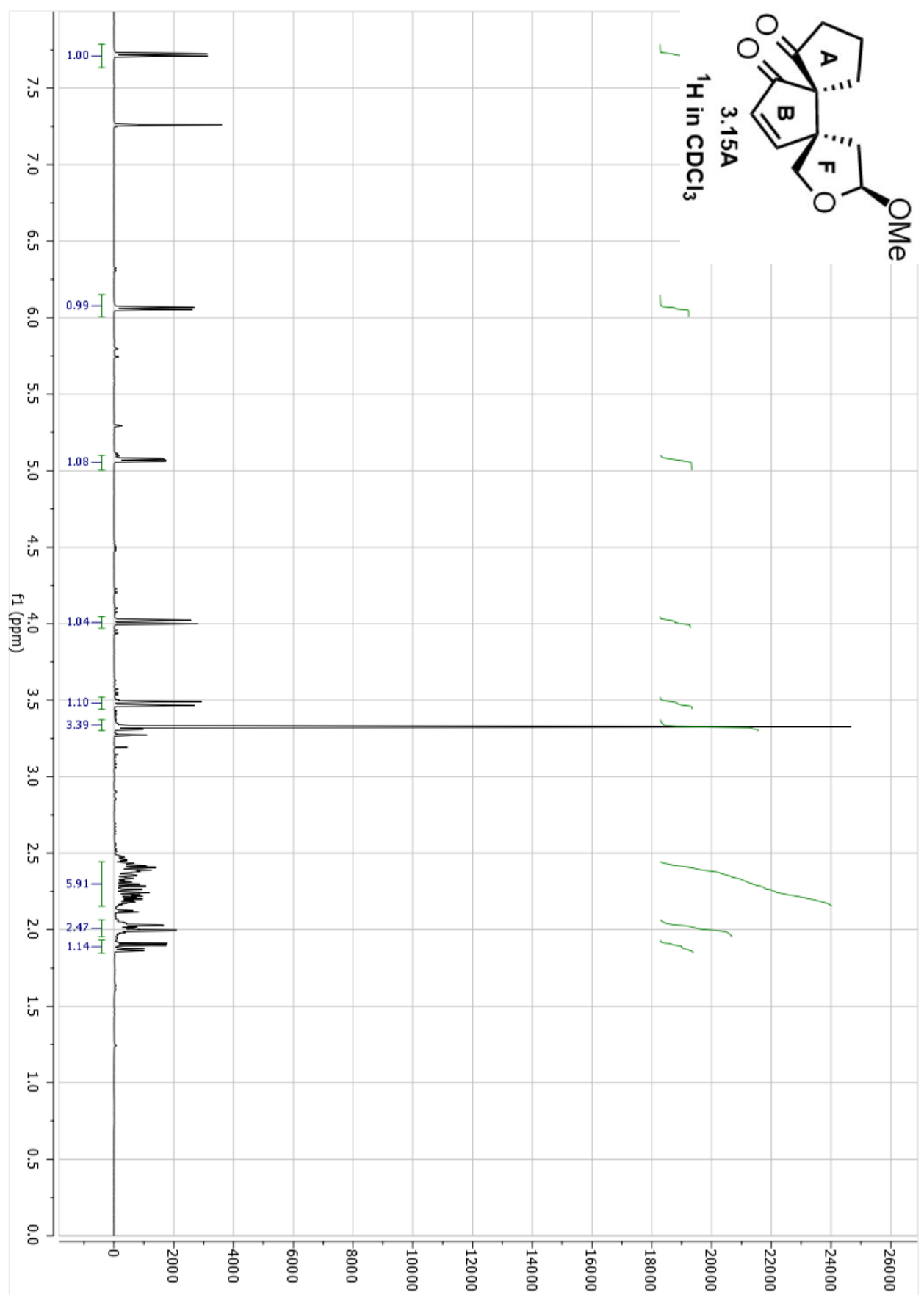


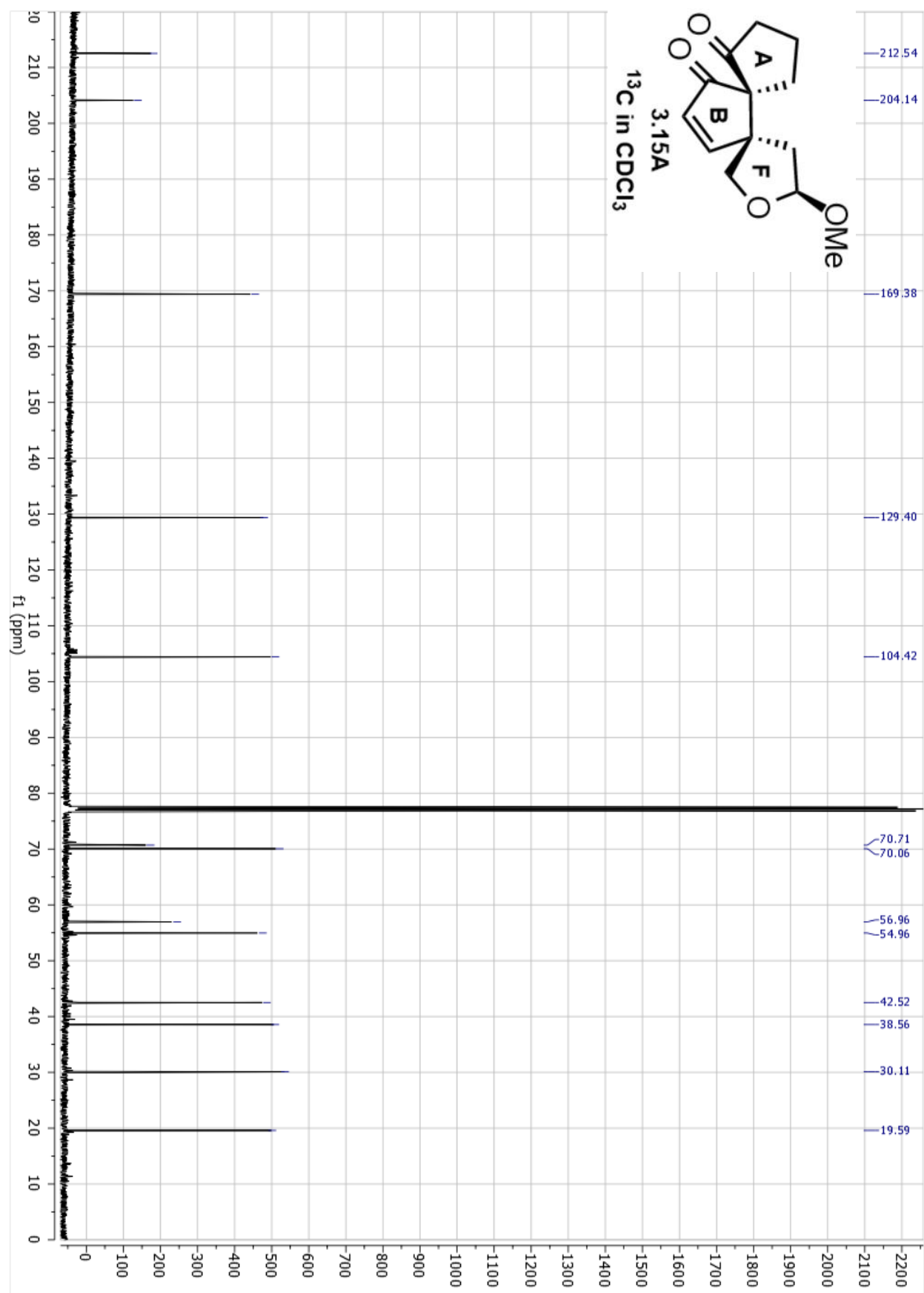


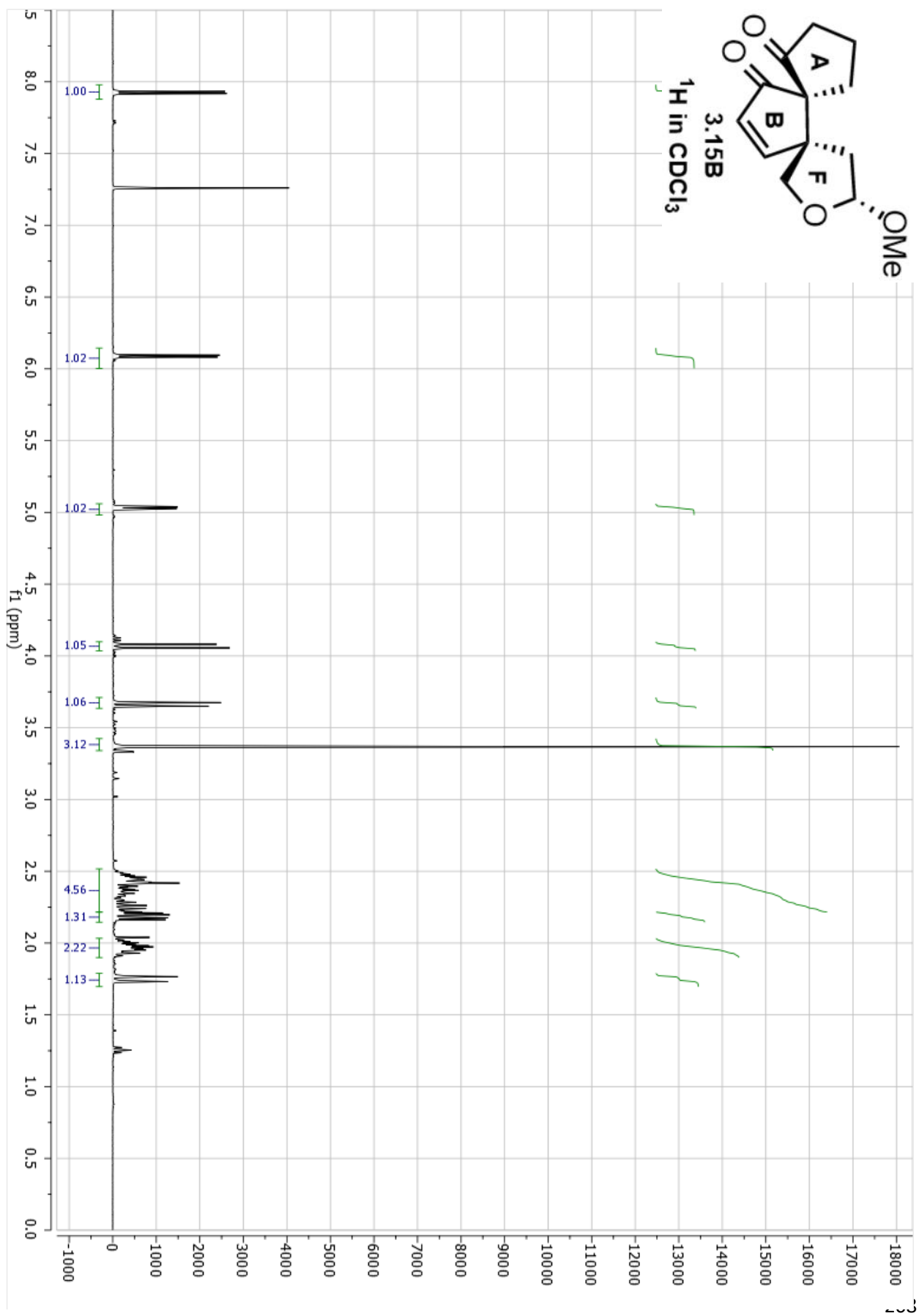
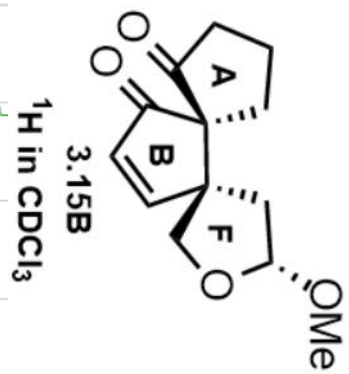


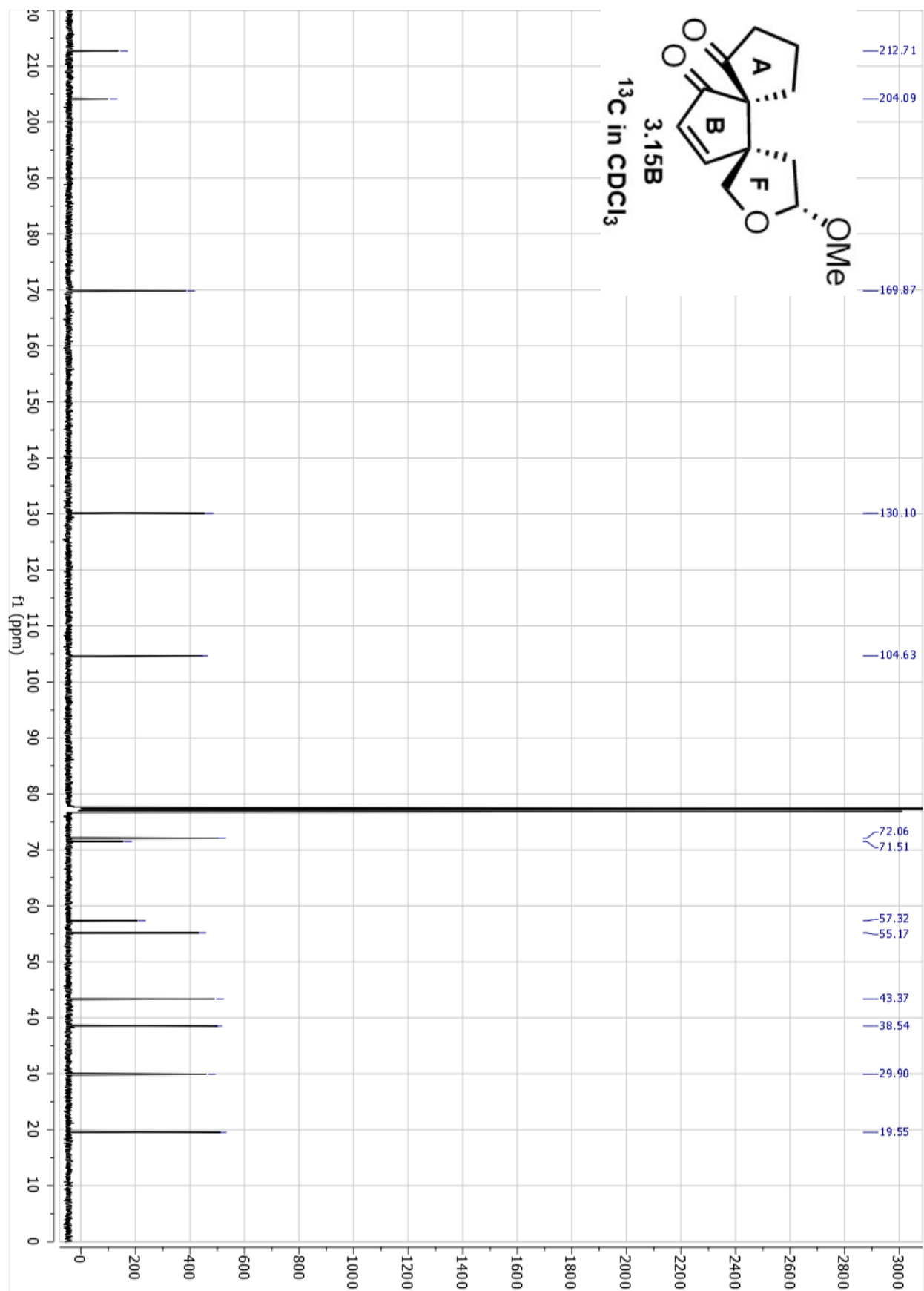


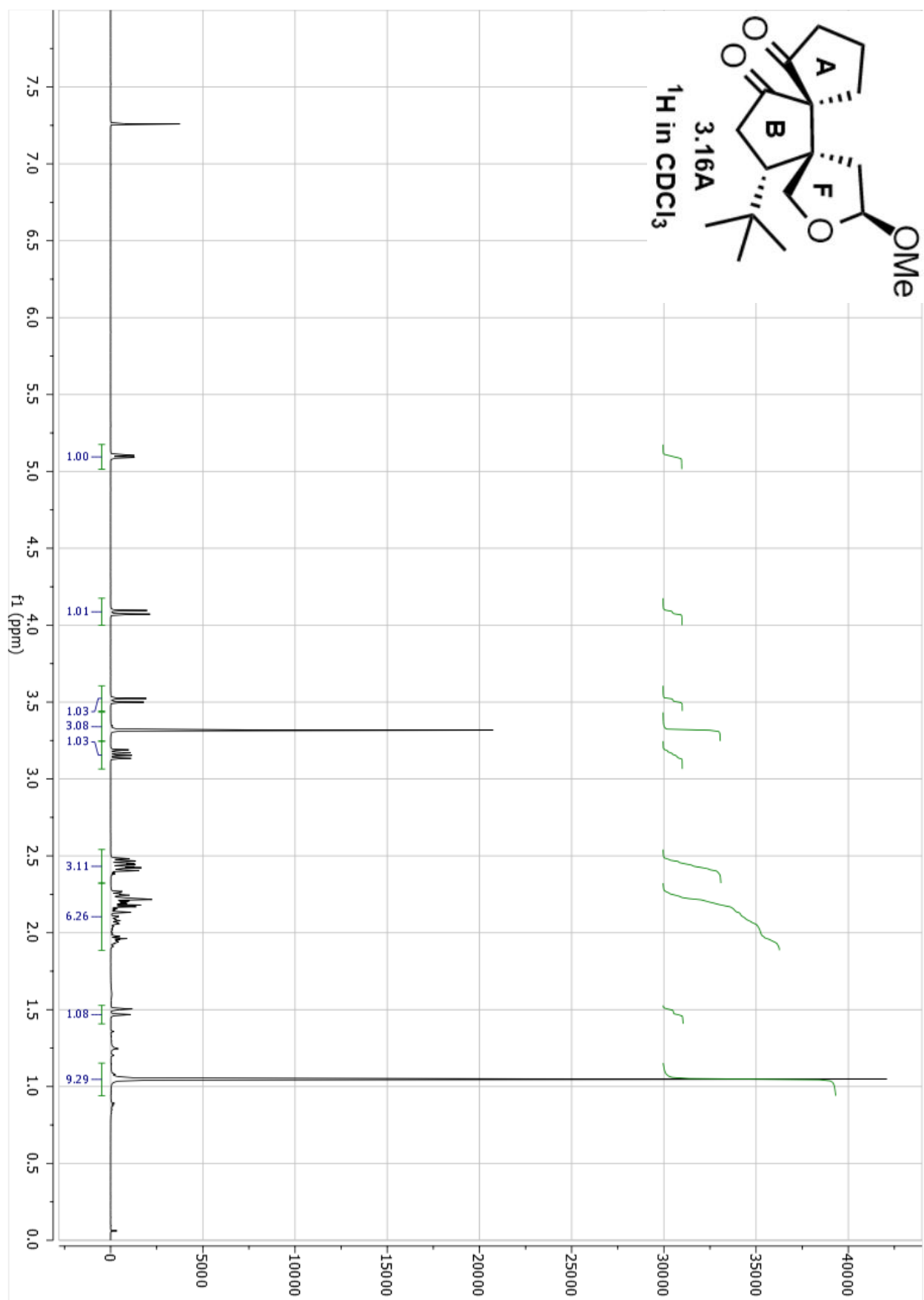


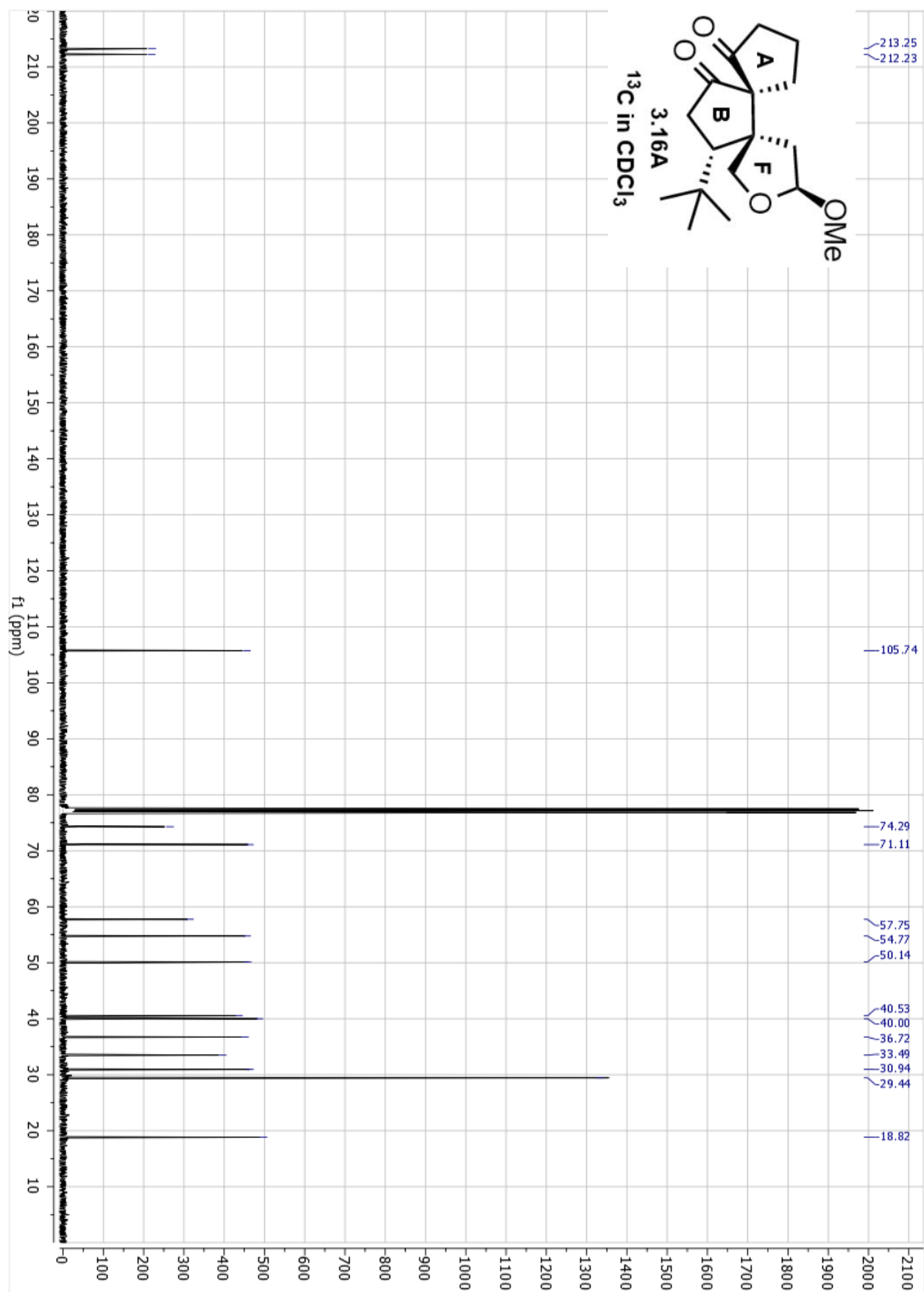


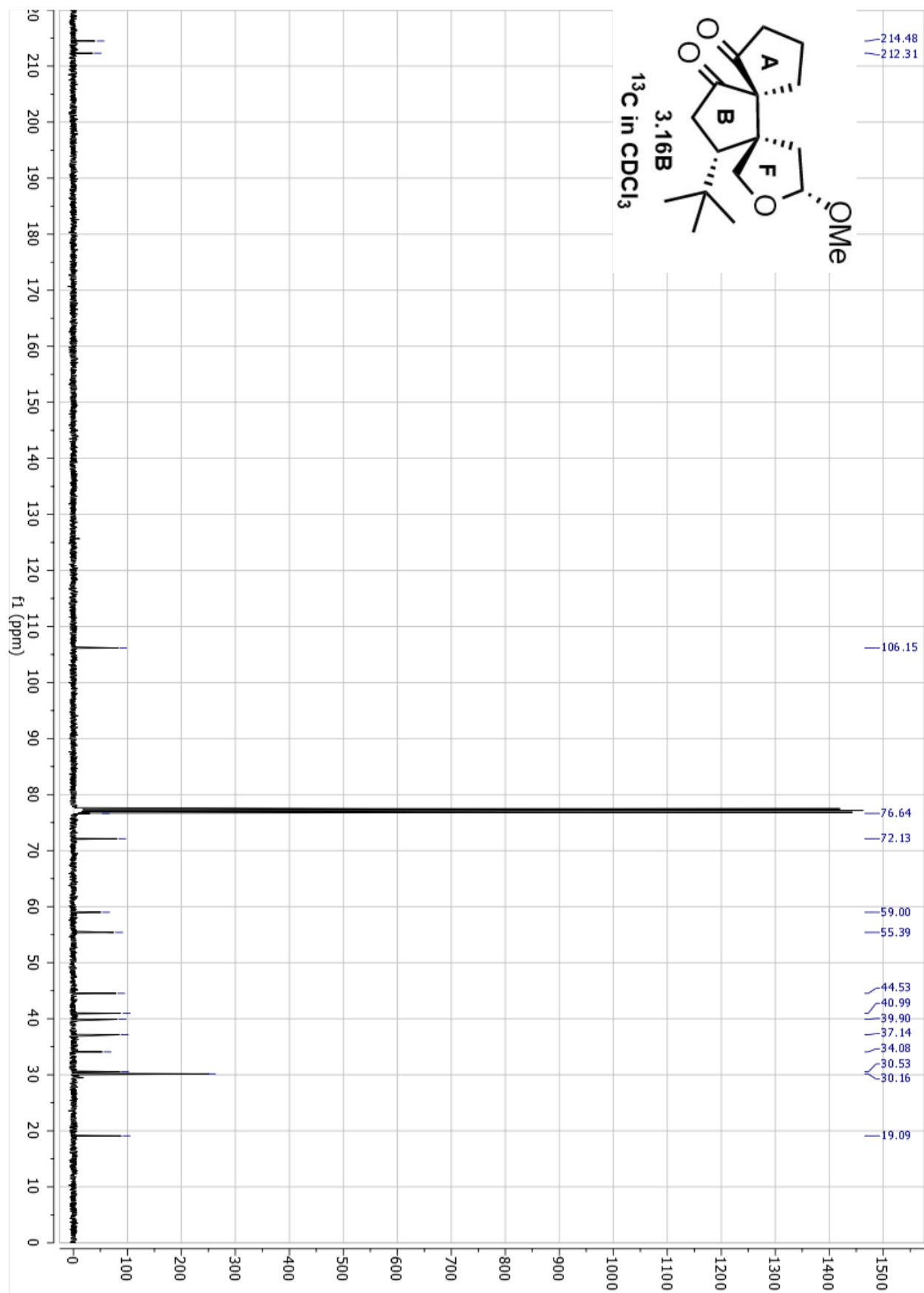


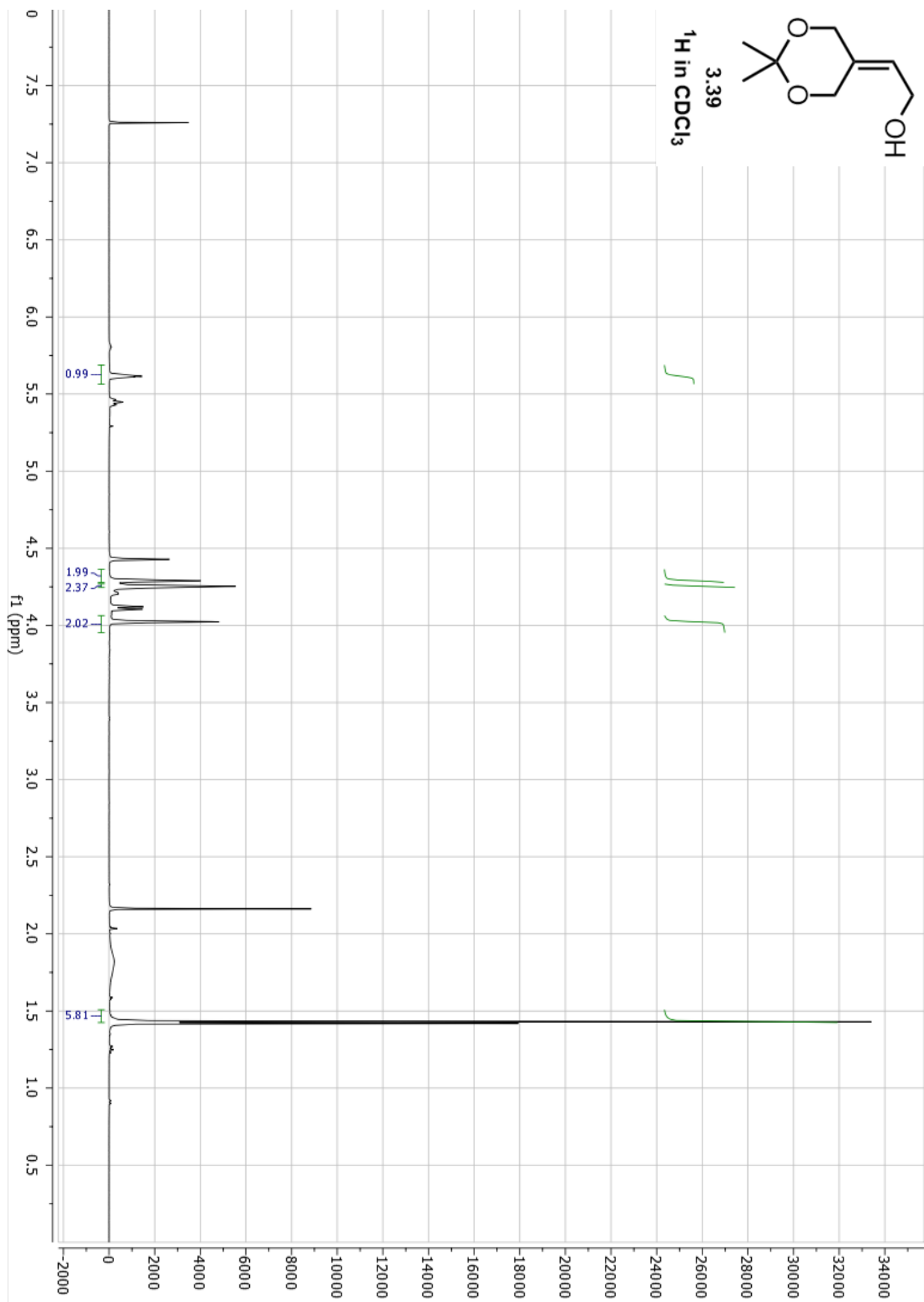


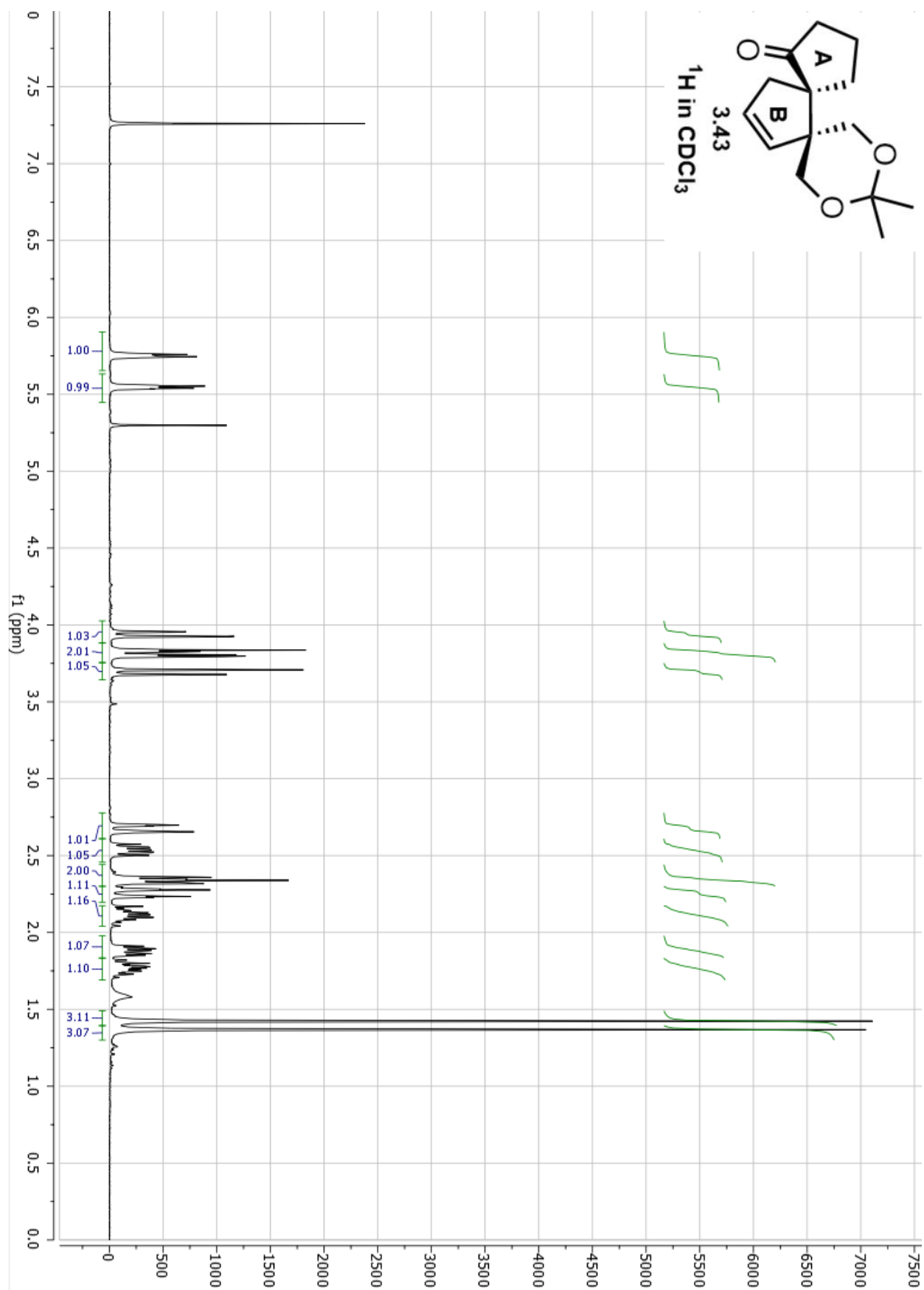


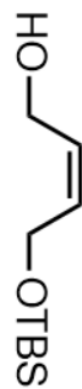






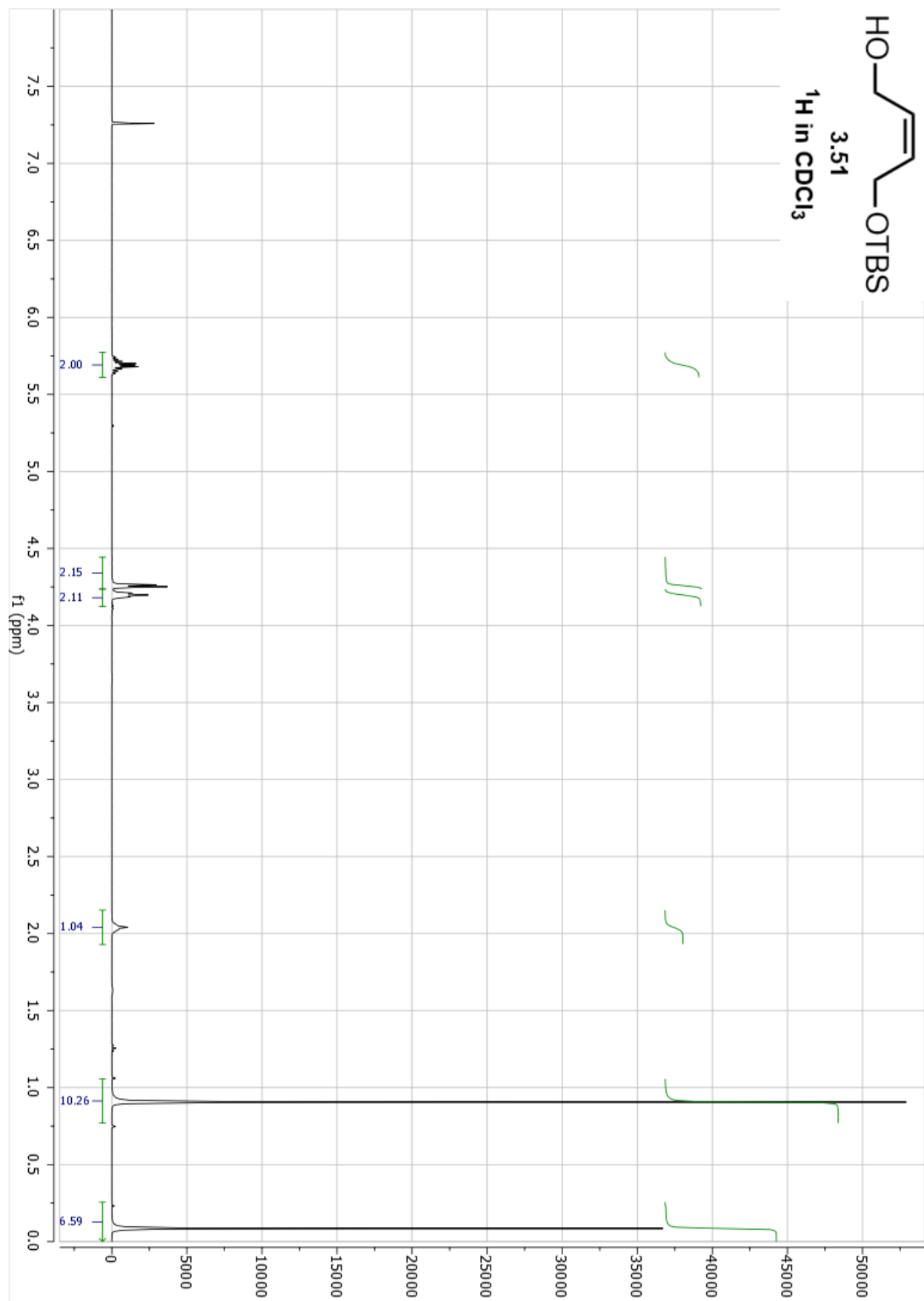


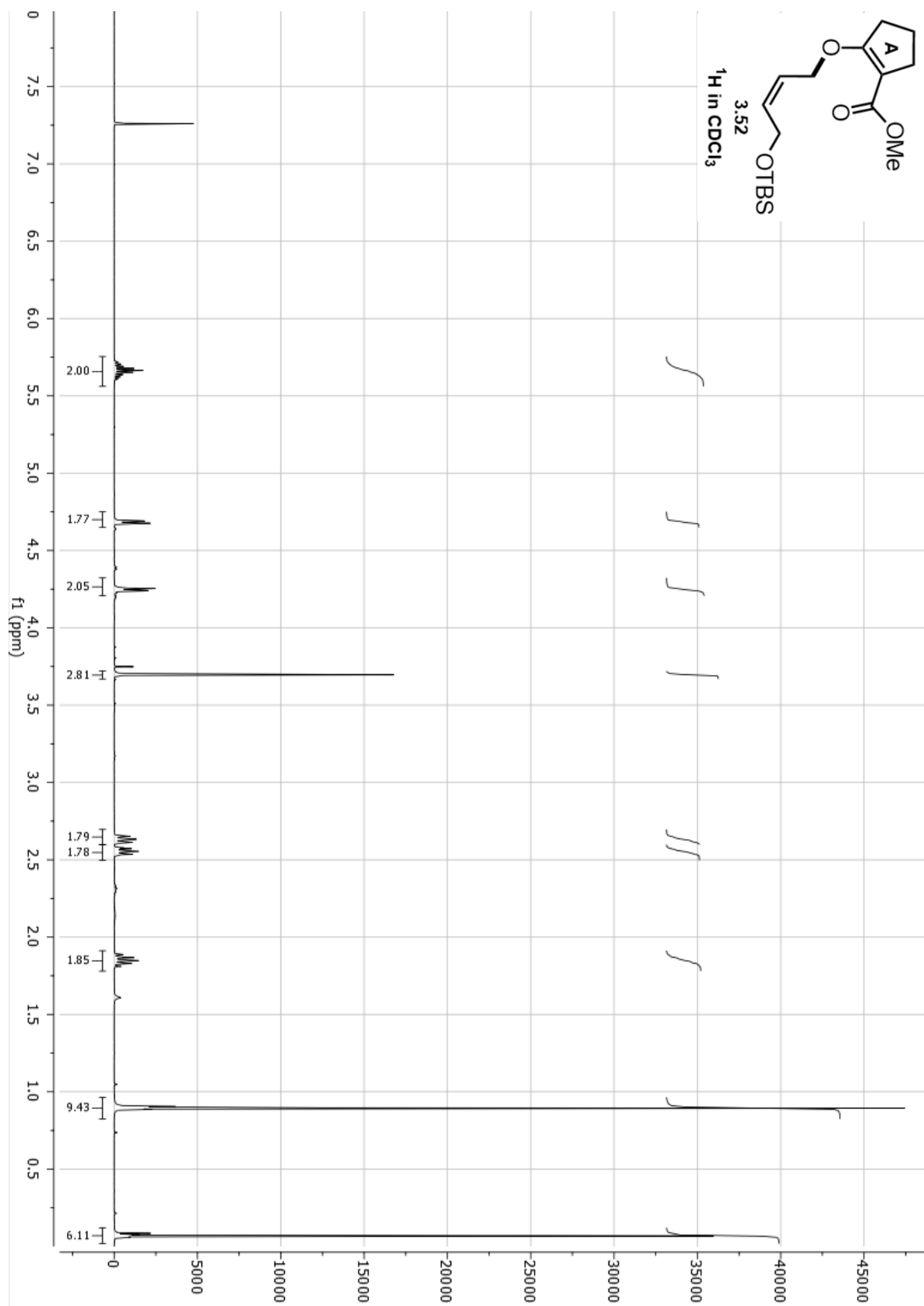


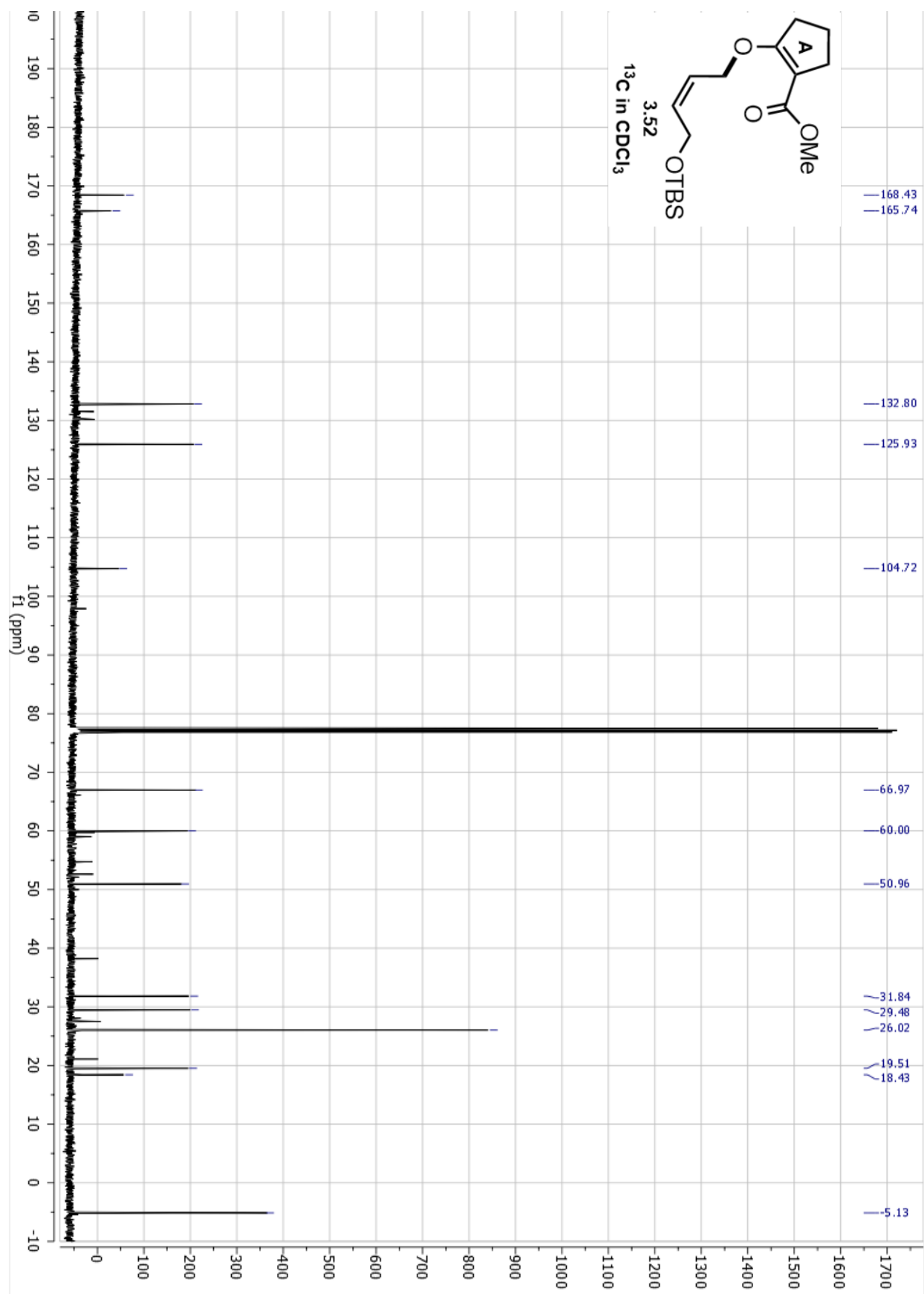


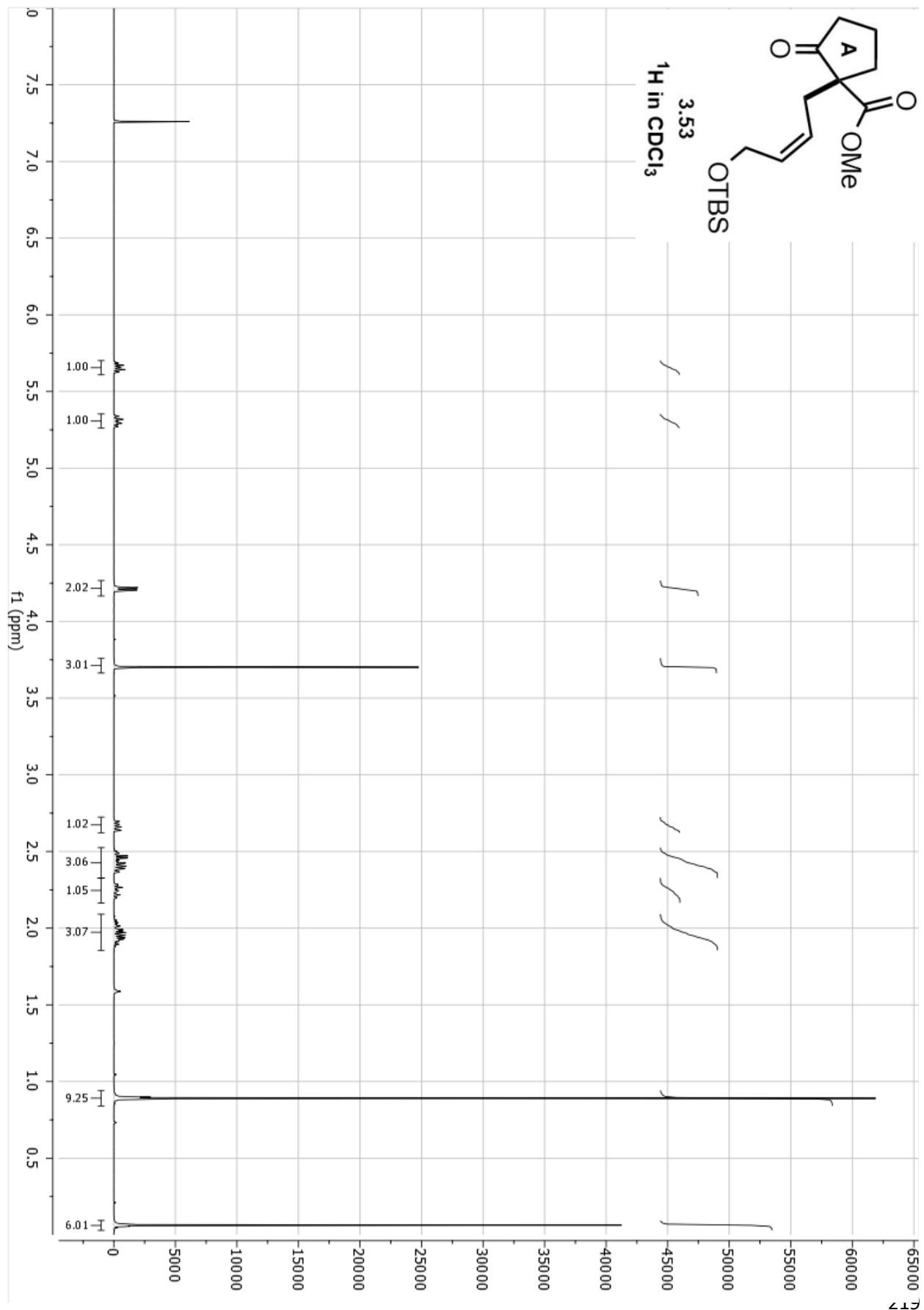
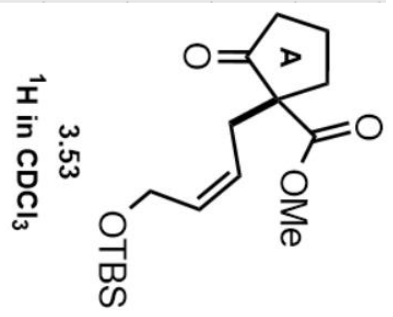
3.51

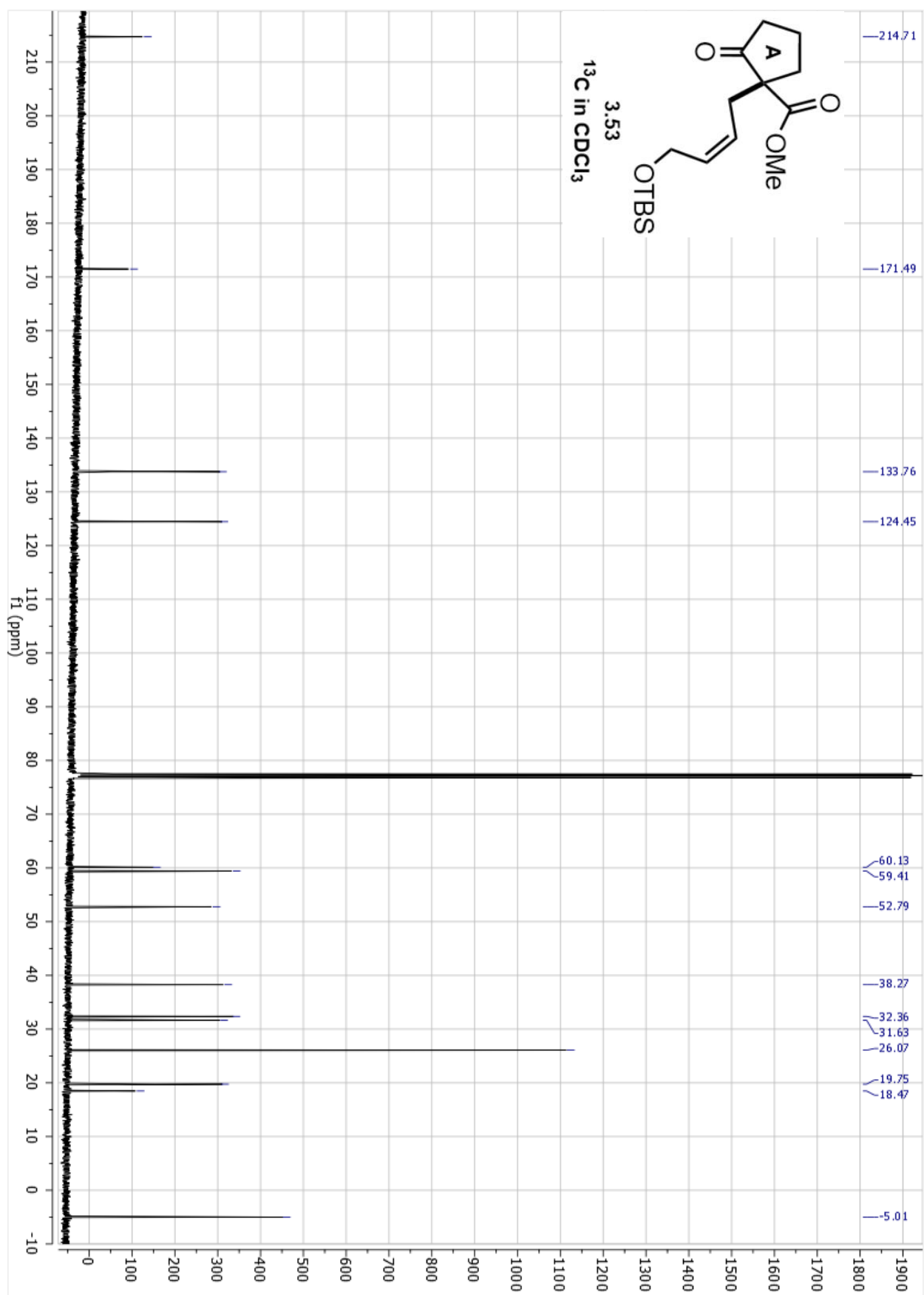
^1H in CDCl_3

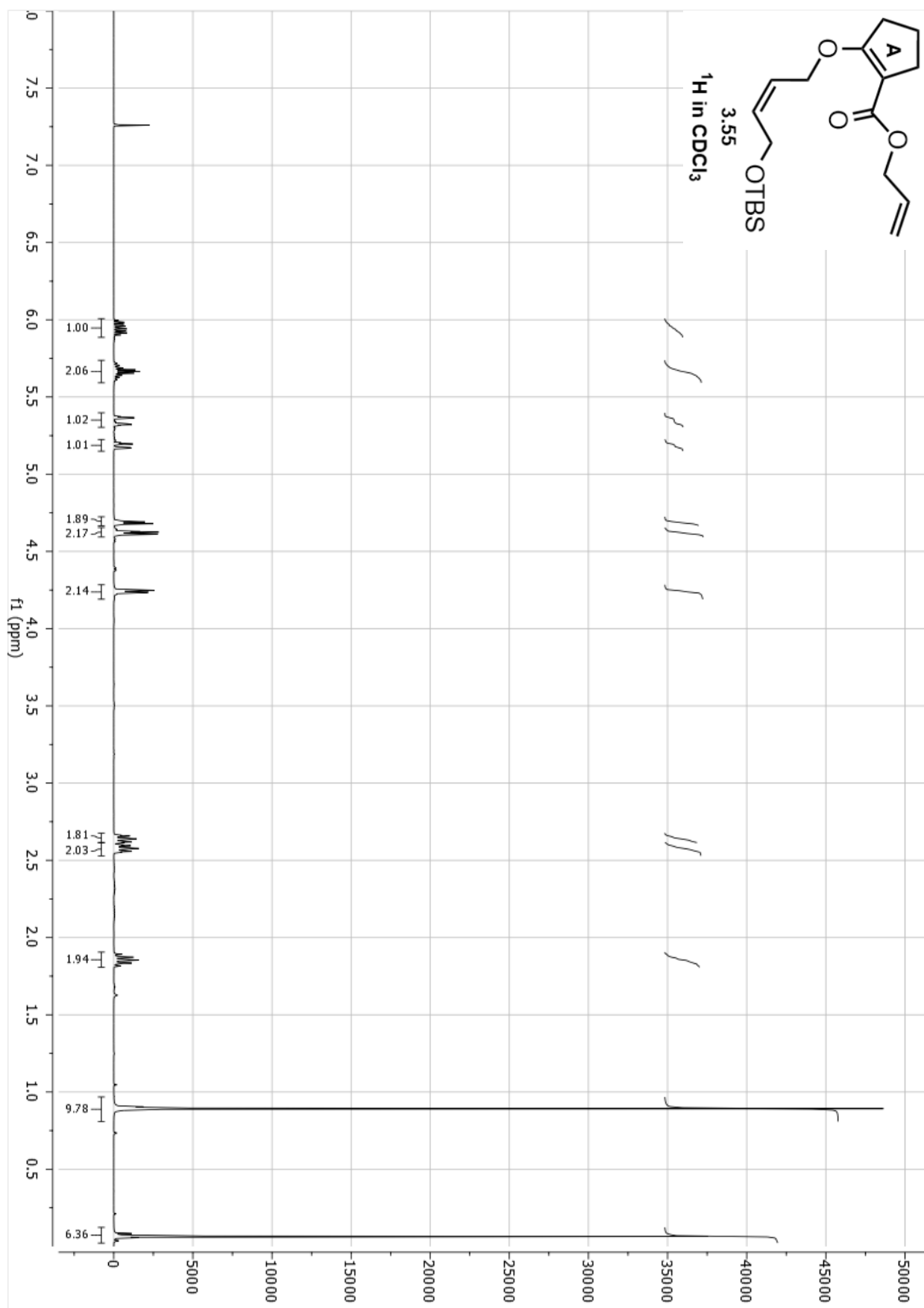


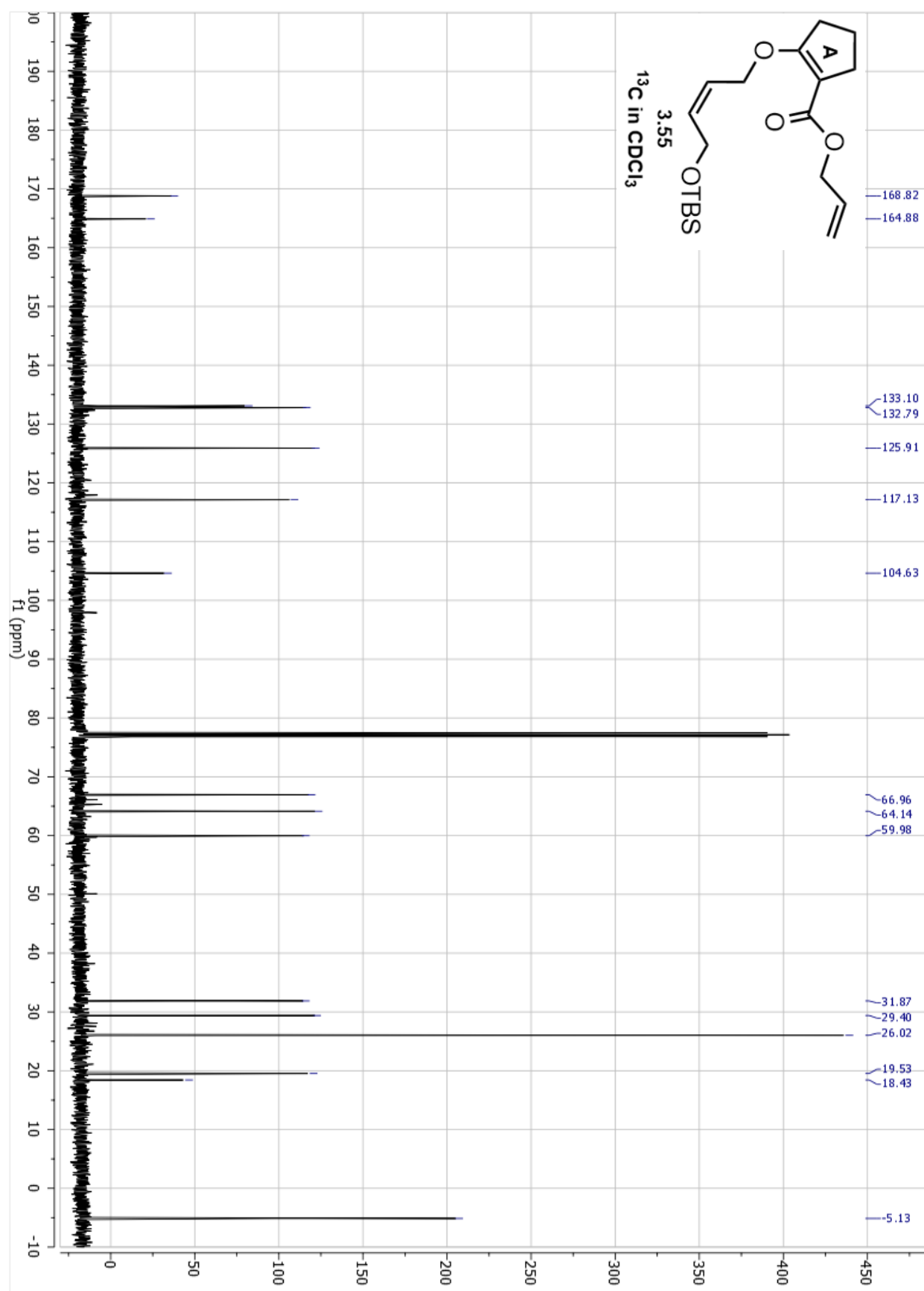


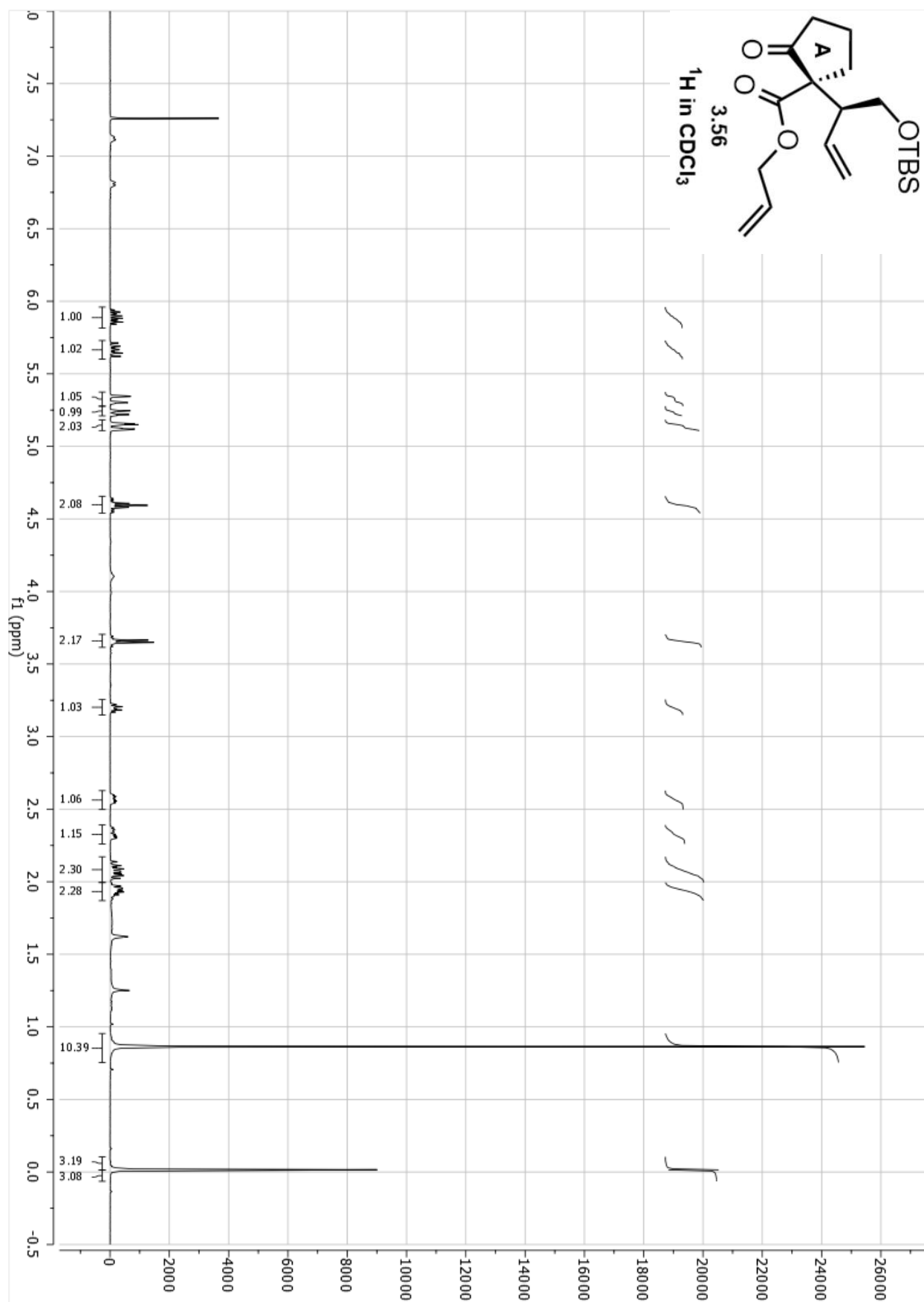


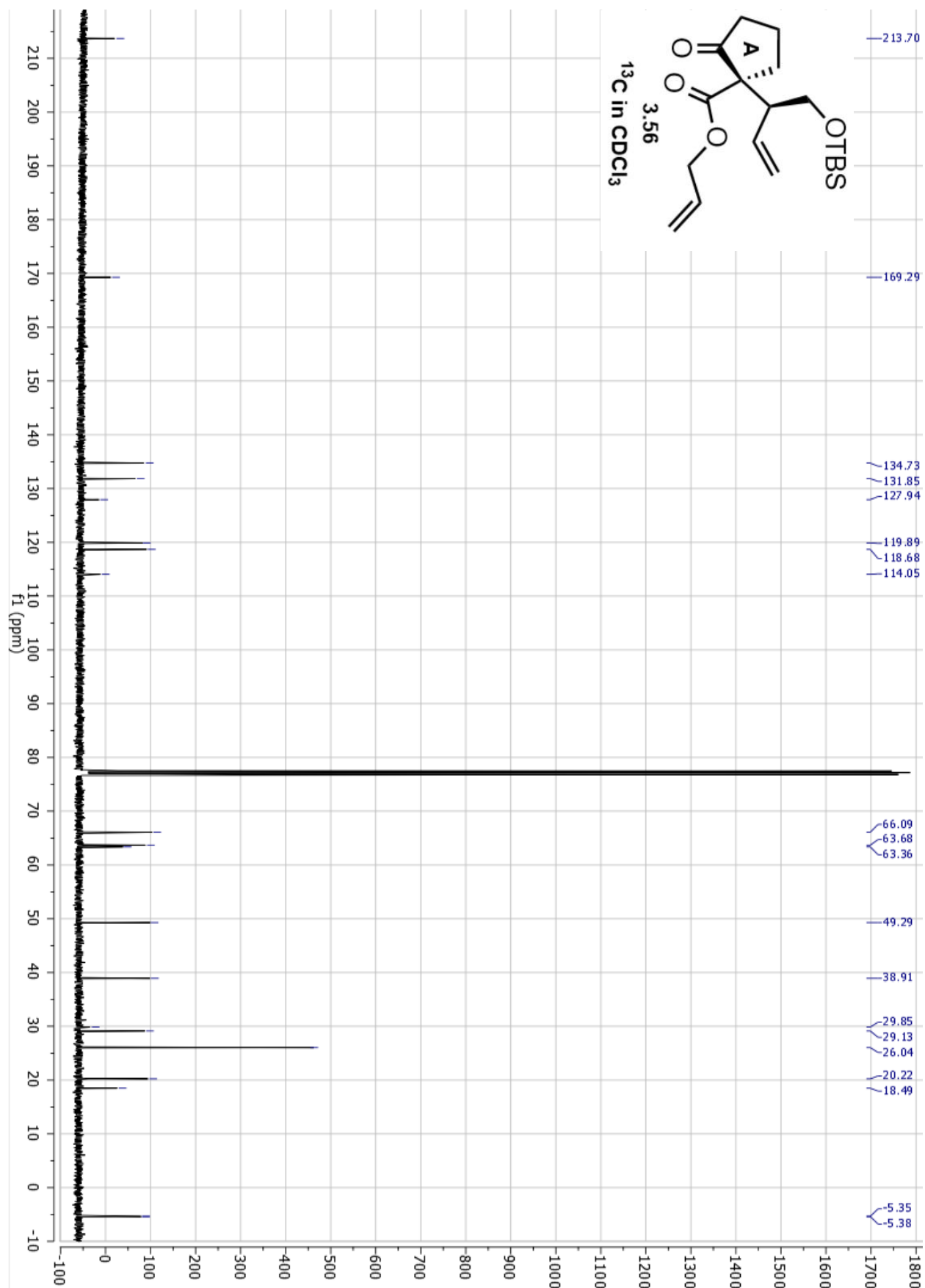


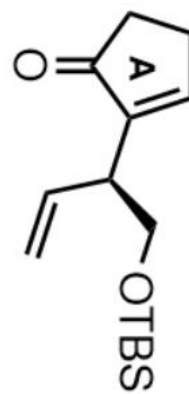






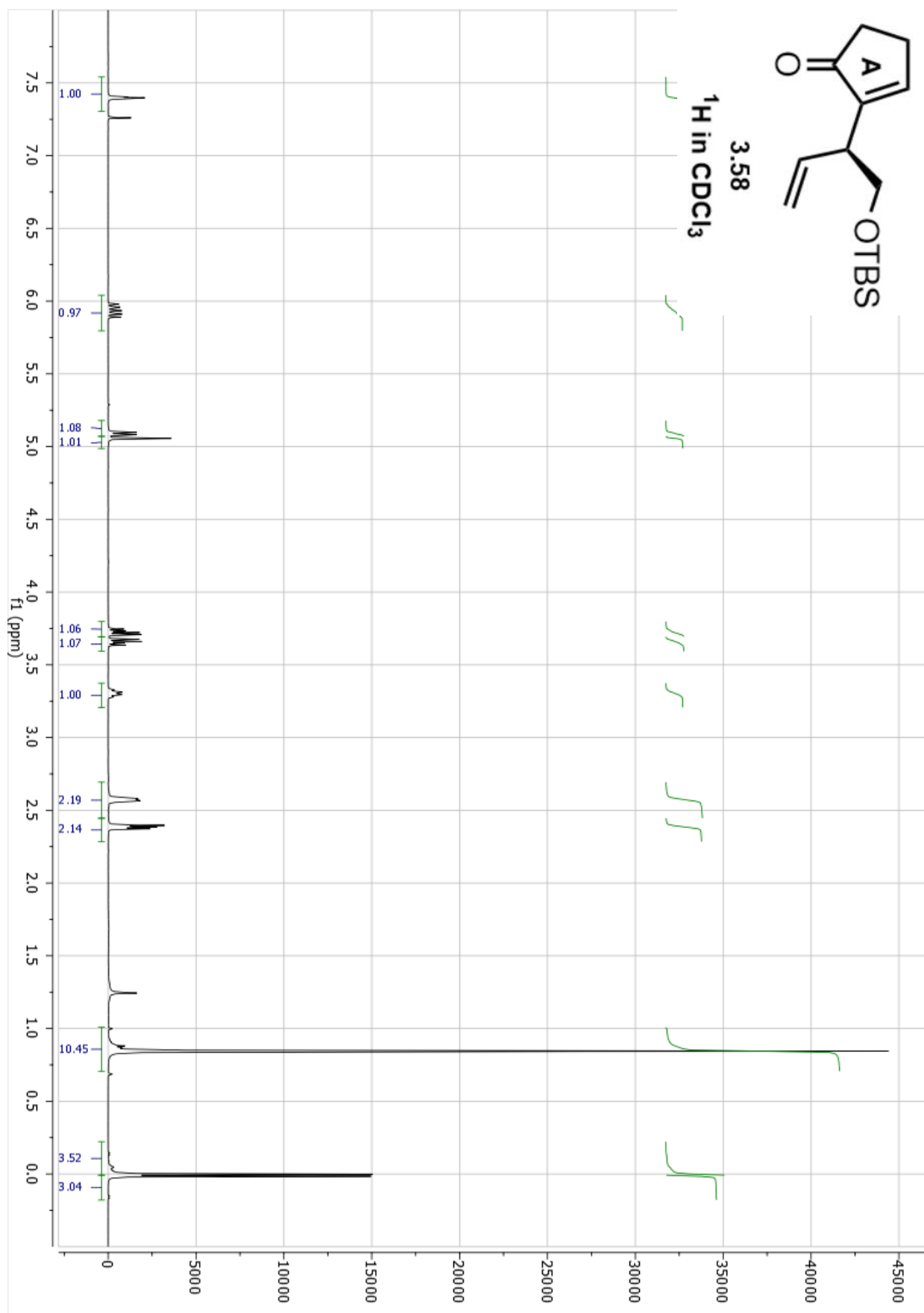


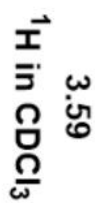


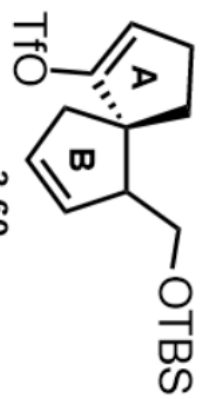


3.58

^1H in CDCl_3

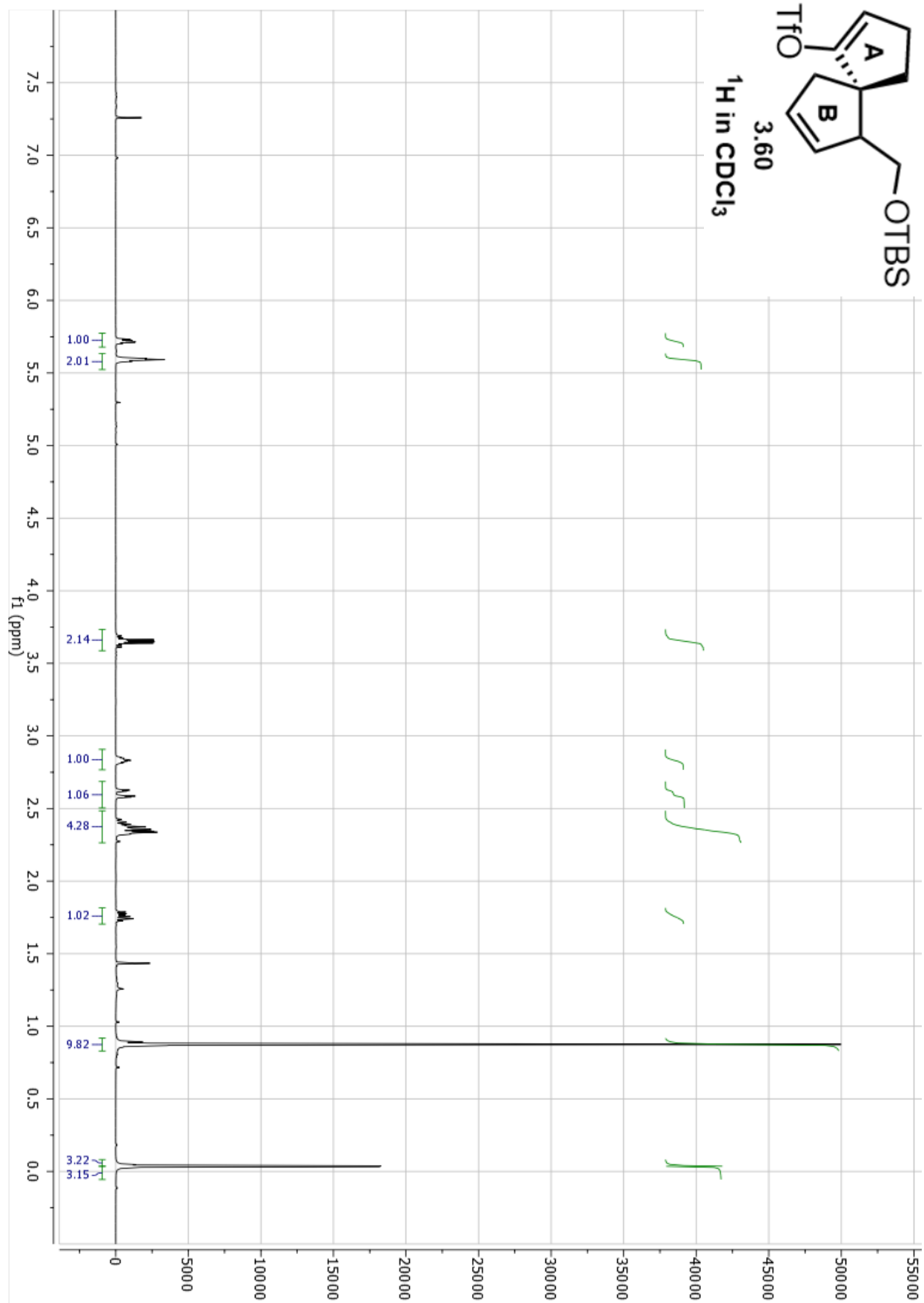


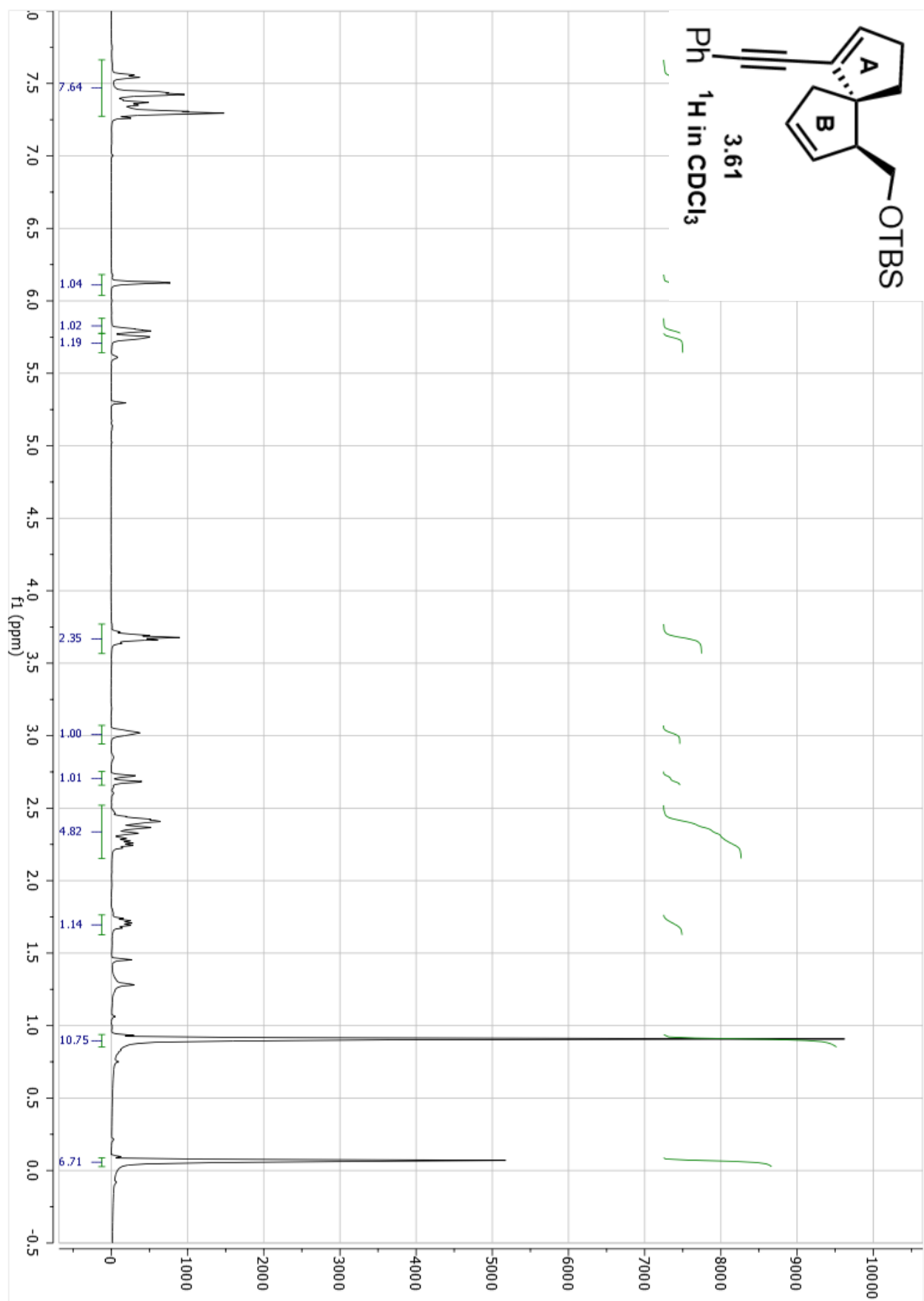


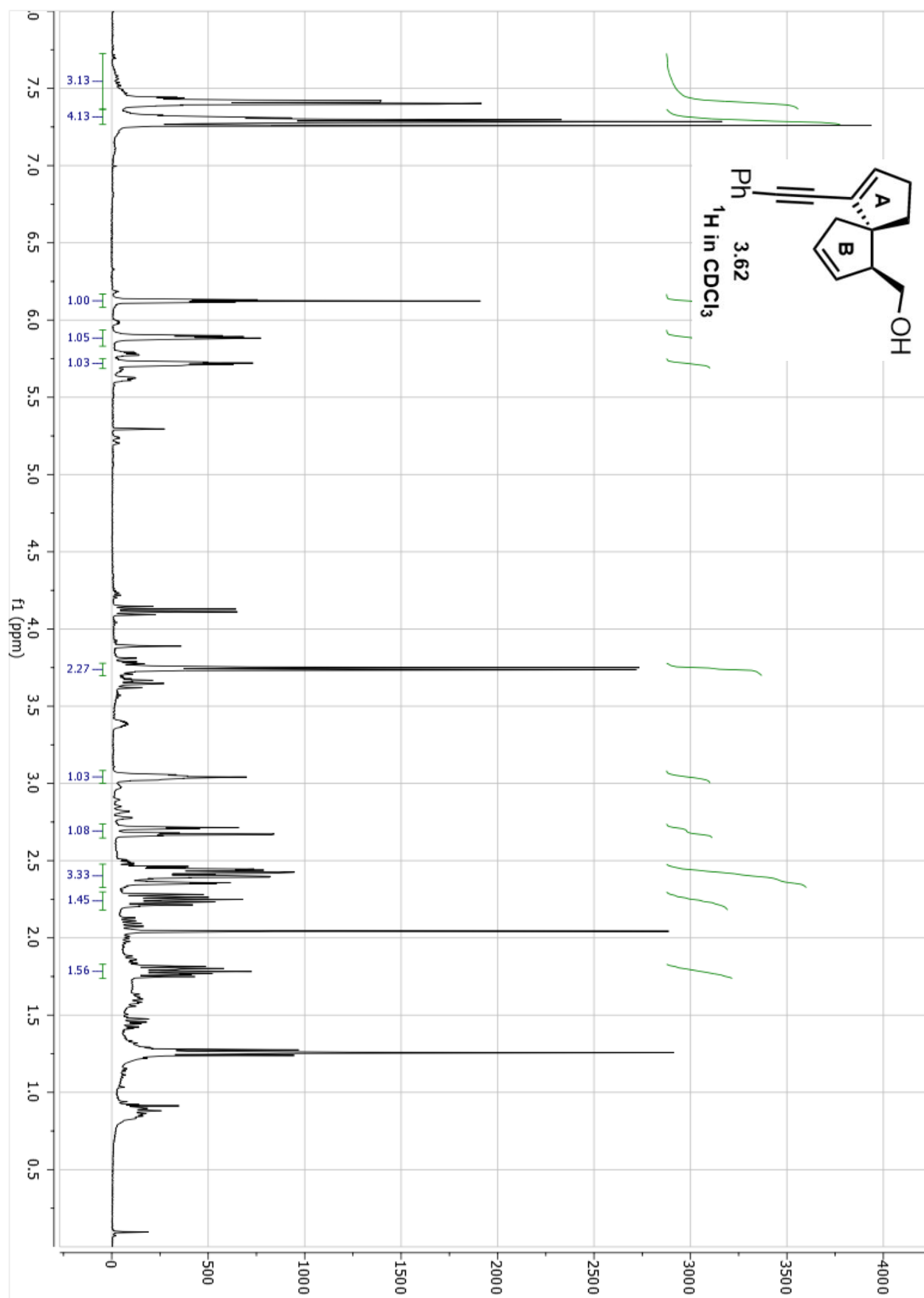


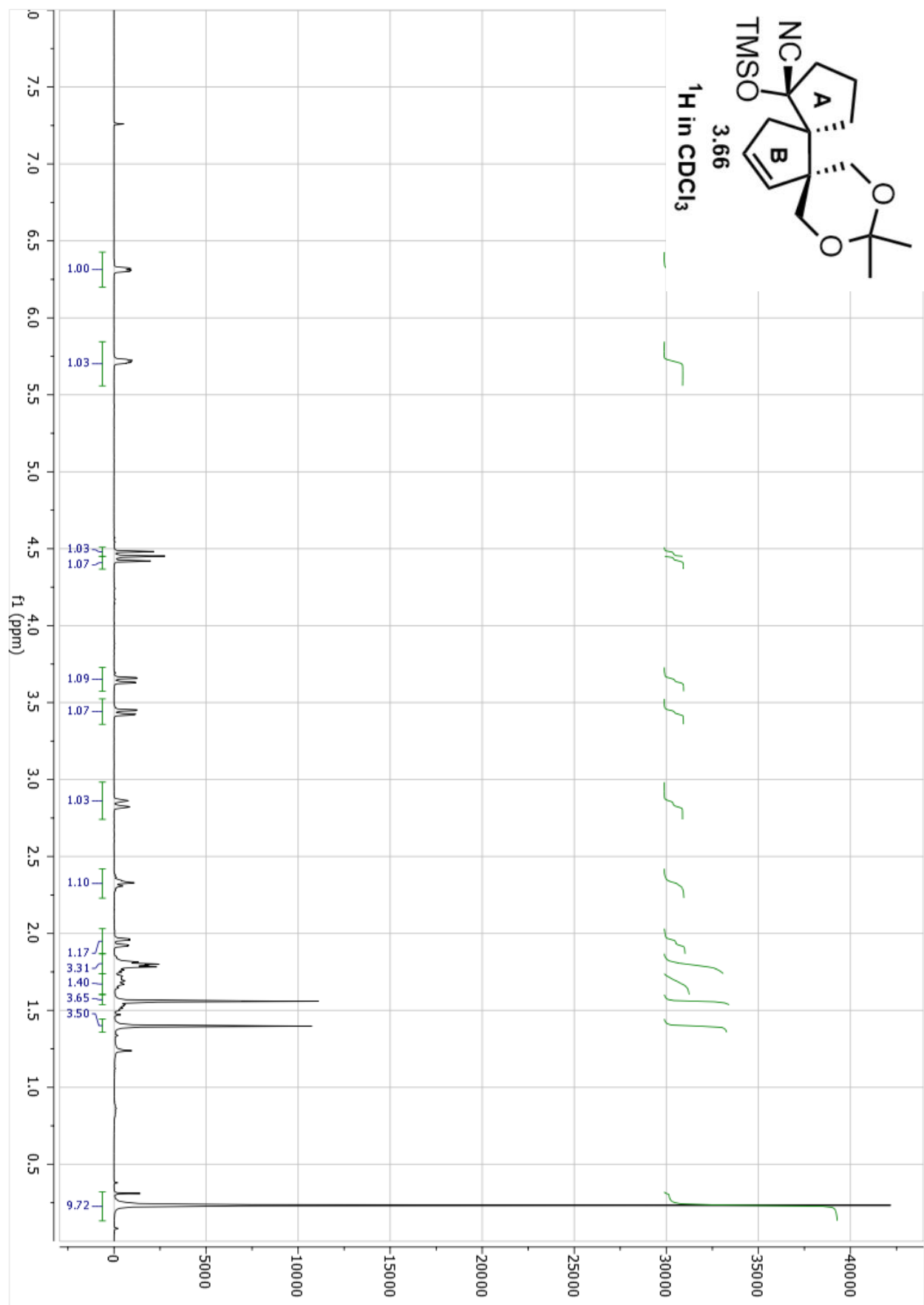
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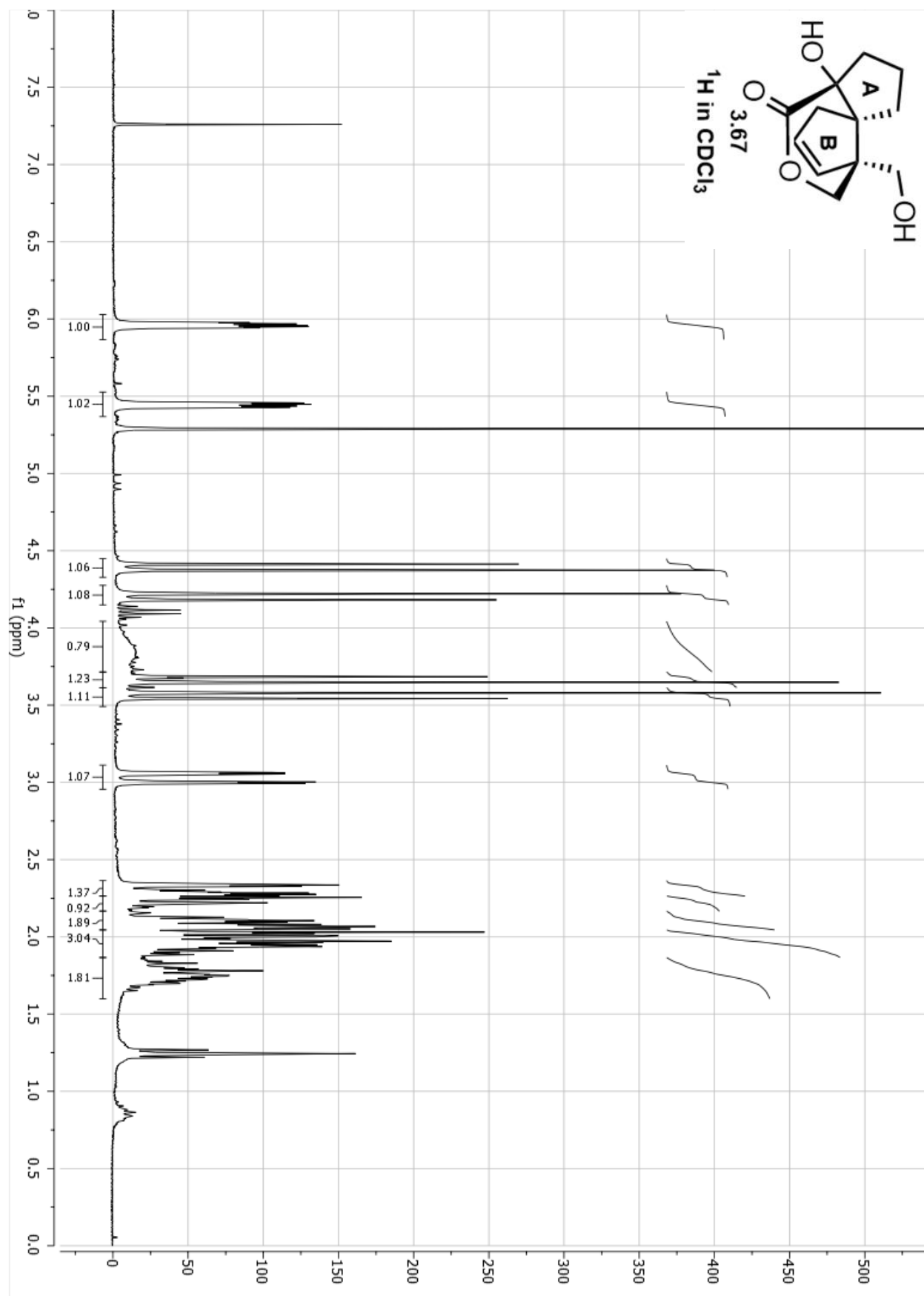
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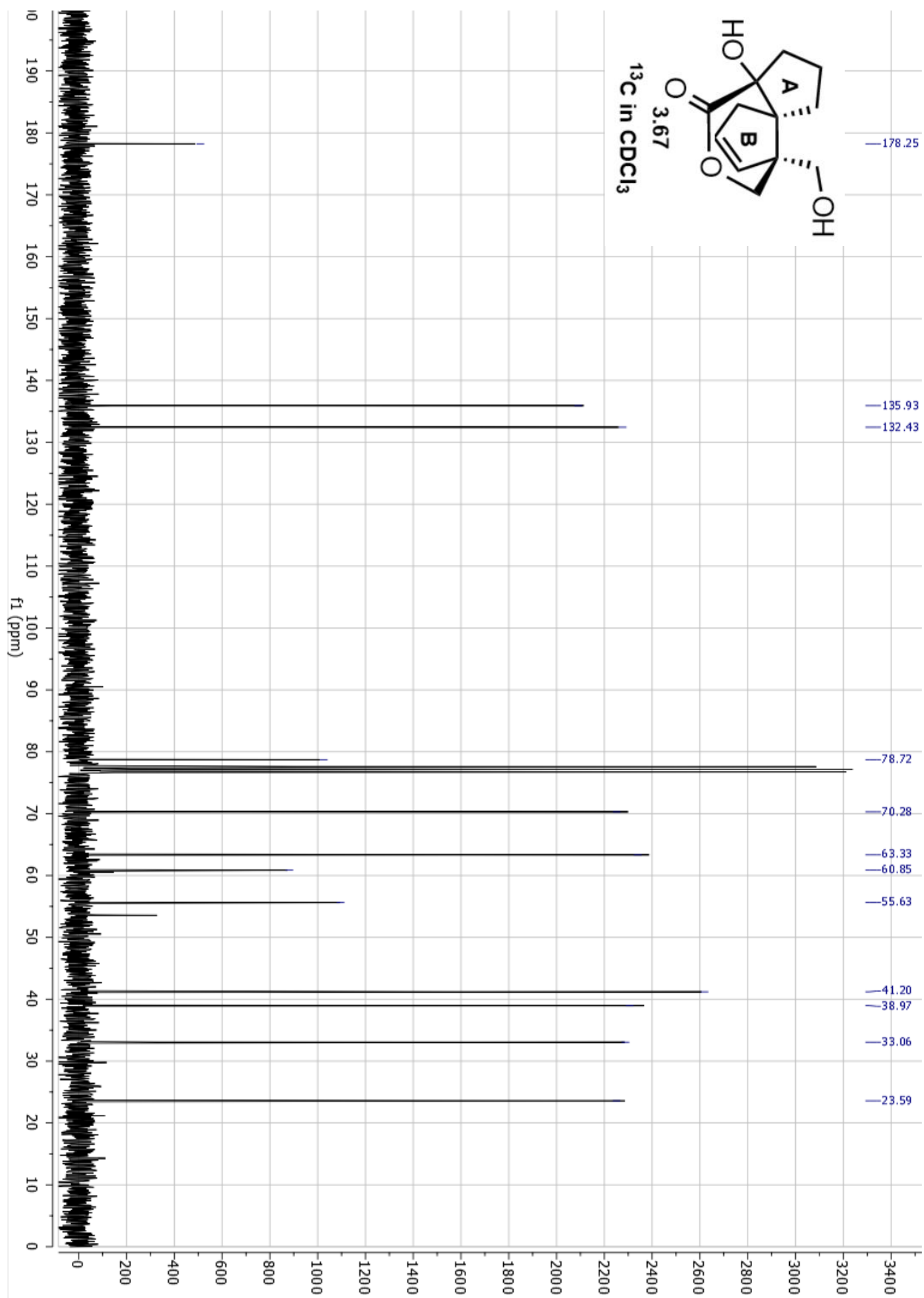


