2,5-Cyclohexadienones as a Useful Launching Point for the Synthesis of the Briarane Diterpenoids

and

A Hypervalent Iodine-Mediated Synthesis of Oxazolines

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Dedication

to my wife Danielle, my soon to be daughter Abigail, and my savior Jesus Christ

Abstract

The briarane diterpenoids are a large class of natural products derived from gorgonians and other corals from throughout the world. Despite the extremely large number of briaranes that have been isolated, along with the potent and diverse range of biological activities that have been observed, the total synthesis of the briaranes remains underexplored. A facile synthetic route to the briarane diterpenoids will aid in the further exploration of these molecules. Herein, we will describe a number of synthetic approaches that were evaluated to access a key fragment of the briarane diterpenoids. A key feature of all routes involves the use of 2,5-cyclohexadienone substrates as a diverse platform for the launching of the synthesis. Chapter 1 will provide background information on 2,5-cyclohexadienones. Methods for their synthesis, a survey of their diverse reactivity, and selected examples of their use in natural product synthesis will all be described. Emphasis will be given to reactivity patterns which aided us in our research. Chapter 2 will provide a brief survey of the briarane diterpenoids as well as some of the major biologically active families. Previous synthetic efforts used to access these molecules will also be described. Chapter 3 will describe our efforts to synthesize a key fragment of the briarane diterpenoids (referred to as the briarane stereotetrad) utilizing intermediates containing a bicyclic lactone. Chapter 4 will describe our successful efforts to access the briarane stereotetrad using monocyclic intermediates. The important influence of torsional strain in key steps, as well as a successful route to access the briarane stereotetrad will be described. Chapter 5 will report the results of a separate research project in which an iodine(III) promoted cyclization of *N*-allylamides to form oxazolines was studied. The development of optimum reaction conditions and the evaluation of the substrate scope will be described. Key results that suggest novel mechanistic details for this electrophilic oxidative cyclization will also be described.

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(-) DET	(-) diethyltartarate
^{13}C NMR	carbon 13 nuclear magnetic resonance
^{1}H NMR	proton nuclear magnetic resonance
Ac	acetyl
AcOH	acetic acid
AIBN	azi-diisobutyl nitrile
Ar	aryl
B_2Pin_2	*bis*-pinacolatodiboron
B3LYP	Becke, 3-parameter, Lee, Yang & Parr
BEA-Cl	benzyltriethylammonium chloride
BINAM	1,1'-binapthyl-2,2'-diamine
BINOL	1,1'-bi-2-napthol
bipy	2,2’-bipyridine
Bn	benzyl
Bu	butyl
Bz	benzoyl
cap	caprolactam
CBS	Corey-Bashki-Shibata
Cy	cyclohexyl
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicycloundec-7-ene
DCC	dicyclohexyl carbodiimide
DCDPH	dichlodiphenylhydantoin
DCE	dichloroethane
DCM	dichloromethane
DIBAL-H	diisobutylaluminum hydride
DIPEA	diisopropylethylamine
DMAP	dimethylamino pyridine
DME	dimethoxyethane
DMF	*N*,*N*-Dimethylformamide
DMM	dimethoxymethane
DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
DMS	dimethylsulfide

DMSO	dimethylsulfoxide
DPEN	diphenylethylenediamine
dppp	1,3-bis-(diphenylphosphino)propane
DTS	dimethylhexylsilyl
EC_{50}	effective concentration 50%
ee	enantiomeric excess
ESI+	electrospray ionization (positive mode)
Et2AlTMP	diethylaluminum tetramethylpiperidine
Et_2O	diethylether
EVE	ethyl vinyl ether
Het	heteroaryl
HFIPA	1,1,1,3,3,3-hexafluoroisoproanol
HMDS	hexamethyldisilazide
HMPA	hexamethylphosphoramide
HSQC	heteronuclear single quantum coupling
IBX	2-iodoxybenzoic acid
IC50	half maximal inhibatory concentration
i-Pr	isopropyl
IR	infrared spectroscopy
LANA	ligand-assisted nucleophilic addition
LDA	lithium diisopropylamide
L-DIPT	L-diisopropyl tartarate
MAD	methylaluminum bis(4-bromo-2,6-di-tert-butylphenoxide)
m-CPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
MoOPD	MoO_5PyDMPU
Ms	methanesulfonyl
MS	mass spectrometry
NBS	*N*-bromosuccinimide
NIS	*N*-iodosuccinimide
NOE	nuclear overhauser effect
NOESY	nuclear overhauser effect spectroscpoy
n-Pr	*n*-propyl
Nuc	nucleophile

OTf	trifluoromethanesulfonate
Ph	phenyl
PIDA	phenyliodine diacetate
PIFA	phenyliodine *bis*-trifluoroacetate
PMB	*para*-methoxybenzyl
ppm	parts per million
p-Tol	*para*-toluenesulfonyl
RCM	ring-closing metathesis
ROESY	rotating-frame nuclear overhauser effect correlation spectroscopy
rt	room temperature
SET	single electron transfer
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
t-Bu	*tert*-butyl
TEMPO	(2,2,6,6-tetramethylpiperidin-1-yl)oxyl
TES	triethylsilyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
TFE	trifluoroethyl
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin-layer chromatography
TMEDA	tetramethylethylenediamine
TMS	trimethylsilyl
Tr	triphenylmethyl
TsOH	*para*-toluenesulfonic acid

CHAPTER 1

2,5-CYCLOHEXADIENONES: SYNTHESIS, REACTIVITY & APPLICATIONS IN ORGANIC SYNTHESIS

1.1 Synthesis of 2,5-Cyclohexadienones

2,5-Cyclohexadienones (**Figure 1.1**) are a synthetic motif that has seen increasing use in the synthesis of complex, organic molecules.[1, 2] They are most commonly accessed through the oxidative dearomatization of phenols, though other methods also exist. It is possible to form the 2,4-regioisomer in addition to the 2,5-regioisomer (**Figure 1.1**), though the 2,4 regioisomer is often difficult to isolate due to its propensity to undergo Diels-Alder dimerization. The regiochemical outcome can often be controlled by the substitution pattern on the parent phenol, though judicious choice of oxidant can also enable selective formation.[1]

Figure 1.1: Cyclohexadienone regioisomers

2,5-cyclohexadienone 2,4-cyclohexadienone

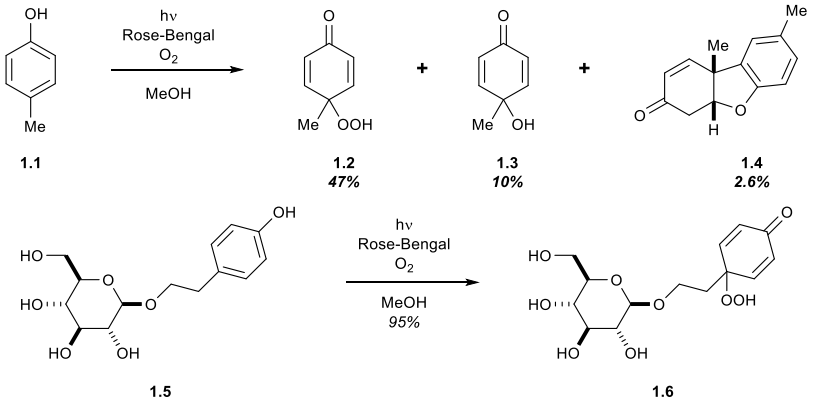
The use of 2,5-cyclohexadienones as synthons in organic synthesis has several advantages. Some advantages include the ready availability of phenols, the wide variety of available reaction conditions on the resulting substrates, and the introduction of a stereogenic carbon atom from an achiral precursor leading to opportunities for stereoselective synthesis. While there are a wide variety of methods to oxidize phenols,

many such oxidants such as electrochemical oxidation and transition metal salts such as Ag_2O[3], MnO_2[4], and $Tl(NO_3)_3$[5] are either inefficient, irreproducible, or highly toxic. However, three major methods have emerged to forge the cyclohexadienone core in a more selective and efficient manner.

1.1.1 Singlet Oxygen Methods

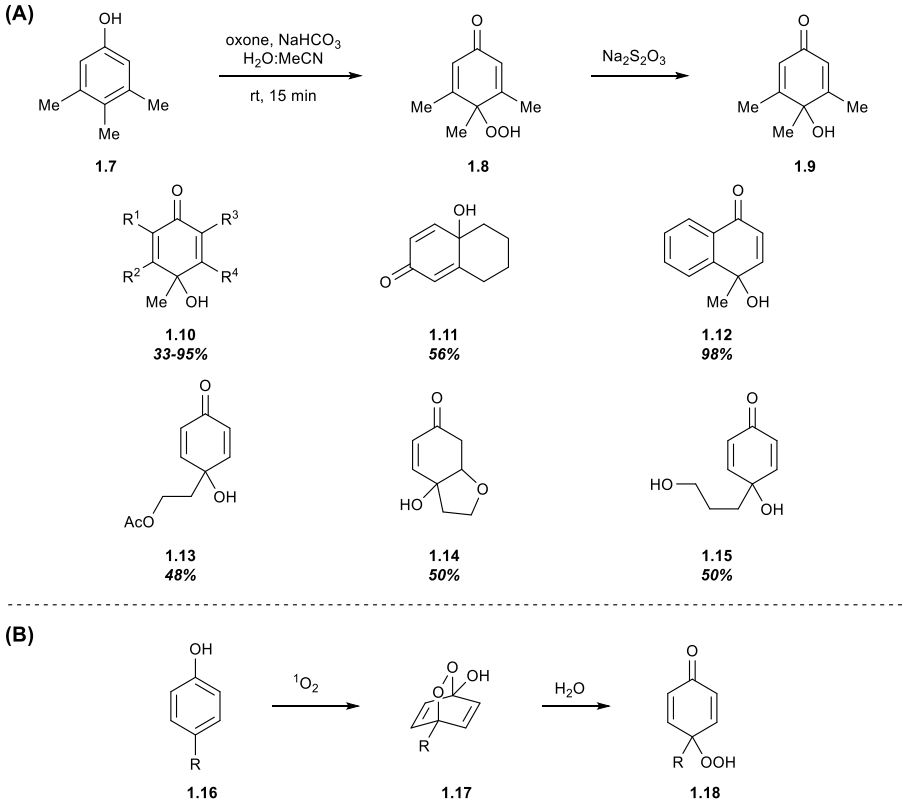
Endo and Hikino reported the oxidative dearomatization of a phenol with singlet oxygen in 1988 (**Scheme 1.1**).[6] In a series of experiments directed toward the synthesis of the natural product rengyol, the authors needed to perform the oxidation of **1.5**. Using *p*-cresol as a model system, the authors irradiated the substrate in the presence of bubbling O_2 with rose-bengal as a sensitizer. They observed a mixture of hydroperoxide **12**, quinol **13**, and side-product **1.4**. The hydroperoxide could be reduced to **1.3** using Me_2S. Further experiments revealed that the oxidation was highly dependent on the solvent, with methanol giving the best results. This method could be applied to the more complex substrate **1.5** in excellent yield.

Scheme 1.1: Endo's photosensitized dearomatization



1.7. Compound **18** could be reduced to quinol **1.9** by quenching the reaction mixture with $Na_2S_2O_3$. The reaction was found to be general for a number of substrates and furnished either the hydroperoxides or quinols in good to excellent yields. Mechanistically, the oxone and base serves as a source singlet oxygen, which forms 1,4-endoperoxide **1.17**. Subsequent attack by water opens the endoperoxide to give peroxyquinol **1.18**.

Scheme 1.2: (A) Carreño & Urbano's $^1O_2$ dearomatization with selected scope; (B) Proposed mechanism

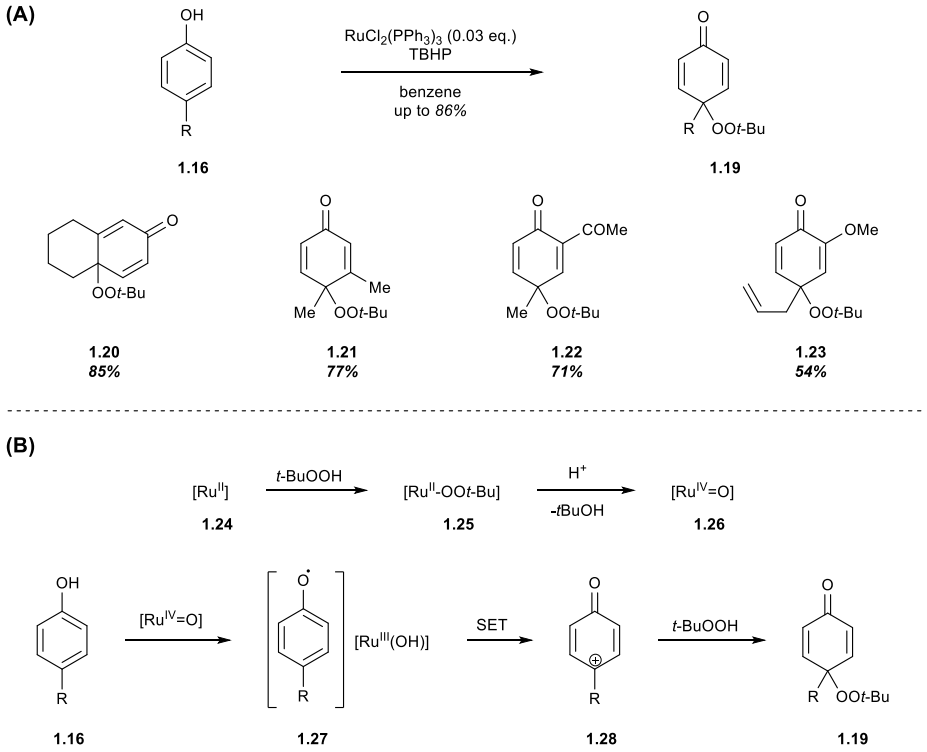


1.1.2. Ru/Rh-Catalyzed Methods

Transition metal-catalyzed oxidative dearomatizations have also been reported. Murahashi disclosed a highly efficient synthesis of mixed-peroxide products **1.19** with *t*-BuOOH catalyzed by Ru complexes (**Scheme 1.3**).[8] A screen of Ru sources found

$RuCl_2(PPh)_3$ to be the ideal catalyst, though simpler systems such as $RuCl_3 \cdot H_2O$ were also viable. The reaction furnished a wide variety of cyclohexadienone substrates in high to very high yields for a variety of electron deficient and electron rich substrates. The authors proposed a mechanism in which Ru-complex **1.26** initiates a single electron transfer (SET) to give phenoxyl radical **1.27**, which rapidly undergoes a subsequent SET to give phenoxenium ion **1.28** that is trapped by a second equivalent of *t*-BuOOH to give the product. They proposed that the rapid second oxidation explains the lack of observed radical-coupling products

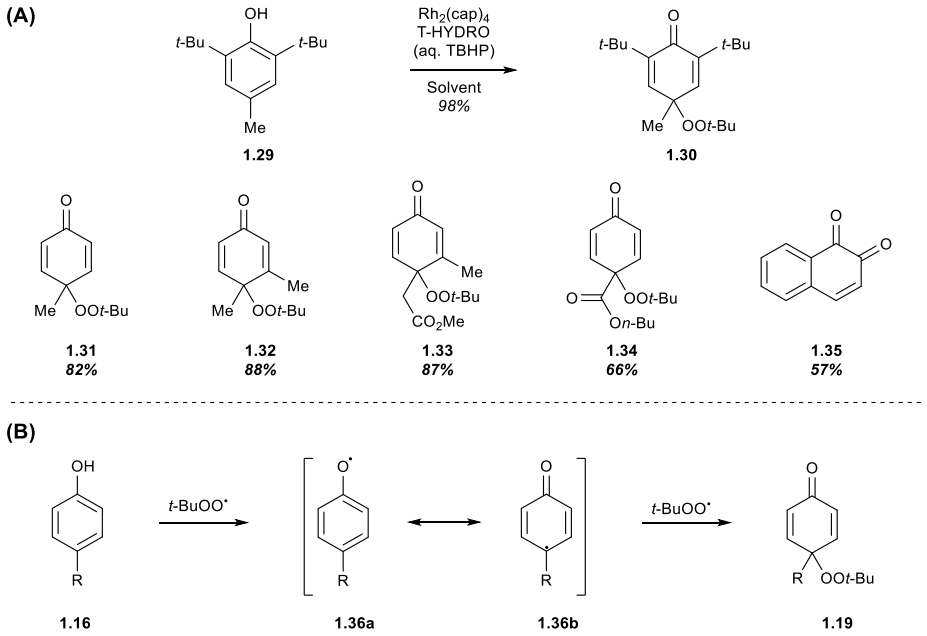
Scheme 1.3: (A) Murahashi's Ru-catalyzed dearomatization; (B) Proposed mechanism



Doyle and coworkers further extended this methodology using $Rh_2(cap)_4$ as a catalyst (**Scheme 1.4**).[9] The use of these conditions allowed the reaction to be performed with the more stable and less expensive T-HYDRO (aqueous *t*-BuOOH) oxidant. The analogous yields were high for a variety of products, often with catalyst

loadings of as low as 0.05%. In contrast to the mechanistic proposal by Murahashi, the authors proposed that the reaction occurs through a radical mechanism, with the $Rh_2(cap)_4$ serving to decompose the T-HYDRO into the *t*-butyl-peroxy radicals (**Scheme 1.4B**). The authors based this hypothesis on the lack of quinol products that should form in the presence of a phenoxenium ion and the aqueous T-HYDRO reagent. A radical mechanism could also explain the high yields for electron-deficient phenols, which would not as easily undergo a cationic pathway.

Scheme 1.4: (A) Doyle's Rh-catalyzed dearomatization; (B) Doyle's revised mechanistic proposal

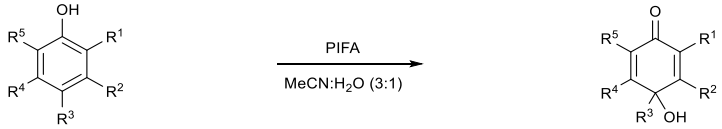


1.1.3. Hypervalent Iodine Mediated Methods

Perhaps the most commonly used method to synthesize 2,5-cyclohexadienones involves the oxidative dearomatization of a phenol with iodine(III)-based oxidants. Phenyliodine diacetate (PIDA) and phenyliodine *bis*-trifluoroacetate (PIFA) are the two most commonly used oxidants, and have been applied to an extremely wide variety of systems.[10] The reactions have been observed to proceed relatively cleanly in both inter-

and intra-molecular fashion. Further investigation by McKillop and Taylor showed that the conversion of the phenol to the silyl-ether can increase the yield and reduce the formation of side-products (**Scheme 1.5**).[11] The reaction was found to be tolerant of alkyl substitution at a number of positions (**Table 1.1**), though the electron deficient ester **1.37e** proceeded in lower yield.

Scheme 1.5: Phenol dearomatization with PIFA

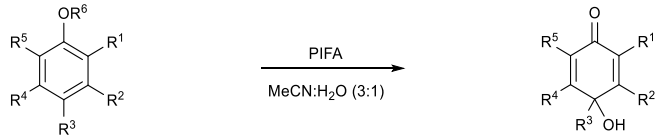


1.37a; R^1=R^5=*t*-Bu, R^2=R^4=H, R^3=Me
1.37b; R^1=R^3=R^5=*t*-Bu,R^2=R^4=H, R^3=Me
1.37c; R^1=R^5=Br, R^2=R^4=H, R^3=Me
1.37d; R^1=R^5=Br, R^2=R^4=H, R^3=CH_2CO_2Et
1.37e; R^1=R^2=R^4=H, R^3=Me, R^5=CO_2Et

1.38a; *78%*
1.38b; *76%*
1.38c; *78%*
1.38d; *67%*
1.38e; *30%*

Though the mechanistic details have not been fully examined, the reaction is believed to proceed through a pathway that exists somewhere between one of the two extremes shown in **Scheme 1.6**. Either an associative mechanism (**Path A**) or a dissociative mechanism (**Path B**) are plausible mechanistic pathways.[12] Both begin with a ligand exchange of the phenol onto the oxidant, giving complex **1.41**. In the associative mechanism, a nucleophile attacks at the 4-position, displacing the iodine nucleus in an S_N2'-like fashion to give the cyclohexadienone directly. The dissociative mechanism involves oxidation of the phenol to give phenoxenium ion **1.42**. This cation is subsequently trapped with a nucleophile to yield cyclohexadienone product **1.43**. Early evidence indicates that the mechanism most-likely occurs through a dissociative-like mechanism.[12] However, recent uses of chiral hypervalent iodine reagents (**Section 1.1.1.4**) to affect enantioselective dearomatizations indicates a reasonable amount of

Table 1.1: Dearomatization of free phenol and TIPS-protected phenol with PIFA



1.39a; R^1=R^2=R^4=H, R^3=Me
1.39b; R^1=R^3=Me; R^2=R^4=R^5=H
1.39c; R^1=R^4=R^5=H, R^2=R^3=Me
1.39d; R^1=R^3=R^5=Me, R^2=R^4=H
1.39e; R^1=R^5=H, R^2=R^3=R^4=Me
1.39f; R^1=R^2=R^4=R^5=H, R^3=CH_2CO_2Me

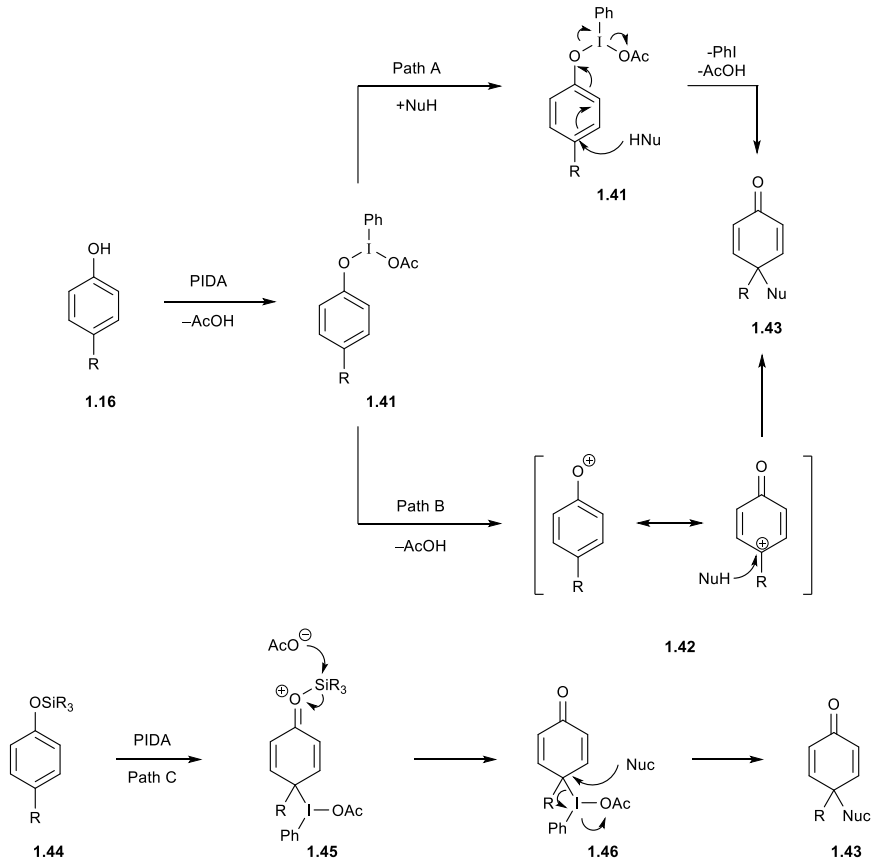
1.40a
1.40b
1.40c
1.40d
1.40e
1.40f

Entry	Compound	Product	Yield (%) R^6 = H	Yield (%) R^6 = TIPS
1	**1.39a**	**1.40a**	48	73
2	**1.39b**	**1.40b**	60	73
3	**1.39c**	**1.40c**	67	75
4	**1.39d**	**1.40d**	67	78
5	**1.39e**	**1.40e**	63	70
6	**1.39f**	**1.40f**	27	59

association in the transition state. As such, the true mechanism probably lies somewhere between the extremes of Path A and Path B, and is likely highly dependent on the reaction conditions. Felpin provided an alternate mechanistic proposal to explain the superiority of silyl-ether protected phenols in the dearomatization reaction (**Scheme 1.6**).[13] His proposal involves initial attack by the oxidant at the 4-position of the silylated phenol to give **1.46** followed by nucleophilic displacement to form the

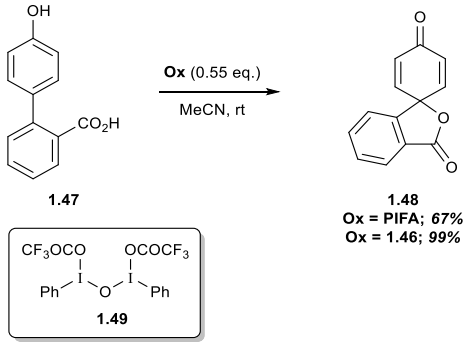
cyclohexadienone (**1.43**). Further investigation into the mechanism of this transformation is warranted.

Scheme 1.6: Possible mechanistic pathways for iodine(III)-mediated oxidative dearomatization



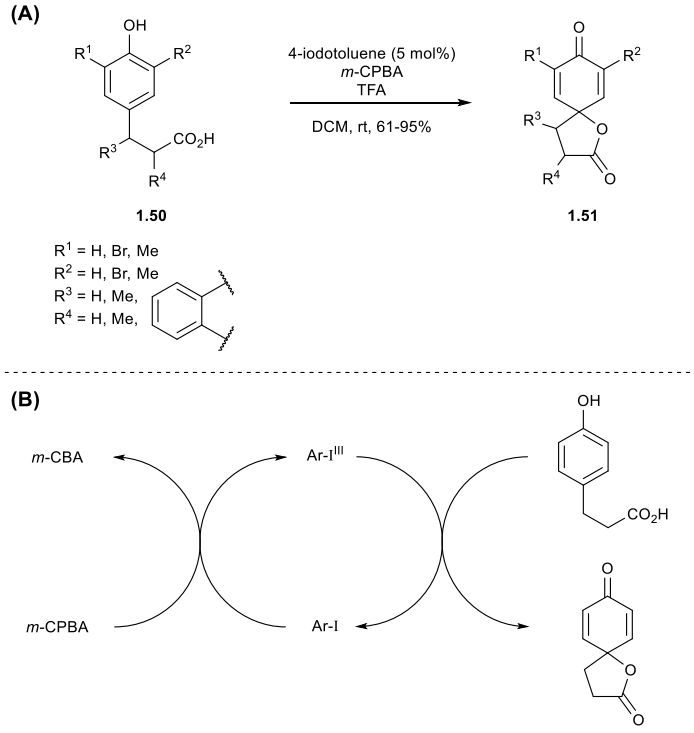
Kita reported the use of μ-oxo-bridged diiodide oxidant **1.49** in the oxidative dearomatization of a number of phenol substrates (**1.47 for example, Scheme 1.7**).[14] The reaction was found to produce superior yields for a variety of nucleophiles compared to the more commonly used PIFA. The authors hypothesize that the longer C-OCOCF$_3$ bond, influenced by the *trans*-bridging oxygen accelerates the ligand exchange, increasing the efficiency of the oxidation.

Scheme 1.7: Kita's improved dearomatization with **1.49**



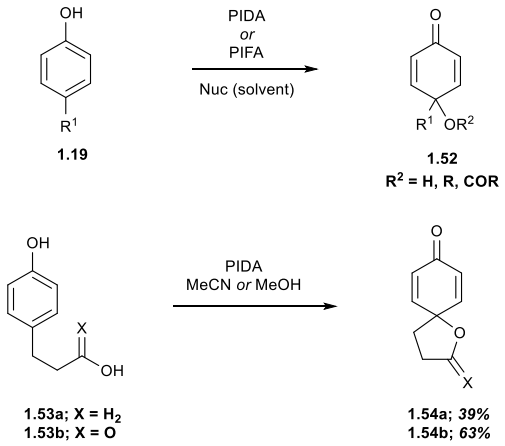
Kita also reported the dearomatization of phenol **1.50** under catalytic conditions (**Scheme 1.8**).[15] Their proposed catalytic cycle involves oxidation of an aryl-iodide to an iodine(III) species with a terminal oxidant (**Scheme 1.8B**). After oxidative dearomatization, the regenerated aryl iodide is reoxidized and enters the cycle again. A screen of aryl iodide sources revealed 4-iodotoluene to be the optimum catalyst. TFA was a necessary additive to achieve high yields and catalytic loadings as low as 5 mol% could be used without a decrease in yield. Of the oxidants screened (CH_3CO_3H, $NaBO_3$, $NaIO_4$, CrO_3, *m*-CPBA) only *m*-CPBA was successful. The authors were able to perform the dearomatization on a number of phenols under these catalytic conditions, further expanding the scope of iodine(III)-mediated dearomatization reactions.

Scheme 1.8: (A) Iodine(III)-catalyzed phenol dearomatization; (B) Proposed catalytic cycle



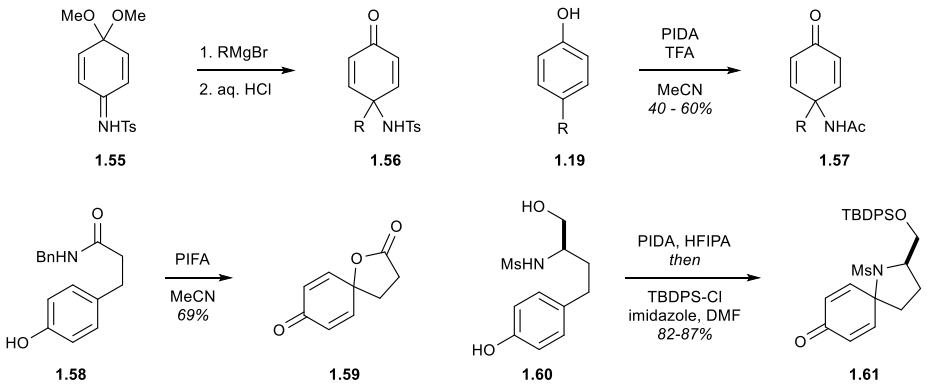
Hypervalent iodine-based oxidations are also particularly appealing due to the wide variety of available nucleophiles that can be used in the dearomatization with oxygen-based nucleophiles being particularly effective (**Scheme 1.9**). Intermolecular oxygen-based nucleophiles that have been used successfully include water (often with MeCN as a cosolvent), alcohols and carboxylic acids. In most cases, the nucleophile is used in solvent quantities to maximize yields. Intramolecular examples can also be achieved if the nucleophile is tethered to the phenol producing lactone and cyclic ether products.[16]

Scheme 1.9: Intramolecular dearomatization with oxygen nucleophiles



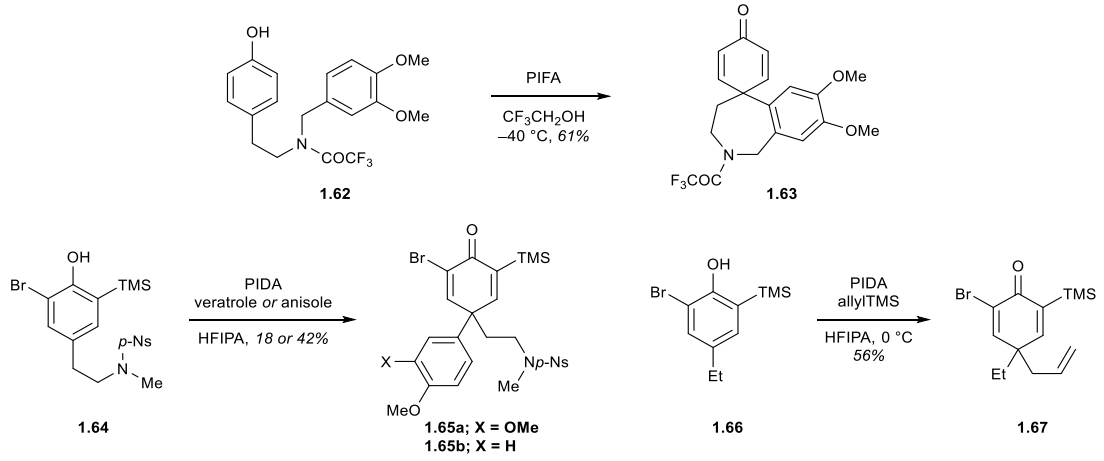
The use of nitrogen-based nucleophiles are rarer. In many cases, cyclohexadienones with *N*-substitution are instead produced from organometallic addition into iminoketal such as **1.55** (**Scheme 1.10**). When PIDA is used as the oxidant along with added TFA, nitriles (**1.57**) can also add into the phenol, giving amide products.[17] Attempts to furnish spiro-lactams have been met with challenges. An early investigation by Kita found that amide **1.58** proceeded through *O*-cyclization, giving spirolactone **1.59** instead.[16] Ciufolini found that sulfonamides perform the cyclization more readily than amides due to their enhanced nucleophilicity relative to amides;[18] phenol **1.60** could be dearomatized to form **1.61** in excellent yield

Scheme 1.10: Dearomatization with nitrogen nucleophiles



A variety of carbon nucleophiles such as electron-rich aromatics and allylsilanes can also be used as nucleophiles (**Scheme 1.11**). In most cases, the nucleophiles are tethered to the substrate resulting in spiro products, such as has been reported by Kita.[19] Although a few examples do exist where the carbon nucleophile can be added in an intermolecular fashion. Canesi added veratrole and anisole into **1.64** to give cyclohexadienone **1.65a&b**.[20] The resulting products (**1.65a**&**b**) were elaborated to access the *Amaryllidacae* alkaloids. A similar approach by Canesi utilized allyltrimethylsilane to furnish **1.67** in acceptable yields *en route* to aspidospermine.[21]

Scheme 1.11: Dearomatization with carbon nucleophiles



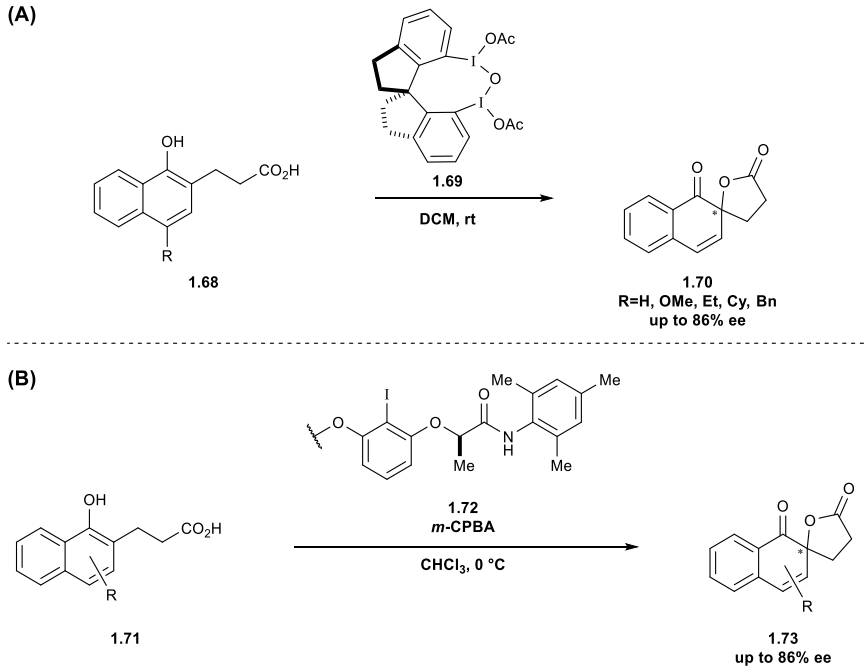
1.1.4. Enantioselective Synthesis of Cyclohexadienones with Chiral Hypervalent Iodine Complexes

The ease of access and diversity of reactions available to cyclohexadienones makes them an appealing target for enantioselective synthesis. However, the synthesis of both 2,5 and 2,4-cyclohexadienones in an enantioselective manner is a highly challenging problem, as the reaction occurs through a potentially dissociated carbocation, meaning that the distance between the chiral oxidant species the developing stereocenter might be unacceptably long. 2,5-Cyclohexadienones are an even more challenging problem, as the iodine nucleus is associated with the phenolic

oxygen while the stereocenter is formed *para* to the phenol; a long distance even if a fully associative mechanism is operative. While several groups have reported methods for the enantioselective synthesis of 2,4-cyclohexadienones, only one report of the enantioselective synthesis of 2,5-cyclohexadienones exists. This has been a significant area of research, and several recent reviews are available.[22] The following section will focus on reports most relevant to our work which is reported in later chapters.

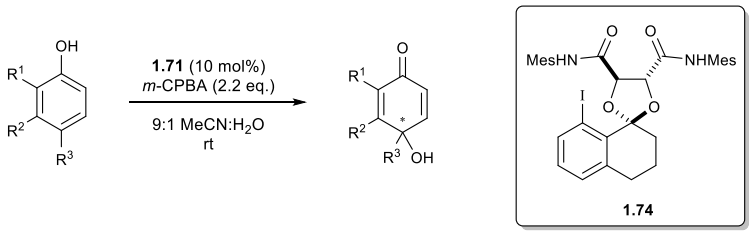
Early reports in the enantioselective synthesis of 2,4-cyclohexadienones came from the labs of Kita and Ishihara (**Scheme 1.12**). Kita utilized a novel spiroindanyldiiodide **1.69** to affect the enantioselective lactonization of **1.68** to give products of type **1.70**.[23] After optimization, the lactones could be obtained in good yields with ee values up to 86%. The reaction could be performed in catalytic fashion using *m*-CPBA as a terminal oxidant though with a reduced ee of 65%. Ishihara investigated related systems that utilized a far more easily synthesized catalyst, **1.72**.[24] The reaction yielded lactone products with ee values up to 86%. Several groups have also reported the use of chiral, iodine(V) reagents to synthesize 2,4-cyclohexadienones in enantioenriched form, though this reaction takes place through a different mechanism.[25, 26]

Scheme 1.12: (A) Kita's enantioselective dearomatization; (B) Ishihara's enantioselective dearomatization



Our group has become interested in the enantioselective synthesis of 2,5-cyclohexadienone substrates through iodine(III)-mediated oxidative dearomatization (**Table 1.2**). Initial work in our group utilized Ishihara-type catalysts (**1.72**) in the dearomatization of 2,4-dimethylphenol.[27] While the initial ee values were low (<25%), our work verified that enantioselective induction could be achieved. The synthesis of novel catalysts identified tartrate-derived catalyst **1.74** as a promising structure. An investigation into the substrate scope revealed that ee values could be improved slightly, giving values up to 60% (Entry 3). Work is ongoing to identify conditions to further improve the enantioselectivity.

Table 1.2: Selected scope of Harned's dearomatization of phenols with **1.74**



Entry	R^1	R^2	R^3	Temp (°C)	Time (h)	Yield (%)	ee (%)
1	Me	H	Me	25	16	52	28
2	Br	H	Me	25	16	52	30
3	TMS	H	Me	25	16	79	60
4	H	Me	Me	25	16	43	0
5	TBS	H	*i*-Pr	25	16	41	26

1.2. Reactions of 2,5-Cyclohexadienones

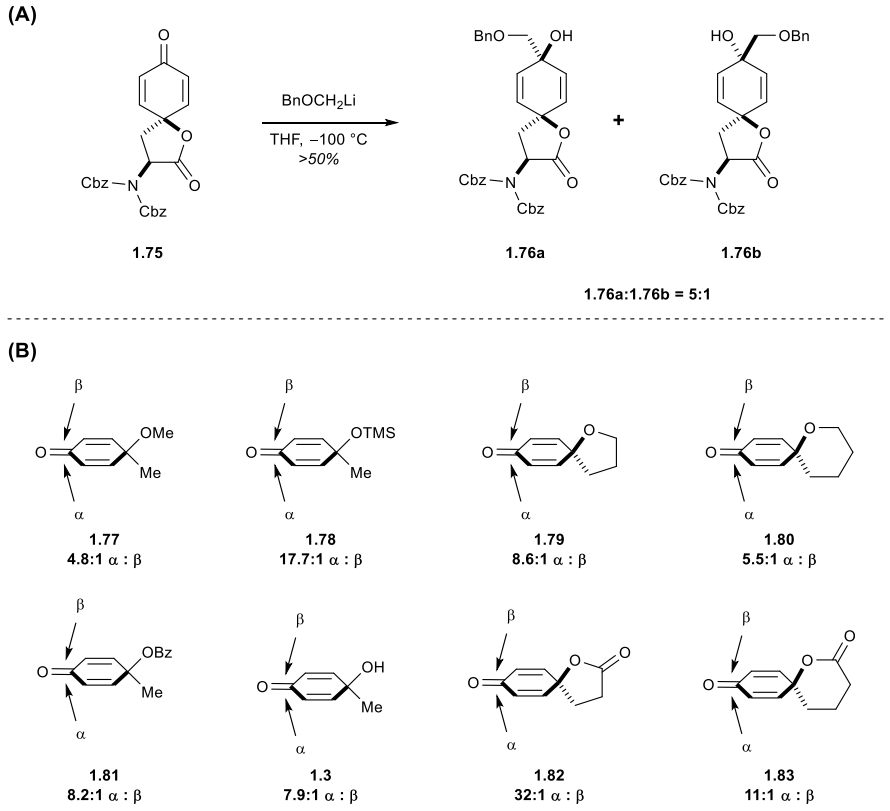
Despite their small size, 2,5-cyclohexadienones possess a dense array of reactive functionality. On a fragment which only contains six carbons, they possess a ketone, two conjugated alkenes (which can often be differentiated if the molecule is not symmetric), as well as potential functionality at the 4-position introduced by the nucleophile. As such, 2,5-cyclohexadienones can readily be engaged in diverse reactions. This section will discuss some of the most important reactivity patterns available to 2,5-cyclohexadienones. Key examples, both selective and unselective, will be introduced for each reaction type, though the reactions mentioned are by no means an exhaustive list.

1.2.1. 1,2-Additions

The cross-conjugated ketone present in 2,5-cyclohexadienones is well suited to undergo 1,2-additions in the presence of an appropriate organometallic reagent. Such reactions present the possibility of introducing an additional stereocenter for further elaboration. Subsequent reductive rearomatization has also proven to be a fruitful method for accessing highly-substituted phenols.

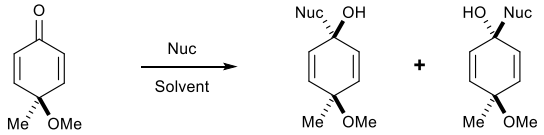
Wipf has examined the stereoselectivity of 1,2-additions of organometallic reagents into 2,5-cyclohexadienones in some detail.[28, 29] Inspired by their work towards the natural product aranorosin (**Scheme 1.13A)**, they observed that nucleophiles preferentially approached **1.75** from the α-face.[30] An investigation into the steric biases in the molecule revealed little steric differentiation between the two trajectories. Intrigued by this result, the authors synthesized a series of cyclohexadienone substrates (**1.77-1.83**) to further investigate the selectivity of 1,2-addition. Addition of MeMgBr revealed that the diastereoselectivity was highly sensitive to substrate and reaction conditions, though attack from the α-face was always preferred. Screening of other nucleophiles demonstrated a strong dependence on nucleophile hybridization, counterion, and solvent (**Table 1.3**).

Scheme 1.13: (A) Selective nucleophilic addition *en route* to aranosin; (B) Selectivity of MeMgBr addition to cyclohexadienone nucleophiles



The intriguing stereoselectivity of these model substrates was not easily explained by many of the existing stereoselectivity models such as the Ahn-Eisenstein model[31], a "vinylogous Cieplak" effect[32], or Burgess' and Liotta's frontier orbital distortion model.[33] The authors proposed that the stereoselectivity was instead governed primarily by ground-state electrostatic effects arising from the sp^3 C-O dipole moment (**Figure 1.2**). Stronger dipoles would lead to preferred attack from the α-face. Calculation of the dipole moments for the substrates that were tested correlated well with the observed selectivity.

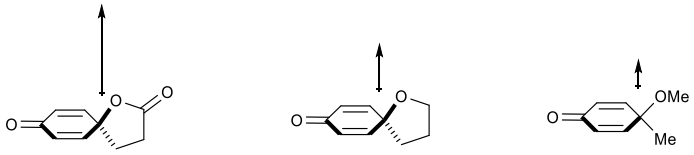
Table 1.3: Scope of selective nucleophilic addition to **1.77a**



1.77 **1.84a** **1.84b**

Entry	Nuc	Yield	1.81a:1.81b	solvent
1	MeMgBr	86	4.8:1	THF
2	$NaBH_4$ *or* $LiAlH_4$	100	1:1	MeOH *or* THF
3	HC≡CMgBr	70	1:1	THF
4	$H_9C_4C{\equiv}CLi$	26	1.1:1	THF
5	PhMgBr	83	3.6:1	THF
6	MeLi	87	2.1:1	THF
7	MeLi	77	3.3:1	Et_2O
8	$BnOCH_2Li$	84	3:1	THF

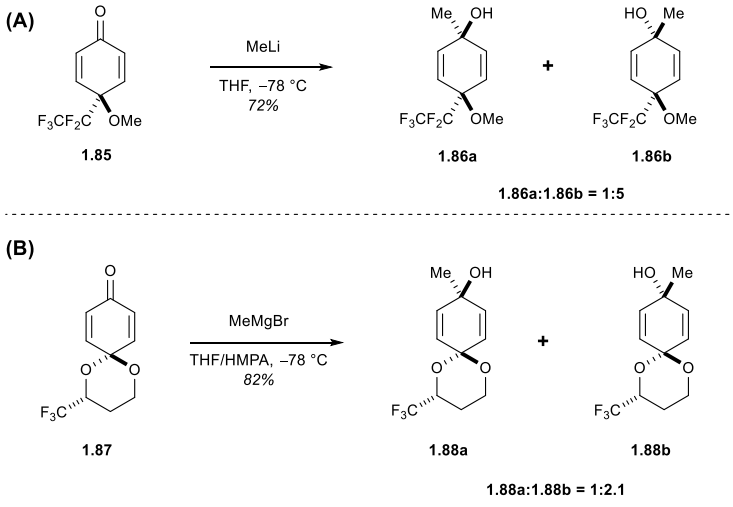
Figure 1.2: Trend in dipole moment and associated selectivity



1.82 **32:1 α : β** | **1.79** **8.6:1 α : β** | **1.77** **4.8:1 α : β**

The authors were further gratified to find that the sense of selectivity could be reversed in fluorinated substrate **1.85**, which possesses a dipole moment opposite that of the previously studied substrates (**Scheme 1.14**). To their delight, addition of MeLi resulted in preferred β-attack. The authors were able to use this information to design a fluorinated chiral auxiliary to direct the attack of a nucleophile into acetal **1.87**.[34] In the presence of THF and HMPA, compounds **1.88a** and **1.88b** could be obtained in 1:2.1 dr.

Scheme 1.14:(A) Stereochemical selectivity reversal in a fluorinated substrate; (B) Chiral auxiliary for selective addition



1.85 | **1.86a** | **1.86b**

1.86a:1.86b = 1:5

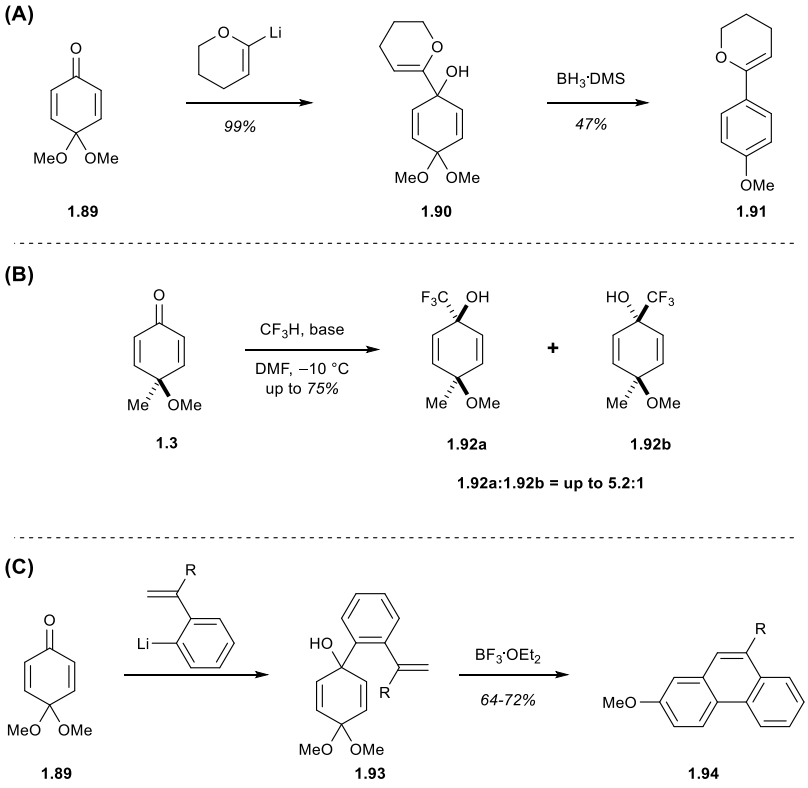
1.87 | **1.88a** | **1.88b**

1.88a:1.88b = 1:2.1

While Wipf's study of 1,2-additions into cyclohexadienones remains the most extensive study to date, 1,2-additions have also been used in the preparation of other molecules. Parker and coworkers performed an addition of lithiated tetrahydropyrans

to give substrate **1.90** as a model study for analogous glycoside additions (**Scheme 1.15A**).[35] Compound **1.90** could then be rearomatized to furnish arylated glycoside-like molecules (**1.91**). Langlois developed an intriguing base-promoted addition of a trifluoromethyl group into dienone **1.3** using CF_3H as the nucleophile (**1.15B**).[36] While the diastereoselectivity could be influenced by the identity of the base, the addition favored attack from the α-face, in accordance with Wipf's observations. Morrow performed the addition of an aryllithium into cyclohexadienone ketal **1.89** (**Scheme 1.15C**).[37] Subsequent treatment with $BF_3{\cdot}OEt_2$ gave substituted phenanthrene substrates (**1.94**).

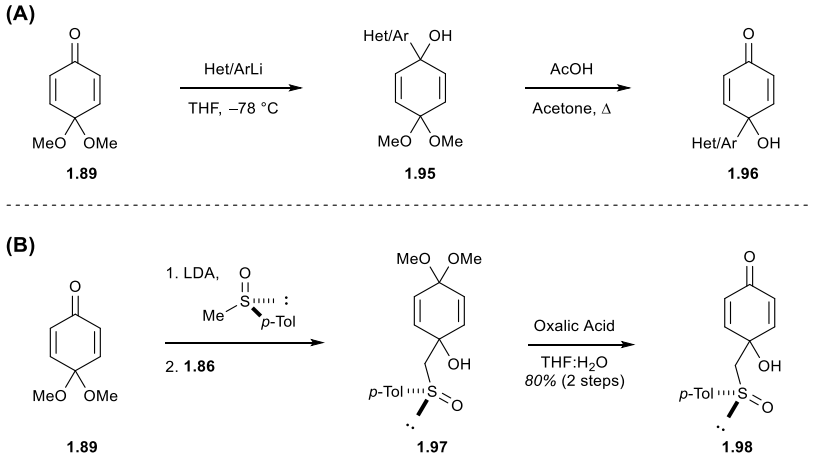
Scheme 1.15: (A) Parker's tetrahydropyran addition; (B) Langlois' trifluoromethyl addition; (C) Morrow's phenanthrene synthesis



1,2-Additions into cyclohexadienone ketals followed by ketal hydrolysis provides a useful strategy to introduce complex groups at the 4-position of

cyclohexadienones. Stevens utilized this strategy to synthesize cyclohexadienones with heteroaromatic groups (**1.96**) at the 4-position from cyclohexadienone **1.89** (**Scheme 1.16A**), which were studied for their activities against renal and colon cancer cell-lines.[38] Carreño performed the addition of the anion of an enantioenriched sulfoxide into ketal **1.89**. Subsequent removal of the ketal furnished quinol **1.98**, which possesses a chiral auxiliary that could be used to direct further asymmetric reactions (**Section 1.2.2a**).[39]

Scheme 1.16: (A) Steven's heteroaromatic addition to **1.89**; (B) Carreño's synthesis of enantioenriched quinol **1.98**

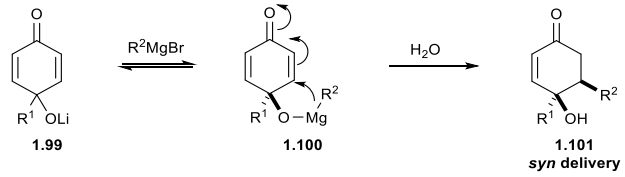


1.2.2. Conjugate Additions

1.2.2.a. Organometallic Nucleophiles

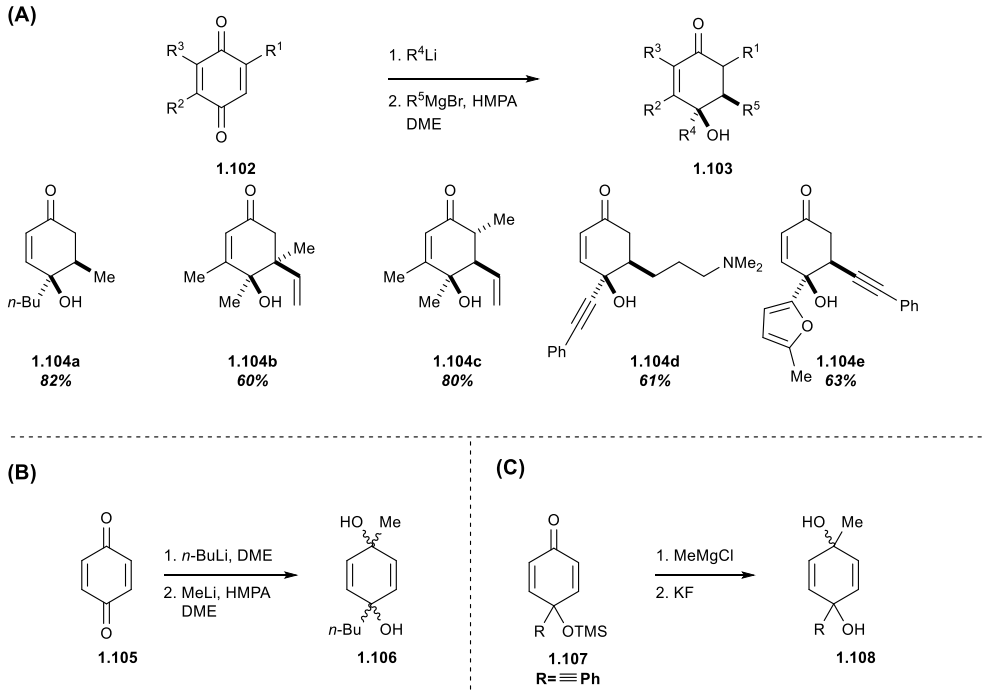
Liotta observed that Grignard reagents undergo conjugate addition reactions in the presence of the lithium alkoxide of cyclohexadienone quinols **1.99** (**Scheme 1.17**).[40] They termed the reaction "Ligand-Assisted Nucleophilic Addition" or LANA. The regiochemistry is determined by initial coordination of the organometallic nucleophile with the alkoxide followed by intramolecular delivery.

Scheme 1.17: Schematic LANA reaction



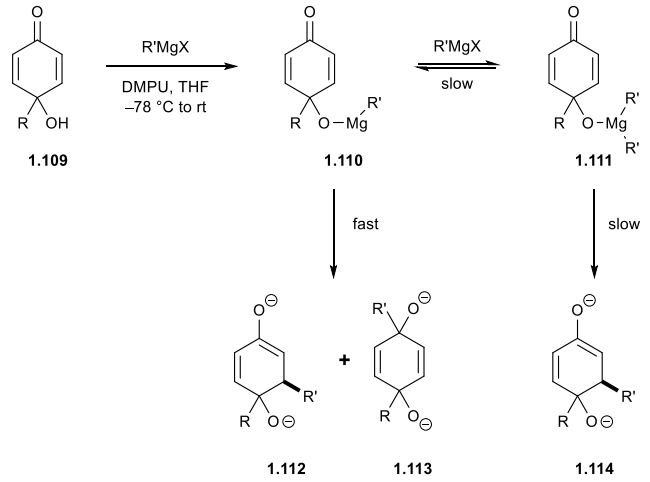
In their early studies, the quinol alkoxide **1.99** was generated *in situ* through an initial 1,2-addition of a lithium organometallic reagent into a benzoquinone (**Scheme 1.18**), though the lithium alkoxide could also be generated by deprotonating the quinol with LDA. In all of their studies, the LANA reaction occurred with complete regioselectivity, with the ligand being delivered *syn* to the alkoxide. Further investigation revealed that excess reagent and higher temperatures (warming to room temperature) were necessary for the reaction to reach completion.[41] The presence of additives such as HMPA, DMPU, or TMEDA were also necessary to suppress competing 1,2-addition. The additive serves to facilitate the metathesis of the Mg counterion with the Li alkoxide. Attempts to perform a LANA reaction with organolithium compounds resulted in isolation of the 1,2-addition products **1.106** as the sole product. When protected quinol **1.107** was used, only 1,2-addition product **1.108** was isolated after desilylation, confirming the necessity for anionic coordination. The reaction was found to be tolerant of substitution on the cyclohexadiene ring, as well as at the 4-position. A wide variety of sp, sp^2 and sp^3 nucleophiles participated in the conjugate addition.

Scheme 1.18: (A) Liotta's LANA reaction with selected scope; (B) Attempt to perform LANA reaction with organolithium nucleophile; (C) Attempt to perform LANA reaction on a protected quinol



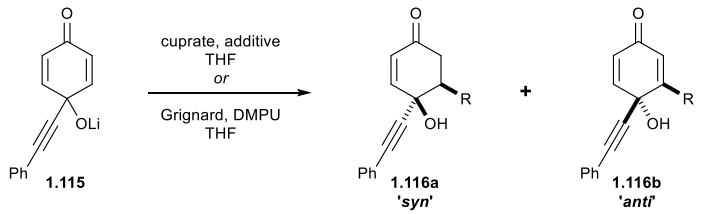
Liotta undertook an investigation into the mechanism of the LANA reaction (**Scheme 1.19**). A screen of various additives confirmed the necessity of aggregate-destabilizing additives to achieve high 1,4 selectivity. The authors also investigated the effect of the alkoxide counterion on the 1,4-selectivity. Potassium was found to give enhanced selectivites relative to Li and Na. Monitoring the reaction at −78 °C over the course of several hours revealed that the reaction stalled at <50% conversion. Warming to room temperature resulted in full conversion. The authors speculate that only the dialkylmagnesium species **1.111** is reactive enough to deliver the ligand at low temperature. Warming the system allows complete organometallic transfer through the monoalkylmagnesium **1.110**.

Scheme 1.19: Mechanistic proposal for LANA reaction



Liotta later noted that the use of higher-order organocuprates resulted in conjugate additions on similar substrates with opposite (*anti* to OH group) selectivity (**Table 1.4**).[42] They hypothesized that the use of a coordinatively saturated cuprate system did not undergo exchange onto the hydroxyl ligand, leading to primarily *anti*-addition product **1.116b**. A screening of different cuprate reagents found that higher-order cuprates were essential, as lower order cuprates led to substantial rearomatization, presumably due to single-electron transfer processes. This methodology was applicable to a wide variety of cuprates with good results, though phenyl cuprates did not add with the intended selectivity (Entry 6).

Table 1.4: Scope of selective cuprate addition into cyclohexadienones

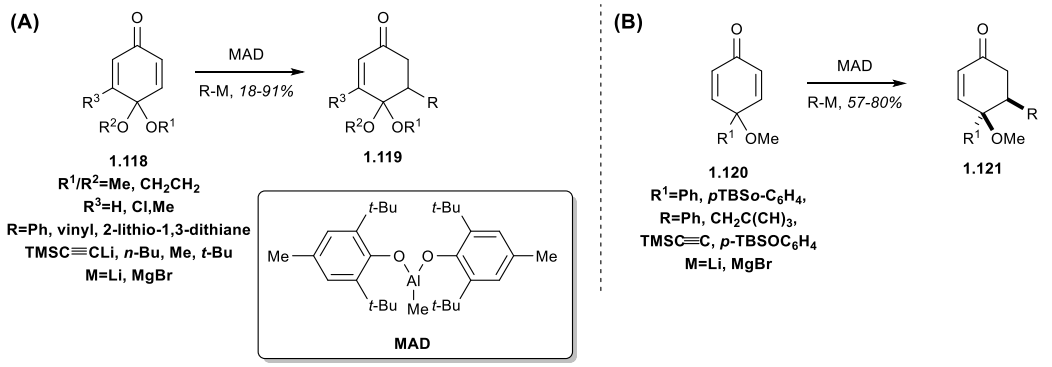


Entry	Organometallic	Additive	R	Yield	1.113a:1.113b
1	BuMgCl	DMPU	Bu	83	0:100
2	Li_2Bu(2-thienyl)CuCN	$BF_3{\cdot}OEt_2$	Bu	61	95:5
3	(vinyl)MgCl	DMPU	vinyl	68	0:100
4	Li_2(vinyl)(2-thienyl)CuCN	$BF_3{\cdot}OEt_2$	vinyl	54	95:5
5	PhMgBr	DMPU	Ph	81	0:100
6	$LiPh_2Cu/Me_2S$	--	Ph	61	10:90

Swenton found that reagents made from an organometallic (Grignard or organolithium) and the MAD reagent (methylaluminum bis(4-bromo-2,6-di-tert-butylphenoxide)) gave a compound which preferentially performed conjugate additions into cyclohexadienones (**Scheme 1.20**). The regioselectivity is presumably due to steric deactivation of the bulky MAD reagent towards the 1,2-addition pathway.[43] A wide variety of organometallic reagents could be added into a series of cyclohexadienones. When quinone monoketals were used, the 1,4-addition proceeded in high yields with a variety of organometallic nucleophiles. The reaction was tolerant of a variety of hybridizations and steric conditions. Yields were slightly lower, though still good,

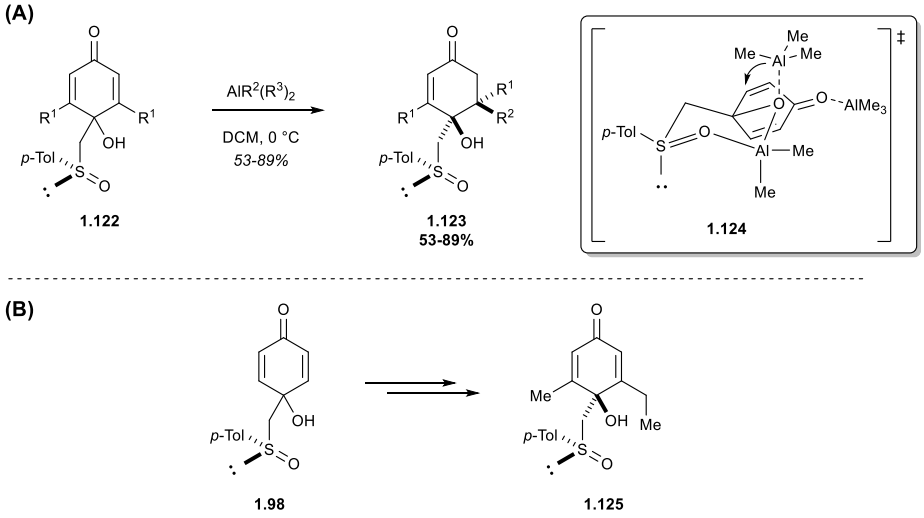
when a variety of quinol ethers were utilized. In all cases, the addition occurred *syn* to the oxygen in the quinol ether.

Scheme 1.20: Swenton's MAD addition to quinone monoketals (A) and quinols (B)



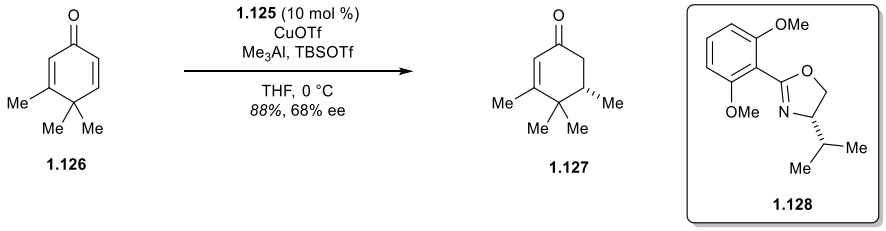
Carreño reported the diastereoselective addition of organoaluminum reagents to quinol **1.122** to give enantioenriched enone **1.123** (**Scheme 1.21**).[44] The reaction was observed to proceed with high diastereoselectivity to give the product resulting from addition *syn* to the oxygen. It was found to be necessary to utilize excess of the organoaluminum reagents to achieve high yields. The authors rationalized this observation, along with the observed stereoselectivity, by invoking pre-coordination by an organoaluminum reagent with the alkoxide. The addition then proceed through chair like transition-state **1.124**. The authors were able to elaborate these products into differentially substituted quinols **1.125** through a multistep sequence.

Scheme 1.21: (A) Carreno's diastereoselective organoaluminum addition; (B) Elaboration to unsymmetrically substituted quinols



Iwata and coworkers were able to achieve the enantioselective addition of trimethylaluminum into cyclohexadienone **1.126**, to give enantioenriched product **1.127**.[45] The reaction was found to proceed in the presence of a Cu^{I} salts and an oxazoline ligand. Further screening found that the sterically-hindered additive TBSOTf improved the enantioselectivity. A number of ligands were screened, and **1.127** could be obtained in 68% ee when ligand **1.128** was used.

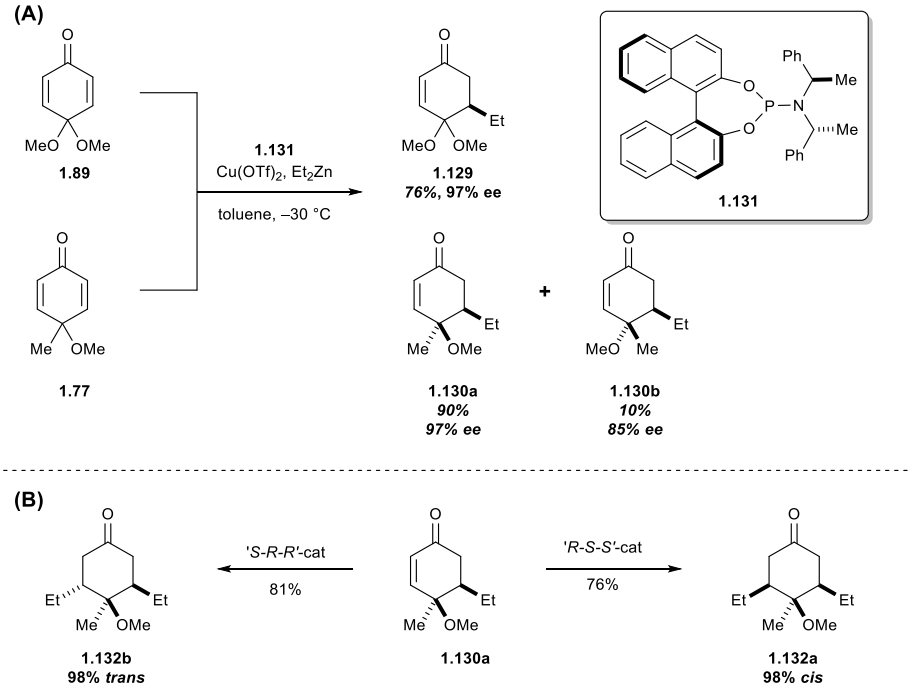
Scheme 1.22: Iwata's enantioselective, copper-catalyzed alkylaluminum addition



Feringa and coworkers were able to achieve a similar enantioselective addition of dialkylzinc reagents into quinone ketal **1.89** (**Scheme 1.23**).[46] The authors found that the addition occurred in the presence of a copper catalyst and phosphoramidite ligand

1.131 to give ee values of <99%. The reaction could be extended to cyclohexadienones of type **1.77**. The addition proceeded with reasonably high selectivity to give addition *syn* to the oxygen. The products could be obtained in analogously high yields and ee. In a later report, the authors found that the addition occurred under complete catalyst control.[47] When mono-addition product **1.130a** was resubjected to the reaction with either enantiomer of the catalyst, either the *syn* (**1.132a**) or *anti* (**1.132b**) products could be obtained depending on which enantiomer of catalyst was used (**Figure 1.23B**).

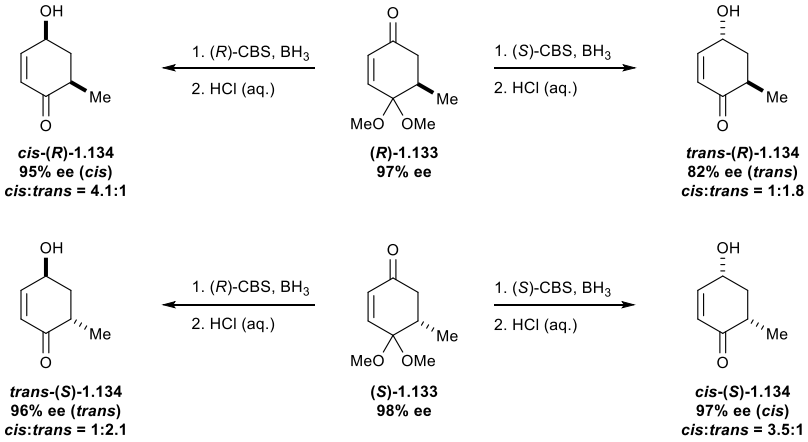
Scheme 1.23: Ferringa's Cu-catalyzed enantioselective Et_2Zn addition; (B) Demonstration of catalyst control



Bräse reported a creative application of Ferringa's methodology (**Scheme 1.24**).[48] Starting from quinone monoketal **1.89**, the authors were able to prepare either enantiomer of enone **1.133** through appropriate ligand selection. The ketone was then stereoselectively reduced with either enantiomer of the CBS catalyst followed by acetal hydrolysis. Depending on the stereochemistry used for both the dimethylzinc addition

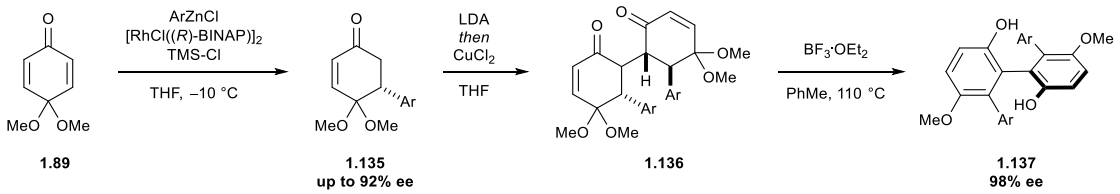
and CBS reduction, any of the four possible stereoisomers of **1.134** could be prepared in 82-97% ee with low to moderate disastereoselectivity.

Scheme 1.24: Bräse's application of Ferringa's methodology



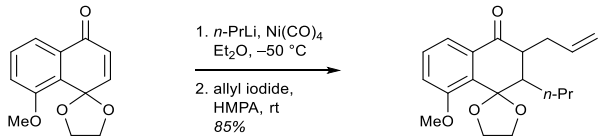
Thomson and coworkers also reported a Rh-catalyzed addition of arylzinc chlorides into quinone monoketal **1.89** (**Scheme 1.25**).[49] A variety of aryl groups could be added in the presence of [RhCl((*R*)-BINAP)]$_2$ to give **1.135** in good yields with ee values up to 92%. The authors were able to utilize this desymmetrization to access enantioenriched biaryl compounds. The enones were subjected to oxidative dimerization conditions to give **1.136**. Subsequent rearomatization occurred with efficient point to axial chirality transfer to give enantioenriched biaryl substrates **1.137** in good yield and 98% ee.

Scheme 1.25: Thompson's enantioselective Rh-catalyzed arylzinc addition



Semmelhack used an acylnickel reagent to add alkyl groups into napthoquinone monoketal products (**Scheme 1.26**).[50] Treatment of *n*-BuLi with $Ni(CO)_4$ followed by addition of the reagent into **1.135** followed by trapping of the enolate with allyl iodide gave **1.139** in 85% yield. Despite the effectiveness of this protocol, subsequent uses of this methodology have not been reported, likely due to the high toxicity of the $Ni(CO)_4$.

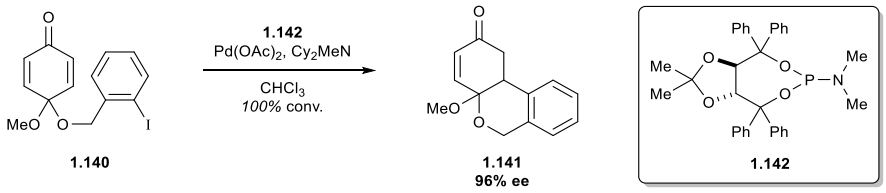
Scheme 1.26: Semmelhack's acylnickel conjugate addition



1.138 **1.139**

There are also several examples of conjugate additions utilizing Pd-based catalysts. Ferringa reported a Heck reaction involving cyclohexadienone **1.140** (**Scheme 1.27**).[51] The authors found that when **1.140** was treated with $Pd(OAc)_2$ in the presence of TADDOL-derived phosphoramidite **1.142**, cyclized product **1.141** was obtained. Optimization of the conditions found the bulky base Cy_2MeN produced the best results, giving **1.141** in 96% ee.

Scheme 1.27: Ferringa's enantioselective Heck reaction

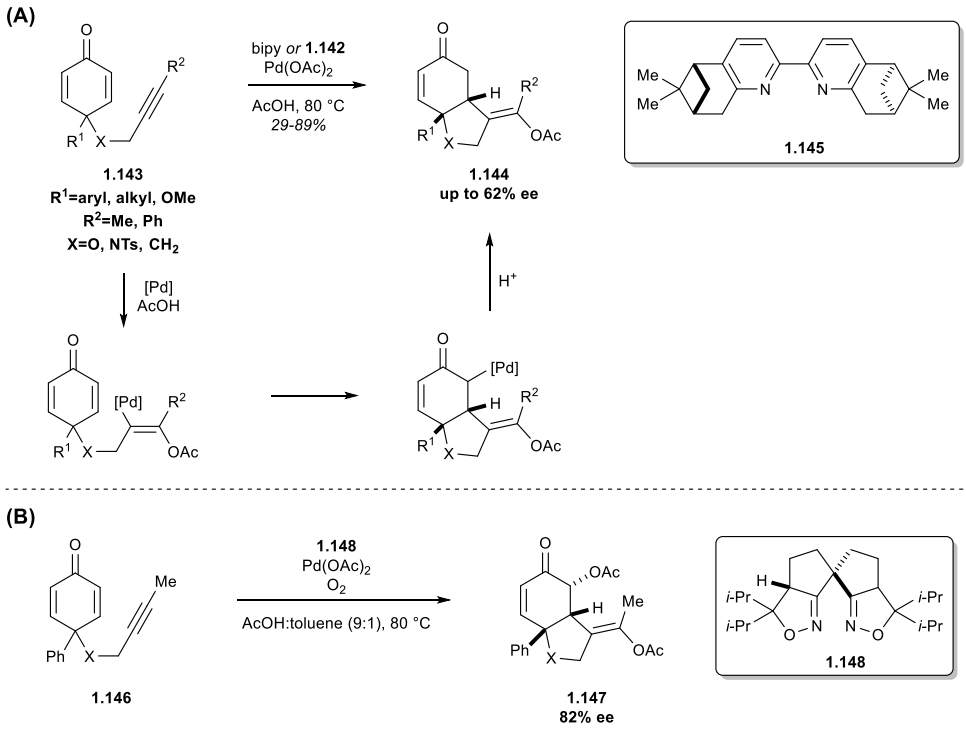


1.140 **1.141** **96% ee** **1.142**

A few authors have also reported palladium-catalyzed cyclizations initiated by alkyne acetoxylation reactions. Harned reported a cascade reaction on cyclohexadienone **1.143** involving the palladium-catalyzed *trans*-acetoxylation of the alkyne followed by insertion and protodemetallation to form bicycle **1.144** (**Scheme 1.28A**).[52] Pyridine-type ligands such as bipy or **1.145** were found to be necessary for

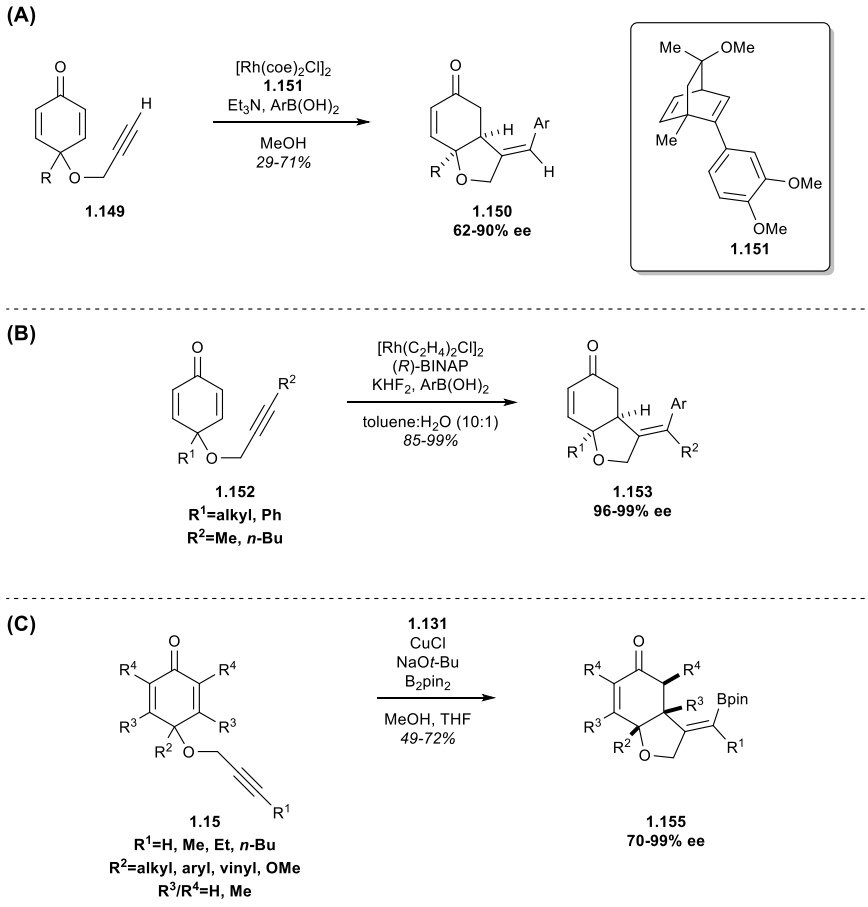
the reaction to occur and acetic acid was required as the solvent. The regioselectivity of the reaction was found to be highly dependent on the pattern of substitution on the cyclohexadienone core. Cyclization occurred opposite from 2-substituted enones, though the selectivity for 3-substituted enones was less pronounced. Oxygen, nitrogen, and carbon tethers participated in the cyclization, though ester substrates did not. A survey of chiral ligands found that (−)*iso*-PINDY ligand **1.145** promoted the cyclization in up to 62% ee, though the selectivity was highly substrate dependent. Shortly thereafter, Sasai reported a similar acetoxylation-cyclization-oxidation cascade reaction (**Scheme 1.28B**) which yielded products of type **1.147**.[53] Oxygen was found to be the ideal terminal oxidant for the reaction. When enantioenriched SPRIX ligand **1.148** was used in the reaction, **1.147** could be obtained in up to 82% ee.

Scheme 1.28: (A) Harned's palladium-catalyzed acetoxylation-insertion; (B) Sasai's acetoxylation-cyclization-oxidation cascade



Several related alkyne cyclizations using boron-containing organometallic reagents and transition-metal catalysts have also been reported. Lautens reported the cyclization of alkyne **1.149** triggered by the rhodium-catalyzed insertion of arylboronic acids followed by enone cyclization (**Scheme 1.29A**).[54] Extensive ligand optimization found diene ligand **1.151** to be the optimum ligand, giving cyclized products in up to 90% ee. Tian and Lin reported a similar cyclization of alkynes triggered by arylboronic acid insertion (**Scheme 1.29B**).[55] The authors found that (*R*)-BINAP was the ideal ligand with KHF_2 as an additive. Performing the reaction under optimized conditions led to cyclized product **1.153** in excellent yield and up to 99% ee. Tian and Lin also reported a similar cyclization initiated by copper-catalyzed alkyne diboration with B_2Pin_2 (**Scheme 1.29C**).[56] Phosphoramidite ligand **1.131** was found to yield the boronate product **1.155** in good yield and up to 99% ee.

Scheme 1.29: Enantioselective boronation/cyclization by Lautens (A) and Tian/Lin (B & C)

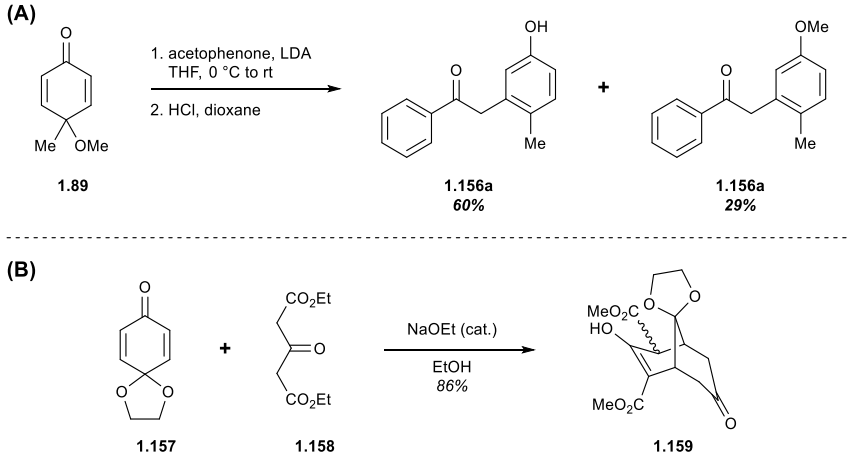


1.2.2.b. Carbon Nucleophiles

Chittimalla studied the conjugate addition of the lithium enolate of acetophenone into cyclohexadienone ketal **1.89** to give phenol **1.56a&b** after rearomatization (**Scheme 1.30A**).[57] Their study focused mainly on 2,4-cyclohexdinones, though they also reported a few examples of addition into quinone monoketal **1.89** to give phenol **1.156a** in 60% yield along with **1.156b**. Another early example of the application of stabilized carbon nucleophiles was reported by McDonald and Dreiding (**Scheme 1.30B**).[58] The authors treated quinone monoketal **1.157** with

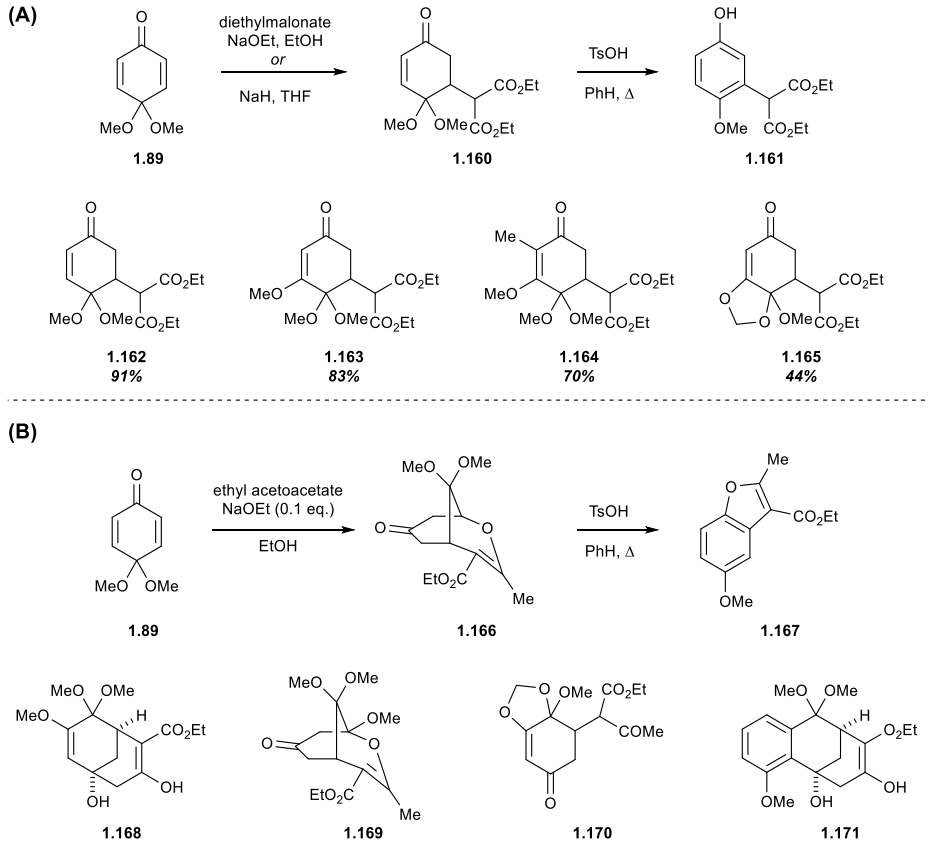
acetone dicarboxylic acid dimethylester **1.158** and catalytic NaOEt to give tricycle **1.159** in 86% yield as a mixture of diastereomers.

Scheme 1.30: (A) Chittimalla's conjugate addition of acetophenone; (B) McDonald & Dreiding's double conjugate addition



Parker and coworkers engaged in one of the first thorough investigations into the conjugate addition of malonate anions into cyclohexadienones (**Scheme 1.31**).[59] The authors added the sodium salt of diethylmalonate into quinone monoketals **1.89**. A variety of substrates were amenable to the addition. An investigation of various bases found either catalytic amounts of NaOEt in EtOH or stoichiometric NaH in THF to be optimum, depending on the substrate. The resulting adducts were treated under acidic conditions to furnish rearomatized products **1.161** in good yield. The use of ketoester nucleophiles with NaOEt as a base led to the isolation of tricyclic products **1.166**, which result from initial Michael addition into the cyclohexadienone, followed by intramolecular conjugate-addition into the remaining enone. This methodology was applicable to a number of cyclohexadienone and napthoquinone substrates. Treatment of **1.166** with acid led to the isolation of furan product **1.167**.

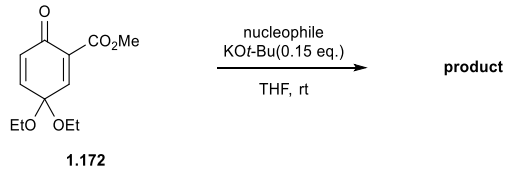
Scheme 1.31: (A) Parker's conjugate addition of malonate and (B) ketoester nucleophiles



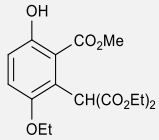
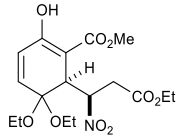
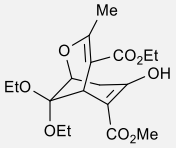
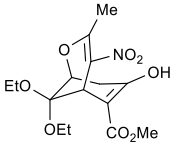
Aubé and coworkers reported a similar conjugate addition of carbon nucleophiles into electron-deficient quinone monoketals **1.172** (**Table 1.5**).[60] A number of nucleophiles were found to add in the presence of catalytic KO*t*-Bu. The identity of the isolated products depended heavily on the nature of the nucleophile. Diethylmalonate led to immediate rearomatization of the unstable substrate, giving phenol **1.173**. Ethyl-3-nitropropionate resulted in only monoaddition, giving enol-substrate **1.174**. The authors noted that the substrate was unstable to chromatographic purification; attempts at purification with silica gel led to the isolation of large quantities of rearomatized product. In the presence of stoichiometric base, the resulting enolate **1.177** could be trapped with MeI, giving enone **1.174** as the major diastereomers (**Scheme 1.32A**). The use of ethyl acetoacetate and 2-nitroacetone both resulted in

isolation of the double-addition products **1.175** and **1.176** respectively. The authors investigated the addition of various nucleophiles into other electron-deficient quinone monoketals to give a variety of phenols, mono-addition, and double-addition products (**Scheme 1.32B**).

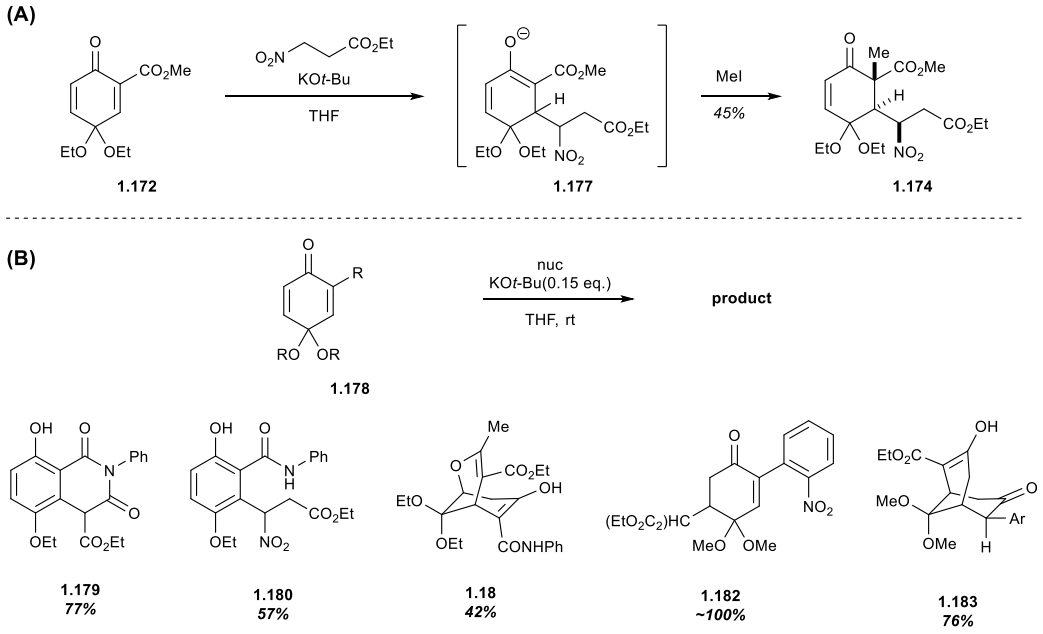
Table 1.5: Scope of Aubé's nucleophilic addition to electron deficient cyclohexadienone **1.172**



1.172

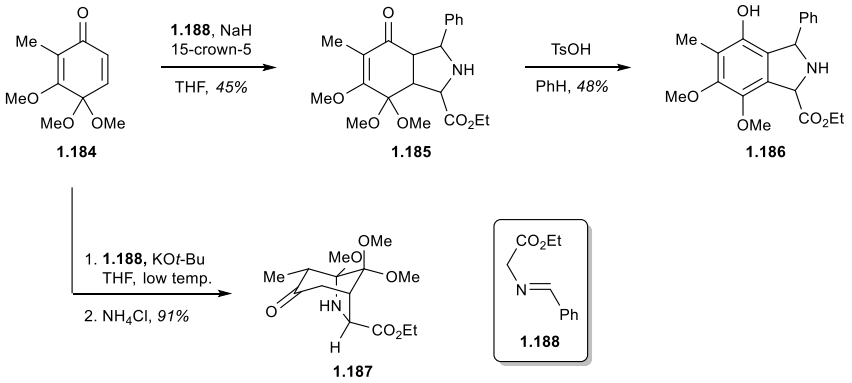
Entry	Nucleophile	Product	Yield (%)
1	diethyl malonate	 **1.173**	74
2	ethyl 3-nitro-propionate	 **1.174** **10:1 dr**	ca. 100
3	ethyl acetoacetate	 **1.175**	84
4	2-nitroacetone	 **1.176**	52

Scheme 1.32: (A) One-pot nucleophilic addition/methylation; (B) Scope of cyclohexadienones for Aubé's nucleophilic addition



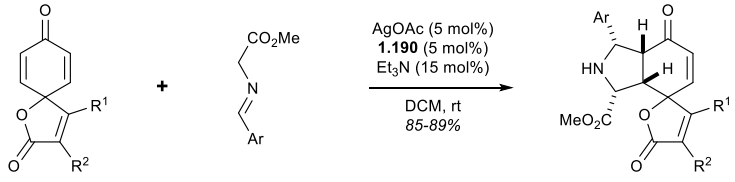
Parker accomplished the double-addition of *N*-benzylidine glycine methyl ester into quinone monoketal **1.184**.[61] Treatment of **1.184** with **1.188** in the presence of NaH and 15-crown-5 gave isoindole **1.185**. Subsequent treatment with acid led to the isolation of phenol **1.186**. When the compounds were reacted with KO*t*-Bu in THF at low temperature followed by workup with NH_4Cl, bicyclic **1.187** was isolated instead.

Scheme 1.33: Parker's double addition of *N*-benzylidine glycine methyl ester



In analogy to the work of Parker, Wang reported an asymmetric [3+2] cycloaddition of azo-methine ylides on **1.189** to give tricycle **1.191**.[62] A screen of catalyst conditions found AgOAc and ligand **1.131** to be the ideal catalyst. The reaction could be extended to a variety of substitution patterns, allowing for the isolation of products with up to 5 stereocenters.

Scheme 1.34: Wang's asymmetric [3+2] cycloaddition



1.189
R^1/R^2 = Ph/I, CO2Me/OMe, benzo

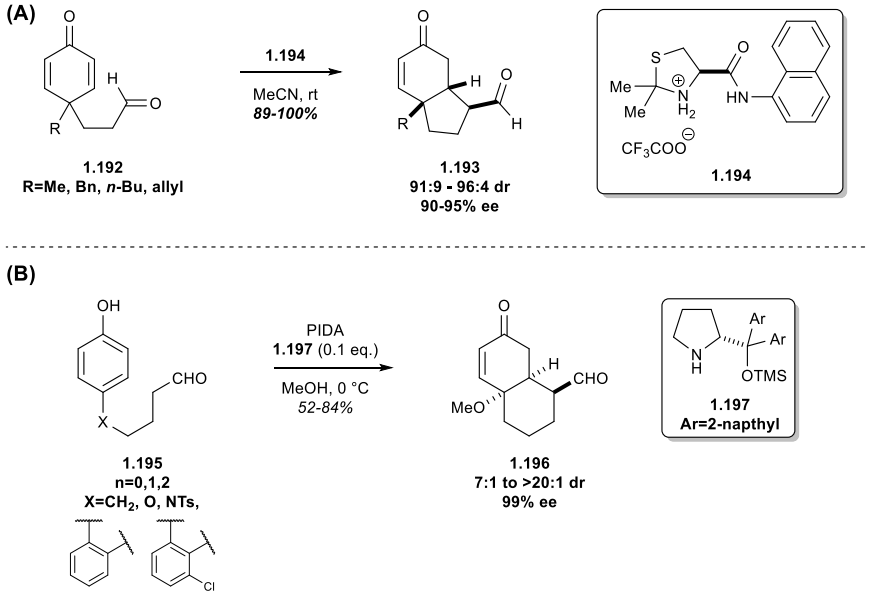
1.190
Ar = *p*-ClC_6H_4

1.191
95-96% ee

Intramolecular conjugate additions into cyclohexadienones have also been reported. In many cases, these conjugate additions involve enantioselective desymmetrization reactions due to the propensity of the intramolecular conjugate additions to occur diastereoselectively, simplifying desymmetrization efforts. An early report came from the lab of Hayashi (**1.35A**).[63] They performed an organocatalytic, enantioselective addition of cyclohexadienone aldehyde **1.192** to give cyclic substrate **1.193**. A screen of catalysts found the trifluoroacetate salt **1.194** to be the ideal catalyst, giving **1.193** in very good yield, high diastereoselectivity, and up to 95% ee.

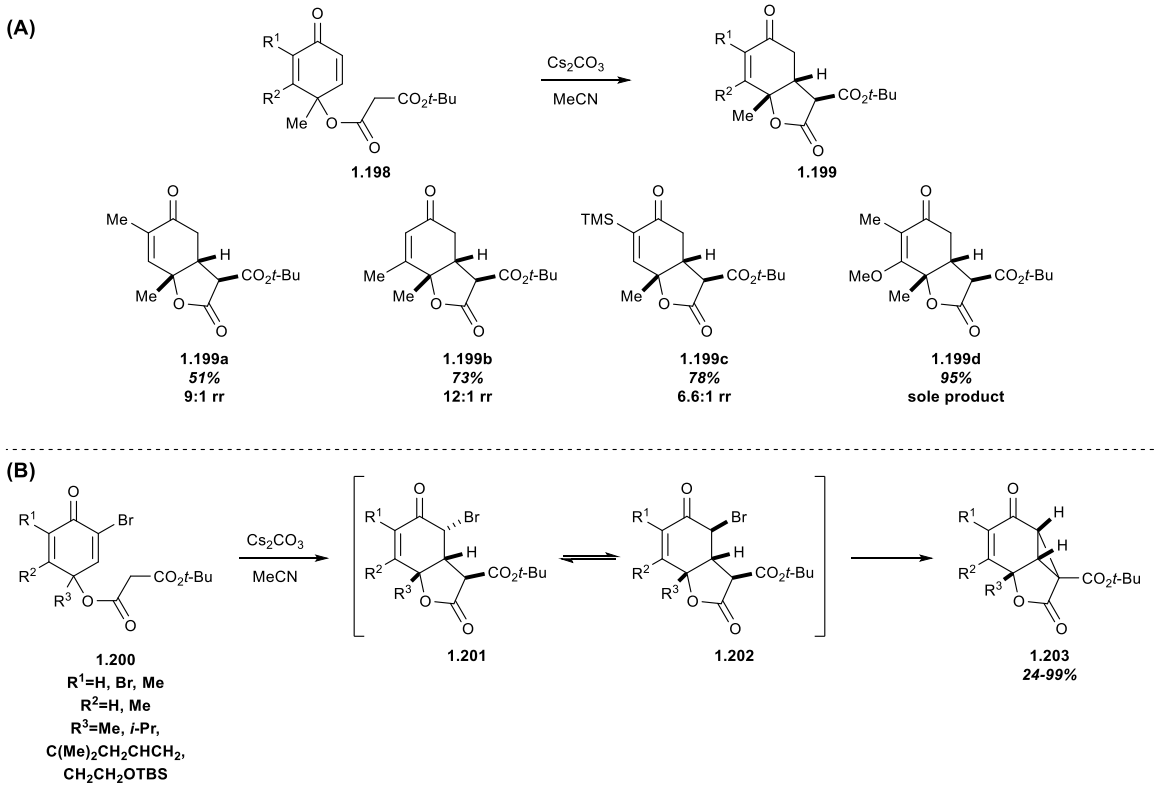
Gaunt reported a similar one-pot dearomatization-Michael addition cascade (**Scheme 1.35B**).[64] Phenol aldehyde **1.195** was treated with PIDA in the presence of proline-derived catalyst **1.197**. When methanol was used as the nucleophile, enone **1.196** could be obtained in good yield with ee values of up to 99%.

Scheme 1.35: (A) Hiyashi's enantioselective conjugate addition; (B) Gaunt's enantioselective dearomatization-conjugate addition cascade



Harned reported the conjugate-addition of cyclohexadienone-tethered malonates promoted by weak bases (**Scheme 1.36**).[65] When **1.198** was treated with Cs_2CO_3 in MeCN, bicycle **1.199** was obtained in good yield. Further study found that asymmetrically-substituted substrates could be cyclized regioselectively, with conjugate addition into the more electron deficient enone being preferred. Cyclization on methylated substrates occurred selectively opposite to the methyl group. The regioselectivity was reversed for silylated and brominated substrates. In the case of brominated substrates, the authors were surprised to isolate cyclopropane **1.203** as the sole product. Further investigation revealed that the reaction occurs via an initial conjugate-addition followed by isomerization of the bromoketone. Subsequent nucleophilic displacement by the malonate gives the cyclopropane.

Scheme 1.36: (A) Harned's regioselective malonate conjugate addition; (B) Formation of tricyclic cyclopropane **1.203**

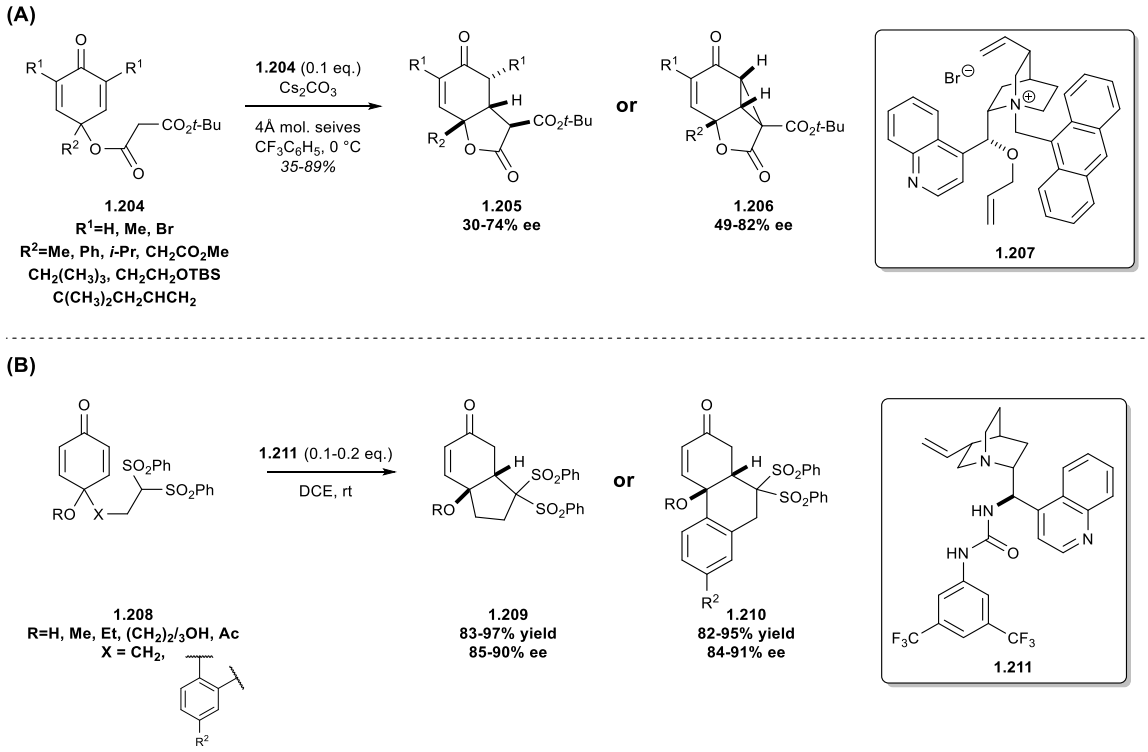


An enantioselective variant of the above reaction was also reported (**Scheme 1.37A**). Cinchona alkaloid-derived phase transfer catalysts **1.207** was screened in the reaction. The reactions were found to proceed with moderate to good selectivity. The reaction was tolerant of different substitution patterns on the substrate, though substrates with sterically demanding substituents resulted in higher ee values. When the dibromide was used, cyclopropane **1.206** was obtained in high ee.

You reported a similar conjugate addition of *bis*-sulfone **1.208** to form bicycle **1.209** (**Scheme 1.37B**).[66] A survey of catalysts found cinchona-derived urea **1.211** to be the ideal catalyst. A variety of substrates were screened, giving sulfone products

1.209 and **1210** in good yields and ee. The reaction could also be performed in a one-pot manner from the phenol, giving **1.209** in 33% yield and 88% ee.

Scheme 1.37: (A) Harned's enantioselective malonate conjugate addition; (B) You's enantioselective *bis*-sulfone conjugate addition

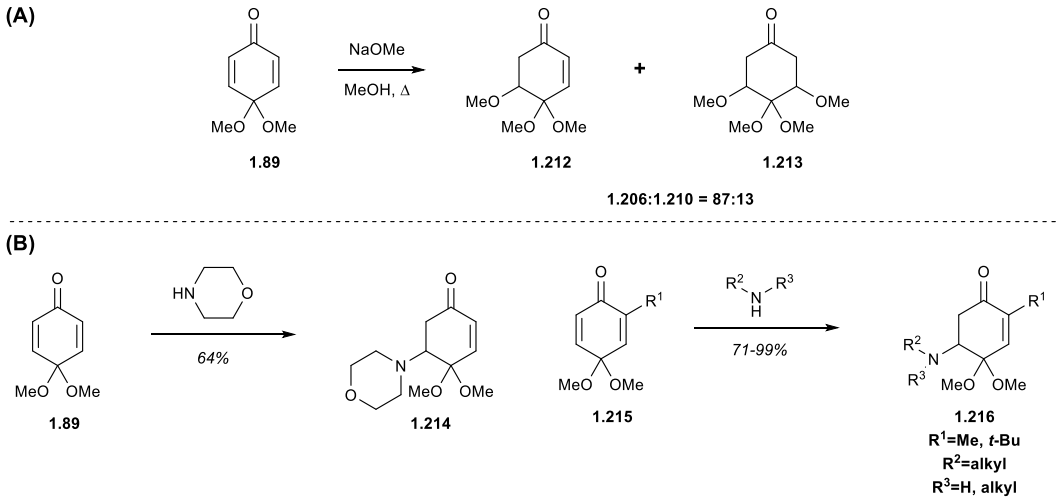


1.2.2.c. Heteroatom Nucleophiles

Reports of intermolecular heteroatom conjugate additions are significantly rarer. Rolán reported the conjugate addition of sodium methoxide into **1.89** (**Scheme 1.38)**.[67] The addition resulted in a mixture of monoaddition product **1.212** and *bis*-addition product **1.213**. Foster further studied the addition of heteroatom nucleophiles into **1.89**. When **1.89** was refluxed in methanol, *mono*-addition and *bis*-addition products were isolated in an 83:17 ratio of **1.212**:**1.213**. This ratio appears to reflect the thermodynamic product, as it did not change after extended reaction times. Foster also

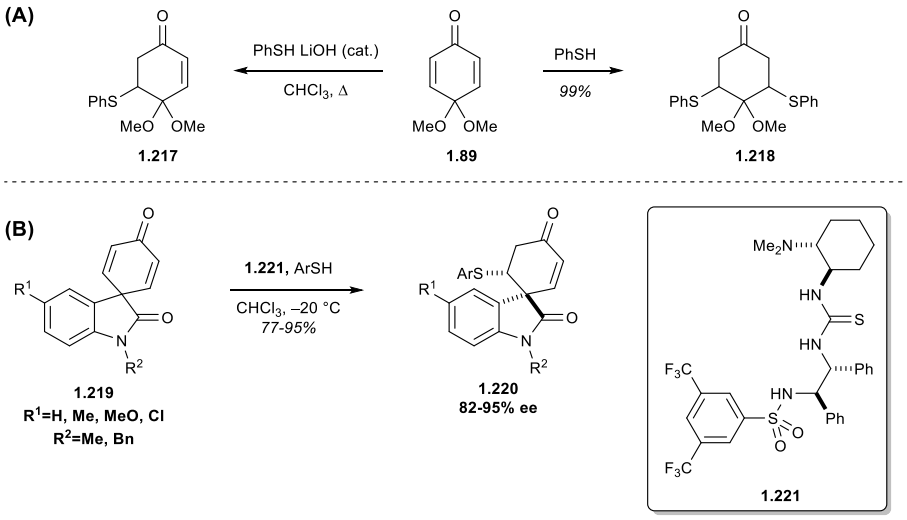
observed that morpholine added into **1.89** cleanly to give mono-addition product **1.214**.[68] Cuifolini studied the scope of this amine addition reaction further.[69] He found that the conjugate addition occurred regioselectively, with the nucleophile adding to the sterically less demanding enone of **1.216**. Numerous primary and secondary amines could be added to the substrate (**Scheme 1.38B**).

Scheme 1.38: (A) Rolán's addition of sodium methoxide; (B) Foster and Cuifolini's reports of amine conjugate addition



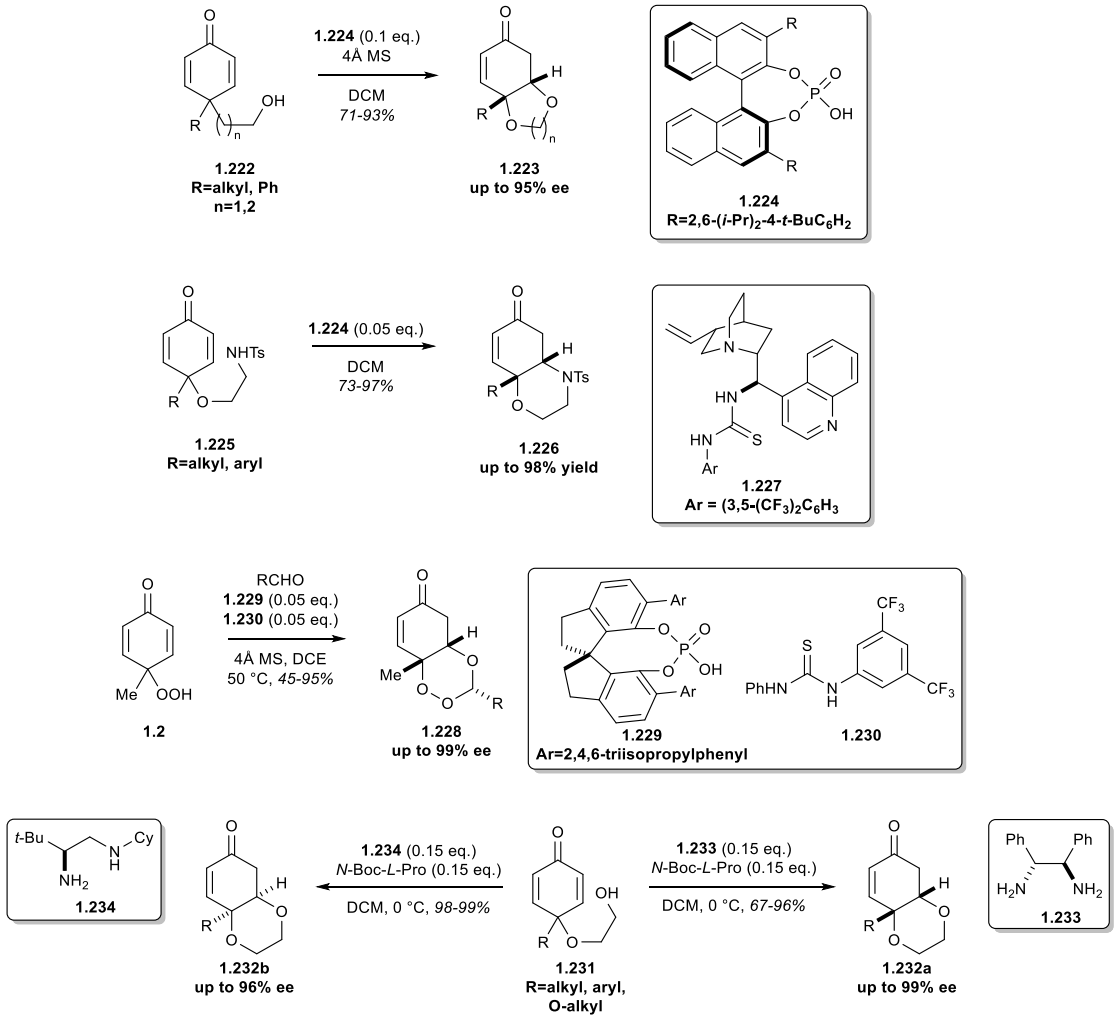
Foster observed that thiol additions occur rapidly to give the *bis*-addition product **1.218** (**Scheme 1.39A**).[68] In a later report, DeMarch found that *mono*-addition product **1.217** could be obtained using a catalytic amount of LiOH in $CHCl_3$.[70] Wang reported an intriguing extension of this methodology (**Scheme 1.39B**). When cyclohexadienone oxindole **1.219** was treated with a thiol in the presence of bifunctional thiourea catalyst **1.221**, desymmetrized substrate **1.220** could be obtained in up to 95% ee.[71]

Scheme 1.39: (A) Foster's double thiol addition; (B) Wang's enantioselective thiol addition



Several authors have published related approaches to the desymmetrization of cyclohexadieones through the use of intramolecular oxa-or aza-Michael additions. You reported an early example of the intramolecular cyclization of **1.22** to give **1.223** catalyzed by phosphoric acid **1.224** (**Scheme 1.40**).[72] You later published a follow up paper disclosing an analogous aza-Michael addition of **1.225** to give **1.226**.[73] In this case, thiourea **1.227** was the ideal catalyst. Substrates could be synthesized in up to 99% ee. Rovis synthesized a series of 1,2,4-trioxane substrates through an acetalization-oxo-michael cascade sequence on peroxyquinol **1.2** to give **1.228**.[74] A screen of phosphoric acid catalysts found **1.229** to be ideal. Substrates could be cyclized in up to 98% ee. Ye was able to achieve a vast improvement in oxo-Michael additions to cyclohexadienones.[75] He performed an oxo-Michael addition of **1.231** using highly simplified catalysts. When (*R*,*R*)-DPEN was utilized as a catalyst along with *N*-Boc-*L*-Pro as an additive, dioxane **1.232** could be obtained in up to 99% ee. The enantiomer of **1.232** could be accessed using **1.234** as the catalyst instead. The simplicity of these catalysts makes them a significant improvement over previous efforts.

Scheme 1.40: Examples of enantioselective heteroatom conjugate additions

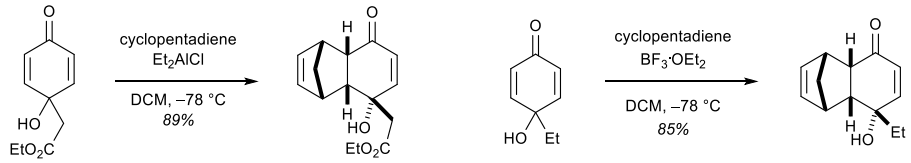


1.2.3. Diels-Alder Cycloadditions

2,5-Cyclohexadienones also readily undergo Diels-Alder cycloadditions. These reactions are often promoted by a Lewis acid such as Et_2AlCl[76] or $BF_3{\cdot}OEt_2$[77], though thermal conditions, particularly in the protic solvent CF_3CH_2OH are also known (**Scheme 1.41**).[78] The reactions are known to occur in a highly stereoselective manner,

giving almost exclusively the *endo* product with the approach of the diene *syn* to the oxygen substituent.

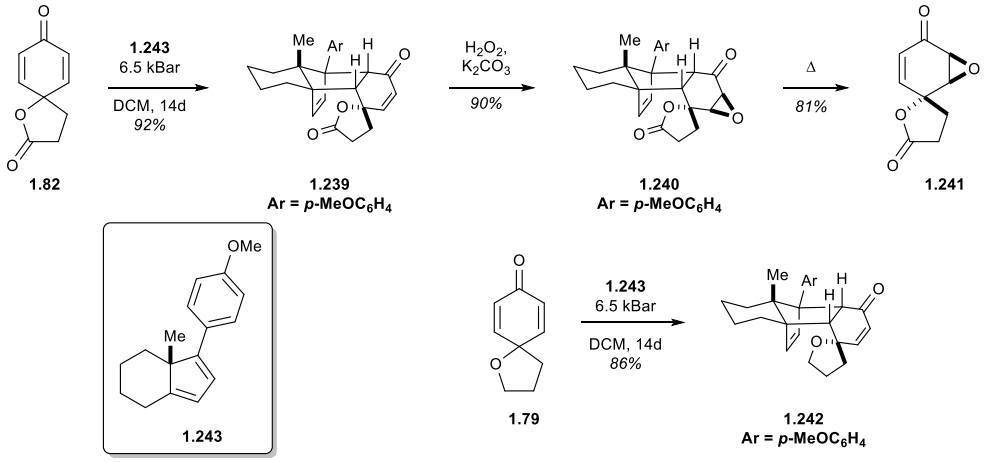
Scheme 1.41: Lewis-acid promoted Diels-Alder cycloadditions



1.235 **1.236** **1.237** **1.238**

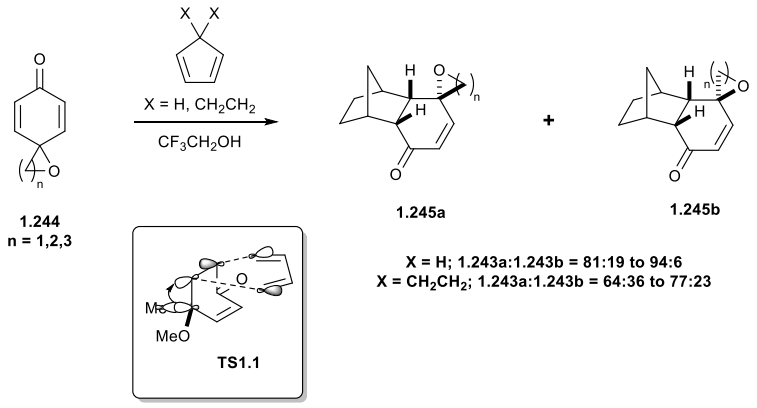
A particularly useful application of cycloadditions on 2,5-cyclohexadienones has been reported by Winterfeldt (**Scheme 1.42**).[79] The Diels-Alder cyclization of lactone **182** with chiral diene **1243** under high-pressure conditions led to adduct **1.239** as a single diastereomer. The resulting enantioenriched adduct was epoxidized to give **1.240**. The chiral auxiliary could be removed by flash-vacuum pyrolysis yielding **1.241**, the result of a formal enantioselective epoxidation of **1.82**. This methodology has been extended to a variety of other substrates such as ether **1.79**, though the retro-Diels-Alder reaction was not attempted on this substrate. A particularly striking aspect of this methodology is the extremely high *syn* diastereoselectivity observed in the cycloaddition. Houk studied this effect computationally at the semi-empirical level.[80] The authors posited that the decreased steric demand of the oxygen-substituent relative to the alkyl substituent is primarily responsible for the observed level of selectivity.

Scheme 1.42: Cycloaddition and elaboration using chiral diene **1.243**



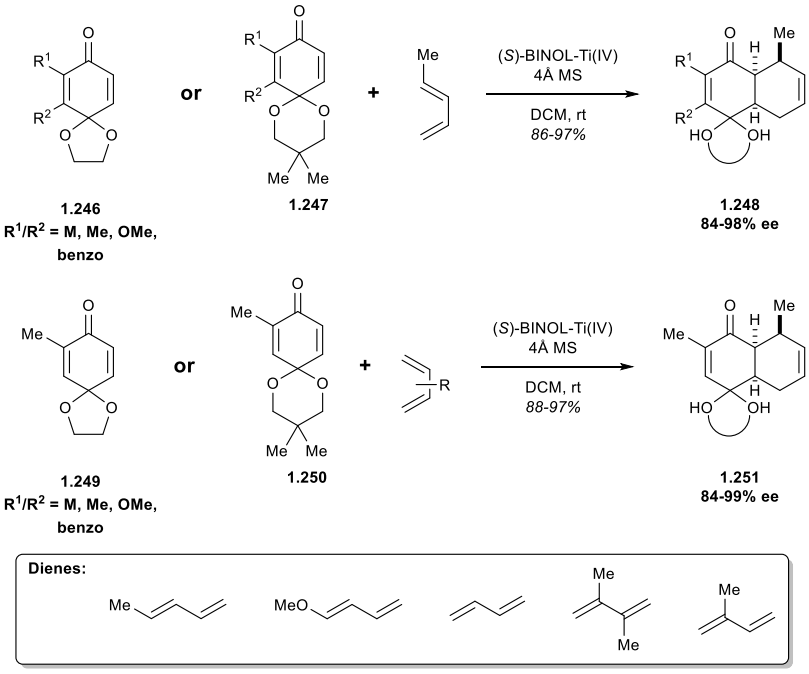
A more thorough study into the origin of the so-called "*syn*-oxygen effect" was undertaken by Ohkata and Paquette (**Scheme 1.43**).[78] The authors attempted the cycloaddition of a number of cyclohexadienones with cyclopentadiene and spiro[2.4]-hepta-4,6-diene. The ratio of *syn* to *anti* adducts were studied. In all cases, the *syn* adduct (**1.245a**) predominated, often with extremely high selectivity. Oxygen substituents were confirmed to be necessary for achieving high selectivity. The relative insensitivity of the selectivity to steric demands led the authors to further investigate this reaction computationally. Computation at the Hartree-Fock level led the authors to conclude that other effects in addition to the steric demands proposed by Houk are operative. Investigation of the frontier orbitals led to the hypothesis that approach *syn* to the oxygen minimizes unfavorable secondary orbital overlap. Their computational results also give credence to a Cieplack-like model, in which hyperconjugative effects between the more electron-donating alkyl group and the developing *anti*-periplanar bond stabilizes the developing σ* in the transition state (**TS1.1**).

Scheme 1.43: Investigation into the "syn oxygen effect" in Diels-Alder reactions of cyclohexadienones



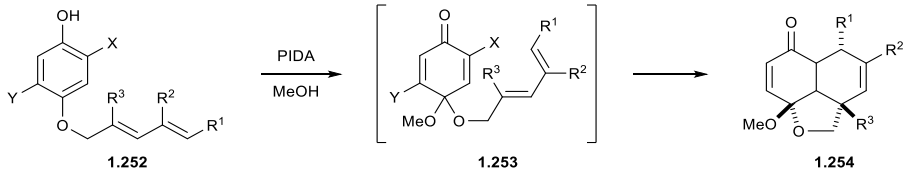
Corey has also reported an example of an enantioselective Diels-Alder desymmetrization reaction of quinone monoketals **1.246** (**Scheme 1.44**).[81] When **1.246** was treated with (*E*)-1,3-pentadienedthe Mikami (*S*)-BINOL-Ti(IV) complex, product **1.248** could be obtained in high yield and enantioselectivity. A substrate with a more-hindered acetal (**1.247**) was also well-tolerated as was substitution on the alkenes. A wide variety of dienes also participated in the cycloaddition.

Scheme 1.44: Corey's enantioselective Diels-Alder cycloaddition



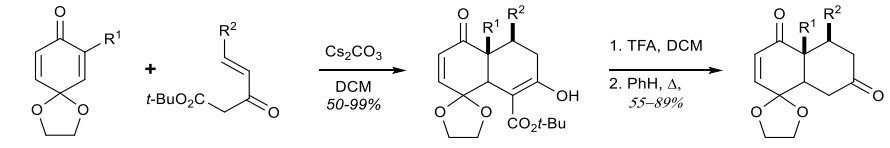
Liao has reported the intramolecular Diels-Alder cycloaddition of masked *p*-benzoquinone ketals **1.253** (**Scheme 1.45**).[82] Dearomatization of phenol **1.252** with PIDA in MeOH gave ketal **1.253** which spontaneously underwent an *in situ* cycloaddition to give tricyclic product **1.254** in good yield. A limited investigation into the substrate scope found that some substitution was tolerated on both the phenol and the diene portion of the molecule. In most cases, the expected *endo* products were obtained.

Scheme 1.45: Liao's intramolecular Diels-Alder cycloaddition



Brückner reported a Delongchamps annulation of electron-deficient quinone monoketals **1.255a** (**Scheme 1.46**).[83] Monoketal **1.255a** was treated with Nazarov reagent **1.256** in the presence of Cs_2CO_3. The resulting product could be treated with acid to give diketone **1.258**. Several substituents on the Nazarov reagent were screened and resulted in moderate to good yields. Dienone **1.255b**, which possesses a conjugated ketone was also amenable to the cyclization.

Scheme 1.46: Brückner's Delongchamps annulation



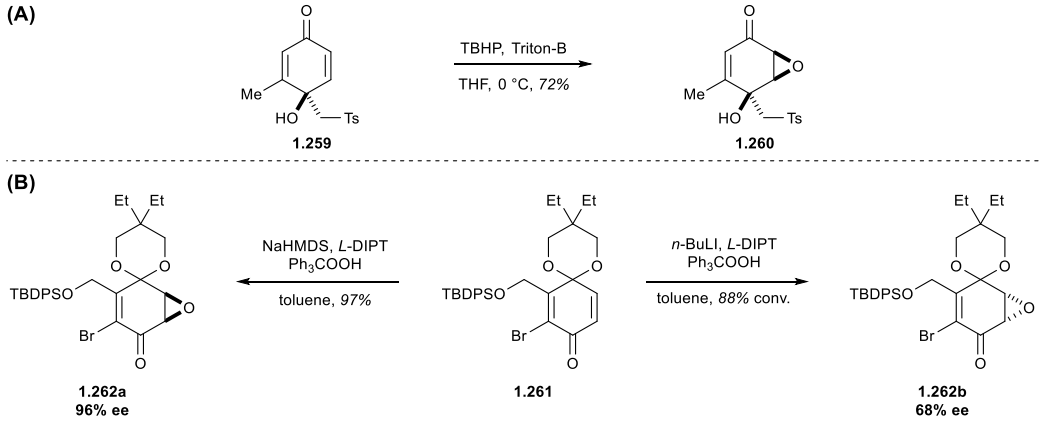
1.255a; R^1=CO_2Me **1.255b; R^1=CO*i*Pr** **1.256** **R^2=*i*-Bu, *i*-Pr, Ph** **1.257** **1.258** **55-89%**

1.2.4. Epoxidations

A number of groups have successfully engaged 2,5-cyclohexadienone substrates in epoxidation reactions. The majority of examples utilize nucleophilic epoxidation methods. Oxidizing agents include HOOH and *t*-BuOOH. Bases such as K_2CO_3, KOH, KO*t*-Bu, and DBU have been used. Carreño used this approach to transform dienone **1.259**, which was obtained through his previously reported methodology, into epoxide **1.260**.[84]

Porco has also reported an enantioselective epoxidation on cyclohexadienone systems (**Scheme 1.47**).[85] The authors found that when TrOOH was used as the oxidizing agent in the presence of L-DIPT with *n*-BuLi as the base, epoxide **1.262a** could be obtained in good ee. To their surprise, when NaHMDS was used as the base instead, the opposite enantiomer was obtained. The authors attributed this result to the differing stereochemical environments of the substrate-counterion complexes.

Scheme 1.47: (A) Representative cyclohexadienone epoxidations; (B) Porco's enantioselective cyclohexadienone epoxidation



1.3. 2,5-Cyclohexadienones in Natural Product Synthesis

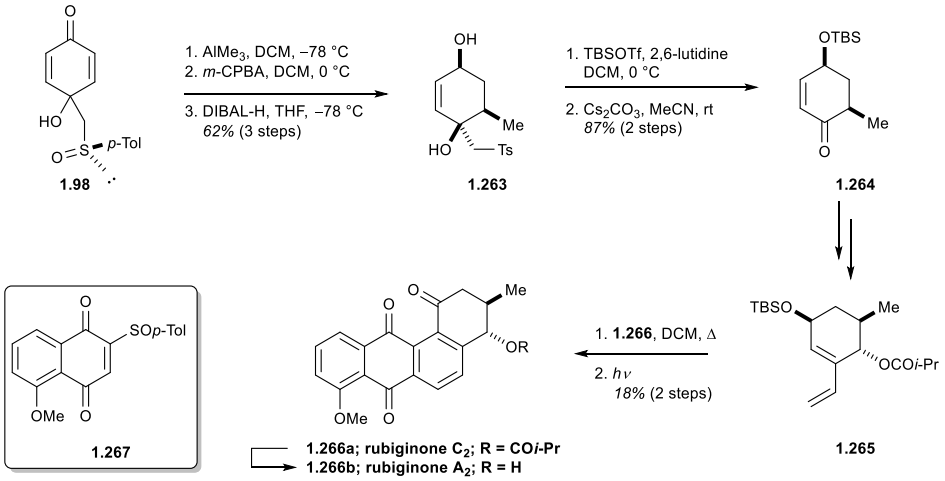
The ease with which 2,5-cyclohexadienones can be synthesized, along with the wide variety of reactions which they undergo has led them to be used in the synthesis of numerous natural products. Many such synthetic strategies feature a late-stage dearomatization on a relatively complex substrate. The use of 2,5-cyclohexadienones as building blocks early in a synthetic sequence is rarer. Several examples of the early-stage use of 2,5-cyclohexadienones will be highlighted below.

1.3.1. Rubiginones A and C

Carreño reported the synthesis of the antibiotic molecules rubiginones A_2 and C_2 (**Scheme 1.48**).[86] The authors utilized their aforementioned sulfoxide-directed trimethylaluminum addition to desymmetrize dienone **1.98**. Subsequent DIBAL-H reduction gave alcohol **1.263**. Oxidation to the sulfone followed by alcohol protection and sulfone elimination gave ketone **1.264**. The substrate could be further elaborated to diene **1.265**. A Diels-Alder reaction with **1.267** followed by aromatization under

photolytic conditions gave rubiginone C_2 (**1.266a**), which could be readily converted to rubiginone A_2 (**1.266b**).

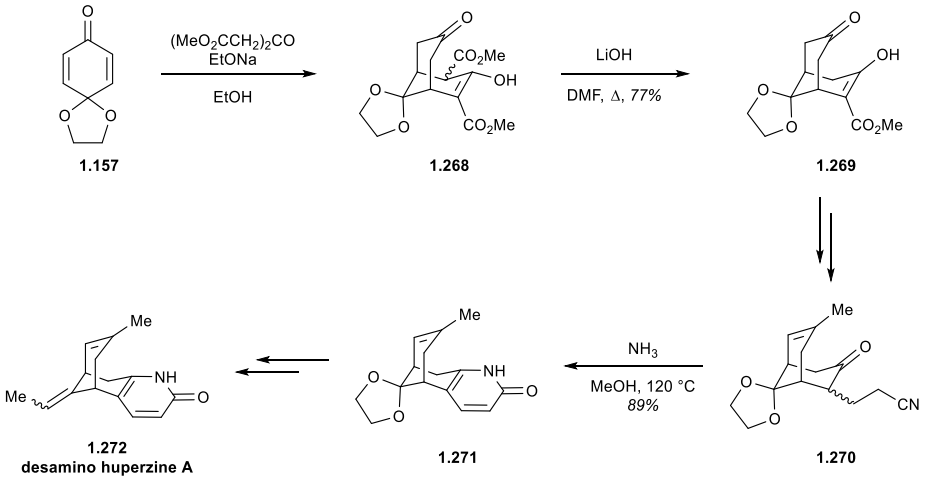
Scheme 1.48: Carreño's synthesis of rubiginones A and C



1.3.2. Desamino Huperzine A

Mulzer described the synthesis of the lycopodium alkaloid natural product desamino huperzine A (**Scheme 1.49**).[87] The authors began their synthesis with quinone monoketal **1.157**. When **1.157** was treated with acetone dicarboxylate dimethyl ester, bridged-bicyclic product **1.268** could be obtained. The material could be decarboxylated with LiOH to give **1.269**. Further elaboration gave ketonitrile **1.270**, which could be cyclized to give the pyridine **1.271**. Deprotection and functional group manipulation gave the final desamino huperizine A product **1.272**.

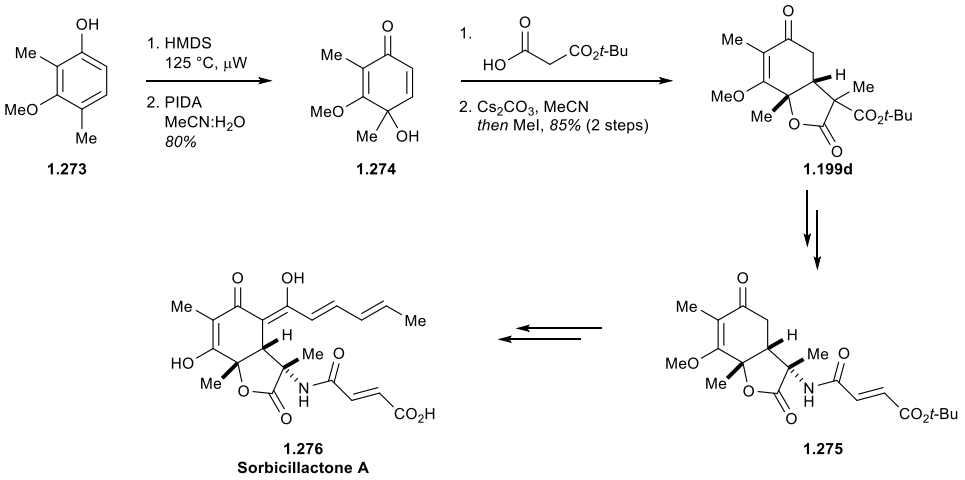
Scheme 1.49: Mulzer's synthesis of desamino huperizine A



1.3.3. Sorbicillactone A

Harned has utilized an intramolecular Michael addition (**Scheme 1.50**) in the synthesis of the marine natural product sorbicillactone A (**1.276**).[88] The TMS ether of phenol **1.273** was dearomatized with PIDA to give cyclohexadienone **1.274**. Installation of the malonate side-chain followed by cyclization and *in situ* methylation gave lactone **1.199d** as a 6.1:1 ratio of diastereomers. Though the desired diastereomer was the minor isomer, enough material could be isolated to complete the synthesis. The amide side-chain was installed through a sequence involving a key Curtius rearrangement to give amide **1.275**. Installation of the final side-chain followed by deprotection gave the natural product **1.276**.

Scheme 1.50: Harned's synthesis of sorbicillactone A



1.4 Conclusion

In conclusion, 2,5-cyclohexadienones are a class of substrates that can be easily accessed by a variety of methods. In particular, their ready availability from a wide variety of phenols through oxidative dearomatization greatly increases the potential of these molecules. Despite their relative simplicity, the molecules undergo a wide variety of reactions with many different substrates. It is often possible to achieve high regio- and stereoselectivity as well, enabling rapid construction of molecular complexity. However, their use as building blocks in natural product synthesis is still relatively sparse. Further examples, as well as an expanded arsenal of available reactions will increase their synthetic utility. In future chapters, we will report the use 2,5-cyclohexadienones as a launching point in the synthesis of the briarane diterpenoids. In the course of our studies, we utilized the impressive array of reactions which 2,5-cyclohexadienones are known to undergo to evaluate several different routes. Our efforts also took advantage of the often extremely high degree of stereoselectivity observed to set key stereocenters. The versatility and ease of access associated with

2,5-cyclohexadienones enabled a highly efficient synthesis of a complex fragment of the briarane diterpenoids.

CHAPTER 2

THE BRIARANE DITERPENOIDS: ISOLATION, BIOACTIVITY & SYNTHETIC APPROACHES

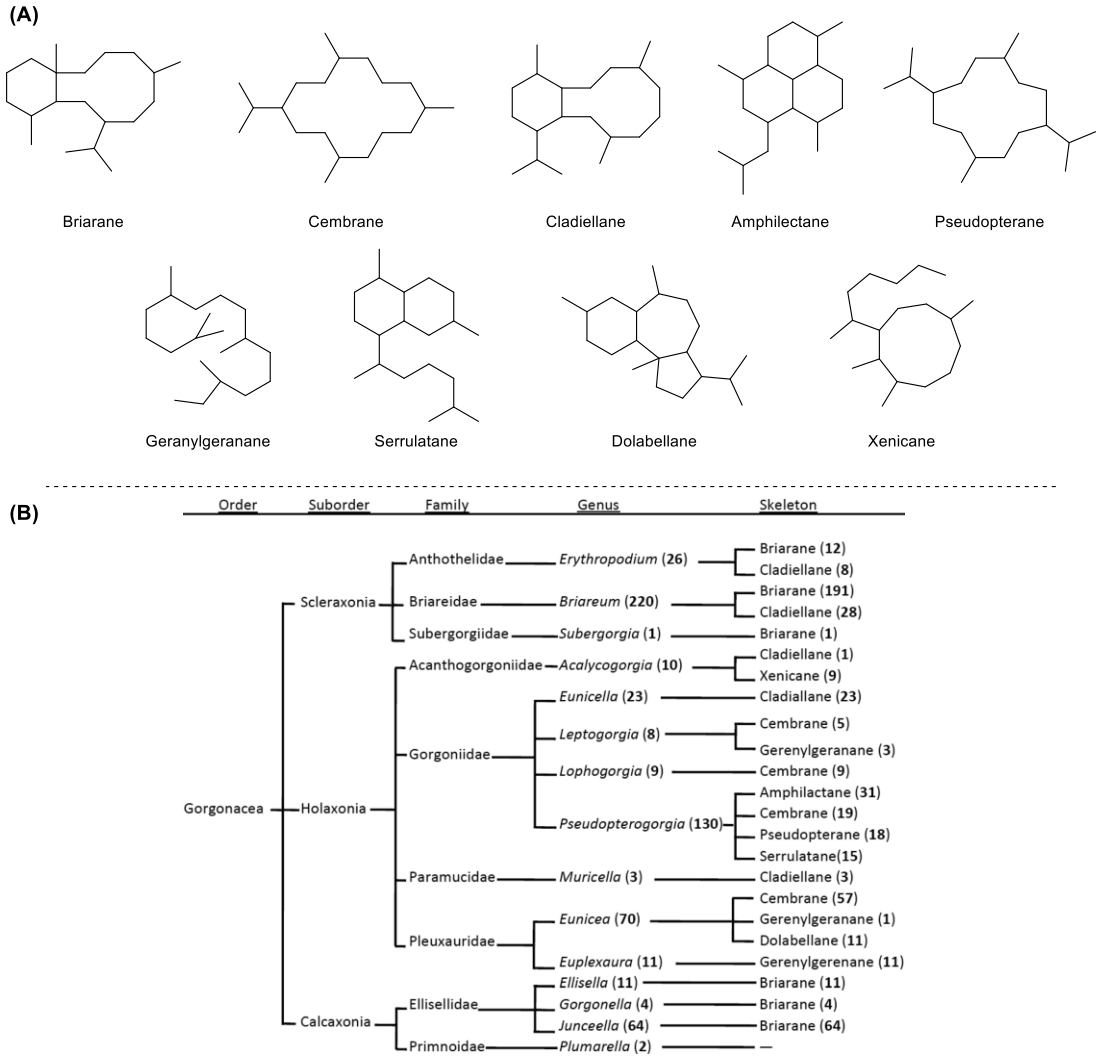
2.1 Marine Gorgonians and the Briarane Diterpenoids

2.1.1 Taxonomy & Natural Product Distribution

The marine gorgonians represent a diverse set of octocoral marine organisms which dominate coral reefs throughout the world. While their taxonomy has been a subject of significant study, their precise identification has often been difficult.[89] The gorgonians can be further divided into three orders; Scleraxonia, Holaxonia, and Calaxonia. Among these suborders, multiple families and genuses exist for each. As a result of the abundance of such corals, combined with their wide geographic distribution, the gorgonians have been a fruitful area of study for natural products chemists.

Diterpenoids represent one of the more important classes of natural products which have been isolated from gorgonian sources. As of 2009, Kerr has noted 40 different diterpenoid skeletal structures isolated from gorgonians.[89] Figure **2.1** shows the nine most common skeletal structures, along with their taxonomic distribution among the gorgonian family. In fact, the chemical makeup of a particular gorgonian sample can often aid as a taxonomic marker in gorgonian classsification.[90]

Figure 2.1: (A) Eight most common diterpenoid skeletons isolated from gorgonians; (B) Distribution of natural products across the gorgonian family[i]



2.1.2 Overview of the Briarane Diterpenoids

The briarane skeletal system represents one of the more common natural product families that have been isolated from the gorgonian octocorals. Briarane-type diterpenoids have been isolated from both the Scleraxonia and Calaxonia suborders, but not the

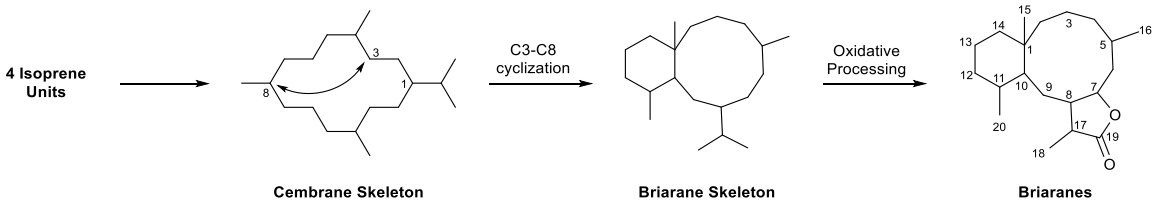
[i] Image from *Nat. Prod. Rep.,* **2009**, *26*, 681-710.

Holaxonia suborder. The family Briareidae (suborder Scleraxonia) is by far the most plentiful source of briarane diterpenoid compounds. In addition to gorgonian sources, Briaranes have also been found in non-gorgonian sources such as sea-pen corals and nudibranchs.

The briarane skeleton (**Scheme 2.1**) consists of a *trans*-fused bicyclo[8.4.0]tetradecane ring system. Most members also possess a γ-lactone comprising the C7-C8-C17-C19 carbons. Another common feature is a congested set of four, contiguous stereogenic centers comprising C1-C2-C10-C14. Oxidative processing by the organism can install oxygenation at nearly every other carbon in the system.

The briaranes are hypothesized to be biosynthetically derived from the cembrane skeleton, which is another commonly found skeletal structure in marine gorgonian species, through cyclization between C3 and C8 followed by oxidative processing. However, to date, no biosynthetic studies have been published.[91]

Scheme 2.1: Proposed biosynthesis of the briarane skeleton



2.2. Isolation and Bioactivities of Select Briarane Diterpenoids

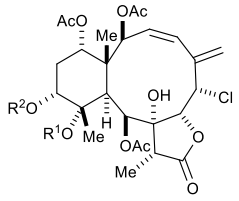
The wide distribution of gorgonian corals has led to the isolation of an extremely large number of briarane-type diterpenoids. To date, over 600 unique briarane diterpenoids have been characterized.[91, 92] Several examples have also been reported from non-gorgonian sources such as the sea pansy *R. reniformis*,[93] the sea pen octocoral *S. tentaculatum*,[94], and the Mediterranean nudibranch mollusk *Armina maculata*.[95] Some of the key briarane diterpenoid families, along with their relevant bioactivity will be discussed

below. Emphasis will be given to families which either display potent biological activity or possess a large number of family members.

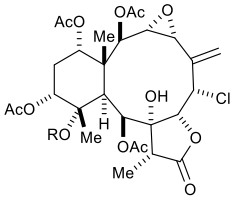
2.2.1. Briaranes from *Briareum abestinum*

Briareum abestinum is a species of gorgonian octocoral found throughout the Caribbean. In 1977, Cierezco and coworkers isolated the first known briarane diterpenoid briarein A (**2.1a, Figure 2.2**) from this source.[96] The structure of briarein A was identified through the use of x-ray crystallography. Later work by Cóbar and coworkers further confirmed the structure, as well as the structures of briareins B-L through the use of extensive 2D NMR spectroscopy.[97] Key features of the briareins include the presence of a tertiary oxygen (hydroxyl or acetate) at C11 and a secondary *cis* alcohol at C12. The briareins also contain either a C3-C4 double-bond or epoxide. Briareins A-E & G contain an exocyclic C5-C16 double bond and a C6-Cl. The remaining briareins contain an endocyclic C5-C6 double bond, which likely arises from singlet-oxygen induced rearrangement. To date, no biological activity of the briareins has been reported.

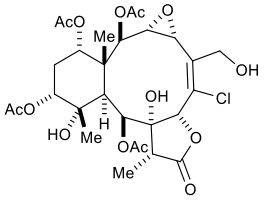
Figure 2.2: Select members of the briarein family



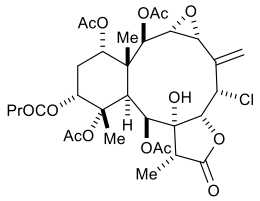
2.1a; Briarein A; R^1=R^2=Ac
2.1b; Briarein B; R^1=Ac, R^2=CO_2Pr
2.1c; Briarein C; R^1=H, R^2=CO_2Pr



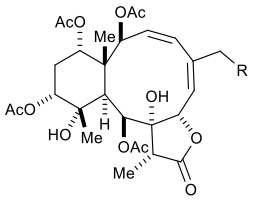
2.1d; Briarein D; R=Ac
2.1e; Briarein E; R=H



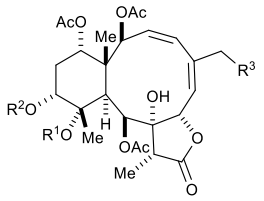
2.1f; Briarein F



2.1g; Briarein G



2.1h; Briarein H; R=OAc
2.1i; Briarein I; R=$OCOC_7H_{15}$
2.1j; Briarein J; R=Cl



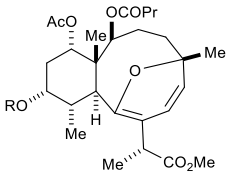
2.1k; Briarein K; R^1=H, R^2=COC_7H_{15}, R^3=OCOPr
2.1l; Briarein L; R^1=Ac, R^2=COPr, R^3=OAc

Briareum abestinum has also been the source of a particularly unique class of briarane diterpenoids known as the briareolate esters (**Figure 2.3**). These family members are noteworthy in that they possess a C19 methyl ester instead of the more common C7-C8-C17-C19 lactone moiety. The first such example, briareolate ester A (**2.2a**), was discovered by Tinto and coworkers from a sample collected off the coast of Tobago.[98] Further isolation studies led to the discovery of related briareolate esters B-K, though the C7-C8 double bond geometry of briareolate ester G (**2.2e**) could not be assigned at the time.[99] Many of the family members were found to possess weak activity against brine shrimp.

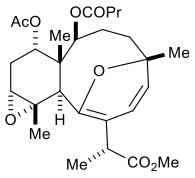
Some years later, West isolated additional members of the briareolate ester family from a sample collected off the coast of Florida. Most noteworthy among these family members was briareolate ester L (**2.2h**).[100] Like briareolate ester G (**2.2e**), briareolate ester L was found to possess an α, β, γ δ unsaturated C9 ketone, though the ^{1}H NMR signals for the alkene signified a different geometry than that of the isomeric briareolate ester G. A 2D ROESY experiment identified H7 correlations with H2 and H10, indicating that the H7 proton was placed inside the ring, suggesting a *Z* configuration at the C5-C6 double bond. From this information, the authors also assigned the configuration of the C5-C6 double bond in **2.2e** to be *E*. West would later report the isolation of briareolate esters J & K.[101]

Some members of the briareolate ester family were found to possess activity against the human embryonic stem cell (hSEC) line BG02 and the pancreatic cancer cell line BxPC-3. Briareolate ester L (**2.2h**) was found to possess potent activity against both cell lines (**Table 2.1**). Interestingly, the double bond isomer **2.2e** was found to display no inhibitory activity against either cell-line. Briareolate ester M (**2.2i**) was also found to display some activity, though the activity was much lower than that observed for **2.2h**. The other briareolate esters screened by West displayed either little or nonexistent activity against either cell line.

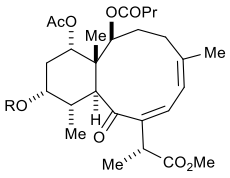
Figure 2.3: Select members of the briareolate ester family



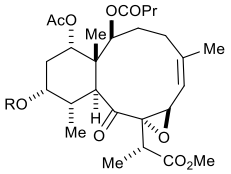
2.2a; Briareolate ester A; R=COPr
2.2b; Briareolate ester B; R=H
2.2c; Briareolate ester N; R=CO(CH$_2$)$_4$CH$_3$



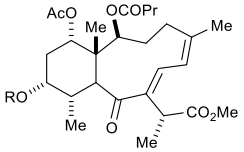
2.2d; Briareolate ester C



2.2e; Briareolate ester G; R=H
2.2f; Briareolate ester J; R=CO(CH$_2$)$_4$CH$_3$



2.2g; Briareolate ester K; R=CO(CH$_2$)$_4$CH$_3$



2.2h; Briareolate ester L; R=H
2.2i; Briareolate ester M; R=CO(CH$_2$)$_4$CH$_3$

Table 2.1: Cytotoxicity of the briareolate esters

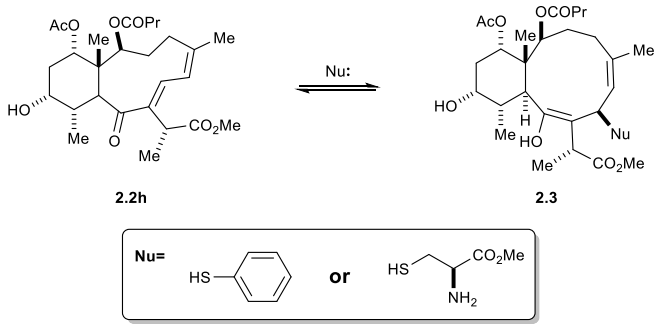
Entry	Briareolate Ester	EC_{50} BG02 (µM)	EC_{50} BxPC-3 (µM)
1	B (**2.2b**)	>40	>40
2	C (**2.2d**)	>40	>40
3	G (**2.2e**)	>20	>20
4	J (**2.2f**)	>40	N/A[a]
5	K (**2.2g**)	40	N/A[a]
6	L (**2.2h**)	2.4	9.3
7	M (**2.2l**)	8.0	13.0
8	N (**2.2c**)	>40	>40

a. No data reported

West and coworkers were intrigued by the significant activity of **2.2h** over related family members. They hypothesized that this increased activity was due to the conformation of the *E,Z* dienone in **2.2h**. A shorter UV absorption maximum for **2.2h** over the double-bond isomer **2.2e** (284 and 288 nm respectively) suggested that **2.2h** might be less conjugated, making the dienone 'spring loaded' for attack by a Michael donor. B3LYP calculations revealed the *Z,Z*-dienone to be approximately 29 kcal/mol more stable that the *E,Z*,-isomer

They investigated this hypothesis by treating **2.2h** with a variety of nucleophiles (**Scheme 2.2**). When **2.2h** was treated with thiophenol in methanol-d_4, **2.2h** reacted to form Michael adduct **2.3** in 5 minutes. Compound **2.2h** also reacted with cysteine methyl ester, though the reaction was significantly slower, and DMAP was required. Neither Michael adduct could be isolated, and experiments with nitrogen and oxygen-based nucleophiles failed. Performing an analogous experiment on **2.2e** resulted in no in nucleophilic addition, further confirming their hypothesis.

Scheme 2.2: Nucleophilic additions into briareolate ester L

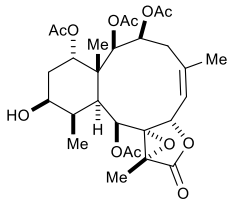


2.2.2. Briaranes from *Briareum excavatum*

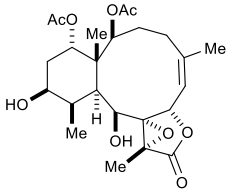
Briareum excavatum is a species of gorgonian coral found in regions of the South Pacific such as Taiwan, Indonesia, and Australia. The species has been a fruitful source of bioactive diterpenoids of both the excavatolide and the briaexcavatolide families.[102] A few members of the brianthein family have also been isolated.[103] The excavatolides and

briaexcavatolides are a large family of natural products with potent biological activity (**Figure 2.4**). Over thirty members of these compounds have been isolated. The members do not possess a C11-C12 double bond, though there is significant variation in other structural details such as the extent and placement of unsaturation, extent of oxygenation, and the presence or absence of an epoxide or chloride. Many of the family members have been screened for biological activity and have been found to be toxic against various cancer cell lines (**Table 2.2**). Some of the more potent members of the excavatolide and briaexcavatolide family include excavatolides C, E, K, M, and briaexcavatolide P.

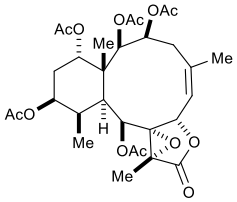
Figure 2.4: Select members of the excavatolide and briaexcavatolide families



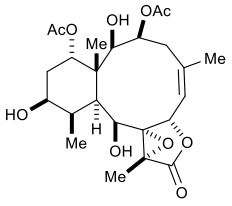
2.4a; Excavatolide C



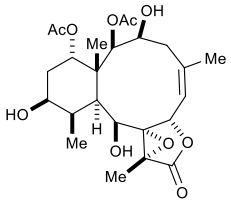
2.4b; Excavatolide E



2.4c; Excavatolide K



2.4d; Excavatolide M



2.4e; Briaexcavatolide P

Table 2.2: Cytotoxicity of the excavatolides

Entry	Compound	IC_{50} (P-388) (μg/mL)	IC_{50} (KB) (μg/mL)	IC_{50} (A-549) (μg/mL)	IC_{50} (HT-29) (μg/mL)
1	excavatolide C (**2.4a**)	0.3	1.9	1.9	1.9
2	excavatolide E (**2.4b**)	1.6	0.8	1.2	1.6
3	excavatolide K (**2.4c**)	0.9	3.3	3.0	1.3
4	excavatolide M (**2.4d**)	0.001	1.0	0.1	2.2
5	briaexcavatolide P (**2.4e**)	0.9	N/A[a]	4.8	3.1

a. No data reported

A few cytotoxic members of the briantheins family (briantheins A-C) have also been isolated from *briareum excavatum*.[103] Some, but not all, of the briantheins possess unsaturation at the C8-C17 and C11-C12 positions. Briantheins A-C were found to possess growth inhibition against the KB 3-1 and the multidrug resistant KB-C2 cell lines (**Table 2.3**).

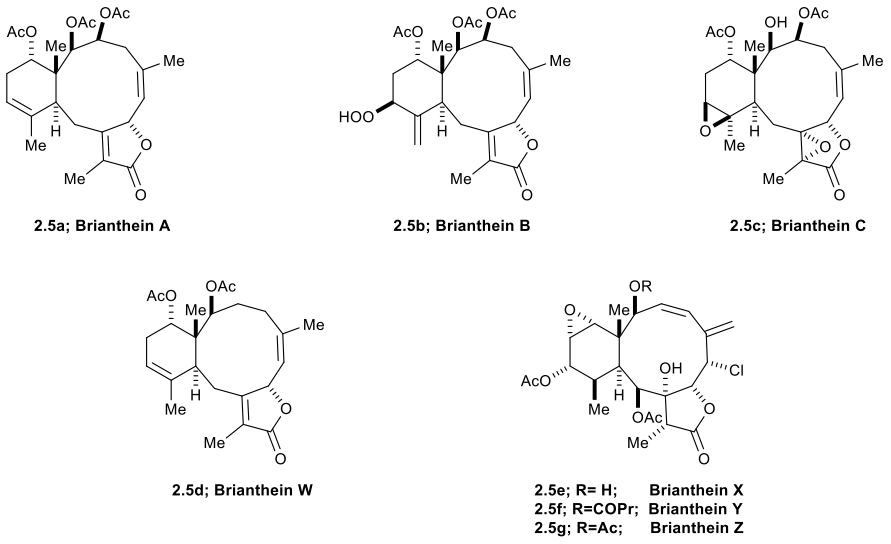
Table 2.3: Growth inhibition by brianthein A-C

Entry	Compound	Dose (μg/mL)	Growth Inhibition (%)	
			KB 3-1	KB-C2
1	brianthein A (**2.5a**)	10	27 ± 5	84 ± 3
		3	11 ± 6	60 ± 2
2	brianthein B (**2.5b**)	10	26 ± 4	37 ± 6
		3	5 ± 1	26 ± 4
3	brianthein C (**2.5c**)	10	17 ± 6	15 ± 2
		3	11 ± 1	0 ± 0

2.2.3. Briaranes from *Briareum polyanthes*

Additional members of the brianthein family were isolated from the gorgonian *Briareum polyanthes,* found in the eastern end of the Bermuda archipelago (**Figure 2.5**).[104, 105] Of the compounds isolated, Brianthein W (**2.5d**) stands out as one of the simplest briaranes isolated to date. Evaluation of **2.5d** against the P-388, KB, A-549, and HT-29 cell lines showed ED_{50} values of 0.76, >50, >50, >50 μg/mL respectively. Interestingly, brianthein W was also isolated from the luminescent sea pen coral *Funiculina quadrangularis* in the Vada and Capraia Islands in the Ligurian Sea.[104] Briantheins X-Z were also isolated from *Briareum polyanthes* and displayed varied activities. Brianthein Y (**2.5f**) was found to exhibit viral inhibition against the mouse corona virus assay at a concentration of 400 μg/mL. Brianthein Z (**2.5g**) exhibited stronger antiviral inhibition at 80 μg/mL. Brianthein Z also displayed activity against the herpes-simplex virus at 80 μg/mL and cytotoxicity against the P-388 cell line at a concentration of 10 μg/mL.[106]

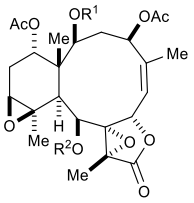
Figure 2.5: Select members of the brianthein family



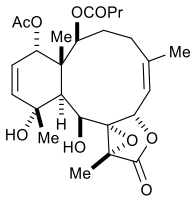
2.2.4. Briaranes from *Briareum stechi*

Briareum stechi is a species of gorgonian that is found in the shallow waters of the Great Barrier Reef. It has been the source of several classes of briarane diterpenoids. The stecholides are a class of highly oxygenated compounds isolated from *Briareum stechi* (**Figure 2.6**).[107] Some examples such as stecholides A, B, and H have been found to display activity against the P-388 cancer cell-line (**Table 2.4**).

Figure 2.6: Select members of the stecholide family



2.6a; R^1 = COPr, R^2 = H Stecholide A
2.6b; R^1=COEt, R^2 = Ac; Stecholide B



2.6c; Stecholide H

Table 2.4: Cytotoxicity of the stecholides

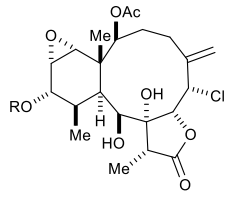
Entry	Compound	ED_{50} (P-388) (μg/mL)
1	stecholide A (**2.6a**)	45
2	stecholide B (**2.6b**)	5.4
3	stecholide H (**2.6c**)	10

2.2.5. Briaranes from *Briareum spp.*

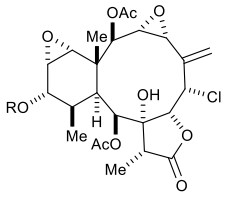
A number of bioactive briarane diterpenoids were collected from a gorgonian in Palau which was originally identified to be *Pachyclavularia violaea*. Examination of its chemical makeup led to the revision of its order to be an unidentified member of the

Briareum order *Briareum spp.* From this sample a number of solenolides (solenolide A-F) were isolated (**Figure 2.7**).[108] They were found to affect a reduction of edema at a concentration range of 15 μg. Some family members also possess antiviral activity.

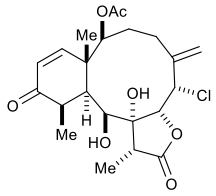
Figure 2.7: Select members of the solenolide family



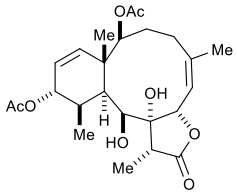
2.7a; R = COC_5H_{11}; Solenolide A
2.7b; R = Ac; Solenolide B



2.7c; R = H; Solenolide C
2.7d; R = Ac; Solenolide D



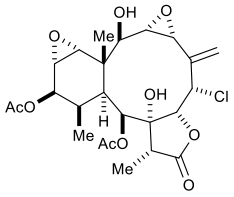
2.7e; Solenolide E



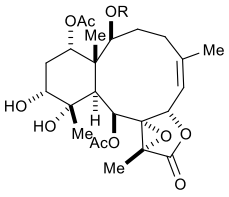
2.7f; Solenolide F

A number of briareolides were isolated from *Briareum sp* (**Figure 2.8**).[109] Briareolides were reported to display moderate anti-inflammatory activity in a mouse ear assay. A number of violides were also isolated from *Briareum sp.*[110] The violides all possess a C13-C14 double bond. Several members were found to have biological activity against the Vero and MDCK cell lines (**Table 2.5**). Some of the violides also possess rare C2-C3-C4 oxygenation. Violides K & L (**2.10k&l)** are the only known briarane-type diterpenoids found to possess 5 hydroxyl groups.

