Part I. Transition Metal Catalyzed Cycloisomerizations of Allenes

Part II. Synthetic Small Molecule Ionophores

By

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Part I. Transition Metal Catalyzed Cycloisomerizations of Allenes

Part II. Synthetic Small Molecule Ionophores

Ryan Dean Reeves

Under the Supervision of Professor Jennifer M. Schomaker

University of Wisconsin-Madison

Part I Abstract

Transition metal catalyzed allene cycloisomerizations provide rapid entry into five-membered carbocyclic frameworks, a common motif in various natural products and pharmaceuticals. Site- and regiocontrolled Au-catalyzed allene cycloisomerizations furnish highly substituted cyclopentenes in >1:1 *dr*. Significant substitution on the allene substrate is tolerated, with potential to install five contiguous stereocenters after alkene functionalization. Major challenges included identifying a Au/Cu catalyst system that controls the relative rates of allene epimerization, cycloisomerization, and the facial selectivity of a metal enolate addition to the activated allene complex.

Similarly, Pd(0) catalysts facilitate the cycloisomerization of allenes to prepare substituted cyclopentene motifs. While both Au(I) and Pd(0)-catalyzed allene cycloisomerizations give 5-*endo*-dig cyclization, Pd catalysts typically prefer the *syn* diastereomer in contrast to the *anti* isomer observed with Au. The change in stereoselectivity is proposed to arise from buildup of $A^{1,3}$ strain during the key carbopalladation step to furnish the cycloisomerized products in moderate to good *dr* with yields comparable to Au(I) catalysts. Additional developments with

Pd(0) catalysts have allowed for the regiocontrolled formation of two new C-C bonds via a tandem carbopalladation/cycloisomerization strategy. Experiments to achieve stereodivergent cyclizations and transform key cyclopentenes into useful synthetic building blocks are described.

Part II Abstract

Previous work with bis-crown ether motifs linked by a photoswitchable azobenzene moiety have demonstrated the ability of this class of molecules to facilitate ion transport in liquid membranes in a photocontrollable manner. Methods to prepare these compounds are often unreliable and result in low yields, hindering further study of their intrinsic properties. An optimized route to these compounds has led to significant improvements in both yield and reproducibility, in turn allowing for the investigation of their transport abilities in synthetic bilayers. Additionally, the preparation and evaluation of compounds derived from 4,13-diaza-18-crown-6 motifs that are hypothesized to exhibit channel-like behavior are described. Initial studies indicate that lariat ethers derived from these motifs act primarily as lytic agents as opposed to synthetic ion channels.

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List of Abbreviations

(o-tolyl)$_3$P	tri(*o*-tolyl)phosphine
(PhO)$_3$P	tripenylphosphite
Å	angstrom
AcOH	acetic acid
AIBN	azobisisobutyronitrile
aq	aqueous
Ar	aryl
B3LYP	Becke, 3-parameter, Lee-Yang-Parr functional
Bn	benzyl
BnBr	benzyl bromide
BnOH	benzyl alcohol
BOX	bis-oxazoline
br d	broad doublet
br s	broad singlet
BSA	N,O-bis(trimethylsilyl)acetamide
Bz	benzoate
Cat.	catalytic
ClogP	computed partition coefficient
Cy	cylohexyl
Cy$_3$P	tricyclohexylphosphine
D	deuterium
d	doublet

DCE	1,2-dichloroethane
dCype	1,2-bis(dicyclohexylphosphino)ethane
dCypm	1,2-bis(dicyclohexylphosphino)methane
dd	doublet of doublets
ddd	doublet of doublet of doublets
DFT	Density Functional Theory
DIAPHOX	diaminophosphine oxide
DIBAL	diisobutylaluminum hydride
DIPEA	N,N-diisopropylethylamine
$DISC_3(5)$	3,3-dipropylthiadicarbocyanine
DMAP	4-dimethylaminopyridine
DMDO	dimethyldioxirane
DMF	N,N-dimethylformamide
DMP	Dess-Martin periodinane
DMS	dimethylsulfide
DMSO	dimethylsulfoxide
dq	doublet of quartets
dr	diastereomeric ratio
dt	doublet of triplets
ee	enantiometic excess
EI	electrospray ionization
equiv.	equivalents
er	enantiomeric ratio

Et	ethyl
Et$_2$O	diethyl ether
Et$_3$N	triethylamine
EtOAc	ethyl acetate
EtOH	ethanol
GABA	γ-aminobutyric acid
GABA$_A$R	γ-aminobutyric acid A receptor
GlyRs	glycine receptors
h	hour
HMPA	hexamethylphosphoramide
HRMS	high resolution mass spectrometry
IBX	iodoxybenzoic acid
iPr	isopropyl
IPr	1,3-diisopropylimidazolium
KHMDS	potassium hexamethyldisilazide
LDA	lithium diisopropylamide
LDH	lactate dehydrogenase
LiHMDS	lithium hexamethyldisilazide
logP	partition coefficient
M	molar
m	minute
mCPBA	*meta*-chloroperbenzoic acid
Me	methyl

MeCN	acetonitrile
MeOH	methanol
mL	milliliter
mmol	millimole
mol	mole
$NAD^+/NADH$	nicotinamide adenosine dinucleotide
NBS	N-bromosuccinimide
nBu_4N	tetrabuylammonium
NIS	N-iodosuccinimide
NMDA	N-methyl-d-aspartate
NMDG	N-methyl-d-glucamine
NMO	N-methylmorpholine N-oxide
NMR	nuclear magnetic resonance
Nu	nucleophile
OAc	acetate
OMe	methoxy
OTf	trifluoromethansulfonate
PDC	pyridinium chlorochromate
Ph	phenyl
Ph_3P	triphenylphosphine
PhCHO	benzaldehyde
PI3K	phosphatidylinositol 3-kinase
Pr	normal propyl

Py	pyridine
ROS	reactive oxygen species
s	singlet
SMD	solute molecular density
t	triplet
T.S.	transition state
TBAB	tetrabutylammonium bromide
TBS	*tert*-butyldimethylsilyl
tBu	*tert*-butyl
tBu$_3$P	tri-*tert*-butylphosphine
tBuO	*tert*-butoxide
Tces	trichloroethyl sulfonate
TEA	triethylamine
Tf	trifluoromethanesulfonate
TFA	trifluoracetic acid
TfOH	trifluoromethansulfonic acid
THACl	tetrahexylammounium chloride
THF	tetrahydrofuran
THP	tetrahydropyran
TLC	thin layer chromatography
TMS	trimethylsilyl
Ts	tosyl
pTsOH	*para*-toluenesulfonic acid

Aβ	amyloid beta
μL	microliter
μM	micromolar
δ	chemical shift

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List of Schemes

Scheme 4.8. Benzoate ester route to C-12 hydraphile **4.14**.

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Part I. Transition Metal Catalyzed Cycloisomerizations of Allenes

Chapter 1

Diastereoselective Au(I)-Catalyzed Allene Cycloisomerizations to Furnish Highly

Substituted Cyclopentenes

Adapted with permission from:

Reeves, R. D.; Phelps, A. M.; Raimbach, W. A. T.; Schomaker, J. M. *Org. Lett.* **2017**, *19*, 3394-

3397.

1.1. Introduction to Gold-Catalyzed Cycloisomerizations

1.1.1. Bilobalide and neuroprotection

(-)-Bilobalide (Figure 1.1) is a sesquiterpene trilactone isolated from the leaves of the *Gingko biloba* tree.[1] The bilobalide-containing leaves of *G. biloba* have been used in traditional Chinese medicine for the past 2000 years.[2] In 1964, the widespread use of *Gingko biloba* extract EGb 761 emerged in Western medicine in 1964 to aid in the treatment of age-related memory deficits, dementia, and a variety of vascular impairments.[3] More recent studies have suggested that bilobalide possesses several neuroprotective properties, including antioxidant activity as a reactive oxygen species (ROS) scavenger[4], NMDA receptor antagonism[5], inhibition of recombinant glycine receptor C1 (GlyRs) channels[6], and as an antagonist of γ-aminobutyric acid A receptors (GABA$_A$Rs)[7], among others.[8] A series of additional studies have demonstrated that bilobalide is capable of reducing the level of amyloid beta (αβ) accumulation within neuronal cells[9], which may be valuable to the field of Alzheimer's disease research.[10]

Figure 1.1. (-)-Bilobalide.

1.1
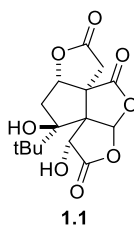
Although many studies have reported on the potential utility of bilobalide as a neuroprotective therapeutic, additional follow-up investigations do not completely support previous conclusions, and in some cases, directly contradict reported results. In a report by Schimke and coworkers, bilobalide was shown to act as a ROS scavenger only in aprotic

environments; in protic environments, such as the cytosolic interior of a cell, bilobalide failed to exhibit any ROS scavenging ability.[11] The mode of NMDA receptor antagonism by bilobalide has been contradicted in a report by Klein and coworkers,[12] while the mode of GABA$_A$R antagonism is poorly understood; it has been postulated that GABA$_A$R antagonism may be the result of an interaction between bilobalide and a yet unidentified target.[13] Furthermore, bilobalide's ability to suppress αβ has been demonstrated to occur in a phosphatidyl inositol 3-kinase (PI3K) dependent manner, however the precise target(s) in the PI3K pathway with which bilobalide interacts remain elusive.[9c,d]

Further structure-activity relationship (SAR) studies of bilobalide have been hampered by a lack of orthogonality in the bilobalide framework; selectivity regarding modification of the functional groups and structural skeleton of bilobalide continues to challenge synthetic chemists. Additional studies have cited issues related to the serum stability of bilobalide and related derivatives, which has severely impacted target validation studies for bilobalide.[3b,c] In order to effectively conduct SAR studies and identify cellular targets for bilobalide, an efficient, modular route to bilobalide and related analogs is required.

1.1.2. Previous Syntheses of Bilobalide

The first synthesis of bilobalide was described in 1987 by the Corey group (Scheme 1.1).[14] Lithiation of **1.2** with LDA in HMPA and cyclization with ynoate **1.3**, followed by reduction with NaBH$_4$ produced dienoate **1.4**. Interestingly, dienoate **1.4** contains all of the carbon atoms required to complete the synthesis of bilobalide. Ozonolysis of **1.4** and ketal formation of the resulting aldehyde gave bicyclic cyclopentene intermediate **1.5**. LiAlH$_4$ reduction of the carboxyethyl groups followed by oxidation of the subsequent diol furnished bis-aldehyde **1.6**, which upon

treatment with acid produced tetracycle **1.7**. Further oxidation of lactol **1.7** and conversion of the methoxy group at C11 to chloroether **1.8** with MsCl and Et_3N allowed for the installation of the C10-C11 double bond in intermediate **1.9** after elimination of the chloride. The C10 hydroxyl group was installed via stereoselective epoxidation of both the C7-C8 and C10-C11 alkenes, followed by hydrolysis of the C10-C11 epoxide to give diol **1.10**.

To complete the synthesis of the trilactone component of bilobalide, diol **1.10** was protected with acetic anhydride, followed by BF_3-OEt_2 mediated cleavage of the C2 methoxy group, which was further oxidized to the corresponding lactone with *m*CPBA. Selective deprotection of the C11 acetate with 0.5 N HCl resulted in lactol **1.11**. It was initially envisioned that oxidation of lactol **1.11** and hydrogenolysis of the epoxide would lead directly to bilobalide, however, several attempts at this transformation failed to deliver **1.1**.[14] To circumvent this issue, an alternative redox strategy was employed to produce trilactone **1.12**. PDC-mediated oxidation of lactol **1.11**, followed by deoxygenation of the epoxide and dihydroxylation of the resultant alkene produced **1.12**, which contains the desired tertiary alcohol at C8 of bilobalide. Deoxygenation of the C7 hydroxyl group of **1.12** was accomplished in a two-step sequence[15] to give acetate **1.13**, which was deprotected to give bilobalide (**1.1**) upon treatment with 3 N HCl.

Scheme 1.1. Corey's total synthesis of (±)-bilobalide.
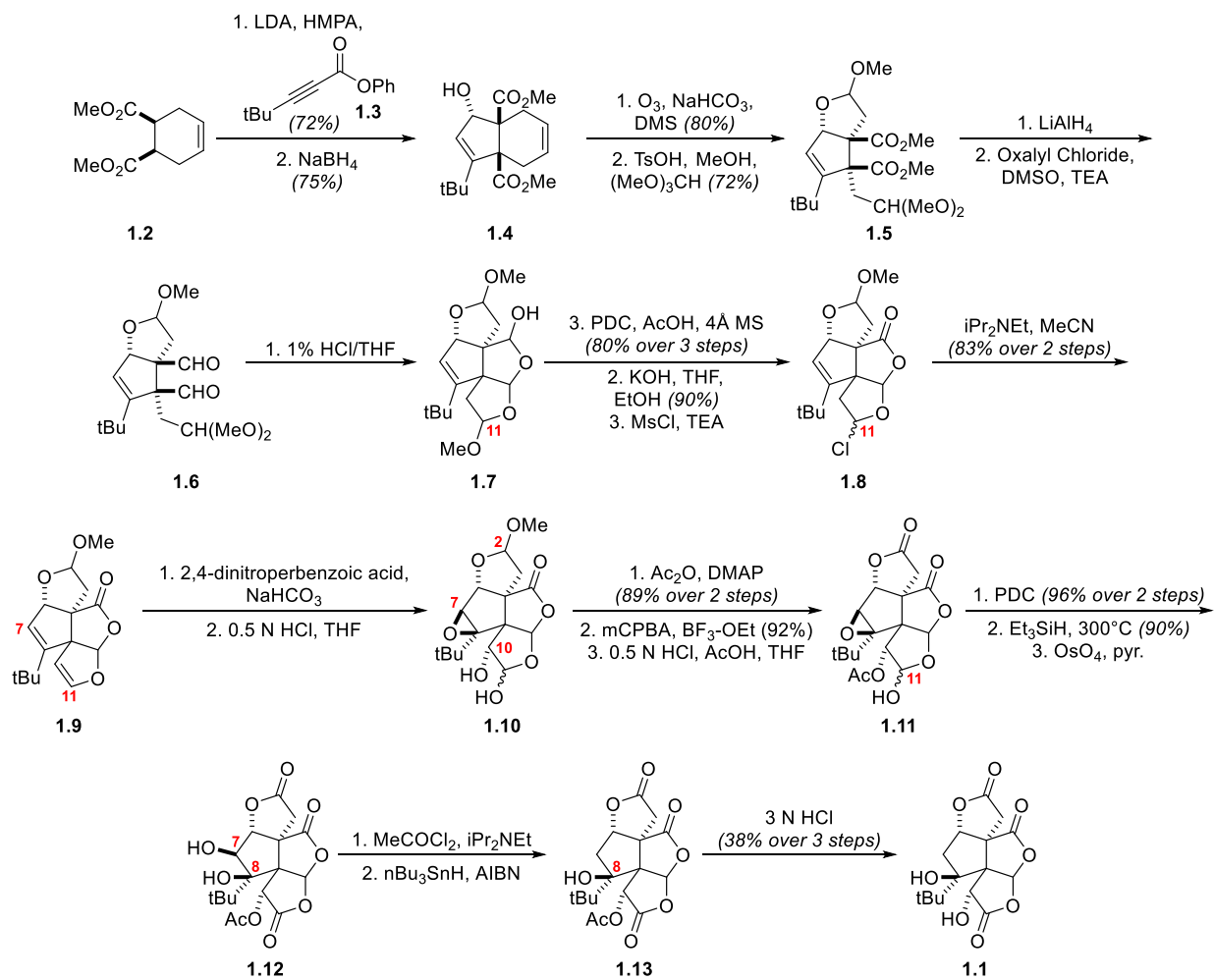
In a follow-up publication in 1988, the Corey group disclosed an asymmetric synthesis of (-)-bilobalide via modifications to their original route (Scheme 1.2).[16] The menthol derivative of fumaric acid, **1.14**, was treated with 1,3-butadiene in the presence of iBu$_2$AlCl to give the *trans* diester **1.15**. Attempts to carry out transesterification of **1.15** to the corresponding methyl ester resulted in rapid epimerization. Enolization of **1.15** with 1.0 equiv. LDA and addition of ynoate **1.3** resulted in the optically pure Claisen product **1.16**, with no conjugate addition byproducts detected. Optically pure enone **1.17** was prepared by treating **1.16** with KHMDS, which was further reduced with (*R*)-oxazaborolidine **1.18** to give intermediate **1.19**. The remaining synthetic

steps were carried out as described in Scheme 1.1[14] to give optically active (-)-bilobalide in 24 steps.

Scheme 1.2. Corey's asymmetric synthesis of (-)-bilobalide.
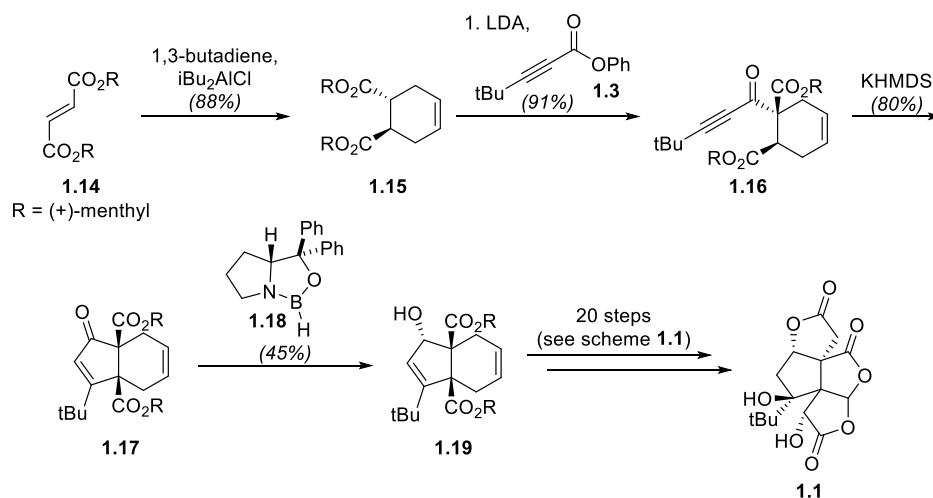
An alternative approach to construct the tetracyclic framework of (±) bilobalide via a [2+2] photocycloaddition strategy was described by the Crimmins group in a series of papers published in 1992 and 1993 (Scheme 1.3).[17] Installation of the C8 tertiary alcohol was accomplished via addition of an organocerium reagent to **1.20**, followed by Swern oxidation to give ketone **1.21**. Addition of lithiated acetonitrile and DIBAL reduction to the corresponding aldehyde gave the C8 tertiary alcohol **1.22**. Nucleophilic addition of lithioalkoxide **1.23** to aldehyde **1.22** resulted in **1.24**, which was further elaborated to generate the [2+2] cycloaddition precursor **1.25**. Upon irradiation with >350 nm light, **1.25** underwent [2+2] cycloaddition to give tetracycle **1.26**; treatment with LDA and oxidation of the subsequent enolate with MoOPH gave **1.27**. Oxidative cleavage of the α-hydroxy ketone **1.27** was accomplished with Pb(OAc)$_4$ to give intermediate **1.28**, which was converted to **1.29** upon exposure to a methanol solution of TsOH. LiAlH$_4$ mediated

reduction to the corresponding 1,2-diol and oxidative cleavage with Pb(OAc)₄ furnished cyclobutanone **1.30**, which underwent Baeyer-Villiger oxidation to deliver lactone **1.31**.

To complete the synthesis of (±)-bilobalide, **1.31** was treated with the Jones reagent to furnish dilactone **1.32**. The C10 hydroxyl group was installed via epoxidation with DMDO to give **1.33** and treatment with the Jones reagent to give (±)-bilobalide **1.1** in 17 steps from 3-furaldehyde **1.20**.

Scheme 1.3. Crimmins' total synthesis of (±)-bilobalide.
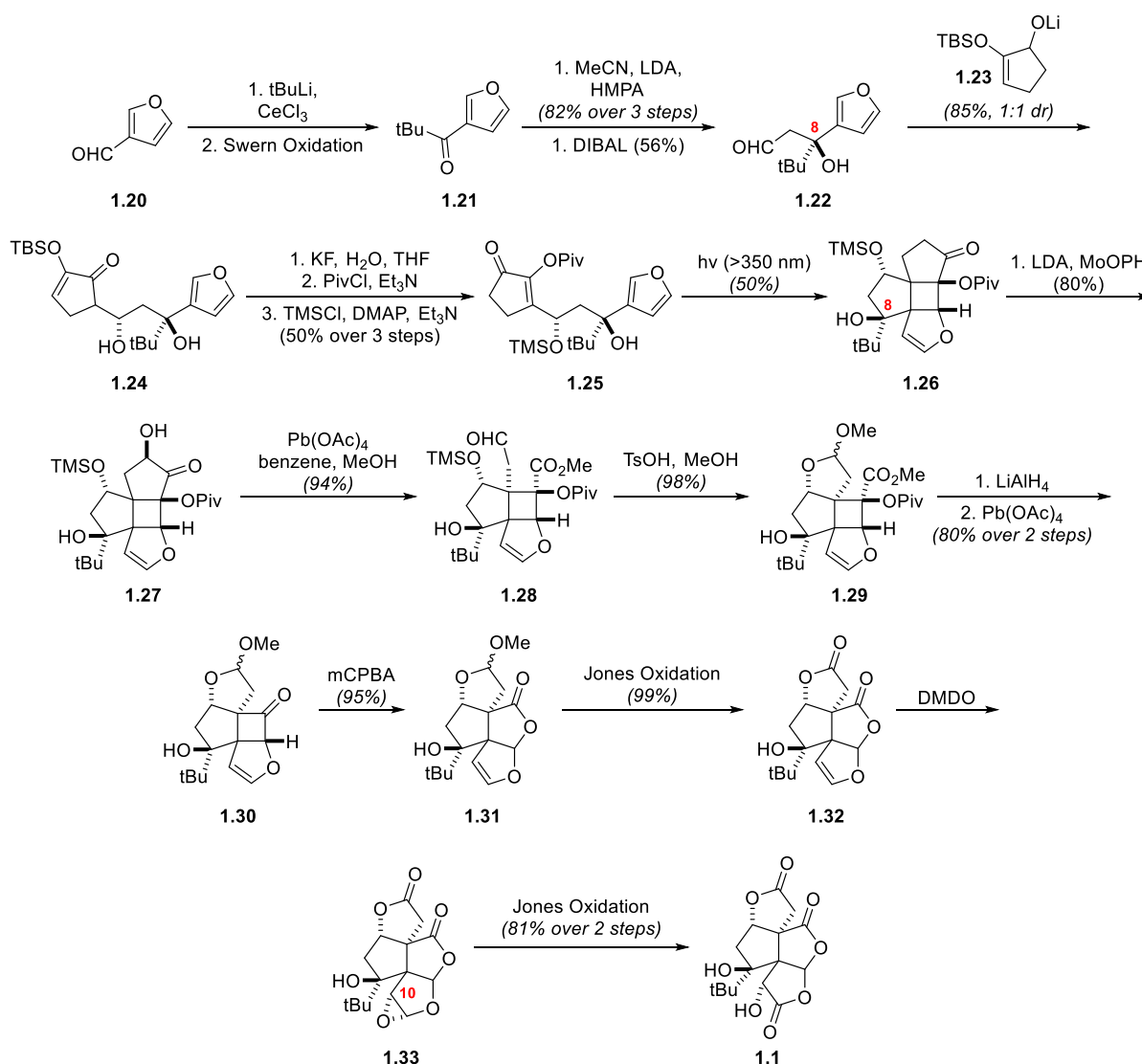
Although attempts to synthesize bilobalide have been reported since the work done by the Crimmins lab in 1993[18], it was 26 years later when the Shenvi lab disclosed a successful asymmetric synthesis of (-)-bilobalide (Scheme 1.4).[19] Wittig olefination with **1.34** and ketone **1.35** resulted in alkene **1.36**, which could be further functionalized to furnish the cyclopentane of bilobalide. To set the C6 stereochemistry required for bilobalide, an asymmetric Reformatsky reaction was carried out between **1.36** and aldehyde **1.37** using indabox ligand **1.38**, delivering **1.39** in 64% yield and 94% *ee*. Cyclopentene **1.40** was prepared via a Giese-type 5-*exo* cyclization, establishing the stereochemistry of the all-carbon quaternary stereocenter at C9. Mukaiyama hydration of **1.40** to **1.41** in methylcyclohexane installed the C8 tertiary alcohol present in bilobalide. Chiral phosphoric acid **1.42** facilitated the conversion of **1.41** to acetal **1.43** in 71% yield and 4.5:1 *dr*. It was envisioned that the severe steric congestion present in acetal **1.43** could be further leveraged to install the final all-carbon quaternary stereocenter at C5.

Given the steric hindrance present in **1.43**, it was postulated that an alkyne electrophile would provide the necessary functionality to stereoselectively incorporate the northern lactone moiety present in bilobalide. Conversion of acetal **1.43** to **1.47** proved difficult due to instability of intermediates **1.44** and **1.46**. A three-step sequence involving a single isolation, whereby the desired alkynyl substituent was installed via IBX oxidation of **1.43** to ketone **1.44**, followed by alkynylation with Waser's reagent[20] (**1.45**), furnished **1.46**. Reduction of ketone **1.46** with SmI_2 gave **1.47** in 60% yield over three steps, which contains all of the carbon atoms and the correct stereochemistry required to complete the synthesis of (-)-bilboalide **1.1**. Lithiation of the alkyne in the presence of trimethylborate presumably results in the formation of a ketene or mixed anhydride intermediate, which was attacked by the C6 alcohol of **1.47** and subsequently oxidized with *m*CPBA to give lactone **1.48** in 55% yield. Reduction of the benzyl esters with H_2 and Pd/C

followed by acidic hydrolysis resulted in trilactone **1.49**. Several attempts to convert **1.41** to **1.1**

via installation of the C10 hydroxyl proved challenging.[19] Successful installation of the C10

alcohol resulted from benzoylation of **1.49**, followed by enolization with KHMDS and subsequent

oxidation with the Davis oxazirdine, delivering (-)-bilobalide (**1.1**) in only 11 steps from **1.36**.

Scheme 1.4. Shenvi's total synthesis of (-)-bilobalide.
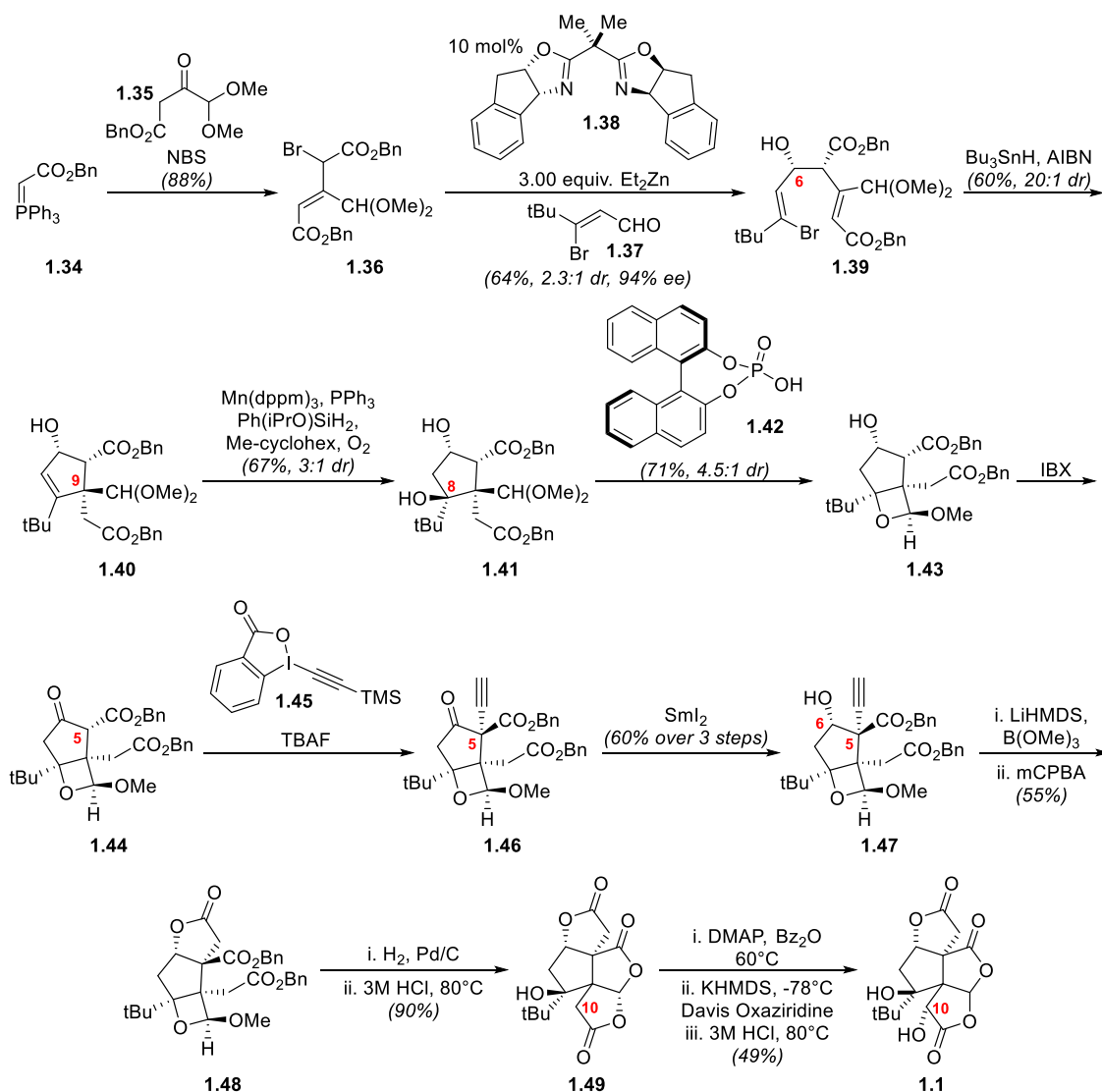
Although considerable advances have been made in the asymmetric synthesis of bilobalide

since Corey's seminal publication in 1987, the deep-seated structural modifications to the

bilobalide scaffold that are necessary for structure-activity relationship studies remain a challenge. Some structural modifications with each of the described routes are possible, however a complete overhaul of the synthetic approach used to access potential analogs may be required. Alternatively, a transition metal catalyzed cycloisomerization strategy employing highly substituted and stereochemically complex allenes may provide rapid entry into the bilobalide scaffold, in turn allowing for the preparation of a diverse library of bilobalide analogs suitable for structure-activity relationship studies. Over the past two decades, the development of gold catalysts as soft, carbophilic π-acids in organic synthesis[21] provides an intriguing opportunity for further development of concise strategies to prepare bilobalide and related analogs.

1.1.3. Gold-Catalyzed Cycloisomerization of Alkynes

The Toste group was one of the first to realize the synthetic potential of gold catalysts in Conia-ene type reactions with alkynes.[22] When treated with a catalytic amount of the catalytically active Ph₃PAuOTf, β-ketoester **1.50** (Scheme 1.5) underwent cycloisomerization to furnish *exo*-methylene cyclopentane **1.51** in 95% yield. Surprisingly, when compared to traditional Conia-ene type conditions,[23a] this reaction was complete in under 15 minutes at ambient temperatures thus establishing gold catalysts as a mild alternative to the harsh conditions previously employed.[23]

Scheme 1.5. Au(I)-catalyzed alkyne cycloisomerization.
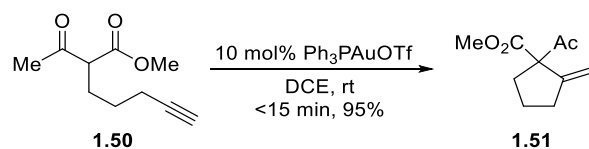
Two possible mechanistic scenarios for this transformation are described in Scheme 1.6.[22] In pathway A, the active Au(I) catalyst exclusively coordinates the alkyne of **1.50**, followed by

subsequent attack of the enol tautomer (**T.S. 1.52**) of the tethered β-ketoester moiety to furnish the vinyl gold species **1.53**. Protodeauration of **1.53** produces *exo*-methylene cyclopentane **1.51**. In pathway B, the cationic gold catalyst coordinates the alkyne **1.50** and enolate simultaneously, which undergoes cycloisomerization via **T.S. 1.54** to give vinyl gold intermediate **1.55**. As in pathway A, protodeauration results in the formation of **1.51**.

Scheme 1.6. Proposed 5-*exo*-dig alkyne cycloisomerization mechanism.
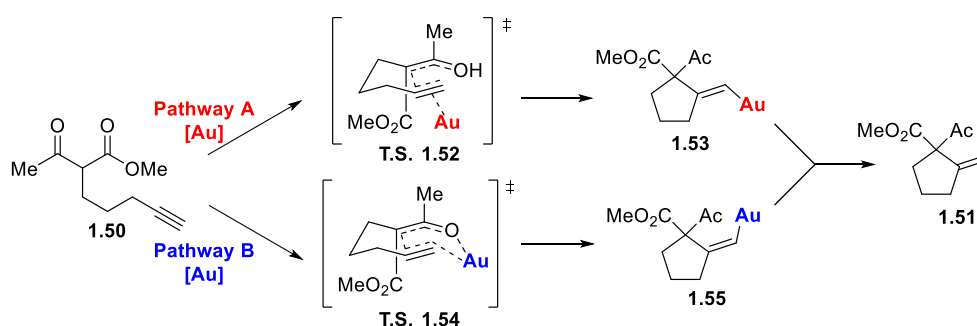
To gain further insight into the mechanism of this transformation, a series of deuterium-labeling experiments were conducted (Scheme 1.7) by Toste.[22] Deuteration of the alkyne C-H bond in **1.56** resulted in the incorporation of 90% deuterium in *syn*-**1.57**, while deuteration at the acidic methine of the β-ketoester pronucleophile in **1.58** resulted in 48% deuterium incorporation in *anti*-**1.59**. These results suggested that pathway A (Scheme 1.6), whereby the enol tautomer attacks the activated Au(I)-alkyne complex, is most likely operative.[22]

Scheme 1.7. Deuterium labeling experiments.
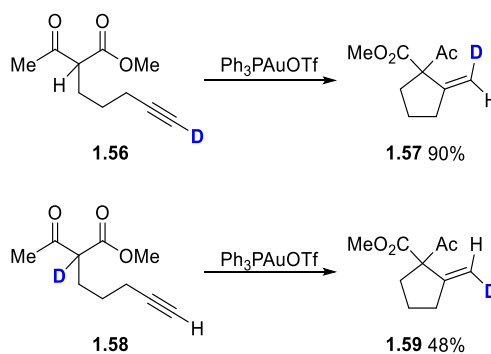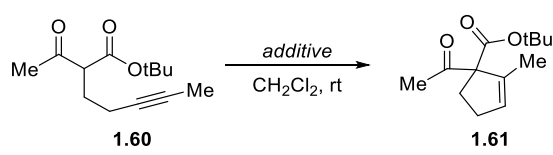
Computational DFT investigations into the mechanisms proposed in Scheme 1.6 resulted in several interesting findings.[24] The rate determining step of the cycloisomerization was found to be the keto-enol tautomerization step, rather than addition of the nucleophile to the activated Au(I)-alkyne complex. Coordination of the alkyne by the Au(I) catalysts substantially weakens the C-C π bond of the alkyne, which enhances the electrophilicity of the alkyne and promotes effective cycloisomerization. Additionally, the presence of the triflate anion in solution not only facilitates keto-enol tautomerization, it also serves as a proton shuttle to promote the near-barrierless protodeauration step to regenerate the active Ph₃PAuOTf catalyst and release the cycloisomerized product.[24] These results support Toste's conclusion that pathway A (Scheme 1.6), is most likely occurring.[22]

While terminal alkynes resulted in the formation of *exo*-methylene cyclopentane products, incorporation of a terminal alkyne to give the 5-*endo* cycloisomerization products provided a complementary methodology, whereby the location of the C-C double bond in the product could be controlled. To develop conditions capable of converting internal alkynes to the corresponding cyclopentenes, Toste and coworkers investigated a series of metal triflate catalysts (Table 1.1).[25] When subjected to copper additives (entry 1), alkyne **1.60** failed to undergo cycloisomerization. Additionally, silver additives (entry 2) were not capable of promoting effective cycloisomerization.

Smooth cycloisomerization of **1.60** to cyclopentene **1.61** was observed when Ph₃PAuOTf (entry 3) was employed as a catalyst, suggesting that both the Au(I) catalyst and the triflate counteranion were important for the desired reactivity.[25]   This approach was not limited to β-ketoester pronucleophiles; β-diketones were also found to undergo rapid cycloisomerization in the presence of Ph₃PAuOTf catalysts.[25]

Table 1.1. Au(I)-catalyzed *5-endo-dig* alkyne cycloisomerizations.

Entry	Additive	Time	Yield
1	5 mol% CuOTf-PhMe	18h	0%
2	5 mol% AgOTf	18h	<5%
3	1 mol% Ph₃PAuOTf	10 min.	93%

Although internal alkynes were tolerated under the reaction conditions, the regioselectivity of the nucleophilic attack could not be controlled to form the substituted *exo*-methylene cyclopentane product (Scheme 1.8).[25] The introduction of an additional methylene unit into **1.62** (n=3) failed to undergo 5-*exo*-dig cycloisomerization to give **1.65** via 5-*exo* **T.S. 1.63**. It was hypothesized that the incorporation of substitution on the alkyne results in increased $A^{1,3}$ strain in 5-*exo* **T.S. 1.63**, which inhibits the formation **1.64** and the resulting *exo*-methylene cyclopentene **1.65**. This additional steric strain is not present in 5-*endo* **T.S. 1.66** when one methylene unit is removed from the tether (**1.62**, n=2), resulting in the formation of **1.67** followed by protodeauration to give endocyclic cyclopentene **1.68**.

Scheme 1.8. Proposed 5-*endo* alkyne cycloisomerization mechanism.
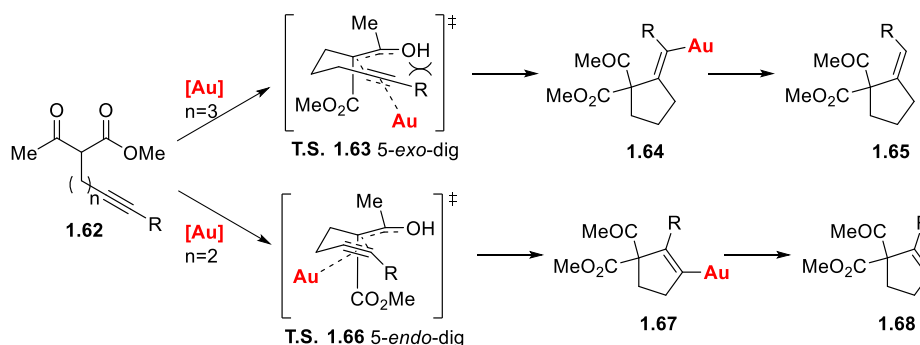
Bicyclic cyclopentane motifs are ubiquitous in natural products and pharmaceutically relevant compounds[26]. The synthetic preparation of these motifs often relies on several synthetic operations, highlighting the necessity for simple methods for their construction.[27] By employing allenyltriphenylstannane[28] as organometallic nucleophiles to generate an alkynyl intermediate, the Toste group was able to implement their methodology to synthesize bicyclic cyclopentenes using Au(I) catalysts (Scheme 1.9).[25] When treated with allenyltriphenylstannane, enone **1.69** was converted to the alkyne **1.70**, which underwent cycloisomerization in the presence of Au(I) catalysts to form bicyclic cyclopentene **1.71** as a single diastereomer.

Scheme 1.9. Cyclopentene annulation with Au(I) catalysts.
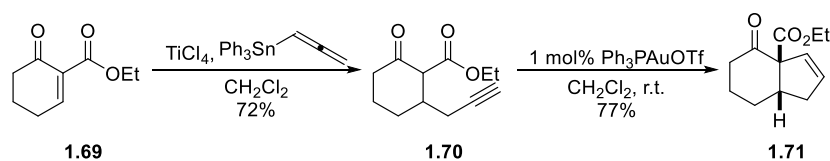
Previous studies with Au(I)-catalyzed cycloisomerizations relied on pronucleophiles containing two adjacent carbonyl groups to increase the acidity of the C-H bond of the pronucleophile.[22,25] To extend the utility of this method with respect to the synthesis of complex carbocyclic frameworks, a method that provides cyclized products with all carbon quaternary centers that do no feature the 1,3-dicarbonyl moiety was desired. To this end, the Toste group

explored the efficacy of silyl enol ethers as nucleophiles in Au(I)-catalyzed cycloisomerizations (Scheme 1.10).[29] By employing a 10:1 mixture of CH_2Cl_2 and MeOH at elevated temperatures, the nucleophilic enolate could be unmasked while simultaneously generating an acidic proton required for protodeauration to liberate the cyclopentane products and turn the catalytic cycle over. This methodology proved useful in the synthesis of *exo*-methylene cyclopentane **1.73** from alkyne **1.72**, which bears an all-carbon quaternary stereocenter.

Scheme 1.10. Au(I)-catalyzed 5-*exo* cyclopentene annulation with silyl enol ethers.
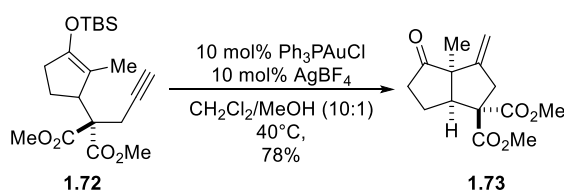
This method was further expanded to produce the corresponding 5-*endo* cyclopentene products.[29] When subjected to the optimized Au(I) reaction conditions, alkyne **1.74** (Scheme 1.11) underwent 5-*endo*-dig cycloisomerization to produce cyclopentene **1.75** in 77% yield. These complementary modifications allow for the construction of functionalized cyclopentane scaffolds containing an all-carbon stereocenter and precise control over the positioning of the double bond in the cyclized products, features that are desirable for the preparation of molecules that contain greater complexity.[26,27]

Scheme 1.11. Au(I)-catalyzed 5-*endo* cyclopentene annulation with silyl enol ethers.
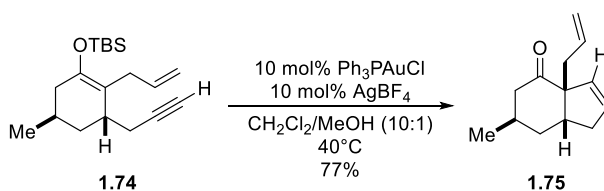
This methodology was utilized again in 2006 to synthesize the cyclopentane component of (+)-lycopladine-A (**1.78**) by the Toste group (Scheme 1.12).[29] Treatment of **1.76** with Ph₃PAuCl in the presence of a silver additive at 40 °C resulted in cycloisomerization to furnish vinyl iodide intermediate **1.77**. Three additional reaction steps furnished (+)-lycopladine A (**1.78**) in 8 total steps and 17% overall yield from (*R*)-5-methyl-2-cyclohexenone.

Scheme 1.12. Toste's synthesis of (+)-lycopladine A.
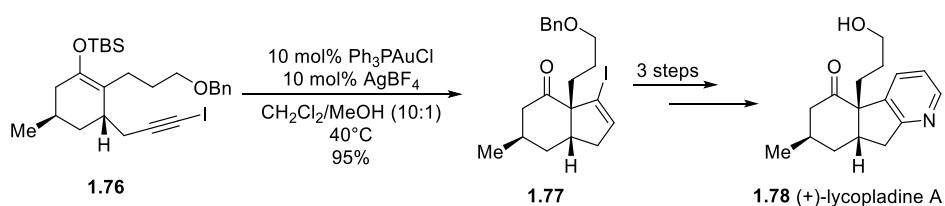
A similar strategy was used to complete the first asymmetric total synthesis of the related *Lycopodium* alkaloid (+)-fawcettimine (Scheme 1.13).[30] Iodoalkyne **1.80** was prepared by treating enone **1.79** with allenyltriphenylstannane in the presence of TBSOTf in CH₂Cl₂ at -78°C. Iodination of the subsequent alkyne was achieved with N-iodosuccinimide and AgNO₃ in DMF at 0°C. The key cyclopentene annulation step was completed by treating **1.80** with 10 mol% Ph₃PAuCl with 10 mol% AgBF4 in a 10:1 mixture of CH₂Cl₂/MeOH at 40°C to furnish vinyl iodide **1.81** in 69% over three steps.[30] After additional elaboration of vinyl iodide **1.81**, (+)-fawcettimine (**1.82**) was obtained in 13 total steps from commercially available crotonaldehyde.[30]

Scheme 1.13. Toste's synthesis of (+)-fawcettimine.
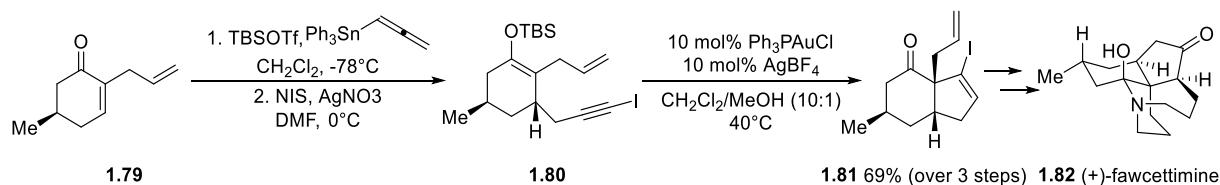
1.1.4. Gold-Catalyzed Cycloisomerizations of Alkenes

In contrast to the work described with alkyne cycloisomerizations with gold catalysts, considerably less attention has been paid to related cycloisomerizations using alkene substrates. Alkene cycloisomerizations typically require higher temperatures to achieve complete conversion as compared to alkyne substrates, which results in problems related to the stability of the Au(I) catalysts employed in these studies.[31] At elevated temperatures, Au(I) catalysts readily undergo disproportionation to give inactive Au(0) species[32]; this problem is exacerbated with silver salts, which undergo a rapid salt metathesis with Au(I) precatalysts to generate the thermally-less stable catalytically active Au(I) species.[33]

To circumvent the decomposition of Au(I) catalysts at elevated temperatures, the Gandon group chose to evaluate copper additives in place of the traditionally employed silver additives.[34] Copper additives are thought to initiate the requisite salt metathesis step much more slowly than silver additives, thus slowing decomposition of the Au(I) catalyst in solution.[34] Whereas silver halide salts are typically insoluble in the reaction solvent, copper halide additives remain soluble; this solubility difference may render the metathesis step reversible under Cu conditions, in turn slowing the decomposition of the Au(I) catalyst.[34] Given the high temperatures required for alkene activation with Au(I) catalysts, a Cu additive was hypothesized to provide the best yields with minimal Au(I) catalyst loadings. When 10 mol% Cu(OTf)$_2$ was employed as an additive with 1 mol% tBuJohnPhosAuCl (**1.84**), alkene **1.83** was converted to **1.85** in 95% yield and >95:5 *dr* (Scheme 1.14). Silver additives, in comparison, typically provided <20% conversion of **1.83** to

1.85, most likely a result of rapid decomposition of the gold catalyst due to the high reaction temperature.[34]

Scheme 1.14. Au/Cu system for alkene cycloisomerizations.
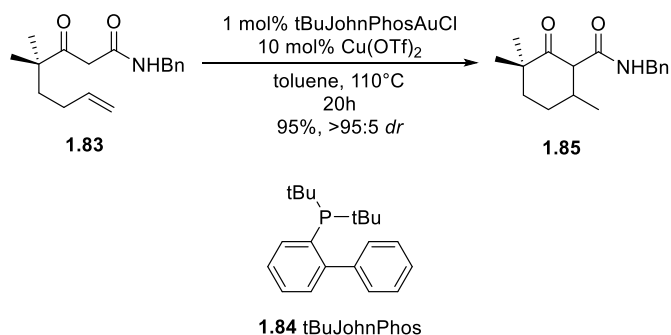
Although copper additives were found to be superior to silver additives when using β-dicarbonyl nucleophiles, they can be detrimental when ketone pronucleophiles are employed (Scheme 1.15).[35] When ketone **1.86** was treated with 0.1 mol% IPrAuCl and 5 mol% Cu(OTf)$_2$, lactone **1.87** was observed as the sole reaction product. The formation of lactone **1.87** is thought to arise via the Au(I)-catalyzed cyclization of the dimethyl 2-allylmalonate anion, the result of a retro Michael addition from ketone **1.86**. In contrast, 5 mol% of AgClO$_4$ results in the desired cycloisomerization of ketone **1.86** to bicycle **1.88**.[36]

Scheme 1.15. Divergent reactivity with Au/Cu vs. Au/Ag systems.
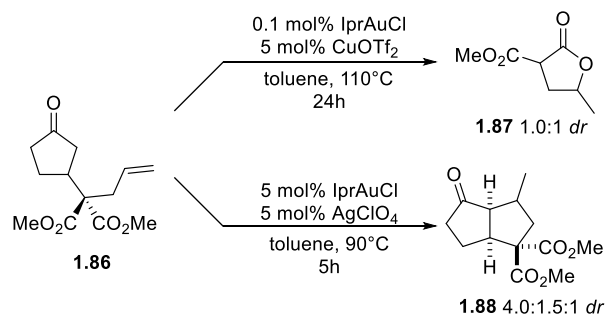
In addition to copper additives, the Gandon group explored additional Lewis acid additives (Table 1.2).[35] Of the additives evaluated, the triflates were the most successful at converting **1.83** to **1.85**. Zn(OTf)$_2$ furnished **1.85** with 83% conversion (entry 1), while Al(OTf)$_3$ (entry 2) produced **1.85** with only 26% conversion. In(OTf)$_3$ (entry 3), Me$_3$SiOTf (entry 4), and Bi(OTf)$_3$ (entry 5) all resulted in 100% conversion to **1.85**. Surprisingly, triflic acid (entry 6) resulted in no conversion **1.85**, thus demonstrating that activation via a metal additive is required for efficient cycloisomerization of **1.83** to **1.85**. In all cases where conversion was observed, the observed cycloisomerization *dr* remained relatively consistent.[35]

Table 1.2. Two-component Au(I) systems.

Entry	Additive	% conversion	*dr*
1	Zn(OTf)$_2$	83%	73:27
2	Al(OTf)$_3$	26%	72:28
3	In(OTf)$_3$	100%	74:26
4	Me$_3$SiOTf	100%	73:27
5	Bi(OTf)$_3$	100%	72:28
6	TfOH	0%	--
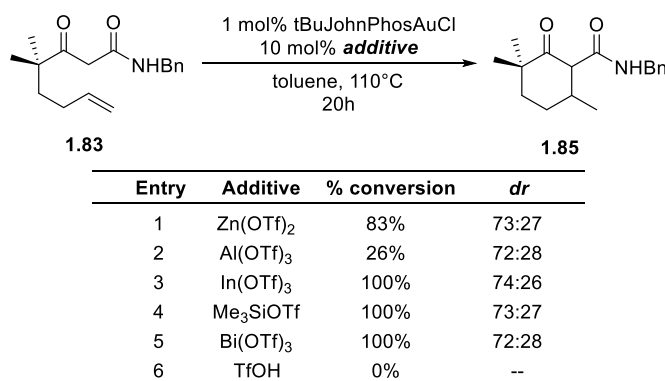
Reports describing asymmetric methods to generate enantioenriched products via C-C bond formation using gold catalysts, although highly desirable, are rare. An asymmetric alkene hydroalkylation to generate spirocyclic compounds was described by Gandon and coworkers in 2014.[37] Instead of the commonly utilized mononuclear Au(I) catalysts, the Gandon group turned to a chiral dinuclear Au catalyst and (*R*)-DTBM-MeOBIPHEP ligand **1.90** to achieve the spirocyclization of **1.89** to **1.91** and **1.92** (Table 1.3). Silver, indium, and bismuth additives (entries 1-3) effectively promoted cycloisomerization of **1.89** to **1.91** and **1.92** in good yields and moderate to good stereoselectivities. Initial attempts using chiral mononuclear Au(I) catalysts gave minimal

conversion to the desired spirocycle; in cases where conversion was observed, the mesaured *ee* was typically <10%.[37]

Table 1.3. Asymmetric Au(I)-catalyzed alkene spirocyclizations.
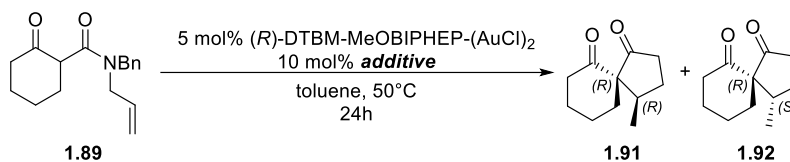
Entry	Additive	% conversion	dr (1.91/1.92)	% ee (1.91/1.92)
1	AgOTf	100%	43/57	82/96
2	In(OTf)$_3$	100%	48/52	80/85
3	Bi(OTf)$_3$	100%	43/57	83/95

1.90 (*R*)-DTBM-MeOBIPHEP
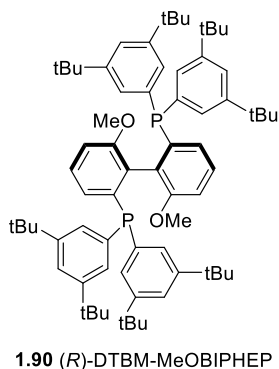
1.1.5. Gold-Catalyzed Cycloisomerizations of Allenes

Au(I)-catalyzed Conia-ene type cycloisomerizations utilizing chiral allenes are exceedingly rare in the literature. Few examples exist whereby enol and enolate-type nucleophiles were successfully added to allenes activated by Au(I) catalysts. In most cases of described Conia-ene-like reactivity, terminal allenes that do not possess axial chirality were utilized as cycloisomerization substrates. Much of the work in this field related to the formation of C-C bonds and allene substrates involved Au catalyzed hydroarylation chemistry; only hydroarylation examples utilizing allene substrates which form new C-C bonds are discussed here.

In 2006, the Toste group successfully translated their silyl enol ether approach to the cycloisomerization of terminal allene substrates with Au(I) catalysts (Scheme 1.16).[29] Silyl enol ether **1.93** underwent cycloisomerization when subjected to the Au/Ag catalyst system to give the 6,5-bicyclic cyclopentene **1.94** in 97% yield. To carry out the conversion of **1.95** to the 6,5-bicyclic cyclopentene **1.95**, a 10:1 solvent mixture of $CH_2Cl_2:H_2O$ was required.[29] This methodology also proved capable of forming the related 5,5-bicycle **1.98** in 59% yield from silyl enol ether **1.97**. The use of allene substrates provided a means to further control the positioning of the double bond in the cyclopentene products.[29]
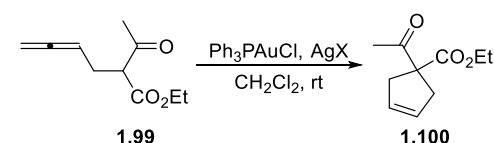
Scheme 1.16. Au(I)-Catalyzed cycloisomerizations with silyl enol ethers.

1.93 R_1=Me, R_2=Me, R_3=H (Y=Me)
1.95 R_1=allyl, R_2=Et, R_3=Me (Y=H)

1.94 97%
1.96 72%

1.97

1.98
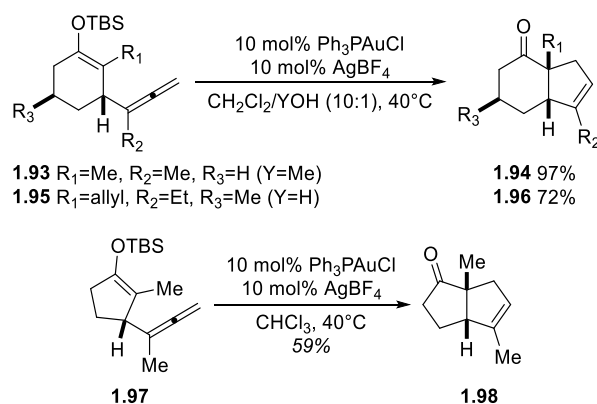
In addition to Toste's work[29] with allenes, in 2008 the Ma group described an Au(I)-catalyzed cycloisomerization strategy employing acyclic β-ketoesters as pronucleophiles without the need for pre-functionalization of the nucleophile (Table 1.4).[38] When no Ag additive was used (entry 1), conversion of **1.99** to cyclopentene **1.100** was not observed (entry 1). The addition of AgBF₄ (entry 2) resulted in 5% of cyclopentene **1.100** after 17 h, while switching to AgOTf (entry 3) provided 43% of **1.100** in just 3 h. The utilization of AgBF₆ (entry 5) as an additive proved to be most useful, delivering 68% of cyclopentene **1.100** in 1h. In the absence of Au(I) catalysts,

AgOTf provided cyclopentene **1.100** in 8% yield (entry 5), demonstrating the non-innocent behavior of some silver additives.[39]

Table 1.4. Au(I)-catalyzed cycloisomerization of β-ketoesters.

Entry	mol% Au	AgX (mol%)	time	yield
1	5	--	24 h	0%
2	5	AgBF$_4$	17 h	5%
3	5	AgOTf	3 h	43%
4	5	AgSbF$_6$	1 h	68%
5	0	AgOTf	12 h	8%

Electron rich aromatic and heteroaromatic nucleophiles have also been utilized to form new C-C bonds with Au(I) catalysts and allene substrates. In 2006, Nelson and coworkers developed a methodology whereby a tethered pyrrole substituent attacked an Au(I)-allene complex (Scheme 1.17).[40] Interestingly, the axial chirality present in **1.101** was transferred to the cyclic product **1.102** in high yield. Epimerization of allene **1.101** was thought to be suppressed by coordination of the ester carbonyl with the Au(I)-allene complex.[40] While Au(I) catalysts were successful in carrying out the conversion of **1.101** to **1.102**, both palladium and silver catalysts either failed to promote conversion or provided inferior *ee* in the cyclized product. Synthetic intermediate **1.102** was further elaborated to provide (-)-rhazinilam **1.103** in seven additional steps.[40]

Scheme 1.17. Tethered pyrroles in the Au(I)-catalyzed cycloisomerization of allenes.

1.101   **1.102**   **1.103** (-)-rhazinilam
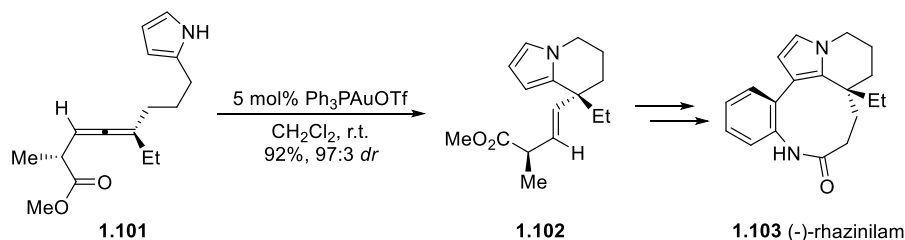
Tethered indole nucleophiles were also shown to be competent nucleophiles under Au(I) catalyzed conditions by Widenhoefer in 2007 (Scheme 1.18).[41] Treatment of **1.104** with a chiral digold catalyst **1.105** provided the 6-*exo* product **1.106** with high *ee*. Additionally, the 7-*exo* product **1.108** could be obtained in comparable *ee* from allene **1.107**.[41]

Scheme 1.18. Cycloisomerization with tethered indole nucleophiles.

1.104 n=1   **1.106** n=1, 88%, 92% *ee*
1.107 n=2   **1.108** n=2, 80%, 91% *ee*

1.105 (*S*)-tBuMeOBIPHEP
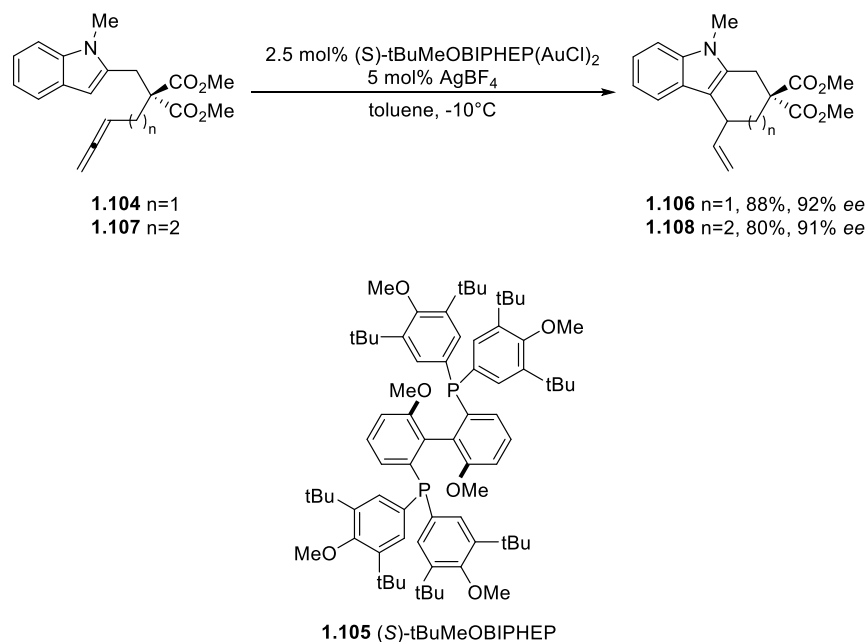
In a report from the Ohno group in 2007, electron rich aromatic **1.109** underwent 6-*endo* cycloisomerization (Scheme 1.19) in the presence of tBu$_2$(o-biphenyl)AuOTf to give the 6-*endo* bicyclic product **1.110** in 96% yield.[42] Attack of the terminal allene carbon by the aromatic

nucleophile was the only product observed under these conditions; no 5-*exo* products were detected.[42]

Scheme 1.19. 6-*endo* cycloisomerization with electron rich aromatic nucleophiles.
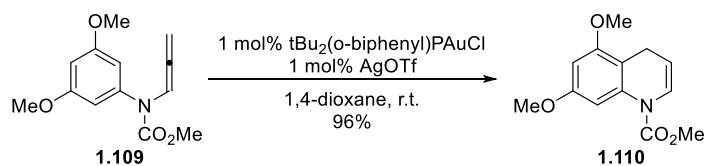
The 6-*exo* product **1.112** could be obtained under the same reaction conditions simply by extending the length of the tether by one methylene unit, as shown in **1.111** (Scheme 1.20).[42] 6-*exo* cyclization results from attack of the aromatic ring on the central carbon of the allene as opposed to the terminal carbon, thus allowing for regiocontrol over the placement of the double bond in the products.

Scheme 1.20. 6-*exo* cycloisomerization with electron rich aromatic nucleophiles.
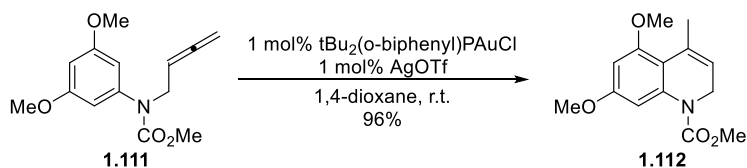
The scope of products obtained from electron rich aromatic nucleophiles was further extended by Gagné and coworkers in 2008 to include all-carbon tethers (Scheme 1.21).[43] Allene **1.113** was effectively converted to bicycle **1.114** in 85% yield when treated with a catalytic amount of $(PhO)_3PAuCl$ and $AgSBF_6$. In a series of mechanistic studies in 2009, Gagne and coworkers were able to demonstrate that the resting state of the catalytic cycle is a dinuclear Au species; the silver additives facilitate the activation of this dinuclear Au species to generate the catalytically active Au complex.[44a,b]

Scheme 1.21. 6-*exo* cycloisomerization with an all-carbon tether.

1.113 → **1.114**

Reagents: 3 mol% (PhO)$_3$PAuCl, 5 mol% AgSBF$_6$, CH$_2$Cl$_2$, r.t., 85%
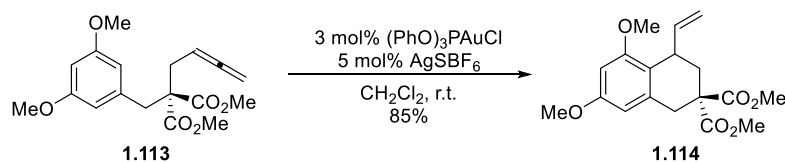
1.1.6. Gold-Allene Complexes

In contrast to alkynes and alkenes, the coordination of Au(I) catalysts to allenes poses a series of potential challenges with respect to the development of a stereocontrolled cycloisomerization methodology. Given the orthogonal π bonds present in allenes, several possible Au(I)-allene complexes are possible (Figure 1.2).[45] Coordination to the C-C π in an η^2 fashion results in intermediate **1.115**, where the Au-C bond lengths between the Au catalyst and both the central and distal carbon atoms are equidistant. An additional slipped η^2 complex **1.116** is possible, where the Au-C bond distance from the central carbon to the Au catalyst is shorter than the distal Au-C bond length. Alternatively, slipped η^2 complex **1.117** could form, where the Au-C bond length of the distal carbon to the gold catalyst is shorter than the bond between the central carbon and Au. It was envisioned that the electronic nature of the substituents on the allene can strongly influence the bonding in η^2 complexes **1.115**, **1.116**, and **1.117**.[46] Coordination to the central allene carbon results in the formation of the η^1-π-allyl Au complex **1.118**, or to the zwitterionic carbene-like complex **1.119**. Bent allenyl gold complexes of type **1.120** have also been proposed.

Figure 1.2. Possible Au(I)-allene complexes.
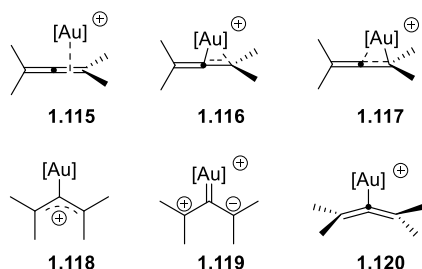
The solid phase structure of Au(I)-allene complexes was described by Malacria and coworkers in 2008 (Scheme 1.22).[46] The phosphinogold complex **1.121** was treated with AgSbF$_6$ to give active catalyst species **1.122**; the silver chloride salt formed during the initial metathesis step could be quantitatively removed via filtration. Complex **1.122** was then treated with a solution of allene **1.123**. Slow diffusion of hexanes at 4 °C resulted in the crystallization of Au(I)-allene complex **1.124**. XRD analysis of **1.124** revealed several notable features. The Au(I) catalyst preferentially coordinated the terminal allene π bond (denoted as C1-C2 in **1.124**). The Au-C1 bond length was found to be 2.191 Å, while the Au-C2 bond length was 2.306 Å, suggesting a slipped η^2 structure of type **1.117** (Figure 1.2). Additionally, the C1-C2 bond was slightly elongated at 1.340 Å compared to the C2-C3 bond length (1.311 Å). The allene component of complex **1.124** was distorted from linearity with a C1-C2-C3 bond angle of 165.0°, indicative of the formation of a bent η^2 complex.[46]

Scheme 1.22. Solid-state structure of Au(I)-allene complex **1.124**.
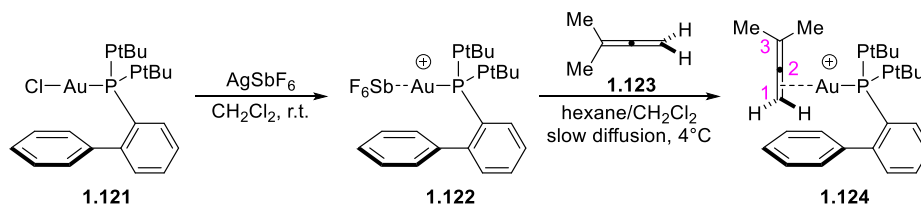
While a rigid complex is formed in the solid phase, the solution phase behavior of complex **1.124** is quite flexible (Figure 1.3, where L denotes the tBuJohnPhos ligand).[47] ^{1}H and ^{13}C NMR

spectra show equivalent methyl groups down to -30°C. Upon additional cooling to -60°C, **1.124**

shows two distinct methyl resonances in the ^{1}H and ^{13}C NMR spectra, indicated with blue and red

methyls, suggesting that facial migration of the gold catalyst occurs rapidly at elevated

temperatures.[47] This migration is thought to take place via an η^2-η^1-η^2 migration involving the

bent allene intermediates **1.124** and **1.127**. Coordination of the Au catalyst to the C2-C3 π bond

in **1.126** was hypothesized as an intermediate structure between **1.124** and **1.128**.[47]

Figure 1.3. Dynamic solution behavior of Au(I)-allene complex **1.124**.
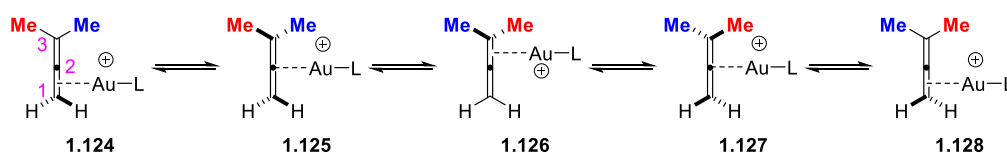
Additional investigation of these proposed Au-allene intermediates was conducted in a

subsequent report by Widenhoefer in 2014.[48] It was found that the slipped η^2 Au-allene complex

INT 1.129 (Figure 1.4) can interconvert to η^1-π-allyl intermediate **INT 1.131** via the bent and

twisted **T.S. 1.130**.[48] When Ph$_3$P was investigated as an Au ligand (depicted as L in Figure 1.4),

the $\Delta G^{\ddagger}$ was computationally determined to be 11.6 kcal/mol higher in energy relative to **INT**

1.129, an energy value that is attainable under most commonly employed reaction conditions.[48] It

was also determined that the ΔG value for **INT 1.131** was 6.7 kcal/mol higher in energy relative

to **INT 1.129**, suggesting **INT 1.131** is a plausible intermediate for Au(I)-allene complexes.[48]

From this data, it can be concluded that Au(I) catalysts are capable of promoting racemization of

axially chiral allenes under common conditions used to effect Au(I)-catalyzed cycloisomerizations.

These energy values are largely dependent on the electronic nature of the substituents attached to

the allene. In addition to the reaction solvent, the nature of the phosphine ligand on Au plays a

major role in the relative energies of these intermediates. The authors indicate that while

increasing the rate of nucleophilic additions to Au(I)-allene complexes may be accomplished by reducing the σ-donating ability of the phosphine ligands on Au, this modification also increases the rate of allene epimerization by Au(I) catalysts, thus rendering the transfer of axial chirality to point chirality with Au(I) catalysts particularly challenging.[48]

Figure 1.4. Racemization of allenes with Au(I) catalysts via η^1-π-allyl intermediates.
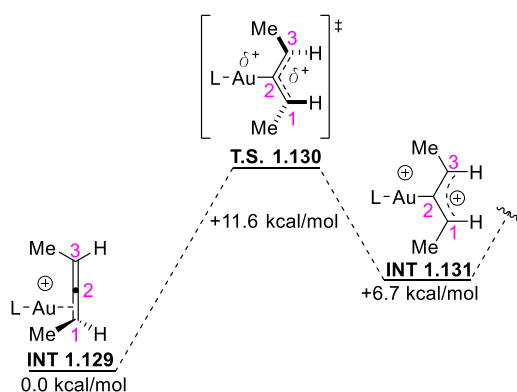
1.1.7. Conclusions

Over the past 20 years, the cycloisomerization methodology described with alkyne substrates has demonstrated the ability of Au(I) catalyst systems as an attractive, mild alternative to traditionally employed Conia-ene approaches to cyclic products[23]. Small variations in the substrate have led to the regiocontrolled installation of C-C π bonds in cyclic frameworks via 5-*endo* and 5-*exo* cycloisomerizations. Related developments with alkene substrates have demonstrated the ability of Au catalysts to provide cycloisomerized products in a stereocontrolled manner, thus paving the way for the development of additional enantioselective variations of this chemistry.

Challenges that remain unaddressed include the utilization of highly substituted, stereochemically complex allenes, as well as methods to control the subsequent cycloisomerization

stereochemistry of this class of substrates. Development of a method involving highly substituted allenes may prove beneficial for the construction of highly complex natural products and pharmaceutically relevant scaffolds from simple, easily synthesized allene precursors.

1.2 Results and Discussion

Previous work in the Schomaker group exploited the divergent reactivity of α-diazomalonates to furnish C-H insertion or cyclopropanation products depending on the nature of the catalyst employed[49]. When treated with a rhodium catalyst at ambient temperatures, α-diazomalonate **1.132** (Scheme 1.23) underwent smooth insertion into an allenyl C-H bond to give lactone **1.133**, where all three allene carbons remain unfunctionalized under the reaction conditions. It was envisioned that lactone **1.133** may undergo additional cycloisomerization with the tethered lactone moiety in the presence of a catalytic amount of an Au(I) catalyst to furnish bicyclic cyclopentene **1.134**. Elaboration of **1.134** provides access to the core structure of bilobalide (**1.1**, core denoted in red) and related analogs, which can be used to further elucidate the underlying mechanisms responsible for bilobalide's reported neuroprotective activity.

Scheme 1.23. Allene cycloisomerization route to access bilobalide core.
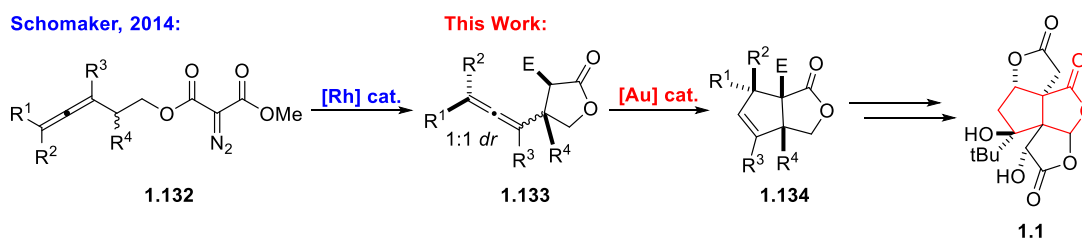
Initial investigations into the cycloisomerization of lactone **1.135** to cyclopentene **1.136** with Au(I) catalysts and silver additives are shown in Table 1.5. In the absence of exogenous acids, silver salts are incapable of promoting the conversion of **1.135** to cyclopentene **1.136** (entry 1).

Addition of bis(trifluoromethane)sulfonamide (entry 2) also resulted in no conversion to **1.136**, while camphorsulfonic acid (entry 3) only resulted in 10% conversion to **1.136** and 1:1 *dr*. Bi(OTf)$_3$ improved conversion of **1.135** to **1.136** (entry 4), however **1.136** was generated with 1:1 *dr*. When AgOTf and triflic acid were employed, 90% of **1.135** was converted to **1.136** in 2.5:1 *dr*. Unfortunately, these results with silver additives were difficult to reproduce and did not translate well to other substrates. A more robust additive was required to facilitate the cycloisomerization of lactone **1.135** to cyclopentene **1.136**.

Table 1.5. Initial cycloisomerization conditions.
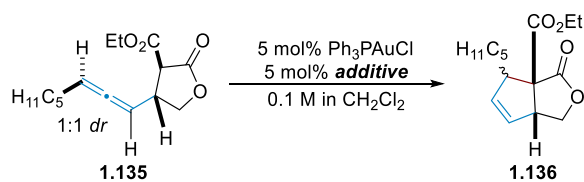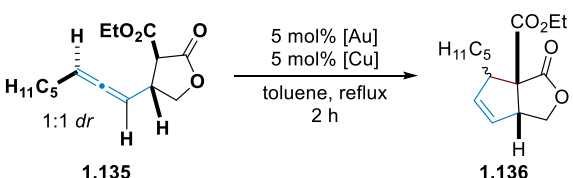
entry	additive	% conversion[a]	*dr*[b]
1	AgOTf	0%	---
2	AgOTf, Tf$_2$NH	0%	---
3	AgOTf, CSA	10%	1:1
4	AgOTf, Bi(OTf)$_3$	100%	1:1
5	AgOTf, TfOH	90%	2.5:1

[a]Used mesitylene as ^{1}H NMR standard. [b]*Anti:syn.*

Based on previous reports in the literature.[34,35], a series of gold catalysts and copper additives were explored to promote the cycloisomerization of **1.135** to **1.136** (Table 1.6). Treatment of a 1:1 mix of stereoisomers of **1.135** with Ph$_3$PAuCl and Cu(OTf)$_2$ resulted in cyclopentene **1.136** with excellent conversion as a 1.1:1 mix of diastereomers. This result indicated that Cu additives are capable of promoting the requisite salt metathesis to form the active R$_3$PAuOTf catalyst, as well as engaging the lactone carbonyls to promote generation of the putative enolate intermediate required for effective cycloisomerization. Dinuclear Au catalysts (entry 2) were capable of promoting conversion of **1.135** to **1.136**, however no improvements in diastereoselectivity were observed. Strong σ-donor ligands, such as N-heterocyclic carbenes

(entry 3), did exhibit slight improvements in *dr* with a reduction in conversion. Changing the

phosphine ligands on the Au species resulted in slightly diminished yields and 1:1 *dr* (entries 4

and 5). Electron rich alkyl phosphine ligands (entry 7) improved the *dr* of the reaction, however

a reduction of yield was observed. Electron-deficient phosphite ligands also provided a slight

increase in *dr*, albeit with a reduction in conversion (entry 9). Au(III) catalysts were not capable

of converting the allene to the desired cyclopentene (entry 10). Changing to a more strongly

coordinating acetate ligand on Cu (entry 11) resulted in a complete loss of reactivity. Although

Cu(I) salts (entry 12) were capable of promoting conversion of **1.135** to **1.136**, they were also

capable of promoting background cycloisomerization in the absence of Au(I) catalysts. Based on

these observations, a Cu(II) additive with weakly coordinating ligands, namely Cu(OTf)$_2$, was

selected for further optimization.

Table 1.6. Initial development of an Au/Cu catalyst system.
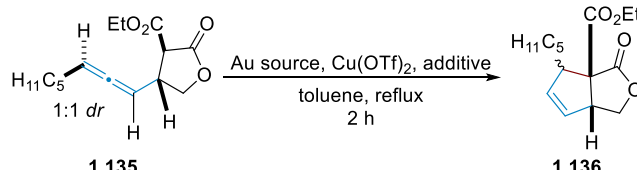
entry	Au source	Cu source	conversion[a]	*dr*[b]
1	Ph$_3$PAuCl	Cu(OTf)$_2$	100%	1.3:1
2	dppm(AuCl)$_2$	Cu(OTf)$_2$	100%	1.1:1
3	IPrAuCl	Cu(OTf)$_2$	88%	1.3:1
4	^{t}Bu$_2$JohnPhosAuCl	Cu(OTf)$_2$	81%	1:1
5	Cy$_2$JohnPhosAuCl	Cu(OTf)$_2$	100%	1:1
6	^{t}Bu$_3$PAuCl	Cu(OTf)$_2$	100%	1:1
7	(o-tolyl)$_3$PAuCl	Cu(OTf)$_2$	70%	1:1
8	Cy$_3$PAuCl	Cu(OTf)$_2$	85%	1.3:1
9	(PhO)$_3$PAuCl	Cu(OTf)$_2$	55%	1.6:1
10	AuCl$_3$	Cu(OTf)$_2$	0%	--
11	Ph$_3$PAuCl	Cu(OAc)$_2$	0%	--
12	Ph$_3$PAuCl	(CuOTf)-toluene	82%	1:1

[a] Mesitylene used as an internal standard. [b] *anti:syn.*

Once a competent Lewis-acid additive was identified, efforts to optimize the yield and

diastereoselectivity of the cycloisomerization were pursued (Table 1.7). Introduction of chirality

via dinuclear Au catalysts resulted in a loss of reactivity (entries 1-2), while chiral mononuclear Au(I) catalysts (entry 3) produced cyclopentene **1.136** in a modest 46% yield with no noticeable change in *dr*. Addition of a chiral additive had no effect on the diastereoselectivity of the reaction; Ph₃PAuCl catalyst and chiral phosphoric acid **1.42** (entry 4) produced cyclopentene **1.136** in 76% yield and 1.6:1 *dr*. When used in conjunction with chiral Au(I) catalysts, chiral phosphoric acid **1.42** failed to improve the observed diastereoselectivity of the cycloisomerization reaction (entries 6-8). It was hypothesized that, given the linear nature of Au(I) catalysts, any chirality introduced either via the phosphine ligand on the Au(I) catalyst or from a chiral additive is too far removed from the reactive sites in the molecule to impart adequate diastereocontrol over the cycloisomerization.[50]

Table 1.7. Chiral catalyst and additive screening.

entry	Au source	additive	yield*a*	*dr*[b]
1	*R*-DTBM-SEGPHOS(AuCl)₂	none	0%	--
2	*R*-SEGPHOS(AuCl)₂	none	0%	--
3	*S*-MonoPhosAuCl	none	46%	1.6:1
4	Ph₃PAuCl	1 equiv. **1.42**	76%	1.6:1
5	dppm(AuCl)₂	1 equiv. **1.42**	22%	1.5:1
6	*S*-MonoPhosAuCl	1 equiv. **1.42**	83%	1.8:1
7	*R*-MonoPhosAuCl	1 equiv. **1.42**	53%	1.5:1
8	*S*-MonoPhosAuCl	5 mol% **1.42**	76%	1.7:1

[a] ¹H-NMR yield with mesitylene as internal standard. [b] *anti:syn.*
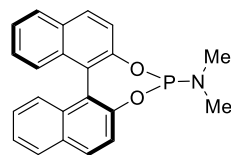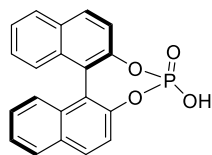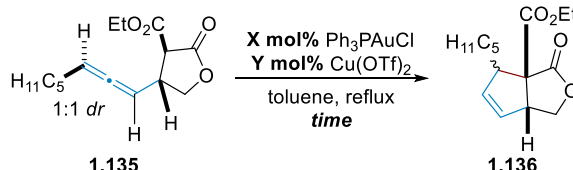
Further efforts to improve the diastereoselectivity were made by varying the Au:Cu ratio (Table 1.8). A 1:1 ratio of Au:Cu resulted in an observed *dr* of 1.3:1 (entry 1), while reducing the

Au(I) catalyst loading (entry 2) resulted in an improvement in *dr* while substantially reducing the yield. Increasing the loading of Cu(OTf)$_2$ from 5 mol% to 25 mol% (entry 3) led to a slight increase in yield with no reduction in *dr*. Further increases in the Cu:Au ratio (entry 4) were not detrimental to the reaction outcome, while increasing the reaction time resulted in significant improvements in yield (entry 5). An increase in Au(I) catalyst loading while maintaining the 10:1 Cu:Au ratio resulted in further improvements to the yield of the reaction (entry 6). An electron-rich PCy$_3$ ligand furnished additional increases in the yield of the cycloisomerization reaction while preserving the observed *dr*. This result is thought to arise from the increased ability of electron-rich ligands to preserve the cationic Au(I) catalyst, preventing decomposition during the course of the reaction.

Table 1.8. Au(I)-catalyzed cycloisomerization optimization.

entry	X	Y	time	yield^a	dr^b
1	5	5	2 h	72%	1.3 : 1
2	1	5	2 h	35%	1.7 : 1
3	5	25	2 h	41%	1.8 : 1
4	1	10	2 h	34%	2.0 : 1
5	1	10	12 h	50%	1.9 : 1
6	2.5	25	24 h	68%	1.6 : 1
7^c	2.5	25	24 h	93%	1.8 : 1

^{a} ^{1}H-NMR yield with mesitylene as internal standard. ^{b} *anti:syn.*
^{c} Cy$_3$PAuCl used in place of Ph$_3$PAuCl.

A proposed catalytic cycle for the Au(I)-catalyzed cycloisomerization of allenes is shown in Figure 1.5. The active catalyst, PCy$_3$AuOTf, is formed via a salt metathesis step involving Cu(OTf)$_2$. Coordination of allene **1.133**, followed by a Cu-mediated enolization step results in intermediate **1.138**. Vinyl Au intermediate **1.139** arises as a result of nucleophilic attack of the

putative Cu enolate on the η^1-π-allyl Au complex. Protodeauration to liberate cyclopentene **1.134** is promoted by trace amounts of triflic acid generated *in situ* during the formation of the Cu enolate. Given the ability of Au(I) catalysts to rapidly epimerize allenes[47,48], it was hypothesized that axial-to-point transfer of chirality under the optimized reaction conditions would not occur.

Figure 1.5. Proposed Au(I) catalytic cycle.
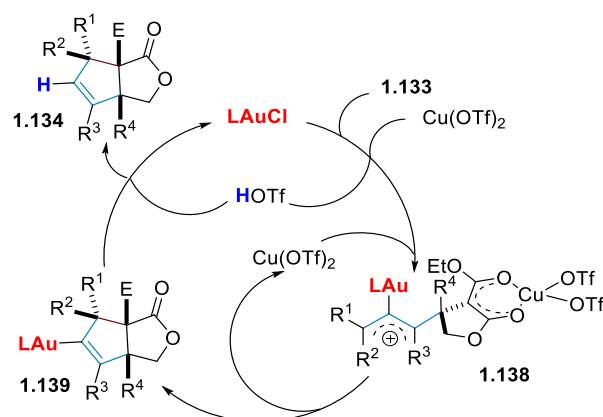
The nature of catalytic intermediate **1.138** (Figure 1.5) illustrates the difficulties inherent in promoting a catalyst-controlled diastereoselective cycloisomerization of allene **1.133**. Intermediate **1.138** may adopt several possible conformations, as depicted in Figure 1.6.[46-48] Epimerization of Cu enolates **1.140** and **1.141** results from a rapid facial migration of the Au(I) catalyst, presumably via η^1-π-allyl Au complexes **1.142** and **1.143**[47], thus rendering axial-to-point transfers of allene chirality ineffective in promoting a diastereoselective transformation. Attack of the Cu enolate in intermediate **1.142** likely results in the observed *anti* cyclopentene, while subsequent nucleophilic attack in intermediate **1.143** results in the *syn* diastereomer. To further complicate matters, rotation about the lactone-allene σ bond in **1.142** results in **1.144**, which if attacked by the Cu enolate results in the *syn* diastereomer. Alternatively, rotation about the lactone-allene σ bond of **1.143** furnishes **1.145**, producing the *anti* diastereomer after C-C bond

formation and subsequent protodeauration. Once the protodeauration step has occurred and **1.134** is released from the Au(I) catalyst (Figure 1.5), the Au/Cu catalyst system is incapable of promoting epimerization of either diastereomer of the cyclopentene products.

Figure 1.6. Possible conformations of catalytic intermediate **1.138**.
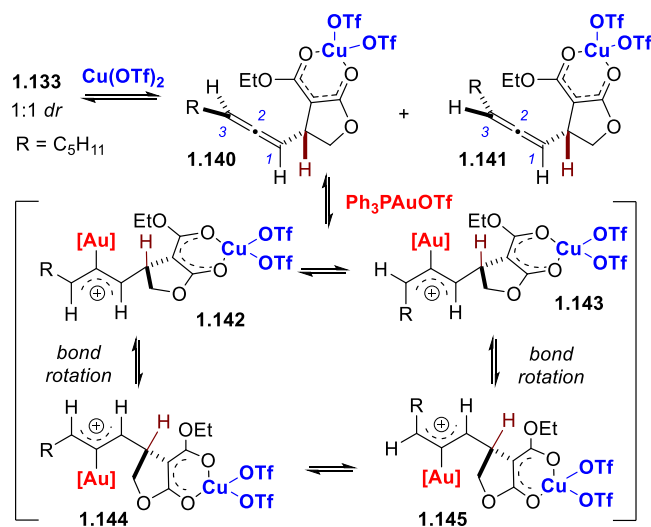
Given the aforementioned results, it was surmised that the observed diastereoselectivity of the Au(I)-catalyzed allene cycloisomerization would be largely substrate controlled. To further investigate this, a series of disubstituted allenes were explored (Table 1.9). When exposed to the optimized reaction conditions, lactone **1.135** furnished cyclopentene **1.136** in 93% yield and 1.8:1 *dr*. Changing the identity of the ester **1.146** had no effect on the *dr* of cyclopentene **1.152**, while incorporation of a methyl group in **1.147** furnished cyclopentene **1.153** in 1.0:1 *dr*. This reduction in observed *dr* is thought to arise from minimal energetic differences between catalytic intermediates **1.142-1.145** (Figure 1.6). Introduction of a remote phenyl substituent in **1.148** provided cyclopentene **1.154** in 4.0:1 *dr*, while increasing the steric profile of the ester in **1.149** furnished cyclopentene **1.155** in 4.6:1 *dr*. Branching in the alkyl substituent of **1.150** resulted in further improvements in the *dr* of **1.156**, however this was at the expense of the reaction yield.

Intriguingly, increasing the steric profile of the ring junction in **1.151** gave cyclopentene **1.157** in 54% yield and 3.6:1 *dr*.

Table 1.9. Disubstituted allene cycloisomerization scope.
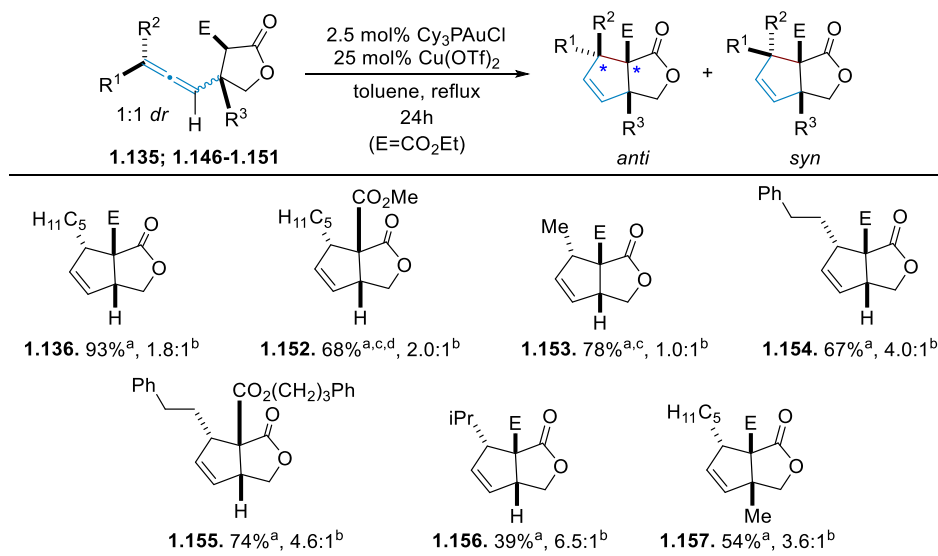
a ^{1}H-NMR yield with mesitylene as internal standard. ^{b} *anti:syn*. ^{c} 1:1 ratio of Au:Cu. ^{d} Used Ph$_3$PAuCl.

A series of trisubsubstituted allenes were also evaluated for competency with Au(I) catalysts (Table 1.10). It was hypothesized that incorporation of a large substituent on the carbon proximal to the lactone moiety would favor intermediate **1.142** (Figure 1.6), where A^{1,3} interactions between the substituents on the allene would be minimized, thus producing the *anti* diastereomer in excess. Furthermore, sterically demanding substituents on the proximal carbon would presumably result in unfavorable steric interactions with the Cu enolate of intermediate **1.145**, leading to a preference for the conformation in **1.142**. TBS-substituted allene **1.158** furnished cyclopentene **1.162** in 51% and 4.5:1 *dr*. The reduced steric demand present in methyl substituted allene **1.159** resulted in cyclopentene **1.163** in 37% yield and 1.8:1 *dr*. Dialkyl substitution in **1.160** was tolerated under the reaction conditions to furnish **1.164** in 62% yield. The additional branching present in allene **1.161** presented a scenario where unfavorable interactions between the isobutyl group and the η^1-

π-allyl Au complexes are present in intermediates **1.142** and **1.144**. Additional unfavorable A^{1,3} interactions are present in intermediates **1.143** and **1.145**, therefore minimal diastereoselectivity was expected to result when allene **1.161** was subjected to the reaction conditions. Indeed, allene **1.161** furnished cyclopentene **1.165** in 32% yield with 1.1:1 *dr*.

Table 1.10. Trisubstituted allene cycloisomerization scope.

1.162. 51%[a,b], 4.5:1[c]	**1.163.** 37%[a,b], 1.8:1[c]	**1.164.** 62%[a,b,d], 4.5:1[c]	**1.165.** 32%[a], 1.1:1[c]

[a] ^{1}H-NMR yield with mesitylene as internal standard. [b] Used Ph$_3$PAuCl. [c] *anti:syn.* [d] 1:1 ratio of Au:Cu.
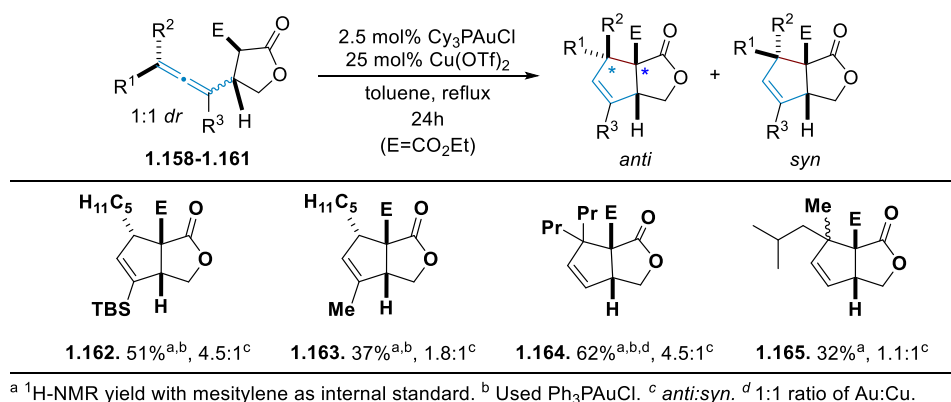
It was envisioned that substitution on the lactone moiety could be leveraged to further control the equilibrium present in η^1-π-allyl Au complexes **1.142-1.145** (Figure 1.6). Incorporation of *gem*-dimethyl substitution on lactone **1.166** (Table 1.11) resulted in cyclopentene **1.167** in 70% yield and 2.6:1 *dr*, a slight improvement in *dr* as compared to **1.169** (Table 1.9). Increasing the steric nature of the ligand furnished **1.167** in 89% yield and 6.6:1 *dr*. This dramatic increase in observed *dr* may be a result of increased steric interaction in η^1-π-allyl Au complexes **1.144** and **1.155** and the substitution on the lactone, thus resulting in a preference for intermediate **1.142**.

Table 1.11. *Gem*-dimethyl substituted lactones.

1.166

entry	[Au]	X:Y	time (h)	yield[a]	dr (*anti:syn*)
1	Ph₃PAuCl	2.5:25	24	70%	2.6:1
2	Cy₃PAuCl	2.5:25	24	89%	6.6:1

[a] ¹H-NMR yields using mesitylene as the internal standard.
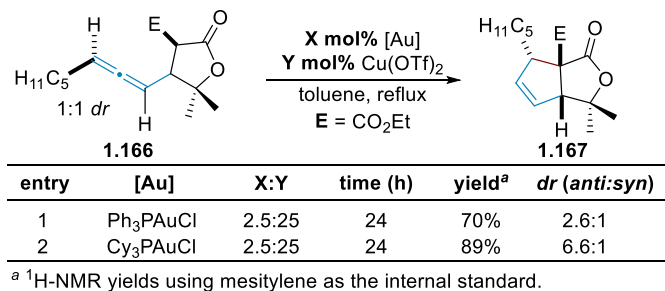
Although chiral ligands and additives failed to increase the observed diastereoselectivity of the reaction, it was thought that introduction of chirality via the Cu enolate may be able to switch the selectivity in favor of the *syn* diastereomer (Scheme 1.24). Introduction of 25 mol% indapybox ligand **1.168** resulted in a reduction of the *dr* and a modest drop in yield. Though additional modifications to the steric environment of the Cu enolate did impact the *dr*, the *syn* diastereomer was never observed in excess. Based on reports by Gandon, changing the identity of the Lewis acid may facilitate a change in the observed diastereoselectivity of the cycloisomerization.[35,37]

Scheme 1.24. Ligated Cu additives.

Standard Conditions: 89%, 6.6:1 *dr*
with 25 mol% **1.168**: 60%, 2:1 *dr*
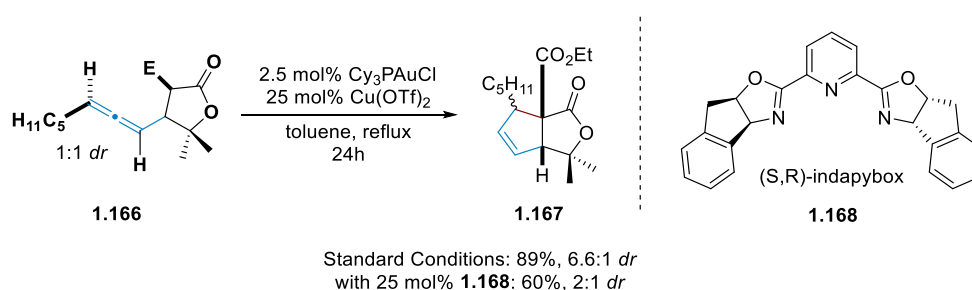
Intriguingly, the use of In(OTf)₃ as a Lews acid additive furnished cyclopentene **1.167** in 43% yield and 1.2:1 *dr* in favor of the *syn* diastereomer (entry 1, Table 1.12). Sn(OTf)₂ produced cyclopentene **1.167** in an improved 70% yield and 1.5:1 *dr* (entry 2). Zinc and ytterbium Lewis acids (entries 3-4) resulted in cycloisomerization to give cyclopentene **1.168** with slight improvements in *syn:anti* ratios, albeit at lower yields. Eu(OTf)₃ gave cyclopentene **1.168** in 83%

yield and 1.9:1 *syn:anti*, a result complementary to that of Cu(OTf)$_2$. The nature of the observed switch in diastereoselectivity is not well understood; trends in *dr* do not correlate directly to the atomic radius of the additive. Given the increased coordination number of several lanthanide salts in the +3 oxidation state, it may be possible that one molecule of Lewis acid is capable of coordinating to multiple enolates, which, in turn, increases the sterics of the enolate and drives selectivity for the *syn* diastereomer.

Table 1.12. Additional Lewis acid additives and their effect on diastereoselectivity.
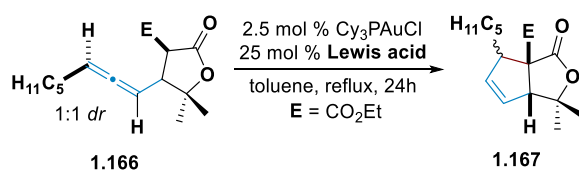
entry	Lewis acid	time (h)	yield[a]	dr (syn:anti)
1	In(OTf)$_3$	24	43%	1.2:1
2	Sn(OTf)$_2$	24	70%	1.5:1
3	Zn(OTf)$_2$	24	62%	1.9:1
4	Yb(OTf)$_3$	24	56%	1.7:1
5	Eu(OTf)$_3$	24	83%	1.9:1

[a] ^{1}H-NMR yields using mesitylene as the internal standard.

The convex nature of cyclopentenes **1.166** and **1.169** was leveraged to further explore diastereoselective functionalizations to highly substituted cyclopentane frameworks (Scheme 1.25). Treatment of **1.169** with *m*CPBA resulted in the formation of expoxide **1.170** in 69% yield and >19:1 *dr*. Dihydroxylation using Upjohn conditions furnished diol **1.171** in 70% yield and >19:1 *dr*, while hydroboration oxidation produced alcohol **1.172** in 64% yield and >19:1 *dr*. Additionally, the carboxymethyl group of **1.169** could be removed using LiCl in wet DMSO at elevated temperatures, generating lactone **1.172** in 86% yield and >19:1 *dr*. Cyclopentene **1.169** failed to react under the Rh-mediated nitrene transfer conditions described by Du Bois[51] due to the sterics imparted by the carboxymethyl group; however, decarboxylated **1.173** provided aziridine **1.174** in 66% yield and >19:1 *dr* under Du Bois' conditions.

Scheme 1.25. Preparation of highly substituted cyclopentane frameworks.
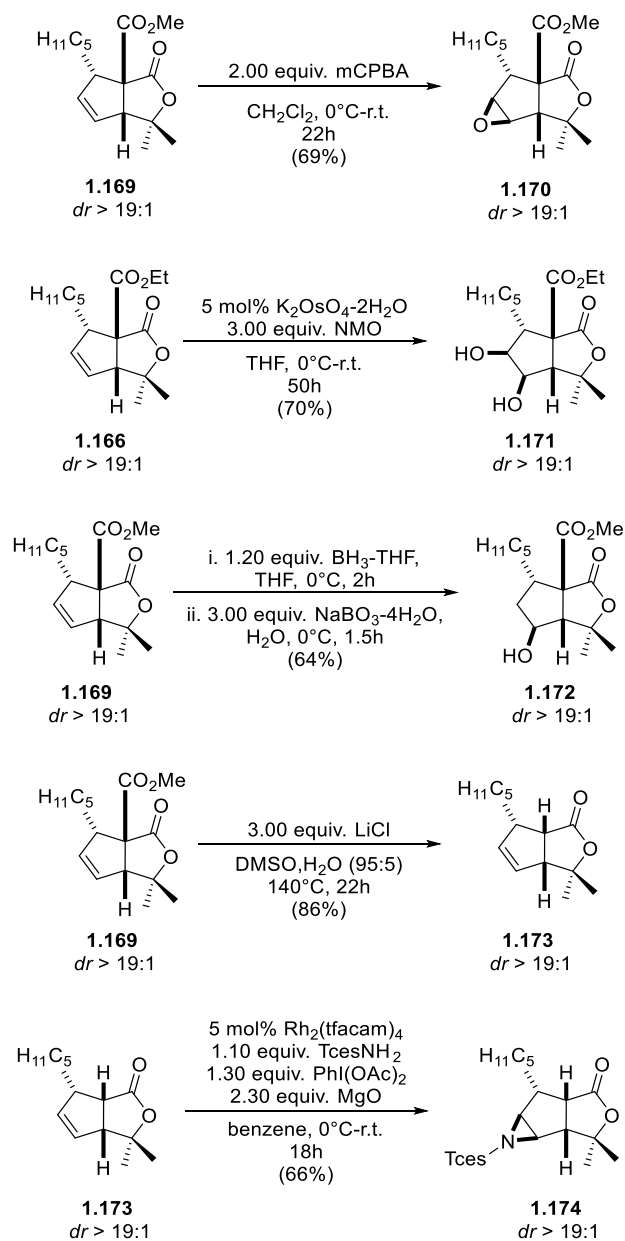
1.2.1. Conclusions and Future Directions

This work identified conditions to expand the scope of Au(I) catalyzed allene cycloisomerizations to include highly substituted, stereochemically complex allene substrates. A variety of substituted allenes have been shown to undergo cycloisomerization to provide bicyclic

cyclopentene products in moderate to good diastereoselectivity in favor of the *anti* diastereomer. Additionally, a stereochemical model has been developed to describe how varying degrees of substitution on the allene impact the stereochemical outcome of the 5-*endo*-trig cycloisomerization. Interestingly, the identity of the Lewis acid additive can be leveraged to promote 5-*endo*-trig cycloisomerization with preference for the *syn* diastereomer. The highly convex nature of the bicyclic cyclopentene product was further utilized to generate a series of highly substituted cyclopentane motifs in good *dr*, highlighting the potential use of this methodology to prepare complex natural product and pharmaceutical scaffolds from easily obtained allene precursors.

While exploring potential synthetic routes to bilobalide (**1.1**, Figure 1.1), two shortfalls of the described Au(I) cycloisomerization methodology were observed (Scheme 1.26). Disubstituted allene **1.175**, which bears additional alkyl substitution at the ring junction, failed to undergo cycloisomerization to cyclopentene **1.176** under the optimized reaction conditions. Several steric and electronic modifications to the ligand on Au also failed to provide conversion of **1.175** to **1.176**. Surprisingly, terminal allene **1.177** also failed to yield cyclopentene **1.178** when subjected to the optimized conditions. In order to facilitate the development of a synthetic route to bilobalide and related analogs, a new conditions to promote the cycloisomerization of allenes **1.175** and **1.177** needed to be developed.

Scheme 1.26. Challenging cycloisomerization substrates.
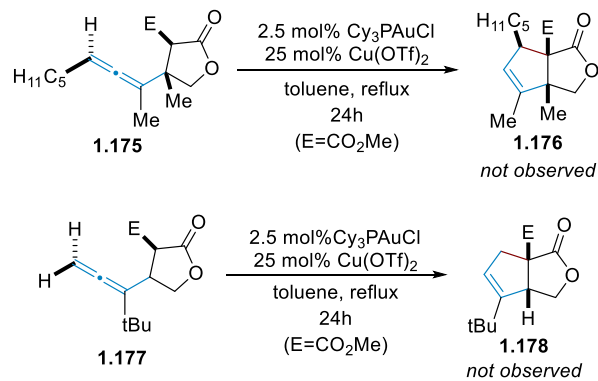
1.3. Experimental Procedures for Au(I)-Catalyzed Cycloisomerizations

1.3.1. General Experimental Information

All glassware was either oven dried at 130 °C or flame dried under vacuum and purged with nitrogen immediately prior to use. Unless otherwise specified, reagents were used as obtained from the supplier without further purification. Ph$_3$PAuCl was obtained from Strem Chemicals; Cy$_3$PAuCl was obtained from Sigma-Aldrich and used without additional purification. Tetrahydrofuran was passed through an alumina column before use or freshly distilled from Na/benzophenone ketyl. Dichloromethane was freshly distilled from calcium hydride or passed through an alumina column before use. Acetonitrile, toluene, and benzene were freshly distilled from calcium hydride immediately prior to use. Other solvents were purified using accepted procedures from the sixth edition of "Purification of Laboratory Chemicals".[52] Air- and moisture-sensitive reactions were performed using standard Schlenk techniques under an inert nitrogen atmosphere. Analytical thin layer chromatography (TLC) was performed using pre-coated silica gel 60 F24 plates containing a fluorescent indicator. Either ceric ammonium molybdate (CAM stain) or KMnO$_4$ were used to visualize the reaction products, unless otherwise specified. Preparative chromatography using a gradient method with mixtures of EtOAc and hexanes, unless

otherwise specified, was performed using SilicaFlash P60 silica gel (230-400 mesh) via Still's method.[53]

^{1}H NMR and ^{13}C NMR spectra were obtained using Bruker Avance-500 spectrometers. Chemical shifts are reported relative to the tetramethylsilane peak (δ 0.00 ppm). Accurate mass measurements were acquired at the University of Wisconsin, Madison, using a Micromass LCT (electrospray ionization or electron impact methods). The NMR and Mass Spectrometry facilities are funded by the NSF (CHE-1048642, CHE-0342998, CHE-9304546 and CHE-9208463), the University of Wisconsin as well as a generous gift by Paul J. Bender.

1.3.2. Experimental Procedures for C-H Insertion Reactions.
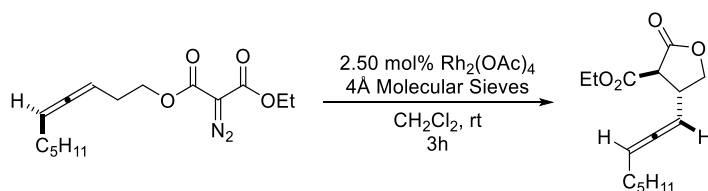
Lactone 1.135. To a stirred solution of 53 mg (0.12 mmol, 0.025 equiv) Rh$_2$(OAc)$_4$ in 47 mL CH$_2$Cl$_2$ was added 4.68 g 4Å molecular sieves. A solution of 1.38 g (4.68 mmol, 1.00 equiv) of the diazoester in 47 mL CH$_2$Cl$_2$ was added dropwise over a period of 3 h via syringe pump. The resulting green suspension was filtered through a pad of celite using additional CH$_2$Cl$_2$ to aid in the transfer, and the volatiles were removed in vacuo to afford crude lactone **1.135**. The crude material was purified on silica gel using a 0-10% gradient of EtOAc in hexanes as eluent to afford 972 mg (3.65 mmol, 78%) of lactone **1.135** as a pale-yellow oil. Characterization data for lactone **1.135** matches that which has been previously published.
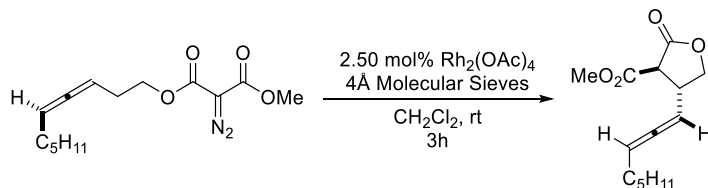
Lactone 1.146. To a stirred solution of 40 mg (0.09 mmol, 0.025 equiv) Rh$_2$(OAc)$_4$ in 36 mL CH$_2$Cl$_2$ was added 3.56 g 4Å molecular sieves. A solution of 998 mg (3.56 mmol, 1.00 equiv) of the diazoester in 36 mL CH$_2$Cl$_2$ was added dropwise over a period of 3 h via syringe pump. The resulting green suspension was filtered through a pad of celite using additional CH$_2$Cl$_2$ to aid in the transfer, and the volatiles were removed in vacuo to afford crude lactone **1.146**. The crude material was purified on silica gel using a 0-10% gradient of EtOAc in hexanes as eluent to afford 772 mg (3.06 mmol, 86%) of lactone **1.146** as a pale-yellow oil. Characterization data for lactone **1.146** matches that which has been previously published.
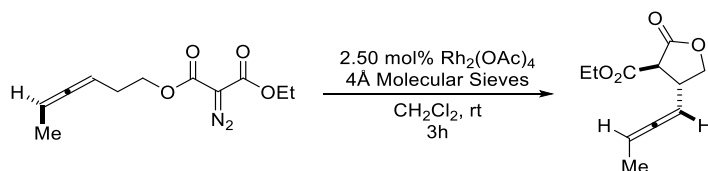
Lactone 1.147. To a stirred solution of 62.0 mg (0.0.14 mmol, 0.025 equiv) Rh$_2$(OAc)$_4$ in 55 mL CH$_2$Cl$_2$ was added 5.50 g 4Å molecular sieves. A solution of 1.25 g (5.50 mmol, 1.00 equiv) of the diazoester in 55 mL CH$_2$Cl$_2$ was added dropwise over a period of 3 h via syringe pump. The resulting green suspension was filtered through a pad of celite using additional CH$_2$Cl$_2$ to aid in the transfer, and the volatiles were removed in vacuo to afford crude lactone **1.147**. The crude material was purified on silica gel using a 0-10% gradient of EtOAc in hexanes as eluent to afford 917 mg (4.67 mmol, 84%) of lactone **1.147** as a pale-yellow oil. Characterization data for lactone **1.147** matches that which has been previously published.
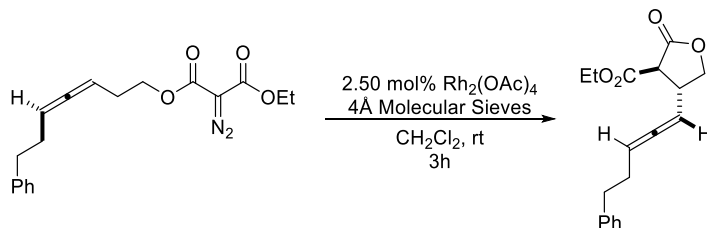
Lactone 1.148. To a stirred solution of 36.0 mg (0.08 mmol, 0.025 equiv) $Rh_2(OAc)_4$ in 33 mL CH_2Cl_2 was added 3.0 g 4Å molecular sieves. A solution of 1.07 g (3.26 mmol, 1.00 equiv) of the diazoester in 33 mL CH_2Cl_2 was added dropwise over a period of 3 h via syringe pump. The resulting green suspension was filtered through a pad of celite using additional CH_2Cl_2 to aid in the transfer, and the volatiles were removed in vacuo to afford crude lactone **1.148**. The crude material was purified on silica gel using a 0-10% gradient of EtOAc in hexanes as eluent to afford 518 mg (1.72 mmol, 53%) of lactone **1.148** as a pale-yellow oil. Characterization data for lactone **1.148** matches that which has been previously published.
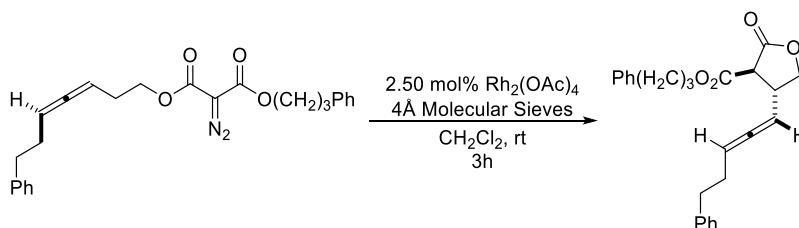
Lactone 1.149. To a stirred solution of 37.1 mg (0.084 mmol, 0.025 equiv) $Rh_2(OAc)_4$ in 33.5 mL CH_2Cl_2 was added 3.35 g 4Å molecular sieves. A solution of 1.40 g (3.35 mmol, 1.00 equiv) of the diazoester in 33.5 mL CH_2Cl_2 was added dropwise over a period of 3 h via syringe pump. The resulting green suspension was filtered through a pad of celite using additional CH_2Cl_2 to aid in the transfer, and the volatiles were removed in vacuo to afford crude lactone **1.149**. The crude material was purified on silica gel using a 0-10% gradient of EtOAc in hexanes as eluent to afford 1.05 g (2.68 mmol, 80%) of lactone **1.149** as a pale-yellow oil. ^{1}H NMR (500 MHz, CDCl$_3$) δ

7.32 – 7.26 (m, 4H), 7.22 – 7.14 (m, 6H), 5.41 – 5.34 (m, 1H), 5.16 (tq, J = 6.3, 3.1 Hz, 1H), 4.38 (ddd, J = 14.3, 8.8, 7.5 Hz, 1H), 4.28 – 4.15 (m, 2H), 3.84 (dt, J = 20.6, 8.6 Hz, 1H), 3.47 – 3.39 (m, 1H), 3.26 (dd, J = 18.8, 9.2 Hz, 1H), 2.75 – 2.66 (m, 4H), 2.45 – 2.27 (m, 2H), 2.04 – 1.96 (m, 2H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 203.81, 203.73, 171.30, 171.25, 167.00, 166.96, 141.04, 141.00, 140.88, 128.51, 128.47, 128.44, 128.41, 128.39, 128.38, 128.29, 126.22, 126.15, 126.07, 94.65, 94.51, 88.94, 88.90, 71.21, 71.11, 65.42, 65.39, 52.12, 51.74, 39.06, 39.02, 34.97, 34.85, 31.92, 31.90, 30.10, 30.08, 29.95. HRMS (ESI) m/z calculated for C$_{25}$H$_{26}$O$_4$ [M + NH$_4$]$^+$ 408.2169, found 408.2166.
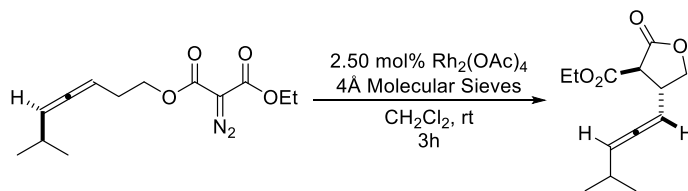
Lactone 1.150. To a stirred solution of 20.8 mg (0.047 mmol, 0.025 equiv) Rh$_2$(OAc)$_4$ in 18.9 mL CH$_2$Cl$_2$ was added 1.89 g 4Å molecular sieves. A solution of 503 mg (1.89 mmol, 1.00 equiv) of the diazoester in 18.9 mL CH$_2$Cl$_2$ was added dropwise over a period of 3 h via syringe pump. The resulting green suspension was filtered through a pad of celite using additional CH$_2$Cl$_2$ to aid in the transfer, and the volatiles were removed in vacuo to afford crude lactone **1.150**. The crude material was purified on silica gel using a 0-10% gradient of EtOAc in hexanes as eluent to afford 242 mg (1.02 mmol, 54%) of lactone **1.150** as a pale-yellow oil. ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.39 (td, J = 6.0, 2.6 Hz, 1H), 5.24 (dtd, J = 7.3, 5.9, 3.1 Hz, 1H), 4.54 (ddd, J = 8.8, 7.5, 5.0 Hz, 1H), 4.30 – 4.24 (m, 2H), 4.04 (ddd, J = 8.9, 7.9, 3.2 Hz, 1H), 3.62 – 3.51 (m, 1H), 3.44 (t, J = 8.6 Hz, 1H), 2.40 – 2.26 (m, 1H), 1.32 (td, J = 7.2, 2.2 Hz, 3H), 1.00 (ddd, J = 6.7, 3.3, 1.3 Hz, 6H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 202.2, 201.9, 171.5, 171.5, 167.1, 167.1, 102.9, 102.7, 90.0, 89.8,

71.5, 71.4, 62.3, 62.2, 52.0, 52.0, 39.5, 39.1, 27.8, 27.7, 22.2, 22.1, 14.1, 14.1. HRMS (ESI) *m/z*

calculated for C$_{13}$H$_{18}$O$_4$ [M + Na]$^+$ 261.1097, found 261.1096.
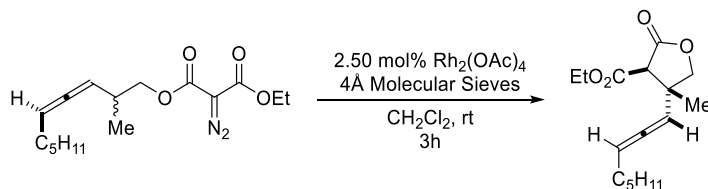
Lactone 1.151. To a stirred solution of 44.0 mg (0.10 mmol, 0.025 equiv) Rh$_2$(OAc)$_4$ in 40 mL

CH$_2$Cl$_2$ was added 4.00 g 4Å molecular sieves. A solution of 1.24 g (4.02 mmol, 1.00 equiv) of

the diazoester in 40 mL CH$_2$Cl$_2$ was added dropwise over a period of 3 h via syringe pump. The

resulting green suspension was filtered through a pad of celite using additional CH$_2$Cl$_2$ to aid in

the transfer, and the volatiles were removed in vacuo to afford crude lactone **1.151**. The crude

material was purified on silica gel using a 0-10% gradient of EtOAc in hexanes as eluent to afford

754 mg (2.69 mmol, 67%) of lactone **1.151** as a pale-yellow oil. Characterization data for lactone

1.151 matches that which has been previously published.
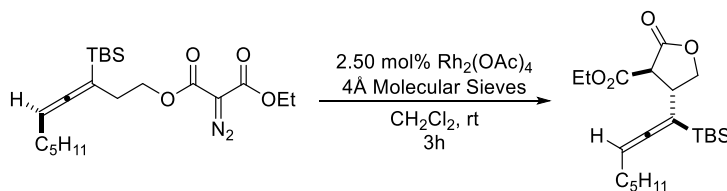
Lactone 1.158. To a stirred solution of 16.8 mg (0.038 mmol, 0.025 equiv) Rh$_2$(OAc)$_4$ in 15.3

mL CH$_2$Cl$_2$ was added 1.53 g 4Å molecular sieves. A solution of 625 mg (1.53 mmol, 1.00 equiv)

of the diazoester in 15.3 mL CH$_2$Cl$_2$ was added dropwise over a period of 3 h via syringe pump.

The resulting green suspension was filtered through a pad of celite using additional CH$_2$Cl$_2$ to aid

in the transfer, and the volatiles were removed in vacuo to afford crude lactone **1.158**. The crude

material was purified on silica gel using a 0-10% gradient of EtOAc in hexanes as eluent to afford

307 mg (0.81 mmol, 53%, 2:1 mixture of diastereomers) of lactone **1.158** as a pale-yellow oil.

Isolated as a 2:1 mixture of diastereomers. ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.13 (td, J = 6.9, 1.7 Hz, 1H), 4.56 – 4.52 (m, 1H), 4.24 (tdd, J = 8.1, 6.7, 1.0 Hz, 2H), 3.89 (td, J = 8.6, 4.2 Hz, 1H), 3.58 (d, J = 9.1 Hz, 1H), 3.49 – 3.40 (m, 1H), 2.02 – 1.96 (m, 2H), 1.37 (dtd, J = 8.6, 6.7, 1.9 Hz, 2H), 1.30 (td, J = 7.1, 3.1 Hz, 7H), 0.97 – 0.92 (m, 3H), 0.89 (overlapping signals, 9H), 0.07 (d, J = 4.6 Hz, 6H). Minor diastereomer: δ 5.07 (td, J = 7.0, 1.6 Hz, 1H), 4.53 – 4.47 (m, 1H), 4.33 – 4.27 (m, 2H), 3.89 (td, J = 8.6, 4.2 Hz, 1H), 3.61 (d, J = 9.8 Hz, 1H), 3.54 – 3.40 (m, 1H), 1.96 – 1.89 (m, 2H), 1.37 (dtd, J = 8.6, 6.7, 1.9 Hz, 2H), 1.30 (tt, J = 8.4, 3.1 Hz, 7H), 0.95 – 0.92 (m, 3H), 0.90 (overlapping signals, 9H), 0.08 – 0.06 (m, 6H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 206.8, 206.7, 171.8, 167.3, 167.3, 93.5, 90.5, 73.5, 73.1, 62.1, 62.0, 52.6, 52.6, 41.0, 40.8, 31.6, 31.5, 31.5, 29.4, 29.3, 28.5, 28.2, 26.7, 26.6, 26.6, 26.5, 26.3, 22.5, 22.5, 22.4, 17.9, 17.7, 14.1, 14.1, 14.0, 14.0, 14.0, -0.0, -5.5, -5.6, -5.7, -5.8. HRMS (ESI) m/z calculated for C$_{21}$H$_{36}$O$_4$Si [M + Na]$^+$ 403.2275, found 403.2275.
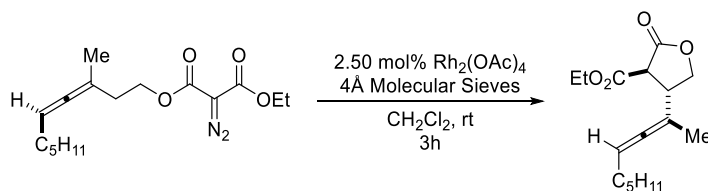
Lactone 1.159. To a stirred solution of 22 mg (0.05 mmol, 0.025 equiv) Rh$_2$(OAc)$_4$ in 21 mL CH$_2$Cl$_2$ was added 2.11 g 4Å molecular sieves. A solution of 651 mg (2.11 mmol, 1.00 equiv) of the diazoester in 21 mL CH$_2$Cl$_2$ was added dropwise over a period of 3 h via syringe pump. The resulting green suspension was filtered through a pad of celite using additional CH$_2$Cl$_2$ to aid in the transfer, and the volatiles were removed in vacuo to afford crude lactone **1.159**. The crude material was purified on silica gel using a 0-10% gradient of EtOAc in hexanes as eluent to afford

345 mg (1.24 mmol, 59%) of lactone **1.159** as a pale-yellow oil. Characterization data for lactone

1.159 matches that which has been previously published.
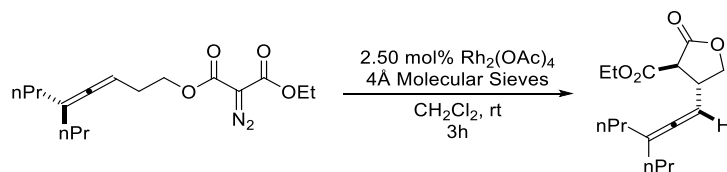
Lactone 1.160. To a stirred solution of 16 mg (0.04 mmol, 0.025 equiv) Rh$_2$(OAc)$_4$ in 14 mL

CH$_2$Cl$_2$ was added 1.41 g 4Å molecular sieves. A solution of 352 mg (1.41 mmol, 1.00 equiv) of

the diazoester in 14 mL CH$_2$Cl$_2$ was added dropwise over a period of 3 h via syringe pump. The

resulting green suspension was filtered through a pad of celite using additional CH$_2$Cl$_2$ to aid in

the transfer, and the volatiles were removed in vacuo to afford crude lactone **1.160**. The crude

material was purified on silica gel using a 0-10% gradient of EtOAc in hexanes as eluent to afford

244 mg (0.87 mmol, 62%) of lactone **1.160** as a pale-yellow oil. Characterization data for lactone

1.160 matches that which has been previously published.
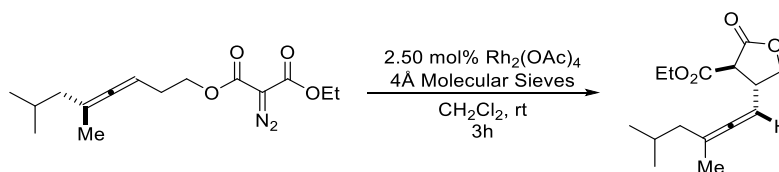
Lactone 1.161. To a stirred solution of 37.6 mg (0.085 mmol, 0.025 equiv) Rh$_2$(OAc)$_4$ in 33.8

mL CH$_2$Cl$_2$ was added 3.38 g 4Å molecular sieves. A solution of 945 mg (3.38 mmol, 1.00 equiv)

of the diazoester in 3.38 mL CH$_2$Cl$_2$ was added dropwise over a period of 3 h via syringe pump.

The resulting green suspension was filtered through a pad of celite using additional CH$_2$Cl$_2$ to aid

in the transfer, and the volatiles were removed in vacuo to afford crude lactone **1.161**. The crude

material was purified on silica gel using a 0-10% gradient of EtOAc in hexanes as eluent to afford

523 mg (1.96 mmol, 58%) of lactone **1.161** as a clear, colorless oil. ¹H NMR (500 MHz, Chloroform-*d*) δ 5.07 (dqd, *J* = 5.5, 2.7, 1.5 Hz, 1H), 4.53 (dd, *J* = 8.8, 7.5 Hz, 1H), 4.26 (qt, *J* = 7.0, 1.9 Hz, 2H), 4.02 (ddd, *J* = 8.8, 7.9, 6.2 Hz, 1H), 3.52 (dddd, *J* = 11.5, 5.8, 3.1, 1.5 Hz, 1H), 3.41 (dd, *J* = 8.9, 0.9 Hz, 1H), 1.91 – 1.79 (m, 2H), 1.71 (ddd, *J* = 13.4, 6.9, 2.3 Hz, 1H), 1.67 (dd, *J* = 2.9, 1.6 Hz, 3H), 1.32 (t, *J* = 7.1 Hz, 3H), 0.92 – 0.87 (m, 6H). ¹³C NMR (126 MHz, CDCl₃) δ 201.8, 201.8, 171.7, 171.6, 167.2, 167.2, 103.2, 103.2, 87.2, 87.0, 71.8, 71.7, 62.2, 62.2, 52.2, 52.2, 43.5, 43.4, 40.1, 39.9, 26.3, 26.2, 22.5, 22.5, 22.5, 19.0, 18.9, 14.1, 14.1. HRMS (ESI) *m/z* calculated for $C_{15}H_{22}O_4$ $[M + Na]^+$ 289.1410, found 289.1407.
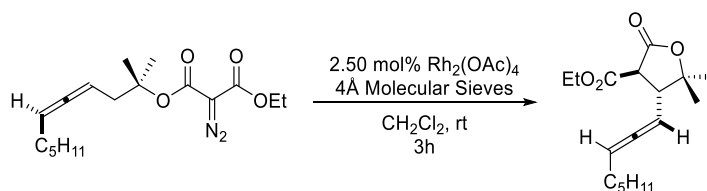
Lactone 1.166. To a stirred solution of 62 mg (0.39 mmol, 0.14 equiv) Rh₂(OAc)₄ in 56 mL CH₂Cl₂ was added 5.64 g 4Å molecular sieves. A solution of 1.82 g (5.64 mmol, 1.00 equiv) of the diazoester in 56 mL CH₂Cl₂ was added dropwise over a period of 3 h via syringe pump. The resulting green suspension was filtered through a pad of celite using additional CH₂Cl₂ to aid in the transfer, and the volatiles were removed in vacuo to afford crude lactone **1.166**. The crude material was purified on silica gel using a 0-10% gradient of EtOAc in hexanes as eluent to afford 1.31 g (4.46 mmol, 79%) of lactone **1.166** as a clear, colorless oil. Characterization data for lactone **1.166** matches that which has been previously published.
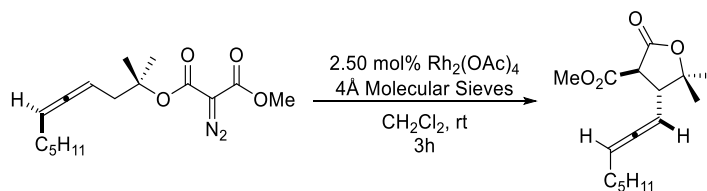
Lactone 1.169. To a stirred solution of 172.4 mg (0.39 mmol, 0.025 equiv) $Rh_2(OAc)_4$ in 157 mL CH_2Cl_2 was added 15.7 g 4Å molecular sieves. A solution of 4.84 g (15.7 mmol, 1.00 equiv) of the diazoester in 157 mL CH_2Cl_2 was added dropwise over a period of 3 h via syringe pump. The resulting green suspension was filtered through a pad of celite using additional CH_2Cl_2 to aid in the transfer, and the volatiles were removed in vacuo to afford crude lactone **1.169**. The crude material was purified on silica gel using a 0-10% gradient of EtOAc in hexanes as eluent to afford 3.00 g (10.7 mmol, 68%) of lactone **1.169** as a clear, colorless oil. ^1H NMR (500 MHz, CDCl$_3$) δ 5.33 (qd, J = 6.7, 2.6 Hz, 1H), 5.06 (tq, J = 6.5, 3.2 Hz, 1H), 3.80 (s, 3H), 3.65 (d, J = 12.5 Hz, 1H), 3.61 (d, J = 12.4 Hz, 1H), 3.34 (dddd, J = 12.5, 9.8, 6.3, 2.6 Hz, 1H), 1.99 (dtdd, J = 15.6, 8.1, 5.0, 2.0 Hz, 2H), 1.52 (s, 3H), 1.43 – 1.34 (m, 1H), 1.34 – 1.26 (overlapping signals, 7H), 0.92 – 0.86 (m, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 204.5, 204.5, 170.2, 170.2, 167.7, 167.7, 94.7, 94.5, 86.2, 86.2, 85.8, 85.7, 52.9, 52.9, 51.6, 51.3, 49.5, 49.3, 31.4, 31.3, 28.7, 28.6, 28.5, 28.5, 27.0, 27.0, 23.2, 23.2, 22.5, 22.5, 14.0, 14.0. HRMS (ESI) m/z calculated for $C_{16}H_{24}O_4$ [M + NH$_4$]$^+$ 298.2013, found 298.2010.

1.3.3. Experimental Procedures for Au(I)-catalyzed Cycloisomerizations.
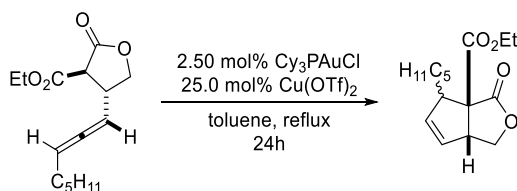
Cyclopentene 1.136. A 10 mL round bottom flask equipped with a reflux condenser was charged with 5.64 mg Cy$_3$PAuCl (0.011 mmol, 0.025 equiv.) and 39.8 mg Cu(OTf)$_2$ (0.11 mmol, 0.25 equiv.) in 2.2 mL dry toluene and allowed to stir for *ca.* 15 minutes at room temperature under N$_2$. To this was added 114.5 mg (0.43 mmol, 1.00 equiv.) of allene **1.135** in 2.1 mL toluene, and the

reaction mixture heated to reflux for 24 h. The resulting dark brown solution was cooled to room temperature and 5 mL saturated aqueous NH4Cl was added. The biphasic solution was stirred at room temperature for 2h, then diluted in EtOAc and washed with additional saturated aqueous NH4Cl, followed by dilute NH4OH, and then brine. The organics were dried over Na2SO4 and the volatiles removed *in vacuo* to afford crude cyclopentene **1.136**. The crude material was purified on silica gel using a 0-10% gradient of EtOAc in hexanes as eluent to afford 72 mg (0.27 mmol, 63% isolated yield) of **1.136** as a yellow oil. ^{1}H NMR (500 MHz, CDCl3), <u>Major diastereomer:</u> δ 5.84 (dt, *J* = 5.5, 2.0 Hz, 1H), 5.53 (dt, *J* = 5.3, 2.3 Hz, 1H), 4.44 (dd, *J* = 8.7, 7.3 Hz, 1H), 4.26 (q, *J* = 6.8 Hz, 2H), 4.17 (dd, *J* = 8.9, 1.8 Hz, 1H), 3.80 (dt, *J* = 7.1, 2.1 Hz, 1H), 3.51 (ddd, *J* = 9.2, 5.4, 2.4 Hz, 1H), 2.01 − 1.92 (m, 1H), 1.48 − 1.17 (m, 10H), 0.96 − 0.82 (m, 3H). <u>Minor diastereomer:</u> δ 5.89 (dt, *J* = 5.3, 2.4 Hz, 1H), 5.63 (dt, *J* = 5.8, 1.5 Hz, 1H), 4.41 (dd, *J* = 9.1, 6.0 Hz, 1H), 4.26 (q, *J* = 6.8 Hz, 2H), 4.23 (m, 1H), 4.02 − 3.94 (m, 1H), 3.37 − 3.27 (m, 1H), 1.58 (dt, *J* = 11.0, 4.2 Hz, 1H), 1.50 − 1.18 (m, 10H), 0.91 − 0.86 (m, 3H). ^{13}C NMR (126 MHz, CDCl3) δ 175.5, 173.1, 169.6, 166.8, 136.3, 136.0, 129.2, 127.5, 70.3, 70.2, 63.8, 62.2, 62.2, 61.7, 53.4, 52.1, 51.4, 49.1, 31.9, 31.8, 31.6, 30.0, 28.4, 26.3, 22.6, 22.5, 14.1, 14.1, 14.0. HRMS (ESI) *m/z* calculated for C15H22O4 [M + H]$^+$ 267.1591, found 267.1595.
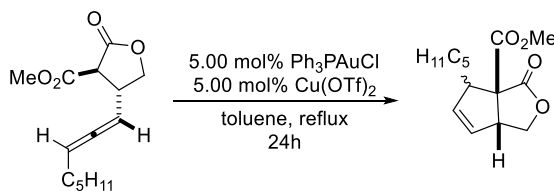
Cyclopentene 1.152. A 25 mL round bottom flask equipped with a reflux condenser was charged with 20.8 mg Ph3PAuCl (0.042 mmol, 0.05 equiv.) and 15.2 mg Cu(OTf)2 (0.042 mmol, 0.05 equiv.) in 4.2 mL dry toluene and allowed to stir for *ca.* 15 minutes at room temperature under N2. To this was added 212 mg (0.84 mmol, 1.00 equiv.) of allene **1.146** in 4.2 mL toluene, and the

reaction mixture heated to reflux for 24 h. The resulting dark brown solution was cooled to room temperature and 9 mL saturated aqueous NH4Cl was added. The biphasic solution was stirred at room temperature for 2h, then diluted in EtOAc and washed with additional saturated aqueous NH4Cl, followed by dilute NH4OH, and then brine. The organics were dried over Na2SO4 and the volatiles removed *in vacuo* to afford crude cyclopentene **1.152**. The crude material was purified on silica gel using a 0-10% gradient of EtOAc in hexanes as eluent to afford 128 mg (0.57 mmol, 68% isolated yield) of **1.152** as a yellow oil. ^{1}H NMR (500 MHz, CDCl3) <u>Major diastereomer:</u> δ 5.85 (dt, $J = 5.8$, 2.0 Hz, 1H), 5.54 (dt, $J = 5.7$, 2.3 Hz, 1H), 4.44 (dd, $J = 9.0$, 7.3 Hz, 1H), 4.16 (dd, $J = 8.9$, 2.0 Hz, 1H), 3.83 – 3.81 (m, 1H), 3.80 (s, 3H), 3.51 (ddt, $J = 9.5$, 5.1, 2.4 Hz, 1H), 2.01 – 1.90 (m, 1H), 1.48 – 1.17 (m, 8H), 0.91 – 0.86 (m, 3H). <u>Minor diastereomer:</u> δ 5.90 (dt, $J = 5.8$, 2.4 Hz, 1H), 5.63 (dt, $J = 5.8$, 1.5 Hz, 1H), 4.43 (s, 1H), 4.24 (d, $J = 9.2$ Hz, 1H), 4.02 – 3.97 (m, 1H), 3.80 (s, 3H), 3.33 (dtd, $J = 9.4$, 3.7, 1.8 Hz, 1H), 1.55 – 1.47 (m, 1H), 1.49 – 1.17 (m, 8H), 0.96 – 0.73 (m, 3H). ^{13}C NMR (126 MHz, CDCl3) δ 175.4, 173.0, 170.2, 167.3, 136.2, 135.9, 129.2, 127.6, 70.3, 70.2, 63.8, 61.6, 53.3, 53.2, 52.9, 52.4, 51.6, 49.1, 31.9, 31.8, 31.7, 30.0, 28.4, 26.4, 22.6, 22.5, 14.1, 13.9. HRMS (ESI) *m/z* calculated for $C_{14}H_{20}O_4$ $[M + NH_4]^+$ 270.1700, found 270.1696.

Cyclopentene 1.153. A 50 mL round bottom flask equipped with a reflux condenser was charged with 23.1 mg Cy3PAuCl (0.045 mmol, 0.025 equiv.) and 162.3 mg Cu(OTf)2 (0.45 mmol, 0.25 equiv.) in 9.0 mL dry toluene and allowed to stir for *ca.* 15 minutes at room temperature under N2. To this was added 353 mg (1.80 mmol, 1.00 equiv.) of allene **1.147** in 9.0 mL toluene, and the

reaction mixture heated to reflux for 24 h. The resulting dark brown solution was cooled to room temperature and 20 mL saturated aqueous NH$_4$Cl was added. The biphasic solution was stirred at room temperature for 2h, then diluted in EtOAc and washed with additional saturated aqueous NH$_4$Cl, followed by dilute NH$_4$OH, and then brine. The organics were dried over Na$_2$SO$_4$ and the volatiles removed *in vacuo* to afford crude cyclopentene **1.153**. The crude material was purified on silica gel using a 0-10% gradient of EtOAc in hexanes as eluent to afford 210 mg (1.08 mmol, 60% isolated yield) of **1.153** as a yellow oil. ^{1}H NMR (500 MHz, CDCl$_3$), <u>Major diastereomer:</u> δ 5.73 – 5.67 (m, 1H), 5.52 (dt, *J* = 4.8, 2.3 Hz, 1H), 4.47 (ddd, *J* = 8.5, 7.3, 0.9 Hz, 1H), 4.16 (ddd, *J* = 8.9, 2.1, 0.8 Hz, 1H), 3.85 (dtd, *J* = 7.3, 2.1, 0.9 Hz, 1H), 3.80 (d, *J* = 1.2 Hz, 3H), 3.69 – 3.61 (m, 1H), 1.30 (dd, *J* = 7.5, 1.3 Hz, 3H). <u>Minor diastereomer:</u> δ 5.81 – 5.78 (m, 1H), 5.58 (dp, *J* = 5.8, 0.9 Hz, 1H), 4.43 (ddd, *J* = 9.2, 5.9, 1.0 Hz, 1H), 4.25 (dd, *J* = 9.2, 0.8 Hz, 1H), 4.03 (ddq, *J* = 5.1, 2.0, 1.0 Hz, 1H), 3.81 (d, *J* = 1.2 Hz, 3H), 3.44 – 3.38 (m, 1H), 1.04 (dd, *J* = 7.1, 1.1 Hz, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 175.3, 172.9, 169.9, 167.3, 137.9, 137.5, 128.3, 127.3, 70.4, 70.3, 64.0, 61.7, 53.2, 53.2, 53.0, 48.6, 47.5, 46.1, 16.8, 15.5. HRMS (ESI) *m/z* calculated for C$_{10}$H$_{12}$O$_4$ [M + H]$^+$ 197.0808, found 197.0808.

Cyclopentene 1.154. A 10 mL round bottom flask equipped with a reflux condenser was charged with 2.00 mg Ph$_3$PAuCl (0.004 mmol, 0.01 equiv.) and 7.23 mg Cu(OTf)$_2$ (0.02 mmol, 0.05 equiv.) in 2.0 mL dry toluene and allowed to stir for *ca.* 15 minutes at room temperature under N$_2$. To this was added 120 mg (0.40 mmol, 1.00 equiv.) of allene **1.148** in 2.0 mL toluene, and the reaction

mixture heated to reflux for 24 h. The resulting dark brown solution was cooled to room temperature and 5 mL saturated aqueous NH_4Cl was added. The biphasic solution was stirred at room temperature for 2h, then diluted in EtOAc and washed with additional saturated aqueous NH_4Cl, followed by dilute NH_4OH, and then brine. The organics were dried over Na_2SO_4 and the volatiles removed *in vacuo* to afford crude cyclopentene **1.154**. The crude material was purified on silica gel using a 0-10% gradient of EtOAc in hexanes as eluent to afford 89 g (0.29 mmol, 72% isolated yield) of **1.154** as a pale-yellow oil. ^{1}H NMR (500 MHz, CDCl$_3$) <u>Major diastereomer:</u> δ 7.30 – 7.21 (m, 3H), 7.21 – 7.11 (m, 2H), 5.82 (dt, *J* = 5.7, 2.0 Hz, 1H), 5.55 (dt, *J* = 5.8, 2.4 Hz, 1H), 4.44 (overlapping t, *J* = 6.4 Hz, 1H), 4.29 – 4.21 (m, 3H), 4.19 (dd, *J* = 8.9, 1.7 Hz, 1H), 3.80 (dt, *J* = 7.1, 2.0 Hz, 1H), 3.57 (ddq, *J* = 8.7, 6.3, 2.3 Hz, 1H), 2.86 – 2.73 (m, 1H), 2.59 (dd, *J* = 9.2, 7.5 Hz, 1H), 2.31 (ddt, *J* = 13.3, 9.8, 6.5 Hz, 1H), 1.75 (dtd, *J* = 13.8, 9.4, 5.7 Hz, 1H), 1.28 (overlapping t, 3H). <u>Minor diastereomer:</u> δ 7.30 – 7.21 (m, 3H), 7.21 – 7.11 (m, 2H), 5.96 (dt, *J* = 5.8, 2.4 Hz, 1H), 5.69 (dt, *J* = 5.8, 1.5 Hz, 1H), 4.44 (overlapping t, *J* = 6.4 Hz, 1H), 4.29 – 4.21 (m, 3H), 4.02 (dt, *J* = 5.8, 2.0 Hz, 1H), 3.41 (ddq, *J* = 9.3, 3.5, 1.8 Hz, 1H), 2.86 – 2.73 (m, 1H), 2.59 (dd, *J* = 9.2, 7.5 Hz, 1H), 1.94 (dtd, *J* = 12.9, 8.6, 8.0, 4.3 Hz, 1H), 1.67 – 1.58 (m, 1H), 1.28 (overlapping t, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 175.3, 173.1, 169.5, 166.7, 141.9, 141.5, 135.9, 135.7, 134.2, 134.1, 129.8, 129.3, 129.2, 128.5, 128.5, 128.3, 128.2, 127.9, 126.0, 125.8, 70.3, 70.1, 63.7, 62.3, 62.3, 61.7, 53.4, 51.9, 50.9, 49.2, 34.9, 33.7, 33.0, 31.9, 14.1, 14.0. HRMS (ESI) *m/z* calculated for C$_{18}$H$_{20}$O$_4$ [M + NH$_4$]$^+$ 318.1700, found 318.1699.

Cyclopentene 1.155. A 25 mL round bottom flask equipped with a reflux condenser was charged with 9.23 mg Cy$_3$PAuCl (0.018 mmol, 0.025 equiv.) and 43.4 mg Cu(OTf)$_2$ (0.12 mmol, 0.25 equiv.) in 3.6 mL dry toluene and allowed to stir for *ca.* 15 minutes at room temperature under N$_2$. To this was added 555 mg (0.71 mmol, 1.00 equiv.) of allene **1.149** in 3.5 mL toluene, and the reaction mixture heated to reflux for 24 h. The resulting dark brown solution was cooled to room temperature and 10 mL saturated aqueous NH$_4$Cl was added. The biphasic solution was stirred at room temperature for 2h, then diluted in EtOAc and washed with additional saturated aqueous NH$_4$Cl, followed by dilute NH$_4$OH, and then brine. The organics were dried over Na$_2$SO$_4$ and the volatiles removed *in vacuo* to afford crude cyclopentene **1.155**. The crude material was purified on silica gel using a 0-10% gradient of EtOAc in hexanes as eluent to afford 180 mg (0.49 mmol, 69% isolated yield) of **1.155** as a pale-yellow oil. ^{1}H NMR (500 MHz, CDCl$_3$) Major diastereomer: δ 7.36 – 7.03 (m, 10H), 5.82 (dt, *J* = 5.8, 2.1 Hz, 1H), 5.55 (dt, *J* = 5.7, 2.4 Hz, 1H), 4.43 (dt, *J* = 9.1, 6.6 Hz, 1H), 4.20 (d, *J* = 2.1 Hz, 2H), 4.20 – 4.15 (m, 1H), 3.78 (dp, *J* = 6.3, 2.1 Hz, 1H), 3.57 (ddq, *J* = 8.6, 6.4, 2.3 Hz, 1H), 2.79 (qdd, *J* = 13.7, 9.7, 6.1 Hz, 1H), 2.68 (td, *J* = 8.2, 7.7, 2.5 Hz, 2H), 2.60 (dd, *J* = 9.7, 7.0 Hz, 1H), 2.33 (ddt, *J* = 13.2, 9.9, 6.5 Hz, 1H), 2.02 – 1.93 (m, 2H), 1.76 (dtd, *J* = 13.8, 9.4, 5.6 Hz, 1H). Minor diastereomer: δ 7.31 – 7.07 (m, 10H), 5.97 (dt, *J* = 5.8, 2.4 Hz, 1H), 5.70 (dt, *J* = 5.9, 1.5 Hz, 1H), 4.43 (dt, *J* = 9.1, 6.6 Hz, 2H), 4.26 (d, *J* = 9.2 Hz, 1H), 4.22 – 4.15 (m, 2H), 4.02 – 3.96 (m, 1H), 3.43 (ddd, *J* = 9.7, 4.1, 2.0 Hz, 1H), 2.79 (qdd, *J* = 13.7, 9.7, 6.1 Hz, 1H), 2.68 (td, *J* = 8.2, 7.7, 2.5 Hz, 2H), 2.60 (dd, *J* = 9.7, 7.0 Hz, 1H), 2.03 – 1.93 (m, 2H), 1.94 – 1.90 (m, 1H), 1.65 – 1.55 (m, 1H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 175.1, 172.9, 169.5, 166.7, 141.8, 141.4, 140.7, 140.7, 135.9, 135.7, 129.8, 128.5, 128.5, 128.5, 128.4, 128.4, 128.3, 128.2, 127.9, 126.1, 126.1, 126.1, 125.9, 70.2, 70.1, 65.4, 65.4, 63.8, 61.7,

53.4, 51.9, 50.9, 49.2, 34.9, 33.8, 33.1, 31.9, 31.9, 30.0, 29.9. HRMS (ESI) *m/z* calculated for

$C_{25}H_{26}O_4$ [M + NH₄]⁺ 408.2169, found 408.2167.

Cyclopentene 1.156. A 10 mL round bottom flask equipped with a reflux condenser was charged

with 3.10 mg Cy₃PAuCl (0.006 mmol, 0.025 equiv.) and 21.7 mg Cu(OTf)₂ (0.06 mmol, 0.25

equiv.) in 1.10 mL dry toluene and allowed to stir for *ca.* 15 minutes at room temperature under

N₂. To this was added 52.4 mg (0.22 mmol, 1.00 equiv.) of allene **1.150** in 1.10 mL toluene, and

the reaction mixture heated to reflux for 24 h. The resulting dark brown solution was cooled to

room temperature and 5 mL saturated aqueous NH₄Cl was added. The biphasic solution was

stirred at room temperature for 2h, then diluted in EtOAc and washed with additional saturated

aqueous NH₄Cl, followed by dilute NH₄OH, and then brine. The organics were dried over Na₂SO₄

and the volatiles removed *in vacuo* to afford crude cyclopentene **1.156**. The crude material was

purified on silica gel using a 0-10% gradient of EtOAc in hexanes as eluent to afford 18 mg (0.08

mmol, 36% isolated yield) of **1.156** as a pale-yellow oil. Isolated as a single diastereomer. ¹H

NMR (500 MHz, CDCl₃) δ 5.91 (dt, *J* = 5.8, 2.0 Hz, 1H), 5.55 (ddd, *J* = 5.9, 2.8, 2.0 Hz, 1H), 4.38

(dd, *J* = 9.0, 7.0 Hz, 1H), 4.27 (q, *J* = 7.1 Hz, 2H), 4.18 (dd, *J* = 9.0, 1.7 Hz, 1H), 3.74 (dt, *J* = 7.0,

2.1 Hz, 1H), 3.38 (ddt, *J* = 8.5, 4.5, 2.1 Hz, 1H), 2.18 (dp, *J* = 8.6, 6.7 Hz, 1H), 1.30 (t, *J* = 7.2 Hz,

3H), 1.08 (d, *J* = 6.6 Hz, 3H), 0.95 (d, *J* = 6.6 Hz, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 173.2,

170.3, 135.1, 127.7, 69.4, 62.2, 62.2, 59.0, 54.4, 27.5, 23.0, 21.2, 14.1. HRMS (ESI) *m/z* calculated

for $C_{13}H_{18}O_4$ [M + H]⁺ 239.1278, found 239.1274.
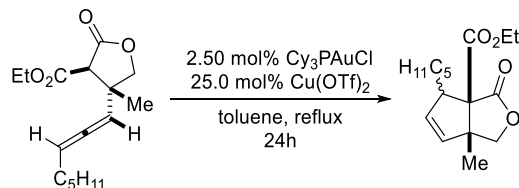
Cyclopentene 1.157. A 25 mL round bottom flask equipped with a reflux condenser was charged with 17.4 mg Cy$_3$PAuCl (0.034 mmol, 0.025 equiv.) and 123 mg Cu(OTf)$_2$ (0.34 mmol, 0.25 equiv.) in 6.6 mL dry toluene and allowed to stir for *ca.* 15 minutes at room temperature under N$_2$. To this was added 378 mg (1.35 mmol, 1.00 equiv.) of allene **1.151** in 6.5 mL toluene, and the reaction mixture heated to reflux for 24 h. The resulting dark brown solution was cooled to room temperature and 15 mL saturated aqueous NH$_4$Cl was added. The biphasic solution was stirred at room temperature for 2h, then diluted in EtOAc and washed with additional saturated aqueous NH$_4$Cl, followed by dilute NH$_4$OH, and then brine. The organics were dried over Na$_2$SO$_4$ and the volatiles removed *in vacuo* to afford crude cyclopentene **1.157**. The crude material was purified on silica gel using a 0-10% gradient of EtOAc in hexanes as eluent to afford 204 mg (0.73 mmol, 54% isolated yield) of **1.157** as a light brown oil. ^{1}H NMR (500 MHz, CDCl$_3$) Major diastereomer: δ 5.75 (dd, *J* = 5.7, 1.6 Hz, 1H), 5.40 (dd, *J* = 5.7, 2.7 Hz, 1H), 4.33 – 4.16 (m, 2H), 4.21 (d, *J* = 8.8 Hz, 1H), 4.05 (d, *J* = 8.8 Hz, 1H), 3.58 (dddd, *J* = 9.2, 6.0, 2.8, 1.7 Hz, 1H), 1.87 (ddt, *J* = 12.7, 8.6, 5.9 Hz, 1H), 1.48 (ddd, *J* = 13.0, 9.2, 5.0 Hz, 1H), 1.44 – 1.38 (m, 1H), 1.36 – 1.26 (m, 8H), 1.12 (s, 3H), 0.92 – 0.85 (m, 3H). Minor diastereomer: δ 5.95 (dd, *J* = 5.7, 2.6 Hz, 1H), 5.52 (dd, *J* = 5.7, 1.3 Hz, 1H), 4.28 (d, *J* = 7.2 Hz, 2H), 4.33 – 4.16 (m, 1H), 4.24 (d, *J* = 7.1 Hz, 1H), 3.27 (dq, *J* = 6.4, 3.4 Hz, 1H), 1.87 (ddt, *J* = 12.7, 8.6, 5.9 Hz, 1H), 1.48 (ddd, *J* = 13.0, 9.2, 5.0 Hz, 1H), 1.44 – 1.38 (m, 2H), 1.36 – 1.26 (m, 8H), 1.12 (s, 3H), 0.92 – 0.85 (m, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 176.8, 173.8, 168.3, 166.6, 135.5, 134.6, 134.3, 132.9, 75.1, 74.5, 64.9,

61.9, 61.5, 58.3, 56.3, 51.9, 49.5, 32.4, 31.9, 31.9, 28.9, 28.6, 27.5, 22.6, 19.4, 17.9, 14.2, 14.2, 14.1, 14.0. HRMS (ESI) *m/z* calculated for $C_{16}H_{24}O_4$ [M + H]$^+$ 281.1747, found 281.1746.
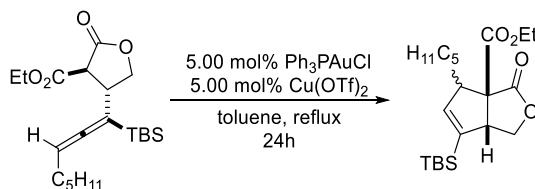
Cyclopentene 1.162. A 10 mL round bottom flask equipped with a reflux condenser was charged with 3.46 mg Ph₃PAuCl (0.007 mmol, 0.05 equiv.) and 2.53 mg Cu(OTf)₂ (0.007 mmol, 0.05 equiv.) in 0.7 mL dry toluene and allowed to stir for *ca.* 15 minutes at room temperature under N₂. To this was added 53.3 mg (0.14 mmol, 1.00 equiv.) of allene **1.158** in 0.7 mL toluene, and the reaction mixture heated to reflux for 24 h. The resulting dark brown solution was cooled to room temperature and 5 mL saturated aqueous NH₄Cl was added. The biphasic solution was stirred at room temperature for 2h, then diluted in EtOAc and washed with additional saturated aqueous NH₄Cl, followed by dilute NH₄OH, and then brine. The organics were dried over Na₂SO₄ and the volatiles removed *in vacuo* to afford crude cyclopentene **1.162**. The crude material was purified on silica gel using a 0-10% gradient of EtOAc in hexanes as eluent to afford 22 mg (0.06 mmol, 42% isolated yield) of **1.162** as a yellow oil. ¹H NMR (500 MHz, CDCl₃) <u>Major diastereomer:</u> δ 6.04 (t, *J* = 1.9 Hz, 1H), 4.47 (dd, *J* = 8.9, 7.8 Hz, 1H), 4.25 (p, *J* = 6.7 Hz, 3H), 4.13 (dd, *J* = 8.9, 3.5 Hz, 1H), 3.90 (ddt, *J* = 7.8, 3.5, 1.6 Hz, 1H), 3.56 (ddt, *J* = 9.5, 5.7, 1.8 Hz, 1H), 1.94 – 1.84 (m, 1H), 1.68 (dtd, *J* = 8.3, 6.2, 2.1 Hz, 1H), 1.49 – 1.38 (m, 2H), 1.36 – 1.24 (m, 5H), 0.90 – 0.88 (m, 4H), 0.87 (s, 9H), 0.07 (d, *J* = 6.2 Hz, 6H). <u>Minor diastereomer:</u> δ 6.09 (t, *J* = 2.3 Hz, 1H), 4.42 (dd, *J* = 9.3, 5.9 Hz, 1H), 4.32 – 4.25 (m, 3H), 4.03 (ddt, *J* = 6.3, 2.0, 1.0 Hz, 1H), 3.63 – 3.57 (m, 1H), 2.03 – 1.94 (m, 1H), 1.68 (dtd, *J* = 8.3, 6.2, 2.1 Hz, 1H), 1.46 – 1.39 (m, 2H), 1.36 – 1.22 (m, 5H), 0.91 – 0.89 (m, 4H), 0.87 (s, 9H), 0.09 (d, *J* = 7.2 Hz, 6H). ¹³C NMR (126 MHz, CDCl₃)

δ 175.7, 173.4, 170.2, 170.0, 168.0, 147.5, 147.5, 140.6, 139.2, 70.9, 63.0, 62.2, 62.0, 58.5, 53.4, 37.3, 36.1, 31.9, 31.5, 30.5, 28.3, 26.6, 26.3, 23.7, 22.5, 22.5, 22.4, 18.8, 17.1, 16.9, 14.1, 14.1, 14.0, 14.0, 13.9, 1.0, -4.7, -5.6, -5.9, -6.3. HRMS (ESI) *m/z* calculated for $C_{21}H_{36}O_4Si$ [M + H]$^+$ 381.2456, found 381.2455.
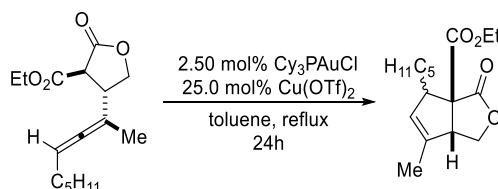
Cyclopentene 1.163. A 10 mL round bottom flask equipped with a reflux condenser was charged with 1.54 mg PCy₃AuCl (0.003 mmol, 0.025 equiv.) and 10.9 mg Cu(OTf)₂ (0.03 mmol, 0.25 equiv.) in 0.6 mL dry toluene and allowed to stir for *ca.* 15 minutes at room temperature under N_2. To this was added 36.4 mg (0.13 mmol, 1.00 equiv.) of allene **1.159** in 0.5 mL toluene, and the reaction mixture heated to reflux for 24 h. The resulting dark brown solution was cooled to room temperature and 5 mL saturated aqueous NH₄Cl was added. The biphasic solution was stirred at room temperature for 2h, then diluted in EtOAc and washed with additional saturated aqueous NH₄Cl, followed by dilute NH₄OH, and then brine. The organics were dried over Na₂SO₄ and the volatiles removed *in vacuo* to afford crude cyclopentene **1.163**. The crude material was purified on silica gel using a 0-10% gradient of EtOAc in hexanes as eluent to afford 12 mg (0.04 mmol, 30% isolated yield) of **1.163** as a brown oil. ^{1}H NMR (500 MHz, CDCl₃), <u>Major diastereomer:</u> δ 5.46 (q, *J* = 1.7 Hz, 1H), 4.41 – 4.19 (m, 4H), 3.61 (dt, *J* = 7.5, 1.8 Hz, 1H), 3.44 (ddd, *J* = 9.8, 5.2, 2.5 Hz, 1H), 1.98 – 1.87 (m,1H), 1.72 (dt, *J* = 2.5, 1.3 Hz, 3H), 1.36 – 1.22 (m, 10H), 0.93 – 0.82 (m, 3H). <u>Minor diastereomer:</u> δ 5.52 (q, *J* = 1.9 Hz, 1H), 4.41 – 4.19 (m, 4H), 3.80 (ddt, *J* = 5.0, 2.7, 1.4 Hz, 1H), 3.24 – 3.18 (m, 1H), 1.97 – 1.88 (m, 1H), 1.76 (q, *J* = 1.4 Hz, 3H), 1.36 – 1.18 (m, 10H), 0.93 – 0.83 (m, 3H). ^{13}C NMR (126 MHz, CDCl₃) δ 175.7, 173.3, 169.7, 167.0,

136.5, 134.9, 130.2, 130.1, 68.1, 68.0, 64.2, 62.1, 62.1, 62.0, 56.0, 51.7, 51.0, 50.6, 31.9, 31.9, 31.8, 30.5, 28.4, 26.3, 22.6, 22.5, 14.1, 14.1, 14.1, 14.0. HRMS (ESI) m/z calculated for $C_{16}H_{24}O_4$ [M + H]$^+$ 281.1747, found 281.1749.
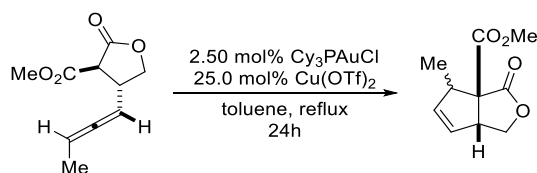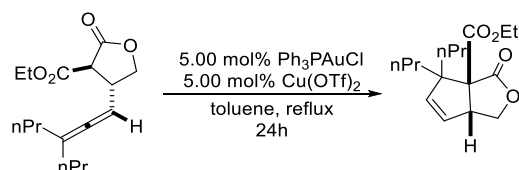

Cyclopentene 1.164. A 10 mL round bottom flask equipped with a reflux condenser was charged with 5.4 mg Ph$_3$PAuCl (0.011 mmol, 0.05 equiv.) and 4.0 mg Cu(OTf)$_2$ (0.011 mmol, 0.05 equiv.) in 1.1 mL dry toluene and allowed to stir for *ca.* 15 minutes at room temperature under N$_2$. To this was added 61.7 mg (0.22 mmol, 1.00 equiv.) of allene **1.160** in 1.1 mL toluene, and the reaction mixture heated to reflux for 24 h. The resulting dark brown solution was cooled to room temperature and 5 mL saturated aqueous NH$_4$Cl was added. The biphasic solution was stirred at room temperature for 2h, then diluted in EtOAc and washed with additional saturated aqueous NH$_4$Cl, followed by dilute NH$_4$OH, and then brine. The organics were dried over Na$_2$SO$_4$ and the volatiles removed *in vacuo* to afford crude cyclopentene **1.164**. The crude material was purified on silica gel using a 0-10% gradient of EtOAc in hexanes as eluent to afford 31 mg (0.11 mmol, 49% isolated yield) of **1.164** as a brown oil. ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.65 (dd, J = 5.9, 2.3 Hz, 1H), 5.56 (dd, J = 5.9, 1.8 Hz, 1H), 4.32 (dd, J = 8.8, 6.5 Hz, 1H), 4.31 – 4.17 (m, 2H), 4.14 (dd, J = 8.8, 1.1 Hz, 1H), 4.04 (dtd, J = 6.6, 2.1, 1.1 Hz, 1H), 1.91 – 1.74 (m, 2H), 1.67 (tqd, J = 12.2, 7.1, 5.0 Hz, 1H), 1.51 – 1.45 (m, 2H), 1.32 (t, J = 7.1 Hz, 3H), 1.29 – 1.16 (m, 2H), 1.15 – 1.03 (m, 1H), 0.93 (t, J = 7.2 Hz, 3H), 0.85 (t, J = 7.2 Hz, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 172.6, 167.6, 139.9, 127.3, 69.2, 66.2, 62.1, 58.4, 50.9, 39.0, 36.8, 18.6, 17.4, 14.9, 14.7, 14.0. HRMS (ESI) m/z calculated for $C_{16}H_{24}O_4$ [M + H]$^+$ 281.1747, found 281.1744.
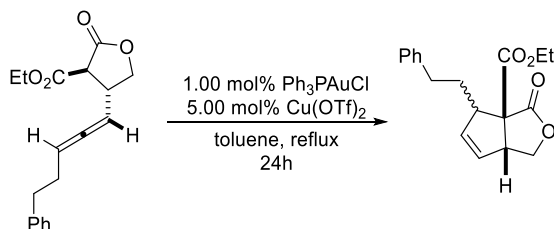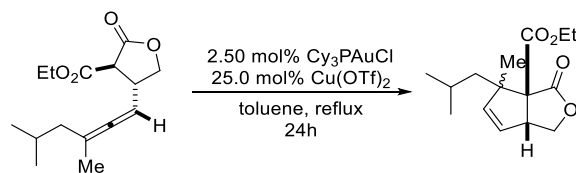
Cyclopentene 1.165. A 10 mL round bottom flask equipped with a reflux condenser was charged with 2.56 mg Cy$_3$PAuCl (0.005 mmol, 0.025 equiv.) and 18.1 mg Cu(OTf)$_2$ (0.05 mmol, 0.25 equiv.) in 1.0 mL dry toluene and allowed to stir for *ca.* 15 minutes at room temperature under N$_2$. To this was added 50.6 mg (0.19 mmol, 1.00 equiv.) of allene **1.161** in 0.9 mL toluene, and the reaction mixture heated to reflux for 24 h. The resulting dark brown solution was cooled to room temperature and 5 mL saturated aqueous NH$_4$Cl was added. The biphasic solution was stirred at room temperature for 2h, then diluted in EtOAc and washed with additional saturated aqueous NH$_4$Cl, followed by dilute NH$_4$OH, and then brine. The organics were dried over Na$_2$SO$_4$ and the volatiles removed *in vacuo* to afford crude cyclopentene **1.165**. The crude material was purified on silica gel using a 0-10% gradient of EtOAc in hexanes as eluent to afford 13 mg (0.05 mmol, 26% isolated yield) of **1.165** as a brown oil. ^{1}H NMR (600 MHz, CDCl$_3$) δ 5.91 (dd, *J* = 5.9, 2.3 Hz, 1H), 5.52 (ddd, *J* = 7.9, 5.8, 1.8 Hz, 1H), 4.30 (dddd, *J* = 16.5, 13.1, 6.9, 1.8 Hz, 2H), 4.15 (dd, *J* = 8.9, 1.1 Hz, 1H), 4.08 – 4.04 (m, 1H), 1.79 – 1.61 (m, 2H), 1.36 – 1.30 (m, 5H), 1.07 (s, 3H), 1.00 (d, *J* = 6.5 Hz, 3H), 0.96 (d, *J* = 6.5 Hz, 3H). Minor diastereomer: δ 5.75 (dd, *J* = 5.8, 2.4 Hz, 1H), 5.52 (ddd, *J* = 7.9, 5.8, 1.8 Hz, 1H), 4.22 (dqd, *J* = 10.8, 7.1, 1.0 Hz, 2H), 4.15 (dd, *J* = 8.9, 1.1 Hz, 1H), 4.09 – 4.04 (m, 1H), 1.80 – 1.62 (m, 2H), 1.48 (s, 3H), 1.36 – 1.29 (m, 5H), 0.92 (d, *J* = 6.7 Hz, 3H), 0.85 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (151 MHz, CDCl$_3$) δ 172.3, 172.1, 167.2, 167.0, 141.5, 140.9, 127.1, 126.9, 68.9, 68.8, 67.0, 66.9, 62.1, 62.0, 54.9, 54.8, 49.7, 48.9, 48.0, 43.0, 25.6, 25.4, 25.2, 25.1, 24.6, 24.6, 23.1, 20.3, 14.1, 14.1. HRMS (ESI) *m/z* calculated for C$_{15}$H$_{22}$O$_4$ [M + H]$^+$ 267.1591, found 267.1588.
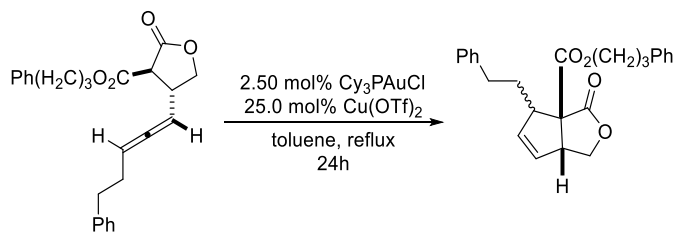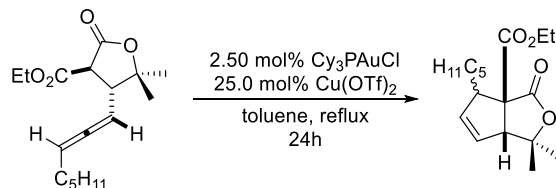
Cyclopentene 1.167. A 50 mL round bottom flask equipped with a reflux condenser was charged

with 27.2 mg Cy₃PAuCl (0.053 mmol, 0.025 equiv.) and 192 mg Cu(OTf)$_2$ (0.53 mmol, 0.25

equiv.) in 10.5 mL dry toluene and allowed to stir for *ca.* 15 minutes at room temperature under

N$_2$. To this was added 618 mg (2.10 mmol, 1.00 equiv.) of allene **1.166** in 10.5 mL toluene, and

the reaction mixture heated to reflux for 24 h. The resulting dark brown solution was cooled to

room temperature and 25 mL saturated aqueous NH$_4$Cl was added. The biphasic solution was

stirred at room temperature for 2h, then diluted in EtOAc and washed with additional saturated

aqueous NH$_4$Cl, followed by dilute NH$_4$OH, and then brine. The organics were dried over Na$_2$SO$_4$

and the volatiles removed *in vacuo* to afford crude cyclopentene **1.167**. The crude material was

purified on silica gel using a 0-10% gradient of EtOAc in hexanes as eluent to afford 501 mg (1.70

mmol, 81% isolated yield) of a 6:1 mixture of **1.167** as a brown oil. Partial separation of the major

diastereomer was achieved via purification of the mixture of diastereomers on silica gel using a 0-

20% gradient of Et$_2$O in hexanes to afford 370 mg of the major diastereomer in >19:1 *dr*. ^{1}H NMR

(500 MHz, CDCl$_3$), <u>Major diastereomer:</u> δ 5.83 (dt, *J* = 5.8, 2.1 Hz, 1H), 5.54 (dt, *J* = 5.8, 2.4 Hz,

1H), 4.27 (q, *J* = 7.1 Hz, 2H), 3.64 (q, *J* = 2.1 Hz, 1H), 3.45 (ddq, *J* = 9.8, 5.8, 2.1 Hz, 1H), 1.97

(m, 1H), 1.50 (s, 3H), 1.40 (d, *J* = 7.2 Hz, 3H), 1.36 – 1.24 (m, 10H), 0.93 – 0.84 (m, 3H). <u>Minor</u>

<u>diastereomer:</u> δ 5.86 (dt, *J* = 5.9, 2.3 Hz, 1H), 5.65 (dt, *J* = 5.9, 1.7 Hz, 1H), 4.28 (q, *J* = 7.2 Hz,

2H), 3.82 (q, *J* = 2.1 Hz, 1H), 3.36 (dtt, *J* = 10.9, 4.3, 1.9 Hz, 1H), 1.97 (m, 1H), 1.50 (s, 3H), 1.40

(d, *J* = 7.2 Hz, 3H), 1.36 – 1.24 (m, 10H), 0.92 – 0.84 (m, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ

174.8, 171.7, 170.9, 168.5, 135.4, 135.4, 127.4, 125.8, 84.9, 84.0, 65.7, 64.5, 62.5, 62.3, 62.2, 58.6,

53.8, 53.4, 32.1, 31.9, 31.8, 30.8, 29.6, 28.8, 28.1, 26.8, 25.2, 24.9, 22.5, 22.5, 22.5, 14.2, 14.0, 14.0. HRMS (ESI) *m/z* calculated for C$_{17}$H$_{26}$O$_4$ [M + H]$^+$ 295.1904, found 295.1901.
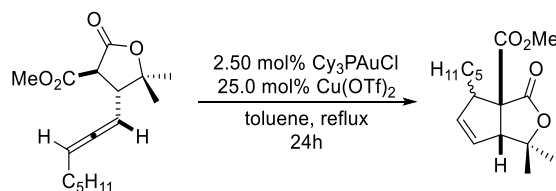
Cyclopentene 1.169. A 250 mL round bottom flask equipped with a reflux condenser was charged with 92.3 mg Cy$_3$PAuCl (0.18 mmol, 0.025 equiv.) and 651 mg Cu(OTf)$_2$ (1.80 mmol, 0.25 equiv.) in 35 mL dry toluene and allowed to stir for *ca.* 15 minutes at room temperature under N$_2$. To this was added 1.98 g (7.06 m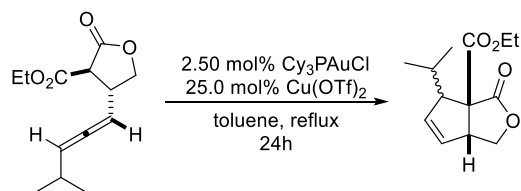mol, 1.00 equiv.) of allene **1.175** in 35 mL toluene, and the reaction mixture heated to reflux for 24 h. The resulting dark brown solution was cooled to room temperature and 100 mL saturated aqueous NH$_4$Cl was added. The biphasic solution was stirred at room temperature for 2h, then diluted in EtOAc and washed with additional saturated aqueous NH$_4$Cl, followed by dilute NH$_4$OH, and then brine. The organics were dried over Na$_2$SO$_4$ and the volatiles removed *in vacuo* to afford crude cyclopentene **1.169**. The crude material was purified on silica gel using a 0-10% gradient of EtOAc in hexanes as eluent to afford 1.67 g (6.00 mmol, 85% isolated yield) of a 6:1 mixture of **1.169** as a brown oil. Partial separation of the major diastereomer was achieved via purification of the mixture of diastereomers on silica gel using a 0-20% gradient of Et$_2$O in hexanes to afford 754 mg of the major diastereomer in >19:1 *dr*. ^{1}H NMR (500 MHz, CDCl$_3$), <u>Major diastereomer:</u> δ 5.84 (dt, *J* = 5.8, 2.1 Hz, 1H), 5.54 (dt, *J* = 5.8, 2.3 Hz, 1H), 3.82 (s, 3H), 3.65 (q, *J* = 2.1 Hz, 1H), 3.47 – 3.40 (m, 1H), 2.02 – 1.93 (m, 1H), 1.49 (s, 3H), 1.44 – 1.37 (m, 1H), 1.34 (s, 3H), 1.33 – 1.24 (m, 4H), 0.88 (tt, *J* = 4.8, 2.5 Hz, 5H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 171.6, 171.5, 135.3, 125.8, 84.0, 64.4, 62.5, 53.6, 53.3, 31.8, 30.8, 29.6, 28.1, 25.2, 22.5, 14.0. HRMS (ESI) *m/z* calculated for C$_{16}$H$_{24}$O$_4$ [M + H]$^+$ 281.1747, found 281.1747.