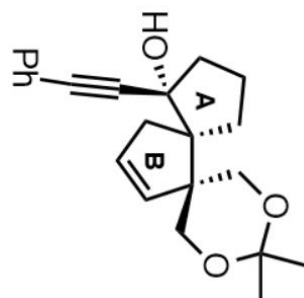




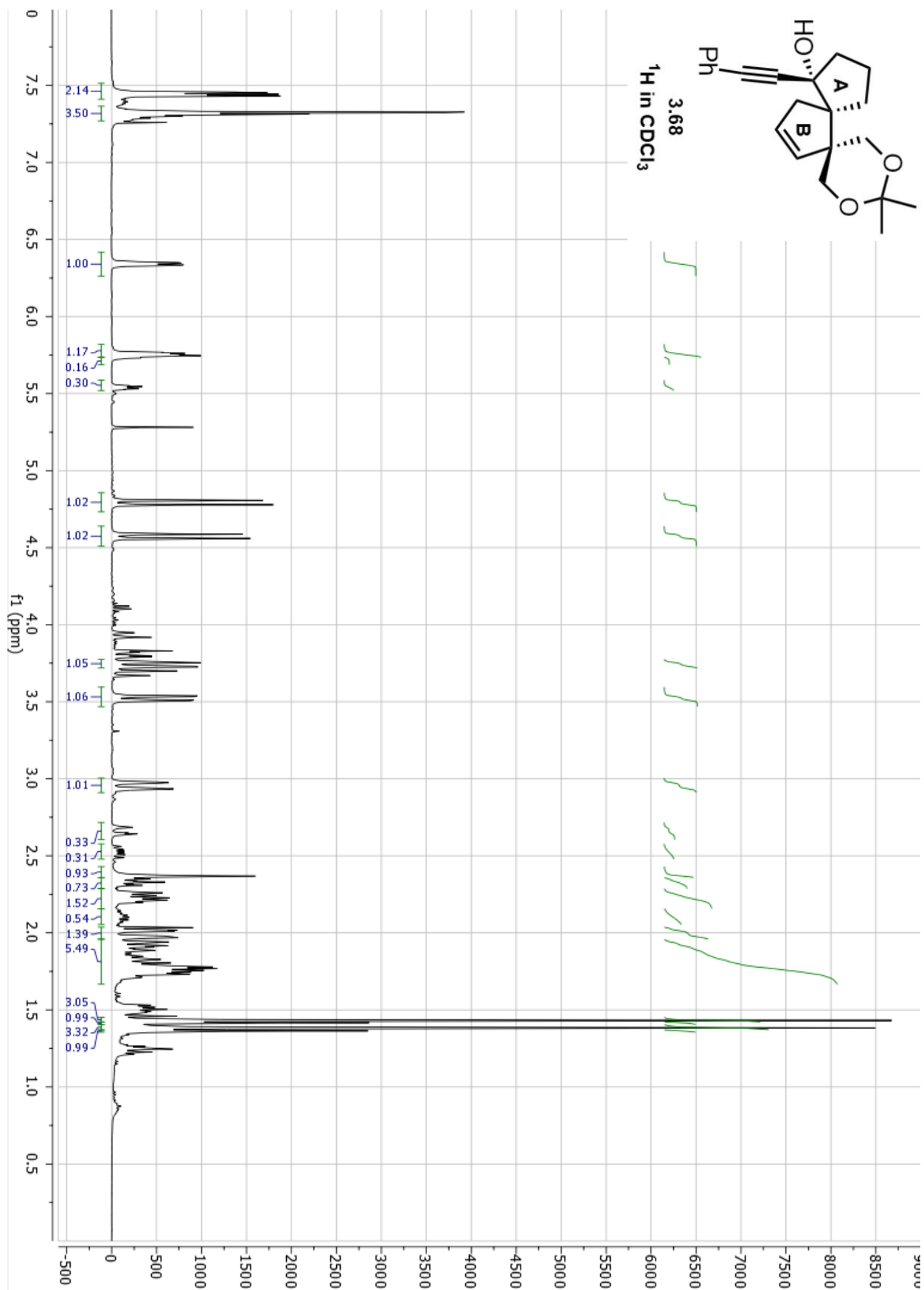


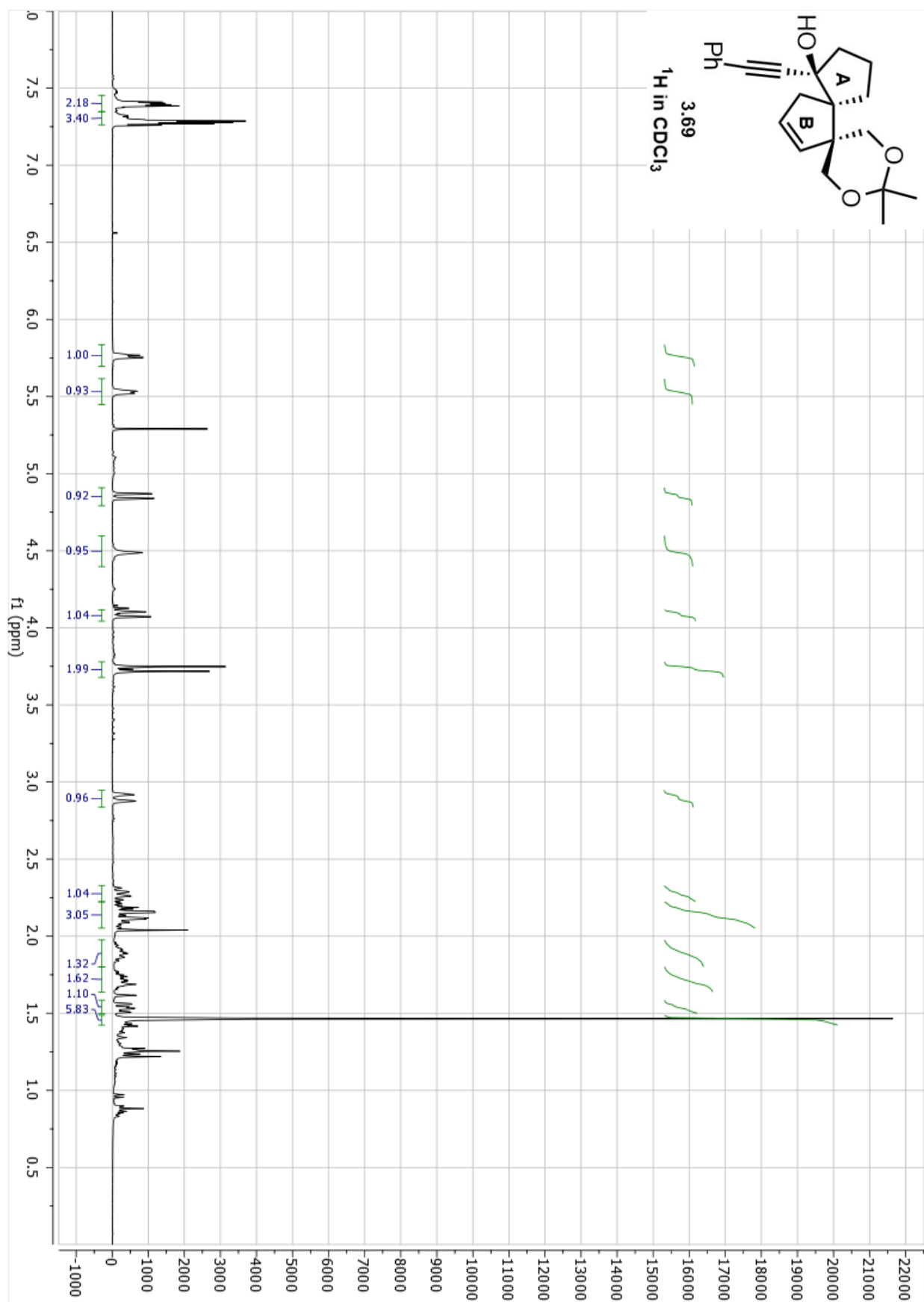


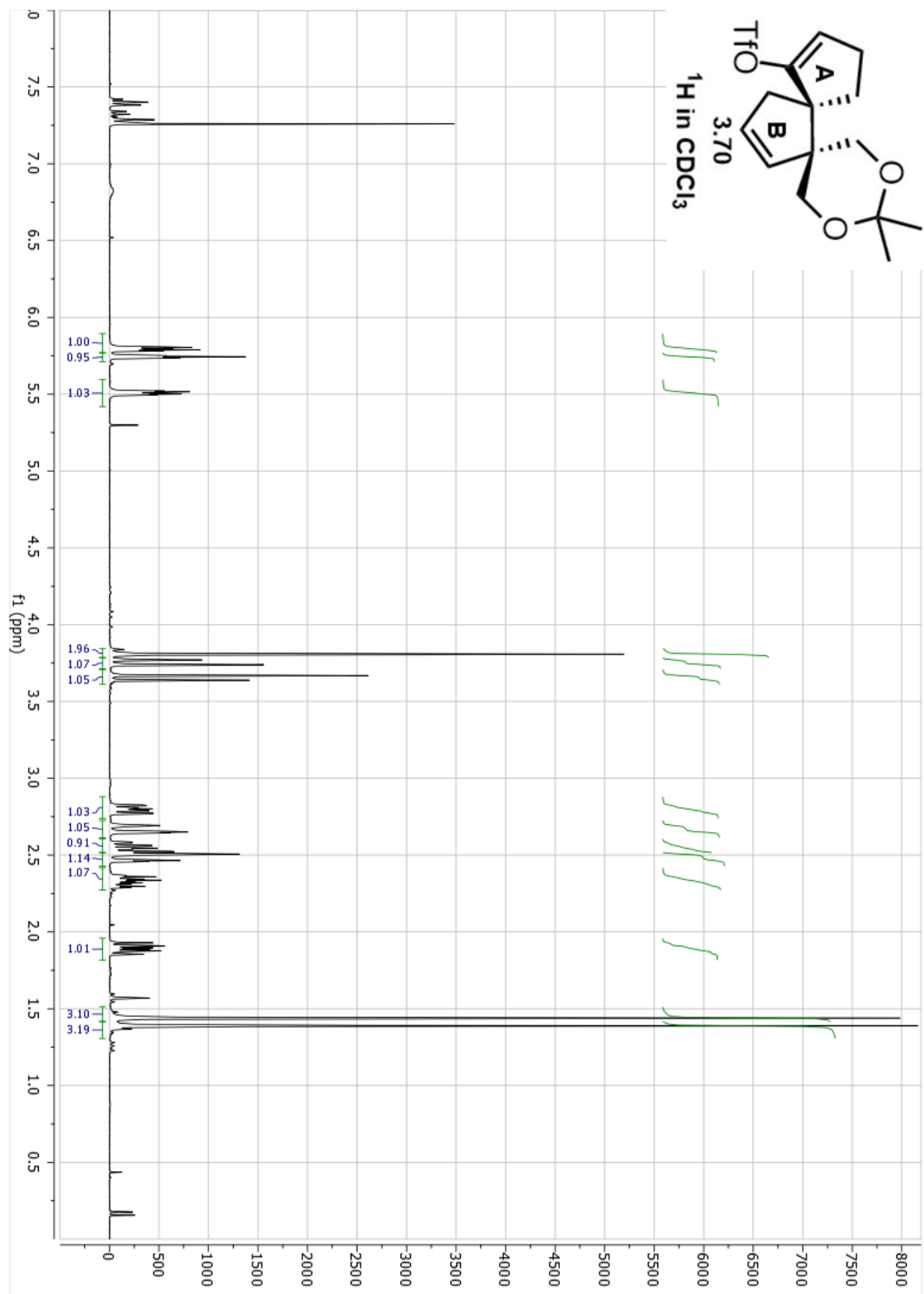


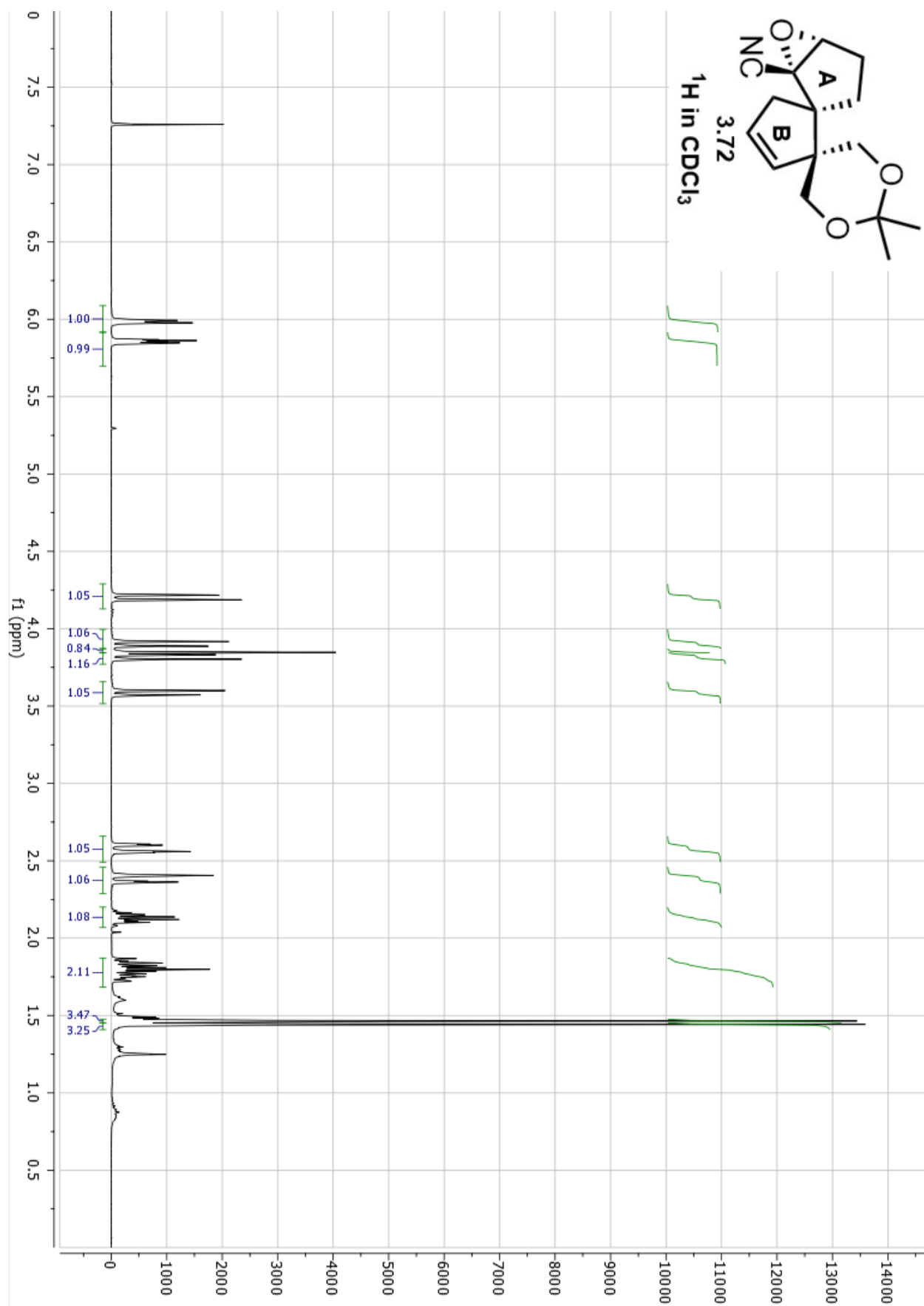


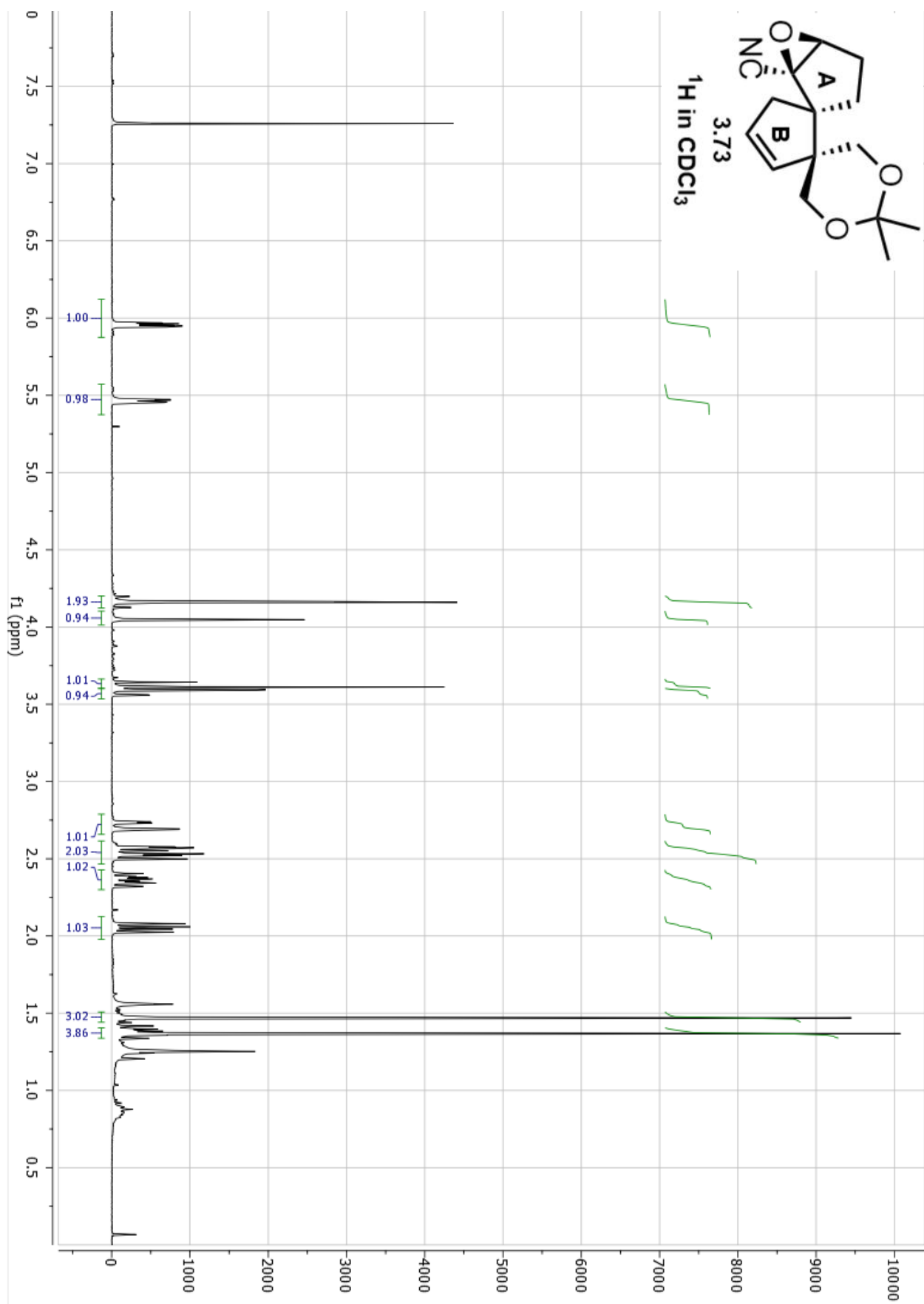
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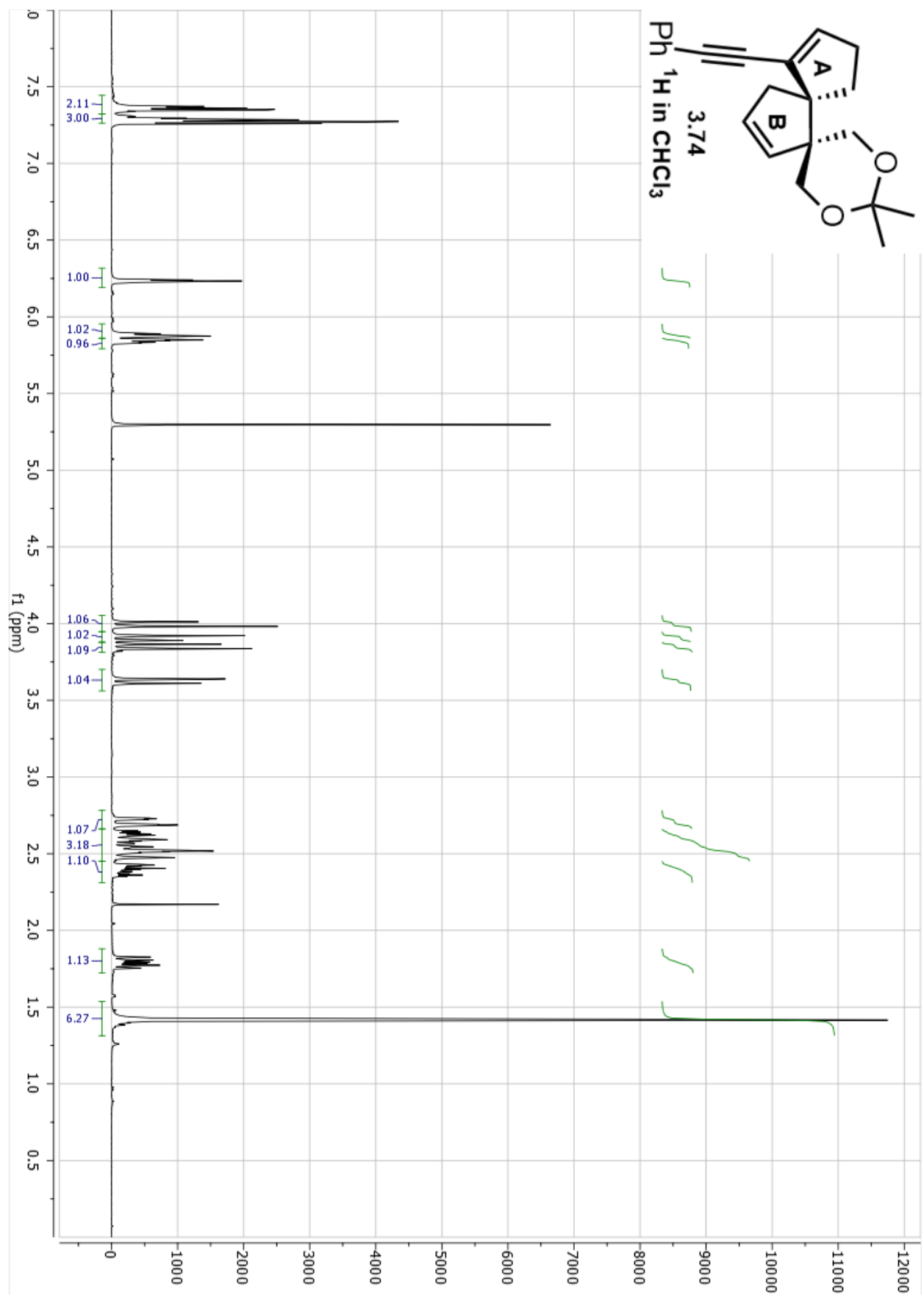


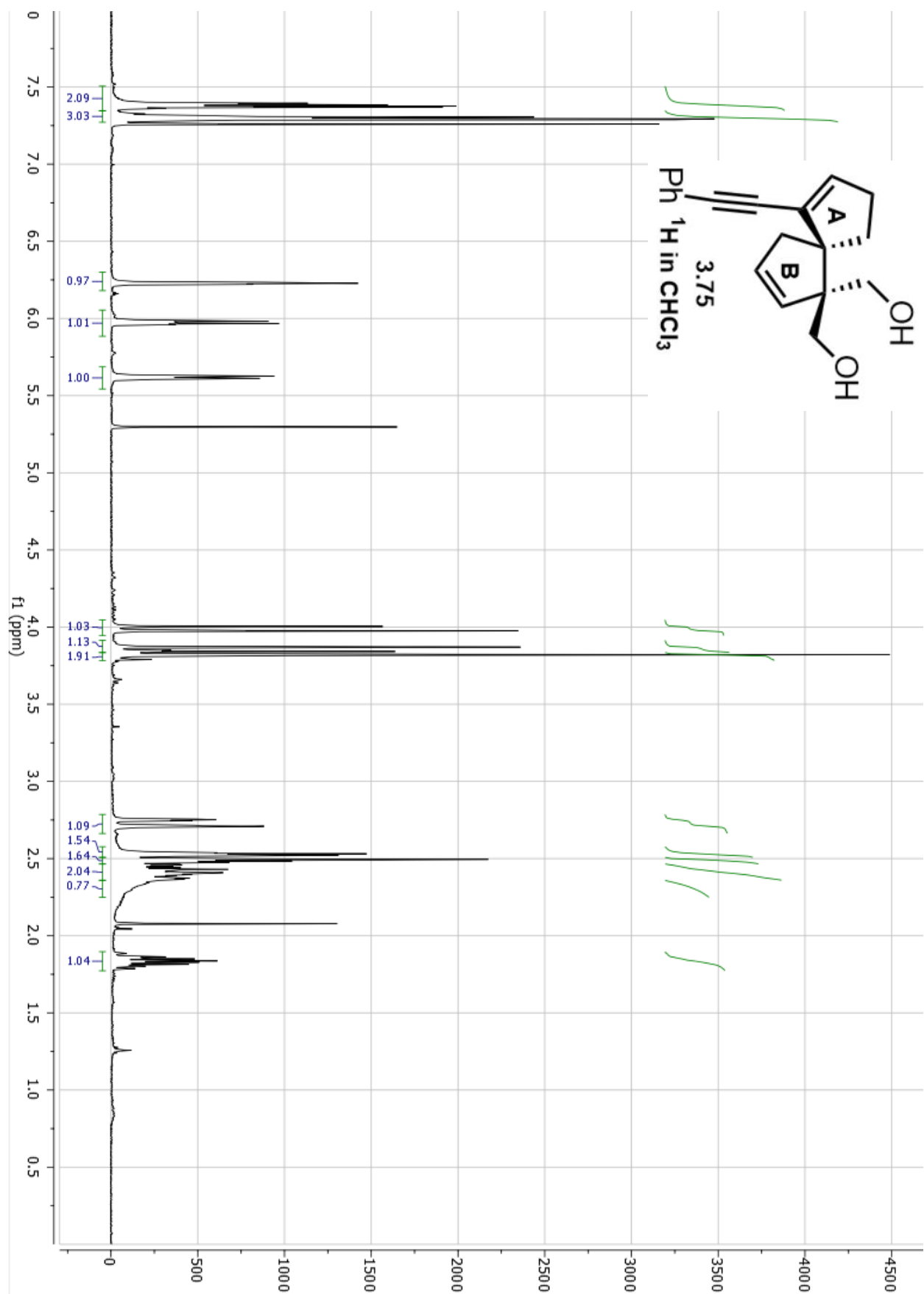


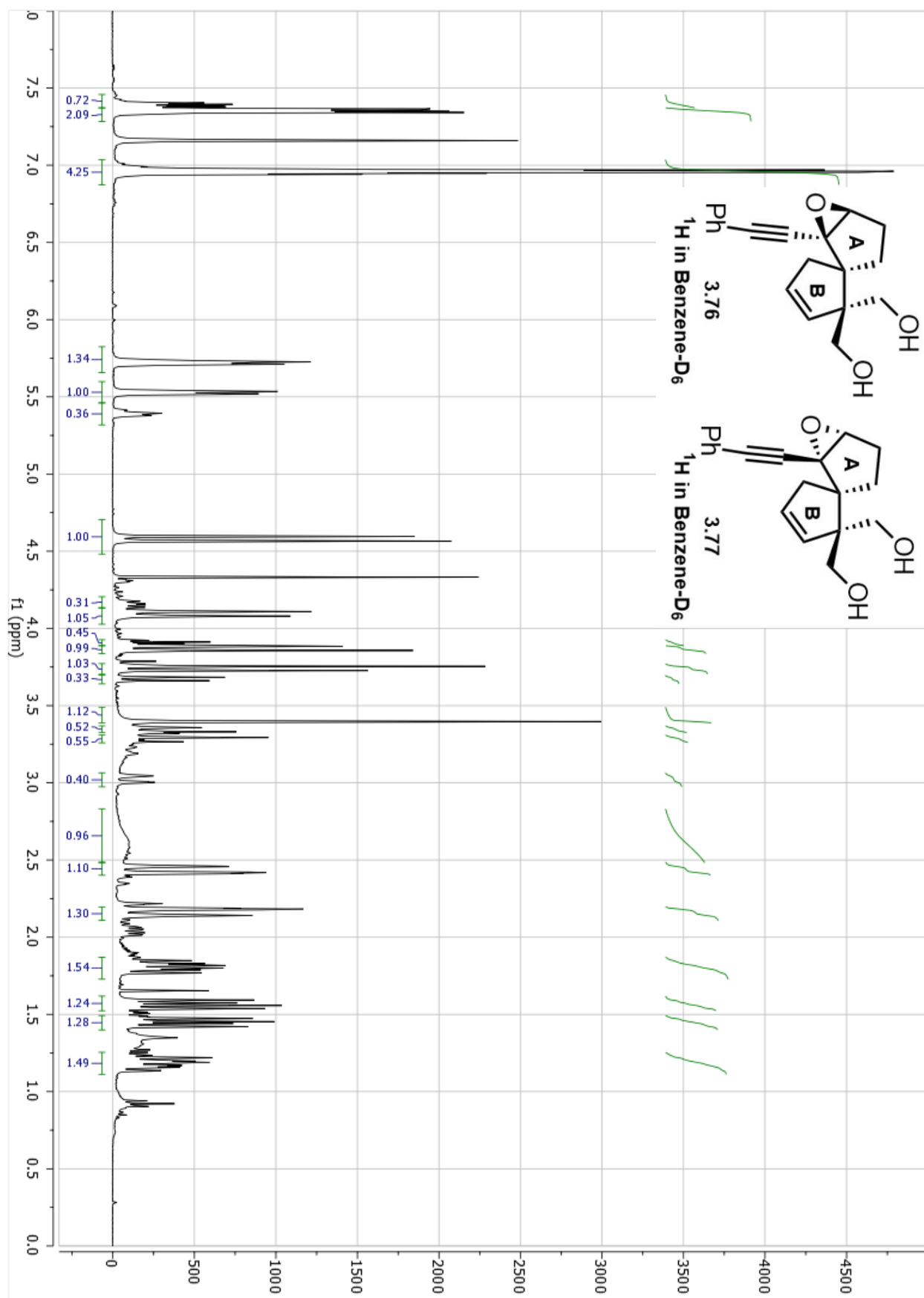


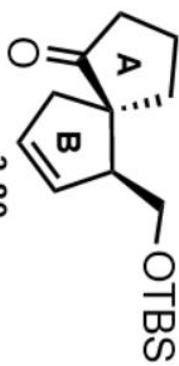






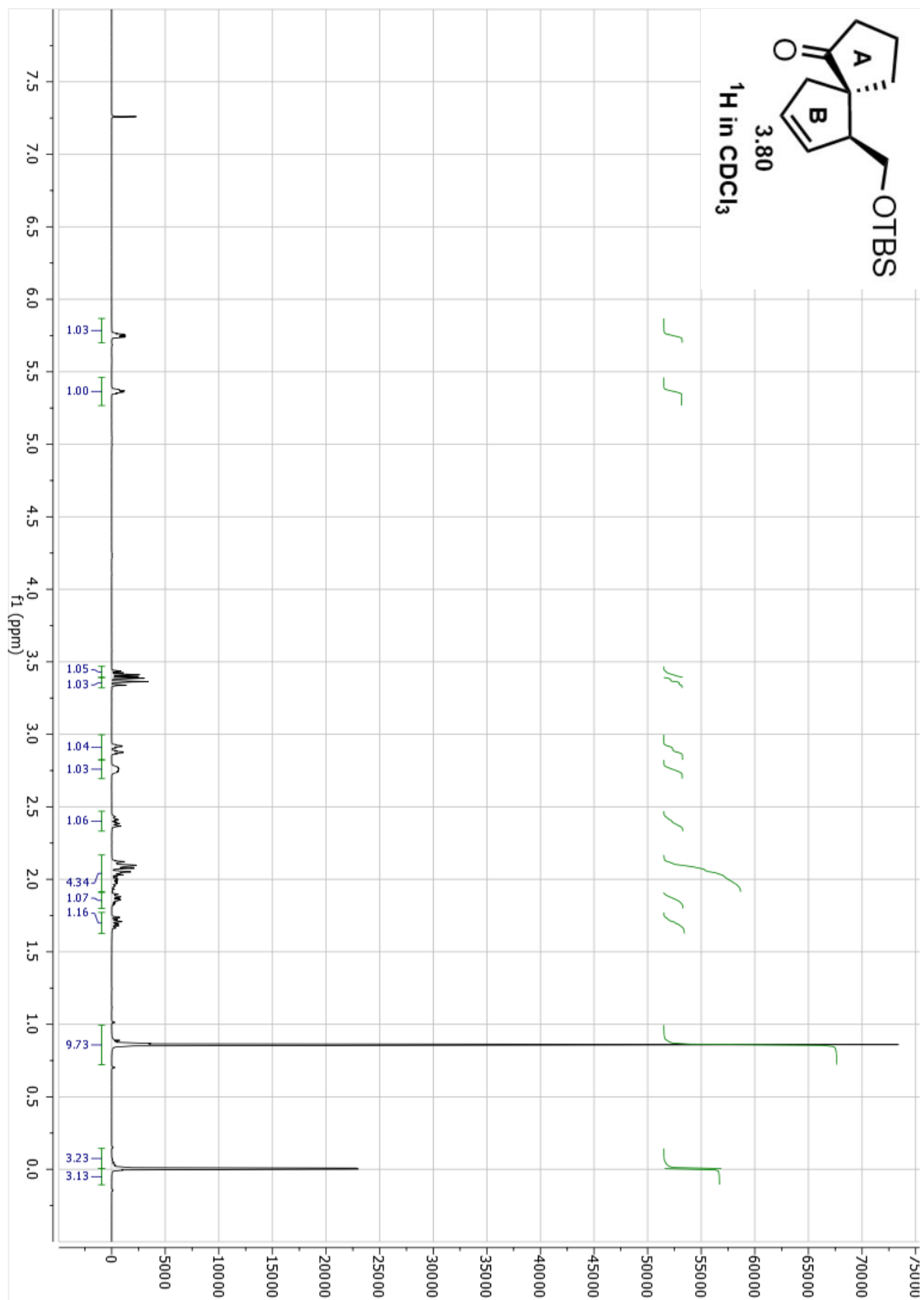


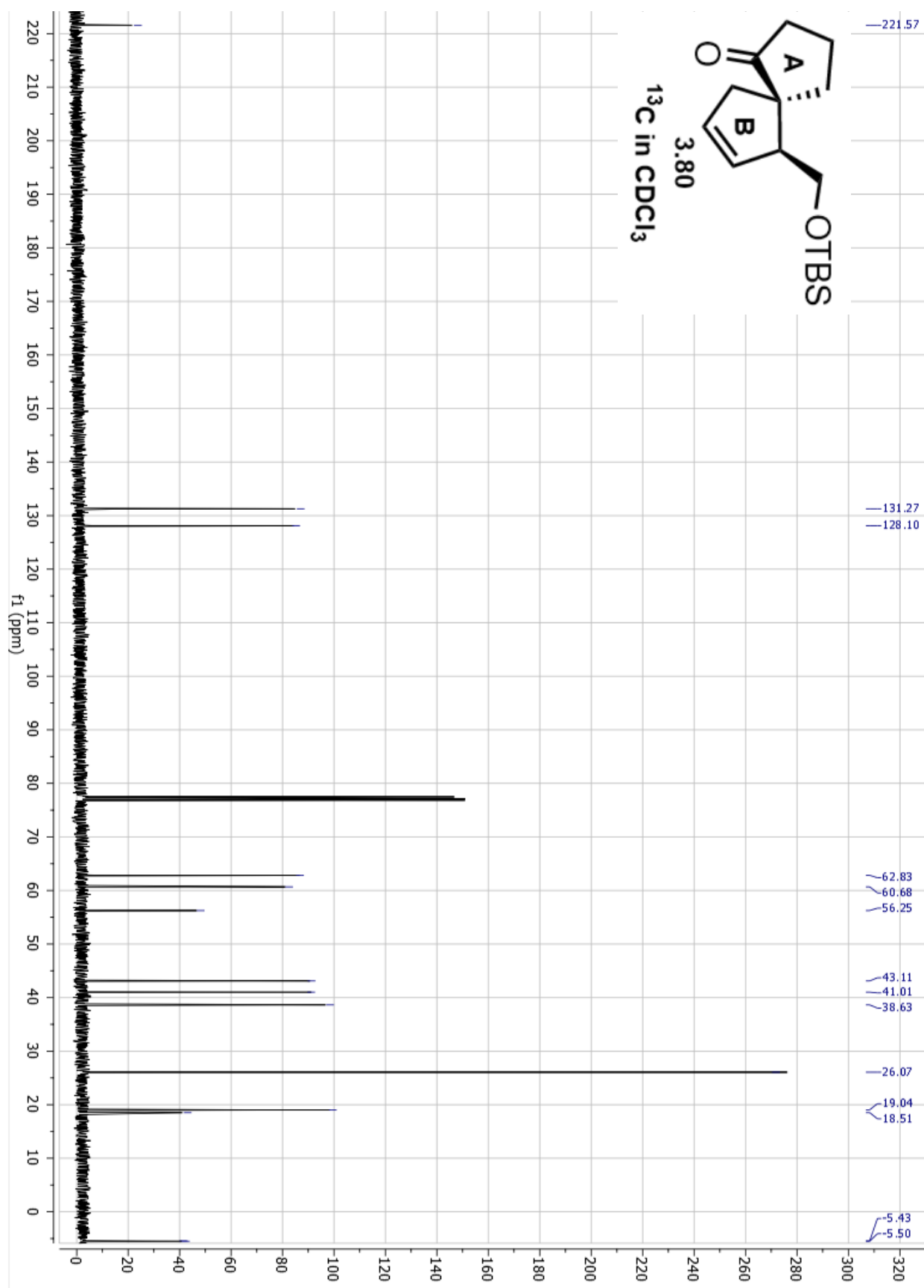


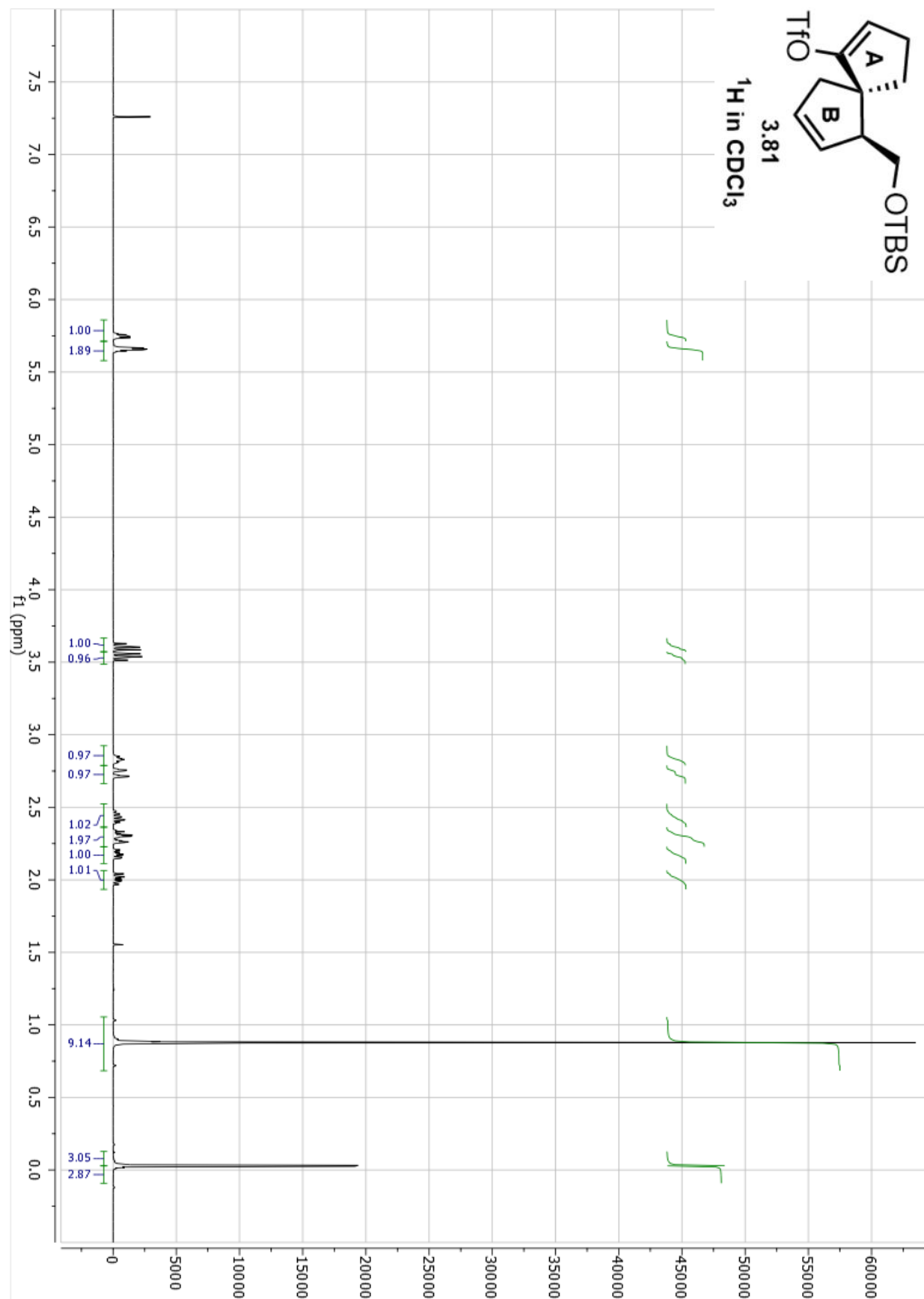


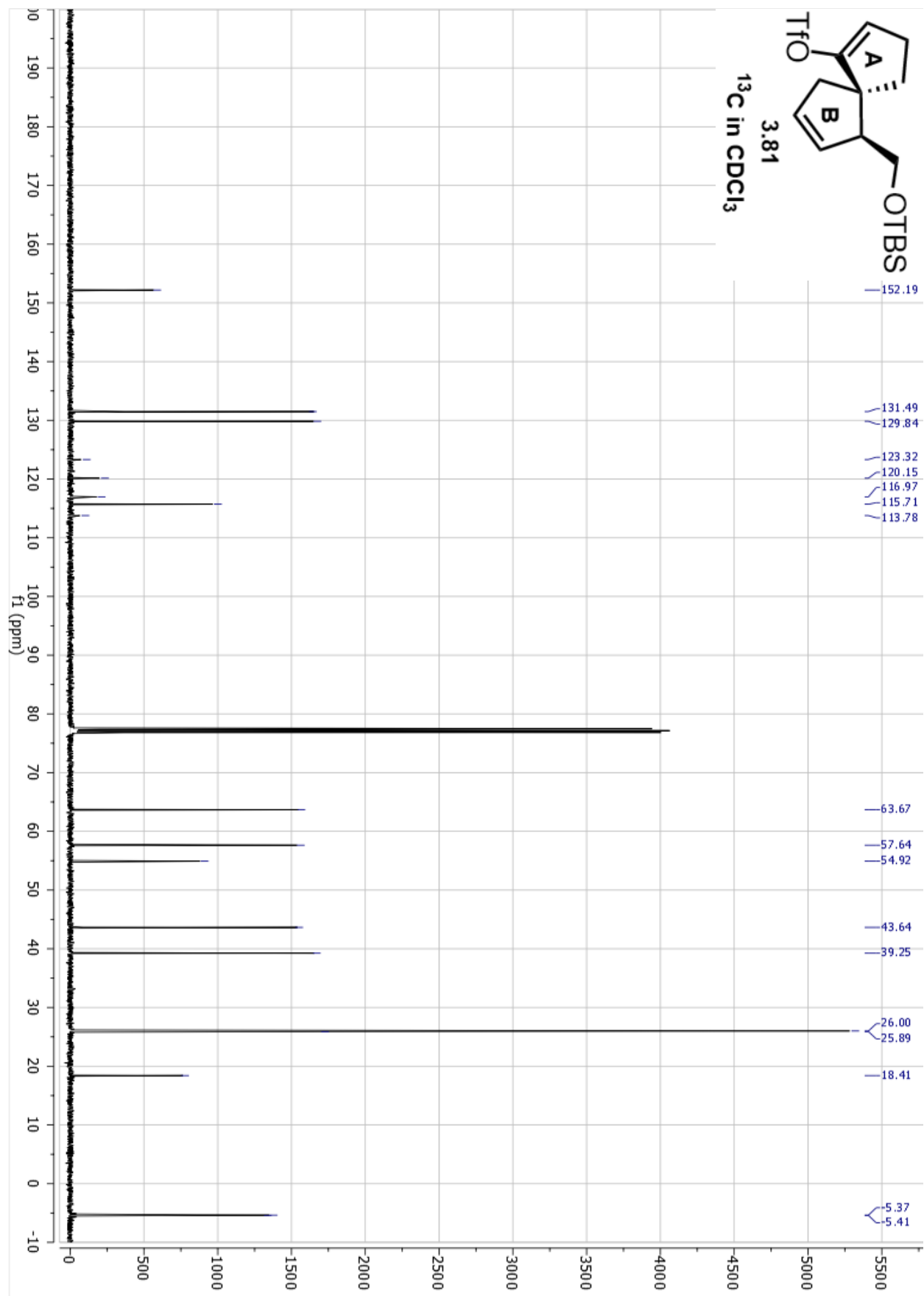
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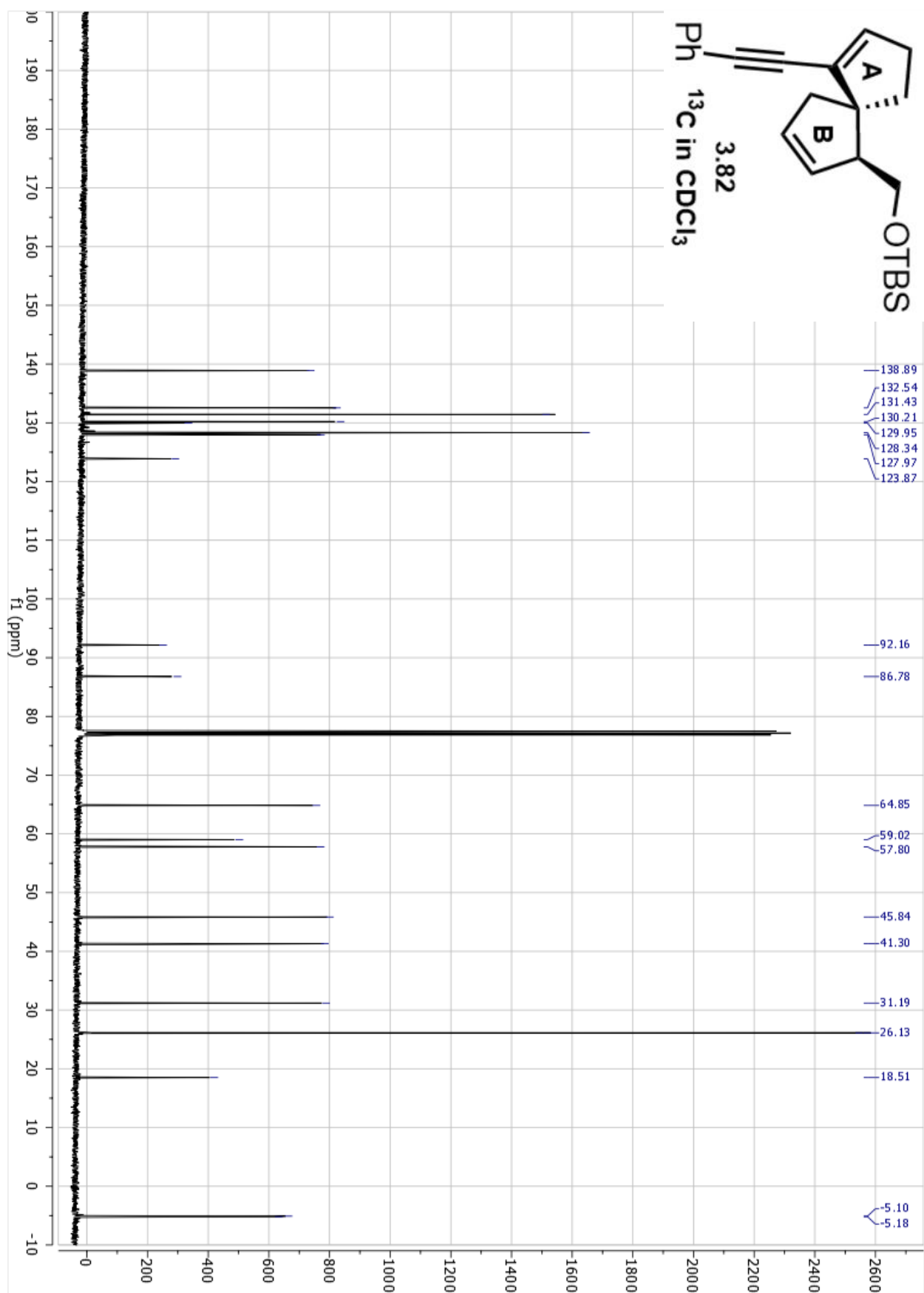
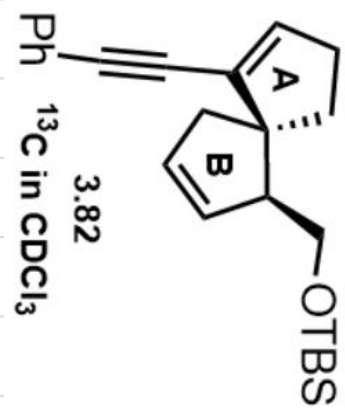
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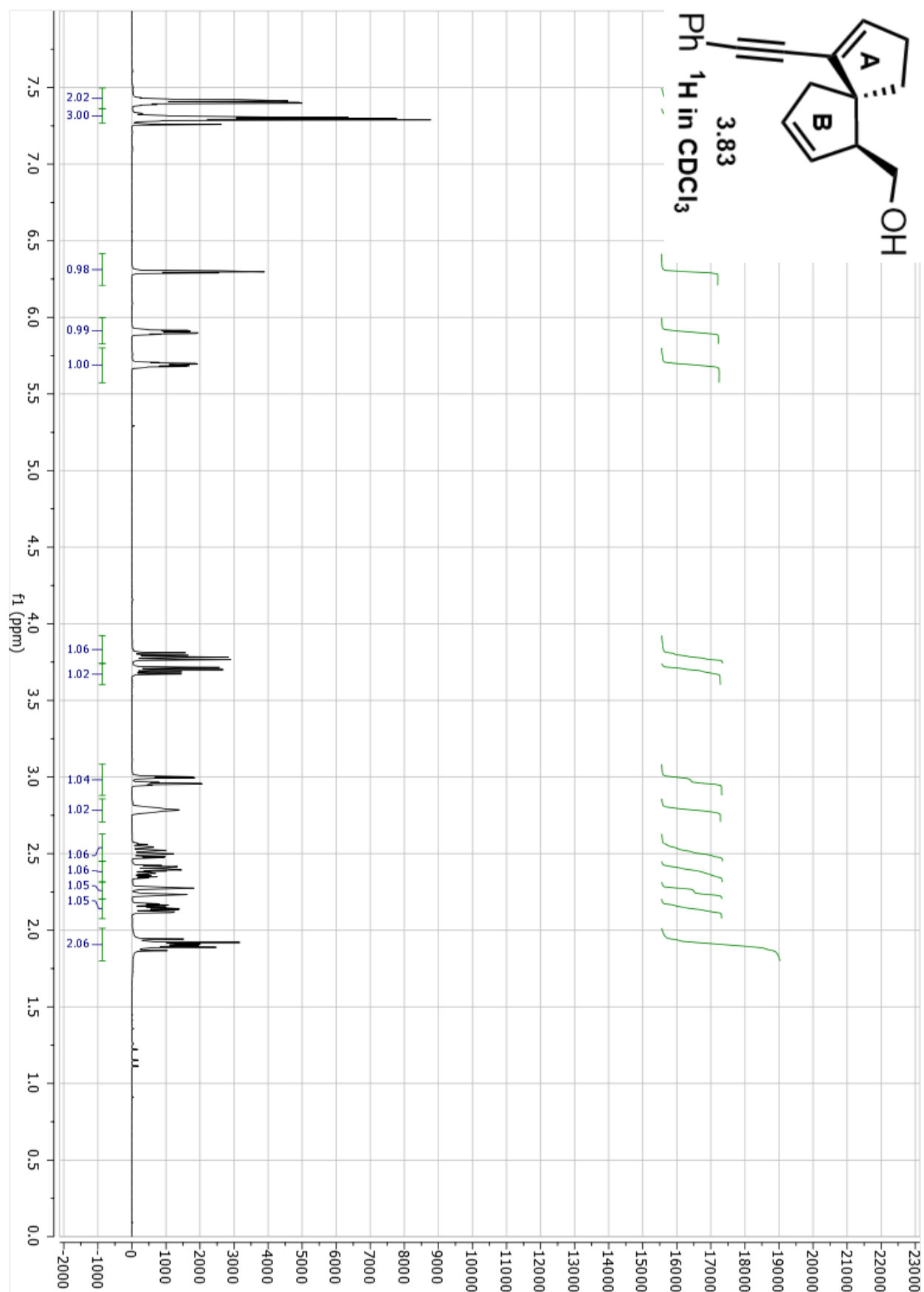


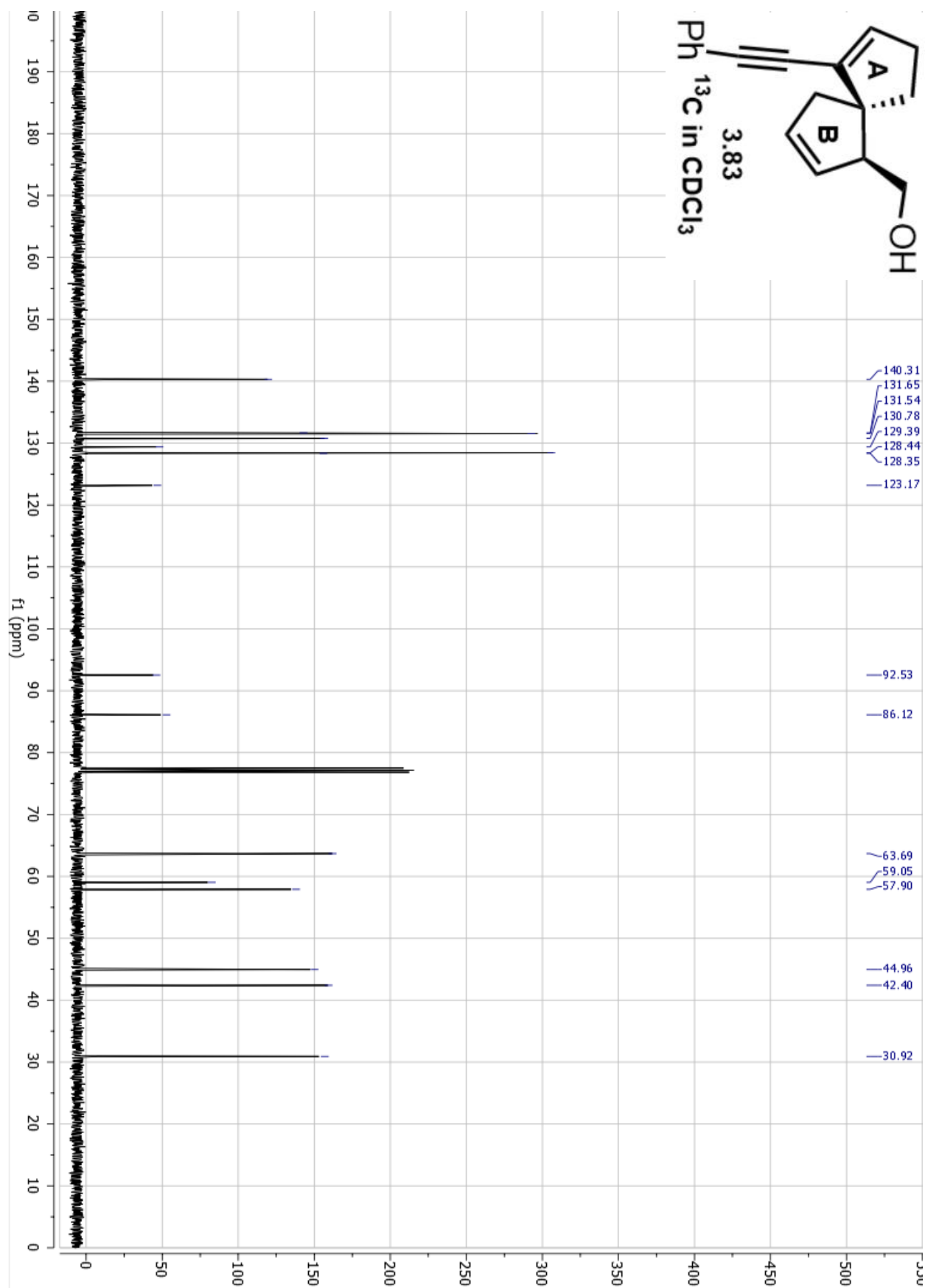
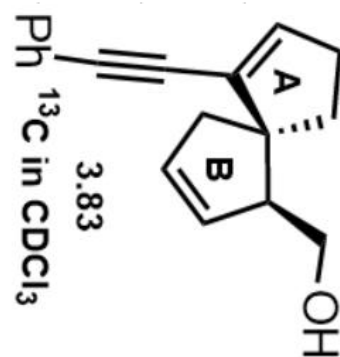


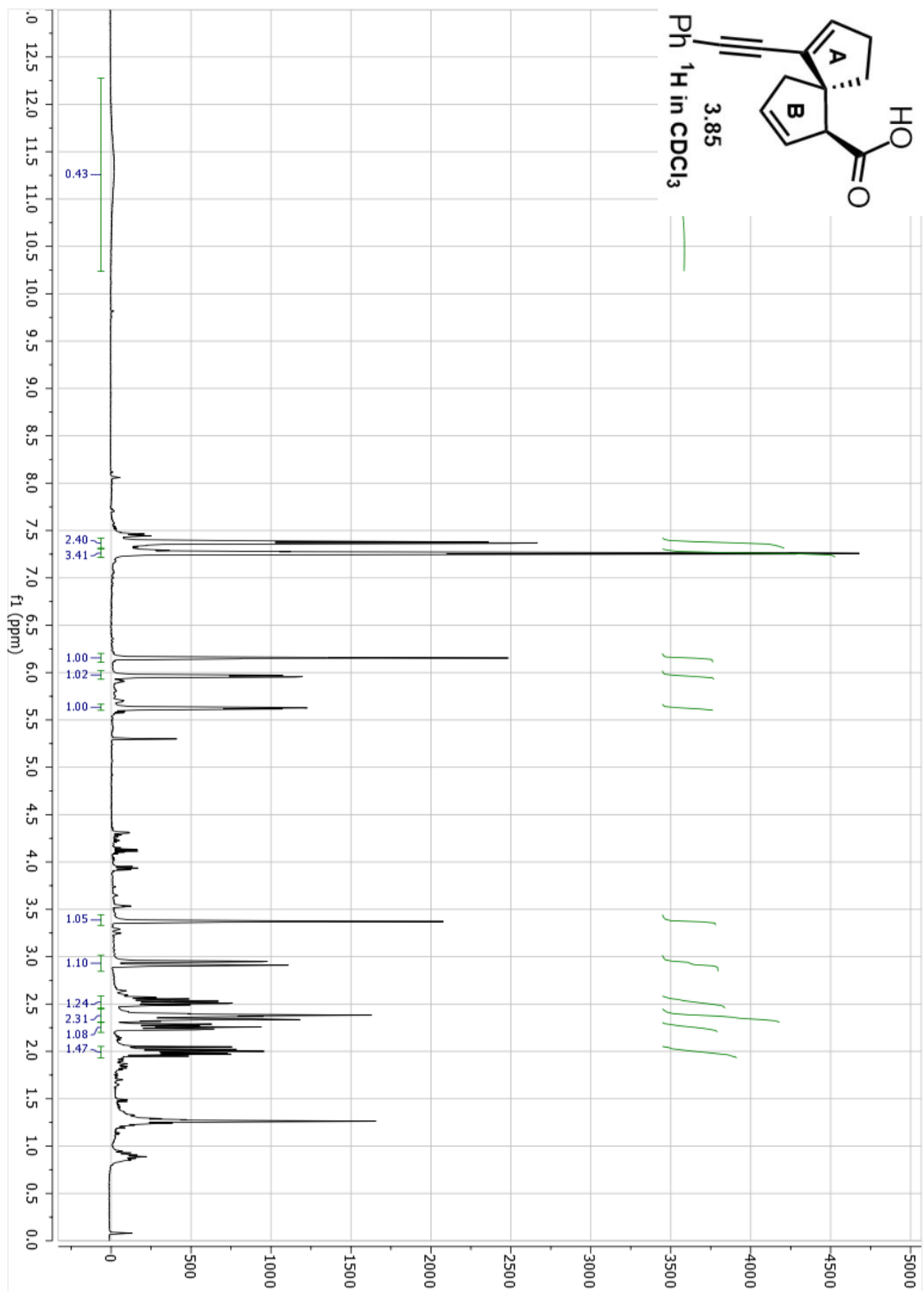
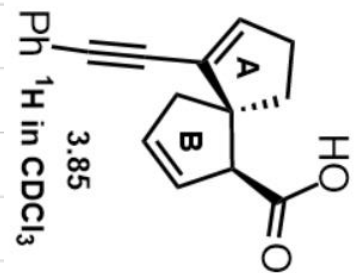


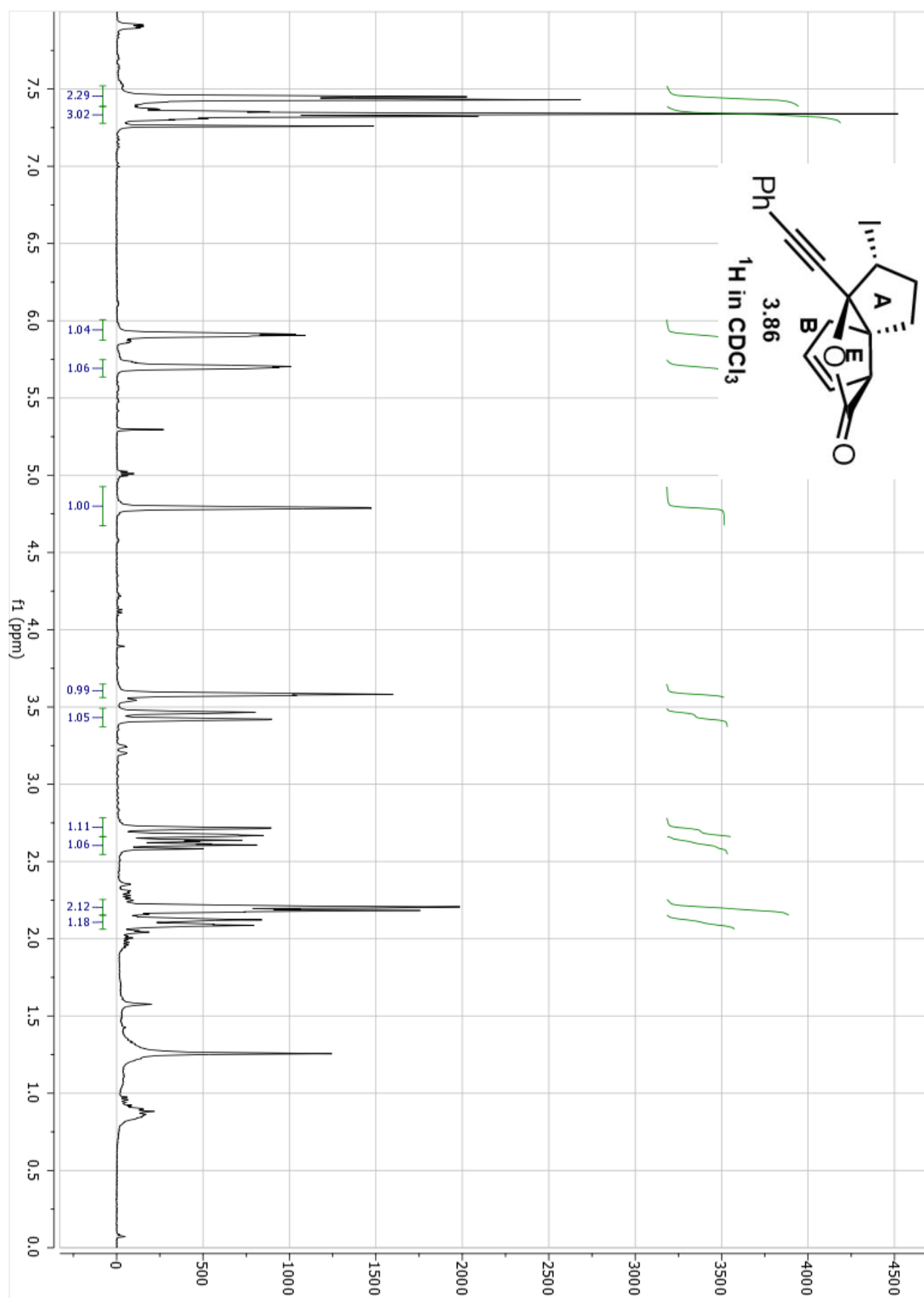


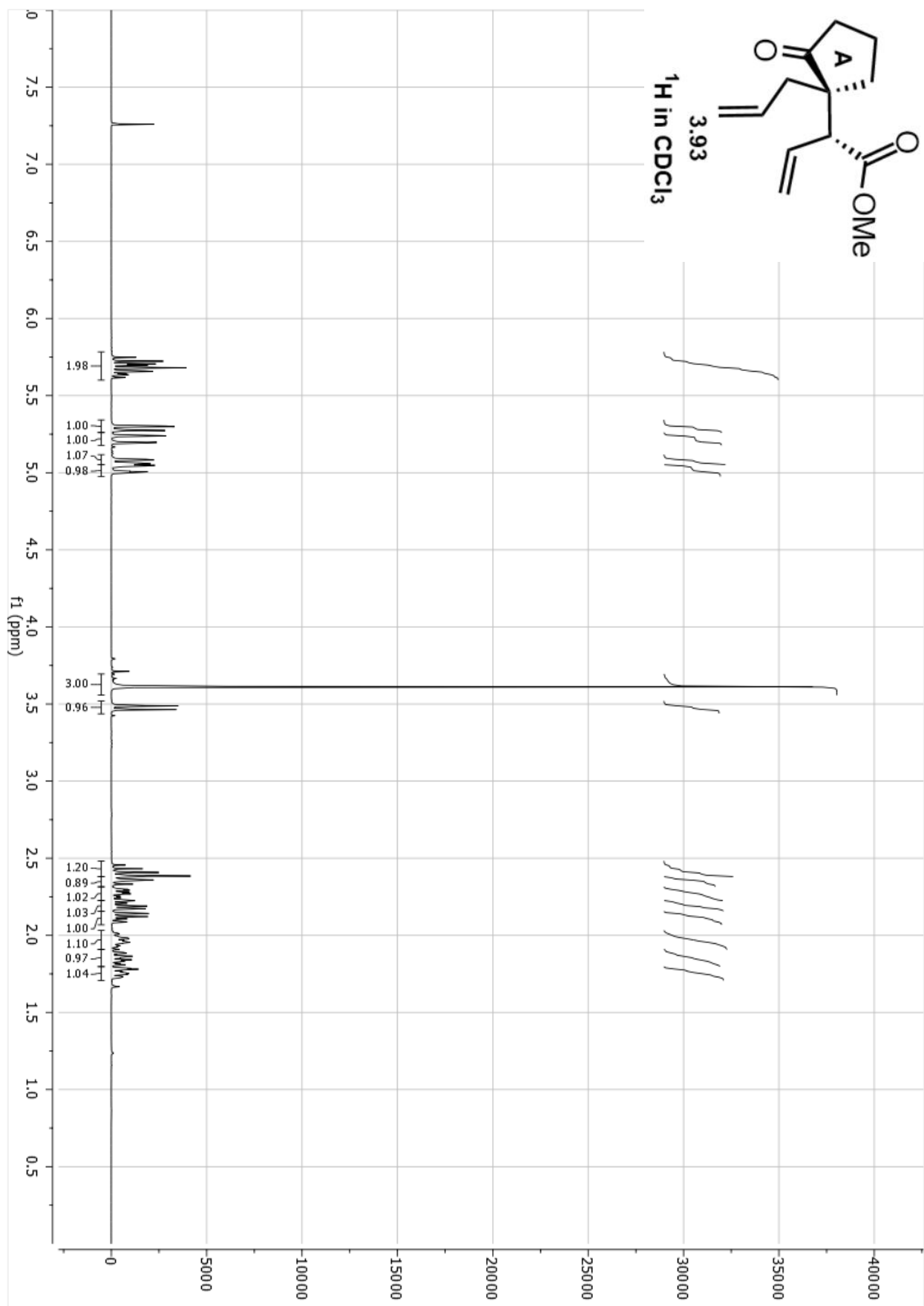


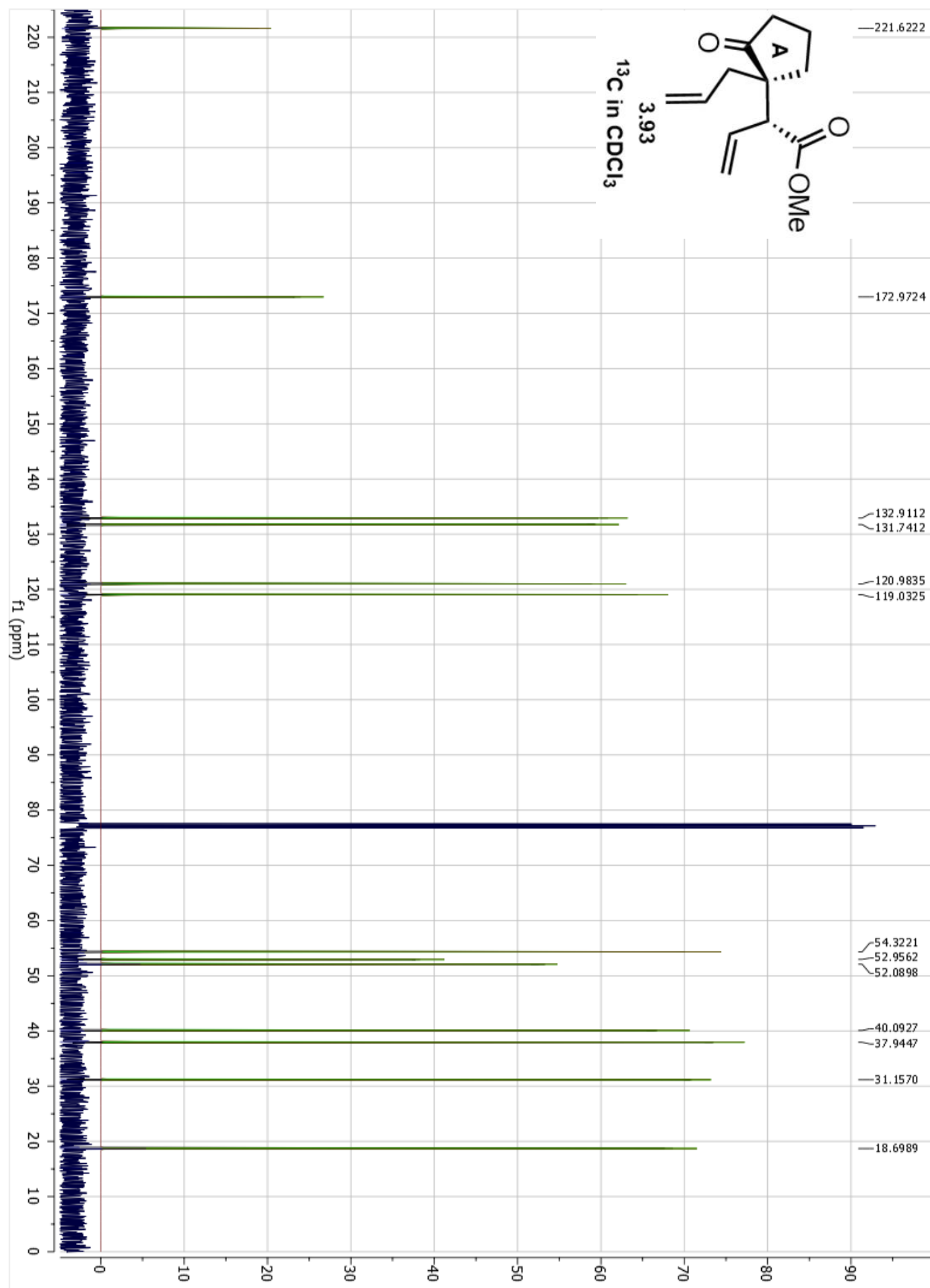


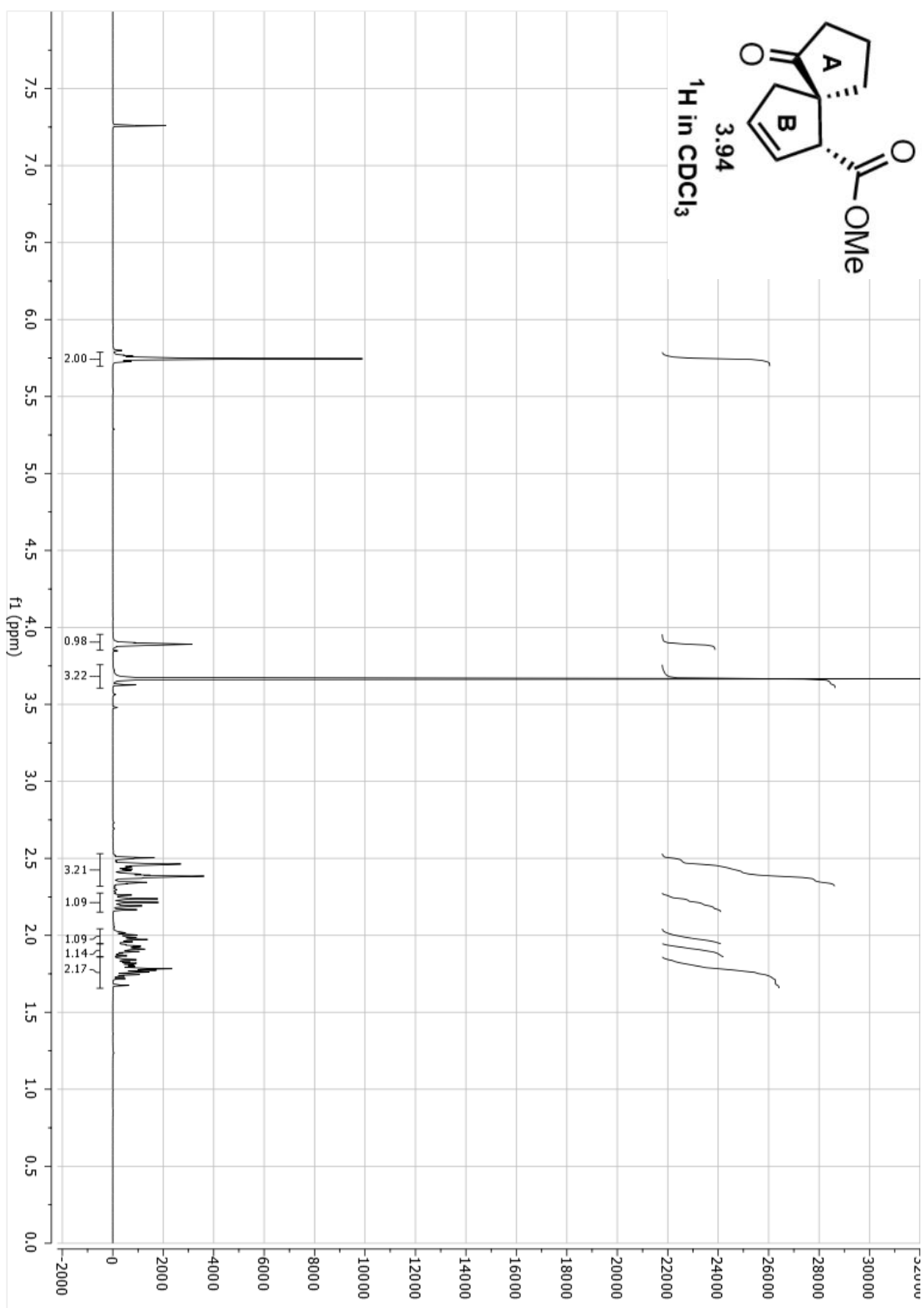
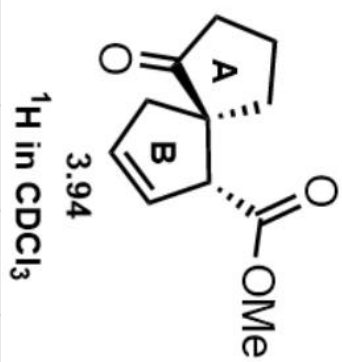