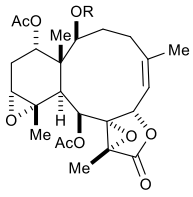
Figure 2.8: Select members of the brianolide, briareolide and violide families



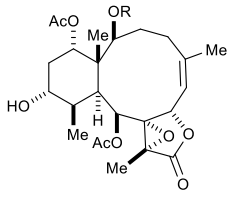
2.8; Brianolide



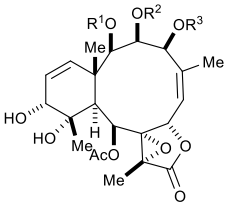
2.9a; R = COPr; Briareolide A
2.9b; R = OAc; Briareolide B



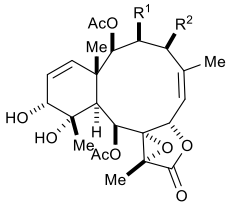
2.9c; R = COPr; Briareolide C
2.9d; R = OAc; Briareolide D



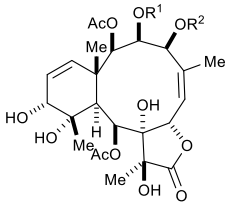
2.9e; R = COPr; Briareolide E
2.9f; R = OAc; Briareolide F



2.10a; R^1 = Ac, R^2 = H, R^3 = COC_7H_{15}; Violide A
2.10b; R^1 = R^2 = R^3 = Ac; Violide B
2.10c; R^1 = R^2 = Ac, R^3 = COC_7H_{15}; Violide C
2.10d; R^1 = R^2 = Ac, R^3 = COC_5H_{11}; Violide D
2.10e; R^1 = R^2 = Ac, R^3 = COPr; Violide E
2.10f; R^1 = R^2 = H, R^3 = COC_7H_{15}; Violide F



2.10g; R^1 = OAc, R^2 = H; Violide G
2.10h; R^1 = H, R^2 = $OCOC_7H_{15}$; Violide H
2.10i; R^1 = H, R^2 = $OCOC_5H_{11}$; Violide I



2.10j; R^1 = R^2 = Ac; Violide J
2.10k; R^1 = H, R^2 = $OCOC_7H_{15}$; Violide K
2.10l; R^1 = H, R^2 = COC_5H_{11}; Violide L

2.2.6. Briaranes from other marine organisms

While briarane diterpenoids are most commonly found in gorgonian sources, they have also been isolated from other marine organisms. The funicolides (A-E) were isolated from the luminescent sea pen *Funiculina quadranglaris* (**Figure 2.9**).[111] The family members possess the same substitution pattern, and vary only in oxygen substituents and the substitution at C7. Brianthein W, which is simply the C9 oxidized version of the funicolides, was isolated as well.[104] No biological data has been reported for the funicolides.

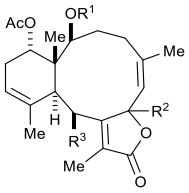
Table 2.5: Cytotoxicity of the violides

Entry	Product	CC_{50} (Vero) (μg/mL)	CC_{50} (MDCK) (μg/mL)
1	violide A (**2.10a**)	1.90	1.90
2	violide B (**2.10b**)	--	--
3	violide C (**2.10c**)	1.69	1.67
4	violide D (**2.10d**)	2.53	3.57
5	violide E (**2.10e**)	3.65	4.69
6	violide F (**2.10f**)	3.93	4.03
7	violide G (**2.10g**)	9.37	11.7
8	violide H (**2.10h**)	0.85	0.85
9	violide I (**2.10i**)	1.41	1.30
10	violide J (**2.10j**)	>100	>100
11	violide K (**2.10k**)	>100	>100
12	violide L (**2.10l**)	>100	>100

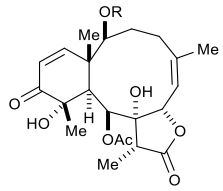
The renillafoulins (A-C) were isolated from the sea pansy *Renilla reniformis.*[93, 112] these compounds were found to inhibit the settlement of barnacle larvae with varying degrees of potency. Briaranes have also been isolated from a limited number of non-coral organisms. The verecynamins were isolated from extracts of the nudibranch mollusk

Armina maculata, though it is possible that the source of the compound is from the nudibranch's diet, as the same compounds were isolated from the sea-pen coral *Veretillum cynomouium* which is a part of the *Armina maculata's* diet.[95, 113] Unlike most briaranes, the verecynarmins possess a furan instead of the more common lactone.

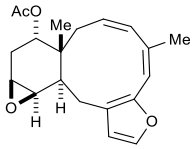
Figure 2.9: Select members of the funicolide, renillafoulin and verecynarmin families



2.11a; R^1 = COEt, R^2 = H_β, R^3 = H; Funicolide A
2.11b; R^1 = COEt, R^2 = α-OH, R^3 = H; Funicolide B
2.11c; R^1 = COEt, R^2 = H_β, R^3 = OAc; Funicolide C
2.11d; R^1 = COPr, R^2 = H_β, R^3 = H; Funicolide D
2.11e; R^1 = Ac, R^2 = α-OH, R^3 = H; Funicolide E



2.12a; R = Ac; Renillafoulin A
2.12b; R = COEt; Renillafoulin B
2.12c; R = COPr; Renillafoulin C



2.13; Verecynarmin A

2.3. Previous Synthetic Approaches to the Briarane Diterpenoids

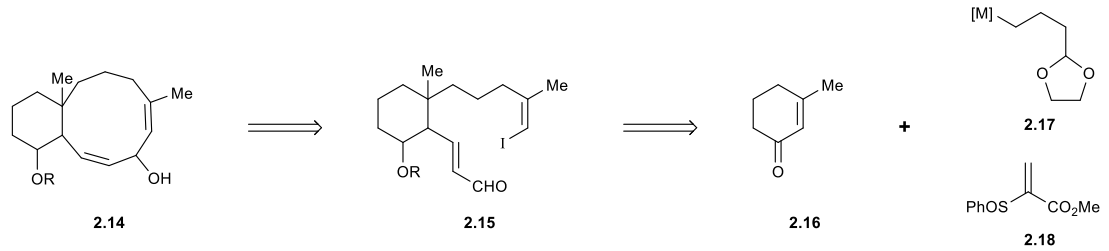
Despite the wide structural diversity and potent biological activity associated with the briaranes, relatively little synthetic effort has been expended in their synthesis. Only a few groups have reported synthetic progress towards any member of the briaranes. To date, no completed total syntheses have been reported; a fact that illustrates the significant challenge which the briarane diterpenoids pose. While early reports focus on the synthesis of various small or highly simplified fragments of the briaranes, including the ten-membered ring and various stereogenic elements, later reports focus on the formation of the C1-C2-C10-C14 stereotetrad core. Previous reported efforts toward the briarane diterpenoids will be presented in chronological order.

2.3.1. Procter's Synthesis of Briarane 10-Membered Ring of Solenolide F

2.3.1.a. Motivation & Retrosynthesis

Procter published the first synthetic approach to a portion of the briaranes.[114] The authors targeted Solenolide F (**2.7f, Figure 2.7**), which was isolated from the Indopacific gorgonian *Solenopodium sp.* Their efforts focused specifically on the efficient formation of the ten-membered ring from a substrate that already contained the six-membered ring. Bicycle **2.14** was selected as their initial synthetic target, which would be formed through a Cr^{II}-mediated cyclization of vinyl-iodide **2.15** (**Scheme 2.3**). Compound **2.15** could be obtained through the connection of three components **2.16**, **2.17**, and **2.18**. Ketal **2.17** could undergo organometallic conjugate-addition into enone **2.16**. The resulting enolate would then intercept sulfoxide **2.18**.

Scheme 2.3: Procter's retrosynthesis of a solenolide F model system

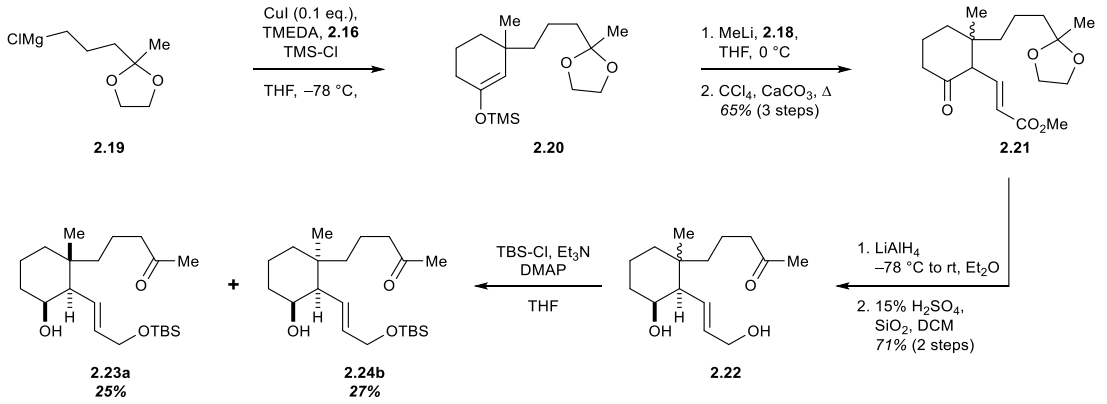


2.3.1.b. Synthesis of the Ten-Membered Ring

The authors began by investigating the organometallic addition of Grignard reagent **2.19** into enone **2.16** (**Scheme 2.4**). They found that the conjugate addition proceeded well in the presence of a catalytic amount of CuI, but it was necessary to trap the resulting enolate as silyl-enol ether **2.20** in order to perform the desired conjugate addition. Compound **2.20** could be converted to the lithium enolate by treatment with MeLi followed by conjugate addition into **2.18**. After elimination, ketone **2.21** could be obtained in good overall yield as a 1:1 mixture of diastereomers. The ketone and ester moieties in the product were reduced with $LiAlH_4$ and the ketal protecting group was removed to give

allylic alcohol **2.22**. The allylic alcohol was selectively protected as a TBS-ether and the resulting diastereomers **2.23a&b** could be separated chromatographically. The relative stereochemistry of **2.23a&b** was assigned on the basis of coupling-constant analysis.

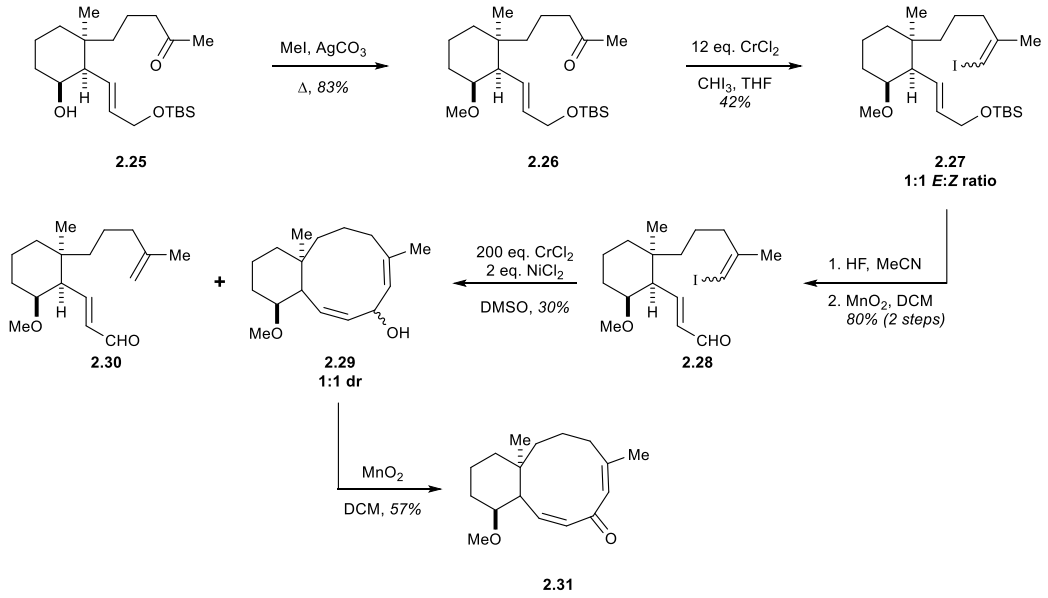
Scheme 2.4: Synthesis of diastereomeric alcohols **2.24a** & **2.24b**



The authors hypothesized that **2.28** would more readily undergo the required cyclization due to the *trans*-diaxial conformation of **2.28**, which would position the reacting groups far from each other (**Scheme 2.5**). The secondary alcohol of **2.25** was converted to a methyl ether and ketone **2.26** was converted to vinyl iodide **2.27** through a Takai olefination, giving a 1:1 mixture of inseparable *E* and *Z* isomers. Subsequent removal of the TBS-ether followed by allylic oxidation gave the cyclization precursor **2.28**. After optimization, the authors found that cyclized product **2.29** could be obtained, though in low yield, by using a massive excess (200 equivalents) of $CrCl_2$ in DMSO. Despite their best efforts, substantial amounts of uncylized, deiodinated compound **2.30** was also isolated. The authors hypothesized that this product likely results from deiodination of the unreactive *E*-vinyl iodide. As the product was obtained as a 1:1 mixture of diastereomers, the authors performed an allylic oxidation of the substrate to give cross-conjugated ketone **2.31** in order to simplify spectral analysis. While they were able to successfully form the 10-membered ring, the poor diastereoselectivity as well as the use of an extremely large

amount of toxic, expensive $CrCl_2$ makes this route intractable towards further optimization. No further studies by the Procter lab have since been reported.

Scheme 2.5: Cyclization of a briarane analogue



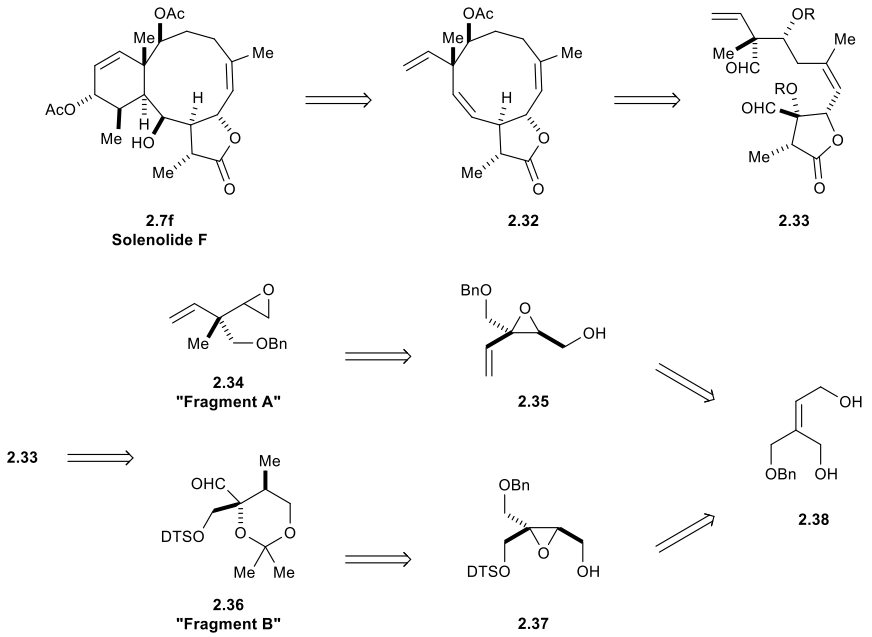
2.3.2. Nantz's Synthesis of Two Fragments of Solenolide F

2.3.2.a. Motivation and Retrosynthesis

Nantz and coworkers sought to develop a method to synthesize the 10-membered ring portion (**2.32**) of Solenolide F (**2.7f**) in a highly convergent fashion (**Scheme 2.6**).[115] They hoped to forge the ten-membered ring through a McMurray coupling of dialdehyde **2.33**. Inspired by the presence of oxygenation α-to the methyl-containing quaternary carbons at C1 and C17, they hypothesized that the skeleton could be broken into three fragments, two of which contain the aforementioned quaternary centers. These two fragments could be connected through a C4-C6 fragment capable of undergoing nucleophilic addition at both ends (referred to by the authors as a 'propyne equivalent').

The authors proposed epoxide **2.34** (Fragment A) and acetal **2.36** (Fragment B) as the key fragments to target. The presence of oxygenation next to the methylated, quaternary centers led Nantz to consider regioselective epoxide opening with a methyl anion equivalent as a viable method to form both fragments. Fragment B (**2.36**) could be made through the known addition of a methyl-group into epoxide **2.37** at the less-hindered position. The formation of fragment A (**2.34**) would be more challenging, as it would necessitate the addition of the methyl group into the fully-substituted carbon of epoxide **2.35**; a transformation which had not been previously reported. Both epoxides **2.35** and **2.37** could be derived from the diol **2.38**.

Scheme 2.6: Nantz's retrosynthesis of solenolide F

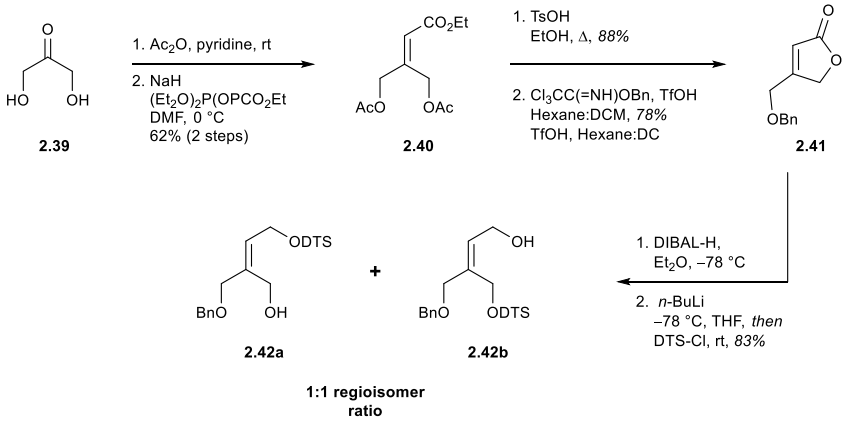


*2.3.2.b. Synthesis of Diol Precursor **2.42a&b***

The authors began by synthesizing the diol precursor to both **2.34** and **2.36** (**Scheme 2.7**). Commercially available 1,3-dihydroxyacetone was acetylated to give the *bis*-acetate. The resulting ketone was converted to triester **2.40** by means of a HWE olefination. Cleavage of the acetate protecting groups under acidic conditions led to spontaneous

lactonization. The lactone was benzylated to give **2.41** in good yield. The lactone was reduced with DIBAL-H followed by mono-silylation of the resulting diol. After a survey of protecting groups, the authors found that the DTS (dimethylthexylsilyl) protecting group led selectively to mono-silylated products **2.42a&b** which could be chromatographically separated and used in subsequent reaction. Compound **2.42a** was used to form fragment A and **2.42b** was used to form fragment B.

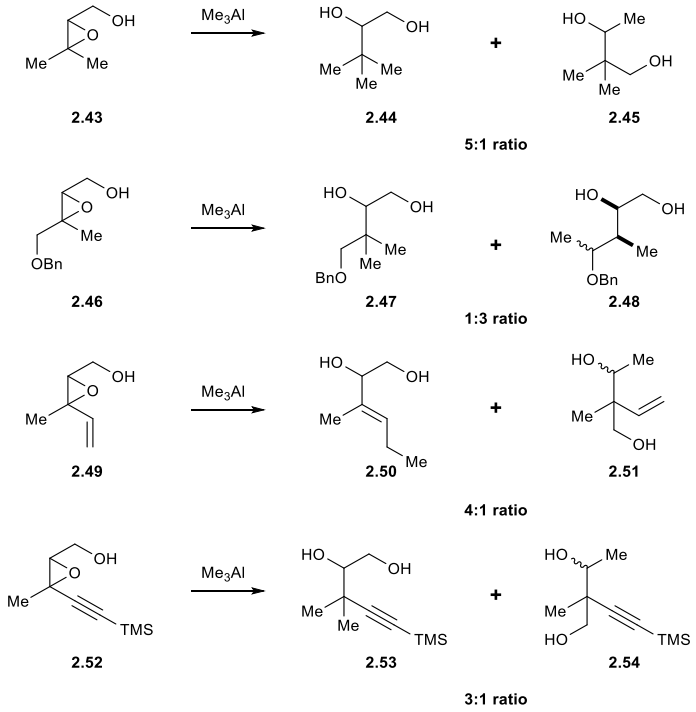
Scheme 2.7: Synthesis of regioisomeric fragments **2.42a** & **2.42b**



2.3.2.c. Synthesis of Fragment A

Prior to performing the epoxide-opening of fragment **2.42a**, the authors investigated a similar reaction on a number of model substrates (**Scheme 2.8**). Epoxide opening of substrate **2.43** with trimethylaluminum proceeded to give desired **2.44** as the major product, with diol **2.45**, which results from a 1,2 alkyl migration, as a minor product. Use of bulkier, benzyl-protected epoxide **2.46** led to **2.47** as the major product, with the desired **2.48** as a minor product. Vinyl epoxide **2.49** resulted primarily in the isolation of S_N2' product **2.50** along with the alkyl-migration product **2.51**. Encouragingly, propargylic epoxide **2.52** provided the desired product **2.53** as the major product. The alkyne could then be potentially converted to a vinyl group if similar reactivity patterns were observed in the actual synthesis.

Scheme 2.8: Model studies of epoxide opening

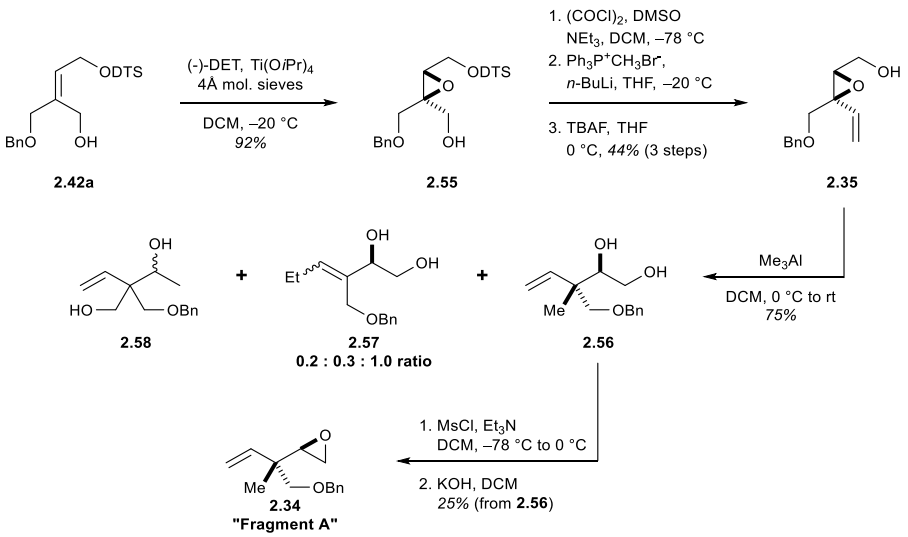


Having observed promising reactivity in model systems, the authors sought to synthesize fragment A from alcohol **2.42a** (**Scheme 2.9**). Compound **2.42a** was subjected to a Sharpless asymmetric expoxidation to give epoxide **2.55** in good yield with an enantiomeric purity of 90% (as determined by Mosher's method). The primary alcohol was oxidized under Swern conditions and subjected to Wittig olefination to give vinyl epoxide **2.35** after silyl-group removal.

The authors were pleased to discover that the addition of trimethylaluminum into epoxide **2.35** proceeded to give the desired diol **2.56** as the major product, with products **2.57** and **2.58** formed as side products in a (1.0:0.3:0.2) ratio. Unlike the case of model substrate **2.49**, it appeared that the bulkier, benzyl-protected group in **2.35** discouraged S_N2' addition. They also hypothesize that the adjacent π-system served to enhance the addition at C3 relative to migrating-group participation. The resulting product **2.56** was

methylated followed by treatment with KOH to form epoxide fragment A (**2.34**) in 25% yield from **2.56**.

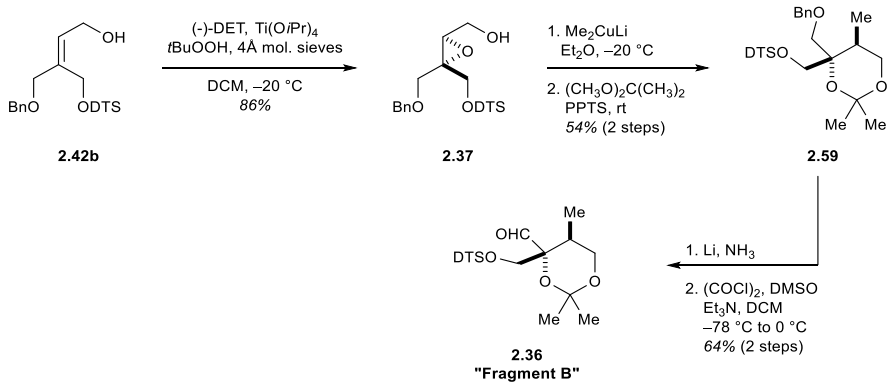
Scheme 2.9: Synthesis of "Fragment A" (**2.34**)



2.3.2.d. Synthesis of Fragment B

The synthesis of fragment B (**2.36**) began by performing an analogous Sharpless asymmetric epoxidation on substrate **2.42b**, to give epoxide **2.37** in 86% yield and 92% ee (as assigned by Mosher's method) (**Scheme 2.10**). A methyl group was added into the less hindered carbon of the epoxide using Me_2CuLi in Et_2O. The resulting diol was protected as an acetonide (**2.59**). The benzyl protecting group was removed with Li in NH_3, followed by Swern oxidation to give **2.36** (Fragment B) in good yield. In summary, the Nantz group was able to furnish the two quaternary carbon-containing fragments that could be used in the synthesis of Solenolide F. However, no further work towards solenlide F or any other briarane targets using this approach has been reported.

Scheme 2.10: Synthesis of "Fragment B" (**2.36**)

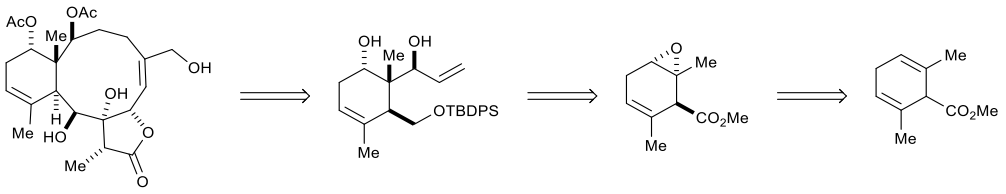


2.3.3. Ito & Iguchi's Synthesis of the Stereotetrad Core of Pachyclavulide B

2.3.3.a. Motivation & Retrosynthesis

Pachuclavulide B (**2.60**) is a briarane-type diterpenoid isolated by the Iguchi lab from the Okinawan soft coral *Pachyclavularia violacaea* (**Scheme 2.11**).[116] The compound was found to exhibit growth-inhibitory activity against the SNB-75 central-nervous system cancer cell line. Ito and Iguchi identified core structure **2.61** as an ideal initial synthetic goal.[117] This stereotetrad core possesses the six-membered ring, along with four contiguous C1-C2-C10-C14 stereocenters that are commonly found in the briaranes and could be easily converted to many family members. In examining this potential substructure, the authors identified latent symmetry within the molecule which they hoped to exploit. To that end, they postulated that **2.61** could come from epoxide **2.62**. Compound **2.62** could in turn be made through a desymmetrizing epoxidiation of achiral diene **2.63**, which is itself available from the birch reduction of 2,6,-methylbenzoic acid.

Scheme 2.11: Ito/Iguchi's retrosynthesis of pachyclavulide B

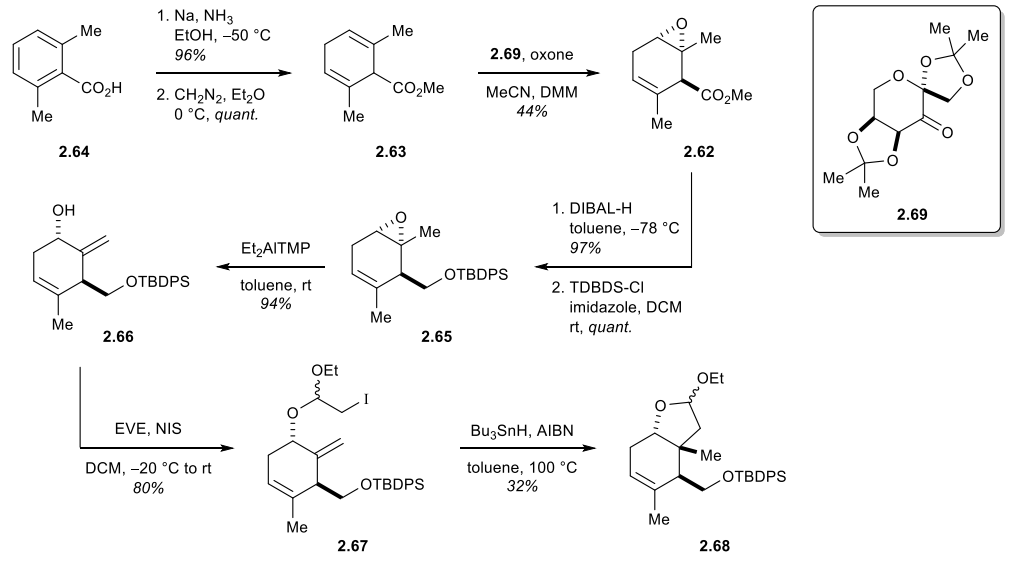


2.60 Pachyclavulide B — **2.61** — **2.62** — **2.63**

*3.3.3.b. Synthesis of Briarane Stereotetrad **2.61***

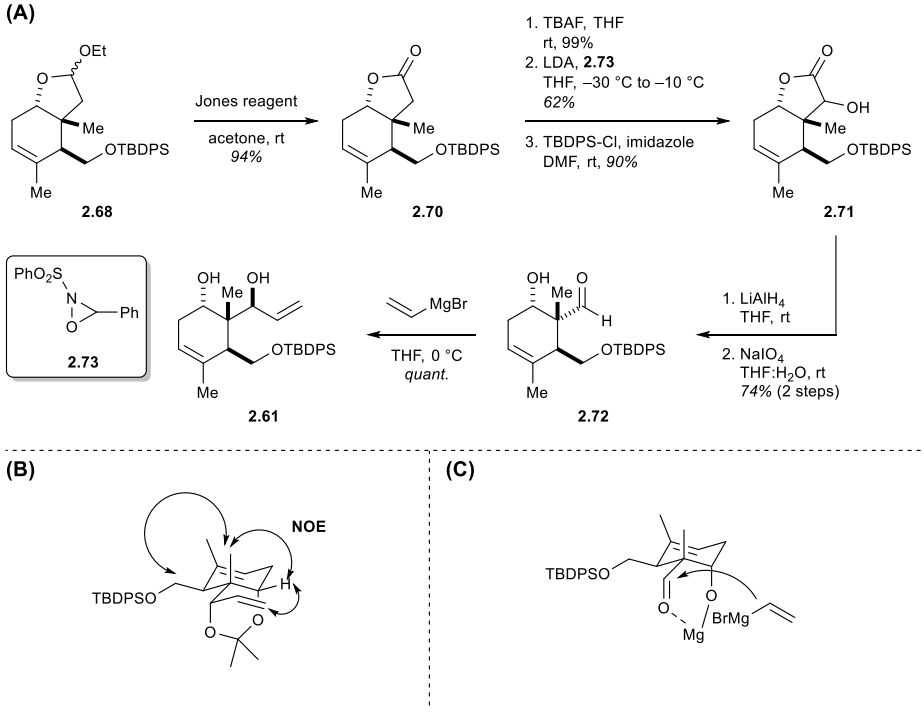
The authors began their synthesis by performing the Birch reduction of 2,6-dimethylbenzoic acid using Na in NH_3 followed by conversion to methyl ester **2.63** (**Scheme 2.12**). After optimization, it was found that the ideal epoxidation conditions employed a stoichiometric amount of D-sorbose-derived catalyst **2.69** with oxone as the oxidant. Under these conditions, epoxide **2.62** could be obtained in 44% yield with 81% de and 87% ee. The ester in **2.62** was reduced with DIBAL-H followed by protection of the alcohol to give silyl-ether **2.65**. The enantiopurity could be further improved at this stage through recrystallization. Epoxide **2.65** was converted to allylic alcohol **2.66** by treatment with Et_2AlTMP. The alcohol was treated with NIS and ethyl vinyl ether to give iodide **2.67** in good yield. Attempts to cyclize **2.67** using Bu_3SnH were met with mediocre results. The desired cyclized acetal **2.68** could only be obtained in a disappointing 32% yield, along with deiodinated products and 6-*endo* cyclized products. Nevertheless, the authors elected to carry the material forward.

Scheme 2.12: Synthesis of acetal 2.68



Acetal **2.68** was oxidized to the lactone using Jones' reagent to give **2.70** (**Scheme 2.13**). At this point, the authors encountered difficulty achieving the desired α-hydroxylation. They speculated that the bulky TBDPS group prevented the reaction from occurring. When the silyl ether was removed, hydroxylation with Davis' oxaziridine proceeded smoothly to give lactone **2.71** after reinstallation of the TBDPS ether. Lactone **2.71** was reduced with $LiAlH_4$ followed by oxidative cleavage with $NaIO_4$ to give aldehyde **2.72**. Addition of vinylmagnesium bromide led to the isolation of diol **2.61** in quantitative yield as a single diastereomer. The authors were able to confirm that the stereochemistry through NOE correlations (**Scheme 2.13B**) of the resulting acetonide. They postulated that coordination of the free hydroxyl group at C14 with Mg leads to rigid metallobicycle, in which one face of the aldehyde is effectively blocked by the TBDBS group, leading to selective addition of the Grignard reagent from the *Si* face (**Scheme 2.13C**). In summary, Ito and Iguchi were able to afford the stereotetrad core of the briarane diterpenoids in enantioenriched form in 18 steps from starting material, though no further synthetic efforts have been reported.

Scheme 2.13: (A) Synthesis of briarane stereotetrad 2.61; (B) Rationalization of stereoselective Grignard addition

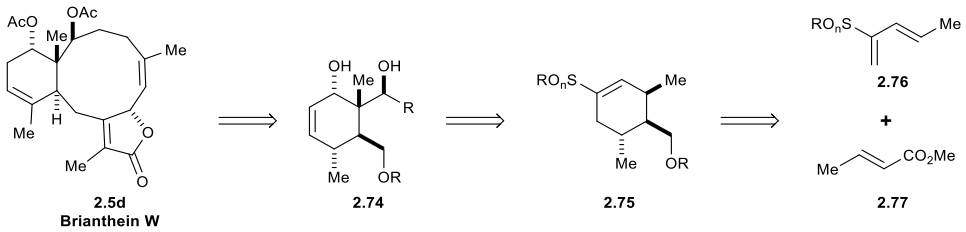


2.3.4. Bates' Synthesis of the Briarane Stereotetrad

2.3.4.a. Motivation & Retrosynthesis

As in the previous report by Ito and Iguchi, Bates identified stereotetrad core **2.74** (referred to by the authors as the 'northern hemisphere') of the briaranes to be a key synthetic target (**Scheme 2.14**).[118] Their approach to the stereotetrad core hinged on the setting the stereocenter at C1 through a sigmatropic rearrangement, and the formation of the six-membered ring **2.75** through a crotonate Diels-Alder reaction using sulfonyl diene **2.76** and methyl crotonate.

Scheme 2.14: Bates' retrosynthesis of brianthein W

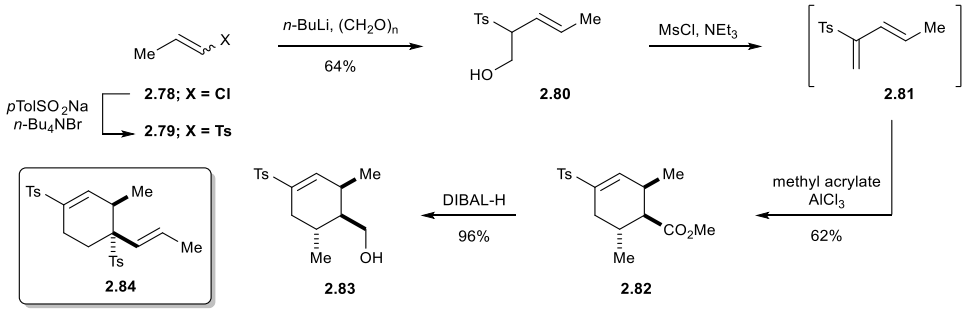


2.3.4.b. Synthesis of the Briarane Stereotetrad

The authors began by synthesizing the sulfonyl diene **2.76** (**Scheme 2.15**). Crotyl chloride and sodium *p*-toluenesulfinate were combined under phase-transfer conditions to give sulfone **2.79**. Sulfone **2.79** was then treated with *n*-BuLi followed by the addition of formaldehyde to give alcohol **2.80**. Elimination of the alcohol was affected using MsCl and excess NEt_3. The resulting diene **2.81** was observed to dimerise spontaneously to give cyclohexene **2.84** when stored in neat form. As such, the diene was kept as a solution in DCM and stored at cryogenic temperatures.

When diene **2.81** was reacted with methyl crotonate in the presence of $AlCl_3$, the Diels-Alder adduct **2.82** was obtained. Extended reaction times (7 days) were necessary to achieve high conversions. A related sulfoxide diene was also evaluated in the Diels-Alder reaction. However, the sulfoxide was not used as the reaction proceeded even more slowly and gave an intractable mixture of diastereomers due to the additional stereogenic center at sulfur. The ester in **2.82** was reduced with DIBAL-H to give alcohol **2.83**. The relative stereochemistry of **2.83** was confirmed by X-ray crystallography.

Scheme 2.15: Synthesis of Diels-Alder adduct **2.83**

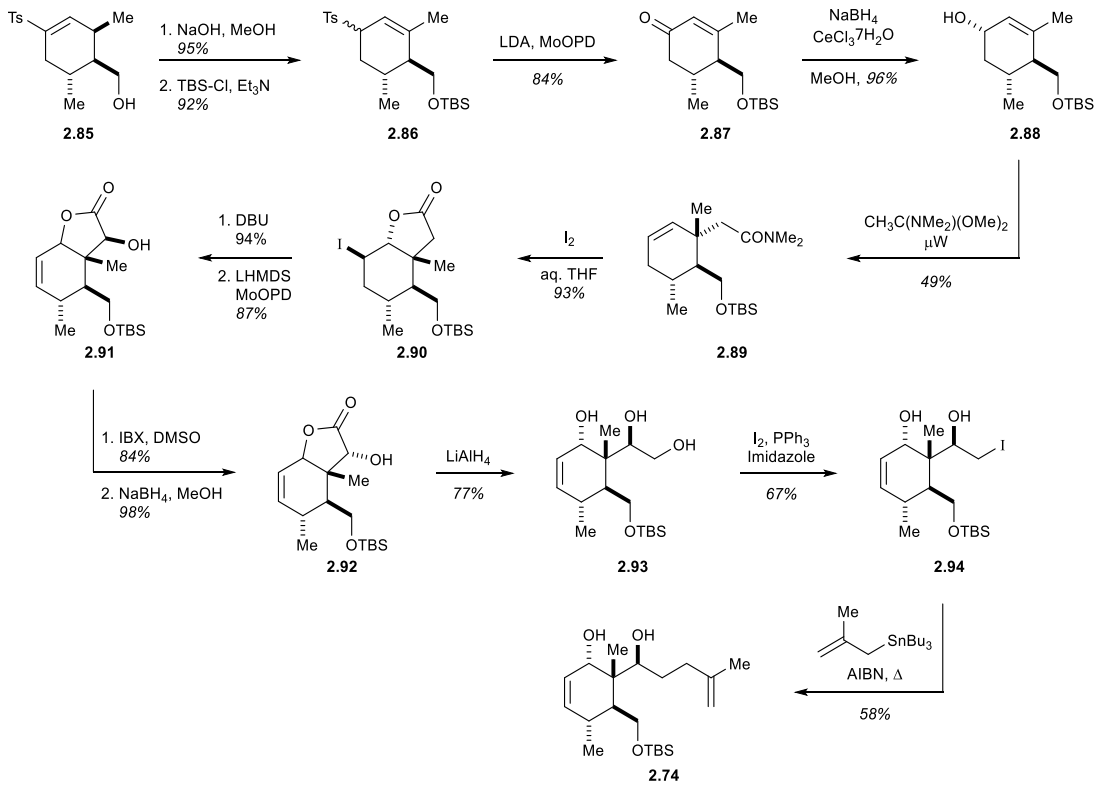


The authors found the removal of the sulfone to be quite challenging. A number of oxidative methods were evaluated with little success. It was discovered that the sulfone **2.83** could be isomerized by heating in MeOH in the presence of NaOH (**Scheme 2.16**). The resulting allylic-sulfone was protected as the TBS ether **2.86**, and the sulfone was oxidatively removed by treatment with LDA and MoOPD to give enone **2.87** along with a small amount of over-oxidized products.

The carbonyl moiety was reduced under Luche conditions to give equatorial alcohol **2.88**. The authors found the allylic alcohol to be resistant to numerous sigmatropic rearrangement conditions. After extensive screening, they found that an Eschenmoser-Claisen rearrangement could be performed successfully. Treatment of the allylic alcohol **2.88** with dimethylacetamide dimethylacetal in xylene under microwave irradiation gave the desired rearranged product **2.89** in acceptable yield. This material was treated with I_2 in wet THF to perform an iodolactonization reaction to afford iodide **2.90**, which underwent elimination with DBU. α-Oxygenation of the lactone with LiHMDS and MoOPD gave lactone-alcohol **2.91**. Unfortunately, compound **2.91** possessed the opposite relative stereochemistry of the natural products. The stereochemistry was inverted through a two-step sequence involving oxidation with IBX followed by reduction of the ketone with $NaBH_4$ to give the isomer **2.92**. Reduction with $LiAlH_4$ gave triol **2.93**. The primary alcohol could be selectively converted to an iodide by treatment with I_2 and PPh_3. The

remainder of the side-chain was installed through a Keck allylation to give the briarane stereotetrad **2.74** in 16 steps, though no further progress has been reported.

Scheme 2.16: Synthesis of briarane stereotetrad **2.74**



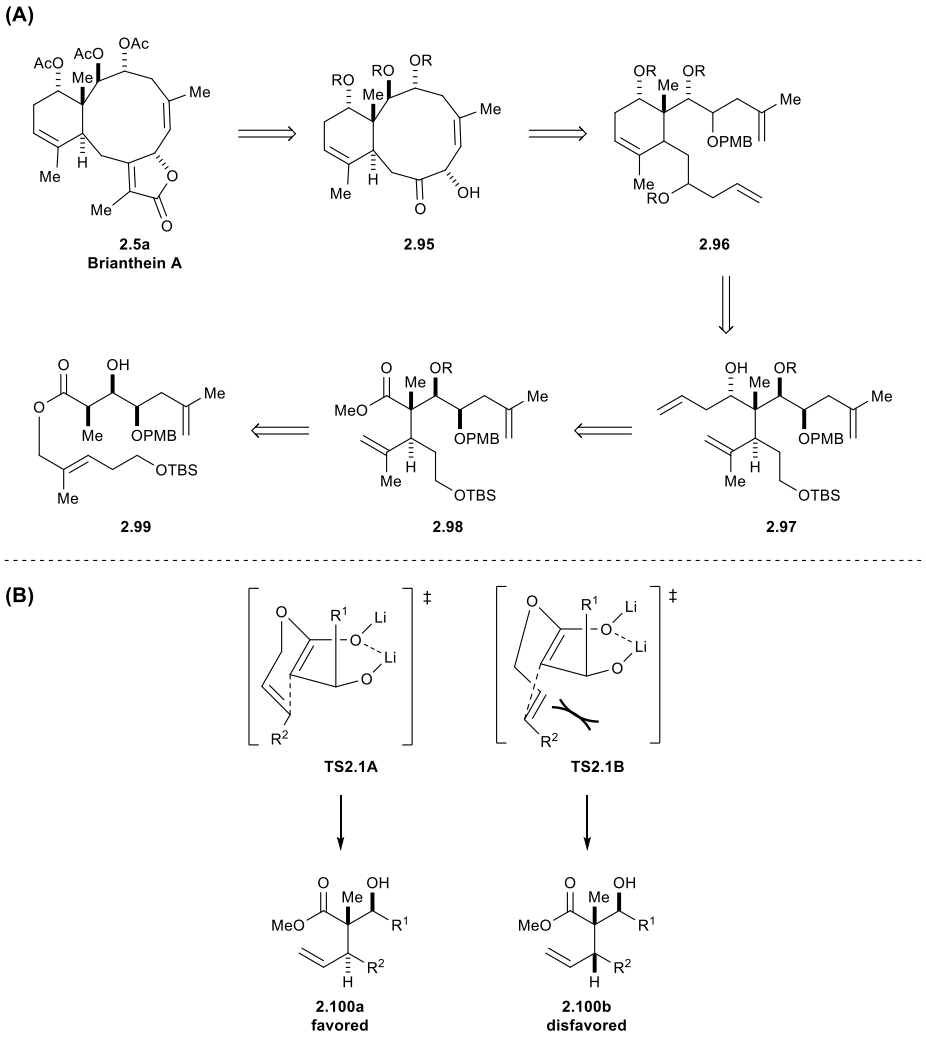
2.3.5. Crimmins' Ireand-Claisen Approach to Brianthein A

2.3.5.a. Motivation & Retrosynthesis

In the course of their studies on the dianionic Ireland-Claisen rearrangement, Crimmins found that substrates such as **2.98** could be furnished through treatment of **2.99** with LiHMDS in toluene/THF (**Scheme 2.17**).[119] The authors proposed to utilize this facile reaction to set three of the four contiguous stereocenters present in the briarane natural product brianthein A (**2.5a**). Their retrosynthetic plan involved the formation of brianthein A from bicyclic core **2.95**. This in turn would be made from the cyclohexene **2.96** which

could come from ring-closing metathesis on substrate **2.79**. Substrate **2.97** in turn would be the result of the aforementioned dianionic Ireland-Claisen rearrangement of substrate **2.98**. The authors expected the rearrangement to proceed through chair-like transition state **TS2.1A** which is favored over **TS2.1B**.

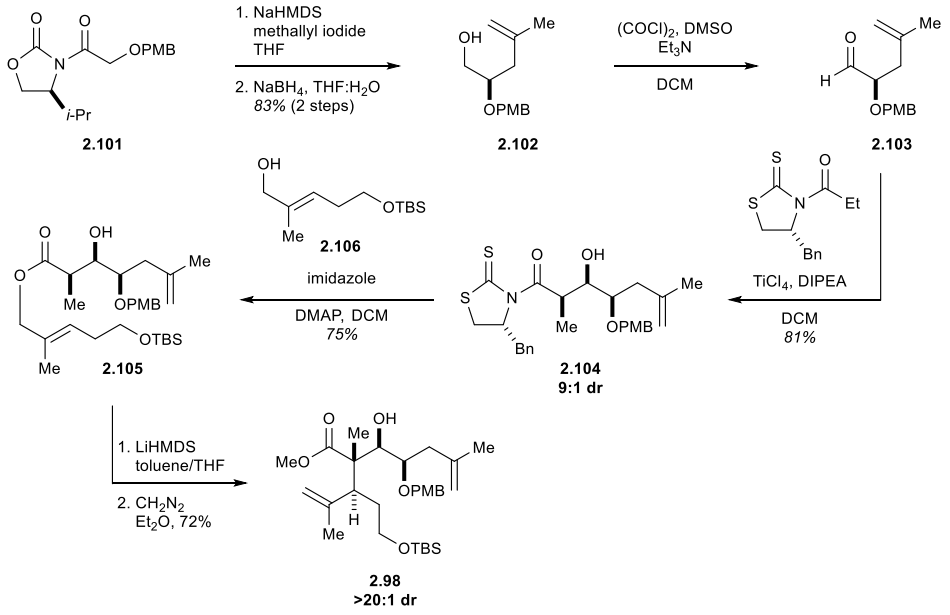
Scheme 2.17: (A) Crimmins' retrosynthesis of brianthein A; (B) Stereochemical rationalization for dianionic Ireland-Claisen rearrangement



*2.3.5.b. Synthesis of the Ireland-Claisen Product **2.98**.*

The authors began with oxazolidineone **2.101**, which was stereoselectively alkylated followed by auxiliary removal with $NaBH_4$ to give alcohol **2.102** (**Scheme 2.18**). Oxidation of compound **2.102** under Swern conditions gave aldehyde **2.13** which was reacted with *N*-proplthiazolidenthione under aldol conditions to give adduct **2.104** in a stereoselective fashion. Compound **2.105** was converted to the Ireland-Claisen precursor **2.105** by treatment of **2.104** with alcohol **2.106** under basic conditions. Treatment of **2.105** with LiHMDS followed by methylation with CH_2N_2 gave the product **2.98** as a single diastereomer in good yield. The elaboration of this product into brianthein A is currently under investigation.

Scheme 2.18: Ireland-Claisen rearrangement to form briarane precursor **2.98**



2.4 Conclusion

In conclusion, the briarane diterpenoids are an intriguing class of substrates isolated from coral sources from around the world. While their diverse, and often quite potent,

biological activity makes them prime targets for synthesis, little synthetic effort has been reported. Early work utilized highly inefficient and toxic reagents to form a key ring. Other early attempts only furnished very small pieces of the briaranes, and no further reports of their use exist. Later work shifted from the ten-membered ring to the C1-C2-C10-C14 stereotetrad. To date, work by Ito/Iguchi and Bates require extended reaction sequences to forge the stereotetrad, potentially diminishing the utility of their routes in accessing full briarane structures. Crimmins' work is a significant improvement, forming three of the four stereocenters of the stereotetrad in rapid fashion. However, their route still requires the forging of two ring systems plus functional group manipulation to complete the synthesis. Thus, there is still significant room for the improvement of synthetic routes to access the briaranes.

CHAPTER 3

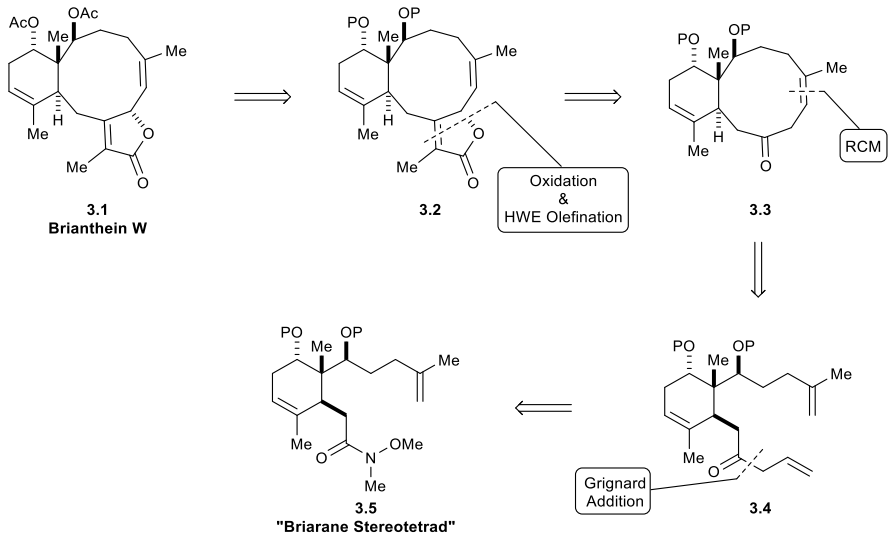
BICYCLIC APPROACHES TO THE BRIARANE DITERPENOIDS

3.1 The Stereotetrad Core as a Key Synthetic Intermediate

Inspired by the work of Ito/Iguchi[117] and Bates[118], we identified briarane stereotetrad fragment **3.5** as our initial target *en route* to the briarane diterpenoids (**Scheme 3.1**). This fragment contains the congested C1-C2-C10-C14 stereotetrad that presents a significant challenge for any synthetic approach to the briaranes. We believed that a viable route to this core structure will be useful as a common launching point in the synthesis of numerous briarane family members as well as non-natural analogues.

We selected brianthein W (**3.1**) as our initial target due to its relative simplicity. A successful route to brianthein W could be modified at later stages to access other members of the briarane family. Brianthein W would come from **3.2** after deprotection and acylation. The butenolide in **3.2** would be installed through the oxidation and HWE olefination of bicycle **3.3**. The ten-membered ring could come from the ring-closing metathesis of **3.4**.[120] The allyl ketone fragment in **3.4** would be installed through a Grignard addition into Weinreb amide **3.5**, which contains the key structural components of the aforementioned briarane stereotetrad.

Scheme 3.1: Retrosynthesis of brianthein W to the briarane stereotetrad



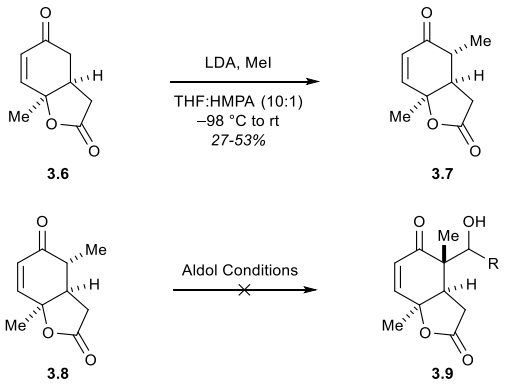
3.2 Initial Synthetic Approach

3.2.1. Nucleophilic Cyclopropane Opening

Our initial strategy sought to overcome some of the challenges that our group encountered in previous investigations related to the briaranes.[ii] Previous attempts to methylate bicyclic lactone **3.6** proceeded in low yields and low conversion (**Scheme 3.2**). Subsequent attempts at an aldol addition also failed to produce the desired adducts (**3.9**). It was our hope that milder aldol conditions would overcome the inherent instability of these substrates and allow for product formation.

[ii] Work performed by Kyle Kalstabakken

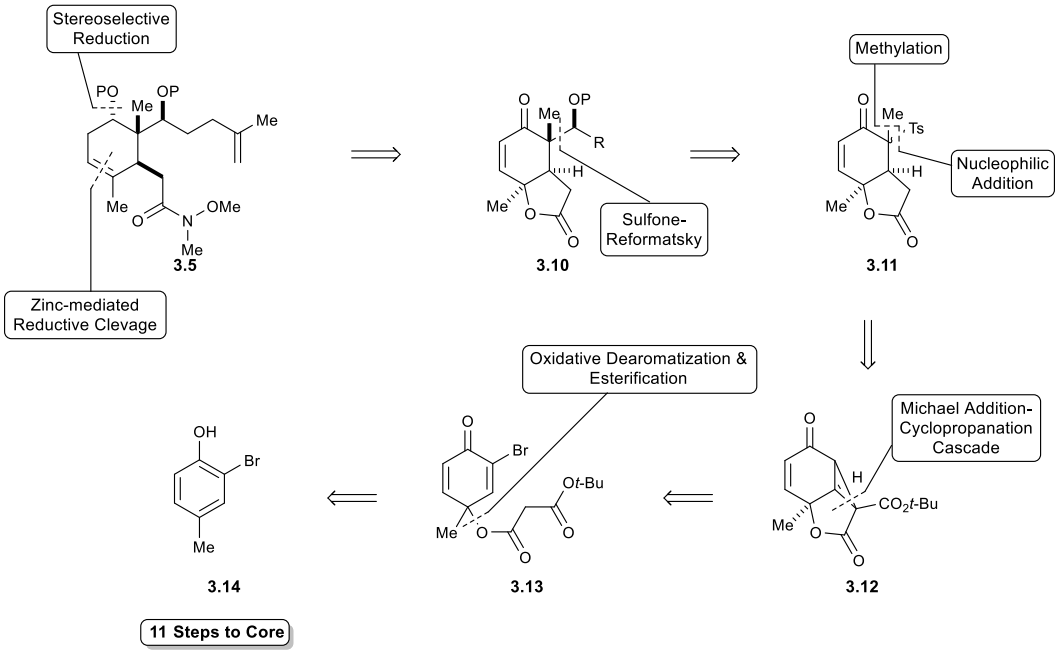
Scheme 3.2: Previous efforts towards the briaranes



3.2.2. Initial Retrosynthetic Proposal

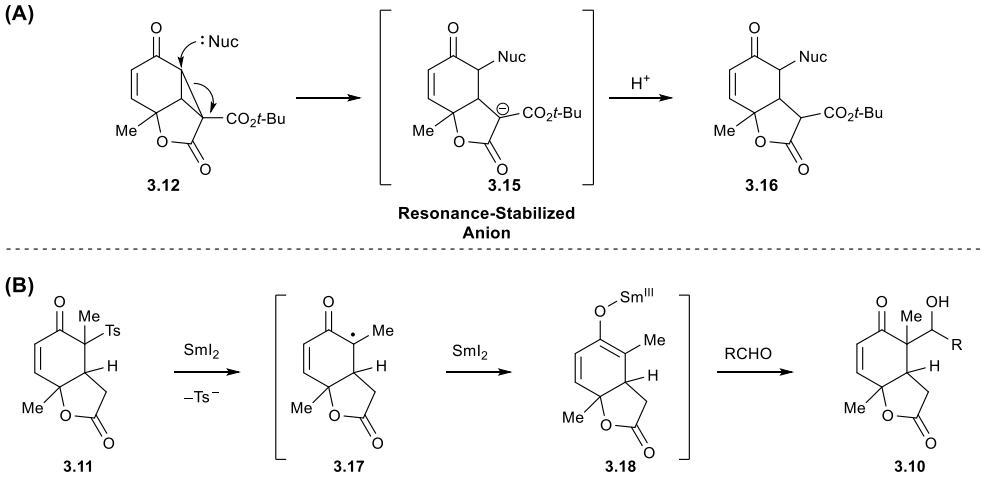
Our initial retrosynthetic proposal involved the formation of the C14 carbinol through a stereoselective reduction. The trisubstituted double-bond of **3.5** could be produced via a zinc-mediated reductive cleavage of the C11 lactone in **3.10**.[121] We planned to set the all-carbon quaternary center at C1 through a sulfone Reformatsky reaction of methylated β-ketosulfone **3.11** (**Scheme 3.3A**). Mild methylation conditions could be used to access **3.11** due to the increased acidity of the ketosulfone. It was our hope that the use of milder conditions would allow the methylation to be performed in improved yield. Sulfone **3.11** could be obtained through nucleophilic addition of a sulfur-based nucleophile into known cyclopropane **3.12** followed by decarboxylation and methylation.[65] We expected the cyclopropane to be electrophilic at C1 due to the high strain in the tricyclic system along with the stabilized anion that would result from such an addition (**Scheme 3.3A**).[122, 123]

Scheme 3.3: Initial retrosynthetic proposal of the briarane stereotetrad **3.5**



To affect the key sulfone Reformatsky reaction, β-ketosulfone **3.11** would be treated with a suitable single-electron reducing agent such as SmI_2 (**Scheme 3.4B**).[124] After initial reduction of either the sulfone or the enone, the system would fragment into the *p*-toluenesulfinate anion and α-keto radical **3.17**. Reduction by a second equivalent of SmI_2 would give the samarium enolate **3.18** that will undergo an aldol-type addition with an aldehyde, present in the reaction mixture, to give the desired product **3.10**. We hoped that the generation of the enolate under such mild conditions, and in the presence of the aldehyde, would minimize competitive rearomatization reactions that have we have observed in similar systems.

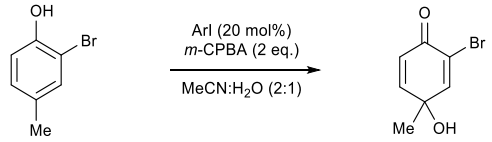
Scheme 3.4: (A) Proposed cyclopropane opening; (B) Proposed sulfone-Reformatsky reaction



3.2.3. Enantioselective Oxidative Dearomatization Studies

Phenol **3.14** was synthesized on the 10+ gram scale by a known procedure.[125] With phenol **3.14** in hand, we evaluated the catalytic, oxidative dearomatization of **3.14**. A variety of aryl-iodide catalysts were screened using *m*-CPBA as the terminal oxidant (**Table 3.1**) and H_2O as the nucleophile. Iodobenzene and 4-iodotoluene produced quinol **3.19** in acceptable yield. 4-Iodoanisole and 4-iodobiphenyl gave lower yields. Surprisingly, converting the phenol to the TMS-ether[11] prior to dearomatization resulted in no isolation of product. We decided to use iodotoluene as the optimum catalyst due to the high reaction yield and ease of handling the solid reagent.

Table 3.1: Optimization of catalytic dearomatization conditions



3.14 **3.19**

Entry	Catalyst	Yield (%)
1	iodobenzene	57
2	4-iodotoluene	58
3	4-iodoanisole	36
4	4-iodobiphenyl	37
5	4-iodotoluene[a]	N/R

a. Phenol **3.14** was converted to the TMS ether before reaction

We recognized that the unsymmetrical nature of phenol **3.3** generates a new stereogenic carbon upon dearomatization. A suitable chiral catalyst would enable the synthesis of enantioenriched quinol **3.19** and thus lead to enantioenriched Brianthein W. Our lab developed a series of tartrate-derived catalysts that were able to furnish compound **3.19** in up to 35% ee (**Section 1.1.4)**.[27] While these results clearly demonstrate the potential to synthesize **3.19** in an enantioselective manner, further improvement is needed to obtain synthetically viable selectivity. We briefly investigated other potential catalyst substructures in order to identify new lead structures for future optimization. In order to maximize the potential for later optimization, we targeted structures that were readily amenable to library synthesis and screening.

We began by evaluating a series of iodoaryl oxazolines which are similar to those that have been used by Birman in enantioselective Iodine(V) oxidations.[26] A series of amides (**3.21a&b**) were synthesized from the respective acid-chloride and amino-acid derived amino alcohols (**Scheme 3.5**). Subsequent cyclization gave oxazolines **3.22a&b** in acceptable yield. We were encouraged to find that oxazolines **3.22a&b** resulted in some, albeit extremely low, selectivity (**Table 3.2**). Tetrafluoroborate salts **3.23a&b** led to slightly higher selectivity.[126] We also investigated camphor-derived oxazoline **3.26**, which again resulted in low selectivity.[127] A catalyst derived from naphthalene-based iodoacid **3.29** gave little improvement.[128]

Scheme 3.5: Synthesis of oxazoline catalysts

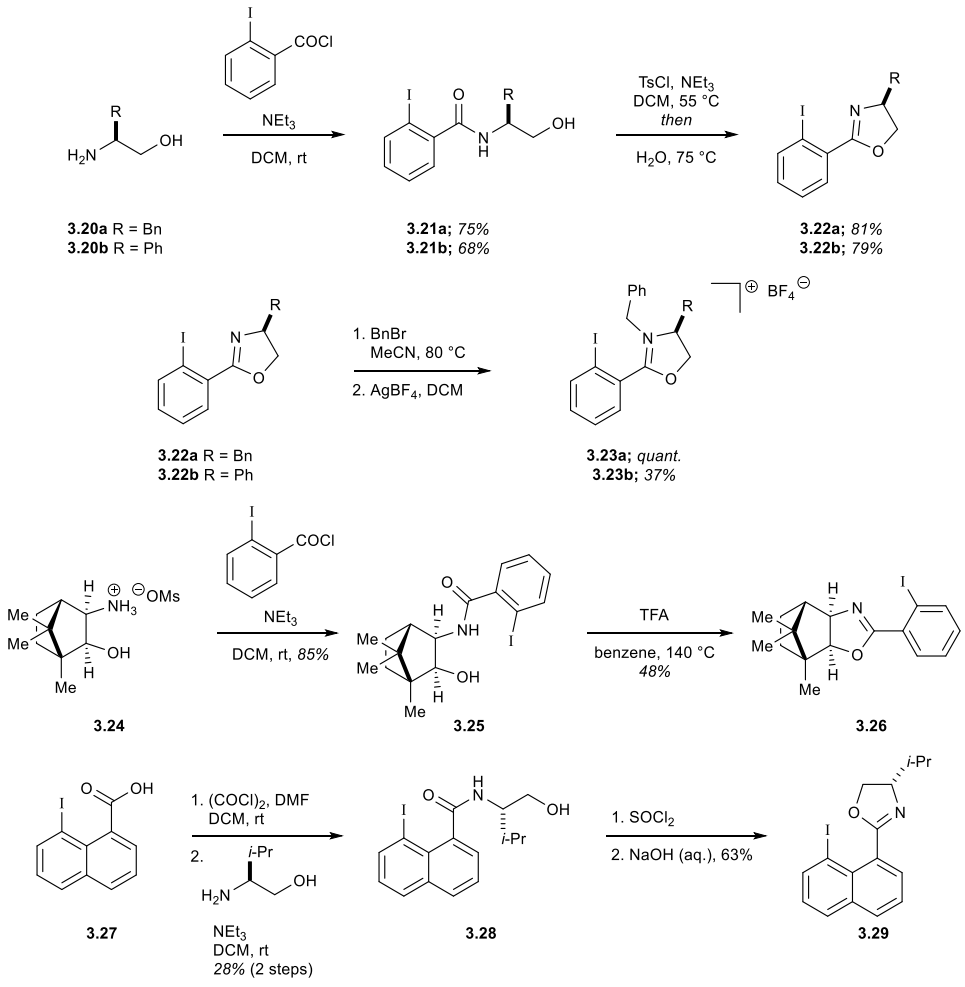
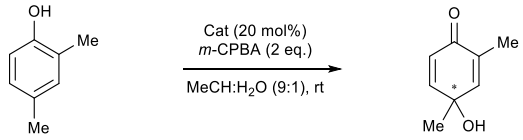


Table 3.2: Oxazoline catalysts in enantioselective dearomatization



Entry	Compound	ee (%)
1	**3.22a**	7
2	**3.22b**	2
3	**3.23a**	8
4	**3.23b**	5
5	**3.26**	7
6	**3.29**	6

While the above results showed potential, altering the structure of the oxazoline catalysts resulted in only minor changes in selectivity, casting doubt on whether significant improvement was possible using this catalyst substructure. We turned our attention instead to other substructures in hopes of locating a more promising catalyst.

Curran reported the use of configurationally stable iodine-substituted *N*-aryl amides in radical reactions.[129] To our knowledge, the use of this class of substrates as catalyst motifs has not been reported. The ease with which these structures can be synthesized inspired us to synthesize amides **3.31a&b** for evaluation (**Scheme 3.6**). The enantiomers could be resolved using chiral HPLC. Preliminary resolutions for screening purposes were performed on very small scale using repeated injections of the substrate onto an analytical-scale HPLC column. If a promising catalyst was found, subsequent resolutions could be

performed using preparative or semi-preparative HPLC conditions. When we evaluated compounds **3.31a&b** in the dearomatization of **3.19**, low selectivity was again observed (**Table 3.3**).

We hoped that better selectivity could be achieved if the stereochemical arrangement of the substituents on the amide was reversed, with the sterically bulky portion of the catalyst being directly bonded to the nitrogen and the sterically small portion of the catalyst bonded to the carbonyl. However, despite repeated attempts, we were unable to synthesize catalyst **3.32a**. An analogous trifluoroacetate substrate **3.32b** could be prepared, though we were unable to separate the enantiomers by HPLC. It is unclear at this time whether **3.32b** is configurationally unstable or simply unable to be separated using our HPLC columns. Recent renewed interest in these structures has shown that substrate **3.33**[iii] provides the quinol in an encouraging 11% ee. Work is underway in our lab to further investigate this promising result.

[iii] Work performed by Dr. Andrew Harned

Scheme 3.6: Synthesis of iodoamide catalysts

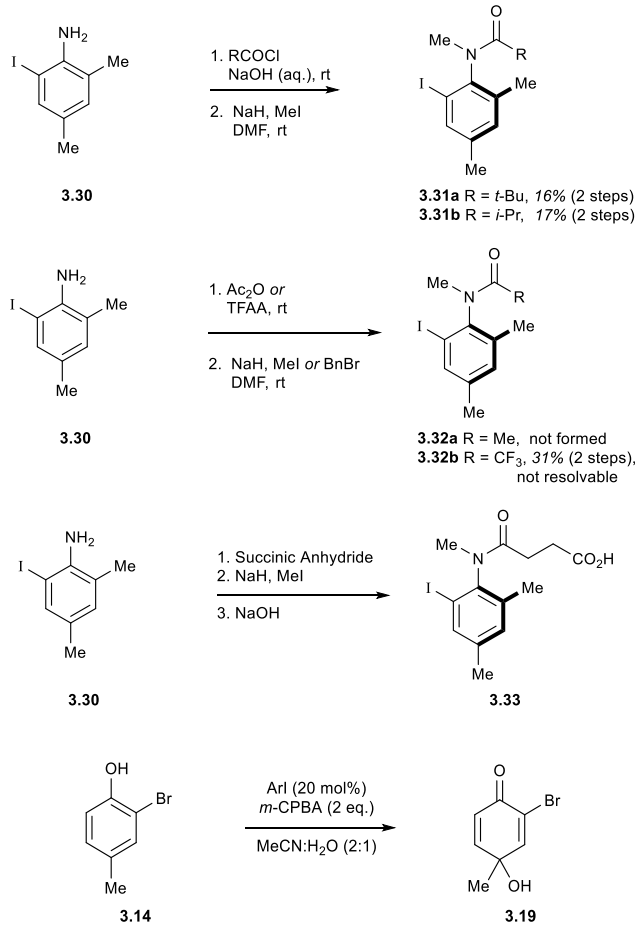
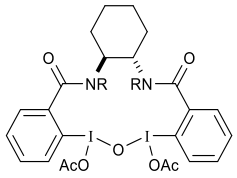


Table 3.3: Iodoamide catalysts in enantioselective dearomatizations

Entry	Catalyst	ee (%)
1	**3.31a**	5
2	**3.31b**	6
3	**3.33**	11

The final substructure that we investigated drew inspiration from the work of Kita (**Section 1.1.3**).[130] While their μ-oxo-bridged diiodide catalyst **1.66** performs excellently in *ortho* dearomatization reactions to give 2,4-cyclohexadienones, its preparation is quite lengthy and the substrate must be resolved via HPLC prior to use. As such, it is not easily amenable to modification. We decided to target diiodides **3.35**–**3.47** as similar, though significantly easier to access, analogues. These structures have the advantage of being available in a minimum number of steps from known and commercially available chiral diamines and diols. It was our hope that the more rigid, bridged diiodide structure (**Figure 3.1**) would restrict the number of available conformations, leading to higher selectivity. Bridging oxygen atoms have also been shown to be beneficial for increasing dearomatization yields.[14]

Figure 3.1: Proposed bridging structure



We began by synthesizing *bis*-amide **3.55**[iv]. While the conversion and yield for the dearomatization using catalyst **3.55** was very low, a small amount of quinol **3.19** could be isolated in a promising 8% ee (**Scheme 3.7**). To our delight, both the yield and selectivity increased significantly when **3.55** was methylated (**3.56a**). Inspired by this significant improvement, we sought to evaluate the effect of different *N*-substituents on the selectivity. All *bis*-tertiary amides displayed extremely broad ^{1}H NMR spectra, which precluded any spectral interpretation. The identity of the catalyst could be confirmed instead by mass spectrometry. The selectivity did not change significantly when benzylated substrate **3.58b** was utilized. Pentafluorobenzyl catalyst **3.56c** gave lower selectivity (**Table 3.4**). Switching from a *trans*-cyclohexanediamine backbone to a DPEN backbone (**3.39a&b**)

[iv] Work performed with the assistance of Eve Yang

led to improved selectivity. The BINAM backbone (**3.41a&b**) resulted in significantly diminished selectivity. *Bis*-pyrrolidine catalyst **3.43** also gave reasonably promising results, though this substructure is not as easily modified. The presence of an amide in the catalyst was confirmed to be important; when dimethltartrate-derived catalyst **3.45** or BINOL-derived catalyst **3.47** were screened, significantly diminished selectivity was observed.

These *bis*-amide catalysts showed great promise in the enantioselective *para*-dearomatization of phenols with external nucleophiles. At this point, multiple questions regarding these catalysts still remain. It is unclear whether the system adopts the proposed bridging structure or if the selectivity is simply due to the sterically congested nature of the catalysts. Work is ongoing to determine the exact nature of the active catalyst structure, as well as to further optimize the dearomatization selectivity.

Scheme 3.7: Synthesis of *bis*-amide catalysts

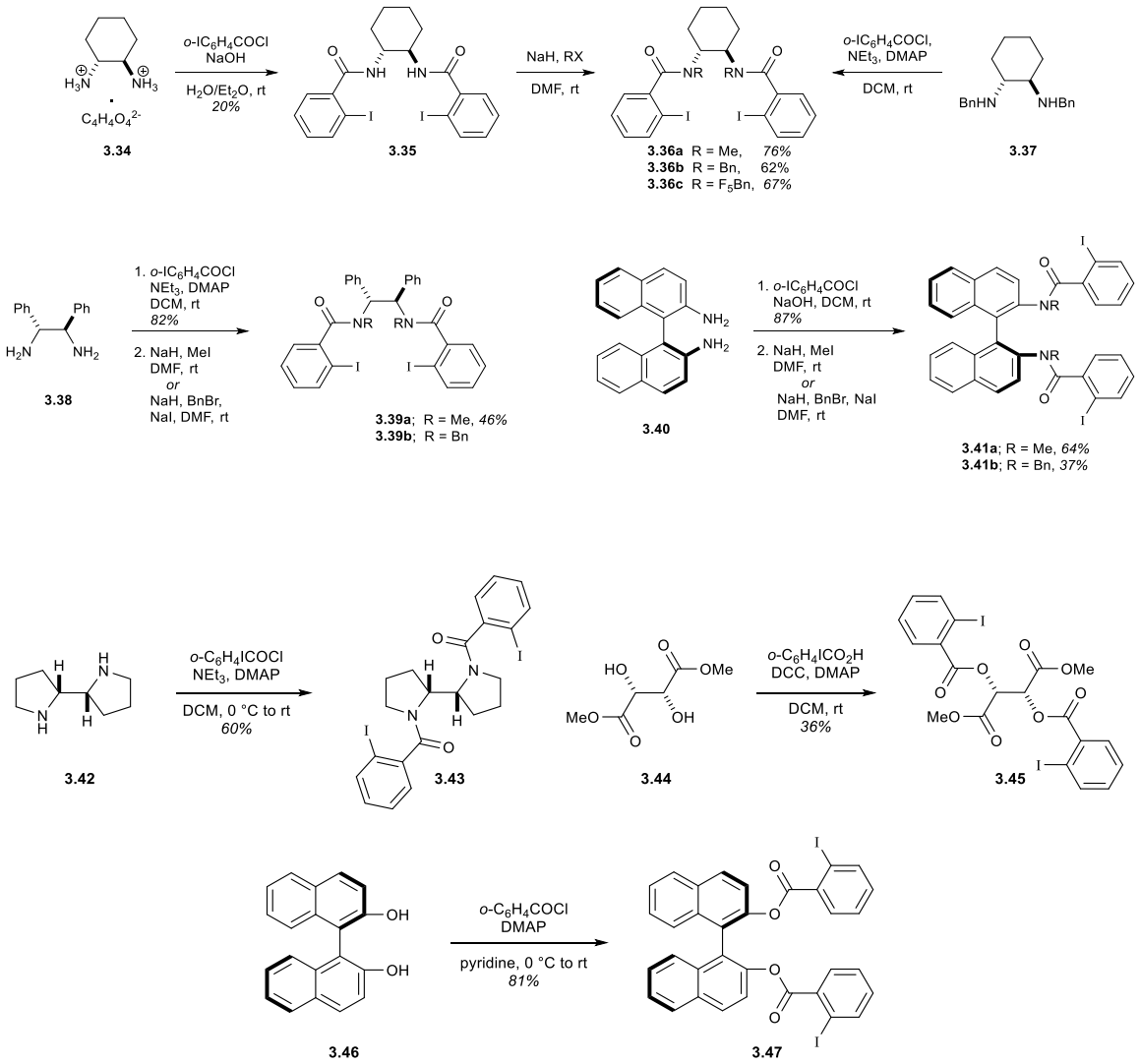
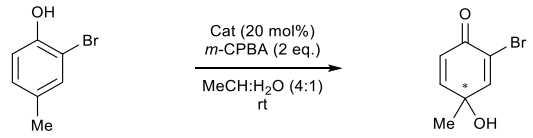


Table 3.4: *Bis*-amide catalysts in enantioselective dearomatization



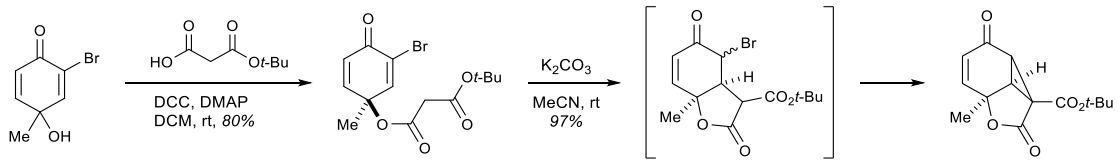
Entry	Catalyst	ee (%)
1	**3.37**	8
2	**3.38a**	15
3	**3.38b**	16
4	**3.38c**	6
5	**3.41a**	20
6	**3.41b**	4
7	**3.43a**	2
8	**3.43b**	3
9	**3.45**	17
10	**3.47**	4
11	**3.49**	5

3.2.4. Synthesis of the Sulfone-Reformatsky Precursor

After briefly investigating the potential for forming **3.19** enantioselectively, we elected to move forward with the synthesis of racemic **3.12** (**Scheme 3.8**) with hopes of

revisiting this problem once a viable route had been determined. Racemic quinol[v] **3.19** was esterified using DCC and DMAP to furnish malonate ester **3.13**. Treatment of **3.13** with two equivalents of K_2CO_3 led to direct formation of cyclopropane **3.12** by way of presumed intermediate lactone **3.48**. The cyclopropane was found to be highly unstable to silica-gel chromatography. However, filtration of the reaction mixture through a plug of florisil furnished the cyclopropane in nearly quantitative yield and with high purity. Once isolated, the highly strained molecule was stable indefinitely in the freezer.

Scheme 3.8: Synthesis of cyclopropane **3.12**



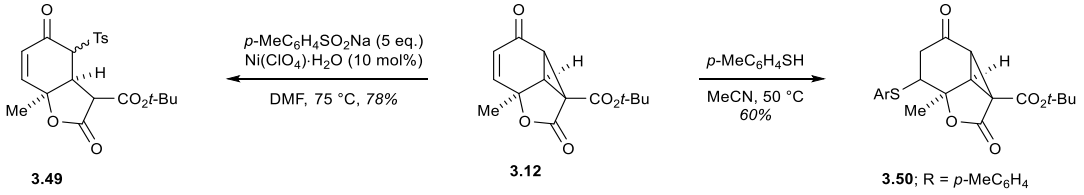
3.19 **3.13** **3.48** not isolated **3.12**

With cyclopropane **3.12** in hand, we began to investigate conditions for the proposed nucleophilic cyclopropane opening. To our surprise, treating cyclopropane **3.12** with *p*-toluenethiol in acetonitrile at 50 °C cleanly gave the conjugate-addition product **3.50** in 60% yield with no observed cyclopropane opening (**Scheme 3.9**). Changing the reaction time, temperature, solvent, or the addition of a Lewis acid did not alter the result. We decided to turn instead to the harder nucleophile sodium *p*-toluenesulfinate. Treatment of **3.12** with sodium *p*-toluenesulfinate at 75 °C in DMF gave the desired **3.49** as the sole product. The reaction could be slightly improved by adding an excess of the nucleophile along with a catalytic amount of $NiClO_4 \cdot 6H_2O$.[123] We observed a significant discrepancy between the crude yield of **3.49** and the yield after silica-gel chromatography. The use of stationary phases other than silica gel did not improve this result. As the crude product was satisfactorily clean by ^1H NMR spectroscopy, we elected to avoid chromatographic

[v] Unless otherwise stated, all compounds were synthesized in racemic form. All specified stereochemistry is relative, not absolute.

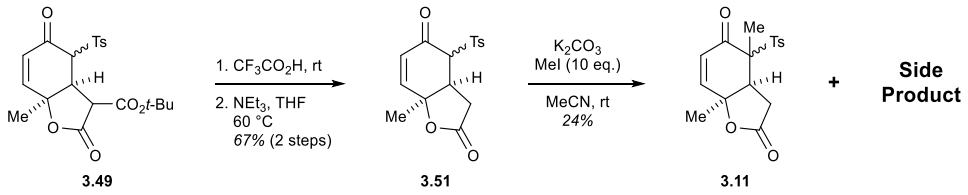
purification entirely and carry the crude material forward directly. This change improved the isolated yield of **3.51** from 50% to 78%.

Scheme 3.9: Nucleophile addition to cyclopropane **3.12**



Sulfone **3.49** was decarboxylated to give **3.51** through a procedure involving the cleavage of the *tert*-butyl ester with TFA followed by decarboxylation with NEt_3 in THF (**Scheme 3.10**). Significant material loss was again observed upon attempted chromatographic purification. As the crude material was again sufficiently clean, we again elected to carry the material forward into the subsequent methylation step without further purification.

Scheme 3.10: Elaboration to the sulfone-Reformatsky precursor **3.11**

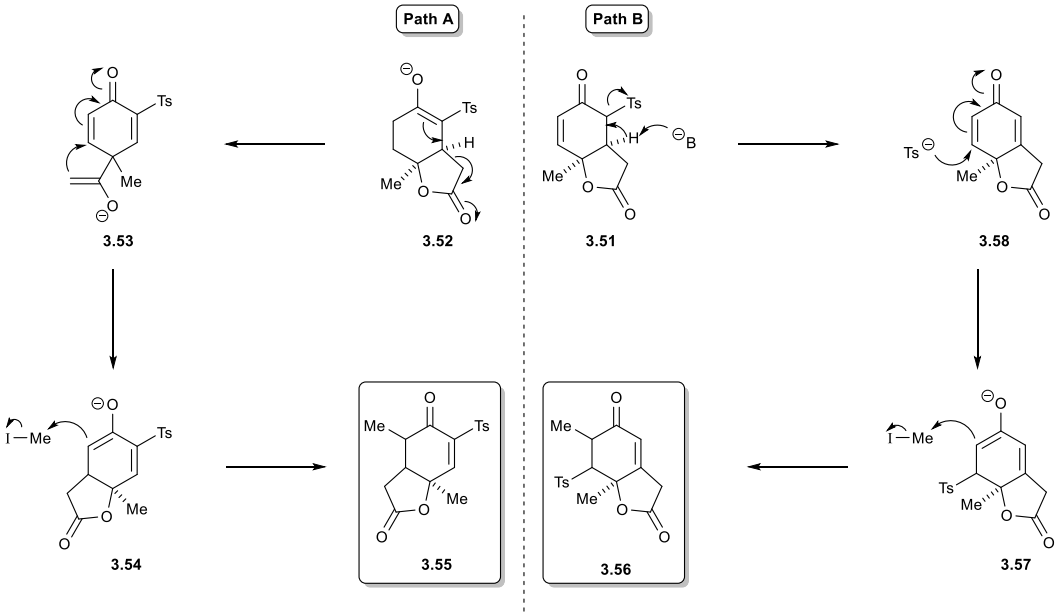


Our initial attempts to methylate sulfone **3.51** produced the desired methylated product **3.11** as an inconsequential mixture of diastereomers in 24% yield. Along with **3.11**, we also isolated a large amount of an unidentified side-product. Examination of the crude ^1H NMR spectrum revealed that the product existed as a 5.2:1 mixture of diastereomers, and the combined diastereomeric products were formed in a 2:1 ratio with the side-product. In light of previous observations, we hypothesized that the lower yields could be due in part to material loss during chromatographic purification. We decided to

find conditions such that the side-product was formed in sufficiently small quantities as to allow direct use of the crude material in the key sulfone Reformatsky reaction.

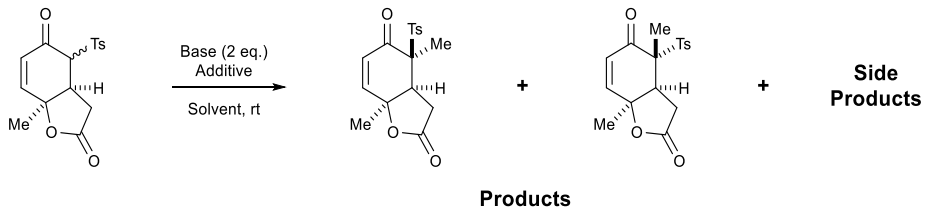
While we were able to isolate a very small amount of the undesired side-product, various impurities co-eluted, complicating ^{1}H NMR analysis. Examination of the side-product by mass spectrometry revealed it to be an isomer of **3.11**. We proposed compounds **3.55** and **3.56** as plausible structures of the side-product (**Scheme 3.11**). Both of these structures are consistent with the observed ^{1}H NMR spectrum, which contained a distinctive singlet in the alkene region of the ^{1}H NMR spectrum at 6.07 ppm. Compound **3.55** could be formed via base-promoted elimination of the sulfone followed by addition of the resulting sulfinate anion into the other alkene with subsequent methylation (**Scheme 3.11, Path A**). Alternatively, compound **3.56** could be formed via a retro-Michael reaction followed by Michael addition into the opposite enone with subsequent methylation (**Scheme 3.11, Path B**). While we did not make any effort to determine the exact identity of the side-product, we were optimistic that the proper choice of base and solvent conditions would minimize the formation of the undesired side-product.

Scheme 3.11: Possible mechanisms for side-product formation



We screened a variety of bases and solvents in the reaction (**Table 3.5**). A brief survey of bases revealed little effect on the ratio of products to side-product. We turned instead to a survey of solvents. Because of its low price and availability, we elected to use K_2CO_3 as the base for the solvent screening. Several polar, aprotic solvents were screened. The nature of the solvent appeared to exert some influence on the diastereomer ratio of the methylated products, though this change was inconsequential as the stereocenter at C1 would be ablated in the subsequent sulfone Reformatsky reaction. None of the polar, aprotic solvents that were screened improved the ratio of products to side-products to synthetically useful levels. However, when the reaction was performed in the toluene with a catalytic amount of 18-crown-6, the ratio of methylated products to side product increased to an encouraging 7.5:1 (with a concomitant increase in the dr). Switching the solvent to DCM or using BTEA-Cl as the phase transfer catalyst resulted in no reaction. We found that we could improve the ratio of products further to 9.1:1 by using only 1.2 equivalents of K_2CO_3. It is likely that the nonpolar nature of the solvent decreases the amount of base present in solution, which in turn decreases the rate of side-product formation. The less-coordinated 18-crown-6-complexed potassium counterion also likely increases the nucleophilicity of the enolate, increasing the rate of methylation relative to side-product formation. We decided to use these conditions as the optimum conditions to synthesize the sulfone Reformatsky precursor.

Table 3.5: Optimization of methylation conditions



Entry	Base	Solvent	Additive	Products:Side-Product	dr
1	K_2CO_3	MeCN	--	2.0:1	5.0:1
2	Cs_2CO_3	MeCN	--	2.2:1	4.7:1
3	NaH	THF	--	decomp	decomp
4	$KF{\cdot}H_2O$	DMF	--	3.1:1	5.4:1
5	Na_2CO_3	DMF	--	3.3:1	5.7:1
6	KOH	DMF	--	mixture	mixture
7	K_2CO_3	DMF	--	3.1:1	7.7:1
8	K_2CO_3	DMF	HMPA	3.0:1	11.2:1
9	K_2CO_3	Acetone	--	2.1:1	8.0:1
10	Cs_2CO_3	Acetone	--	2.2:1	7.1:1
11	K_2CO_3	Acetone	18-cr-6	2.5:1	4.7:1
12	K_2CO_3	DMSO	--	3.5:1	6.9:1
13	K_2CO_3	Toluene	18-cr-6	7.:1	10.5:1

14	K_2CO_3[a]	Toluene	18-cr-6	9.1:1	16.2:1
15	K_2CO_3	DCM	18-cr-6	mixture	mixture
16	K_2CO_3	Toluene	BTEA-Cl	NR	NR

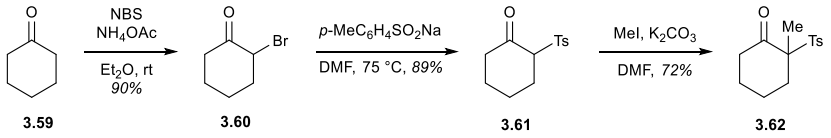
a. 1.2 eq. K_2CO_3

3.2.5. Evaluation of the Sulfone Reformatsky Reaction

3.2.5.a. Evaluation of a Model Substrate

As we were optimizing the methylation conditions, we investigated model substrate **3.62** in order to study the proposed sulfone Reformatsky reaction (**Figure 3.12**). Compound **3.60** could be synthesized by brominating cyclohexanone with NBS and NH_4OAc to give **3.60** in excellent yield.[123] Displacement of the bromine with sodium *p*-toluenesulfinate followed by methylation gave the model substrate **3.62** in good yield.

Scheme 3.12: Synthesis of model substrate

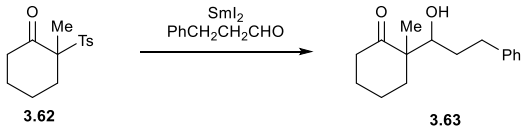


3.59 3.60 3.61 3.62

Investigation into the SmI_2 promoted sulfone Reformatksy reaction revealed that the reaction was highly sensitive to temperature and the order of addition (**Table 3.6**). Adding the substrate and aldehyde to SmI_2 led to a complex mixture of products. Use of the SmI_2/HMPA complex did not improve the results. If the order of addition was reversed such that the SmI_2 was added to a concentrated solution of the aldehyde and ketone, a complex and inseparable mixture of products were isolated (**Figure 3.2**). Investigation of the products by mass spectrometry revealed that the observed products were the result of various pinacol-type additions between **3.62**, itself, and hydrocinnimaldehyde. Reformatsky product **3.63** could be obtained in low yield when the temperature was

lowered to −78 °C. Use of a large excess (5 eq.) of aldehyde gave sulfone Reformatsky product **3.63** in acceptable yield as a ~19:1 mixture of unassigned diastereomers.

Table 3.6: Optimization of model sulfone-Reformatsky reaction

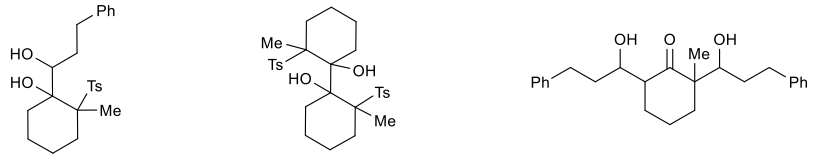


3.62 3.63

Entry	Conditions	Temperature (°C)	Result
1	SmI_2[ac]	0	mixture
2	SmI_2/HMPA[ac]	0	decomp.
3	SmI_2[bce]	0	side product
4	SmI_2[bc]	−78 °C	32%
5	SmI_2[bd]	−78 °C	66%

a. Substrate added to SmI_2; b. SmI_2 added to substrate; c.1.5 eq. aldehyde; d. 5.0 eq. aldehyde; e.See figure **3.2.**

Figure 3.2: Possible pinacol and aldol-type products



3.64 3.65 3.66

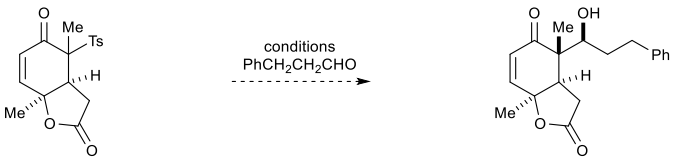
3.2.5.b Evaluation of the cyclohexadienone-derived substrate

When **3.11** was subjected to the optimized reaction conditions, no reaction was observed (**Table 3.7**). Performing the reaction at 0 °C led to a complex mixture of products that could not be chromatographically separated. Though carbinol signals in the ^{1}H NMR spectrum indicated the possible formation of aldol-like products, mass spectrometry

showed no evidence of the desired product **3.10**. The observed masses corresponded instead to a mixture of pinacol-type coupling products between the aldehyde and the keto-sulfone. We hypothesized that the low solubility of **3.11** in THF could be preventing effective reaction. However, using MeCN as the solvent did not improve the reaction. Other reducing agents including Zn, Mg, and photocatalytic conditions were also evaluated. In all cases, either no reaction or decomposition was observed.

While we were able to achieve the sulfone Reformatsky reaction in simplified systems, the reaction was not amenable to the synthesis of briarane intermediate **3.5**. Low substrate solubilities at cryogenic temperatures could have precluded initial reduction, leading to the reisolation of starting material. In cases where higher temperatures were used, the enone moiety is likely more readily reduced than the sulfone, leading to preferential pinacol coupling products instead of undergoing the desired sulfone fragmentation. At this point, we turned our attention from our proposed sulfone Reformatsky reaction and focused on other potential methods to form the key stereocenter at C1.

Table 3.7: Sulfone-Reformatsky studies on **3.11**



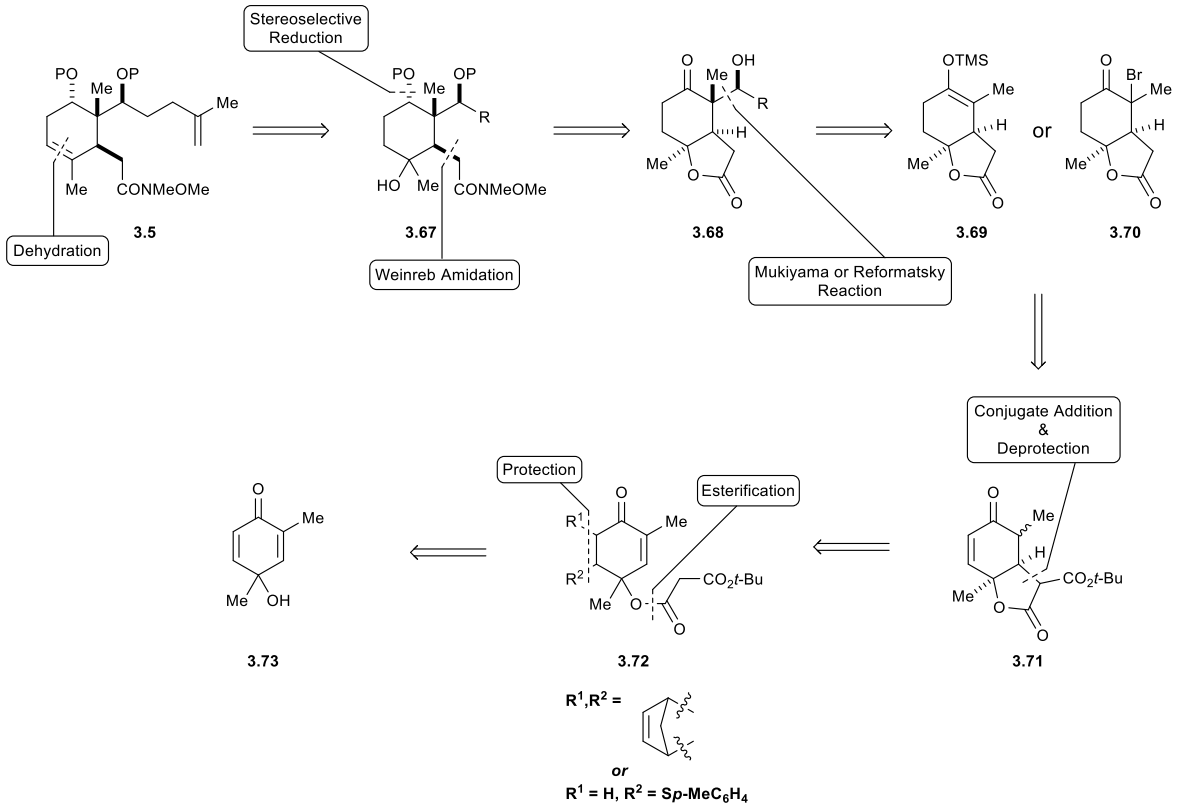
Entry	Reductant	Temperature (°C)	Solvent	Additive	Result
1	SmI_2	−78	THF	--	NR
2	SmI_2	rt	THF	--	Pinacol Products
3	SmI_2	0	MeCN	--	NR
4	SmI_2	0	MeCN	HMPA	NR
5	Zn	rt	THF/MeCN	$BrCH_2CH_2Br$	NR
6	Mg	rt	MeOH	--	NR
7	Bu_3SnH	reflux	toluene	AIBN	NR
8	$Ru(bipy)_3(PF_6)$ hν	rt	DCM	CuTC	NR
9	$Ru(bipy)_3(PF_6)$ hν	rt	DCM	CuI	NR
10	$Ir(ppy)_3$	rt	DMF	$DIPEA/HCO_2H$	decomp.

3.3. Second Synthetic Approach

3.3.1. Second Retrosynthetic Proposal

In formulating a new strategy, we reconsidered some of the assumptions which had guided our previous efforts. We speculated that the C11-C12 alkene could be formed through dehydration of intermediate **3.67** instead of the previously proposed Zn-mediated reductive cleavage (**Scheme 3.13**). The hydrogenated substrate **3.71** would be more resistant to rearomatization which would enable the use of harsher conditions to perform the key aldol-type addition. The amide bond would be installed directly from **3.68** through a Weinreb amidation.[131] The key stereocenter at C1 could be forged through either a Mukaiyama aldol reaction from silyl-enol ether **3.69**, or a Reformatsky reaction from α-bromoketone **3.70**. Both **3.69** and **3.70** could be obtained from bicyclic lactone **3.71**. In order to form lactone **3.71** through the conjugate addition of a tethered malonate, the regioselectivity of the conjugate addition would need to be reversed in order to direct the addition into the more-hindered enone. This reversal could be accomplished by first protecting the less-hindered enone as compound **3.72**. Removal of the protecting group after the desired conjugate addition would give the result of a formal conjugate addition into the more hindered enone of **3.73**. Both Diels-Alder adduct and sulfide conjugate addition-based protecting groups would be evaluated for their relative ease of installation and removal. Compound **3.72** could be synthesized from **3.73** through protection and esterification of cyclohexadienone quinol **3.73**.

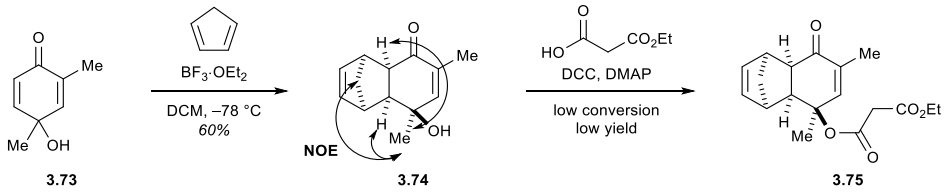
Scheme 3.13: Second retrosynthetic proposal



3.3.2. Studies Utilizing a Diels-Alder Adduct as a Protecting Group

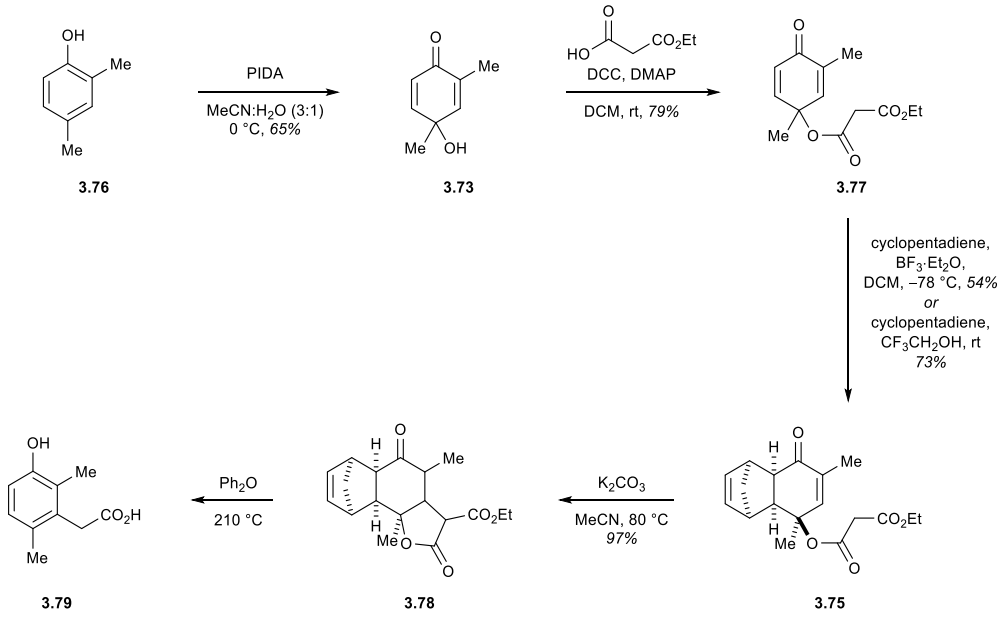
We selected a cyclopentadiene Diels-Alder adduct as the first protecting group to evaluate. Cyclopentadiene is known to perform cycloadditions with 2,5-cyclohexadienones with high stereo- and regioselectivity (**Section 1.2.3**).[77, 78] Diels-Alder cycloaddition of **3.73** promoted by $BF_3 \cdot OEt_2$ cleanly gave adduct **3.74** as a single diastereomers (**Scheme 3.14**). We were able to confirm the relative stereochemistry of **3.74** as *endo* through NOE correlations. Unfortunately, attempts to install the malonate side-chain on this highly hindered substrate were unsuccessful.

Scheme 3.14: Initial Diels-Alder studies



We then attempted the Diels-Alder reaction on substrate **3.77** which already possesses the malonate ester (**Scheme 3.15**). When **3.77** was subjected to the previous Diels-Alder conditions, the desired adduct **3.78** could be formed, though in modest yield. Performing the Diels-Alder reaction under thermal conditions in trifluoroethanol significantly improved the yield, once again giving the product as a single diastereomer. With malonate **3.78** in hand, we were pleased to find that the desired lactone **3.78** could be obtained in 97% yield by heating **3.75** in MeCN with K_2CO_3. Unfortunately, attempts to perform the retro Diels-Alder reaction were met with rearomatization, giving phenol **3.79** instead of the desired product. This propensity for rearomatization is presumably due to the thermal instability of the lactone. Use of additives in the retro Diels-Alder reaction such as maleic anhydride did not improve the results.

Scheme 3.15: Evaluation of the Diels-Alder protecting group



3.3.3. Studies Utilizing a Sulfide as a Protecting Group

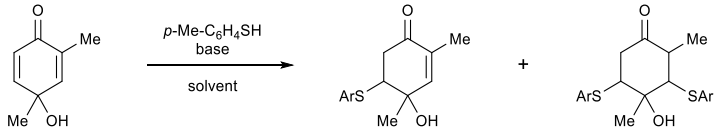
3.3.3.a. Initial Studies and Optimization

We then decided to consider other protecting groups that could be removed under milder conditions. Sulfides, which are known to facilely undergo retro-conjugate additions would be an ideal candidate (**Section 1.2.2.c**). The addition should occur with the desired regiochemistry and the sulfide could be removed under mild, basic conditions after the lactone is forged.

We selected *p*-toluenethiol as the nucleophilie due to its ease of handling and relatively manageable odor. When quinol **3.73** was treated with *p*-toluenethiol and stoichiometric triethylamine, the desired mono-addition product **3.80** was formed along with the double-addition product **3.81** in a 10:1 ratio (**Table 3.8**). The mono-addition product could be isolated chromatographically in 64% yield. The yield, though not the

product ratio, could be improved by switching the solvent to THF. Lowering the temperature to 0 °C resulted in a significantly decreased yield, though the ratio of mono to double-addition products increased. A less polar solvent such as toluene resulted in good yield, but a slightly lower ratio of products. To our delight, the ratio increased to almost 50:1 when a base such as DABCO was used in catalytic quantities. Switching the base to quinine gave higher yield with a similarly good ratio of products.

Table 3.8: Optimization of sulfide addition



3.73 | 3.80 Ar = *p*-Me-C_6H_4 | 3.81 Ar = *p*-Me-C_6H_4

Entry	Base (eq.)	Solvent	3.80:3.81	Yield 3.80 (%)
1	NEt_3 (2)	DCM	10:1	65
2	NEt_3 (2)	THF	11:1	75
3	NEt_3 (2)	THF	20:1	35
4	NEt_3 (2)	toluene	8:1	70
5	DABCO	toluene	48:1	63
6	quinine	toluene	56:1	71

3.3.3.b. Kinetic Resolution of Quinols

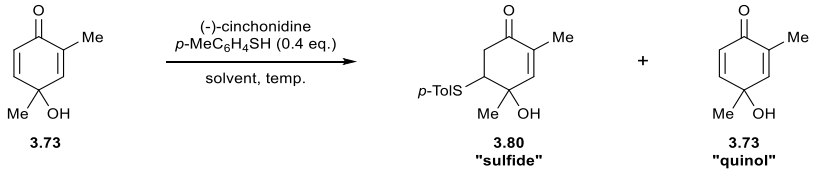
After observing the success of the sulfide conjugate addition when catalytic quantities of quinine were used as a base, we wondered if a chiral base such as quinine could be used to accomplish a kinetic resolution of 2,5-cyclohexadienones.[132] The reaction

could easily be run to incomplete conversion by controlling the stoichiometry of the sulfide, providing either enantioenriched sulfide **3.80** or quinol **3.73** after chromatographic purification (**Table 3.9**). As current methods to access quinols such as **3.73** in enantioenriched form through enantioselective oxidative dearomatization are not yet synthetically useful (**Section 1.1.4**), kinetic resolution might be a viable alternative to obtain enantioenriched **3.73**.

We were able to determine HPLC conditions that could resolve the enantiomers of both the starting material and product in a single run. To our delight, when the reaction was conducted with quinine as the catalyst to approximately 60% conversion (determined by ^{1}H NMR spectroscopy), the resulting quinol could be obtained in 27% ee. Because it gave slightly better results, (-)-cinchonidine was selected as the catalyst for further screening. A survey of solvents found toluene to be optimal. The k_{rel} value decreased slightly when the reaction was warmed to room temperature. Running the reaction at cryogenic temperatures resulted in an even lower k_{rel} and an extremely sluggish reaction. This change in k_{rel} is possibly due to the highly decreased solubility of the catalyst at lower temperatures, leading to different catalyst aggregation states.

A series of known or commercially available organocatalysts were screened in the resolution (**Table 3.10**).[133, 134] Other cinchona alkaloids did not significantly improve the selectivity. Increasing the steric bulk (**3.84**)[135] or restricting the conformational flexibility (**3.85**)[136] were also ineffective. The dimer $(DHQD)_2Pyr$ (**3.90**) did not give significant selectivity.[133] The k_{rel} values could be significantly improved when bifunctional, thiourea catalysts were used (**3.86**-**3.88**). To date, Takemoto's catalyst[137] (**3.88**) has given the best result, though significant improvement is still necessary; k_{rel} values of upwards of 50 are usually necessary to obtain synthetically useful enantioenrichment of the product.[132] Future work will focus on the synthesis of other catalyst substructures known to facilitate enantioselective thio-Michael addition reactions on cyclic enone substrates (**Section 1.2.2.c**).[71]

Table 3.9: Optimization of sulfide-addition kinetic resolution



Entry	Solvent	Temp (° C)	Conversion (%)	Sulfide ee (%)	Quinol ee (%)	k_{rel}*
1	DCM	0	33.3	8.4	4.2	1.23
2	$CHCl_3$	0	31.0	−1.8	2.8	1.04
3	CCl_4	0	43.8	10.6	7.8	1.33
4	THF	0	25.4	−8.4	−2.4	1.21
5	Et_2O	0	40.8	0	1.2	1.0
6	trifluorotoluene	0	42.2	6.6	4.3	1.19
7	toluene	0	41.0	17.0	12.1	1.57
8	toluene	22	35.5	16.2	8.4	1.50
9	toluene	−50	38.3	14.2	5.2	1.44

* k_{rel} determined based on the conversion and ee of the sulfide product

Table 3.10: Catalyst screening in sulfide-addition kinetic resolution

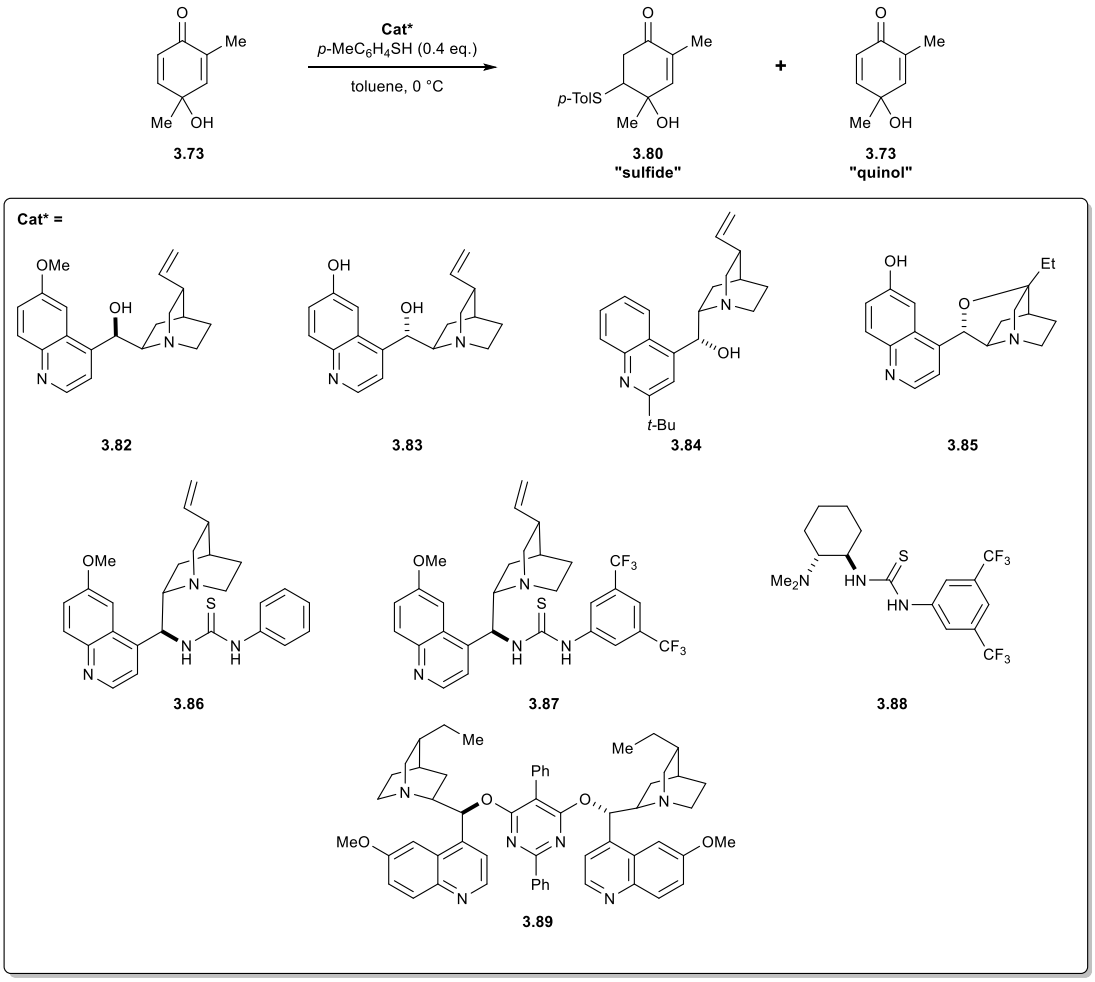


Table 3.10 Continued:

Entry	Catalyst	Conversion (%)[a]	Sulfide ee (%)[b]	Quinol ee (%)[b]	k_{rel}[c]
1	**3.85**	37.1	29.6	17.7	2.17
2	**3.86**	41.9	−33.2	−22.0	2.49
3	**3.87**	39.8	17.8	11.4	1.60
4	**3.88**	27.0	−3.6	0.0	1.09
5	**3.89**	50.2	−56.6	−43.8	6.28
6	**3.90**	40.1	−62.2	−37.2	6.50
7	**3.91**	40.6	64.4	45.4	7.05
8	**3.92**	37.0	18.7	12.7	1.62

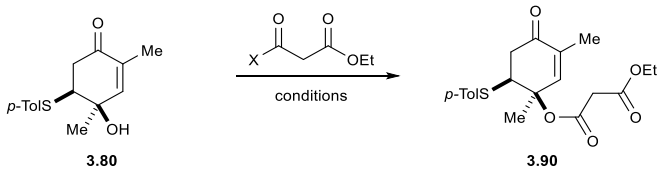
a. Determined by ^{1}H NMR spectroscopy of crude product; b. Determined by chiral HPLC; c. k_{rel} determined from conversion and ee of sulfide product **3.80**

3.3.3.c. Elaboration to the Mukaiyama and Reformatsky Precursors

With racemic sulfide **3.80** in hand, we set out to prepare the precursor for the key aldol-type reaction at C1. When we attempted to prepare the malonate ester as before (DCC/DMAP), we were disappointed to find that the reaction only proceeded to low

conversion, even after extended reaction times (**Table 3.11**). This observation is not surprising given the highly hindered nature of the sulfide-flanked tertiary alcohol. When we attempted the sulfide addition into malonate **3.72**, a mixture the desired **3.90** as well as the product resulting from the addition of the malonate chain resulted. As such, alternative esterification conditions were screened. The acid-chloride of monoethyl malonate produced complex reaction mixtures, though some product (**3.90**) could be isolated. The yield could be increased by adding the acid-chloride slowly to a solution of the alcohol and 2,6-lutidine. When the half-ester was first converted to the mixed anhydride with TFAA and subsequently treated with **3.80** in DME, **3.90** could be obtained in quantitative yield.[65]

Table 3.11: Survey of esterification conditions



Entry	X	Conditions	Yield
1	OH	DCC, DMAP, DCM, rt	decomp.
2	Cl	2,6-lutidine, DCM, rt	48%
3	$OCOCF_3$	DME, rt	quant.

To our surprise, when **3.90** was treated with NaH, lactone **3.91** was isolated (**Scheme 3.16A**). This product is the result of conjugate addition into the enone with concomitant sulfide elimination. As the sulfide elimination was the next step in our intended synthetic sequence, this was a welcome discovery. Using DBU as a base resulted in the isolation of the other lactone regioisomer **3.93**, resulting from elimination of the

sulfide followed by conjugate addition into the less-hindered enone (**Scheme 3.16B**). Further screening (**Table 3.12**) found K_2CO_3 in MeCN to be the ideal conditions.

Scheme 3.16: (A) Cyclization-elimination cascade; (B) Divergent pathways in regioisomer formation

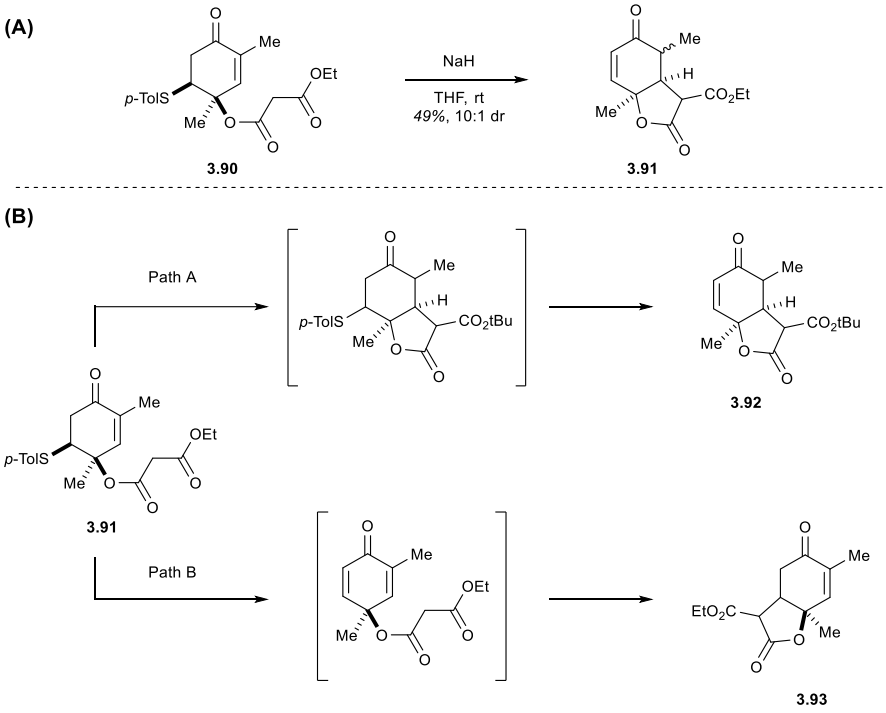
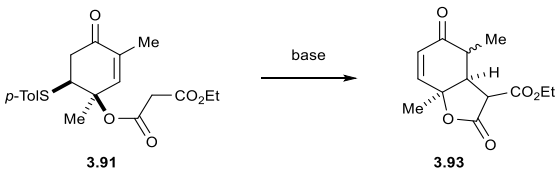


Table 3.12: Base screening in cyclization reaction

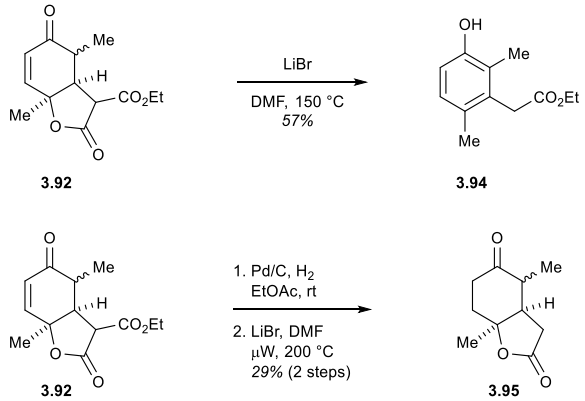


3.91 3.93

Entry	Base	eq.	solvent	2.92:2.93	dr	yield (%)
1	NaH	1.2	THF	<50:1	10:1	49
2	DBU	2.0	THF	2.2:1	4.4:1	37
3	KO*t*-Bu	3.0	THF	NA	NA	decomp.
4	K_2CO_3	3.0	MeCN	<50:1	3.6:1	53
5	Cs_2CO_3	3.0	MeCN	<50:1	8.3:1	58

We then began to investigate the decarboxylation of the ethyl ester in **3.92**. Subjection of lactone **3.92** to Krapcho conditions (**Scheme 3.17**) led to the isolation of rearomatized product **3.94**. Once again, we attributed the observed rearomatization to the thermal instability of the enone-lactone. As this thermal instability appeared to be a general feature in these bicyclic lactones, we reduced the enone double-bond first in order to increase stability. The material was cleanly hydrogenated and taken directly forward into the Krapcho decarboxylation. While the reaction successfully gave **3.95**, the sequence occurred in low yield that could not be improved.

Scheme 3.17: Krapcho decarboxylation studies



We hoped to find a different ester substituent that could be more amenable to decarboxylation. A benzyl ester was an ideal candidate, as it could be possible to reduce the enone and decarboxylate the ester in a single step under hydrogenation conditions. The benzyl malonate **3.96** could be synthesized in excellent yield using our established conditions (**Scheme 3.18**). However, when malonate **3.96** was subjected to the optimized cyclization & elimination conditions, a small amount of an impurity corresponding to regioisomer **3.98** was also observed in addition to desired **3.97**. The bulkier benzyl ester likely cyclizes at a slower rate than the ethyl ester, leading to competitive sulfide elimination. A second screen of bases (**Table 3.13**) found that the formation of **3.97** could be minimized by using Cs_2CO_3 as a base and running the reaction at lower temperatures for extended times. This led to an inconsequential change in dr presumably due to base-catalyzed equilibration. On larger scales, we found it sometimes necessary to heat the reaction mixture after all starting material was consumed (as determined by TLC) to 50 °C in order to drive the sulfide elimination to completion. Under these conditions, **3.97** could reliably be obtained in good yields. With substrate **3.97** in hand, we investigated hydrogenation conditions. Unfortunately, the molecule appeared to be highly recalcitrant to catalytic hydrogenation, and starting material was returned instead.

Scheme 3.18: Evaluation of a benzyl ester substrate

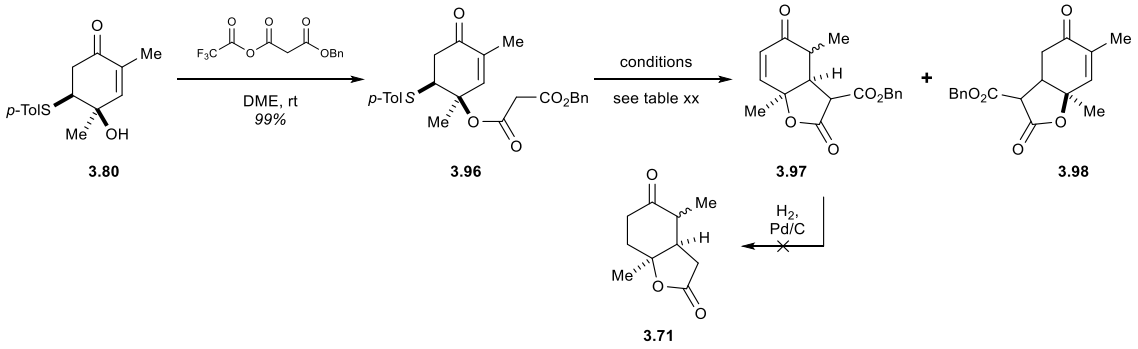


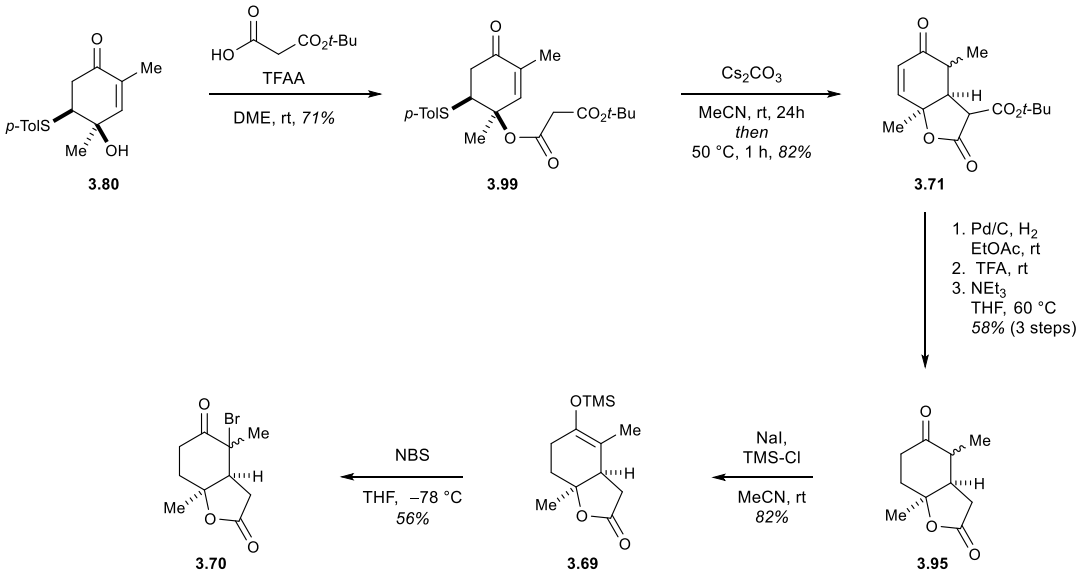
Table 3.13: Reoptimization of cyclization for the cyclization of benzyl ester **3.96**

Entry	Base (3 eq.)	Solvent	Temp (°C)	3.97:3.98	dr
1	Cs_2CO_3	MeCN	50	21.7:1	8.5:1
2	NaH (1.2 eq.) *then* DBU	THF	0	7.7:1	10.6:1
3	NaH	THF	0	1:1	13.8:1
4	Cs_2CO_3	MeCN	22	64.8:1	1:1.2

Given our previous successes (**Scheme 3.10**), we decided to return to *t*-butyl esters. The ester **3.99** could be formed using our established mixed anhydride method (**Scheme 3.19**). The optimized cyclization conditions gave lactone **3.70** in good yield. Compound **3.70** was hydrogenated using Pd/C in EtOAc followed by decarboxylation using the conditions previously described to give hydrogenated lactone **3.95**. This lactone could be converted to silyl enol ether **3.68** using TMS-Cl and NaI with NEt_3, which was used

without further purification. Silyl-enol ether **3.68** could be converted to bromide **3.69** through treatment with NBS in THF.

Scheme 3.19: Synthesis of Mukaiyama/Reformatsky precursors



3.3.3.d. Evaluation of the Mukaiyama & Reformatsky Conditions

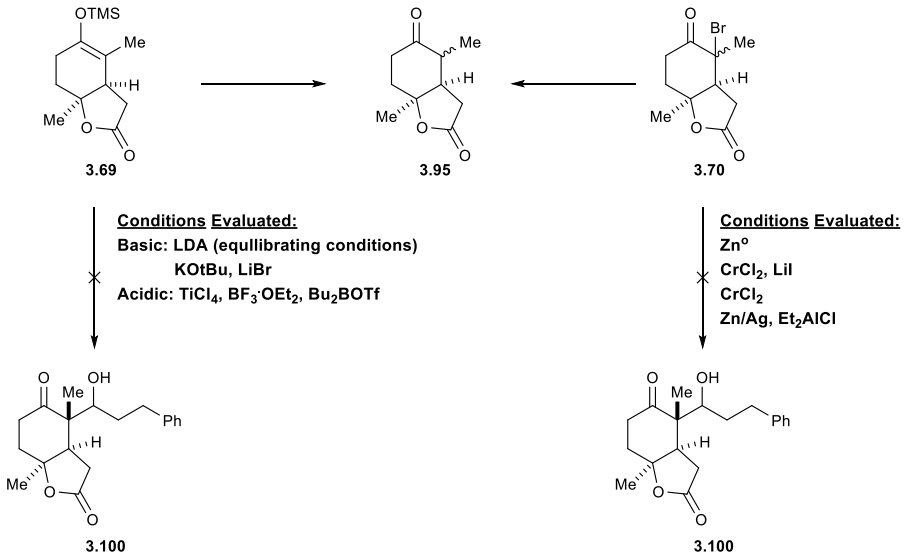
We undertook an evaluation of conditions to affect the addition to form the C1 stereocenter through Mukaiyama-type aldol reactions on silyl enol ether **3.68** (**Scheme 3.20**). The silyl enol ether was cleaved using a number of Lewis Acids such as Li, Ti, and B to generate their respective enolates followed by treatment with hydrocinnimaldehyde.[138] In all cases, we reisolated the 'protonated' lactone **3.95** instead of the desired adduct **3.100**. Lactone **3.100** results from cleavage of the silyl enol ether followed by protonation instead of aldol addition.

Attempts to perform more traditional Mukaiyama addition reactions by changing the order of substrate addition did not lead to product formation. Only the protonated lactone **3.95** was observed when $TiCl_4$ was added to a cold mixture of **3.68** and hydrocinnimaldehyde.[139] Other Lewis acids were also screened. A mild Lewis Acid such

as $InCl_3$ resulted in no reaction.[140] Stronger Lewis Acids such as $BF_3{\cdot}Et_2O$, $Yb(OTf)_3$ resulted in isolation of **3.95**.[141]

We turned our attention instead to Reformatsky reactions. Use of reducing agents such as Zn[142] or Zn/Ag activated by Et_2AlCl[143] led to the isolation of **3.95** as well. We also screened homogenous reducing agents such as $CrCl_2$, which also led to the reisolation of **3.95**.[144] A large excess of aldehyde or a catalytic amount of LiI did not improve the result.

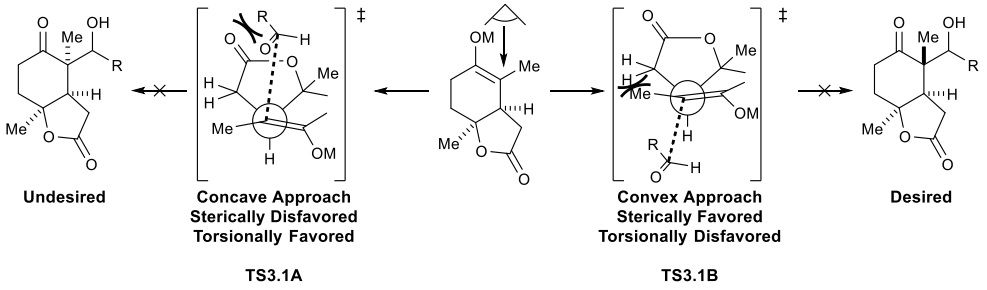
Scheme 3.20: Evaluation of Mukaiyama & Reformatsky conditions



It was clear at this time that the enolates formed from either reduction of the α-bromoketone or cleavage of the silyl enol ether are extremely unreactive. We believe that this unreactivity is due to the doubly deactivated nature of the enolate derived from **3.68** or **3.69** (**Scheme 3.21**). We anticipated that the concave approach of the aldehyde through **TS3.1A** would be deactivated due to steric congestion from the lactone ring. However, we were surprised by the effect of torsional strain in this system.[145] If the aldehyde approaches the convex face through **TS3.2B**, the methyl group at C1 begins to eclipse the lactone ring. This eclipsing interaction raises the energy of the transition state, and deactivates the convex approach as well. It is likely that the extremely unreactive enolate is formed either

from the silyl enol ether or the α-bromoketone. However, it does not react with the aldehyde and is instead protonated either by exogenous proton sources or upon workup. This unreactivity demonstrated the unsuitability 2,5-cyclohexadienone derived bicyclic lactones in our synthetic route.

Scheme 3.21: Stereochemical rationalization of lactone unreactivity



3.4. Conclusion

Two routes to the briarane stereotetrad were investigated. The first took advantage of a reactive cyclopropane to install a sulfone moiety. However, this sulfone did not undergo the proposed sulfone Reformatsky reaction. When a new route was evaluated involving a more stable hydrogenated lactone, we were able to furnish an enolate at C1. However, this enolate was extremely unreactive, and did not lead to the desired product. We concluded that the presence of the lactone moiety decreases the reactivity and is likely responsible for product instability as well. As a result, we decided to turn our attention to systems which did not possess this strained, bicyclic lactone.

CHAPTER 4

MONOCYCLIC APPROACHES TO THE BRIARANE DITERPENOIDS

After evaluating several approaches to the briarane stereotetrad core involving the use of bicyclic lactones, we hypothesized that the bicyclic nature of our intermediates could in fact be responsible for the difficulties that we had experienced. The highly strained bicyclic lactone substrates appear to be highly recalcitrant to aldol additions. The rigidity imparted by the lactone would prevent conversion to a more reactive conformer, precluding any desired reactivity. Additionally, the ring-strain from the lactone could be responsible for the facile rearomatization that we often observed. We hoped that alleviating the ring strain would in turn decrease the propensity towards elimination and rearomatization, allowing us to utilize strong bases in order to affect productive reactions such as methylations and aldol additions. The more conformationally mobile system might also allow for access to a reactive conformer in the key aldol addition step.

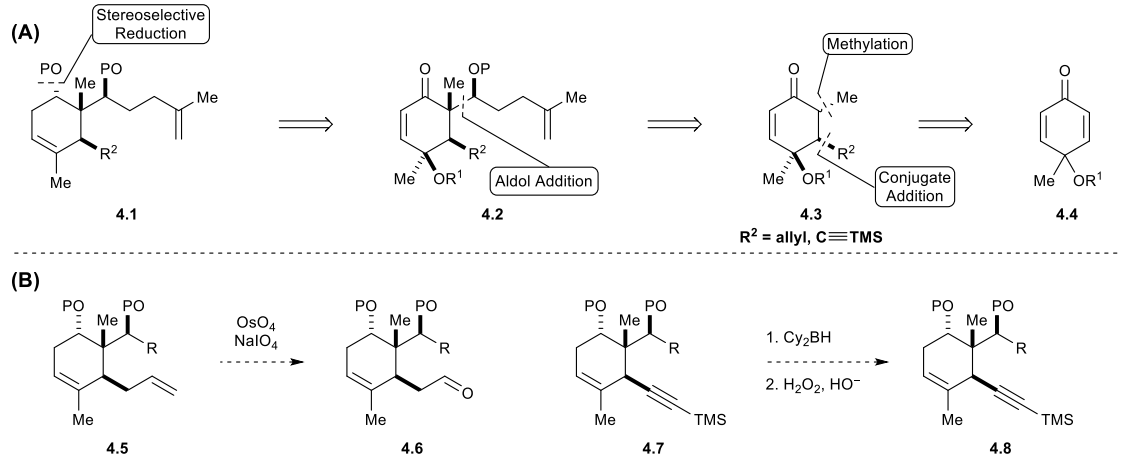
4.1. Third Synthetic Approach

4.1.1. Retrosynthetic proposal

We postulated **4.1** as a suitable briarane stereotetrad structure (**Scheme 4.1**). This structure could be made from **4.2** from a Zn-mediated reductive cleavage and stereoselective ketone reduction. The key bond at C1 would come through a boron-mediated aldol addition.[146] While such reactions were not successful on bicyclic substrates, we hoped that the reduced ring strain on ketone **4.3** would result in a more stable and sterically accessible enolate. Compound **4.3** would be made through C10

fragment instillation and C1 methylation of substrate **4.4**. Once again, we hoped that the increased stability of monocyclic derivatives will allow methylation to occur under strongly basic conditions, which did not work well in our previous efforts. The functionality of the C10 fragment would be selected such that it could later be converted into an aldehyde or carboxylic acid. We proposed an allyl group or a protected acetylide (**Scheme 4.1B**) as possible candidates for this fragment. The allyl group (**4.5**) could be converted into an aldehyde (**4.6**) through dihydroxylation and oxidative cleavage.[147] The TMS-acetylide (**4.7**) could be directly converted to a carboxylic acid (**4.8**) through hydroboration-oxidation.[148] Achieving the conjugate addition was expected to be challenging, as reagents known to typically undergo conjugate additions, such as cuprates, have been observed to often lead to rearomatization of 2,5-cyclohexadienones.[67] We were aware that the enolate resulting from a conjugate addition could also undergo rearomatization under basic conditions. Aubé observed that the products of conjugate addition into electron-deficient cyclohexadienones display a tendency towards rearomatization **(Section 1.2.2.b)**.[60] Nevertheless, we were optimistic that suitable conditions could be found that would enable the isolation of product.

Scheme 4.1: Retrosynthetic proposal utilizing monocyclic systems



4.1.2 Synthesis of the Aldol Precursor

We began by attempting the conjugate addition of an allyl fragment into quinol (**4.9a&b, Scheme 4.2**). Attempted ligand-assisted nucleophilic addition (LANA) into quinol **4.9b** using allylmagnesium bromide gave exclusively the 1,2 addition product **4.10**.[40, 41]

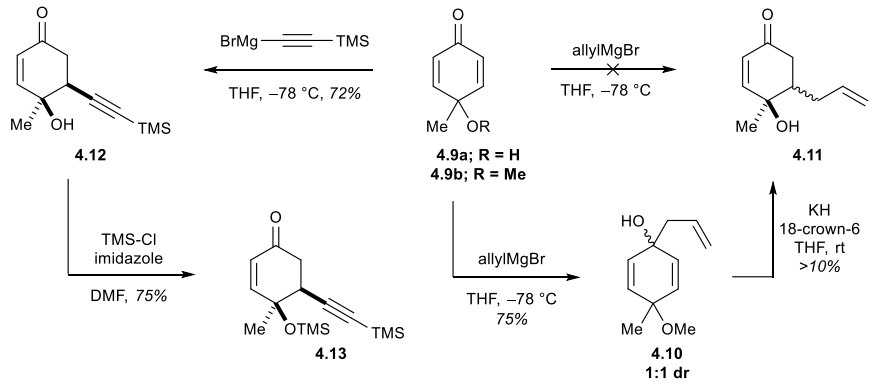
We were inspired by a report by Taber, in which a formal conjugate addition of an allyl fragment could be accomplished in two steps by first performing a 1,2-addition of allylmagnesium bromide followed by an anionic oxy-cope rearrangement.[149] Allylmagnesium bromide was added into cyclohexadienone **4.9a** in acceptable yield to give **4.10**, as an approximately 1:1 mixture of diastereomers.[28] When **4.10** was treated with KH and 18-crown-6 in THF, the product **4.11** could be obtained in 10% yield along with 10% recovered starting material, indicating substantial decomposition. Interestingly, the dr of **4.11** and **4.10** were not identical, indicating that one diastereomer of **4.10** reacts preferentially over the other, though no effort was made to assign the relative stereochemistry of either product.

With this encouraging result, we sought to optimize this reaction. Heating the reaction mixture to 60 °C led to decomposition of the substrate. Decomposition was also observed when the base was switched to KO*t*-Bu. Attempts to perform the reaction thermally led to rearomatization, which is consistent with our previous observations of the thermal instability of cyclohexadienone-derived products (**Section 3.3.2**). We also attempted to install an allyl group through Sakurai chemistry (allyltrimethylsilane, $TiCl_4$), but our limited investigation yielded no promising results; only rearomatized products were observed.

At this time, we began to investigate C10 side-chains other than allyl. Inspired by the wide variety of chemistry that can be performed on acetylides, we proposed trimethylsilylacetylene as a suitable alternative. Attempted addition of a reagent made from the magnesium acetylide of trimethylsilylacetylene and MAD gave no product.[43]

A Ni-catalyzed Al acetylide addition was similarly unsuccesful.[150] We were delighted to find that the LANA addition of 2 equivalents of the Mg acetylide of trimethylsilylacetylene into **4.9a** at −78 °C for 1.5 hours followed by stirring at room temperature for 1 hour led to incomplete conversion of the compound into **4.12** as the only observed product. The reaction could be driven to completion by adding 3 equivalents of the acetylide at −78 °C, stirring for 15 minutes, then warming to room temperature for 2 hours. Conversion of **4.9a** to the lithium alkoxide prior to acetylide addition as well as the addition of HMPA was not necessary in this case. The hydroxyl group in **412** could be protected as a TMS ether giving **4.13** in good yield.

Scheme 4.2: Initial C10 functionalization studies



We began to evaluate conditions for the C1 methylation of enone **4.13**. Initial deprotonation of **4.12** with LDA in THF for 30 minutes at –78 °C led to isolation of **4.14** in 76% conversion, along with unreacted starting material (**Table 4.1**). Unfortunately, **4.14** was inseparable from the starting material (**4.13**), complicating purification. Extending the reaction time did not improve the conversion. Allowing the deprotonation to occur for extended times led to very low conversion, though the conversion improved significantly when HMPA was added. Deprotonating at 0 °C led to side-product formation. We also screened several other bases. While initial results with LiHMDS gave better results, these results were inconsistent from run to run.

$LiNEt_2$ performed poorly. Due to the good conversion and consistency when LDA was used as a base, these were taken as the optimum conditions (Entry 4).

Table 4.6: Optimization of methylation conditions

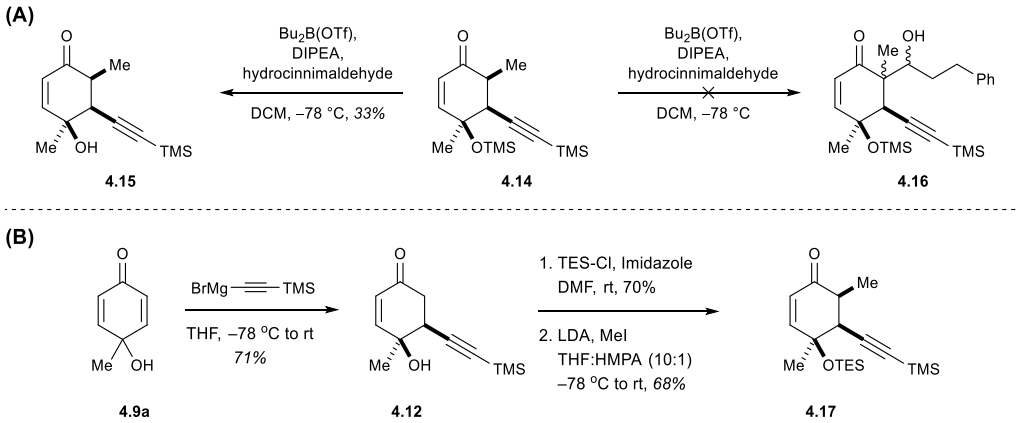
4.13 4.14

Entry	Base	Additive	Deprot. Temp (°C)	Deprot. Time (min)	Rxn Time (h)	Conversion (%)
1	LDA	--	−78	30	1.5	76
2	LDA	--	−78	30	4.5	77
3	LDA	--	−78	60	4.5	17
4	LDA	HMPA	−78	60	4.5	90
5	LDA	HMPA	0	60	4.5	94[a]
6[c]	LiHMDS	HMPA	−78	60	2	~100[b]
7[c]	$LiNEt_2$	HMPA	−78	60	2.5	47

a. A significant number of side-products formed as well; b. Conversions were not consistent between runs; c. Reaction performed with enone **4.12** instead.

Subjecting **4.14** to boron-aldol conditions resulted in the isolation of desilylated **4.15** as the only observed product (**Scheme 4.3A**). Attempts to install more acid-stable protecting groups such as TBS of Bz were met with failure, presumably due to the sterically hindered nature of the tertiary alcohol in **4.12**. However, we were able to successfully install a TES ether which we hoped would be stable to aldol conditions (**Scheme 4.3B**). Synthesis of methylated TES substrate **4.17** proceeded according to our previous methods from **4.12** without incident.

Scheme 4.3: (A) Initial aldol studies; (B) Synthesis of TES-protected substrate

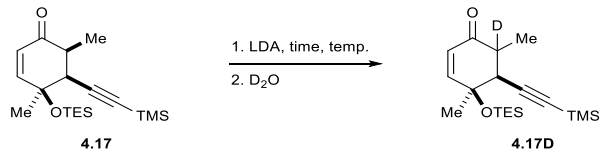


4.1.3. Evaluation of Aldol Conditions

When **4.17** was subjected to boron-aldol addition conditions, we were excited to isolate a small amount of material that was identified by mass spectrometry to be aldol adduct **4.18**. Starting material **4.17** and desilylated product **4.15** were also isolated. Encouraged by this result, we investigated other boron Lewis acids. Lewis-acids such as Cy_2BOTf or $PhBCl_2$[151] gave aldol products in very low conversion and yield. We determined that the desilylation could be minimized by changing the order of addition and adding the Lewis acid to a mixture of the substrate and base.

We were unsure at this time whether the incomplete conversion of the substrate was due simply to incomplete deprotonation or the unreactivity of the resulting enolate due to steric and torsional strain, in analogy to substrates **3.71 & 3.72** (**Section 3.3.3.d**). In order to probe this question, we undertook a brief deuterium incorporation study (**Table 4.2**). Deprotonation of **4.17** with LDA at −78 °C for 1h led to only 30% observed D incorporation. However, adding the LDA at −78 °C followed by warming to 0 °C for 30 minutes resulted in complete deuterium incorporation, with no observed decomposition.

Table 4.2: Deuterium incorporation studies



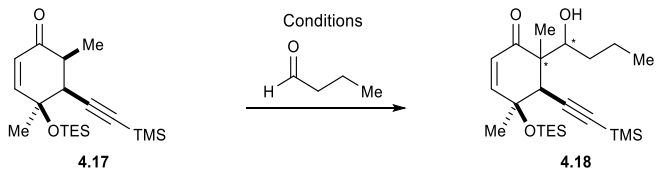
4.17 4.17D

Entry	Time (min)	Temp (°C)	D Incorporation (%)
1	60	−78	30
2	30	0	100

We then returned to the investigation of Li, B, and Ti enolates using our improved deprotonation conditions (**Table 4.3**). We were able to achieve 50% conversion from the Li enolate which was a significant improvement. The aldol addition of the Li enolate resulted in an inseparable mixture of all four possible diastereomers in a 10:6.2:3.9:1 ratio. Due to significant spectral overlap, we were unable to assign the relative configuration of these products. Formation of a Ti enolate resulted in improved conversion of 70%.[138] In this instance, only two diastereomers were obtained, in a 3.2:1 dr. The improved selectivity is likely due to the transition from an open to a closed transition state under the Ti-promoted conditions. To our delight, performing a boron aldol reaction utilizing elevated deprotonation temperatures and the less-bulky base NEt_3 led to full consumption of the starting material.[vi] The resulting aldol adduct **4.18** could be obtained in 67% yield as a single diastereomer.

[vi] Subsequent attempts to replicate this result at a later date were unsuccessful

Table 4.3: Aldol addition studies



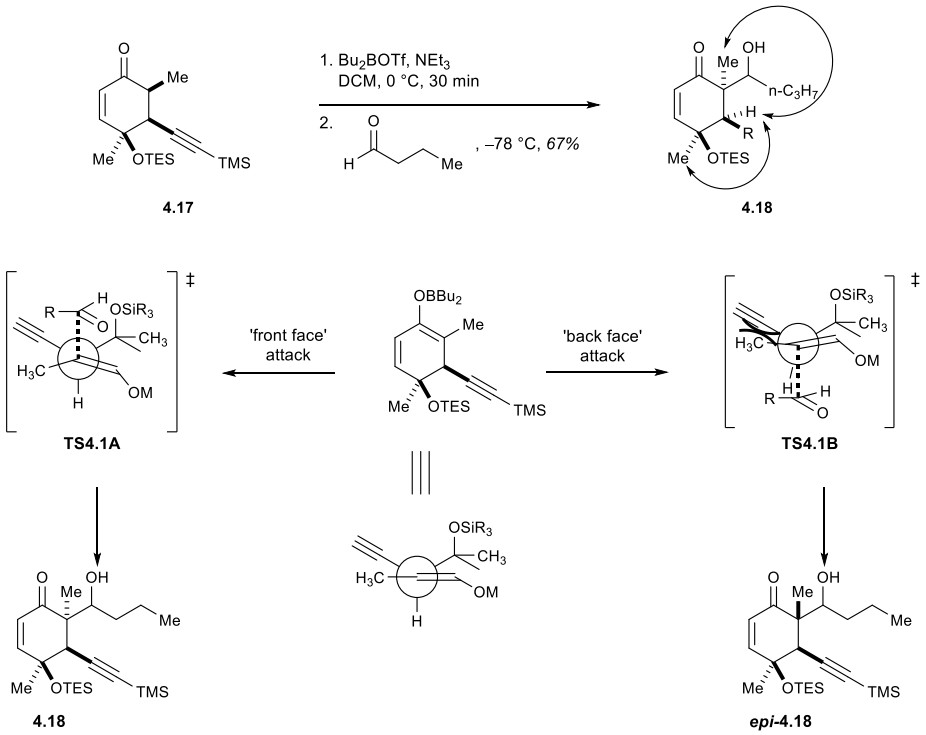
4.17 4.18

Entry	Conditions	Conversion (%)	dr[a]
1	LDA	50	10 : 6.2 : 3.9 : 1
2	LDA *then* $Ti(OiPr)_3Cl$	70	10 : 3.1
3	Bu_2BOTf, NEt_3	100	>20:1

a. Diastereomers were inseparable, relative configurations unassigned

Unfortunately, a clear NOE correlation between the C10 methine and both the C15 and C20 methyl groups in **4.18** indicated that the product possessed the undesired C1 stereochemistry (**Scheme 4.4**). Once again, the influence of torsional strain appears to dominate the stereoselectivity in these systems.[145] In this case, developing eclipsing interactions in **TS4.1A** led to more favorable electrophilic approach from the same side as the alkyne (**TS4.1B**). We were surprised at the extent to which this torsional steering operates in these systems, as it appears to be common occurrence in these rigid, highly substituted molecules. The generality of this trend has not been further studied, though such studies are warranted.

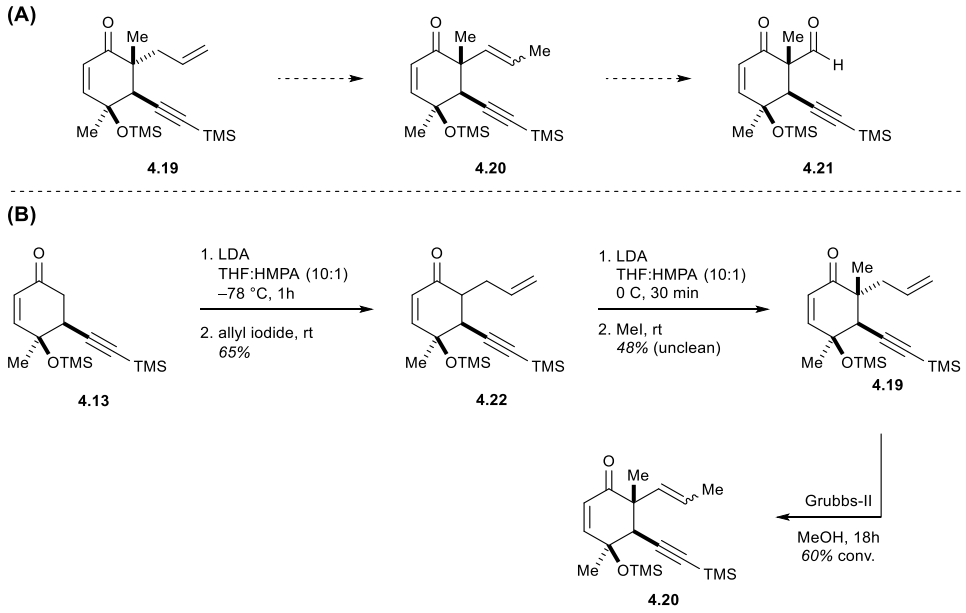
Scheme 4.4: Rationale for aldol stereochemical outcome



We briefly attempted to coopt our existing route to take advantage of the preference for electrophilic approach *syn* to the acetylide. We postulated that the proper stereochemistry could be introduced by first alkylating at C1 with a moiety that could serve as a masked aldehyde followed by methylation at C1 (**Scheme 4.5A**). After elaboration, the aldehyde could be revealed and a side chain could be introduced in a manner similar to that used by Ito/Iguchi.[117] We selected an allyl group, which could be converted to an aldehyde after isomerization to the internal alkene (**4.20**) and oxidative cleavage (**4.21**). Allylated ketone **4.22** could be synthesized using our previously optimized conditions using allyl iodide as the electrophile. Unfortunately, attempted methylation of **4.22** resulted in low yields and numerous, inseparable side-products, though with the desired relative stereochemistry. While we were able to achieve promising success in affecting the isomerization to **4.20** using the Grubbs' second generation catalyst in MeOH[152], we elected to abandon this route. The relatively

low yields, higher step-count, and required use of highly toxic reagents such as OsO_4 suggested that there could be a more efficient way to take advantage of the inherent selectivity of these substrates.

Scheme 4.5: (A) Proposed conversion of **4.19** to aldehyde **4.20**; (B) Synthetic elaboration to that end



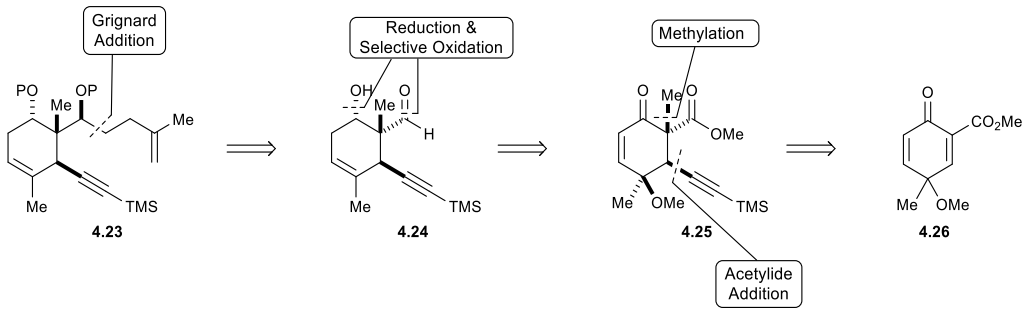
4.2. Fourth Synthetic Approach

4.2.1. Retrosynthetic Proposal

In light of the fact that the electrophilic approach to substrates such as **4.17** appears to be directed primarily by torsional steering effects, we decided to take advantage of this selectivity and introduce the methyl group after the other carbon fragment at C1 (**Scheme 4.6**). This approach would require a significant revision of the retrosynthesis in order to allow methylation at C1 after a second fragment had been introduced. We proposed that the alcohol at C2 would now be formed through a stereoselective organometallic addition to aldehyde (**4.24, Scheme 4.6**). Ito & Iguchi employed a similar strategy in their synthesis of a briarane fragment.[117] Aldehyde **4.24**

could be furnished from ketoester **4.25** through a stereoselective reduction of the C14 ketone followed by functional-group manipulations. Methylated ketoester **4.25** would be formed through conjugate addition of an acetylide into cyclohexadienone **4.26** followed by stereoselective methylation.

Scheme 4.6: Revised retrosynthetic proposal



4.2.2. Initial Synthetic Studies

Attempts at dearomatizing phenol **4.27** using PIDA as the oxidant in MeOH proceeded to incomplete conversion. The salicylate ester is presumably less active in the dearomatization due to the electron-withdrawing ester group. We were pleased to discover that μ-oxo-bridged diiodide **4.29** provided **4.26** in good yield (**Scheme 4.7**).[14] Use of H_2O as a nucleophile gave unstable products which could not be isolated cleanly.

We began to investigate methods to add an acetylide into **4.26** (**Table 4.4**). Addition of a Mg-acetylide gave primarily 1,2-addition. A promising result came from the addition of a Zn-acetylide using conditions reported by Carriera.[153] While the crude ^{1}H NMR spectrum suggested **4.28** as a product from the acetylide addition, the crude material was subjected to methylation immediately to minimize rearomatization of the sensitive compound. MeI and Cs_2CO_3 were used as the initial methylation conditions for the optimization of the acetylide addition. The resulting compound appeared to be diastereomerically pure **4.25** by ^{1}H NMR spectroscopy, though the relative stereochemistry could not be confirmed due to the lack of any diagnostic NOE

correlations. The stereochemistry could be confirmed by later NOE investigation of acetonide **4.32a** (**Section 4.2.3**). Further optimization using Zn acetylides was unable to improve the yield. Attempts to utilize catalytic amounts of the expensive $Zn(OTf)_2$ resulted in no conversion of the starting material. The conjugate addition could be performed using Mg acetylides by adding catalytic quantities of Cu(I) salts, though a significant amount of unidentified side-products formed as well.[154] The use of Al acetylides in a nonpolar solvent such as toluene allowed the formation of the desired methylated product in 25 % yield as a single diastereomer.[155] While the yield was nominally lower than that obtained under the Cu-catalyzed conditions, the isolated products were significantly cleaner by ^{1}H NMR spectroscopy. A survey of methylation conditions revealed that the use of K_2CO_3 in toluene with 18-crown-6 once again provided optimum results, giving an acceptable 41% yield over two steps, and minimizing rearomatization of the product. Though the yield of this sequence is lower than we would have liked, the low yield is balanced by the significant increase in molecular complexity; a key carbon fragment, an all-carbon quaternary stereocenter, and the C1–C10 stereochemical relationship are all set with almost perfect selectivity in only a few synthetic transformations.

Treatment of ketoester **4.25** with Zn in AcOH provided the reduced product **4.29** in good yield.[121] Use of a 10-fold excess of activated Zn allowed the reaction to be performed at room temperature, which further improved the yield. Use of cosolvents such as THF along with AcOH led to decreased yields.

Scheme 4.7: Elaboration to fragment **4.29**

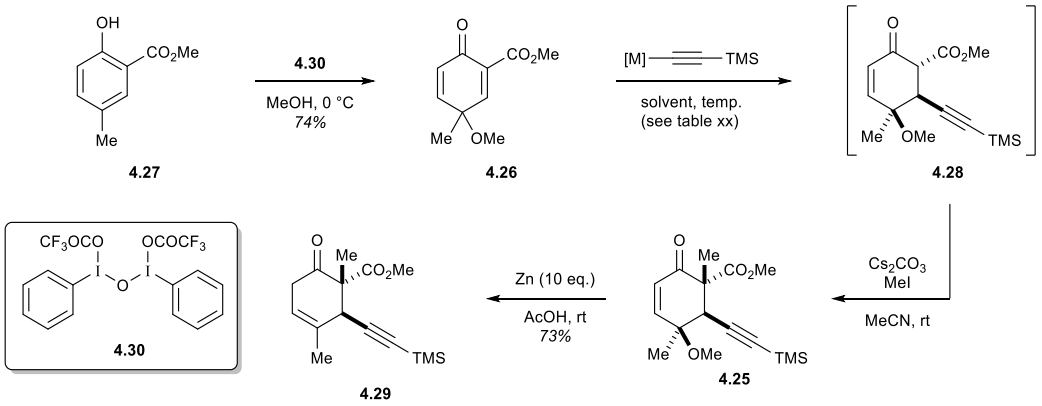


Table 4.4: Screening of acetylide/methylation conditions

Entry	**[M]**	**Solvent (temp)**	**Methylation Conditions**	**Yield of** 4.25 (%)[a]
1	MgBr	THF (–78 °C)	Cs_2CO_3, MeI MeCN, rt	decomp
2	ZnOTf	MeCN (60 °C)	Cs_2CO_3, MeI MeCN, rt	10
3	MgBr[b]	THF (–78 °C)	Cs_2CO_3, MeI MeCN, rt	33
4	Et_2Al	Et_2O/toluene/Hexane (0 °C)	Cs_2CO_3, MeI MeCN, rt	25
5	Et_2Al	Et_2O/toluene/Hexane (0 °C)	K_2CO_3, MeI 18-crown-6 toluene, rt	37
6	Et_2Al	Et_2O/toluene/Hexane (0 °C)	K_2CO_3, MeI 18-crown-6 toluene, rt	41[c]

a. After isolation by chromatography; b. w/ 0.1 eq. CuCl; c. reaction performed on a 1.44 mmol scale

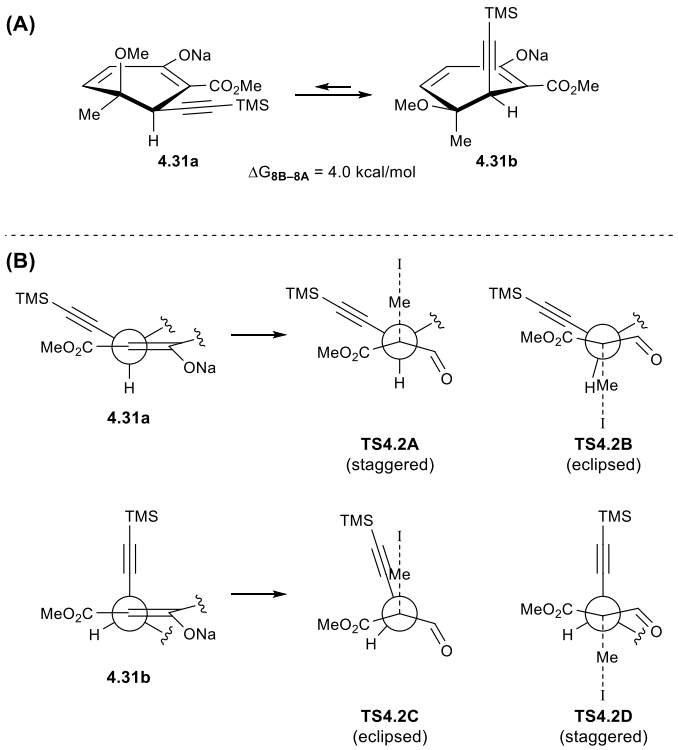
To our great delight, the stereoselectivity of both the acetylide addition and methylation appeared to be very high, giving the desired diastereomer of **4.25** almost exclusively. The stereochemistry of the acetylide addition could be rationalized through

coordination of the Lewis acid on the acetylide with the oxygen of the methyl ether. An alternative, plausible explanation for the selectivity could be the "syn oxygen effect" which has been investigated computationally by Houk and Paquette (**Section 1.2.3**).[44, 78]

We sought to briefly investigate the preference for methylation *syn* to the acetylide computationally (**Figure 4.1**)[vii]. The enolate of ketoester **4.28** can exist with the acetylide in either the axial (**4.31a**) or equatorial (**4.31b**) conformer. DFT ground-state calculations indicate that the axial conformer is more stable by about 4.0 kcal/mol. From these two conformers, four possible transition states could be envisioned. From **4.31b**, the electrophile could approach either *syn* to the acetylide (**TS4.2A**) or *anti* to the acetylide (**TS4.2B**). The axial conformer would have two similar *syn* and *anti*-transition states (**TS4.2C**) and **TS4.2D** respectively). **TS4.2B** and **TS4.2C** would be disfavored due to torsional strain. However, the two remaining transition states (**TS4.2A** and **TS4.2D**) would give diastereomeric products. Given the high observed selectivity, another effect is clearly operative. We hypothesize that the reaction proceeds under Curtin-Hammett conditions. While conformer **4.31b** is thermodynamically favored, **4.31a** is the more reactive conformer. Initial calculations on a related substrate indicate that this is a plausible explanation, though additional computational and experimental work is needed to more fully investigate this hypothesis.