1.3.4. Experimental Procedures for Olefin Functionalizations.

>20:1 dr
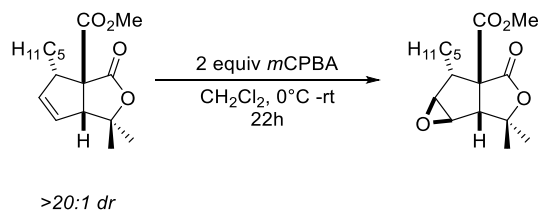
Epoxide 1.170. A 50 mL round bottom flask was charged with 284 mg (1.01 mmol, 1.00 equiv) cyclopentene **1.169** in 10.1 mL CH_2Cl_2 and cooled to 0 °C. A portion of 453 mg (2.02 mmol, 2.00 equiv) ≥77% *m*CPBA (obtained from Sigma Aldrich; used without additional purification) was added slowly in one portion and the resulting solution slowly warmed to room temperature and stirred for 22 h. A 10 mL portion of saturated aqueous $Na_2S_2O_3$ was added and the mixture stirred at room temperature for an additional 30 minutes. The biphasic solution was poured into a separatory funnel containing 25 mL saturated aqueous $NaHCO_3$ and extracted with 3 x 25 mL portions of CH_2Cl_2. The combined organics were dried over Na_2SO_4, and the volatiles removed *in vacuo* to afford the crude epoxide. The crude material was purified via column chromatography using 0-20% EtOAc in hexanes as eluent to give 207 mg (0.70 mmol, 69% yield) epoxide **1.170** as a clear, colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.80 (s, 3H), 3.61 (ddd, *J* = 11.8, 2.7, 1.5 Hz, 2H), 2.97 (d, *J* = 1.7 Hz, 1H), 2.74 (ddd, *J* = 9.6, 5.7, 1.2 Hz, 1H), 2.07 – 1.98 (m, 1H), 1.87 – 1.77 (m, 1H), 1.64 (s, 3H), 1.48 – 1.40 (m, 2H), 1.37 (s, 3H), 1.36 – 1.29 (m, 4H), 0.89 (ddt, *J* = 7.2, 4.3, 2.5 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.4, 170.6, 81.6, 60.0, 59.2, 56.3, 56.2, 53.5, 51.1, 31.7, 28.7, 28.2, 25.6, 25.2, 22.5, 14.0. HRMS (ESI) *m/z* calculated for $C_{16}H_{24}O_5$ [M + H][+] 297.1697, found 297.1692.

>20:1 *dr*
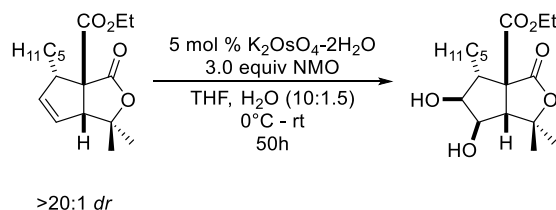
Diol 1.171. A round bottom flask was charged with 56 mg (0.19 mmol, 1.00 equiv) cyclopentene

1.166 in 1.9 mL THF. A portion of 67 mg (0.57 mmol, 3.00 equiv) NMO was added, followed by

0.29 mL of H_2O. The resulting solution was cooled to 0 °C, 3.7 mg (0.01 mmol, 0.05 equiv)

$K_2OsO_4 \cdot 2H_2O$ was added, and the reaction mixture slowly warmed to rt and stirred for 50 h. The

crude reaction mixture was poured into 15 mL H_2O and extracted with 3 x 15 mL portions of

EtOAc. The combined organics were dried over Na_2SO_4 and the volatiles removed *in vacuo*. The

crude material was purified via column chromatography using a 0-50% gradient of EtOAc in

hexanes as eluent to afford 44 mg (0.13 mmol, 70% yield) diol **1.171** as a clear, colorless oil. ^{1}H

NMR (500 MHz, CDCl$_3$) δ 4.34 – 4.23 (m, 2H), 4.20 (q, *J* = 4.3 Hz, 1H), 3.80 (td, *J* = 6.6, 4.2 Hz,

1H), 2.87 – 2.80 (m, 2H), 2.70 (dd, *J* = 19.8, 5.7 Hz, 2H), 1.78 (dddd, *J* = 13.7, 10.6, 6.9, 5.4 Hz,

1H), 1.53 (s, 3H), 1.47 (s, 3H), 1.42 (dddd, *J* = 13.3, 10.4, 6.8, 4.1 Hz, 2H), 1.35 – 1.24 (m, 8H),

0.92 – 0.84 (m, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 171.5, 171.4, 83.1, 77.8, 74.2, 62.9, 62.8,

60.1, 49.0, 32.0, 31.2, 28.5, 27.9, 24.6, 22.5, 14.0, 13.9. HRMS (ESI) *m/z* calculated for $C_{17}H_{28}O_6$

$[M + NH_4]^+$ 346.2224, found 346.2220.

>20:1 *dr*
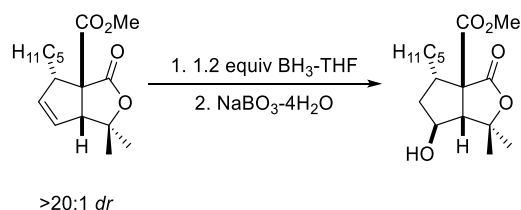
Alcohol 1.172. A 50 mL round bottom flask was charged with 242 mg (0.86 mmol, 1 equiv)

cyclopentene **1.169** in 8.60 mL dry THF and cooled to 0°C. 1.29 mL (1.29 mmol, 1.5 equiv)

BH$_3$·THF was added dropwise and the resulting solution stirred at 0°C for 2h. 400 mg (2.60 mmol, 3.00 equiv) NaBO$_3$·4H$_2$O was added in one portion, followed by 8.60 mL H$_2$O. The resulting suspension was stirred at 0°C for 1.5 hours. The reaction mixture was poured into a separatory funnel containing 50 mL H$_2$O and extracted with 3x50 mL portions of EtOAc. The combined organics were dried over Na$_2$SO$_4$ and the volatiles removed *in vacuo*. Final purification was completed *via* column chromatography using a 0-30% gradient of EtOAc in hexanes to afford 164 mg (0.55 mmol, 64%) alcohol **1.172** as a clear, colorless oil. ^{1}H NMR (500 MHz, CDCl$_3$) δ 4.42 (d, *J* = 4.0 Hz, 1H), 3.81 (s, 3H), 3.09 – 2.97 (m, 1H), 2.87 (t, *J* = 1.3 Hz, 1H), 2.42 (s, 1H), 2.12 – 2.06 (m, 1H), 1.91 – 1.82 (m, 1H), 1.51 (s, 3H), 1.41 (s, 3H), 1.38 (q, *J* = 4.5 Hz, 1H), 1.30 (dtt, *J* = 21.8, 13.7, 3.4 Hz, 7H), 0.88 (q, *J* = 6.4, 4.6 Hz, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 172.1, 171.4, 83.5, 73.2, 64.8, 64.3, 53.2, 45.1, 41.0, 31.9, 31.4, 29.9, 28.5, 24.4, 22.5, 14.0. HRMS (ESI) *m/z* calculated for C$_{16}$H$_{26}$O$_5$ [M + Na]$^+$ 321.1673, found 321.1666.

>20:1 *dr*
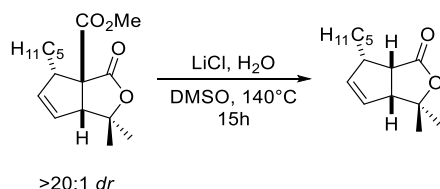
Cyclopentene 1.173. A round bottom flask equipped with a reflux condenser was charged with 292 mg (1.04 mmol, 1.00 equiv) methyl ester **1.169** in 10.4 mL DMSO. A portion of 132 mg (3.12 mmol, 3.00 equiv) LiCl was added, followed by 0.52 mL of H$_2$O. The resulting solution was heated to 140°C for 15 h, cooled to room temperature and poured into a separatory funnel containing 25 mL H$_2$O and extracted with 3 x 25 mL portions EtOAc. The combined organics were washed with brine, dried over Na$_2$SO$_4$, and the volatiles removed *in vacuo*. The crude residue was purified *via* flash chromatography using a 0-10% gradient of EtOAc in hexanes to afford 198 mg (0.89 mmol, 86% yield) decarboxylated product **1.173** as a clear, pale yellow oil. ^{1}H NMR

(500 MHz, CDCl$_3$) δ 5.87 (dt, J = 5.8, 2.0 Hz, 1H), 5.64 (dt, J = 5.8, 2.3 Hz, 1H), 3.33 (t, J = 8.2

Hz, 1H), 3.29 (dq, J = 8.0, 2.4 Hz, 1H), 2.97 (dddd, J = 13.0, 8.6, 5.8, 1.7 Hz, 1H), 1.99 – 1.90 (m,

1H), 1.51 – 1.42 (m, 2H), 1.42 (s, 3H), 1.38 (s, 3H), 1.36 – 1.24 (m, 5H), 0.89 (td, J = 6.0, 5.1, 2.3

Hz, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 176.2, 137.4, 127.3, 83.5, 57.1, 48.3, 46.0, 31.9, 30.2,

29.7, 28.6, 24.5, 22.6, 14.1. HRMS (ESI) m/z calculated for C$_{14}$H$_{22}$O$_2$ [M + H]$^+$ 223.1693, found

223.1691.

>20:1 *dr*
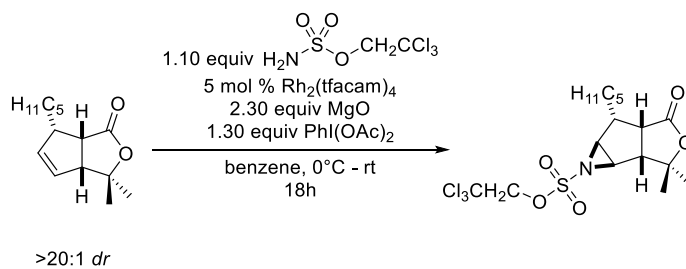
Aziridine 1.174. A portion of 171 mg (0.77 mmol, 1.00 equiv) decarboxylated cyclopentene **5**

was converted to aziridine **1.174** using conditions previously described by DuBois.[51] To a stirred

solution of 194 mg (0.85 mmol, 1.10 equiv.) Tces-NH$_2$ in 1.5 mL benzene was added 171 mg (0.77

mmol, 1.00 equiv.) cyclopentene **1.173**. A portion of 71 mg (1.77 mmol, 2.30 equiv.) MgO was

added, followed by 26 mg (0.04 mmol, 0.05 equiv.) Rh$_2$(tfacam)$_4$. The resulting solution was

cooled to 0°C and 322 mg (1.00 mmol, 1.30 equiv.) PhI(OAc)$_2$ was added in one portion. The

reaction was slowly warmed to room temperature and stirred for an additional 18h, then filtered

through a plug of celite using CH$_2$Cl$_2$ to aid in the transfer. The crude material was purified via

column chromatography using a 0-10% gradient of EtOAc in hexanes (KMnO$_4$ stain) to give 227

mg (0.51 mmol, 66% yield) aziridine as a clear, colorless oil. ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.97

(s, 2H), 4.65 – 4.56 (m, 2H), 3.77 (d, J = 8.6 Hz, 1H), 3.69 (d, J = 8.5 Hz, 1H), 2.14 (ddd, J = 14.1,

11.4, 4.5 Hz, 1H), 1.74 (ddd, J = 16.1, 9.9, 3.5 Hz, 1H), 1.60 – 1.52 (m, 2H), 1.46 (s, 3H), 1.36 (s,

3H), 1.35 – 1.30 (m, 5H), 0.91 – 0.86 (m, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 174.2, 133.8, 133.7,

93.4, 84.1, 78.2, 74.2, 56.6, 55.2, 37.4, 31.8, 30.5, 25.0, 24.5, 22.5, 14.0. HRMS (ESI) *m/z* calculated for $C_{16}H_{24}Cl_3NO_5S$ $[M + H]^+$ 448.0514, found 448.0509.

1.4. Bibliography

1.   (a) Major, R. T. *Science* **1967**, 157, 1270-1273. (b) Weinges, K.; Bähr, W. *Justues Liebigs Ann. Chem.* **1969**, 724, 214. (c) Nakanishi, K.; Habaguchi, K.; Nakadaira, Y.; Woods, M. C.; Maruyama, M.; Majore, R. T.; Alauddin, M.; Patel, A. R.; Weinges, K.; Baher, W. *J. Am. Chem. Soc.* **1971**, 93, 3544-3546.

2.   Chassagne, F.; Huang, X.; Lyles, J. T.; Quave, C. L. *Front. Microbiol.* **2019**, 10, 775, 1-13.

3.   (a) Ude, C.; Schubert-Zsilavecz, M.; Wurglics, M. *Clin. Pharmacokinet.* **2013**, 52, 727-749. (b) van Beek, T. A.; Taylor, L. T. *Phytochem. Anal.* **1996**, 7, 185-191. (c) Wang, J.; Ouyang, J.; Liu, Y.; Jia, X.; He, X.; Di, X. *J. Pharmaceut. Biomed.* **2014**, 95, 238-244.

4.   Li-Jun, Z.; Zhu, X-Z. *Journal of Pharmacology and Experimental Therapeutics* **2000**, 293, 982-988.

5.   Chandrasekaran, K.; Mehrabian, Z.; Spinnewyn, B.; Chinopoulos, C.; Drieu, K.; Fiskum, G. *Cell. Mol. Biol.* **2002**, 48, 663-669.

6.   Lynch, J. W.; Chen, X. *Neuroscience Letters* **2008**, 435, 147-151.

7.   (a) Janssesns, D.; Remacle, J.; Drieu, K.; Michiels, C. *Biochem. Pharmacol.* **1999**, 58, 109-119. (b) Fernandez, F.; Morishita, W.; Zuniga, E.; Nguyen, J.; Blank, M.; Malenka, R. C.; Garner, C. C. *Nat. Neurosci.* **2007**, 10, 411-413.

8.   Defeundis, F. V. *Pharmacol. Res.* **2002**, 46, 565-568.

9. (a) Li-Jun, Z.; Wei, S.; Zhu, X.-Z.; Chen, Z.-L.; Yin, M.-L.; Cheng, X.-F. *Acta Pharmacologica Sinica* **2000**, 1, 75-79. (b) Shi, C.; Wu, F.; Yew, D. T. *Apoptosis* **2010**, 15, 715-727. (c) Shi, C. Wu, F.; Xu, J.; Zhou, J. *Neurochem. Int.* **2011**, 59, 59-64. (d) Shi, C.; Zheng, D.-D.; Wu, F.; Liu, J.; Xu, J. *Neurochem. Res.* **2012**, 37, 298-306. (e) Xie, H.; Wang, J.-R.; Yau, L.-F.; Liu, Y.; Liu, L.; Han, Q.-B.; Zhao, Z.; Jiang, Z.-H. *Molecules* **2014**, 19, 4466-4478.

10. (a) Sandoval-Heras, D.; Avila-Muñoz, E.; Arias, C. *Pharmaceuticals* **2011**, 4, 1070-1087. (b) Awasthi, M.; Singh, S.; Pandey, V. P.; Dwivedi, U. N. *Journal of the Neurological Sciences* **2016**, 361, 256-271. (c) Choi, H.; Koh, S.-H. *J. Alzheimers Dis Parkinsonism* **2016**, 6, 269-270. (d) Kuruva, C. S.; Reddy, P. H. *Drug Disc.* **2017**, 22, 223-233. (e) Hardy, J.; Selkoe, D. J. *Science* **2002**, 297, 353-356. (f) Danysz, W.; Parsons, C. G. *Br. J. Pharmacol.* **2012**, 167, 324-352.

11. Scholtyssek, H.; Damerau, W.; Wessel, R.; Schimke, I. *Chemico-Biological Interactions* **1997**, 106, 183-190.

12. Klein, J.; Wiechel, O.; Hilgert, M.; Rupp, J.; Chatterjee, S. S.; Nawrath, H. *Pharmacopsychiatry* **2003**, 36, S78-S83.

13. Kiewert, C.; Kumar, V.; Hildmann, O.; Rueda, M.; Hartmann, J.; Naik, R. S.; Klein, J. *Brain Res.* **2007**, 1128, 70-78.

14. Corey, E. J.; Su, W.-g. *J. Am. Chem. Soc.* **1987**, 109, 7534-7536.

15. Dolan, S. C.; MacMillan, J. *J. Chem. Soc., Chem. Commun.* **1985**, 1588-1589.

16. Corey, E. J.; Su, W.-g. *Tetrahedron Lett.* **1988**, 29, 3423-3426.

17. (a) Crimmins, M. T.; Jung, D. K.; Gray, J. L. *J. Am. Chem. Soc.* **1992**, 114, 5445-5447. (b) Crimmins, M. T.; Jung, D. K.; Gray, J. L. *J. Am. Chem. Soc.* **1993**, 115, 3146-3155.

18. Emmsermann, J.; Opatz, T. *Eur. J. Org. Chem.* **2017**, 3362-3372.

19. Baker, M. A.; Demoret, R. M.; Ohtawa, M.; Shenvi, R. A. *Nature* **2019**, 575, 643-647.

20. Fernandez-Gonzalez, D. F.; Brand, J. P.; Waser, J. *Chem. -Eur. J.* **2010**, 16, 9457-9461.

21. (a) Gorin, D. J.; Toste, D. F. *Nature* **2007**, 446, 395-403. (b) Toste, F. D.; Campbell, M. J. *Comprehensive Chirality* **2012**, 4, 378-390.

22. Kennedy-Smith, J. J.; Staben, S. T.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, 126, 4526-4527.

23. Conia, J. M.; Le Perchec, P.; *Synthesis* **1975**, 1-19.

24. Yin, Y.; Wang, M.; Wang, J.; Longchang, Z.; Duan, W. *Chin. J. Chem.* **2011**, 29, 2320-2326.

25. Staben, S. T.; Kennedy-Smith, J. J.; Toste, F. D. *Angew. Chem. Int. Ed.* **2004**, 43, 5350-5352.

26. Civjan, N., Ed. *Natural Products in Chemical Biology*; John Wiley & Sons: Hoboken, N.J. **2012**.

27. (a) Heasley, B. *Eur. J. Org. Chem.* **2009**, 1477-1489. (b) Heasley, B. *Curr. Org. Chem.* **2014**, 18, 641-686.

28. Haruta, J.; Nishi, K.; Matsuda, S.; Akai, S.; Tamaura, Y.; Kita, Y. *J. Org. Chem.* **1990**, 55, 4853-4859.

29. Staben, S. T.; Kennedy-Smith, J. j.; Huang, D.; Corkey, B. K.; LaLonde, R. L.; Toste, F. D. *Angew. Chem. Int. Ed.* **2006**, 45, 5991-5994.

30.   Linghu, X.; Kennedy-Smith, J. J.; Toste, F. D. *Angew. Chem. Int. Ed.* **2007**, 46, 7671-7673.

31.   Wang, W.; Hammond, G. B.; Xu, B. *J. Am. Chem. Soc.* **2012**, 134, 5697-5705.

32.   Kumar, M.; Jasinksi, J.; Hammond, G. B.; Xu, B. *Chem. –Eur. J.* **2014**, 20, 3113-3119.

33.   Hashmi, A. S. K., Ed.; Toste, F. D., Ed. *Modern Gold-Catalyzed Synthesis*, Wiley-VCH, Weinheim, **2012**.

34.   Guérinot, A.; Fang, W.; Sircoglou, M.; Bour, C.; Bezzenine-Lafollée, S.; Gandon, V. *Angew. Chem. Int. Ed.* **2013**, 52, 5848-5852.

35.   Fang, W.; Presset, M.; Guérinot, A.; Bour, C.; Bezzenine-Lafollée, S.; Gandon, V. *Chem. -Eur. J.* **2014**, 20, 5439-5446.

36.   Nguyen, R.-V.; Yao, X. Q.; Bohle, D. S.; Li, C.-J. *Org. Lett.* **2005**, 7, 673.

37.   Fang, W.; Presset, M.; Guérinot, A.; Bour, C.; Bezzenine-Lafollée, S.; Gandon, V. *Org. Chem. Front.* **2014**, 1, 608-614.

38.   Jiang, X.; Ma, X.; Zheng, Z.; Ma, S. *Chem. -Eur. J.* **2008**, 14, 8572-8578.

39.   (a) Horns, A.; Escofet, I.; Echavarren, A. M. *Org. Lett.* **2013**, 15, 5782-5785. (b) Zhu, Y.; Day, C. S.; Zhang, L.; Hauser, K. J. Jones, A. C. *Chem. –Eur. J.* **2013**, 19, 12264-12271. (c) Wang, D.; Cai, R.; Sharma, S.; Jirak, J.; Thummanapelli, S. K.; Akhmedov, N. G.; Zhang, H.; Liu, X.; Petersen, J. L.; Shi, X. *J. Am. Chem. Soc.* **2012**, 134, 9012-9019.

40.   Liu, Z.; Wasmuth, A. S.; Nelson, S. G. *J. Am. Chem. Soc.* **2006**, 128, 10352-10353.

41.   Liu, C.; Widenhoefer, R. A. *Org. Lett.* **2007**, 9, 1935-1938.

42. Watanabe, T.; Oishi, S.; Fuiji, N.; Ohno, H. *Org. Lett.* **2007**, 9, 4821-4824.

43. Tarselli, M. A.; Gagné, M. R. *J. Org. Chem.* **2008**, 73, 2439-2441.

44. (a) Weber, D.; Tarselli, M. A.; Gagné, M. R. *Angew. Chem. Int. Ed.* **2009**, 48, 5733-5736. (b) Weber, D.; Gagné, M. R. *Org. Lett.* **2009**, 11, 4692-4695.

45. Transition metal bonding to allenes: (a) Jacobs, T. L.; Landor, S. R., Ed. *The Chemistry of the Allenes, vol. 2*, Academic Press, London, **1982**, pp. 277. (b) Shaw, B. L.; Stringer, A. J. *Inorg. Chim. Acta Rev.* **1973**, 7, 1.

46. Gandon, V.; Lemiére, A. H.; Fensterbank, L.; Malacria, M. *Angew. Chem. Int. Ed.* **2008**, 47, 7534-7538.

47. Brown, T. J.; Sugie, A.; Leed, M. G. D.; Widenhoefer, R. A. *Chem. -Eur. J.* **2012**, 18, 6959-6971.

48. Harris, R. J.; Nakafuku, K.; Widenhoefer, R. A. *Chem. –Eur. J.* **2014**, 20, 12245-12254.

49. Phelps, A. M.; Dolan, N. S.; Connell, N. T.; Schomaker, J. M. *Tetrahedron* **2013**, 69, 5614-5621.

50. Corkey, B. K.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, 127, 17168-17169.

51. Guthikonda, K.; DuBois, J. *J. Am. Chem. Soc.* **2002**, 124, 13672-13673.

52. Armarego, W. L. F.; Chai, C. L. L. Chapter 4 – Purification of Organic Chemicals. In *Purification of Laboratory Chemicals (sixth edition)*, Butterworth-Heinemann: Oxford, 2009; 88-44.

53. Still, W. C.; Kahn, M.; Mitra, A. *J. Am. Chem. Soc.* **1978**, 43, 2923-2925.

Chapter 2

Pd Catalyzed Cycloisomerizations of Allenes

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2.1. Introduction to Pd Catalyzed Reactions of Allenes

Palladium catalysis has received much attention by synthetic chemists over the past five decades. The use of palladium catalysts has allowed for the preparation of molecules in ways not attainable via traditional synthetic methods. Many of these methods catalyzed by Pd are relatively mild, display good functional group compatibility, and proceed with excellent yields. Pd catalyzed C-C bond formations have become particularly valuable to the synthetic community, allowing for the preparation of highly functionalized linear and cyclic carbon frameworks found in a diverse array of pharmaceuticals and natural products. Allenes, molecules that contain two cumulated C-C π bonds, have received considerable attention as three carbon synthons in transition metal catalysis. Methods to form new C-C bonds with allene substrates via Pd catalyzed additions of carbon pronucleophiles and insertions into aryl and vinyl Pd species are discussed here.

2.1.1. Pd catalyzed additions of carbon pronucleophiles to allenes

In 1984, Gore and coworkers extended the Tsuji-Trost reaction[1] to include allene substrates (Scheme 2.1).[2] When treated with catalytic $Pd(PPh_3)_4$ and the sodium enolate of diethyl malonate, allenyl acetate **2.1** was converted to **2.2** in modest yield with significant formation of dimer **2.3** observed. By switching to a phosphonate leaving group, allene **2.4** provided **2.2** in similar yields with a reduction in the formation of dimer **2.3**. The additional alkyl substitution in the tether of allenyl phosphonate **2.5** provided both an increase in the yield of **2.6** and complete suppression of dimer **2.7**.[2]

Scheme 2.1. Pd catalyzed allylic alkylations of allenes.
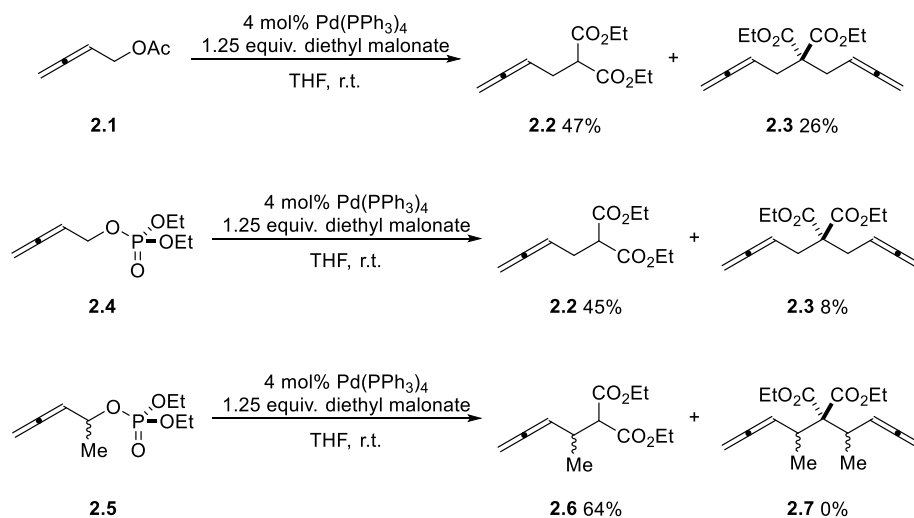
En route to ene-allene substrates, Trost developed a method to convert silyl allenyl acetate **2.8** to **2.9** by way of Pd catalysis (Scheme 2.2).[3] Bromine and carbonate leaving groups proved too reactive under these conditions, resulting in trace **2.9** and significant amounts of the elimination product **2.10**. Acetate leaving groups were found to provide superior yields of **2.9** while reducing the undesired decomposition of **2.8**. The authors noted that preparation of **2.9** via traditional S_N2 methods often resulted in the formation of enyne **2.10** as the major product; Pd catalysis provided the most reliable means to prepare **2.9**.[3]

Scheme 2.2. Allylic alkylations with silyl allenes.
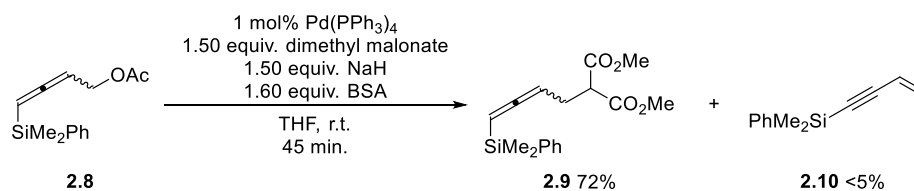
Although several advancements had been made regarding the Pd-catalyzed allylic alkylations of allene substrates,[4] preparation of optically pure allenes via palladium catalysis was limited to hydrosilylation[5] and protonation[6] in the presence of chiral Pd catalysts. Based on

previous reports by Gore,[2] Murahashi and coworkers developed a method to generate chiral allenes from racemic precursors in the presence of a chiral Pd catalyst (Scheme 2.3) in 2002.[7] When (R)-MeOBIPHEP was employed as a ligand, allenyl phosphonate **2.11** was converted to **2.12** in 90% *ee*. Additional modifications to the alkyl substituent were tolerated, however the observed *ee* was typically <90%.[7]

Scheme 2.3. Asymmetric allylic alkylations with phosphonate leaving groups.
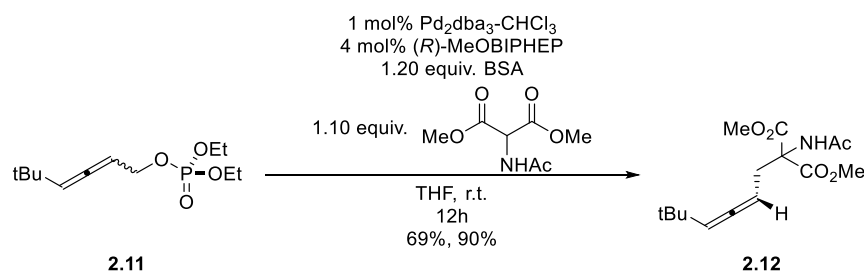
In 2005, Trost and coworkers were able to extend their asymmetric allylic alkylation (AAA)[1e] chemistry to include allene substrates (Scheme 2.4).[8] Allenes featuring benzyl protected tertiary alcohols were found to give the best yield and *ee* of the substrates evaluated, with **2.13** producing **2.15** in 91% yield and 95% *ee*. Alkyl substitution on the allene was well tolerated, as was alkyl substitution on the pronucleophile. Unsubstituted malonate nucleophiles required increased loading to prevent undesired dimerization byproducts.[8]

Scheme 2.4. Asymmetric allylic alkylations with acetate leaving groups.

2.14 (*S*,*S*)-DACH Phenyl
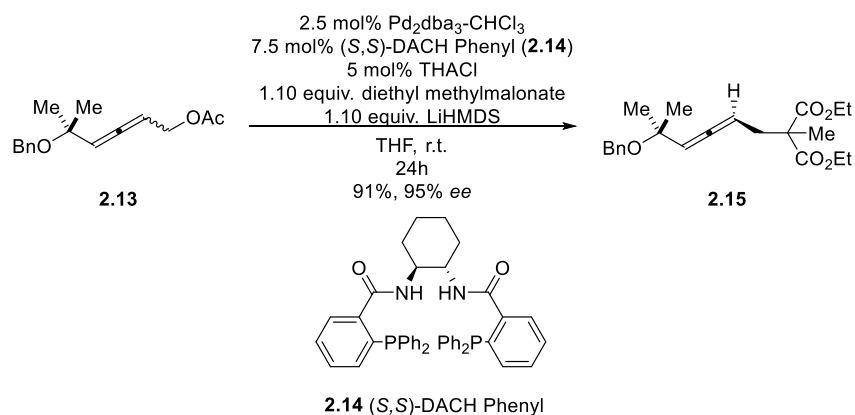
In 2009, the Hamada group was able to translate their AAA conditions[9] to allene substrates (Scheme 2.5) using chiral diaminophosphine oxide (DIAPHOX) preligands.[10,11] When treated with a chiral Pd-DIAPHOX catalyst, allenyl acetate **2.16** was converted to **2.18** in 99% yield and 98% *ee*. Some variation in the identity of the alkyl substituent on the allene was tolerated, providing products in exceptional yields and 66-98% *ee*. The addition of N,O-bis(trimethylsilyl)acetamide (BSA) was required to convert preligand **2.19** to the active trivalent DIAPHOX ligand **2.17**.[9-11]

Scheme 2.5. Chiral DIAPHOX ligands in asymmetric allylic alkylations.
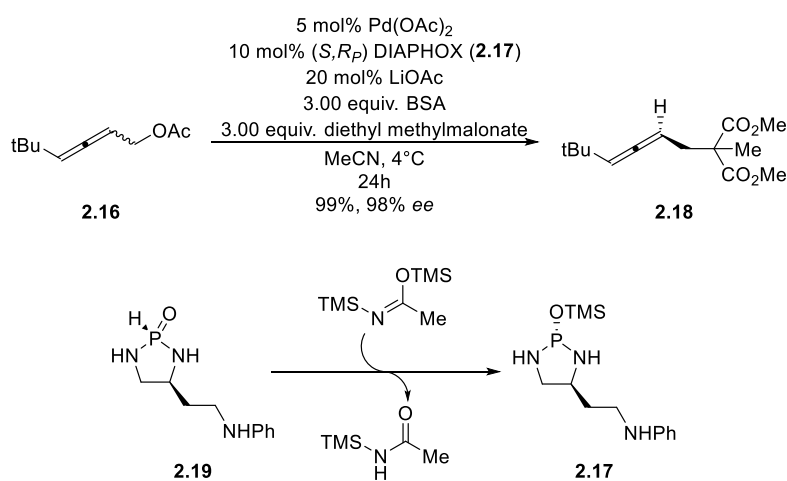
2.1.2. Pd catalyzed additions of carbon pronucleophiles to furnish alkenes

One of the first reports of a Pd catalyzed addition of a malonate pronucleophile to generate olefin-containing products was disclosed by Coulson in 1973 (Scheme **2.6**).[12] Pd(PPh$_3$)$_2$(maleic anhydride) was found to be the optimal catalyst; at elevated temperatures, it was hypothesized that two equivalents of allene **2.20** undergoes dimerization to form palladacycle **2.21**.[12] Protonation of palladacycle **2.21** and nucleophilic attack of the sodium enolate of diethyl malonate resulted in the formation of diene **2.22** in good yield. Additional heating of diene **2.22** results in dimerization in the presence of Pd catalysts.[12]

Scheme 2.6. Allene dimerization and nucleophilic addition with Pd catalysts.
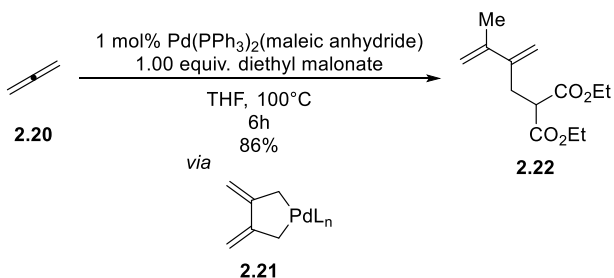
In 1994, Yamamoto and coworkers disclosed the addition of malononitrile pronucleophiles to allenes with Pd catalysts (Scheme **2.7**).[13] When dppb was used as a ligand, Pd$_2$dba$_3$ promoted the nucleophilic addition of methyl malononitrile into benzyl allene **2.23**, furnishing **2.24** in good yields and near perfect *E/Z* ratios. The additional methyl substitution in **2.25** was well tolerated, however the *E/Z* ratio in **2.26** was reduced. The methyl substitution in the pronucleophile was important for suppression of dimerized byproducts.[13] Malononitrile nucleophiles resulted in the conversion of benzyl allene **2.23** to **2.27** in 30% yield; significant amounts of dimer **2.28** were also observed.[13]

Scheme 2.7. Regioselective additions of carbon pronucleophiles to allenes.
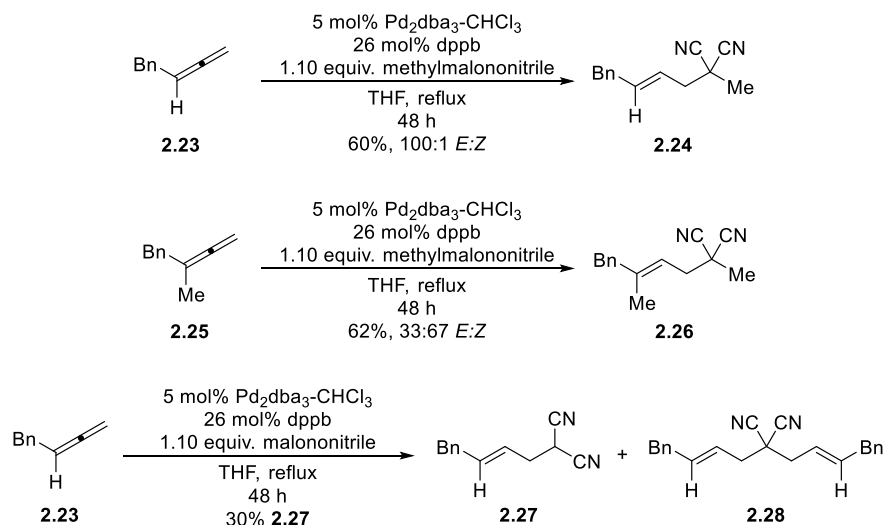
In a follow up report in 1995, Yamamoto and coworkers reported a regioselective process for incorporation of malononitriles into aryl allenes **2.29** (Table 2.1).[14] When subjected to the optimized Pd conditions, phenyl allene (entry 1) produced terminal addition product **2.30** as the major product, with additional products **2.31** and **2.32**, which result from the addition of the malononitrile nucleophile to the internal allene carbon. Introduction of fluorine at the para position of the aryl ring (entry 2) resulted in a switch in regioselectivity; **2.31** was formed in 24% as the major product. Further increases to the electron withdrawing nature of the substituent resulted complete suppression of nucleophilic addition at the terminal carbon (entries 3-4). When an electron-donating *para*-methoxy substituent was employed (entry 5), **2.30** was observed as the only reaction product; no nucleophilic addition at the internal carbon was observed.

Table 2.1. Modulation of allene electronics allows for regiocontrolled nucleophilic additions.

The reaction scheme shows:

5.0 mol% Pd$_2$dba$_3$-CHCl$_3$
26 mol% dppb
1.10 equiv. malononitrile
THF, reflux
48h
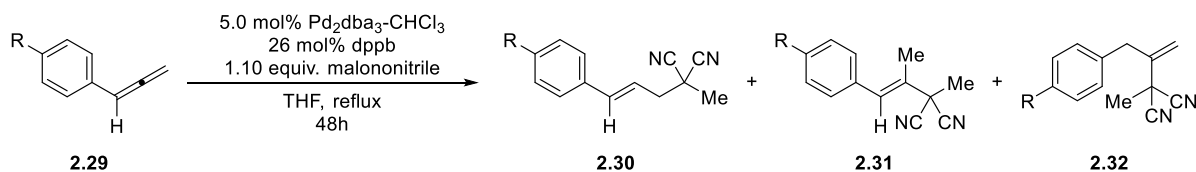
2.29 → **2.30** + **2.31** + **2.32**

Entry	R	2.30	2.31	2.32
1	H	33%	19%	6%
2	F	19%	24%	8%
3	CF$_3$	0%	47%	20%
4	OCF$_3$	0%	68%	16%
5	OMe	85%	0%	0%

Utilizing conditions previously reported by Hata[15] for the addition of carbon nucleophiles to alkenes, the Cazes group was able to show that unactivated allenes were also competent substrates under basic Pd conditions (Table 2.2).[16] Sodium phenoxide in THF (entry 1) resulted in 30% of **2.34**, with 12% addition of the malonate nucleophile at the proximal carbon. Replacing THF with EtOH at lower temperatures (entry 2) resulted in a slight reduction of **2.35**, however the E/Z ratio was also reduced. In the absence of base, conversion of **2.33** to **2.34** took significantly longer (entry 3) with only a slight reduction in the amount of **2.35** formed. Additional β-ketoester pronucleophiles were explored with basic conditions, resulting in the formation of only 25% of the terminal addition product **2.34** (entry 4); the major observed product was dimer **2.36**. After the first addition reaction to form **2.34**, the increased acidity of β-ketoester **2.34** was thought to promote rapid dimerization, thus resulting in **2.36** as the predominant reaction product. In an attempt to slow dimerization, the base loading was decreased (entry 5), resulting in improvements in the yield of **2.34** and suppression of the dimer **2.36**.

Table 2.2. Condition-dependent regiocontrolled addition of carbon pronucleophiles.

Entry	R^1	R^2	Base	Equiv. Base	Solvent	Temp.	Time	2.34 (E:Z)^a	2.35	2.36
1	CO$_2$Et	CO$_2$Et	NaOPh	0.30	THF	130°C	28h	30% (100:0)	12%	0%
2	CO$_2$Et	CO$_2$Et	NaOEt	0.20	EtOH	60°C	28	30% (89:11)	7%	0%
3	CO$_2$Et	CO$_2$Et	--	--	EtOH	80°C	168h	20% (88:12)	5%	0%
4	C(O)Me	CO$_2$Et	NaOEt	0.30	EtOH	60°C	23h	25% (93:7)	11%	46%
5^b	C(O)Me	CO$_2$Et	NaOEt	0.09	EtOH	80°C	32h	50% (91:9)	10%	25%
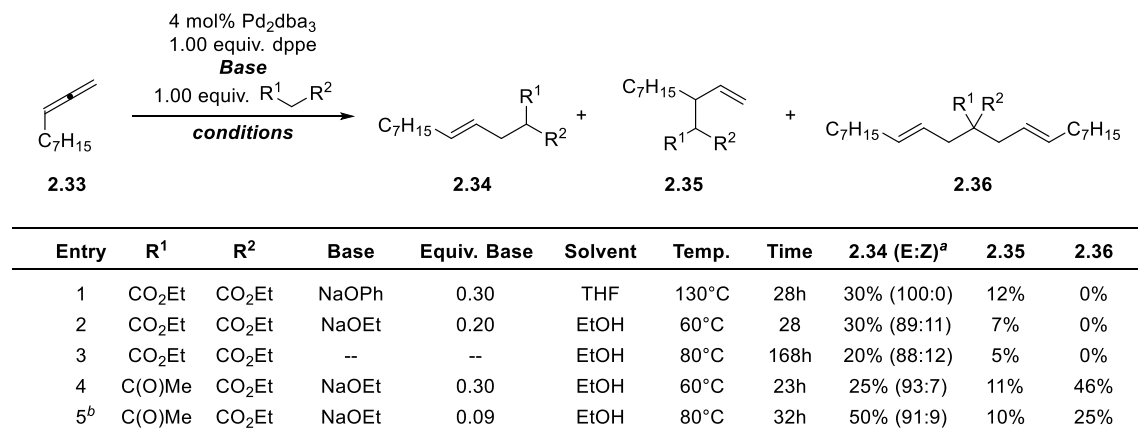
^{a} E:Z ratio expressed as % E isomer : % Z isomer. ^{b} 1.50 equiv. pronucleophlie used.

Further developments by the Trost group in 1995 were focused on expanding the scope of carbon pronucleophiles employed in Pd catalyzed additions to allenes (Scheme 2.8).[17] Allene **2.37**, which bears an unprotected secondary hydroxyl group, furnished **2.38** in 71% yield as a 3:1 mixture of *E/Z* isomers. TBDPS protection of the secondary alcohol resulted in similar yields with near perfect *E/Z* ratios. When Meldrum's acid was utilized as a pronucleophile, dppf ligands were found superior to dmppp, however mono addition products were difficult to obtain. Monosubstituted Meldrum's acid derivatives underwent smooth addition to allene **2.39** in the presence of Pd catalysts, furnishing **2.40** in 72% yield as the *E* isomer. In the absence of a palladium catalyst, derivatives of Meldrum's acid undergo direct S$_N$2 displacement of the iodide functionality in **2.39**.

Scheme 2.8. Pd catalyzed addition of bis-sulfonyl and Meldrum's acid nucleophiles.
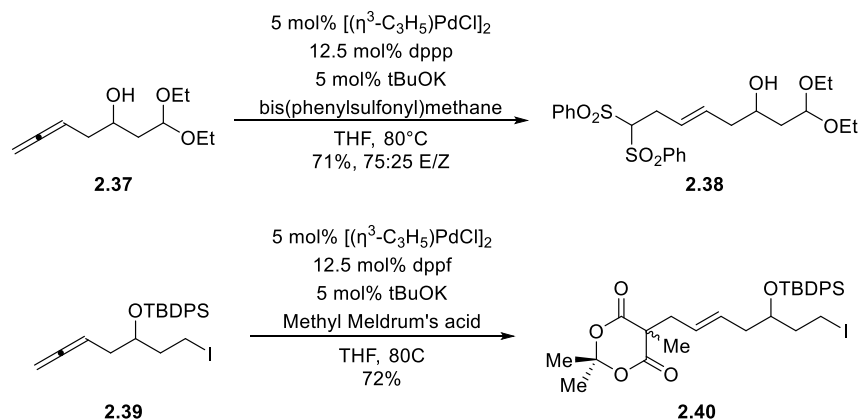
2.1.3. Pd catalyzed cycloisomerizations of allenes

The chemoselectivity observed by the Trost group allowed for the preparation of carbocyclic scaffolds via intramolecular additions of carbon pronucleophiles with Pd catalysts (Scheme 2.9).[17] Iodide **2.39** underwent S_N2 displacement in the presence of bis(benzenesulfonyl) methane, furnishing cycloisomerization precursor **2.41** in 81% yield. Slight modifications to the intermolecular conditions identified dppp as the optimal ligand, resulting in the conversion of **2.41** to **2.42** in 68% yield and 3:1 *dr*. Meldrum's acid was also found to be a competent nucleophile under Trost's cycloisomerization conditions when dppf was employed as a ligand.

Scheme 2.9. Intramolecular additions of bis-sulfonyl carbon pronucleophiles.
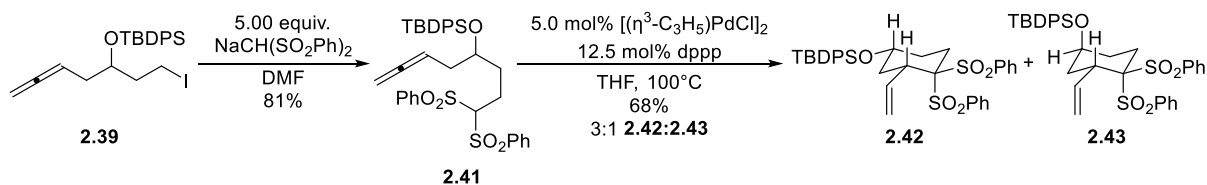
Additional modifications to the identity of the carbon pronucleophile were disclosed in a related publication by Yamamoto and coworkers in 1996 (Scheme 2.10).[18] The basic conditions employed by Trost[17] resulted in the conversion of allene **2.44** to cyclopentane **2.45** in <10% yield.

Interestingly, under neutral conditions with dppf ligands, the conversion of malononitrile **2.44** to cyclopentane **2.45** proceeded in 88% yield. These neutral conditions were also capable of promoting the cycloisomerization of the unsymmetrical pronucleophile **2.46**, resulting in 82% yield of cyclopentane **2.47**. Extension of the carbon tether by one methylene unit to furnish the corresponding cyclohexane products was also described, however the addition of 10 mol% tBuOK was required.[18]

Scheme 2.10. Pd catalyzed allene cycloisomerization to vinyl cyclopentanes.
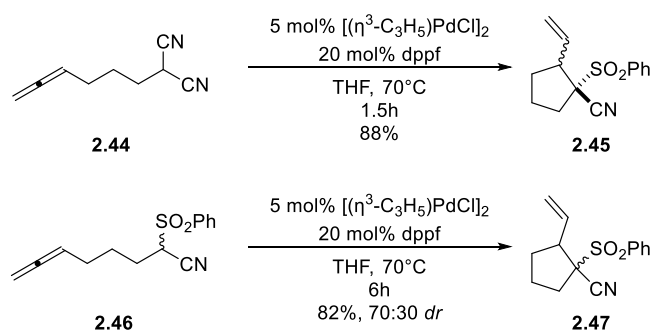
Allene cycloisomerization has also provided a useful entry into macrocyclic frameworks (Scheme 2.11).[19] Previously described conditions for the formation of small rings via Pd catalyzed cycloisomerizations utilizing tBuOK as an additive[17] proved unsuccessful with allene **2.48**,[19] often resulting in trace amounts of the 16-membered macrocycle **2.49**. It was discovered that the addition of catalytic DMAP promoted smooth conversion of **2.48** to **2.49**; the addition of catalytic tBuOK was unnecessary in this system.[19] Interestingly, decreasing the length of the tether in **2.48** by one methylene unit produced the corresponding 15-membered macrocycle in only 28% yield; the addition of 15 mol% AcOH was required for successful cycloisomerization.[19]

Scheme 2.11. Pd catalyzed allene cycloisomerization to afford macrocyclic products.

3 mol% [(η^3-C$_3$H$_5$)PdCl]$_2$
7.5 mol% dppp
15 mol% DMAP
THF, 100°C
67%

SO$_2$Ph
CN
2.48

SO$_2$Ph
CN
2.49
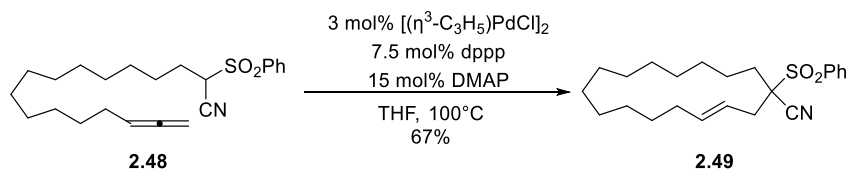
When subjected to the optimized conditions, allene **2.50** can presumably result in the formation of cycloisomerization products **2.52** or **2.54**.[19] Given the thermodynamic preference for the *syn* η^3-Pd-π-allyl-Pd intermediate **2.51**, it was expected that the seven-membered **2.52** would be the predominant cycloisomerization product.[19] Surprisingly, the nine-membered cycloisomerization product **2.54** was the only cycloisomerization product observed.[19]

Scheme 2.12. Seven vs. nine-membered carbocycle formation.

SO$_2$Ph
O
O
2.50

3 mol% [(η^3-C$_3$H$_5$)PdCl]$_2$
7.5 mol% dppp
15 mol% DMAP
THF, 100°C
65% of **2.54**

SO$_2$Ph
PdL$_n$
2.51

PhO$_2$S
O
O
2.52

SO$_2$Ph
PdL$_n$
2.53

SO$_2$Ph
O
O
2.54
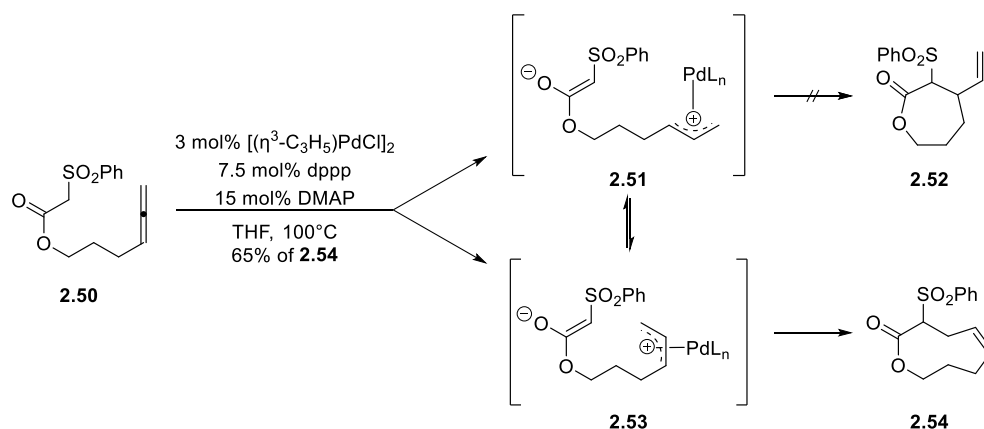
A Pd catalyzed allylic alkylation strategy[20] was employed by Johnson and coworkers to access the macrolactam structure of CGS25155, an inhibitor of neutral endopeptidase enzyme (Scheme 2.13).[21] Conversion of allene **2.55** to allylic acetate **2.56** was carried out in 94% yield, which, when subjected to Pd catalyzed allylic alkylation conditions, produced macrolactam **2.57** in moderate yields.[20] When subjected to Trost's Pd catalyzed macrocyclization conditions, allene **2.58** underwent cycloisomerization to furnish lactam **2.59** in 86% yield.[19] In addition to producing macrolactam **2.59** in higher yields as compared to the allylic alkylation approach,[20] direct

cycloisomerization of **2.58** to **2.59** obviates the need for the use of expensive silver salts in stoichiometric quantities to produce the requisite allylic acetate precursor.[19,20]

Scheme 2.13. Comparison of alkene and allene strategies en route to CGS25155.
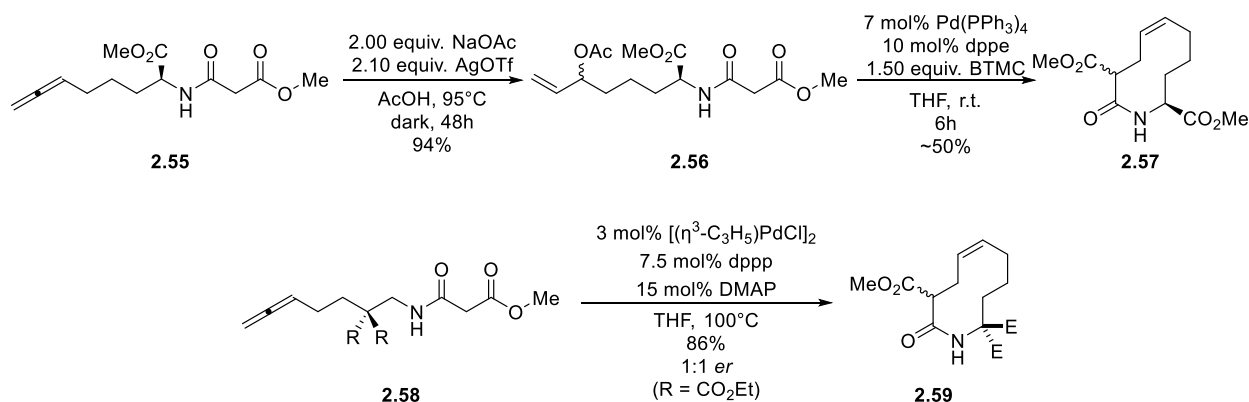
2.1.4. Two plausible mechanisms: carbopalladation and hydropalladation

Two prevailing mechanisms have been hypothesized to describe the Pd catalyzed addition of malonate and related pronucleophiles to allenes; the proposed carbopalladation mechanism is outlined in Scheme 2.14. Oxidative addition of the Pd[0] catalyst into the acidic C-H bond of pronucleophile **2.60** results in the formation of **2.61**. Coordination of the allene **2.62** by **2.61** results in the Pd-allene complex **2.63**, which undergoes carbopalladation to generate the vinyl Pd[II]-H species **2.64**. Reductive elimination of this complex results in adduct **2.65** and regenerates the active Pd[0] catalyst species. Yamamoto and coworkers[13] argue in favor of the carbopalladation mechanism depicted in Scheme 2.14. If a hydropalladation mechanism was operative, the authors hypothesized the formation of byproducts resulting from the reduction of allene **2.23** (Scheme 2.7) by the transient Pd[II]-H species would be detected.[13] These byproducts were not detected under their experimental conditions. Additionally, the reaction between methylmalononitrile and phenylacetylene did not proceed in the presence of Pd[0] catalysts; if a Pd[II]-H species was generated

by the addition of malononitrile derivatives to a Pd^0 catalyst, the reduction of phenylacetylene should occur.[13]

Scheme 2.14. Proposed carbopalladation mechanism.
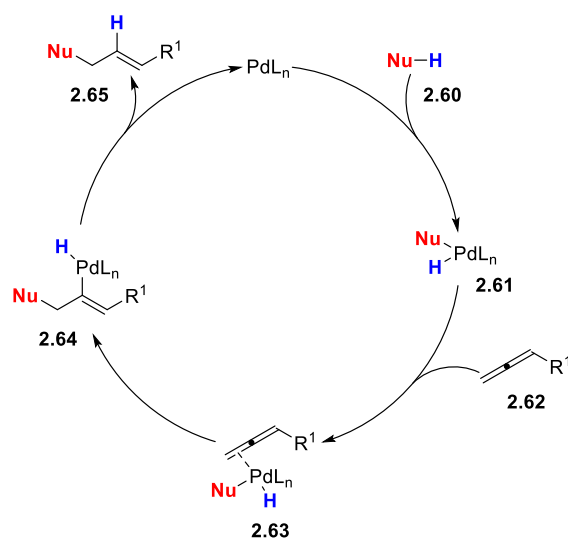
An alternative hypothesis involving an allene hydropalladation process is depicted in Scheme 2.15. Protonation of the Pd^0 catalyst by the acidic C-H bond of the pronucleophile results in Pd^{II}-H intermediate **2.67**. Coordination of the allene **2.61** furnishes Pd-allene complex **2.68**, which undergoes migratory insertion to produce a η^3-Pd-π-allyl species **2.69**. The anionic nucleophile which was generated during formation of Pd^{II}-H intermediate **2.67** attacks η^3-Pd-π-allyl species **2.69**, releasing allylic alkylation product **2.65** and regenerating the catalytic Pd^0 species.

Scheme 2.15. Proposed hydropalladation mechanism.
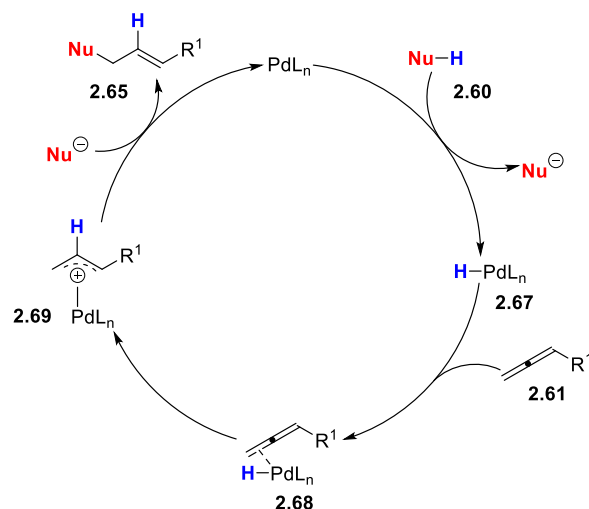
Although direct mechanistic support for the carbopalladation[13] (Scheme 2.14) and hydropalladation (Scheme 2.15) catalytic cycles are somewhat scarce, Trost[17] and others[16] argue in favor of the hydropalladation mechanism based on the olefin geometry obtained in Scheme 2.16. Cyclic allene **2.70** could potentially form Z-**2.72** and E-**2.75** stereoisomers under the reaction conditions.[17] Carbopalladation of **2.70** (pathway A) would result in the formation of vinyl Pd species **2.71**, which leads to Z-**2.72** after a reductive elimination step. Hydropalladation of **2.70** (pathway B) leads to **2.73**, which can be alkylated directly to form E-**2.75**. Alternatively, equilibration of **2.73** to *syn,syn*-**2.74** and subsequent alkylation results in E-**2.75**. When subjected to the experimental conditions, allene **2.70** resulted in the formation of E-**2.75** in 59% yield as the sole stereoisomeric product.[17]

Scheme 2.16. Hydropalladation mechanistic probe.
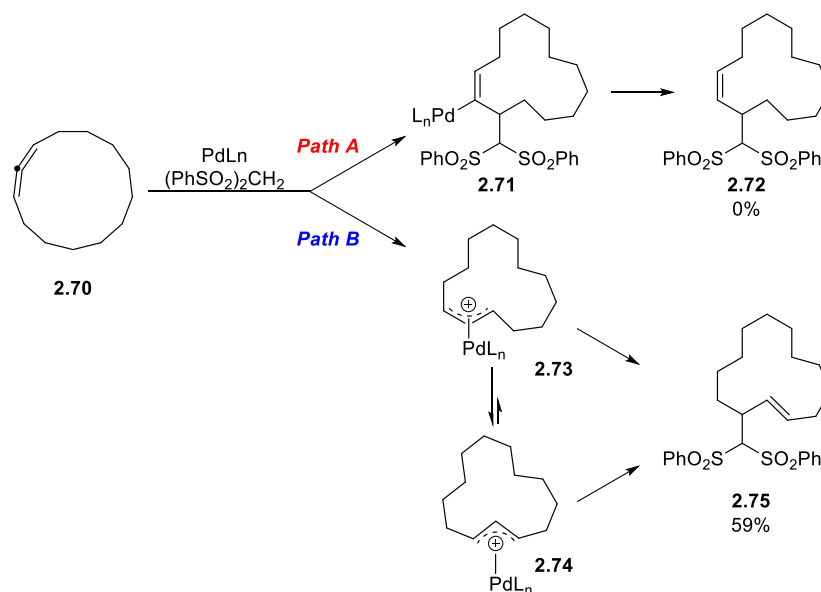
2.1.5. Insertion reactions to generate 1,3-dienes via η^3-Pd-π-allyl intermediates

A considerable amount of work has been devoted to the generation of 1,3-diene species via Pd catalyzed organometallic additions to allenes that proceed through η^3-Pd-π-allyl species.[2-4,7-9] In 1983, Vermeer and coworkers utilized organozinc reagents (Scheme 2.17) to intercept the η^3-Pd-π-allyl generated from allene **2.76** and Pd(PPh3)4, resulting in the functionalized diene **2.77** in 95% yield.[22] Organozinc reagents in the absence of Pd catalysts failed to promote the conversion of **2.76** to **2.77**.[22] The regiochemical outcome of this reaction was controlled by the methoxy group of the allene; no additional regioisomers were observed (cf. section 2.1.1).

Scheme 2.17. Addition of organozinc reagents to a Pd-allene complex.
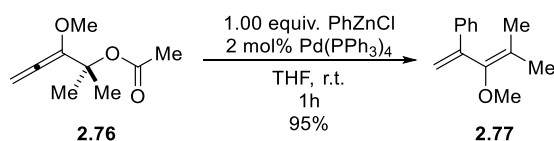
In addition to their work with carbon nucleophiles, the Trost group was interested in creating highly unsaturated molecules from readily available allene precursors with Pd catalysts

(Table 2.3).[23] When Pd(OAc)$_2$ and tris(2,6-dimethoxyphenyl)phosphine (TDMPP, entry 1) were employed, allene **2.78** underwent cross-coupling with phenyl acetylene to form a 3:1 regioisomeric mix of **2.79** and **2.80**. Some degree of catalyst control regarding the regioselectivity of the coupling reaction was achieved when tetrakis(carbomethoxy)-palladacyclopentadiene (TCPC) was used as a Pd source in the presence of tris(2,4,6-trimethoxyphenyl)phosphine (TTMPP) ligands (entry 2). The authors did note that in several cases the substitution pattern on the allene dictated the regiochemical outcome independent of the catalyst system employed; 1,1-disubstituted and 1,1,3-trisubstituted allenes gave exclusively conjugated enoate products, while β,β-disubstituted allenes give the β,γ enoate products exclusively.

Table 2.3. Regioselective allene carbopalladation with alkynes.

Entry	[Pd]	Ligand	% 2.79	% 2.80	2.80 E/Z
1	Pd(OAc)$_2$	TDMPP	42%	13%	3:1
2	TCPC	TTMPP	6%	58%	~1:1

Organoboron compounds were also shown to undergo coupling with allenes in the presence of Pd catalysts (Scheme 2.18).[24] In contrast to previously described conditions for Suzuki-Miyaura cross-couplings,[25] the addition of exogenous base with allene **2.81** was not required. The alkoxide generated upon oxidative addition of carbonate **2.81** to Pd(PPh$_3$)$_4$ results in alkoxo-Pd intermediate **2.82**, which is capable of engaging an arylboronic acid to form **2.83** in high yields.[24] Alkyl substituted 9-BBN derivatives were also effective under the reaction conditions, however yields typically ranged from 30-60%. The addition of K$_3$PO$_4$ and Pd(OAc)$_2$ dramatically accelerated the reaction of allene **2.84** to diene **2.85**.[24]

Scheme 2.18. Cross-coupling of vinyl Pd-alkoxo intermediates with boron reagents.
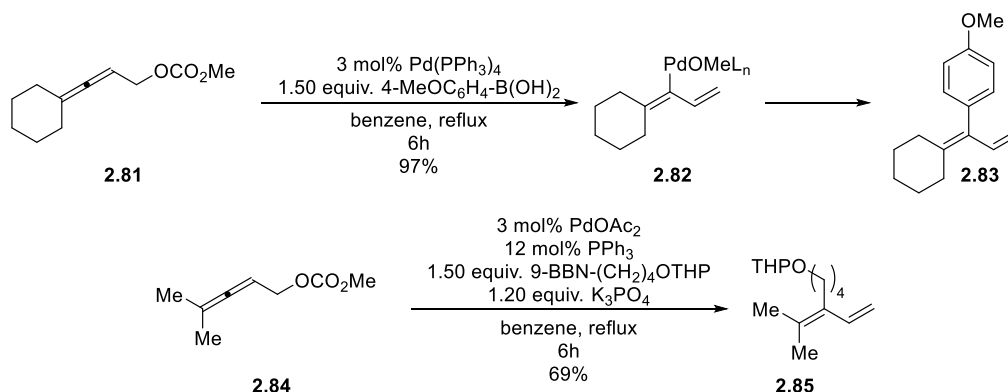
The Negishi group has conducted an extensive investigation into the carbopalladation of alkene substrates to generate carbocyclic frameworks containing 5-8 membered rings.[26] In a report in 1995, they extended this methodology to include allenes as viable substrates (Scheme 2.19).[27] When treated with a Pd[II] catalyst under basic conditions, allenes **2.86** and **2.87** were converted to the five- and seven membered carbocycles **2.87** and **2.89** in moderate yields. These conditions were also effective at generating the nine-membered ring **2.97** from allene **2.90** in 55% yield. Interestingly, the 20-membered macrocycle **2.93** was prepared from allene **2.92** in 86%; alkene substrates provided similar macrocycles in reduced yields. The authors attribute this to the increased reactivity of allenes toward organopalladium species as compared to alkenes, which is most likely a result of the increase in strain energy of allenes relative to alkenes.[28]

Scheme 2.19. Intramolecular carbopalladation strategy to generate macrocyclic frameworks.
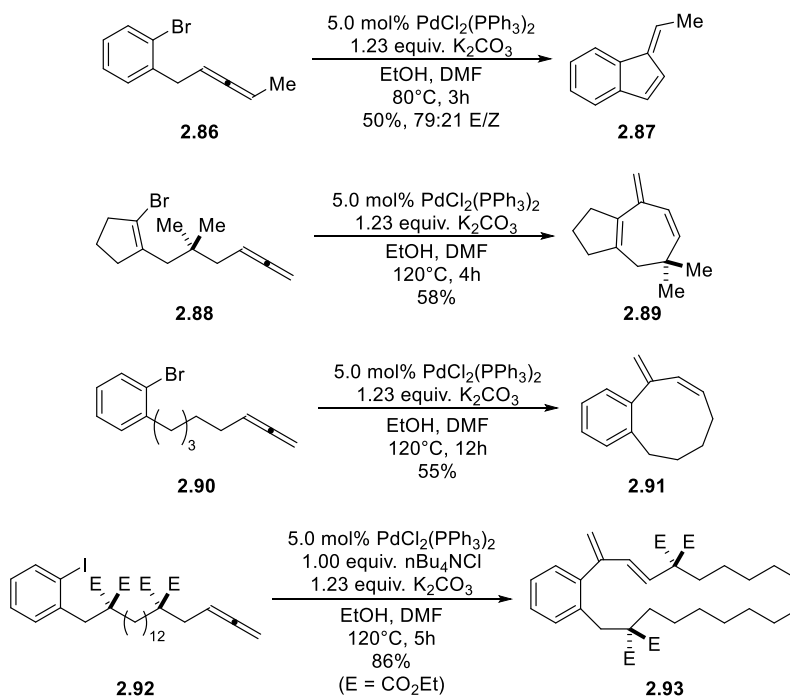
2.1.6. Tandem Pd catalyzed insertion/nucleophilic addition reactions of allenes

The development of Pd catalyzed methods to promote carbon pronucleophile addition and carbopalladations of allene substrates has provided a valuable tool for the preparation of substituted alkene products. Additional investigations into these reactions have allowed for the merger of these two strategies into one synthetic operation, allowing for the preparation of substituted olefin products in a mild, straight-forward manner.

Early efforts to intercept η^3-Pd-π-allyl species generated from carbopalladation of allenes into Pd-aryl and Pd-vinyl species with carbon pronucleophiles was disclosed by Gore and coworkers in 1984 (Scheme 2.20).[29] When treated with a Pd catalyst in the presence of bromobenzene and diethyl malonate, allene **2.33** was converted to **2.94** in 67% yield as a single regioisomer with a 5.7:1 *E/Z* ratio. Gore and coworkers also showed that vinyl halides were capable of undergoing a carbopalladation/nucleophilic addition sequence, with allene **2.33**

furnishing **2.95** in 85% yield as a single stereoisomer. The difference in *E/Z* ratios was attributed to $A^{1,3}$ strain in the η^3-Pd-π-allyl intermediates **2.96** and **2.97**. When R = aryl, only a slight preference for *anti-***2.97** is thought to occur, leading to moderate *E/Z* ratios in the products. When R = vinyl, it was hypothesized that intermediate *anti-***2.97** predominates, leading to alkene products with nearly complete selectivity for the *E* stereoisomer. This method was later extended to include silyl substitution[30] on the vinyl halide coupling partners and α-imino ester pronucleophiles.[31]

Scheme 2.20. Tandem carbopalladation/nucleophilic additions.
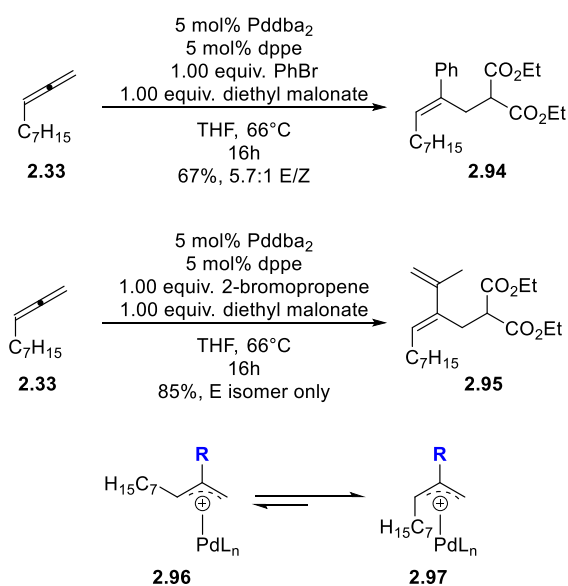
In a follow-up report in 1988, Gore and coworkers evaluated vinyl triflates as coupling partners (Scheme 2.21).[32] At the time of publication, regiocontrolled methods for the preparation of a diverse library of substituted vinyl halides was challenging; alternatively, vinyl triflates could be readily accessed via trapping of an enolate regiospecifically derived from ketones.[33] With slight modifications to their previously reported systems, the conversion of allene **2.33** to **2.98** proceeded in 80% yield and 9:1 *E/Z* ratio. The introduction of LiCl was thought to increase the reactivity of the vinyl Pd species via ligand exchange.[34] It was also noted that by employing DMSO as a

reaction solvent, the yields were typically higher than when THF was used as a solvent. Triflates derived from N-heterocycles were disclosed in 1995.[35]

Scheme 2.21. Carbopalladation with triflate sources.
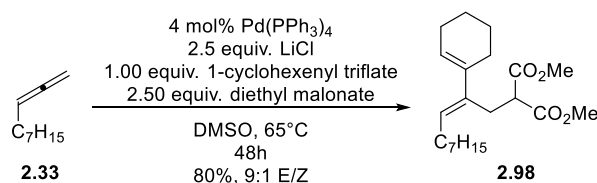
In addition to the identity of the coupling partner employed,[29-31] the nature of the substitution on the allene also has an influential effect on the regiochemical outcome of the reaction (Scheme 2.22).[36]   Gore and coworkers hypothesized that the β-silicon effect may promote nucleophilic attack at the substituted allene carbon as opposed to the terminal carbon as observed in their previous investigations. When subjected to the Pd reaction conditions, allene **2.99** furnished **2.100** as a single regioisomer in 47% yield. They concluded that the neopentyl character of this substrate played a major role in the regiochemical outcome; the β-silicon effect did not seem to influence the regiochemistry.[36]   Aromatic substituents typically gave 10:1 mixes of regioisomers, again favoring nucleophilic attack at the unsubstituted carbon. When methoxyallene **2.101** was subjected to the Pd conditions, **2.102** was obtained in 94% yield as the sole regioisomer observed. Stabilization of the positive charge in the η^3-Pd-π allyl intermediate by the methoxy group renders the more substituted carbon more electrophilic.[36]

Scheme 2.22. Regiocontrolled carbopalladation/nucleophilic additions.
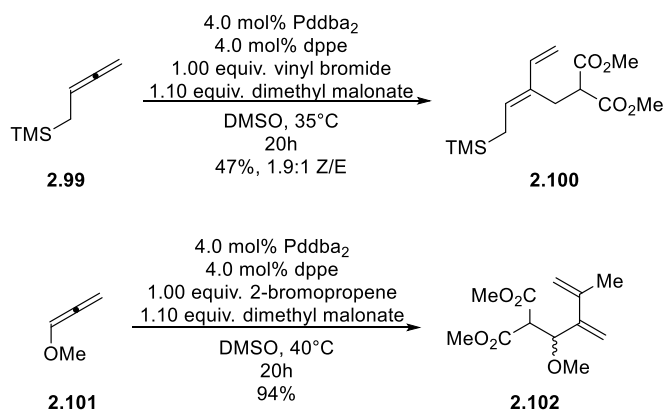
Alkynes were also shown to undergo an allene carbopalladation/nucleophilic addition sequence (Scheme 2.23) by Gore and coworkers, with allene **2.33** resulting in 30% **2.103** as the *Z* isomer only.[37]   Additionally, a carbopalladation/nucleophilic addition approach was utilized by Gore to prepare diene **2.104** from allene **2.20** en route to the steroidal framework **2.105**.[38]   When heated to 90°C in the presence of TMSOTf, **2.104** was converted to **2.105** in 90% yield.[38]

Scheme 2.23. Additional tandem carbopalladations/nucleophilic additions described by Gore.
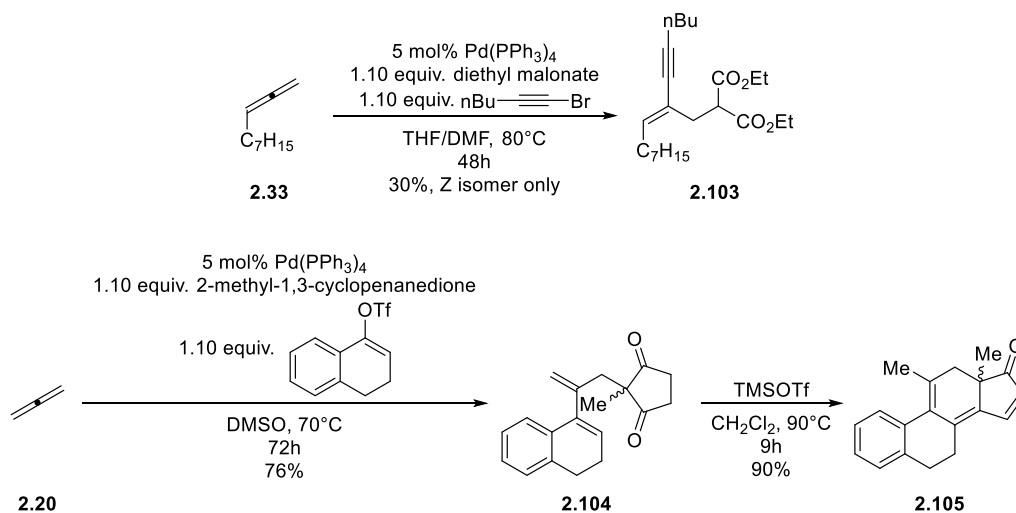
In 1998, Hiroi and coworkers disclosed an asymmetric addition of a malonate nucleophile to an η³-Pd-π-allyl complex generated from an allene (Scheme 2.24).[39]   The chiral phosphine

ligand (+)-MOD-DIOP was found to give the best enantioselectivity in the conversion of racemic

allene **2.106** to **2.107**. Additional ligand provided increases in the *ee* of the reaction at the expense

of reaction yield. Although this method could provide enantioenriched products from racemic

starting materials, the authors also disclosed the observation that axially chiral allenes react with

complete transfer of chirality to the products.[39]

Scheme 2.24. Asymmetric tandem carbopalladation/nucleophilic additions of allenes.
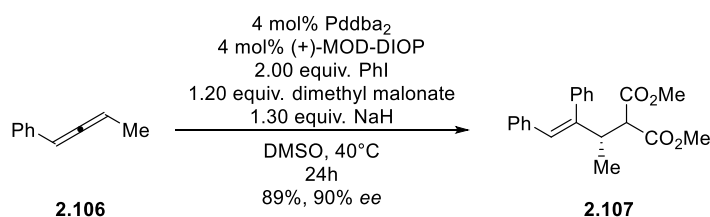
2.1.7. Tandem Pd catalyzed insertion/cycloisomerization reactions of allenes

Carbopalladations/nucleophilic additions with allene substrates featuring a tethered

pronucleophile has also been a valuable strategy for the preparation of cyclic products. Based on

their previous work with nucleophilic additions and carbopalladations of allenes, Gore and

coworkers investigated the carbopalladation/nucleophilic addition of tethered pronucleophiles to

generate carbocyclic products (Table 2.4).[40] As described in their previous reports, the identity of

the coupling partner had a dramatic influence over the regiochemistry of the reaction.[29-31] Vinyl

bromide (entry 1) resulted in exclusive formation of vinyl cyclopropane **2.110**, while 2-

bromopropene (entry 2) resulted in a mixture of **2.109** and **2.110**, with a preference for the five-

membered carbocycle **2.109**. Cyclohexenyl bromide (entry 3) provided further improvements in

the ratio of **2.109** to **2.110**, while iodobenzene (entry 4) resulted in exclusive formation of the five-

membered carbocycle **2.109**.

Table 2.4. Preparation of carbocycles via tandem carbopalladation/cycloisomerization.

Entry	R-X	Temp.	Time	2.109	2.110
1	vinyl bromide	65°C	15 h	0%	80%
2	2-bromopropene	40°C	16 h	53%	18%
3	cyclohexenyl bromide	65°C	12 h	47%	2%
4	iodobenzene	65°C	5 h	65%	0%

Additionally, Gore and coworkers demonstrated that the substitution on the allene can influence the regiochemical outcome of the carbopalladation/nucleophilic addition sequence (Scheme 2.25).[41] Methyl substitution distal to the tethered nucleophile in allene **2.111** resulted in cyclopentene **2.112** in 84% yield when 2-bromopropene was used as a coupling partner; no vinyl cyclopropane products were observed (compare to entry 2, Table 2.4). Methyl substitution proximal to the tethered pronucleophile also favored cyclopentene formation, with allene **2.113** furnishing cyclopentene **2.114** in 72% yield.

Scheme 2.25. Substituent effects in tandem carbopalladation/cycloisomerizations.
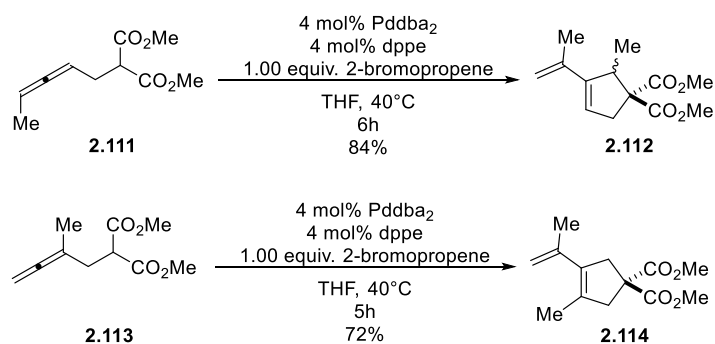
Exocyclic cyclopentene products were obtained when the pronucleophile was tethered to the aryl coupling partner (Scheme 2.26).[42] Symmetric allene **2.115** was converted to **2.117** in 86%

yield when aryl iodide **2.116** was used. Larock expanded this methodology to include vinyl iodide

coupling partners in 1998, with formation of the six-membered ring **2.120** in 67% yield from allene

2.118.[42b] This study included a large array of vinyl iodide coupling partners bearing diverse

functional groups and substituted allenes. The authors concluded that the regiochemical outcome

of the nucleophilic addition is largely a result of the substitution pattern on the η^3-Pd-π-allyl

intermediate.[42b]

Scheme 2.26. Aryl and vinyl iodide coupling partners with tethered pronucleophiles.
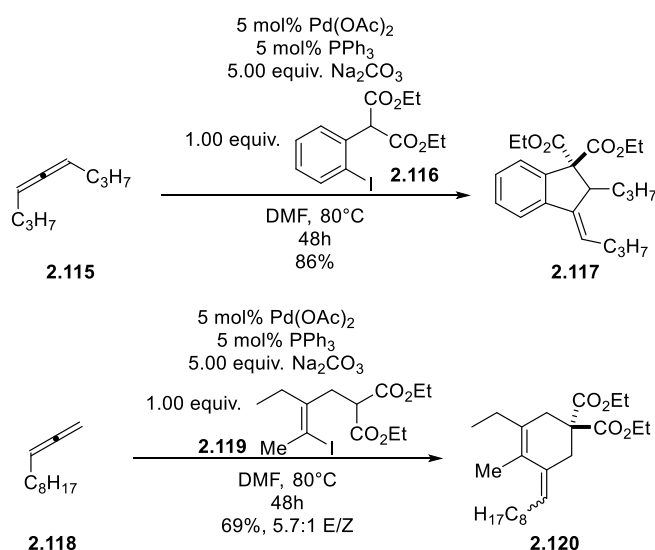
In a similar study, Hiroi disclosed that the chirality of the allene substrate could be

transferred to the products via Pd catalysts (Scheme 2.27).[43] Enantioenriched allene **2.121** resulted

in the six-membered carbocycle **2.123** in 68% yield and 50% *ee*.

Scheme 2.27. Axial-to-point transfer of chirality in tandem carbopalladation/cycloisomerizations.
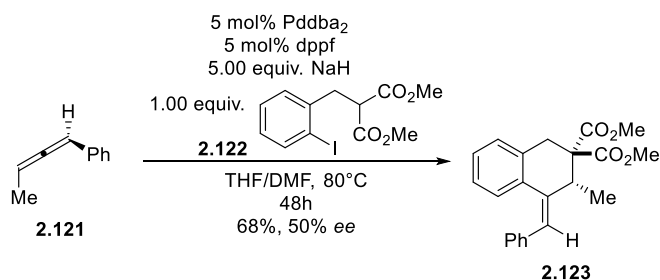
The Ma group has also extensively studied the carbopalladation/nucleophilic addition reactions of allenes (Scheme 2.28) with both oxygen[44] and carbon[45] nucleophiles. Interestingly, in all cases observed, the regioselectivity of this reaction contrasted with that observed by Gore and coworkers;[40,41] formation of the vinyl cyclopropane **2.125** was observed as the major product. In a subsequent publication in 2002,[45b] Ma and coworkers described conditions for the formation of cyclopentene **2.126** from allene **2.124**. They attributed this change in regioselectivity to three factors: the identity of the halide coupling partner, the electronic and steric nature of the substituents on the allene, and to the strength of the base used to deprotonate the tethered pronucleophile.[45b] When weaker bases are used, formation of the vinyl cyclopropane product dominates; under strongly basic conditions, the cyclopentene product is formed preferentially.[45]

Scheme 2.28. Divergent reactivity in tandem carbopalladation/cycloisomerizations.
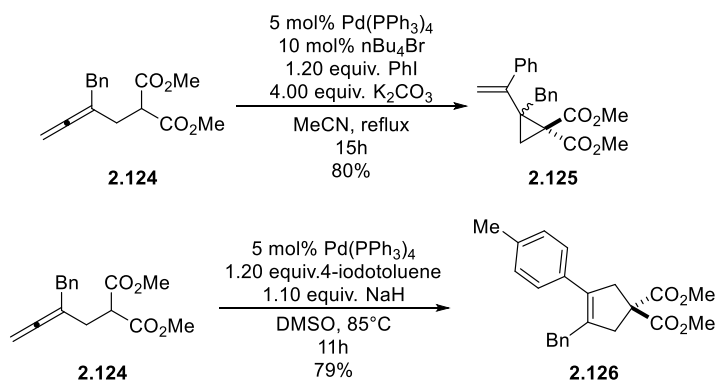
Further developments led to the disclosure of a macrocyclic protocol by the Ma group in 2013 (Scheme 2.29).[46] The 15-membered macrocycle **2.128** was prepared by treating allene **2.127** with Pd(PPh$_3$)$_4$ and PhI under basic conditions. The length of the tether could be extended to furnish up to 20-membered macrocyclic products.[46] In contrast to other techniques used to make macrocyclic carbocycles, high dilution was not necessary to achieve satisfactory yields.[46]

Scheme 2.29. Tandem carbopalladation/cycloisomerization as a strategy to prepare macrocycles.
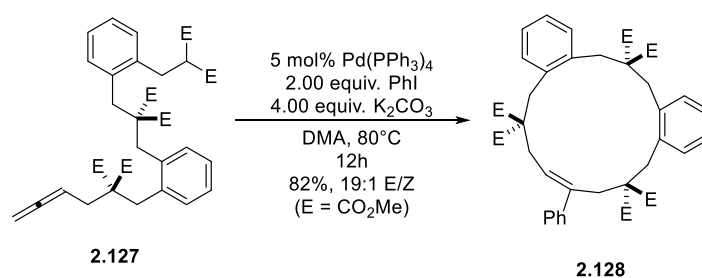
2.1.8. Conclusions

The past 40 years have led to many important developments in the synthesis of substituted olefins by way of Pd catalyzed allene functionalizations. Several studies have demonstrated that the regiochemical outcome of the addition of pronucleophiles can be controlled by modifying the steric and electronic nature of the substituents on the allene, as well as by changing the nature of the carbon pronucleophile.   Additional developments have shown that regioselective carbopalladation of allene substrates with Pd-aryl and Pd-vinyl intermediates can be achieved to deliver a wide array of acyclic and cyclic 1,3-diene motifs. Tandem carbopalladation/nucleophilic additions have also proven quite valuable, as two new C-C bonds can be formed in a single synthetic operation.

Although a highly effective strategy for the preparation of substituted olefins, several challenges remain unaddressed regarding the chemistry of allenes and Pd catalysts. Methods to control the stereochemistry at newly formed sp^3 centers are somewhat scarce, as is the implementation of highly functionalized, stereochemically complex allenes. Development of a catalyst controlled system for the regio- and stereocontrolled formation of carbocyclic scaffolds may provide rapid access to biologically active pharmaceuticals and natural products from readily available allene precursors.

2.2. Results and Discussion

2.2.1. Pd catalyzed cycloisomerizations with lactone substrates

Previous work in the Schomaker group described the Au(I) catalyzed diastereoselective cycloisomerization of allenes[47] to substituted bicyclic cyclopentenes en route to the core structure of bilobalide and related analogs (Scheme 2.30). When treated with an Au(I) catalyst and a Cu Lewis acid additive, allenes of type **2.129** were converted to **2.130** in moderate to good yields and diastereoselectivities. During the course of this investigation, it was observed that for allenes of type **2.129**, where R^1, R^3, and R^4 are alkyl groups, cycloisomerization to afford **2.130** does not occur with the optimized Au(I) conditions. Additionally, when $R^1=R^2=H$ and $R^3=tBu$, a substitution pattern necessary for the synthesis of bilobalide and related analogs **2.131**, Au(I) catalysts failed to produce the desired cycloisomerized product **2.130**.

Palladium catalysts may provide a complementary strategy to access these bicyclic motifs where Au(I) catalysts had previously failed. The use of Pd catalysts may also allow for the cycloisomerization of acyclic malonate substrates, leading to a more generalized method for the preparation of substituted cyclopentanes. Furthermore, Pd catalysts may allow for the formation

of two new C-C bonds, such as in **2.133**, in a regio- and stereocontrolled process in a single synthetic operation.

Scheme 2.30. Previous work with Au(I) catalysts.
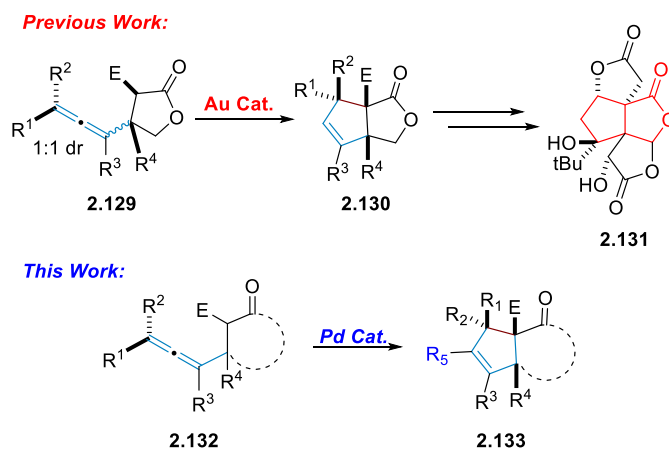
In order to identify suitable conditions for the conversion of **2.134** to cyclopentene **2.135**, several conditions previously reported in the literature were evaluated (Table 2.5). The use of both Brønsted[48] and Lewis acids[49] resulted in no conversion to **2.135** (entries 1 and 2). The acidic C-H bond of the lactone pronucleophile was also insufficient to promote effective cycloisomerization via a Pd-H intermediate (entry 3), despite previous reports in the literature.[8,16,17] Addition of a copper additive (entry 4) resulted in a 15% yield of **2.135**, however significant isomerization to the undesired 1,3-diene was observed.

Given the inability of both acidic and neutral conditions to convert **2.134** to **2.135**, attention was then focused on basic conditions. Neutral nitrogen bases (entries 5-7) were also found to be ineffective in converting **2.134** to **2.135**, instead promoting isomerization to the 1,3-diene product. Although the addition of sodium hydride (entry 8) resulted in the complete deprotonation of lactone **2.134**, only trace amounts of the desired cycloisomerized product were observed upon

workup. This result suggested that the basic additive must have sufficient strength to effect deprotonation of the pronucleophile, however the conjugate acid must be acidic enough to protonate the presumed vinyl Pd intermediate and turn over the catalytic cycle. Carbonate bases gave varying levels of success (entries 9-11), with Cs_2CO_3 producing cyclopentene **2.135** in 53% yield. The differences in performance of each carbonate base may be attributed to the increasing solubility of entries 9-11. Further improvements in both yield and diastereoselectivity were observed with NaOMe was employed as a base (entries 12-13). NaOMe is sufficiently basic to deprotonate the pronucleophile while MeOH generated *in situ* promotes protodemetallation of the hypothesized vinyl palladium intermediate.

Table 2.5. Initial Pd optimization.
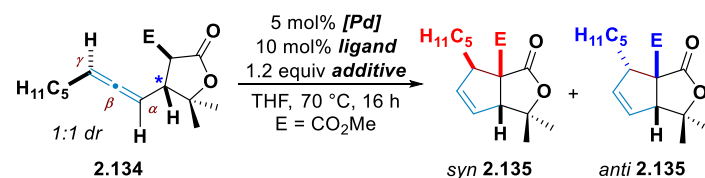
Entry	[Pd]	Ligand	Additive	% Yield[a]	dr[b]
1	(DTBM-SEGPHOS)PdOTf$_2$	--	Yb(OTf)$_3$/AcOH	0%	--
2	Pd$_2$dba$_3$	dppe	AcOH	0%[c]	--
3	Pd$_2$dba$_3$	dppe	--	0%[c]	--
4	Pd$_2$dba$_3$	dppm	Cu(OTf)$_2$	15%[c]	1.1:1
5	Pd$_2$dba$_3$	dppm	Et$_3$N	0%[c]	--
6	Pd$_2$dba$_3$	dppm	iPrNEt	trace[c]	--
7	Pd$_2$dba$_3$	dppm	DBU	trace[c]	--
8	Pd$_2$dba$_3$	dppm	NaH	trace[c]	--
9	Pd$_2$dba$_3$	dppm	Na$_2$CO$_3$	0%	--
10	Pd$_2$dba$_3$	dppm	K$_2$CO$_3$	24%[c]	1:1
11	Pd$_2$dba$_3$	dppm	Cs$_2$CO$_3$	53%	--
12	Pd(OAc)$_2$	dppe/LiBr	NaOMe	43%	1.3:1
13	Pd$_2$dba$_3$	dppe	NaOMe	68%	2.5:1

[a]NMR yield using mesitylene as internal standard; [b]*syn:anti*; [c]The major identifiable product results from isomerization of the allene to the 1,3-diene.

Once a suitable basic additive was identified, a series of ligands were evaluated for improvements in the observed diastereoselectivity (Table 2.6). Neocuproine[50] (entry 1) preserved the yield observed with phosphorus ligands but reduced the diastereoselectivity of the reaction,

while substituted pyridine ligands (entry 2) resulted in trace **2.135** and isomerization to the 1,3-diene. Monodentate phosphorus ligands (entries 3-4) gave moderate yields with no improvements in diastereoselectivity. Bidentate phosphorus ligands (entries 5-11) gave cyclopentene **2.135** with varying degrees of success, with dppm (entry 11) promoting cycloisomerization to **2.135** in 77% yield and 3:1 *syn*:*anti*. There were no clear correlations of either bite angle or the donating abilities of the phosphorus ligands to reaction yield or observed diastereoselectivity. Intriguingly, in contrast to Au(I) catalysts, the palladium catalysts evaluated preferentially gave the *syn* diastereomer, resulting in a stereodivergent method to access bicyclic cyclopentenes.

Table 2.6. Pd ligand optimization.

Entry	Ligand	Yield^a	dr^b	Entry	Ligand	Yield^a	dr^b
1	neocuproine	71%	1.4:1	7	dppbz	39%	2.4:1
2	2,6-bis(tBu$_2$MeP)py	trace^c	--	8	dppe	68%	2.5:1
3	PPh$_3$	56%	1.4:1	9	dCype	54%	2.5:1
4	PCy$_3$	47%	1.4:1	10	dCypm	49%	1.8:1
5	dppf	63%	2:1	11	dppm	77%	3:1
6	dppp	39%	4:1				

^{a}NMR yield using mesitylene as internal standard; ^{b}*syn*:*anti*; ^{c} The major identifiable product results from isomerization to the 1,3-diene.

A series of chiral ligands were also explored in an attempt to increase the observed diastereoselectivity of the cycloisomerization reaction (Table 2.7). Both stereoisomers of tol-BINAP (entries 1-2) failed to promote formation of **2.135**, while (*R*)-DM-BINAP resulted in 27% **2.135** with a 2.4:1 *syn*:*anti* ratio. (*R*)-DTBM-SEGPHOS and (*R*)-BINAP produced **2.135** in 16% and 18% yield, respectively, with no improvements in diastereoselectivity as compared to dppm (Table 2.6, entry 11). Trost's ligand (entry 6) resulted in slight improvements in yield with no notable improvements in diastereoselectivity.

Table 2.7. Chiral ligand data.

Entry	Ligand	Yield[a]	dr[b]
1	(R)-tol-BINAP	0%	--
2	(S)-tol-BINAP	0%	--
3	(R)-DM-BINAP	27%	2.4:1
4	(R)-DTBM-SEGPHOS	16%	1.7:1
5	(R)-BINAP	18%	2.0:1
6	(S,S)-DACH-Phenyl	33%	2.1:1

[a]NMR yield using mesitylene as internal standard. [b]syn:anti

A series of additional solvents were evaluated to increase the yield of the cycloisomerization reaction (Table 2.8). DMSO (entry 1) afforded **2.135** in reduced yields and diastereoselectivity when compared to THF, as did toluene (entry 2). Dioxane (entry 3) only resulted in trace formation of cyclopentene **2.135**. There were also no trends observed regarding the identity of the cationic component of the base and observed yield or diastereoselectivity (entries 4-6). Based on these results, NaOMe in refluxing THF was chosen as the optimal set of conditions to promote cycloisomerization of **2.134** to **2.135** with minimal 1,3-diene formation.
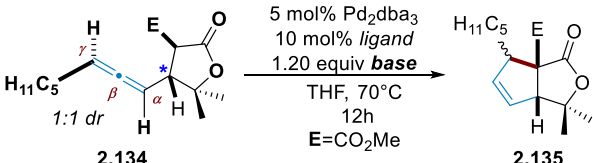
Table 2.8. Additional screening parameters.

Entry	Base	Solvent	Yield[a]	dr[b]
1	NaOMe	DMSO	60%	1.2:1
2	NaOMe	toluene	47%	2.2:1
3	NaOMe	1,4-dioxane	trace	--
4	LiOMe	THF	trace	--
5	KOMe	THF	trace	--
6	KOtBu	THF	5%	2.0:1

[a]NMR yield using mesitylene as internal standard; [b]syn:anti

In order to ensure each component of the reaction was necessary for cycloisomerization, a series of control experiments were conducted (Table 2.9). The palladium catalyst (entry 1), in the absence of both exogenous ligand and base, resulted in isomerization to the 1,3-diene. Dppm (entry 2) and NaOMe (entry 3) do not promote any conversion to **2.135** or the 1,3-diene byproduct. A mix of palladium catalyst and dppm (entry 4) did not yield **2.135** but rather isomerization to the 1,3-diene. The palladium catalyst and NaOMe (entry 5) resulted in 14% of **2.135** in addition to significant amounts of isomerization byproducts, while dppm and NaOMe in the absence of palladium (entry 6) resulted in no conversion to **2.135**. In addition to highlighting the importance of each reaction component for cycloisomerization, this data gives valuable insight into experimental setup. To prevent unwanted isomerization of allene **2.134** to the 1,3-diene, a pre-stir period prior to introducing the allene substrate is required to ensure proper ligation of the palladium catalyst.

Table 2.9. Cycloisomerization control experiments.

Entry	[Pd]	Ligand	Base	Yield[a]
1	Pd$_2$dba$_3$	--	--	0%[b]
2	--	dppm	--	0%
3	--	--	NaOMe	0%
4	Pd$_2$dba$_3$	dppm	--	0%[b]
5	Pd$_2$dba$_3$	--	NaOMe	14%[b]
6	--	dppm	NaOMe	0%

[a]NMR yield using mesitylene as internal standard. [b]The major identifiable product results from isomerization of allene to the 1,3-diene.

With an optimized set of conditions in hand, the scope of the palladium catalyzed allene cycloisomerization was explored (Table 2.10). Alkyl substitution on the allene was tolerated,

providing **2.144** in moderate yields and 2.0:1 *dr*. The methyl substitution of lactone **2.137** resulted in an increase in the yield of cyclopentene **2.145** with a reduced *syn*:*anti* ratio. Branching of the alkyl chain, as in lactone **2.138**, furnished cyclopentene **2.146** in diminished yields and *syn*:*anti* ratios. Introduction of a methyl group at the ring junction of **2.147** improved the diastereoselectivity to 2.4:1 with modest improvements in yield. Trisubstituted lactone **2.140** furnished cyclopentene **2.148** in 37% yield and 1.3:1 *dr*, while trisubstituted allene **2.141** resulted in cyclopentene **2.149** in 48% yield and 2.0:1 *dr*. Previous work with Au(I) catalysts[47] failed to effectively generate cycloisomerized products **2.150** and **2.151**, both of which contain substitution patterns that may be relevant to the synthesis of bilobalide. Intriguingly, trisubstituted allene **2.142** furnished cyclopentene **2.150** in 54% yield, while allene **2.143** underwent cycloisomerization to form **2.151** in 60% yield. *Gem*-dimethyl substitution on the lactone of **2.134** was also well tolerated, furnishing cyclopentene **2.135** in 77% yield and 3.0:1.0 *dr*.

Table 2.10. Pd catalyzed allene cycloisomerization scope.

2.134; 2.136-2.143

5 mol% Pd$_2$dba$_3$
10 mol% dppm
1.2 equiv NaOMe

THF, 70 °C
16 h

syn + *anti*

2.144 54%[a]; 2.0:1.0 dr[b]

2.155 83%[a]; 1.0:1.0 dr[b]

2.146 40%[a,c]; 1.2:1.0 dr[b]

2.147 46%[a,c]; 2.4:1.0 dr[b]

2.148 37%[a,c]; 1.3:1.0 dr[b]

2.149 48%[a,c]; 2.0:1.0 dr[b]

2.150 54%[a,c]; 1.2:1.0 dr[b]

2.151 60%[a]

2.135 77%[a]; 3.0:1.0 dr[b]

[a] ^{1}H-NMR yield with mesitylene as internal standard. [b] *syn:anti.* [c] Sealed vial.
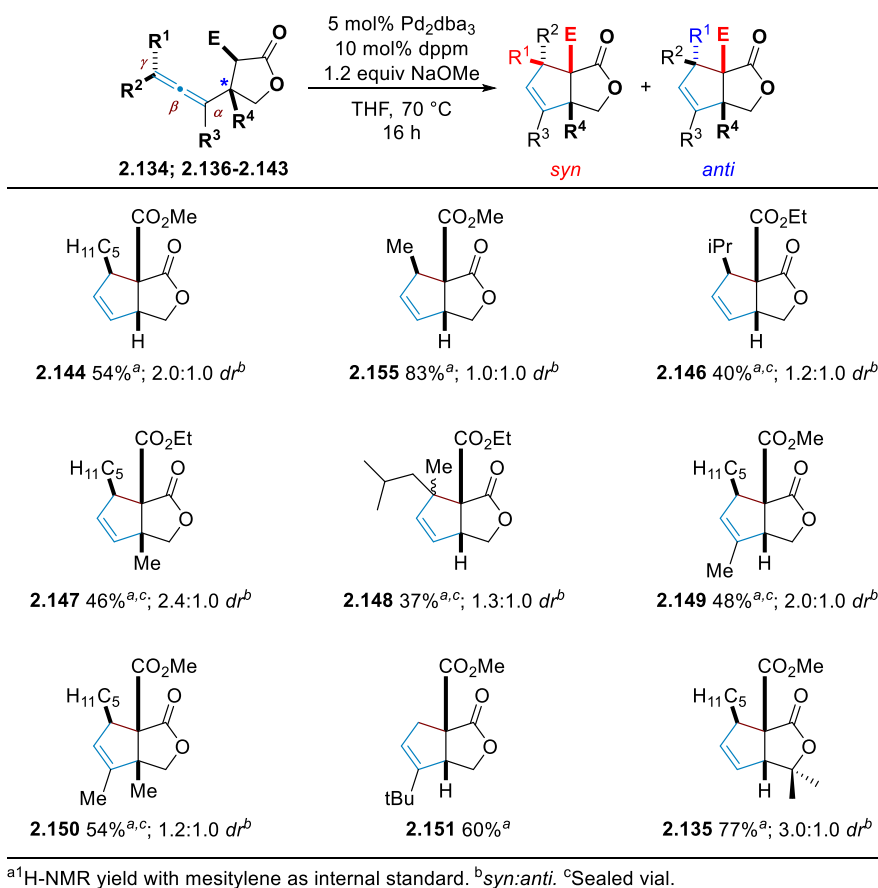
A proposed catalytic cycle for the palladium-catalyzed cycloisomerization is presented in Scheme 2.31. NaOMe-promoted enolization of **2.129**, followed by coordination of the distal C-C π bond[51] of the allene by the palladium catalyst results in intermediate **2.152**. Attack of the nucleophilic enolate on the activated Pd-allene complex of **2.152** results in the formation of the vinyl palladium species **2.153**. MeOH, generated *in situ* during the formation of the enolate, facilitates protodepalladation to release the cyclopentene product **2.130** and regenerate the active palladium catalyst.

Scheme 2.31. Proposed Pd cycloisomerization catalytic cycle.
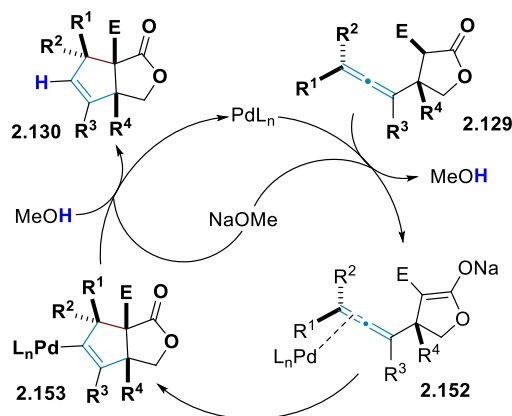
2.2.2. Pd cycloisomerizations with acylic malonate substrates

The Pd catalyzed cycloisomerization of acyclic malonate substrates may offer a way to generate highly substituted cyclopentenes in a concise, stereocontrolled manner from easily synthesized allene precursors. The optimized conditions for the cycloisomerization of lactone substrates did not promote effective cycloisomerization of **2.154** to **2.155** (Table 2.11, entry 1), instead resulting isomerized byproducts. Isomerization of **2.154** was suppressed at lower temperatures (entry 2), however no conversion to **2.155** was observed. The Lewis acid-like characteristics[52] of Pd(OAc)$_2$ also failed to promote conversion (entries 3-4) to cyclopentene **2.155**. Switching to electron deficient phosphite ligands in refluxing THF (entry 5) resulted in the formation of **2.155** in 27% yield, while DMF (entry 6) provided slight improvements in the yield. At lower temperatures, NaOMe (entry 7) is not sufficient to deprotonate the acidic C-H bond of **2.154**, which results in no cycloisomerization to **2.155**. Stronger bases (entries 8-10) restored the reactivity at room temperature, with KH (entry 10) furnishing **2.155** in 67% yield.

Table 2.11. Initial optimization.

2.154 → **2.155**
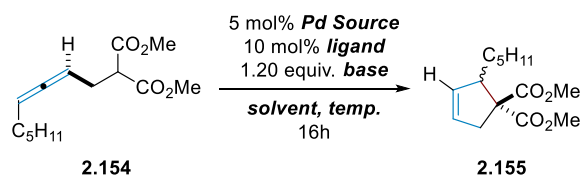
Entry	Pd Source	Ligand	Base	Solvent	Temp	Time	% Yield[a]
1	Pd_2dba_3	dppm	NaOMe	THF	reflux	16h	0%[b]
2	Pd_2dba_3	dppm	NaOMe	THF	r.t.	16h	0%
3	$Pd(OAc)_2$	--	NaOMe	THF	reflux	16h	*trace[b]*
4	$Pd(OAc)_2$	dppm	--	THF	reflux	16h	*0%*
5	Pd_2dba_3	$P(OPh)_3$	NaOMe	THF	reflux	16h	27%
6	Pd_2dba_3	$P(OPh)_3$	NaOMe	DMF	70°C	16h	34%
7	Pd_2dba_3	$P(OPh)_3$	NaOMe	DMF	r.t.	16h	*trace*
8	Pd_2dba_3	$P(OPh)_3$	NaH[c]	DMF	r.t.	16h	41%
9	Pd_2dba_3	$P(OPh)_3$	KHMDS	DMF	r.t.	16h	48%
10	Pd_2dba_3	$P(OPh)_3$	KH[d]	DMF	r.t.	16h	67%[e]

[a] ^{1}H NMR yield using mesitylene as internal standard. [b] Isomerization to the 1,3-diene observed. [c] 60% wt. dispersion in mineral oil. [d] 50% w/w in paraffin. [e] isolated yied.

Additional additives invoked in the formation of Pd-H hydride species[53] from Pd(0) catalysts were also evaluated (Table 2.12). Brønsted acids[53a,b] (entries 1-2) failed to promote cycloisomerization of **2.154** to **2.155** either via Pd-H species or acid catalyzed tautomerization to the enol form of **2.154** and subsequent nucleophilic attack. Adventitious alcohol or water present in the reaction solvent[53e] is not responsible for the formation of a catalytically active Pd-H species as previously reported, as deuterated MeOD (entry 3) and D_2O (entry 4) failed to promote the formation of **2.155**. Additionally, in the absence of either acidic or basic additives (entry 5), conversion of **2.154** to **2.155** was not observed, suggesting that insertion into the acidic C-H bond of the malonate by Pd^0 is most likely not occurring.

Table 2.12. Evaluation of additional additives.
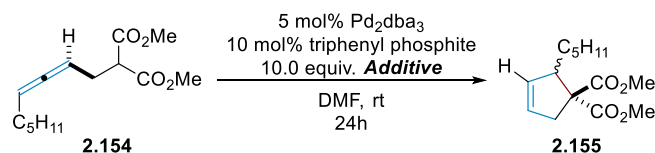
Entry	Additive	% Yield[a]	% rsm[a]
1	TFA	0%	79%
2	AcOH	0%	88%
3	MeOD	0%	85%
4	D_2O	0%	86%
5	--	0%	90%

[a] ^{1}H NMR yield using mesitylene as internal standard

2.2.3. Pd catalyzed tandem insertion/cycloisomerizations with lactone substrates

Given the rich history of palladium catalyzed cross-coupling reactions, it was envisioned that addition of an aryl halide component to the reaction mixture may facilitate a one pot, tandem coupling/cycloisomerization sequence to sequentially form two new C-C bonds. The proposed catalytic cycle is depicted in Scheme 2.32. Oxidative addition of the palladium catalyst and the aryl halide results in intermediate **2.157**, which then coordinates enolate **2.156** (derived from the acid/base reaction of **2.132** and an exogenous base) to form **2.158**. Migratory insertion of the allene affords intermediate **2.159**, which can rearrange to give the η^3-Pd-π-allyl species **2.160**. The tethered nucleophile attacks the distal carbon of the Pd-π-allyl species **2.160**, generating the coordinated cyclopentene complex **2.161**. Release of the cycloisomerized product regenerates the active Pd^0 catalyst.

Scheme 2.32. Proposed Pd cross-coupling/cycloisomerization catalytic cycle.
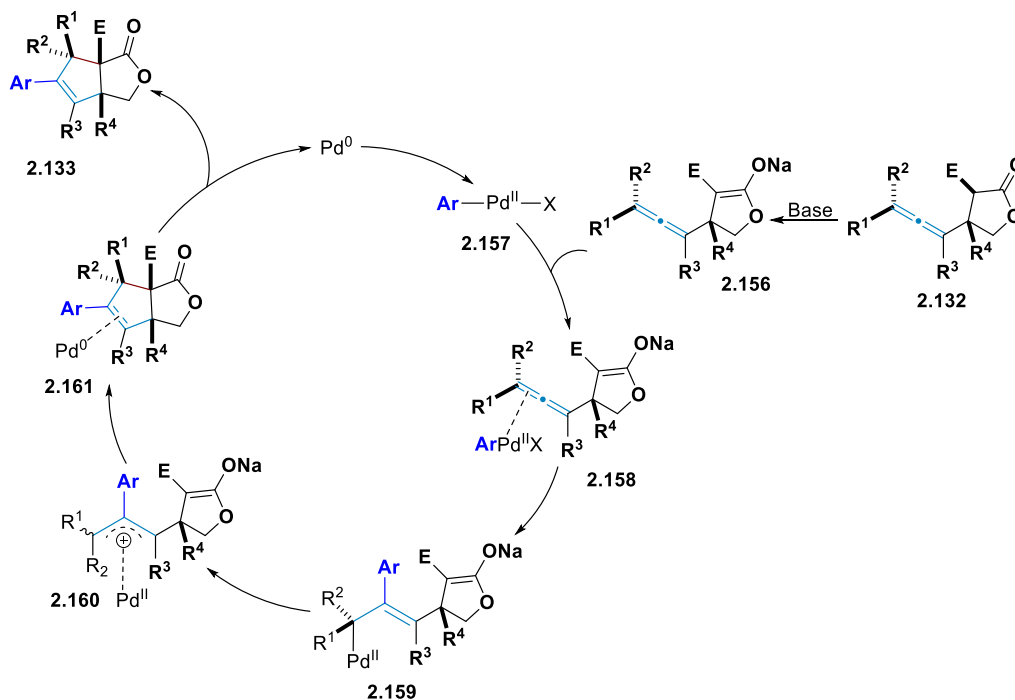
Initial attempts of optimizing the tandem cross-coupling/cycloisomerization reaction focused on Pd(PPh$_3$)$_4$ as a catalyst (Table 2.13). In the absence of exogenous ligand, Pd(PPh$_3$)$_4$ catalysts furnished the desired cross-coupled product **2.162** in 24% yield (entry 1), however a significant amount of undesired background cycloisomerization gave **2.135** in 19% yield and consumed the remaining allene to form the isomerized 1,3-diene products. Changing the base to K$_2$CO$_3$ (entry 2) inhibited isomerization to the 1,3-diene but reduced the yield of **2.162** while increasing the yield of the undesired cycloisomerization process to form **2.135**. Introduction of a bidentate phosphine ligand (entries 3-4) produced increased yields of **2.162**, but background cycloisomerization was still observed. Implementing either Pd(OAc)$_2$ or Pd(MeCN)$_2$Cl$_2$ (entries 5-8) as the palladium source resulted in a reduction in yield of **2.162** and significant amounts of both cycloisomerized product **2.135** and isomerization to the 1,3-diene. Pd$_2$dba$_3$ with dppm ligands (entry 9) resulted in only 10% of the desired **2.162**, while furnishing 40% of the cycloisomerized product **2.135**.

Based on these results, it was determined that aryl bromide coupling partners do not undergo oxidative addition with the Pd^0 catalyst at a rapid enough rate to suppress the background cycloisomerization reaction.[54] To circumvent this issue, aryl iodide coupling partners were employed (entry 10), delivering **2.162** in 34% yield and no observed background reactivity. In an attempt to improve the diastereoselectivity of the reaction, allene **2.134** was subjected to the reaction conditions at room temperature, which resulted in decreased conversion of **2.134** to **2.162** over 16 h (entry 11), although background cycloisomerization to **2.135** was completely suppressed. Increasing the reaction time to 45 h (entry 12) resulted in a modest improvement in the yield of **2.162**, however these extended reaction times failed to give complete conversion of **2.134** to **2.162** and displayed no notable improvements in dr. Since the acidic proton of the pronucleophile is no longer required during the coupling/cycloisomerization sequence, increasing the strength of the base may promote an increase in the formation of **2.162**. Indeed, when NaHMDS was used in place of NaOMe (entry 13) in refluxing THF, **2.162** was obtained in 72% yield with no competing cycloisomerization to **2.135** detected.

Table 2.13. Initial optimization with lactone substrates.
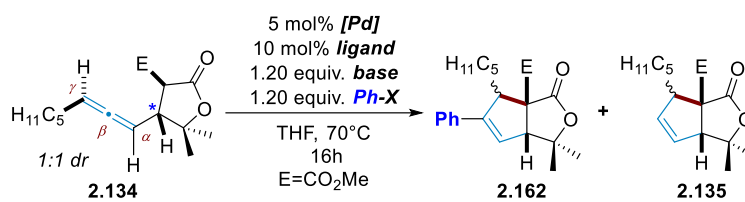
Entry	[Pd]	Ligand	Base	Ph-X	% 2.162[a]	% 2.135[a]	%rsm[a]
1	Pd(PPh$_3$)$_4$	--	NaOMe	PhBr	24%	19%	trace[b]
2	Pd(PPh$_3$)$_4$	--	K$_2$CO$_3$	PhBr	18%	24%	37%
3	Pd(PPh$_3$)$_4$	dppe	NaOMe	PhBr	39%	20%	*trace*
4	Pd(PPh$_3$)$_4$	dppm	NaOMe	PhBr	42%	20%	trace
5	Pd(OAc)$_2$	--	NaOMe	PhBr	<5%	28%	0%[b]
6	Pd(OAc)$_2$	dppe	NaOMe	PhBr	10%	20%	0%[b]
7	Pd(MeCN)$_2$Cl$_2$	--	NaOMe	PhBr	0%	10%	0%[b]
8	Pd(MeCN)$_2$Cl$_2$	dppe	NaOMe	PhBr	10%	12%	trace[b]
9	Pd$_2$dba$_3$	dppm	NaOMe	PhBr	10%	40%	0%[b]
10	Pd$_2$dba$_3$	dppm	NaOMe	PhI	34%	0%	40%
11	Pd$_2$dba$_3$	dppm	NaOMe	PhI	25%[c]	0%	55%
12	Pd$_2$dba$_3$	dppm	NaOMe	PhI	36%[d]	0%	37%
13	Pd$_2$dba$_3$	dppm	NaHMDS	PhI	72%	0%	0%

[a] ^{1}H NMR using mesitylene as internal standard. [b] isomerization to the corresponding 1,3-diene.
[c] reaction ran at r.t. for 16h. [d] reaction ran at r.t. for 45h.

The preliminary substrate scope utilizing lactones is shown in Table 2.14. *Gem*-dimethyl **2.134** underwent the palladium catalyzed coupling/cycloisomerization sequence to give cyclopentene **2.162** in 72% yield and 1.0:1.0 *dr*. Alkyl substituted **2.136** resulted in cyclopentene **2.164** in 58% yield and 1.0:1.0 *dr*, while introduction of a tethered silyl ether furnished cyclopentene **2.165** in 37% yield and 1.0:1.0 *dr*.

Table 2.14. Initial lactone substrates.
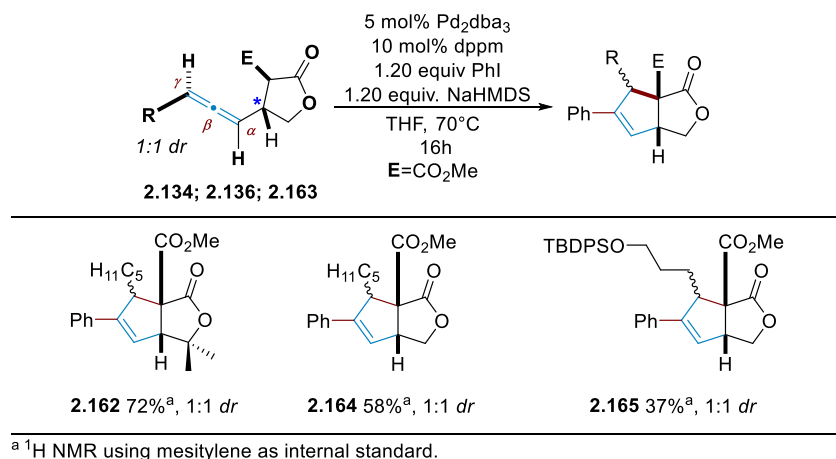
2.2.4. Pd catalyzed tandem insertions/cycloisomerizations with acyclic malonates

Efforts to control the cycloisomerization stereoselectivity using lactone substrates and Pd catalysts proved quite difficult. It was hypothesized that implementation of chiral ligands may be ineffective due to the non-selective nature of the C-H insertion reaction used to generate the lactone ring of **2.132** (R[4], Scheme 2.30). Replacing the lactone moiety with an acylic malonate group may allow for the development of a regio- and stereocontrolled method to prepare functionalized carbocyclic products.

A variety of conditions were explored to promote the conversion of acyclic allene **2.154** to cyclopentene **2.166** (Scheme 2.15). When dppf and NaH were used in refluxing THF (entry 1), the desired cyclopentene product **2.166** was obtained in 52% yield. Reducing the temperature to 0°C (entry 2) resulted in no conversion, while modest conversion to **2.166** was observed at room temperature (entry 3). The use of a more strongly coordinating polar solvent may be better able to stabilize the Pd catalyst and intermediates in solution. DMSO (entry 4) resulted in only trace conversion of allene **2.154** to cyclopentene **2.166**, while DMF at room temperature (entry 5) provided cyclopentene **2.156** in 44% yield. Switching to dppp (entry 6) resulted in a slight increase in the yield of **2.166**, while dppe (entry 7) resulted in a reduction in the yield of **2.166**. The yield

of **2.166** was further increased to 65% by employing dppm (entry 8) as a ligand. Intriguingly, the

identity of the countercation[55] had a substantial impact on the regiochemistry of the nucleophilic

addition step.[45]   Potassium hydride (entry 9) provided vinyl cyclopropane **2.167** in 34% yield

without producing any cyclopentene **2.166**. This change in regiochemistry may be due to the

hardness of the enolate nucleophile; potassium enolates are typically more reactive than their

sodium and lithium counterparts.[55]   Switching to NaHMDS (entry 10) delivered cyclopentene

2.166 in 72% yield.

Table 2.15. Pd ligand optimization.

Entry	ligand	base	solvent	temp.	% 2.166[a]	% 2.167[a]
1	dppf	NaH	THF	70°C	52%	0%
2	dppf	NaH	THF	0°C	0%	0%
3	dppf	NaH	THF	r.t.	36%	0%
4	dppf	NaH	DMSO	r.t.	trace	0%
5	dppf	NaH	DMF	r.t.	44%	0%
6	dppp	NaH	DMF	r.t.	51%	0%
7	dppe	NaH	DMF	r.t.	38%	0%
8	dppm	NaH	DMF	r.t.	65%	0%
9	dppm	KH	DMF	r.t.	0%	34%
10	dppm	NaHMDS	DMF	r.t.	72%	0%

[a] ^{1}H NMR using mesitylene as internal standard.

A series of aryl iodide coupling partners were evaluated using the optimized cross-

coupling/cycloisomerization conditions in Table 2.16. Iodobenzene resulted in the formation of

cyclopentene **2.166** in 72% yield. Additional aromatic rings were well tolerated, as were additional

alkyl groups, furnishing cyclopentenes **2.168** and **2.169** in 51% and 60%, respectively. When

subjected to the reaction conditions, electron withdrawing aryl esters and aldehydes underwent the

coupling/cycloisomerization sequence to give cyclopentenes **2.170** and **2.171** in moderate yields.

Bromine substitution on the aromatic ring was tolerated, resulting in cyclopentene **2.172** in 73% yield; no dimerization to form the bis-coupled product was observed. Interestingly, strongly electron withdrawing groups were tolerated under the reaction conditions, with the trifluoromethyl substituted cyclopentene **2.173** forming in 73% yield. Additionally, heteroaromatic coupling partners also seemed to be tolerated, furnishing the pyridine-substituted cyclopentene **2.174** in 77% yield.

Table 2.16. Initial acyclic substrate scope.
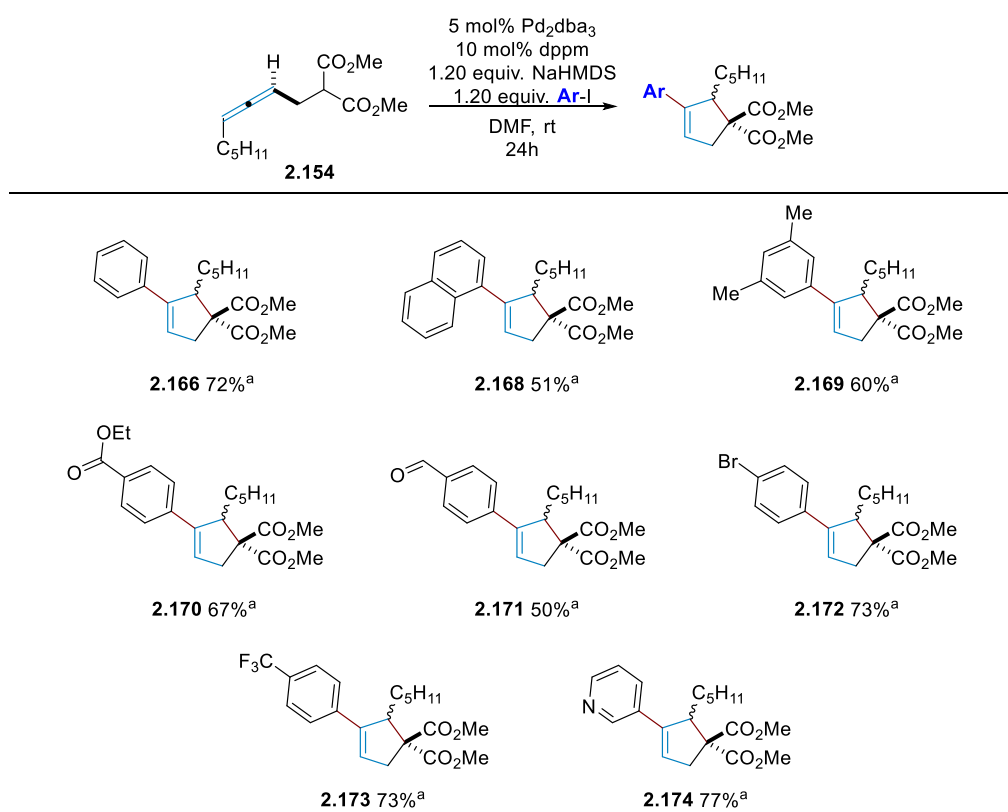
^a ¹H NMR yield using mesitylene as internal standard.

A series of chiral ligands were evaluated (Table 2.17) to generate enantioenriched **2.166** from **2.154** (Table 2.17). Variations of the DuanPhos, BINAP, JosiPhos, and TangPhos ligands (entries 1-4) did not produce the desired product **2.166**. Trost's ligand (entry 5) and (*R,R*)-Me-

DuPhos (entry 6) resulted in only trace amounts of **2.166**, while (*R*)-ProPhos (entry 7) produced

20% of the uncoupled product **2.155** and 7% of the desired product **2.166**. Switching to the

WalPhos ligand scaffold (entry 8) provided **2.166** with some improvements in yield, while (+/-)-

SPANPHOS (entry 9) generated **2.166** in 52% yield with no background cycloisomerization to

2.155. Phosphoramidite ligand **2.175** (entry 10), produced the tandem reaction product **2.166** in

24% yield, while phosphoramidite ligand **2.176** resulted in 67% of the coupled product **2.166** and

no background cycloisomerization products.

Table 2.17. Chiral ligand screening.

Entry	Ligand	% 2.166[a]	% 2.155[a]	%rsm[a]
1	(1*S*,1'*S*,2*S*,2'*S*)-DuanPhos	0%	0%	14%
2	(*R*)-DM-BINAP	0%	0%	24%
3	JosiPhos	0%	0%	83%
4	(*S*,*S*',*R*,*R*')-TangPhos	0%	0%	93%
5	(*S*,*S*)-DACH-Phenyl	<5%	0%	76%
6	(*R*,*R*)-Me-DuPhos	6%	0%	83%
7	(*R*)-ProPhos	7%	20%	0%
8	WalPhos	32%	0%	18%
9	(+/-)-SPANPHOS	58%	0%	8%
10	Phosphoramidite **2.175**	24%	0%	0%
11	Phosphoramidite **2.176**	67%	0%	0%

[a] ^{1}H NMR yield using mesitylene as internal standard.
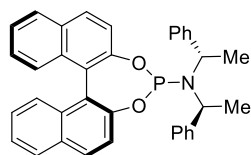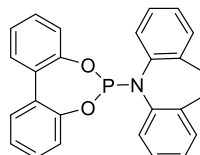
Phosphoramidite **2.175**   Phosphoramidite **2.176**

2.2.5. Conclusions and future directions

This work has identified conditions to expand the scope of Pd catalyzed allene

cycloisomerizations to generate highly substituted cyclopentene scaffolds where Au(I) catalysts

had previously failed. Interestingly, this approach provides complementary stereoselectivity to that observed with Au(I) catalysts. Further developments have resulted in a methodology capable of generating bicyclic products containing two new C-C bonds in a single synthetic operation.

Initial investigations with acyclic malonate substrates shows increasing promise as a general method to prepare complex five-membered carbocycles from relatively simple, readily accessible allenes. This work has identified triphenyl phosphite as the optimal ligand to carry out the cycloisomerization reaction, while dppm and aryl iodides facilitate the coupling/cycloisomerization of acyclic substrates in moderate to good yields. Additionally, vinyl cyclopropanes can be prepared in a divergent manner simply by changing the nature of the base employed. Future work in this area includes the elaboration of the substrate scope to include highly substituted and optically pure allenes, as well as studies to further understand the underlying factors responsible for the regiochemical outcome of this reaction.

Additional investigations into the mechanisms of the cycloisomerization and tandem coupling/cycloisomerization reactions may provide the necessary insight to render these transformations asymmetric. Many of the traditionally used chiral ligand scaffolds resulted in substantial decreases in reactivity; in some cases, these ligands shut down reactivity completely, resulting in complete recovery of starting material. Chiral monodentate phosphine ligands, such as phosphoramidite **2.176** (Table 2.17, entry 11), show promise and warrant further investigation with this methodology.

2.3. Experimental Procedures for Pd Catalyzed Cycloisomerizations

2.3.1. General experimental information

All glassware was either oven dried at 140 °C or flame dried under vacuum and purged with nitrogen immediately prior to use. Unless otherwise specified, reagents were used as obtained from the supplier without further purification. Pd_2dba_3 was obtained from Oakwood Chemicals and recrystallized according to a published procedure.[56] Phosphine ligands were obtained from Millipore Sigma and Strem Chemicals and stored in an inert atmosphere glove box. Tetrahydrofuran (THF) and 1,4-dioxane were freshly distilled from Na/benzophenone ketyl immediately prior to use. Acetonitrile (MeCN), benzene, dichloromethane (CH_2Cl_2), dimethylsulfoxide (DMSO), and toluene were freshly distilled from calcium hydride immediately prior to use. Other solvents were purified using accepted procedures from the sixth edition of "Purification of Laboratory Chemicals".[57] Air- and moisture- sensitive reactions were performed using standard Schlenk techniques under an inert atmosphere of nitrogen unless otherwise specified. Analytical thin layer chromatography (TLC) was performed using pre-coated silica gel 60 F24 plates containing a fluorescent indicator. Ceric ammonium molybdate (CAM stain) and 254 nm UV light were used to visualize the reaction products, unless otherwise specified. Preparative chromatography using a gradient method with mixtures of EtOAc and hexanes, unless otherwise specified, was performed using SilicaFlash P60 silica gel (230-400 mesh) via Still's method.[58]

^1H NMR and ^{13}C NMR spectra were obtained using Bruker Avance-500 spectrometers. Chemical shifts are reported relative to the tetramethylsilane peak (δ 0.00 ppm). Accurate mass measurements were acquired at the University of Wisconsin, Madison, using a Micromass LCT (electrospray ionization or electron impact methods). The NMR and Mass Spectrometry facilities are funded by the NSF (CHE-1048642, CHE-0342998, CHE-9304546 and CHE-9208463), the University of Wisconsin as well as a generous gift by Paul J. Bender.

2.3.2. Experimental Procedures for C-H Insertion Reactions
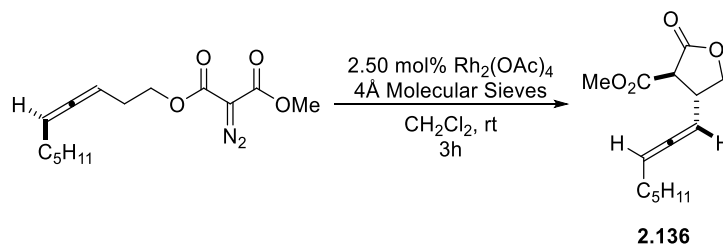
2.136

Lactone 2.136. To a stirred solution of 17.7 mg (0.04 mmol, 0.025 equiv) $Rh_2(OAc)_4$ in 16 mL

CH_2Cl_2 was added 1.63 g 4Å molecular sieves. A solution of 456 mg (1.63 mmol, 1.00 equiv) of

the diazoester in 16 mL CH_2Cl_2 was added dropwise over a period of 3 h via syringe pump. The

resulting green suspension was filtered through a pad of celite using additional CH_2Cl_2 to aid in

the transfer, and the volatiles were removed in vacuo to afford crude lactone **2.136**. The crude

material was purified on silica gel using a 0-10% gradient of EtOAc in hexanes as eluent to afford

325 mg (1.29 mmol, 79%) of lactone **2.136** as a pale-yellow oil. Characterization data for lactone

2.136 matches that which has been previously published.[59]
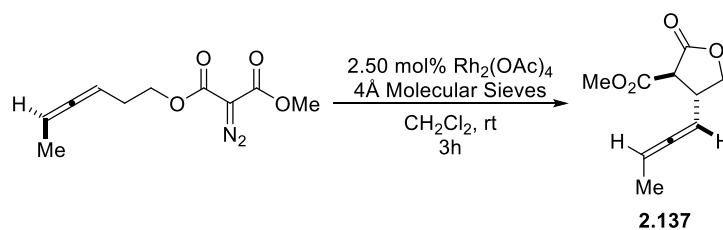
2.137

Lactone 2.137. To a stirred solution of 86.0 mg (0.19 mmol, 0.025 equiv) $Rh_2(OAc)_4$ in 78 mL

CH_2Cl_2 was added 7.80 g 4Å molecular sieves. A solution of 1.75 g (7.80 mmol, 1.00 equiv) of

the diazoester in 78 mL CH_2Cl_2 was added dropwise over a period of 3 h via syringe pump. The

resulting green suspension was filtered through a pad of celite using additional CH_2Cl_2 to aid in

the transfer, and the volatiles were removed in vacuo to afford crude lactone **2.137**. The crude

material was purified via flash column chromatography on silica gel using a gradient of 0-10%

EtOAc in hexanes to give 540 mg (2.75 mmol, 35%) of lactone **2.137** as a white solid. ^{1}H NMR

(500 MHz, CDCl$_3$) δ 5.37 – 5.27 (m, 1H), 5.15 (tqd, J = 6.3, 3.2, 1.5 Hz, 1H), 4.54 (ddd, J = 9.0,

7.5, 3.3 Hz, 1H), 4.05 (dt, J = 8.9, 7.6 Hz, 1H), 3.82 (s, 3H), 3.60 – 3.49 (m, 1H), 3.46 (dd, J = 8.7,

4.9 Hz, 1H), 1.68 (dt, J = 7.1, 2.9 Hz, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 204.5, 204.4, 171.3,

171.3, 167.5, 167.5, 90.2, 90.2, 88.2, 88.0, 71.5, 71.5, 53.1, 53.1, 51.9, 51.9, 39.3, 39.2, 14.1, 14.1.

HRMS (ESI) *m/z* calculated for C$_{10}$H$_{12}$O$_4$ [M + NH$_4$]$^+$ 214.1074, found 214.1074.
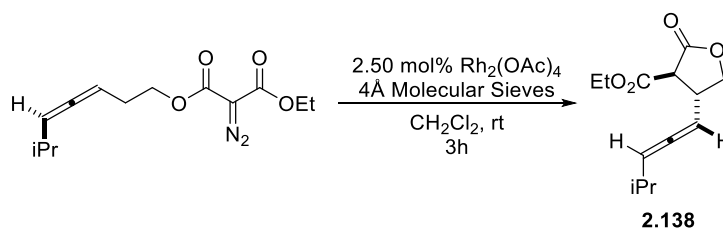
Lactone 2.138. To a stirred solution of 48.6 mg (0.11 mmol, 0.025 equiv) Rh$_2$(OAc)$_4$ in 45 mL

CH$_2$Cl$_2$ was added 4.54 g 4Å molecular sieves. A solution of 1.21 g (4.54 mmol, 1.00 equiv) of

the diazoester in 45 mL CH$_2$Cl$_2$ was added dropwise over a period of 3 h via syringe pump. The

resulting green suspension was filtered through a pad of celite using additional CH$_2$Cl$_2$ to aid in

the transfer, and the volatiles were removed in vacuo to afford crude lactone **2.138**. The crude

material was purified on silica gel using a 0-10% gradient of EtOAc in hexanes as eluent to afford

660 mg (2.77 mmol, 61%) of lactone **2.138** as a pale-yellow oil. Characterization data for lactone

2.138 matches that which has been previously published.[59]
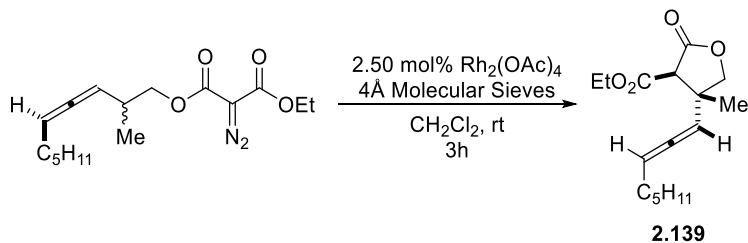
2.139

Lactone 2.139. To a stirred solution of 13.3 mg (0.03 mmol, 0.025 equiv) $Rh_2(OAc)_4$ in 10 mL

CH_2Cl_2 was added 1.04 g 4Å molecular sieves. A solution of 322 mg (1.04 mmol, 1.00 equiv) of

the diazoester in 10 mL CH_2Cl_2 was added dropwise over a period of 3 h via syringe pump. The

resulting green suspension was filtered through a pad of celite using additional CH_2Cl_2 to aid in

the transfer, and the volatiles were removed in vacuo to afford crude lactone **2.139**. The crude

material was purified on silica gel using a 0-10% gradient of EtOAc in hexanes as eluent to afford

216 mg (0.77 mmol, 74%) of lactone **2.139** as a pale-yellow oil. Characterization data for lactone

2.139 matches that which has been previously published.[59]
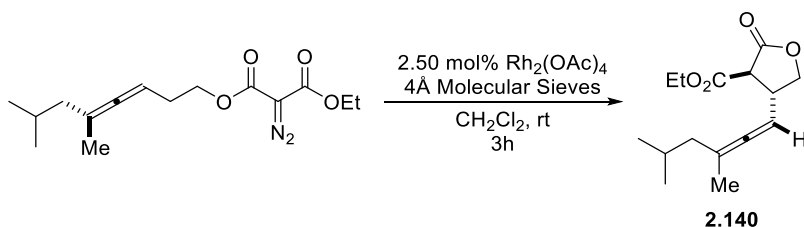
2.140

Lactone 2.140. To a stirred solution of 44.2 mg (0.10 mmol, 0.025 equiv) $Rh_2(OAc)_4$ in 38 mL

CH_2Cl_2 was added 3.84 g 4Å molecular sieves. A solution of 1.13 g (3.84 mmol, 1.00 equiv) of

the diazoester in 38 mL CH_2Cl_2 was added dropwise over a period of 3 h via syringe pump. The

resulting green suspension was filtered through a pad of celite using additional CH_2Cl_2 to aid in

the transfer, and the volatiles were removed in vacuo to afford crude lactone **2.140**. The crude

material was purified on silica gel using a 0-10% gradient of EtOAc in hexanes as eluent to afford

471 mg (1.77 mmol, 46%) of lactone **2.140** as a pale-yellow oil. Characterization data for lactone

2.140 matches that which has been previously published.[47]
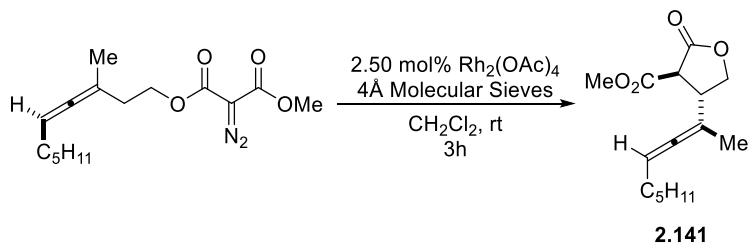
2.141

Lactone 2.141. To a stirred solution of 113 mg (0.25 mmol, 0.025 equiv) Rh$_2$(OAc)$_4$ in 102 mL

CH$_2$Cl$_2$ was added 10.2 g 4Å molecular sieves. A solution of 3.00 g (10.2 mmol, 1.00 equiv) of

the diazoester in 102 mL CH$_2$Cl$_2$ was added dropwise over a period of 3 h via syringe pump. The

resulting green suspension was filtered through a pad of celite using additional CH$_2$Cl$_2$ to aid in

the transfer, and the volatiles were removed in vacuo to afford crude lactone **2.141**. The crude

material was purified via flash column chromatography on silica gel using a gradient of 0-10%

EtOAc in hexanes to give 1.06 g (3.98 mmol, 39%) of lactone **2.141** as a clear pale yellow oil. ^{1}H

NMR (500 MHz, CDCl$_3$) δ 5.28 (ddt, J = 9.5, 6.4, 3.5 Hz, 1H), 4.55 (dd, J = 8.8, 7.5 Hz, 1H), 4.12

– 4.03 (m, 1H), 3.81 (d, J = 1.0 Hz, 3H), 3.54 – 3.48 (m, 1H), 3.44 (dqd, J = 16.5, 8.0, 2.6 Hz, 1H),

1.97 (p, J = 7.2 Hz, 2H), 1.72 (d, J = 2.9 Hz, 3H), 1.40 – 1.33 (m, 2H), 1.33 – 1.25 (m, 4H), 0.93

– 0.85 (m, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 200.2, 200.1, 171.6, 167.9, 167.9, 97.2, 97.1, 95.0,

94.9, 71.2, 71.1, 53.1, 53.1, 51.5, 51.5, 43.2, 43.2, 31.4, 31.3, 28.9, 28.8, 28.8, 28.7, 28.7, 28.6,

22.5, 22.5, 22.4, 17.9, 14.0. HRMS (ESI) m/z calculated for C$_{15}$H$_{22}$O$_4$ [M + NH$_4$]$^+$ 284.1856,

found 284.1854.
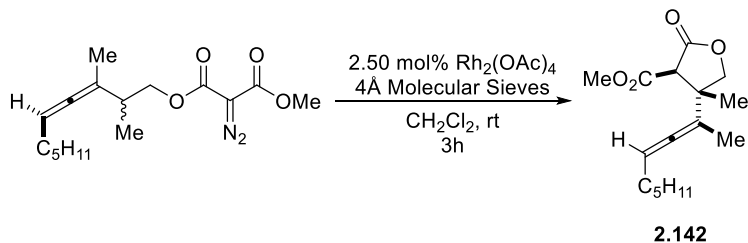
2.142

Lactone 2.142. To a stirred solution of 106 mg (0.24 mmol, 0.025 equiv) $Rh_2(OAc)_4$ in 95 mL CH_2Cl_2 was added 9.5 g 4Å molecular sieves. A solution of 2.94 g (9.53 mmol, 1.00 equiv) of the diazoester in 95 mL CH_2Cl_2 was added dropwise over a period of 3 h via syringe pump. The resulting green suspension was filtered through a pad of celite using additional CH_2Cl_2 to aid in the transfer, and the volatiles were removed in vacuo to afford crude lactone **2.142**. The crude material was purified via flash column chromatography on silica gel using a gradient of 0-10% EtOAc in hexanes to give 1.07 g (3.82 mmol, 40%) of lactone **2.142** as a mixture of diastereomers. ^1H NMR (500 MHz, CDCl$_3$) δ 5.27 (qd, J = 6.7, 2.9 Hz, 1H), 5.18 (tt, J = 6.1, 3.0 Hz, 0H), 5.15 – 5.10 (m, 0H), 4.64 – 4.53 (m, 1H), 4.32 (dd, J = 8.8, 5.4 Hz, 1H), 4.13 (dd, J = 8.8, 1.9 Hz, 1H), 3.95 (dd, J = 13.6, 8.7 Hz, 1H), 3.78 (s, 3H), 3.74 (s, 1H), 3.72 (s, 1H), 3.62 (d, J = 10.0 Hz, 1H), 3.31 (d, J = 5.1 Hz, 1H), 2.02 – 1.91 (m, 3H), 1.75 (t, J = 2.7 Hz, 3H), 1.73 (dd, J = 2.9, 1.6 Hz, 2H), 1.45 – 1.34 (m, 4H), 1.30 (tdd, J = 7.6, 3.7, 2.0 Hz, 5H), 1.25 (d, J = 3.2 Hz, 3H), 0.89 (tt, J = 7.2, 2.5 Hz, 5H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 200.8, 200.8, 200.8, 200.5, 172.2, 172.2, 172.1, 171.9, 167.6, 167.5, 166.8, 166.7, 101.4, 98.8, 98.6, 94.7, 94.7, 93.4, 93.4, 76.3, 76.0, 58.1, 58.1, 55.9, 55.7, 52.6, 52.5, 52.5, 46.9, 46.7, 46.6, 46.5, 31.6, 31.4, 31.3, 31.3, 29.2, 29.0, 28.9, 28.8, 28.8, 28.7, 28.6, 28.5, 25.0, 25.0, 22.5, 22.5, 22.4, 19.0, 19.0, 15.9, 15.9, 15.1, 14.1, 14.1, 14.0. HRMS (ESI) *m/z* calculated for $C_{16}H_{22}O_4$ [M + NH$_4$]$^+$ 298.2013, found 298.2009.
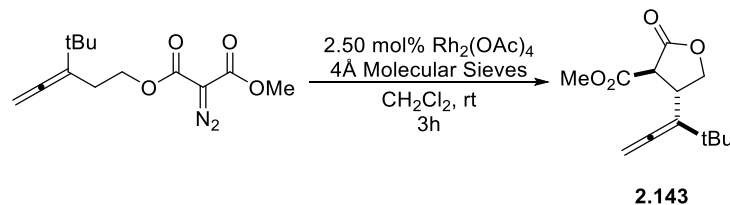
2.143

Lactone 2.143. To a stirred solution of 13 mg (0.03 mmol, 0.025 equiv) Rh$_2$(OAc)$_4$ in 12.3 mL CH$_2$Cl$_2$ was added 1.23 g 4Å molecular sieves. A solution of 327 mg (1.23 mmol, 1.00 equiv) of the diazoester in 12.3 mL CH$_2$Cl$_2$ was added dropwise over a period of 3 h via syringe pump. The resulting green suspension was filtered through a pad of celite using additional CH$_2$Cl$_2$ to aid in the transfer, and the volatiles were removed in vacuo to afford crude lactone **2.143**. The crude material was purified via flash column chromatography on silica gel using a gradient of 0-10% EtOAc in hexanes to give 156 mg (0.65 mmol, 53%) of lactone **2.143** as a a clear, colorless oil. ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.00 (dd, J = 10.5, 1.2 Hz, 1H), 4.94 (dd, J = 10.5, 0.9 Hz, 1H), 4.57 (dd, J = 8.7, 7.5 Hz, 1H), 3.93 (t, J = 8.7 Hz, 1H), 3.81 (s, 3H), 3.59 (d, J = 10.3 Hz, 1H), 3.53 (dddt, J = 10.1, 8.8, 7.6, 1.0 Hz, 1H), 1.06 (s, 9H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 203.6, 171.5, 167.8, 112.1, 81.2, 73.6, 53.0, 53.0, 38.4, 33.2, 29.1, 29.1. HRMS (ESI) *m/z* calculated for C$_{13}$H$_{18}$O$_4$ [M + NH$_4$]$^+$ 256.1543, found 256.1539.
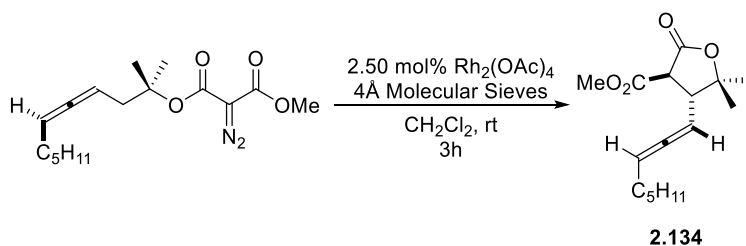
2.134

Lactone 2.134. To a stirred solution of 53.0 mg (0.12 mmol, 0.025 equiv) Rh$_2$(OAc)$_4$ in 49 mL CH$_2$Cl$_2$ was added 4.93 g 4Å molecular sieves. A solution of 1.52 g (4.93 mmol, 1.00 equiv) of the diazoester in 49 mL CH$_2$Cl$_2$ was added dropwise over a period of 3 h via syringe pump. The

resulting green suspension was filtered through a pad of celite using additional CH_2Cl_2 to aid in the transfer, and the volatiles were removed in vacuo to afford crude lactone **2.134**. The crude material was purified on silica gel using a 0-10% gradient of EtOAc in hexanes as eluent to afford 1.09 g (3.89 mmol, 79%) of lactone **2.134** as a pale-yellow oil. Characterization data for lactone **2.134** matches that which has been previously published.[47]
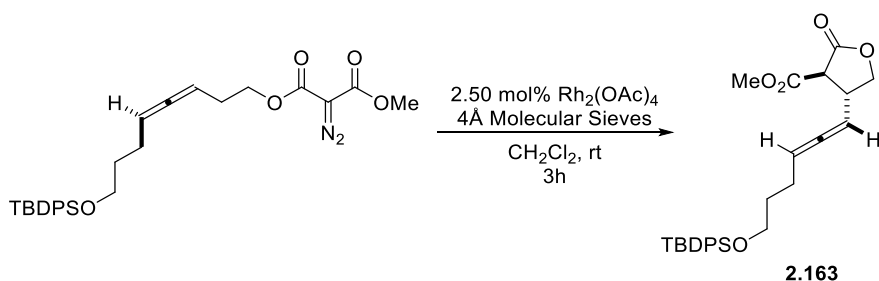
2.163

Lactone 2.163. To a stirred solution of 79.5 mg (0.18 mmol, 0.025 equiv) $Rh_2(OAc)_4$ in 72 mL CH_2Cl_2 was added 7.18 g 4Å molecular sieves. A solution of 3.67 g (7.18 mmol, 1.00 equiv) of the diazoester in 73 mL CH_2Cl_2 was added dropwise over a period of 3 h via syringe pump. The resulting green suspension was filtered through a pad of celite using additional CH_2Cl_2 to aid in the transfer, and the volatiles were removed in vacuo to afford crude lactone **2.163**. The crude material was purified on silica gel using a 0-10% gradient of EtOAc in hexanes as eluent to afford 1.70 g (3.55 mmol, 49%) of lactone **2.163** as a yellow oil. ^1H NMR (500 MHz, Chloroform-d) δ 7.70 – 7.61 (m, 4H), 7.47 – 7.34 (m, 6H), 5.37 (qt, J = 6.4, 2.9 Hz, 1H), 5.15 (ttd, J = 6.2, 3.1, 1.2 Hz, 1H), 4.49 (ddd, J = 9.1, 7.5, 1.8 Hz, 1H), 4.01 (td, J = 8.4, 3.4 Hz, 1H), 3.79 (s, 3H), 3.68 (t, J = 6.2 Hz, 2H), 3.52 (dddd, J = 16.4, 13.7, 7.3, 2.9 Hz, 1H), 3.43 (dd, J = 9.1, 7.0 Hz, 1H), 2.12 (qt, J = 8.5, 4.3 Hz, 2H), 1.63 (dhept, J = 13.6, 6.8 Hz, 2H), 1.05 (s, 9H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 203.5, 203.4, 171.4, 171.3, 167.4, 167.4, 135.5, 133.8, 129.6, 129.5, 127.6, 127.6, 95.2, 95.1,

88.9, 88.8, 71.4, 71.4, 63.0, 63.0, 53.1, 51.9, 51.7, 39.2, 39.2, 31.6, 31.5, 26.8, 24.8, 24.8, 19.2.

HRMS (ESI) *m/z* calculated for $C_{28}H_{34}O_5Si$ [M + Na]$^+$ 501.2068, found 501.2069.

2.3.3. Experimental Procedures for Pd catalyzed Cycloisomerizations of allenyl lactones

2.136
1:1 allene *dr*
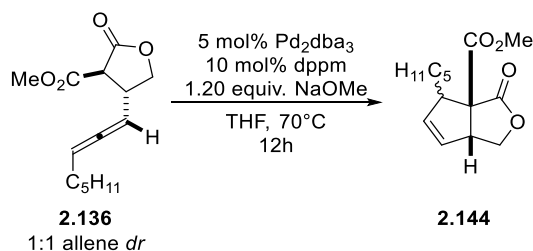
2.144

Cyclopentene 2.144. A 25 mL round bottom flask was charged with 44.0 mg (0.048 mmol, 0.05 equiv) Pd_2dba_3 and 37.0 mg (0.095 mmol, 0.10 equiv) bis(diphenylphosphino)methane (dppm) in a glove box. The flask was removed from the glovebox and 4.7 mL anhydrous THF was added. The resulting orange solution was stirred at room temperature under an N_2 atmosphere for 15 minutes before a solution of 240 mg (0.95 mmol, 1.00 equiv) lactone **2.136** in 4.7 mL anhydrous THF was added, followed by the addition of 62.0 mg (1.14 mmol, 1.20 equiv.) NaOMe. The resulting suspension was heated to 70 °C and stirred at this temperature for 12 h. After stirring was complete, the solution was cooled to room temperature and quenched by the addition of 20 mL aqueous NH_4Cl and extracted with 3x20 mL portions of EtOAc. The combined organics were dried over Na_2SO_4 and the volatiles removed in vacuo to afford the crude cyclization products. The crude material was purified via flash column chromatography on silica gel using a gradient of 0-20% EtOAc in hexanes to give 120 mg (0.48 mmol, 50% isolated yield) of cyclopentene **2.144** as a pale yellow oil. Characterization data for cyclopentene **2.144** matched that which has been previously published.[47]
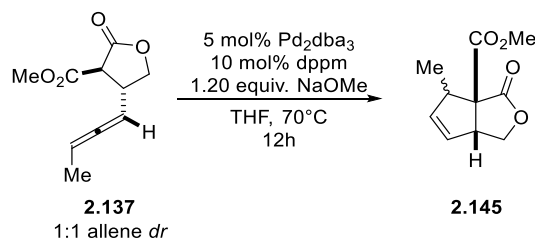
Cyclopentene 2.145. A 25 mL round bottom flask was charged with 37.5 mg (0.041 mmol, 0.05 equiv) Pd$_2$dba$_3$ and 31.5 mg (0.082, 0.10 equiv.) dppm in a glove box. The flask was removed from the glovebox and 4.1 mL anhydrous THF was added. The resulting uspension orange solution was stirred at room temperature under an N$_2$ atmosphere for 15 minutes before a solution of 160 mg (0.82 mmol, 1.00 equiv) lactone **2.137** in 4.1 mL anhydrous THF was added, followed by the addition of 53.0 mg (0.98 mmol, 1.20 equiv) of NaOMe. The resulting was heated to 70 °C and stirred at this temperature for 12 h. After stirring was complete, the solution was cooled to room temperature and quenched by the addition of 15 mL aqueous NH$_4$Cl and extracted with 3x15 mL portions of EtOAc. The combined organics were dried over Na$_2$SO$_4$ and the volatiles removed in vacuo to afford the crude cyclopentene **2.145**. The crude material was purified via flash column chromatography on silica gel using a gradient of 0-20% EtOAc in hexanes to give 96.1 mg (0.49 mmol, 60% isolated yield) of cyclopentene **2.145** as a pale yellow oil. ^{1}H NMR (500 MHz, CDCl$_3$) Major Diastereomer: δ 5.80 (dt, J = 5.6, 2.4 Hz, 1H), 5.58 (dt, J = 5.7, 1.6 Hz, 1H), 4.44 – 4.40 (m, 1H), 4.25 (d, J = 9.1 Hz, 1H), 4.03 (dt, J = 6.0, 2.1 Hz, 1H), 3.81 (s, 3H), 3.41 (tdd, J = 7.0, 5.0, 1.8 Hz, 1H), 1.04 (d, J = 7.0 Hz, 3H). Minor Diastereomer: δ 5.70 (dt, J = 5.7, 2.0 Hz, 1H), 5.52 (dt, J = 5.6, 2.3 Hz, 1H), 4.47 (dd, J = 8.9, 7.4 Hz, 1H), 4.16 (dd, J = 8.9, 2.0 Hz, 1H), 3.85 (dp, J = 6.3, 2.1 Hz, 1H), 3.80 (s, 3H), 3.70 – 3.61 (m, 1H), 1.30 (d, J = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 175.3, 172.9, 169.9, 167.3, 138.0, 137.5, 128.3, 127.3, 70.4, 70.3, 64.0, 61.8,

53.2, 53.0, 48.6, 47.5, 46.1, 16.8, 15.5. HRMS (ESI) *m/z* calculated for $C_{10}H_{12}O_4$ [M + H]$^+$ 197.0808, found 197.0808.

2.138
1:1 allene *dr*
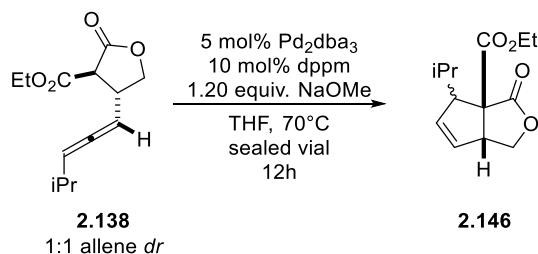
2.146

Cyclopentene 2.146. A flame-dried screw top vial was charged with 12.9 mg (0.014 mmol, 0.05 equiv) Pd$_2$dba$_3$ and 10.8 mg (0.028 mmol, 0.10 equiv) dppm in a glove box. The vial was sealed with a septum and removed from the glovebox, and 1.4 mL anhydrous THF was added. The resulting orange solution was stirred at room temperature under an N$_2$ atmosphere for 15 minutes before a solution of 67 mg (0.28 mmol, 1.00 equiv) lactone **2.138** in 1.4 mL anhydrous THF was added, followed by the addition of 18.2 mg (0.34 mmol, 1.20 equiv) NaOMe. The septum was replaced with a screw top and the resulting suspension was heated to 70 °C and stirred at this temperature for 12 h. After stirring was complete, the solution was cooled to room temperature and quenched by the addition of 10 mL aqueous NH$_4$Cl and extracted with 3x10 mL portions of EtOAc. The combined organics were dried over Na$_2$SO$_4$ and the volatiles removed in vacuo to afford the crude cyclopentene **2.146**. The crude material was purified via flash column chromatography on silica gel using a gradient of 0-20% EtOAc in hexanes to give 23.8 mg (0.10 mmol, 36% isolated yield) of cyclopentene **2.146** as a pale yellow oil. Characterization data for cyclopentene **2.146** matched that which has been previously published.[47]
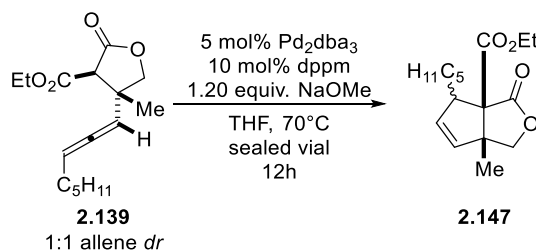
Cyclopentene 2.147. A flame-dried screw top vial was charged with 26.6 mg (0.029 mmol, 0.05 equiv) Pd$_2$dba$_3$ and 21.9 mg (0.057 mmol, 0.10 equiv.) dppm in a glove box. The vial was sealed with a septum and removed from the glovebox, and 2.9 mL anhydrous THF was added. The resulting orange solution was stirred at room temperature under an N$_2$ atmosphere for 15 minutes before a solution of 160 mg (0.57 mmol, 1.00 equiv) lactone **2.139** in 2.8 mL anhydrous THF was added, followed by the addition of 36.9 mg (0.68 mmol, 1.20 equiv) NaOMe. The septum was replaced with a screw top and the resulting suspension was heated to 70°C and stirred at this temperature for 12 h. After stirring was complete, the solution was cooled to room temperature and quenched by the addition of 15 mL aqueous NH$_4$Cl and extracted with 3x15 mL portions of EtOAc. The combined organics were dried over Na$_2$SO$_4$ and the volatiles removed in vacuo to afford the crude cyclopentene **2.147**. The crude material was purified via flash column chromatography on silica gel using a gradient of 0-20% EtOAc in hexanes to give 72.8 mg (0.26 mmol, 45% isolated yield) of cyclopentene **2e** as a pale yellow oil. Characterization data for cyclopentene **2.147** matched previously published data.[47]
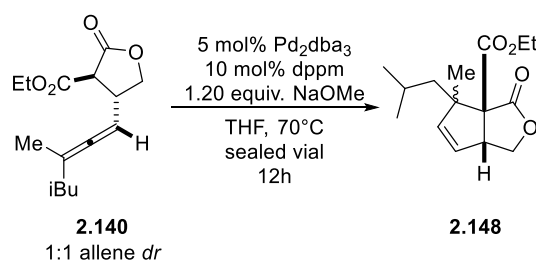
Cyclopentene 2.148. A flame-dried screw top vial was charged with 69.6 mg (0.076 mmol, 0.05 equiv) Pd$_2$dba$_3$ and 58.0 mg (0.076 mmol, 0.10 equiv) dppm in a glove box. The vial was sealed with a septum and removed from the glovebox, and 7.5 mL anhydrous THF was added. The resulting orange solution was stirred at room temperature under an N$_2$ atmosphere for 15 minutes before a solution of 380 mg (1.51 mmol, 1.00 equiv) lactone **2.140** in 7.5 mL anhydrous THF was added, followed by the addition of 97.8 mg (1.81 mmol, 1.20 equiv) NaOMe. The septum was replaced with a screw top and the resulting suspension was heated to 70 °C and stirred at this temperature for 12 h. After stirring was complete, the solution was cooled to room temperature and quenched by the addition of 30 mL aqueous NH$_4$Cl and extracted with 3x30 mL portions of EtOAc. The combined organics were dried over Na$_2$SO$_4$ and the volatiles removed in vacuo to afford the crude cyclization products. The crude material was purified via flash column chromatography on silica gel using a gradient of 0-20% EtOAc in hexanes to give 124.6 mg (0.46 mmol, 31% isolated yield) of cyclopentene **2.148** as a pale yellow oil. Characterization data for cyclopentene **2.148** matched previously published data.[47]
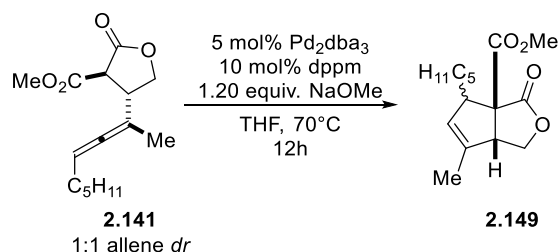
Cyclopentene 2.149. A 25 mL round bottom flask was charged with 27.5 mg (0.03 mmol, 0.05 equiv) Pd$_2$dba$_3$ and 27.5 mg (0.06 mmol, 0.10 equiv) dppm in a glove box. The flask was removed from the glovebox and 2.8 mL anhydrous THF was added. The resulting orange solution was stirred at room temperature under an N$_2$ atmosphere for 15 minutes before a solution of 152 mg (0.76 mmol, 1.00 equiv) lactone **2.141** in 2.8 mL anhydrous THF was added, followed by the

addition of 36.7 mg (0.68 mmol, 1.20 equiv) NaOMe. The resulting suspension was heated to 70 °C and stirred at this temperature for 12 h. After stirring was complete, the solution was cooled to room temperature and quenched by the addition of 15 mL aqueous NH₄Cl and extracted with 3x15 mL portions of EtOAc. The combined organics were dried over Na₂SO₄ and the volatiles removed in vacuo to afford the crude cyclization products. The crude material was purified via flash column chromatography on silica gel using a gradient of 0-20% EtOAc in hexanes to give 93.2 mg (0.35 mmol, 46% isolated yield) of cyclopentene **2.149** as a pale yellow oil. ^{1}H NMR (500 MHz, CDCl₃) <u>Major Diastereomer:</u> δ 5.52 (q, J = 1.9 Hz, 1H), 4.36 – 4.30 (m, 2H), 3.83 – 3.80 (m, 1H), 3.79 (s, 3H), 3.26 – 3.17 (m, 1H), 1.97 – 1.86 (m, 1H), 1.76 (q, J = 1.4 Hz, 3H), 1.51 – 1.15 (m, overlapping signals 7H), 0.88 (q, J = 6.9 Hz, 3H). <u>Minor Diastereomer:</u> δ 5.46 (q, J = 1.7 Hz, 1H), 4.39 (dd, J = 9.1, 7.3 Hz, 1H), 4.24 (dd, J = 9.1, 2.1 Hz, 1H), 3.79 (s, 3H), 3.65 – 3.59 (m, 1H), 3.44 (ddd, J = 9.8, 5.1, 2.5 Hz, 1H), 1.96 – 1.88 (m, 1H), 1.72 (dt, J = 2.7, 1.4 Hz, 3H), 1.52 – 1.15 (m, 7H), 0.88 (q, J = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, CDCl₃) δ 175.7, 173.1, 170.3, 167.5, 136.5, 135.0, 130.1, 130.0, 68.1, 68.0, 64.2, 61.9, 56.0, 53.1, 52.9, 51.7, 51.2, 50.8, 32.0, 31.9, 31.9, 30.5, 28.4, 26.4, 22.6, 22.5, 14.1, 14.1, 14.0. HRMS (ESI) m/z calculated for C₁₅H₂₂O₄ [M + H]$^+$ 267.1591, found 267.1587.

2.142
1:1 allene *dr*
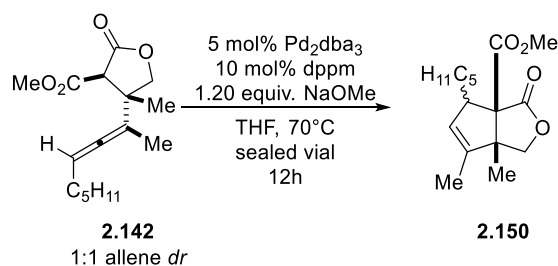
2.150

Cyclopentene 2.150. A flame-dried screw top vial was charged with 11.0 mg (0.012 mmol, 0.05 equiv) Pd₂dba₃ and 9.2 mg (0.024 mmol, 0.10 equiv) dppm in a glove box. The vial was sealed with a septum and removed from the glovebox, and 1.2 mL anhydrous THF was added. The

resulting orange solution was stirred at room temperature under an N$_2$ atmosphere for 15 minutes before a solution of 66.0 mg (0.24 mmol, 1.00 equiv) lactone **2.142** in 1.2 mL anhydrous THF was added, followed by the addition of 15.2 mg (0.28 mmol, 1.20 equiv) NaOMe. The septum was replaced with a screw top and the resulting suspension was heated to 70 °C and stirred at this temperature for 12 h. After stirring was complete, the solution was cooled to room temperature and quenched by the addition of 15 mL aqueous NH$_4$Cl and extracted with 3x15 mL portions of EtOAc. The combined organics were dried over Na$_2$SO$_4$ and the volatiles removed in vacuo to afford the crude cyclization products. The crude material was purified via flash column chromatography on silica gel using a gradient of 0-20% EtOAc in hexanes to give 33.6 mg (0.12 mmol, 50% isolated yield) of cyclopentene **2.150** as a pale yellow oil. ^{1}H NMR (500 MHz, CDCl$_3$) Major Diastereomer: δ 5.61 (dt, J = 3.1, 1.6 Hz, 1H), 4.24 (d, J = 9.0 Hz, 1H), 4.05 (d, J = 9.1 Hz, 1H), 3.76 (s, 3H), 3.16 (t, J = 6.9 Hz, 1H), 1.95 – 1.85 (m, 1H), 1.69 (t, J = 1.5 Hz, 3H), 1.49 – 1.22 (m, overlapping signals, 7H), 1.28 (s, 3H), 0.89 (ddd, J = 8.7, 4.4, 2.1 Hz, 3H). Minor Diastereomer: δ 5.41 (q, J = 1.7 Hz, 1H), 4.27 (d, J = 9.0 Hz, 1H), 3.94 (d, J = 9.0 Hz, 1H), 3.79 (s, 3H), 3.46 (dddd, J = 9.7, 5.8, 2.8, 1.8 Hz, 1H), 1.86 – 1.76 (m, 1H), 1.66 (dd, J = 2.7, 1.5 Hz, 3H), 1.50 – 1.22 (m, overlapping signals, 7H), 1.07 (s, 3H), 0.89 (ddd, J = 8.8, 4.4, 2.1 Hz, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 177.0, 173.9, 169.0, 167.2, 140.1, 138.3, 130.3, 129.4, 72.5, 71.7, 65.7, 65.3, 59.7, 57.6, 52.7, 52.3, 50.2, 47.8, 32.4, 31.9, 31.9, 29.1, 28.6, 27.6, 22.6, 22.6, 17.7, 16.4, 14.1, 14.0, 11.9, 11.8. HRMS (ESI) m/z calculated for C$_{16}$H$_{24}$O$_4$ [M + H]$^+$ 281.1747, found 281.1744.

2.143   **2.151**

Cyclopentene 2.151. A 25 mL round bottom flask was charged with 25.6 mg (0.028 mmol, 0.05 equiv) Pd$_2$dba$_3$ and 21.5 mg (0.056 mmol, 0.10 equiv) dppm in a glove box. The flask was removed from the glovebox and 2.8 mL anhydrous THF was added. The resulting orange solution was stirred at room temperature under an N$_2$ atmosphere for 15 minutes before a solution of 134 mg (0.56 mmol, 1.00 equiv) lactone **2.143** in 2.8 mL anhydrous THF was added, followed by the addition of 36.2 mg (0.67 mmol, 1.20 equiv) NaOMe. The resulting suspension was heated to 70 °C and stirred at this temperature for 12 h. After stirring was complete, the solution was cooled to room temperature and quenched by the addition of 15 mL aqueous NH$_4$Cl and extracted with 3x15 mL portions of EtOAc. The combined organics were dried over Na$_2$SO$_4$ and the volatiles removed in vacuo to afford the crude cyclization products. The crude material was purified via flash column chromatography on silica gel using a gradient of 0-20% EtOAc in hexanes to give 79 mg (0.33 mmol, 59% isolated yield) of cyclopentene **2.151** as a pale yellow oil. ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.47 (q, J = 2.1 Hz, 1H), 4.59 (dd, J = 9.3, 7.6 Hz, 1H), 4.44 (dd, J = 9.3, 3.3 Hz, 1H), 3.88 (ddq, J = 6.9, 3.4, 1.7 Hz, 1H), 3.80 (s, 3H), 3.18 (dt, J = 17.5, 1.9 Hz, 1H), 2.90 (dt, J = 17.4, 2.2 Hz, 1H), 1.10 (s, 9H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 176.2, 169.9, 150.2, 123.1, 71.5, 59.9, 53.2, 53.1, 39.0, 33.0, 30.3. HRMS (ESI) m/z calculated for C$_{13}$H$_{18}$O$_4$ [M + NH$_4$]$^+$ 256.1543, found 256.1540.