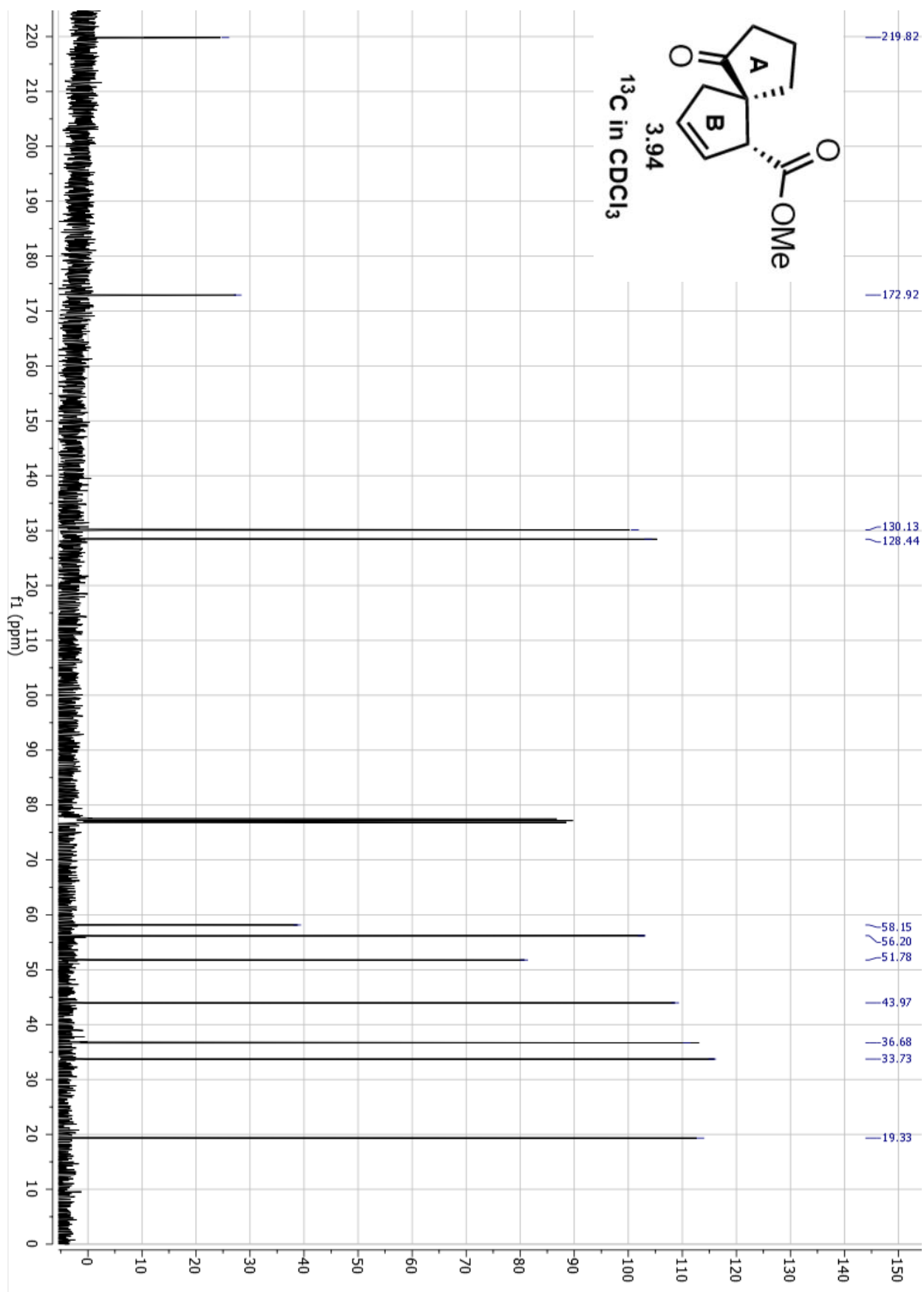


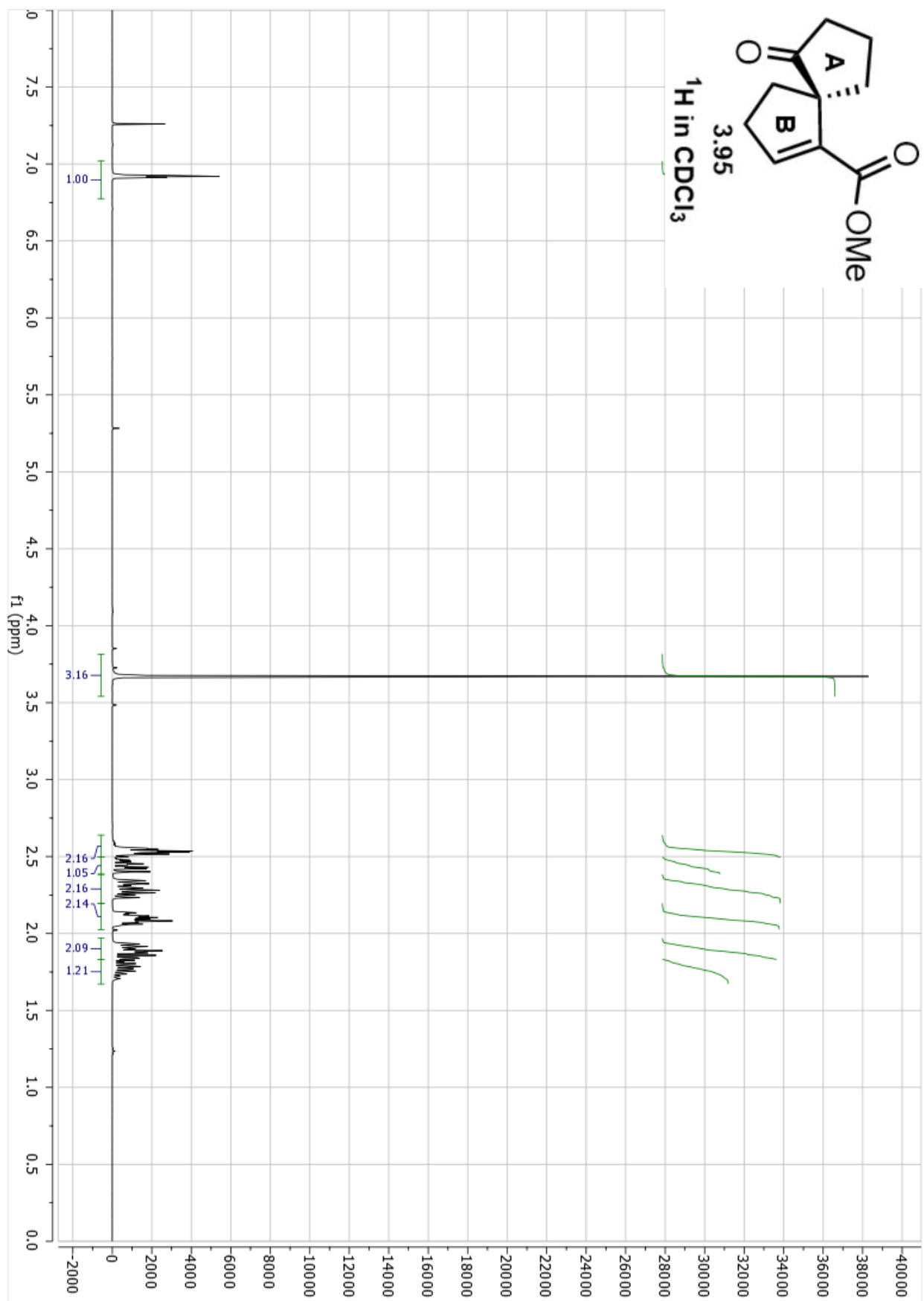


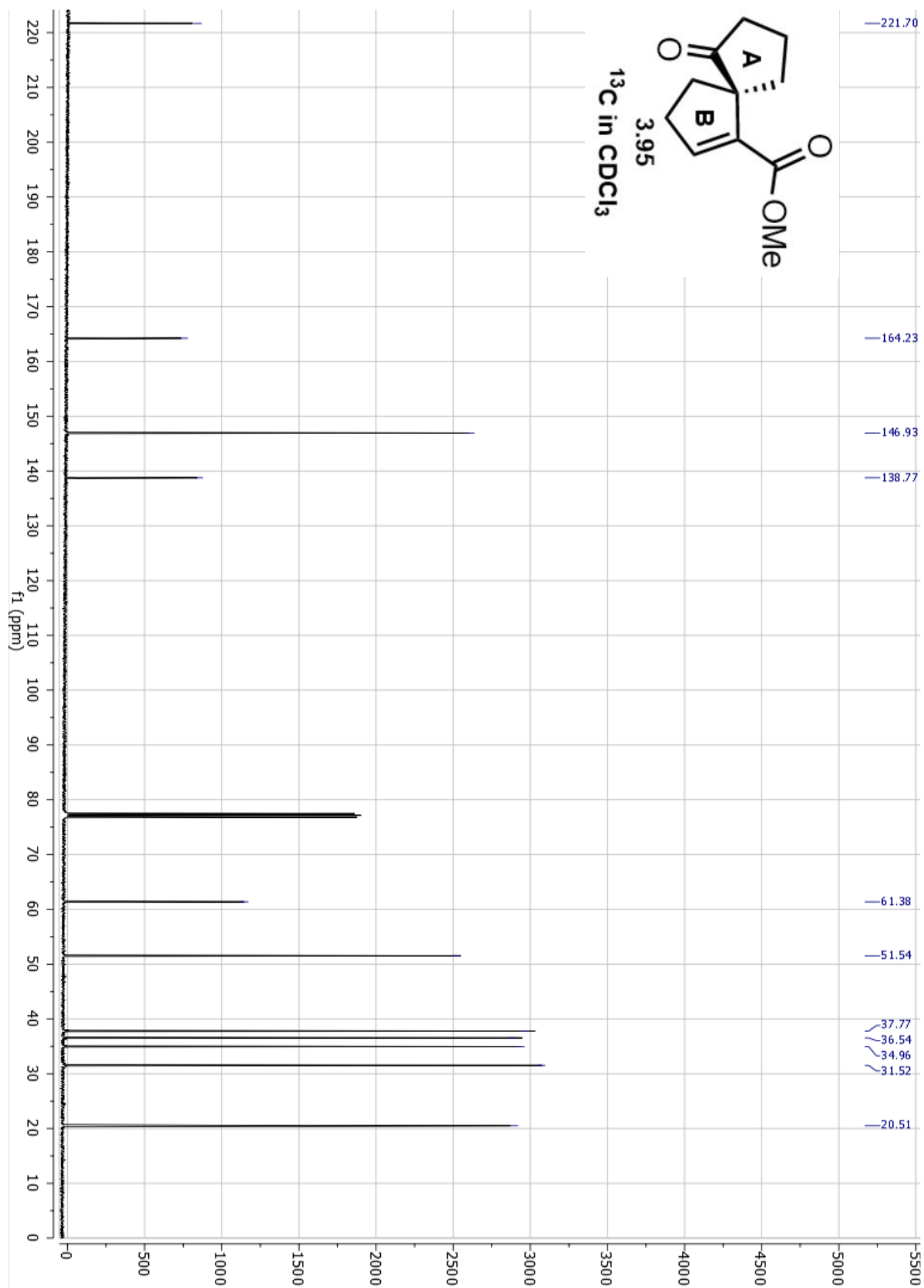


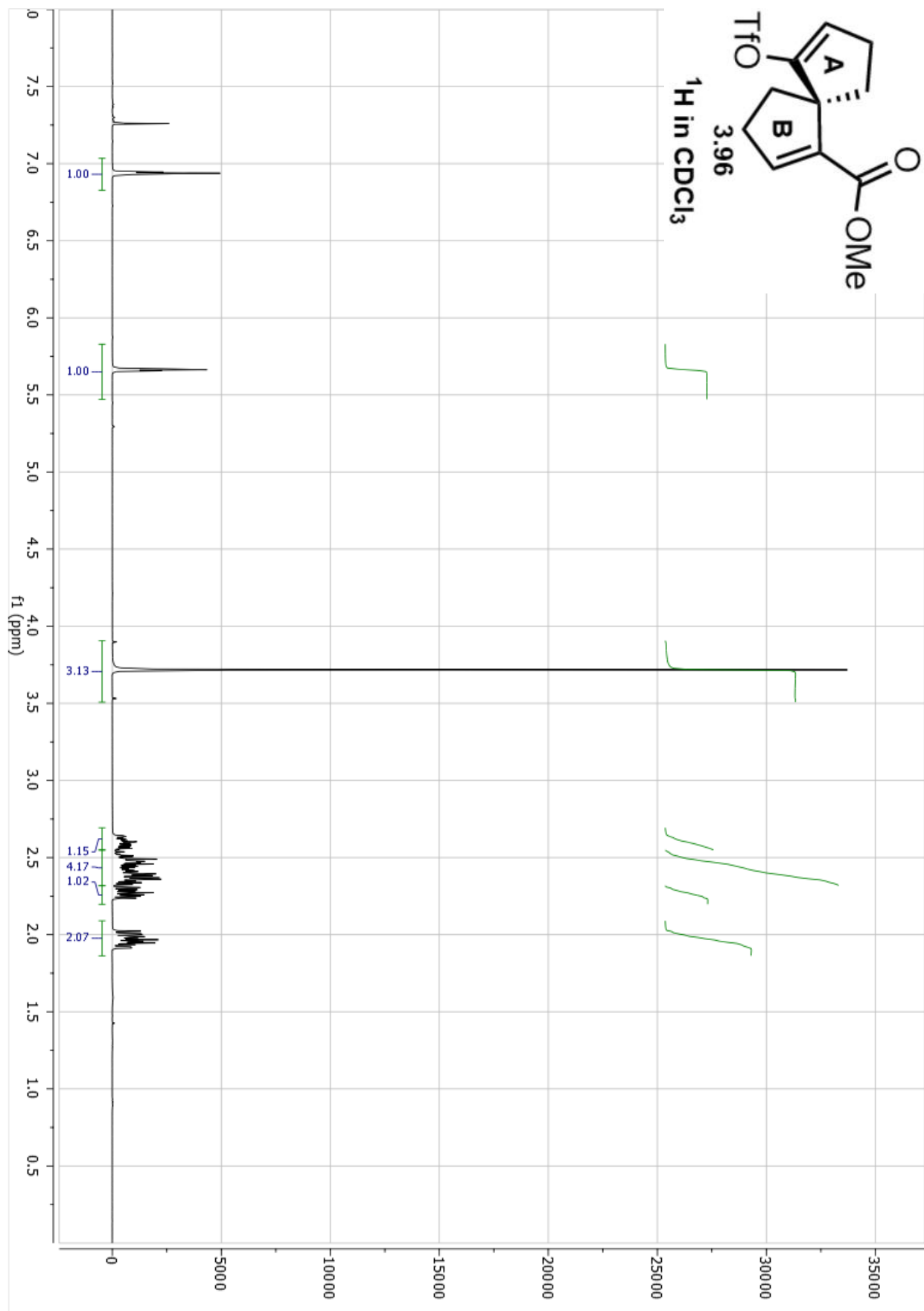


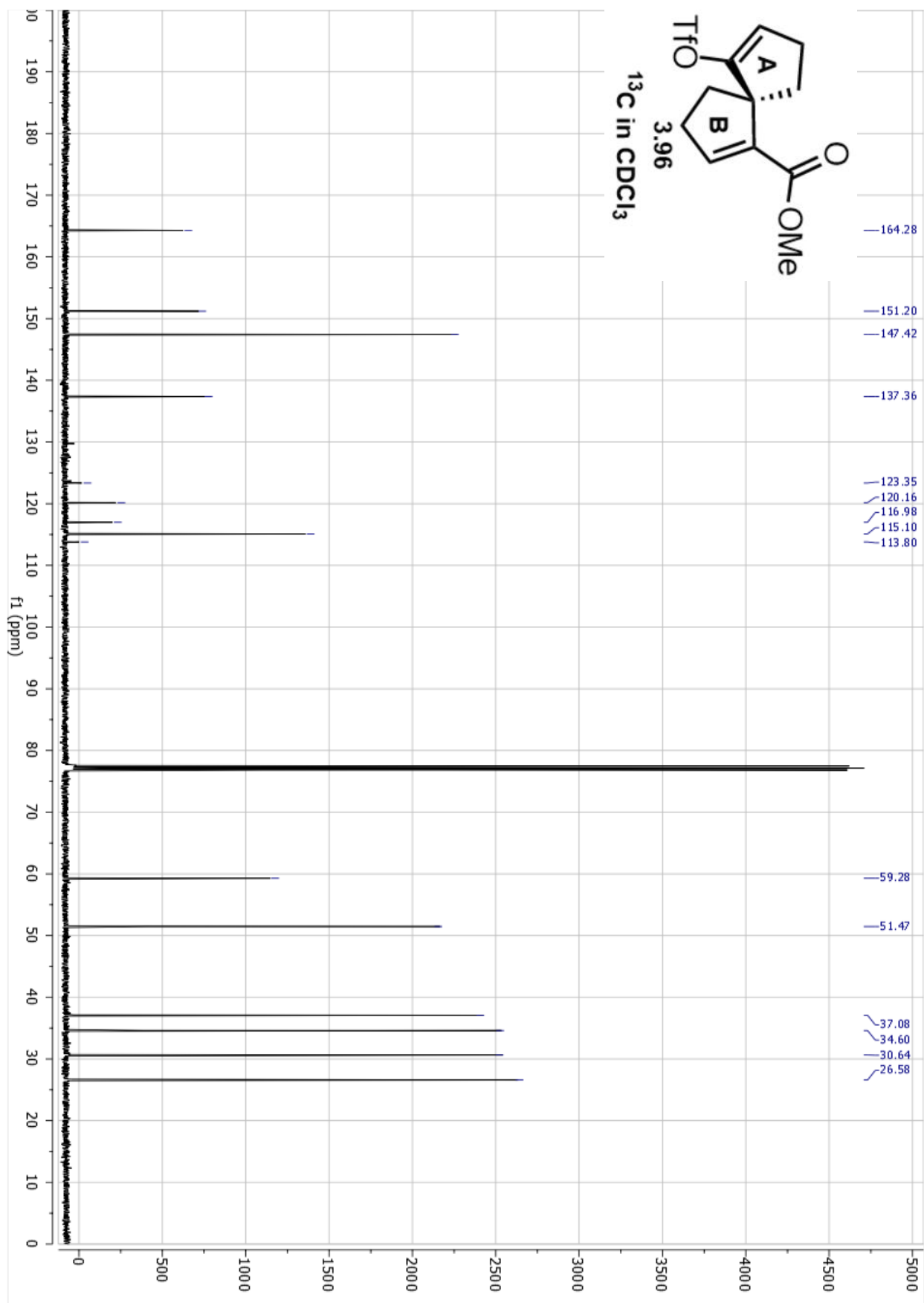


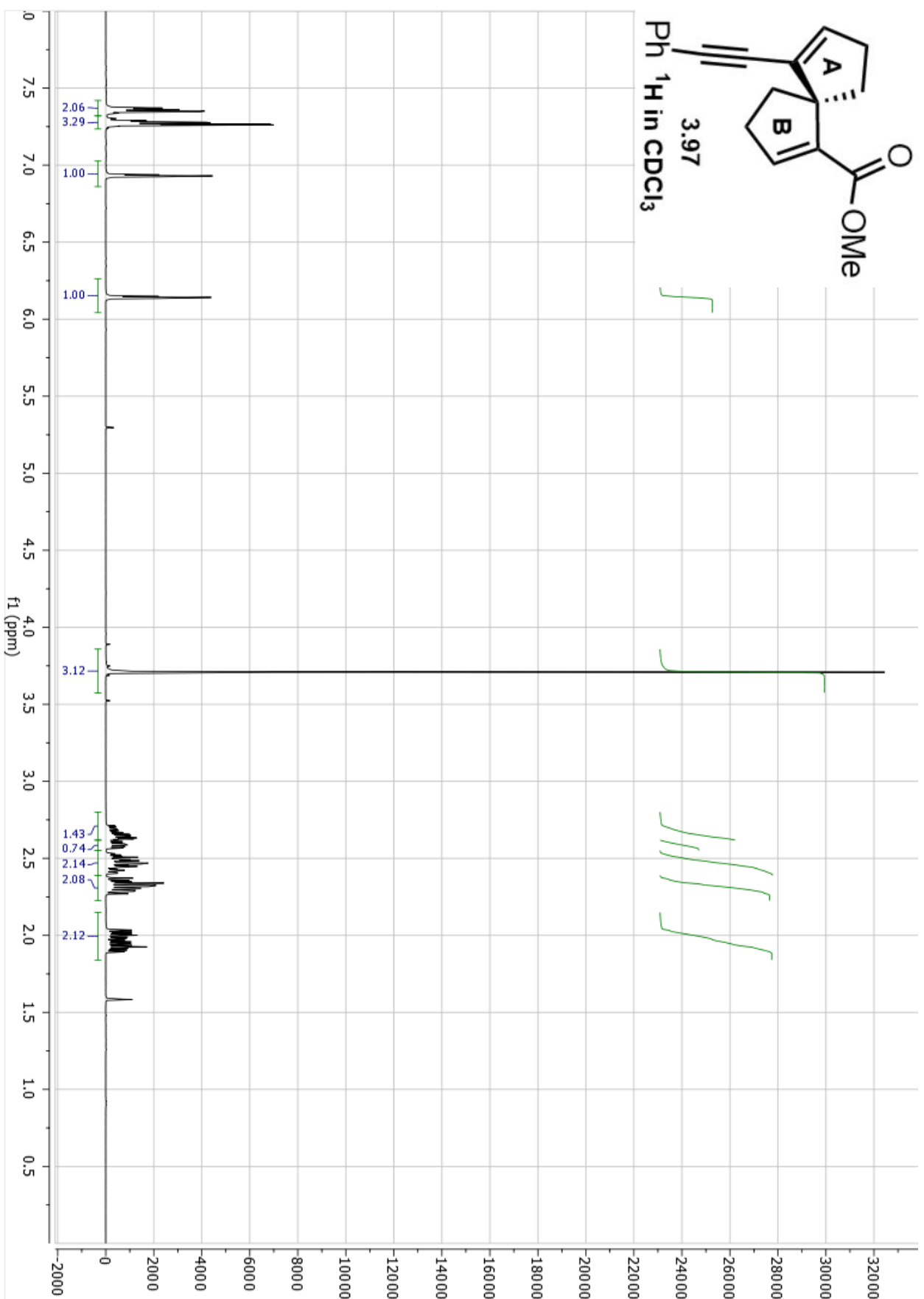
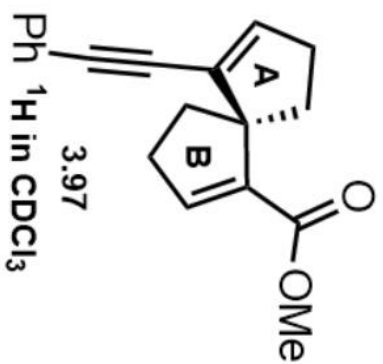


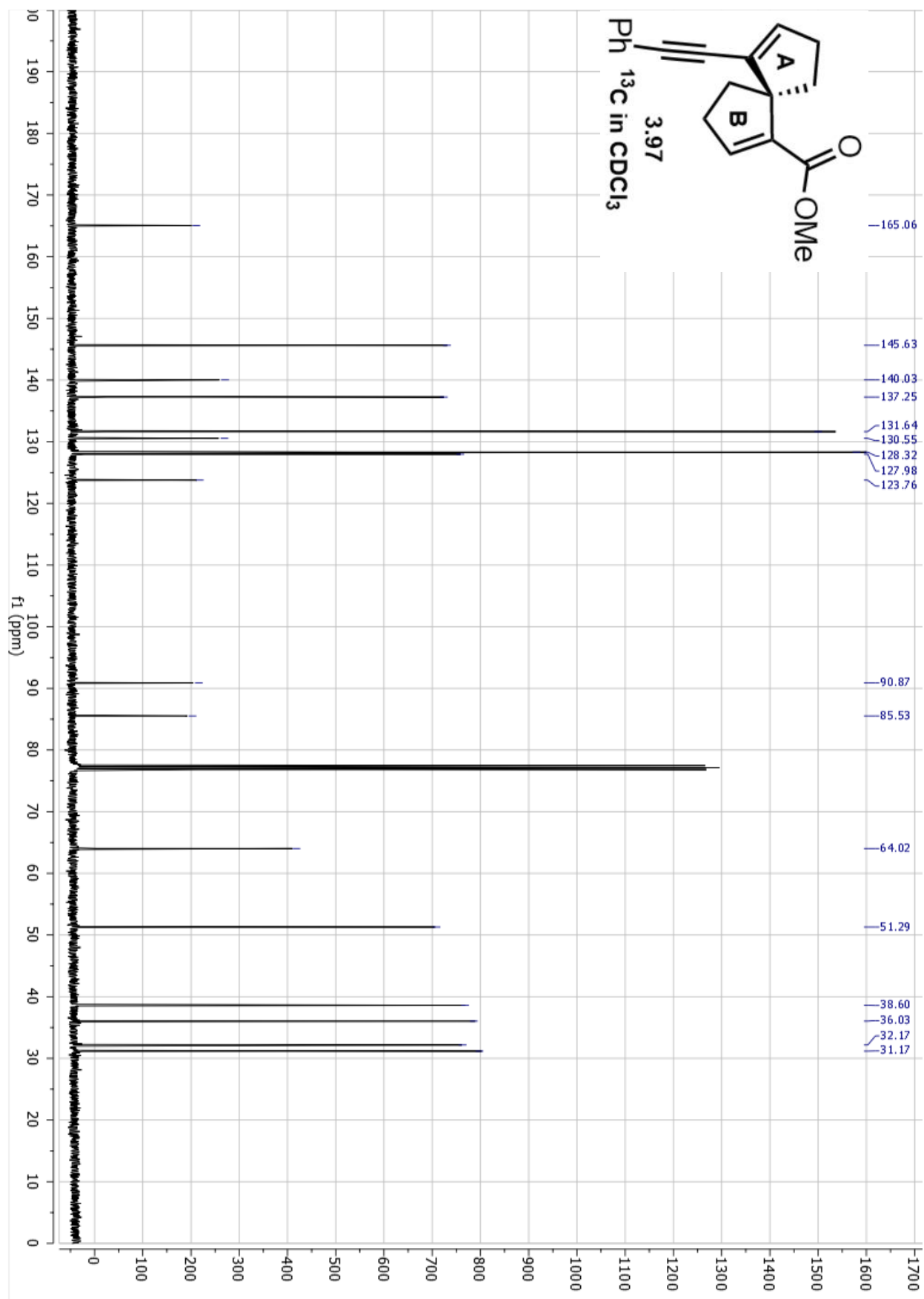


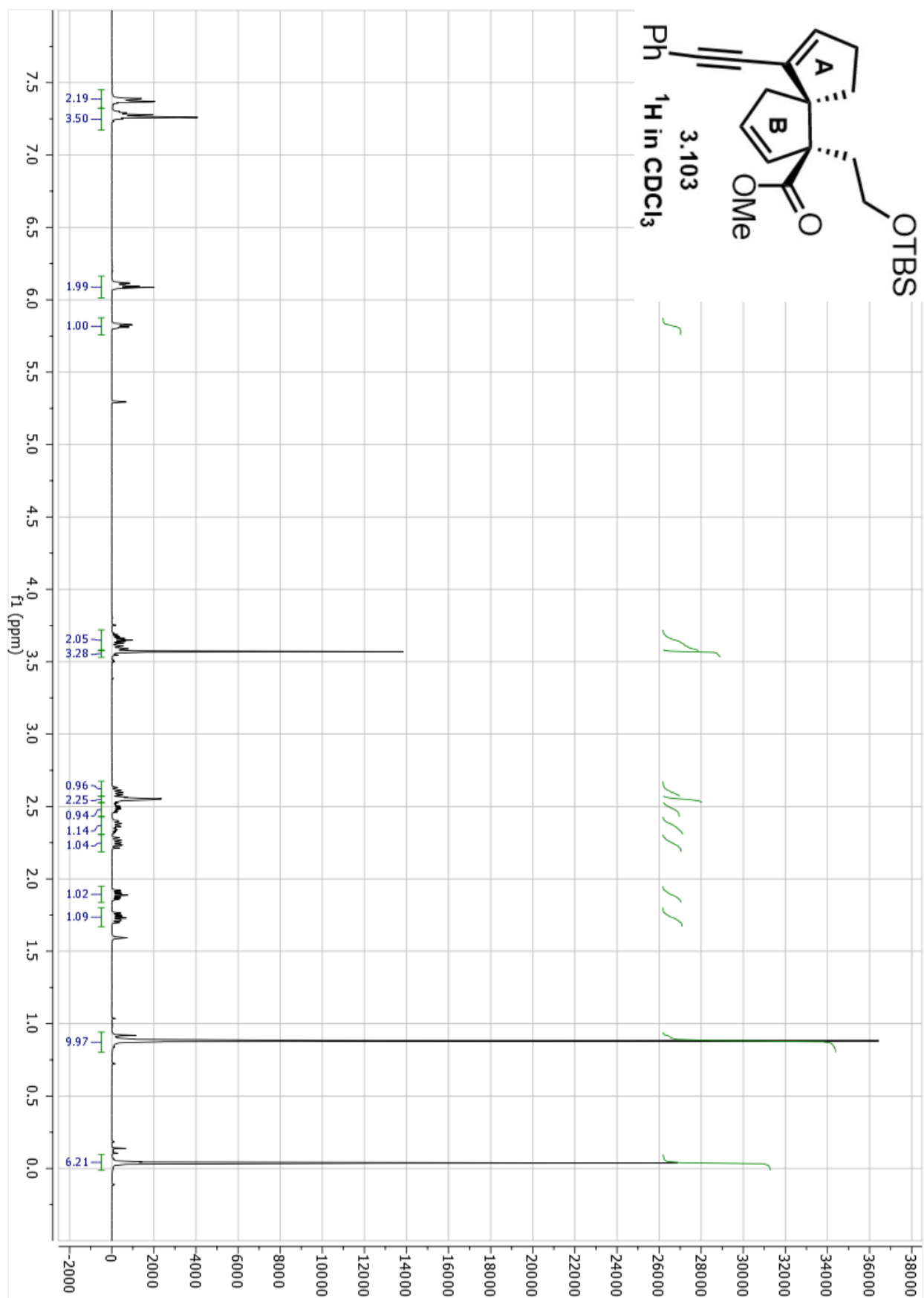


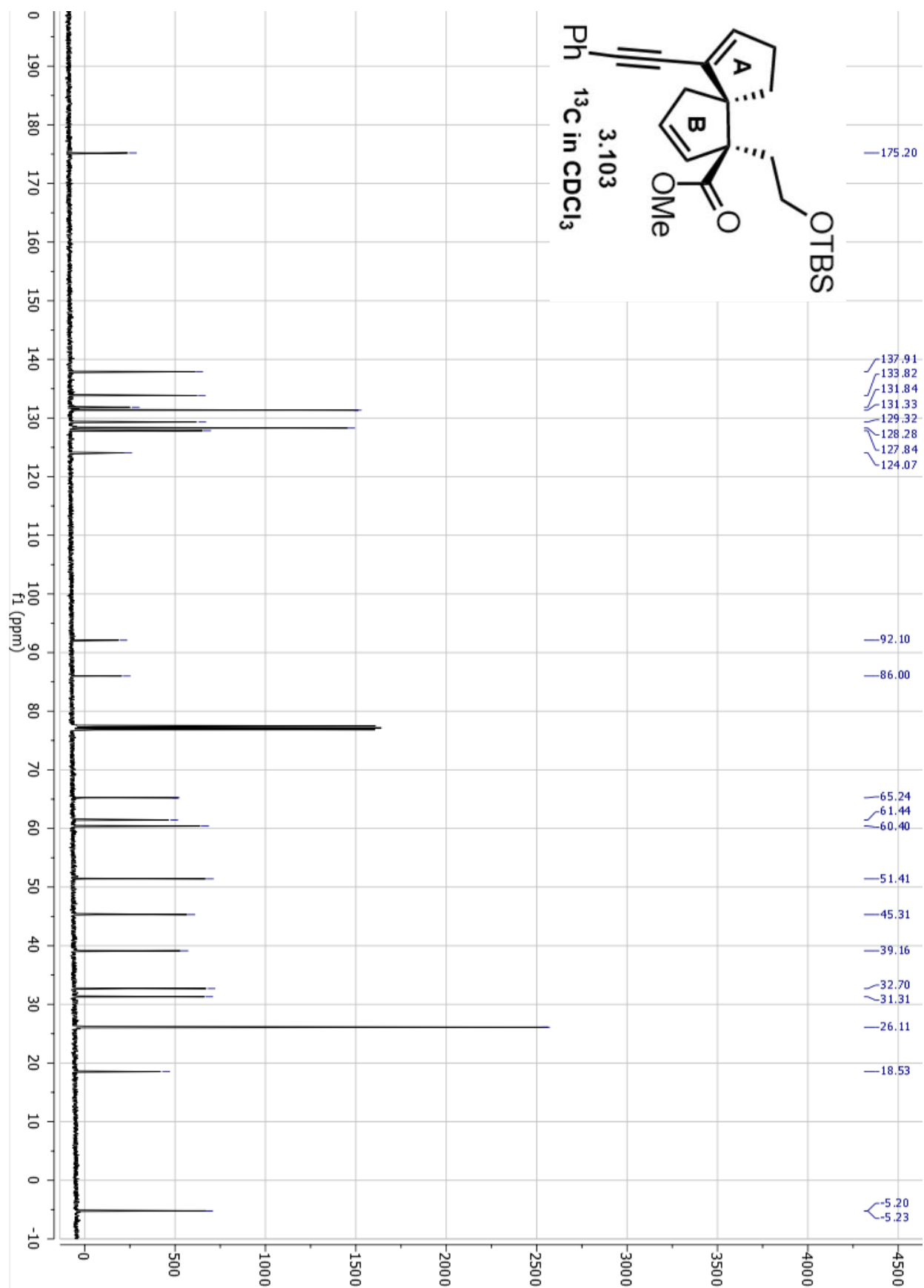


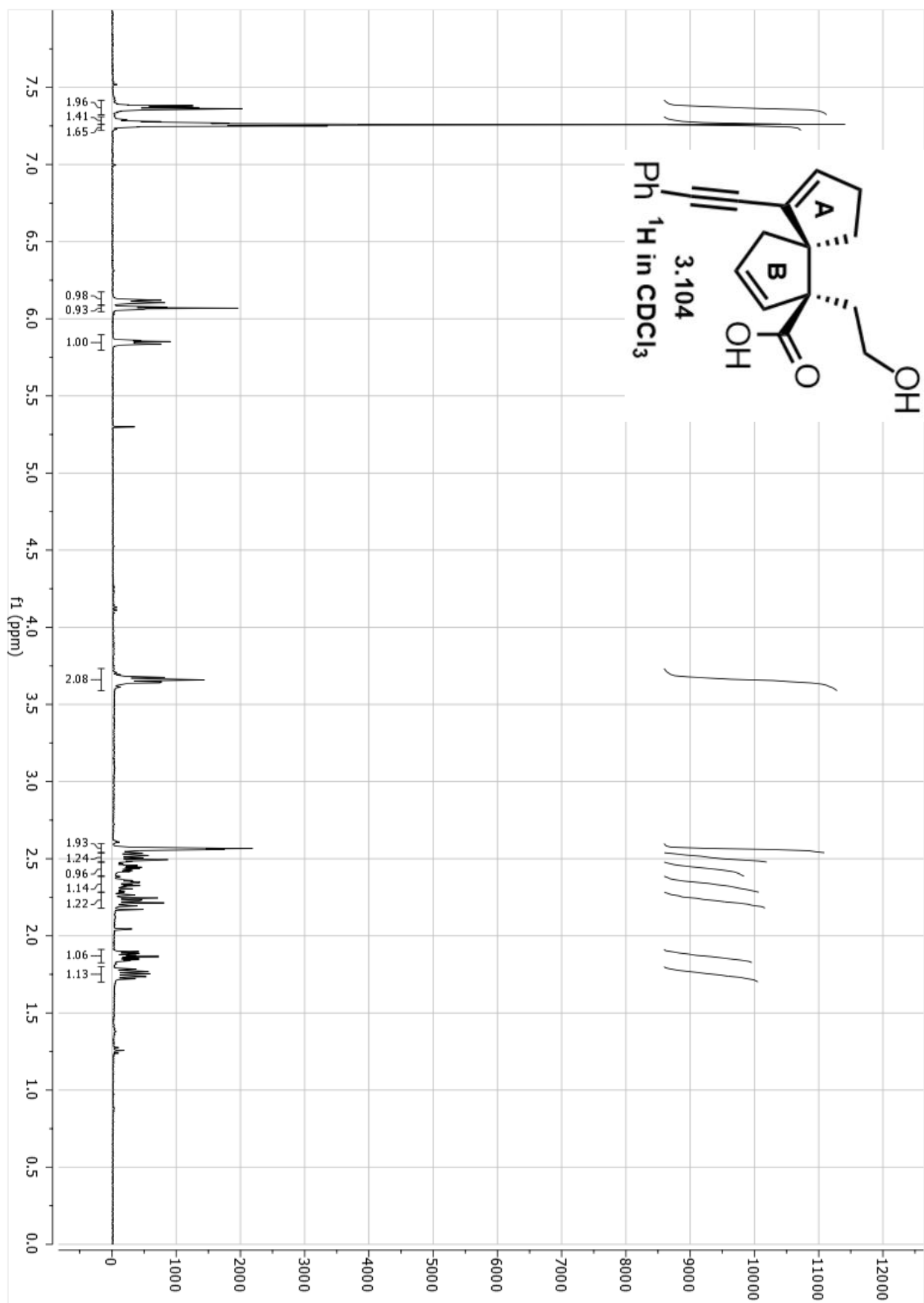


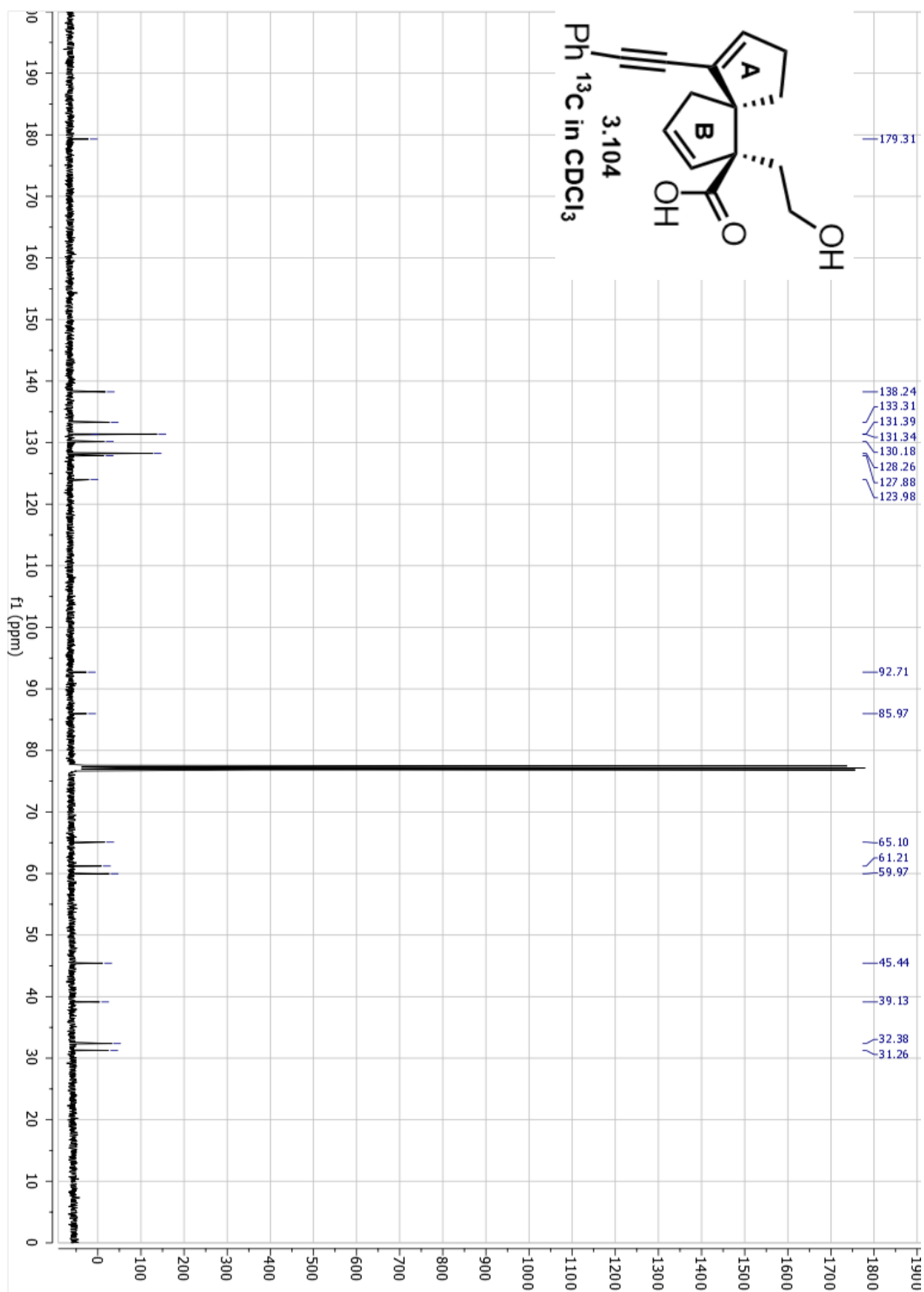


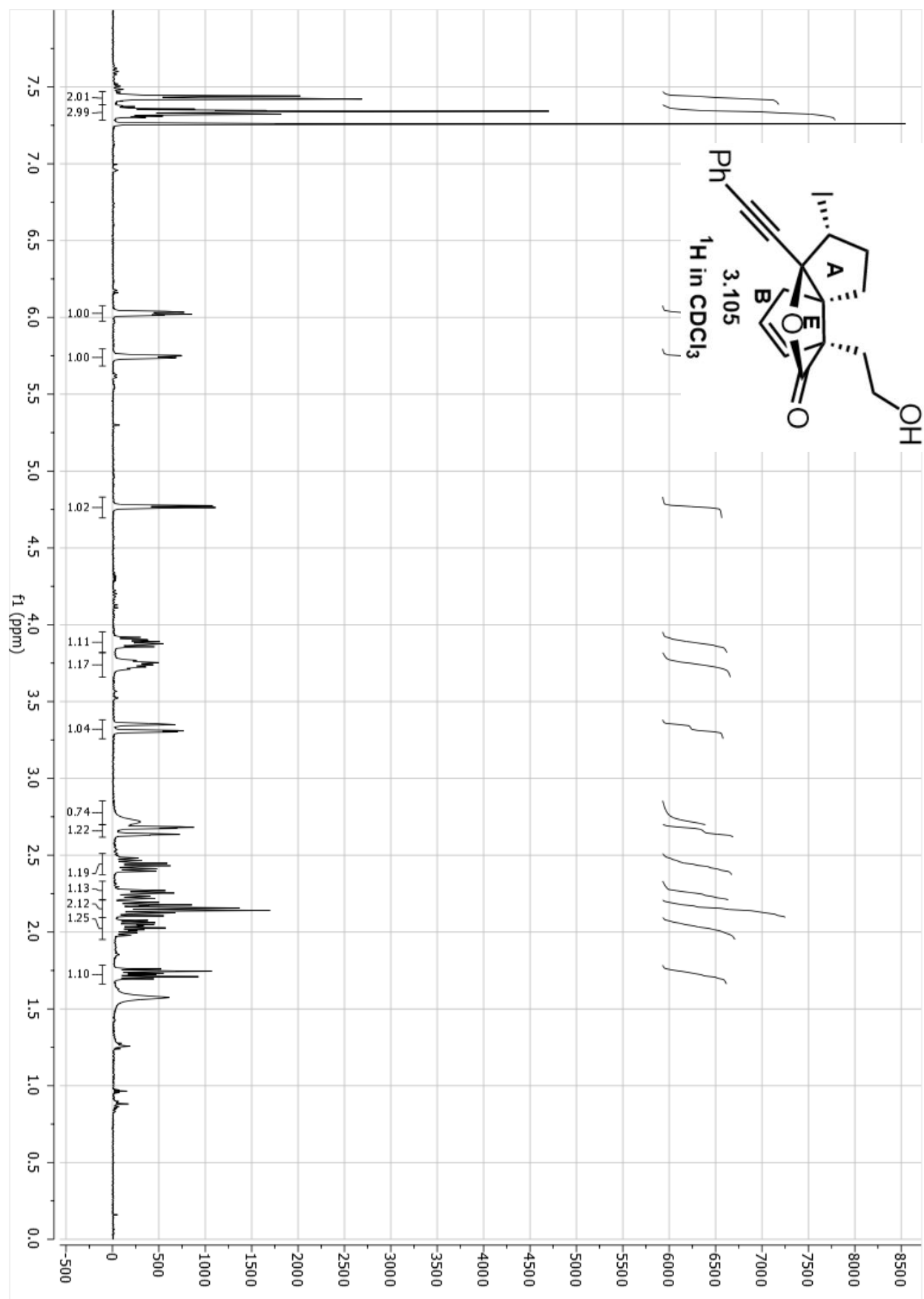


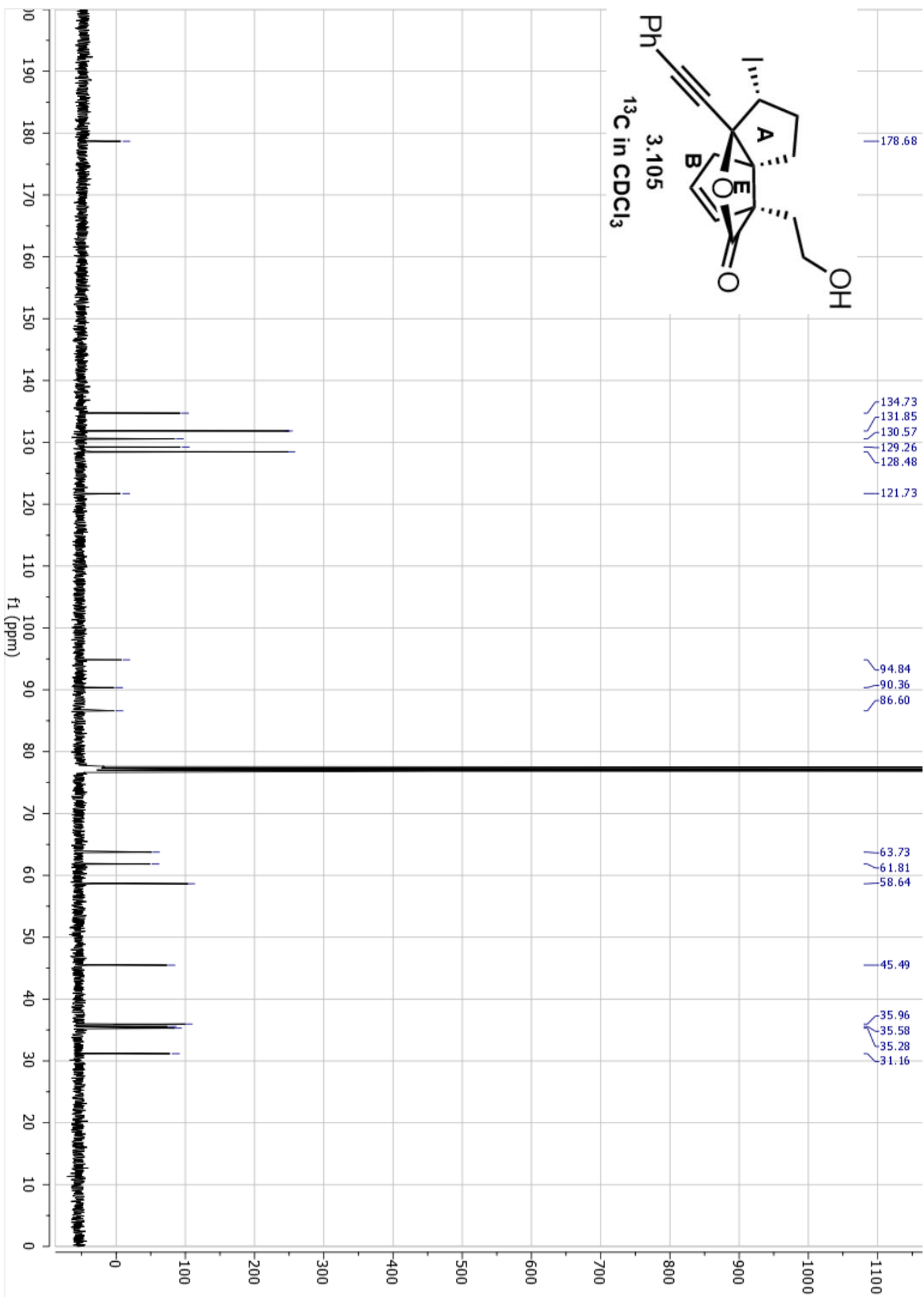


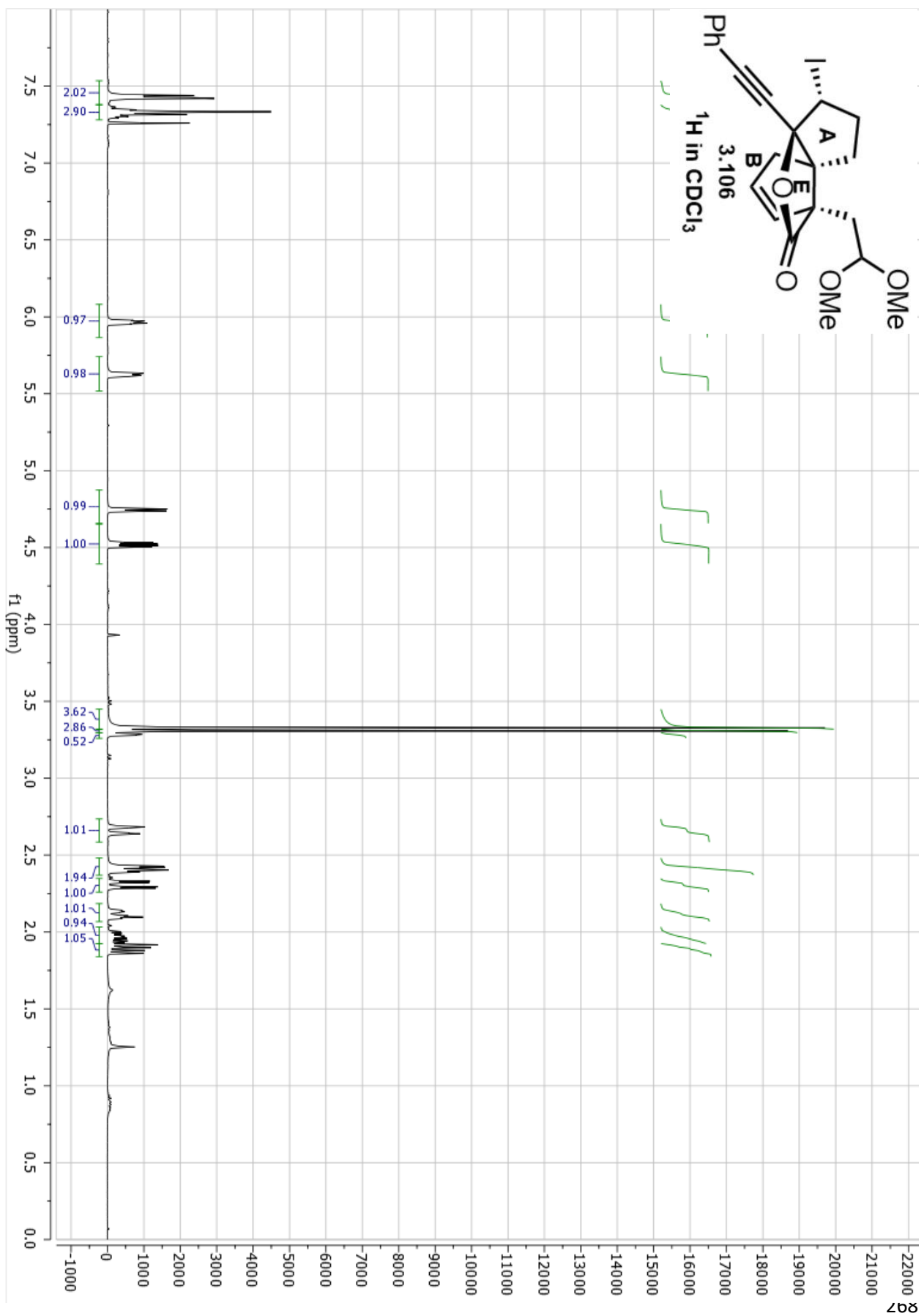


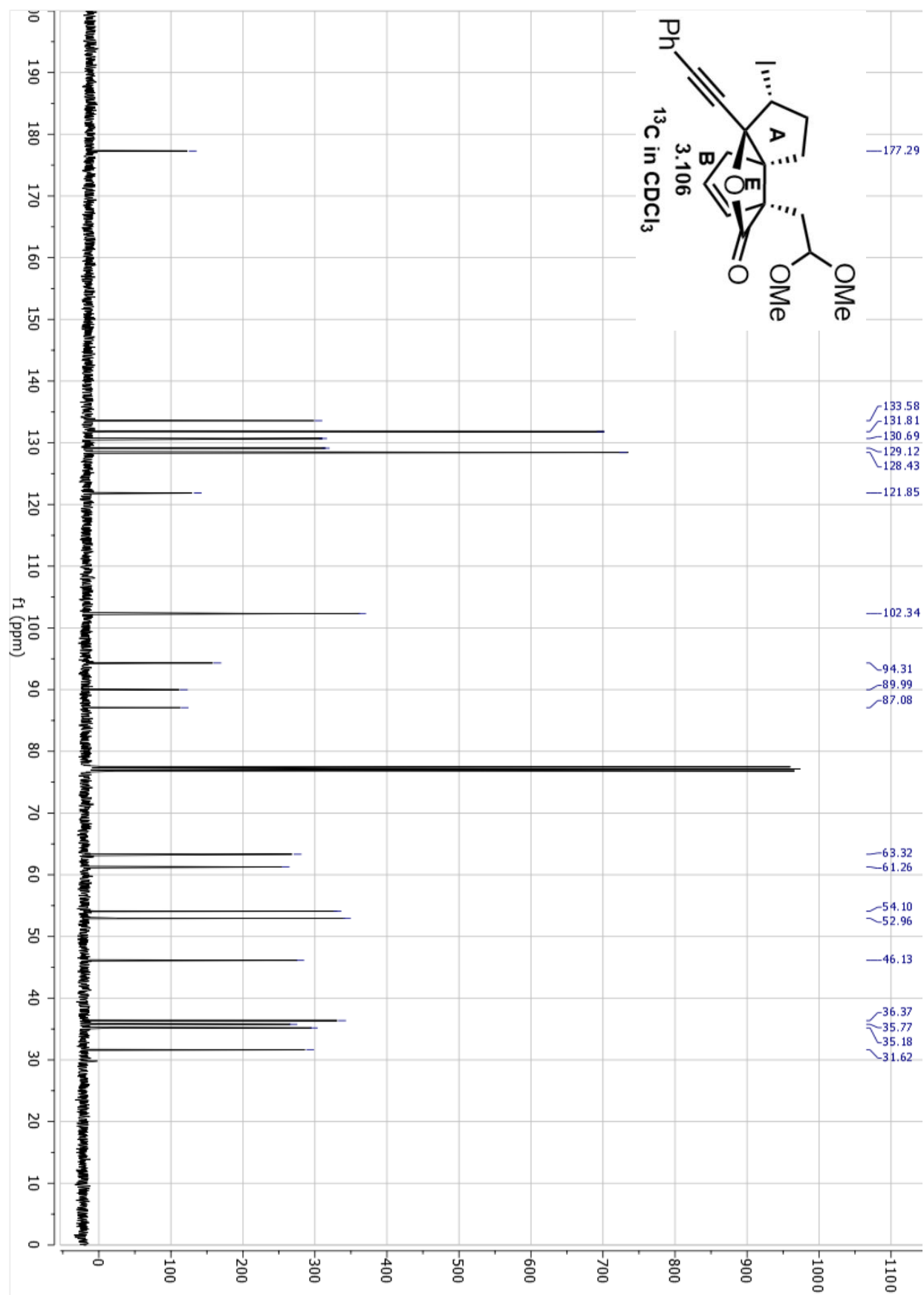


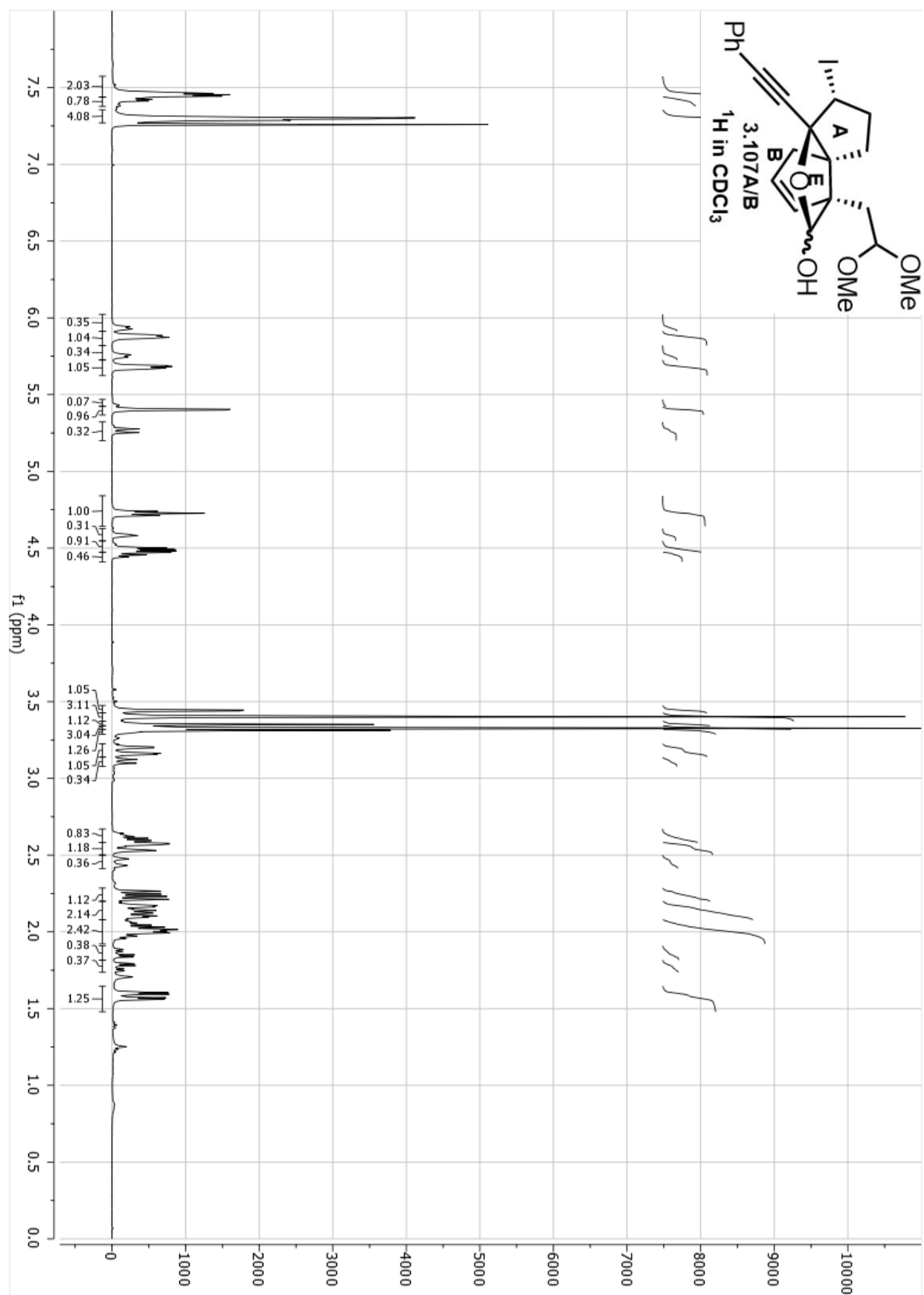


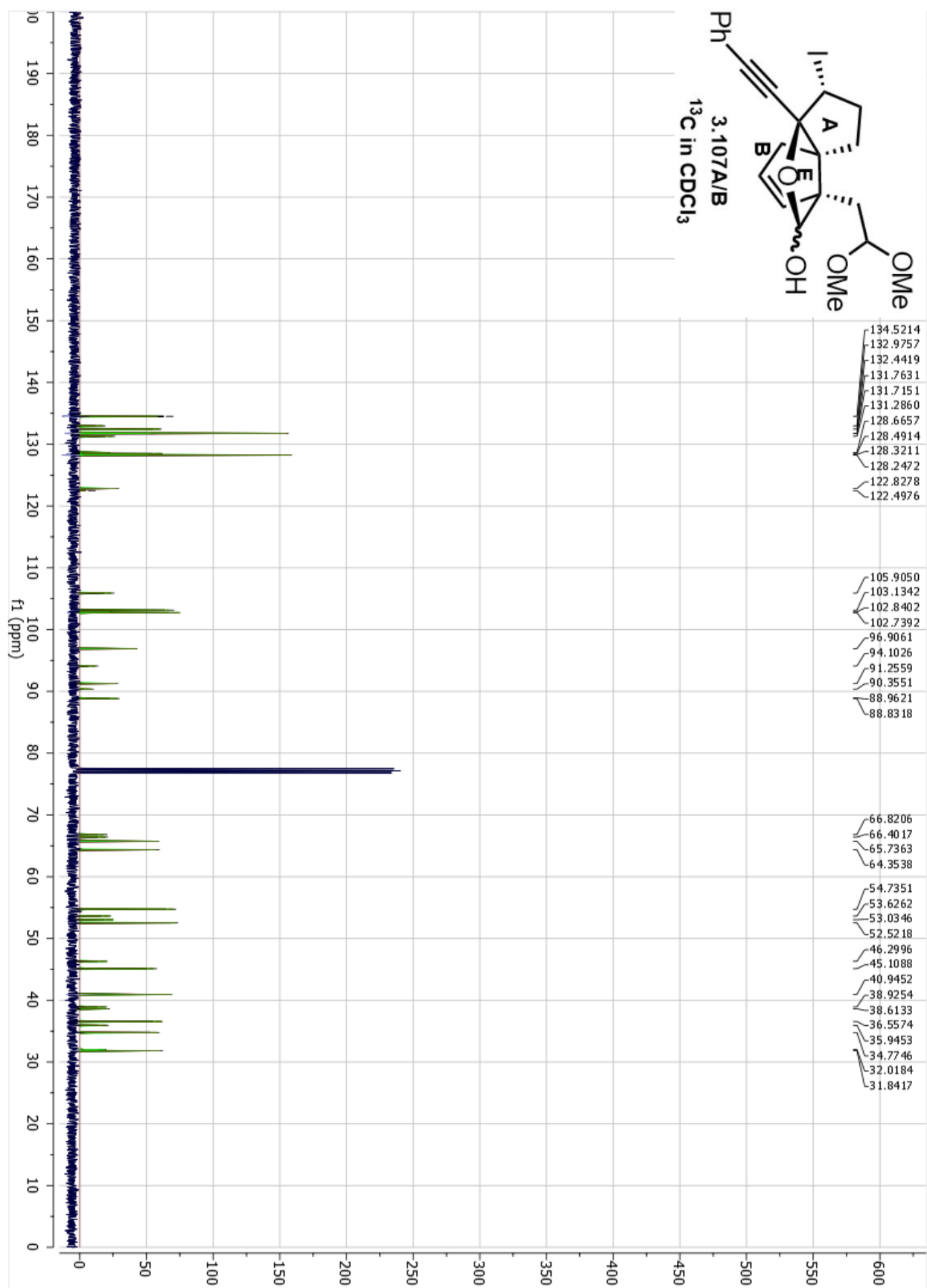


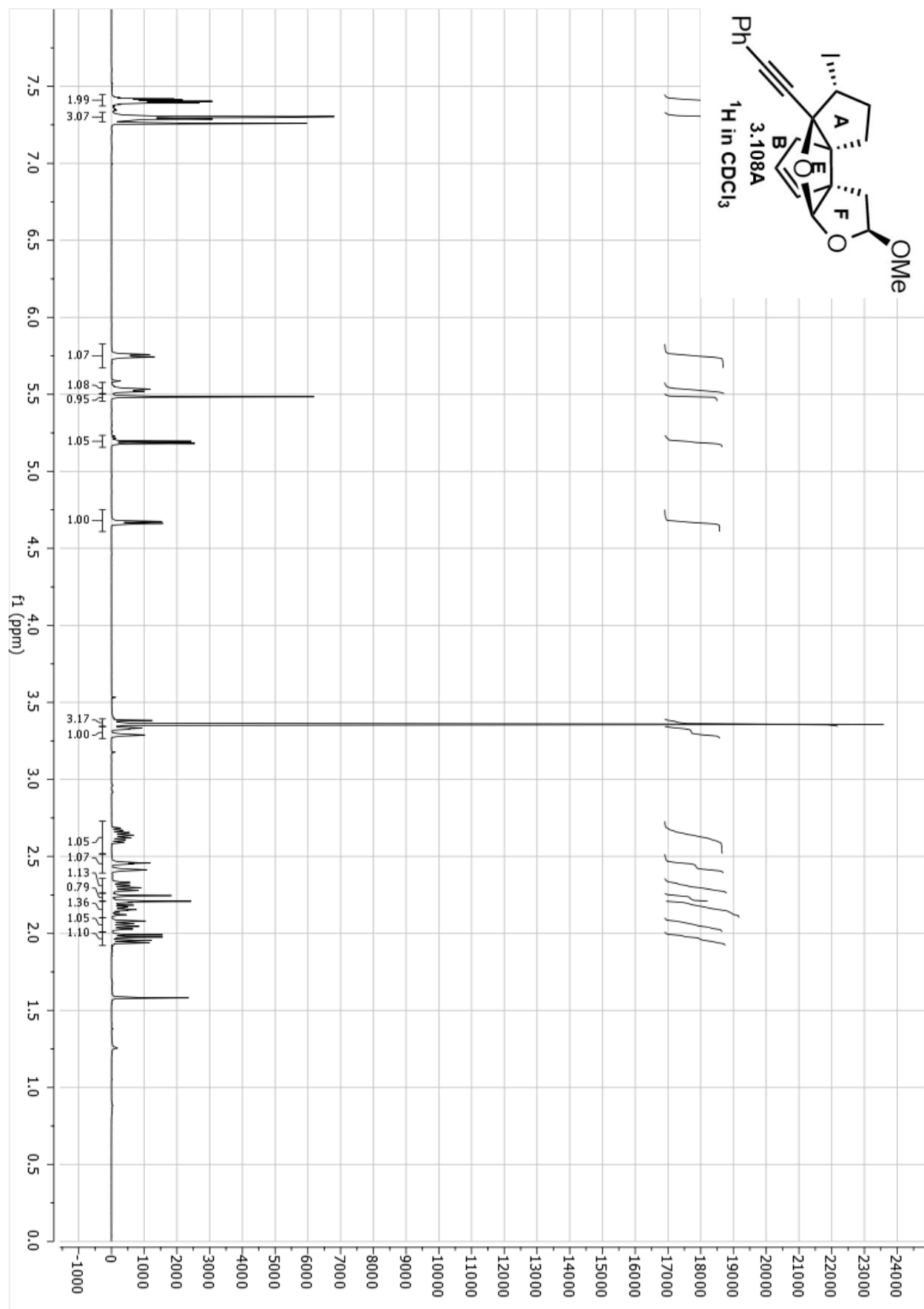


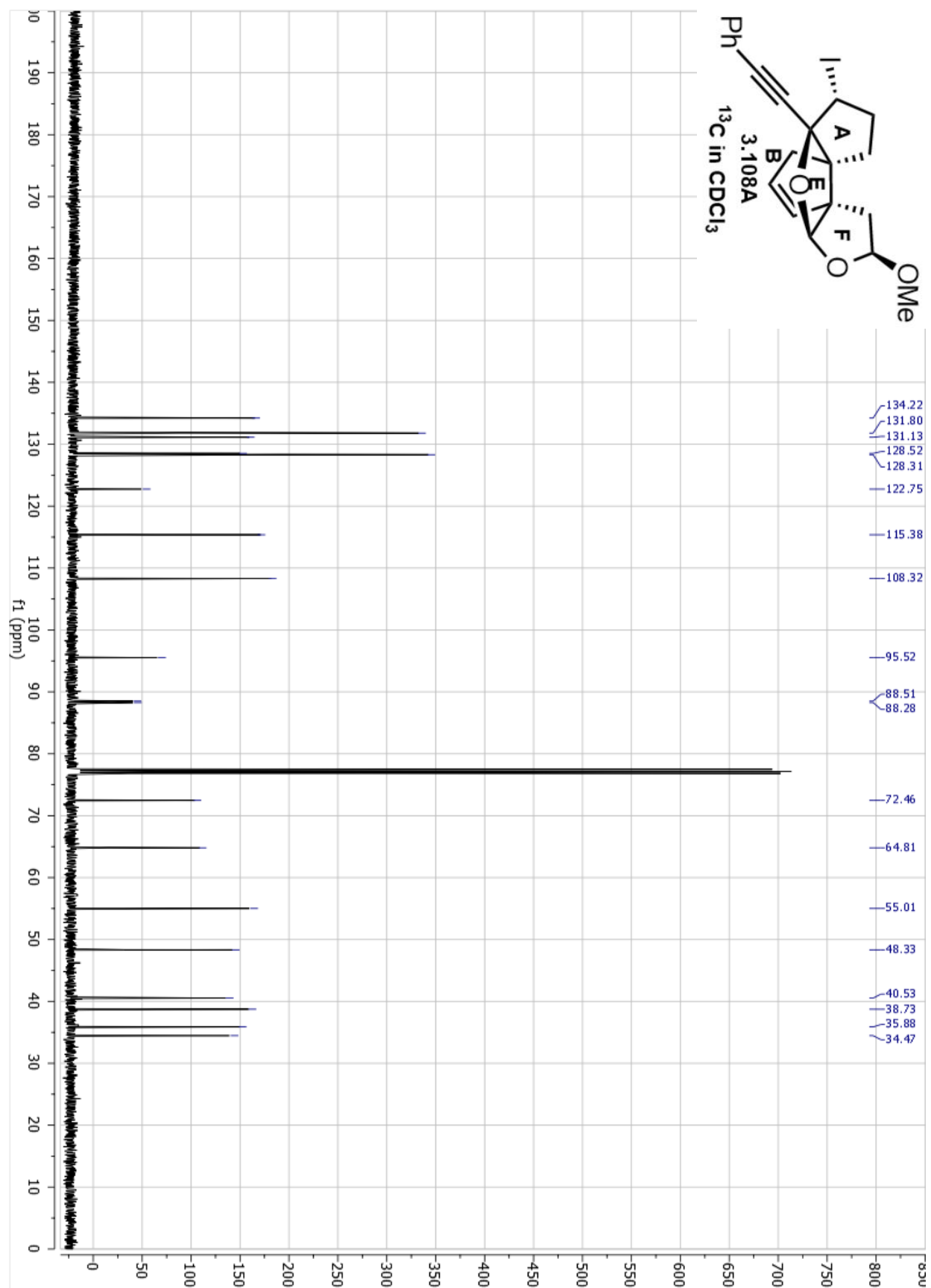


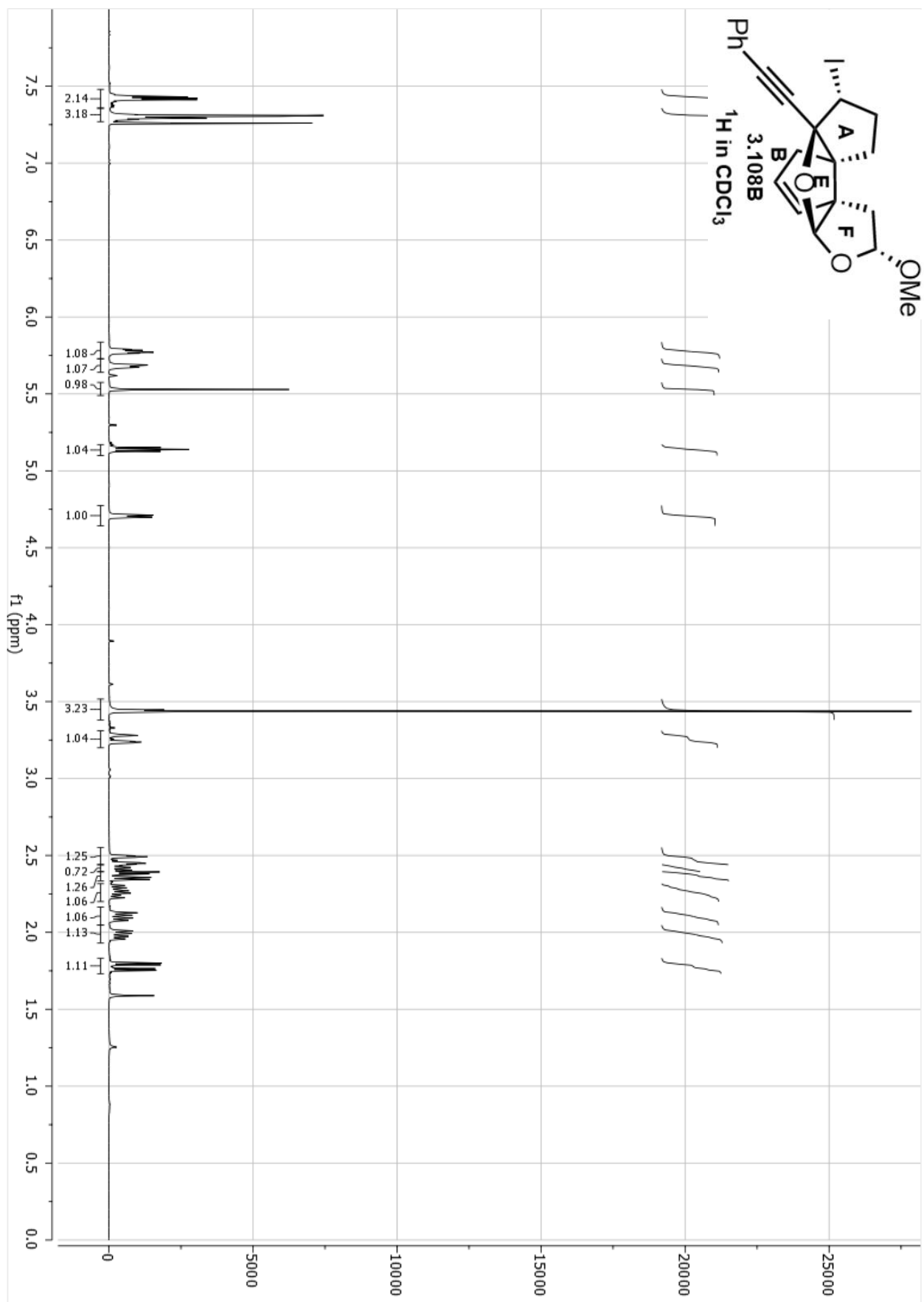


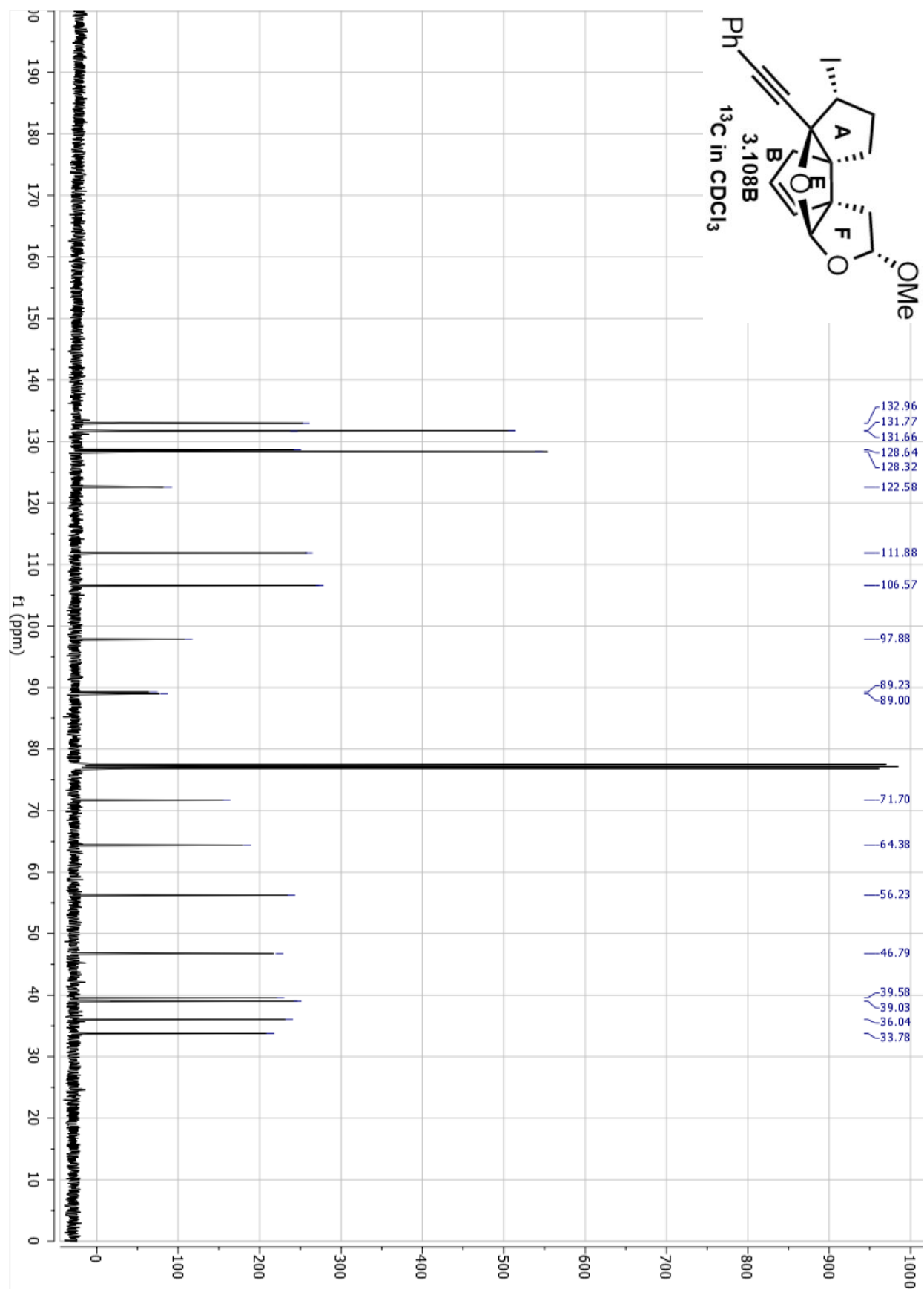


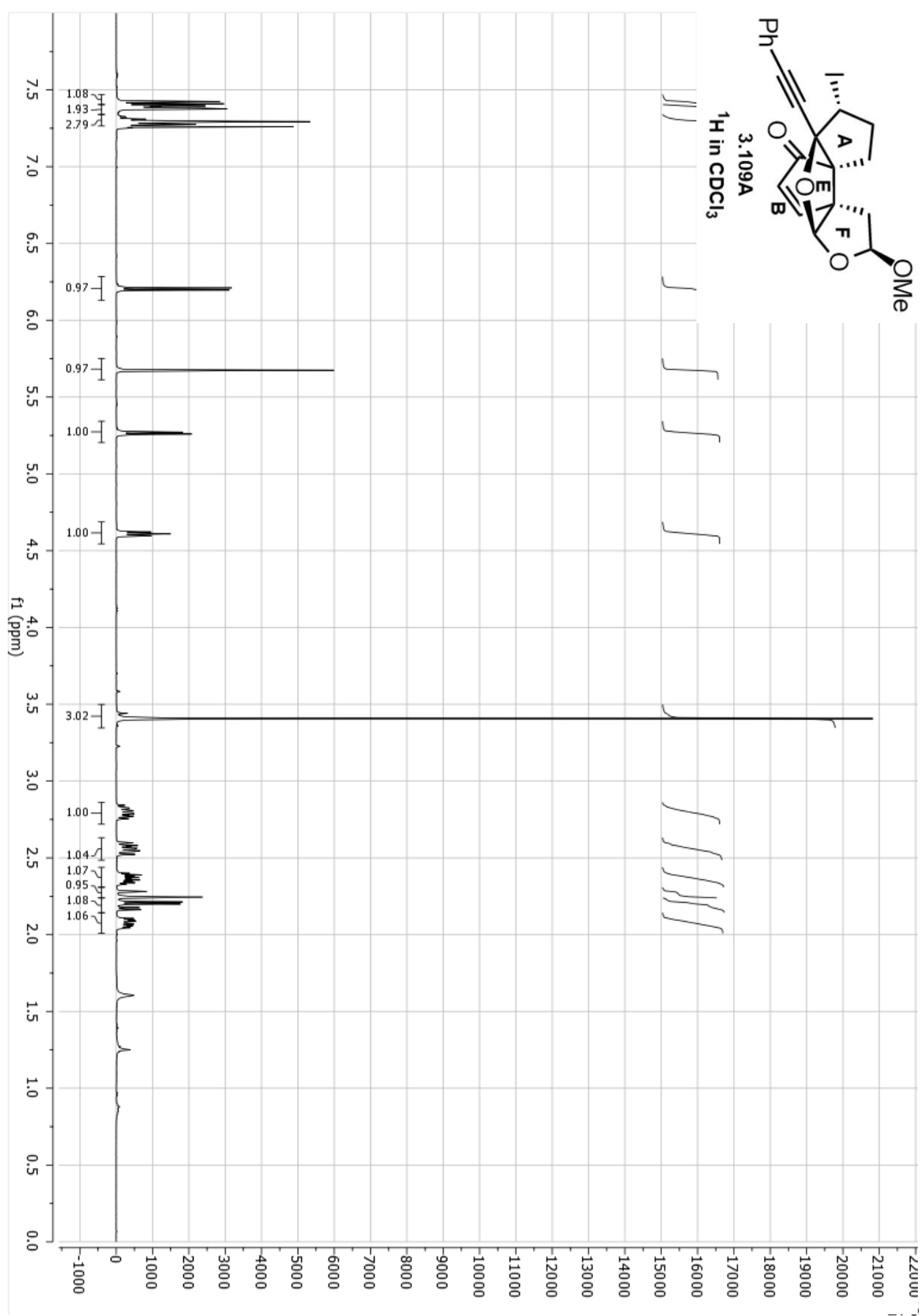
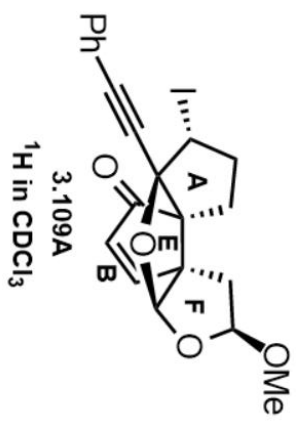


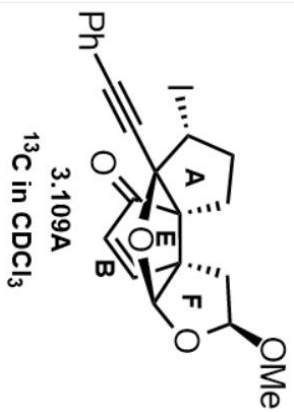


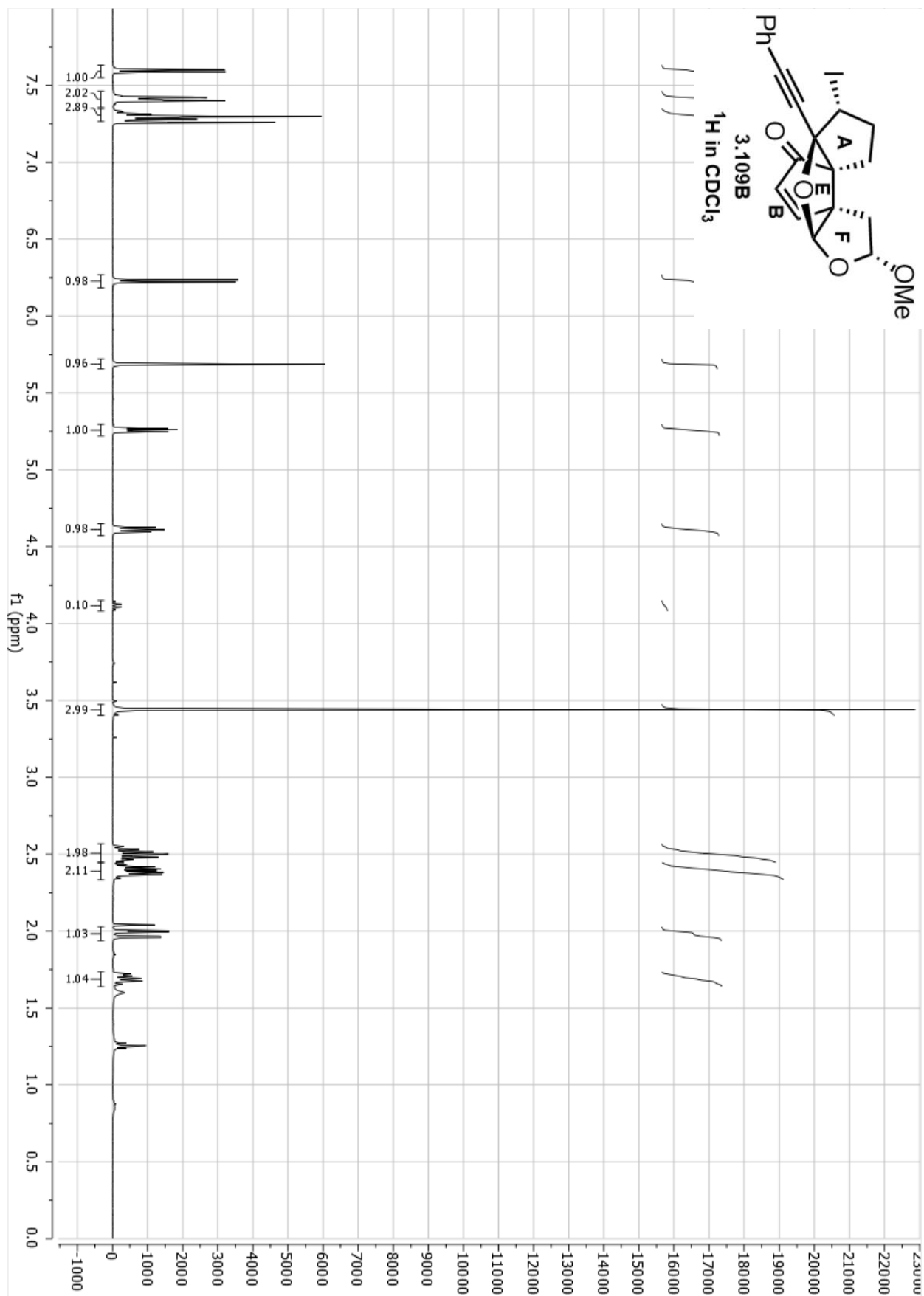


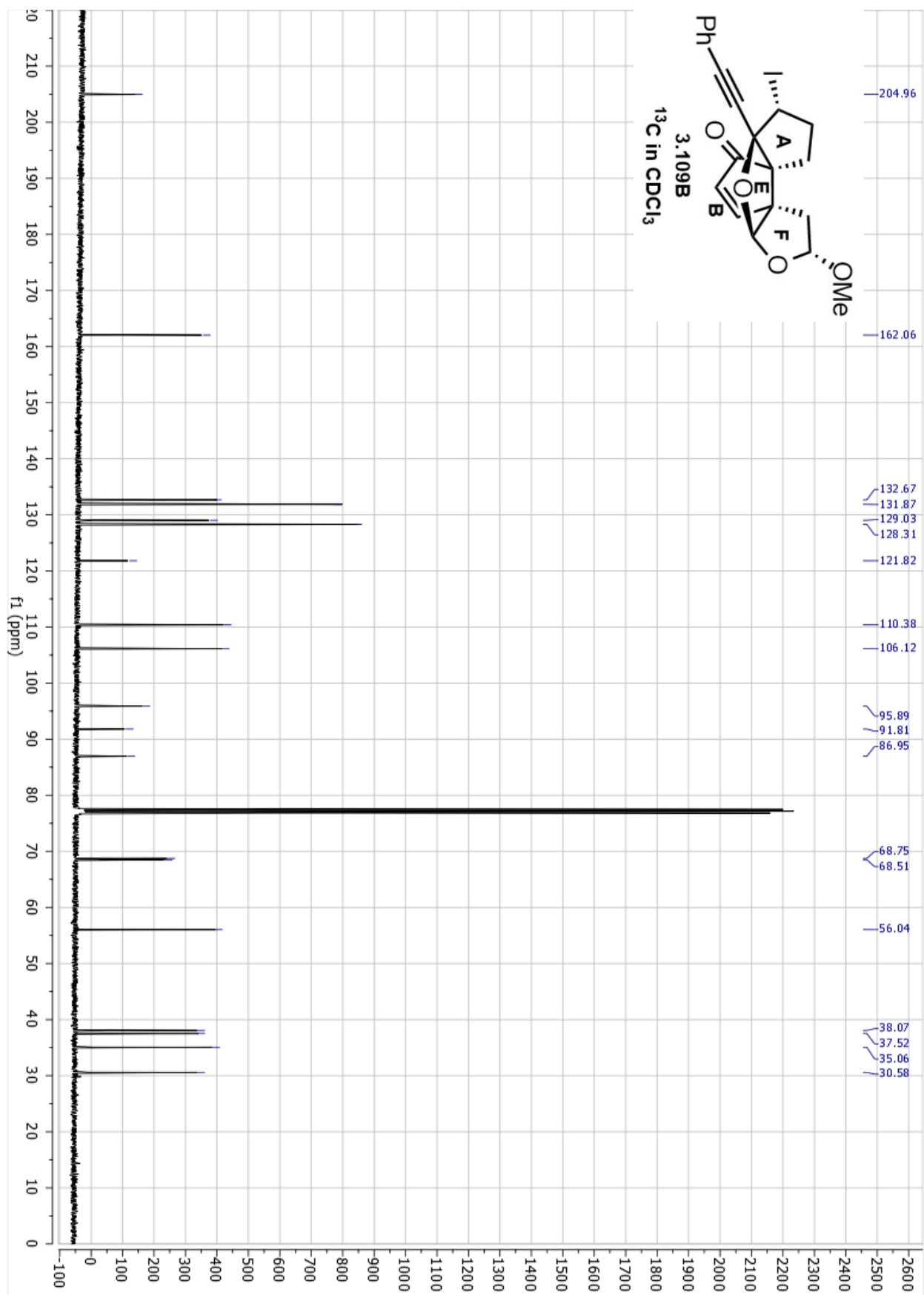


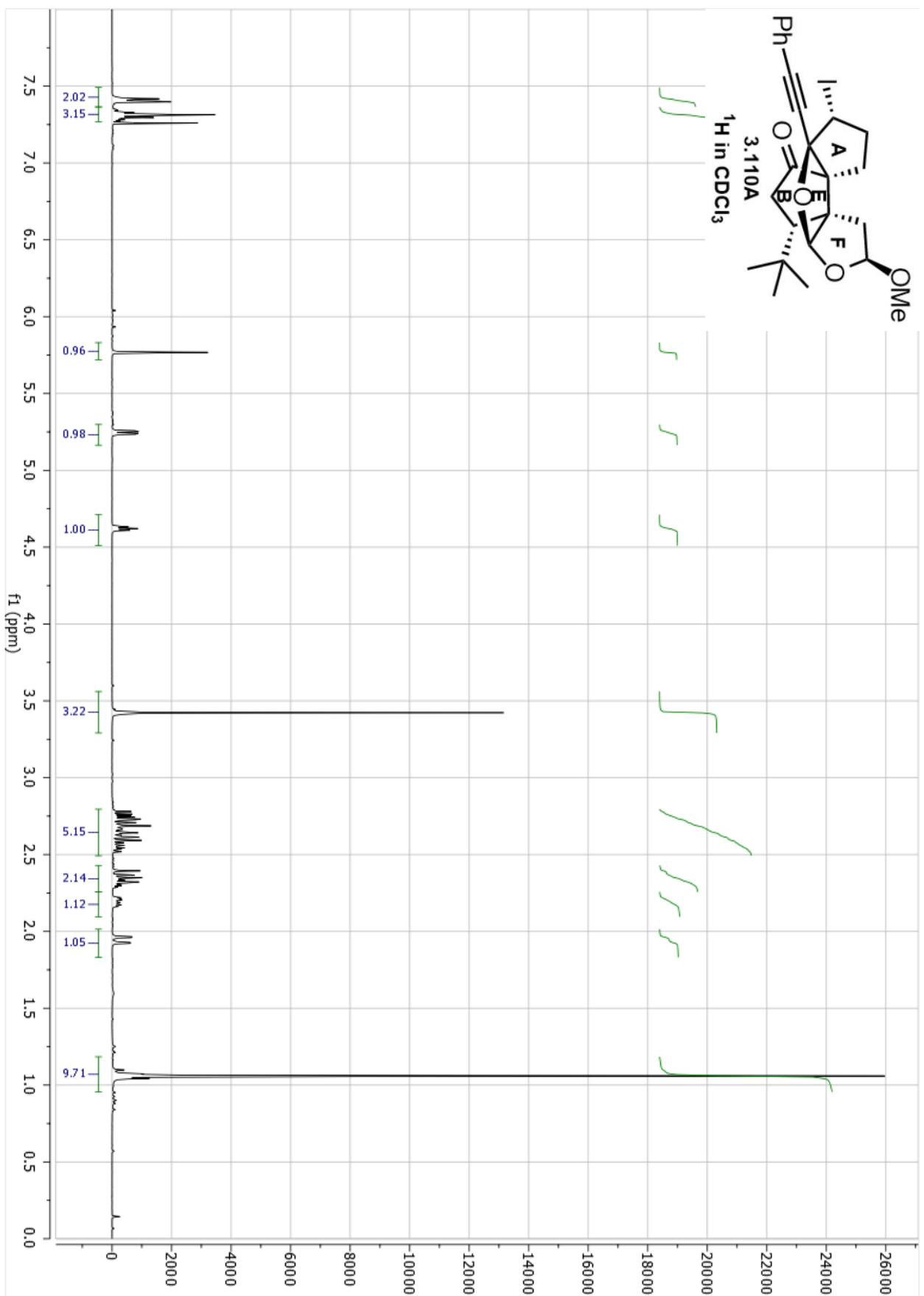


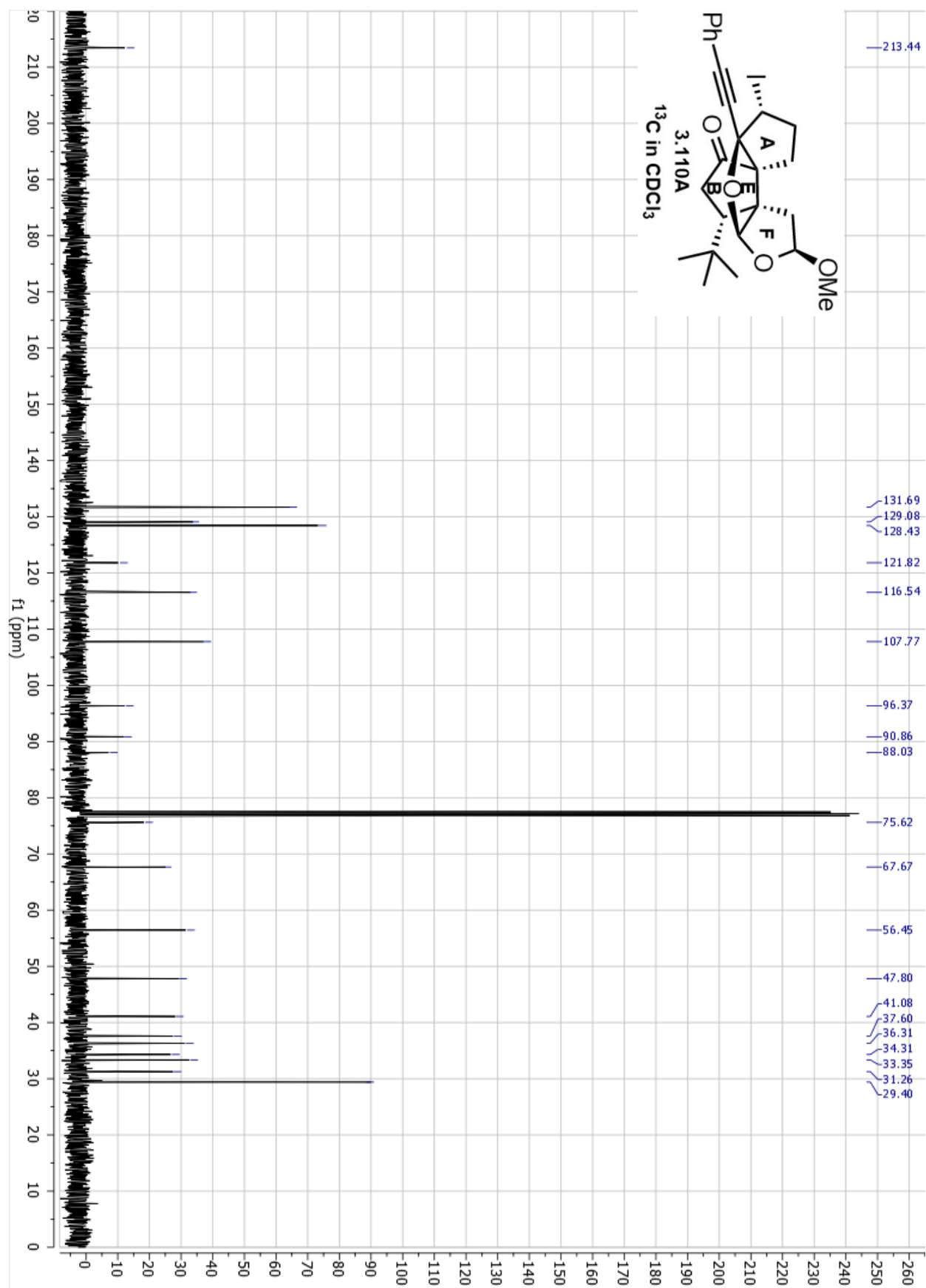


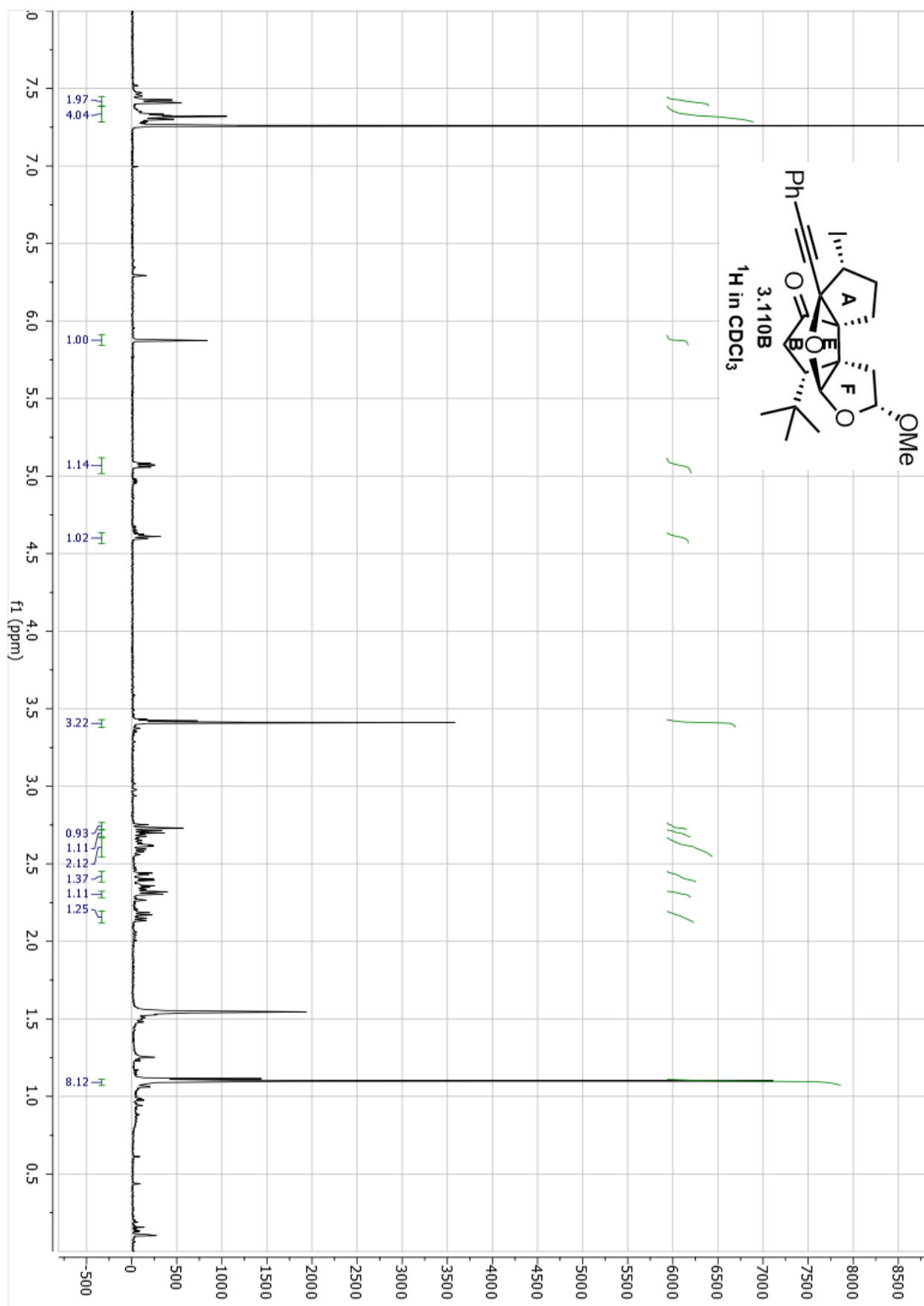


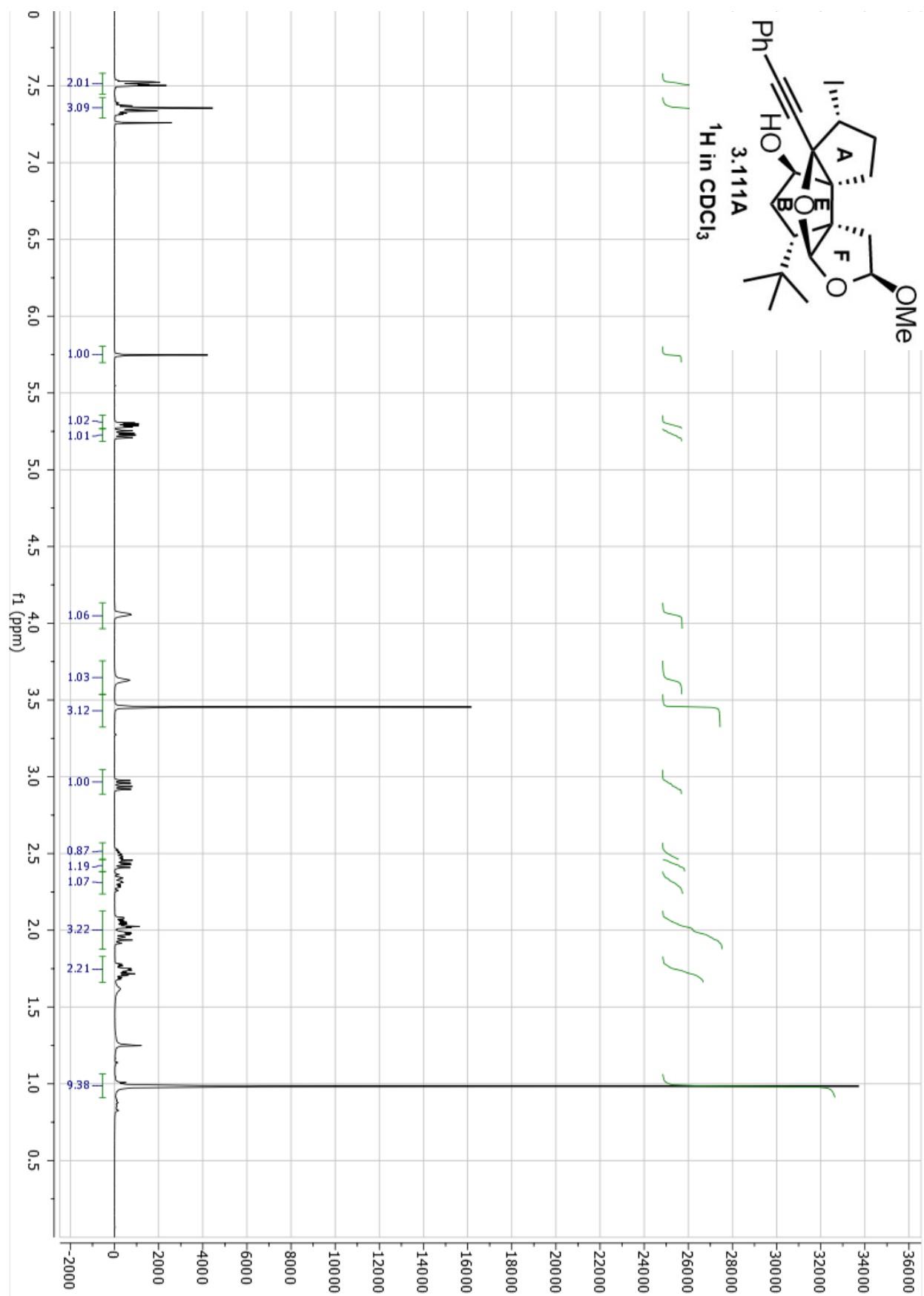


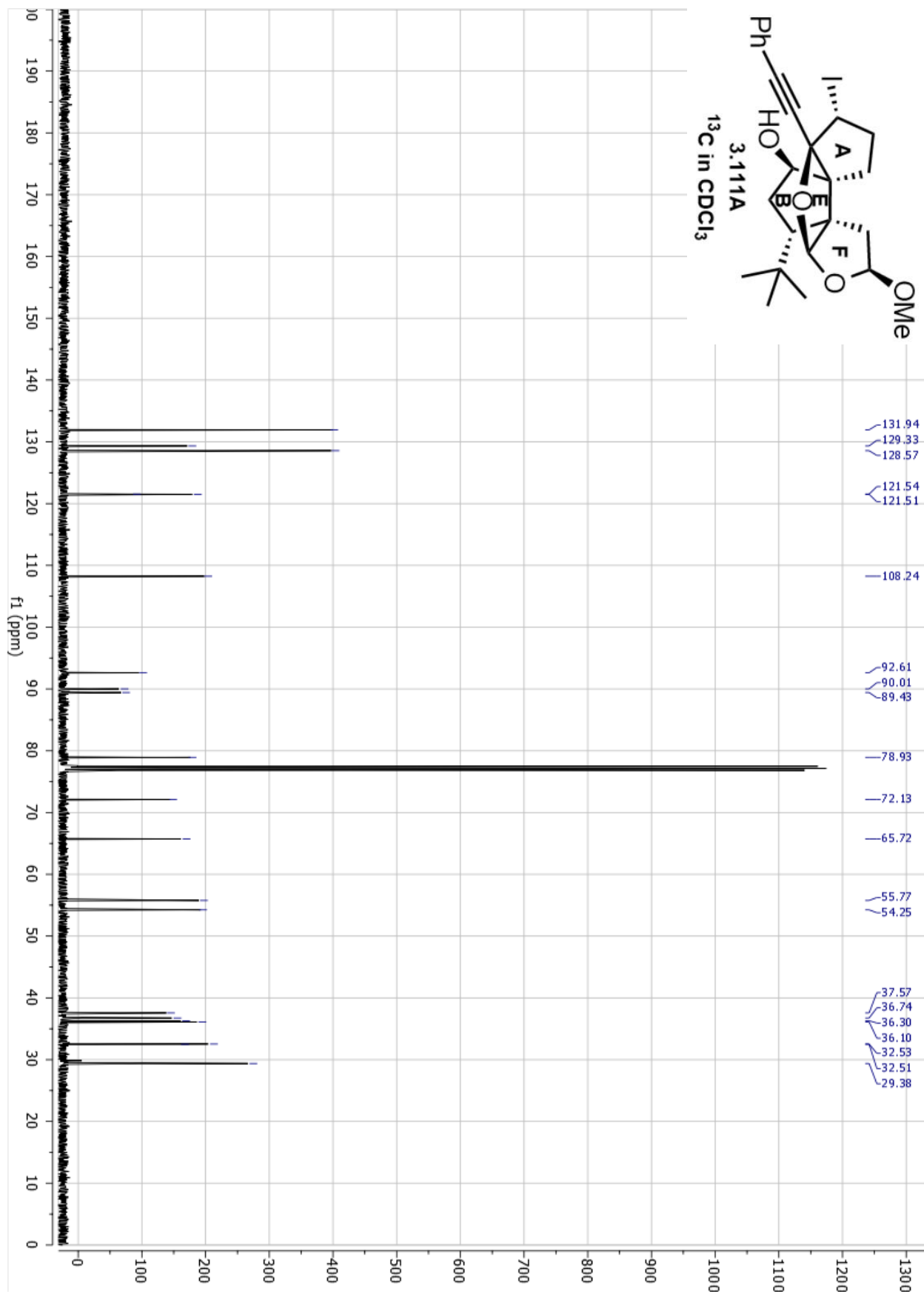


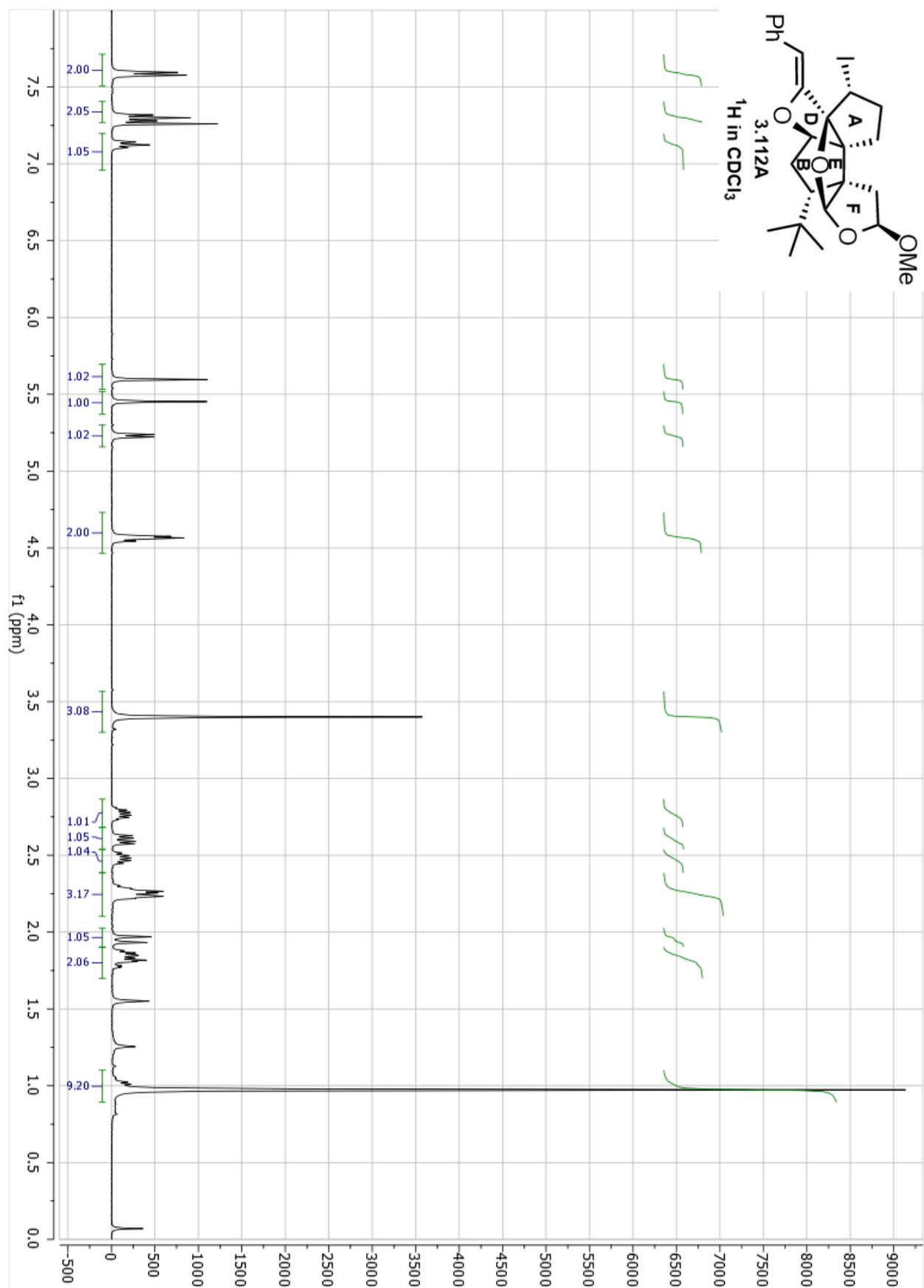
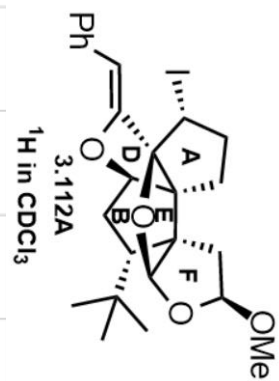