[vii] Computations performed by Dr. Andrew Harned

Figure 4.1: (a) Conformational analysis of enolate **4.31**; (b) Transition-state analysis of **4.31a** and **4.31b**

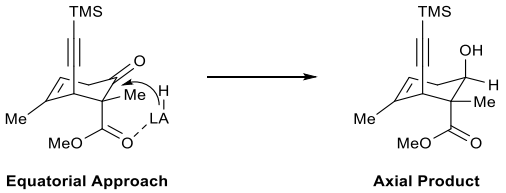


4.2.3. Completion of the Briarane Stereotetrad Synthesis

With ketone **4.29**, which possesses the heretofore unattainable correct C1 stereocenter, in hand, we began to investigate the stereoselective reduction of the C14 ketone (**Table 4.5**). We were extremely surprised to find that both $LiAl(O\textit{t}\text{-}Bu)_3H$ and $NaBH_4$ gave the same diastereomeric product **4.32b**. The relative stereochemistry could be confirmed by reducing **4.32b** to the diol followed by conversion to acetonide **4.33b**. The lack of NOE enhancement between the C14 methine and C15 methyl group led us to tentatively assign the product as the undesired, axial alcohol product **4.32b.** The stereoselectivity is perhaps due to complexation of the Al or B Lewis acids with the carbonyl of the ester, resulting in equatorial approach of the hydride (**Figure 4.2**). The preference for axial-disposition of the acetylide could be further biasing the approach

of the hydride towards and equatorial trajectory by blocking the top face from nucleophilic approach.

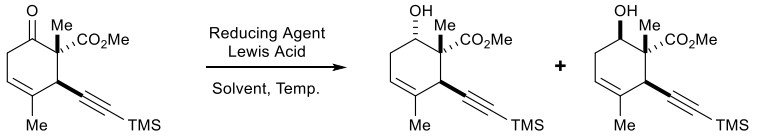
Figure 4.2: Stereoselectivity model for equatorial hydride attack



Drawing inspiration from work by Fraga[156] in which Lewis acids played an important role in the stereochemical outcome of the reduction of cyclic ketoesters, we screened a variety of Lewis acids and reducing agents. Changing the BH_4^- counterion to either Bu_4N^+ or Li^+ (Entries 3 & 27) did not significantly improve the ratio. The use of other reduction conditions such as SmI_2 or $Al(O\textit{i}\text{-}Pr)_3$ in *i*-PrOH did not give promising results either. Gratifyingly, when a Lewis acid such as $CaCl_2$ was used, the ratio improved somewhat (Entry 4). However, the improvement was not significant enough to be synthetically useful. We undertook an extensive screen of Lewis acids to further improve the selectivity. Mn(II), Mg(II), Fe(II), and Ti(IV) all led to rapid conversion, though the diastereomer ratio was not improved. Some Lewis acids such as $Bi(OTf)_3$, $SnCl_2$, $FeCl_3$ and $ZnCl_2$ appeared to give other either metal hydride or boride products; addition of the $NaBH_4$ led to rapid and often highly exothermic formation of solids and incomplete conversions even after extended reaction times (24h). The selectivity favored the axial alcohol in all cases. The only exception was when L-selectride was used as a reducing agent. In this case, the products could be produced in a 1.9:1 ratio of **4.32a**:**4.32b** (as observed by crude ^1H NMR spectroscopy). However, the reaction did not proceed to completion and significant decomposition and side-product formation was observed. Further investigation into this class of reagents is needed in order to determine better conditions.

The first truly promising result came when the lanthanide salt $CeCl_3 \cdot 7H_2O$ was employed as the Lewis acid. The diastereomer ratio improved significantly to 1:2.9, though still favoring axial alcohol **4.32b**. We found that the reaction could be run at room temperature with no erosion in selectivity. However, the use of isopropanol as the solvent led to decreased selectivity. A screen of various other lanthanide salts found $Y(OTf)_3$ to be best. The triflate counterion appears to be important, as a decrease in selectivity was observed when $YCl_3 \cdot 6H_2O$ was used. Methanol was once again the best solvent. It is possible that the less-coordinating nature of the triflate counterion increases the coordination number of solvent ligands on the Lewis acid. Higher coordination could lead to a more sterically demanding substrate and better shield the equatorial trajectory of hydride attack. Further study is necessary to fully understand the details of this reduction. Though the nearly 1:1 diastereoselectivity was not ideal, we decided to carry the material forward at this point in order to evaluate the remainder of the sequence.

Table 4.5: Screening of ketone reduction conditions



4.29 4.32a 4.32b

Entry	Reductant	Lewis Acid	Solvent	Temp (°C)	conv. [a] (%)	4.32a:4.32b[b]
1	$LiAlH(O\textit{t}\text{-}Bu)_3$	--	THF	−78	100	1:49.0
2	$NaBH_4$	--	MeOH	0	100	1:16.2
3	Bu_4NBH_4	--	MeOH	0	100	1:24.6
4	$NaBH_4$	$CaCl_2$	MeOH	0	100	1:7.9

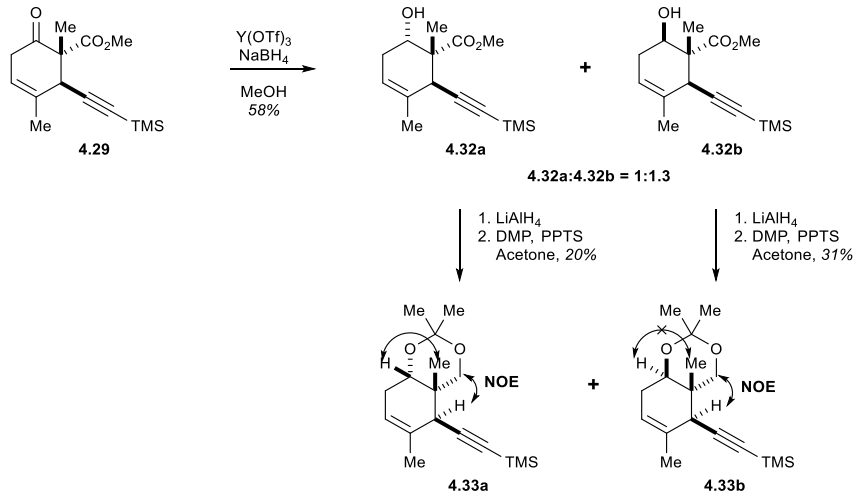
5	$NaBH_4$	$CeCl_3 \cdot 7H_2O$	MeOH	0	100	1:2.9
6	$NaBH_4$	$CeCl_3 \cdot 7H_2O$	*i*-PrOH	0	100	1:8.1
7	$NaBH_4$	$CeCl_3 \cdot 7H_2O$	MeOH	rt	100	1:2.7
8	$NaBH_4$	$MnSO_4 \cdot H_2O$	MeOH	rt	100	1:12.8
9	$NaBH_4$	$ZnCl_2$	MeOH	rt	37	1:28.8
10	$NaBH_4$	$MgCl_2$	MeOH	rt	100	1:8.4
11	$NaBH_4$	$FeCl_2$	MeOH	rt	100	1:7.5
12	$NaBH_4$	$FeCl_3$	MeOH	rt	89	1:10.8
13	$NaBH_4$	$AlCl_3$	MeOH	rt	33	1:4.1
14	$NaBH_4$	$Ti(i\text{-}PrO)_4$	MeOH	rt	100	1:10.8
15	$NaBH_4$	$SnCl_2 \cdot 2H_2O$	MeOH	rt	62	1:22.6
16	$NaBH_4$	$InCl_3$	MeOH	rt	90	1:32.5
17	$NaBH_4$	$Y(OTf)_3$	MeOH	rt	100	1:1.3
18	$NaBH_4$	$Y(OTf)_3$	THF	rt	100	decomp.
19	$NaBH_4$	$Y(OTf)_3$	EtOH	rt	100	1:9.8
20	$NaBH_4$	$YCl_3 \cdot H_2O$	MeOH	rt	100	1:2.2
21	$NaBH_4$	$Yb(OTf)_3$	MeOH	rt	100	1:1.5
22	$NaBH_4$	$Sc(OTf)_3$	MeOH	rt	100	1:6.9
23	$NaBH_4$	$Eu(OTf)_3$	MeOH	rt	100	1:1.7

24	$NaBH_4$	$Bi(OTf)_3$	MeOH	rt	22	<1:50
25	$NaBH_4$	LiBr	DME	rt	0	NA
26	$NaBH_4$	Amberlyst-15	THF	rt	100	deomp
27	$LiBH_4$	--	THF	rt	100	decomp
28	SmI_2	--	THF/H_2O	rt	100	1:6.6
29	$Al(i\text{-}PrO)_3$	--	*i*-PrOH	80	17	1:1.8
30	L-Selectride	--	THF	rt	76%	1.9:1

a.After 24 h of reaction; b. Determined by crude ^{1}H NMR Spectroscopy using the integration of the C15 Me signals (δ 1.43 for **10a** & 1.31 for **10b**); b. Significant impurities were observed in crude ^{1}H NMR spectrum. Ratio was determined using C12 vinyl protons (δ 5.27 ppm for **10a** and 5.32 ppm for **10b**).

Gratifyingly, the reduction of **4.29** on a larger scale allowed for the clean isolation of **4.32a** and **4.32b** in reasonable quantities. The relative stereochemistry of the reduction products was further confirmed by reducing the ester to the diols followed by immediate conversion to the acetonides **4.33a** and **4.33b**. The acetonide (**4.33a**) from equatorial alcohol **4.32a** showed NOESY enhancement between the C14 methine and the C15 methyl group, which was absent in **4.33b** (**Scheme 4.8**). Enhancement between the C10 methine and the C2 methylene in both substrates also confirmed the correct relative stereochemistry of the acetylide and methyl group.

Scheme 4.8: Stereochemical confirmation of the reduction



We then carried **4.32a** forward to complete the synthesis of the briarane stereotetrad (**Scheme 4.9**). Reduction of the ester in **4.32a** with $LiAlH_4$ followed by immediate oxidation of the primary alcohol with TEMPO gave aldehyde **4.24** in acceptable yield. When we attempted the Grignard addition of allylmagnesium bromide, followed by immediate conversion to the acetonide, we isolated 1:1.4 mixture of inseparable diastereomers **4.34a**:**4.34b** in poor yield. Examination of the NOESY spectrum of the two diastereomers was inconclusive due to the significant spectral overlap between the two diastereomers. We were however able to identify the ^{13}C NMR shifts for the acetonide methyl groups in both diastereomers through the use of HSQC. The chemical shifts for the major diastereomer (δ 30.33, 19.55 ppm) are consistent with Rychnovsky's prediction for *syn* 1,3-diols.[157] Similarly, the values for the minor diastereomer (δ 27.35, 25.24 ppm) are consistent with the desired *anti* 1,3-diol. Gratifyingly, when the same reaction was attempted in Et_2O, a significantly improved dr of 3.1:1 (observed in crude NMR spectrum) in favor of the desired *anti* diol **4.34a** was obtained. Examination of the NOESY spectrum of this compound confirmed the relative stereochemistry. The reaction also proceeded in DME, though with a decreased ratio of **4.34a**:**4.34b** of 2.2:1.

The selectivity of Grignard addition to our system appears to be significantly lower than that observed by Ito and Iguchi, who observed a single diastereomer. There could be several factors affecting the selectivity. First, the smaller TMS-acetylide moiety in the analogous equatorial conformer **4.35b** is smaller than the bulky $CH_2OTBDPS$ group, which could provide less effective steric shielding (**Figure 4.3**). We have previously observed a preference for the acetylide moiety in these substrates to adopt an axial conformation, which could be occurring in this situation as well. A different conformational population relative to the one observed by Ito and Iguchi could also lead to different levels of selectivity. Finally, the less-coordinating solvent Et_2O could be improving the extent of chelation of the Mg with the aldehyde prior to addition. Further work, both computational and experimental, is necessary to more fully reveal the nature of these preferences. Solving some of the problems encountered earlier (see section 4.3 for potential solutions), will result in higher material throughput that will easily enable further investigation of this key step.

Scheme 4.9: Completion of the synthesis

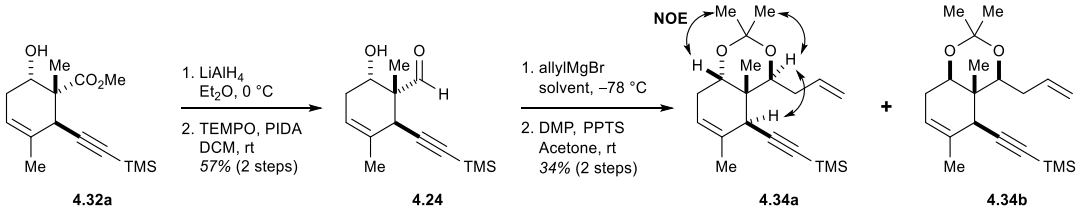
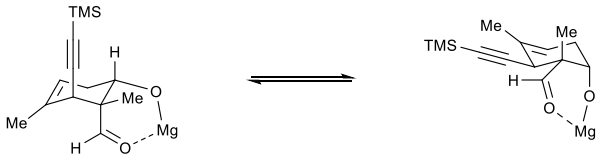


Table 4.6: Screening of solvent conditions in Grignard addition to **4.24**

Entry	Solvent	4.34a:4.34b	Yield (%)
1	THF	1:1.4	34
2	Et_2O	4.2:1	34
3	DME	2.2:1	N/A

Figure 4.3: Possible chelated conformers



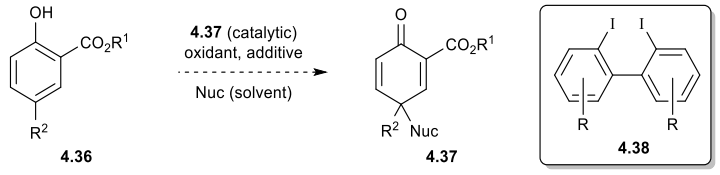
4.3. Future Work

We have demonstrated a promising strategy towards the synthesis of the stereotetrad core of the briarane diterpenoids. While some of the steps in our current strategy are far from ideal, solutions to each of the problems are quite tractable. The desire to solve those problems is especially motivated by the significantly abbreviated nature of the synthesis; the best current method to access a similar stereotetrad core reported by Bates involves 16 steps while ours only requires 8.[118]

The first major problem that should be solved involves the development of a catalytic version of the oxidative dearomatization. While the dearomatization using oxidant **4.30** proceeds well, the reaction is far from ideal. Compound **4.30** is not commercially available, and its preparation requires large amounts of other oxidants such as PIDA along with large volumes of solvent, which limits the amount that can be practically made at one time. Additionally, the potentially explosive nature of the iodosobenzene intermediate would make the large-scale preparation of **4.30** particularly hazardous. The challenge of preparing **4.30** on large-enough scales, coupled with the formally 2 equivalents of oxidant (relative to I) and the large molecular weight difference between the substrate and the oxidant (approximately 4 g of oxidant needed for every 1 g of substrate) severely limited the material throughput of the sequence. A catalytic version of the dearomatization would ameliorate many of these difficulties.

As it appears that the bridged-nature of the oxidant significantly improved the reaction, similar substructures should be investigated in the catalytic reaction (**Scheme 4.10**). Kita has reported diiodobiaryl substrates **4.38** for iodine(III) mediated organocatalytic cross-coupling reactions.[158] These substrates can be easily synthesized with a variety of substituents on the aromatic rings. A screen of a variety of these catalysts, along with potential additives such as TFA, TFE, and HFIPA would likely lead to conditions for a catalytic dearomatization of electron-deficient phenols. This would be a useful discovery in and of itself, as the efficient iodine-based dearomatization of electron deficient phenols is currently an unsolved problem. A reliable method to access such substrates would open the door to further synthetic investigations. It is likely that the development of a catalyst such as **4.38** would further improve the yields of catalytic dearomatizations generally, which are often lackluster.

Scheme 4.10: Proposed catalyst for dearomatization

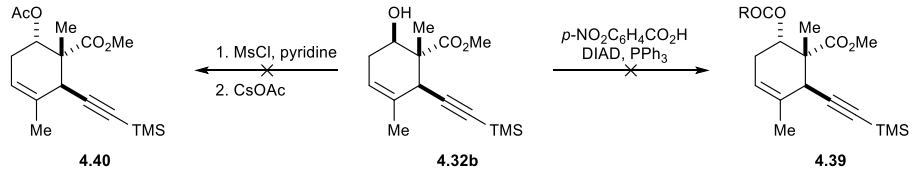


The most important step to improve is the ketone reduction to give **4.32a**. While the exact reasons for the strong preference for equatorial hydride delivery remain unclear, it is apparent that this is a significant selectivity barrier to overcome. Given the fact that the poor selectivity and yield of this step greatly diminished the material throughput of the sequence, solving this problem is of utmost importance. The problem could be solved in one of two ways. The first would be to further screen reducing agents in the reduction. The promising result using L-Selectride warrants further investigation. It is possible that the efficiency of the reduction will be highly solvent and counterion dependent. Other related reducing agents such as superhydride ($LiEt_3BH$) could also be investigated. Stereoselective, reagent-controlled reduction conditions should also be investigated. Brown has reported reasonable levels of control over the reduction of

a related substrate.[159] His DIP-Cl reagent would be an ideal candidate due to its ease of preparation and handling, along with the ready and inexpensive availability of both enantiomers of the reagent. Noyori and CBS reduction conditions could also be screened.

The other approach to the reduction problem would be to invert the stereocenter after its formation (**Scheme 4.11**). Preliminary investigations into performing a Mitsunobu reaction on this highly hindered substrate were not promising. Additionally, Huffman has reported the inversion of hindered stereocenters through reaction of alkyl-mesylates with CsOAc.[160] We were able to easily prepare the mesylate of **4.32b**, though reaction with CsOAc was not promising. An inversion approach also adds steps to the reaction sequence, which decreases its synthetic utility.

Scheme 4.11: Attempted hydroxyl inversion



4.40 **4.32b** **4.39**

Solving the aforementioned problems will allow access to more material to further optimize the Grignard addition to the aldehyde. Variation of the order of addition, nature of the Mg counterion, or even the investigation of other organometallic reagents could all be investigated. In analogy to Liottta's LANA procedure, the formation of the lithium alkoxide of the alcohol at C14 could also be accomplished. Optimization of the yield and selectivity of this addition will lead to a highly useful synthesis of the briarane stereotetrad, which can be used to rapidly access the remainder of the briarane molecules.

4.4 Conclusion

In conclusion, we have investigated two routes to the briarane stereotetrad core that utilize monocyclic intermediates.[viii] While we were validated in our hypothesis that monocyclic derivatives would be significantly more stable, aldol additions proceeded with the incorrect diastereoselectivity due to torsional steering effects. A route that utilized conjugate addition into a cyclohexadienone ester was significantly more successful, and the stereotetrad core could be obtained in only 8 steps. Future efforts geared at improving the weaker steps in the sequence are underway and will enable the efficient synthesis of the briarane diterpenoids.

[viii] Published as: Moon, N. G.; Harned, A. M. *Org. Lett.* **2015**, *17*, 2218-2221.

CHAPTER 5

IODINE(III) MEDIATED OXIDATIVE CYCLIZATIONS TO FORM OXAZOLINES

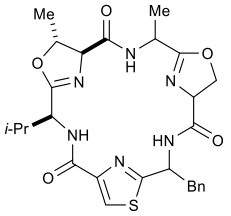
5.1. Introduction and Background

5.1.1. Synthesis of Oxazolines

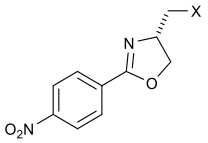
5.1.1.a. Traditional Method of Oxazoline Synthesis

Oxazolines are a heterocyclic motif that have found extensive applications as bioactive compounds (**5.2a, Figure 5.1**)[161] and organometallic ligands (**5.3**).[162] Additionally, the oxazoline substructure has been found in various natural products such as bistramide A (**5.1**).[163] As such, numerous methods have been developed to access oxazolines.

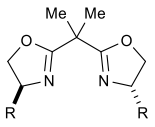
Figure 5.1: Oxazolines in natural products, bioactive compounds, and as ligands in organic synthesis



5.1
Bistratamide A



5.2a; X = NEt_2
5.2b; X = pyrrolidine
Active against human DNMT1



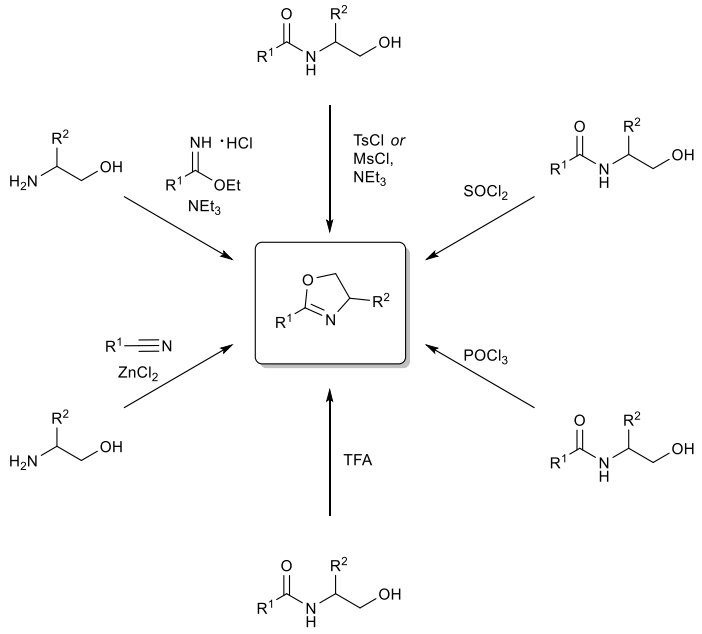
5.3; R = Ph, Bn, *t*-Bu, *i*-Pr
Useful ligand in organic synthesis

Many traditional methods to synthesize oxazolines involve the dehydration of a β-hydroxyamide (**Figure 5.2**), which can be readily prepared from the corresponding amino alcohols. Common dehydration methods include, but are not limited to: conversion of the

hydroxyl group to a tosylate/mesylate followed by nucleophilic displacement[164] and dehydration with a variety of dehydrating agents such as $SOCl_2$[165], $POCl_3$[127], and TFA[166]. These methods necessitate the formation of the amide in a separate step, which often requires chromatographic purification. The subsequent cyclization often takes place under harsh conditions, and requires the eventual removal of the dehydrating reagents and other byproducts, which are often used in large excess.

Methods also exist to convert an amino-alcohol to an oxazoline directly. Nitriles can be directly converted to oxazolines at elevated temperatures in the presence of a suitable Lewis acid catalyst such as $ZnCl_2$.[167] Alternatively, treatment of the imidate salt obtained from the corresponding nitrile in ethanolic HCl with an amino alcohol and base also leads directly to the oxazoline.[168] Once again, these methods require the action of harsh conditions including high temperatures and strong acids. The imidate substrate is also quite sensitive, and can be challenging to prepare. Since the methods traditionally used to access oxazolines are often unsuitable for more complex and sensitive substrates, there is demand for the development of milder methods to synthesize oxazolines.

Figure 5.2: Traditional methods for synthesizing oxazolines

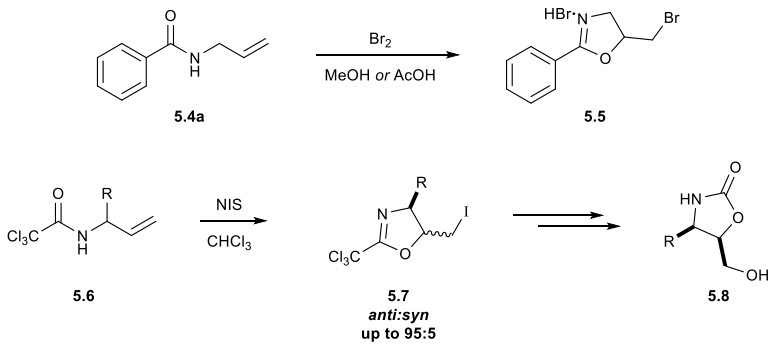


5.1.1.b. Oxazolines Through Electrophilic Cyclization

Electrophilic cyclization is a general and useful method to forge heterocycles. In an electrophilic cyclization, an alkene or alkyne is initially activated with an electrophile (I, Br, S, Se etc.) that undergoes a nucleophilic attack, forming a new ring along with an additional substituent that is determined by identity of the electrophile. This method is useful not only due to the mild conditions under which the cyclization proceeds, but also due to the additional substituent (such as an alkyl halide) which is available for further elaboration.

Early reports of oxazoline synthesis via electrophilic cyclization involved the use of halogens as the electrophile. In the course of studying neighboring group participation in reactions of benzamidopropene, Winstein observed that oxazoline **5.5** could be obtained when allylamide **5.4a** was treated with Br_2 (**Scheme 5.1**).[169] Some years later, Cardillo and coworkers synthesized iodooxazolines **5.7a** and **5.7b** by treatment of trichloroamide **5.6** with NIS *en route* to oxazolidinone **5.8**.[170]

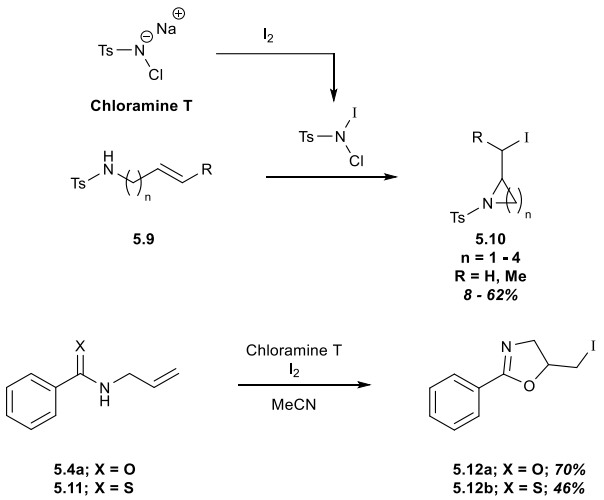
Scheme 5.1: Early reports of oxazoline synthesis by electrophilic cyclization



A related iodocyclization was reported by Mikinata and Komatsu (**Scheme 5.2**).[171] In this report, unsaturated sulfonamides **5.9** were treated with an electrophile derived from Chloramine T and I_2 to give *N*-heterocycles such as **5.10**. This reaction was found to occur with a variety of substrates, including terminal and internal alkenes. The cyclization did not proceed when the nitrogen atom was protected with a Boc-group, possibly due to the reduced acidity of the N-H bond in this case. The authors also found that *N*-allylamides

and *N*-thioamides underwent cyclization to give the oxazoline and thiazoline products **5.12a** and **5.12b**.

Scheme 5.2: Mikinata & Komatsu's electrophilic cyclization

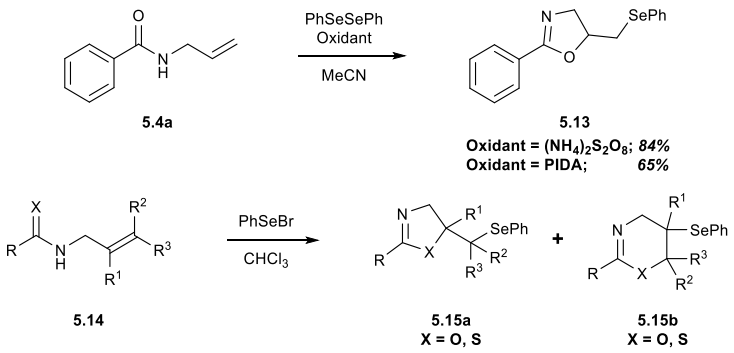


Oxazolines can also be formed through electrophilic cyclization using non-halogen electrophiles. Tiecco/Tingoli, and Engman, have reported the synthesis of oxazolines using selenium electrophiles (**Scheme 5.3**). Tingoli found that diphenyl diselenide could be treated with ammonium peroxydisulfate to generate an active electrophile that was able to affect the cyclization of numerous substrates.[172] When compound **5.4** was subjected to the reaction conditions, oxazolines **5.13** were obtained in good yield. A similar cyclization using PhSeSePh could be performed using PIDA to generate the selenium electrophile.[173]

Engman further investigated the synthesis of oxazolines through selenium-mediated oxidative cyclizations.[174] A variety of allylamides were treated with PhSeBr to furnish both the *endo* and *exo* products. In cases where the allyl group was unsubstituted, the *exo* product was isolated as the sole product. Similar results were observed for both phenyl and methyl substituents on the portion of the molecule bonded to the carbonyl. Substitution of the allyl group at the 1-position also led to exclusive *exo* product formation. Use of internal alkene **5.14** led to the isolation of a mixture of *endo* and *exo* products **5.15a** and **5.15b**, with the *endo* product predominating. Disubstitution at the terminal position

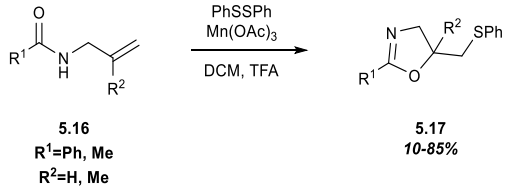
did not result in any productive reaction. The authors also found that thioamides were also nucleophiles for the reaction.

Scheme 5.3: Oxazoline formation with selenium electrophiles



Sulfur electrophiles have also been used in the synthesis of oxazolines (**Scheme 5.4**).[175] When *N*-allylamides (**5.16**) were treated with PhSSPh and $Mn(OAc)_3$, oxazoline **5.17** could be obtained in good yield. A variety of substituents were tolerated on the position bound to the carbonyl.

Scheme 5.4: Oxazoline formation with sulfur electrophiles



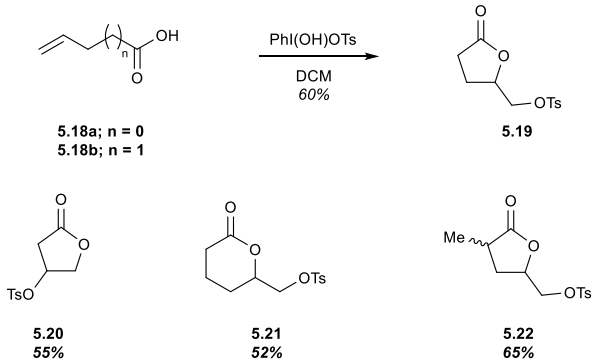
5.1.2. Hypervalent Iodine-Promoted Oxidative Cyclizations of Alkenes & Alkynes

5.1.2.a. Iodine(III)-mediated Cyclizations Involving Alkenes

The first example on a hypervalent iodine-mediated cyclization was reported by Koser and coworkers. Inspired by earlier results in which they were able to achieve ditosylation of alkenes using Koser's reagent (PhI(OH)OTs),[176] the authors hypothesized that an analogous lactonization reaction could be accomplished.[177] When 4-pentenoic acid (**5.18b**) was added slowly to Koser's reagent in DCM, tosyllactone **5.19** could be isolated in reasonable yield (**Scheme 5.5**). Use of acid **5.18a** led to regioisomer **5.20**. Further

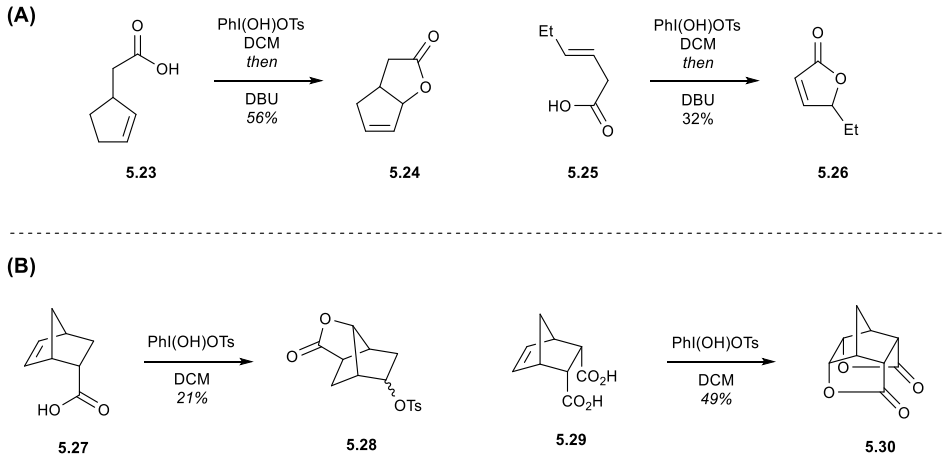
investigation of the scope of the reaction allowed for the formation of larger rings (**5.21**). Substituents α to the acid were also tolerated (**5.22**).

Scheme 5.5: Koser's oxidative lactonization with selected substrate scope



The authors discovered that when cyclic substrate **5.23**, which possesses an internal alkene, was subjected to the reaction conditions, bicyclic lactone **5.24** was obtained (**Scheme 5.6**). This product likely results from the elimination of the intermediate tosylate. The authors were able to maximize the yield by treating the reaction mixture with DBU after initial consumption of the starting material. Similar results were observed, albeit in lower yield, for internal alkene **5.25**. Investigation of norbornene-derived substrates led to isolation of rearranged substrate **5.28** in the case of the monoacid **5.27**. The diacid **5.29** furnished *bis*-lactone **5.30**.

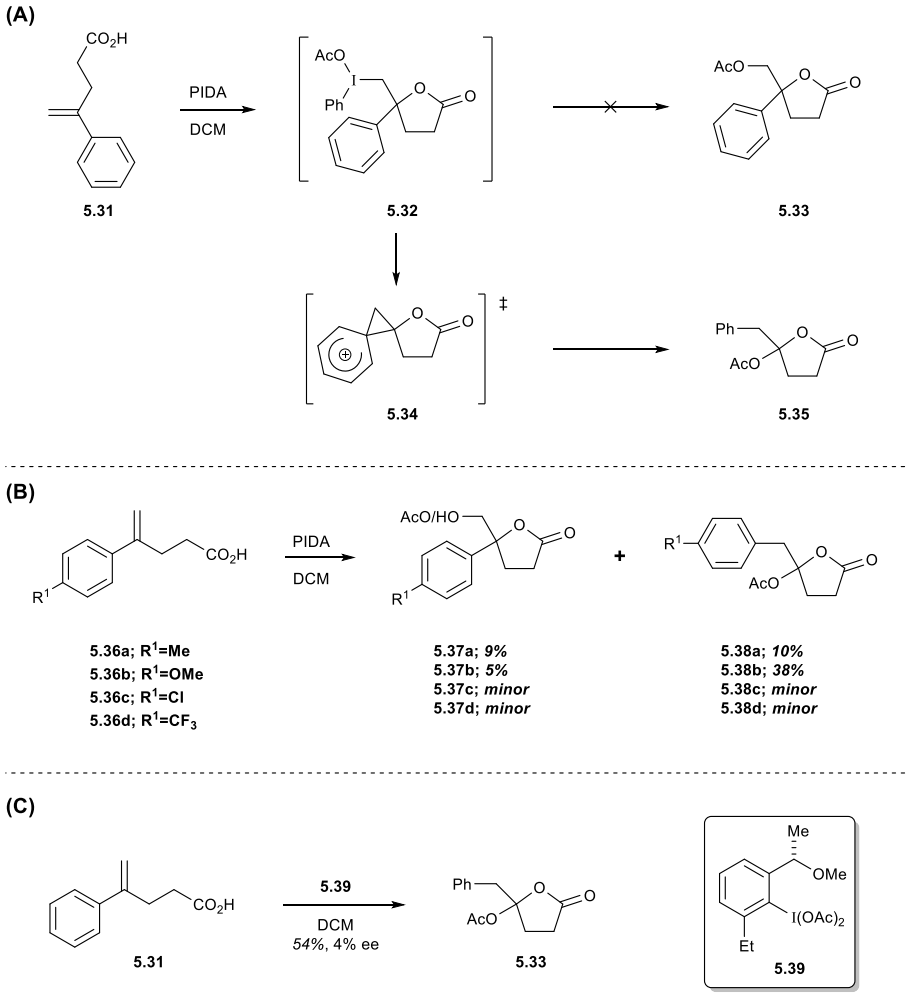
Scheme 5.6: (A) Cyclization on internal alkenes; (B) Cyclization of norbornene derivatives



In investigating a similar cyclization of substrate **5.31**, Wirth and coworkers observed an intriguing aryl shift involving an intermediate phenonium ion (**Scheme 5.7A**).[178] When **5.31** was treated with PIDA, compound **5.35**, resulting from a phenyl shift, was observed instead of the expected product **5.33**. The authors attribute this result to formation of phenonium ion **5.34** after displacement of the aryliodane moiety in **5.32**. Subsequent attack by acetate yields the observed product.

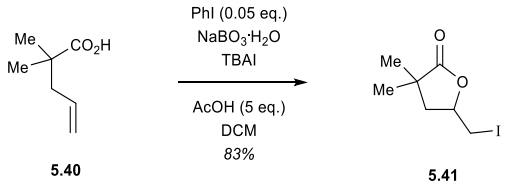
A screen of other phenyl group substituents revealed that *para*-substituted aryl acids proceeded more slowly than the parent compound (**Scheme 5.7B**). In some cases, unrearranged products were also observed. A brief attempt to utilize chiral, nonracemic oxidant **5.39** (**Scheme 5.7C**) led to product, though the observed ee was a paltry 4%.

Scheme 5.7: (A) Mechanism of cyclization with phenonium-ion shift; (B) Scope of cyclization; (C) Cyclization with chiral oxidant



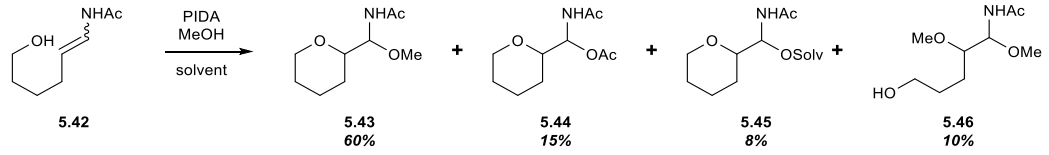
Tan and coworkers found that a similar lactonization could be performed using a catalytic amount of hypervalent iodine oxidant (**Scheme 5.8**).[179] When substrate **5.40** was treated with PIDA along with TBAI, iodolactone **5.41** was isolated in good yield. Further investigation found that when the amount of PIDA was decreased to 10 mol% with *m*-CPBA as the stoichiometric oxidant, the product was obtained in 16% yield. Use of $NaBO_3 \cdot H_2O$ significantly improved the yield. Iodobenzene could be used instead of PIDA with similar yields. The addition of five equivalents of AcOH further improved the yield. An investigation into the scope found that the reaction was tolerant of a number of substituents α to the acid.

Scheme 5.8: Tan's catalytic iodine(III) oxidative cyclization



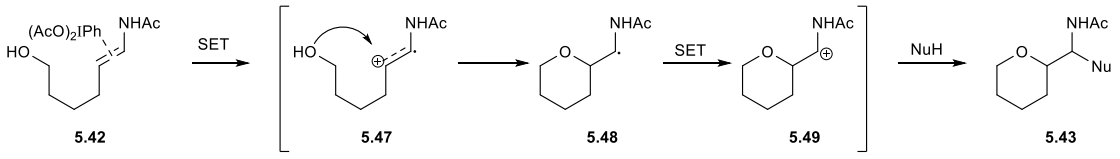
Huang reported the synthesis of *N*-acyl aminals through oxidative cyclization of *N*-acylenamines (**5.42, Scheme 5.9**).[180] Compound **5.42** was treated with PIDA and MeOH in a variety of solvents to give mixtures of methyl ether **5.43** along with acetate **5.44** as a side product. In cases where TFE was used, some trifluoroethyl ether **5.45** was also observed. Use of HFIPA in place of TFE suppressed this undesired side-reaction. The cyclization was found to be amenable to a number of different substrates.

Scheme 5.9: Huang's *N*-acylenamine cyclization



In contrast to previous examples, the authors proposed a mechanism in which the hypervalent iodine reagent performs a single-electron oxidation to generate radical cation (**5.47, Figure 5.10**), which subsequently undergoes cyclization. After subsequent oxidation, the resulting carbocation is trapped by the nucleophile which leads to the formation of product **5.43**. An S_N2'-like mechanism is also possible (not shown).

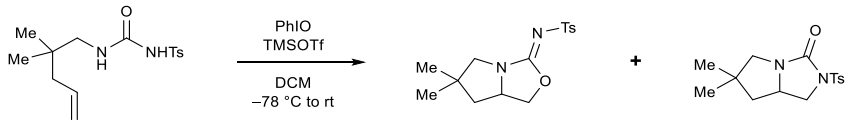
Scheme 5.10: Huang's proposed cyclization mechanism



A particularly intriguing set of examples of iodine(III)-promoted oxidative cyclizations were reported by the Michael group (**Scheme 5.11**). In the first report, the authors investigated the iodine(III)-promoted cyclization of unsaturated ureas (**5.50**) onto

unactivated alkenes.[181] While catalytic Pd was necessary for cyclization to occur in the presence of PIDA, the more active oxidant formed from PhIO and TMSOTf (PhI(OTMS)(OTf)) formed isourea compound **5.51** in the absence of Pd. Only trace quantities of the diamination product **5.52** were observed. The reaction was found to proceed with PIDA in the presence of TMSOTf as well.

Scheme 5.11: Michael's urea cyclization

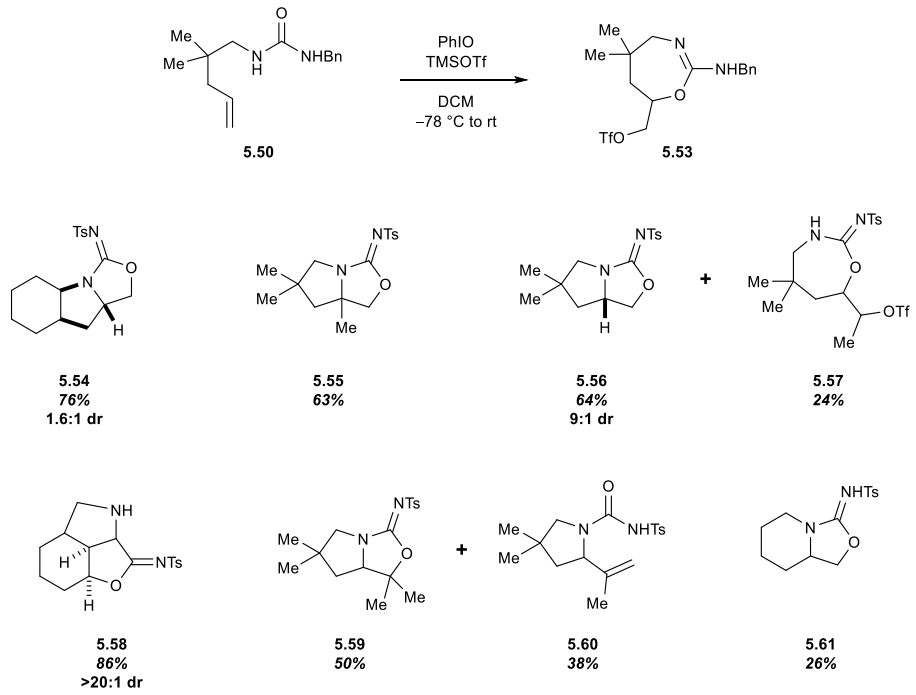


5.50 | **5.51** *89%* | **5.52** *trace*

A number of Lewis and Brønsted acids such as TIPSOTf, TfOH, Tf_2O, HBF_4, $BF_3{\cdot}OEt_2$, (*R*)-CSA, $Sc(OTf)_3$, $Zn(OTf)_2$, TFA, BzOH, and AcOH were able to promote the reaction. Interestingly, the ratio of oxyamination to diamination (**5.51**:**5.52**) was found to be highly dependent on the strength of the acid used. Stronger acids such as TfOH and (*R*)-CSA furnished isourea **5.51** in >20:1 ratio. In contrast, the use of weaker acids such as BzOH or AcOH reversed the selectivity, giving urea **5.52** in 1:>20 ratio of **5.51**:**5.52**. The authors attribute the greater preference for oxygen attack under strongly acidic conditions to the greater nucleophilicity of the oxygen atom.

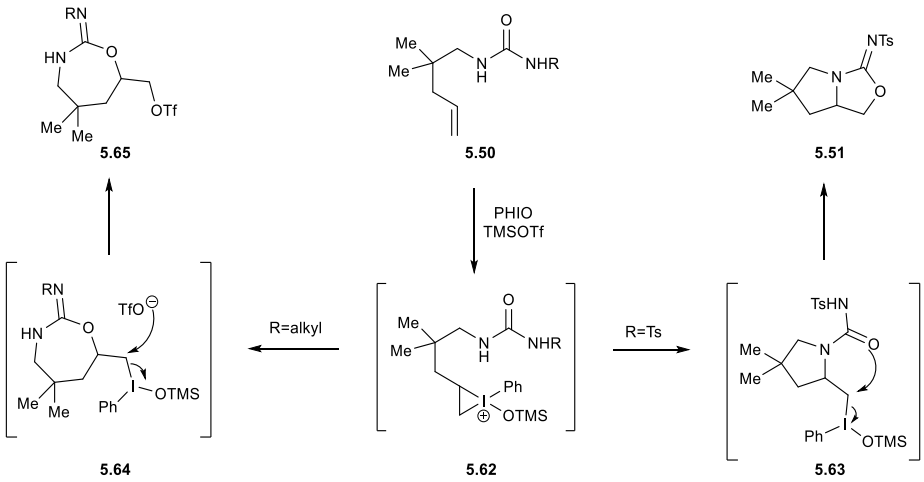
The authors investigated the effect of *N*-substituents in the reaction. A 3-trifluoromethylphenyl group proceeded well and gave the isourea product exclusively. An *N*-Benzoyl substrate also proceeded, though the urea product was also isolated. Surprisingly, when *N*-alkyl substituted ureas were used, 7-membered ring compound **5.53** was isolated instead (**Scheme 5.12**). The authors undertook an investigation into the reaction scope. Polycyclic products such as **5.54** and **5.55** could be formed efficiently and internal alkenes were tolerated. Compound **5.56** could be formed using a *Z*-methyl substrate, though a reasonable amount of the 7-membered ring side-product **5.57** was also formed. When germinal, disubstituted alkenes were used, eliminated product **5.60** was obtained in addition to the expected **5.59**.

Scheme 5.12: Scope of Michael's urea cyclization



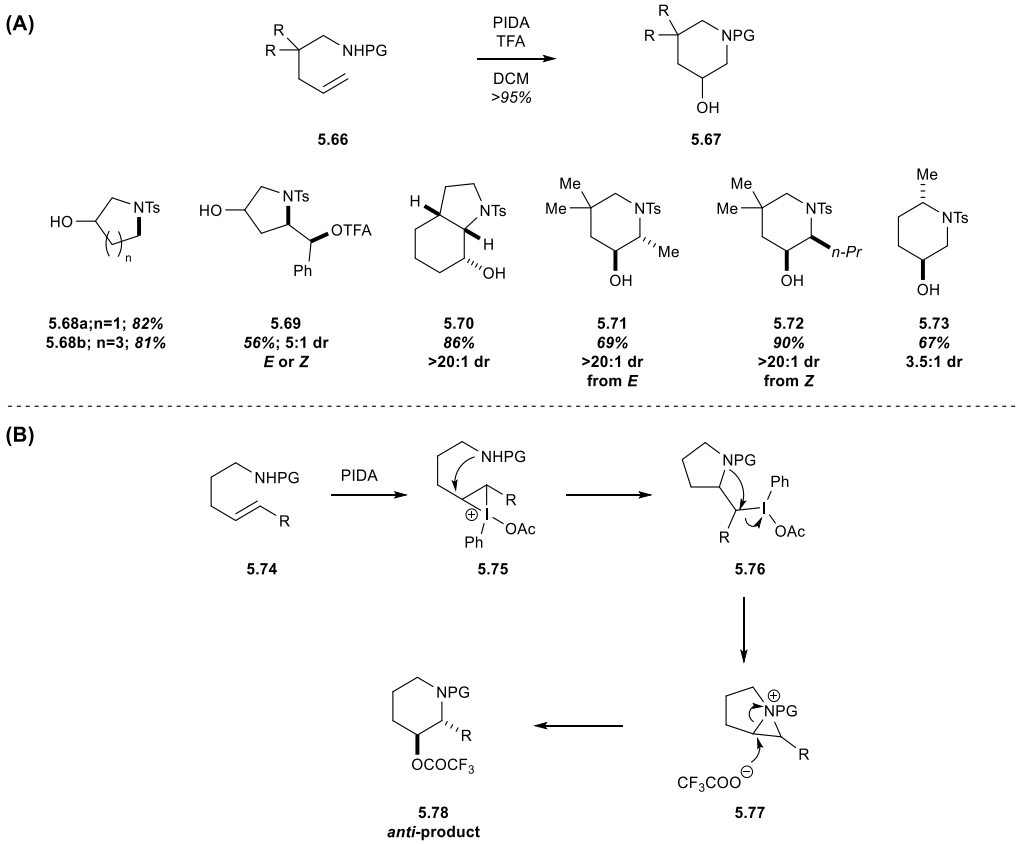
The authors advanced a mechanism wherein the alkene is initially activated by the potent electrophile PhI(OTMS)(OTf) (**Scheme 5.13**). When R is an electron-deficient group such as Ts, the initial nucleophilic attack by nitrogen gives intermediate **5.62**. Subsequent intramolecular attack by either O (strongly acidic conditions) or N (weakly acidic conditions) in a 5-*exo* fashion leads to products **5.51** or **5.52** respectively. In contrast, when **562** contains an electron-rich *N*-alkyl group, 7-*exo* attack predominates, leading to 7-membered ring product **5.65**. In this intermediate, no further intramolecular attack is possible. The aryoiodanyl group is instead displaced by the triflate counterion, to give product **5.65**.

Scheme 5.13: Mechanism of regiodivergent product formation



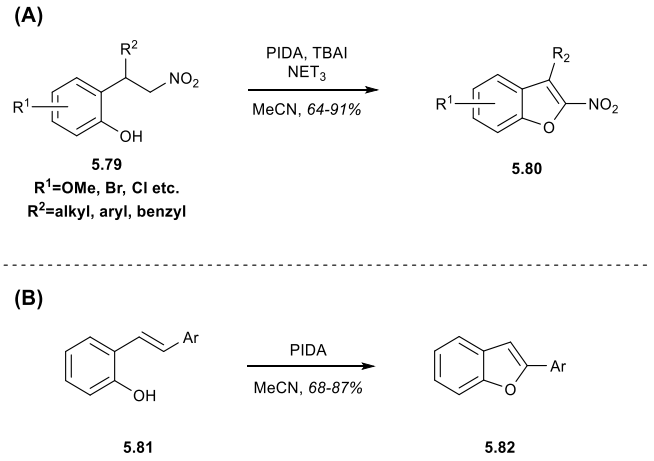
A few years later, the Michael group reported a PIDA-mediated regioselective aminotrifluroracetoxylation of alkenes (**Scheme 5.14**).[182] When sulfonyl alkene **5.66** was treated with PIDA activated by TFA, they were surprised to isolate 6-*endo* product **5.67** as opposed to the expected 5-*exo* product. The reaction was found to be tolerant of a variety of ring sizes and *N*-substituents. When screening the scope of the cyclization with various tethers, the authors found the reaction to be *anti*-selective in the case of the 6-*endo* cyclization, as opposed to the *syn* selectivity which would be the result of a double S_N2 displacement mechanism that is usually proposed in electrophilic cyclizations. The authors proposed the initial formation of aziridinium ion **5.75** after the initial iodonium opening. Nucleophilic attack on the aziridinium would yield the product as the observed *anti*-diastereomer.

Scheme 5.14: (A) Michael's oxidative aminotrifluoroacetoxylation reaction with selected scope; (B) Mechanism of 6-*endo* product formation



Oxidative cyclization strategies have also been applied to the synthesis of aromatic heterocycles such as benzofurans and 2-nitrobenzofurans (**Scheme 5.15**). Liu and coworkers synthesized a variety of nitrobenzofurans (**5.80**) by treating nitro compound **5.79** with PIDA and NEt_3.[183] The addition of TBAI was also found to be beneficial. A wide variety of heterocycles could be synthesized in this manner. A related report by Wirth furnished benzofurans (**5.82**) from styrenes (**5.81**) using PIDA in MeCN.[184] A wide variety of substrates were amenable to the cyclization conditions.

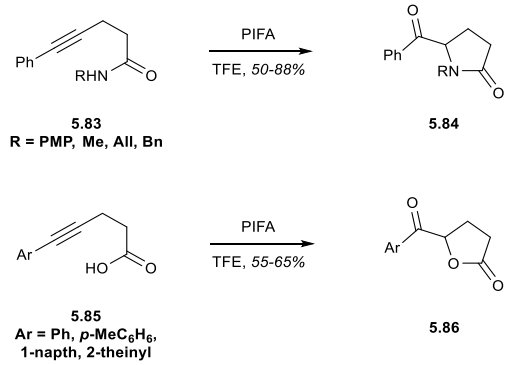
Scheme 5.15: (A) Liu's oxidative nitrobenzofuran synthesis; (B) Wirth's oxidative furan synthesis



5.1.2.b. Iodine(III)-mediated Cyclizations Involving Alkynes

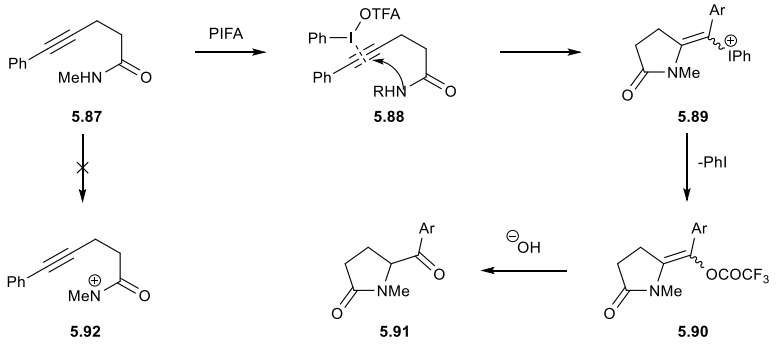
Iodine(III) oxidants have been used to synthesize a variety of heterocycles from alkynes through electrophilic cyclization. An early report came from the labs of Tellitu and Dominguez.[185] In their study, they performed the cyclization of *N*-substituted amides (**5.83**) to form pyrrolidinones (**5.84, Scheme 5.16**). In previous work, they had demonstrated a similar reaction using *N*-aryl amides and it was believed that these reactions proceeded through acyl-nitrenium intermediates. The authors were surprised to find that substituents that should not stabilize the nitrenium, such as alkyl, allyl, and benzyl groups, were also competent to undergo the cyclization. The authors also subjected carboxylic acid **5.85**, which is incapable of forming a nitrenium, to similar conditions, giving lactone **5.86**.

Scheme 5.16: Oxidative cyclizations on alkynes



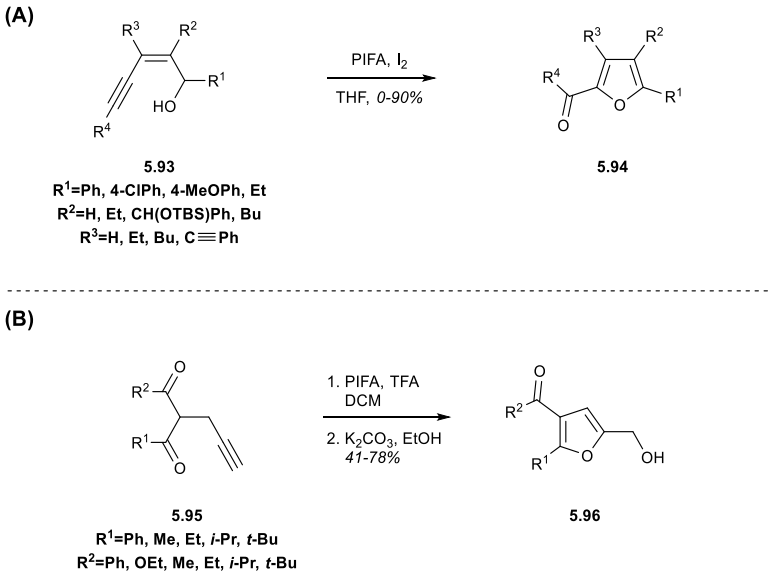
With this data, the authors speculated that the reaction proceeds *via* a different mechanism (**Scheme 5.17**). Instead of forming a nitrenenium ion (**5.92**), the PIFA serves to electrophilically activate the alkyne, giving intermediate **5.88**. Nucleophilic attack by the nitrogen yields vinyliodane **5.89**. Displacement of the aryliodane by the trifluoroacetate counterion generates the final pyrrolidinone **5.91** after trifluoroacetate cleavage. These observations demonstrate that alkynes are capable of undergoing electrophilic activation by hypervalent iodine compounds in a manner analogous to alkenes.

Scheme 5.17: Mechanism of oxidative cyclization on alkynes



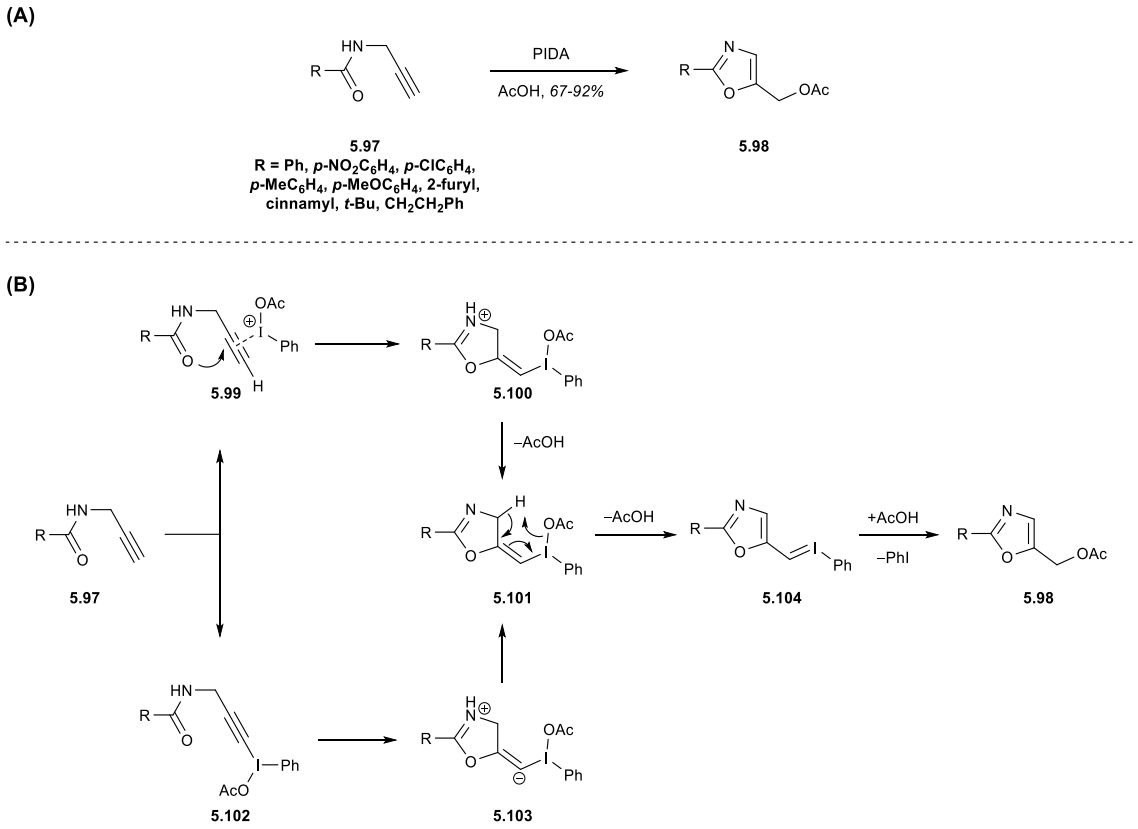
Furans have also been synthesized through oxidative cyclization (**Scheme 5.18**). Liu found that highly unsaturated allylic alcohols of type **5.93** could be treated with PIFA along with I_2 and $NaHCO_3$ to form furan product **5.94**.[186] The reaction was found to be amenable to substitution at multiple positions, though highly unsubstituted substrates did not cyclize efficiently. The authors proposed a mechanism similar to that proposed by Dominguez and Telliteu. Furans could also be synthesized by treating propargyl-substituted β-diketones with PIFA activated by TFA (**Scheme 5.18B**).[187] Furans could be obtained after carbonate workup.

Scheme 5.18: Furan synthesis by oxidative cyclization by (A) Liu and (B) Saito



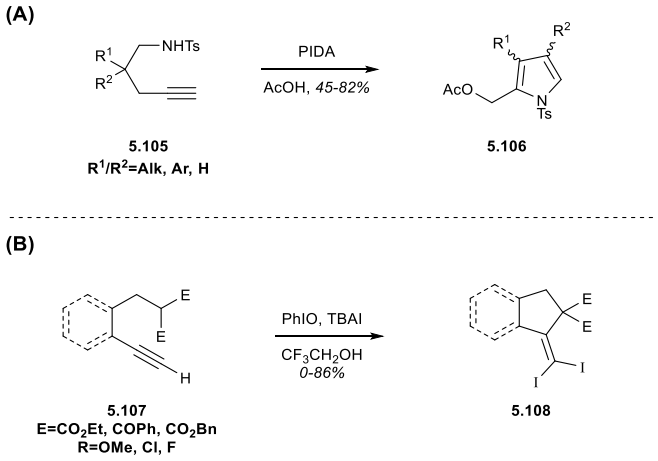
Hanzawa reported a useful synthesis of oxazoles through the oxidative cycloisomerization of propargylamide substrates (**Scheme 5.19**).[188] Treatment of propargylamide **5.97** with PIDA produced oxazole **5.98**. A screen of solvent conditions found HFIPA to be important. The yield could be further improved by performing the reaction in AcOH, though the reaction proceeded more slowly. The reaction was found to be tolerant of several different substituents on the amide including electron-deficient and electron-rich aromatics, heteroromatics, alkenes, and alkyl groups. The authors proposed a mechanism in which the oxidant initially activates the alkyne. Attack by the carbonyl gives intermediate **5.100**, which is deprotonated to give **5.101**. Cycloisomerization of **5.101** gives phenyliodonium **5.104** that undergoes nucleophilic attack by AcOH gives the final product **5.98**.

Scheme 5.19: (A) Oxazoles by oxidative cyclization; (B) Mechanism of oxazole formation



Hou synthesized pyrroles (**5.106**) through treatment of 3-alkynylamines (**5.105**) with PIDA (**Scheme 5.20**).[189] AcOH was found to be the ideal solvent. A variety of substituents on the tether were tolerated in the cyclization. Carbocycles have also been synthesized by the Fan group by treatment of alkynylmalonate **5.107** with iodosobenzene activated by TBAI to give diidomethylene indane substrate **5.108**.[190] Trifluoroethanol was found to be the ideal solvent in this case. The reaction was found to be tolerant of methoxide and halide substitution of the aryl group tether.

Scheme 5.20: (A) Hou's oxidative pyrrole synthesis; (B) Fan's oxidative diiodimethylene indane synthesis

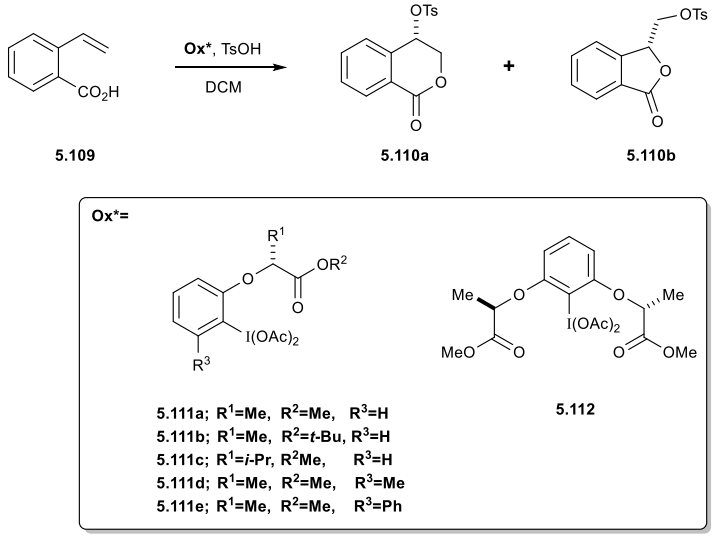


5.1.3. Enantioselective Oxidative Cyclizations of Alkenes

5.1.3.a. Iodine(III)-promoted cyclizations

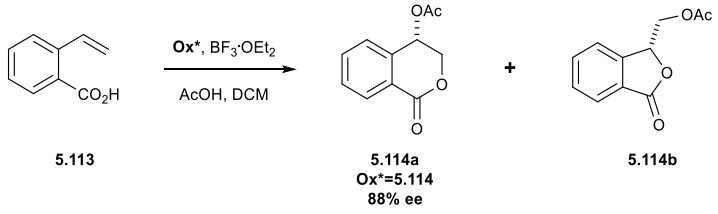
To date, the use of chiral, hypervalent iodine reagents or catalysts to affect enantioselective electrophilic cyclizations remains rare. The only reports to date come from the Fujita lab and involve the use of lactate-derived hypervalent iodine reagents **5.113a-e & 5.114**.[191] The initial screen involved the treatment of substrate **5.109** with $TsOH \cdot H_2O$ as an activating reagent to give *endo*-tosylate **5.110a** as the primary product, along with a small amount of *exo*-tosylate **5.110b** (**Table 5.1**). *Bis*-lactate reagent **5.112** was found to be ideal, giving lactone **5.110a** in 97% ee and 65% yield. They were also able to perform the reaction with $BF_3 \cdot Et_2O$ and AcOH, to give acetate **5.114a**. After optimization, **5.114a** could be obtained in 88% ee and 68% yield with reagent **5.112**.

Table 5.1: Enantioselective iodine(III)-promoted oxidative cyclizations



Entry	Ox*	Yield (%) (5.110a:5.110b)	ee 5.110a (%)	ee 5.110b (%)
1	**5.111a**	66 (93:7)	75	18
2	**5.111b**	69 (96:4)	90	42
3	**5.111d**	70 (96:4)	76	22
4	**5.111e**	74 (86:14)	60	28
5	**5.112**	65 (95:5)	97	26

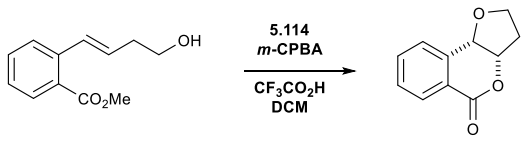
Scheme 5.21: Formation of acetate product **5.114a**

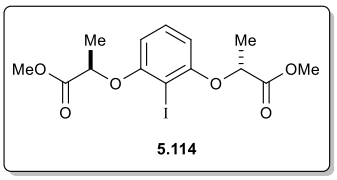


In a later report, the authors reported the synthesis of dihydrofuran **5.116** under catalytic conditions (**Scheme 5.22**).[192] When aryl iodide **5.114** was utilized along with *m*-

CPBA as the terminal oxidant with added TFA, compound **5.116** was isolated in up to 91% ee. This result gives hope that similar cyclizations can be performed using catalytic quantities of chiral aryl iodides.

Scheme 5.22: Enantioselective dihydrofuran synthesis

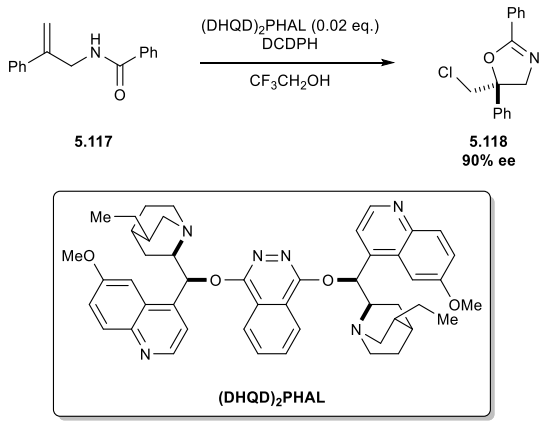




5.1.3.b. Enantioselective Synthesis of Oxazolines Through Electrophilic Cyclization

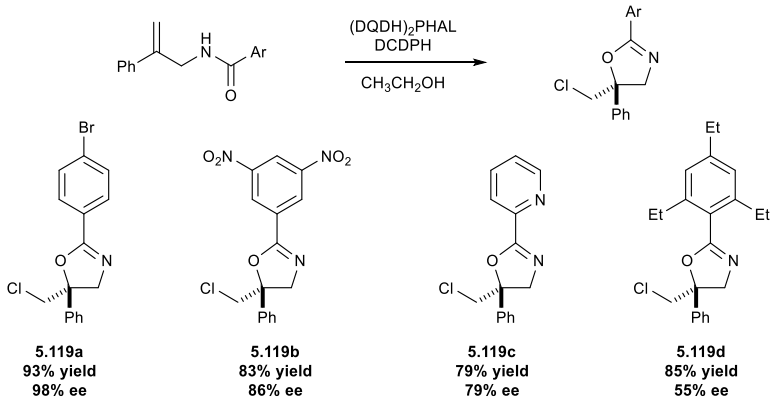
Despite their utility, only a few reports of the enantioselective synthesis of oxazolines through electrophilic cyclization have been reported. Borhan reported a chlorocyclization promoted by an amine organocatalyst (**Scheme 5.23**).[193] The authors chose amide **5.117** as the ideal substrate for optimization, which cyclized to give oxazoline **5.118**. After catalyst screening, the authors found cinchonidine dimer $(DQDH)_2PHAL$ to be the optimum catalyst. An extensive screen of solvent and chlorine source revealed DCDPH (dichlorodiphenyl hydantoin) to be the ideal chlorine source and trifluoroethanol to be the ideal solvent. Under these conditions, chlorooxazoline **5.118** could be obtained in 90% ee with catalyst loadings as low as 2%.

Scheme 5.23: Borhan's enantioselective chlorocyclization



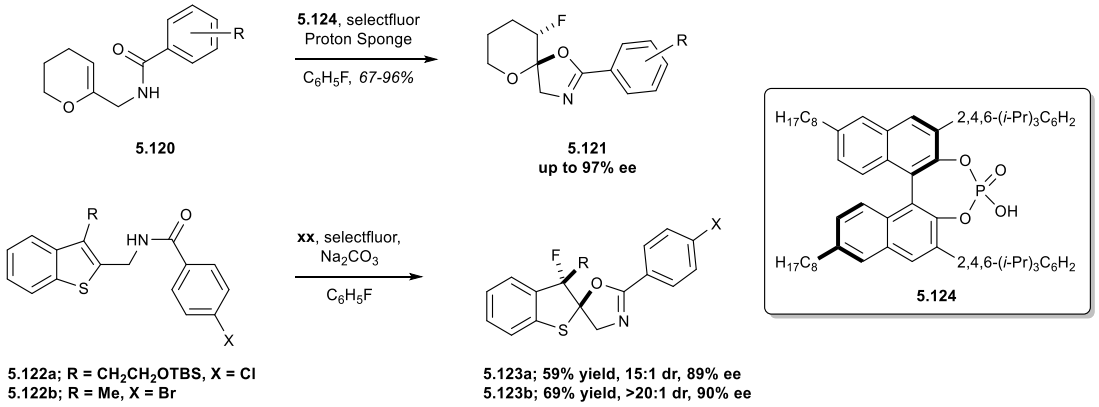
The authors then screened the identity of the aromatic substituent on the amide in an attempt to increase the selectivity (**Scheme 5.24**). They note that that substituent can be thought of as a traceless directing group, as the aryl moiety is removed upon oxazoline hydrolysis. Screening a variety of groups revealed that *para*-substituted aryl groups improved the selectivity, while ortho-substituted groups led to highly diminished selectivity. The *p*-bromophenyl substrate **5.119a** was selected as the ideal substrate for future reactions. The authors screened the scope of the reaction of a variety of substrates with substitution on the alkene. The reaction was tolerant of a variety of aryl groups with substituents including halogens, electron-withdrawing groups, and electron-donating groups.

Scheme 5.24: Scope of aryl-group substitution in Borhan's chlorocyclization



Another particularly striking example of enantioselective cyclization to form oxazolines comes from Toste and coworkers (**Scheme 5.25b)**.[194] They used phosphoric acid **5.124** as a chiral phase-transfer catalyst to promote an electrophilic fluorination reaction. In the reaction, the chiral phosphate solubilizes the electrophilic fluorinating reagent Selectfluor to achieve an electrophilic cyclization. The resulting products are highly intriguing, incorporating a stereogenic carbon containing a fluoride, a motif that is quite difficult to access. Amide **5.120** was treated with **5.124** along with Selectfluor and proton sponge in fluorobenzene to give *spiro*-oxazoline **5.121** in excellent yields and ee. The reaction was found to be tolerant of halide, alkyl, and electron withdrawing substituents on the aryl group. Dihydropyran and dihydronapthalene substrates also underwent in the reaction. The authors demonstrated the unique mildness of their phase-transfer methodology by subjecting benzothiophene substrate **5.122a&b** to cyclization conditions under homogenous (MeCN) and phase-transfer conditions. While the homogenous conditions resulted in a complex mixture of products, the sensitive oxazoline **5.123a&b** could be obtained in reasonable yield and high ee using phase-transfer conditions. This methodology represents a useful method to introduce a stereogenic fluoride through electrophilic cyclization. More generally, the use of anionic phase-transfer catalysts is a potentially fruitful strategy form many other related transformations.

Scheme 5.25: Toste's enantioselective electrophilic fluorocyclization



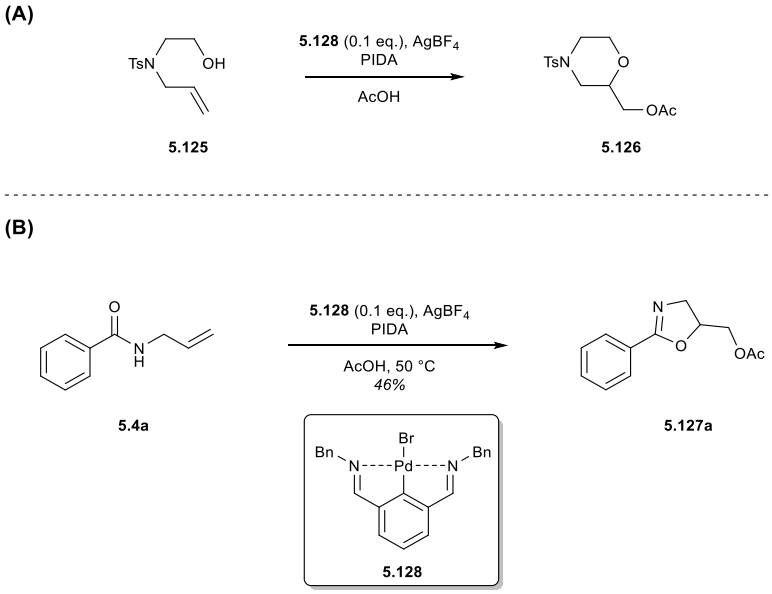
Electrophilic cyclization has been shown to be a highly versatile method for synthesizing heterocycles. The relatively mild conditions, as well as the wide variety of

available electrophiles enable the accessing of many important motifs. Though electrophiles such as halogens are widely used, the use of hypervalent iodine reagents in electrophilic cyclization remains relatively rare. As a part of our program studying the reactions of hypervalent iodine reactions, we became interested in other possible iodine(III)-promoted electrophilic cyclizations.

5.2 Initial Reaction Discovery & Optimization

In the course of studying palladium-catalyzed oxidative cyclizations, we investigated the cyclization of allyl sulfonamide **5.125** to give morpholine **5.126** (**Scheme 5.26**). We discovered that the reaction cold be achieved using a presumed Pd^{II}-Pd^{IV} catalytic cycle with PIDA as the terminal oxidant, though in low yield. Due to the formation other side-products including the 7-*endo* isomer, we decided to pursue the cyclization of the simpler *N*-allyl amide **5.4a** instead.

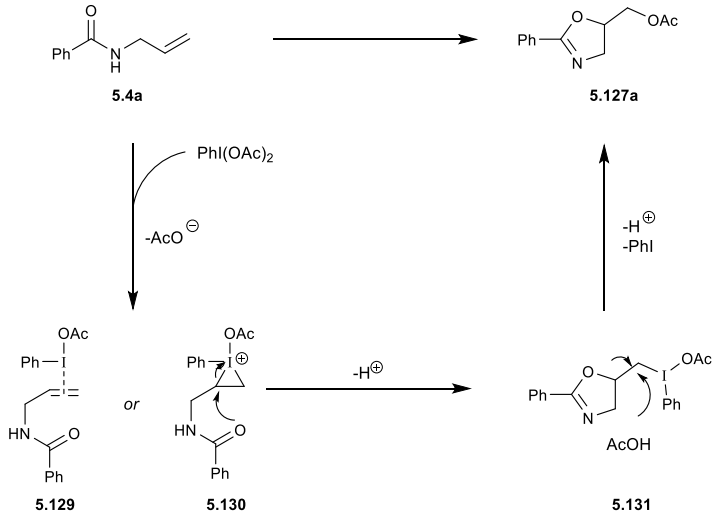
Scheme 5.26: (A) Proposed Pd-catalyzed morpholine formation; (B) Initially observed oxazoline formation



To our delight, we discovered that when amide **5.4a** was treated with palladium pincer complex **5.128** and PIDA in AcOH, the resulting oxazoline **5.127a** could be obtained in 66% conversion and 46% isolated yield. Upon further investigation, the

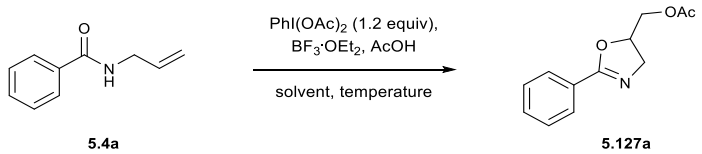
reaction was found to proceed in the absence of Pd catalyst. We hypothesized that the reaction proceeds through an electrophilic iodonium species **5.130** (**Figure 5.27)**. Subsequent nucleophilic attack by the amide leads to aryliodane species **5.131** which is displaced by AcOH to give **5.127a**. Because of the utility of oxazolines in natural-product synthesis, medicinal chemistry, and organometallic catalysis, we decided to further investigate the generality of this transformation. A deeper understanding of the behavior of the reaction would also facilitate the development of more complicated reaction systems.

Scheme 5.27: Proposed mechanism of oxazoline formation



Treatment of amide **5.4a** with PIDA in AcOH at 50 °C led to low conversion after 24 h (**Table 5.2**). We found that the addition of catalytic amounts of $BF_3 \cdot OEt_2$ improved the conversion and yield somewhat. In light of this observation, it is possible that the increased conversion under the Pd catalyzed conditions proceeds through activation of the PIDA by exogenous triflic acid from the Pd catalyst, and not the Pd itself. Pd could also be functioning as a Lewis acid to activate the PIDA. We found that the use of a stoichiometric amount of $BF_3 \cdot OEt_2$ led to complete conversion. Further optimization revealed that the reaction could also be carried out in DCM with added AcOH with similar yields. The reaction did proceeded in the absence of added AcOH, albeit in lower yield and with longer reaction times. In this case, the trapping acetate nucleophile is provided by the oxidant itself. As was expected, no reaction occurred in the absence of PIDA.

Table 5.2: Optimization of cyclization conditions



5.4a 5.127a

Entry	Additive (eq.)	Solvent	Temp (°C)	Yield (%)[a]
1	--	5:1 AcOH:Ac_2O	50	23[b]
2	$BF_3{\cdot}OEt_2$	5:1 AcOH:Ac_2O	50	45[c]
3	$BF_3{\cdot}OEt_2$	5:1 AcOH:Ac_2O	50	86
4	$BF_3{\cdot}OEt_2$	5:1 AcOH:Ac_2O	25	64
5[d]	$BF_3{\cdot}OEt_2$	DCM w/ 10 eq. AcOH	25	84
6[e]	$BF_3{\cdot}OEt_2$	DCM (no AcOH)	25	55
7[f]	$BF_3{\cdot}OEt_2$	DCM	25	N.R.

a. After chromatographic purification; b. 31% conversion after 24h by ^{1}H NMR analysis; c. 68% conversion after 24h by ^{1}H NMR analysis; d. Reaction time = 2h; e. Reaction time = 5h; f. Without PIDA

Observation of the crude ^{1}H NMR spectrum of the product from entry **xx** showed signals shifted relative to the isolated product. We hypothesized that the BF_3 strongly coordinates to the oxazoline product, forming a relatively stable adduct. This tendency was confirmed when oxazoline **5.127a** was treated with $BF_3{\cdot}OEt_2$ in an NMR tube. Complete consumption of the oxazoline product was observed immediately. Operationally, we observed that the direct, chromatographic purification of the BF_3 adduct was problematic, with the product eluting very slowly in a wide band with concomitant material loss. This problem could be solved by quenching the reaction with aqueous NH_3. This modification significantly improved the isolated yield.

5.3. Evaluation of the Substrate Scope

5.3.1. Synthesis of Starting Materials

We began our investigation into the scope of the reaction by synthesizing a series of amides with varying substitution on the carbonyl portion of the amide. We treated allylamine with either the requisite acid chloride or anhydride (**Scheme 5.28, Path A**) or the mixed ethyl carbonate the carboxylic acid (**Scheme 5.28, Path B**). In some cases, coupling with DCC gave superior results (**Scheme 5.28, Path C**). The results are summarized below (**Table 5.3**).

Scheme 5.28: Methods for substrate synthesis

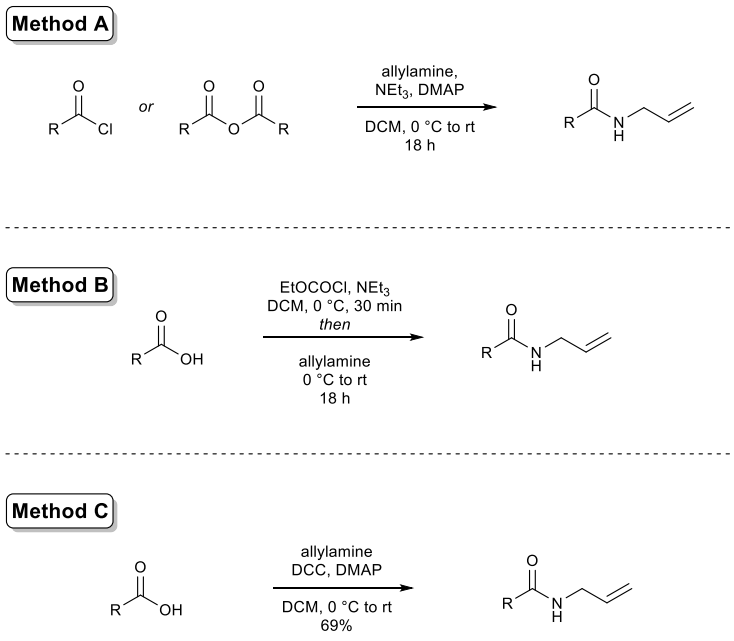
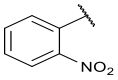
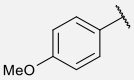
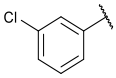
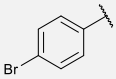
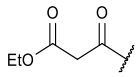


Table 5.3: Summary of substrate synthesis results

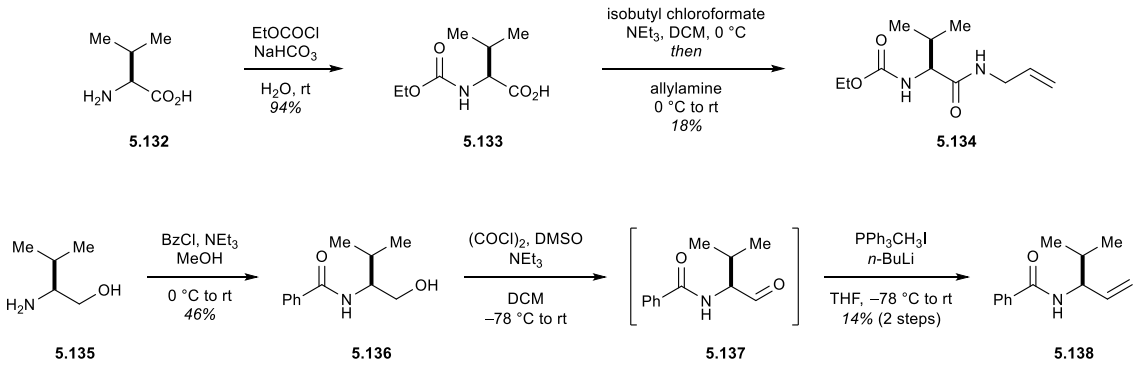
Entry	R	Compound	Method	Yield (%)
1		a	A	78
2		b	B	69
3		c	B	23
4		d	B	53
5		e	A	38
6		f	B	76
7		g	B	64
8		h	A	36
9		i	B	77
10		j	A	50

11		k	A	76
12		l	A	48
13		m	A	90
14		n	C	69

We also synthesized a set of substrates that contained stereogenic carbons in order to evaluate the diastereoselectivity of the cyclization. To install a stereogenic element on the fragment bound to the carbonyl, we began by forming the carbamate of (L)-valine (**5.132, Scheme 5.29**). Attempts to form the amide through DCC coupling led to formation of **5.133**. However, we were unable to separate **5.133** from the dicylohexylurea byproduct. Using method B instead cleanly led to formation of substrate **5.133**, albeit in low yield.

Attempts to synthesize substrates with stereogenic elements on the nitrogen-bound portion of the molecule were significantly more difficult. (**Figure 5.29**). We synthesized compound **5.136** from (L)-phenylalaninol **5.135** and benzoyl chloride. Attempts to oxidize the alcohol to an aldehyde were met with difficulty. A variety of conditions including Parikh-Doering, Swern, and DMP oxidations were screened. The aldehyde from successful oxidations was found to be highly unstable. After screening a variety of oxidation conditions, we found that Swern oxidation on **5.137** followed by immediate Wittig olefination gave compound **5.138** in low yield.

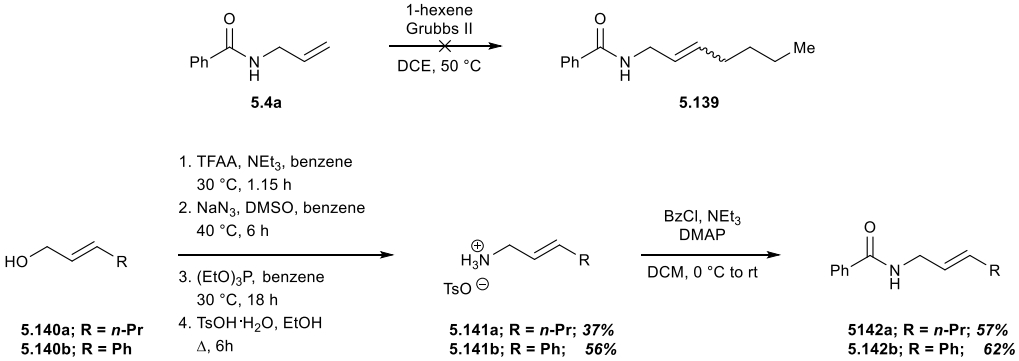
Scheme 5.29: Synthesis of substrates containing a stereogenic carbon



5.132 5.133 5.134 5.135 5.136 5.137 5.138

We envisioned that internal alkenes could be accessed through the use of cross-metathesis on substrate **5.4a**. However, attempts to affect the cross-metathesis were met with no observed reactivity. We decided to instead furnish the amides from the requisite amines, which could in turn be accessed from the appropriate alcohol (**5.140a&b**). A procedure involving the conversion of the alcohol to the trifluoroacetate mixed-anhydride followed by displacement with sodium azide, immediate Staudinger reduction, and acidification with *p*-toluenesulfonic acid allowed the tosylate salt of the amines (**5141a&b**) to be isolated as stable solids.[195] This procedure was selected because it did not require the isolation or even concentration of the potentially explosive azide intermediates or volatile amines. The amides (**5.142**) could be formed directly from tosylate salts **5.141** using conditions A, though with additional added base (**Figure 5.30**), giving the desired amides in reasonable yield.

Scheme 5.30: Synthesis of substrates containing an internal alkene



5.4a 5.139

5.140a; R = *n*-Pr
5.140b; R = Ph

5.141a; R = *n*-Pr; *37%*
5.141b; R = Ph; *56%*

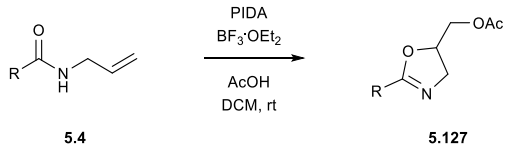
5142a; R = *n*-Pr; *57%*
5.142b; R = Ph; *62%*

5.3.2. Evaluation of the Substrate Scope

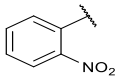
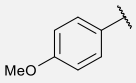
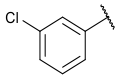
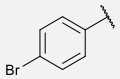
We began by evaluating the effect of substrate substitution at R (**Table 5.4**). The reaction was tolerant of a wide-variety of aromatic substituents. Both electron rich and poor aromatic substituents were suitable in the reaction (Entries 1-5). Additionally, both nitrogen and oxygen heteroaromatic compounds were tolerated (Entries 6-7). The 2-pyridyl substrate **5.4a** cyclized more slowly and with decreased yield. The decrease in rate could be due to competitive coordination of the BF_3 Lewis acid to the Lewis basic pyridyl group. The high polarity of the substrate could have also complicated the isolation of the product. Surprisingly, furan substrate **5.4g** cyclized with no observed Friedel-Crafts products.

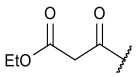
The reaction of vinyl-substituted substrate **5.4h** led to decomposition. However, cinnamyl-substituted substrate **5.4i** proceeded normally. Attempts to perform the reaction with aliphatic substituents were more problematic. The resulting oxazolines were highly polar and difficult to visualize on a TLC plate. As such, their chromatographic isolation resulted in significantly diminished yields. When the yield of aliphatic products **5.4j** and **5.4k** was determined by ^{1}H NMR spectroscopy using mesitylene as an internal standard, the yields improved. Trifluoroacetate substrate **5.4l** resulted in decomposition and malonate ester product **5.4n** proceeded with only trace-products observed. The unreactivity of malonate **5.4n** is again likely due to competitive coordination of **5.4n** with the $BF_3{\cdot}OEt_2$ Lewis acid.

Table 5.4: Summary of substrate scope



5.4 5.127

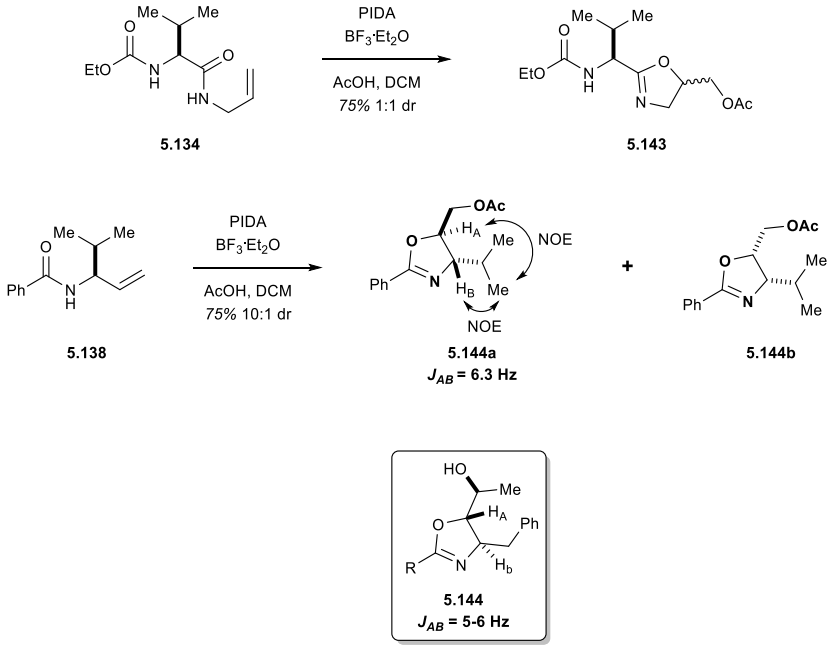
Entry	R	Compound	Time (h)	Yield (%) [a]
1		a	2	84
2		b	2	77
3		c	2	68
4		d	2	85
5		e	2.5	80
6		f	5.5	44
7		g	2	75
8		h	2	decomp.
9		i	2.5	74

10		j	2	24 (48[b])
11		k	2	57 (78[b])
12		l	2	decomp.
13		m	2	decomp
14		n	2	trace[c,d]

a. After chromatographic purification; b. Yield determined by ^{1}H NMR w/ mesitylene as an internal standard; c. 3 eq. $BF_3{\cdot}OEt_2$ used; d. <10% observed by ^{1}H NMR.

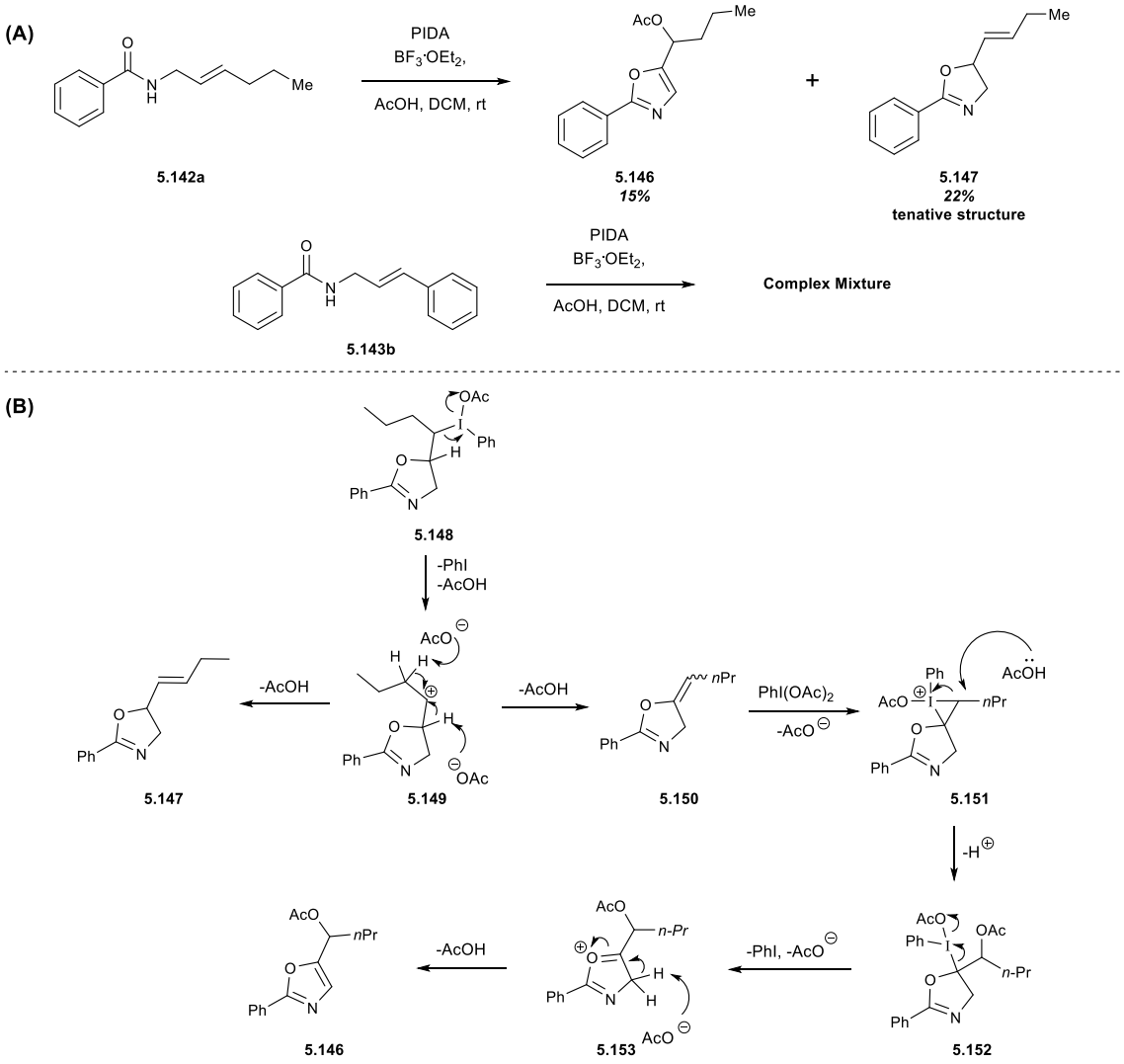
We investigated the influence of a stereogenic carbon on the substrates (**Scheme 5.31**). When substrate **5.134** was subjected to the cyclization conditions, a 1:1 mixture of inseparable diastereomers of **5.143** was isolated in good yield. The low diastereoselectivity is not surprising given the relative flexibility of the portion of the molecule that contains the stereogenic center as well as its distance from the reacting center. The influence of a stereogenic carbon in **5.138** was significantly higher. The oxazoline **5.144** was isolated in good yield as a 10:1 mixture of diastereomers. We were able to assign the relative stereochemistry in the oxazoline in the major product to be *trans* through the NOE correlation between H_A and the isopropyl group (**Scheme 5.31**). The J_A-J_B coupling constant was consistent with that observed in an analogous substrate **5.145** prepared by Roush and coworkers.[196]

Scheme 5.31: Scope of substrates containing a stereogenic carbon



Attempts to cyclize internal alkenes led the isolation of oxazole **5.146** and oxazoline **5.147** as the presumed products in low yield. We speculate that the super leaving-group ability of the aryoiodanyl group (~10^6 x better than triflate) is responsible for this observation.[197] Fragmentation leads to the relatively more stable (compared to primary) carbocation **5.149** (**Figure 5.32B**). Elimination leads to either vinyl-oxazoline **5.147** or **5.150**. An additional oxidation of **5.151** gives the oxazole product **5.146**. Subjecting aryl alkene **5.142b** to the reaction conditions led to decomposition. Work subsequent to ours by the Nachtsheim group discovered that this problem could be solved through the use of TMSOTf as the Lewis acid at cryogenic temperatures to give similar cyclization products on internal alkenes.[198]

Scheme 5.32: (A) Attempts to cyclize substrates with internal alkenes; (B) Proposed mechanism for product formation



5.4. Experiments with Other Nucleophiles

We attempted to perform the reaction using nucleophiles other than acetic acid. To our surprise, when we performed the reaction with 10 equivalents of benzoic acid instead of acetic acid, the benzoate product **5.154** was obtained along with acetate product **5.127a** in a 1:1 ratio (**Scheme 5.33**), despite the large excess of benzoic acid used relative to the acetate from the PIDA. A brief survey of the effect of stoichiometry (**Table 5.5**) on the product ratio revealed that even a full 25 equivalents (leading to a saturated solution of benzoic acid) still only resulted in a 1:2.3 ratio of the acetate to the benzoate. Use of an

electron-deficient benzoic acid derivative did not change the ratio of products (**Scheme 5.33**). NaCN did not participate in the nucleophilic displacement, leading to only isolation of the acetate product. We also evaluated the effect of solvent on the product distribution. The use of low-polarity solvents led to an increased acetate incorporation, though the effect was not particularly pronounced.

Scheme 5.33: Reactions with added nucleophiles

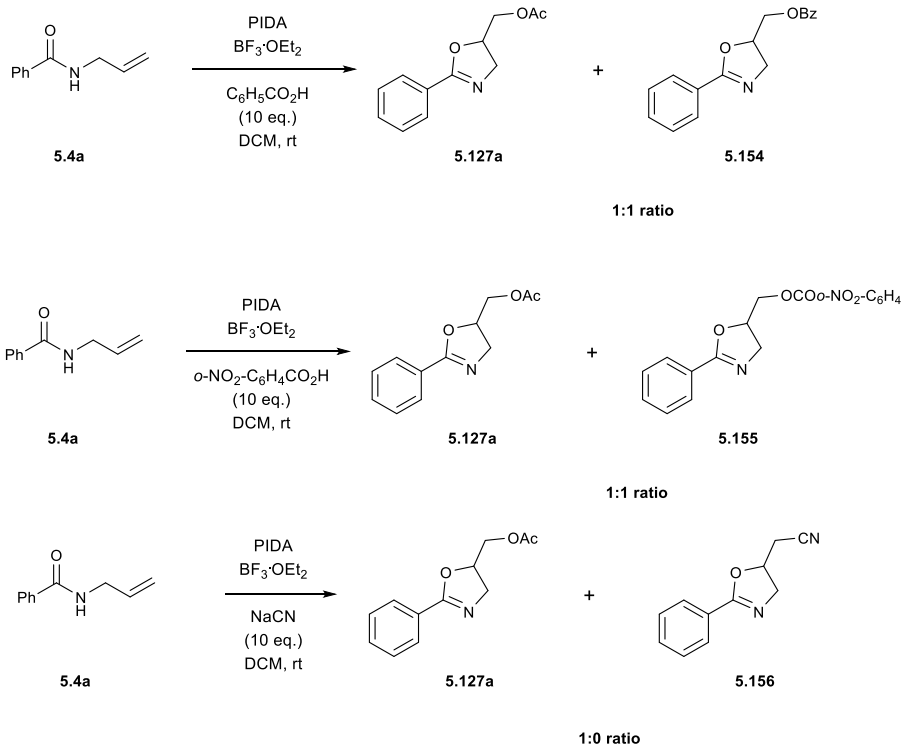
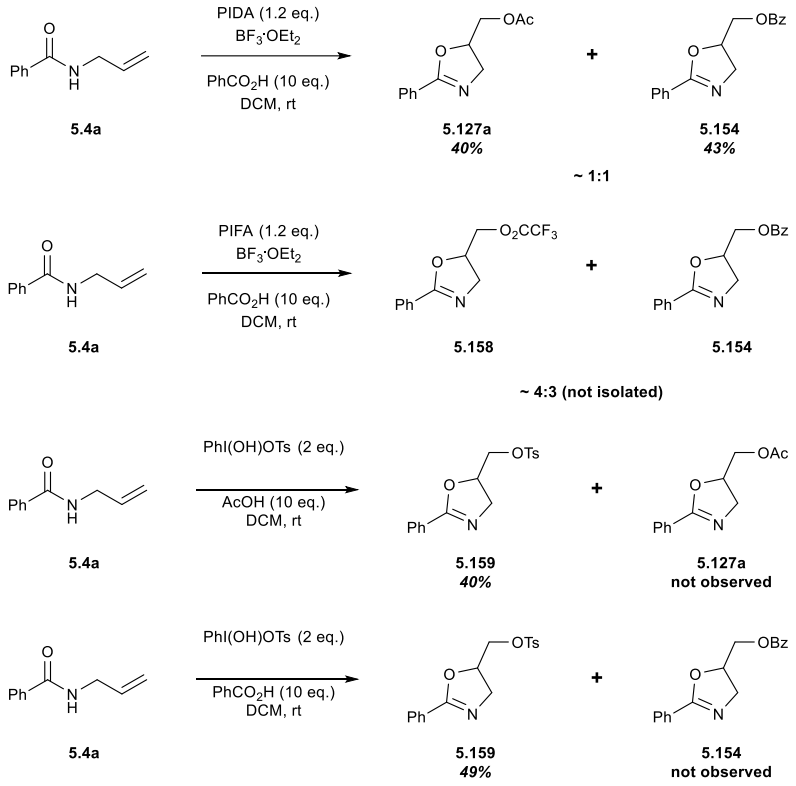


Table 5.5: Effect of stoichiometry and solvent on nucleophile incorporation

Entry	Equiv. BzOH	Solvent	5.127a:5.154
1	1.2	DCM	7.7:1
2	10	DCM	1:1
3	25	DCM	1:2.3
4	10	CCl_4	2.6:1
5	10	benzene	2.0:1
6	10	$CHCl_3$	1.4:1
7	10	MeCN	1.3:1

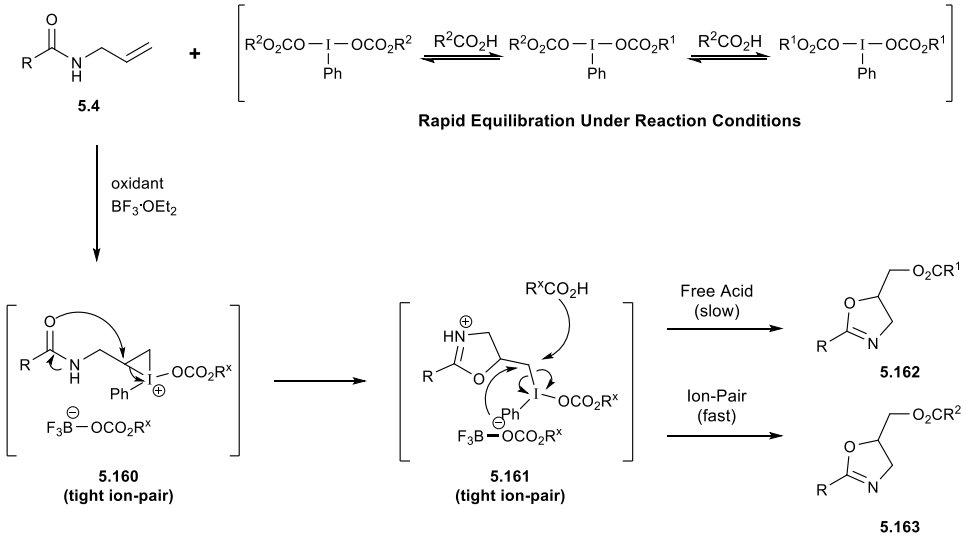
A significant discovery came when the related iodine(III) oxidant PhI(OH)OTs (Koser's reagent) was used in place of PIDA (**Scheme 5.34**). In this case, $BF_3{\cdot}OEt_2$ was not necessary to obtain conversion to the product. To our surprise, when the reaction was performed with 10 equivalents of either benzoic or acetic acid, tosylate **5.159** was the only observed product. Similarly, use of PIFA led to slightly higher amounts of trifluoroacetate incorporation over the benzoate product **5.158**, which was not isolated due to instability.

Scheme 5.34: Effect of oxidant on reactions with added nucleophile



These observations indicate that the mechanism of this reaction is more complicated than that which is usually invoked for iodine(III)-mediated oxidative cyclizations. We propose that the oxidant is initially activated through carboxylate extraction by the $BF_3{\cdot}OEt_2$ (**Scheme 5.35**). The resulting iodonium cation exists as a tight-ion pair with the BF_3 carboxylate. After the initial nucleophilic attack, the second nucleophilic displacement occurs through the aforementioned tight ion-pair (**5.161**), leading to preferential incorporation of the nucleophile that was initially bound to the oxidant. The product distribution is then governed by the equilibrium distribution of carboxylate ligands on the iodine(III) nucleus. A less polar solvent would result in a stronger ion-pair, which would in turn increase the incorporation of the acetate on the Iodine nucleus. Further study is needed to confirm this mechanistic proposal.

Scheme 5.35: Revised mechanistic proposal



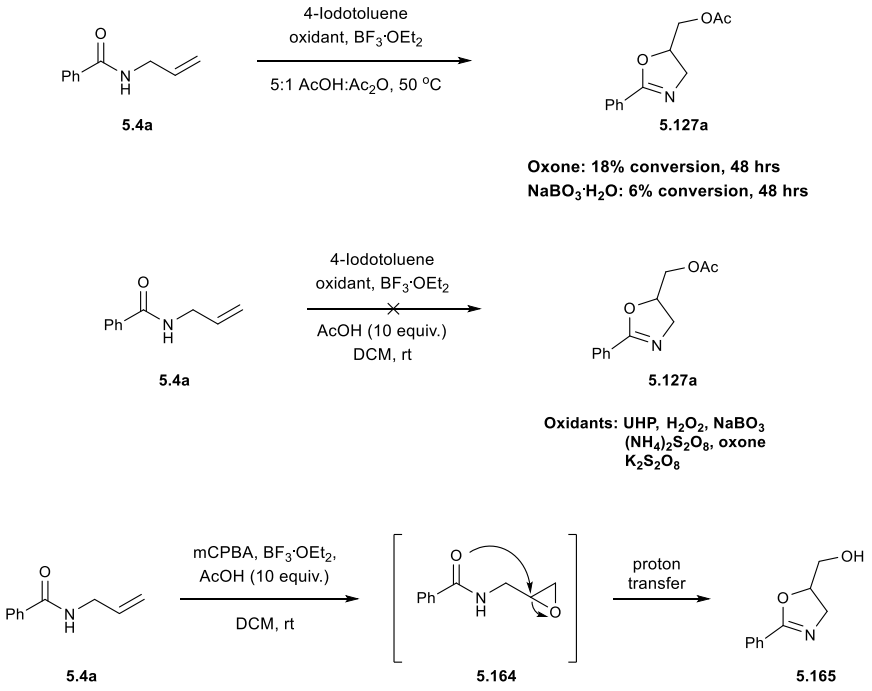
5.5. Miscellaneous Experiments

We briefly evaluated cyclization conditions using catalytic quantities of an aryl-iodide. Catalytic versions of these reactions would result in simpler purifications and would decrease reliance on relatively expensive PIDA as the oxidant. Catalytic variants could also eliminate the need for two potentially competitive nucleophiles, further expanding the scope of potential products. Most importantly, the development of catalytic conditions would enable the use of catalytic amounts of chiral aryl-iodide substrates, simplifying the discovery of an enantioselective version of this cyclization.

Using 4-iodotoluene as the iodine source and AcOH/Ac_2O as the solvent, we screened a wide variety of oxidant sources including *m*-CPBA, H_2O_2, benzoyl peroxide, oxone, $NaBO_3$, and $K_2S_2O_8$. We were only able to obtain a small amount of oxidized product when oxone or $NaBO_3$ were used as oxidants, even after extended reaction times. When DCM was used as the solvent, no conversion was obtained with a variety of terminal oxidants with the exception of *m*-CPBA, which is known to be a good oxidant for catalytic iodine(III) oxidations. However, when the reaction was performed in the absence of 4-iodotoluene, a similar cyclization occurred to give **5.127a**. Presumably, the reaction proceeds through initial formation of the epoxide **5.164**, followed by BF_3 promoted ring-

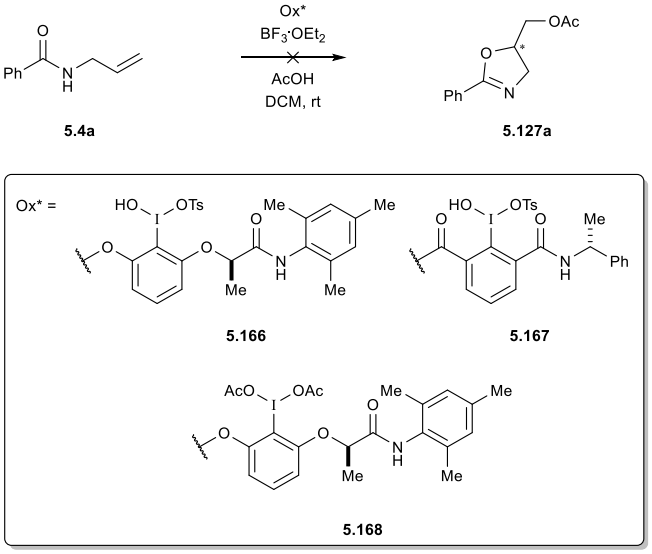
opening. This reaction is known, though previous observations have demonstrated extremely slow epoxidations. The $BF_3{\cdot}OEt_2$ likely accelerates both steps of the reaction.

Scheme 5.36: Catalytic oxidation attempts



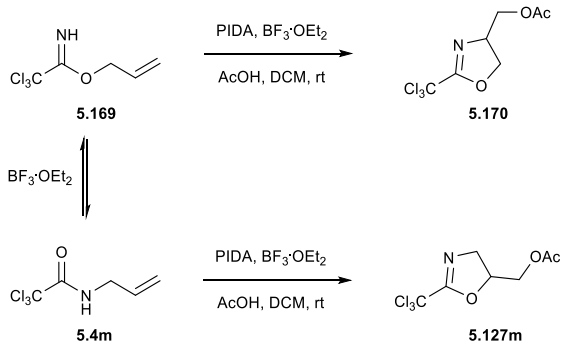
While we were not able to achieve a useful catalytic version of the reaction (though preliminary evidence indicates that it is possible), we decided to investigate enantioselective versions of the reaction using stoichiometric amounts of oxidant. While this approach is far from ideal, it would allow us to discover promising oxidant structures which could then drive further efforts towards catalytic variants of the reaction. None of the oxidants prepared (**5.166 – 5.168**) resulted in cyclization.

Scheme 5.37: Enantioselective cyclization attempts



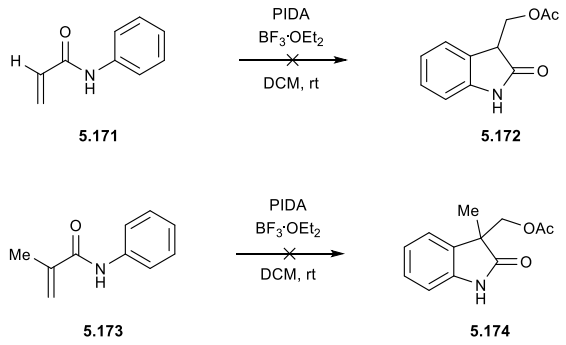
We also attempted to apply our conditions to iodine(III)-promoted oxidative cyclizations on several other substrates. We prepared trichloroacetimidate **5.169** from allyl alcohol. A successful cyclization of substrate **5.169** would result in isomeric oxazoline **5.170**. Additionally, the well-established use of stereoselective aza-Claisen rearrangements would give branched alkenes that could lead to potentially useful oxazolines in enantioenriched form.[199] When substrate **5.169** was subjected to the reaction conditions, a complex mixture of at least two compounds which could not be separated resulted. The similarity of ^{1}H NMR signals between the two products led us to speculate that there might be a competitive BF_3 promoted aza-Claisen rearrangement[200] followed by cyclization, resulting in a mixture of oxazolines **5.170** and **5.127m**. Using Koser's reagent instead did not lead to improvement in the reaction.

Scheme 5.38: Trichloroacetimidate cyclization attempts



We also attempted the cyclization of amide **5.171** to give potentially useful oxindole product **5.172**. When a variety of arylamides were subjected to the reaction conditions with both PIDA and Koser's reagent, only decomposition was observed. Methylated analogue **5.173** gave similar results. To date, we have not observed any other successful cyclization reactions under our previously reported conditions, though we believe these problems could be overcome.

Scheme 5.39: Oxindole formation attempts



5.6 Conclusion

In conclusion, we developed an oxidative cyclization of *N*-allylamides to form oxazolines.[ix] The reaction was highly tolerant of a number of substituents, though aliphatic substrates did not perform as well. Internal alkenes were not tolerated under our reaction

[ix] Published as: Moon, N. G.; Harned, A. M. *Tetrahedron Letters* **2013,** *54*, 2960-2963.

conditions. We also uncovered the likely role of a tight-ion pair in the reaction mechanism, leading to preferential incorporation of the carboxylate species present on the iodine prior to reaction initiation. This observation will aid in future reaction development both in our and others' labs.

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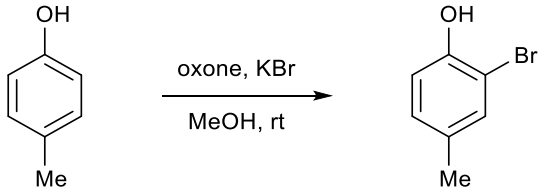
Appendix 1

MATERIALS & METHODS

Unless otherwise stated, reactions were performed in flame- or oven-dried glassware under an argon or nitrogen atmosphere using anhydrous solvents. Tetrahydrofuran (THF) was distilled from sodium/benzophenone or purchased in anhydrous form from Sigma Aldrich. Unless otherwise stated, reactions were monitored using thin-layer chromatography (TLC) using plates precoated with silica gel XHL w/ UV254 (250 mm) and visualized by UV light or $KMnO_4$, phosphomolybdic acid, or anisaldehyde stains, followed by heating. Silica gel (particle size 32–63 mm) was used for flash column chromatography. ^1H and ^{13}C NMR spectra are reported relative to the residual solvent peak (δ 7.26 and δ 77.16 for ^1H and ^{13}C in $CDCl_3$, δ 3.31 and δ 49.0 for ^1H and ^{13}C in CD_3OD, respectively), or tetramethylsilane (δ 0.00 for ^1H) when the residual solvent peak is obscured. Data for ^1H NMR spectra are reported as follows: chemical shift (ppm) (multiplicity, coupling constant (Hz), integration). Multiplicity is described using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, bs = broad singlet, app = apparent. FTIR samples were prepared on NaCl plates either neat or by evaporation from $CHCl_3$ or CH_2Cl_2.

CHAPTER 3 EXPERIMENTAL

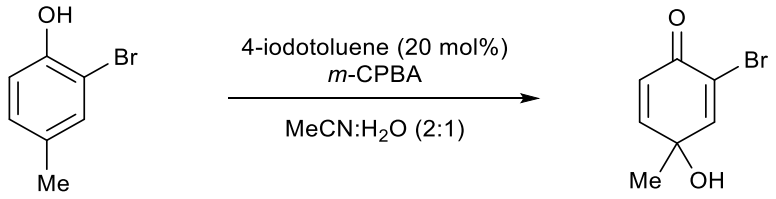


3.14

2-bromo-4-methylphenol (3.14):

p-Cresol (10.0 g, 92.5 mol, 1 eq.) and KBr (12.1 g, 101.7 mmol, 1.1 eq.) were suspended in MeOH (470 mL, 0.2M). Oxone (62.5 g, 101.7 mmol, 1.1 eq.) was added and the mixture was stirred until the reaction was complete by TLC. The mixture was filtered and the MeOH was removed by rotary evaporation and purified by filtration through a silica plug with EtOAc. The material was isolated as a reddish oil (18.18 g, 81% w/w, 85% yield). The remainder of the material was determined to be EtOAc by ^{1}H NMR spectroscopy. The crude **xx** was carried forward into the next step without further purification.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (dd, *J* = 0.6, 1.9 Hz, 1H), 7.01 (dd, *J* = 1.7, 8.2 Hz, 1H), 6.90 (d, *J* = 8.3 Hz, 1H), 2.26 (s, 3H).

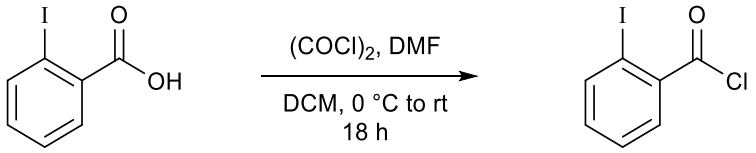


3.14 **3.19**

2-bromo-4-hydroxy-4-methylcyclohexa-2,5-dien-1-one (3.19):

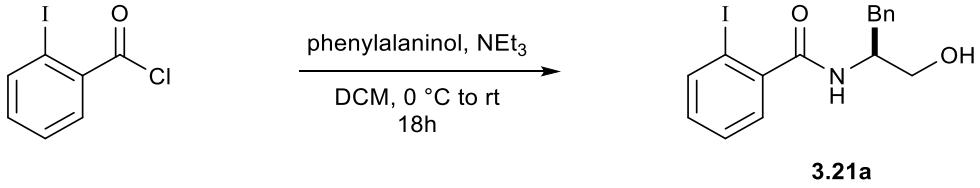
2-bromo-4-methyl phenol (6.17 g 85 wt %, 5.00g actual, 26.73 mmol, 1 eq.) and 4-iodotoluene (1.16 g, 5.35 mmol, 0.2 mmol) were dissolved in MeCN:H_2O (2:1). *m*-CPBA (55 wt%, 16.8g, 53.5 mmol, 2 eq.) was added and the solution was stirred at room temperature for 18h. Solid $Na_2S_2O_3$ (13.3 g, 23.7 mmol, 1 eq.) was added and the

mixture was stirred for 1h. $NaHCO_3$ (4.5 g) was added and the mixture was stirred 15 min. The mixture was partially concentrated under vacuum and diluted with 50 mL H_2O. The aqueous layer was extracted with 3 x 50 mL DCM. The combined organic extracts were washed with brine, dried with Na_2SO_4 and concentrated. Purification by f.c.c. (1:2 EtOAc:Hexane) gave the product as a yellow solid (2.55g, 47%).
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (d, *J* = 2.9 Hz, 1H), 6.91 (dd, *J* = 2.8, 10.0 Hz, 1H), 6.24 (d, *J* = 10.0 Hz, 1H), 1.52 (s, 3H).



2-iodobenzoyl chloride:

o-Iodobenzoic acid (5.0 g, 20.16 mmol, 1 eq.) was suspended in DCM along with 5 drops of DMF. The suspension was cooled to 0 °C and $(COCl)_2$ was added dropwise. The solution was stirred for 18h and concentrated under vacuum to give a yellow solid (5.25 g, 98%) which was stored under nitrogen in the freezer. The compound was used without further purification.



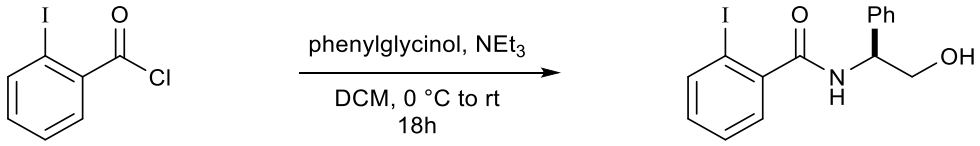
3.21a

(*S*)-N-(1-hydroxy-3-phenylpropan-2-yl)-2-iodobenzamide (3.21a):

(*L*)-Phenylalaninol (170.5 mg, 1.12 mmol, 1.2 eq.) was suspended in DCM (5 mL) and NEt_3 (200 mg, 1.97 mmol, 2.1 eq.) was added. The solution was cooled to 0 °C and *o*-iodobenzoyl chloride (250 mg, 0.94 mmol, 1 eq.) dissolved in ~1 mL DCM was added dropwise. The solution was stirred overnight, allowing the reaction mixture to come to room temperature. The solution was quenched with 10 mL of saturated $NaHCO_3$. The mixture was diluted with DCM (~20 mL) until all solids dissolved. The layers were separated and the aqueous layer was extracted with 3 x 5 mL DCM. The combined organic layers were washed with brine, dried with Na_2SO_4, dried and concentrated. The crude mixture was recrystallized from EtOAc:Hexane to give white crystals (262 mg, 73%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (dd, *J* = 0.8, 8.0 Hz, 1H), 7.21-7.33 (m, 7H), 7.07 (dt, *J* = 1.5, 7.7 Hz, 1H), 6.10 (bd, *J* = 7.5 Hz, 1H), 4.42-4.36 (m, 1H), 3.81 (dd, *J* = 3.6, 11.2 Hz, 1H), 3.70 (dd, *J* = 4.7, 11.2 Hz, 1H), 3.00 (d, *J* = 7.4 Hz, 2H), 2.62 (bs, 1H).

^{13}C NMR (125 MHz, $CDCl_3$, DEPT) δ 166.85 (C), 142.19 (C), 139.91 (CH), 137.63 (C), 131.27 (CH), 129.50 (CH) 128.84 (CH), 128.30 (CH), 128.24 (CH), 126.89 (CH), 100.11 (C), 92.54 (C), 63.76 (CH_2), 53.38 (CH), 36.98 (CH_2).

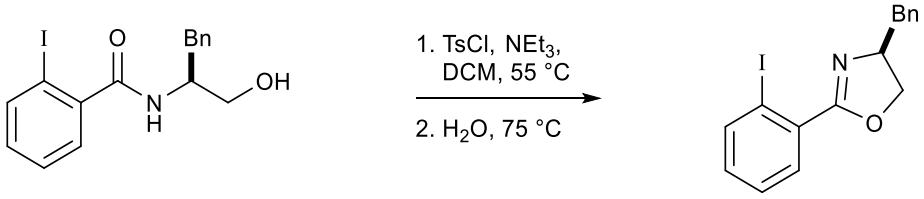


3.21b

(*S*)-N-(2-hydroxy-1-phenylethyl)-2-iodobenzamide (3.21b):

Compound **3.2b** was synthesized in the same manner and scale as **3.21a**. The compound was isolated in 68% yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (dd, *J* = 0.9, 8.0 Hz, 1H), 7.33-7.49 (m, 7H), 7.12 (dt, *J* = 1.9, 7.6 Hz, 1H), 6.47 (bd, *J* = 6.8 Hz, 1H), 5.29 (dt, *J* = 4.7, 7.3 Hz- 1H), 4.05 (d, *J* = 4.6, 2H), 2.41 (bs, 1H).

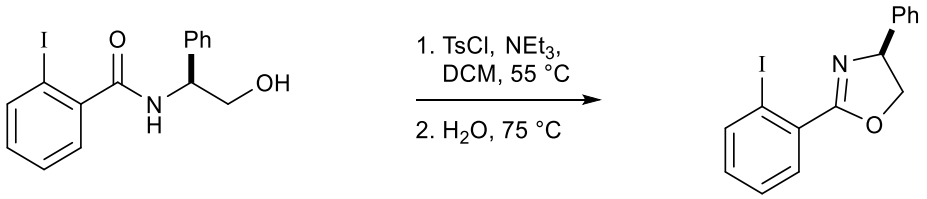


3.21a **3.22a**

(*S*)-4-benzyl-2-(2-iodophenyl)-4,5-dihydrooxazole (3.22a):

Amide **3.21a** (100 mg, 0.26 mmol, 1 eq.) and NEt_3 (132 mg, 1.31 mmol, 5 eq.) were dissolved in DCM (2 mL, 0.15 M). TsCl (68 mg, 0.36 mmol, 1.3 eq.) was added and the solution was heated under N_2 at 55 °C for 6.5 h. H_2O (0.4 mL) was added and the temperature was increased to 75 °C for 2h. The reaction was cooled to rt and let stand overnight. The solution was quenched with 5 mL saturated NH_4Cl. The aqueous layer was extracted with 3 x 5 mL DCM. The combined organic extracts were washed with brine, dried with Na_2SO_4 and concentrated. The compound was purified by f.c.c. (1:4 EtOAc:Hexane) to give **3.22a** (77 mg, 81%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (app. d, *J* = 7.9 Hz, 1H), 7.59 (dd, *J* = 1.5, 7.7 Hz, 1H), 7.39-7.22 (m, 6H), 7.11 (ddd, *J* = 0.9, 7.3, 8.1 Hz, 1H), 4.67-4.61 (m, 1H), 4.39 (t, *J* = 8.9 Hz, 1H), 4.18 (t, *J* = 7.9 Hz, 1H), 3.26 (dd, *J* = 5.4, 13.8 Hz, 1H), 2.82 (dd, *J* = 8.4, 13.8 Hz, 1H).

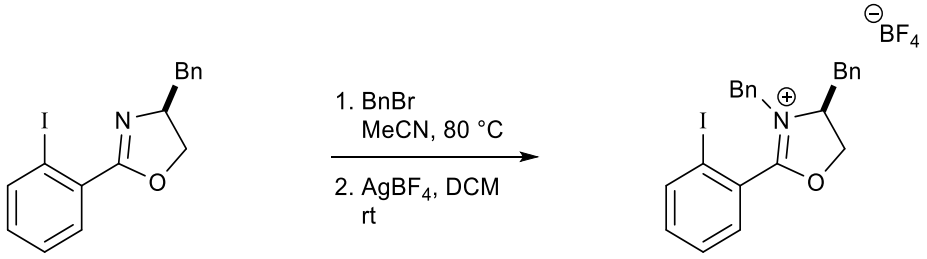


3.21b **3.22b**

(*S*)-2-(2-iodophenyl)-4-phenyl-4,5-dihydrooxazole (3.22b):

The reaction was performed using the same procedure reported for **3.22a** using 200 mg (0.54 mmol) of **3.21b**. Compound **3.22b** was isolated (148.1 mg,79%)

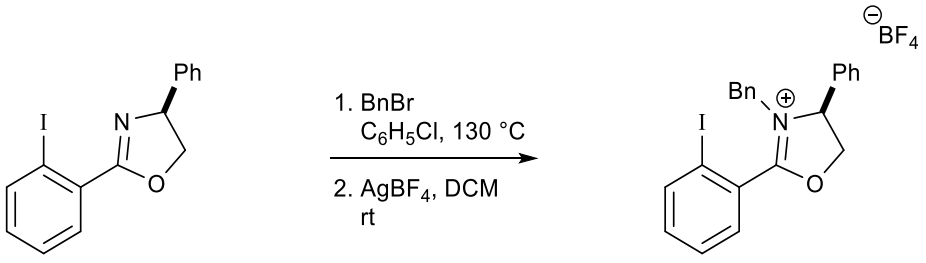
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 (dd, *J* = 1.1, 8.0 Hz, 1H), 7.72 (dd, *J* = 1.7, 7.7Hz, 1H), 7.44-7.32 (m, 6H), 7.15 (dt, *J* = 1.7, 7.7 Hz, 1H), 5.46 (dd, *J* = 86, 10.2 Hz, 1H), 4.85 (dd, *J* = 8.4, 10.2 Hz, 1H), 4.30 (t, *J* = 8.5 Hz, 1H).



3.22a **3.23a**

(*S*)-3,4-dibenzyl-2-(2-iodophenyl)-4,5-dihydrooxazol-3-ium tetrafluoroborate (3.23a):

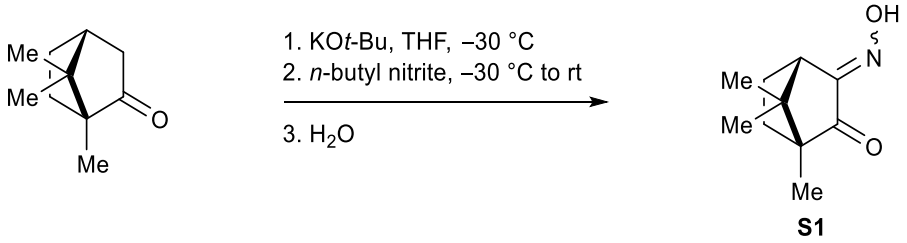
Oxazoline **3.22a** (25 mg, 0.069 mmol, 1 eq.) was dissolved in MeCN (0.45 mL, 0.15 M). BnBr (353 mg, 0.206 mmol, 3 eq.) was added and the mixture was stirred at 80 °C for 18 h. The solution was concentrated under vacuum to remove excess BnBr. The crude material was dissolved in DCM and $AgBF_4$ was added. The mixture was stirred for 15 min., filtered, and concentrated to give **3.23a** as a brown solid (49.4 mg, <100%), which was used directly without further purification.



3.22b **3.23b**

(*S*)-3-benzyl-2-(2-iodophenyl)-4-phenyl-4,5-dihydrooxazol-3-ium tetrafluoroborate (2.32b):

Oxazoline **3.22b** (20 mg, 0.0572 mmol) was dissolved in chlorobenzene (0.1 mL) and BnBr (9.8 mg, 0.572 mmol, 1 eq.) was added. The mixture was stirred for 18 h at 130 °C. After concentration, successful benzylation was confirmed by MS. The salt metathesis was performed in an analogous manner. The final salt was isolated as a brown salt (11.2 mg, 37%).

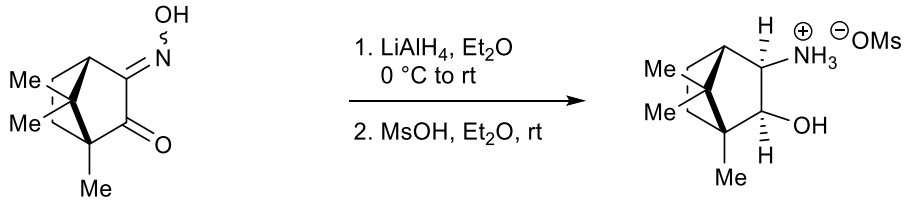


S1

(1*R*,4*S*)-3-(hydroxyimino)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one (S1):

KO*t*-Bu (8.85g, 78.8 mmol, 1.2 eq.) was suspended in THF (26 mL) and cooled to –20 °C. (*R*)-(+)-Camphor (10.0 g, 65.7 mmol, 1 eq.) dissolved in THF (14 mL) was added dropwise and stirred for 10 min. *n*-Butyl nitrite (8.13 g, 78.8 mmol, 1.2 eq.) was added dropwise. The solution was stirred for 30 min. at –20 °C and allowed to warm to rt. The solution was stirred at rt for 18 h. The THF was removed under vacuum and ~60 mL H_2O was added and was acidified with HCl. The aqueous layer was extracted with 3 x 20 mL Et_2O. The combined organic layers were washed with brine, dried with Na_2SO_4, and concentrated. The crude material was recrystallized from pentane to give oxime **S1** (5.17 g, 43%).

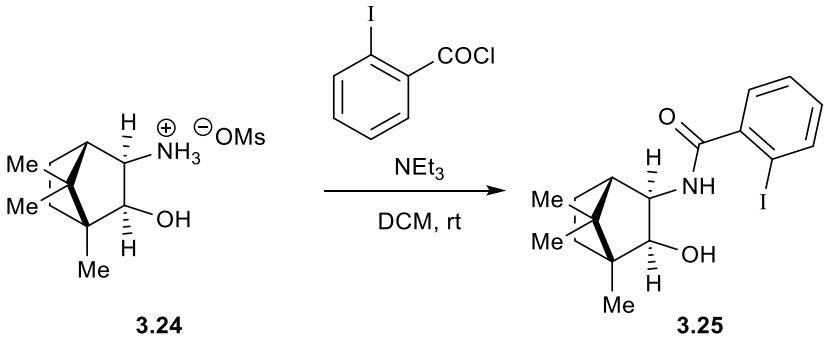
^{1}H NMR (500 MHz, $CDCl_3$) δ 9.93 (bs, 1H), 3.25 (d, *J* = 4.5 Hz, 1H), 2.10-1.97 (m, 1H), 1.81-1.70 (m, 1H), 1.56 (td, *J* = 5.9, 9.0 Hz, 2H), 1.00 (s, 3H), 0.97 (s, 3H), 0.85 (s, 3H).



S1 **3.24**

(1*S*,2*R*,3*S*,4*R*)-3-hydroxy-4,7,7-trimethylbicyclo[2.2.1]heptan-2-aminium methanesulfonate (3.24):

$LiAlH_4$ (630 mg, 16.6 mmol, 1.2 eq.) was suspended in Et_2O (70 mL) and cooled to –78 °C. Oxime **S1** (2.5 g, 13.8 mmol, 1 eq) was added. The solution was allowed to warm to rt and stirred for 18 h. The reaction was quenched with 1.5 mL H_2O followed by 1.5 mL of 3M NaOH sol'n then 4.5 mL H_2O. The mixture was stirred for 1h, filtered, and concentrated. The crude mixture was redissolved in 10 mL Et_2O and methanesulfonic acid (1.33g, 13.8 mmol, 1 eq.) was added. The salt was collected as a precipitate from ether (569.3 mg, 16%).



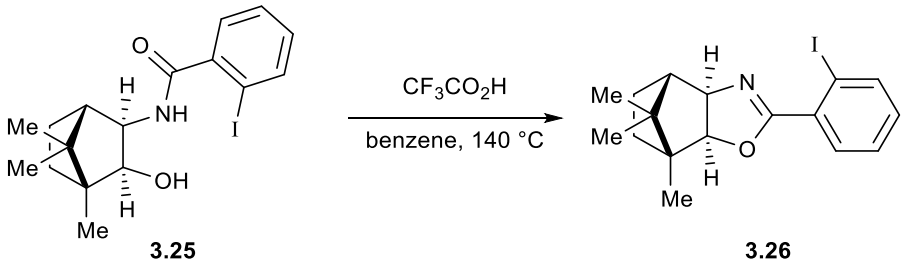
3.24 **3.25**

***N*-((1*S*,2*R*,3*S*,4*R*)-3-hydroxy-4,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)-2-iodobenzamide (3.25):**

Amino-alcohol **3.24** (150 mg, 0.41 mmol, 1.1 eq.) and NEt_3 (165 mg, 1.64 mmol, 4 eq.) were dissolved in DCM (2 mL) and cooled to 0 °C. *o*-Iodobenzoyl chloride was added and the reaction was allowed to stir for 18 h. The reaction was quenched with 5 mL saturated $NaHCO_3$ and extracted with 3 x 2 mL DCM. The combined organic layers were washed with brine, dried with Na_2SO_4 and concentrated. The amide was purified by f.c.c. (5% MeOH in DCM) to give product **3.25** (127 mg, 85%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (dd, *J* = 0.5, 8.0 Hz, 1H), 7.37-7.36 (m, 2H), 7.09 (ddd, *J* = 3.2, 5.9, 8.0 Hz, 1H), 6.47 (bd, *J* = 3.6 Hz, 1H), 3.99 (t, *J* = 6.8 Hz, 1H), 3.90 (dd, *J* = 3.9, 7.6 Hz, 1H), 2.27 (d, *J* = 3.7 Hz, 1H), 2.01 (d, *J* = 4.5 Hz, 1H), 1.77 (tt, *J* = 4.6, 12.4 Hz, 1H), 1.54 (dt, *J* = 4.1, 12.5 Hz, 1H), 1.25 (ddd, *J* = 3.8, 9.3, 12.8 Hz, 1H), 1.13 (s, 3H), 1.08 (ddd, *J* = 5.6, 3.5, 14.7 Hz, 1H), 0.96 (s, 3H), 0.84 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$, DEPT) δ 169.40 (C), 142.53 (C), 140.04 (CH), 131.12 (CH), 128.26 (CH), 128.17 (CH), 92.83 (C), 80.06 (CH), 58.47 (CH), 50.29 (CH), 49.43 (C), 47.10 (C), 33.36 (CH_2), 26.39 (CH_2), 21.66 (CH_3), 21.44 (CH_3), 11.45 (CH_3).

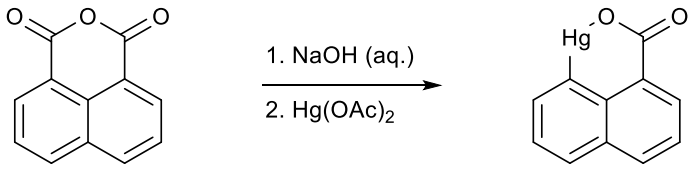


3.25 **3.26**

(3a*R*,4*S*,7*R*,7a*S*)-2-(2-iodophenyl)-7,8,8-trimethyl-3a,4,5,6,7,7a-hexahydro-4,7-methanobenzo[d]oxazole (3.26):

Amide **3.25** (10 mg, 0.025 mmol, 1 eq.) was suspended in benzene (0.1 mL) in a sealed tube. TFA (~1 drop) was added. The mixture was stirred for 10 min. at rt then heated to 140 °C for 2h. The reaction was quenched with aqueous $NaHCO_3$ and extracted with EtOAc (3 x 1 mL). The combined organic extracts were washed with brine, dried with Na_2SO_4 and concentrated. The product was purified by f.c.c. (1:6 to 1:2 EtOAc:Hexane) to give oxazoline **3.26** (4.6 mg, 48%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (dd, *J* = 1.0, 8.0 Hz, 1H), 7.66 (dd, *J* = 1.6, 7.7 Hz, 1H), 7.37 (dt, *J* = 1.1, 7.7 Hz, 1H), 7.09 (dt, *J* = 1.5, 7.7 Hz, 1H), 4.45 (d, 8.6, 1H), 4.26 (d, *J* = 8.6 Hz, 1H), 2.21 (d, *J* = 4.6 Hz, 1H), 1.82-1.75 (m, 1H), 1.58-1.52 (m, 3H), 1.12-1.08 (m, 4H), 1.03 (m, 3H), 0.89 (s, 3H).

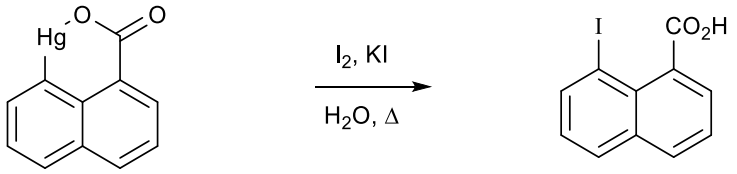


S2

***o*-(hydroxymercuri)-1-napthoic acid anhydride (S2):**

Napthoic anhydride (5.00 g, 25.22 mmol, 1 eq.) was suspended in an aqueous NaOH sol'n prepared from NaOH (3.53 g, 88.27 mmol, 3.5 eq.) in 150 mL H_2O. The suspension was refluxed until all solids had dissolved. Excess NaOH was neutralized with glacial AcOH. $Hg(OAc)_2$, prepared by dissolving HgO (6.00 g, 27.7 mmol, 1.1 eq.) in 14 mL hot, glacial acetic acid and diluting with 30 mL H_2O, was added in one portion. The solution was refluxed for 30 min. and an additional 5 mL AcOH was added. The reaction mixture was refluxed for an additional 48 h and cooled to rt. The resulting solid was filtered, washed with H_2O and dried under vacuum, giving the

product (7.84g, 84%) which was stored in the freezer and used without further purification.

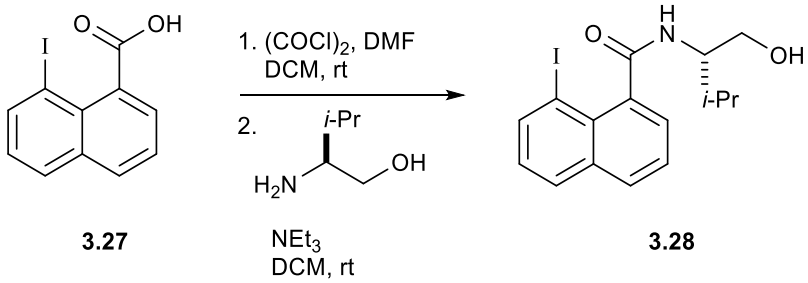


S2 **3.27**

8-iodo-1-naphthoic acid (3.27)

Organomercury compound **S2** (3.0 g, 8.1 mmol, 1 eq.) and KI (5.64 g, 34.02 mmol, 4.2 eq.) were suspended in H_2O. I_2 (2.16 g, 8.5 mmol, 1.05 eq.) was added and the solution was refluxed for 15 h. The solution was cooled to rt and filtered. The filtrate was quenched with NaS_2O_3 and acidified with HCl. The resulting solid was filtered and recrystallized from $CHCl_3$ to give **3.27** as a white solid (514.6 mg, 21%).

^{1}H NMR (500 MHz, DMSO-d_6) δ8.27 (d, *J* = 7.3 Hz, 1H), 8.07-8.04 (m, 2H), 7.70 (d, *J* = 7.1 Hz, 1H), 7.58-7.55 (m, 1H), 7.30-7.27 (m, 1H).

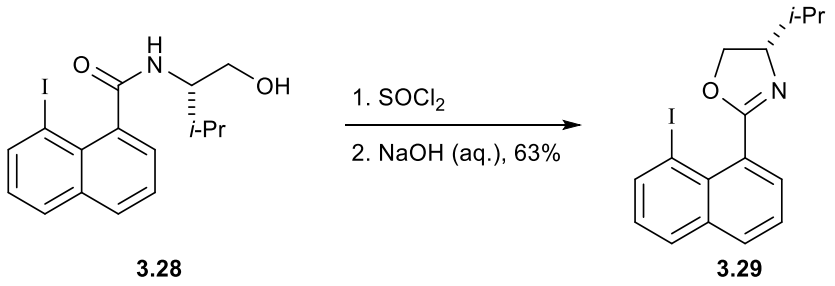


3.27 **3.28**

(*S*)-N-(1-hydroxy-3-methylbutan-2-yl)-8-iodo-1-naphthamide (3.28):

8-Iodo-1-napthoic acid (500 mg, 1.67 mmol, 1 eq.) was suspended in DCM (7 mL) along with 1 drop of DMF. $(COCl)_2$ (276 mg, 2.17 mmol, 1.3 eq.) was added dropwise and stirred for 18 h. The solvent and excess $(COCl)_2$ was removed under vacuum and the crude product was used directly. (*S*)-Valinol (215 mg, 2.08 mmol, 1.3 eq.) and NEt_3 (506 mg, 5.01 mmol, 3.0 eq.) were dissolved in DCM (4 mL) and cooled to 0 °C. The crude acid chloride in 8 mL DCM was added dropwise and stirred for 18 h. The reaction was diluted with DCM (10 mL) and quenched with 1M HCl (10 mL). The aqueous layers were extracted with 2 x 10 mL DCM. The organic layers were washed with brine, dried with Na_2SO_4 and concentrated. The product was recrystallized from EtOAc:Hexane to give the product (245.7 mg, 38%).

^{1}H NMR (500MHz, $CDCl_3$) δ 8.24 (dd, *J* = 1.1, 7.4 Hz, 1H), 7.86 (ddd, *J* = 1.0, 4.6, 8.1 Hz, 2H), 7.62 (d, *J* = 6.8 Hz, 1H), 7.43 (dd, *J* = 7.1, 8.1 Hz, 1H), 7.16 (t, *J* = 7.8 Hz, 1H), 6.26 (bs, 1H), 3.97 (d, *J* = 9.4 Hz, 2H), 3.88-3.86 (m, 1H), 2.09 (dd, *J* = 6.5, 13.2 Hz, 1H), 1.07 (d, *J* = 6.9 Hz, 3H), 1.05 (d, *J* = 6.8 Hz, 3H).

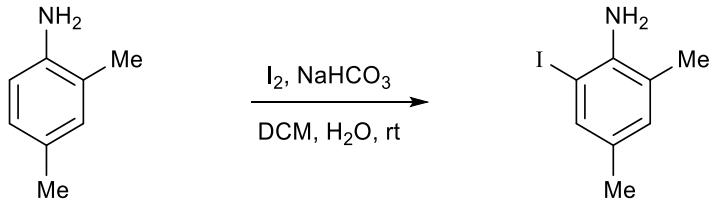


3.28 **3.29**

(*S*)-2-(8-iodonaphthalen-1-yl)-4-isopropyl-4,5-dihydrooxazole (3.29):

$SOCl_2$ (1.85 g, 15.6 mmol, 120 eq.) was cooled to 0 °C. Amide **3.28** (50 ng, 0.13 mmol, 1 eq.) in DCM (1.5 mL) was added dropswise. The solution was allowed to warm slowly to rt and stirred for 24 h. The solution was concentrated under vacuum to remove excess $SOCl_2$. The product was dissolved in 10 mL DCM and washed with 10 mL 1M NaOH. The aqueous layer was washed with 2 x 5 mL DCM. The combined organic layers were washed with brine, dried with Na_2SO_4 and concentrated. The product was purified by f.c.c. (1:4 EtOAc:Hexane) to give product **xx** (29.9 mg, 63%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24 (dd, *J* = 1.2, 7.4 Hz, 1H), 7.87 (ddd, *J* = 1.1, 8.2, 16.8 Hz, 2H), 7.80 (dd, *J* = 1.2, 7.1 Hz, 1H), 7.47 (dd, *J* = 7.1, 8.2 Hz, 1H), 7.13 (dd, *J* = 7.4, 8.1 Hz, 1H), 4.64-4.60 (m, 1H), 4.25 (t, *J* = 7.8 Hz, 1H), 4.19 (d, *J* = 5.3 Hz, 1H), 2.06-2.00 (m, 1H), 1.13 (d, *J* = 6.4 Hz, 3H), 1.02 (d, *J* = 6.8 Hz, 3H).



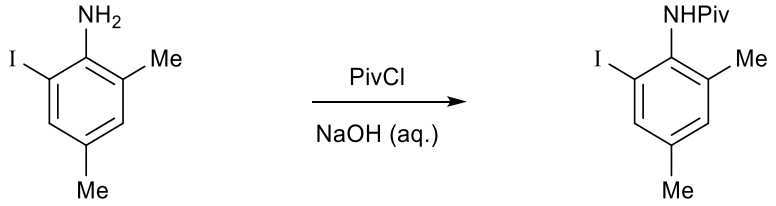
3.30

2-iodo-4,6-dimethylaniline (3.30):

4,6-Dimethylaniline (1.5 g, 12.37 mmol, 1 eq.) and $NaHCO_3$ (3.2 g, 37.1 mmol, 3 eq.) were suspended in DCM:H_2O (75 mL total, 2:1 DCM:H_2) and stirred vigorously. I_2 (3.14 g, 12.37 mmol, 1 eq.) and the mixture was stirred for 18 h. The organic layer was separated and the aqueous layer was washed with 2 x 20 mL DCM. The combined

layers were washed with brine, dried with Na_2SO_4 and concentrated to give **3.30** as a brown, sticky solid (2.22 g, 73%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (app. s, 1H), 6.84 (app. s, 1H), 3.93 (s, 2H), 2.20 (s, 3H), 2.19 (s, 3H).

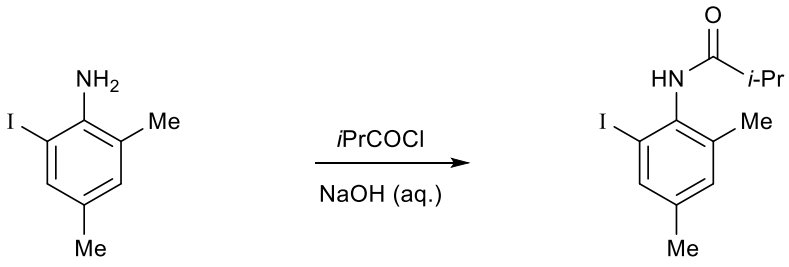


3.30 **S3**

***N*-(2-iodo-4,6-dimethylphenyl)pivalamide (S3):**

Iodoaniline **3.30** (250 mg, 1.01 mmol, 1 eq.) was dissolved in DCM (1 mL). NaOH (1 mL of a 10% aqueous sol'n) was added and the mixture was stirred vigorously for 4h. The aqueous layer was diluted with 5 mL H_2O and extracted with 2 x 2 mL DCM. The combined organic layers were washed with brine, dried with Na_2SO_4 and concentrated. Purification by f.c.c. (1:5 EtOAc:Hexane) gave amide **S3** (160.7 mg, 46%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 (app. s, 1H), 7.01 (app. s, 1H), 2.26 (s, 3H), 2.21 (s, 3H), 1.59 (s, 1H), 1.37 (s, 9H).

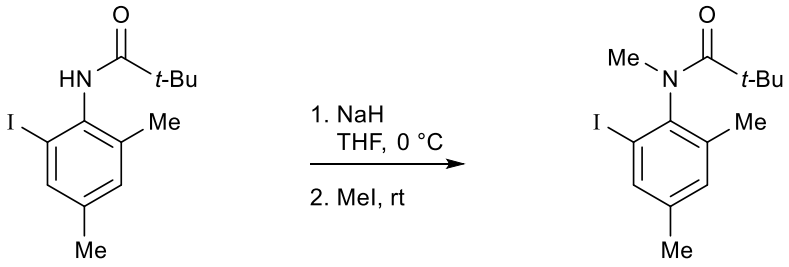


3.30 **S4**

***N*-(2-iodo-4,6-dimethylphenyl)isobutyramide (S4):**

The reaction was performed in the same manner and on the same scale as in the previous example. Compound **S4** was isolated in 24% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (dd, *J* = 0.6, 1.3 Hz, 1H), 7.02 (d, *J* = 0.4 Hz, 1H), 6.80 (bs, 1H), 2.62 (td, *J* = 6.9, 13.9 Hz, 1H), 2.26 (s, 3H), 2.23 (s, 3H), 1.32 (d, *J* = 6.9 Hz, 6 H).

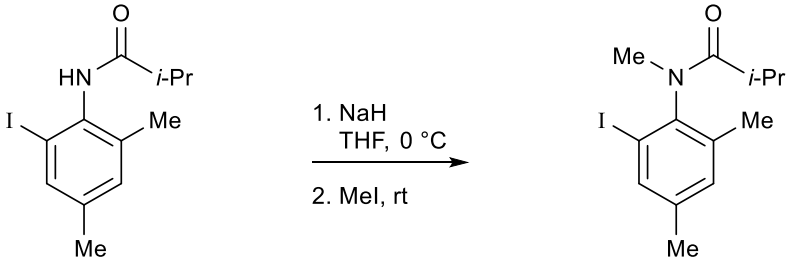


S3 **3.31a**

***N*-(2-iodo-4,6-dimethylphenyl)-N-methylpivalamide (3.31a):**

Iodoamide **S3** (50 mg, 0.15 mmol, 1 eq.) was dissolved in THF (1.5 mL) and cooled to 0 °C. NaH (8 mg of a 60 wt% powder in mineral oil, 0.19 mmol, 1.25 eq.) was added and the solution was stirred at 0 °C for 30 min. MeI was added and the solution was allowed to warm to rt and stirred for 18 h. The solution was quenched with aqueous NH_4Cl (5 mL) and extracted with 3 x 2 mL EtOAc. The combined organic layers were washed with brine, dried with Na_2SO_4 and concentrated. The crude product was purified by f.c.c. (1:6 EtOAc:Hexane) to give a white solid (33.1 mg, 64%). A small amount of material could be resolved through repeated injections onto an analytical-scale HPLC column (2% *i*-PrOH in Hexane, 1 mL/min, Chiralcel OJ, approx.. 8 injections) and collection of the resulting waste stream.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (dd, *J* = 0.6, 1.3 Hz, 1H), 7.01 (td, *J* = 0.6, 1.3 Hz, 1H), 3.08 (s, 3H), 2.28(+) (s, 3H), 2.28(-) (s, 3H), 1.05 (s, 9H).

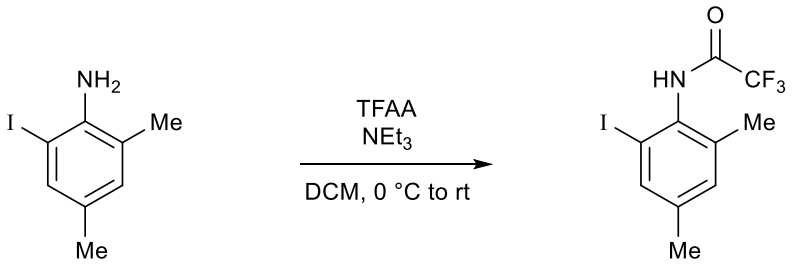


S4 **3.31b**

***N*-(2-iodo-4,6-dimethylphenyl)-N-methylisobutyramide (3.31b):**

The reaction was performed on **S4** (50 mg, 0.157 mmol) in the same manner as **3.31a** to give **3.31b** after purification by f.c.c. (1:6 EtOAc:Hexane) (37.1 mg, 71%). A small amount of material could be resolved through repeated injections onto an analytical-scale HPLC column (2% *i*-PrOH in Hexane, 1 mL/min, Chiralcel OJ, approx.. 8 injections) and collection of the resulting waste stream.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (dd, *J* = 0.6, 1.3 Hz, 1H), 7.05 (07, 1.3 Hz, 1H), 3.09 (s, 3H), 2.28 (s, 3H), 2.24 (s, 3H), 2.19 (tt, *J* = 5.9, 12.0 Hz, 1H), 1.13 (d, *J* = 6.7 Hz, 3H), 0.98 (d, *J* = 6.8 Hz, 3H).

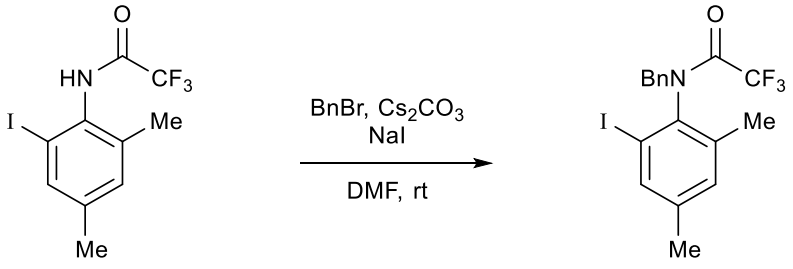


3.30 **S5**

2,2,2-trifluoro-*N*-(2-iodo-4,6-dimethylphenyl)acetamide (S5):

Iodoaniline **3.30** (50 mg, 0.2 mmol, 1 eq.) was dissolved in DCM (1 mL). NEt_3 (41 mg, 0.4 mmol, 2 eq.) was added and the solution was cooled to 0 °C. TFAA (53 mg, 0.25 mmol, 1.25 eq.) was added. The reaction was allowed to warm to rt and stirred for 24h. TLC showed incomplete conversion. An additional ~10 µL of TFAA and ~10 mg DMAP were added and stirred an additional 24h, at which time full consumption was achieved. The reaction was quenched with 5 mL saturated $NaHCO_3$ and the aqueous layer was extracted with 3 x 2 mL DCM. The combined organic layers were washed with brine, dried with Na_2SO_4 and concentrated. Purification by f.c.c. (1:6 EtOAc:Hexane) gave the product (37.6 mg, 55%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (s, 1H), 7.55 (d, *J* = 0.6 Hz, 1H), 7.06 (s, 1H), 2.29 (s, 3H), 2.24 (s, 3H).

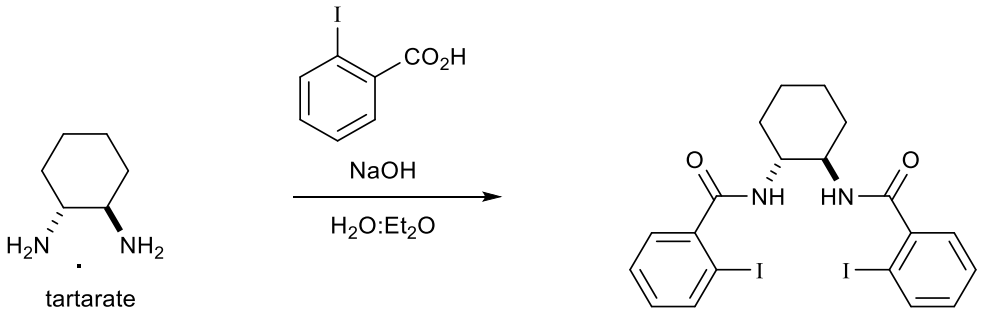


S5 **3.32b**

***N*-benzyl-2,2,2-trifluoro-*N*-(2-iodo-4,6-dimethylphenyl)acetamide (3.32b):**

Trifluoroacetamide **S5** (37.6 mg, 0.11 mmol, 1 eq.), Cs_2CO_3 (71 mg, 0.22 mmol, 2 eq.), BnBr (19 mg, 0.17 mmol, 1.5 eq.), and NaI (18 mg, 0.12 mmol, 1.1 eq.) were dissolved in DMF (1 mL) and stirred at rt for 48 h. The reaction mixture was diluted with 5 mL H_2O and extracted with 3 x 2 mL EtOAc. The combined organic layers were washed with brine, dried with Na_2SO_4 and concentrated. The crude material was purified by f.c.c. (1:20 EtOAc:Hexane) to give the product (26.6 mg, 56%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (dd, *J* = 0.6, 1.3 Hz, 1H), 7.32-7.24 (m, 3H), 7.22-7.19 (m, 2H), 6.90 (dd, *J* = 0.7, 1.3 Hz, 1H), 5.59 (d, *J* = 13.8 Hz, 1H), 4.14 (d, *J* = 13.8 Hz, 1H), 2.28 (s, 3H), 1.50 (s, 3H).