2.134
1:1 allene *dr*
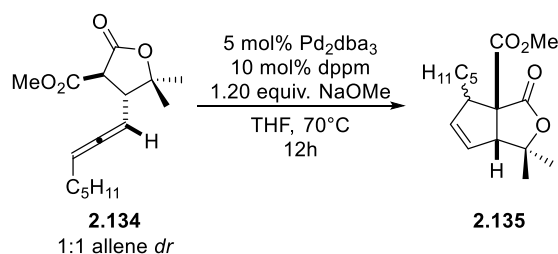
2.135

Cyclopentene 2.135. A 25 mL round bottom flask was charged with 25.6 mg (0.028 mmol, 0.05 equiv) Pd$_2$dba$_3$ and 21.5 mg (0.056 mmol, 0.10 equiv.) dppm in a glove box. The flask was

removed from the glovebox and 2.8 mL anhydrous THF was added. The resulting orange solution was stirred at room temperature under an N_2 atmosphere for 15 minutes before a solution of 134 mg (0.56 mmol, 1.00 equiv) lactone **2.134** in 2.8 mL anhydrous THF was added, followed by the addition of 36.2 mg (0.67 mmol, 1.20 equiv) NaOMe. The resulting suspension was heated to 70 °C and stirred at this temperature for 12 h. After stirring was complete, the solution was cooled to room temperature and quenched by the addition of 15 mL aqueous NH_4Cl and extracted with 3x15 mL portions of EtOAc. The combined organics were dried over Na_2SO_4 and the volatiles removed in vacuo to afford the crude cyclization products. The crude material was purified via flash column chromatography on silica gel using a gradient of 0-20% EtOAc in hexanes to give 79 mg (0.33 mmol, 59% isolated yield) of cyclopentene **2.134** as a pale yellow oil. Characterization data for cyclopentene **2.134** matched previously published data.[47]

2.3.4. Experimental procedures for Pd catalyzed cycloisomerizations of acyclic malonates
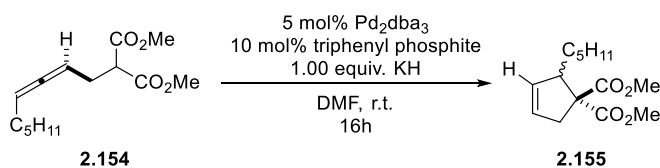
Cyclopentene 2.155. A 5 mL round bottom flask was charged with 9.2 mg (0.01 mmol, 0.05 equiv) Pd_2dba_3, 5.3 μL (0.02 mmol, 0.10 equiv.) triphenyl phosphite, and 1.0 mL DMF in a glove box. The resulting solution was stirred at room temperature for 15 minutes. A solution of 50.9 mg (0.20 mmol, 1.00 equiv.) malonate **2.154** in 1.0 mL DMF was added, followed by the addition of 8.0 mg (0.20 mmol, 1.00 equiv., 50% by weight in paraffin) KH. The flask was removed from the glovebox and stirred for an additional 16h at room temperature. After stirring was complete, the crude reaction was quenched by the addition of 2 mL aqueous NH_4Cl and extracted with 3x5 mL portions of Et_2O. The combined organics were washed with an additional 5x5 mL H2O and

1x5 mL brine, then dried over Na$_2$SO$_4$. The volatiles were removed in vacuo to afford the crude

cyclization products. The crude material was purified via flash column chromatography on silica

gel using a gradient of 0-20% EtOAc in hexanes to give 31 mg (0.12 mmol, 61% isolated yield)

of cyclopentene **2.155** as a pale yellow oil. ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.73 (dq, J = 6.4, 2.2

Hz, 1H), 5.62 (dq, J = 6.1, 2.1 Hz, 1H), 3.72 (s, 3H), 3.72 (s, 3H), 3.50 – 3.43 (m, 1H), 3.24 (dq,

J = 17.1, 2.3 Hz, 1H), 2.74 (ddt, J = 17.2, 2.7, 1.3 Hz, 1H), 1.41 – 1.33 (m, 2H), 1.32 – 1.21 (m,

5H), 1.18 – 1.08 (m, 1H), 0.88 (t, J = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 172.84, 171.02,

132.69, 127.03, 63.47, 52.69, 52.22, 50.42, 39.98, 31.96, 30.86, 27.41, 22.55, 14.04.

2.3.5. Experimental procedures for tandem insertion/cycloisomerizations of lactones
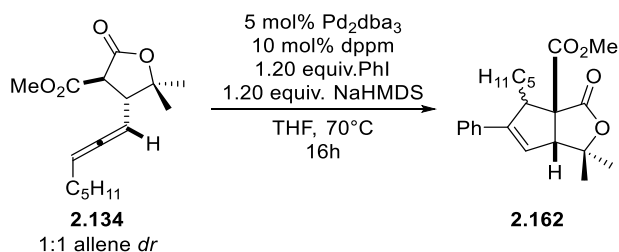
Cyclopentene 2.162. A 10 mL round bottom flask was charged with 9.2 mg (0.01 mmol, 0.05

equiv.) Pd$_2$dba$_3$ and 7.7 mg (0.02 mmol, 0.10 equiv.) dppm in a glove box. The flask was removed

from the glovebox and 1.0 mL anhydrous THF was added. The resulting orange solution was

stirred at room temperature for ca. 15 minutes before 27 μL (0.24 mmol, 1.20 equiv.) iodobenzene

was added. The catalyst solution was stirred for an additional 15 minutes, then a solution of 56

mg (0.20 mmol, 1.00 equiv.) lactone **2.134** in 1.0 mL THF was added, followed by the addition of

0.24 mL (0.24 mmol, 1.20 equiv., 1 M solution in THF) NaHMDS. The resulting mixture was

then heated to reflux for 16 h. The crude mixture was then cooled to room temperature and

quenched with 5 mL NH$_4$Cl and extracted with 3x5 mL portions of EtOAc. The combined

organics were washed with 5x5 mL portions of H$_2$O, 1x5 mL brine, and dried over Na$_2$SO$_4$ to give

crude cyclopentene **2.162**. The crude material was purified on silica gel using a gradient of 0-10%

EtOAc in hexanes to give 50 mg (0.14 mmol, 68%) of a 1:1 diastereomeric mixture of

cyclopentene **2.162** as a pale yellow oil. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.43 – 7.28 (m, overlapping

signals, 10H), 5.92 (dd, J = 2.0, 1.0 Hz, 1H), 5.64 (t, J = 2.4 Hz, 1H), 4.10 (dt, J = 9.2, 2.1 Hz,

1H), 3.97 – 3.94 (m, 1H), 3.94 – 3.91 (m, 1H), 3.85 (s, 3H), 3.85 (s, 3H), 3.71 (dd, J = 2.8, 1.4 Hz,

1H), 1.76 (dddd, J = 14.3, 11.3, 5.2, 2.9 Hz, 2H), 1.56 (s, 3H), 1.46 (s, 3H), 1.44 (s, 3H), 1.43 (s,

3H), 1.42 – 1.33 (m, overlapping signals, 2H), 1.26 (m, overlapping signals, J = 5.2 Hz, 2H), 1.23

– 1.00 (m, overlapping signals, 10H), 0.78 (t, overlapping signals, J = 7.0, 4.0 Hz, 6H). ^{13}C NMR

(126 MHz, CDCl$_3$) δ 174.83, 171.96, 171.82, 169.11, 148.16, 146.81, 135.34, 134.31, 128.61,

128.46, 128.25, 127.96, 126.81, 126.57, 122.03, 122.01, 85.42, 84.55, 65.89, 65.07, 61.75, 58.55,

53.53, 53.41, 53.08, 52.74, 31.94, 31.82, 29.97, 29.88, 29.07, 28.48, 26.99, 25.67, 25.45, 25.14,

22.33, 22.32, 13.98, 13.93. HRMS (ESI) m/z calculated for C$_{22}$H$_{28}$O$_4$ [M + NH$_4$]$^+$ 374.2326, found

374.2326.
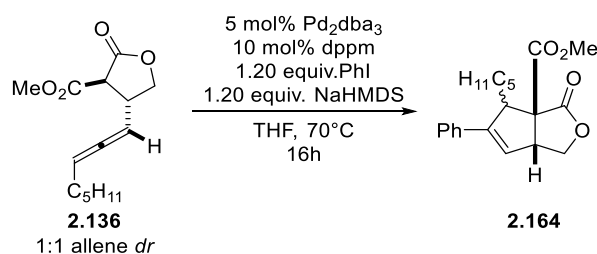
Cyclopentene 2.164. A 10 mL round bottom flask was charged with 9.2 mg (0.01 mmol, 0.05

equiv.) Pd$_2$dba$_3$ and 7.7 mg (0.02 mmol, 0.10 equiv.) dppm in a glove box. The flask was removed

from the glovebox and 1.0 mL anhydrous THF was added. The resulting orange solution was

stirred at room temperature for ca. 15 minutes before 27 µL (0.24 mmol, 1.20 equiv.) iodobenzene

was added. The catalyst solution was stirred for an additional 15 minutes, then a solution of 50

mg (0.20 mmol, 1.00 equiv.) lactone **2.136** in 1.0 mL THF was added, followed by the addition of 0.24 mL (0.24 mmol, 1.20 equiv., 1 M solution in THF) NaHMDS. The resulting mixture was then heated to reflux for 16 h. The crude mixture was then cooled to room temperature and quenched with 5 mL NH$_4$Cl and extracted with 3x5 mL portions of EtOAc. The combined organics were washed with 5x5 mL portions of H$_2$O, 1x5 mL brine, and dried over Na$_2$SO$_4$ to give crude cyclopentene **2.164**. The crude material was purified on silica gel using a gradient of 0-10% EtOAc in hexanes to give 33 mg (0.10 mmol, 51%) of a 1:1 diastereomeric mixture of cyclopentene **2.164** as a pale yellow oil. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.42 – 7.27 (m, overlapping signals, 10H), 5.89 (t, J = 1.3 Hz, 1H), 5.64 (t, J = 2.4 Hz, 1H), 4.52 (dd, J = 9.0, 7.8 Hz, 1H), 4.48 (t, J = 5.7 Hz, 1H), 4.31 (d, J = 9.1 Hz, 1H), 4.24 (dd, J = 8.9, 2.9 Hz, 1H), 4.18 – 4.13 (m, 1H), 4.11 (d, J = 5.5 Hz, 1H), 3.96 – 3.92 (m, 1H), 3.90 (dq, J = 7.4, 2.5 Hz, 1H), 3.84 (s, 6H), 1.73 (dddd, J = 11.2, 8.6, 6.2, 3.6 Hz, 2H), 1.50 – 1.39 (m, 2H), 1.32 – 0.96 (m, overlapping signals, 12H), 0.81 (t, J = 6.8 Hz, 3H), 0.76 (d, J = 7.2 Hz, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 175.47, 173.15, 170.81, 167.34, 149.00, 147.38, 135.38, 134.03, 128.62, 128.42, 128.36, 127.93, 126.84, 126.52, 123.66, 123.59, 70.63, 70.36, 63.89, 62.17, 53.38, 53.08, 52.53, 51.93, 51.43, 49.63, 31.94, 31.91, 29.69, 28.91, 27.39, 24.90, 22.40, 22.29, 14.04, 13.91. HRMS (ESI) *m/z* calculated for C$_{20}$H$_{24}$O$_4$ [M + NH$_4$]$^+$ 346.2013, found 346.2011.
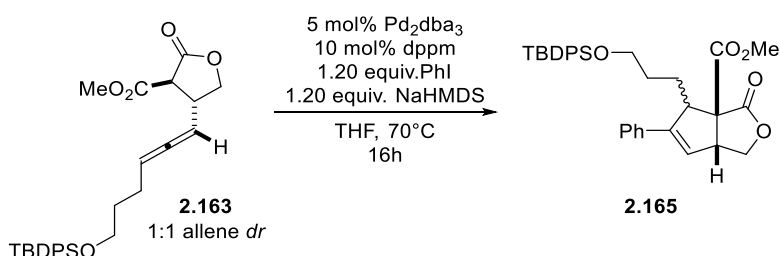
Cyclopentene 2.165. A 10 mL round bottom flask was charged with 9.2 mg (0.01 mmol, 0.05 equiv.) Pd$_2$dba$_3$ and 7.7 mg (0.02 mmol, 0.10 equiv.) dppm in a glove box. The flask was removed

from the glovebox and 1.0 mL anhydrous THF was added. The resulting orange solution was stirred at room temperature for ca. 15 minutes before 27 μL (0.24 mmol, 1.20 equiv.) iodobenzene was added. The catalyst solution was stirred for an additional 15 minutes, then a solution of 96 mg (0.20 mmol, 1.00 equiv.) lactone **2.163** in 1.0 mL THF was added, followed by the addition of 0.24 mL (0.24 mmol, 1.20 equiv., 1 M solution in THF) NaHMDS. The resulting mixture was then heated to reflux for 16 h. The crude mixture was then cooled to room temperature and quenched with 5 mL NH₄Cl and extracted with 3x5 mL portions of EtOAc. The combined organics were washed with 5x5 mL portions of H₂O, 1x5 mL brine, and dried over Na₂SO₄ to give crude cyclopentene **2.165**. The crude material was purified on silica gel using a gradient of 0-10% EtOAc in hexanes to give 20 mg (0.04 mmol, 18%) of cyclopentene **2.165** as a yellow-orange oil; isolated as a single diastereomer. ^{1}H NMR (500 MHz, CDCl₃) δ 7.65 – 7.49 (m, 5H), 7.44 – 7.28 (m, 10H), 5.65 (t, J = 2.4 Hz, 1H), 4.52 (dd, J = 8.9, 7.6 Hz, 1H), 4.24 (dd, J = 9.0, 2.7 Hz, 1H), 4.18 (d, J = 8.2 Hz, 1H), 3.90 (dt, J = 7.3, 2.4 Hz, 1H), 3.83 (s, 3H), 3.65 (dt, J = 10.8, 6.0 Hz, 1H), 3.52 (dt, J = 10.9, 6.1 Hz, 1H), 2.11 – 1.97 (m, 2H), 1.82 – 1.70 (m, 2H), 0.96 (s, 9H). ^{13}C NMR (126 MHz, CDCl₃) δ 173.07, 170.72, 148.96, 135.50, 135.22, 134.00, 133.97, 129.37, 129.35, 128.47, 127.94, 127.50, 127.47, 126.88, 123.69, 70.32, 63.58, 62.08, 53.38, 52.52, 51.16, 30.67, 29.70, 26.78, 25.22, 19.15, 1.03. HRMS (ESI) m/z calculated for C₃₄H₃₈O₅Si [M + NH₄]$^+$ 557.2381, found 557.2382.

2.3.6. Experimental procedures for tandem insertions/cycloisomerizations of malonates

2.154   **2.166**
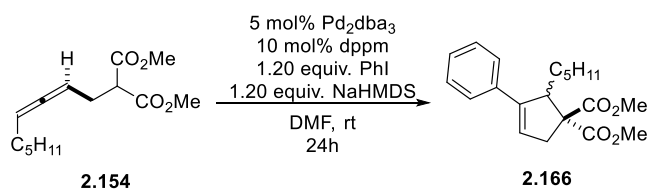
Cyclopentene 2.166. A 10 mL round bottom flask was charged with 11.4 mg (0.013 mmol, 0.05 equiv.) Pd$_2$dba$_3$ and 9.6 mg (0.025 mmol, 0.10 equiv.) dppm in a glove box. The flask was removed from the glovebox and 1.25 mL anhydrous DMF was added. The resulting orange solution was stirred at room temperature for ca. 15 minutes before 34 μL (0.30 mmol, 1.20 equiv.) iodobenzene was added. The catalyst solution was stirred for an additional 15 minutes, then a solution of 64 mg (0.25 mmol, 1.00 equiv.) malonate **2.154** in 1.25 mL DMF was added, followed by the addition of 0.30 mL (0.30 mmol, 1.20 equiv., 1.0 M in THF) NaHMDS. The resulting mixture was stirred at room temperature for 24h, then quenched with 5 mL NH$_4$Cl and extracted with 3x5 mL portions of EtOAc. The combined organics were washed with 5x5 mL portions of H$_2$O, 1x5 mL brine, and dried over Na$_2$SO$_4$ to give crude cyclopentene **2.166**. The crude material was purified on silica gel using a gradient of 0-10% EtOAc in hexanes to give 59 mg (0.18 mmol, 72%) cyclopentene **2.166** as a yellow oil. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.46 – 7.42 (m, 2H), 7.33 (td, J = 8.2, 6.3 Hz, 3H), 5.87 (t, J = 2.7 Hz, 1H), 4.03 – 3.98 (m, 1H), 3.77 (s, 3H), 3.73 (s, 3H), 3.44 – 3.37 (m, 1H), 2.94 (dd, J = 17.5, 3.2 Hz, 1H), 1.41 (tt, J = 14.1, 7.1 Hz, 2H), 1.12 (dt, J = 19.8, 7.0 Hz, 6H), 0.77 (t, J = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 172.83, 170.65, 145.97, 135.62, 128.56, 128.40, 128.36, 127.42, 126.20, 121.74, 64.48, 52.92, 52.45, 49.86, 39.16, 32.10, 29.44, 26.60, 22.36, 13.96. HRMS (ESI) m/z calculated for C$_{20}$H$_{26}$O$_4$ [M + H]$^+$ 331.1904, found 331.1901.
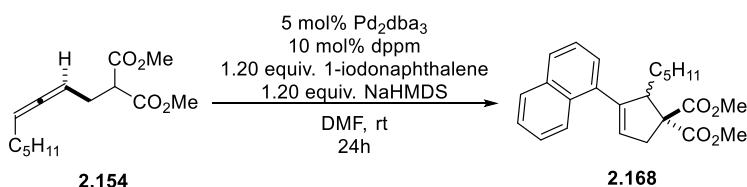

Cyclopentene 2.168. A 10 mL round bottom flask was charged with 9.2 mg (0.01 mmol, 0.05 equiv.) Pd$_2$dba$_3$ and 7.7 mg (0.20 mmol, 0.10 equiv.) dppm in a glove box. The flask was removed

from the glovebox and 1.0 mL anhydrous DMF was added. The resulting orange solution was stirred at room temperature for ca. 15 minutes before 35 μL (0.24 mmol, 1.20 equiv.) 1-iodonaphthalene was added. The catalyst solution was stirred for an additional 15 minutes, then a solution of 51 mg (0.20 mmol, 1.00 equiv.) malonate **2.154** in 1.0 mL DMF was added, followed by the addition of 0.24 mL (0.24 mmol, 1.20 equiv., 1.0 M in THF) NaHMDS. The resulting mixture was stirred at room temperature for 24h, then quenched with 5 mL NH$_4$Cl and extracted with 3x5 mL portions of EtOAc. The combined organics were washed with 5x5 mL portions of H$_2$O, 1x5 mL brine, and dried over Na$_2$SO$_4$ to give crude cyclopentene **2.166**. The crude material was purified on silica gel using a gradient of 0-10% EtOAc in hexanes to give 39 mg (0.10 mmol, 51%) cyclopentene **2.168** as a yellow oil. ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.32 (dd, J = 8.1, 1.6 Hz, 1H), 7.83 (dd, J = 7.7, 1.8 Hz, 1H), 7.76 (dd, J = 6.7, 2.7 Hz, 1H), 7.55 – 7.38 (m, 4H), 5.73 (d, J = 2.7 Hz, 1H), 4.08 (t, J = 6.1 Hz, 1H), 3.82 (s, 3H), 3.77 (s, 3H), 3.54 (dt, J = 17.4, 2.0 Hz, 1H), 2.99 (dd, J = 17.3, 2.8 Hz, 1H), 1.45 – 1.23 (m, 2H), 1.05 – 0.89 (m, 6H), 0.66 – 0.58 (m, 3H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 173.19, 170.93, 145.36, 135.41, 133.76, 131.85, 128.23, 127.71, 126.05, 126.00, 125.94, 125.72, 125.20, 64.38, 53.58, 52.94, 52.43, 39.79, 31.85, 30.01, 26.41, 22.18, 13.79.
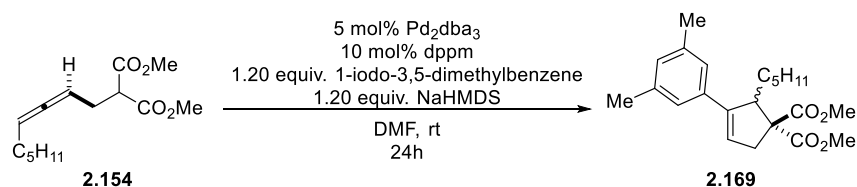

Cyclopentene 2.169. A 10 mL round bottom flask was charged with 9.2 mg (0.01 mmol, 0.05 equiv.) Pd$_2$dba$_3$ and 7.7 mg (0.20 mmol, 0.10 equiv.) dppm in a glove box. The flask was removed from the glovebox and 1.0 mL anhydrous DMF was added. The resulting orange solution was stirred at room temperature for ca. 15 minutes before 35 μL (0.24 mmol, 1.20 equiv.) 1-iodo-3,5-

dimethylbenzene was added. The catalyst solution was stirred for an additional 15 minutes, then

a solution of 51 mg (0.20 mmol, 1.00 equiv.) malonate **2.154** in 1.0 mL DMF was added, followed

by the addition of 0.24 mL (0.24 mmol, 1.20 equiv., 1.0 M in THF) NaHMDS. The resulting

mixture was stirred at room temperature for 24h, then quenched with 5 mL NH$_4$Cl and extracted

with 3x5 mL portions of EtOAc. The combined organics were washed with 5x5 mL portions of

H$_2$O, 1x5 mL brine, and dried over Na$_2$SO$_4$ to give crude cyclopentene **2.169**. The crude material

was purified on silica gel using a gradient of 0-10% EtOAc in hexanes to give 43 mg (0.12 mmol,

60%) cyclopentene **2.169** as a yellow oil. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.05 (s, 2H), 6.88 (s, 1H),

5.82 (t, J = 2.6 Hz, 1H), 4.05 – 3.91 (m, 1H), 3.75 (s, 3H), 3.72 (s, 3H), 3.38 (dt, J = 17.5, 2.0 Hz,

1H), 2.92 (dd, J = 17.4, 3.2 Hz, 1H), 2.30 (s, 6H), 1.41 (dddd, J = 19.3, 14.3, 7.9, 4.8 Hz, 2H),

1.22 – 1.03 (m, 6H), 0.79 (t, J = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 172.90, 170.75,

146.24, 137.78, 135.56, 129.17, 124.13, 121.29, 64.51, 52.88, 52.39, 49.98, 39.16, 32.10, 29.44,

26.52, 22.38, 21.36, 13.98. HRMS (ESI) m/z calculated for C$_{22}$H$_{30}$O$_4$ [M + H]$^+$ 359.2217, found

359.2211.
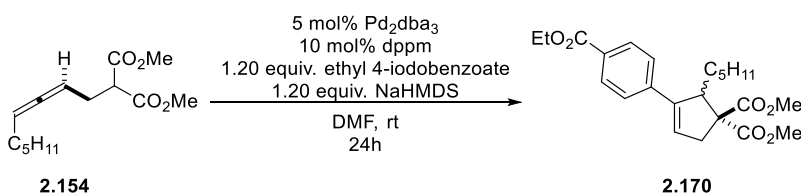
Cyclopentene 2.170. A 10 mL round bottom flask was charged with 9.2 mg (0.01 mmol, 0.05

equiv.) Pd$_2$dba$_3$ and 7.7 mg (0.20 mmol, 0.10 equiv.) dppm in a glove box. The flask was removed

from the glovebox and 1.0 mL anhydrous DMF was added. The resulting orange solution was

stirred at room temperature for ca. 15 minutes before 40 μL (0.24 mmol, 1.20 equiv.) ethyl 4-

iodobenzoate was added. The catalyst solution was stirred for an additional 15 minutes, then a

solution of 51 mg (0.20 mmol, 1.00 equiv.) malonate **2.154** in 1.0 mL DMF was added, followed

by the addition of 0.24 mL (0.24 mmol, 1.20 equiv., 1.0 M in THF) NaHMDS. The resulting

mixture was stirred at room temperature for 24h, then quenched with 5 mL NH₄Cl and extracted

with 3x5 mL portions of EtOAc. The combined organics were washed with 5x5 mL portions of

H₂O, 1x5 mL brine, and dried over Na₂SO₄ to give crude cyclopentene **2.170**. The crude material

was purified on silica gel using a gradient of 0-10% EtOAc in hexanes to give 52 mg (0.13 mmol,

67%) cyclopentene **2.170** as a yellow oil. ¹H NMR (600 MHz, CDCl₃) δ 8.04 – 7.99 (m, 2H), 7.54

– 7.48 (m, 2H), 6.04 – 5.99 (m, 1H), 4.39 (q, *J* = 7.1 Hz, 2H), 4.04 (td, *J* = 6.0, 1.8 Hz, 1H), 4.04

(td, *J* = 6.0, 1.8 Hz, 1H), 3.74 (s, 6H), 3.74 (s, 3H), 3.44 (t, *J* = 2.0 Hz, 1H), 3.44 (t, *J* = 2.0 Hz,

1H), 2.96 (d, *J* = 3.3 Hz, 1H), 2.96 (d, *J* = 3.3 Hz, 1H), 1.49 – 1.36 (m, 5H), 1.50 – 1.37 (m, 5H),

1.20 – 1.03 (m, 6H), 1.20 – 1.06 (m, 6H), 0.78 (t, *J* = 7.1 Hz, 3H), 0.78 (t, *J* = 7.1 Hz, 3H). ¹³C

NMR (151 MHz, CDCl₃) δ 172.67, 170.43, 166.42, 145.46, 140.12, 129.78, 129.25, 126.09,

124.42, 64.56, 60.92, 52.96, 52.49, 49.86, 39.32, 32.10, 29.59, 26.65, 22.32, 14.36, 13.94. HRMS

(ESI) *m/z* calculated for C₂₃H₃₀O₆ [M + Na]⁺ 425.1935, found 425.1933.
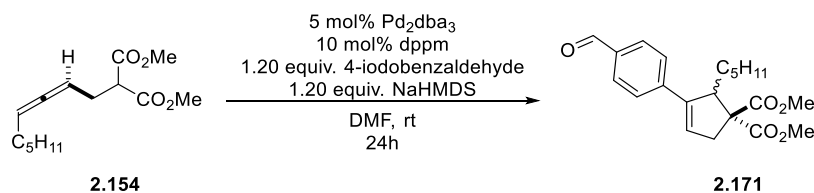
Cyclopentene 2.171. A 10 mL round bottom flask was charged with 9.2 mg (0.01 mmol, 0.05

equiv.) Pd₂dba₃ and 7.7 mg (0.20 mmol, 0.10 equiv.) dppm in a glove box. The flask was removed

from the glovebox and 1.0 mL anhydrous DMF was added. The resulting orange solution was

stirred at room temperature for ca. 15 minutes before 56 mg (0.24 mmol, 1.20 equiv.) 4-

iodobenzaldehyde was added. The catalyst solution was stirred for an additional 15 minutes, then

a solution of 51 mg (0.20 mmol, 1.00 equiv.) malonate **2.154** in 1.0 mL DMF was added, followed

by the addition of 0.24 mL (0.24 mmol, 1.20 equiv., 1.0 M in THF) NaHMDS. The resulting

mixture was stirred at room temperature for 24h, then quenched with 5 mL NH$_4$Cl and extracted with 3x5 mL portions of EtOAc. The combined organics were washed with 5x5 mL portions of H$_2$O, 1x5 mL brine, and dried over Na$_2$SO$_4$ to give crude cyclopentene **2.171**. The crude material was purified on silica gel using a gradient of 0-10% EtOAc in hexanes to give 36 mg (0.10 mmol, 50%) cyclopentene **2.171** as a yellow oil. ^{1}H NMR (500 MHz, CDCl$_3$) δ 9.99 (s, 1H), 7.91 – 7.77 (m, 2H), 7.64 – 7.54 (m, 2H), 6.06 (t, J = 2.7 Hz, 1H), 4.03 (td, J = 6.0, 1.7 Hz, 1H), 3.77 (s, 3H), 3.73 (s, 3H), 3.45 (dt, J = 18.0, 2.1 Hz, 1H), 2.97 (dd, J = 18.0, 3.3 Hz, 1H), 1.51 – 1.33 (m, 2H), 1.20 – 1.02 (m, 6H), 0.77 (t, J = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 191.70, 172.56, 170.30, 145.39, 141.80, 135.29, 130.02, 126.70, 125.56, 64.57, 52.96, 52.49, 49.83, 39.36, 32.04, 29.61, 26.66, 22.29, 13.87.
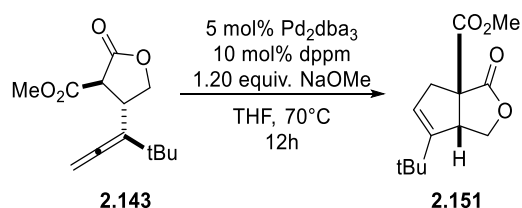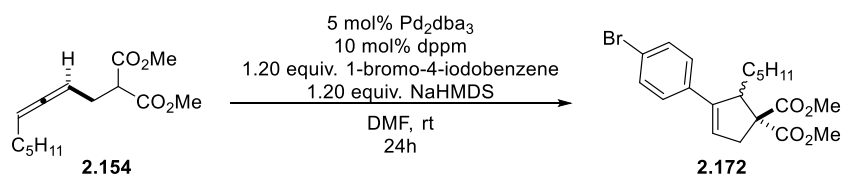

Cyclopentene 2.172. A 10 mL round bottom flask was charged with 9.2 mg (0.01 mmol, 0.05 equiv.) Pd$_2$dba$_3$ and 7.7 mg (0.20 mmol, 0.10 equiv.) dppm in a glove box. The flask was removed from the glovebox and 1.0 mL anhydrous DMF was added. The resulting orange solution was stirred at room temperature for ca. 15 minutes before 68 mg (0.24 mmol, 1.20 equiv.) 1-bromo-4-iodobenzene was added. The catalyst solution was stirred for an additional 15 minutes, then a solution of 51 mg (0.20 mmol, 1.00 equiv.) malonate **2.154** in 1.0 mL DMF was added, followed by the addition of 0.24 mL (0.24 mmol, 1.20 equiv., 1.0 M in THF) NaHMDS. The resulting mixture was stirred at room temperature for 24h, then quenched with 5 mL NH$_4$Cl and extracted with 3x5 mL portions of EtOAc. The combined organics were washed with 5x5 mL portions of H$_2$O, 1x5 mL brine, and dried over Na$_2$SO$_4$ to give crude cyclopentene **2.172**. The crude material

was purified on silica gel using a gradient of 0-10% EtOAc in hexanes to give 61 mg (0.15 mmol, 73%) cyclopentene **2.172** as a yellow oil. [^1]H NMR (500 MHz, CDCl$_3$) δ 7.44 (d, J = 8.5 Hz, 2H), 7.30 (d, J = 8.5 Hz, 2H), 5.87 (s, 1H), 3.97 – 3.92 (m, 1H), 3.76 (s, 3H), 3.72 (s, 3H), 3.39 (dt, J = 17.7, 2.0 Hz, 1H), 2.92 (dd, J = 17.6, 3.2 Hz, 1H), 1.47 – 1.32 (m, 2H), 1.12 (dt, J = 25.4, 7.0 Hz, 6H), 0.78 (t, J = 7.0 Hz, 3H). [^13]C NMR (126 MHz, CDCl$_3$) δ 172.70, 170.47, 145.13, 134.73, 131.56, 127.85, 122.67, 121.28, 64.54, 52.92, 52.44, 49.94, 39.25, 32.10, 29.48, 26.61, 22.34, 13.93. HRMS (ESI) m/z calculated for C$_{20}$H$_{25}$BrO$_4$ [M + Na]$^+$ 431.0826, found 431.0830.
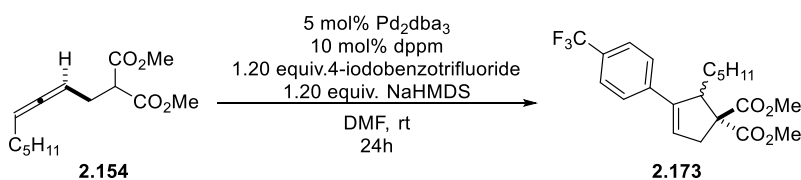
Cyclopentene 2.173. A 10 mL round bottom flask was charged with 9.2 mg (0.01 mmol, 0.05 equiv.) Pd$_2$dba$_3$ and 7.7 mg (0.20 mmol, 0.10 equiv.) dppm in a glove box. The flask was removed from the glovebox and 1.0 mL anhydrous DMF was added. The resulting orange solution was stirred at room temperature for ca. 15 minutes before 35 μL (0.24 mmol, 1.20 equiv.) 4-iodobenzotrifluoride was added. The catalyst solution was stirred for an additional 15 minutes, then a solution of 51 mg (0.20 mmol, 1.00 equiv.) malonate **2.154** in 1.0 mL DMF was added, followed by the addition of 0.24 mL (0.24 mmol, 1.20 equiv., 1.0 M in THF) NaHMDS. The resulting mixture was stirred at room temperature for 24h, then quenched with 5 mL NH$_4$Cl and extracted with 3x5 mL portions of EtOAc. The combined organics were washed with 5x5 mL portions of H$_2$O, 1x5 mL brine, and dried over Na$_2$SO$_4$ to give crude cyclopentene **2.173**. The crude material was purified on silica gel using a gradient of 0-10% EtOAc in hexanes to give 60 mg (0.15 mmol, 73%) cyclopentene **2.173** as a yellow oil. [^1]H NMR (500 MHz, CDCl$_3$) δ 7.58 (d, J = 8.4 Hz, 2H), 7.53 (d, J = 8.3 Hz, 2H), 5.98 (t, J = 2.6 Hz, 1H), 4.04 – 3.98 (m, 1H), 3.77 (s,

3H), 3.73 (s, 3H), 3.44 (dt, J = 17.8, 2.0 Hz, 1H), 2.96 (dd, J = 17.8, 3.2 Hz, 1H), 1.42 (dddd, J =

20.2, 14.1, 8.5, 6.0 Hz, 2H), 1.20 – 1.03 (m, 6H), 0.77 (t, J = 6.9 Hz, 3H). ^{13}C NMR (126 MHz,

CDCl$_3$) δ 172.62, 170.37, 145.07, 139.24, 139.23, 129.42, 129.16, 126.41, 125.48, 125.45, 125.42,

125.39, 125.26, 124.45, 123.10, 64.55, 52.97, 52.51, 49.89, 39.30, 32.07, 29.50, 26.65, 22.33,

13.91. HRMS (ESI) m/z calculated for C$_{21}$H$_{25}$F$_3$O$_4$ [M + H]$^+$ 399.1778, found 399.1778.
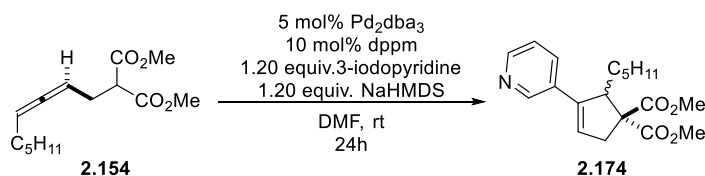
Cyclopentene 2.174. A 10 mL round bottom flask was charged with 9.2 mg (0.01 mmol, 0.05

equiv.) Pd$_2$dba$_3$ and 7.7 mg (0.20 mmol, 0.10 equiv.) dppm in a glove box. The flask was removed

from the glovebox and 1.0 mL anhydrous DMF was added. The resulting orange solution was

stirred at room temperature for ca. 15 minutes before 49 mg (0.24 mmol, 1.20 equiv.) 3-

iodopyridine was added. The catalyst solution was stirred for an additional 15 minutes, then a

solution of 51 mg (0.20 mmol, 1.00 equiv.) malonate **2.154** in 1.0 mL DMF was added, followed

by the addition of 0.24 mL (0.24 mmol, 1.20 equiv., 1.0 M in THF) NaHMDS. The resulting

mixture was stirred at room temperature for 24h, then quenched with 5 mL NH$_4$Cl and extracted

with 3x5 mL portions of EtOAc. The combined organics were washed with 5x5 mL portions of

H$_2$O, 1x5 mL brine, and dried over Na$_2$SO$_4$ to give crude cyclopentene **2.173**. The crude material

was purified on silica gel using a gradient of 0-10% EtOAc in hexanes to give 50 mg (0.15 mmol,

77%) cyclopentene **2.173** as a yellow oil. ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.70 (d, J = 2.3 Hz, 1H),

8.48 (dd, J = 4.8, 1.7 Hz, 1H), 7.71 (dt, J = 7.9, 1.9 Hz, 1H), 7.25 (dd, J = 7.9, 4.8 Hz, 1H), 5.97

(t, J = 2.6 Hz, 1H), 4.00 (td, J = 5.9, 1.7 Hz, 1H), 3.77 (s, 3H), 3.73 (s, 3H), 3.44 (dt, J = 17.7, 2.0

Hz, 1H), 2.96 (dd, J = 17.7, 3.2 Hz, 1H), 1.42 (dddd, J = 19.8, 14.2, 8.5, 5.9 Hz, 2H), 1.12 (dqt, J

= 11.3, 4.6, 2.4 Hz, 6H), 0.77 (t, J = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 172.59, 170.32, 148.53, 147.65, 143.15, 133.31, 131.44, 124.00, 123.30, 64.48, 52.95, 52.48, 49.77, 39.31, 32.06, 29.45, 26.64, 22.31, 13.89. HRMS (ESI) *m/z* calculated for C$_{19}$H$_{25}$NO$_4$ [M + H]$^+$ 332.1856, found 332.1850.

2.4. Bibliography

1. (a) Tsuji, J.; Takahashi, H.; Morikawa, M. *Tetrahedron Lett.* **1965**, 49, 4387-4388. (b) Trost, B. M.; Fullerton, T. J. *J. Am. Chem. Soc.* **1973**, 95, 292-294. (c) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, 103, 2921-2944. (d) Butt, N. A.; Zhang, W. *Chem. Soc. Rev.* **2015**, 44, 7929-7967. (e) Trost, B. M. *Tetrahedron* **2015**, 71, 5708-5733. (f) James, J.; Jackson, M.; Guiry, P. J. *Adv. Synth. Catal.* **2019**, 361, 3061-3049. (g) Fernandes, R. A.; Nallasivam, J. L. *Org. Biomol. Chem.* **2019**, 17, 8647-8672.

2. (a) Djahanbini, D.; Cazes, B.; Gore, J. *Tet. Lett.* **1984**, 25, 203-206. (b) Djahanbini, D.; Cases, B.; Gore, J. *Tetrahedron* **1987**, 43, 3441-3452. (c) Cazes, B.; Djahanbini, D.; Gore, J.; Genêt, J.-P.; Gaudin, J.-M. *Synthesis* **1988**, 983-985.

3. Trost, B. M.; Tour, J. M. *J. Org. Chem.* **1989**, 54, 484-486

4. Selected Reviews: (a) Zimmer, R.; Dinesh, C. U.; Nandanan, E.; Khan, F. A. *Chem. Rev.* **2000**, 100, 3067-3125. (b) Lechel, T.; Pfrengle, F.; Reissig, H. –U.; Zimmer, R. *ChemCatChem* **2013**, 5, 2100-2130.

5. Han, J. W.; Tokunaga, N.; Hayashi, T. *J. Am. Chem. Soc.* **2001**, 123, 12915-12916

6. Mikami, K.; Yoshida, A. *Angew. Chem. Int. Ed.* **1997**, 36, 858-860.

7. Imada, Y.; Ueno, K.; Kutsuwa, K.; Murahashi, S.-I. *Chem. Lett.* **2002**, 140-141.

8. (a) Trost, B. M.; Fandrick, D. R.; Dinh, D. C. *J. Am. Chem. Soc.* **2005**, 127, 14186-14187. (b) Trost, B. M.; Simas, A. B. C.; Plietker, B.; Jäkel, C.; Xie, J. *Chem Eur. J.* **2005**, 11, 7075-7082.

9. (a) Nemoto, T.; Matsumoto, T.; Masuda, T.; Hitomi, T.; Hatano, K.; Hamada, Y. *J. Am. Chem. Soc.* **2004**, 126, 3690-3691. (b) Nemoto, T.; Masuda,T.; Matsumoto, T.; Hamada, Y. *J. Org. Chem.* **2005**, 70, 7172-7178. (c) Nemoto, T.; Fukuda, T.; Matsumoto, T.; Hitomi, T.; Hamada, Y. *Adv. Synth. Catal.* **2005**, 347, 1504-1506. (d) Nemoto, T.; Masuda, T.; Akimoto, Y.; Fukuyama, T.; Hamada, Y. *Org. Lett.* **2005**, 7, 4447-4450. (e) Nemoto, T.; Jin, L.; Nakamura, H.; Hamada, Y. *Tetrahedron Lett.* **2006**, 47, 6577-6581. (f) Nemoto, T.; Fukuyama, T.; Yamamoto, E.; Tamura, S.; Fukuda, T.; Matsumoto, T.; Akimoto, Y.; Hamada, Y. *Org. Lett.* **2007**, 9, 927-930. (g) Nemoto, T.; Harada, T.; Matsumoto, T.; Hamada, Y. *Tetrahedron Lett.* **2007**, 48, 6304-6307. (h) Jin, L.; Nemoto, T.; Nakamura, H.; Hamada, Y. *Tetrahedron: Asymmetry* **2008**, 19, 1106-1113 (i) Nemoto, T.; Tamura, S.; Sakamoto, T.; Hamada, Y. *Tetrahedron: Asymmetry* **2008**, 19, 1751-1759.

10. Phosphine oxide preligands in transition metal catalyzed reactions: (a) Dubrovina, N. V.; Börner, A. Angew. *Angew. Chem. Int. Ed.* **2004**, 43, 5883-5886. (b) Ackermann, L. *Synthesis* **2006**, 1557-1571. (c) Ackermann, L. *Synlett* **2007**, 507-526. (d) Nemoto, T.; Hamada, Y. *Chem. Rec.* **2007**, 7, 150-158. (e) Nemoto, T. *Chem. Pharm. Bull.* **2008**, 56, 1213-1228.

11. Nemoto, T.; Kanematsu, M.; Tamura, S.; Hamada, Y. *Adv. Synth. Catal.* **2009**, 351, 1773-1778.

12. Coulson, R. D. *J. Org. Chem.* **1973**¸38, 1483-1490.

13. Yamamoto, Y.; Al-Masum, M.; Asao, N. *J. Am. Chem. Soc.* **1994**, 116, 6019-6020.

14. Yamamoto, Y.; Al-Masum, M.; Fujiwara, N.; Asao, N. *Tet. Lett.* **1995**, 36, 2811-2814.

15. Takahashi, K.; Miyake, A.; Hata, G. *Chem. Ind.* **1972**, 45, 1183-1191.

16. Besson, L.; Gore, J.; Cazes, B. *Tetrahedron Lett.* **1995**, 36, 3853-3856.

17. Trost, B. M.; Gerusz, V. *J. Am. Chem. Soc.* **1995**, 117, 5156-5157.

18. Meguro, M.; Kamijo, S.; Yamamoto, Y. *Tetrahedron Lett.* **1996**¸37, 7453-7456.

19. Trost, B. M.; Michellys, P. –Y.; Gerusz, V. *Angew. Chem. Int. Ed.* **1997**, 36, 1750-1753.

20. Johnson, E. P.; Chen, G. –P.; Fales, K. R.; Lenk, B. E.; Szendroi, R. J.; Wang, X. –J.; Carlson, J. A. *J. Org. Chem.* **1995**, 60, 6595-6598.

21. (a) MacPherson, L. J.; Bayburt, E. K.; Capparelli, M. P.; Bohacek, R. S.; Clarke, F. H.; Ghai, R. D.; Sakane, Y.; Berry, C. J.; Peppard, J. V.; Trapani, A. J. *J. Med. Chem.* **1993**, 36, 3821-3828. (b) Stanton, J. L.; Sperbeck, D. M.; Trapana, A. J.; Cote, D.; Sakane, Y.; Berry, C. J.; Ghai, R. D. *J. Med. Chem.* **1993**, 36, 3829-3833.

22. Kleijn, H.; Wesmijze, H.; Meijer, J.; Vermeer, P. *Recl. Trav. Chim. Phys-Bas* **1983**, 102, 378-380.

23. Trost, B. M.; Kottirsch, G. *J. Am. Chem. Soc.* **1990**, 112, 2816-2818.

24. Moriya, T. Furuuchi, T.; Miyaura, N. *Tetrahedron* **1994**, 50, 7961-7968.

25. (a) Miyaura, N.; Yamada, K.; Suginome, H.; Suzuki, A. *J. Am. Chem. Soc.* **1989**, 107, 972-980. (b) Miyaura, N.; Ishiyama T.; Sasaki, H.; Ishikawa, M.; Suzuki, A. *J. Am. Chem. Soc.*

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1989, 111, 314-321. (c) Oh-e, T.; Miyaura, N.; Suzuki, A. *J. Org. Chem.* **1993**, 58, 2201-2208.

26. (a) Tour, J. M.; Negishi, E. –i. *J. Am. Chem. Soc.* **1985**, 107, 8289-8291. (b) Negishi, E. –i.; Zhang, Y.; O'Connor, B. *Tetrahedron Lett.* **1988**, 29, 2915-2918. (c) Negishi, E. –i.; Iyer, S.; Rousset, C. J. *Tetrahedron Lett.* **1989**, 30, 291-294. (d) Zhang, Y.; Negishi, E. –i. *J. Am. Chem. Soc.* **1989**, 111, 3454-3456. (e) Zhang, Y.; Wu, G. –z.; Agnel, G.; Negishi, E. –i. *J. Am. Chem. Soc.* **1990**, 112, 8590-8592.

27. (a) Ma, S.; Negishi, E. –i. *J. Org. Chem.* **1994**, 59, 4730-4732. (b) Negishi, E. –i.; Ma, S. *J. Am. Chem. Soc.* **1995**, 117, 6345-6357.

28. Patai, S., Ed; *The chemistry of ketenes, allenes, and related compounds part I*; John Wiley & Sons: New York, **1980**; pp 157.

29. Ahmar, M.; Cazes, B.; Gore, J. *Tetrahedron Lett.* **1984**, 25, 4505-4508.

30. Cazes, B. Colovray, V.; Gore, J. *Tetrahedron Lett.* **1988**, 29, 627-630.

31. Kopola, N.; Friess, B.; Cazes, B.; Gore, J. *Tetrahedron Lett.* **1989**, 30, 3963-3966.

32. Friess, B.; Cazes, B.; Gore, J. *Tetrahedron Lett.* **1988**, 29, 4089-4092.

33. (a) Stang, P. J.; Hanack, M.; Subramanian, L. R. *Synthesis* **1982**, 85-126. (b) McMurry, J. E.; Scott, J. W. *Tetrahedron Lett.* **1983**, 979-982.

34. Cacchi, S.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1984**, 25, 2271-2274.

35. Vicart, N.; Cazes, B.; Gore, J. *Tetrahedron Lett.* **1995**, 36, 5015-5018.

36. Chaptal, N.; Colovray-Gotteland, V.; Grandjean, C.; Cazes, B.; Gore, J. *Tetrahedron Lett.* **1991**, 32, 1795-1798.

37. Anies, C.; Cazes, B.; Gore, J. *J. Chem. Res. (S)* **1996**, 116-117.

38. Gauthier, V.; Cazes, B.; Gore, J. *Tetrahedron Lett.* **1991**, 32, 915-918.

39. Hiroi, K.; Kato, F.; Yamagata, A. *Chem. Lett.* **1998**, 397-398.

40. Ahmar, M.; Cazes, B.; Gore, J. *Tetrahedron Lett.* **1985**, 26, 3795-3798.

41. Ahmar, M.; Cazes, B.; Gore, J. *Tetrahedron* **1987**, 43, 3453-3463.

42. (a) Larock, R. C.; Berrios-Peña, N. G.; Fried, C. A. *J. Org. Chem.* **1991**, 56, 2615-2617. (b) Larock, R. C.; He, Y.; Leong, W. W.; Han, X.; Refvik, M. D.; Zenner, J. M. *J. Org. Chem.* **1998**, 63, 2154-2160.

43. Kato, F.; Hiratsuka, Y.; Mitsui, T.; Watanabe, T.; Hiroi, K. *Heterocycles* **1999**, 50, 83-87.

44. (a) Shi, Z.; Ma, S. *J. Org. Chem.* **1998**, 63, 6387-6389. (b) Ma, S.; Wu, S. *J. Org. Chem.* **1999**, 64, 9314-9317. (c) Ma, S.; Zhao, S. *J. Am. Chem. Soc.* **1999**, 121, 7943-7944. (d) Ma, S.; Li, L. *Org. Lett.* **2000**, 2, 941-944. (e) Ma, S.; Xie, H. *Org. Lett.* **2000**, 2, 3801-3803. (f) Ma, S.; Duan, D.; Shi, Z. *Org. Lett.* **2000**, 2, 1419-1422. (g) Ma, S.; Zhang, J. *Chem. Commun.* **2000**, 117-118. (h) Ma, S.; Shi, Z.; Wu, S. *Tetrahedron Asymmetry* **2001**, 12, 193-195.

45. (a) Ma, S.; Zhao, S. *Org. Lett.* **2000**, 2, 2495-2497. (b) Ma, S.; Jiao, N.; Zhao, S.; Hou, H. *J. Org. Chem.* **2002**, 67, 2837-2847.

46. Huang, X.; Jiang, X.; Fu, C.; Ma, S. *Adv. Synth. Catal.* **2013**, 355, 3295-3303.

47. Reeves, R. D.; Phelps, A. M.; Raimbach, W. A. T.; Schomaker, J. M. *Org. Lett.* **2017**, 19, 3394-3397.

48. Amatore, C.; Jutand, A.; Meyer, G.; Carelli, I.; Chiarotto, I. *Eur. J. Inorg. Chem.* **2000**, 1855-1859.

49. Corkey, B. K.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, 127, 17168-17169.

50.   Rülke, R. E.; Kliphuis, D.; Elsevier, C. J.; Fraanje, J.; Goubitz, K.; van Leeuwen, P. W. N. M.; Vrieze, K. *J. Chem. Soc., Chem. Commun.* **1994**, 1817-1819.

51. Okamoto, K.; Kai, Y.; Yasuoka, N.; Kasai, N. *J. Organomet. Chem.* **1974**, 65, 427-4413

52. (a) Asao, N.; Nogami, T.; Takahashi, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **2002**, 124, 764-765. (b) Mikami K., Hatano M., Akiyama K. Active Pd(II) Complexes as Either Lewis Acid Catalysts or Transition Metal Catalysts. In: Tsuji J. (eds) Palladium in Organic Synthesis. Topics in Organometallic Chemistry, vol 14. Springer, Berlin, Heidelberg

53. (a) Grushin, V. V. *Chem Rev.* **1996**, 96, 2011-2033. (b) Curtis, C. J.; Miedaner, A.; Raebiger, J. W.; DuBois, D. J. *Organometallics* **2004**, 23, 511-516. (c) Amatore, Jutand, A.; Meyer, G.; Carelli, I.; Chiarotto, I. *Eur. J. Inorg. Chem.* **2000**, 1855-1859. (d) Mikami, K.; Hatano, M. *Proceedings of the National Academy of Sciences of the United States of America* **2004**, 101, 5767-5769.

54. Senn, H. M.; Ziegler, T. *Organometallics* **2004**, 23, 2980-2988.

55. (a) Zook, H. D.; Gumby, W. L; *J. Org. Chem.* **1960**, 82, 1386-1389. (b) O'Donnell, M. J.; Chen, N.; Zhou, C.; Murray, A. *J. Org. Chem.* **1997**, 62, 3962-3975. (c) Carey, F. A.;

Sundberg, R. J. *Advanced Organic Chemistry Part A: Structure and Mechanisms, 5ᵗʰ edition*; Springer: New York, NY, **2007**; pp 614.

56. Ukai, T.; Kawazura, H.; Ishii, Y.; Bonnett, J.; Ibers, J. A. *J. Organomet. Chem.* **1974**, 65, 253-266.

57. Armarego, W. L. F.; Chai, C. L. L. Chapter 4 – Purification of Organic Chemicals. In *Purification of Laboratory Chemicals (Sixth Edition)*, Butterworth-Heinemann: Oxford, 2009; pp 88-444.

58. Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, 43, 2923-2925.

59. Phelps, A. M.; Dolan, N. S.; Connell, N. T.; Schomaker, J. M. *Tetrahedron* **2013**, 69, 5614-5621.

Part II. Synthetic Small Molecule Ionophores

Chapter 3

Synthesis and Evaluation of the Ion Transport Properties of Photoswitchable

Azobenzene Crown Ethers in Planar Bilayers

This work was conducted in collaboration with the Chanda lab at the University of Wisconsin-

Madison

3.1 Introduction to Electrophysiological Methods

3.1.1. Ion transport in biological systems

Since the observation that the function of the nervous system is controlled by electrical activity in 1791 by Galvani,[1] bioelectric signaling has been implicated in a host of biological processes, including neuronal function,[2] cardiac function,[3] early development,[4] wound healing,[5] and cancer.[6] Two important classes of ionophoric compounds which have received much attention due to their ability move of ions and establish a membrane potential are ion carriers[7] and ion channels (Figure 3.1).[8]

Ion carriers function by capturing and facilitating the transfer of an ion across the membrane; release of the ion results in a change in membrane potential (Figure 3.1, A).[7] Ion selectivity is permitted by the pore size. Unlike ion carriers, ion channels form hydrophobic pores in the membrane which are capable of opening and closing based on the introduction of a stimulus (Figure 3.1, B).[8] These stimuli can include changes in membrane voltage,[8b,c] mechanical stimuli,[8d] and ligand binding.[8e,f] Ion channels transport ions significantly faster than carriers, typically exhibiting rates $>10^5$ that of carriers.[8a] Similar to ion carriers, ion channels exhibit ion selectivity through constriction of the channel width.[8a] Both ion carriers and ion channels are passive facilitators of ion transport; as such, ions diffuse down their respective electrochemical gradients.[9]

Figure 3.1. Ion transport across biological membranes facilitated by ion channels.

A. Transport via Ion Carriers

B. Transport via Ion Channels
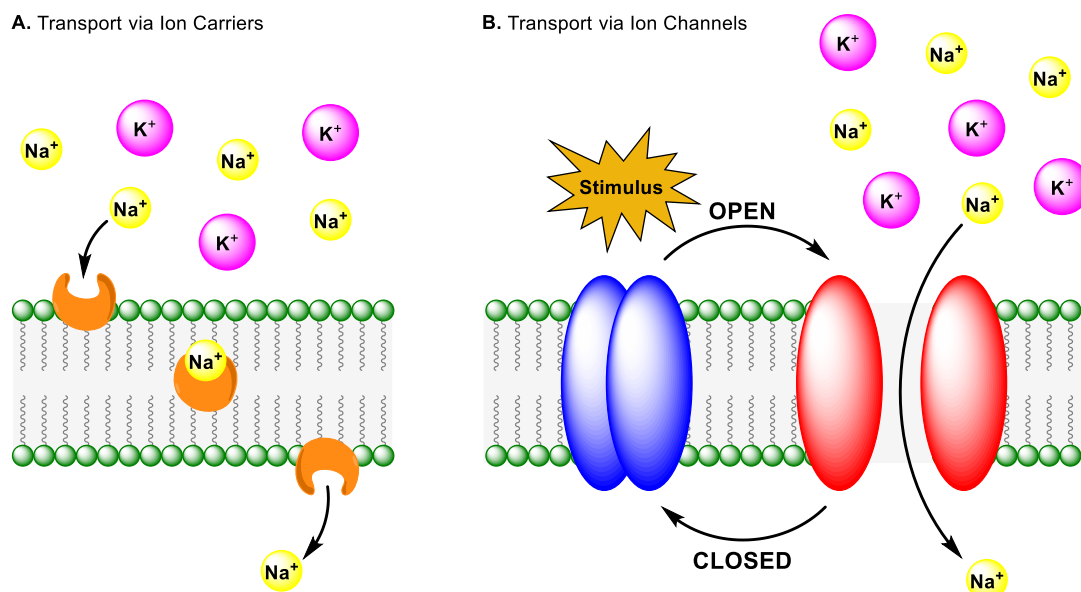
3.1.2. Microelectrode-based approaches for the study of ion transport

Patch clamp techniques are among the most widely used methods to study the currents induced by ion channels in living cells.[10] The cell-attached method (Figure 3.2, A)[11] allows for the study of a small section of a membrane, often containing only a single ion channel. When a cell-attached clamp is used, the membrane of the cell is not ruptured, rendering control over the intracellular environment of the patch exceedingly difficult. This method also does not allow for control of the membrane potential.[10]

The whole-cell patch clamp technique (Figure 3.2, B) has become the method of choice for the study of entire cellular systems.[10] By applying either a small burst of suction or voltage to the membrane of the cell, the membrane ruptures and forms a tight seal to the pipette.[10b] Whole-cell techniques allow for voltage control across the membrane of the entire cell, in turn allowing for the measurement of current from all ion channels within the cell membrane to be observed. Additionally, the chemical composition of both the interior and exterior of the cell can be modulated to distinguish between different types of ion channel activities.[10b]

Figure 3.2. Cell-attached and whole-cell patch clamp techniques.

A. Cell-attached patch clamp   B. Whole-cell patch clamp
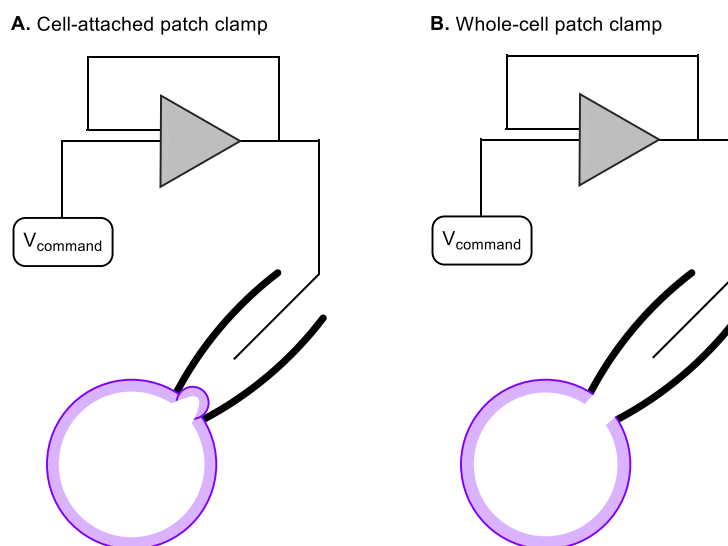
Removal of the pipette from the membrane of a cell-attached setup results in the formation

of the inside-out configuration (Figure 3.3, A), where the interior of the cell membrane is exposed

to the bath solution.[10] This method allows for the observation of individual ion channels contained

within the excised portion of the membrane. As with whole-cell techniques, the chemical

composition on both sides of the clamped membrane can be controlled, which is particularly useful

for studying ion channel processes that are facilitated by intracellular ligands.[10b,c] Withdrawing

the pipette from the whole-cell clamp results in the formation of the outside-out configuration

(Figure 3.3, B), where the outside of the membrane is exposed to the bath solution.[10b] Although

harder to obtain, the outside-in configuration is particularly useful for the study of ligand gated ion

channels.[10b,c]

Figure 3.3. Inside-out and outside-out patch clamp techniques.

A. Inside-out patch clamp

B. Outside-in patch clamp

$V_{command}$

$V_{command}$
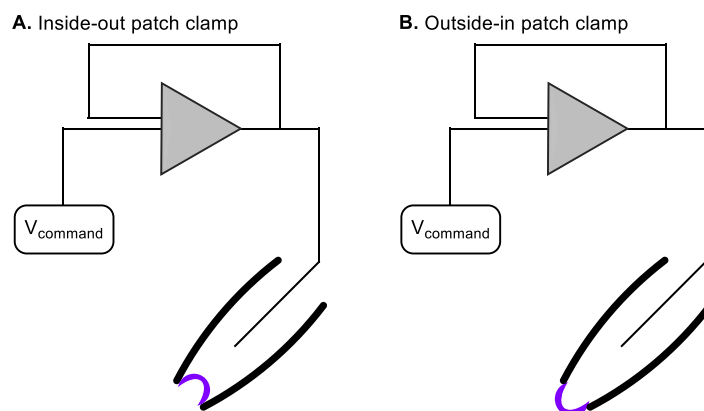
The development of planar patch clamp arrays (Figure 3.4) has allowed for the automation of electrophysiological measurements, in turn providing a potential platform for high throughput measurements.[12] In this method, the cell culture is suspended above a dielectric partition that is etched with several openings that resemble pipette tips and connected to an amplifier.[10b,c;12] Applying suction through these openings results in rupture of the cell membrane and formation of gigaseals to generate whole-cell configurations.[10b] In most cases, the success rate for forming whole-cell patches with planar arrays is quite low due to the difficulties associated with successfully guiding the cells to the recording sites on the array.[10b,c]

Figure 3.4. Planar patch clamp array.
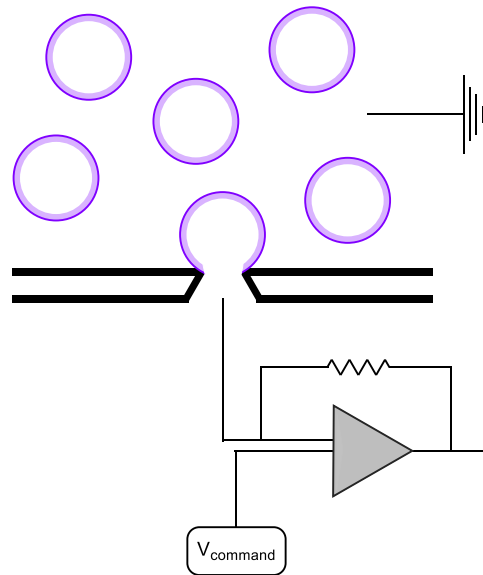
Despite their widespread use in a variety of applications, patch clamp techniques possess limitations that inhibit their ability to study complicated cellular architectures in living systems.[13] Measurements of certain cell structures, such as the dendritic spines, dendritic shafts, axons, and nerve terminals of neurons, is particularly challenging with microelectrode-based approaches.[14] Microelectrode-based approaches have only been able to control the voltage present in the soma of neurons; this is problematic as the voltage changes across the membrane of a neuron are highly non-uniform in nature.[14a] In addition to being highly invasive, microelectrode-based approaches are often not amenable to high throughput screening.[10b]

3.1.3. Optogenetics-based approaches for the study of ion transport

The implementation of prokaryotic opsins and optical methods, termed optogenetics, to regulate membrane voltage have allowed for several advancements in the study of neuronal circuitry.[15] Three types of opsins have found somewhat widespread use in optogenetics-based approaches: bacteriorhodopsins,[16] halorhodopsins,[17] and channelrhodopsins.[18] Bacteriorhodopsins and halorhodopsins are involved in the transport of protons and chloride ions,

respectively; these opsins typically have an inhibitory response caused from hyperpolarization of the membrane, thus inhibiting neuron's ability to fire action potentials.[16,17] Alternatively, channelrhodopsins typically display an excitatory effect by allowing the passage of cations through the membrane, resulting in membrane depolarization.[18] As compared to traditional patch clamp methods, optogenetics-based approaches provide superb spatial control, allowing for multi-site measurements across cells possessing high degrees of arborization.[19]

Upon irradiation, channelrhodopsins undergo a conformational change from a closed state to an open state, allowing for the movement of ions down a concentration gradient across a membrane (Figure 3.5). Advancements in fluorescent voltage-sensing dyes (orange ellipse, Figure 3.5)[20] and other voltage sensors[21] have allowed for the resolution of small changes in membrane potential. In the simple system depicted in Figure 3.5, excitation of the voltage-sensing dye with an LED results in fluorescence of the dye, which is detected by a photodiode. This signal can then be used to modulate a second LED which opens the channel and allows for the passage of ions, thus resulting in a change in membrane conductance. Modifications to the channelrhodopsin structure, either by natural or engineered methods,[22] have allowed for some control regarding the kinetics, open/closed stability of the ion channel, ion conductance, and excitatory wavelength tunability of these systems. Additional advancements in this field have allowed for the targeted delivery and expression of opsins in a host of cell types.[22]

Figure 3.5. All-optical channelrhodopsin electrophysiology system.
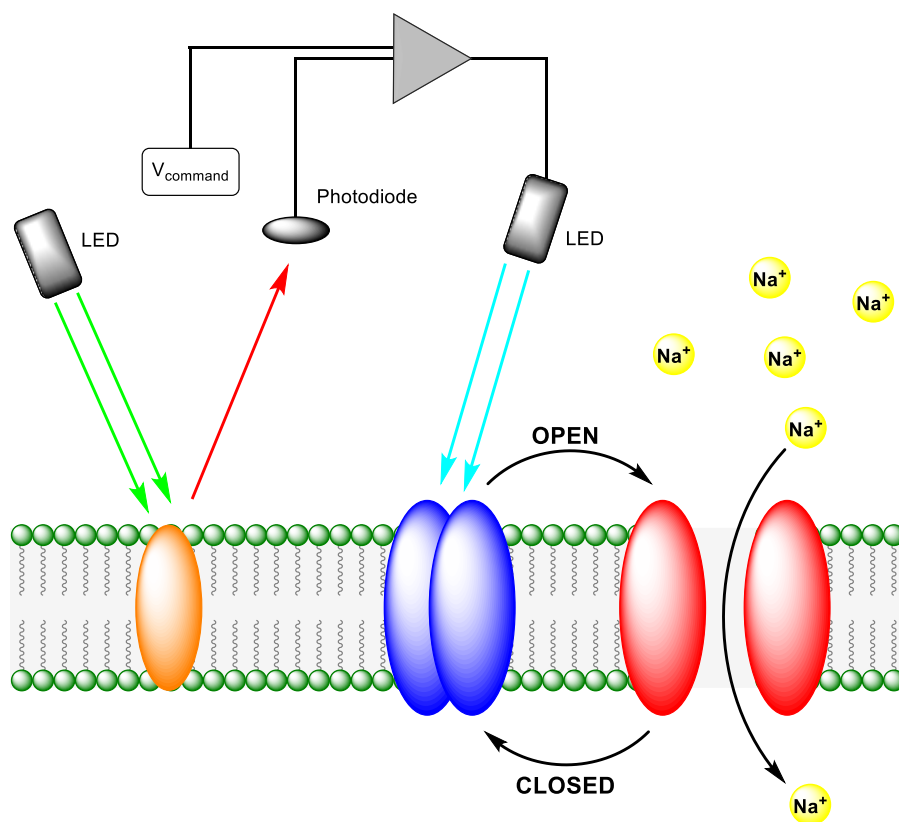
Although optogenetics-based approaches typically provide improved spatial control, are amenable to high throughput screening efforts, and are less invasive than traditional patch clamp methods, they have not been able to completely replace patch clamp methods for neuronal study.[23] Channelrhodopsins are capable of moving one ion per photocycle, in turn altering the membrane potential only by a few millivolts; to obtain complete control over the electrical activity of a cell, ion throughput via channelrhodopsins needs to be substantially increased. In addition to the challenges associated with improving ion flux, many channelrhodopsins are often mislocalized or poorly expressed in target cells, further limiting the potential utility of these methods.

3.1.4. Previous work with crown ether azobenzenes

Small molecule actuators of membrane potential may be used to overcome some of the limitations associated with both patch clamp and optogenetics-based methods. Since their

accidental discovery in 1967,[24] crown ether containing motifs have been utilized in a variety of settings, including increasing the solubility of salts in organic solvents, as phase transfer catalysts, mediators of ion selective extractions, coordination and supramolecular chemistry, host-guest interactions, and as sensors, among others.[25] Additional developments in this area led to the disclosure of the bis-crown ether structures **3.1** and **3.2** (Figure 3.6), which are linked with an azobenzene photoswitch.[26] The efficacy of these crown ether azobenzenes as photocontrollable ion extraction reagents have been evaluated in a variety of settings,[27] most notably for their ability to transport ions across phase boundaries upon irradiation with light.[26]

Figure 3.6. Crown ether azobenzenes.
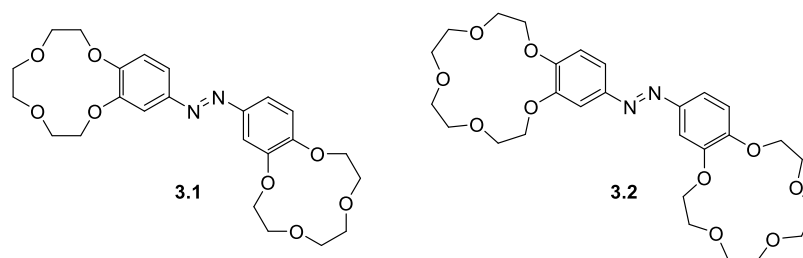
The synthesis of crown ether azobenzenes **3.1** and **3.2** were first reported by Shinkai and coworkers in the early 1980s (Scheme 3.1).[26] Nitrated benzocrown ethers **3.4** and **3.5** were prepared by bis-alkylation of catechol **3.3** followed by nitration with HNO_3. Nitrated **3.4** was obtained in only 4% after two reaction steps. The authors noted that after the initial alkylation step, a significant amount of dimerized product had formed; they were unable to cleanly isolate the desired benzo-12-crown-4 from this mixture. The two step yield for the formation of **3.5** was not reported; only the yield for the nitration step was published.

A reductive dimerization strategy was used to convert **3.4** and **3.5** to the corresponding azobenzene crown ethers **3.1** and **3.2**. Upon heating in the presence of aqueous base and zinc

metal, the 12-crown-4 and 15-crown-5 azobenzenes **3.1** and **3.2** were obtained in 11% and 9%, respectively. In order to prepare the required amount of material for their studies in liquid membranes, Shinkai and coworkers started with >40g of catechol **3.3** to offset losses due to poor yields.

Scheme 3.1. Previous syntheses of azobenzene crown ethers.
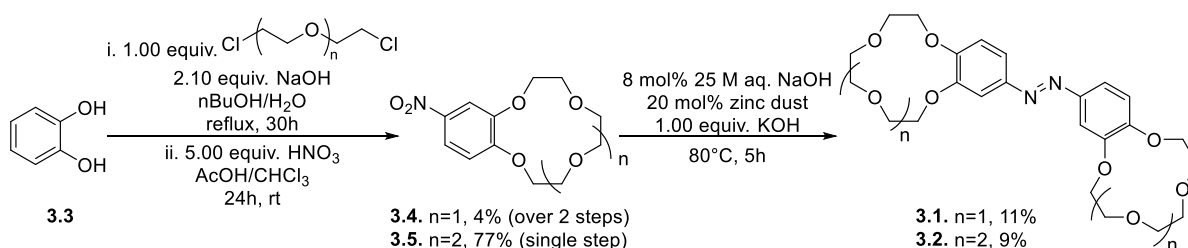
Mandolini and coworkers[28] utilized an oxidative dimerization methodology described by Noureldin[29] in 1999 to synthesize the 18-crown-6 derivative **3.7** (Figure 3.2). Nitrated **3.6** was reduced to the corresponding aniline, followed by oxidation to **3.7** with a heterogeneous Cu-supported KMnO4 reagent. Although the yields obtained from this approach were three-fold higher than those in previous reports, the required reaction times were significantly longer.

Scheme 3.2. Oxidative dimerization strategy to furnish azobenzene crown ethers.
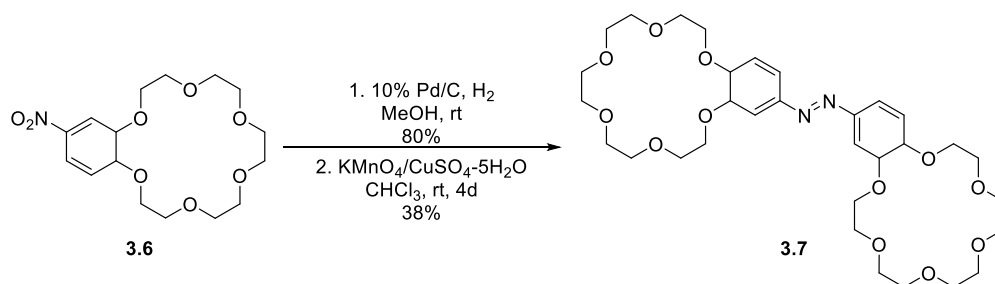
The transport properties of azobenzene crown ethers **3.1** and **3.2** were evaluated in liquid membranes prepared from *o*-dichlorobenzene and aqueous salt solutions in a U-tube apparatus.[26c]

When irradiated at 365 nm, *trans/cis* photoisomerization of **3.2** occurs, resulting in complexation of an ion and transport across the liquid membrane phase (Figure 3.7). Irradiation at 525 nm results in *cis/trans* photoisomerization, and the cycle can be repeated. Some ion selectivity was achieved by changing the size of the crown ether; 15-crown-5 **3.2** transported K^+ preferentially while 12-crown-4 **3.1** transported Na^+. The counteranion of each salt investigated was also found to impact the ability of **3.1** and **3.2** to successfully transport ions across liquid membranes.[26]

Figure 3.7. Ion transport in bulk membranes with azobenzene crown ethers.
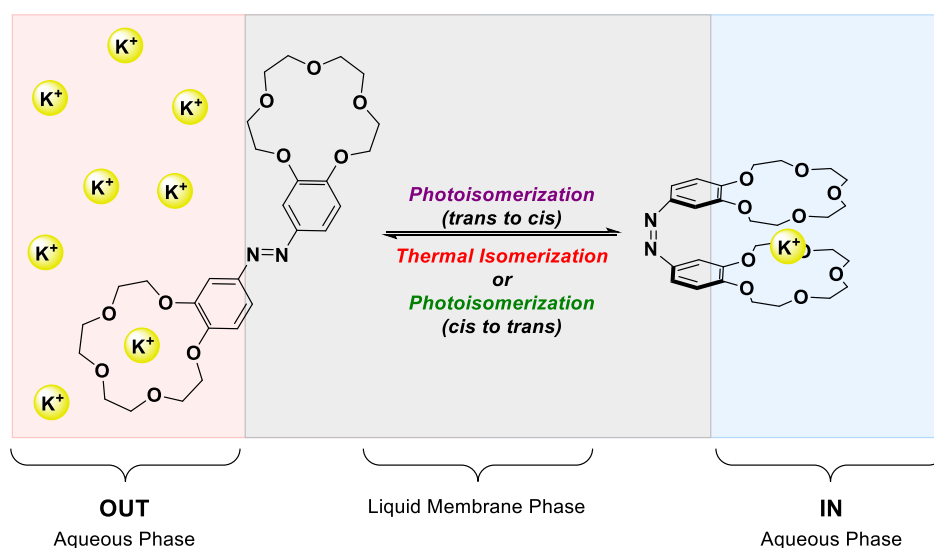
3.1.5. Conclusions

While the development of patch clamp and optogenetics-based techniques have revolutionized the field of electrophysiology, each method possesses limitations that still remain unaddressed. In addition to the invasiveness of the techniques involved, patch clamp methods suffer from a lack of spatial control in complex cell architectures and are typically limited with respect to high throughput screening. Optogenetics-based approaches have allowed for high degrees of spatial control, allowing for the study of a multitude of cell types, however temporal

control is somewhat limited. Additionally, the expression of channelrhodopsins in certain cell types remains challenging. Based on their ability to transport ions in liquid membranes, crown ether azobenzenes may provide an alternative to patch clamp and optogenetics-based techniques, forgoing the invasiveness and expression issues present in previously established methods while maintaining both temporal and spatial control.

3.2. Results and Discussion

Previous studies using liquid membranes have demonstrated the ability of azobenzene crown ethers **3.1** and **3.2** to transport ions across a phase boundary in a photocontrollable manner. Several of these studies have postulated that **3.1** and **3.2** are suitable scaffolds for the photoinduced transport of ions across synthetic and biological membranes. A proposed depiction of photoinduced ion transport by azobenzene **3.2** in a planar bilayer is depicted in Figure 3.8. Irradiation at 365 nm results in the isomerization of *trans*-**3.2** to *cis*-**3.2**, which is capable of ligating an ion. The ion-bound *cis* form shuttles the ion to the interior of the bilayer and releases the ion upon isomerization to *trans*-**3.2** when irradiated at 525 nm. In collaboration with the Chanda lab at the University of Wisconsin-Madison, the photoswitchable ion transport properties of **3.1** and **3.2** were evaluated in planar bilayers.

Figure 3.8. Photoswitchable ion transport across a bilayer with crown ether azobenzenes.
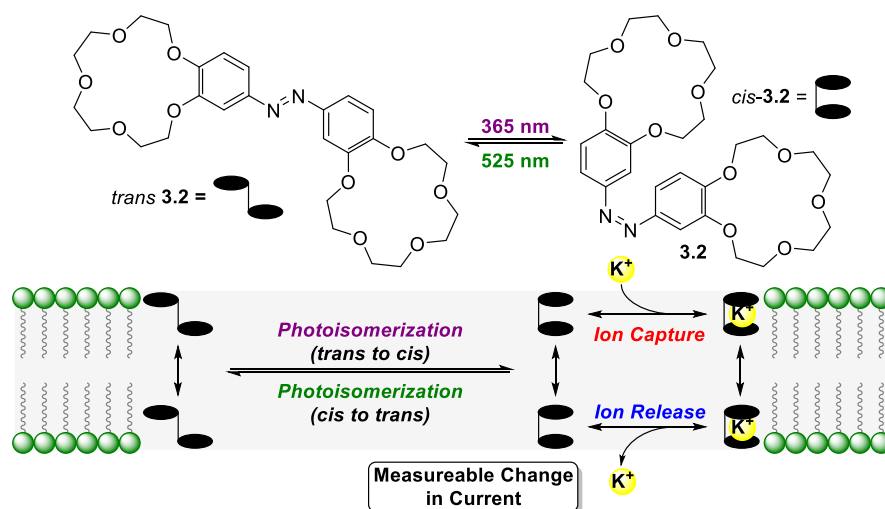
3.2.1. Route optimization for azobenzene crown ethers

Previous reports describing the preparation of crown ether azobenzene complexes are generally low yielding and often suffer from significant amounts of dimerized products.[26,28] Removal of these byproducts via chromatographic separations or recrystallization has traditionally posed a challenge to synthetic chemists.[26] Prior to investigating ion transport in planar bilayers with **3.1** and **3.2**, a reliable, reproducible synthetic approach to these compounds needed to be developed.

To streamline the preparation of these compounds, a variety of conditions to improve the yields benzocrown ether **3.9** and minimize byproduct formation were evaluated (Table 3.1). S_N2 alkylations of catechol employing aqueous sodium hydroxide in alcohol solvents with bis-chloroether **3.8** (X=Cl) resulted in low yields of benzocrown ether **3.9** (entries 1-2). Switching to toluene as a solvent provided modest increases in the yield of **3.9** (entry 3), however dimerization was an issue. Changing the nature of the electrophile (entry 4, X=OTs) provided further increases in the yield of **3.9**, while DMF provided substantial increases in yield (entry 5).

Oxidation byproducts derived from catechol were typically formed when aqueous bases were used (entries 1-5) and no additional precautions were taken to exclude oxygen from the reaction. The formation of these oxidation byproducts were minimized when Na_2CO_3 was employed as a base in rigorously degassed DMF (entry 6). To reduce the amount of undesired dimerized product, the concentration of the reaction was reduced to 0.05M (entry 7), which produced benzocrown **3.9** in 92% yield.

Table 3.1. Benzocrown ether conditions.

Entry	X	Base	Solvent	Temp	Yield
1	Cl	2.5 equiv. NaOH	n-propanol	97°C	8%[a,b]
2	Cl	2.5 equiv. NaOH	n-butanol	116°C	10%[a,b]
3	Cl	2.5 equiv. NaOH	toluene	110°C	25%[a,b,c]
4	OTs	2.5 equiv. NaOH	toluene	110°C	32%[b,c]
5	OTs	2.5 equiv. NaOH	DMF	100°C	52%[b,c]
6	OTs	2.5 equiv. Na_2CO_3	DMF	100°C	56%[c,d]
7	OTs	5.0 equiv. Na_2CO_3	DMF	100°C	92%[e]

[a] Electrophile was hydrolyzed to tetraethylene glycol. [b] Oxidative degradation of catechol. [c] Significant dimerization occured. [d] Employed rigorously degassed solvent. [e] Reaction concentration was 0.05 M.

With an optimized procedure for preparing benzo-15-crown-5 **3.9** in hand, the remaining transformations to synthesize azobenzene **3.2** were evaluated (Scheme 3.3). Nitration of **3.9** with nitric acid produced **3.5** in 98% yield. Attempts to convert **3.5** directly to azobenzene **3.5** using established protocols[29,30] were met with limited success. An alternative strategy involving reduction of **3.5** to aniline **3.10**, followed by oxidative dimerization to give **3.2** was employed. Pd/C reduction of **3.5** in 1,4-dioxane furnished **3.10** in 72% yield after only 4h. Several methods to oxidatively dimerize **3.10** to azobenzene **3.2** were explored,[31] however these methods often resulted in inseparable mixtures of oxidized byproducts. By using 20.0 equivalents of activated

MnO$_2$ in refluxing toluene, **3.10** was converted to azobenzene **3.2** in 54% yield. The 12-crown-4

analog **3.1** was prepared in an analogous manner.

Scheme 3.3. Improved route to 15-Crown-5 azobenzenes.
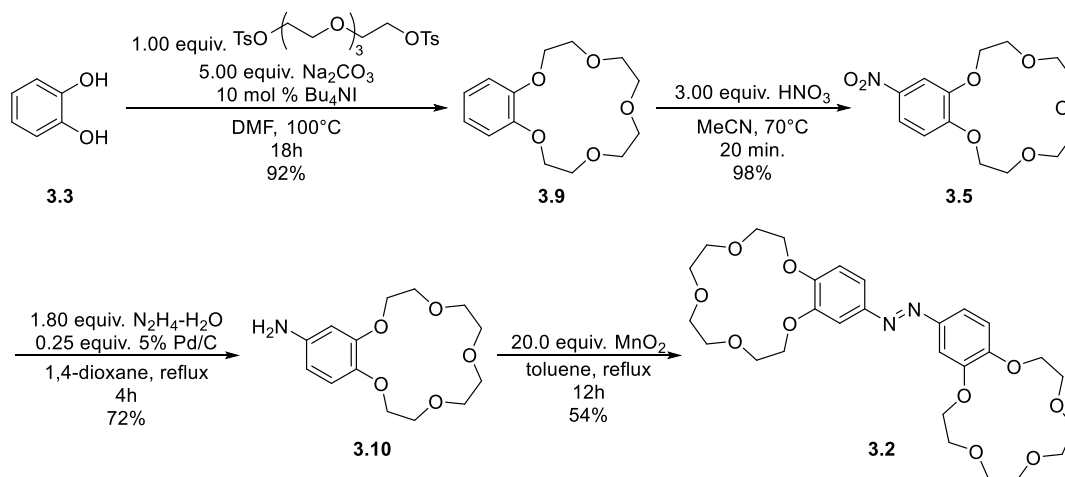
3.2.2. Initial Evaluation and Revision of Hypotheses

The photoisomerization of azobenzene **3.2** was evaluated using UV-Vis spectroscopy

(Figure 3.9). When irradiated at 365 nm (Figure 3.9, A), the absorbance of *trans*-**3.2** at 382 nm is

reduced, presumably the result of *trans* to *cis* photoisomerization. When irradiated at 525 nm

(Figure 3.9, B), cis-**3.2** undergoes isomerization back to *trans*-**3.2**, which is indicated by an

increase in absorbance at 382 nm. The *cis* to *trans* isomerization also occurs thermally in the

absence of light, however this process is significantly slower than light-induced isomerization.[26]

Figure 3.9. UV-Vis photoisomerization of **3.2** in water
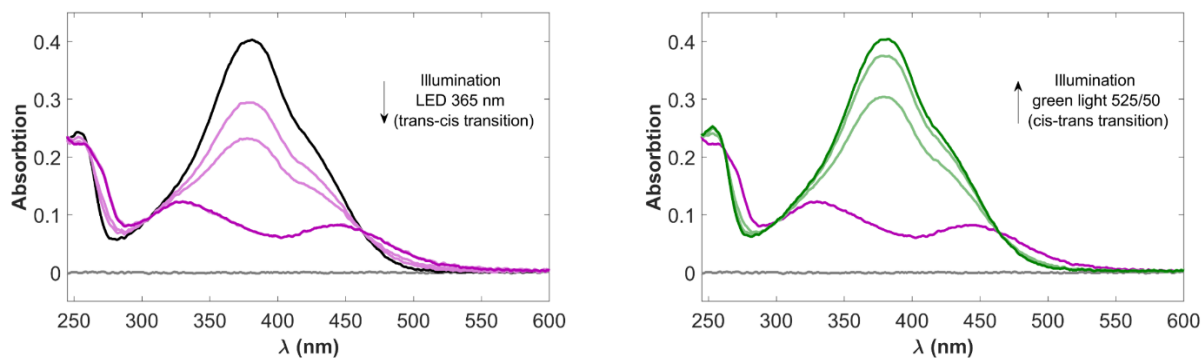
NMR techniques were utilized to further demonstrate that the change in absorbance observed during UV-Vis studies of azobenzene **3.2** is a result of reversible *trans* to *cis* photoisomerization (Figure 3.10). Prior to irradiation at 405 nm, *trans*-**3.2** was the only stereoisomer observed (Figure 3.10, A). Irradiation for one minute resulted in trace amounts of *cis*-**3.2** (Figure 3.10, B). Continued irradiation resulted in an 1.0:1 mixture of *cis*-**3.2** to *trans*-**3.2** (Figure 3.10, C). After 30 minutes of irradiation, a 2.0:1 mixture of *cis*-**3.2** to *trans*-**3.2** was observed (Figure 3.10, D). Despite continued irradiation at 405 nm, complete isomerization of *trans*-**3.2** to *cis*-**3.2** was not observed; this is likely a result of irradiation at 405 nm as opposed to the optimum wavelength of 365 nm.

Figure 3.10. NMR photoisomerization of azobenzene-15-crown-5 ether **3.2**.

A. t = 0

B. t = 1.0 min.

C. t = 10.0 min.

D. t = 30.0 min.
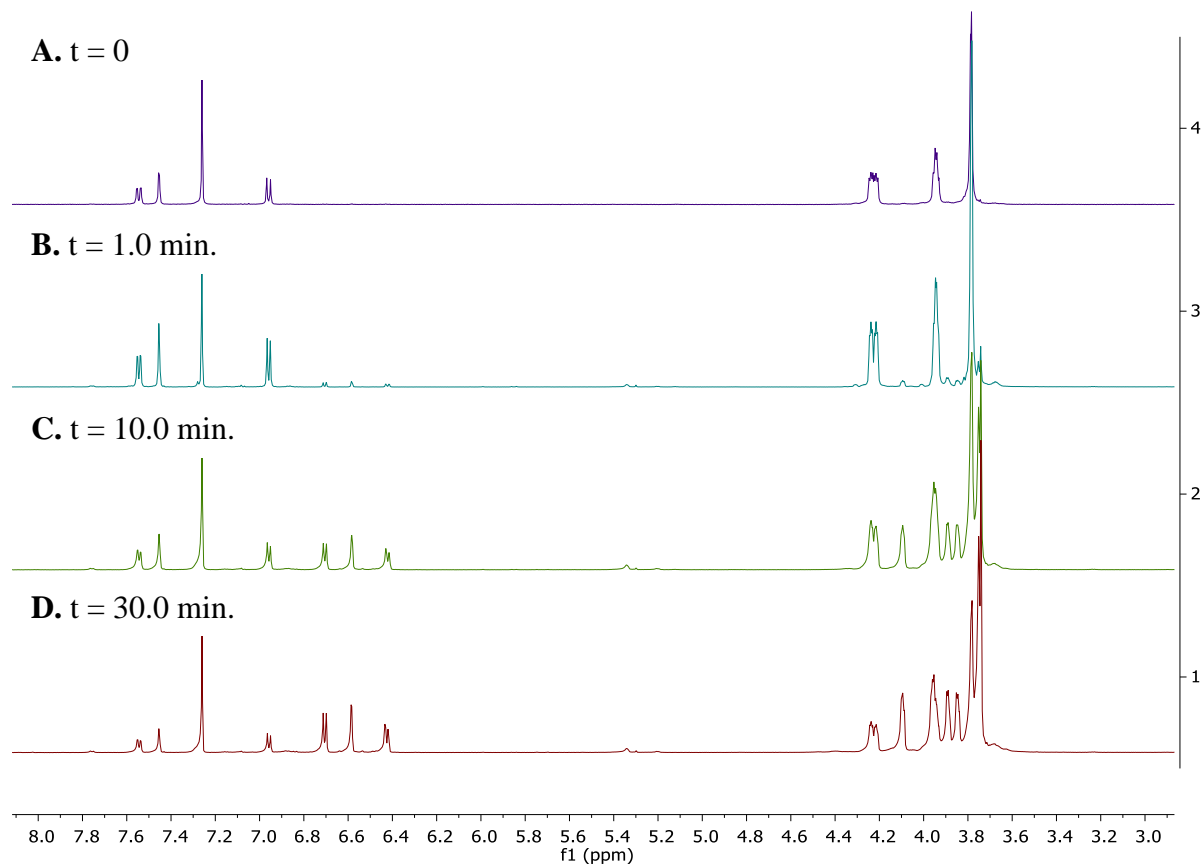
The ion transport ability of **3.2** was evaluated in planar phospholipid bilayers using the Orbit Nanion mini apparatus (Figure 3.11). In the absence of compound (Figure 3.11, A), no current was detected regardless of the on/off state of the 365 nm and 525 nm light sources. When a saturated solution of **3.2** was applied (Figure 3.11, B), no current was observed upon irradiation at 365 nm or at 525 nm. It was hypothesized that **3.2** may not be present in the bilayer at sufficient concentrations to detect the movement of ions. In Figure 3.11, C, the phospholipid mix was prepared with azobenzene **3.2** present. When irradiated with 365 nm and 525 nm light, no current was detected. Compound **3.1** produced similar results in planar bilayers.

Figure 3.11. Evaluation of 15-crown-5 azobenzene **3.2** in synthetic bilayers.
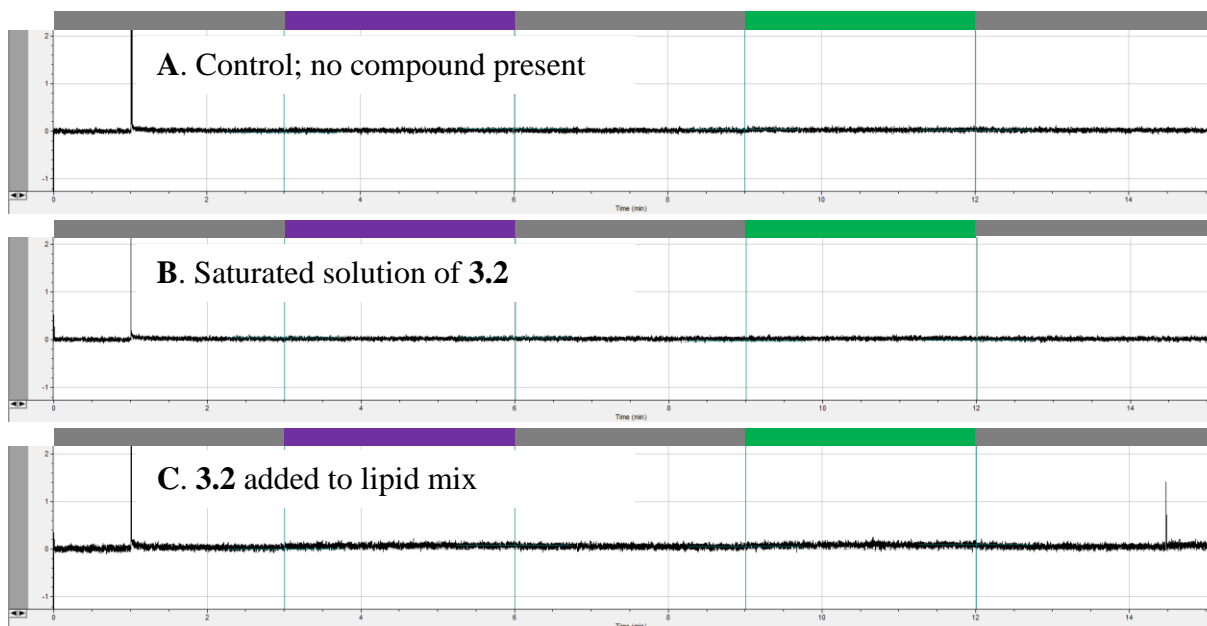
The inability of azobenzenes **3.1** and **3.2** to transport ions in synthetic bilayers can be rationalized with two hypotheses (Figure 3.12). In the first scenario, the compound *trans*-**3.1** is not lipophilic enough to permeate the bilayer, thus establishing an equilibrium where *trans*-**3.1** is mostly, if not completely, concentrated in solution rather than the bilayer. Additionally, *cis*-**3.1** was expected to display a lower lipophilicity than *trans*-**3.1**, resulting in leaching of *cis*-**3.1** from the bilayer upon photoisomerization. A combination of these factors would result in either reduced or complete suppression of the photoinduced ion transport properties of **3.1** and **3.2**.

Free ions are required for detection by the Ag/AgCl electrode utilized in the bilayer experiments depicted in Figure 3.11. In the second scenario (Figure 3.11), the ligation of an ion by cis-**3.1** may result in the formation of a stable complex. This stable complex slows the rate of ion release, thus resulting in no observable current in planar bilayer experiments.

Figure 3.11. Potential issues with azobenzene crown ethers.
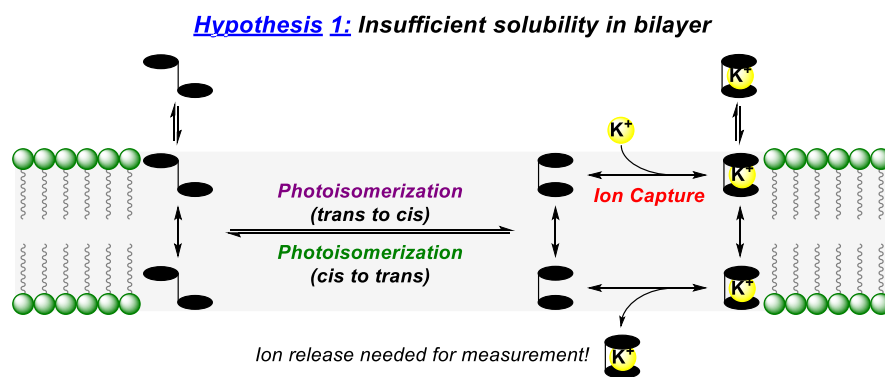
The solubility of *trans*-**3.1** and *cis*-**3.1** were evaluated computationally using Gaussian16[32] (Table 3.2) following established protocols.[33] *Trans*-**3.1** (entry 1) displays a lower ClogP value than *cis*-**3.1** (entry 2), suggesting that leaching of azobenzene **3.1** from the bilayer upon irradiation may be occurring. Complexation of **3.1** with Na^+ (entry 3) and K^+ (entry 4) does provide a slight improvement in the ClogP values, however the computationally derived values are still negative and fall outside of generally implemented ranges for permeability models.[34] This data seems to suggest that the poor solubility/lipophilicity of compounds **3.1** and **3.2** is, at least in part, responsible for the lack of transport in planar bilayers. When the transport abilities of **3.1** and **3.2** in liquid membranes are considered, it seems unlikely that inefficient ion release is the sole culprit for negative results in planar bilayers.

Table 3.2. ClogP values of crown ether azobenzene **3.1**.

Entry	Parameter[a]	12-crown-4 3.1
1	$ClogP_{trans}$	-0.62
2	$ClogP_{cis}$	-2.80
3	$ClogP_{cis-Na+}$	-0.40
4	$ClogP_{cis-K+}$	-0.38

[a] B3LYP/6-311+G(2d,p) level with SMD solvent model for H_2O and n-Octanol

3.2.3. Conclusions

Although promising results were obtained with liquid bilayers, azobenzene crown ethers **3.1** and **3.2** do not appear to transport ions in planar bilayers as previously postulated.[26] Computational modeling of **3.1** suggested that both *trans* and *cis* forms of **3.1** do not possess the solubility/lipophilicity required to transverse phospholipid bilayers. Further modifications to these scaffolds, such as the introduction of hydrophobic/lipophilic groups that do not interfere with the ion-binding abilities of **3.1** and **3.2**, may rectify the issues identified in this study.

3.3 Experimental Procedures

3.3.1. General Experimental Information

All glassware was either oven dried at 140°C or flame dried under vacuum and purged with nitrogen immediately prior to use. MnO_2 was obtained from Millipore Sigma and activated immediately prior to use. Unless otherwise specified, reagents were used as obtained from the supplier without further purification. Acetonitrile (MeCN), toluene, dimethylformamide (DMF) and dichloromethane (CH_2Cl_2) were freshly distilled from calcium hydride or passed through an alumina column before use. Other solvents were purified using accepted procedures from the sixth edition of "Purification of Laboratory Chemicals".[35] Air- and moisture- sensitive reactions were performed using standard Schlenk techniques under an inert nitrogen atmosphere, unless otherwise specified. Analytical thin layer chromatography (TLC) was performed using pre-coated silica gel 60 F24 plates containing a fluorescent indicator. Reaction products were visualized using 254 nm UV light and ceric ammonium molybdate (CAM) stain unless otherwise specified. Preparative chromatography using a gradient method with mixtures of MeOH and CH_2Cl_2 or EtOAc and

hexanes, unless otherwise specified, was performed using SilicaFlash P60 silica gel (230-400 mesh) via Still's method.[36]

^{1}H NMR and ^{13}C NMR spectra were obtained using Bruker Avance-500 spectrometers. Chemical shifts are reported relative to the tetramethylsilane peak (δ 0.00 ppm). Accurate mass measurements were acquired at the University of Wisconsin, Madison, using a Micromass LCT (electrospray ionization or electron impact methods). The NMR and Mass Spectrometry facilities are funded by the NSF (CHE-1048642, CHE-0342998, CHE-9304546 and CHE-9208463), the University of Wisconsin as well as a generous gift by Paul J. Bender.

*3.3.1. Synthesis of 12-crown-4 azobenzene **3.1***

3.3 **3.11**
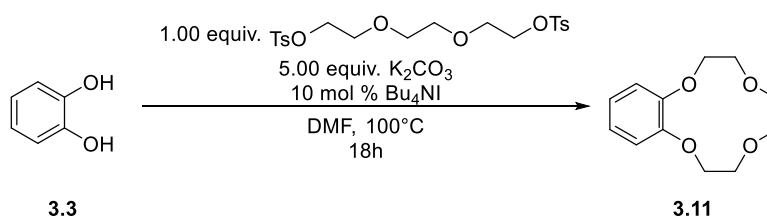
Benzo-12-crown-4 3.11. A three-neck round bottom flask was charged with 182 mL DMF and sparged with N_2 for 1h. A portion of 1.00 g (9.08 mmol, 1.00 equiv.) catechol and 4.16 g (9.08 mmol, 1.00 equiv.) ditosylate was added, and sparging continued for an additional 15 minutes. To this solution was added 6.27 g (45.4 mmol, 5.00 equiv.) K_2CO_3 was added, followed by 336 mg (0.91 mmol, 0.10 equiv.) tetrabutylammonium iodide (TBAI). The resulting suspension was heated to 100°C for 18h with vigorous stirring. The suspension was cooled to rt and poured into 200 mL H_2O and extracted with 3x200 mL portions of EtOAc. The combined organics were then washed with an additional 5x200 mL H_2O, 1x200 mL saturated aqueous NaCl, and dried over Na_2SO_4. The volatiles were removed in vacuo to give crude benzo-12-crown-4 ether. The crude material was purified via flash column chromatography on silica gel using 0-50% EtOAc in

hexanes as eluent to afford 1.18 g (5.26 mmol, 58%) benzo-12-crown-4 ether **3.4** as a white solid. If no dimerized product is present, crude benzo-12-crown-4 can also be recrystallized from hot EtOH. ^{1}H NMR (500 MHz, CDCl$_3$) δ 6.97 (qd, J = 6.1, 5.4, 3.4 Hz, 4H), 4.21 – 4.15 (m, 4H), 3.89 – 3.85 (m, 4H), 3.81 (s, 4H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 150.6, 122.8, 118.1, 71.7, 71.2, 70.0. HRMS (ESI) m/z calculated for C$_{12}$H$_{16}$O$_4$ [M + NH$_4$]$^+$ 242.1387, found 242.1385.

3.11 → 3.4
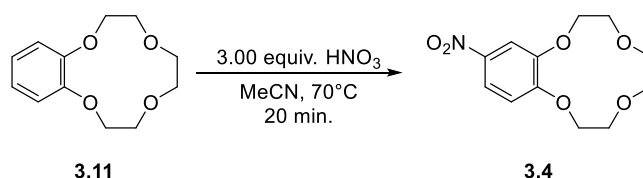
4-nitro-benzo-12-crown-4 3.4. To a stirred solution of 1.33 g (5.93 mmol, 1.00 equiv.) benzo12-crown-4 ether **3.11** in 12 mL MeCN was added 1.13 mL (17.8 mmol, 3.00 equiv.) 70% HNO$_3$ dropwise. The resulting solution was then heated to 70°C for 20 minutes before being cooled to room temperature and diluted with 50 mL H$_2$O. The aqueous phase was extracted with 3x50 mL EtOAc, and the combined organics were dried over Na$_2$SO$_4$. The volatiles were removed in vacuo to give crude nitrobenzocrown ether **3.4**. The crude material was purified via flash column chromatography using a 0-50% gradient of EtOAc in hexanes to give 1.26 g (4.68 mmol, 79%) nitro-12-crown-4 **3.4** as a pale yellow solid. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.94 (dd, J = 8.9, 2.7 Hz, 1H), 7.89 (d, J = 2.7 Hz, 1H), 7.00 (d, J = 8.9 Hz, 1H), 4.29 – 4.24 (m, 4H), 3.94 – 3.89 (m, 2H), 3.87 – 3.83 (m, 2H), 3.78 (s, 4H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 156.7, 150.1, 142.2, 119.5, 115.5, 114.5, 73.1, 71.4, 71.1, 71.0, 69.6, 69.5. HRMS (ESI) m/z calculated for C$_{12}$H$_{15}$NO$_6$ [M + NH$_4$]$^+$ 287.1238, found 287.1233.

3.4 → 3.12
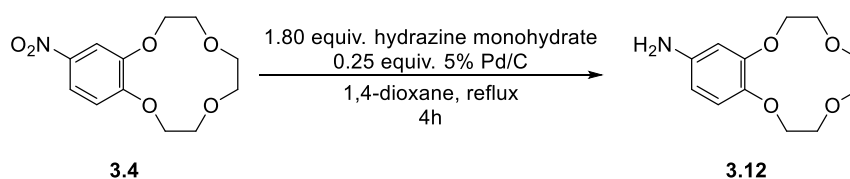
4-amino-benzo-12-crown-4 3.12. To a stirred solution of 269 mg (1.00 mmol, 1.00 equiv.) nitro-12-crown-4 **3.4** in 10 mL 1,4-dioxane was added 27 mg (0.25 mmol, 0.25 equiv.) 5% Pd/C, followed by 0.13 mL (1.80 mmol, 1.80 equiv.) 65% hydrazine monohydrate. The resulting black suspension was heated to reflux for 12 h before cooling to room temperature and filtered through a pad of celite. The filter pad was washed with additional CH_2Cl_2, and the volatiles removed in vacuo to afford crude aniline-12-crown-4 as a yellow solid. The crude solid was purified via flash column chromatography using silica gel and a 0-10% gradient of MeOH in CH_2Cl_2 as eluent to give 195 mg (0.81 mmol, 81%) aniline-12-crown-4 **3.12** as a yellow solid. ^1H NMR (500 MHz, CDCl$_3$) δ 6.83 (d, J = 8.4 Hz, 1H), 6.33 (d, J = 2.7 Hz, 1H), 6.26 (dd, J = 8.4, 2.7 Hz, 1H), 4.14 – 4.07 (m, 4H), 3.91 – 3.86 (m, 2H), 3.79 (d, J = 5.2 Hz, 6H), 3.75 – 3.62 (br S, 2H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 151.7, 142.8, 142.5, 120.9, 108.4, 104.5, 73.7, 71.6, 70.8, 70.3, 70.0, 70.0. HRMS (ESI) m/z calculated for $C_{12}H_{17}NO_4$ [M + NH$_4$]$^+$ 257.1496, found 257.1489.
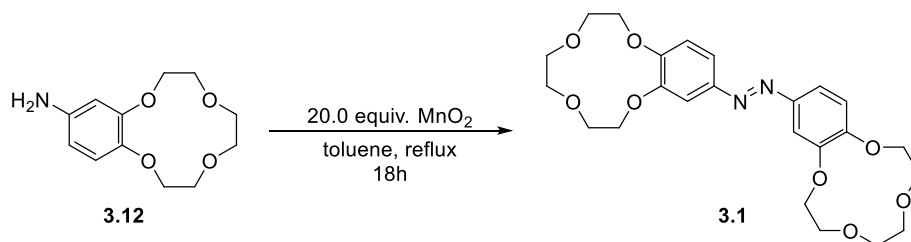
12-crown-4 Azobenzene 3.1. To a stirred solution of 129 mg (0.54 mmol, 1.00 equiv.) 12-crown-4 aniline **3.12** in 5.4 mL anhydrous toluene was added 939 mg (10.8 mmol, 20.0 equiv.) freshly activated MnO_2. The resulting black suspension was vigorously stirred at reflux for 18h, then cooled to room temperature and filtered through a pad of celite using CH_2Cl_2 as eluent. The volatiles were removed in vacuo to afford crude 12-crown-4 azobenzene, which was recrystallized from hot EtOH to give 123 mg (0.26 mmol, 48%) pure azobenzene **3.1** as fine yellow needles. ^1H NMR (500 MHz, CDCl$_3$) δ 7.60 (dd, J = 8.4, 2.3 Hz, 2H), 7.56 (d, J = 2.3 Hz, 2H), 7.08 (d, J =

8.4 Hz, 2H), 4.27 (ddd, J = 8.1, 5.2, 3.2 Hz, 8H), 3.92 – 3.86 (m, 8H), 3.81 (s, 8H). ^{13}C NMR (126

MHz, CDCl$_3$) δ 153.1, 150.9, 148.1, 120.6, 117.1, 109.9, 72.0, 71.5, 71.3, 71.1, 69.8, 69.8. HRMS

(ESI) m/z calculated for C$_{24}$H$_{30}$NO$_8$ [M + H]$^+$ 475.2075, found 475.2075.

*3.3.2. Preparation of 15-crown-5-azobenzene **3.2***

3.3 **3.9**
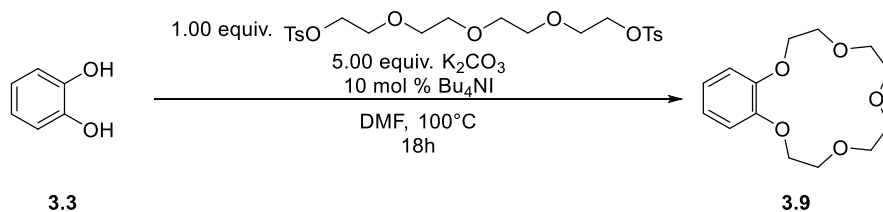
Benzo-15-crown-5 3.9. A three-neck round bottom flask was charged with 182 mL DMF and

sparged with N$_2$ for 1h. A portion of 1.00 g (9.08 mmol, 1.00 equiv.) catechol and 4.60 g (9.08

mmol, 1.00 equiv.) ditosylate was added, and sparging continued for an additional 15 minutes. To

this solution was added 6.27 g (45.4 mmol, 5.00 equiv.) K$_2$CO$_3$ was added, followed by 336 mg

(0.91 mmol, 0.10 equiv.) tetrabutylammonium iodide (TBAI). The resulting suspension was

heated to 100°C for 18h with vigorous stirring. The suspension was cooled to rt and poured into

200 mL H$_2$O and extracted with 3x200 mL portions of EtOAc. The combined organics were then

washed with an additional 5x200 mL H$_2$O, 1x200 mL saturated aqueous NaCl, and dried over

Na$_2$SO$_4$. The volatiles were removed in vacuo to give crude benzo-15-crown-5 ether. The crude

material was purified via flash column chromatography on silica gel using 0-50% EtOAc in

hexanes as eluent to afford 2.23 g (8.31 mmol, 92%) benzo-15-crown-5 **3.9** ether as a white solid.

If no dimerized product is present, crude benzo-12-crown-4 can also be recrystallized from hot

EtOH. ^{1}H NMR (500 MHz, CDCl$_3$) δ 6.93 – 6.85 (m, 4H), 4.17 – 4.11 (m, 4H), 3.93 – 3.90 (m,

4H), 3.77 (d, J = 1.6 Hz, 8H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 149.2, 121.4, 114.2, 71.1, 70.6, 69.7,

69.1. HRMS (ESI) m/z calculated for C$_{14}$H$_{19}$NO$_7$ [2M + NH$_4$]$^+$ 644.2661, found 644.2659.
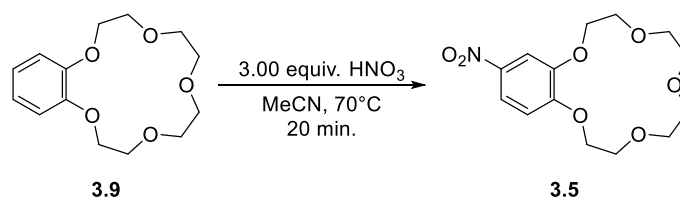
4-nitro-benzo-15-crown-5 3.5. A stirred solution of 4.25 g (15.9 mmol, 1.00 equiv.) benzo-15-crown-5 ether **3.9** in 32 mL MeCN was heated to 70°C, and 3.00 mL (47.7 mmol, 3.00 equiv.) 70% nitric acid was added dropwise. The orange solution was stirred at 70°C for 20 minutes, then poured into a separatory funnel containing 100 mL H_2O. The aqueous solution was then extracted with 3x100 mL EtOAc and the combined organics were washed with 1x100 mL saturated aqueous NaCl, dried over Na_2SO_4, and the volatiles removed in vacuo to afford crude 4-nitrobenzo-15-crown-5 ether. The crude material was then further purified via flash column chromatography on silica gel using EtOAc in hexanes as eluent to afford 3.92 g (12.5 mmol; 79%) nitro benzo-15-crown-5 **3.5** as a yellow solid. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.90 (dd, J = 8.9, 2.6 Hz, 1H), 7.73 (d, J = 2.6 Hz, 1H), 6.87 (d, J = 8.9 Hz, 1H), 4.28 – 4.15 (m, 4H), 3.99 – 3.88 (m, 4H), 3.77 (qd, J = 5.1, 4.6, 2.8 Hz, 8H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 154.6, 148.6, 141.4, 118.1, 111.2, 108.4, 71.2, 70.7, 70.3, 70.2, 69.1, 69.0, 68.9. HRMS (ESI) m/z calculated for $C_{14}H_{20}O_5$ [M + NH$_4$]$^+$ 286.1649, found 286.1644.
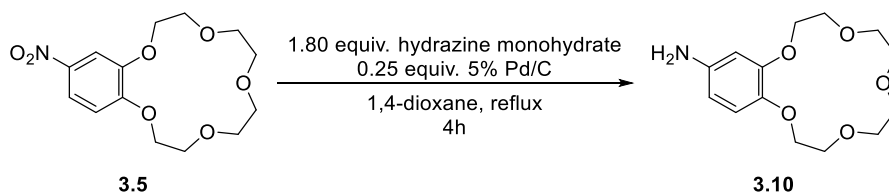
4-amino-benzo-15-crown-5 3.10. To a stirred solution of 220 mg (0.71 mmol, 1.00 equiv.) nitro-15-crown-5 **3.5** in 7.1 mL 1,4-dioxane was added 380 mg (0.18 mmol, 0.25 equiv.) 5% Pd/C, followed by 89 μL (1.28 mmol, 1.80 equiv.) 65% hydrazine monohydrate. The resulting black

suspension was heated to reflux for 4h before cooling to room temperature and filtered through a pad of celite. The filter pad was washed with additional CH_2Cl_2, and the volatiles removed in vacuo to afford crude aniline-15-crown-5 as a yellow solid. The crude solid was purified via flash column chromatography using silica gel and a 0-10% gradient of MeOH in CH_2Cl_2 as eluent to give 144 mg (0.51 mmol, 72%) aniline-15-crown-5 **3.10** as a yellow solid. Characterization data for 4-amino-benzo-15-crown-5 **3.10** matches that which has been previously reported.[26]

Benzo-15-crown-5 3.2. To a stirred solution of 335 mg (1.18 mmol, 1.00 equiv.) 15-crown-5 aniline **3.10** in 12 mL anhydrous toluene was added 2.05 g (23.6 mmol, 20.0 equiv.) freshly activated MnO_2. The resulting black suspension was vigorously stirred at reflux for 12h, then cooled to room temperature and filtered through a pad of celite using CH_2Cl_2 as eluent. The volatiles were removed in vacuo to afford crude 15-crown-5 azobenzene, which was recrystallized from hot EtOH to give 178 mg (0.32 mmol, 54%) pure azobenzene **3.2** as fine yellow needles. ^{1}H NMR (500 MHz, CDCl_3) δ 7.55 (dd, J = 8.4, 2.2 Hz, 2H), 7.45 (d, J = 2.2 Hz, 2H), 6.96 (d, J = 8.5 Hz, 2H), 4.23 (dt, J = 11.5, 4.3 Hz, 8H), 3.94 (q, J = 4.6 Hz, 8H), 3.79 (d, J = 2.5 Hz, 16H). ^{13}C NMR (126 MHz, CDCl_3) δ 151.5, 149.4, 147.1, 120.1, 112.5, 104.3, 71.3, 71.2, 70.4, 69.4, 68.8, 68.8. HRMS (ESI) *m/z* calculated for $C_{28}H_{38}O_{10}$ [M + H]$^+$ 563.2599, found 563.2592.

3.4. Bibliography

1.   Galvani, L. *Bonon. Sci. Art. Inst. Acad.* **1791**, 364-415.

2.   Levin, M. *Mol. Biol. Cell.* **2014**, 25, 3835-3850.

3.   O'Shea, C.; Holmes, A. P.; Winter, J.; Correia, J.; Ou, X.; Dong, R.; He, S.; Kirchof, P.; Fabritz, L.; Rajpoot, K.; Pavlovic, D. *Front. Physiol.* **2019**, 10, 182, 1-14.

4.   (a) Pitcairn, E.; Harris, H.; Epiney, J.; Pai, V. P.; Lemire, J. M.; Ye, B.; Shi, N.-Q.; Levin, M.; McLaughlin, K. A. *Commun. Integr. Biol.* **2017**, 10, e1306488. (b) Pai, V. P.; Lemire, J. M.; Paré, J.-F.; Lin, G.; Chen, Y.; Levin, M. *J. Neurosci.* **2015**, 35, 4366-4385. (c) Vandenberg, L. N.; Morrie, R. D.; Adams, D. S. *Dev. Dynam.* **2011**, 240, 1889-1904.

5.   (a) Jaffe , L. F.; Nuccitelli , R. *J. Cell. Biol.* **1974**, 63, 614-628. (b) Borgens, R. B.; Vanable Jr., J. W.; Jaffe, L. F. *J. Exp. Zool.* **1977**, 200, 403-416. (c) Chiang, M.; Robinson, K. R.; Vanable, J. W. *Exp. Eye Res.* **1992**, 54, 999-1003.

6.   (a) Yang, M.; Brackenbury, W. *Front. Physiol.* **2013**, 4, 1-10. (b) Leithe, E.; Sirnes, S.; Omori, Y.; Rivedal, E. *Crit. Rev. Oncology* **2006**, 12, 225-256.

7.   (a) Daniele, R. P.; Holian, S. K. *Proc. Natl. Acad. Sci. USA* **1976**, 73, 3599-3602. (b) Schiefer, H.; Schummer, U.; Gerhardt, U. *Curr. Microbiol.* **1979**, 3, 85-88. (c) Varma, S.; Sabo, D.; Rempe, S. B. *J. Mol. Biol.* **2008**, 376, 13-22.

8.   (a) Alberts, B.; Johnson, A.; Lewis, J.; Raff, M.; Roberts, K. Ion Channels and the Electrical Properties of Membranes. In *Molecular Biology of the Cell, 4th Edition*; Garland Sciences: New York, NY **2002**; pp 631-658. (b) Catterall, W. A.; *J. Physiol.* **2012**, 590, 2577-2589. (c) Duménieu, M.; Oulé, M.; Kreutz, M. R.; Lopez-Rojas, J. *Front. Cell. Neurosci.* **2017**, 11, 115-134. (d) Ranade, S. S.; Syeda, R.; Patapoutian, A. *Neuron* **2015**, 87, 1162-1179. (e)

Lemoine, D.; Jiang, R.; Taly, A.; Chatagineau, T.; Specht, A.; Grutter, T. *Chem. Rev.* **2012**, 112, 6285-6318. (f) Hüll, K.; Morstein, J.; Trauner, D. *Chem. Rev.* **2018**, 118, 10710-10747.

9.   Yang, N. J.; Hinner, M. J. *Methods Mol. Biol.* **2015**, 1266, 29-53.

10.   (a) Neher, E.; Sakmann, B. *Ann. Rev. Physiol.* **1984**, 46, 455-472. (b) Zhao, Y.; Inayat, S.; Dikin, D. A.; Singer, J. H.; Ruoff, R. S.; Troy, J. B. *Proceedings of the Institution of Mechanical Engineers, Part N: Journal of Nanoengineering and Nanosystems* **2008**, 222, 1-11. (c) Rubaiy, H. N. *J. Pharm. Pharm. Sci.* **2017**, 20, 48-67.

11.   Hamill, O. P.; Marty, A.; Neher, E.; Sakmann, B.; Sigworth, F. J. *Pflugers Arch.* **1981**, 391, 85-100.

12.   (a) Xu, J.; Wang, X.; Ensign, B.; Li, M.; Wu, L.; Guia, A.; *Drug Discovery Today* **2001**, 6, 1278-1287. (b) Schmidt, C.; Mayer, M.; Vogel, H. *Angew. Chem. Int. Ed.* **2000**, 39, 3137-3140. (c) Pantoja, R.; Sigg, D.; Blunck, R.; Bezanilla, F.; Heath, J. R. *Biophys. J.* **2001**, 81, 2389-2394.

13.   (a) Tsai, D, Sawyer, D.; Bradd, A.; Yuste, R.; Shepard, K. L. *Nat. Commun.* **2017**, 8, 1802. (b) Blunck, R.; Chanda, B.; Bezanilla, F. *J. Membr. Biol.* **2005**, 208, 91-92. (c) Mathias, R. T.; Cohen, I. S.; Oliva, C. *Biophys. J.* **1990**, 58, 759-770.

14.   (a) Swanson, L. W.; Lichtman, J. W. *Annu. Rev. Neurosci.* **2016**, 39, 197-216. (b) Tononi, G.; Boly, M.; Massimini, M; Koch, C. *Nat. Rev. Neurosci.* **2016**, 39, 197-216.

15.   Deisseroth, K. *Nat. Neurosci.* **2015**, 18, 1213-1225.

16. (a) Khorana, H. G. *J. Biol. Chem.* **1988**, 263, 7439-7442. (b) Haupts, U.; Tittor, J.; Oesterhelt, D. *Annu. Rev. Biophys. Biomol. Struct.* **1999**, 28, 367-399. (c) Lanyi, J. K. *Annu. Rev. Physiol.* **2004**, 66, 665-688.

17. Engelhard, C.; Chizhov, I.; Siebert, F.; Engelhard, M. *Chem. Rev.* **2018**, 118, 10629-10645.

18. (a) Schneider, F.; Grimm, C.; Hegemann, P. *Annu. Rev. Biophys.* **2015**, 44, 167-186. (b) Deisseroth, K.; Hegemann, P. *Science* **2017**, 357, 6356, eaan5544. (c) Govorunova, E. G.; Sineschekov, O. A.; Spudich, J. L. *Neurosci. Behav. Physiol.* **2019**, 49, 163-168.

19. (a) Berndt, A.; Deisseroth, K. *Science* **2015**, 349, 590-591. (b) Paoletti, P.; Ellis-Davies, G. C. R.; Mourot, A. *Nat. Rev. Neurosci.* **2019**, 20, 514-532.

20. (a) Miller, E. W.; Lin, J. Y.; Frady, P.; Steinbach, P. A.; Kristan Jr., W. B.; Tsien, R. Y. *Proc. Natl. Acad. Sci. USA* **2012**, 109, 2114-2119. (b) Yan, P.; Acker, C. D.; Zhou, W.-L.; Lee, P.; Bollensdorff, C.; Negrean, A.; Lotti, J.; Sacconi, L.; Antic, S. D.; Kohl, P.; Mansvelder, H. D.; Pavon, F. S.; Loew, L. M. *Proc. Natl. Acad. Sci. USA* **2012**, 109, 20443-20448. (c) Miller, E. W. *Curr. Opin. Chem. Biol.* **2016**, 33, 74-80.

21. Hochbaum, D. R; Zhao, Y.; Farhi, S. L.; Klapoetke, N.; Werley, C. A.; Kapoor, V.; Zou, P.; Kralj, J. M.; Maclaurin, D.; Smedemark-Margulies, N.; Saulnier, J. L.; Boulting, G. L.; Straub, C.; Cho, Y. K.; Melkonian, M.; Wong, G. K.-S.; Harrison, D. J.; Murthy, V. N.; Sabatini, B. L.; Boyden, E. S.; Campbell, R. E.; Cohen, A. E. *Nat. Methods* **2014**, 11, 825-833.

22. (a) Lin, J. Y.; Lin, M. Z.; Steinbach, P.; Tsien, R. Y. *Biophys. J.* **2009**, 96, 1803-1814. (b) Berglund, K.; Birkner, E.; Augustine, G. J.; Hochgeschwender, U. *PloS ONE* **2013**, 8, 3,

e59759. (c) Bedbrook, C. N.; Yang, K. K.; Robinson, E.; Mackey, E. D.; Gradinaru, V.; Arnold, F. H. *Nature Methods* **2019**, 16, 1176-1184.

23. (a) Emiliani, V.; Cohen, A. E.; Deisseroth, K.; Haüsser, M. *J. Neurosci.* **2015**, 35, 13917-13926. (b) Rivnay, J.; Wang, H.; Fenno, L.; Deisseroth, K.; Malliaras, G. C. *Sci. Adv.* **2017**, 3, e1601649.

24. Pedersen, C. J. *J. Am. Chem. Soc.* **1967**, 89, 2495-2496.

25. (a) Pedersen, C. J.; Frensdorff, H. K. *Angew. Chem. Int. Ed.* **1972**, 11, 16-25. (b) Steed, J. W. *Coord. Chem. Rev.* **2001**, 215, 171-221. (c) Tsukube, H. *Coord. Chem. Rev.* **1996**, 148, 1-17. (c) Cook, T. R.; Stang, P. J. *Chem. Rev.* **2015**, 115, 7001-7045. (d) Christensen, J. J.; Hill, J. O.; Izatt, R. M. *Science* **1971**, 174, 459-467. (e) Cook, F. L.; Bowers, C. W.; Liotta, C. L. *J. Org. Chem.* **1974**, 39, 3416-3418. (f) Yu, G.; Jie, K.; Huang, F. .*Chem. Rev.* **2015**, 115, 7240-7303. (g) Li, J.; Yim, D.; Jang, W. –D.; Yoon, J. *Chem. Soc. Rev.* **2017**, 46, 2437-2458. (h) Gokel, G. W.; Leevy, W. M.; Weber, M. E. *Chem. Rev.* **2004**, 104, 2723-2750. (i) Beklemishev, M. K.; Eishani, S.; Wai, C. M. *Anal. Chem.* **1994**, 66, 3521-3524. (j) Visser, A. E.; Swatloski, R. P.; Reichert, W. M.; Griffin, S. T.; Rogers, R. D. *Ind. Eng. Chem. Res.* **2000**, 39, 3596-3604. (k) Bond, A. H.; Dietz, M. L.; Chiarizia, R. *Ind. Eng. Chem. Res.* **2000**, 39, 3442-3464. (l) Talanova, G. G.; Elkarim, N. S. A.; Hanes, R. E.; Hwang, H. S.; Rogers, R. D.; Bartsch, R. A. *Anal. Chem.* **1999**, 71, 672-677. (m) Liu, Z.; Nalluri, S. K. M.; Stoddart, J. F. *Chem. Soc. Rec.* **2017**, 46, 2459-2478.

26. (a) Shinkai, S.; Ogawa, T.; Kusano, Y.; Manabe, O. *Chem. Lett.* **1980**, 3, 283-286. (b) Shinkai, S.; Ogawa, T.; Nakaji, T.; Manabe, O. *J. Chem. Soc.* **1980**, 9, 375-377. (c) Shinkai, S.; Nakaji, T.; Ogawa, T.; Shigematsu, K.; Manabe, O. *J. Am. Chem. Soc.* **1981**, 103, 111-115. (d)

Shinkai, S.; Shigematsu, K.; Sato, M.; Manabe, O. *J. Chem. Soc. Perkin Trans. 1* **1982**, 2735-2739. (e) Shinkai, S.; Ogawa, T.; Kusano, Y.; Manabe, O.; Kikukawa, K.; Goto, T.; Matsuda, T. *J. Am. Chem. Soc.* **1982**, 104, 1960-1967. (f) Kumano, A.; Niwa, O.; Kajiyama, T.; Takayanagi, M.; Kano, K.; Shinkai, S. *Chem. Lett.* **1983**, 8, 1327-1330. (g) Kajiyama, T.; Washizu, S.; Kumano, A.; Terada, I.; Takayanagi, M.; Shinkai, S. *J. Appl. Polym. Sci.* **1985**, 41, 327-346. (h) Shinkai, S.; Yoshida, T.; Manabe, O.; Fuchita, Y. *J. Chem. Soc. Perkin Trans. 1* **1988**, 6, 1431-1437.

27. (a) Vedernikov, A. I.; Kuz'mina, L. G.; Botsmanova, A. A.; Strelenko, Y. A.; Howard, J. A.; Alfimov, M. V.; Gromov, S. P. *Mendeleev. Commun.* **2007**, 17, 148-150. (b) Xu, L.-P.; Wan, L.-J. *J. Phys. Chem. B* **2006**, 110, 3185-3188. (c) Klaussner, B.; Nees, D.; Schmidt, F.; Wolff, T. *J. Colloid. Interface Sci.* **1994**, 162, 481-486. (d) Wolff, T.; Klaussner, B.; Von Bunau, G. *Progr. Colloid Polymer Sci.* **1990**, 83, 176-180.

28. Cacciapaglia, R.; Di Stefano, S.; Mandolini, L. *J. Am. Chem. Soc.* **2003**, 125, 2224-2227.

29. Noureldin, N. A.; Bellegarde, J. W. *Synthesis* **1999**, 6, 939-942.

30. (a) Di Gioia, M. L.; Leggio, A.; Guarino, I. F.; Leotta, V.; Romio, E.; Liguori, A. *Tetrahedron Lett.* **2015**, 56, 5341-5344. (b) Sakai, N.; Fujii, K.; Nabeshima, S.; Ikeda, R.; Konakahra, T. *Chem. Commun.* **2010**, 46, 3173-3175. (c) Gund, S. H.; Shelkar, R. S.; Nagarkar, J. M. *RSC Adv.* **2014**, 4, 42947-42951. (d) Bigelow, H. E.; Robinson, D. B. *Org. Syn.* **1955**, 3, 103-104.

31. (a) Salaheldin, A. M.; Oliveira-Campos, A. M. F.; Rodrigues, L. M. *Tetrahedron Lett.* **2007**, 48, 8819-8822. (b) Mohammad, J.; Rafiee, E.; Shahbazi, F.; Jafari, H.; Amiri, S.; Omidi, M.

ARKIVOC **2007**, 1, 164-17.. (c) Pausacker, K. H. *J. Chem. Soc.* **1953**, 1989-1990. (d) Karunakaran, C.; Palanisamy, P. N. *J. Mol. Catal. A Chem.* **2001**, 172, 9-17.

32. Gaussian 16, Revision B.01, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, G. A. Petersson, H. Nakatsuji, X. Li, M. Caricato, A. V. Marenich, J. Bloino, B. G. Janesko, R. Gomperts, B. Mennucci, H. P. Hratchian, J. V. Ortiz, A. F. Izmaylov, J. L. Sonnenberg, D. Williams-Young, F. Ding, F. Lipparini, F. Egidi, J. Goings, B. Peng, A. Petrone, T. Henderson, D. Ranasinghe, V. G. Zakrzewski, J. Gao, N. Rega, G. Zheng, W. Liang, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, K. Throssell, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. J. Bearpark, J. J. Heyd, E. N. Brothers, K. N. Kudin, V. N. Staroverov, T. A. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. P. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, J. M. Millam, M. Klene, C. Adamo, R. Cammi, J. W. Ochterski, R. L. Martin, K. Morokuma, O. Farkas, J. B. Foresman, and D. J. Fox, Gaussian, Inc., Wallingford CT, 2016.

33. (a) Kim, T.; Park, H. *J. Mol. Graph. Model.* **2015**, 60, 108-117. (b) Bannan, C. C.; Calabro, G.; Kyu, D. Y.; Mobley, D. L. *J. Chem. Theory Comput.* **2016**, 12, 4015-4024. (c) Marenich, A. V.; Cramer, C. J.; Truhlar, D. G. *J. Phys. Chem. B.* **2009**, 113, 6378-6396.

34. (a) Lipinski, C. A.; Lombardo, F.; Dominy, B. W.; Feeney, P. J. *Adv. Drug Deliv. Rev.* **2001**, 46, 3-26. (b) Lipinski, C. A. *Drug Discov. Today Technol.* **2004**, 1, 337-341.

35. Armarego, W. L. F.; Chai, C. L. L. Chapter 4 – Purification of Organic Chemicals. In *Purification of Laboratory Chemicals (Sixth Edition)*, Butterworth-Heinemann: Oxford, 2009; pp 88-444.

36.   Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, 43, 2923-2925.

Chapter 4

Synthesis and Evaluation of Ion Transporters Derived from 4,13-Diaza-18-crown-6

Ethers

4.1. Introduction to Synthetic Ion Channels Derived from 4,13-Diaza-18-Crown-6 Ethers

4.1.1. Previous work with dialkyl diaza 18-crown-6 derivatives

In a series of reports regarding the binding of cationic species by crown ether-based molecules, it was demonstrated that coordination of cation by a crown ether molecule is more complex than the "hole size" paradigm usually inferred by chemists.[1] The addition of various substituents to crown ethers demonstrated that organization of these substituents around the metal center plays an equally important role in the complexation of a cationic species.[1] Furthermore, these substituents can be utilized to enhance the solubility properties of the crown ether/cation complex in a host of solvents.[1] Modifications to the identity of these substituents may also allow for control regarding ion selectivity exhibited by crown ether species.

In 1986, Gokel and coworkers described the preparation and ion extraction abilities of a series of alkyl substituted lariat ethers (Scheme 4.1) aimed to probe these questions.[2] It was initially thought that compounds based on the 4,13-diaza-18-crown-6 ether scaffold **4.2** may show enhanced properties when compared to other previously described crown ethers.[1b,c] The results of this extensive investigation indicated that, in some cases, ion selectivity can be achieved via changes to the nitrogen substituents of **4.2**. Furthermore, these complexes exhibited increased solubility as compared to the unsubstituted compound **4.3**.[2]

Scheme 4.1. Previous syntheses of dialkyl diaza-18-crown-6 ethers.
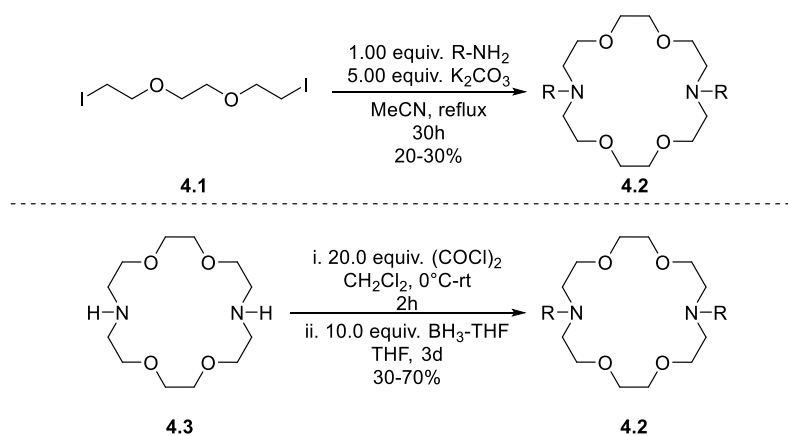
While early reports highlighted the utility of crown ether compounds in traditional organic and inorganic chemistry settings,[1] crown ethers have seen increased attention in biological applications over the past three decades.[3] A series of alkyl substituted lariat ethers were shown to be toxic towards cultures of *B. subtilis*, *E. coli*, and *S. cerevisiae* by Gokel in 2005 (Table 4.1).[4] The addition of octyl chains in **4.4** (entry 1) resulted in good MIC values with respect to *B. subtilis* and modest activity with *E. coli* and *S. cerevisiae*.[4] Further extension of these chains to decyl (entry 2) resulted in a substantial reduction in MIC values across all three cell lines. Interestingly, dodecyl chains (entry 3) resulted in slightly reduced MICs in *B. subtilis* and *S. cerevisiae* as compared to **4.5**, however no activity was detected in *E. coli*.[4] Further extensions of the alkyl chains resulted in no activity (entries 4-6); the amide derivatives **4.10** and **4.11** (entries 7-8) also resulted in no observable effect.[4] The naturally occurring ion transporter valinomycin (entry 9) was used as a comparison.[4,5]

Table 4.1. MIC values of lariat ethers.
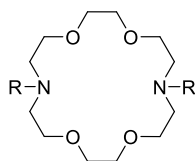
Entry	Compound	R	B. subtilis[a,b]	E. coli[a,b]	S. cerevisiae[a,b]
1	**4.4**	C_8H_{17}	26	206	103
2	**4.5**	$C_{10}H_{21}$	2.8	11	2.8
3	**4.6**	$C_{12}H_{25}$	2.5	360	2.5
4	**4.7**	$C_{14}H_{29}$	360	360	360
5	**4.8**	$C_{16}H_{33}$	360	360	360
6	**4.9**	$C_{18}H_{37}$	360	360	360
7	**4.10**	$(O)C_{10}H_{19}$	360	360	360
8	**4.11**	$(O)C_{12}H_{23}$	360	360	360
9	valinomycin	--	50	50	--

[a] MIC values reported in μM. [b] MIC values above 360 μM were considered to be inactive.

Relative hydrophobicity has been used in previous studies as an indicator of membrane permeability and ion transport.[6] The logP values of compounds **4.4**-**4.9** span nearly four orders magnitude and seem to increase linearly with respect to alkyl chain size, however the activity of these compounds does not directly coordinate with their respective logP value.[4] If the alkyl chains are too short, the compound does not possess the lipophilicity to transport ions, while increasingly large alkyl chains also inhibit transport.[4] To account for this observation, Gokel and coworkers postulated that longer alkyl chains present in **4.7**-**4.9** (entries 4-6) inhibit the required conformational change to transport ions successfully.[4] Differences in membrane composition between *B. subtilis*, *E. coli*, and *S. cerevisiae* may also account for differences in activity.

In a subsequent report in 2016, Gokel and coworkers evaluated the efficacy of lariat ethers containing octyl and undecyl side chains as agents to improve the potency of various antibiotics in *E. coli*.[7] When administered at concentrations below their respective MICs, these lariat ethers displayed a 4-48 fold increase in the potency of rifampicin[8] and tetracycline[9] in DH5α *E. coli* cells. Additional experiments using planar bilayers derived from soybean asolectin show that these lariat ethers exhibit single channel conductances, behavior typically produced by ion channels. These

results were somewhat unexpected as dialkyl diaza lariat ethers were expected to behave as ion carriers.[7]

To account for this observation, five potential models for the formation of ion channels in bilayers by lariat ethers were proposed (Figure 4.1).[4] Insertion of the lariat ether into the bilayer and reorganization of the membrane[10] results in **A**; the dynamic nature of the leaflet could result in the open/closed behavior observed in bilayer studies. Two lariat ethers may come together in a tail-to-tail fashion in the bilayer, resulting in the formation of a pore as shown in **B**. In order for this to happen, one lariat ether molecule must "flip" at the inner leaflet; although possible, Gokel and coworkers discounted the arrangement shown in **B** based on the energetics required for this flip to occur. Additionally, single channel conductances were observed in <10s in planar bilayer experiments, suggesting this arrangement is less likely.

In Figure 4.1, **C**, multiple lariat ethers could span the bilayer with the diaza-18-crown-6 moieties located at the midplane of the bilayer, resulting in either pore formation or disruption of the membrane. This seems less likely as the polar crown ether constituent would reside in the hydrophobic interior of the bilayer. Aggregation of the crown ethers as shown in **D** may result in the formation of a pore, where the extended alkyl chains provide stabilization through interactions with the midplane of the bilayer.

One additional model was proposed by Gokel where multiple lariat ethers aggregate to form the pore show in Figure 4.1, **E**. Varying numbers of conductance states could be observed in this arrangement, depending on the number of lariat ethers involved in the formation of each pore. Gokel and coworkers favor this model, as three different conductance states were observed in planar bilayer experiments.

Figure 4.1. Proposed modes of channel formation by dialkyl diaza-18-crown-6 ethers
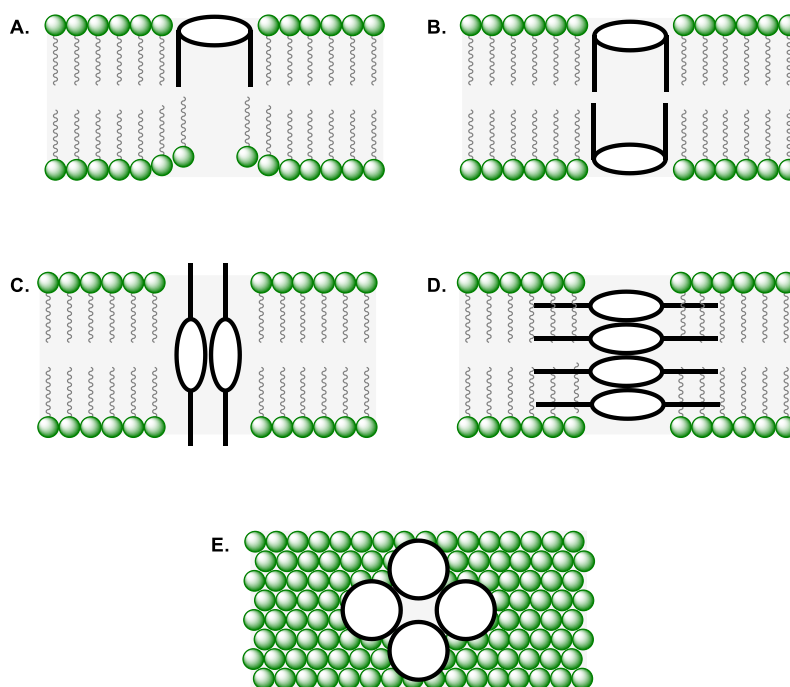
Interestingly, additional crown ether complexes have been shown to form channels in planar bilayer experiments, however these compounds typically exhibit additional functionality to facilitate channel formation.[11] Hydrogen bonding interactions and π-π stacking by pendant aromatic groups have been implicated in models for channel formation with these compounds.

4.1.2. Previous work with hydraphiles

In addition to their work with lariat ether complexes, Gokel and coworkers developed a class of molecules consisting of tethered tris(macrocycles) derived from 4,13-diaza-18-crown-6 ethers, termed hydraphiles.[12] Several reports from the Gokel group[13] have described the ability of these hydraphiles to transport ions across synthetic and biological membranes in a manner similar to that of an ion channel. Of the hydraphiles evaluated, the N-benzyl C-12 hydraphile has displayed some of the highest transport rates observed throughout their investigations.[13]

The first synthesis of C-12 hydraphile **4.14** is shown in Scheme 4.2.[13a] The pore fragment **4.12** was prepared by direct alkylation of 4,13-diaza-18-crown 6 (**4.3**; kryptofix-22); yields for this step were typically low, with varying amounts of the dialkylated product **4.13** forming. The central ring fragment was synthesized by acylation of **4.3**, followed by BH$_3$-THF mediated reduction of the amide carbonyls.   The pore fragment **4.12** was installed in an S$_N$2 displacement of the dibromide intermediate to form **4.14** in 48% yield.

Scheme 4.2. Alkylation route to C-12 hydraphiles.
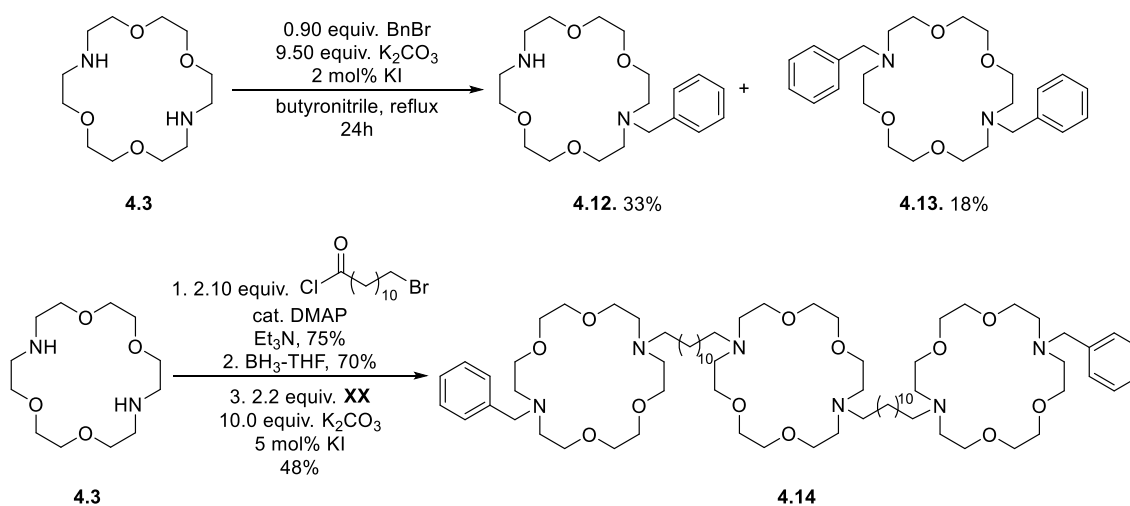
Throughout their investigations into the channel-forming ion transport properties of hydraphiles, difficulties regarding the reliable preparation of **4.14** necessitated an improved synthetic approach (Scheme 4.3).[13k] Mono-protected **4.16**, which was prepared via alkylation of dodecanedioic acid **4.15**, was coupled to **4.3** to generate the transmembrane fragment **4.17**. Removal of the benzyl ester protecting groups furnished diacid **4.18**, which was coupled with the pore fragment **4.12** to generate tetraamide **4.19**. Treatment of **4.19** with BH$_3$-THF over a 72h period furnished hydraphile **4.14** in 60% yield.

Scheme 4.3. Improved route to C-12 hydraphile **4.14**.
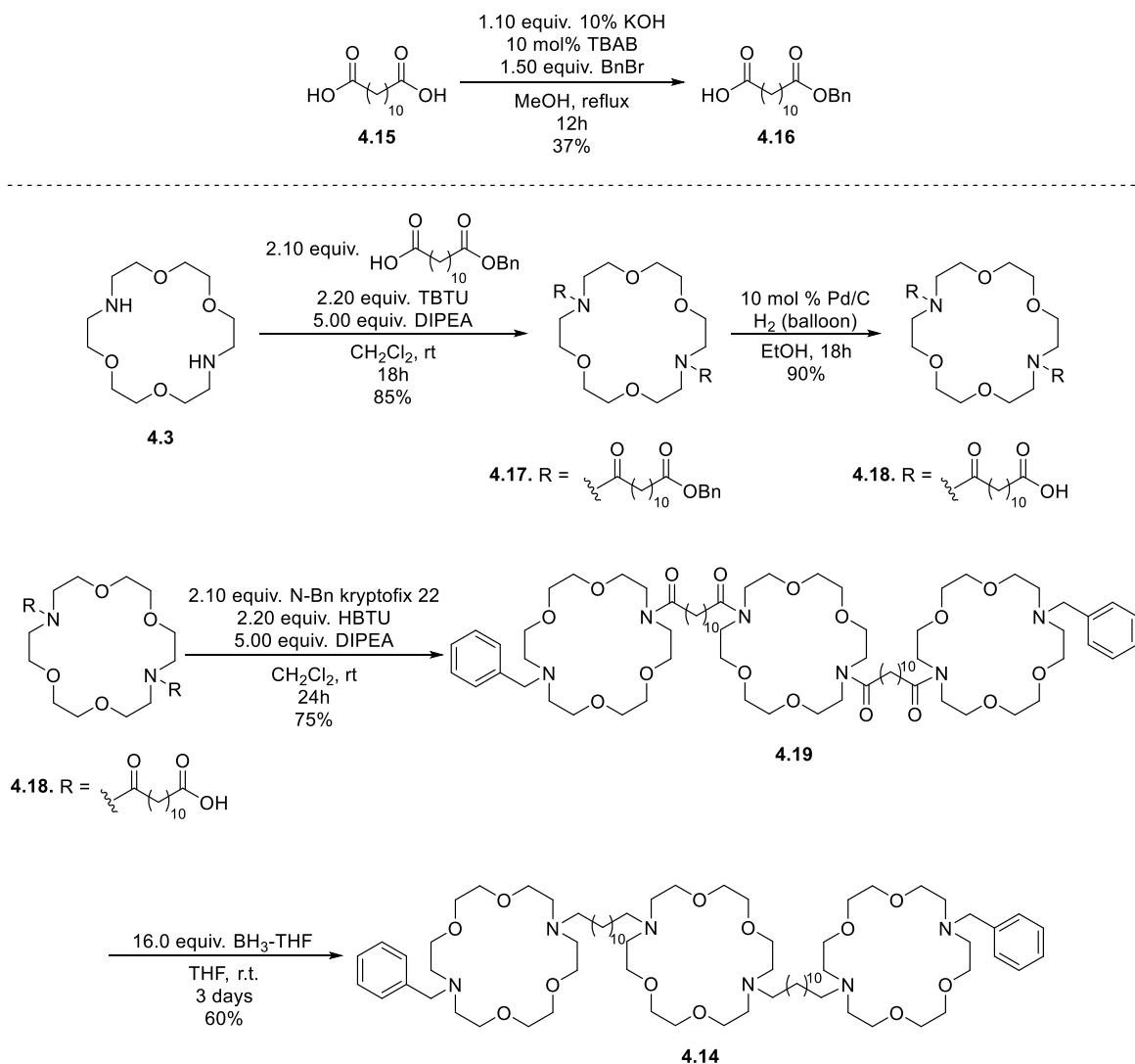
The observation of single channel conductances in bilayer experiments suggested that **4.14** forms ion channels in the membrane; a proposed model is outlined in Figure 4.2.[13b] The two polar head groups act as ion entry portals, while the central diaza crown ether moiety functions as an ion relay unit.[13b] Gokel and coworkers hypothesize that the orientation of the central macrocycle is perpendicular to the polar head groups as shown in Figure 4.2, as opposed to a "tube" shaped channel where an ion passes through all three macrocyclic units. The substitution of dansyl groups (**4.20**) in place of the benzyl groups in **4.14** allowed for Gokel and coworkers to show that hydraphile **4.14** aggregates in the membrane of cells.[13b,e]

Figure 4.2. Ion transport across a bilayer by a hydraphile.
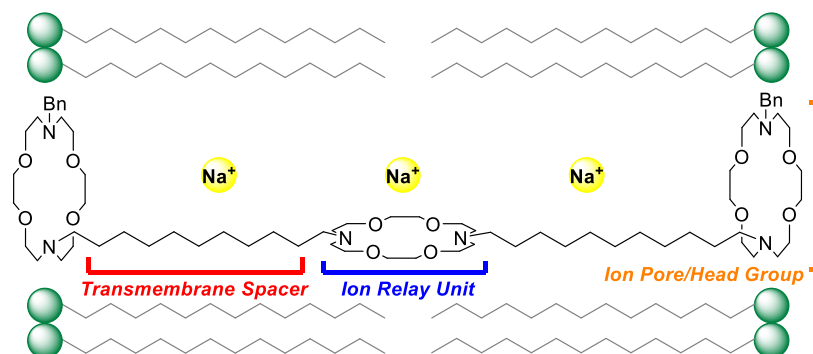
To further probe the model shown in Figure 4.2, Gokel synthesized a series of hydraphiles with modified spacer lengths (Table 4.2).[13e] If the spacer lengths are too short to adequately span the bilayer and form channels, a reduction in the transport rate should occur.[13e] The C-8 derivative (entry 2) shows a significant reduction in relative transport rate as compared to the N-dansyl C-10 **4.20** (entry 1). The N-benzyl substituted C-10 **4.22** (entry 3) showed rates similar to **4.20**, while the C-12 compound **4.14** showed a significant increase in the rate of transport. Additional methylene extensions beyond C-12 (entries 5-6) show a reduction in the rate of transport; this is thought to arise from an increased flexibility in the transmembrane fragment, resulting in poorly defined channels.[13e]

Table 4.2. Na$^+$ transport rates of substituted hydraphiles.
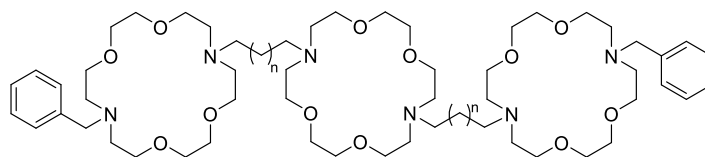
Entry	Compound	n	Relative Rate[a,b]
1	**4.20**[c]	10	100[d]
2	**4.21**	6	<2
3	**4.22**	8	96
4	**4.14**	10	211[e]
5	**4.23**	12	201
6	**4.24**	14	109

[a] Measured using ^{23}Na NMR in phospholipid liposomes.
[b] Relative rate scaled to entry 1. [c] Dansyl group in place
of benzyl group. [d] Rate relative to gramicidin = 23.
[e] Rate relative to gramicidin = 39.

Gokel and coworkers have explored additional modifications to the hydraphile scaffold, including electronic modifications to the N-benzyl substituent,[13c] N-alkyl substitutions,[13a,f] rigidification of the transmembrane fragments via introduction of sp^2 hybridized carbons,[13g] amide linkers,[13i] and changes to the identity of the ion relay unit.[13j] Many of these bilayer studies were conducted in membranes of various compositions, which makes direct comparisons of the relative rates of transport difficult.

4.1.3. Conclusions

Substituted lariat ethers have been shown to act as ion extraction reagents in a host of settings. The identity of the substituents plays a role in both the solubility and ion extraction efficiency of this class of compounds. Further investigations have revealed that these compounds can enhance the potency of antibiotics, demonstrating their potential in the development of future therapeutic agents. Additionally, the work with hydraphiles has shown that synthetic variants of ion channels can provide valuable details regarding the transfer of ions in biological membranes.

As with the lariat ether compounds, hydraphiles can enhance the effectiveness of a variety of antibiotics.

Although preliminary evidence suggests that both lariat ethers and hydraphiles act as ion channels rather than ion carriers, specifics regarding the details of the mechanism of ion transfer remain elusive. An enhanced understanding of the mode of action of these classes of interesting compounds may provide the framework for the development of synthetic ion channels with enhanced physical and kinetic properties.

4.2. Results and Discussion

A detailed understanding of the mechanism(s) involved in ion transport mediated by synthetic ionophores in both synthetic and biological membranes is relevant to many scientific disciplines, particularly the field of electrophysiology. By refining existing models for membrane transport facilitated by these synthetic compounds,[4,14] or by developing new models based on empirical evidence, it may be possible to outline a general set of criteria for the creation of new platforms that exhibit enhanced kinetic and physical properties. Additionally, these design principles can be applied to the development of an optically controlled synthetic transport system. In collaboration with the Chanda lab at the University of Wisconsin-Madison, the mechanism of ion transport exhibited by lariat ethers and hydraphiles were evaluated in synthetic and biological membranes.

4.2.1. Dialkyl diaza-18-crown-6 lariat ether ionophores

To further probe the mechanism of ion transport in bilayers with various derivatives of 4,13-diaza-18-crown-6 ethers, a series of alkyl substituted lariat ethers were prepared with chain lengths ranging from 6-14 carbon atoms (Scheme 4.4). Compounds **4.4**-**4.7** and **4.25**-**4.29** were

prepared in moderate to good yields in a single step using a reductive amination strategy as opposed to previously described macrocyclization or acylation/reduction approaches (Scheme 4.1).[4]

Scheme 4.4. Synthesis of dialkyl diaza-18-crown-6 lariat ethers.

4.25. R = C_6H_{13} **4.28**. R = $C_{11}H_{23}$
4.26. R = C_7H_{15} **4.6**. R = $C_{12}H_{25}$
4.4. R = C_8H_{17} **4.29**. R = $C_{13}H_{27}$
4.27. R = C_9H_{19} **4.7**. R = $C_{14}H_{29}$
4.5. R = $C_{10}H_{21}$
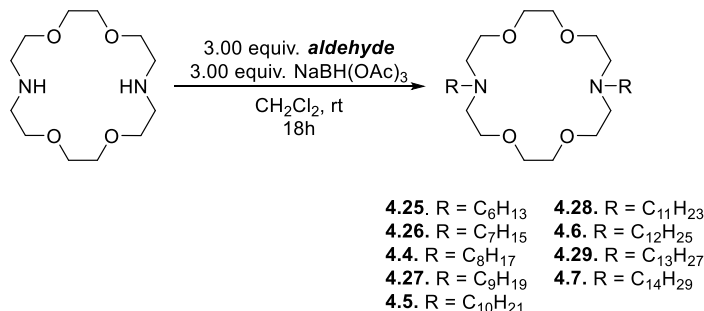
The MICs for lariat ethers **4.4**-**4.7** and **4.25**-**4.29** were determined in three different cellular systems (Figure 4.3); compounds with MIC values >400 µM were considered inactive and indicated with open circles. The lariat ether toxicity in both bacterial species show similarities to reports by Gokel and coworkers;[4a] *B. subtilis* is more susceptible to compounds **4.4**-**4.7** and **4.25**-**4.29** as judged by its lower MICs; **4.5** is the most toxic to *E. coli* (MIC = 10 µM), while **4.5**, **4.28** and **4.6** are the most toxic to *B. subtilis* at concentrations as low as 2 µM. Interestingly, the discontinuity in toxicity related to the length of the alkyl chain observed by Gokel observed in this experimental data set.[4a] Lariat ether **4.6** is highly toxic to *B. subtilis* (MIC = 2 µM) while **4.29** and **4.7** exhibit no toxicity up to concentrations as high as 400 µM. The effect of the alkyl chain length on MIC values in HEK293 cells seems to be more continuous over the range of compounds evaluated when compared to *B. subtilis* and *E. coli*. In all three cell lines evaluated, C-10 lariat ether **4.5** appears to be the most toxic of the set evaluated.

Figure 4.3. MIC values of lariat ethers in *B. subtilis*, *E. coli*, and HEK293 cells.
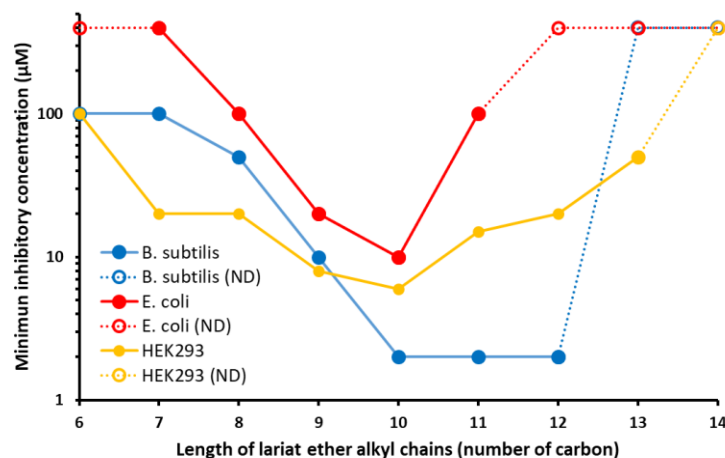
The ClogP values of lariat ethers **4.4**-**4.7** and **4.25**-**4.29** were computed using Gaussian16[14] according to established protocols (Table 4.3).[15] These values ranged from 4.35-11.25 and were dependent on the length of the alkyl chain. Shorter alkyl chains (entries 1-3) resulted in reduced toxicity in all three cell lines evaluated (*cf* Figure 4.3), suggesting that compounds with ClogP <6 may not be sufficiently hydrophobic to transport ions across bilayers.[4] The ClogP of compounds **4.27** and **4.5** were determined to fall between 6 and 7 (entries 4-5); these compounds resulted in the highest toxicity in Figure 4.3. As suggested by Gokel,[4] increasing the hydrophobicity of the lariat ether does not directly correlate to observed toxicity; compounds **4.28**, **4.6**, **4.29**, and **4.7**(entries 6-9) exhibited substantially reduced toxicities in *E. coli* and HEK293 cells, while **4.29** and **4.7** (entries 8-9) were not toxic to *B. subtilis*.

Table 4.3. ClogP values of lariat ethers.
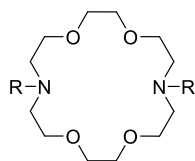
Entry	Compound	Side Chain	ClogP[a]
1	**4.25**	C_6H_{13}	4.35
2	4.26	C_7H_{15}	5.36
3	**4.4**	C_8H_{17}	5.64
4	4.27	C_9H_{19}	6.58
5	**4.5**	$C_{10}H_{21}$	6.88
6	4.28	$C_{11}H_{23}$	8.29
7	**4.6**	$C_{12}H_{25}$	9.24
8	4.29	$C_{13}H_{27}$	10.28
9	**4.7**	$C_{14}H_{29}$	11.25

[a] Calculated using Gaussian16, B3LYP/6+G(2d,p) with SMD solvent model for H_2O and n-Octanol.

To further probe the activity of lariat ether **4.5** as an ion transporter, fluorescence assays utilizing cyanine dyes were implemented.[16] The cyanine dye 3,3-dipropylthiadicarbocyanine (DISC$_3$(5)) undergoes a potential-dependent partitioning between the intra- and extracellular medium; hyperpolarization of the cell membrane results in cellular uptake of DISC$_3$(5).[17] Uptake of DISC$_3$(5) by a cell results in a reduction of fluorescence via self-quenching, presumably due to aggregation of the dye. Conversely, depolarization of the membrane results in release of the dye into the extracellular medium and an increase in fluorescence.[17] The changes in fluorescence exhibited by DISC$_3$(5) can be used to indirectly monitor changes in the membrane potential of cells.[17]

The hypothesized ionophoric behavior of lariat ethers **4.4**-**4.7** and **4.25**-**4.29**[4] were probed using the DISC$_3$(5) assay;[17] the results obtained from the C-10 **4.5** compound are shown in Figure 4.4, **A**. At t = 0, 3.0 mL solution of the NMDG$^+$ buffer is added; upon addition of the DISC$_3$(5) dye (timepoint a), a rapid increase in fluorescence is observed. Addition of *B. subtilis* at timepoint b results in a rapid decrease in fluorescence due to uptake of the dye. At timepoint c, either a

control solution of NMDG$^+$ (grey trace) or a 2M solution of KCl (purple trace) was added. An aliquot of lariat ether **4.5** in trifluoroethanol (TFE) was added at timepoint d.

Initial experiments with KCl (purple trace, Figure 4.4, A) seemed to suggest rapid depolarization of the membrane, resulting in an increase in fluorescence. In the absence of K$^+$, depolarization of the cell membrane via ion transport mediated by **4.5** should not occur, therefore rapid increases in the fluorescence of DISC$_3$(5) were not expected. Control experiments with the NMDG$^+$ buffer (grey trace) produced an unexpected increase in fluorescence of the DISC$_3$(5) dye; this could be due to the unlikely transport of NMDG$^+$ by **4.5**, the DISC$_3$(5) assay results for valinomycin are shown in Figure 4.4, **B**. Valinomycin displays an ion-dependent fluorescence response; under conditions where valinomycin is not capable of promoting membrane depolarization (LiCl, red trace, NaCl, orange trace; NMDG$^+$ buffer, grey trace), rapid increases in fluorescence are not observed.

Figure 4.4. DISC$_3$(5) membrane depolarization assay results for lariat ether **4.5**.
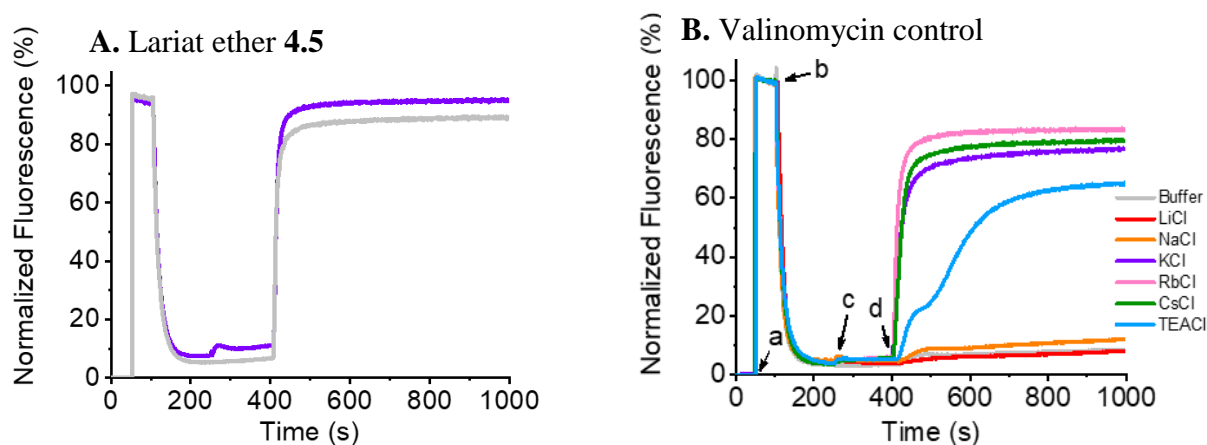
Lactate dehydrogenases (LDH)[18] couple the oxidation of lactate to pyruvate with the reduction of NAD$^+$ to NADH in the last step of the glycolysis cycle. The oxidation of NADH to

NAD$^+$ can be coupled to the diaphorase catalyzed oxidation of resazurin to the highly fluorescent resorufin (Figure 4.5).[18b] This coupling of redox reactions can be used to detect the acute release of LDH from damaged cells.[19] If the toxicity of lariat ether **4.5** is a result of hypothesized lytic activity rather than the ionophoric behavior previously proposed by Gokel,[4] resorufin flurorescence in LDH assays should be detectable.

Figure 4.5. Resorufin fluorescence as a result of membrane degradation.
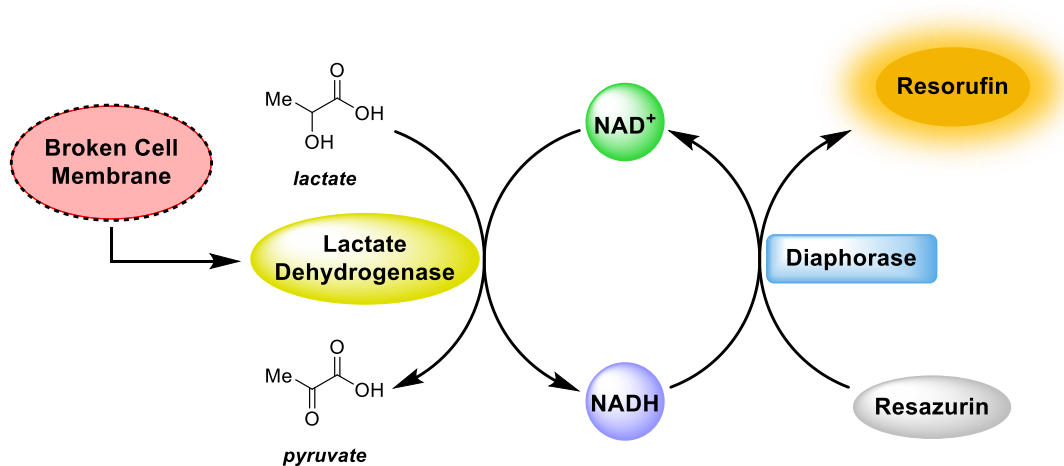
The LDH assay results for lariat ether **4.5** are shown in Figure 4.6. At timepoint a, resazurin dye was added to the solution resulting in an increase in fluorescence. A suspension of *B. subtilis* was added at timepoint b, followed by the addition of diaphorase at timepoint c. At timepoint d, a solution of **4.5** in TFE was added (purple trace), at which point an increase in fluorescence was detected as compared to the TFE control (grey trace). These initial results suggest that the toxicity of lariat ethers **4.4**-**4.7** and **4.25**-**4.29** observed in cellular assays (Figure 4.3) is most likely a result of lytic activity and not ionophoric activity as previously described.[4]

Figure 4.6. LADH/resorufin fluorescence assay results for lariat ether **4.5**.
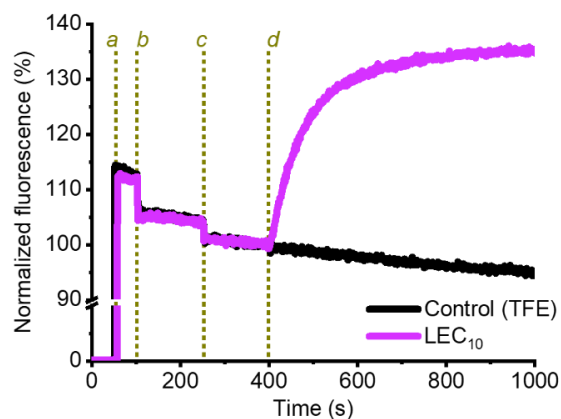
4.2.2. Revised Synthesis of Hydraphiles

To further interrogate the proposed channel-forming properties of C-12 hydraphile **4.14** developed by Gokel and coworkers, the synthesis of **4.14** was attempted as reported. Alkylations of **4.3** (Scheme 4.2) resulted in unusable yields of benzyl ester **4.16** under several conditions. Furthermore, the approach detailed in Schemes 4.2 often led to inseparable mixtures of products and unreliable yields. To circumvent this issue, macrocyclic anhydride **4.30** (Scheme 4.5) was prepared from dodecandioic acid, followed by ring opening with benzyl alcohol to give **4.16** in 84% yield. Coupling of **4.16** with **4.3** and subsequent reduction produced transmembrane fragment **4.18** in similar yields to those previously described.

Scheme 4.5. Modified route to transmembrane fragment **4.18**.
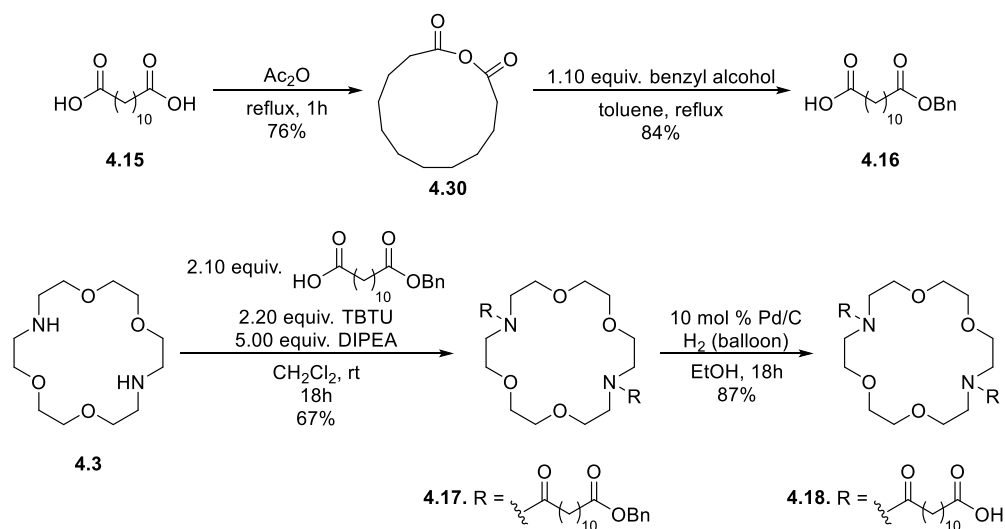
The pore fragment **4.12** was prepared via reductive amination with benzaldehyde (Scheme 4.6).[13k] Coupling with the transmembrane fragment **4.18** resulted in tetraamide **4.19** in 64% yield. Several attempts to reduce tetraamide **4.19** to hydraphile **4.14** with modifications to Gokel's procedure or other methods[20] were unsuccessful. To reliably prepare C-12 hydraphile **4.14** and related derivatives for further study, a new route needed to be developed.

Scheme 4.6. Attempted synthesis of hydraphile **4.14** via Gokel's route.

Scheme 4.7. Revised route to transmembrane fragment **4.34**.
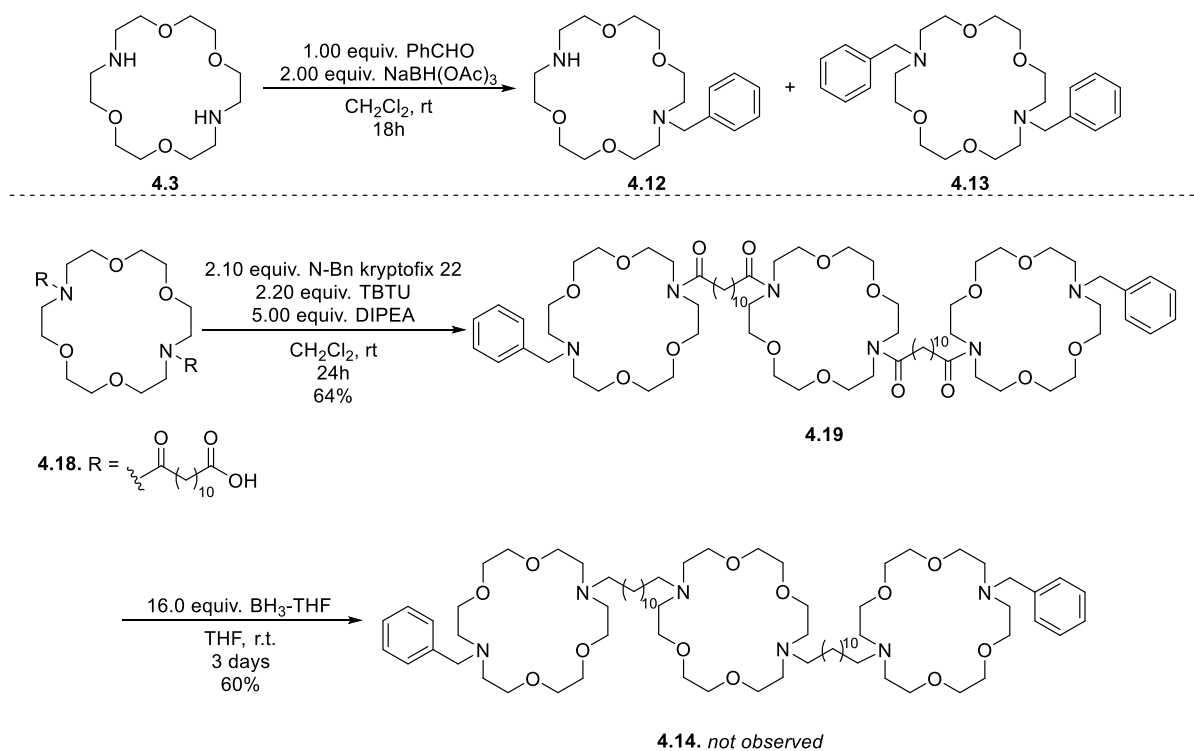
A reductive amination strategy to directly prepare the tertiary amines of **4.14** without an amide reduction step was evaluated (Scheme 4.7). Monoprotection of diol **4.31** and subsequent PCC oxidation furnished the C-12 linker fragment **4.33**. Reductive amination with 4,13-diaza-18-crown-6 generated transmembrane fragment **4.34**. Although issues encountered with amide reduction were mitigated with this route, removal of the silyl ether protecting groups proved rather difficult. Treatment with TBAF resulted in complete loss of product, most likely due to solubility issues resulting complexation of the diaza crown ether and the tetrabutylammonium cation.[21] Various other fluoride reagents resulted in similar outcomes; deprotected **4.34** was not isolated.