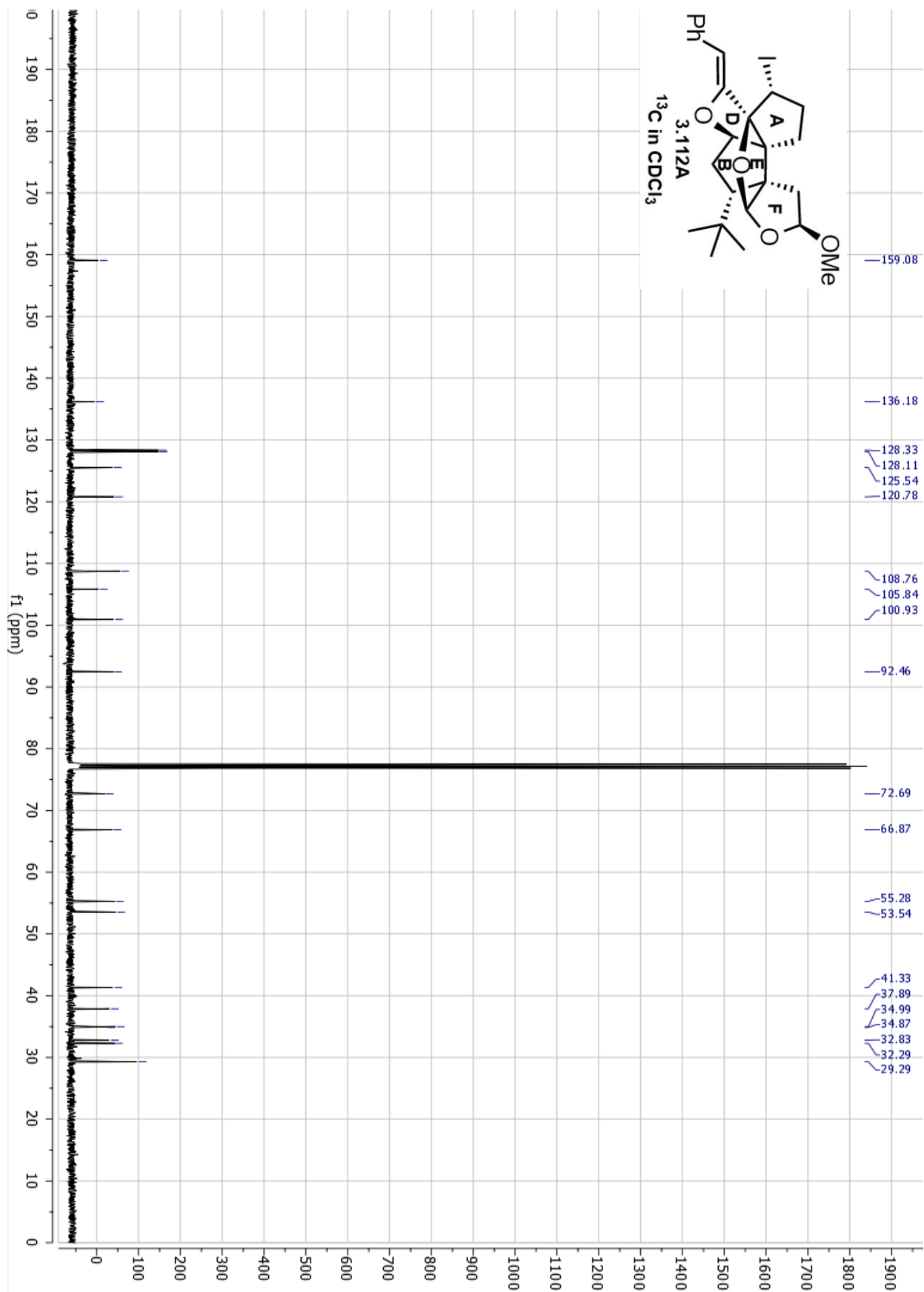


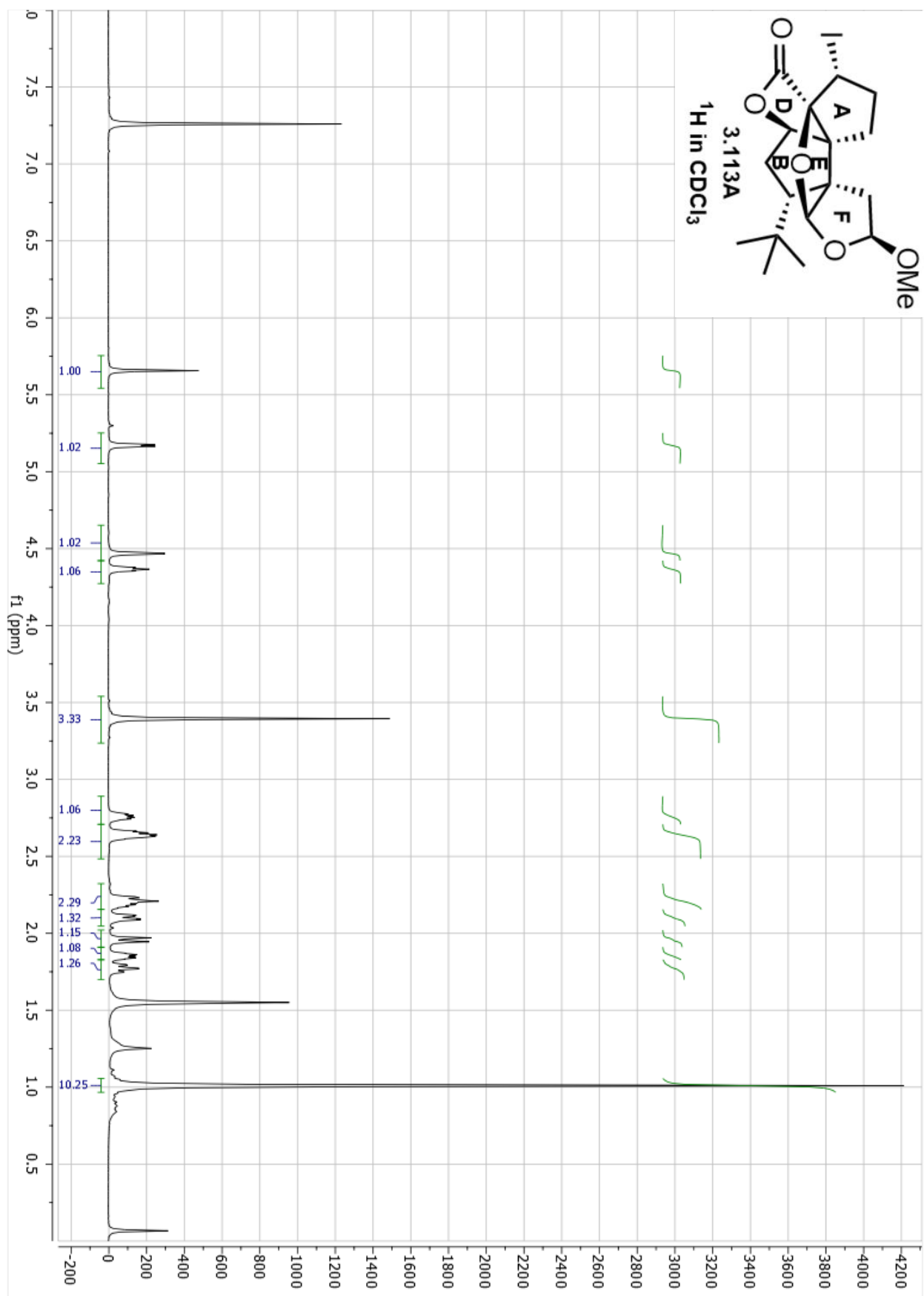


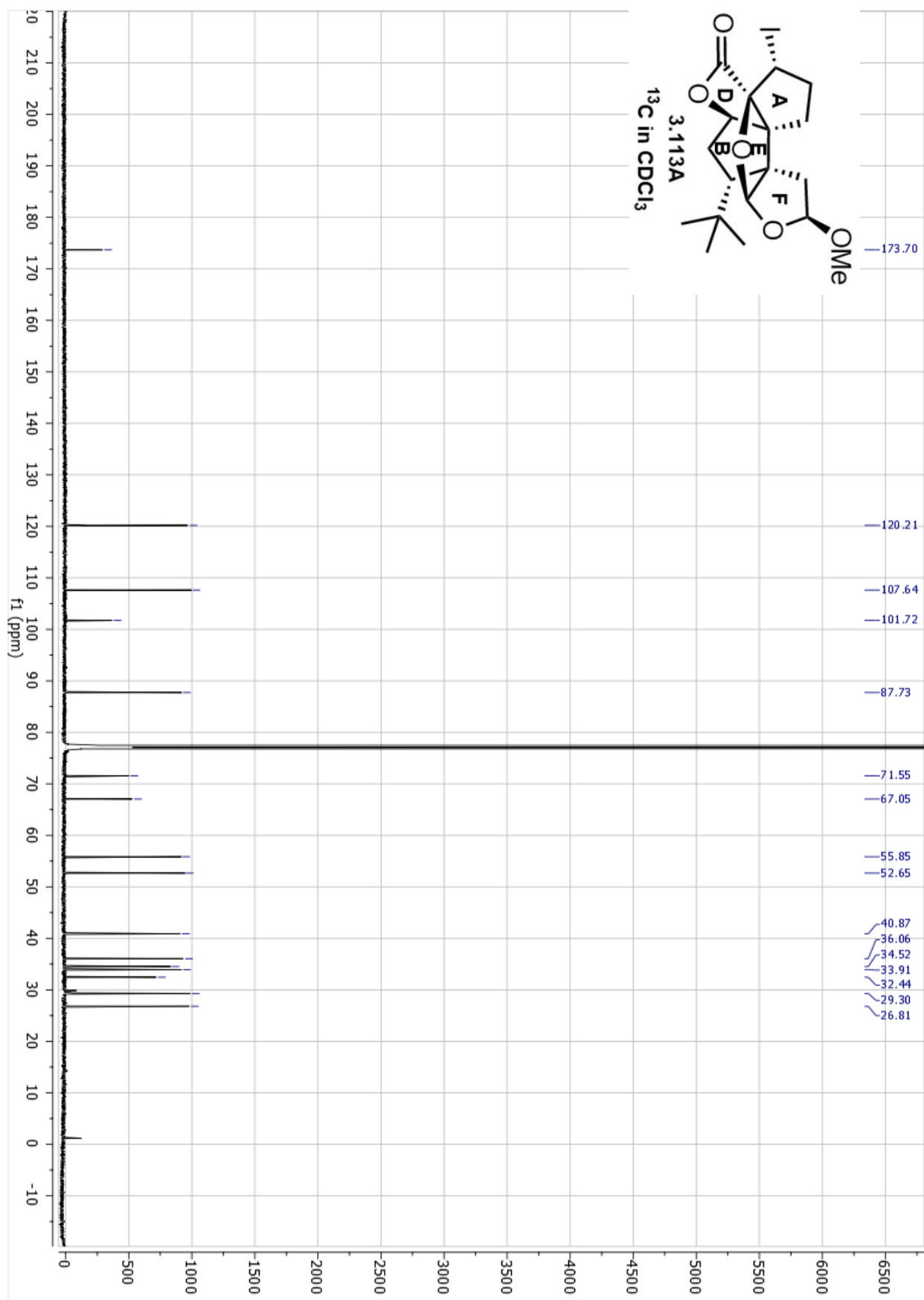


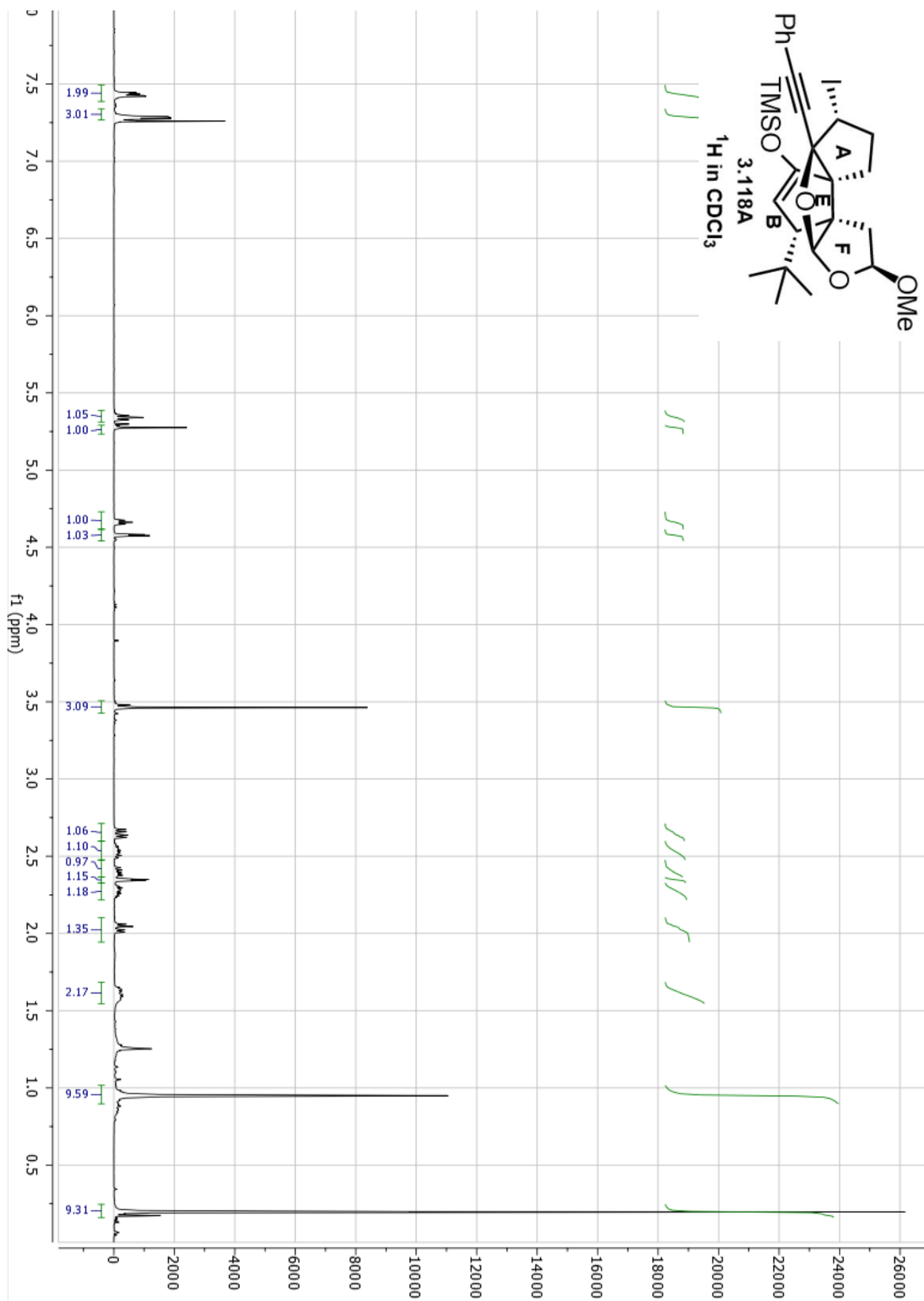


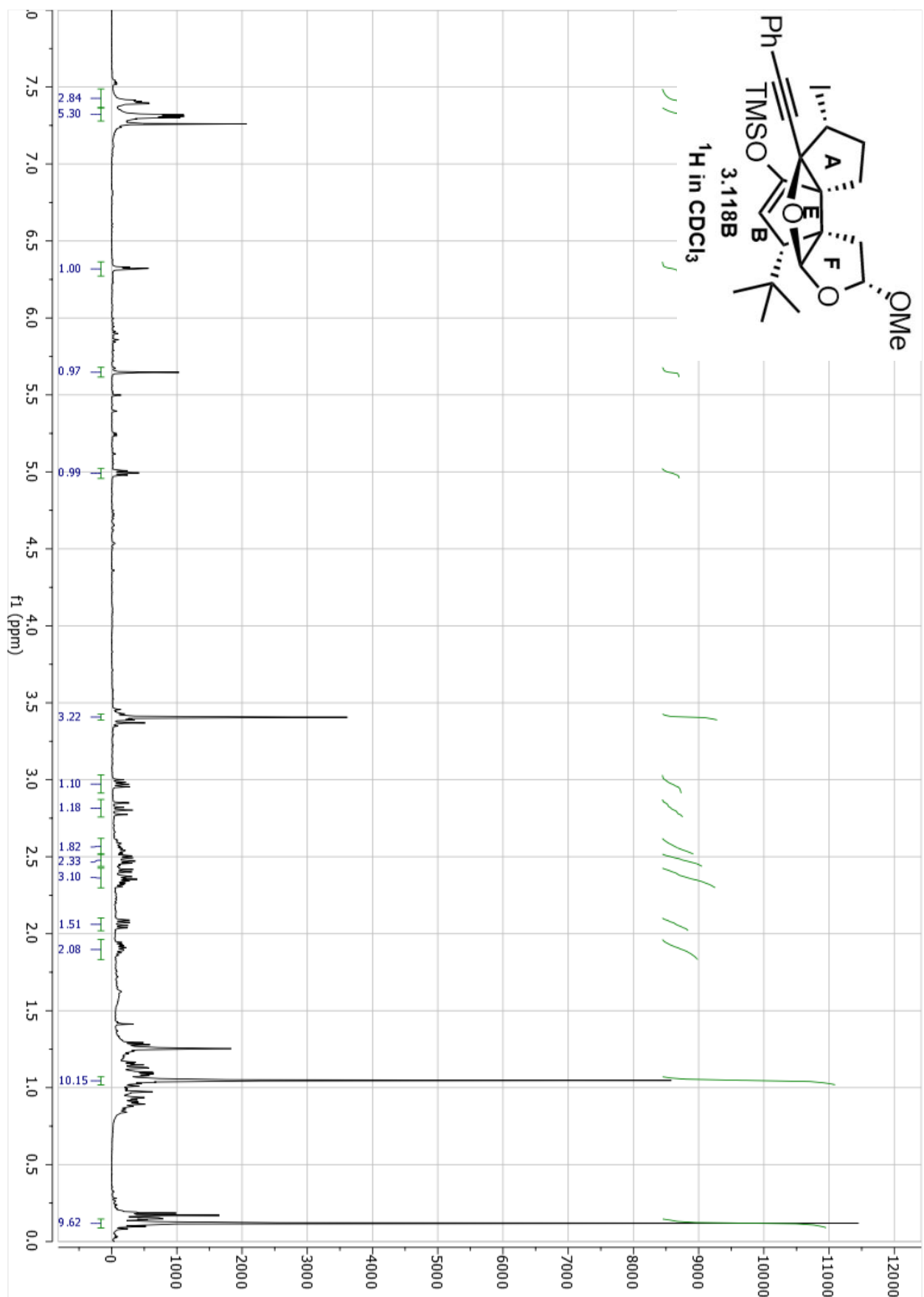


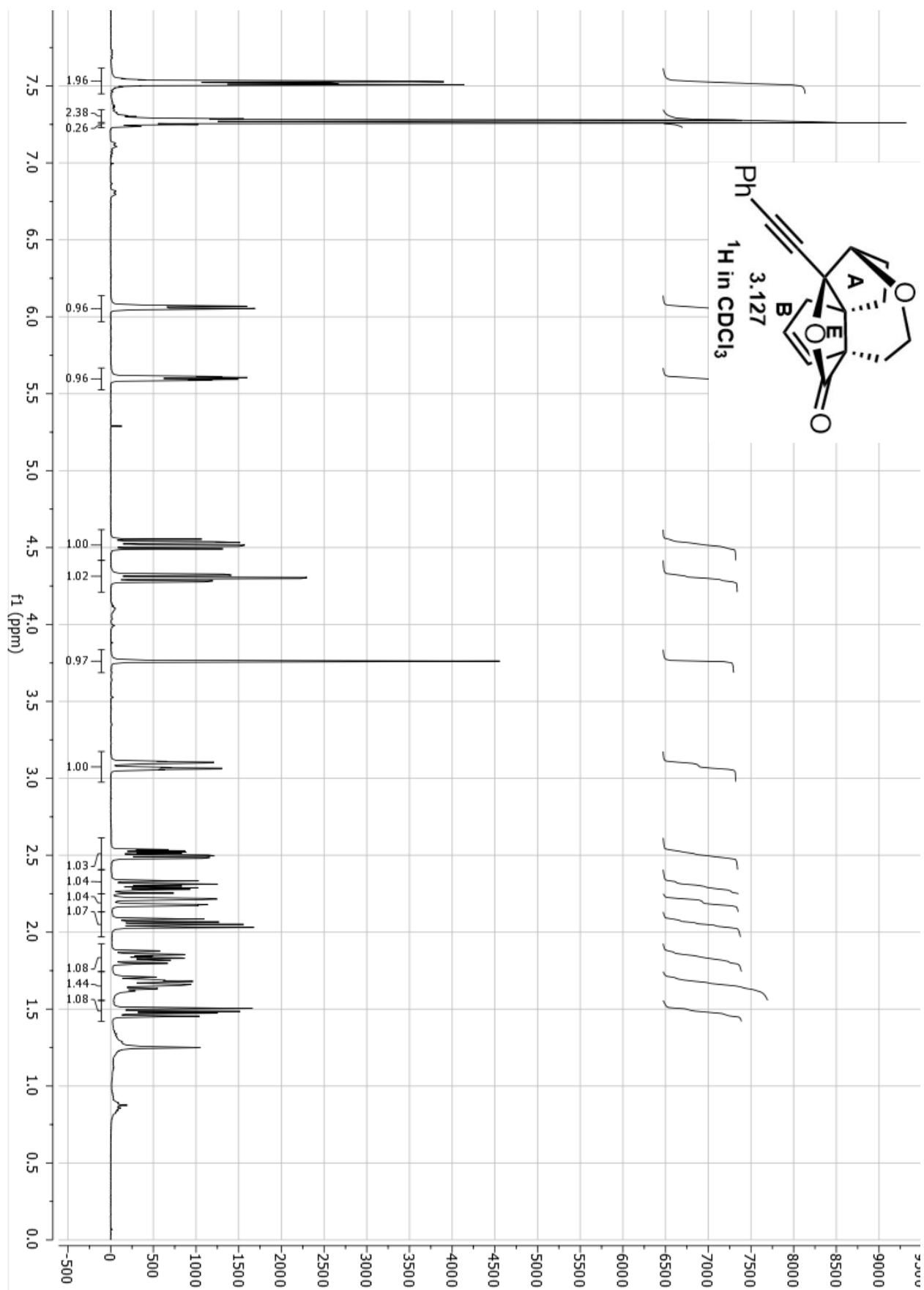


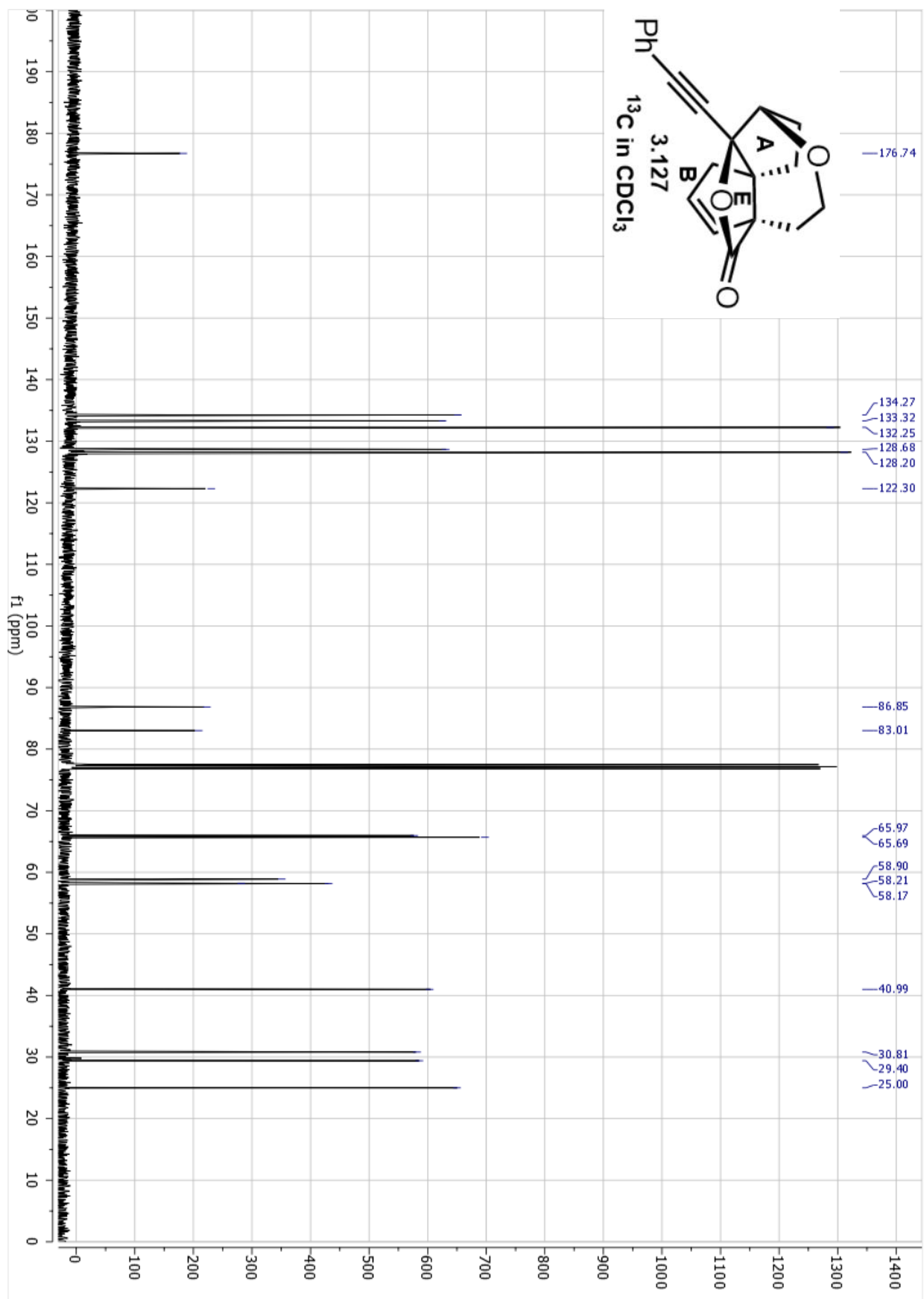


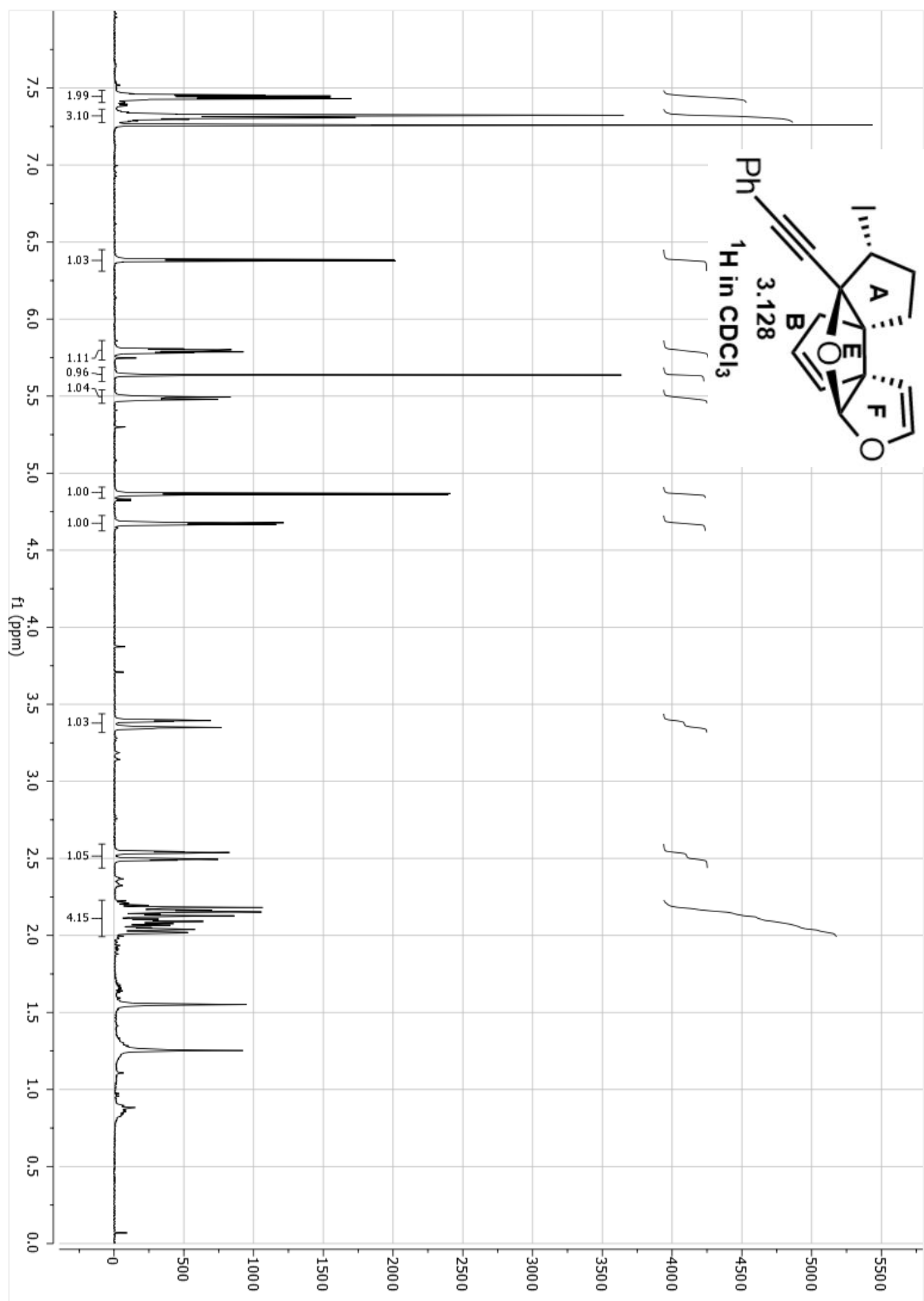


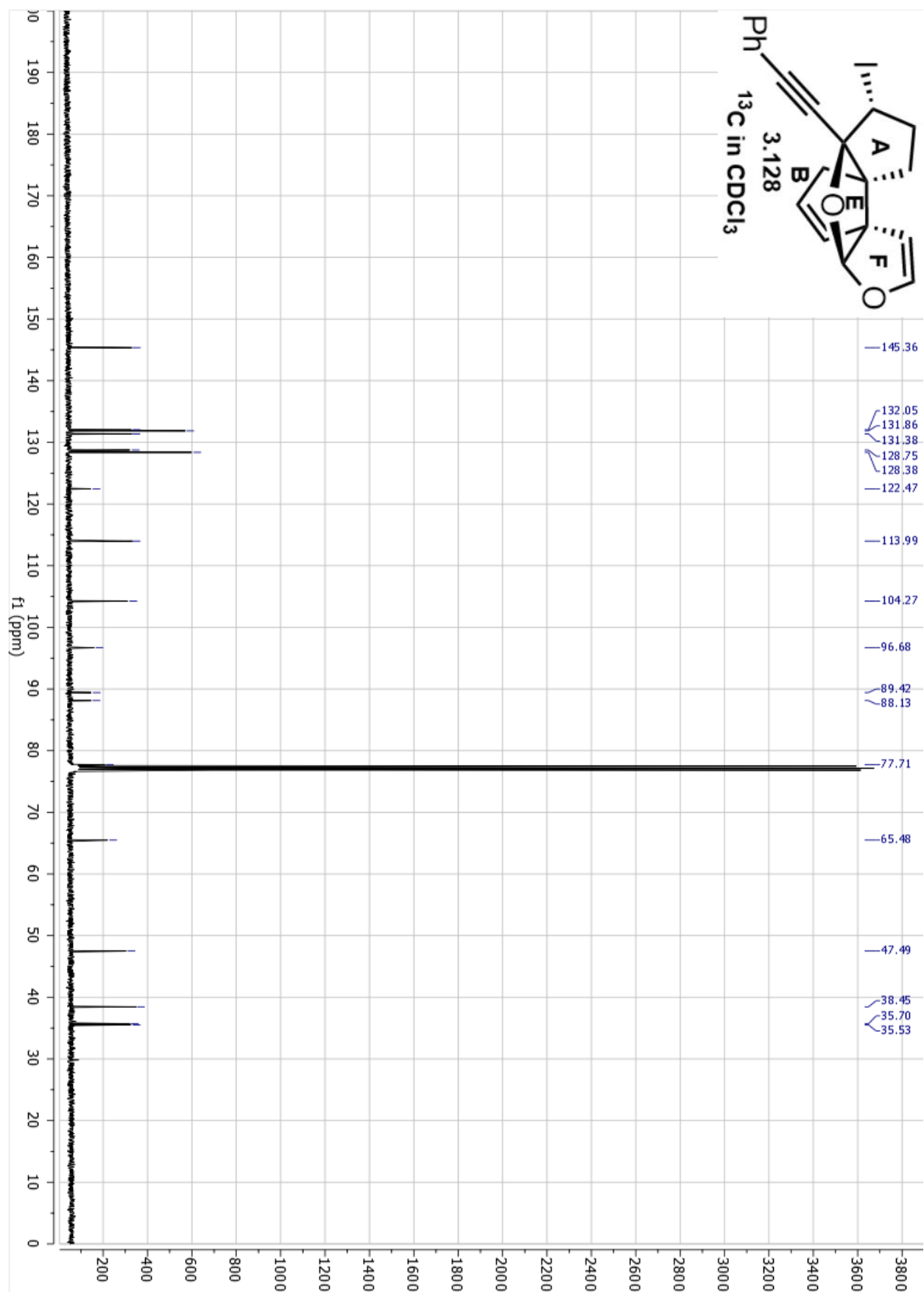


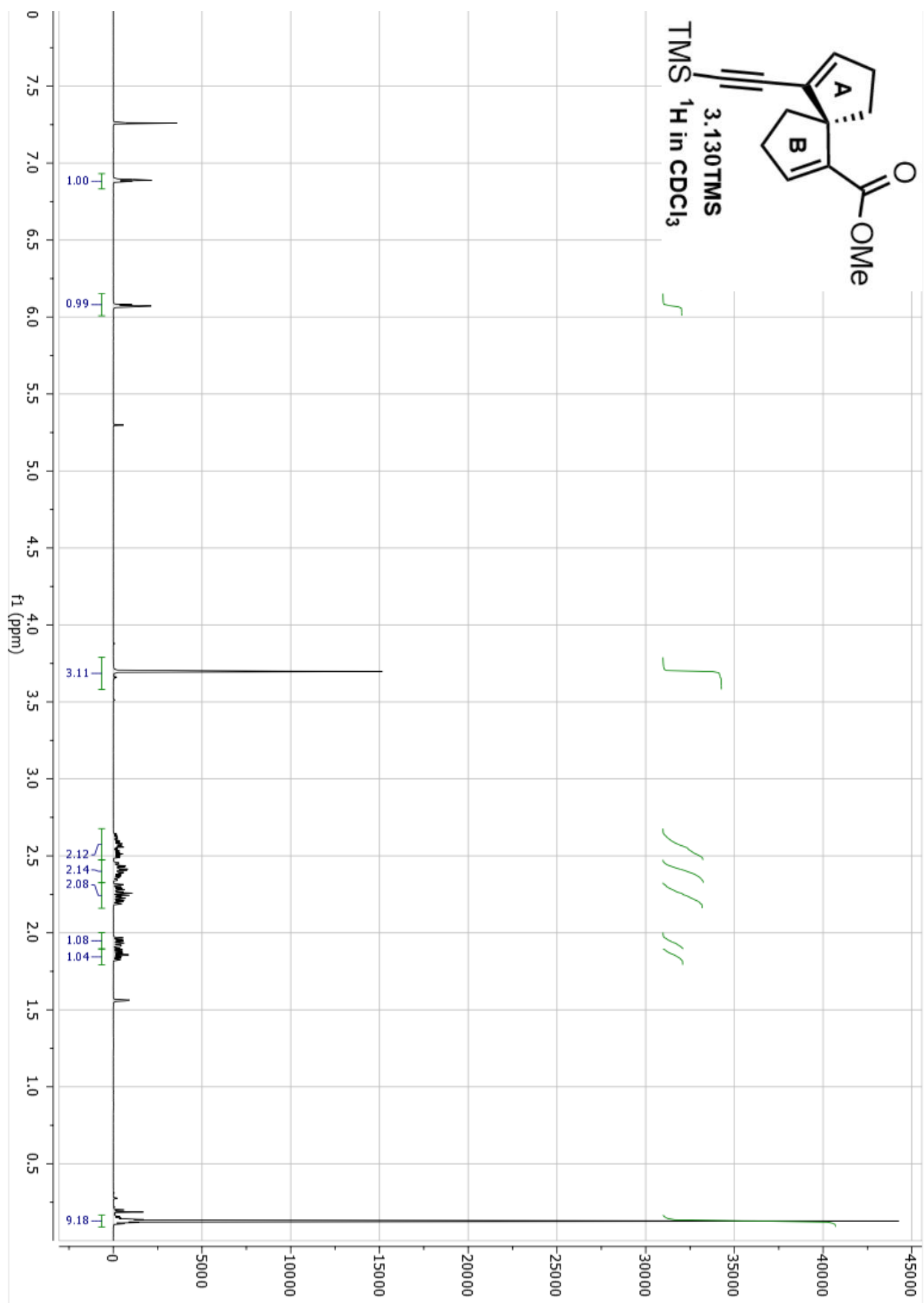


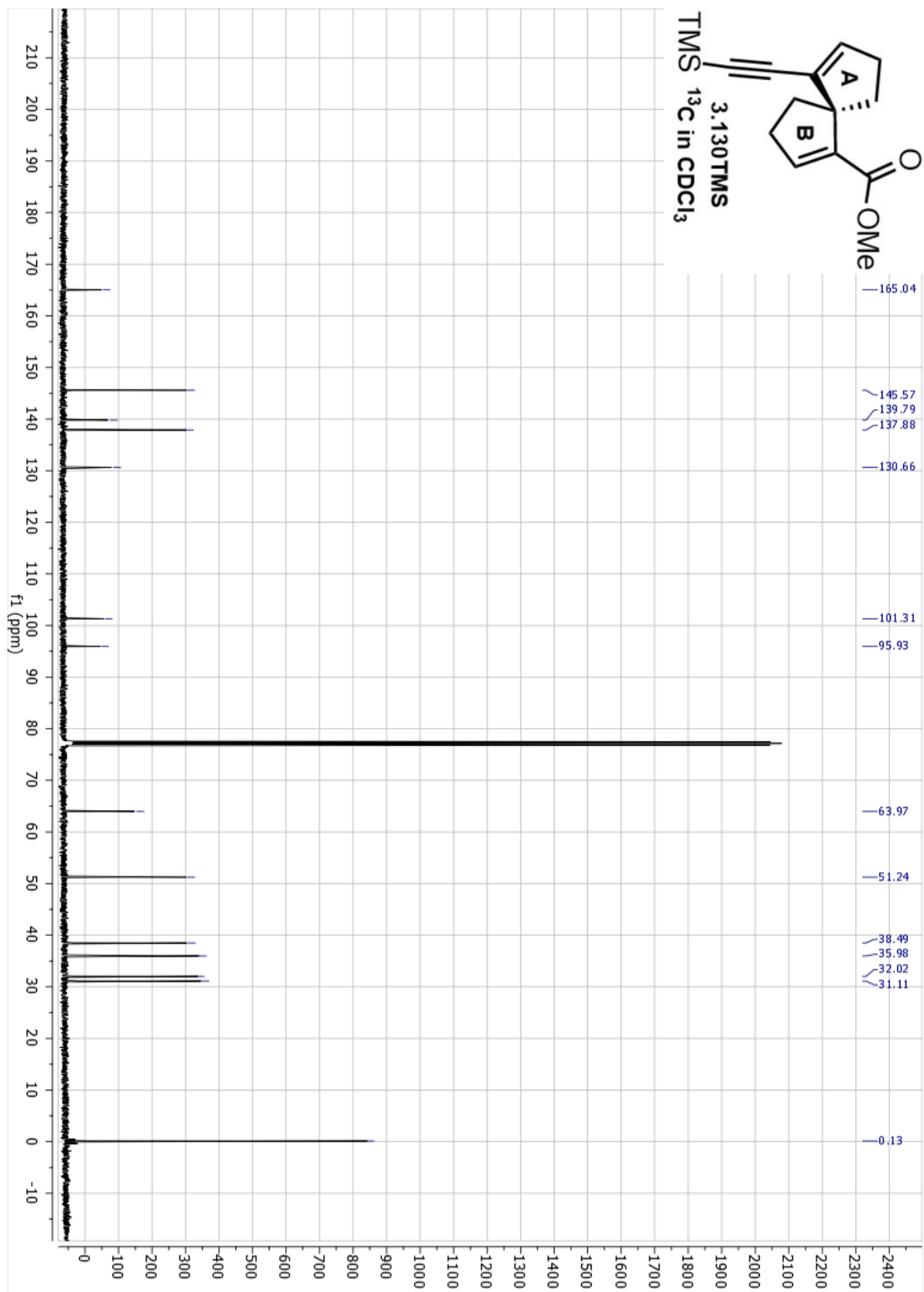


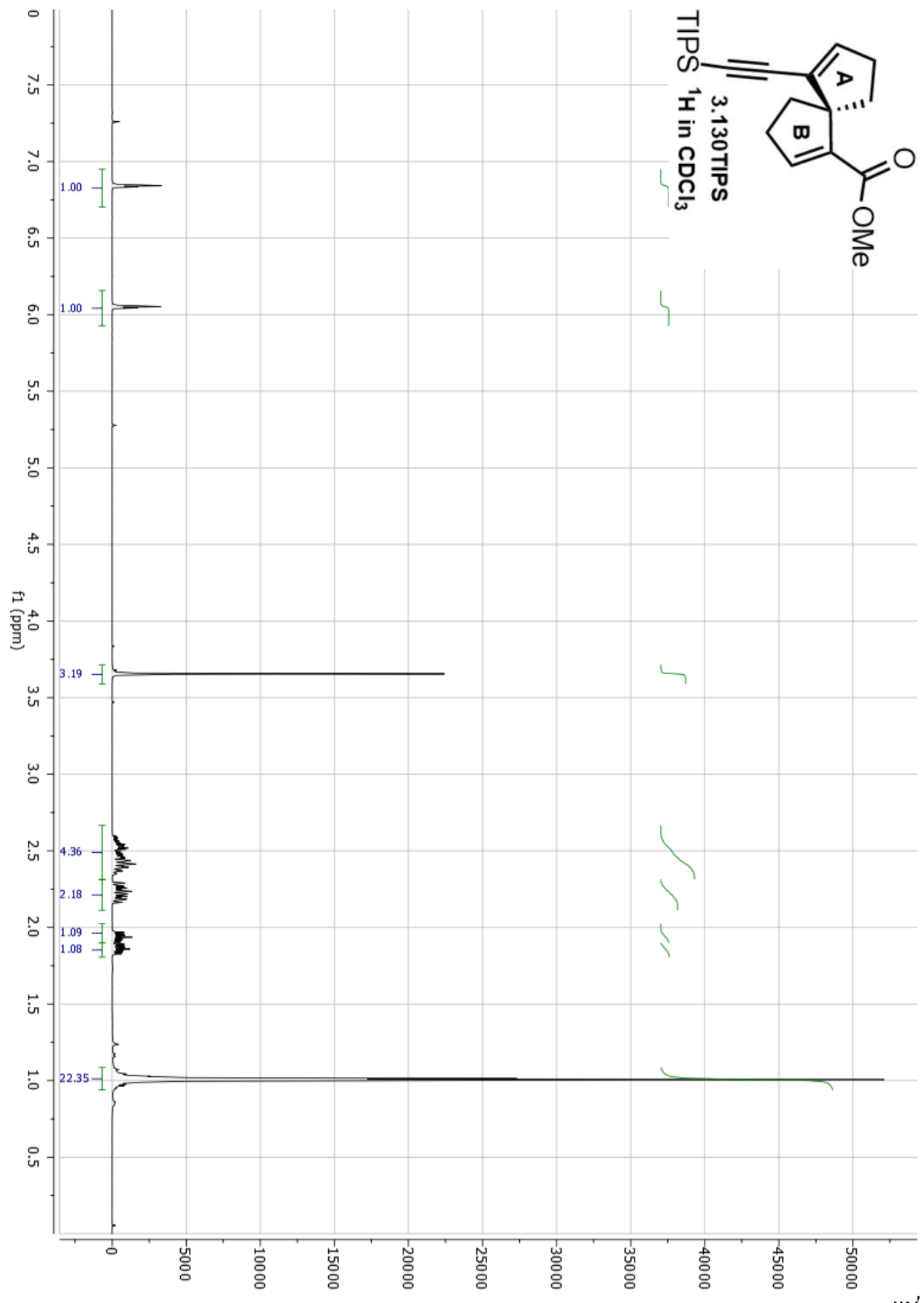


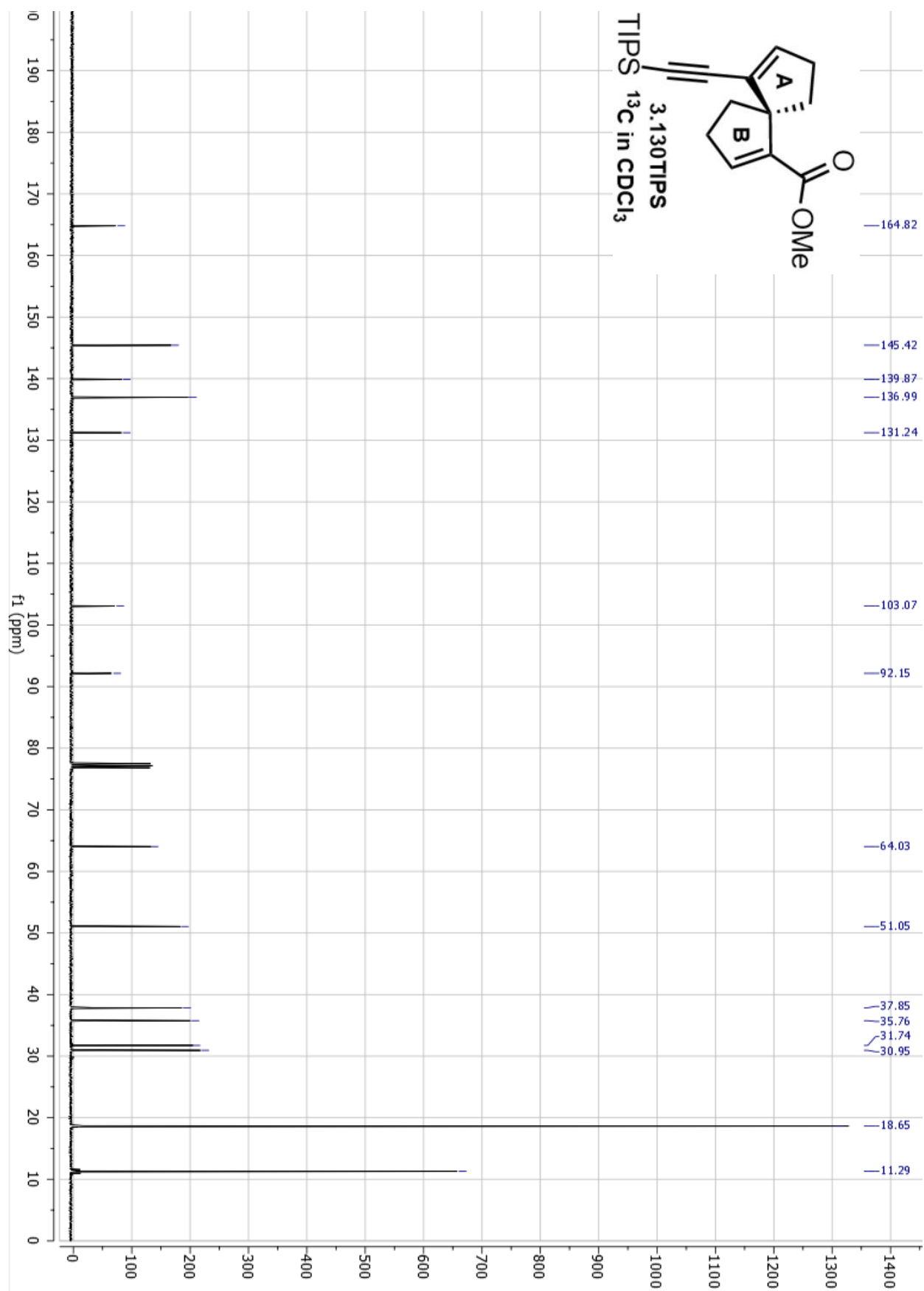




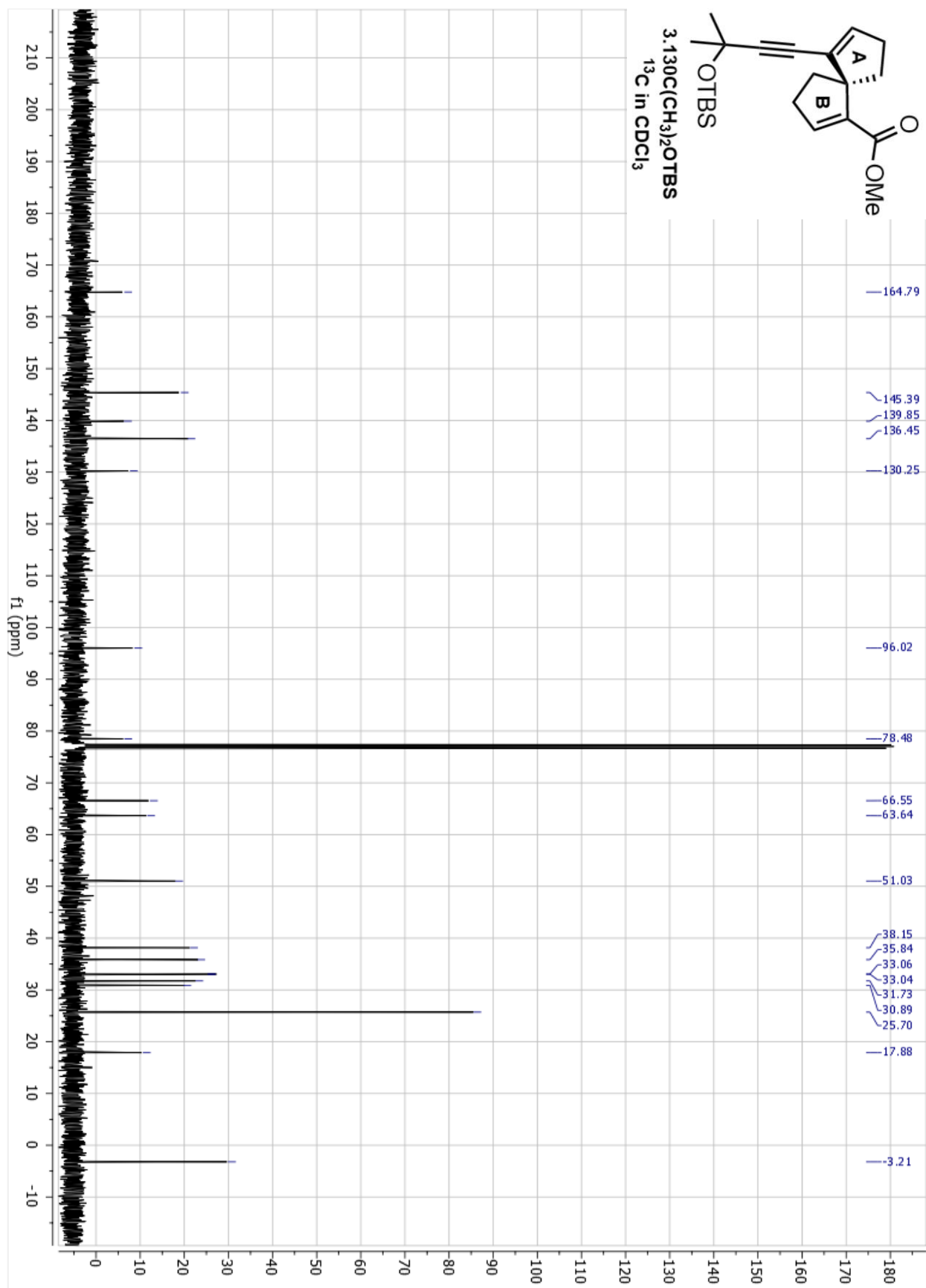


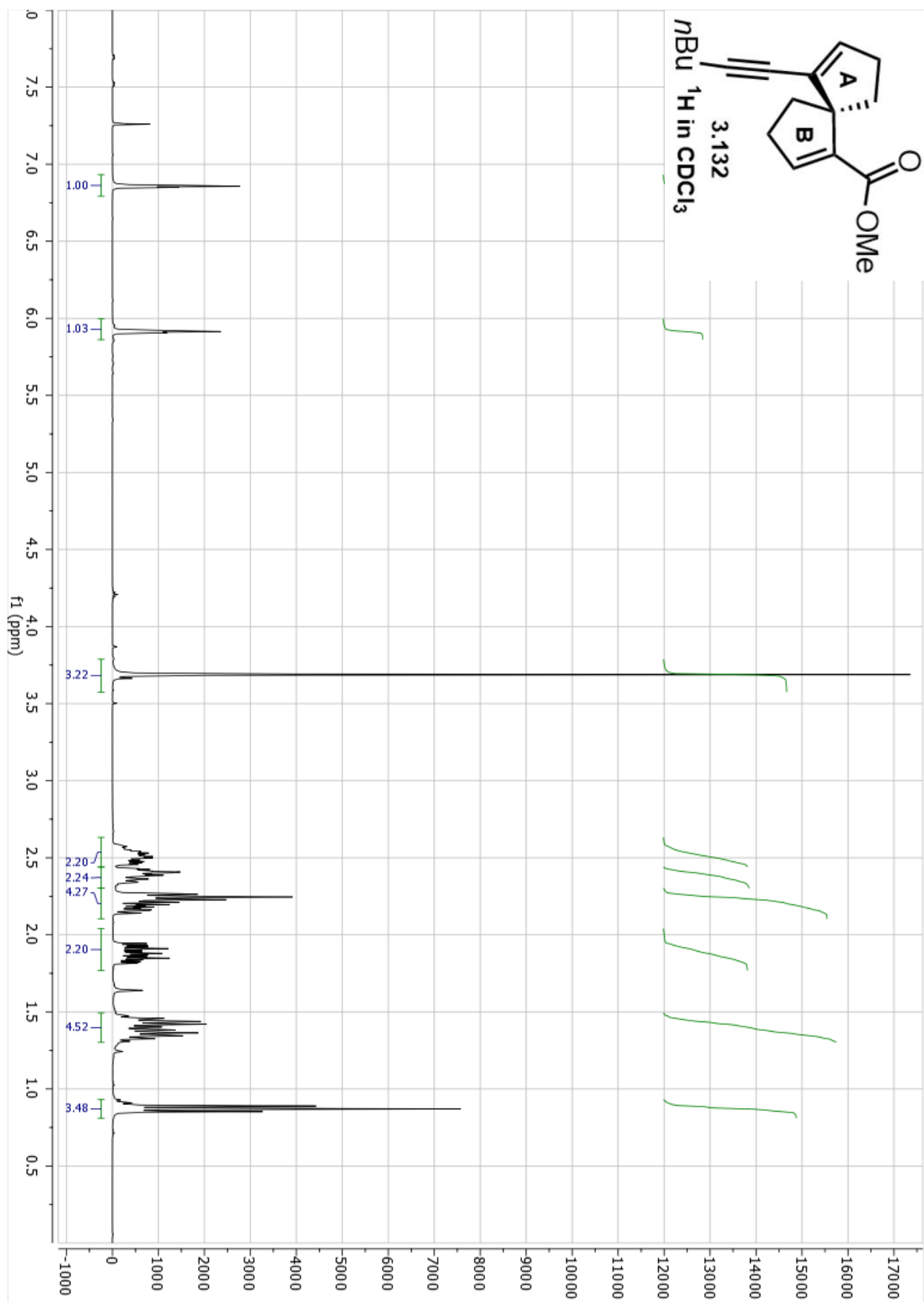


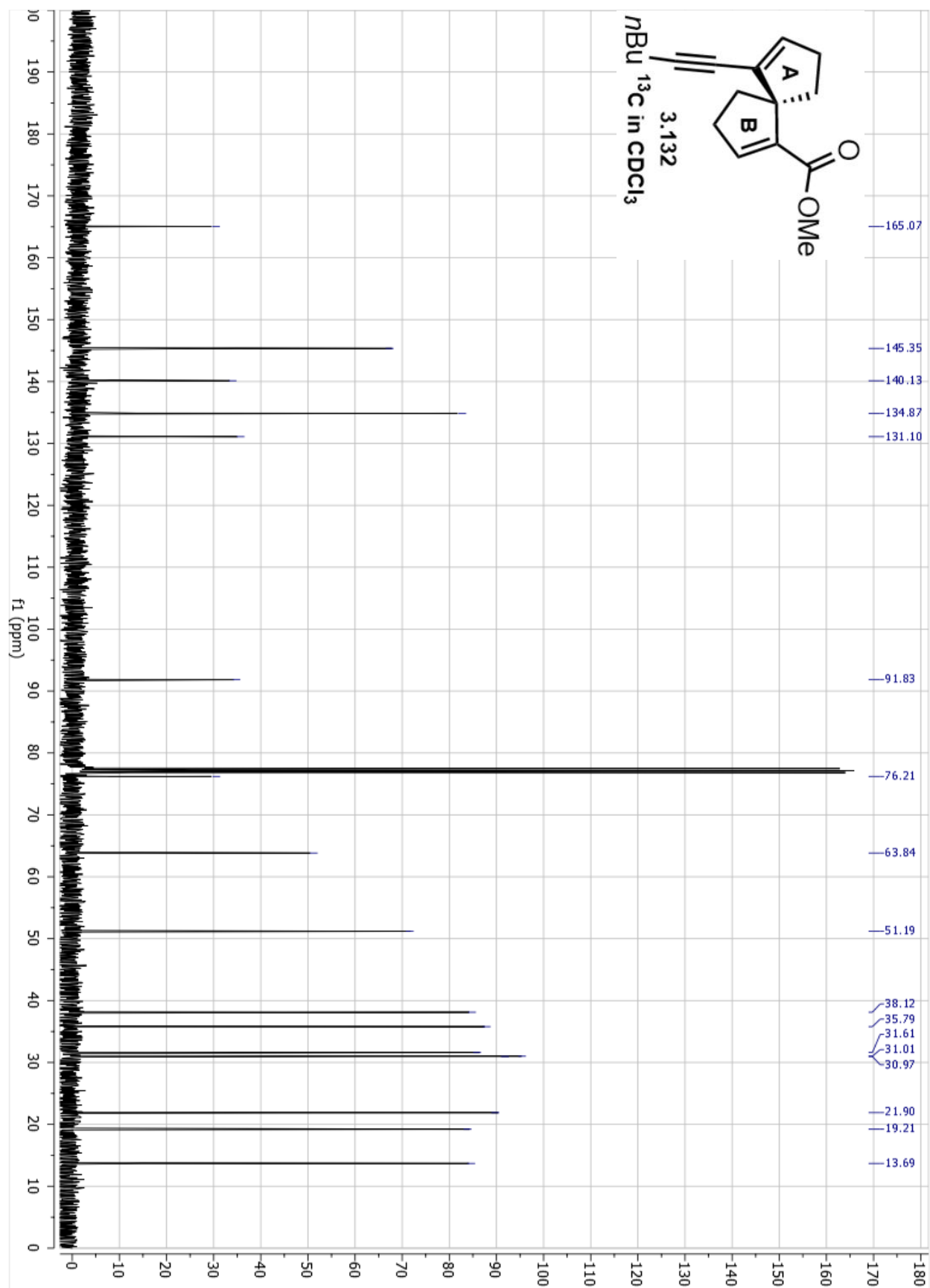


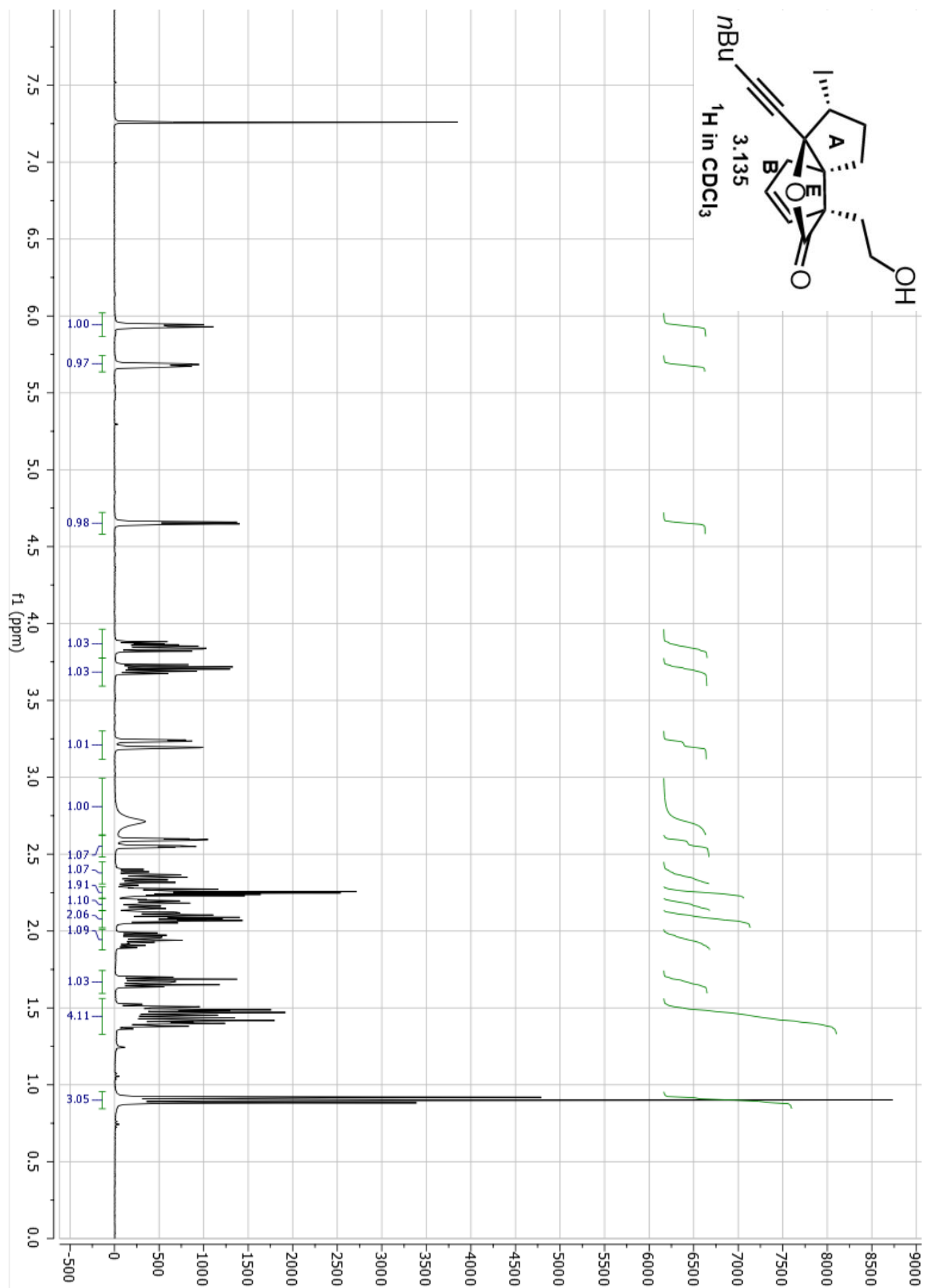


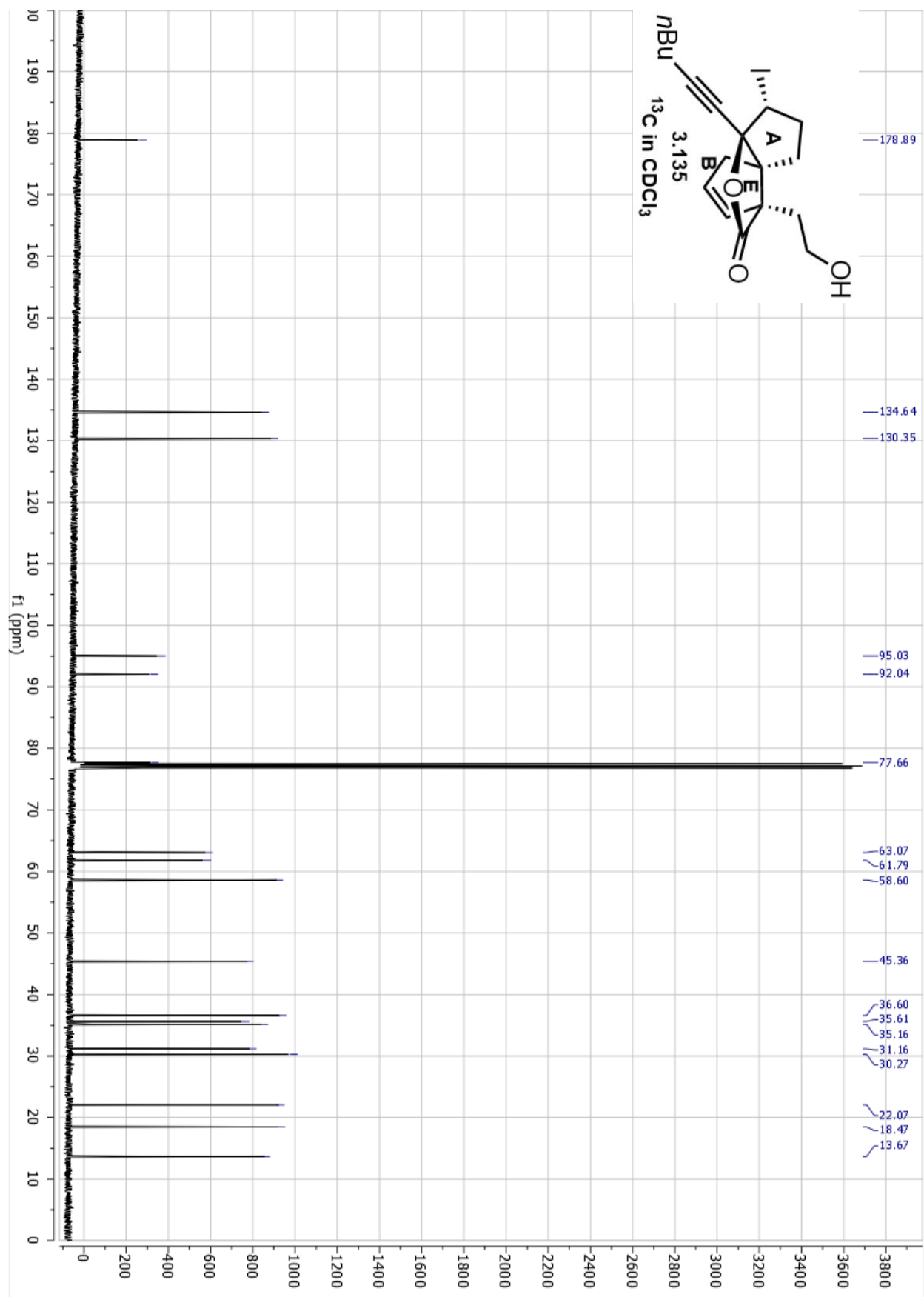


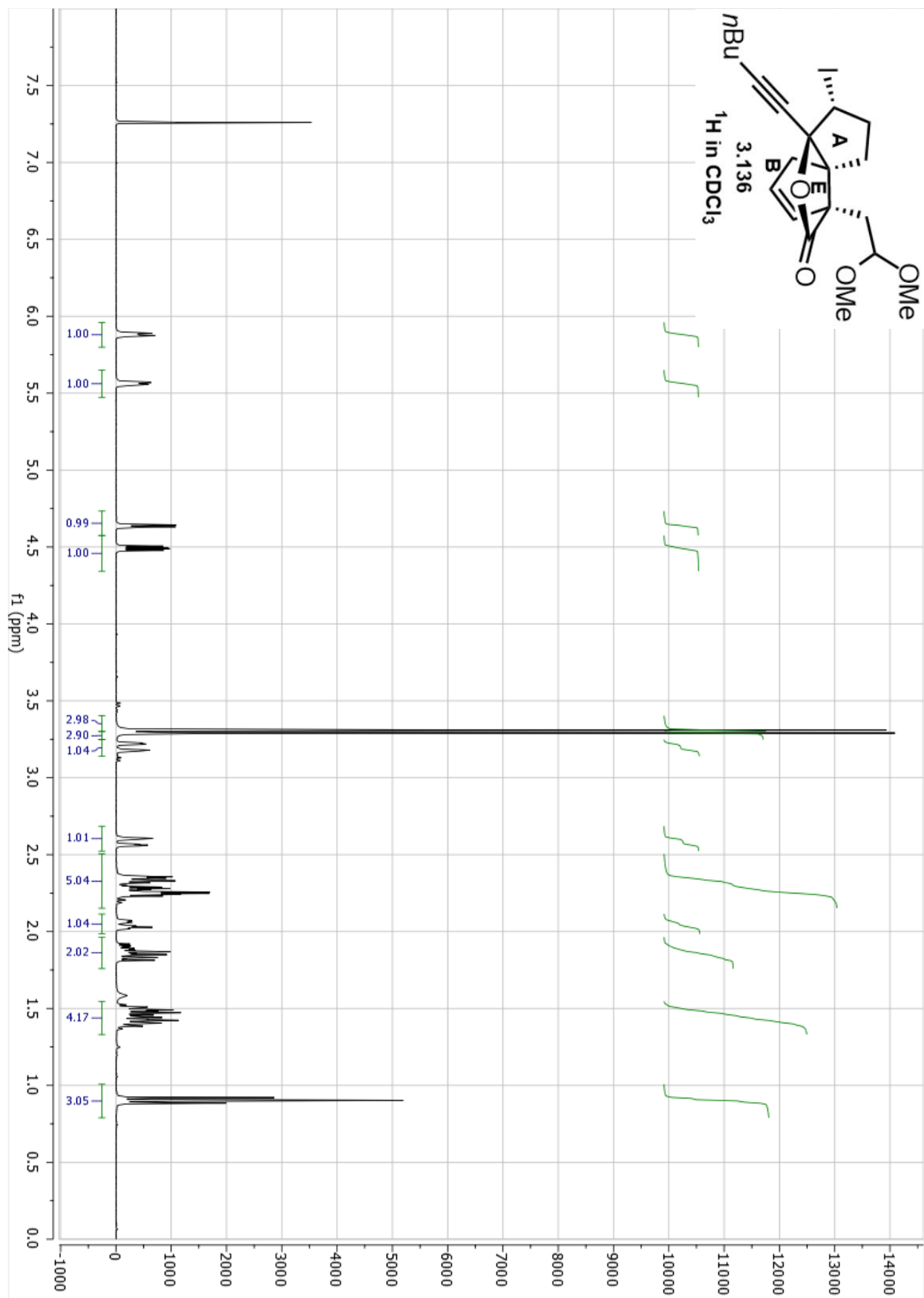


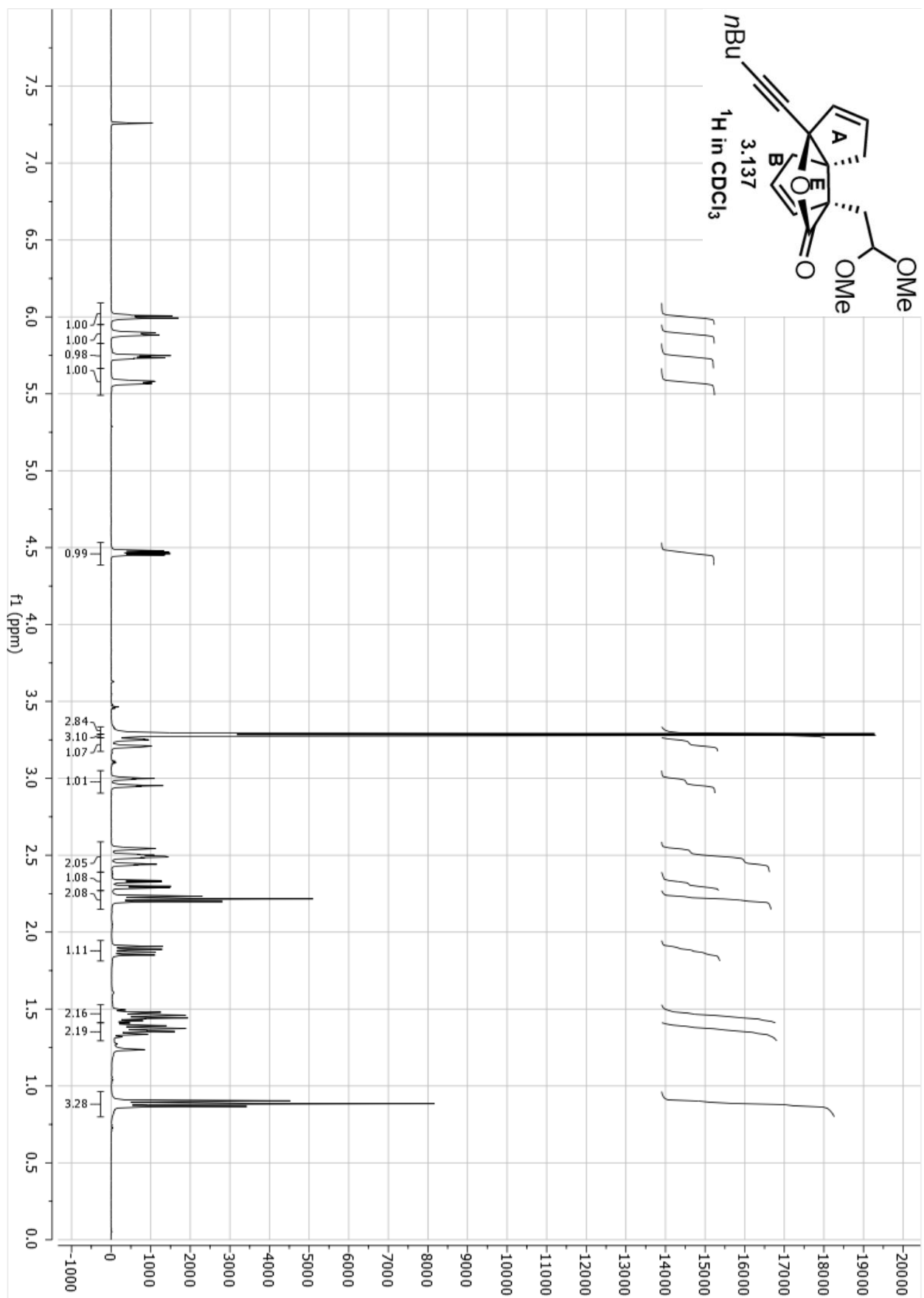


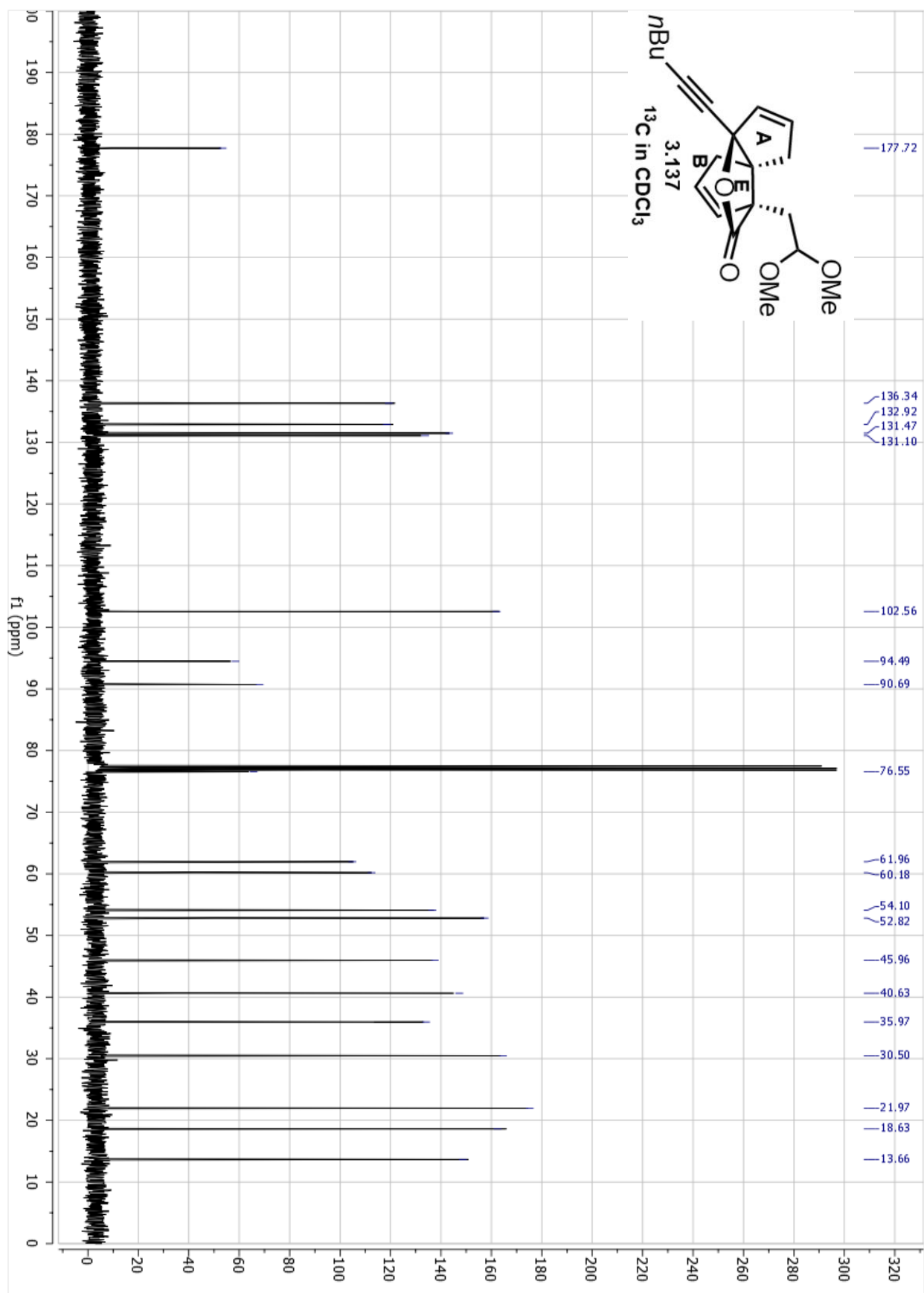


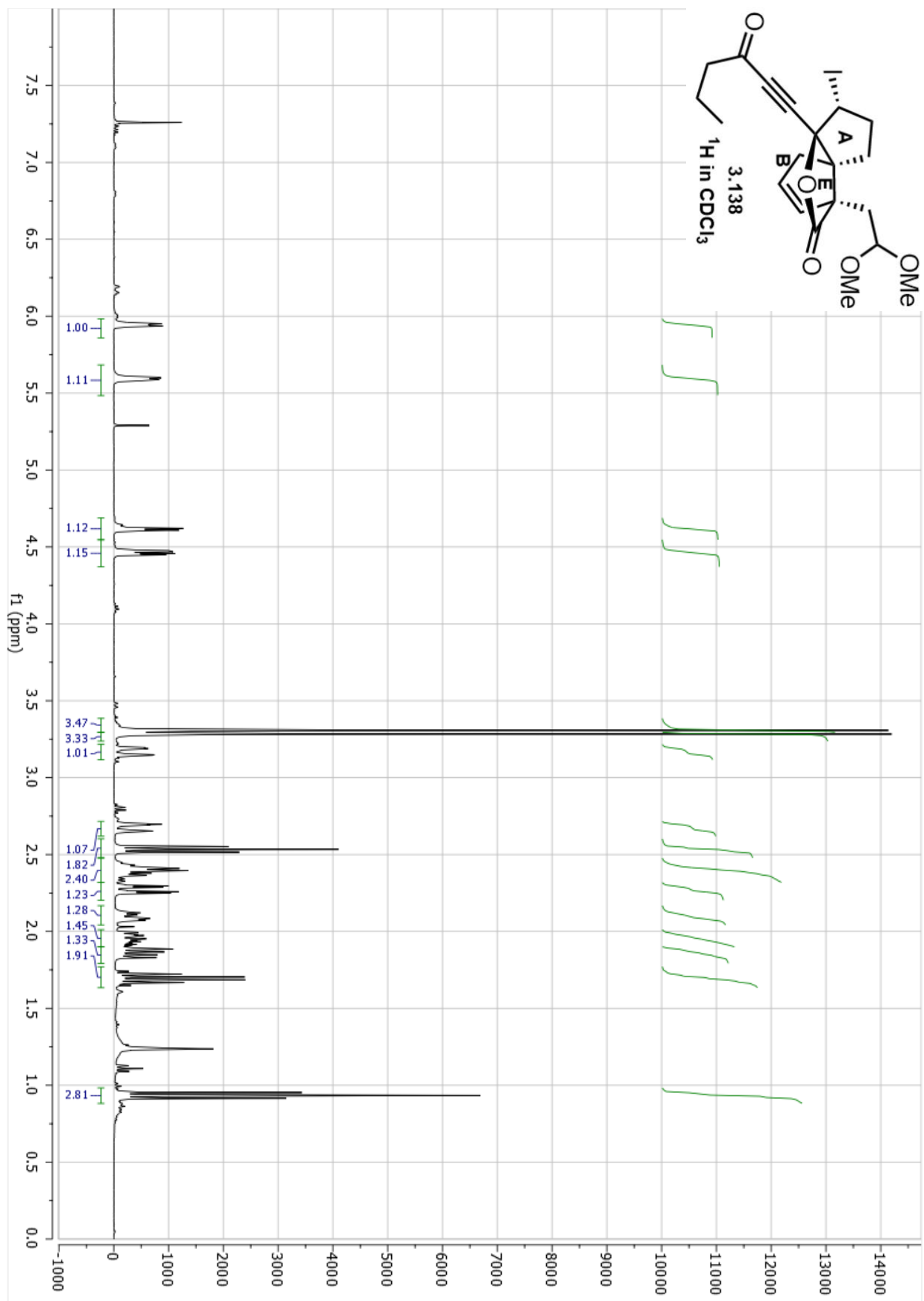


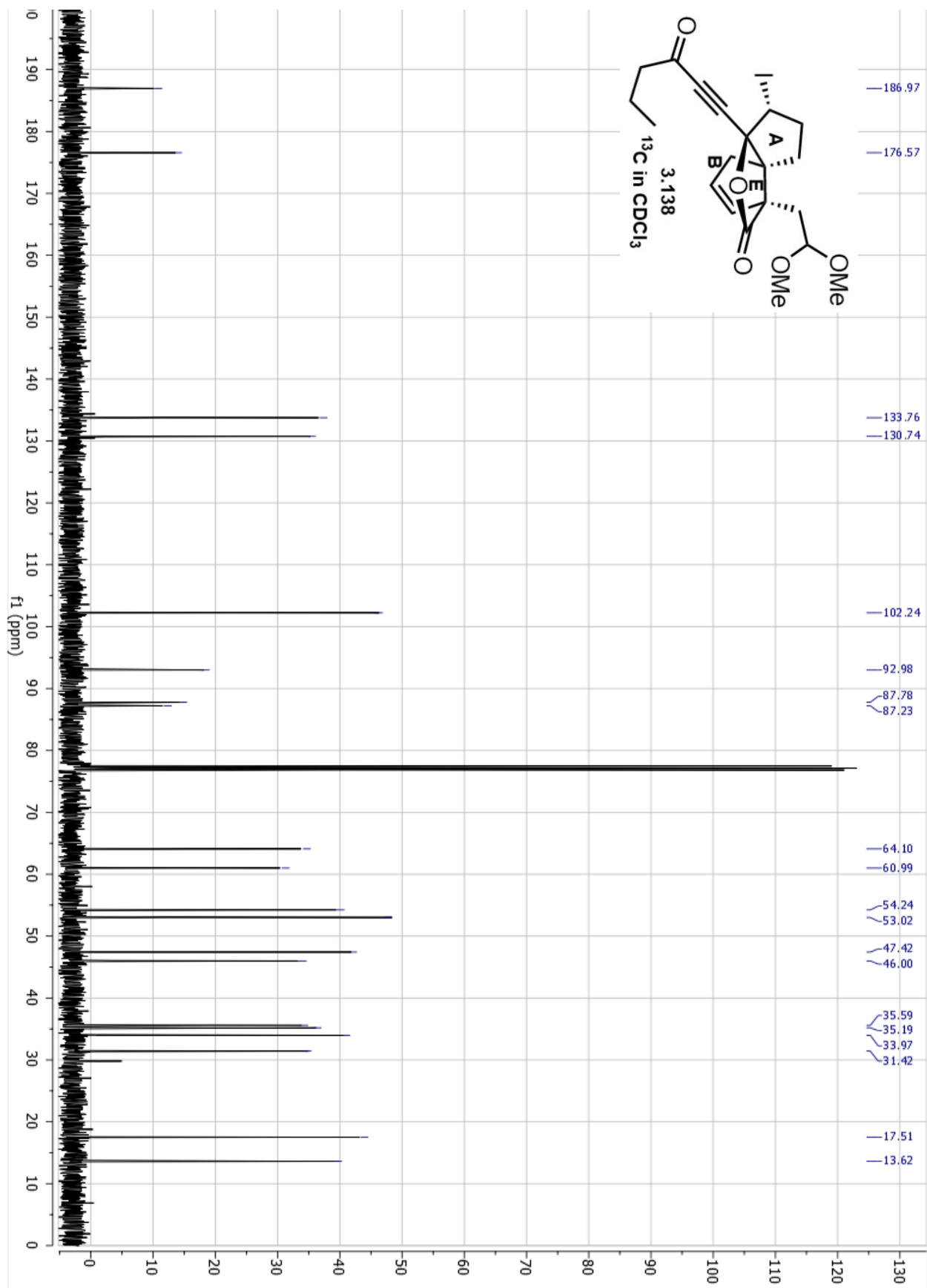


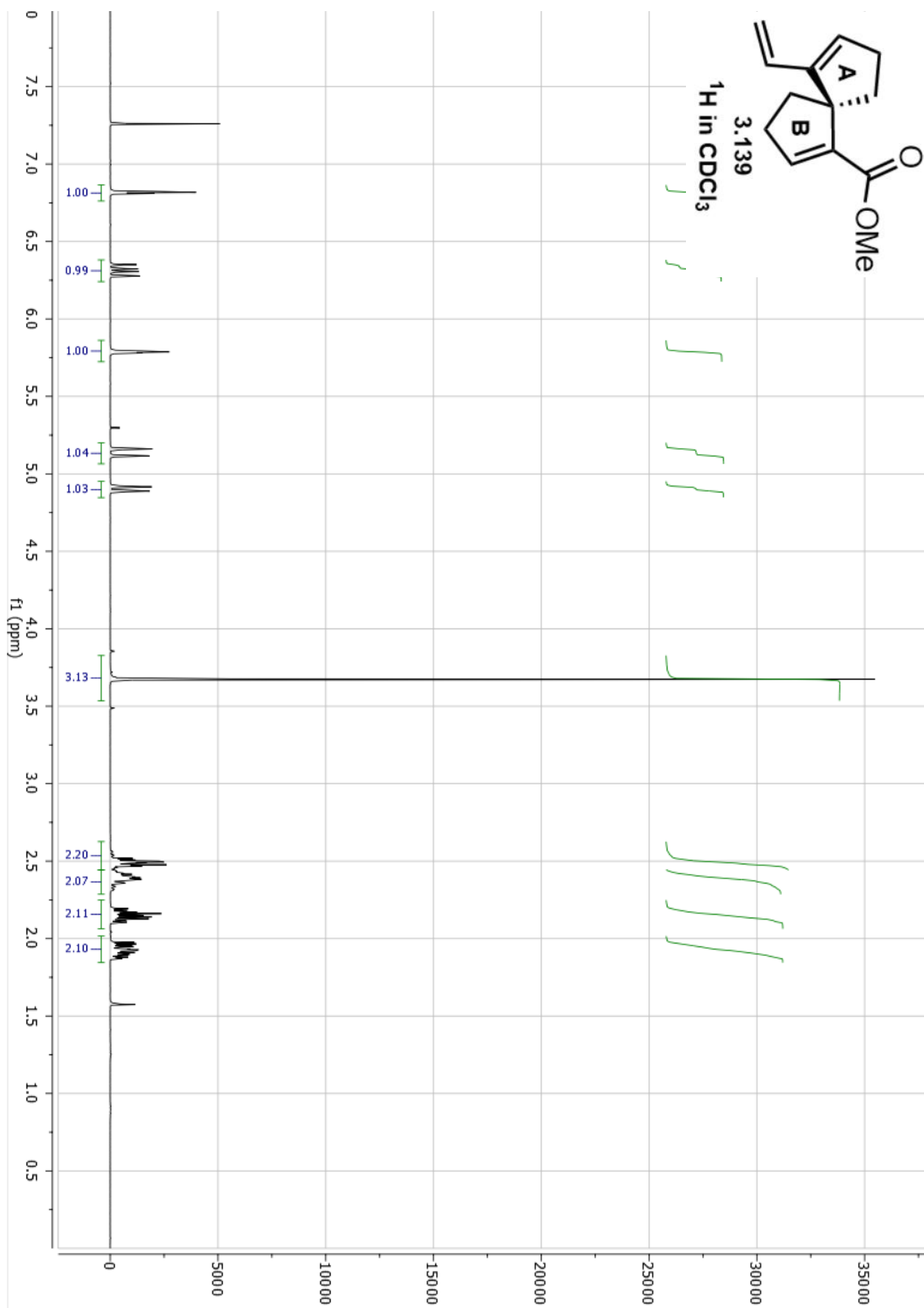


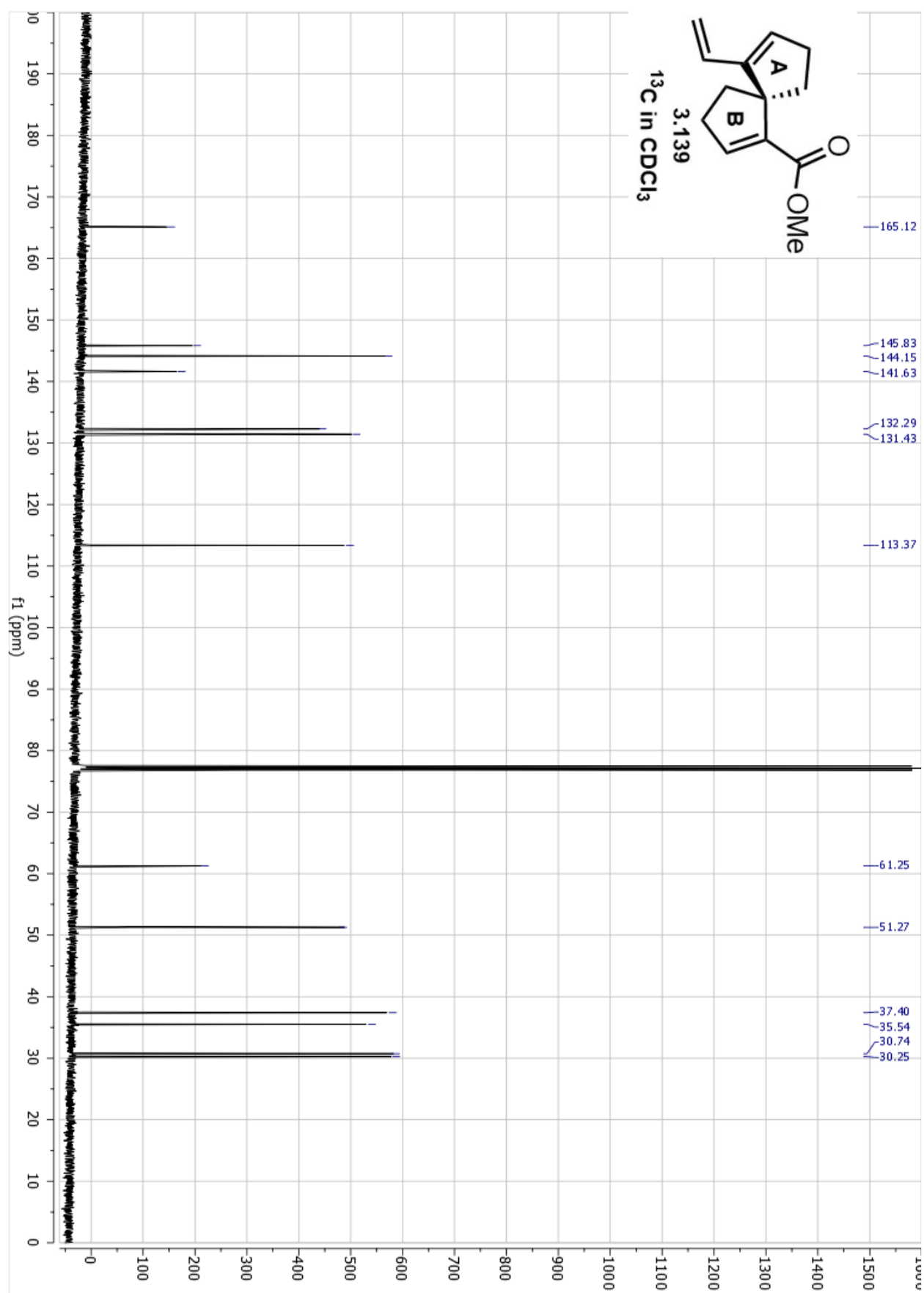