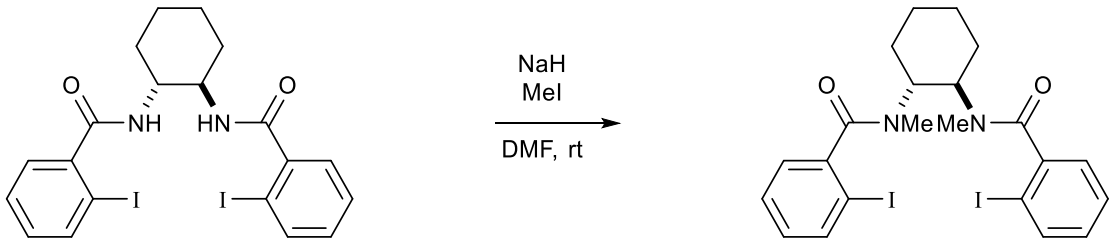


3.35

***N*,*N*'-((1*R*,2*R*)-cyclohexane-1,2-diyl)bis(2-iodobenzamide) (3.35):**

Cyclohexanediamine tartrate (500 mg, 1.88 mmol, 1 eq.) was suspended in Et_2O (13 mL) and NaOH (15 mL of a 2M sol'n, 30 mmol, 16 eq.) was added. *o*-Iodobenzoyl chloride was added and the mixture was stirred vigorously overnight. The resulting solid was filtered to give *bis*-amide **3.35** (216.5 mg, 20%) as a white solid.

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.30 (t, *J* = 7.7 Hz, 2H), 7.86 (dd, *J* = 1.0, 7.9 Hz, 2H), 7.41 (dt, *J* = 1.1, 7.5 Hz, 2H), 7.30 (dd, *J* = 1.7, 7.6 Hz, 2H), 7.13 (dt, *J* = 1.7, 7.7 Hz, 2H), 3.80 (td, *J* = 4.4, 9.5 Hz, 2H), 1.93 (d, *J* = 13.3 Hz, 2H), 1.72 (dd, *J* = 2.5, 5.2 Hz, 2H), 1.48-1.41 (m, 2H), 1.28-1.24 (2H).



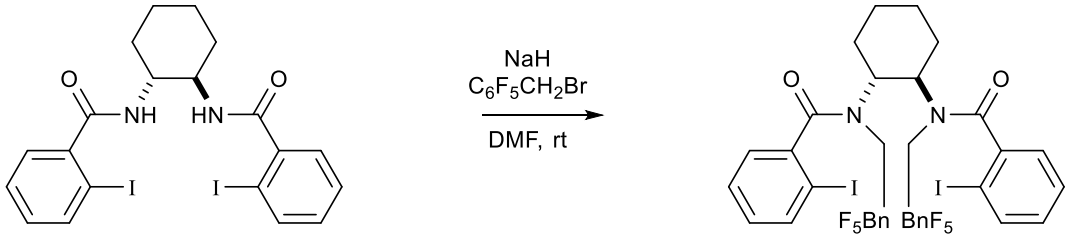
3.35 **3.36a**

***N*,*N*'-((1*R*,2*R*)-cyclohexane-1,2-diyl)bis(2-iodo-*N*-methylbenzamide) (3.36a):**

Bis-amide **3.35** (50 mg, 0.087 mmol, 1 eq.) was dissolved in DMF (0.9 mL). NaH (10 mg of a 60 wt% slurry in mineral oil, 0.26 mmol, 3 eq.) was added and the mixture was stirred for 15 min. MeI (37 mg, 0.26 mmol, 3 eq.) was added and the mixture was

stirred for 18 h. The solution was diluted with 5 mL H_2O and extracted with 3 x 2 mL EtOAc. The combined organic fractions were washed with brine, dried with Na_2SO_4 and concentrated. The compound was purified by f.c.c. (1:4 to 1:2 EtOAc:Hexane) to give the product as a white solid (40.1 mg, 76%). The structure was confirmed by MS.

MS (ESI+) Calc'd for $C_{22}H_{24}I_2N_2O_2Na^+$ 624.9819, found 624.9830.

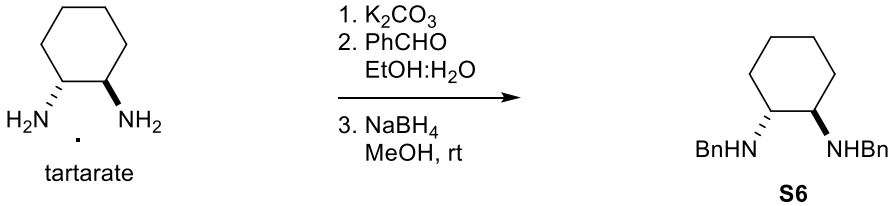


3.35 **3.36c**

***N*,*N*'-((1*R*,2*R*)-cyclohexane-1,2-diyl)bis(2-iodo-*N*-(2-(perfluorophenyl)ethyl)benzamide) (3.36c):**

Compound **xx** was synthesized in the same manner as **3.36a**, but Pentafluorobenzyl bromide was utilized as the electrophile. The compound was purified by f.c.c. (1:6 EtOAc:Hexane) to give the product as a white solid (54.8 mg, 67%). The compound identity was confirmed by MS

MS (ESI+) Calc'd for $C_{34}H_{22}F_{10}N_2O_2Na^+$ 956.9503 found 956.9531.

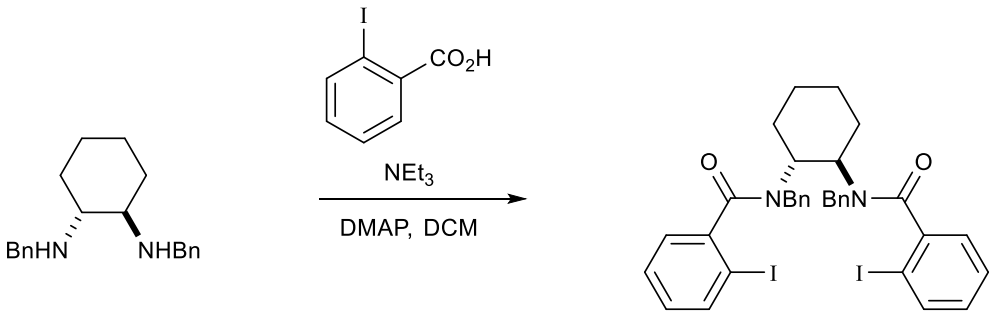


S6

(1*R*,2*R*)-*N*1,*N*2-dibenzylcyclohexane-1,2-diamine (S6):

R,*R*-Cyclohexadiamine tartrate (500 mg, 1.88 mmol, 1 eq.) and K_2CO_3 (519.6 mg. 3.76 mmol, 2 eq.) were stirred in H_2O (2.5 mL) until all solids had dissolved. EtOH (10 mL) was added and heated to reflux. Benzaldehyde (399.0 mg, 3.76 mmol, 2 eq.) in EtOH (4 mL) was added slowly over 30 min. The solution was refluxed for 2.5 h and cooled to rt. H_2O (2.5 mL) was added and the mixture was placed in the freezer for 5.5 h. The solvent was removed and the aqueous layer was extracted with 3 x 10 mL DCM. The combined organic layers were washed with brine, dried with Na_2SO_4 and concentrated. The crude material (369.7 mg, 68%) was pure by ^1H NMR spectroscopy and was used directly in the next step.

The *bis*-imine (345.5 mg, 1.2 mmol, 1 eq.) from the previous step was dissolved in MeOH (2.5 mL). $NaBH_4$ was added portionwise and stirred for 24 h. The reaction was quenched by added H_2O (3 mL) dropwise to the solution. The solution was extracted with 3 x 3 mL DCM. The combined organic layers were washed with brine, dried with Na_2SO_4 and concentrated. The compound was pure by ^1H NMR spectroscopy (299.2 mg, 85%).

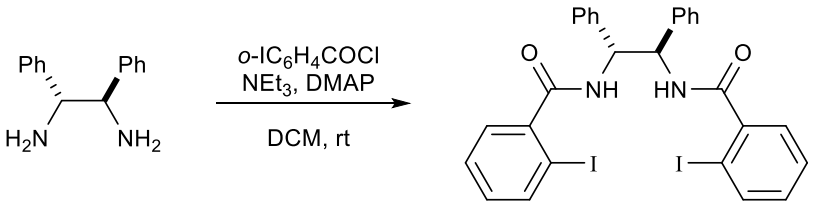


S6 **3.36b**

***N*,*N*'-((1*R*,2*R*)-cyclohexane-1,2-diyl)bis(2-iodobenzamide) (3.36b):**

Bis-benzyl cyclohexanediamine **S6** (100 mg, 0.34 mmol, 1 eq.) was dissolved in DCM (2 mL) and NEt_3 (103 mg, 0.68 mmol, 2 eq.) and DMAP (~10 mg) were added. The solution was cooled to 0 °C and 2-iodobenzoyl chloride was added and the solution was stirred for 18 h. The reaction was quenched with 5 mL saturated $NaHCO_3$. The solution was extracted with 3 x 2 mL DCM. The combined organic layers were washed with brine, dried with Na_2SO_4 and concentrated. Purification by f.c.c. (1:4 to 1:2 EtOAc:Hexane) gave the product as a white solid (158.1 mg, 62%). The product was confirmed by MS.

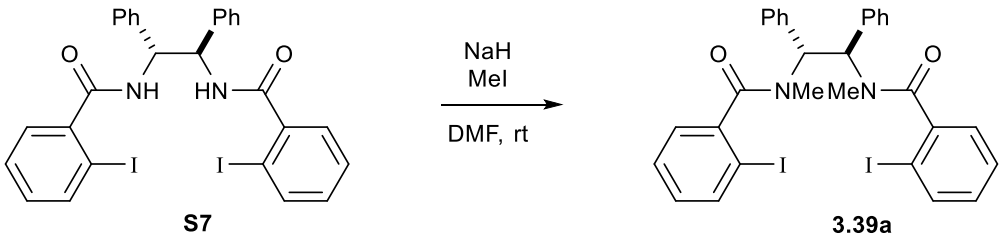
MS (ESI+) 777.0445 calc'd for $C_{34}H_{32}I_2N_2O_2Na^+$, 777.0282 found.



3.38 **S7**

***N*,*N*'-((1*R*,2*R*)-1,2-diphenylethane-1,2-diyl)bis(2-iodobenzamide) (S7):**

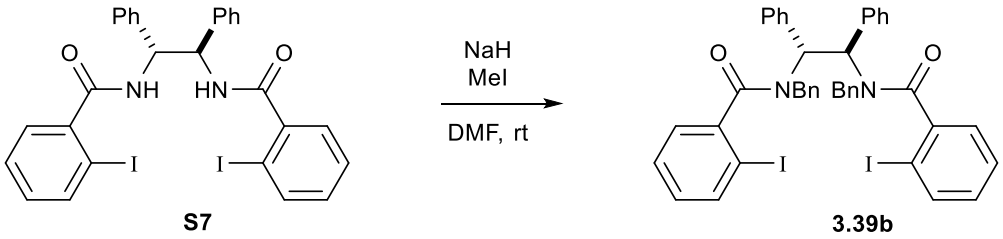
R-*R*-DPEN (100 mg, 0.47 mmol, 1 eq.) was dissolved in DCM (5 mL). NEt_3 (190 mg, 1.88 mmol, 4 eq.) and DMAP (6 mg, 0.05 mmol, 0.1 eq.) were added and the solution was cooled to 0 °C. *o*-Iodobenzoyl chloride (263 mg, 0.99 mmol, 2.1 eq.) was added. The solution was allowed to warm slowly to rt and stirred at rt for 18h. The reaction was quenched with aqueous HCl and filtered. To give 259.8 mg of a white solid (82%) which was carried forward directly.



***N*,*N*'-((1*R*,2*R*)-1,2-diphenylethane-1,2-diyl)bis(2-iodo-*N*-methylbenzamide) (3.39a):**

Bis-amide **S7** (50 mg, 0.074 mmol, 1 eq.) was dissolved in DMF (0.75 mL) and NaH (12 mg of a 60% suspension, 0.3 mmol, 4 eq.) was added. The solution was stirred for 10 min. and MeI (42.6 mg, 0.3, 4 eq.) was added. The solution was stirred for 48 hours. The solution was diluted with 5 mL H_2O and extracted with 3 x 2 mL EtOAc. The combined organic fractions were washed with brine, dried with Na_2SO_4 and concentrated. Purification by f.c.c. (1:4 EtOAc:Hexane) gave the product as a white solid (21.8 mg, 42%). The product identity was confirmed by MS.

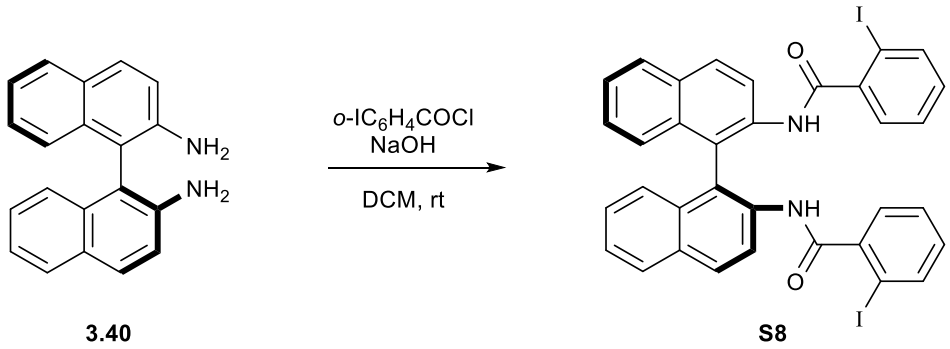
MS (ESI+) 723.0 found for $C_{30}H_{26}I_2N_2O_2Na^+$, 723.1 found.



***N*,*N*'-((1*R*,2*R*)-1,2-diphenylethane-1,2-diyl)bis(*N*-benzyl-2-iodobenzamide) (3.39b):**

Compound **S7** was made using the same procedure as was used to make **3.39b**.

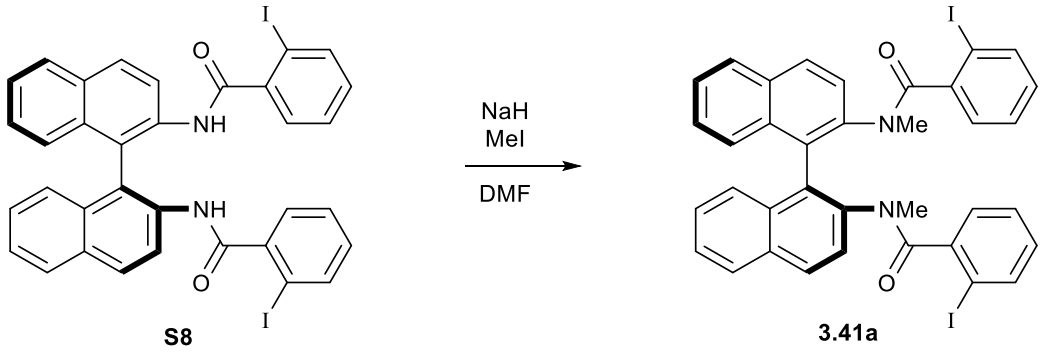
MS (ESI+) 875.0602 calc'd for $C_{42}H_{34}I_2N_2O_2Na^+$, 875.0668 found.



3.40 **S8**

(*S*)-*N*,*N*'-([1,1'-binaphthalene]-2,2'-diyl)bis(2-iodobenzamide) (S8):

R-BINAM (100 mg, 0.35 mmol, 1 eq.) was dissolved in DCM (3 mL). 2M NaOH (3 mL, 6 mmol, 15 eq.) was added followed by *o*-iodobenzoyl chloride. The mixture was stirred vigorously for 18h. The solid product was filtered and dried under vacuum. The product amide was isolated as a white solid (266.8 mg, 87%) and used directly in the next step.

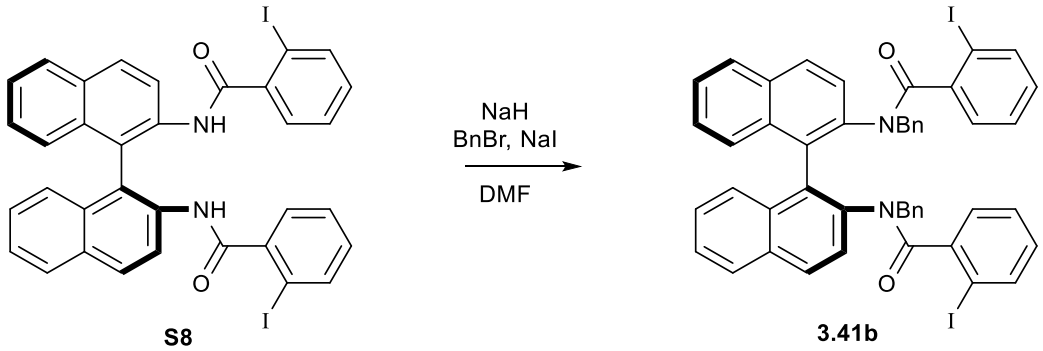


S8 **3.41a**

(*S*)-*N*,*N*'-([1,1'-binaphthalene]-2,2'-diyl)bis(2-iodo-*N*-methylbenzamide) (3.41a):

Bis-amide (**S8**) (50 mg, 0.067 mmol, 1 eq.) was dissolved in DMF (0.7 mL) and NaH (8 mg of a 60% dispersion in mineral oil, 0.2 mmol, 3 eq.) was added. The solution was stirred for 15 min. and MeI (30 mg, 0.2 mmol, 3 eq.) was added. The solution was stirred for 18 h. The reaction was quenched with H_2O (5 mL) and extracted with 3 x 2 mL EtOAc. The combined organic layers were washed with brine, dried with Na_2SO_4 and concentrated. Purification by f.c.c. (1:4 EtOAc:Hexane) gave the product as a white solid (33.1 mg, 64%). The product was confirmed by MS.

MS (ESI+) 794.9976 calc'd for $C_{36}H_{26}I_2N_2O_2Na^+$, 795.0 found.

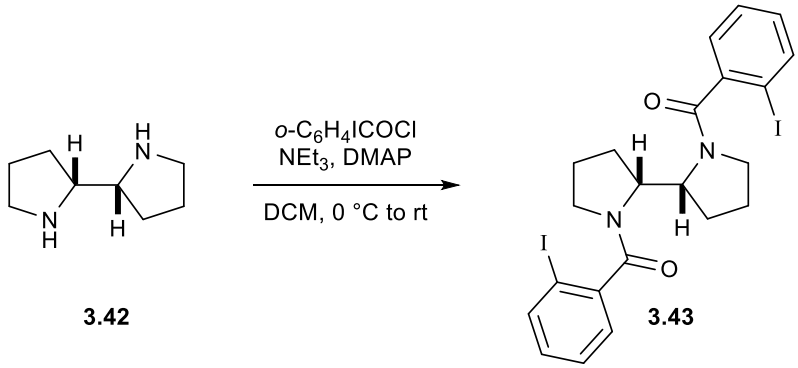


S8 3.41b

(*S*)-*N*,*N*'-([1,1'-binaphthalene]-2,2'-diyl)bis(*N*-benzyl-2-iodobenzamide) (xx):

Compound **S8** was synthesized on in the same manner using BnBr as the electrophile, along with 0.2 eq. NaI (~2 mg). Compound **xx** could be obtained after f.c.c. (1:4 EtOAc:Hexane) (22.7 mg, 37%). The compound was confirmed by mass spectrometry.

MS (ESI+) 947.0602 calc'd for $C_{48}H_{34}I_2N_2O_2Na^+$, 947.1 found.

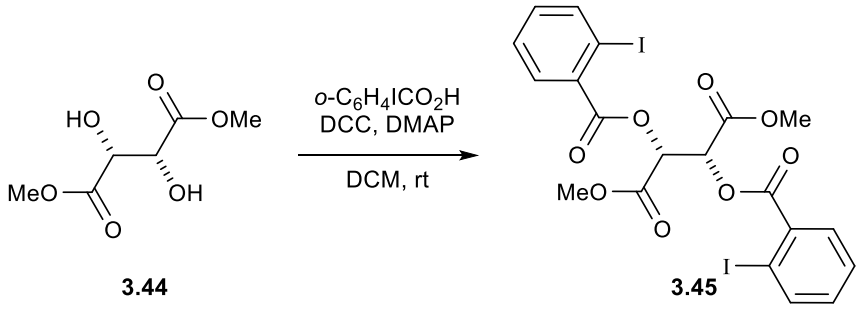


3.42 3.43

((2*R*,2'*R*)-[2,2'-bipyrrolidine]-1,1'-diyl)*bis*((2-iodophenyl)methanone) (3.43):

(2*R*,2'*R*)-2,2'-bipyrrolidine (30 mg, 0.214 mmol, 1 eq.) was dissolved in DCM. NEt_3 (87 mg, 0.856 mmol, 4 eq.) and DMAP (~10 mg) were added and the solution was cooled to 0 °C. *o*-Iodobenzoyl chloride (128.3 mg, 0.48 mmol, 2.25 eq.) was added and the solution was allowed to warm to rt and stirred overnight. The reaction was quenched with 5 mL $NaHCO_3$ and extracted with 3 x 2 mL DCM. The combined organic extracts were washed with brine, dried with Na_2SO_4 and concentrated. Purification by f.c.c. (1:4 EtOAc:Hexane) gave **3.43** as a white solid (77.5 mg, 60%).

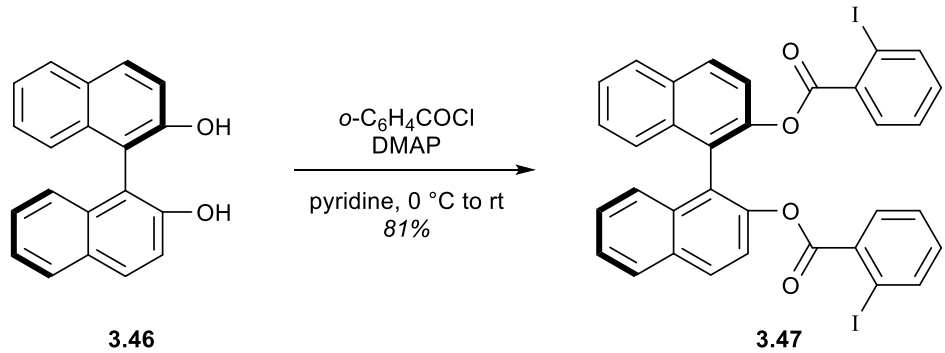
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (dd, *J* = 0.8, 8.0 Hz, 2H), 7.39 (dd, *J* = 1.6, 7.6 Hz, 2H), 7.28 (dd, *J* = 1.0, 7.5 Hz, 2H), 7.01 (dt, *J* = 1.6, 7.7 Hz, 2H), 4.61-4.60 (m, 2H), 3.55 (ddd, *J* = 4.4, 9.0, 10.6 Hz, 1H), 3.07 (td, *J* = 7.9, 10.6 Hz, 2H), 2.27-2.18 (m, 2H), 2.11-2.04 (m, 2H), 1.97 (dtd, *J* = 4.4, 8.0, 15.9 Hz, 2H), 1.81 (ddd, *J* = 3.4, 8.0, 12.0 Hz, 2H).



dimethyl (2*R*,3*R*)-2,3-*bis*((2-iodobenzoyl)oxy)succinate (3.45):

(+)-Dimethyl tartrate (250 mg, 2.8 mmol, 1 eq.), *o*-iodobenzoic acid (690 mg, 5.6 mmol, 2 eq.) and DMAP (35 mg, 0.28 mmol, 0.1 eq.) were suspended in DCM (8 mL) and cooled to 0 °C. DCC (580 mg, 5.6 mmol, 2 eq.) was added and the reaction mixture was stirred at rt for 18 h. The solid was filtered off and the resulting filtrate was washed with saturated $NaHCO_3$ (10 mL) and brine. The solution was dried with Na_2SO_4 and concentrated to give **3.45** as a white solid (635.5 mg, 36%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (dd, *J* = 1.1, 8.0 Hz, 2H), 7.96 (dd, *J* = 1.7, 7.8 Hz, 2H), 7.43 (dt, *J* = 1.2, 7.6 Hz, 2H), 7.20 (dt, *J* = 1.7, 7.7 Hz, 2H), 6.06 (s, 2H), 3.83 (s, 6H).
^{13}C NMR (125 MHz, $CDCl_3$, DEPT) δ 166.19 (C), 164.81 (C), 141.80 (CH), 133.61 (CH), 133.02 (C), 132.01 (CH), 128.26 (CH), 94.83 (C), 71.73 (CH), 53.49 (CH_3).



(*R*)-[1,1'-binaphthalene]-2,2'-diyl *bis*(2-iodobenzoate) (3.47):

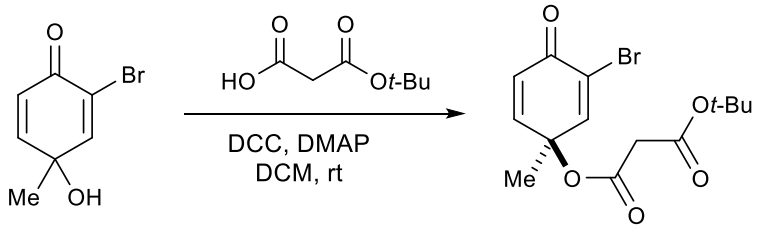
(*R*)-BINOL (50 mg, 0.175 mmol, 1 eq.) and DMAP (~10 mg) was dissolved in pyridine (0.6 mL) and cooled to 0 °C. *o*-Iodobenzoyl chloride was added and the reaction was stirred at rt for 24 h. The reaction was quenched with 10 mL H_2O. The aqueous layer was extracted with 3 x 5 mL DCM. The combined organic layers were washed with 10

mL 10% HCl and brine, dried with Na_2SO_4 and concentrated to give **3.47** as a white solid (106.4 mg, 81%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (d, *J* = 8.8 Hz, 2H), 7.95 (d, *J* = 8.2 Hz, 2H), 7.85-7.82 (m, 2H), 7.63 (d, *J* = 8.9 Hz, 2H), 7.47 (ddd, *J* = 1.7, 6.4 8.2 Hz, 2H), 7.42-7.32 (m, 4H), 7.09 (dt, *J* = 1.3, 7.5 Hz, 2H), 7.01 (dd, *J* = 1.9, 7.7 Hz, 2H), 6.95 (dd, *J* = 1.7, 6.7 Hz, 2H).

General Procedure for Enantioselective Dearomatization:

The appropriate phenol (amount) and catalyst (amount) were dissolved in MeCN:H_2O (3:1) (amount). *m*-CPBA was added and the solution was stirred for 18 h. The reaction was quenched with 2 mL 10% aq. $Na_2S_2O_3$ (2 mL) and saturated aq. $NaHCO_3$. The reaction was stirred for 15 min and extracted with 3 x 2 mL EtOAc. The combined organic fractions were dried with Na_2SO_4 and concentrated. The product was purified by f.c.c. (1:4 to 1:2 EtOAc:Hexane). The ee was determined by chiral HPLC (Compound **3.19**: 8% *i*-PrOH in Hexane, Chiralcel OD-H, 1 mL/min; Compound **3.72**: 10% *i*-PrOH in Hexane, Chiralcel OD-H, 1 mL/min.)

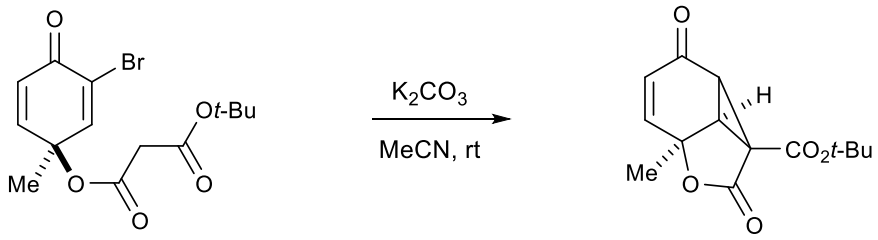


3.19 **3.13**

3-bromo-1-methyl-4-oxocyclohexa-2,5-dien-1-yl *tert*-butyl malonate (3.13):

Quinol **3.19** (2.56g, 12.6 mmol, 1 eq.), *t*-butyl malonate half ester (4.03g, 25.2 mmol, 2 eq.), and DMAP (154 mg, 0.126 mmol, 0.1 eq.) were dissolved in DCM (30 mL) and cooled to 0°C. DCC (5.20g, 25.2 mmol, 2 eq.) was added and the mixture was stirred overnight. The reaction mixture was diluted with DCM and filtered through celite. The organic filtrate was washed with saturated $NaHCO_3$ (25 mL). The organic layers were washed with brine, dried with Na_2SO_4 and concentrated. The compound was purified by f.c.c. (1:4 EtOAc:Hexane) to give a yellow solid (3.59g, 82%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (d, *J* = 2.93 Hz, 1H), 6.93 (dd, *J* = 2.9, 10.1 Hz, 1H), 6.37 (d, *J* = 10.1 Hz, 1H), 3.29 (s, 2H), 1.61 (s, 3H), 1.48 (s, 9H).

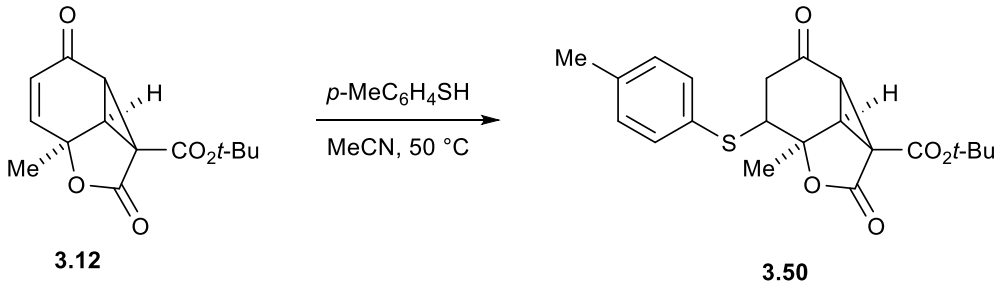


3.13 **3.12**

***tert*-butyl (2a1*S**,5a*S**)-5a-methyl-2,3-dioxo-2a1,2b,3,5a-tetrahydrocyclopropa[cd]benzofuran-2a(2H)-carboxylate (3.12):**

Malonate **3.13** (1.15g, 3.33 mmol, 1 eq.) was dissolved in MeCN and K_2CO_3 (460 mg, 3.33 mmol, 1 eq.) was added. The mixture was stirred overnight. The solution was diluted with ethyl acetate, filtered through a plug of florisil, and concentrated to give a yellow solid (844mg, 96%). The cyclopropane was used without further purification as it was found to be unstable to chromatographic purification.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.87 (dd, *J* = 0.2, 10.0 Hz, 1H), 6.19 (dd, *J* = 1.2, 9.8 Hz, 1H), 3.18 (dd, *J* = 0.2, 7.5 Hz, 1H), 3.03 (dd, *J* = 1.2, 7.5 Hz, 1H), 1.80 (s, 3H), 1.51 (s, 9H).

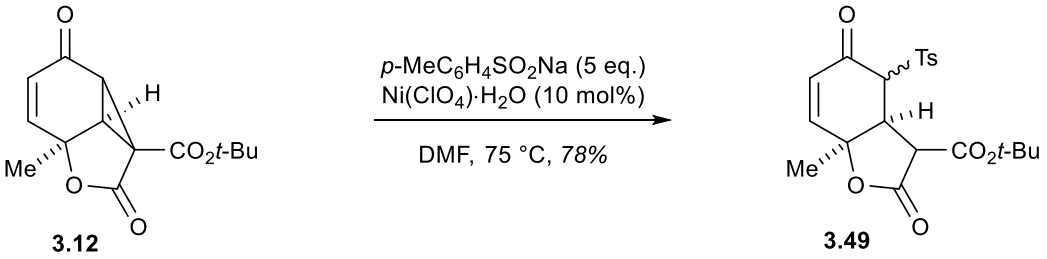


3.12 **3.50**

***tert*-butyl (2a1*S**,5a*R**)-5a-methyl-2,3-dioxo-5-(p-tolylthio)hexahydrocyclopropa[cd]benzofuran-2a(2H)-carboxylate (3.50):**

Cyclopropane **3.12** (10 mg, 0.038 mmol, 1 eq.) and *p*-toluenethiol (6 mg, 0.046 mmol, 1.2 eq.) were dissolved in MeCN (0.15 mL). The solution was heated to 50 °C for 1h 20 min. The solvent was removed and the compound was purified by f.c.c (1:2 EtOAc:Hexane) to give sulfide **3.50** (10 mg, 60%).

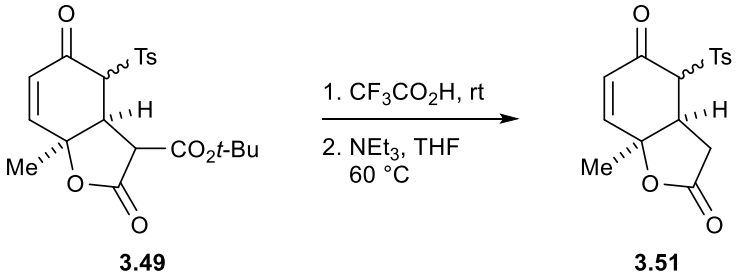
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34-7.32 (m, 2H), 7.17-7.15 (m, 2H), 3.56 (dd, *J* = 2.1, 4.6 Hz, 1H), 3.08 (d, *J* = 7.3 Hz, 1H), 2.84 (td, *J* = 1.0, 7.3 Hz, 1H), 2.66 (ddd, *J* = 0.7, 4.6, 18.7 Hz, 1H), 2.57 (ddd, *J* = 1.4, 1.9, 18.7 Hz, 1H), 2.35 (s, 3H), 1.88 (s, 3H), 1.50 (s, 9H).



***tert*-butyl (3a*S**,7a*S**)-7a-methyl-2,5-dioxo-4-tosyl-2,3,3a,4,5,7a-hexahydrobenzofuran-3-carboxylate (3.49):**

The cyclopropane **3.12** (844 mg, 3.19mmol, 1 eq.) and $Ni(ClO_4)_2 \cdot 6H_2O$ (116mg, 0.32 mmol, 0.1 eq.) were dissolved in DMF (13 mL). Sodium *p*-toluenesulfinate hydrate (1.70g, 9.58 mmol, 3 eq.) was added and the mixture was stirred at 75 °C for 3h. The reaction was cooled to room temperature and quenched with 50 mL of a 10% $NaHSO_4$ solution. The mixture was extracted with 3 x 25 mL EtOAc, washed with brine, dried with Na_2SO_4, filtered and concentrated giving a tan solid (893 mg, 67%) which was used without further purification.

IR (thin film) 2979, 2933, 2874, 1788, 1730, 1680, 1319, 1149 cm^{-1}.
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 – 7.67 (m, 2H), 7.39 (d, *J*=8.1 Hz, 2H), 6.79 (dd, *J*=1.8, 10.5 Hz, 1H), 6.21 (d, *J*=10.5 Hz, 1H), 4.13 (ddd, *J*=1.6, 1.6, 12.5 Hz, 1H), 3.99 (d, *J*=0.7 Hz, 1H), 3.27 (d, *J*=12.4 Hz, 1H), 2.48 (s, 3H), 2.01 (s, 3H), 1.50 (s, 9H).
^{13}C NMR (125 MHz, $CDCl_3$, DEPT**)** δ 186.33 (C), 167.30 (C), 164.18 (C), 147.76 (CH), 146.27 (C), 134.69 (C), 130.21 (CH), 129.16 (CH), 128.96 (CH), 84.48 (C), 79.50 (C), 70.01 (CH), 52.55 (CH), 43.27 (CH), 28.06 (CH_3), 25.67 (CH_3), 21.96 (CH_3).
HRMS (ESI+) 443.1135 calc'd for $C_{21}H_{24}O_7SNa^+$, found 443.1444.

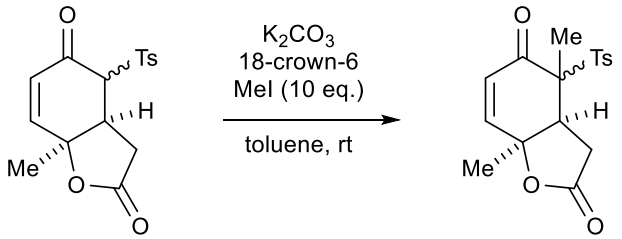


(3a*S,7a*S**)-7a-methyl-4-tosyl-3a,7a-dihydrobenzofuran-2,5(3H,4H)-dione (3.51):**

Sulfone ester **3.49** (893 mg, 2.12 mmol, 1 eq.) was dissolved in TFA (15 mL) and stirred at rt for 3 h. The TFA was removed under vacuum and the residue was dissolved in THF (15 mL). The solution was treated with NEt_3 (1.07g, 10.6 mmol, 5 eq.) and the solution was heated to 60 °C for 1.5 h. The reaction was cooled to rt and quenched with 75 mL of 10% $NaHSO_4$ solution. The mixture was extracted with 3 x 25 mL EtOAc.

The combined organic extracts were washed with brine, dried with Na_2SO_4, filtered, and concentrated to give a brown solid (454mg, 3:1 dr, 67%). The substrate was used without further purification.

IR (thin film) 2931.88, 1780.28, 1682.99, 1318.30, 1148.37 cm^{-1}.
^{1}H NMR (500 MHz, $CDCl_3$) **Major** δ 7.66-7.68 (m, 2H), 7.38-7.40 (m, 2H), 6.78 (dd, *J*=1.8, 10.5 Hz, 1H), 6.20 (d, *J*=10.4 Hz, 1H), 3.94 (d, *J*=1.2 Hz, 1H), 3.84 (dddd, *J*=1.6, 1.6, 9.2, 12.2 Hz, 1H), 2.89 (dd, *J*=9.2, 17.5 Hz, 1H), 2.45 (s, 3H), 2.40 (dd, *J*=12.4, 17.7 Hz, 1H), 1.99 (s, 3H). **Minor** δ 7.97-7.99 (m, 2H), 7.38-7.40 (m, 2H), 6.67 (dd, *J*=2.0, 10.2 Hz, 1H), 6.02 (d, *J*=10.2 Hz, 1H), 4.17 (d, *J*=4.7 Hz, 1H), 3.61 (dddd, *J*=2.0, 4.7, 8.2, 12.9 Hz, 1H), 3.07 (dd, *J*=8.3, 18.0 Hz, 1H), 2.69 (dd, *J*=12.4, 18.0 Hz, 1H), 2.46 (s, 3H), 1.73 (s, 3H).
^{13}C NMR (125 MHz, $CDCl_3$, DEPT) δ 186.61 (C), 171.95 (C), 147.68 (CH), 146.24 (C), 134.43 (C), 130.15 (CH), 129.16 (CH), 128.62 (CH), 81.15 (C), 7.45 (CH), 39.45 (CH), 35.43 (CH_2), 25.78 (CH_3), 21.95 (CH_3).
HRMS (ESI+) 343.0611 calc'd for $C_{16}H_{16}O_5SNa^+$, 343.0553 found.



3.51 **3.11**

(3a*S,7a*S**)-4,7a-dimethyl-4-tosyl-3a,7a-dihydrobenzofuran-2,5(3H,4H)-dione (3.11):**

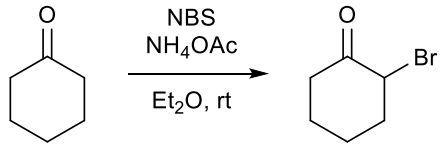
The sulfone (200 mg, 0.62 mmol, 1 eq.), 18-crown-6 (15 mg, 0.06 mmol, 0.1 eq.), K_2CO_3 (102 mg, 0.74 mmol, 1.2 eq.), and MeI (880 mg, 6.2 mmol, 10 eq.) were suspended in toluene (6.2 mL) and stirred for 18 h at which time an additional 100 mg K_2CO_3 and 15 mg 18-crown-6 was added. The reaction was stirred for an additional 24 h and quenched with 10 mL 10% aq. HCl. The reaction mixture was extracted with 3 x 10 mL DCM (NOTE: The product is much less soluble in EtOAc). The combined organic layers were washed with brine, dried with Na_2SO_4, filtered, and concentrated to give a brown solid (190.4 mg, 86% pure by ^{1}H NMR, 79%). This solid was used without further purification.

IR (thin film) 2927.38, 1787.09, 1773.95, 1302.40, 1145.34 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97-7.99 (m, 2H), 7.37-7.38 (m, 2H), 6.68 (dd, *J*=1.8, 10.3 Hz, 1H), 6.03 (d, *J*=10.2Hz, 1H), 3.30-3.23 (m, 2H), 3.08-3.01 (m, 1H), 2.46 (s, 3H), 1.78 (s, 3H), 1.51 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$, DEPT) δ 191.989 (C), 172.91 (C), 146.15 (CH), 145.77 (C), 133.76 (C), 131.76 (CH), 129.44 (CH), 127.55 (CH), 82.11 (C), 71.35 (C), 47.16 (CH), 34.44 (CH_2), 26.47 (CH_3), 23.65 (CH_3), 21.86 (CH_3).

HRMS (ESI+) 357.0767 calc'd for $C_{17}H_{18}O_5SNa^+$, 357.0782 found.

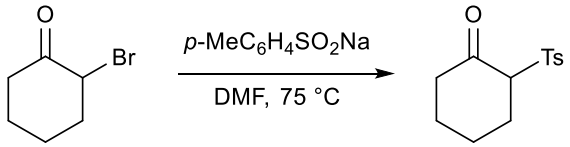


3.59 **3.60**

2-bromocyclohexan-1-one (3.59):

Cyclohexanone (1.00 g, 10.18 mmol, 1 eq.) and NBS (1.90 g, 10.68 mmol, 1.05 eq.) were suspended in Et_2O (10 mL). NH_4OAc (7 mg, 0.1 mmol, 0.1 eq.) was added and the reaction was stirred at rt for 30 min. The mixture was filtered and the filtrate was washed with H_2O, dried with Na_2SO_4 and concentrated. The product was 92% pure by ^{1}H NMR spectroscopy (1.62g, 90%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.44 (ddd, *J* = 1.4, 4.7, 6.2 Hz, 1H), 3.03-2.93 (m, 1H), 2.38-2.17 (m, 3H), 2.09-1.68 (m, 4H).

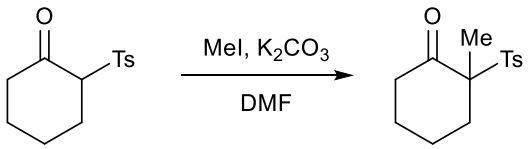


3.60 **3.61**

2-tosylcyclohexan-1-one (3.61):

2-Bromocyclohexan-1-one (500 mg, 2.82 mmol, 1 eq.) and sodium *p*-toluenesulfinate (1.5g, 8.47 mmol, 3 eq.) were combined in DMF (10 mL) and heated to 75 °C for 1 h. The solution was cooled to rt and quenched with 50 mL H_2). The mixture was extracted with 3 x 15 mL EtOAc. The combined organic extracts were washed with saturated $NaHCO_3$, 5% aqueous LiCl, and brine, dried with Na_2SO_4 and concentrated to give a product that was 92% pure by ^{1}H NMR spectroscopy (687.8 mg, 89%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77-7.75 (m, 2H), 7.35-7.33 (m, 2H), 3.81-3.79 (m, 1H), 2.82 (ddd, *J* = 5.7, 10.1, 14.5 Hz, 1H), 2.58-2.53 (m, 1H), 2.45-2.40 (m, 4H), 2.23-2.20 (m, 2H), 2.03-1.99 (m, 1H), 1.86-1.71 (m, 3H).

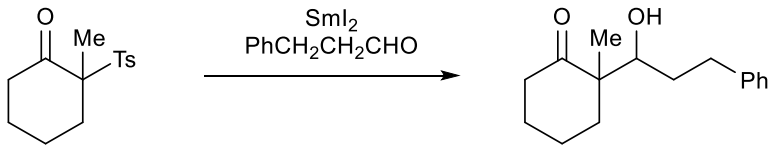


3.61 **3.62**

2-methyl-2-tosylcyclohexan-1-one (3.61):

Sulfone **3.61** (250 mg, 0.99 mmol, 1 eq.) was dissolved in DMF (4 mL). MeI (703 mg, 4.95 mmol, 5 eq.) and K_2CO_3 (274 mg, 1.98 mmol, 2 eq.) were added and the solution was stirred at rt for 18 h. The reaction was quenched with 20 mL H_2O and the mixture was extracted with 3 x 10 mL EtOAc. The combined organic fractions were washed with brine, dried with Na_2SO_4, and concentrated to give product **3.62** as a white solid (226mg, 72%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.3 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 3.14 (ddd, *J* = 6.5, 12.4, 14.9 Hz, 1H), 2.89-2.83 (m, 1H), 2.58-2.53 (m, 1H), 2.47-2.37 (m, 4H), 2.18-2.11 (m, 1H), 1.81-1.68 (m, 3H), 1.23 (s, 3H).



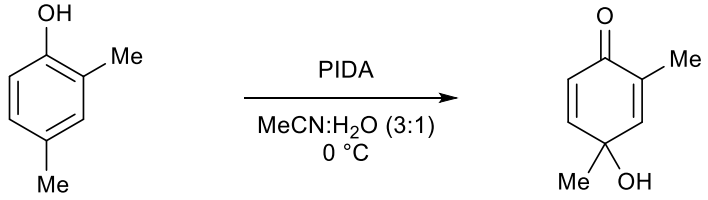
3.62 **3.63**

2-(1-hydroxy-3-phenylpropyl)-2-methylcyclohexan-1-one (3.63):

Sulfone **3.62** (10 mg, 0.037 mmol, 1 eq.) was dissolved in THF (0.2 mL) and cooled to –78 °C. SmI_2 (0.1M in THF, 1 mL, 0.1 mmol) was added (0.8 mL at first) dropwise. At this point, investigation by TLC revealed incomplete reaction. An additional 0.2 mL SmI_2 solution was added, at which time the reaction was deemed to be complete by TLC. The reaction was quenched with 0.2 mL saturated NH_4Cl and the mixture was passed through a florisil plug with EtOAc. The filtrate was washed with brine, dried

with Na_2SO_4, and concentrated. Purification by f.c.c (1:6 EtOAc:Hexane) gave the product (6 mg, 66%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30-7.27 (m, 2H), 7.23-7.17 (m, 3H), 3.79-3.76 (m, 1H), 3.51 (d, *J* = 3.3 Hz, 1H), 2.97 (td, *J* = 7.1, 13.6 Hz, 1H), 2.66-2.60 (m, 1H), 2.54 (ddd, *J* = 61, 12.6, 14.3 Hz, 1H), 2.30-2.35 (m, 1H), 2.02-1.96 (m, 1H), 1.78-1.6 (m, 6H), 1.19 (s, 3H).

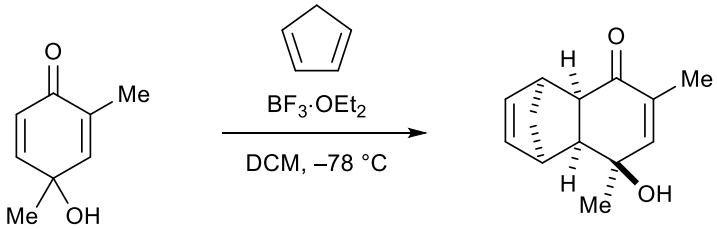


3.73

4-hydroxy-2,4-dimethylcyclohexa-2,5-dien-1-one (3.73):

2,4-Dimethylphenol (2.5 g, 20.46 mmol, 1 eq.) was dissolved in MeCN:H2O (100 mL 3:1 MeCN:H_2O) and cooled to 0 °C. Phenyliodine diacetate (PIDA) (7.25 g, 22.5 mmol, 1.1 eq.) was added in one portion and the solution was stirred at 0 °C for 1h. The solution was partially concentrated under vacuum and the residue was dissolved in EtOAc (50 mL) and quenched with saturated, aqueous $NaHCO_3$ (100 mL). The organic layer was separated and the aqueous layer was extracted with 2 x 50 mL of EtOAc. The combined organic fractions were washed with brine, dried with Na_2SO_4 and concentrated. The compound was purified by f.c.c (1:4 to 1:2 EtOAc:Hexane) to give compound **3.73** as a yellow, amorphous solid (1.85 g, 65%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.84 (dd, *J* = 3.1, 10.1 Hz, 1H), 6.64 (dd, *J* = 1.4, 3.0 Hz, 1H), 6.10 (d, *J* = 10.0 Hz, 1H), 2.10 (s, 1H), 1.86 (d, *J* = 1.3 Hz, 1H), 1.45 (s, 3H).



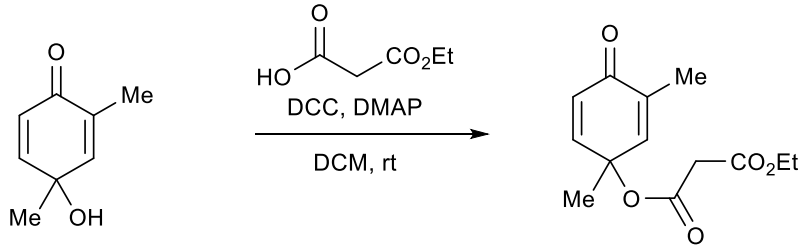
3.73 **3.74**

(1*R,4*S**,4a*R**,8*S**,8a*S**)-8-hydroxy-6,8-dimethyl-4,4a,8,8a-tetrahydro-1,4-methanonaphthalen-5(1H)-one (3.73):**

Cyclohexadienone **3.73** (250 mg, 1.81 mmol, 1 eq.) was dissolved in DCM (9 mL) and cooled to –78 °C. $BF_3{\cdot}OEt_2$ (282 mg, 2.0 mmol, 1.1 eq.) was added followed by

cyclopentadiene (239 mg, 3.62 mmol, 2 eq.). The reaction was stirred at –78 °C for 2 h. The reaction was quenched with saturated, aqueous $NaHCO_3$ (15 mL). The aqueous layer was extracted with 3 x 10 mL DCM. The combined organic layers were washed with brine, dried with Na_2SO_4, and concentrated. Purification by f.c.c. (1:2 EtOAc:Hexane) gave the product (265.6 mg, 72%).

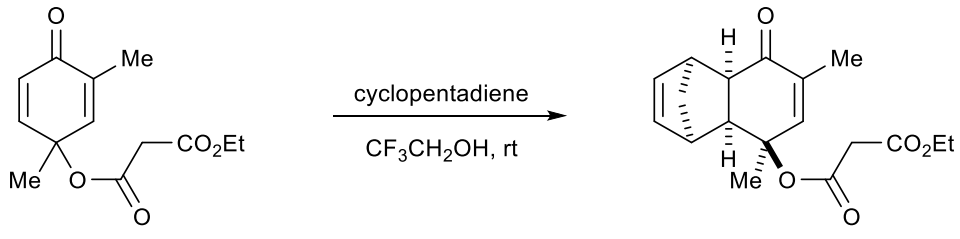
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.21 (t, *J* = 1.4 Hz, 1H), 6.10 (dd, *J* = 2.9, 5.6 Hz, 1H), 5.78 (dd, *J* = 2.9, 5.6 Hz, 1H), 3.32 (dq, *J* = 1.5, 2.7 Hz, 1H), 3.18 (d, *J* = 0.9 Hz, 1H), 3.02 (dd, *J* = 4.4, 8.9 Hz, 1H), 2.71 (ddd, *J* = 1.3, 3.5, 8.9 Hz, 1H), 1.79 (s, 1H), 1.62 (d, *J* = 1.5 Hz, 3H), 1.41 (td, *J* = 1.8, 8.4 Hz, 1H), 1.37 (s, 3H), 1.33 (d, *J* = 8.4 Hz, 1H).
^{13}C NMR (125 MHz, $CDCl_3$) δ 201.16, 149.51, 135.63, 135.24, 134.12, 69.66, 51.37, 49.25, 48.48, 48.29, 46.64, 35.30, 15.60.



3.73 **3.77**

1,3-dimethyl-4-oxocyclohexa-2,5-dien-1-yl ethyl malonate (3.76):

Quinol **3.73** (250 mg, 1.8 mmol, 1 eq.), monoethyl malonate (478 mg, 3.62 mmol, 2 eq.) and DMAP (22 mg, 0.18 mmol, 0.1 eq.) were dissolved in DCM (4.5 mL) and the solution was cooled in an ice bath. DCC (747 mg, 3.62 mmol, 2 eq.) was added. The ice bath was removed and the reaction was stirred at rt for 2 h. The solution was diluted with EtOAc and filtered through celite. The filtrate was washed with 10 mL saturated $NaHCO_3$. The organic layer was washed with brine, dried with Na_2SO_4, and concentrated. Purification by f.c.c. (1:4 to 1:2 EtOAc:Hexane) gave the product **3.77** (360.1 mg, 79%).
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.88 (dd, *J* = 3.1, 10.0 Hz, 1H), 6.67-6.66 (m, 1H), 6.22 (d, *J* = 10.0 Hz, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 3.35 (s, 2H), 1.90 (d, *J* = 1.5 Hz, 3H), 1.55 (s, 3H), 1.29 (t, *J* = 7.2 Hz, 3H).

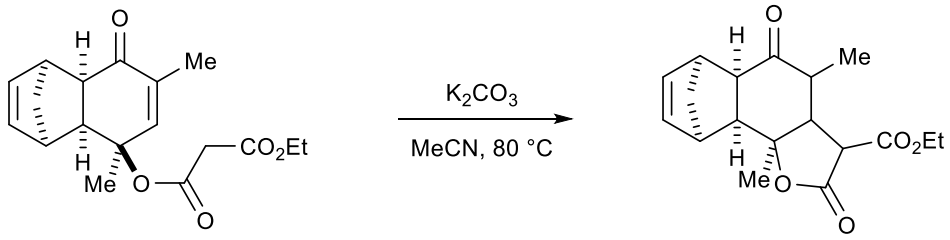


3.77 **3.75**

(1*S,4*R**,4a*S**,5*S**,8a*R**)-5,7-dimethyl-8-oxo-1,4,4a,5,8,8a-hexahydro-1,4-methanonaphthalen-5-yl ethyl malonate (3.75):**

Malonate **3.77** (200 mg, 0.792 mmol, 1 eq.) was dissolved in trifluoroethanol (0.8 mL). Cyclopentadiene (524 mg, 7.9 mmol, 10 eq.) was added. The reaction was protected from light and stirred for 48h. The solution was concentrated and purified by f.c.c. (1:4 to 1:2 EtOAc:Hexane) to give the product (182.9 mg, 73%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.39 (quint. *J* = 1.4 Hz, 1H), 5.96 (dd, *J* = 2.9, 5.5 Hz, 1H), 5.72 (dd, *J* = 2.8, 5.6 Hz, 1H), 4.21 (dq, *J* = 1.6, 7.2 Hz, 1H), 3.37 (s, 2H), 3.28 (ddd, *J* = 1.3, 2.6, 4.0 Hz, 1H), 3.17 (ddd, *J* = 1.4, 3.3, 8.7 Hz, 1H), 3.04-3.01 (m, 2H), 1.65 (s, 3H), 1.62 (d, *J* = 1.5 Hz, 3H), 1.37 (td, *J* = 1.8, 8.6 Hz, 1H), 1.34-1.32 (m, 1H), 1.28 (t, *J* = 7.2 Hz, 3H).
^{13}C NMR (125 MHz, $CDCl_3$, DEPT) δ 200.44 (C), 166.58 (C), 165.74 (C), 144.40 (CH), 136.22 (C), 135.52 (CH), 133.77 (CH), 82.17 (C), 61.73 (CH_2), 51.68 (CH), 49.02 (CH_2), 48.23 (CH), 47.42 (CH), 46.19 (CH), 42.88 (CH_2), 30.51 (CH_3), 15.47 (CH_3), 14.21 (CH_3).



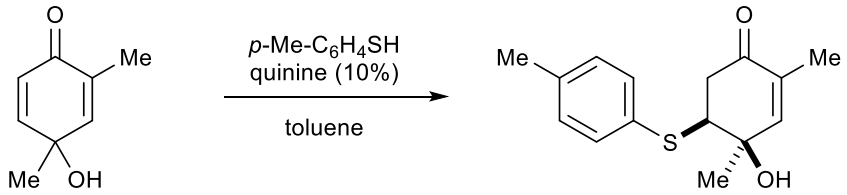
3.75 **3.78**

ethyl (5a*R,6*S**,9*R**,9a*S**,9b*S**)-4,9b-dimethyl-2,5-dioxo-2,3,3a,4,5,5a,6,9,9a,9b-decahydro-6,9-methanonaphtho[1,2-b]furan-3-carboxylate (3.78):**

Malonate **3.74** (44.6 mg, 0.14 mmol, 1 eq.) was dissolved in MeCN (1.4 mL) and K_2CO_3 (21.3 mg, 0.15, 1.1 eq.) was added. The reaction mixture was heated to 85 °C for 1.5 h. The reaction was quenched with 5 mL 10% $NaHSO_4$ solution. The aqueous layer was extracted with 3 x 5 mL EtOAc. The combined organic layers were washed with brine, dried with Na_2SO_4 and concentrated. Purification by f.c.c. (1:4 EtOAc: Hexane) to give the product as a yellow oil (43.4 mg, 97%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.27 (dd, *J* = 3.1, 5.7 Hz, 1H), 6.05-6.04 (m, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 3.26 (bs, 1H), 3.19 (dd, *J* = 5.1, 12.2 Hz, 1H), 3.18-3.16 (m, 1H), 3.08-3.07 (m, 2H), 2.82-2.78 (m, 1H), 2.78 (d, *J* = 12.2 Hz, 1H), 1.81 (s, 3H), 1.44 (td, *J* = 1.9, 8.6 Hz, 1H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.25-1.23 (m, 1H), 0.87 (d, *J* = 6.7 Hz, 3H).
^{13}C NMR (125 MHz, $CDCl_3$, DEPT) δ 210.46 (C), 170.47 (C), 168.06 (C), 138.57 (CH), 135.97 (CH), 84.26 (C), 62.48 (CH_2), 55.51 (CH), 53.78 (CH), 52.58 (CH), 50.48

(CH), 48.72 (CH_2), 46.61 (CH), 43.95 (CH), 42.37 (CH), 32.91 (CH_3), 14.10 (CH_3), 11.96 (CH_3).

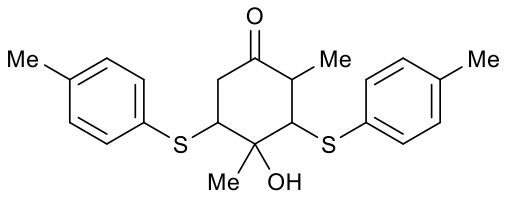


3.73 **3.80**

(4*R,5*S**)-4-hydroxy-2,4-dimethyl-5-(p-tolylthio)cyclohex-2-en-1-one (3.80):**

Quinol **3.72** (1.538 g, 10.41 mmol, 1 eq.) and quinine (170 mg, 0.52 mmol, 0.05 eq.) was dissolved in toluene (50 mL) and p-toluenethiol (1.357 g, 10.93 mmol,1.05 eq.) was added. The solution was stirred for8.5 h until all starting material had been consumed. The toluene was removed and the crude material was purified directly by f.c.c. (1:4 to 1:2 EtOAc:Hexane) to give compound **3.80** as a yellow oil which solidified upon standing (1.851 g, 64%).

IR (thin film) 3446, 3019, 2975, 2922, 1677, 1492, 1360, 1118 cm^{-1}.
^{1}H NMR (500 MHz, CDCl3) δ7.34-7.37 (m, 2H), 7.10-7.13 (m, 2H), 3.51-3.52 m, 1H), 3.51 (ddd, *J*=0.7, 5.3, 8.0 Hz, 1H), 3.10 (s, 1H), 2.93 (dd, *J*=8.1, 17.0 Hz, 1H), 2.81 (dd, *J*=4.5, 16.8 Hz, 1H), 2.32 (s, 3H), 1.76 (d, *J*=1.5 Hz, 3H), 1.55 (s, 3H).
^{13}C NMR (125 MHz, CDCl3, DEPT) δ 196.94 (C), 148.57 (CH), 138.45 (C), 135.35 (C), 133.46 (C), 130.28 (CH), 130.21 (CH), 70.36 (C), 59.07 (CH), 42.31 (CH2), 27.30 (CH3), 21.24 (CH3), 15.57 (CH3).
HRMS (ESI+) 285.0920 calc'd for $C_{15}H_{18}O_2SNa$, found 285.0907.



3.81

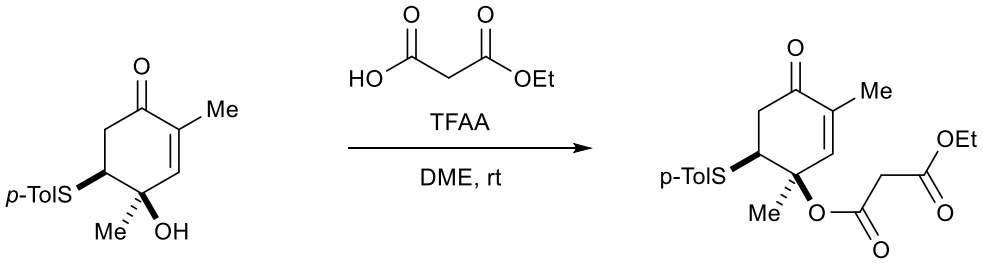
4-hydroxy-2,4-dimethyl-3,5-bis(p-tolylthio)cyclohexan-1-one (3.81):

Obtained as a side-product from previous reaction when NEt_3 was used as a base.
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36-7.34 (m, 2H), 7.29-7.27 (m, 2H), 7.13 (d, *J* = 7.9 Hz, 2H), 7.08 (d, *J* = 7.9 Hz, 2H), 3.73 (dd, *J* = 5.5, 12.9 Hz, 1H), 3.63-3.58 (m, 1H),

3.44 (d, *J* = 4.7 Hz, 1H), 2.69 (t, *J* = 13.6 Hz, 1H), 2.60 (dd, *J* = 5.5, 14.5 Hz, 1H), 2.49-2.49 (m, 1H), 2.34 (s, 3H), 2.31 (s, 3H), 1.62 (s, 3H), 1.17 (d, *J* = 6.5 Hz, 3H).

General Procedure for Sulfide Kinetic Resolution:

Quinol **3.72** and the catalyst (0.1 eq) were dissolved in toluene and cooled to 0 °C. *p*-Toluenethiol (0.4 eq.) was added and the mixture was stirred until the reaction had reached approximately 40% conversion (as determined by ^{1}H NMR spectroscopy of the reaction mixture). The mixture was quenched with 10% aq. HCl and extracted with EtOAc. The combined organic fractions were concentrated. The conversion was determined by ^{1}H NMR spectroscopy. The ee values were determined using chiral HPLC (CHIRALPAK AS, 7% EtOH in *i*-PrOH, 0.75 mL/min). The starting material eluted at 8.24 and 9.79 min. The sulfide product eluted at 8.95 and 10.51 min.



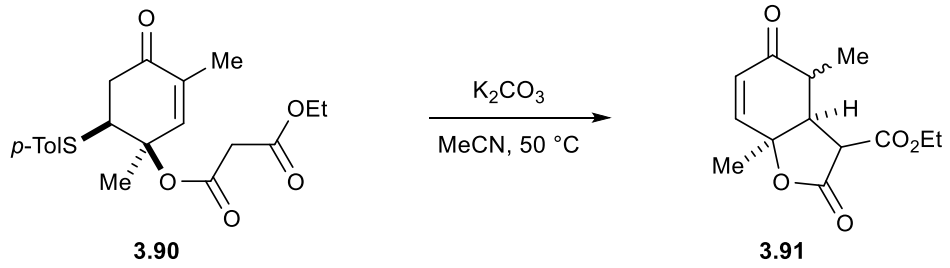
3.80 **3.90**

(1*R,6*S**)-1,3-dimethyl-4-oxo-6-(p-tolylthio)cyclohex-2-en-1-yl ethyl malonate (3.90):**

Monoethyl malonate (562 mg, 4.26 mmol, 3 eq.) was dissolved in freshly distilled TFAA (2.8 mL, 2 mL/mmol substrate). The reaction was stirred for 30 min. Excess TFAA was removed under high-vacuum. The resulting residue was dissolved in DME (7mL) and sulfide **3.80** (353.4 mg, 1.27 mmol, 1 eq.) was added. The reaction was stirred at rt for 24h. The reaction was quenched with 25 mL saturated $NaHCO_3$. The aqueous layer was extracted with 3 x 10 mL EtOAc. The combined organic extracts were washed with brine, dried with Na_2SO_4 and concentrated. Purification by f.c.c. (1:4 EtOAc:Hexane) gave the product as a colorless or yellow oil (338.8 mg, 71% yield).

IR (thin film) 2982, 1732, 1683, 1148 cm^{-1}.
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36-7.34 (m, 2H), 7.12-7.10 (m, 2H), 7.01 (d, *J* = 1.5 Hz, 1H), 4.20 (dq, *J* = 1.7, 7.2 Hz, 2H), 3.49 (dd, *J* = 4.4, 11.1 Hz, 1H), 3.33 (d, *J* = 1.3 Hz, 2H), 2.91 (dd, *J* = 11.1, 17.2 Hz, 1H), 2.76 (dd, *J* = 4.4, 17.2 Hz, 1H), 2.33 (s, 3H), 1.93 (s, 3H), 1.78 (d, *J* = 1.5 Hz, 3H) 1.27 (t, *J* = 7.2 Hz, 3H).
^{13}C NMR (125 MHz, $CDCl_3$, DEPT) δ 197.35 (C), 166.35 (C), 165.51 (C), 144.55 (CH), 138.52 (C), 136.74 (C), 134.00 (CH), 130.14 (C), 130.12 (CH), 80.41 (C), 61.82 (CH_2), 55.77 (CH), 42.18 (CH_2), 41.59 (CH_2), 24.01 (CH_3), 21.25 (CH_3), 15.54 (CH_3), 14.22 (CH_3).

HRMS (ESI+) 399.1237 calc'd for $C_{20}H_{24}O_5SNa^+$, 399.1236 found.

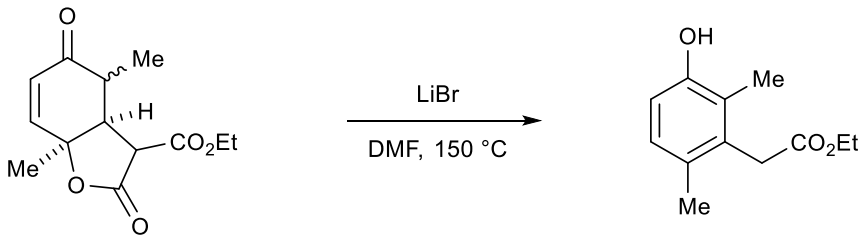


3.90 **3.91**

ethyl (3a*S,7a*S**)-4,7a-dimethyl-2,5-dioxo-2,3,3a,4,5,7a-hexahydrobenzofuran-3-carboxylate (3.91):**

Sulfide **3.90** (1256 mg, 0.33 mmol, 1 eq.) and K_2CO_3 (138.2 mg, 1.0 mmol, 3 eq.) were suspended in MeCN (1.7 mL). The solution was heated to 50 °C for 7h. The mixture was filtered through a plug of florisil (1:4 EtOAc :Hexane) to give the product (55.1 mg, 66%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.58 (dd, *J* = 2.0, 10.3 Hz, 1H), 6.04 (d, *J* = 10.3 Hz, 1H), 4.26-4.21 (m, 3H), 3.40 (ddd, *J* = 2.0, 5.0, 12.1 Hz, 1H), 3.27 (d, *J* = 12.2 Hz, 1H), 2.81 (dq, *J* = 5.0, 6.9 Hz, 1H), 1.73 (s, 3H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.07 (d, *J* = 69 Hz, 3H).
^{13}C NMR (125 MHz, $CDCl_3$, DEPT) δ 197.04 (C), 169.54 (C), 167.53 (C), 145.68 (CH), 129.16 (CH), 81.77 (C), 62.59 (CH_2), 51.44 (CH), 50.22 (CH), 40.33 (CH), 23.72 (CH_3), 14.04 (CH_3), 12.53 (CH_3).

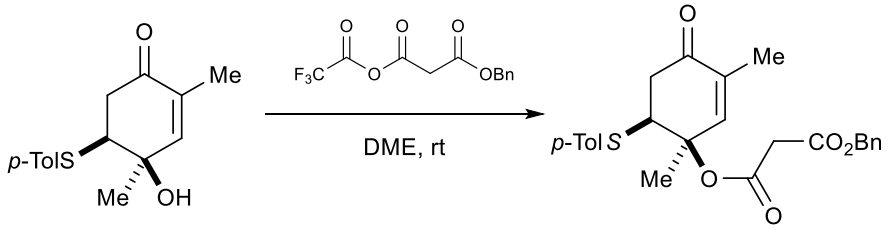


3.91 **3.94**

ethyl 2-(3-hydroxy-2,6-dimethylphenyl)acetate (xx):

Lactone **3.91** (20 mg, 0.08 mmol, 1 eq.) and LiBr (35 mg, 0.4 mmol, 5 eq.) were dissolved in DMF (0.4 mL) under N_2. The solution was heated to 150 °C for 1h. The reaction was quenched with 5 mL H_2O and extracted with 3 x 1 mL EtOAc. The combined organic layers were washed with brine, dried with Na_2SO_4 and concentrated. Purification by f.c.c. (1:4 to 1:2 EtOAc:Hexane) to give phenol **3.94** (9.8 mg, 57%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.88 (d, *J* = 8.1 Hz, 1H), 6.59 (d, *J* = 81 Hz, 1H), 4.82 (s, 1H), 4.15 (q, *J* = 7.1 Hz, 2H), 3.68 (s, 2H), 2.25 (s, 3H), 2.20 (s, 3H), 1.25 (t, *J* = 7.1 Hz, 3H).

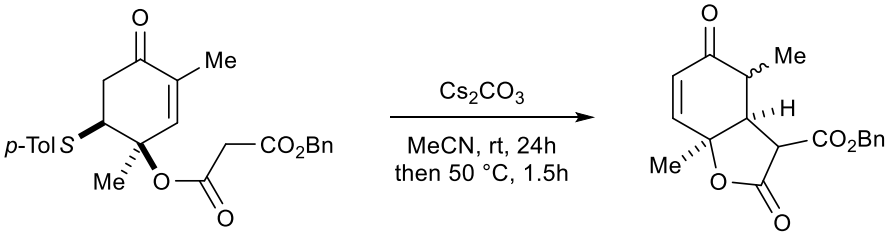


3.80 **3.96**

benzyl ((1*R,6*S**)-1,3-dimethyl-4-oxo-6-(p-tolylthio)cyclohex-2-en-1-yl) malonate (3.96):**

Compound **3.96** was synthesized using the same procedure as that which was used to synthesize **xx**. The reaction was performed with 250 mg sulfide **3.80** (0.90 mmol). The product was isolated by f.c.c. (1:6 to 1:4 EtOAc:Hexane) to give product **3.96** (390.78 mg, 99%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37-7.33 (m, 7H), 7.10 (d, *J* = 7.9 Hz, 2H), 6.97 (d, *J* = 1.4 Hz, 1H), 5.19 (s, 2H), 3.51-3.48 (m, 1H), 3.39 (s, 2H), 3.89 (dd, *J* = 11.0, 17.2 Hz, 1H), 2.74 (dd, *J* = 4.4, 17.2 Hz, 1H), 2.32 (s, 3H), 1.90 (s, 3H), 1.76 (d, *J* = 1.4 Hz, 3H).

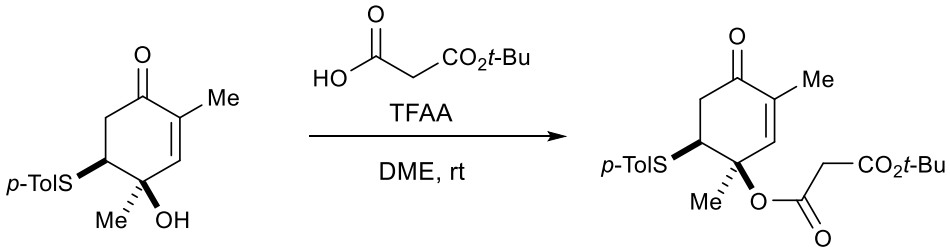


3.96 **3.97**

benzyl (3a*S,7a*S**)-4,7a-dimethyl-2,5-dioxo-2,3,3a,4,5,7a-hexahydrobenzofuran-3-carboxylate (3.97):**

Sulfide **3.96** (259 mg, 0.59 mmol, 1 eq.) and Cs_2CO_3 (576.7 mg, 1.77 mmol, 3 eq.) were suspended in MeCN (2.3 mL). The suspension was stirred at rt for 24h at which point the reaction was heated to 50 °C for 1.5 h. The reaction was cooled to rt and quenched with 10 mL H_2O. The solution was extracted with 3 x 5 mL EtOAc. The combined organic layers were washed with brine, dried with Na_2SO_4, and concentrated. The crude material was purified by f.c.c. (1:4 to 1:1 EtOAc:Hexane) to give the product (128.5 mg, 69%) as a 1:1.1 mixture of diastereomers.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38-7.33 (m, 10H), 6.66 (dd, *J* = 1.7, 10.3 Hz, 1H), 6.60 (dd, *J* = 2.0, 10.3 Hz, 1H), 6.07-6.04 (m, 2H), 529-5.20 (m, 4H), 3.48 (d, *J* = 11.2 Hz, 1H), 3.43 (ddd, *J* = 1.8, 2.7, 11.2 Hz, 1H), 2.80 (dq, *J* = 4.9, 69 Hz, 1H), 2.36 (dq, *J* = 2.7, 7.6 Hz, 1H), 1.75 (s, 2H), 1.74 (s, 3H), 1.32 (d, *J* = 7.6 Hz, 3H), 1.00 (d, *J* = 6.9 Hz, 3H).

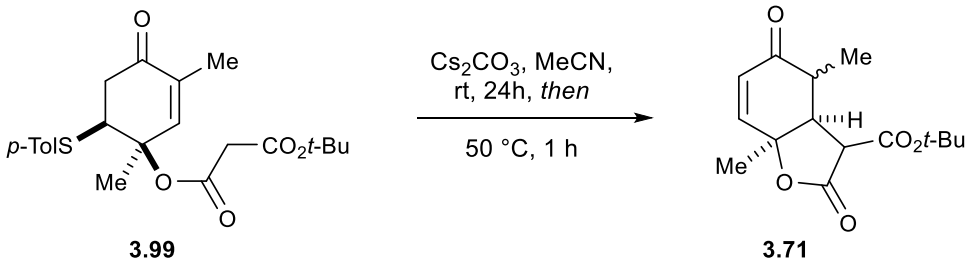


3.80 **3.99**

***tert*-butyl ((1*R**,6*S**)-1,3-dimethyl-4-oxo-6-(p-tolylthio)cyclohex-2-en-1-yl) malonate (3.99):**

t-Butyl malonate half ester (8.3 g (84 wt %), 43.4 mmol, 3 eq.) was dissolved in trifluoroacetic anhydride (TFAA) (29 mL, 2 mmol/mmol substrate). The solution was stirred for 45 minutes and excess TFAA and trifluoroacetic acid were distilled off under high vacuum. Compound **3.80** (4.00 g, 14.47 mmol, 1 eq.) was dissolved in ethylene glycol dimethyl ether (30 mL) and added to the solution at rt, and the solution was stirred for 18 h. The reaction was quenched with saturated, aqueous $NaHCO_3$ (50 mL) and extracted with 3 x 30 mL EtOAc. The combined organic layers were washed with brine, dried with Na_2SO_4, and concentrated. The compound was purified by f.c.c. (1:6 to 1:4 EtOAc:Hexane) to give compound **3.99** as a white solid. (4.177 g, 71%).

IR (thin film) 2979, 2925, 1728, 1684, 1368, 1331, 1145 cm^{-1}.
^{1}H NMR (500 MHz, CDCl3) δ 7.36 (app d, *J*=8.1 Hz, 2H), 7.11 (app. D, *J*=7.9 Hz, 2H), 7.03 (app d, *J*=1.3 Hz, 1H), 3.49 (dd, *J*=4.4, 11.1 Hz, 1H), 3.25 (s, 2H), 2.92 (dd, *J*=11.1, 17.1 Hz, 1H), 2.75 (dd, *J*=4.3, 17.3 Hz, 1H), 2.33 (s, 3H), 1.94 (s, 3H), 1.78 (s, 9H).
^{13}C NMR (125 MHz, CDCl3, DEPT) δ 197.34(C), 165.79(X), 165.39(C), 144.73(CH), 138.42(C), 136.53(C), 133.98(CH), 130.14(C), 130.05(CH), 82.36(C), 80.09(C), 43.44(CH_2), 41.54(CH_2), 28.07(CH_3), 23.96(CH_3), 21.20(CH_3), 15.46(CH_3).
HRMS (ESI+) 427.1550 calc'd for $C_{22}H_{28}O_5SNa^+$, 427.1456 found.

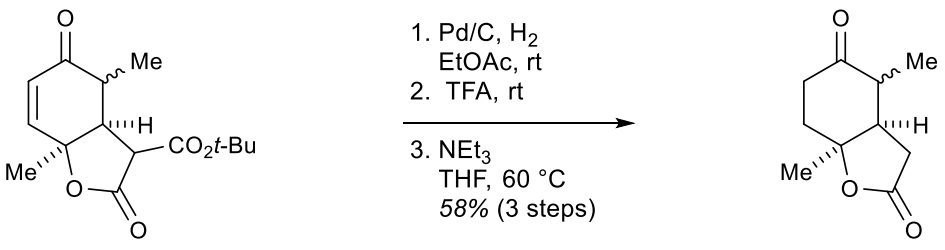


3.99 **3.71**

***tert*-butyl (3a*S**,7a*S**)-4,7a-dimethyl-2,5-dioxo-2,3,3a,4,5,7a-hexahydrobenzofuran-3-carboxylate (3.71):**

Compound **3.99** (1.00 g, 2.47 mmol, 1 eq.) was dissolved in MeCN (25 mL)and Cs_2CO_3 (2.41 g, 7.41 mmol, 3 eq.) was added. The reaction was stirred for 24 h until all starting material had been consumed. The flask was then fitted with a reflux condenser and heated to 50 °C for 1 h until all sulfide elimination was complete by TLC. The reaction was cooled to rt and quenched with saturated, aq. NH_4Cl (30 mL). The aqueous layer was extracted with 3 x 20 mL EtOAc. The combined organic layers were washed with brine and dried with Na_2SO_4. The solution was concentrated and the compound was purified by f.c.c. (1:6 to 1:4 EtOAc:Hexane) to give compound **xx** as an oil which solidified upon standing as a 1:1 mixture of diastereomers that was 93% pure by ^1H NMR spectroscopy (623.8 mg, 84%).

IR (thin film) 2978, 2935, 1783, 1728, 1685, 1150 cm^{-1}.
1H NMR (500 MHz, CDCl3) δ 6.64 (dd, *J*=1.8, 10.3 Hz, 1H), 6.58 (dd, *J*=2.1, 10.2 Hz, 1H), 3.36 (ddd, *J*=2.0, 5.0, 12.1 Hz, 1H), 3.31 (d, *J*=11.1 Hz, 1H), 3.18 (d, *J*=12.1 Hz, 1H), 3.04 (ddd, *J*=1.8, 2.7, 11.1 Hz, 1H), 2.81 (dq, *J*=5.3, 7.0 Hz, 1H), 2.61 (dq, *J*=2.9, 7.8 Hz, 1H), 1.72 (2 x s, 3H each), 1.48 (s, 9H), 1.47 (s, 9H), 1.32 (d, *J*=7.4 Hz, 3H), 1.11 (d, *J*=7.0 Hz, 3H).
13C NMR (125 MHz, CDCl3, DEPT) δ 198.56 (C), 197.32 (C), 169.96 (C), 169.08 (C), 166.54 (C), 165.56 (C), 145.93 (CH), 145.78 (CH), 129.14 (CH), 128.04 (CH), 83.79 (C), 83.43, (C), 81.50 (C), 79.77 (C), 54.04 (CH), 51.29 (CH), 51.14 (CH), 49.97 (CH), 42.15 (CH), 40.40 (CH), 28.01 (CH3), 27.85 (CH3), 27.01 (CH3), 23.80 (CH3), 18.32 (CH3), 12.64 (CH3).
HRMS (ESI+) 303.1203 calc'd for $C_{15}H_{20}O_5Na^+$, 303.1215 found.

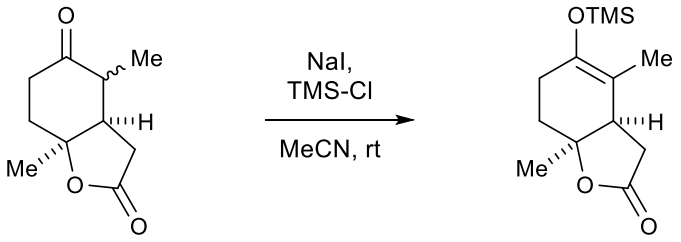


3.70 **3.95**

(3a*R,7a*S**)-4,7a-dimethyltetrahydrobenzofuran-2,5(3H,4H)-dione (3.95):**

Lactone **3.70** (403 mg, 1.44 mmol, 1 eq.) and 10 wt. % Pd/C (Aldrich, 100 mg, 25 wt% was suspended in ethyl acetate (15 mL) and placed under a H_2 atmosphere (balloon). The reaction was stirred for 1h (on some runs, additional Pd/C needed to be added to achieve complete reaction). The mixture was filtered through celite and concentrated. The resulting material was dissolved in TFA (10 mL) and stirred for 45 min. When the reaction was complete by TLC, the TFA was removed under vacuum and dissolved in THF (10 mL). NEt_3 (728 mg, 7.2 mmol, 5 eq.) was added and the reaction was heated to 60 ^oC for 2h. The solution was cooled to room temperature and quenched with 25 mL 10% HCl. The organic layer was extracted with 3 x 10 mL EtOAc. The combined organic extracts were washed with brine, dried with Na_2SO_4, and concentrated. The residue was purified by f.c.c. (1:1 EtOAc:Hexane) as a tan solid (153 mg, 58%, mixture of diastereomers).

IR (thin film) 2973.70, 2935.35, 1766.23, 1715.42 cm^{-1}.
^{1}H NMR (500 MHz, $CDCl_3$) δ 3.02(dd, *J*=8.9, 18.3 Hz, 1H), 2.67-2.76(m, 4.4H), 2.56(ddd, *J*=5.2, 6.2, 17.1 Hz, 1H), 2.49 (dd, *J*= 3.0, 18.3 Hz, 1H), 2.34-2.45(m, 4H), 2.06-2.30(m, 9H), 1.62(s, 4.3H), 1.43(s, 3H), 1.07(d, *J*=6.5 Hz, 3H), 1.04(d, *J*=6.4 Hz, 4.3 H).
^{13}C NMR (125 MHz, $CDCl_3$, DEPT) δ 210.84(C), 210.59(C), 175.28(C), 175.28(C), 174.75(C), 85.16(C), 84.51(C), 47.06(CH), 45.34(CH), 45.27(CH), 43.07(CH), 35.70(CH_2), 35.25(CH_2), 34.76(CH_2), 33.36(CH_2), 32.99(CH_2), 32.07(CH_2), 28.28(CH_3), 26.80(CH_3), 12.57(CH_3), 12.23(CH_3).
HRMS (ESI+) 205.0835 calc'd for $C_{10}H_{14}O_3Na^+$, 205.0834 found.



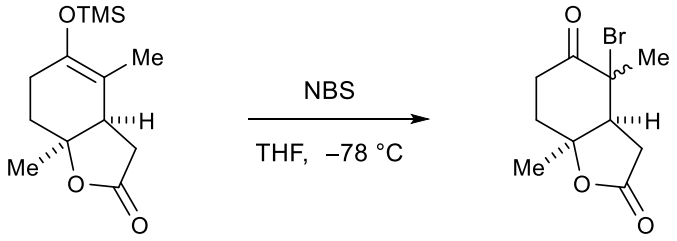
3.95 **3.69**

(3a*R,7a*S**)-4,7a-dimethyl-5-((trimethylsilyl)oxy)-3a,6,7,7a-tetrahydrobenzofuran-2(3H)-one (3.69):**

Lactone **3.95** (364 mg, 1.94 mmol, 1 eq.) was dissolved in anhydrous MeCN (8 mL) along with NaI (350 mg, 2.33 mmol, 1.2 eq.), which had been dried overnight at 110 ^oC. NEt_3 (236 mg, 2.33 mmol, 1.2 eq.) was added followed by TMS-Cl (253 mg, 2.33 mmol, 1.2 eq.). The mixture was stirred at rt for 2.5 h and was quenched with saturated NH_4Cl (25 mL) and extracted with 3 x 10 mL EtOAc. The combined organic fractions

were dried with Na_2SO_4, filtered, and concentrated to give a brown solid (405 mg, 82%) which was used without further purification.

IR (thin film) 2958, 2933, 1776, 1718, 1683, 1182, 1147, 846 cm^{-1}.
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.30 (s, 1H), 2.87 (dd, *J*=8.5, 17.4 Hz, 1H), 2.61 (t, *J*= 7.5 Hz, 1H), 6.71 (dd, *J*=6.4, 17.5 Hz, 1H), 2.18-2.42 (m, 1H), 1.95-2.01 (m, 1H), 1.76-1.81 (m, 1H), 1.55-1.56 (m, 3H), 1.43 (s, 3H), 0.17 (s, 9H).
^{13}C NMR (500 MHz, $CDCl_3$, DEPT) δ 174.50 (C), 144.19 (C), 110.29 (C), 82.81 (C), 45.69 (CH), 35.56 (CH_2), 32.38 (CH_2), 27.15 (CH_2), 25.21 (CH_3), 14.58 (CH_3), 0.57 (CH_3).
HRMS (ESI+) 277.1230 calc'd for $C_{13}H_{22}O_3SiNa^+$ 277.1159 found.



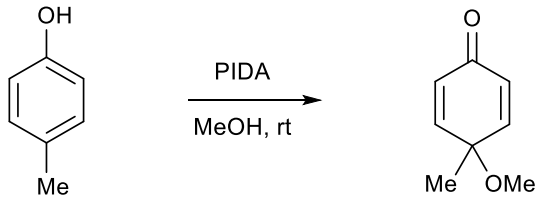
3.68 **3.69**

(3a*S,7a*S**)-4-bromo-4,7a-dimethyltetrahydrobenzofuran-2,5(3H,4H)-dione (3.69):**

The silyl-enol ether **3.68** (167 mg, 0.65 mmol, 1 eq.) was dissolved in anhydrous THF (6.5 mL) which was cooled to 0 °C. NBS (178 mg, 0.68 mmol, 1.05 eq.) was added. The mixture was stirred for 15 minutes and quenched with 15 mL of a 1:1 mixture of saturated $NaHCO_3$ and $Na_2S_2O_3$. The aqueous layer was extracted with 3 x 10 mL EtOAc. The combined organic layers were washed with brine, dried with Na_2SO_4, filtered, and concentrated to give the product (96 mg, 56%) as a white solid.

IR (thin film) 2978, 2953, 1768, 1718, 1271, 1093, 957 cm^{-1}.
^{1}H NMR (500 MHz, $CDCl_3$) δ 3.21 (t, *J*=10.4 Hz, 1H), 2.81-2.90 (m, 2H), 2.71 (ddd, *J*=4.6, 11.4, 14.8 Hz, 1H), 2.29 (ddd, *J*=5.4, 11.6, 18.4 Hz, 1H), 2.16-2.24 (m, 2H), 1.82 (s, 3H), 1.77 (s, 3H).
^{13}C NMR (125 MHz, $CDCl_3$, DEPT) δ 201.21 (C), 172.30 (C), 84.63 (C), 58.76 (C), 52.82 (CH), 34.24 (CH_2), 32.85 (CH_2), 32.63 (CH_2), 29.19 (CH_3), 26.47 (CH_3).
HRMS (ESI+) 282.9940 calc'd for $C_{10}H_{13}BrO_3Na^+$, 282.9935.

CHAPTER 4 EXPERIMENTAL

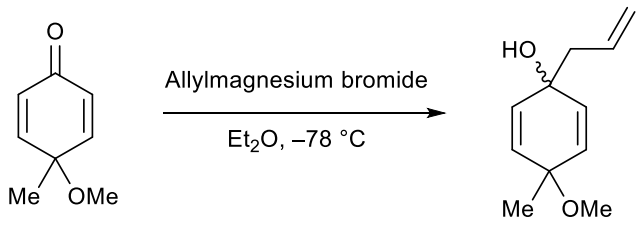


4.9b

4-methoxy-4-methylcyclohexa-2,5-dien-1-one (4.9b):

p-Cresol (1.00 g, 9.25 mmol, 1 eq.) was dissolved in MeOH (46 mL). PIDA (3.13 g, 9.7 mmol, 1.05 eq.) was added. The reaction was stirred at rt for 1.5 h. The reaction mixture was concentrated and quenched with 100 mL saturated $NaHCO_3$. The mixture was extracted with 3 x 50 mL EtOAc, washed with brine, dried with Na_2SO_4, and concentrated. The crude material was purified by f.c.c. (1:4 EtOAc:Hexane) to give the product as a yellow oil that solidified upon standing (729.2 mg, 64%)

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.76 (d, *J* = 8.4 Hz, 2H), 6.31 (d, *J* = 8.1 Hz, 2H), 3.19 (s, 3H), 1.42 (s, 3H).

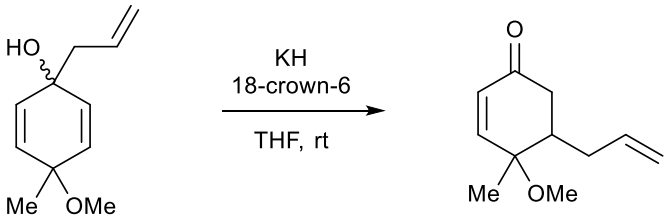


4.9b **4.10**

1-allyl-4-methoxy-4-methylcyclohexa-2,5-dien-1-ol (4.10):

Cyclohexadienone **4.9b** (722.3 mg, 5.22 mmol, 1 eq.) was dissolved in Et_2O and cooled to –78 °C. Allylmagnesium bromide was added dropwise and stirred at –78 °C for 1h. The reaction was quenched with 100 mL saturated NH_4Cl. The system was extracted with 3 x 30 mL EtOAc. The combined organic layers were washed with brine, dried with Na_2SO_4 and concentrated. The product was isolated as a 1:1 mixture of diastereomers (704.1 mg, 75%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.98-5.96 (m, 2H), 5.92-5.89 (m, 2H), 5.83-5.77 (m, 1H), 5.70-5.66 (m, 5H), 5.13-5.06 (m, 4H), 3.12 (s, 3H), 3.05 (s, 3H), 2.38 (td, *J* = 1.1, 7.4 H, 2H), 2.34 (td, *J* = 1.1, 7.4 Hz, 2H), 1.79 (s, 1H), 1.70 (s, 1H), 1.31 (s, 3H), 1.24 (s, 3H).

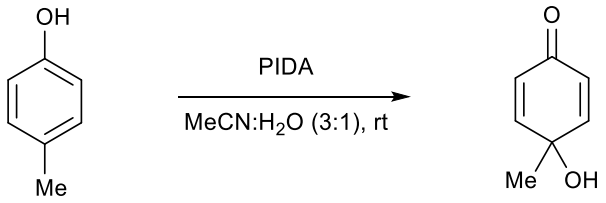


4.10 **4.11**

5-allyl-4-methoxy-4-methylcyclohex-2-en-1-one (xx):

Alcohol **4.10** (25 mg, 0.14 mmol, 1 eq.) and 18-crown-6 (45 mg, 0.17 mmol, 1.2 eq.) were dissolved in THF (1.4 mL). KH (38 mg, 0.28 mmol, 2 eq.) was added and the reaction was stirred at rt for 8 h. The reaction was quenched with H_2O (5 mL) and extracted with 3 x 2 mL EtOAc. The combined organic layers were dried with Na_2SO_4 and concentrated. The reaction was found to have proceeded to only 54% conversion by ^{1}H NMR spectroscopy. Purification by f.c.c (1:10 to 1:4 EtOAc:Hexane) gave the product in a 1:4 dr (2.5 mg, 10%).

^{1}H NMR (major isomer) (500 MHz, $CDCl_3$) δ 6.85 (d, *J* = 10.3 Hz, 1H), 6.01 Hz, dd, *J* = 1.2, 10.3 Hz, 1H), 5.79-5.68 (m, 1H), 5.10-5.08 (m, 1H), 5.07-5.06 (m, 1H), 3.25 (s, 3H), 2.65 (ddd, *J* = 1.2, 4.2, 17.1 Hz, 1H), 2.52 (dd, *J* = 9.1, 17.2 Hz, 1H), 2.50-2.41 (m, 2H), 2.09 (dd, *J* = 13.2, 17.1 Hz, 1H), 1.87-1.80 (m, 1H), 1.25 (s, 3H).



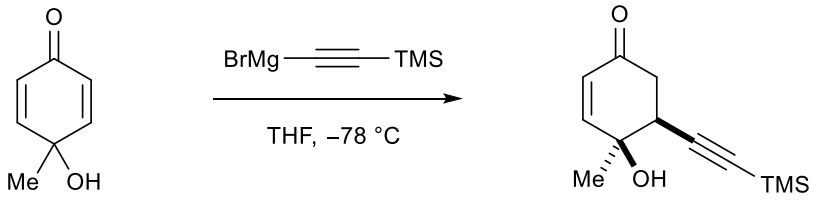
4.9a

4-hydroxy-4-methylcyclohexa-2,5-dien-1-one (4.9a):

p-Cresol (3.00g, 27.7 mmol, 1 eq.) was dissolved in 140 mL of a mixture of MeCN:H_2O (3:1). PIDA (9.4g, 29.1 mmol, 1.05 eq.) was added and the reaction was stirred for 1h. When the reaction was complete by TLC, the mixture was partially concentrated by rotary evaporation and quenched with 50 mL 10 wt.% $Na_2S_2O_3$ solution and 200 mL of H_2O. The aqueous layer was extracted with 3 x 100 mL EtOAc. The combined organic

layers were washed with brine, dried with Na_2SO_4, filtered, and concentrated. Purification by f.c.c. (1:4 to 1:1 EtOAc:Hexane) gave a yellow solid (1.49g, 39%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.90-6.86 (m, 2H), 6.14-6.11 (m, 2H), 2.23 (s, 1H), 1.48 (s, 3H).

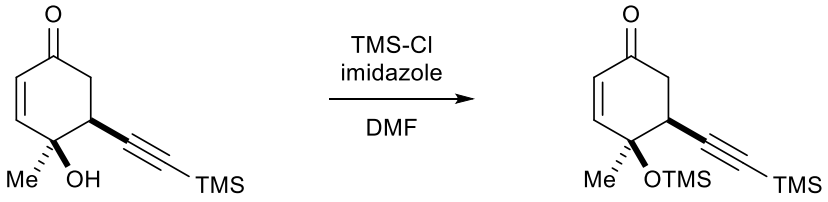


4.9a **4.12**

(4*S,5*S**)-4-hydroxy-4-methyl-5-((trimethylsilyl)ethynyl)cyclohex-2-en-1-one (4.12):**

TMS acetylene (2.13 g, 21.7 mmol, 3 eq.) was dissolved in 50 mL of anhydrous THF and cooled to 0 °C. EtMgBr (7.23 mL of a 3M sol'n, 21.7 mmol, 3 eq.) was added. The solution was stirred for 1 h and cooled to −78 °C. In a separate flask, quinol **4.12** (1.00 g, 7.24 mmol, 1 eq.) was dissolved in 25 mL of anhydrous THF. The quinol solution was added to the cold acetylide solution via cannula and stirred at −78 °C for 15 min. The solution was then warmed to rt for 2 h. The reaction was quenched by adding 100 mL of a saturated NH_4Cl solution to the reaction mixture. The organic layer was extracted with 3 x 50 mL EtOAc. The combined organic layers were washed with brine, dried with Na_2SO_4, filtered, and concentrated. The product was purified by f.c.c. (1:4 EtOAc:Hexane) to give the product (1.17 g, 72%).

IR (thin film) 3455, 2961, 2899, 2175, 1681, 1250, 1129, 843 cm^{-1}.
^{1}H NMR δ 6.67 (dd, *J*=0.6, 10.2 H, 1H), 5.92(d, *J*=10.2 Hz, 1H), 3.08(ddd, *J*=0.3, 4.6, 8.0 Hz, 1H), 2.75(dd, *J*=8.1, 16.7 Hz, 1H), 2.61(bs, 1H), 2.59(dd, *J*=4.7, 16.8Hz, 1H), 1.50(s, 3H), 0.14(s, 9H).
^{13}C NMR (125 MHz, $CDCl_3$, DEPT) δ 196.64(C), 152.18(CH), 128.48(CH), 103.46(C), 90.85(C), 68.38(C), 40.70(CH), 39.84(CH_2), 26.64(CH_3), 0.03(CH_3).
HRMS (ESI+) 245.0968 calc'd for $C_{12}H_{18}O_2SiNa^+$, 245.0987 found.

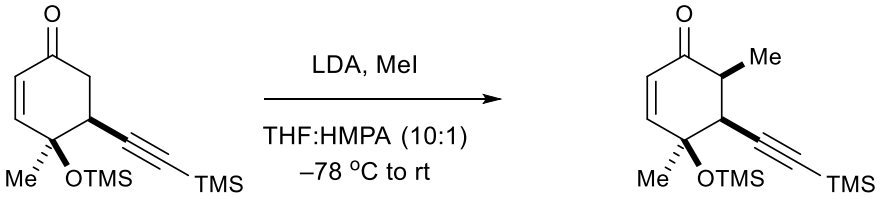


4.12 **4.13**

(4*S,5*S**)-4-methyl-5-((trimethylsilyl)ethynyl)-4-((trimethylsilyl)oxy)cyclohex-2-en-1-one (4.13):**

Alkyne **4.12** (376.7 mg, 1.69 mmol, 1 eq.) and imidazole (460 mg, 6.76 mmol, 4 eq.) were dissolved in DMF (5.6 mL). TMS-Cl (367.2 mg, 3.38 mmol, 2 eq.) was added and the solution was stirred at rt for 30 min. The reaction was quenched with 50 mL H_2O and extracted with 3 x 20 mL EtOAc. The combined organic fractions were washed with brine, dried with Na_2SO_4 and concentrated. Purification by f.c.c. (1:10 EtOAc:Hexane) gave compound **4.13** as an off-white solid (374.2 mg, 75%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.70 (d, *J* = 10.1 Hz, 1H), 5.86 (dd, *J* = 0.9, 10.1 Hz, 1H), 2.89 (dd, *J* = 3.0, 11.4 Hz, 1H), 2.84 (dd, *J* = 11.4, 15.8 Hz, 1H), 2.52 (ddd, *J* = 0.9, 3.0, 15.8 Hz, 1H), 1.55 (s, 3H), 0.15 (s, 18H).
^{13}C NMR (125 MHz, $CDCl_3$, DEPT) δ 198.24 (C), 152.81 (CH), 127.80 (CH), 105.22 (C), 87.84 (C), 70.52 (C), 41.06 (CH), 39.83 (CH_2), 27.86 (CH_3), 2.51 (CH_3), 0.17 (CH_3).

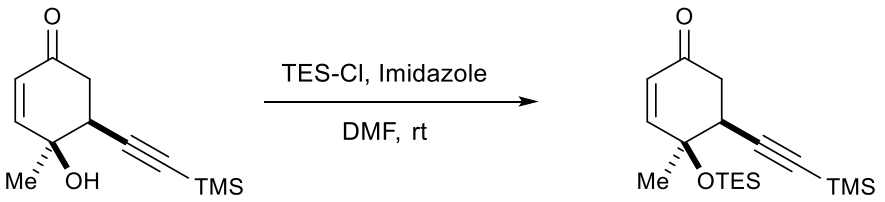


4.13 **4.14**

(4*S, 5*S**, 6*S**)-4,6-dimethyl-5-((trimethylsilyl)ethynyl)-4-((trimethylsilyl)oxy)cyclohex-2-en-1-one (4.14):**

Enone **4.13** (25 mg, 0.085 mmol, 1 eq.) was dissolved in THF:HMPA (0.9 mL, 10:1 THF:HMPA) and cooled to –78 °C. Freshly-prepared LDA (1M in THF, 0.1 mL, 0.1 mmol, 1.25 eq.) was added. The solution was stirred for 1h at –78 °C and MeI (18 mg, 0.13 mmol, 1.5 eq.) was added. The reaction was allowed to warm to rt for 3.5 h. The reaction was quenched with 5 mL saturated NH_4Cl and extracted with 3 x 2 mL EtOAc. The combined organic fractions were washed with brine, dried with Na_2SO_4 and concentrated. Purification by f.c.c. (1:10 EtOAc:Hexane) gave the product, which contained ~10% starting material (16.7 mg, 57%)

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.64 (dd, *J* = 1.7, 10.3 Hz, 1H), 5.84 (d, *J* = 10.3 Hz, 1H), 3.03 (dd, *J* = 1.7, 4.4 Hz, 1H), 2.61 (dq, *J* = 4.4, 6.8 Hz, 1H), 1.53 (s, 3H), 1.26 (d, *J* = 6.8 Hz, 3H), 0.20 (s, 9H), 0.10 (s, 9H).

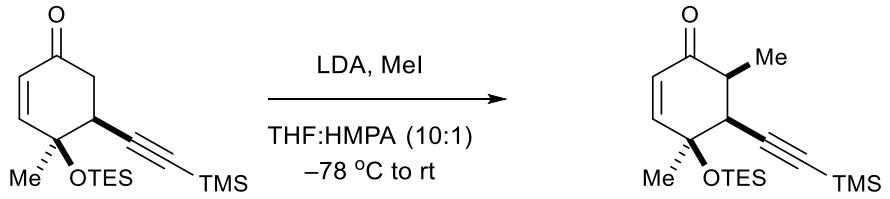


4.12 **S1**

(4*S,5*S**)-4-methyl-4-((triethylsilyl)oxy)-5-((trimethylsilyl)ethynyl)cyclohex-2-en-1-one (S1):**

Enone **4.12** (1.19 g, 5.37 mmol, 1 eq.) and imidazole (1.46 g, 21.48 mmol, 4 eq.) were dissolved in DMF (18 mL). TES-Cl (1.62 g, 10.74 mmol, 2 eq.) was added and the solution was stirred at rt for 3 h. The reaction mixture was quenched with water (100 mL) and extracted with 3 x 20 mL EtOAc. The combined organic layers were washed with brine, dried with Na_2SO_4, and concentrated. The residue was purified by f.c.c. (1:20 EtOAc:Hexane) to give the product (1.25 g, 66%) as a colorless oil.

IR (thin film) 2958, 2912, 2877, 2178, 1693, 1458, 1412, 1249, 1116, 1013, 842, 728 cm^{-1}.
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.71 (d, *J*=10.1 Hz, 1H), 5.86 (d, *J*=10.1 Hz, 1H), 2.86-2.93 (m, 2H), 2.51-2.57 (m, 1H), 1.55 (s, 3H), 0.96 (t, *J*=7.9 Hz, 9H), 0.57-0.66 (m, 6H), 0.15 (s, 9H).
^{13}C NMR (125 MHz, $CDCl_3$, DEPT) δ 198.30 (C), 152.80 (CH), 127.95 (CH), 105.09 (C), 87.87 (C), 69.87 (C), 41.76 (CH), 39.82 (CH_2), 28.01 (CH_3), 7.12 (CH_3), 6.84 (CH_2), 0.90 (CH_3).
HRMS (ESI+) 359.1833 calc'd for $C_{18}H_{32}O_2Si_2Na^+$, 359.1840 found.

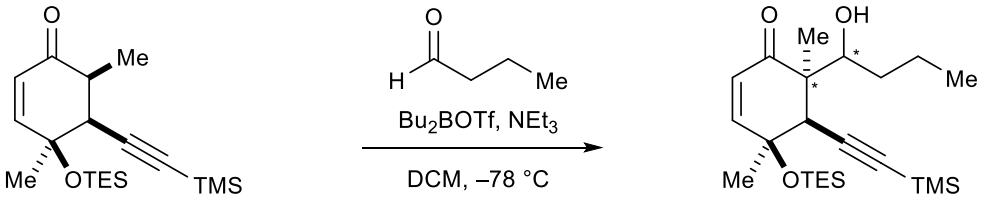


S1 **4.17**

(4*S,5*S**,6*S**)-4,6-dimethyl-4-((triethylsilyl)oxy)-5-((trimethylsilyl)ethynyl)cyclohex-2-en-1-one (4.17):**

Enone **S1** (200 mg, 0.59 mmol, 1 eq.) was dissolved in 6 mL of a 10:1 THF:HMPA solution. The solution was cooled to −78 °C and 0.76 mL of a 1M solution of LDA (freshly prepared in THF, 0.71 mmol, 1.2 eq.) was added. The solution was stirred at −78 °C for 1 h and MeI (419 mg, 2.95 mmol, 5 eq.) was added. The reaction was allowed to warm to room temperature and stirred for 2 h at which time it was quenched with 25 mL of a saturated NH_4Cl solution. The organic layer was extracted with 3 x 10 mL EtOAc. The combined organic extracts were washed with brine, dried with Na_2SO_3, and concentrated. Purification by f.c.c. (1:10 EtOAc:Hexane) gave the product as a colorless oil (129 mg, 63%).

IR (Thin Film) 2957.64, 2788, 2176, 1690, 1249, 1106 cm^{-1}.
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.62 (dd, *J*=1.6, 10.3 Hz, 1H), 5.83 (d, *J*=10.3 Hz, 1H), 3.00 (dd, *J*=1.6, 4.4 Hz, 1H), 2.61(dq, *J*=4.4, 6.7 Hz, 1H), 1.52 (s, 3H), 1.27 (d, *J*=6.8 Hz, 3H), 0.99 (t, *J*=7.9 Hz, 9H), 0.66 (q, *J*=7.9 Hz, 6H), 0.09 (s, 9H).
^{13}C NMR (125 MHz, $CDCl_3$, DEPT) δ 199.58 (C), 153.13 (CH), 126.59 (CH), 103.84 (C), 89.61 (C), 73.36 (C), 49.14 (CH), 43.60 (C), 27.74 (CH_3), 13.82 (CH_3), 7.26 (CH_3), 6.95 (CH_2), 0.06 (CH_3).
HRMS (ESI+) 373.1990 calc'd for $C_{19}H_{34}O_2Si_2Na^+$, 373.1993 found.



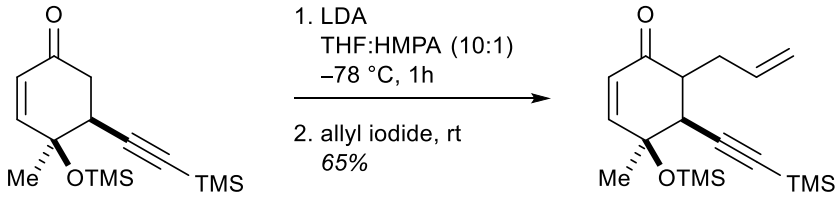
4.17 **4.18**

(4*S,5*S**,6*R**)-6-(1-hydroxybutyl)-4,6-dimethyl-4-((triethylsilyl)oxy)-5-((trimethylsilyl)ethynyl)cyclohex-2-en-1-one (4.18):**

Compound **4.17** (20 mg, 0.057 mmol, 1 eq.) was dissolved in 0.6 mL of DCM. NEt_3 (17 mg, 0.17 mmol, 3 eq.) was added. The solution was cooled to −78 °C and Bu_2BOTf (70 μL of a 1M sol'n in DCM, 0.07 mmol, 1.2 eq.) was added. The solution was

warmed to 0 °C for 30 min and cooled to −78 °C. Butanal (21 mg, 0.29 mmol, 5 eq.) was added. The solution was stirred at −78 °C for 1.5 h and quenched with 1 mL saturated $NaHCO_3$. The organic layer was extracted with 3 x 1 mL DCM. The combined organic layers were dried with Na_2SO_4 and concentrated. The residue was purified by f.c.c. (1:4 EtOAc:Hexane) to give the product as a colorless oil (16.1 mg, 67%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.51 (d, *J*=10.2 Hz, 1H), 6.00 (d, *J*=10.2 Hz, 1H), 4.72 (t, *J*=2.32 Hz, 1H), 4.08 (td, *J*=2.2, 10.5 Hz, 1H), 2.92 (s, 1H), 1.63 (s, 3H), 1.27-1.59 (m, 8H), 1.17 (s, 3H), 1.01 (t, *J*=7.0 Hz, 9H), 0.89-0.96 (m, 3H), 0.70-0.79 (m, 6H), 0.19 (s, 9H).
^{13}C NMR (500 MHz, $CDCl_3$) δ 200.74, 147.63, 129.99, 102.32, 91.41, 72.86, 70.43, 52.57, 52.27, 33.03, 29.81, 21.28, 19.76, 13.89, 7.03, 6.84, 0.10.
HRMS (ESI+) 445.2565 calc'd for $C_{23}H_{42}O_3Si_2Na^+$, 445.2615 found.

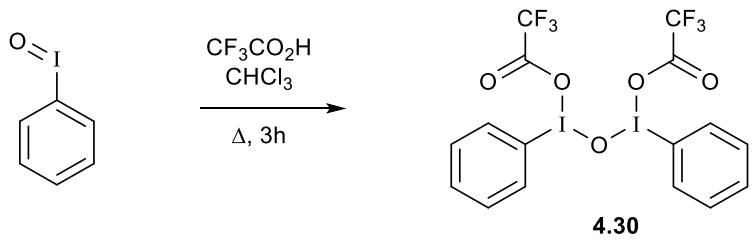


4.13 **4.22**

(4*S,5*S**)-6-allyl-4-methyl-5-((trimethylsilyl)ethynyl)-4-((trimethylsilyl)oxy)cyclohex-2-en-1-one (4.22):**

Enone **4.13** (250 mg, 0.85 mmol, 1 eq.) was dissolved in THF:HMPA (8.5 mL, 10:1 THF:HMPA). The solution was cooled to –78 °C. LDA (1M in THF, 1.02 mL, 1.02 mmol, 1.2 eq.) was added and the solution was stirred at –78 °C for 1h. Allyl iodide (285.6 mg, 1.7 mmol, 2 eq.) was added. The solution was stirred for 15 min. at –78 °C then warmed to rt for 15 min. The reaction was quenched with 40 mL saturated NH_4Cl. The solution was extracted with 4 x 10 mL EtOAc. The combined organic layers were washed with brine, dried with Na_2SO_4 and concentrated. Purification by f.c.c. (1:35 EtOAc:Hexane) gave the product as a colorless oil in a 12:1 dr (184.1 mg, 65%).

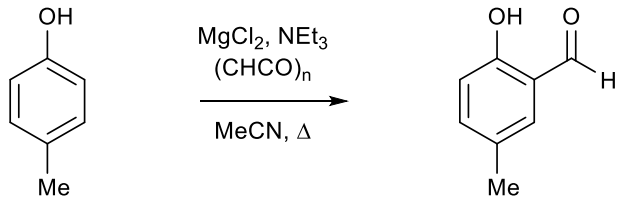
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.65 (d, *J* = 10.0 Hz, 1H), 5.85 (d, *J* = 10.0 Hz, 1H), 5.76-5.68 (m, 1H), 5.16 (dd, *J* = 1.1, 17.2 Hz, 1H), 5.02 (dd, *J* = 2.2, 10.2 Hz, 1H), 2.92-2.85 (m, 2H), 2.70 (d, *J* = 11.8 Hz, 1H), 2.50-2.45 (m, 1H), 1.56 (s, 3H), 0.18 (s, 9H), 0.14 (s, 9H).
^{13}C NMR (125 MHz, $CDCl_3$, DEPT) δ 199.31 (C), 151.39 (CH), 134.72 (CH), 127.93 (CH), 117.90 (CH_2), 104.45 (C), 89.23 (C), 70.62 (C), 45.76 (CH), 44.78 (CH), 30.92 (CH_2), 28.44 (CH_3), 2.53 (CH_3), 0.20 (CH_3).



4.30

Oxybis(phenyl-l3-iodanediyl) bis(2,2,2-trifluoroacetate) (4.30):

Iodosobenzene (11.09 g, 50.4 mmol, 1 eq.) was suspended in $CHCl_3$ (390 mL). TFA (5.75 g, 50.4 mmol, 1 eq.) was added and the solution was refluxed for 3 h and cooled to room temperature. Unreacted iodosobenzene was filtered off and the solution was concentrated to give a thick oil that solidified upon trituration with hexanes. The compound was recrystallized from $CHCl_3$ and hexane to give a white solid as needlelike crystals (9.01 g, 55%). The ^{1}H NMR spectrum was consistent with previously reported values.[1]



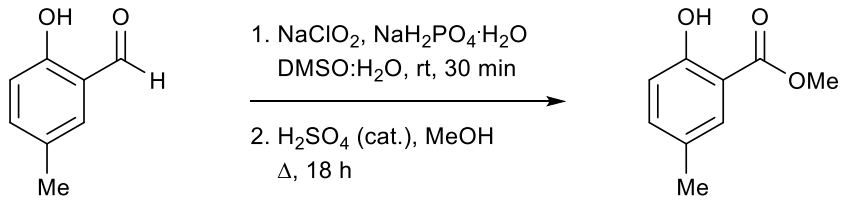
S2

2-Hydroxy-5-methylbenzaldehyde (S2):

p-Cresol (10.0 g, 92.5 mmol, 1 eq.) was dissolved in MeCN (450 mL). $MgCl_2$ (13.2 g, 138.7, 1.5 eq.) and NEt_3 (35.1 g, 346.9 mmol, 3.75 eq.) were added followed by paraformaldehyde (18.75 g, 624.2 mmol, 6.75 eq.). The mixture was stirred at reflux for 4h. The reaction was cooled to room temperature and quenched with 200 mL 10% HCl. The mixture was partially concentrated under vacuum and the aqueous layer was extracted with 3 x 100 mL EtOAc. The combined organic extracts were washed with brine, dried with Na_2SO_4, and concentrated. The resulting yellow solid (11.96 g, 95%) was sufficiently clean by ^{1}H NMR spectroscopy and was used without further purification.

^{1}H NMR (500 MHz, $CDCl_3$) δ 10.83 (s, 1H), 9.85 (s, 1H), 7.35-7.32 (m, 2H), 6.89 (d, *J* = 9.2 Hz, 1H), 2.33 (s, 3H).

[1] Saltzman, H.; Sharefkin, J. G. *Org. Synth.* **1963**, *43*, 60.



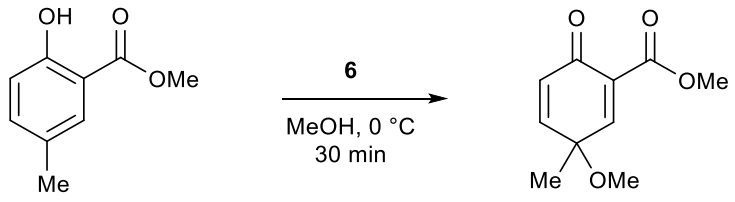
S2 **4.27**

Methyl 2-hydroxy-5-methylbenzoate (4.27):

Aldehyde **S2** (5.00 g, 36.7 mmol, 1 eq.) was dissolved in DMSO (100 mL) and cooled to 0 °C. A solution of $NaClO_2$ (10.37 g, 91.75 mmol, 2.5 eq.) and $NaH_2PO_4 \cdot H_2O$ (12.70 g, 91.75 mmol, 2.5 eq.) in 100 mL H_2O was added dropwise. The reaction mixture was warmed to room temperature and stirred for 30 min. The reaction was quenched with 3 eq. Na_2SO_3 (13.80 g) and stirred for 15 min. The solution was acidified with HCl and diluted with 400 mL H_2O. The aqueous layer was extracted with 4 x 100 mL EtOAc. The combined organic layers were dried with Na_2SO_4 and concentrated. The crude acid was taken forward directly into the next step.

The acid was dissolved in 100 mL MeOH. Concentrated H_2SO_4 was added (1.1 mL) and the reaction was refluxed for 18 h. The mixture was cooled to rt, concentrated, and quenched with 100 mL of saturated, aqueous $NaHCO_3$. The aqueous layer was extracted with 3 x 30 mL EtOAc. The combined organic layers were washed with brine, dried with Na_2SO_4 and concentrated. The resulting brown oil (4.34 g, 71% over 2 steps) was sufficiently pure by ^{1}H NMR spectroscopy for the next step without further purification.

^{1}H NMR (500 MHz, $CDCl_3$) δ 10.55 (s, 1H), 7.62 (d, *J* = 1.9 Hz, 1H), 7.26 (dd, *J* = 2.3, 8.4 Hz, 1H), 6.88 (d, *J* = 8.5 Hz, 1H), 3.94 (s, 3H), 2.99 (s, 1H), 2.28 (s, 3H).



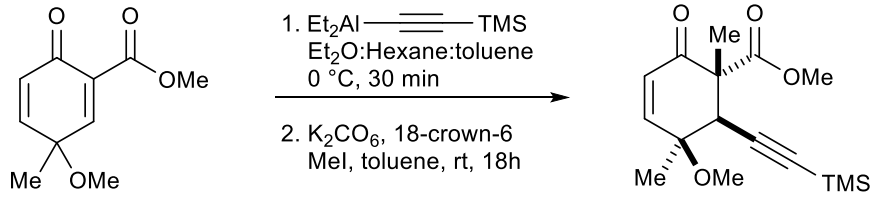
4.27 **4.26**

Methyl 3-methoxy-3-methyl-6-oxocyclohexa-1,4-diene-1-carboxylate (4.26):

Ester **4.27** (2.00 g, 12.0 mmol, 1 eq.) was dissolved in MeOH (60 mL) and cooled to 0 °C. Oxidant **4.30** (7.82 g, 12.0 mmol, 1 eq.) was added in one portion and the solution

was stirred at 0 °C for 30 min. The reaction mixture was partially concentrated under vacuum and quenched with a 100 mL of a 1:1 mixture of 10% $Na_2S_2O_3$ and saturated $NaHCO_3$. The aqueous layer was washed with 3 x 30 mL EtOAc. The combined organic layers were washed with brine, dried with Na_2SO_4, and concentrated. The crude product was purified by flash chromatography (1:2 EtOAc:Hexane) to give an orange oil (1.44 g, 61%). On some runs, the product was contaminated with an unidentified side-product which co-eluted with the material. The presence of this side product did not interfere with the subsequent reactions.

IR (thin film) 2985, 2952, 2827, 1745, 1675, 1642, 1585, 1436, 1272, 1129, 1040 cm^{-1}.
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (d, *J* = 3.1 Hz, 1H), 6.77 (dd, *J* = 3.1, 10.2 Hz, 1H), 6.35 (d, *J* = 10.2 Hz, 1H), 3.86 (s, 3H), 3.22 (s, 3H), 1.47 (s, 3H).
^{13}C NMR (125 MHz, $CDCl_3$, DEPT) δ 180.80 (C), 164.39 (C), 156.49 (CH), 150.44 (CH), 133.25 (C), 131.05 (CH), 72.88 (C), 53.97 (CH_3), 52.67 (CH_3), 26.32 (CH_3).
HRMS (ESI+) 219.0628 calc'd for $C_{10}H_{12}O_4Na^+$, 219.0670 found.



4.26 **4.25**

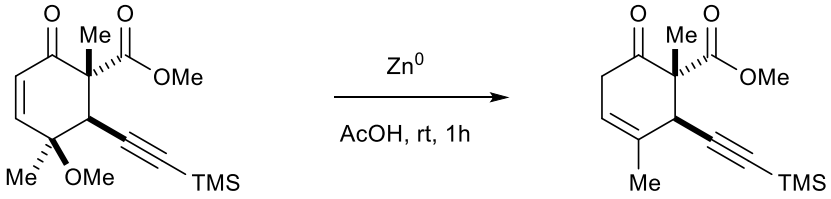
Methyl (1*R,5*S**,6*S**)-5-methoxy-1,5-dimethyl-2-oxo-6-((trimethylsilyl)ethynyl)cyclohex-3-ene-1-carboxylate (4.25):**

TMS-acetylene (2.18 g, 22.2 mmol, 3.5 eq.) was dissolved in Et_2O (6.4 mL) and cooled to −78 °C. *n*-BuLi (9.25 mL of a 2.4 M sol'n, 22.2 mmol, 3.5 eq.) was added and the solution was stirred for 30 min. Et_2AlCl (22.2 mL of a 1M solution in hexane, 22.2 mmol, 3.5 eq.) was added and the mixture was stirred at 0 °C for 4 h. The solution was diluted with 36 mL toluene and allowed to cool to 0 °C. The cyclohexadienone **4.26** (1.25 g, 6.35 mmol, 1 eq.) was added in 40 mL of toluene and stirred for 15 min. The reaction was quenched with 100 mL of a saturated solution of Rochelle's salt. The mixture was stirred vigorously for 30 min and transferred to a separatory funnel. About 10 mL of 10% HCl was added to the funnel. The aqueous layer was extracted with 4 x 50 mL EtOAc. The combined organic extracts were washed with brine, dried with Na_2SO_4, and concentrated. Due to the presumed instability of the product, the crude material was immediately carried forward into the next step.

The crude material (1.51 g, 5.14 mmol, 1 eq.) and 18-crown-6 (134 mg, 0.51 mmol, 0.1 eq.) were dissolved in toluene (26 mL). MeI (7.29 g, 51.4 mmol, 10 eq.) was added

followed by K_2CO_3 (1.06 g, 7.71 mmol, 1.5 eq.). The mixture was stirred at room temperature for 18 h. The reaction mixture was filtered through a plug of florisil and concentrated. Purification by flash chromatography (1:4 EtOAc:Hexane) gave the product as a colorless oil (836 mg, 43% over 2 steps). On some runs, the product was contaminated with an unidentified side-product which could not be removed.

IR (thin film) 2954, 2174, 1740, 1686, 1123 cm^{-1}.
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.76 (d, *J* = 10.4 Hz, 1H), 5.99 (d, *J* = 10.3 Hz, 1H), 3.73 (s, 3H), 3.63 (s, 1H), 3.38 (s, 3H), 1.63 (s, 3H), 1.52 (s, 3H), 0.14 (s, 9H).
^{13}C NMR (125 MHz, $CDCl_3$, DEPT) δ 197.21 (C), 172.02 (C), 150.22 (CH), 127.11 (CH), 101.38 (C), 91.13 (C), 71.64 (C), 57.74 (C), 52.80 (CH_3), 50.98 (CH_3), 45.45 (CH), 23.30 (CH_3), 18.66 (CH_3), 0.03 (CH_3).
HRMS (ESI+) 331.1336 calc'd for $C_{16}H_{24}O_4SiNa^+$, 331.1339 found.

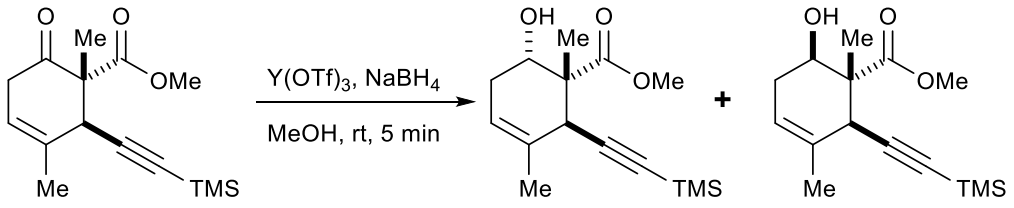


4.25 **4.29**

Methyl (1*R,2*S**)-1,3-dimethyl-6-oxo-2-((trimethylsilyl)ethynyl)cyclohex-3-ene-1-carboxylate (4.29):**

Enone **4.25** (836 mg, 2.71 mmol, 1 eq.) was dissolved in AcOH (10 mL). HCl-washed Zn (1.77 g, 27.1 mmol, 10 eq.) was added and the reaction was stirred at room temperature for 1 h. The mixture was diluted with EtOAc, filtered through a plug of celite, and concentrated. The crude mixture was purified by flash chromatography (1:6 EtOAc:Hexane) to give the product as a colorless oil (536 mg, 71%).

IR (thin film) 2958, 2171, 1723, 1250, 845 cm^{-1}.
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.42 (tq, *J* = 1.5, 3.0 Hz, 1H), 3.68 (s, 3H), 3.65 (s, 1H), 3.02 (qdd, *J* = 2.0, 4.2, 22.3 Hz, 1H), 2.87 (quintd, *J* = 2.5, 22.3 Hz, 1H), 1.87 (q, *J* = 2.0 Hz, 3H), 1.42 (s, 3H), 0.10 (s, 9H).
^{13}C NMR (125 MHz, $CDCl_3$, DEPT) δ 204.38 (C), 172.18 (C), 136.02 (C), 119.36 (CH), 101.64 (C), 89.60 (C), 58.62 (C), 52.83 (CH_3), 42.58 (CH), 38.26 (CH_2), 22.49 (CH_3), 17.89 (CH_3), 0.04 (CH_3).
HRMS (ESI+) 301.1230 calc'd for $C_{15}H_{22}O_3SiNa^+$, 301.1229 found.



4.29 **4.32a** **4.32b**

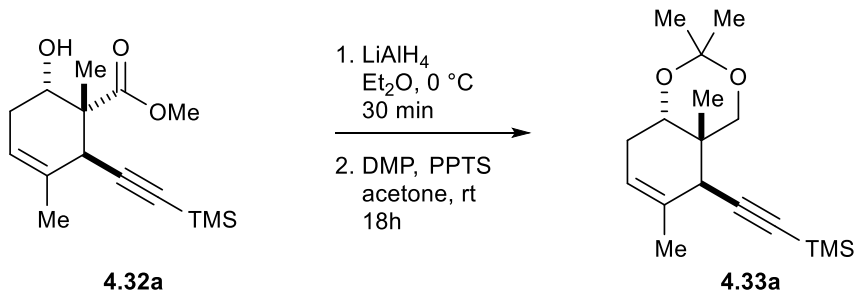
Methyl (1*R,2*S**,6*S**)-6-hydroxy-1,3-dimethyl-2-((trimethylsilyl)ethynyl)cyclohex-3-ene-1-carboxylate (4.32a):**

Ester **4.29** (250 mg, 0.90 mmol, 1 eq.) was dissolved in MeOH (6 mL) and $Y(OTf)_3$ (964 mg, 1.80 mmol, 2 eq.) was added. The solution was stirred for 30 min. at room temperature and $NaBH_4$ (43 mg, 1.13 mmol, 1.25 eq.) was added portion-wise. The reaction was stirred for 5 min. and quenched with 20 mL 10% $NaHSO_4$. The aqueous layer was extracted with 3 x 10 mL EtOAc. The combined organic layers were combined and washed with brine, dried with Na_2SO_4 and concentrated. Flash chromatography (1:10 to 1:2 EtOAc:Hexane) gave the product (69.5 mg, 27%) along with its epimer (89.2 mg, 35 %).

IR (thin film) 3527, 2957, 2916, 2170, 1728, 1451, 1249, 843 cm^{-1}.
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.27 (t, *J* = 3.5 Hz, 1H), 3.97 (ddd, *J* = 5.9, 8.1, 9.7 Hz, 1H), 3.71 (s, 3H), 3.55 (s, 1H), 3.00 (d, *J* = 9.8 Hz, 1H), 2.47 (tddd, *J* = 1.9, 3.8, 5.7, 18.1 Hz, 1H), 2.08 (tddd, *J* = 1.9, 3.4, 7.8, 18.1 Hz, 1H), 1.79 (d, *J* = 1.6 Hz, 3H), 1.44 (s, 3H), 0.14 (s, 9H).
^{13}C NMR (125 MHz, $CDCl_3$, DEPT) δ 176.89 (C), 133.05 (C), 120.13 (CH), 104.42 (C), 88.53 (C), 69.94 (CH), 52.29 (CH_3), 49.13 (C), 40.60 (CH), 32.81 (CH_2), 22.32 (CH_3), 20.18 (CH_3), 0.18 (CH_3).
HRMS (ESI+) 303.1387 calc'd for $C_{15}H_{24}O_3SiNa^+$, 303.1382 found.

Analytical data for Epimer 4.32b:

IR (thin film) 3469, 2955, 2171, 1726, 1435, 1280, 1330, 1019 cm^{-1}.
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.32-5.34 (m, 1H), 4.11 (td, *J* = 6.2, 8.2 Hz, 1H), 3.74 (s, 3H), 3.61 (t, *J* = 1.0 Hz, 1H), 2.28-2.35 (m, 1H), 2.19 (d, *J* = 6.7 Hz, 1H), 2.05(sextetdd, *J* = 2.7, 8.2, 17.8 H, 1H), 1.81 (s, 3H), 1.30 (s, 3H), 0.14 (s, 9H).
^{13}C NMR (125 MHz, $CDCl_3$, DEPT) δ 176.11 (C), 131.20 (C), 119.10 (CH), 103.75 (C), 89.30 (C), 70.87 (CH), 52.40 (CH_3), 50.73 (C), 41.06 (CH), 31.29 (CH_2), 22.06 (CH_3), 12.60 (CH_3), 0.10 (CH_3).
HRMS (ESI+) 303.1387 calc'd for $C_{15}H_{24}O_3SiNa^+$, 303.1383 found.

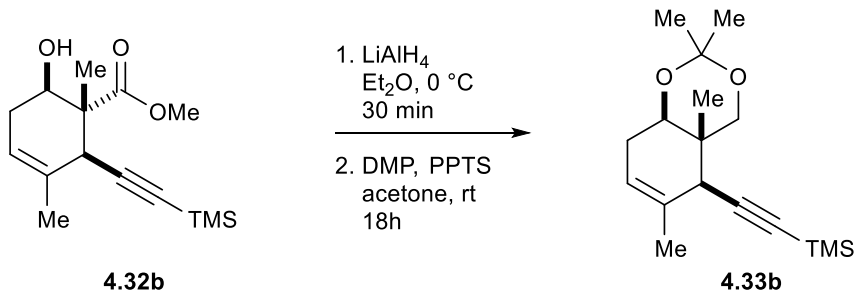


4.32a **4.33a**

Trimethyl(((4a*S,5*S**,8aS*)-2,2,4a,6-tetramethyl-4a,5,8,8a-tetrahydro-4H-benzo[d][1,3]dioxin-5-yl)ethynyl)silane (4.33a):**

$LiAlH_4$ (5.6 mg, 0.15 mmol, 2 eq.) was suspended in 0.3mL Et_2O and cooled to 0 °C. Ester **4.32a** (20.7 mg, 0.074 mmol, 1 eq.) in 0.1 mL Et_2 O was added and the solution was stirred for 30 min. The reaction was quenched by adding 1 mL 10% aq. HCl. The aqueous layer was extracted with 3 x 1 mL EtOAc, dried with Na_2SO_4 and concentrated. The crude diol was dissolved in acetone (3 mL) and 2,2-dimethoxypropane (77.1 mg, 0.74 mmol, 10 eq) was added along with 2 mg PPTS (0.0074 mmol, 0.1 eq.). The solution was stirred at room temperature overnight and concentrated. The residue was dissolved in 1 mL DCM and quenched with 2 mL saturated $NaHCO_3$. The organic layer was separated and the aqueous layer was extracted with 2 x 1 mL DCM. The combined organic fractions were dried with Na_2SO_4 and concentrated. The compound was purified by flash chromatography (1:20 EtOAc:Hexane) to give acetonide **4.33a** as a colorless oil (4.1 mg, 20%).

IR (thin film) 2994, 2964, 2893, 2169, 1380, 1250, 1075, 858, 839 cm^{-1}.
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.32 (d, *J* = 2.0 Hz, 1H), 3.86-3.88 (m, 2H), 3.79 (d, *J* = 11.6 Hz, 1H), 3.55 (d, *J* = 11.6 H, 1H), 2.36-2.44 (m, 1H), 1.91-1.96 (m, 1H), 1.86 (dd, *J* = 1.4, 2.4 Hz, 3H), 1.46 (s, 3H), 1.40 (s, 3H), 0.80 (s, 3H), 0.14 (s, 9H).
^{13}C NMR (125 MHz, $CDCl_3$, DEPT) δ 130.37 (C), 117.04 (CH), 105.53 (C), 99.03 (C), 87.97 (C), 70.88 (CH), 68.03 (CH_2), 35.22 (C), 34.58 (CH), 30.21 (CH_3), 28.84 (CH_2), 22.82 (CH_3), 18.96 (CH_3), 16.06 (CH_3), 0.30 (CH_3)
HRMS (ESI+) 315.1751 calc'd for $C_{17}H_{28}O_2SiNa^+$, 315.1758 found.

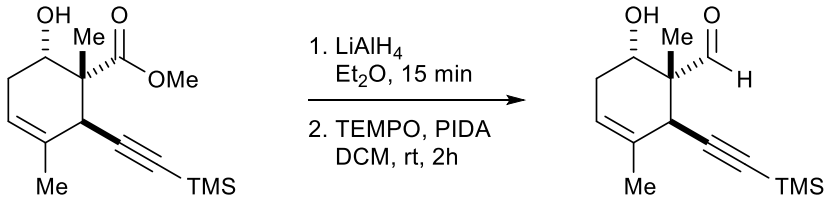


4.32b **4.33b**

Trimethyl(((4a*S,5*S**,8a*R**)-2,2,4a,6-tetramethyl-4a,5,8,8a-tetrahydro-4H-benzo[d][1,3]dioxin-5-yl)ethynyl)silane (4.33b):**

Compound **4.32b** was synthesized in the same manner as **4.32a** starting with 20 mg ester **4.32b**. Compound **4.33b** was obtained as a colorless oil (6.5 mg, 31%).

IR (thin film) 2990, 2961, 2855, 2172, 1382, 1250, 879 cm^{-1}.
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.36 (dt, *J* = 1.4, 2.7 Hz, 1H), 3.80 (dd, *J* = 6.0, 10.4 Hz, 1H), 3.75 (d, *J* = 11.3 Hz, 1H), 3.68 (d, *J* = 11.3 Hz, 1H), 2.86 (t, *J* = 1.1 Hz, 1H), 2.03-2.10 (m, 1H), 1.93-2.00 (m, 1H), 1.78 (qd, *J* = 1.4, 2.6 Hz, 3H), 1.45 (s, 3H), 1.43 (s, 3H), 1.13 (s, 3H), 0.14 (s, 9H).
^{13}C NMR (125 MHz, $CDCl_3$, DEPT) δ 130.73 (C), 119.57 (CH), 103.31 (C), 99.03 (C), 88.90 (C), 71.55 (CH), 71.06 (CH_2), 41.13 (CH), 35.61 (C), 29.95 (CH_3), 28.29 (CH_2), 22.06 (CH_3), 18.97 (CH_3), 11.70 (CH_3), 0.19 (CH_3)
HRMS (ESI+) 315.1751 calc'd for $C_{17}H_{28}O_2SiNa^+$, 315.1751 found.



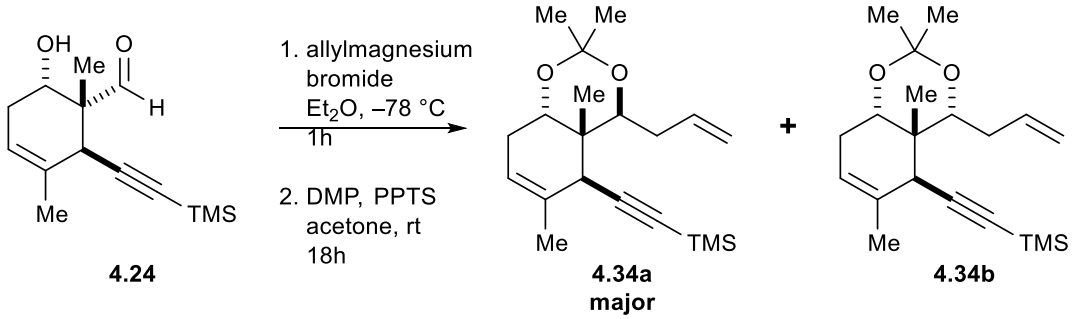
4.32a **4.24**

(1*R,2*S**,6*S**)-6-Hydroxy-1,3-dimethyl-2-((trimethylsilyl)ethynyl)cyclohex-3-ene-1-carbaldehyde (4.24):**

$LiAlH_4$ (13.5 mg, 0.36 mmol, 2 eq.) was suspended in Et_2O (0.72 mL) and cooled to 0 °C. Compound **4.32a** (50 mg, 0.18 mL, 1 eq.) in 0.2 mL Et_2O was added dropwise and stirred for 15 min. The reaction was quenched with 2 mL 10% aqueous HCl. The aqueous layer was extracted with 3 x 2 mL EtOAc. The combined organic extracts were washed with brine, dried with Na_2SO_4 and concentrated. The crude diol was carried forward directly.

The crude diol (39.5 mg, 0.156 mmol, 1 eq.) and TEMPO (5 mg, 0.03 mmol, 0.2 eq.) were dissolved in DCM and PIDA (361 mg, 1.124 mmol, 2 eq.) was added. The solution was stirred for 2 h and silica gel was added to the reaction mixture. The solvent removed and the crude product was loaded directly onto a column. Flash chromatography (1:10 EtOAc:Hexane) gave the product (25.6 mg, 57% over 2 steps) as a colorless oil.

IR (thin film) 3442, 2964, 2937, 2915, 2170, 1723, 1448, 1249, 1075, 1048, 843 cm^{-1}.
^{1}H NMR (500 MHz, C_6D_6) δ 9.57 (s, 1H), 5.01 (s, 1H), 4.28-4.29 (m, ~0.5 H, 1H), 3.88-3.89 (m, 1H), 3.45 (s, 1H), 2.05-2.09 (m, 1H), 1.77-1.79 (m, 4H), 1.16 (s, 3H), 0.14 (s, 9H).
^{13}C NMR (125 MHz, C_6D_6, DEPT) δ 204.93 (CH), 131.54 (C), 120.07 (CH), 105.04 (C), 88.79 (C), 69.12 (CH), 51.79 (C), 37.79 (CH), 32.22 (CH_2), 22.21 (CH_3), 16.27 (CH_3), 0.12 (CH_3).
HRMS (ESI+) 273.1281 calc'd for $C_{14}H_{22}O_2Si$, 273.1264 found.



(1*R,2*S**,6*S**)-6-hydroxy-1,3-dimethyl-2-((trimethylsilyl)ethynyl)cyclohex-3-ene-1-carbaldehyde (4.34a):**

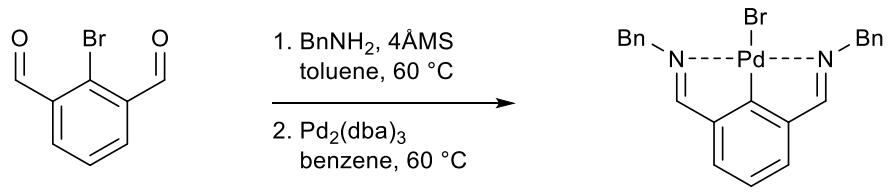
Aldehyde **4.24** (14.3 mg, 0.06 mmol, 1 eq.) was dissolved in anhydrous Et_2O (0.6 mL) and cooled to −78 °C. Allylmagnesium bromide (0.17 mL of a 1M sol'n, 0.17 mmol, 3 eq.) was added drop-wise. The reaction was stirred for 1h and quenched with 2 mL saturated NH_4Cl. The aqueous layer was extracted with 3 x 1 mL EtOAc. The combined organic extracts were dried with Na_2SO_4 and concentrated. The crude material was converted to the acetonide immediately.

The crude diol (0.06 mmol) was dissolved in acetone (1.2 mL) and 2,2-dimethoxypropane (63 mg, 0.6 mmol, 10 eq.) was added. PPTS (1.5 mg, 0.006 mmol, 0.1 eq.) was added and the solution was stirred at rt for 18 h. The solution was quenched with aqueous $NaHCO_3$ and the aqueous layer was extracted with 3 x 1 mL DCM. The combined organic extracts were dried with Na_2SO_4 and concentrated. Purification by

flash chromatography (1:10 EtOAc:Hexane) gave the product (5.9 mg, 34% over 2 steps) as a 3.1:1 ratio of diastereomers (4.1:1 observed in the crude ^{1}H NMR spectrum).

IR (thin film) 2963, 2914, 2170, 1379, 1249, 1221, 1077 cm^{-1}.
^{1}H NMR (500 MHz, $CDCl_3$, major diastereomer) δ 5.80-5.95 (m, 1H), 5.34 (td, *J* = 1.4,2.7 Hz, 1H), 5.08-5.13 (m, 1H), 5.04-5.07 (m, 1H), 3.91 (dd, *J* = 3.9, 4.1 Hz, 1H), 3.87 (dd, *J* = 3.8, 10.6 Hz, 1H), 3.59-3.61 (m, 1H), 2.50 – 2.53 (m, 1H), 2.36 – 2.49 (m, 3H), 2.00 (ddd, *J* = 1.9, 6.2, 19.0 Hz, 1H), 1.83 – 1.84 (m, 3H), 1.41 (s, 3H), 1.36 (s, 3H), 0.88 (s, 3H), 0.15 (s, 9H).
^{13}C NMR (125 MHz, $CDCl_3$, DEPT, major diastereomer) δ 136.76 (CH), 130.54 (C), 117.62 (CH), 116.16 (CH_2), 106.09 (C), 100.13 (C), 88.35 (C), 78.25 (C), 67.24 (CH), 40.57 (C), 39.32 (CH), 35.92 (CH_2), 2.36 (CH_3), 25.24 (CH_3), 22.61 (CH_3), 14.81 (CH_3), 0.25 (CH_3).
HRMS (ESI+) 355.2064 calc'd for $C_{20}H_{32}O_2SiNa^+$, 355.2034 found.

CHAPTER 5 EXPERIMENTAL



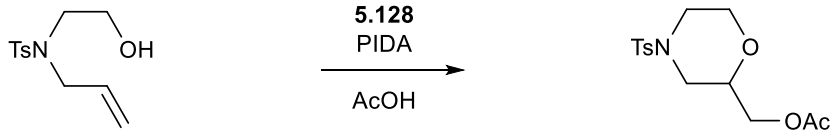
5.128

(2,6-bis((*E*)-(benzylimino)methyl)phenyl)palladium(II) bromide (5.128):

2-bromoisophthalaldehyde (50 mg, 0.23 mmol, 1 eq.), and benzylamine (49.2 mg, 0.46 mmol, 2 eq.) were dissolved in toluene (2 mL) and 4Å molecular sieves were added. The solution was heated to 60 °C for 48 h. The product was filtered and concentrated. The crude material was carried forward directly.

The crude product and $Pd_2(dba)_3$ (65 mg, 0.0714 mmol, 0.51 eq.) were dissolved in benzene (14 mL). The solution was degassed by bubbling N_2 through the solution for 15 min. The reaction mixture was heated to 60 °C for 18 h. The mixture was concentrated and the crude material was purified by f.c.c. (1:2 to 1:4 EtOAc:Hexane followed by flushing the column with EtOAc) to give the product (44.1 mg, 63%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (s, 2H), 7.48 (d, *J* = 7.4 Hz, 4H), 7.39 (t, *J* = 7.4 Hz, 4H), 7.33 (t, *J* = 7.2 Hz, 2H), 5.17 (s, 4H).



5.125 **5.126**

(4-tosylmorpholin-2-yl)methyl acetate (5.126):

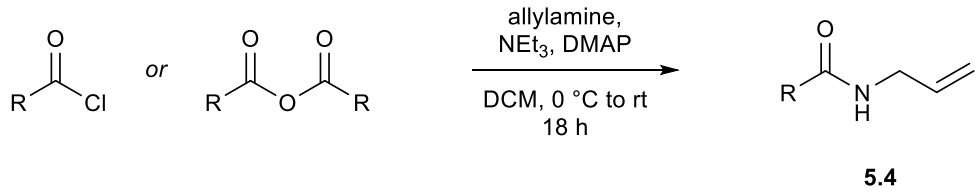
Palladium catalyst **5.128** (2.9 mg, 0.0058 mmol, 0.05 eq.) and $AgBF_4$ (1.36 mg, 0.007 mmol, 1.25 eq.) were dissolved in DCM and stirred for 1h at rt. The solution was filtered through celite and concentrated. The catalyst was dissolved in AcOH (1 mL). Alcohol **5.125** (30 mg, 0.117 mmol, 1 eq.) and PIDA (48.3 mg, 0.15 mmol, 1.25 eq.)

were added. The reaction was stirred at 50 °C for 1.75 h. The solution was concentrated and the product was purified by f.c.c. (1:4 to 1:2 EtOAc:Hexane) to give the product (3.8 mg, 10% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64-7.63 (m, 2H), 7.36 (m, 2H), 4.07 (dd, *J* = 5.9, 11.8 Hz, 1H), 4.02 (dd, *J* = 4.7, 11.8 Hz, 1H), 3.94 (ddd, *J* = 1.6, 3.4, 11.6 Hz, 1H), 3.80 (dddd, *J* = 2.6, 4.7, 5.8, 10.4 Hz, 1H), 3.70 (dt, 2.7, 11.5 Hz, 1H), 3.61 (td, *J* = 3.1, 11.3 Hz, 1H), 3.53 (tdd, *J* = 1.5, 2.8, 11.7 Hz, 1H), 2.45 (s, 3H), 2.44 (dd, *J* = 3.0, 4.0 Hz, 1H), 2.19-2.16 (m, 1H), 2.08 (s, 3H).
^{13}C NMR (125 MHz, $CDCl_3$, DEPT) δ 170.75 (C), 144.27 (C), 132.14 (C), 129.98 (CH), 128.01 (CH), 73.17 (CH), 66.10 (CH_2), 64.38 (CH_2), 47.53 (CH_2), 45.52 (CH_2), 21.71 (CH_3), 20.93 (CH_3).

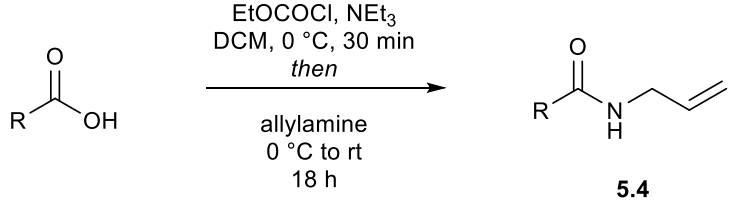
General procedure for the synthesis of N-Allylamides:

Method A



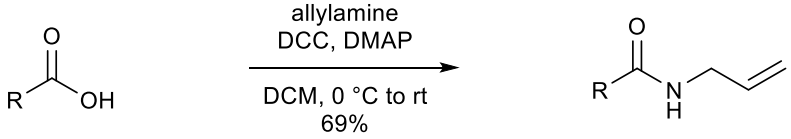
5.4

Method B



5.4

Method C



5.4

Procedure A:

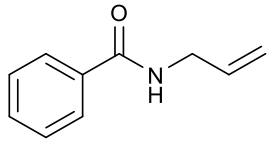
Allylamine (1.2 eq.), triethylamine (2 eq.) and DMAP (0.1 eq.) were dissolved in DCM (0.5 M). The solution was cooled to 0 °C and the corresponding acid chloride or anhydride was added dropwise. The solution was allowed to warm to room temperature and stirred overnight. The reaction was quenched with saturated, aqueous $NaHCO_3$ and extracted with 3 x 20 mL DCM. The combined organic solution was washed with brine and dried with Na_2SO_4. The solution was concentrated and purified by f.c.c. to give the pure amide.

Procedure B:

The corresponding carboxylic acid (1 eq.) was suspended in DCM (0.3M) and triethylamine (2.0 eq.) was added. The solution was cooled to 0 °C and ethyl chloroformate (1 eq.) was added drop-wise. The solution was stirred at 0 °C for 30 min. Allylamine (1.2 eq.) was added dropwise. The solution was allowed to warm to room temperature and stirred overnight. The reaction was quenched with saturated aqueous $NaHCO_3$ and extracted with 2 x 20 mL DCM. The combined organic layers were washed with brine and dried with Na_2SO_4. The solution was concentrated and purified by f.c.c. to give the pure amide.

Procedure C:

Allylamine (1 eq.) and carboxylic acid (1.25 eq.) were dissolved in DCM (0.2 M) along with a catalytic amount of DMAP (0.1 eq.). To this solution was added DCC (1.25 eq.). The mixture was stirred overnight. The mixture was diluted with EtOAc and filtered. The organic layer was washed with saturated, aqueous $NaHCO_3$ followed by brine, dried with Na_2SO_4 and concentrated. The title compound was purified by f.c.c to give the pure amide.



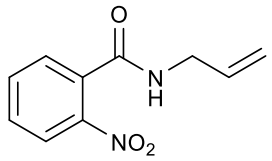
5.4a

***N*-allylbenzamide (5.4a):**[2]

Synthesized by method A. Purified by f.c.c. (1:2 EtOAc:Hexane) to give a yellow oil (2.21 g, 78%).
IR (Thin Film) 3312, 3065, 1640, 1540, 1307, 921 cm^{-1}**.**

[2] J.-F. Soulé, H. Miyamura and S. Kobayashi, *Journal of the American Chemical Society*, 2011, **133**, 18550-18553.

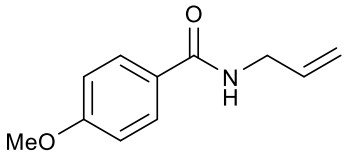
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79-7.77 (m, 2H), 7.52-7.49 (m, 1H), 7.45-7.42 (m, 2H), 6.20 (bs, 1H), 5.95 (ddt, *J* = 5.7, 10.3, 17.1 Hz, 1H), 5.27 (dtd, *J* = 1.5, 1.5, 17.2 Hz, 1H), 5.19 (dtd, *J* = 1.3, 1.3, 10.2 Hz, 1H), 4.10 (ddd, *J* = 1.5, 1.5, 5.7 Hz, 2H).
^{13}C NMR (125 MHz, $CDCl_3$, DEPT) δ 167.4 (C), 134.6 (CH), 134.3 (CH), 131.7 (CH), 128.7 (CH), 127.0 (CH), 116.9 (CH_2), 42.6 (CH_2).



5.4b

***N*-allyl-2-nitrobenzamide (5.4b):[3]**

Synthesized by method B. Purified by f.c.c. (2:1 EtOAc:Hexane) to give a white solid (211.4 mg, 69%).
IR (Thin Film) 3272, 1644, 1545, 1527, 1355 cm^{-1}.
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (dd, *J* = 1.2, 8.2 Hz, 1H), 7.66 (ddd, *J* = 1.2, 7.5, Hz, 1H), 7.57 (ddd, *J* = 1.4, 7.5, 8.2, Hz, 1H), 7.51 (dd, *J* = 1.4, 7.5 Hz, 1H), 6.00 (bs, 1H), 5.97-5.91 (m, 1H), 5.30 (dtd, *J* = 1.4, 1.4, 17.2, Hz, 1H), 5.20 (dtd, *J* = 1.3, 1.3, 10.3, Hz, 1H), 4.07 (ddd, *J* = 1.5, 1.5, 5.8 Hz, 2H).
^{13}C NMR (125 MHz, $CDCl_3$, DEPT) δ 166.5 (C), 146.6 (C), 133.8 (CH), 133.5 (CH), 133.0 (C), 130.6 (CH), 128.9 (CH), 124.7 (CH), 117.4 (CH_2), 42.7 (CH_2).



5.4c

***N*-allyl-4-methoxybenzamide (5.4c):[4]**

Synthesized by method B. Purified by f.c.c. (1:2 EtOAc:Hexane) to give a white solid (87.7 mg, 23% yield).

IR (Thin Film) 3315, 1633, 1607, 1543, 1504, 1254, 1180, 1031 cm^{-1}.

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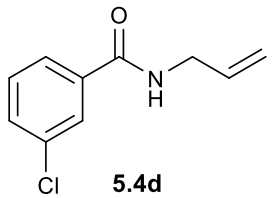
[3] V. C. Agwada, *Journal of Chemical & Engineering Data*, 1984, **29**, 231-235.
[4] D. F. Harvey and D. M. Sigano, *The Journal of Organic Chemistry*, 1996, **61**, 2268-2272.

^{1}H NMR (500 MHz, $CDCl_3$ δ 7.77-7.74 (m, 2H), 6.92-6.89 (m, 2H), 6.22 (bs, 1H), 5.97-5.89 (m, 1H), 5.24 (dtd, *J* = 1.5, 1.5, 17.2 Hz, 1H), 5.16 (dd, *J* = 1.4, 10.2 Hz, 1H), 4.06 (ddd, *J* = 1.4, 1.4, 5.7 Hz, 2H), 3.84 (s, 3H).
^{13}C NMR (125 MHz, $CDCl_3$, DEPT) δ 167.0 (C), 162.3 (C), 134.5 (CH), 128.8 (CH), 126.9 (C), 116.6 (CH_2), 113.9 (CH), 55.5 (CH_3), 42.5 (CH_2).

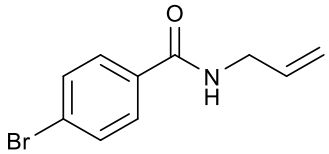


5.4d

***N*-allyl-3-chlorobenzamide (5.4d):[3]**

Synthesized by method B. Purified by f.c.c. (1:3 EtOAc:Hexane) as a white solid (165.1 mg, 53%).

IR (Thin Film) 3309, 3069, 1640, 1570, 1541, 1312, 920 cm^{-1}.
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.77 (t, *J* = 1.8 Hz, 1H), 7.65 (d, *J* = 7.7 Hz, 1H), 7.47 (ddd, *J* = 1.0, 8.0, 8.0 Hz, 1H), 7.37 (t, *J* = 7.9 Hz, 1H), 6.20 (bs, 1H), 5.97-5.89 (m, 1H), 5.27 (dd, *J* = 1.4, 17.1 Hz, 1H), 5.20 (dd, *J* = 1.2, 10.2 Hz, 1H), 4.09-4.07 (m, 2H).
^{13}C NMR (125 MHz, $CDCl_3$, DEPT) δ 166.1 (C), 136.4 (C), 134.9 (C), 134.0 (CH), 131.7 (CH), 130.0 (CH), 127.4 (CH), 125.2 (CH), 117.1 (CH_2), 42.7 (CH_2).



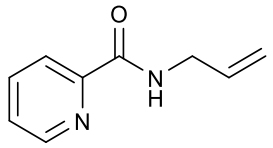
5.4e

***N*-allyl-4-bromobenzamide (5.4e):**

Synthesized by method A. Purified by f.c.c. (1:2 EtOAc:Hexane) as a white solid (105.1 mg, 38%).

IR (Thin Film) 3298, 1631, 1536, 931, 844 cm^{-1}.
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66-7.64 (m, 2H), 7.58-7.55 (m, 2H), 6.22 (bs, 1H), 5.93 (ddt, *J* = 5.7, 10.3,17.1 Hz, 1H), 5.26 (dtd, *J* = 1.5, 1.5, 17.1 Hz, 1H), 5.19 (dtd, *J* = 1.3, 1.3, 10.2 Hz, 1H), 4.09-4.06 (m, 2H).
^{13}C NMR (125 MHz, $CDCl_3$, DEPT) δ 166.5 (C), 134.0 (CH), 133.4 (C), 131.9 (CH), 128.7 (CH), 126.3 (CH), 117.0 (CH_2), 42.6 (CH_2).

HRMS (ESI+) 261.9838 calc'd for $C_{10}H_{10}BrNONa$, found 261.9823.

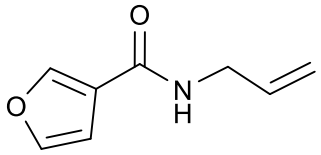


5.4f

***N*-allylpicolinamide (5.4f):**

Synthesized by method B. Purified by f.c.c. (2:1 EtOAc:Hexane) as a yellow oil (251.3 mg, 76%).

IR (Thin Film) 3388, 3059, 3012, 2985, 2919, 1668, 1526, 1456, 1434, 1288, 997, 821, 751 cm^{-1}.
^{1}H NMR (500 MHz, $CDCl_3$) 8.55-8.54 (m, 1H), 8.20 (dd, *J* = 0.9, 7.8 Hz, 1H), 8.14 (bs, 1H), 7.84 (ddd, *J* = 1.7, 17.7,17.7 Hz, 1H), 7.42 (ddd, *J* = 1.2, 4.8, 7.6 1H), 5.94 (ddt, *J* = 5.5, 10.3, 17.1 Hz, 1H), 5.27 (dtd, *J* = 1.5, 1.5, 17.1 Hz, 1H), 5.18 (dt, *J* = 1.4, 10.2 Hz, 1H), 4.11 (ddd, *J* = 1.4, 1.4, 5.8 Hz, 2H).
^{13}C NMR (125 MHz, $CDCl_3$, DEPT) δ 164.3 (C), 150.0 (C), 148.2 (CH), 137.5 (CH), 134.2 (CH), 126.3 (CH), 122.4 (CH), 116.6 (CH_2), 41.9 (CH_2).
HRMS (ESI+) 185.0685 calc'd for $C_9H_{10}N_2ONa$, found 185.0670.



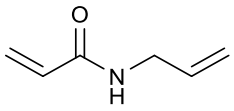
5.4g

***N*-allylfuran-3-carboxamide (5.4g):**[5]

Synthesized by method B. Purified by f.c.c. (1:2 EtOAc:Hexane) as a white solid (215.7 mg, 64%).

[5] N. Zanatta, D. Faoro, S. C. Silva, H. G. Bonacorso and M. A. P. Martins, *Tetrahedron Letters*, 2004, **45**, 5689-5691.

IR (Thin Film) 3292, 1634, 1589, 1571, 1538, 1201, 1162, 1019, 986, 875 cm^{-1}.
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.42 (t, *J* = 1.7 Hz, 1H), 6.64 (dd, *J* = 0.76, 2.0 Hz, 1H), 6.17 (bs, 1H), 5.88 (ddt, *J* = 5.7, 10.2, 17.1 Hz, 1H), 5.22 (dtd (*J* = 1.5, 1.5, 17.2 Hz, 1H), 5.15 (dtd, *J* = 1.5, 1.5, 10.1 Hz, 1H), 4.01 (ddd, *J* = 1.5, 1.5, 5.7 Hz, 2H).
^{13}C NMR (125 MHz, $CDCl_3$, DEPT) δ 162.6 (C), 144.9 (CH), 143.9 (CH), 134.2 (CH), 122.6 (C), 116.7 (CH_2), 108.4 (CH), 42.0 (CH).

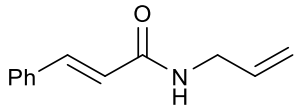


5.4h

N-allylacrylamide (5.4h):

Synthesized by method A. Purified by f.c.c (1:1 EtOAc:Hexane) as an orange oil (110.1 mg, 36%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.29 (dd, *J* = 1.4, 17.0 Hz, 1H), 6.11 (dd, *J* = 10.3, 17.0 Hz, 1H), 5.86 (tdd, *J* = 5.7, 10.3, 17.1 Hz, 1H), 5.75 (bs, 1H), 5.65 (dd, *J* = 1.4, 10.3 Hz, 1H), 5.23-513 (m, 2H), 3.96 (tt, *J* = 1.5, 5.8 Hz, 2H).
^{13}C NMR (125 MHz, $CDCl_3$, DEPT) δ 165.47 (C), 134.09 (CH), 130.82 (CH), 126.75 (CH_2), 116.79 (CH_2), 42.12 (CH_2).



5.4i

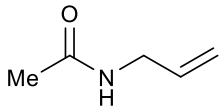
***N*-allylcinnamamide (5.4i):[6]**

Synthesized by method B. Purified by f.c.c. (1:2 EtOAc:Hexane) as a white solid (485.9 mg, 77%).

IR (Thin Film) 3289, 3066, 1654, 1624, 1547, 1353, 990, 975, 914 cm^{-1}.
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (d, *J* = 15.6 Hz, 1H), 7.49 (dd, *J* = 3.1, 6.5 Hz, 2H), 7.35 (ddd, *J* = 1.9, 4.4, 4.4 Hz, 3H), 6.45 (d, *J* = 15.6 Hz, 1H), 5.98 (bs, 1H), 5.90 (tdd),

[6] S. De Sarkar and A. Studer, *Organic Letters*, 2010, **12**, 1992-1995.