Scheme 4.7. Revised route to transmembrane fragment **4.34**.
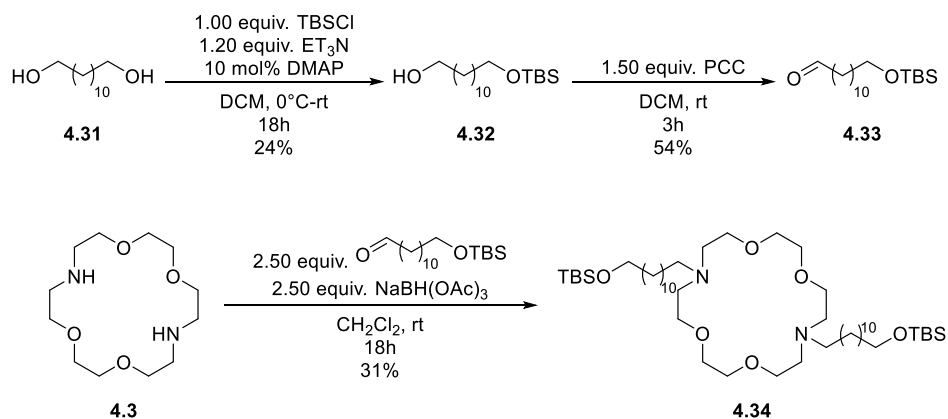
A similar strategy was used to synthesize benzyl ester **4.36** from diol **4.31** (Scheme 4.8). Benzyl protected transmembrane fragment **4.37** was synthesized via reductive aminatiaion of **4.3** with 2.50 equivalents of **4.36**. Successful deprotection of **4.37** to diol **4.38** was achieved by using LiAlH₄. Oxidation of diol **4.38** with DMP and reductive amination with **4.12** resulted in 58% of the alcohol **4.39** and trace amounts of C-12 hydraphile **4.14**. Additional modifications to this procedure, namely the final reductive amination step, may allow for the preparation of C-12 hydraphile **4.14** via a reductive amination protocol without the need for amide reduction.

Scheme 4.8. Benzoate ester route to C-12 hydraphile **4.14**.
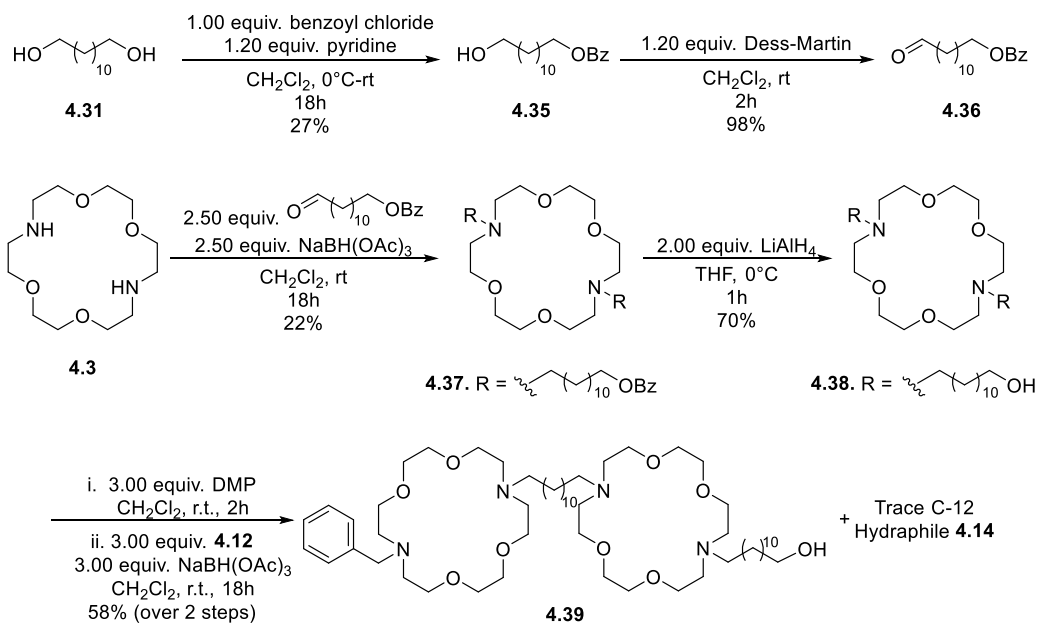
4.2.3. Conclusions and Future Work

Although alkyl substituted lariat ethers do show toxicity towards *B. subtilis*, *E. coli*, and HEK293 cell lines, initial mechanistic evidence suggests lytic activity rather than ionophoric activity is responsible for this effect. In DISC$_3$(5) membrane depolarization assays, no difference was observed between the KCl and salt free control conditions, indicating that the release of the DISC$_3$(5) dye is not occurring as a result of membrane depolarization by K$^+$ influx mediated by lariat ethers. This conclusion was further supported by the detection of resorufin fluorescence in LDH assays, which seems to indicate that the membrane of the cell is lysed in the presence of lariat ethers.

A reevaluation of the synthetic approaches toward N-benzyl C-12 hydraphile **4.14** have shown that alkylation and tetraamide reduction strategies can be problematic and somewhat unreliable approaches to this class of compounds. Optimization of the reductive amination

approach described herein may facilitate a streamlined preparation of these compounds, in turn allowing for the underlying mechanism(s) of their transport abilities to be probed more thoroughly.

4.3. Experimental Procedures

4.3.1. General Experimental Information

All glassware was either oven dried at 140°C or flame dried under vacuum and purged with nitrogen immediately prior to use. Benzaldehyde (PhCHO), benzylamine, and N,N-diisopropylethylamine (DIPEA) were obtained from Millipore Sigma and distilled immediately prior to use. *O*-(Benzotriazol-1-yl)-*N,N,N′,N′*-tetramethyluronium tetrafluoroborate (TBTU) and 2-(1H-Benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU) were obtained from Millipore Sigma and stored at -20°C prior to use. Unless otherwise specified, reagents were used as obtained from the supplier without further purification. Acetonitrile (MeCN), toluene, and dichloromethane (CH_2Cl_2) were freshly distilled from calcium hydride or passed through an alumina column immediately prior to use. Other solvents were purified using accepted procedures from the sixth edition of "Purification of Laboratory Chemicals".[22] Air- and moisture- sensitive reactions were performed using standard Schlenk techniques under an inert nitrogen atmosphere, unless otherwise specified. Analytical thin layer chromatography (TLC) was performed using pre-coated silica gel 60 F24 plates containing a fluorescent indicator. Reaction products were visualized using 254 nm UV light and ceric ammonium molybdate (CAM), $KMnO_4$, and I_2 stains unless otherwise specified. Preparative chromatography using a gradient method with mixtures of MeOH and CH_2Cl_2 or EtOAc and hexanes, unless otherwise specified, was performed using SilicaFlash P60 silica gel (230-400 mesh) via Still's method.[23]

4.3.2. Preparation of Dialkyl Diaza 18-Crown-6 Lariat Ethers
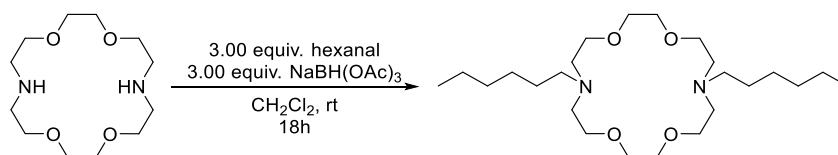
C-6 Lariat Ether (4.25). To a stirred solution of 100.0 mg (0.38 mmol, 1.00 equiv.) 1,4,10,13-tetraoxa-7,16-diazacyclooctadecane in 3.80 mL CH$_2$Cl$_2$ was added 0.14 mL (1.14 mmol, 3.00 equiv.) hexanal, followed by 242 mg (1.14 mmol, 3.00 equiv.) NaBH(OAc)$_3$. The white suspension was stirred at room temperature for 18h, then filtered through a pad of celite. The filter pad was washed with additional CH$_2$Cl$_2$, and the volatiles removed in vacuo to afford crude **4.25**. The crude material was purified via flash column chromatography on alumina using a 0-25% gradient of EtOAc in hexanes to afford 95.0 mg (0.22 mmol, 58%) of **4.25** as a white solid. ¹H NMR (500 MHz, CDCl$_3$) δ 3.71 – 3.51 (m, 16H), 2.85 – 2.69 (m, 8H), 2.58 – 2.41 (m, 4H), 1.51 – 1.37 (m, 4H), 1.35 – 1.20 (m, 12H), 0.88 (t, *J* = 6.9 Hz, 6H). ¹³C NMR (126 MHz, CDCl$_3$) δ 70.8, 70.1, 56.1, 53.9, 31.8, 27.2, 22.7, 14.1. HRMS (ESI) *m/z* calculated for C$_{24}$H$_{50}$N$_2$O$_4$ [M + H]$^+$ 431.3843, found 431.3843.
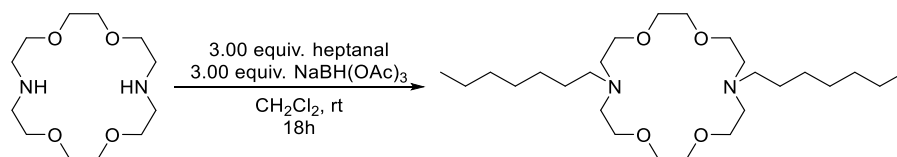
C-7 Lariat Ether (4.26). To a stirred solution of 100.0 mg (0.38 mmol, 1.00 equiv.) 1,4,10,13-tetraoxa-7,16-diazacyclooctadecane in 3.80 mL CH_2Cl_2 was added 0.16 mL (1.14 mmol, 3.00 equiv.) heptanal, followed by 242 mg (1.14 mmol, 3.00 equiv.) $NaBH(OAc)_3$.   The white suspension was stirred at room temperature for 18h, then filtered through a pad of celite. The filter pad was washed with additional CH_2Cl_2, and the volatiles removed in vacuo to afford crude **4.26**. The crude material was purified via flash column chromatography on alumina using a 0-25% gradient of EtOAc in hexanes to afford 49.0 mg (0.11 mmol, 29%) of **4.26** as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.64 – 3.56 (m, 16H), 2.77 (t, J = 6.0 Hz, 8H), 2.51 – 2.44 (m, 4H), 1.49 – 1.39 (m, 4H), 1.33 – 1.21 (m, 16H), 0.91 – 0.84 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 70.8, 70.8, 70.1, 70.1, 56.1, 54.0, 31.9, 29.3, 27.5, 27.3, 22.6, 14.1. HRMS (ESI) m/z calculated for $C_{26}H_{54}N_2O_4$ $[M + H]^+$ 459.4156, found 459.4153.
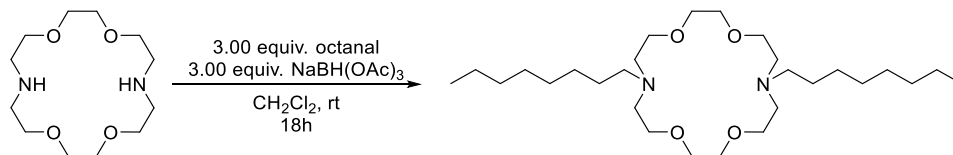
C-8 Lariat Ether (4.4). To a stirred solution of 100.0 mg (0.38 mmol, 1.00 equiv.) 1,4,10,13-tetraoxa-7,16-diazacyclooctadecane in 3.80 mL CH_2Cl_2 was added 0.18 mL (1.14 mmol, 3.00 equiv.) octanal, followed by 242 mg (1.14 mmol, 3.00 equiv.) $NaBH(OAc)_3$. The white suspension was stirred at room temperature for 18h, then filtered through a pad of celite. The filter pad was washed with additional CH_2Cl_2, and the volatiles removed in vacuo to afford crude **4.4**. The crude material was purified via flash column chromatography on alumina using a 0-25% gradient of

EtOAc in hexanes to afford 49.0 mg (0.10 mmol, 26%) of **4.4** as a white solid. ^{1}H NMR (500 MHz, CDCl$_3$) δ 3.64 – 3.56 (m, 16H), 2.77 (t, J = 6.0 Hz, 8H), 2.53 – 2.44 (m, 4H), 1.48 – 1.38 (m, 4H), 1.32 – 1.18 (m, 20H), 0.91 – 0.86 (m, 6H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 70.7, 69.8, 55.9, 53.8, 31.8, 29.7, 29.5, 29.4, 29.3, 27.5, 22.7, 22.7, 14.1. HRMS (ESI) *m/z* calculated for C$_{28}$H$_{58}$N$_2$O$_4$ [M + H]$^+$ 487.4469, found 487.4471.
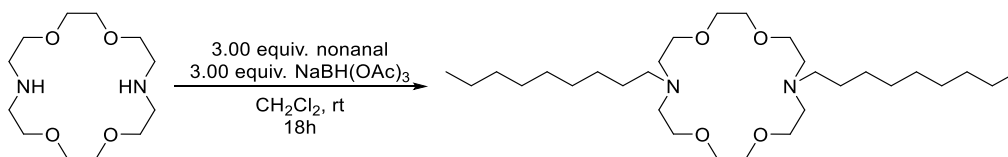
C-9 Lariat Ether (4.27). To a stirred solution of 100.0 mg (0.38 mmol, 1.00 equiv.) 1,4,10,13-tetraoxa-7,16-diazacyclooctadecane in 3.80 mL CH$_2$Cl$_2$ was added 0.20 mL (1.14 mmol, 3.00 equiv.) nonanal, followed by 242 mg (1.14 mmol, 3.00 equiv.) NaBH(OAc)$_3$. The white suspension was stirred at room temperature for 18h, then filtered through a pad of celite. The filter pad was washed with additional CH$_2$Cl$_2$, and the volatiles removed in vacuo to afford crude **4.27**. The crude material was purified via flash column chromatography on alumina using a 0-25% gradient of EtOAc in hexanes to afford 66.0 mg (0.13 mmol, 34%) of **4.27** as a white solid. ^{1}H NMR (500 MHz, CDCl$_3$) δ 3.61 (d, J = 7.4 Hz, 16H), 2.77 (t, J = 6.0 Hz, 8H), 2.52 – 2.43 (m, 4H), 1.48 – 1.38 (m, 4H), 1.26 (s, 24H), 0.88 (t, J = 6.9 Hz, 6H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 70.8, 70.0, 56.1, 53.9, 31.9, 29.7, 29.6, 29.6, 29.3, 27.5, 27.3, 22.7, 14.1. HRMS (ESI) *m/z* calculated for C$_{30}$H$_{62}$N$_2$O$_4$ [M + H]$^+$ 515.4782, found 515.4787.
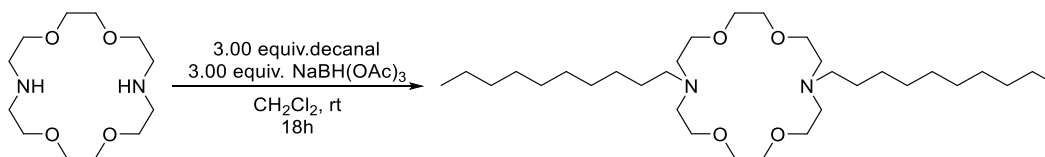
C-10 Lariat Ether (4.5). To a stirred solution of 100.0 mg (0.38 mmol, 1.00 equiv.) 1,4,10,13-tetraoxa-7,16-diazacyclooctadecane in 3.80 mL CH_2Cl_2 was added 0.21 mL (1.14 mmol, 3.00 equiv.) decanal, followed by 242 mg (1.14 mmol, 3.00 equiv.) $NaBH(OAc)_3$. The white suspension was stirred at room temperature for 18h, then filtered through a pad of celite. The filter pad was washed with additional CH_2Cl_2, and the volatiles removed in vacuo to afford crude **4.5**. The crude material was purified via flash column chromatography on alumina using a 0-25% gradient of EtOAc in hexanes to afford 19.0 mg (0.03 mmol, 8%) of **4.5** as a white solid. ^{1}H NMR (500 MHz, CDCl$_3$) δ 3.61 (d, J = 8.6 Hz, 16H), 2.77 (t, J = 6.0 Hz, 8H), 2.52 – 2.43 (m, 4H), 1.43 (dq, J = 13.3, 6.7, 6.0 Hz, 4H), 1.26 (s, 28H), 0.88 (t, J = 6.9 Hz, 6H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 70.8, 70.1, 56.1, 54.0, 31.9, 29.7, 29.7, 29.6, 29.6, 29.3, 27.5, 27.3, 22.7, 14.1. HRMS (ESI) m/z calculated for $C_{32}H_{66}N_2O_4$ [M + H]$^+$ 543.5095, found 543.5097.
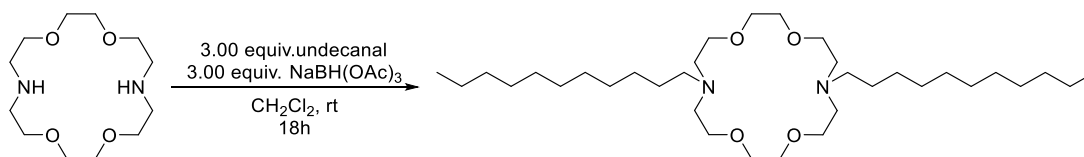
C-11 Lariat Ether (4.28). To a stirred solution of 100.0 mg (0.38 mmol, 1.00 equiv.) 1,4,10,13-tetraoxa-7,16-diazacyclooctadecane in 3.80 mL CH_2Cl_2 was added 0.24 mL (1.14 mmol, 3.00 equiv.) undecanal, followed by 242 mg (1.14 mmol, 3.00 equiv.) $NaBH(OAc)_3$. The white suspension was stirred at room temperature for 18h, then filtered through a pad of celite. The filter pad was washed with additional CH_2Cl_2, and the volatiles removed in vacuo to afford crude **4.28**. The crude material was purified via flash column chromatography on alumina using a 0-25% gradient of EtOAc in hexanes to afford 119 mg (0.21 mmol, 55%) of **4.28** as a white solid. ^{1}H NMR (500 MHz, CDCl$_3$) δ 3.76 – 3.47 (m, 16H), 2.90 – 2.64 (m, 8H), 2.57 – 2.41 (m, 4H), 1.51 – 1.37 (m, 4H), 1.34 – 1.18 (m, 32H), 0.88 (t, J = 6.9 Hz, 6H). ^{13}C NMR (126 MHz, CDCl$_3$) δ

70.7, 70.0, 63.1, 56.0, 53.9, 32.8, 31.9, 31.9, 29.6, 29.6, 29.4, 29.4, 27.5, 27.2, 25.7, 22.7, 14.1.

HRMS (ESI) m/z calculated for $C_{34}H_{70}N_2O_4$ [M + H]$^+$ 571.5408, found 571.5405.
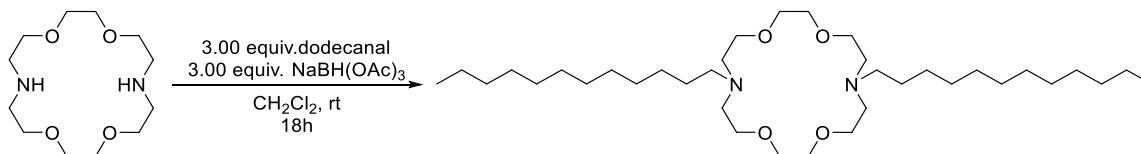
C-12 Lariat Ether (4.6). To a stirred solution of 100.0 mg (0.38 mmol, 1.00 equiv.) 1,4,10,13-tetraoxa-7,16-diazacyclooctadecane in 3.80 mL CH$_2$Cl$_2$ was added 0.25 mL (1.14 mmol, 3.00 equiv.) dodecanal, followed by 242 mg (1.14 mmol, 3.00 equiv.) NaBH(OAc)$_3$. The white suspension was stirred at room temperature for 18h, then filtered through a pad of celite. The filter pad was washed with additional CH$_2$Cl$_2$, and the volatiles removed in vacuo to afford crude **4.6**. The crude material was purified via flash column chromatography on alumina using a 0-25% gradient of EtOAc in hexanes to afford 118 mg (0.20 mmol, 53%) of **4.6** as a white solid. ^{1}H NMR (500 MHz, Chloroform-d) δ 3.61 (d, J = 8.7 Hz, 16H), 2.77 (t, J = 6.0 Hz, 8H), 2.51 – 2.44 (m, 4H), 1.76 – 1.69 (m, 2H), 1.43 (dq, J = 12.9, 6.9, 6.5 Hz, 4H), 1.26 (s, 34H), 0.88 (t, J = 6.9 Hz, 6H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 70.8, 70.1, 56.1, 54.0, 31.9, 29.7, 29.7, 29.6, 29.4, 27.5, 27.3, 22.7, 14.1. HRMS (ESI) m/z calculated for $C_{36}H_{74}N_2O_4$ [M + H]$^+$ 599.5721, found 599.5716.
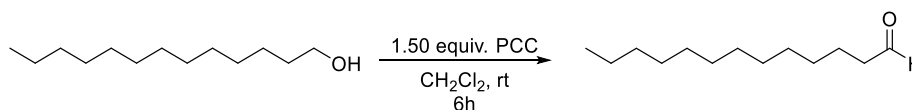
Tridecanal. To a stirred solution of 1.00 g (4.99 mmol, 1.00 equiv.) tridecanol in 50 mL CH$_2$Cl$_2$ was added 1.61 g (7.49 mmol, 1.50 equiv.) PCC. The resulting black solution was stirred at room temperature for 6h, then 1.61 g celite was added and the light brown suspension stirred at room temperature for an additional 30 minutes. The crude reaction mixture was then filtered through a

plug of silica gel using CH_2Cl_2 as eluent to afford 732 mg (3.69 mmol; 74%) tridecanal as a white solid which was used without any additional purification. ^{1}H NMR (500 MHz, CDCl$_3$) δ 9.76 (t, $J = 1.9$ Hz, 1H), 2.41 (td, $J = 7.3$, 1.9 Hz, 2H), 1.63 (p, $J = 7.4$ Hz, 2H), 1.37 − 1.20 (m, 18H), 0.88 (t, $J = 6.9$ Hz, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 202.9, 43.9, 31.9, 29.6, 29.6, 29.6, 29.4, 29.4, 29.3, 29.2, 22.7, 22.1, 14.1. HRMS (ESI) m/z calculated for $C_{13}H_{26}O$ [M + H]$^+$ 199.2056, found 199.2055.
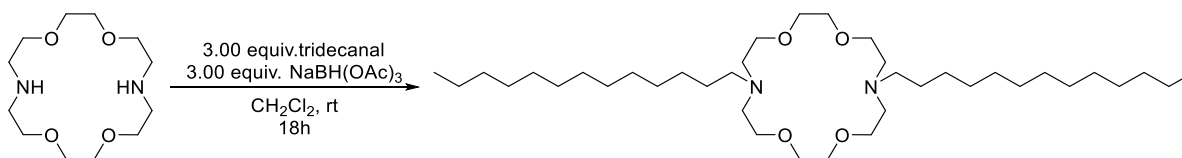
C-13 Lariat Ether (4.29). To a stirred solution of 100.0 mg (0.38 mmol, 1.00 equiv.) 1,4,10,13-tetraoxa-7,16-diazacyclooctadecane in 3.80 mL CH_2Cl_2 was added 0.27 mL (1.14 mmol, 3.00 equiv.) tridecanal, followed by 242 mg (1.14 mmol, 3.00 equiv.) NaBH(OAc)$_3$. The white suspension was stirred at room temperature for 18h, then filtered through a pad of celite. The filter pad was washed with additional CH_2Cl_2, and the volatiles removed in vacuo to afford crude **4.29**. The crude material was purified via flash column chromatography on alumina using a 0-25% gradient of EtOAc in hexanes to afford 58.0 mg (0.09 mmol, 24%) of **4.29** as a white solid. ^{1}H NMR (500 MHz, CDCl$_3$) δ 3.66 − 3.55 (m, 16H), 2.77 (t, $J = 6.0$ Hz, 8H), 2.51 − 2.45 (m, 4H), 1.78 (s, 2H), 1.43 (p, $J = 7.1$ Hz, 4H), 1.25 (s, 38H), 0.88 (t, $J = 6.9$ Hz, 6H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 70.8, 70.1, 56.1, 54.0, 31.9, 29.7, 29.7, 29.7, 29.6, 29.4, 27.5, 27.3, 22.7, 14.1. HRMS (ESI) m/z calculated for $C_{38}H_{78}N_2O_4$ [M + H]$^+$ 627.6034, found 627.6021.
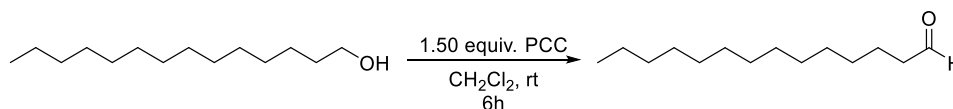
Tetradecanal. To a stirred solution of 1.00 g (4.66 mmol, 1.00 equiv.) tetradecanol in 47 mL CH$_2$Cl$_2$ was added 1.51 g (6.99 mmol, 1.50 equiv.) PCC. The resulting black solution was stirred at room temperature for 6h, then 1.51 g celite was added and the light brown suspension stirred at room temperature for an additional 30 minutes. The crude reaction mixture was then filtered through a plug of silica gel using CH$_2$Cl$_2$ as eluent to afford 801 mg (3.77 mmol; 81%) tetradecanal as a white solid which was used without any additional purification. ^{1}H NMR (500 MHz, CDCl$_3$) δ 9.76 (t, J = 1.9 Hz, 1H), 2.42 (td, J = 7.3, 1.9 Hz, 2H), 1.63 (p, J = 7.4 Hz, 2H), 1.37 – 1.19 (m, 20H), 0.88 (t, J = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 202.9, 43.9, 31.9, 29.7, 29.6, 29.6, 29.4, 29.4, 29.2, 22.7, 22.1, 14.1. HRMS (ESI) m/z calculated for C$_{14}$H$_{28}$O [M + H]$^+$ 213.2213, found 213.2210.
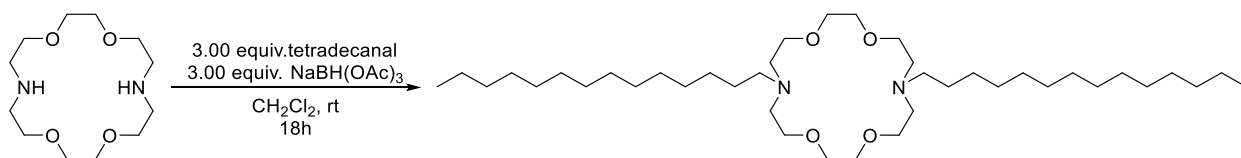
C-14 Lariat Ether (4.7). To a stirred solution of 100.0 mg (0.38 mmol, 1.00 equiv.) 1,4,10,13-tetraoxa-7,16-diazacyclooctadecane in 3.80 mL CH$_2$Cl$_2$ was added 242 mg (1.14 mmol, 3.00 equiv.) tetradecanal, followed by 242 mg (1.14 mmol, 3.00 equiv.) NaBH(OAc)$_3$. The white suspension was stirred at room temperature for 18h, then filtered through a pad of celite. The filter pad was washed with additional CH$_2$Cl$_2$, and the volatiles removed in vacuo to afford crude **4.7**. The crude material was purified via flash column chromatography on alumina using a 0-25% gradient of EtOAc in hexanes to afford 78.0 mg (0.12 mmol, 32%) of **4.7** as a white solid. ^{1}H NMR (500 MHz, CDCl$_3$) δ 3.67 – 3.53 (m, 16H), 2.77 (t, J = 6.0 Hz, 8H), 2.52 – 2.42 (m, 4H), 1.58 (s, 8H), 1.43 (s, 4H), 1.25 (s, 36H), 0.88 (t, J = 6.9 Hz, 6H). ^{13}C NMR (126 MHz, CDCl$_3$) δ

70.8, 70.1, 56.1, 54.0, 31.9, 29.7, 29.7, 29.7, 29.4, 27.5, 27.3, 22.7, 14.1. HRMS (ESI) *m/z* calculated for $C_{40}H_{82}N_2O_4$ [M + H]$^+$ 655.6347, found 655.6339.

4.3.3. Revised Route to Synthetic Hydraphiles
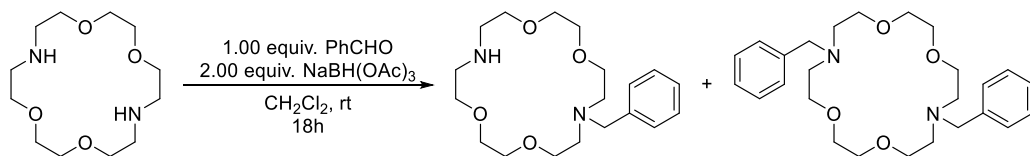
N-Bn kryptofix 22 (4.12). Initial attempts to synthesize N-benzyl kryptofix 22 were conducted according to a previously published procedure.[13k] To a stirred solution of 250 mg (0.95 mmol, 1.00 equiv.) kryptofix 22 in 9.5 mL CH_2Cl_2 was added 604 mg (2.85 mmol, 3.00 equiv.) NaBH(OAc)$_3$, followed by the addition of 97 µL (0.95 mmol, 1.00 equiv.) freshly distilled benzaldehyde. The resulting suspension was stirred at room temperature for 18h, then quenched by the dropwise addition of 1 mL MeOH. The solids were removed via filtration through a pad of celite using additional CH_2Cl_2 to rinse the filter pad. The volatiles were removed in vacuo to give a mixture of unreacted kryptofix 22, N-benzyl kryptofix 22 **4.12**, and N,N'-dibenzyl kryptofix 22 **4.12**. Flash chromatography on silica gel using a gradient of MeOH in CH_2Cl_2 afforded 50 mg (0.14 mmol, 15%) pure N-benzyl kryptofix 22 **4.12**. The remaining fractions were pooled and concentrated to give a mixture of N,N'-dibenzyl kryptofix 22 **4.13** and unreacted kryptofix 22 **4.3**. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.35 – 7.32 (m, 2H), 7.29 (t, *J* = 7.6 Hz, 2H), 7.24 – 7.20 (m, 1H), 3.69 (s, 2H), 3.62 (td, *J* = 5.8, 5.2, 2.7 Hz, 8H), 3.60 (s, 8H), 2.82 (q, *J* = 5.6 Hz, 8H), 2.29 (br s, 1H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 139.7, 128.8, 128.1, 126.8, 70.9, 70.2, 70.2, 70.0, 59.7, 53.7, 49.3. HRMS (ESI) *m/z* calculated for $C_{19}H_{32}N_2O_4$ [M + H]$^+$ 353.2435, found 353.2428. Characterization data for N,N'-dibenzyl kryptofix 22 matches that previously reported in the literature.[13k]
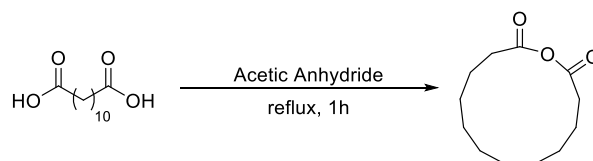
Anhydride 4.30. A solution of 2.30 g (9.90 mmol, 1.00 equiv.) dodecanedioic acid **4.15** in 100 mL Ac$_2$O was heated to reflux for 1h. The solution was cooled to room temperature and the volatiles removed in vacuo to afford the crude anhydride as an off-white solid. The crude material was purified via filtration though a plug of silica gel using hexanes as eluent to afford 1.61 g (7.58 mmol, 76%) cyclic anhydride **4.30** as a white solid. ^{1}H NMR (500 MHz, CDCl$_3$) δ 2.45 (td, J = 7.4, 3.8 Hz, 4H), 1.65 (pd, J = 7.3, 1.7 Hz, 4H), 1.38 – 1.25 (m, 12H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 169.4, 35.3, 35.2, 29.3, 29.3, 29.1, 29.1, 28.8, 28.8, 24.2, 24.1. HRMS (ESI) m/z calculated for C$_{12}$H$_{20}$O$_3$ [M + NH$_4$]$^+$ 230.1751, found 230.1750.
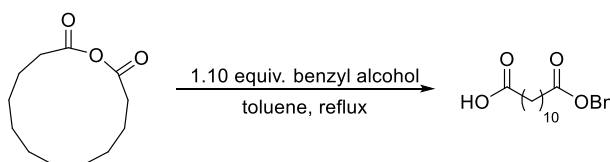
Monobenzyl Ester 4.16. To a stirred solution of 9.21 g (43.4 mmol, 1.00 equiv.) cyclic anhydride **4.30** in 100 mL toluene was added 4.94 mL (47.7 mmol, 1.10 equiv.) distilled benzyl alcohol. The resulting solution was heated to reflux for 18h and cooled to room temperature. The volatiles were removed in vacuo to afford crude the crude monobenzyl ester. The crude material was purified via flash column chromatography on silica gel using a gradient of 0-10% EtOAc in hexanes to afford 11.7 g (36.4 mmol, 84%) monobenzyl ester **4.16** as a white solid. ^{1}H NMR (500 MHz, CDCl3) δ 7.39 – 7.30 (m, 5H), 5.11 (s, 2H), 2.44 (t, J = 7.4 Hz, 2H), 2.35 (t, J = 7.5 Hz, 2H), 1.68 – 1.60 (m, 4H), 1.27 (overlapping methylene signals, 12H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 173.7,

169.6, 136.1, 128.5, 128.2, 66.1, 35.3, 34.3, 29.3, 29.3, 29.2, 29.2, 29.1, 28.8, 24.9, 24.2. HRMS

(ESI) m/z calculated for $C_{19}H_{28}O_4$ [M - H]$^-$ 319.1915, found 319.1913.
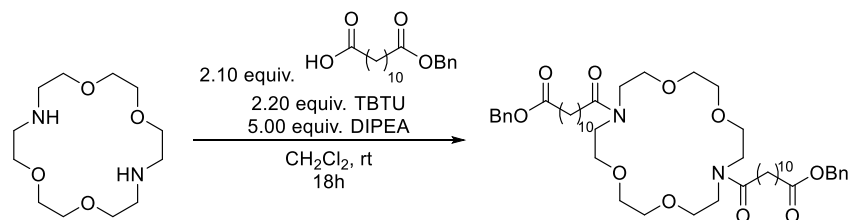
Transmembrane Fragment 4.17. To a stirred solution of 40.0 mg (0.12 mmol, 2.10 equiv.)

monobenzyl ester **4.16** in 1.0 mL CH_2Cl_2 was added 41.7 mg (0.13 mmol; 2.20 equiv.) TBTU,

followed by the addition of 52 µL (0.30 mmol, 5.00 equiv.) DIPEA. The resulting solution was

stirred at room temperature for 15 minutes before 16.0 mg (0.06 mmol, 1.00 equiv.) kryptofix-22

4.3 was added. After stirring for an additional 18h, the crude reaction mixture was poured into 10

mL CH_2Cl_2 and washed with 2x10 mL portions of H_2O. The organics were dried over $MgSO_4$ and

the volatiles removed in vacuo to give the crude coupling product **4.17**. The crude material was

purified via flash column chromatography on silica gel using a 0-10% gradient of MeOH in CH_2Cl_2

to afford 34 mg (0.04 mmol; 67%) of compound **4.17** as a viscous yellow oil. ^{1}H NMR (500 MHz,

CDCl$_3$) δ 7.40 – 7.29 (m, 10H), 5.11 (s, 4H), 3.68 – 3.56 (m, 21H), 2.35 (t, J = 7.6 Hz, 5H), 2.31

(td, J = 7.7, 4.0 Hz, 4H), 1.62 (p, J = 7.4 Hz, 9H), 1.35 – 1.22 (m, 25H). ^{13}C NMR (126 MHz,

CDCl$_3$) δ 173.7, 173.4, 173.3, 136.1, 128.5, 128.2, 70.9, 70.8, 70.5, 70.5, 70.4, 70.1, 70.0, 69.6,

66.1, 48.8, 48.7, 47.0, 46.9, 34.3, 33.2, 33.1, 29.5, 29.5, 29.4, 29.4, 29.2, 29.1, 25.4, 25.3, 24.9.

HRMS (ESI) m/z calculated for $C_{50}H_{78}N_2O_{10}$ [M + H]$^+$ 867.5729, found 867.5723.
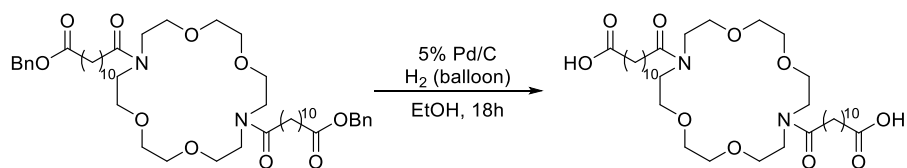
Diacid 4.18. To a stirred solution of 619 mg (0.71 mmol, 1.00 equiv.) diester **4.17** in 7.10 mL anhydrous EtOH was added 192 mg of 5% wt. Pd/C. The resulting black suspension was vigorously stirred, and the flask was purged with H_2 gas. A balloon of H_2 was attached via needle and H_2 gas was bubbled through the suspension for 18h. After stirring was complete, the Pd/C was removed via filtration through a pad of celite using additional EtOH to wash the solids. The volatiles were removed in vacuo to afford 426 mg (0.62 mmol; 87%) pure diacid **4.18** as a white solid. If necessary, additional purification can be achieved via flash column chromatography on silica gel using a gradient of MeOH in CH_2Cl_2 as eluent. ^1H NMR (500 MHz, CDCl$_3$) δ 3.70 – 3.59 (m, 18H), 3.60 – 3.57 (m, 4H), 2.38 – 2.28 (m, 9H), 1.68 – 1.58 (m, 9H), 1.38 – 1.23 (m, 24H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 178.7, 178.6, 173.7, 173.7, 70.9, 70.8, 70.6, 70.5, 70.5, 70.1, 70.0, 69.3, 49.0, 48.8, 47.2, 46.8, 34.0, 33.1, 33.0, 29.2, 29.2, 29.1, 29.1, 29.1, 29.0, 29.0, 28.9, 28.7, 28.7, 25.3, 25.3, 24.6. HRMS (ESI) m/z calculated for $C_{36}H_{66}N_2O_{10}$ [M + H]$^+$ 687.4790, found 687.4785.
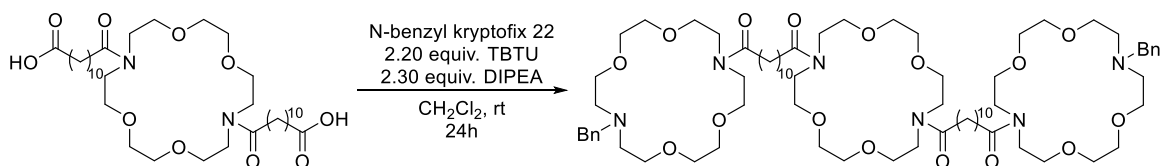
Tetraamide 4.19. To a stirred solution of 61 mg (0.097 mmol, 1.00 equiv.) diacid **4.18** in 1.0 mL CH_2Cl_2 was added 64 mg (0.19 mmol, 2.20 equiv.) TBTU and 78 µL (0.45 mmol, 5.00 equiv.) DIPEA. The resulting solution was stirred at room temperature for 15 minutes before 68 mg (0.20 mmol, 2.10 equiv.) N-benzyl kryptofix 22 in 0.5 mL CH_2Cl_2 and stirring continued for an additional 24h. The reaction mixture was then poured into 5 mL H_2O and extracted with 5 mL CH_2Cl_2. The volatiles were removed in vacuo to afford crude tetraamide **4.19**, which was further purified via flash column chromatography on silica gel using MeOH in CH_2Cl_2 as eluent to afford

84 mg (0.062 mmol, 64%) tetraamide as a viscous yellow oil. 1H ^{13}C NMR (126 MHz, CDCl$_3$) δ 173.39, 173.35, 128.92, 128.20, 126.97, 70.95, 70.91, 70.76, 70.66, 70.55, 70.42, 70.32, 70.09, 70.03, 69.87, 69.77, 69.61, 59.81, 53.73, 53.64, 53.43, 50.87, 48.86, 48.78, 47.01, 46.89, 33.19, 33.14, 29.71, 29.51, 25.38, 25.35. HRMS (ESI) m/z calculated for C$_{74}$H$_{126}$N$_6$O$_{16}$ [M + H]$^+$ 1355.9303, found 1355.9296.
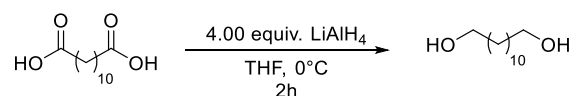
1,12-dodecanediol 4.31. A three neck round bottom flask was charged with 1.52 g (40.0 mmol, 4.00 equiv.) LiAlH$_4$ and 50 mL THF at 0°C. A solution of 2.02 g (10.0 mmol, 1.00 equiv.) 1,12-dodecanedioic acid in 50 mL THF was added dropwise, and the resulting grey suspension stirred at 0°C for 2 h. The reaction was quenched by the careful sequential of addition of 2.00 mL H$_2$O, 2.00 mL 15% NaOH, then 6.00 mL H$_2$O. Na$_2$SO$_4$ was added, and the resulting white suspension stirred at room temperature for 30 minutes then filtered through a pad of celite. The volatiles were removed in vacuo to afford 1.99 g (9.83 mmol, 98%) 1,12-dodecanediol as a white solid which was used without any additional purification. ^{1}H NMR (500 MHz, CDCl$_3$) δ 3.64 (q, J = 6.3 Hz, 4H), 1.56 (p, 4H), 1.40 – 1.24 (m, 16H), 1.19 (t, J = 5.3 Hz, 2H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 63.1, 32.8, 29.6, 29.5, 29.4, 25.7. HRMS (ESI) m/z calculated for C$_{12}$H$_{26}$O$_2$ [M + Na]$^+$ 225.1825, found 225.1820.
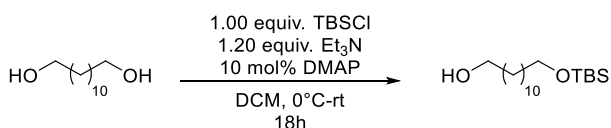
Monoprotected diol 4.32. A solution of 2.02 g (10.0 mmol, 1.00 equiv.) diol, 1.67 mL (12.0 mmol, 1.20 equiv.) Et$_3$N, and 122.2 mg (1.00 mmol, 0.010 equiv.) DMAP in 50 mL CH$_2$Cl$_2$ was

cooled to 0°C, and 1.50 g TBSCl (10.0 mmol, 1.00 equiv.) in 50 mL CH_2Cl_2 was added dropwise over a 30 minute period. The resulting mixture was then allowed to warm to room temperature and stirred for an additional 18 h at room temperature. The crude reaction mixture was poured into a separatory funnel containing 50 ml H_2O and extracted with 3x50 mL portions of CH_2Cl_2. The combined organics were dried over $MgSO_4$ and the volatiles removed in vacuo to afford the crude silyl ether **4.32**. The crude mixture was purified via flash column chromatography on silica gel using a 0-10% gradient of EtOAc in hexanes to afford 766 mg (2.42 mmol, 24%) silyl ether **4.32** as a clear, colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.66 – 3.61 (m, 2H), 3.60 (t, J = 6.7 Hz, 2H), 1.61 – 1.53 (m, 2H), 1.50 (q, J = 6.9 Hz, 2H), 1.39 – 1.23 (m, 16H), 1.20 (t, J = 4.8 Hz, 1H), 0.89 (s, 9H), 0.05 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 63.4, 63.1, 32.9, 32.8, 29.6, 29.6, 29.6, 29.6, 29.4, 29.4, 26.0, 25.8, 25.7, 18.4, -5.2. HRMS (ESI) m/z calculated for $C_{18}H_{40}O_2Si$ [M + H]$^+$ 317.2870, found 317.2869.
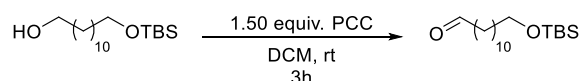
Aldehyde 4.33. To a stirred solution of 766 mg (2.42 mmol, 1.00 equiv.) alcohol **4.32** in 25 mL CH_2Cl_2 was added 782 mg (3.63 mmol, 1.50 equiv.) pyridinium chlorochromate (PCC). The resulting black solution was stirred at room temperature for 3h before 782 mg celite was added. The brown suspension was stirred for an additional 30 minutes at room temperature before being filtered through a pad of silica gel. The silica gel was rinsed with additional CH_2Cl_2 and the volatiles were removed in vacuo to afford 412 mg (1.31 mmol, 54%) aldehyde **4.33** as a pale yellow oil, which was carried forward without any additional purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.76 (t, J = 1.9 Hz, 1H), 3.59 (t, J = 6.6 Hz, 2H), 2.41 (td, J = 7.4, 1.9 Hz, 2H), 1.63 (p, J = 7.3 Hz, 2H), 1.50 (p, J = 6.8 Hz, 2H), 1.36 – 1.20 (m, 14H), 0.89 (s, 9H), 0.05 (s, 6H). ^{13}C

NMR (126 MHz, CDCl$_3$) δ 202.9, 63.3, 43.9, 32.9, 29.6, 29.5, 29.4, 29.4, 29.4, 29.2, 26.0, 25.8, 22.1, 18.4, -5.2. HRMS (ESI) *m/z* calculated for C$_{18}$H$_{38}$O$_2$Si [M + H]$^+$ 315.2714, found 315.2712.
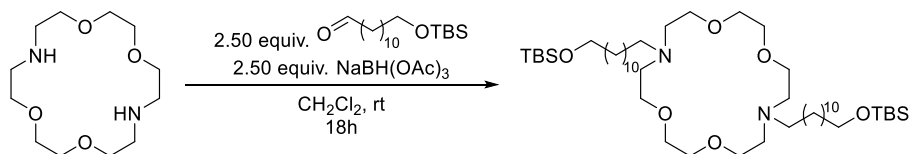
Bis-Silyl Ether Transmembrane Fragment 4.34. To a stirred solution of 136 mg (0.52 mmol, 1.00 equiv.) kryptofix-22 **4.3** in 5.2 mL CH$_2$Cl$_2$ was added 421 mg (1.31 mmol, 2.50 equiv.) aldehyde **4.33** and 278 mg (1.31 mmol, 2.50 equiv.) NaBH(OAc)$_3$. The resulting suspension was stirred at room temperature for 18h, then filtered through a pad of celite. The celite pad was washed with additional CH$_2$Cl$_2$, and the volatiles removed in vacuo to give crude **4.33**. The crude material was purified via flash column chromatography on alumina using a gradient of 0-25% EtOAc in hexanes to afford 135 mg (0.16 mmol; 31%) **4.33** as a pale yellow oil. ^{1}H NMR (500 MHz, CDCl$_3$) δ 3.63 – 3.57 (m, 16H), 2.77 (t, *J* = 6.0 Hz, 8H), 2.51 – 2.43 (m, 4H), 1.64 (s, 4H), 1.50 (q, *J* = 6.9 Hz, 4H), 1.43 (s, 4H), 1.27 (d, *J* = 12.1 Hz, 32H), 0.89 (s, 18H), 0.05 (s, 12H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 70.8, 70.1, 63.4, 56.1, 54.0, 32.9, 29.7, 29.6, 29.6, 29.5, 27.5, 27.3, 26.0, 25.8, 18.4, -5.2. HRMS (ESI) *m/z* calculated for C$_{48}$H$_{102}$N$_2$O$_6$Si$_2$ [M + H]$^+$ 859.7349, found 859.7352.
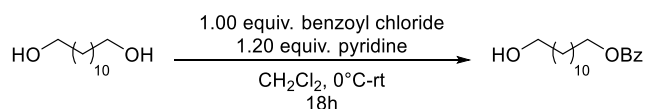
Monobenzoate 4.35. To a stirred solution of 1.20 g (5.93 mmol, 1.00 equiv.) 1,12-dodecanediol in 60 mL CH$_2$Cl$_2$ at 0°C was added 0.58 mL (7.12 mmol, 1.20 equiv.) pyridine, followed by the dropwise addition of 0.69 mL (5.93 mmol, 1.00 equiv.) benzoyl chloride in 60 mL CH$_2$Cl$_2$. The

reaction mixture was slowly warmed to room temperature and stirred for an additional 18h, then quenched by the addition of 150 mL NH$_4$Cl. The biphasic mixture was extracted with 3x150 mL CH$_2$Cl$_2$ and the combined organics were dried over Na$_2$SO$_4$. The volatiles were removed in vacuo to afford crude **4.35**, which was further purified via flash column chromatography on silica gel using 0-25% EtOAc in hexanes to afford 500 mg (1.63 mmol; 27%) monobenzoate alcohol **4.35** as a white solid. ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.08 – 8.01 (m, 2H), 7.58 – 7.52 (m, 1H), 7.44 (t, J = 7.8 Hz, 2H), 4.32 (t, J = 6.7 Hz, 2H), 3.64 (t, J = 6.7 Hz, 2H), 1.82 – 1.71 (m, 2H), 1.61 – 1.51 (m, 4H), 1.43 (td, J = 9.6, 8.7, 4.8 Hz, 2H), 1.39 – 1.23 (m, 12H), 1.20 (s, 1H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 166.7, 132.8, 130.6, 129.5, 128.3, 65.1, 63.1, 32.8, 29.6, 29.5, 29.5, 29.4, 29.3, 28.7, 26.0, 25.7. HRMS (ESI) m/z calculated for C$_{19}$H$_{30}$O$_3$ [M + Na]$^+$ 329.2087, found 329.2084.
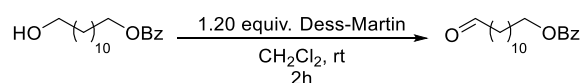
Aldehyde 4.36. To a stirred solution of 500 mg (1.63 mmol, 1.00 equiv.) alcohol **4.35** in 16 mL CH$_2$Cl$_2$ at room temperature was added 1.04 g (2.45 mmol, 1.50 equiv.) Dess-Martin periodinane (DMP). The resulting solution was stirred for 3 h, then quenched by the addition of a 15% Na$_2$S$_2$SO$_3$/NaHCO$_3$ solution. The biphasic mixture was stirred at room temperature for an additional 30 minutes, then extracted with 3x15 mL portions of CH$_2$Cl$_2$. The combined organics were dried over Na$_2$SO$_4$, and the volatiles removed in vacuo to afford 489 mg (1.61 mmol; 98%) of aldehyde **4.36** as a clear, colorless oil which was used without any additional purification. ^{1}H NMR (500 MHz, CDCl$_3$) δ 9.76 (t, J = 1.9 Hz, 1H), 8.08 – 8.01 (m, 2H), 7.59 – 7.51 (m, 1H), 7.44 (t, J = 7.7 Hz, 2H), 4.32 (t, J = 6.7 Hz, 2H), 2.41 (td, J = 7.4, 1.9 Hz, 2H), 1.76 (p, J = 6.8 Hz, 2H), 1.62 (p, J = 7.1 Hz, 2H), 1.49 – 1.39 (m, 2H), 1.39 – 1.19 (m, 12H). ^{13}C NMR (126 MHz, CDCl$_3$)

δ 202.9, 166.7, 132.8, 130.5, 129.5, 128.3, 65.1, 43.9, 29.5, 29.5, 29.4, 29.3, 29.3, 29.2, 28.7, 26.0,

22.1. HRMS (ESI) *m/z* calculated for $C_{19}H_{28}O_3$ [M + Na]$^+$ 327.1931, found 327.1926.
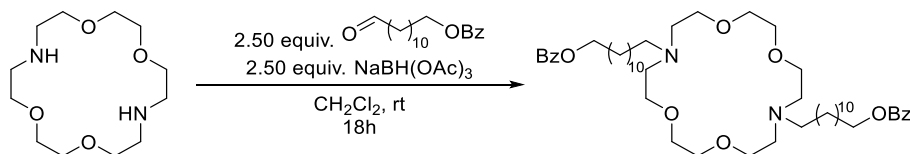
Dibenzoate Transmembrane Fragment 4.37. To a stirred solution of 168 mg (0.64 mmol, 1.00

equiv.) kryptofix-22 in 6.4 mL CH_2Cl_2 was added 489 mg (1.61 mmol, 2.50 equiv.) aldehyde **4.36**,

followed by 341 mg (1.61 mmol, 2.50 equiv.) NaBH(OAc)$_3$. The resulting suspension was stirred

at room temperature for 18h before being filtered through a plug of celite. The filter pad was

rinsed with additional CH_2Cl_2, and the volatiles removed in vacuo to afford crude **4.36**. The crude

reaction mixture was purified via flash column chromatography on alumina using a gradient of 0-

25% EtOAc in hexanes to afford 115 mg (0.14 mmol; 22%) **4.36** as a clear, colorless oil. ^{1}H NMR

(500 MHz, CDCl$_3$) δ 8.07 – 8.02 (m, 4H), 7.57 – 7.52 (m, 2H), 7.44 (t, *J* = 7.7 Hz, 4H), 4.31 (t, *J*

= 6.7 Hz, 4H), 3.61 (d, *J* = 5.1 Hz, 16H), 2.78 (t, *J* = 6.0 Hz, 8H), 2.52 – 2.43 (m, 4H), 1.80 – 1.71

(m, 4H), 1.48 – 1.39 (m, 8H), 1.27 (d, *J* = 9.4 Hz, 28H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 166.7,

132.8, 130.6, 129.5, 128.3, 70.8, 70.0, 65.2, 56.0, 53.9, 29.6, 29.6, 29.6, 29.5, 29.3, 28.7, 27.5,

27.2, 26.1. HRMS (ESI) *m/z* calculated for $C_{50}H_{82}N_2O_8$ [M + H]$^+$ 839.6144, found 839.6139.
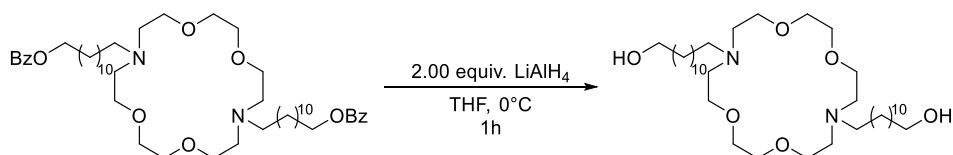
Diol 4.38. To a stirred suspension of 7.6 mg (0.20 mmol, 2.00 equiv.) LiAlH$_4$ in 0.50 mL THF at

0°C was added a solution of 83 mg (0.10 mmol, 1.00 equiv.) dibenzoate diester **4.37** in 0.50 mL

THF dropwise. The suspension was stirred at 0°C for 1 h, then quenched by the successive

dropwise addition of 0.1 mL H_2O, 0.1 mL 15% aq. NaOH, then 0.30 mL H_2O. Na_2SO_4 was added

to the suspension and stirred at room temperature for 15 minutes, then filtered through a plug of

celite. The filter pad was washed with an additional 5 mL of CH_2Cl_2, and the volatiles removed

in vacuo to afford crude diol **4.38**; residual benzyl alcohol byproducts were removed by gently

heating to 40°C under vacuum for 18h. After cooling to room temperature, 43 mg (0.07 mmol;

70%) diol **4.38** was obtained as a white solid and used without any additional purification. [1]H

NMR (500 MHz, $CDCl_3$) δ 3.71 – 3.49 (m, 20H), 2.77 (t, J = 6.0 Hz, 8H), 2.50 – 2.41 (m, 4H),

1.62 – 1.51 (m, 4H), 1.43 (dd, J = 10.0, 4.9 Hz, 4H), 1.38 – 1.18 (m, 32H). ^{13}C NMR (126 MHz,

$CDCl_3$) δ 70.8, 70.1, 63.1, 56.1, 53.9, 32.8, 29.6, 29.6, 29.6, 29.5, 29.4, 27.5, 27.3, 25.7. HRMS

(ESI) m/z calculated for $C_{36}H_{74}N_2O_6$ $[M + H]^+$ 631.5620, found 631.5618.
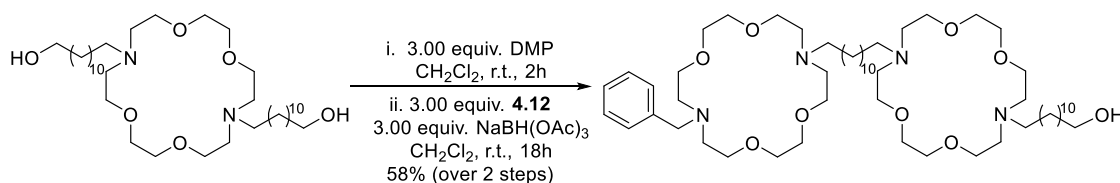
Alcohol 4.39. To a stirred solution of 43.0 mg (0.068 mmol, 1.00 equiv.) diol **4.38** in 1 mL CH_2Cl_2

was added 85 mg (0.20 mmol, 3.00 equiv.) Dess-Martin periodinane. The resulting suspension

was stirred at room temperature for 2 hours, then quenched by the addition of 2 mL of an aq.

$NaHCO_3/Na_2S_2O_3$ mix. The biphasic mixture was stirred at room temperature for an additional

15 minutes, then extracted with 3x5 mL portions of CH_2Cl_2. The combined organics were dried

over Na_2SO_4, and the volatiles removed in vacuo to afford the crude oxidized product. The crude

material was immediately moved forward without any additional purification.

The crude oxidation products were dissolved in 1 mL CH_2Cl_2, and 74 mg (0.20 mmol, 3.00 equiv.)

N-Bn kryptofix 22 (**4.12**) was added in one portion, followed by the addition of 43 mg (0.20 mmol,

3.00 equiv.) NaBH(OAc)$_3$. The white suspension was stirred at room temperature for 18h, then filtered through a plug of alumina. The volatiles were removed in vacuo to afford crude **4.39**. The crude material was purified via flash column chromatography on alumina using a 0-5% gradient of iPrOH in CH$_2$Cl$_2$ as eluent to afford 38 mg (0.039 mmol; 58%) of alcohol **4.39** as a clear, colorless oil. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.31 (dd, J = 16.1, 7.4 Hz, 4H), 7.22 (t, J = 7.2 Hz, 1H), 3.67 (s, 2H), 3.66 – 3.51 (m, 30H), 2.84 – 2.74 (m, 14H), 2.71 (q, J = 5.9 Hz, 2H), 2.52 – 2.43 (m, 4H), 2.36 – 2.28 (m, 1H), 1.56 (p, J = 6.7 Hz, 2H), 1.49 – 1.39 (m, 4H), 1.26 (s, 34H), 0.96 – 0.71 (m, 6H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 139.7, 128.8, 128.1, 126.8, 70.8, 70.7, 70.7, 70.7, 70.6, 70.1, 70.1, 70.0, 69.4, 63.0, 60.0, 60.0, 56.8, 56.1, 56.0, 53.9, 53.9, 53.8, 53.4, 43.9, 32.8, 31.9, 29.7, 29.7, 29.6, 29.6, 29.6, 29.5, 29.4, 29.4, 27.5, 27.5, 27.3, 27.2, 25.8, 22.7, 22.7, 14.1. HRMS (ESI) m/z calculated for C$_{55}$H$_{104}$N$_4$O$_9$ [M + 2H]$^{2+}$ 483.3974, found 483.3969. Trace amounts of hydraphile **4.14** were observed via HRMS of the crude reaction material, however **4.14** was not located after chromatography.

4.4. Bibliography

1.   (a) Liu, Z.; Nalluri, S. K. M.; Stoddart, J. F. *Chem. Soc. Rev.* **2017**, 46, 2459-2478. (b) Muñoz, S.; Mallén, J.; Nakano, A.; Chen, Z.; Gay, I.; Echegoyen, L.; Gokel, G. W. *J. Am. Chem. Soc.* **1993**, 115, 1705-1711. (c) Xie, Q.; Li, Y.; Gokel, G.; Hernández, J.; Echegoyen, L. *J. Am. Chem. Soc.* **1994**, 116, 690-696.

2.   Gatto, V. J.; Arnold, K. A.; Viscariello, A. M.; Miller, S. R.; Morgan, C. R.; Gokel, G. W. *J. Org. Chem.* **1986**, 51, 5373-5384.

3.   Gokel, G. W.; Leevy, W. M.; Weber, M. E. *Chem. Rev.* **2004**, 104, 2723-2750.

4. Leevy, W. M.; Weber, M. E.; Gokel, M. R.; Hughes-Strange, G. B.; Daranciang, D. D.; Ferdani, R.; Gokel, G. W. *Org. Biomol. Chem.* **2005**, 3, 1647-1652.

5. (a) Cockrell, R. S.; Harris, E. J.; Pressman, B. C. *Biochemistry* **1966**, 5, 2326-2335. (b) Naumann, R.; Walz, D.; Schiller, S. M.; Knoll, W. *J. Electroanal Chem.* **2003**, 550, 241-252.

6. Yang, N. J.; Hinner, M. J. *Methods Mol. Biol.* **2015**, 1266, 29-53.

7. Negin, S.; Patel, M. B.; Gokel, M. R.; Meisel, J. W.; Gokel, G. W. *ChemBioChem* **2016**, 17, 2153-2161.

8. (a) Ellard, G. A.; Fourie, P. B. *Int. J. Tuberc. Lung D.* **1999**, 3, S301-S308. (b) Goldstein, B. P. *J. Antibiot.* **2014**, 67, 625-630.

9. Sum, P.-E.; Sum, F.-W.; Projan, S. J. *Curr. Pharm. Des.* **1998**, 4, 119-132.

10. (a) Yang, L.; Harroun, T. A.; Weiss, T. M.; Ding, L.; Huang, H. W. **2001**, 81, 1475-1485. (b) Wi, S.; Kim, C. *J. Phys. Chem. B* **2008**, 112, 11402-11414.

11. (a) Liu, T.; Bao, C.; Wang, H.; Fei, L.; Yang, R.; Long, Y.; Zhu, L. *New. J. Chem.* **2014**, 38, 3507-3513. (b) Liu, T.; Bao, C.; Wang, H.; Lin, Y.; Jia, H.; Zhu, L. *Chem. Commun.* **2013**, 49, 10311-10313.

12. (a) Gokel, G. W.; Murillo, O. *Acc. Chem. Res.* **1996**, 29, 425-432. (b) Sisson, A. L.; Shah, M. R.; Bhosale, S.; Matile, S. *Chem. Soc. Rev.* **2006**, 35, 1269-1286. (c) Gokel, G. W.; Negin, S. *Acc. Chem. Res.* **2013**, 46, 2824-2833.

13. (a) Murillo, O.; Watanabe, S.; Nakano, A.; Gokel, G. W. *J. Am. Chem. Soc.* **1995**, 117, 7665-7679. (b) Murillo, O.; Suzuki, I.; Abel, E.; Murray, C. L.; Meadows, E. S.; Jin, T.; Gokel, G.

W. *J. Am. Chem. Soc.* **1997**, 119, 5540-5549. (c) Maguire, G. E. M.; Meadows, E. S.; Murray, C. L.; Gokel, G. W. *Tetrahedron Lett.* **1997**, 38, 6339-6342. (d) Abel, E.; Meadows, E. S.; Suzuki, I.; Jin, T.; Gokel, G. W. *Chem. Commun.* **1997**, 1145-1146. (e) Murray, C. L.; Gokel, G. W. *J. Supramol. Chem.* **2001**, 1, 23-30. (f) Leevy, W. M.; Huettner, J. E.; Pajewski, R.; Schlessinger, P. H.; Gokel, G. W. *J. Am. Chem. Soc.* **2004**, 126, 15747-15753. (g) Meyer, A. E.; Leevy, W. M.; Pajewski, R.; Suzuki, I.; Weber, M. E.; Gokel, G. W. *Biorg. Med. Chem.* **2005**, 13, 3321-3327. (h) Leevy, W. M.; Weber, M. E.; Shlessinger, P. H.; Gokel, G. W. *Chem. Commun.* **2005**, 89-91. (i) Weber, M. E.; Wang, W.; Steinhardt, S. E.; Gokel, M. R.; Leevy, W. M.; Gokel, G. W. *New J. Chem.* **2006**, 30, 177-184. (j) Wang, W.; Yamnitz, C. R.; Gokel, G. W. *Heterocycles* **2007**, 73, 825-839. (k) Curvey, N. S.; Luderer, S. E.; Walker, J. K.; Gokel, G. W. *Synthesis* **2014**, 2771-2779. (l) Patel, M. B.; Garrad, E. C.; Stavri, A.; Gokel, M. R.; Negin, S.; Meisel, J. W.; Cusumano, Z.; Gokel, G. W. *Bioorg. Med. Chem.* **2016**, 24, 2864-2870.

14. Gaussian 16, Revision B.01, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, G. A. Petersson, H. Nakatsuji, X. Li, M. Caricato, A. V. Marenich, J. Bloino, B. G. Janesko, R. Gomperts, B. Mennucci, H. P. Hratchian, J. V. Ortiz, A. F. Izmaylov, J. L. Sonnenberg, D. Williams-Young, F. Ding, F. Lipparini, F. Egidi, J. Goings, B. Peng, A. Petrone, T. Henderson, D. Ranasinghe, V. G. Zakrzewski, J. Gao, N. Rega, G. Zheng, W. Liang, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, K. Throssell, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. J. Bearpark, J. J. Heyd, E. N. Brothers, K. N. Kudin, V. N. Staroverov, T. A. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. P. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, J. M. Millam, M. Klene, C.

Adamo, R. Cammi, J. W. Ochterski, R. L. Martin, K. Morokuma, O. Farkas, J. B. Foresman, and D. J. Fox, Gaussian, Inc., Wallingford CT, 2016.

15. (a) Kim, T.; Park, H. *J. Mol. Graph. Model.* **2015**, 60, 108-117. (b) Bannan, C. C.; Calabro, G.; Kyu, D. Y.; Mobley, D. L. *J. Chem. Theory Comput.* **2016**, 12, 4015-4024. (c) Marenich, A. V.; Cramer, C. J.; Truhlar, D. G. *J. Phys. Chem. B.* **2009**, 113, 6378-6396.

16. Sims, P. J.; Waggoner, A. S.; Wang, C. H.; Hoffman, J. F. *Biochemistry* **1974**, 13, 3315-3330.

17. Wu, M.; Maier, R. B.; Hancock, R. E. *Biochemistry* **1999**, 38, 7235-7242.

18. (a) Alkhatib, A. J.; Alkrakaf, N. A. M. *Am. J. Biomed. Sci.* **2019**, 3, 415-416. (b) Davis, M. I.; Shen, M.; Simeonov, A.; Hall, M. D. *Assay Drug Dev. Tehnol.* **2016**, 14, 207-212.

19. (a) Korzeniewski, C.; Callewaert, D. M. *J. Immunol. Methods* **1983**, 64, 313-320. (b) Decker, T.; Lohmann-Matthes, M. L. *J. Immunol. Methods* **1988**, 115, 61-69.

20. (a) Das, S.; Addis, D.; Zhou, S.; Junge, K.; Beller, M. *J. Am. Chem. Soc.* **2010**, 132, 1770-1771. (b) Bailey, C. L.; Joh, A. Y.; Hurley, Z. Q.; Anderson, C. L.; Singaram, B. *J. Org. Chem.* **2016**, 81, 3619-3628. (c) Barbe, G.; Charette, A. B. *J. Am. Chem. Soc.* **2008**, 130, 18-19. (d) Xiang, S.-H.; Xu, J.; Yuan, H. –Q.; Huang, P. –Q. *Synlett* **2010**, 12, 1829-1832.

21. Izatt, R. M.; Bradshaw, J. S.; Nielsen, S. A.; Lamb, J. D.; Christensen, J. J. *Chem. Rev.* **1985**, 85, 271-339.

22. Armarego, W. L. F.; Chai, C. L. L. Chapter 4 – Purification of Organic Chemicals. In *Purification of Laboratory Chemicals (Sixth Edition)*, Butterworth-Heinemann: Oxford, 2009; pp 88-444.

23.   Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, 43, 2923-2925.

Appendix I

^{1}H and ^{13}C NMR Spectra for Synthesized Compounds

Lactone 1.149 – ^{1}H NMR (500 MHz)
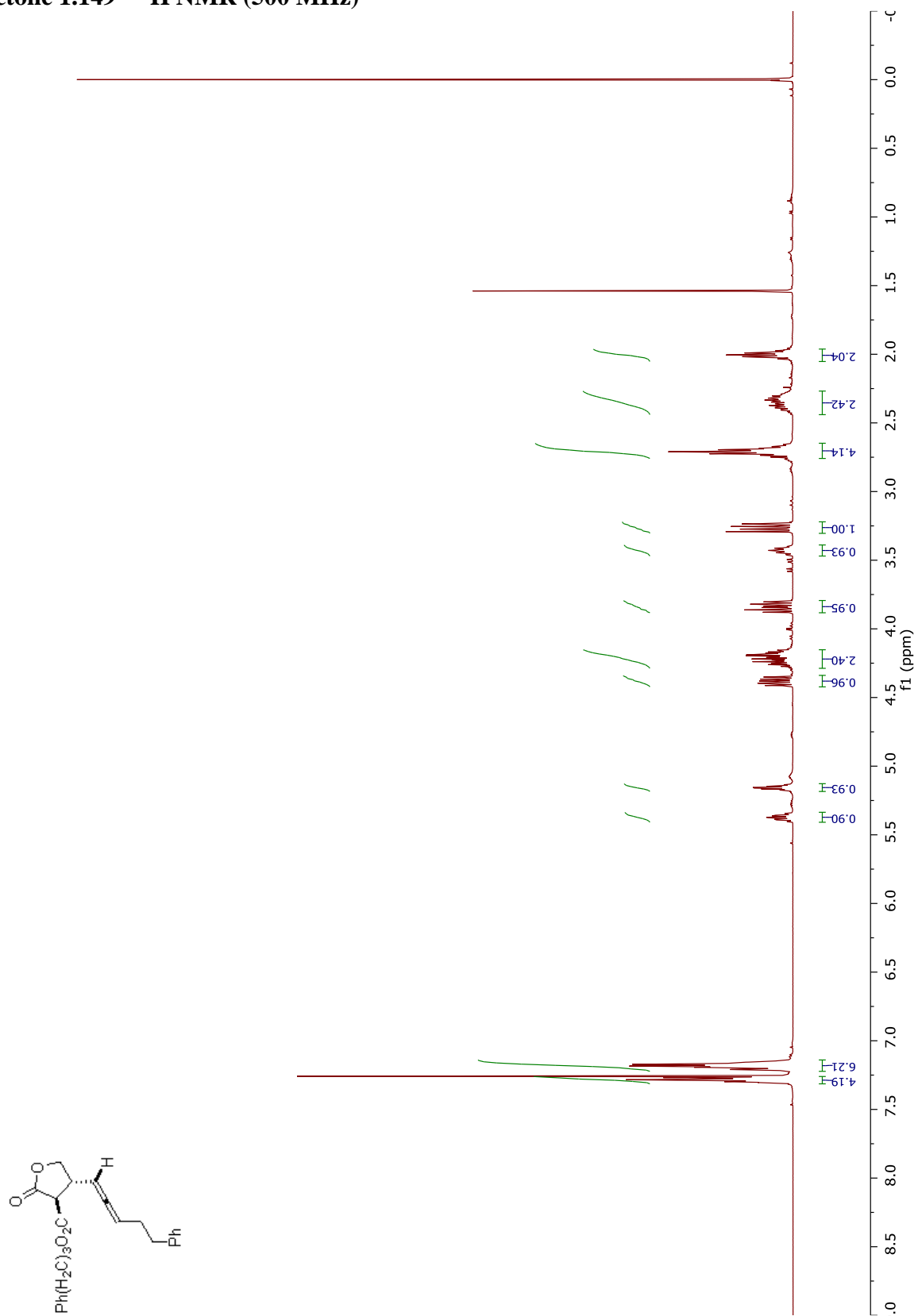
Lactone 1.149 – ^{13}C NMR (126 MHz)

29.95
30.08
30.10
31.90
31.92
34.85
34.97
39.02
39.06
51.74
52.12
65.39
65.42
71.11
71.21
88.90
88.94
94.51
94.65
126.07
126.15
126.22
128.29
128.38
128.39
128.41
128.44
128.47
128.51
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141.00
141.04
166.96
167.00
171.25
171.30
203.73
203.81

f1 (ppm)
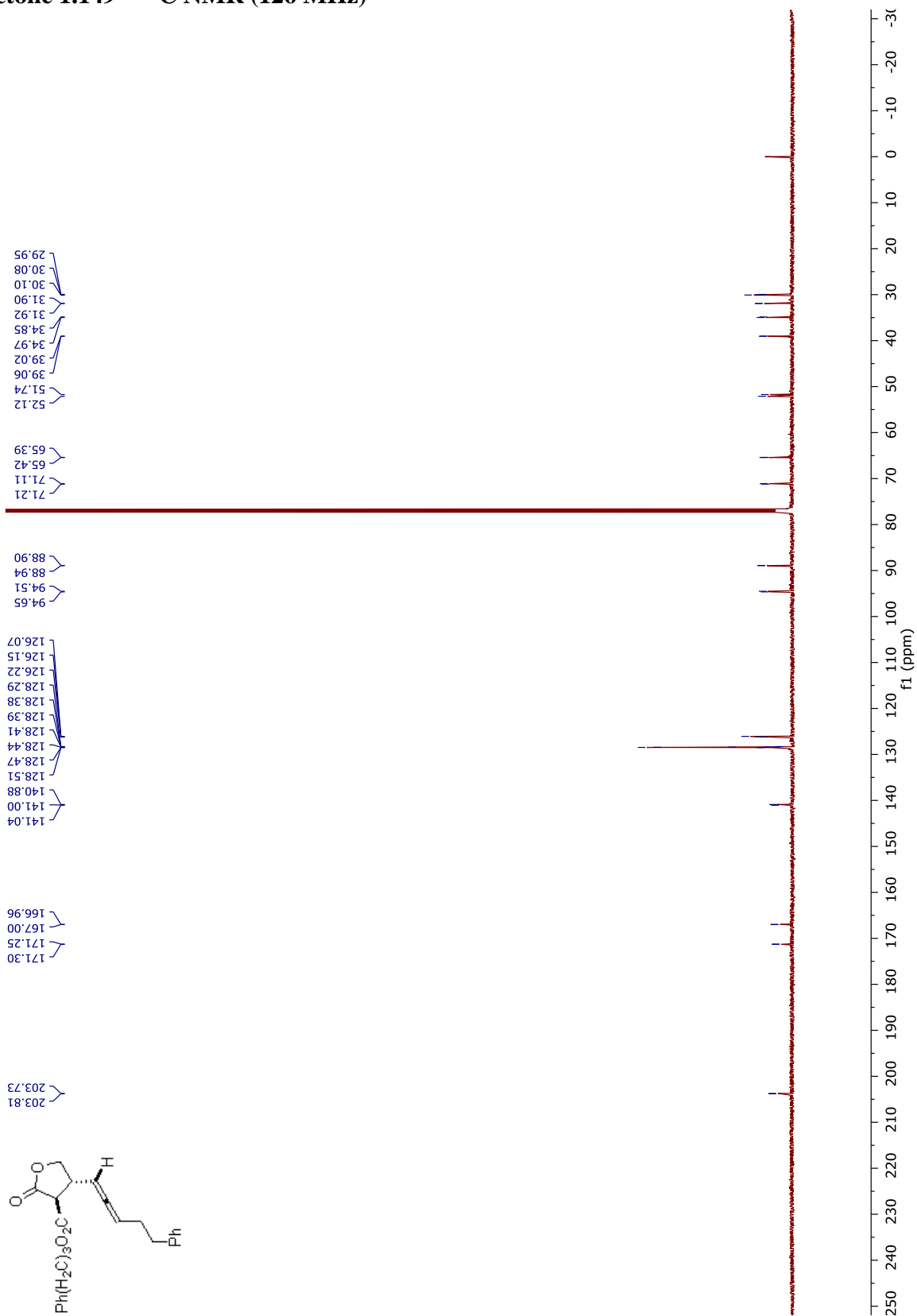
Lactone 1.150 – ¹H NMR (500 MHz)
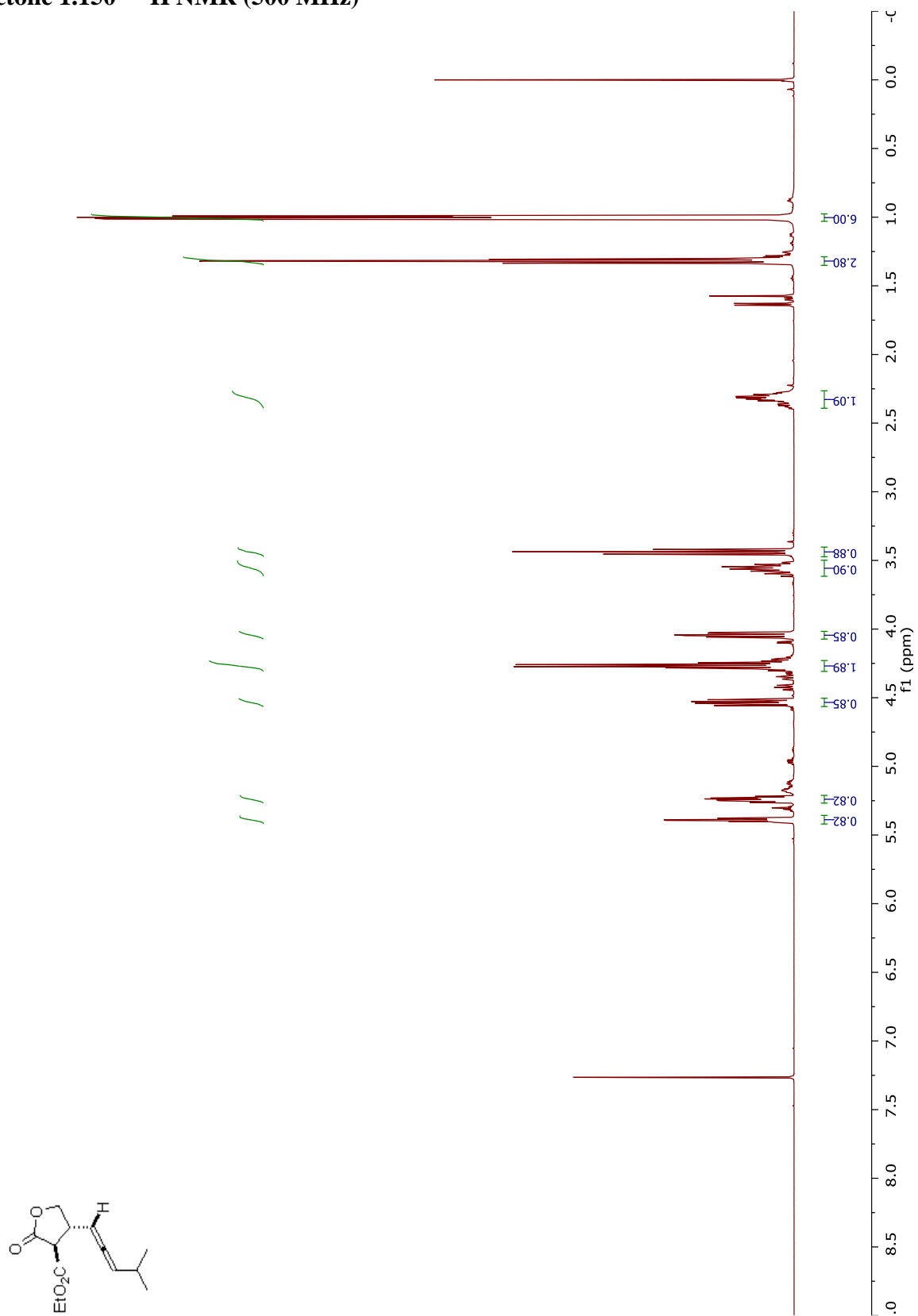
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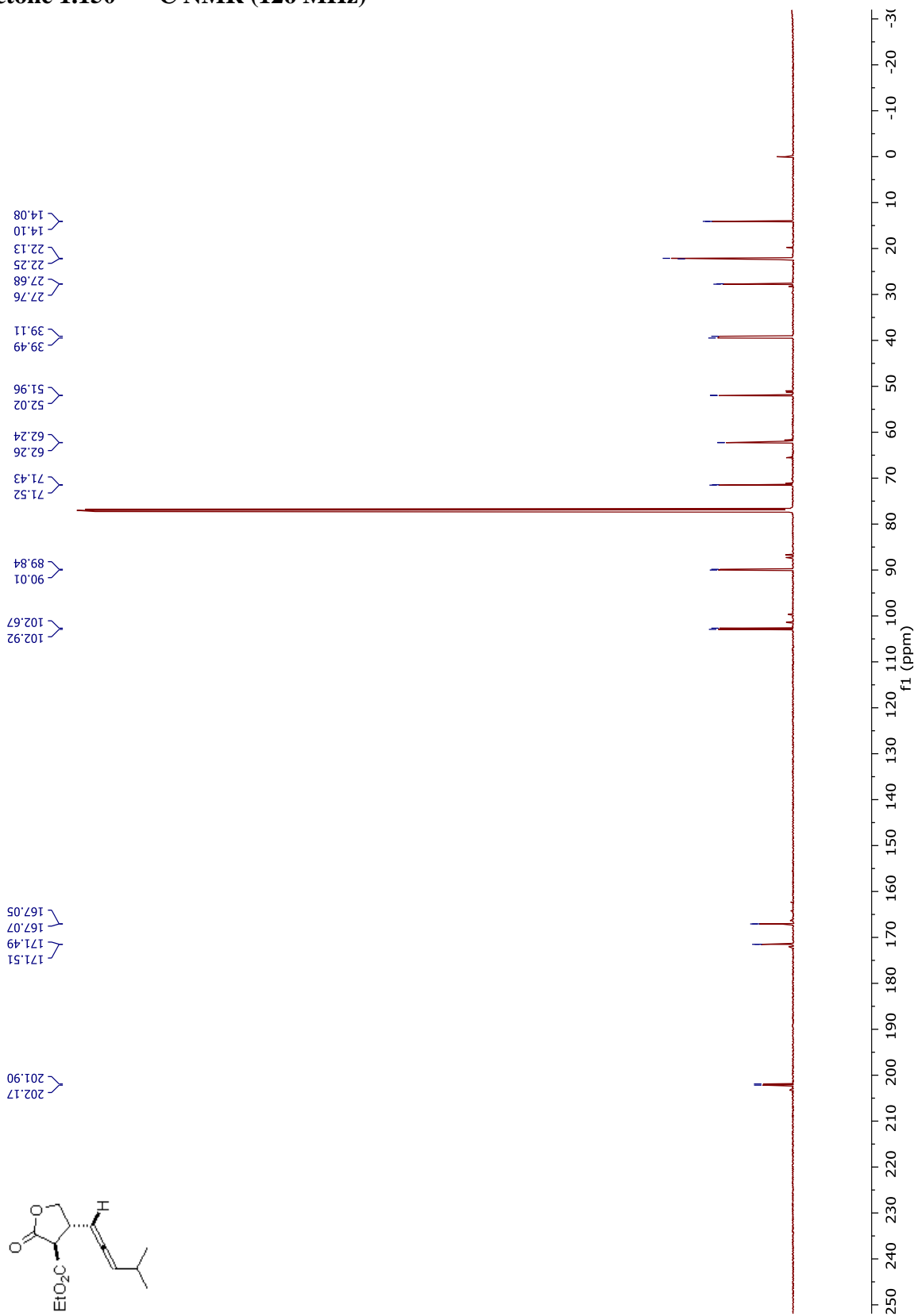
Lactone 1.158 – ¹H NMR (500 MHz)
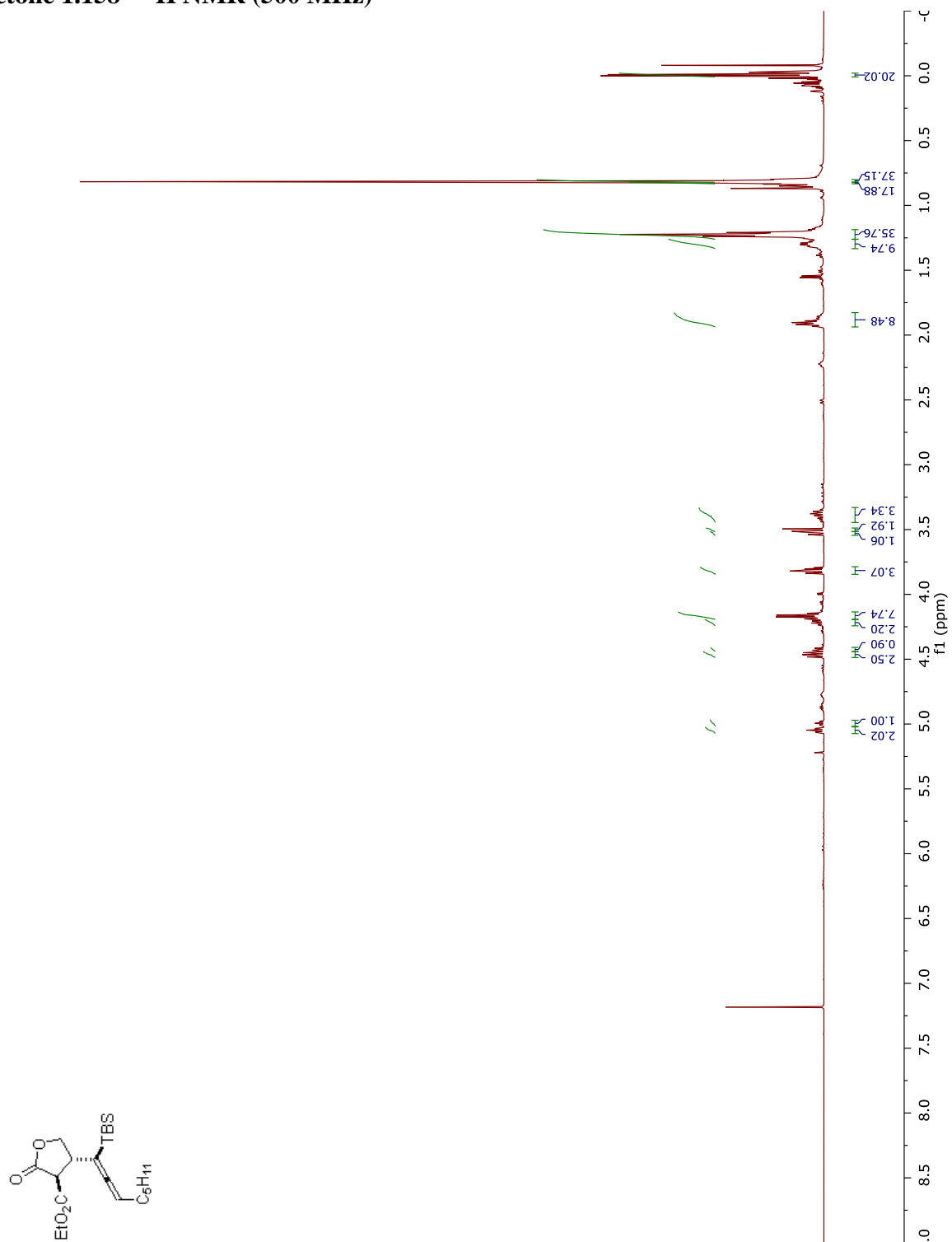
Lactone 1.158 – ¹³C NMR (126 MHz)

206.7
206.8

171.8
167.3
167.3

93.5
90.5

73.5
73.1

62.1
62.0

52.6
52.6

41.0
40.8
31.6
31.5
29.4
29.3
28.5
28.2
26.7
26.6
26.6
26.3
22.5
22.5
22.4
17.9
14.1
14.1
14.0
14.0
-5.5
-5.6
-5.7
-5.8

f1 (ppm)
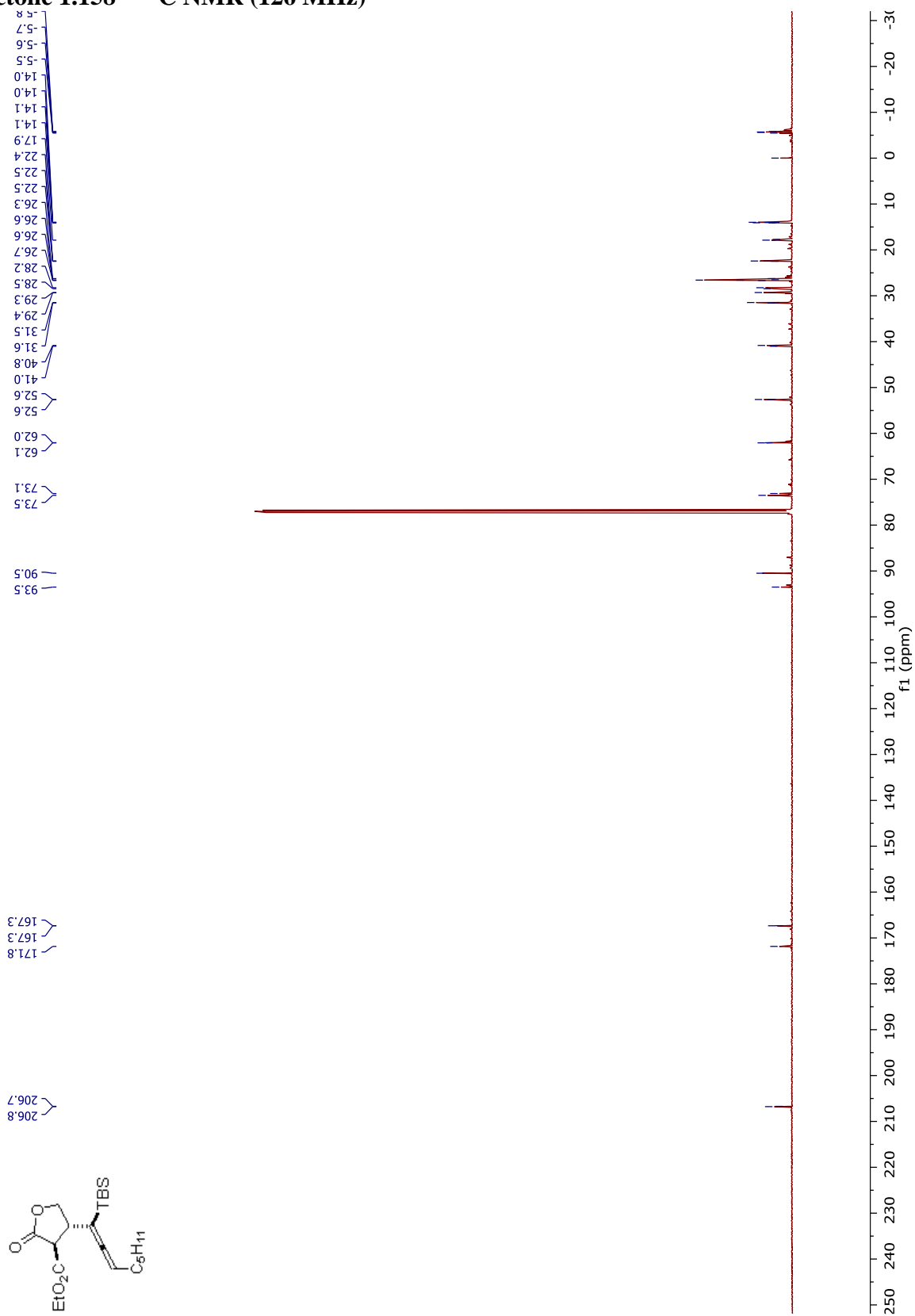
Lactone 1.161 – ¹H NMR (500 MHz)
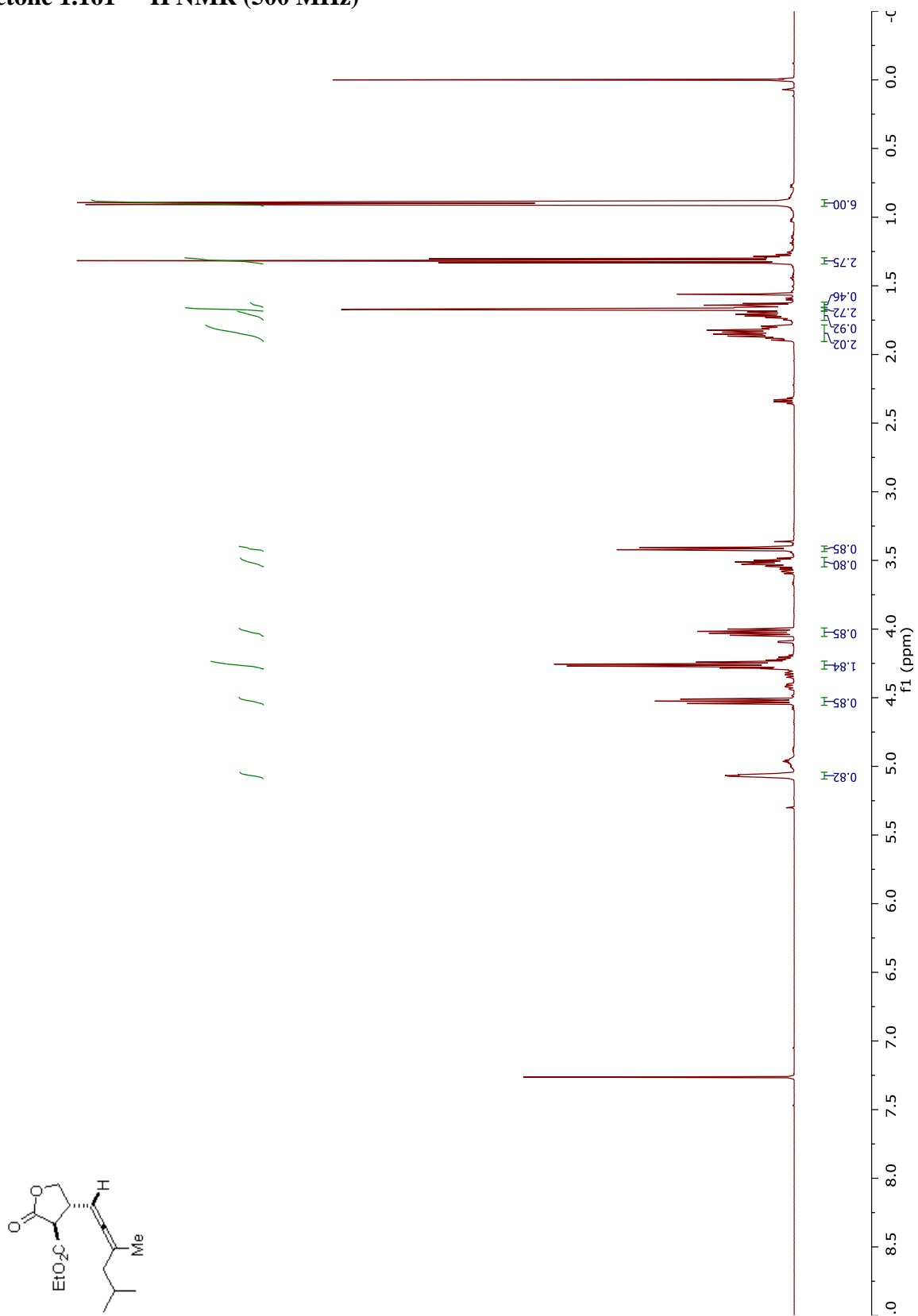
Lactone 1.161 – ¹³C NMR (126 MHz)
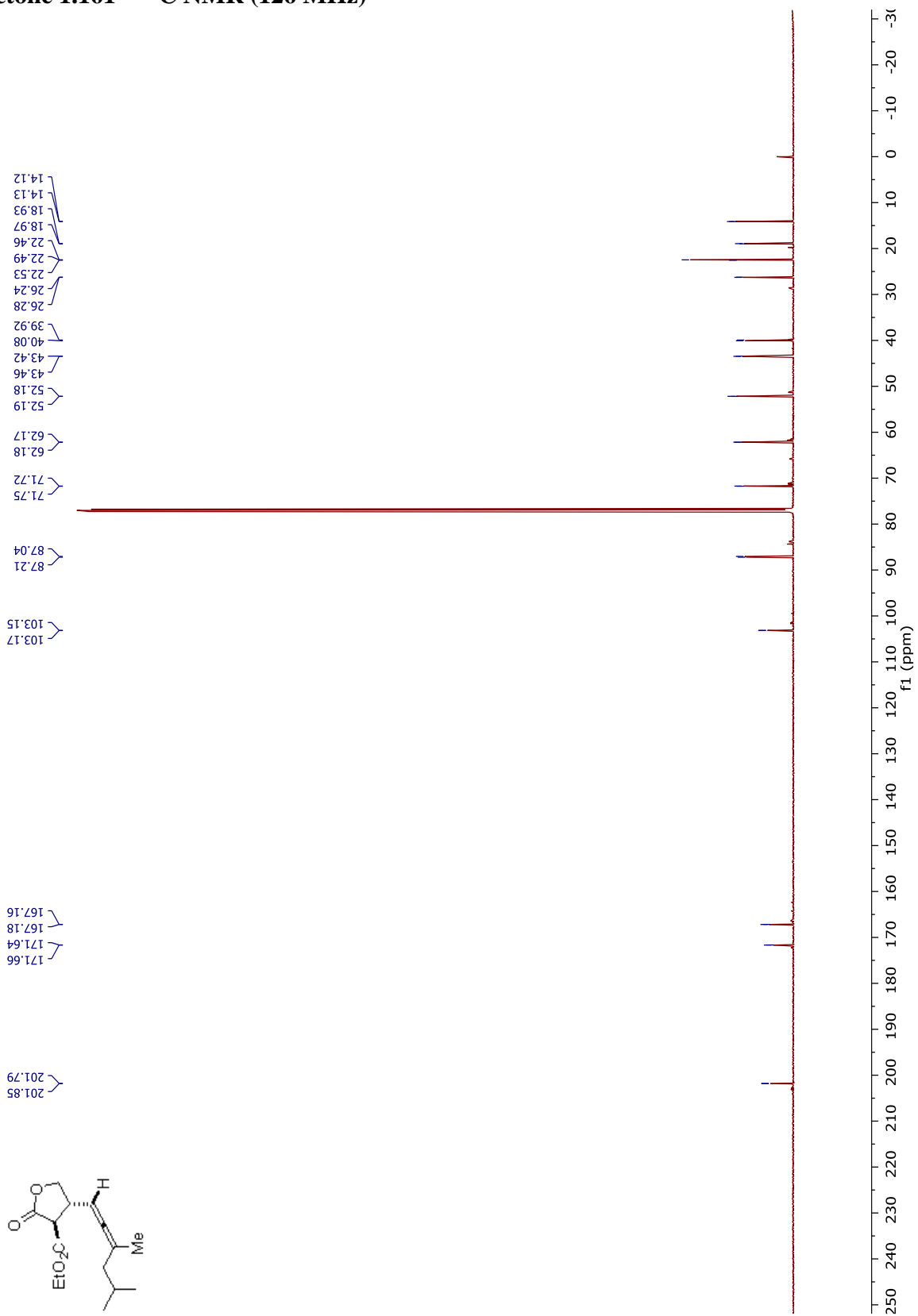
Lactone 1.169 – ¹H NMR (500 MHz)

Lactone 1.169 – ¹³C NMR (126 MHz)

14.01
14.03
22.46
22.49
23.18
23.20
26.96
26.99
28.52
28.53
28.56
28.66
31.30
31.38
49.31
49.47
51.34
51.55
52.93
52.96

85.70
85.81
86.17
86.22
94.52
94.70

167.72
170.16
170.17

204.54

f1 (ppm)
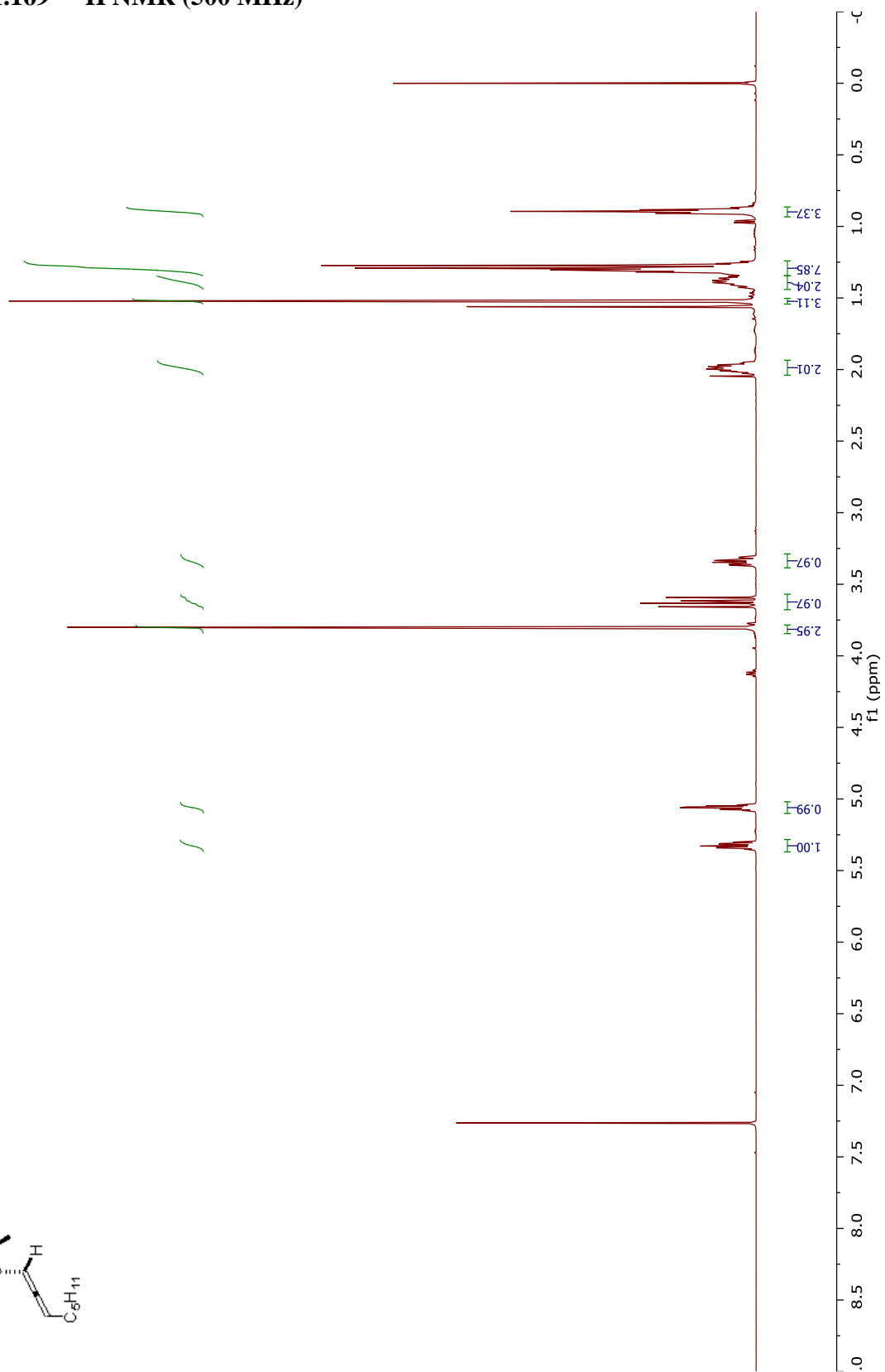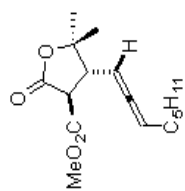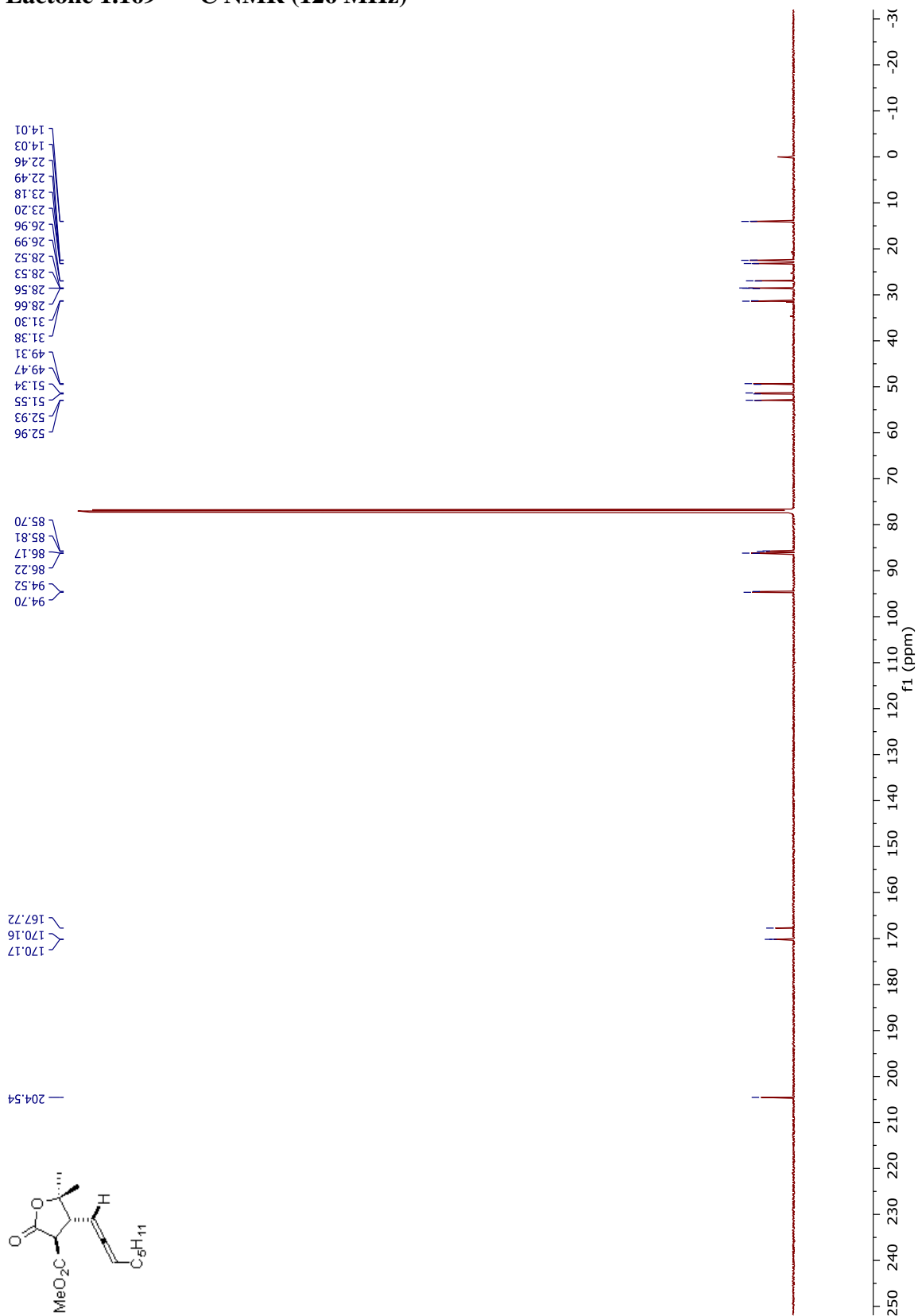
Cyclopentene 1.136 – ^{1}H NMR (500 MHz)
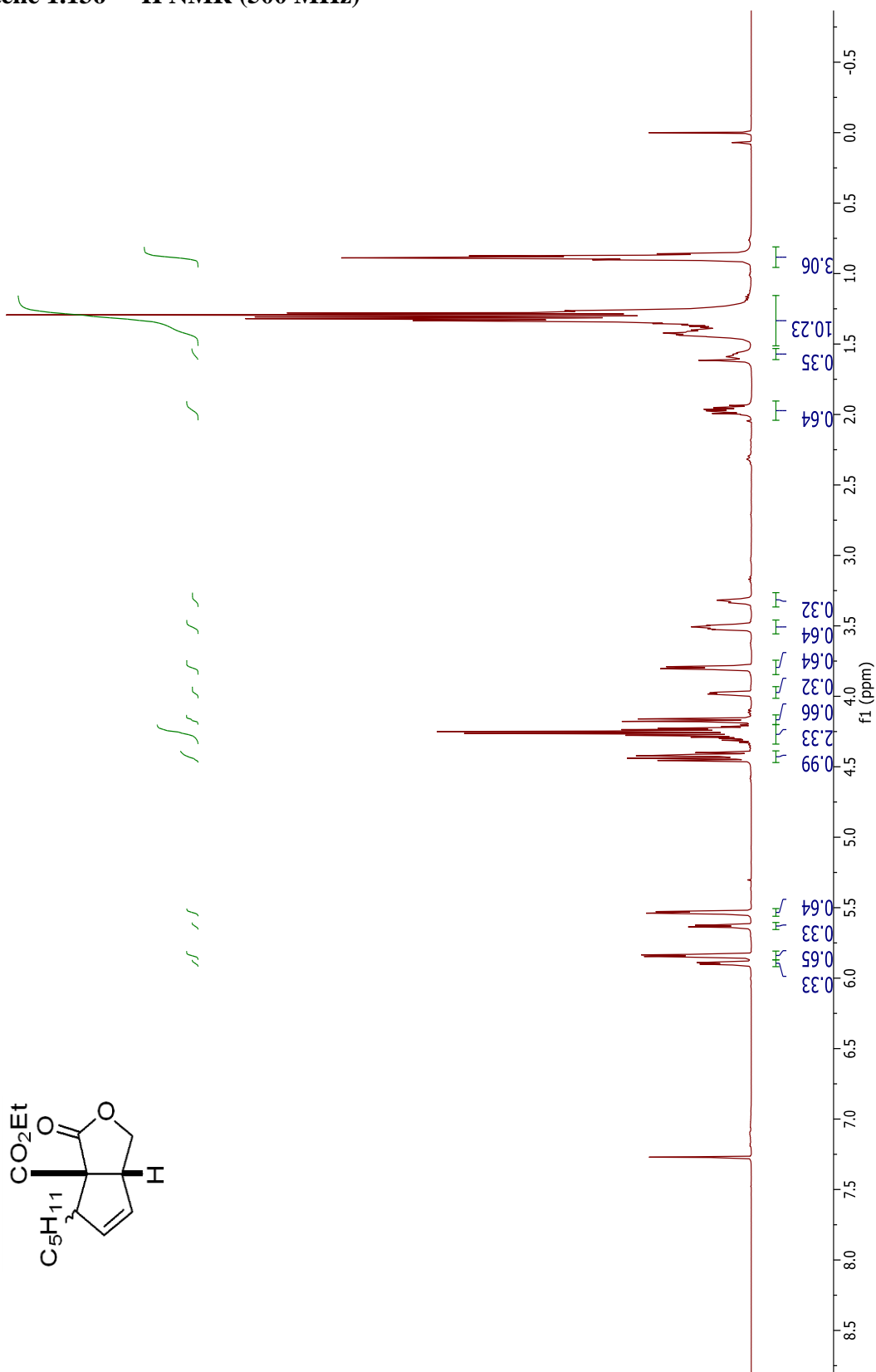
Cyclopentene 1.169 – ^{13}C NMR (126 MHz)
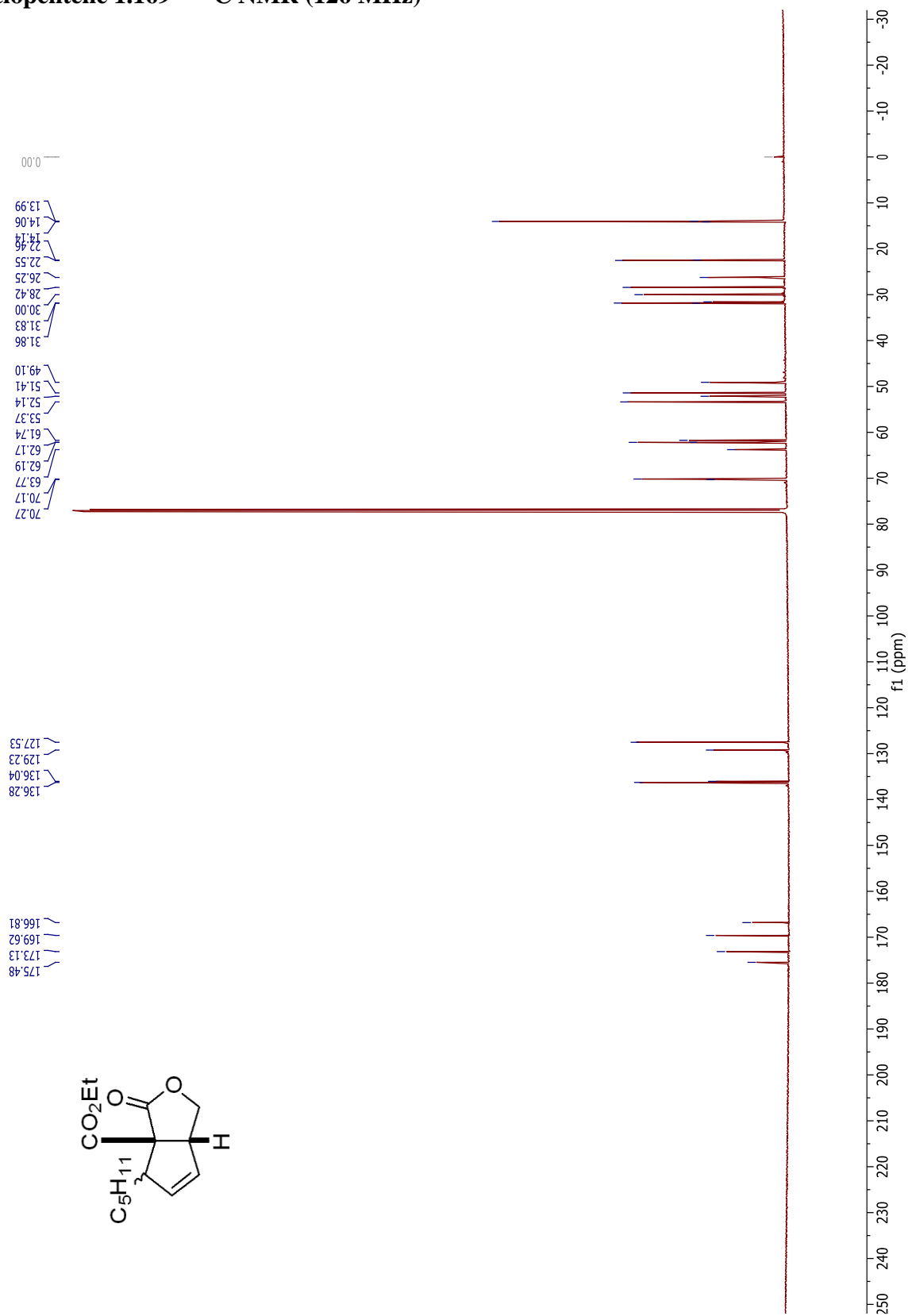
Cyclopentene 1.152 – ¹H NMR (500 MHz)
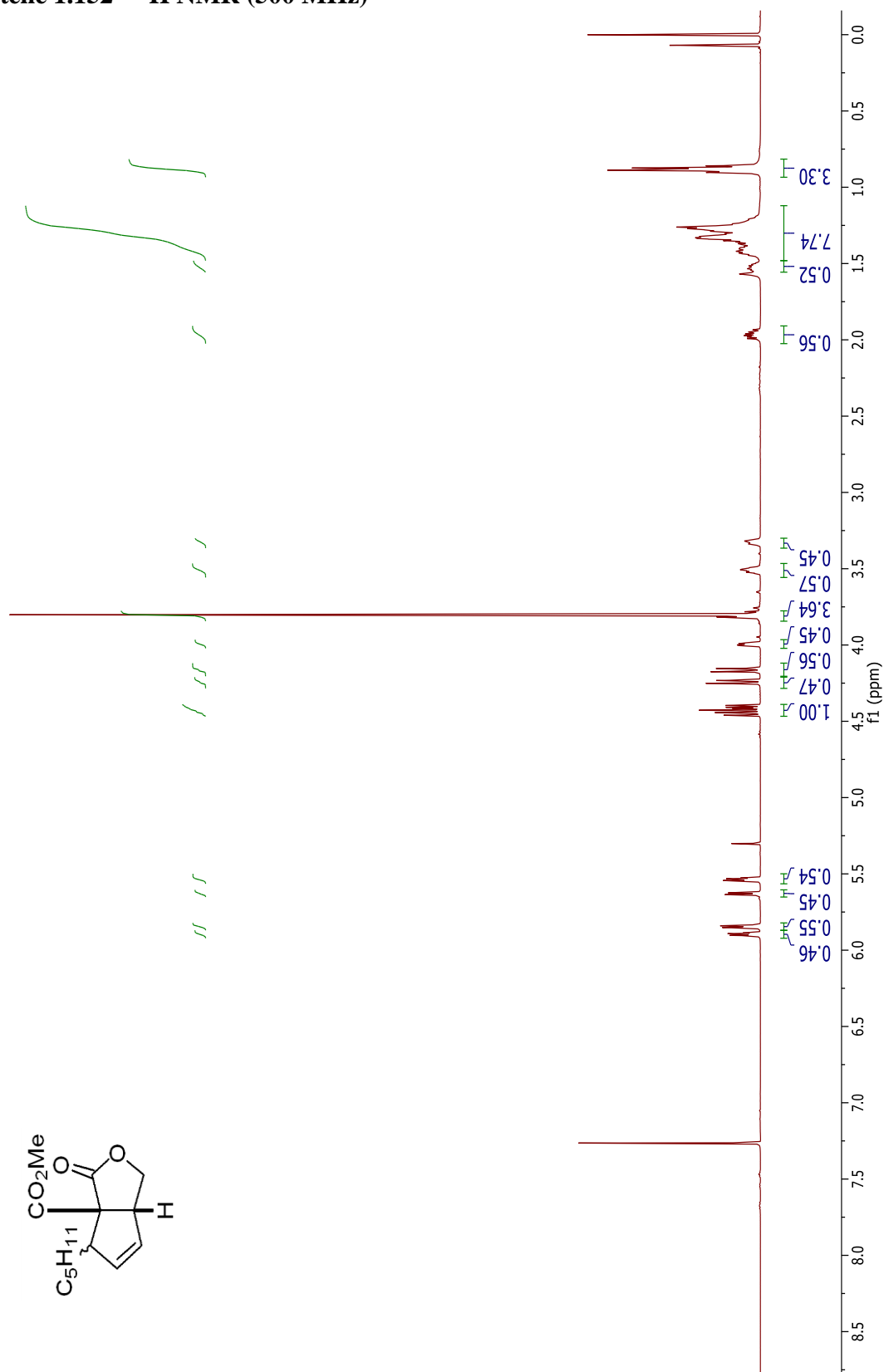
Cyclopentene 1.152 – ¹³C NMR (126 MHz)

13.99
14.06
22.48
22.55
28.41
30.03
31.84
31.86

49.06
51.60
52.35
53.18
53.29

61.60
63.79
70.19
70.26

127.56
129.18
135.98
136.20

167.34
170.16
173.02
175.42

f1 (ppm)
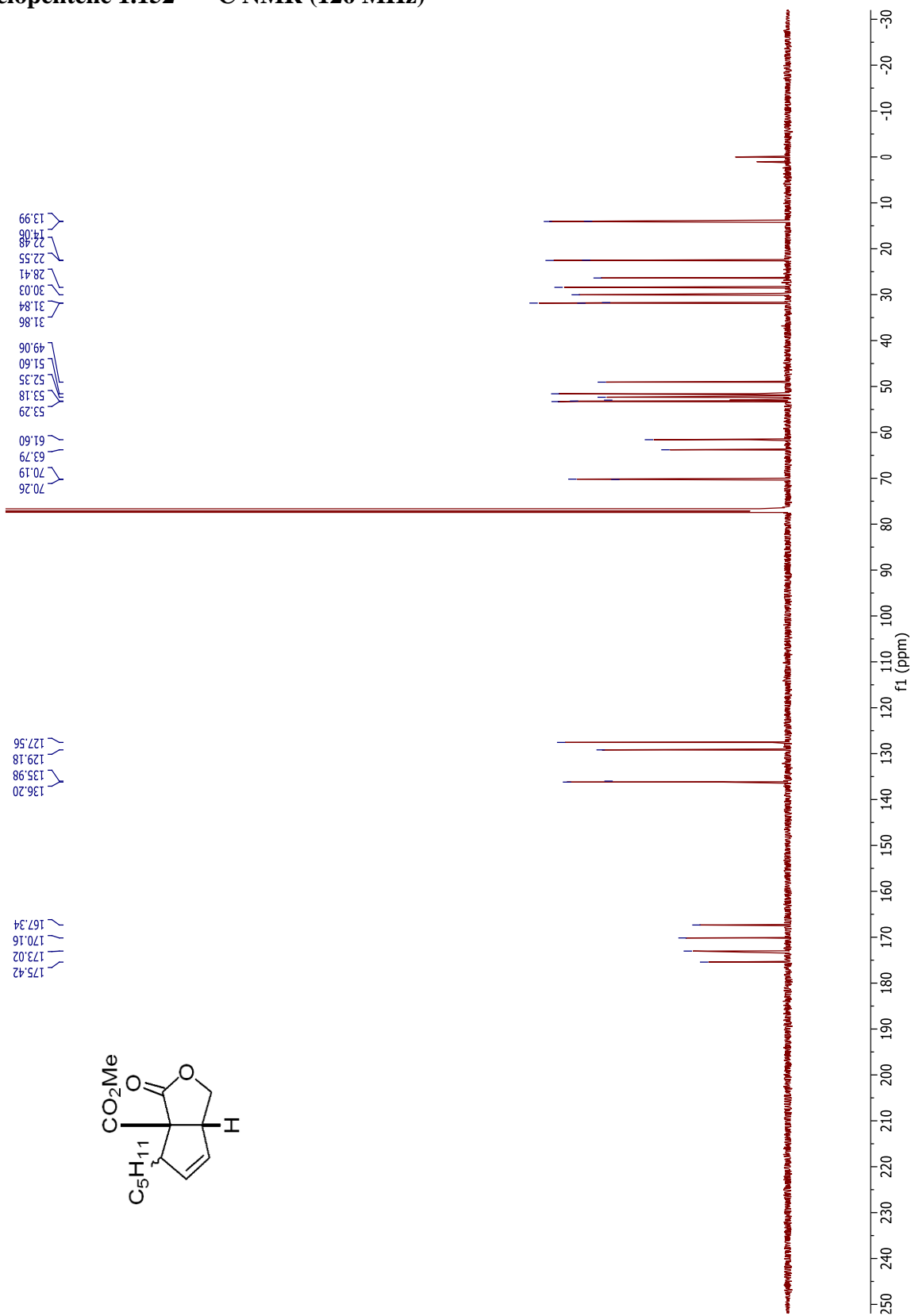
Cyclopentene 1.153 – ¹H NMR (500 MHz)
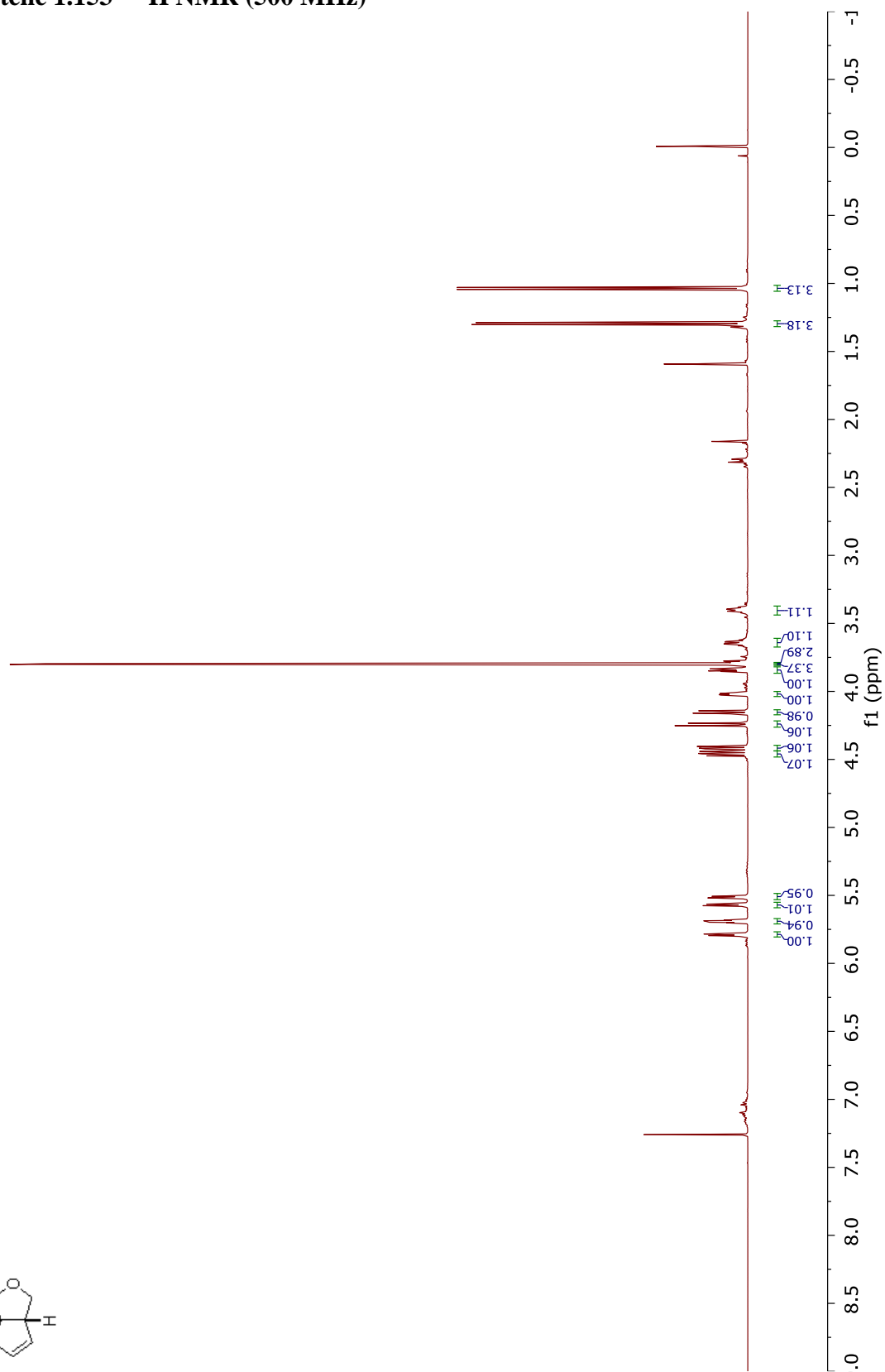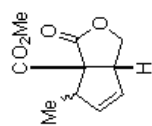
Cyclopentene 1.153 – ^{13}C NMR (126 MHz)

15.54
16.81

46.08
47.48
48.63
53.00
53.18
53.19
61.76
63.96
70.33
70.36

127.33
128.28

137.52
137.95

167.30
169.87
172.93
175.30
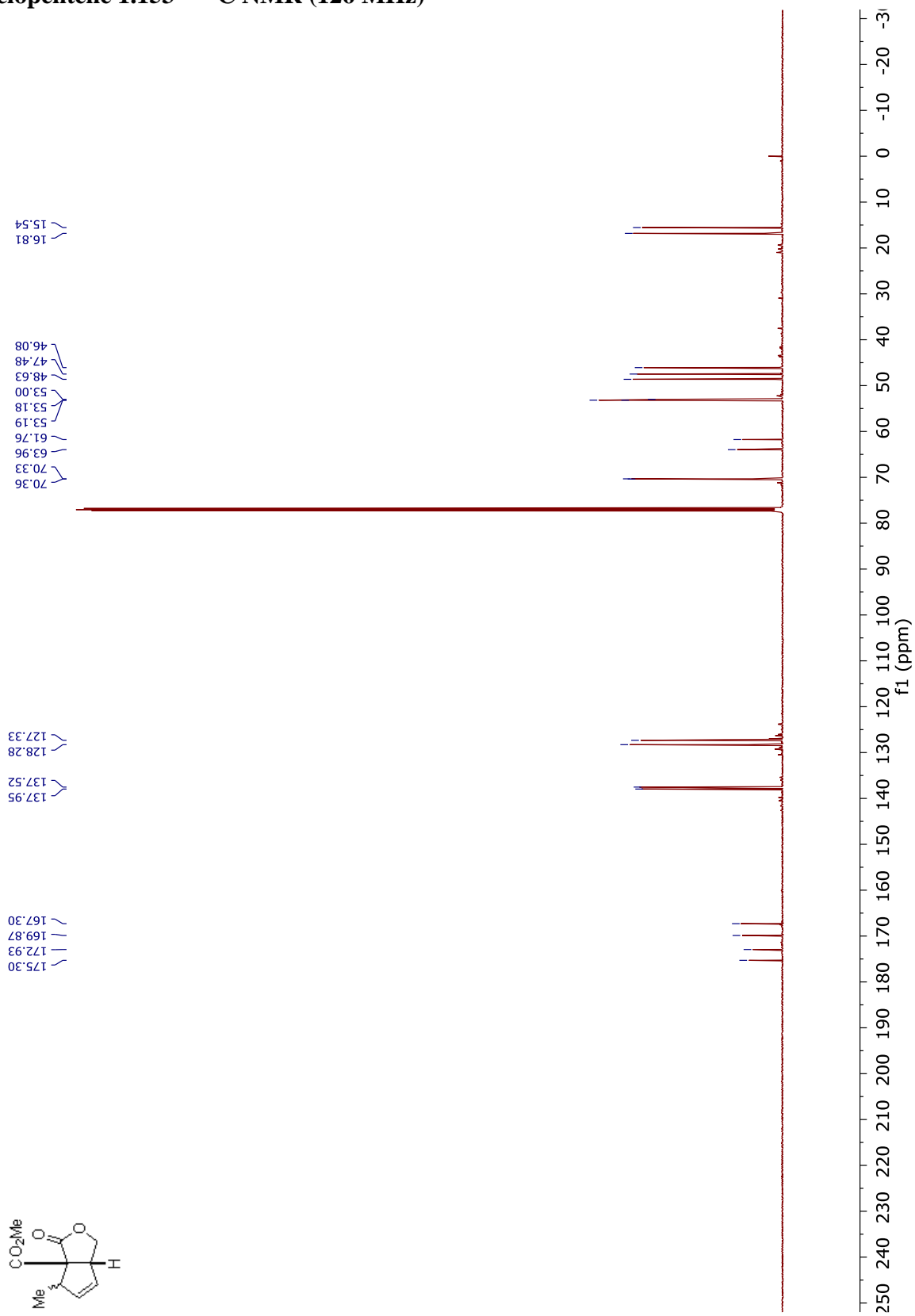
Cyclopentene 1.154 – ¹H NMR (500 MHz)
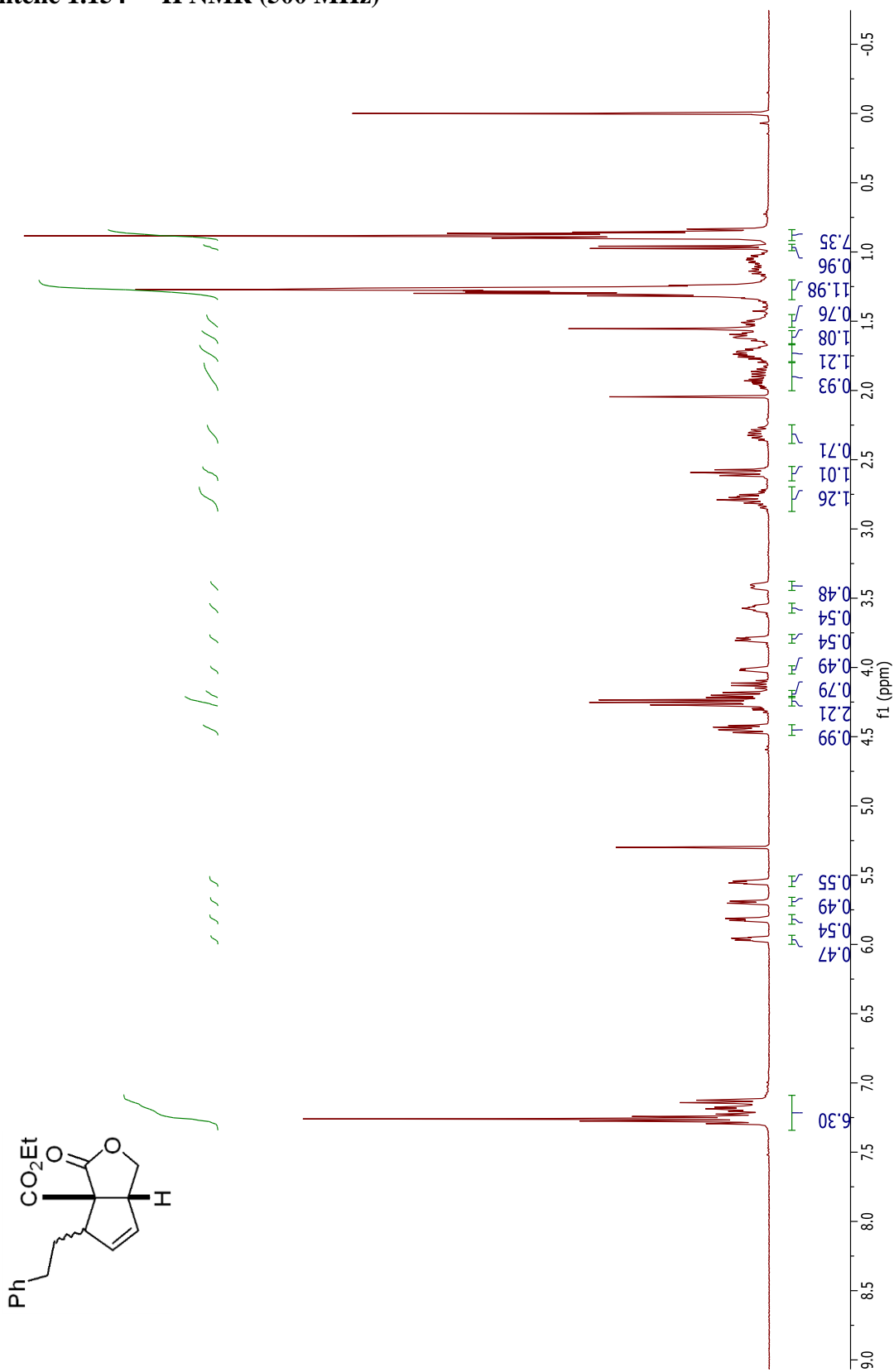
Cyclopentene 1.154 – ^{13}C NMR (126 MHz)

14.04
14.14

31.89
33.00
33.66
34.86

49.22
50.91
51.90
53.41
61.69
62.27
62.30
63.74
70.12
70.26

125.83
126.04
127.86
128.20
128.31
128.48
128.50
129.19
129.28
129.77
134.10
134.21
135.67
135.97
141.49
141.88

166.70
169.47
173.05
175.27

f1 (ppm)
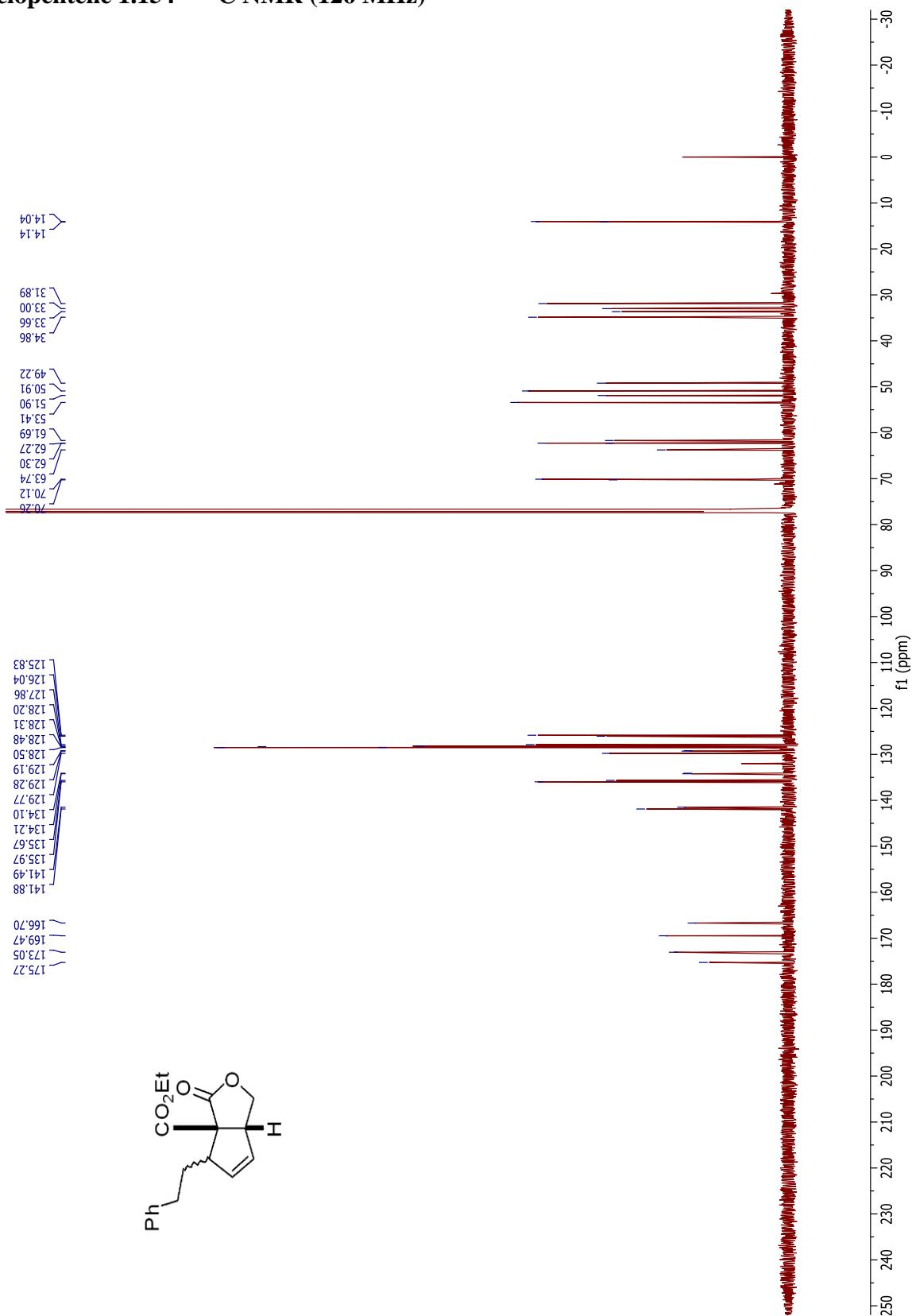
Cyclopentene 1.155 – ¹H NMR (500 MHz)
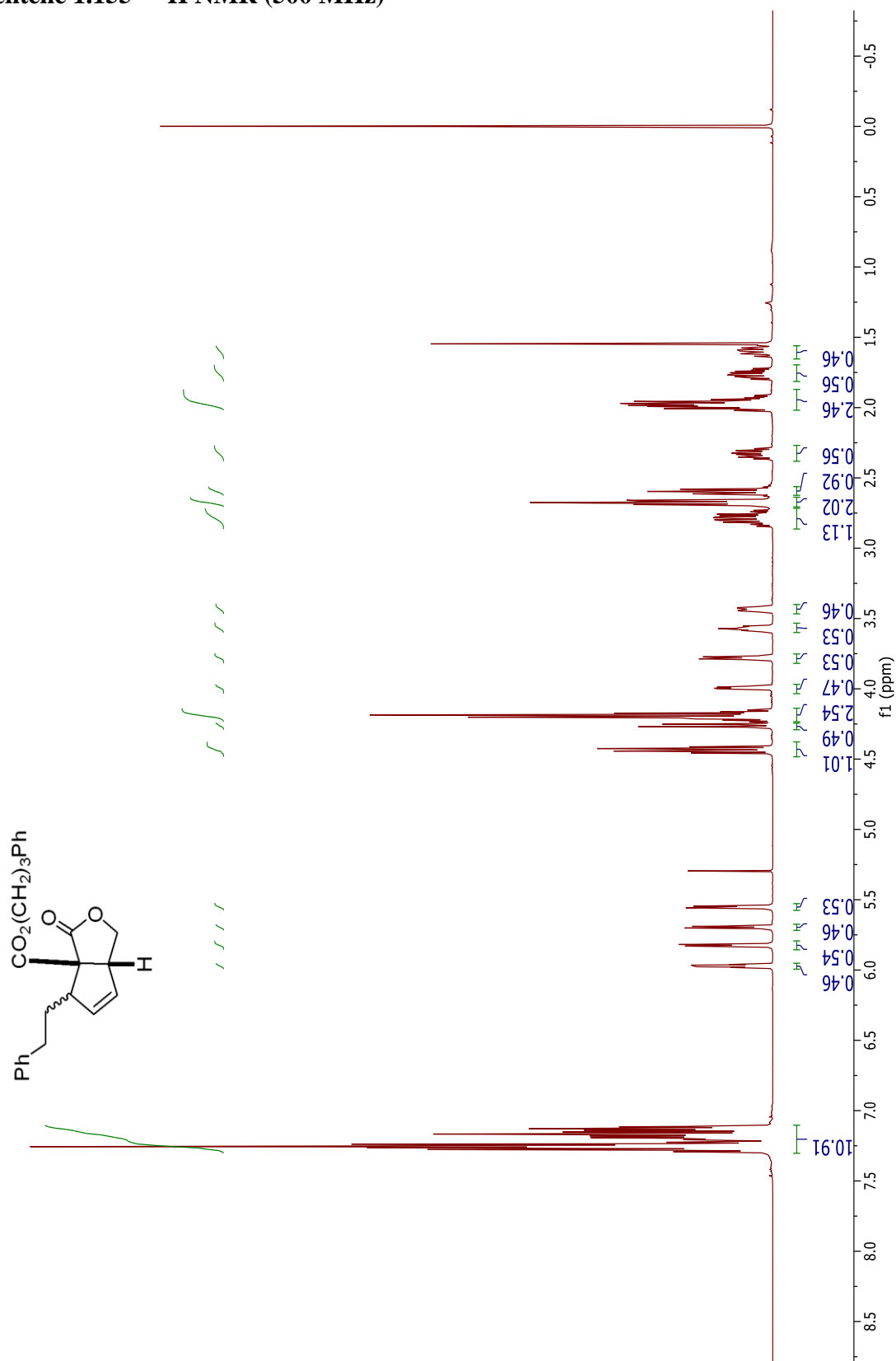
Cyclopentene 1.155 – ^{13}C NMR (126 MHz)
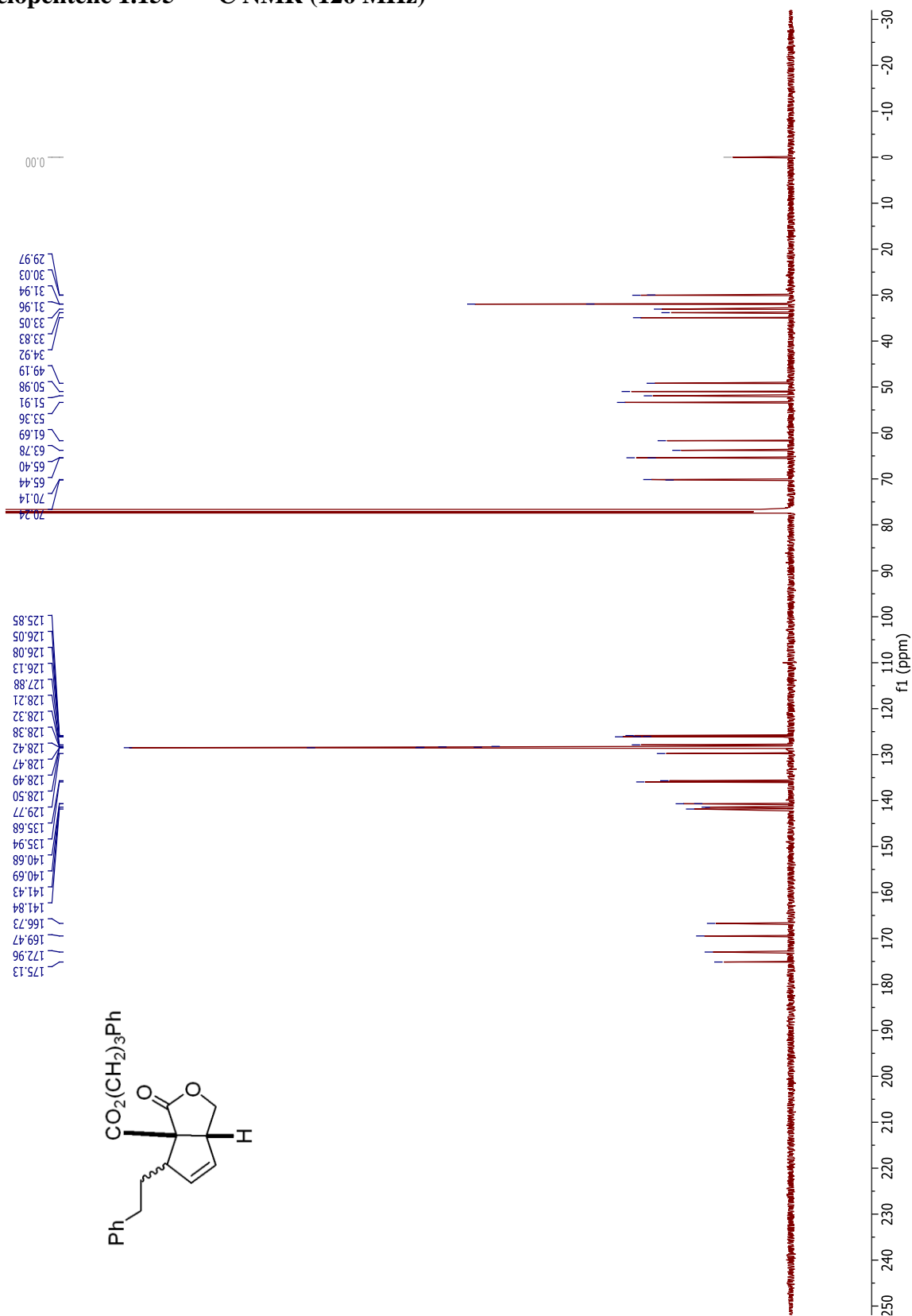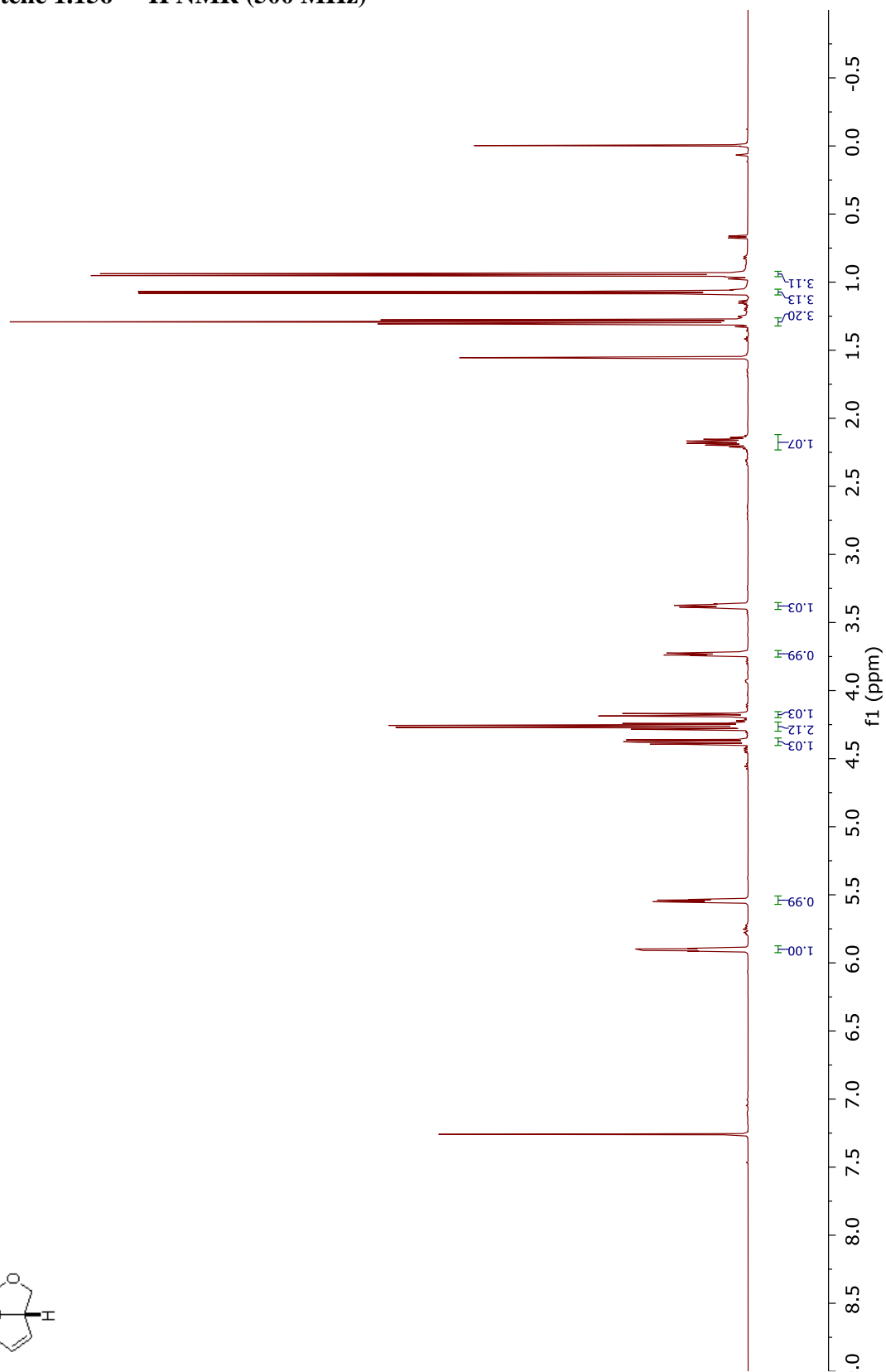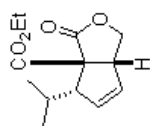
29.97
30.03
31.94
31.96
33.05
33.83
34.92
49.19
50.98
51.91
53.36
61.69
63.78
65.40
65.44
70.14
70.24

125.85
126.05
126.08
127.13
127.88
128.21
128.32
128.38
128.42
128.47
128.49
128.50
129.77
135.68
135.94
140.68
140.69
141.43
141.84
166.73
169.47
172.96
175.13

Cyclopentene 1.156 – ^{1}H NMR (500 MHz)

Cyclopentene 1.156 – ^{13}C NMR (126 MHz)

14.06

21.16
23.00
27.50

54.43
59.05
61.38
62.21

69.37

127.75

135.09

170.34
173.20

f1 (ppm)
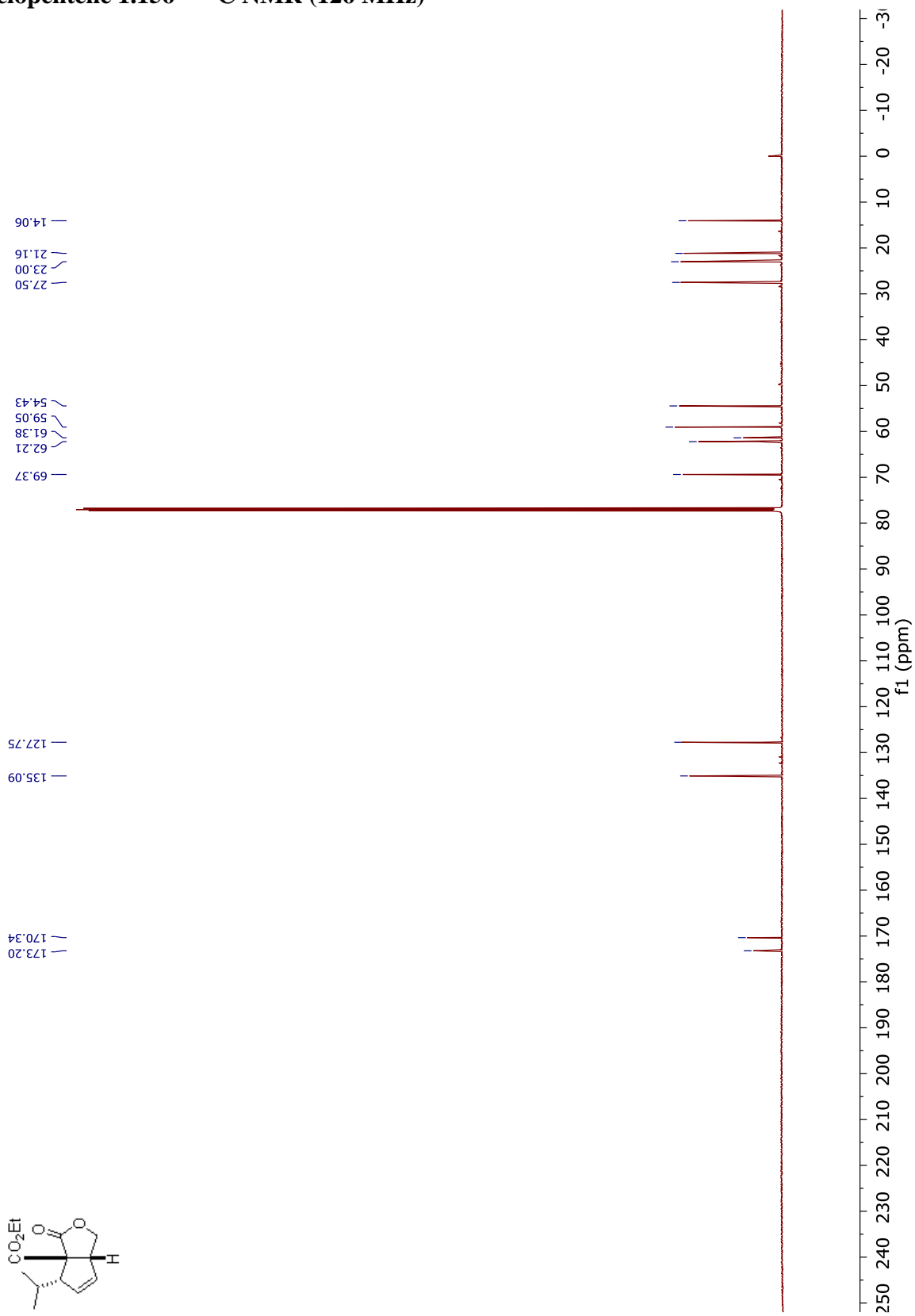
Cyclopentene 1.156 – ¹H NMR (500 MHz)
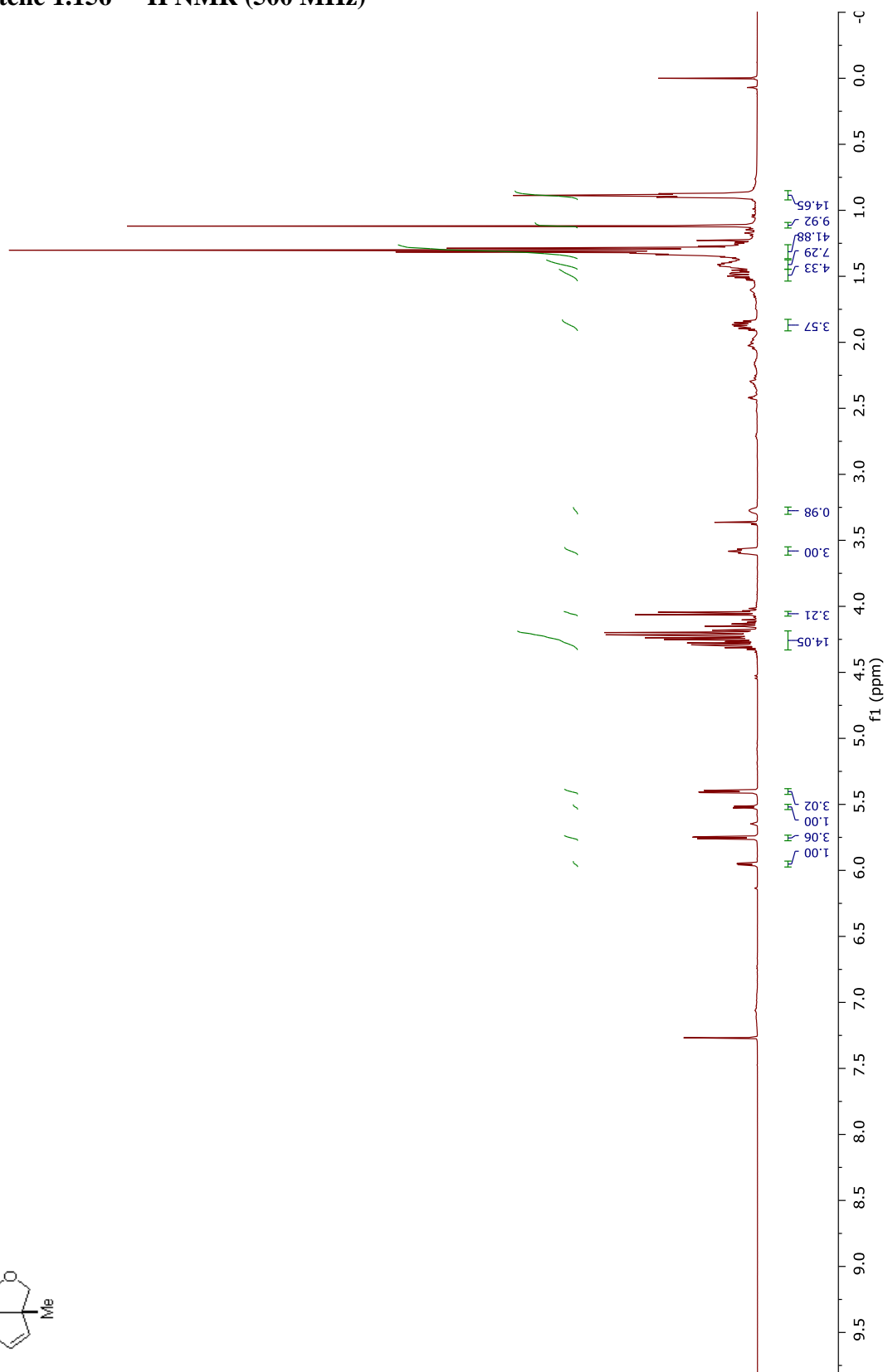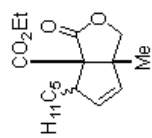
Cyclopentene 1.156 – ^{13}C NMR (126 MHz)
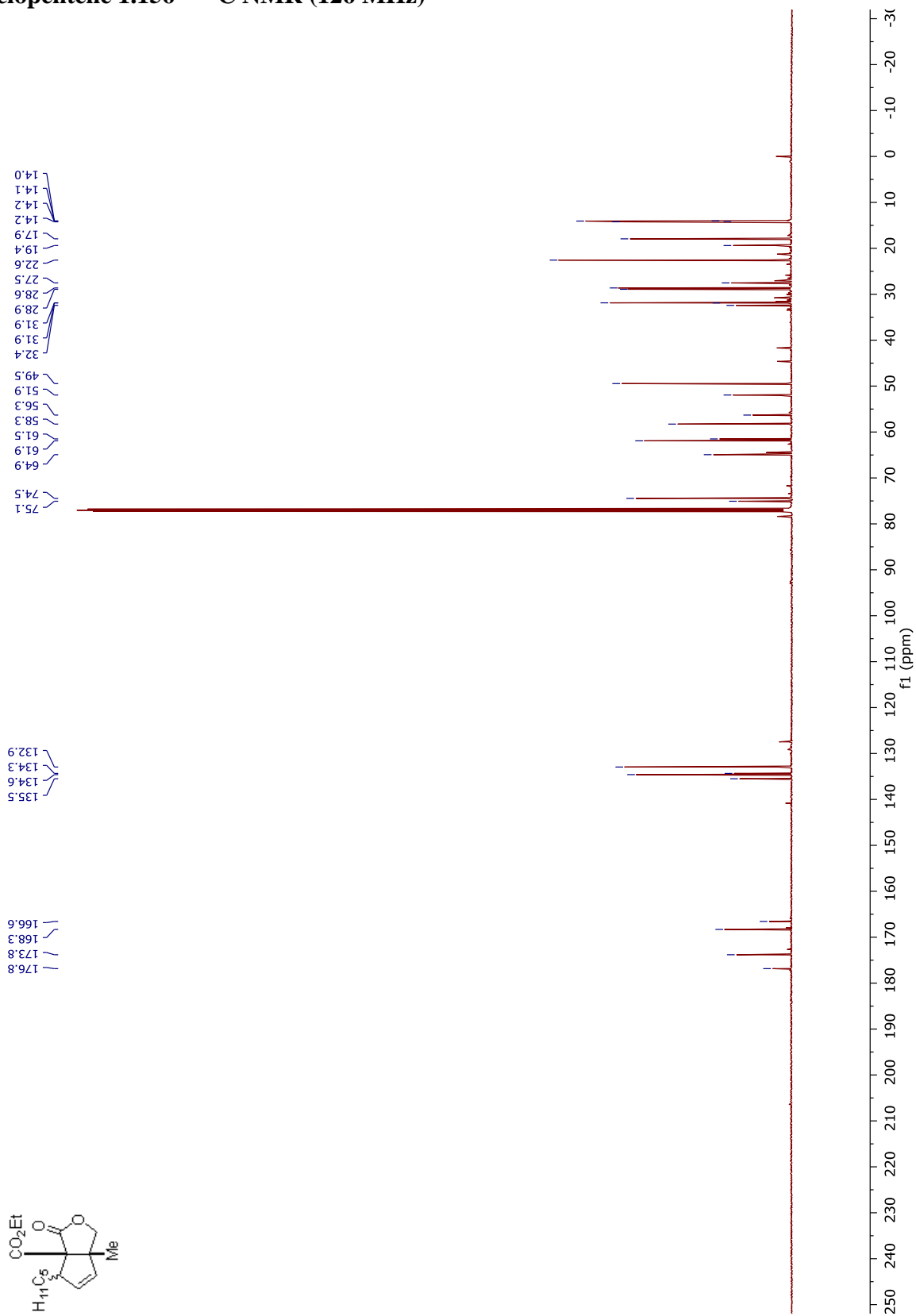
Cyclopentene 1.162 – ¹H NMR (500 MHz)
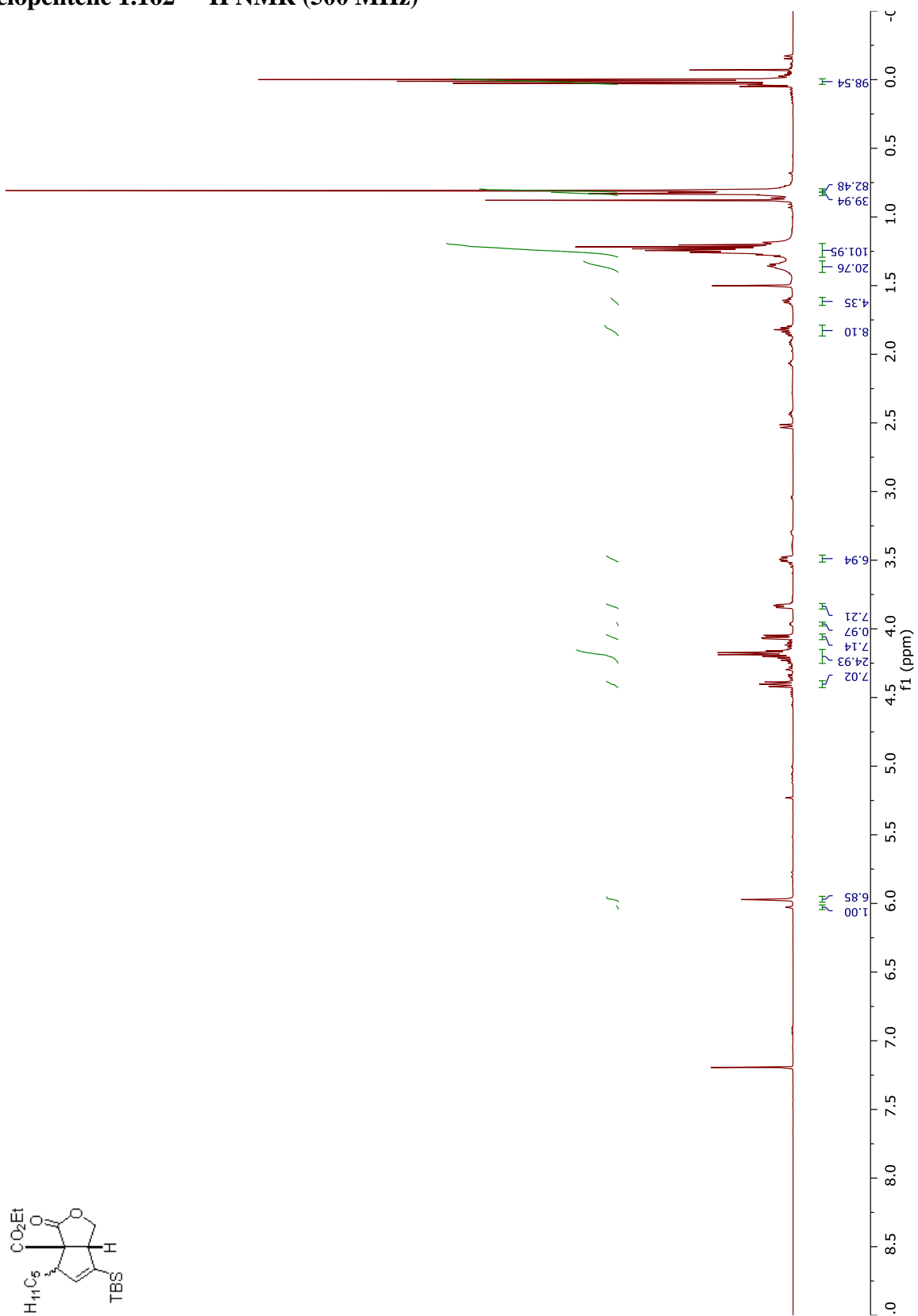
Cyclopentene 1.162 – ^{13}C NMR (126 MHz)
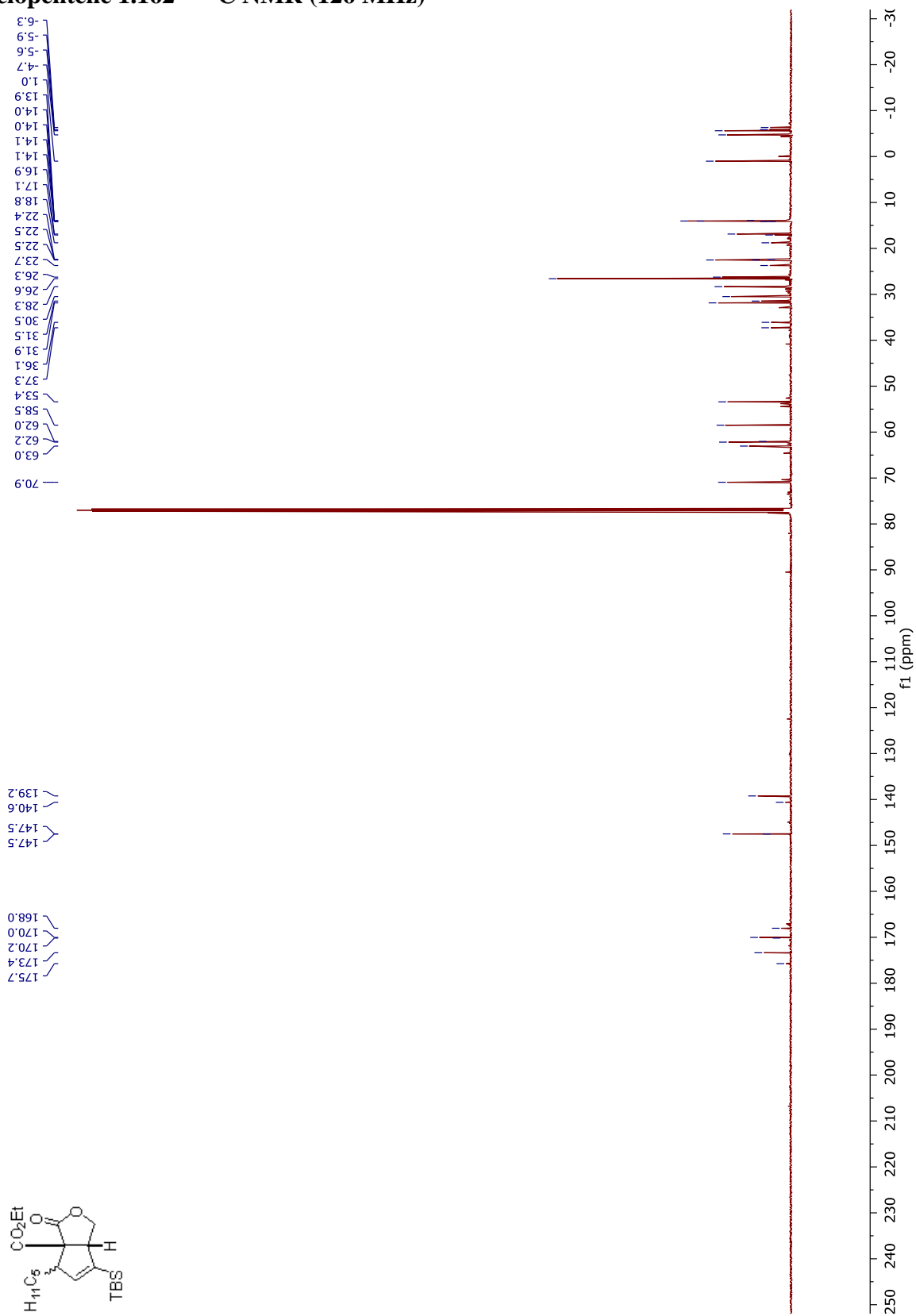
Cyclopentene 1.163 – ¹H NMR (500 MHz)
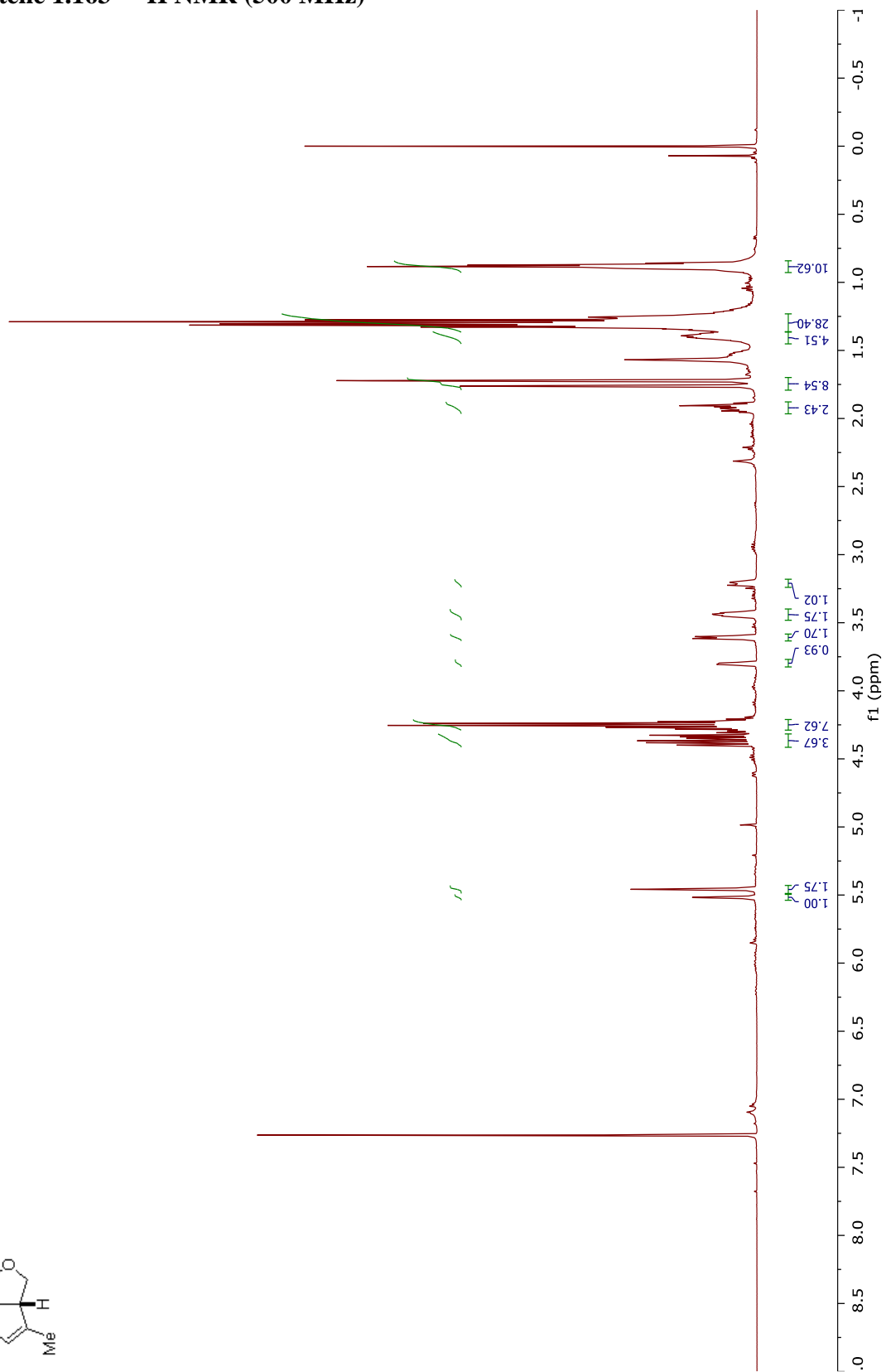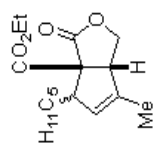
Cyclopentene 1.163 – ^{13}C NMR (126 MHz)