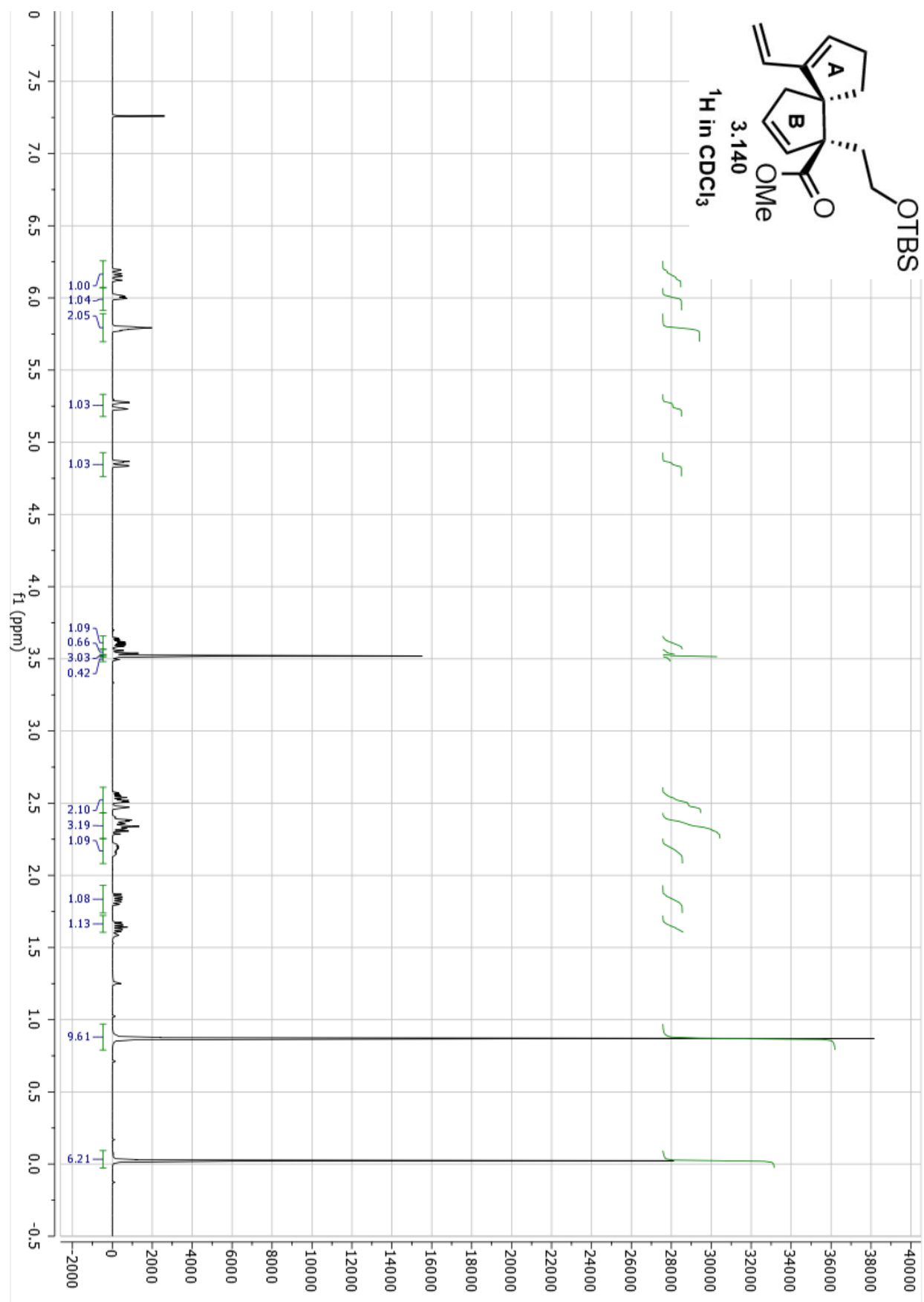


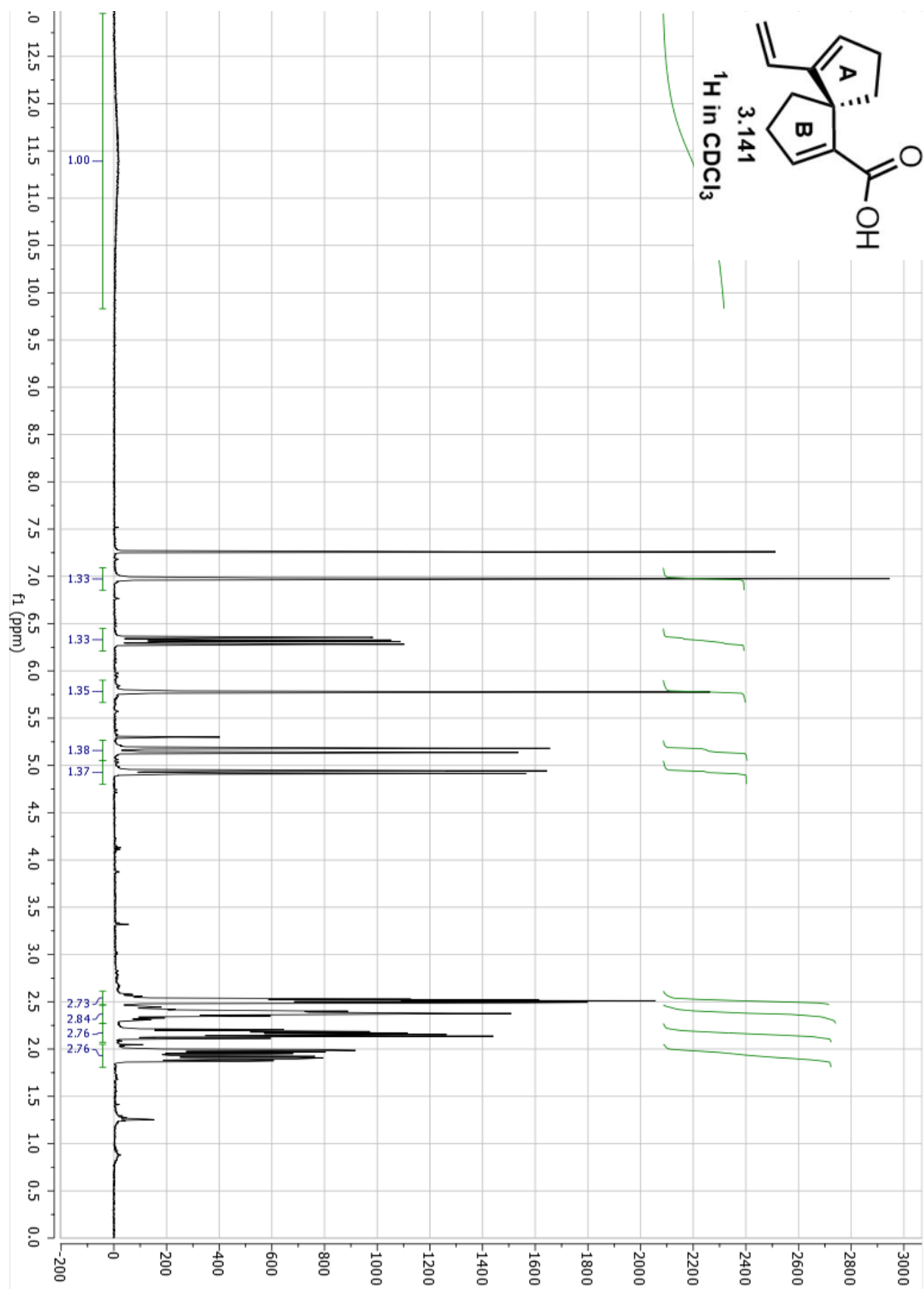


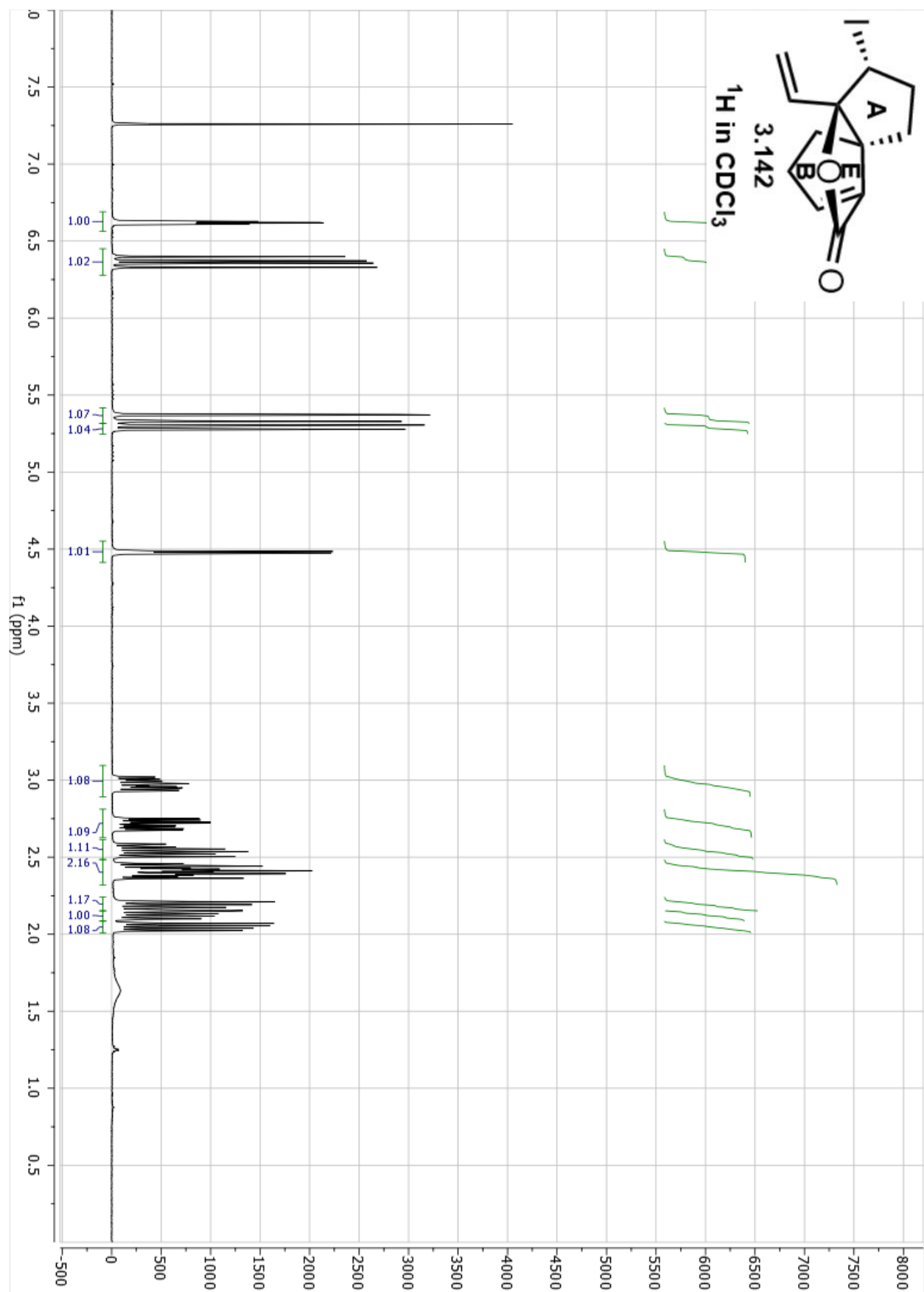


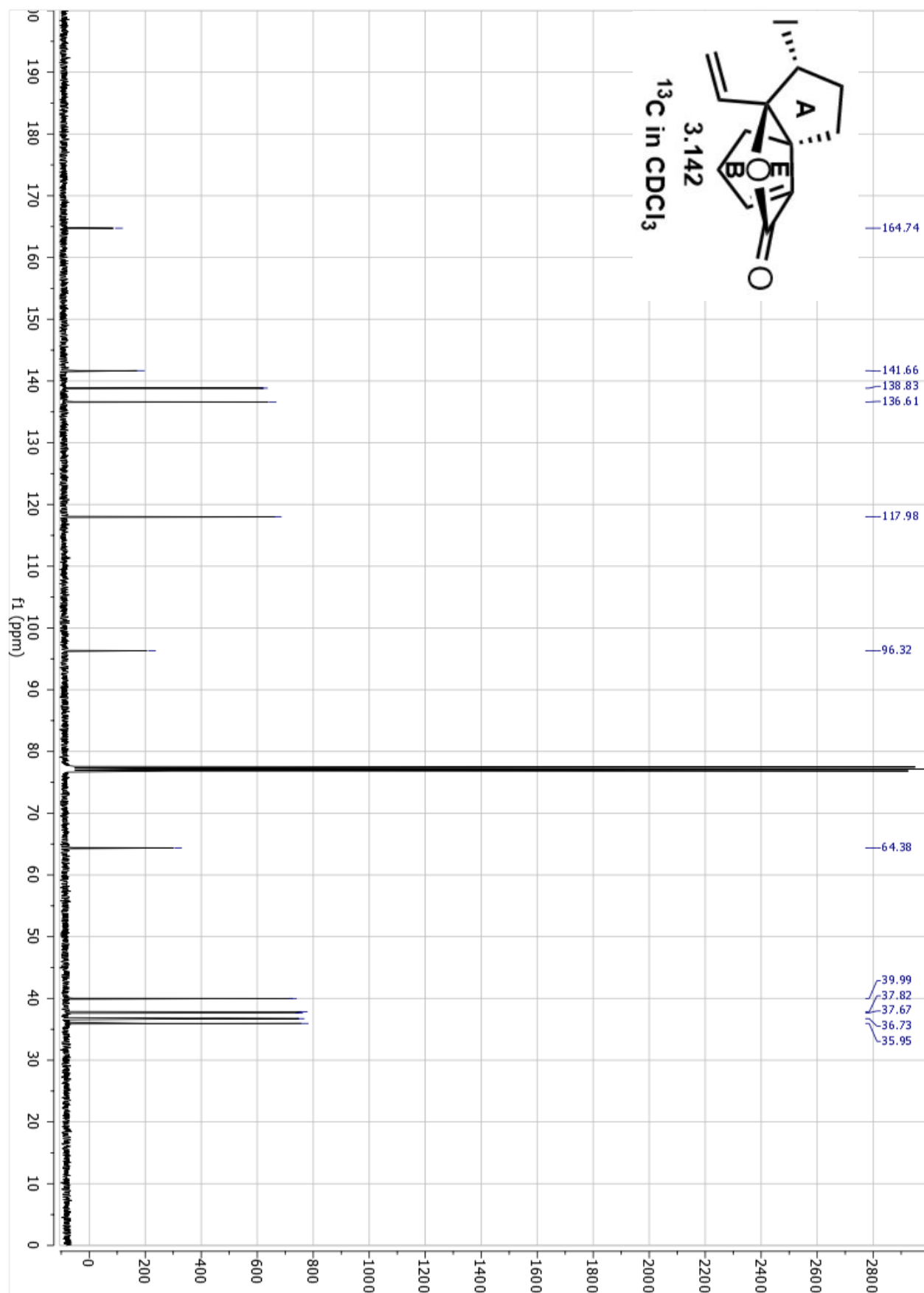


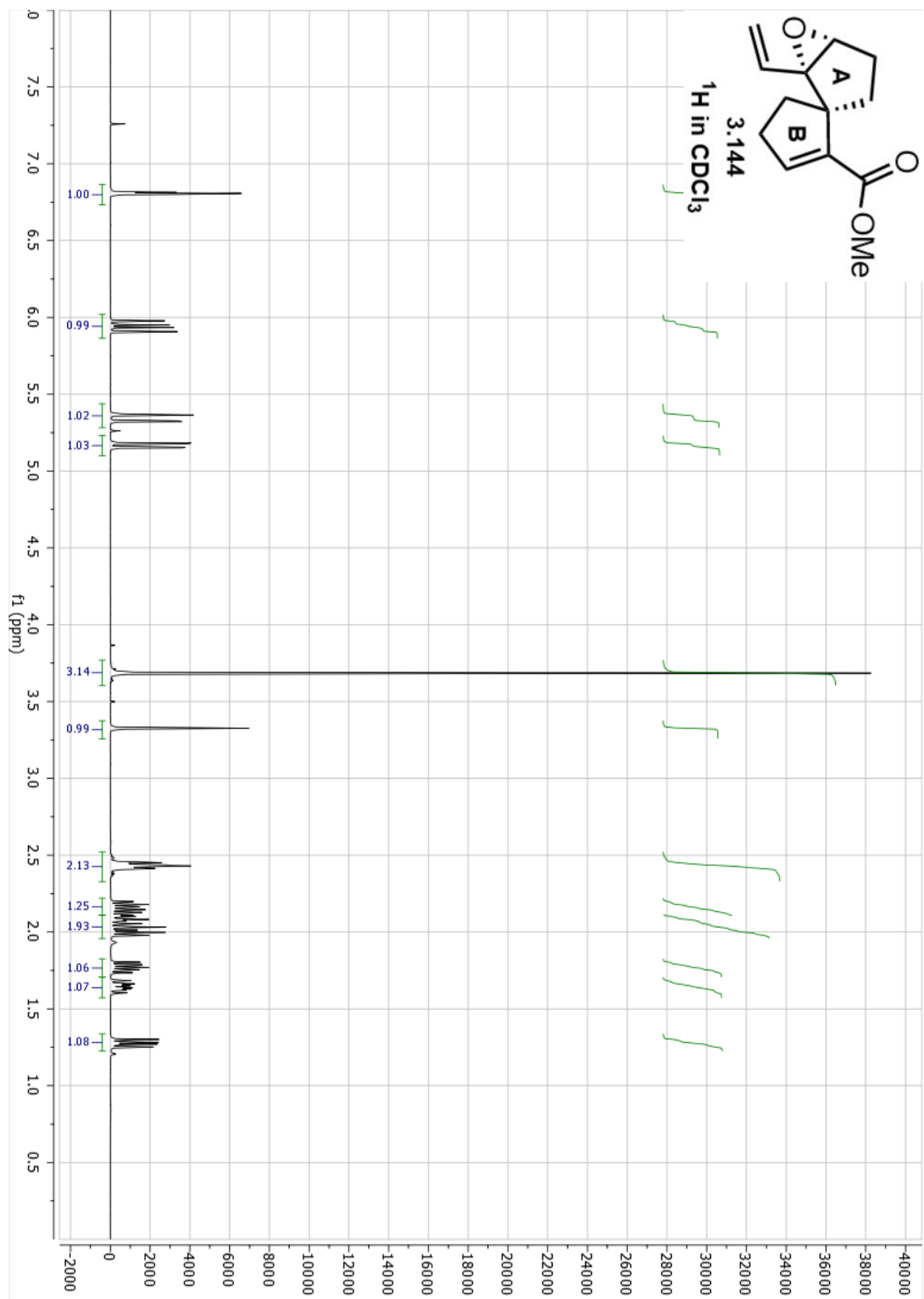


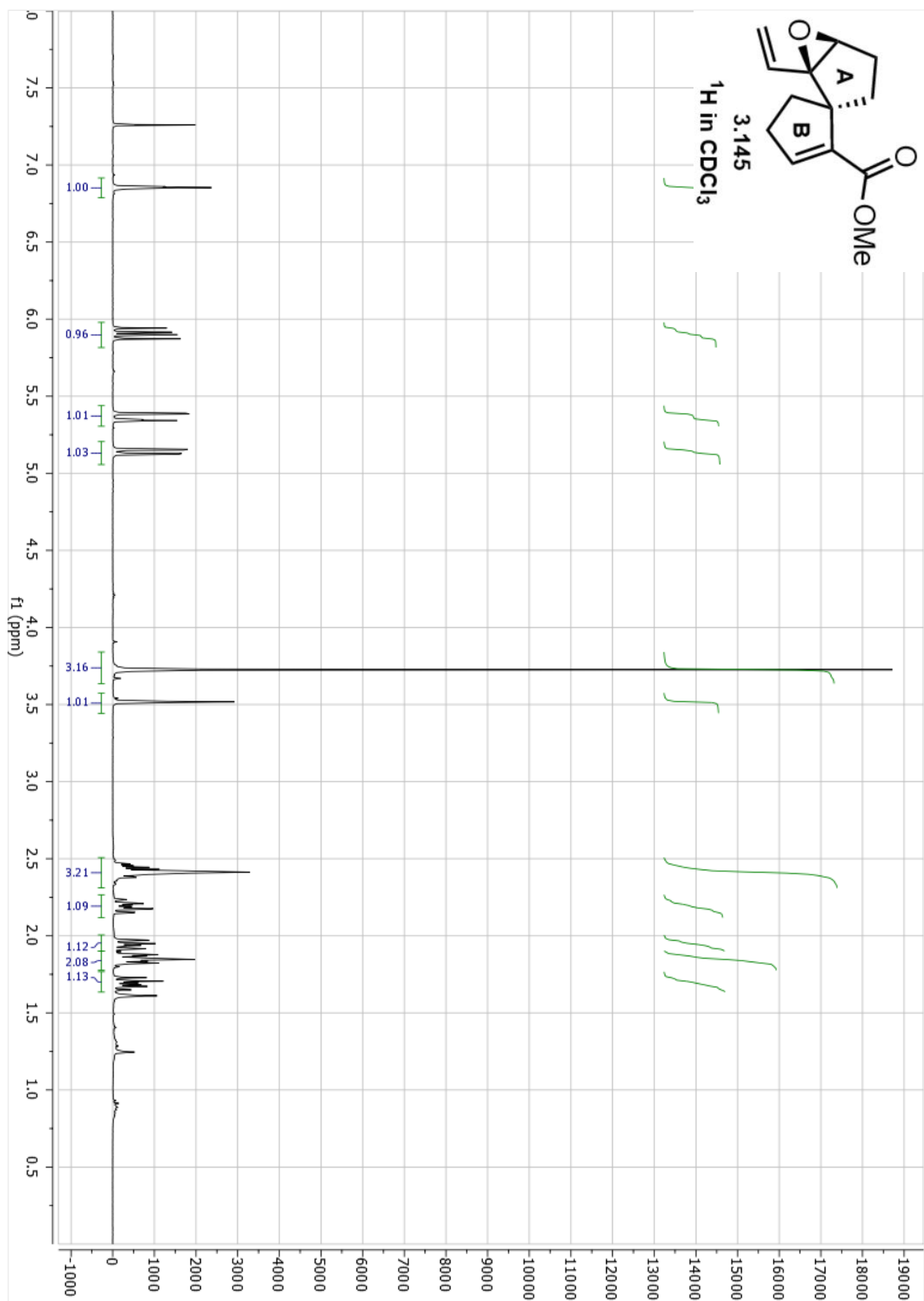


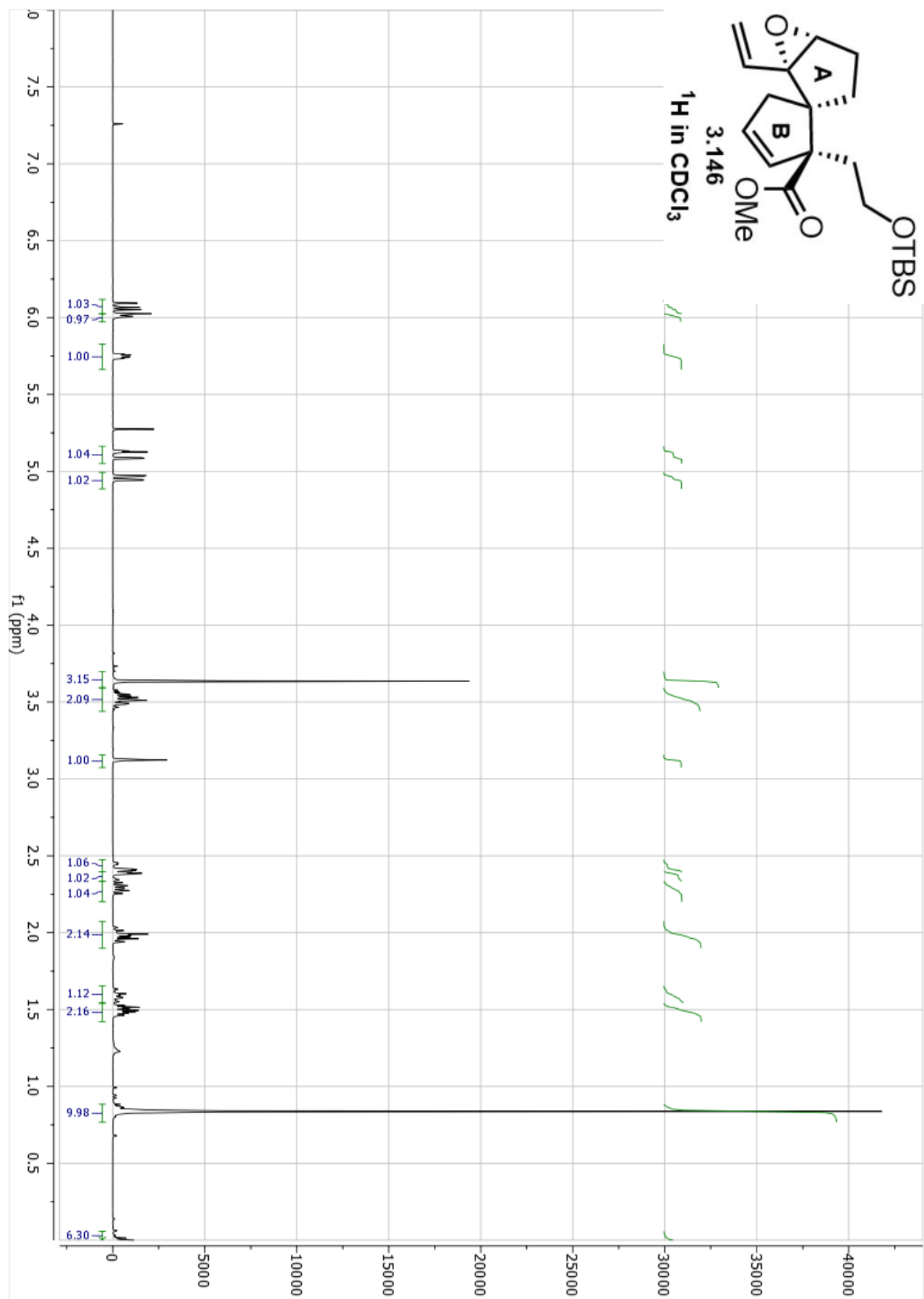


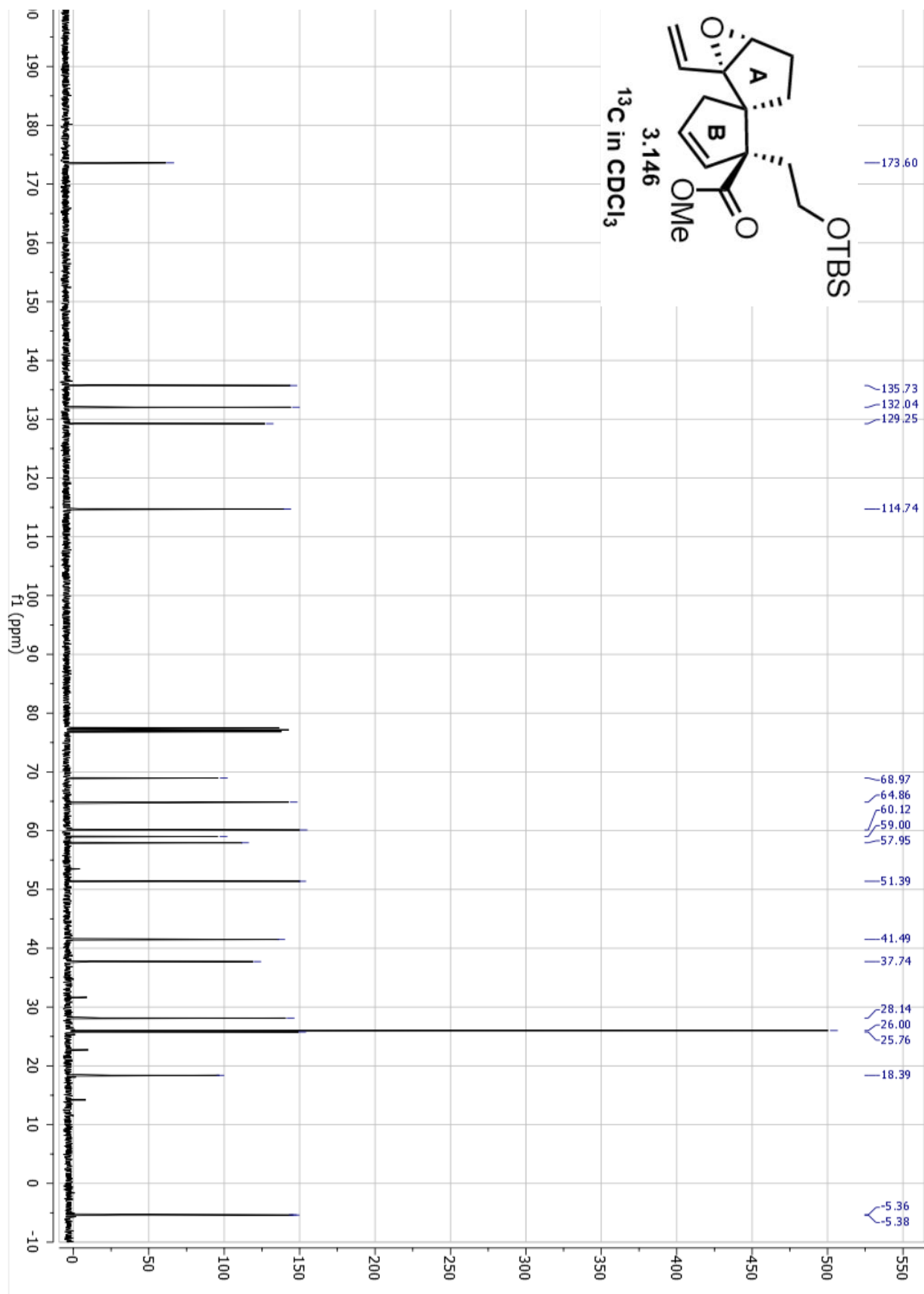


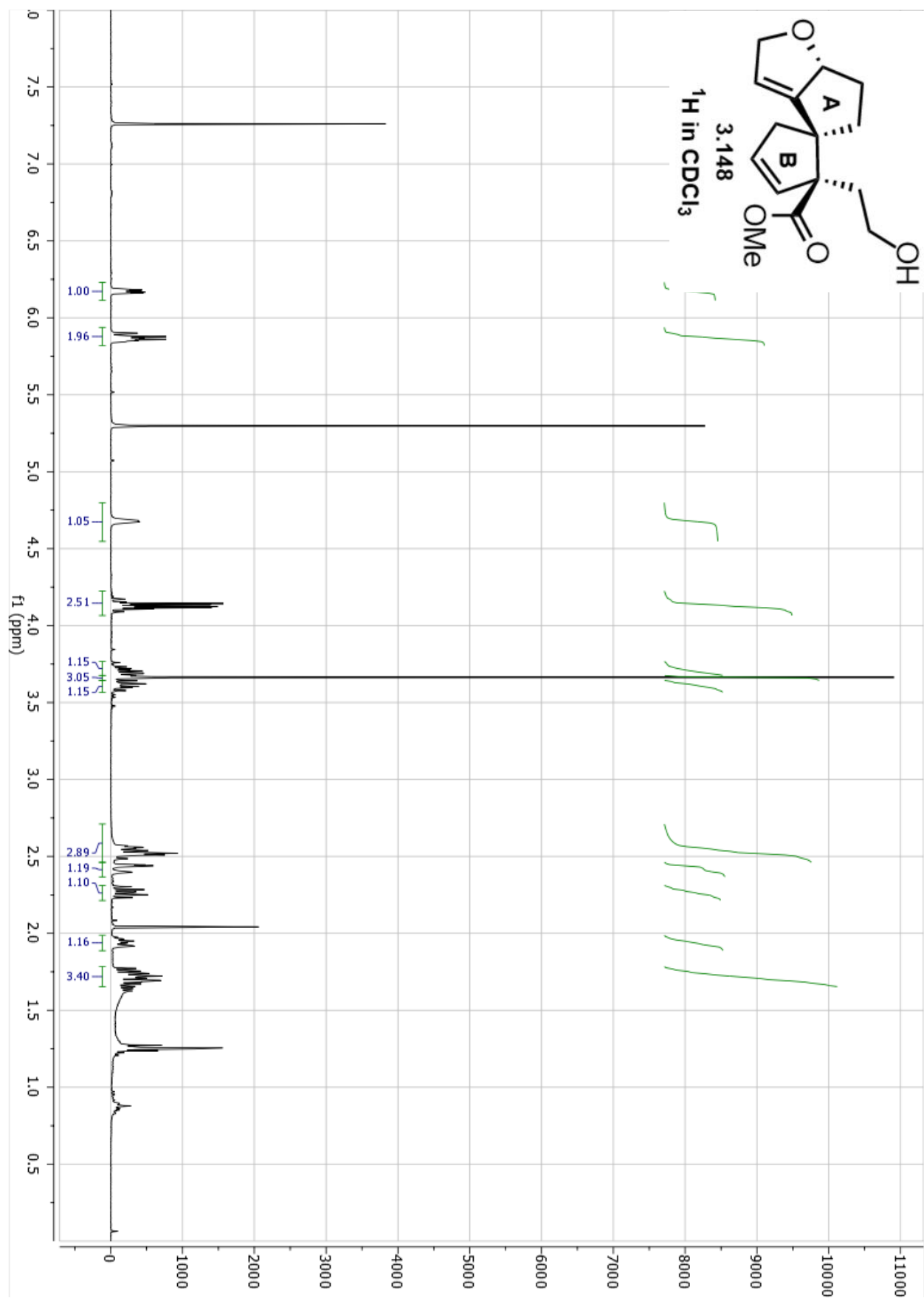


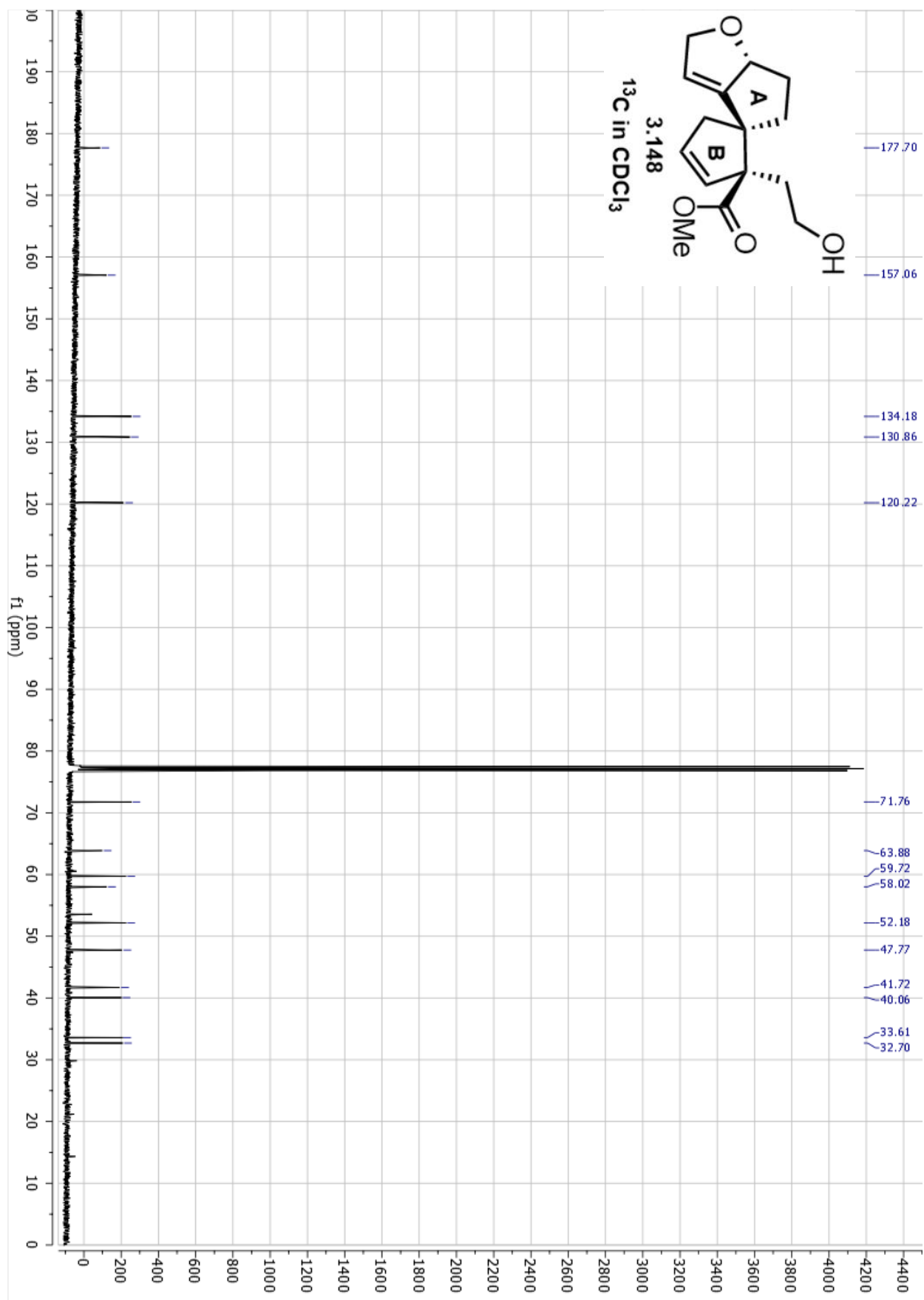


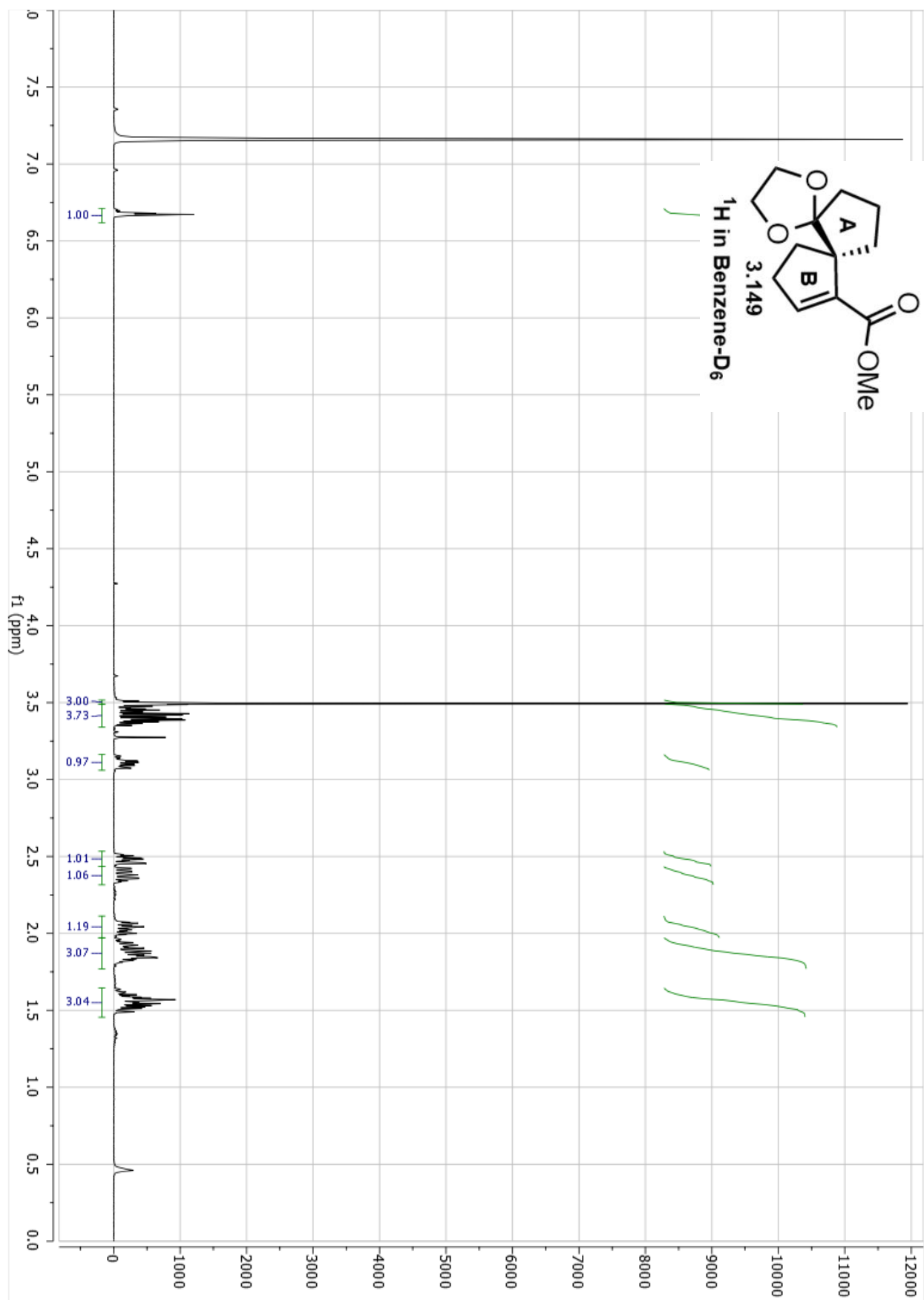


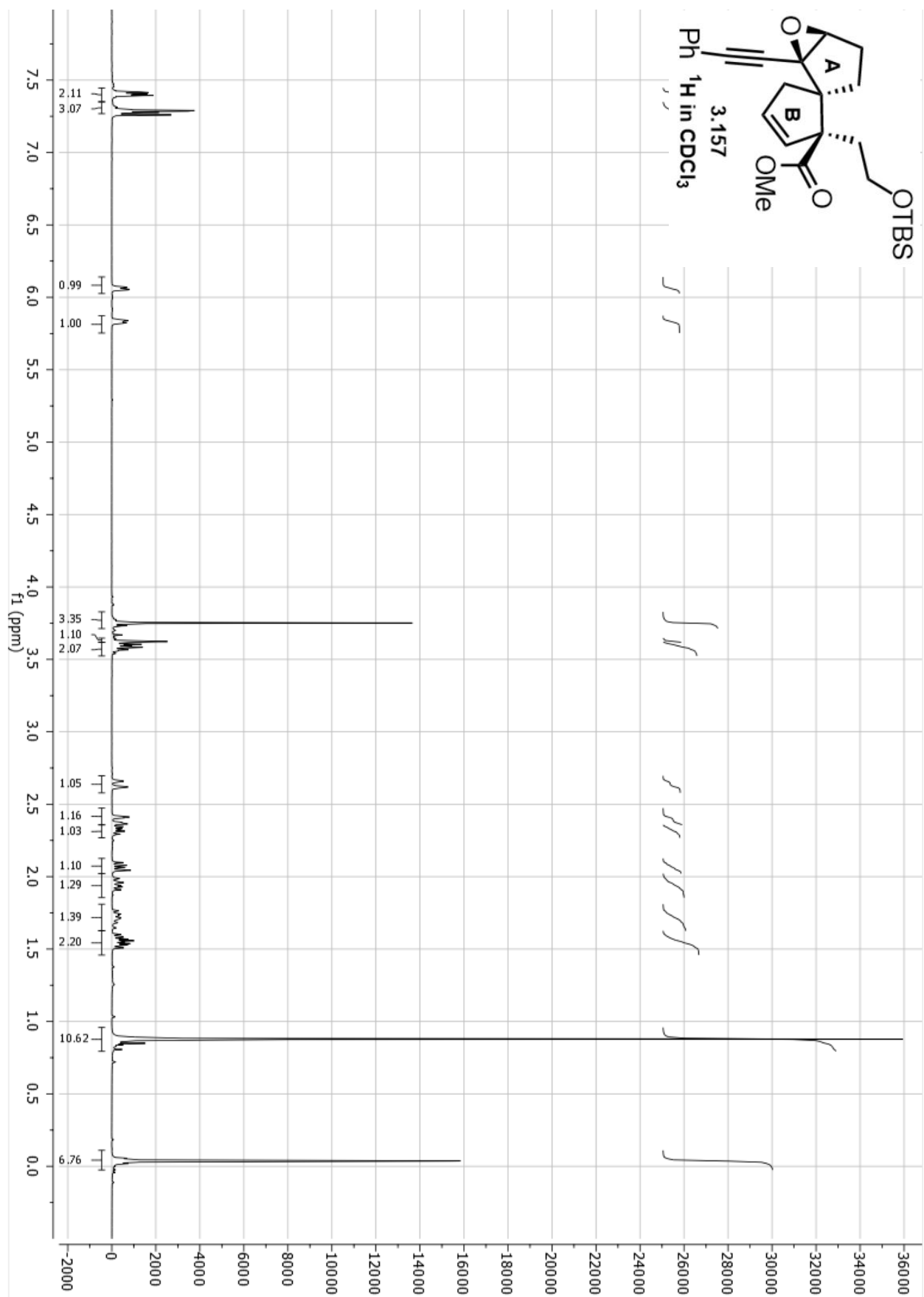


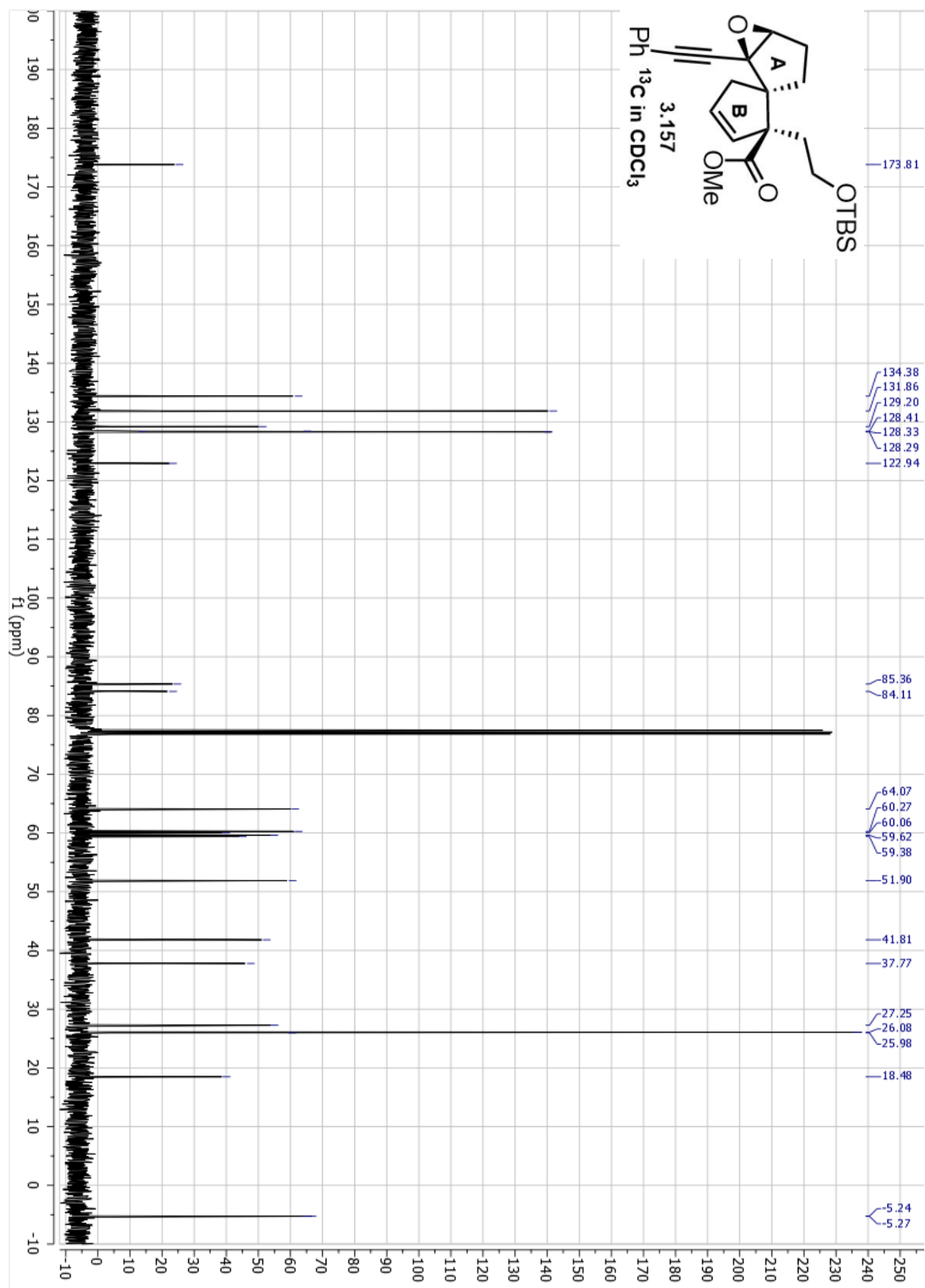


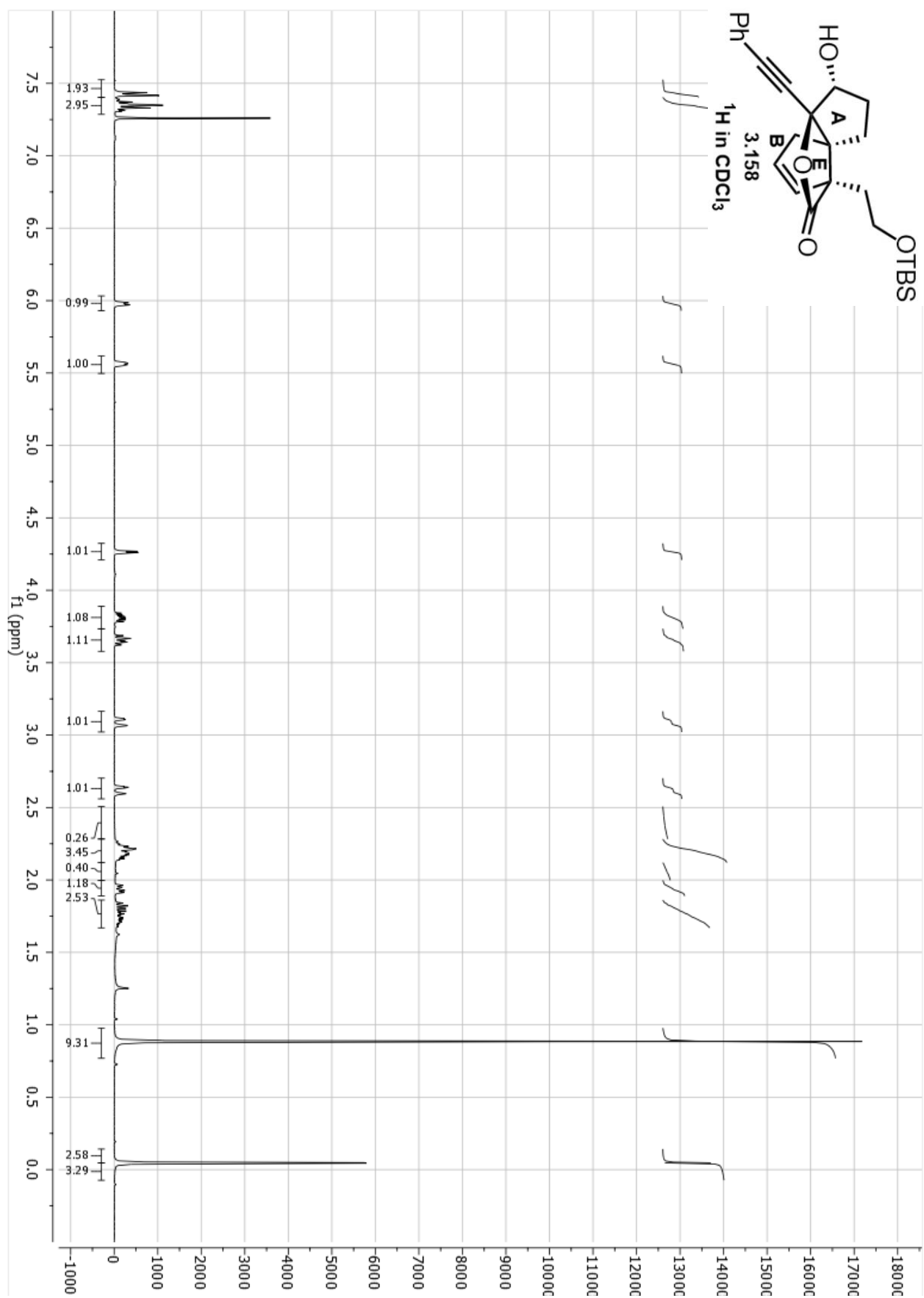


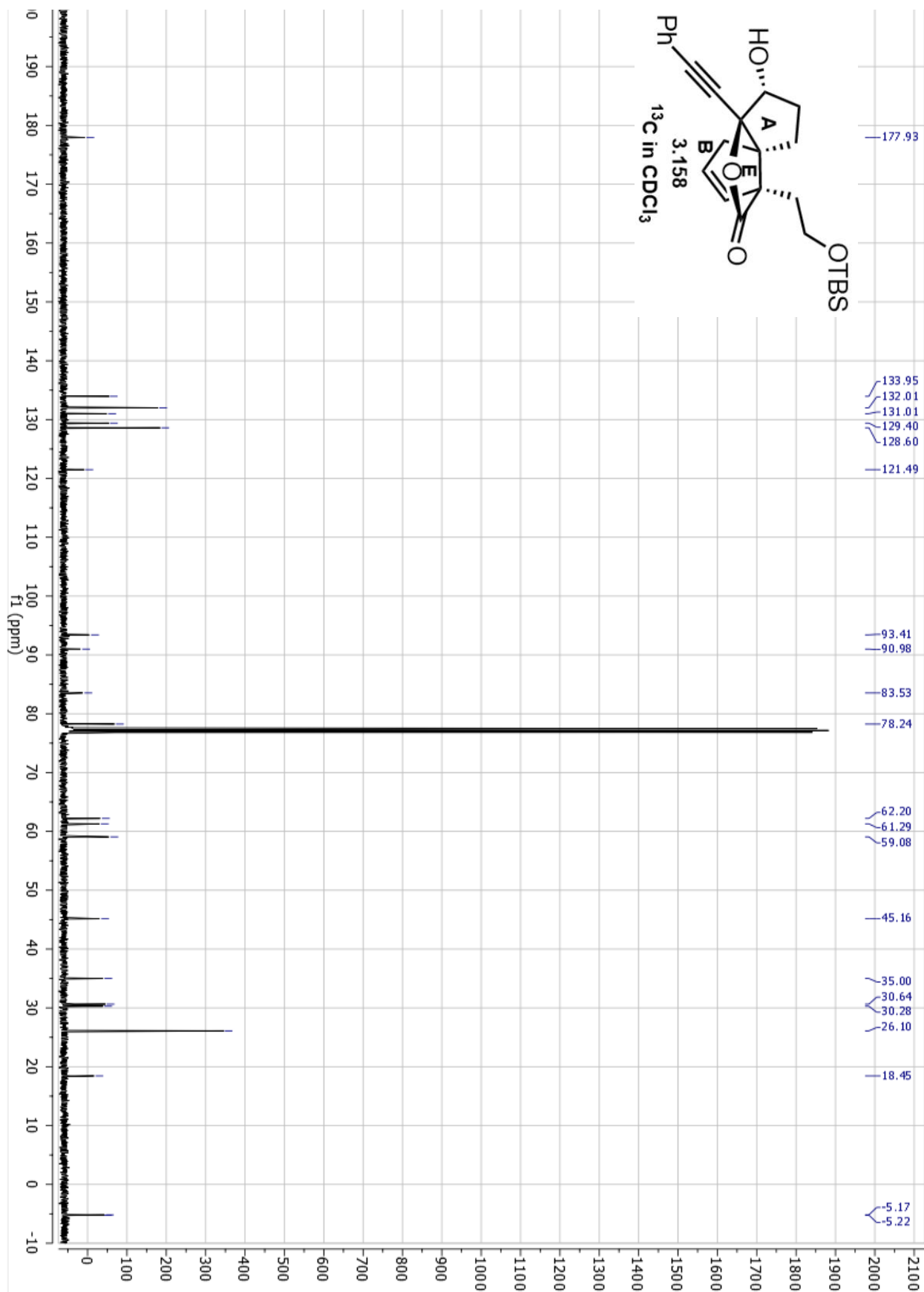


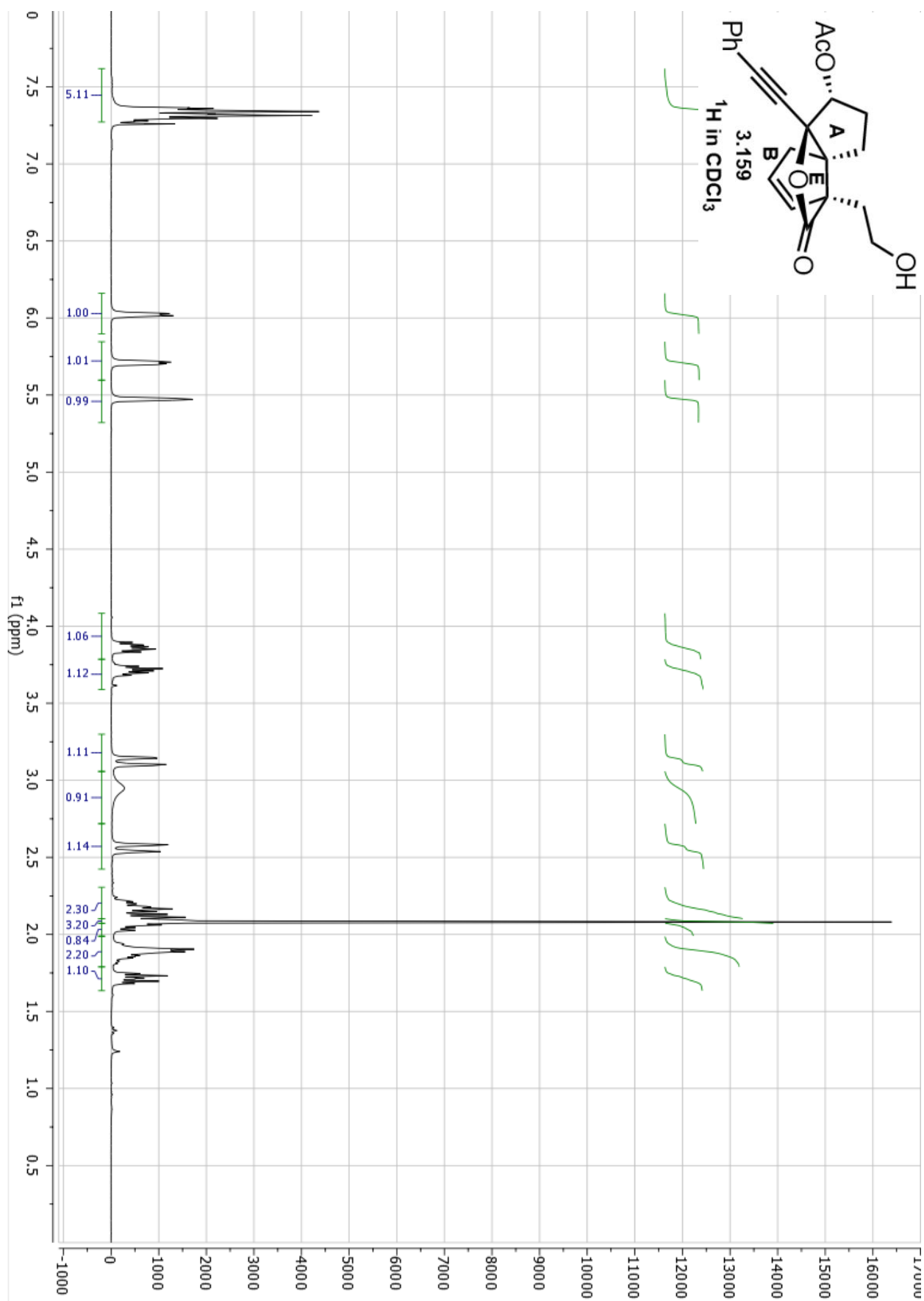


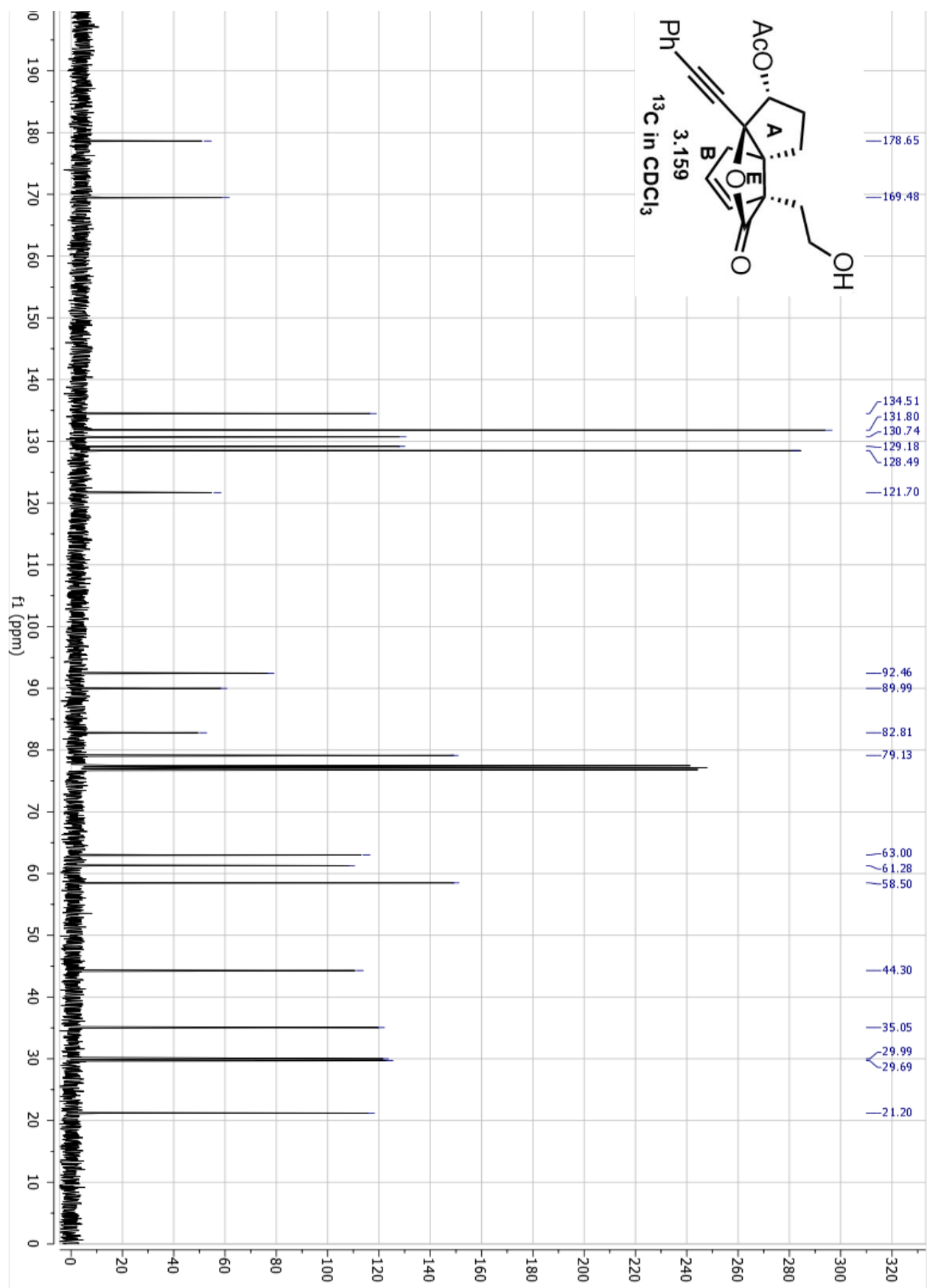


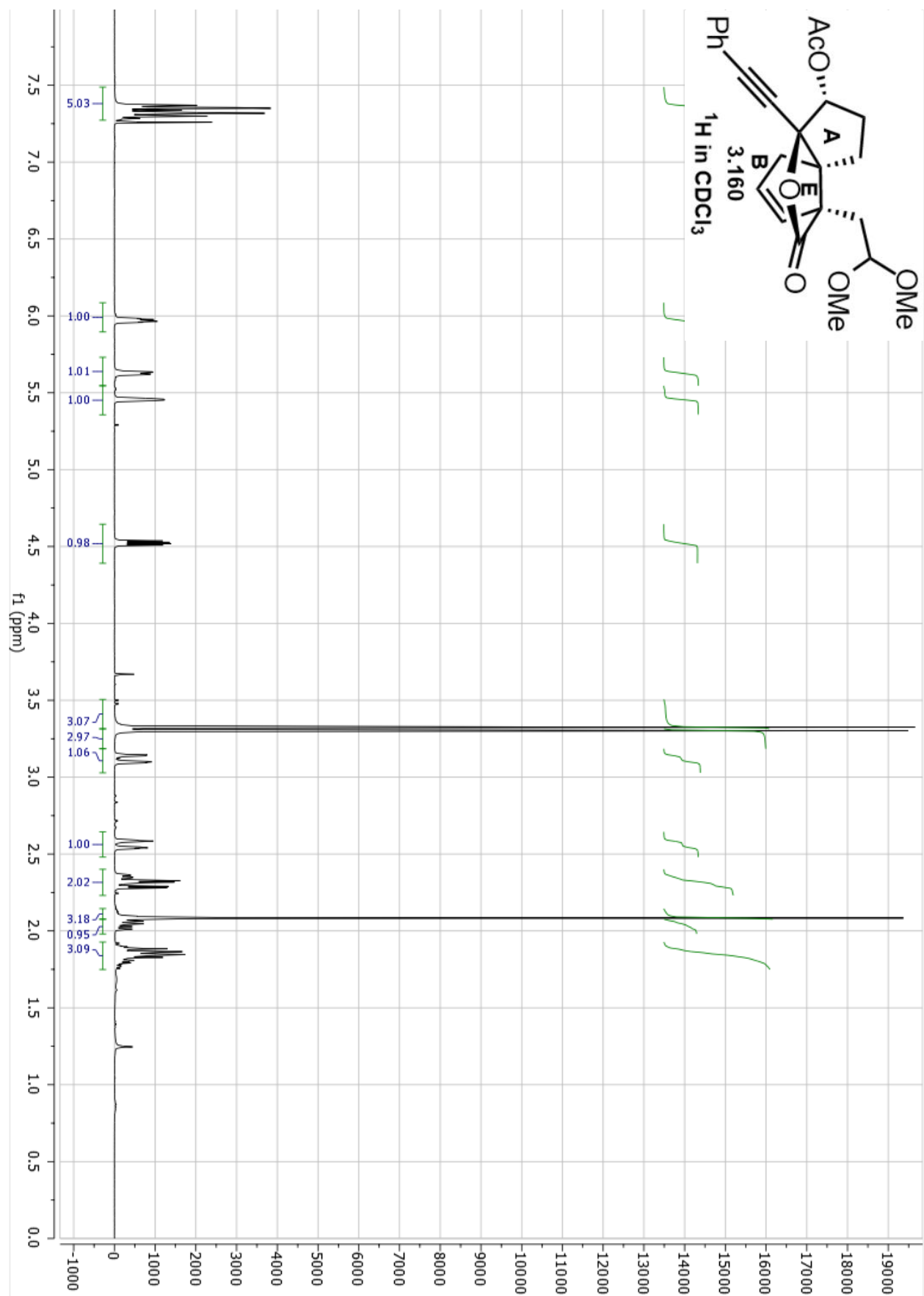


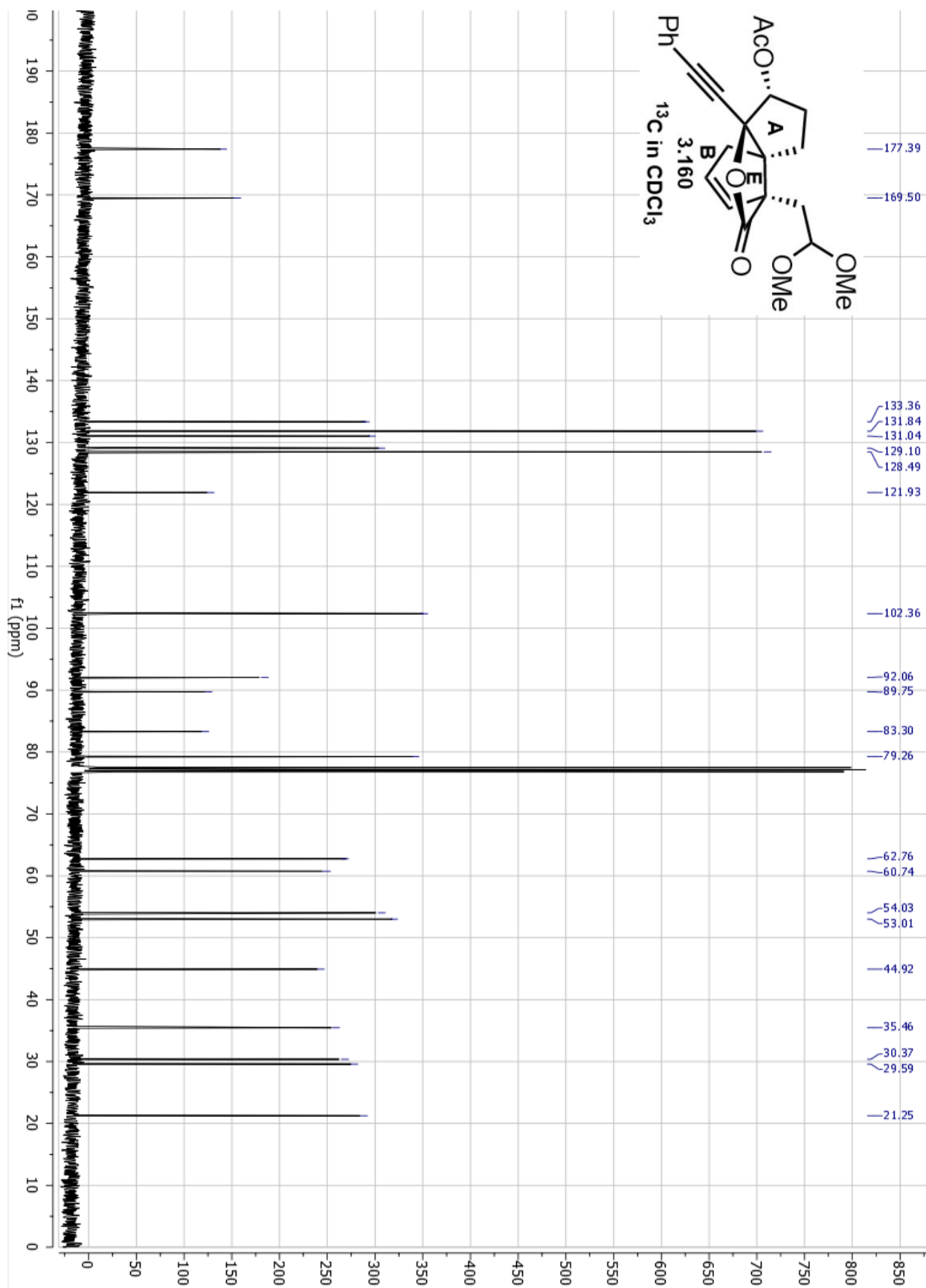


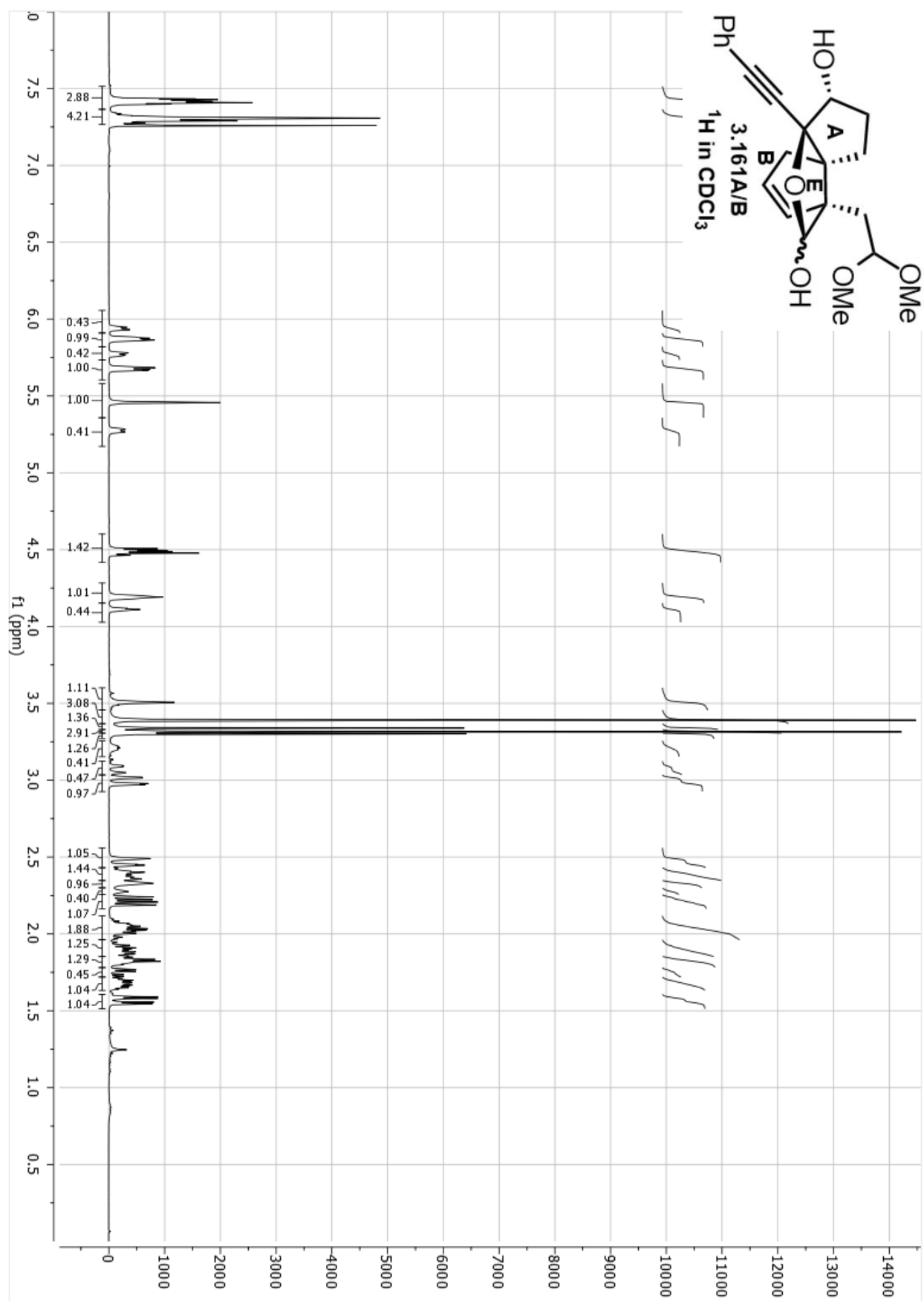


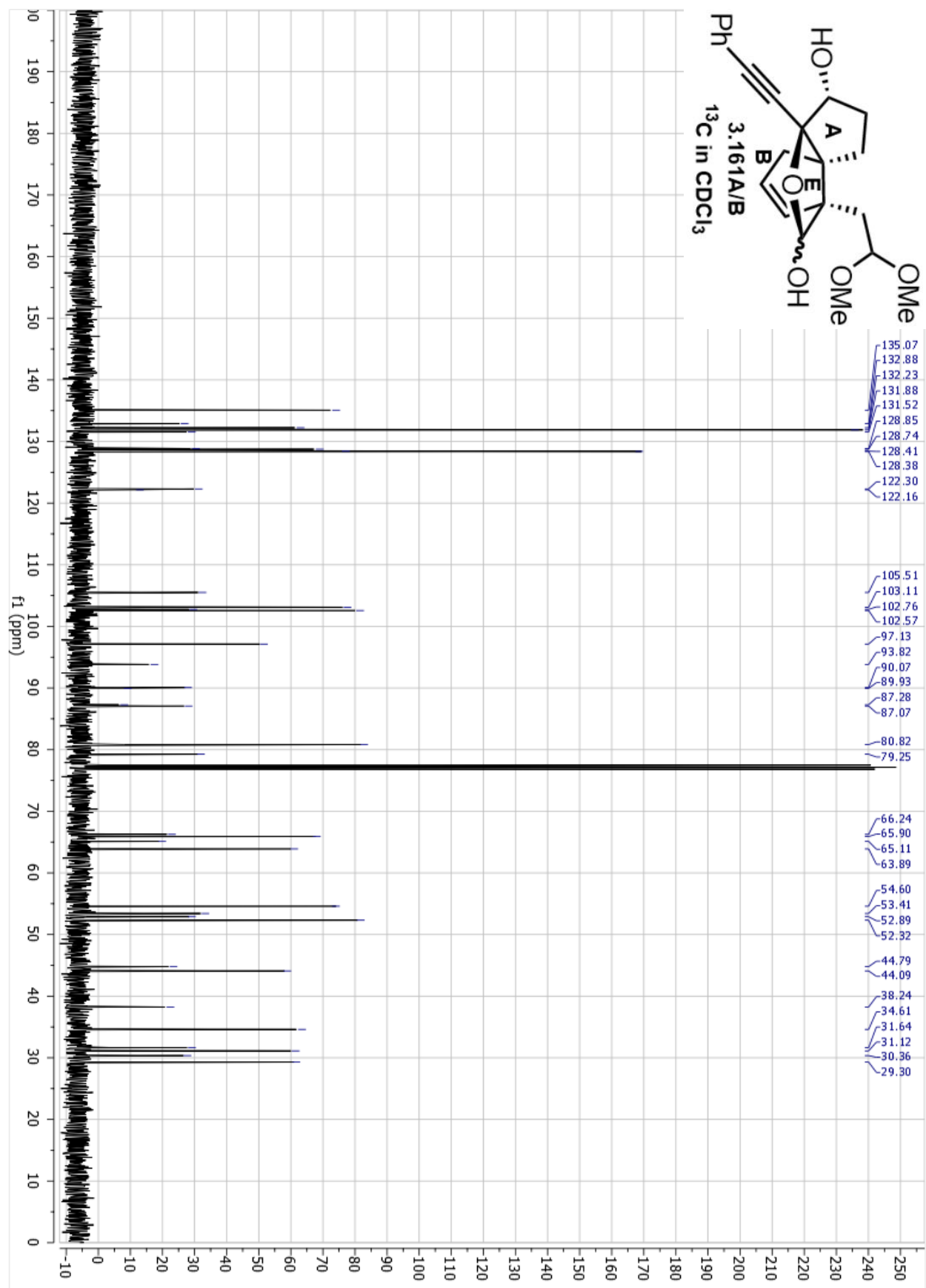


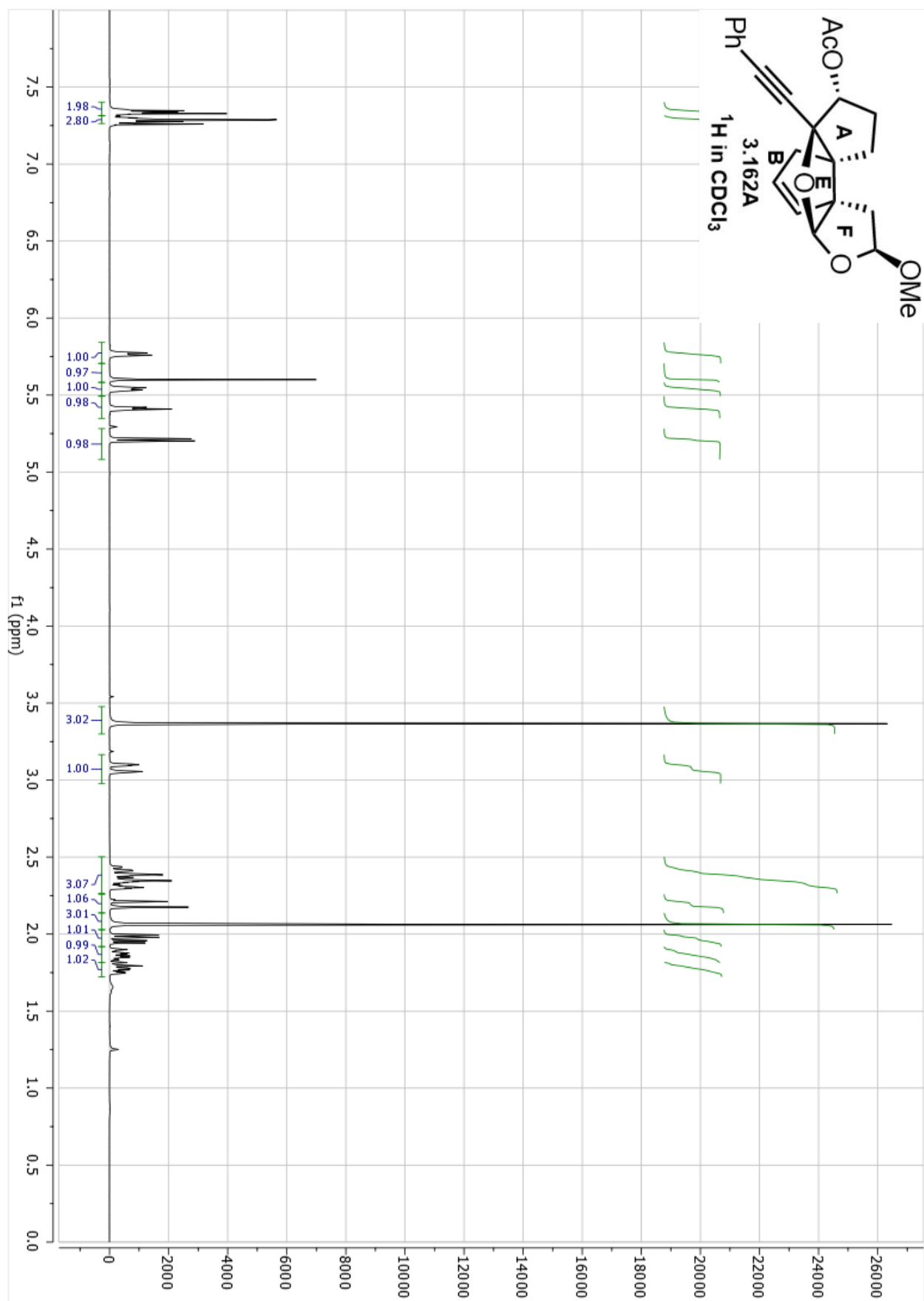


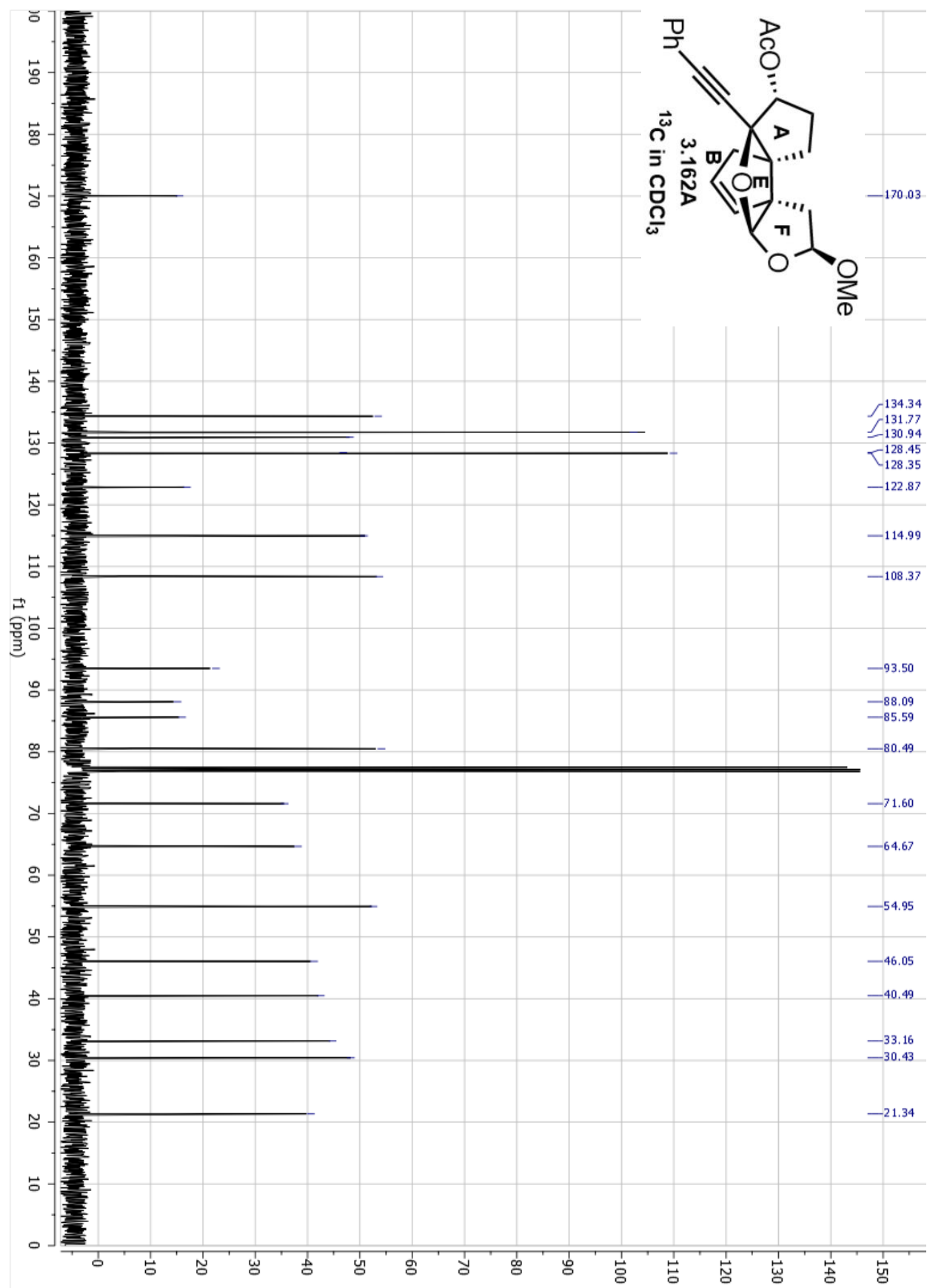


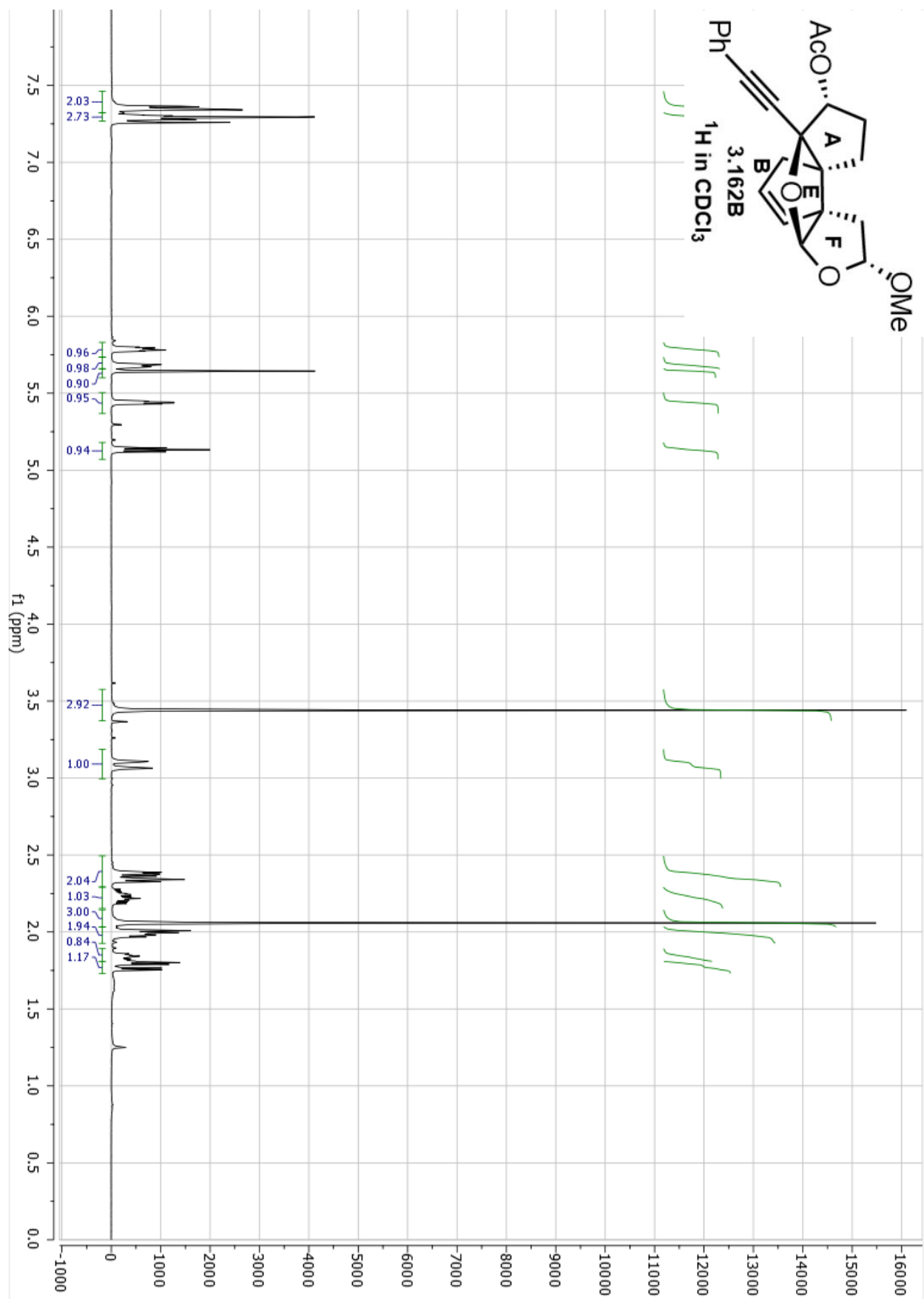