J = 5.7, 10.2, 17.1 Hz, 1H), 5.24 (dtd, *J* = 1.5, 1.5, 17.1 Hz, 1H), 5.16 (dtd, *J* = 1.4, 1.4, 10.2 Hz, 1H), 4.02 (ddd, *J* = 1.5, 1.5, 5.8 Hz, 2H).
^{13}C NMR (125 MHz, $CDCl_3$, DEPT) δ 165.9 (C), 141.3 (CH), 134.9 (C), 134.2 (CH), 129.8 (CH), 128.9 (CH), 127.9 (CH), 120.7 (CH), 116.7 (CH_2), 42.3 (CH_2).

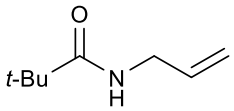


5.4j

***N*-allylacetamide (5.4j):[7]**

Synthesized by method A. Purified by f.c.c. (1:20 MeOH:DCM) as a red oil (217.8 mg, 50%).

IR (Thin Film) 3290, 3083, 1655, 1552, 1429, 1283, 920 cm^{-1}.
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.86-5.77 (m, 2H), 5.17 (dt, *J* = 1.1, 17.2 Hz, 1H), 5.11 (dt, *J* = 1.2, 10.2 Hz, 1H), 3.87-3.84 (m, 2H), 1.99 (s, 3H).
^{13}C NMR (125 MHz, $CDCl_3$, DEPT) δ 170.1 (C), 134.3 (CH), 116.5 (CH_2), 42.2 (CH_2), 23.3 (CH_3).



5.4k

***N*-allylpivalamide (5.4k):[8]**

Synthesized by method A. Purified by f.c.c. (1:2 EtOAc:Hexane) as a yellow oil which gelled upon standing (223.2 mg, 76%).

IR (Thin Film) 3341, 2965, 1640, 1532, 1211, 985, 914 cm^{-1}.
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.85 (tdd, *J* = 5.6, 10.3, 17.2 Hz, 1H), 5.67 (bs, 1H), 5.17 (dtd, *J* = 1.6, 1.6, 17.2 Hz, 1H), 5.13 (dtd, *J* = 1.4, 1.4, 10.2 Hz, 1H), 3.88 (ddd, *J* = 1.6, 1.6, 5.7 Hz, 2H), 1.21 (s, 9H).
^{13}C NMR (125 MHz, $CDCl_3$, DEPT) δ 178.3 (C), 134.7 (CH), 116.2 (CH_2), 42.0 (CH_2), 38.9 (C), 27.8 (CH_3).

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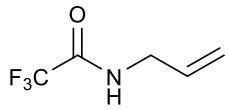
[7] G. C. Tsui, F. Menard and M. Lautens, *Organic Letters*, 2010, **12**, 2456-2459.
[8] E. Alonso, D. J. Ramón and M. Yus, *Tetrahedron*, 1997, **53**, 14355-14368.

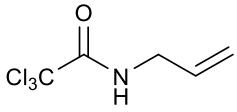


5.4l

***N*-allyl-2,2,2-trifluoroacetamide (5.4l):[9]**

Synthesized by method A. Isolated by f.c.c. (1:2 EtOAc:Hexane) as a yellow oil (257.2 mg, 48%).

IR (Thin Film) 3310, 3094, 1704, 1557, 1434, 1161, 994, 931, 726 cm^{-1}.
^{1}H NMR (500 MHz, $CDCl_3$) 6.39 (bs, 1H), 5.89-5.80 (m, 1H), 5.29-5.24 (m, 2H), 3.99 (t, *J* = 5.5 Hz, 2H);
^{13}C NMR (125 MHz, $CDCl_3$, DEPT) 157.4 (q, *J* = 36.3 Hz, C), 131.9 (CH), 118.2 (CH_2), 116.0 (q, *J* = 286.3 Hz, CF_3), 42.3 (CH_2).



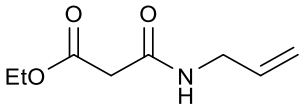
5.4m

***N*-allyl-2,2,2-trichloroacetamide (5.4m):**

Synthesized by method A. Isolated by f.c.c. (1:2 EtOAc:Hexane) (249.1 mg, 90%)

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.77 (bs, 1H), 5.89 (tdd, *J* = 5.6, 10.3, 17.1 Hz, 1H), 5.33-5.23 (m, 2H), 4.00 (tt, *J* = 1.5, 5.7 Hz, 2H).

[9] P. C. Prediger, L. s. F. Barbosa, Y. Génisson and C. R. D. Correia, *The Journal of Organic Chemistry*, 2011, **76**, 7737-7749.

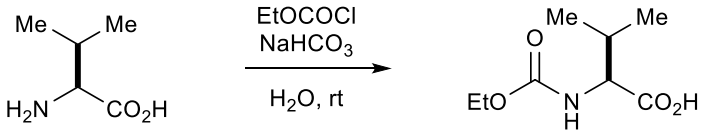


5.4n

ethyl 3-(allylamino)-3-oxopropanoate (5.4n):[10]

Synthesized by method C. Purified by f.c.c. (1:2 EtOAc:Hexane) as a cream solid (215.2 mg, 69%).

IR (Thin Film) 3313, 2984, 1736, 1665, 1554, 1273, 1159, 1032, 927 cm^{-1}.
^{1}H NMR (500 MHz, $CDCl_3$) 7.23 b(s, 1H), 5.88-5.80 (m, 1H), 5.20 (dd, *J* = 1.2, 17.2 Hz, 1H), 5.14 (dd, *J* = 1.2, 10.3 Hz, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 3.92 (t, *J* = 5.6 Hz, 2H), 3.32 (s, 2H), 1.28 (t, *J* = 7.2 Hz, 3H).
^{13}C NMR (125 MHz, $CDCl_3$, DEPT) δ 169.8 (C), 164.9 (C), 133.9 (CH), 116.5 (CH_2), 61.7 (CH_2), 42.0 (CH_2), 41.2 (CH_2), 14.2 (CH_3).



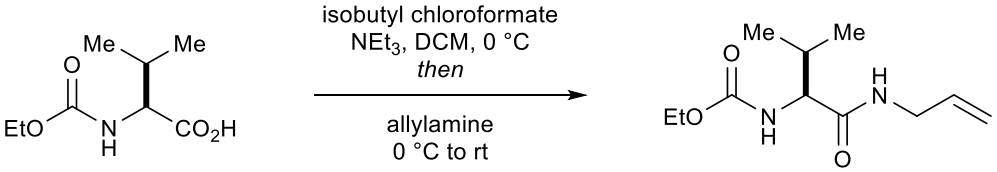
5.132 **5.133**

(*S*)-2-((ethoxycarbonyl)amino)-3-methylbutanoic acid (5.133):[11]

L-Valine (1.00g, 8.53 mmol) and $NaHCO_3$ (3g, 37.5 mmol) were suspended in water and ethyl chloroformate (1.4 g, 12.8 mmol) was added dropwise. The mixture was stirred at room temperature for 4.5 hours. The solution was extracted with 2 x 30 mL DCM. The aqueous layer was acidified and extracted with EtOAc (3x50 mL). The combined organic layers were washed with brine and dried with Na_2SO_4. The organic layer was concentrated and the resulting solid was used without further purification (1.51 g, 94%).

[10] Y. Nakaike, N. Taba, S. Itoh, Y. Tobe, N. Nishiwaki and M. Ariga, *Bulletin of the Chemical Society of Japan*, 2007, **80**, 2413-2417.
[11] K. M. Engle, D.-H. Wang and J.-Q. Yu, *Journal of the American Chemical Society*, 2010, **132**, 14137-14151.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.11-5.10 (m, 1H), 4.34-4.30 (m, 1H), 4.16-4.10 (m, 2H), 2.27-2.20 (m, 1H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.01 (d, *J* = 6.9 Hz, 3H), 0.94 (d, *J* = 6.9 Hz, 3H).

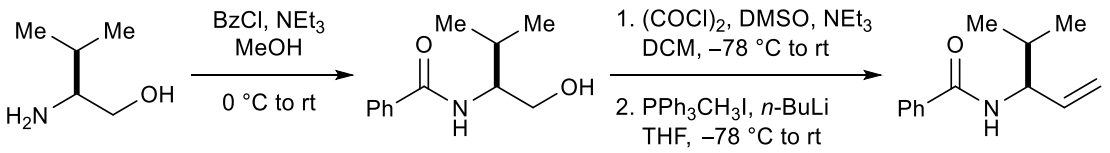


5.133 **5.134**

(*S*)-ethyl (1-(allylamino)-3-methyl-1-oxobutan-2-yl)carbamate (5.134):

Compound **S1** (414 mg, 2.19 mmol) and triethylamine (553 mg, 5.47 mmol) were dissolved in DCM (6 mL) and the solution was cooled to 0 °C. Isobutyl chloroformate (299.1 mg, 2.19 mmol) was added dropwise and the solution was stirred at 0 °C for 1 h. Allylamine (250 mg, 4.38 mmol) was added and the solution was allowed to slowly warm to room temperature and stirred for 18 h. The solution was quenched with saturated $NaHCO_3$ solution (10 mL) and extracted with DCM (2 x 10 mL). The combined organic layers were washed with brine and dried with Na_2SO_4. The solution was concentrated under reduced pressure and recrystallized from $EtOH/H_2O$ as fluffy, white crystals (154.8 mg, 31%).

IR (Thin Film) 3298, 1686, 1650 cm^{-1};
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.22 (bs, 1H), 5.85-5.78 (m, 1H), 5.28 (d, *J* = 8.5 Hz, 1H), 5.18 (dd, *J* = 1.3, 17.2 Hz, 1H), 5.13 (dd, *J* = 1.2, 10.3 Hz, 1H), 4.10 (q, *J* = 6.9 Hz, 2H), 3.98-3.93 (m, 1H), 3.92-3.83 (m, 2H), 2.13 (dd, *J* = 6.6, 12.7 Hz, 1H), 1.24 (t, *J* = 7.1 Hz, 3H), 0.97 (d, *J* = 6.8 Hz, 3H), 0.93 (d, *J* = 6.8 Hz, 3H).
^{13}C NMR (125 MHz, $CDCl_3$, DEPT) δ 171.4 (C), 156.9 (C), 134.0 (CH), 116.7 (CH_2), 61.4 (CH_2), 60.6 (CH), 42.0 (CH_2), 31.1 (CH), 19.5 (CH_3), 18.0 (CH_3), 14.7 (CH_3).
HRMS (ESI+) 251.1366 calc'd for $C_{11}H_{20}N_2O_3Na$, found 251.1352.
[α]$_D$ = –13.7 (c = 0.0041, DCM).



5.135 **5.136** **5.138**

(*S*)-*N*-(4-methylpent-1-en-3-yl)benzamide (5.138)

L-valinol (500 mg, 4.85 mmol) and triethylamine (540 mg, 5.3 mmol) were dissolved in methanol (25 mL) and the solution was cooled to 0 °C. Benzoyl chloride (745 mg, 5.3 mmol) was added dropwise and the solution was allowed to slowly reach room temperature. The solution was stirred for 18 h. The methanol was removed under reduced pressure and the resulting product was dissolved in EtOAc (30 mL) and extracted with 30 mL H_2O. The aqueous layer was extracted with 2 x 30 mL EtOAc. The combined organic layers were washed with brine, dried with Na_2SO_4, and concentrated under reduced pressure. The product was purified by f.c.c. (1:3 EtOAc:Hexane) to yield a colorless oil which solidified upon standing (463.6 mg, 46%).

DMSO (234 mg, 3.0 mmol) was dissolved in 0.75 mL of dry DCM. The solution was cooled to –78 °C and a solution of oxalyl chloride (168 mg, 1.33 mmol) dissolved in 3.3 mL of dry DCM was added dropwise. The solution was stirred for 30 min. The amide alcohol prepared above (250 mg, 1.21 mmol) was dissolved in 1.7 mL of dry DCM and added drop-wise. The solution was stirred at –78 °C and triethylamine (612 mg, 5.0 mmol) was added drop-wise. The solution was allowed to warm to rt and stirred for an additional 30 min. The reaction was quenched with 20 mL H_2O and extracted with 3 x 10 mL DCM. The combined organic layers were washed with 10% aqueous HCl. The organic layer was washed with brine and dried with Na_2SO_4. The solvent was removed under reduced pressure and the crude aldehyde was used directly in the next step.

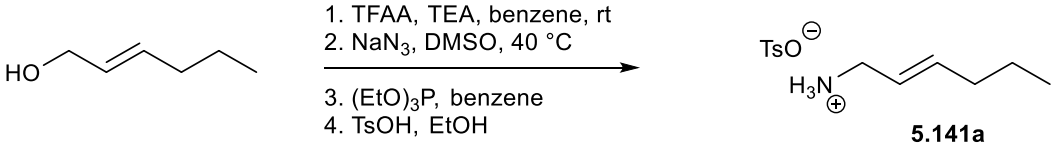
PPh_3CH_3I (848.8 mg, 2.1 mmol) was dissolved in THF (4 mL) and cooled to –78 °C. *n*-BuLi (0.84mL, 2.5M in hexanes, 2.1 mmol) was added dropwise. The solution was warmed to 0 °C for 45 min. and cooled to –78 °C. The aldehyde from the previous step dissolved in 1 mL of THF was added dropwise. The solution was allowed to warm to rt and stirred for 18 h. The reaction was quenched with 10 mL saturated aqueous NH_4Cl. The aqueous layer was extracted with 3 x 10 mL EtOAc. The combined organic layers were washed with brine and dried with Na_2SO_4. The compound was purified by f.c.c. (1:4 EtOAc:Hexane) to give a yellow solid (35.2 mg, 14 %).

IR (Thin Film) 3290, 3055, 2955, 2933, 1633, 1530, 1333, 917, 694 cm^{-1}
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77-7.79 (m, 2H), 7.47-7.50 (m, 1H), 7.40-7.43 (m, 1H), 6.16 (d, *J* = 7.9 Hz, 1H), 5.84 (ddd, *J* = 5.8, 10.5, 17.2 Hz, 1H), 5.21 (td, *J* = 1.5,

17.2 Hz, 1H), 5.17 (td, *J* = 1.3, 10.3 Hz, 1H), 4.55 (dtt, *J* = 9.1, 5.8, 1.5 Hz, 1H), 1.88-1.97 (m, 1H); 0.97 (dd, *J* = 6.7, 1.5 Hz, 6H).

^{13}CNMR (125 MHz, $CDCl_3$, DEPT) δ 167.1 (C), 136.8 (CH), 135.0 (C), 131.5 (CH), 128.7 (CH), 127.0 (CH), 116.0 (CH_2), 57.1 (CH), 32.3 (CH), 18.9 (CH_3), 18.4 (CH_3).

$[\alpha]_D$ = 56.5 (c = 0.0058, DCM)

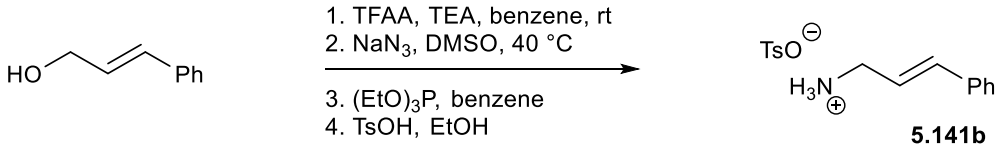


5.141a

(*E*)-hex-2-en-1-aminium 4-methylbenzenesulfonate (5.141a):

E-hex-2-en-1-ol (500 mg, 5 mmol, 1 eq.) and NEt_3 (556 mg, 5.5 mmol, 1.1 eq.) were dissolved in benzene (16 mL). TFAA (1.15 g, 5.5 mmol, 1.1 eq.) was added dropwise and stirred for 1.15 h. NaN_3 (650 mg, 10 mmol, 2 eq.) and DMSO (10 mL) were added. The reaction was stirred at 40 °C for 6 h. The solution was cooled to rt and poured into H_2O (30 mL). The organic layer was separated. The aqueous layer was extracted with 3 x 5 mL benzene. The combined extracts were dried with Na_2SO_4 and filtered. Triethyl phosphite (913 mg, 5.5 mmol, 1.1 eq.) was added to the benzene extracts and the solution was stirred at 30 °C for 18 h. The solvent was removed and the residue was dissolved in EtOH (2.5 mL). $TsOH \cdot H_2O$ (951.1 mg, 5 mmol, 1 eq.) was added and the solution was stirred for 6 h. The solvent was removed and the residue was treated with Et_2O (9 mL). The flask was placed in the freezer overnight and filtered to give **5.141a** as a white solid (494.2 mg, 37%).

^{1}H NMR (300 MHz, DMSO-d_6) δ 7.80 (dd, *J* = 1.8, 8.3 Hz, 2H), 7.47 (d, *J* = 8.0 Hz, 2H), 6.07-5.98 (m, 1H), 5.70-5.59 (m, 1H), 3.63 (d, *J* = 6.7 Hz, 2H), 2.50 (s, 3H), 2.15 (q, *J* = 7.0 Hz, 2H), 1.53-1.49 (m, 2H), 0.98 (dt, *J* = 1.8, 7.4 Hz, 3H).

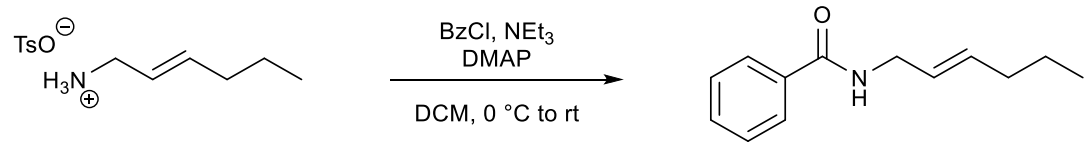


5.141b

(*E*)-3-phenylprop-2-en-1-aminium 4-methylbenzenesulfonate (5.141b):

The same procedure as **5.141a** was utilized to synthesize **5.141b**. Compound **5.141b** was isolated as a white solid (862.9 mg, 56%).

^{1}H NMR (300 MHz, DMSO-d_6) δ 7.79 (d, *J* = 8.2 Hz, 2H), 7.63 (dd, *J* = 2.0, 5.9 Hz, 2H), 7.57-7.46 (m, 5H), 6.95-6.89 (m, 1H), 6.49-638 (m, 1H), 3.89 (d, *J* = 6.9 Hz, 2H), 2.50 (s, 3H).

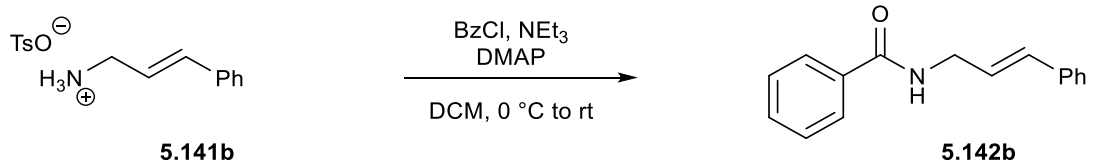


5.141a **5.142a**

(*E*)-*N*-(hex-2-en-1-yl)benzamide (5.412a):

Tosylate **5.141a** (494.2 mg, 1.82 mmol, 1 eq.), DMAP (25 mg, 0.2 mmol, 0.1 eq.) and NEt_3 (736 mg, 7.28 mmol, 4 eq.) were dissolved in DCM (5 mL) and the solution was cooled to 0 °C. Benzoyl chloride (281 mg, 2 mmol, 1.1 eq.) was added. The reaction was allowed to warm to rt and stirred for 18 h. The reaction was quenched with 10 mL H_2O and he organic layer was separated. The aqueous layer was extracted with 2 x 10 mL DCM. The combined organic layers were washed with brine, dried with Na_2SO_4 and concentrated. Purification by f.c.c. (1:4 EtOAc:Hexane) gave the product (210.3 mg, 57%).

IR (thin film) 3312, 3063, 2958, 2927, 2871, 1638, 1578, 1310, 968, 695 cm^{-1}.
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78-7.76 (m, 2H), 7.51-7.47 (m, 1H), 7.44-7.41 (m, 2H), 6.11 (bs, 1H), 5.73-5.67 (m, 1H), 5.55 (ttd, *J* = 1.4, 6.3, 15.3 Hz, 1H), 4.04-4.01 (m, 2H), 2.02-2.00 (m, 2H), 1.40 (sextet, *J* = 7.4 Hz, 2H), 0.90 (t, *J* = 7.4 Hz, 3H).
^{13}C NMR (125 MHz, $CDCl_3$, DEPT) δ 167.31 (C), 134.82 (C), 134.25 (CH), 131.52 (CH), 128.69 (CH), 127.02 (CH), 125.77 (CH), 42.16 (CH_2), 34.48 (CH_2), 22.40 (CH_2), 13.82 (CH_3).
HRMS (ESI+) 226.1202 calc'd for $C_{13}H_{17}NONa^+$, 226.1193 found.

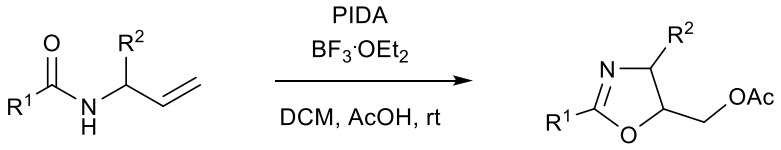


5.141b **5.142b**

***N*-cinnamylbenzamide (5.142b):**

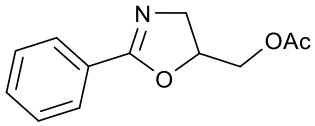
Compound **5.142a** was synthesized from 500 mg (1.67 mmol) of **5.141b** using the same procedure that was used to synthesize **5.142a**. Amide **5.142b** was obtained after purification by f.c.c. (1:4 EtOAc:Hexane) (242.7 mg, 62%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.8-7.79 (m, 2H), 7.51-7.48 (m, 1H), 7.44-7.41 (m, 2H), 7.37-7.35 (m, 2H), 7.32-7.29 (m, 2H), 7.25-7.22 (m, 1H), 6.58 (d, *J* = 15.6 Hz, 1H), 6.37 (s, 1H), 6.28 (td, *J* = 6.4, 15.8 Hz, 1H), 4.24 (dt, *J* = 1.2, 6.1 Hz, 2H).
^{13}C NMR (125 MHz, $CDCl_3$, DEPT) δ 167.44 (C), 136.60 (C), 134.56 (C), 132.61 (CH), 131.65 (CH), 128.73 (2xCH), 127.91 (CH), 127.08 (CH), 126.53 (CH), 125.55 (CH), 42.25 (CH_2).



General procedure for the cyclization reaction:

PIDA (1.2 eq.) was added to a flask and dissolved in DCM (0.1M). Acetic acid (0.11 mL, 10 equiv.) was added followed by $BF_3{\cdot}Et_2O$ (1.2 eq). The corresponding allylamide was added and the solution was stirred at rt until complete by TLC. The reaction was quenched with 1 eq. solid Na_2SO_3 and 0.2 eq. NaOAc and the mixture was stirred for an hour. The mixture was diluted with DCM to 5 mL and 5 mL 30% aq. NH_4OH was added. The organic layer was separated and the aqueous layer was extracted with 2 x 5 mL DCM. The combined organic fractions were dried with Na_2SO_4 and concentrated. The residue was purified by f.c.c to obtain the pure oxazoline.

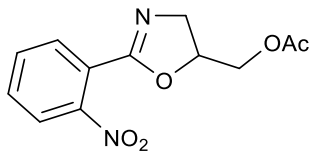


5.127a

(2-phenyl-4,5-dihydrooxazol-5-yl)methyl acetate (5.127a)

Isolated by f.c.c. (1:1 EtOAc:Hexane) as a brown solid (35.6 mg, 84%).

IR (Thin Film) 3062, 2945, 2875, 1743, 1652, 1369, 1233, 1078, 696 cm^{-1}.
^{1}H NMR (500 MHz, $CDCl_3$) 7.94-7.92 (m, 2H), 7.49-7.46 (m, 1H), 7.40 (t, *J* = 7.7 Hz, 2H), 4.93-4.87 (m, 1H), 4.31 (dd, *J* = 3.5, 12.1 Hz, 1H), 4.18 (dd, *J* = 6.1, 11.9 Hz, 1H), 4.14 (dd, *J* = 9.8, 14.7 Hz, 1H), 3.81 (dd, *J* = 7.3, 14.9 Hz, 1H), 2.08 (s, 3H).
^{13}C NMR (125 MHz, $CDCl_3$, DEPT) δ 170.9 (C), 164.1 (C), 131.6 (CH), 128.5 (CH), 128.3 (CH), 127.5 (C), 77.1 (CH), 65.3 (CH_2), 57.1 (CH_2), 20.9 (CH_3).
HRMS (ESI+) 272.0788 calc'd for $C_{12}H_{13}NO_3Na$, found 242.0777.

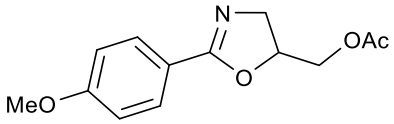


5.127b

(2-(2-nitrophenyl)-4,5-dihydrooxazol-5-yl)methyl acetate (5.127b)

Purified by f.c.c. (1:1 EtOAc:Hexane) as a brown oil (41.1 mg, 77%).

IR (Thin Film) 3074, 2947, 1743, 1666, 1537, 1367, 1234, 1105, 1050, 975, 786, 721, 705 cm^{-1}.
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86-7.84 (m, 1H), 7.80 (dd, *J* = 1.6, 7.5 Hz, 1H), 7.66-7.59 (m, 2H), 4.96-4.91 (m, 1H), 4.30 (dd, *J* = 3.5, 12.2 Hz, 1H), 4.21 (dd, *J* = 6.6, 12.5 Hz, 2H), 4.16 (dd, *J* = 10.1, 15.0 Hz, 2H), 3.84 (dd, *J* = 7.3, 14.9 Hz, 1H), 2.11 (s, 3H).
^{13}C NMR (125 MHz, $CDCl_3$, DEPT) δ 170.9 (C), 161.4 (C), 149.3 (C), 132.6 (CH), 131.7 (CH), 131.1 (CH), 124.0 (CH), 123.0 (C), 78.1 (CH), 64.8 (CH_2), 57.4 (CH_2), 20.9 (CH_3).
HRMS (ESI+) 287.0638 calc'd for $C_{12}H_{12}N_2O_5Na$, found 287.0638.

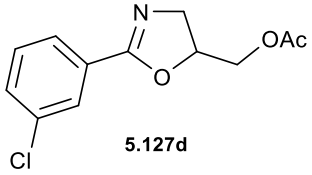


5.127c

(2-(4-methoxyphenyl)-4,5-dihydrooxazol-5-yl)methyl acetate (5127c)

Purified by f.c.c. (1:1 EtOAc:Hexane) as a clear oil (33.2 mg, 68%).

IR (Thin Film) 2939, 1742, 1650, 1513, 1369, 1255, 1170, 1072, 1027, 842, 677 cm^{-1}.
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88-7.85 (m, 2H), 6.91-6.88 (m, 2H), 4.86 (dddd, *J* = 3.6, 6.3, 7.2, 9.9 Hz, 1H), 4.29 (dd, *J* = 3.6, 12.0 Hz, 1H), 4.16 (dd, *J* = 6.2, 12.1 Hz, 1H), 4.10 (dd, *J* = 10.0, 14.7 Hz, 1H), 3.82 (s, 3H), 3.77 (dd, *J* = 7.3, 14.7 Hz, 1H), 2.07 (s, 3H).
^{13}C NMR (125 MHz, $CDCl_3$, DEPT) δ 170.9 (C), 163.9 (C), 162.2 (C), 130.0 (CH), 120.0 (C), 113.8 (CH), 76.9 (CH), 65.4 (CH_2), 57.1 (CH_2), 55.4 (CH_3), 20.9 (CH_3).
HRMS (ESI+) 272.0893 calc'd for $C_{13}H_{15}NO_4Na$, found 272.0892.

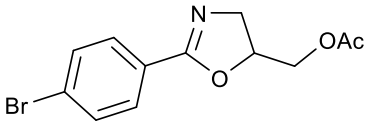


5.127d

(2-(3-chlorophenyl)-4,5-dihydrooxazol-5-yl)methyl acetate (5.127d)

Isolated by f.c.c. (1:1 EtOAc:Hexane) as a yellow solid (43.3 mg, 85%).

IR (Thin Film) 3070, 2946, 2875, 1740, 1652, 1573, 1432, 1368, 1234, 1077, 980, 904, 761, 709, 659 cm-^{1}.
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (t, *J* = 1.7 Hz, 1H), 7.82 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.45 (ddd, *J* = 1.0, 2.0, 8.0 Hz, 1H), 7.34 (t, *J* = 7.9 Hz, 1H), 4.94-4.89 (m, 1H), 4.31 (dd, *J* = 3.5, 12.2 Hz, 1H), 4.18 (dd, *J* = 6.1, 12.2 Hz, 1H), 4.15 (dd, *J* = 10.1, 15.7 Hz, 1H), 3.82 (dd, *J* = 7.4, 15.0 Hz, 1H), 2.09 (s, 3H).
^{13}C NMR (125 MHz, $CDCl_3$, DEPT) δ 170.9 (C), 163.0 (C), 134.6 (C), 131.6 (CH), 129.8 (CH), 129.3 (C), 128.4 (CH), 126.4 (CH), 77.4 (CH), 65.2 (CH_2), 57.1 (CH_2), 20.9 (CH_3).
HRMS (ESI+) 279.0398 calc'd for $C_{12}H_{12}ClNO_3Na$, found 276.0411.

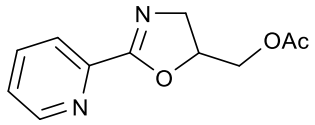


5.127e

(2-(4-bromophenyl)-4,5-dihydrooxazol-5-yl)methyl acetate (5.127e)

Isolated by f.c.c. (1:1 EtOAc:Hexane) as a white solid (47.7 mg, 80%).

IR (Thin Film) 2945, 2875, 1743, 1652, 1593, 1486, 1398, 1369,1232, 1050, 1011, 837, 726, 669 cm^{-1}.
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (q, *J* = 4.5 Hz, 2H), 7.53 (q, *J* = 4.5 Hz, 2H), 4.89 (dddd, *J* = 3.6, 6.3, 7.3, 9.9 Hz, 1H), 4.30 (dd, *J* = 3.5, 12.1 Hz, 1H), 4.17 (dd, *J* = 6.1, 12.1 Hz, 1H), 4.12 (dd, *J* = 10.0, 15.0 Hz, 1H), 3.79 (dd, *J* = 7.4, 15.0 Hz, 1H), 2.07 (s, 3H).
^{13}C NMR (125 MHz, $CDCl_3$, DEPT) 170.8 (C), 163.3 (C), 131.7 (CH), 129.8 (CH), 126.5 (C), 126.3 (C), 77.3 (CH), 65.2 (CH_2), 57.2 (CH_2), 20.9 (CH_3).
HRMS (ESI+) 319.9893 calc'd for $C_{12}H_{12}BrNO_3Na$, found 319.9907.

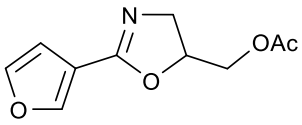


5.127f

(2-(pyridin-2-yl)-4,5-dihydrooxazol-5-yl)methyl acetate (5.127f)

Isolated by f.c.c. on basic alumina using 2.5% MeOH in DCM as elutant) as a brown oil (19.0 mg, 44%).

IR (Thin Film) 3059, 2944, 2876, 1741, 1646, 1371, 1235, 1096, 1043, 677 cm^{-1}.
^{1}H NMR (500 MHz, $CDCl_3$) 8.70 (ddd, *J* = 0.8, 4.8, 4.8 Hz, 1H), 8.02-8.01 (m, 1H), 7.78-7.75 (m, 1H), 7.39-7.37 (m, 1H), 5.02-4.96 (m, 1H), 4.33 (dd, *J* = 3.5, 12.2 Hz, 1H), 4.23 (dd, *J* = 5.8, 12.0 Hz, 1H), 4.20 (dd, *J* = 10.3, 15.1 Hz, 1H), 3.87 (dd, *J* = 7.7, 15.2 Hz, 1H), 2.06 (s, 3H).
^{13}C NMR (125 MHz, $CDCl_3$, DEPT) 170.9 (C), 163.3 (C), 149.9 (CH), 146.5 (C), 136.8 (CH), 125.8 (CH), 124.0 (CH), 77.8 (CH), 65.1, (CH_2), 57.1 (CH_2), 20.9 (CH_3).
HRMS (ESI+) 243.0740 calc'd for $C_{11}H_{12}N_2O_3Na$, found 243.0730.

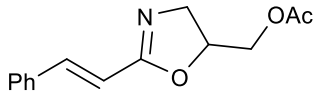


5.127g

(2-(furan-3-yl)-4,5-dihydrooxazol-5-yl)methyl acetate (5.127g)

Isolated by f.c.c. (2:1 EtOAc:Hexane) as a colorless oil (32.2 mg, 75%).

IR (Thin Film) 3146, 2949, 1742, 1674, 1233, 1113, 1009, 874 cm^{-1}.
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (s, 1H), 7.41 (d, *J* = 3.4 Hz, 1H), 6.73 (dd, *J* = 0.5, 1.8 Hz, 1H), 4.82 (dddd, *J* = 3.4, 6.5, 7.0, 10.1 Hz, 1H), 4.26 (dd, *J* = 3.5, 12.1 Hz, 1H), 4.14 (dd, *J* = 6.2, 12.1 Hz, 1H), 4.06 (dd, *J* = 10.0, 14.7 Hz, 1H), 3.72 (dd, *J* = 7.3, 14.7 Hz, 1H), 2.07 (s, 3H).
^{13}C NMR (125 MHz, $CDCl_3$ DEPT) δ 170.9 (C), 159.3 (C), 145.0 (CH), 143.8 (CH), 115.4 (C), 109.4 (CH), 76.8 (CH), 65.2 (CH_2), 56.8 (CH_2), 20.9 (CH_3).
HRMS (ESI+) 232.0580 calc'd for $C_{10}H_{11}NO_4Na$, found 232.0578.

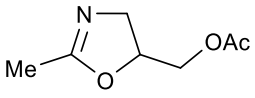


5.127i

(E)-(2-styryl-4,5-dihydrooxazol-5-yl)methyl acetate (5.127i)

Isolated by f.c.c. (1:2 EtOAc:Hexane) as a brown solid (36.4 mg, 74%).

IR (Thin Film) 3060, 3027. 2944, 1743, 1655, 1449, 1370, 1233, 977, 760 cm^{-1}.
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49-7.47 (m, 2H), 7.39-7.33 (m, 4H), 6.61 (d, *J* = 16.3 Hz, 1H), 4.84-4.79 (m, 1H), 4.29 (dd, *J* = 3.5, 12.1 Hz, 1H), 4.14 (dd, *J* = 6.2, 12.1 Hz, 1H), 4.08 (dd, *J* = 10.0, 15.2 Hz, 1H), 3.74 (dd, *J* = 7.3, 15.2 Hz, 1H), 2.10 (s, 3H).
^{13}C NMR (125 MHz, $CDCl_3$, DEPT) δ 170.9 (C), 163.8 (C), 140.3 (CH), 135.2 (C), 129.6 (CH), 128.9 (CH), 127.5 (CH), 114.9 (CH), 76.7 (CH), 65.3 (CH_2), 57.1 (CH_2), 20.9 (CH_3).
HRMS (ESI+) 268.0944 calc'd for $C_{14}H_{15}NO_3Na$, found 268.0935.



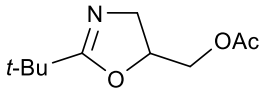
5.127j

(2-methyl-4,5-dihydrooxazol-5-yl)methyl acetate (5127j)

Small amounts of material could be isolated by f.c.c. (5% MeOH in DCM). Yield was determined by ^{1}H NMR using mesitylene as an internal standard by comparison of the mesitylene methyl signals at 2.26 ppm and the methyl group at 2.09. The mesitylene (0.2 eq. wrt. starting material) was added after the product had been worked up prior to

final concentration. Addition of the mesitylene prior to performing the reaction led to side product formation and incomplete reaction.

IR (Thin Film) 2936, 1740, 1659, 1556, 1436, 1372, 1232, 1043 cm^{-1}.
^{1}H NMR (500 MHz, $CDCl_3$) δ 4.70 (dddd, *J* = 3.3, 6.9, 6.9, 10.2 Hz, 1H), 4.19 (dd, *J* = 3.4, 12.1 Hz, 1H), 4.07 (dd, *J* = 6.7, 12.1 Hz, 1H), 3.90 (ddd, *J* = 1.3, 10.1, 14.4 Hz, 1H), 3.54 (ddd, *J* = 1.4, 7.3, 14.3 Hz, 1H), 2.09 (s, 3H), 1.98 (t, *J* = 1.4 Hz, 3H).
^{13}C NMR (125 MHz, $CDCl_3$, DEPT) δ 170.9 (C), 165.0 (C), 76.9 (CH), 65.5 (CH_2), 56.8 (CH_2), 20.9 (CH_3), 14.0 (CH_3).
HRMS (ESI+) 180.0631 calc'd for $C_7H_{11}NO_3Na$, found 180.0609.

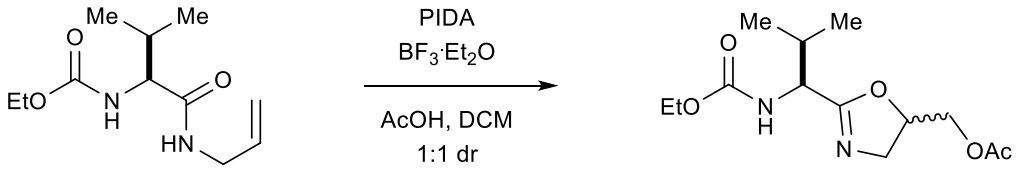


5.127k

(2-(tert-butyl)-4,5-dihydrooxazol-5-yl)methyl acetate (5.127k)

Small amounts of material could be isolated by f.c.c. (1:1 EtOAc:Hex). Yield was determined by ^{1}H NMR using mesitylene as an internal standard by comparing the mesitylene methyl signals at 2.26 ppm and the methyl group at 2.07 ppm. The mesitylene (0.2 eq. wrt. starting material) was added after the product had been worked up prior to final concentration. Addition of the mesitylene prior to performing the reaction led to side product formation and incomplete reaction.

IR (Thin Film) 2972, 2875, 1732, 1659, 1460, 1368, 1159, 1048, 995 cm^{-1}.
^{1}H NMR (500 MHz, $CDCl_3$) δ 4.68 (dddd, *J* = 3.7, 6.2, 6.2, 9.9 Hz, 1H), 4.16 (dd, *J* = 3.6, 12.0 Hz, 1H), 4.05 (dd, *J* = 5.7, 12.0 Hz, 1H), 3.88 (dd, *J* = 10.0, 14.3 Hz, 1H), 3.57 (dd, *J* = 6.7, 14.3 Hz, 1H), 2.07 (s, 3H), 1.20 (s, 9H).
^{13}C NMR (125 MHz, $CDCl_3$, DEPT) δ 174.3 (C), 170.9 (C), 76.5 (CH), 65.4 (CH_2), 56.6 (CH_2), 33.3 (C), 27.7 (CH_3), 20.9 (CH_3).
HRMS (ESI+) 222.1101 calc'd for $C_{10}H_{17}NO_3Na$, found 222.1088.

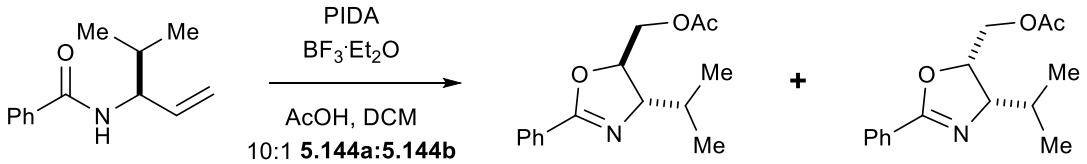


5.124 **5.143**

(2-((*S*)-1-((ethoxycarbonyl)amino)-2-methylpropyl)-4,5-dihydrooxazol-5-yl)methyl acetate (5.143)

Isolated by f.c.c. (1:1 EtOAc:Hexane) as a 1:1 inseparable mixture of diastereomers (43.1 mg, 75%).

IR (Thin Film) 2964, 2877, 1744, 1721, 1531, 1372, 1235, 1043, 1022 cm^{-1}.
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.19, 5.14 (2 x d, *J* = 7.0 Hz, 1H), 4.82-4.74 (m, 1H), 4.36 (dt, *J* = 6.5, 14.5 Hz, 1H), 4.24-4.19 (m, 1H), 4.11 (tt, *J* = 5.7, 11.8 Hz, 3H), 3.97-3.91 (m, 1H), 3.64-3.59 (m, 1H), 2.15-2.10 (m, 1H), 2.08, 2.09 (2 x s, 3H), 1.24 (t, *J* = 7.1 Hz, 3H), 0.98 (d, *J* = 6.8 Hz, 3H), 0.91 (dd, *J* = 1.9, 6.7 Hz, 3H).
^{13}C NMR (125 MHz, $CDCl_3$, DEPT) δ 170.81 (C), 170.77 (C), 167.0 (C), 166.8 (C), 156.5 (C), 156.4 (C), 77.6 (CH), 77.5 (CH), 65.0 (CH_2), 64.9 (CH_2), 61.2 (CH_2), 56.1 (CH), 56.0 (CH_2), 54.4 (CH), 54.3 (CH), 31.4 (CH), 21.2 (CH), 20.83 (CH_3), 20.81 (CH_3), 19.0 (CH_3), 18.9 (CH_3), 17.5 (CH_3), 17.3 (CH_3), 14.6 (CH_3).
HRMS (ESI+) 309.1421 calc'd for $C_{13}H_{22}N_2O_5Na$, found 309.1388.



5.138 **5.144a** **5.144b**

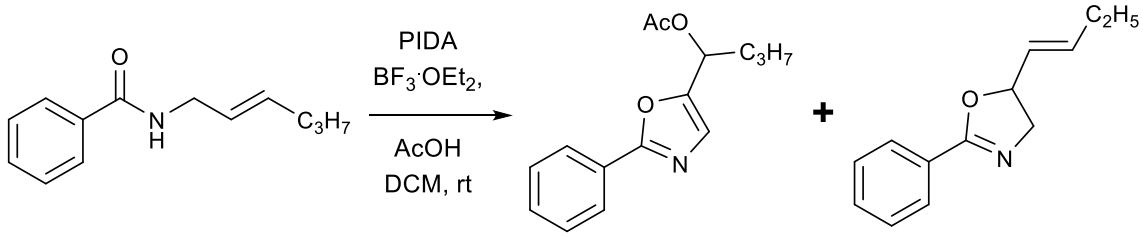
((4*S*,5*R*)-4-isopropyl-2-phenyl-4,5-dihydrooxazol-5-yl)methyl acetate (5.144a)

Purified by f.c.c. (1:4 EtOAc:Hexane) as a brown solid (10.2 mg, 32%).

IR (Thin Film) 3061, 2959, 2873, 1744, 1654, 1580, 1467, 1370, 1229, 1062, 1026, 695 cm^{-1}.
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (d, *J* = 7.6 Hz, 2H), 7.48 (t, *J* = 7.2 Hz, 1H), 7.41 (t, *J* = 7.7 Hz, 2H), 4.56 (ddd, *J* = 3.5, 6.4, 6.4 Hz, 1H), 4.26 (dd, *J* = 3.4, 12.0 Hz, 1H), 4.14 (dd, *J* = 6.5, 12.0 Hz, 1H), 3.80 (dd, *J* = 6.2, 6.2 Hz, 1H), 2.09 (s, 3H), 1.91 (qd, *J* = 6.6, 13.2 Hz, 1H), 1.02 (d, *J* = 6.8 Hz, 3H), 0.95 (d, *J* = 6.8 Hz, 3H).
^{13}C NMR (125 MHz, $CDCl_3$, DEPT) 171.0 (C), 162.6 (C), 131.5 (CH), 128.4 (CH), 127.8 (C), 79.3 (CH), 74.9 (CH), 66.1 (CH_2), 32.5 (CH), 21.0 (CH_3), 18.7 (CH_3), 18.0 (CH_3).
HRMS (ESI+) 284.1257 calc'd for $C_{15}H_{19}NO_3Na$, found 284.1257.
[α]$_D$ = –46.3 (c = 0.0062, DCM).

The relative configuration was determined to be *trans* through NOE studies (see spectral data). The diagnostic enhancement was observed for the methine bonded to

the oxygen when the isopropyl methyl groups were irradiated. Coupling constants between H_a & H_b was also consistent with reported related results. [12]



5.142a **5.146** ***15%*** **5.147** ***22%*** **tenative structure**

1-(2-phenyloxazol-5-yl)butyl acetate (5.146):

The reaction was performed under the general cyclization conditions. The product was isolated by f.c.c. (1:4 to 1:2 EtOAc:Hexane) to give the product (7.3 mg, 15%).

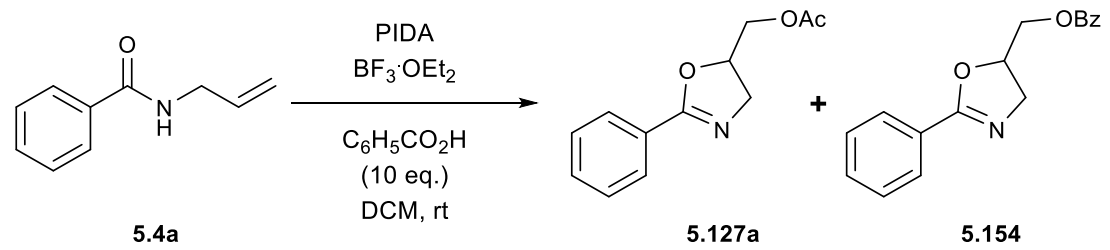
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (td, *J* = 2.4, 5.0 Hz, 2H), 7.47-7.45 (m, 3H), 7.12 (s, 1H), 5.96, t, *J* = 7.2 Hz, 1H), 2.09 (d, *J* = 11.9 Hz, 3H), 2.06-1.93 (m, 2H), 1.46-1.32 (m, 2H), 0.97 (t, *J* = 7.4 Hz, 3H).
^{13}C NMR (125 MHz, $CDCl_3$, DEPT) δ 170.30 (C), 161.89 (C), 150.05 (C), 130.64 (CH), 128.91 (CH), 127.48 (C), 126.82 (CH), 126.56 (CH), 66.68 (CH), 34.49 (CH_2), 21.21 (CH_3), 18.79 (CH_2), 13.80 (CH_3).

(*E*)-5-(but-1-en-1-yl)-2-phenyl-4,5-dihydrooxazole (5.147):

Compound **5.147** was also isolated (9 mg, 22%).

H NMR (500 MHz, $CDCl_3$) δ 7.47 (t, *J* = 7.3 Hz, 1H), 7.40 (t, *J* = 7.2 Hz, 2H), 5.88 (td, *J* = 6.3, 15.3 Hz, 2H), 5.58 (dd, *J* = 7.8, 15.3 Hz, 1H), 5.12-5.07 (m, 1H), 4.20 (app. s, 1H), 3.77 (app. s, 1H), 2.14-2.08 (m, 2H), 1.03 (t, *J* = 7.5 Hz, 3H).

[12] W. R. Roush, J. A. Straub and R. J. Brown, *The Journal of Organic Chemistry*, 1987, **52**, 5127-5136.

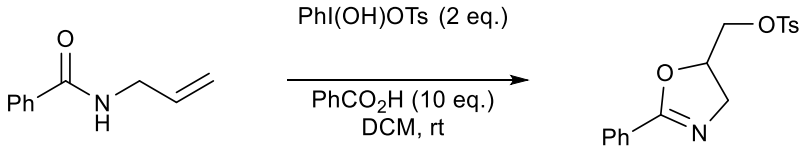


(2-phenyl-4,5-dihydrooxazol-5-yl)methyl benzoate (5.154):

The cyclization was performed under the general cyclization procedures, but with 10 eq. BzOH instead of AcOH. Compound **5.154** was isolated (22.4 mg, 40%) in addition to acetate **5.127a** (16.6 mg, 43%) after f.c.c (1:4 EtOAc:Hexane).

Isolated by f.c.c. (1:4 EtOAc:Hexane) as a yellow oil (22.4 mg, 40% yield).

IR (Thin Film) 3062, 2945, 2875, 1722, 1651, 1450, 1272, 1122, 1062, 1025, 711, 695 cm^{-1};
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04-8.02 (m, 2H), 7.97-7.95 (m, 2H), 7.57-7.54 (m, 1H), 7.50-7.46 (m, 1H), 7.43-7.40 (m, 4H), 5.09-5.04 (m, 1H), 4.57 (dd, *J* = 3.5, 12.1 Hz, 1H), 4.45 (dd, *J* = 5.8, 12.1 Hz, 1H), 4.23 (dd, *J* = 10.0, 14.8 Hz, 1H), 3.97 (dd, *J* = 7.1, 14.9 Hz, 1H).
^{13}C NMR (125 MHz, $CDCl_3$, DEPT) 166.4 (C), 164.3 (C), 133.4 (CH), 131.6 (CH), 129.9 (CH), 129.7 (C), 128.6 (CH), 128.5 (CH), 128.3 (CH), 127.6 (C), 77.1 (CH), 65.8 (CH_2), 57.2 (CH_2).
HRMS (ESI+) 304.0944 calc'd for $C_{17}H_{15}NO_3Na$, found 304.0928.

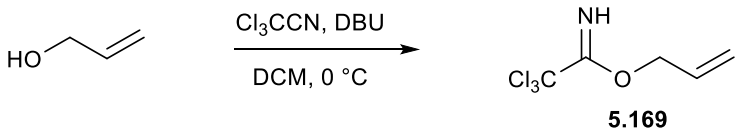


5.127a **5.159**

(2-phenyl-4,5-dihydrooxazol-5-yl)methyl 4-methylbenzenesulfonate (5.159):

Koser's reagent (48 mg, 0.124 mmol) and benzoic acid (75 mg, 0.62 mg) were added to a vial fitted with a Teflon cap. The solids were suspended in DCM (2 mL) and the amide (10 mg, 0.062 mmol) was added. The solution was stirred for 20 minutes at which time all starting material had been consumed. The reaction was quenched with 10% $Na_2S_2O_3$ (0.5 mL) and saturated $NaHCO_3$ (1 mL), which was stirred for 10 minutes. The organic layer was separated, and the aqueous layer was extracted with DCM (2 x 1 mL). The combined organic layers were dried with $MgSO_4$ and concentrated. The compound was isolated by f.c.c (1:1 EtOAc:Hexane) as a tan solid (10.1 mg, 49 %).

IR (Thin Film) 3055, 2953, 2871, 1651, 1449, 1354, 1292, 1271, 1173, 1063, 975, 828, 812, 790 cm-1 . 1
^{1}HNMR (500 MHz, CDCl3) δ 7.83-7.82 (m, 2H), 7.78-7.77 (m, 2H), 7.48 (ddd, J = 1.2, 1.2, 7.5 Hz, 1H), 7.40-7.37 (m, 2H), 7.28 (d, J = 8.3 Hz, 2H), 4.87 (dddd, J = 4.0, 6.0, 7.0, 10.0 Hz, 1H), 4.19 (dd, J = 4.0, 11.0 Hz, 1H), 4.14 (dd, J = 6.0, 11.0 Hz, 1H), 4.11 (dd, J = 10.0, 15.6 Hz, 1H), 3.78 (dd, J = 7.1, 15.0 Hz, 1H), 2.40 (s, 3 H).
^{13}C NMR (125 MHz, CDCl3, DEPT) 163.8 (C), 145.2 (C), 132.7 (C), 131.7 (CH), 130.1 (CH), 128.4 (CH), 128.35 (CH), 128.1 (CH), 127.2 (C), 76.3 (CH), 70.1 (CH2), 56.9 (CH2), 21.8 (CH3).
HRMS (ESI+) 354.0771 calc'd for $C_{17}H_{17}NO_4SNa$, found 354.0768.



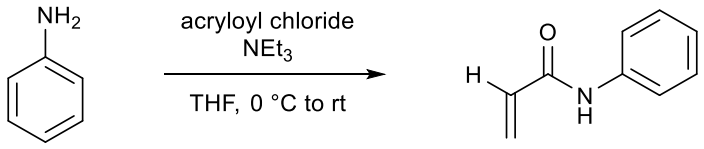
5.169

allyl 2,2,2-trichloroacetimidate (5.169):

Allyl alcohol (500 mg, 8.9 mmol, 1 eq.) was dissolved in DCM (18 mL). DBU (274 mg, 1.8 mmol, 0.2 eq.) was added and the solution was cooled to 0 °C. Trichloroacetonitrile (2.57 g, 17.8 mmol, 2 eq.) was added dropwise. The reaction was

stirred at 0 °C for 1h. The solvent was removed and the crude material was purified by f.c.c. (1:10 EtOAc:Hexane) to give the product (1.136 g, 63%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.32 (bs, 1H), 6.10-5.97 (m, 1H), 5.44 (dd, *J* = 1.5, 17.2 Hz, 1H), 5.31 (dd, *J* = 1.2, 10.5 Hz, 1H), 4.82-4.80 (m, 2H).

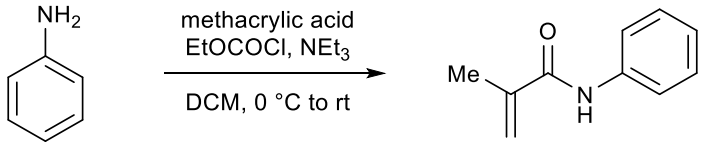


5.172

N-phenylacrylamide (5.172):

Aniline (2.05 g, 22 mmol, 2 eq.) and NEt_3 (1.7 g, 16.5 mmol, 1.5 eq.) were dissolved in THF (40 mL). The solution was cooled to 0 °C and acryloyl chloride (1.0 g, 11 mmol, 1 eq.) was added. The reaction was warmed to rt and stirred for 18 h. The reaction was quenched with 50 mL saturated, aqueous $NaHCO_3$ and extracted with 2 x 20 mL EtOAc. The combined organic fractions were washed with brine, dried with Na_2SO_4 and concentrated. Purification by f.c.c. (1:5 to 1:4 EtOAc:Hexane) gave the product (721.1 mg, 45%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (d, *J* = 7.7 Hz, 2H), 7.50 (bs, 1H), 7.33 (t, *J* = 7.9 Hz, 2H), 7.12 (t, *J* = 7.3 Hz, 1H), 6.44 (dd, *J* = 1.3, 16.8 Hz, 1H), 6.26 (dd, *J* = 10.1, 16.8 Hz, 1H), 5.76 (dd, *J* = 1.3, 10.1 Hz, 1H).



5.174

N-phenylmethacrylamide (5.174):

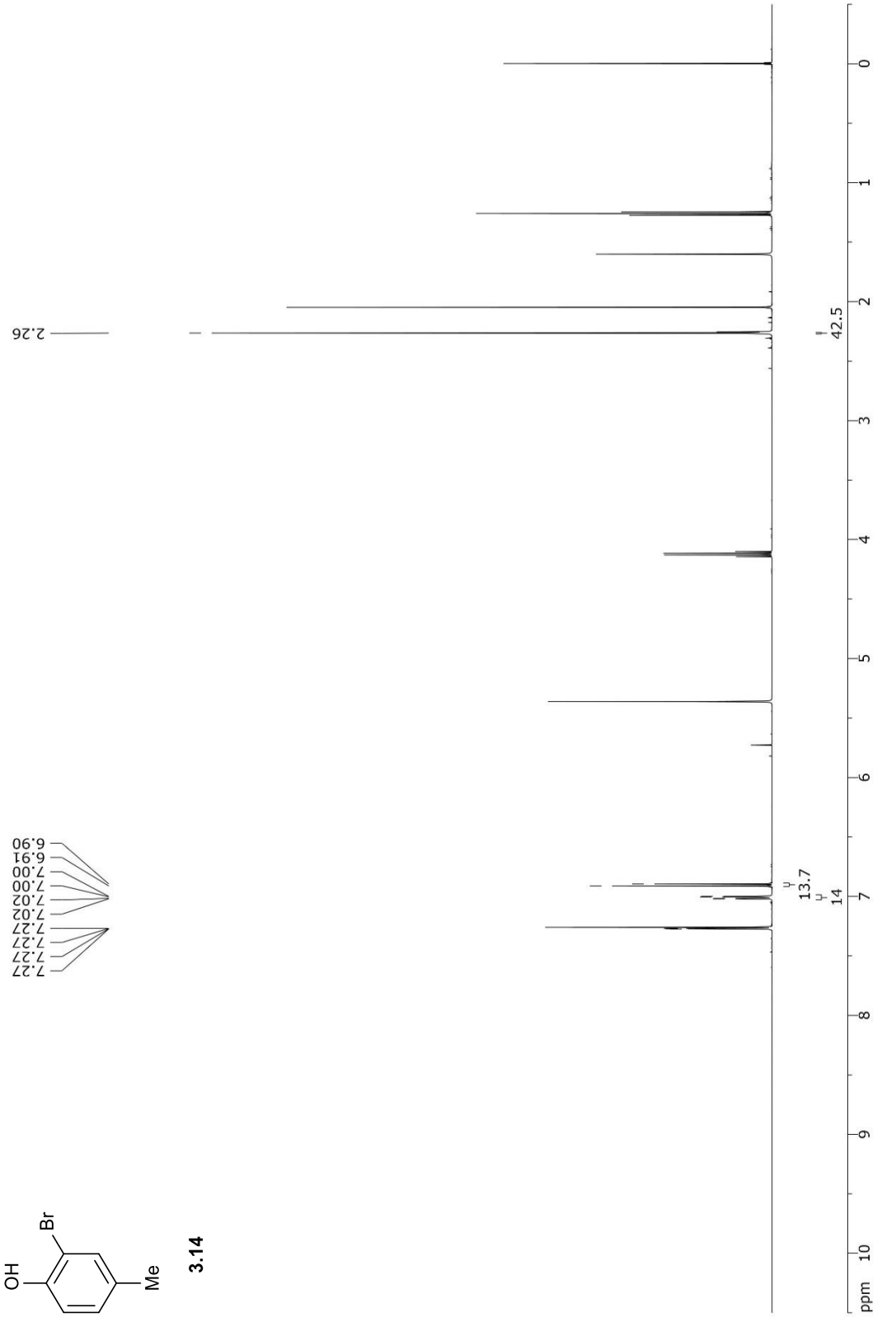
Methacrylic acid (250 mg, 2.9 mmol, 1 eq.) and NEt_3 (586 mg, 5.8 mmol, 2 eq.) were dissolved in DCM (7 mL) and the solution was cooled to 0 °C. Ethyl chloroformate (314.7 mg, 2.9 mmol, 1 eq.) was added. The solution was stirred for 30 min. at 0 °C. Aniline (324 mg, 3.5 mmol, 1.2 eq.) was added and the solution was allowed to warm to rt and stirred for 18 h. The reaction was quenched with 20 mL saturated, aqueous $NaHCO_3$ and the organic layer was separated. The aqueous layer was washed with 2 x 20 mL DCM. The combined organic layers were washed with brine, dried with Na_2SO_4

and concentrated. The crude material was purified by f.c.c (1:6 EtOAc:Hexane) to give the product (214 mg, 46%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (d, *J* = 7.8 Hz, 2H), 7.33 (t, *J* = 7.9 Hz, 2H), 7.12 (t, *J* = 7.4 Hz, 1H), 5.79 (s, 1H), 5.46 (t, *J* = 0.7 Hz, 1H), 2.06 (s, 3H).

Appendix 2

Chapter 3 Spectra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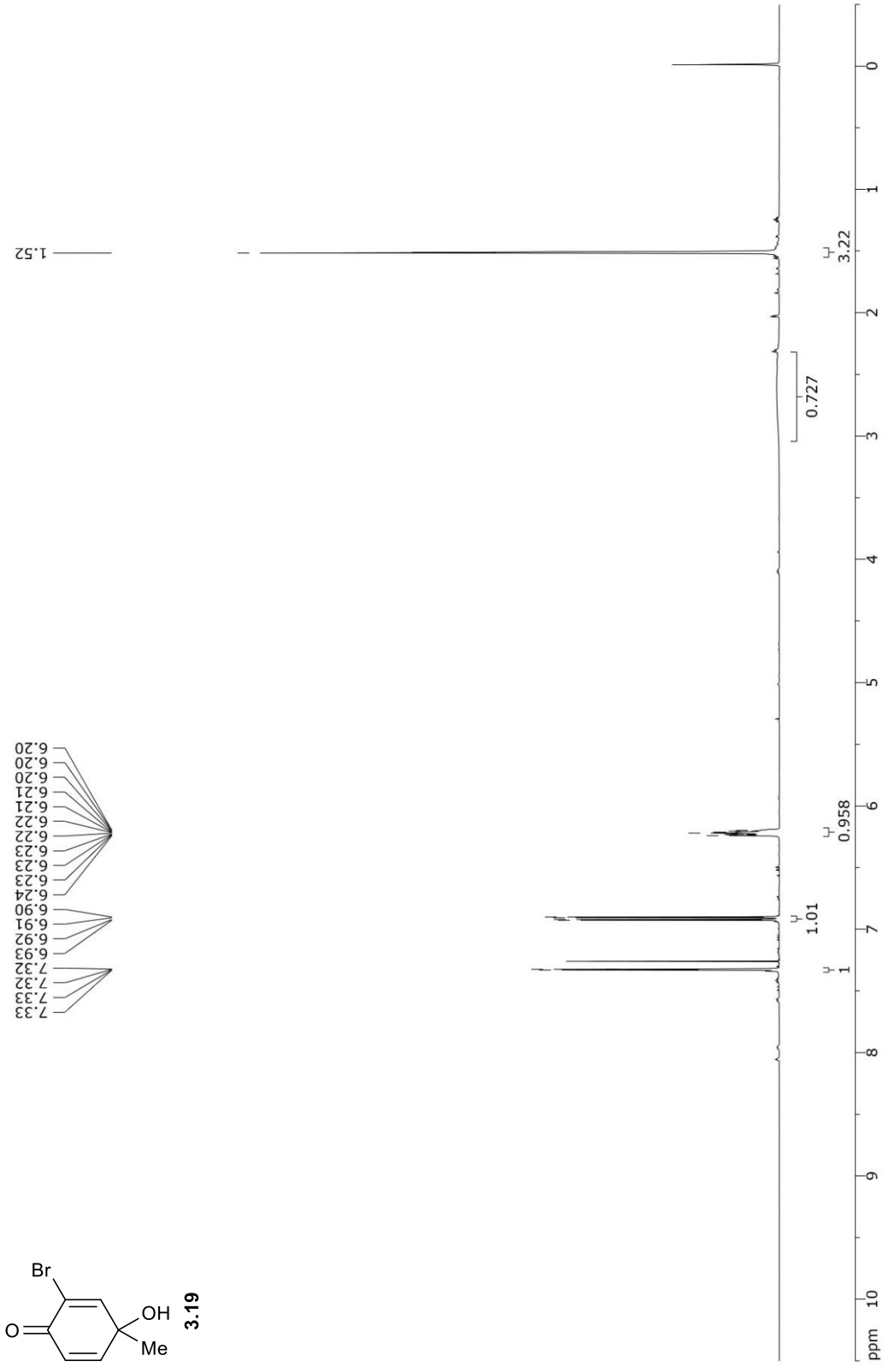
Br
Me
3.14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6.90
6.91
6.92
6.93
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1
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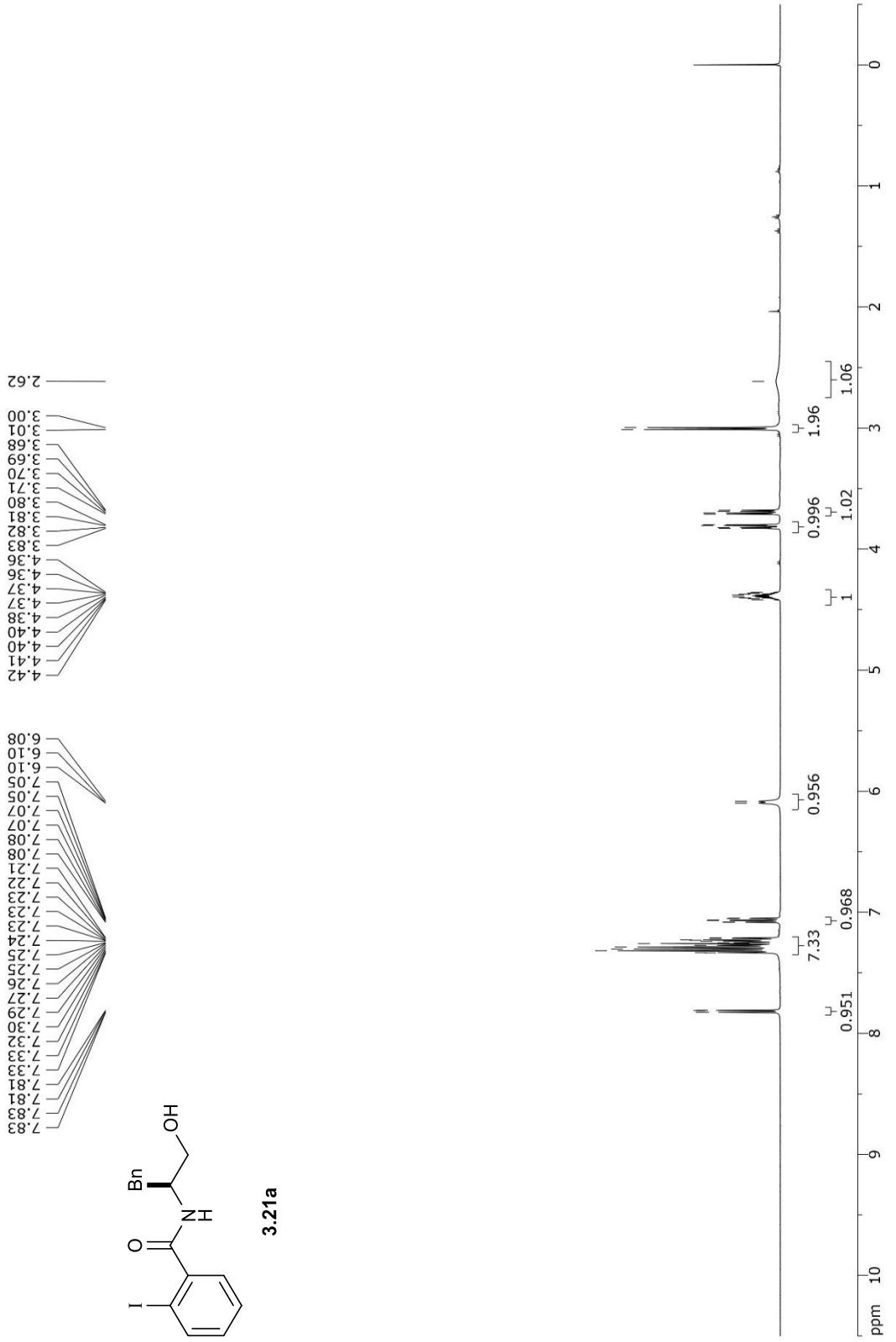
Me
O
3.19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7.83
7.83
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O
N
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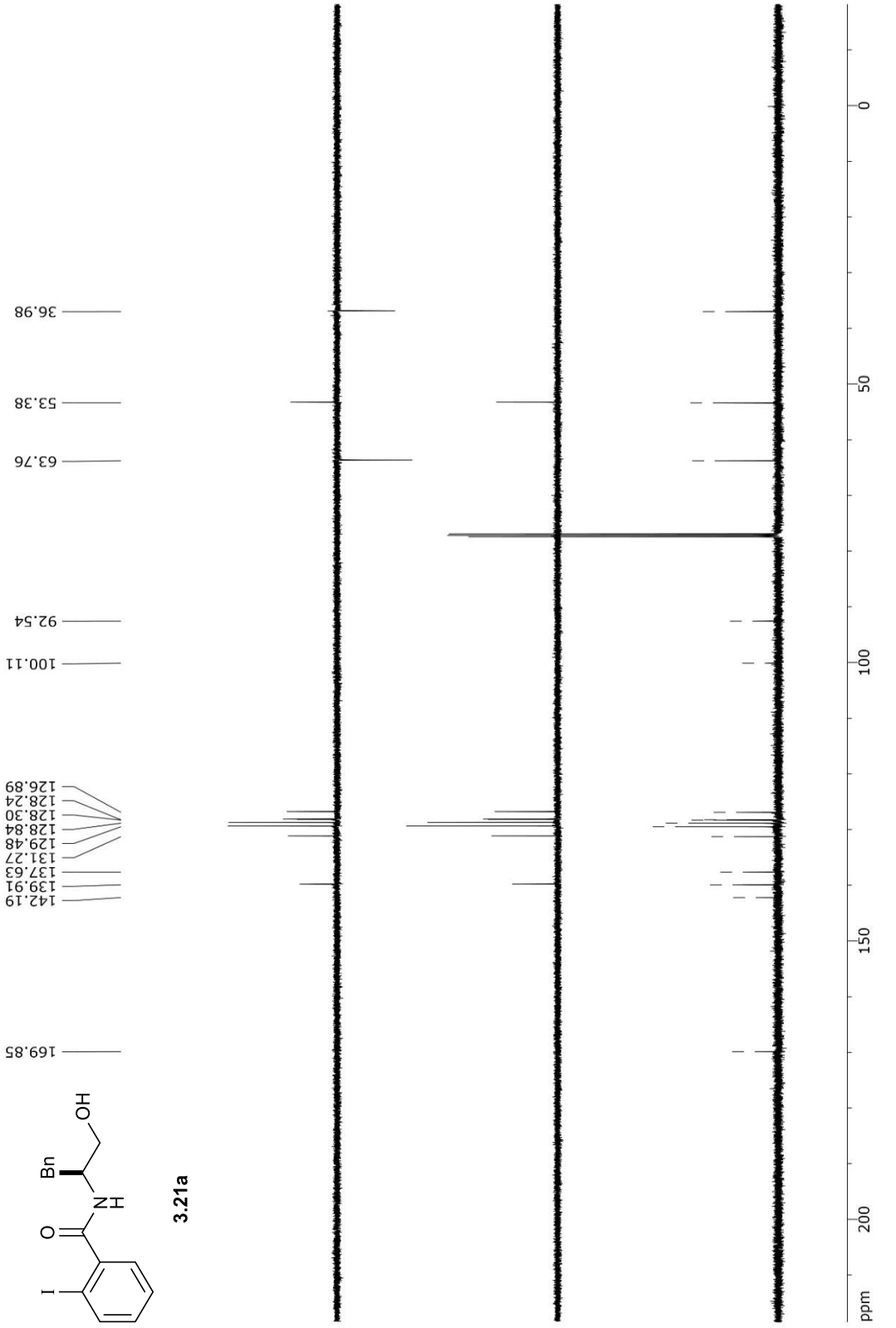
ppm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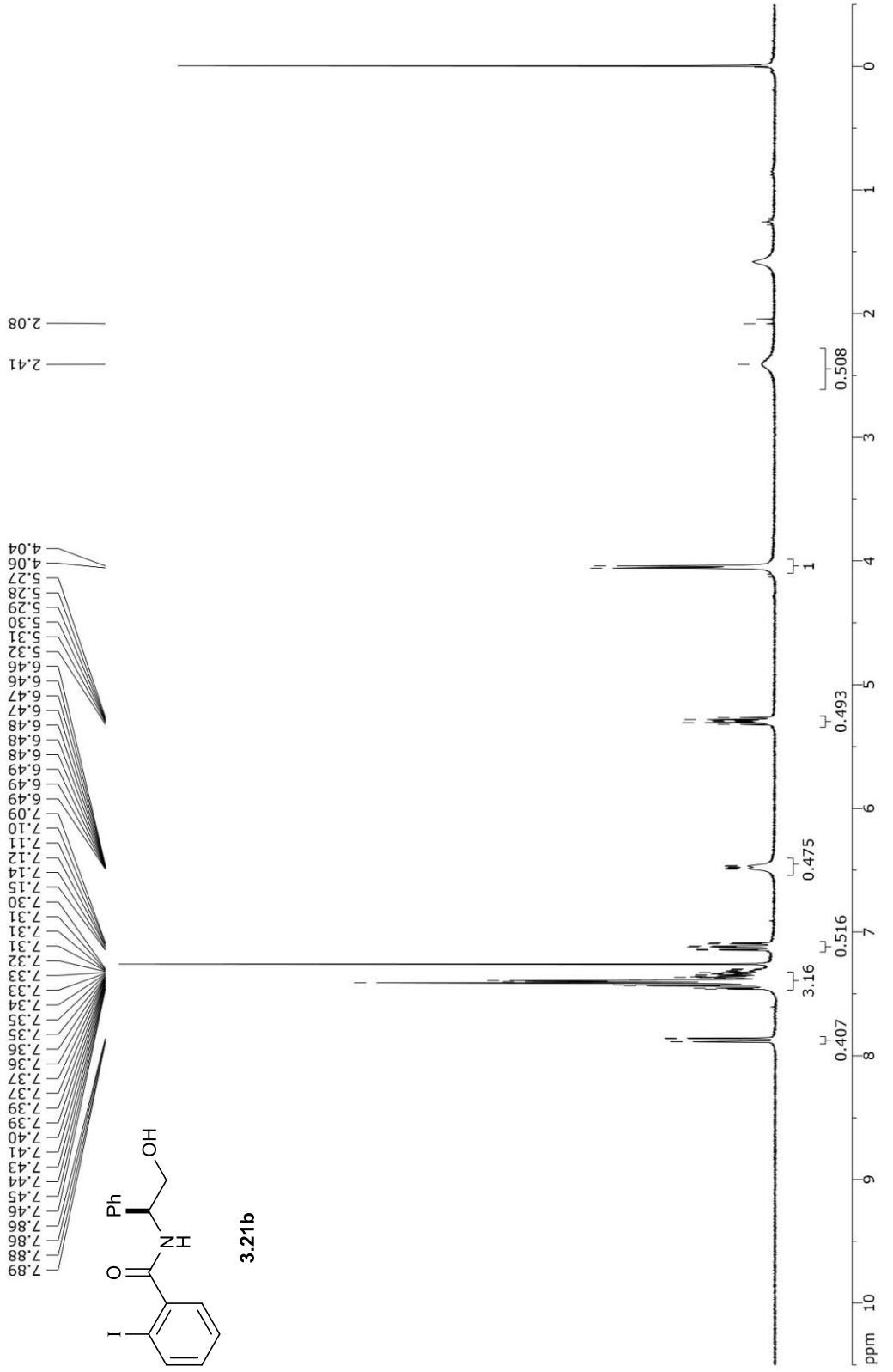
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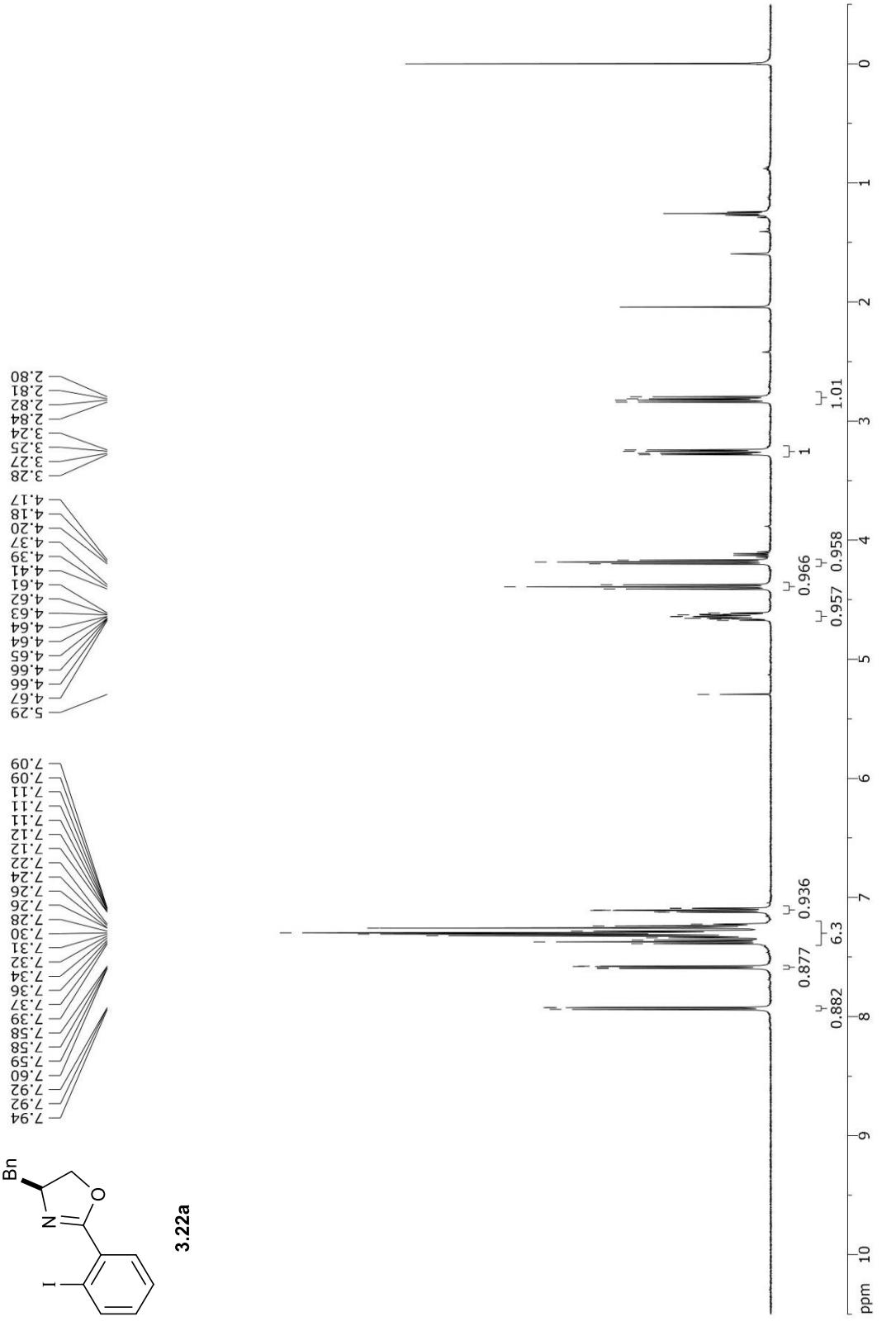
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3.28
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3.25
3.24
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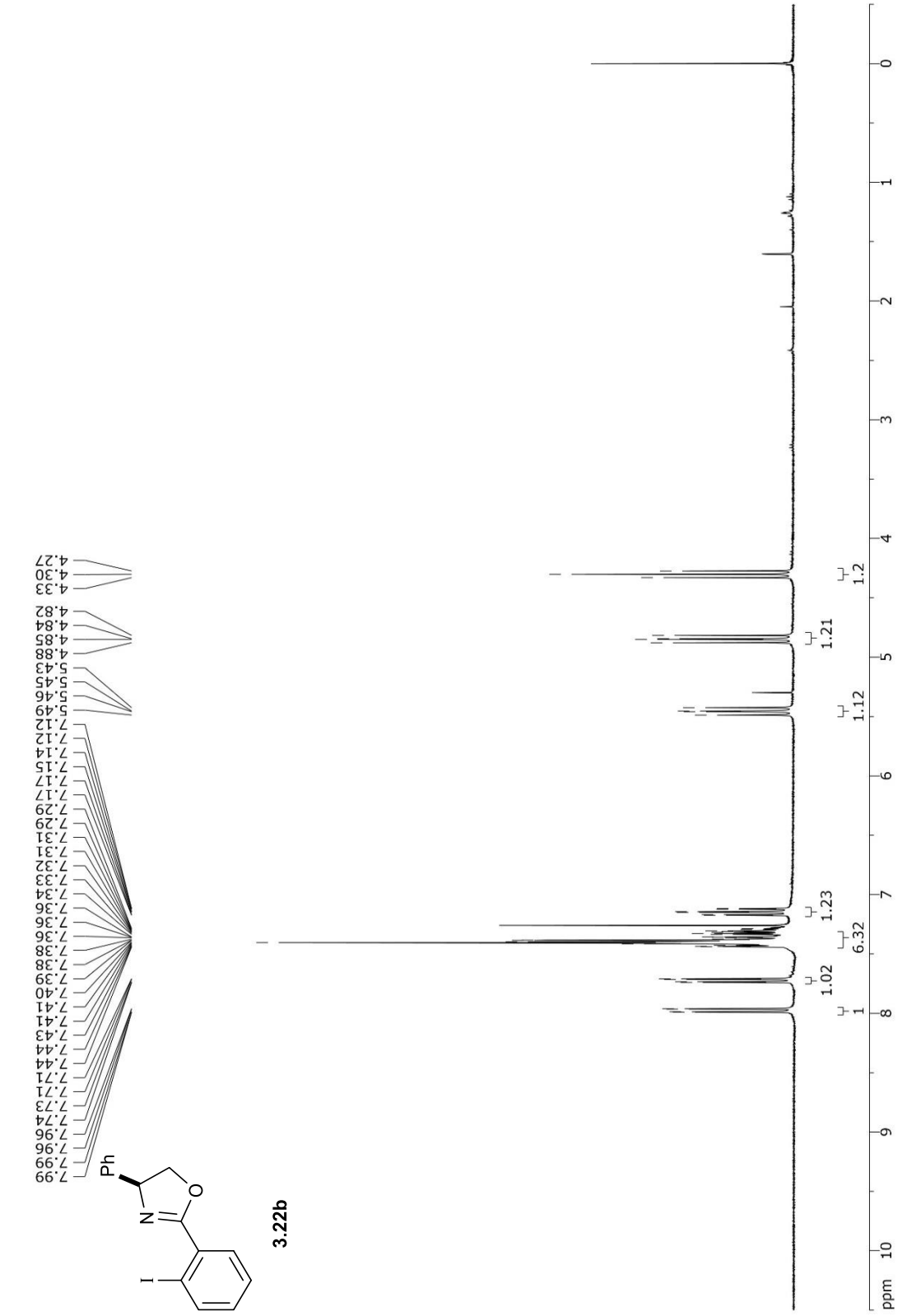
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7.36
7.36
7.36
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7.33
7.32
7.31
7.31
7.29
7.29
7.17
7.17
7.15
7.14
7.12
7.12
5.49
5.46
5.45
5.43
4.88
4.85
4.84
4.82
4.33
4.30
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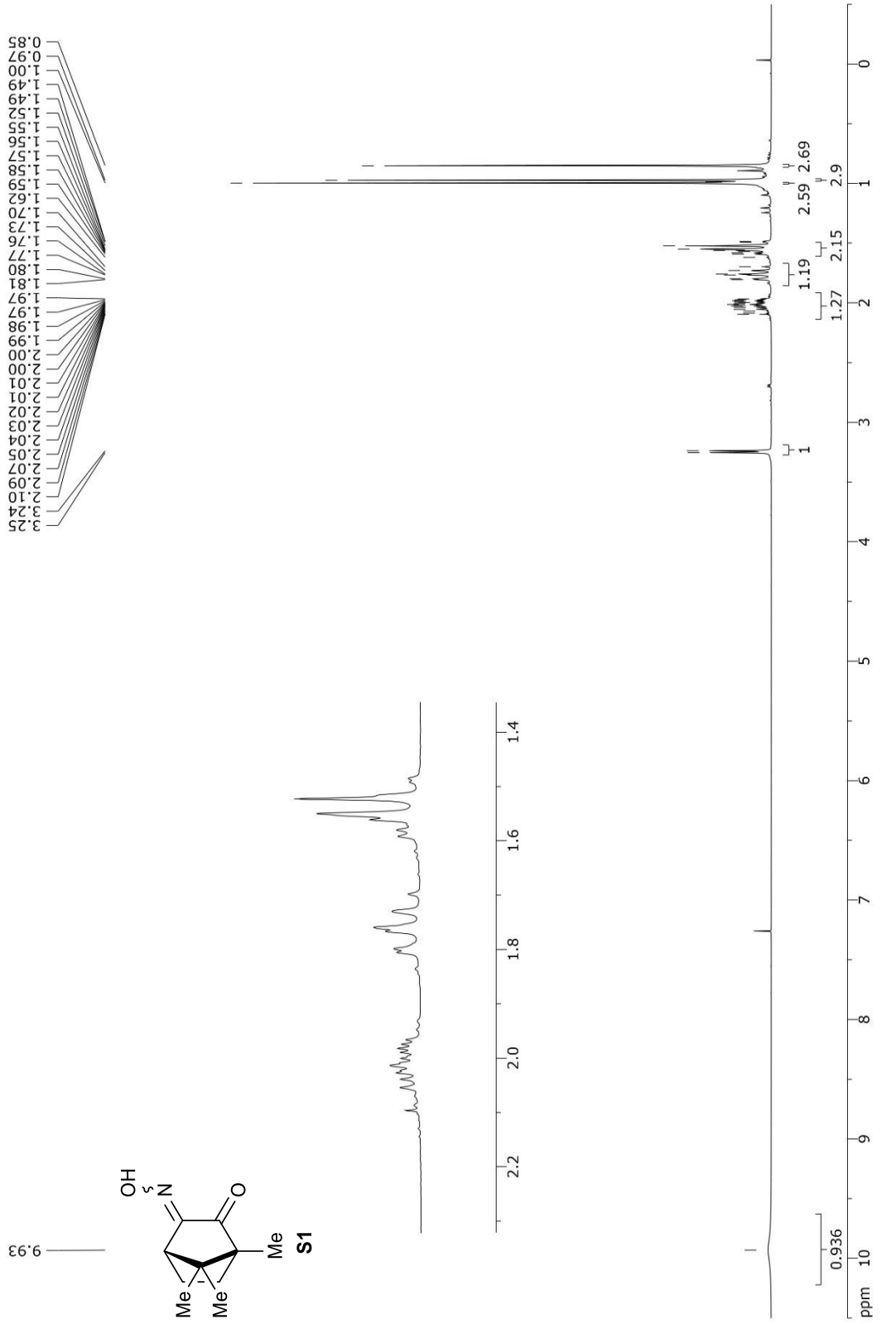
1.2
ppm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O
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2.04
2.03
2.02
2.01
2.01
2.00
2.00
1.99
1.98
1.97
1.97
1.81
1.80
1.77
1.76
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1.62
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1.58
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1.56
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1.52
1.49
1.49
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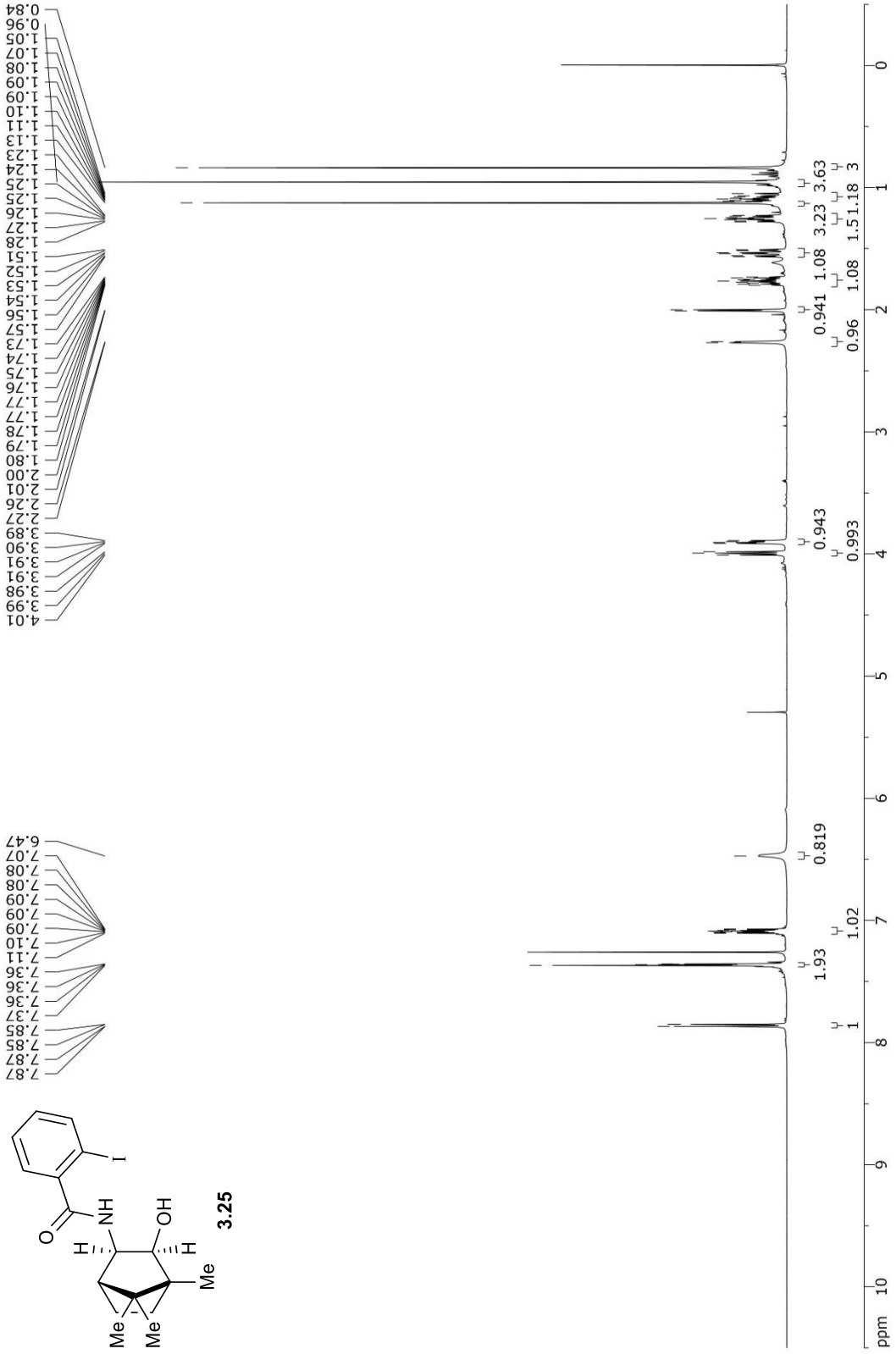
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1.25
1.26
1.27
1.28
1.51
1.52
1.53
1.54
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1.57
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1.74
1.75
1.76
1.77
1.77
1.78
1.79
1.80
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2.27
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3.90
3.91
3.91
3.98
3.99
4.01
6.47
7.07
7.08
7.08
7.09
7.09
7.09
7.10
7.11
7.36
7.36
7.36
7.37
7.85
7.85
7.87
7.87
1
1.93
1.02
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0.96
0.941
1.08
1.08
1.5
3.23
1.18
3.63
3
ppm
10
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3
2
1
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H
OH
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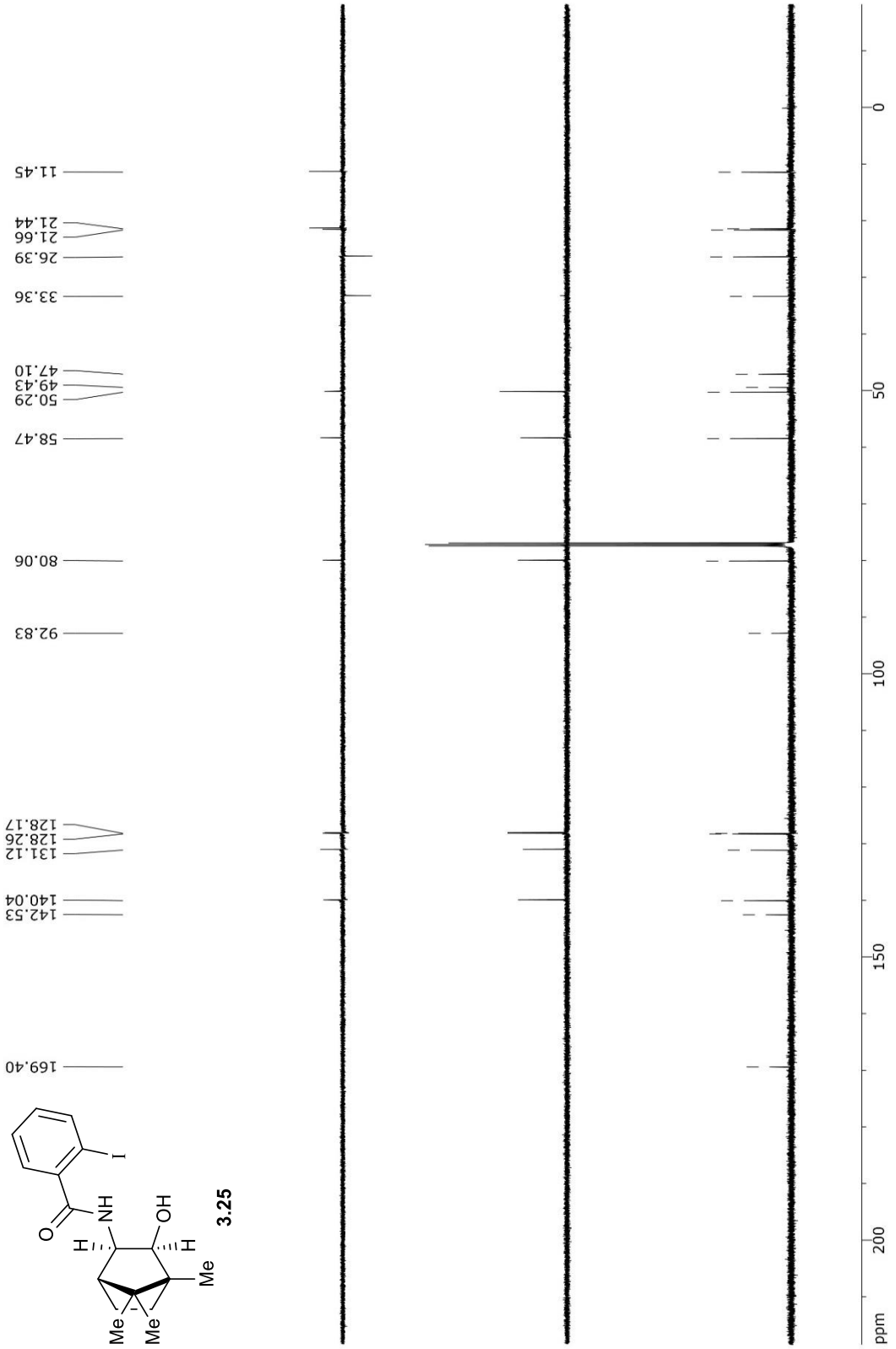
Me
Me
Me
I
3.25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21.66
26.39
33.36
47.10
49.43
50.29
58.47
80.06
92.83
128.17
128.26
131.12
140.04
142.53
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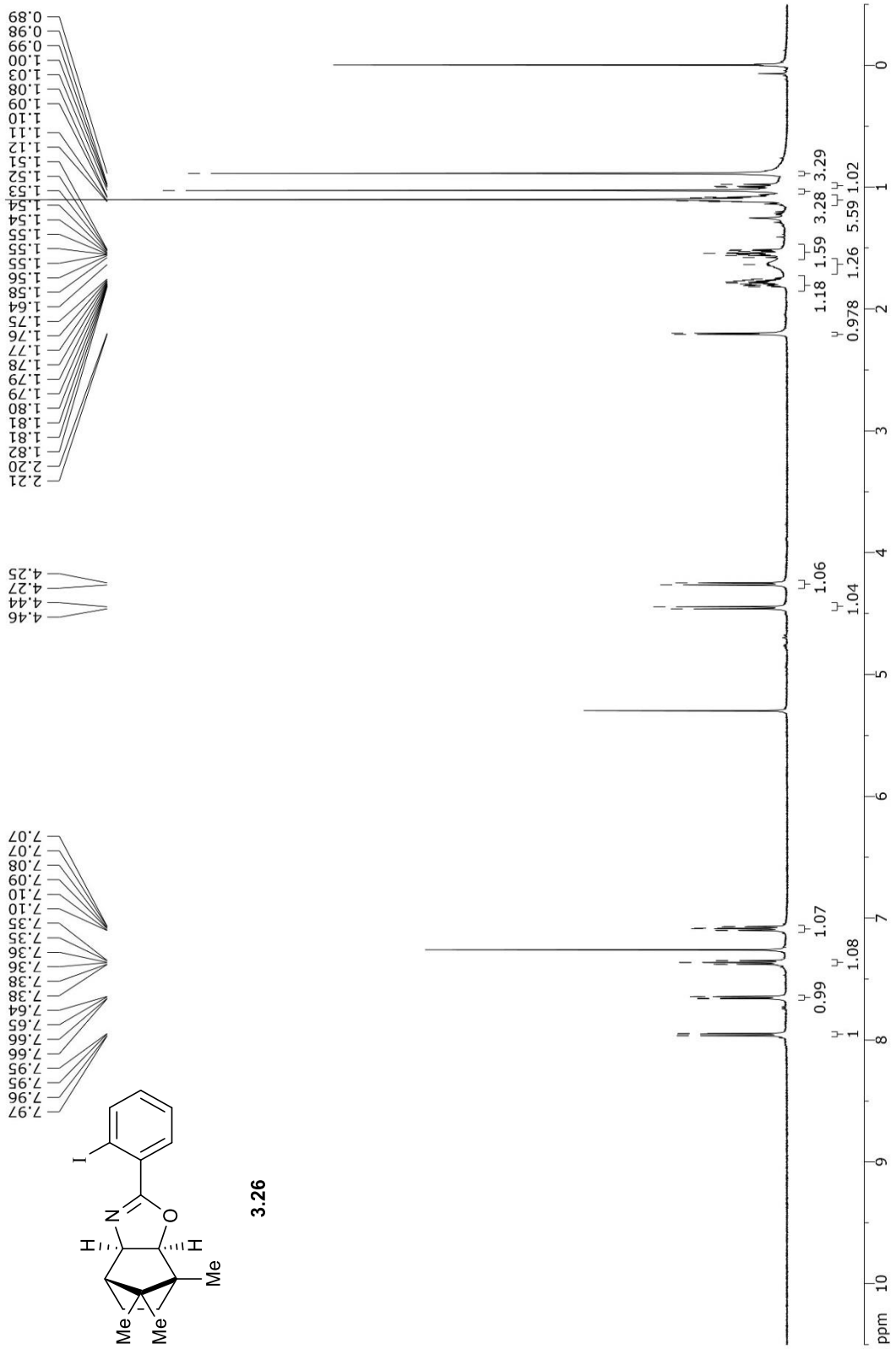
50
100
150
200
I
O
NH
H
OH
H
Me
Me
Me
3.25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0.98
0.99
1.00
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1.10
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1.12
1.51
1.52
1.53
1.54
1.54
1.55
1.55
1.55
1.56
1.58
1.64
1.75
1.76
1.77
1.78
1.79
1.79
1.80
1.81
1.81
1.82
2.20
2.21
4.25
4.27
4.44
4.46
7.07
7.07
7.08
7.09
7.10
7.10
7.35
7.35
7.36
7.36
7.38
7.38
7.64
7.65
7.66
7.66
7.95
7.95
7.96
7.97
I
N
O
H
H
Me
Me
Me
3.26
0.99
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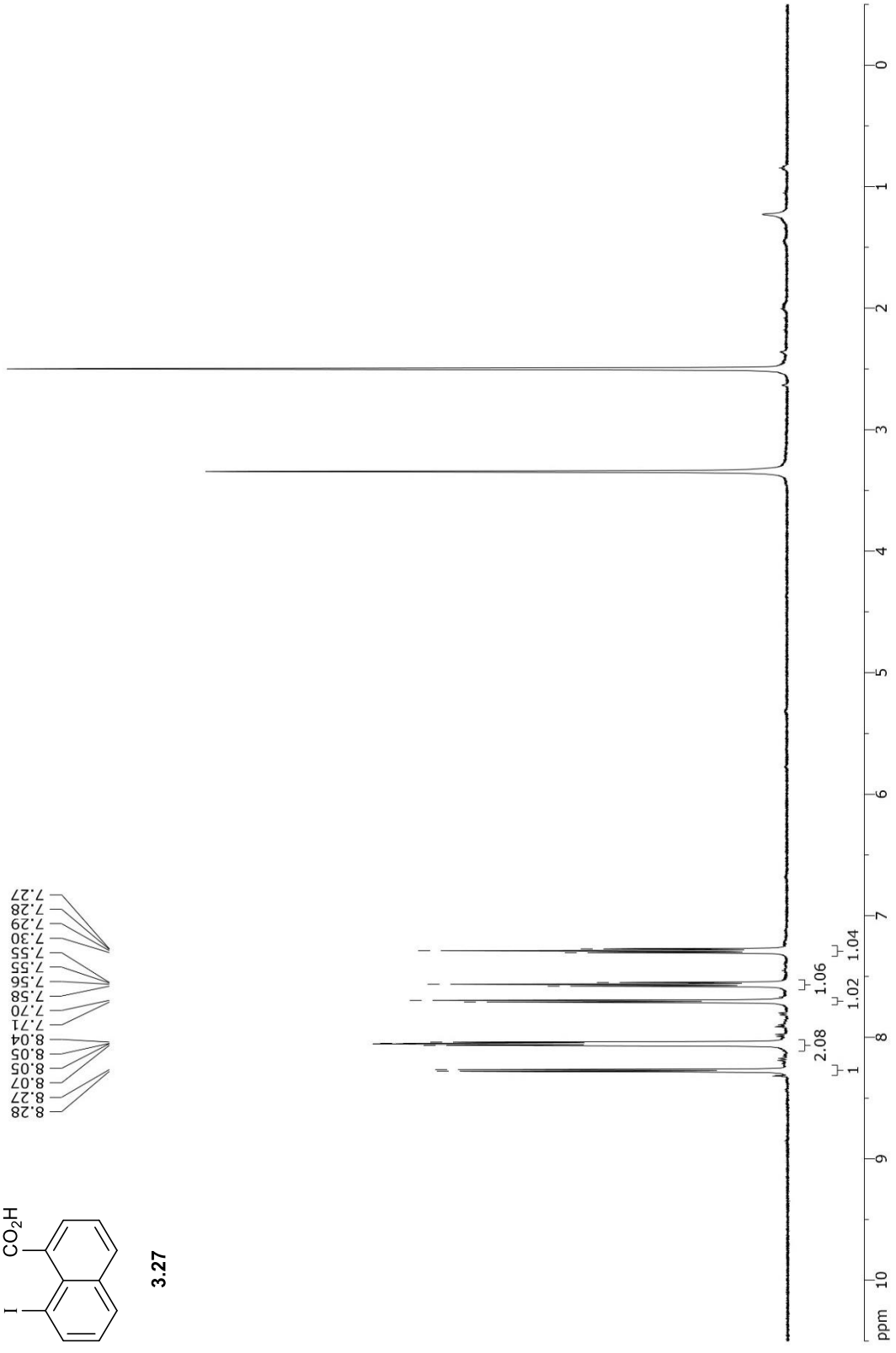
1.02
ppm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7.28
7.27
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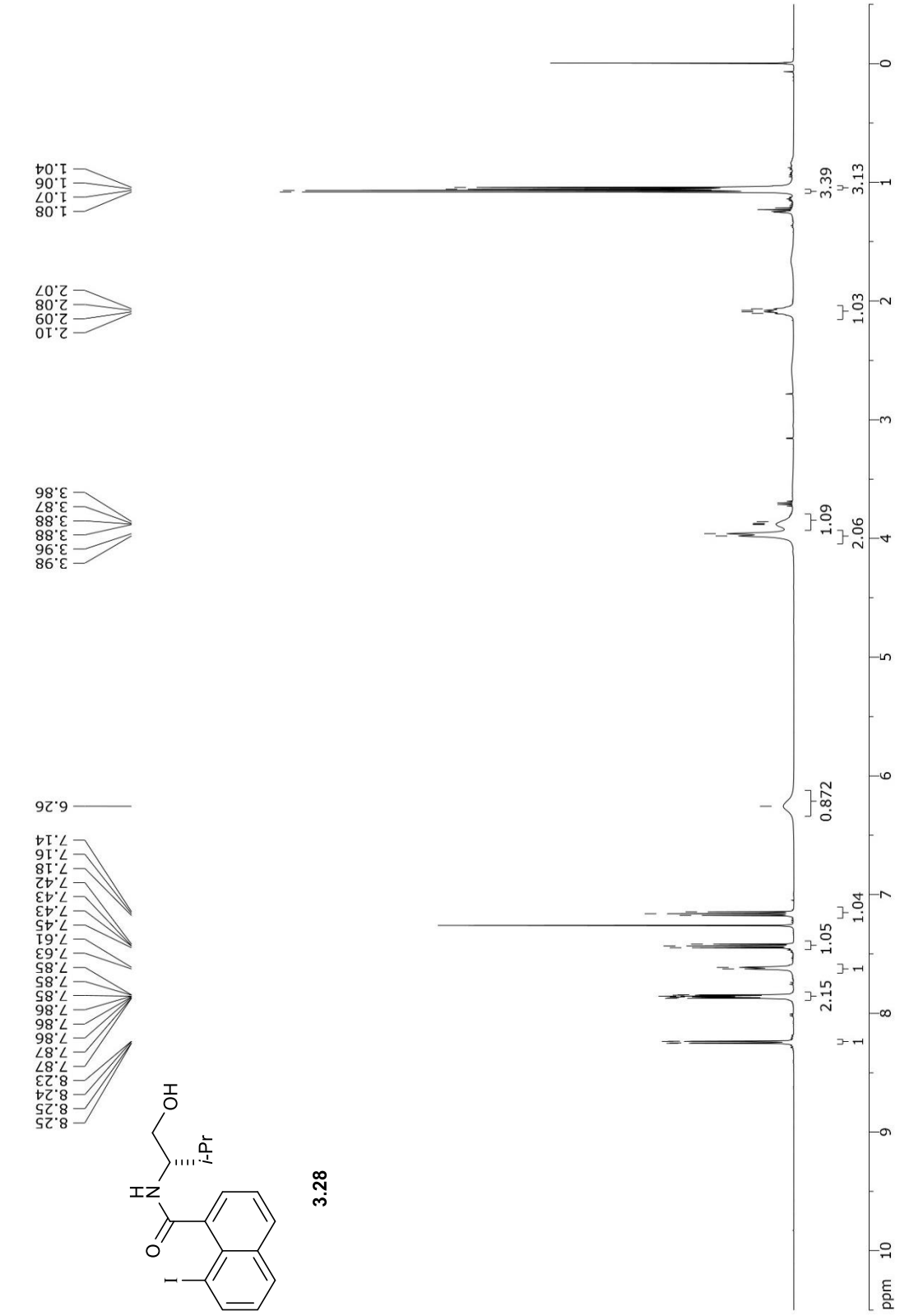
1.02
1.04
ppm
CO2H
I

3.27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8.25
8.24
8.23
7.87
7.87
7.86
7.86
7.86
7.85
7.85
7.85
7.63
7.61
7.45
7.43
7.43
7.42
7.18
7.16
7.14
6.26
3.98
3.96
3.88
3.88
3.87
3.86
2.10
2.09
2.08
2.07
1.08
1.07
1.06
1.04
2.15
1.05
1.04
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2.06
1.03
3.39
3.13
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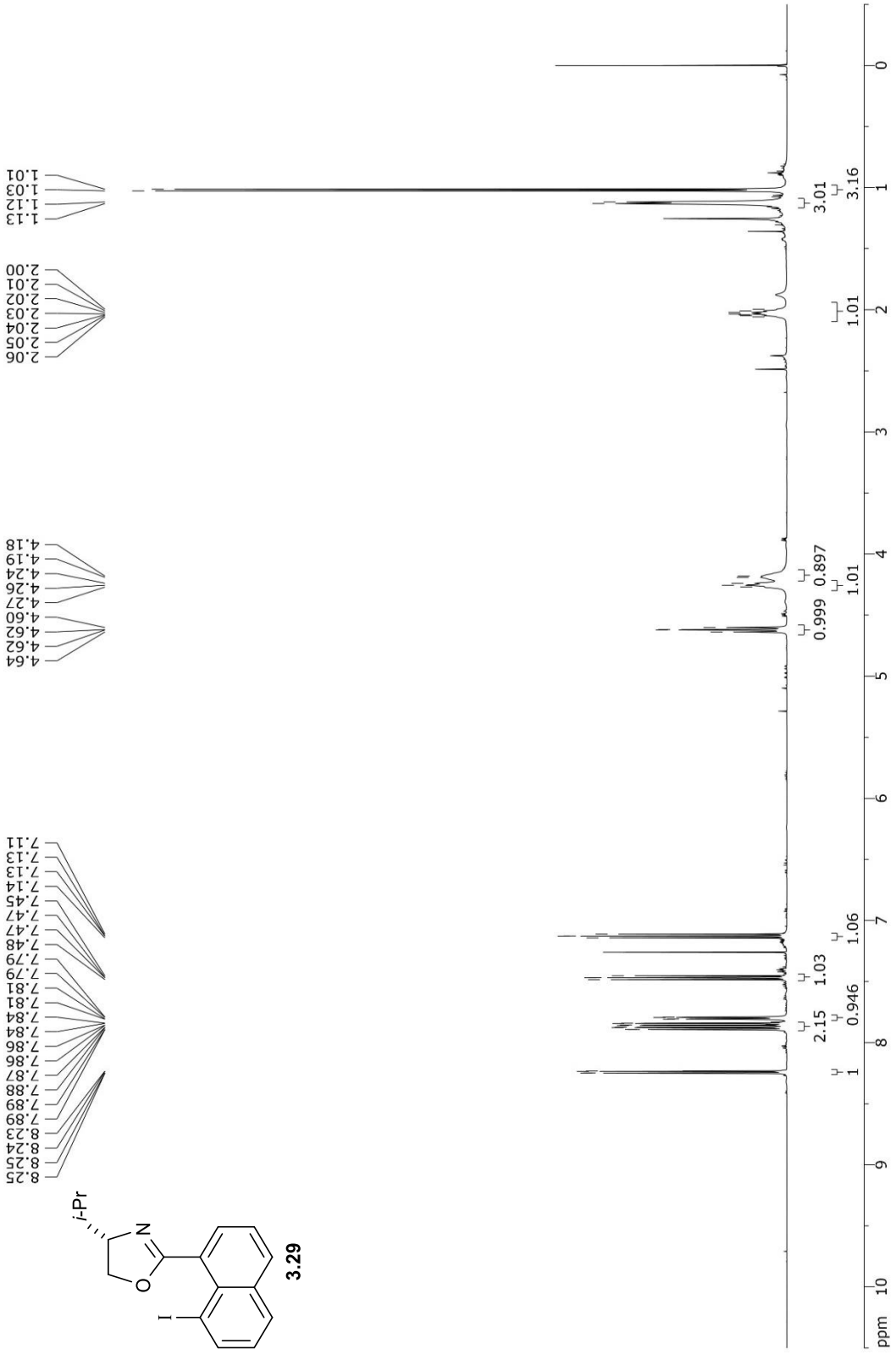
H
N
O
OH
i-Pr
I

3.28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7.87
7.86
7.86
7.84
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7.81
7.81
7.79
7.79
7.48
7.47
7.47
7.45
7.14
7.13
7.13
7.11
4.64
4.62
4.62
4.60
4.27
4.26
4.24
4.19
4.18
2.06
2.05
2.04
2.03
2.02
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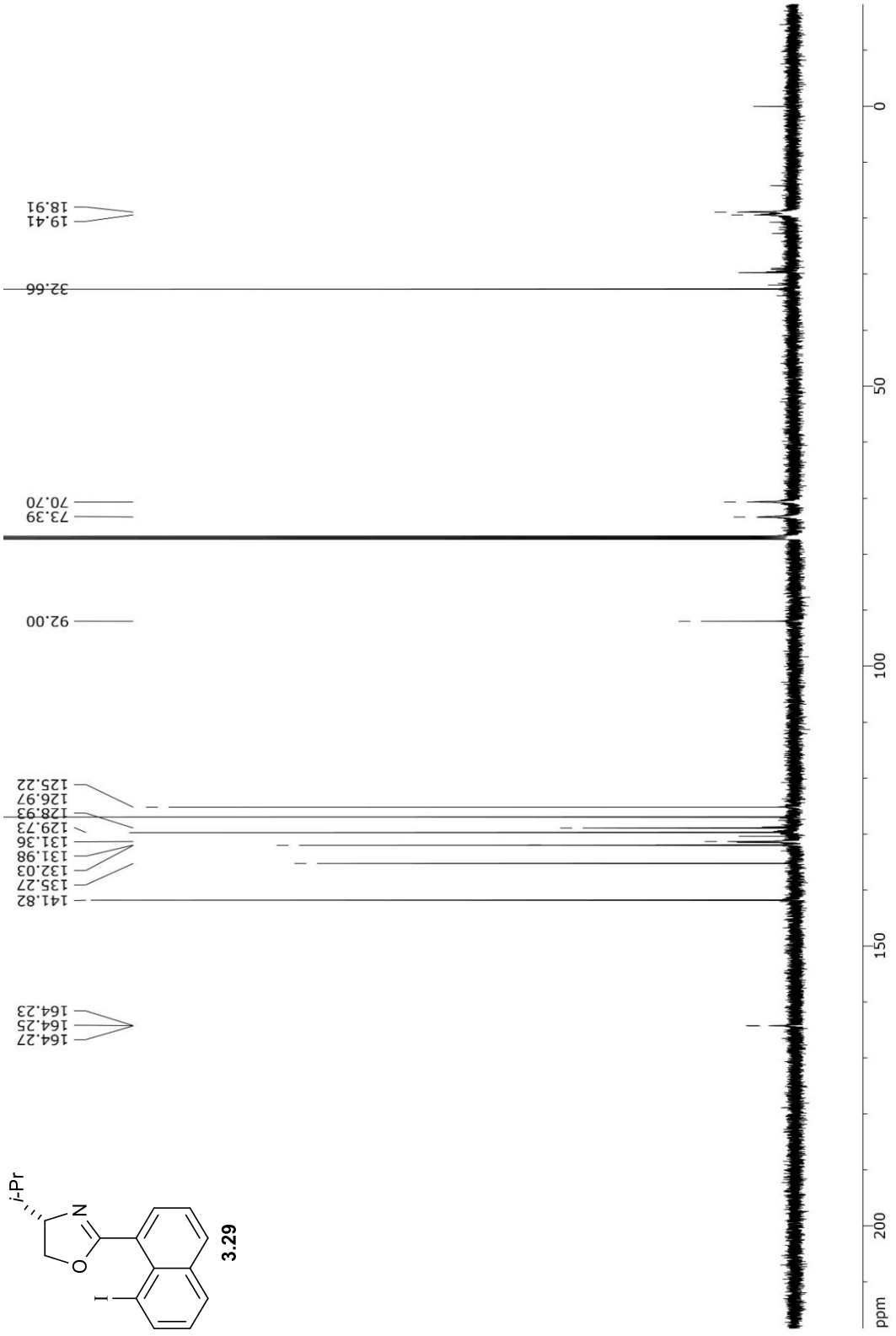
2.00
1.13
1.12
1.03
1.01
i-Pr
N
O
I
3.29
ppm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19.41
32.66
70.70
73.39
92.00
125.22
126.97
128.93
129.73
131.36
131.98
132.03
135.27
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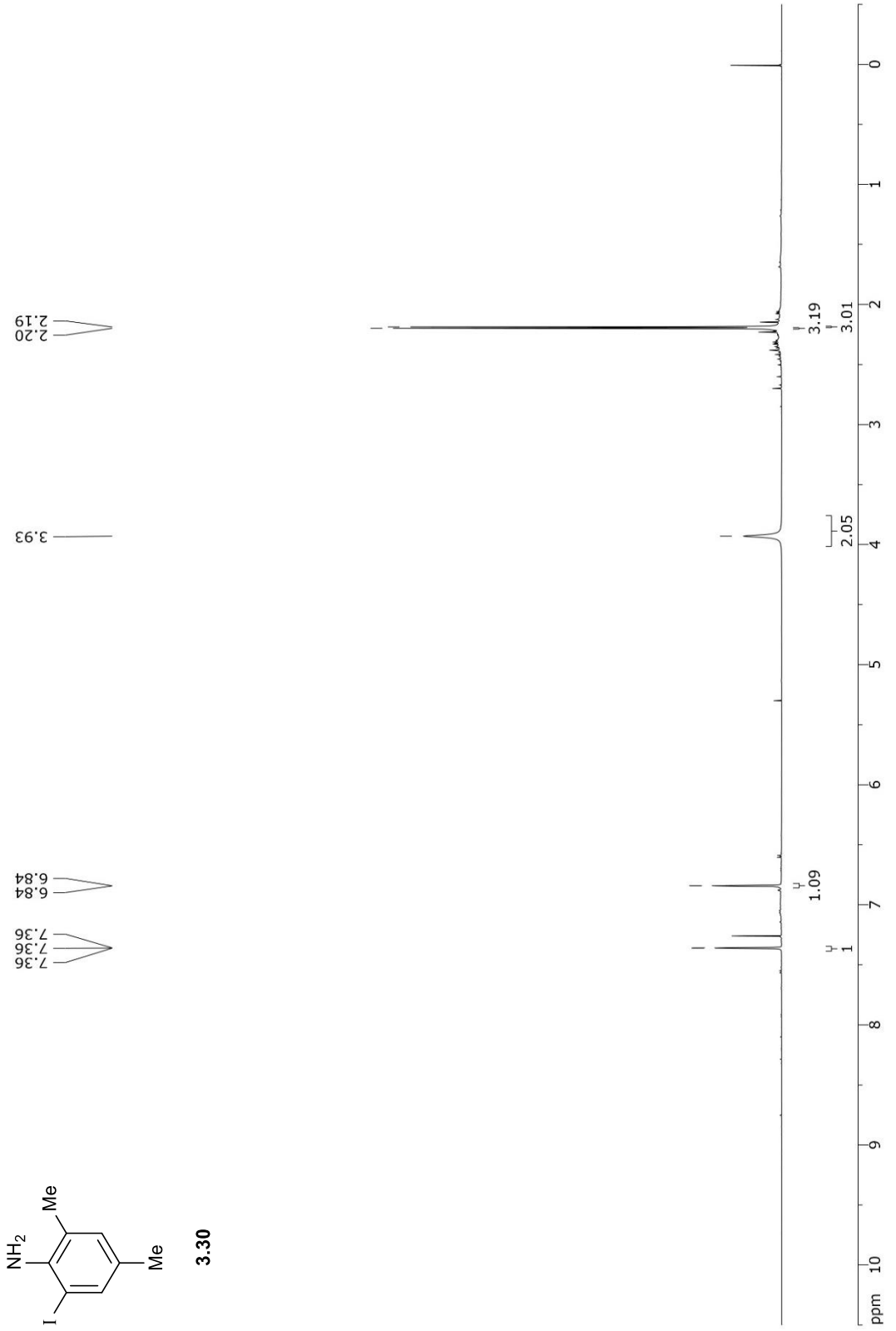
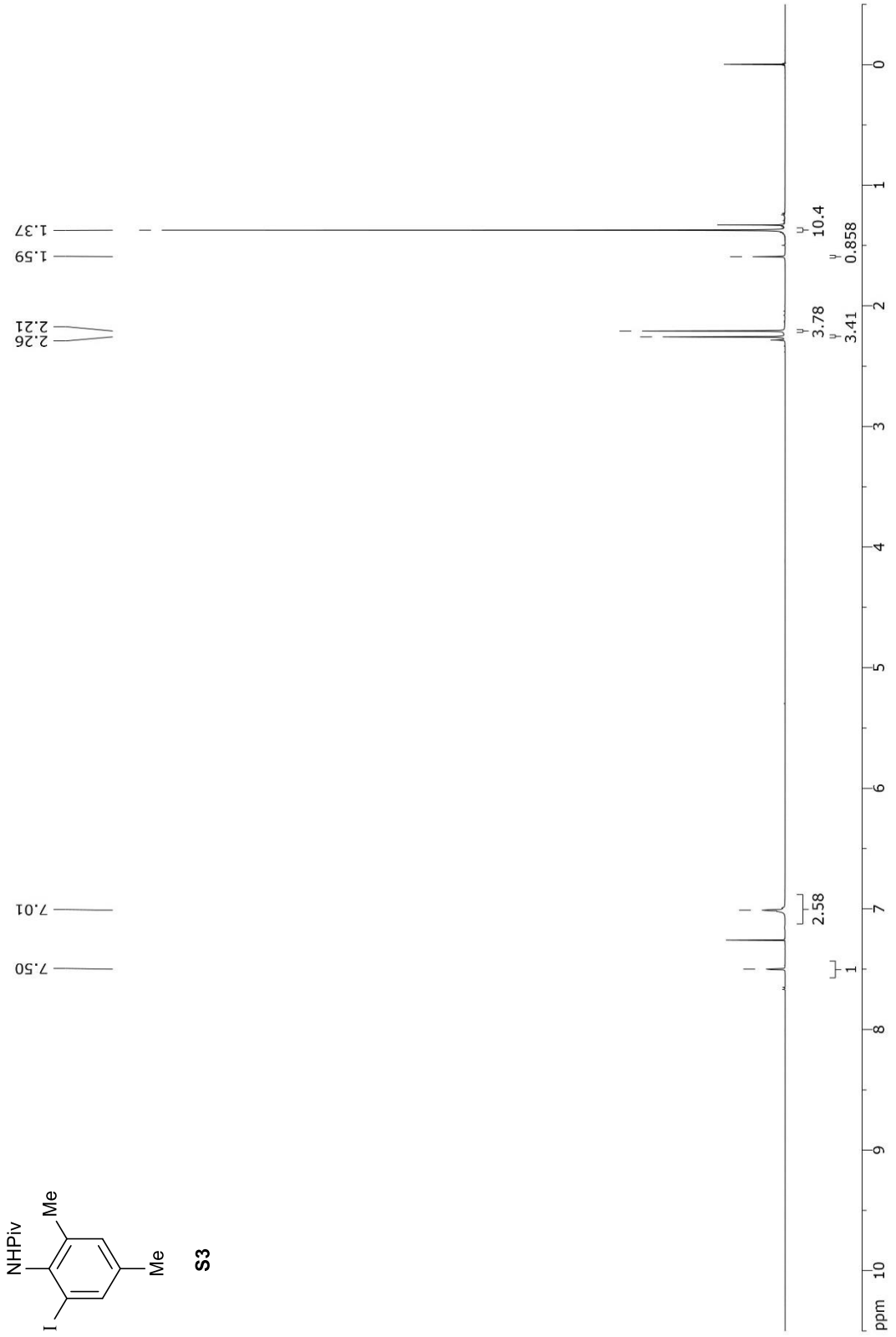
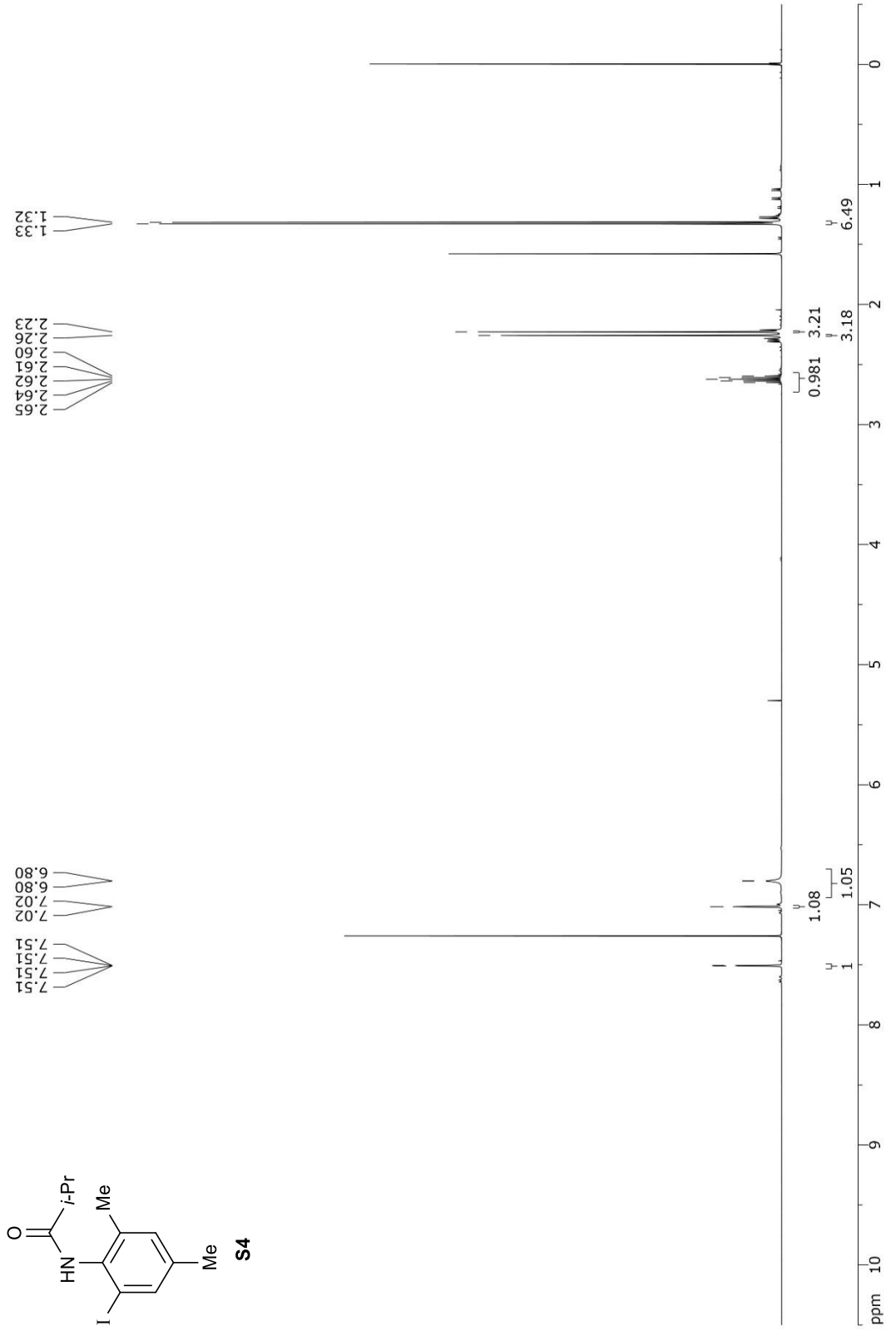
164.27
164.25
164.23
i-Pr
N
O
I
3.29
0
50
100
150
200
ppm



3.30



S3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6.80
7.02
7.02
7.51
7.51
7.51
7.51
6.49
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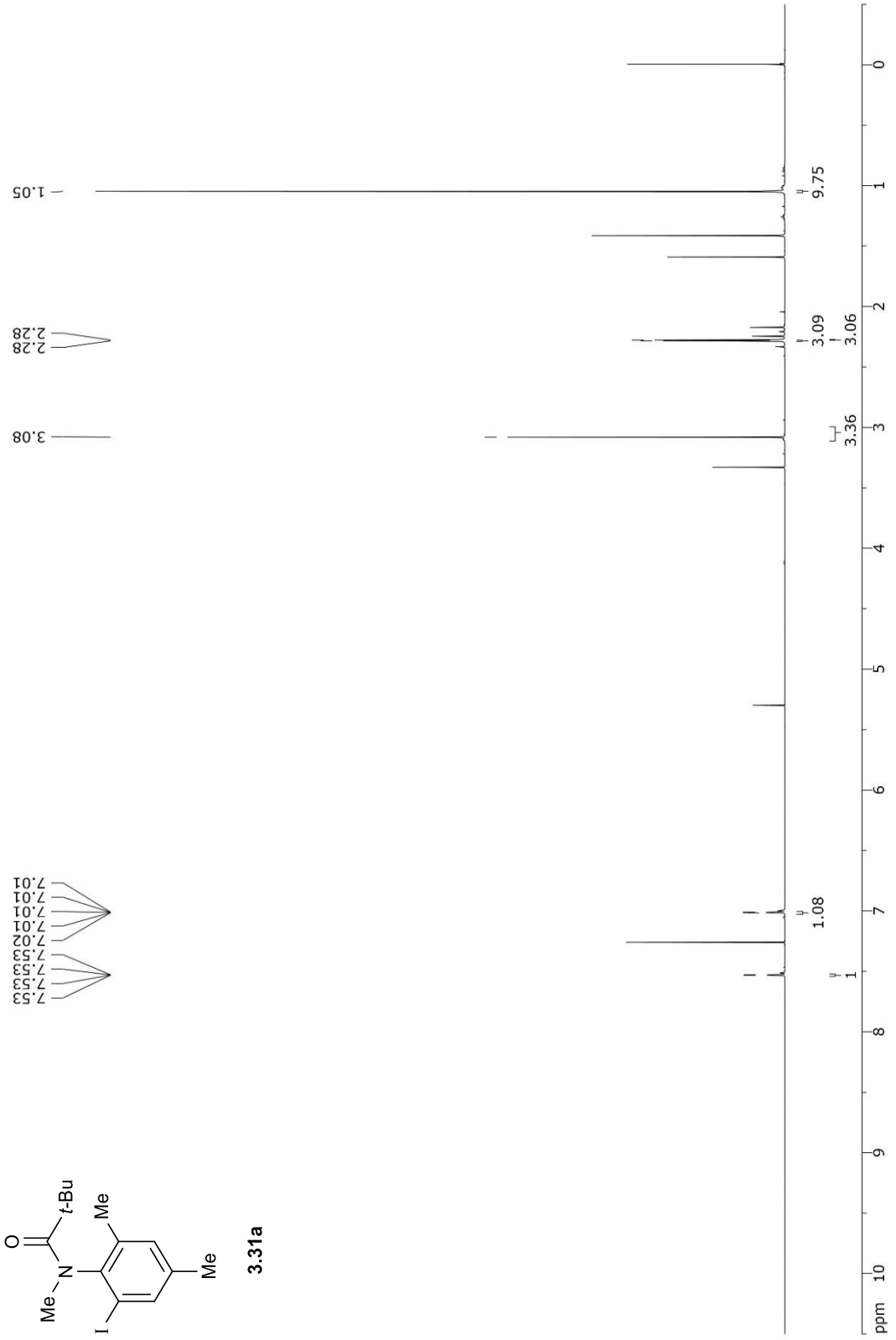
3.18
0.981
1.08
1.05
ppm
O
i-Pr
HN
Me
Me
I
S4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2.28
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7.53
7.53
7.53
7.53
7.02
7.01
7.01
7.01
7.01
1.08
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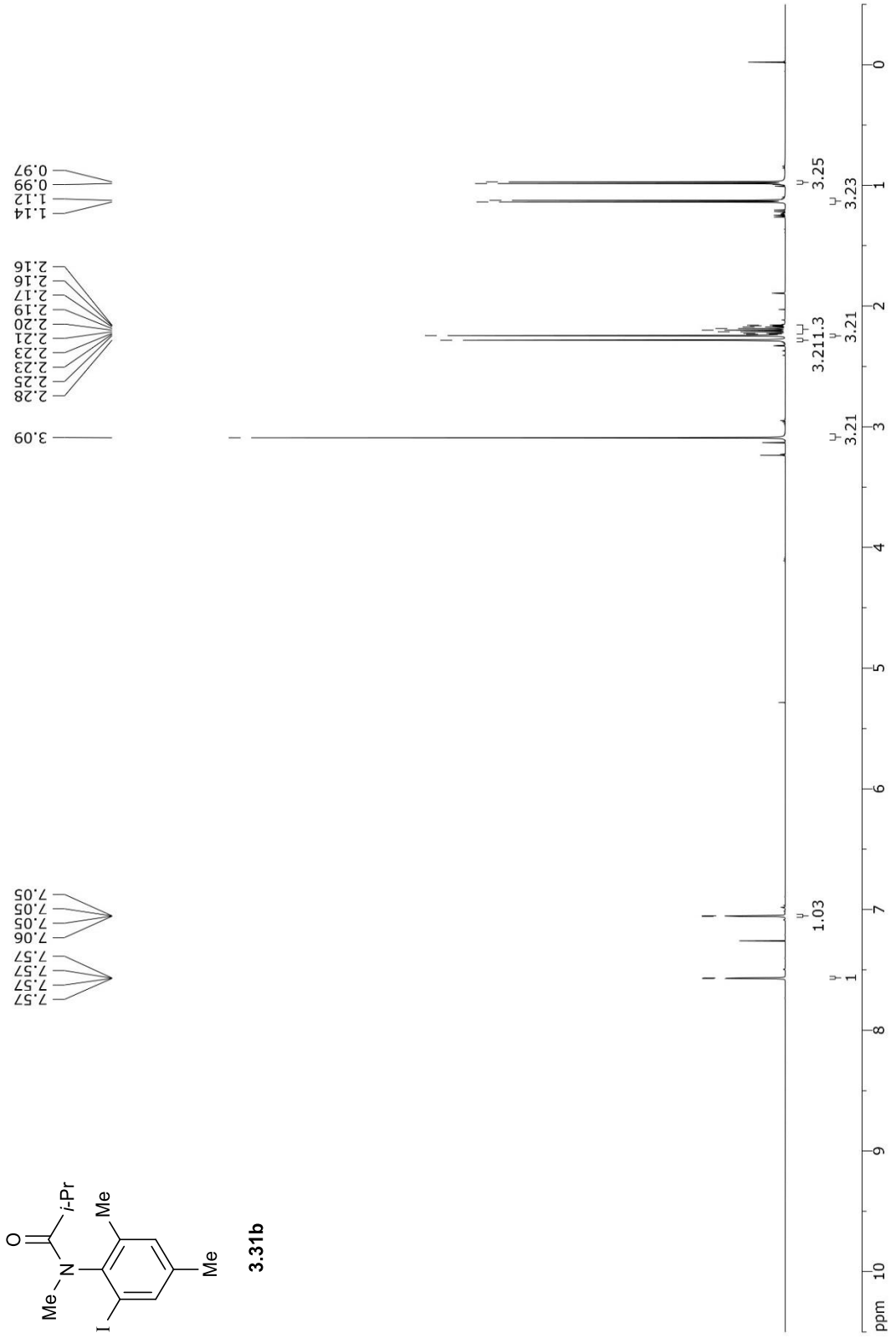
3.09
3.06
3.36
ppm
Me
t-Bu
O
N
Me
Me
I

3.31a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0.99
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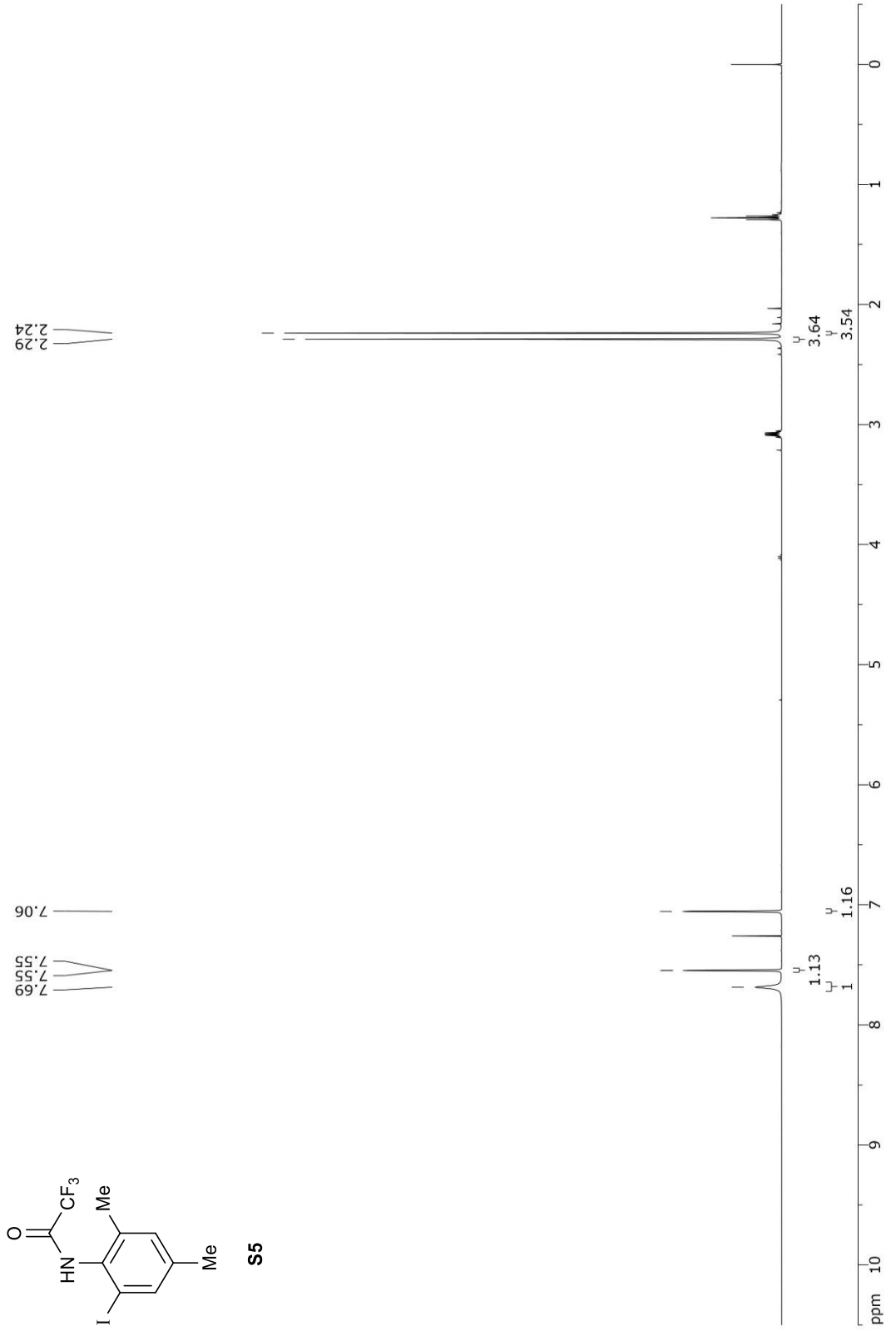
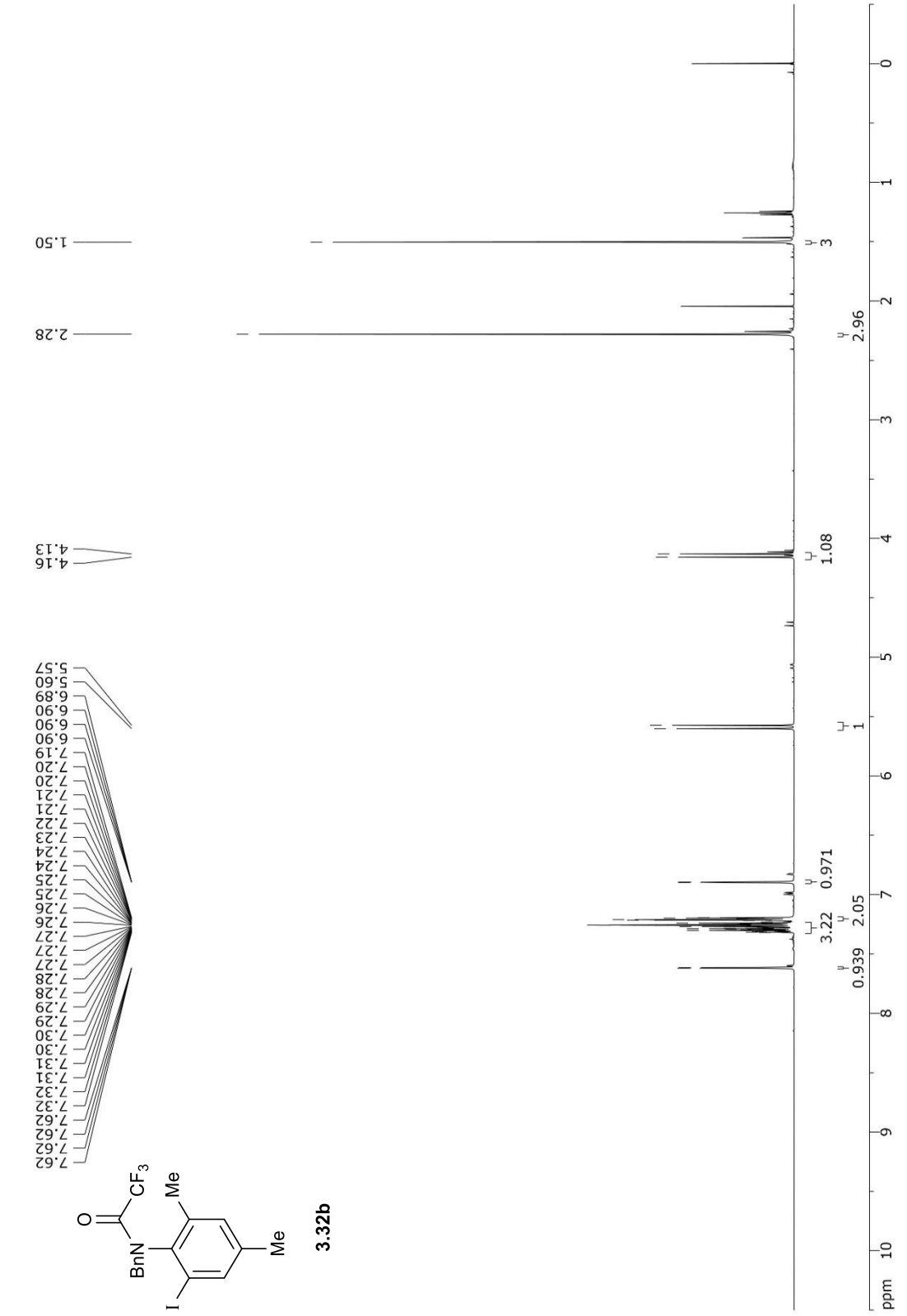
2.16
2.16
2.17
2.19
2.20
2.21
2.23
2.23
2.25
2.28
3.09
7.05
7.05
7.05
7.06
7.57
7.57
7.57
7.57
3.25
3.23
3.21
3.211.3
3.21
1.03
ppm
O
i-Pr
Me
N
Me
Me
I
3.31b


2.24
2.29
7.06
7.55
7.55
7.69
3.64
3.54
1.13
1.16
ppm
O
CF3
HN
Me
Me
I
S5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2.28
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4.16
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7.62
7.62
7.32
7.32
7.31
7.31
7.30
7.30
7.29
7.29
7.28
7.28
7.27
7.27
7.27
7.26
7.26
7.25
7.25
7.24
7.24
7.23
7.22
7.21
7.21
7.20
7.20
7.19
6.90
6.90
6.89
5.60
5.57
3
2.96
1.08
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2.05
3.22
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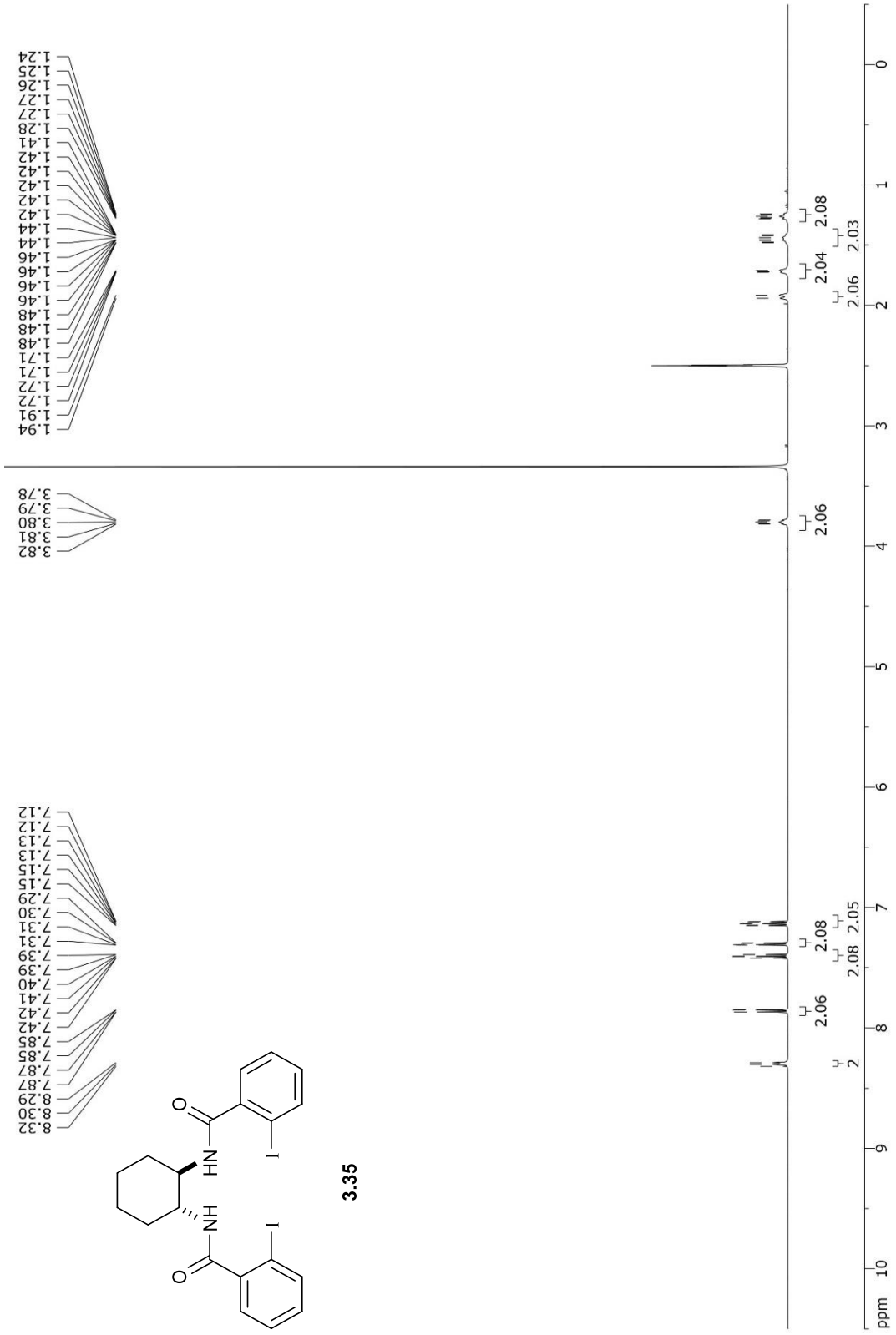
CF3
BnN
Me
Me
I
3.32b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7.39
7.31
7.31
7.30
7.29
7.15
7.15
7.13
7.13
7.12
7.12
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3.81
3.80
3.79
3.78
1.94
1.91
1.72
1.72
1.71
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1.27
1.27
1.26
1.25
1.24
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2.08
2.05
2.08
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2.06
2.06
2.04
2.08
2.03
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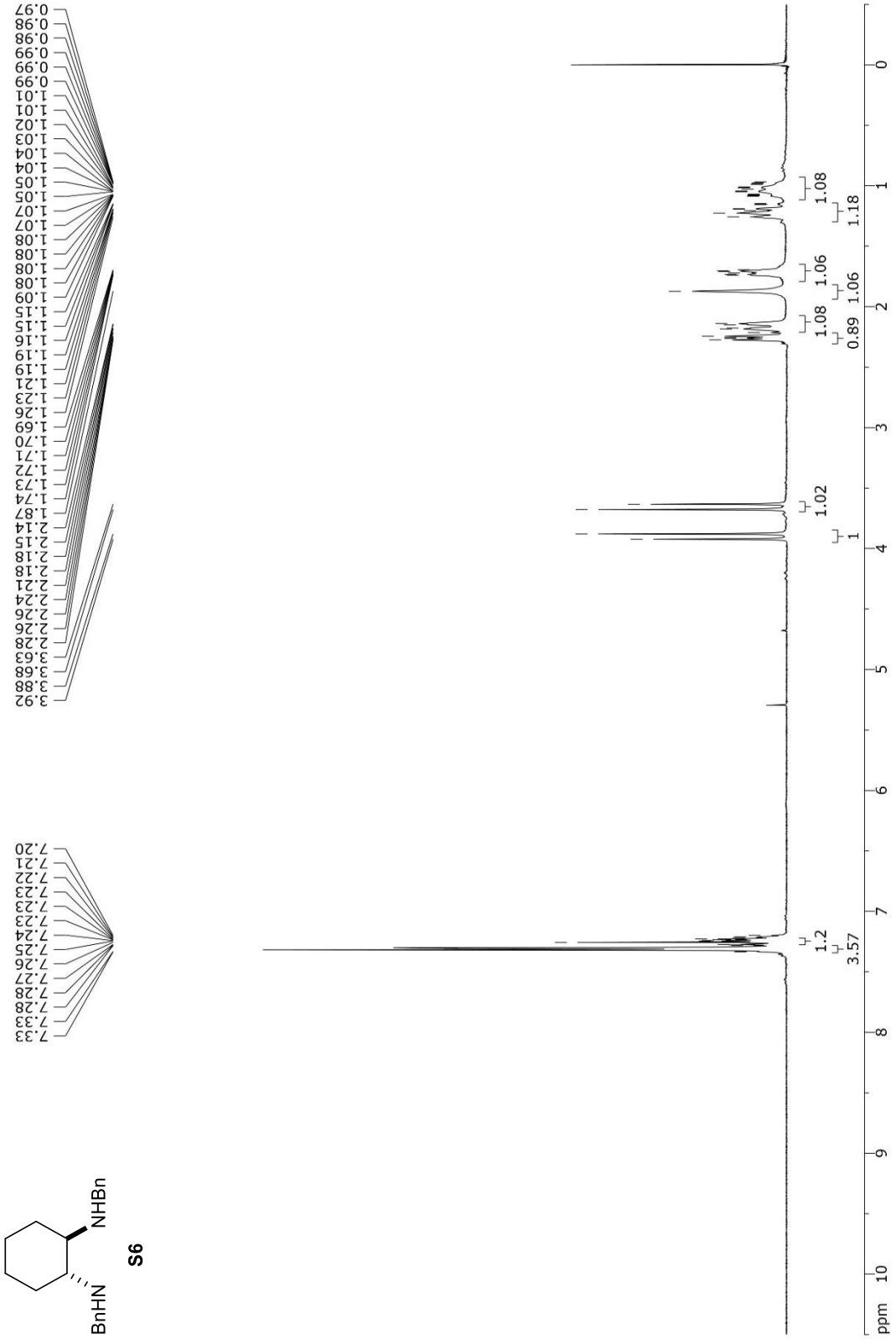
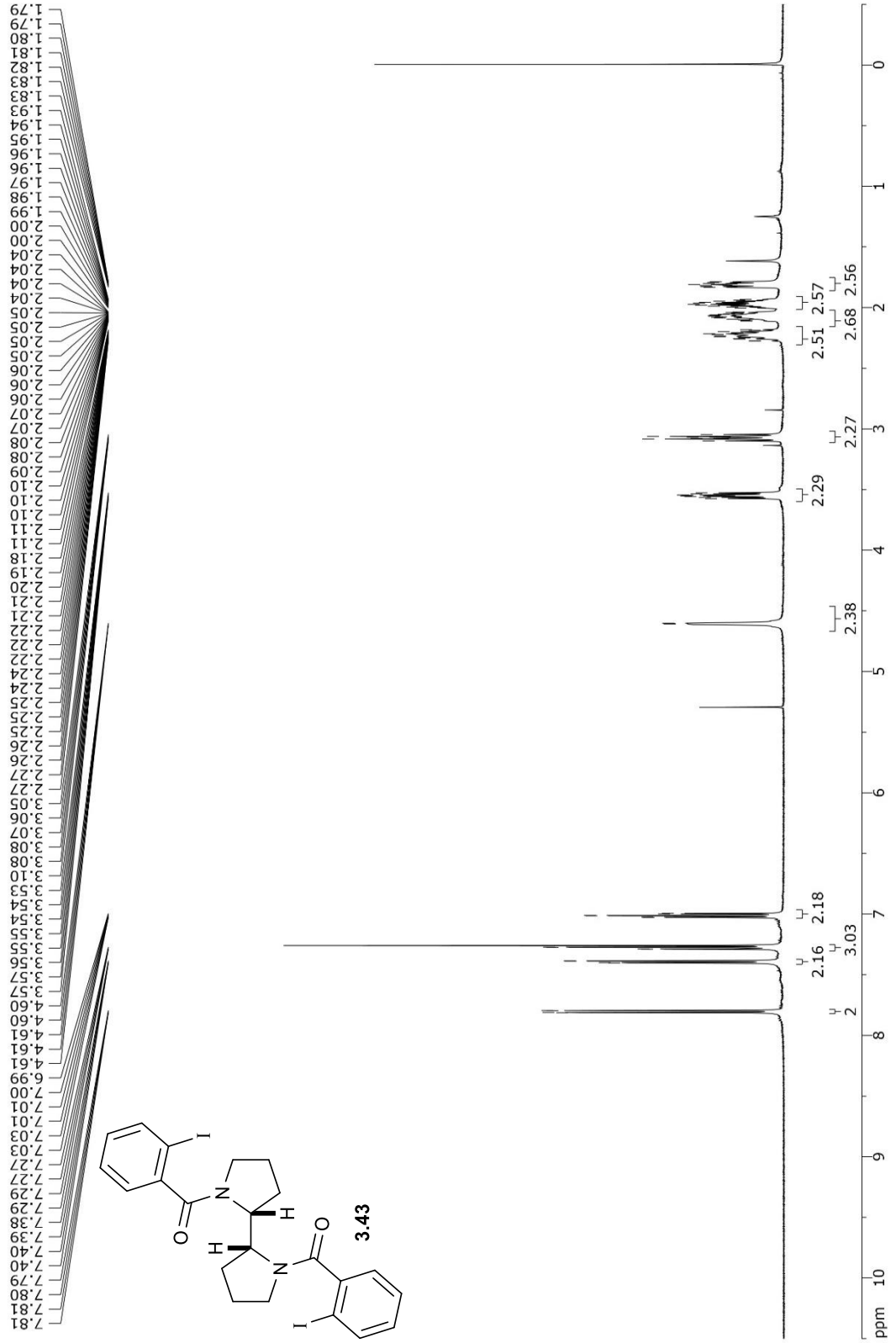
2
3
4
5
6
7
8
9
10