14.01
14.06
14.11
14.14
22.51
22.57
26.35
28.40
30.47
31.83
31.86
31.90
50.55
50.99
51.71
56.03
61.98
62.09
62.12
64.22
68.00
68.05

130.07
130.19
134.92
136.54

166.97
169.73
173.27
175.73
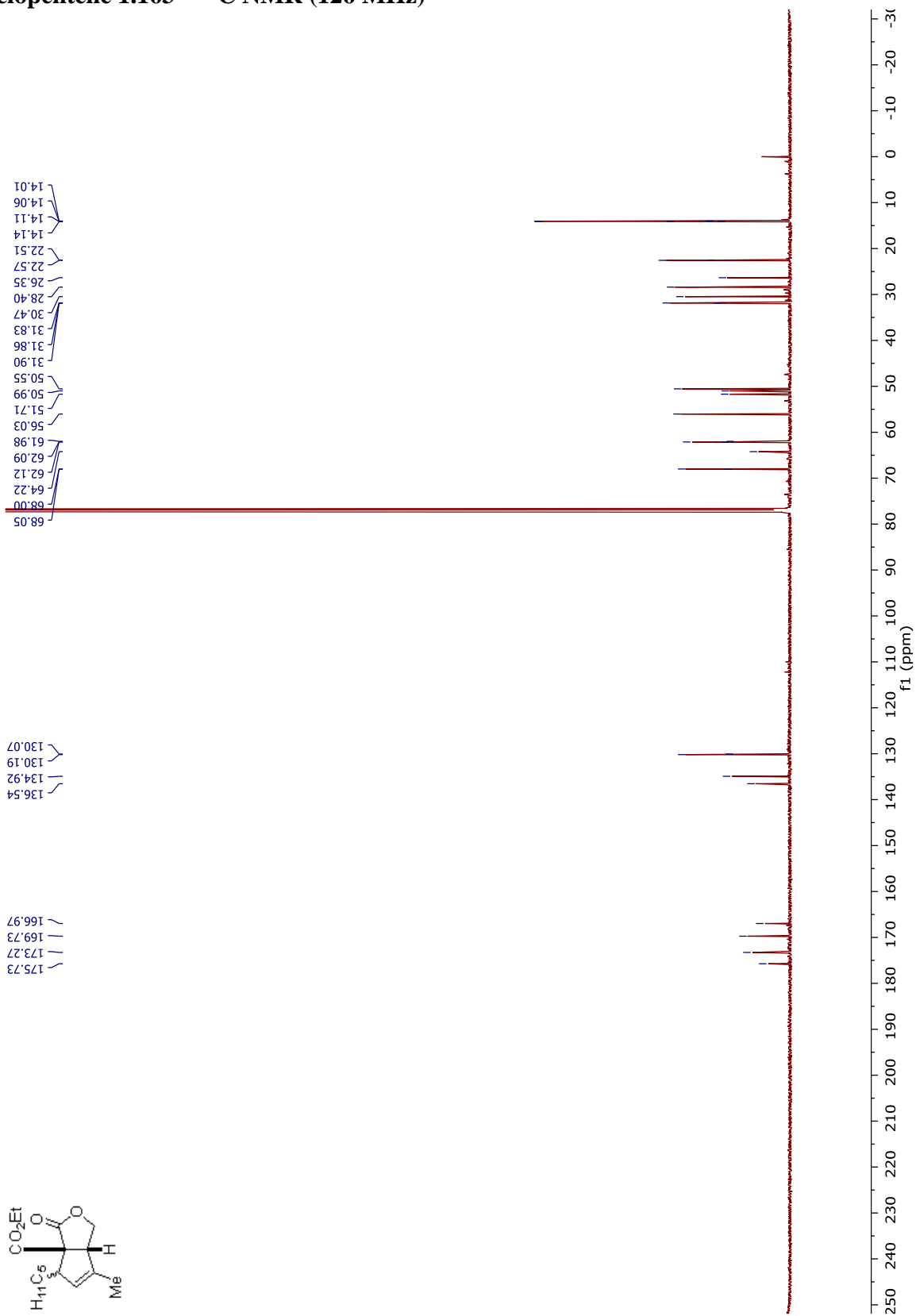
Cyclopentene 1.164 – ¹H NMR (500 MHz)
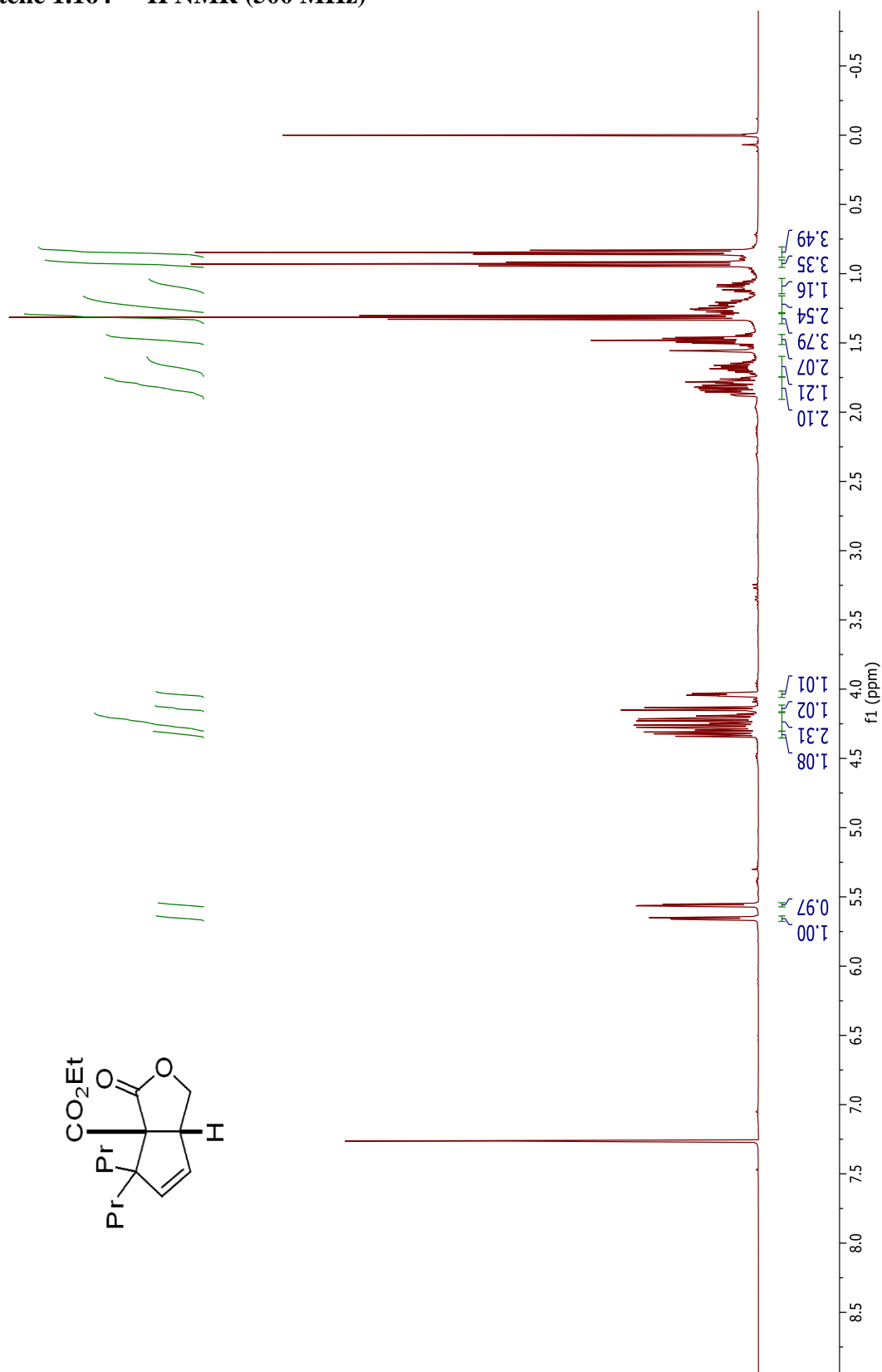
Cyclopentene 1.164 – ^{13}C NMR (126 MHz)
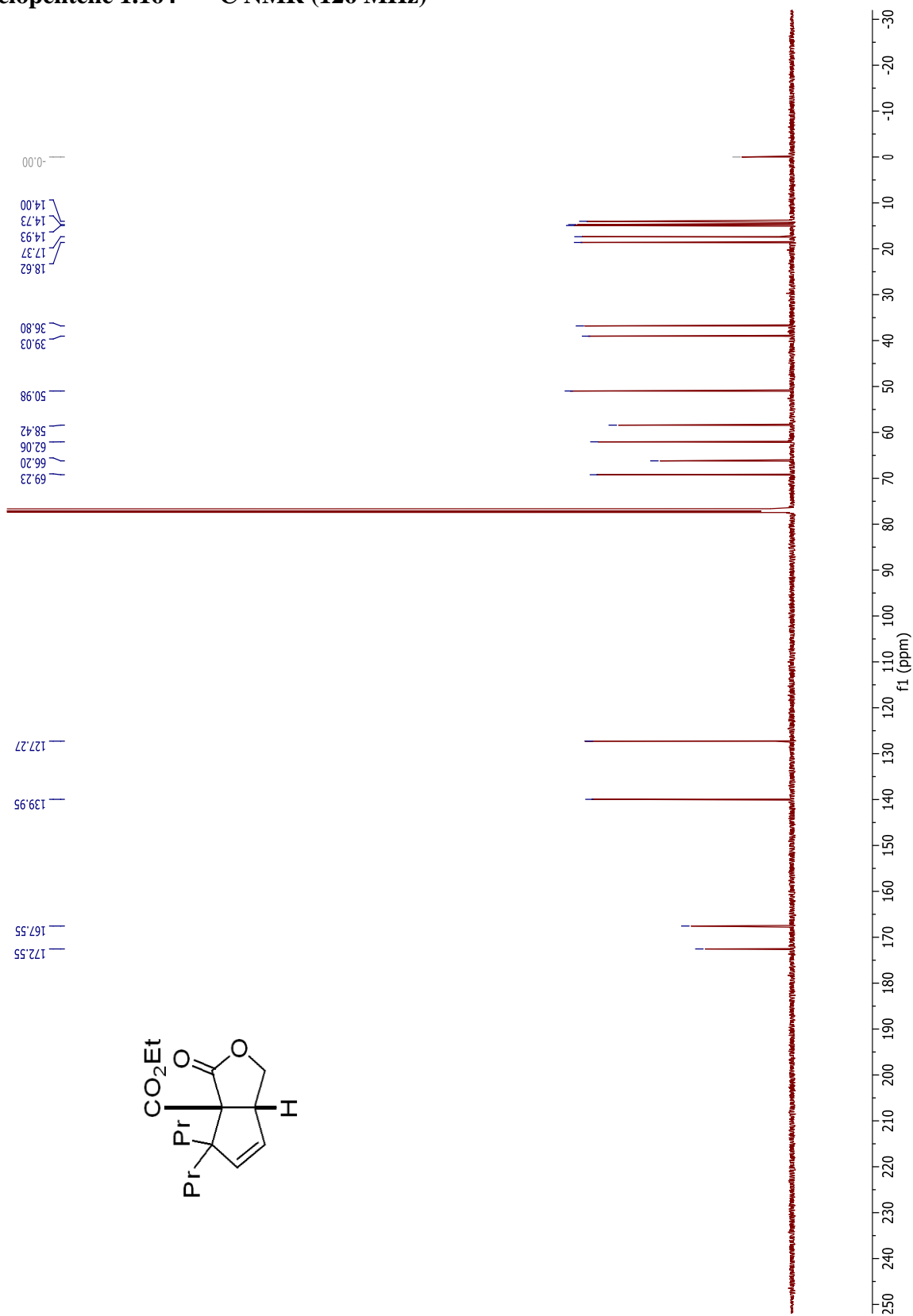
Cyclopentene 1.165 – ¹H NMR (500 MHz)
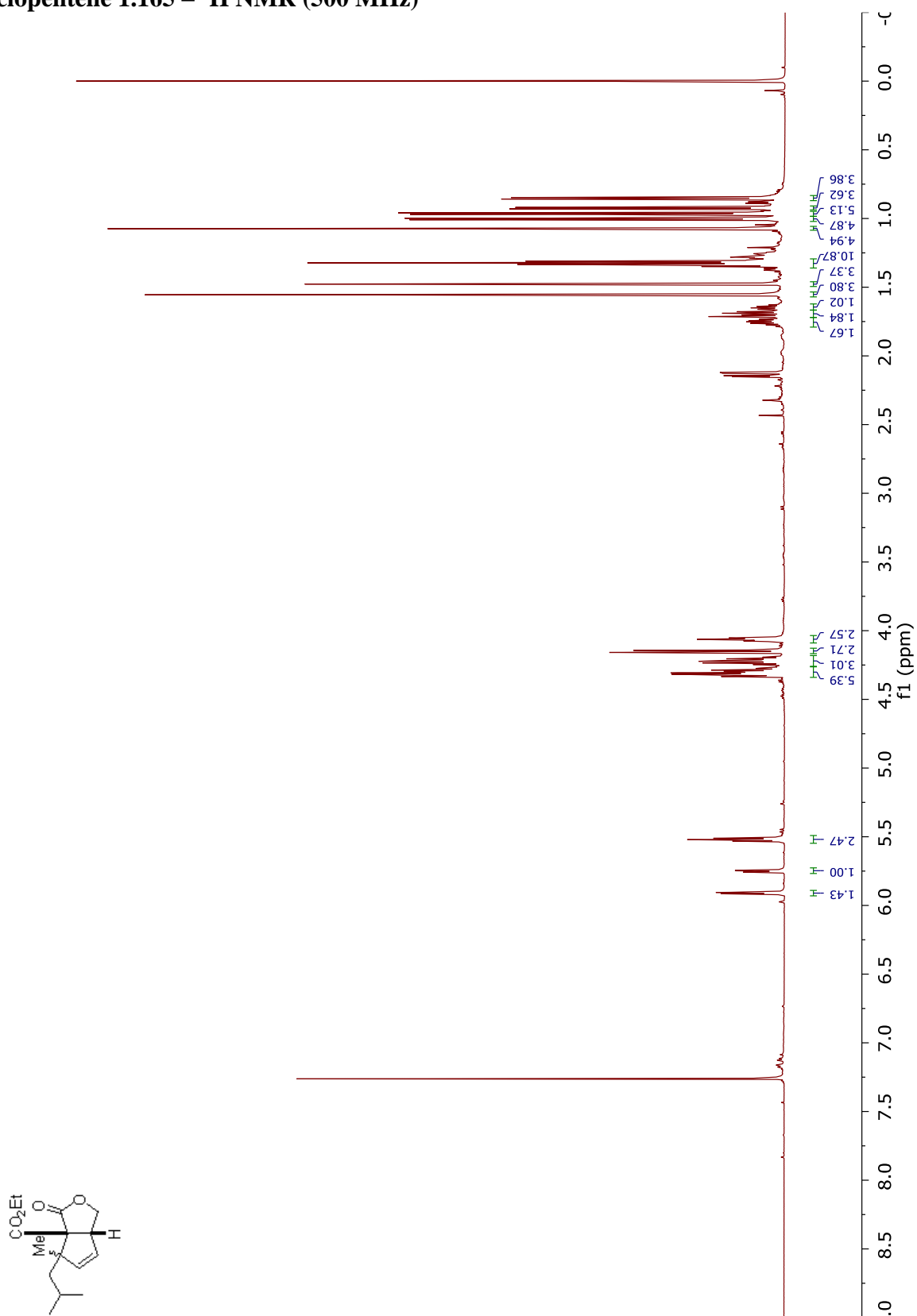
Cyclopentene 1.165 – ^{13}C NMR (126 MHz)

14.09
14.12
20.29
23.08
24.56
24.61
25.14
25.16
25.42
25.57
42.95
47.98
48.88
49.73
54.81
54.93
62.04
62.09
66.95
66.96
68.85
68.93

126.93
127.11

140.89
141.55

166.98
167.18
172.09
172.34

f1 (ppm)
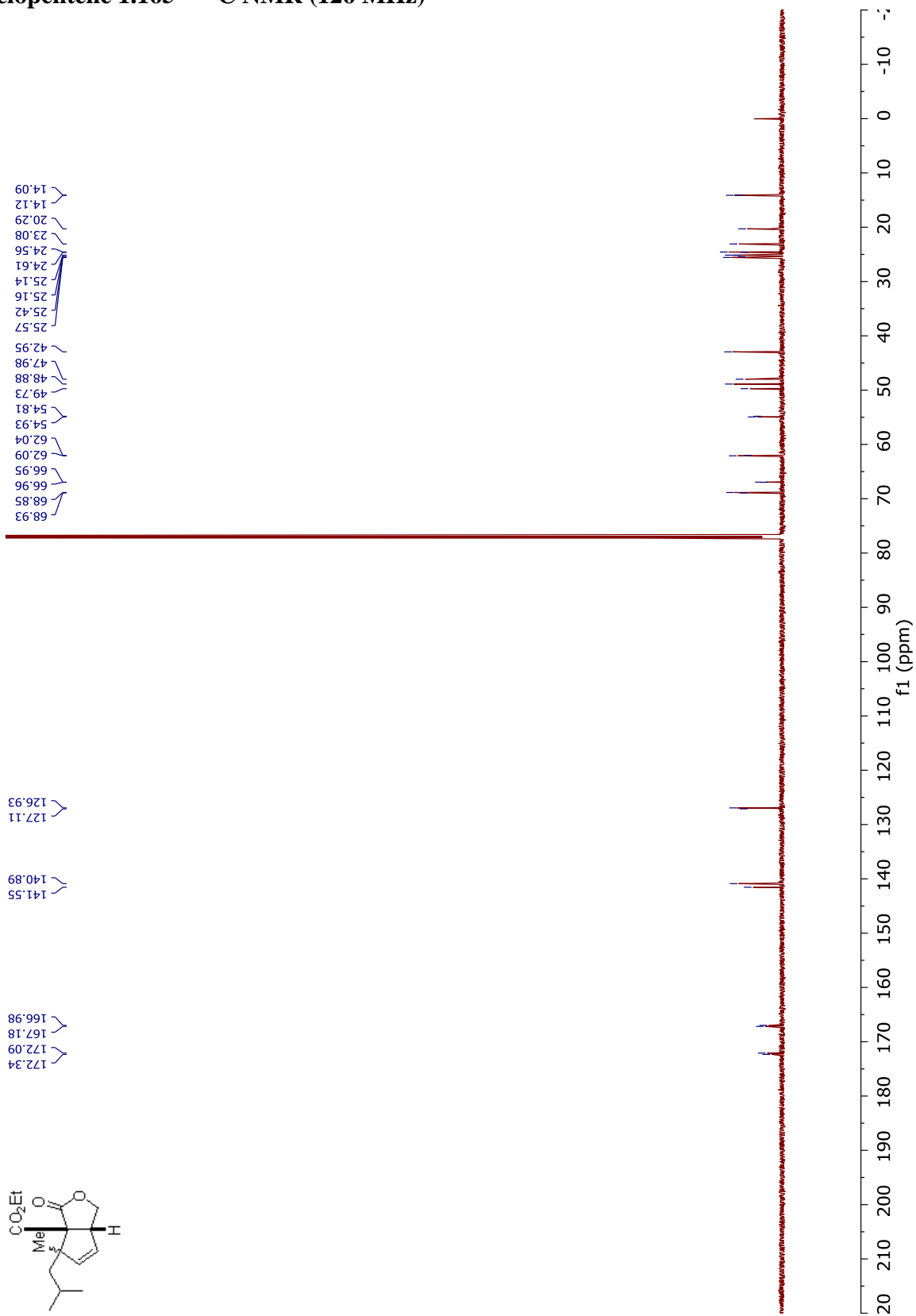
Cyclopentene 1.167 – ¹H NMR (500 MHz)

Cyclopentene 1.167 – ^{13}C NMR (126 MHz)

13.99
14.03
22.55
25.21
28.15
29.57
30.79
31.80

53.38

62.29
62.51
64.50

83.96

125.77

135.38

170.90
171.70

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)
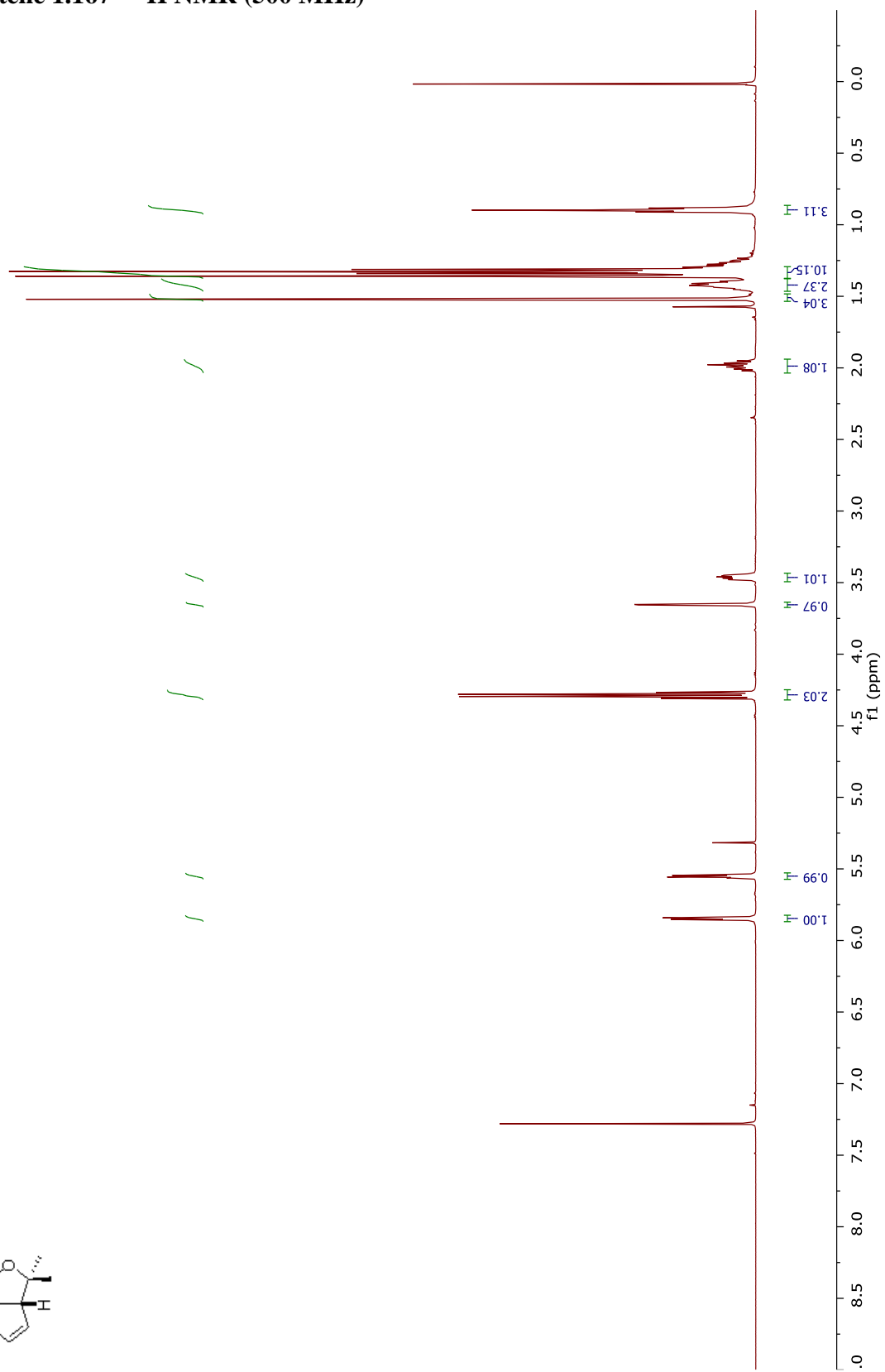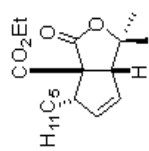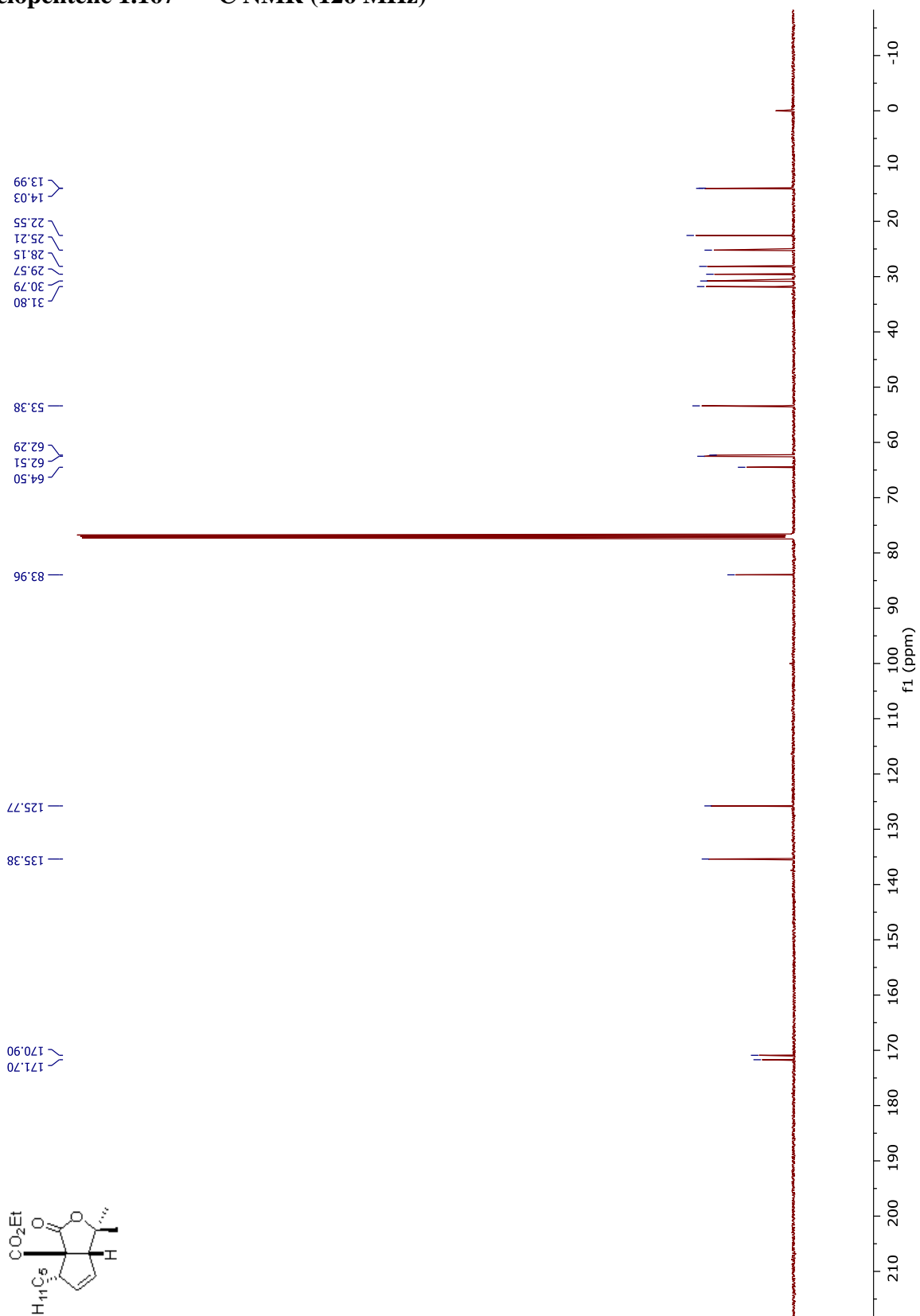
Cyclopentene 1.169 – ¹H NMR (500 MHz)

Cyclopentene 1.167 – ^{13}C NMR (126 MHz)

14.03
22.55
25.17
28.14
29.59
30.80
31.81

53.28
53.57

62.46
64.36

84.03

125.83

135.29

171.47
171.62

f1 (ppm)
250 240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30
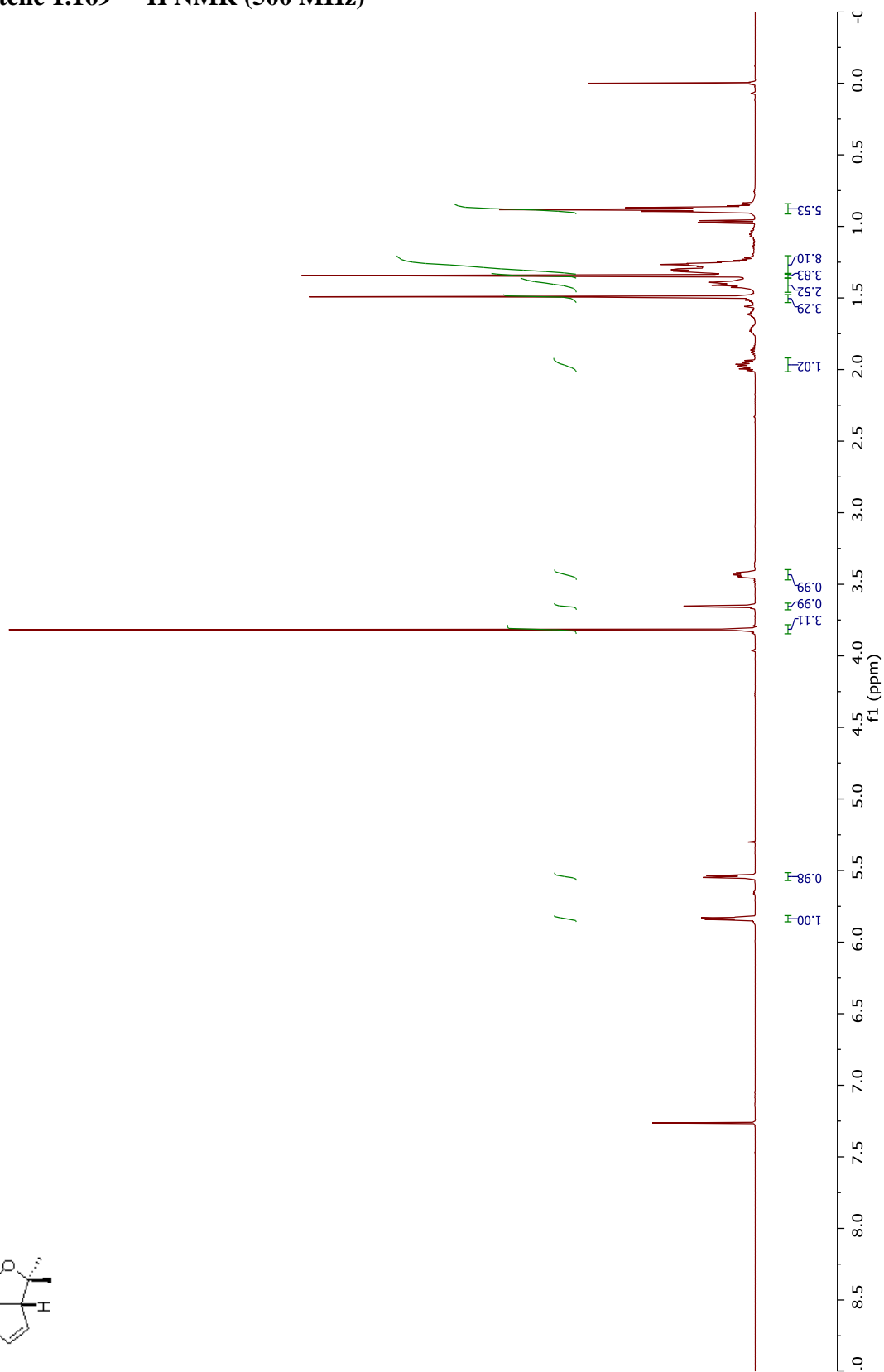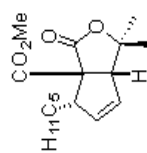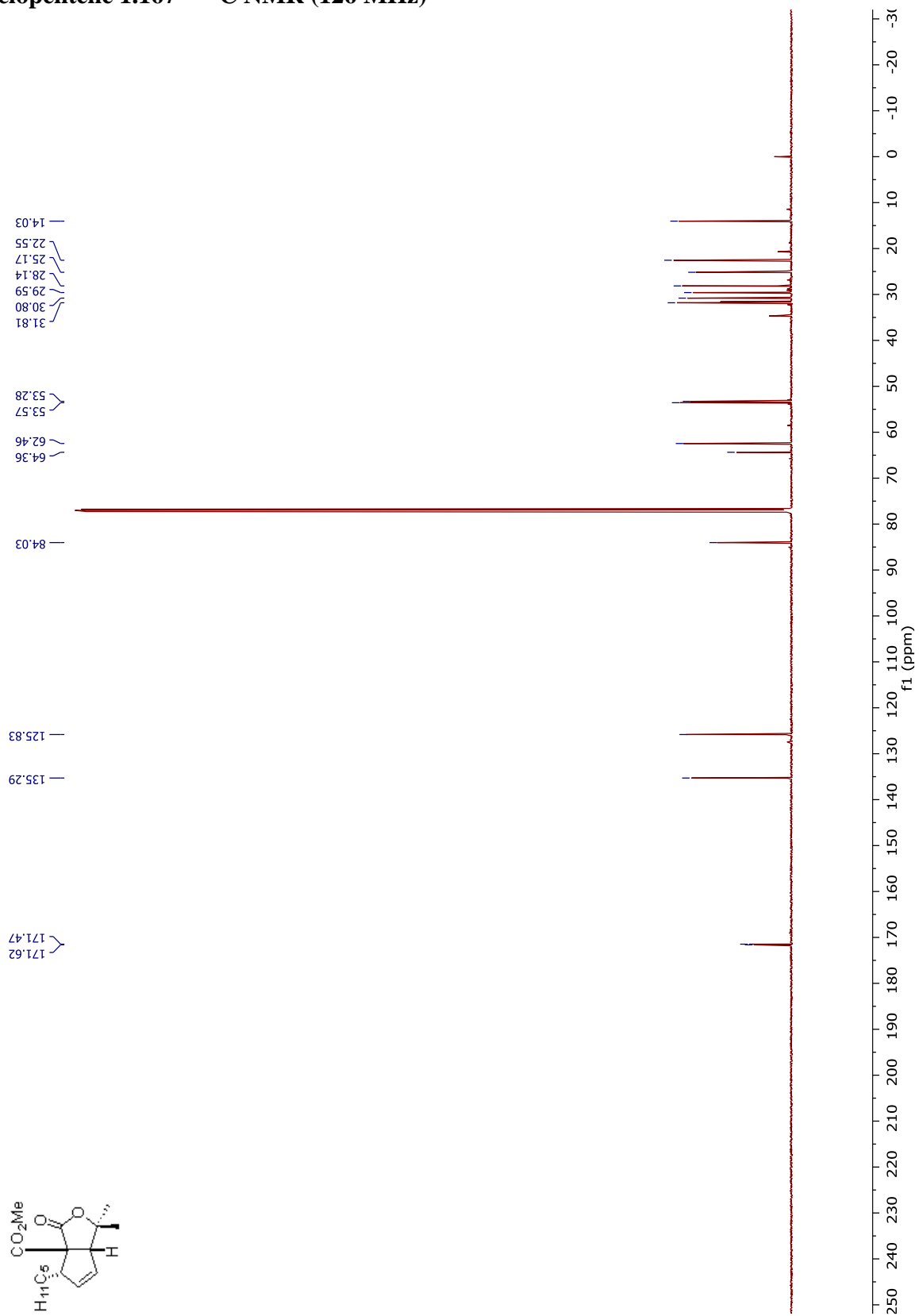
Epoxide 1.170 – ^{1}H NMR (500 MHz)
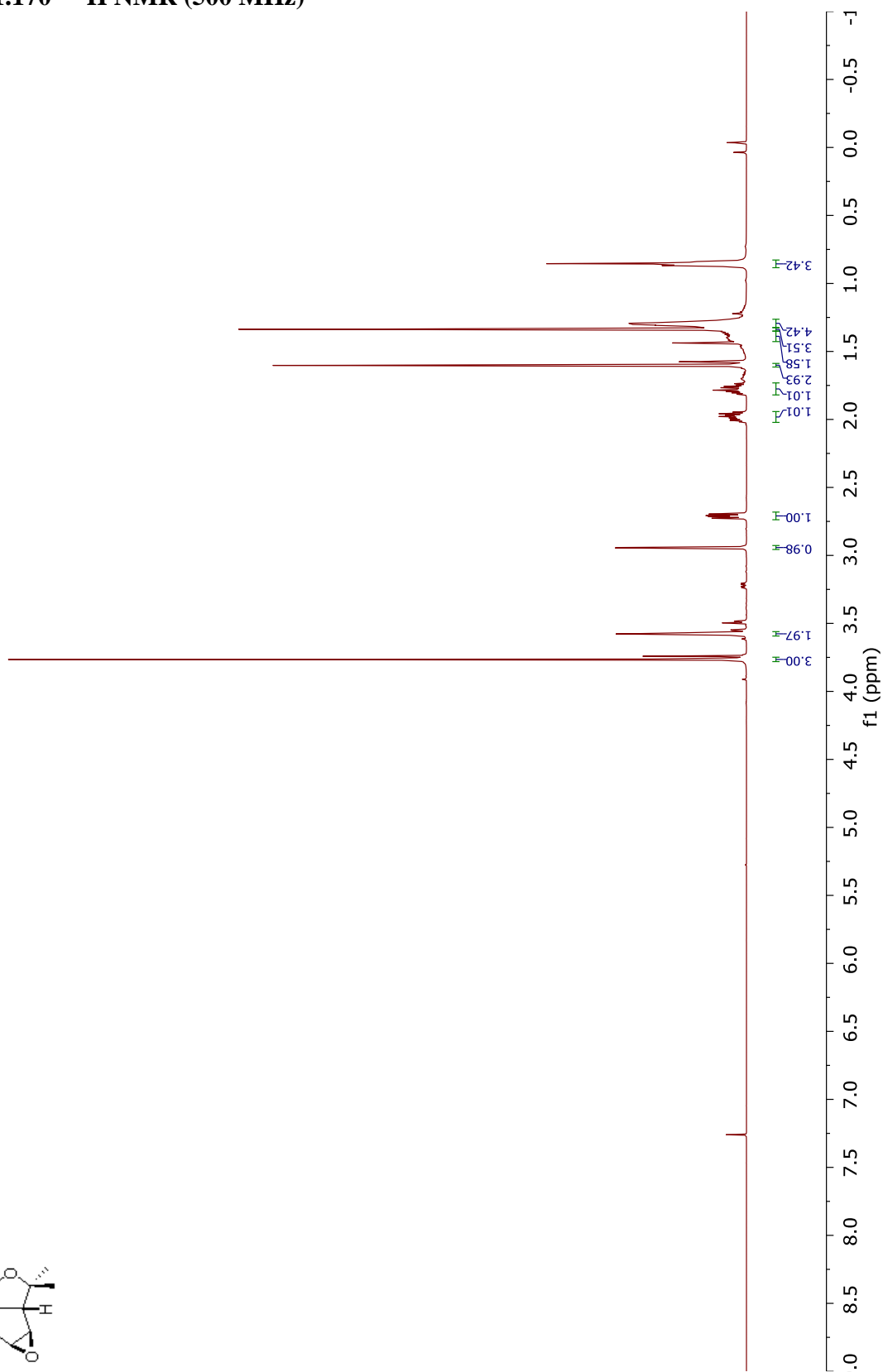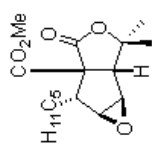
Epoxide 1.170 – ^{13}C NMR (126 MHz)

14.02

22.54
25.20
25.56
28.17
28.74
31.74

51.13
53.50
56.16
56.26
59.20
59.95

81.65

170.58
171.43

f1 (ppm)
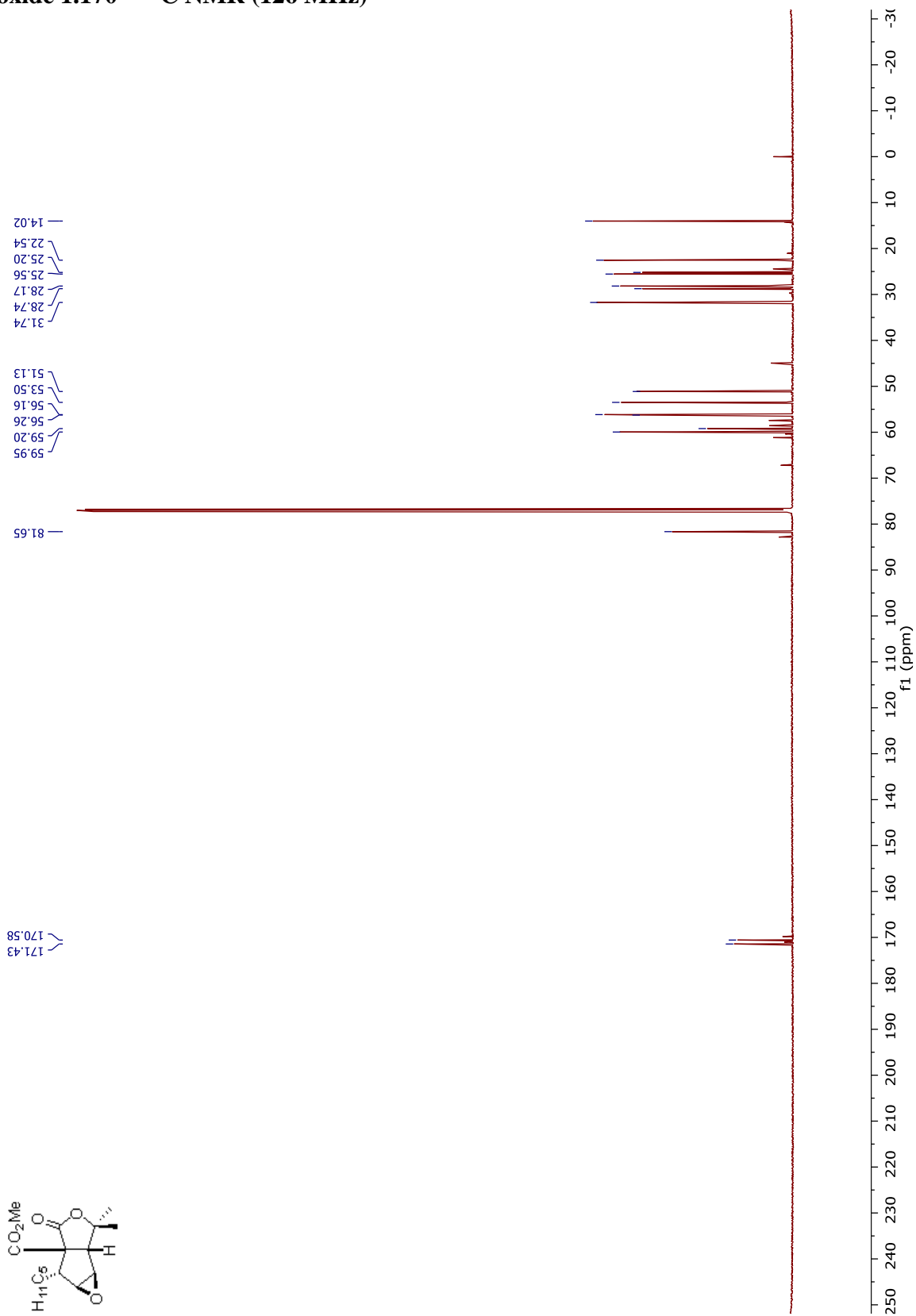
Diol 1.171 – ¹H NMR (500 MHz)
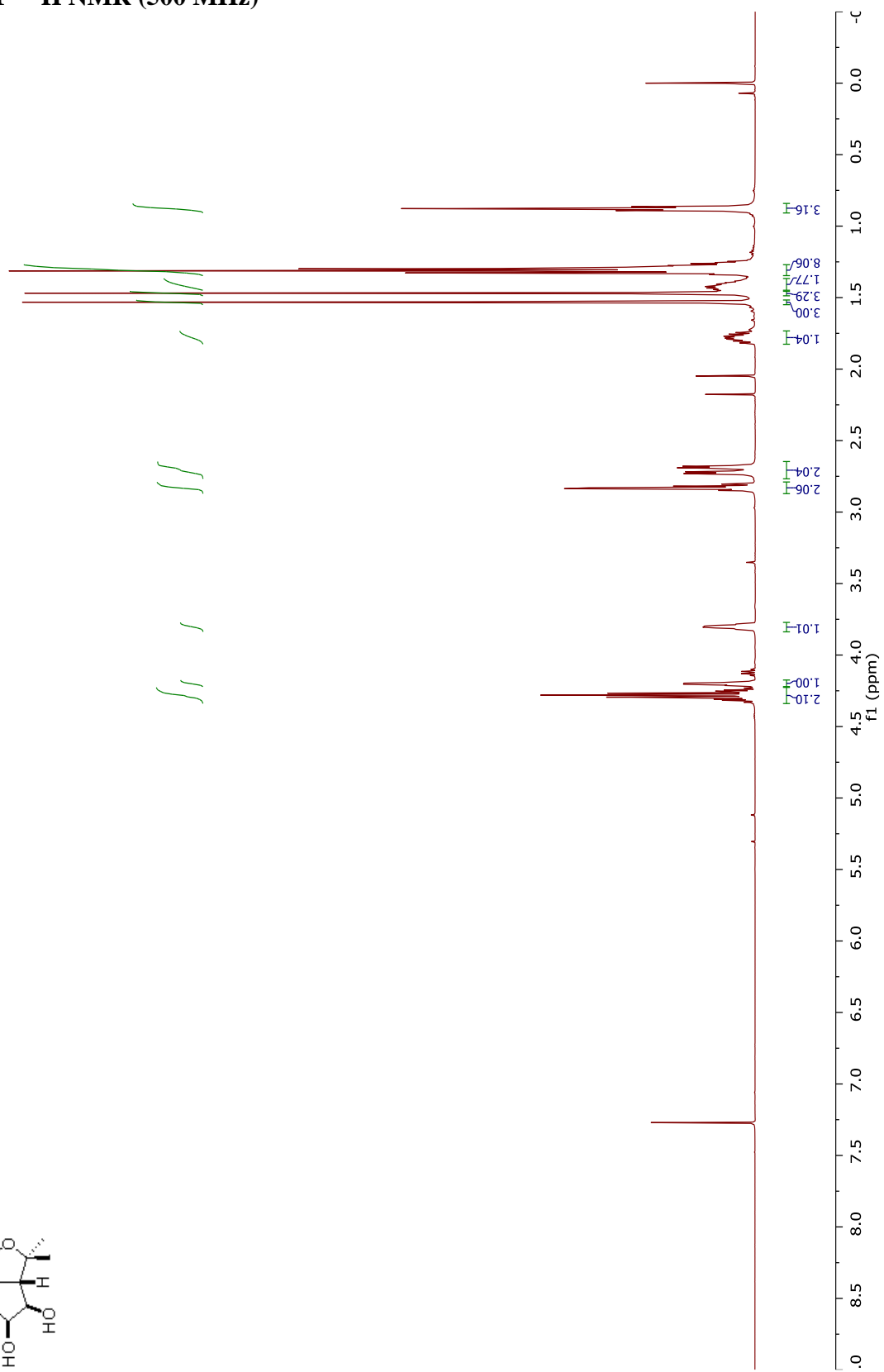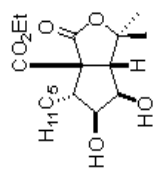
Diol 1.171 – ¹³C NMR (126 MHz)
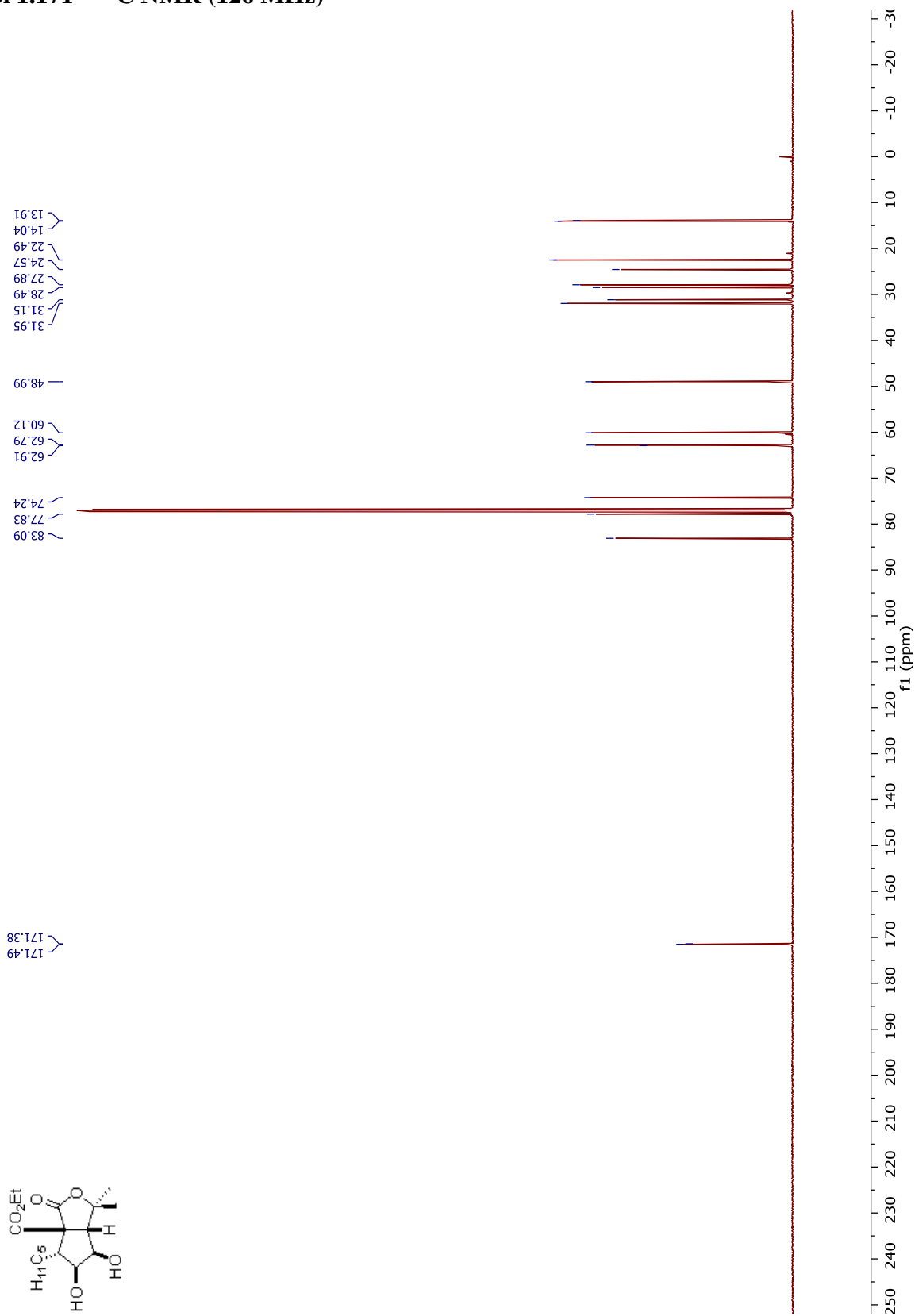
Alcohol 1.172 – ¹H NMR (500 MHz)
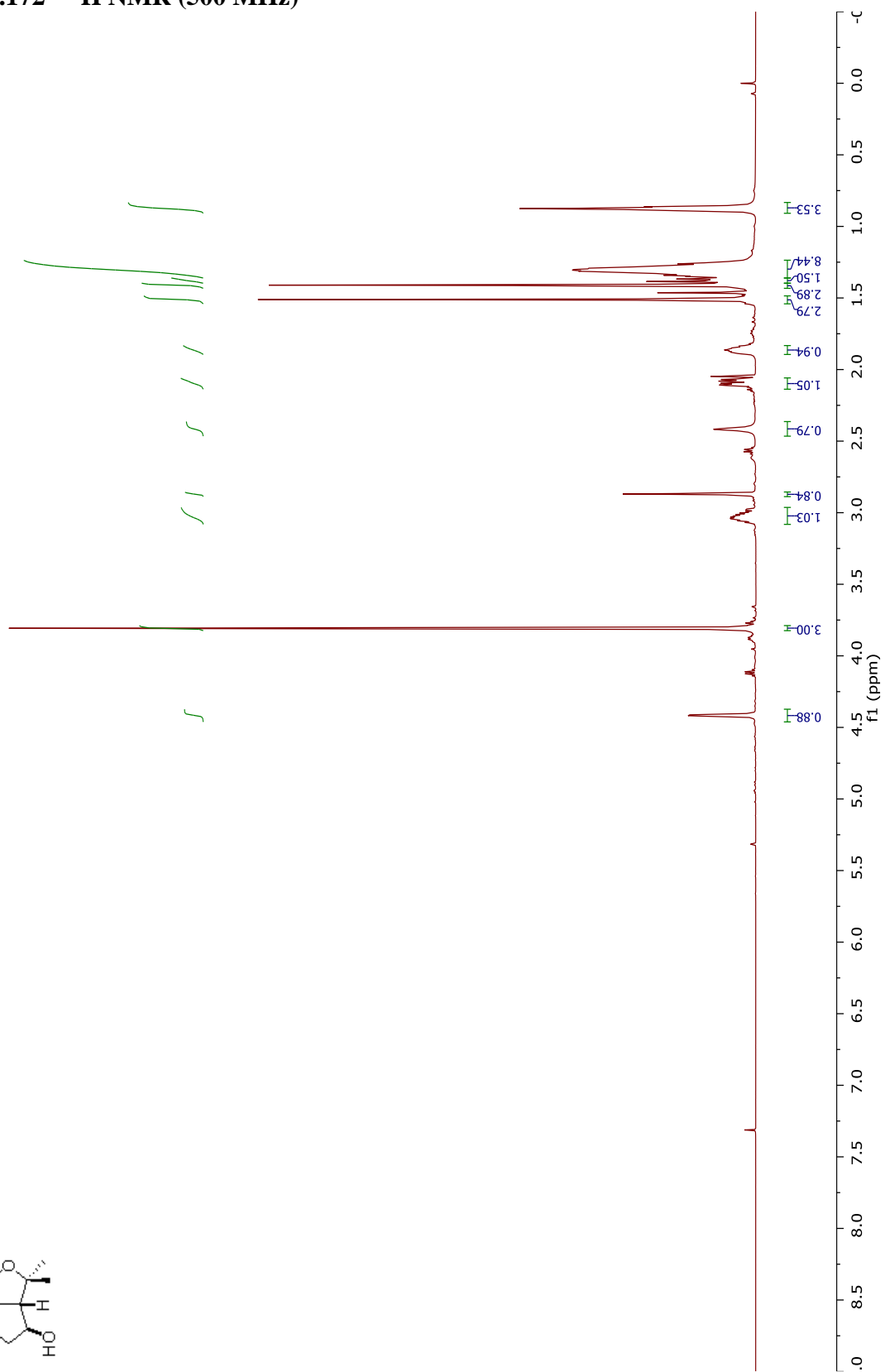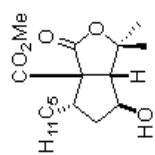
Alcohol 1.172 – ¹³C NMR (126 MHz)
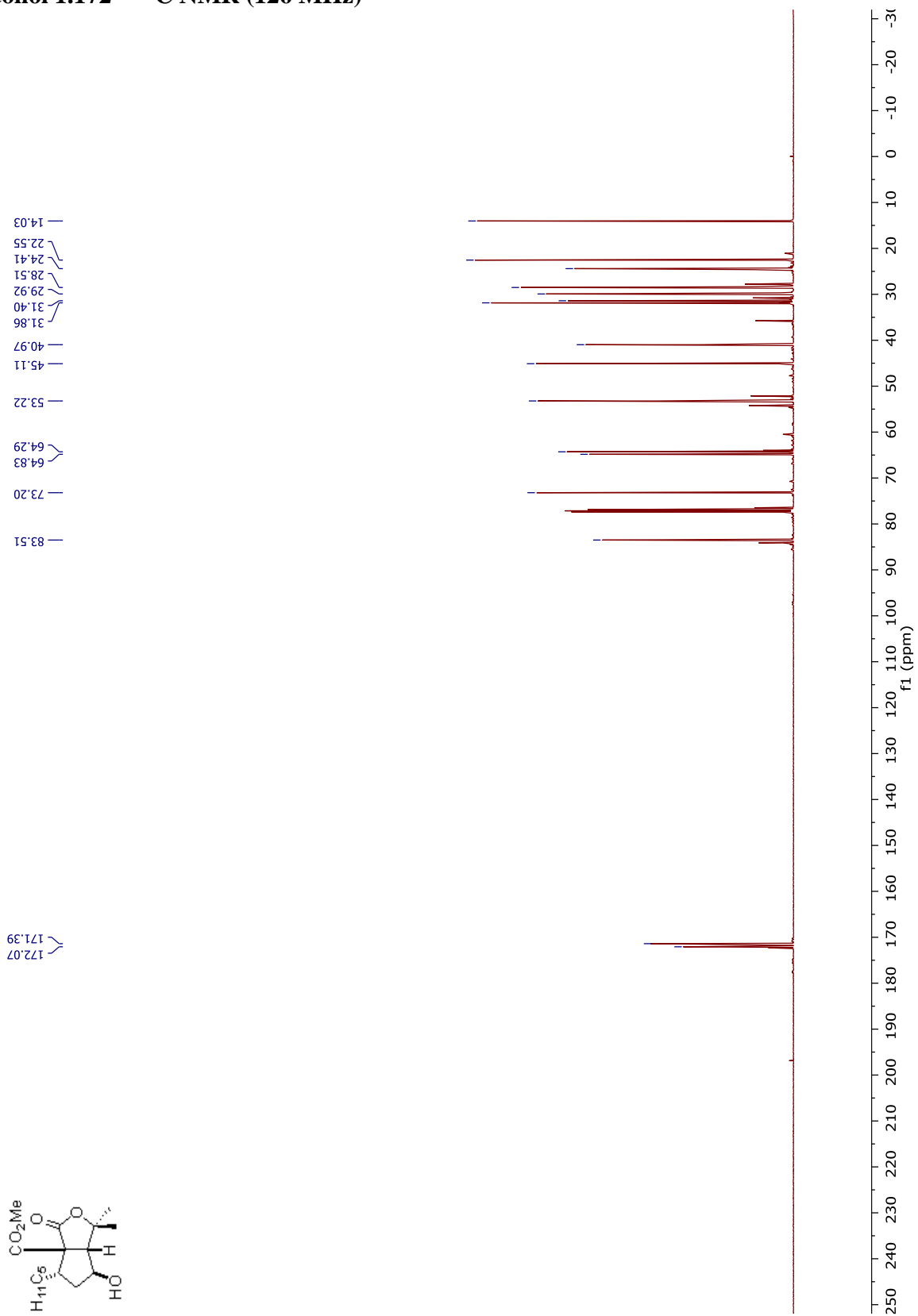
Cyclopentene 1.173 – ¹H NMR (500 MHz)

Cyclopentene 1.173 – ^{13}C NMR (126 MHz)

14.1
22.6
24.5
28.6
29.7
30.2
31.9
46.0
48.3
57.1
83.5
127.3
137.5
176.2

f1 (ppm)
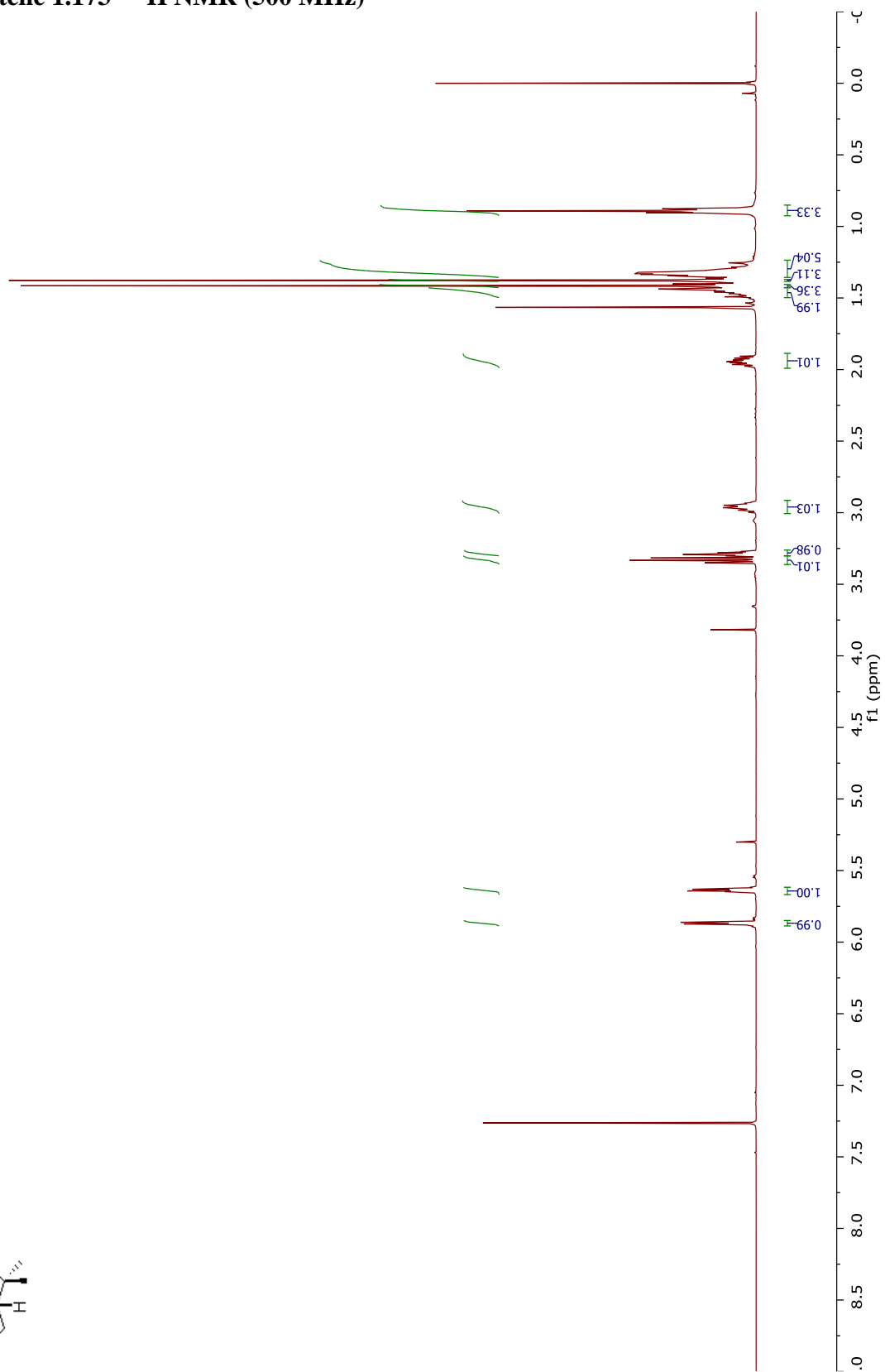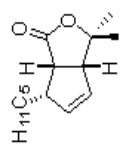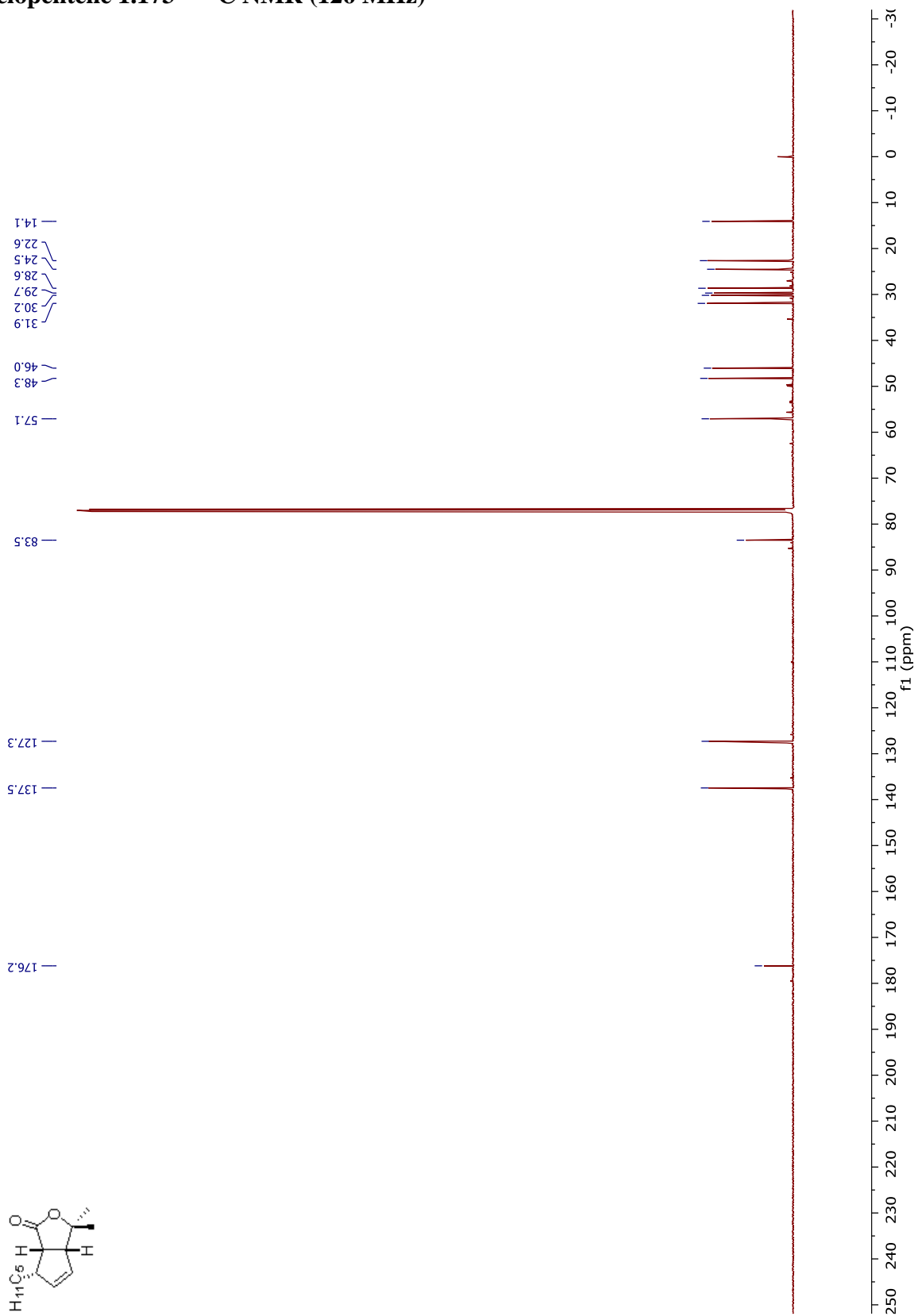
Aziridine 1.174 – ¹H NMR (500 MHz)

Cyclopentene 1.173 – ^{13}C NMR (126 MHz)

13.97

22.49
24.47
24.97
30.51
31.84
37.39

55.19
56.56

74.18
78.17
84.12

93.35

133.73
133.84

174.23
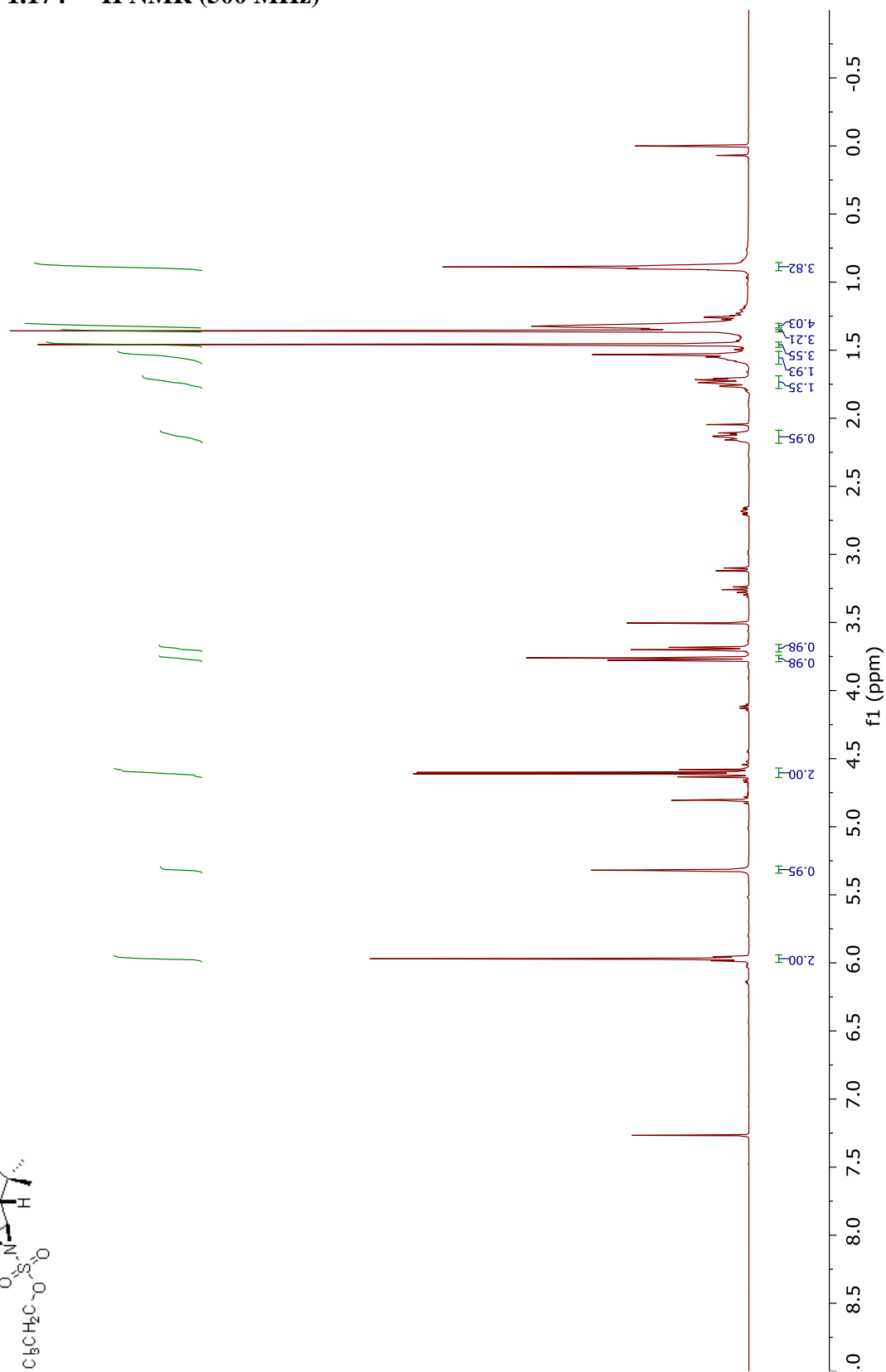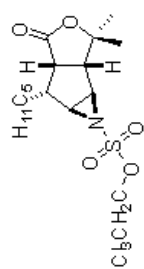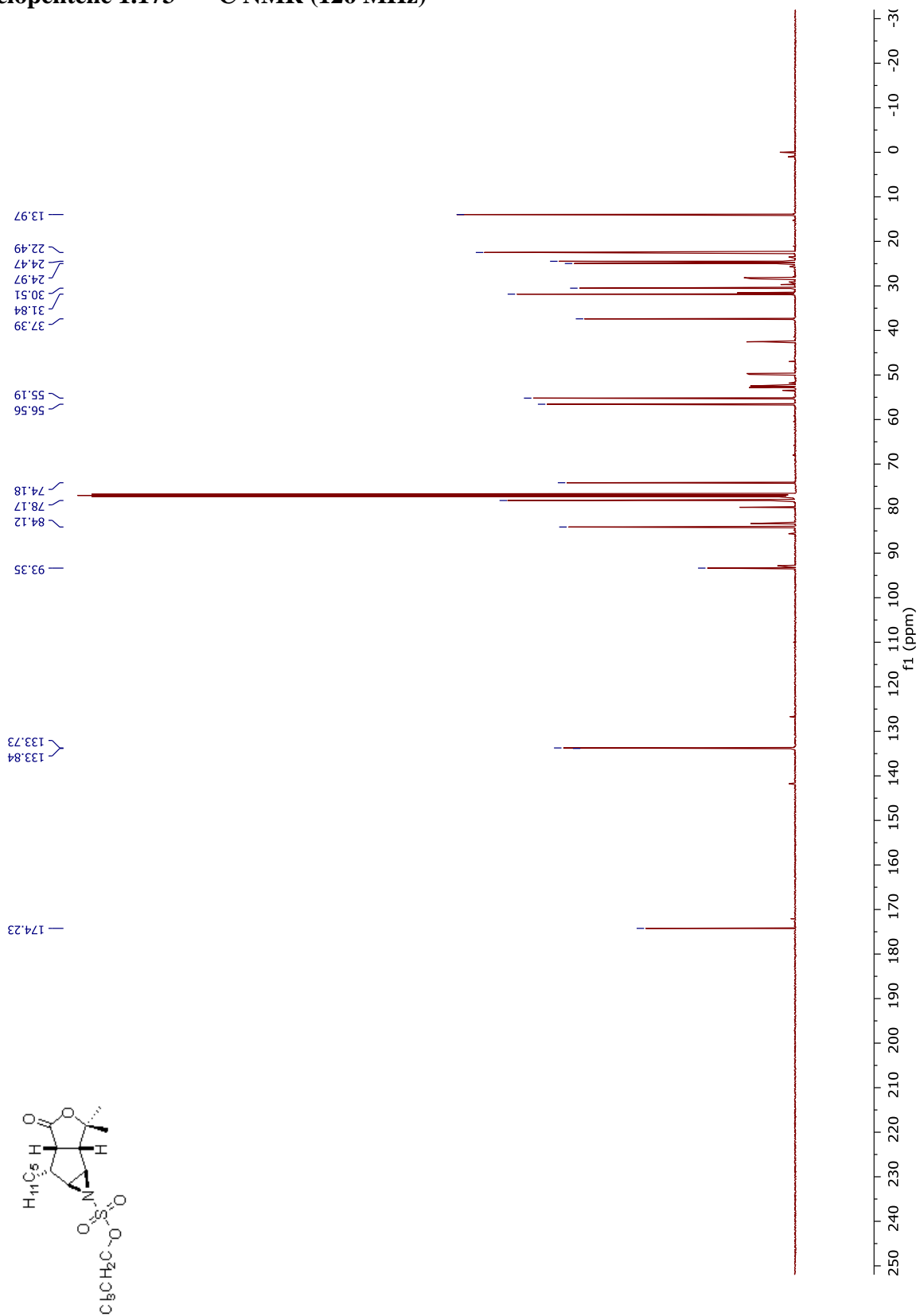
Lactone 2.137 – ¹H NMR (500 MHz)
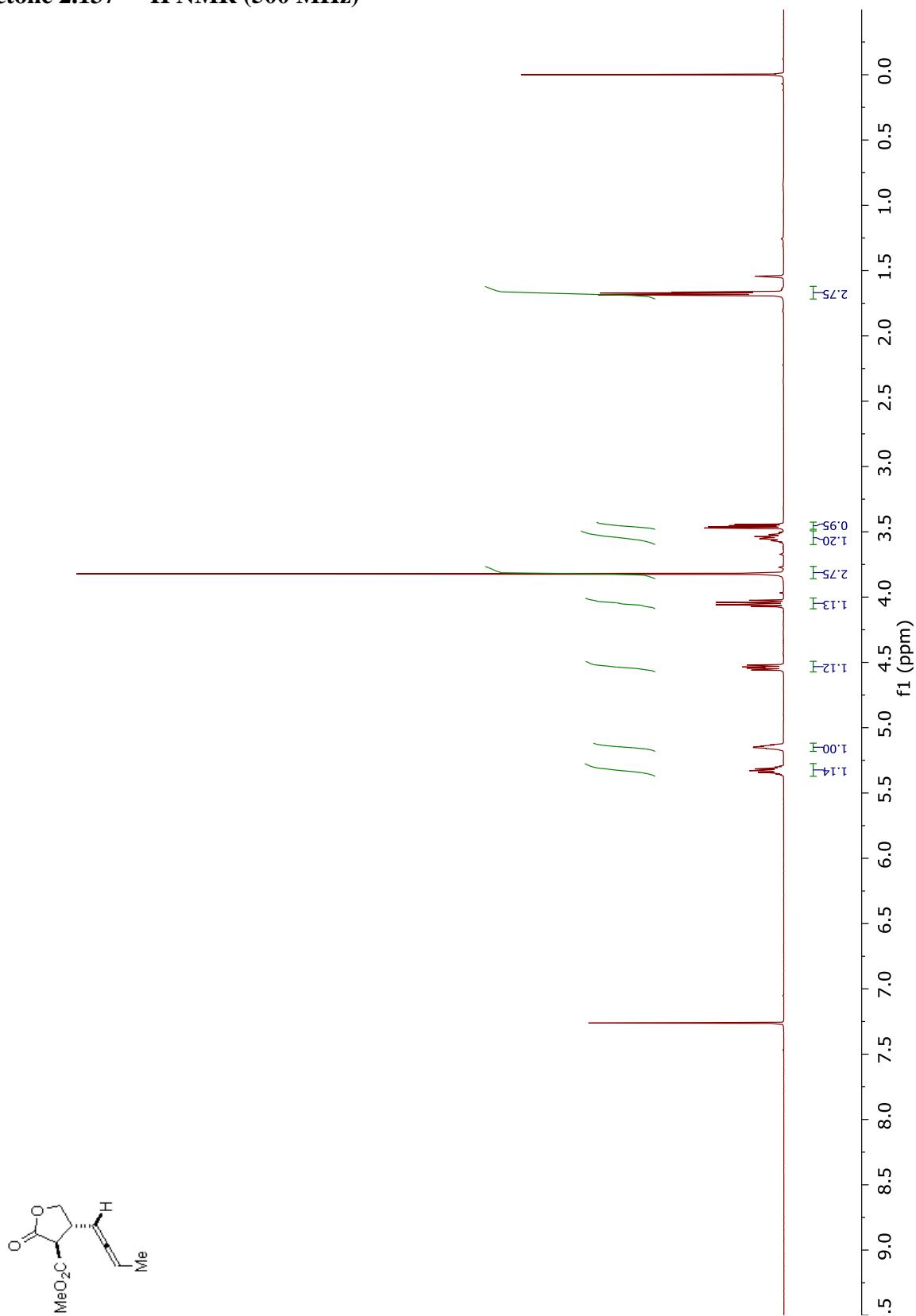
Lactone 2.137 – ^{13}C NMR (126 MHz)
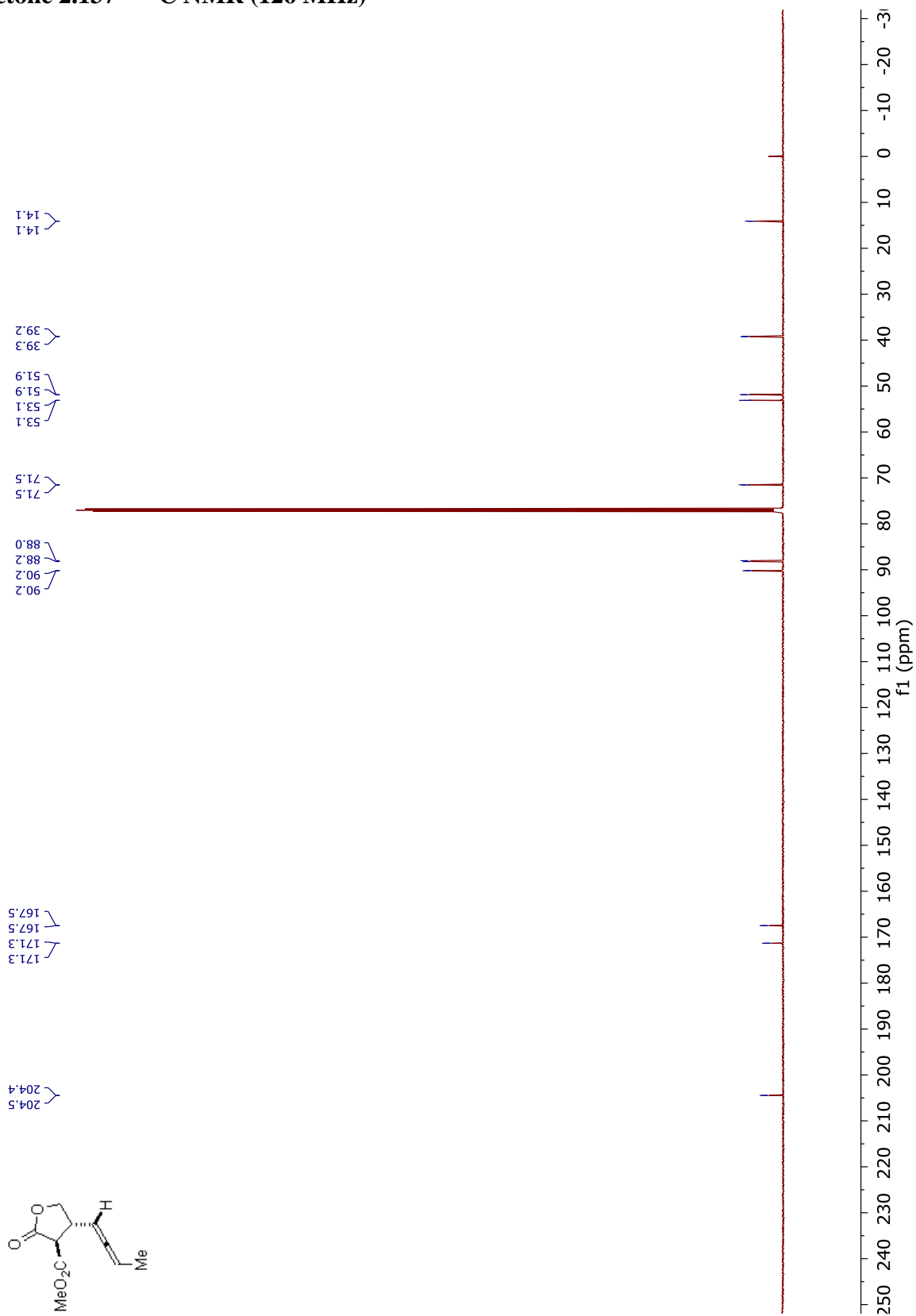
Lactone 2.141 – ¹H NMR (500 MHz)
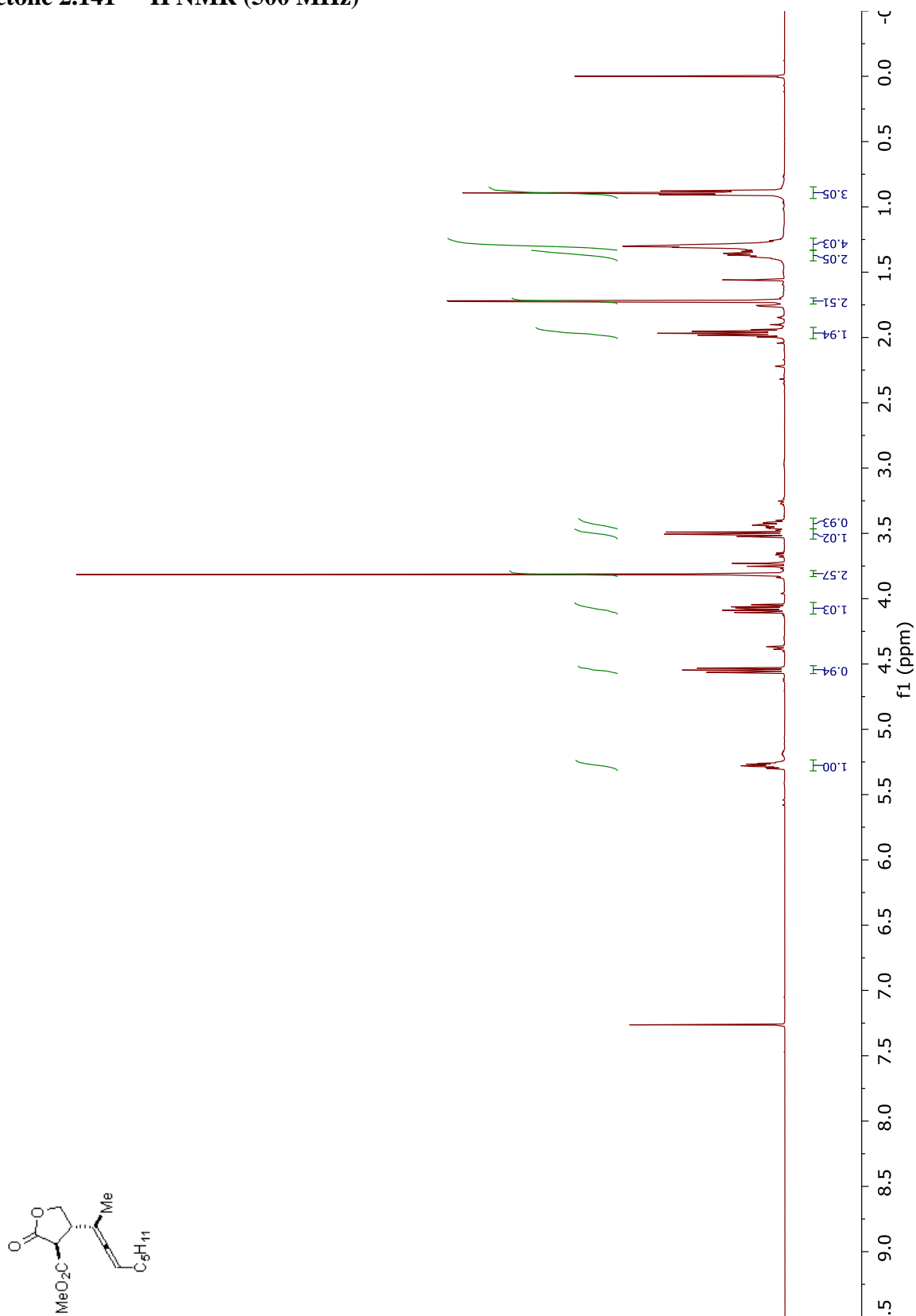
Lactone 2.141 – ¹³C NMR (126 MHz)

14.0
17.9
22.4
22.5
22.5
28.6
28.7
28.7
28.8
28.8
28.9
31.3
31.4
43.2
43.2
51.5
51.5
53.1
53.1

71.1
71.2

94.9
95.0
97.1
97.2

167.9
167.9
171.6

200.1
200.2

f1 (ppm)

250 240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30
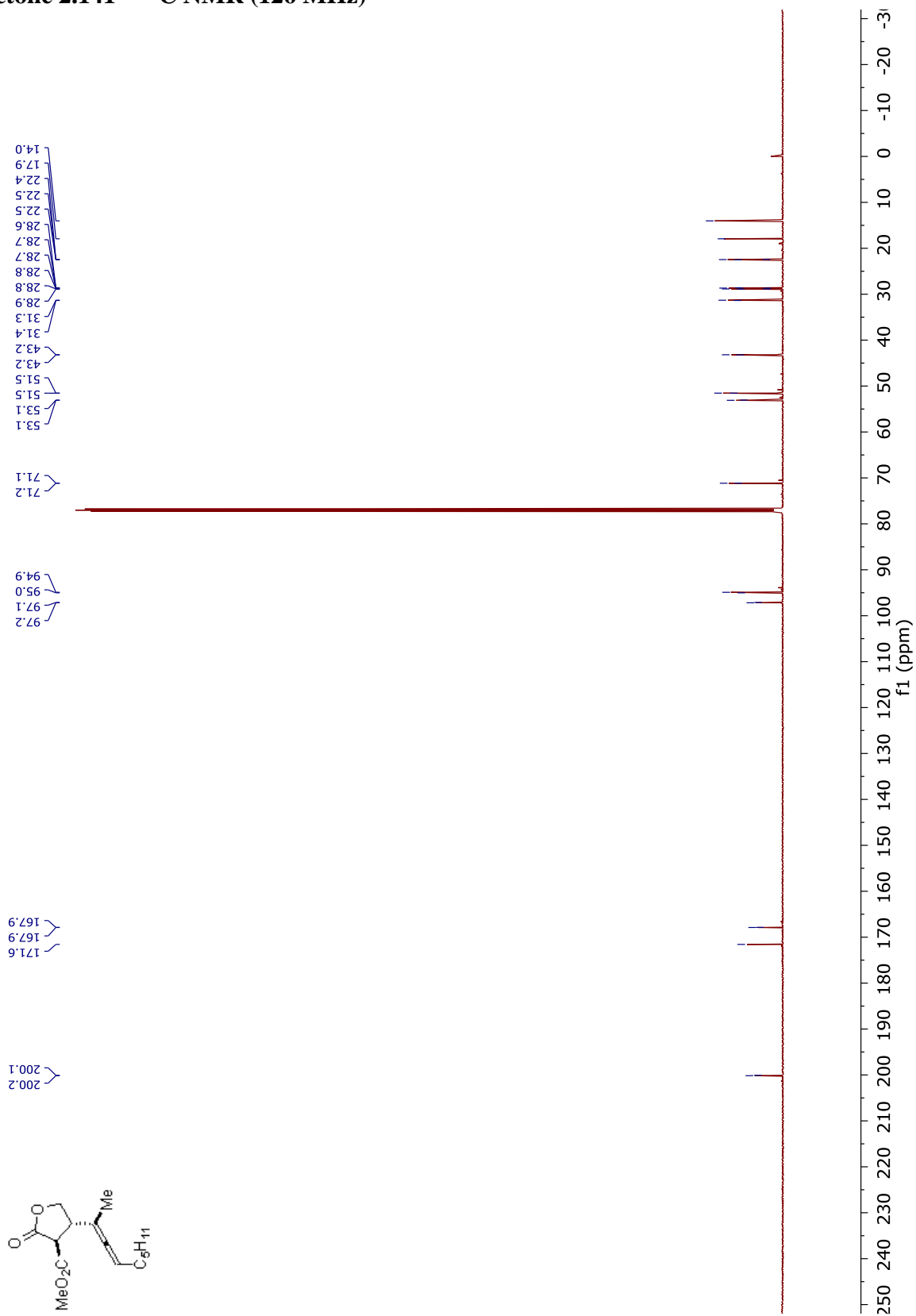
Lactone 2.142 – ¹H NMR (500 MHz)

Lactone 2.142 – ^{13}C NMR (126 MHz)

14.04
14.06
15.09
15.85
18.97
19.02
22.44
22.46
22.48
24.96
28.55
28.58
28.66
28.76
28.81
28.89
28.95
29.21
31.28
31.34
31.37

46.52
46.55
46.70
46.95
52.53
52.55
52.58
55.75
55.89
58.09
58.15
75.99
76.26

93.35
93.40
94.67
94.68
98.62
98.75
101.44

166.70
166.80
167.47
167.56
171.93
172.06
172.18
172.20

200.52
200.79
200.84
200.85

f1 (ppm)
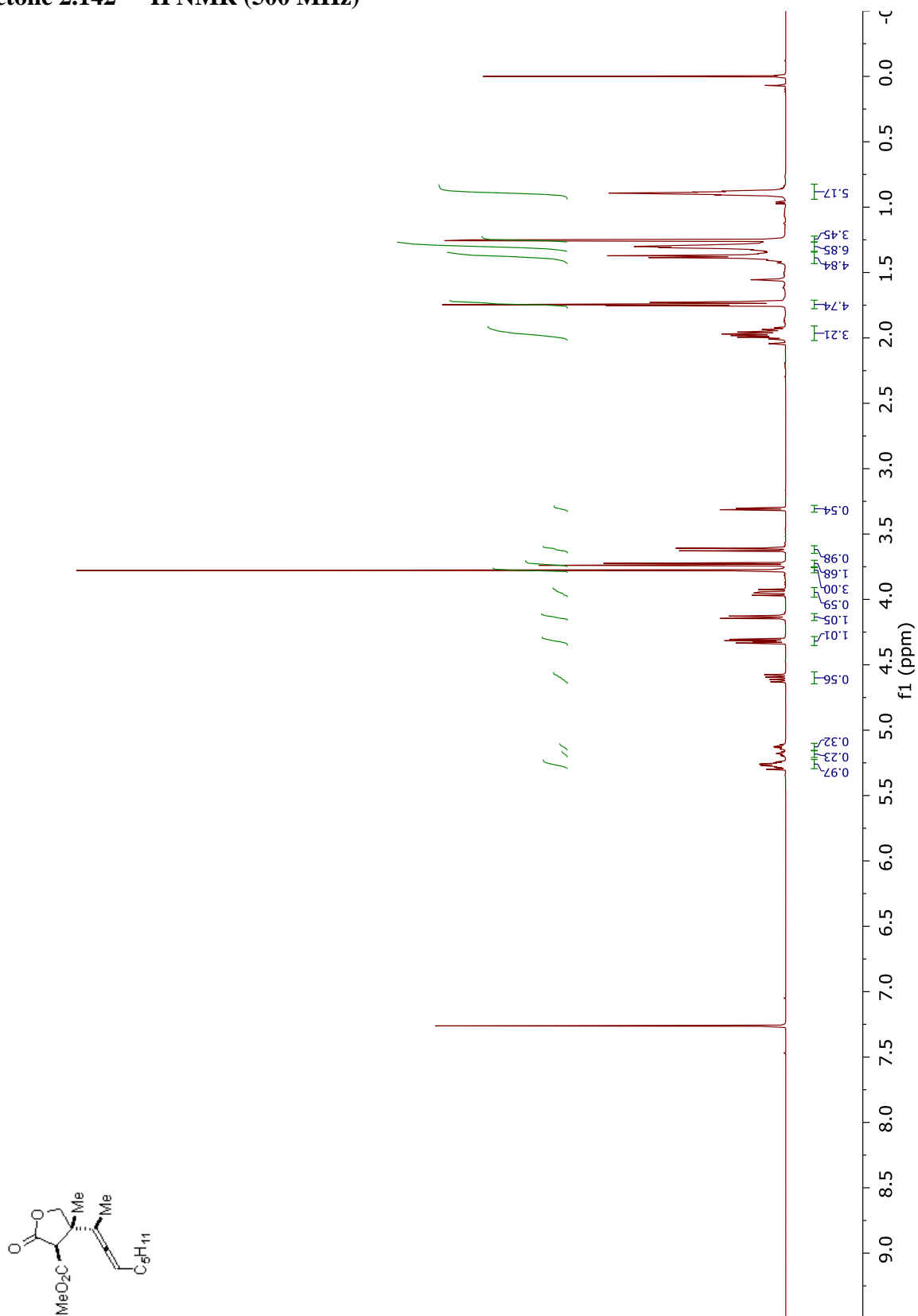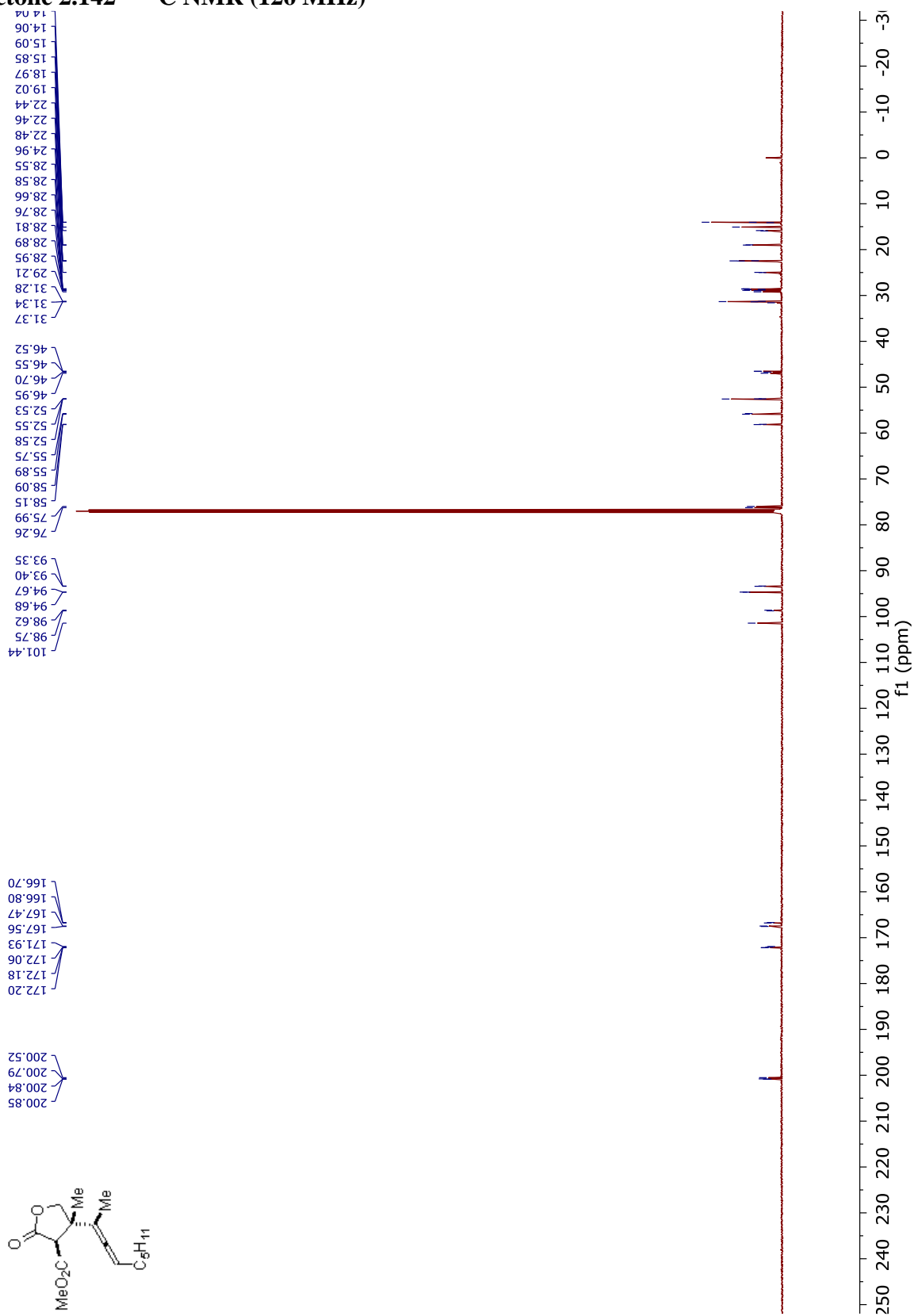
Lactone 2.143 – ¹H NMR (500 MHz)

Lactone 2.142 – ^{13}C NMR (126 MHz)

203.62

171.47
167.76

112.10

81.17
73.61

53.03
52.96

38.37
33.16
29.12
29.09

f1 (ppm)
250 240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -3
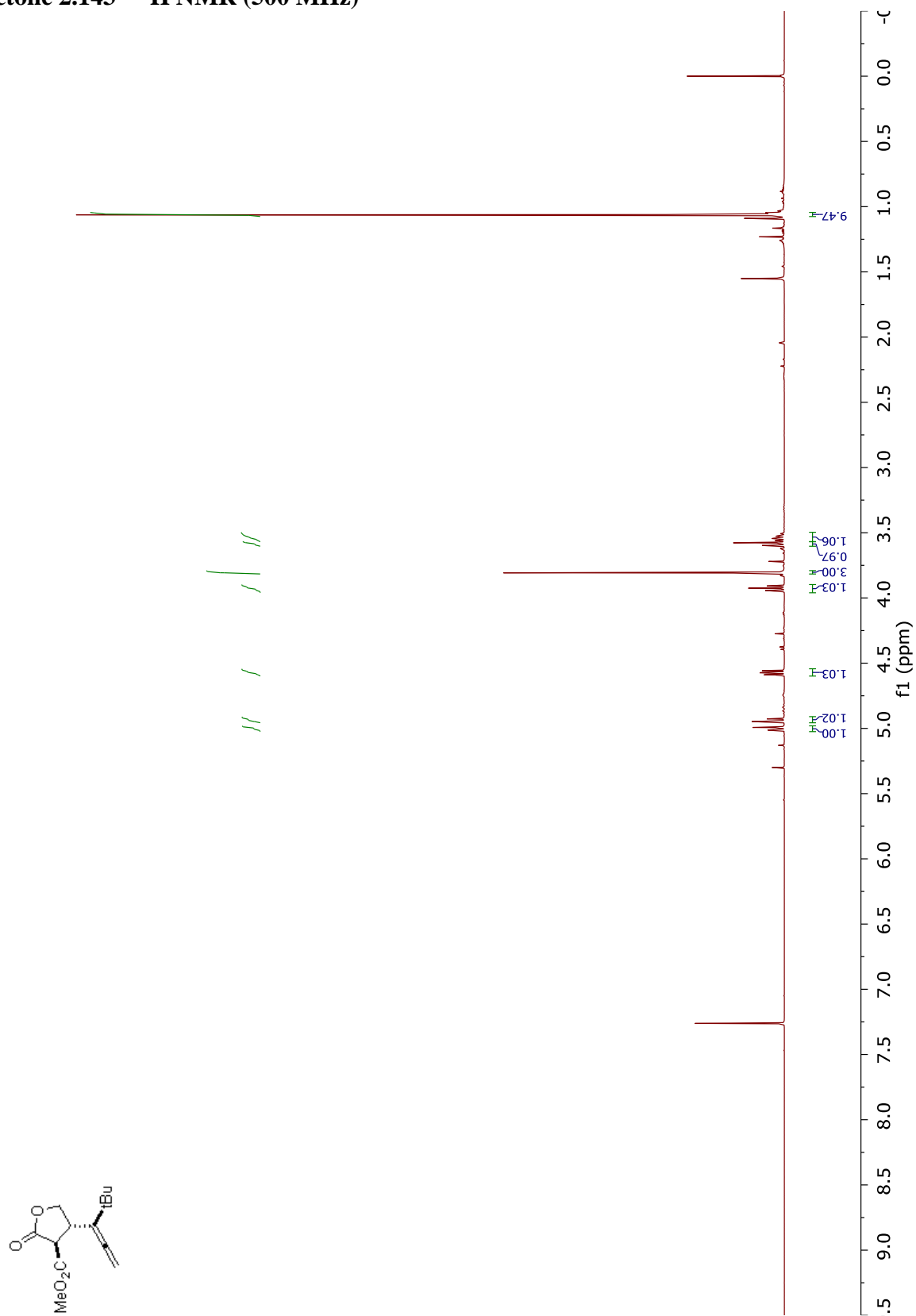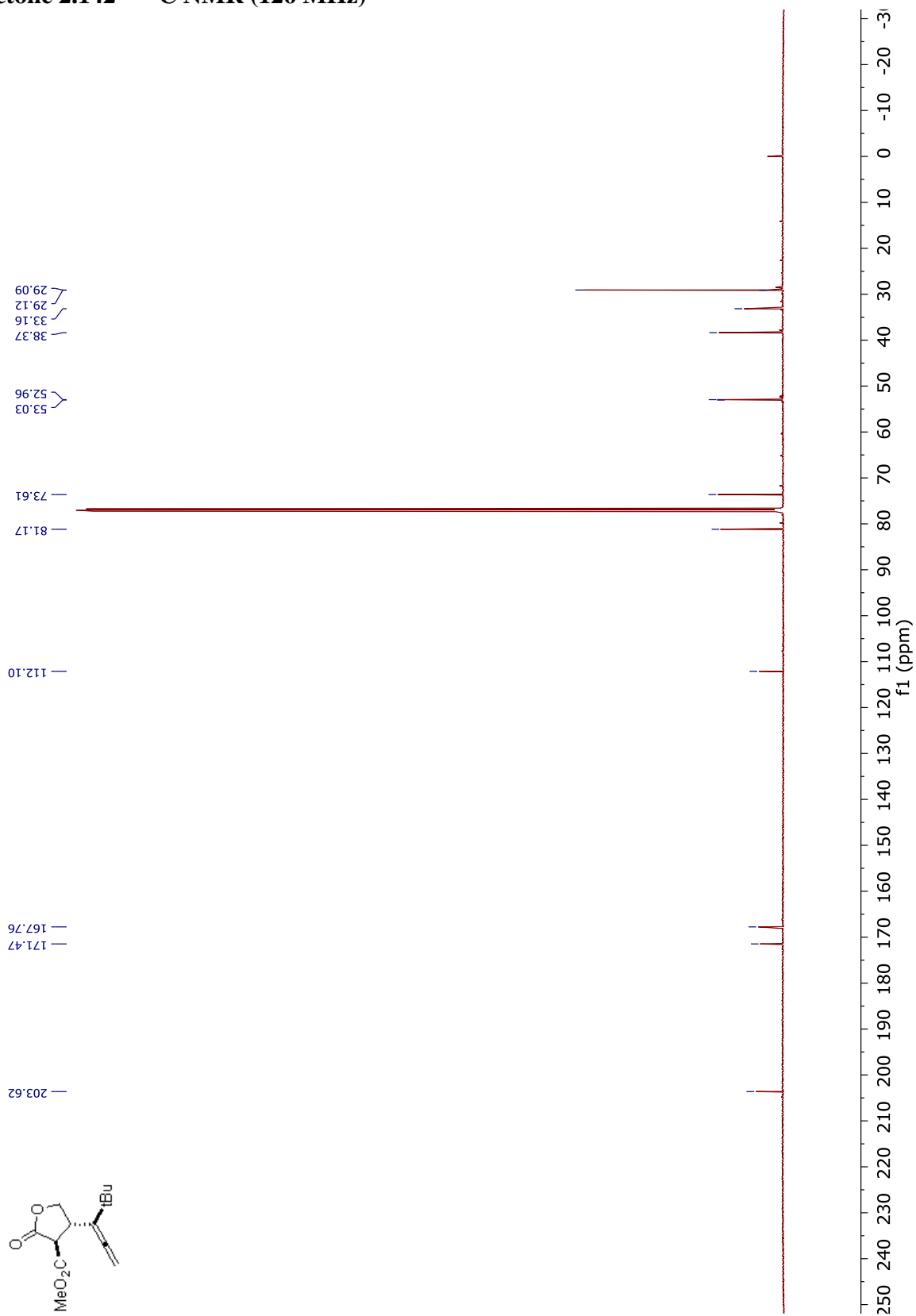
Lactone 2.163 – ¹H NMR (500 MHz)
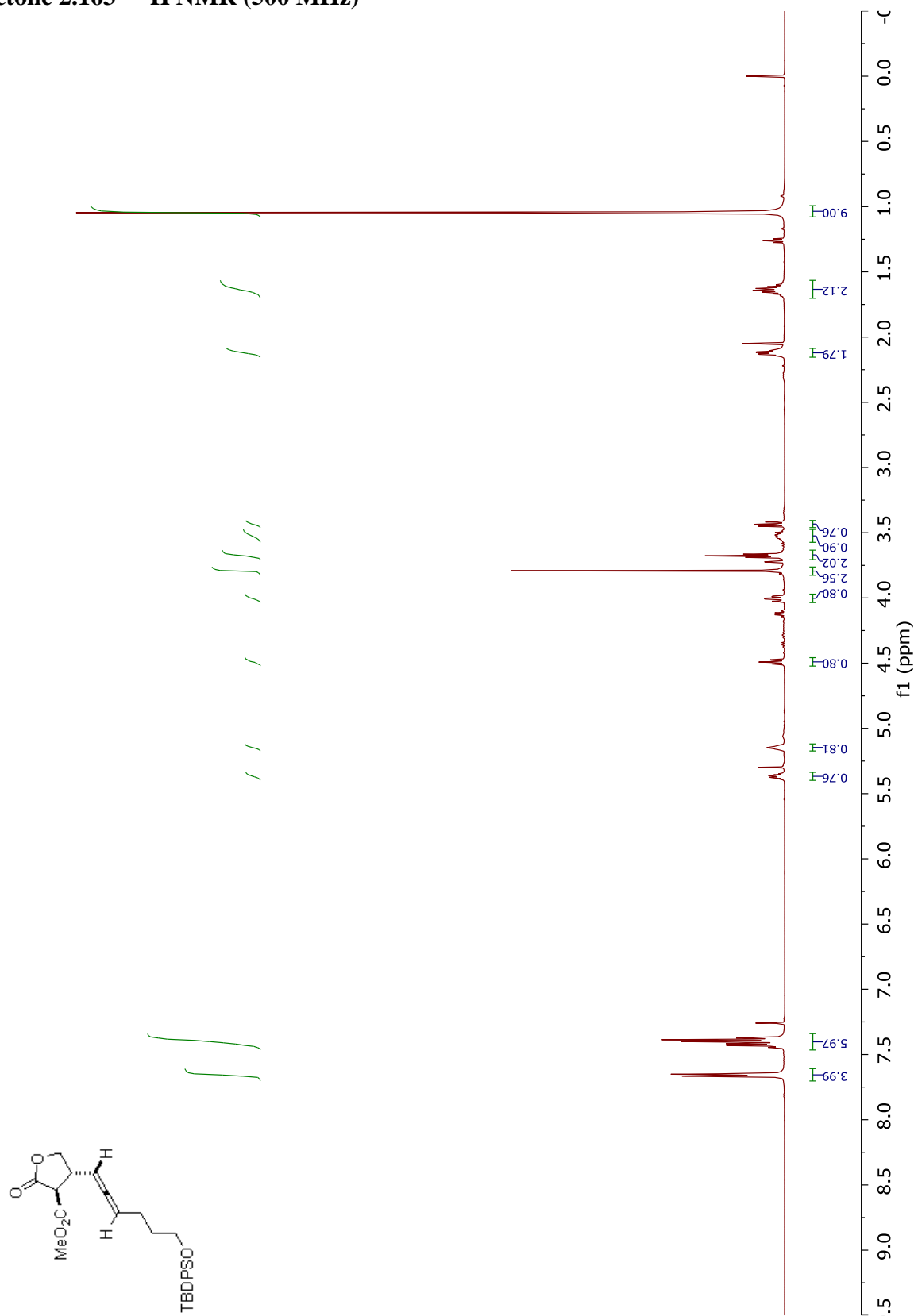
Lactone 2.163 – ¹³C NMR (126 MHz)
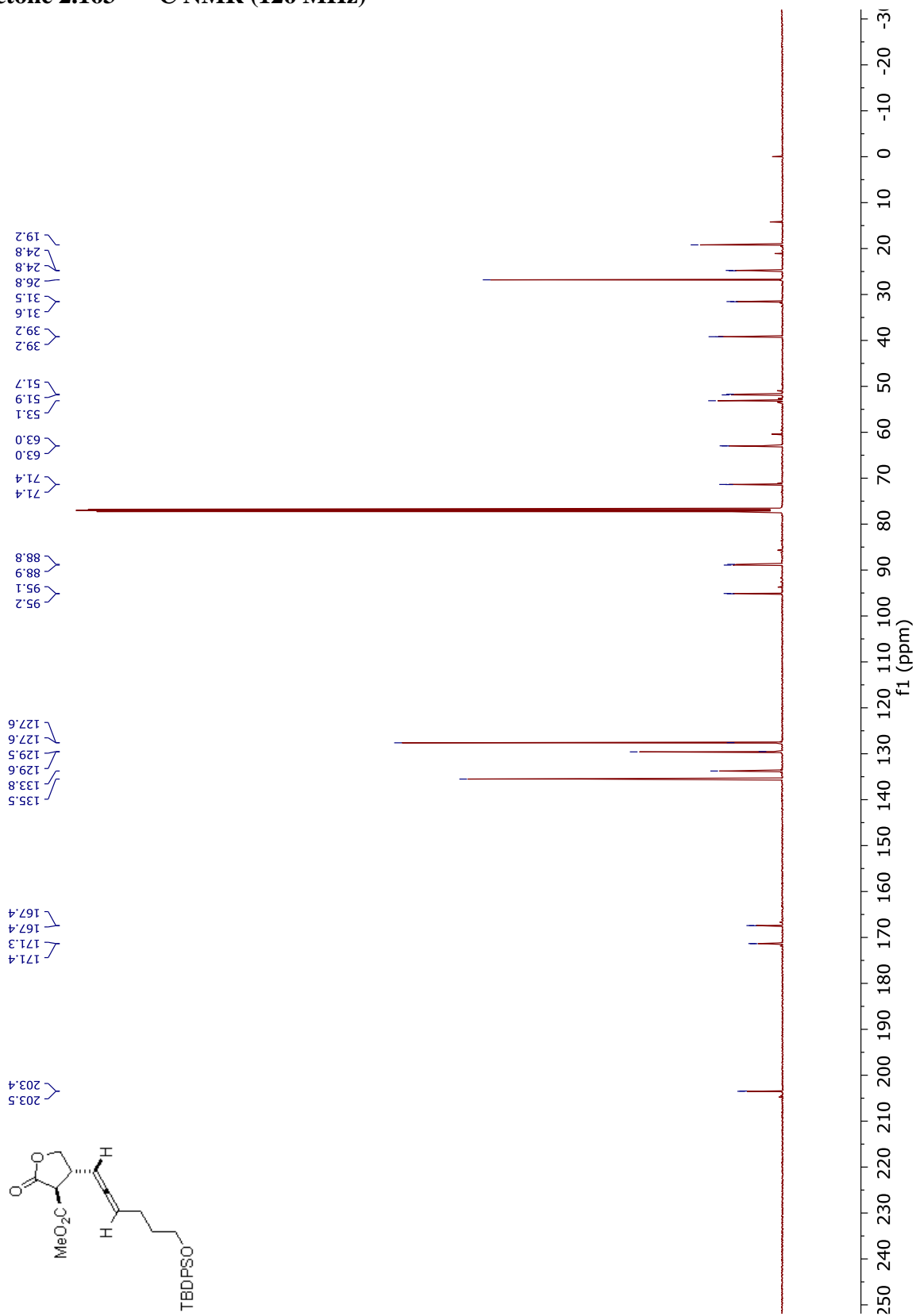
Cyclopentene 2.145 – ¹H NMR (500 MHz)
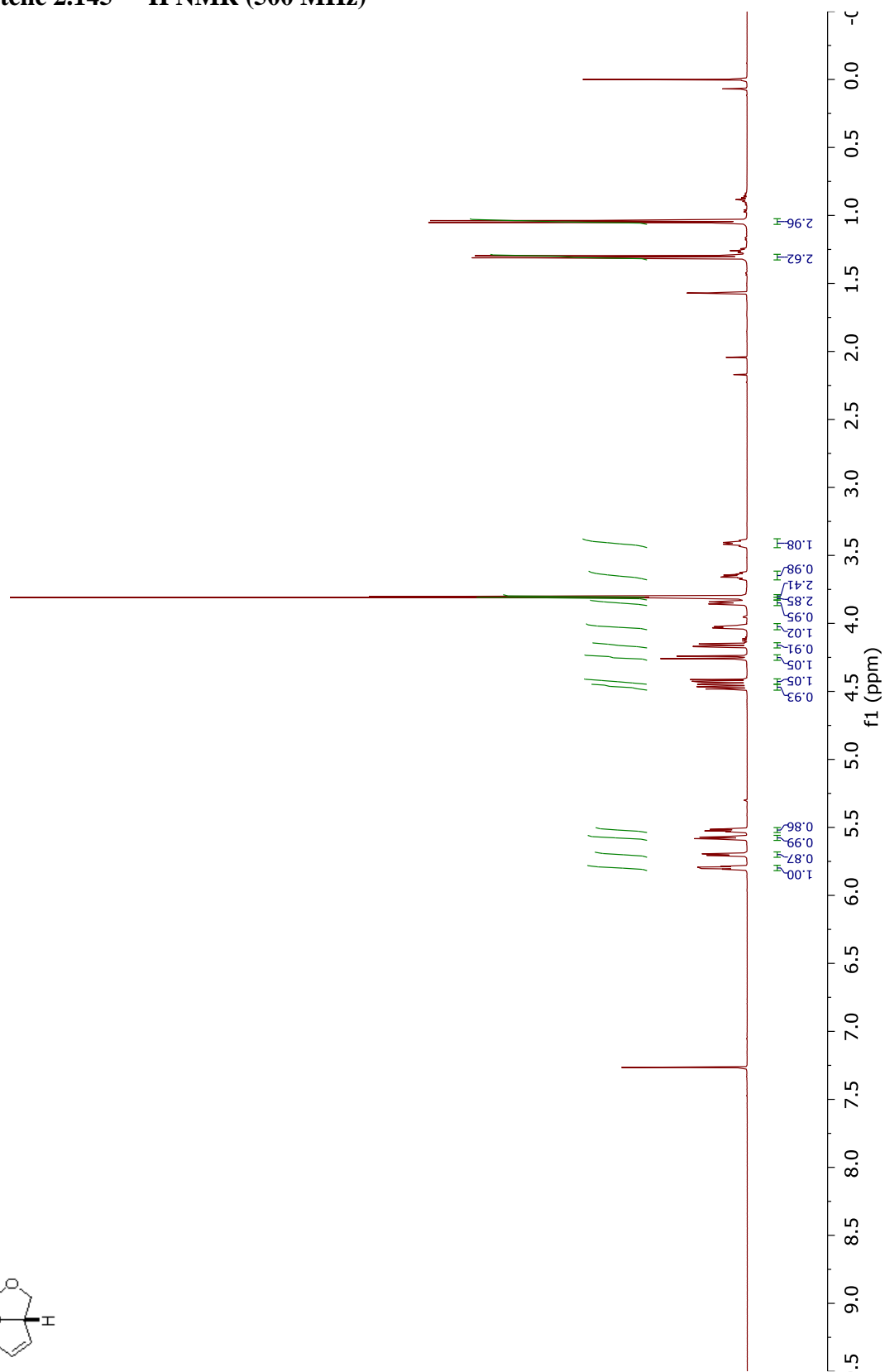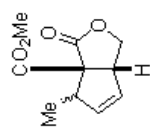
Cyclopentene 2.145 – ¹³C NMR (126 MHz)

15.5
16.8

46.1
47.5
48.6
53.0
53.2

61.8
64.0
70.3
70.4

127.3
128.3

137.5
138.0

167.3
169.9
172.9
175.3

f1 (ppm)
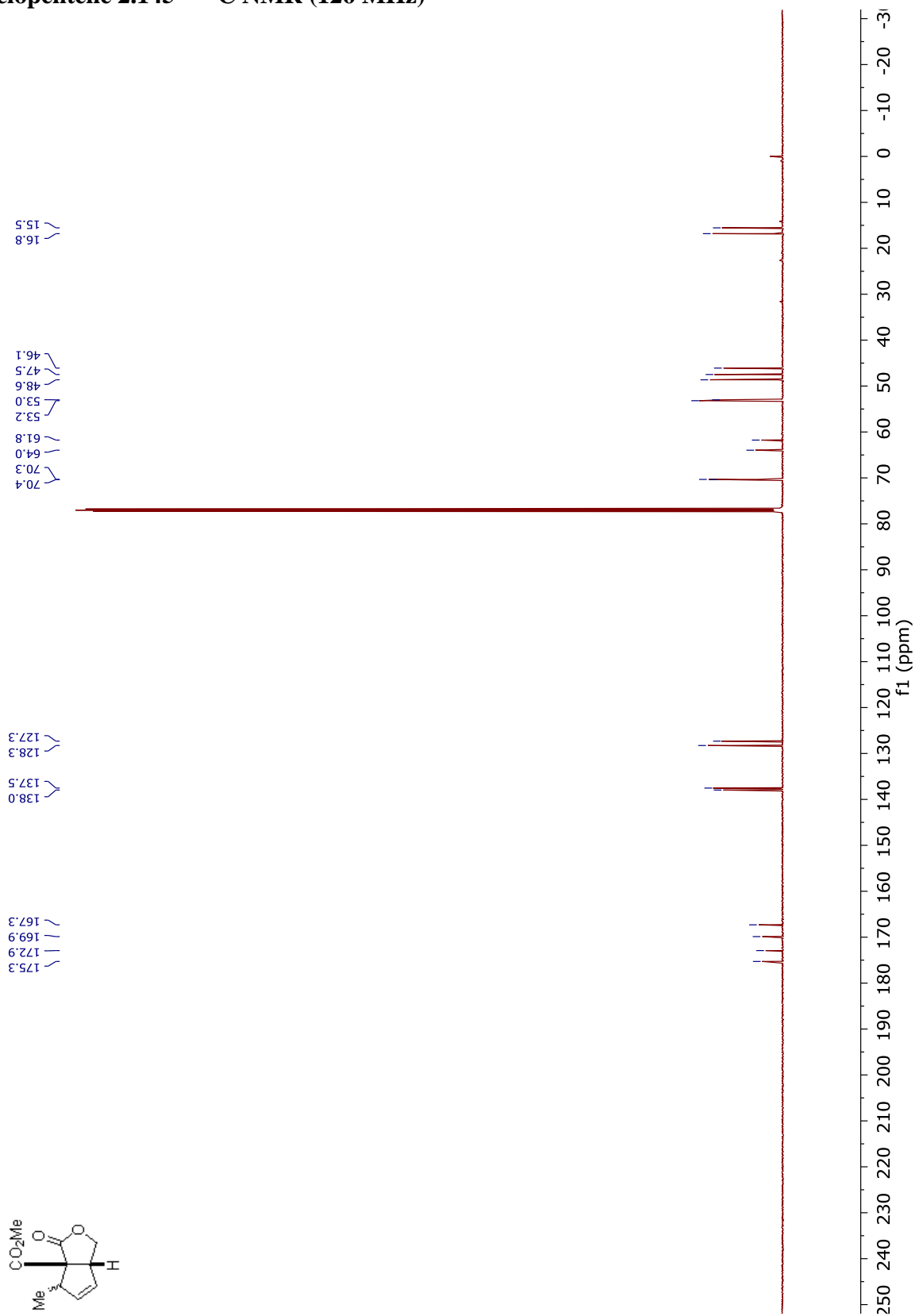
Cyclopentene 2.149 – ¹H NMR (500 MHz)
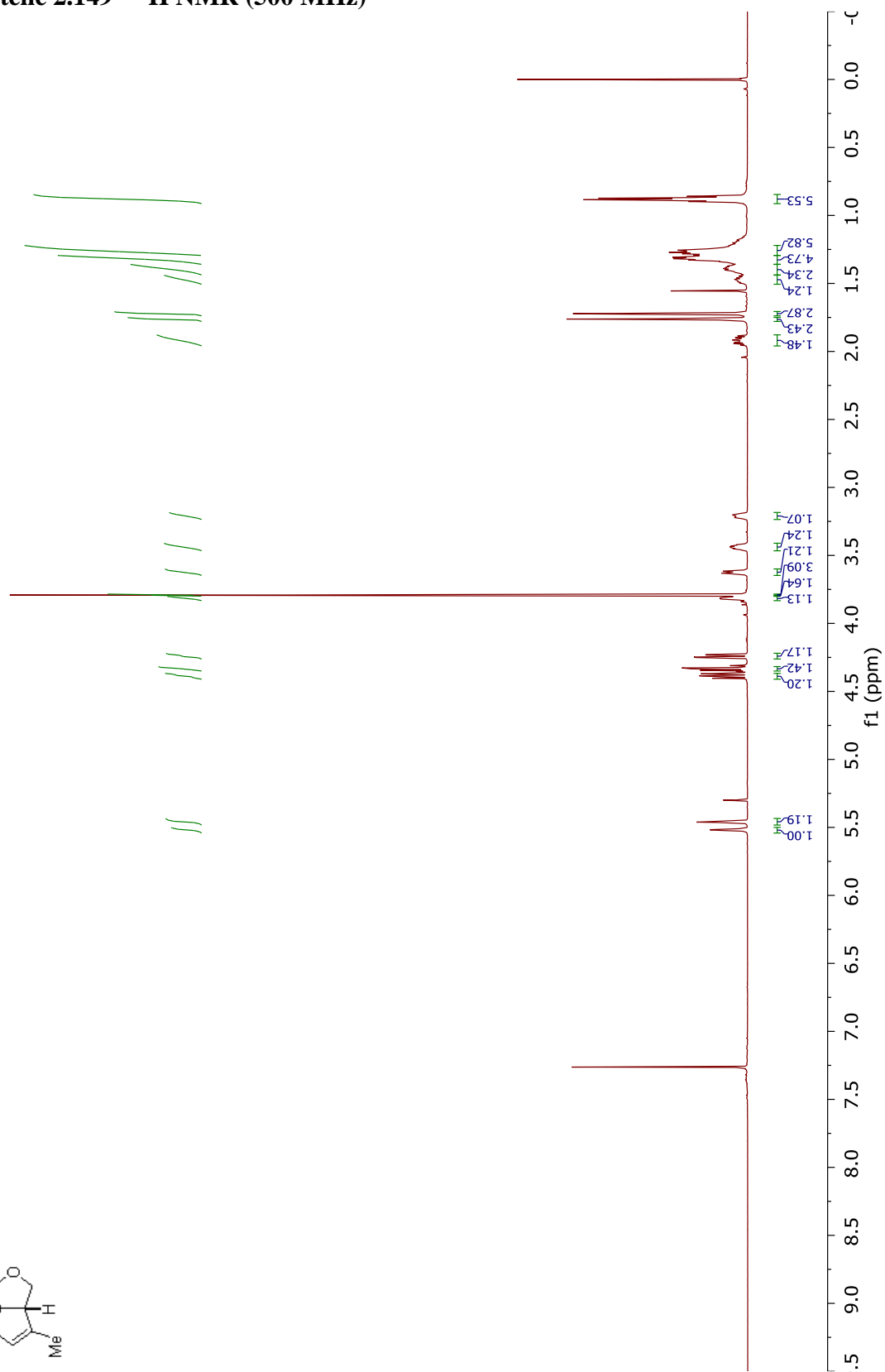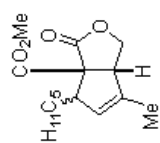
Cyclopentene 2.149 – ^{13}C NMR (126 MHz)

14.0
14.1
14.1
22.5
22.6
26.4
28.4
30.5
31.9
31.9
32.0
50.8
51.2
51.7
52.9
53.1
56.0
61.9
64.2
68.0
68.1

130.0
130.1
135.0
136.5

167.5
170.3
173.1
175.7

f1 (ppm)
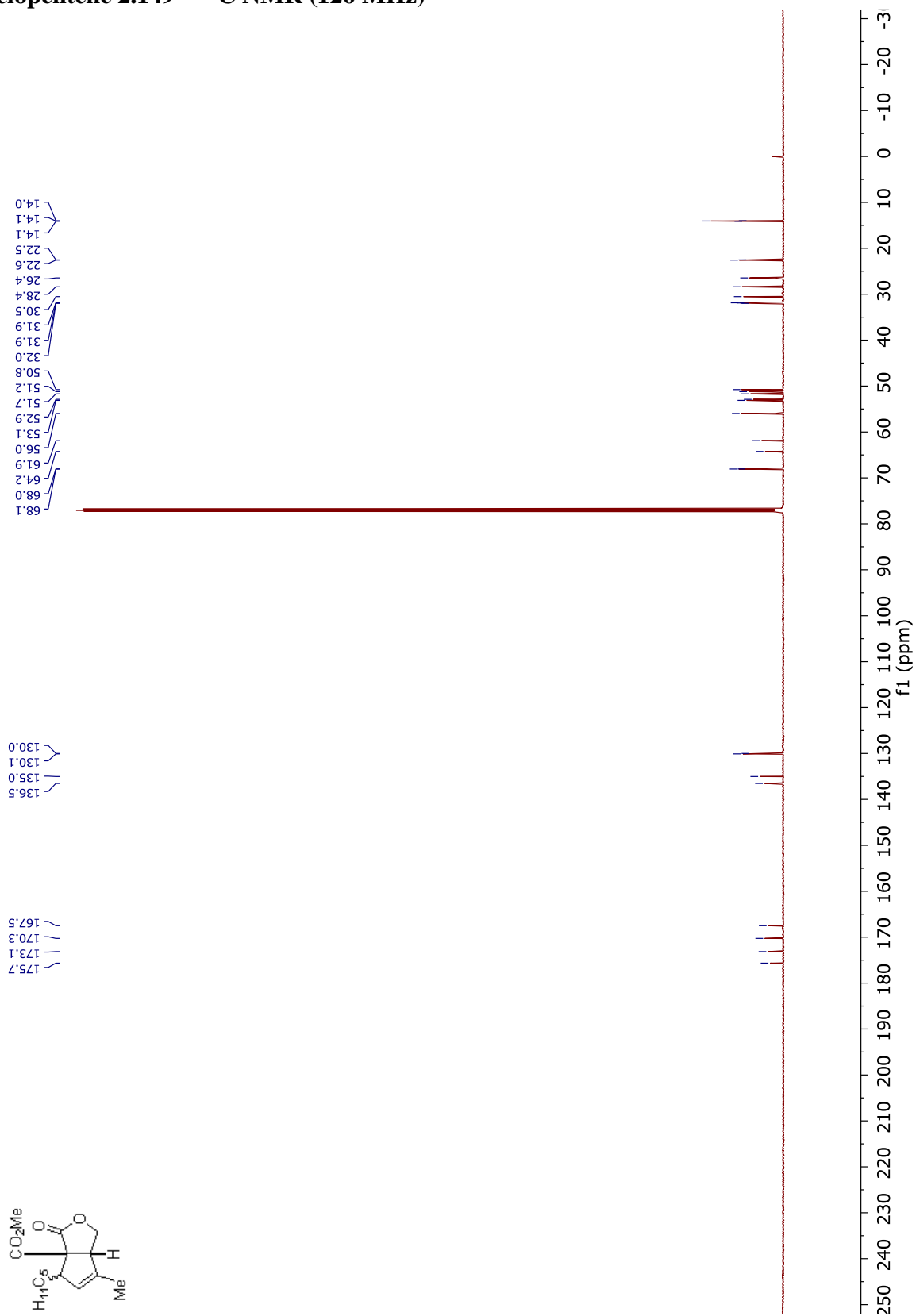
Cyclopentene 2.150 – ¹H NMR (500 MHz)
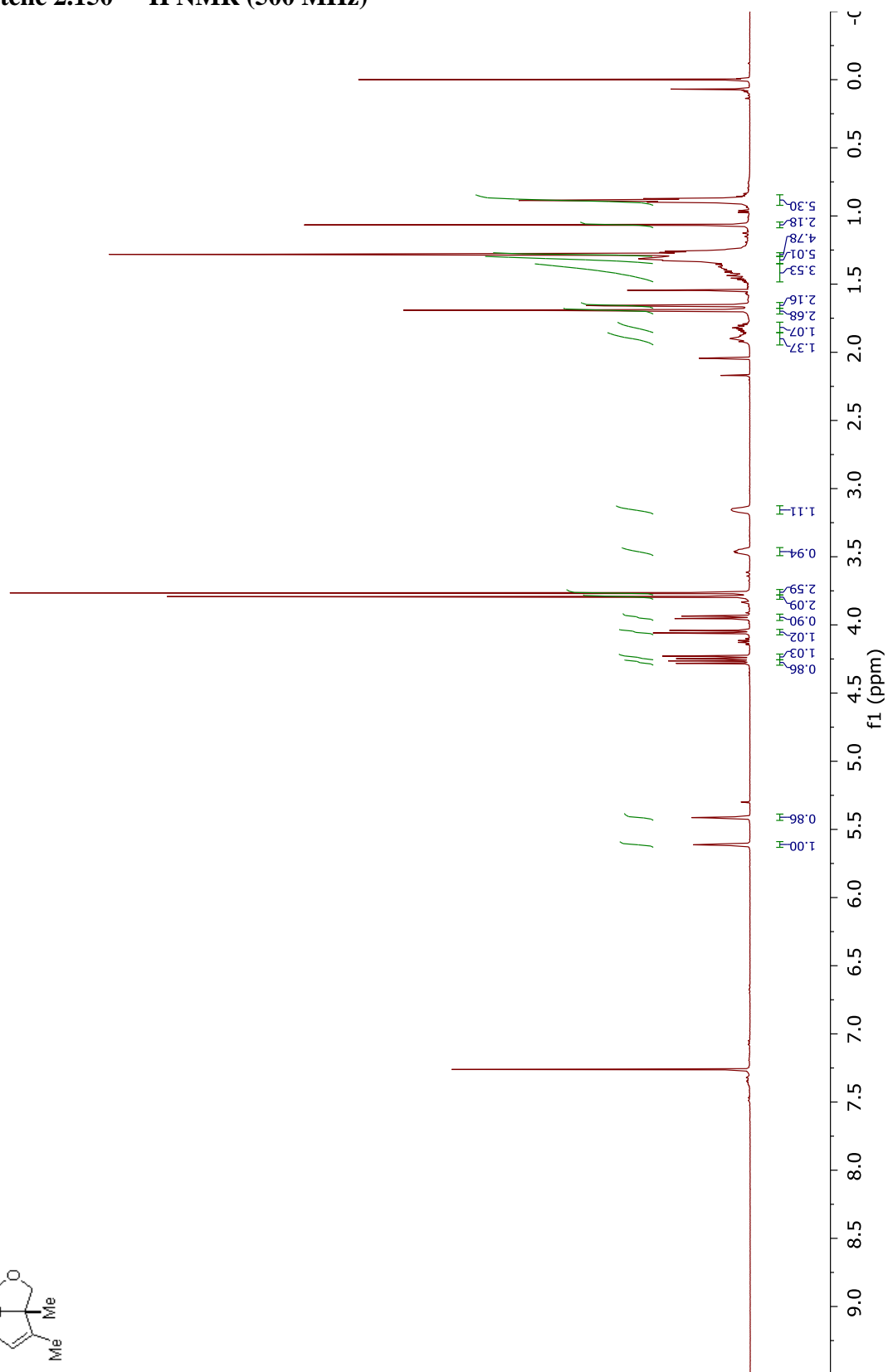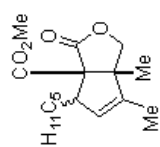
Cyclopentene 2.150 – ^{13}C NMR (126 MHz)
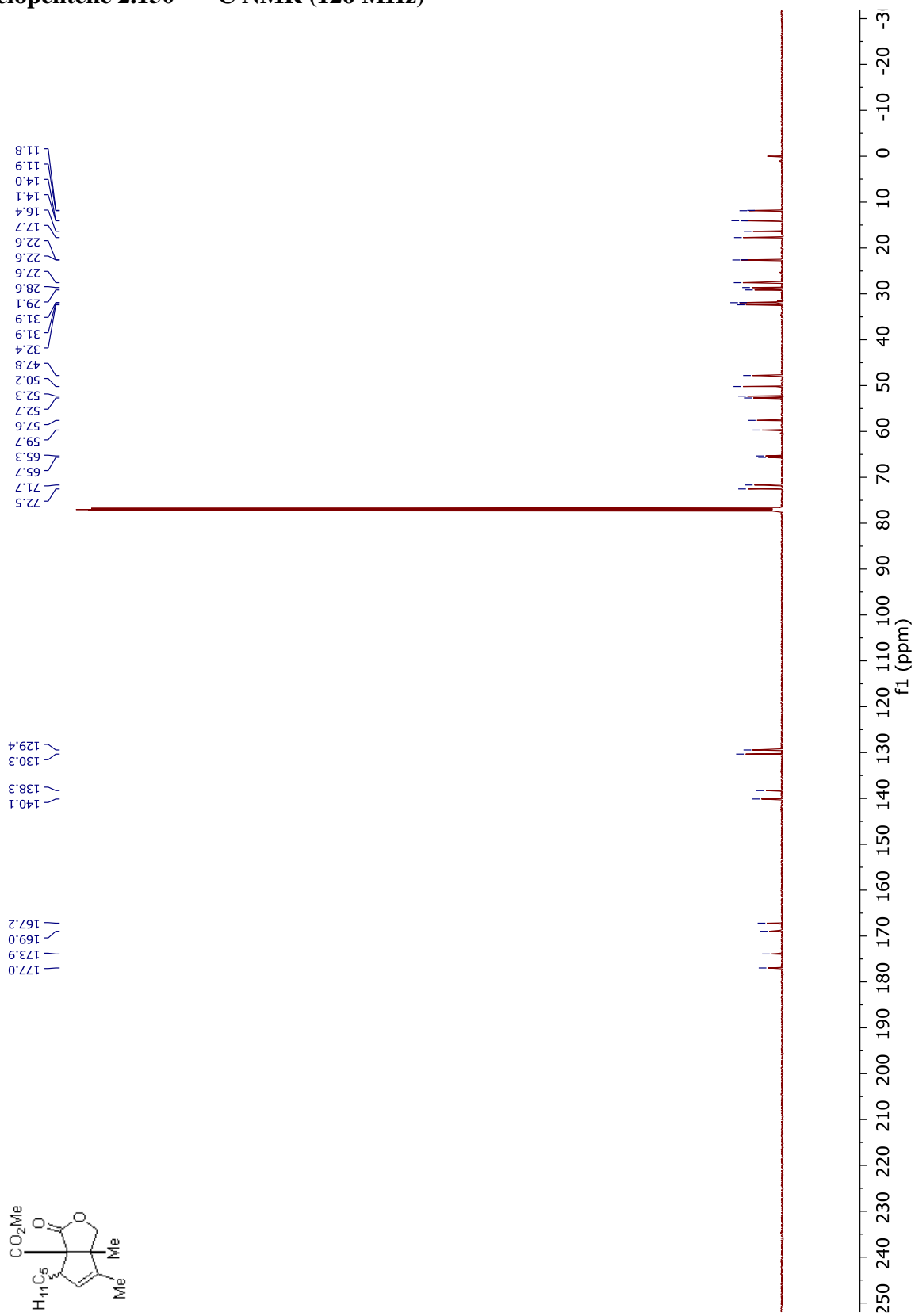
Cyclopentene 2.151 – ¹H NMR (500 MHz)
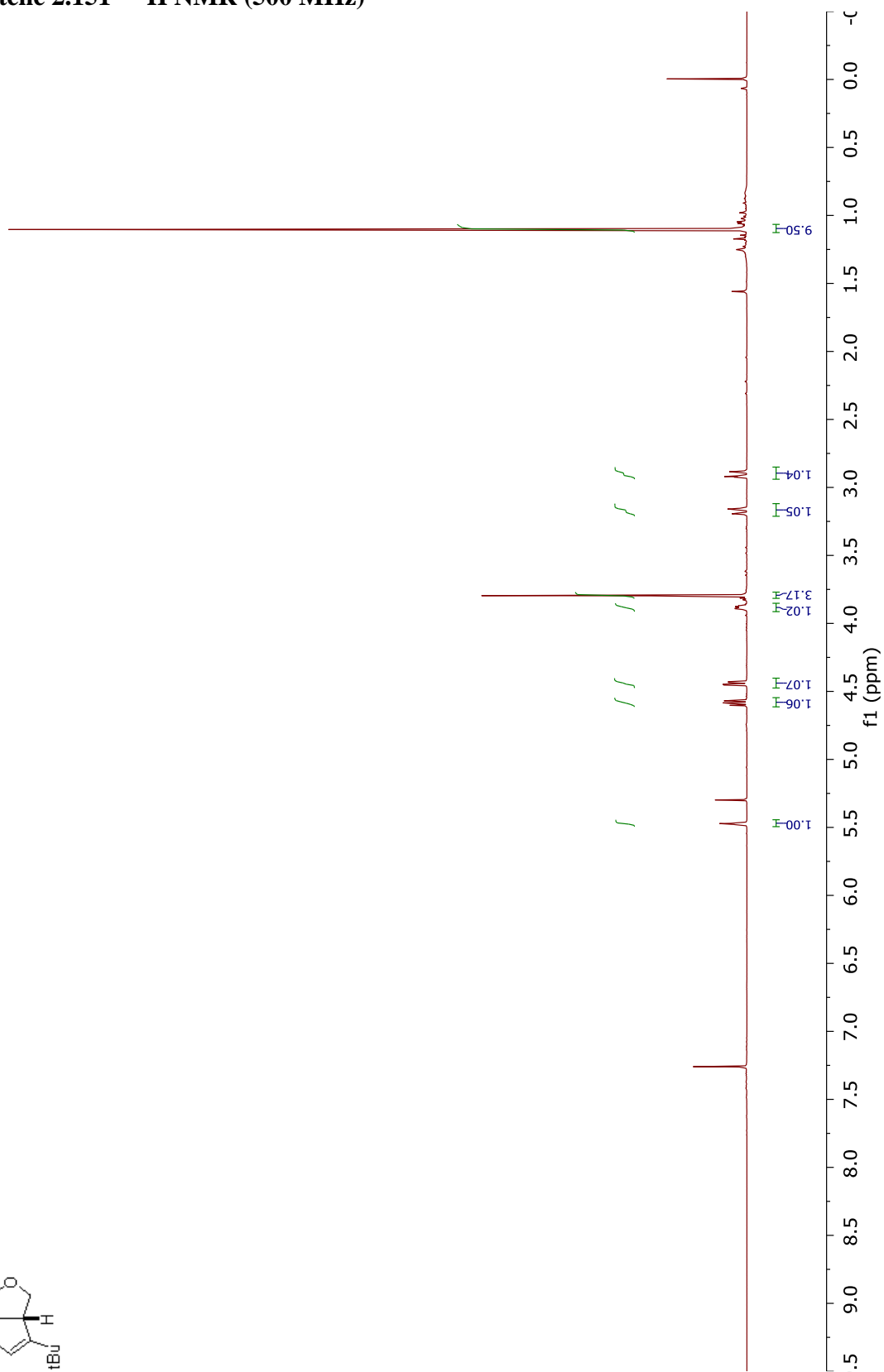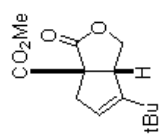
Cyclopentene 2.151 – ¹³C NMR (126 MHz)

30.29
33.01
38.99

53.12
53.25
59.94

71.54

123.13

150.17

169.94
176.18

f1 (ppm)

250 240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -3(
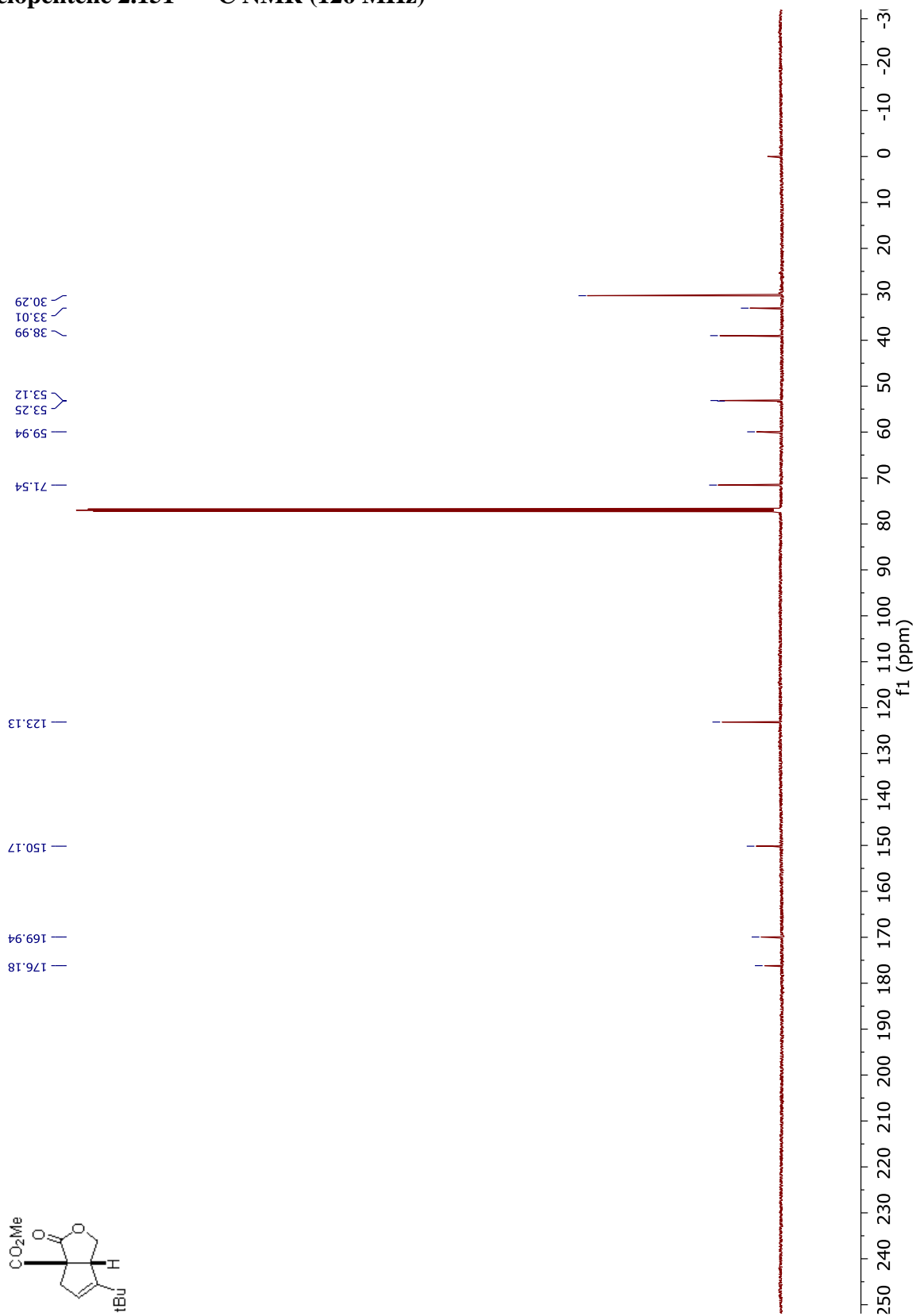
Cyclopentene 2.155 – ¹H NMR (500 MHz)
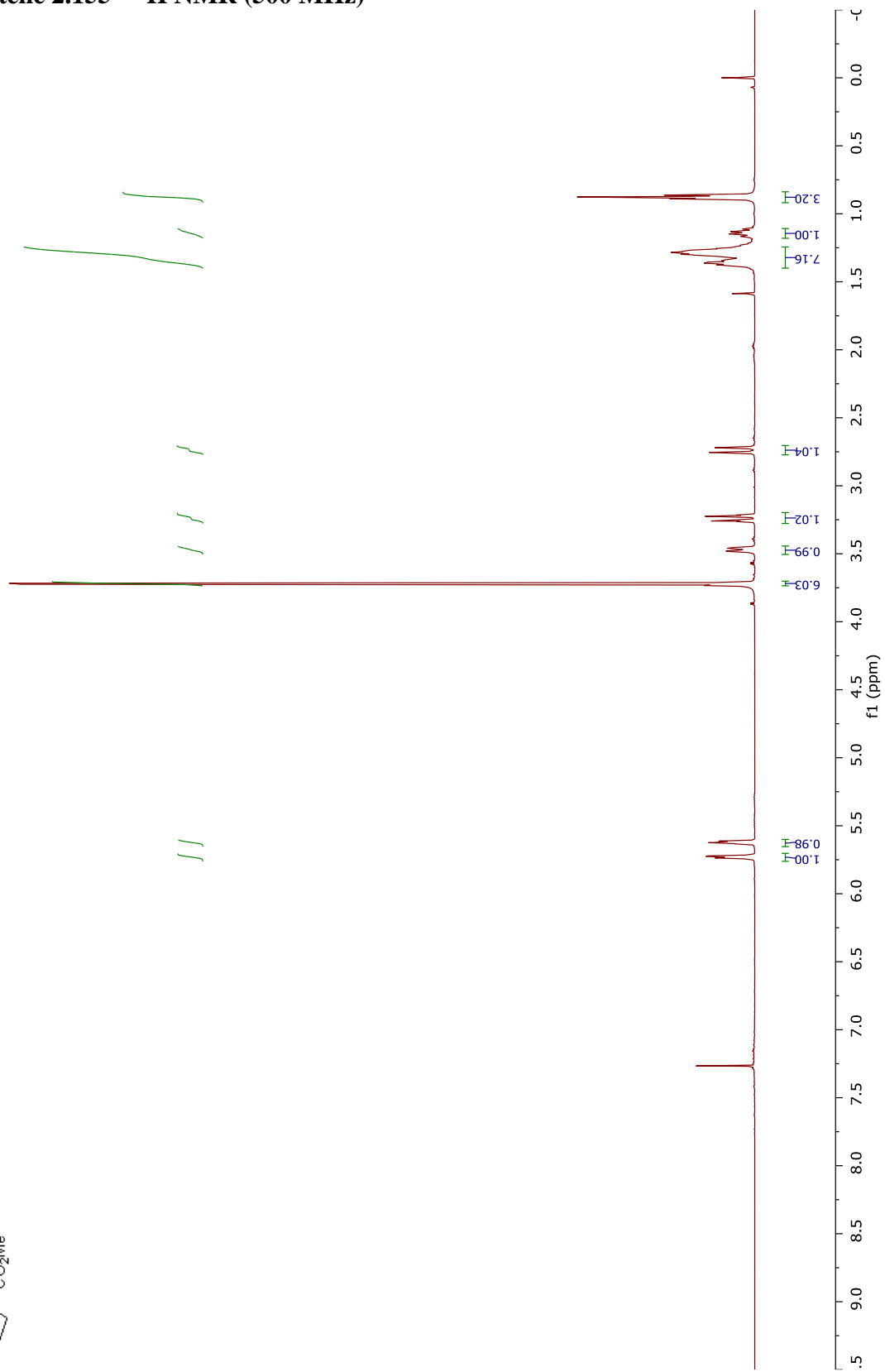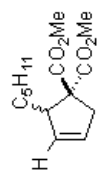
Cyclopentene 2.155 – ^{13}C NMR (126 MHz)

14.0

22.6
27.4
30.9
32.0

40.0

50.4
52.2
52.7

63.5

127.0
132.7

171.0
172.8

C$_5$H$_{11}$
CO$_2$Me
CO$_2$Me
H

f1 (ppm)

250 240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30
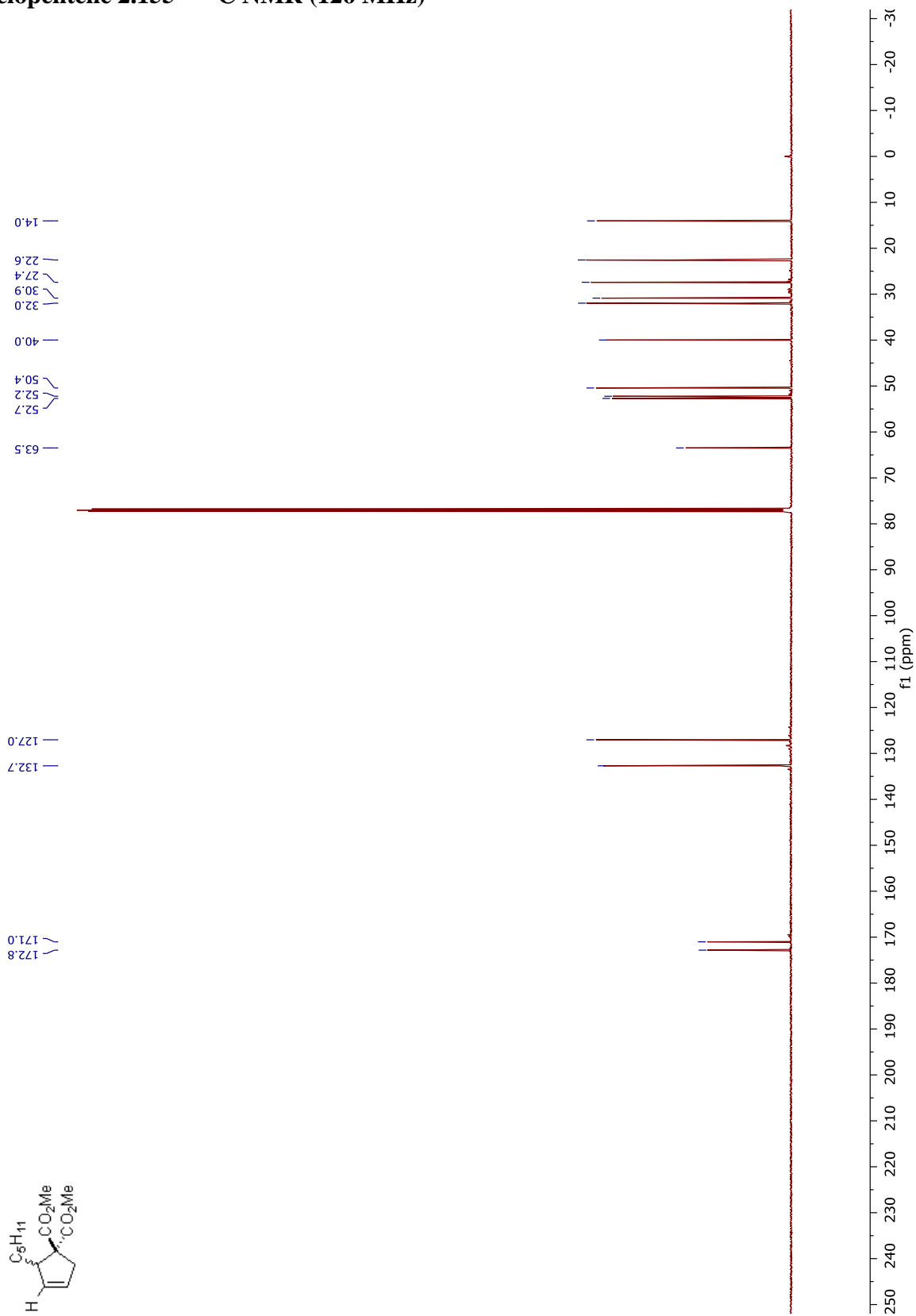
Cyclopentene 2.162 – ¹H NMR (500 MHz)
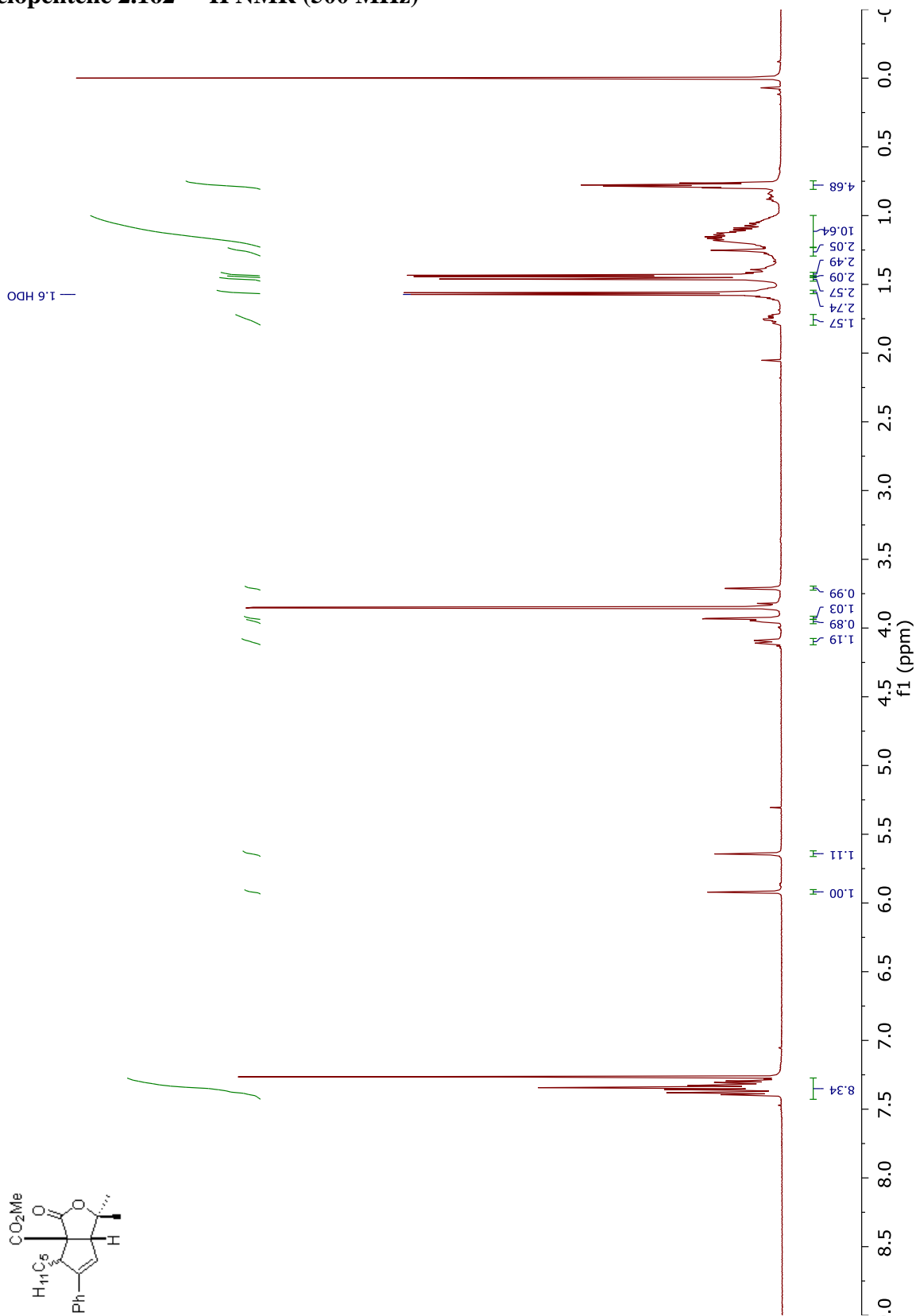
Cyclopentene 2.162 – ^{13}C NMR (126 MHz)
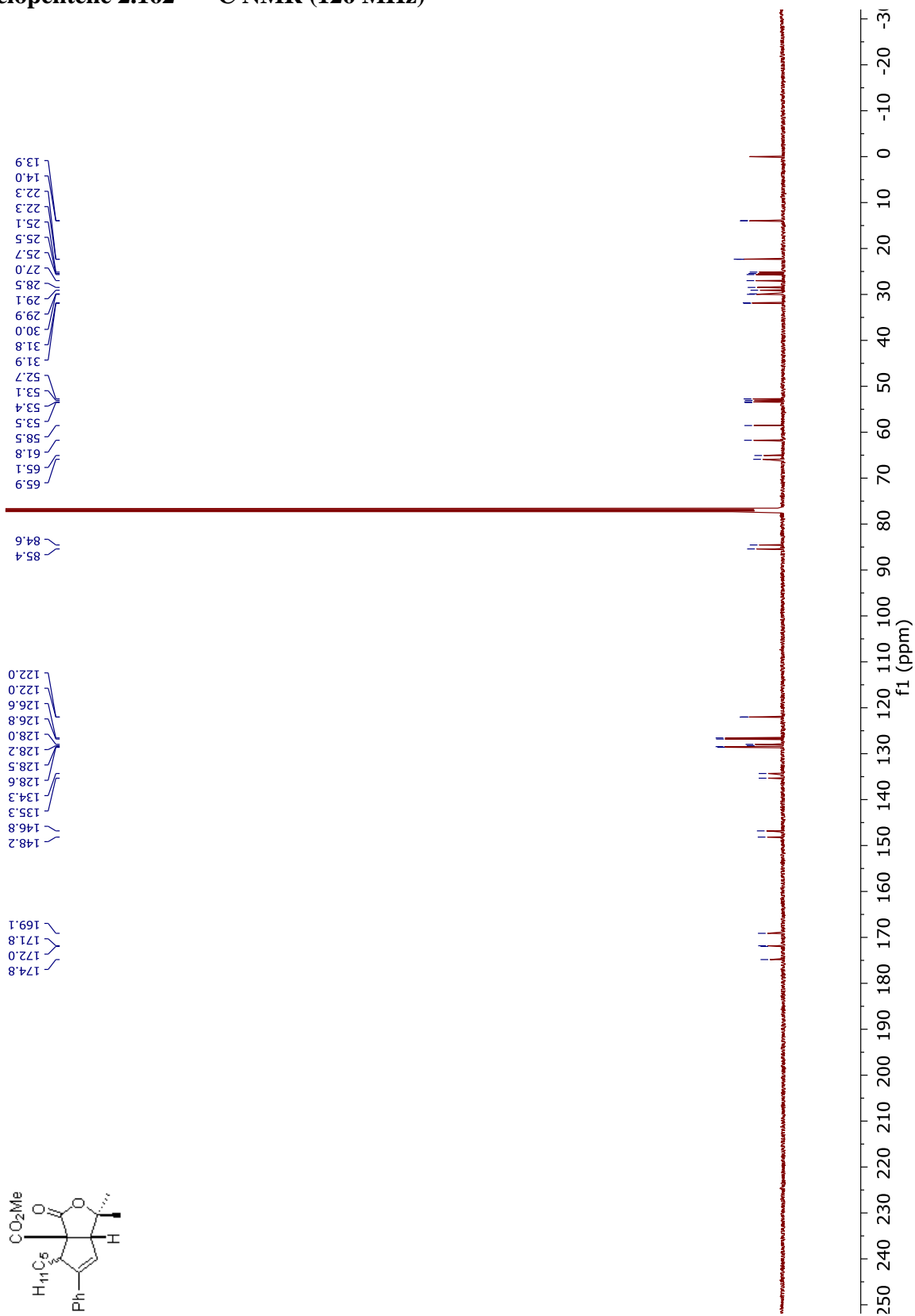
Peaks (ppm): 13.9, 14.0, 22.3, 22.3, 25.1, 25.5, 25.7, 27.0, 28.5, 29.1, 29.9, 30.0, 31.8, 31.9, 52.7, 53.1, 53.4, 53.5, 58.5, 61.8, 65.1, 65.9, 84.6, 85.4, 122.0, 122.0, 126.6, 126.8, 128.0, 128.2, 128.5, 128.6, 134.3, 135.3, 146.8, 148.2, 169.1, 171.8, 172.0, 174.8