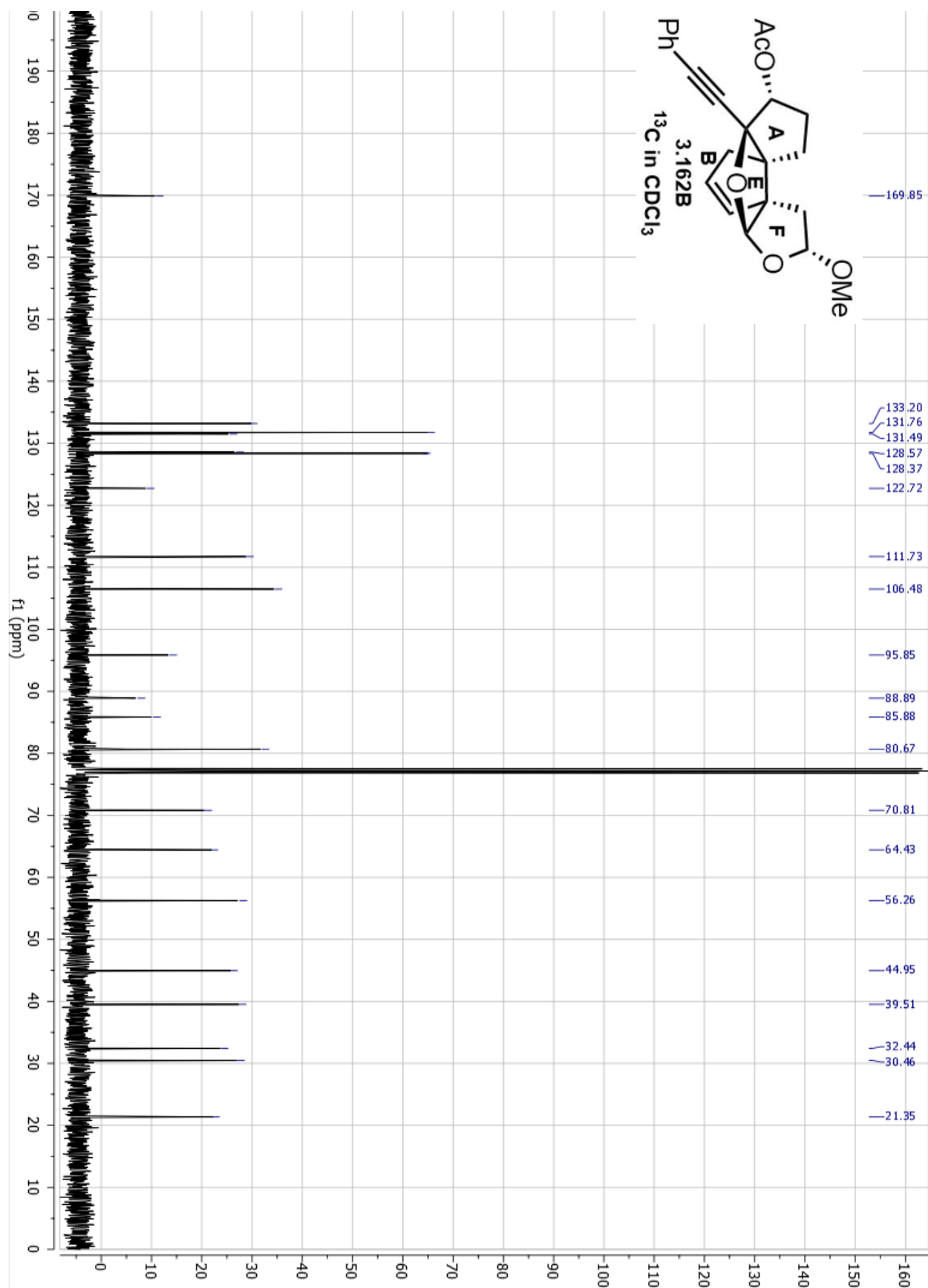


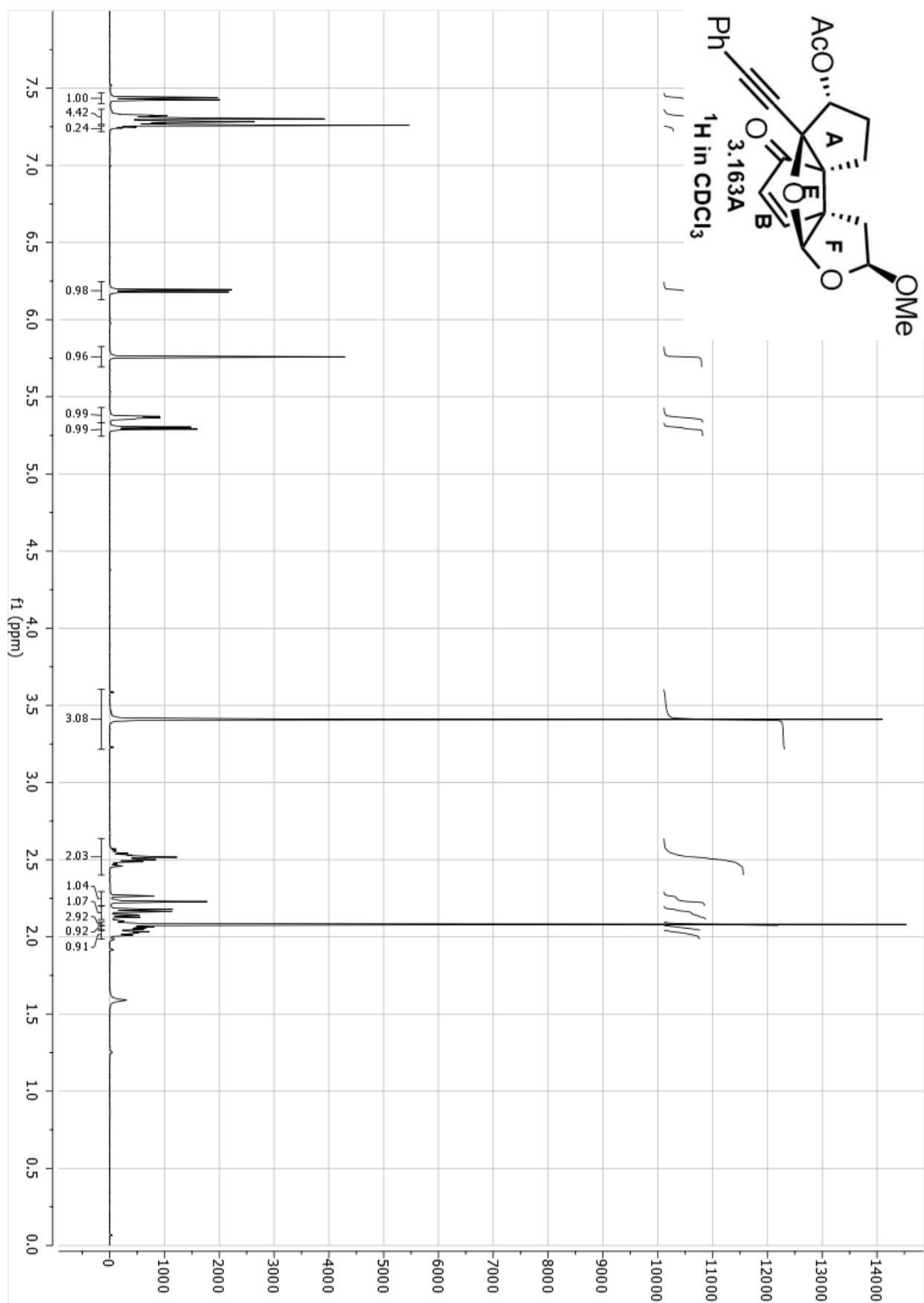


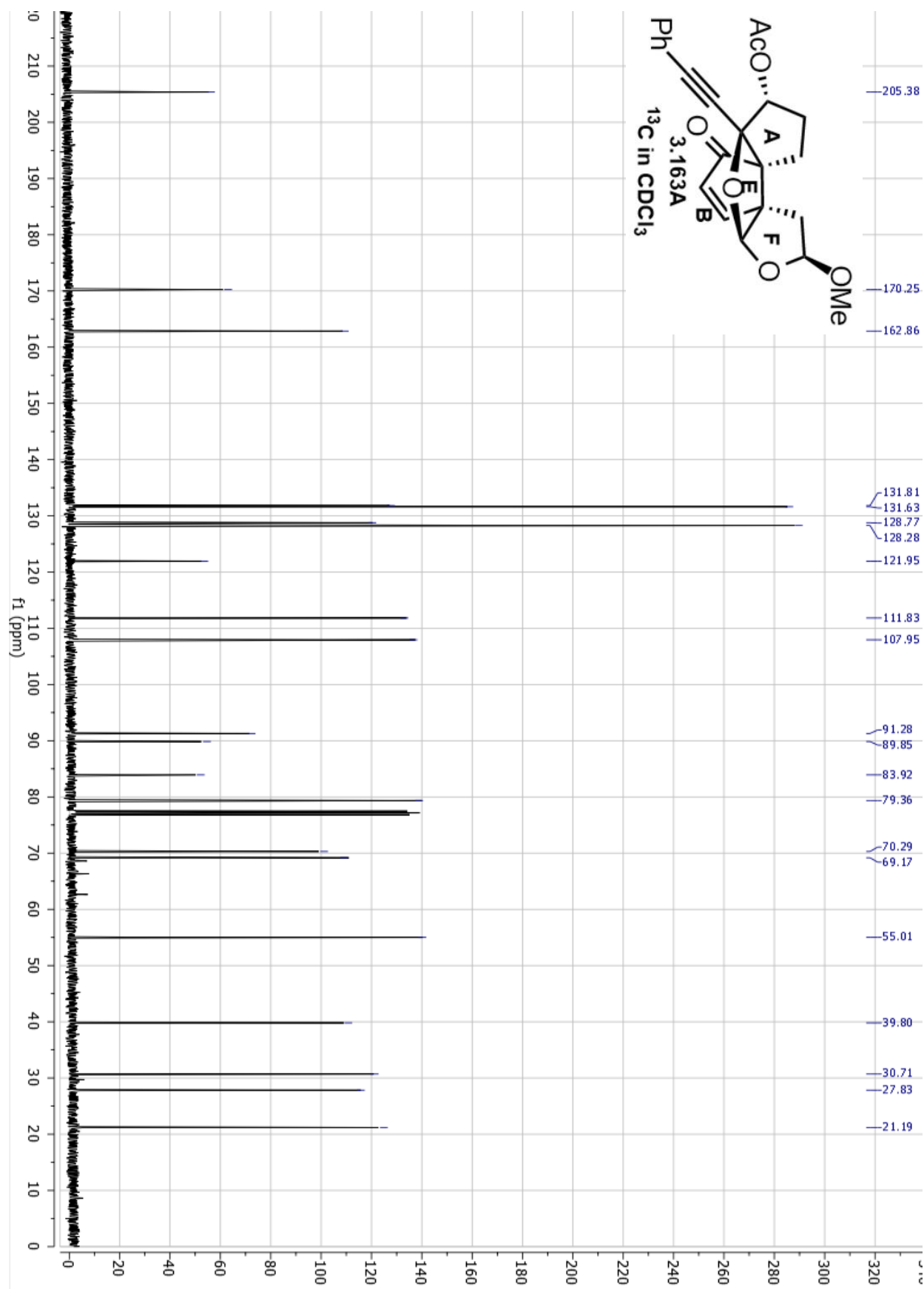


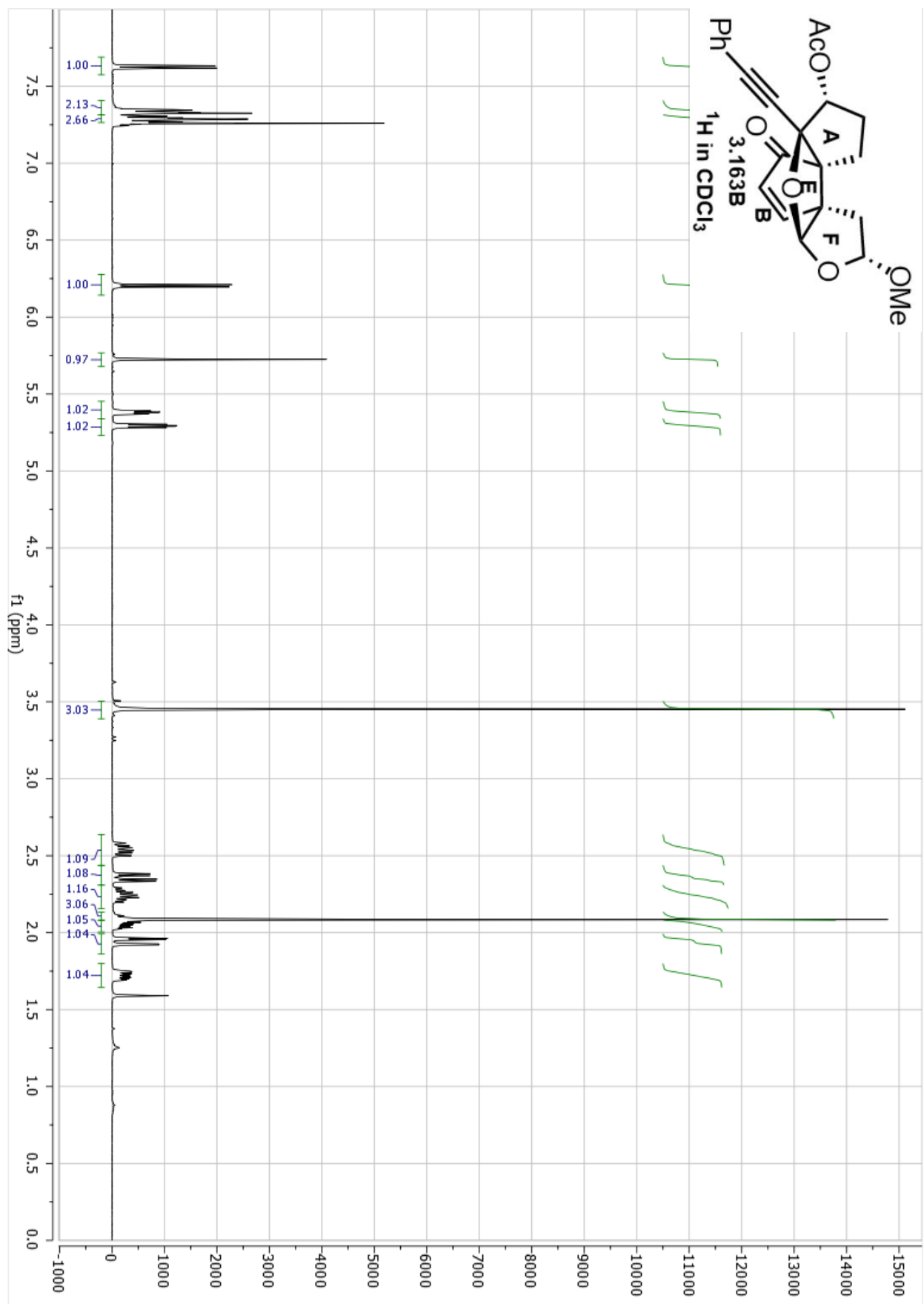


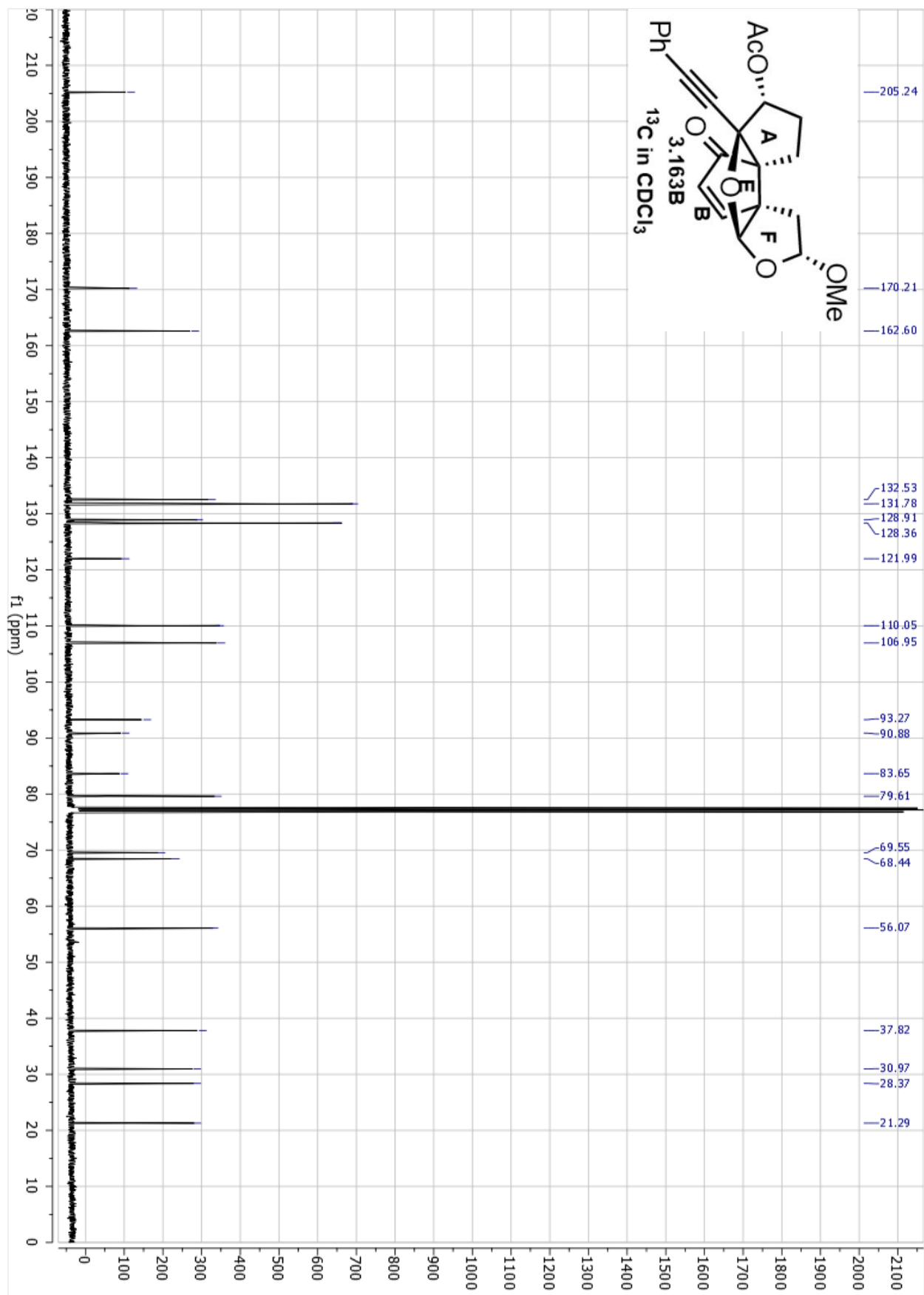


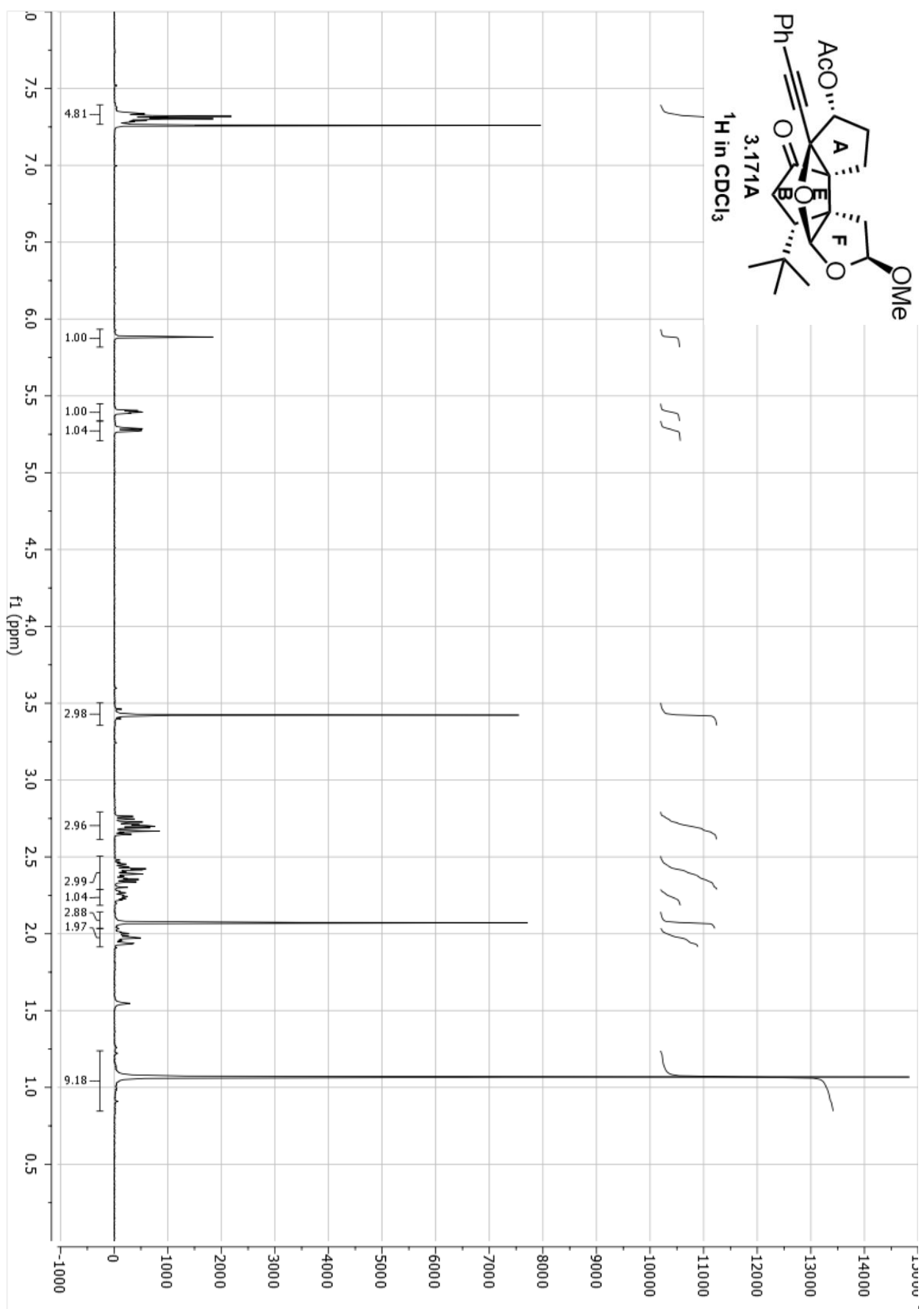
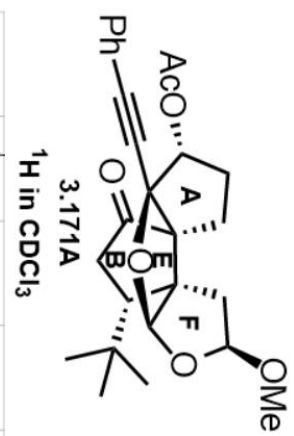


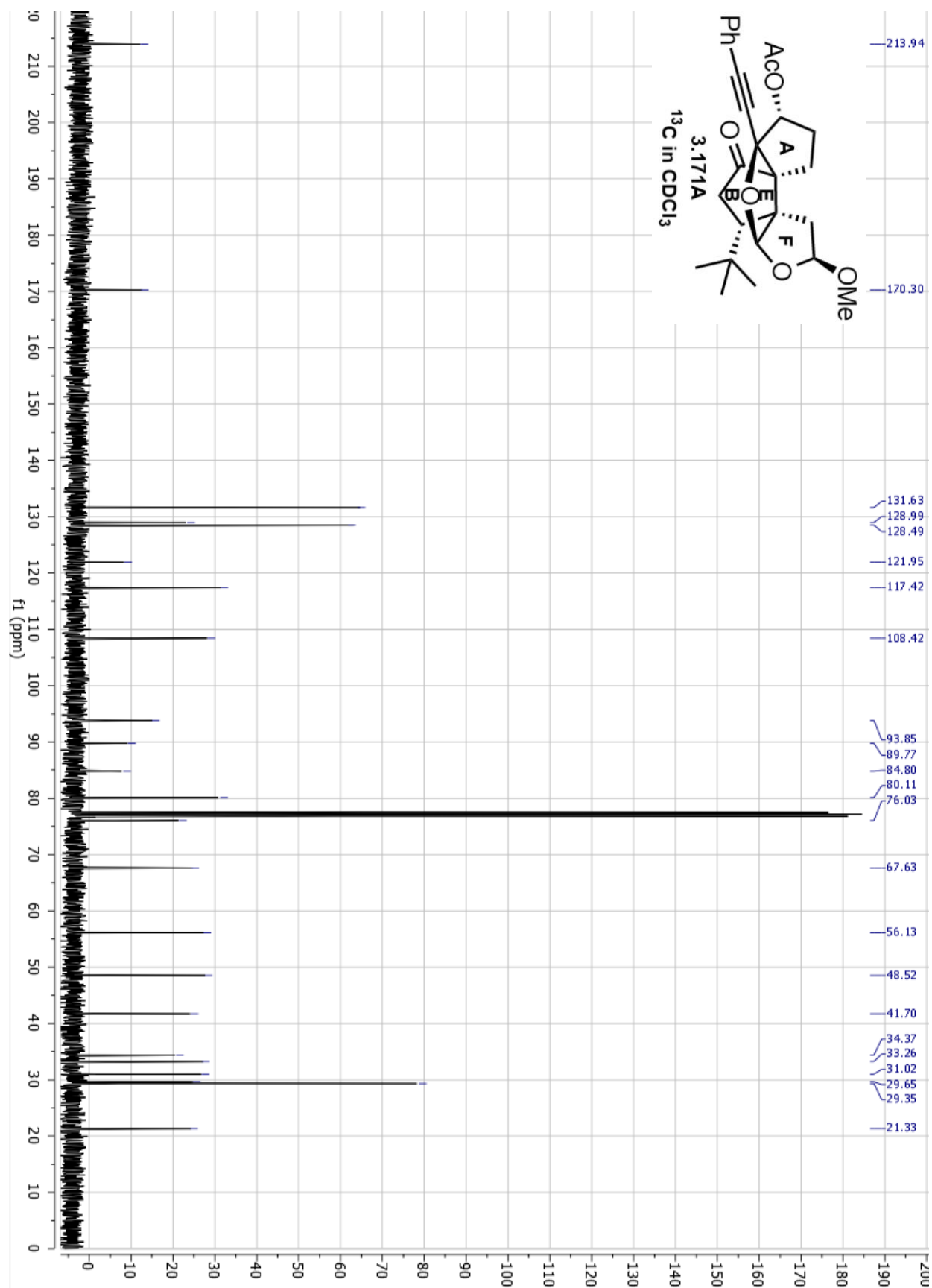


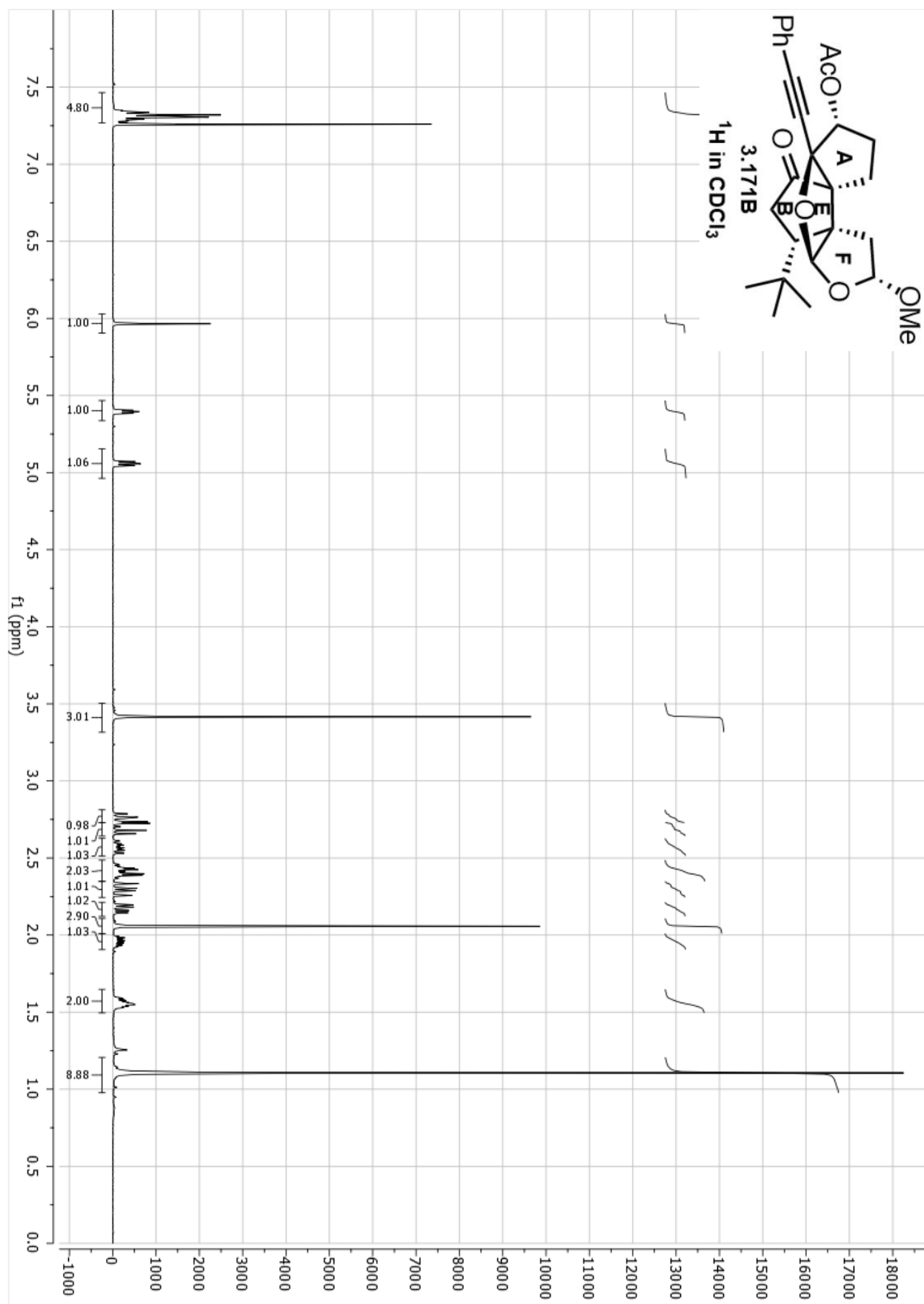


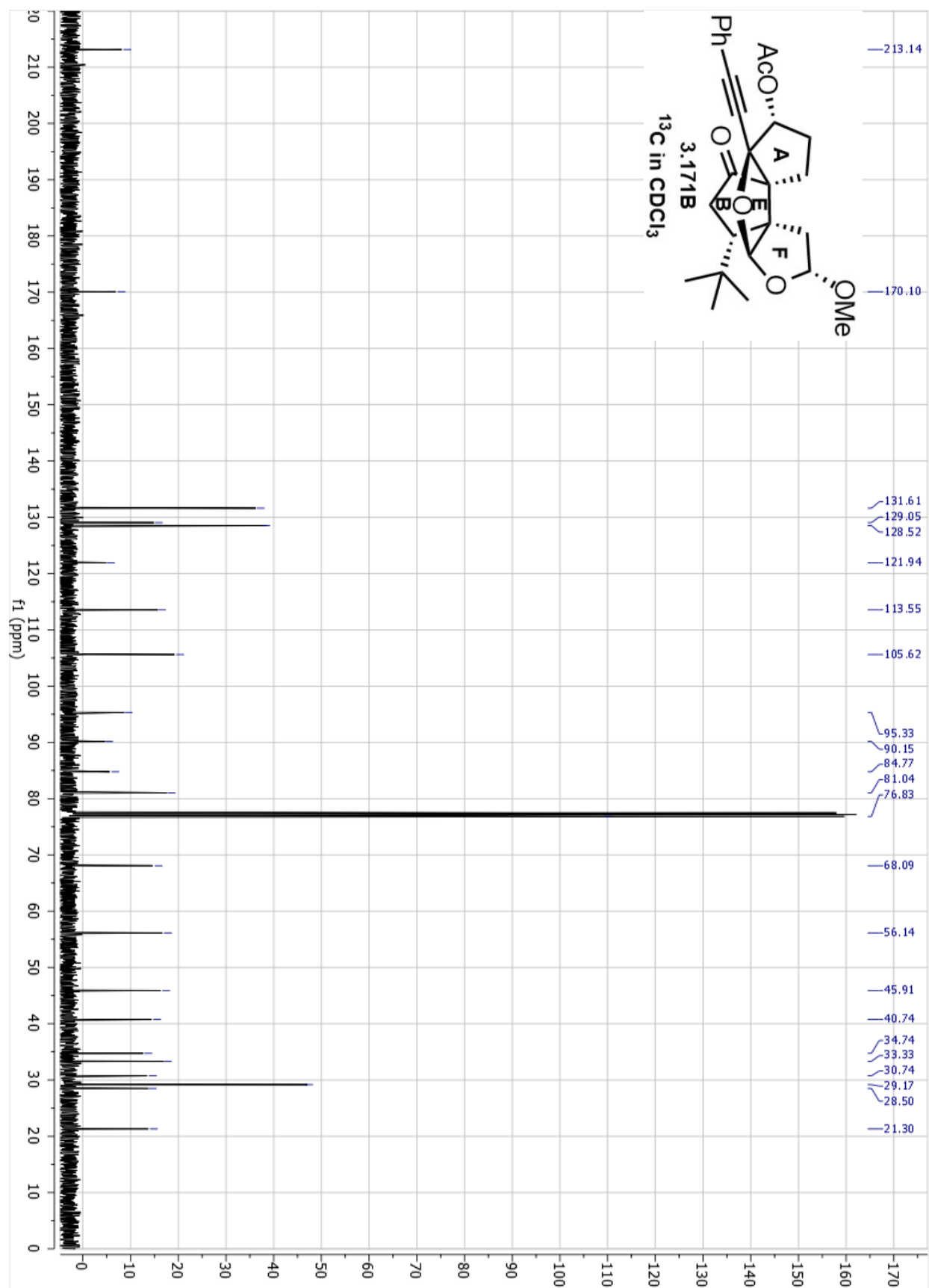


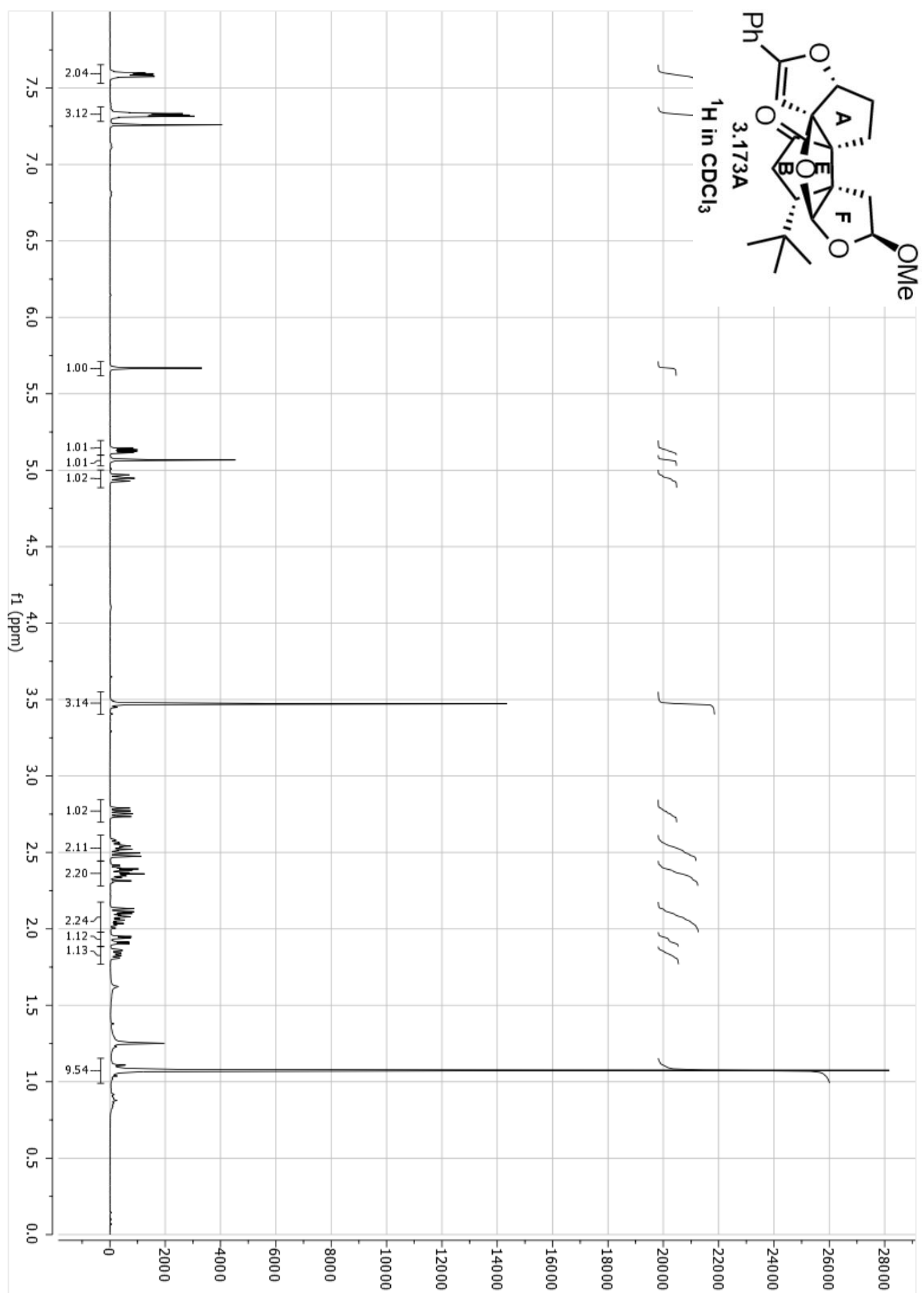


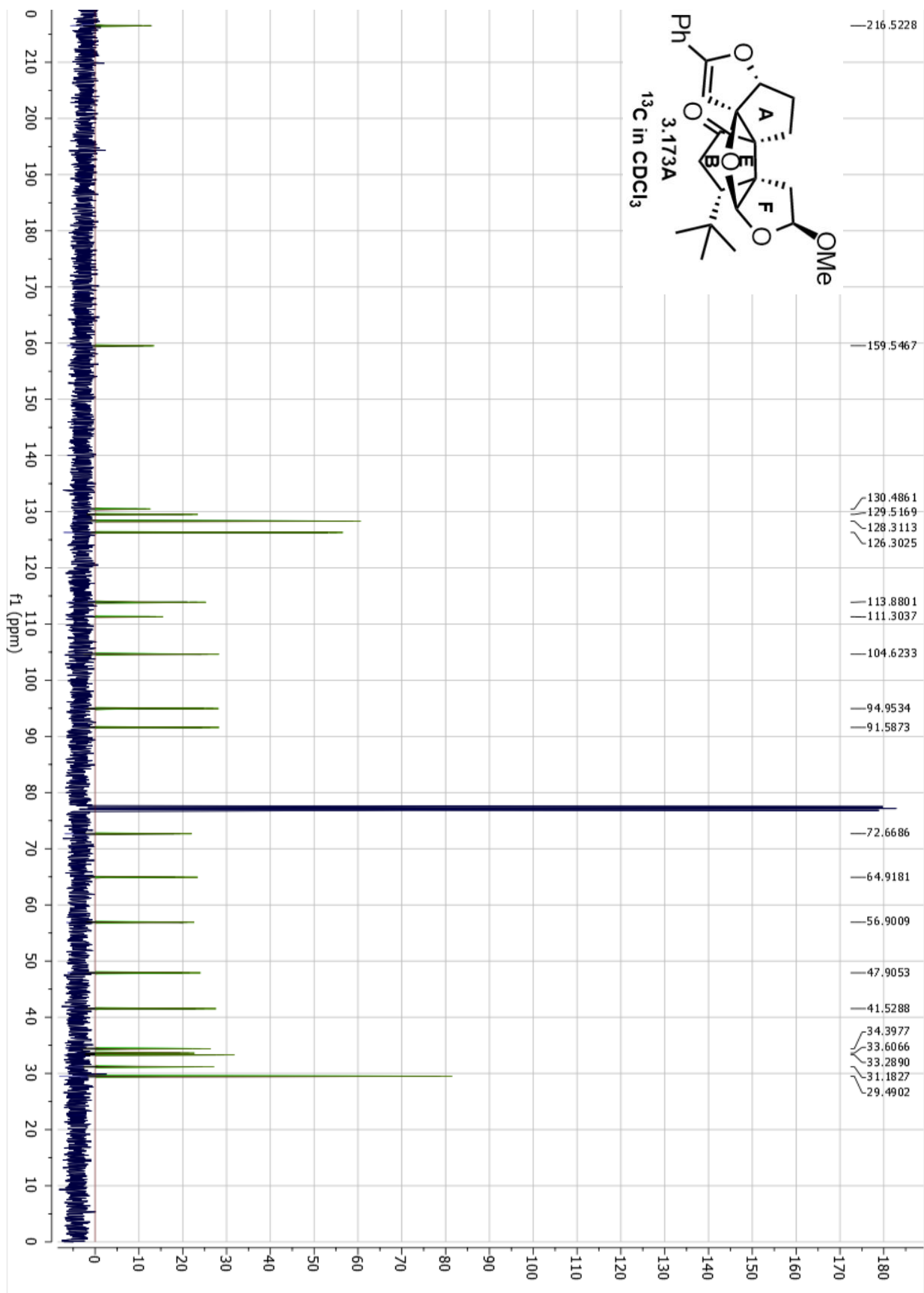


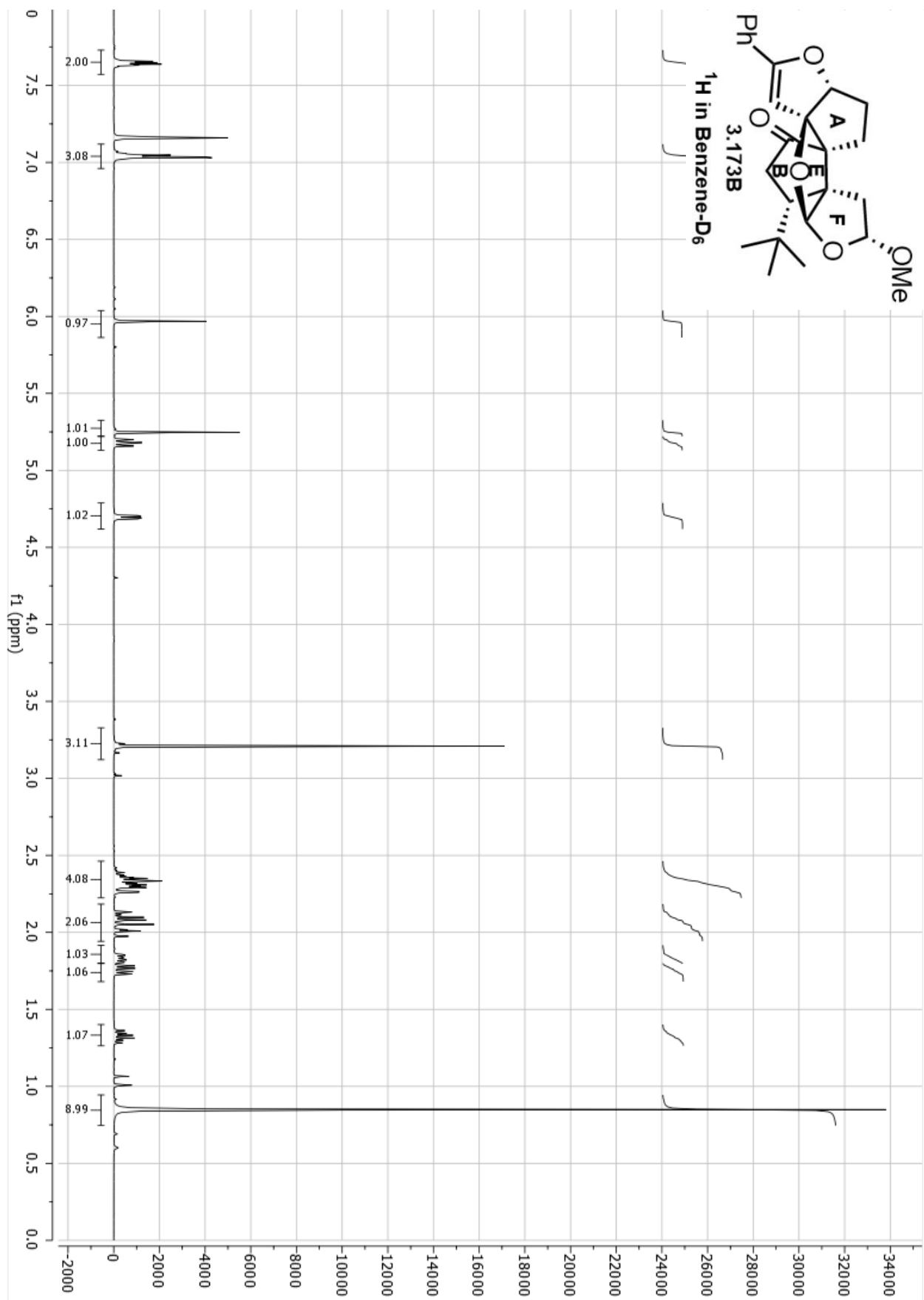


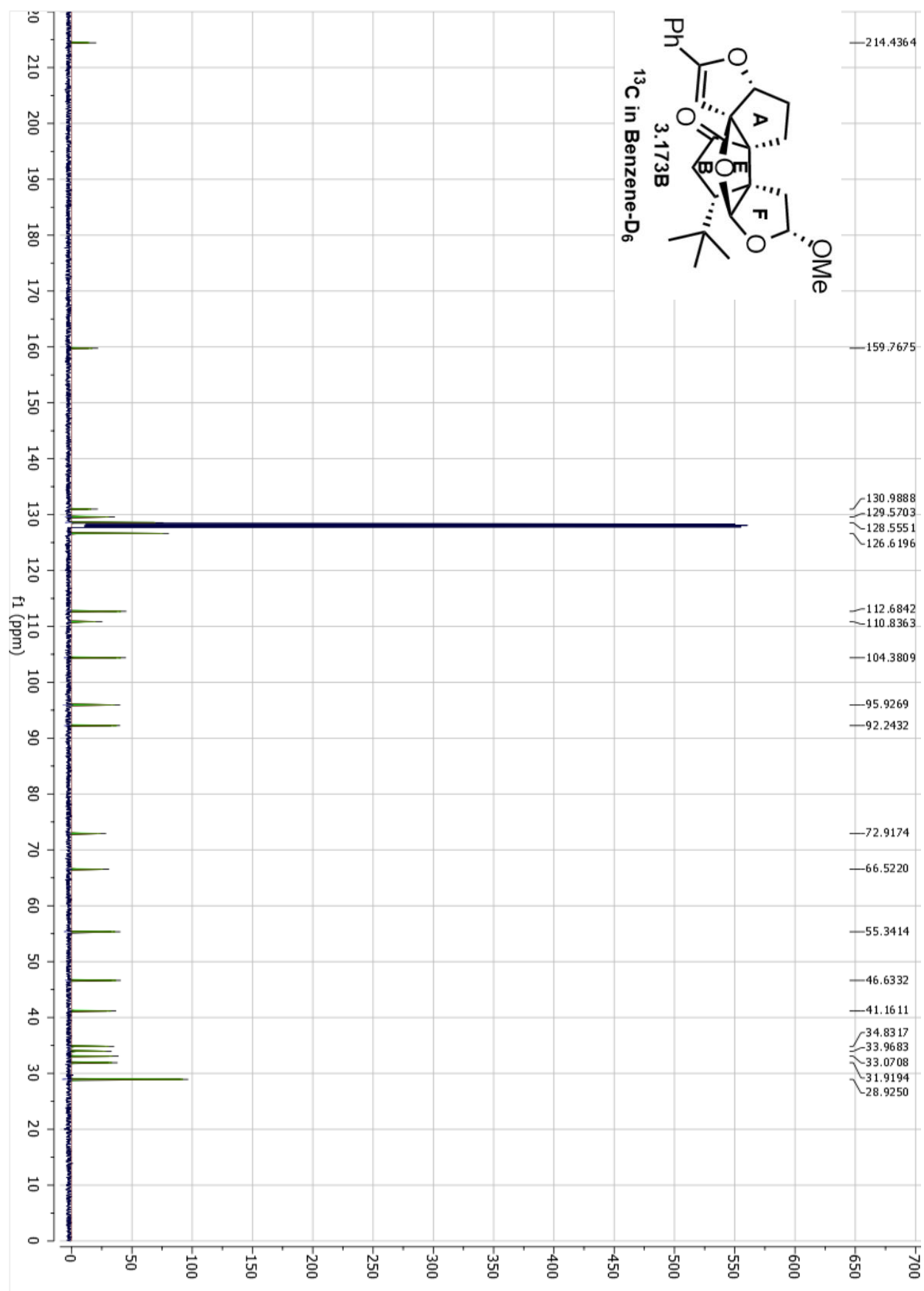


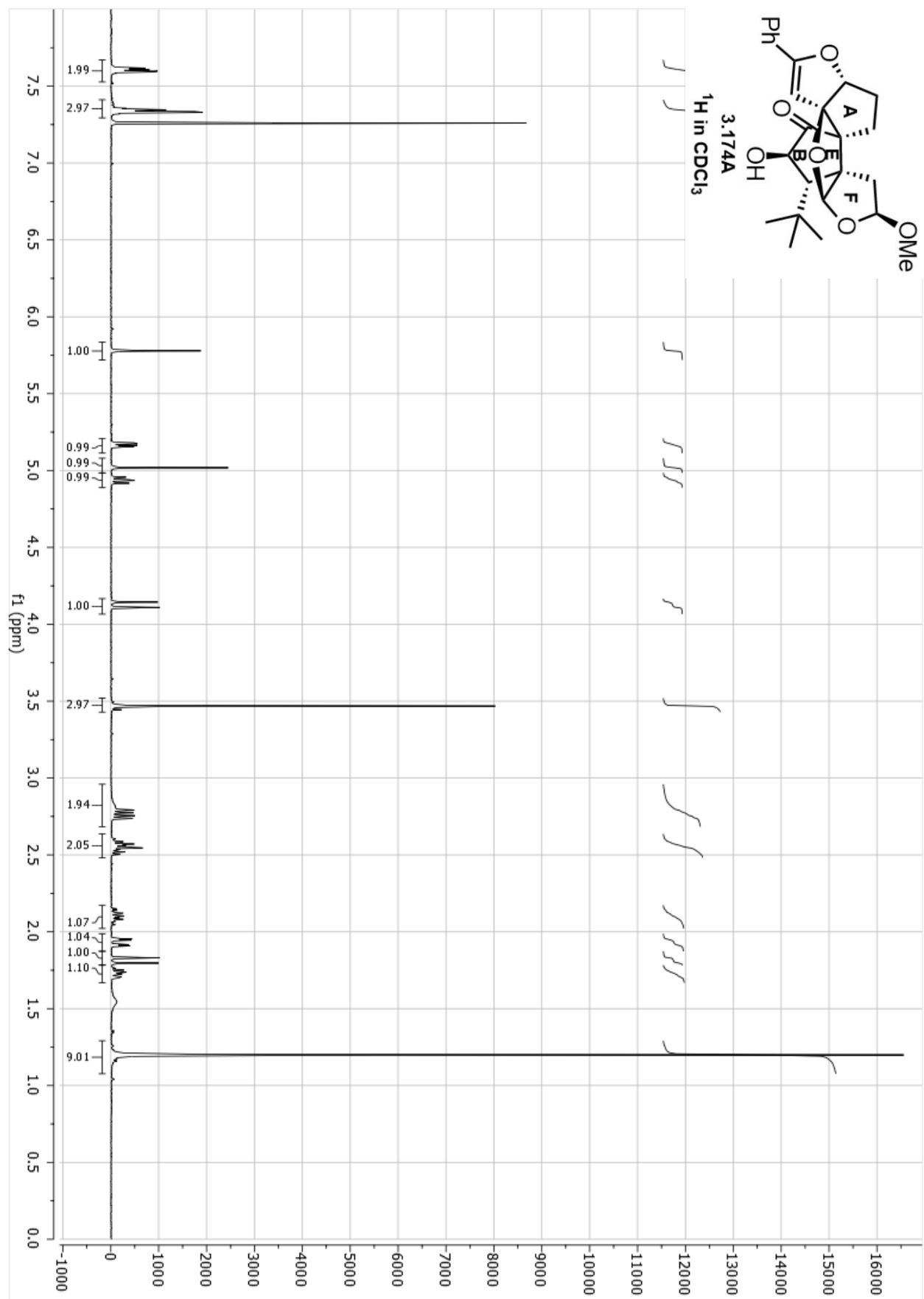


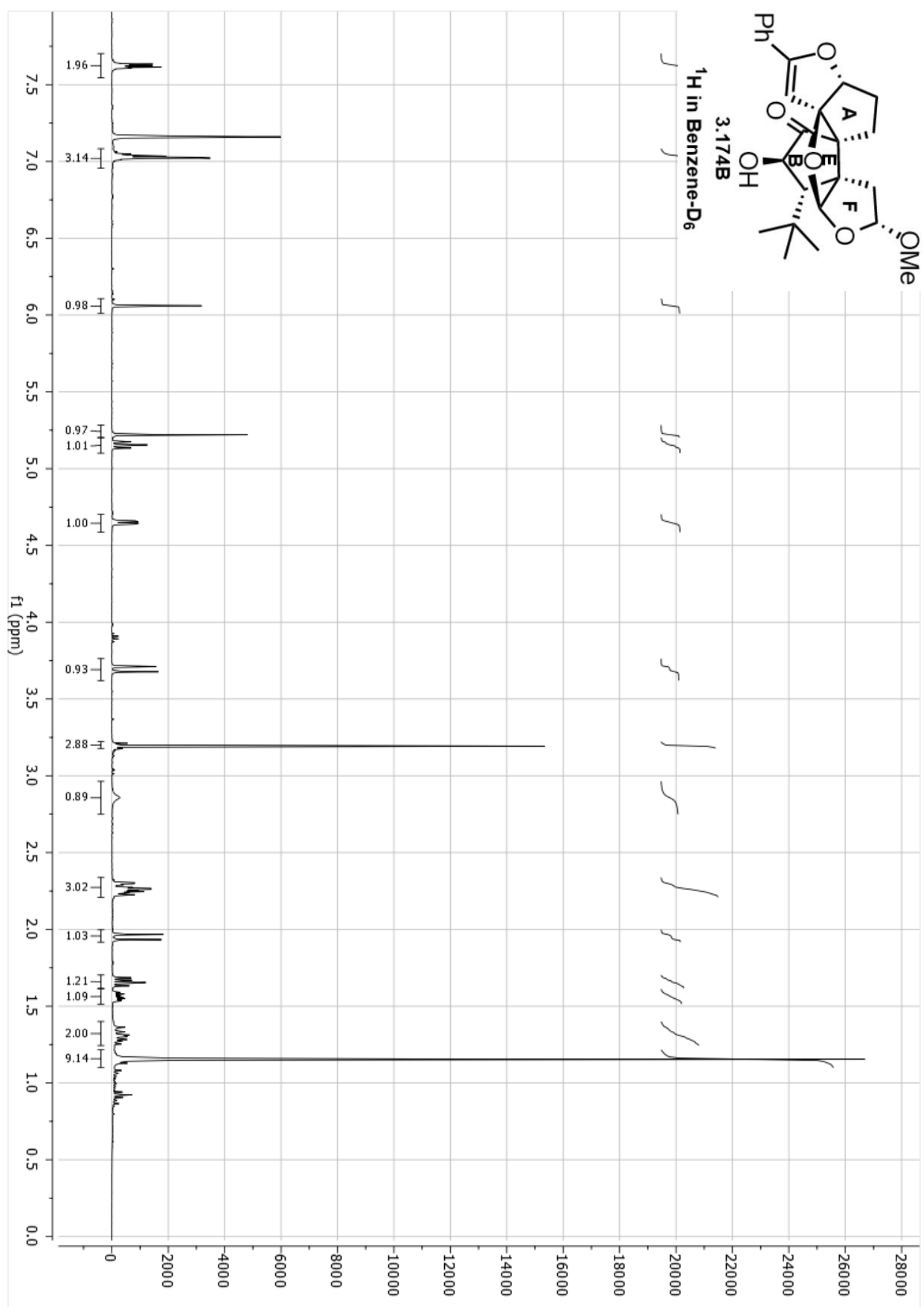


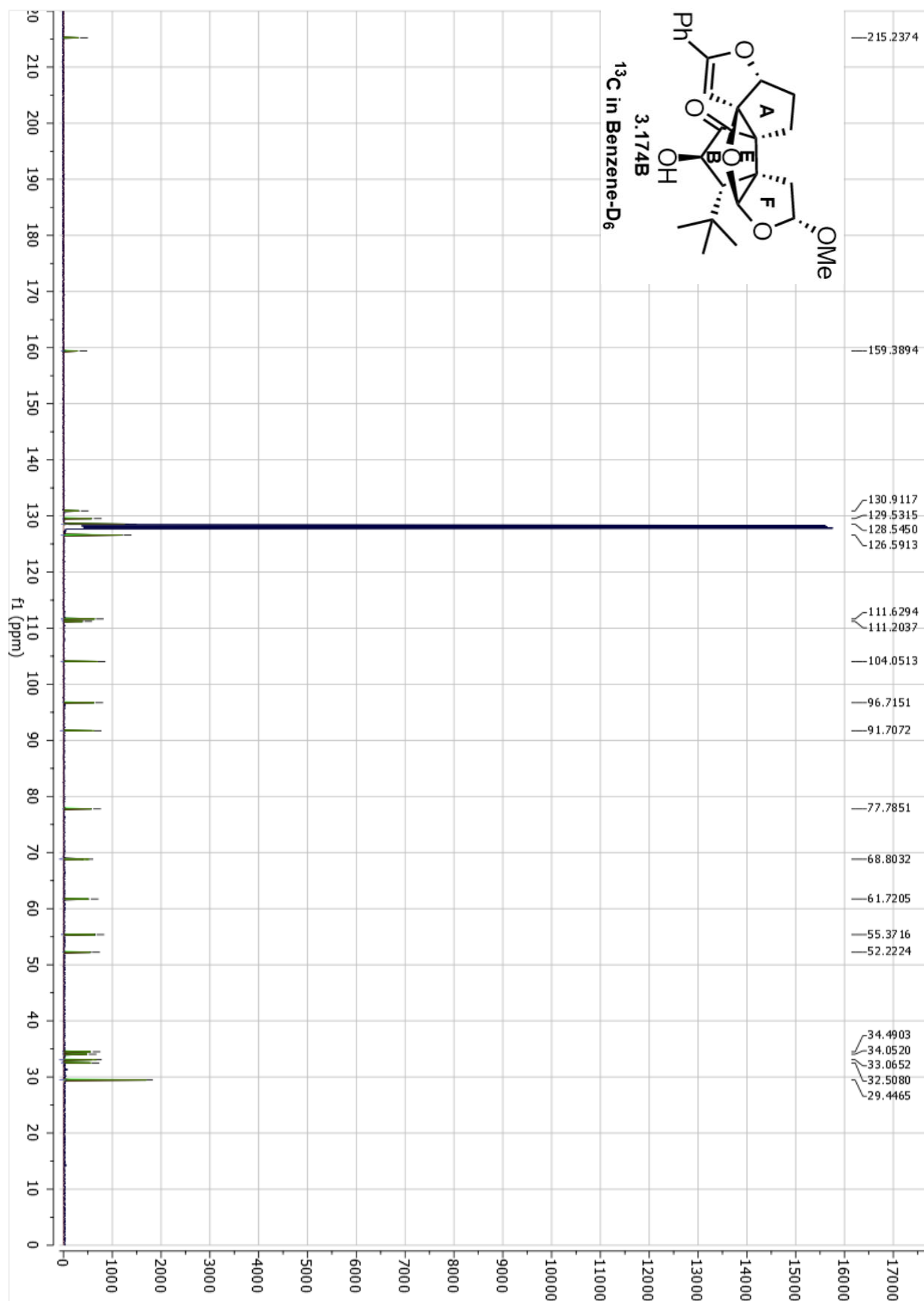


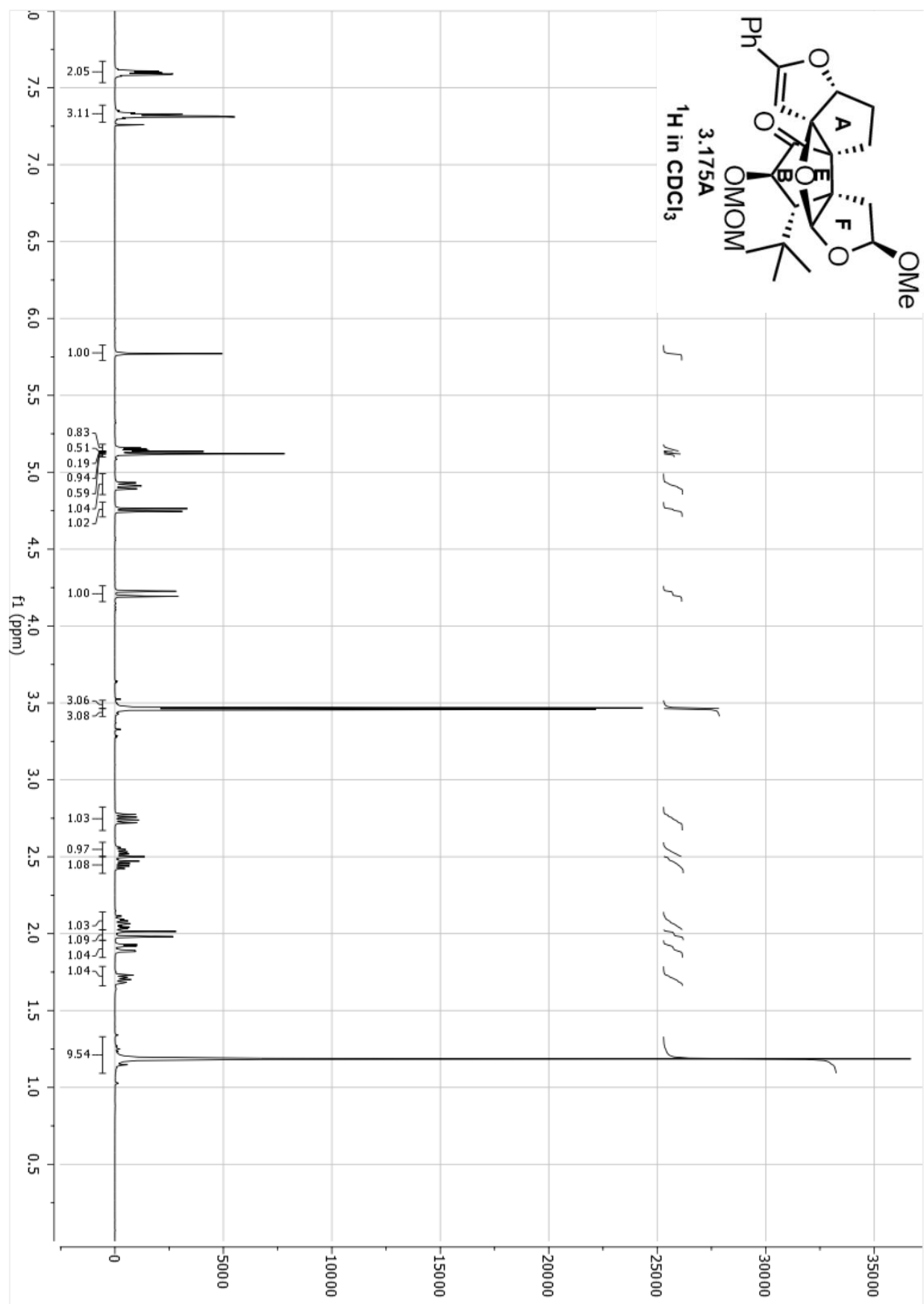


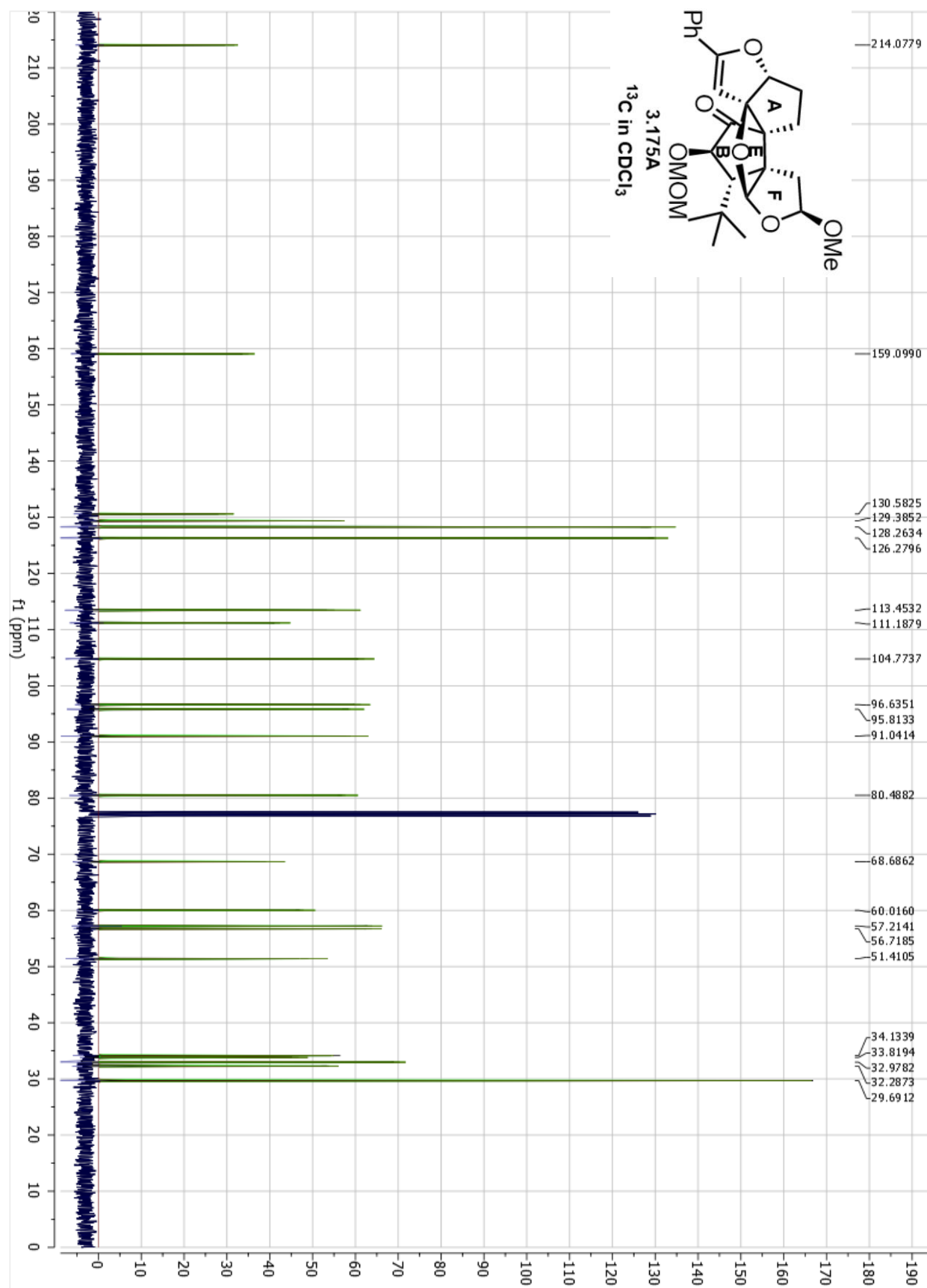


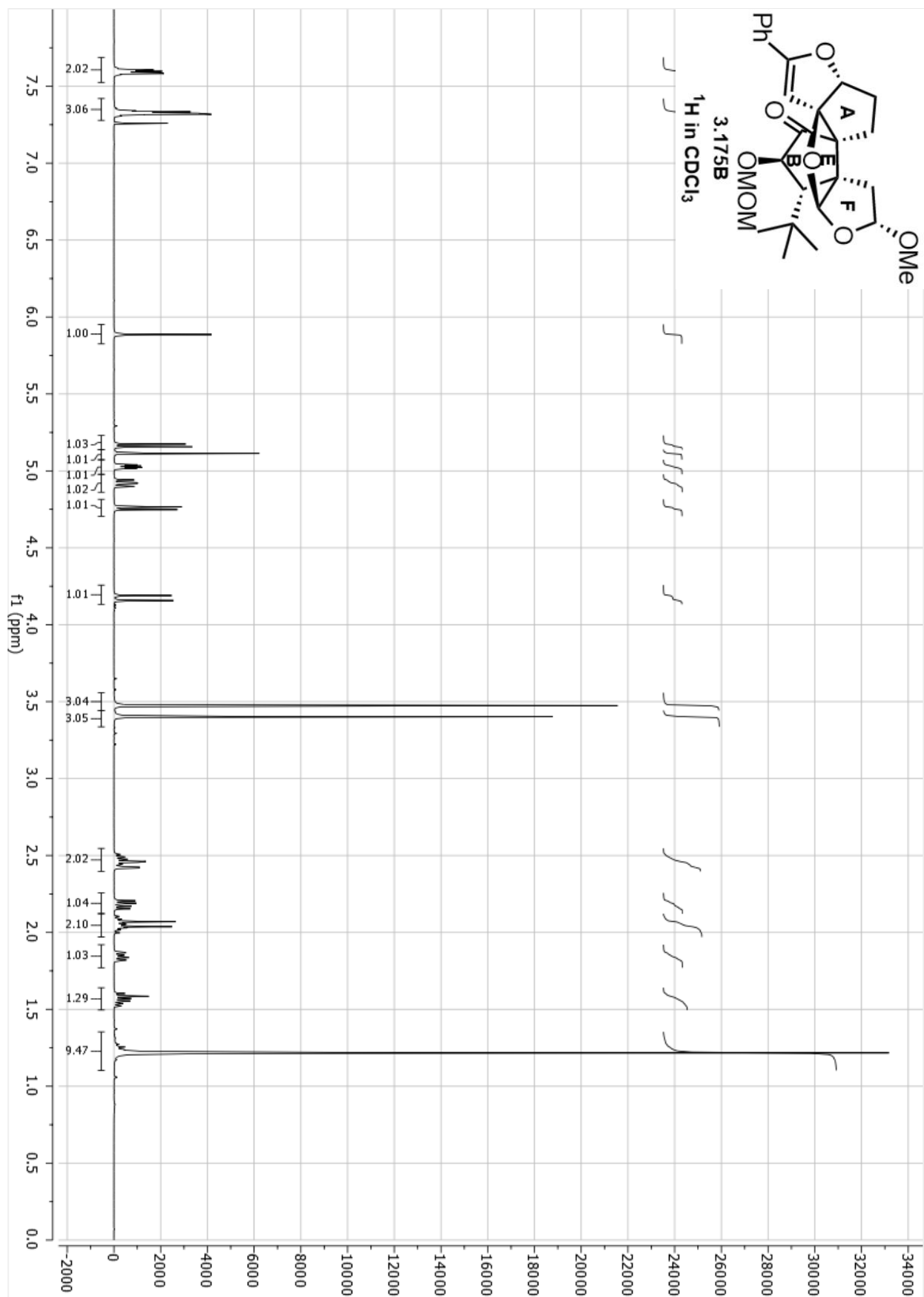


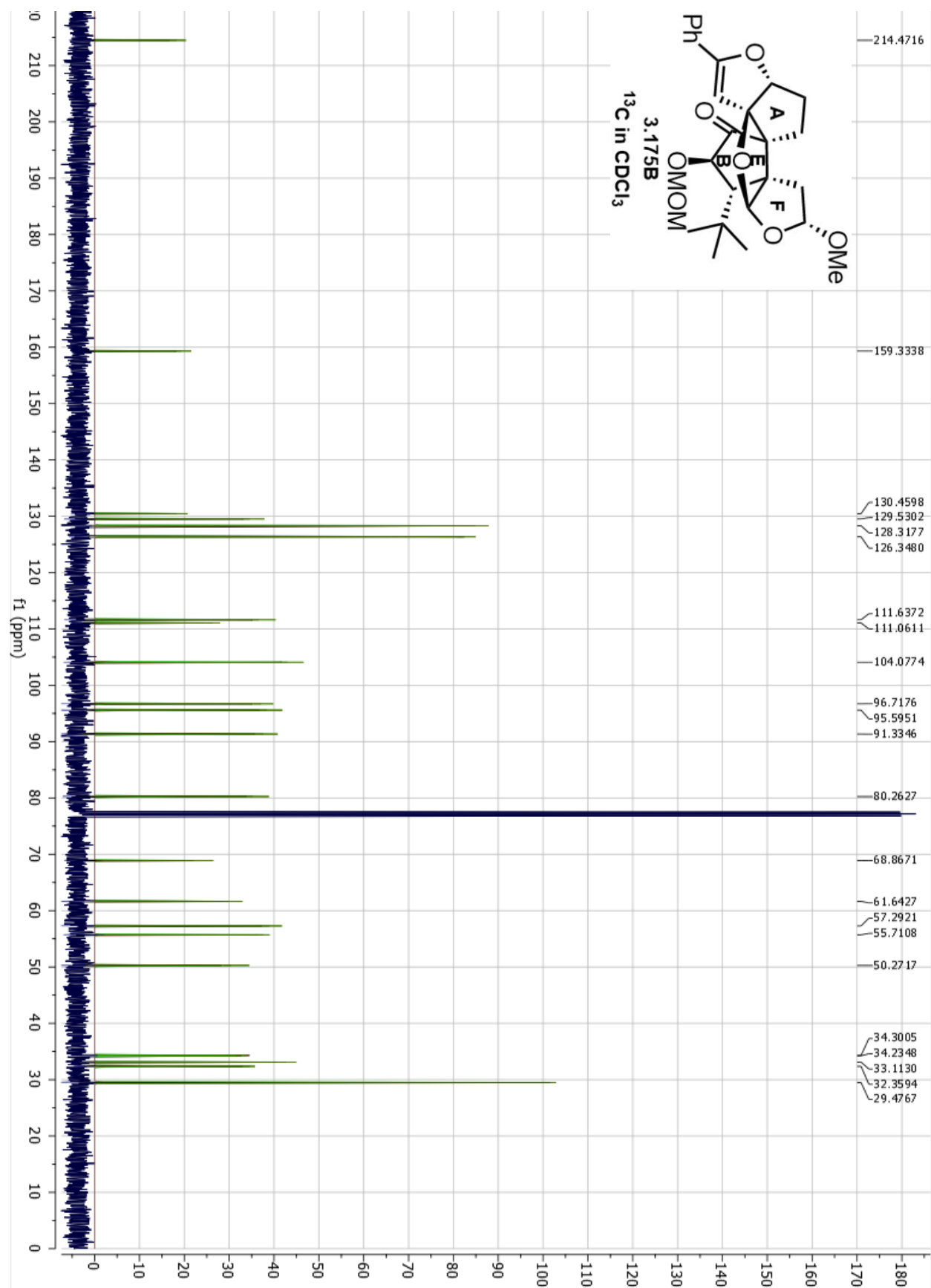


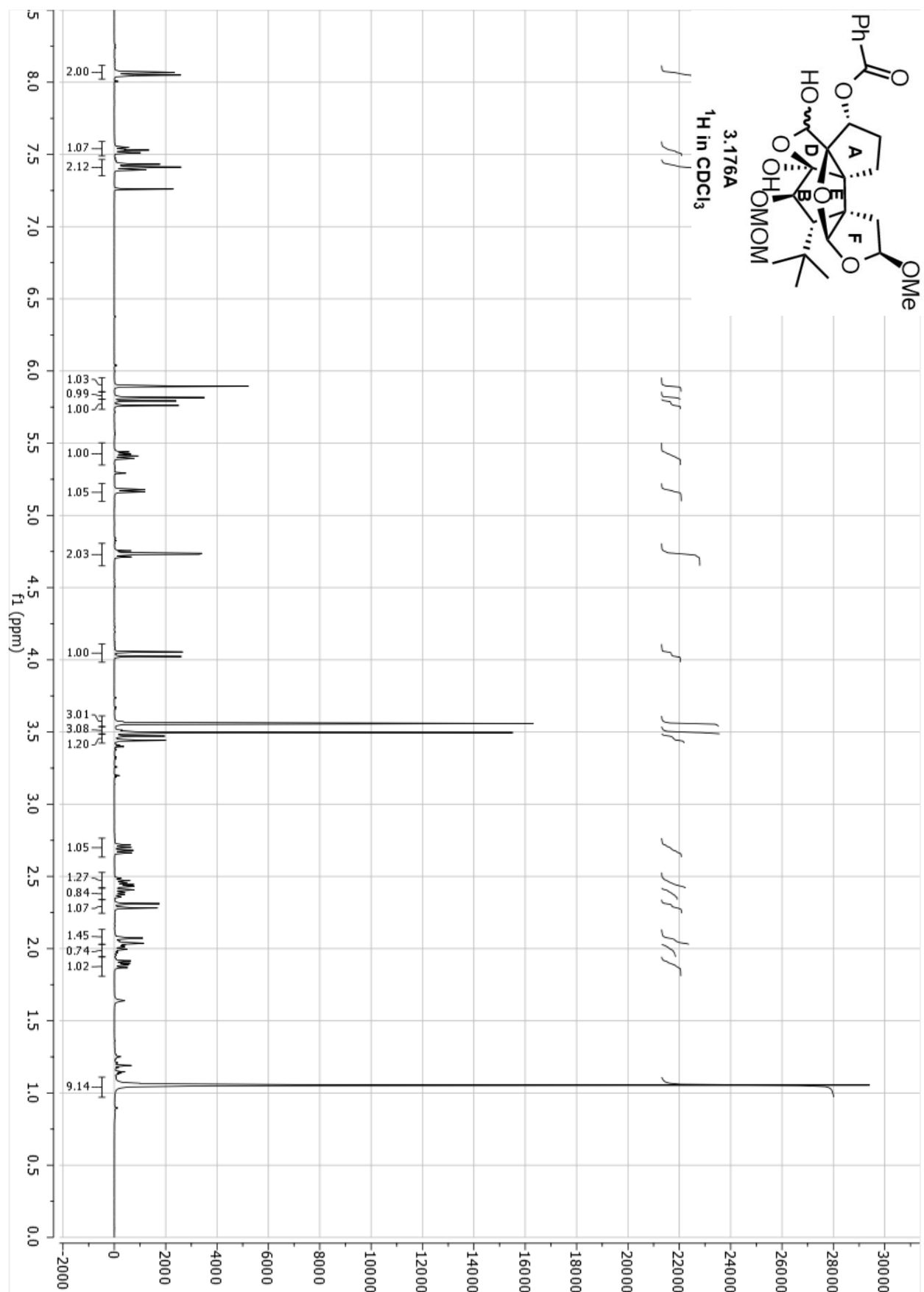


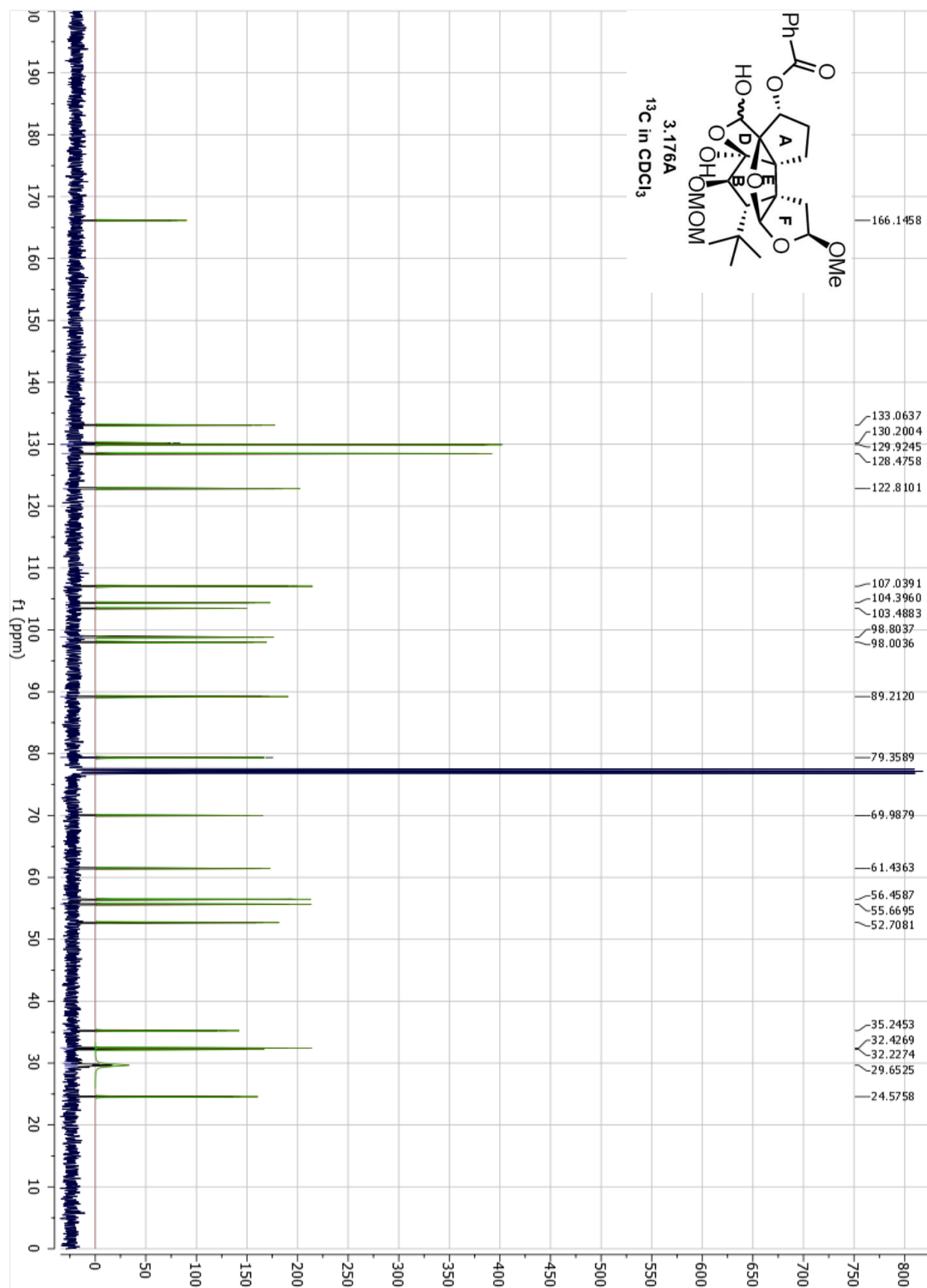


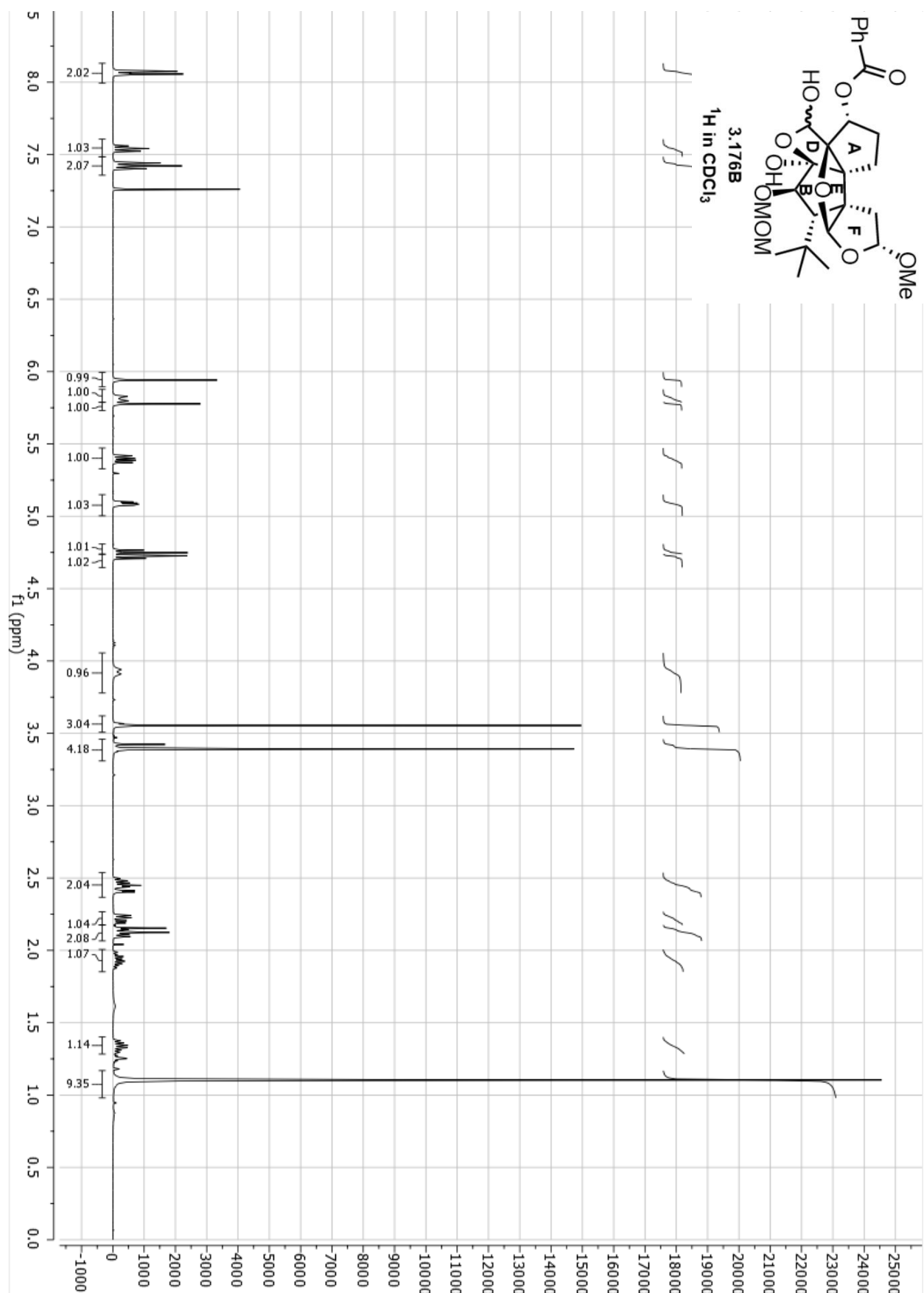
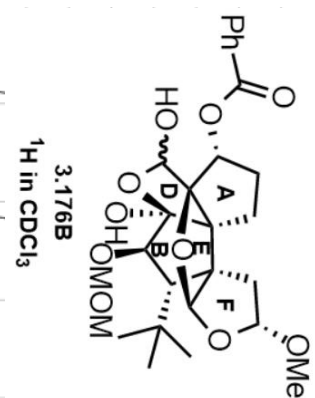