O
HN
I
NH
O
I

3.35


NHBn
BnHN
S6
ppm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2.51
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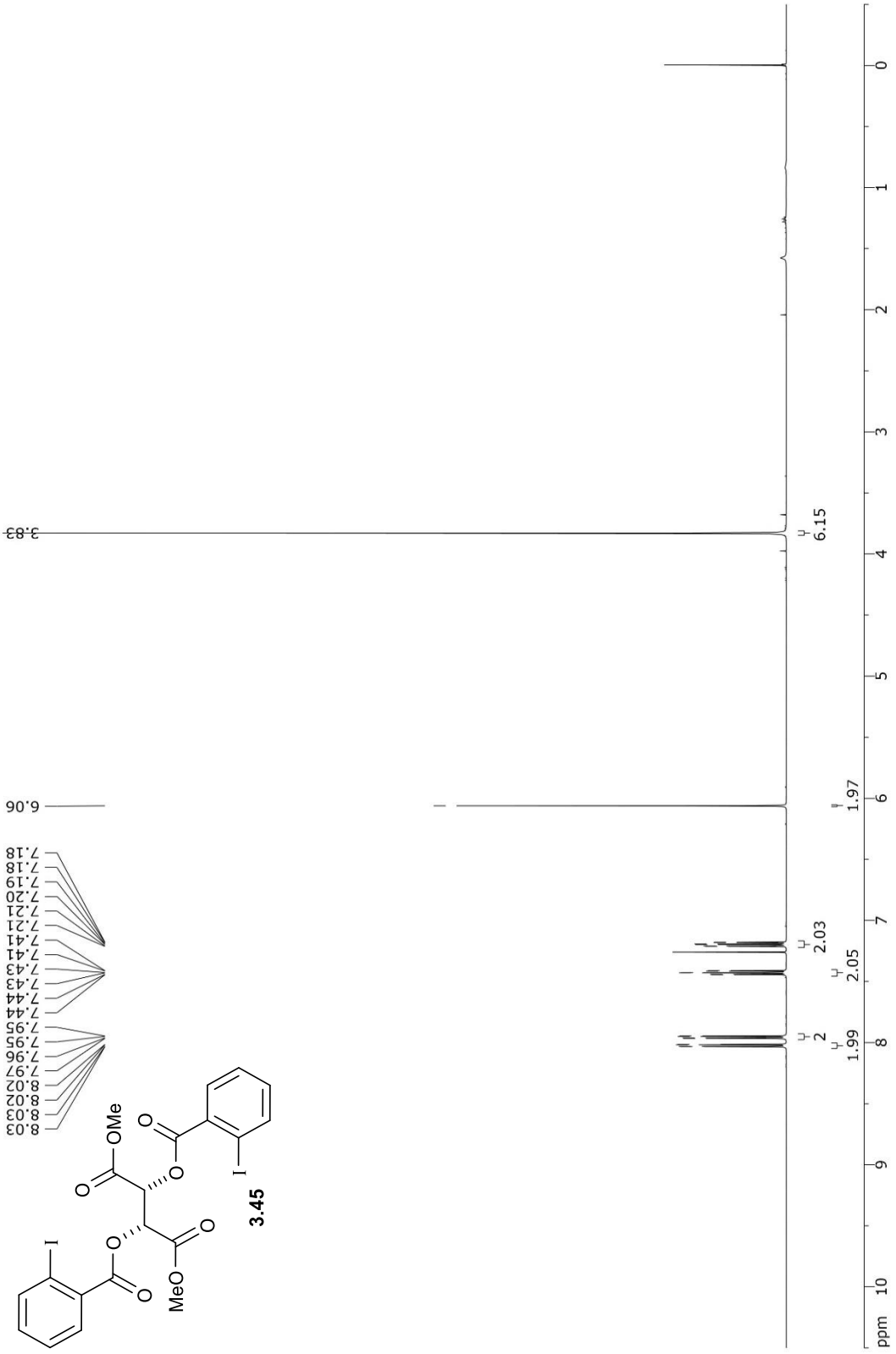
2.68
2.56
ppm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7.21
7.21
7.41
7.41
7.43
7.43
7.44
7.44
7.95
7.95
7.96
7.97
8.02
8.02
8.03
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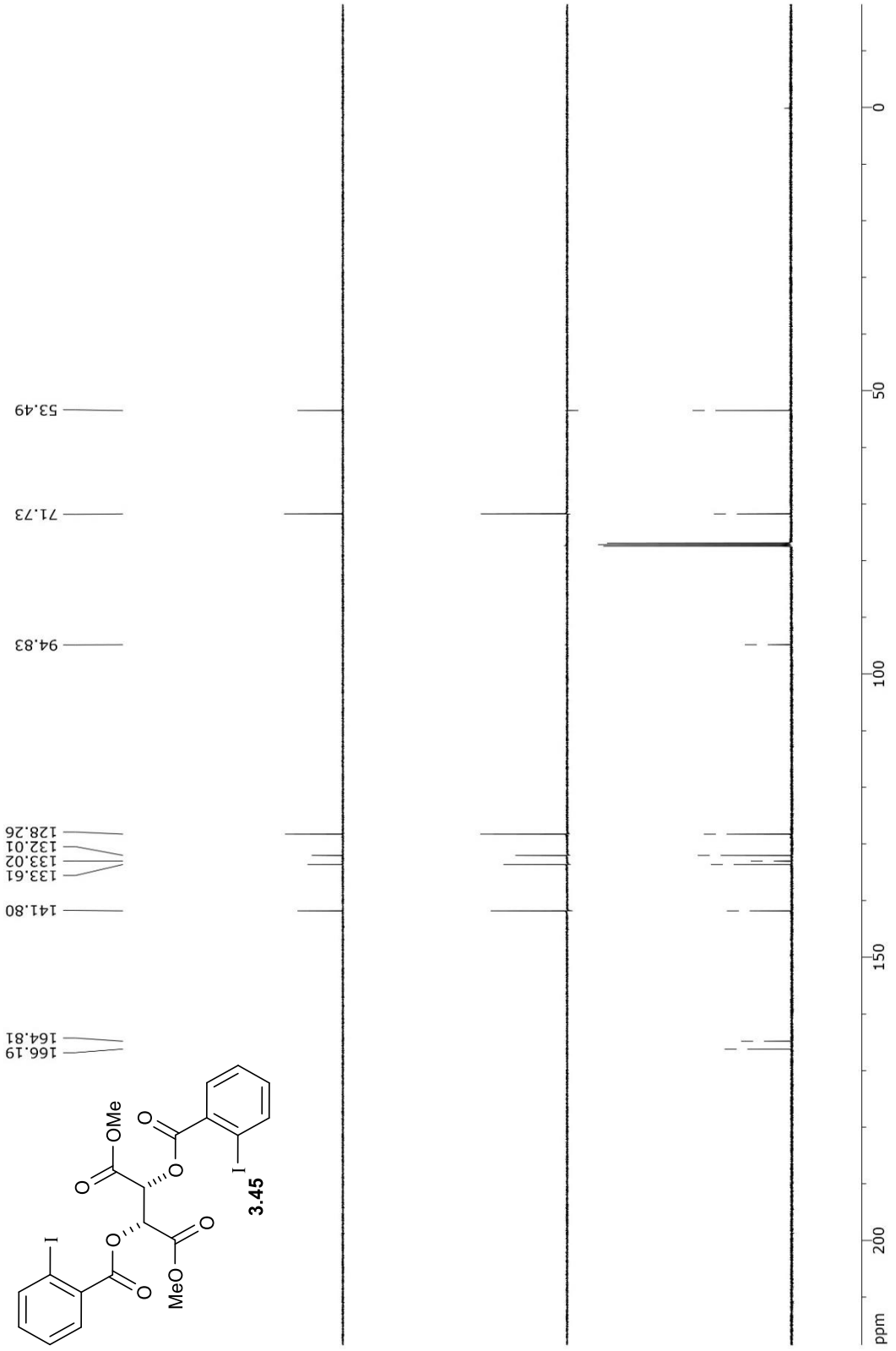
6.15
1.97
2.03
2.05
2
1.99
ppm
OMe
MeO
I
I
3.45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94.83
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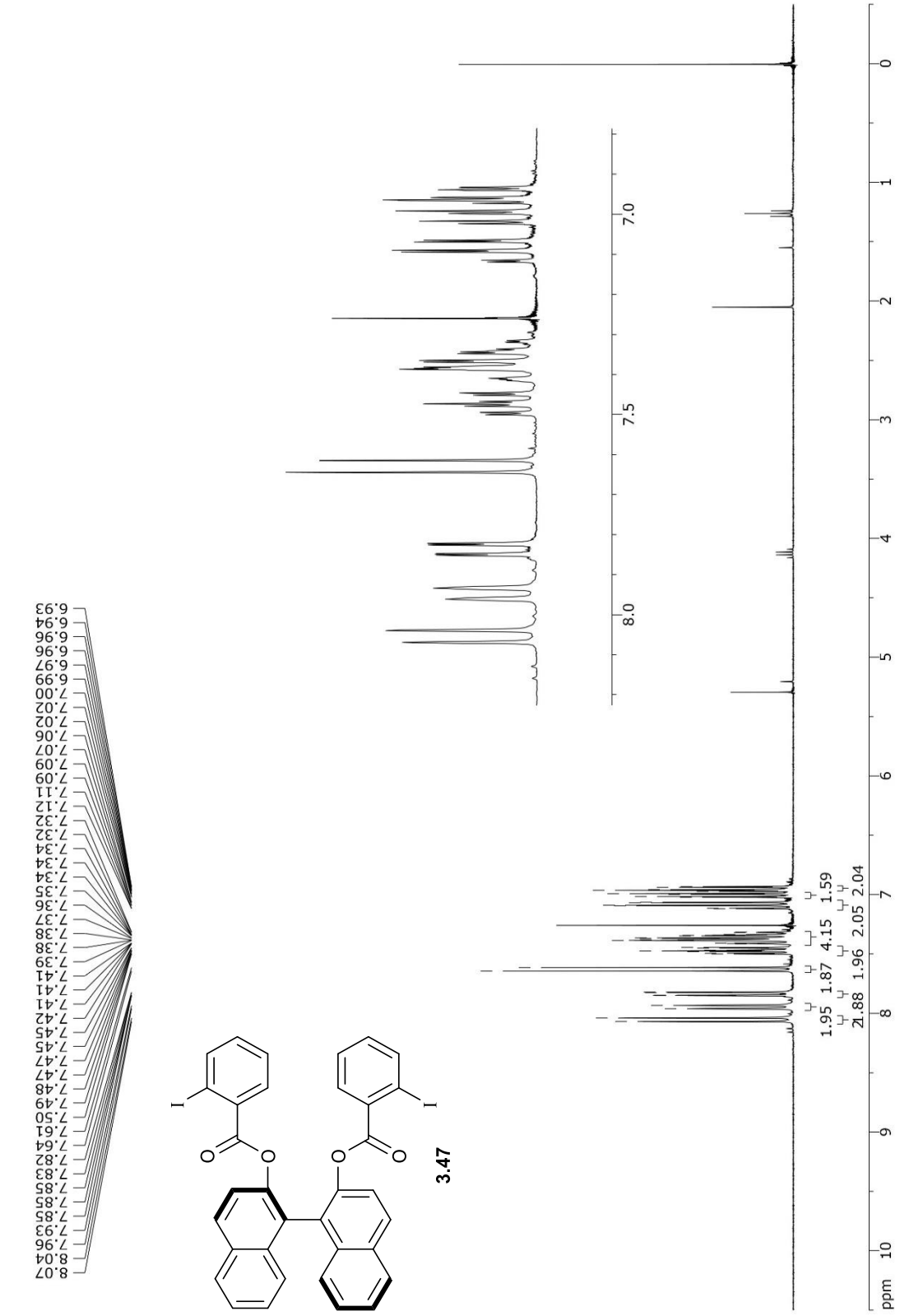
141.80
164.81
166.19
OMe
MeO
I
I
3.45
0
50
100
150
200
ppm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I
I
O
O
O
O
8.07
8.04
7.96
7.93
7.85
7.85
7.85
7.83
7.82
7.64
7.61
7.50
7.49
7.48
7.47
7.47
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7.12
7.11
7.09
7.09
7.07
7.06
7.02
7.02
7.00
6.99
6.97
6.96
6.96
6.94
6.93
8.0
7.5
7.0
1.95 1.87 4.15 1.59
21.88 1.96 2.05 2.04
ppm
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3
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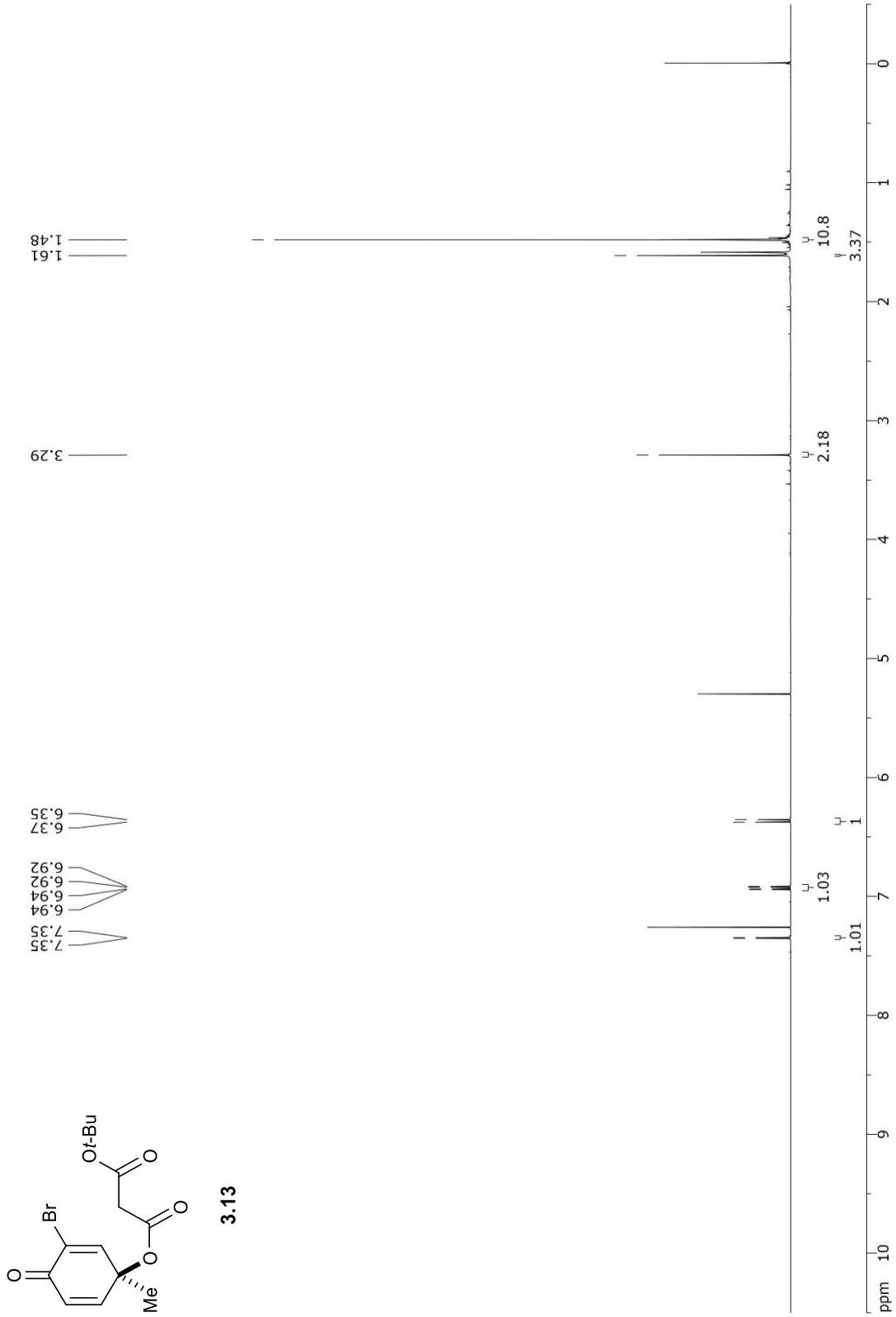
7
8
9
10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6.92
6.94
6.94
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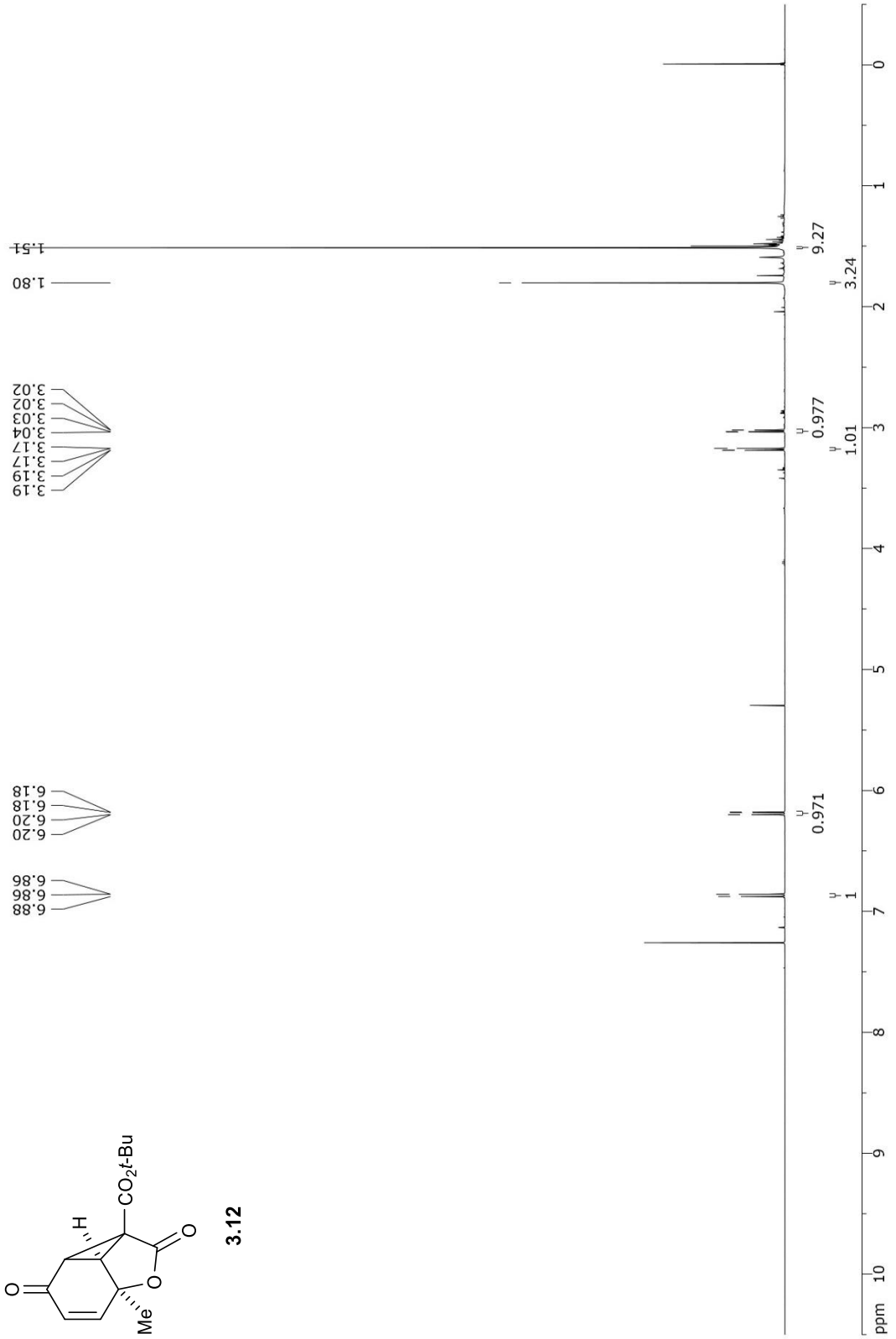
10.8
3.37
2.18
1
1.03
1.01
ppm
Ot-Bu
Br
O
Me
3.13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3.03
3.02
3.02
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6.86
6.20
6.18
6.18
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1
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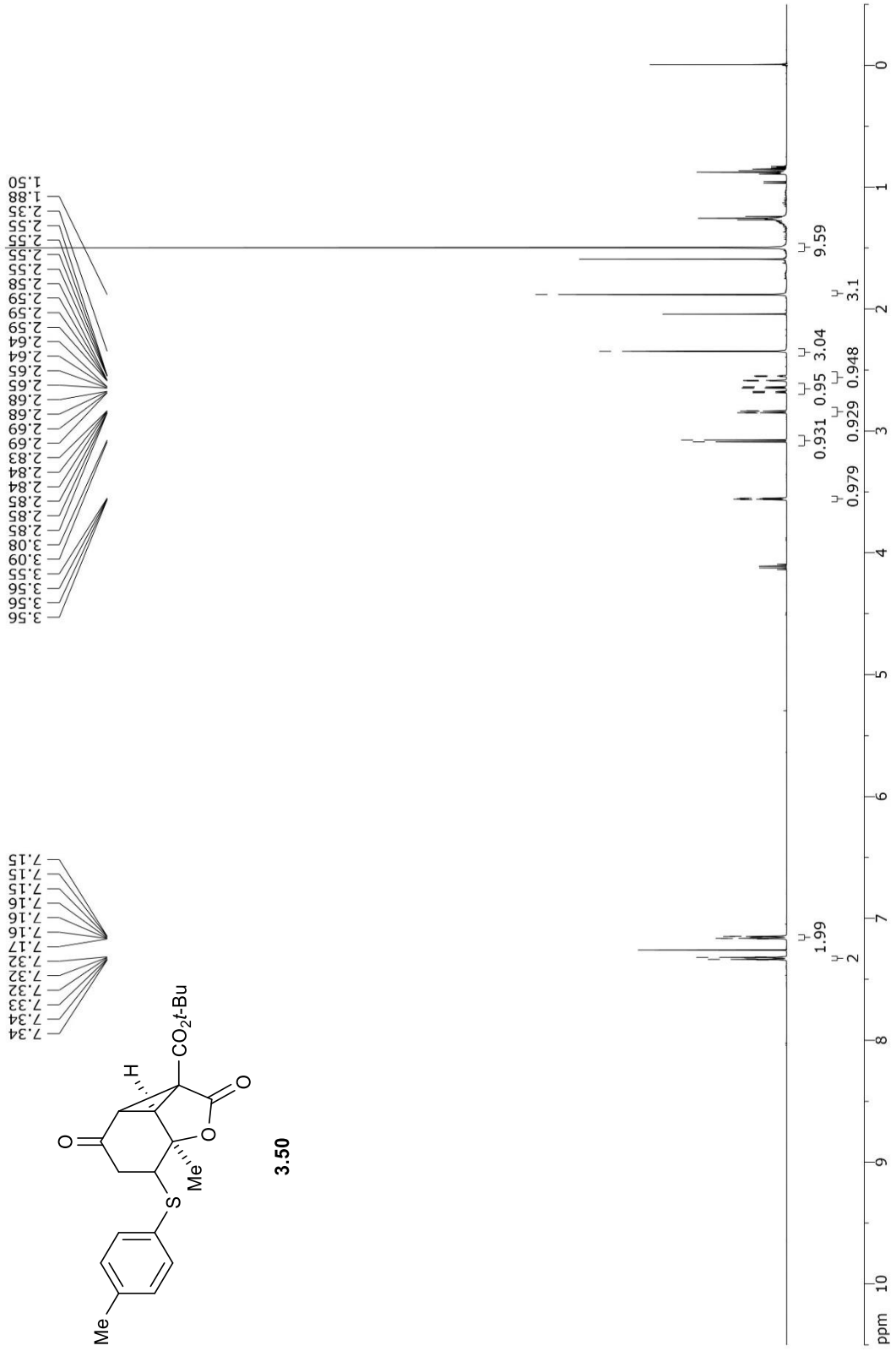
CO2t-Bu
H
O
O
O
Me

3.12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7.15
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3.56
3.55
3.09
3.08
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2.85
2.85
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2.84
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2.68
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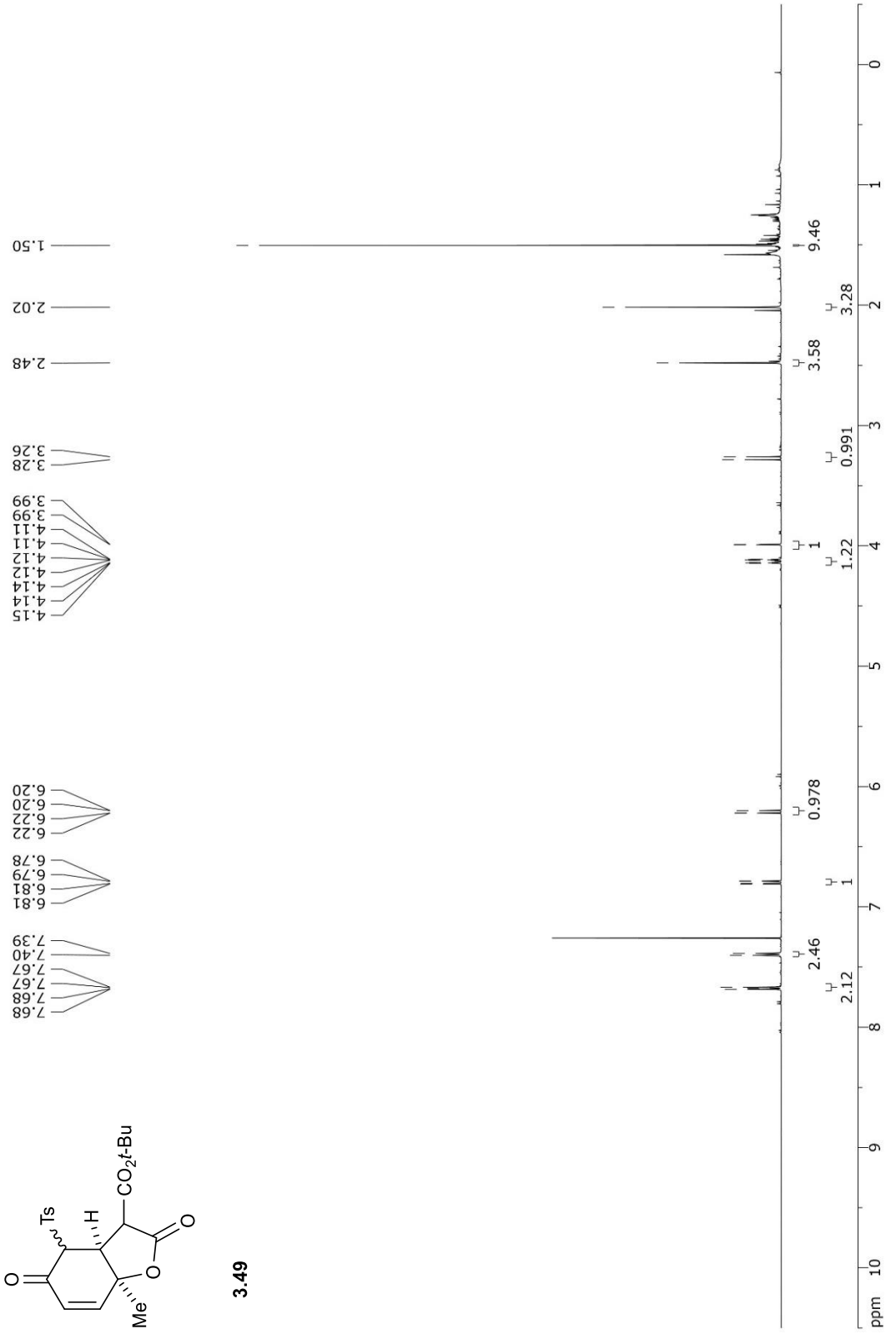
2.59
2.58
2.55
2.55
2.55
2.55
2.35
1.88
1.50
1.99
0.931
0.979
0.95
0.929
3.04
0.948
9.59
3.1
ppm
CO2t-Bu
H
O
O
O
Me
S
Me
3.50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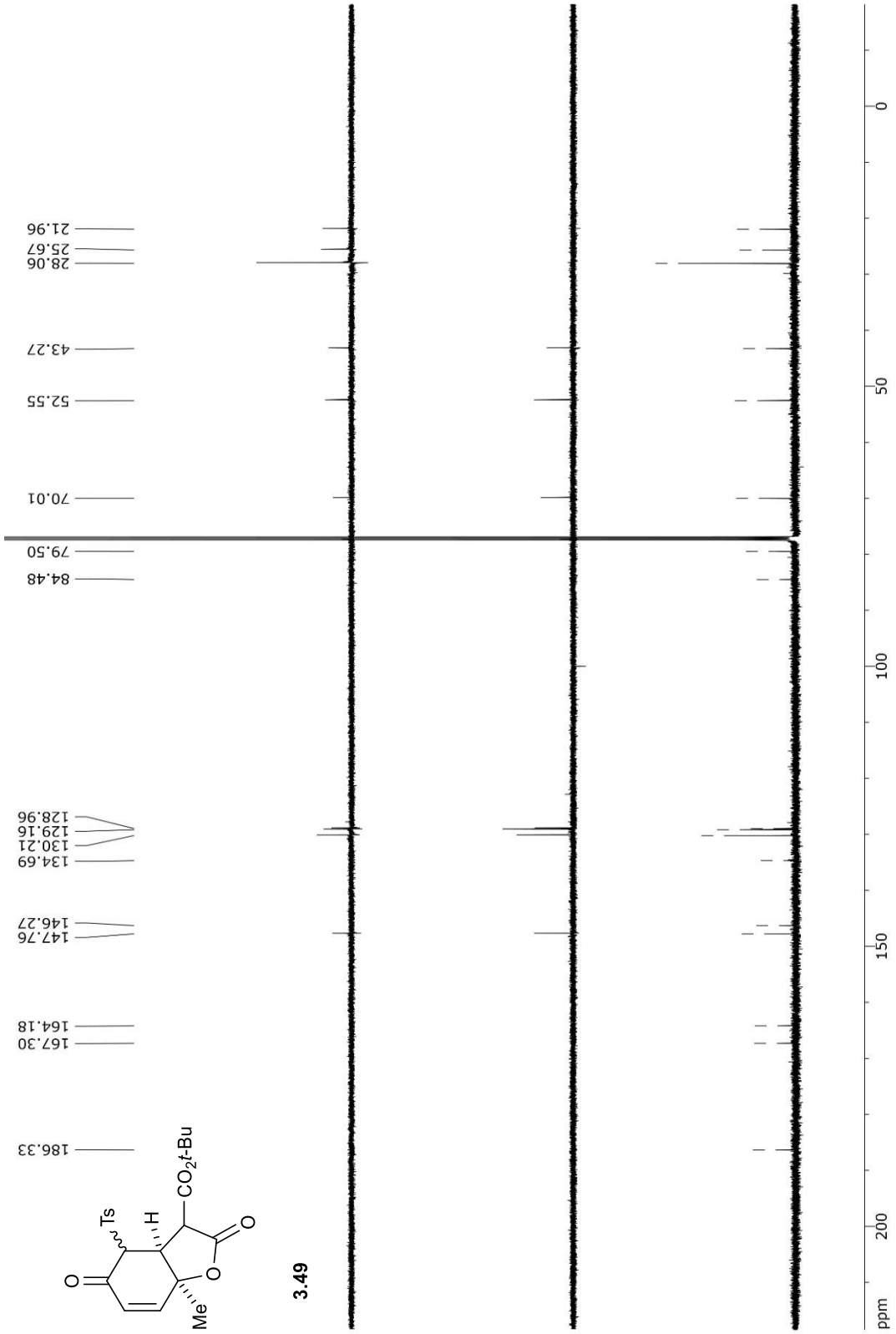
2.02
2.48
3.26
3.28
3.99
3.99
4.11
4.11
4.12
4.12
4.14
4.14
4.15
6.20
6.20
6.22
6.22
6.78
6.79
6.81
6.81
7.39
7.40
7.67
7.67
7.68
7.68
9.46
3.28
3.58
0.991
1.22
1
0.978
1
2.46
2.12
ppm
Ts
H
CO2t-Bu
O
O
O
Me

3.49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79.50
84.48
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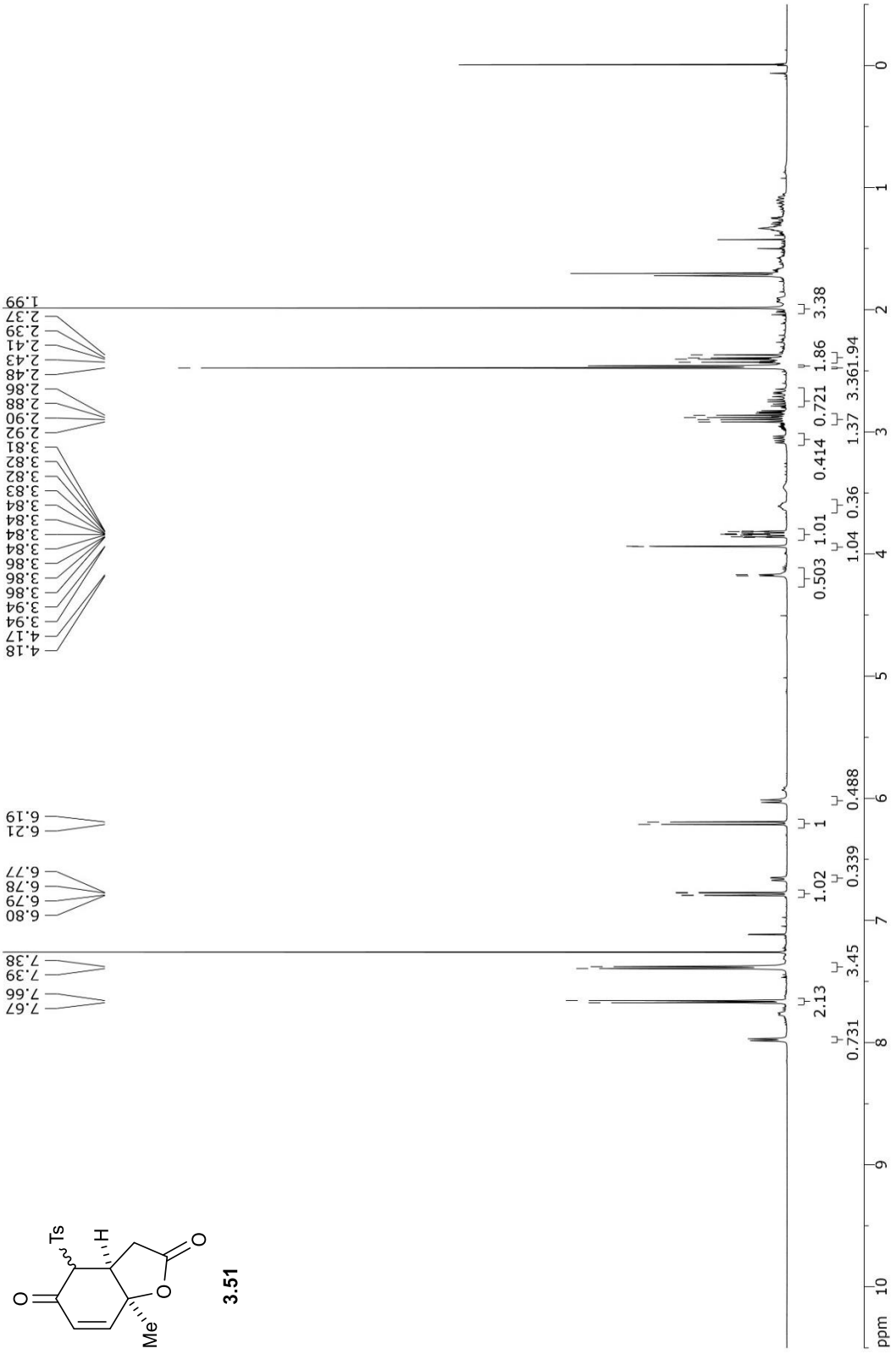
130.21
134.69
146.27
147.76
164.18
167.30
186.33
ppm
0
50
100
150
200
Ts
H
CO2t-Bu
O
O
O
Me
3.49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7.66
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6.79
6.78
6.77
6.21
6.19
4.18
4.17
3.94
3.94
3.86
3.86
3.84
3.84
3.84
3.84
3.83
3.82
3.82
3.81
2.92
2.90
2.88
2.86
2.48
2.43
2.41
2.39
2.37
1.99
0.731
2.13
3.45
1
1.02
0.339
0.488
0.503
1.01
0.414
0.36
1.04
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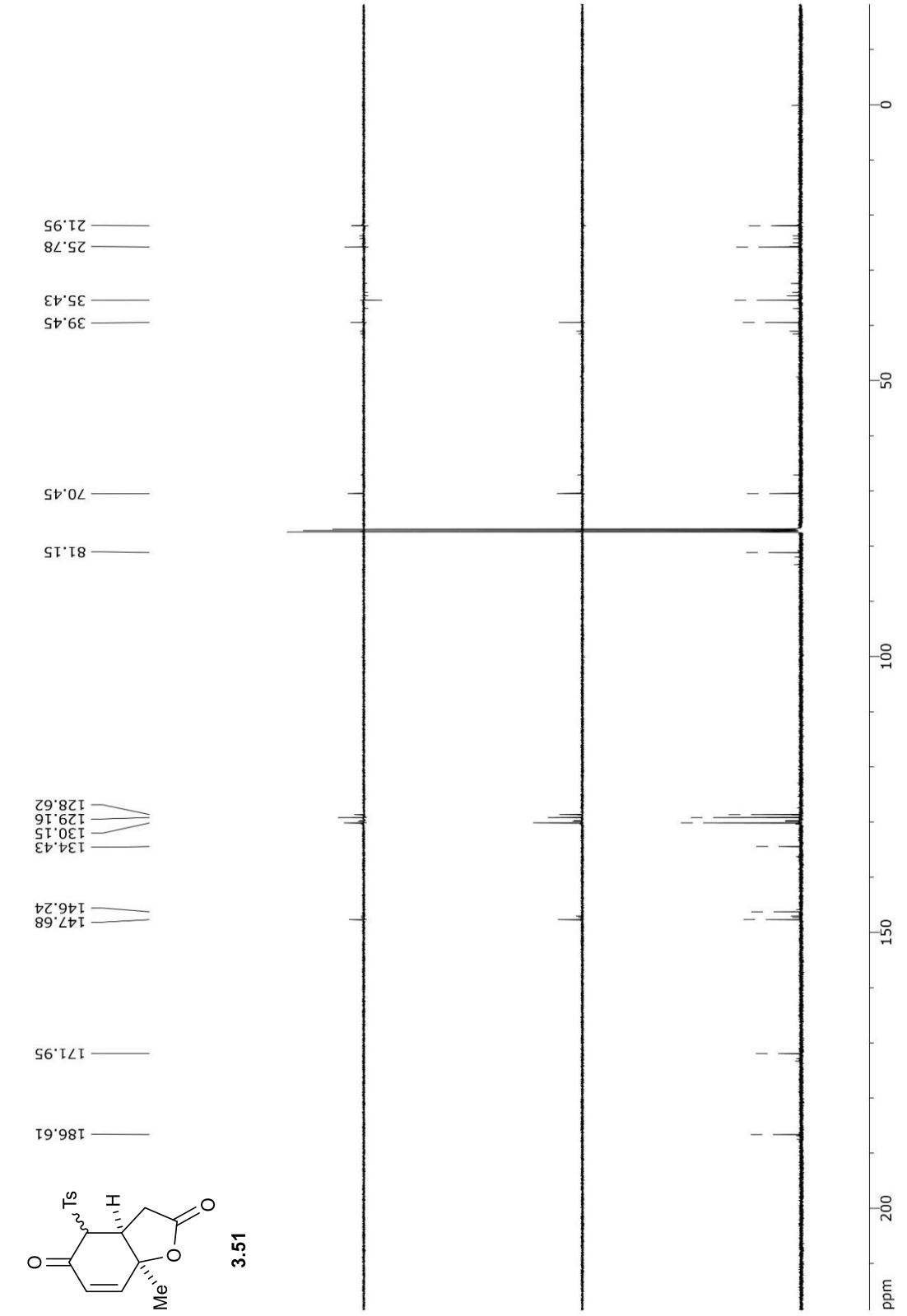
1.37
1.86
3.361.94
3.38
ppm
Ts
H
O
O
O
Me
3.51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25.78
35.43
39.45
70.45
81.15
128.62
129.16
130.15
134.43
146.24
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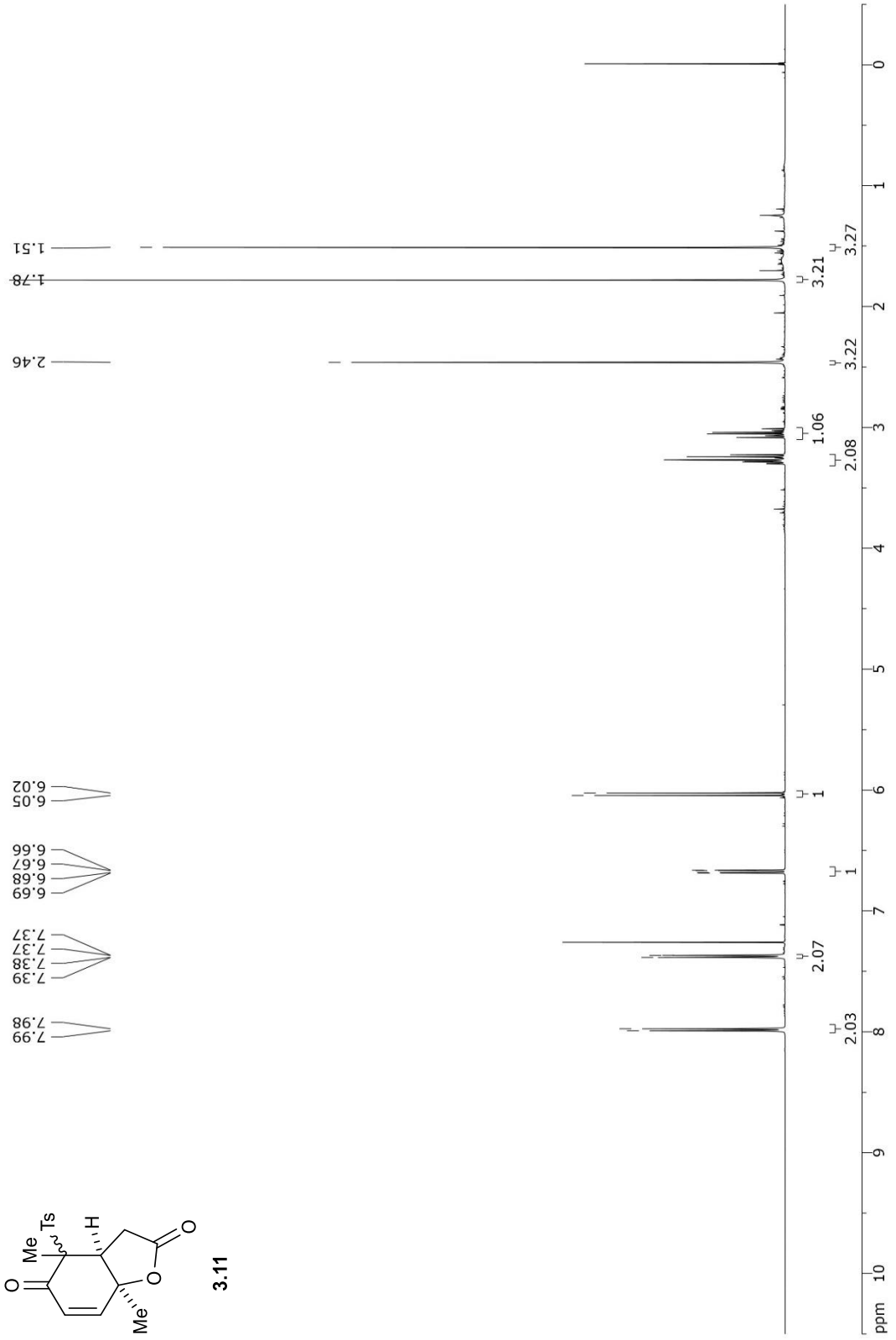
171.95
186.61
0
50
100
150
200
ppm
Ts
H
O
O
O
Me
3.51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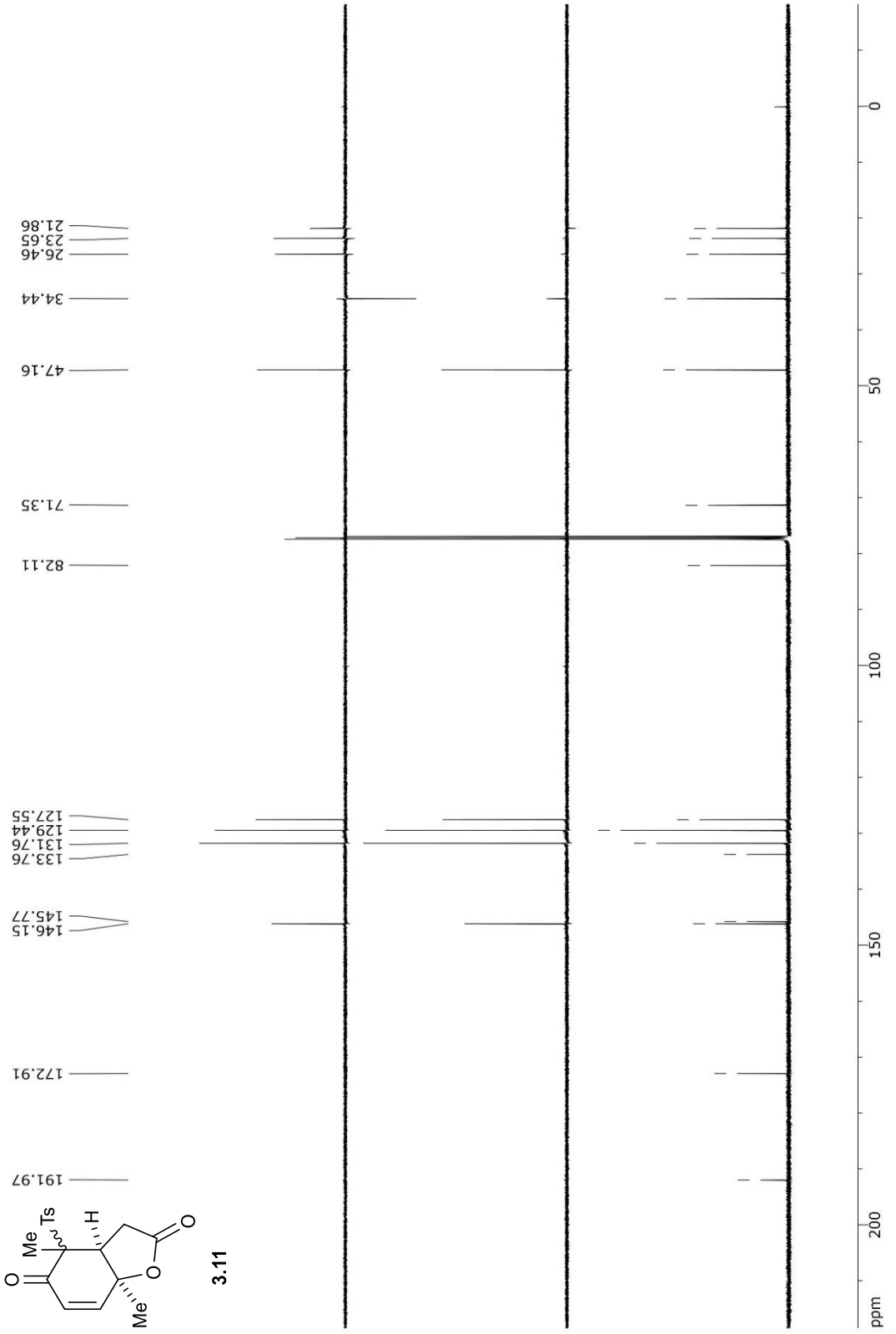
7.98
7.39
7.38
7.37
7.37
6.69
6.68
6.67
6.66
6.05
6.02
2.46
1.78
1.51
2.03
2.07
1
1
1.06
2.08
3.22
3.21
3.27
ppm
Me
Ts
H
O
O
O
Me

3.11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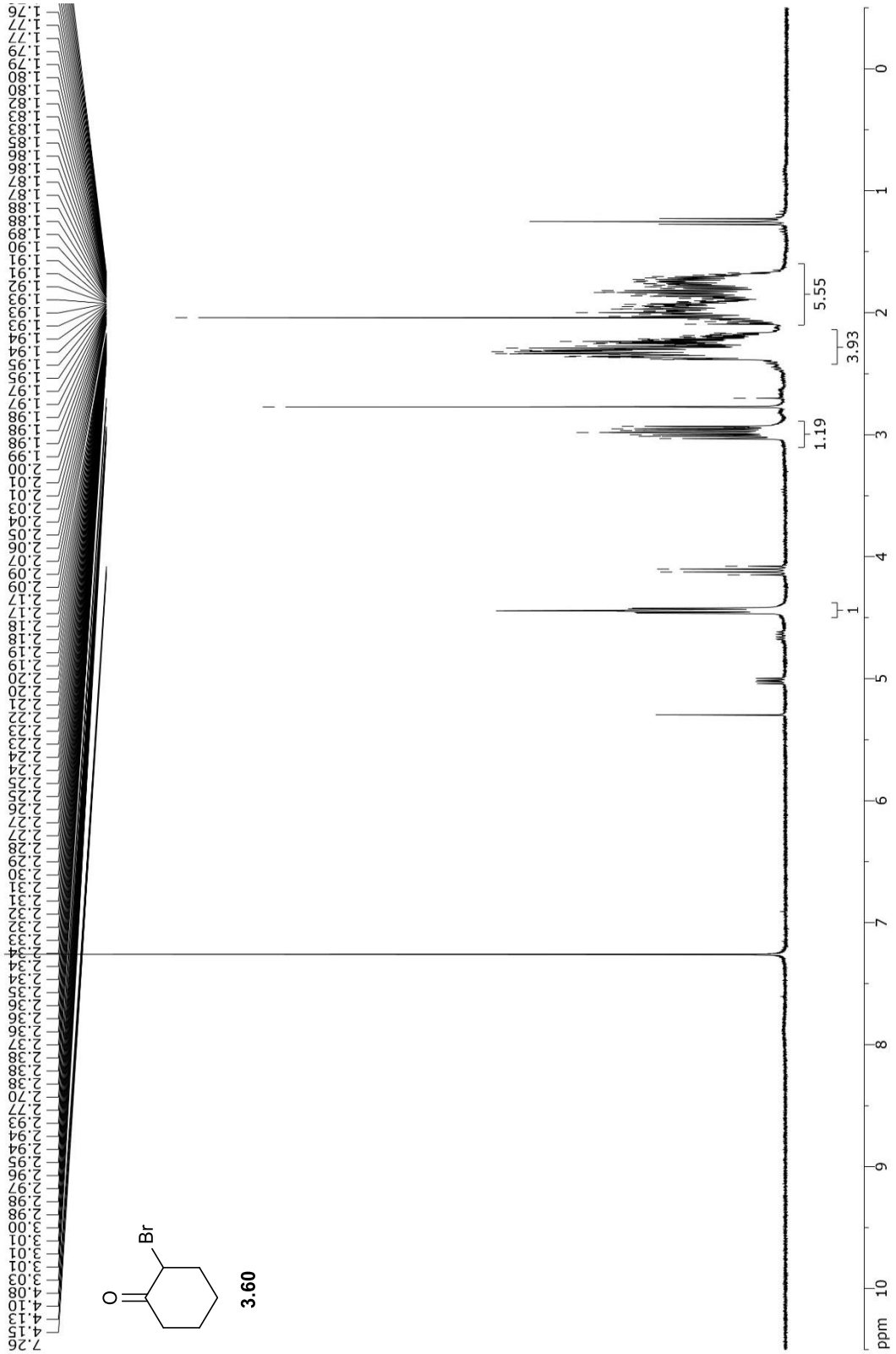
23.65
26.46
34.44
47.16
71.35
82.11
127.55
129.44
131.76
133.76
145.77
146.15
172.91
191.97
ppm
0
50
100
150
200
Me
Ts
H
O
O
O
Me

3.11


Br
O
3.60
5.55
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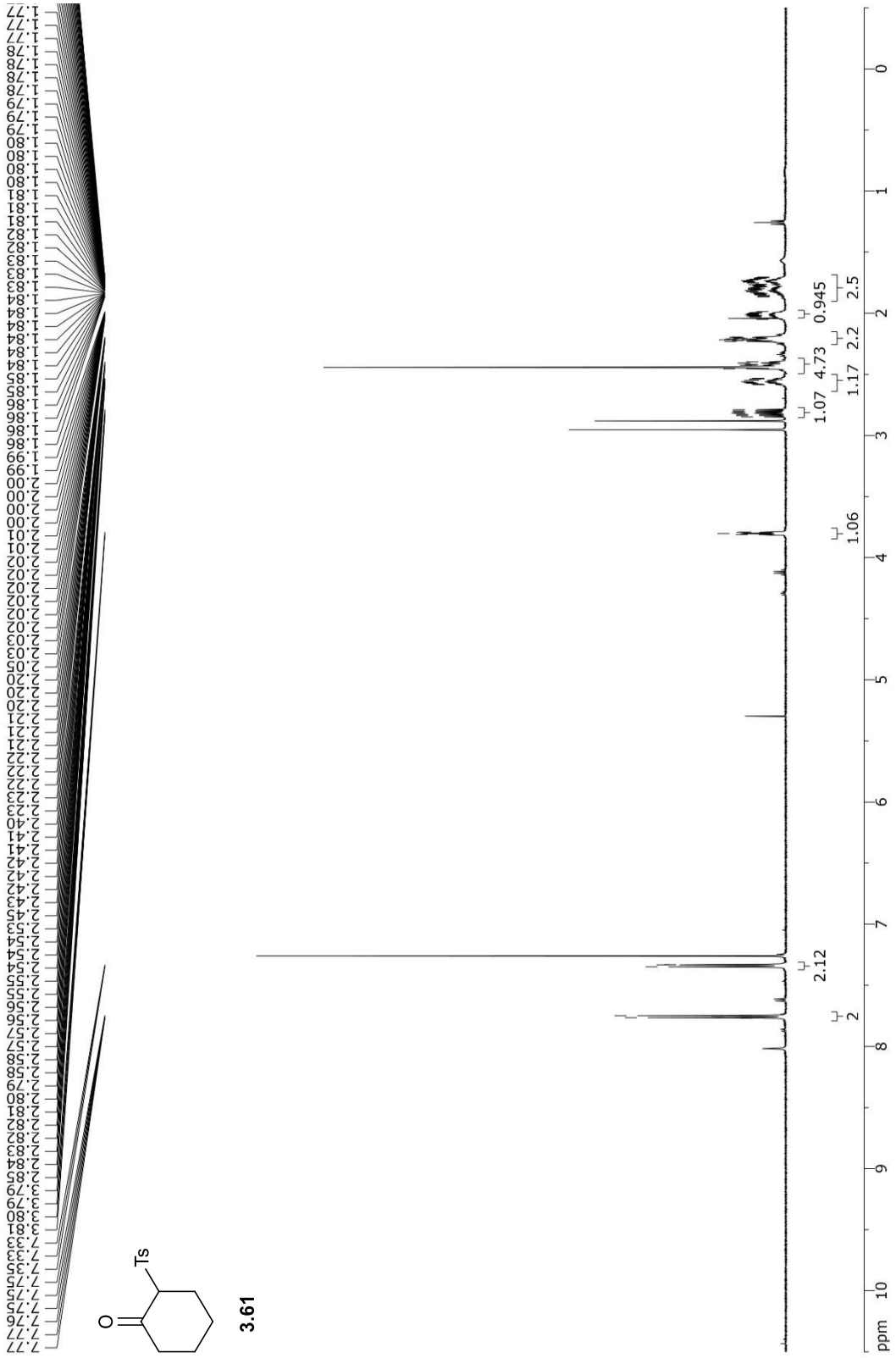
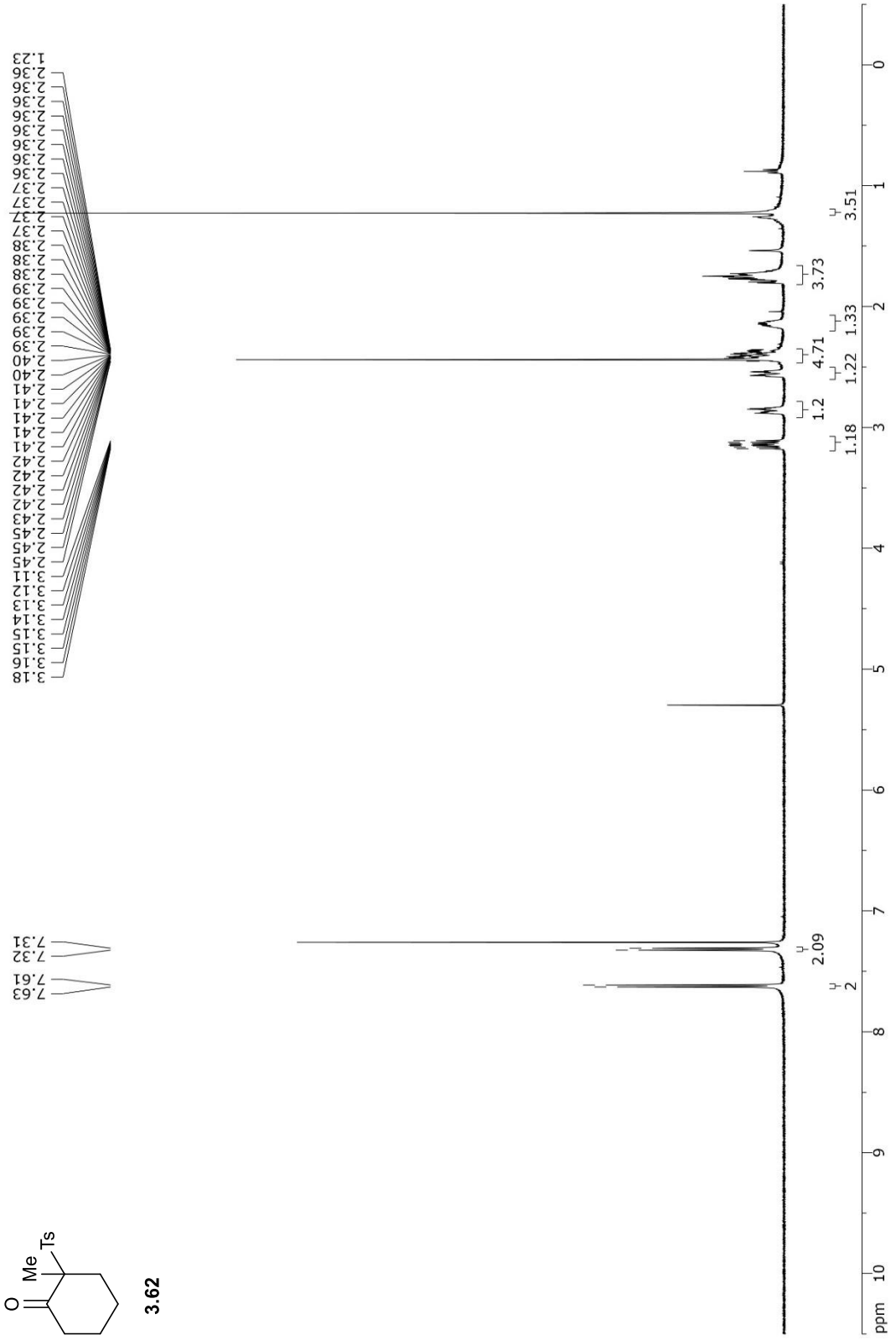
1.19
1
ppm


Ts
O
3.61
2.12
1.06
1.07
4.73
1.17
2.2
0.945
2.5
ppm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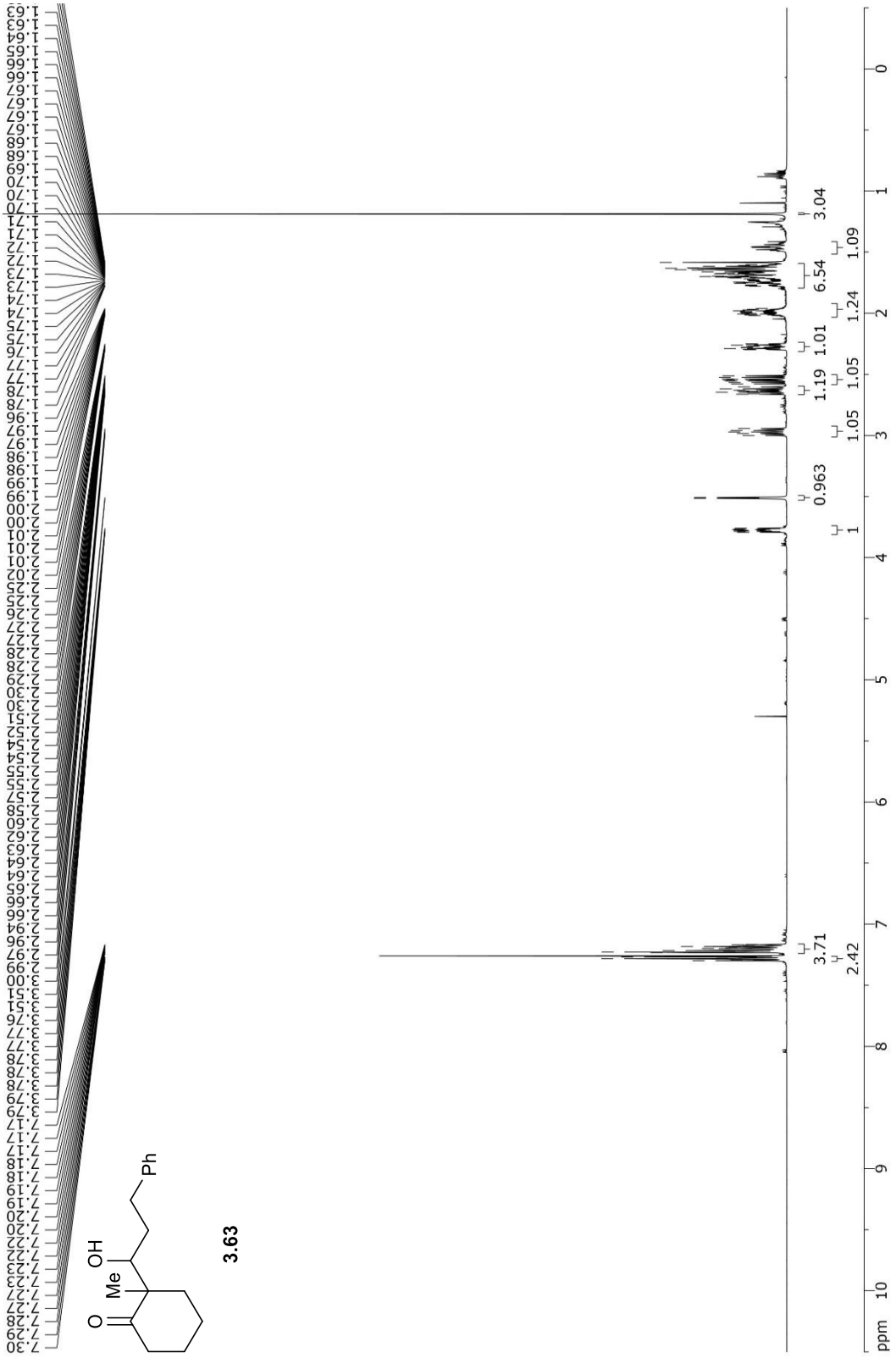
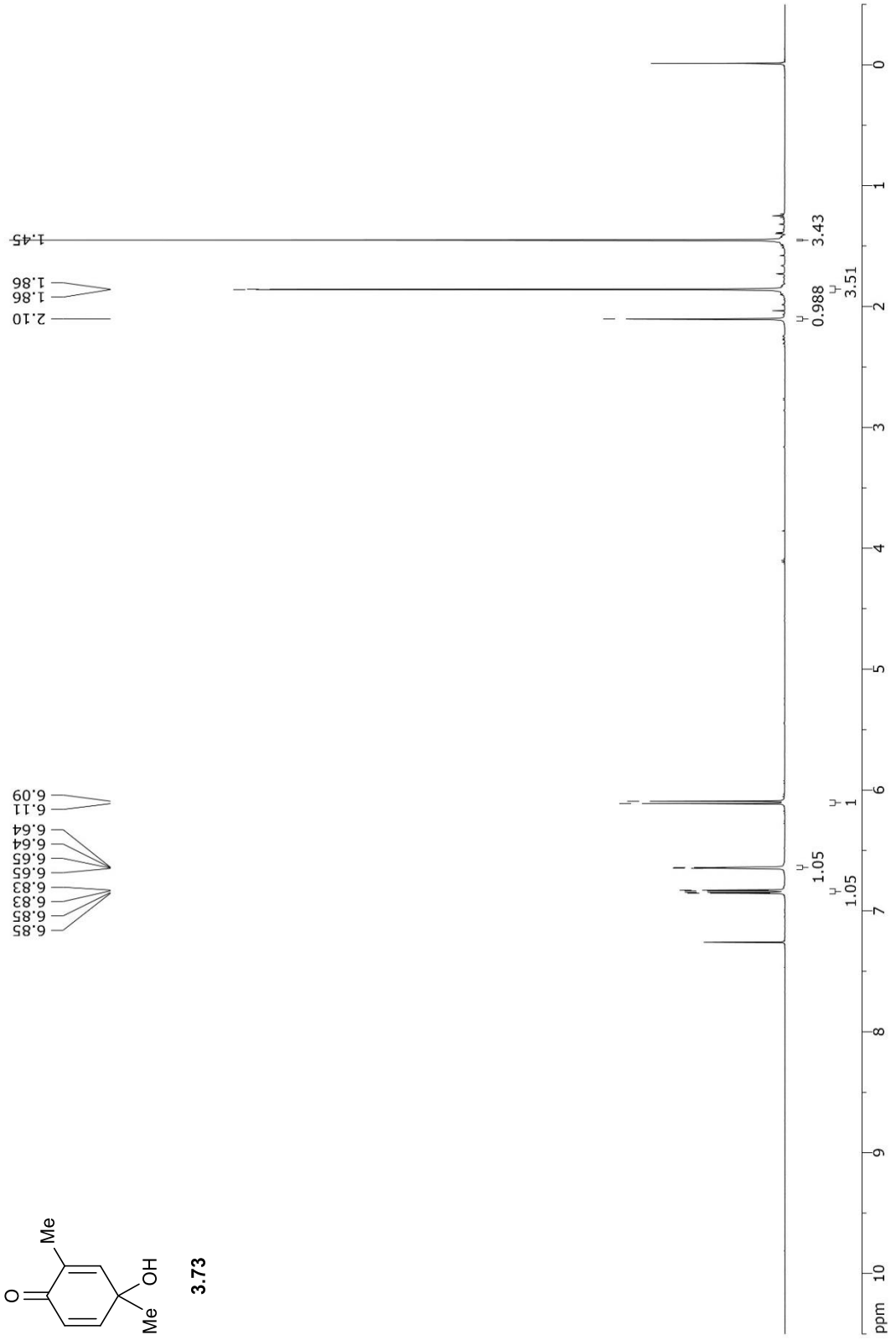
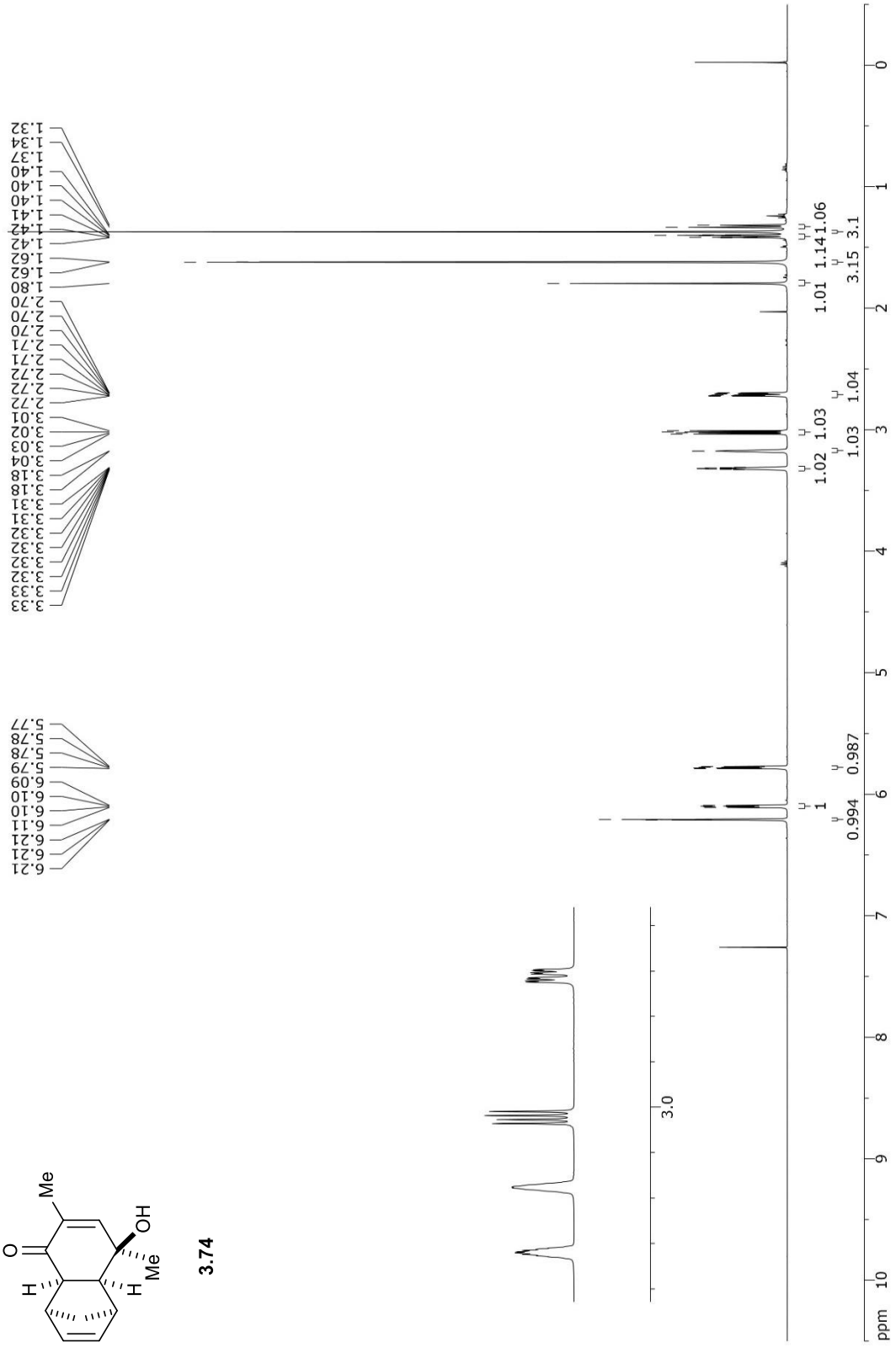
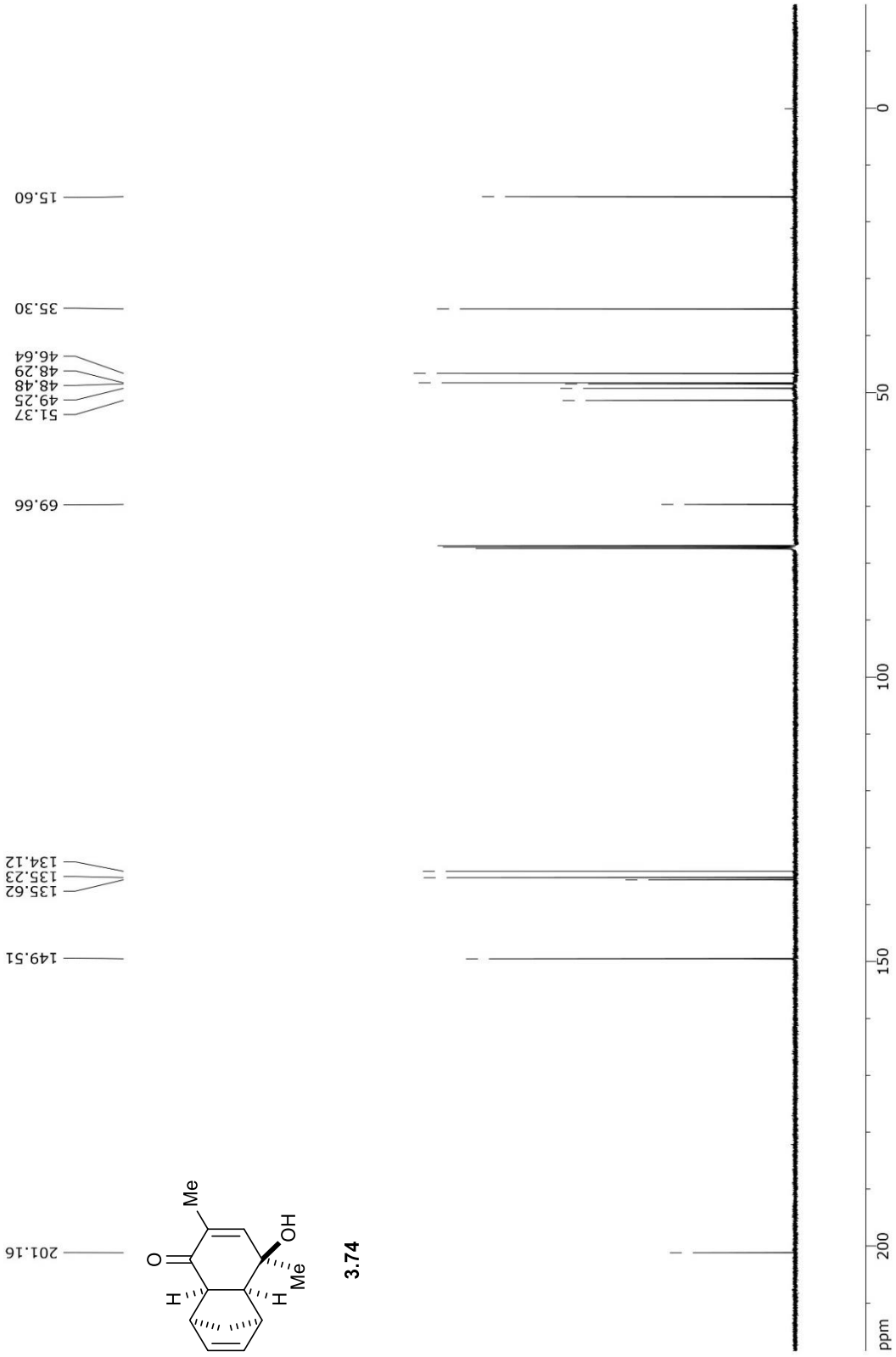
2.36
2.36
2.36
2.36
2.36
2.36
2.36
2.36
2.36
2.37
2.37
2.37
2.37
2.38
2.38
2.38
2.39
2.39
2.39
2.39
2.39
2.40
2.40
2.41
2.41
2.41
2.41
2.41
2.42
2.42
2.42
2.42
2.43
2.45
2.45
2.45
3.11
3.12
3.13
3.14
3.15
3.15
3.16
3.18
7.31
7.32
7.61
7.63
2.09
1.18
1:2
1.22
4.71
1.33
3.73
3.51
ppm
Me
Ts
O
3.62

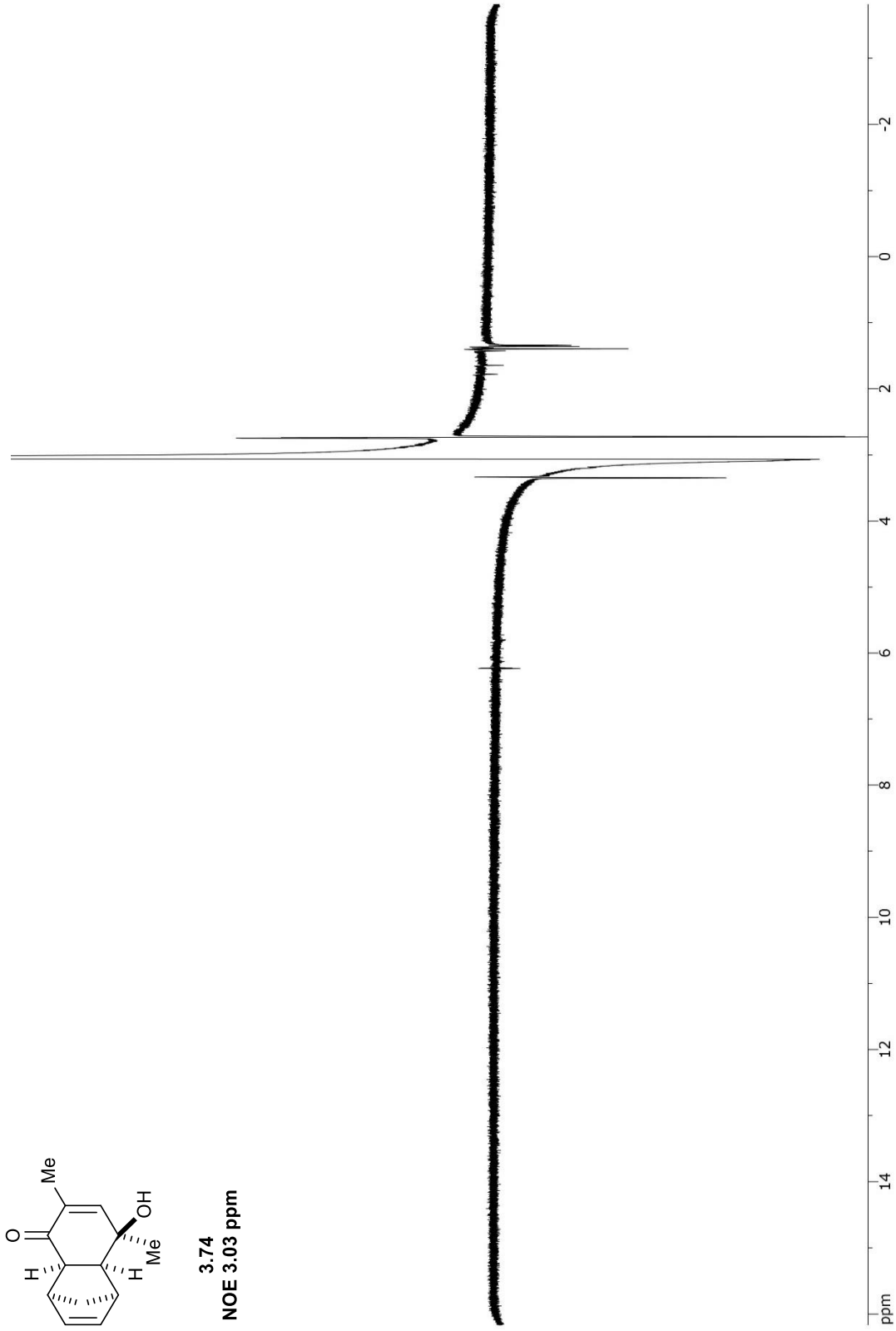

O
Me
OH
Ph
3.63
3.71
2.42
0.963
1.05
1.19
1.05
1.01
1.24
6.54
1.09
3.04
ppm

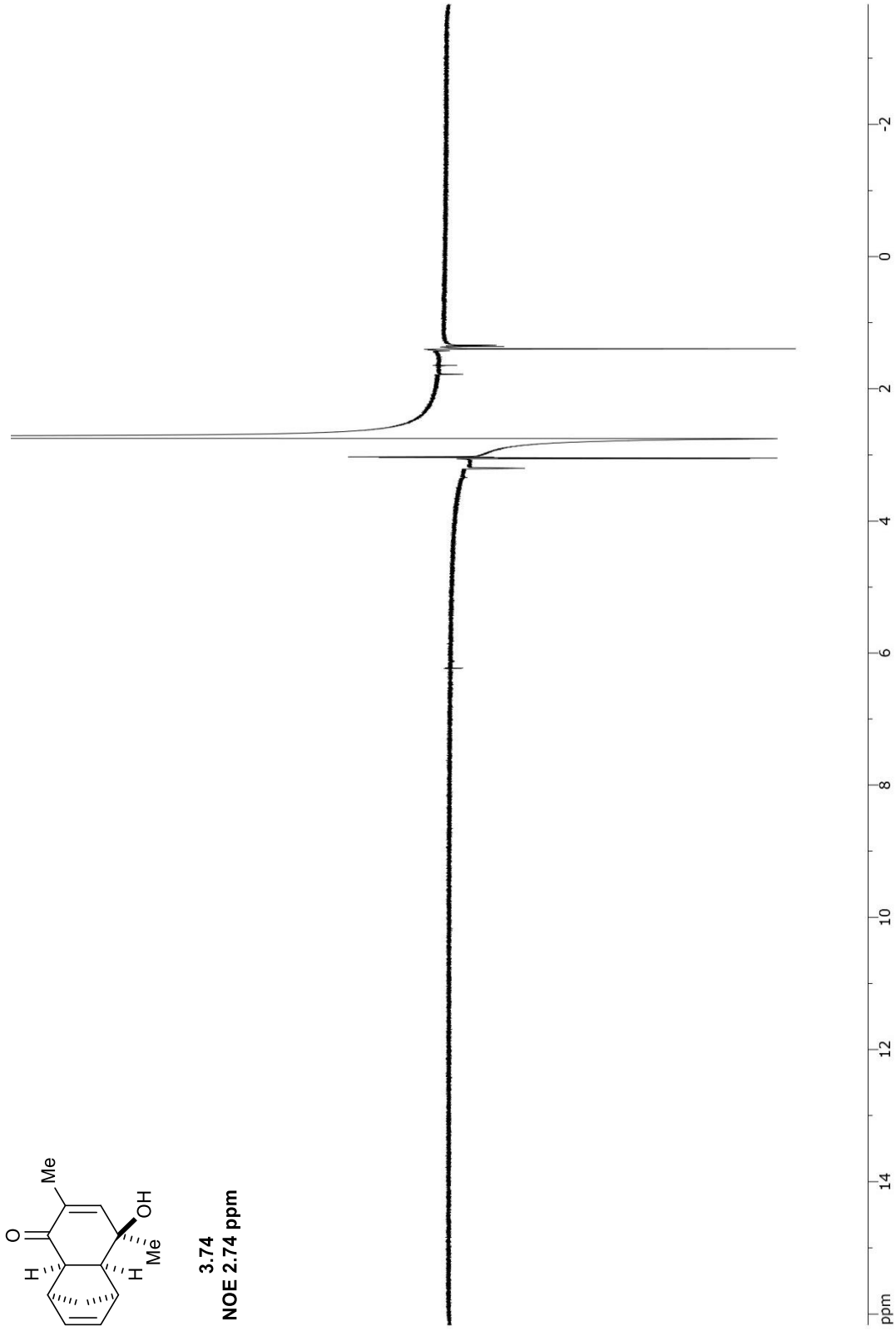

1.45
1.86
1.86
2.10
6.09
6.11
6.64
6.64
6.65
6.65
6.83
6.83
6.85
6.85
3.43
0.988
3.51
1
1.05
1.05
ppm
Me
OH
Me
O

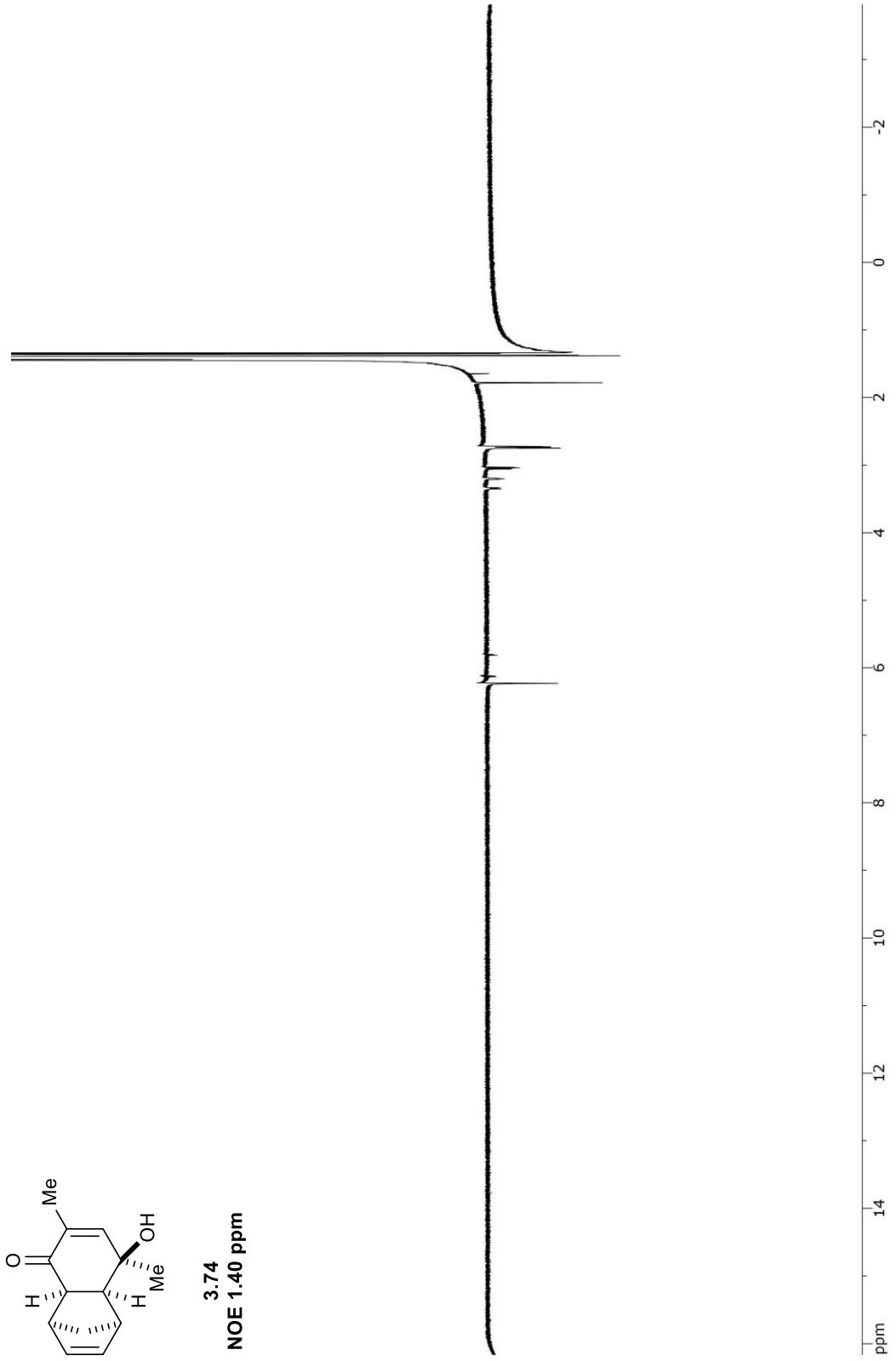
3.73

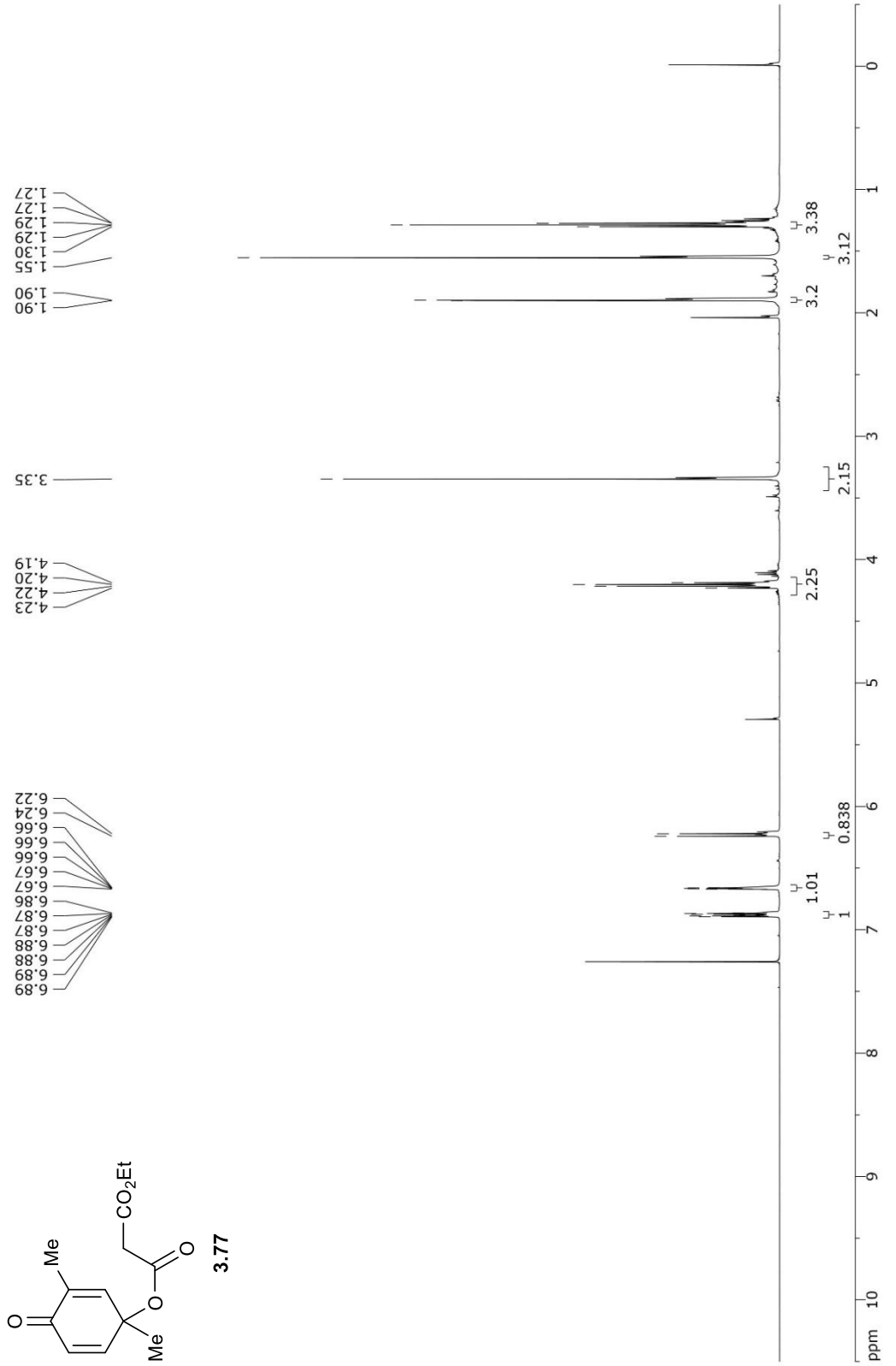

Me
OH
O
H
H
Me
3.74
6.21
6.21
6.21
6.11
6.10
6.10
6.09
5.79
5.78
5.78
5.77
3.33
3.32
3.32
3.32
3.32
3.31
3.31
3.18
3.18
3.04
3.03
3.02
3.01
2.72
2.72
2.72
2.71
2.71
2.70
2.70
2.70
1.80
1.62
1.62
1.42
1.42
1.41
1.40
1.40
1.40
1.37
1.34
1.32
1.01
1.14
1.06
3.15
3.1
1.02
1.03
1.03
1.04
1
0.994
0.987
3.0
ppm


15.60
35.30
46.64
48.29
48.48
49.25
51.37
69.66
134.12
135.23
135.62
149.51
201.16
Me
OH
O
H
H
Me
3.74
0
50
100
150
200
ppm

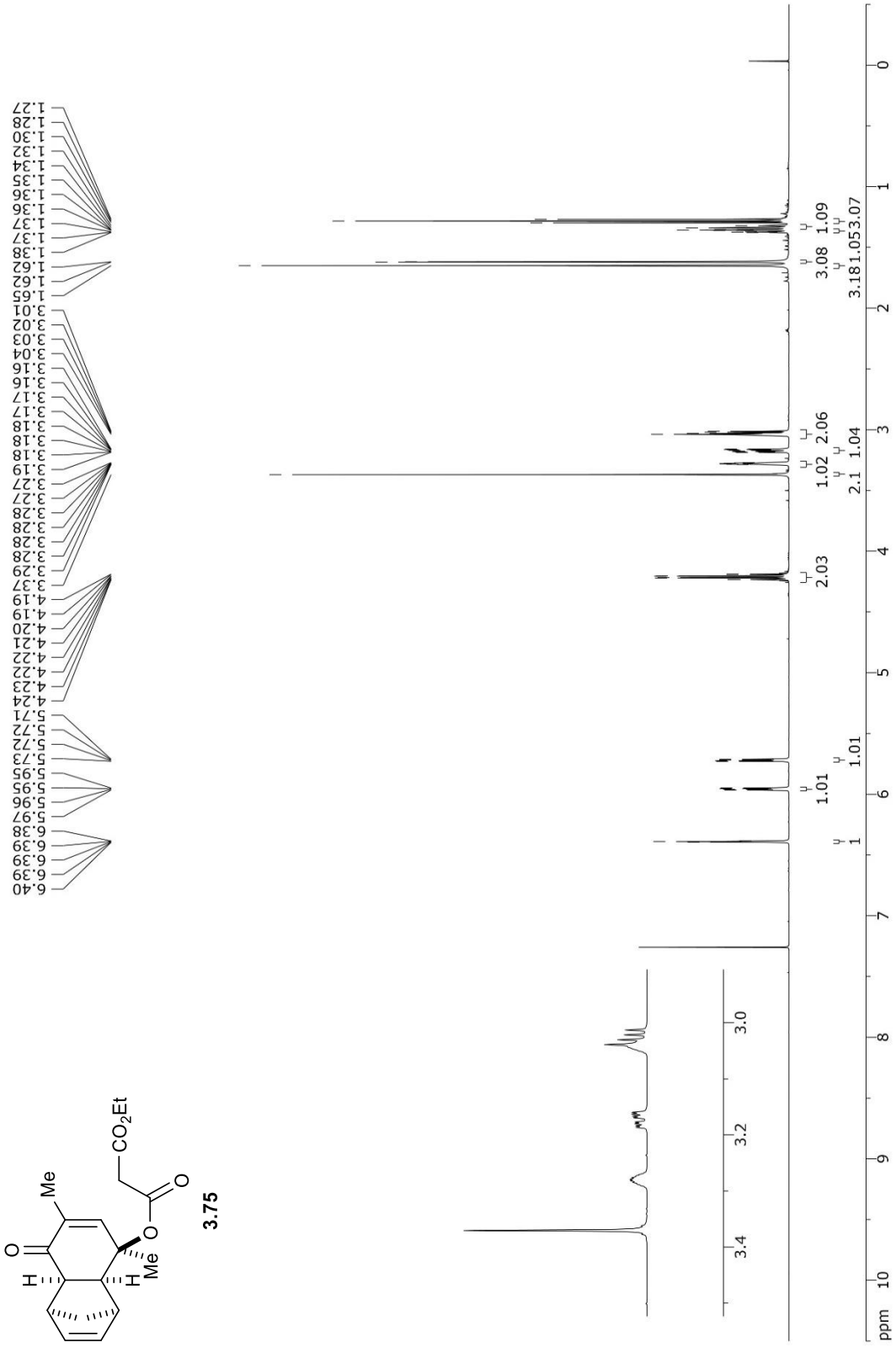

Me
OH
O
H
H
Me
3.74
NOE 3.03 ppm
-2
0
2
4
6
8
10
12
14
ppm

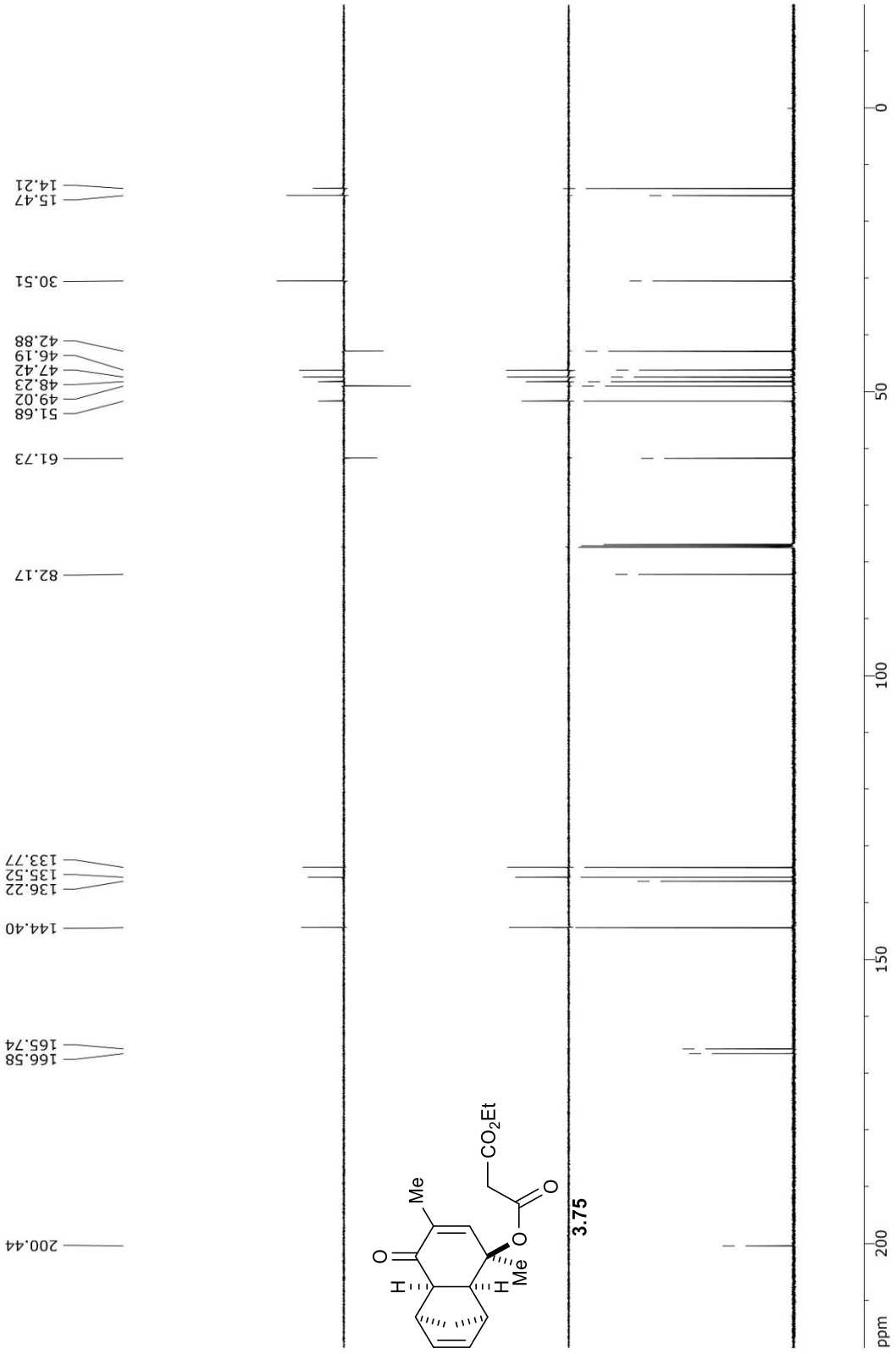

Me
OH
O
H
H
Me
3.74
NOE 2.74 ppm
-2
0
2
4
6
8
10
12
14
ppm


Me
OH
O
H
H
Me
3.74
NOE 1.40 ppm
-2
0
2
4
6
8
10
12
14
ppm


1.27
1.27
1.29
1.29
1.30
1.55
1.90
1.90
3.35
4.19
4.20
4.22
4.23
6.22
6.24
6.66
6.66
6.67
6.67
6.86
6.87
6.87
6.88
6.88
6.89
6.89
1.01
0.838
2.25
2.15
3.2
3.12
3.38
ppm
Me
Me
O
O
O
O
CO2Et

3.77


Me
CO2Et
O
O
O
H
H
Me
3.75
ppm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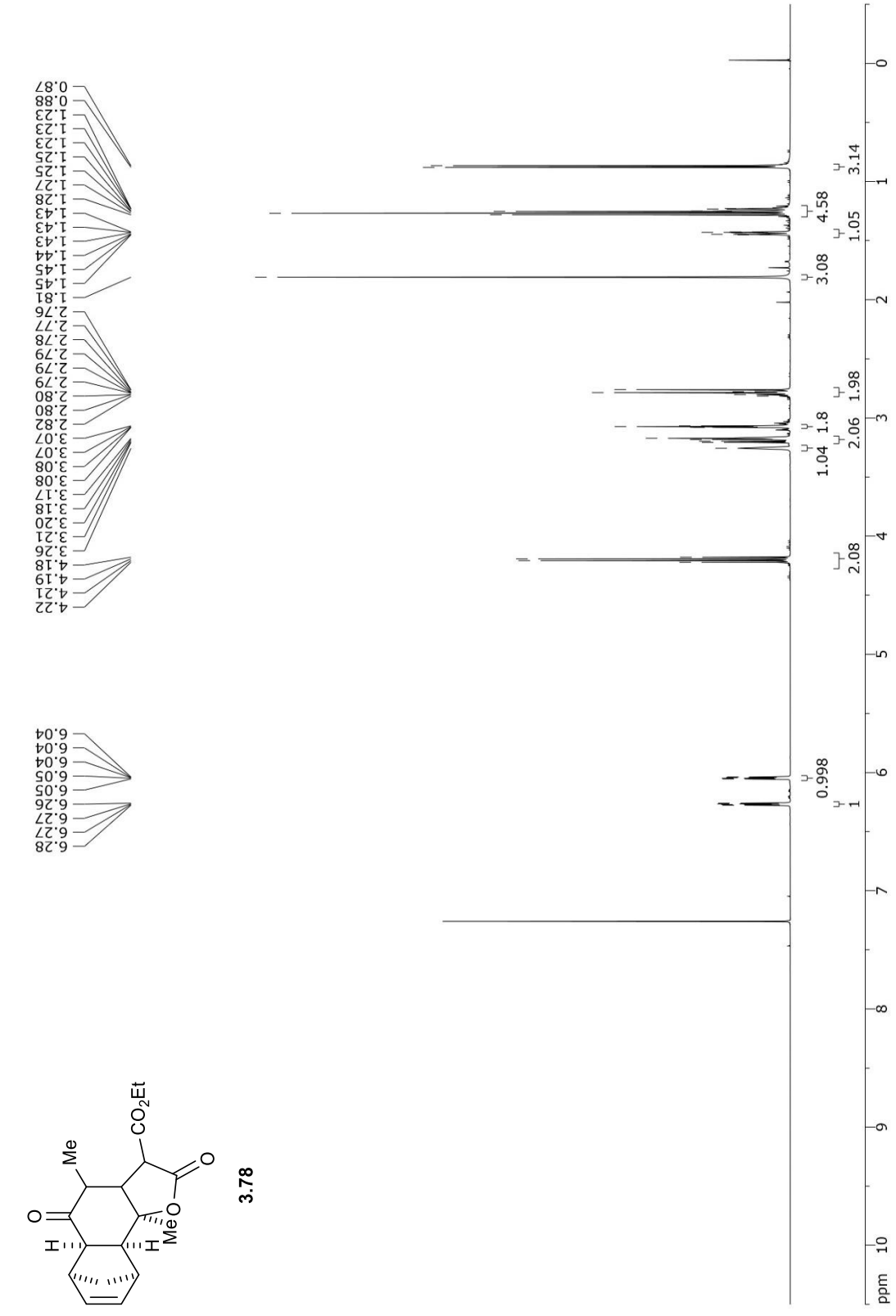
15.47
30.51
42.88
46.19
47.42
48.23
49.02
51.68
61.73
82.17
133.77
135.52
136.22
144.40
165.58
165.74
200.44
3.75
Me
CO2Et
O
O
H
O
Me
H
0
50
100
150
200
ppm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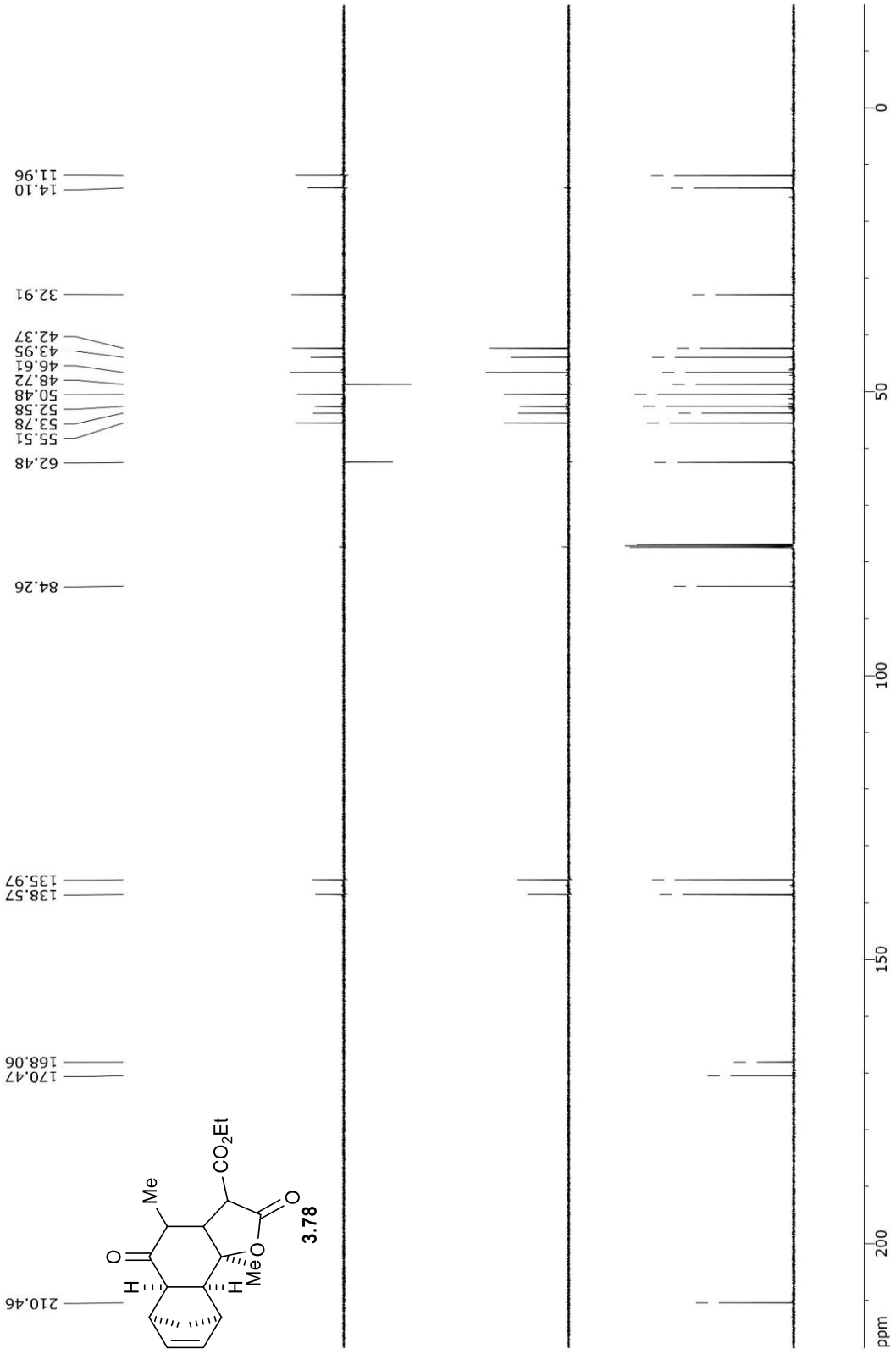
0.88
1.23
1.23
1.23
1.25
1.25
1.27
1.28
1.43
1.43
1.43
1.44
1.45
1.45
1.81
2.76
2.77
2.78
2.79
2.79
2.79
2.80
2.80
2.82
3.07
3.07
3.08
3.08
3.17
3.18
3.20
3.21
3.26
4.18
4.19
4.21
4.22
6.04
6.04
6.04
6.05
6.05
6.26
6.27
6.27
6.28
0.998
2.08
1.04
1.8
2.06
1.98
3.08
4.58
1.05
3.14
ppm

Me
CO2Et
O
O
H
H
MeO

3.78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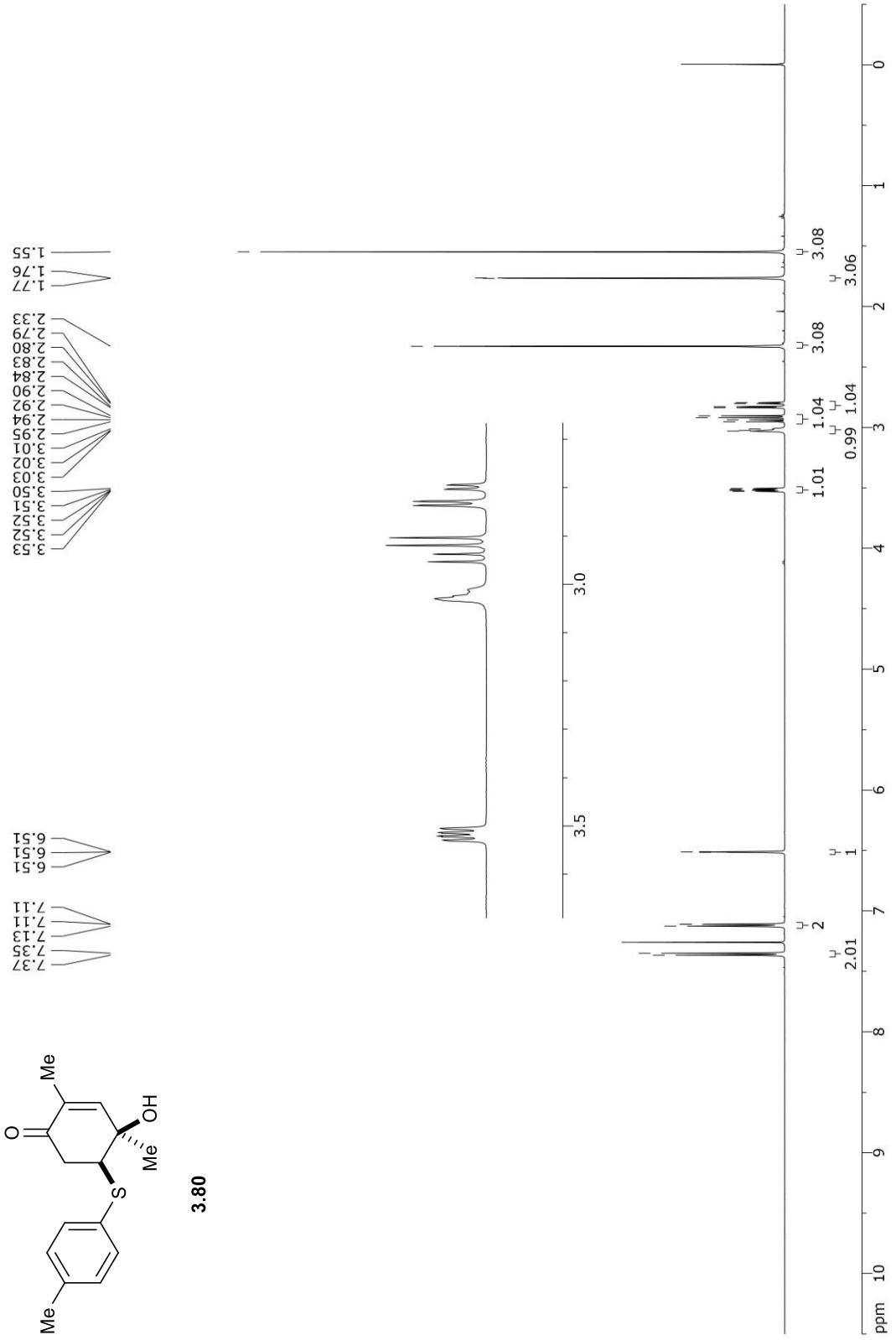
14.10
32.91
42.37
43.95
46.61
48.72
50.48
52.58
53.78
55.51
62.48
84.26
135.97
138.57
168.06
170.47
210.46
ppm
0
50
100
150
200
Me
CO2Et
O
O
O
MeO
H
H
3.78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1.76
2.33
2.79
2.80
2.83
2.84
2.90
2.92
2.94
2.95
3.01
3.02
3.03
3.50
3.51
3.52
3.52
3.53
6.51
6.51
6.51
7.11
7.11
7.13
7.35
7.37
3.08
3.06
3.08
1.04
1.04
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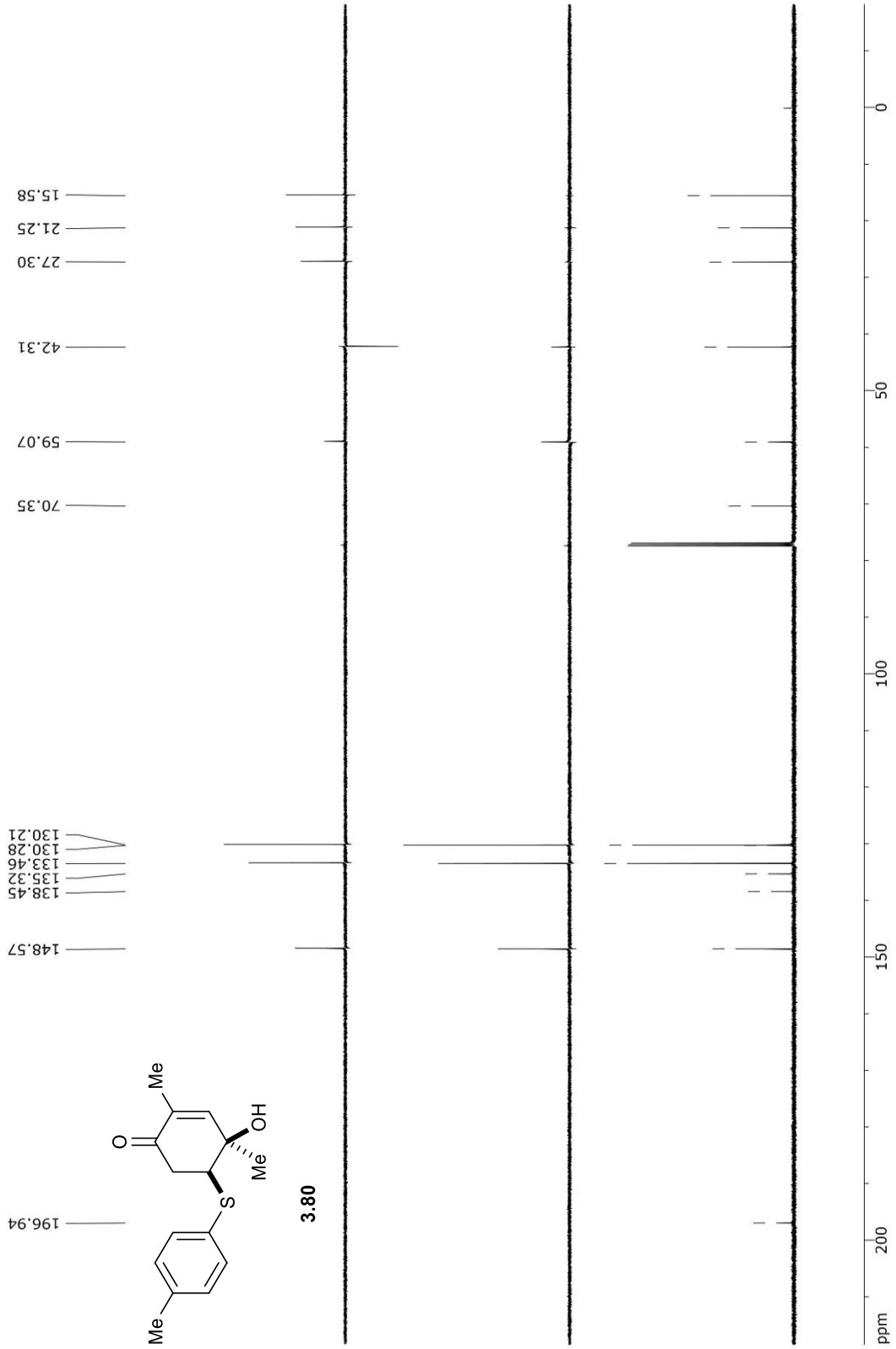
1.01
2.01
3.0
3.5
ppm
Me
OH
Me
O
S
Me

3.80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27.30
42.31
59.07
70.35
130.21
130.28
133.46
135.32
138.45
148.57
196.94
Me
O
OH
Me
S
Me
3.80
0
50
100
150
200
ppm

7.36
7.36
7.36
7.35
7.34
7.34
7.29
7.29
7.27
7.27
7.28
7.29
7.12
7.14
7.27
7.08
7.07
3.75
3.73
3.72
3.71
3.63
3.61
3.60
3.60
3.59
3.59
3.58
3.45
3.44
2.72
2.69
2.67
2.62
2.61
2.59
2.58
2.49
2.48
2.47
2.34
2.31
1.62
1.18
1.16
Me
Me
S
S
OH
Me
Me
O
3.81
ppm
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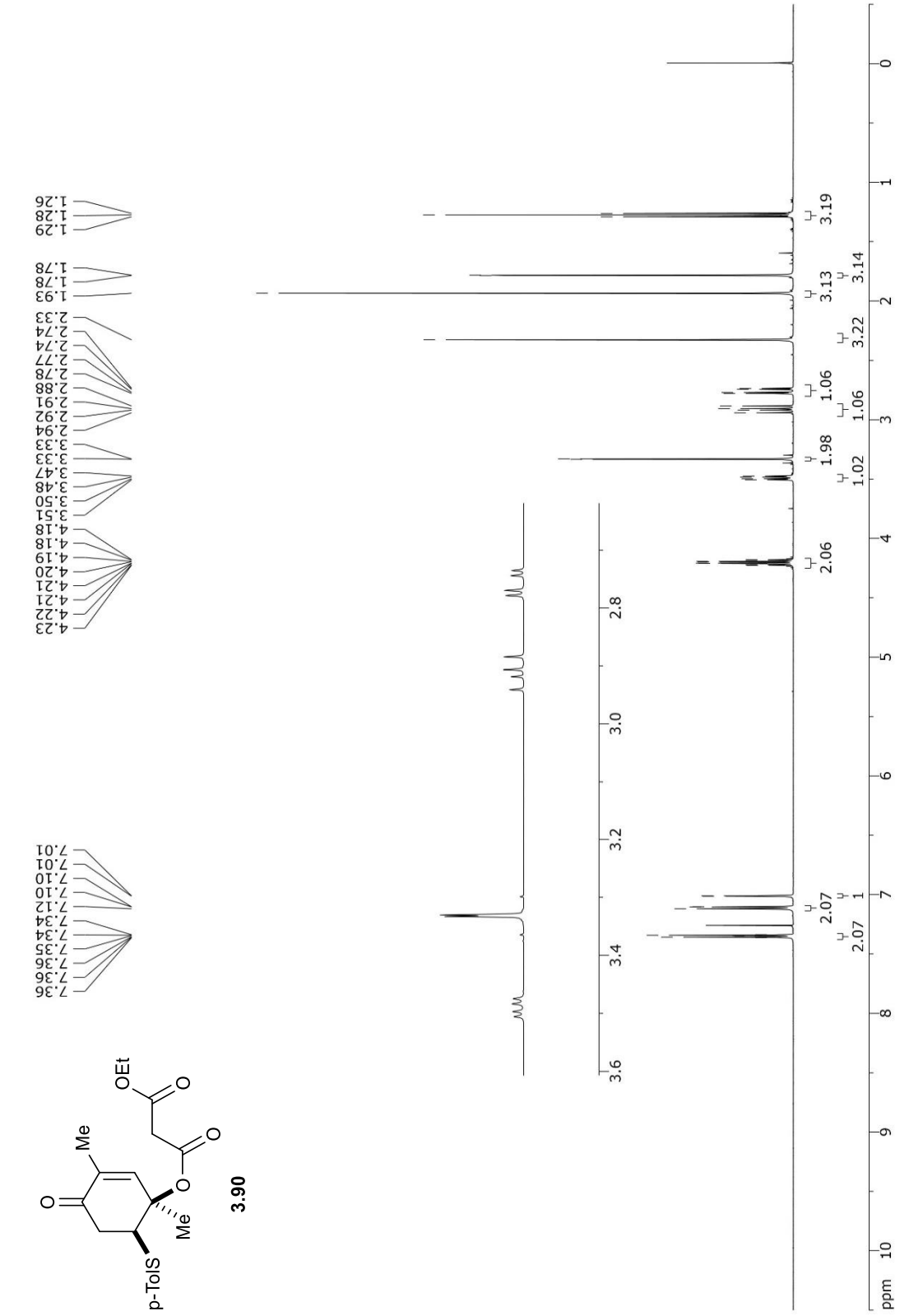
2.25 2.29
0.999
1 1.04
1.03 3.27
1.05 3.52
3.17
3.23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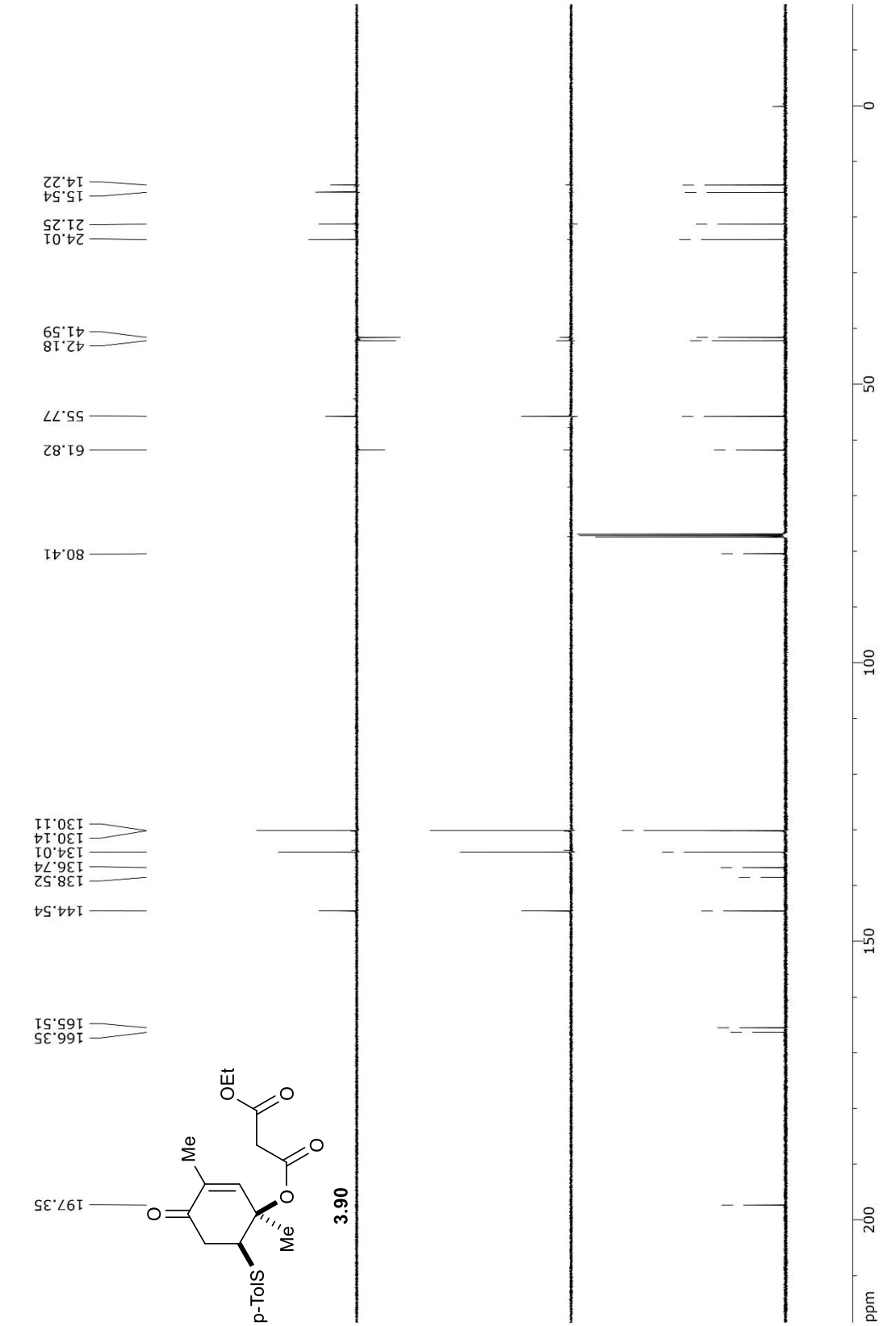
7.36
7.35
7.34
7.34
7.12
7.10
7.10
7.01
7.01
4.23
4.22
4.21
4.21
4.20
4.19
4.18
4.18
3.51
3.50
3.48
3.47
3.33
3.33
2.94
2.92
2.91
2.88
2.78
2.77
2.74
2.74
2.33
1.93
1.78
1.78
1.29
1.28
1.26
2.07
2.07
1
2.06
1.02
1.98
1.06
1.06
3.22
3.13
3.14
3.19
ppm
Me
OEt
O
O
O
O
Me
p-TolS
3.90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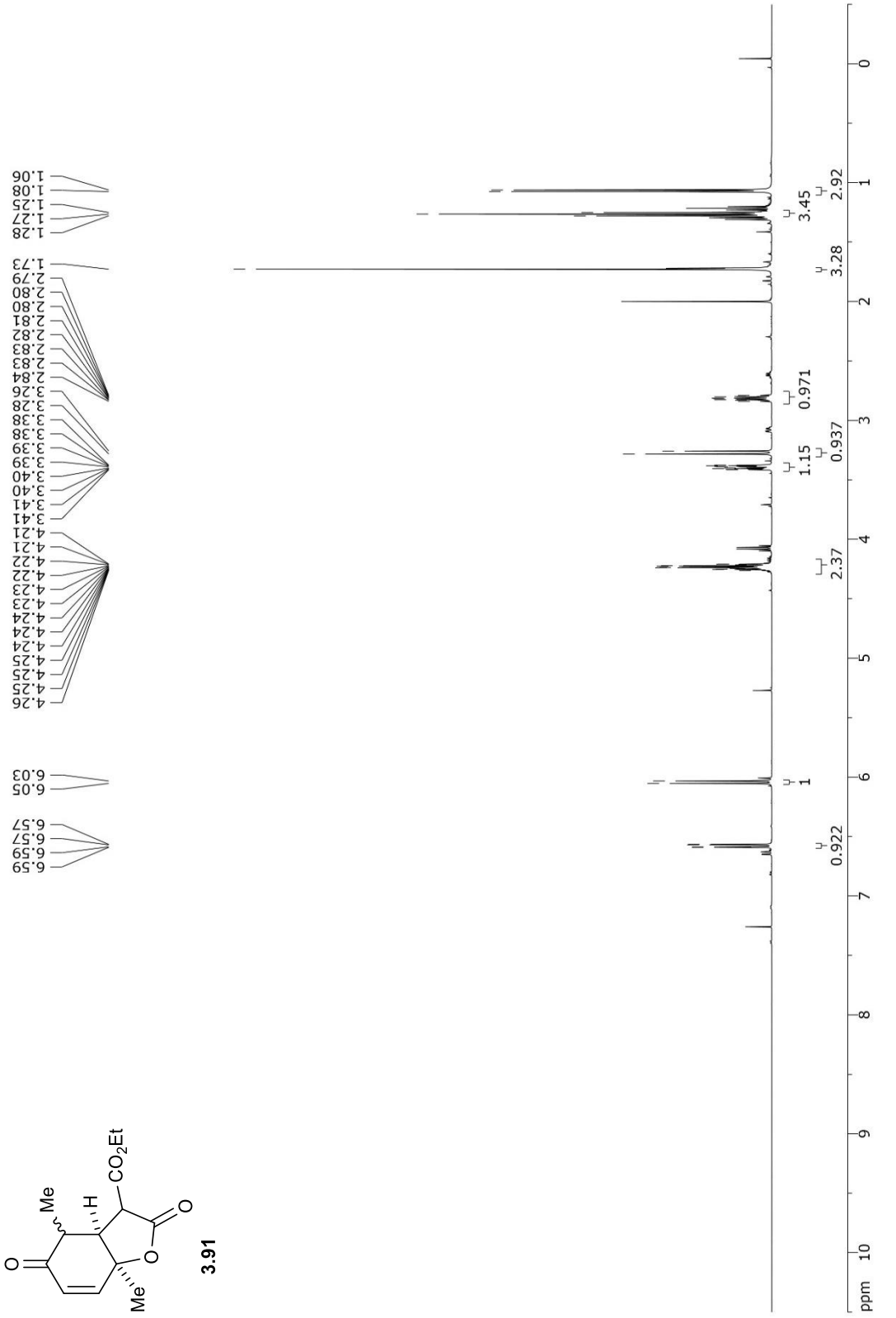
15.54
21.25
24.01
41.59
42.18
55.77
61.82
80.41
130.11
130.14
134.01
136.74
138.52
144.54
165.51
166.35
197.35
3.90
Me
Me
OEt
p-TolS
ppm
0
50
100
150
200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1.27
1.28
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2.80
2.80
2.81
2.82
2.83
2.83
2.84
3.26
3.28
3.38
3.39
3.39
3.40
3.40
3.41
3.41
4.21
4.21
4.22
4.22
4.23
4.23
4.24
4.24
4.24
4.25
4.25
4.25
4.26
6.03
6.05
6.57
6.57
6.59
6.59
1
0.922
2.37
1.15
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3.28
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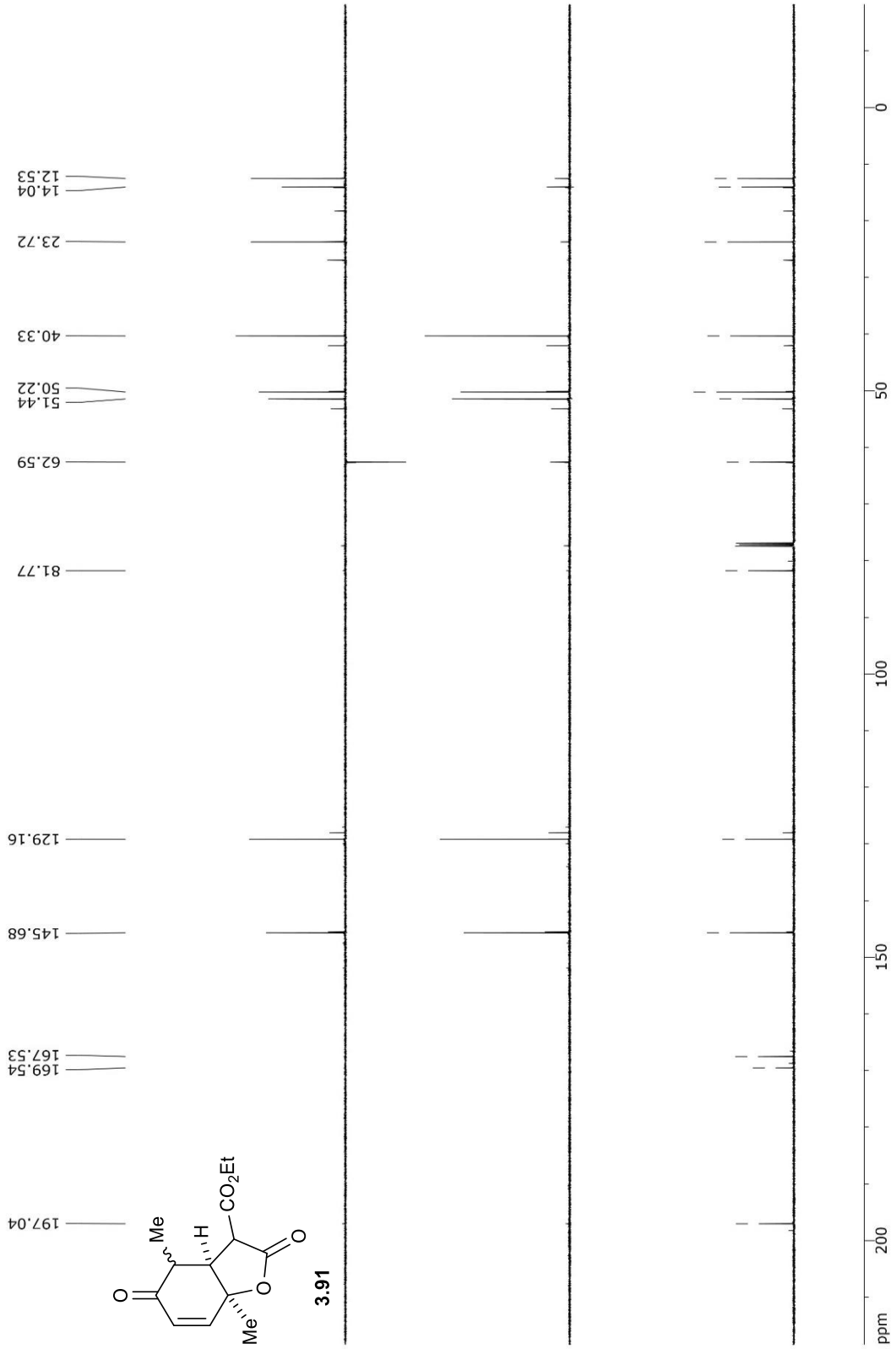
ppm
Me
H
CO2Et
O
O
O
Me
3.91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14.04
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50.22
51.44
62.59
81.77
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145.68
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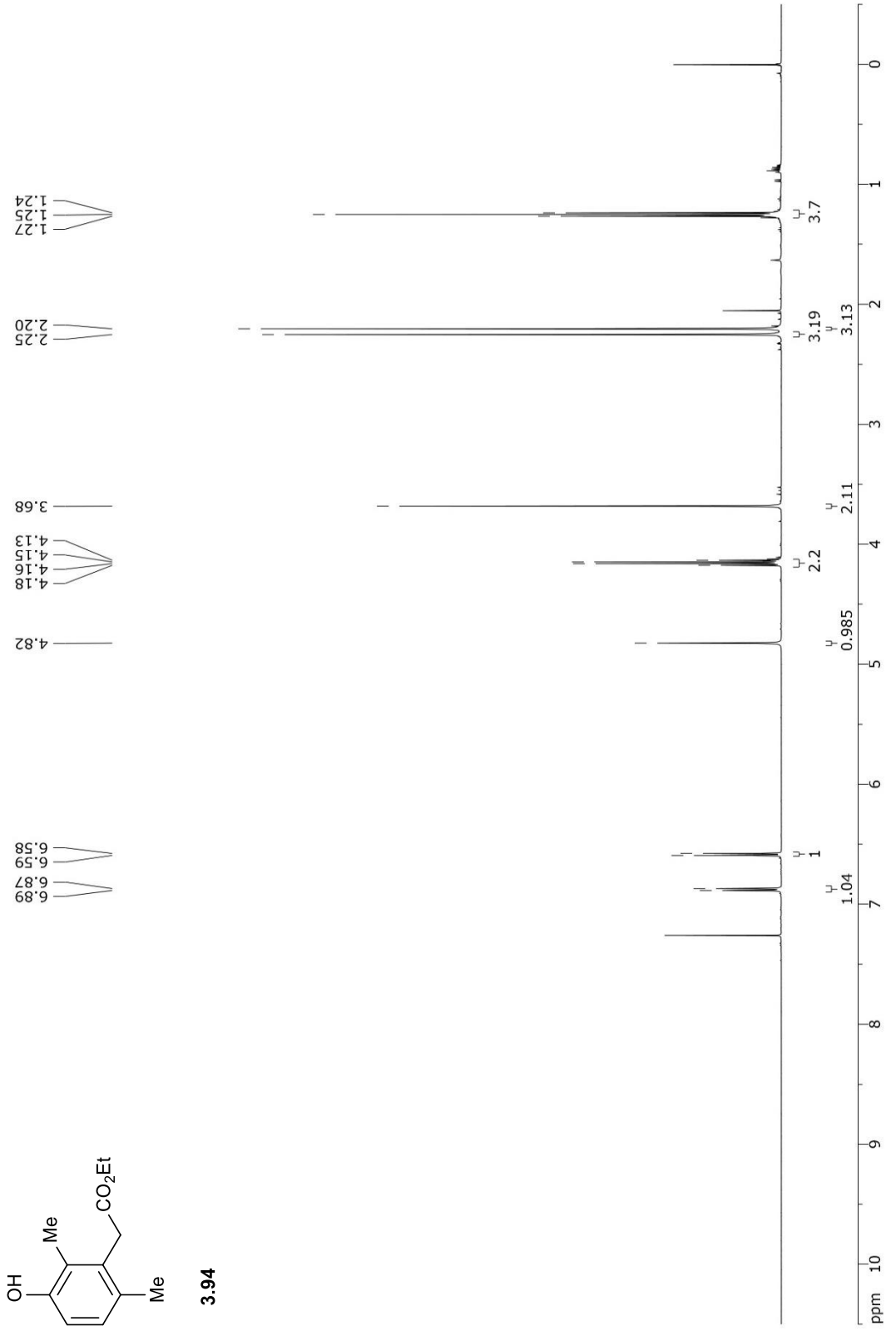
197.04
Me
H
CO2Et
O
O
O
Me
3.91
0
50
100
150
200
ppm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2.20
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4.13
4.15
4.16
4.18
4.82
6.58
6.59
6.87
6.89
3.7
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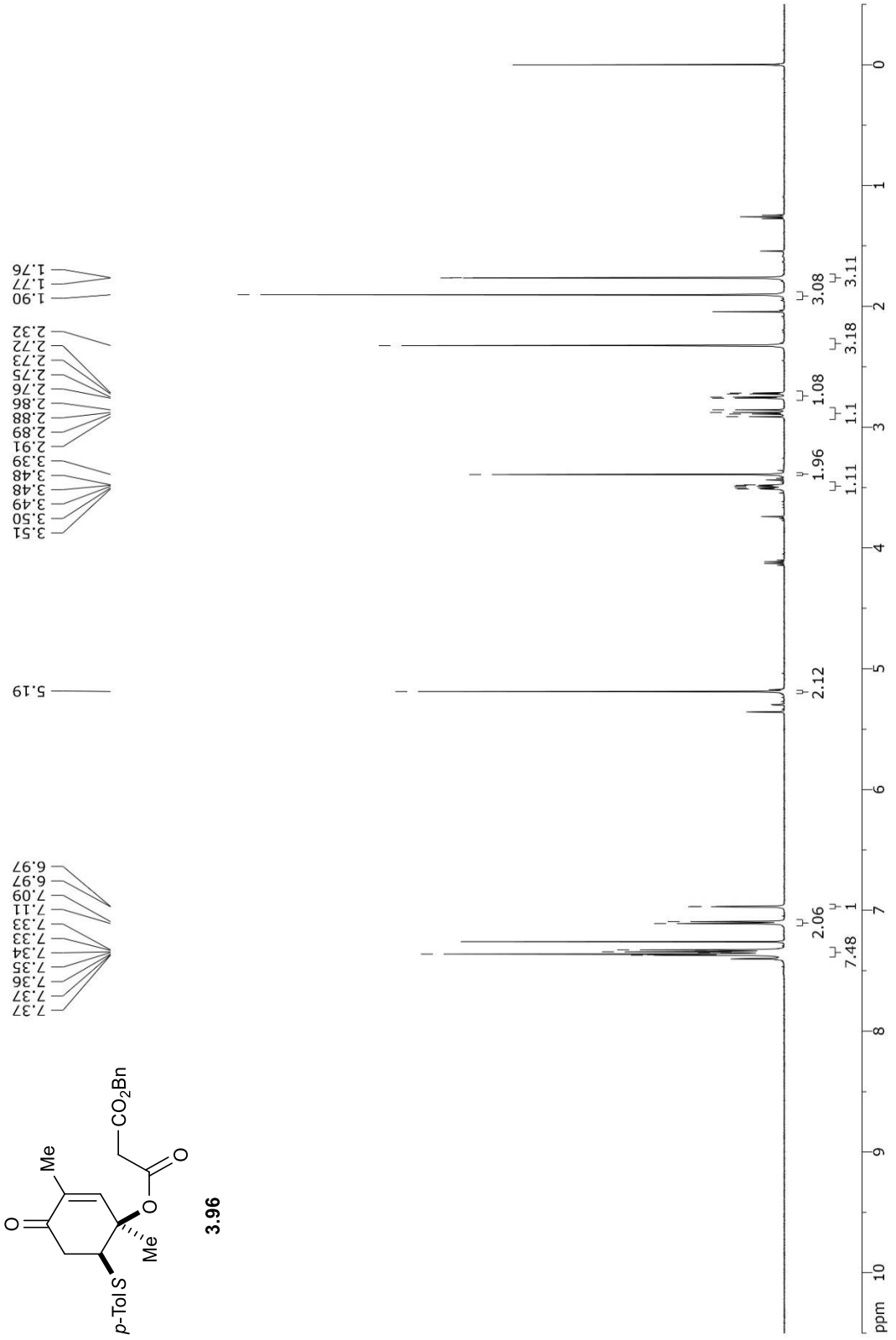
2.11
2.2
0.985
1
1.04
ppm

OH
Me
Me
CO2Et

3.94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2.76
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2.88
2.89
2.91
3.39
3.48
3.48
3.49
3.50
3.51
5.19
6.97
6.97
7.09
7.11
7.33
7.33
7.34
7.35
7.36
7.37
7.37
2.06
7.48
2.12
1.96
1.11
1.08
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3.08
3.11
ppm
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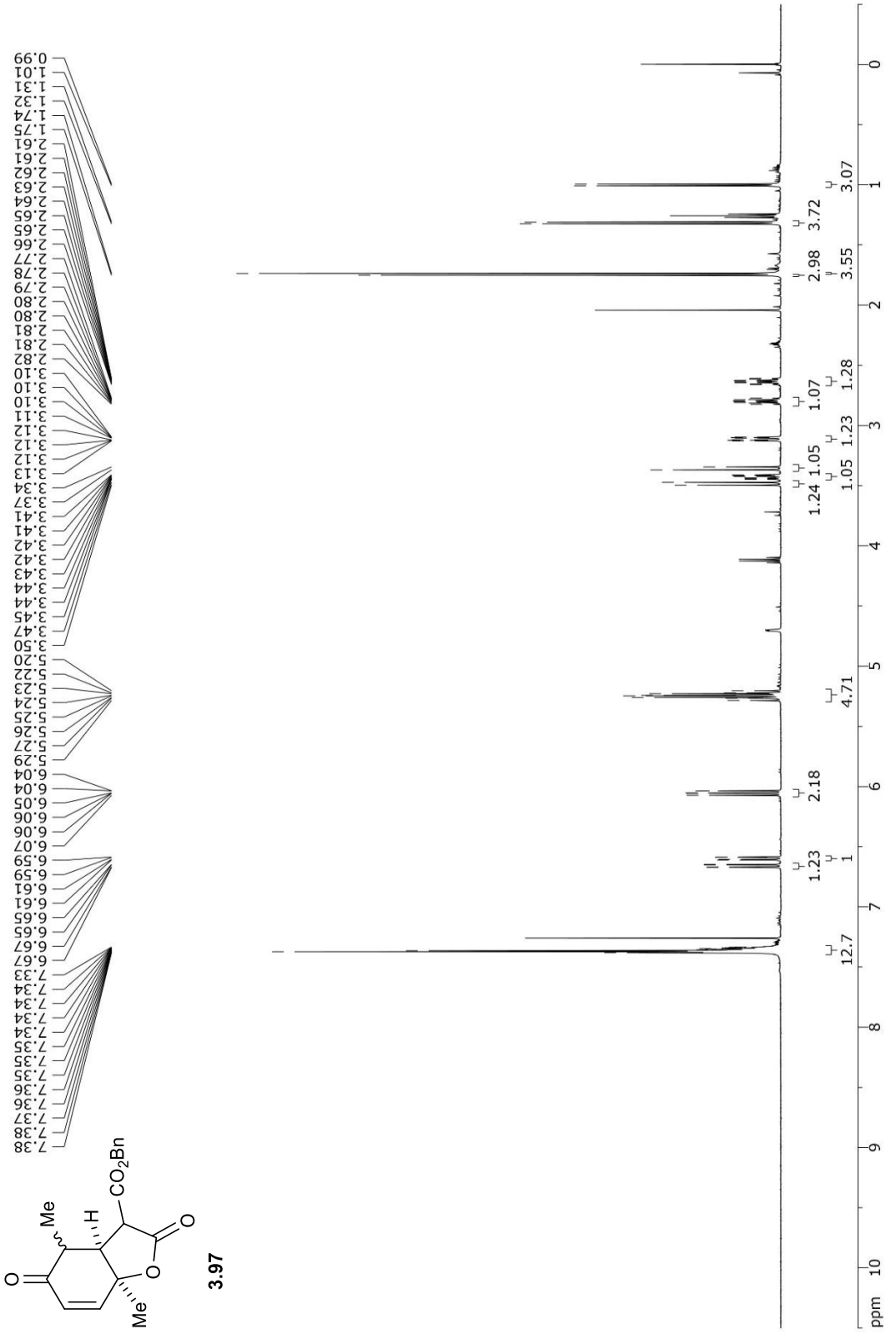
O
O
O
Me
p-Tol S
3.96


Me
H
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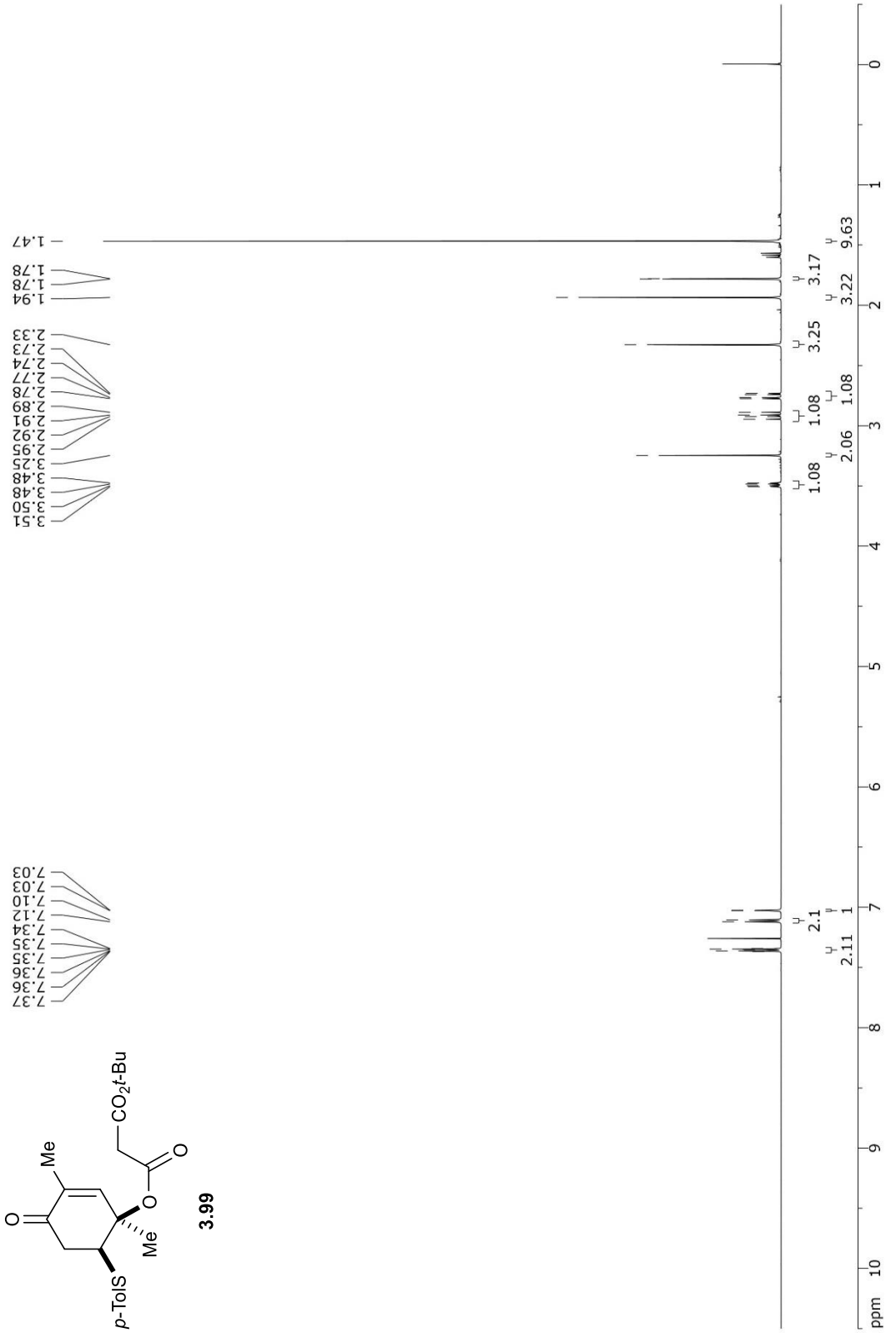
O
O
O
Me
3.97
ppm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1.78
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2.74
2.77
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2.89
2.91
2.92
2.95
3.25
3.48
3.48
3.50
3.51
7.03
7.03
7.10
7.12
7.34
7.35
7.35
7.36
7.36
7.37
2.11
2.1
1
1.08
2.06
1.08
3.25
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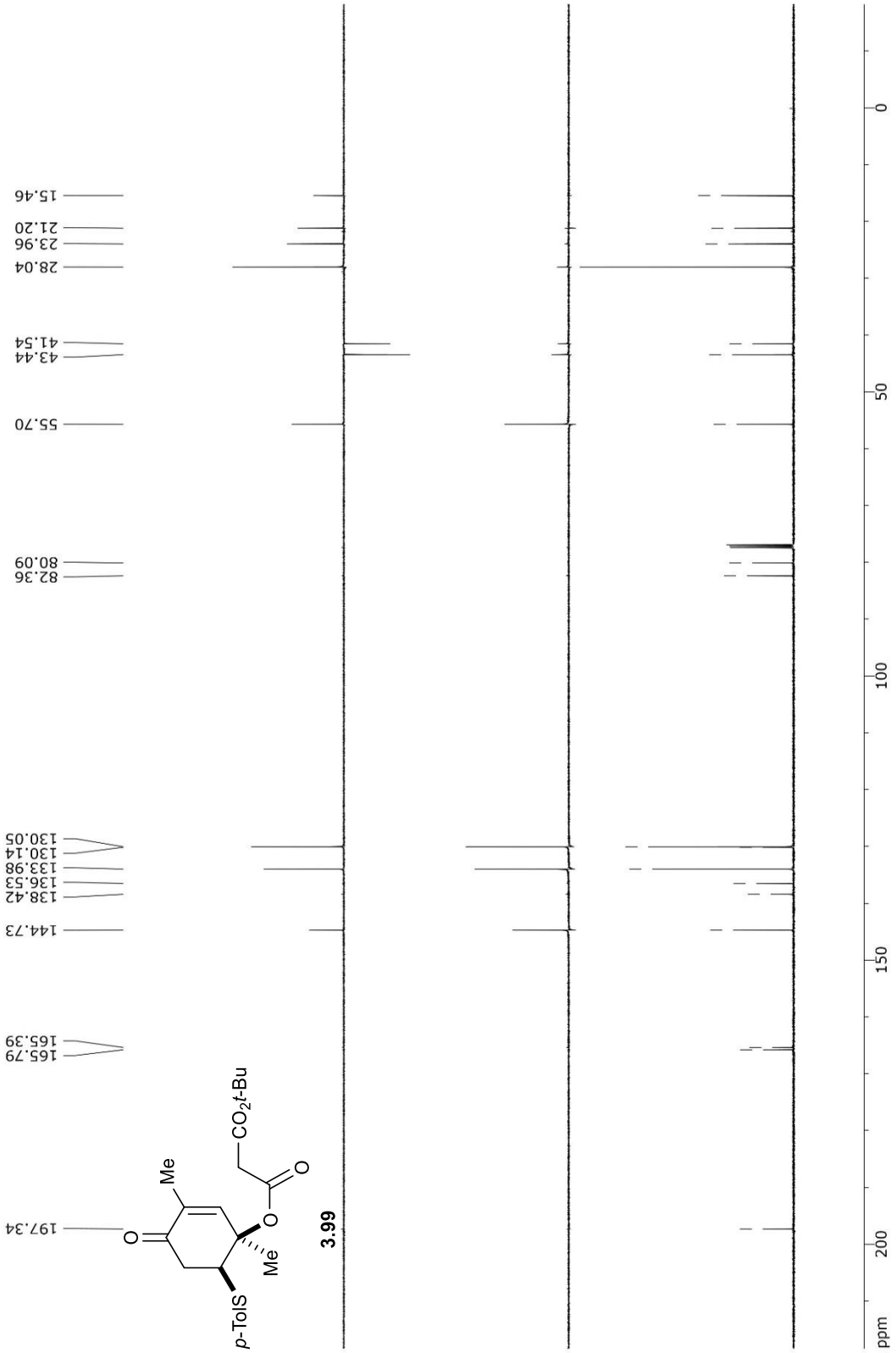
3.22
3.17
9.63
ppm
Me
O
O
O
Me
p-TolS
CO2t-Bu
3.99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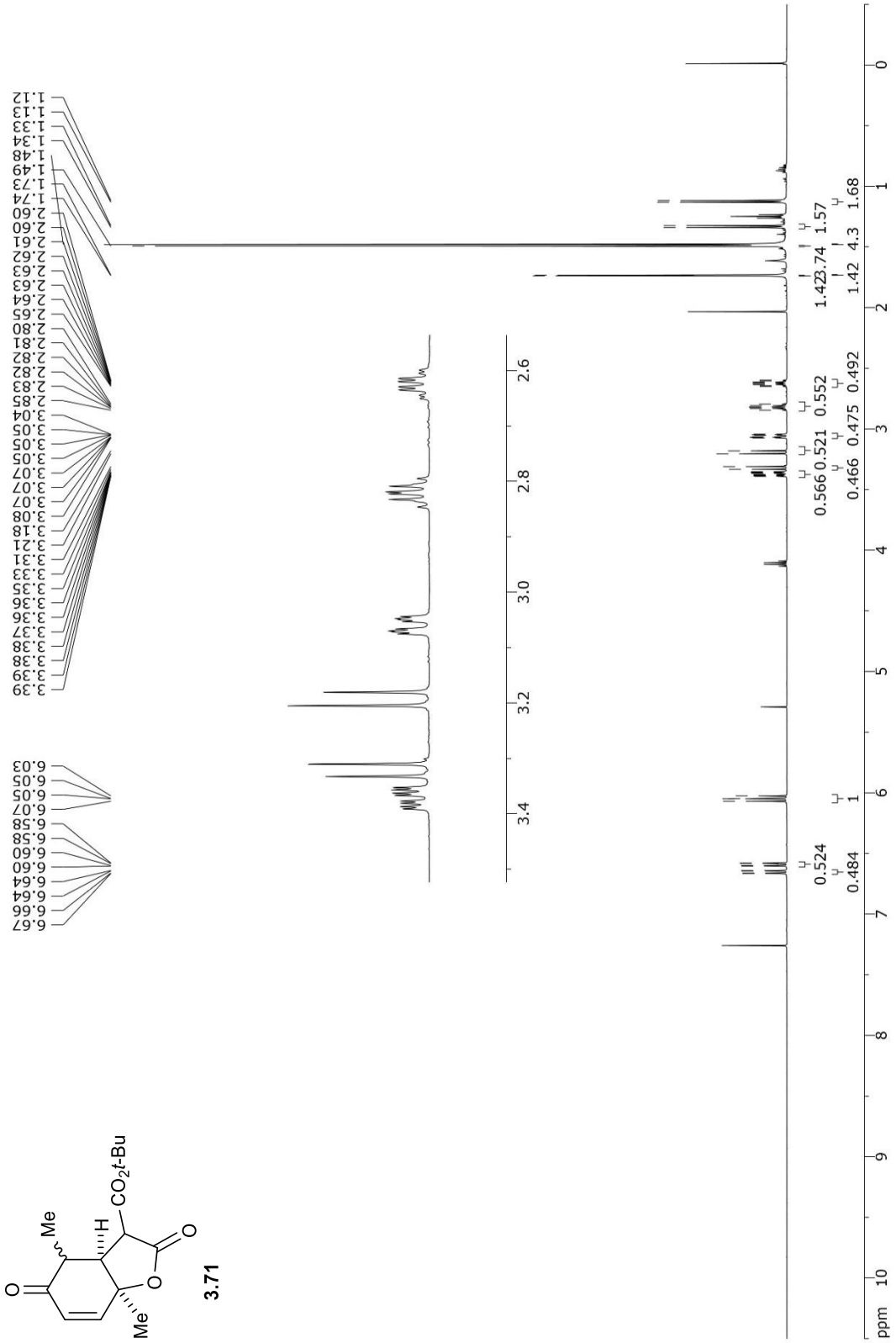
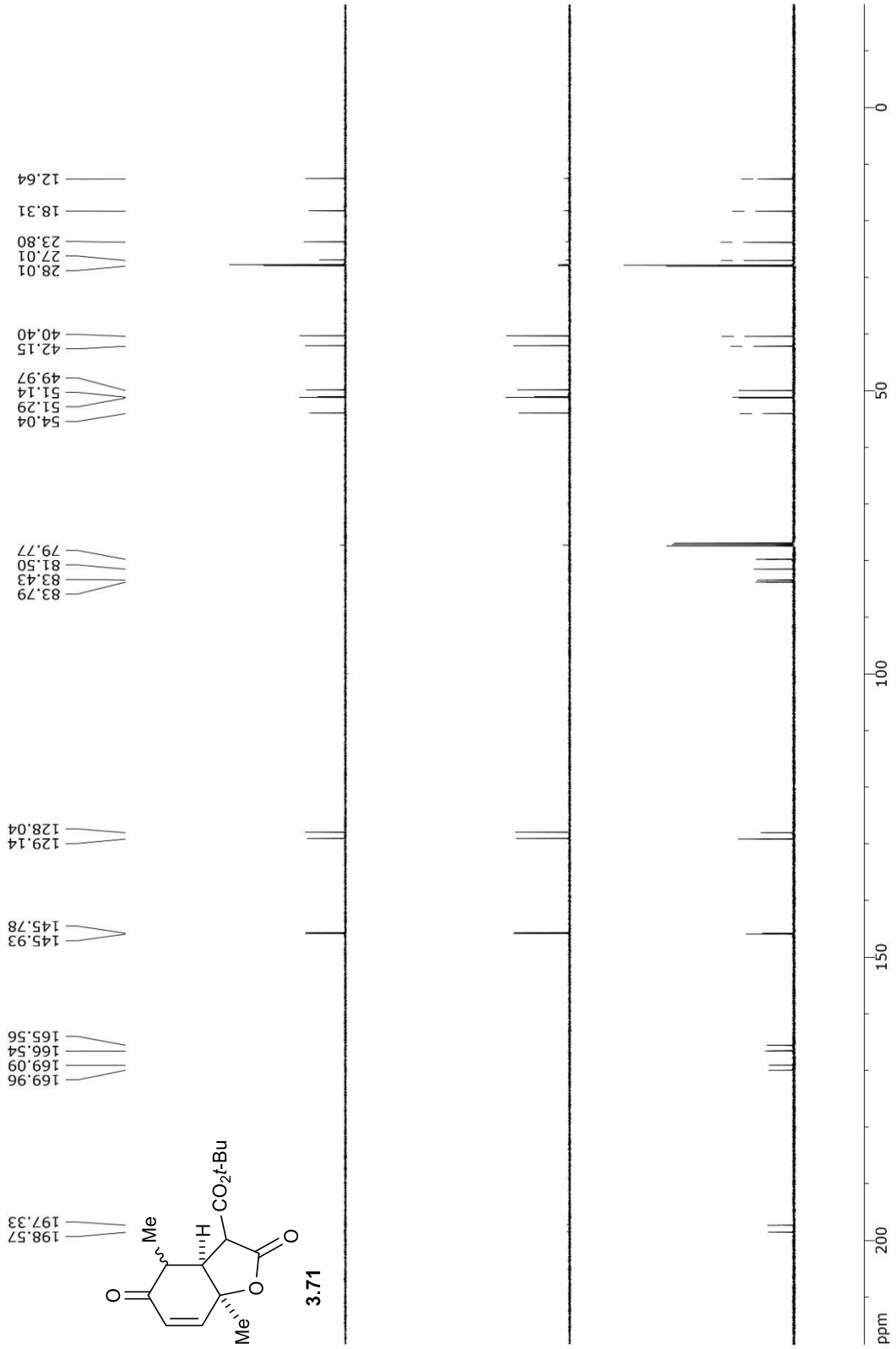
55.70
80.09
82.36
130.05
130.14
133.98
136.53
138.42
144.73
165.39
165.79
197.34
3.99
Me
Me
O
O
O
O
CO2t-Bu
p-TolS
0
50
100
150
200
ppm


Me
H
CO2t-Bu
O
O
O
Me
3.71
ppm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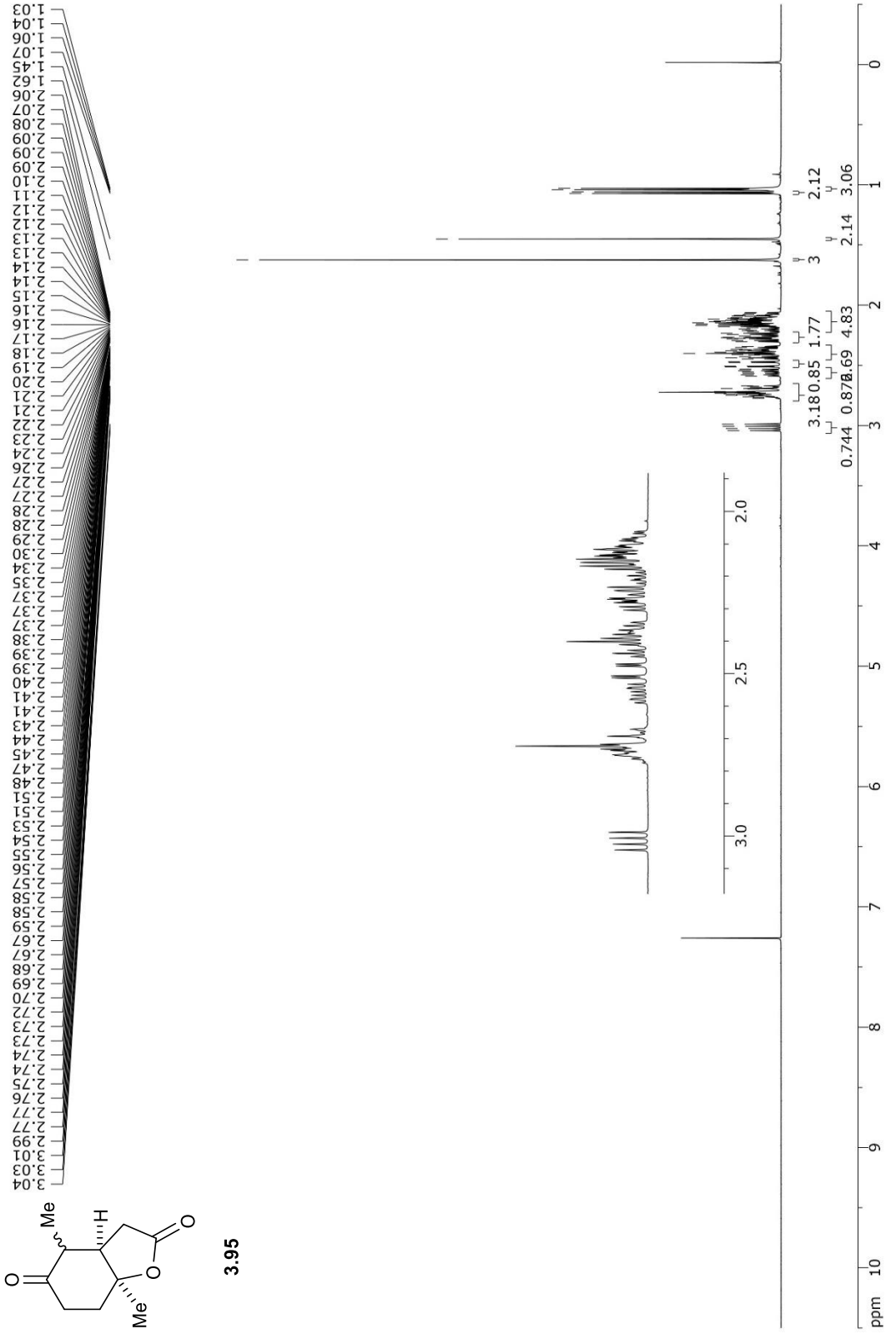
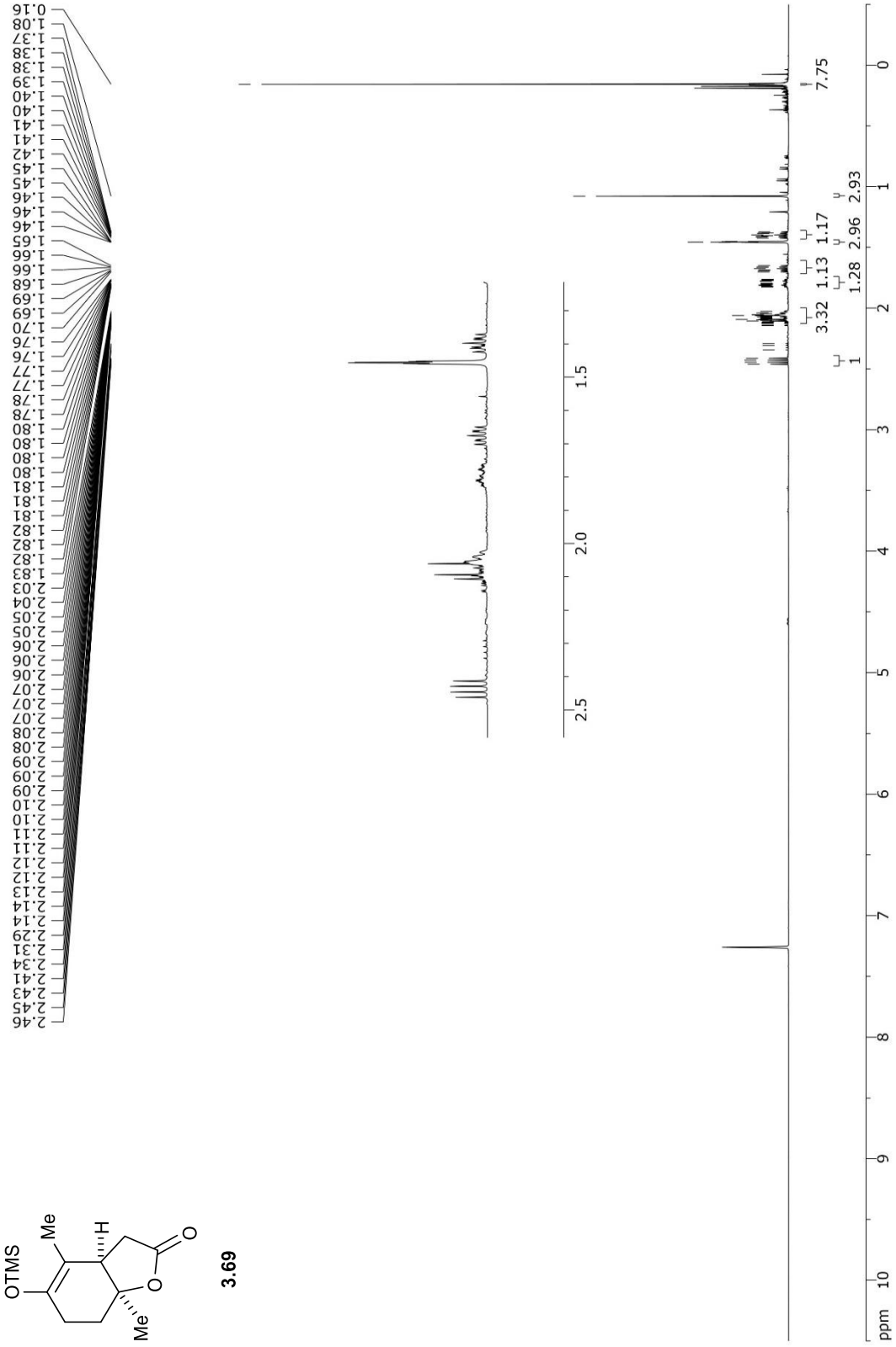
23.80
27.01
28.01
40.40
42.15
49.97
51.14
51.29
54.04
79.77
81.50
83.43
83.79
128.04
129.14
145.78
145.93
165.56
166.54
169.09
169.96
197.33
198.57
Me
H
CO2t-Bu
O
O
O
Me
3.71
0
50
100
150
200
ppm