Cyclopentene 2.164 – ¹H NMR (500 MHz)
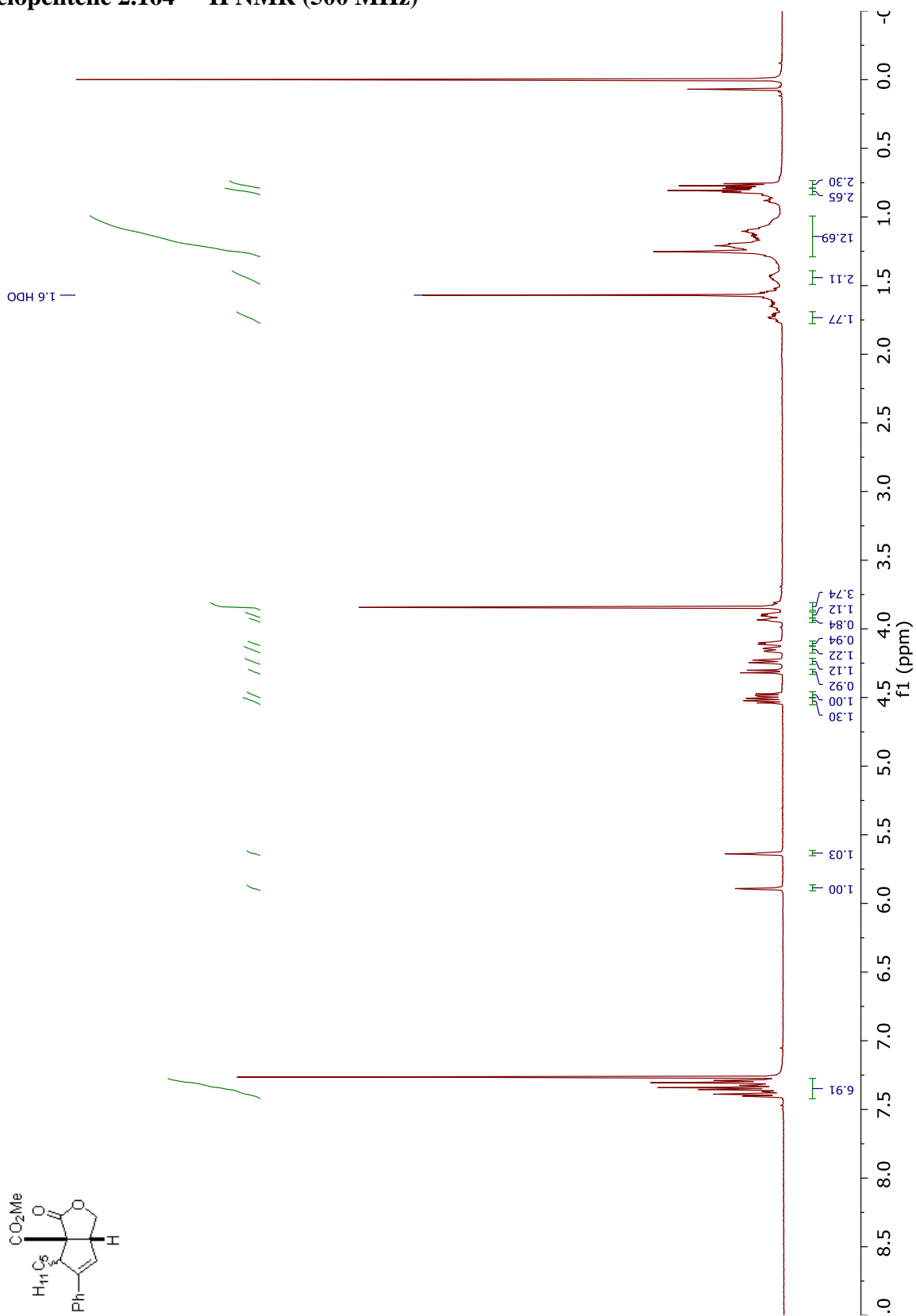
Cyclopentene 2.164 – ^{13}C NMR (126 MHz)
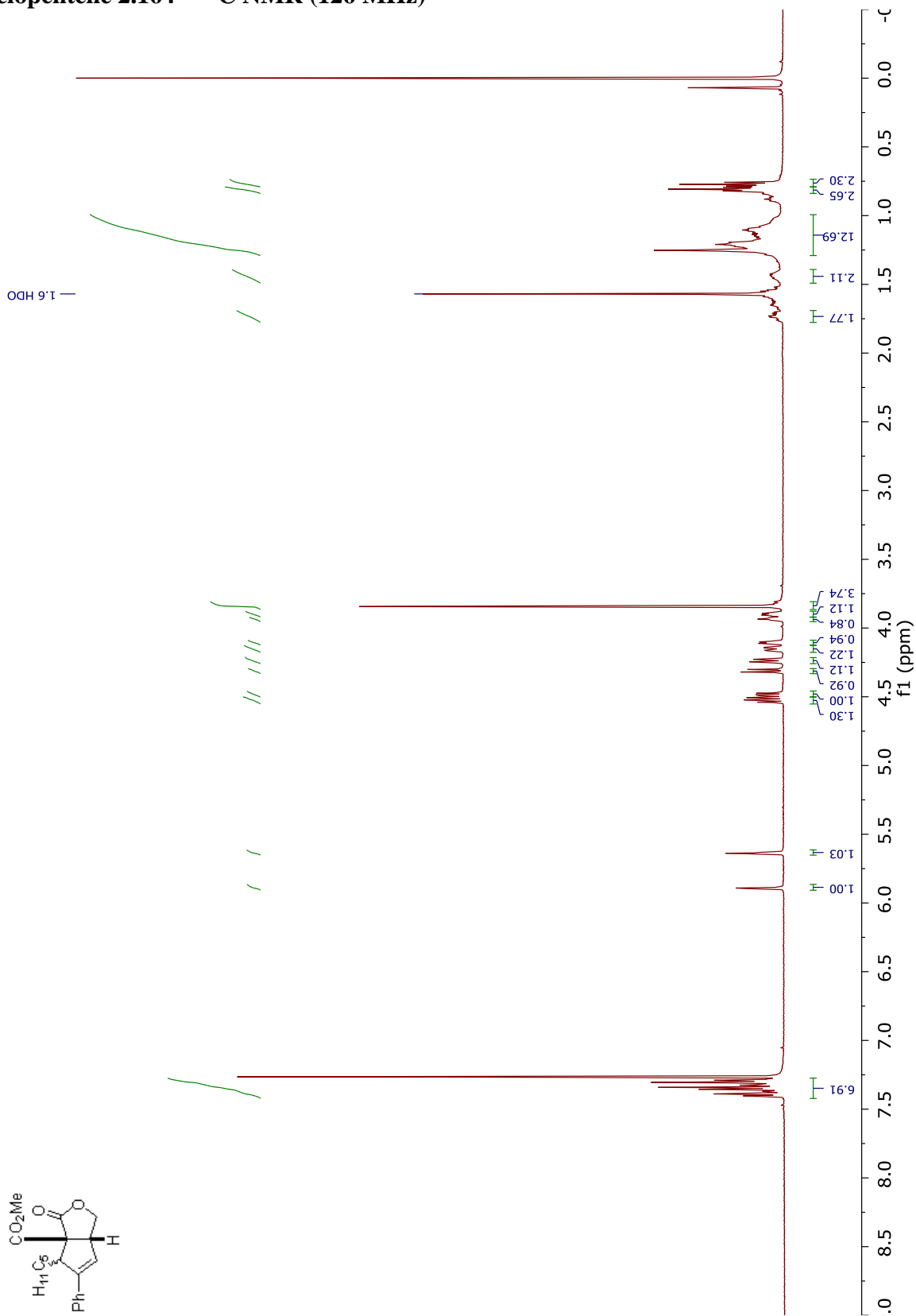
Cyclopentene 2.165 – ¹H NMR (500 MHz)
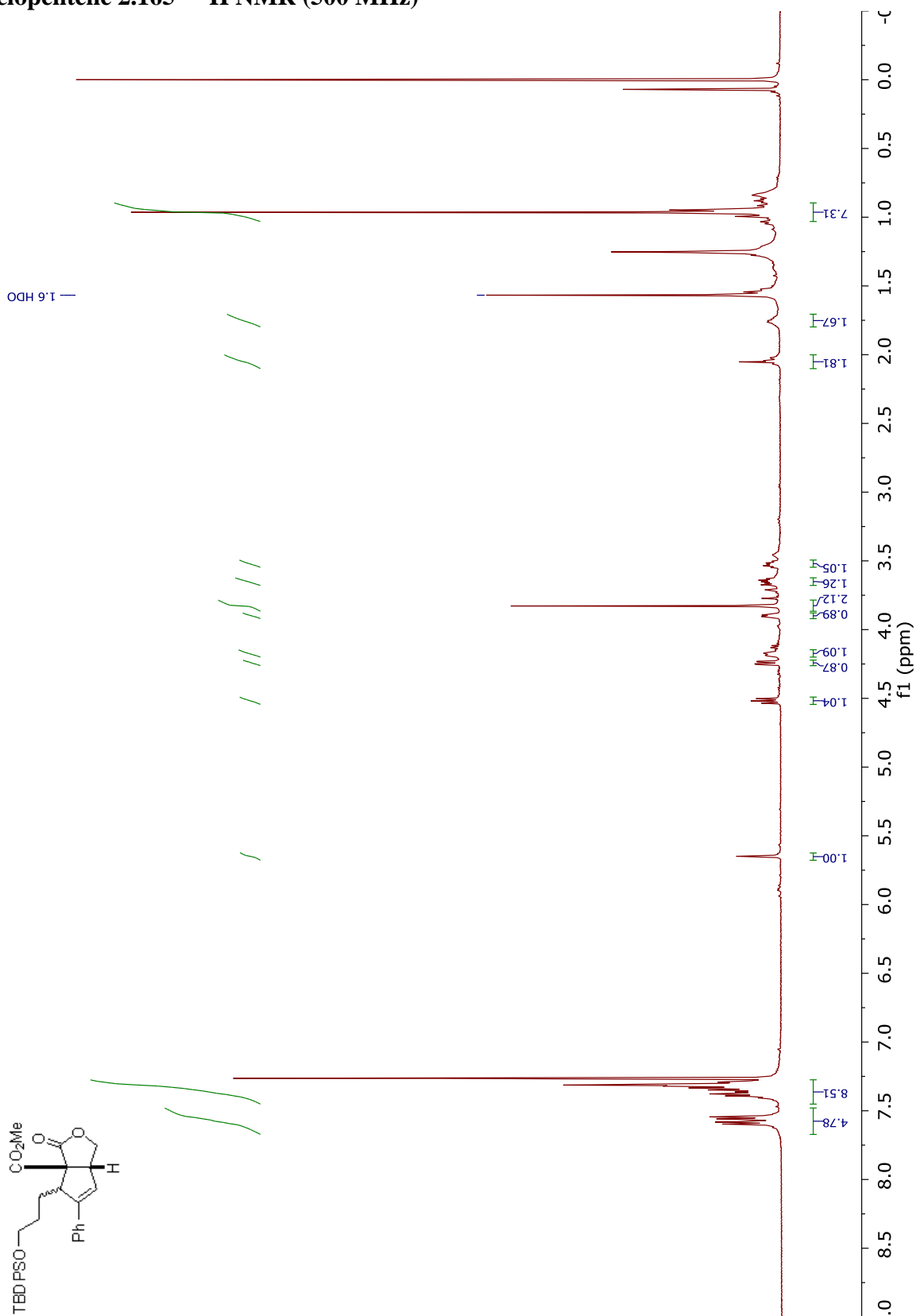
Cyclopentene 2.165 – ¹³C NMR (126 MHz)
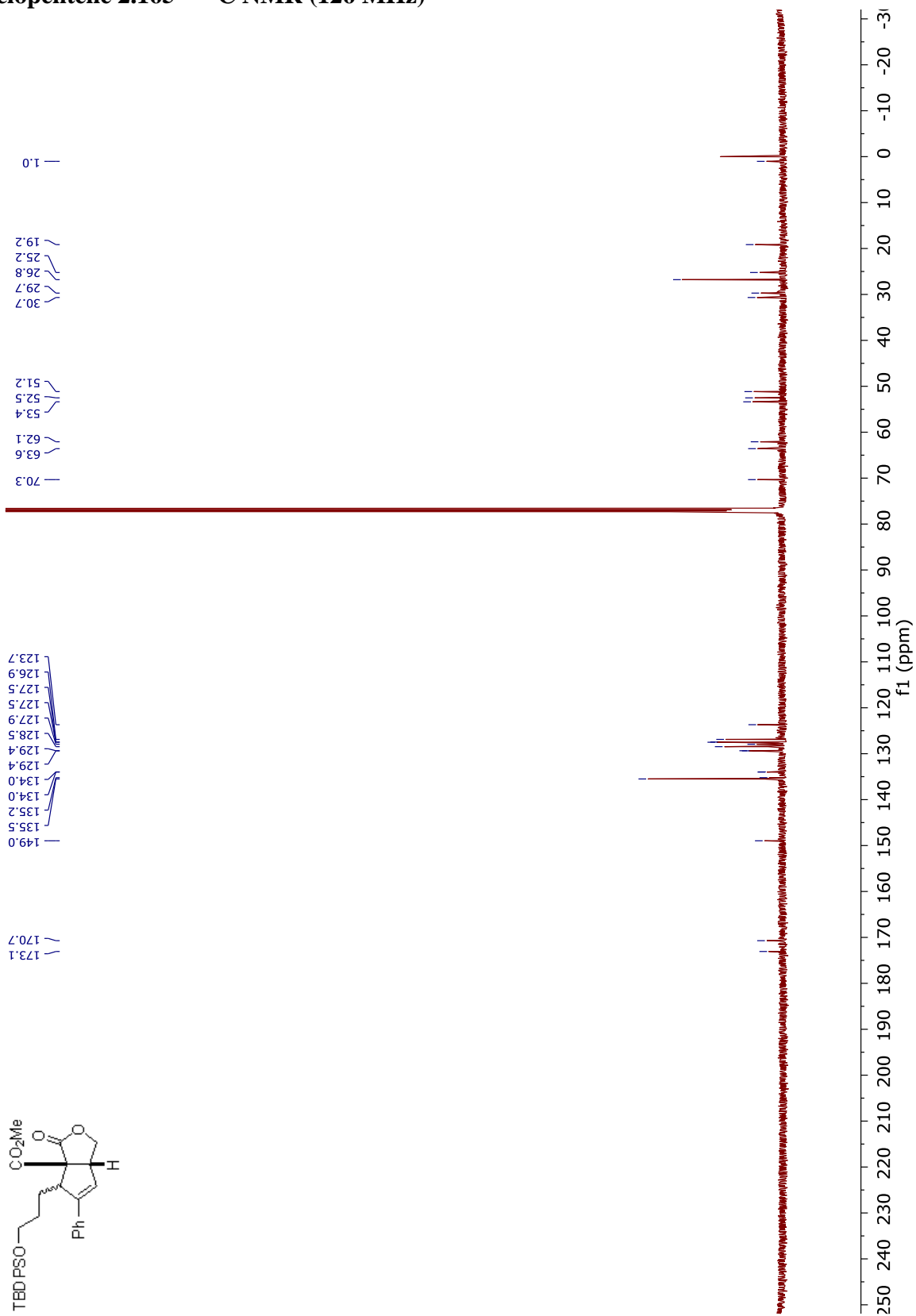
Cyclopentene 2.166 – ¹H NMR (500 MHz)
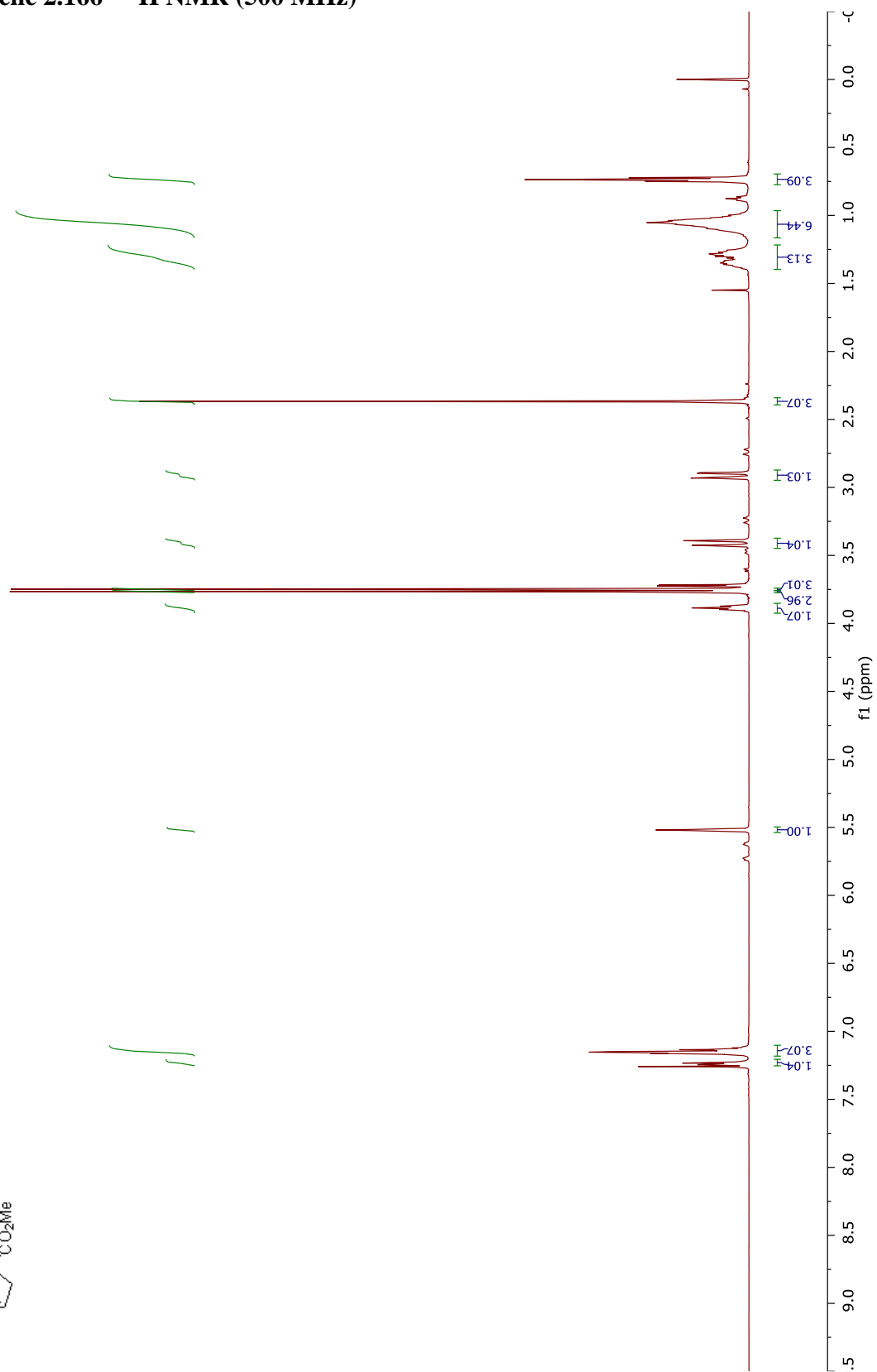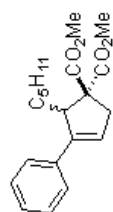
Cyclopentene 2.166 – ^{13}C NMR (126 MHz)

13.88

20.48
22.30
26.55
29.94
31.97

39.60

52.34
52.81
52.82

64.29

124.83
125.48
127.14
128.92
130.32
135.85
136.86

146.17

170.94
173.00

C$_5$H$_{11}$
CO$_2$Me
CO$_2$Me
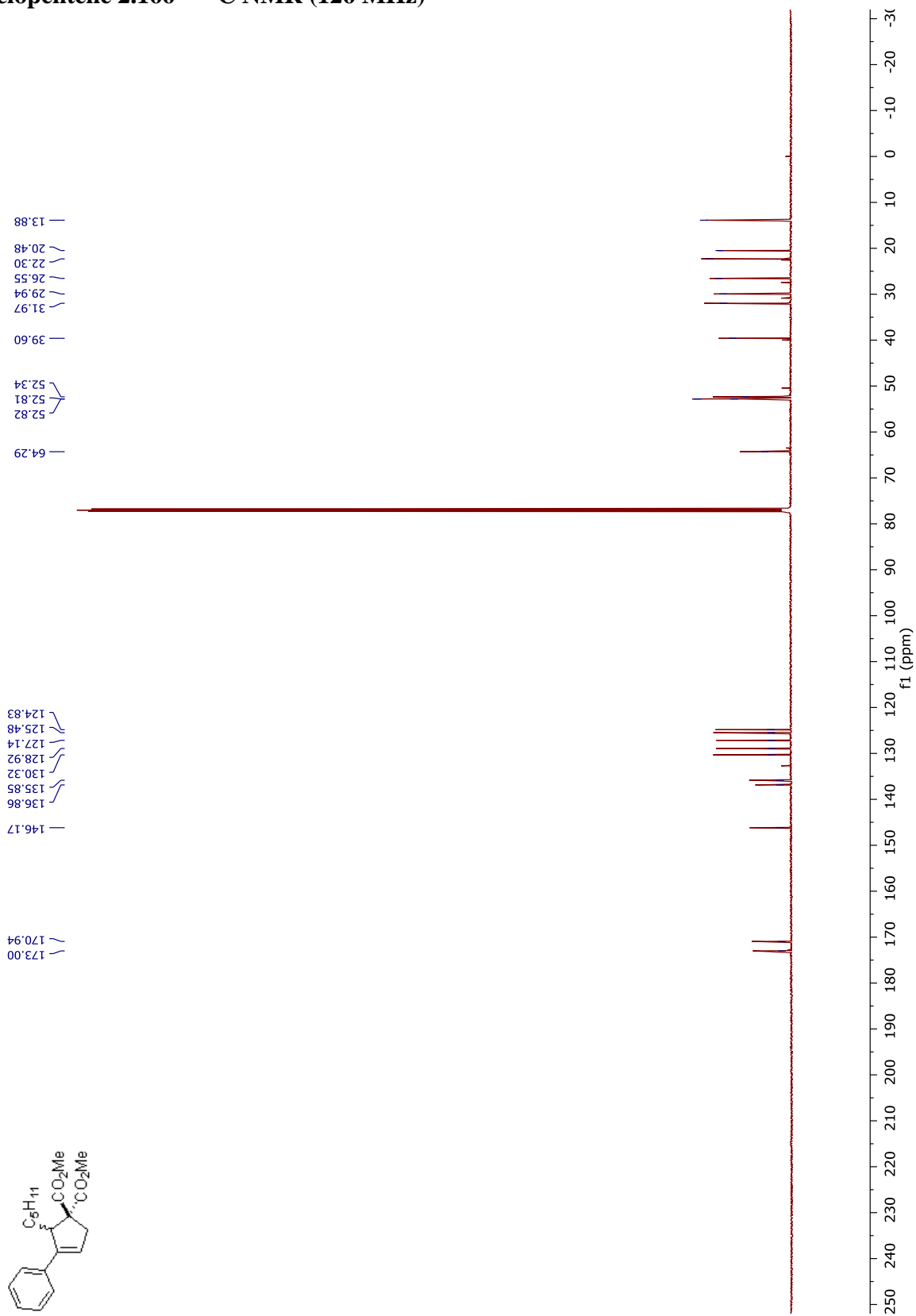
Cyclopentene 2.168 – ¹H NMR (400 MHz)
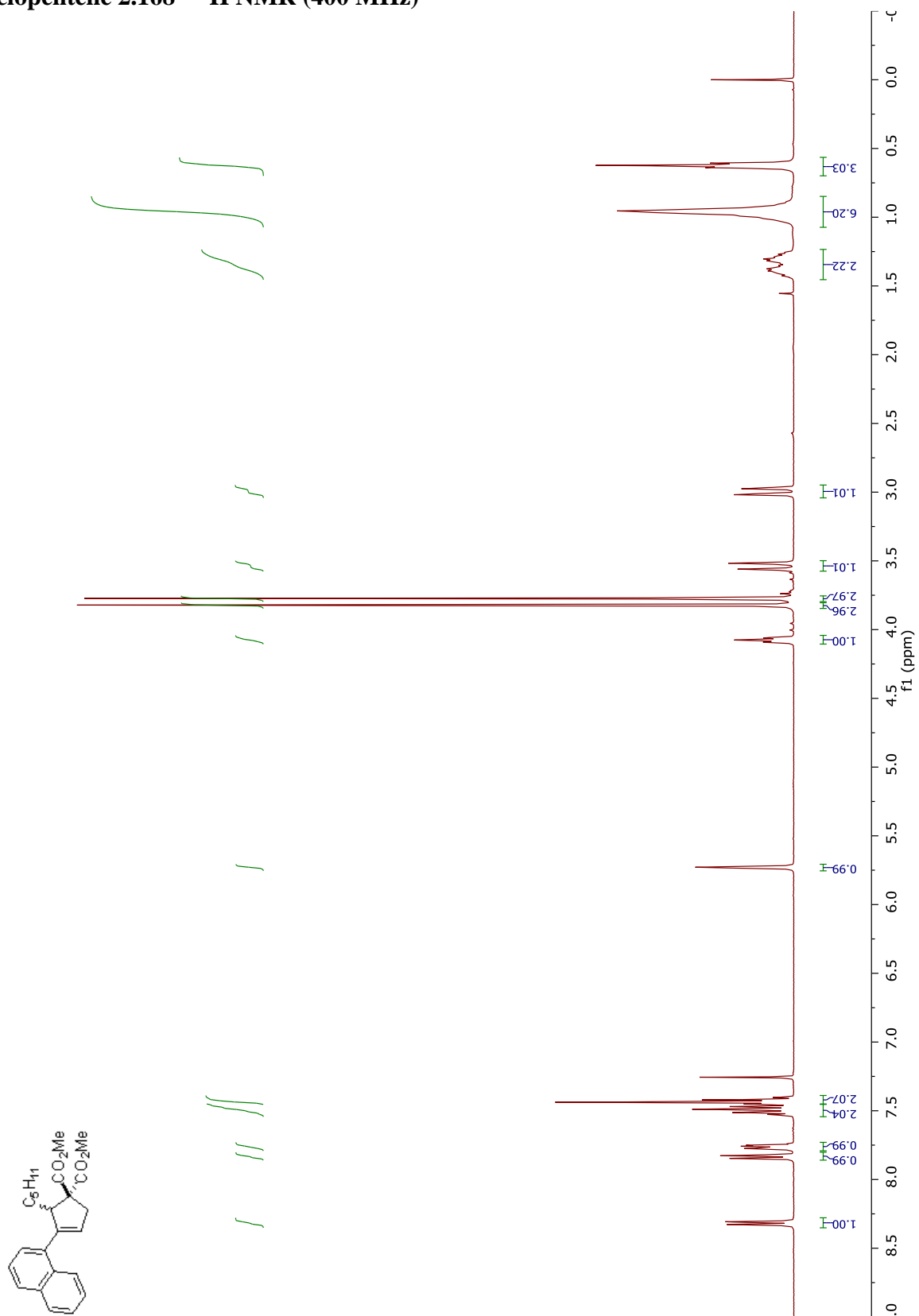
Cyclopentene 2.168 – ^{13}C NMR (101 MHz)

13.8

22.2
26.4
30.0
31.8

39.8

52.4
52.9
53.6

64.4

125.2
125.7
125.9
126.0
126.0
127.7
128.2
131.8
133.8
135.4
145.4

170.9
173.2

f1 (ppm)
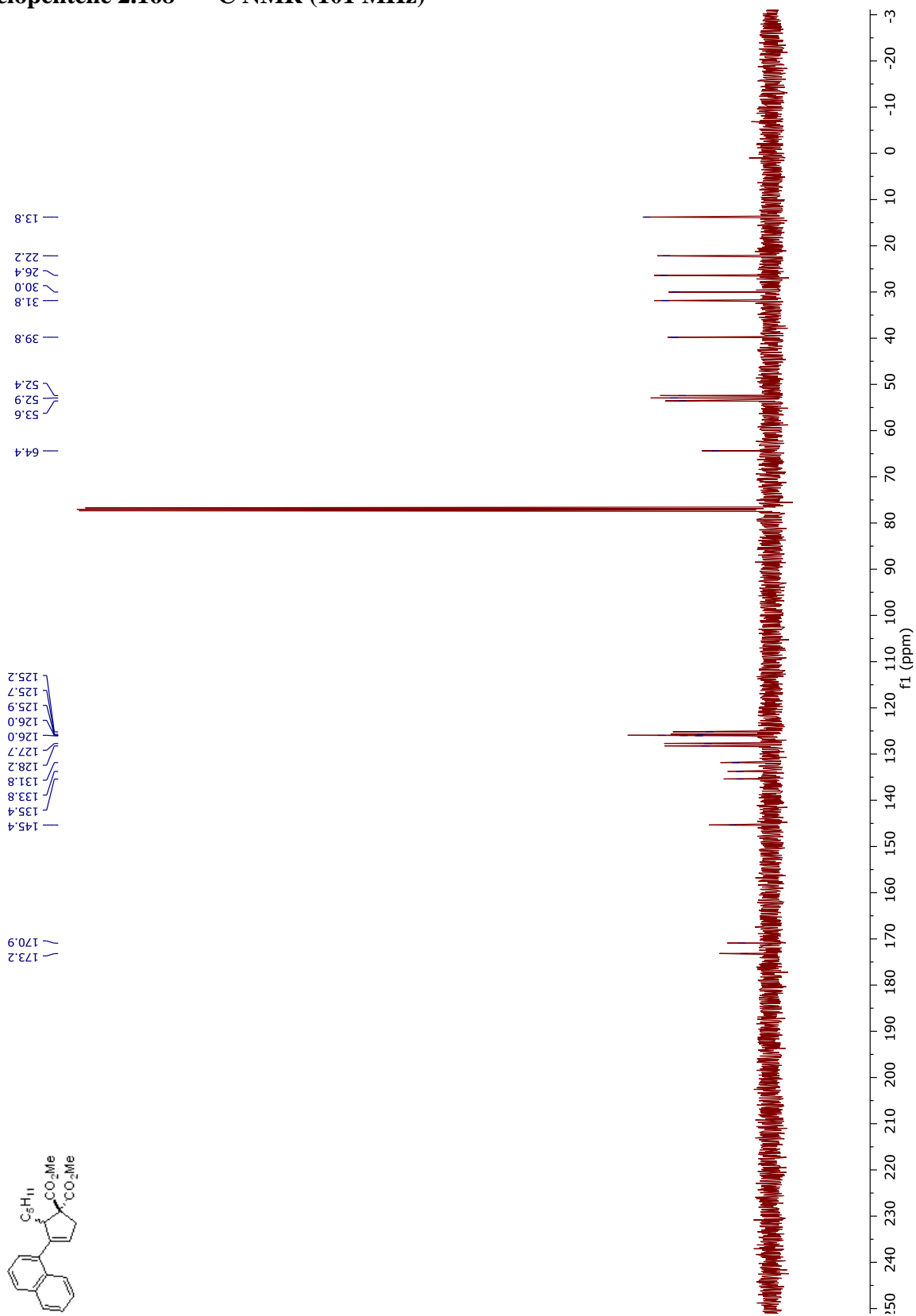
Cyclopentene 2.169 – ¹H NMR (500 MHz)
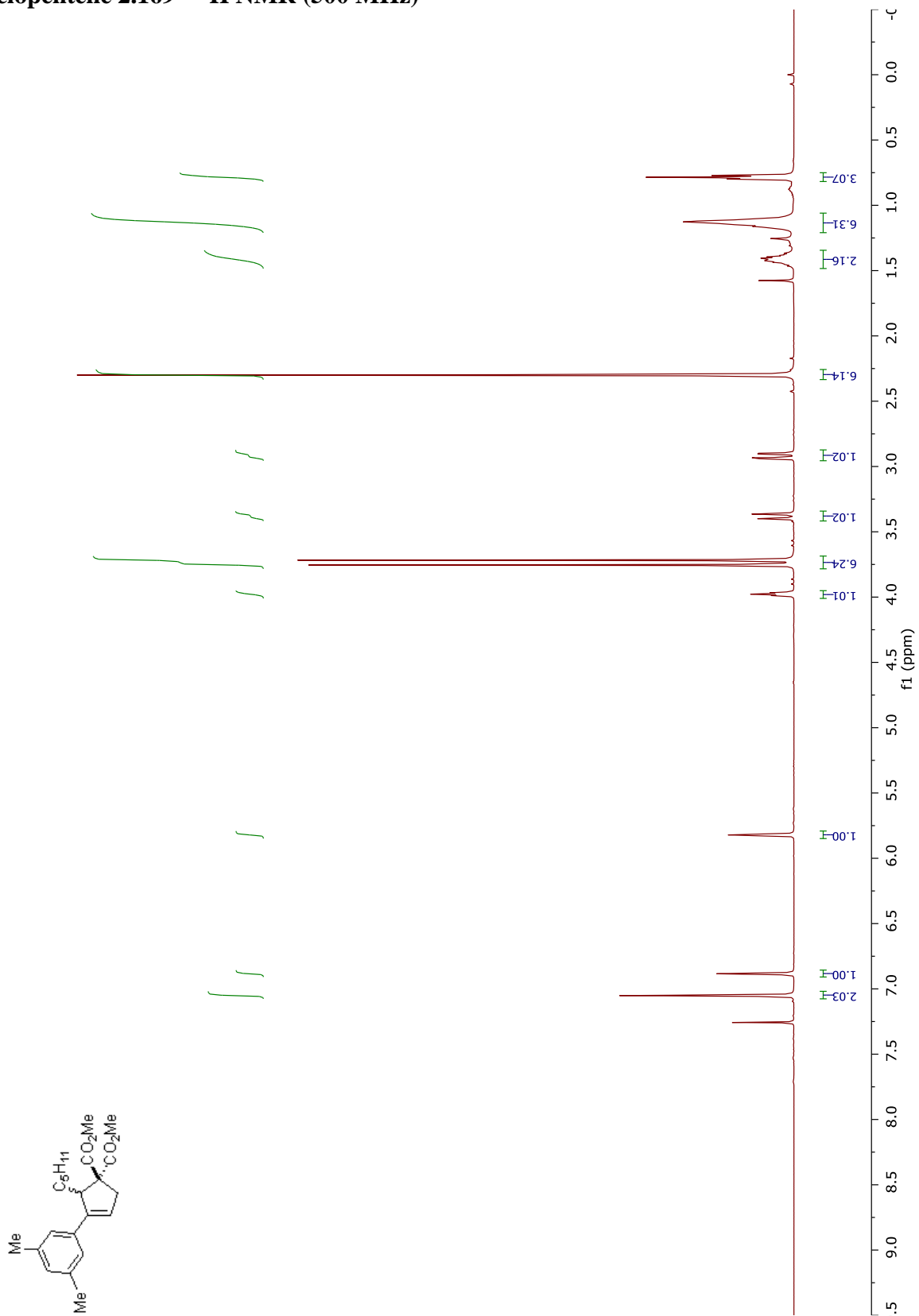
Cyclopentene 2.169 – ^{13}C NMR (126 MHz)

14.0

21.4
22.4
26.5
29.4
32.1

39.2

50.0
52.4
52.9

64.5

121.3
124.1
129.2
135.6
137.8

146.2

170.8
172.9

f1 (ppm)
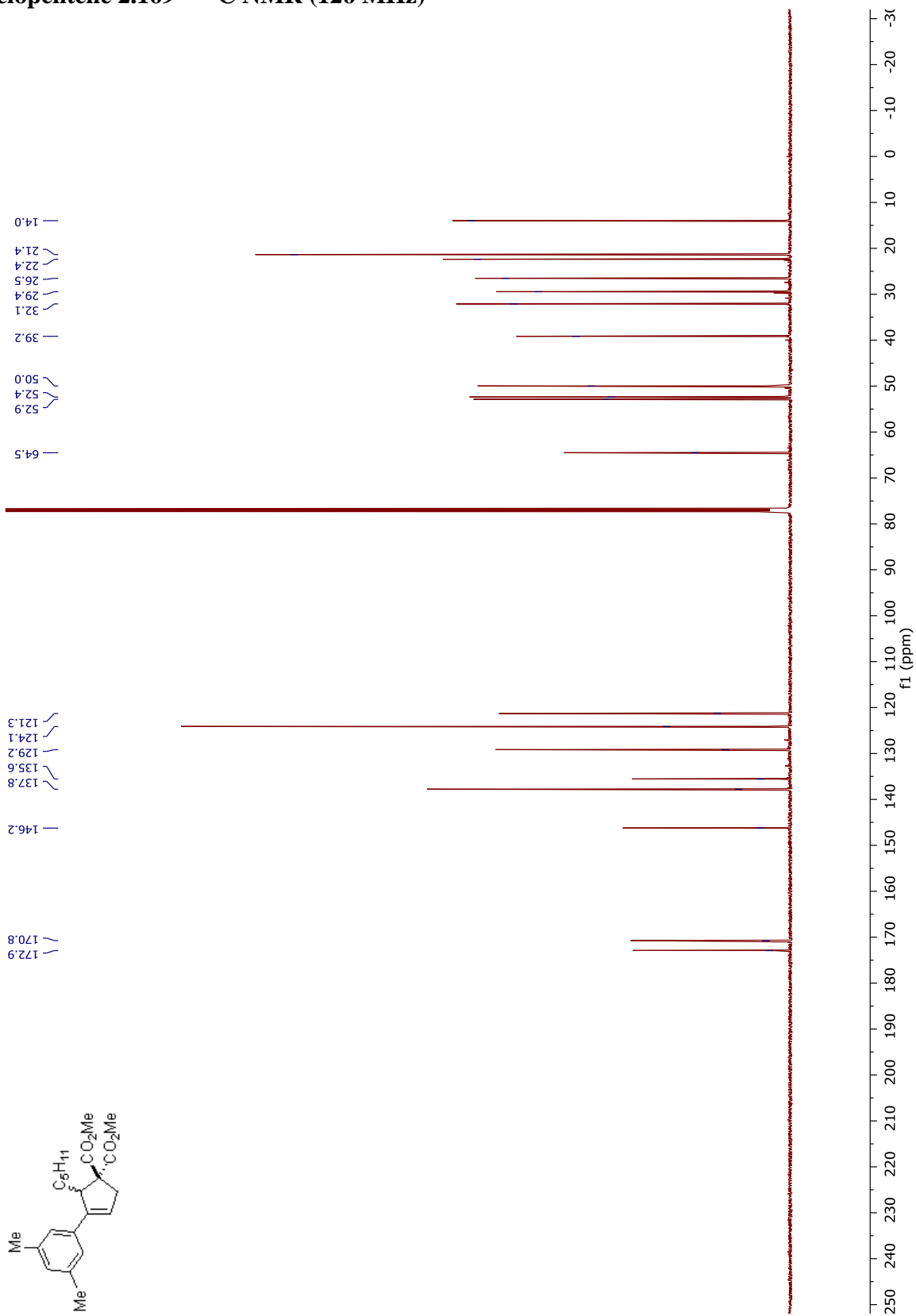
Cyclopentene 2.170 – ¹H NMR (500 MHz)
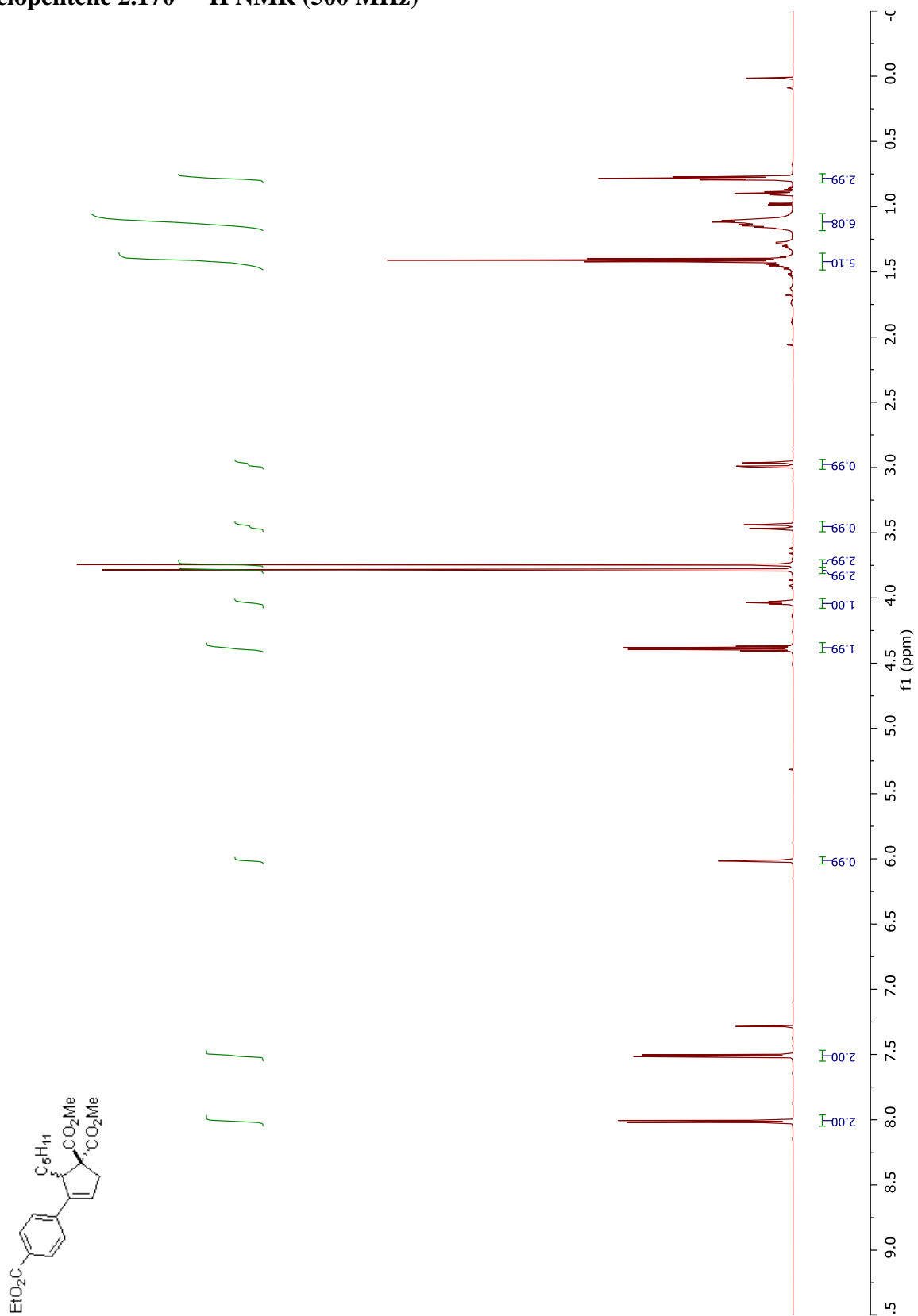
Cyclopentene 2.170 – ^{13}C NMR (126 MHz)

13.9
14.4
22.3
26.6
29.6
32.1
39.3
49.9
52.5
53.0
60.9
64.6
124.4
126.1
129.3
129.8
140.1
145.5
166.4
170.4
172.7
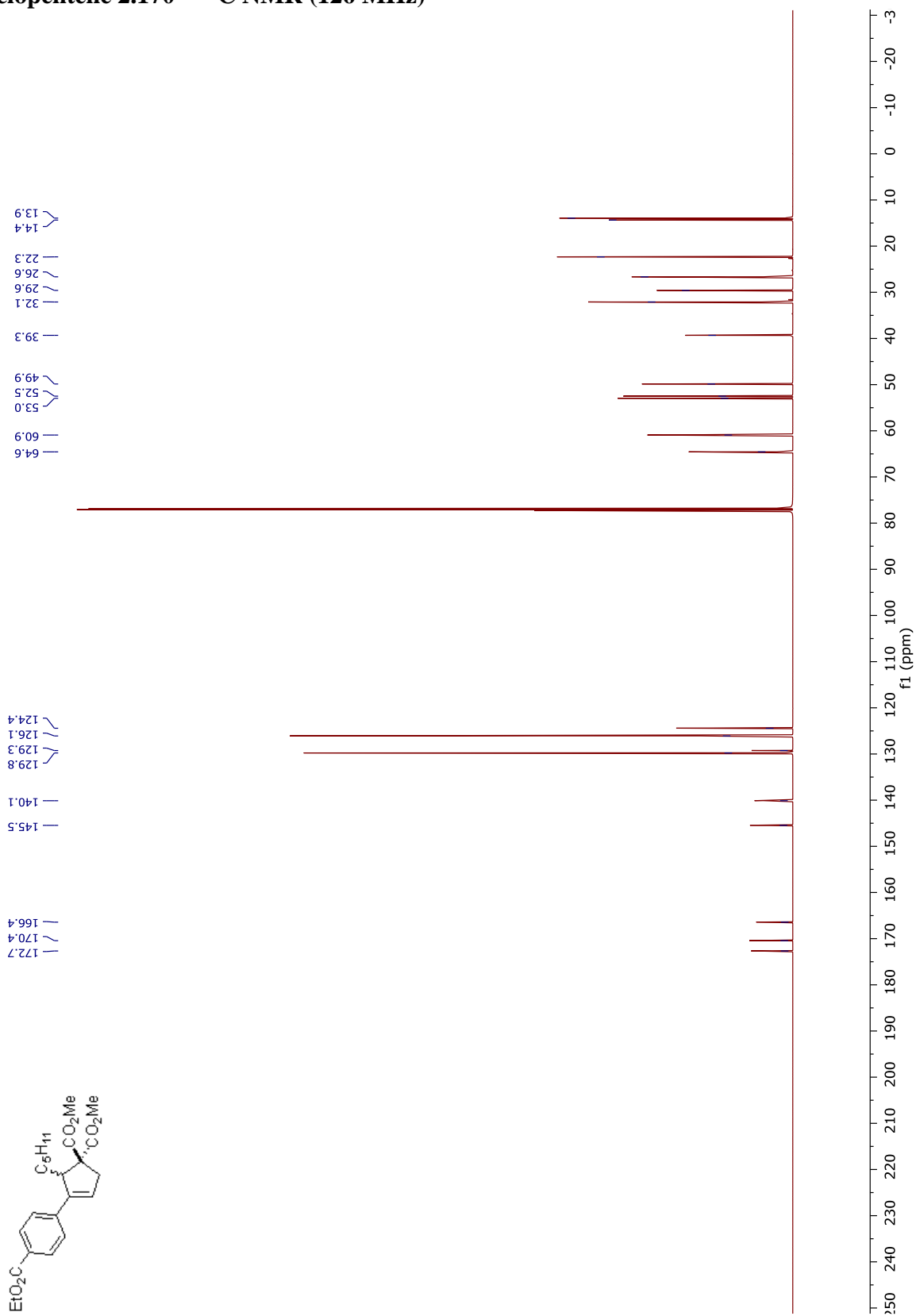
Cyclopentene 2.171 – ¹H NMR (500 MHz)
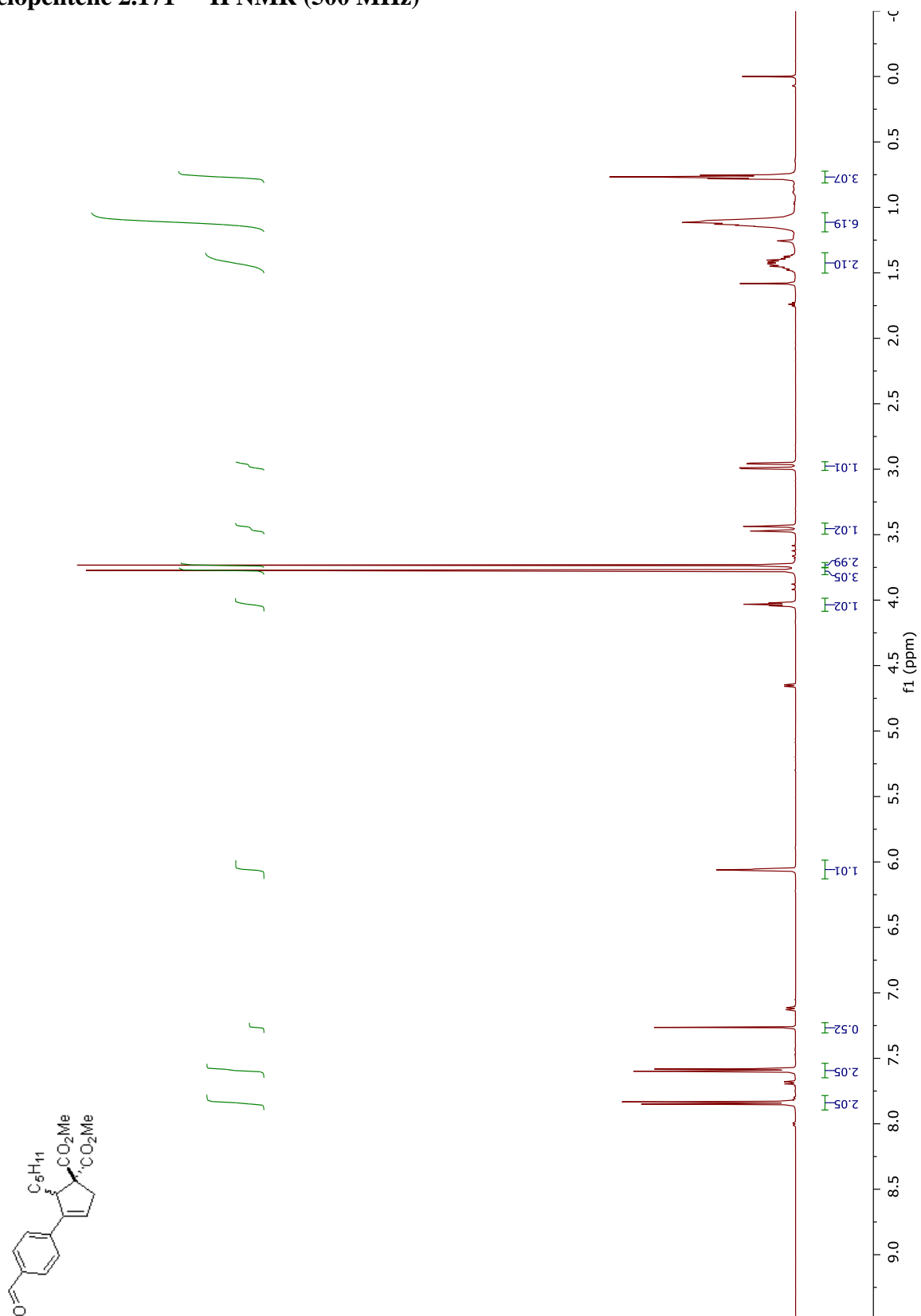
Cyclopentene 2.171 – ^{13}C NMR (126 MHz)
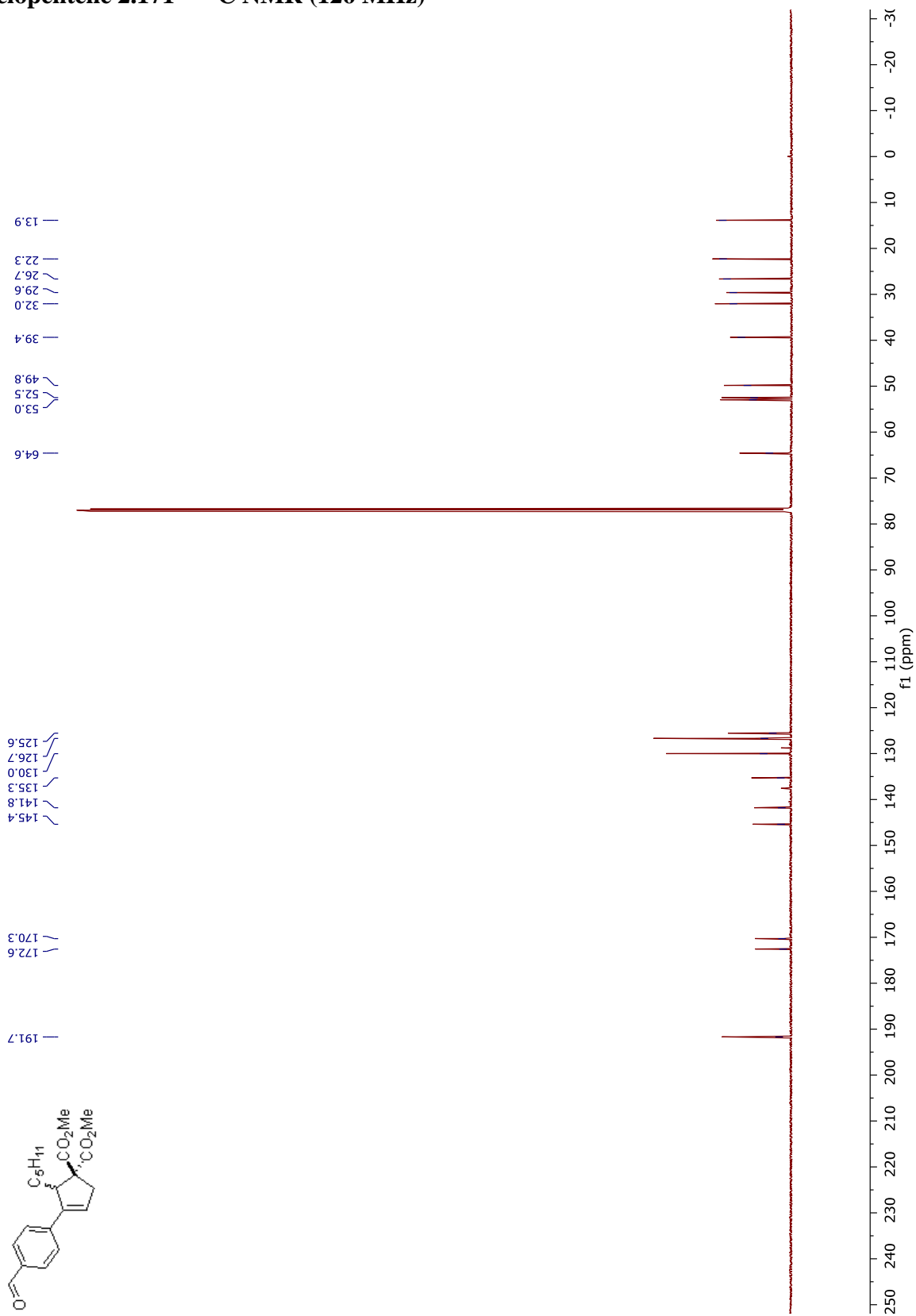
Cyclopentene 2.172 – ¹H NMR (500 MHz)
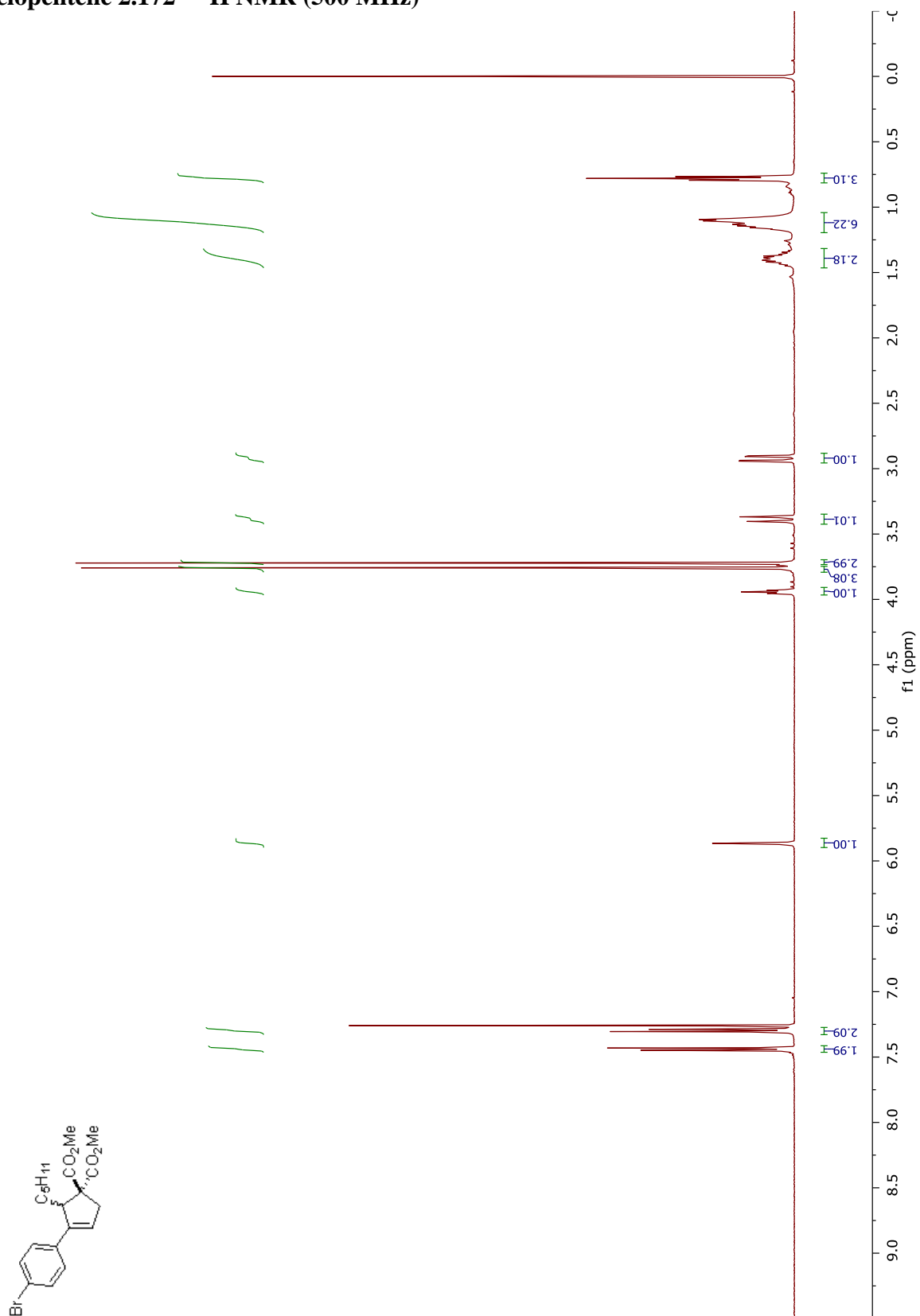
Cyclopentene 2.172 – ¹³C NMR (126 MHz)
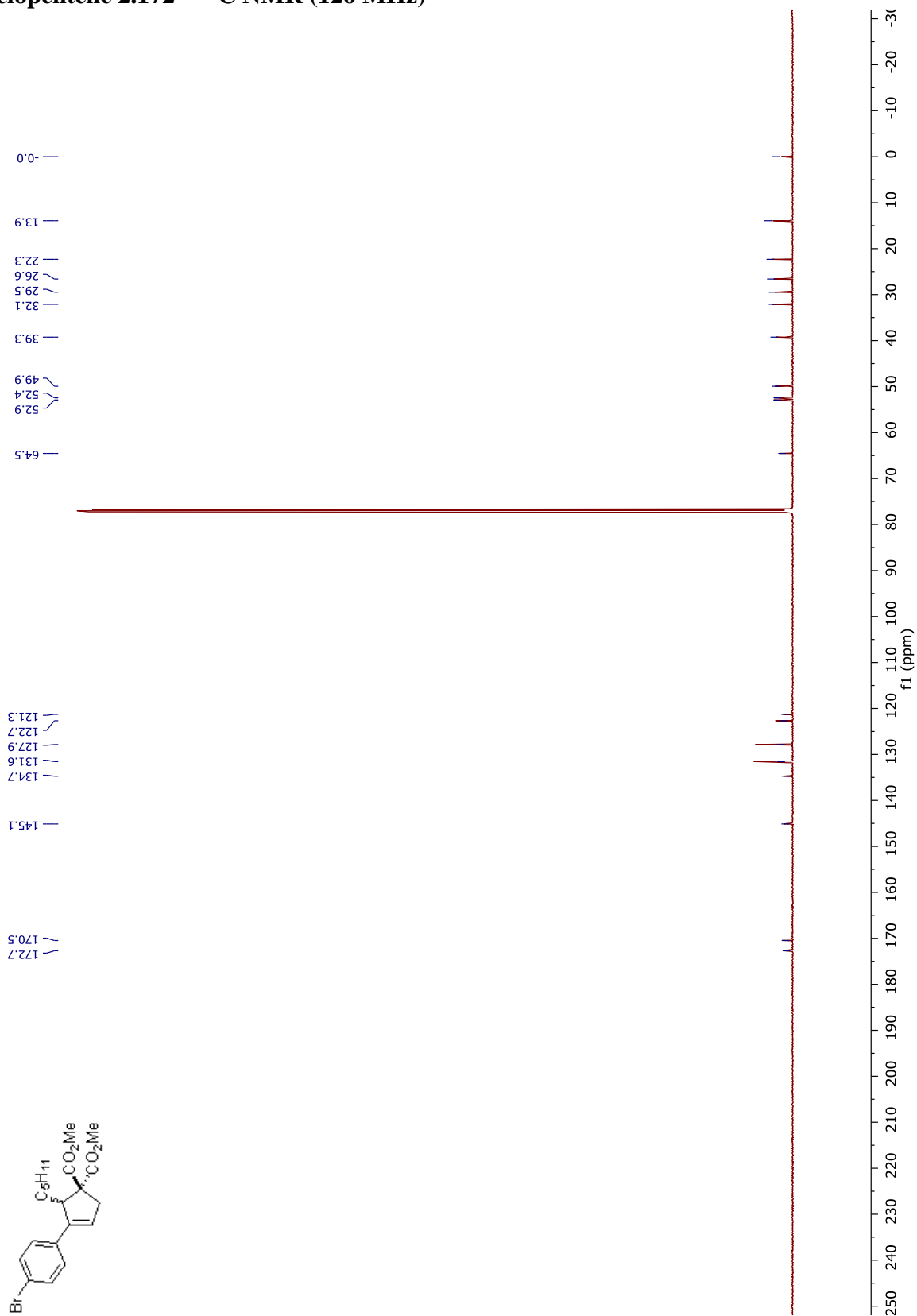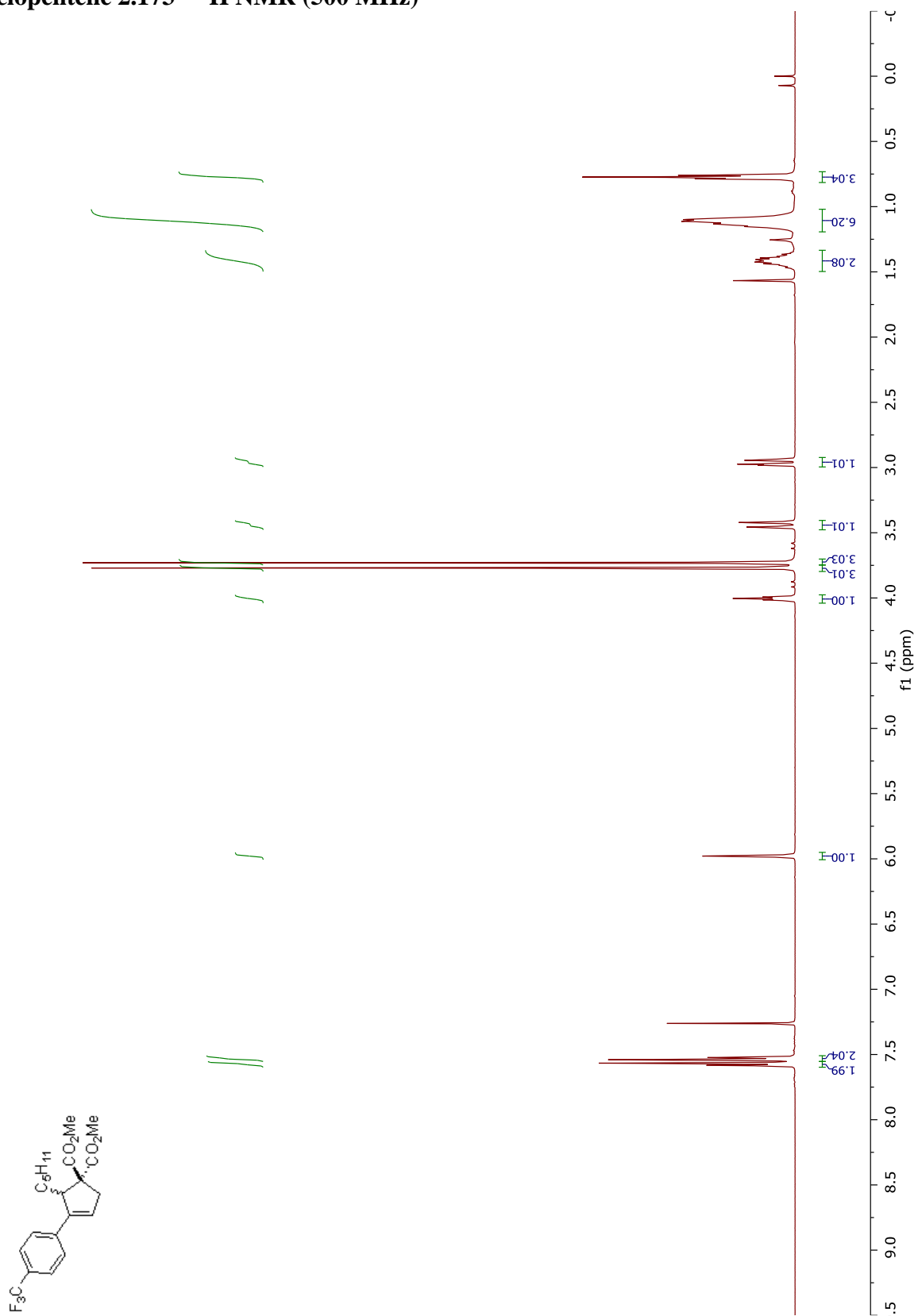
Cyclopentene 2.173 – ^{1}H NMR (500 MHz)

Cyclopentene 2.172 – ^{13}C NMR (126 MHz)

Cyclopentene 2.173 – ¹H NMR (500 MHz)

Cyclopentene 2.172 – ^{13}C NMR (126 MHz)

13.9
22.3
26.6
29.5
32.1
39.3
49.8
52.5
53.0
64.5
123.3
124.0
131.4
133.3
143.1
147.7
148.5
170.3
172.6
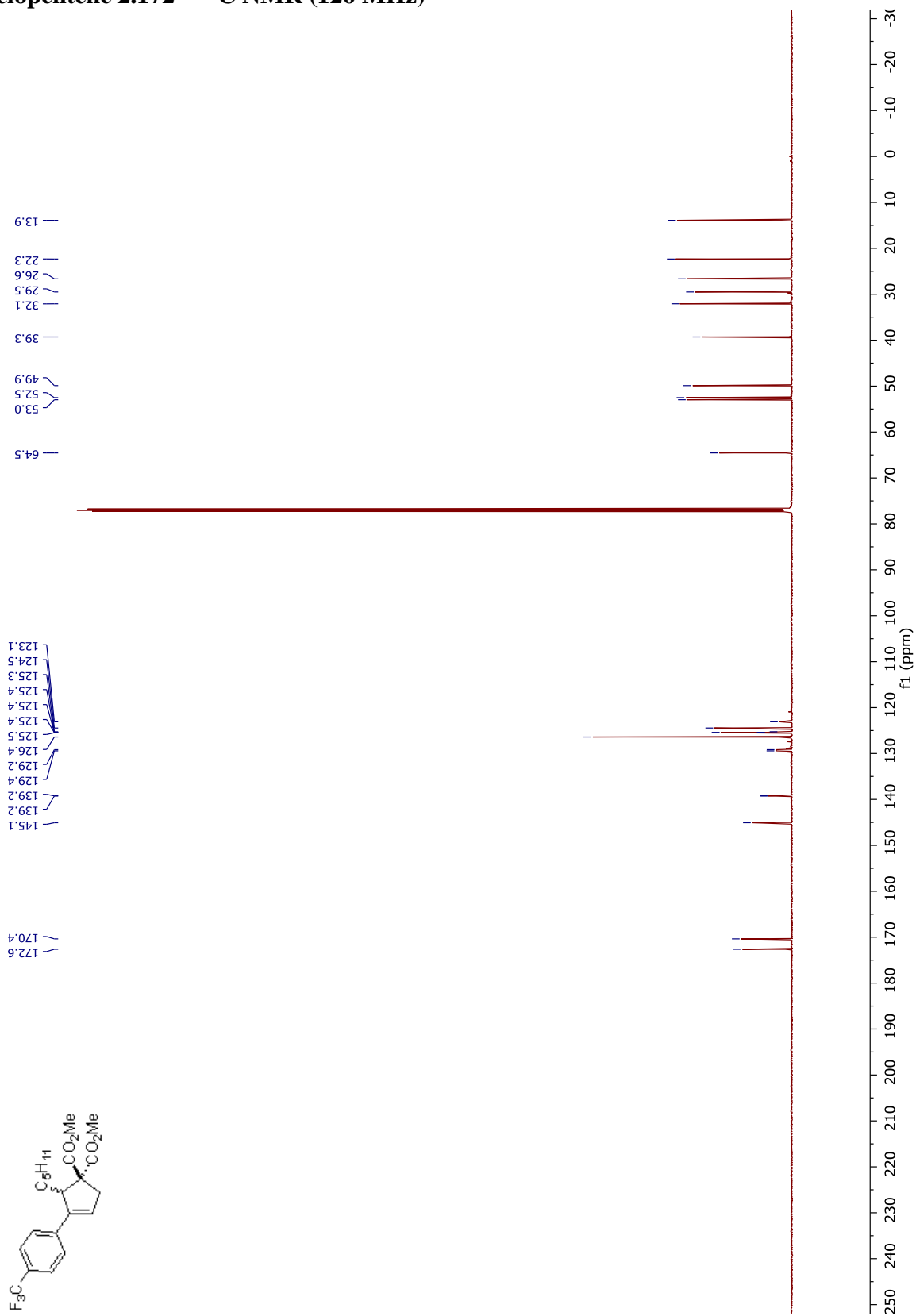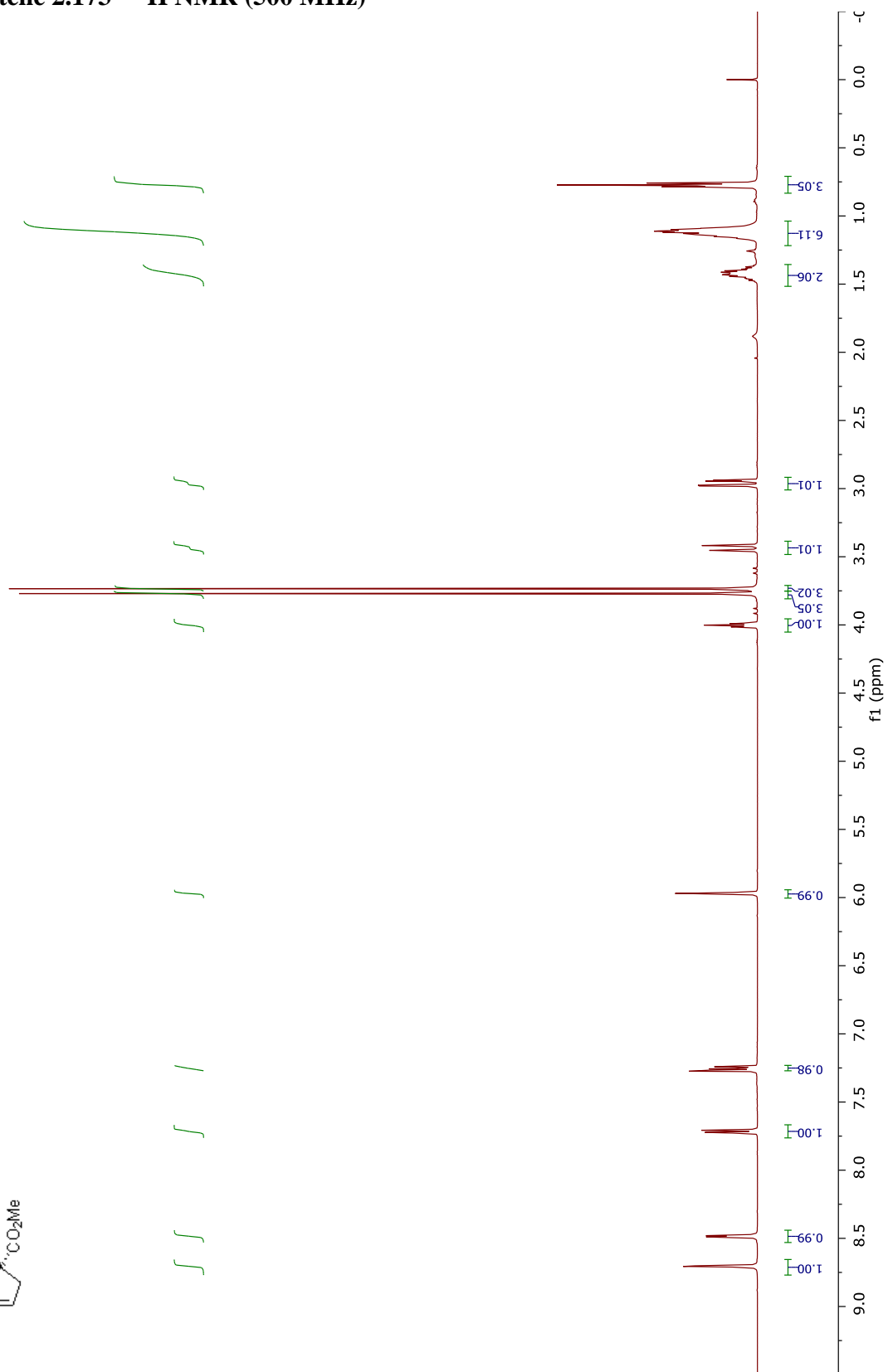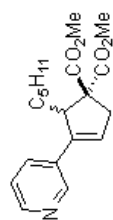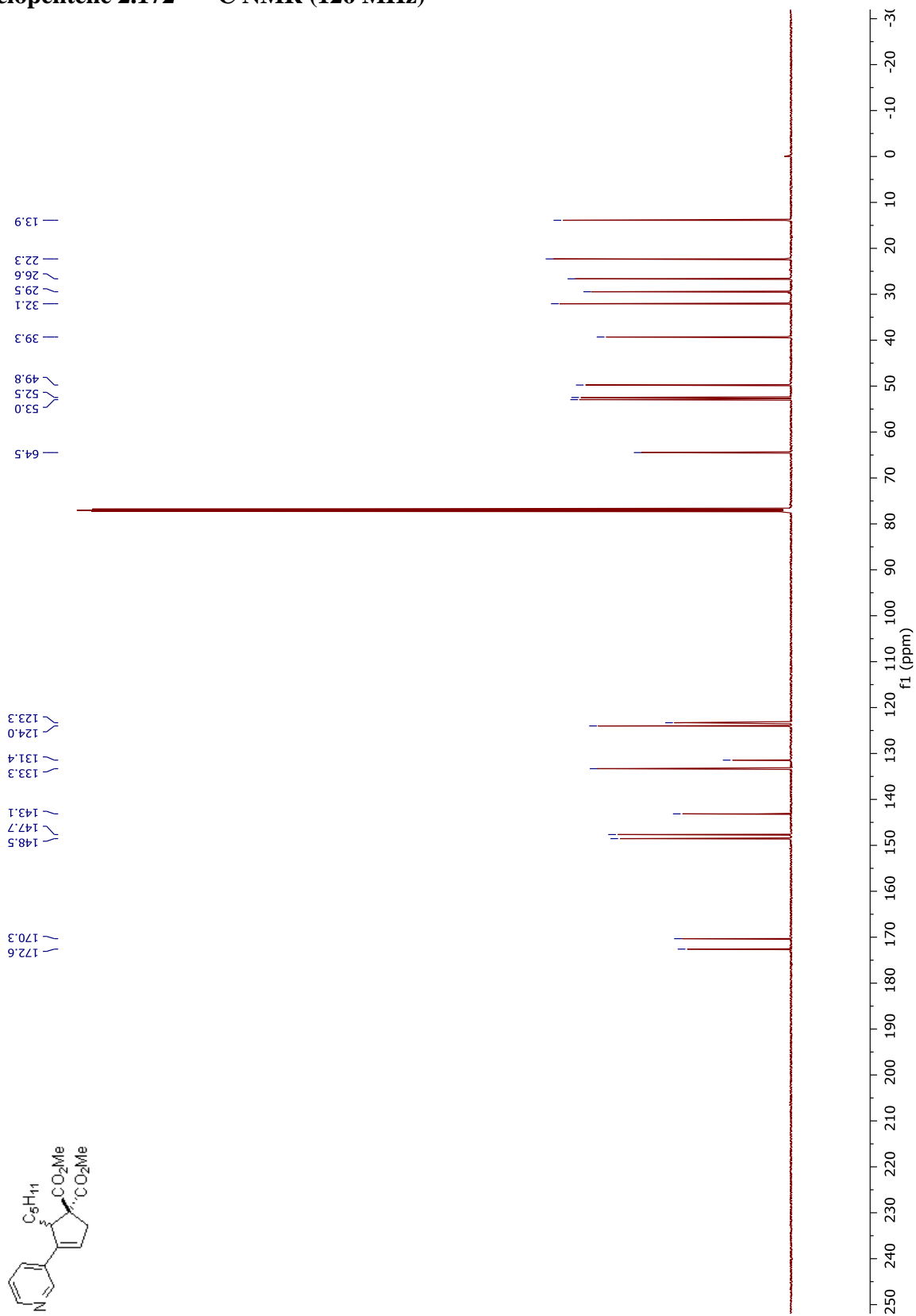
Benzo-12-crown-4 (3.11) – ¹H NMR (500 MHz)
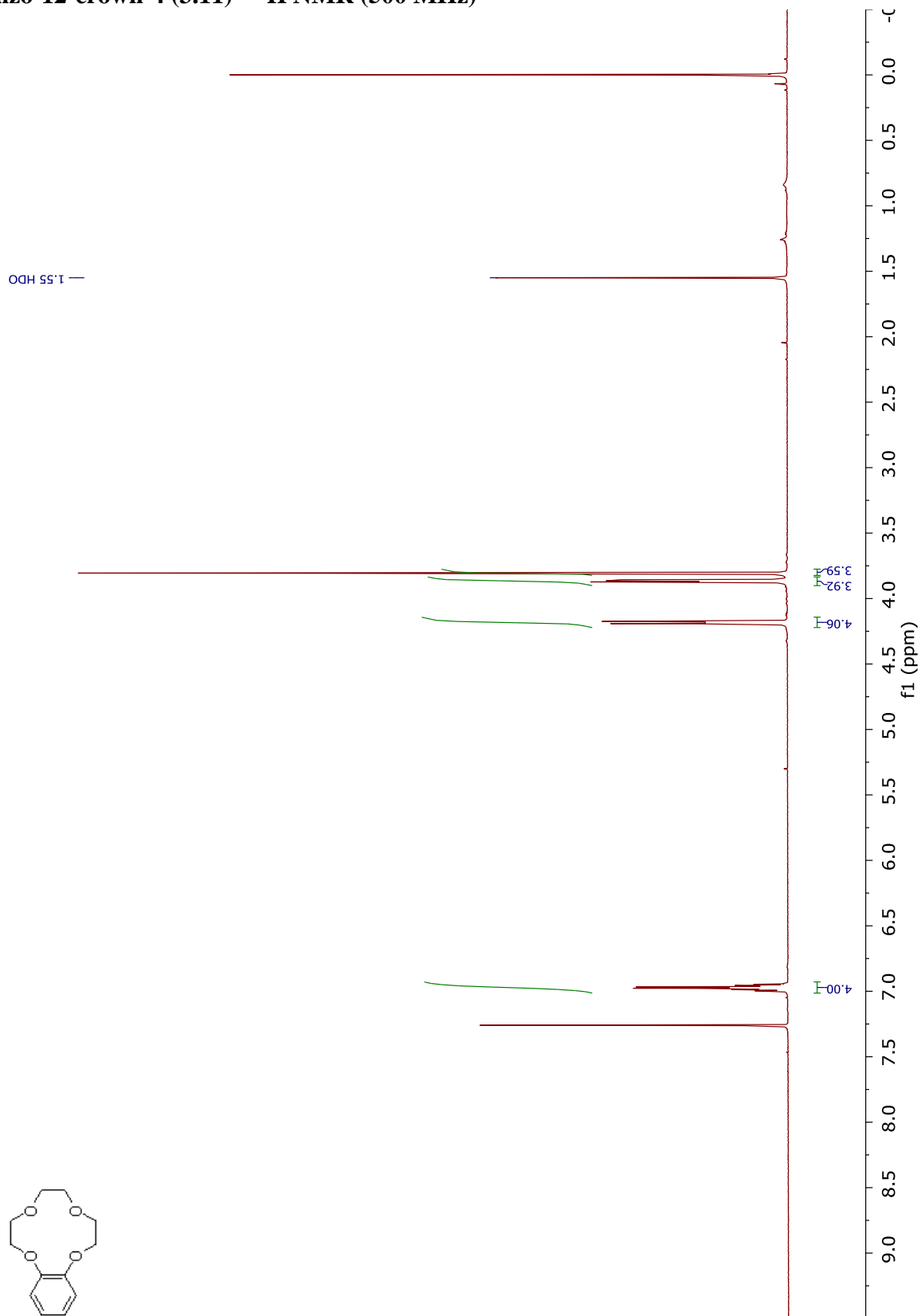
Benzo-12-crown-4 (3.11) – ^{13}C NMR (126 MHz)

150.6

122.8
118.1

71.7
71.2
70.0

f1 (ppm)
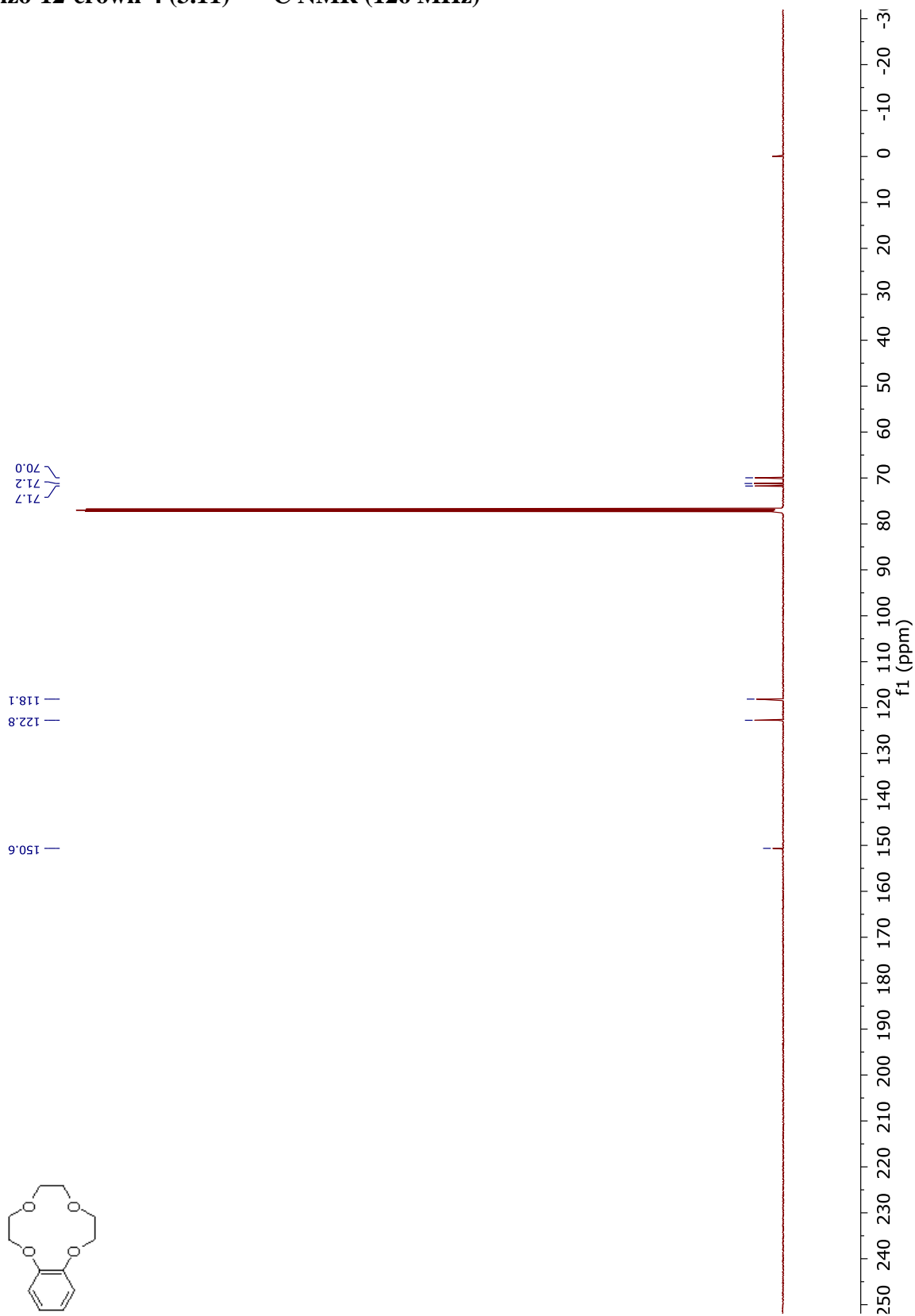
4-nitro-benzo-12-crown-4 (3.4) – ^{1}H NMR (500 MHz)
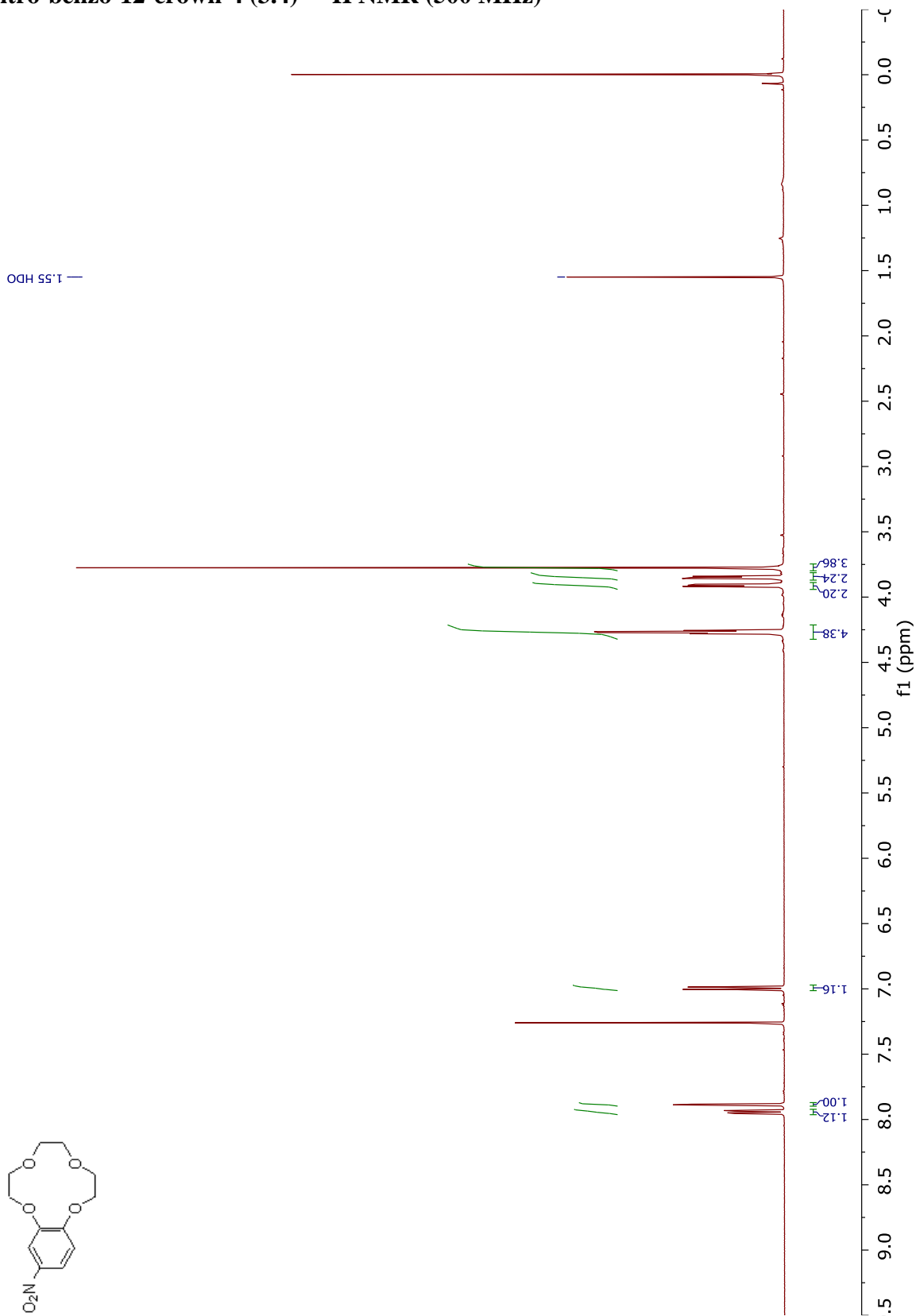
4-nitro-benzo-12-crown-4 (3.4) – ^{13}C NMR (126 MHz)
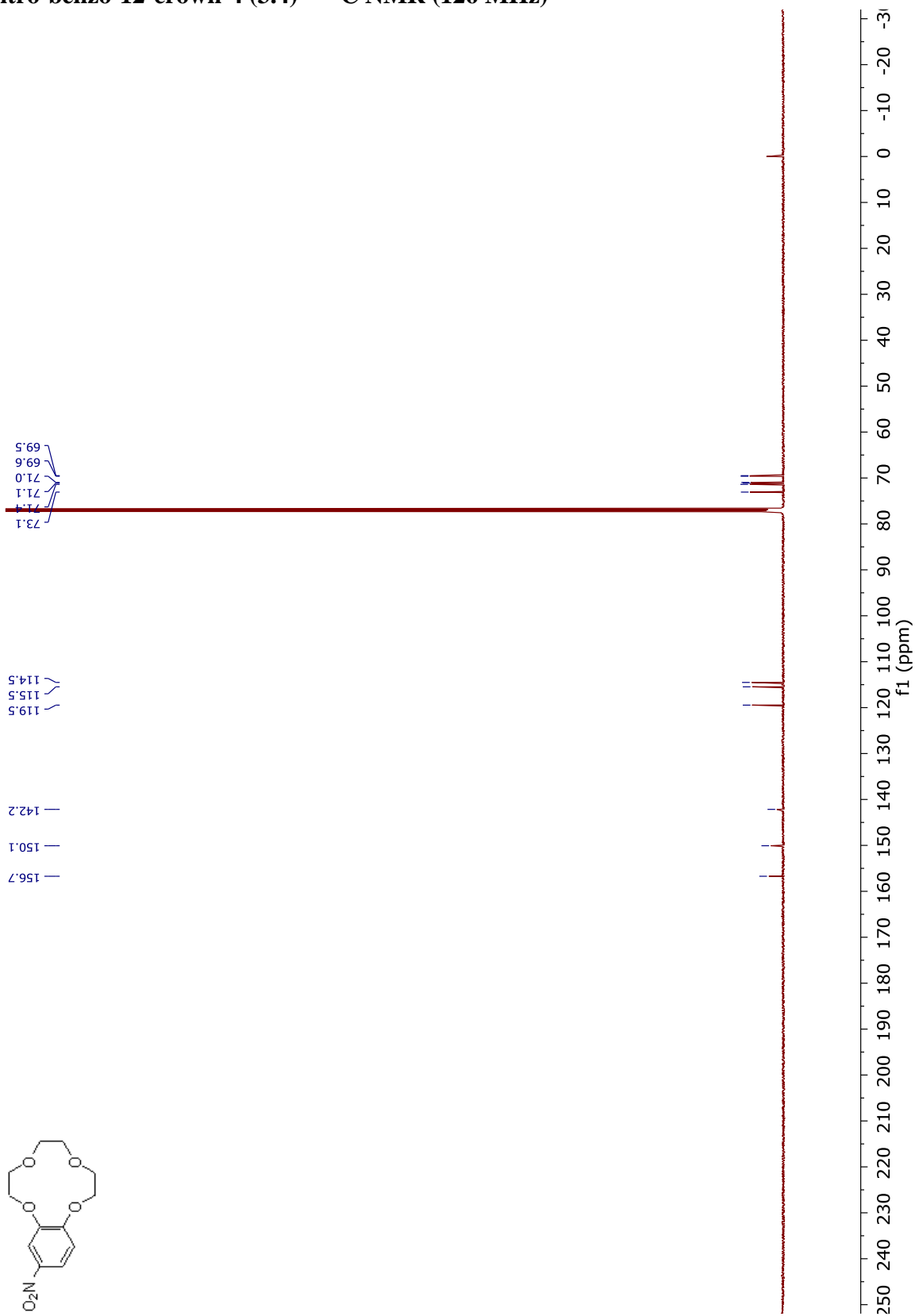
4-amino-benzo-12-crown-4 (3.12) – ¹H NMR (500 MHz)
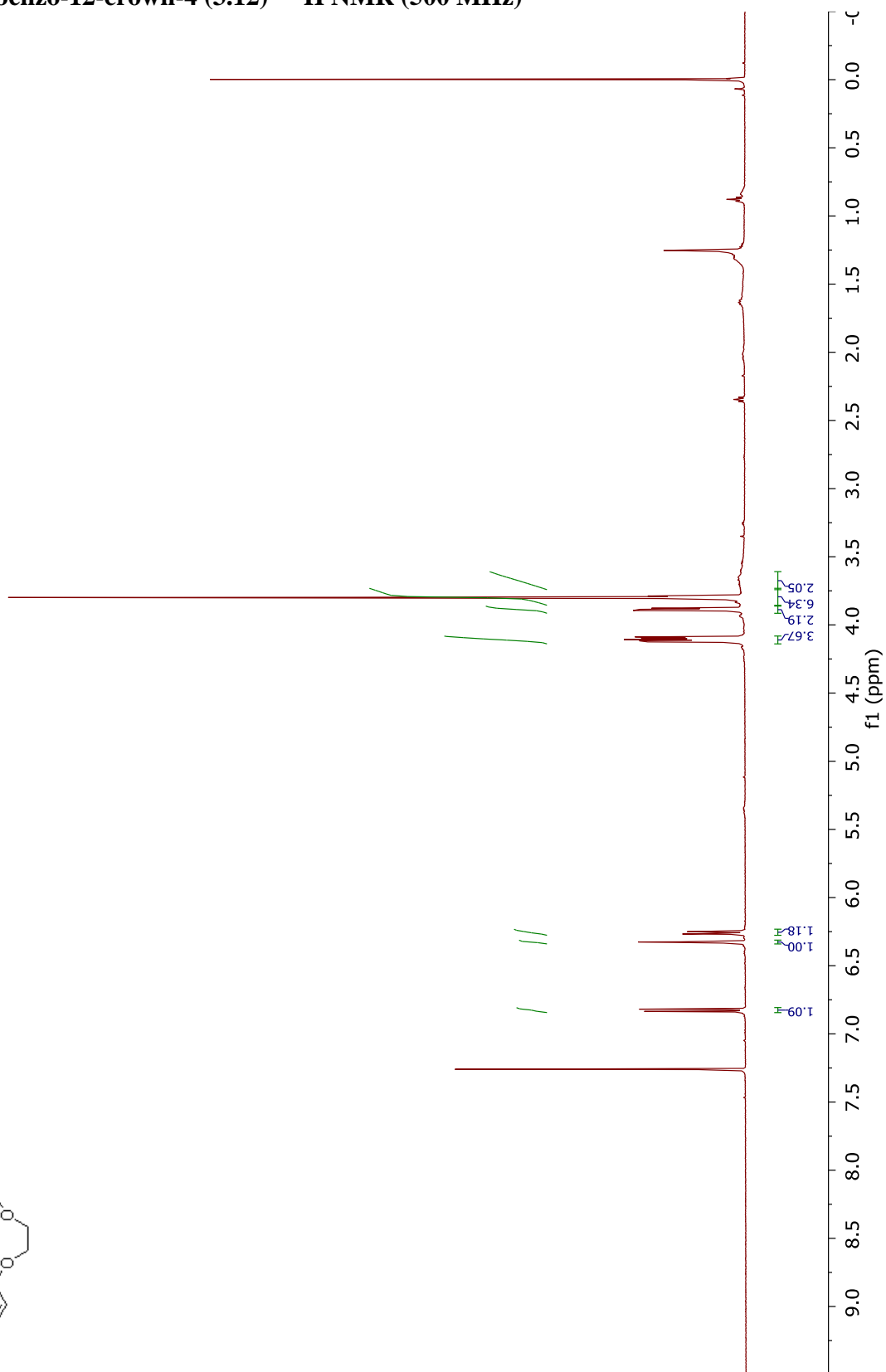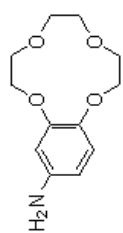
4-amino-benzo-12-crown-4 (3.12) – ^{13}C NMR (126 MHz)
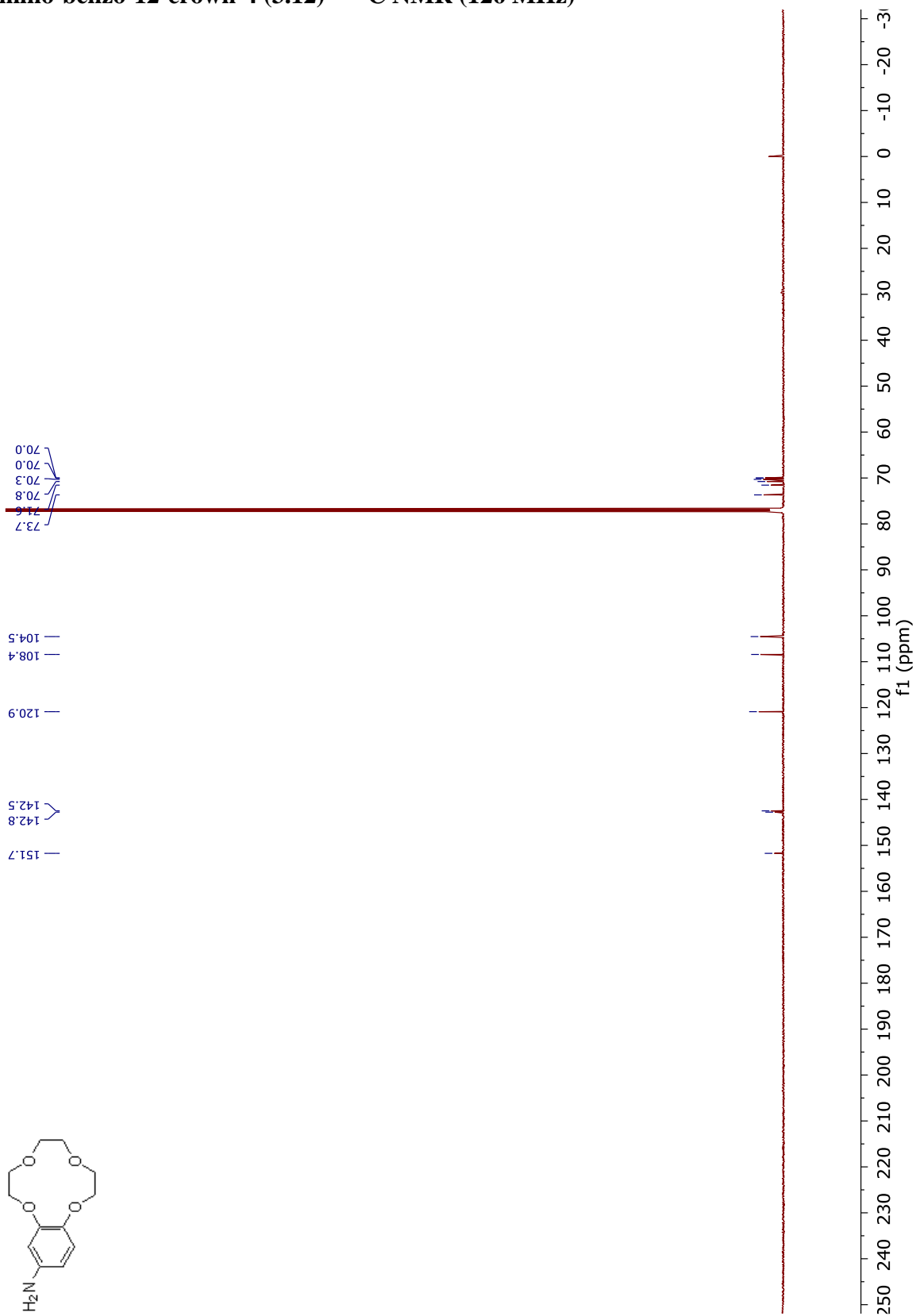
12-crown-4 Azobenzene 3.1 – ¹H NMR (500 MHz)
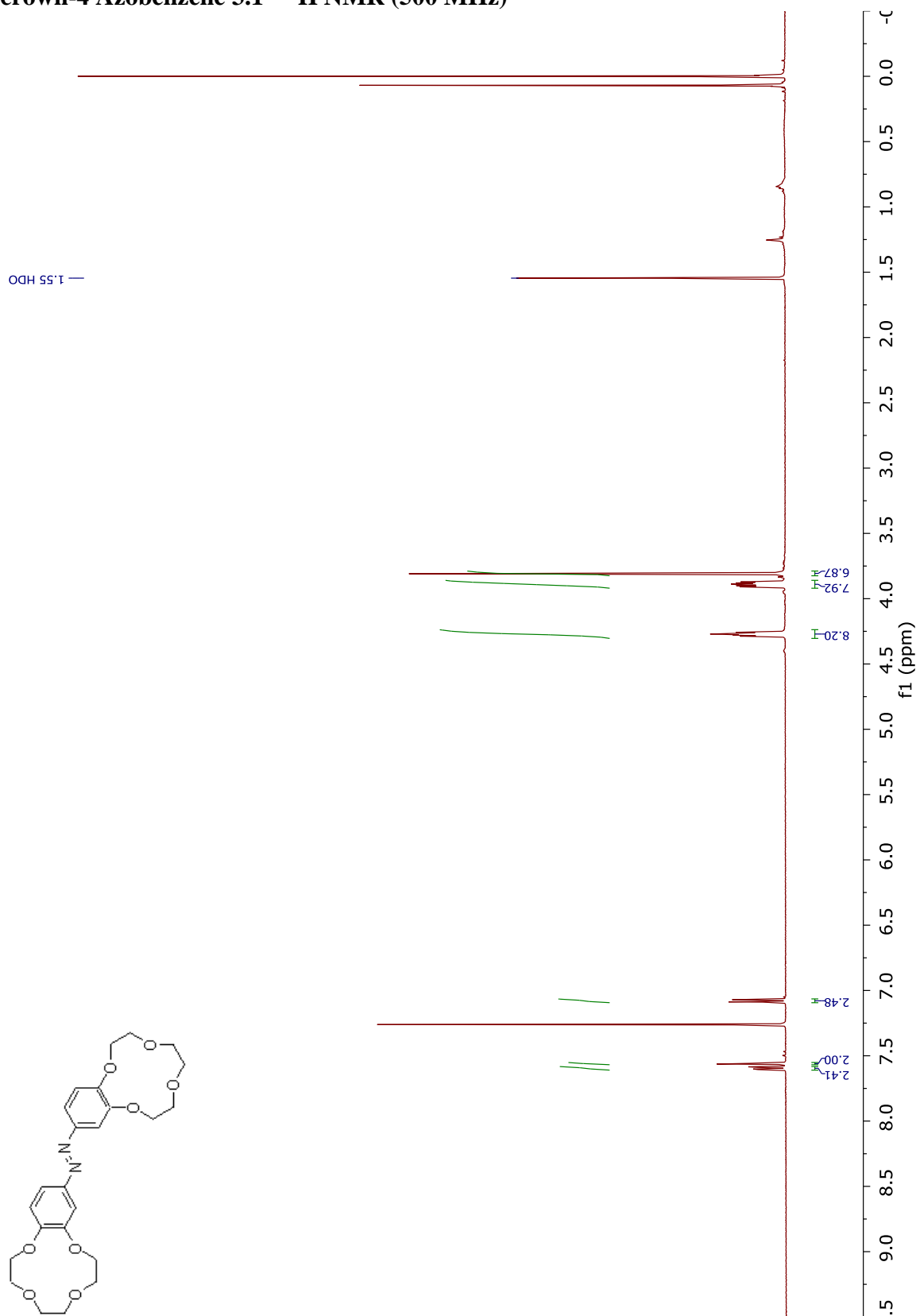
12-crown-4 Azobenzene 3.1 – ^{13}C NMR (126 MHz)

69.8
69.8
71.1
71.3
71.5
72.0

109.9

117.1
120.6

148.1
150.9
153.1

f1 (ppm)
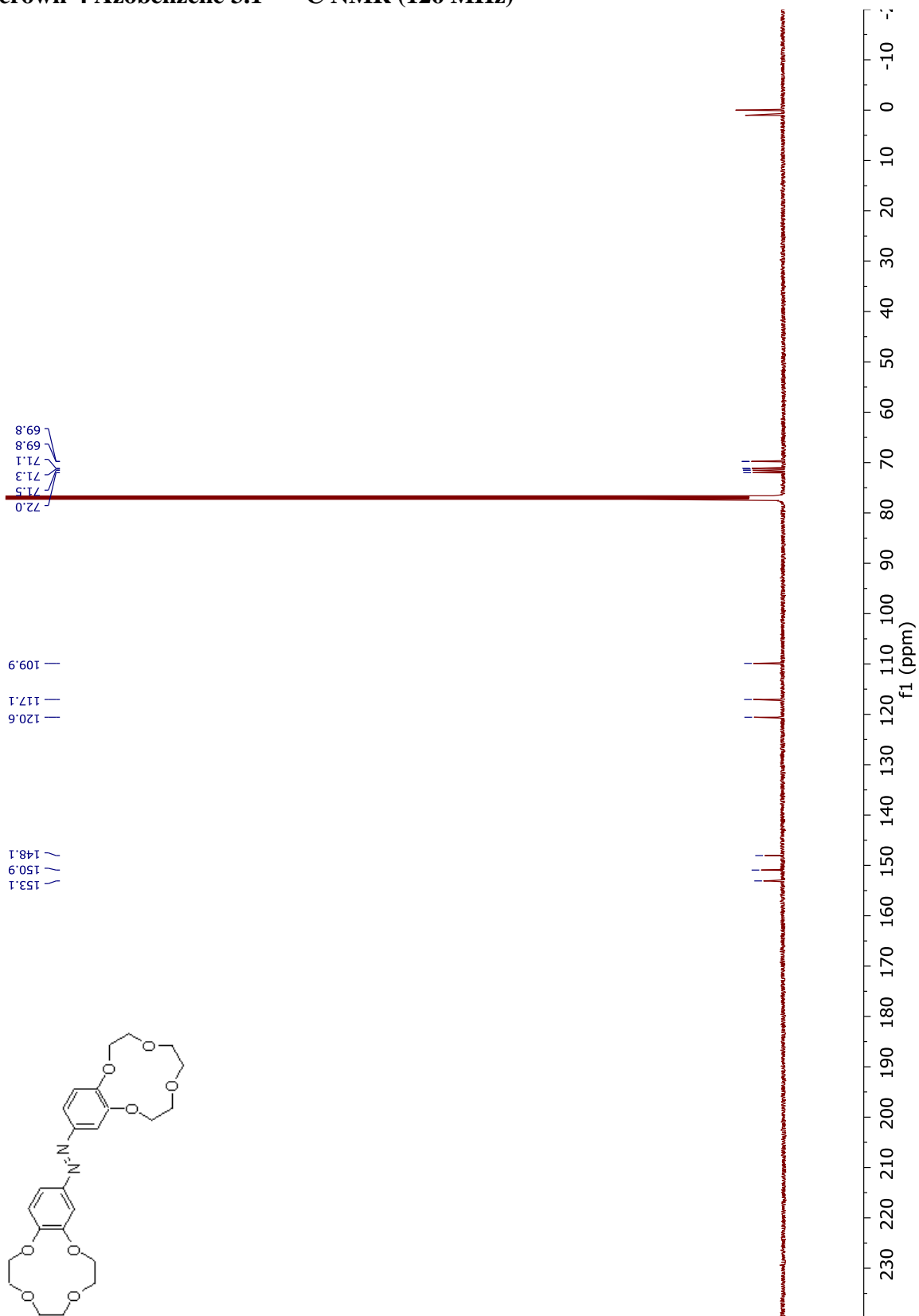
Benzo-15-crown-5 (3.9) – ¹H NMR (500 MHz)
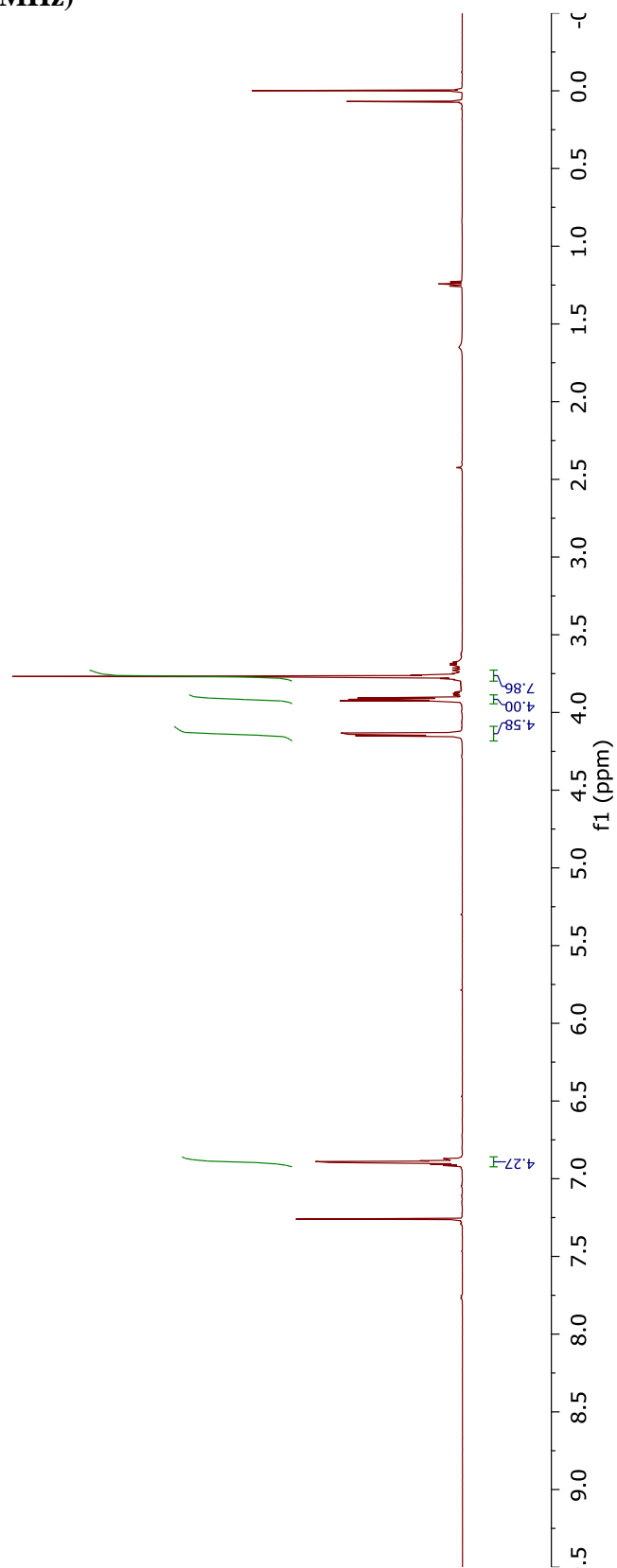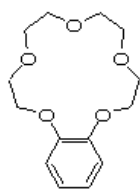
Benzo-15-crown-5 (3.9) – ^{13}C NMR (126 MHz)
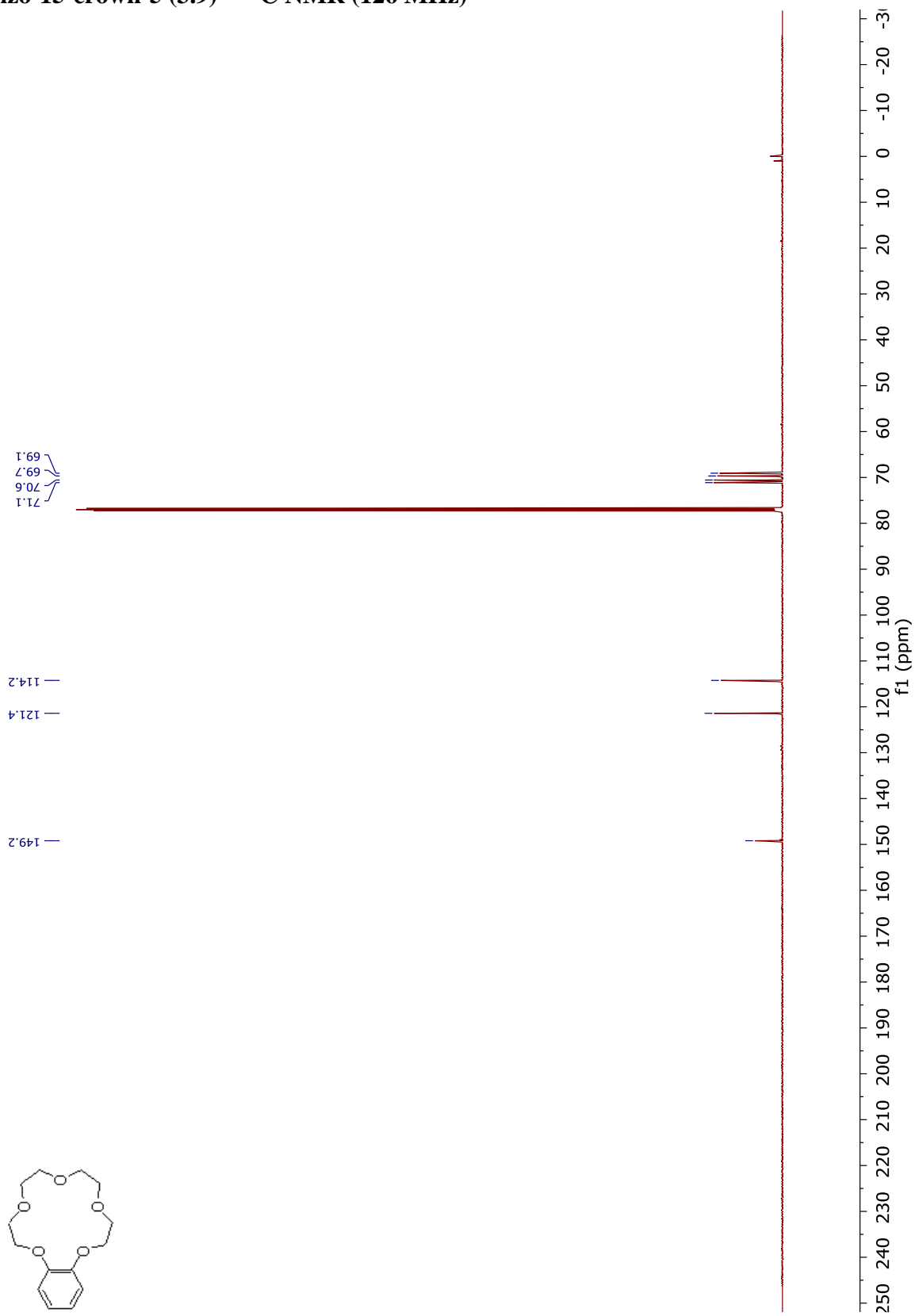
4-nitro-benzo-15-crown-5 (3.5) – ¹H NMR (500 MHz)

1.58 HDO

8.68
4.51
4.31

1.32

1.00
1.35

f1 (ppm)
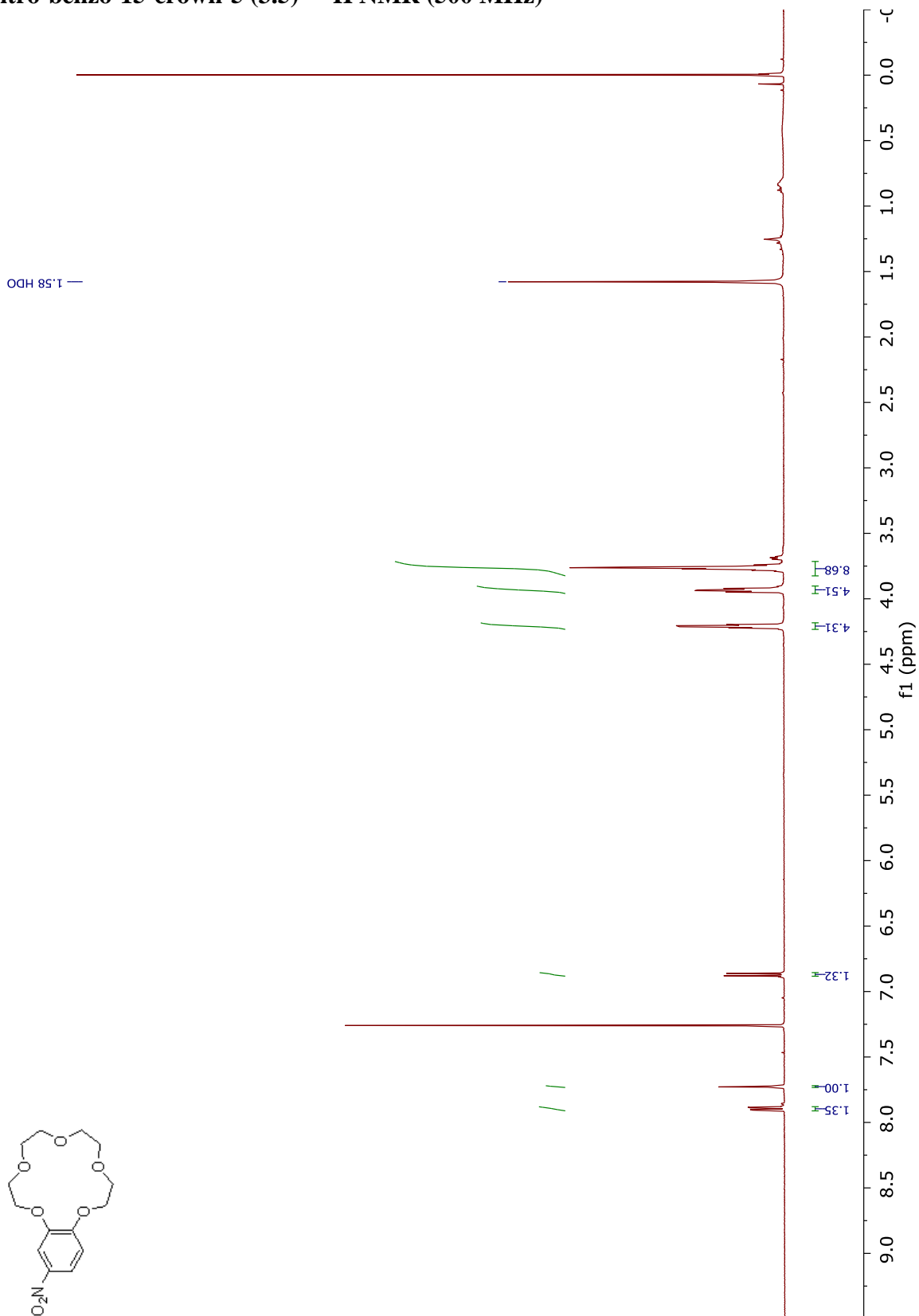
4-nitro-benzo-15-crown-5 (3.5) – ^{13}C NMR (126 MHz)
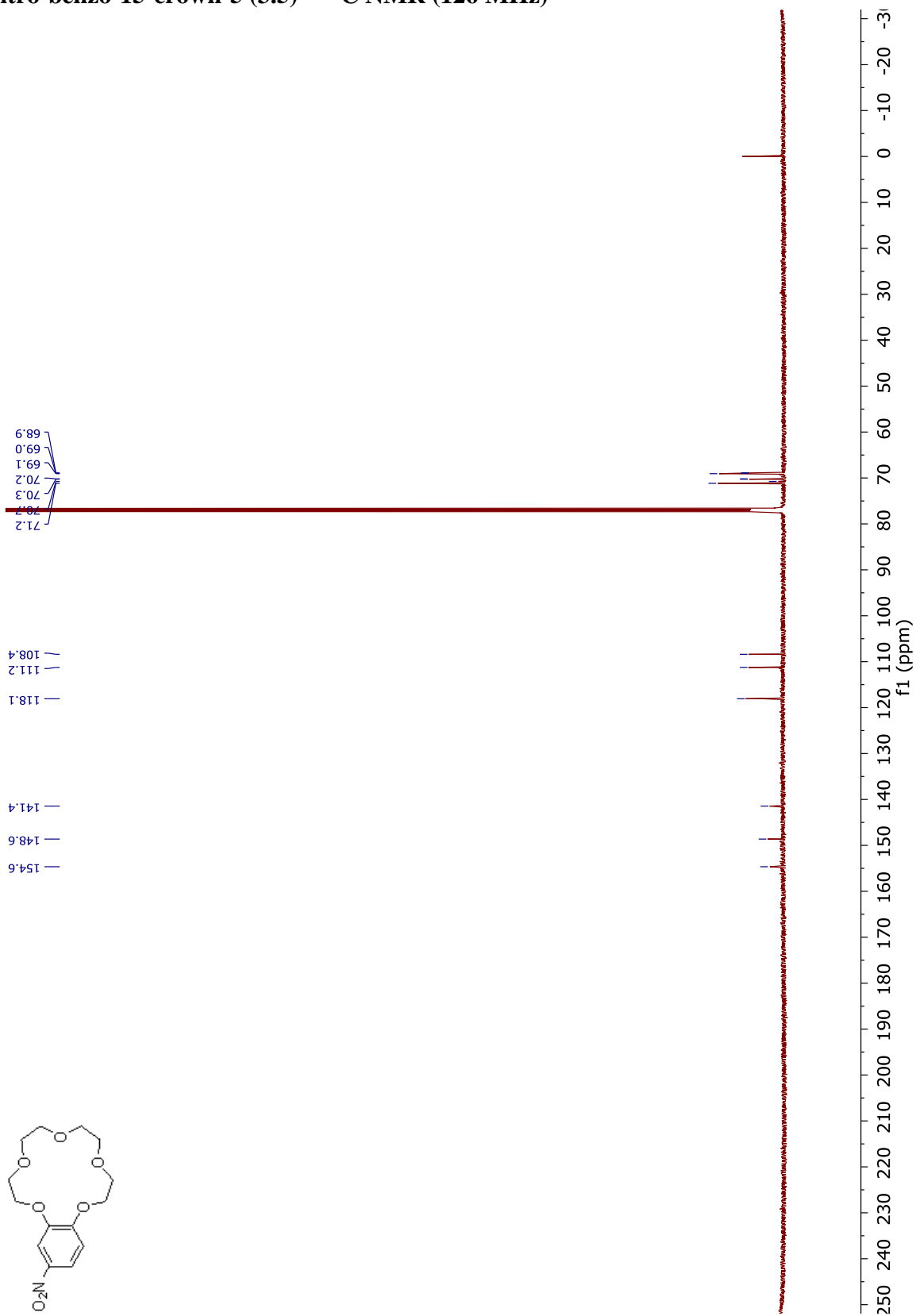
15-crown-5 Azobenzene 3.2 – ¹H NMR (500 MHz)
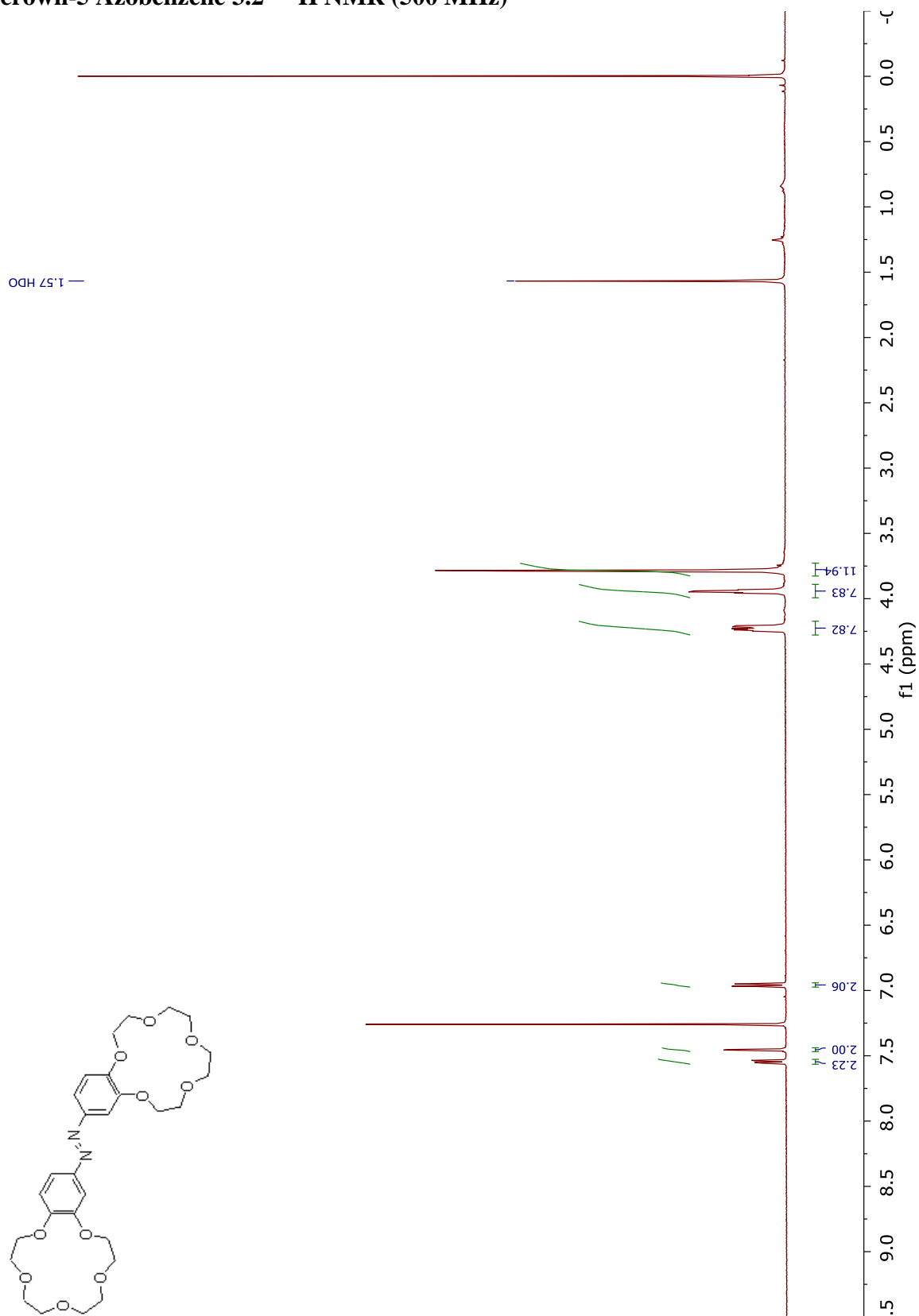
15-crown–5 Azobenzene 3.2 – ^{13}C NMR (126 MHz)
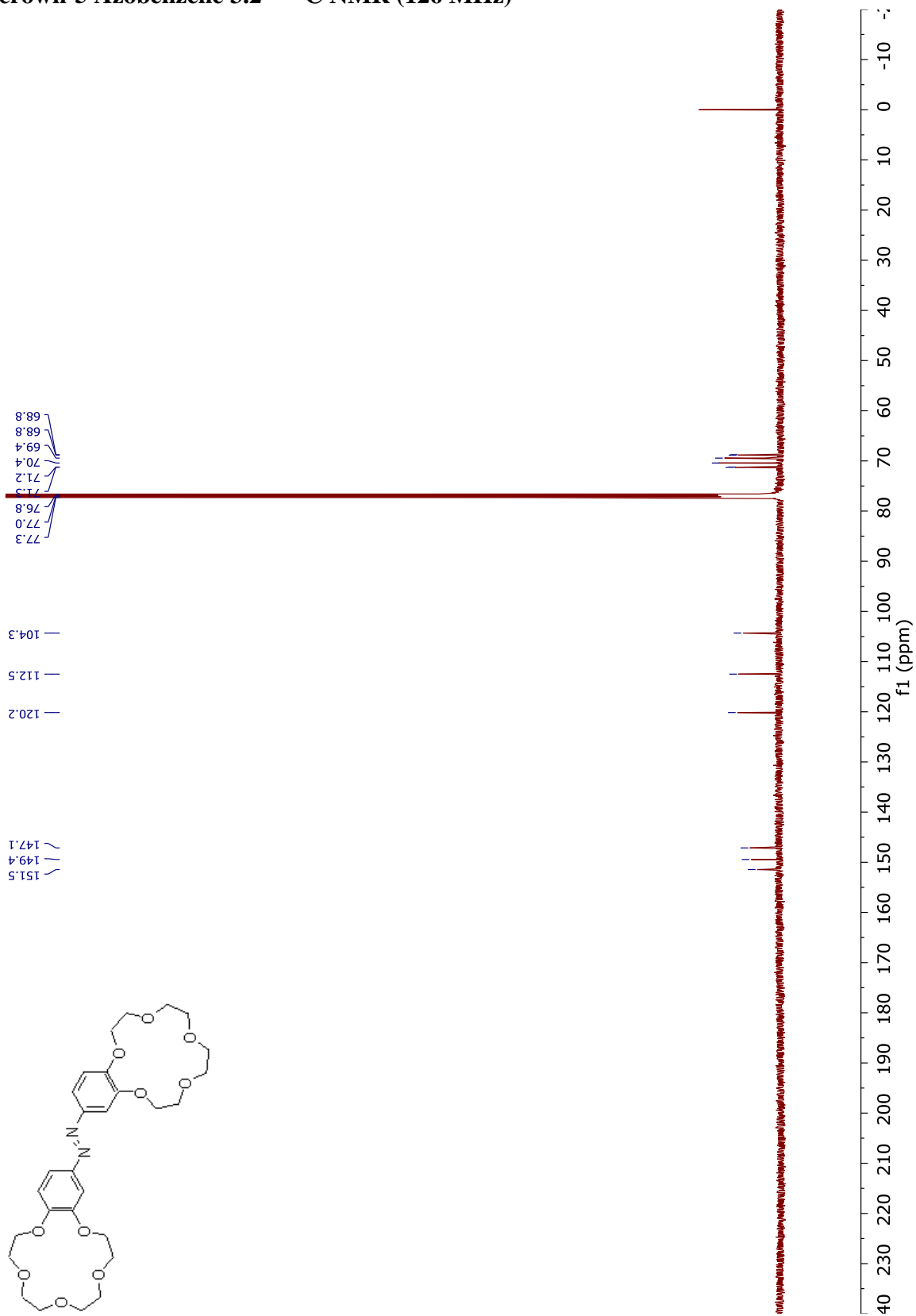
C-6 Lariat Ether (4.25) – ¹H NMR (500 MHz)
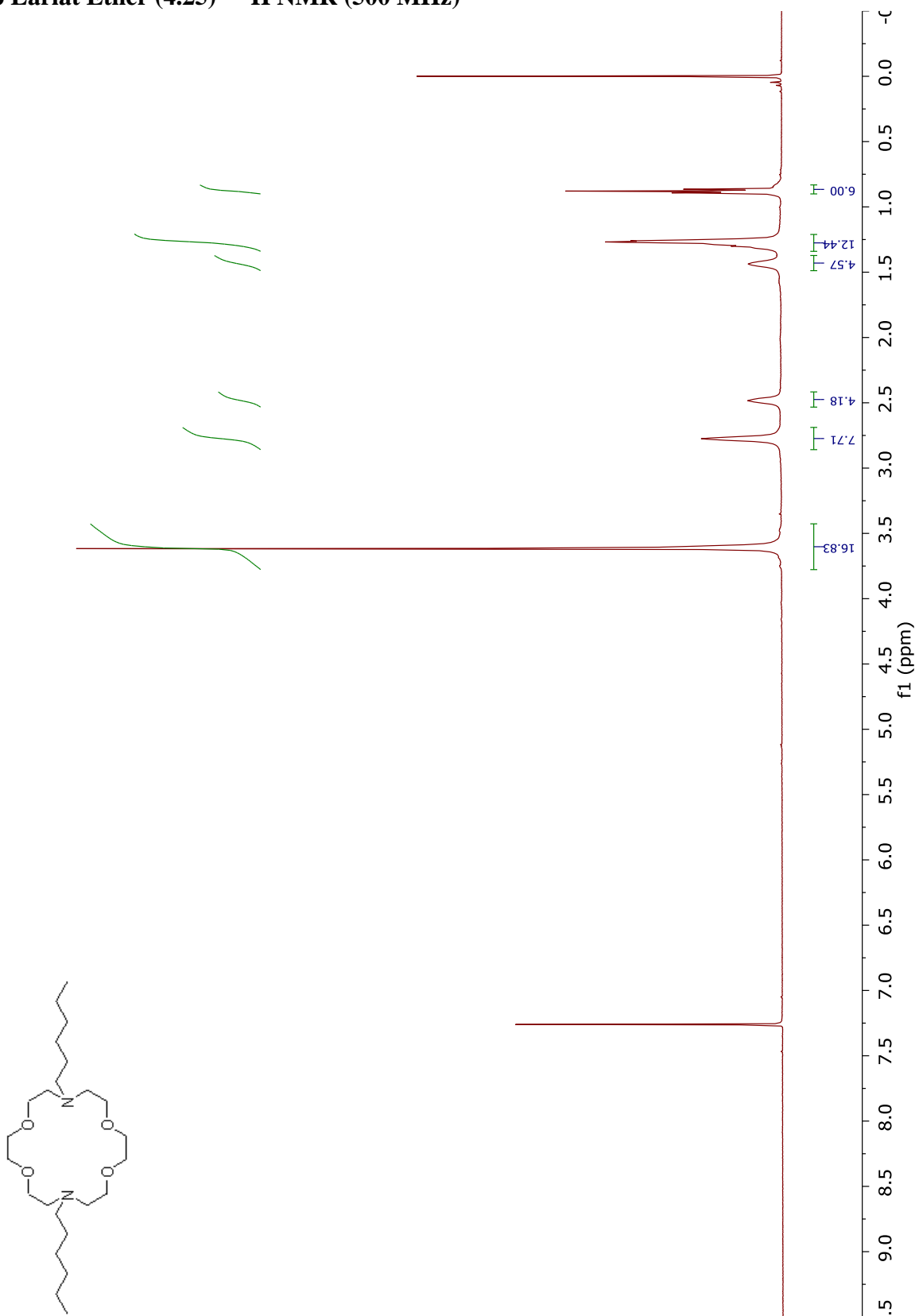
C-6 Lariat Ether (4.25) – ^{13}C NMR (126 MHz)

14.1

22.7
27.2
31.8

53.9
56.1

70.1
70.8

f1 (ppm)
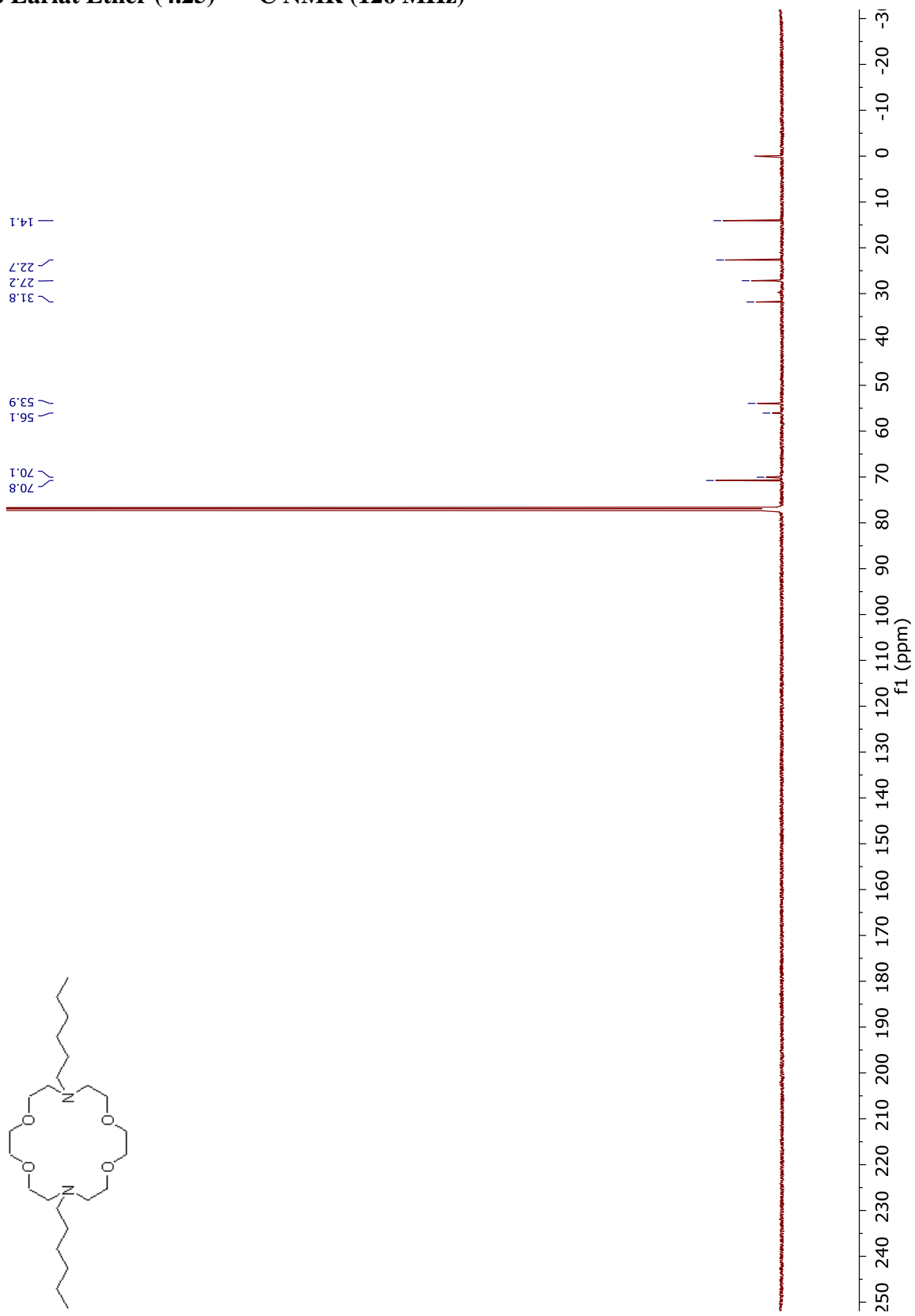
C-7 Lariat Ether (4.26) – ^{1}H NMR (500 MHz)

C-7 Lariat Ether (4.26) – ^{13}C NMR (126 MHz)

14.1

22.6
27.3
27.5
29.3
31.9

54.0
56.1

70.1
70.1
70.8
70.8
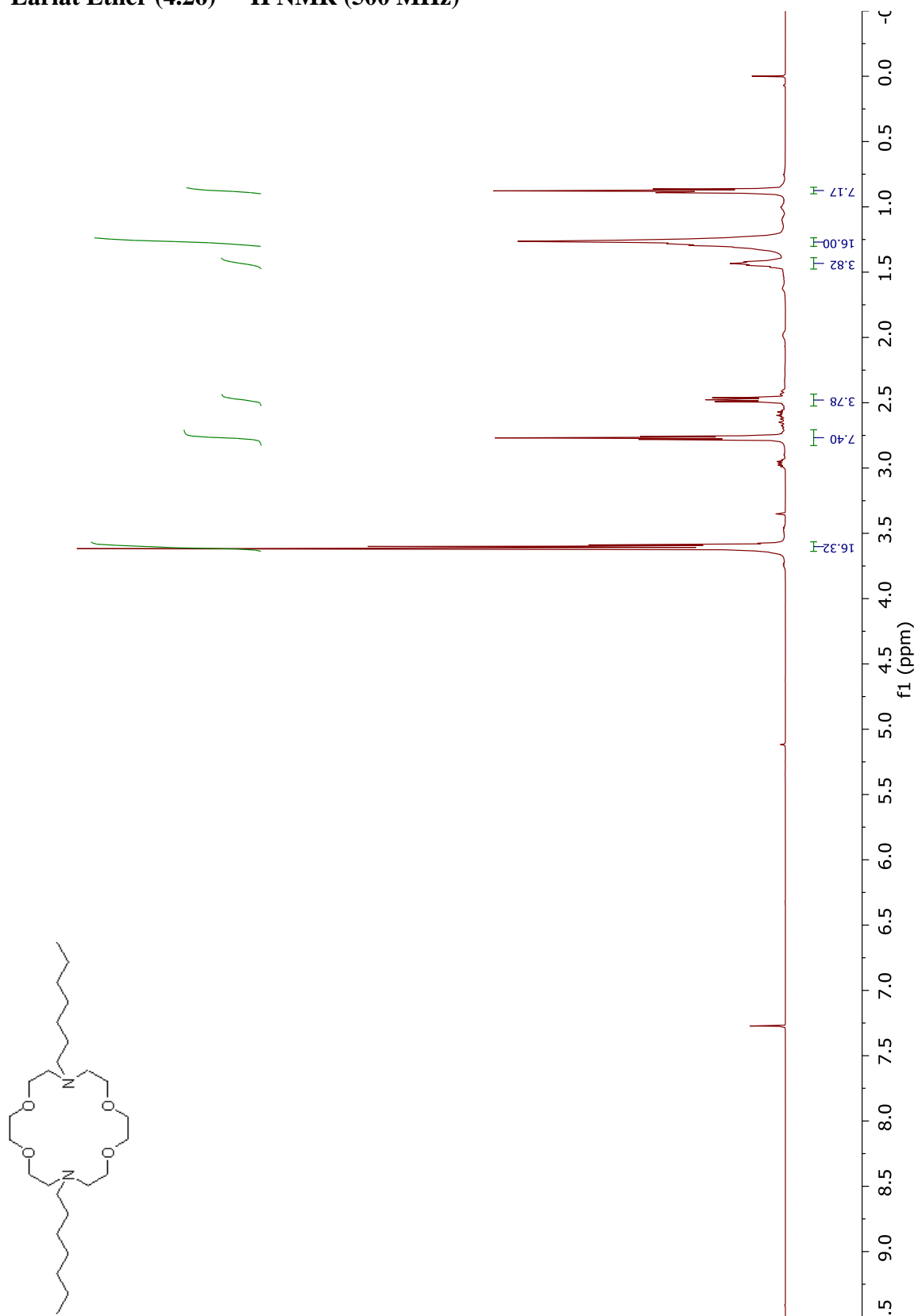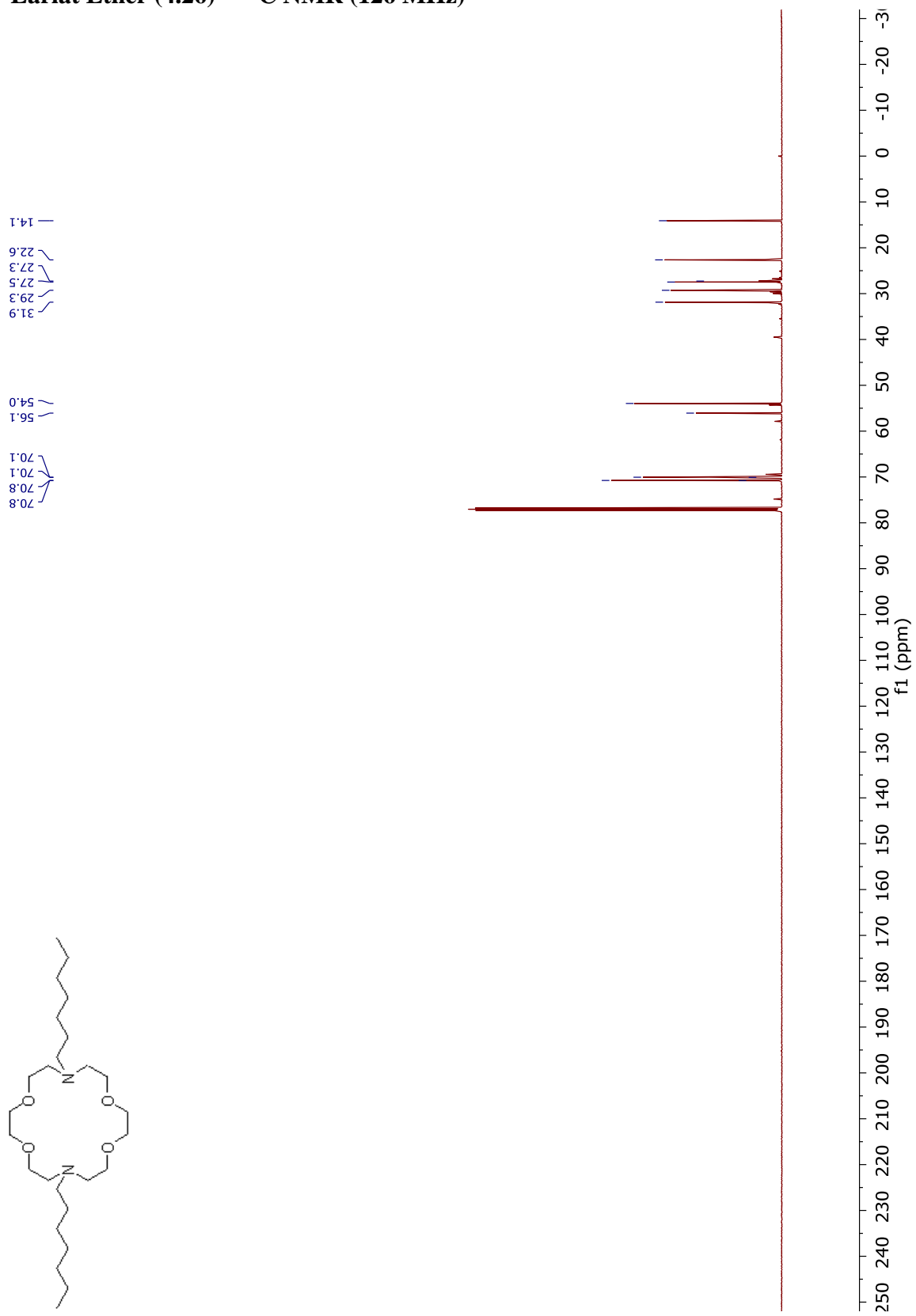
C-8 Lariat Ether (4.4) – ¹H NMR (500 MHz)

C-7 Lariat Ether (4.26) – ^{13}C NMR (126 MHz)

14.1
22.7
22.7
27.5
29.3
29.4
29.5
29.7
31.8

53.8
55.9

69.8
70.7

f1 (ppm)

250 240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -3
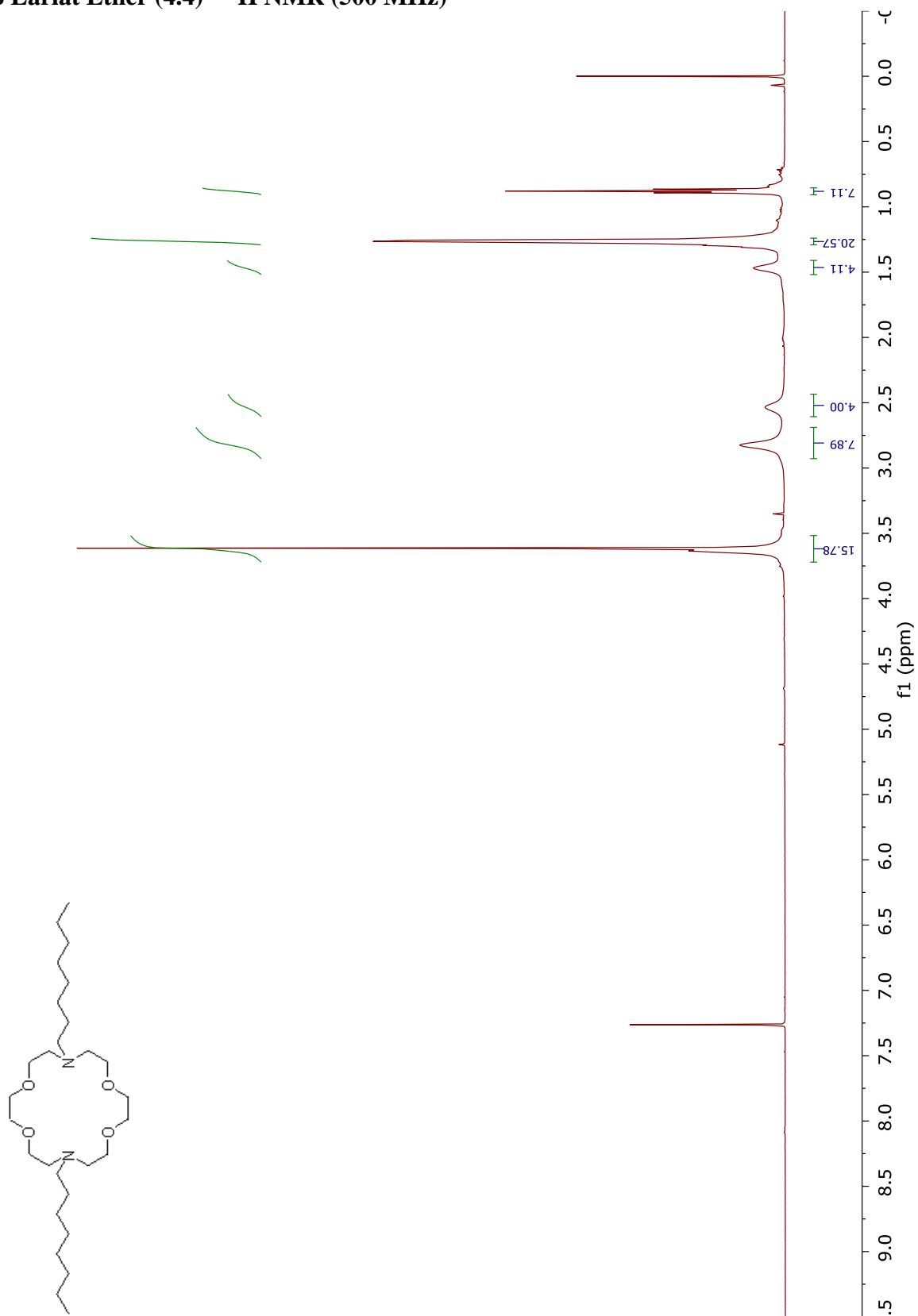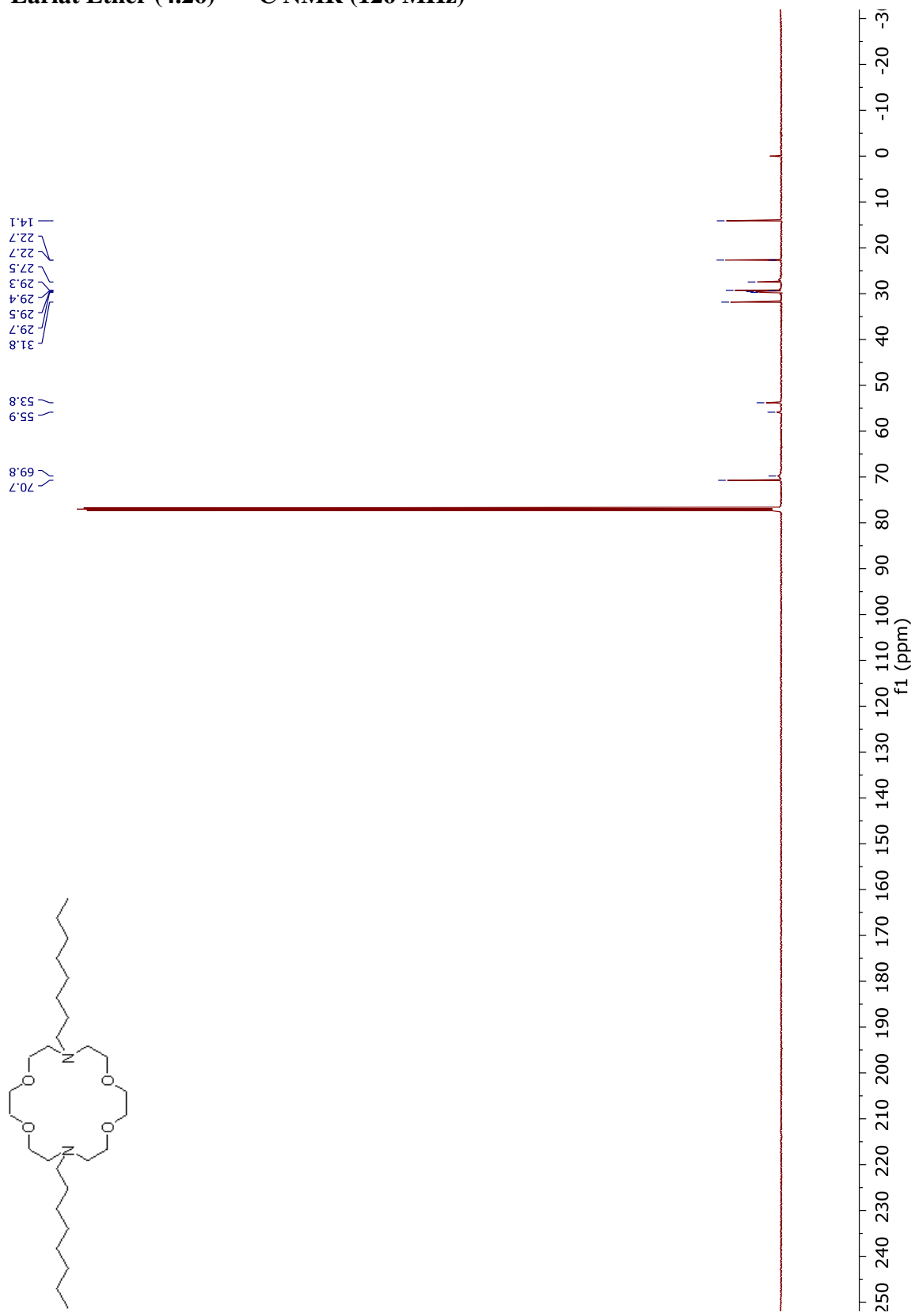
C-9 Lariat Ether (4.27) – ¹H NMR (500 MHz)
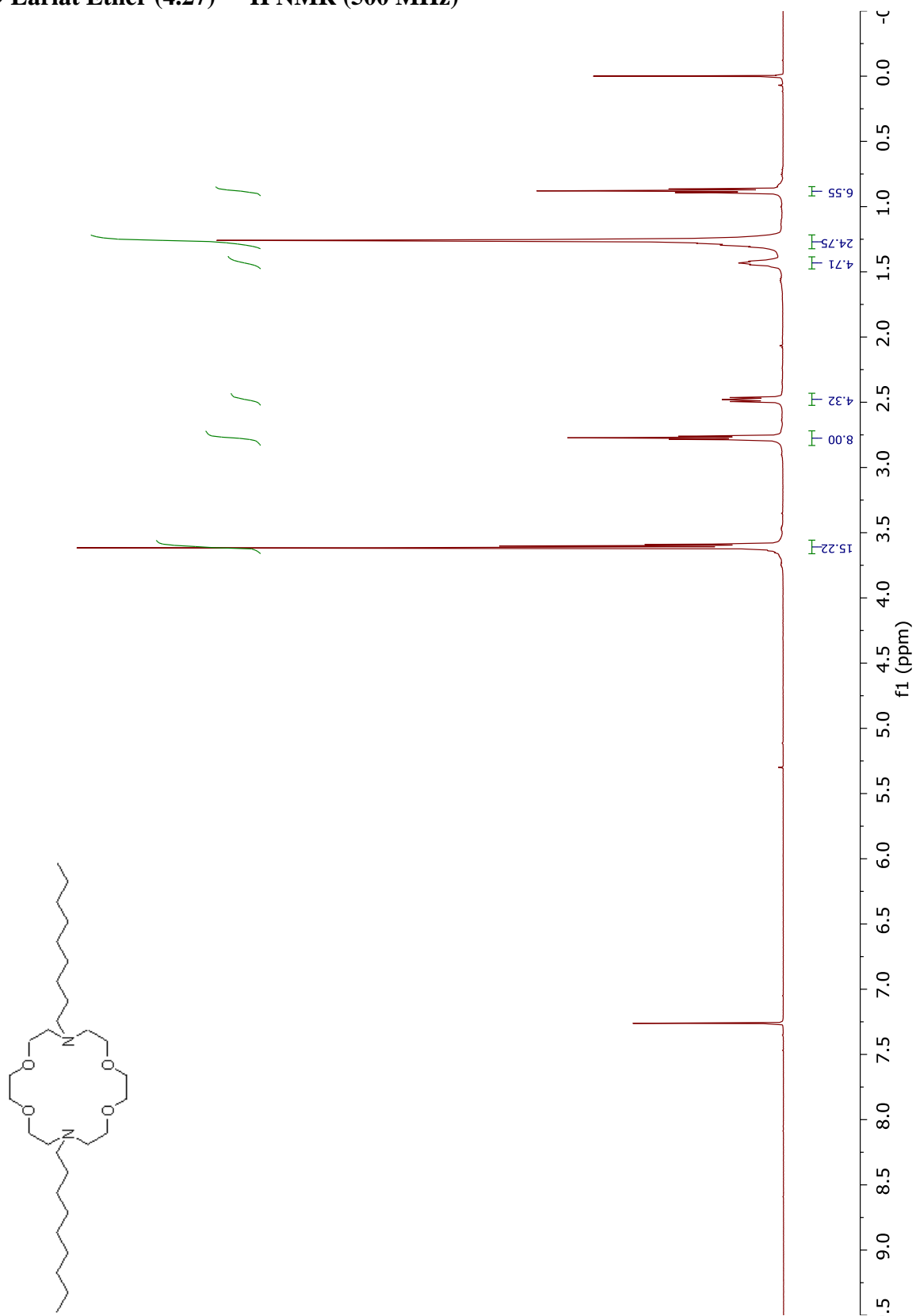
C-9 Lariat Ether (4.27) – ^{13}C NMR (126 MHz)

14.1
22.7
27.3
27.5
29.3
29.6
29.6
29.7
31.9

53.9
56.1

70.0
70.8

f1 (ppm)
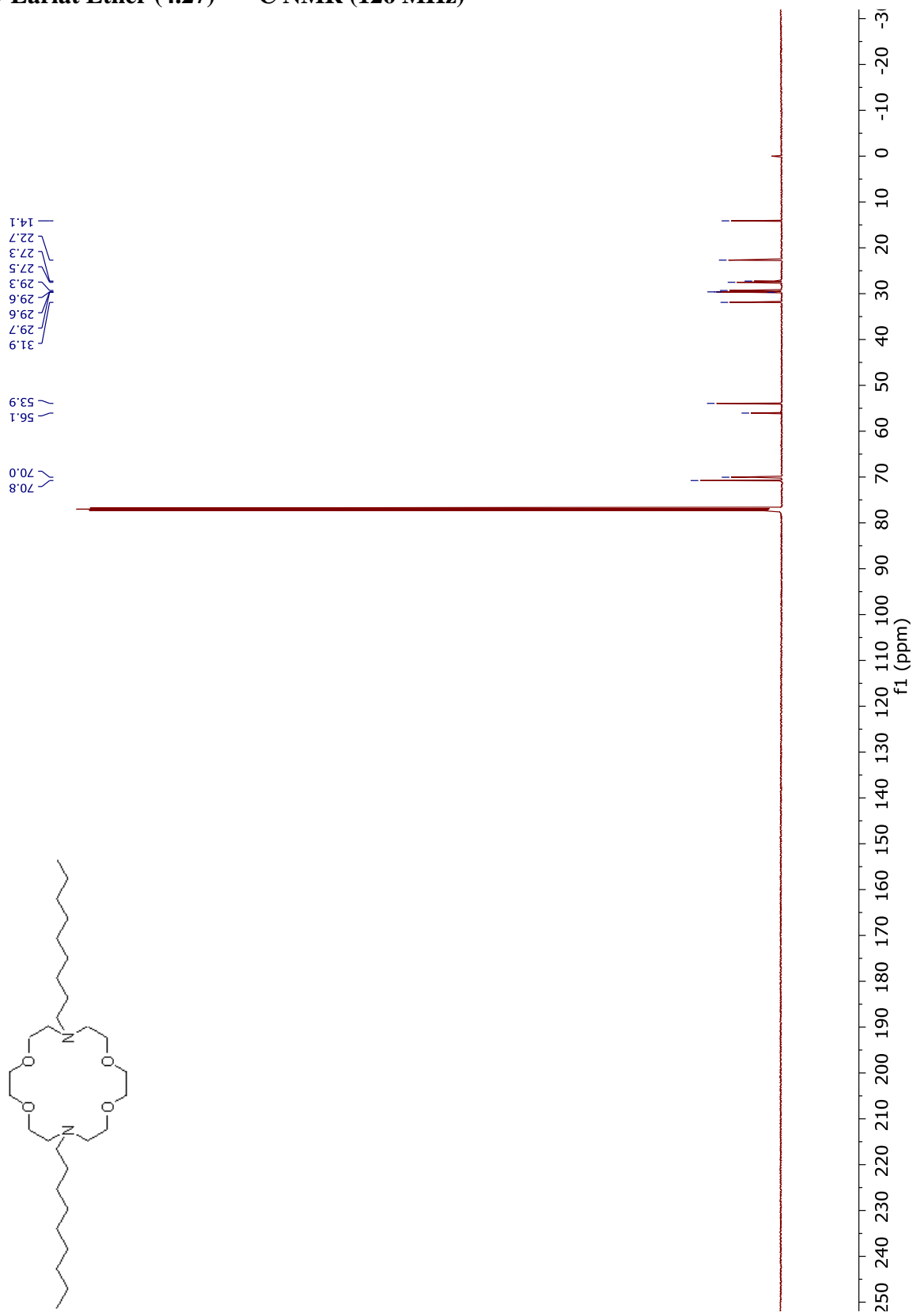
C-10 Lariat Ether (4.5) – ^{1}H NMR (500 MHz)
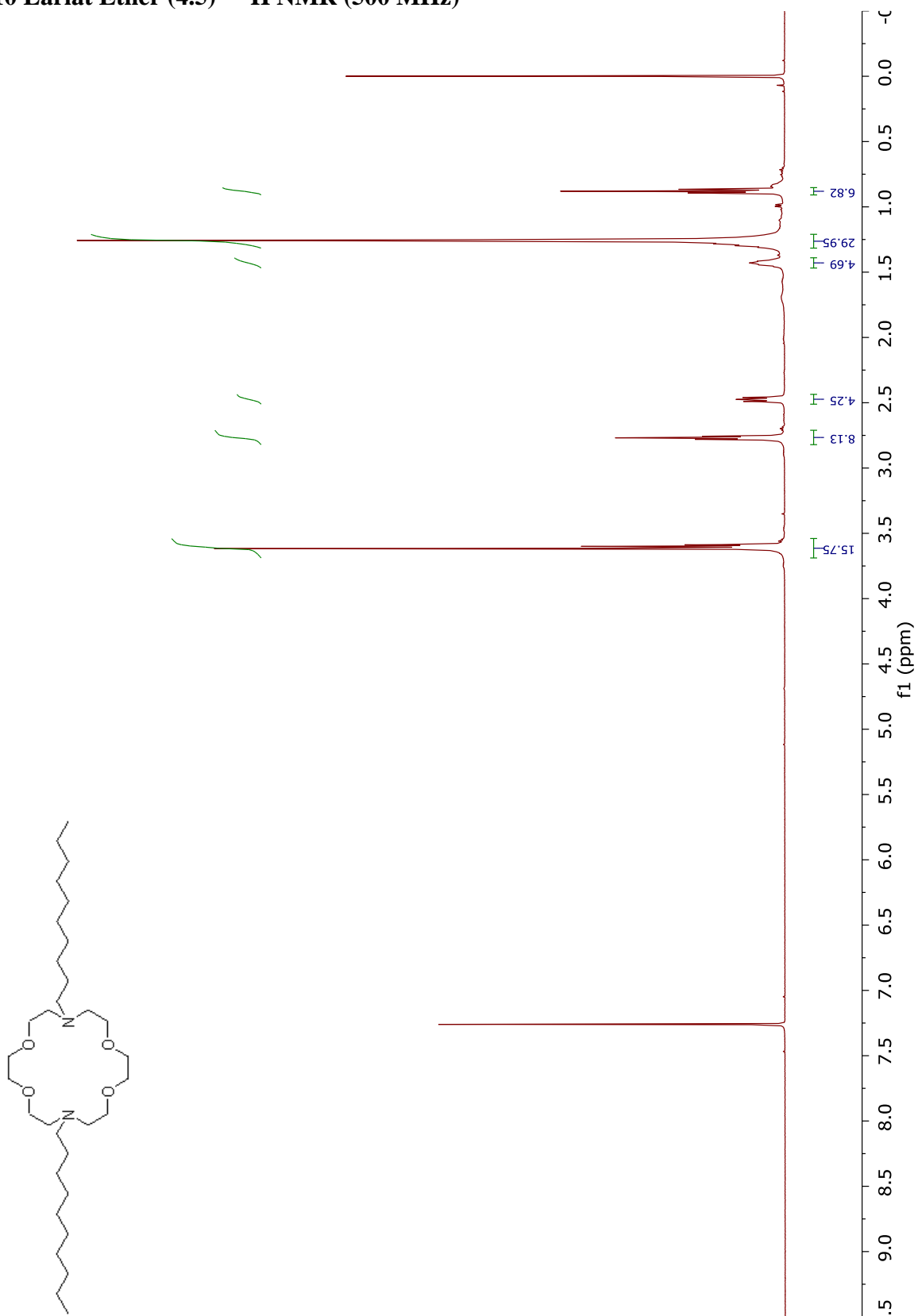
C-10 Lariat Ether (4.5) – ^{13}C NMR (126 MHz)

14.1
22.7
27.3
27.5
29.3
29.6
29.6
29.7
29.7
31.9

54.0
56.1

70.1
70.8

f1 (ppm)

250 240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -3
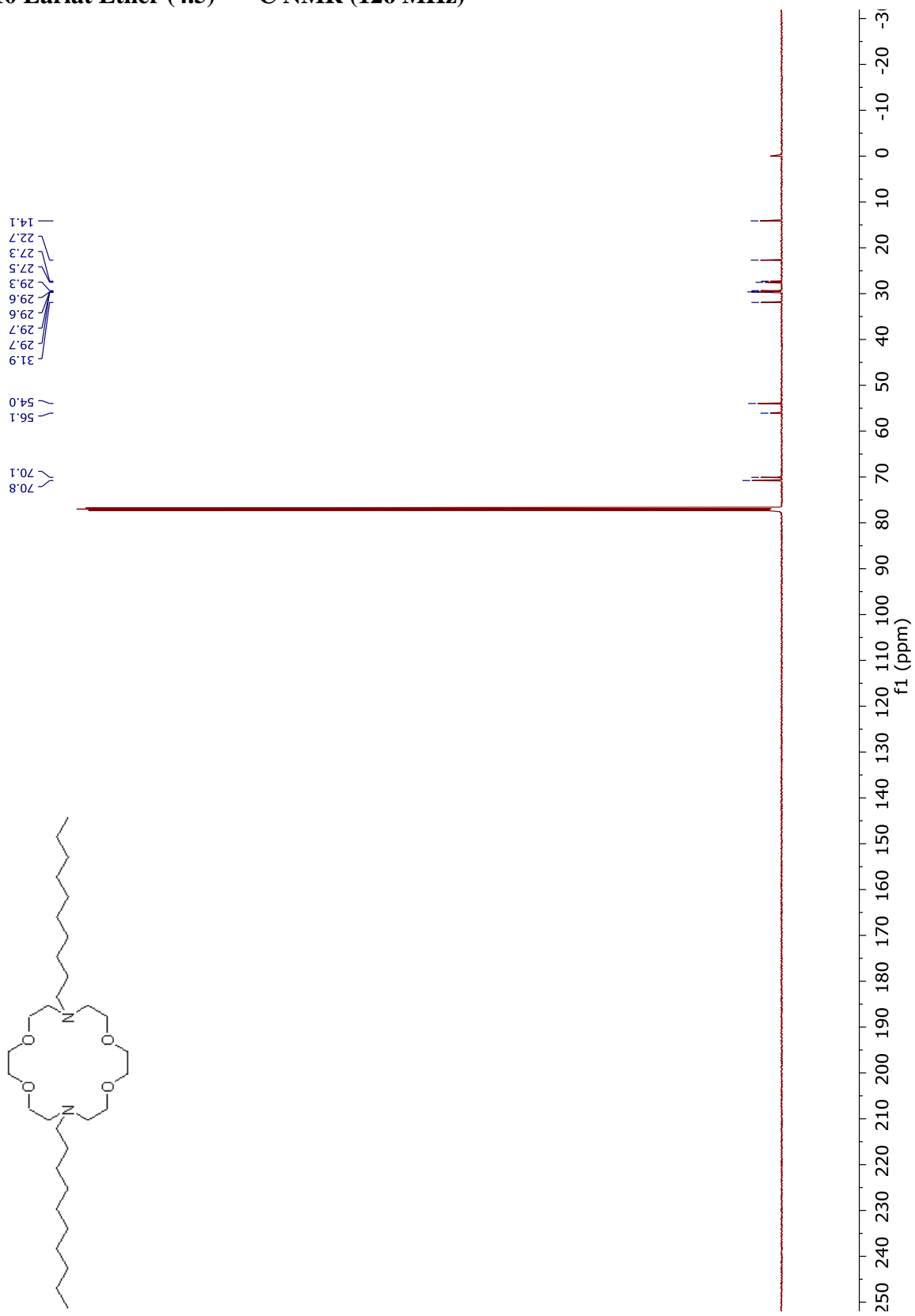
C-11 Lariat Ether (4.28) – ¹H NMR (500 MHz)
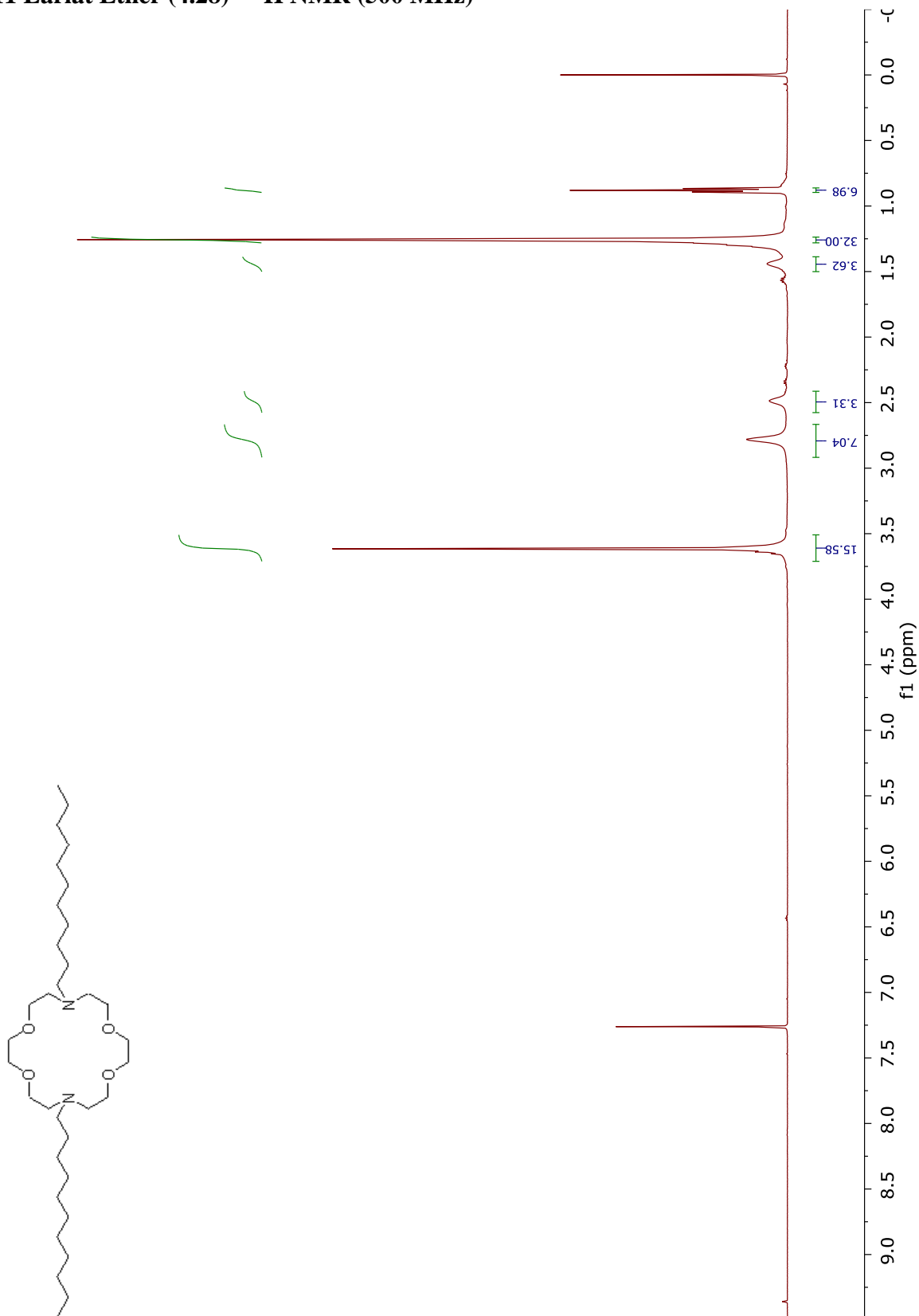
C-11 Lariat Ether (4.28) – ^{13}C NMR (126 MHz)