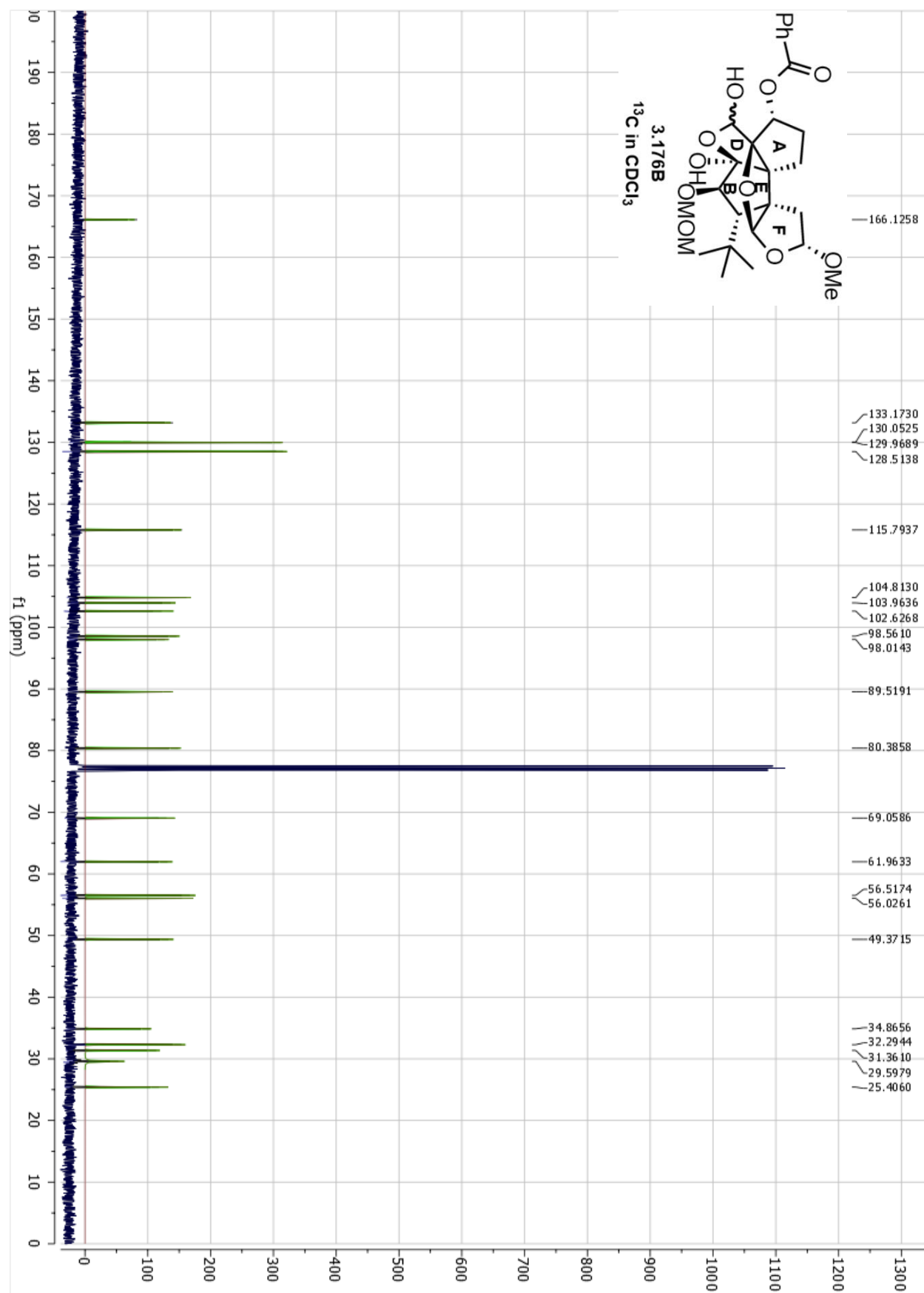


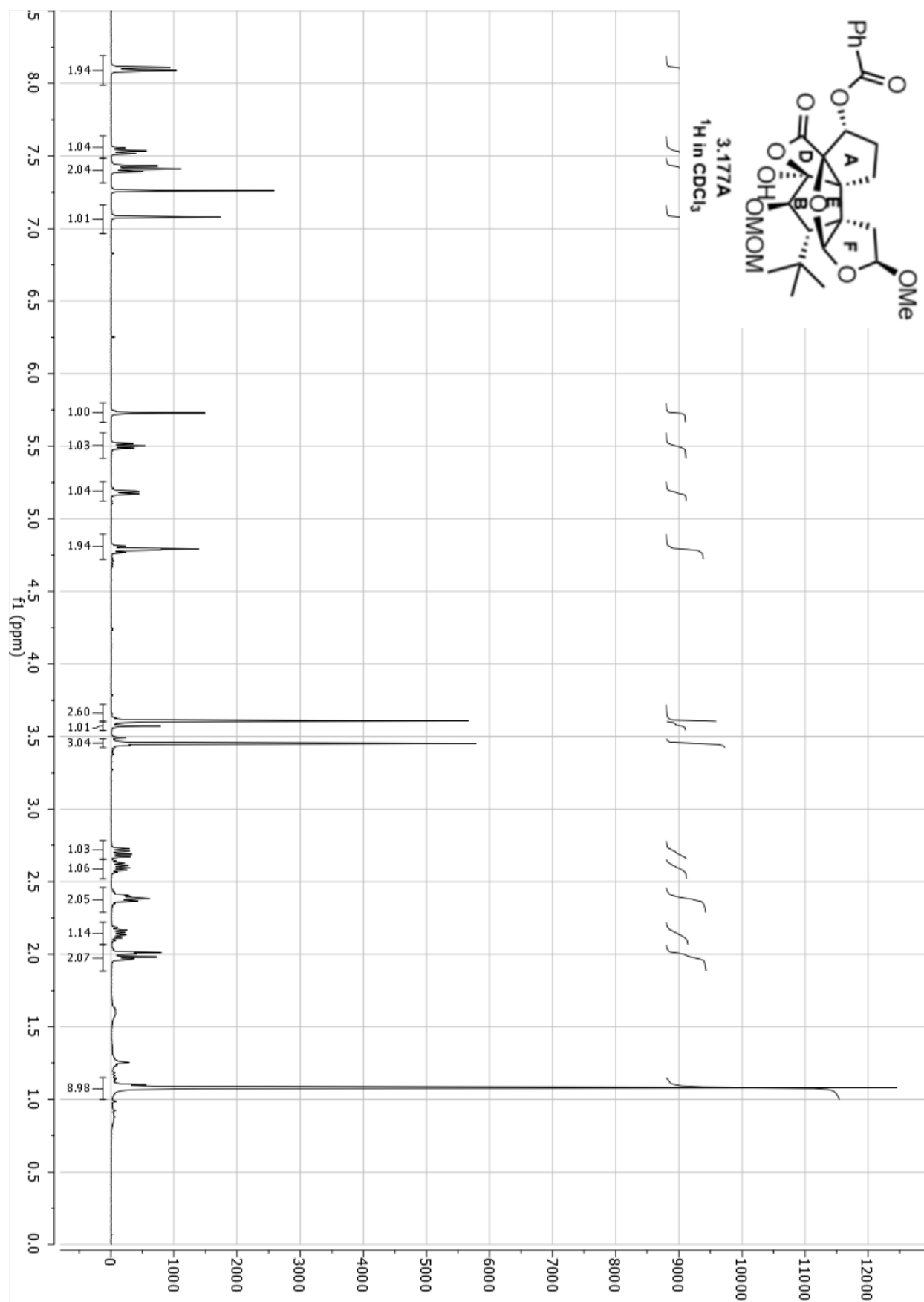


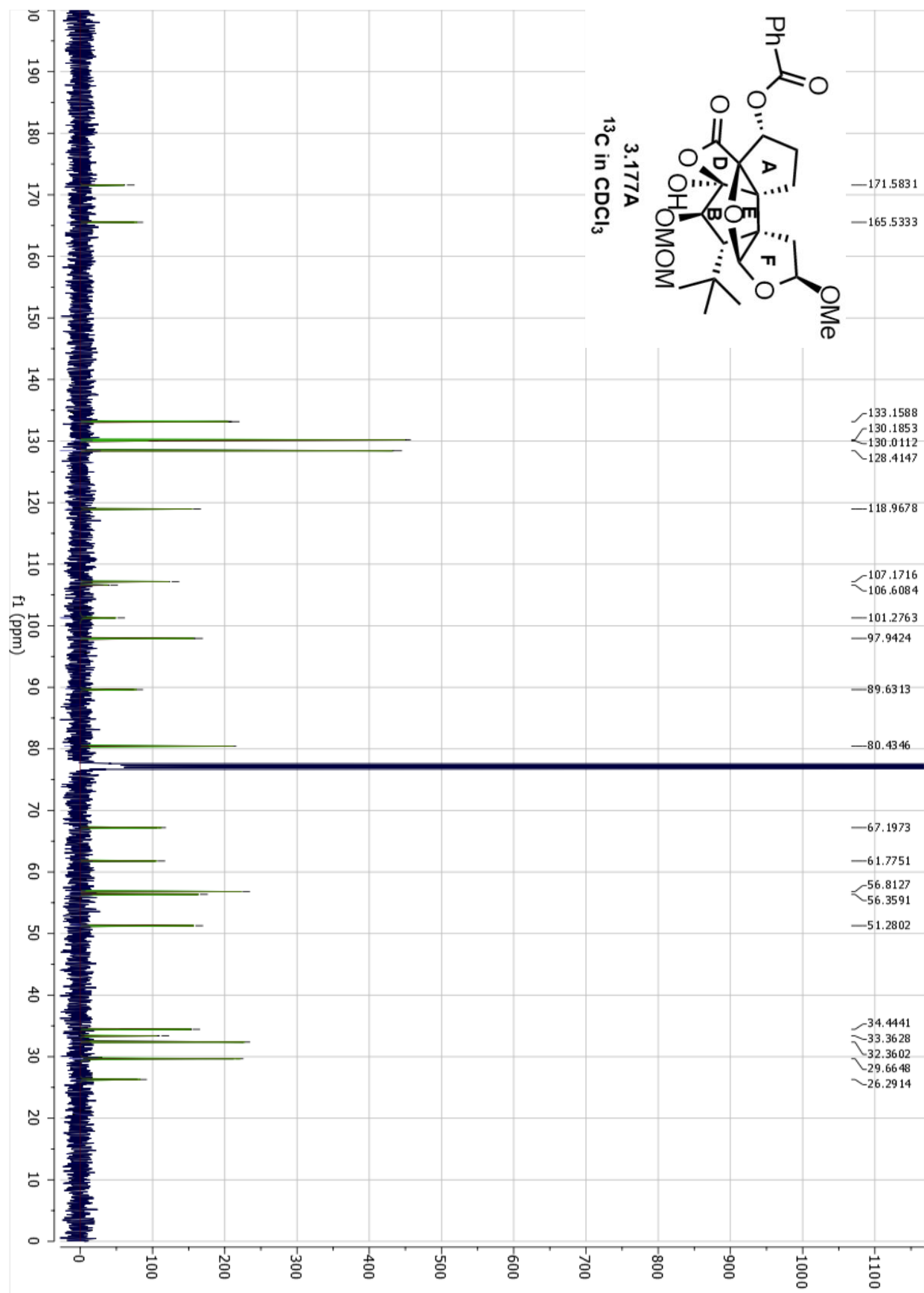


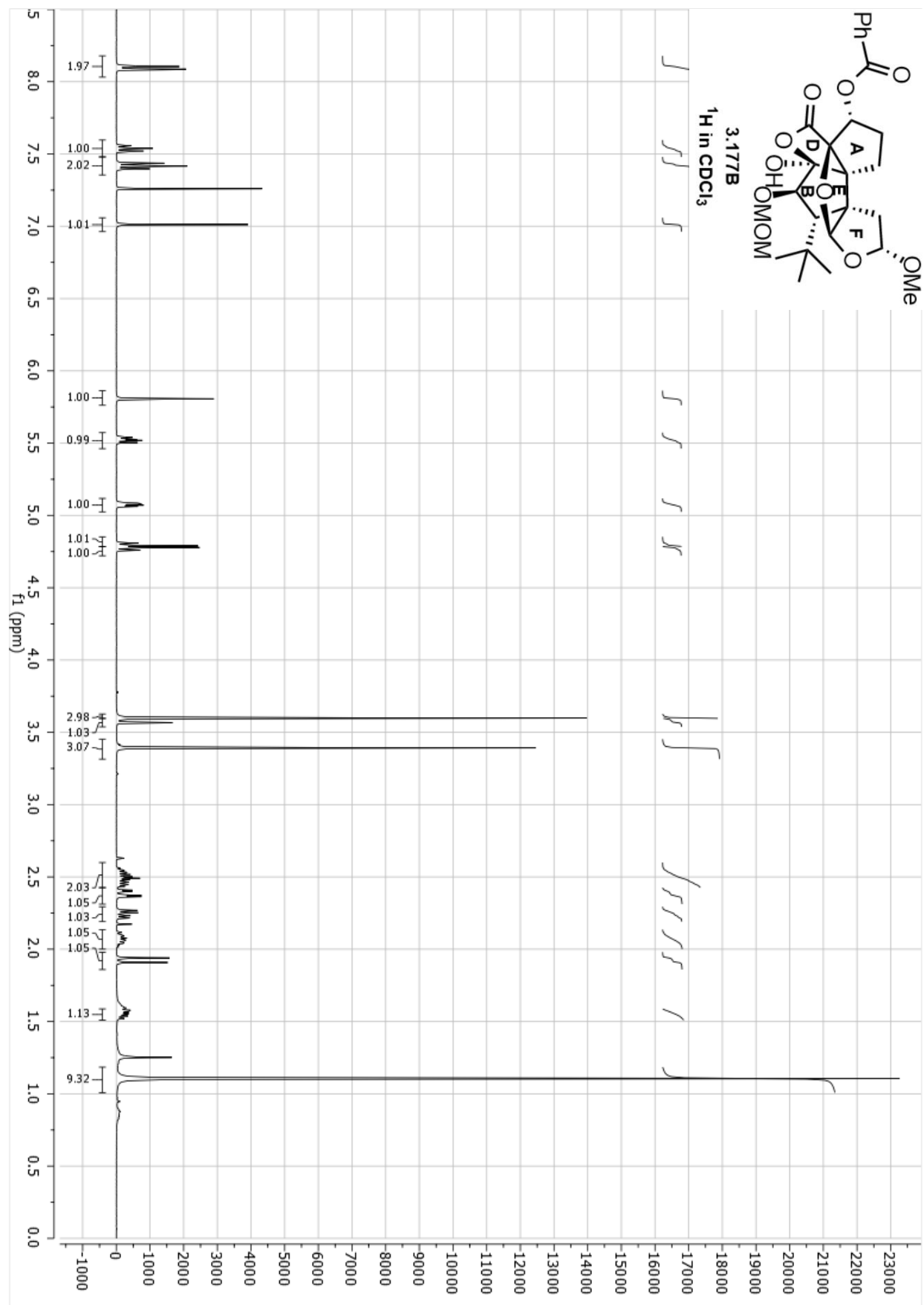


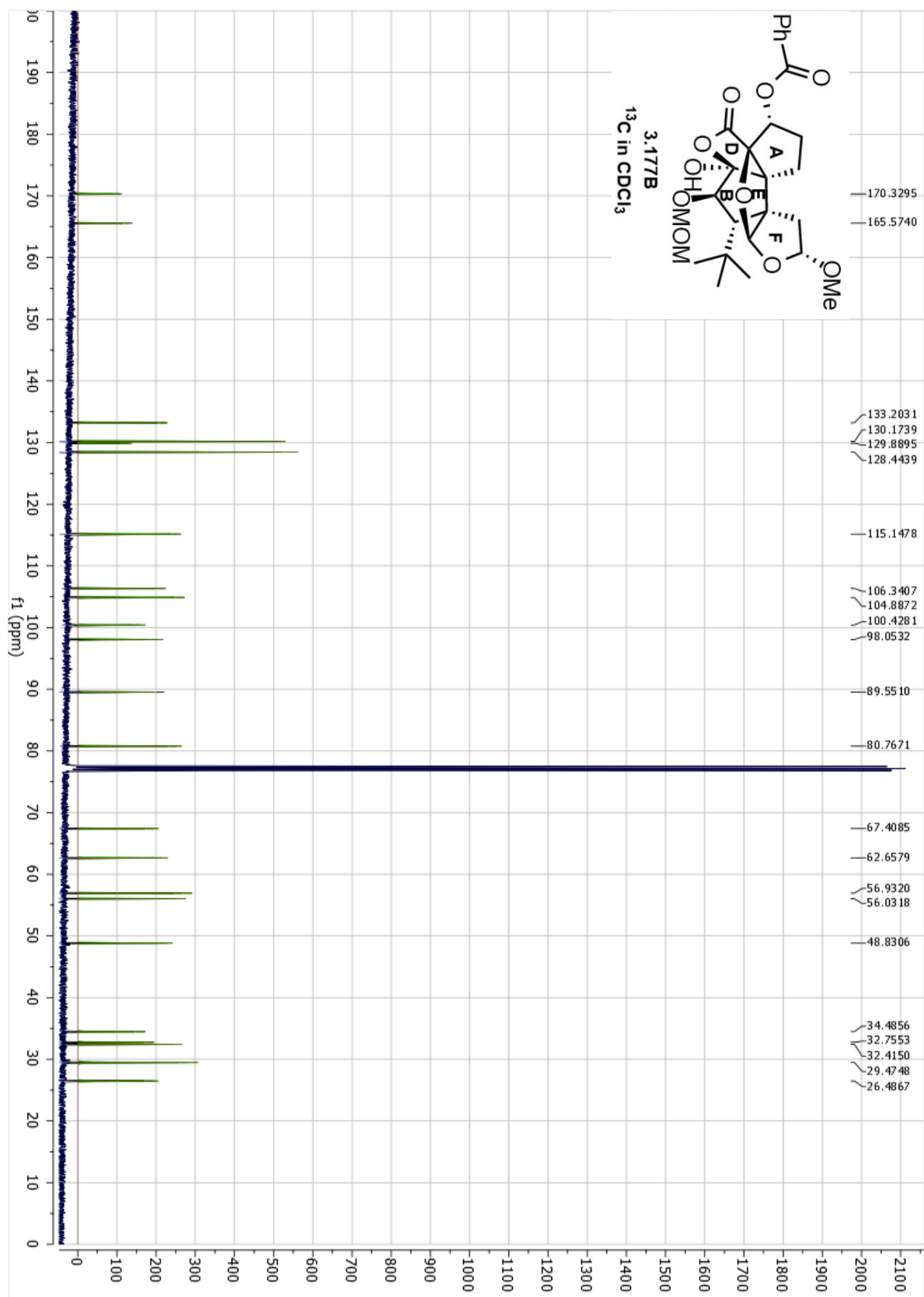


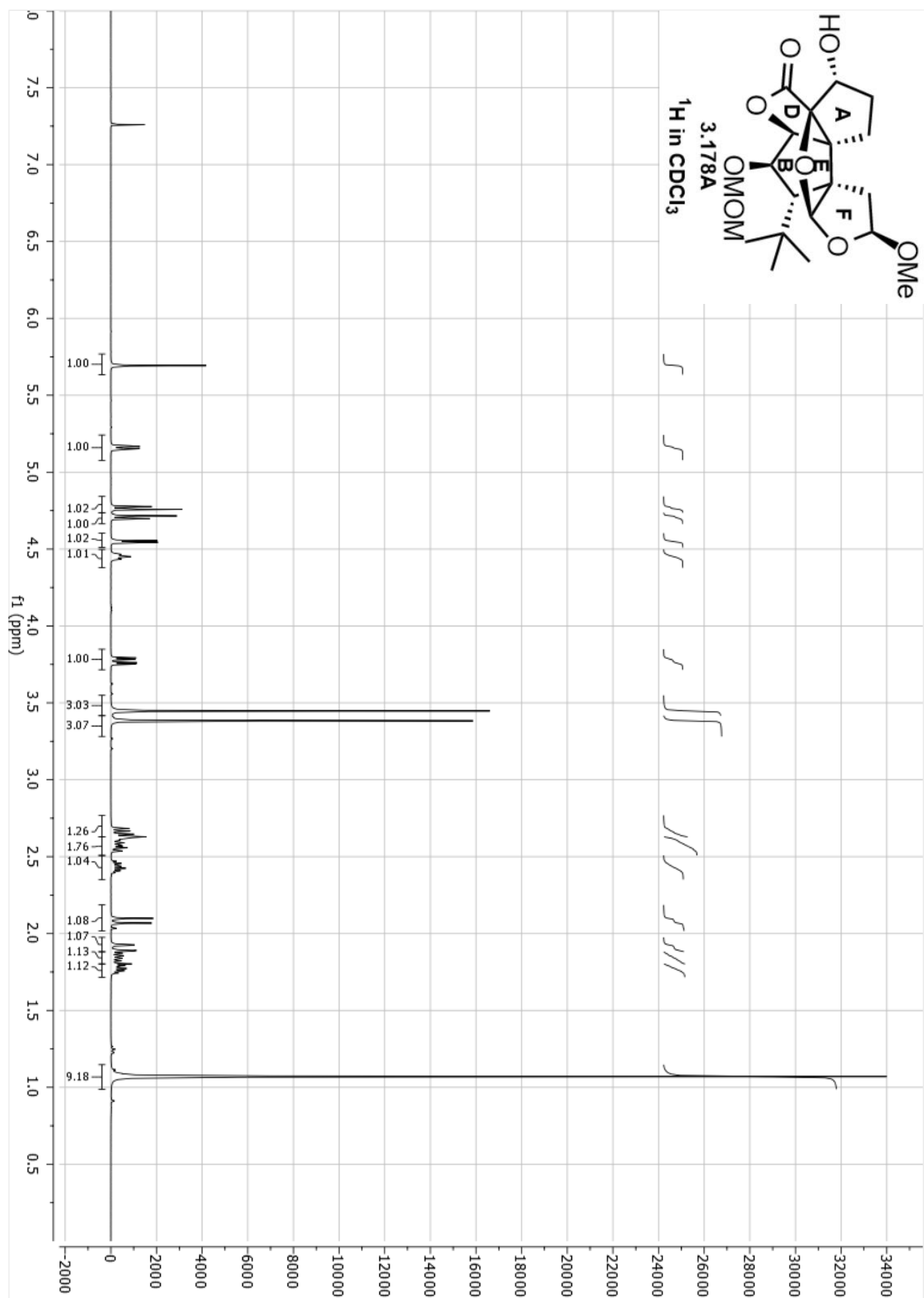
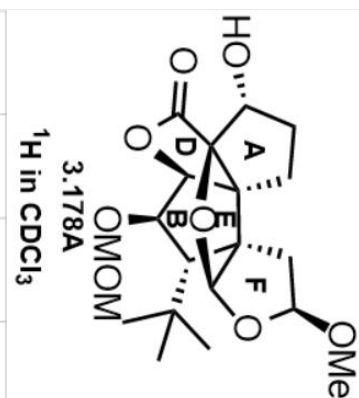