Me
H
O
O
O
Me
3.95
ppm


12.57
12.25
26.80
28.28
32.07
32.99
33.36
34.76
35.25
35.70
43.07
45.27
45.93
47.06
84.50
85.13
174.75
175.28
210.84
210.59
Me
H
O
O
O
Me
3.95
0
50
100
150
200
ppm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1.41
1.41
1.42
1.45
1.45
1.46
1.46
1.46
1.65
1.66
1.66
1.68
1.69
1.69
1.70
1.76
1.76
1.77
1.77
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1.81
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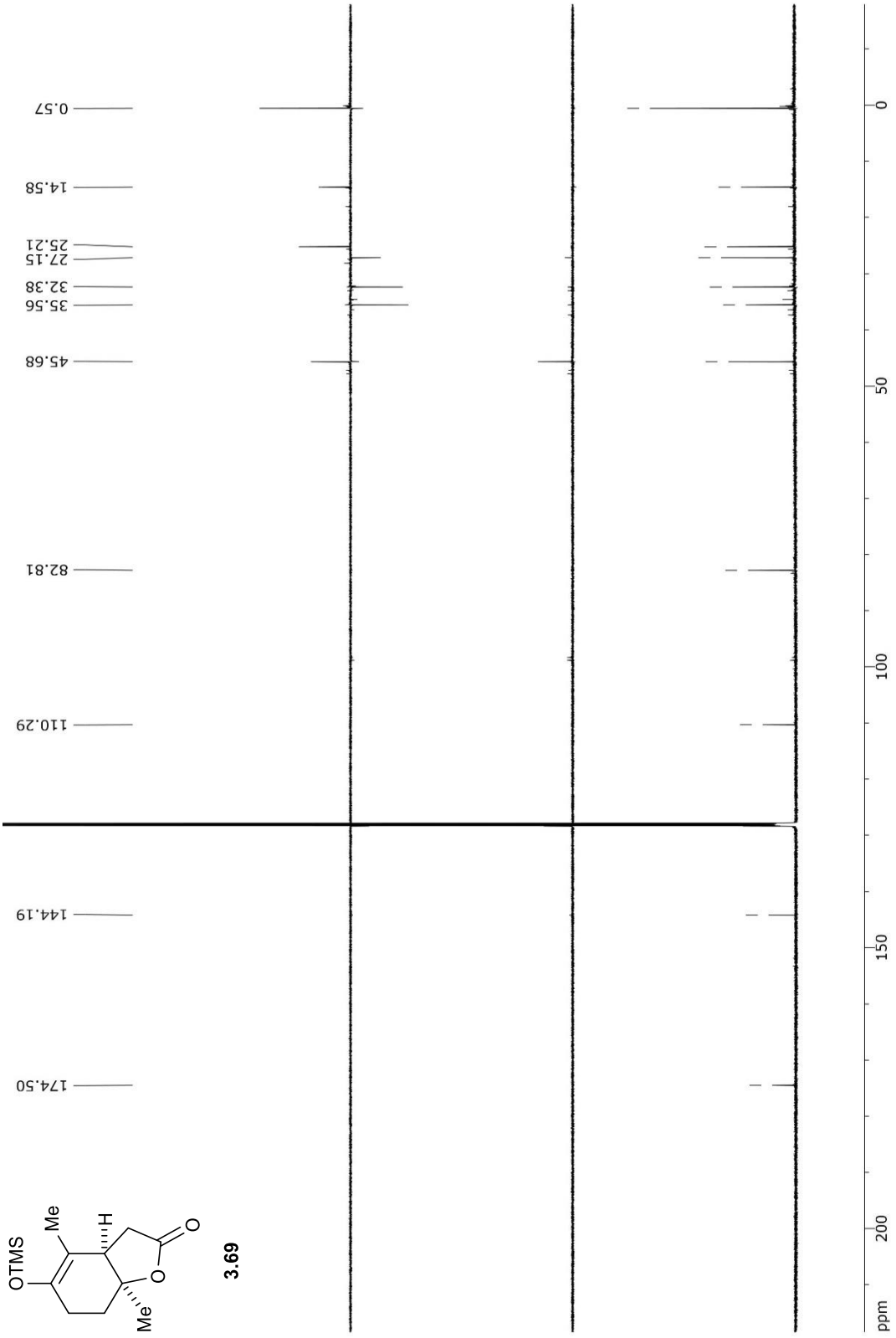
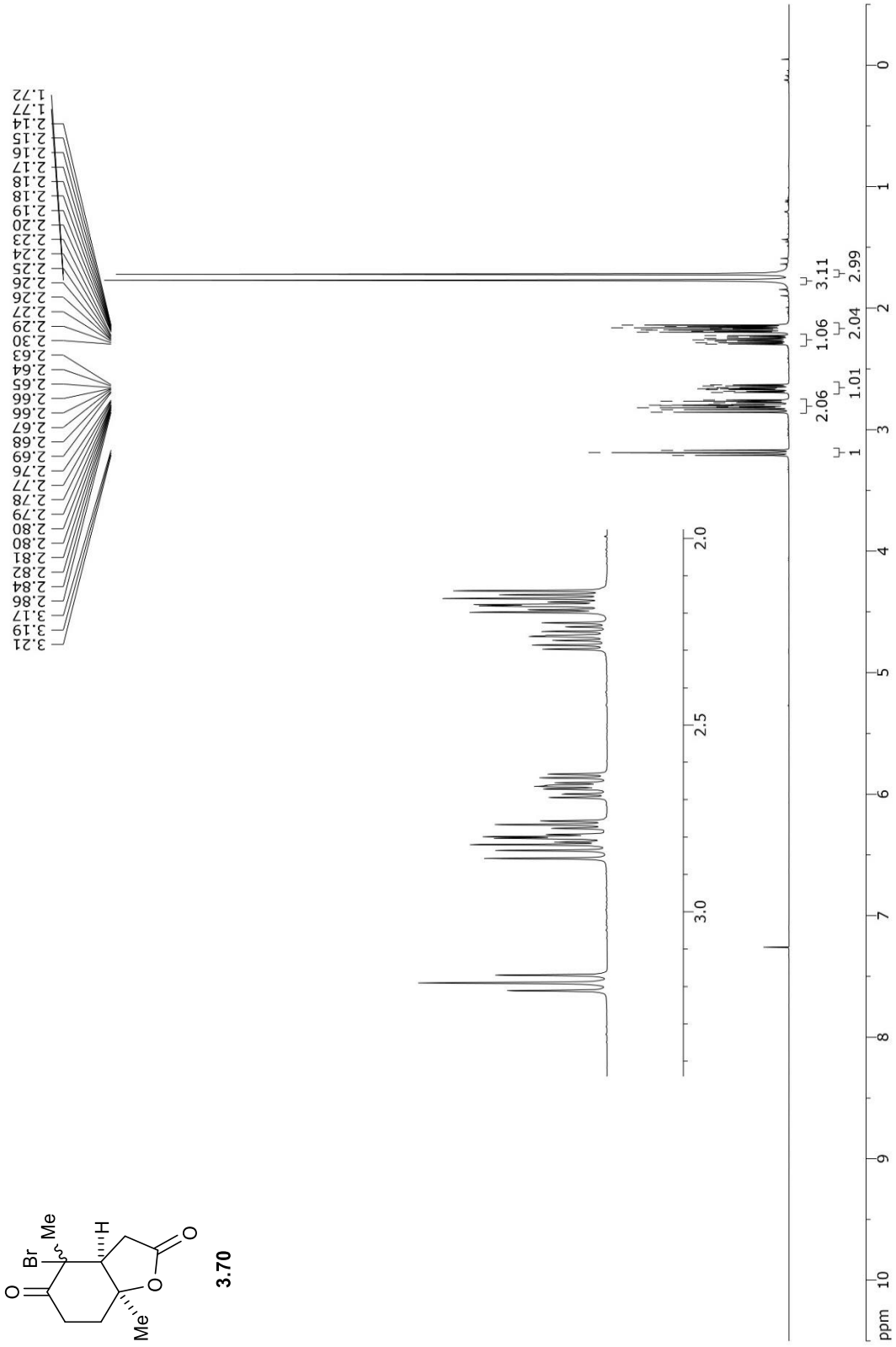
1.81
1.82
1.82
1.82
1.83
2.03
2.04
2.05
2.06
2.06
2.06
2.07
2.07
2.07
2.08
2.08
2.09
2.09
2.09
2.10
2.10
2.11
2.11
2.12
2.12
2.13
2.14
2.14
2.29
2.31
2.34
2.41
2.43
2.45
2.46
2.5
2.0
1.5
7.75
3.32
1.13
1.17
1.28
2.96
2.93
ppm
OTMS
Me
H
O
O
Me

3.69


0.57
14.58
25.21
27.15
32.38
35.56
45.68
82.81
110.29
144.19
174.50
ppm
0
50
100
150
200
OTMS
Me
H
O
O
Me

3.69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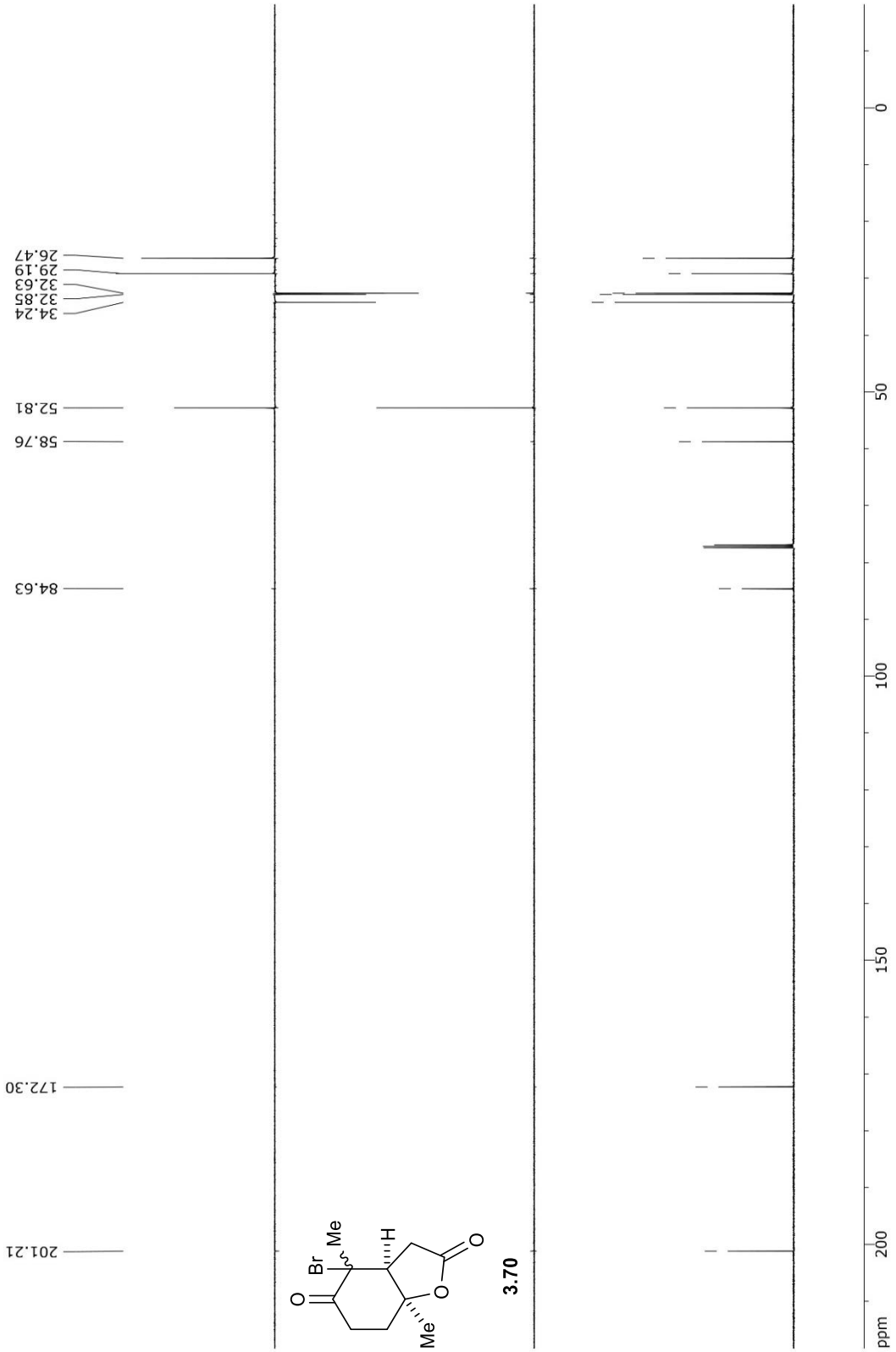
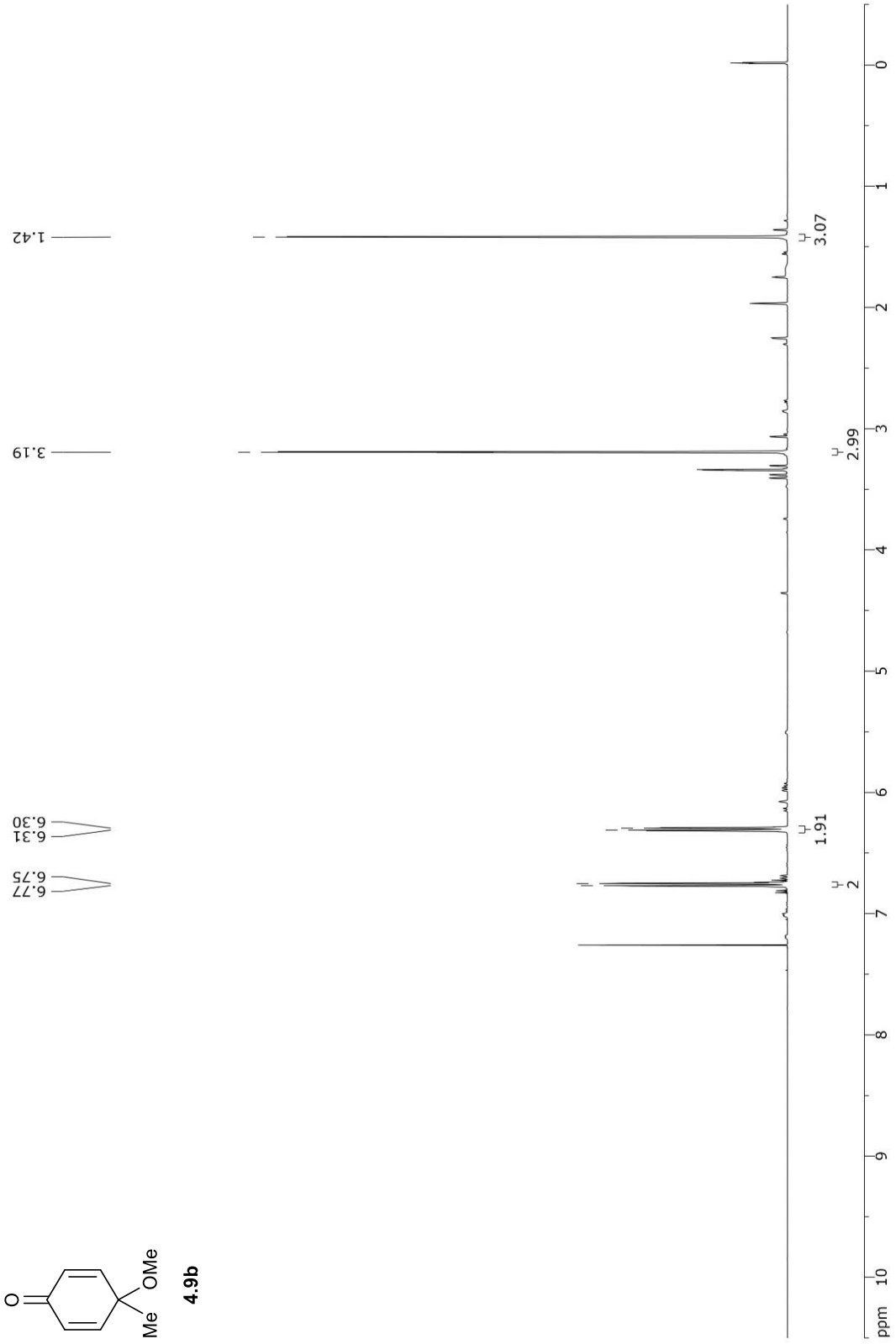
1.77
2.14
2.15
2.16
2.17
2.18
2.18
2.19
2.20
2.23
2.24
2.25
2.26
2.26
2.27
2.29
2.30
2.63
2.64
2.65
2.66
2.66
2.67
2.68
2.69
2.76
2.77
2.78
2.79
2.80
2.80
2.81
2.82
2.84
2.86
3.17
3.19
3.21
2.06
1.01
1.06
2.04
3.11
2.99
2.0
2.5
3.0
ppm
Br
Me
H
O
O
O
Me

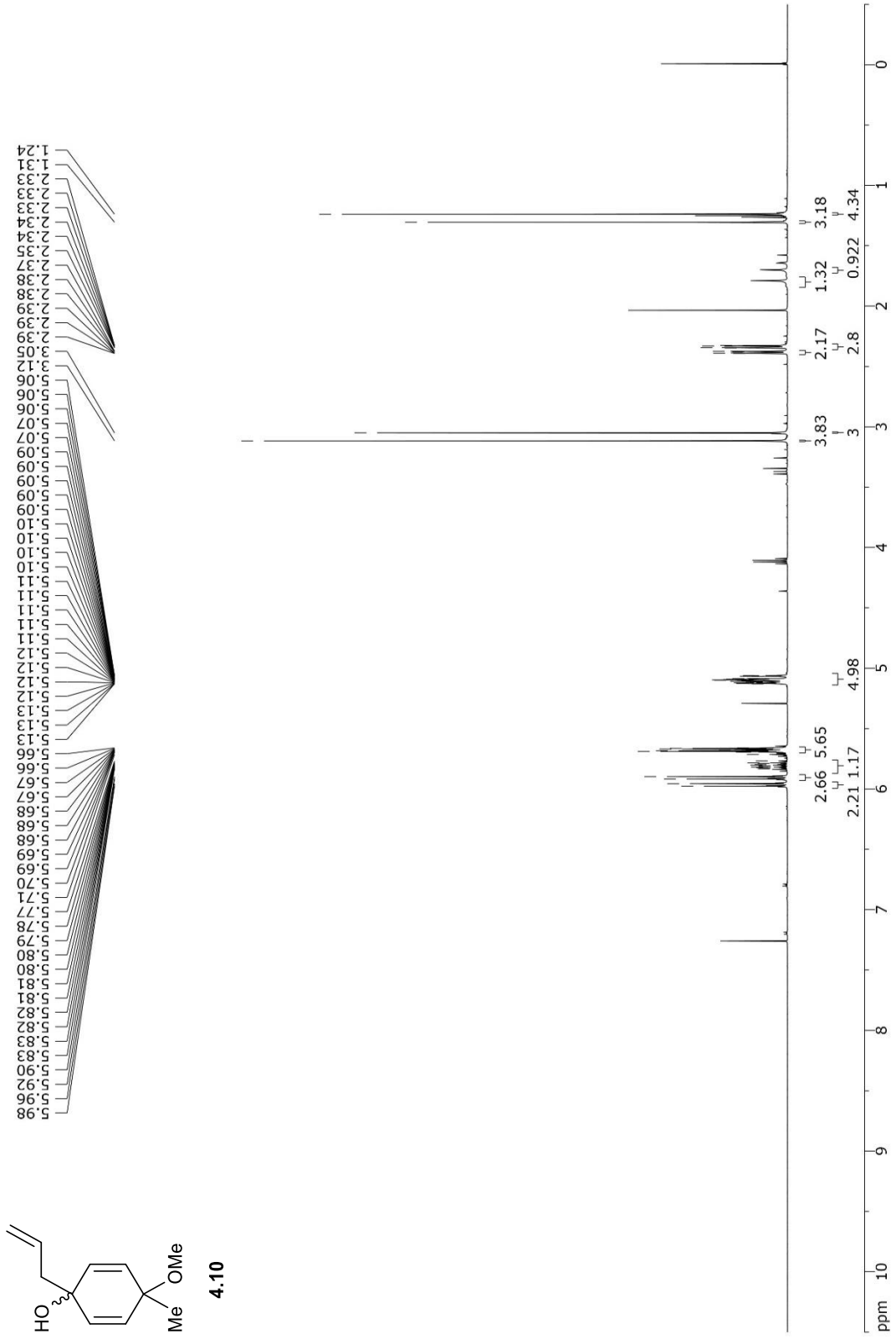
3.70

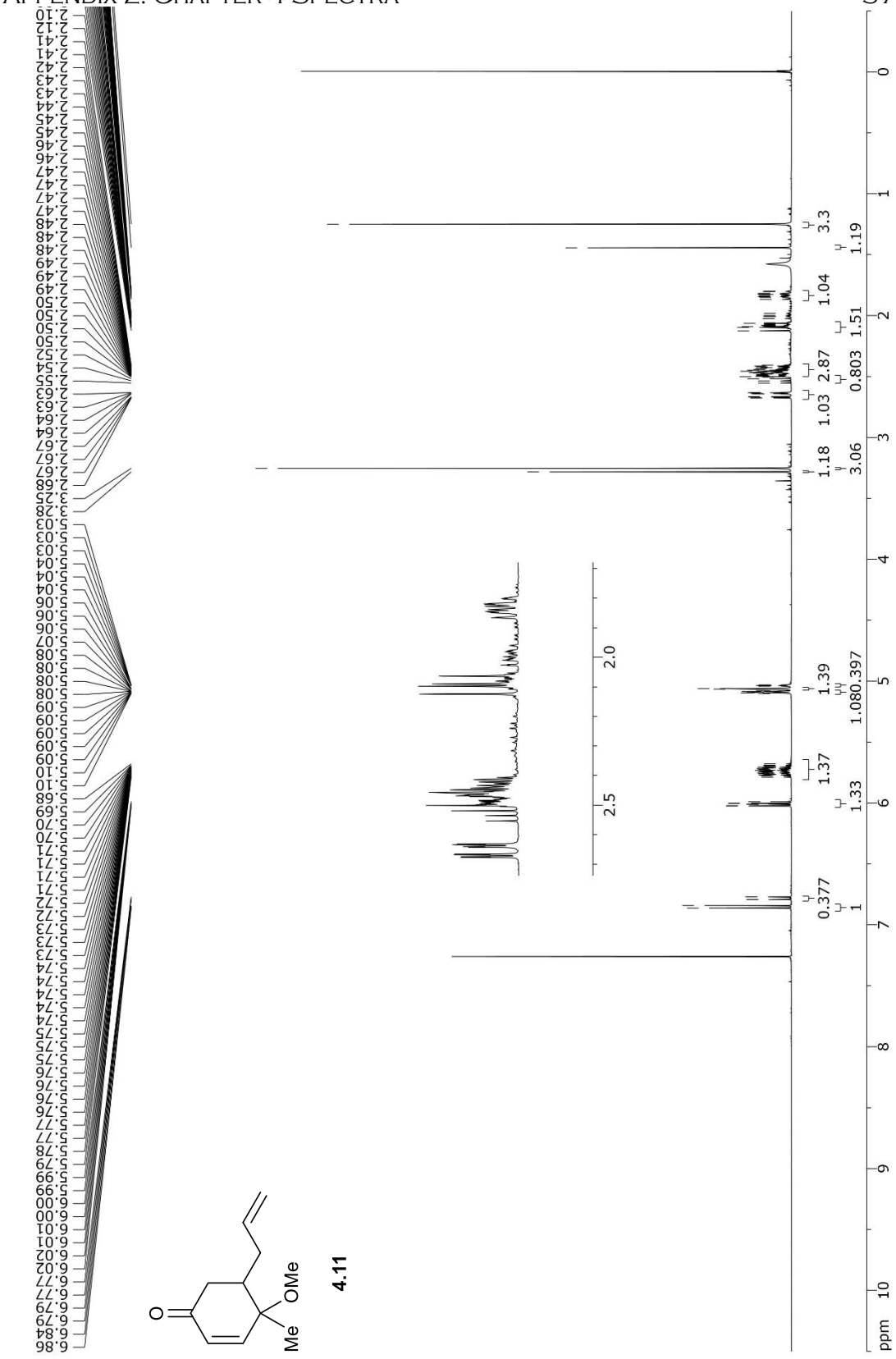

26.47
29.19
32.63
32.85
34.24
52.81
58.76
84.63
172.30
201.21
Br
Me
H
O
O
O
Me
3.70
0
50
100
150
200
ppm

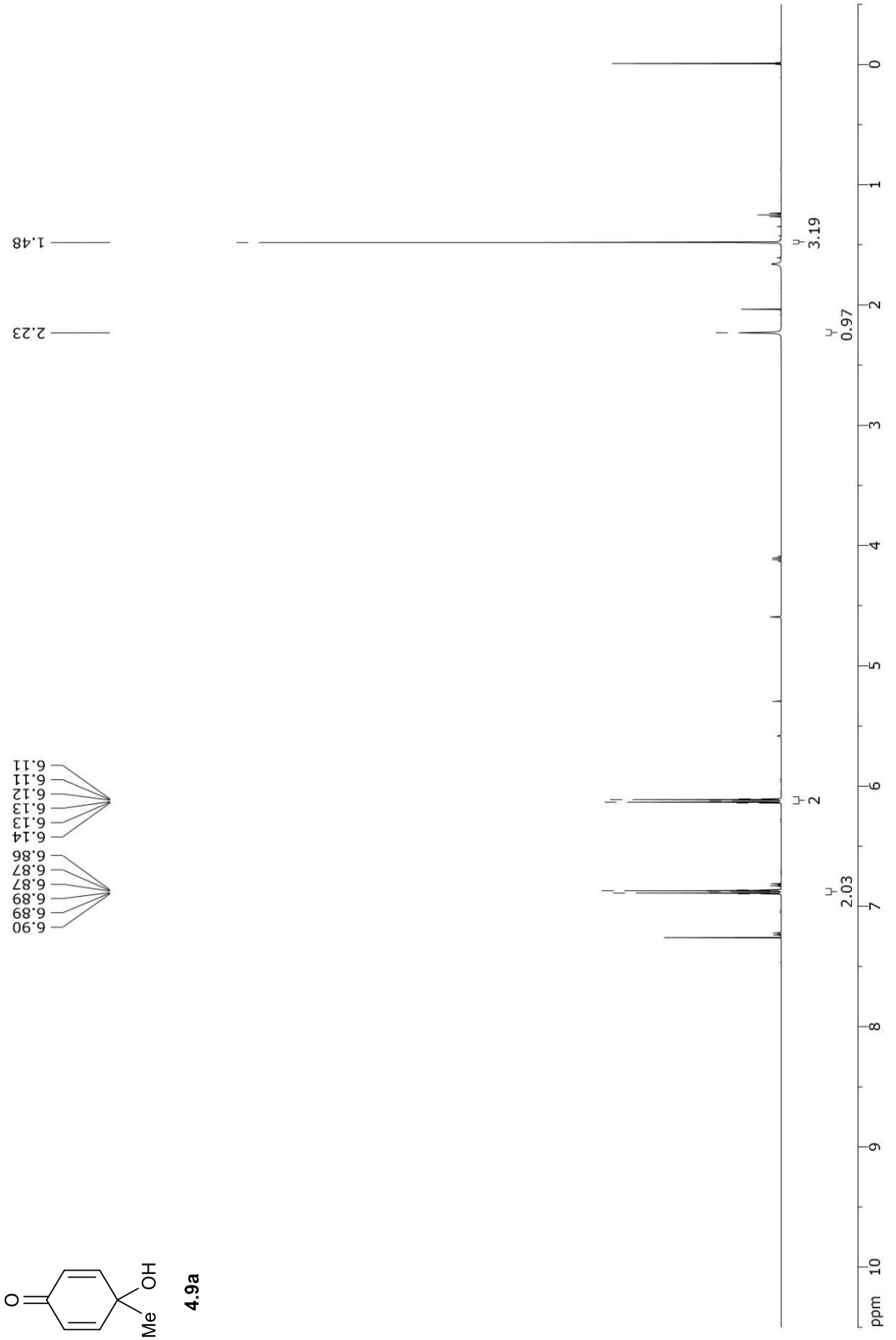
Chapter 4 Spectra



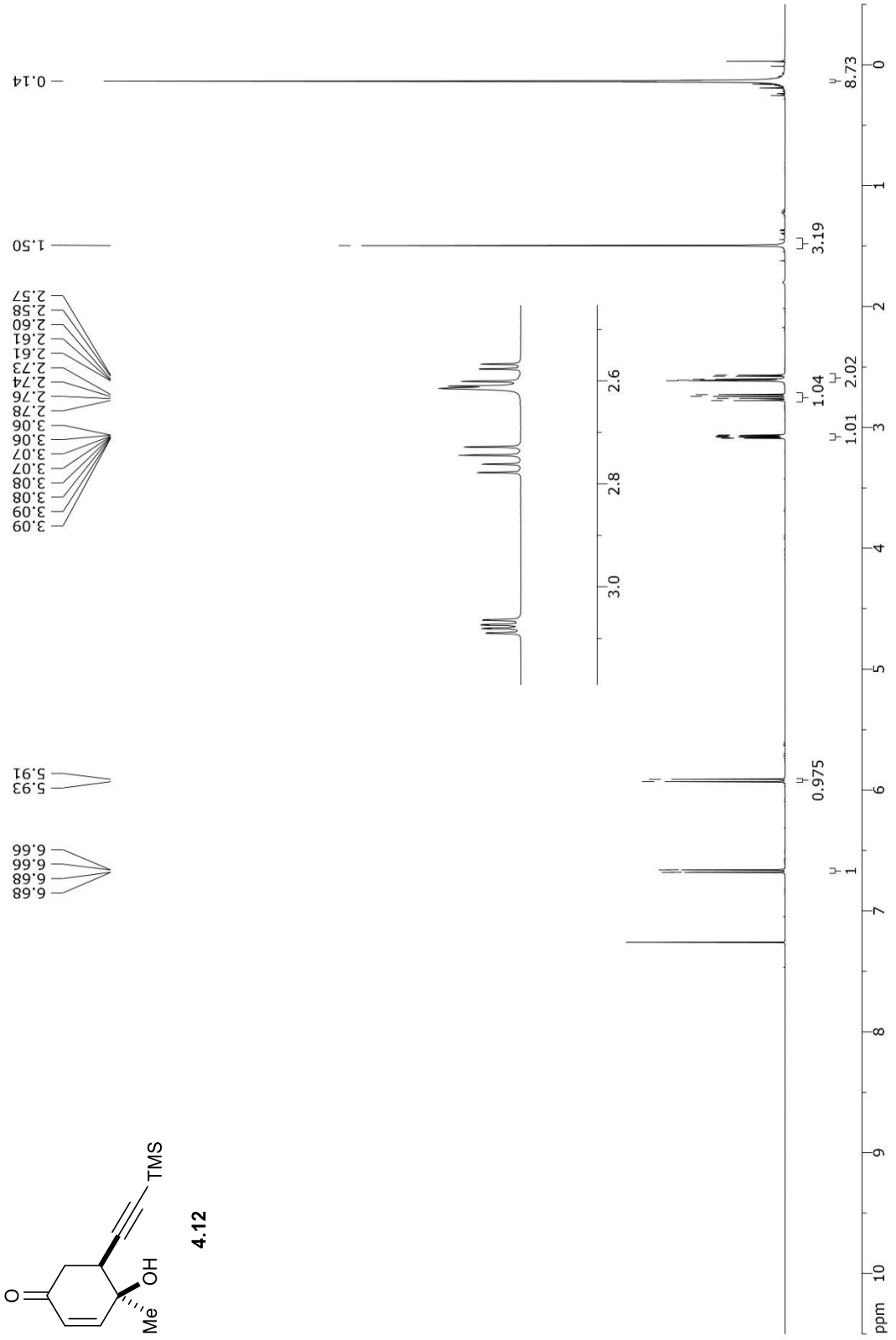
4.9b


HO
OMe
Me
4.10
ppm


OMe
Me
O
4.11
0.377
1.37
1.33
1.39
1.080.397
2.5
2.0
1.18
1.03
2.87
0.803
1.51
1.04
1.19
3.3
3.06
ppm


1.48
2.23
6.11
6.11
6.12
6.13
6.13
6.14
6.86
6.87
6.87
6.89
6.89
6.90
3.19
0.97
2
2.03
ppm
O
OH
Me

4.9a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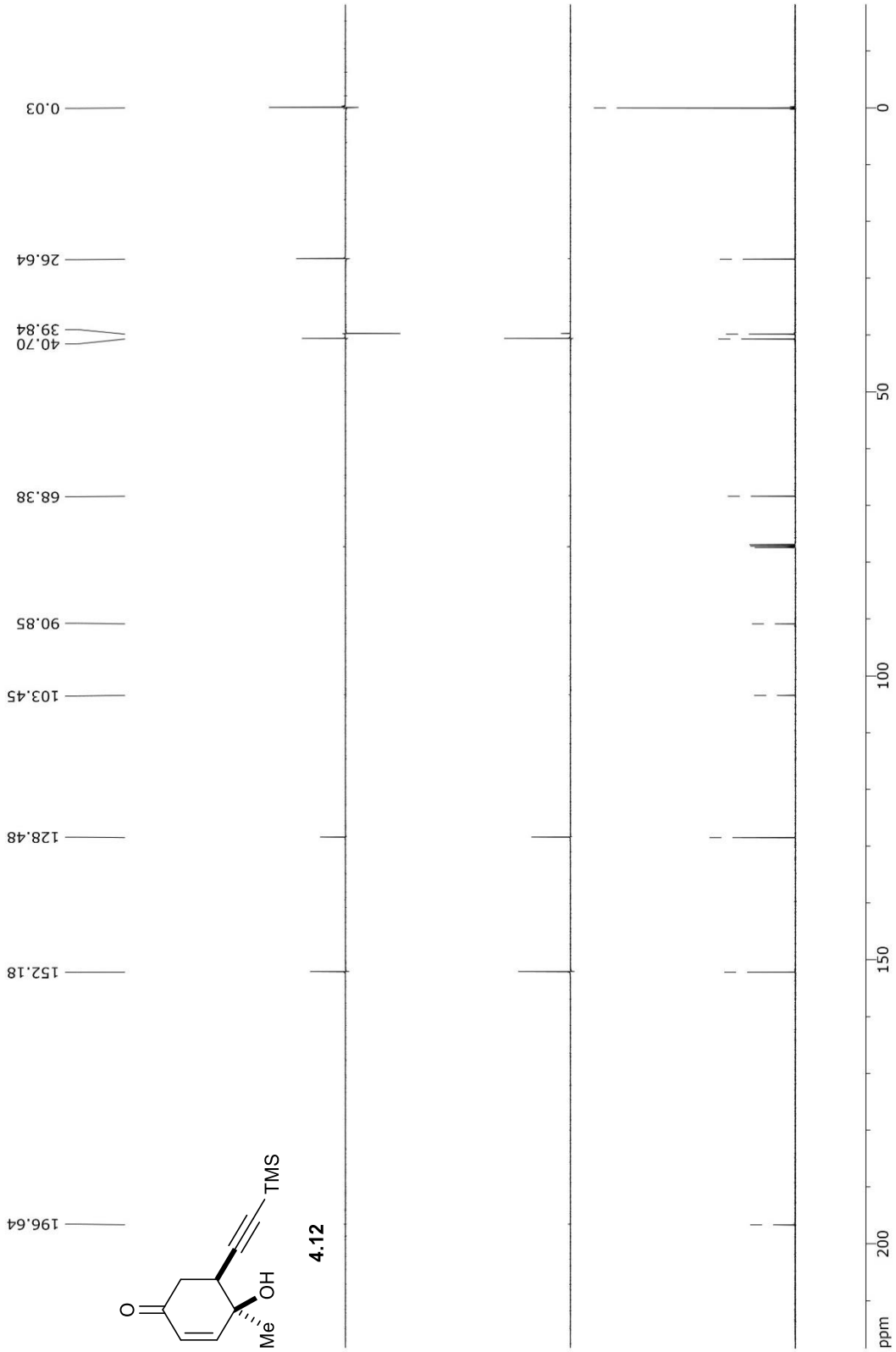
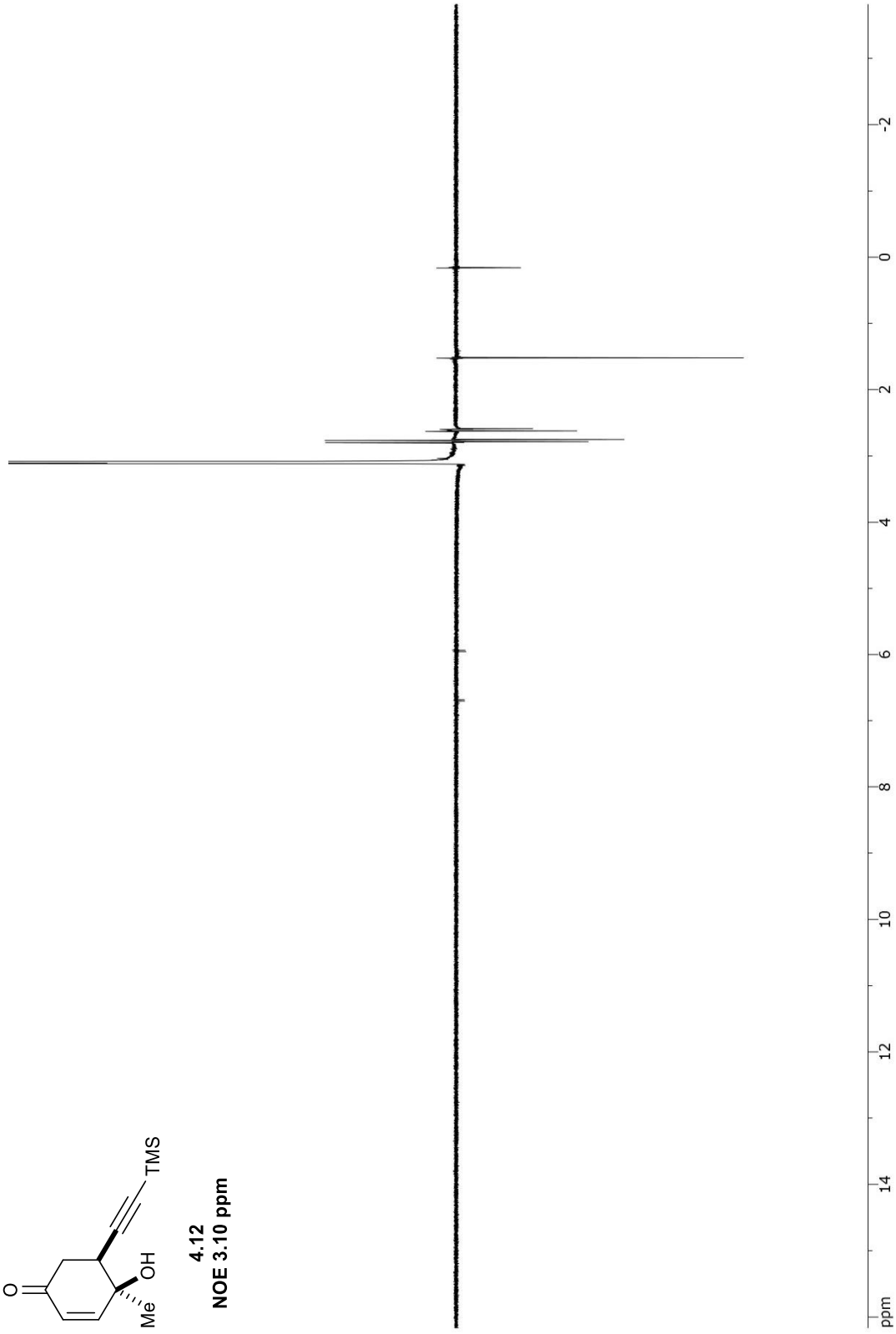
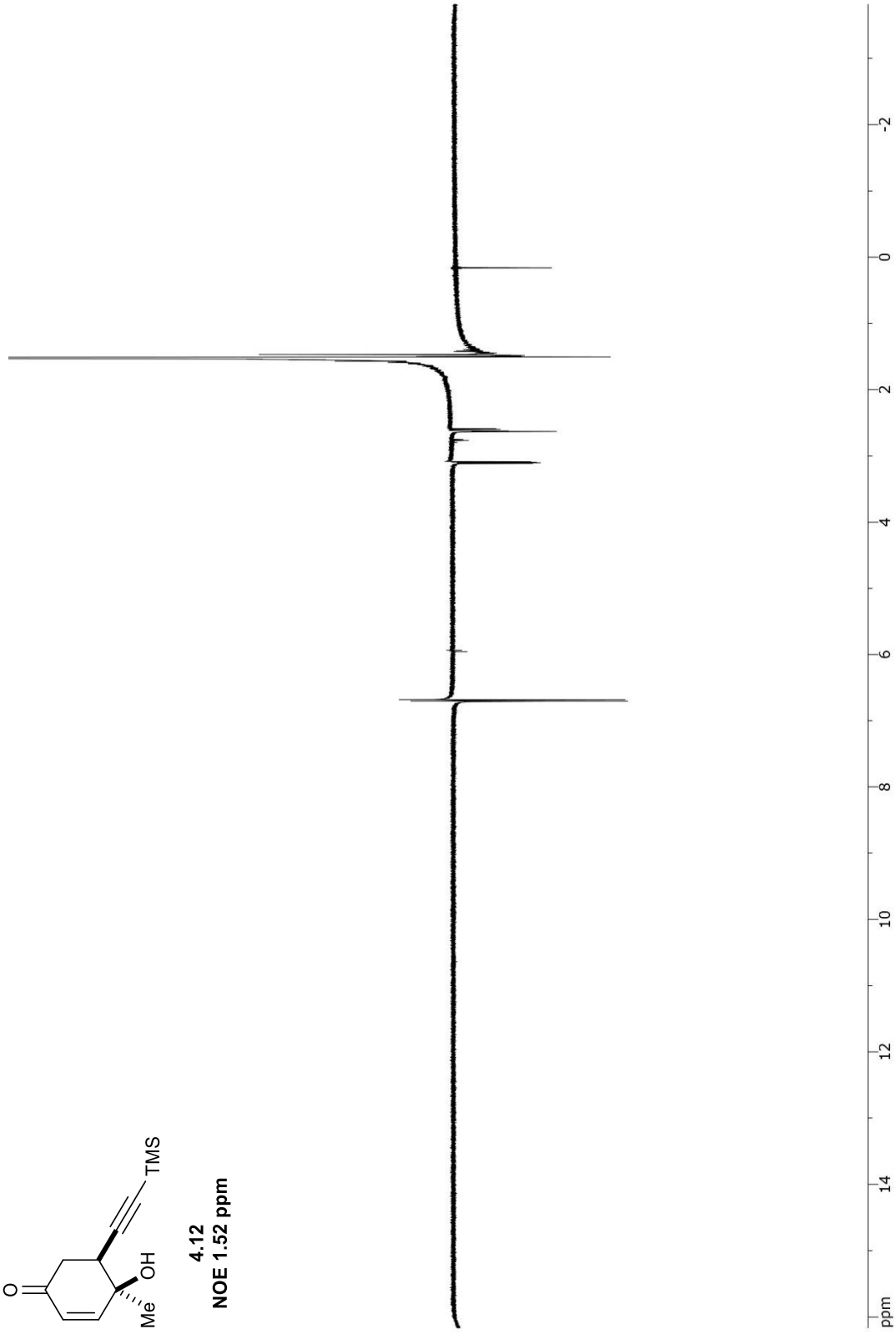
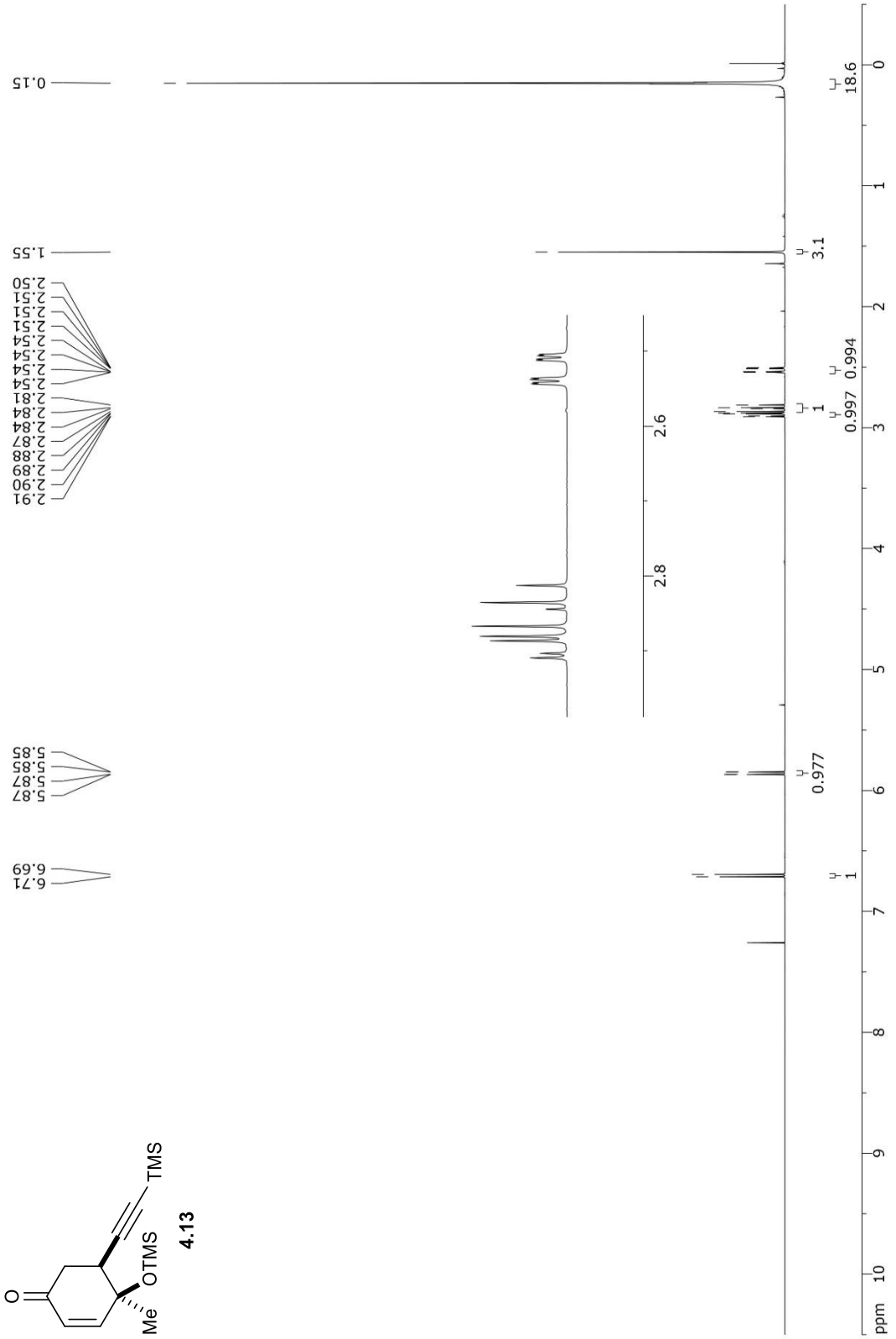
1.50
2.57
2.58
2.60
2.61
2.61
2.73
2.74
2.76
2.78
3.06
3.06
3.07
3.07
3.08
3.08
3.09
3.09
5.91
5.93
6.66
6.66
6.68
6.68
8.73
3.19
1.04
2.02
1.01
0.975
1
2.6
2.8
3.0
ppm
TMS
OH
Me
O

4.12


0.03
26.64
39.84
40.70
68.38
90.85
103.45
128.48
152.18
196.64
ppm
0
50
100
150
200
TMS
OH
Me
O
4.12


TMS
OH
Me
O
4.12
NOE 3.10 ppm
-2
0
2
4
6
8
10
12
14
ppm


TMS
OH
Me
O
4.12
NOE 1.52 ppm
-2
0
2
4
6
8
10
12
14
ppm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2.54
2.54
2.54
2.54
2.81
2.84
2.84
2.87
2.88
2.89
2.90
2.91
5.85
5.85
5.87
5.87
6.69
6.71
18.6
3.1
1
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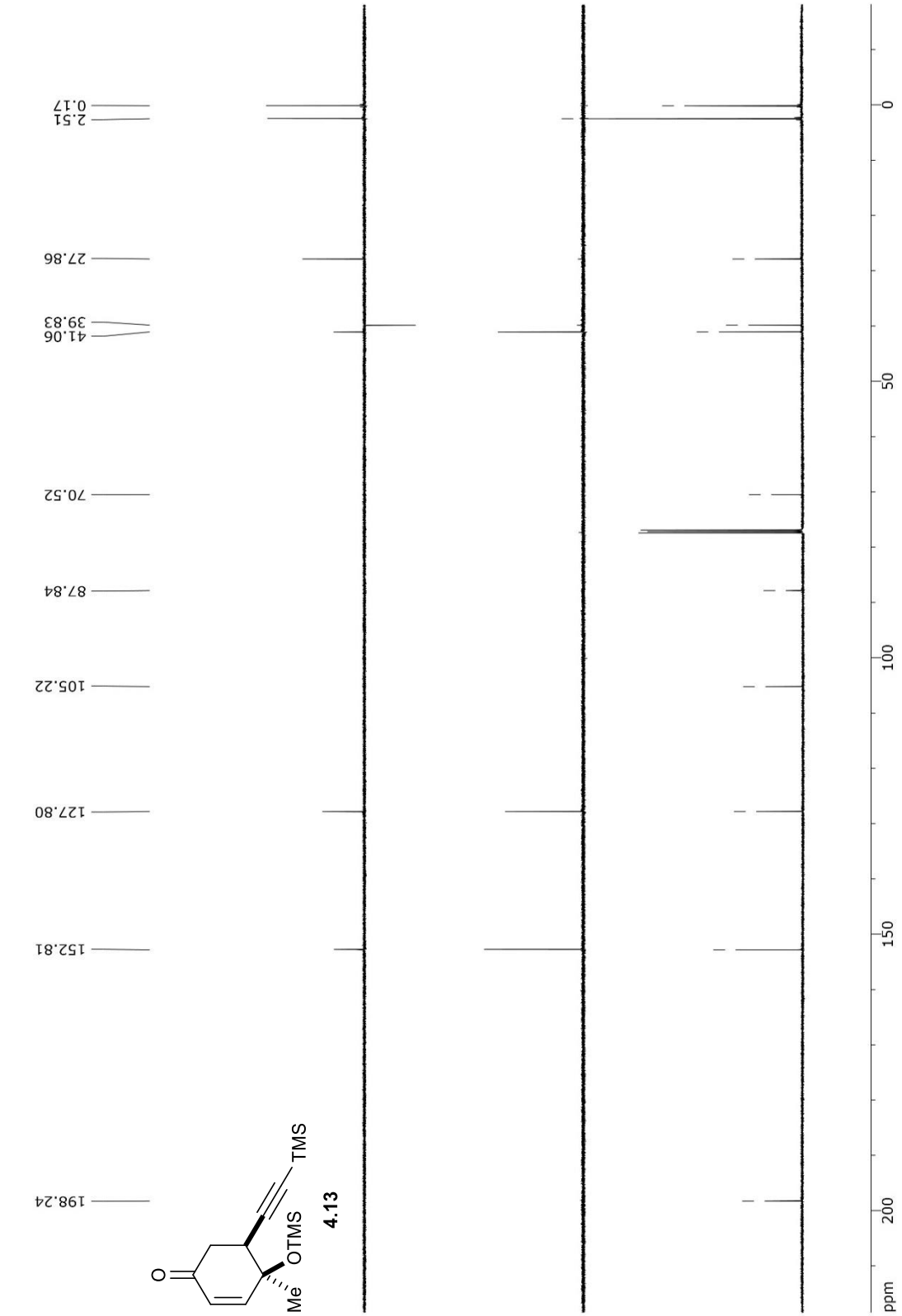
0.994
2.6
2.8
0.977
1
ppm
O
Me
OTMS
TMS
4.13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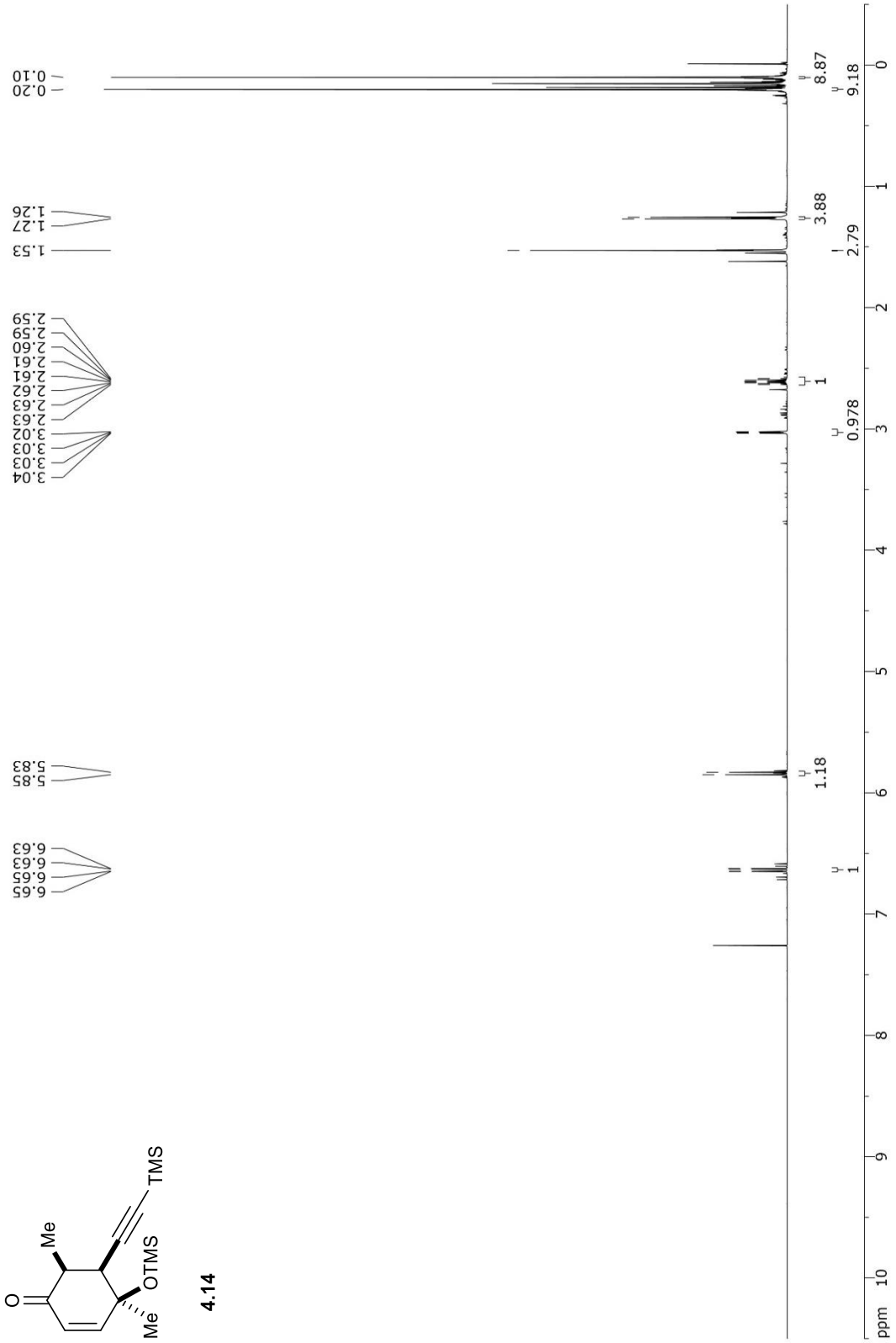
41.06
70.52
87.84
105.22
127.80
152.81
198.24
TMS
OTMS
Me
O
4.13
0
50
100
150
200
ppm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0.20
1.26
1.27
1.53
2.59
2.59
2.60
2.61
2.61
2.62
2.63
2.63
3.02
3.03
3.03
3.04
5.83
5.85
6.63
6.63
6.65
6.65
8.87
9.18
3.88
2.79
1
0.978
1.18
1
ppm
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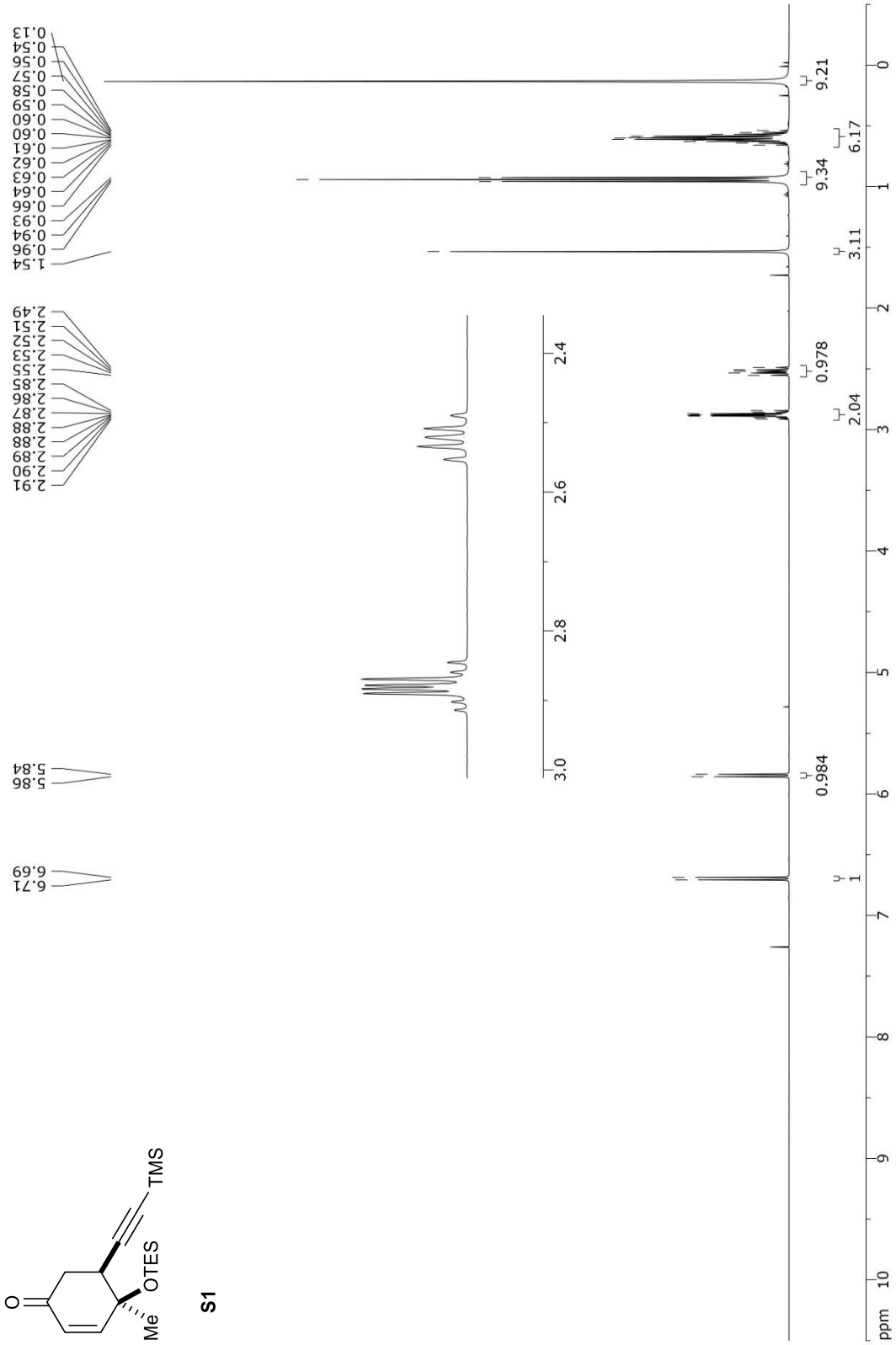
1
2
3
4
5
6
7
8
9
10

O
Me
OTMS
Me
TMS

4.14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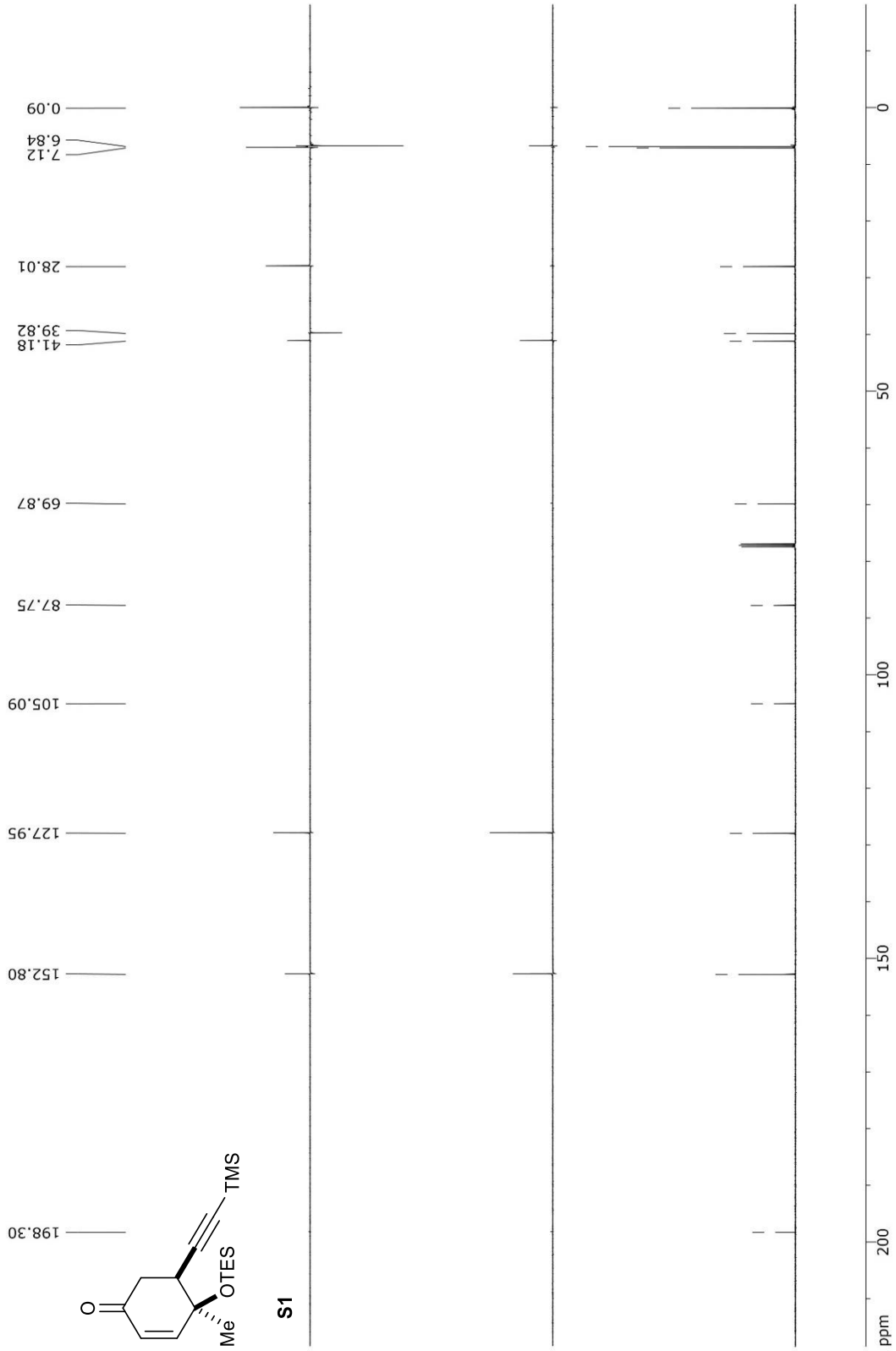
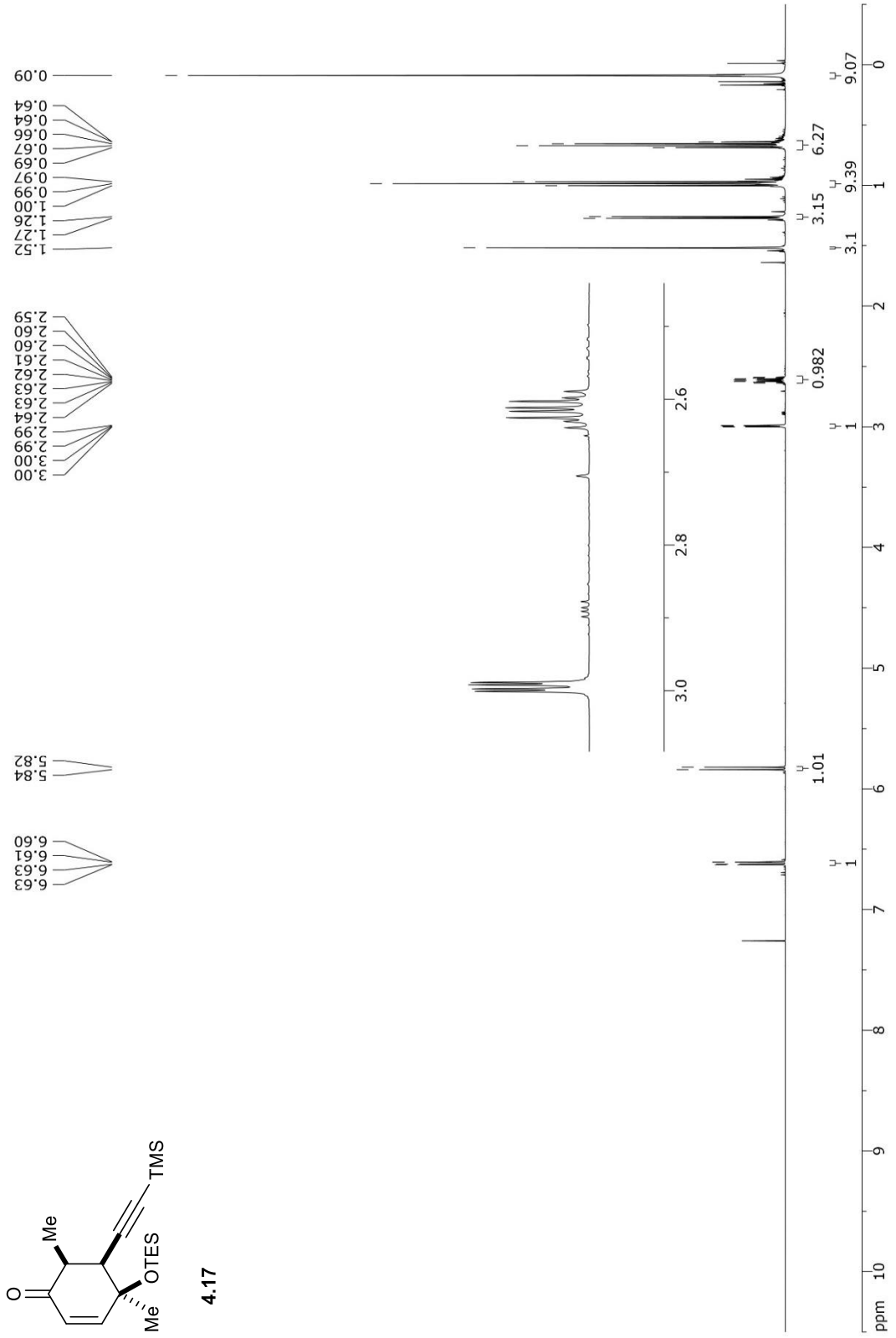
0.56
0.57
0.58
0.59
0.60
0.60
0.61
0.62
0.63
0.64
0.66
0.93
0.94
0.96
1.54
2.49
2.51
2.52
2.53
2.55
2.85
2.86
2.87
2.88
2.88
2.89
2.90
2.91
5.84
5.86
6.69
6.71
0.984
0.978
2.04
3.11
9.34
6.17
9.21
3.0
2.8
2.6
2.4
ppm
TMS
OTES
Me
O

S1


0.09
6.84
7.12
28.01
39.82
41.18
69.87
87.75
105.09
127.95
152.80
198.30
TMS
OTES
Me
O
S1
0
50
100
150
200
ppm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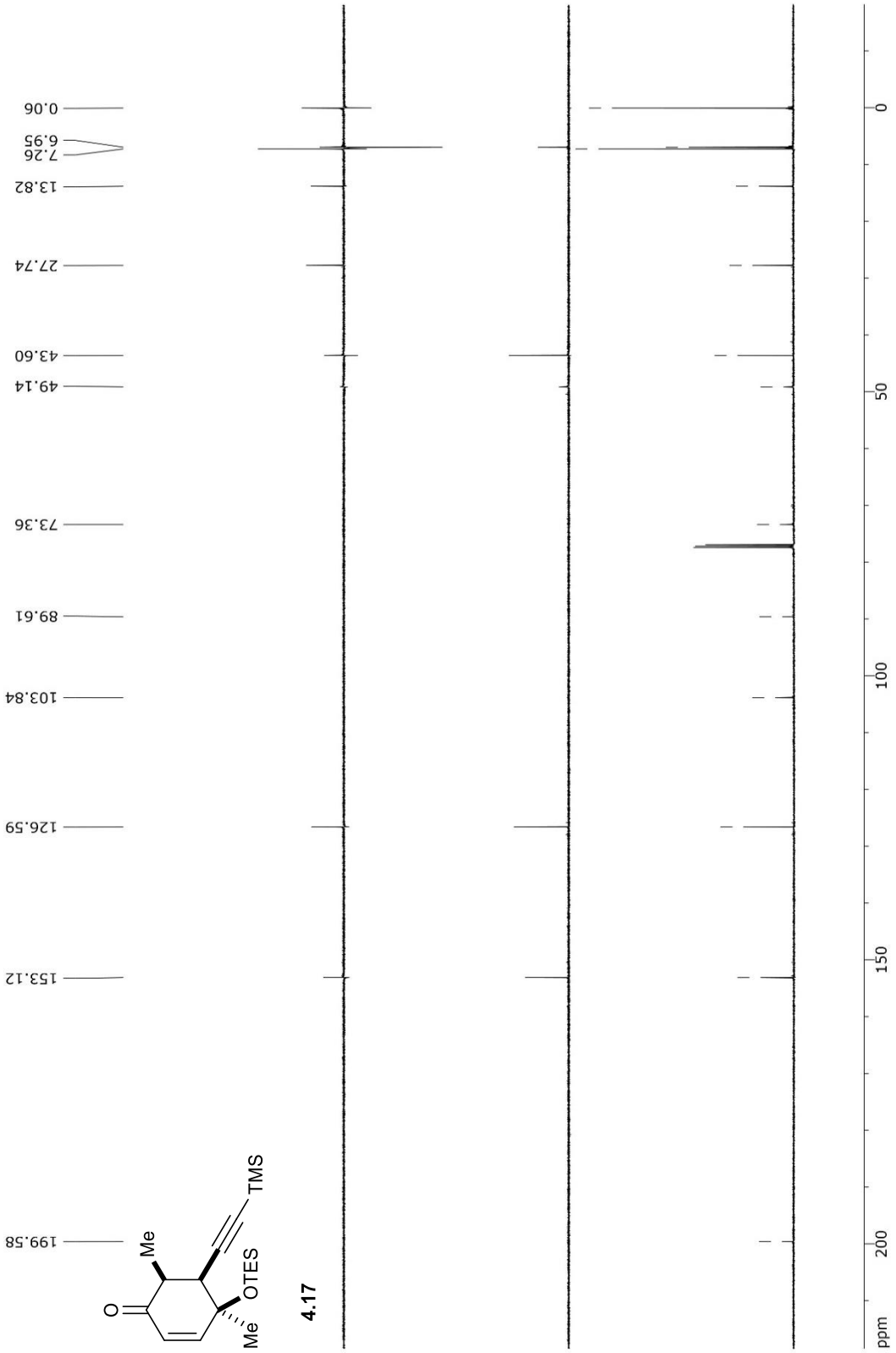
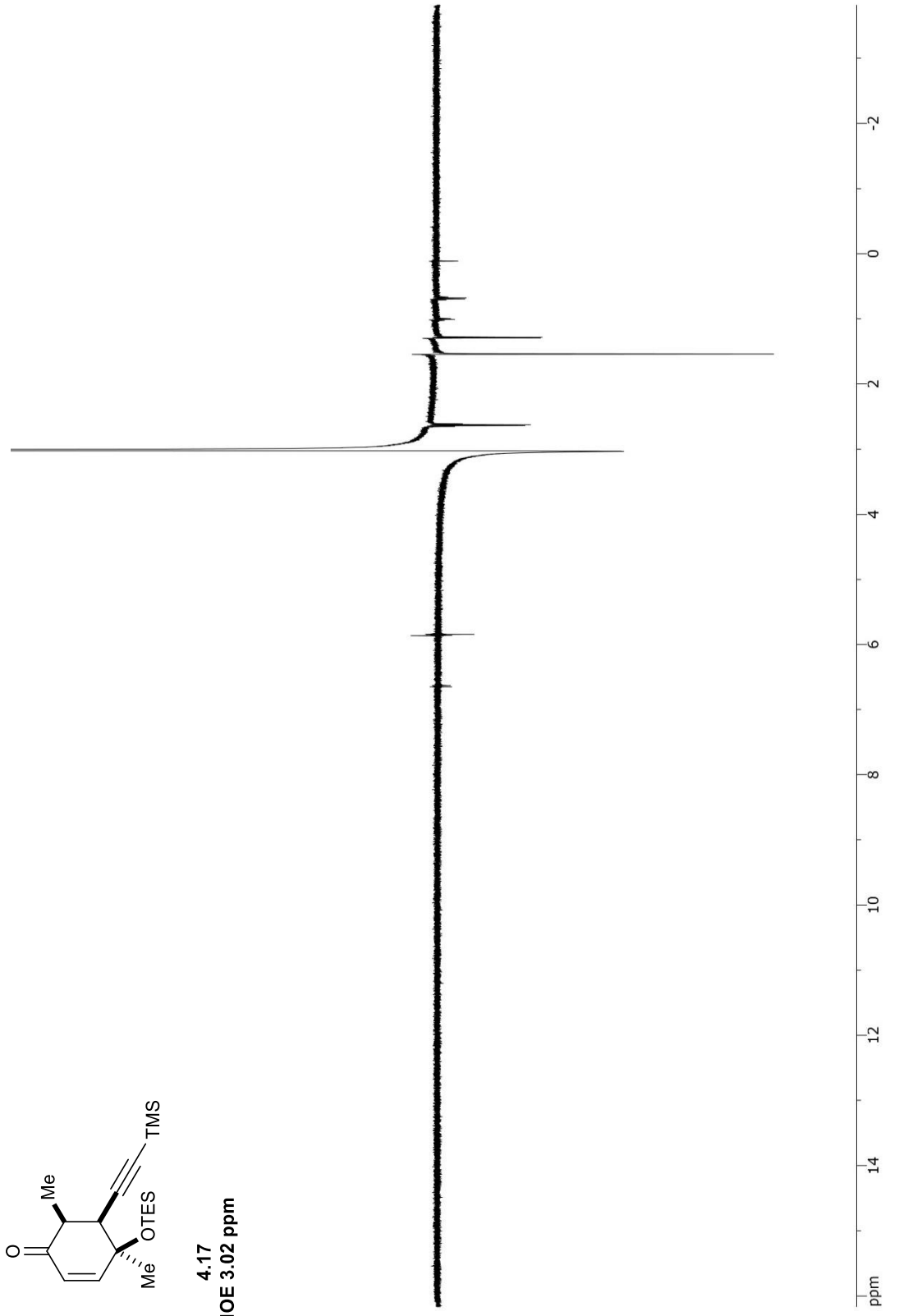
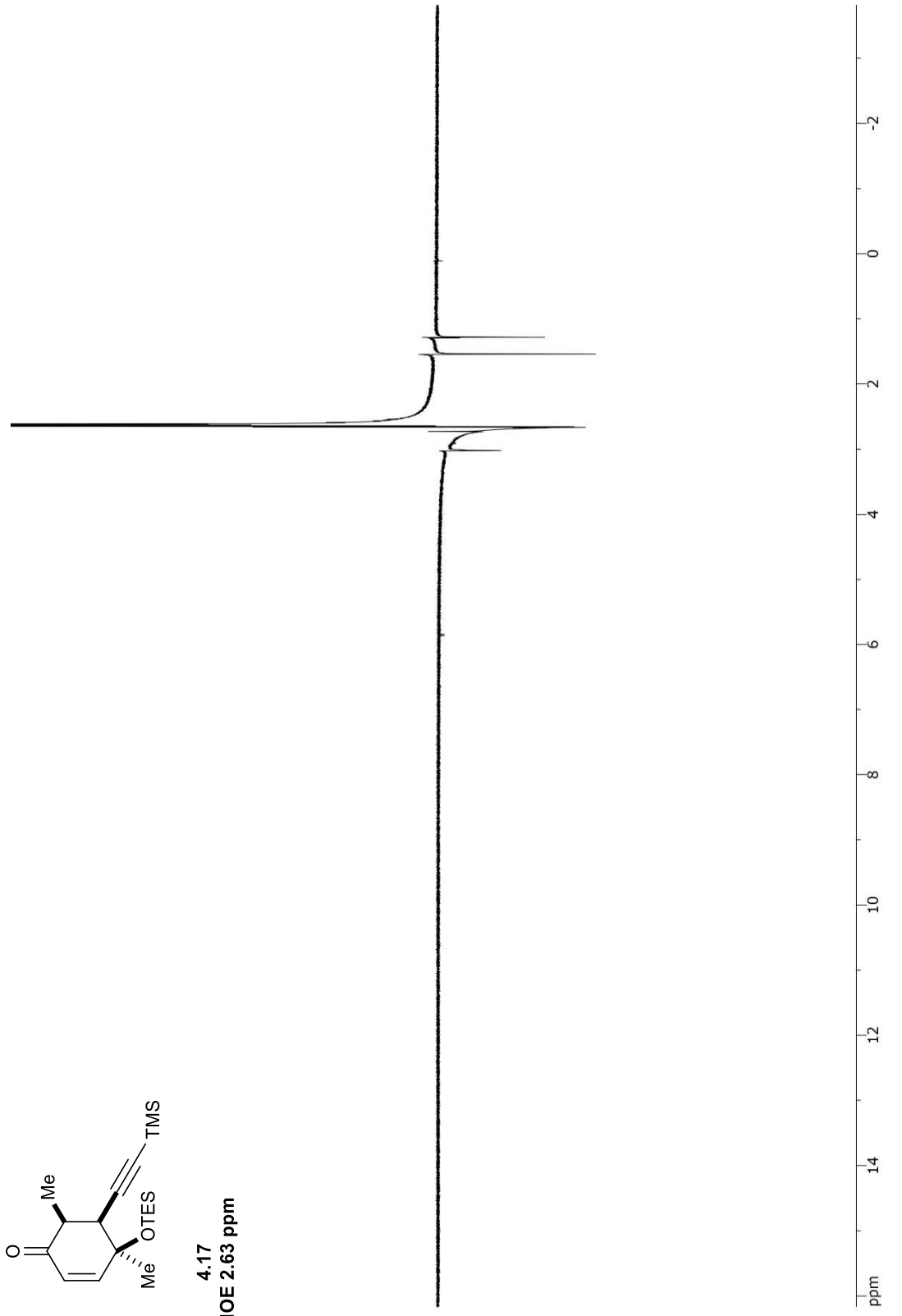
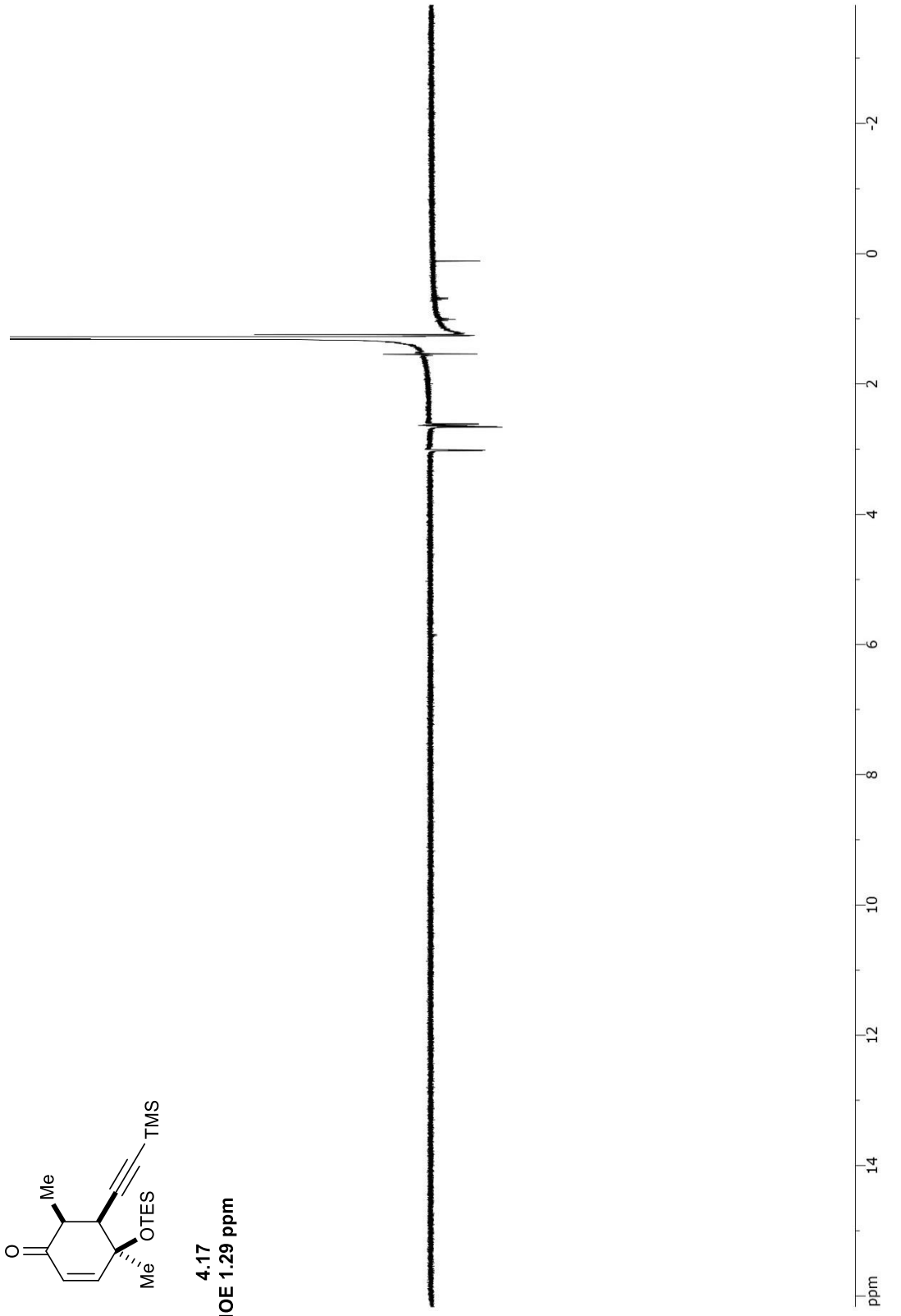
0.64
0.66
0.67
0.69
0.97
0.99
1.00
1.26
1.27
1.52
2.59
2.60
2.60
2.61
2.62
2.63
2.63
2.64
2.99
2.99
3.00
3.00
5.82
5.84
6.60
6.61
6.63
6.63
9.07
6.27
9.39
3.15
3.1
0.982
2.6
2.8
3.0
1.01
ppm
Me
OTES
TMS
Me
O

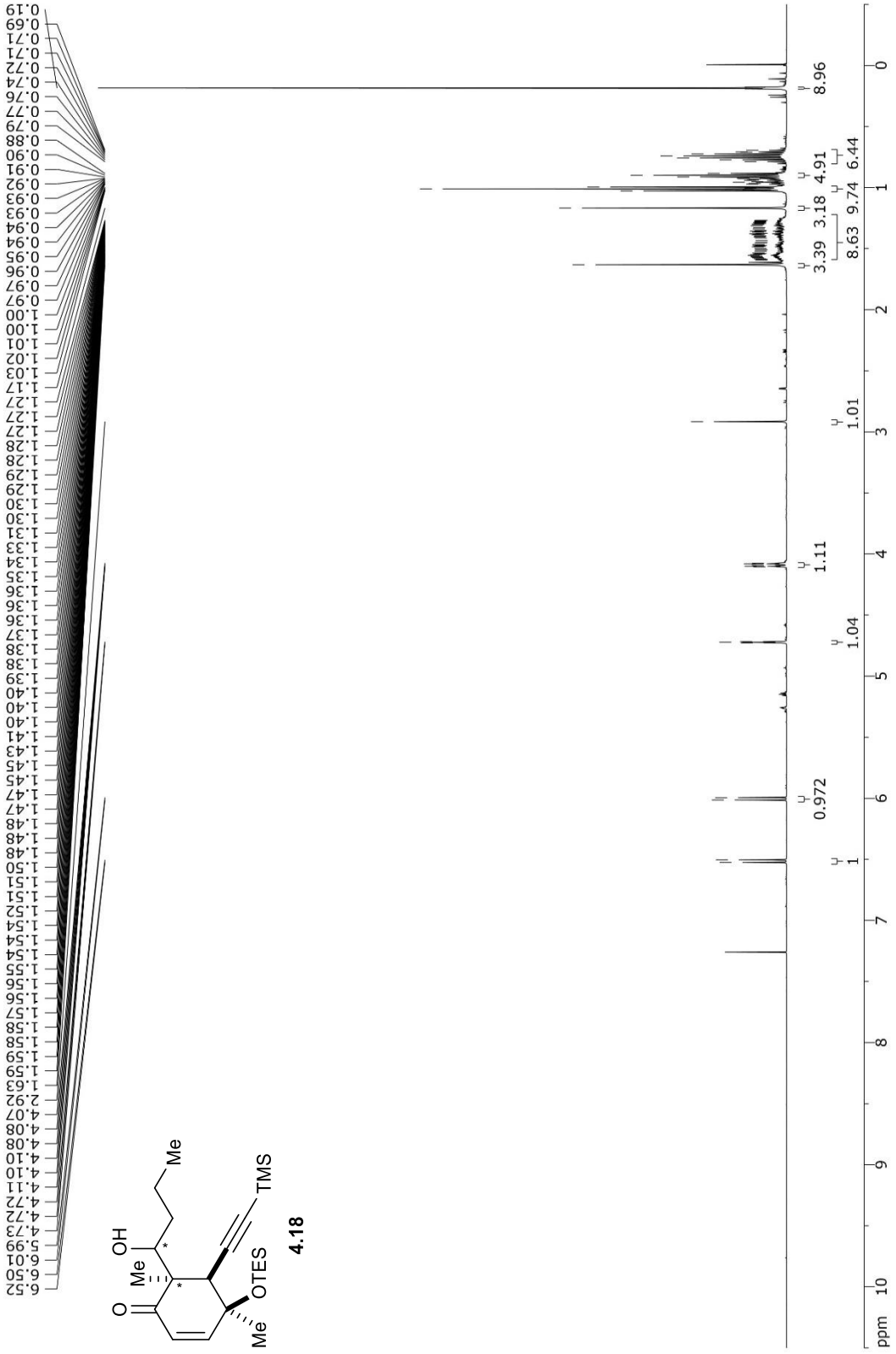
4.17

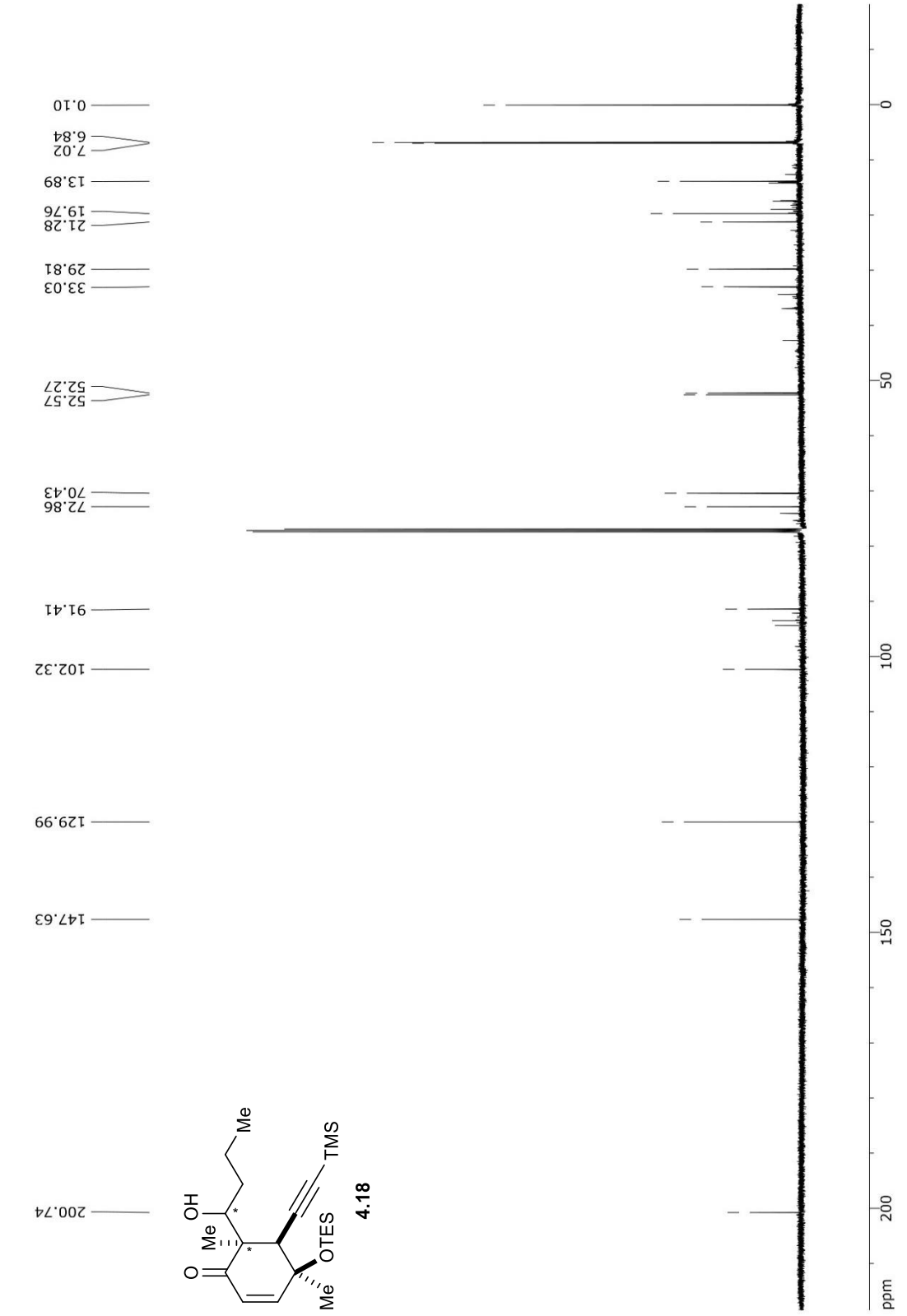

0.06
6.95
7.26
13.82
27.74
43.60
49.14
73.36
89.61
103.84
126.59
153.12
199.58
0
50
100
150
200
ppm
Me
OTES
TMS
Me
O
4.17


TMS
Me
OTES
O
Me
4.17
NOE 3.02 ppm
-2
0
2
4
6
8
10
12
14
ppm


TMS
Me
OTES
O
Me
4.17
NOE 2.63 ppm
-2
0
2
4
6
8
10
12
14
ppm


TMS
Me
OTES
O
Me
4.17
NOE 1.29 ppm
-2
0
2
4
6
8
10
12
14
ppm


Me
OH
Me
O
OTES
TMS
Me
4.18
ppm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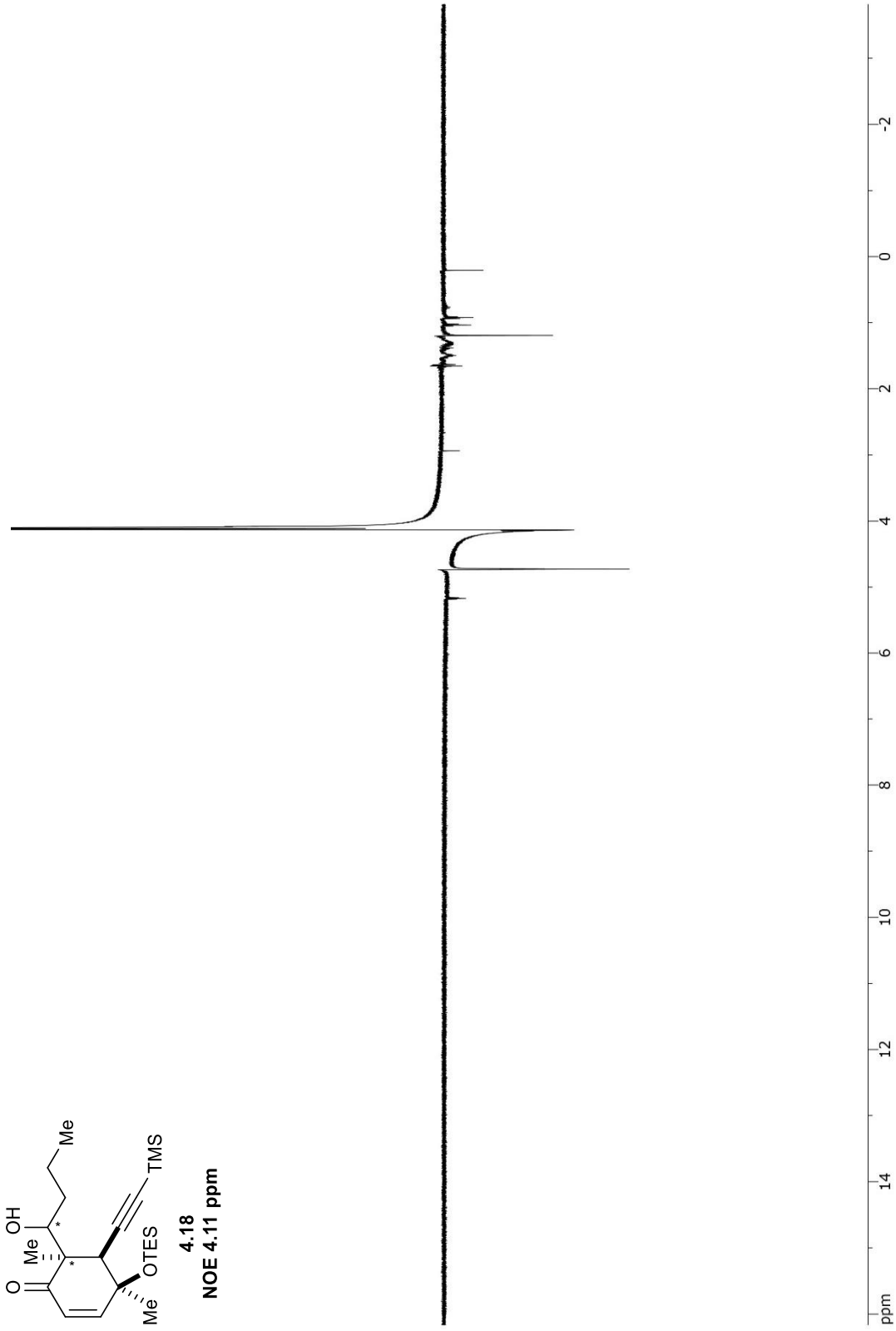
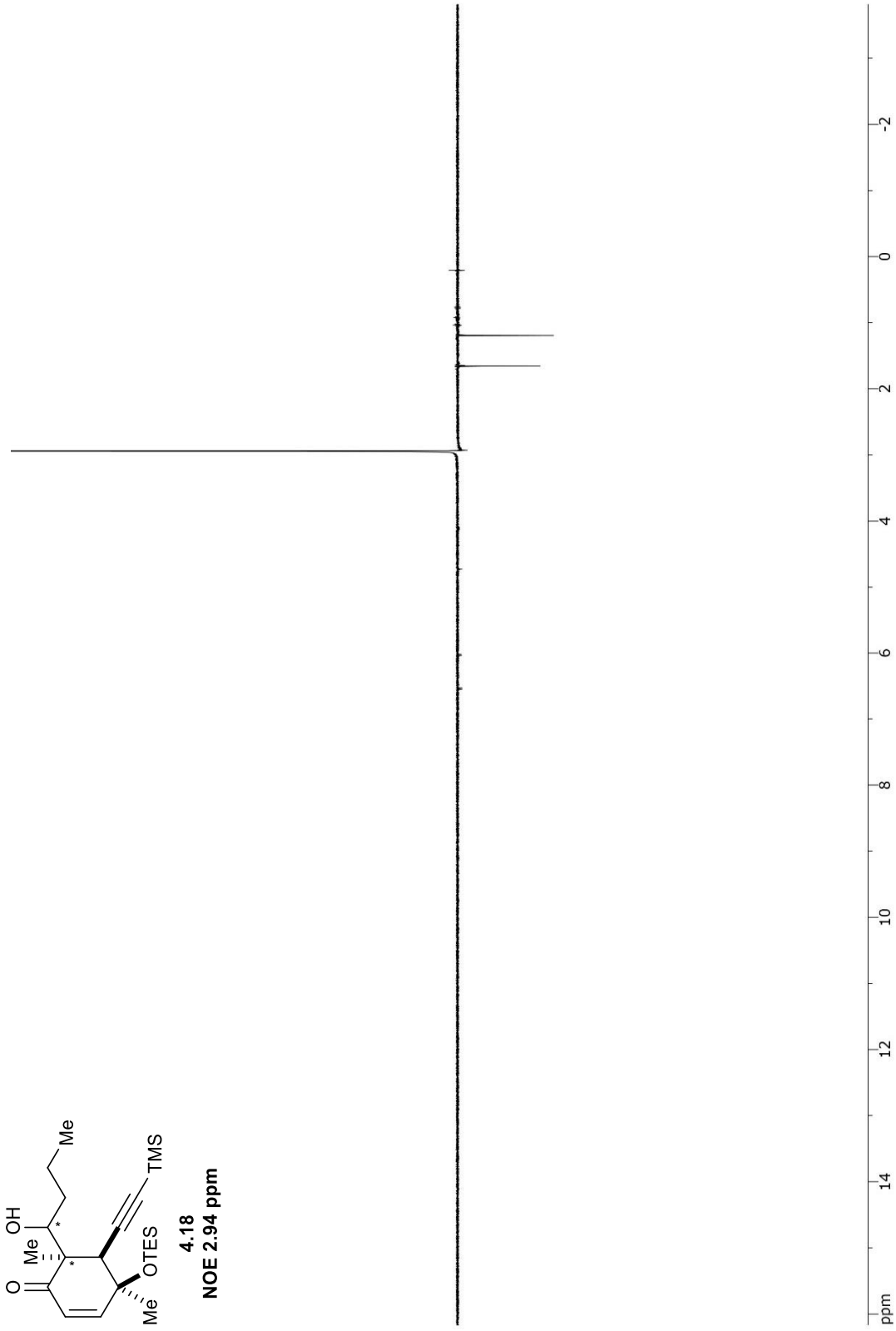
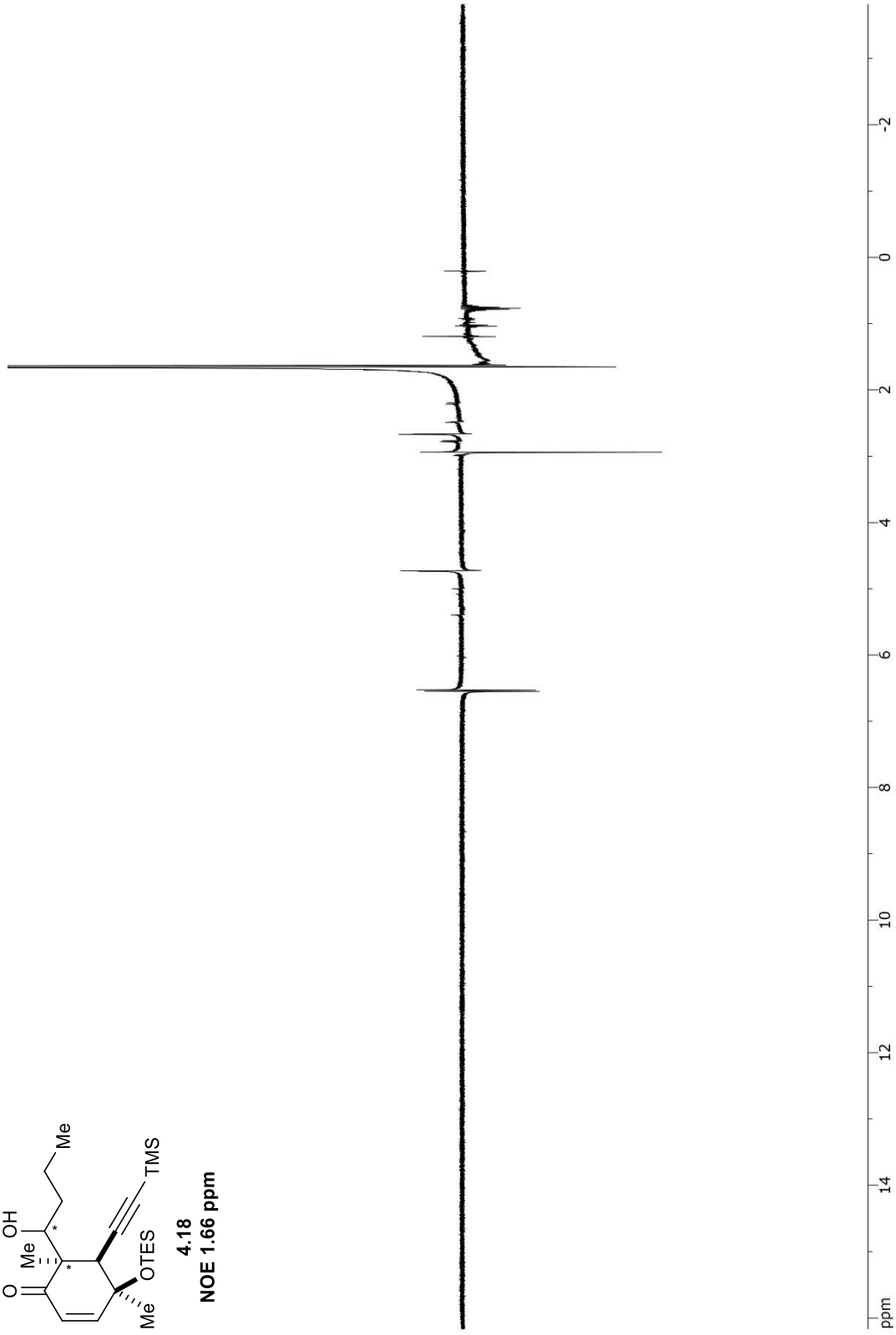
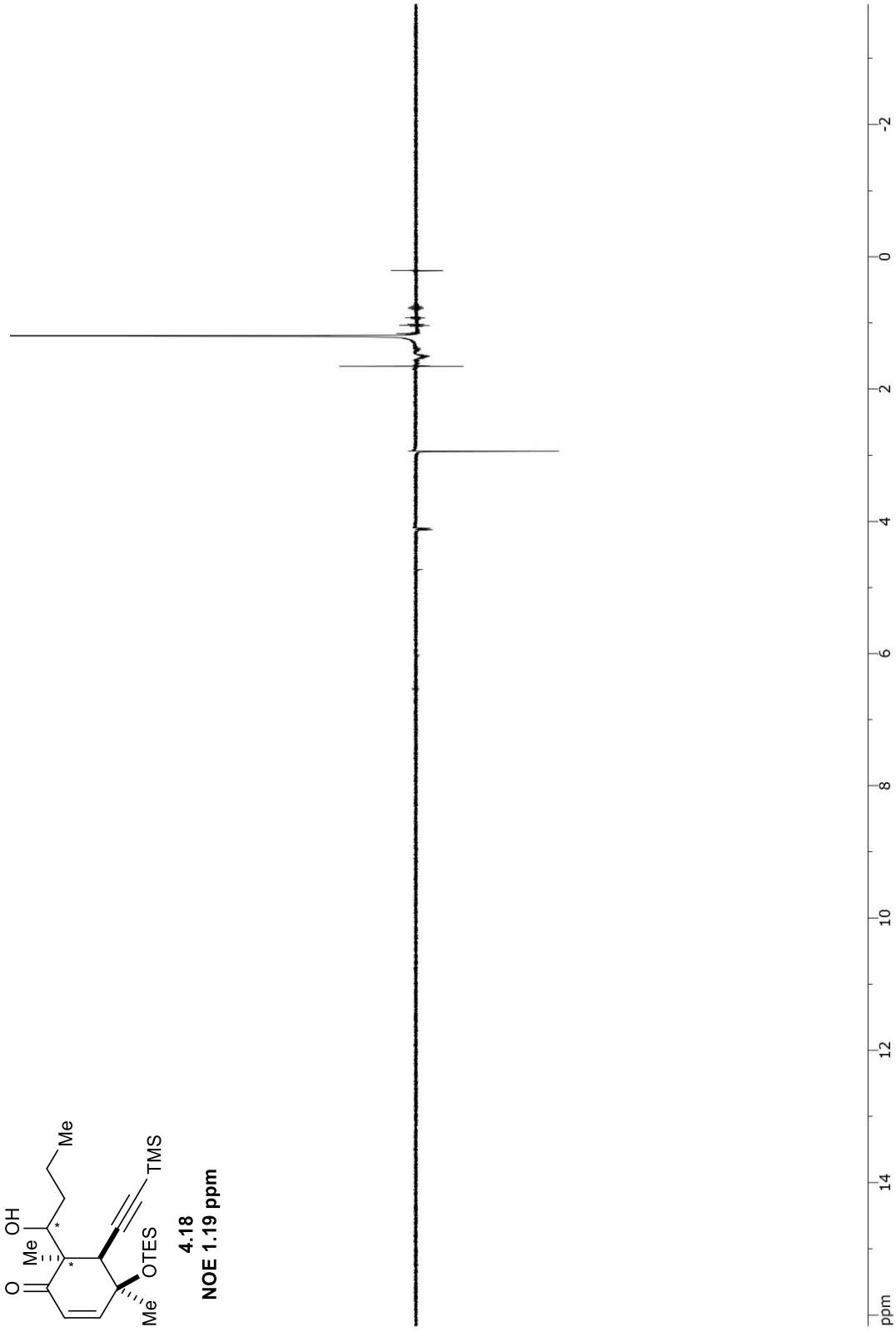
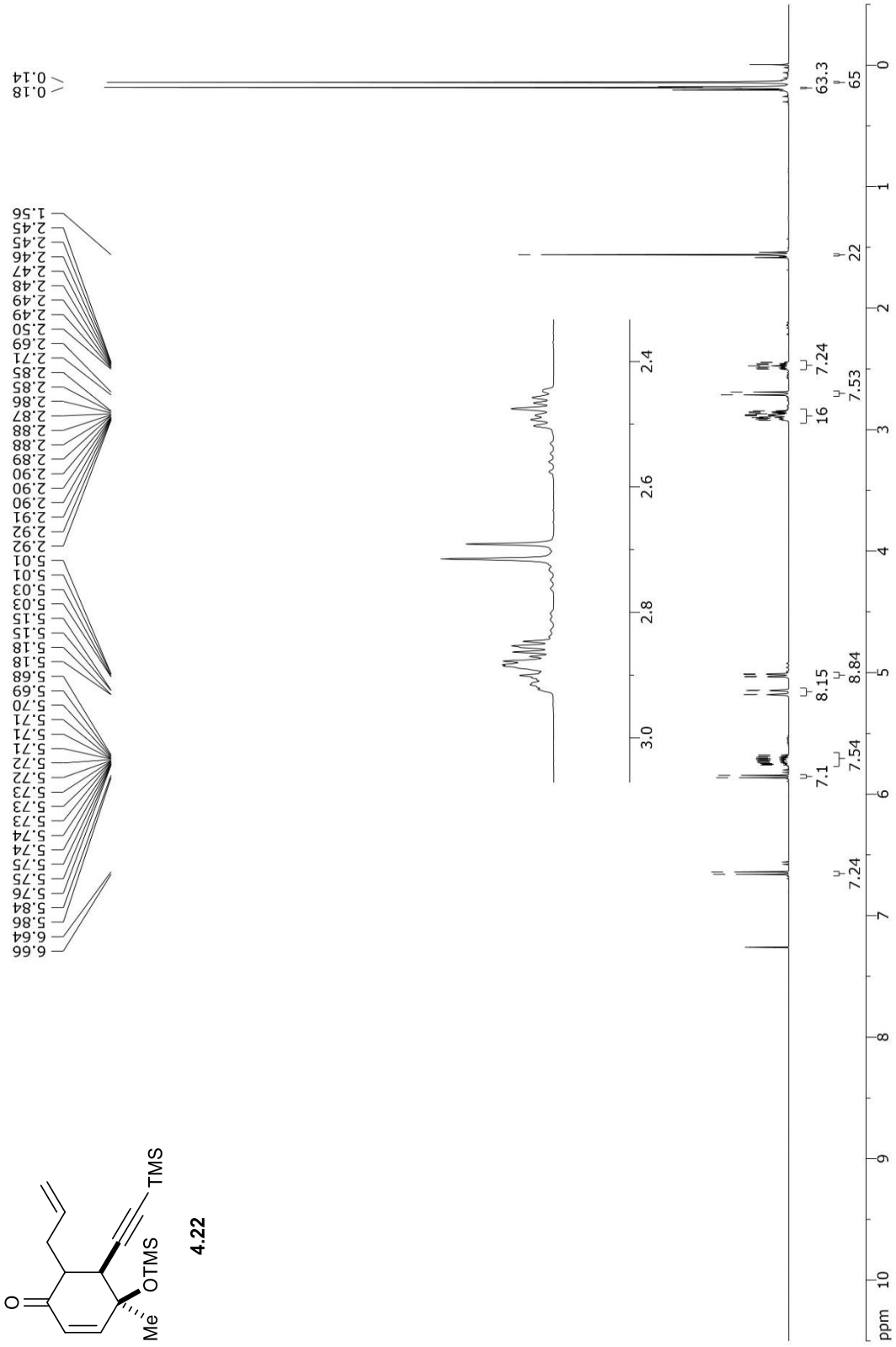
6.84
7.02
13.89
19.76
21.28
29.81
33.03
52.27
52.57
70.43
72.86
91.41
102.32
129.99
147.63
200.74
0
50
100
150
200
ppm
Me
TMS
OH
Me
OTES
Me
O
4.18


Me
OH
Me
O
OTES
Me
TMS
4.18
NOE 4.11 ppm
ppm
-2
0
2
4
6
8
10
12
14


Me
OH
Me
O
OTES
Me
TMS
4.18
NOE 2.94 ppm
-2
0
2
4
6
8
10
12
14
ppm

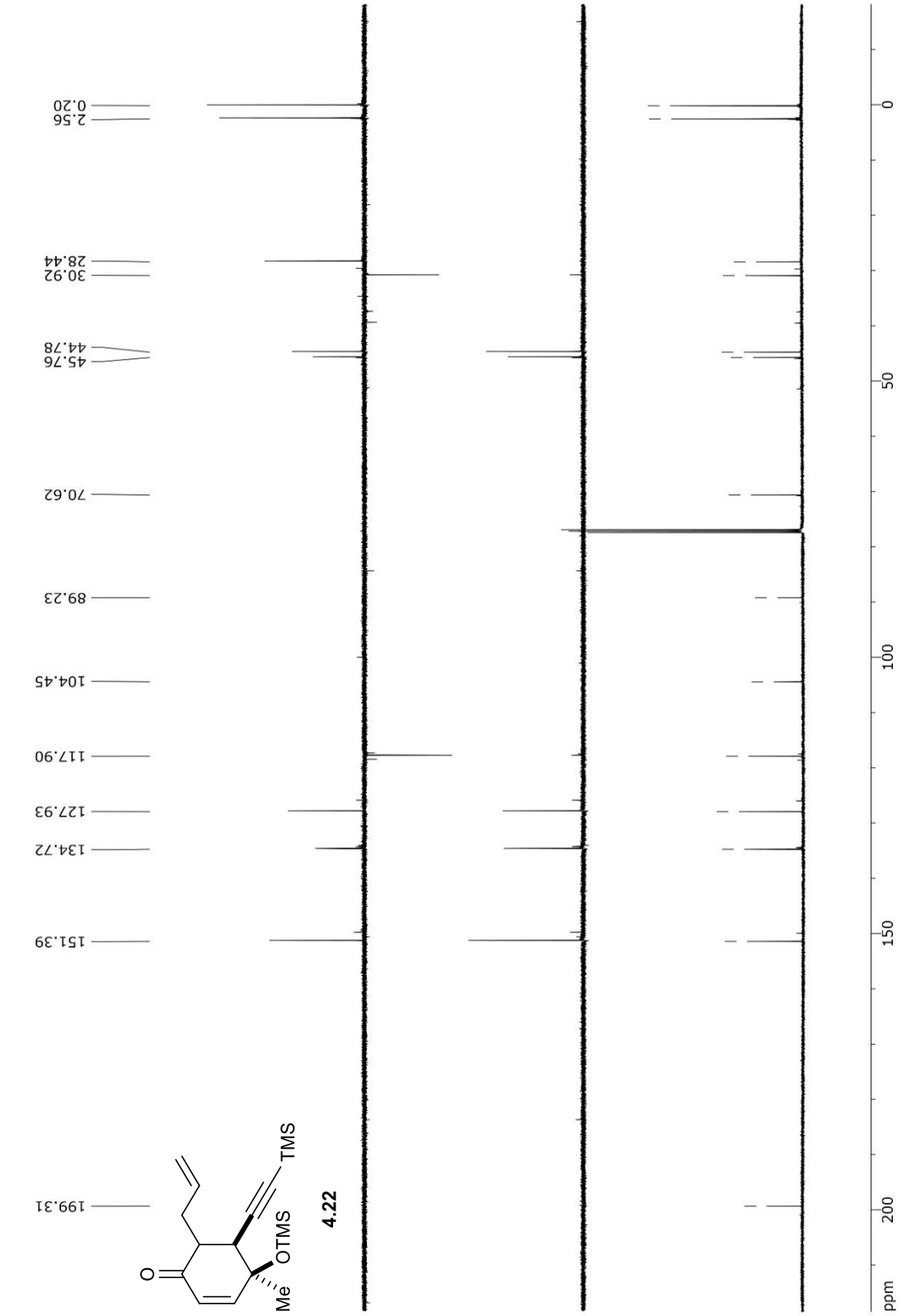

Me
OH
Me
O
OTES
TMS
Me
4.18
NOE 1.66 ppm
-2
0
2
4
6
8
10
12
14
ppm

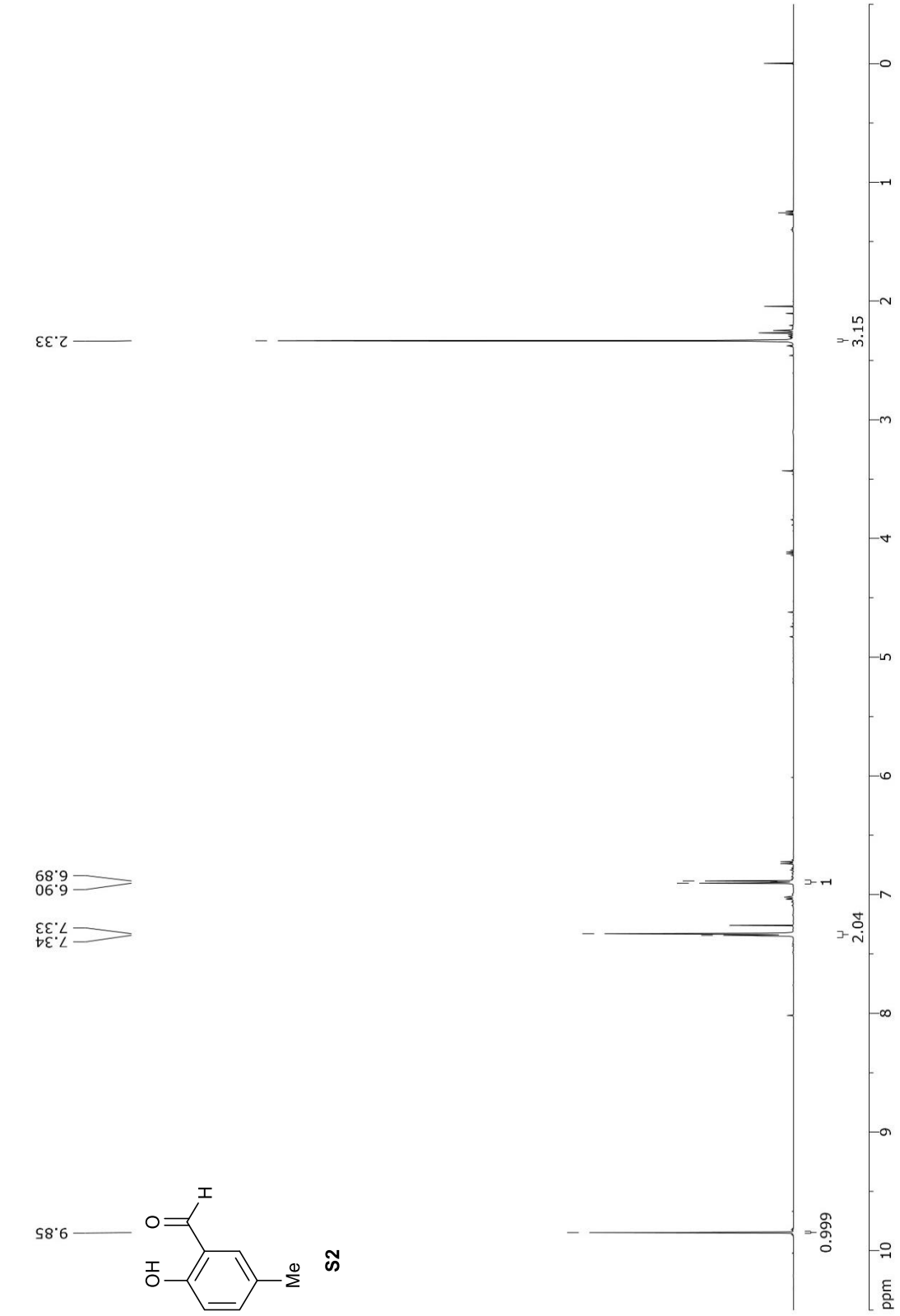

Me
OH
Me
O
OTES
Me
TMS
4.18
NOE 1.19 ppm
-2
0
2
4
6
8
10
12
14
ppm

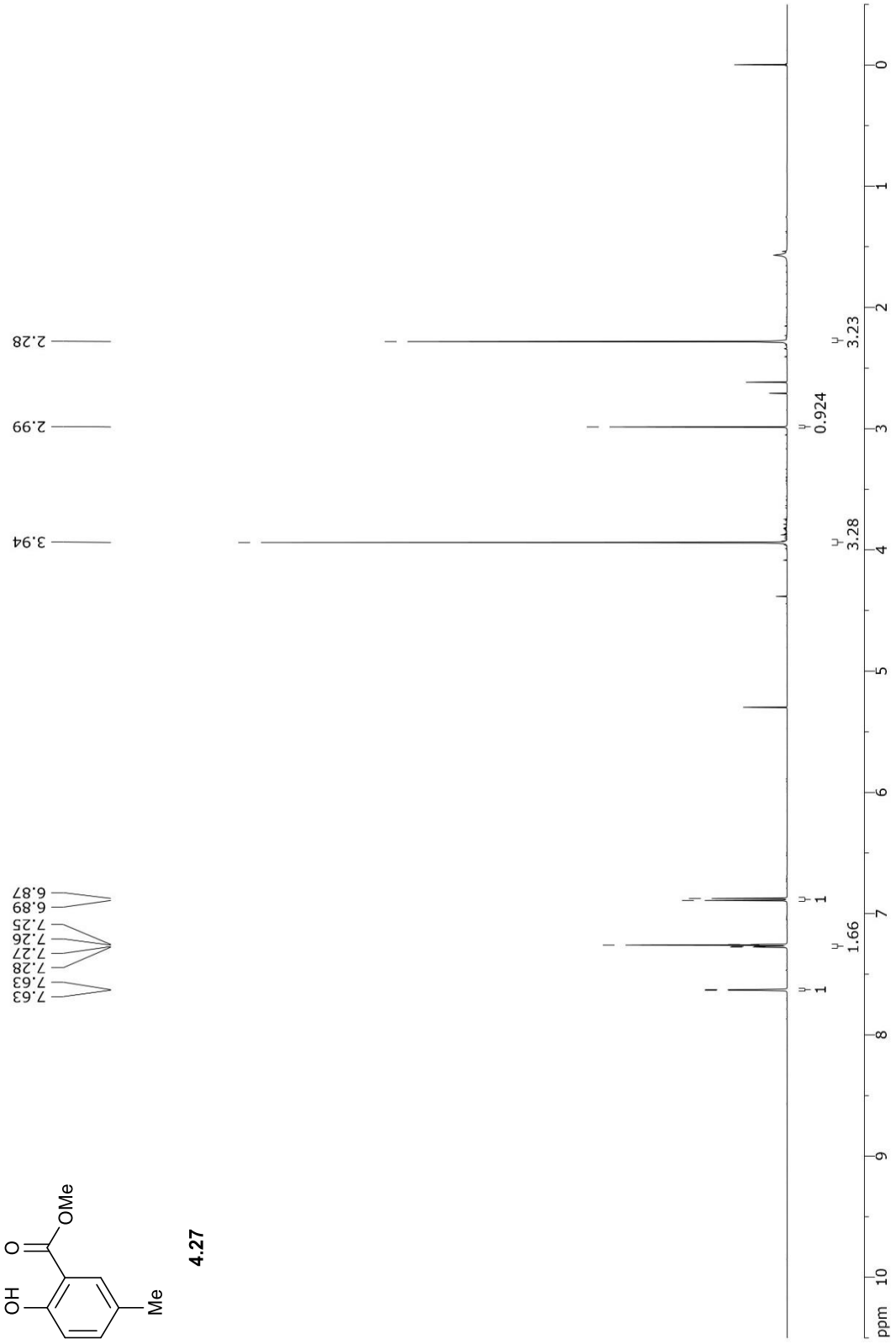

0.18
0.14
1.56
2.45
2.45
2.46
2.47
2.48
2.49
2.49
2.50
2.69
2.71
2.85
2.85
2.86
2.87
2.88
2.88
2.89
2.90
2.90
2.90
2.91
2.92
2.92
5.01
5.01
5.03
5.03
5.15
5.15
5.18
5.18
5.68
5.69
5.70
5.71
5.71
5.71
5.72
5.72
5.73
5.73
5.73
5.74
5.74
5.75
5.75
5.76
5.84
5.86
6.64
6.66
3.0
2.8
2.6
2.4
63.3
65
22
16
7.24
7.53
8.15
8.84
7.1
7.54
7.24
ppm
0
1
2
3
4
5
6
7
8
9
10

O
Me
OTMS
TMS

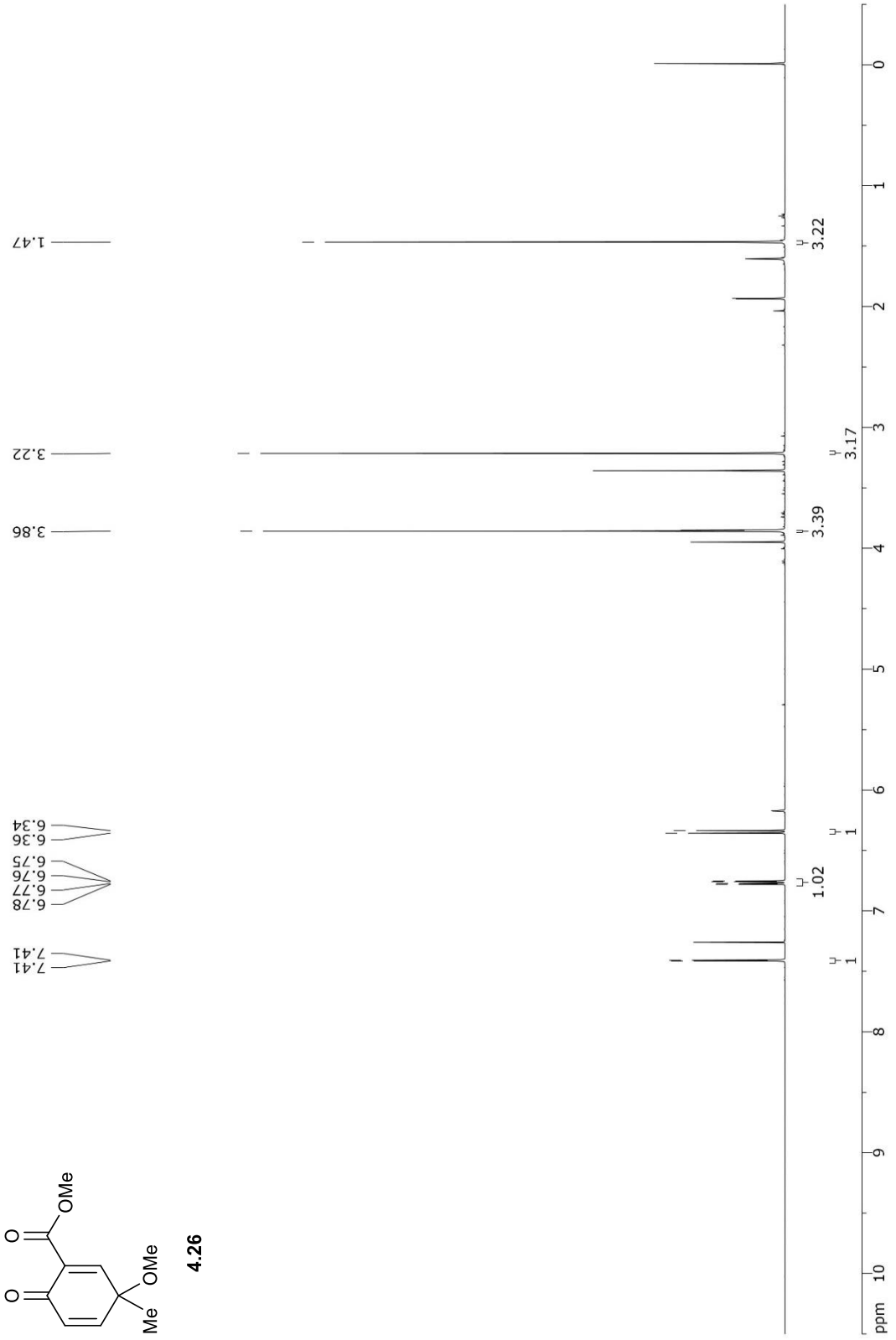
4.22


0.20
2.56
28.44
30.92
44.78
45.76
70.62
89.23
104.45
117.90
127.93
134.72
151.39
199.31
ppm
0
50
100
150
200
TMS
OTMS
Me
O
4.22

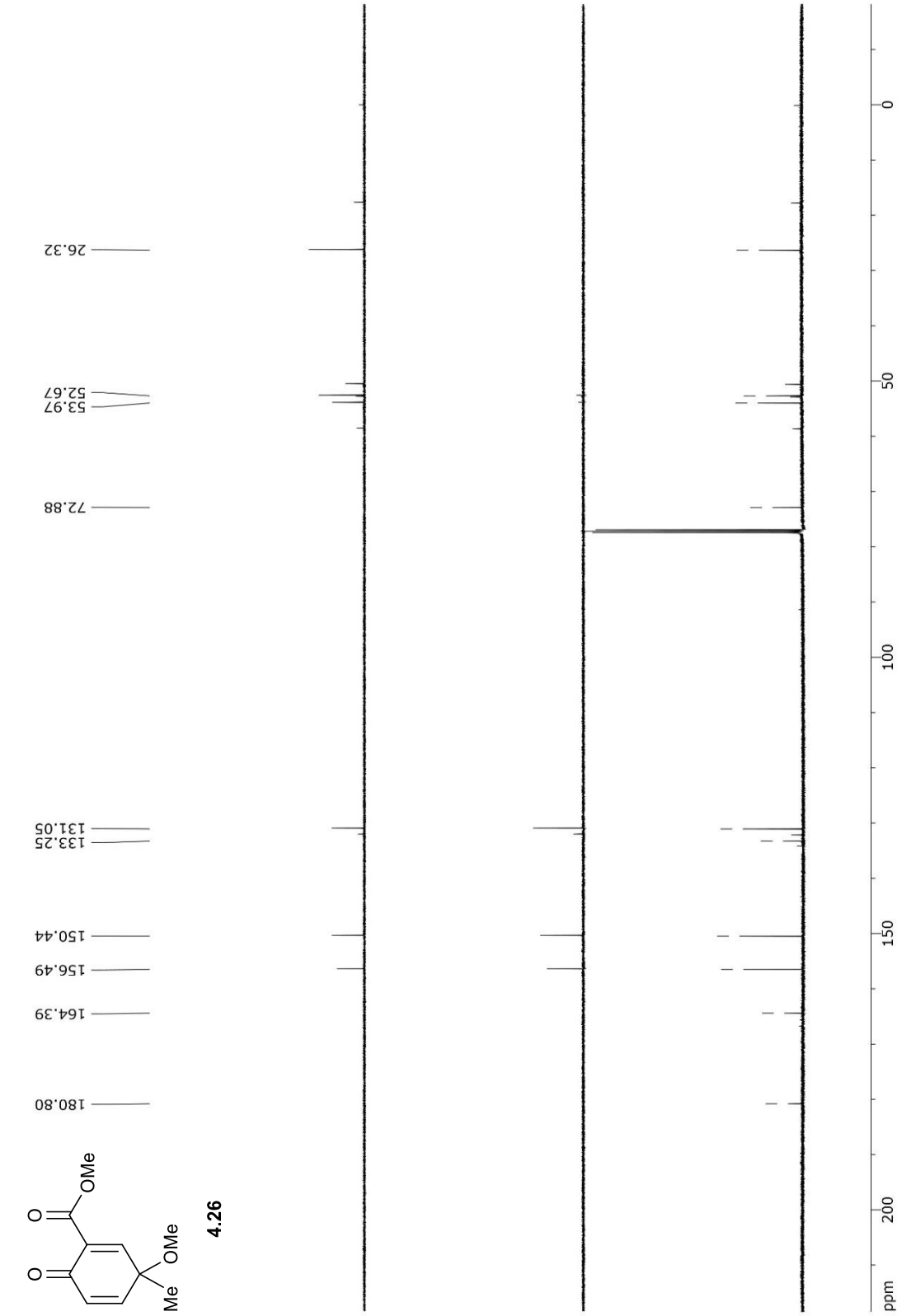

9.85
7.34
7.33
6.90
6.89
2.33
0.999
1
2.04
3.15
ppm
OH
O
H
Me
S2

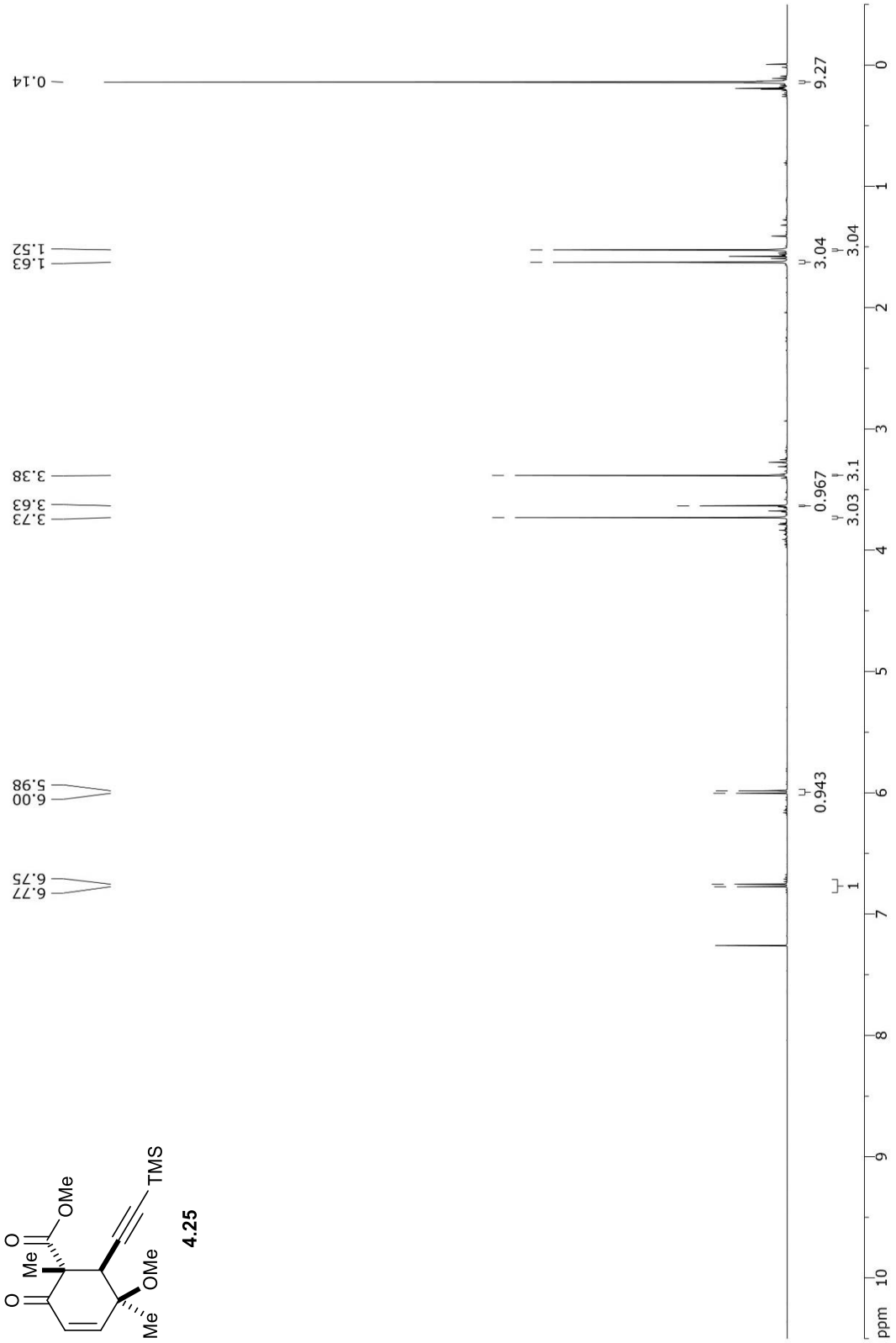

2.28
2.99
3.94
6.87
6.89
7.25
7.26
7.27
7.28
7.63
7.63
3.23
0.924
3.28
1.66
1
1
ppm
OMe
O
OH
Me

4.27

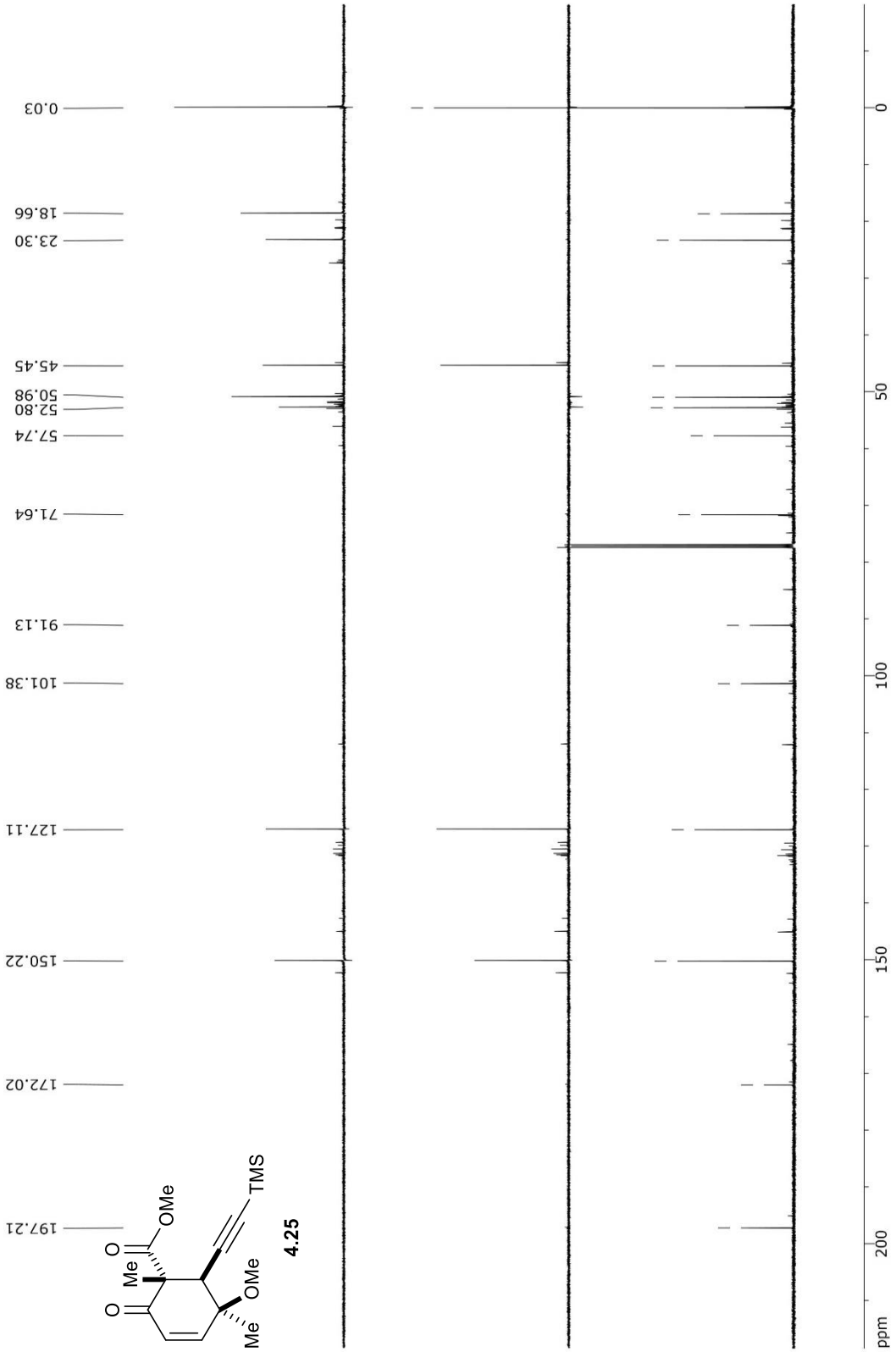

1.47
3.22
3.86
6.34
6.36
6.75
6.76
6.77
6.78
7.41
7.41
3.22
3.17
3.39
1.02
1
1
ppm
OMe
OMe
Me
O
O

4.26

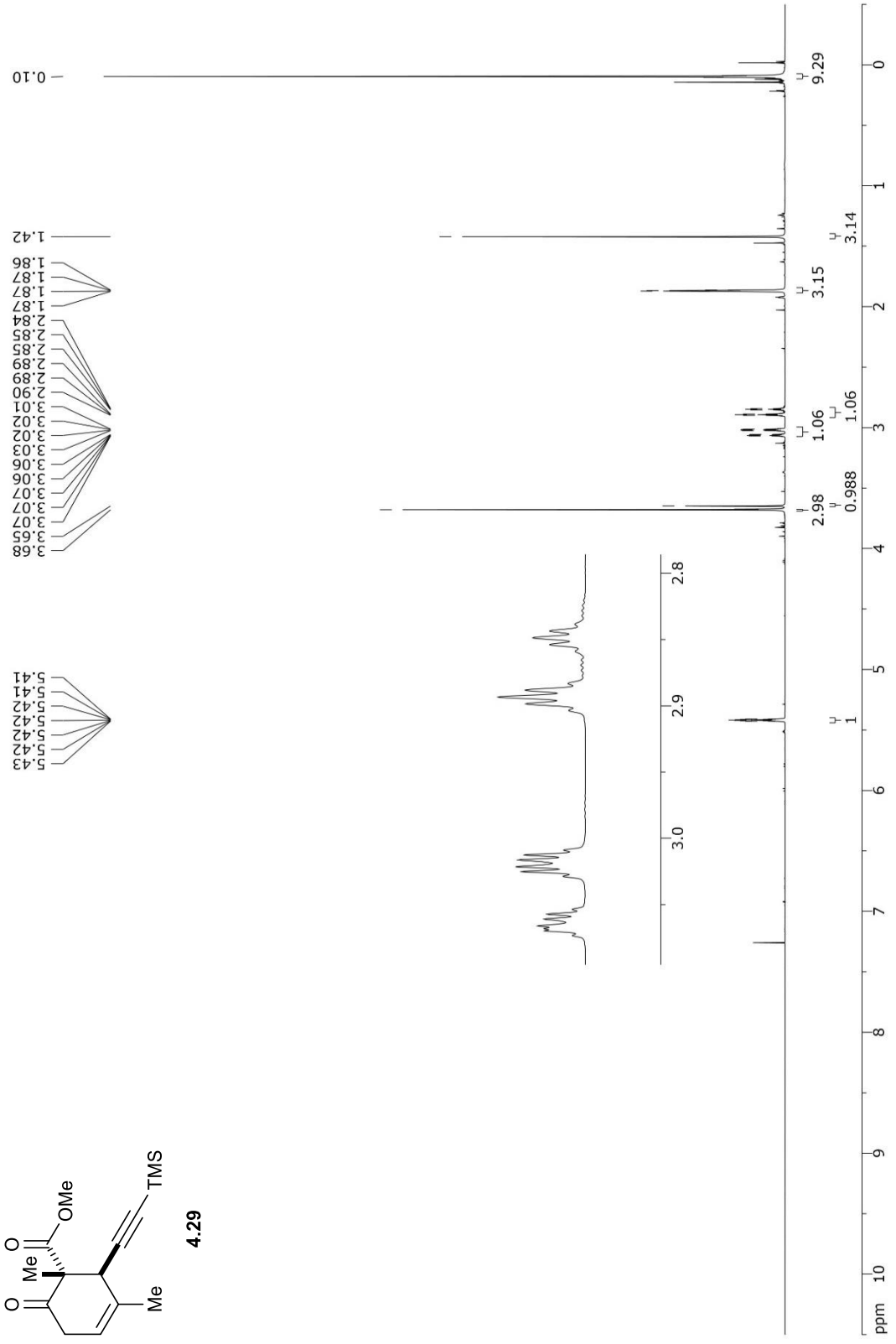

26.32
52.67
53.97
72.88
131.05
133.25
150.44
156.49
164.39
180.80
OMe
OMe
Me
O
O
4.26
0
50
100
150
200
ppm


0.14
1.52
1.63
3.38
3.63
3.73
5.98
6.00
6.75
6.77
9.27
3.04
3.04
0.967
3.03
3.1
0.943
1
ppm
TMS
OMe
Me
OMe
Me
O
O

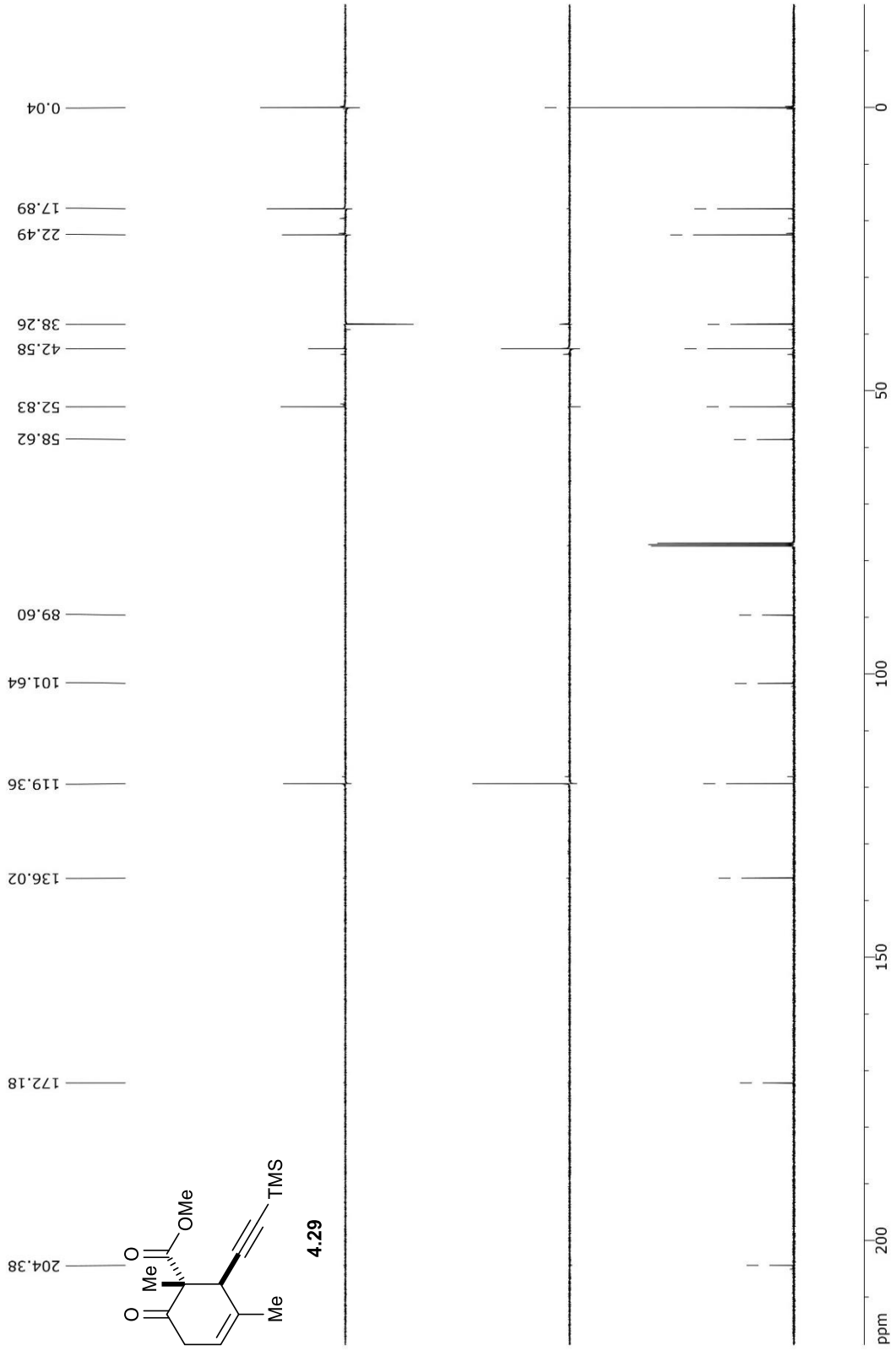
4.25

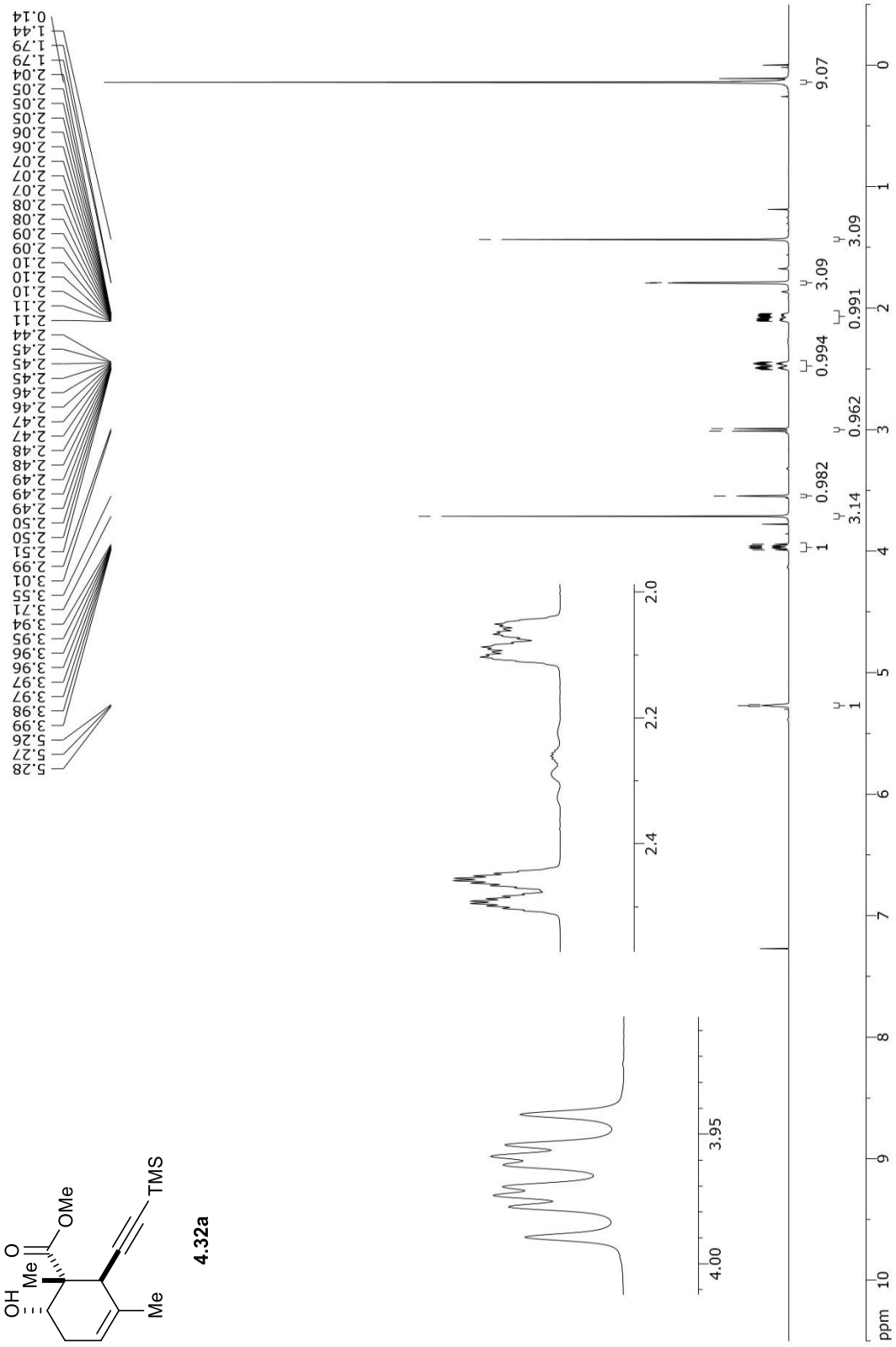

0.03
18.66
23.30
45.45
50.98
52.80
57.74
71.64
91.13
101.38
127.11
150.22
172.02
197.21
ppm
0
50
100
150
200
TMS
OMe
Me
OMe
Me
O
O

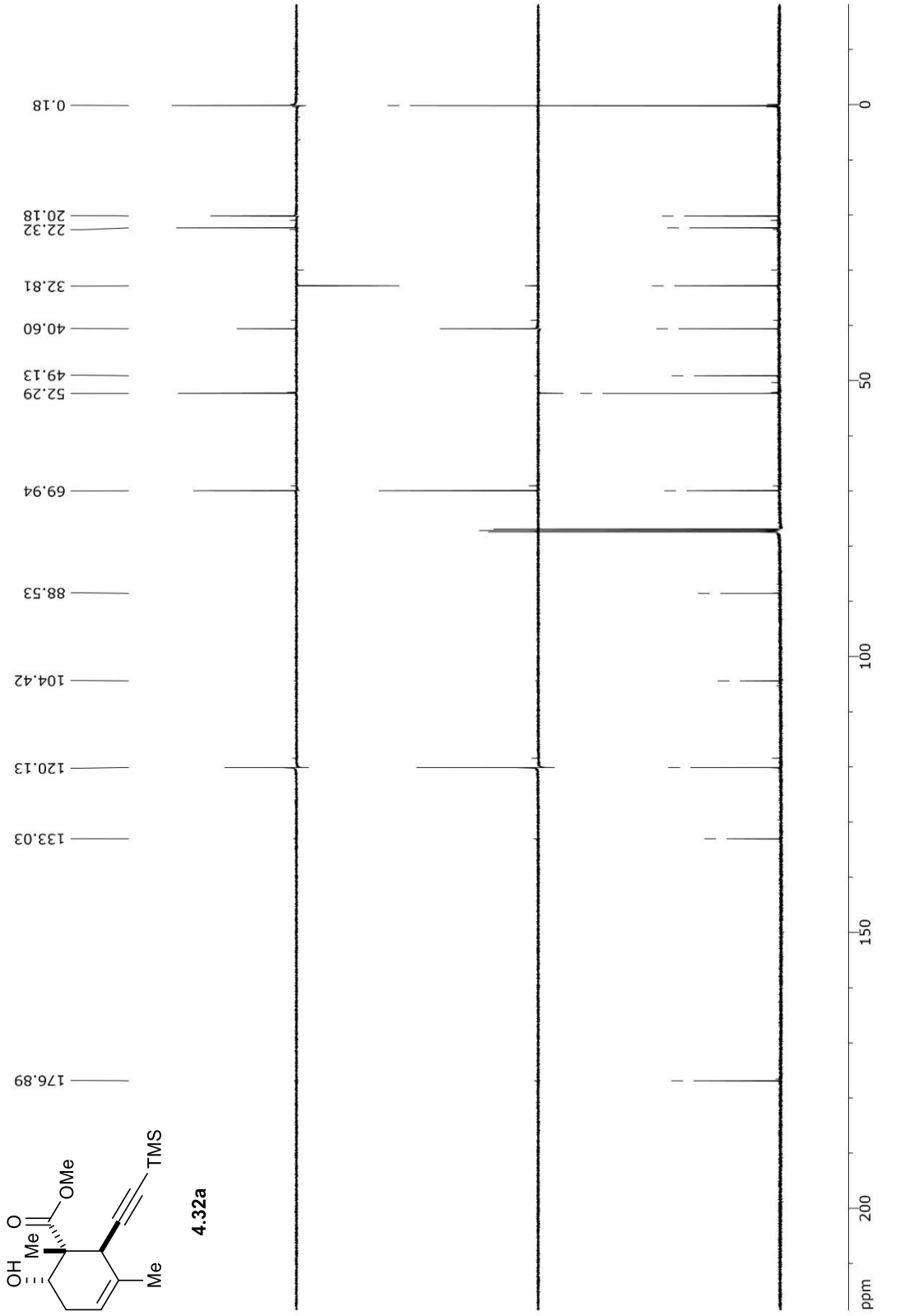
4.25

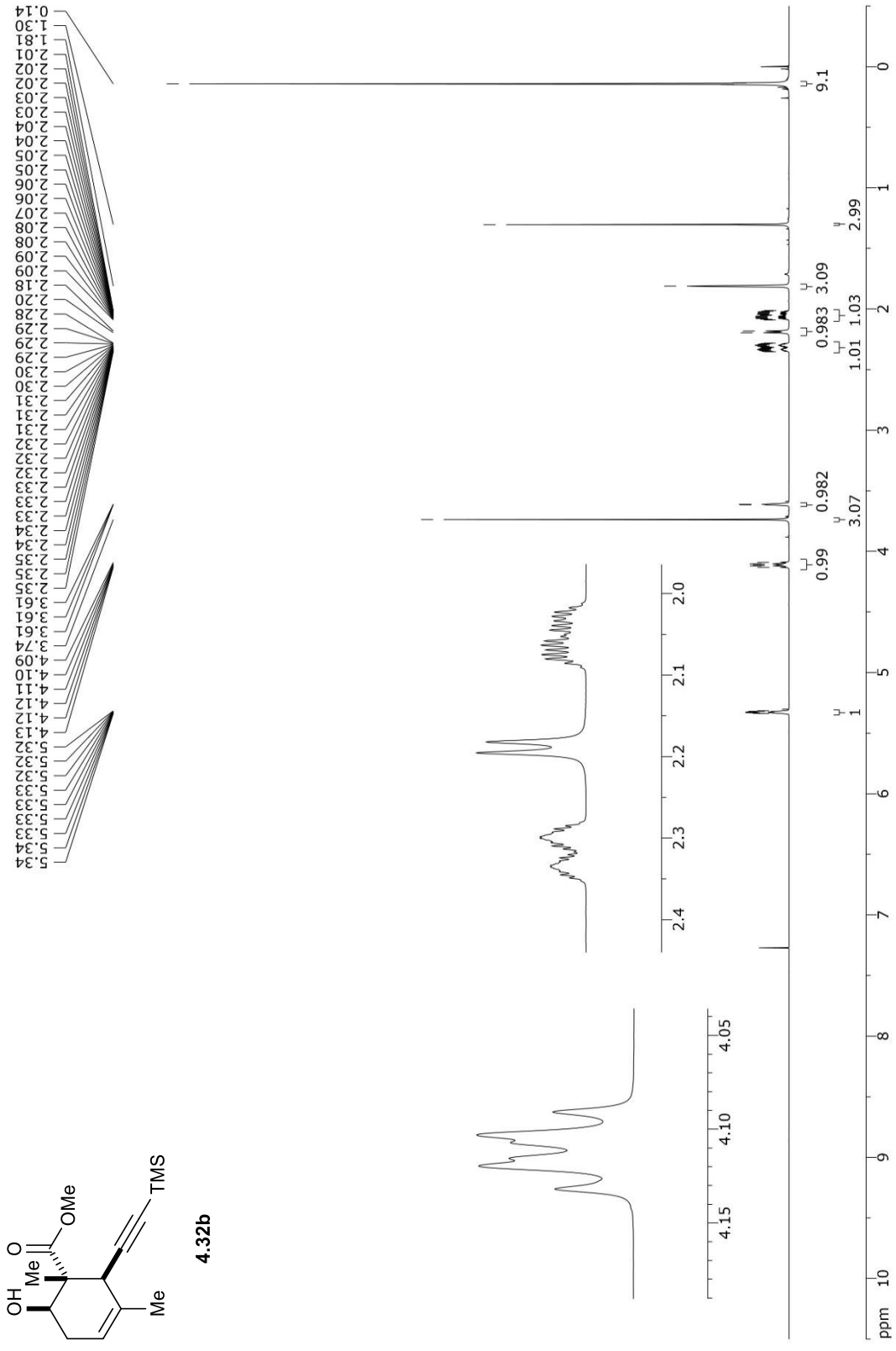

0.10
1.42
1.86
1.87
1.87
2.84
2.85
2.85
2.89
2.89
2.90
3.01
3.02
3.02
3.03
3.06
3.06
3.07
3.07
3.07
3.65
3.68
5.41
5.41
5.42
5.42
5.42
5.42
5.42
5.43
9.29
3.14
3.15
1.06
1.06
0.988
2.98
2.8
2.9
3.0
ppm
O
Me
O
OMe
Me
TMS