14.1
22.7
25.7
27.2
27.5
29.4
29.4
29.6
29.6
31.9
31.9
32.8
53.9
56.0
63.1
70.0
70.7

f1 (ppm)
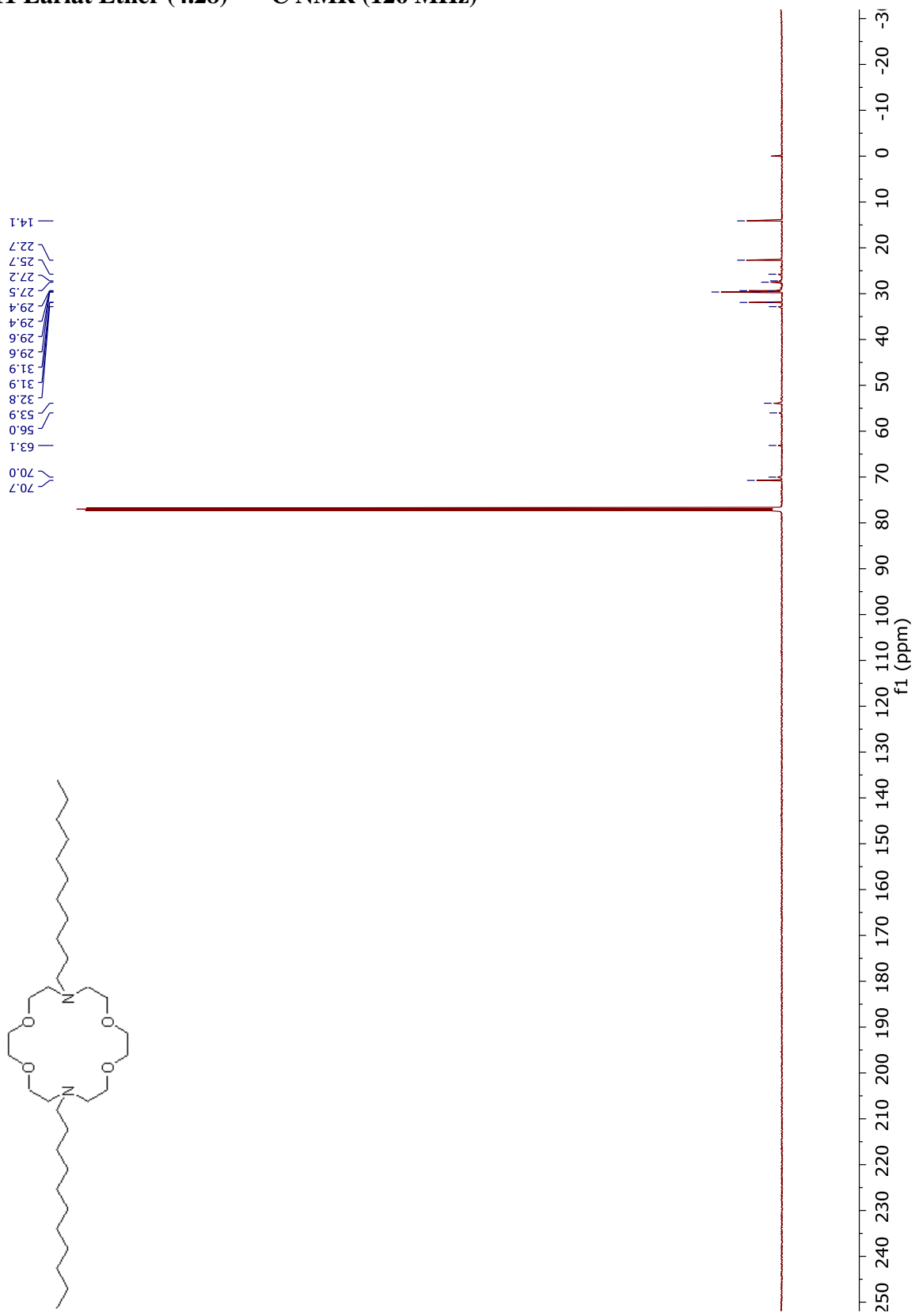
C-12 Lariat Ether (4.6) – ¹H NMR (500 MHz)
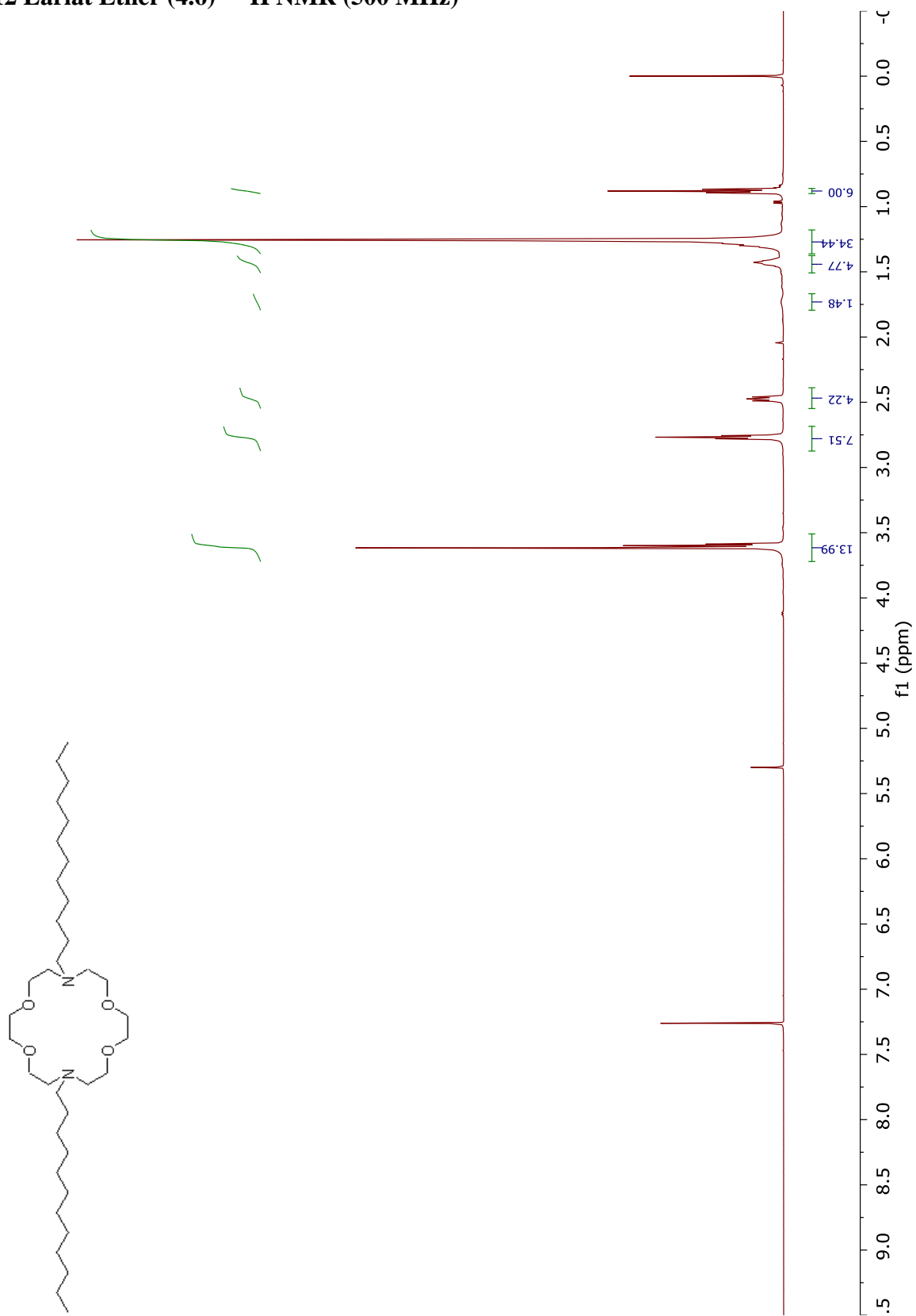
C-12 Lariat Ether (4.6) – ^{13}C NMR (126 MHz)
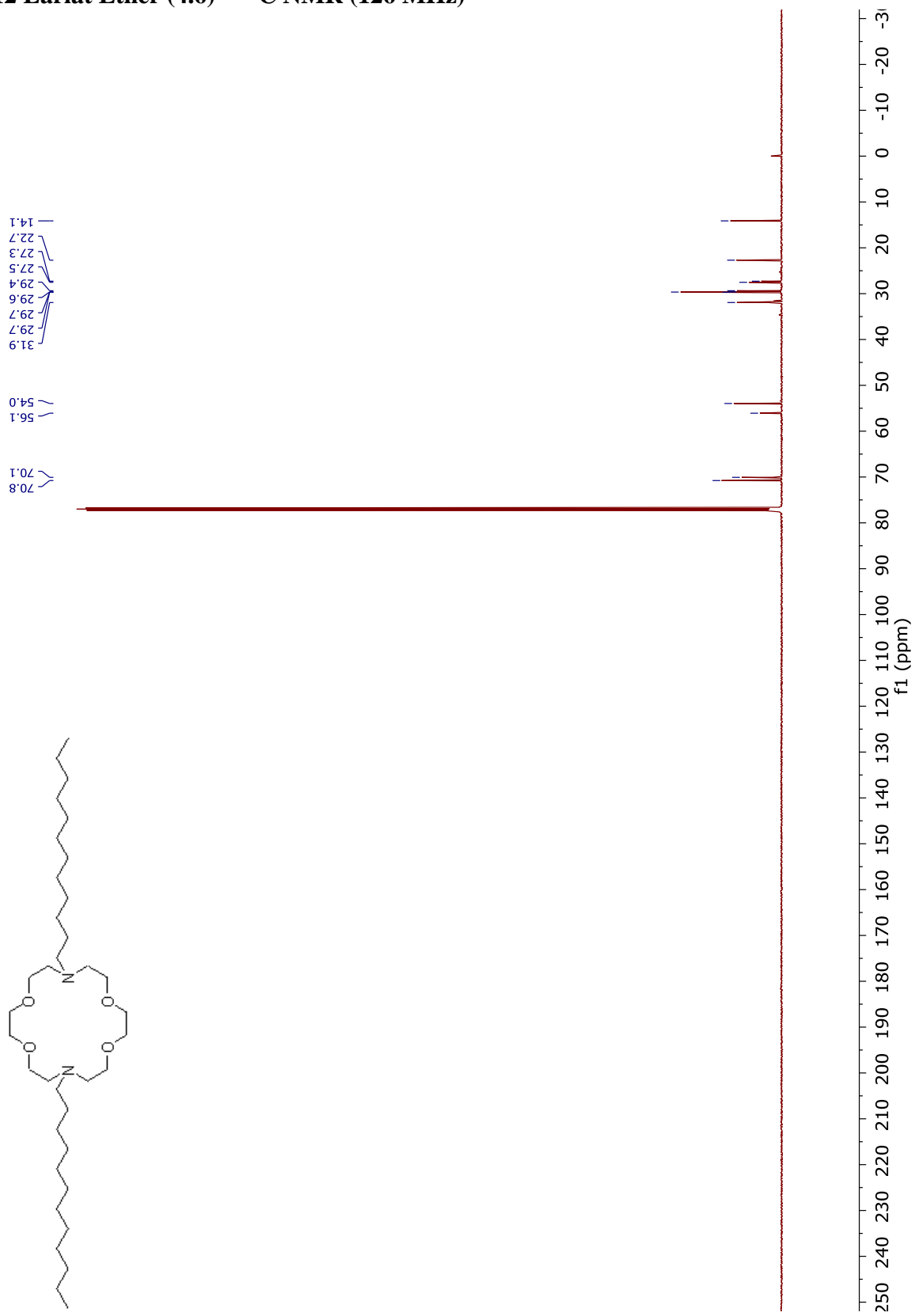
Tridecanal – ¹H NMR (500 MHz)

Tridecanal – ^{13}C NMR (126 MHz)

14.1
22.1
22.7
29.2
29.3
29.4
29.4
29.6
29.6
29.6
31.9
43.9

202.9
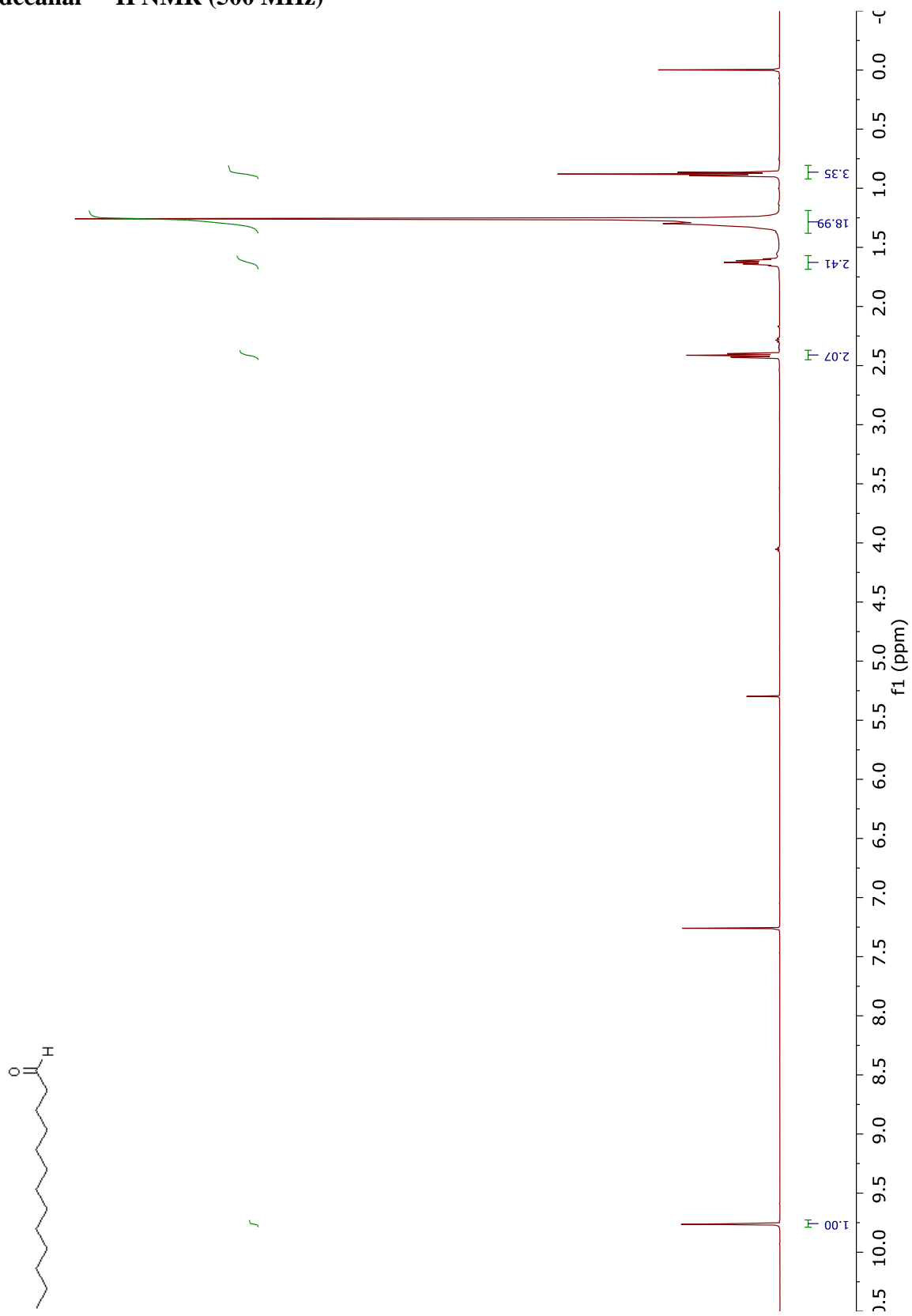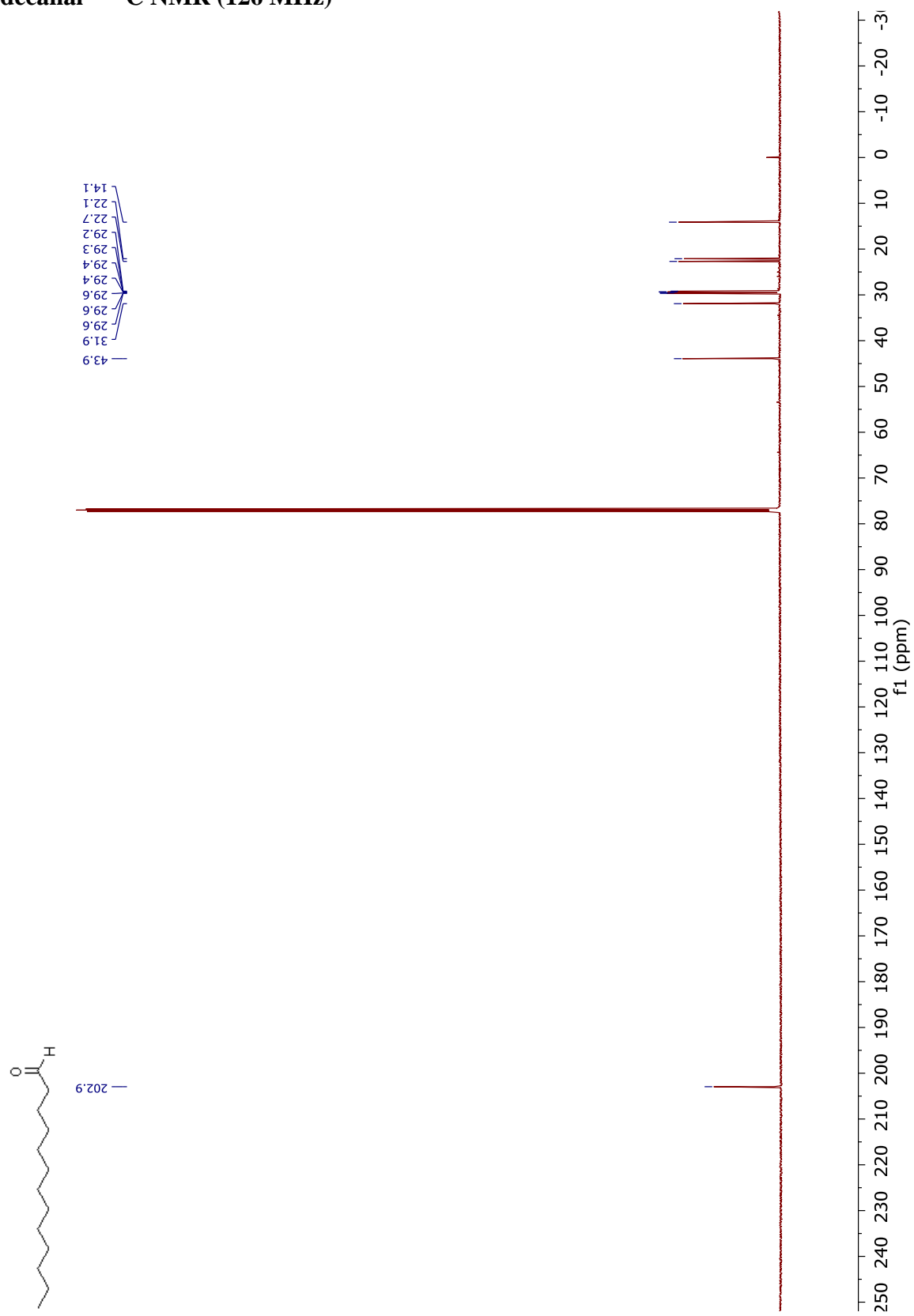
C-13 Lariat Ether (4.29) – ¹H NMR (500 MHz)
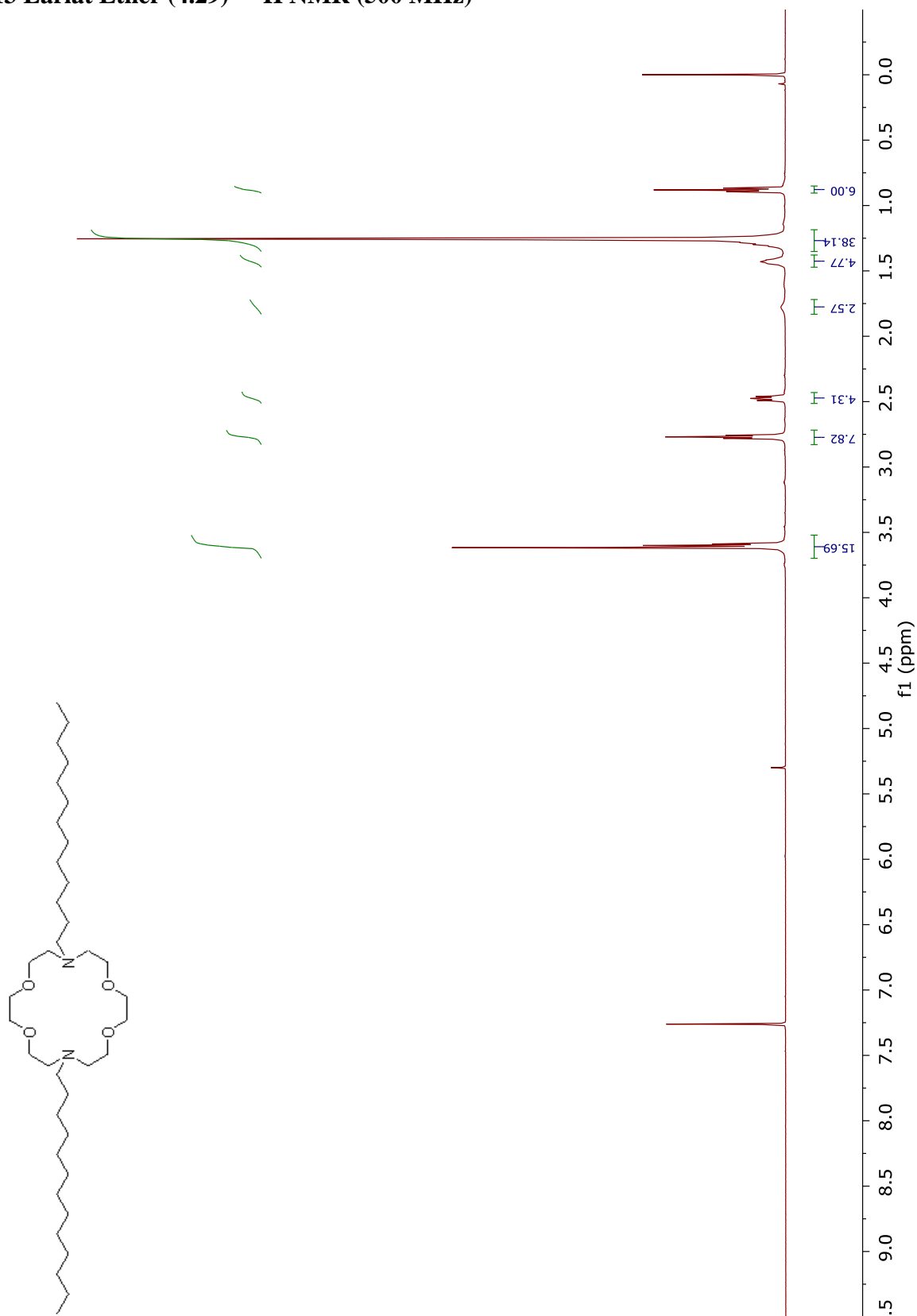
C-13 Lariat Ether (4.29) – ^{13}C NMR (126 MHz)

14.1
22.7
27.3
27.5
29.4
29.6
29.7
29.7
29.7
31.9

54.0
56.1

70.1
70.8

f1 (ppm)
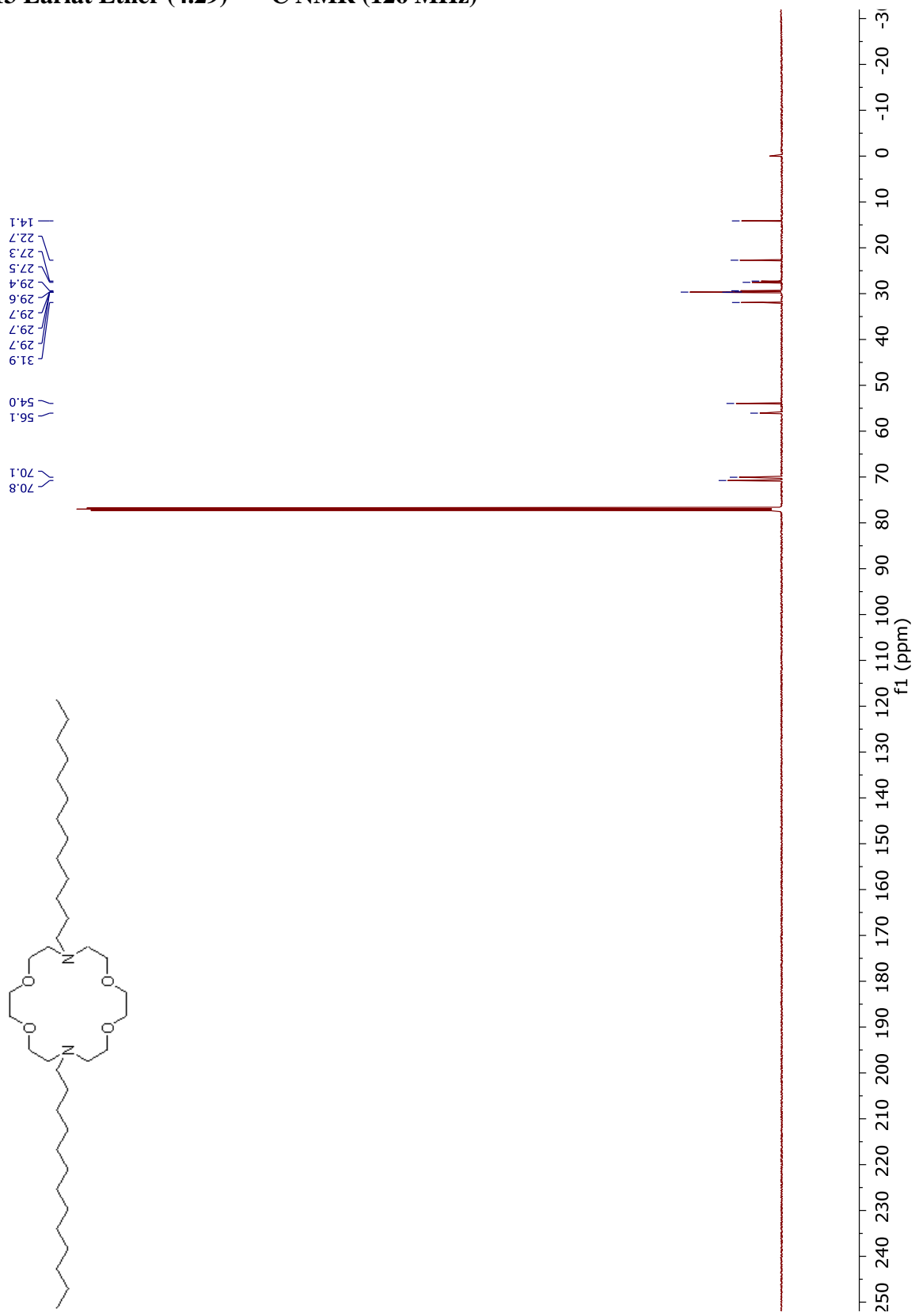
Tetradecanal – ¹H NMR (500 MHz)

Tetradecanal – ^{13}C NMR (126 MHz)

14.1
22.1
22.7
29.2
29.4
29.4
29.6
29.6
29.7
31.9
43.9

202.9

f1 (ppm)

250 240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -3
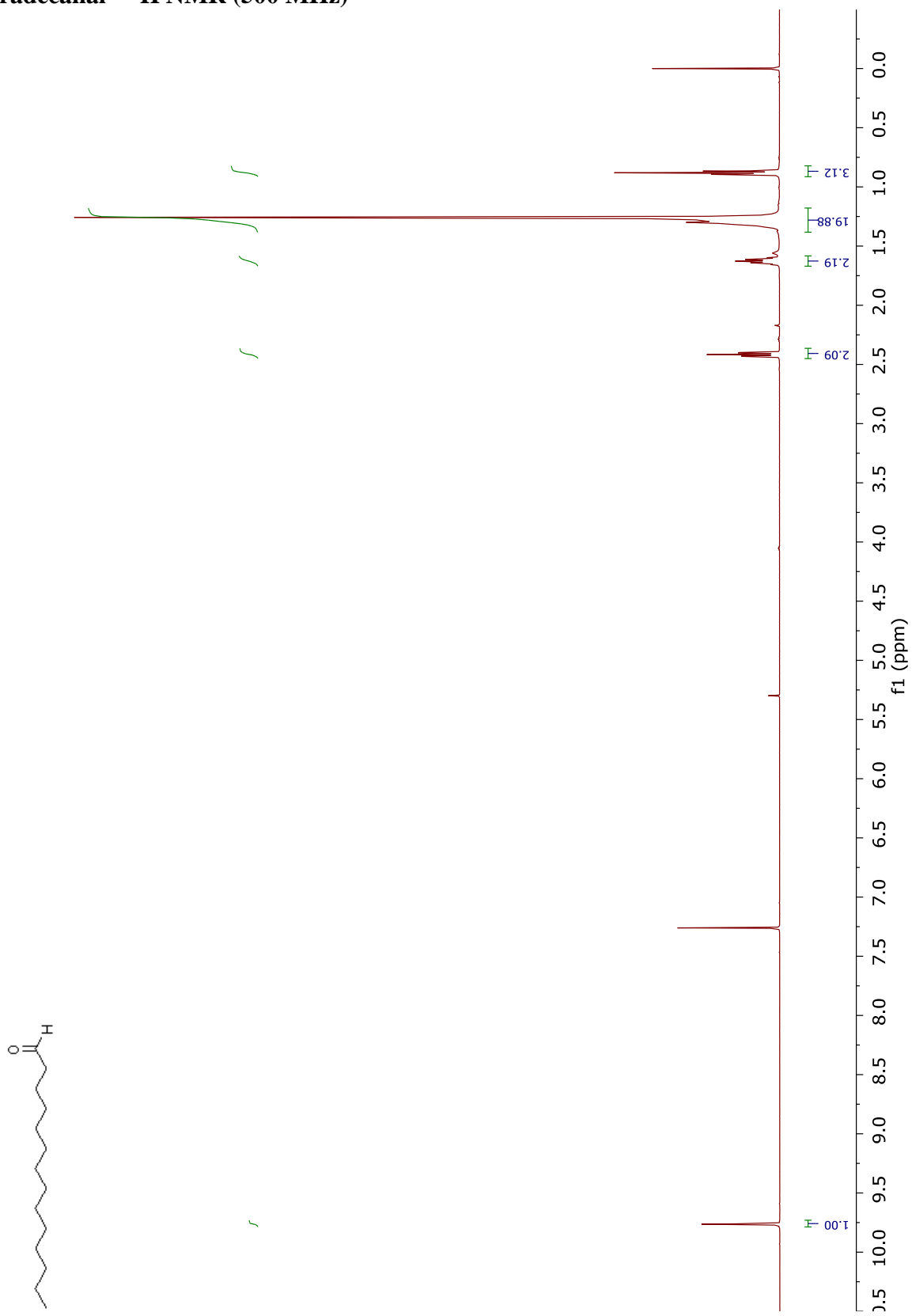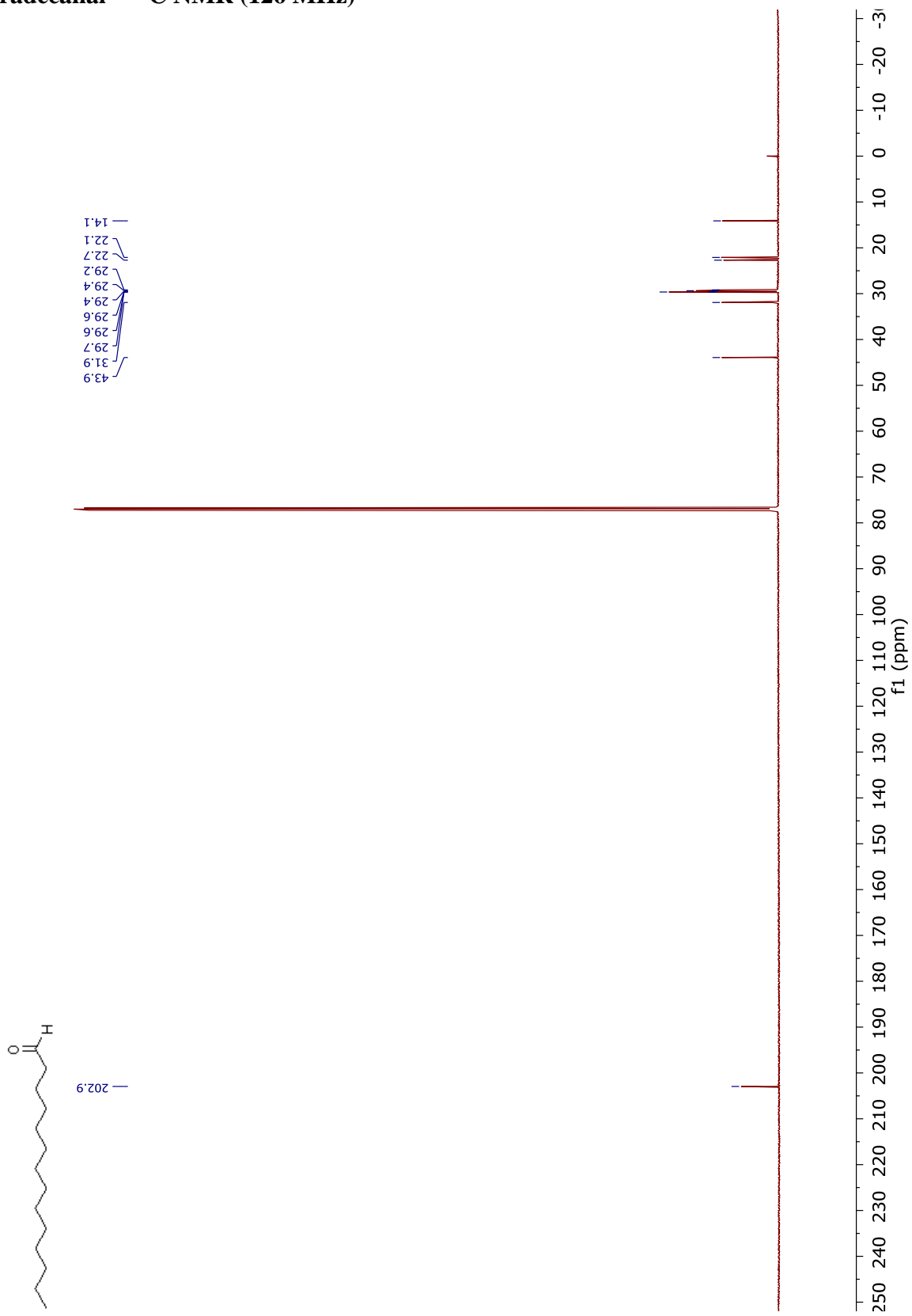
C-14 Lariat Ether (4.7) – ¹H NMR (500 MHz)
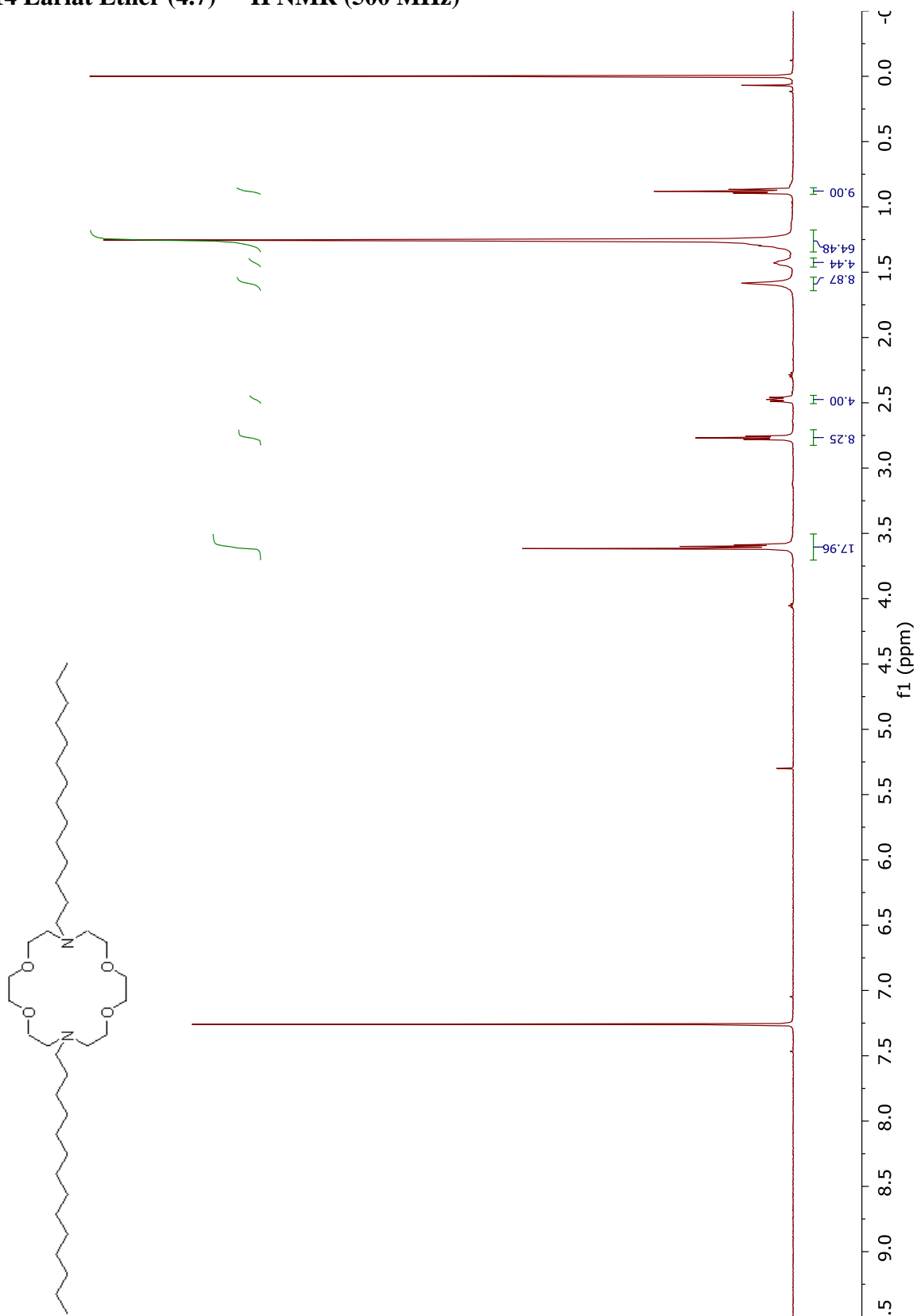
C-14 Lariat Ether (4.7) – ^{13}C NMR (126 MHz)

14.1
22.7
27.3
27.5
29.4
29.7
29.7
29.7
31.9

54.0
56.1

70.1
70.8

f1 (ppm)

250 240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -3
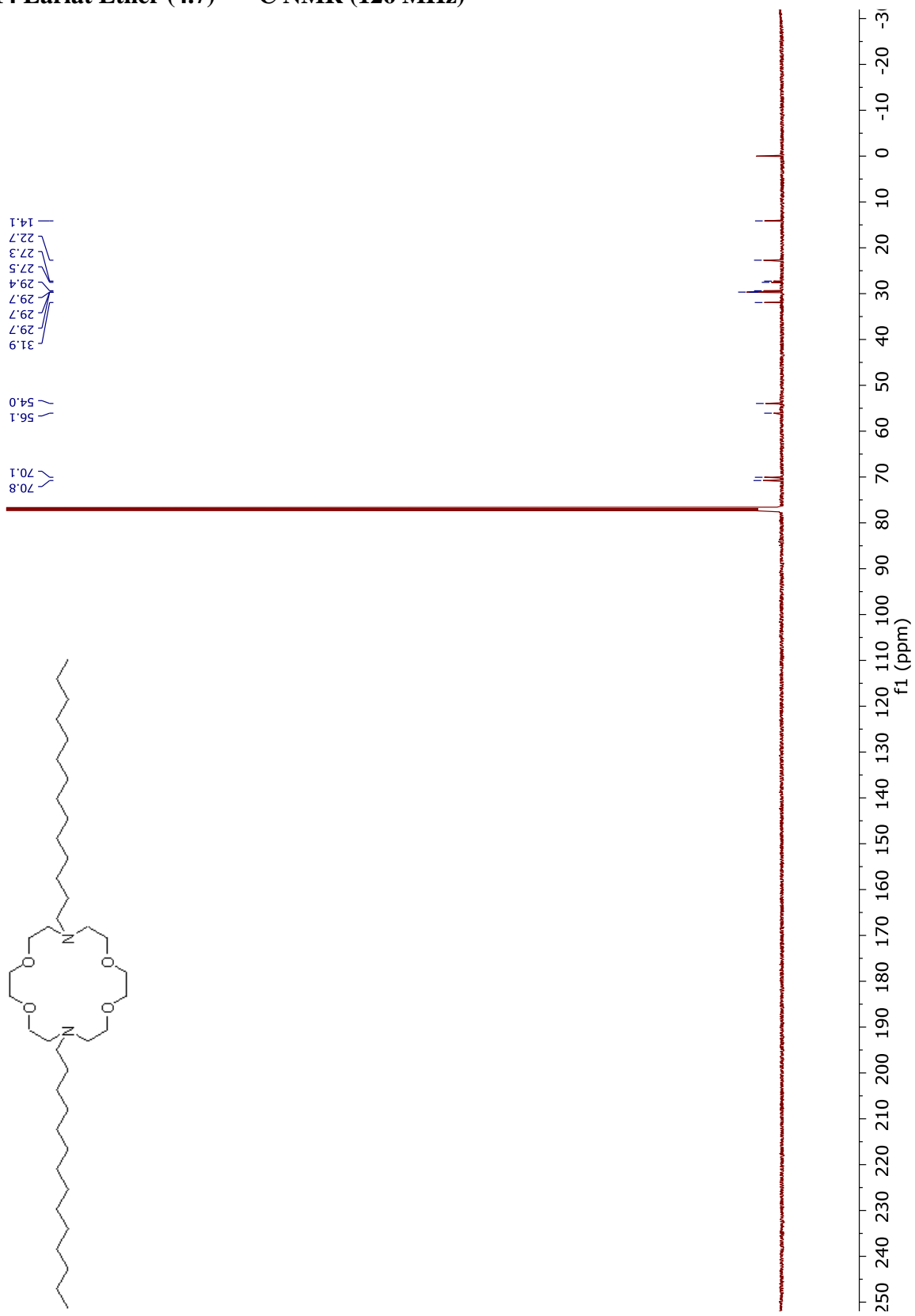
N-Bn kryptofix 22 (4.12) – ^{1}H NMR (500 MHz)
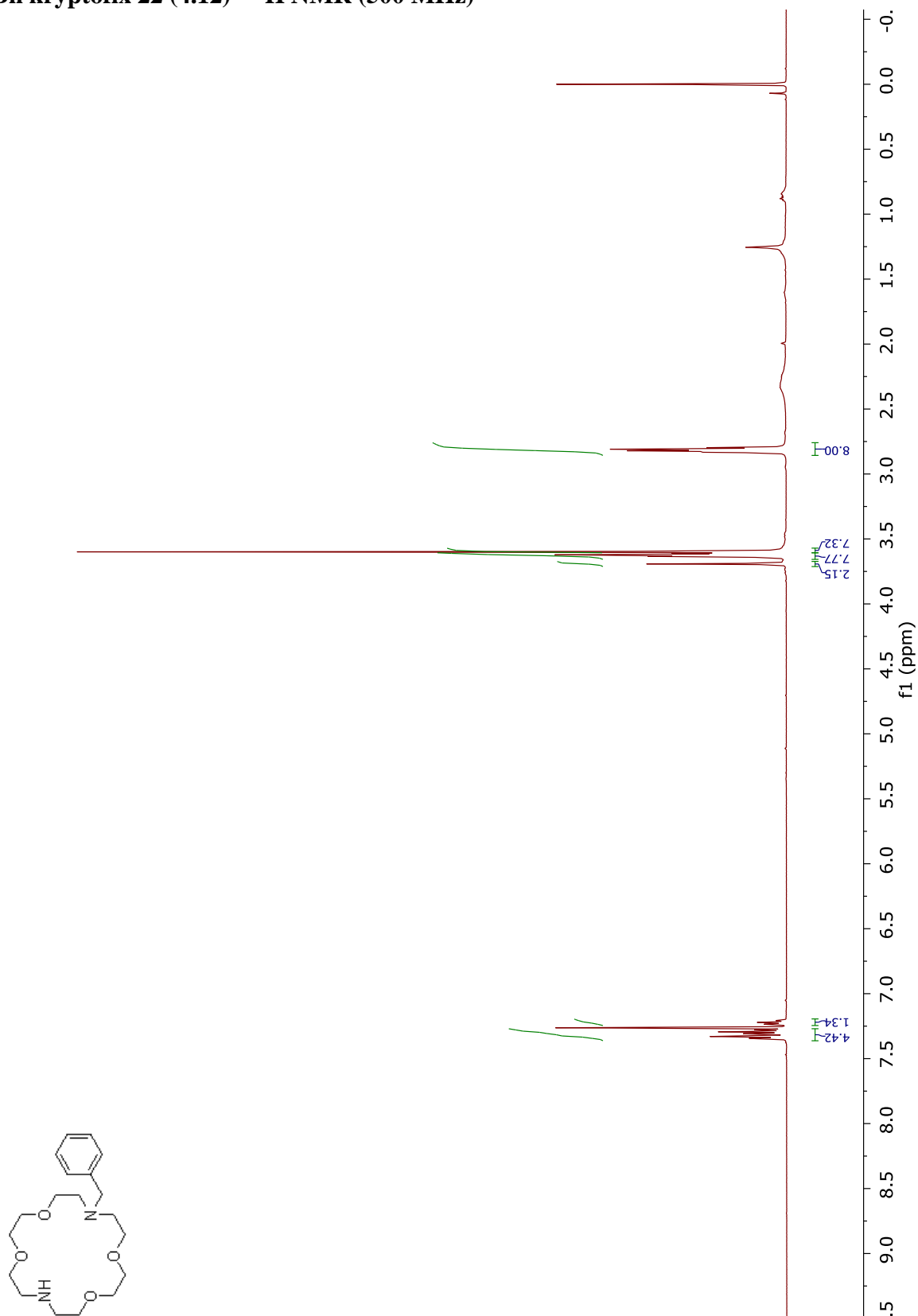
N-Bn kryptofix 22 (4.12) – ^{13}C NMR (126 MHz)
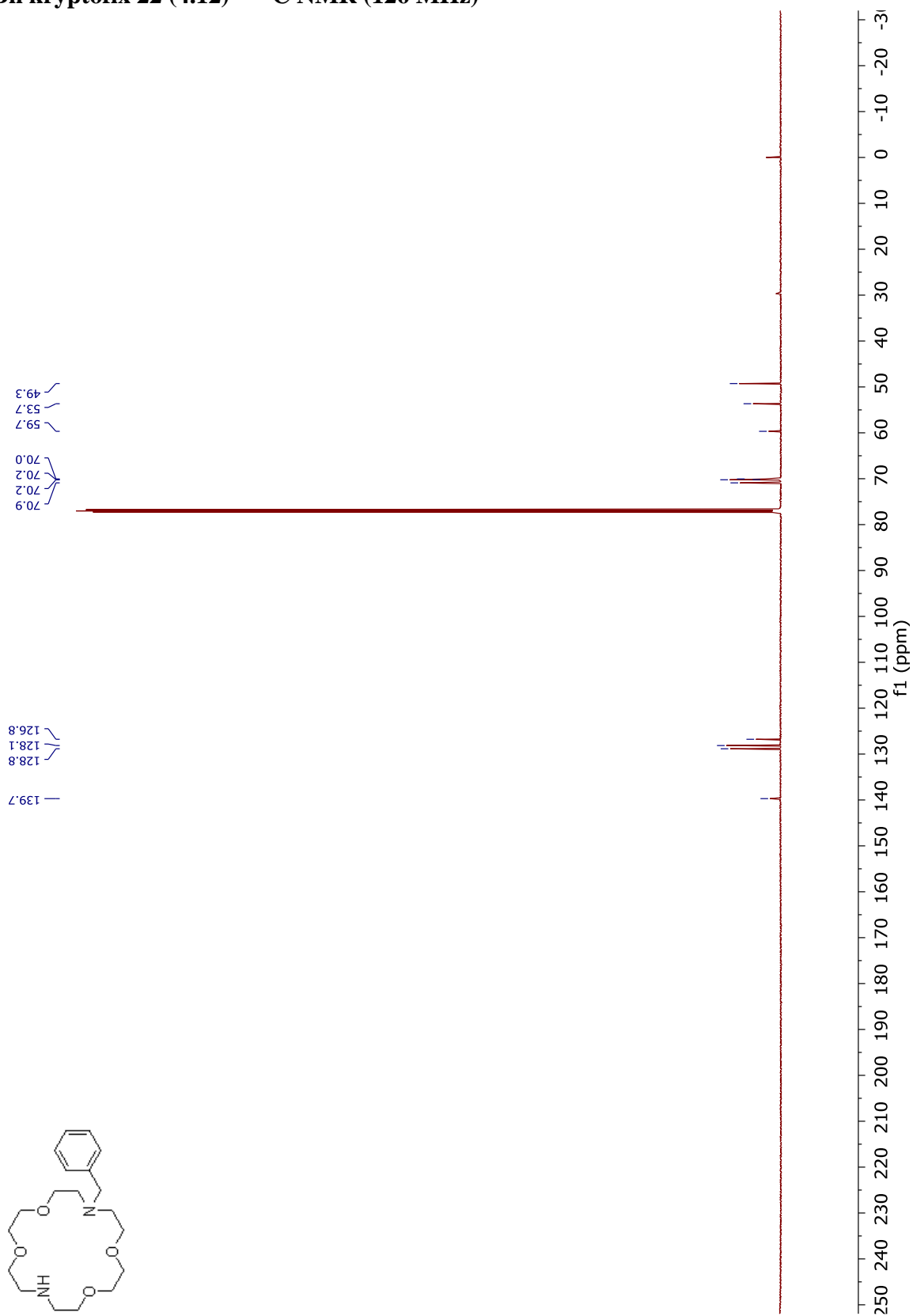
Anhydride 4.30 – ¹H NMR (500 MHz)
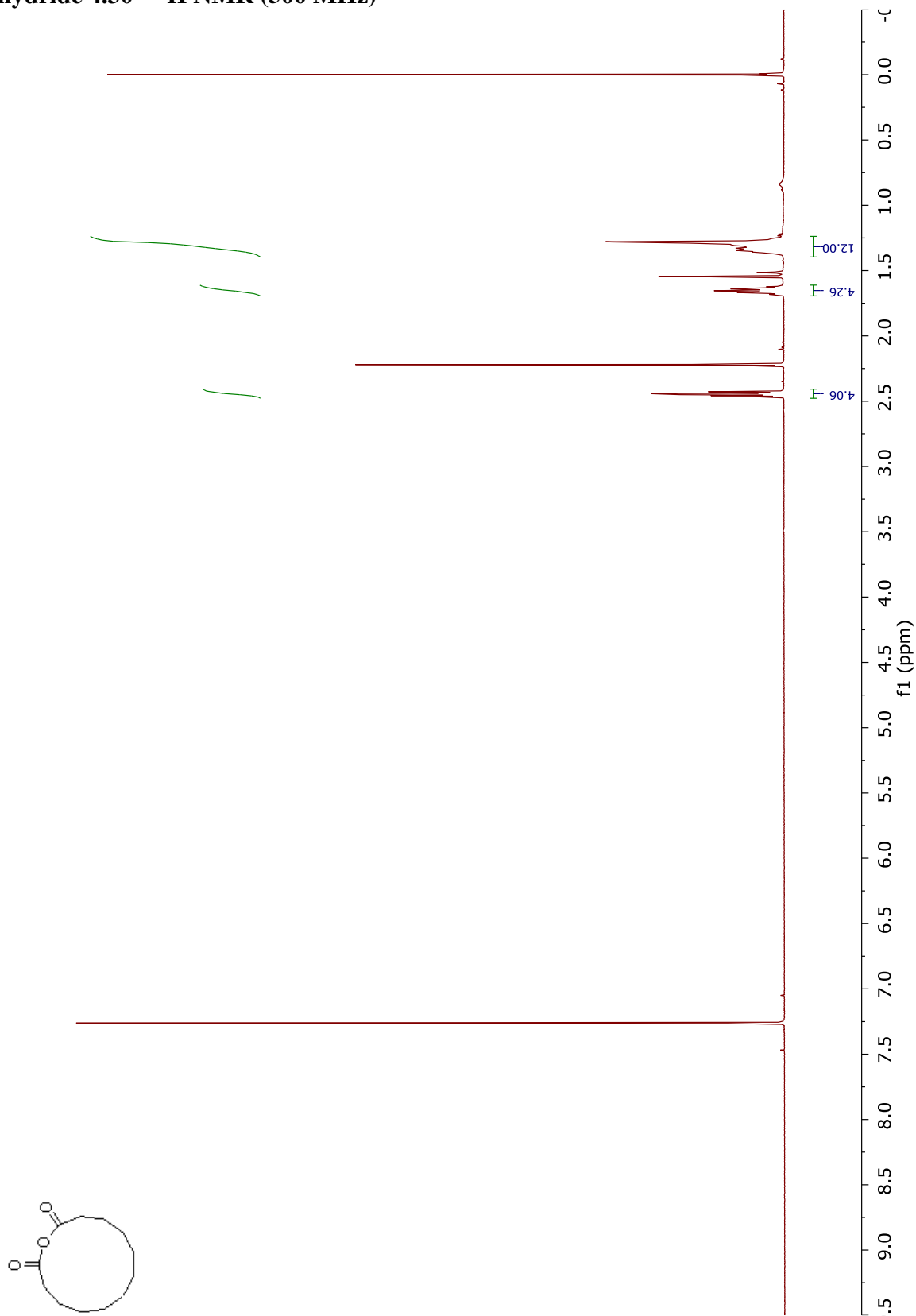
Anhydride 4.30 – ^{13}C NMR (126 MHz)

22.2
24.1
24.2
28.8
28.8
29.1
29.2
29.3
29.3
35.2
35.3

166.6
169.4
169.6

f1 (ppm)
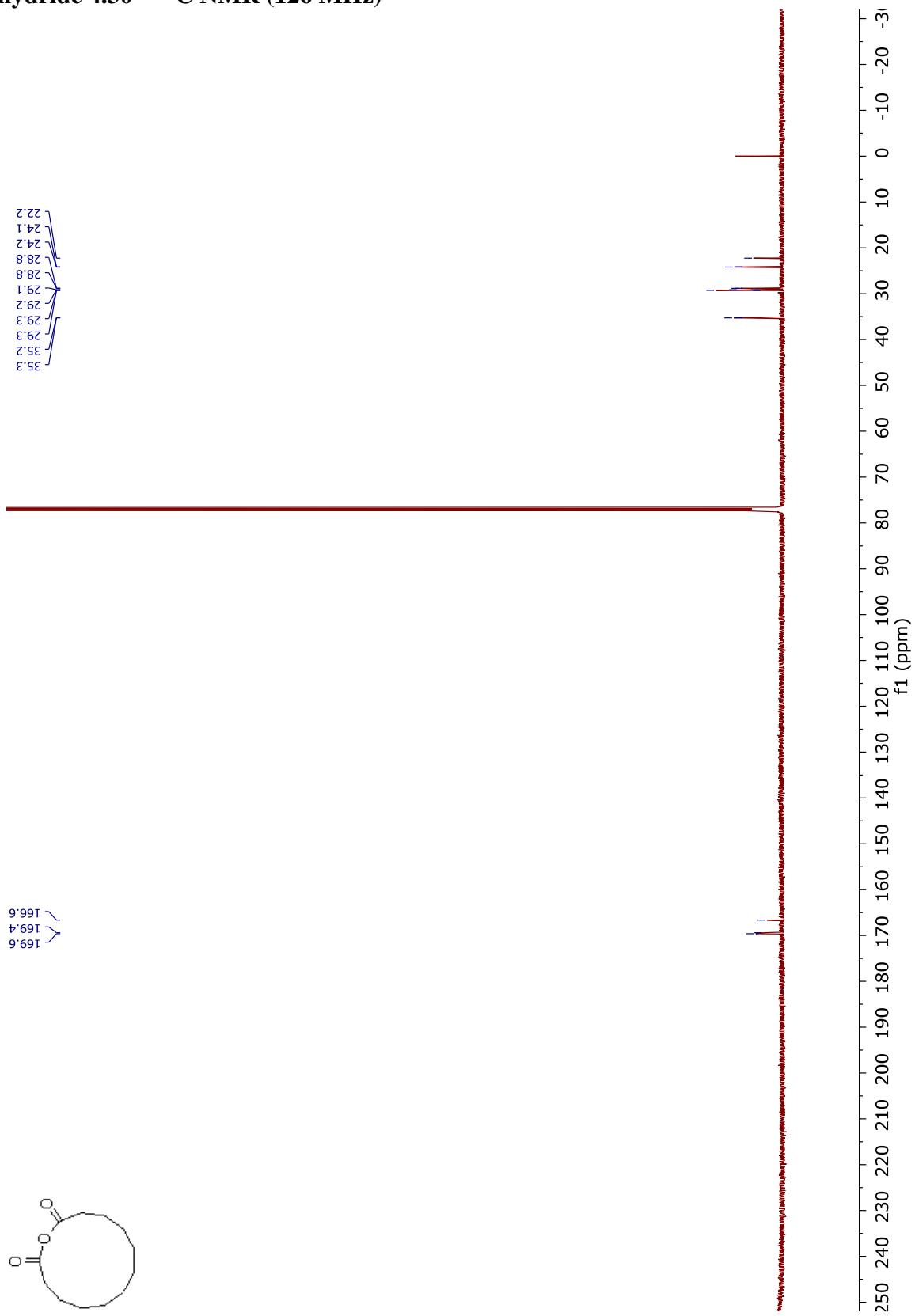
Monobenzyl Ester 4.16 – ^{1}H NMR (500 MHz)
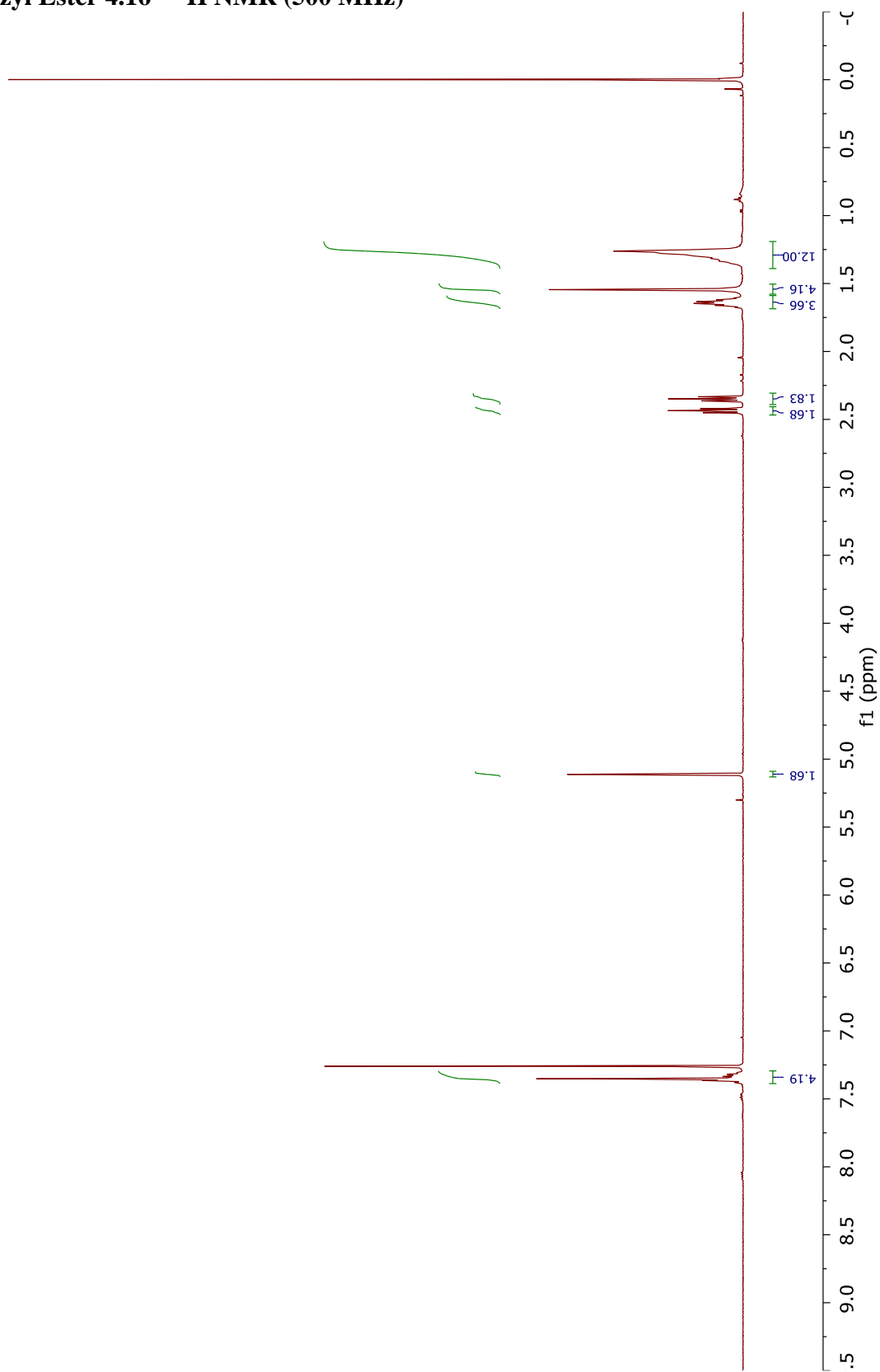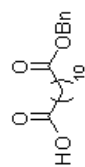
Monobenzyl Ester 4.16 – ^{13}C NMR (126 MHz)

24.2
24.9
28.8
29.1
29.2
29.2
29.3
29.3
34.3
35.3

66.1

128.2
128.5
136.1

169.6
173.7
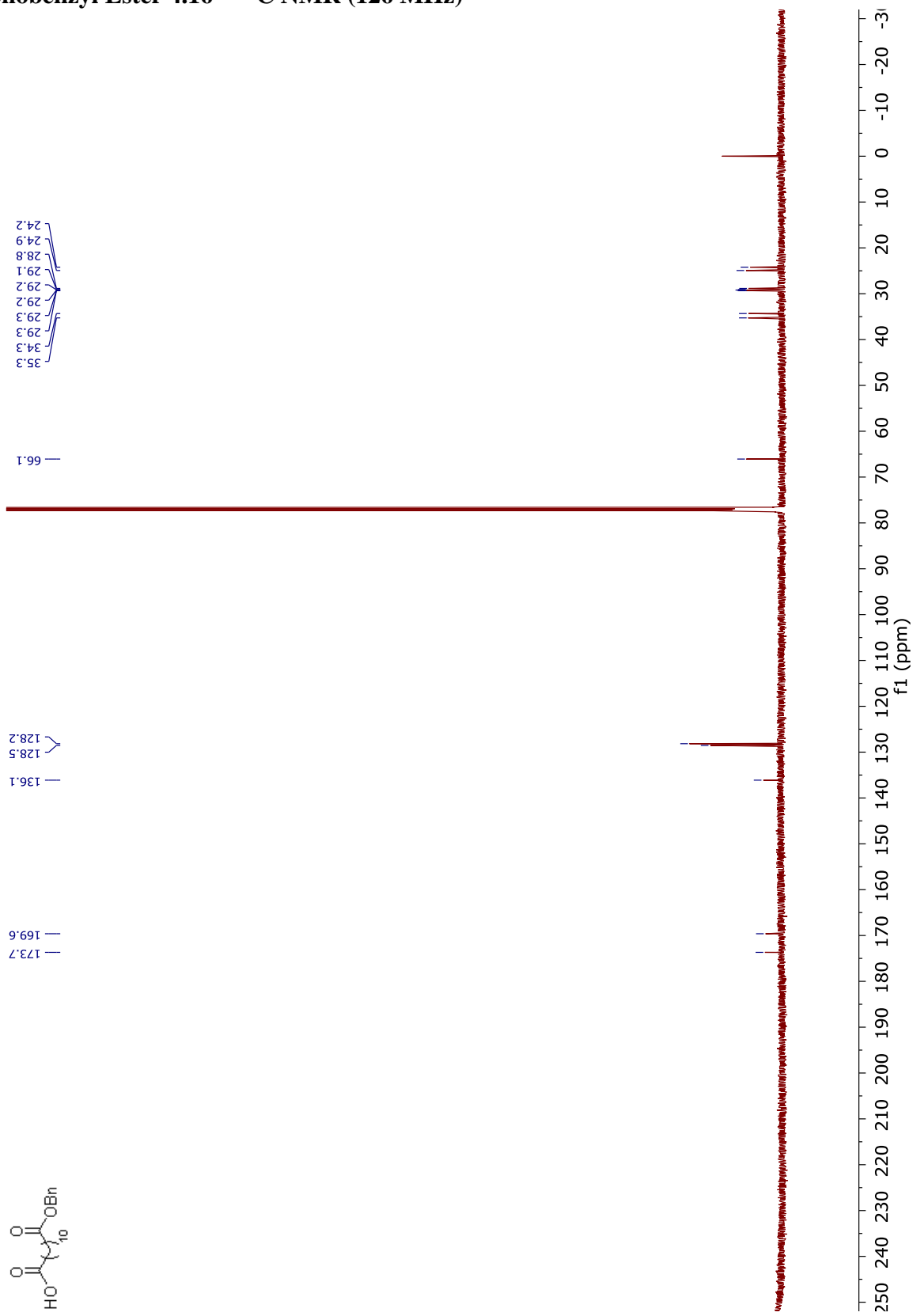
Transmembrane Fragment 4.17 – ^{1}H NMR (500 MHz)
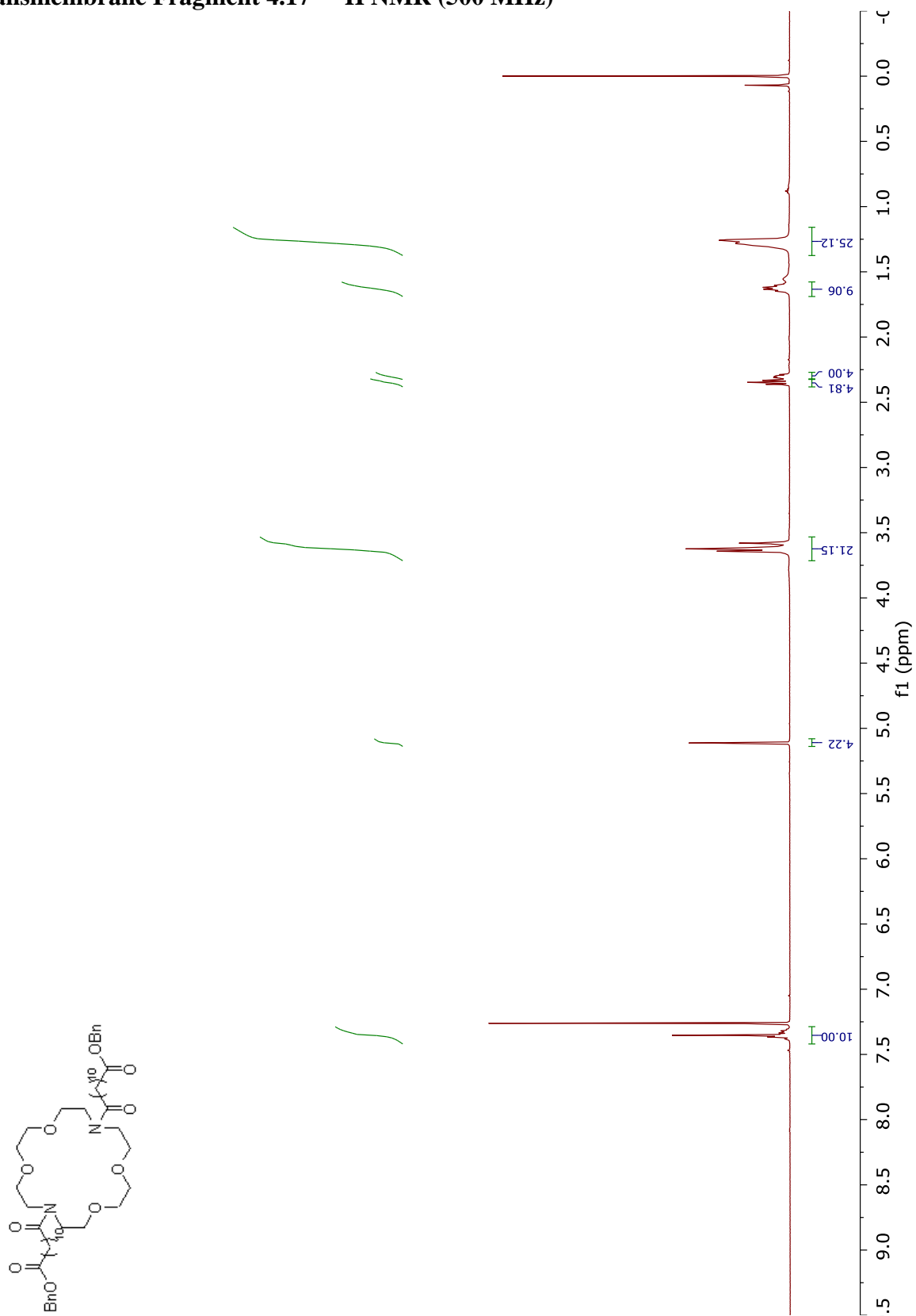
Transmembrane Fragment 4.17 – ^{13}C NMR (126 MHz)
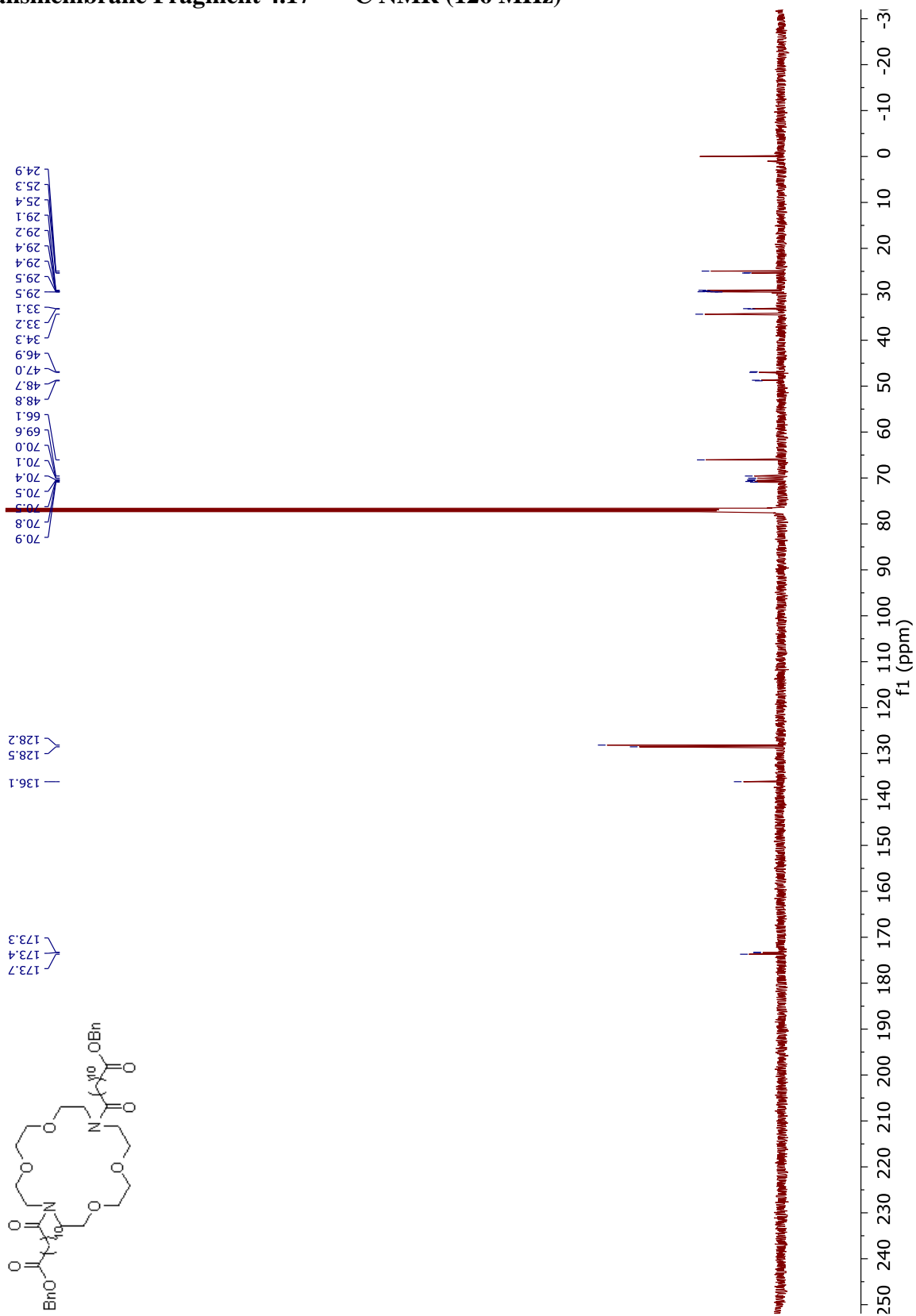
Diacid 4.18 – ¹H NMR (500 MHz)
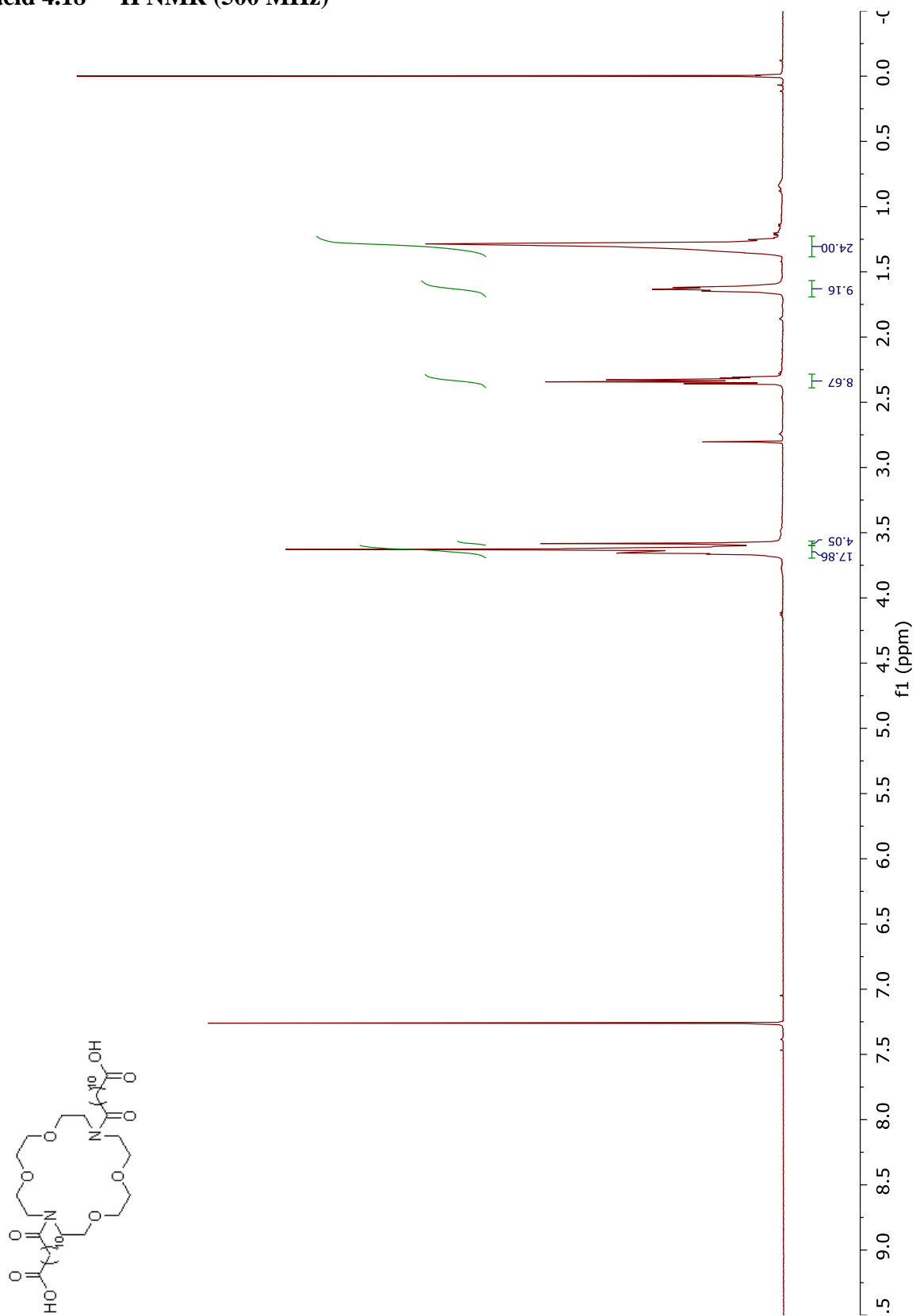
Diacid 4.18 – ¹³C NMR (126 MHz)

24.6
25.3
25.3
28.7
28.7
28.9
29.0
29.0
29.1
29.1
29.1
29.2
29.2
33.0
33.1
34.0
46.8
47.2
48.8
49.0
69.3
70.0
70.1
70.5
70.5
70.6
70.8
70.9

173.7
173.7
178.6
178.7

f1 (ppm)
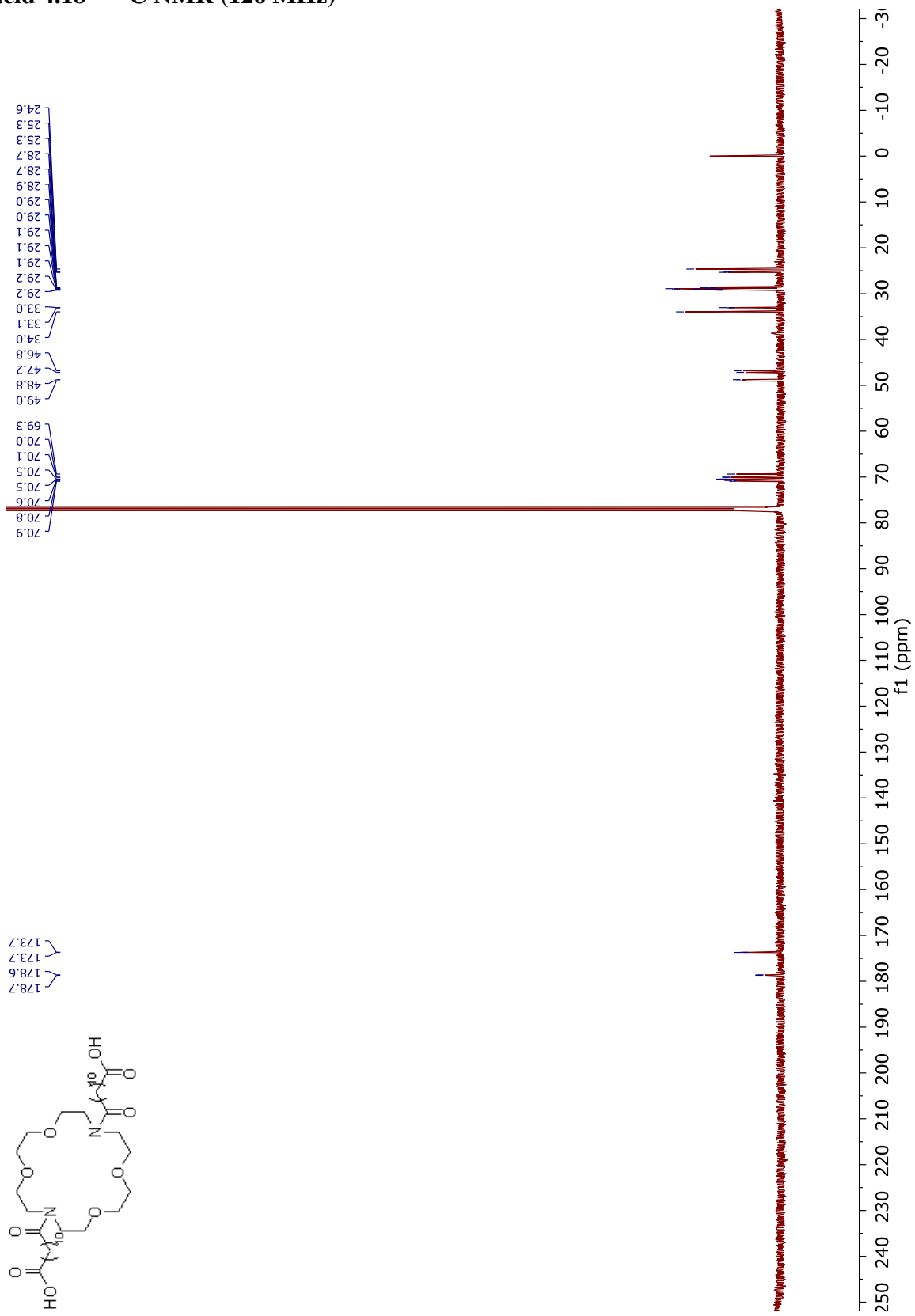
Tetraamide 4.19 – ¹H NMR (500 MHz)
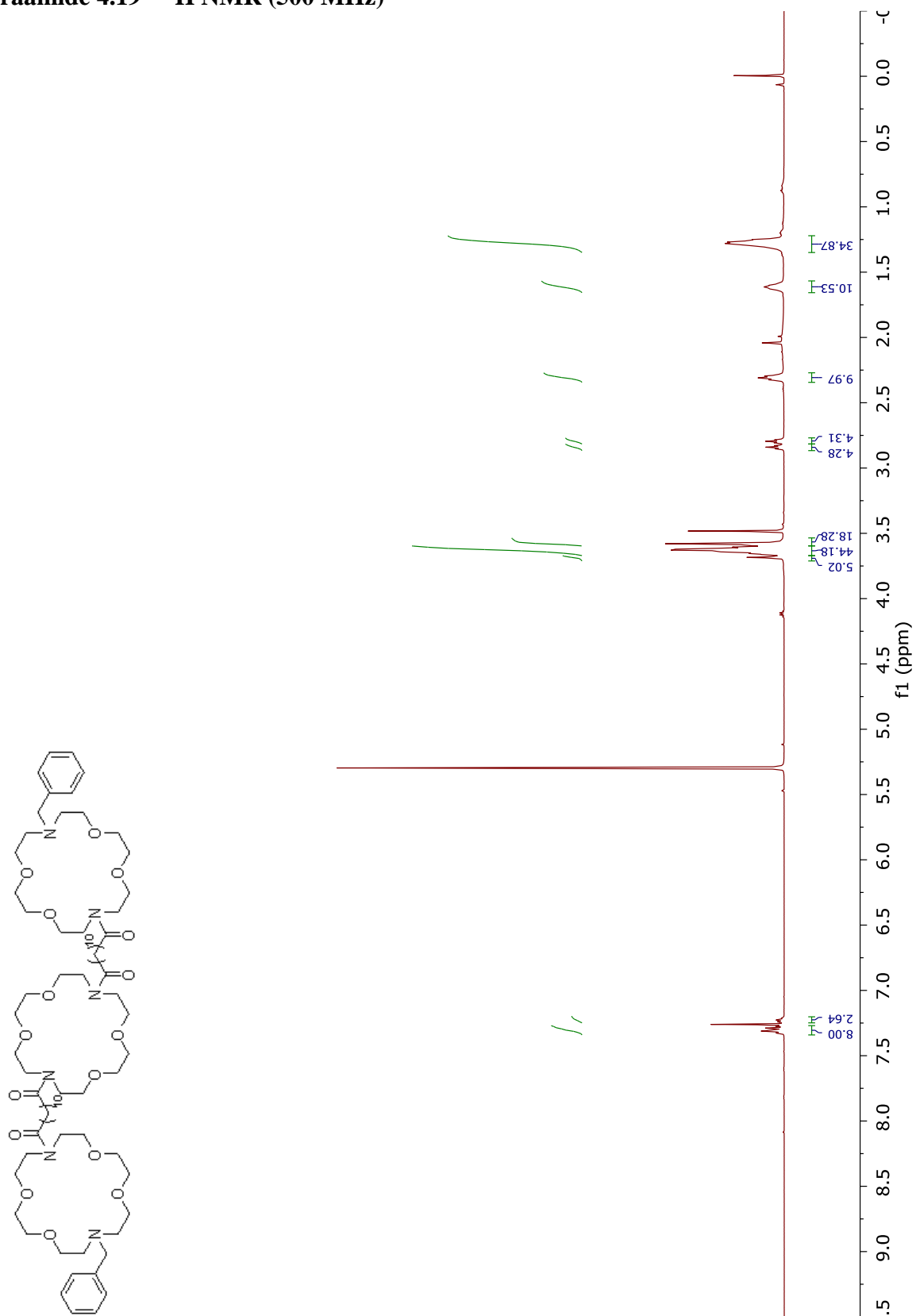
Tetraamide 4.19 – ¹³C NMR (126 MHz)

f1 (ppm)
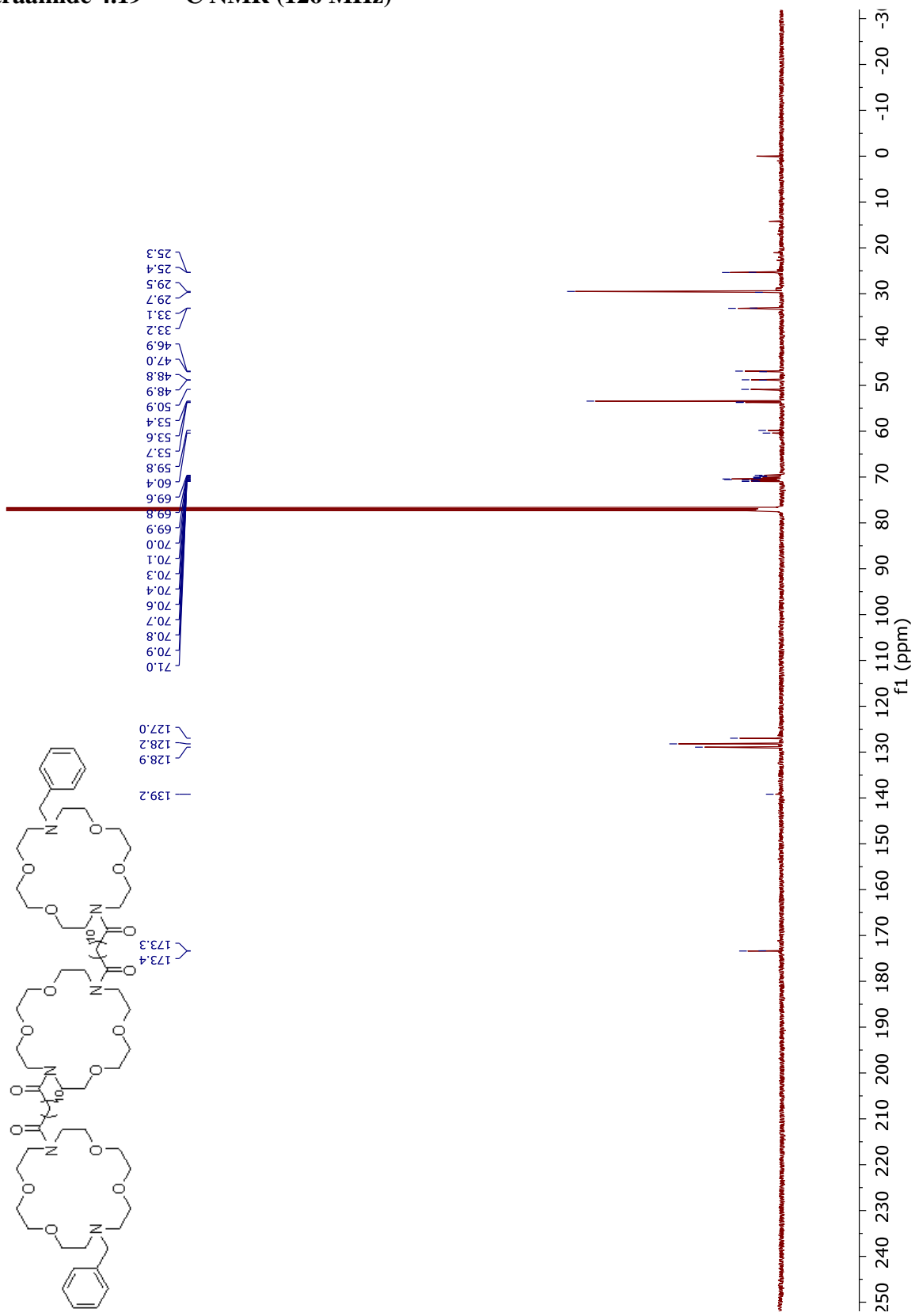
1,12-dodecanediol 4.31 – ¹H NMR (500 MHz)
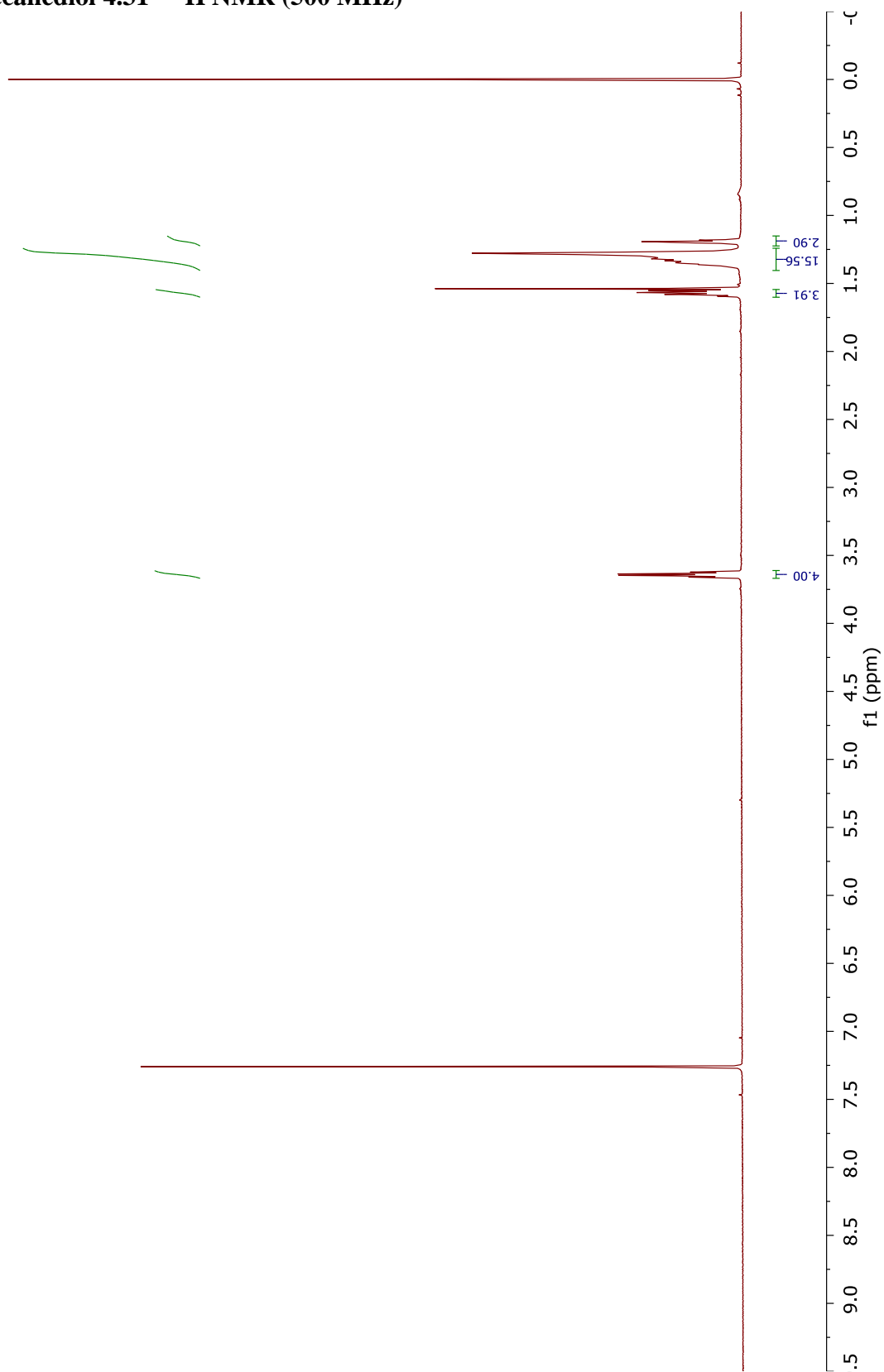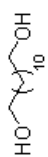
1,12-dodecanediol 4.31 – ^{13}C NMR (126 MHz)

25.7
29.4
29.5
29.6
32.8

63.1

f1 (ppm)
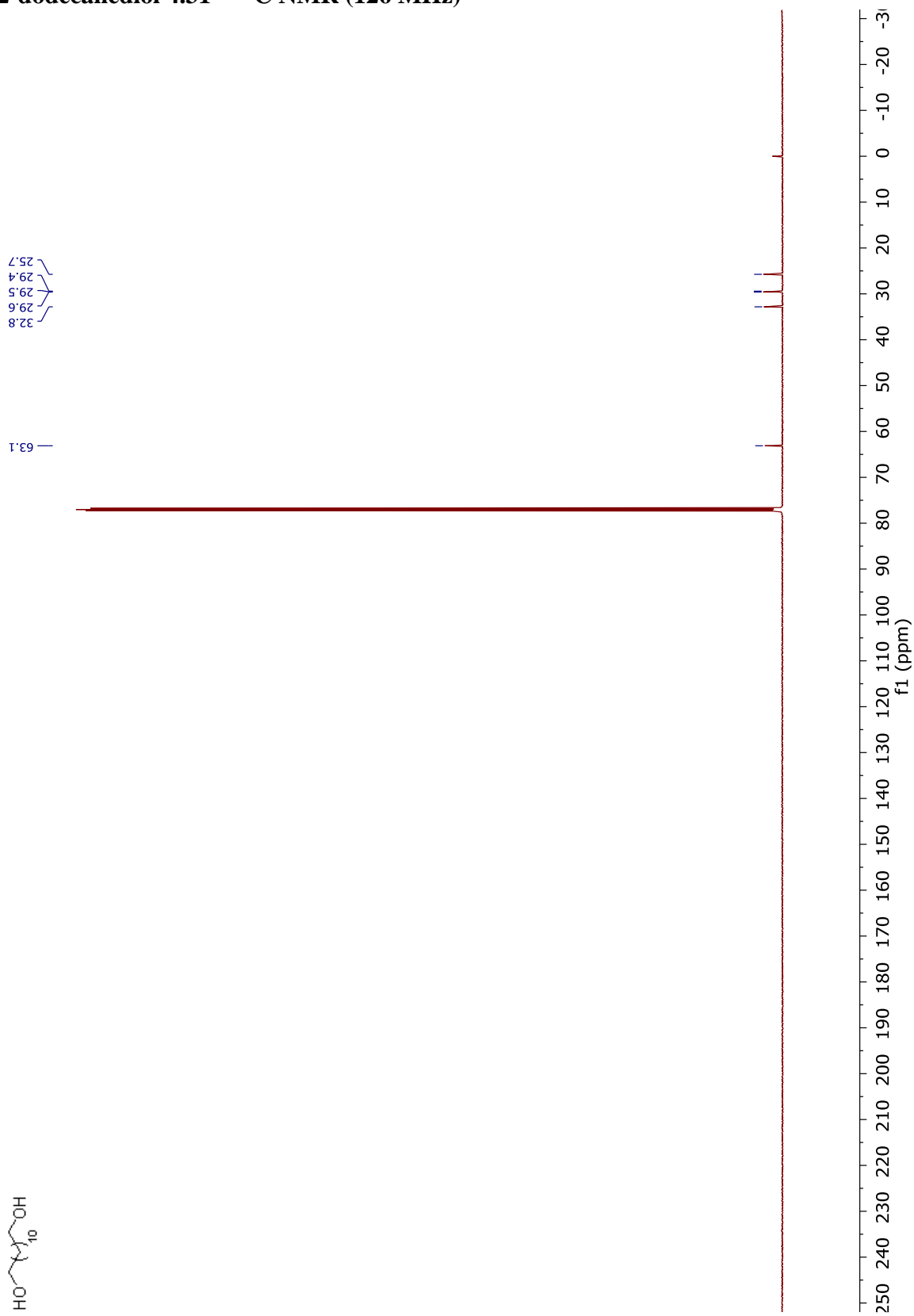
Monoprotected diol 4.32 – ¹H NMR (500 MHz)
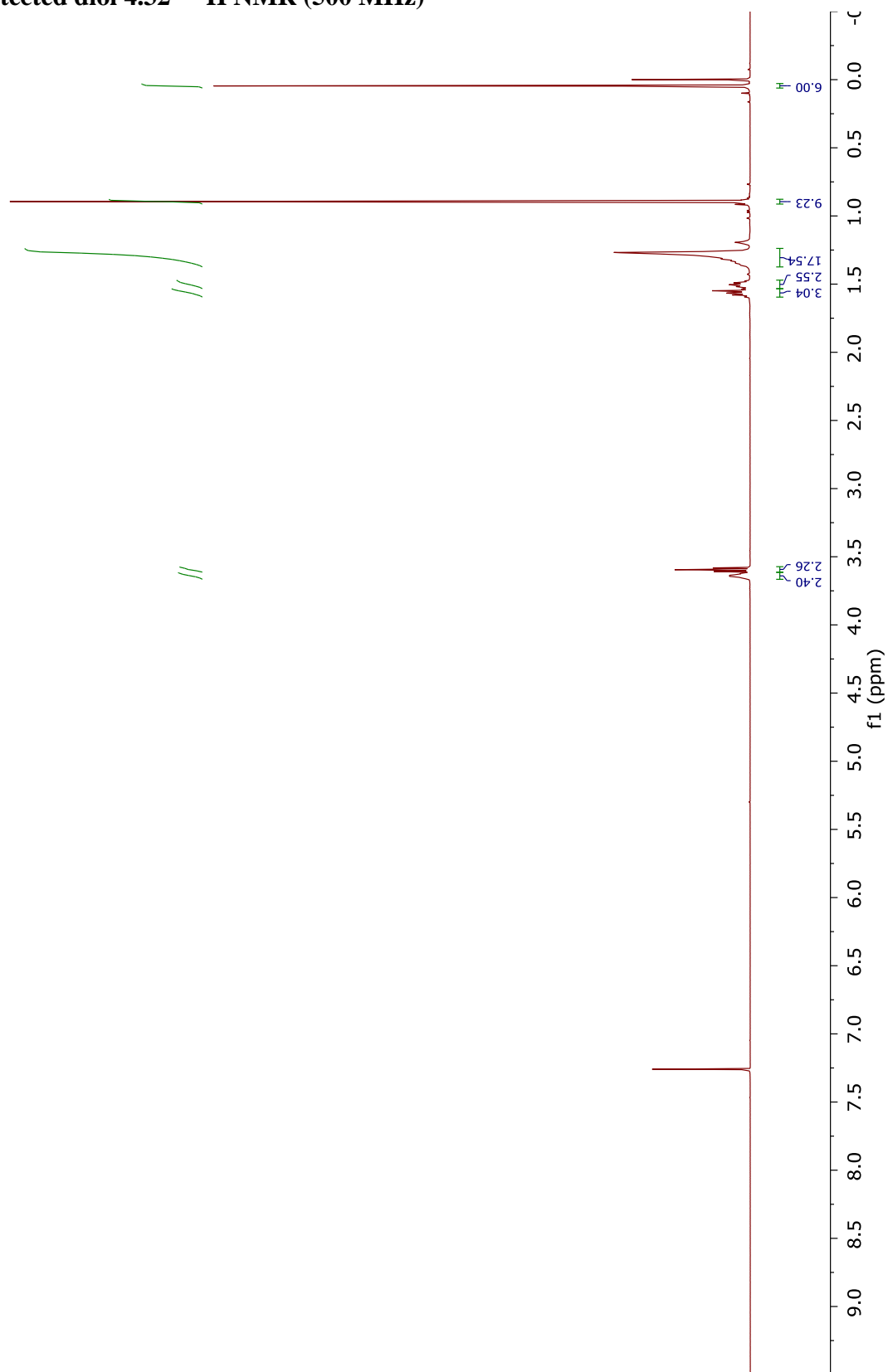
Monoprotected diol 4.32 – ^{13}C NMR (126 MHz)

- −5.2
- 18.4
- 25.7
- 25.8
- 26.0
- 29.4
- 29.4
- 29.6
- 29.6
- 29.6
- 29.6
- 32.8
- 32.9
- 63.1
- 63.4

f1 (ppm)
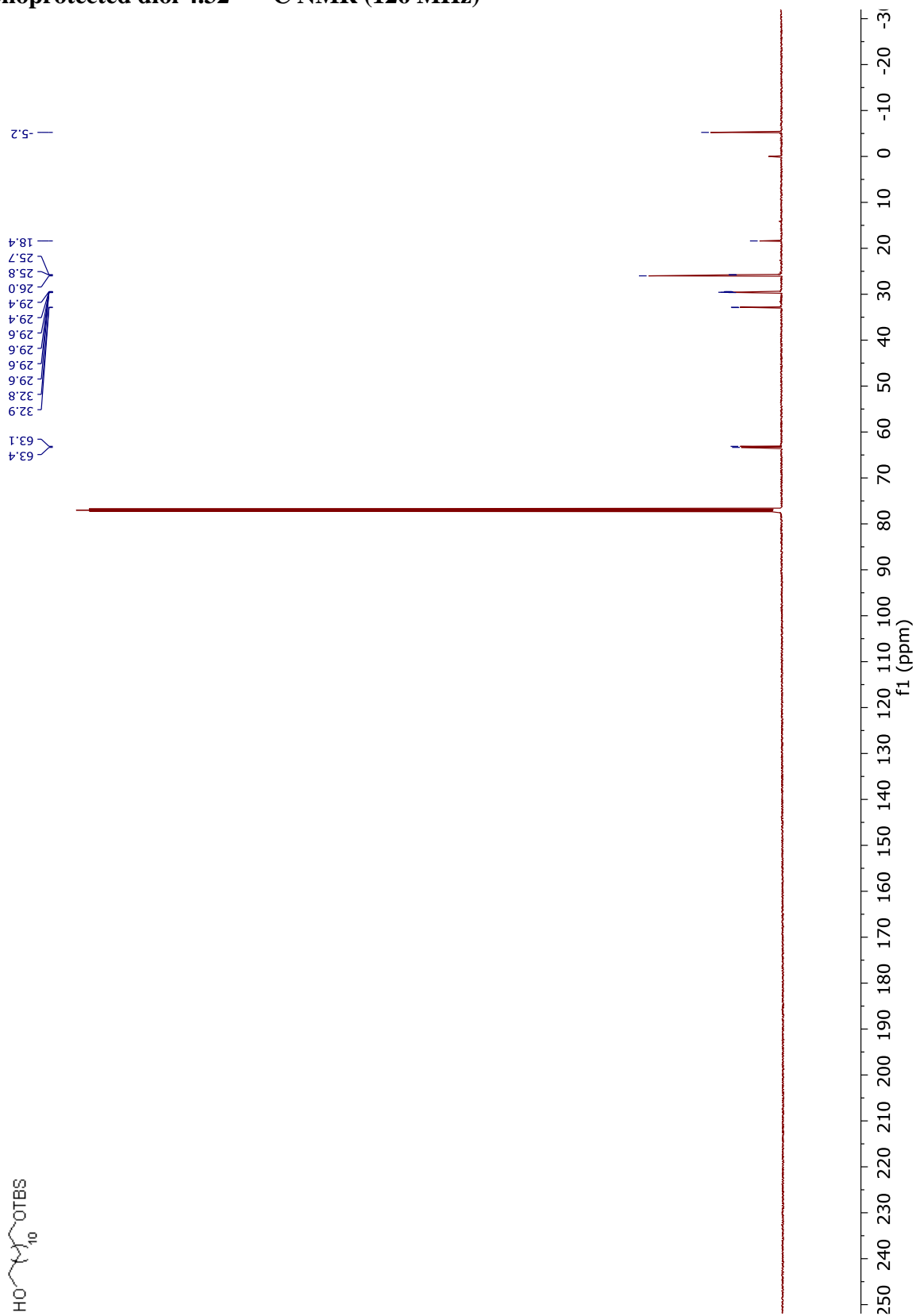
Aldehyde 4.33 – ¹H NMR (500 MHz)
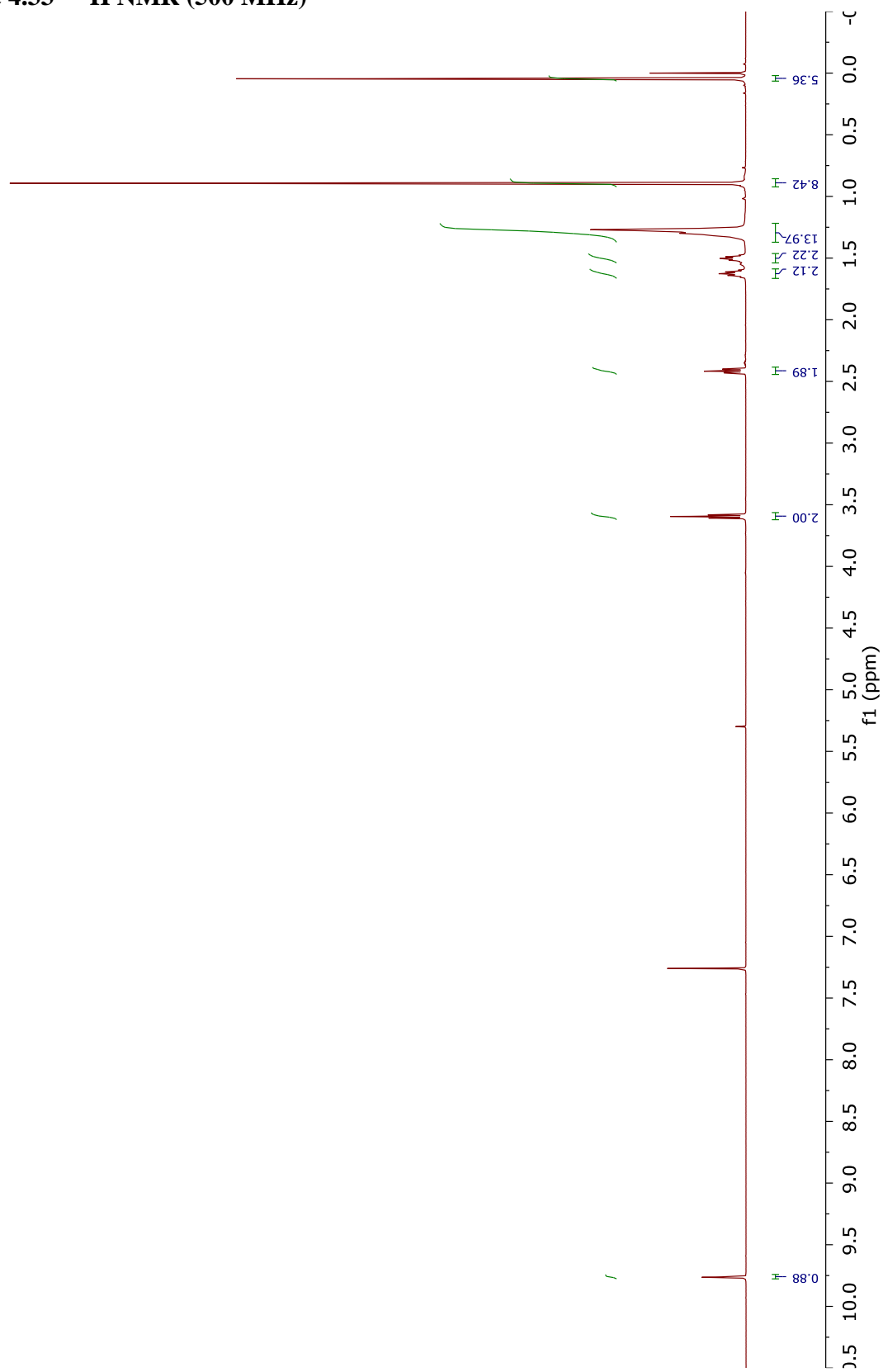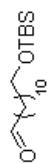
Aldehyde 4.33 – ^{13}C NMR (126 MHz)
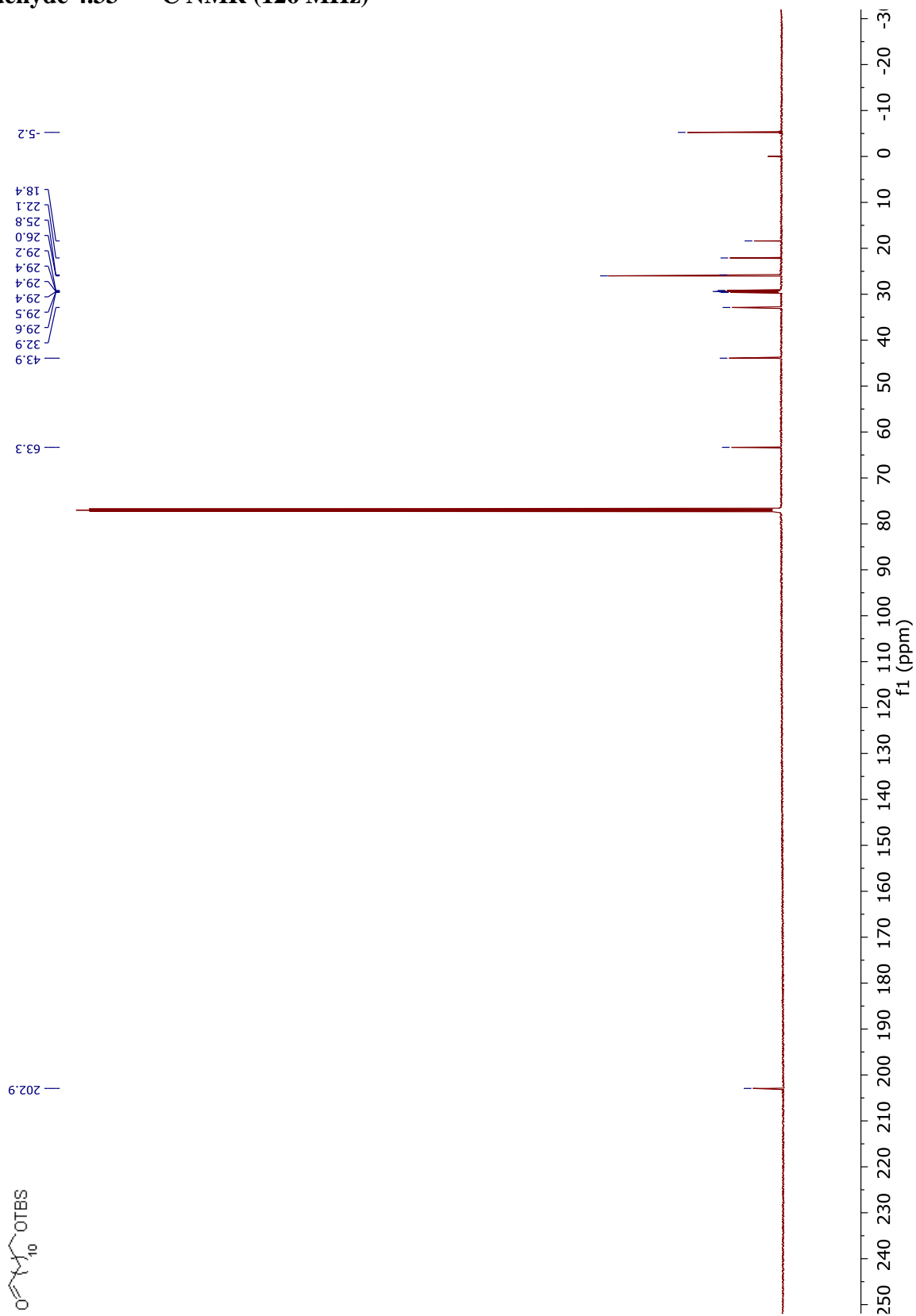
Bis-Silyl Ether Transmembrane Fragment 4.34 – ^{1}H NMR (500 MHz)
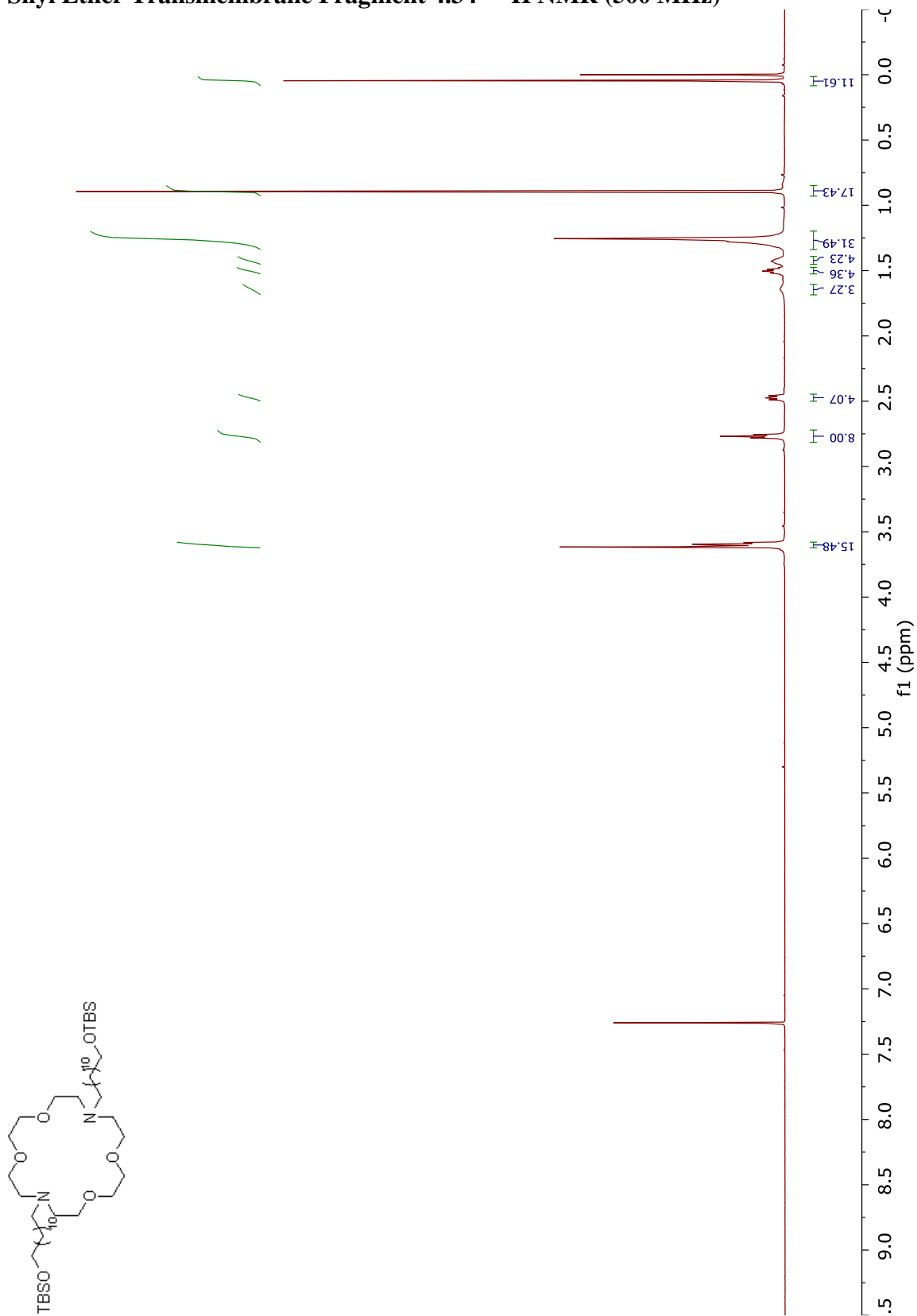
Bis-Silyl Ether Transmembrane Fragment 4.34 – ^{13}C NMR (126 MHz)

-5.2

18.4
25.8
26.0
27.3
27.5
29.5
29.6
29.6
29.7
32.9
54.0
56.1
63.4
70.1
70.8

f1 (ppm)

250 240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -3
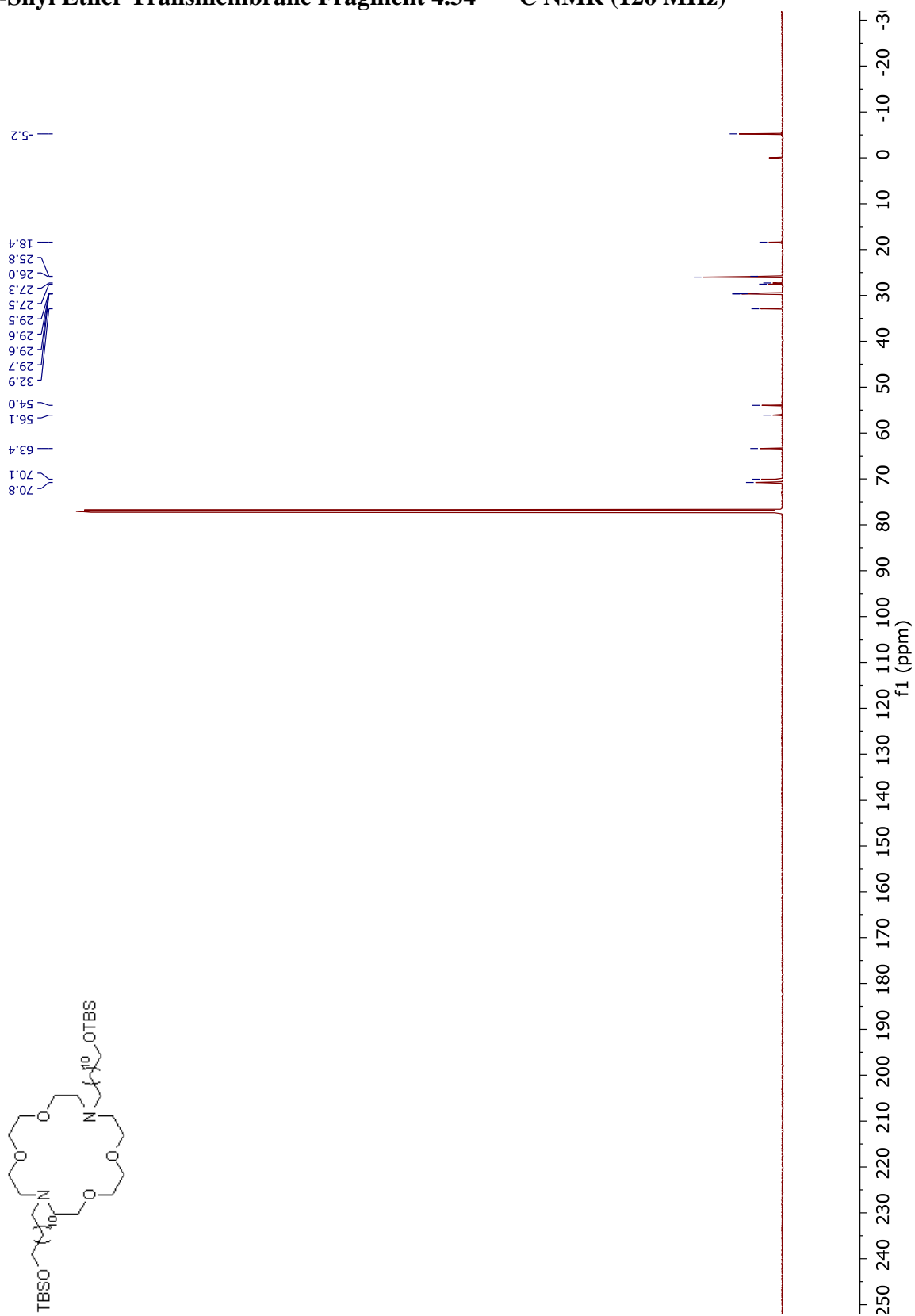
Monobenzoate 4.35 – ¹H NMR (500 MHz)
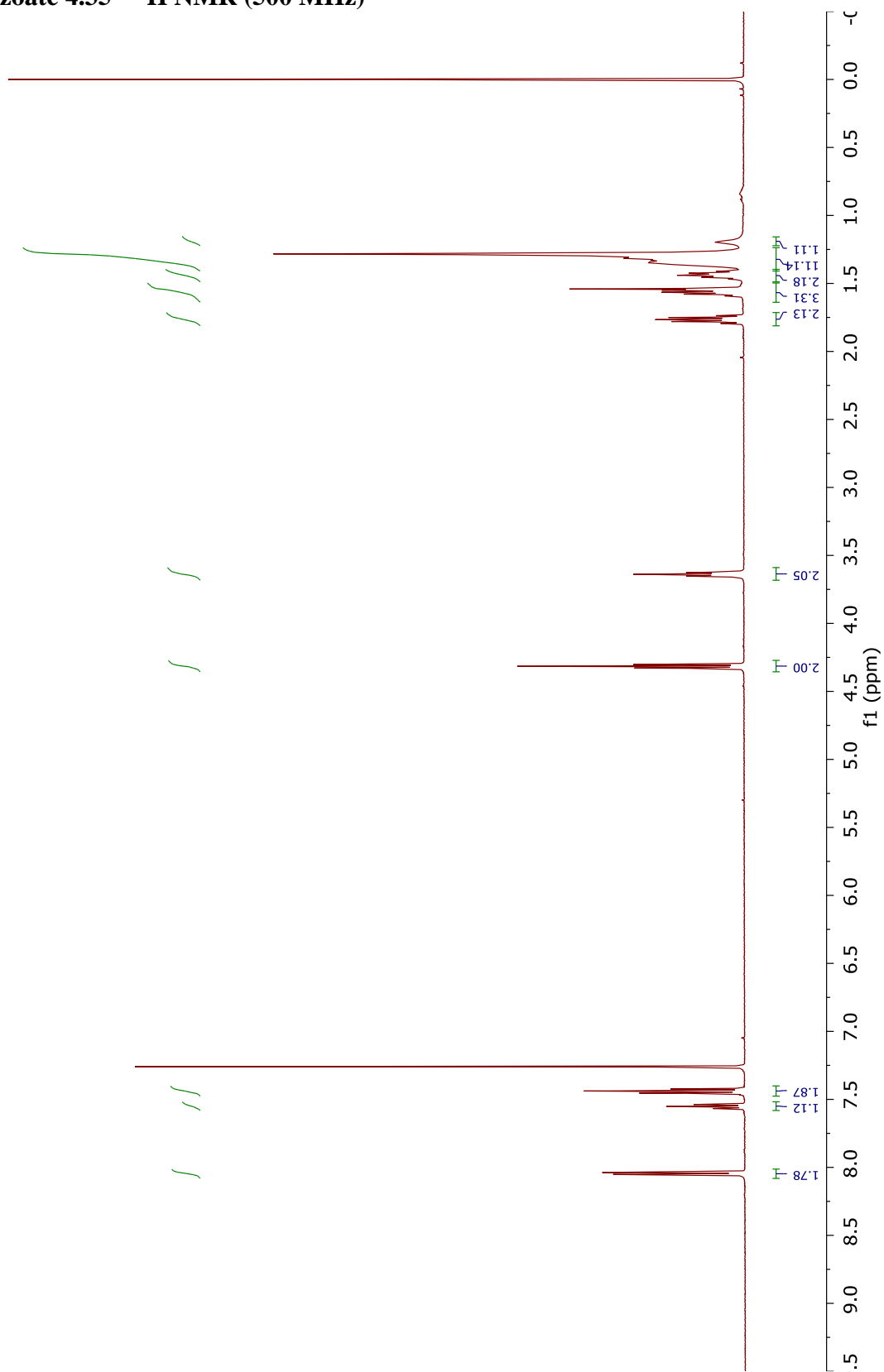
Monobenzoate 4.35 – ^{13}C NMR (126 MHz)

25.7
26.0
28.7
29.3
29.4
29.5
29.5
29.6
32.8

63.1
65.1

128.3
129.5
130.6
132.8

166.7

HO⌒⌒〔⌒〕$_{10}$OBz
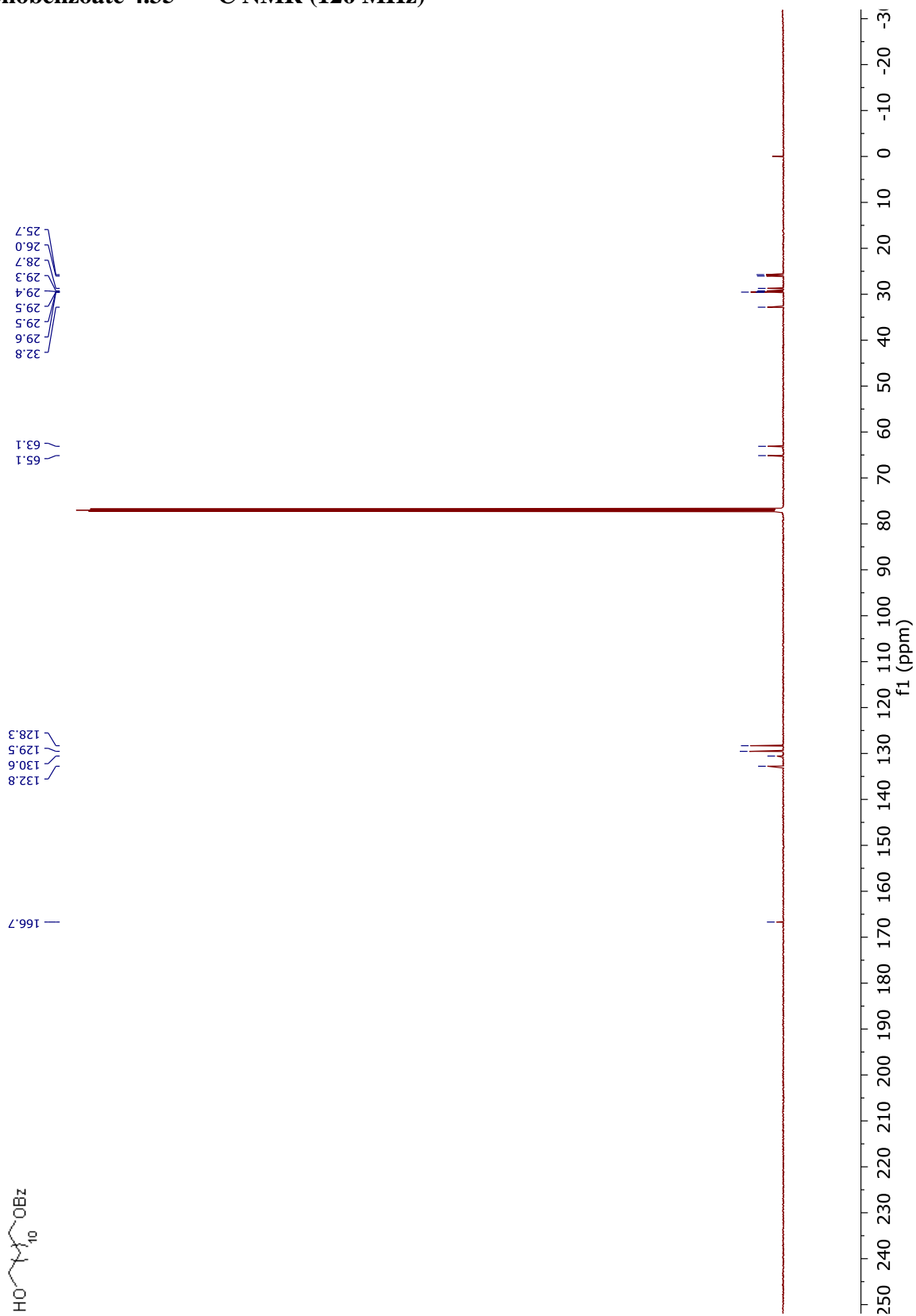
Aldehyde 4.36 – ¹H NMR (500 MHz)
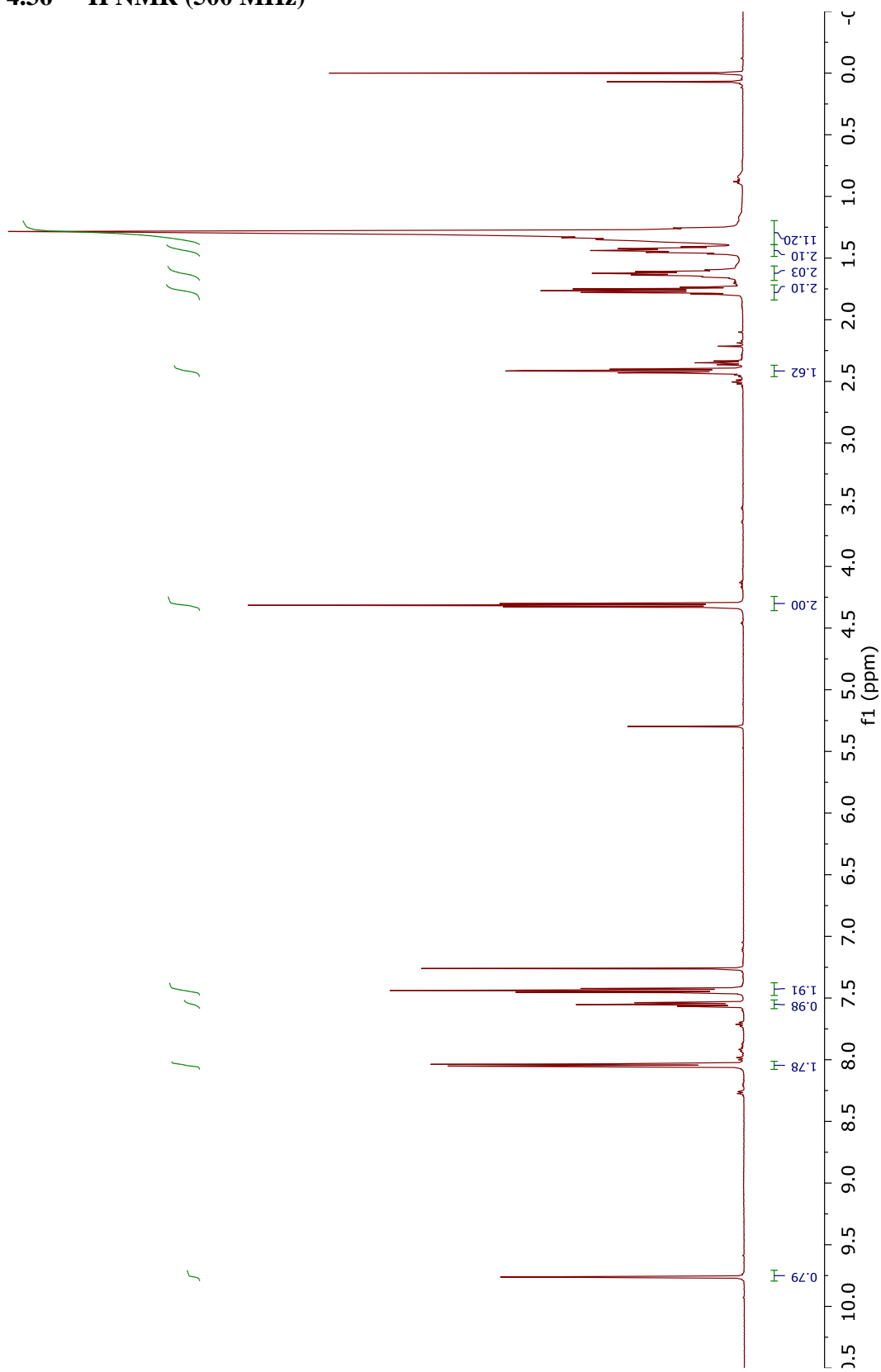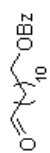
Aldehyde 4.36 – ^{13}C NMR (126 MHz)

22.1
26.0
28.7
29.2
29.3
29.3
29.4
29.5
29.5
43.9
65.1
128.3
129.5
130.5
132.8
166.7
202.9
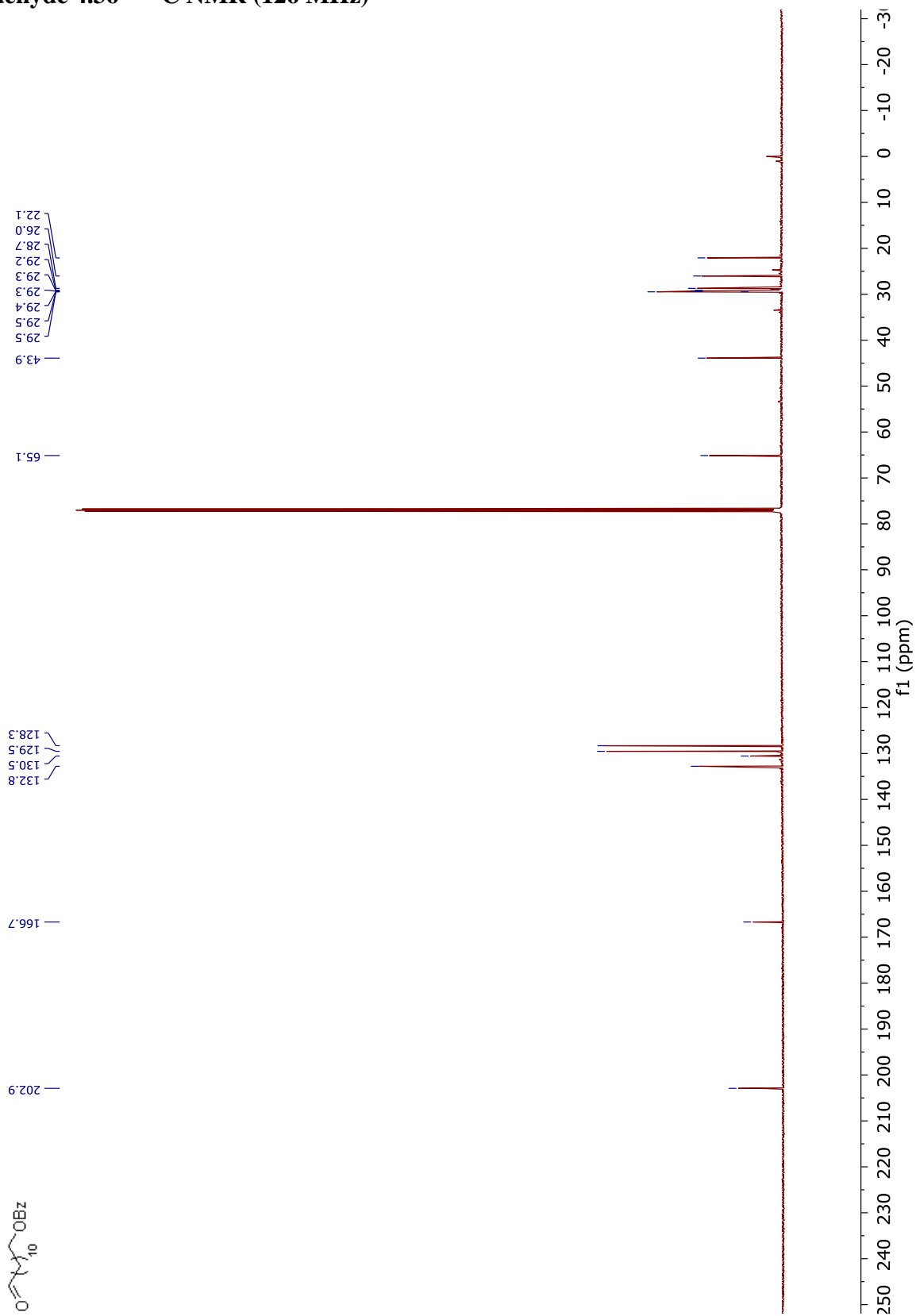
Dibenzoate Transmembrane Fragment 4.37 – ¹H NMR (500 MHz)
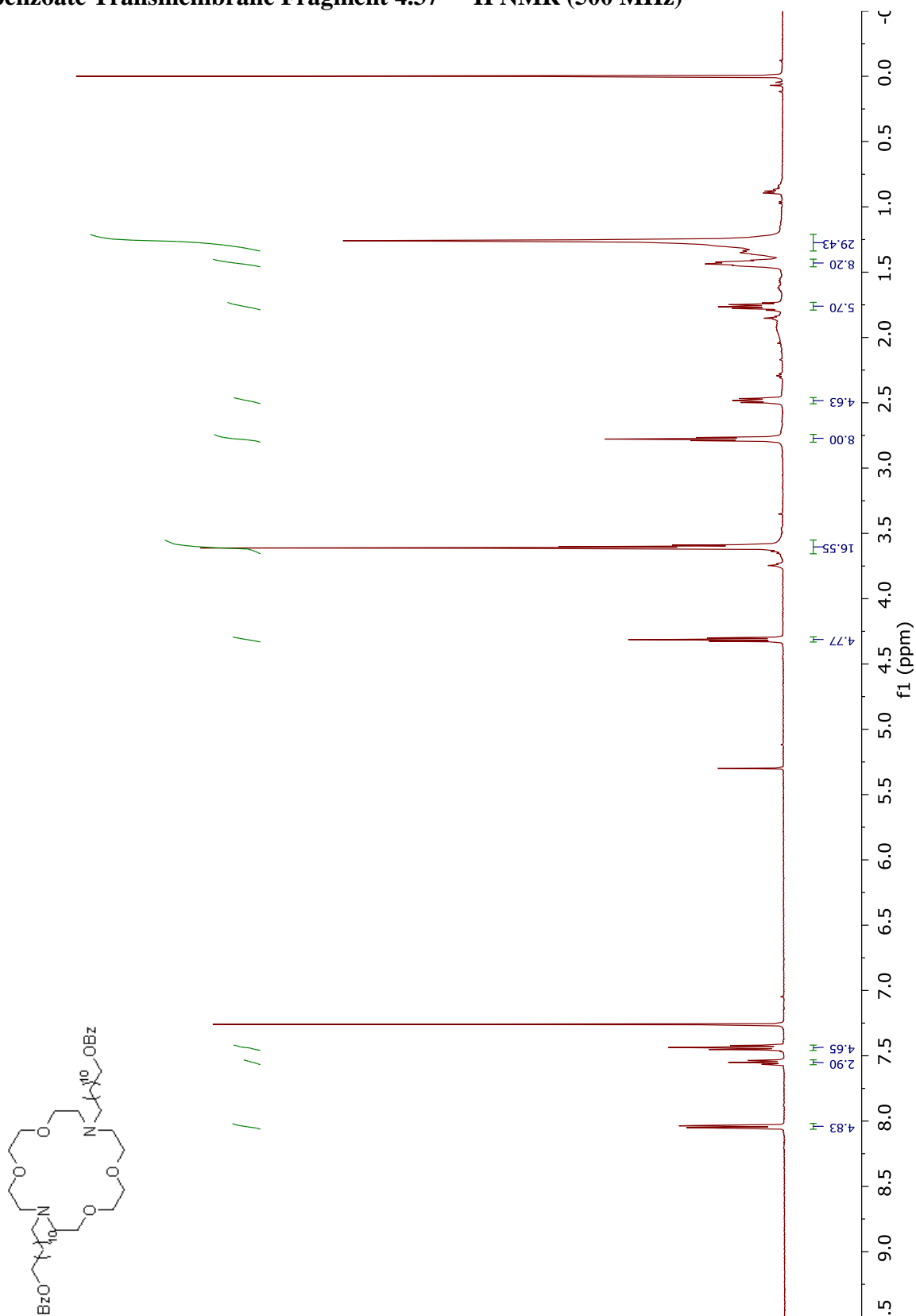
Dibenzoate Transmembrane Fragment 4.37 – ^{13}C NMR (126 MHz)
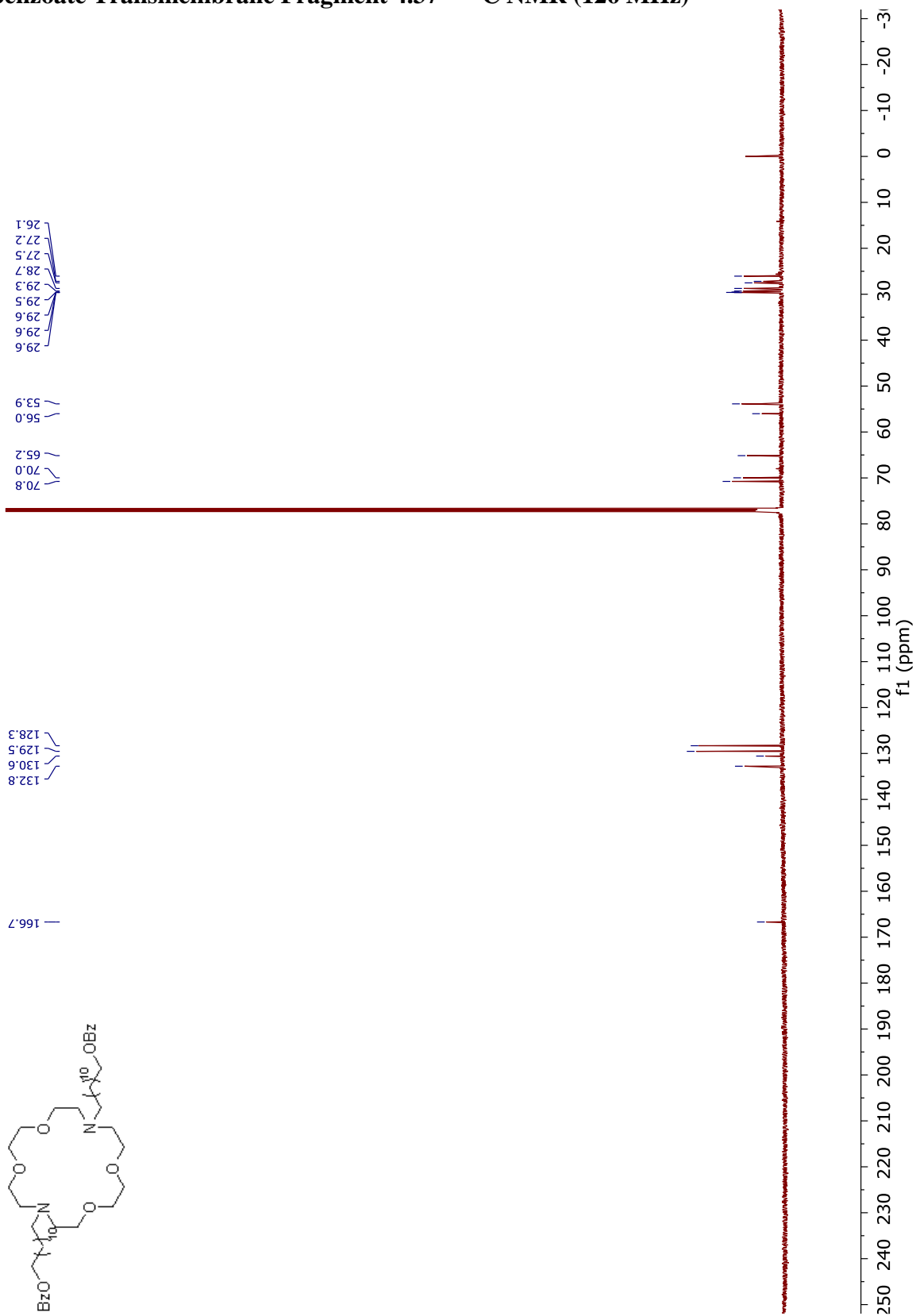
Diol 4.38 – ¹H NMR (500 MHz)
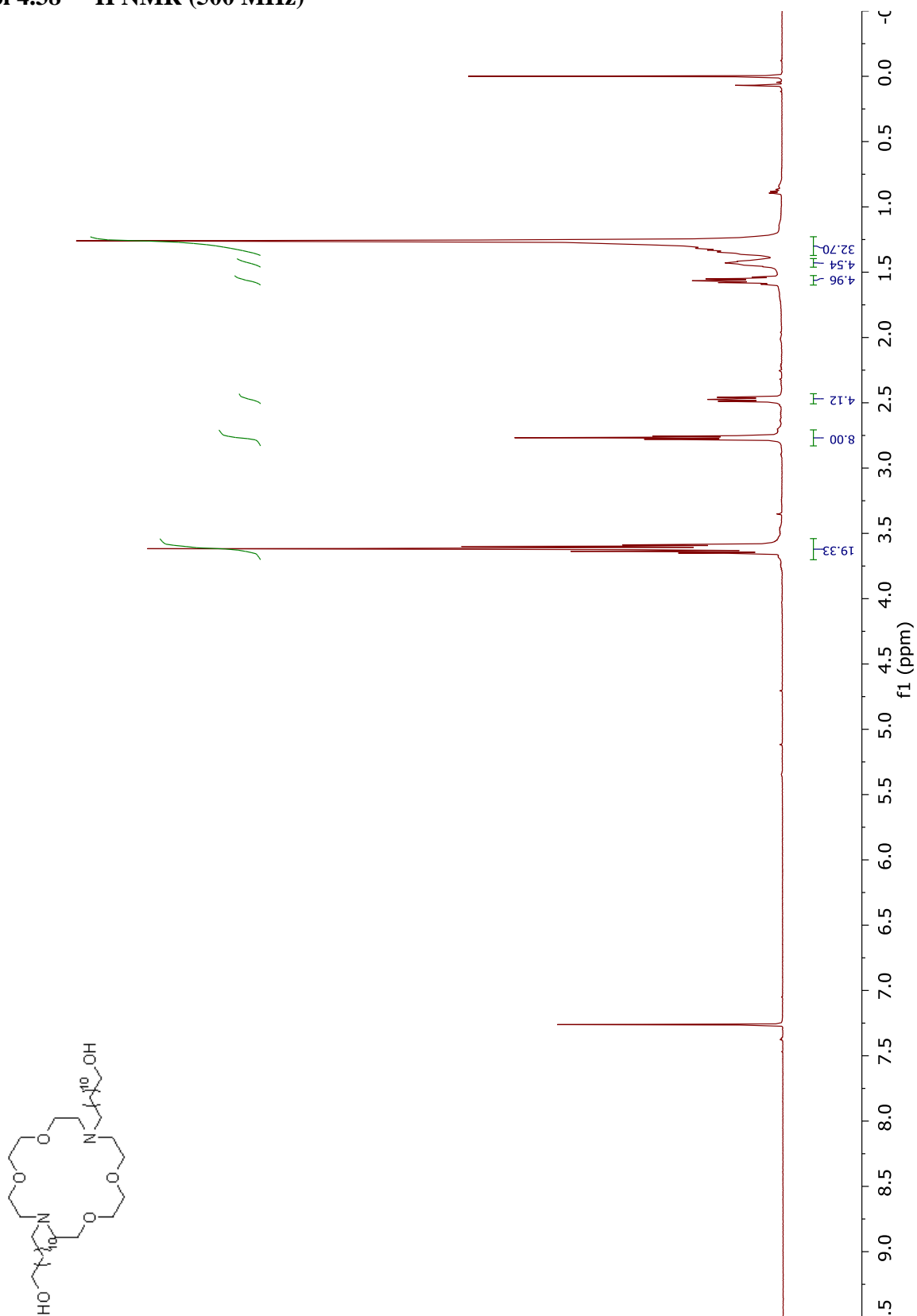
Diol 4.38 – ^{13}C NMR (126 MHz)
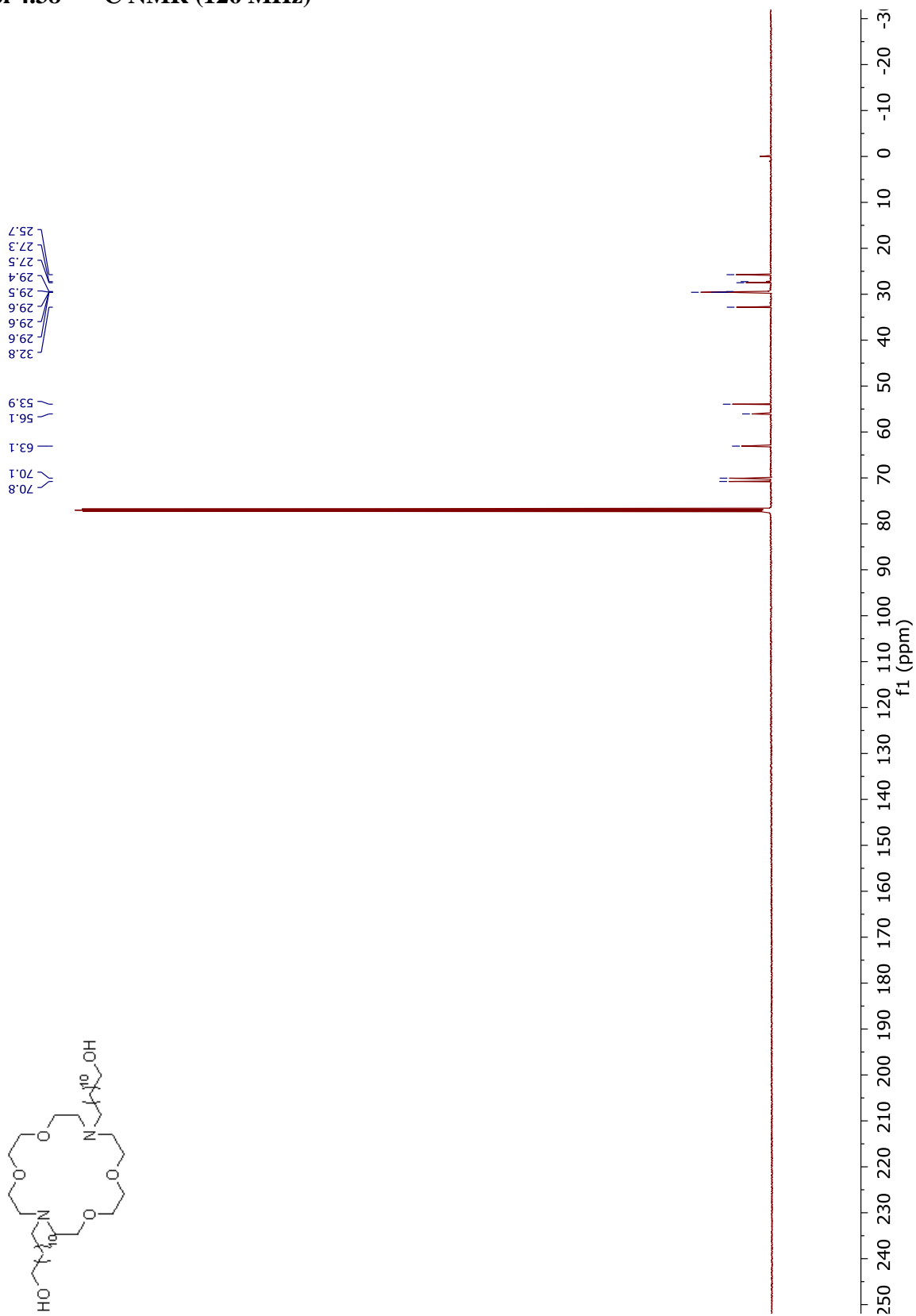
Alcohol 4.39 – ^{1}H NMR (500 MHz)
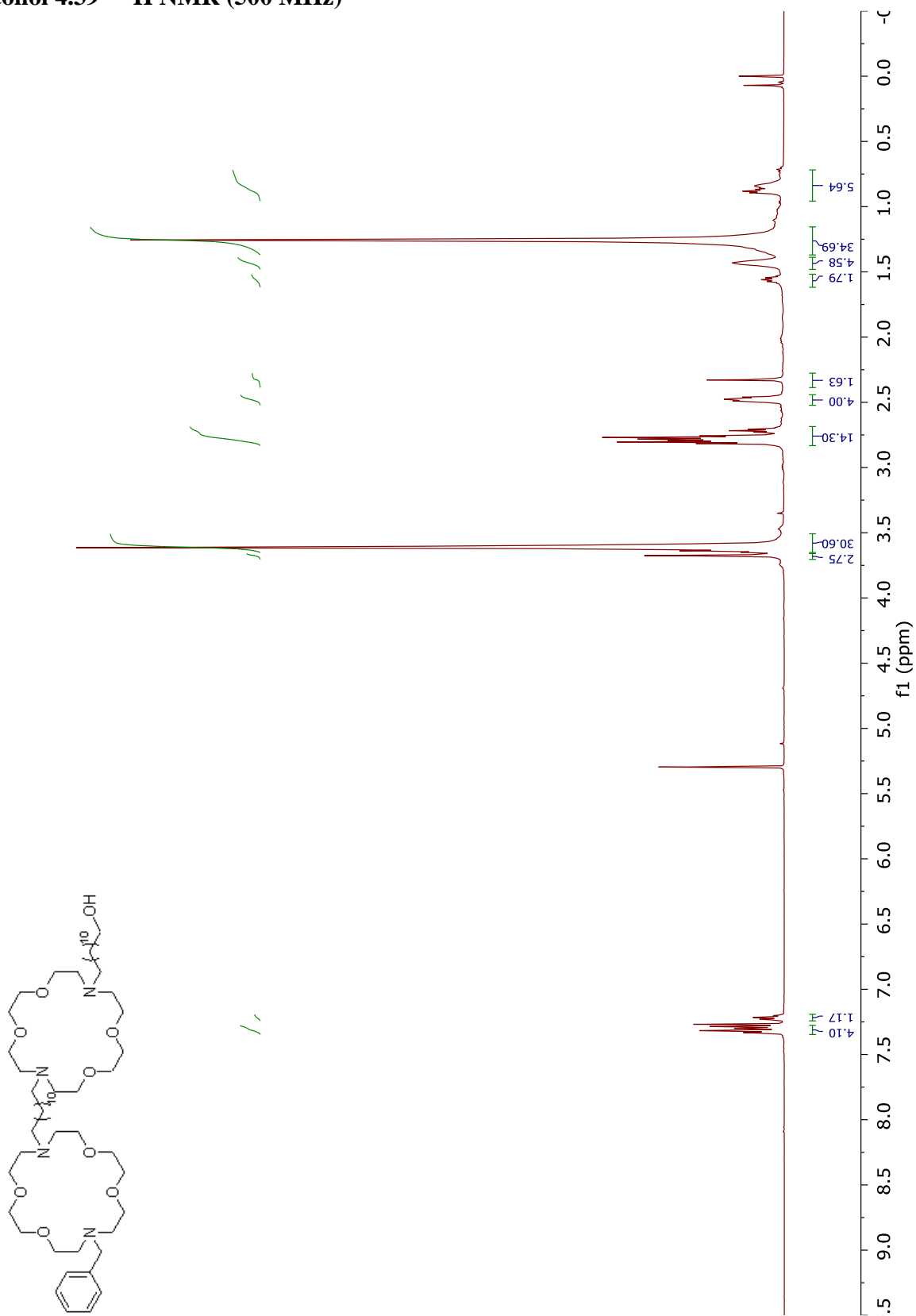
Alcohol 4.39 – ¹³C NMR (126 MHz)
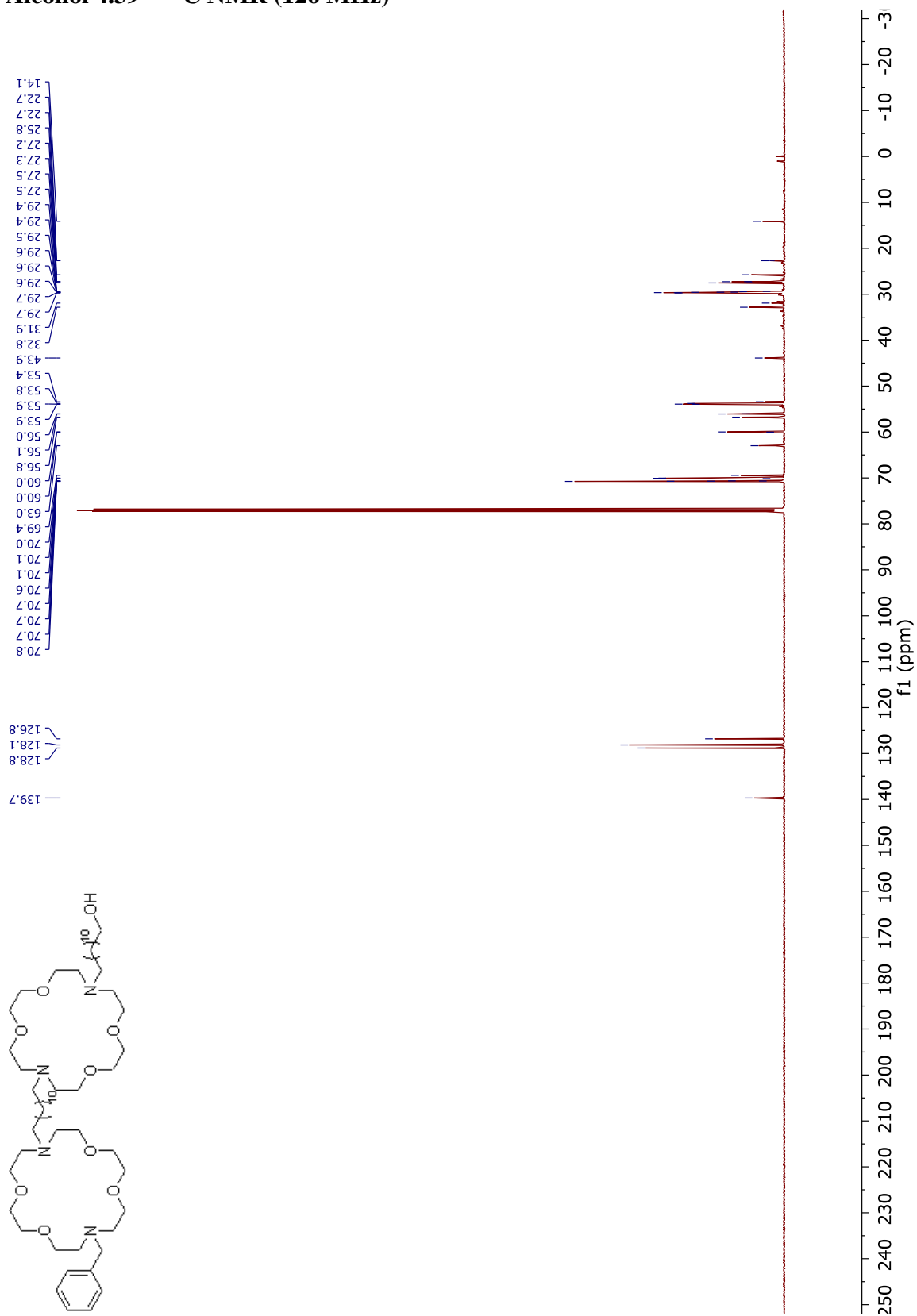
Appendix II

Calculation Geometries

All structures were optimized with Gaussian16[1] using the B3LYP functional[2] with a 6-311+G(2d,p) basis set. An SMD continuum solvent model[3] was used with water and n-octanol as solvents. All minima were checked for the absence of imaginary vibrational modes. All ClogP values were calculated using the relationship[4]

$$ClogP = \frac{\Delta G_s - \Delta G_h}{2.3RT}$$

where ΔG_s is the free energy of solvation (kcal·mol^{-1}), ΔG_h is the free energy of hydration (kcal·mol^{-1}), R is the ideal gas constant (kcal· mol^{-1}· K^{-1}), and T is temperature (K); all computations were conducted at 298K. The following computational coordinates are tabulated as atomic number, atomic type, X, Y, Z; X, Y, Z coordinates are reported in angstroms (Å). Energies are reported as Hartrees/particle.