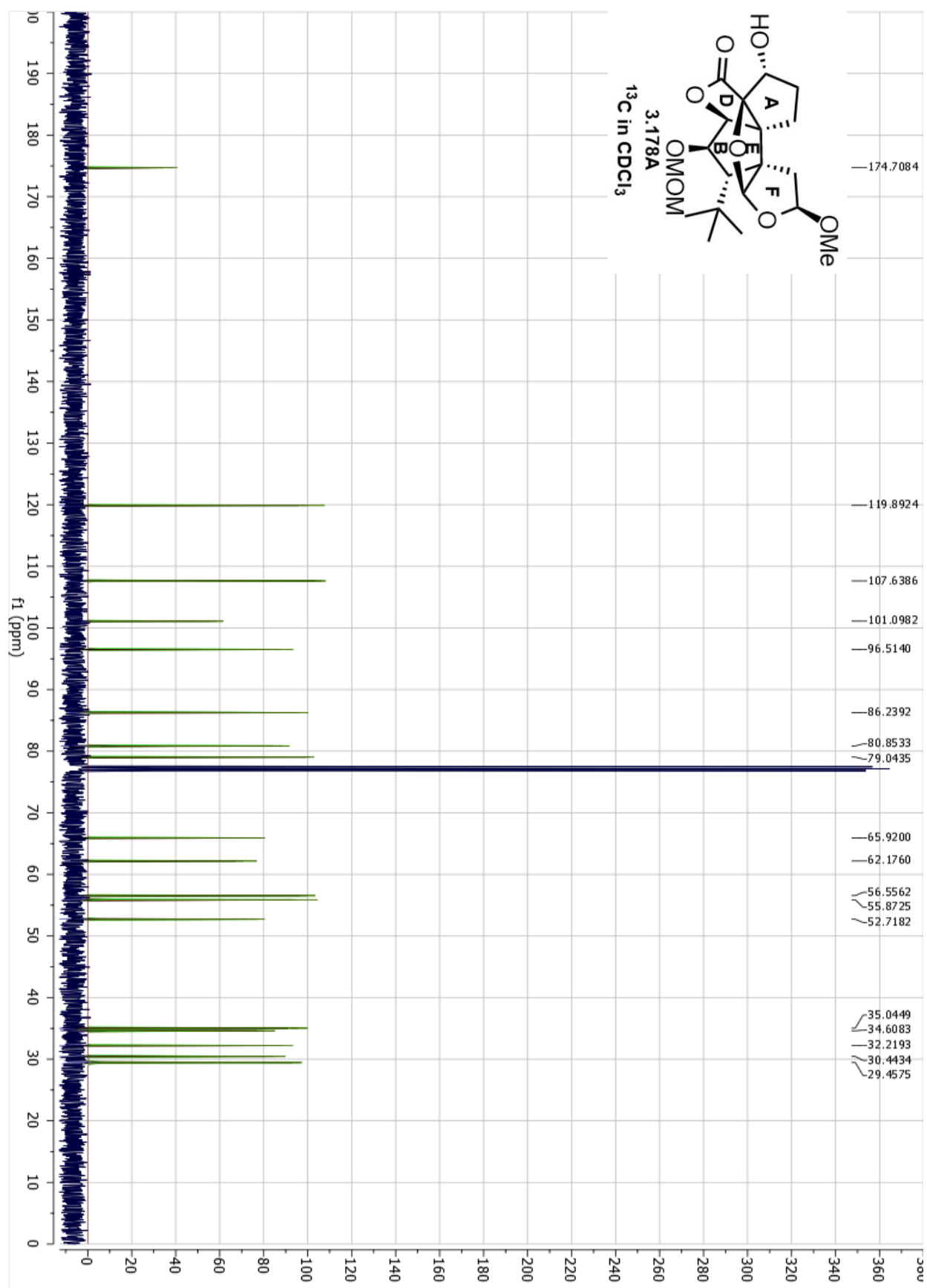


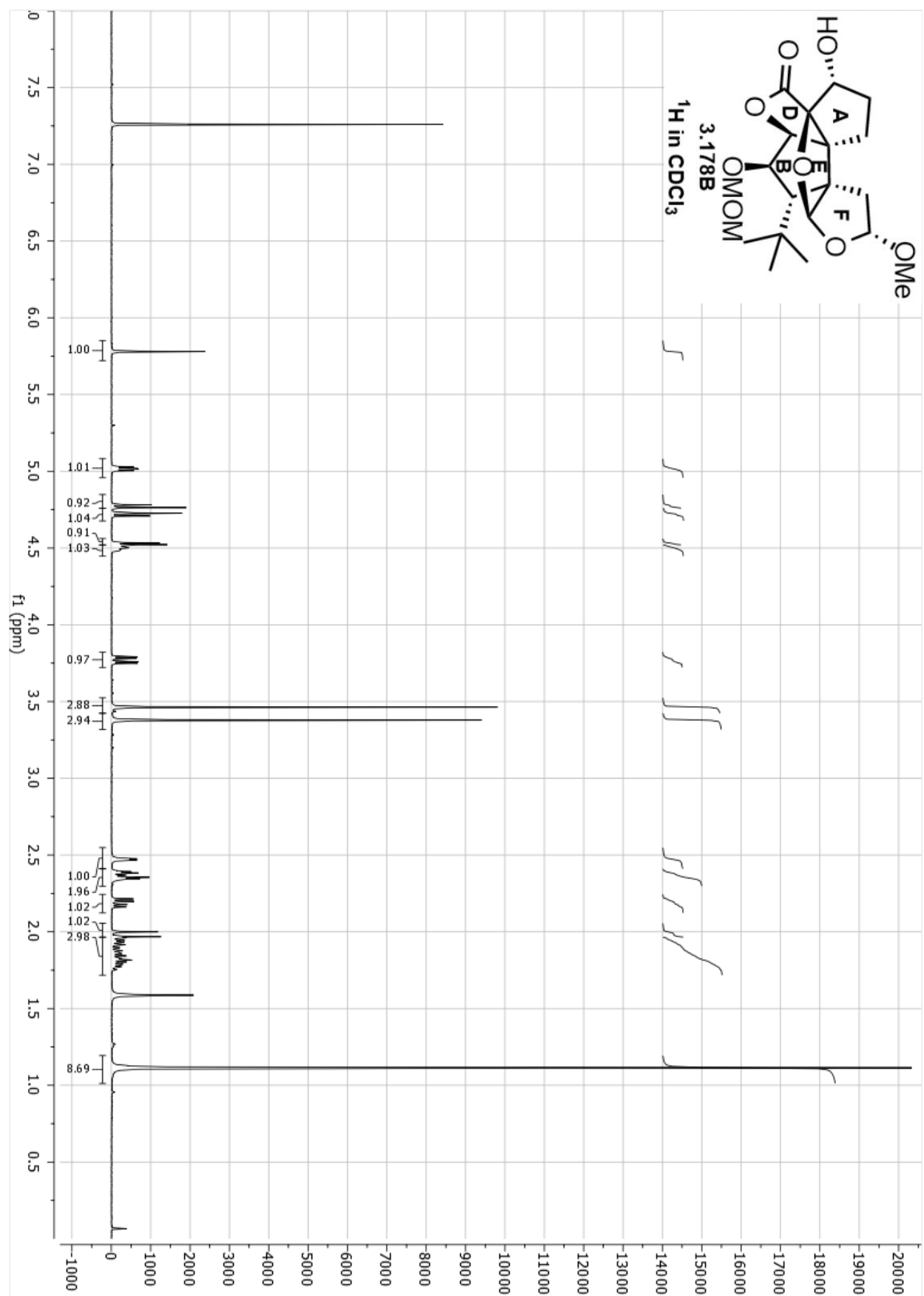


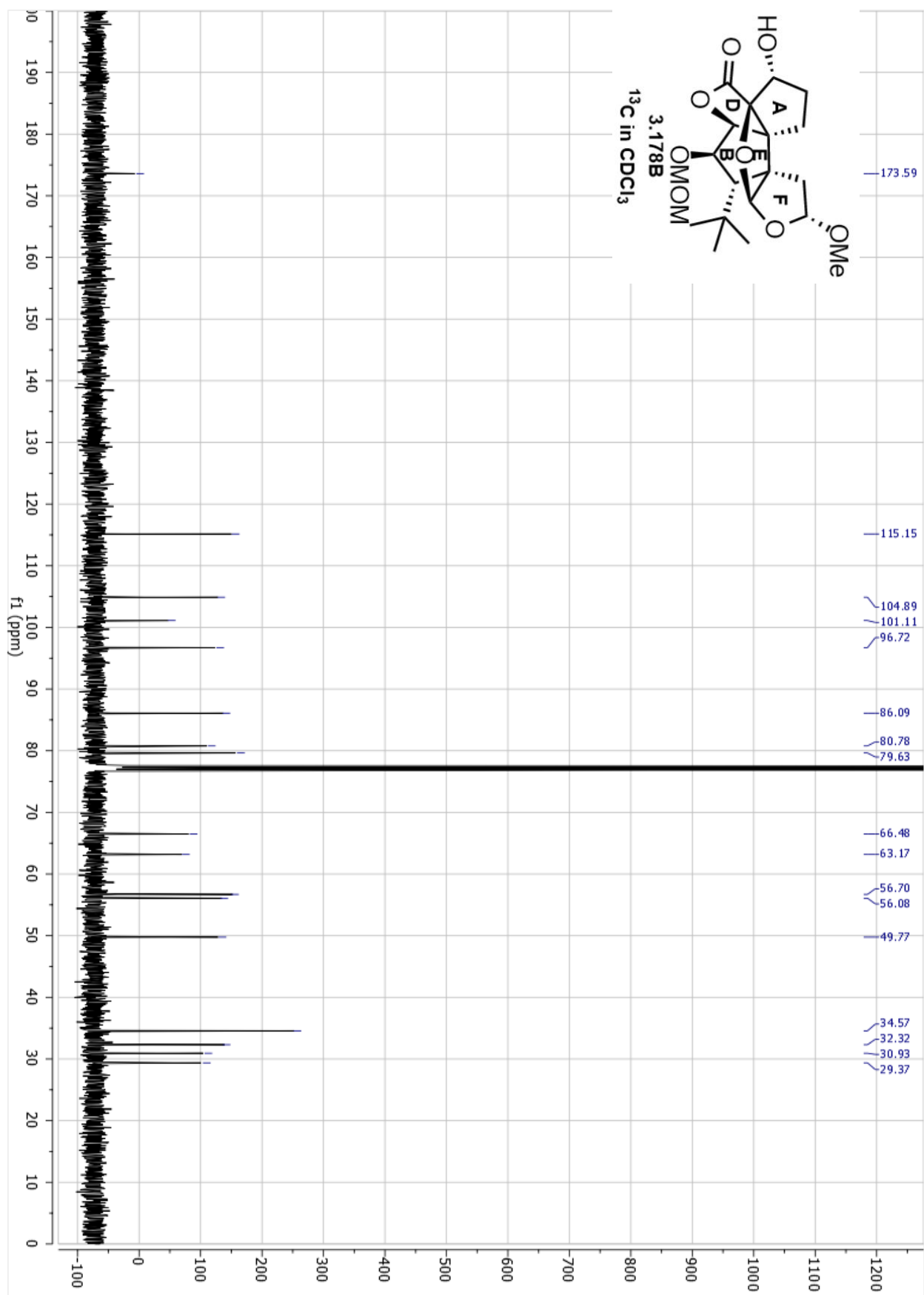


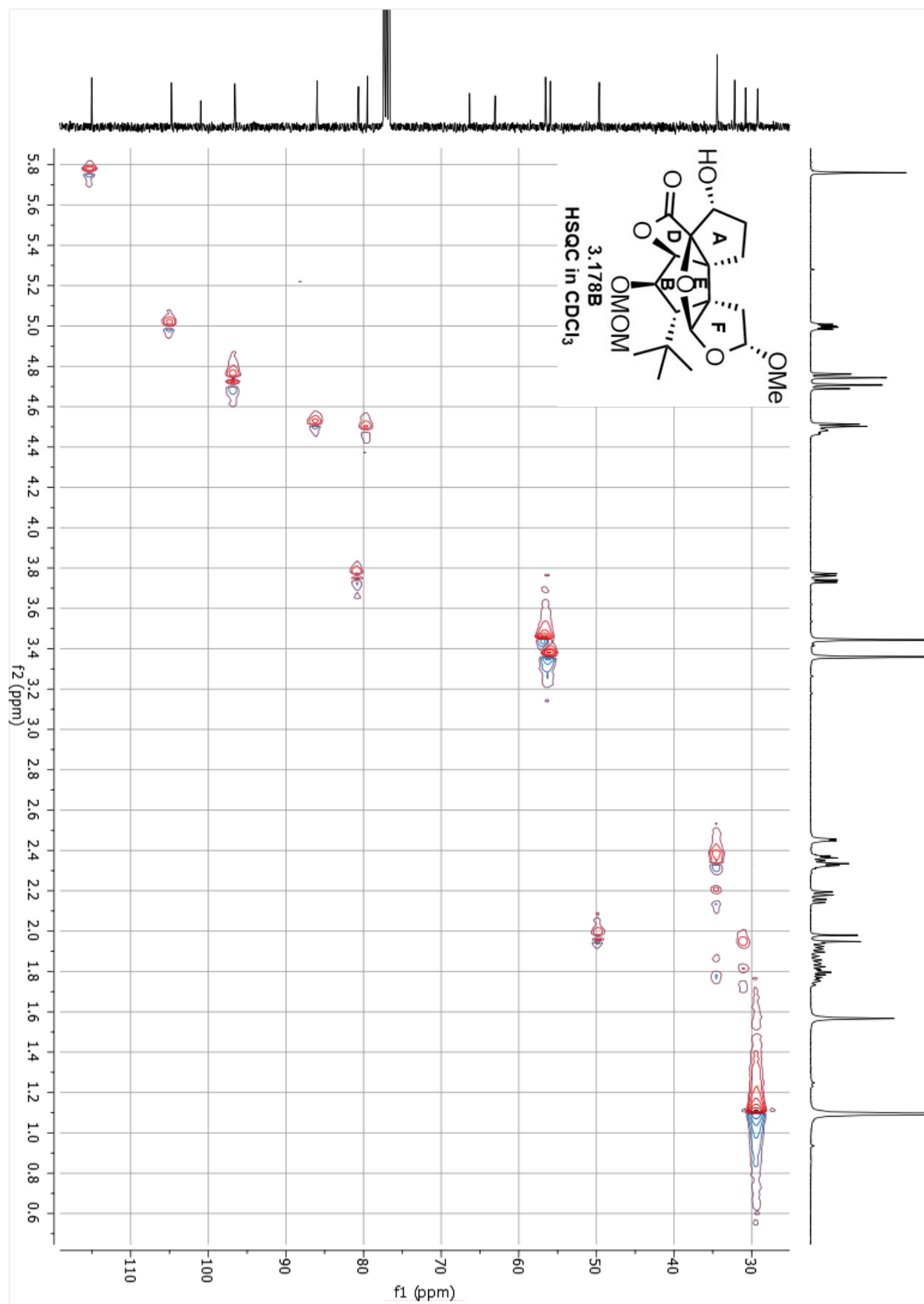


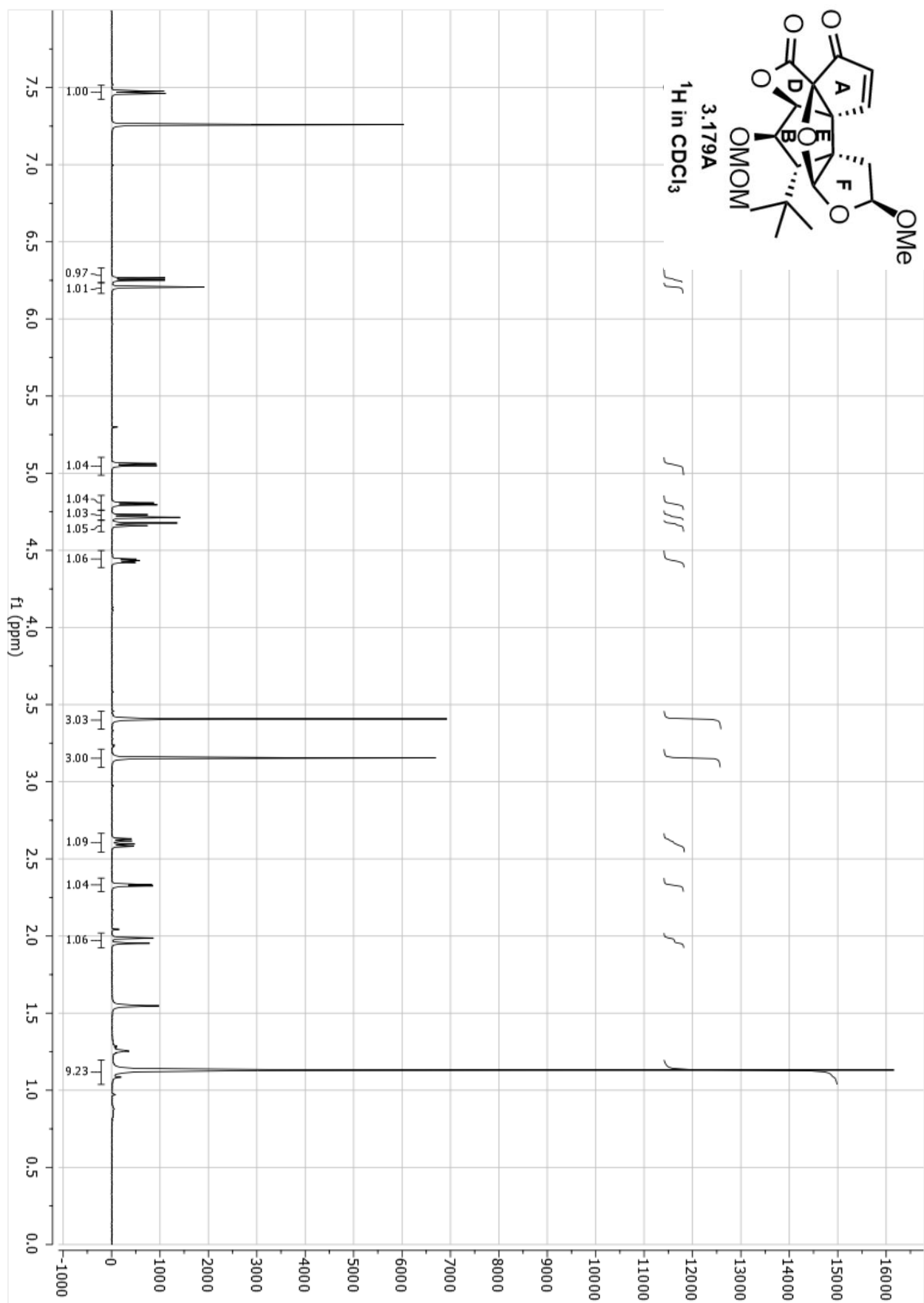


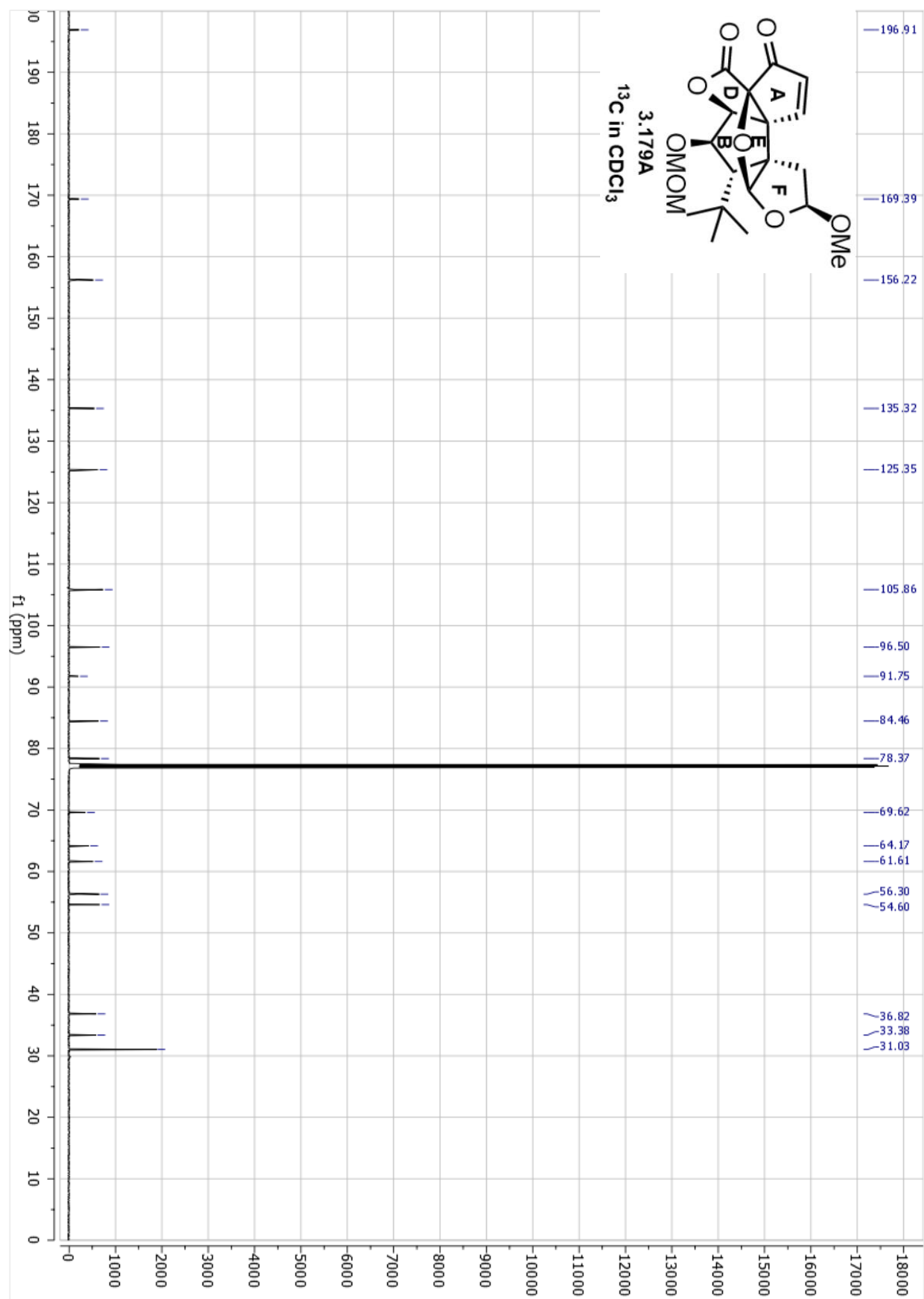


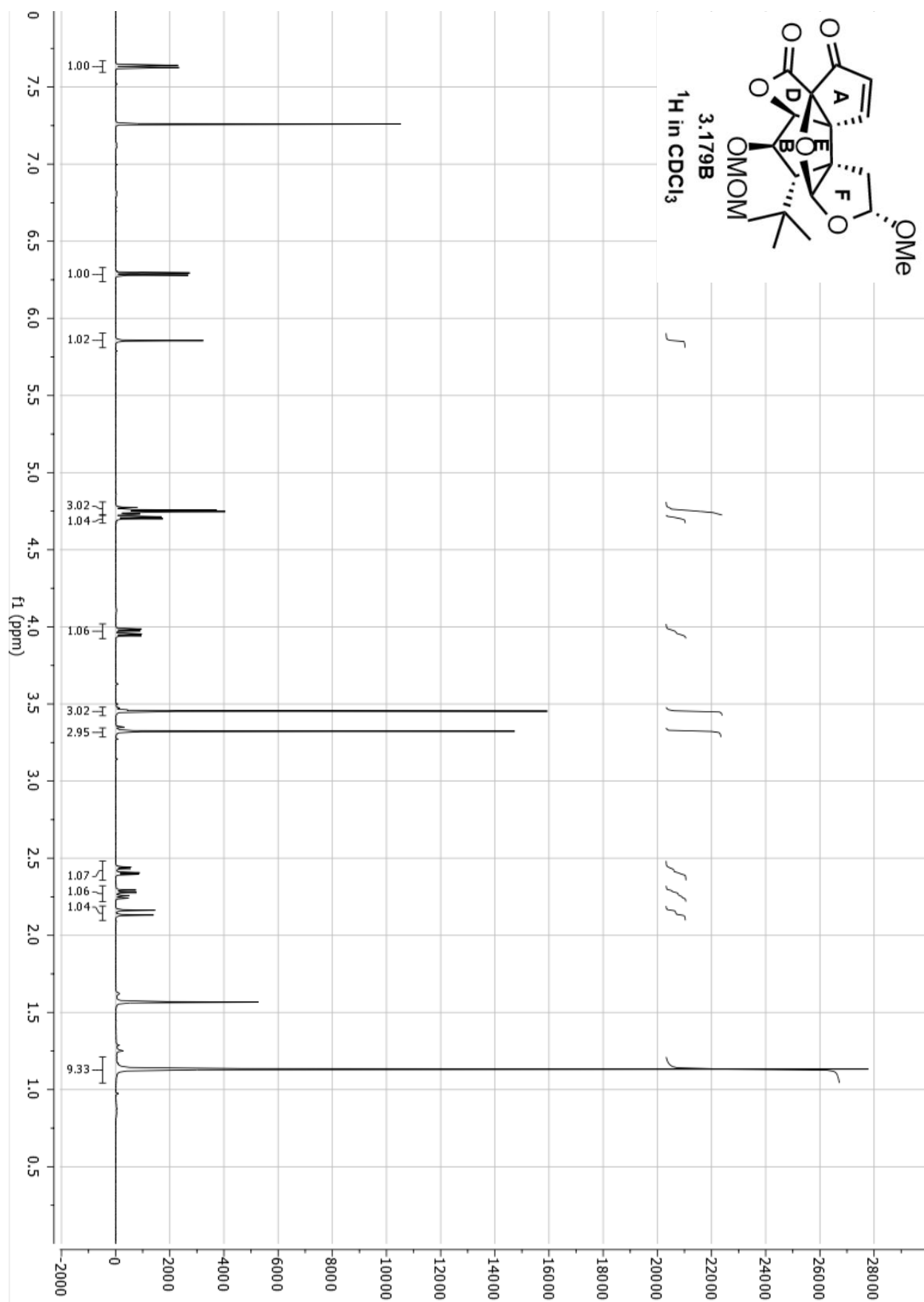


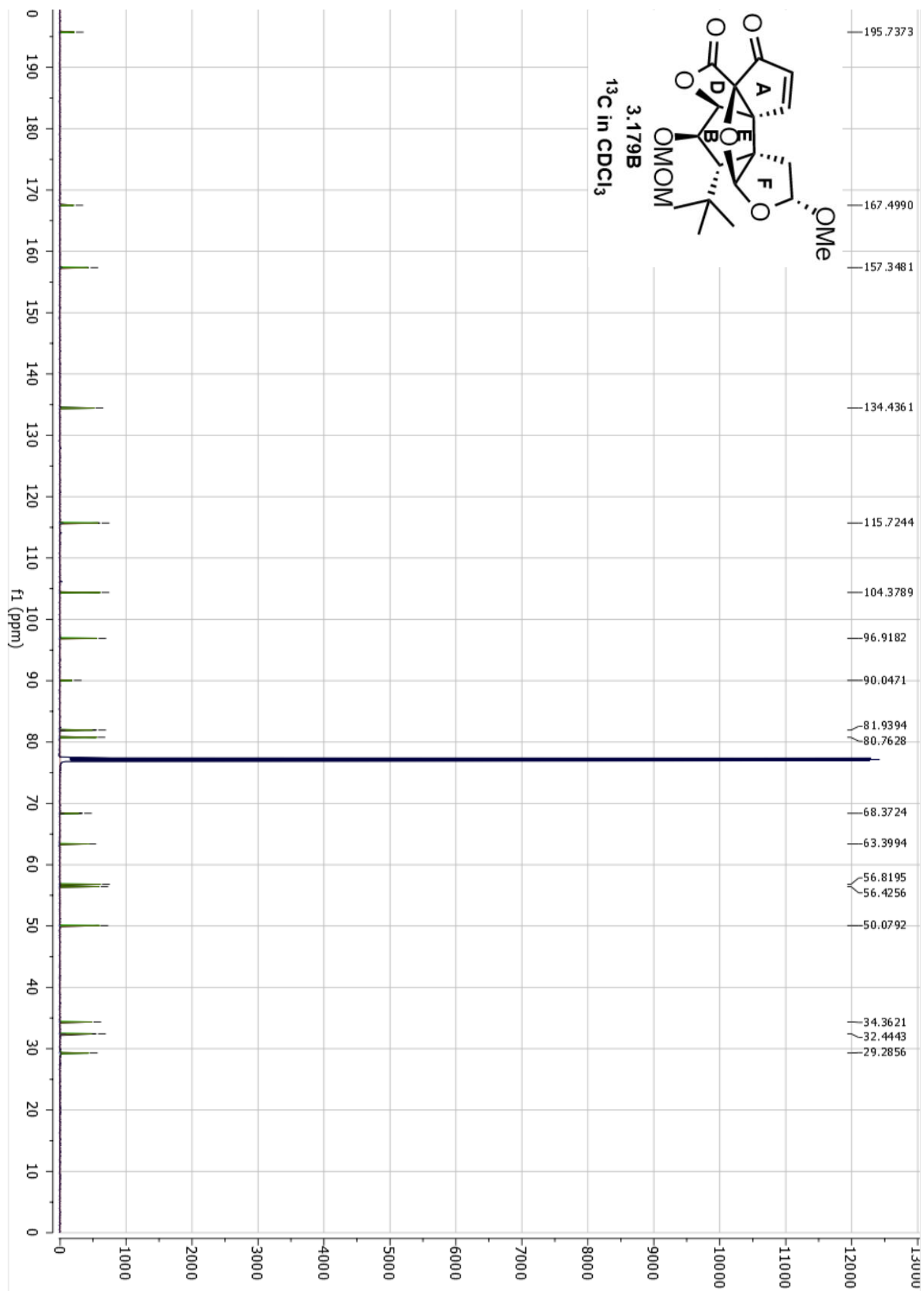


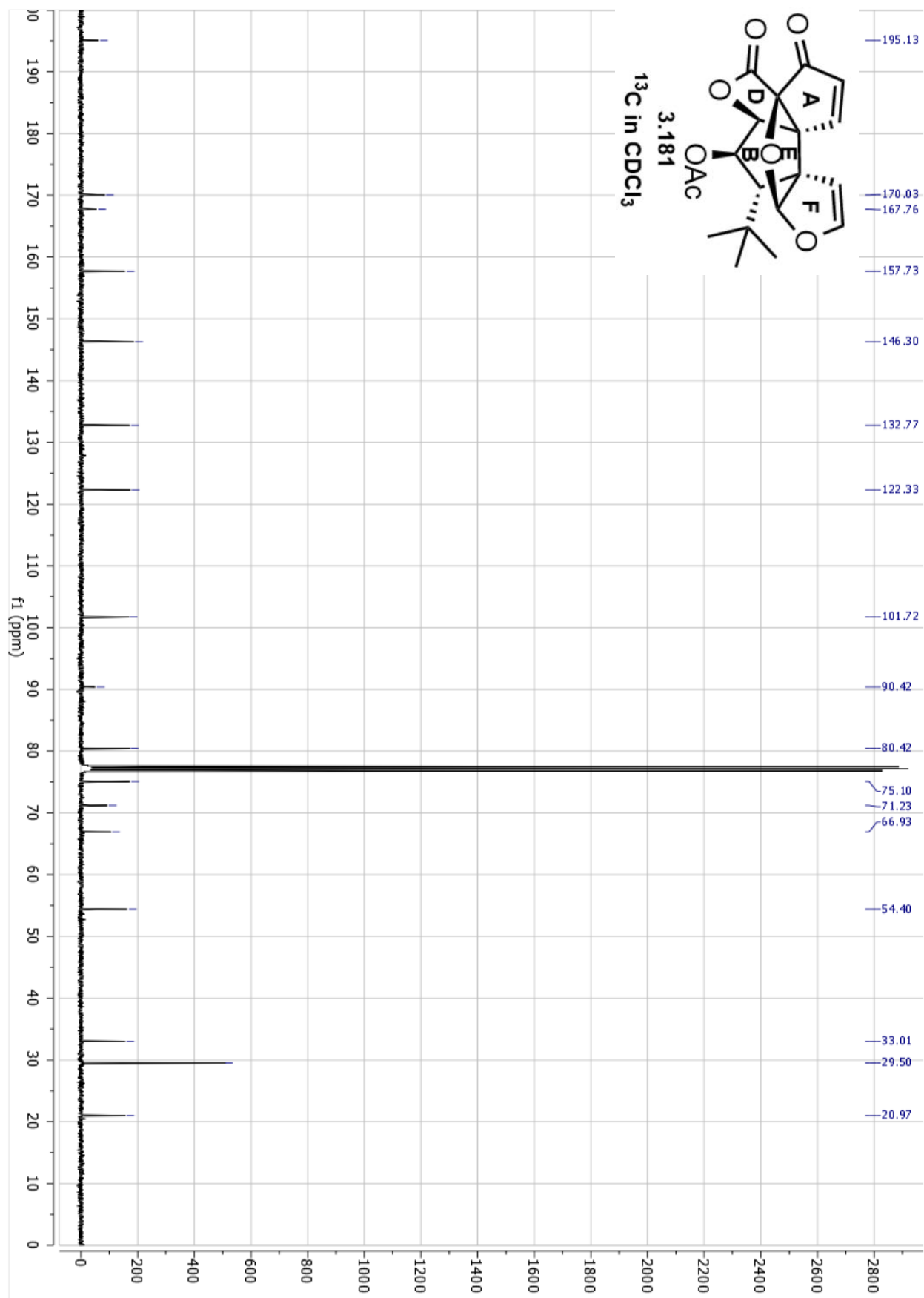


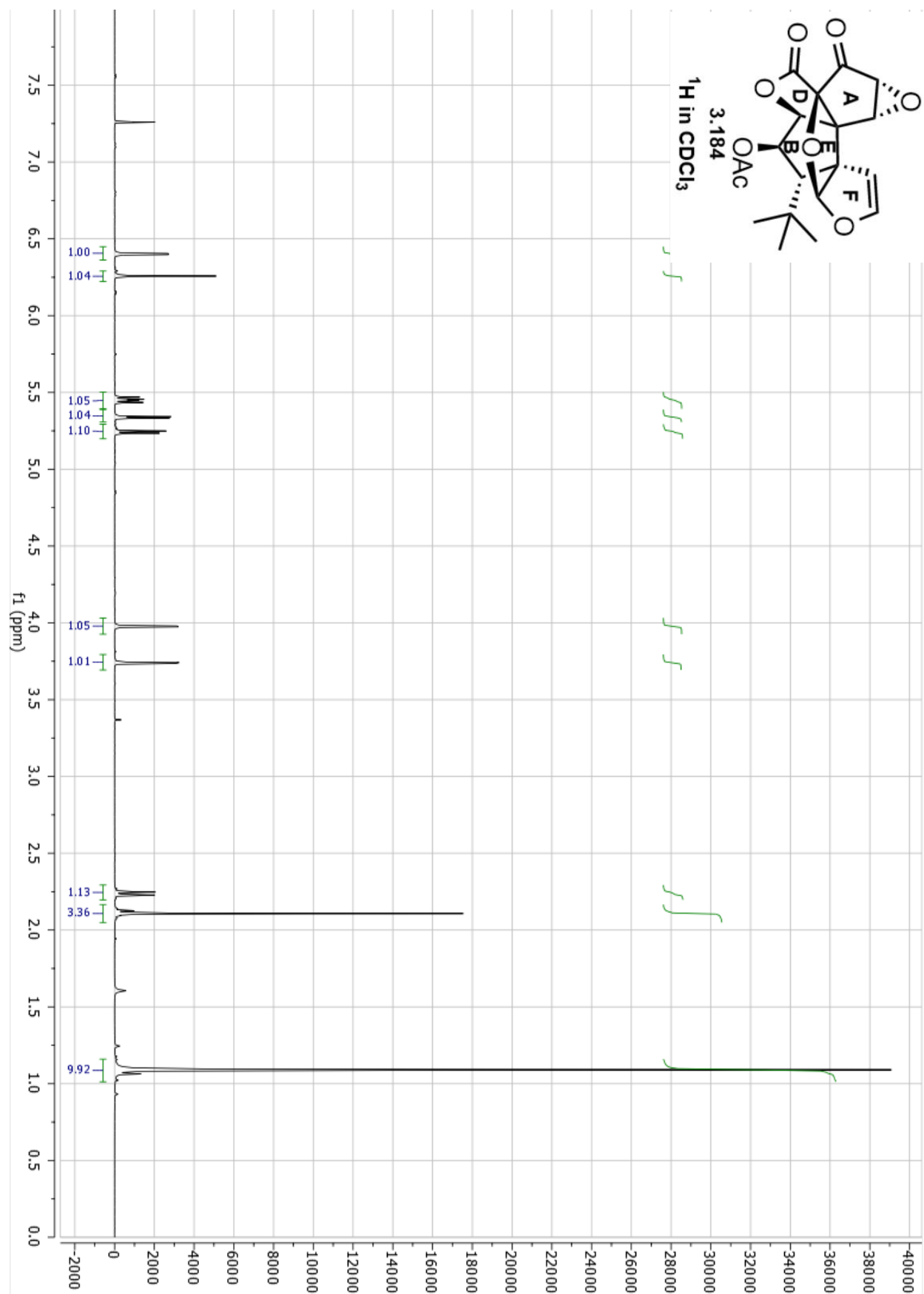


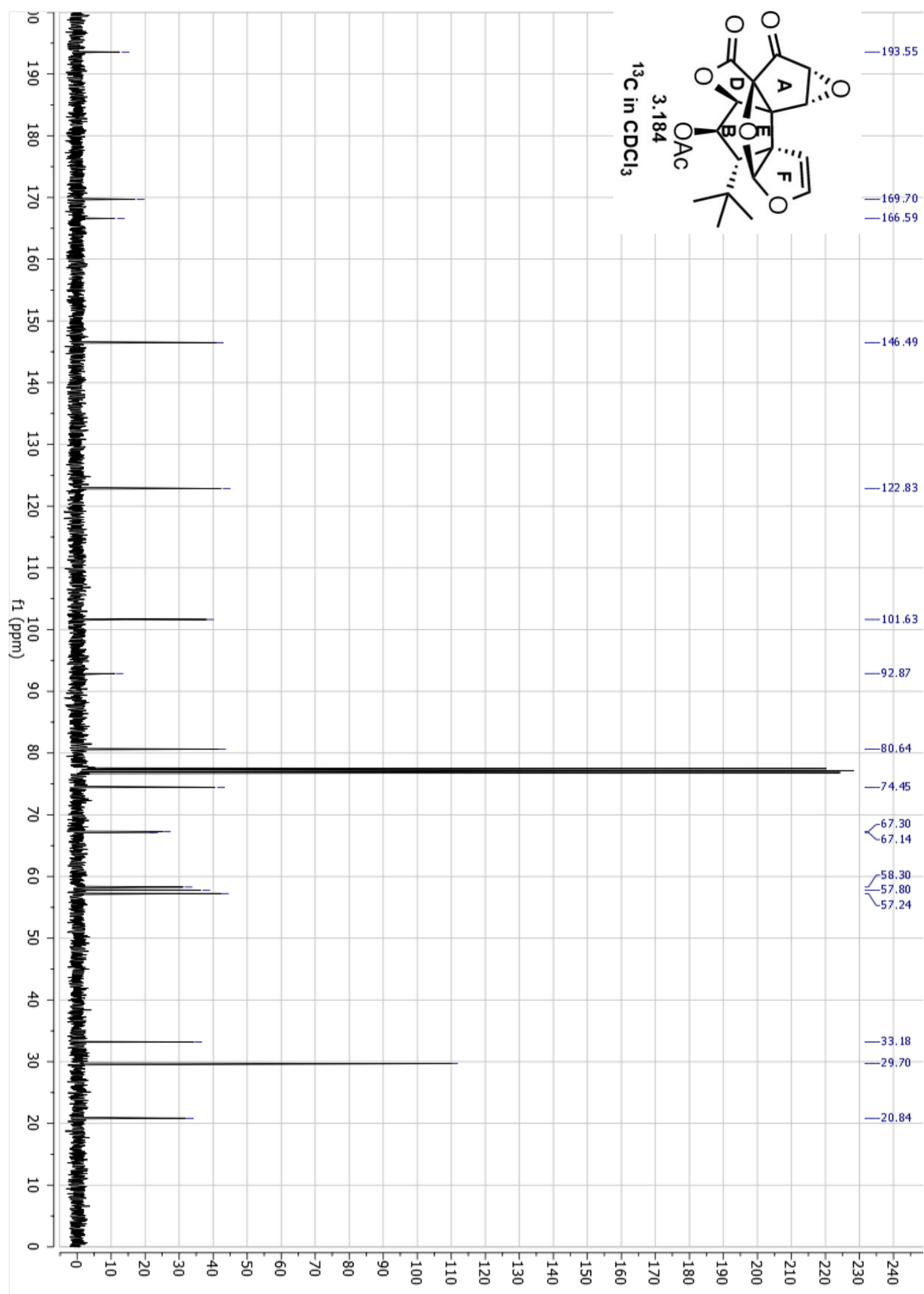


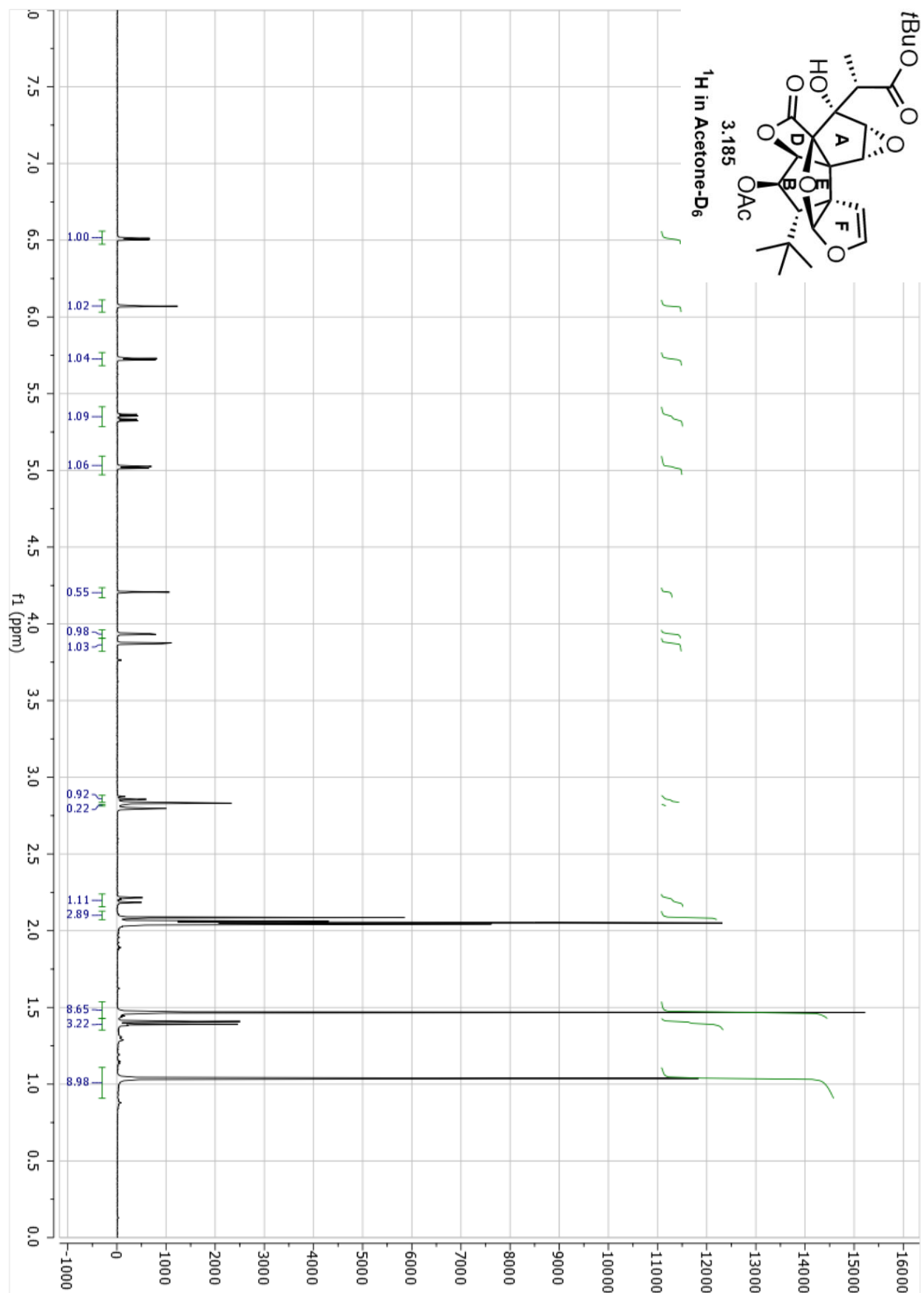


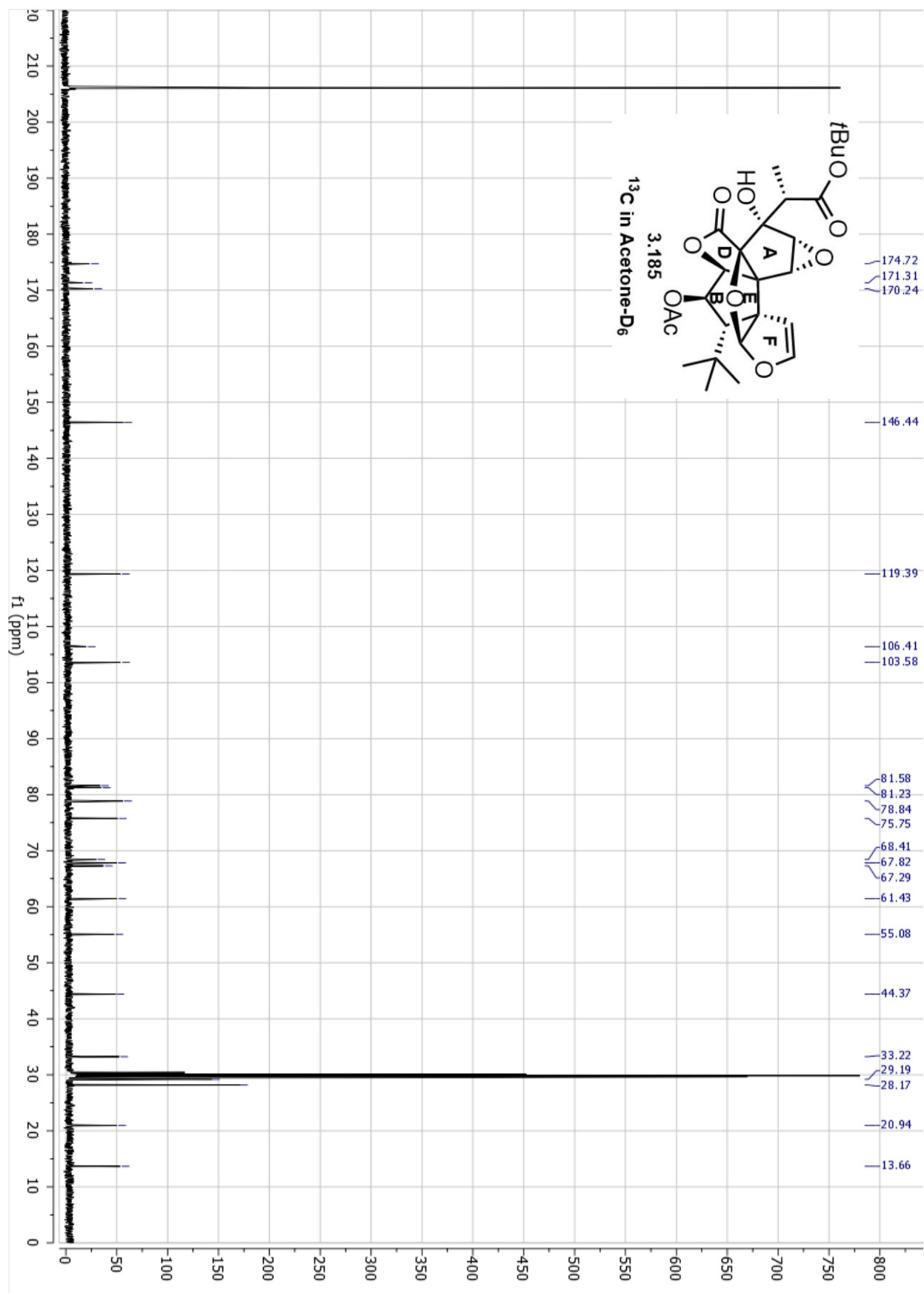


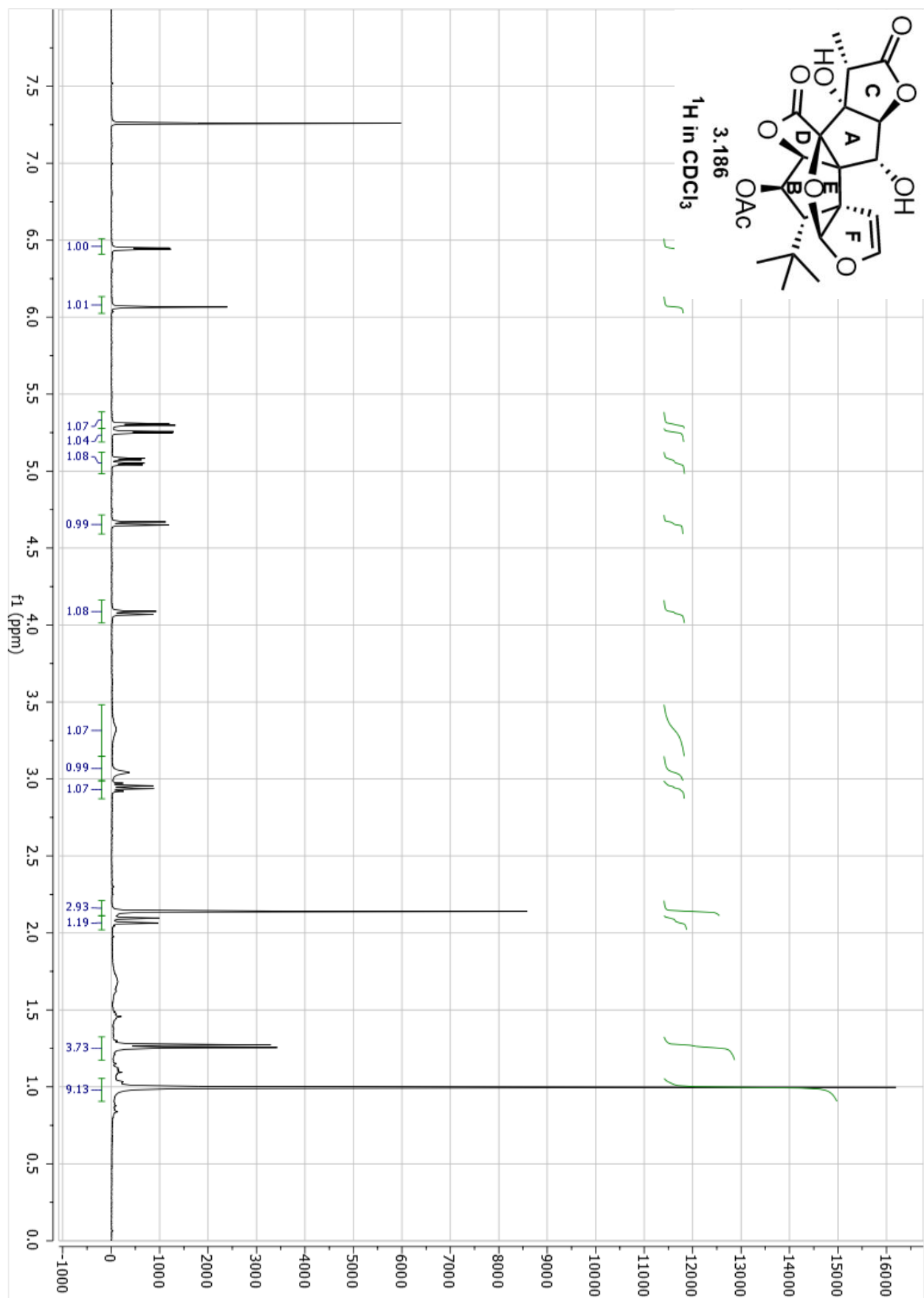


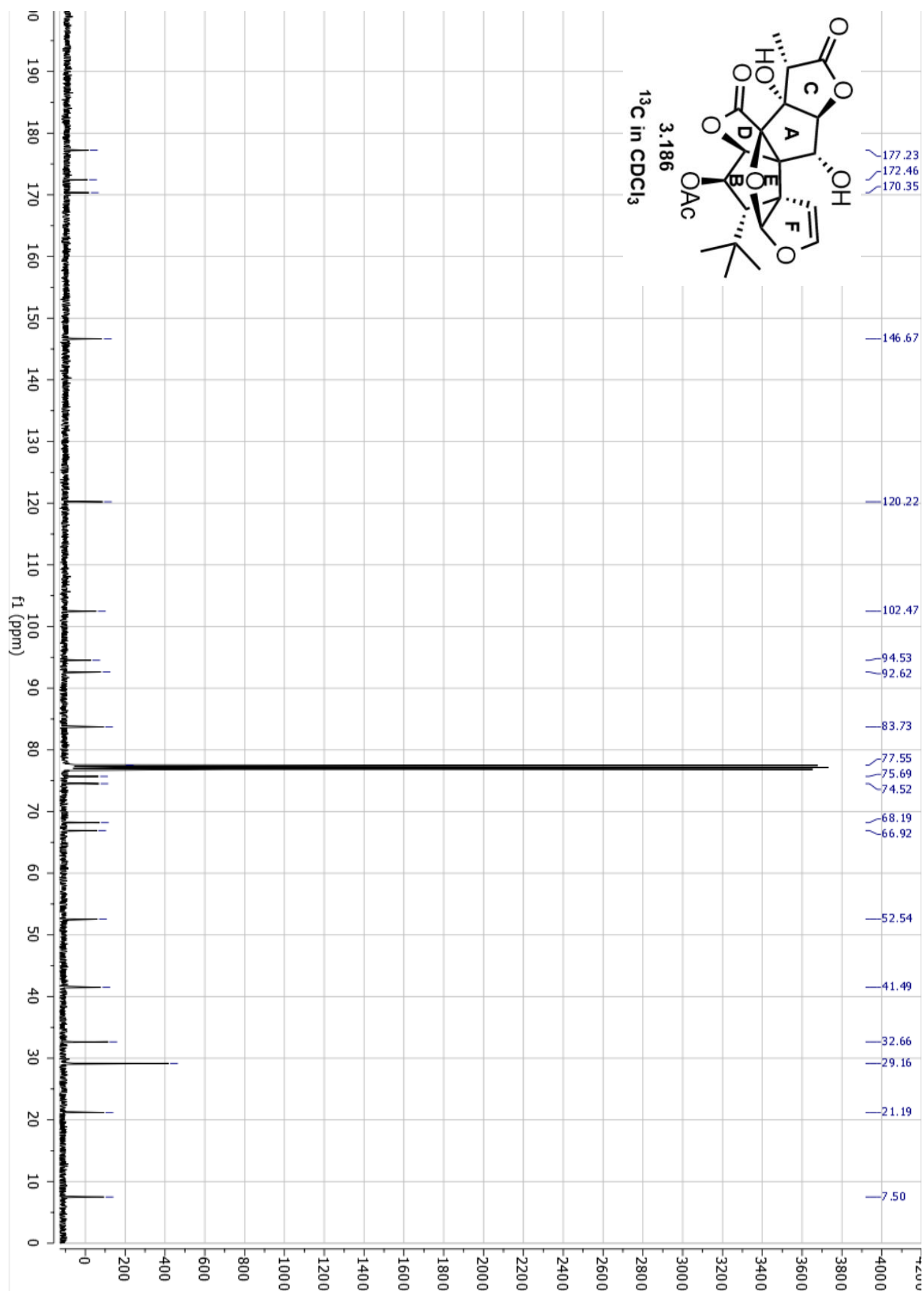


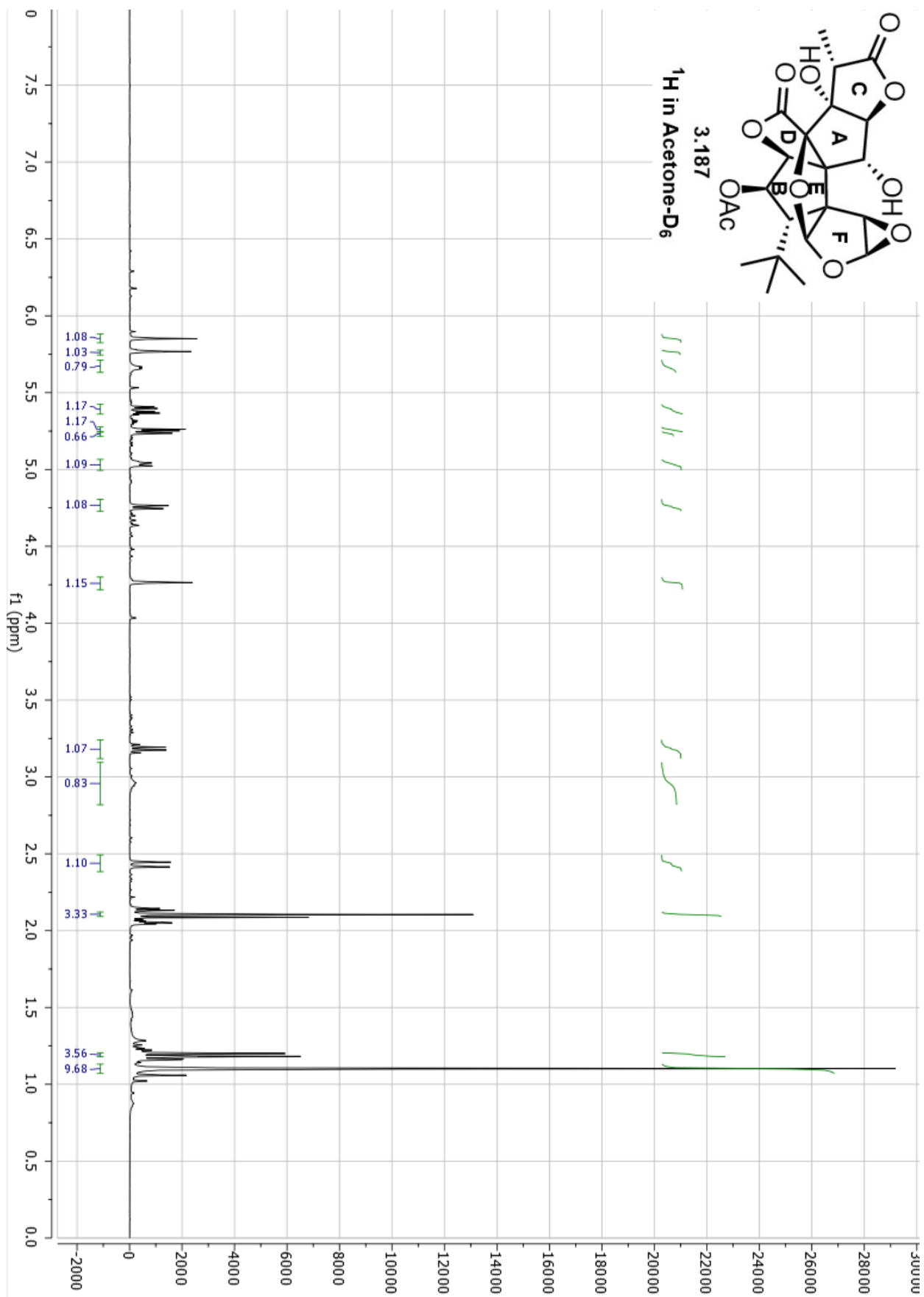


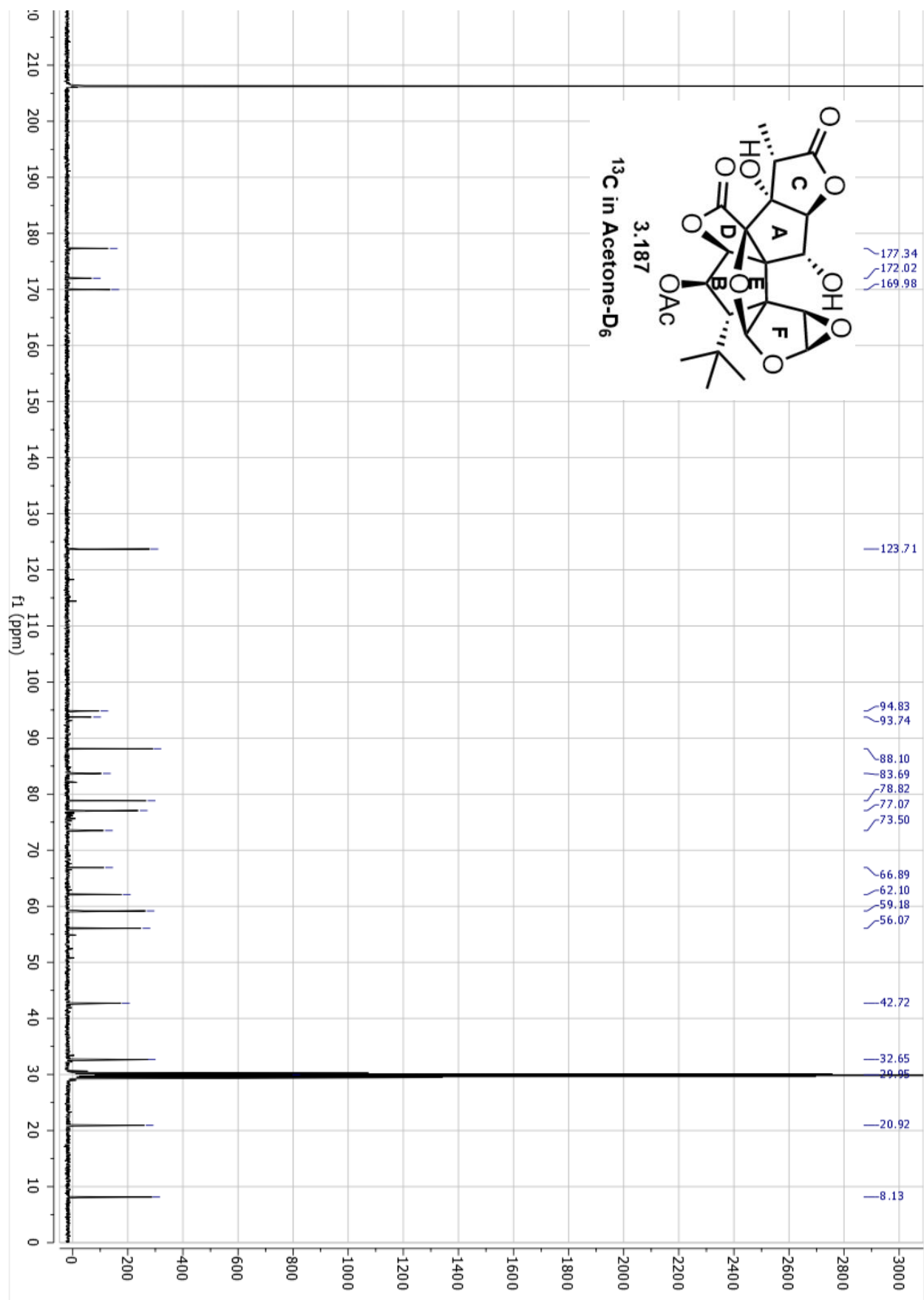


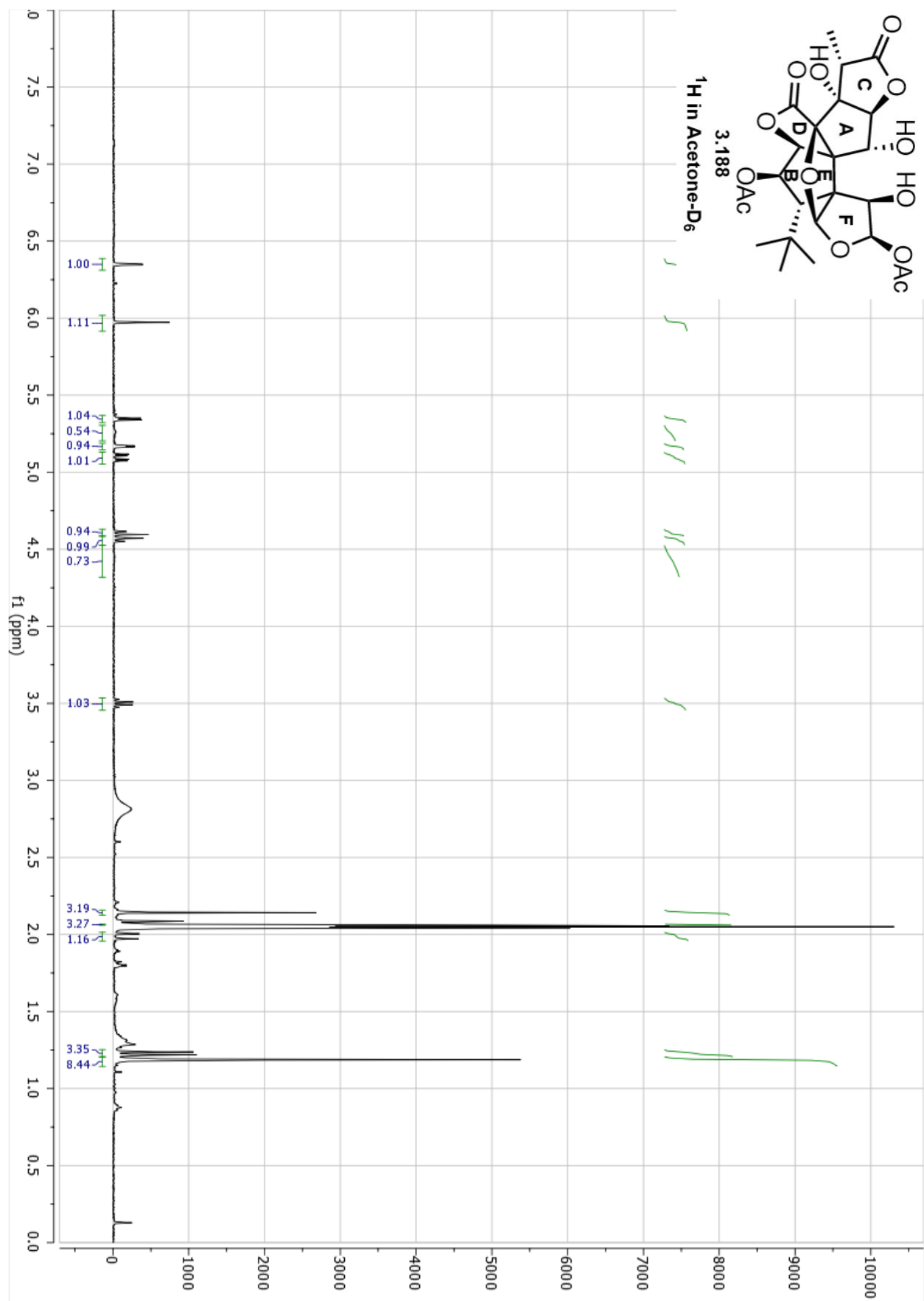


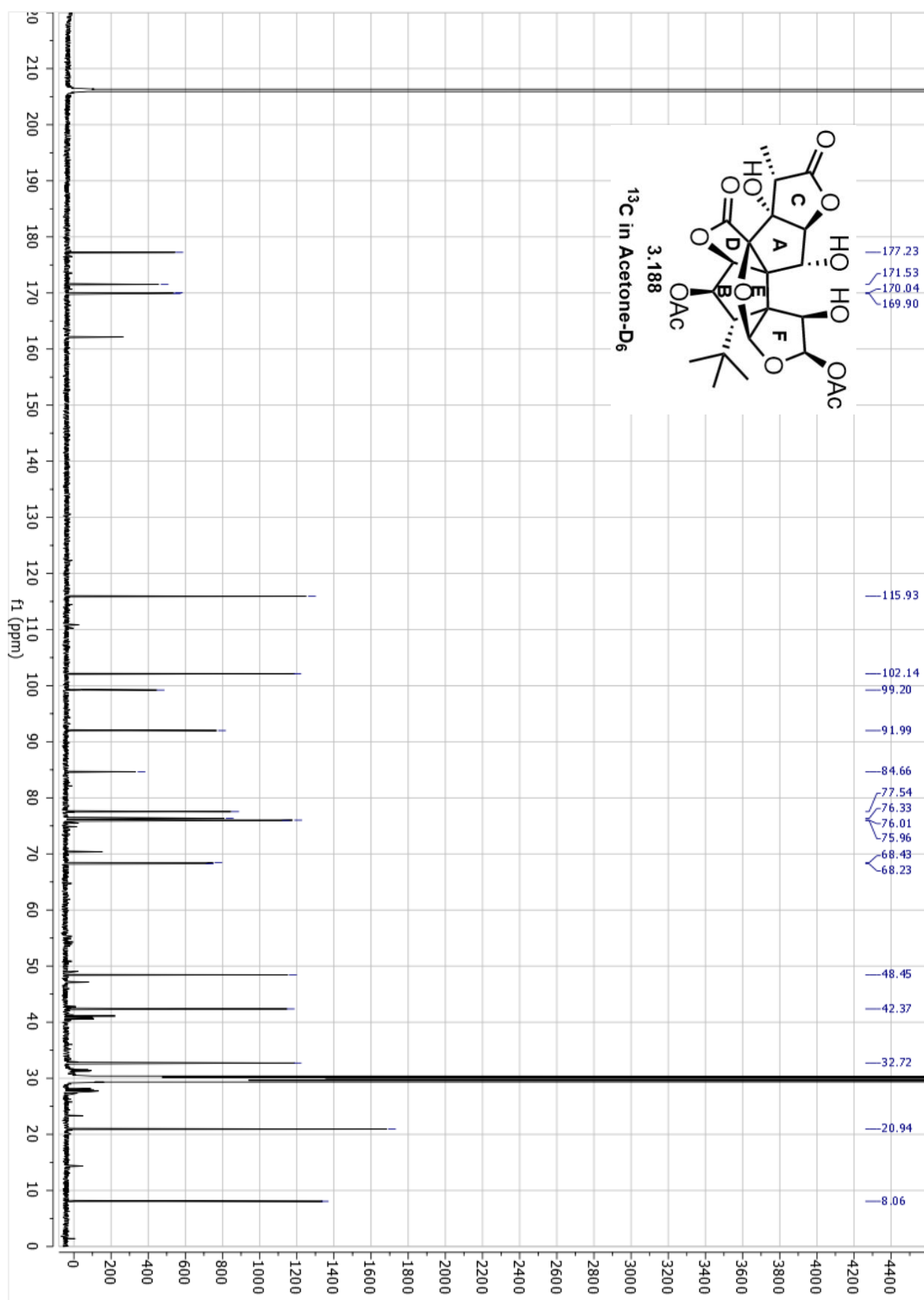


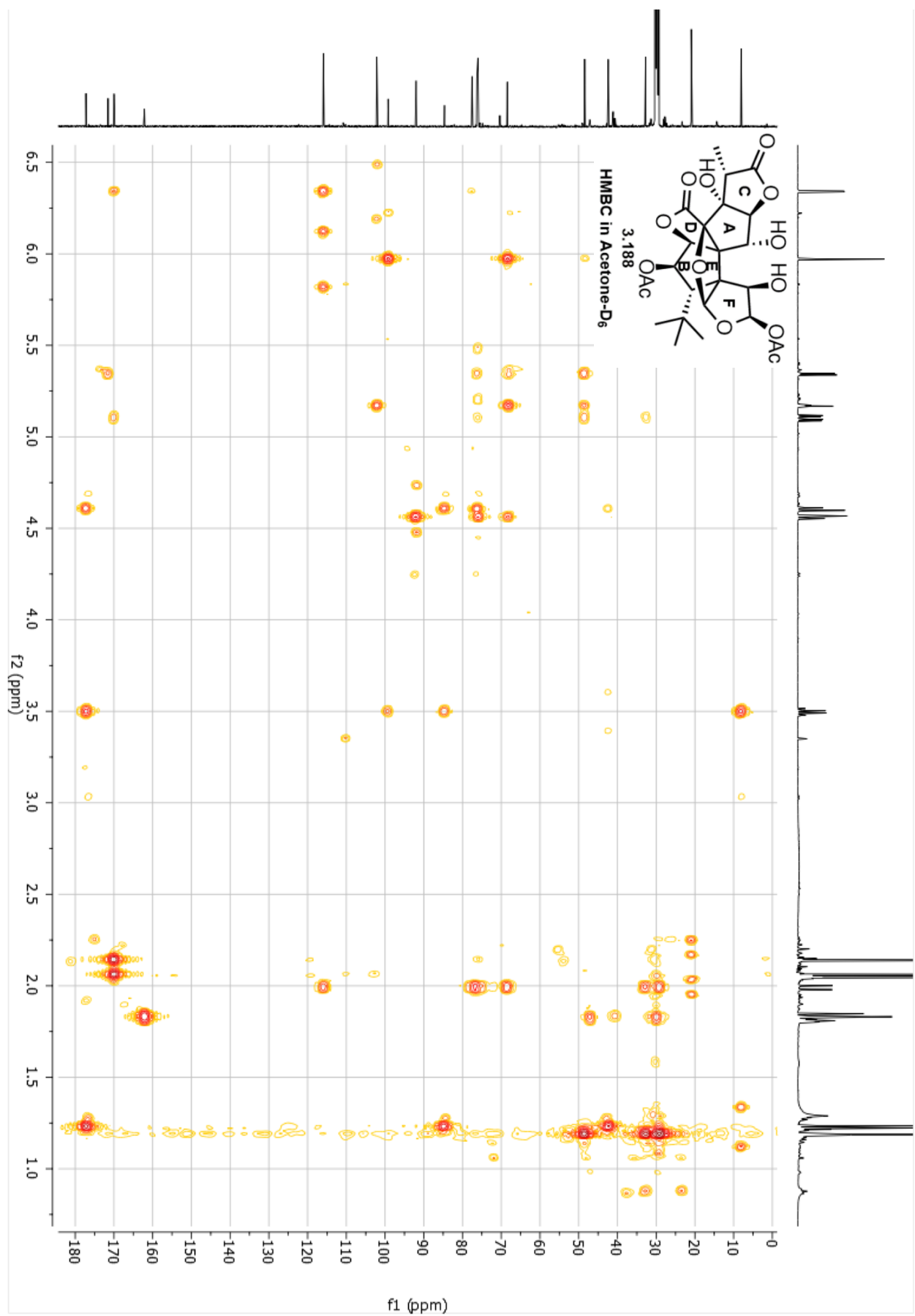


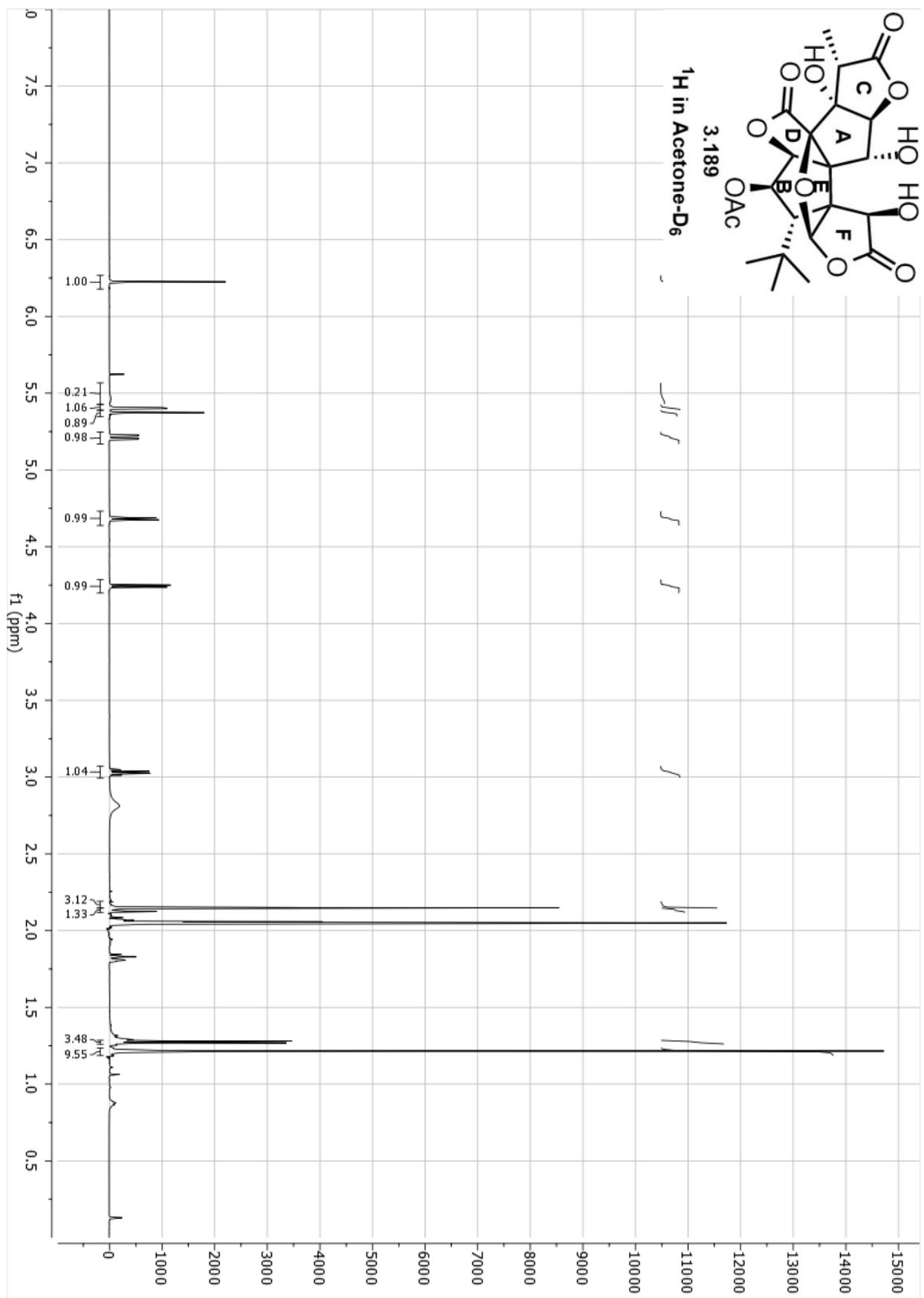


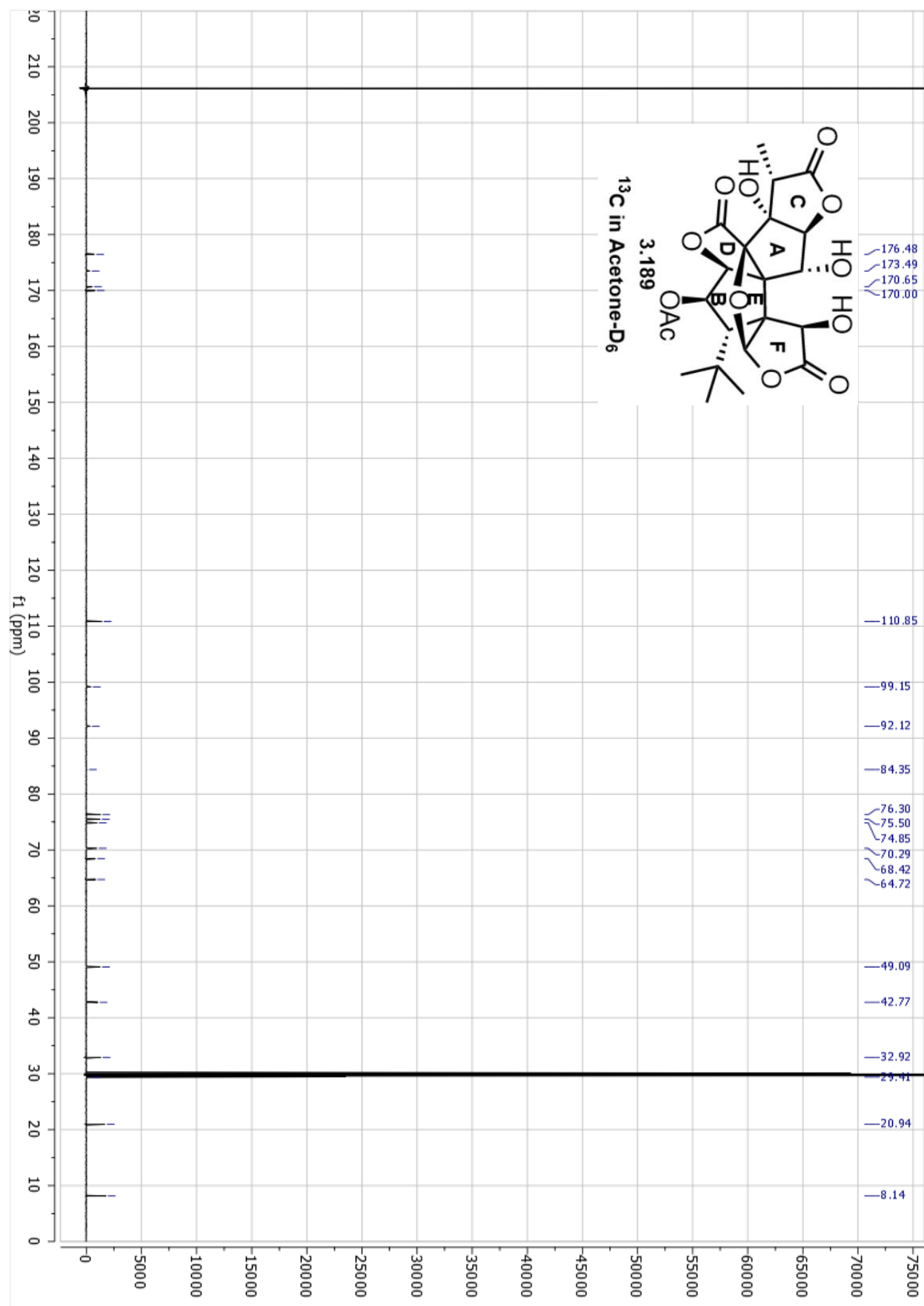


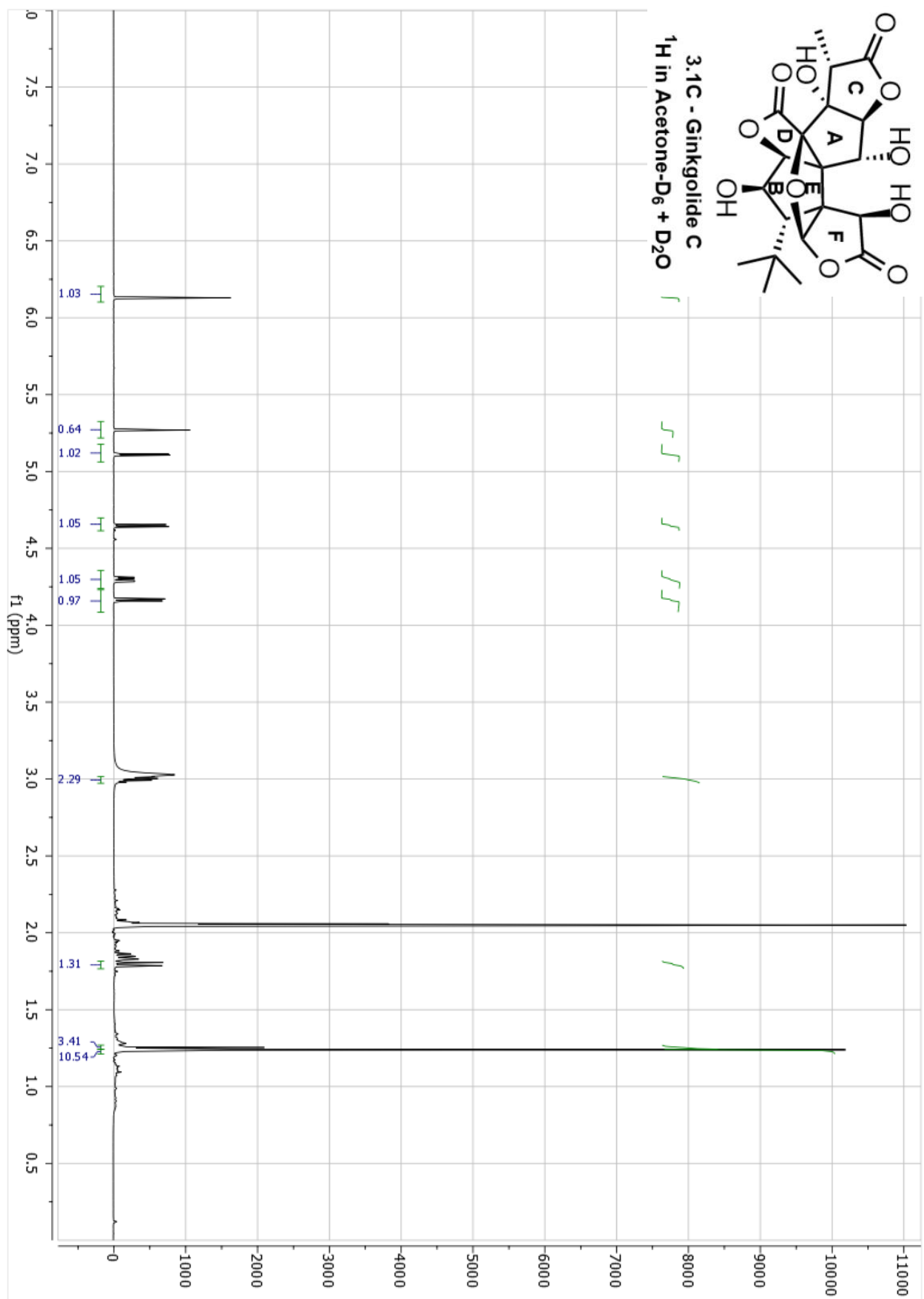


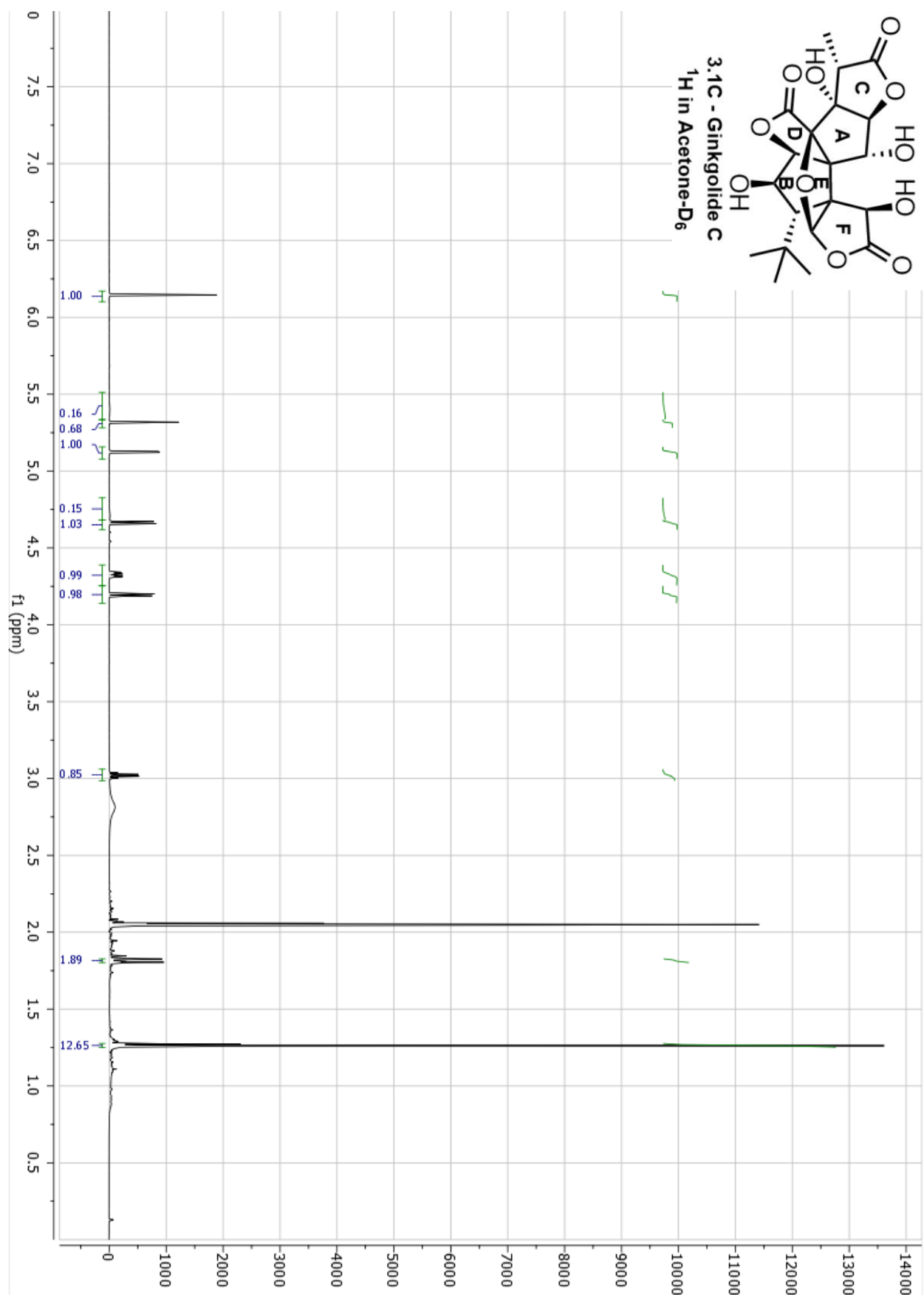
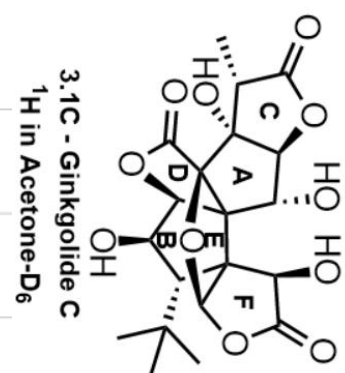


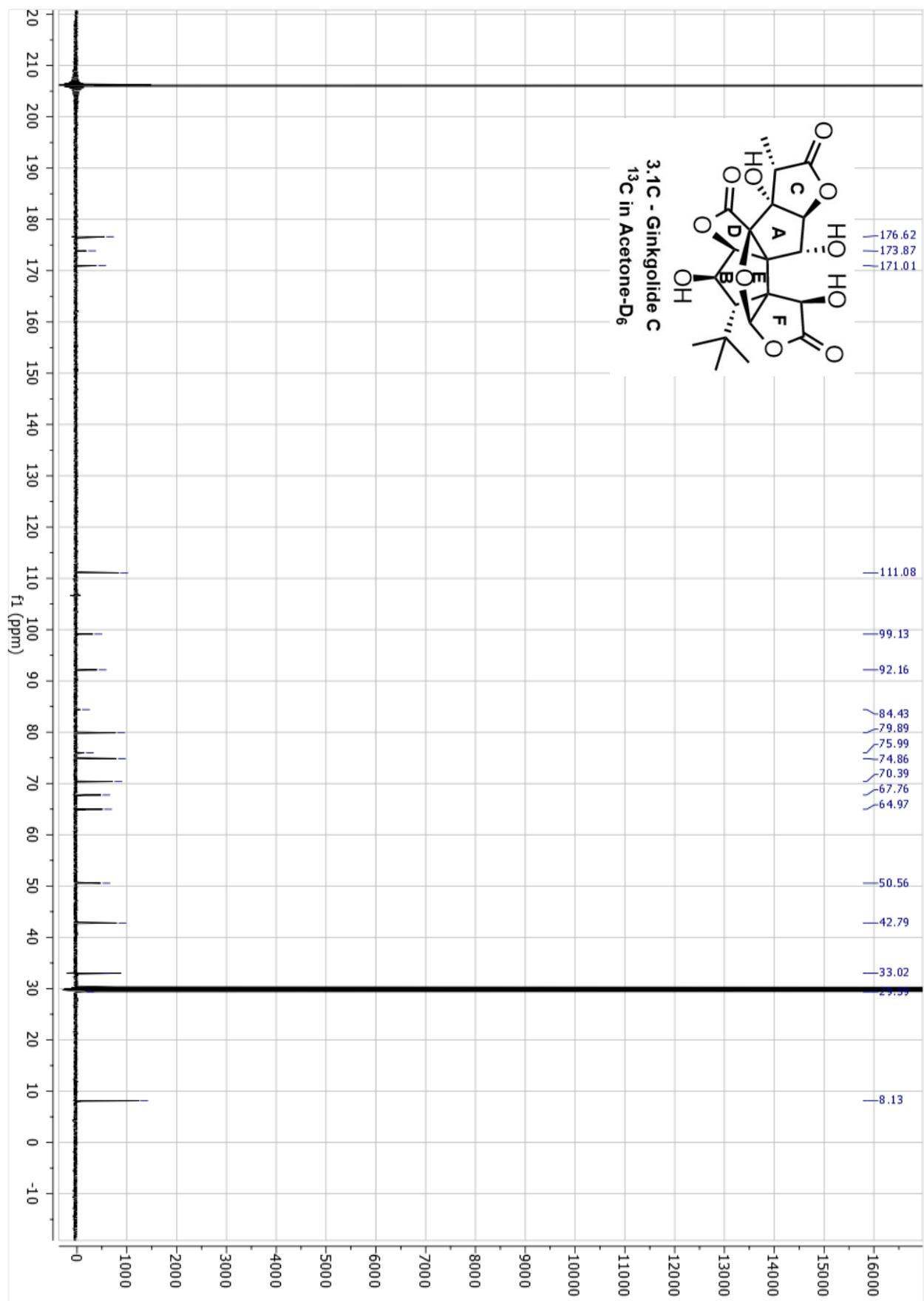


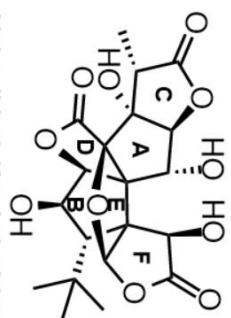




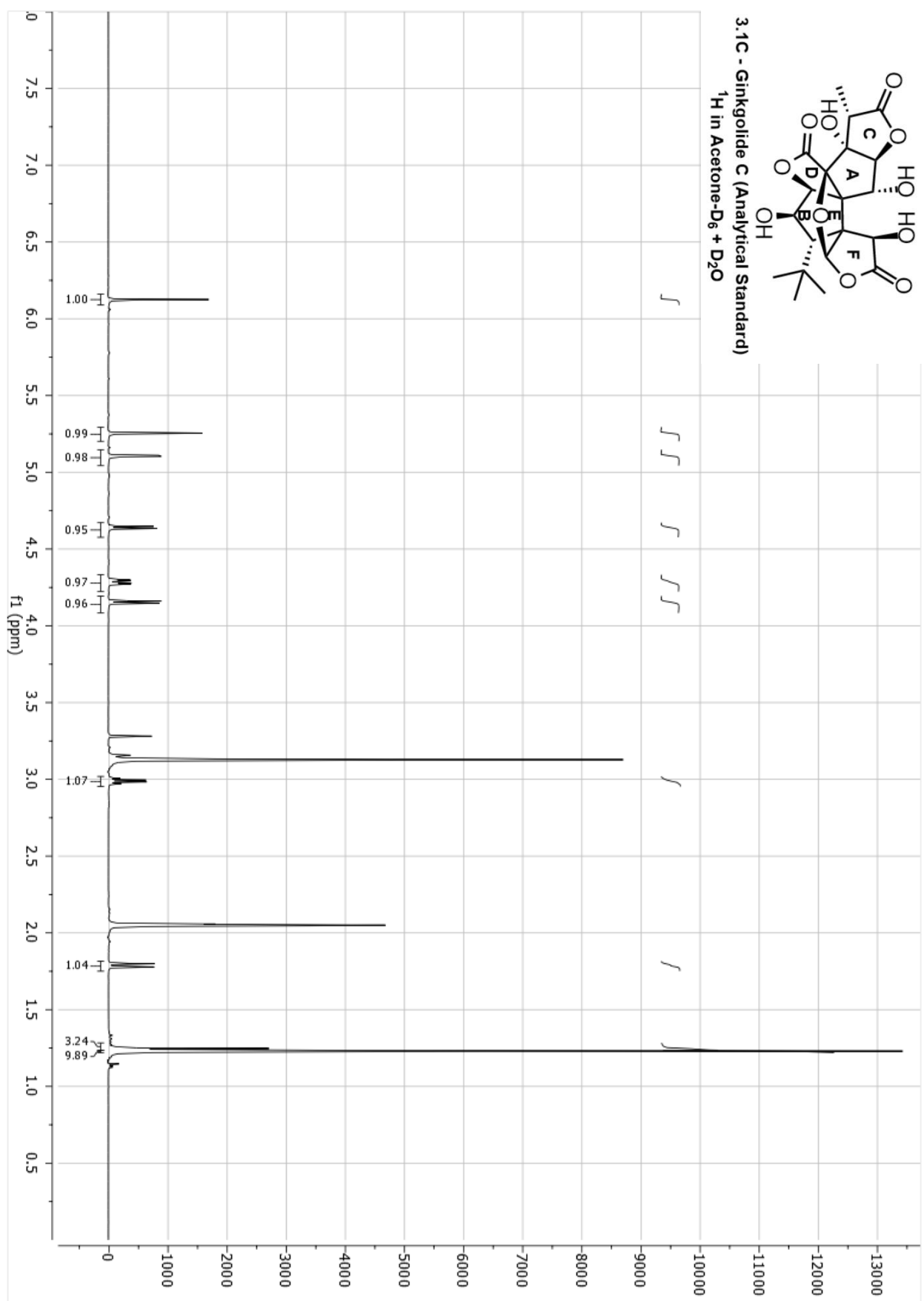


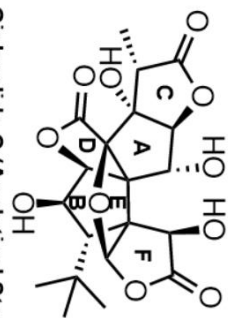




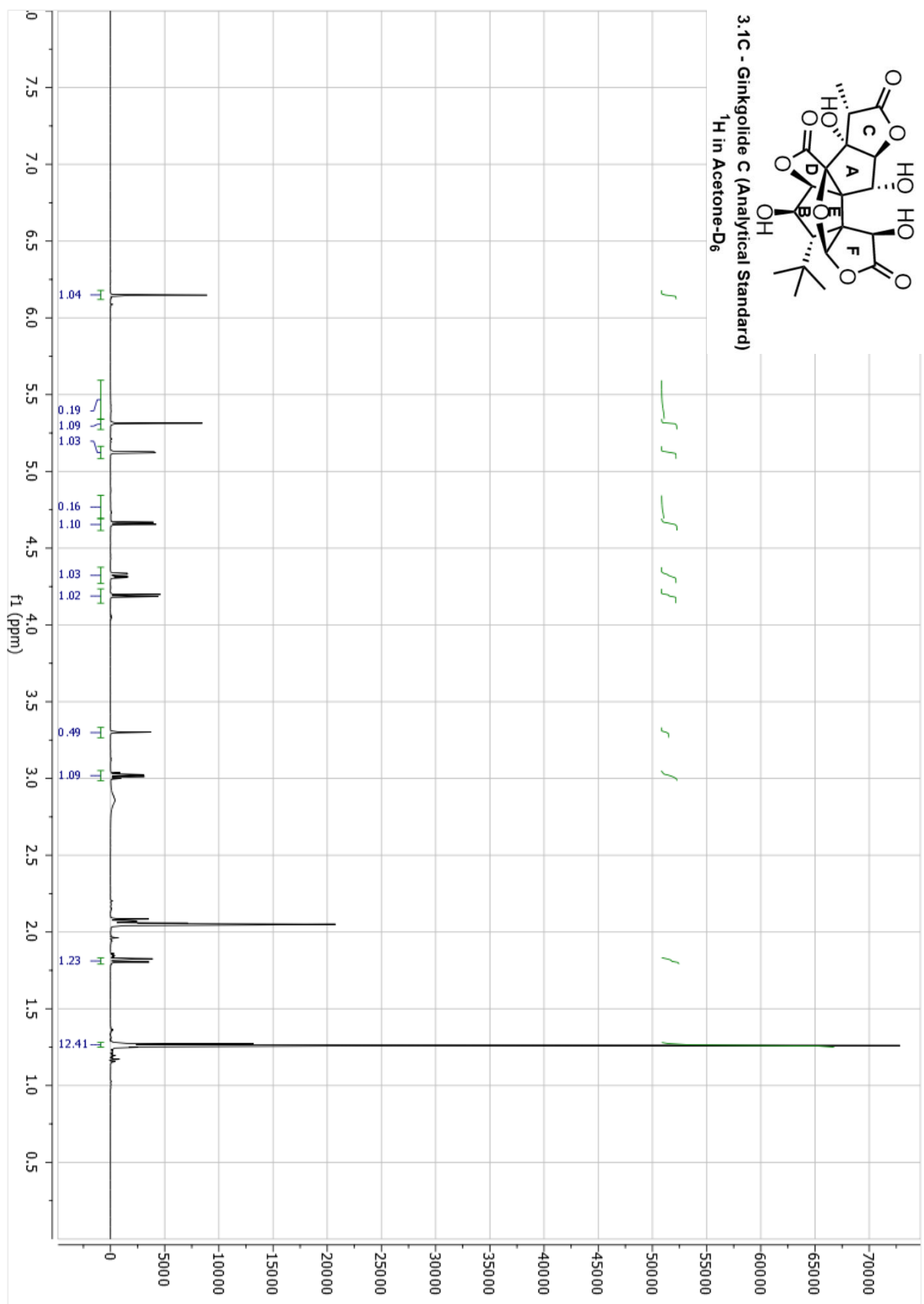


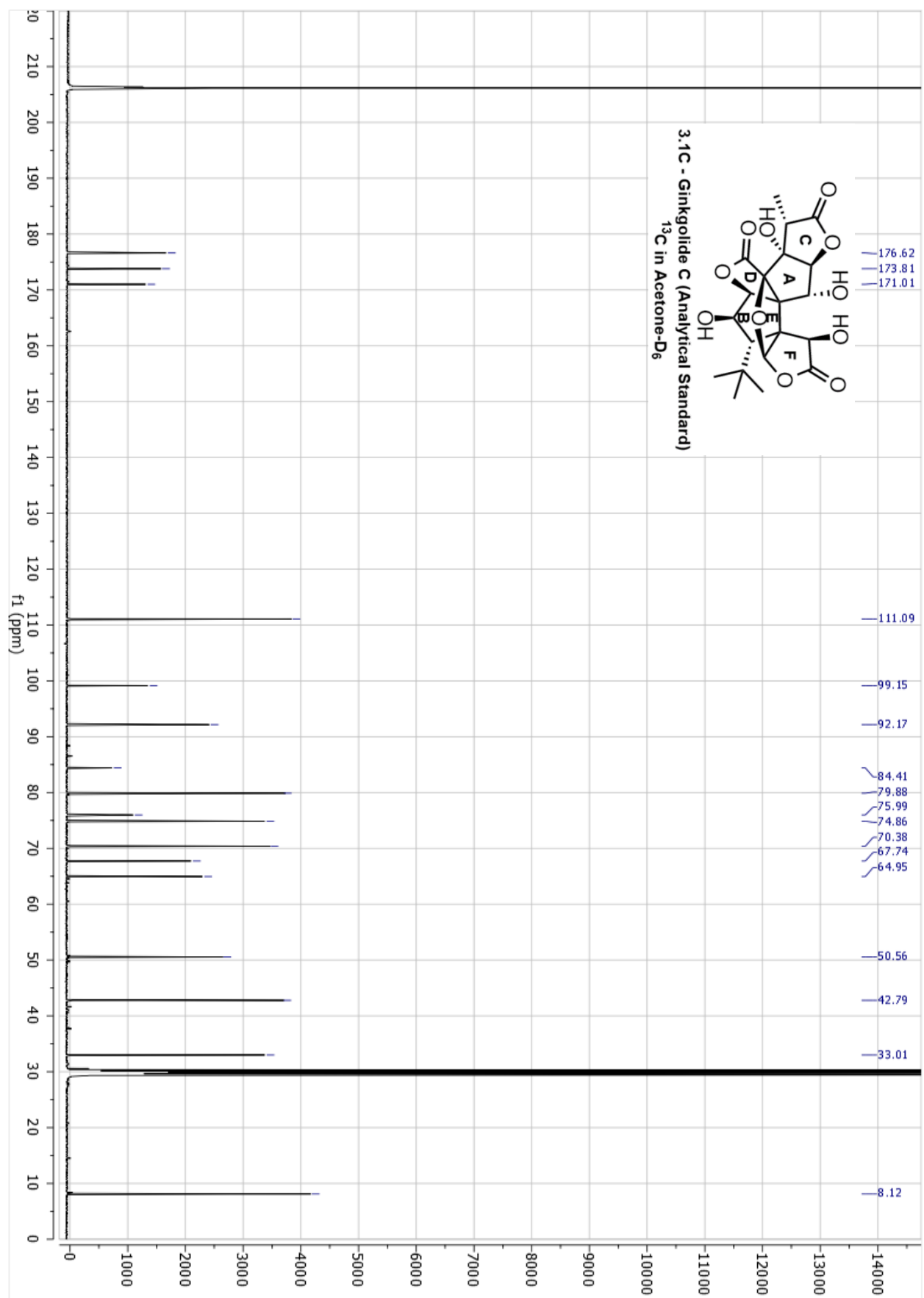
3,1C - Ginkgolide C (Analytical Standard)
 ^1H in Acetone- D_6 + D_2O

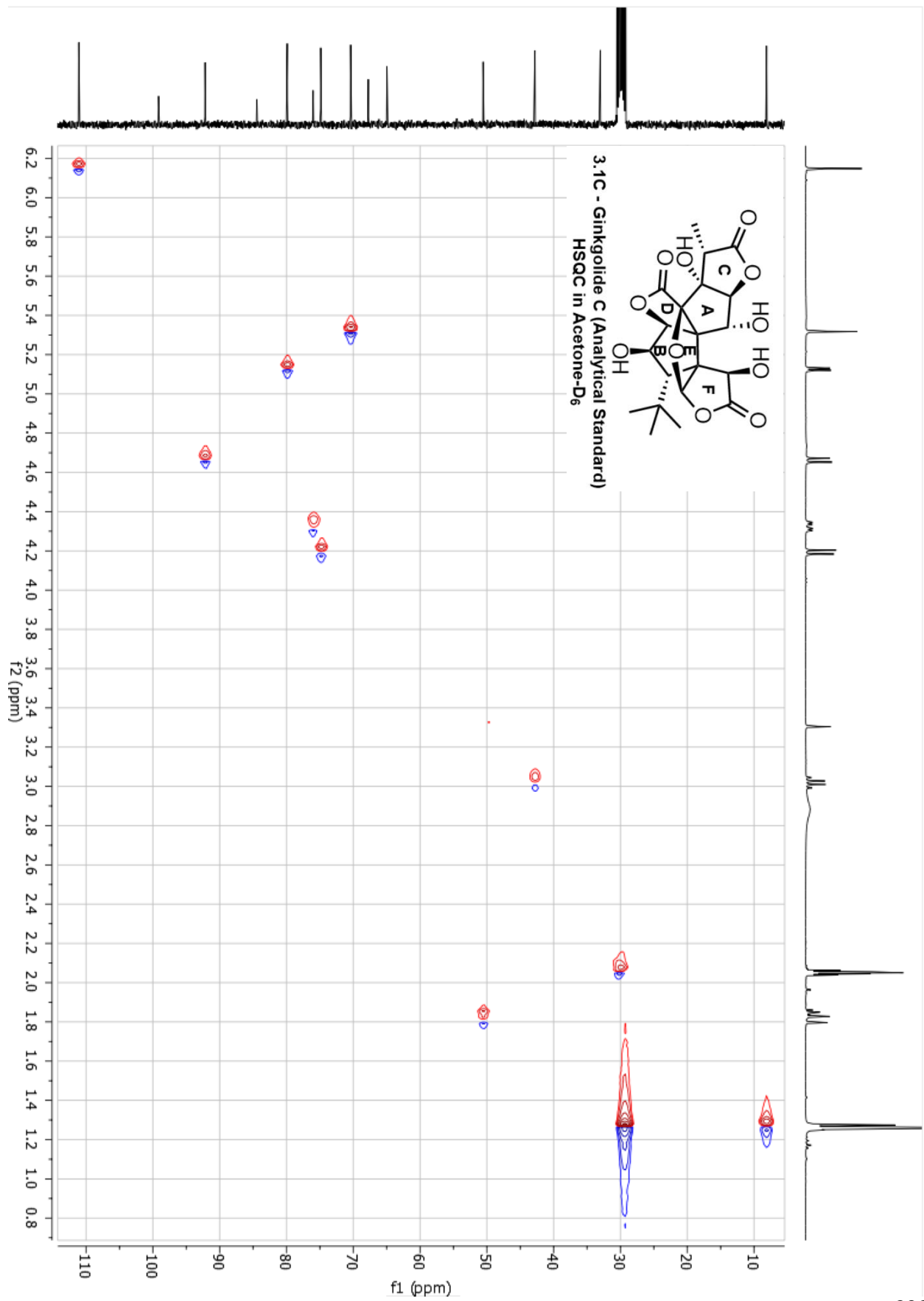


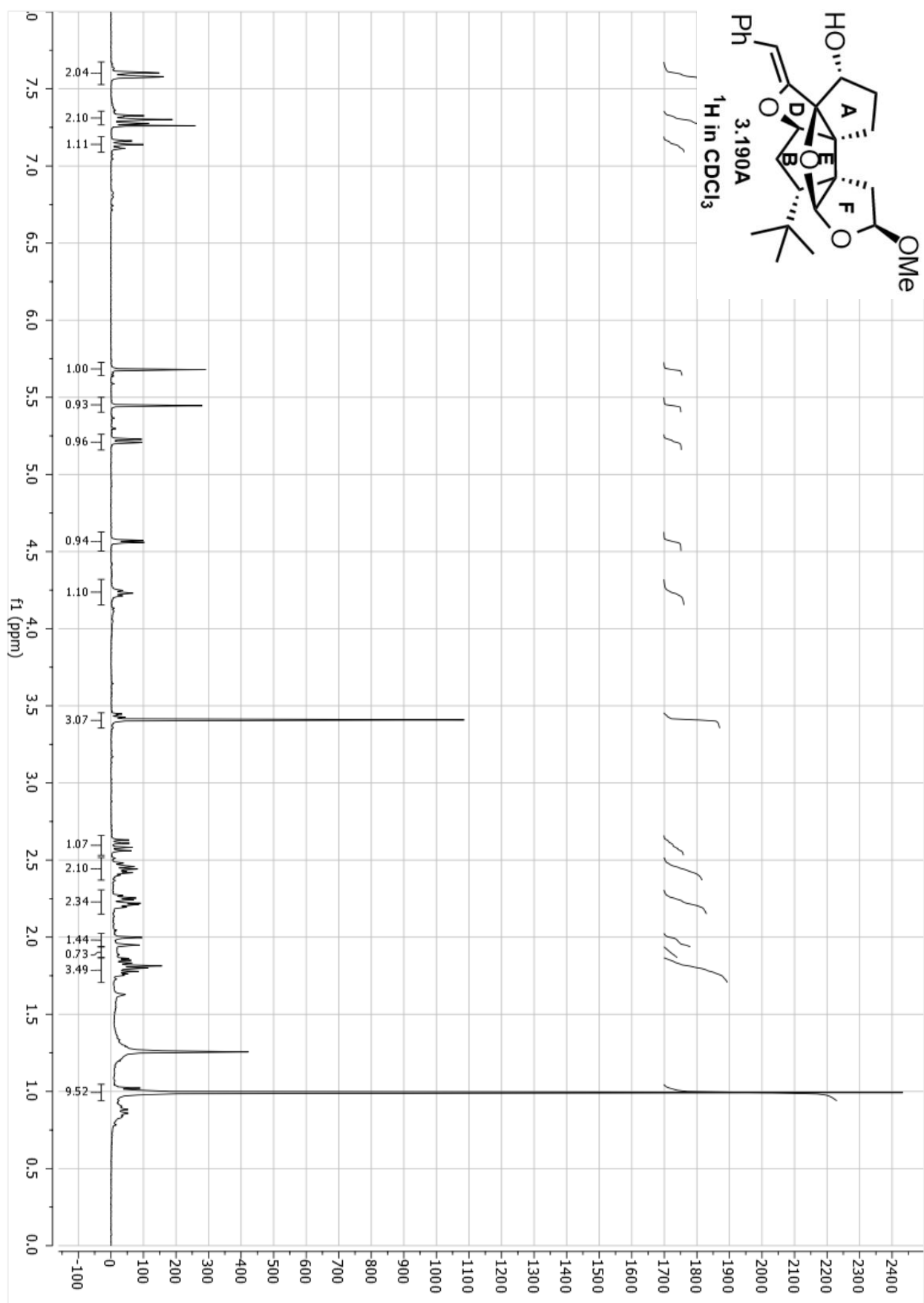


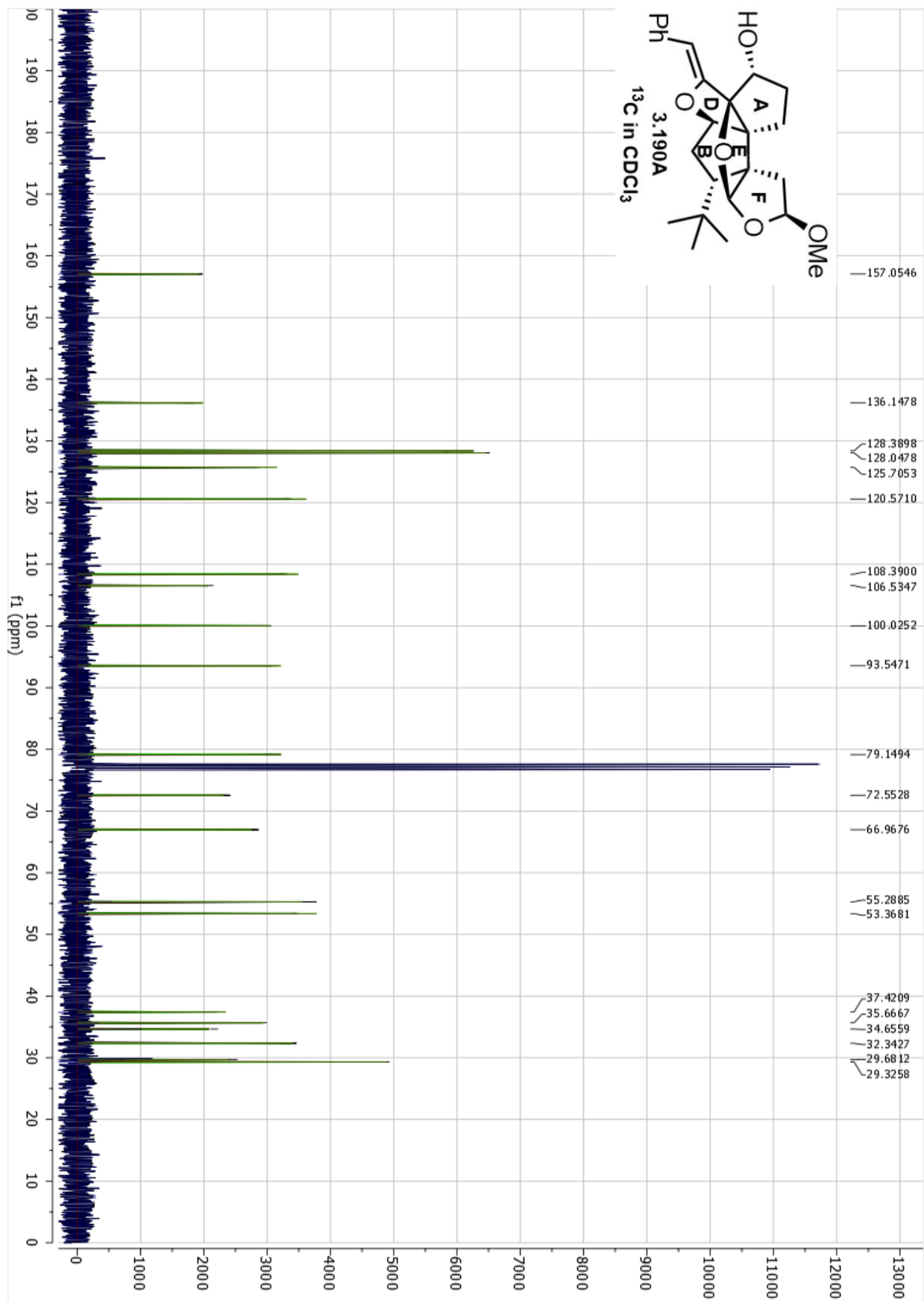
3.1C - Ginkgolide C (Analytical Standard)
¹H in Acetone-D₆

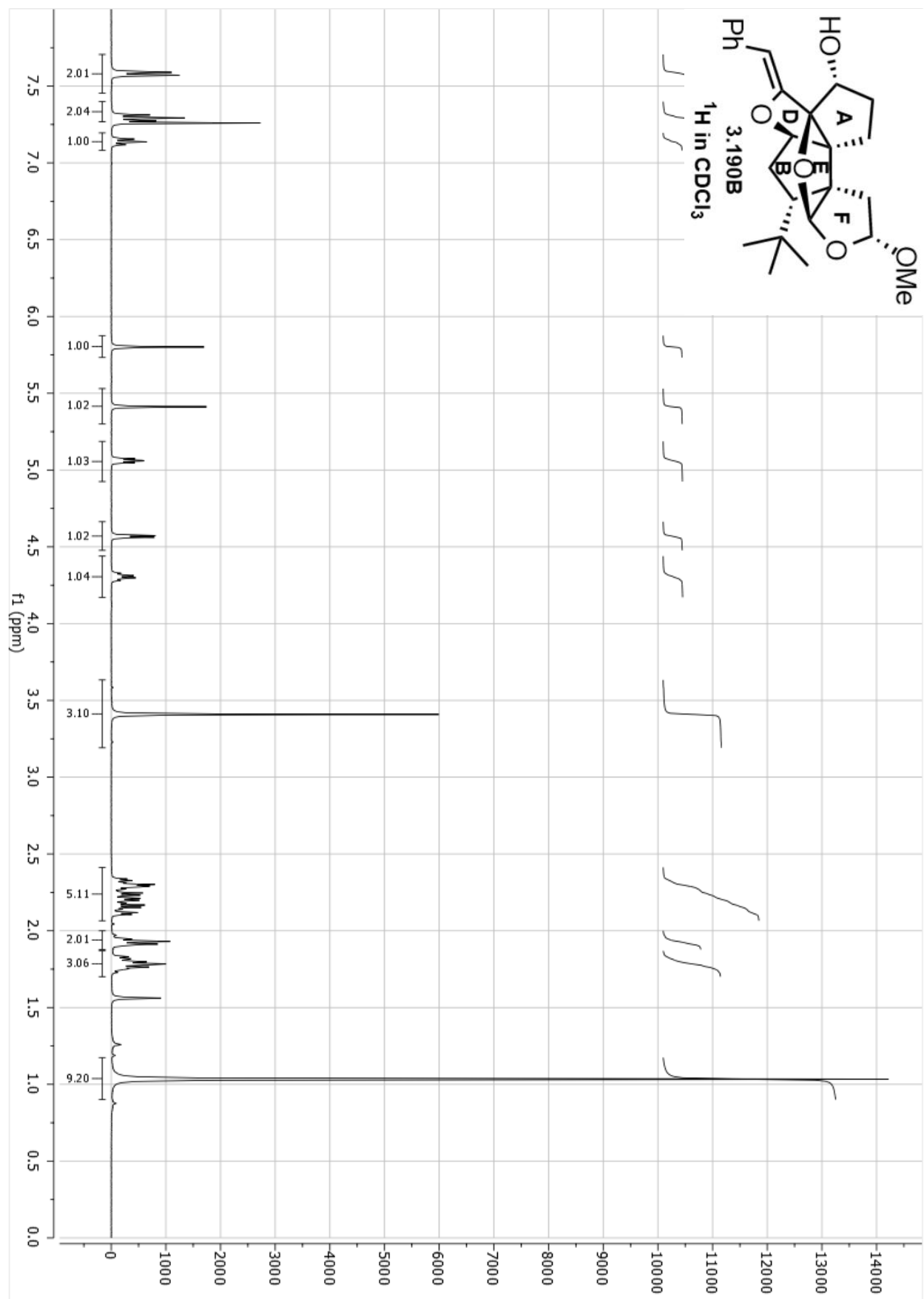


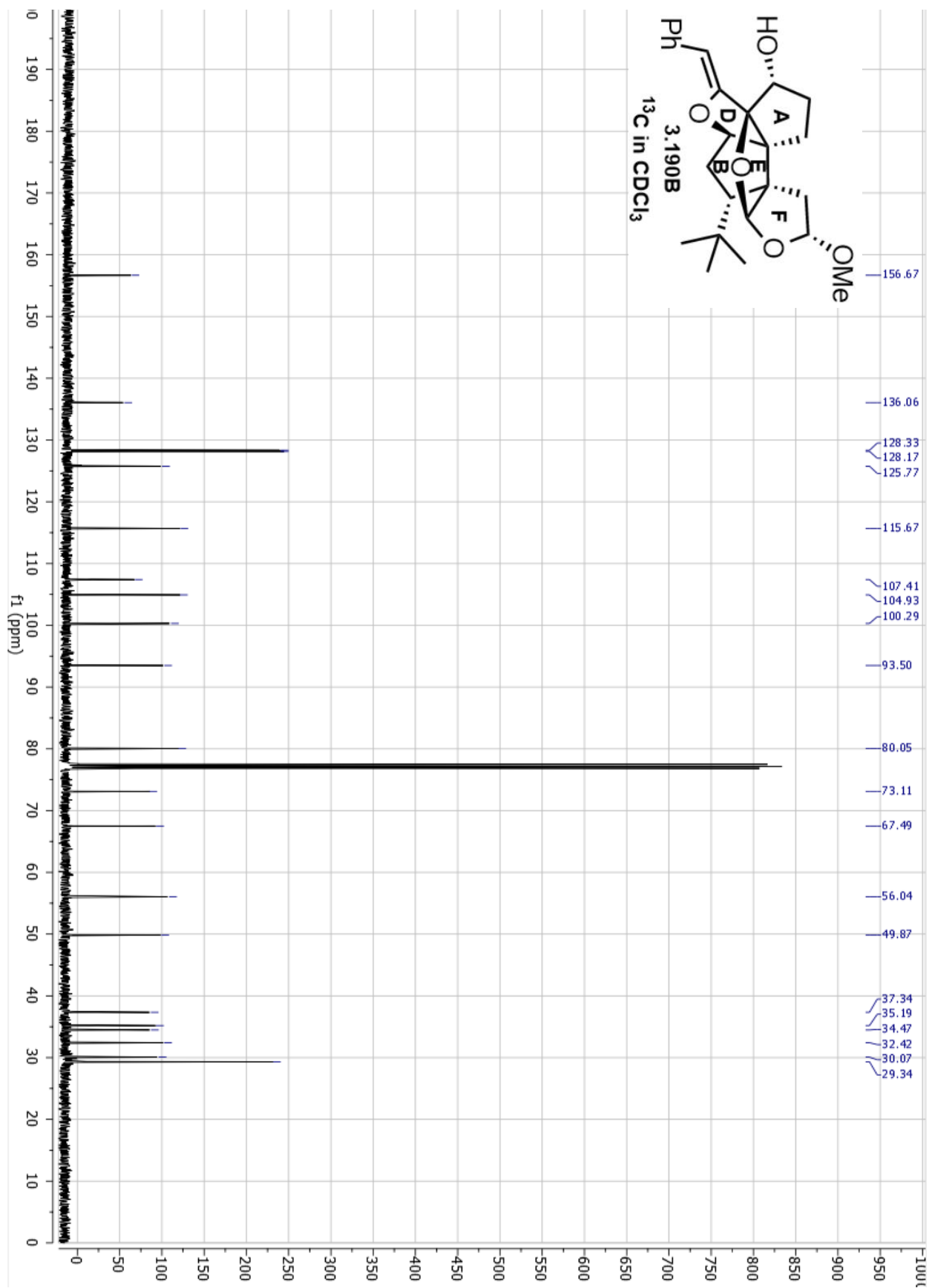


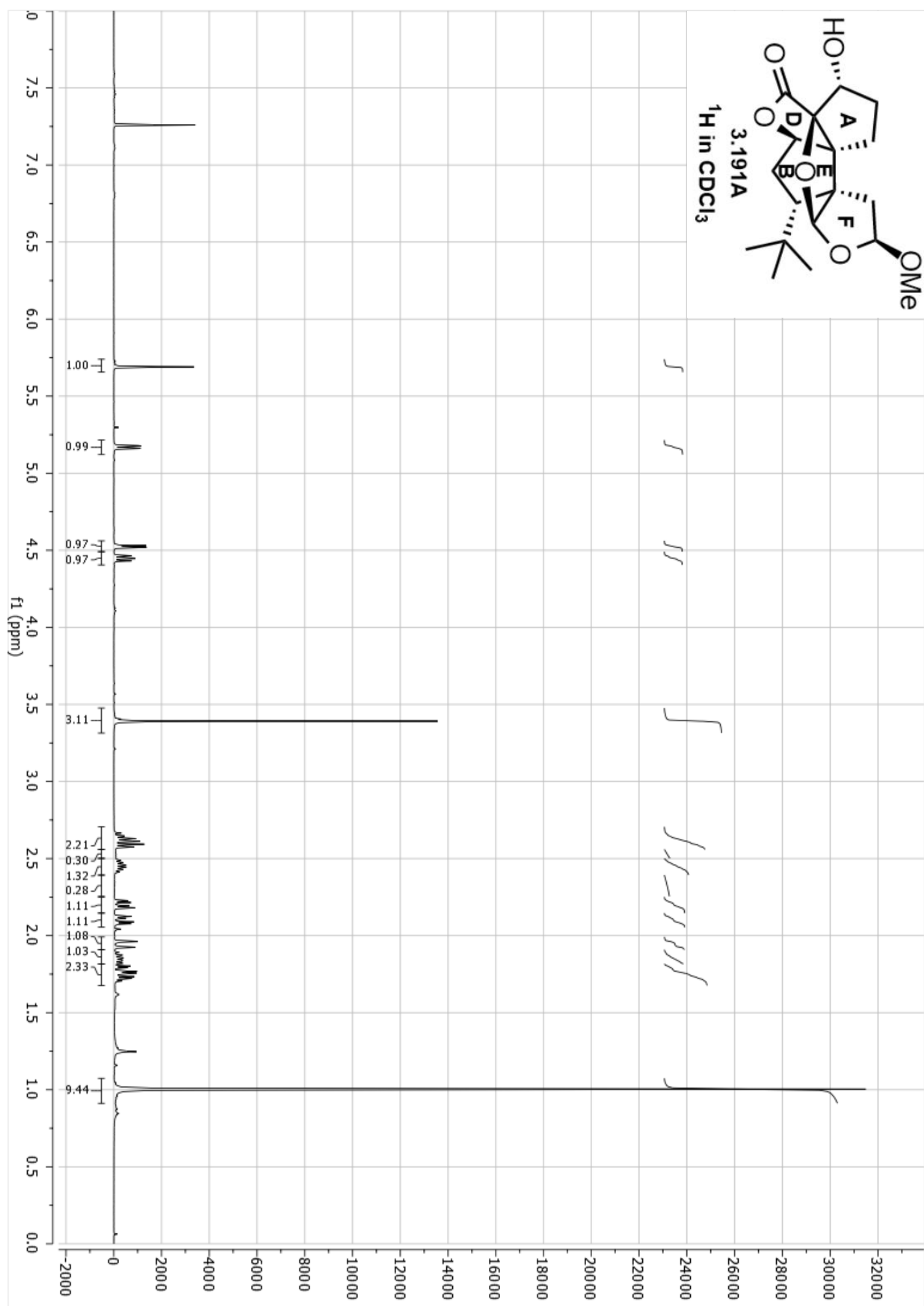


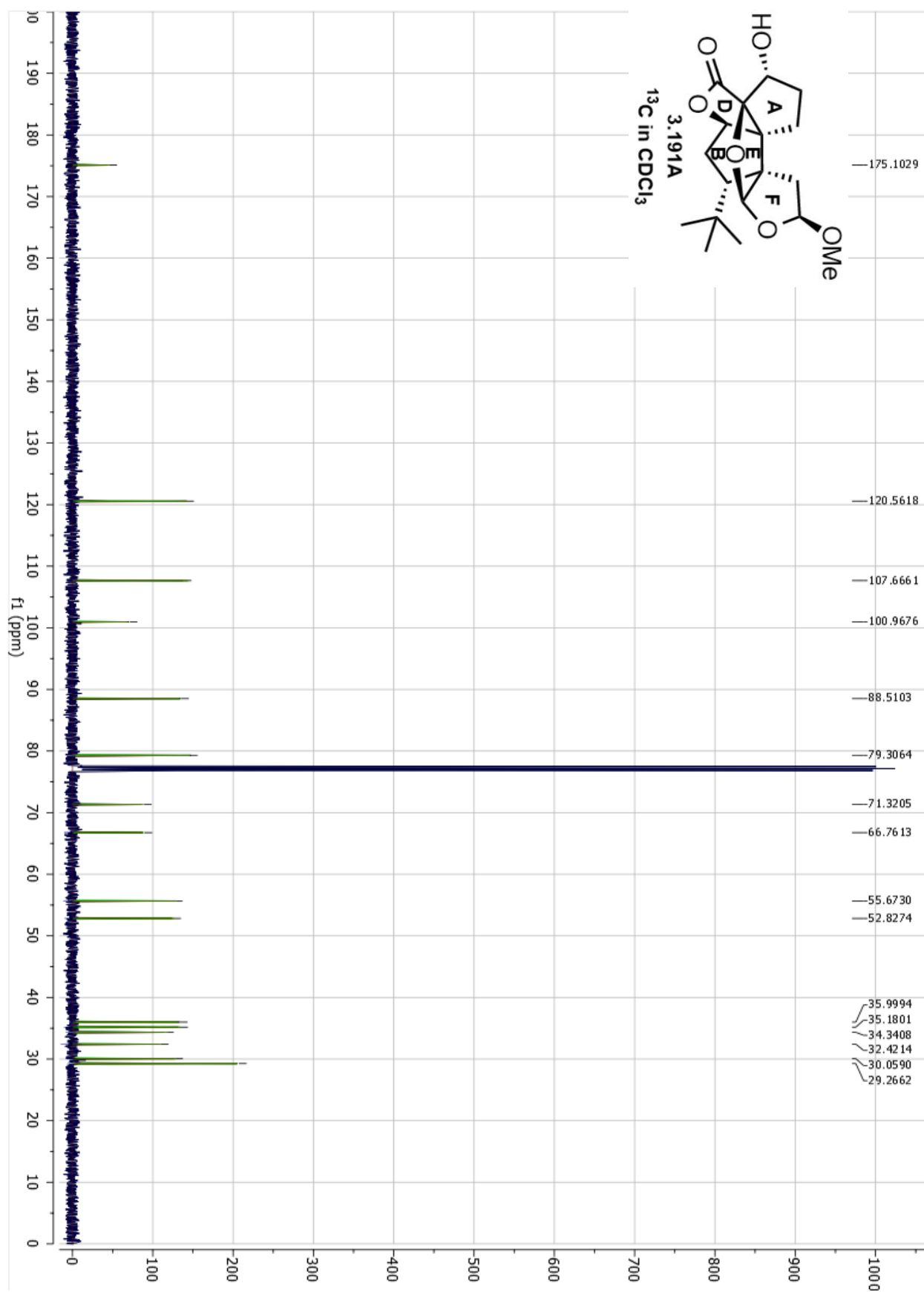


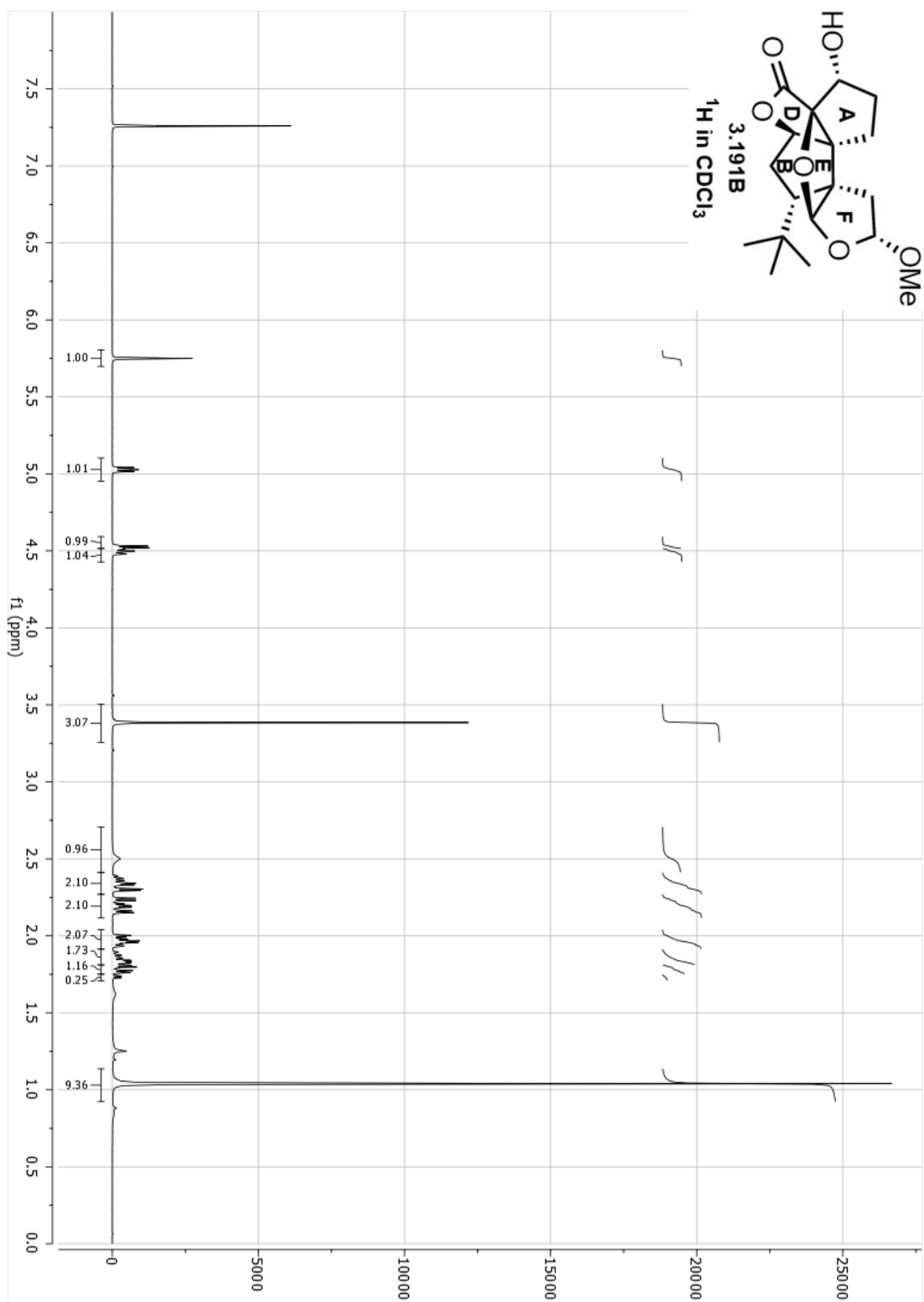
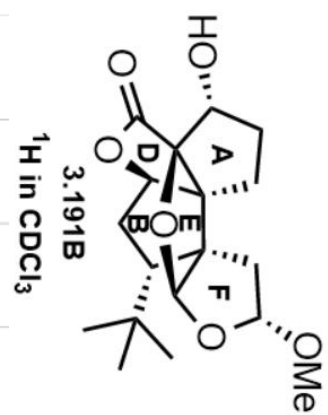


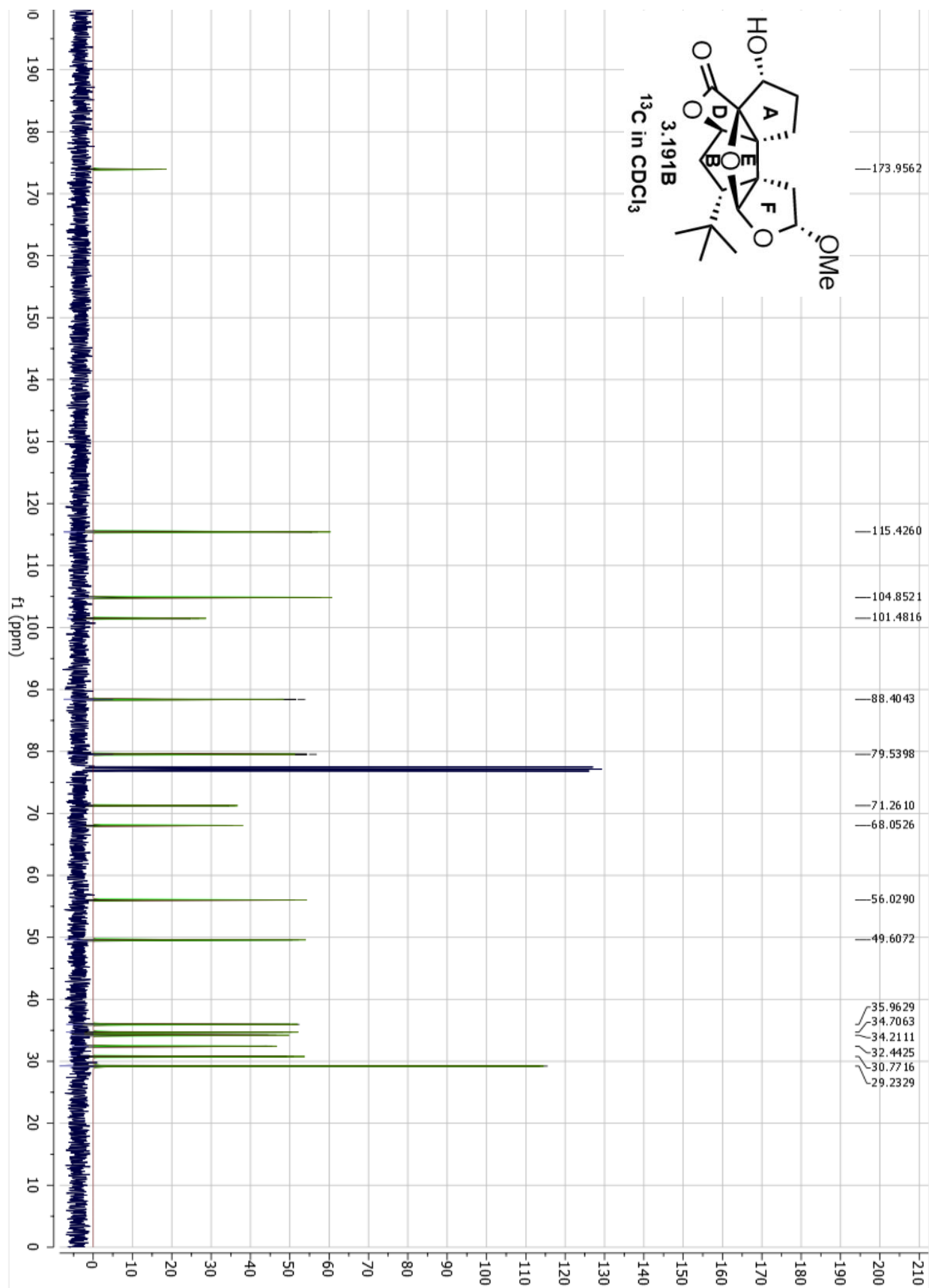


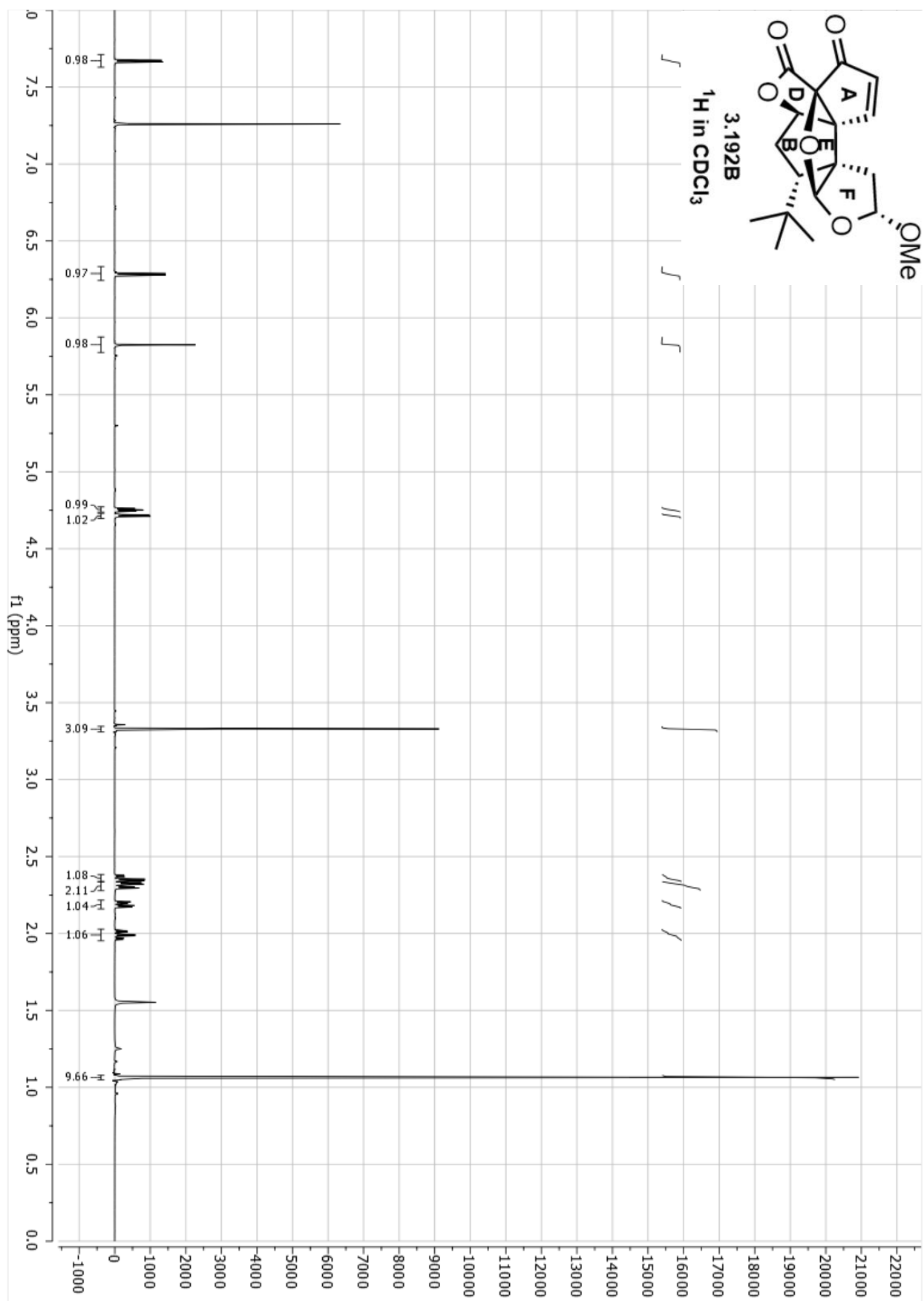


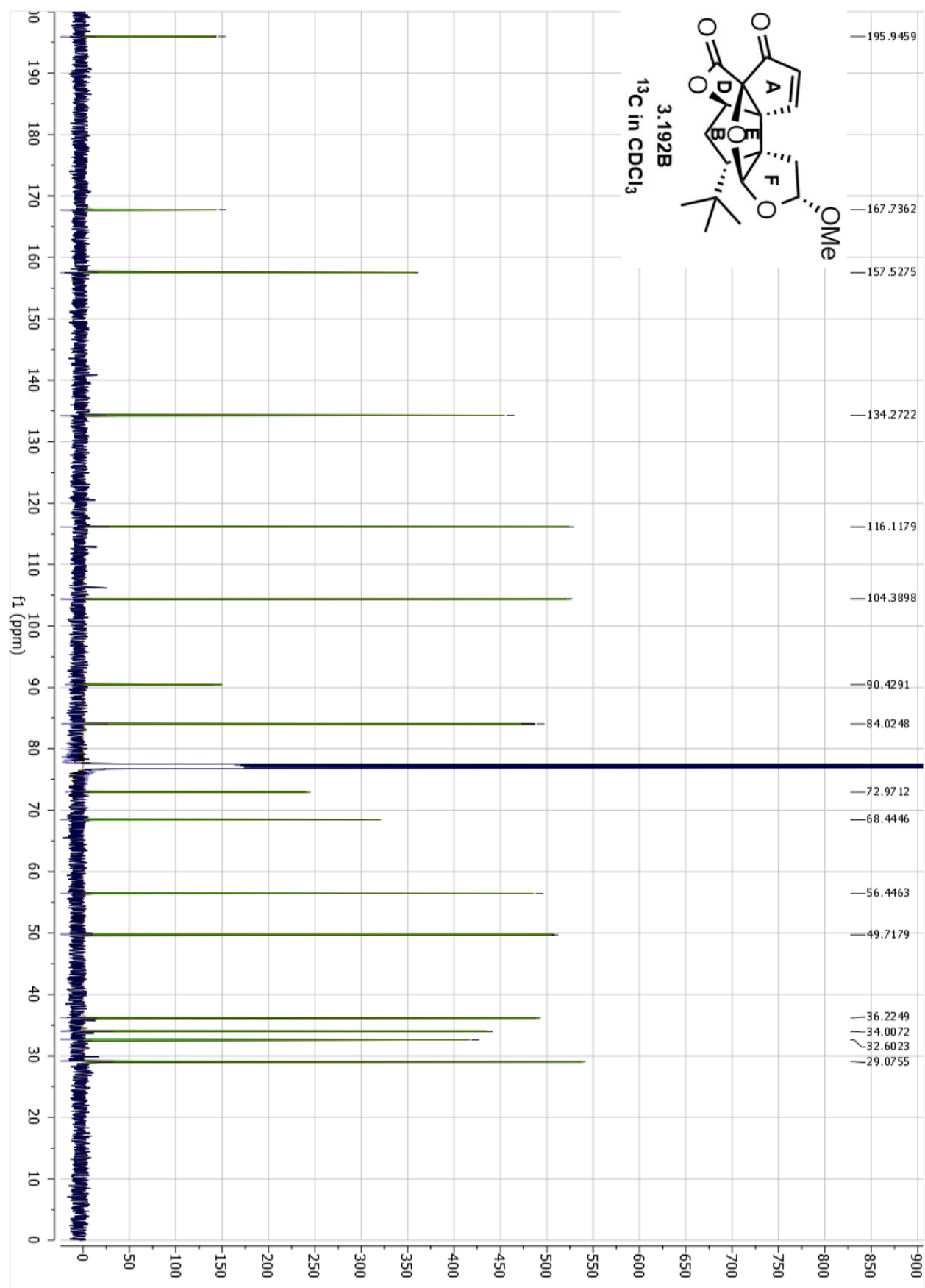


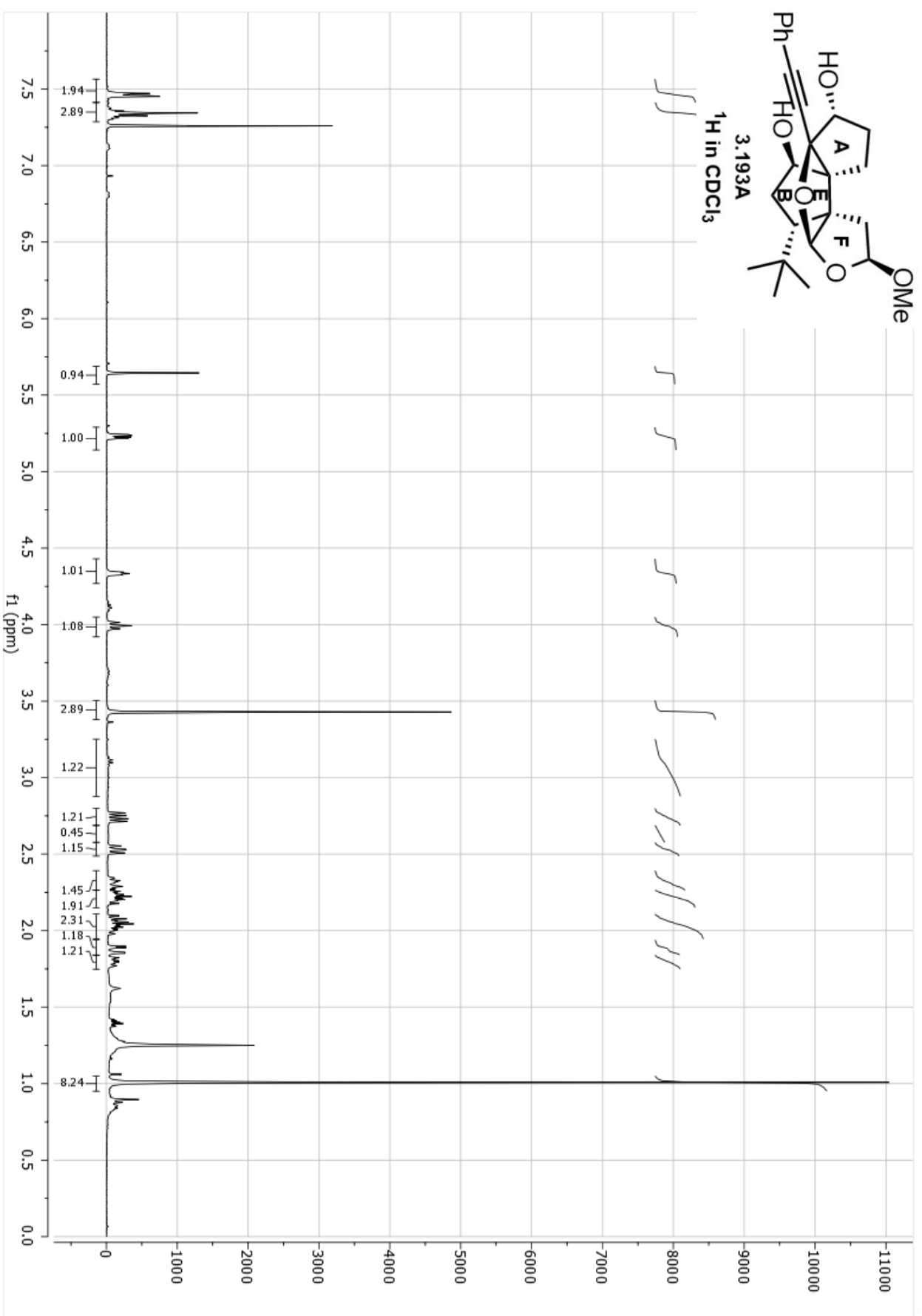
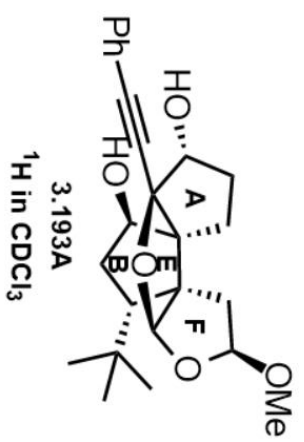












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