Trans-**3.1**

Solvent: *none*
Free Energy: -1643.796883

6	0	6.354461	-2.412810	-0.355937
8	0	5.777425	-1.580852	0.657286
6	0	4.471058	-1.217220	0.512704
6	0	3.449874	-2.126622	0.239988
6	0	2.134907	-1.706339	0.117914
6	0	1.827726	-0.352621	0.277218
6	0	2.846701	0.565073	0.555610
6	0	4.164567	0.145887	0.671226
8	0	5.211769	0.973322	0.940584
6	0	5.169698	2.314108	0.454206
6	0	6.597806	2.788155	0.288146
8	0	7.215288	2.140859	-0.813448
6	0	8.484258	1.551002	-0.559935
6	0	8.420246	0.169066	0.066287
8	0	8.074197	-0.784107	-0.935043
6	0	7.834271	-2.094900	-0.452357
1	0	8.314100	-2.248962	0.521055
1	0	8.285949	-2.795660	-1.162581
1	0	7.689191	0.152307	0.878813
1	0	9.412057	-0.075496	0.476049
1	0	9.085247	2.206347	0.083823

1	0	8.982545	1.481619	-1.528821
1	0	7.146631	2.603431	1.217447
1	0	6.589677	3.871456	0.110097
1	0	4.645203	2.963381	1.165687
1	0	4.651075	2.348506	-0.508005
1	0	2.578640	1.606762	0.672533
7	0	0.530304	0.201885	0.179923
7	0	-0.389998	-0.616814	-0.053451
6	0	-1.685961	-0.064273	-0.154942
6	0	-2.715994	-0.980336	-0.395515
6	0	-4.028043	-0.558407	-0.511256
6	0	-4.332154	0.811196	-0.405993
6	0	-3.302195	1.726479	-0.165072
6	0	-1.991755	1.294705	-0.037919
1	0	-1.195038	2.001592	0.147226
1	0	-3.526324	2.781380	-0.079018
8	0	-5.634875	1.140546	-0.571450
6	0	-6.113607	2.401394	-0.114209
6	0	-7.624396	2.380442	-0.224746
8	0	-8.199238	1.474418	0.700827
6	0	-9.019728	0.448235	0.153463
6	0	-8.266972	-0.740765	-0.416387
8	0	-7.729157	-1.504859	0.656300
6	0	-6.911048	-2.597724	0.272621
6	0	-5.429807	-2.283493	0.341749
8	0	-5.058327	-1.433071	-0.756803
1	0	-4.855232	-3.217086	0.294389

1	0	-5.209313	-1.781850	1.287440
1	0	-7.173089	-2.954560	-0.730631
1	0	-7.113980	-3.408324	0.980113
1	0	-7.473156	-0.412062	-1.091224
1	0	-8.980718	-1.355618	-0.986349
1	0	-9.670635	0.862097	-0.628075
1	0	-9.652339	0.108827	0.975755
1	0	-7.906856	2.130848	-1.252946
1	0	-7.997670	3.389273	-0.008610
1	0	-5.715730	3.215335	-0.732485
1	0	-5.810922	2.560786	0.925388
1	0	-2.472799	-2.031523	-0.488240
1	0	1.343093	-2.410209	-0.095576
1	0	3.696792	-3.174776	0.121950
1	0	6.222772	-3.472356	-0.103271
1	0	5.868561	-2.212394	-1.314413

Trans-**3.1**

Solvent: *water*
Free Energy: -1643.834043

6	0	-6.286554	-2.483980	-0.066840
8	0	-5.682950	-1.442410	-0.861536
6	0	-4.385118	-1.102522	-0.634318
6	0	-3.398723	-2.004018	-0.230764
6	0	-2.094632	-1.579245	-0.030661
6	0	-1.758105	-0.237574	-0.238874
6	0	-2.744434	0.669185	-0.647979
6	0	-4.049260	0.248222	-0.843968
8	0	-5.059525	1.071433	-1.265478
6	0	-5.176994	2.390461	-0.688081
6	0	-6.619723	2.611329	-0.305771
8	0	-6.931612	1.823454	0.847451
6	0	-8.301642	1.416379	0.944130
6	0	-8.586136	0.125886	0.205906
8	0	-7.898552	-0.946173	0.859008
6	0	-7.750104	-2.140597	0.085050
1	0	-8.213161	-2.019812	-0.897221
1	0	-8.252117	-2.966234	0.598814
1	0	-8.259682	0.200660	-0.835399
1	0	-9.668058	-0.057301	0.214346
1	0	-8.963047	2.201946	0.565207
1	0	-8.506471	1.285999	2.008874
1	0	-7.264656	2.340652	-1.146436
1	0	-6.774000	3.673655	-0.081769
1	0	-4.872066	3.132059	-1.429712
1	0	-4.529624	2.474945	0.186165
1	0	-2.475401	1.705642	-0.807553
7	0	-0.467514	0.314267	-0.072784
7	0	0.443177	-0.496135	0.232255
6	0	1.730984	0.056767	0.408706
6	0	2.748446	-0.869517	0.671445

6	0	4.053752	-0.447975	0.854051
6	0	4.363824	0.923386	0.781499
6	0	3.342584	1.847143	0.544501
6	0	2.037916	1.420678	0.354239
1	0	1.257037	2.145098	0.171112
1	0	3.573044	2.903682	0.507928
8	0	5.668374	1.250072	0.970757
6	0	6.202036	2.455625	0.385501
6	0	7.622545	2.161330	-0.029878
8	0	7.607608	1.287998	-1.164377
6	0	8.650586	0.309047	-1.204053
6	0	8.379780	-0.901842	-0.336141
8	0	7.206800	-1.567451	-0.809057
6	0	6.741002	-2.629936	0.029057
6	0	5.263903	-2.467448	0.297888
8	0	5.086925	-1.305031	1.139229
1	0	4.880181	-3.352228	0.812302
1	0	4.714742	-2.331769	-0.635635
1	0	7.290342	-2.638824	0.974227
1	0	6.908234	-3.590170	-0.470706
1	0	8.243321	-0.611159	0.710353
1	0	9.249171	-1.569303	-0.392997
1	0	9.606921	0.752161	-0.906521
1	0	8.728570	0.003587	-2.249325
1	0	8.165060	1.709130	0.803874
1	0	8.119883	3.101191	-0.294809
1	0	6.181044	3.260862	1.123689
1	0	5.606684	2.746967	-0.481375
1	0	2.506661	-1.923836	0.723061
1	0	-1.340348	-2.285878	0.284831
1	0	-3.657932	-3.042603	-0.070851
1	0	-6.174697	-3.449709	-0.566785
1	0	-5.801421	-2.526215	0.910166

Trans-**3.1**

Solvent: *n-octanol*
Free Energy: -1643.832691

6	0	-6.317047	-2.451235	-0.283168
8	0	-5.776106	-1.292534	-0.940864
6	0	-4.466775	-0.982858	-0.775911
6	0	-3.463265	-1.918288	-0.509502
6	0	-2.146316	-1.517208	-0.350321
6	0	-1.809860	-0.164599	-0.466783
6	0	-2.809648	0.773404	-0.755094
6	0	-4.128465	0.378424	-0.903119
8	0	-5.142716	1.243347	-1.206512
6	0	-5.269060	2.464640	-0.449028
6	0	-6.678254	2.564351	0.082969
8	0	-6.846581	1.632096	1.149122
6	0	-8.195560	1.221364	1.378751
6	0	-8.609142	0.042007	0.522628

8	0	-7.897101	-1.118967	0.951931
6	0	-7.776047	-2.168931	-0.006524
1	0	-8.292557	-1.909369	-0.934977
1	0	-8.238491	-3.076939	0.395544
1	0	-8.398964	0.245941	-0.531453
1	0	-9.690959	-0.115730	0.632235
1	0	-8.887387	2.053885	1.205962
1	0	-8.256331	0.947131	2.434680
1	0	-7.385379	2.366018	-0.729017
1	0	-6.853151	3.585484	0.447935
1	0	-5.065280	3.309492	-1.112009
1	0	-4.549478	2.476153	0.371737
1	0	-2.538502	1.817464	-0.853325
7	0	-0.509944	0.366670	-0.324395
7	0	0.391205	-0.454838	-0.022785
6	0	1.690243	0.078292	0.120849
6	0	2.676179	-0.838807	0.507610
6	0	3.986282	-0.432510	0.687655
6	0	4.336549	0.915038	0.477903
6	0	3.349982	1.830334	0.097794
6	0	2.039242	1.418088	-0.081159
1	0	1.283716	2.133349	-0.375843
1	0	3.610053	2.868819	-0.059735
8	0	5.637716	1.224372	0.678540
6	0	6.195304	2.402508	0.076637
6	0	7.688087	2.192032	-0.005969
8	0	7.983701	1.187588	-0.977678
6	0	8.945942	0.206499	-0.588567
6	0	8.385554	-0.897346	0.284537
8	0	7.435822	-1.653791	-0.464410
6	0	6.754386	-2.670271	0.272604
6	0	5.261681	-2.433688	0.279284
8	0	4.978596	-1.282304	1.102648
1	0	4.753834	-3.312815	0.688977
1	0	4.901115	-2.255772	-0.736415
1	0	7.128581	-2.721848	1.299256
1	0	6.948185	-3.637210	-0.205292
1	0	7.915710	-0.484442	1.182862
1	0	9.219941	-1.539571	0.599108
1	0	9.787283	0.678047	-0.067444
1	0	9.323452	-0.221482	-1.520074
1	0	8.074582	1.912686	0.977830
1	0	8.161497	3.135300	-0.303258
1	0	5.973528	3.281504	0.689808
1	0	5.776028	2.544653	-0.922516
1	0	2.402301	-1.875004	0.666457
1	0	-1.378448	-2.249141	-0.141120
1	0	-3.718199	-2.966805	-0.424689
1	0	-6.216902	-3.331366	-0.926154
1	0	-5.785195	-2.627142	0.654524

Cis-**3.1**

Solvent: *none*
Free Energy: -1643.757106

6	0	5.074017	-0.440245	1.468960
8	0	3.696629	-0.612659	1.833825
6	0	2.905620	0.480328	1.584145
6	0	2.541143	1.330994	2.617540
6	0	1.759475	2.454197	2.371827
6	0	1.295659	2.701515	1.083023
6	0	1.651597	1.851018	0.030677
6	0	2.445189	0.737109	0.275776
8	0	2.785904	-0.187593	-0.662264
6	0	2.928115	0.201855	-2.021927
6	0	3.236667	-1.052901	-2.841236
8	0	4.137460	-1.959699	-2.245000
6	0	5.420693	-1.471429	-1.910229
6	0	6.059977	-2.452323	-0.936058
8	0	5.369161	-2.610955	0.291298
6	0	5.762321	-1.790913	1.373751
1	0	6.847898	-1.615866	1.348946
1	0	5.534629	-2.358882	2.279256
1	0	7.101859	-2.149728	-0.759490
1	0	6.067803	-3.440511	-1.402296
1	0	5.363662	-0.473457	-1.467694
1	0	6.056802	-1.402579	-2.807342
1	0	3.585229	-0.727911	-3.833852
1	0	2.319993	-1.627906	-2.977259
1	0	3.718870	0.957028	-2.099196
1	0	2.008205	0.639931	-2.423326
1	0	1.292609	2.056346	-0.967405
7	0	0.599450	3.938671	0.878861
7	0	-0.421964	4.070471	0.181303
6	0	-1.182138	2.989026	-0.372903
6	0	-1.533335	1.841326	0.343489
6	0	-2.389661	0.901313	-0.214954
6	0	-2.915051	1.110723	-1.506891
6	0	-2.548925	2.251965	-2.212405
6	0	-1.712132	3.201637	-1.644196
1	0	-1.471284	4.117591	-2.168946
1	0	-2.965525	2.395271	-3.201569
8	0	-3.745461	0.205705	-2.105616
6	0	-4.991303	-0.065348	-1.433875
6	0	-5.211992	-1.565574	-1.323839
8	0	-6.382714	-1.756325	-0.521224
6	0	-6.298861	-2.737622	0.500177
6	0	-5.474536	-2.317125	1.708479
8	0	-4.093606	-2.487696	1.411297
6	0	-3.179617	-1.753883	2.203441
6	0	-3.024241	-0.300851	1.778590
8	0	-2.692299	-0.288491	0.390676
1	0	-2.233986	0.148905	2.388433
1	0	-3.943085	0.276463	1.934718
1	0	-2.219863	-2.260448	2.087599
1	0	-3.455795	-1.783687	3.266555
1	0	-5.744899	-2.941419	2.572748
1	0	-5.707760	-1.274777	1.954011
1	0	-5.905861	-3.683430	0.107148
1	0	-7.328977	-2.906000	0.822549

1   0   -4.335968   -2.021692   -0.867900
1   0   -5.377216   -2.008040   -2.312292
1   0   -5.791542   0.407732   -2.010343
1   0   -4.988833   0.370715   -0.435730
1   0   -1.119234   1.671904   1.326977
1   0   1.513305   3.148104   3.165570
1   0   2.905514   1.114410   3.614403
1   0   5.142824   0.106973   0.527453
1   0   5.575565   0.153916   2.245031

Cis-**3.1**

Solvent: *water*
Free Energy: -1643.801183

6   0   -5.150726   -0.455182   -1.577631
8   0   -3.727816   -0.725825   -1.592904
6   0   -2.936535   0.391149   -1.409394
6   0   -2.572525   1.182464   -2.494540
6   0   -1.767817   2.297884   -2.312787
6   0   -1.269142   2.591943   -1.044315
6   0   -1.627676   1.805799   0.050867
6   0   -2.468309   0.715120   -0.127511
8   0   -2.802195   -0.100313   0.933073
6   0   -3.720995   0.472738   1.890967
6   0   -4.199570   -0.630885   2.810199
8   0   -4.827663   -1.716469   2.129856
6   0   -6.141601   -1.442130   1.640798
6   0   -6.522806   -2.515667   0.641055
8   0   -5.643545   -2.625317   -0.482978
6   0   -5.901965   -1.768226   -1.596393
1   0   -6.972619   -1.550041   -1.671352
1   0   -5.607106   -2.333727   -2.483703
1   0   -7.549514   -2.337703   0.303583
1   0   -6.487394   -3.491298   1.130923
1   0   -6.189054   -0.450545   1.187136
1   0   -6.862419   -1.466575   2.468748
1   0   -4.874948   -0.193600   3.555118
1   0   -3.347956   -1.067531   3.334738
1   0   -4.546399   0.943637   1.353243
1   0   -3.214977   1.236040   2.489584
1   0   -1.268433   2.036767   1.044951
7   0   -0.529144   3.812597   -0.903910
7   0   0.519240   3.923046   -0.240163
6   0   1.244897   2.815903   0.313032
6   0   1.586915   1.692838   -0.442892
6   0   2.413720   0.720883   0.103363
6   0   2.901329   0.868759   1.413191
6   0   2.547709   1.986736   2.158244
6   0   1.744226   2.974351   1.604173
1   0   1.499224   3.864833   2.169502
1   0   2.934139   2.088337   3.164861
8   0   3.711827   -0.100534   1.971426
6   0   5.052793   -0.128929   1.425030
6   0   5.641144   -1.516487   1.623608

8   0   6.895688   -1.588279   0.933996
6   0   6.926927   -2.387582   -0.256097
6   0   6.128002   -1.865303   -1.436389
8   0   4.757766   -2.257780   -1.304214
6   0   3.866969   -1.677383   -2.256263
6   0   3.369911   -0.304556   -1.855156
8   0   2.725352   -0.436517   -0.568589
1   0   2.659156   0.051314   -2.606065
1   0   4.186326   0.416962   -1.772265
1   0   3.020275   -2.362813   -2.329272
1   0   4.339019   -1.609111   -3.242635
1   0   6.539298   -2.302227   -2.355150
1   0   6.222006   -0.776853   -1.504401
1   0   6.610433   -3.410634   -0.023643
1   0   7.979278   -2.412610   -0.542539
1   0   4.950631   -2.276855   1.257567
1   0   5.834105   -1.703090   2.683021
1   0   5.654781   0.626533   1.938353
1   0   5.026075   0.111452   0.364661
1   0   1.215992   1.568362   -1.451380
1   0   -1.509389   2.932183   -3.151560
1   0   -2.942936   0.924513   -3.479183
1   0   -5.391730   0.144024   -0.699088
1   0   -5.421098   0.113615   -2.473520

Cis-**3.1**

Solvent: *n-octanol*
Free Energy: -1643.795095

6   0   -5.220937   -0.316314   -1.521959
8   0   -3.817086   -0.577207   -1.739273
6   0   -2.994730   0.492265   -1.472900
6   0   -2.616609   1.355111   -2.496984
6   0   -1.792399   2.440356   -2.236377
6   0   -1.287740   2.632735   -0.950399
6   0   -1.652075   1.768338   0.083413
6   0   -2.510220   0.705526   -0.171626
8   0   -2.846617   -0.195508   0.805797
6   0   -3.607979   0.313571   1.916143
6   0   -4.026297   -0.857414   2.785078
8   0   -4.722878   -1.885675   2.092061
6   0   -6.048214   -1.569142   1.679274
6   0   -6.470066   -2.558751   0.608710
8   0   -5.657566   -2.559500   -0.564444
6   0   -5.987585   -1.620024   -1.582633
1   0   -7.059273   -1.388806   -1.559398
1   0   -5.769276   -2.113843   -2.533622
1   0   -7.518564   -2.372783   0.345921
1   0   -6.395105   -3.571048   1.013508
1   0   -6.112976   -0.542685   1.311110
1   0   -6.740973   -1.660766   2.528297
1   0   -4.622954   -0.468640   3.621060
1   0   -3.137719   -1.339878   3.196773
1   0   -4.467353   0.870828   1.533583

1	0	-3.001803	0.993488	2.523768
1	0	-1.278433	1.915321	1.088174
7	0	-0.542397	3.836519	-0.727807
7	0	0.496429	3.913261	-0.045669
6	0	1.230817	2.789572	0.456036
6	0	1.579115	1.695628	-0.340407
6	0	2.423659	0.715266	0.163815
6	0	2.924163	0.826052	1.474584
6	0	2.559067	1.912116	2.261077
6	0	1.738964	2.908002	1.748673
1	0	1.490639	3.779054	2.342923
1	0	2.955116	1.983046	3.267035
8	0	3.754483	-0.139482	1.990981
6	0	5.074886	-0.167028	1.402388
6	0	5.643197	-1.572405	1.507470
8	0	6.891521	-1.608698	0.804763
6	0	6.924965	-2.361321	-0.411150
6	0	6.104126	-1.806899	-1.562478
8	0	4.742717	-2.207885	-1.409930
6	0	3.816115	-1.605543	-2.306857
6	0	3.326120	-0.245940	-1.850159
8	0	2.746774	-0.412332	-0.541962
1	0	2.579489	0.117095	-2.563082
1	0	4.138163	0.484719	-1.792835
1	0	2.968831	-2.292455	-2.363573
1	0	4.244874	-1.508108	-3.311794
1	0	6.500576	-2.214731	-2.502453
1	0	6.197541	-0.715914	-1.599096
1	0	6.626100	-3.398751	-0.218986
1	0	7.975688	-2.359333	-0.707578
1	0	4.937120	-2.295024	1.097649
1	0	5.840829	-1.829316	2.552084
1	0	5.708983	0.548666	1.935649
1	0	5.023581	0.129983	0.356955
1	0	1.197457	1.601953	-1.348292
1	0	-1.529510	3.136602	-3.023636
1	0	-2.997685	1.178145	-3.495818
1	0	-5.353419	0.188801	-0.564569
1	0	-5.591020	0.343668	-2.315772

Cis-**3.1**, Na+ bound

Solvent: *none*
Free Energy: -1805.959092

6	0	0.000062	0.000540	0.000022
8	0	-0.000917	0.001869	1.438594
6	0	1.215922	0.000918	2.083980
6	0	1.580112	-1.080084	2.879605
6	0	2.660283	-0.982563	3.751444
6	0	3.366179	0.214684	3.834833
6	0	3.112444	1.240499	2.926126
6	0	2.014689	1.153294	2.086794
8	0	1.510069	2.255245	1.427797
6	0	2.356619	3.039284	0.578825

6	0	1.589329	4.321846	0.270245
8	0	0.212886	4.081996	-0.015684
6	0	-0.055747	3.460683	-1.273153
6	0	-1.444427	2.853896	-1.202147
8	0	-1.574754	1.896746	-0.147716
6	0	-1.343208	0.520957	-0.473871
1	0	-1.426526	0.368751	-1.554288
1	0	-2.137401	-0.050110	0.011795
1	0	-1.704602	2.406435	-2.166288
1	0	-2.172332	3.639416	-0.987334
1	0	0.687944	2.689353	-1.493156
1	0	-0.018974	4.206524	-2.076662
1	0	2.078653	4.855890	-0.551972
1	0	1.585735	4.967668	1.148582
1	0	2.595438	2.459538	-0.318152
1	0	3.296841	3.297257	1.072355
1	0	3.664070	2.167822	2.985468
7	0	4.263190	0.370624	4.957523
7	0	4.155224	1.340095	5.737005
6	0	3.133002	2.341486	5.534131
6	0	1.786679	2.014358	5.389950
6	0	0.907328	2.949002	4.866099
6	0	1.356580	4.239666	4.551844
6	0	2.664964	4.598281	4.859728
6	0	3.556087	3.657049	5.364615
1	0	4.594275	3.910643	5.537871
1	0	2.991967	5.607588	4.642178
8	0	0.568969	5.081590	3.797788
6	0	-0.550103	5.718489	4.439808
6	0	-1.640909	5.931147	3.406695
8	0	-2.256487	4.714004	2.971359
6	0	-3.269488	4.241523	3.857997
6	0	-3.737996	2.873303	3.393169
8	0	-2.679897	1.930838	3.221422
6	0	-2.256709	1.174762	4.353382
6	0	-1.263175	1.905463	5.254276
8	0	-0.340363	2.591484	4.398692
1	0	-0.754497	1.173407	5.886258
1	0	-1.747482	2.635441	5.909390
1	0	-1.777184	0.291316	3.930187
1	0	-3.117904	0.848964	4.947019
1	0	-4.203436	2.961810	2.409869
1	0	-4.488797	2.488822	4.092125
1	0	-4.125816	4.928153	3.848234
1	0	-2.890504	4.198561	4.883214
1	0	-1.211928	6.389586	2.514530
1	0	-2.398285	6.613343	3.808408
1	0	-0.229553	6.688146	4.835224
1	0	-0.898468	5.109689	5.276205
1	0	1.460483	0.992311	5.524719
1	0	2.906152	-1.794095	4.424576
1	0	0.972345	-1.975898	2.849672
1	0	0.821876	0.610838	-0.376512
1	0	0.135010	-1.026259	-0.357826
11	0	-0.849213	2.897488	1.953933

Cis-**3.1**, Na⁺ bound

Solvent: *water*
Free Energy: -1806.042329

6	0	0.067172	0.007011	-0.061170
8	0	0.045846	-0.125514	1.382179
6	0	1.242738	-0.064043	2.056083
6	0	1.631212	-1.140133	2.848295
6	0	2.694638	-1.018806	3.736551
6	0	3.365833	0.196625	3.836206
6	0	3.084032	1.227868	2.942131
6	0	1.999075	1.119483	2.088015
8	0	1.485164	2.221781	1.449079
6	0	2.308898	2.957780	0.521888
6	0	1.578263	4.256296	0.223547
8	0	0.178825	4.067935	-0.009588
6	0	-0.149469	3.438680	-1.257509
6	0	-1.529777	2.833743	-1.133005
8	0	-1.616288	1.823309	-0.115212
6	0	-1.291344	0.483488	-0.521653
1	0	-1.337271	0.401462	-1.610650
1	0	-2.061824	-0.165905	-0.098677
1	0	-1.837422	2.425412	-2.099528
1	0	-2.245613	3.606638	-0.844229
1	0	0.585299	2.671547	-1.508005
1	0	-0.152285	4.187195	-2.058221
1	0	2.054704	4.750169	-0.629452
1	0	1.635950	4.920443	1.086265
1	0	2.464403	2.345159	-0.368798
1	0	3.281475	3.192355	0.959255
1	0	3.606445	2.171963	3.003834
7	0	4.255891	0.359808	4.960436
7	0	4.161429	1.340749	5.734723
6	0	3.146621	2.350090	5.546780
6	0	1.802045	2.033567	5.366392
6	0	0.930484	2.991585	4.872336
6	0	1.386221	4.298108	4.631294
6	0	2.695452	4.634292	4.962507
6	0	3.579745	3.667647	5.429283
1	0	4.618522	3.914396	5.609896
1	0	3.029690	5.650706	4.794874
8	0	0.616270	5.198758	3.934841
6	0	-0.593279	5.697723	4.558482
6	0	-1.635124	5.946378	3.488793
8	0	-2.228157	4.749567	2.963213
6	0	-3.283660	4.247796	3.795556
6	0	-3.714734	2.881816	3.304020
8	0	-2.649299	1.929283	3.193492
6	0	-2.242104	1.242622	4.382710
6	0	-1.264648	2.017155	5.253760
8	0	-0.302027	2.641122	4.379308
1	0	-0.775159	1.316769	5.933528
1	0	-1.748681	2.796632	5.844456
1	0	-1.760290	0.331748	4.025152

1	0	-3.114585	0.964928	4.982265
1	0	-4.123622	2.965571	2.295278
1	0	-4.498389	2.498030	3.964698
1	0	-4.147131	4.921781	3.739875
1	0	-2.957714	4.208831	4.836196
1	0	-1.174449	6.458672	2.642484
1	0	-2.415348	6.596519	3.897335
1	0	-0.353136	6.645054	5.050139
1	0	-0.943459	4.994819	5.313446
1	0	1.456704	1.013218	5.461410
1	0	2.945232	-1.831371	4.407020
1	0	1.054192	-2.055364	2.802427
1	0	0.859187	0.686226	-0.366357
1	0	0.259703	-0.979827	-0.493862
11	0	-0.823973	2.915052	1.958392

Cis-**3.1**, Na⁺ bound

Solvent: *n-octanol*
Free Energy: -1806.041468

6	0	-0.007446	-0.001505	0.000564
8	0	-0.003450	0.003913	1.447256
6	0	1.206313	0.000150	2.095934
6	0	1.517714	-1.050600	2.953976
6	0	2.599123	-0.958257	3.824177
6	0	3.365765	0.204035	3.838623
6	0	3.158698	1.192490	2.878189
6	0	2.058334	1.115519	2.040551
8	0	1.623605	2.210610	1.332794
6	0	2.489148	2.819312	0.355605
6	0	1.842787	4.137862	-0.038770
8	0	0.434172	4.024040	-0.251839
6	0	0.054381	3.338896	-1.452070
6	0	-1.368609	2.853191	-1.285461
8	0	-1.526837	1.943283	-0.187878
6	0	-1.332535	0.550734	-0.475947
1	0	-1.419298	0.373343	-1.551697
1	0	-2.143680	0.014237	0.023131
1	0	-1.710408	2.391607	-2.216608
1	0	-2.022316	3.700836	-1.065581
1	0	0.726669	2.500158	-1.647572
1	0	0.106918	4.027135	-2.304460
1	0	2.345213	4.535566	-0.927395
1	0	1.951228	4.860153	0.771341
1	0	2.601238	2.131804	-0.486929
1	0	3.478900	3.021612	0.771616
1	0	3.757382	2.092440	2.876233
7	0	4.271634	0.374894	4.948878
7	0	4.250859	1.406464	5.658027
6	0	3.307983	2.470593	5.407754
6	0	1.941929	2.238682	5.261576
6	0	1.135336	3.216958	4.701546
6	0	1.680196	4.464390	4.355885
6	0	3.013158	4.731119	4.655034

6	0	3.831788	3.742031	5.189902
1	0	4.887774	3.925148	5.347755
1	0	3.416478	5.705563	4.406907
8	0	0.969468	5.353636	3.589544
6	0	-0.177590	6.009238	4.178499
6	0	-1.211788	6.253186	3.099867
8	0	-1.897418	5.066685	2.677475
6	0	-2.983177	4.715289	3.543241
6	0	-3.518376	3.351510	3.156539
8	0	-2.525980	2.320752	3.118707
6	0	-2.170185	1.689821	4.351681
6	0	-1.124698	2.442306	5.162950
8	0	-0.125294	2.921167	4.242679
1	0	-0.688252	1.754964	5.891622
1	0	-1.540057	3.298185	5.699862
1	0	-1.768651	0.717937	4.060826
1	0	-3.058398	1.527153	4.971164
1	0	-3.925827	3.389615	2.144003
1	0	-4.326814	3.077283	3.842579
1	0	-3.793562	5.447472	3.435568
1	0	-2.657772	4.730214	4.585776
1	0	-0.724301	6.659683	2.211660
1	0	-1.935376	6.992897	3.458861
1	0	0.151005	6.971185	4.584921
1	0	-0.576179	5.408072	4.995993
1	0	1.528367	1.255110	5.438048
1	0	2.794025	-1.741355	4.546770
1	0	0.866296	-1.916019	2.973821
1	0	0.832605	0.574550	-0.383225
1	0	0.088583	-1.037294	-0.342631
11	0	-0.646731	3.080673	1.800909

Cis-**3.1**, K⁺ bound

Solvent: *none*
Free Energy: -2243.606432

6	0	-0.001970	-0.001193	0.001523
8	0	-0.000732	0.002465	1.437468
6	0	1.222884	0.001857	2.071936
6	0	1.658323	-1.137056	2.742489
6	0	2.750975	-1.078263	3.599988
6	0	3.391039	0.140575	3.809688
6	0	3.059640	1.246251	3.030543
6	0	1.962250	1.187579	2.185796
8	0	1.434451	2.337489	1.633009
6	0	2.173714	3.018000	0.612610
6	0	1.374761	4.261845	0.245705
8	0	-0.002769	3.988714	0.013089
6	0	-0.300178	3.365128	-1.233755
6	0	-1.670843	2.720538	-1.132129
8	0	-1.764973	1.724200	-0.114321
6	0	-1.388413	0.392099	-0.472145
1	0	-1.448228	0.255993	-1.557024
1	0	-2.121944	-0.271380	-0.008444

1	0	-1.950756	2.303453	-2.105653
1	0	-2.408285	3.482968	-0.871421
1	0	0.457644	2.618270	-1.488491
1	0	-0.312978	4.114513	-2.035810
1	0	1.836574	4.750441	-0.620338
1	0	1.392976	4.965090	1.079635
1	0	2.319061	2.347586	-0.240462
1	0	3.162533	3.319033	0.972784
1	0	3.559568	2.193465	3.179435
7	0	4.326161	0.224628	4.908322
7	0	4.159390	1.059169	5.820924
6	0	3.016651	1.942233	5.805045
6	0	1.710118	1.467595	5.713053
6	0	0.679461	2.343568	5.413397
6	0	0.946686	3.709687	5.239856
6	0	2.225507	4.192335	5.503391
6	0	3.259466	3.313398	5.807441
1	0	4.270694	3.675917	5.943746
1	0	2.426527	5.251300	5.394630
8	0	-0.018495	4.492017	4.642462
6	0	-0.698574	5.484931	5.421736
6	0	-1.843330	6.005647	4.567022
8	0	-2.698507	4.967852	4.097428
6	0	-3.660547	4.509764	5.041674
6	0	-4.244665	3.201050	4.540353
8	0	-3.275379	2.176404	4.323328
6	0	-2.875853	1.400039	5.452073
6	0	-1.577167	1.867696	6.084229
8	0	-0.556558	1.826390	5.073978
1	0	-1.312664	1.192117	6.905448
1	0	-1.659528	2.879073	6.487070
1	0	-2.744895	0.379286	5.086271
1	0	-3.662955	1.387922	6.213711
1	0	-4.717551	3.364817	3.570043
1	0	-5.016617	2.857044	5.237789
1	0	-4.470444	5.244130	5.144428
1	0	-3.207207	4.377906	6.029392
1	0	-1.440018	6.483844	3.672914
1	0	-2.406810	6.759661	5.128776
1	0	-0.026417	6.312366	5.672585
1	0	-1.050431	5.041776	6.358003
1	0	1.496659	0.408184	5.746073
1	0	3.053617	-1.945719	4.172961
1	0	1.092887	-2.053854	2.630957
1	0	0.760467	0.681807	-0.375793
1	0	0.228449	-1.009836	-0.360656
19	0	-1.242052	2.807886	2.463246

Cis-**3.1**, K⁺ bound

Solvent: *water*
Free Energy: -2243.686208

6	0	-0.017014	0.003584	0.015548
8	0	-0.010912	0.012584	1.463602

6	0	1.213810	0.007277	2.092396
6	0	1.567843	-1.080102	2.885678
6	0	2.677541	-1.018777	3.721611
6	0	3.423336	0.154636	3.775359
6	0	3.164513	1.193861	2.884724
6	0	2.045516	1.139363	2.067984
8	0	1.602210	2.254901	1.401357
6	0	2.437981	2.829279	0.377861
6	0	1.789761	4.133792	-0.054056
8	0	0.383896	4.025886	-0.285037
6	0	0.014576	3.285734	-1.454693
6	0	-1.410553	2.799680	-1.295494
8	0	-1.607665	1.893996	-0.200826
6	0	-1.357087	0.508133	-0.470907
1	0	-1.429520	0.315383	-1.545138
1	0	-2.151530	-0.052684	0.028120
1	0	-1.735101	2.334610	-2.231542
1	0	-2.065446	3.651266	-1.095683
1	0	0.694744	2.447081	-1.613094
1	0	0.068684	3.936628	-2.336108
1	0	2.307610	4.505976	-0.945180
1	0	1.894140	4.877220	0.737487
1	0	2.530386	2.113690	-0.442683
1	0	3.437013	3.046283	0.763951
1	0	3.748797	2.103442	2.910094
7	0	4.398335	0.281242	4.833914
7	0	4.356734	1.245646	5.631962
6	0	3.305139	2.228803	5.541131
6	0	1.957093	1.871158	5.522807
6	0	1.006982	2.805896	5.152866
6	0	1.401081	4.111930	4.812234
6	0	2.723222	4.500003	5.007372
6	0	3.676596	3.561081	5.390547
1	0	4.720313	3.841862	5.458147
1	0	3.021343	5.516039	4.780364
8	0	0.484064	4.881791	4.148475
6	0	0.134913	6.185947	4.649918
6	0	-0.898379	6.756183	3.693831
8	0	-1.964148	5.851491	3.398662
6	0	-2.911128	5.670117	4.456163
6	0	-3.728434	4.427110	4.173989
8	0	-2.966236	3.214101	4.105811
6	0	-2.654901	2.577936	5.351528
6	0	-1.272711	2.888041	5.880996
8	0	-0.290792	2.387555	4.939363
1	0	-1.137487	2.371465	6.836635
1	0	-1.123032	3.955190	6.035347
1	0	-2.737876	1.503068	5.173510
1	0	-3.388464	2.854232	6.114792
1	0	-4.210705	4.521494	3.198609
1	0	-4.510498	4.336138	4.934711
1	0	-3.590038	6.531308	4.498940
1	0	-2.407535	5.593057	5.421606
1	0	-0.427970	6.970803	2.733066
1	0	-1.283254	7.695453	4.106424
1	0	1.005878	6.846230	4.665021

1	0	-0.244961	6.082229	5.668614
1	0	1.645285	0.849930	5.694072
1	0	2.907660	-1.838765	4.390398
1	0	0.931408	-1.956444	2.880847
1	0	0.804895	0.604129	-0.366294
1	0	0.113585	-1.029065	-0.324614
19	0	-0.917516	3.289159	2.195497

Cis-**3.1**, K$^+$ bound

Solvent: *n-octanol*
Free Energy: -2243.685391

6	0	-0.022857	0.012948	0.022679
8	0	-0.005117	0.031288	1.467541
6	0	1.221515	0.020151	2.088423
6	0	1.602055	-1.087978	2.839788
6	0	2.709131	-1.030336	3.679561
6	0	3.422298	0.160590	3.782811
6	0	3.141498	1.224600	2.928770
6	0	2.028637	1.169517	2.104099
8	0	1.560503	2.296398	1.472707
6	0	2.372212	2.910469	0.455661
6	0	1.669968	4.192885	0.037912
8	0	0.270042	4.028789	-0.184511
6	0	-0.078456	3.320655	-1.377456
6	0	-1.490450	2.790865	-1.235011
8	0	-1.663863	1.859036	-0.161254
6	0	-1.379812	0.485603	-0.451727
1	0	-1.455777	0.302391	-1.528201
1	0	-2.155716	-0.102054	0.046200
1	0	-1.799721	2.338381	-2.183170
1	0	-2.170289	3.619470	-1.020527
1	0	0.624107	2.505512	-1.564719
1	0	-0.041931	4.001743	-2.237673
1	0	2.167441	4.597187	-0.851546
1	0	1.749482	4.932270	0.836738
1	0	2.496001	2.207188	-0.372321
1	0	3.363517	3.161889	0.843548
1	0	3.700852	2.148111	2.992751
7	0	4.378667	0.277780	4.858883
7	0	4.291224	1.203711	5.695708
6	0	3.205290	2.151794	5.633264
6	0	1.872416	1.746021	5.588602
6	0	0.889329	2.656359	5.239856
6	0	1.235584	3.988992	4.957977
6	0	2.542269	4.416443	5.176248
6	0	3.528778	3.501821	5.532048
1	0	4.561645	3.816821	5.618979
1	0	2.802436	5.450934	4.986655
8	0	0.306487	4.762020	4.308500
6	0	-0.209985	5.948860	4.939491
6	0	-1.271944	6.507869	4.009736
8	0	-2.245775	5.540159	3.619171
6	0	-3.229836	5.244638	4.612522

6	0	-3.932163	3.955976	4.237775
8	0	-3.070309	2.816540	4.143720
6	0	-2.747239	2.139805	5.362633
6	0	-1.401572	2.521109	5.941260
8	0	-0.379794	2.189319	4.973537
1	0	-1.230882	1.940297	6.854290
1	0	-1.345607	3.580709	6.187504
1	0	-2.745509	1.072499	5.126970
1	0	-3.517945	2.318617	6.119340
1	0	-4.382187	4.061450	3.247716
1	0	-4.735962	3.764900	4.957101
1	0	-3.975300	6.050088	4.650768
1	0	-2.773581	5.165691	5.602252
1	0	-0.805041	6.844299	3.082075
1	0	-1.745843	7.373569	4.486860
1	0	0.579583	6.694725	5.071076
1	0	-0.609572	5.689013	5.922809
1	0	1.598018	0.707503	5.713707
1	0	2.960659	-1.867819	4.318997
1	0	0.984869	-1.977684	2.803698
1	0	0.781032	0.632660	-0.369866
1	0	0.130624	-1.017483	-0.317176
19	0	-1.012716	3.141240	2.284834

C6 LARIAT ETHER

Solvent: *none*
Free Energy: -1354.753729

6	0	-0.174379	0.035797	-0.053089
7	0	-0.077225	0.049011	1.401861
6	0	1.290485	0.032533	1.900146
6	0	1.499042	0.755848	3.223064
8	0	1.396521	2.155312	3.037752
6	0	1.770972	2.883516	4.192076
6	0	1.633850	4.369419	3.943503
8	0	0.303468	4.793523	4.180095
6	0	0.139228	6.187980	3.955627
6	0	-1.242505	6.658492	4.393182
7	0	-2.298663	6.460627	3.407309
6	0	-2.744567	5.075216	3.247758
6	0	-3.180538	4.739342	1.829202
8	0	-2.032806	4.571427	1.018661
6	0	-2.315094	4.257828	-0.330461
6	0	-1.148329	3.490441	-0.910908
8	0	-1.202497	2.157974	-0.438998
6	0	-0.023981	1.414880	-0.680475
1	0	0.843794	1.940606	-0.260330
1	0	0.140372	1.304195	-1.764368
1	0	-0.211296	3.971514	-0.601502
1	0	-1.198577	3.510013	-2.010646
1	0	-2.484247	5.177486	-0.910116
1	0	-3.217119	3.636675	-0.406535
1	0	-3.830656	5.524363	1.416799
1	0	-3.759199	3.804124	1.843315

1	0	-3.572719	4.826010	3.931428
1	0	-1.916348	4.412747	3.496247
6	0	-3.385197	7.434613	3.519252
6	0	-4.197074	7.449535	4.827984
6	0	-5.323145	8.486270	4.797560
6	0	-6.142911	8.542774	6.088960
6	0	-7.269512	9.578702	6.057679
6	0	-8.082411	9.627372	7.352308
1	0	-8.877221	10.375185	7.297990
1	0	-8.549928	8.661116	7.561875
1	0	-7.448711	9.878474	8.207612
1	0	-6.843570	10.568322	5.856896
1	0	-7.936567	9.360228	5.216038
1	0	-6.569388	7.552521	6.290645
1	0	-5.475935	8.761195	6.931937
1	0	-4.898385	9.477830	4.597310
1	0	-5.992307	8.270273	3.955507
1	0	-4.624686	6.459252	5.016106
1	0	-3.533087	7.663272	5.672258
1	0	-2.955709	8.430424	3.361043
1	0	-4.070645	7.270184	2.682605
1	0	-1.163135	7.736109	4.563521
1	0	-1.464503	6.201026	5.372137
1	0	0.290790	6.422076	2.894484
1	0	0.895186	6.732367	4.542615
1	0	1.934971	4.592395	2.911461
1	0	2.313358	4.910173	4.619891
1	0	2.818306	2.658650	4.446138
1	0	1.147880	2.600850	5.051759
1	0	2.503403	0.503256	3.598117
1	0	0.776629	0.421688	3.980562
1	0	1.684324	-0.993206	2.014799
1	0	1.930633	0.524592	1.165074
6	0	-1.000808	-0.854736	2.081925
6	0	-0.814745	-2.365473	1.846875
6	0	-1.844681	-3.201188	2.611389
6	0	-1.696732	-4.709500	2.396967
6	0	-2.728318	-5.543289	3.161152
6	0	-2.572564	-7.048745	2.940776
1	0	-3.322460	-7.614581	3.498782
1	0	-2.681494	-7.306751	1.883547
1	0	-1.587031	-7.395696	3.264140
1	0	-2.649614	-5.321141	4.231441
1	0	-3.735650	-5.232918	2.861292
1	0	-1.775516	-4.932380	1.325839
1	0	-0.688477	-5.021032	2.696525
1	0	-1.766854	-2.980604	3.683214
1	0	-2.854220	-2.892223	2.313628
1	0	-0.894935	-2.583497	0.776251
1	0	0.192141	-2.673066	2.148941
1	0	-0.943153	-0.654079	3.156088
1	0	-2.014143	-0.569786	1.782031
1	0	0.564686	-0.639536	-0.517691
1	0	-1.160208	-0.341095	-0.334395

C6 LARIAT ETHER

Solvent: *water*
Free Energy: -1354.78397

6	0	-0.666494	-0.056998	-0.025300
7	0	-0.449055	-0.063561	1.429405
6	0	0.972787	0.126921	1.750828
6	0	1.265304	0.549044	3.178013
8	0	0.920609	1.924676	3.379298
6	0	1.205135	2.347841	4.712090
6	0	1.123223	3.847334	4.831238
8	0	-0.228227	4.302591	4.763743
6	0	-0.298669	5.720010	4.952554
6	0	-1.726577	6.230757	5.016329
7	0	-2.465926	6.231145	3.742466
6	0	-3.225260	4.981222	3.569261
6	0	-3.729702	4.719458	2.163254
8	0	-2.640011	4.341864	1.318603
6	0	-3.038001	4.092436	-0.027868
6	0	-1.932338	3.355280	-0.739941
8	0	-1.846385	2.033759	-0.213509
6	0	-0.689067	1.323836	-0.654604
1	0	0.208909	1.900009	-0.403274
1	0	-0.717723	1.211784	-1.746265
1	0	-0.978757	3.878505	-0.598456
1	0	-2.148716	3.323094	-1.815240
1	0	-3.241767	5.037861	-0.545618
1	0	-3.954786	3.490426	-0.042006
1	0	-4.241547	5.591062	1.740527
1	0	-4.454792	3.897024	2.200893
1	0	-4.091863	4.937159	4.245178
1	0	-2.575080	4.151822	3.846816
6	0	-3.304118	7.440921	3.601997
6	0	-4.444073	7.644670	4.610139
6	0	-5.165890	8.975975	4.385203
6	0	-6.317272	9.218901	5.363095
6	0	-7.036379	10.551826	5.145209
6	0	-8.183358	10.784486	6.128101
1	0	-8.676787	11.743282	5.947763
1	0	-8.941413	10.000115	6.043132
1	0	-7.823647	10.785818	7.161411
1	0	-6.311877	11.369633	5.230655
1	0	-7.421616	10.589683	4.119945
1	0	-7.043084	8.400994	5.277918
1	0	-5.933361	9.181836	6.389921
1	0	-4.443735	9.797285	4.467906
1	0	-5.551569	9.009883	3.358981
1	0	-5.169170	6.828934	4.532182
1	0	-4.048884	7.618025	5.630964
1	0	-2.629821	8.300271	3.655936
1	0	-3.721648	7.448439	2.592428
1	0	-1.642373	7.263692	5.360526
1	0	-2.267899	5.686347	5.803309
1	0	0.249087	6.221524	4.145199
1	0	0.194987	5.972360	5.900777
1	0	1.716175	4.320493	4.038563
1	0	1.557105	4.137257	5.796796
1	0	2.225212	2.047480	4.982226
1	0	0.513343	1.866760	5.414856
1	0	2.339372	0.423196	3.363807
1	0	0.730636	-0.072285	3.904812
1	0	1.559815	-0.781502	1.549653
1	0	1.372795	0.899255	1.091619
6	0	-1.033340	-1.264549	2.059113
6	0	-0.497858	-2.637688	1.627156
6	0	-1.209545	-3.775580	2.363876
6	0	-0.715076	-5.166921	1.963062
6	0	-1.420270	-6.304980	2.703886
6	0	-0.920959	-7.690269	2.294705
1	0	-1.441899	-8.480984	2.841222
1	0	-1.077829	-7.866865	1.226382
1	0	0.149356	-7.799085	2.494033
1	0	-1.281909	-6.171892	3.782839
1	0	-2.499050	-6.238442	2.522787
1	0	-0.851668	-5.302157	0.883191
1	0	0.364337	-5.233917	2.146082
1	0	-1.077524	-3.644246	3.444735
1	0	-2.288278	-3.709141	2.177091
1	0	-0.631849	-2.768484	0.548540
1	0	0.576891	-2.705532	1.821444
1	0	-0.918350	-1.167208	3.141258
1	0	-2.109279	-1.233023	1.863902
1	0	0.094268	-0.647758	-0.558325
1	0	-1.629205	-0.531722	-0.227209

C6 LARIAT ETHER

Solvent: *n-octanol*
Free Energy: -1354.79341

6	0	-0.401218	-0.001063	-0.065131
7	0	-0.242332	-0.004307	1.392125
6	0	1.162112	0.098199	1.792578
6	0	1.397992	0.600668	3.206194
8	0	1.107988	1.994162	3.298132
6	0	1.440545	2.523210	4.576504
6	0	1.327348	4.027043	4.580115
8	0	-0.034080	4.440996	4.622912
6	0	-0.143384	5.863862	4.671889
6	0	-1.579861	6.325155	4.858580
7	0	-2.426520	6.244982	3.663538
6	0	-3.047915	4.925197	3.498632
6	0	-3.530664	4.623461	2.091336
8	0	-2.411878	4.399929	1.238475
6	0	-2.771389	4.129937	-0.110929
6	0	-1.630918	3.414395	-0.792605
8	0	-1.564270	2.083838	-0.295837
6	0	-0.385315	1.386923	-0.682406
1	0	0.498393	1.956246	-0.369012

1	0	-0.349322	1.289609	-1.777063
1	0	-0.689280	3.942041	-0.594500
1	0	-1.798906	3.408977	-1.878667
1	0	-2.989495	5.066422	-0.642094
1	0	-3.669541	3.500416	-0.147798
1	0	-4.154313	5.431980	1.689986
1	0	-4.149007	3.716356	2.122547
1	0	-3.899997	4.781993	4.182393
1	0	-2.306281	4.170148	3.759081
6	0	-3.372061	7.369464	3.567710
6	0	-4.448263	7.496375	4.658602
6	0	-5.340732	8.721217	4.438786
6	0	-6.430112	8.886887	5.501146
6	0	-7.325519	10.107888	5.277253
6	0	-8.410587	10.265469	6.342126
1	0	-9.031873	11.145383	6.152361
1	0	-9.071567	9.393453	6.367146
1	0	-7.974441	10.377721	7.339662
1	0	-6.704754	11.011177	5.254471
1	0	-7.794387	10.034519	4.289034
1	0	-7.053124	7.984104	5.524529
1	0	-5.962470	8.960699	6.490878
1	0	-4.717922	9.624240	4.417956
1	0	-5.810815	8.652712	3.449809
1	0	-5.073742	6.598203	4.678000
1	0	-3.973143	7.567932	5.642942
1	0	-2.776377	8.287789	3.552301
1	0	-3.863980	7.315492	2.593030
1	0	-1.511821	7.376637	5.148448
1	0	-2.015304	5.792545	5.718802
1	0	0.273347	6.298872	3.754546
1	0	0.447964	6.233486	5.522431
1	0	1.820698	4.438965	3.690086
1	0	1.853138	4.409848	5.466055
1	0	2.478548	2.261397	4.824056
1	0	0.790332	2.091789	5.349390
1	0	2.455530	0.436051	3.455813
1	0	0.799462	0.047550	3.940254
1	0	1.691482	-0.863786	1.693054
1	0	1.660906	0.792959	1.113658
6	0	-0.979586	-1.096874	2.043597
6	0	-0.570100	-2.539284	1.701381
6	0	-1.441390	-3.567501	2.428260
6	0	-1.075987	-5.018745	2.107210
6	0	-1.948347	-6.046947	2.831373
6	0	-1.578815	-7.492755	2.500833
1	0	-2.219347	-8.201029	3.034047
1	0	-1.683424	-7.693942	1.430076
1	0	-0.542652	-7.710875	2.777854
1	0	-1.868661	-5.889521	3.913328
1	0	-2.999630	-5.872680	2.574186
1	0	-1.154265	-5.180283	1.024828
1	0	-0.024295	-5.193621	2.366451
1	0	-1.363531	-3.407400	3.510827
1	0	-2.493822	-3.396041	2.170299
1	0	-0.649574	-2.700527	0.620854

1	0	0.478780	-2.708454	1.966272
1	0	-0.907879	-0.955763	3.125364
1	0	-2.036254	-0.962054	1.792304
1	0	0.371372	-0.602994	-0.570945
1	0	-1.362760	-0.459049	-0.308490

C7 LARIAT ETHER

Solvent: *none*
Free Energy: -1433.355444

6	0	0.045508	0.016020	-0.016560
7	0	0.044083	0.017575	1.441662
6	0	1.374931	0.016228	2.031534
6	0	1.482590	0.732248	3.370386
8	0	1.369117	2.131167	3.187849
6	0	1.654726	2.857121	4.368692
6	0	1.502959	4.341943	4.121814
8	0	0.151955	4.736989	4.278328
6	0	-0.027688	6.129474	4.053027
6	0	-1.444082	6.566787	4.406183
7	0	-2.430984	6.358704	3.352920
6	0	-2.831060	4.965603	3.145375
6	0	-3.161989	4.640964	1.696128
8	0	-1.958093	4.509910	0.963849
6	0	-2.139902	4.206109	-0.404703
6	0	-0.922879	3.463350	-0.909071
8	0	-0.987331	2.125906	-0.452853
6	0	0.216041	1.402829	-0.621386
1	0	1.045883	1.937543	-0.140344
1	0	0.453662	1.304426	-1.692815
1	0	-0.017679	3.956618	-0.531523
1	0	-0.897207	3.492348	-2.009466
1	0	-2.283255	5.129010	-0.986095
1	0	-3.023895	3.571535	-0.549774
1	0	-3.800143	5.417728	1.250729
1	0	-3.718629	3.693153	1.658343
1	0	-3.697099	4.687072	3.767995
1	0	-2.005774	4.318867	3.440599
6	0	-3.547368	7.303385	3.411369
6	0	-4.437163	7.276613	4.668125
6	0	-5.587375	8.283587	4.585129
6	0	-6.483950	8.295369	5.825892
6	0	-7.634213	9.301848	5.744570
6	0	-8.530145	9.312158	6.985653
6	0	-9.676481	10.320740	6.896581
1	0	-9.297938	11.339593	6.774775
1	0	-10.325646	10.106856	6.042753
1	0	-10.296051	10.302895	7.796434
1	0	-8.939347	8.307713	7.142669
1	0	-7.919383	9.531157	7.868864
1	0	-7.225537	10.307611	5.586926
1	0	-8.245800	9.082887	4.860589
1	0	-6.893690	7.290465	5.984498
1	0	-5.873462	8.515264	6.710112

1	0	-5.178869	9.289362	4.426437
1	0	-6.198599	8.064386	3.700948
1	0	-4.848147	6.272506	4.815669
1	0	-3.831424	7.494088	5.554213
1	0	-3.135230	8.312093	3.293920
1	0	-4.175920	7.134616	2.531983
1	0	-1.398973	7.643831	4.592068
1	0	-1.717865	6.093576	5.364311
1	0	0.185014	6.375108	3.005094
1	0	0.678127	6.684898	4.689939
1	0	1.862403	4.578801	3.111781
1	0	2.128061	4.891149	4.842401
1	0	2.688143	2.650980	4.687375
1	0	0.984092	2.555255	5.184967
1	0	2.463717	0.492970	3.810096
1	0	0.716797	0.380515	4.075525
1	0	1.774906	-1.004748	2.165905
1	0	2.056280	0.522855	1.344989
6	0	-0.910190	-0.904714	2.050707
6	0	-0.687141	-2.410529	1.816404
6	0	-1.754596	-3.267464	2.501839
6	0	-1.571442	-4.771547	2.283324
6	0	-2.641415	-5.626316	2.966810
6	0	-2.459639	-7.130355	2.747656
6	0	-3.533251	-7.976062	3.434244
1	0	-3.375356	-9.042916	3.258697
1	0	-3.532003	-7.814221	4.515898
1	0	-4.531266	-7.723390	3.065105
1	0	-2.462289	-7.340483	1.672072
1	0	-1.470542	-7.430547	3.111894
1	0	-2.639800	-5.416399	4.043535
1	0	-3.631743	-5.326364	2.602683
1	0	-1.573526	-4.982790	1.207092
1	0	-0.581597	-5.071955	2.648044
1	0	-1.752304	-3.057002	3.578473
1	0	-2.745911	-2.968769	2.139478
1	0	-0.691345	-2.619492	0.740988
1	0	0.301251	-2.707095	2.183590
1	0	-0.927794	-0.712807	3.127867
1	0	-1.905012	-0.631053	1.685436
1	0	0.824695	-0.643814	-0.435619
1	0	-0.913091	-0.373149	-0.366804

C7 LARIAT ETHER

Solvent: *water*
Free Energy: -1433.381501

6	0	-0.806741	-0.076000	0.000812
7	0	-0.579850	-0.103718	1.453862
6	0	0.842270	0.093862	1.769723
6	0	1.139686	0.498586	3.201000
8	0	0.790161	1.870104	3.421820
6	0	1.079697	2.277146	4.758580
6	0	0.996944	3.774975	4.896658

8	0	-0.355185	4.229904	4.841746
6	0	-0.425098	5.645352	5.045099
6	0	-1.852787	6.154730	5.123486
7	0	-2.600982	6.165997	3.854839
6	0	-3.363057	4.918382	3.677510
6	0	-3.877851	4.668018	2.273221
8	0	-2.794597	4.297747	1.417115
6	0	-3.203643	4.059510	0.072014
6	0	-2.100079	3.337245	-0.658189
8	0	-2.000537	2.010596	-0.147227
6	0	-0.842664	1.313893	-0.607568
1	0	0.053906	1.891765	-0.355093
1	0	-0.879351	1.217500	-1.700488
1	0	-1.148637	3.865168	-0.519807
1	0	-2.326200	3.315310	-1.731732
1	0	-3.418326	5.008880	-0.434009
1	0	-4.116728	3.451795	0.060269
1	0	-4.392957	5.543012	1.861575
1	0	-4.602555	3.845182	2.309555
1	0	-4.224952	4.870187	4.359170
1	0	-2.711942	4.086158	3.944248
6	0	-3.438236	7.377977	3.729088
6	0	-4.572505	7.574802	4.745011
6	0	-5.289792	8.911539	4.538714
6	0	-6.437412	9.146967	5.523268
6	0	-7.148789	10.487062	5.325925
6	0	-8.296779	10.722636	6.309737
6	0	-8.998325	12.065226	6.107145
1	0	-8.300587	12.898357	6.234406
1	0	-9.423507	12.140987	5.101858
1	0	-9.813123	12.203035	6.822989
1	0	-9.027112	9.911492	6.211337
1	0	-7.910688	10.664431	7.333749
1	0	-6.419989	11.301149	5.422951
1	0	-7.536387	10.543842	4.301302
1	0	-7.167033	8.333762	5.427801
1	0	-6.050002	9.092318	6.547859
1	0	-4.564010	9.728793	4.629274
1	0	-5.678363	8.959690	3.514164
1	0	-5.301232	6.762864	4.661248
1	0	-4.172519	7.534906	5.763550
1	0	-2.762364	8.235847	3.786694
1	0	-3.861160	7.394736	2.721869
1	0	-1.766660	7.184506	5.476578
1	0	-2.388319	5.602871	5.909206
1	0	0.117090	6.155076	4.239129
1	0	0.074682	5.888619	5.992474
1	0	1.585414	4.258296	4.106783
1	0	1.435623	4.053458	5.863426
1	0	2.101213	1.974624	5.020716
1	0	0.391420	1.786620	5.458267
1	0	2.215124	0.375115	3.380246
1	0	0.611054	-0.134438	3.922097
1	0	1.435481	-0.806739	1.552363
1	0	1.232158	0.878619	1.119192
6	0	-1.149936	-1.319800	2.067586

6	0	-0.606729	-2.681255	1.608943
6	0	-1.304878	-3.837157	2.330432
6	0	-0.801289	-5.217480	1.902764
6	0	-1.492735	-6.373561	2.628216
6	0	-0.991710	-7.754140	2.198936
6	0	-1.685420	-8.901954	2.931775
1	0	-1.307351	-9.873510	2.602424
1	0	-1.527265	-8.833514	4.012249
1	0	-2.764976	-8.888703	2.754270
1	0	-1.138173	-7.870169	1.119072
1	0	0.089216	-7.813621	2.369578
1	0	-1.348838	-6.259624	3.709697
1	0	-2.574350	-6.314321	2.455380
1	0	-0.943270	-5.333830	0.821511
1	0	0.279681	-5.277115	2.078214
1	0	-1.167437	-3.723087	3.412557
1	0	-2.385189	-3.776295	2.151118
1	0	-0.746612	-2.794727	0.529127
1	0	0.469734	-2.744202	1.795326
1	0	-1.027945	-1.239590	3.150365
1	0	-2.227483	-1.293719	1.880505
1	0	-0.045475	-0.653226	-0.546184
1	0	-1.767492	-0.554248	-0.202161

C7 LARIAT ETHER

Solvent: *n-octanol*
Free Energy: -1433.393134

6	0	-0.407323	-0.010914	-0.044620
7	0	-0.272057	-0.012872	1.415098
6	0	1.127284	0.074245	1.837290
6	0	1.346714	0.590385	3.248469
8	0	1.071917	1.988753	3.316736
6	0	1.392085	2.534294	4.591753
6	0	1.276029	4.037592	4.572140
8	0	-0.087576	4.446363	4.605039
6	0	-0.206206	5.869806	4.622390
6	0	-1.643221	6.322732	4.824751
7	0	-2.506299	6.238063	3.641902
6	0	-3.082862	4.900673	3.453059
6	0	-3.545335	4.606532	2.037391
8	0	-2.411597	4.402500	1.197494
6	0	-2.748181	4.136359	-0.159205
6	0	-1.601201	3.409597	-0.817320
8	0	-1.558043	2.077998	-0.318401
6	0	-0.368233	1.375437	-0.664320
1	0	0.505824	1.943483	-0.323616
1	0	-0.298214	1.275945	-1.756976
1	0	-0.658959	3.927672	-0.598995
1	0	-1.746219	3.404544	-1.906516
1	0	-2.946723	5.075054	-0.693717
1	0	-3.651119	3.515396	-0.213109
1	0	-4.171349	5.412333	1.634580
1	0	-4.153032	3.692099	2.050740

1	0	-3.933531	4.719278	4.128935
1	0	-2.319580	4.164655	3.705092
6	0	-3.498108	7.326007	3.597671
6	0	-4.534578	7.397327	4.731112
6	0	-5.477234	8.593205	4.569147
6	0	-6.515734	8.709781	5.687729
6	0	-7.455660	9.907542	5.531740
6	0	-8.490245	10.026562	6.653274
6	0	-9.423236	11.226183	6.490949
1	0	-8.862869	12.166356	6.482485
1	0	-9.984804	11.168325	5.553257
1	0	-10.148813	11.281658	7.307523
1	0	-9.085054	9.106595	6.694444
1	0	-7.971300	10.097907	7.616326
1	0	-6.862801	10.829947	5.490750
1	0	-7.976310	9.836500	4.568505
1	0	-7.109266	7.788023	5.726612
1	0	-5.998814	8.780982	6.652720
1	0	-4.886374	9.516832	4.529210
1	0	-5.993470	8.519849	3.603863
1	0	-5.126571	6.476982	4.760971
1	0	-4.023615	7.471734	5.696943
1	0	-2.939919	8.267580	3.572657
1	0	-4.024247	7.264428	2.641512
1	0	-1.579104	7.375426	5.111146
1	0	-2.062200	5.788530	5.692310
1	0	0.193460	6.286147	3.689205
1	0	0.395401	6.261887	5.455160
1	0	1.769842	4.436756	3.676741
1	0	1.797546	4.436394	5.453331
1	0	2.427765	2.276193	4.852056
1	0	0.734275	2.112940	5.363543
1	0	2.397845	0.416695	3.517695
1	0	0.728688	0.054897	3.979315
1	0	1.644337	-0.896067	1.757323
1	0	1.647239	0.753972	1.159049
6	0	-1.031066	-1.096548	2.056749
6	0	-0.633764	-2.544246	1.723433
6	0	-1.539093	-3.558850	2.427532
6	0	-1.184855	-5.016164	2.120940
6	0	-2.099797	-6.028395	2.814250
6	0	-1.748260	-7.486206	2.508374
6	0	-2.670476	-8.488698	3.201525
1	0	-2.392429	-9.519267	2.962833
1	0	-2.629742	-8.378973	4.289763
1	0	-3.711585	-8.347887	2.894574
1	0	-1.786588	-7.646676	1.424557
1	0	-0.711548	-7.678161	2.808836
1	0	-2.059955	-5.869147	3.899146
1	0	-3.138829	-5.839570	2.516532
1	0	-1.226450	-5.176724	1.036493
1	0	-0.145959	-5.205786	2.418109
1	0	-1.490710	-3.396633	3.511507
1	0	-2.581085	-3.373586	2.138623
1	0	-0.688693	-2.704185	0.641179
1	0	0.405531	-2.729117	2.014450

1	0	-0.974339	-0.954267	3.139301
1	0	-2.082216	-0.950072	1.789371
1	0	0.367907	-0.620776	-0.536474
1	0	-1.368679	-0.460654	-0.303640

C8 LARIAT ETHER

Solvent: *none*
Free Energy: -1511.953794

6	0	0.016064	0.003446	-0.000713
7	0	0.011525	0.009418	1.457486
6	0	1.341103	0.005686	2.050156
6	0	1.448130	0.725044	3.387257
8	0	1.337893	2.123694	3.200774
6	0	1.623335	2.852302	4.380014
6	0	1.473305	4.336633	4.129209
8	0	0.122438	4.733183	4.282974
6	0	-0.055970	6.125181	4.053620
6	0	-1.472479	6.564267	4.404125
7	0	-2.458201	6.354809	3.350038
6	0	-2.857578	4.961397	3.143169
6	0	-3.185395	4.635220	1.693559
8	0	-1.979902	4.503233	0.964039
6	0	-2.158591	4.197369	-0.404490
6	0	-0.941952	3.450804	-0.904184
8	0	-1.010797	2.114416	-0.445522
6	0	0.191301	1.388082	-0.609195
1	0	1.021236	1.922201	-0.127661
1	0	0.431211	1.286101	-1.679778
1	0	-0.036591	3.942660	-0.525187
1	0	-0.913300	3.477609	-2.004563
1	0	-2.298147	5.119559	-0.987911
1	0	-3.043655	3.564623	-0.550900
1	0	-3.822479	5.411614	1.245990
1	0	-3.742016	3.687412	1.655565
1	0	-3.724915	4.683434	3.764208
1	0	-2.032890	4.315035	3.440872
6	0	-3.575107	7.299017	3.406620
6	0	-4.465908	7.272806	4.662652
6	0	-5.617076	8.278563	4.577952
6	0	-6.514549	8.289934	5.818047
6	0	-7.666029	9.295267	5.735555
6	0	-8.562280	9.303839	6.976124
6	0	-9.714508	10.308496	6.896749
1	0	-9.306200	11.313414	6.740248
1	0	-10.323833	10.088764	6.012726
6	0	-10.603949	10.308403	8.140975
1	0	-10.029746	10.559800	9.037227
1	0	-11.415530	11.034703	8.052913
1	0	-11.054835	9.325450	8.304265
1	0	-8.971473	8.298366	7.134110
1	0	-7.953089	9.523802	7.861513
1	0	-7.257525	10.300947	5.577890
1	0	-8.275776	9.074983	4.850800
1	0	-6.923259	7.284658	5.976763
1	0	-5.904915	8.510777	6.702585
1	0	-5.209496	9.284678	4.418984
1	0	-6.227334	8.058139	3.693398
1	0	-4.876063	6.268460	4.810890
1	0	-3.861066	7.491697	5.549000
1	0	-3.163391	8.307837	3.288612
1	0	-4.202796	7.129071	2.526834
1	0	-1.426938	7.641657	4.587927
1	0	-1.747711	6.093107	5.362849
1	0	0.158010	6.367770	3.005243
1	0	0.649533	6.681868	4.689761
1	0	1.834276	4.570641	3.119055
1	0	2.097956	4.887076	4.849246
1	0	2.656256	2.645855	4.700107
1	0	0.951664	2.553256	5.196476
1	0	2.428038	0.484817	3.829160
1	0	0.680466	0.376855	4.092125
1	0	1.737791	-1.016096	2.188163
1	0	2.025357	0.508426	1.363635
6	0	-0.947186	-0.907648	2.067416
6	0	-0.728346	-2.415001	1.839162
6	0	-1.801034	-3.265985	2.523856
6	0	-1.621842	-4.771432	2.311609
6	0	-2.697895	-5.620077	2.993673
6	0	-2.519710	-7.125190	2.780671
6	0	-3.595414	-7.974649	3.462184
6	0	-3.408860	-9.476850	3.243686
1	0	-2.445899	-9.816614	3.635437
1	0	-4.191478	-10.054013	3.741997
1	0	-3.438154	-9.728076	2.179632
1	0	-3.596862	-7.759726	4.536824
1	0	-4.581500	-7.671867	3.092089
1	0	-2.518090	-7.341180	1.705155
1	0	-1.532752	-7.429234	3.150694
1	0	-2.699819	-5.405161	4.069274
1	0	-3.685023	-5.317250	2.623692
1	0	-1.619926	-4.986601	1.236183
1	0	-0.634614	-5.073750	2.681712
1	0	-1.802069	-3.051479	3.599703
1	0	-2.790037	-2.965479	2.156678
1	0	-0.729527	-2.627724	0.764470
1	0	0.257781	-2.713560	2.210801
1	0	-0.966982	-0.711761	3.143822
1	0	-1.940181	-0.632155	1.698574
1	0	0.794526	-0.659545	-0.416093
1	0	-0.942715	-0.384425	-0.351899

C8 LARIAT ETHER

Solvent: *water*
Free Energy: -1511.979436

6	0	-0.950252	-0.111991	0.028664
7	0	-0.705339	-0.150084	1.478583

6	0	0.721259	0.041146	1.777505
6	0	1.038835	0.432494	3.208212
8	0	0.697993	1.803480	3.445316
6	0	1.007823	2.198302	4.781186
6	0	0.931284	3.695161	4.932856
8	0	-0.420241	4.153973	4.900333
6	0	-0.483624	5.568134	5.114309
6	0	-1.908888	6.080550	5.214577
7	0	-2.673766	6.100378	3.956005
6	0	-3.442595	4.856285	3.783393
6	0	-3.979021	4.615178	2.385611
8	0	-2.910224	4.246696	1.510688
6	0	-3.340667	4.023957	0.169601
6	0	-2.250422	3.307131	-0.585422
8	0	-2.146813	1.974664	-0.090502
6	0	-0.993521	1.282426	-0.568847
1	0	-0.094603	1.858859	-0.321490
1	0	-1.041935	1.194534	-1.662035
1	0	-1.295604	3.831042	-0.455503
1	0	-2.492696	3.297692	-1.655602
1	0	-3.560730	4.979302	-0.322681
1	0	-4.255416	3.418620	0.165447
1	0	-4.497571	5.494055	1.986829
1	0	-4.705691	3.794371	2.428219
1	0	-4.294662	4.807456	4.477299
1	0	-2.790530	4.020540	4.036535
6	0	-3.507667	7.316110	3.846049
6	0	-4.629434	7.512367	4.875857
6	0	-5.343542	8.852940	4.683911
6	0	-6.480493	9.087741	5.680904
6	0	-7.188548	10.431813	5.497116
6	0	-8.325488	10.666408	6.493725
6	0	-9.032418	12.011425	6.313746
1	0	-8.298095	12.819338	6.409127
1	0	-9.428313	12.076333	5.293896
6	0	-10.166155	12.234844	7.314011
1	0	-9.795564	12.209085	8.343156
1	0	-10.650576	13.202858	7.160393
1	0	-10.933959	11.461059	7.219885
1	0	-9.061542	9.858515	6.399632
1	0	-7.930244	10.602566	7.515023
1	0	-6.454648	11.241564	5.590502
1	0	-7.585119	10.494148	4.476387
1	0	-7.214111	8.277812	5.588466
1	0	-6.083285	9.026304	6.701334
1	0	-4.613669	9.666877	4.771486
1	0	-5.742029	8.908002	3.663510
1	0	-5.362309	6.703735	4.796363
1	0	-4.218036	7.465807	5.889570
1	0	-2.827811	8.171061	3.899989
1	0	-3.942233	7.339699	2.843946
1	0	-1.815546	7.108087	5.572355
1	0	-2.435316	5.525511	6.004173
1	0	0.049431	6.081943	4.304850
1	0	0.028973	5.803699	6.056760
1	0	1.510047	4.183407	4.138854
1	0	1.384152	3.964488	5.895671
1	0	2.032083	1.890621	5.026103
1	0	0.328150	1.703830	5.486490
1	0	2.115992	0.303178	3.372248
1	0	0.517121	-0.204610	3.930743
1	0	1.309072	-0.859066	1.544394
1	0	1.104567	0.830633	1.128772
6	0	-1.271529	-1.368299	2.091618
6	0	-0.735851	-2.728341	1.620167
6	0	-1.432777	-3.886787	2.338767
6	0	-0.934582	-5.265850	1.900852
6	0	-1.626467	-6.424451	2.622415
6	0	-1.129683	-7.803441	2.183650
6	0	-1.817579	-8.962947	2.907272
6	0	-1.314349	-10.335324	2.461020
1	0	-0.241061	-10.441447	2.645239
1	0	-1.823654	-11.141613	2.995643
1	0	-1.482788	-10.488923	1.390897
1	0	-1.666606	-8.853213	3.987177
1	0	-2.899003	-8.899931	2.741207
1	0	-1.279952	-7.915035	1.102779
1	0	-0.047374	-7.867923	2.350377
1	0	-1.478518	-6.315379	3.703726
1	0	-2.708251	-6.360376	2.453196
1	0	-1.081141	-5.375335	0.819505
1	0	0.146903	-5.329306	2.071609
1	0	-1.289490	-3.779108	3.420803
1	0	-2.513859	-3.822430	2.165399
1	0	-0.883435	-2.834170	0.540589
1	0	0.341654	-2.795788	1.798789
1	0	-1.138400	-1.294214	3.173531
1	0	-2.350849	-1.338952	1.915641
1	0	-0.195893	-0.685363	-0.531772
1	0	-1.913523	-0.588617	-0.165988

C8 LARIAT ETHER

Solvent: *n-octanol*
Free Energy: -1511.99168

6	0	-0.540989	-0.038453	-0.024179
7	0	-0.368648	-0.051591	1.431573
6	0	1.039701	0.041769	1.820805
6	0	1.289521	0.549536	3.230162
8	0	1.010471	1.945624	3.317118
6	0	1.367448	2.480804	4.586265
6	0	1.250649	3.984326	4.585561
8	0	-0.110926	4.394024	4.655755
6	0	-0.224999	5.816649	4.703466
6	0	-1.657862	6.271830	4.930395
7	0	-2.535969	6.197944	3.757905
6	0	-3.140221	4.871234	3.583311
6	0	-3.631940	4.581253	2.176527
8	0	-2.517660	4.367683	1.315009
6	0	-2.883883	4.108327	-0.034745

6	0	-1.750650	3.389654	-0.725228
8	0	-1.690206	2.056081	-0.235822
6	0	-0.519230	1.352501	-0.634342
1	0	0.370952	1.913728	-0.324640
1	0	-0.491953	1.260539	-1.729708
1	0	-0.804854	3.910323	-0.528411
1	0	-1.923374	3.391112	-1.810566
1	0	-3.098100	5.049427	-0.559265
1	0	-3.786060	3.484724	-0.072128
1	0	-4.259074	5.392774	1.786790
1	0	-4.248340	3.672685	2.202380
1	0	-3.983091	4.707654	4.273496
1	0	-2.386121	4.122961	3.826569
6	0	-3.504572	7.306109	3.711749
6	0	-4.541435	7.397827	4.843550
6	0	-5.473750	8.600341	4.670516
6	0	-6.523459	8.724746	5.777824
6	0	-7.463874	9.919957	5.602993
6	0	-8.513817	10.040741	6.710003
6	0	-9.459553	11.231417	6.535061
1	0	-8.872072	12.156168	6.496077
1	0	-9.965900	11.150206	5.566131
6	0	-10.504657	11.341464	7.644932
1	0	-10.031878	11.460745	8.624815
1	0	-11.163978	12.200206	7.489588
1	0	-11.132786	10.446194	7.688385
1	0	-9.104074	9.116695	6.750836
1	0	-8.008638	10.122938	7.680551
1	0	-6.872009	10.842916	5.564673
1	0	-7.970289	9.841350	4.632945
1	0	-7.116460	7.802684	5.816835
1	0	-6.016827	8.803102	6.747653
1	0	-4.876907	9.520229	4.634286
1	0	-5.980948	8.527787	3.700380
1	0	-5.142614	6.483739	4.879274
1	0	-4.030885	7.473905	5.809571
1	0	-2.927202	8.235961	3.686676
1	0	-4.031112	7.254393	2.755179
1	0	-1.586233	7.321763	5.225031
1	0	-2.067915	5.731875	5.798566
1	0	0.163798	6.250790	3.773551
1	0	0.388421	6.191002	5.535990
1	0	1.723731	4.393724	3.683442
1	0	1.793958	4.372574	5.458453
1	0	2.410691	2.221965	4.814189
1	0	0.733609	2.051717	5.373902
1	0	2.347584	0.378176	3.473003
1	0	0.691880	0.004690	3.971179
1	0	1.560439	-0.924953	1.722547
1	0	1.539366	0.728975	1.134939
6	0	-1.103377	-1.146803	2.081773
6	0	-0.711801	-2.587476	1.712280
6	0	-1.575259	-3.619974	2.442460
6	0	-1.234808	-5.068392	2.082243
6	0	-2.100522	-6.101900	2.807233
6	0	-1.768162	-7.549145	2.436334

6	0	-2.631573	-8.584482	3.160994
6	0	-2.294710	-10.025853	2.779951
1	0	-1.253182	-10.265585	3.015922
1	0	-2.927403	-10.739360	3.315571
1	0	-2.438011	-10.196711	1.708402
1	0	-2.514130	-8.457808	4.243554
1	0	-3.688053	-8.388672	2.943559
1	0	-1.883780	-7.680360	1.353112
1	0	-0.711292	-7.745874	2.656109
1	0	-1.987154	-5.971685	3.890645
1	0	-3.156982	-5.906600	2.585245
1	0	-1.342907	-5.204389	0.999066
1	0	-0.178676	-5.258795	2.309905
1	0	-1.467145	-3.482209	3.525471
1	0	-2.632067	-3.432044	2.215778
1	0	-0.815503	-2.733309	0.631666
1	0	0.341237	-2.767762	1.952238
1	0	-1.010661	-1.020503	3.163774
1	0	-2.163389	-1.000650	1.851515
1	0	0.221557	-0.644144	-0.540601
1	0	-1.508714	-0.486836	-0.260940

C9 LARIAT ETHER

Solvent: *none*
Free Energy: -1590.551836

6	0	0.018936	0.012914	-0.017954
7	0	0.024268	0.008781	1.440264
6	0	1.357878	0.012343	2.023876
6	0	1.467849	0.723313	3.365216
8	0	1.345444	2.122323	3.189219
6	0	1.632301	2.844811	4.371878
6	0	1.470049	4.329736	4.132442
8	0	0.117288	4.715481	4.296679
6	0	-0.071982	6.107963	4.079367
6	0	-1.489818	6.534451	4.439911
7	0	-2.479115	6.325709	3.389029
6	0	-2.871667	4.931280	3.176200
6	0	-3.206558	4.611667	1.726753
8	0	-2.004924	4.491671	0.988869
6	0	-2.190442	4.192750	-0.380267
6	0	-0.971523	3.458556	-0.892543
8	0	-1.027039	2.118935	-0.441584
6	0	0.179432	1.402942	-0.618117
1	0	1.008480	1.940233	-0.138589
1	0	0.412914	1.309985	-1.690940
1	0	-0.067443	3.955084	-0.516586
1	0	-0.950436	3.492217	-1.992906
1	0	-2.340855	5.117363	-0.957132
1	0	-3.071664	3.554193	-0.524663
1	0	-3.851404	5.386550	1.287768
1	0	-3.757437	3.660597	1.686671
1	0	-3.733466	4.644463	3.800939
1	0	-2.041286	4.288125	3.464896

6	0	-3.600768	7.263586	3.455779
6	0	-4.486896	7.224810	4.714815
6	0	-5.642262	8.226624	4.641399
6	0	-6.536058	8.224795	5.884208
6	0	-7.691174	9.226821	5.813456
6	0	-8.583884	9.221265	7.056866
6	0	-9.739254	10.222839	6.989660
1	0	-9.335866	11.232180	6.841626
1	0	-10.352138	10.010383	6.104994
6	0	-10.631961	10.215732	8.233091
1	0	-10.019916	10.428173	9.117020
6	0	-11.783184	11.219858	8.157699
1	0	-11.409644	12.241690	8.045798
1	0	-12.433507	11.012093	7.303238
1	0	-12.400396	11.189587	9.058843
1	0	-11.036098	9.207770	8.380444
1	0	-8.988473	8.212768	7.206256
1	0	-7.971927	9.434850	7.941740
1	0	-7.286594	10.235208	5.663363
1	0	-8.302616	9.012081	4.928545
1	0	-6.940852	7.216842	6.035877
1	0	-5.924514	8.440457	6.768717
1	0	-5.239088	9.235532	4.489055
1	0	-6.254312	8.010699	3.756972
1	0	-4.892610	6.217832	4.857298
1	0	-3.879726	7.439723	5.600552
1	0	-3.194718	8.275257	3.342724
1	0	-4.230803	7.096056	2.577217
1	0	-1.450808	7.610753	4.631376
1	0	-1.757209	6.054456	5.396467
1	0	0.135279	6.360443	3.031966
1	0	0.632668	6.664493	4.716611
1	0	1.823535	4.573512	3.121950
1	0	2.094846	4.879572	4.852818
1	0	2.668540	2.643756	4.684605
1	0	0.967568	2.535112	5.190046
1	0	2.452432	0.487832	3.799216
1	0	0.707478	0.364207	4.072502
1	0	1.764128	-1.006951	2.152072
1	0	2.033169	0.525628	1.336289
6	0	-0.922039	-0.921245	2.050035
6	0	-0.692023	-2.424818	1.808280
6	0	-1.751390	-3.290507	2.495284
6	0	-1.561613	-4.792544	2.268542
6	0	-2.624134	-5.656016	2.953183
6	0	-2.435754	-7.157774	2.724306
6	0	-3.497511	-8.021735	3.408943
6	0	-3.310153	-9.523598	3.179824
1	0	-2.317595	-9.821348	3.536541
6	0	-4.375883	-10.378298	3.867521
1	0	-4.214195	-11.443368	3.684733
1	0	-4.369117	-10.222870	4.950100
1	0	-5.377181	-10.128012	3.505685
1	0	-3.318047	-9.727360	2.103036
1	0	-3.490369	-7.818197	4.486863
1	0	-4.491471	-7.724329	3.052634

1	0	-2.443240	-7.362671	1.646787
1	0	-1.442364	-7.455955	3.081257
1	0	-2.617265	-5.450997	4.030664
1	0	-3.617208	-5.357820	2.595645
1	0	-1.567916	-4.998493	1.191320
1	0	-0.568472	-5.089661	2.626873
1	0	-1.744510	-3.085114	3.572882
1	0	-2.746131	-2.995231	2.139542
1	0	-0.700455	-2.629243	0.732016
1	0	0.299792	-2.717564	2.169261
1	0	-0.935449	-0.733920	3.128060
1	0	-1.920085	-0.651445	1.690724
1	0	0.799595	-0.641208	-0.443186
1	0	-0.939244	-0.379882	-0.365282

C9 LARIAT ETHER

Solvent: *water*
Free Energy: -1590.577029

6	0	-1.072275	-0.129575	0.061619
7	0	-0.824818	-0.176433	1.510897
6	0	0.602663	0.010857	1.808138
6	0	0.923988	0.391930	3.240814
8	0	0.587133	1.762183	3.487745
6	0	0.900223	2.147213	4.825726
6	0	0.828269	3.643274	4.987329
8	0	-0.521972	4.106122	4.959467
6	0	-0.580959	5.519433	5.180072
6	0	-2.004653	6.035271	5.284954
7	0	-2.771781	6.061563	4.027840
6	0	-3.545573	4.820800	3.853504
6	0	-4.088232	4.586725	2.456946
8	0	-3.024092	4.219043	1.576042
6	0	-3.460597	4.005679	0.235399
6	0	-2.374267	3.293035	-0.529090
8	0	-2.270070	1.957021	-0.043821
6	0	-1.116772	1.268405	-0.527396
1	0	-0.217963	1.843817	-0.277287
1	0	-1.166069	1.187173	-1.621064
1	0	-1.418426	3.815065	-0.399264
1	0	-2.620773	3.291322	-1.598333
1	0	-3.681838	4.964532	-0.249484
1	0	-4.375978	3.401277	0.231171
1	0	-4.606053	5.468566	2.063835
1	0	-4.816945	3.767710	2.499233
1	0	-4.395209	4.772349	4.550436
1	0	-2.895452	3.981887	4.101208
6	0	-3.600945	7.280913	3.922545
6	0	-4.721374	7.478139	4.953606
6	0	-5.428876	8.823058	4.767665
6	0	-6.565081	9.058963	5.765253
6	0	-7.265691	10.407791	5.587884
6	0	-8.402475	10.643255	6.584872
6	0	-9.100538	11.993652	6.411732

1	0	-8.362039	12.798315	6.514105
1	0	-9.495225	12.068841	5.390993
6	0	-10.238476	12.228713	7.407280
1	0	-9.845455	12.152722	8.427489
6	0	-10.926707	13.581440	7.227675
1	0	-10.218906	14.405181	7.360411
1	0	-11.358599	13.675045	6.226756
1	0	-11.734545	13.718768	7.951459
1	0	-10.978415	11.426956	7.303760
1	0	-9.142213	9.839654	6.484555
1	0	-8.007701	10.570155	7.605596
1	0	-6.527447	11.212985	5.686149
1	0	-7.660880	10.477632	4.567120
1	0	-7.303009	8.253473	5.668354
1	0	-6.168741	8.990226	6.785564
1	0	-4.695014	9.632958	4.859242
1	0	-5.826674	8.884802	3.747375
1	0	-5.458217	6.673449	4.870799
1	0	-4.309869	7.425099	5.966966
1	0	-2.917584	8.132891	3.979104
1	0	-4.035956	7.309883	2.920780
1	0	-1.907958	7.061211	5.646407
1	0	-2.531110	5.478661	6.073408
1	0	-0.047827	6.035410	4.372046
1	0	-0.066165	5.749312	6.122730
1	0	1.407393	4.134961	4.195717
1	0	1.283170	3.905075	5.951260
1	0	1.923960	1.834902	5.066970
1	0	0.220197	1.650071	5.528809
1	0	2.001131	0.258843	3.401828
1	0	0.402126	-0.248661	3.960131
1	0	1.188733	-0.888516	1.567523
1	0	0.985628	0.804304	1.164031
6	0	-1.391726	-1.397473	2.117683
6	0	-0.858708	-2.755477	1.637428
6	0	-1.557899	-3.917201	2.348517
6	0	-1.062961	-5.294380	1.901067
6	0	-1.757481	-6.456418	2.614538
6	0	-1.264286	-7.833552	2.165109
6	0	-1.954476	-8.996287	2.881066
6	0	-1.462310	-10.373392	2.430884
1	0	-0.380641	-10.439862	2.594073
6	0	-2.156702	-11.527580	3.153015
1	0	-1.784556	-12.496441	2.809289
1	0	-1.992284	-11.473545	4.233376
1	0	-3.237166	-11.507661	2.981737
1	0	-1.615869	-10.474779	1.350522
1	0	-1.802140	-8.896599	3.962813
1	0	-3.037146	-8.930770	2.717202
1	0	-1.415829	-7.935385	1.083579
1	0	-0.182012	-7.900384	2.330305
1	0	-1.608705	-6.355603	3.696521
1	0	-2.839166	-6.388232	2.446391
1	0	-1.209870	-5.395970	0.818988
1	0	0.018398	-5.361546	2.071243
1	0	-1.414035	-3.817127	3.431207
1	0	-2.638890	-3.849262	2.175948
1	0	-1.006608	-2.854060	0.557209
1	0	0.218682	-2.826190	1.815488
1	0	-1.256978	-1.329963	3.199823
1	0	-2.471248	-1.365582	1.943426
1	0	-0.318846	-0.699540	-0.503500
1	0	-2.035838	-0.605075	-0.134299

C9 LARIAT ETHER

Solvent: *n-octanol*
Free Energy: -1590.591308

6	0	-0.596258	-0.050386	0.002512
7	0	-0.424247	-0.067729	1.458248
6	0	0.984028	0.022863	1.848515
6	0	1.233537	0.531373	3.257676
8	0	0.958292	1.928341	3.342821
6	0	1.317544	2.464342	4.610973
6	0	1.204106	3.968104	4.608473
8	0	-0.156440	4.380942	4.680683
6	0	-0.267124	5.803902	4.726967
6	0	-1.698091	6.262743	4.958538
7	0	-2.580405	6.191050	3.789103
6	0	-3.187366	4.865535	3.614816
6	0	-3.679090	4.576659	2.207807
8	0	-2.564820	4.359687	1.347120
6	0	-2.930936	4.101595	-0.002877
6	0	-1.798662	3.381359	-0.693275
8	0	-1.740653	2.047376	-0.204671
6	0	-0.571106	1.341985	-0.604225
1	0	0.320228	1.900477	-0.292886
1	0	-0.543594	1.252501	-1.699791
1	0	-0.852049	3.900299	-0.495815
1	0	-1.970969	3.383707	-1.778679
1	0	-3.143360	5.043309	-0.527034
1	0	-3.834162	3.479535	-0.040918
1	0	-4.303441	5.390107	1.817591
1	0	-4.298251	3.669950	2.233259
1	0	-4.030850	4.703923	4.304667
1	0	-2.435038	4.115598	3.858402
6	0	-3.547737	7.300523	3.747568
6	0	-4.578311	7.394085	4.884959
6	0	-5.510782	8.597078	4.716130
6	0	-6.553833	8.723136	5.829532
6	0	-7.494459	9.918905	5.659741
6	0	-8.537569	10.040526	6.773452
6	0	-9.483588	11.231681	6.603726
1	0	-8.896245	12.157498	6.560819
1	0	-9.997015	11.151165	5.637369
6	0	-10.527180	11.351475	7.716886
1	0	-10.015926	11.433708	8.683148
6	0	-11.467912	12.542903	7.538678
1	0	-10.914431	13.487080	7.527023
1	0	-12.022015	12.473584	6.597345

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1	0	-11.115481	10.427454	7.760388
1	0	-9.126827	9.116150	6.817559
1	0	-8.025159	10.122122	7.740102
1	0	-6.902226	10.841431	5.617385
1	0	-8.006757	9.840181	4.692820
1	0	-7.147265	7.801526	5.872686
1	0	-6.041353	8.801690	6.796278
1	0	-4.913523	9.516517	4.675548
1	0	-6.023687	8.523959	3.749045
1	0	-5.179862	6.480424	4.924984
1	0	-4.062377	7.470763	5.848056
1	0	-2.969382	8.229682	3.718947
1	0	-4.079472	7.248905	2.793859
1	0	-1.622783	7.312578	5.252626
1	0	-2.106500	5.724065	5.828277
1	0	0.119397	6.235975	3.795144
1	0	0.350093	6.177831	5.556855
1	0	1.676452	4.375255	3.704956
1	0	1.749842	4.356319	5.479860
1	0	2.360396	2.203427	4.838313
1	0	0.683442	2.037721	5.399736
1	0	2.290808	0.357307	3.502055
1	0	0.633336	-0.011034	3.998431
1	0	1.502596	-0.945133	1.751659
1	0	1.485946	0.708294	1.162539
6	0	-1.160130	-1.164241	2.105037
6	0	-0.771691	-2.604020	1.728806
6	0	-1.636657	-3.638370	2.454604
6	0	-1.300934	-5.085462	2.084692
6	0	-2.170063	-6.121307	2.802226
6	0	-1.843737	-7.566871	2.418522
6	0	-2.712432	-8.604414	3.133548
6	0	-2.390998	-10.049289	2.744059
1	0	-1.335651	-10.254479	2.958457
6	0	-3.263386	-11.078031	3.462936
1	0	-3.009465	-12.098239	3.161285
1	0	-3.139599	-11.013969	4.548515
1	0	-4.323980	-10.922265	3.242037
1	0	-2.510576	-10.165500	1.660535
1	0	-2.594328	-8.489897	4.218375
1	0	-3.769107	-8.401404	2.918802
1	0	-1.959351	-7.686308	1.334071
1	0	-0.787680	-7.768790	2.636824
1	0	-2.055222	-6.000479	3.886550
1	0	-3.225889	-5.919875	2.582810
1	0	-1.409572	-5.213558	1.000596
1	0	-0.245390	-5.280868	2.310869
1	0	-1.526274	-3.507438	3.538229
1	0	-2.693323	-3.446141	2.230873
1	0	-0.876654	-2.744685	0.647644
1	0	0.281218	-2.787476	1.966935
1	0	-1.065506	-1.042533	3.187405
1	0	-2.220232	-1.015279	1.876931
1	0	0.164894	-0.656580	-0.515373
1	0	-1.565039	-0.495838	-0.235492

</div>

<div style="column2">

C10 LARIAT ETHER

Solvent: *none*
Free Energy: -1669.150276

6	0	0.026419	0.005361	-0.003118
7	0	0.020688	0.012156	1.455067
6	0	1.349778	0.007565	2.048771
6	0	1.456286	0.726980	3.385874
8	0	1.345462	2.125569	3.199343
6	0	1.630503	2.854389	4.378541
6	0	1.477880	4.338508	4.128079
8	0	0.126291	4.732501	4.281994
6	0	-0.054851	6.124247	4.053149
6	0	-1.472419	6.560157	4.403408
7	0	-2.457097	6.350158	3.348445
6	0	-2.852600	4.956096	3.138445
6	0	-3.178057	4.631934	1.687854
8	0	-1.971399	4.503852	0.959503
6	0	-2.147622	4.199076	-0.409610
6	0	-0.930160	3.452789	-0.907753
8	0	-0.999775	2.116195	-0.449823
6	0	0.202417	1.389695	-0.612099
1	0	1.031954	1.923895	-0.129969
1	0	0.443318	1.287279	-1.682419
1	0	-0.025390	3.944426	-0.527062
1	0	-0.899759	3.480154	-2.008075
1	0	-2.286074	5.121737	-0.992531
1	0	-3.032443	3.566509	-0.558125
1	0	-3.816259	5.407833	1.241027
1	0	-3.732568	3.683002	1.647426
1	0	-3.719859	4.674688	3.758009
1	0	-2.026596	4.311245	3.435768
6	0	-3.576700	7.291108	3.406597
6	0	-4.468200	7.259162	4.661985
6	0	-5.622182	8.261899	4.579603
6	0	-6.521113	8.265466	5.818684
6	0	-7.675410	9.267857	5.739842
6	0	-8.573066	9.266259	6.979676
6	0	-9.728234	10.267877	6.904998
1	0	-9.323375	11.276290	6.755680
1	0	-10.336678	10.052574	6.018126
6	0	-10.625249	10.263234	8.145037
1	0	-10.017372	10.478141	9.032574
6	0	-11.780925	11.264486	8.073080
1	0	-11.375996	12.272031	7.924917
1	0	-12.388952	11.049740	7.186938
6	0	-12.671101	11.251315	9.316708
1	0	-12.098284	11.497401	10.215322
1	0	-13.485127	11.975515	9.234047
1	0	-13.118703	10.265528	9.471789
1	0	-11.031035	9.255086	8.294608
1	0	-8.978326	8.258268	7.130466
1	0	-7.964570	9.482321	7.866300

</div>

1	0	-7.269772	10.275605	5.588287
1	0	-8.283301	9.050578	4.853097
1	0	-6.927163	7.258331	5.972437
1	0	-5.913012	8.483948	6.704875
1	0	-5.217397	9.269831	4.425093
1	0	-6.230690	8.043106	3.693438
1	0	-4.875696	6.253295	4.807224
1	0	-3.864487	7.477228	5.549305
1	0	-3.167738	8.301365	3.291342
1	0	-4.203328	7.121535	2.525976
1	0	-1.429192	7.637402	4.588627
1	0	-1.747214	6.087184	5.361365
1	0	0.158951	6.367719	3.004945
1	0	0.649324	6.682073	4.689752
1	0	1.838363	4.573413	3.117959
1	0	2.101581	4.889888	4.848225
1	0	2.663935	2.649524	4.698008
1	0	0.959763	2.554153	5.195332
1	0	2.436220	0.487111	3.827910
1	0	0.688666	0.378510	4.090652
1	0	1.745737	-1.014455	2.187200
1	0	2.034843	0.509814	1.362692
6	0	-0.939634	-0.903284	2.064872
6	0	-0.722120	-2.411116	1.838539
6	0	-1.797469	-3.260102	2.521552
6	0	-1.619575	-4.766016	2.311493
6	0	-2.699373	-5.612469	2.990348
6	0	-2.522335	-7.118174	2.779084
6	0	-3.602368	-7.964857	3.457168
6	0	-3.425596	-9.470410	3.246124
1	0	-2.440918	-9.775713	3.621123
6	0	-4.505942	-10.317688	3.922997
6	0	-4.320582	-11.820401	3.706622
1	0	-3.360073	-12.161277	4.103382
1	0	-5.106514	-12.396029	4.201492
1	0	-4.344948	-12.072424	2.642629
1	0	-4.512393	-10.101888	4.997443
1	0	-5.489716	-10.013719	3.547733
1	0	-3.419109	-9.687215	2.170784
1	0	-3.608449	-7.749123	4.532582
1	0	-4.587570	-7.660905	3.082923
1	0	-2.516470	-7.333852	1.703690
1	0	-1.537090	-7.422233	3.153153
1	0	-2.705003	-5.396595	4.065724
1	0	-3.684652	-5.308511	2.616447
1	0	-1.614012	-4.982228	1.236278
1	0	-0.634118	-5.069336	2.685494
1	0	-1.801008	-3.044333	3.597141
1	0	-2.785179	-2.958854	2.151510
1	0	-0.721137	-2.624847	0.764043
1	0	0.262797	-2.710547	2.212684
1	0	-0.960596	-0.706164	3.141031
1	0	-1.931882	-0.627174	1.694492
1	0	0.805107	-0.657992	-0.417475
1	0	-0.932123	-0.382525	-0.354934

C10 LARIAT ETHER

Solvent: *water*
Free Energy: -1669.175758

6	0	-0.278992	-0.005713	-0.038740
7	0	-0.194189	-0.057264	1.428876
6	0	1.204047	0.000229	1.878901
6	0	1.403175	0.381619	3.333609
8	0	1.179209	1.783553	3.523579
6	0	1.393992	2.171708	4.879819
6	0	1.450834	3.671675	5.008876
8	0	0.160281	4.259395	4.842289
6	0	0.217746	5.676790	5.035113
6	0	-1.152445	6.328069	4.990699
7	0	-1.789221	6.390448	3.664313
6	0	-2.661007	5.225433	3.437894
6	0	-3.085082	5.005428	1.998603
8	0	-1.977069	4.526193	1.233329
6	0	-2.294066	4.326790	-0.142602
6	0	-1.203046	3.508458	-0.785092
8	0	-1.267560	2.176983	-0.280433
6	0	-0.133720	1.383769	-0.631632
1	0	0.779601	1.880770	-0.284389
1	0	-0.069196	1.294420	-1.723870
1	0	-0.222910	3.947308	-0.562262
1	0	-1.339025	3.509303	-1.873925
1	0	-2.379585	5.292126	-0.656625
1	0	-3.254265	3.804500	-0.234370
1	0	-3.482072	5.919104	1.542654
1	0	-3.884434	4.254167	1.981847
1	0	-3.575273	5.278038	4.047341
1	0	-2.123652	4.335200	3.764597
6	0	-2.478706	7.680444	3.451742
6	0	-3.664559	8.020024	4.366053
6	0	-4.225804	9.412731	4.067182
6	0	-5.410513	9.798681	4.955692
6	0	-5.973104	11.189679	4.655241
6	0	-7.152378	11.580157	5.548922
6	0	-7.717718	12.969438	5.245763
1	0	-6.919770	13.714473	5.351916
1	0	-8.035263	13.008273	4.196619
6	0	-8.894123	13.362090	6.141818
1	0	-8.577225	13.325836	7.191387
6	0	-9.461038	14.750360	5.837628
1	0	-8.663875	15.495213	5.941436
1	0	-9.779898	14.787041	4.789769
6	0	-10.634301	15.133253	6.739134
1	0	-10.337566	15.139205	7.792240
1	0	-11.016934	16.128379	6.497012
1	0	-11.461441	14.424953	6.632889
1	0	-9.692793	12.617391	6.037493
1	0	-7.949703	10.834893	5.439980
1	0	-6.837464	11.540360	6.598803
1	0	-5.174690	11.933369	4.766944

1	0	-6.286734	11.232455	3.605092
1	0	-6.207211	9.054212	4.838301
1	0	-5.101662	9.753927	6.007083
1	0	-3.429006	10.156908	4.186435
1	0	-4.533772	9.460255	3.015557
1	0	-4.461921	7.280856	4.243175
1	0	-3.352014	7.974946	5.414542
1	0	-1.722123	8.463522	3.553510
1	0	-2.813993	7.718655	2.412658
1	0	-0.991487	7.350382	5.339437
1	0	-1.803472	5.846962	5.734579
1	0	0.874133	6.119958	4.276018
1	0	0.658710	5.879347	6.020536
1	0	2.147402	4.086268	4.269455
1	0	1.834694	3.914333	6.008059
1	0	2.354095	1.770977	5.228112
1	0	0.603369	1.759021	5.519031
1	0	2.437682	0.148335	3.615163
1	0	0.744327	-0.187979	3.998219
1	0	1.722714	-0.955957	1.715147
1	0	1.729877	0.738776	1.271452
6	0	-0.935063	-1.212381	1.974012
6	0	-0.483696	-2.620246	1.557761
6	0	-1.380490	-3.701307	2.167014
6	0	-0.967651	-5.124409	1.784735
6	0	-1.870931	-6.205715	2.381843
6	0	-1.457331	-7.628674	1.999962
6	0	-2.363460	-8.710686	2.591424
6	0	-1.948688	-10.133349	2.210765
1	0	-0.917920	-10.310467	2.541646
6	0	-2.856354	-11.215823	2.798678
6	0	-2.432325	-12.632698	2.413384
1	0	-1.418224	-12.849897	2.762029
1	0	-3.099646	-13.382140	2.847363
1	0	-2.444265	-12.767061	1.327592
1	0	-2.866390	-11.122999	3.890618
1	0	-3.886128	-11.040927	2.467005
1	0	-1.939531	-10.227298	1.117858
1	0	-2.370443	-8.617637	3.684289
1	0	-3.395190	-8.536023	2.262688
1	0	-1.451824	-7.721248	0.907060
1	0	-0.425284	-7.804194	2.327213
1	0	-1.872697	-6.111597	3.474617
1	0	-2.904153	-6.031334	2.057774
1	0	-0.967673	-5.218108	0.692004
1	0	0.065942	-5.298957	2.107216
1	0	-1.372621	-3.605045	3.259551
1	0	-2.417132	-3.530188	1.852374
1	0	-0.502493	-2.711474	0.467009
1	0	0.549959	-2.796971	1.870555
1	0	-0.912056	-1.143892	3.064266
1	0	-1.981670	-1.082323	1.683383
1	0	0.476305	-0.647344	-0.517850
1	0	-1.254763	-0.395276	-0.336973

C10 LARIAT ETHER

Solvent: *n-octanol*

Free Energy: -1669.190705

6	0	-0.697439	-0.087326	0.000130
7	0	-0.504566	-0.098002	1.453445
6	0	0.909569	-0.009375	1.822600
6	0	1.180836	0.504905	3.225552
8	0	0.907721	1.902381	3.308452
6	0	1.287630	2.444289	4.567950
6	0	1.166048	3.947338	4.562512
8	0	-0.195488	4.352587	4.655999
6	0	-0.313557	5.774905	4.703262
6	0	-1.742951	6.225625	4.959253
7	0	-2.643460	6.154730	3.803730
6	0	-3.242916	4.825824	3.628674
6	0	-3.745549	4.541129	2.224641
8	0	-2.637838	4.329201	1.354134
6	0	-3.014501	4.073892	0.006397
6	0	-1.890913	3.348324	-0.692593
8	0	-1.835555	2.014262	-0.203940
6	0	-0.674256	1.301673	-0.614509
1	0	0.223383	1.857961	-0.317692
1	0	-0.661124	1.206197	-1.709835
1	0	-0.940243	3.862652	-0.502727
1	0	-2.071732	3.351266	-1.776626
1	0	-3.225927	5.017027	-0.515569
1	0	-3.921000	3.456366	-0.025832
1	0	-4.374296	5.355102	1.842673
1	0	-4.362884	3.633226	2.251425
1	0	-4.079004	4.655495	4.325291
1	0	-2.483688	4.079432	3.861491
6	0	-3.620990	7.255972	3.787294
6	0	-4.629493	7.334933	4.945492
6	0	-5.573419	8.532271	4.802699
6	0	-6.595045	8.644291	5.937325
6	0	-7.545179	9.836067	5.794972
6	0	-8.567492	9.943363	6.929302
6	0	-9.522843	11.130908	6.786797
1	0	-8.940251	12.059391	6.740339
1	0	-10.052475	11.054602	5.829035
6	0	-10.546057	11.235164	7.920243
1	0	-10.017785	11.313406	8.878761
6	0	-11.504018	12.420384	7.778134
1	0	-10.923973	13.349491	7.731942
1	0	-12.033600	12.343135	6.821380
6	0	-12.522007	12.514652	8.914361
1	0	-12.025854	12.629771	9.883127
1	0	-13.190863	13.369883	8.782145
1	0	-13.142711	11.614673	8.966414
1	0	-11.128607	10.306569	7.968132
1	0	-9.150915	9.015503	6.977221
1	0	-8.037225	10.020044	7.886660
1	0	-6.958782	10.762129	5.748560

1	0	-8.075412	9.762040	4.837384
1	0	-7.182497	7.719093	5.985242
1	0	-6.064099	8.718576	6.894398
1	0	-4.983309	9.456039	4.756208
1	0	-6.104834	8.461699	3.845471
1	0	-5.223506	6.416651	4.991851
1	0	-4.095150	7.409652	5.898623
1	0	-3.051519	8.190417	3.752126
1	0	-4.171140	7.204475	2.844058
1	0	-1.668219	7.274673	5.256267
1	0	-2.134548	5.681417	5.833259
1	0	0.054470	6.208593	3.764744
1	0	0.315663	6.152745	5.522243
1	0	1.621000	4.354279	3.650009
1	0	1.723996	4.341360	5.423495
1	0	2.335829	2.189450	4.776968
1	0	0.670268	2.017195	5.369619
1	0	2.241590	0.331015	3.454520
1	0	0.591577	-0.033675	3.977804
1	0	1.424289	-0.979066	1.722414
1	0	1.403187	0.671776	1.126448
6	0	-1.233087	-1.190157	2.115870
6	0	-0.852560	-2.632240	1.740482
6	0	-1.707168	-3.662417	2.484267
6	0	-1.377162	-5.111312	2.116258
6	0	-2.234620	-6.144121	2.851984
6	0	-1.913094	-7.591174	2.469828
6	0	-2.769084	-8.626502	3.203678
6	0	-2.451594	-10.072356	2.814723
1	0	-1.391599	-10.275914	3.012044
6	0	-3.305665	-11.109251	3.548192
6	0	-2.982351	-12.549268	3.150622
1	0	-1.937683	-12.795096	3.365488
1	0	-3.608097	-13.263912	3.692853
1	0	-3.146279	-12.711803	2.080738
1	0	-3.167138	-10.990918	4.629210
1	0	-4.365218	-10.907433	3.352228
1	0	-2.589222	-10.194382	1.732997
1	0	-2.632967	-8.505760	4.285579
1	0	-3.828909	-8.424339	3.004942
1	0	-2.045957	-7.715681	1.387944
1	0	-0.853435	-7.790912	2.672006
1	0	-2.103077	-6.018185	3.933835
1	0	-3.293838	-5.944317	2.647937
1	0	-1.502499	-5.244599	1.034590
1	0	-0.318193	-5.305439	2.327007
1	0	-1.580450	-3.526261	3.565459
1	0	-2.766991	-3.470856	2.275413
1	0	-0.974378	-2.777796	0.661739
1	0	0.203650	-2.816041	1.963206
1	0	-1.122385	-1.063647	3.196159
1	0	-2.296109	-1.040196	1.902572
1	0	0.053241	-0.699961	-0.525394
1	0	-1.671710	-0.529251	-0.221557

C11 LARIAT ETHER

Solvent: *none*
Free Energy: -1747.748338

6	0	0.041864	0.015521	-0.029387
7	0	0.050451	0.026792	1.428747
6	0	1.385318	0.029201	2.009385
6	0	1.502164	0.753641	3.342906
8	0	1.384969	2.151218	3.152640
6	0	1.678842	2.884928	4.326626
6	0	1.519556	4.367739	4.072649
8	0	0.168312	4.758392	4.237666
6	0	-0.018729	6.148934	4.006283
6	0	-1.434298	6.582113	4.367845
7	0	-2.427736	6.366254	3.322328
6	0	-2.822288	4.970649	3.121056
6	0	-3.160251	4.640396	1.674713
8	0	-1.960028	4.512516	0.935782
6	0	-2.148104	4.201903	-0.430436
6	0	-0.933268	3.457020	-0.936992
8	0	-0.994765	2.122019	-0.473267
6	0	0.207952	1.398410	-0.644401
1	0	1.040374	1.936634	-0.171824
1	0	0.439106	1.293211	-1.716597
1	0	-0.026371	3.952675	-0.566714
1	0	-0.913226	3.480158	-2.037651
1	0	-2.294480	5.121898	-1.015632
1	0	-3.032534	3.566377	-0.568280
1	0	-3.804410	5.413102	1.230911
1	0	-3.712841	3.690016	1.642892
1	0	-3.683299	4.689775	3.749525
1	0	-1.992266	4.328595	3.413211
6	0	-3.548478	7.305430	3.386455
6	0	-4.429571	7.276464	4.649259
6	0	-5.584394	8.278762	4.573794
6	0	-6.473436	8.285015	5.819987
6	0	-7.627558	9.288172	5.748769
6	0	-8.515705	9.288667	6.995446
6	0	-9.670054	10.291789	6.929043
1	0	-9.265022	11.299566	6.776166
1	0	-10.285563	10.076920	6.046992
6	0	-10.557423	10.288614	8.176283
1	0	-9.941376	10.502247	9.058310
6	0	-11.711706	11.291713	8.113020
1	0	-11.307531	12.300307	7.962111
1	0	-12.328698	11.079051	7.231262
6	0	-12.599023	11.287274	9.360273
1	0	-11.982934	11.500218	10.241266
6	0	-13.749422	12.292624	9.288489
1	0	-13.375217	13.313800	9.172910
1	0	-14.404096	12.083987	8.437575
1	0	-14.362344	12.264777	10.192645
1	0	-13.003708	10.279977	9.510660
1	0	-10.962749	9.280815	8.328419

1	0	-8.921118	8.281306	7.150047
1	0	-7.900103	9.504507	7.877218
1	0	-7.222305	10.295426	5.592963
1	0	-8.242371	9.070361	4.866940
1	0	-6.878974	7.278431	5.978625
1	0	-5.858135	8.504495	6.700949
1	0	-5.180998	9.286396	4.413805
1	0	-6.199906	8.057911	3.692995
1	0	-4.835574	6.270874	4.800474
1	0	-3.818605	7.497001	5.530988
1	0	-3.142193	8.315959	3.264332
1	0	-4.182056	7.131782	2.511619
1	0	-1.392281	7.660026	4.549388
1	0	-1.699313	6.111384	5.329655
1	0	0.185009	6.389806	2.955475
1	0	0.689590	6.710597	4.634872
1	0	1.870099	4.600356	3.058506
1	0	2.148235	4.923281	4.785233
1	0	2.715819	2.684186	4.637102
1	0	1.016661	2.585514	5.150672
1	0	2.487052	0.518563	3.776426
1	0	0.742437	0.405101	4.056156
1	0	1.786376	-0.990874	2.147456
1	0	2.061806	0.531544	1.314924
6	0	-0.900003	-0.890784	2.050696
6	0	-0.678995	-2.398354	1.825941
6	0	-1.742905	-3.249721	2.523758
6	0	-1.562465	-4.755422	2.314388
6	0	-2.629534	-5.604349	3.010099
6	0	-2.450509	-7.109791	2.798669
6	0	-3.517842	-7.959041	3.493441
6	0	-3.338598	-9.464456	3.281944
1	0	-2.347306	-9.764551	3.643058
6	0	-4.406145	-10.314036	3.975566
6	0	-4.227666	-11.819656	3.763725
1	0	-3.237272	-12.119321	4.124813
6	0	-5.299226	-12.659944	4.460051
1	0	-5.292330	-12.492348	5.540807
1	0	-6.298641	-12.407660	4.094421
1	0	-5.143907	-13.727999	4.289481
1	0	-4.235771	-12.035570	2.689307
1	0	-4.398537	-10.098277	5.051090
1	0	-5.397946	-10.014785	3.614838
1	0	-3.346564	-9.681688	2.206840
1	0	-3.509285	-7.741652	4.568477
1	0	-4.509317	-7.659058	3.132899
1	0	-2.459347	-7.327126	1.723619
1	0	-1.458962	-7.409965	3.159002
1	0	-2.620397	-5.386716	4.085094
1	0	-3.621114	-5.304290	2.649949
1	0	-1.571112	-4.973919	1.239656
1	0	-0.570784	-5.054378	2.675229
1	0	-1.733860	-3.031853	3.598892
1	0	-2.736164	-2.952592	2.165420
1	0	-0.689637	-2.615042	0.752089
1	0	0.311400	-2.692818	2.189414

1	0	-0.910540	-0.691009	3.126516
1	0	-1.897106	-0.619445	1.689936
1	0	0.818342	-0.646919	-0.449350
1	0	-0.918988	-0.376182	-0.370508

C11 LARIAT ETHER

Solvent: *water*
Free Energy: -1747.772473

6	0	-1.341181	-0.203592	0.146494
7	0	-1.068628	-0.264276	1.590746
6	0	0.363773	-0.079695	1.864807
6	0	0.710150	0.287893	3.295214
8	0	0.378391	1.655902	3.560689
6	0	0.720156	2.030042	4.894729
6	0	0.645018	3.524223	5.071712
8	0	-0.707743	3.980556	5.079687
6	0	-0.768379	5.391013	5.317097
6	0	-2.192252	5.899173	5.452318
7	0	-2.981315	5.932370	4.208972
6	0	-3.760650	4.694038	4.043019
6	0	-4.331935	4.469242	2.656337
8	0	-3.286227	4.109552	1.750557
6	0	-3.749251	3.913257	0.416273
6	0	-2.675301	3.216935	-0.380003
8	0	-2.555680	1.874394	0.083385
6	0	-1.404406	1.200664	-0.425554
1	0	-0.506310	1.779839	-0.181613
1	0	-1.469347	1.132227	-1.519286
1	0	-1.719470	3.741484	-0.261067
1	0	-2.942698	3.229836	-1.444125
1	0	-3.984364	4.877957	-0.050137
1	0	-4.661982	3.304826	0.421978
1	0	-4.858739	5.353317	2.280631
1	0	-5.058887	3.649171	2.707907
1	0	-4.596404	4.642854	4.756446
1	0	-3.107132	3.852610	4.273071
6	0	-3.808139	7.154494	4.121301
6	0	-4.914039	7.349981	5.168252
6	0	-5.616363	8.699939	5.000083
6	0	-6.741593	8.934762	6.010273
6	0	-7.434973	10.289446	5.849720
6	0	-8.562253	10.524501	6.857537
6	0	-9.251720	11.881615	6.700859
1	0	-8.505600	12.678884	6.804325
1	0	-9.652048	11.967371	5.683302
6	0	-10.380760	12.115903	7.706881
1	0	-9.981083	12.027610	8.724498
6	0	-11.067405	13.474460	7.552879
1	0	-10.321010	14.271185	7.659989
1	0	-11.467072	13.564668	6.535293
6	0	-12.197601	13.708821	8.557369
1	0	-11.799571	13.618337	9.574449
6	0	-12.874731	15.069453	8.396194

1	0	-12.158846	15.885432	8.533434
1	0	-13.311606	15.177523	7.398900
1	0	-13.677094	15.206253	9.126143
1	0	-12.945240	12.914821	8.449450
1	0	-11.128347	11.320232	7.601597
1	0	-9.308467	9.727050	6.756212
1	0	-8.160133	10.439897	7.874488
1	0	-6.690663	11.088992	5.948452
1	0	-7.837806	10.370152	4.832740
1	0	-7.485500	8.134733	5.913879
1	0	-6.336264	8.855462	7.026276
1	0	-4.877217	9.505147	5.090486
1	0	-6.023822	8.771706	3.984259
1	0	-5.656062	6.549671	5.089203
1	0	-4.489779	7.287623	6.175830
1	0	-3.121437	8.004079	4.172934
1	0	-4.256692	7.190410	3.125750
1	0	-2.093940	6.922125	5.821725
1	0	-2.702214	5.332858	6.244583
1	0	-0.252008	5.918207	4.505447
1	0	-0.237869	5.612769	6.252988
1	0	1.202980	4.026083	4.271340
1	0	1.121212	3.779454	6.027066
1	0	1.750466	1.720009	5.109611
1	0	0.058494	1.523395	5.608490
1	0	1.789861	0.152939	3.436024
1	0	0.200593	-0.359275	4.017488
1	0	0.945335	-0.976853	1.605626
1	0	0.735633	0.719781	1.221622
6	0	-1.625198	-1.490682	2.196151
6	0	-1.099649	-2.844362	1.695843
6	0	-1.795332	-4.012156	2.400408
6	0	-1.308264	-5.385782	1.933818
6	0	-2.003575	-6.553388	2.637425
6	0	-1.518572	-7.927247	2.169444
6	0	-2.212402	-9.095421	2.873519
6	0	-1.727582	-10.469083	2.404776
1	0	-0.644973	-10.543119	2.564602
6	0	-2.420540	-11.637466	3.108791
6	0	-1.936560	-13.011178	2.639760
1	0	-0.854782	-13.085106	2.798948
6	0	-2.634690	-14.170959	3.349223
1	0	-2.467425	-14.131137	4.429766
1	0	-3.715457	-14.143820	3.180869
1	0	-2.267994	-15.137231	2.992594
1	0	-2.093703	-13.098083	1.558652
1	0	-2.263903	-11.551978	4.191144
1	0	-3.503471	-11.564855	2.949683
1	0	-1.884035	-10.556582	1.322680
1	0	-2.056367	-9.008079	3.955665
1	0	-3.294920	-9.021293	2.713296
1	0	-1.674192	-8.014932	1.087259
1	0	-0.436093	-8.001292	2.330091
1	0	-1.848845	-6.465781	3.719732
1	0	-3.085831	-6.478807	2.475717
1	0	-1.461859	-5.473949	0.851487

1	0	-0.226218	-5.459202	2.096878
1	0	-1.642040	-3.924251	3.482865
1	0	-2.877565	-3.939525	2.237825
1	0	-1.257946	-2.930589	0.616031
1	0	-0.020793	-2.919338	1.862961
1	0	-1.473296	-1.432302	3.276570
1	0	-2.707341	-1.457769	2.039295
1	0	-0.594171	-0.762813	-0.437494
1	0	-2.305104	-0.682740	-0.038385

C11 LARIAT ETHER

Solvent: *n-octanol*
Free Energy: -1747.790471

6	0	-0.744495	-0.101969	0.047869
7	0	-0.558122	-0.119680	1.501927
6	0	0.854175	-0.031794	1.878376
6	0	1.118166	0.480611	3.283440
8	0	0.847773	1.878665	3.366032
6	0	1.223260	2.418849	4.627618
6	0	1.107691	3.922372	4.621959
8	0	-0.252533	4.333168	4.710375
6	0	-0.364911	5.756017	4.756002
6	0	-1.792857	6.212881	5.009183
7	0	-2.691965	6.144153	3.852464
6	0	-3.296588	4.817543	3.677921
6	0	-3.796265	4.532871	2.272833
8	0	-2.686796	4.316037	1.405817
6	0	-3.060518	4.060810	0.057305
6	0	-1.935160	3.335777	-0.639356
8	0	-1.880688	2.001303	-0.151667
6	0	-0.718050	1.289749	-0.560314
1	0	0.178631	1.844294	-0.257394
1	0	-0.700396	1.199001	-1.655980
1	0	-0.985074	3.850186	-0.446779
1	0	-2.113285	3.339422	-1.723825
1	0	-3.271078	5.003959	-0.465009
1	0	-3.966808	3.443041	0.023076
1	0	-4.420972	5.348665	1.888102
1	0	-4.416939	3.627215	2.298920
1	0	-4.135423	4.651865	4.372343
1	0	-2.541243	4.068278	3.914095
6	0	-3.665000	7.249333	3.833207
6	0	-4.673974	7.334274	4.990550
6	0	-5.613227	8.535012	4.845357
6	0	-6.634606	8.652681	5.979620
6	0	-7.579980	9.848086	5.835908
6	0	-8.601864	9.960356	6.970148
6	0	-9.552217	11.151879	6.827398
1	0	-8.965729	12.077880	6.780829
1	0	-10.082127	11.077701	5.869643
6	0	-10.574978	11.260221	7.961212
1	0	-10.045109	11.334846	8.918982
6	0	-11.527098	12.450134	7.819475

1	0	-10.942930	13.377848	7.774170
1	0	-12.057810	12.376900	6.861914
6	0	-12.550561	12.557448	8.952455
1	0	-12.022016	12.631537	9.910041
6	0	-13.496322	13.748775	8.802561
1	0	-12.944704	14.694032	8.790330
1	0	-14.066871	13.687601	7.870540
1	0	-14.213895	13.795765	9.626671
1	0	-13.136419	11.631965	8.997893
1	0	-11.160686	10.333713	8.007931
1	0	-9.189191	9.034976	7.018496
1	0	-8.071208	10.035154	7.927450
1	0	-6.989920	10.771779	5.788675
1	0	-8.110436	9.775246	4.878353
1	0	-7.225773	7.729907	6.028618
1	0	-6.103471	8.725978	6.936666
1	0	-5.019558	9.456430	4.797531
1	0	-6.144661	8.464904	3.888108
1	0	-5.271543	6.418366	5.038159
1	0	-4.139925	7.408547	5.943878
1	0	-3.091763	8.181436	3.796862
1	0	-4.214609	7.198309	2.889626
1	0	-1.714285	7.262023	5.304886
1	0	-2.187964	5.671476	5.883350
1	0	0.006514	6.187237	3.817683
1	0	0.264417	6.132124	5.575692
1	0	1.567784	4.327540	3.711249
1	0	1.663896	4.314083	5.485116
1	0	2.269359	2.159847	4.841908
1	0	0.600170	1.993995	5.426042
1	0	2.177117	0.304181	3.518713
1	0	0.523051	-0.057358	4.031527
1	0	1.369045	-1.001517	1.779685
1	0	1.351667	0.650060	1.185698
6	0	-1.288379	-1.216236	2.155240
6	0	-0.906468	-2.655719	1.771310
6	0	-1.763551	-3.691318	2.504678
6	0	-1.434401	-5.137180	2.124159
6	0	-2.295561	-6.176045	2.846951
6	0	-1.975613	-7.619434	2.449846
6	0	-2.837513	-8.661440	3.167138
6	0	-2.521959	-10.103204	2.760753
1	0	-1.463539	-10.311141	2.961183
6	0	-3.383583	-11.146807	3.475528
6	0	-3.071096	-12.587884	3.065203
1	0	-2.013474	-12.797940	3.263014
6	0	-3.936220	-13.622784	3.784027
1	0	-3.797747	-13.571331	4.868505
1	0	-4.999307	-13.462220	3.579116
1	0	-3.688736	-14.640059	3.467486
1	0	-3.205550	-12.691407	1.982139
1	0	-3.250417	-11.045102	4.559894
1	0	-4.442567	-10.938828	3.277520
1	0	-2.653683	-10.208835	1.676703
1	0	-2.705822	-8.554728	4.251040
1	0	-3.895881	-8.453839	2.966361

1	0	-2.103631	-7.730969	1.365954
1	0	-0.917365	-7.824004	2.654606
1	0	-2.166653	-6.061898	3.930422
1	0	-3.353870	-5.972147	2.642227
1	0	-1.556585	-5.259889	1.040881
1	0	-0.376337	-5.334793	2.336231
1	0	-1.638809	-3.564833	3.587267
1	0	-2.822759	-3.496801	2.295414
1	0	-1.024768	-2.793752	0.691203
1	0	0.149034	-2.841027	1.996110
1	0	-1.180624	-1.096720	3.236629
1	0	-2.350858	-1.065178	1.939937
1	0	0.008254	-0.712412	-0.477260
1	0	-1.717958	-0.542469	-0.180135

C12 LARIAT ETHER

Solvent: *none*
Free Energy: -1826.346701

6	0	0.014737	0.002480	-0.001489
7	0	0.013008	0.006653	1.456717
6	0	1.343747	0.004762	2.046742
6	0	1.451887	0.722097	3.384826
8	0	1.336781	2.120722	3.201126
6	0	1.623011	2.848112	4.380917
6	0	1.465682	4.332285	4.133731
8	0	0.113412	4.722262	4.291772
6	0	-0.071960	6.114083	4.066834
6	0	-1.490072	6.545248	4.420746
7	0	-2.476022	6.335169	3.366985
6	0	-2.868552	4.940589	3.154914
6	0	-3.196658	4.618591	1.704442
8	0	-1.991436	4.495033	0.972935
6	0	-2.170122	4.191887	-0.396217
6	0	-0.952125	3.449104	-0.898260
8	0	-1.017523	2.111730	-0.441990
6	0	0.185914	1.388259	-0.608540
1	0	1.015448	1.923593	-0.127668
1	0	0.424297	1.288204	-1.679646
1	0	-0.047596	3.942336	-0.519058
1	0	-0.924409	3.478029	-1.998616
1	0	-2.311984	5.115087	-0.977460
1	0	-3.053851	3.557545	-0.543641
1	0	-3.837902	5.393747	1.260696
1	0	-3.748861	3.668342	1.663445
1	0	-3.733597	4.655656	3.775966
1	0	-2.040192	4.297221	3.448880
6	0	-3.597698	7.273413	3.428931
6	0	-4.487549	7.236217	4.685346
6	0	-5.643335	8.237235	4.607560
6	0	-6.541277	8.234442	5.847372
6	0	-7.697184	9.235366	5.773710
6	0	-8.594370	9.226247	7.013857
6	0	-9.750913	10.226695	6.945085

1	0	-9.347504	11.236564	6.801980
1	0	-10.359010	10.015959	6.056906
6	0	-10.647775	10.212679	8.185416
1	0	-10.039089	10.421766	9.073587
6	0	-11.804317	11.213360	8.120134
1	0	-11.400802	12.223547	7.979404
1	0	-12.412894	11.005039	7.231682
6	0	-12.700839	11.196911	9.360436
1	0	-12.092885	11.404820	10.249587
6	0	-13.857636	12.197465	9.297509
1	0	-13.453862	13.206693	9.157889
1	0	-14.465736	11.989725	8.409747
6	0	-14.747422	12.172683	10.541256
1	0	-14.174598	12.411728	11.441766
1	0	-15.562265	12.896674	10.465019
1	0	-15.193900	11.185117	10.688039
1	0	-13.105442	10.187049	9.501421
1	0	-11.051544	9.202818	8.327495
1	0	-8.998239	8.216933	7.159521
1	0	-7.985774	9.438408	7.901365
1	0	-7.293213	10.244480	5.626858
1	0	-8.305055	9.021378	4.886149
1	0	-6.945667	7.226061	5.997302
1	0	-5.932783	8.450167	6.733970
1	0	-5.240447	9.246452	4.456526
1	0	-6.252165	8.020690	3.721064
1	0	-4.893187	6.229239	4.828052
1	0	-3.883063	7.452585	5.572558
1	0	-3.191138	8.284867	3.315740
1	0	-4.225053	7.104688	2.548667
1	0	-1.449430	7.622131	4.608604
1	0	-1.761898	6.069121	5.377989
1	0	0.139238	6.360839	3.018865
1	0	0.631874	6.672198	4.703568
1	0	1.823012	4.570190	3.123191
1	0	2.089660	4.883938	4.853430
1	0	2.657859	2.645475	4.697213
1	0	0.955303	2.544494	5.198942
1	0	2.433650	0.484112	3.823809
1	0	0.687106	0.370288	4.091030
1	0	1.742929	-1.016392	2.182289
1	0	2.025532	0.510122	1.359684
6	0	-0.942906	-0.912791	2.067451
6	0	-0.721938	-2.419530	1.837168
6	0	-1.792550	-3.272928	2.522138
6	0	-1.612367	-4.777817	2.306784
6	0	-2.686853	-5.628691	2.988568
6	0	-2.508013	-7.133322	2.771242
6	0	-3.583097	-7.984502	3.451555
6	0	-3.404197	-9.489061	3.233815
1	0	-2.416791	-9.792654	3.602493
6	0	-4.479726	-10.340430	3.913189
6	0	-4.301430	-11.844779	3.694942
1	0	-3.314409	-12.149951	4.063829
6	0	-5.376975	-12.696817	4.373485
1	0	-5.378420	-12.485709	5.448885

1	0	-6.363144	-12.392901	4.004495
6	0	-5.190207	-14.198226	4.149680
1	0	-4.227162	-14.539192	4.540167
1	0	-5.972696	-14.777318	4.645974
1	0	-5.219477	-14.445682	3.084739
1	0	-4.299803	-12.057020	2.618672
1	0	-4.481280	-10.129279	4.989532
1	0	-5.467144	-10.036574	3.544720
1	0	-3.402493	-9.700624	2.157580
1	0	-3.584285	-7.772740	4.527754
1	0	-4.570689	-7.681055	3.083312
1	0	-2.506981	-7.345207	1.695067
1	0	-1.520351	-7.436779	3.139404
1	0	-2.687187	-5.416428	4.064675
1	0	-3.674704	-5.325429	2.620932
1	0	-1.611739	-4.990857	1.230922
1	0	-0.624367	-5.080048	2.674921
1	0	-1.792019	-3.060375	3.598372
1	0	-2.782464	-2.972718	2.157170
1	0	-0.724162	-2.630963	0.762220
1	0	0.265120	-2.717021	2.207190
1	0	-0.961094	-0.718054	3.144094
1	0	-1.937054	-0.638642	1.700714
1	0	0.793798	-0.658354	-0.419177
1	0	-0.943889	-0.386976	-0.351334

C12 LARIAT ETHER

Solvent: *water*
Free Energy: -1826.369867

6	0	-1.467689	-0.251382	0.187134
7	0	-1.184841	-0.316320	1.629237
6	0	0.249872	-0.135216	1.893308
6	0	0.607318	0.227530	3.322225
8	0	0.279754	1.595263	3.594021
6	0	0.633152	1.965577	4.926064
6	0	0.557584	3.459101	5.108361
8	0	-0.795722	3.913447	5.130167
6	0	-0.856212	5.322802	5.374008
6	0	-2.279658	5.828559	5.522101
7	0	-3.077928	5.866151	4.284763
6	0	-3.858292	4.628334	4.119922
6	0	-4.440178	4.408967	2.736732
8	0	-3.401366	4.053360	1.821479
6	0	-3.874094	3.863488	0.489683
6	0	-2.805950	3.170740	-0.317499
8	0	-2.683469	1.825974	0.138604
6	0	-1.535076	1.154684	-0.379977
1	0	-0.635736	1.733470	-0.139727
1	0	-1.606940	1.089950	-1.473502
1	0	-1.849184	3.694490	-0.202721
1	0	-3.080800	3.188860	-1.379644
1	0	-4.112340	4.830434	0.029561
1	0	-4.786883	3.255194	0.499070

1	0	-4.970102	5.294409	2.368730
1	0	-5.166487	3.588471	2.790532
1	0	-4.688558	4.574125	4.839524
1	0	-3.202847	3.786123	4.341646
6	0	-3.905287	7.088570	4.207379
6	0	-5.004021	7.280156	5.262591
6	0	-5.705657	8.631796	5.105539
6	0	-6.824425	8.863263	6.123668
6	0	-7.515660	10.220343	5.974550
6	0	-8.636879	10.452558	6.989774
6	0	-9.323498	11.812373	6.844364
1	0	-8.574520	12.606975	6.947797
1	0	-9.729356	11.904707	5.829568
6	0	-10.446086	12.044592	7.858062
1	0	-10.040862	11.949541	8.872857
6	0	-11.129320	13.406360	7.715077
1	0	-10.378743	14.199079	7.821417
1	0	-11.533795	13.502085	6.700032
6	0	-12.252496	13.638719	8.727697
1	0	-11.849566	13.542440	9.743439
6	0	-12.934279	15.001255	8.586627
1	0	-12.183313	15.792131	8.694446
1	0	-13.337780	15.098457	7.572333
6	0	-14.054591	15.222796	9.602318
1	0	-13.675637	15.165149	10.627118
1	0	-14.521067	16.203511	9.476135
1	0	-14.838374	14.466689	9.496869
1	0	-13.005162	12.847857	8.621056
1	0	-11.196649	11.251750	7.752777
1	0	-9.385720	9.657628	6.888025
1	0	-8.229491	10.361206	8.004044
1	0	-6.768966	11.017622	6.073604
1	0	-7.923864	10.307635	4.960255
1	0	-7.570600	8.065356	6.027235
1	0	-6.413306	8.777501	7.136817
1	0	-4.964860	9.435539	5.195463
1	0	-6.119182	8.709243	4.092584
1	0	-5.747485	6.481084	5.184542
1	0	-4.573159	7.212374	6.267012
1	0	-3.218209	7.937932	4.257605
1	0	-4.360649	7.128438	3.215079
1	0	-2.179847	6.849971	5.895347
1	0	-2.783045	5.258103	6.315577
1	0	-0.346711	5.854109	4.560706
1	0	-0.318880	5.541224	6.306790
1	0	1.107432	3.964307	4.304487
1	0	1.042163	3.712048	6.060091
1	0	1.665756	1.656115	5.130602
1	0	-0.021391	1.455864	5.644204
1	0	1.687793	0.090356	3.454727
1	0	0.101907	-0.420940	4.046252
1	0	0.827771	-1.032749	1.627305
1	0	0.618604	0.665428	1.249768
6	0	-1.739240	-1.543227	2.235581
6	0	-1.219020	-2.896549	1.728777
6	0	-1.914853	-4.064891	2.432271

6	0	-1.432481	-5.438240	1.960019
6	0	-2.129842	-6.606272	2.660888
6	0	-1.649596	-7.979959	2.187508
6	0	-2.346534	-9.148426	2.888038
6	0	-1.866605	-10.522039	2.414145
1	0	-0.784197	-10.600312	2.573204
6	0	-2.563570	-11.690574	3.114520
6	0	-2.084338	-13.064014	2.640266
1	0	-1.001866	-13.144139	2.798939
6	0	-2.780866	-14.232896	3.340196
1	0	-2.623079	-14.150368	4.421552
1	0	-3.862400	-14.154343	3.181602
6	0	-2.295041	-15.599716	2.858988
1	0	-1.222122	-15.721972	3.035156
1	0	-2.810642	-16.412826	3.376993
1	0	-2.470370	-15.726000	1.786399
1	0	-2.241980	-13.148285	1.557959
1	0	-2.406022	-11.607984	4.196840
1	0	-3.646030	-11.612172	2.955800
1	0	-2.023797	-10.605060	1.331819
1	0	-2.189373	-9.065360	3.970367
1	0	-3.428942	-9.070225	2.728953
1	0	-1.806526	-8.063249	1.105162
1	0	-0.567203	-8.057998	2.346841
1	0	-1.973103	-6.522748	3.743230
1	0	-3.212143	-6.528068	2.501213
1	0	-1.588419	-5.522241	0.877690
1	0	-0.350336	-5.515258	2.120726
1	0	-1.757841	-3.980539	3.514479
1	0	-2.997443	-3.989350	2.273443
1	0	-1.381864	-2.978878	0.649335
1	0	-0.139687	-2.974653	1.891307
1	0	-1.580163	-1.487469	3.315114
1	0	-2.822325	-1.508334	2.085867
1	0	-0.724900	-0.808869	-0.403826
1	0	-2.432921	-0.729925	0.007620

C12 LARIAT ETHER

Solvent: *n-octanol*
Free Energy: -1826.389941

6	0	-0.830983	-0.133908	0.030385
7	0	-0.630151	-0.143965	1.482668
6	0	0.786225	-0.058480	1.843959
6	0	1.066245	0.458108	3.244302
8	0	0.796685	1.856352	3.325317
6	0	1.185646	2.400857	4.580884
6	0	1.064772	3.903905	4.572557
8	0	-0.295979	4.309808	4.674204
6	0	-0.413322	5.732309	4.717994
6	0	-1.839990	6.184224	4.986797
7	0	-2.751111	6.114606	3.839609
6	0	-3.350102	4.785321	3.665629
6	0	-3.858228	4.502472	2.263174

8	0	-2.753842	4.289306	1.388680
6	0	-3.135642	4.034412	0.042289
6	0	-2.016629	3.305039	-0.660066
8	0	-1.963621	1.971114	-0.170760
6	0	-0.806430	1.254418	-0.585775
1	0	0.094291	1.808220	-0.293679
1	0	-0.798606	1.157751	-1.681046
1	0	-1.063730	3.816569	-0.473849
1	0	-2.201180	3.307836	-1.743473
1	0	-3.345953	4.977895	-0.479490
1	0	-4.044087	3.419610	0.013347
1	0	-4.486738	5.318006	1.884134
1	0	-4.477057	3.595628	2.291185
1	0	-4.183169	4.613621	4.365459
1	0	-2.589481	4.039019	3.894136
6	0	-3.731140	7.213816	3.836355
6	0	-4.725797	7.289177	5.006737
6	0	-5.670819	8.487319	4.879073
6	0	-6.677646	8.597160	6.027098
6	0	-7.625977	9.792283	5.902128
6	0	-8.633327	9.897758	7.049980
6	0	-9.585672	11.089746	6.925837
1	0	-8.999934	12.016096	6.876600
1	0	-10.127786	11.020521	5.974555
6	0	-10.593880	11.192043	8.073194
1	0	-10.051837	11.262078	9.024457
6	0	-11.548174	12.382484	7.949176
1	0	-10.963867	13.309780	7.900478
1	0	-12.089858	12.312747	6.997669
6	0	-12.556963	12.483347	9.095795
1	0	-12.016639	12.554496	10.048128
6	0	-13.512720	13.672393	8.972197
1	0	-12.930205	14.599847	8.923927
1	0	-14.054414	13.602223	8.021700
6	0	-14.516156	13.763700	10.121538
1	0	-14.007558	13.871730	11.084653
1	0	-15.183681	14.621895	10.002447
1	0	-15.139236	12.865527	10.176350
1	0	-13.141847	11.556322	9.145655
1	0	-11.178593	10.265078	8.122799
1	0	-9.219717	8.971910	7.100697
1	0	-8.090515	9.967455	8.000832
1	0	-7.037348	10.716754	5.852272
1	0	-8.168642	9.724155	4.951087
1	0	-7.267019	7.673379	6.078603
1	0	-6.134276	8.665855	6.977595
1	0	-5.080633	9.410780	4.827581
1	0	-6.214467	8.419806	3.928520
1	0	-5.319316	6.370805	5.057476
1	0	-4.180054	7.361006	5.953591
1	0	-3.164178	8.149588	3.795847
1	0	-4.292394	7.162446	2.899663
1	0	-1.761689	7.233245	5.282994
1	0	-2.223888	5.640329	5.864413
1	0	-0.054362	6.162903	3.774566
1	0	0.223965	6.112502	5.529577

1	0	1.513717	4.308355	3.655976
1	0	1.628642	4.299910	5.428752
1	0	2.235109	2.145870	4.783291
1	0	0.573543	1.976079	5.387795
1	0	2.127813	0.282267	3.467960
1	0	0.479744	-0.077405	4.000895
1	0	1.297746	-1.029760	1.743018
1	0	1.278017	0.619893	1.143834
6	0	-1.357267	-1.234218	2.149840
6	0	-0.981473	-2.677190	1.773134
6	0	-1.834200	-3.705872	2.521157
6	0	-1.508591	-5.155088	2.150496
6	0	-2.364137	-6.187492	2.889041
6	0	-2.046280	-7.634328	2.502958
6	0	-2.901379	-8.670343	3.236893
6	0	-2.586978	-10.115549	2.842023
1	0	-1.526608	-10.319826	3.035707
6	0	-3.441112	-11.153544	3.574291
6	0	-3.128697	-12.597736	3.175180
1	0	-2.068093	-12.804520	3.365734
6	0	-3.980939	-13.637158	3.907216
1	0	-3.837086	-13.524734	4.988172
1	0	-5.041094	-13.432680	3.717348
6	0	-3.661762	-15.075577	3.500621
1	0	-2.616546	-15.324183	3.709536
1	0	-4.286229	-15.792062	4.041901
1	0	-3.830720	-15.232246	2.430645
1	0	-3.272269	-12.713227	2.093511
1	0	-3.298789	-11.039543	4.656134
1	0	-4.501607	-10.948059	3.382607
1	0	-2.727401	-10.231944	1.760186
1	0	-2.761431	-8.552964	4.318666
1	0	-3.961538	-8.465966	3.042317
1	0	-2.182801	-7.756165	1.421213
1	0	-0.986252	-7.836099	2.701196
1	0	-2.227329	-6.063305	3.970440
1	0	-3.424005	-5.985891	2.690197
1	0	-1.639265	-5.287138	1.069308
1	0	-0.448946	-5.351171	2.355996
1	0	-1.701559	-3.570429	3.601725
1	0	-2.894736	-3.512278	2.317874
1	0	-1.108892	-2.822775	0.695043
1	0	0.075466	-2.862957	1.990673
1	0	-1.240321	-1.107204	3.229421
1	0	-2.421135	-1.082291	1.942273
1	0	-0.085269	-0.749534	-0.498692
1	0	-1.807946	-0.572757	-0.185523

C13 LARIAT ETHER

Solvent: *none*
Free Energy: -1904.944684

6	0	0.005126	0.008338	-0.011981
7	0	0.009671	0.004518	1.446234

6	0	1.342968	0.007679	2.030531	1	0	-7.315953	10.210894	5.681113
6	0	1.452452	0.718636	3.371910	1	0	-8.328320	8.991595	4.934895
8	0	1.329572	2.117612	3.195972	1	0	-6.967723	7.190667	6.035820
6	0	1.615977	2.840125	4.378720	1	0	-5.954194	8.411241	6.777469
6	0	1.451844	4.324913	4.139749	1	0	-5.265205	9.219272	4.502860
8	0	0.098556	4.708764	4.304011	1	0	-6.276924	7.996250	3.762891
6	0	-0.092619	6.101128	4.087531	1	0	-4.915037	6.200704	4.860211
6	0	-1.511315	6.525205	4.447600	1	0	-3.904592	7.421652	5.608263
7	0	-2.499480	6.316505	3.395640	1	0	-3.218605	8.264833	3.353150
6	0	-2.889301	4.921723	3.180066	1	0	-4.251653	7.085587	2.583588
6	0	-3.222231	4.603937	1.729770	1	0	-1.474020	7.601299	4.640558
8	0	-2.019621	4.486594	0.993008	1	0	-1.778724	6.043506	5.403297
6	0	-2.203100	4.188503	-0.376592	1	0	0.114812	6.354626	3.040412
6	0	-0.983603	3.454256	-0.887429	1	0	0.610892	6.658233	4.725524
8	0	-1.040005	2.114521	-0.436924	1	0	1.805081	4.569514	3.129368
6	0	0.166443	1.398201	-0.612321	1	0	2.075866	4.875307	4.860375
1	0	0.995224	1.935379	-0.132209	1	0	2.652545	2.640209	4.691093
1	0	0.400780	1.305000	-1.684938	1	0	0.951844	2.529437	5.197001
1	0	-0.079935	3.950481	-0.510083	1	0	2.437038	0.483450	3.806060
1	0	-0.961008	3.488250	-1.987755	1	0	0.692084	0.359253	4.079059
1	0	-2.352392	5.113476	-0.953157	1	0	1.748862	-1.011733	2.158992
1	0	-3.084247	3.550252	-0.522708	1	0	2.018759	0.520743	1.343268
1	0	-3.867581	5.378687	1.291301	6	0	-0.937425	-0.924861	2.055763
1	0	-3.771809	3.652211	1.687619	6	0	-0.708208	-2.428631	1.814432
1	0	-3.751165	4.632304	3.803487	6	0	-1.768540	-3.293468	2.501042
1	0	-2.058071	4.279541	3.468483	6	0	-1.580733	-4.795606	2.273342
6	0	-3.622959	7.252165	3.463299	6	0	-2.644206	-5.658227	2.957623
6	0	-4.510473	7.208627	4.721188	6	0	-2.458374	-7.159980	2.726666
6	0	-5.667159	8.209058	4.649651	6	0	-3.521714	-8.023140	3.410338
6	0	-6.563649	8.199846	5.890488	6	0	-3.336341	-9.524728	3.177956
6	0	-7.719731	9.201000	5.823057	1	0	-2.343409	-9.825605	3.533823
6	0	-8.615941	9.185412	7.063855	6	0	-4.399811	-10.388191	3.861021
6	0	-9.772204	10.186590	7.001354	6	0	-4.215259	-11.889624	3.626943
1	0	-9.368515	11.197110	6.863731	1	0	-3.222355	-12.191363	3.982215
1	0	-10.380825	9.981083	6.112310	6	0	-5.278644	-12.753429	4.309242
6	0	-10.668459	10.165909	8.242042	1	0	-5.270415	-12.553617	5.387857
1	0	-10.059154	10.369293	9.131123	1	0	-6.272131	-12.452489	3.954534
6	0	-11.824266	11.167820	8.183285	6	0	-5.094968	-14.254947	4.074913
1	0	-11.420071	12.178530	8.048630	1	0	-4.102893	-14.556221	4.430001
1	0	-12.433321	10.965447	7.293824	6	0	-6.162244	-15.109525	4.760394
6	0	-12.720258	11.144131	9.424126	1	0	-6.003084	-16.174350	4.573958
1	0	-12.110760	11.345203	10.313624	1	0	-6.154456	-14.957722	5.843483
6	0	-13.875640	12.146363	9.368001	1	0	-7.163192	-14.855755	4.399999
1	0	-13.471978	13.157723	9.235272	1	0	-5.103990	-14.455080	2.997452
1	0	-14.486057	11.946342	8.478735	1	0	-4.223881	-12.090838	2.548729
6	0	-14.771843	12.121799	10.608700	1	0	-4.391028	-10.186799	4.939167
1	0	-14.162345	12.321939	11.497251	1	0	-5.392767	-10.086609	3.505892
6	0	-15.922974	13.126777	10.544049	1	0	-3.344532	-9.727085	2.099973
1	0	-15.549229	14.150092	10.447417	1	0	-3.513384	-7.820509	4.488261
1	0	-16.570844	12.930866	9.684935	1	0	-4.514665	-7.722364	3.054522
1	0	-16.542740	13.083943	11.442934	1	0	-2.466329	-7.363305	1.648870
1	0	-15.176284	11.111846	10.740857	1	0	-1.465423	-7.460301	3.082988
1	0	-13.125011	10.133509	9.557995	1	0	-2.636372	-5.454525	4.035355
1	0	-11.072884	9.155506	8.378354	1	0	-3.637013	-5.357972	2.601035
1	0	-9.020003	8.175445	7.204368	1	0	-1.587576	-5.000826	1.195982
1	0	-8.006602	9.392596	7.952031	1	0	-0.587874	-5.094249	2.631193

1	0	-1.761324	-3.088701	3.578757
1	0	-2.762950	-2.996749	2.145561
1	0	-0.716261	-2.633235	0.738197
1	0	0.283241	-2.721969	2.175934
1	0	-0.951261	-0.737268	3.133734
1	0	-1.935145	-0.654579	1.695904
1	0	0.785801	-0.646137	-0.436640
1	0	-0.952988	-0.384211	-0.359766

C13 LARIAT ETHER

Solvent: *water*
Free Energy: -1904.967531

6	0	-1.577490	-0.278890	0.232967
7	0	-1.295348	-0.346588	1.675108
6	0	0.139757	-0.169557	1.939925
6	0	0.497656	0.189926	3.369553
8	0	0.173831	1.558140	3.643319
6	0	0.527355	1.925358	4.976183
6	0	0.455562	3.418788	5.160806
8	0	-0.896562	3.876664	5.182266
6	0	-0.953463	5.285905	5.427635
6	0	-2.375631	5.795198	5.575881
7	0	-3.173373	5.836560	4.338320
6	0	-3.956541	4.600804	4.171330
6	0	-4.538847	4.385090	2.787741
8	0	-3.500818	4.028527	1.871988
6	0	-3.973907	3.841459	0.539920
6	0	-2.907382	3.147041	-0.267979
8	0	-2.788268	1.801439	0.186547
6	0	-1.641247	1.128069	-0.332329
1	0	-0.740636	1.704413	-0.090958
1	0	-1.712748	1.064889	-1.425970
1	0	-1.949349	3.668308	-0.152460
1	0	-3.182058	3.167102	-1.330134
1	0	-4.209708	4.809549	0.080946
1	0	-4.888195	3.235415	0.548492
1	0	-5.066664	5.272375	2.421148
1	0	-5.267083	3.566215	2.840177
1	0	-4.786966	4.547270	4.890796
1	0	-3.303009	3.756739	4.391663
6	0	-3.997909	7.060996	4.262660
6	0	-5.096521	7.253364	5.317856
6	0	-5.794940	8.606917	5.162951
6	0	-6.913331	8.839260	6.181293
6	0	-7.601207	10.198311	6.034600
6	0	-8.721945	10.431384	7.050162
6	0	-9.405139	11.793207	6.907378
1	0	-8.654176	12.585709	7.012530
1	0	-9.810583	11.888602	5.892698
6	0	-10.527327	12.026205	7.921357
1	0	-10.122554	11.927794	8.936021
6	0	-11.206904	13.390110	7.781321
1	0	-10.454238	14.180535	7.889797

1	0	-11.610647	13.489283	6.766332
6	0	-12.330052	13.622900	8.794274
1	0	-11.926819	13.521969	9.809309
6	0	-13.007448	14.987786	8.656121
1	0	-12.254823	15.778064	8.767310
1	0	-13.410969	15.090419	7.641238
6	0	-14.131453	15.220873	9.667839
1	0	-13.729472	15.118478	10.682231
6	0	-14.799843	16.587540	9.521986
1	0	-14.077663	17.397310	9.662971
1	0	-15.240712	16.707455	8.527810
1	0	-15.597755	16.723401	10.256972
1	0	-14.885071	14.433063	9.556206
1	0	-13.083842	12.833706	8.684541
1	0	-11.279971	11.235584	7.814152
1	0	-9.472769	9.638536	6.946795
1	0	-8.314883	10.337027	8.064288
1	0	-6.852561	10.993563	6.135203
1	0	-8.009099	10.288486	5.020432
1	0	-7.661442	8.043365	6.083264
1	0	-6.502597	8.750619	7.194350
1	0	-5.052267	9.408756	5.254384
1	0	-6.208096	8.687063	4.150057
1	0	-5.841832	6.456169	5.238222
1	0	-4.666121	7.182843	6.322285
1	0	-3.308884	7.908687	4.314508
1	0	-4.452867	7.103553	3.270288
1	0	-2.273299	6.815856	5.950500
1	0	-2.880790	5.224994	6.368416
1	0	-0.442346	5.816764	4.615056
1	0	-0.415840	5.501911	6.360809
1	0	1.007361	3.923797	4.358146
1	0	0.940058	3.668975	6.113304
1	0	1.559026	1.612877	5.180868
1	0	-0.128976	1.416197	5.693079
1	0	1.577681	0.049497	3.502290
1	0	-0.009900	-0.458242	4.092344
1	0	0.715450	-1.068111	1.672607
1	0	0.510743	0.631222	1.297848
6	0	-1.852960	-1.573147	2.279277
6	0	-1.336039	-2.926863	1.770164
6	0	-2.035586	-4.094827	2.470606
6	0	-1.556938	-5.468365	1.995126
6	0	-2.258433	-6.636291	2.692042
6	0	-1.782235	-8.009968	2.214551
6	0	-2.483309	-9.178622	2.910641
6	0	-2.007508	-10.552049	2.432035
1	0	-0.925444	-10.634346	2.591467
6	0	-2.708589	-11.721059	3.127494
6	0	-2.233210	-13.094236	2.647778
1	0	-1.151105	-13.176910	2.806779
6	0	-2.934002	-14.263438	3.342624
1	0	-2.776931	-14.187445	4.425622
1	0	-4.016407	-14.182383	3.184008
6	0	-2.459114	-15.636644	2.862935
1	0	-1.377904	-15.719071	3.021797

6	0	-3.165198	-16.797250	3.563120
1	0	-2.804634	-17.763132	3.199258
1	0	-2.998242	-16.766815	4.644015
1	0	-4.245676	-16.761761	3.394465
1	0	-2.616518	-15.714005	1.781139
1	0	-2.390421	-13.172080	1.565054
1	0	-2.551375	-11.643178	4.210195
1	0	-3.790689	-11.638525	2.968523
1	0	-2.164248	-10.630506	1.349293
1	0	-2.326452	-9.099891	3.993339
1	0	-3.565375	-9.096373	2.751268
1	0	-1.938675	-8.089177	1.131827
1	0	-0.700202	-8.091955	2.374343
1	0	-2.102076	-6.556637	3.774730
1	0	-3.340382	-6.554156	2.531958
1	0	-1.712170	-5.548914	0.912432
1	0	-0.475171	-5.549088	2.156548
1	0	-1.878870	-4.013552	3.553091
1	0	-3.117869	-4.015773	2.311411
1	0	-1.498292	-3.006561	0.690439
1	0	-0.257044	-3.008238	1.933329
1	0	-1.693977	-1.519665	3.358938
1	0	-2.935918	-1.535272	2.129373
1	0	-0.835850	-0.837390	-0.358470
1	0	-2.543821	-0.754820	0.052427

C13 LARIAT ETHER

Solvent: *n-octanol*
Free Energy: -1904.989861

6	0	-0.860923	-0.147110	0.103287
7	0	-0.671049	-0.165725	1.556912
6	0	0.742358	-0.081355	1.930076
6	0	1.010714	0.432504	3.333766
8	0	0.744636	1.831493	3.414439
6	0	1.125029	2.372924	4.674005
6	0	1.012302	3.876615	4.666236
8	0	-0.346878	4.290055	4.758302
6	0	-0.456371	5.713181	4.802235
6	0	-1.882206	6.173206	5.061478
7	0	-2.786530	6.106451	3.908751
6	0	-3.394127	4.781033	3.735554
6	0	-3.896610	4.497504	2.331240
8	0	-2.788885	4.277830	1.462705
6	0	-3.165152	4.022592	0.114903
6	0	-2.042771	3.293976	-0.582800
8	0	-1.991160	1.959749	-0.094140
6	0	-0.831458	1.244567	-0.504854
1	0	0.067483	1.796382	-0.203649
1	0	-0.816146	1.153765	-1.600547
1	0	-1.091001	3.805966	-0.392093
1	0	-2.222507	3.297208	-1.667008
1	0	-3.373858	4.965917	-0.407837
1	0	-4.073170	3.407282	0.082375

1	0	-4.519696	5.314984	1.947433
1	0	-4.519587	3.593456	2.358162
1	0	-4.232181	4.617217	4.431338
1	0	-2.639995	4.030144	3.970455
6	0	-3.758018	7.213097	3.894790
6	0	-4.759892	7.299880	5.058150
6	0	-5.696993	8.503040	4.919401
6	0	-6.710173	8.623193	6.060746
6	0	-7.652171	9.822170	5.924965
6	0	-8.665499	9.936868	7.066627
6	0	-9.612560	11.131990	6.932306
1	0	-9.023081	12.055940	6.882599
6	0	-10.149721	11.060954	5.978352
6	0	-10.626552	11.242442	8.073786
1	0	-10.089297	11.313828	9.027671
6	0	-11.575746	12.435995	7.940660
1	0	-10.987766	13.360956	7.892168
1	0	-12.112487	12.365192	6.986456
6	0	-12.590336	12.543873	9.081835
1	0	-12.053655	12.614402	10.036119
6	0	-13.540009	13.736854	8.949901
1	0	-12.953465	14.663001	8.903234
1	0	-14.077378	13.667864	7.995744
6	0	-14.555491	13.843995	10.090059
1	0	-14.020284	13.913500	11.044284
6	0	-15.498380	15.038796	9.950082
1	0	-14.943814	15.982317	9.937174
1	0	-16.075203	14.982375	9.021631
1	0	-16.210389	15.085503	10.779021
1	0	-15.144002	12.920255	10.136663
1	0	-13.178276	11.618854	9.130063
1	0	-11.214999	10.317844	8.123602
1	0	-9.255824	9.013563	7.118101
1	0	-8.127684	10.008517	8.020170
1	0	-7.059083	10.743755	5.874542
1	0	-8.189687	9.752346	4.971128
1	0	-7.304286	7.702488	6.112892
1	0	-6.172163	8.693552	7.014167
1	0	-5.101200	9.422882	4.867733
1	0	-6.235118	8.434579	3.965781
1	0	-5.359313	6.385353	5.108990
1	0	-4.219912	7.372446	6.008253
1	0	-3.183667	8.144382	3.854830
1	0	-4.313247	7.162552	2.954475
1	0	-1.800021	7.222245	5.356565
1	0	-2.274621	5.632863	5.937507
1	0	-0.088492	6.142269	3.861548
1	0	0.177496	6.089286	5.618404
1	0	1.470270	4.279428	3.753409
1	0	1.571953	4.268720	5.526978
1	0	2.171274	2.112231	4.885529
1	0	0.503548	1.950585	5.475011
1	0	2.069592	0.253272	3.567263
1	0	0.415400	-0.102392	4.083902
1	0	1.254173	-1.052701	1.831733
1	0	1.240376	0.598021	1.235360

6	0	-1.402049	-1.261083	2.211506
6	0	-1.024584	-2.701039	1.825024
6	0	-1.882648	-3.735816	2.558437
6	0	-1.557580	-5.181563	2.173990
6	0	-2.421103	-6.220568	2.893777
6	0	-2.105373	-7.663141	2.490337
6	0	-2.970563	-8.706385	3.201882
6	0	-2.659600	-10.146584	2.786443
1	0	-1.602055	-10.359362	2.986362
6	0	-3.525588	-11.192427	3.493171
6	0	-3.217572	-12.631116	3.070408
1	0	-2.159900	-12.846283	3.267099
6	0	-4.083189	-13.678380	3.774949
1	0	-3.948666	-13.588597	4.860200
1	0	-5.141423	-13.463753	3.580033
6	0	-3.777295	-15.116460	3.349400
1	0	-2.720424	-15.333086	3.544094
6	0	-4.646234	-16.155015	4.058292
1	0	-4.403402	-17.170015	3.731030
1	0	-4.506550	-16.115373	5.143112
1	0	-5.708803	-15.987799	3.856039
1	0	-3.913128	-15.208180	2.265447
1	0	-3.351252	-12.724195	1.985451
1	0	-3.391864	-11.098500	4.578012
1	0	-4.583228	-10.977500	3.296246
1	0	-2.790586	-10.244331	1.701573
1	0	-2.838386	-8.606547	4.286386
1	0	-4.028273	-8.494156	3.002437
1	0	-2.233244	-7.769094	1.405865
1	0	-1.047800	-7.871780	2.694486
1	0	-2.291000	-6.111040	3.977580
1	0	-3.478987	-6.012914	2.690644
1	0	-1.680554	-5.300822	1.090413
1	0	-0.499933	-5.382545	2.384961
1	0	-1.755357	-3.611785	3.641008
1	0	-2.941807	-3.538368	2.351690
1	0	-1.145470	-2.837317	0.744988
1	0	0.030930	-2.889260	2.047334
1	0	-1.290782	-1.142719	3.292669
1	0	-2.464797	-1.107346	1.999440
1	0	-0.111455	-0.759894	-0.423795
1	0	-1.836369	-0.584434	-0.122371

C14 LARIAT ETHER

Solvent: *none*
Free Energy: -1983.543206

6	0	0.034893	0.008738	-0.008725
7	0	0.030541	0.014809	1.449466
6	0	1.360228	0.010758	2.041802
6	0	1.467449	0.728622	3.379666
8	0	1.353886	2.127253	3.195149
6	0	1.639323	2.855005	4.374900
6	0	1.482420	4.339095	4.127004

8	0	0.129921	4.729072	4.283001
6	0	-0.055291	6.120819	4.057414
6	0	-1.474106	6.551708	4.408876
7	0	-2.458092	6.341841	3.353227
6	0	-2.849316	4.947167	3.139277
6	0	-3.174486	4.626130	1.687932
8	0	-1.967781	4.503475	0.958680
6	0	-2.143560	4.200489	-0.410904
6	0	-0.925386	3.456000	-0.910018
8	0	-0.993620	2.118845	-0.453526
6	0	0.209133	1.393560	-0.617119
1	0	1.038531	1.928264	-0.135312
1	0	0.449321	1.291991	-1.687680
1	0	-0.021058	3.948110	-0.528882
1	0	-0.895145	3.484619	-2.010316
1	0	-2.282782	5.123848	-0.992516
1	0	-3.027774	3.567335	-0.560431
1	0	-3.815117	5.401404	1.243515
1	0	-3.726262	3.675719	1.645169
1	0	-3.715348	4.661186	3.758452
1	0	-2.021136	4.304060	3.434306
6	0	-3.580561	7.279227	3.414131
6	0	-4.472802	7.239849	4.668776
6	0	-5.629014	8.240327	4.590282
6	0	-6.530183	8.233825	5.827730
6	0	-7.686289	9.234525	5.754062
6	0	-8.587234	9.220286	6.991433
6	0	-9.743980	10.220560	6.923390
1	0	-9.340570	11.231300	6.786575
1	0	-10.348913	10.013829	6.032115
6	0	-10.645043	10.199935	8.160585
1	0	-10.039339	10.404374	9.051884
6	0	-11.801661	11.200638	8.097030
1	0	-11.398040	12.211788	7.963910
1	0	-12.406966	10.997503	7.205176
6	0	-12.702406	11.175827	9.334381
1	0	-12.096575	11.377445	10.226223
6	0	-13.858918	12.176842	9.273923
1	0	-13.455125	13.188232	9.142977
1	0	-14.464637	11.975931	8.381817
6	0	-14.759408	12.149874	10.511173
1	0	-14.154347	12.350434	11.403979
6	0	-15.916167	13.150751	10.452878
1	0	-15.512096	14.161160	10.323009
1	0	-16.521327	12.950336	9.561431
6	0	-16.809986	13.115441	11.693473
1	0	-16.240123	13.346964	12.597818
1	0	-17.624684	13.839949	11.620682
1	0	-17.256796	12.126625	11.830519
1	0	-15.164294	11.138810	10.642412
1	0	-13.106433	10.164722	9.466570
1	0	-11.049017	9.189221	8.295942
1	0	-8.991184	8.210254	7.131824
1	0	-7.981379	9.429042	7.881622
1	0	-7.282348	10.244356	5.612145
1	0	-8.291335	9.023484	4.863870

1	0	-6.934608	7.224881	5.973733
1	0	-5.924066	8.447199	6.716523
1	0	-5.226403	9.250165	4.442723
1	0	-6.235381	8.025494	3.701682
1	0	-4.878200	6.232462	4.809252
1	0	-3.870151	7.455239	5.557471
1	0	-3.174483	8.291094	3.302931
1	0	-4.206104	7.111112	2.532456
1	0	-1.434024	7.628540	4.597157
1	0	-1.747568	6.075205	5.365466
1	0	0.157600	6.367366	3.009743
1	0	0.647386	6.679192	4.695191
1	0	1.841171	4.576678	3.116892
1	0	2.105395	4.890955	4.847417
1	0	2.673872	2.652302	4.692138
1	0	0.970869	2.551832	5.192482
1	0	2.448454	0.489849	3.819912
1	0	0.701505	0.377909	4.085157
1	0	1.757354	-1.011043	2.178587
1	0	2.044062	0.514523	1.355602
6	0	-0.928762	-0.901343	2.059788
6	0	-0.710569	-2.409036	1.833128
6	0	-1.785746	-3.258486	2.515853
6	0	-1.607918	-4.764303	2.305055
6	0	-2.688052	-5.610976	2.983136
6	0	-2.511507	-7.116591	2.770780
6	0	-3.592815	-7.963391	3.446695
6	0	-3.416167	-9.468985	3.234273
1	0	-2.432161	-9.774052	3.610765
6	0	-4.498702	-10.315818	3.908166
6	0	-4.322355	-11.821333	3.694966
1	0	-3.338896	-12.126984	4.072381
6	0	-5.405894	-12.668233	4.367166
1	0	-5.416134	-12.454415	5.442937
1	0	-6.389320	-12.362730	3.989487
6	0	-5.229661	-14.173583	4.154182
1	0	-4.246714	-14.480396	4.532461
6	0	-6.313349	-15.021136	4.825352
6	0	-6.128510	-16.523614	4.606961
1	0	-5.169822	-16.866065	5.006758
1	0	-6.916830	-17.099463	5.097769
1	0	-6.149014	-16.773685	3.542425
1	0	-6.323729	-14.807286	5.900160
1	0	-7.295420	-14.715604	4.446887
1	0	-5.219156	-14.388508	3.078493
1	0	-4.312389	-12.035117	2.619214
1	0	-4.507544	-10.101771	4.983879
1	0	-5.482631	-10.010467	3.531743
1	0	-3.407338	-9.683417	2.158631
1	0	-3.600298	-7.748610	4.522271
1	0	-4.577345	-7.658647	3.071386
1	0	-2.504442	-7.331275	1.695182
1	0	-1.526839	-7.421465	3.145732
1	0	-2.693871	-5.395868	4.058664
1	0	-3.673155	-5.306435	2.609234
1	0	-1.602121	-4.979937	1.229724

1	0	-0.622587	-5.067948	2.679126
1	0	-1.789222	-3.043217	3.591542
1	0	-2.773501	-2.957097	2.146038
1	0	-0.709449	-2.622518	0.758579
1	0	0.274430	-2.708194	2.207272
1	0	-0.949186	-0.704367	3.135982
1	0	-1.921406	-0.625778	1.690070
1	0	0.813771	-0.653729	-0.424141
1	0	-0.923636	-0.379800	-0.359855

C14 LARIAT ETHER

Solvent: *water*
Free Energy: -1983.565171

6	0	-1.728516	-0.343707	0.289152
7	0	-1.436625	-0.418213	1.729034
6	0	-0.000296	-0.238299	1.985184
6	0	0.366107	0.114058	3.414427
8	0	0.040144	1.479764	3.697945
6	0	0.401749	1.840870	5.030311
6	0	0.325990	3.333007	5.223587
8	0	-1.027596	3.785932	5.256859
6	0	-1.087684	5.193601	5.510305
6	0	-2.510641	5.697153	5.670114
7	0	-3.316347	5.741774	4.437807
6	0	-4.098296	4.505226	4.271078
6	0	-4.690277	4.294445	2.890810
8	0	-3.658078	3.945615	1.965591
6	0	-4.140306	3.764217	0.636028
6	0	-3.076851	3.078941	-0.183675
8	0	-2.948840	1.731207	0.261971
6	0	-1.801918	1.066129	-0.267751
1	0	-0.902495	1.645192	-0.028495
1	0	-1.879808	1.008927	-1.361282
1	0	-2.120195	3.603547	-0.072009
1	0	-3.359340	3.104136	-1.243669
1	0	-4.383431	4.733953	0.184400
1	0	-5.052033	3.154372	0.647870
1	0	-5.223531	5.181880	2.532556
1	0	-5.415638	3.473113	2.944713
1	0	-4.923379	4.446840	4.996319
1	0	-3.441440	3.661527	4.482943
6	0	-4.143255	6.965118	4.371787
6	0	-5.236015	7.151555	5.434102
6	0	-5.935052	8.506026	5.290458
6	0	-7.047612	8.733464	6.316273
6	0	-7.734126	10.094439	6.181595
6	0	-8.848646	10.323606	7.204870
6	0	-9.528908	11.688151	7.074660
1	0	-8.775085	12.477848	7.180461
1	0	-9.939880	11.791111	6.062945
6	0	-10.644559	11.918104	8.096531
1	0	-10.234370	11.811540	9.108196
6	0	-11.320041	13.285310	7.969404

1	0	-10.563795	14.072248	8.078421
1	0	-11.729429	13.392503	6.957484
6	0	-12.436240	13.515875	8.990521
1	0	-12.027373	13.406644	10.002426
6	0	-13.108781	14.884677	8.865079
1	0	-12.351138	15.670012	8.975996
1	0	-13.517283	14.994313	7.853056
6	0	-14.225163	15.115792	9.885477
1	0	-13.818117	15.006162	10.898222
6	0	-14.896668	16.485059	9.761292
1	0	-14.138843	17.268816	9.873029
1	0	-15.304448	16.595445	8.750062
6	0	-16.010081	16.705564	10.784770
1	0	-15.626451	16.635089	11.807025
1	0	-16.469422	17.691075	10.670341
1	0	-16.800326	15.956679	10.676066
1	0	-14.984654	14.332062	9.774647
1	0	-13.193811	12.730424	8.880139
1	0	-11.400537	11.130804	7.988350
1	0	-9.602087	9.533370	7.100554
1	0	-8.436190	10.221652	8.216079
1	0	-6.983531	10.887796	6.282652
1	0	-8.147580	10.191358	5.170304
1	0	-7.797373	7.939223	6.217450
1	0	-6.631482	8.638072	7.326511
1	0	-5.191589	9.307114	5.382057
1	0	-6.353813	8.591802	4.280328
1	0	-5.981739	6.354757	5.354256
1	0	-4.799997	7.075551	6.435706
1	0	-3.455255	7.813670	4.423112
1	0	-4.603994	7.011097	3.382241
1	0	-2.409452	6.716235	6.049298
1	0	-3.008814	5.121200	6.462887
1	0	-0.583477	5.730653	4.697483
1	0	-0.544991	5.406329	6.441297
1	0	0.870387	3.844369	4.419897
1	0	0.816166	3.579773	6.174063
1	0	1.435898	1.530845	5.226050
1	0	-0.247794	1.325521	5.748974
1	0	1.447386	-0.023948	3.539210
1	0	-0.134797	-0.539661	4.136863
1	0	0.576276	-1.133543	1.708835
1	0	0.363976	0.567291	1.345289
6	0	-1.986451	-1.649730	2.330256
6	0	-1.467848	-2.999087	1.811372
6	0	-2.161008	-4.172941	2.508307
6	0	-1.678914	-5.542439	2.024730
6	0	-2.374771	-6.716186	2.717499
6	0	-1.894493	-8.085883	2.232710
6	0	-2.590265	-9.260262	2.924475
6	0	-2.110047	-10.629792	2.439145
1	0	-1.027515	-10.708885	2.597015
6	0	-2.806159	-11.804426	3.130126
6	0	-2.326314	-13.173798	2.644019
1	0	-1.243805	-13.253288	2.801789
6	0	-3.022696	-14.348526	3.334547

1	0	-2.864873	-14.275167	4.417494
1	0	-4.105227	-14.269144	3.176801
6	0	-2.543101	-15.717683	2.848414
1	0	-1.460574	-15.798796	3.006207
6	0	-3.239104	-16.892777	3.538389
6	0	-2.752779	-18.255247	3.045481
1	0	-1.679808	-18.378594	3.220558
1	0	-3.268051	-19.072942	3.556546
1	0	-2.928107	-18.372404	1.971858
1	0	-3.081258	-16.819432	4.620399
1	0	-4.320683	-16.813303	3.380559
1	0	-2.700900	-15.792701	1.765448
1	0	-2.484085	-13.247404	1.561095
1	0	-2.648191	-11.730679	4.213016
1	0	-3.888713	-11.725109	2.972552
1	0	-2.267709	-10.703938	1.356231
1	0	-2.432245	-9.185786	4.007306
1	0	-3.672844	-9.181312	2.766916
1	0	-2.052450	-8.160558	1.149884
1	0	-0.811912	-8.164759	2.390339
1	0	-2.216604	-6.641030	3.800247
1	0	-3.457322	-6.637254	2.559888
1	0	-1.836518	-5.618099	0.942024
1	0	-0.596490	-5.620294	2.183124
1	0	-2.001194	-4.096363	3.590684
1	0	-3.244057	-4.096980	2.352870
1	0	-1.634451	-3.073274	0.731911
1	0	-0.387938	-3.078234	1.969505
1	0	-1.821416	-1.601119	3.409246
1	0	-3.070376	-1.614810	2.186807
1	0	-0.988492	-0.895830	-0.310223
1	0	-2.694039	-0.822627	0.112255

C14 LARIAT ETHER

Solvent: *n-octanol*
Free Energy: -1983.589595

6	0	-1.728516	-0.343707	0.289152
7	0	-1.436625	-0.418213	1.729034
6	0	-0.000296	-0.238299	1.985184
6	0	0.366107	0.114058	3.414427
8	0	0.040144	1.479764	3.697945
6	0	0.401749	1.840870	5.030311
6	0	0.325990	3.333007	5.223587
8	0	-1.027596	3.785932	5.256859
6	0	-1.087684	5.193601	5.510305
6	0	-2.510641	5.697153	5.670114
7	0	-3.316347	5.741774	4.437807
6	0	-4.098296	4.505226	4.271078
6	0	-4.690277	4.294445	2.890810
8	0	-3.658078	3.945615	1.965591
6	0	-4.140306	3.764217	0.636028
6	0	-3.076851	3.078941	-0.183675
8	0	-2.948840	1.731207	0.261971

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6	0	-1.801918	1.066129	-0.267751		1	0	-0.583477	5.730653	4.697483
1	0	-0.902495	1.645192	-0.028495		1	0	-0.544991	5.406329	6.441297
1	0	-1.879808	1.008927	-1.361282		1	0	0.870387	3.844369	4.419897
1	0	-2.120195	3.603547	-0.072009		1	0	0.816166	3.579773	6.174063
1	0	-3.359340	3.104136	-1.243669		1	0	1.435898	1.530845	5.226050
1	0	-4.383431	4.733953	0.184400		1	0	-0.247794	1.325521	5.748974
1	0	-5.052033	3.154372	0.647870		1	0	1.447386	-0.023948	3.539210
1	0	-5.223531	5.181880	2.532556		1	0	-0.134797	-0.539661	4.136863
1	0	-5.415638	3.473113	2.944713		1	0	0.576276	-1.133543	1.708835
1	0	-4.923379	4.446840	4.996319		1	0	0.363976	0.567291	1.345289
1	0	-3.441440	3.661527	4.482943		6	0	-1.986451	-1.649730	2.330256
6	0	-4.143255	6.965118	4.371787		6	0	-1.467848	-2.999087	1.811372
6	0	-5.236015	7.151555	5.434102		6	0	-2.161008	-4.172941	2.508307
6	0	-5.935052	8.506026	5.290458		6	0	-1.678914	-5.542439	2.024730
6	0	-7.047612	8.733464	6.316273		6	0	-2.374771	-6.716186	2.717499
6	0	-7.734126	10.094439	6.181595		6	0	-1.894493	-8.085883	2.232710
6	0	-8.848646	10.323606	7.204870		6	0	-2.590265	-9.260262	2.924475
6	0	-9.528908	11.688151	7.074660		6	0	-2.110047	-10.629792	2.439145
1	0	-8.775085	12.477848	7.180461		1	0	-1.027515	-10.708885	2.597015
1	0	-9.939880	11.791111	6.062945		6	0	-2.806159	-11.804426	3.130126
6	0	-10.644559	11.918104	8.096531		6	0	-2.326314	-13.173798	2.644019
1	0	-10.234370	11.811540	9.108196		1	0	-1.243805	-13.253288	2.801789
6	0	-11.320041	13.285310	7.969404		6	0	-3.022696	-14.348526	3.334547
1	0	-10.563795	14.072248	8.078421		1	0	-2.864873	-14.275167	4.417494
1	0	-11.729429	13.392503	6.957484		1	0	-4.105227	-14.269144	3.176801
6	0	-12.436240	13.515875	8.990521		6	0	-2.543101	-15.717683	2.848414
1	0	-12.027373	13.406644	10.002426		1	0	-1.460574	-15.798796	3.006207
6	0	-13.108781	14.884677	8.865079		6	0	-3.239104	-16.892777	3.538389
1	0	-12.351138	15.670012	8.975996		6	0	-2.752779	-18.255247	3.045481
1	0	-13.517283	14.994313	7.853056		1	0	-1.679808	-18.378594	3.220558
6	0	-14.225163	15.115792	9.885477		1	0	-3.268051	-19.072942	3.556546
1	0	-13.818117	15.006162	10.898222		1	0	-2.928107	-18.372404	1.971858
6	0	-14.896668	16.485059	9.761292		1	0	-3.081258	-16.819432	4.620399
1	0	-14.138843	17.268816	9.873029		1	0	-4.320683	-16.813303	3.380559
1	0	-15.304448	16.595445	8.750062		1	0	-2.700900	-15.792701	1.765448
6	0	-16.010081	16.705564	10.784770		1	0	-2.484085	-13.247404	1.561095
1	0	-15.626451	16.635089	11.807025		1	0	-2.648191	-11.730679	4.213016
1	0	-16.469422	17.691075	10.670341		1	0	-3.888713	-11.725109	2.972552
1	0	-16.800326	15.956679	10.676066		1	0	-2.267709	-10.703938	1.356231
1	0	-14.984654	14.332062	9.774647		1	0	-2.432245	-9.185786	4.007306
1	0	-13.193811	12.730424	8.880139		1	0	-3.672844	-9.181312	2.766916
1	0	-11.400537	11.130804	7.988350		1	0	-2.052450	-8.160558	1.149884
1	0	-9.602087	9.533370	7.100554		1	0	-0.811912	-8.164759	2.390339
1	0	-8.436190	10.221652	8.216079		1	0	-2.216604	-6.641030	3.800247
1	0	-6.983531	10.887796	6.282652		1	0	-3.457322	-6.637254	2.559888
1	0	-8.147580	10.191358	5.170304		1	0	-1.836518	-5.618099	0.942024
1	0	-7.797373	7.939223	6.217450		1	0	-0.596490	-5.620294	2.183124
1	0	-6.631482	8.638072	7.326511		1	0	-2.001194	-4.096363	3.590684
1	0	-5.191589	9.307114	5.382057		1	0	-3.244057	-4.096980	2.352870
1	0	-6.353813	8.591802	4.280328		1	0	-1.634451	-3.073274	0.731911
1	0	-5.981739	6.354757	5.354256		1	0	-0.387938	-3.078234	1.969505
1	0	-4.799997	7.075551	6.435706		1	0	-1.821416	-1.601119	3.409246
1	0	-3.455255	7.813670	4.423112		1	0	-3.070376	-1.614810	2.186807
1	0	-4.603994	7.011097	3.382241		1	0	-0.988492	-0.895830	-0.310223
1	0	-2.409452	6.716235	6.049298		1	0	-2.694039	-0.822627	0.112255
1	0	-3.008814	5.121200	6.462887						

References:

1.   Gaussian 16, Revision B.01, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, G. A. Petersson, H. Nakatsuji, X. Li, M. Caricato, A. V. Marenich, J. Bloino, B. G. Janesko, R. Gomperts, B. Mennucci, H. P. Hratchian, J. V. Ortiz, A. F. Izmaylov, J. L. Sonnenberg, D. Williams-Young, F. Ding, F. Lipparini, F. Egidi, J. Goings, B. Peng, A. Petrone, T. Henderson, D. Ranasinghe, V. G. Zakrzewski, J. Gao, N. Rega, G. Zheng, W. Liang, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, K. Throssell, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. J. Bearpark, J. J. Heyd, E. N. Brothers, K. N. Kudin, V. N. Staroverov, T. A. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. P. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, J. M. Millam, M. Klene, C. Adamo, R. Cammi, J. W. Ochterski, R. L. Martin, K. Morokuma, O. Farkas, J. B. Foresman, and D. J. Fox, Gaussian, Inc., Wallingford CT, 2016.

2.   (a) Becke, A. D. *Phys. Rev. A* **1988**, 38, 3098-3100.; (b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, 37, 785-789.

3.   Marenich, A. V.; Cramer, C. J.; Truhlar, D. G J. Phys. Chem. B. 2009, 113, 6378-6396

4.   Kim, T.; Park, H. *J. Mol. Graph. Model.* **2015**, 60, 108-117.

Appendix III

**Additional Crown Ether Assay Information**

Normalized changes in DiSC$_3$(5) fluorescence due to the activity of lariat ethers with alkyl chains of 6 to 14 carbons length are shown in Figure A.1. The additions depicted in A are representative for each panel shown (*a*, addition of dye; *b*, addition of *B. subtilis*; *c*, addition of 2 M KCl or NMDG solution; *d*, addition of lariat ether up to 2 µM). Violet traces represent fluorescence intensity when a concentrated KCl solution was added at time *c* until a final concentration of 60 mM, while black traces are the control when the same volume of NMDG buffer solution was added. Cyan and gray traces are similar experiments as the two previously described except the buffer without cells was added at time point *b*. Traces were normalized by dividing by the final averaged fluorescence intensity in the experiments without adding *B. subtilis* cells (cyan and gray traces). Each trace is representative of at least three replicas. In each instance where cell toxicity is observed (Figure A.2, *vide infra*), the corresponding DISC$_3$(5) assay result suggests that this toxicity event is not a result of ionophoric behaviour.

Figure A.1. DISC$_3$(5) assay results for all lariat ethers evaluated in chapter 4.
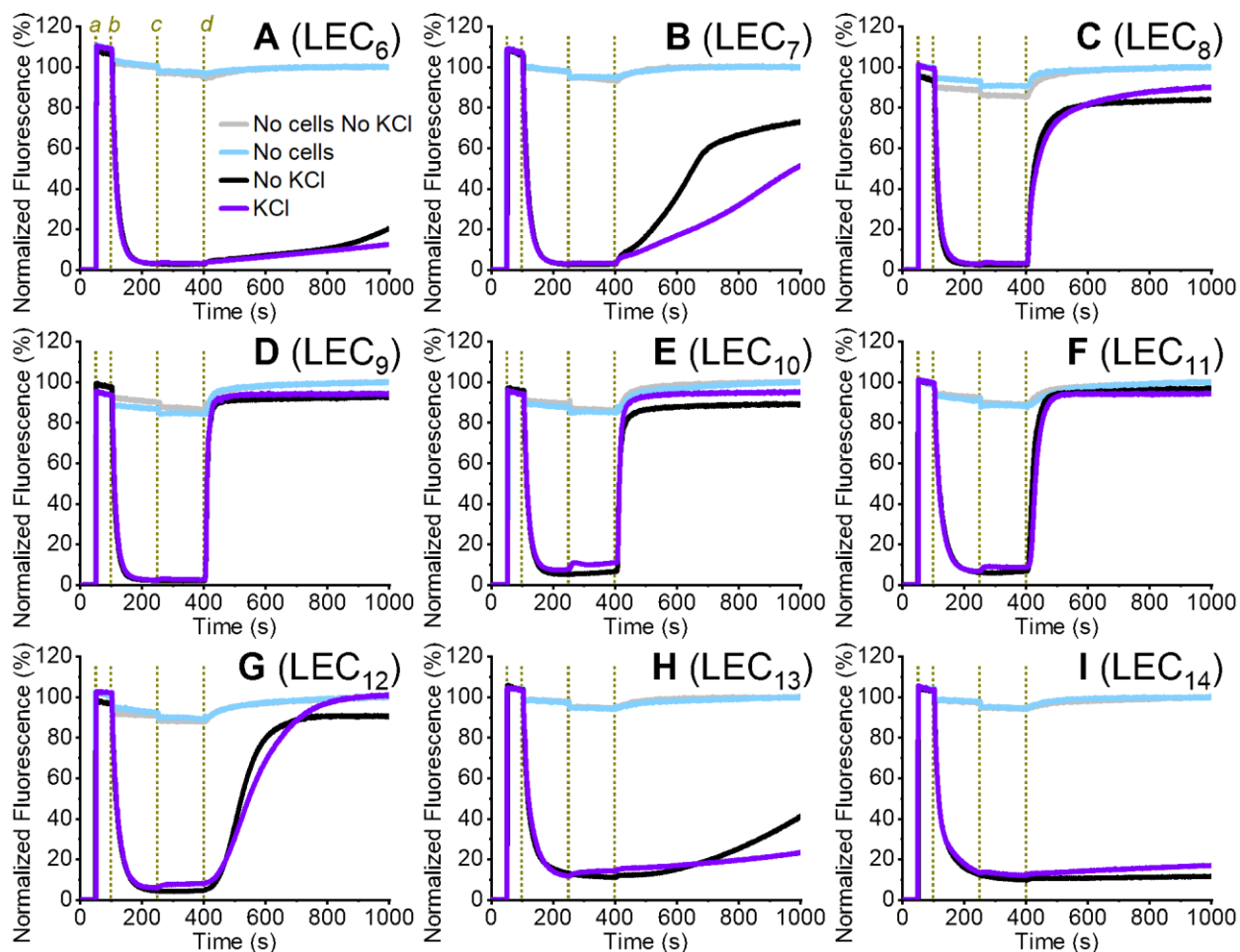
The minimum inhibitory concentrations of the lariat ether series (evaluated in chapter 4) in *B. subtilis*, *E. coli*, and human HEK293 cells are shown in Figure A.2, A. Open circles represent non determined values because they exceed 400 µM and are considered to be inactive. Each compound was assayed a minimum of three times at each concentration tested. Figure A.2, B, depicts the fraction of the $Disc_3(5)$ released after 10 minutes of treatment with 2 µM of each lariat ether in the presence of 60 mM KCl (violet points) and in the absence of KCl (black lines). Indicated values are the average of fluorescence measurements taken after 10 minutes in Figure A.1.

Figure A.2. Comparison of MIC values and $DISC_3(5)$ assay results of lariat ethers.
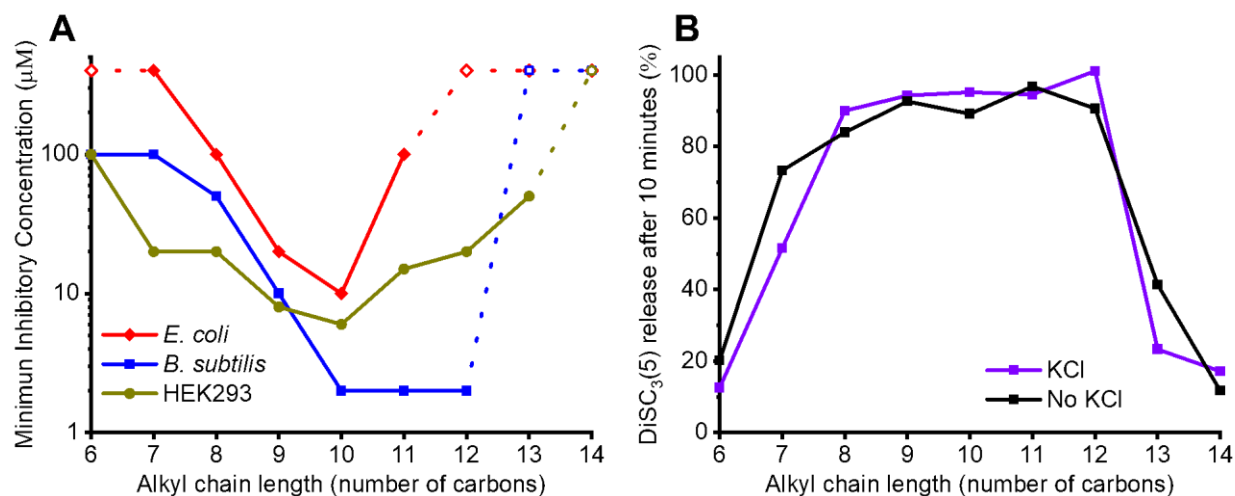
Current through asolectin planar lipid bilayer clamped at 100 mV was recorded in the presence of 2 µM gramicidin (Figure A.3, A) and 2 µM of C-10 lariat ether (Figure A.3, B). In both cases, the solution composition was 150 mM KCl and HEPES 10 buffer adjusted to pH 7. When compared to the data obtained from gramicidin, the C-10 lariat ether does not exhibit single channel conductance as previously reported.

Figure A.3. Planar bilayer experiments with C-10 lariat ether and gramicidin control.