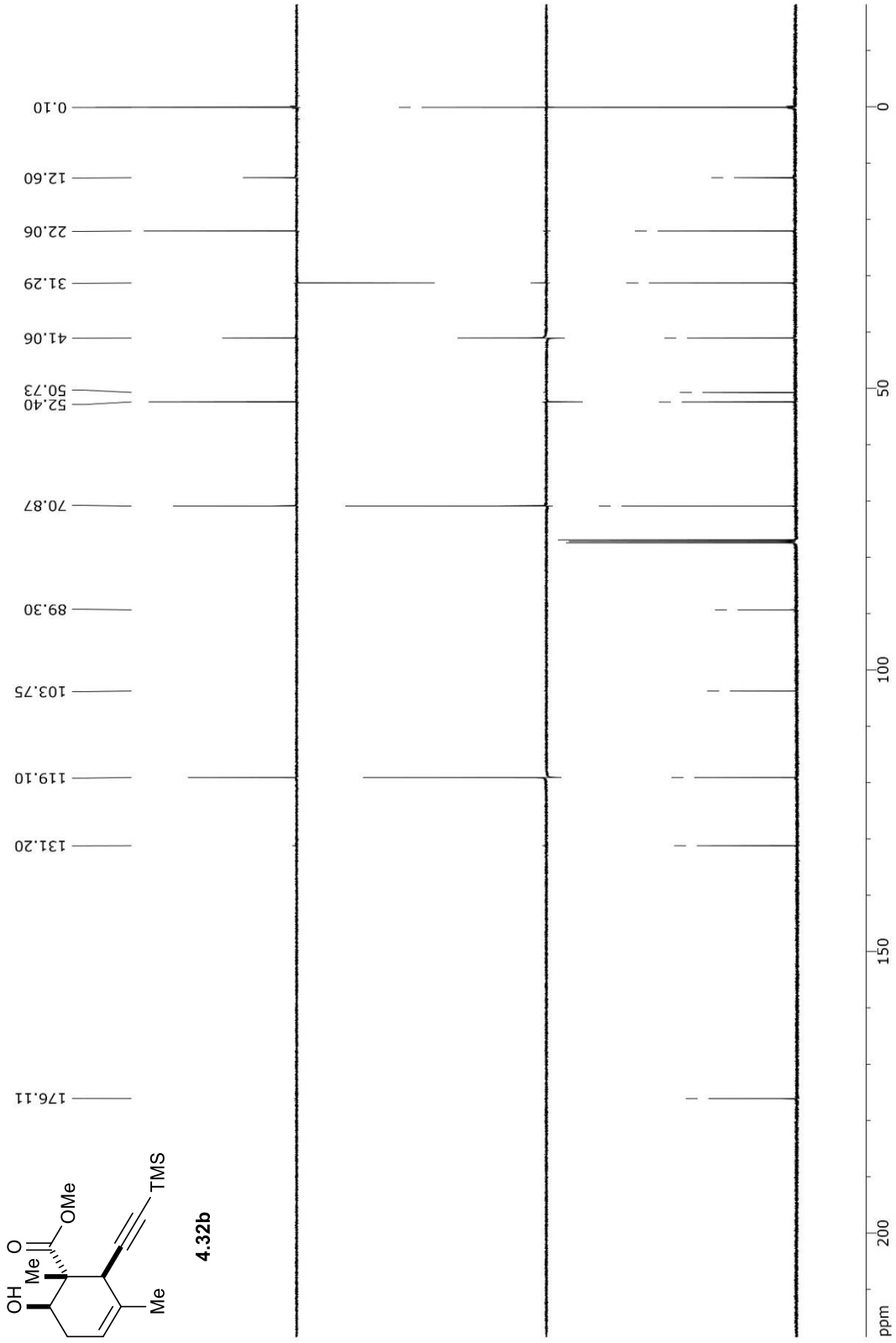
4.29

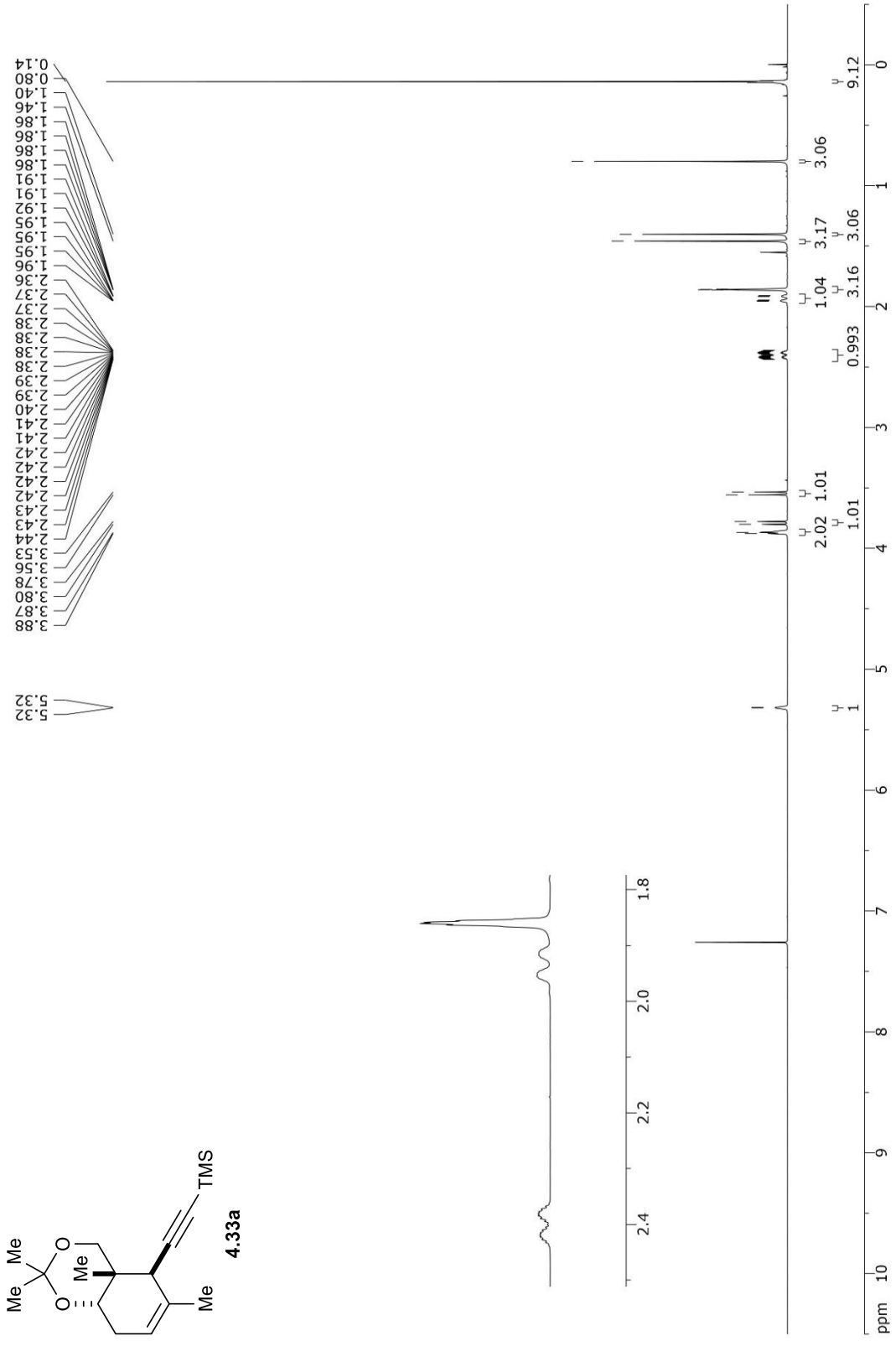

0.04
17.89
22.49
38.26
42.58
52.83
58.62
89.60
101.64
119.36
136.02
172.18
204.38
ppm
0
50
100
150
200
4.29
TMS
OMe
Me
Me
O
O

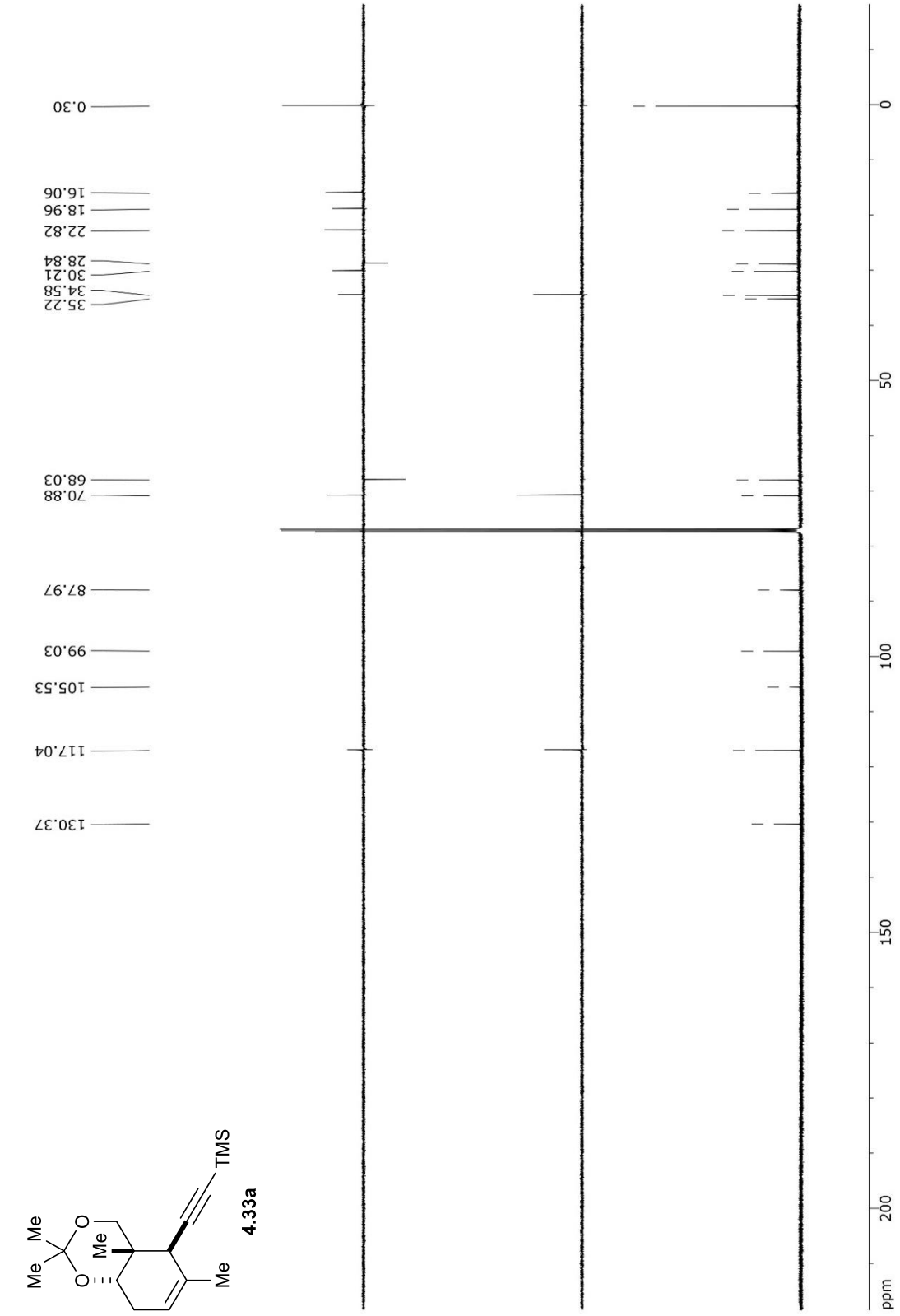

OH
O
Me
OMe
Me
TMS
4.32a
ppm

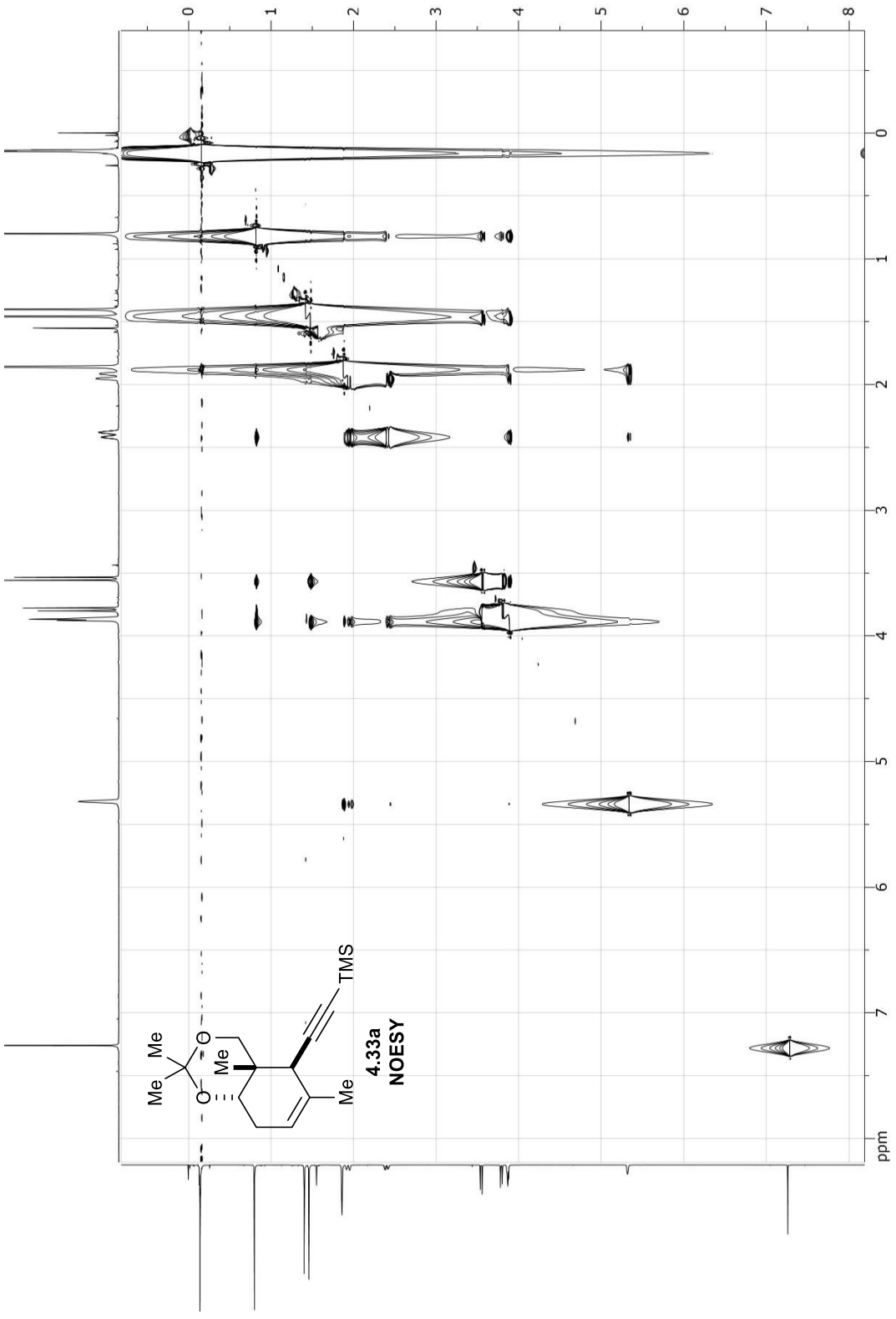

0.18
20.18
22.32
32.81
40.60
49.13
52.29
69.94
88.53
104.42
120.13
133.03
176.89
ppm
0
50
100
150
200
OH
Me
O
OMe
Me
TMS
4.32a

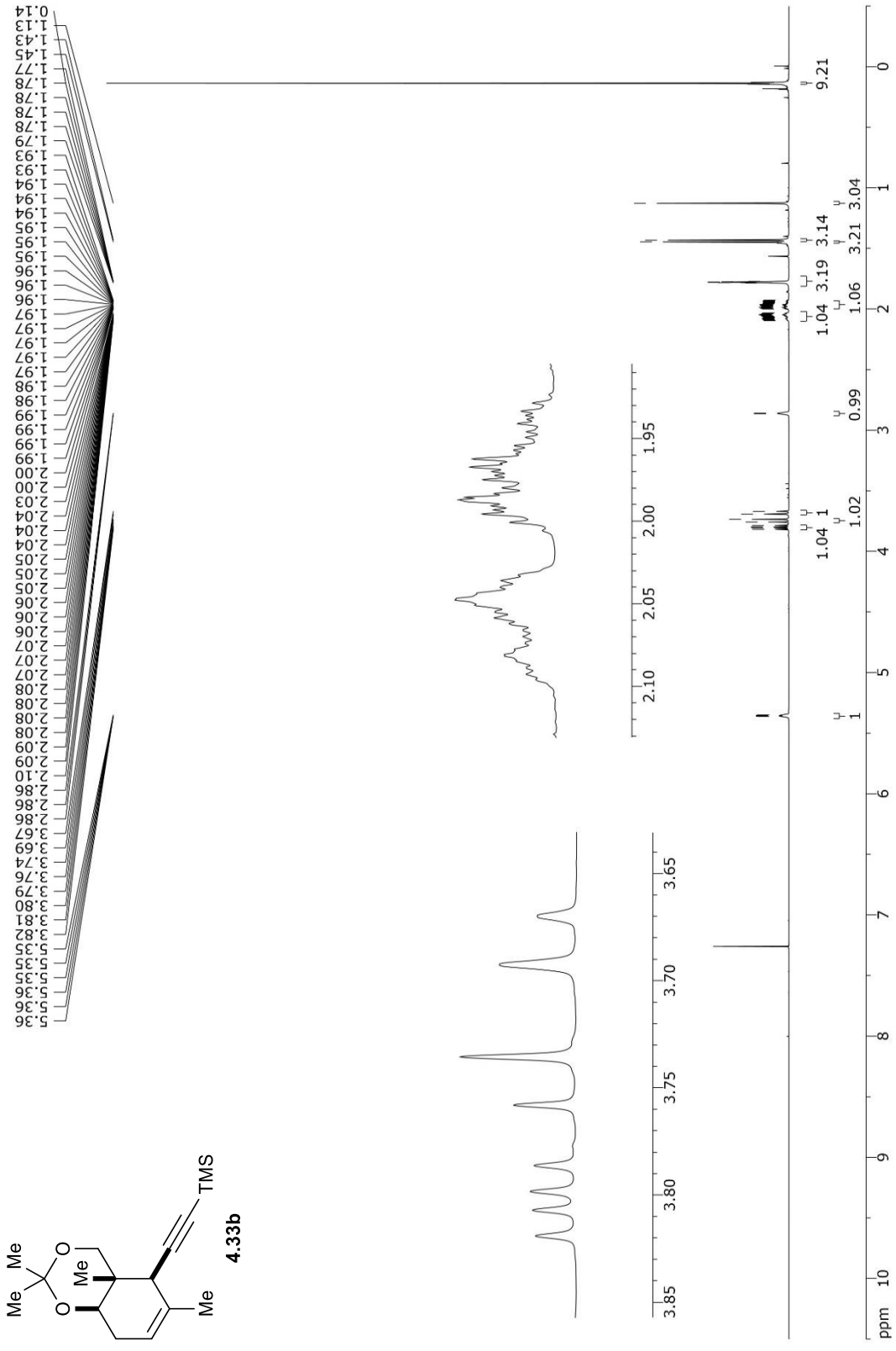

OH
Me
O
OMe
Me
TMS
4.32b
ppm

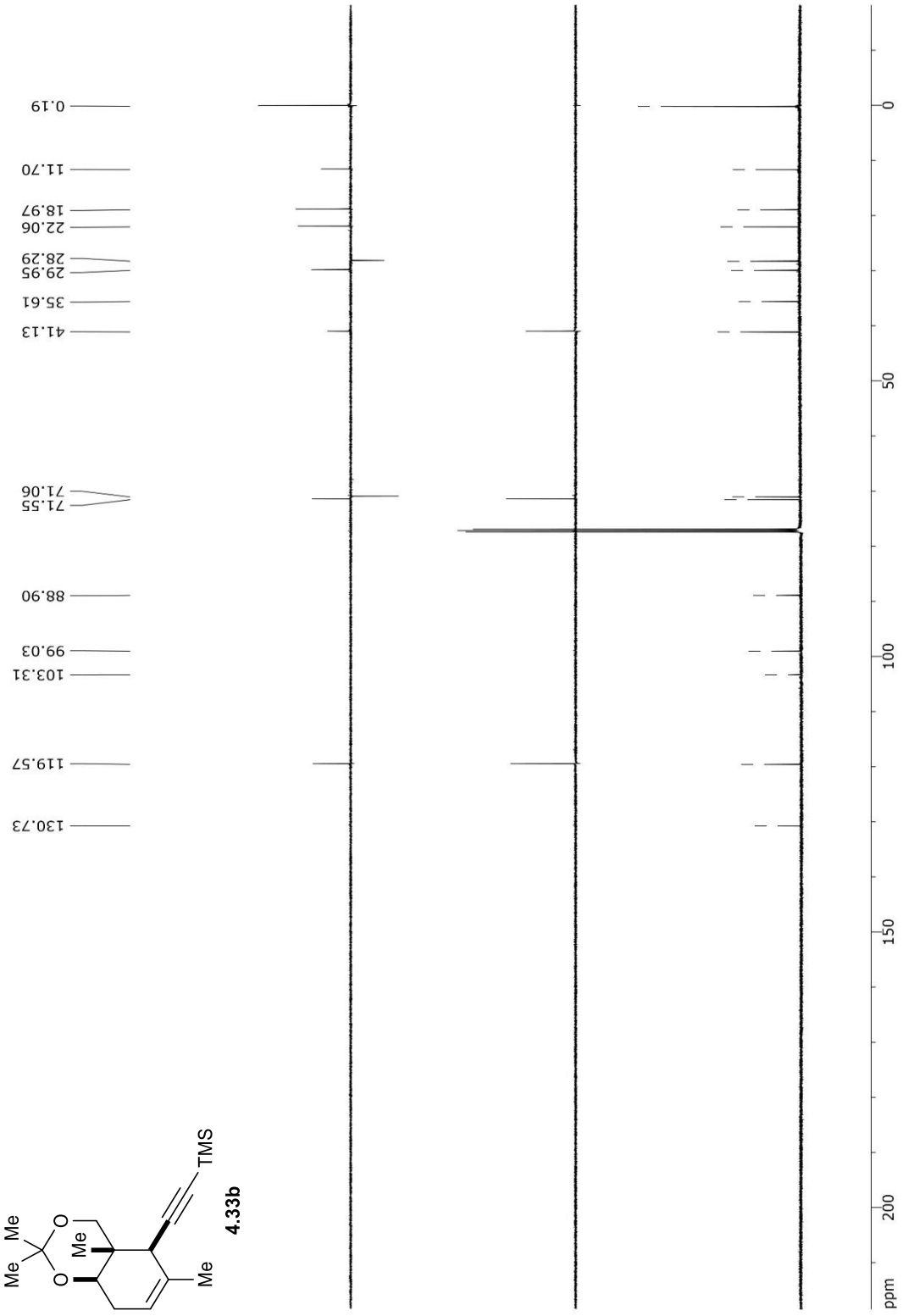

0.10
12.60
22.06
31.29
41.06
50.73
52.40
70.87
89.30
103.75
119.10
131.20
176.11
ppm
0
50
100
150
200
OH
Me
O
OMe
Me
TMS
4.32b

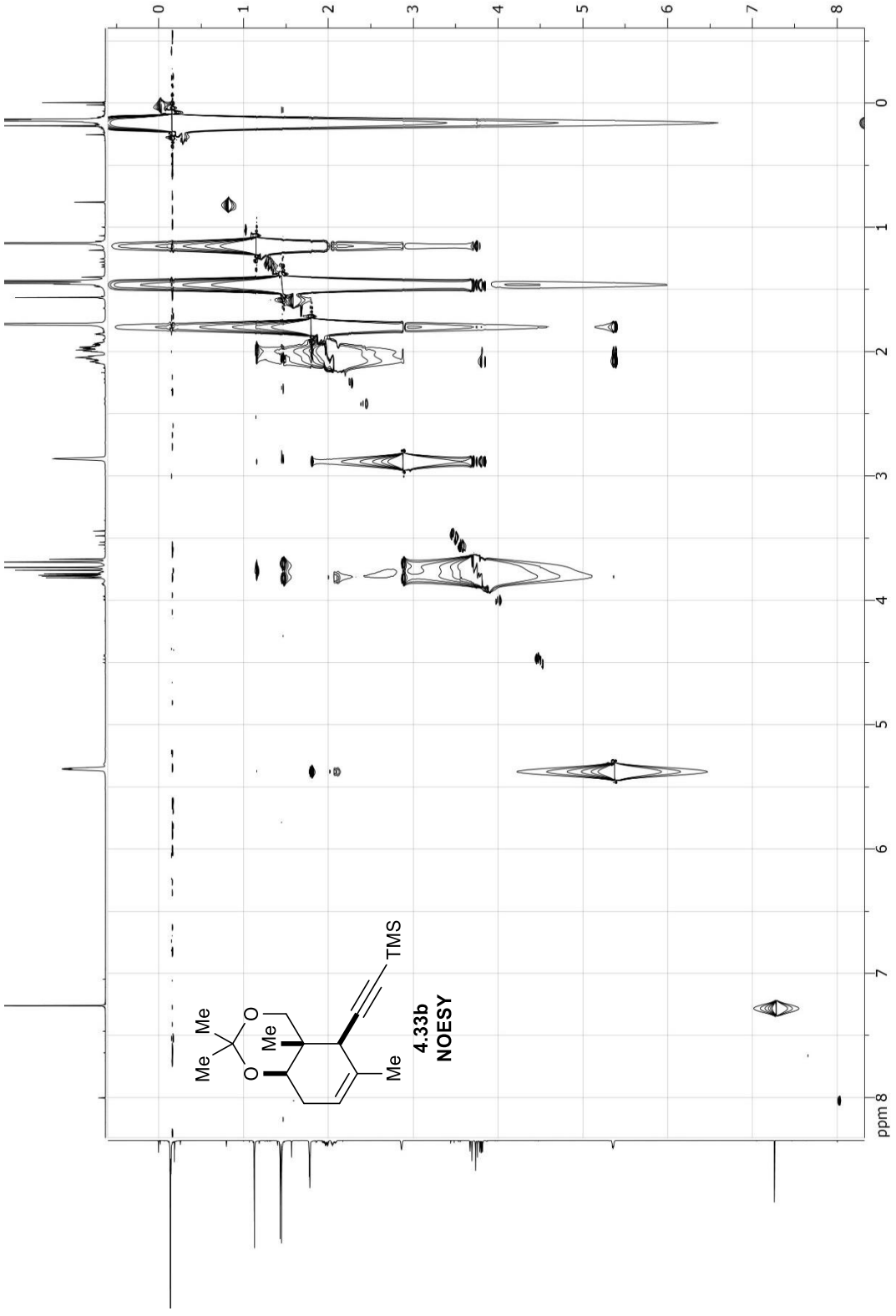

TMS
Me
Me
Me
Me
O
O
4.33a
ppm

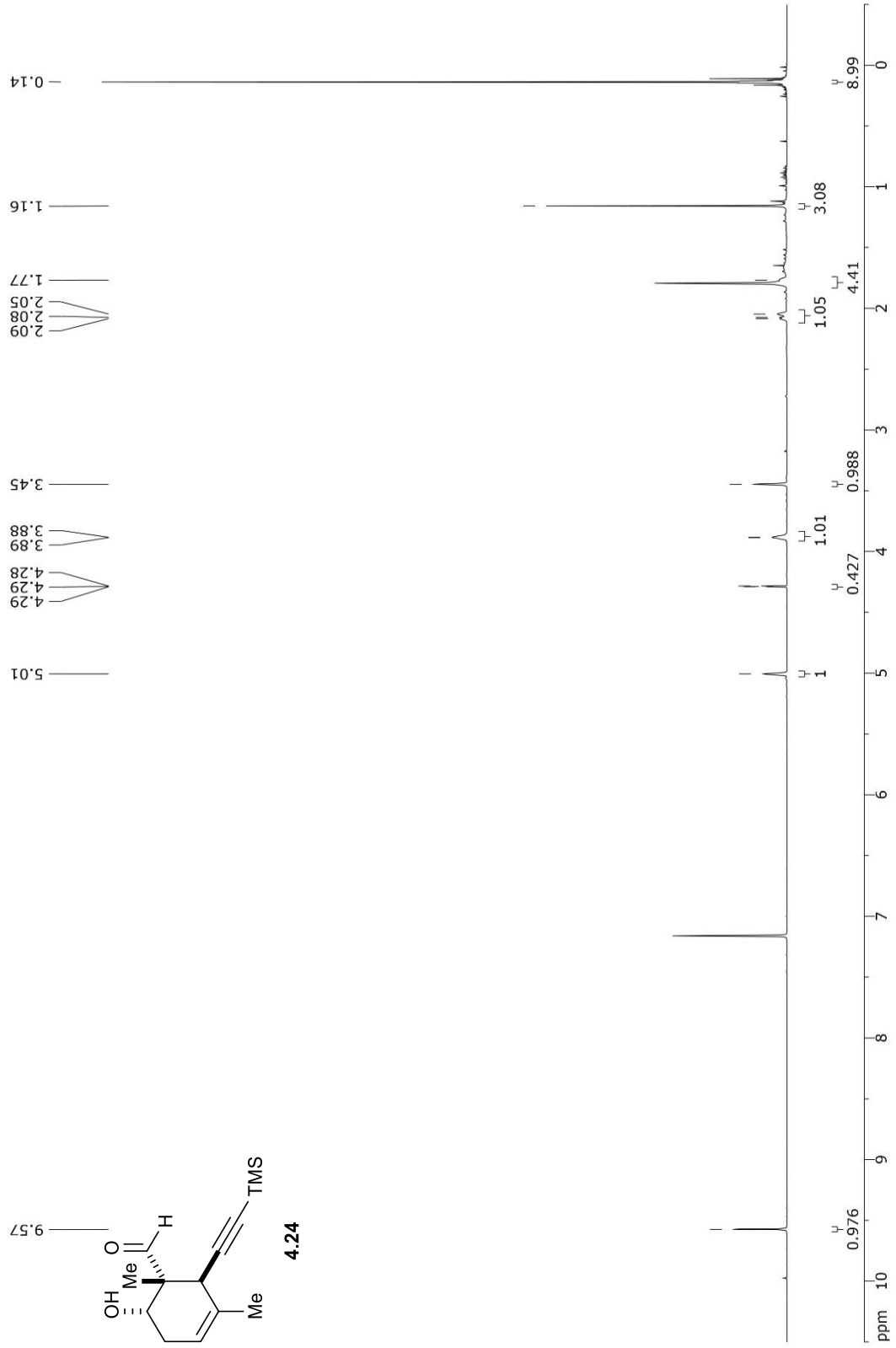

0.30
16.06
18.96
22.82
28.84
30.21
34.58
35.22
68.03
70.88
87.97
99.03
105.53
117.04
130.37
0
50
100
150
200
ppm
TMS
Me
Me
Me
O
O
Me
4.33a


0
1
2
3
4
5
6
7
8
ppm
Me
Me
Me
O
O
Me
Me
TMS
4.33a
NOESY

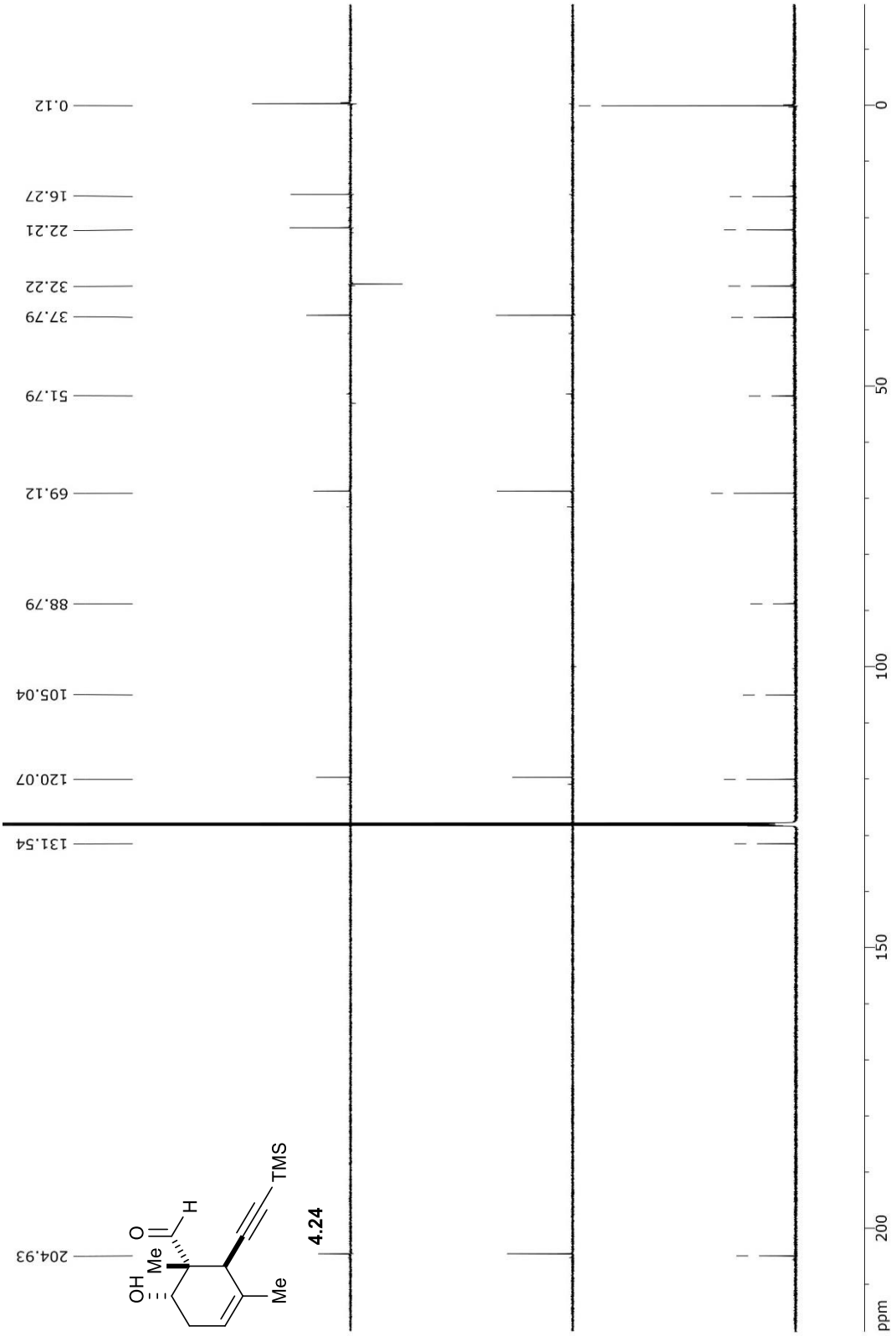

Me
Me
O
O
Me
Me
TMS
4.33b
ppm

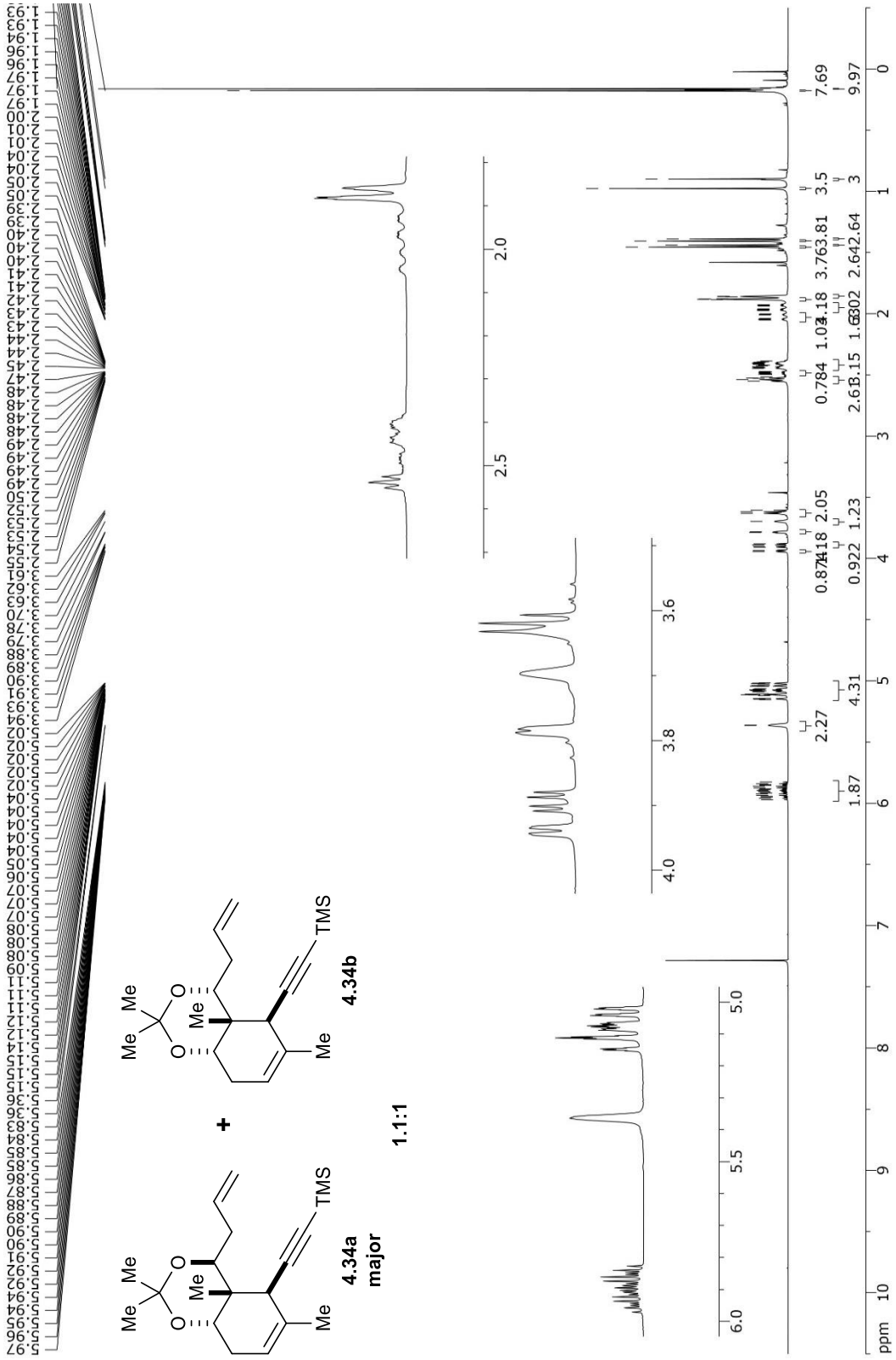

0.19
11.70
18.97
22.06
28.29
29.95
35.61
41.13
71.06
71.55
88.90
99.03
103.31
119.57
130.73
0
50
100
150
200
ppm
Me
Me
Me
O
O
Me
TMS
4.33b

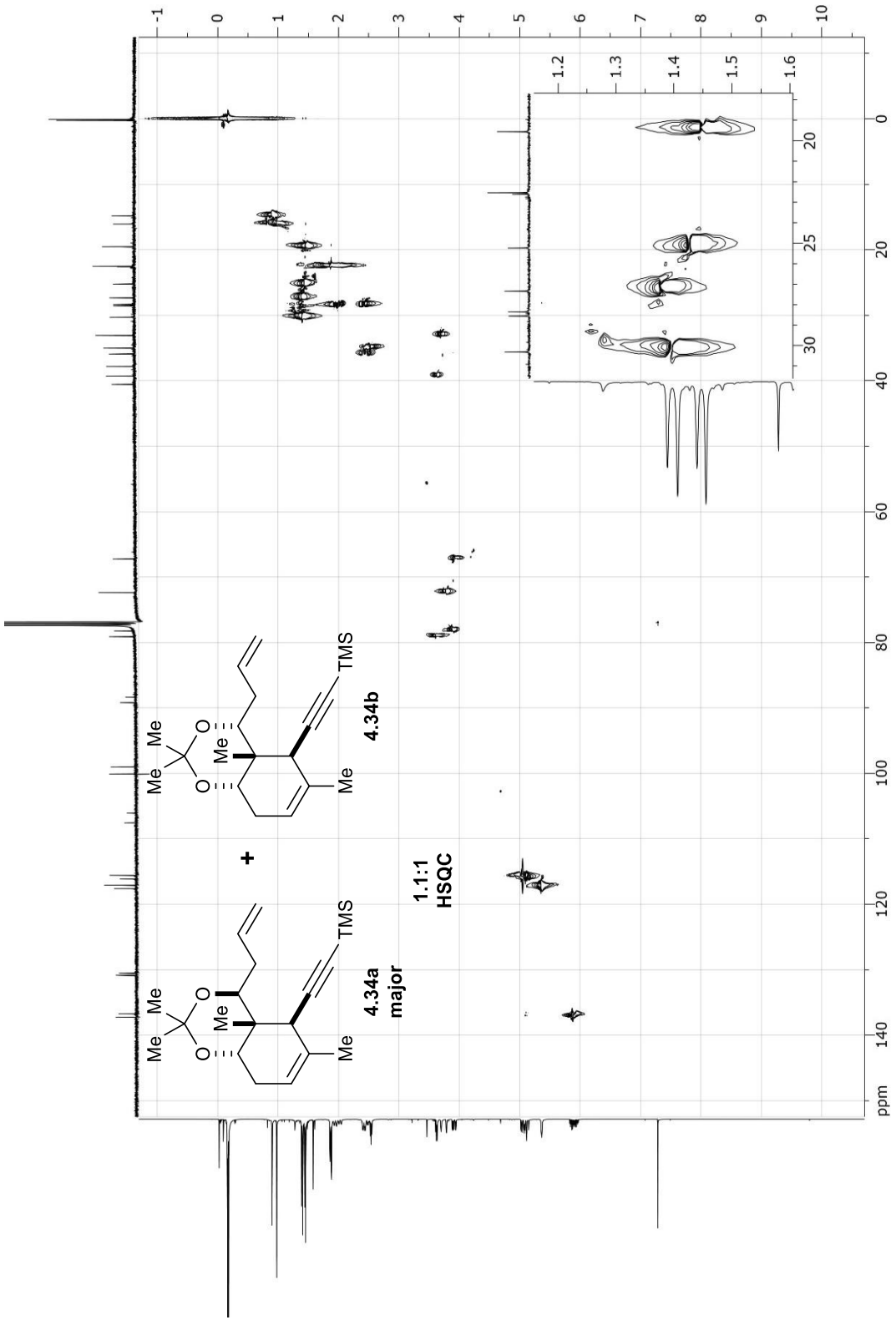

TMS
Me
Me
Me
Me
O
O
4.33b
NOESY
ppm

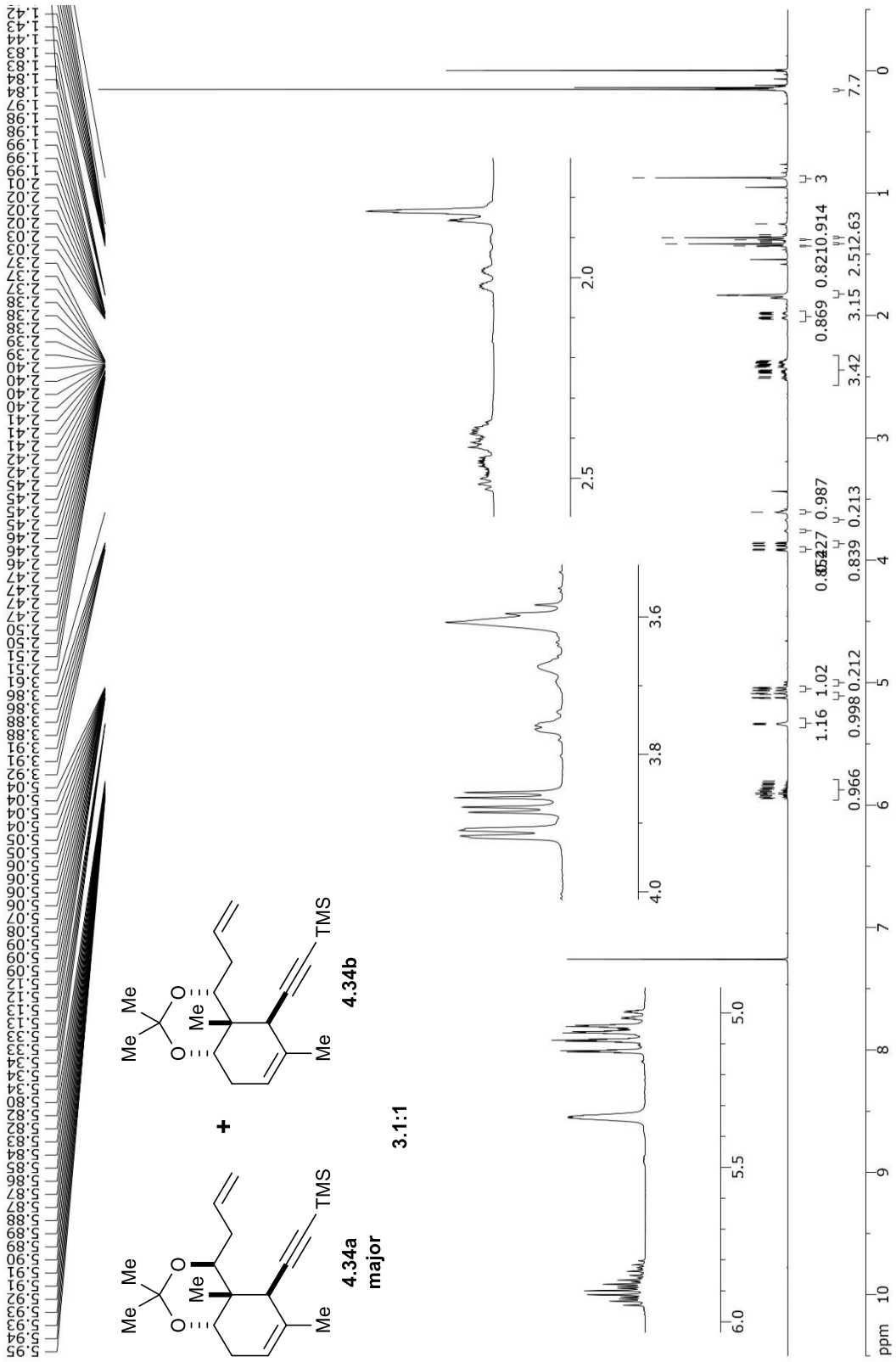

0.14
1.16
1.77
2.09
2.08
2.05
3.45
3.89
3.88
4.29
4.29
4.28
5.01
9.57
8.99
3.08
4.41
1.05
0.988
1.01
0.427
1
0.976
ppm
TMS
H
O
Me
OH
Me

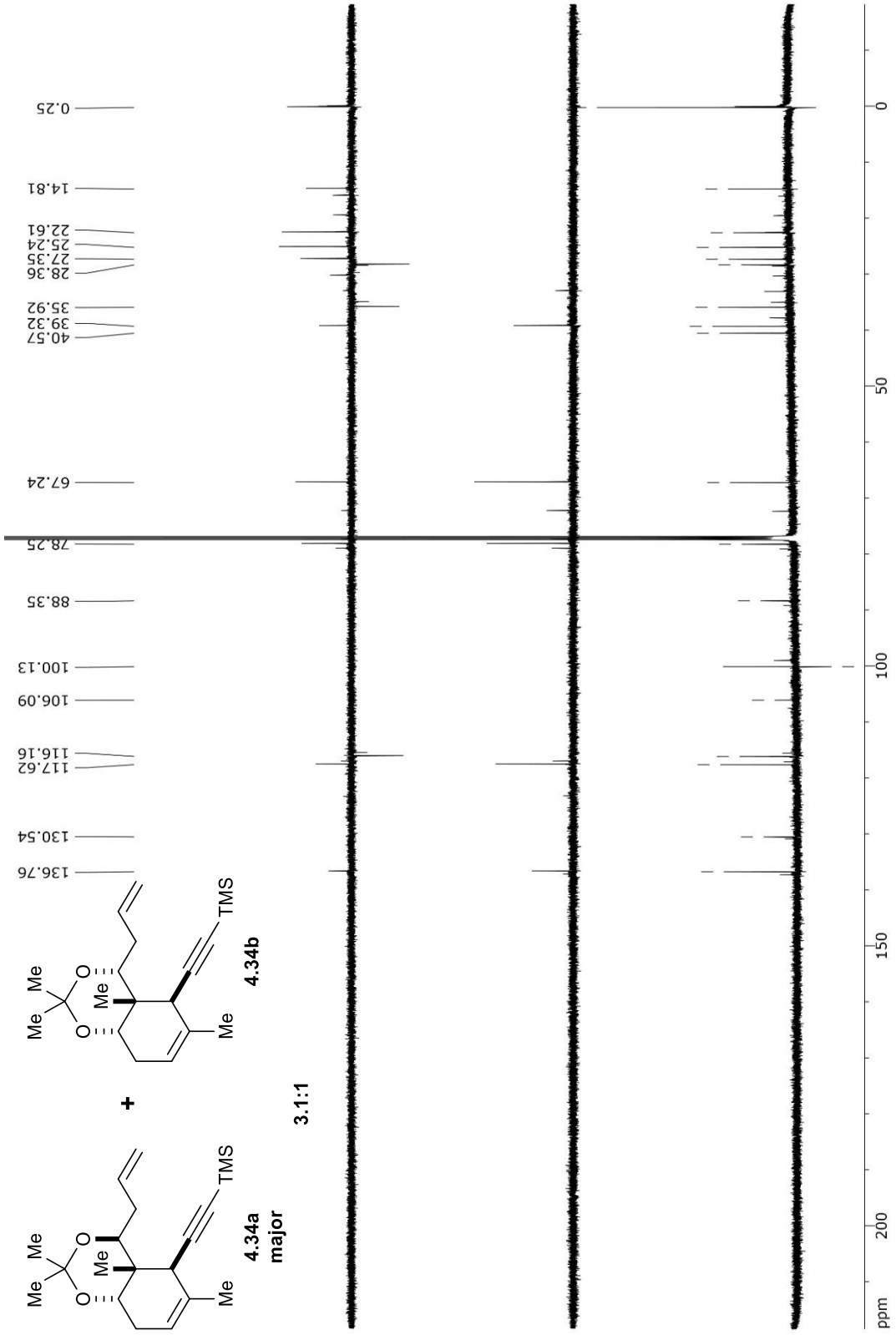
4.24


0.12
16.27
22.21
32.22
37.79
51.79
69.12
88.79
105.04
120.07
131.54
204.93
4.24
TMS
H
O
Me
OH
Me
0
50
100
150
200
ppm


Me
Me
Me
O
O
Me
Me
TMS
4.34a
major
+
1.1:1
4.34b
ppm


4.34a
major
+
4.34b
1.1:1
HSQC
TMS
Me
O
ppm


Me
Me
Me
O
O
Me
Me
TMS
4.34a
major
+
4.34b
3.1:1
ppm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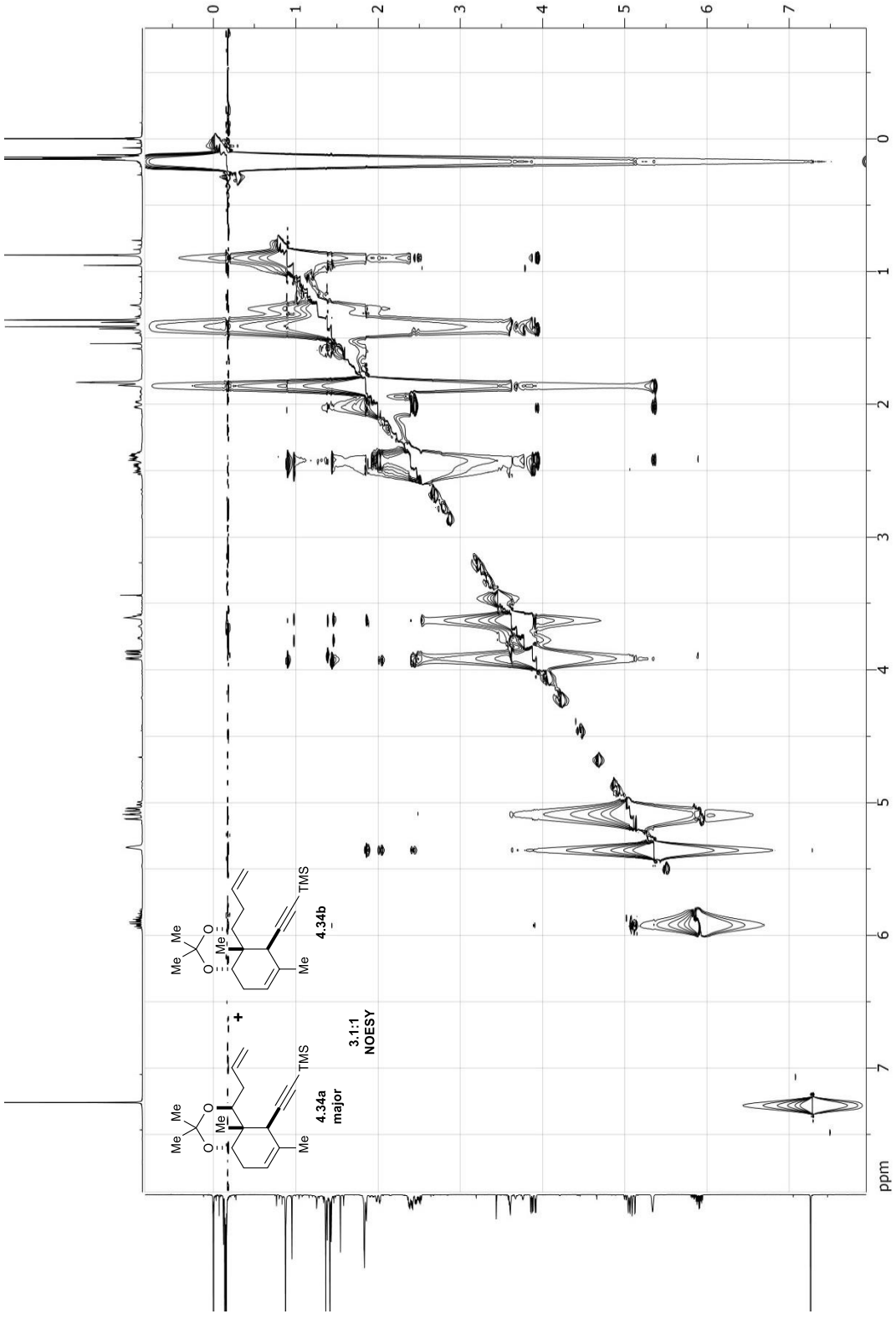
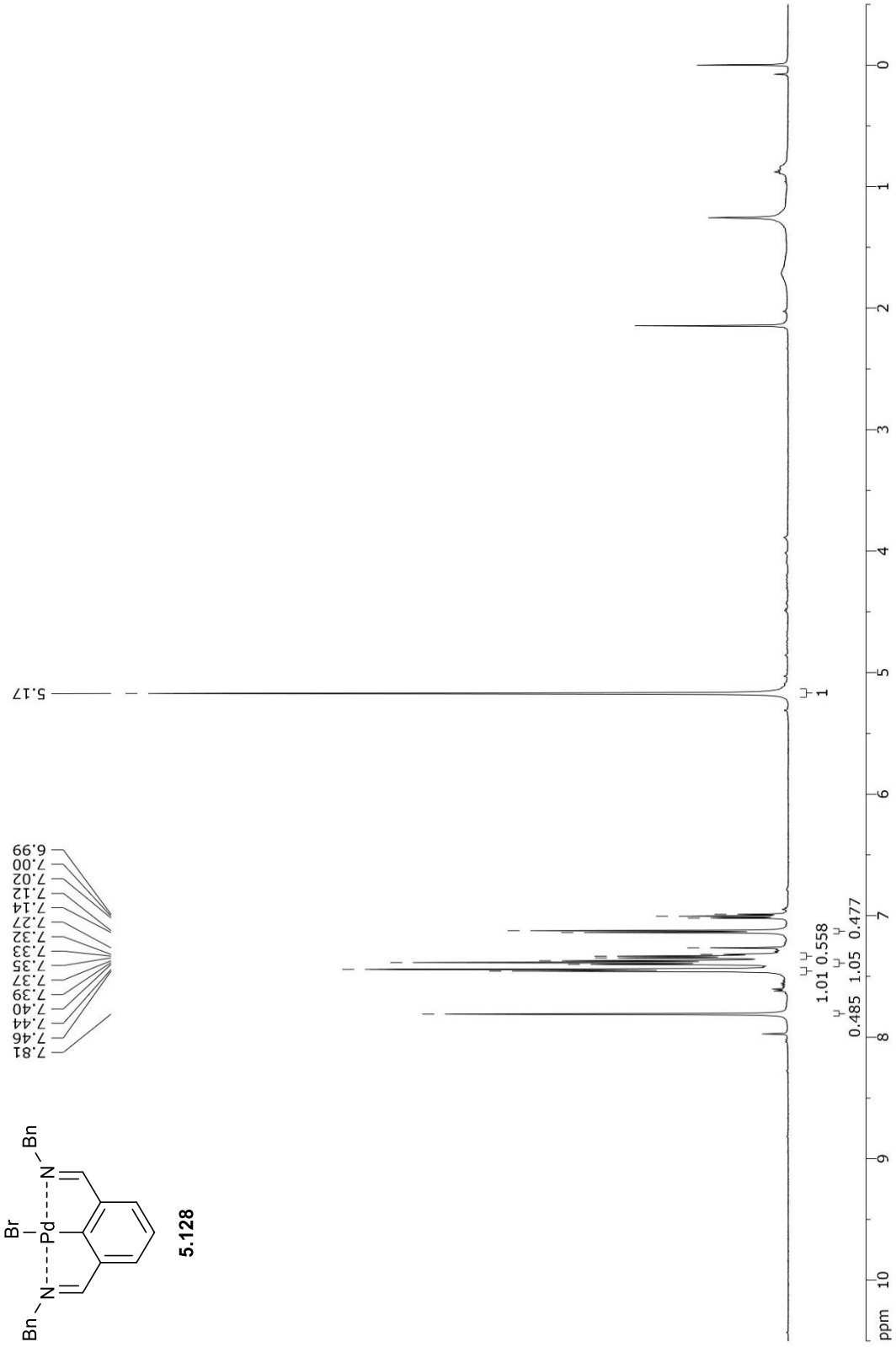
14.81
22.61
25.24
27.35
28.36
35.92
39.32
40.57
67.24
78.25
88.35
100.13
106.09
116.16
117.62
130.54
136.76
ppm
0
50
100
150
200
Me
Me
Me
O
O
Me
Me
TMS
4.34b
+
3.1:1
4.34a
major


0
1
2
3
4
5
6
7
ppm
TMS
Me
Me
Me
Me
Me
O
O
4.34b
+
3.1:1
NOESY
4.34a
major

Chapter 5 Spectra


5.128
Br
Pd
N
Bn
7.81
7.46
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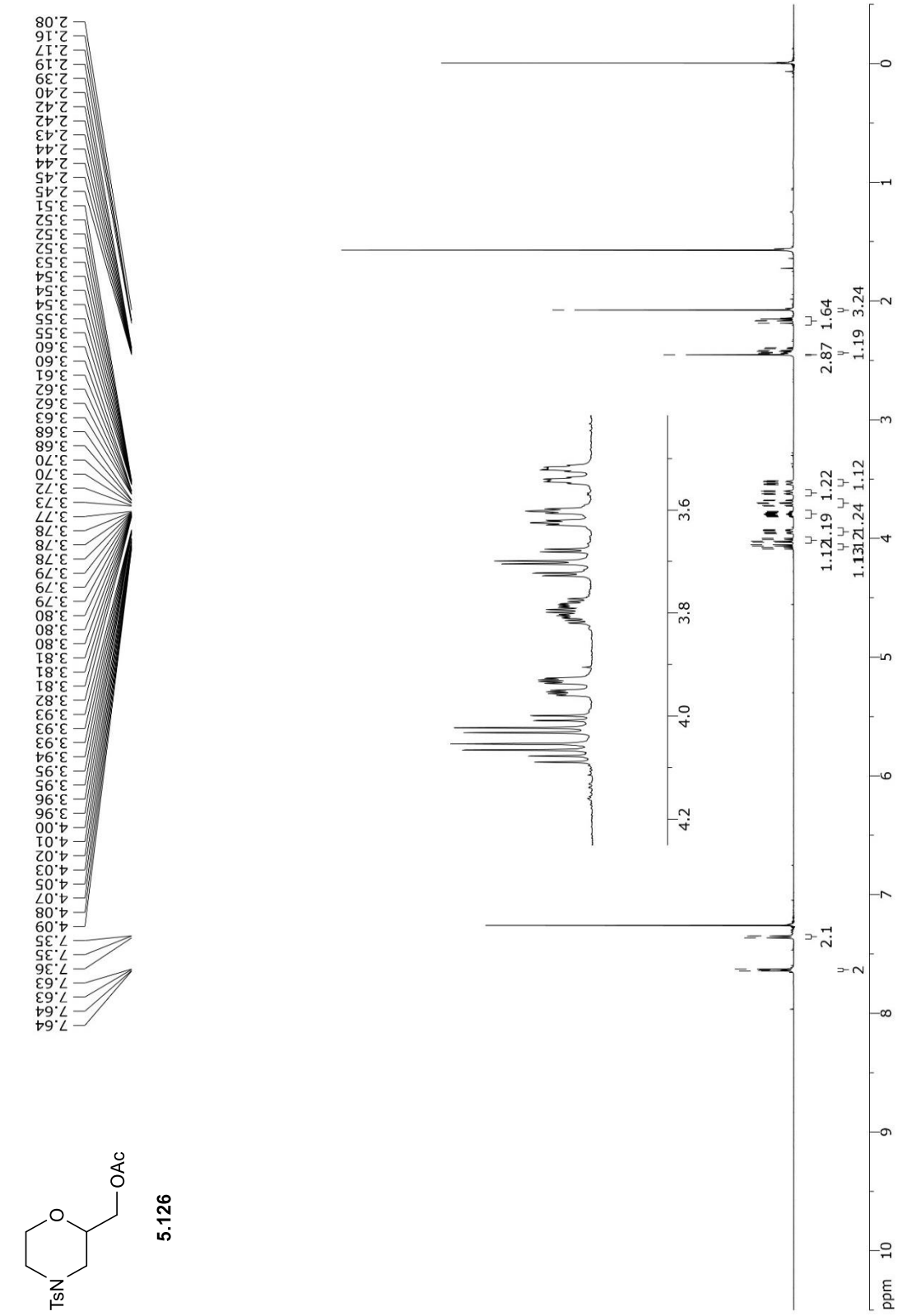
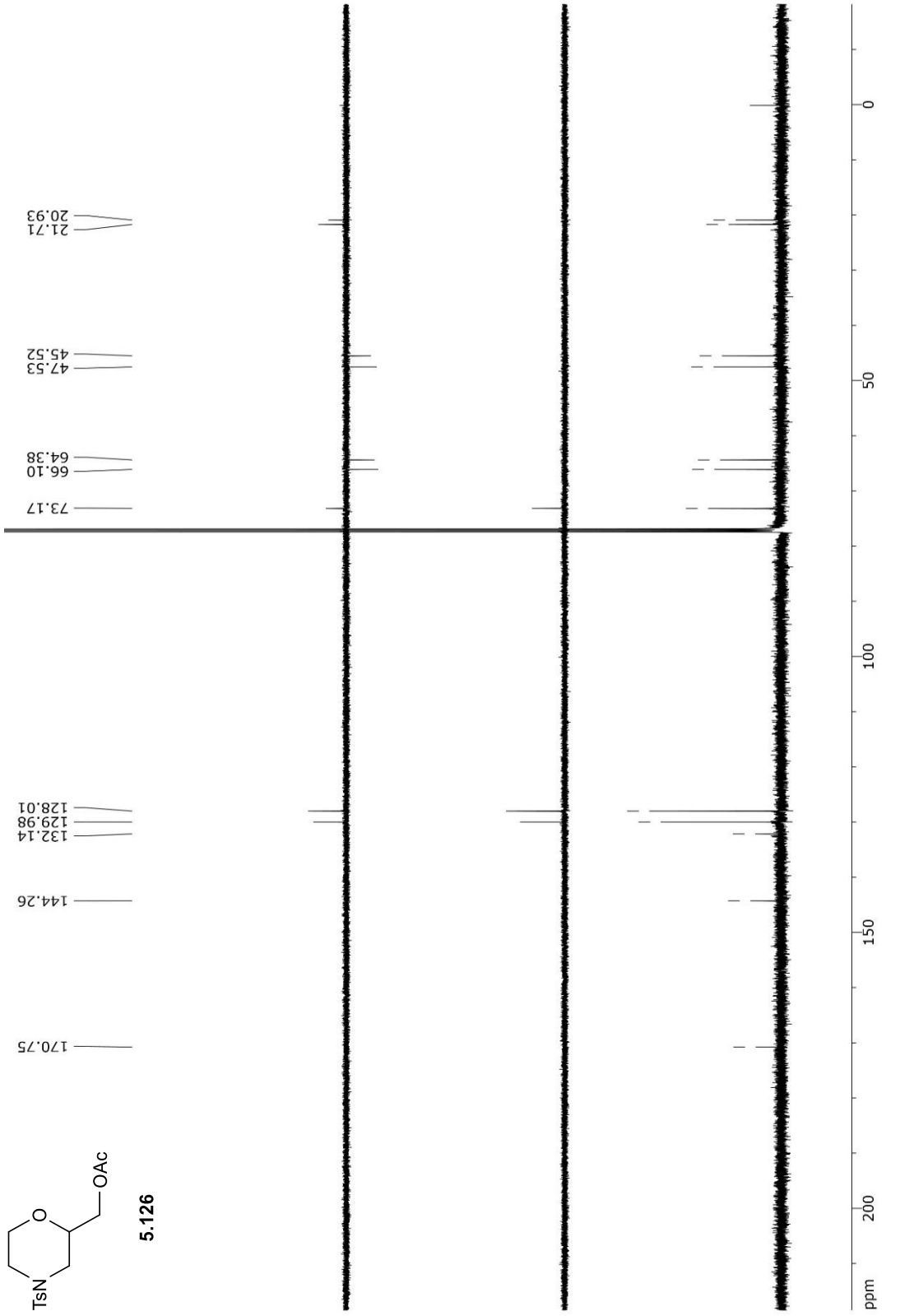
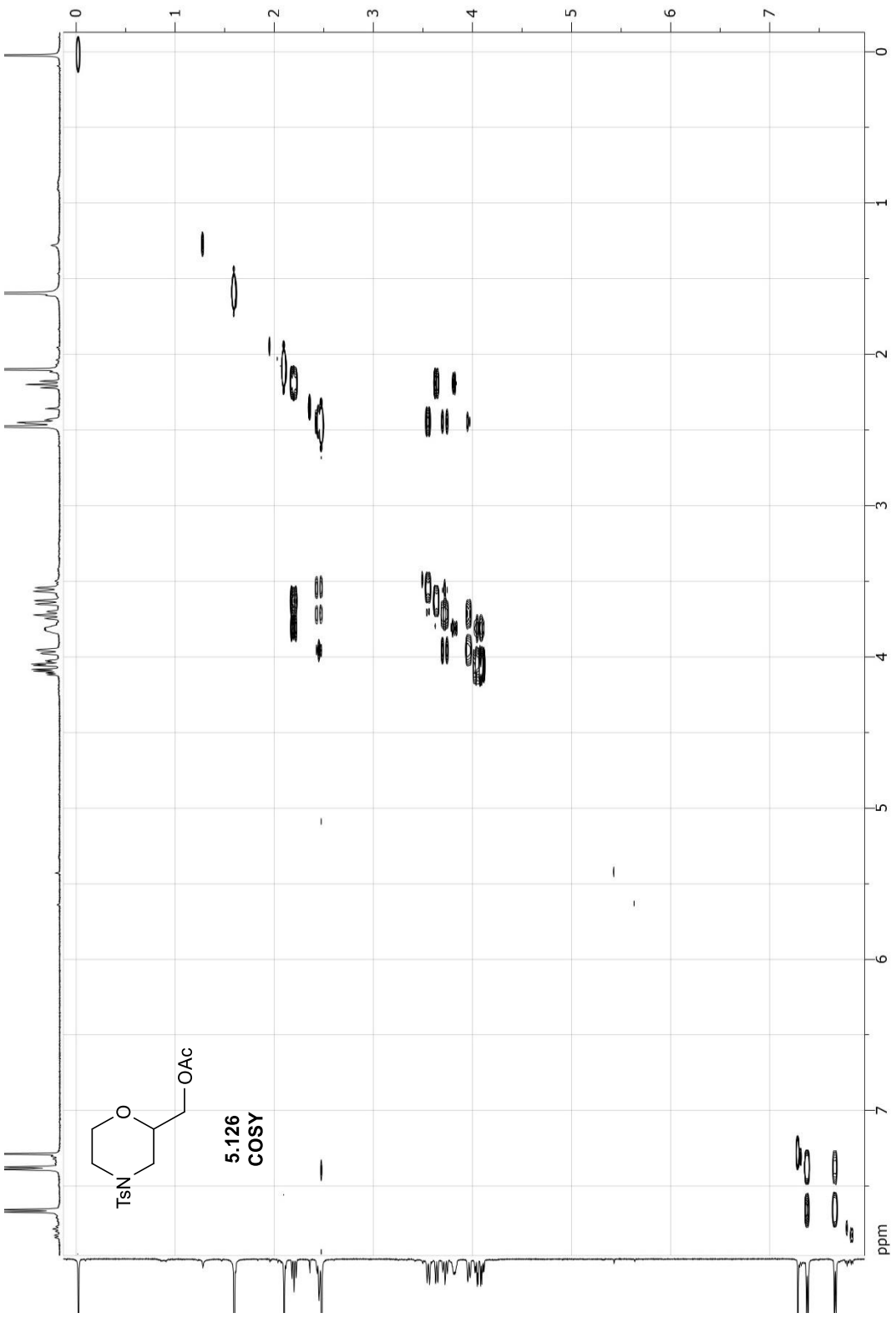
7.39
7.37
7.35
7.33
7.32
7.27
7.14
7.12
7.02
7.00
6.99
5.17
1
1.01
0.558
0.485
1.05
0.477
ppm


TsN
O
OAc
5.126
ppm


170.75
144.26
132.14
129.98
128.01
73.17
66.10
64.38
47.53
45.52
21.71
20.93
TsN
O
OAc
5.126
ppm
0
50
100
150
200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O
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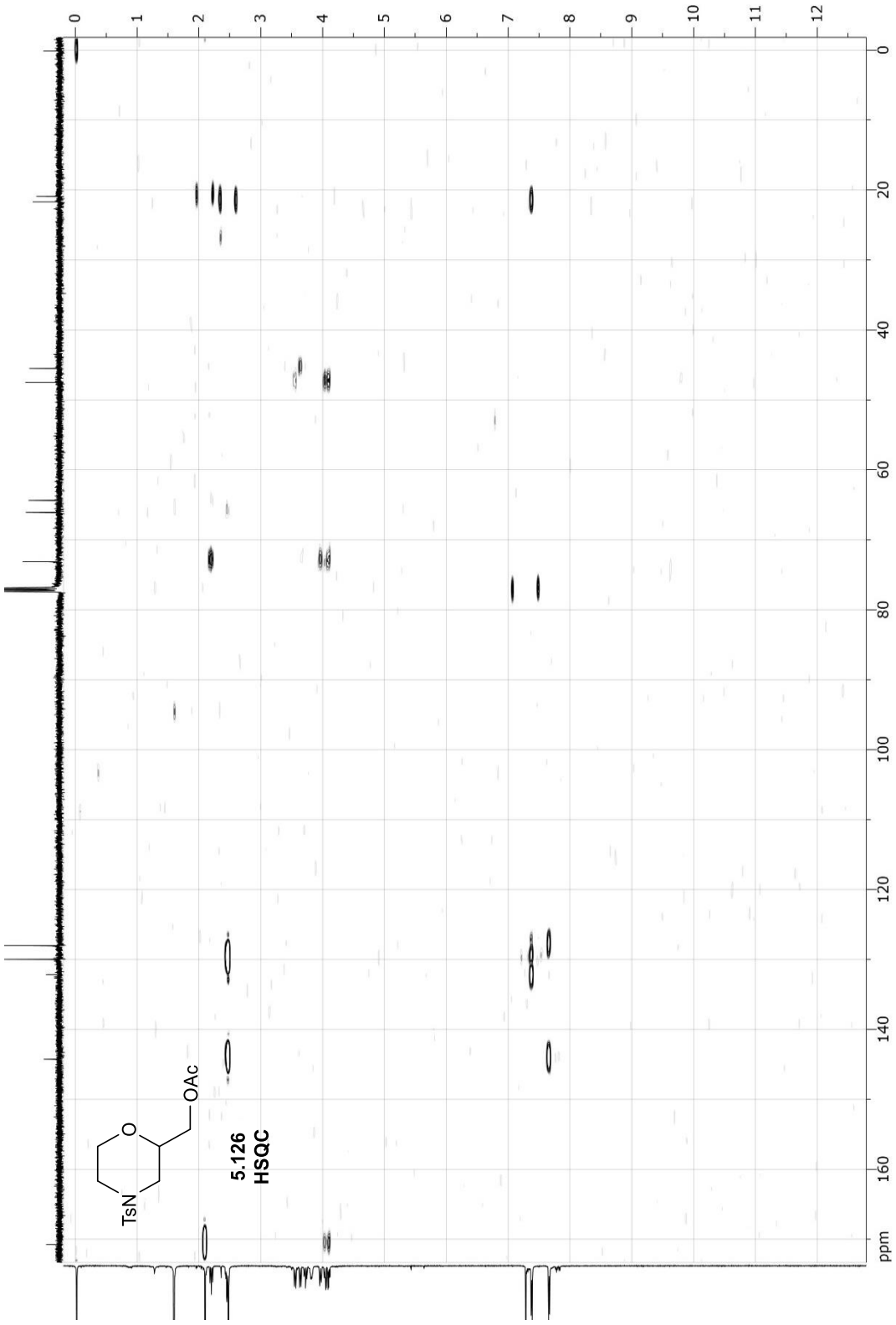
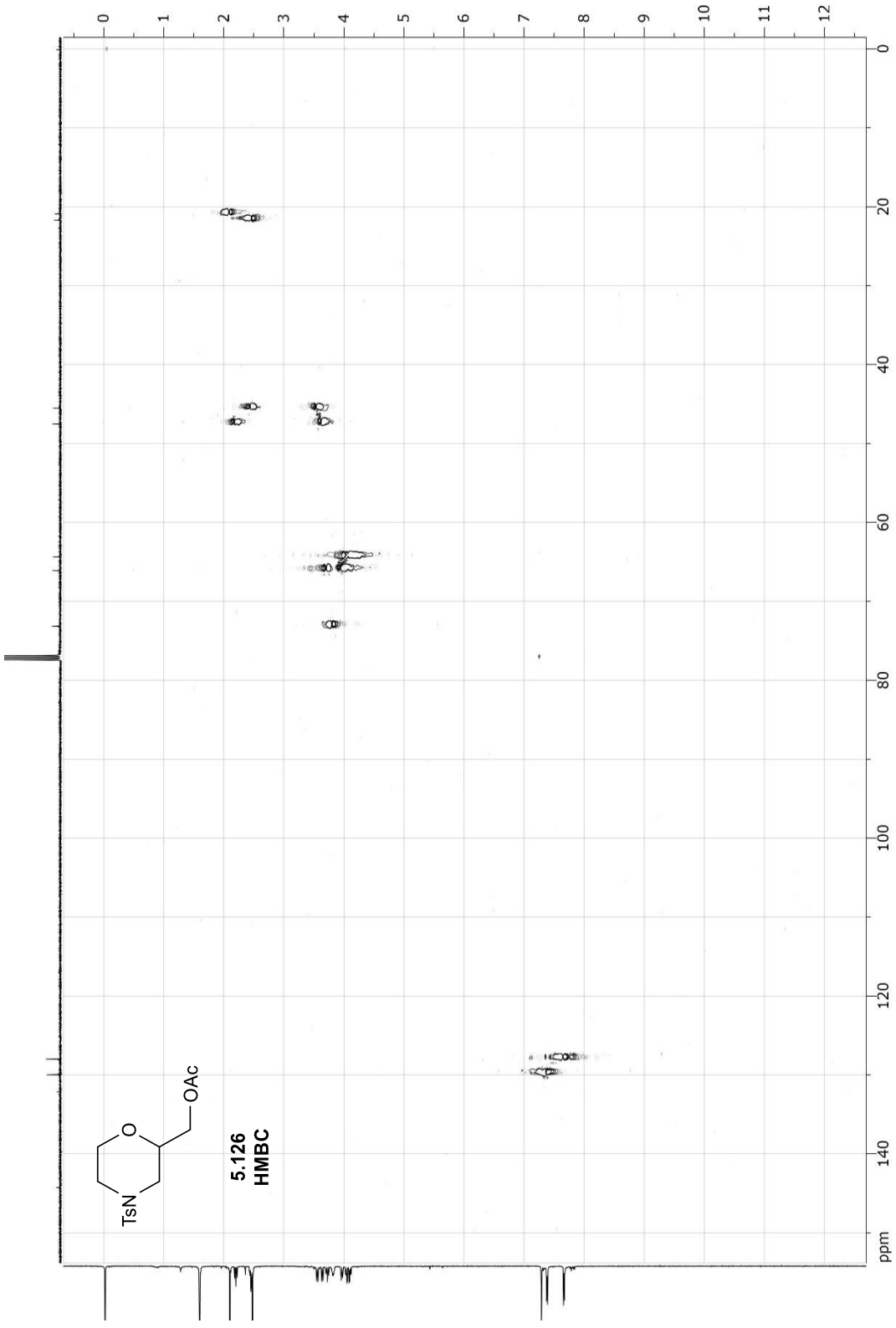
COSY
ppm


5.126
HSQC
OAc
O
TsN
ppm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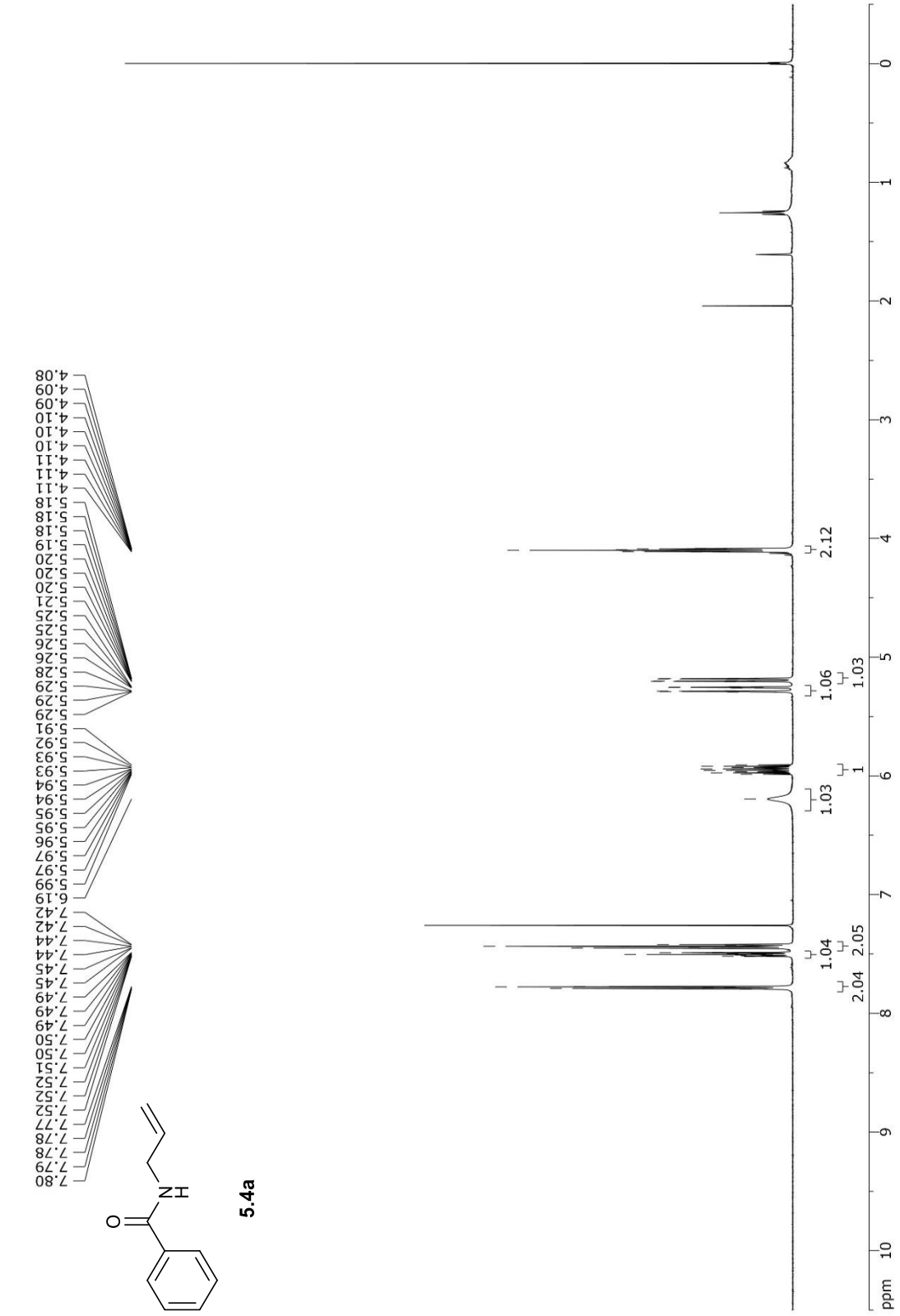
1
2
3
4
5
6
7
8
9
10
11
12
0
20
40
60
80
100
120
140
ppm
OAc
O
TsN
5.126
HMBC


7.80
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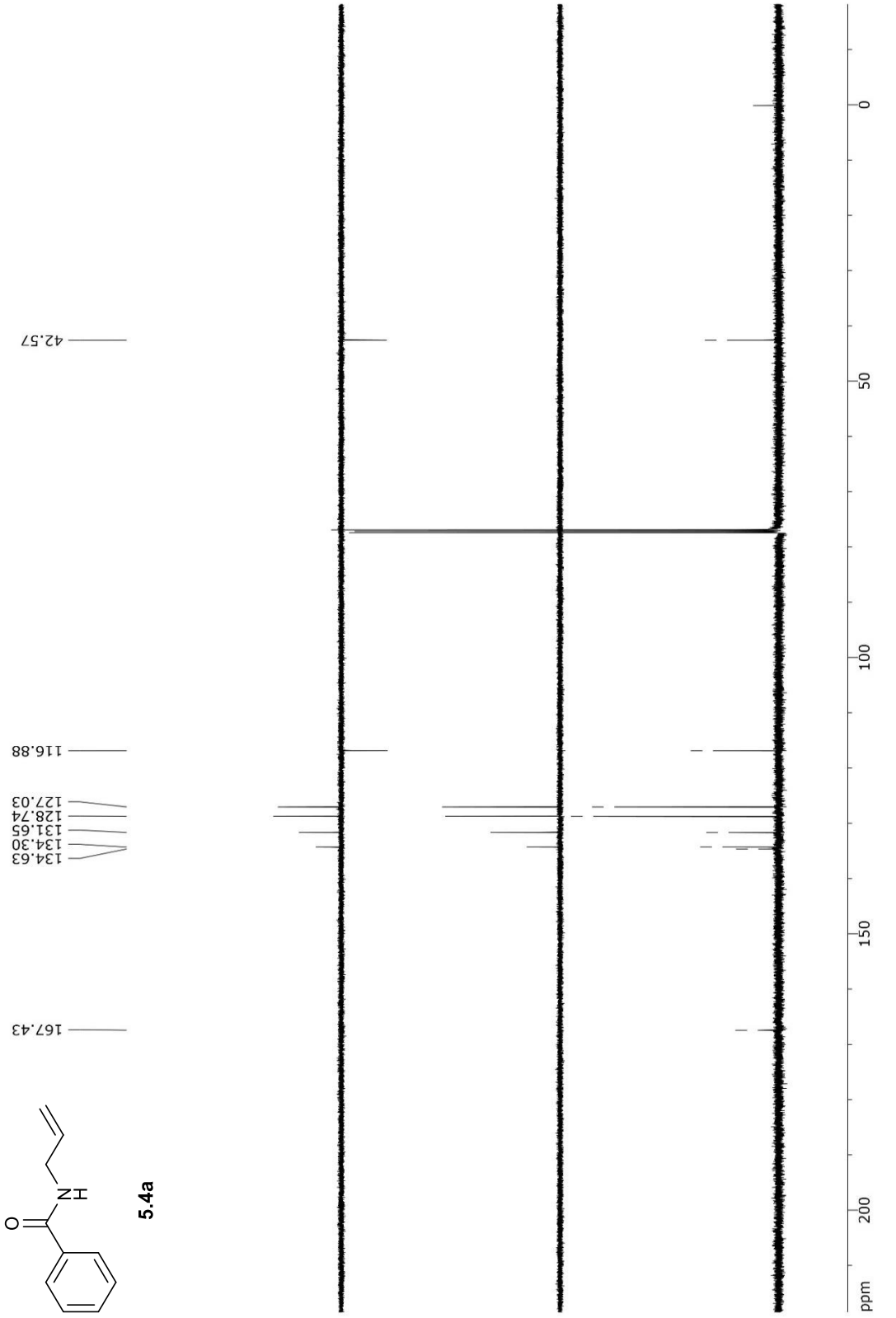
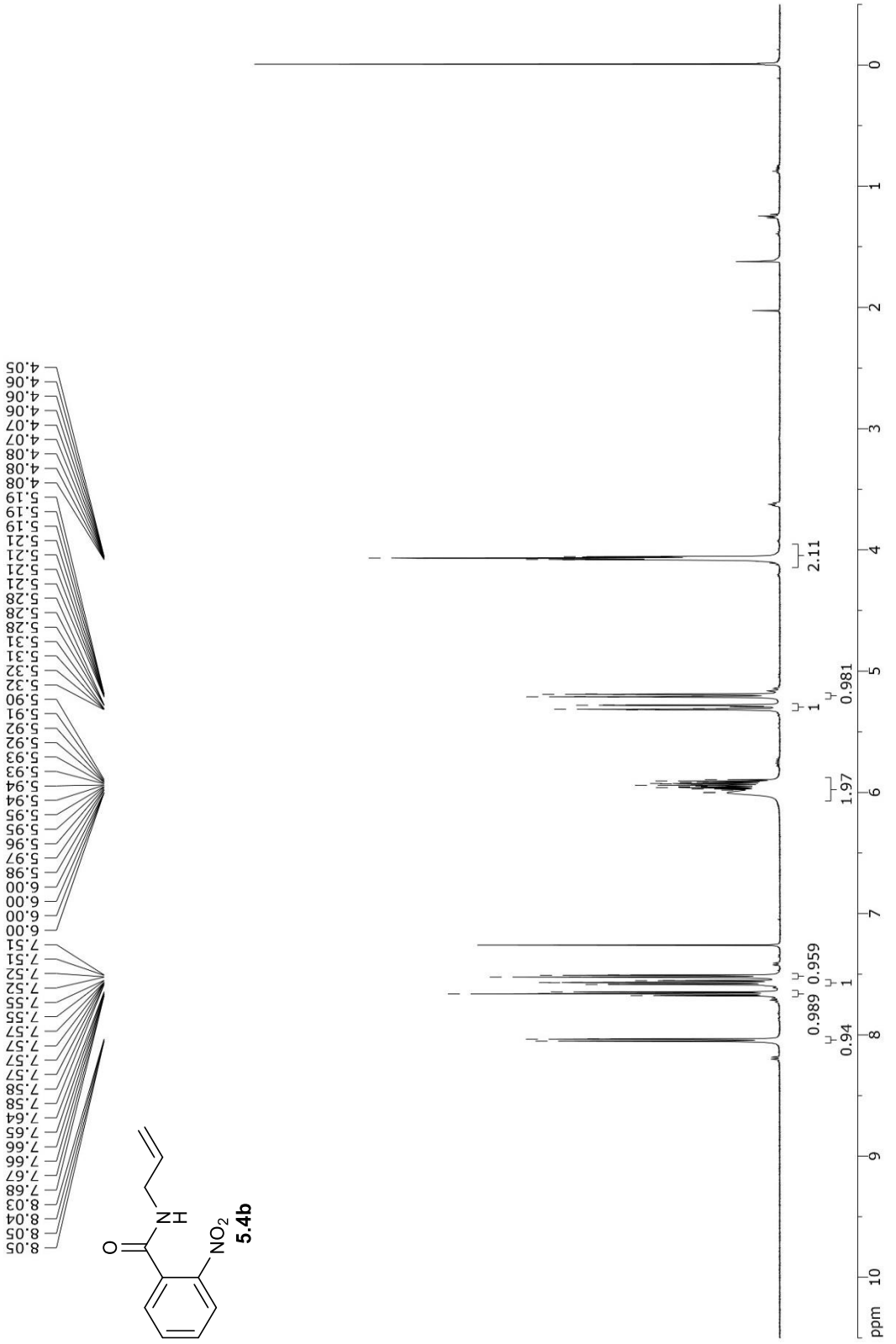
7.78
7.78
7.77
7.52
7.52
7.52
7.51
7.50
7.50
7.49
7.49
7.49
7.45
7.45
7.44
7.44
7.42
7.42
6.19
5.99
5.97
5.97
5.96
5.95
5.95
5.94
5.94
5.93
5.93
5.92
5.91
5.29
5.29
5.29
5.28
5.26
5.26
5.25
5.25
5.21
5.20
5.20
5.20
5.19
5.18
5.18
5.18
4.11
4.11
4.11
4.10
4.10
4.10
4.09
4.09
4.08
O
N
H
5.4a
2.12
1.06
1.03
1.03
1
1.04
2.05
2.04
ppm


42.57
116.88
127.03
128.74
131.65
134.30
134.63
167.43
5.4a
0
50
100
150
200
ppm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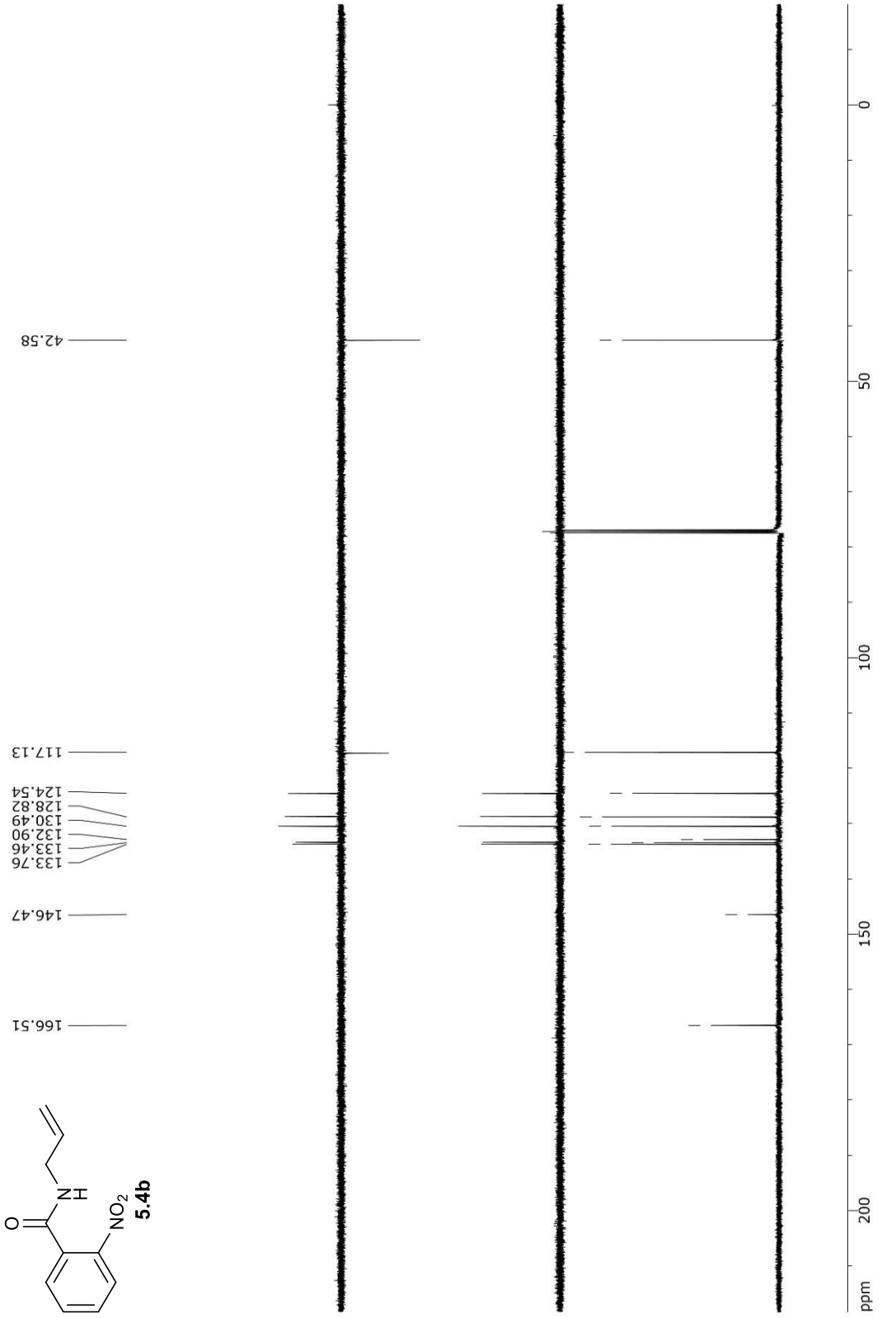
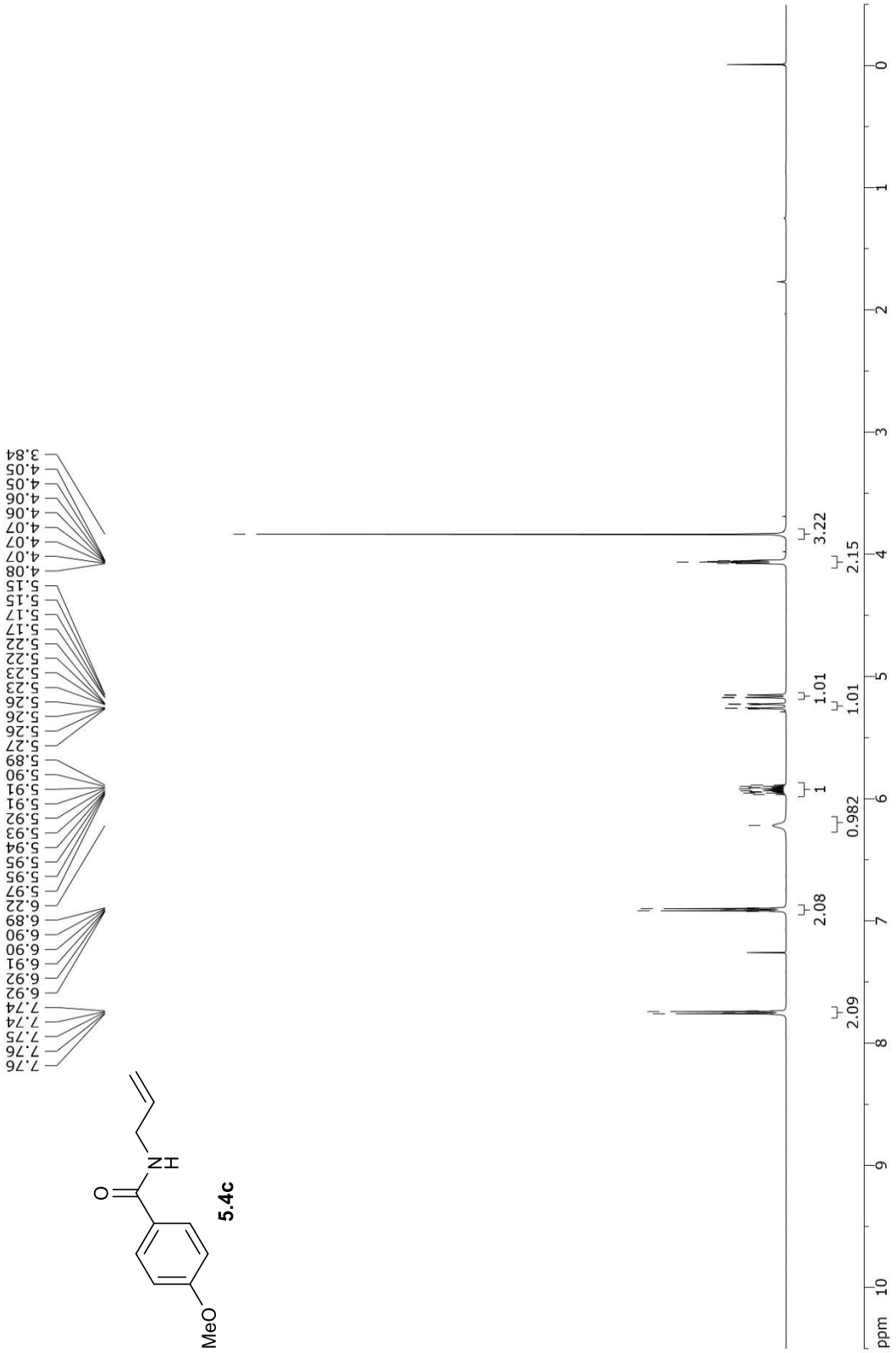
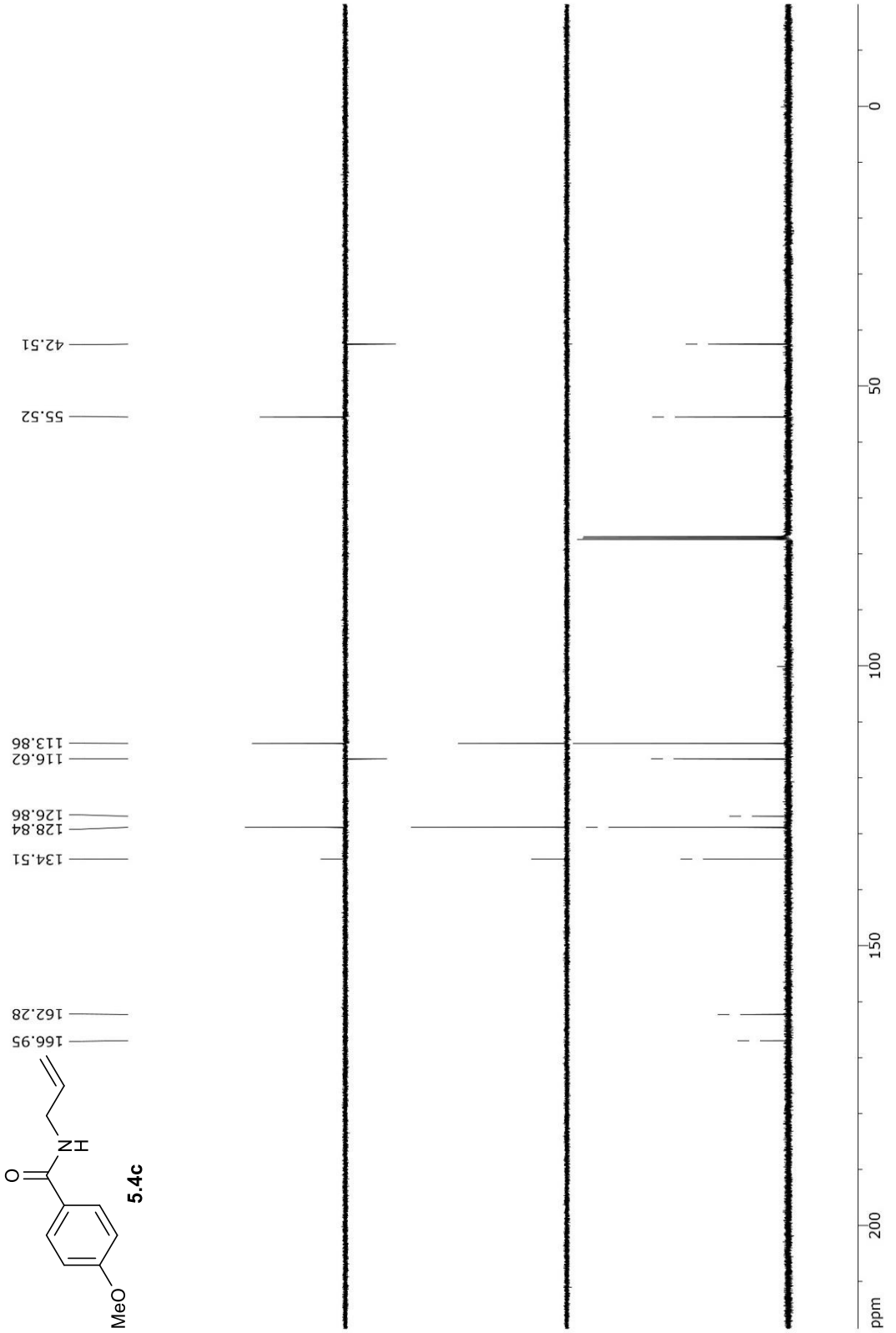
8.04
8.03
7.68
7.67
7.66
7.66
7.65
7.64
7.58
7.58
7.57
7.57
7.57
7.57
7.55
7.55
7.52
7.52
7.51
7.51
6.00
6.00
6.00
5.98
5.97
5.96
5.95
5.95
5.94
5.94
5.93
5.93
5.92
5.92
5.91
5.90
5.32
5.32
5.31
5.31
5.28
5.28
5.28
5.21
5.21
5.21
5.19
5.19
5.19
4.08
4.08
4.07
4.07
4.06
4.06
4.06
4.05
O
N
H
NO2
5.4b
2.11
1
0.981
1.97
0.989
0.959
1
0.94
ppm
0
1
2
3
4
5
6
7
8
9
10


42.58
117.13
124.54
128.82
130.49
132.90
133.46
133.76
146.47
166.51
O
NH
NO2
5.4b
0
50
100
150
200
ppm


7.76
7.76
7.75
7.74
7.74
6.92
6.92
6.91
6.90
6.90
6.89
6.22
5.97
5.95
5.94
5.93
5.92
5.91
5.91
5.90
5.89
5.27
5.26
5.26
5.26
5.23
5.22
5.22
5.17
5.17
5.15
5.15
4.08
4.07
4.07
4.06
4.05
4.05
3.84
O
NH
MeO
5.4c
3.22
2.15
1.01
1.01
1
0.982
2.08
2.09
ppm


42.51
55.52
113.86
116.62
126.86
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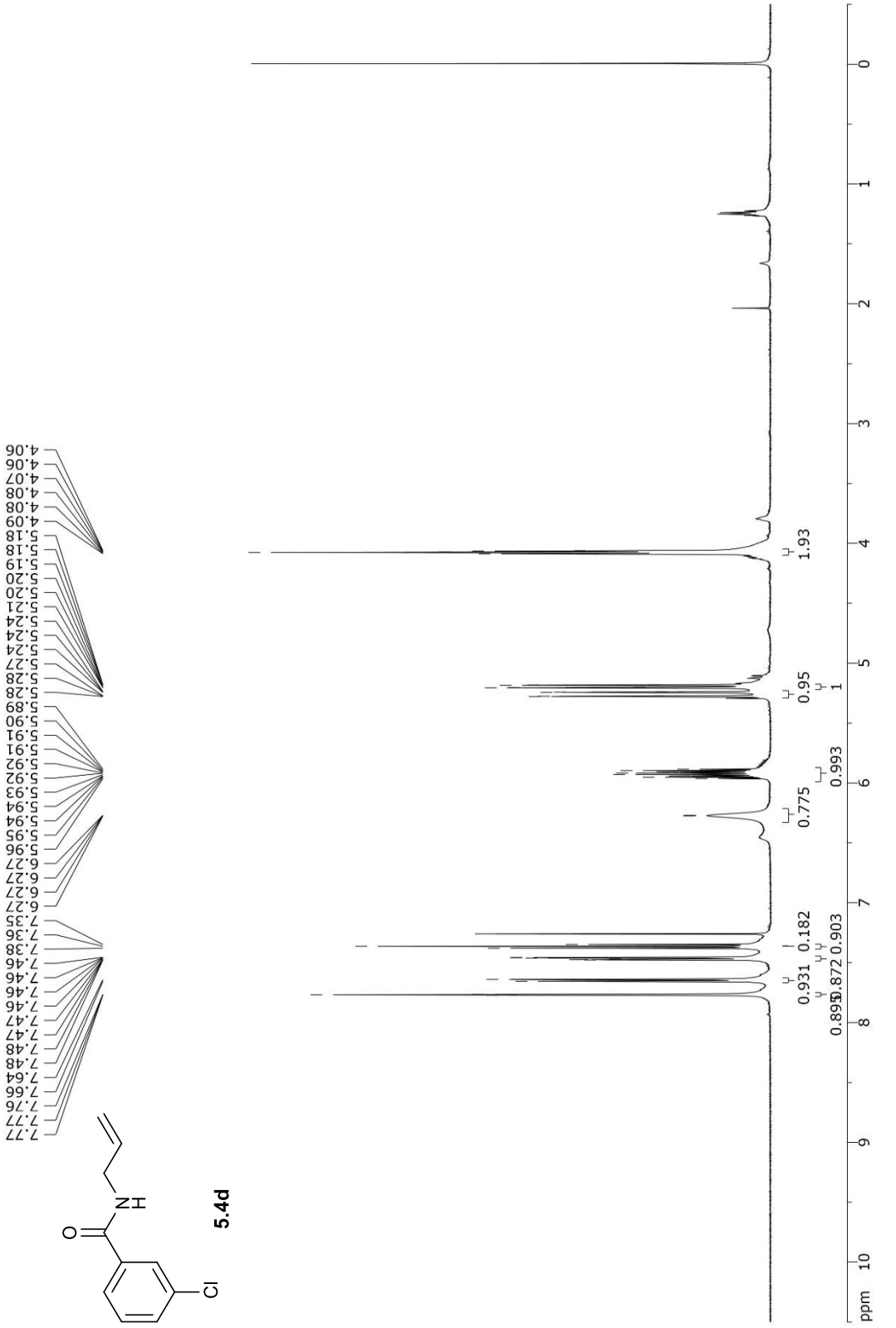
134.51
162.28
166.95
O
NH
MeO
5.4c
0
50
100
150
200
ppm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7.64
7.48
7.48
7.47
7.47
7.46
7.46
7.46
7.46
7.38
7.36
7.35
6.27
6.27
6.27
5.96
5.95
5.94
5.94
5.93
5.92
5.92
5.91
5.91
5.90
5.89
5.28
5.28
5.27
5.24
5.24
5.24
5.21
5.20
5.20
5.19
5.18
5.18
4.09
4.08
4.08
4.07
4.06
4.06
O
N
H
Cl
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0.182
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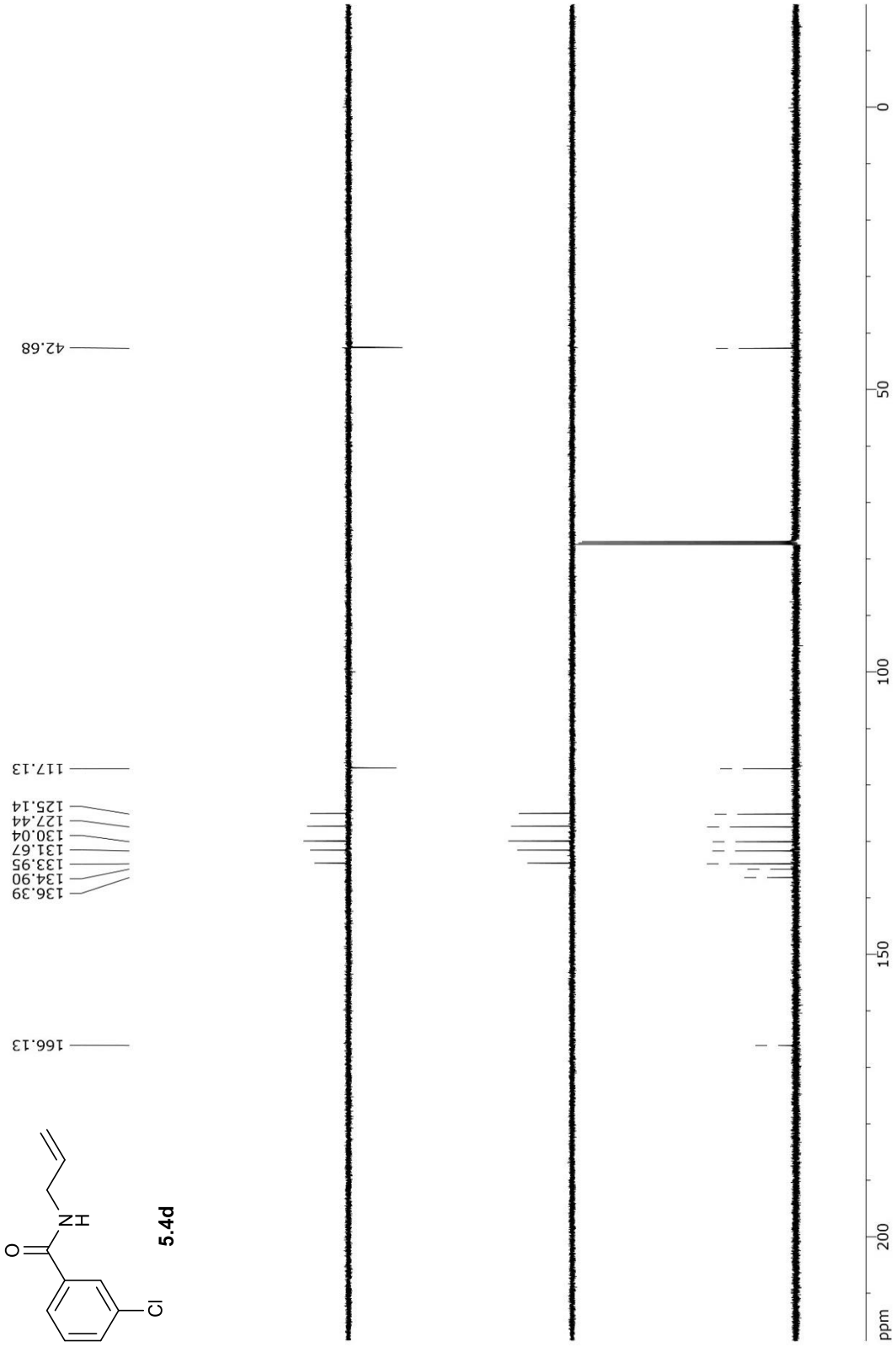
0.903
0.775
0.993
0.95
1.93
ppm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117.13
125.14
127.44
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131.67
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134.90
136.39
166.13
O
NH
Cl
5.4d
ppm
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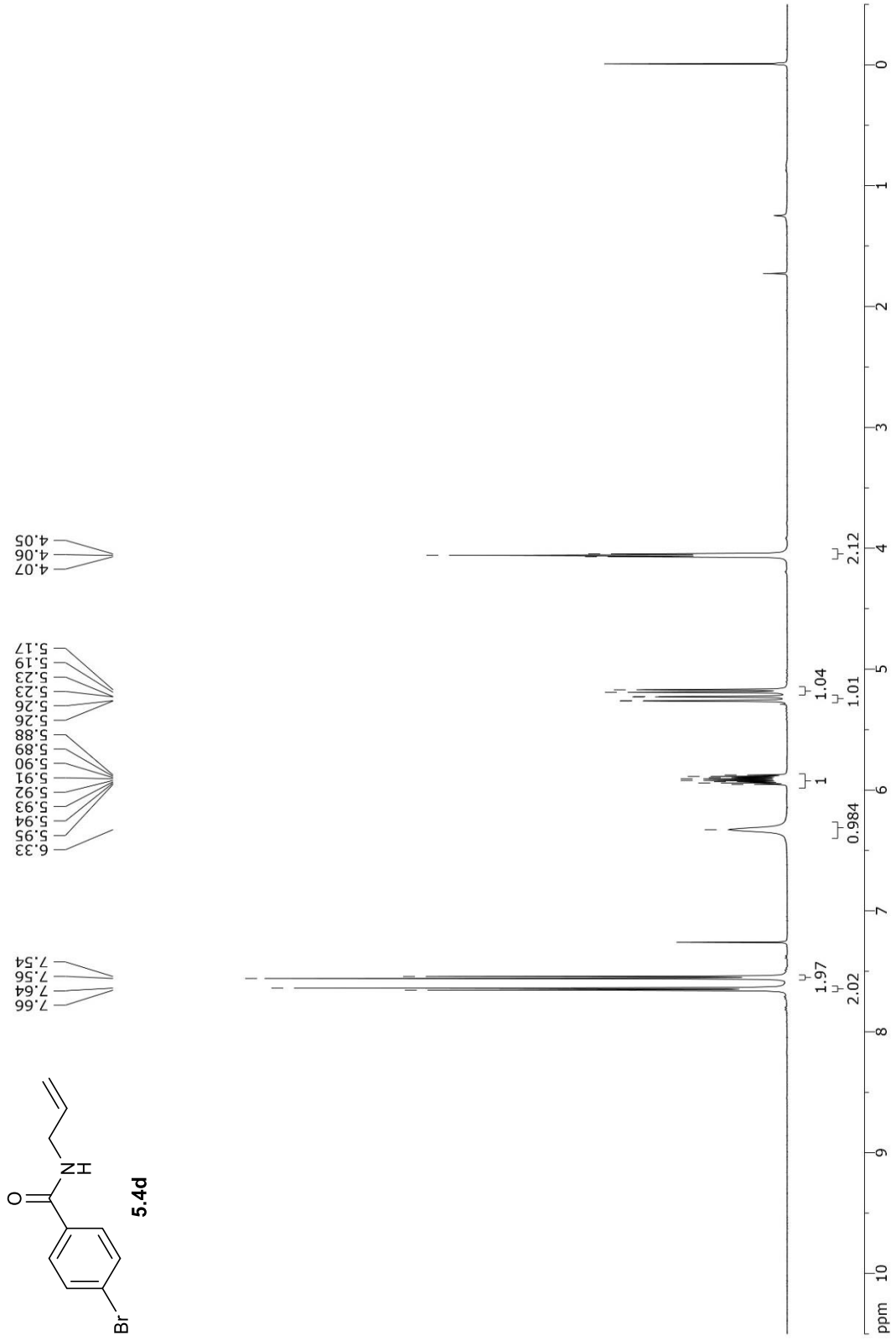
50
100
150
200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7.64
7.56
7.54
6.33
5.95
5.94
5.93
5.92
5.91
5.90
5.89
5.88
5.26
5.26
5.23
5.23
5.19
5.17
4.07
4.06
4.05
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2.02
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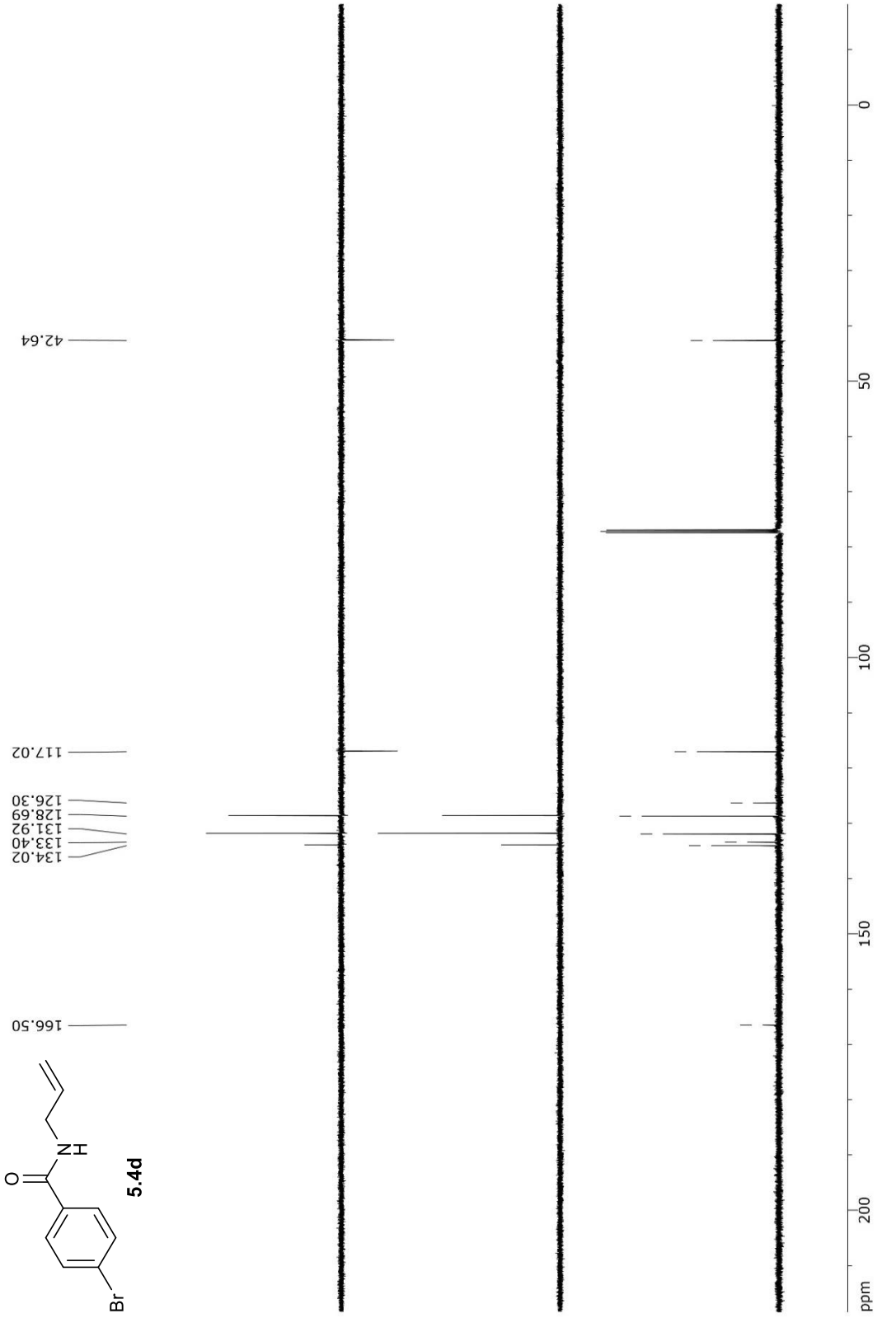
1
1.04
1.01
2.12
ppm
O
NH
Br
5.4d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128.69
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133.40
134.02
166.50
O
NH
Br
5.4d
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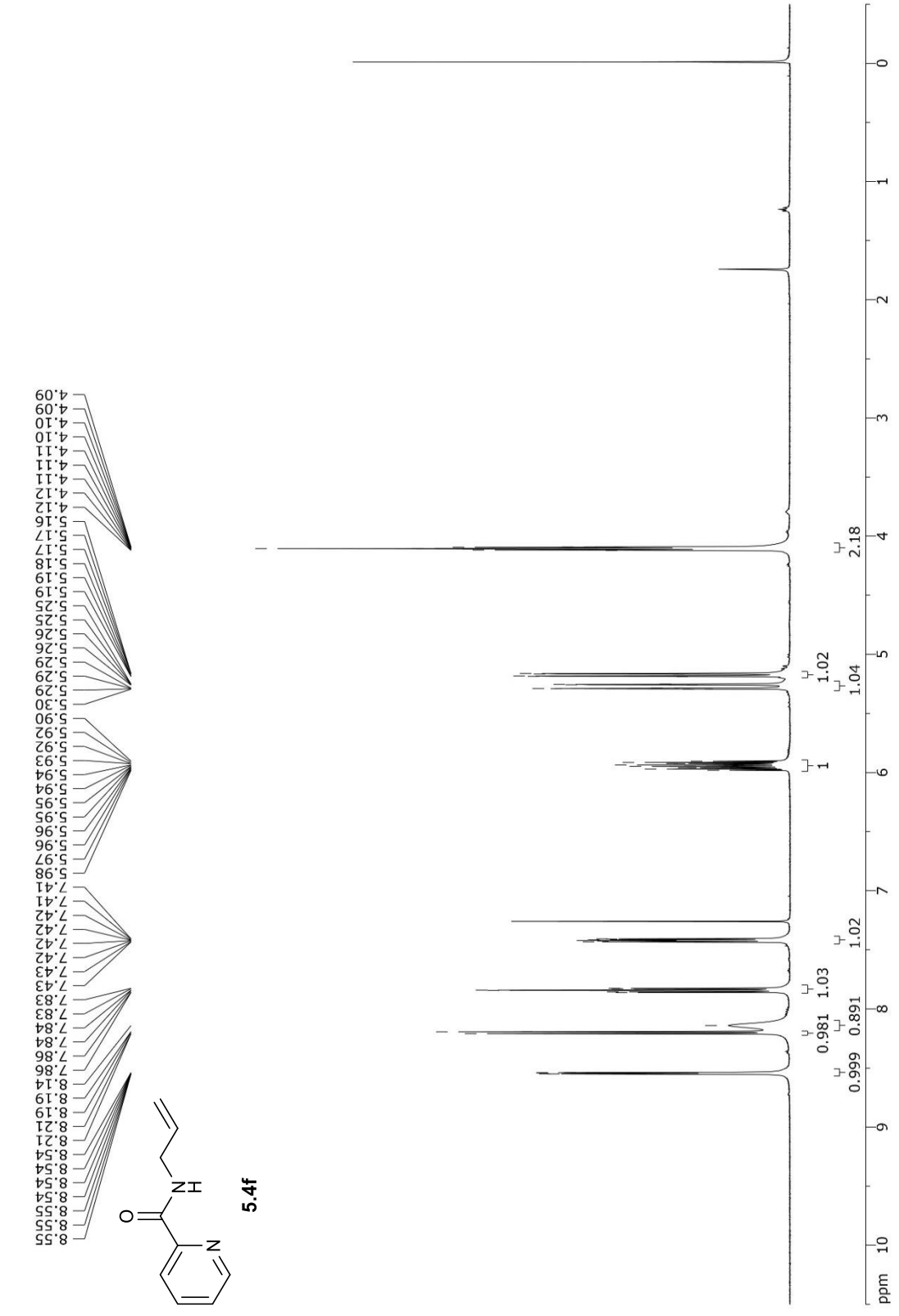
100
150
200
ppm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8.54
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8.21
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8.14
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7.84
7.84
7.83
7.83
7.43
7.42
7.42
7.42
7.42
7.41
7.41
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5.97
5.96
5.96
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5.94
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5.90
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5.25
5.25
5.19
5.19
5.18
5.17
5.17
5.16
4.12
4.12
4.11
4.11
4.11
4.10
4.10
4.09
4.09
O
N
H
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1.04
2.18
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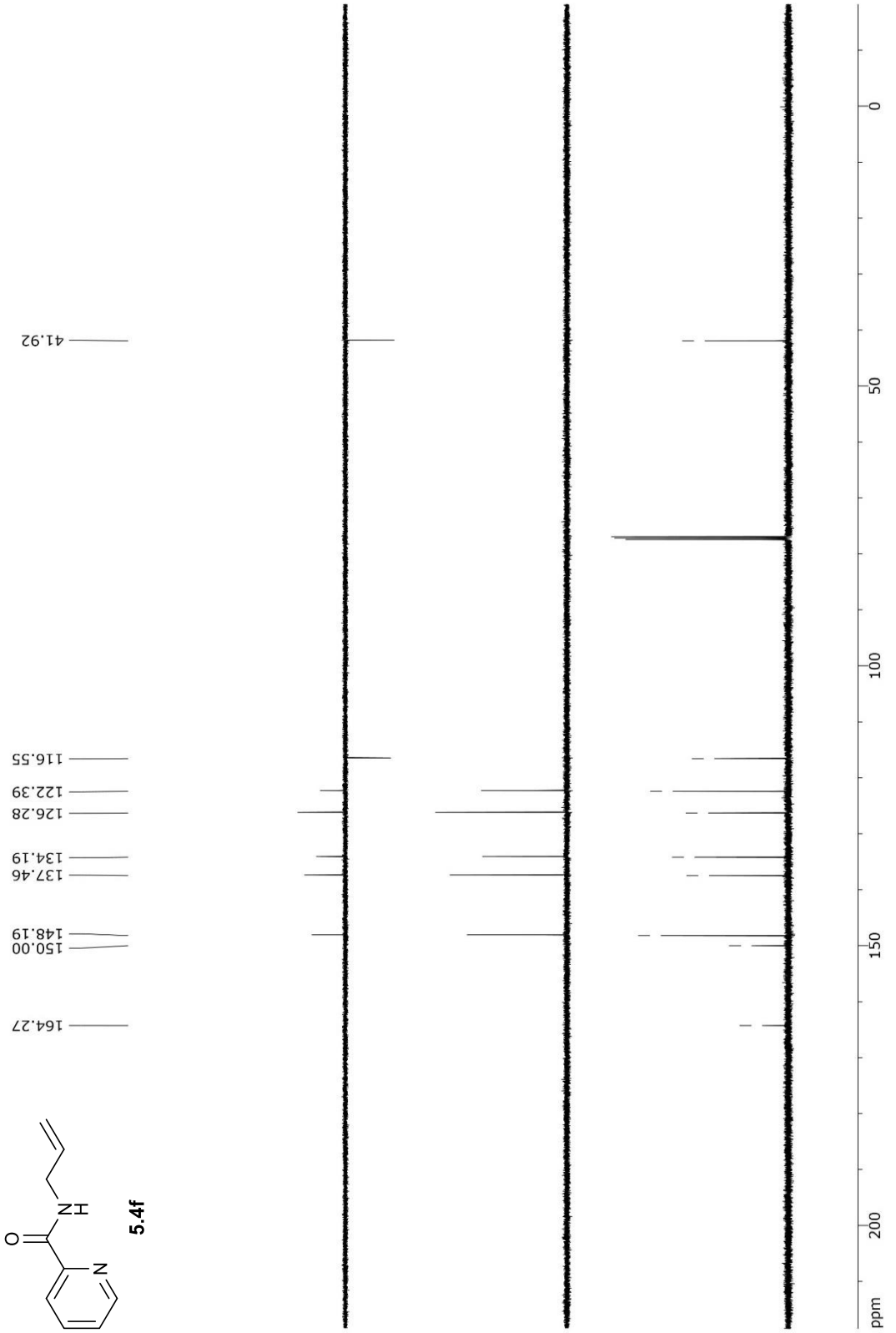
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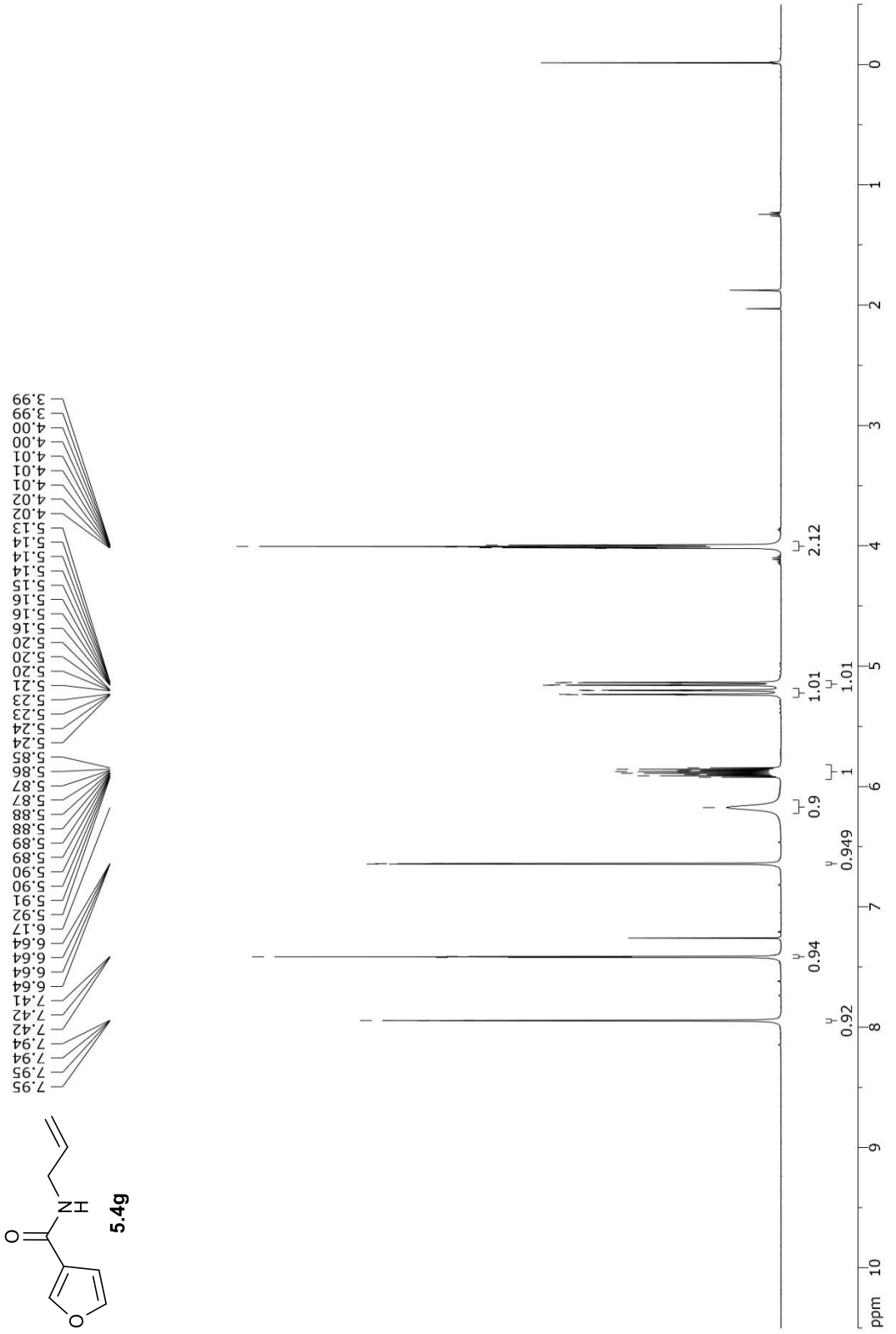
134.19
137.46
148.19
150.00
164.27
5.4f
ppm
0
50
100
150
200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7.95
7.94
7.94
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7.42
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6.64
6.64
6.64
6.17
5.92
5.91
5.90
5.90
5.89
5.89
5.88
5.88
5.87
5.87
5.86
5.85
5.24
5.24
5.23
5.23
5.21
5.20
5.20
5.20
5.16
5.16
5.16
5.15
5.14
5.14
5.14
5.13
4.02
4.02
4.01
4.01
4.01
4.00
4.00
3.99
3.99
5.4g
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N
H
O
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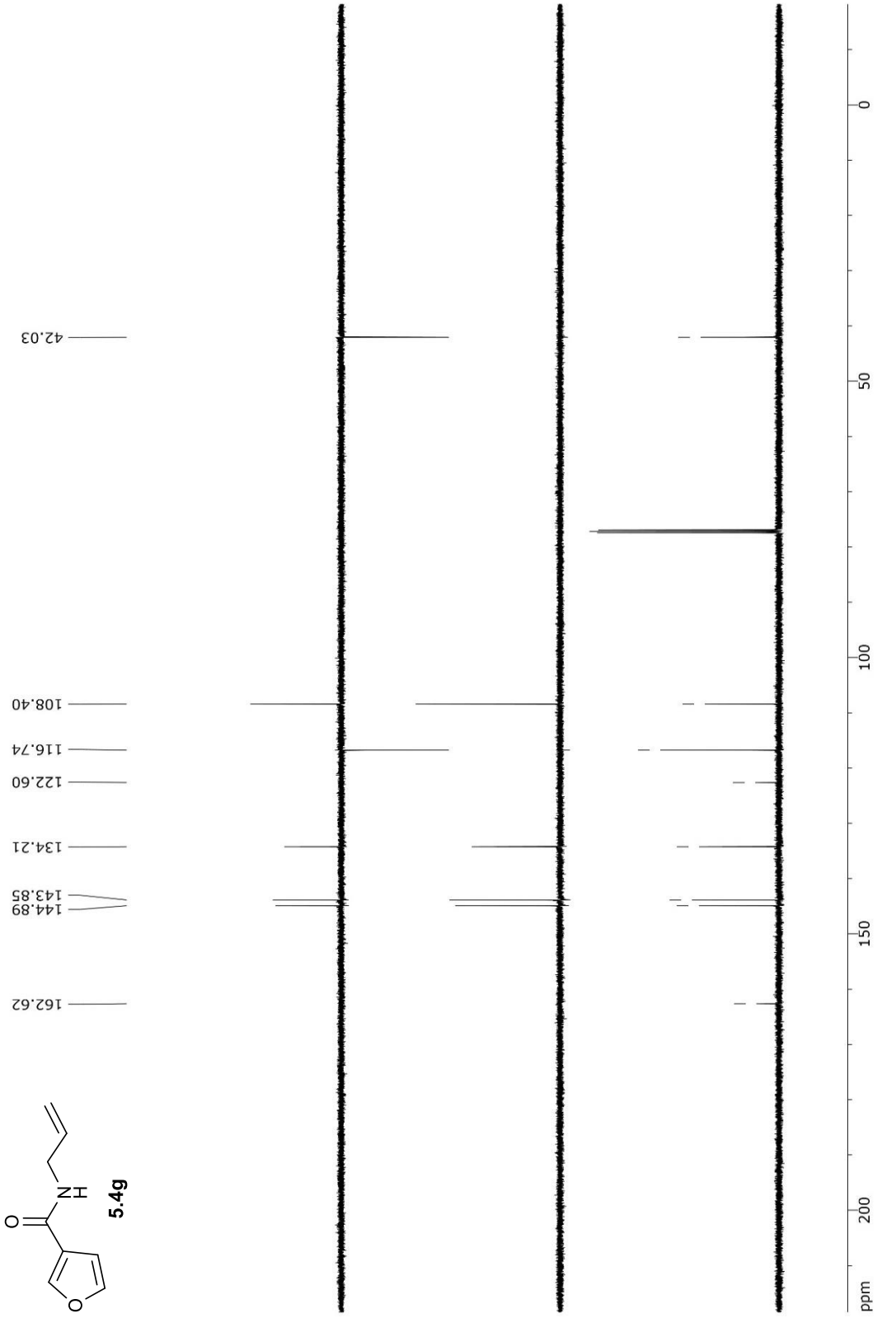
0.92
ppm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108.40
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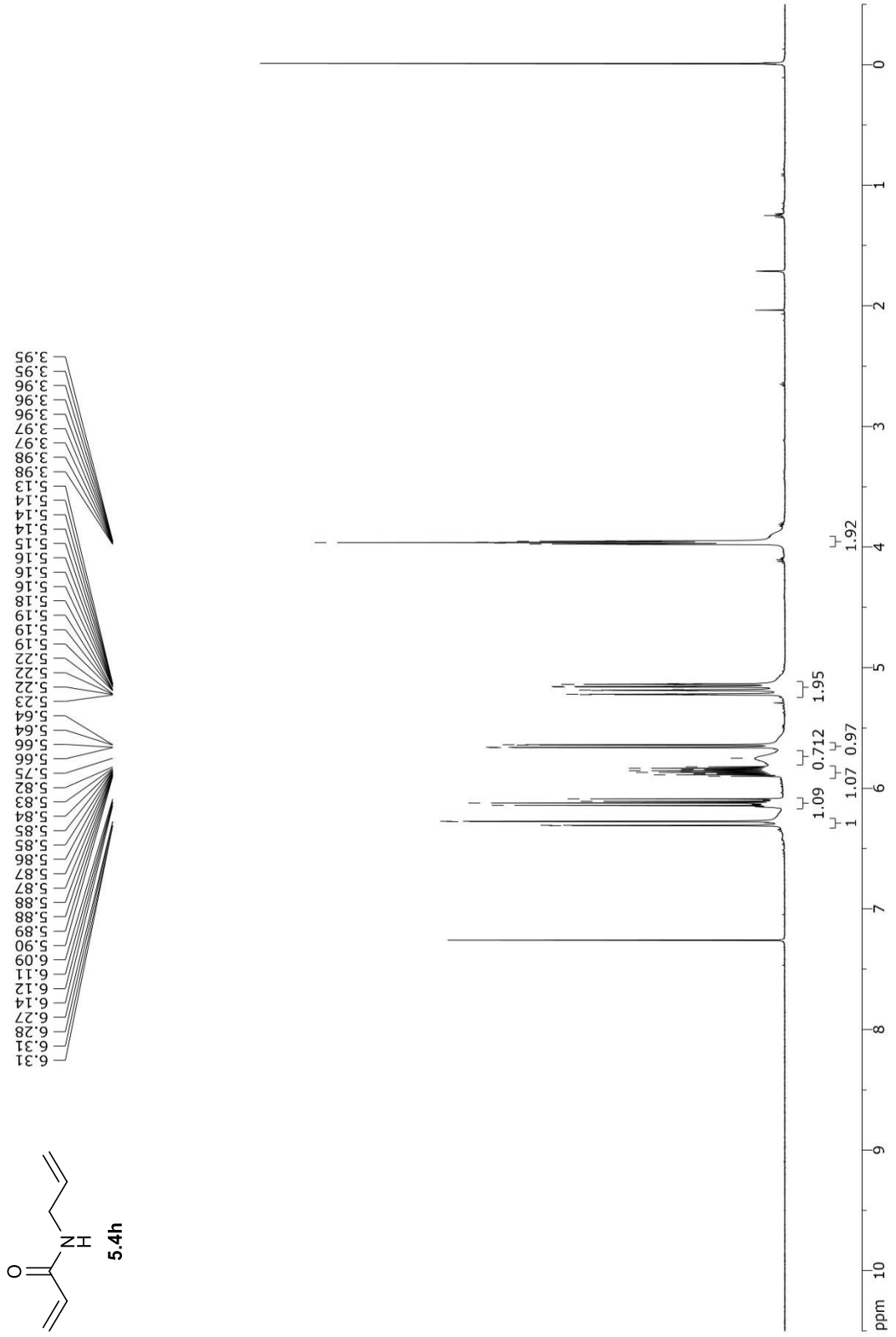
143.85
144.89
162.62
5.4g
O
NH
O
0
50
100
150
200
ppm


5.4h
6.31
6.28
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6.12
6.11
6.09
5.90
5.89
5.88
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5.87
5.87
5.86
5.85
5.85
5.84
5.83
5.82
5.75
5.66
5.66
5.64
5.64
5.23
5.22
5.22
5.22
5.19
5.19
5.19
5.18
5.16
5.16
5.16
5.15
5.14
5.14
5.14
5.13
3.98
3.98
3.97
3.97
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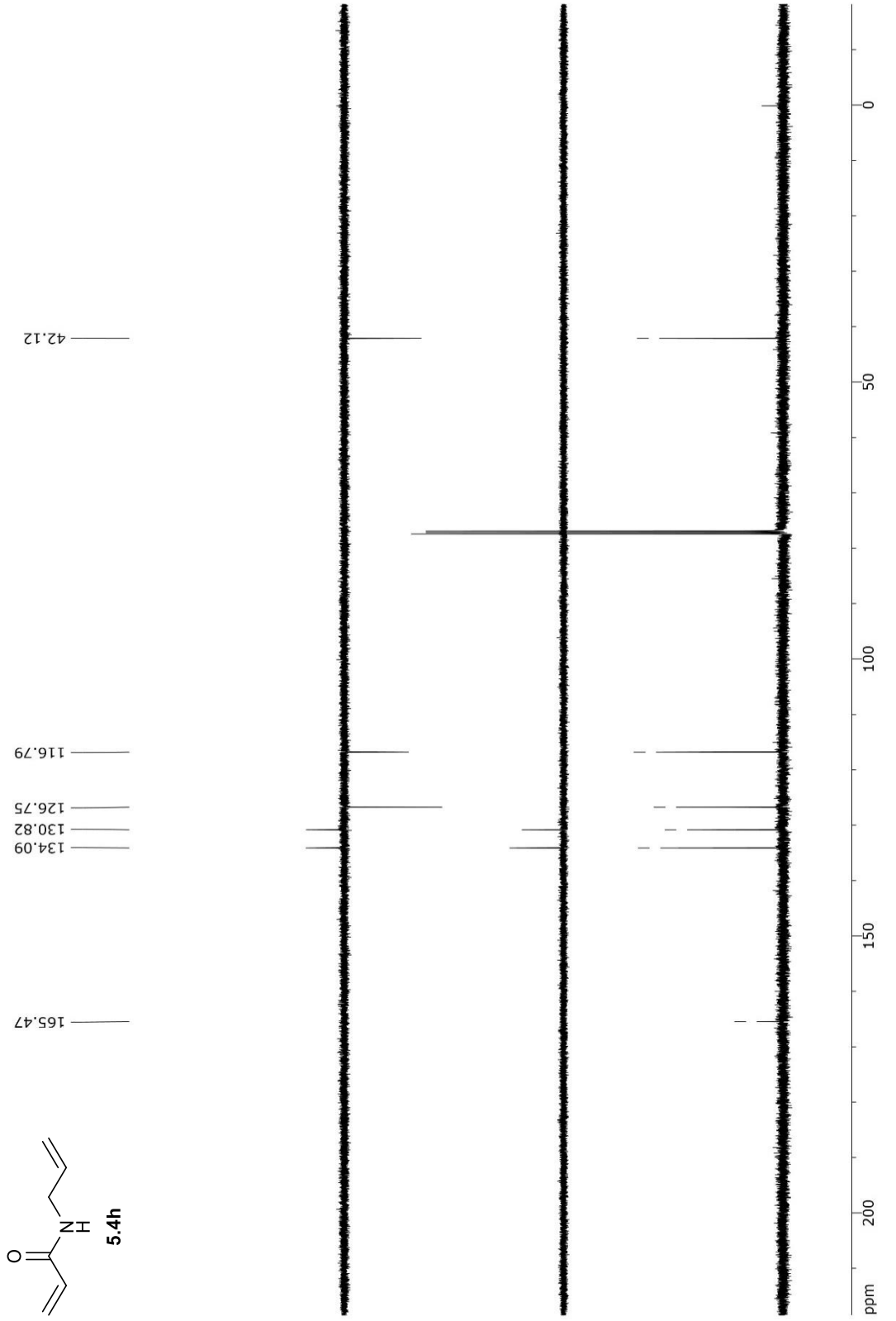
1
ppm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O
NH
0
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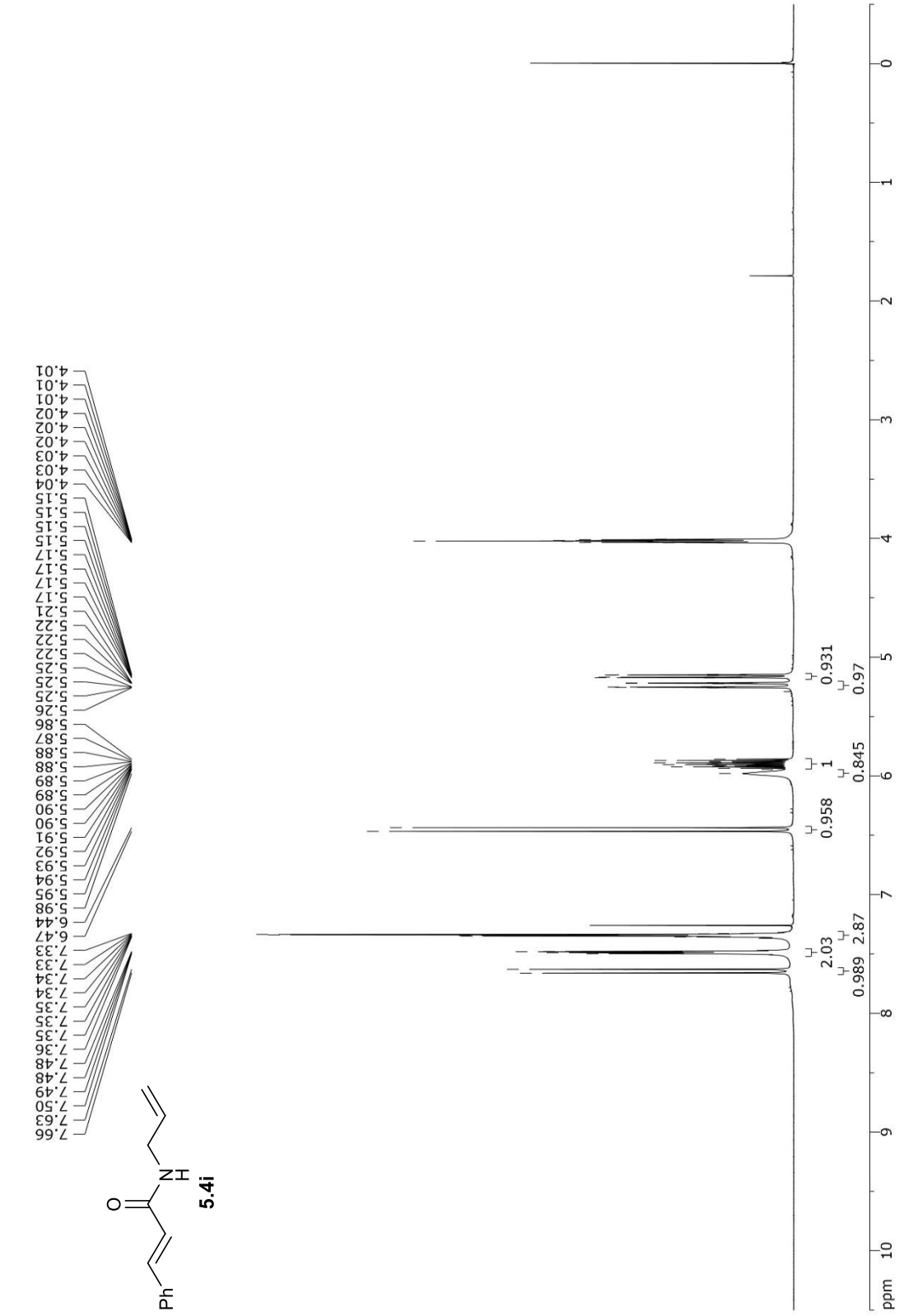
100
150
200
ppm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7.35
7.35
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7.33
6.47
6.44
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5.88
5.87
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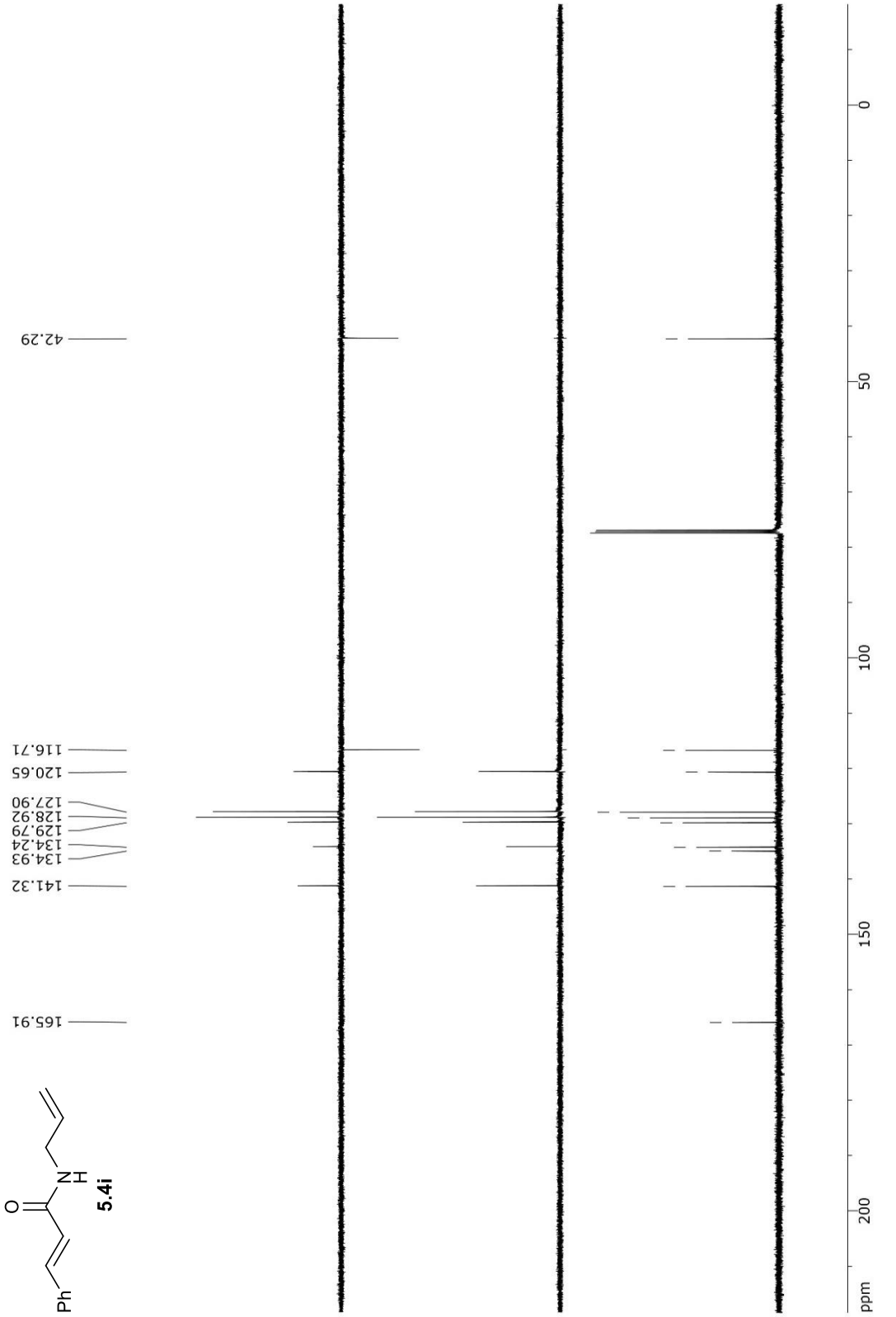
5.26
5.25
5.25
5.22
5.22
5.22
5.21
5.17
5.17
5.17
5.17
5.15
5.15
5.15
4.04
4.03
4.03
4.02
4.02
4.02
4.01
4.01
4.01
O
N
H
Ph
5.4i
2.03
0.989
2.87
0.958
1
0.845
0.931
0.97
ppm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O
NH
Ph
5.4i
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100
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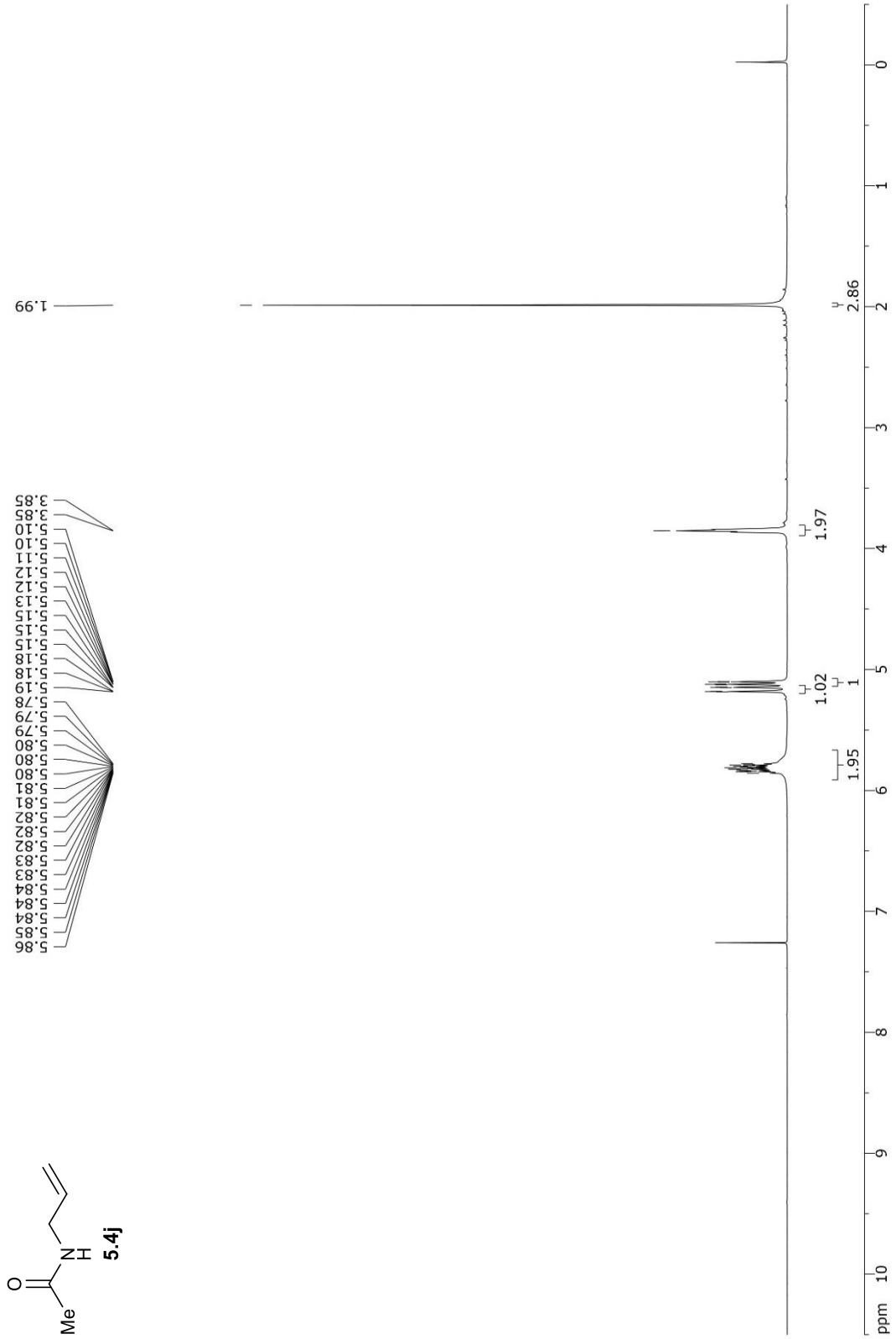
200
ppm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5.83
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5.82
5.82
5.81
5.81
5.80
5.80
5.80
5.79
5.79
5.78
5.19
5.18
5.18
5.15
5.15
5.15
5.13
5.12
5.12
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3.85
2.86
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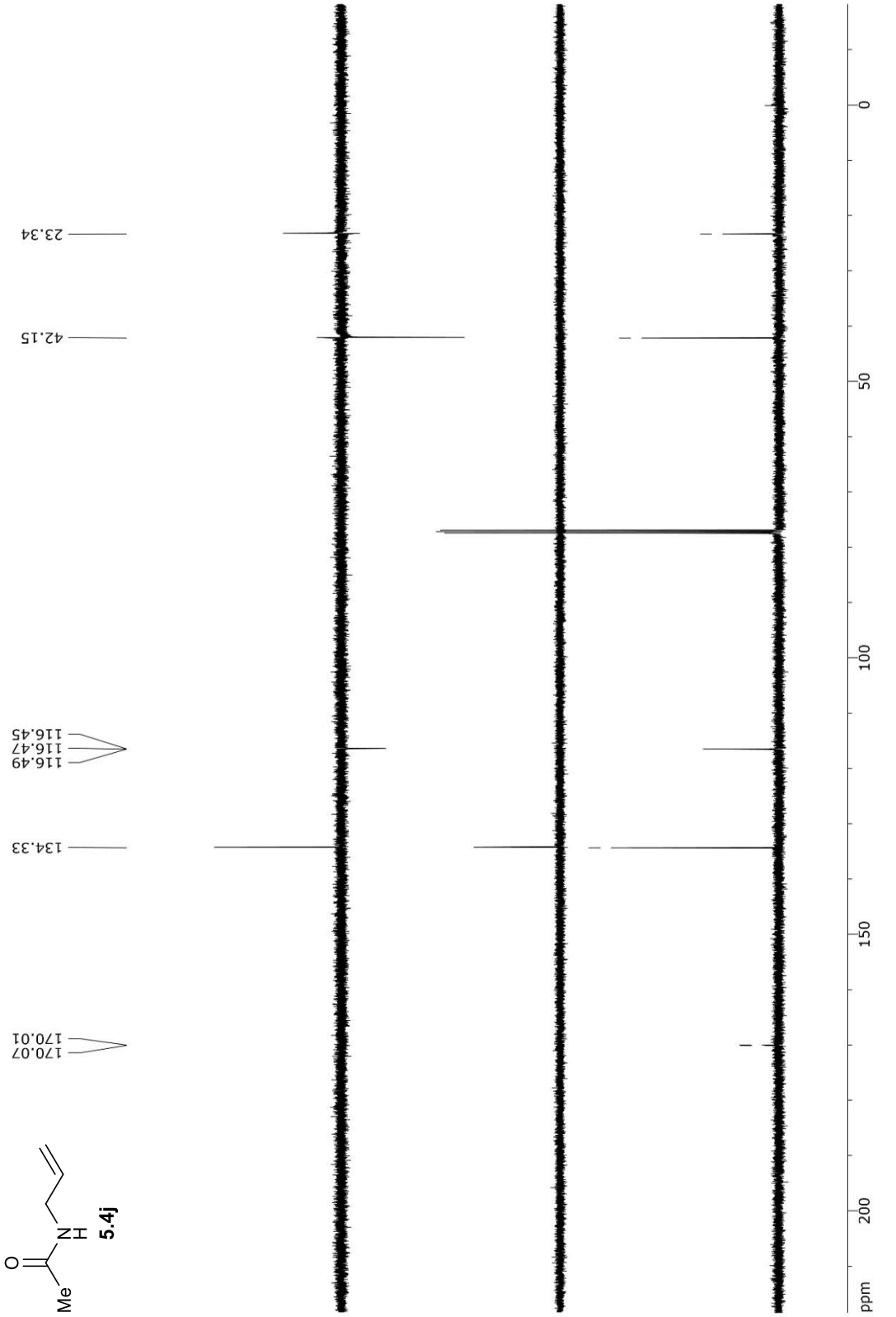
1.02
1.95
ppm
Me
NH
O
5.4j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170.01
134.33
116.49
116.47
116.45
42.15
23.34
Me
N
H
O
5.4j
ppm
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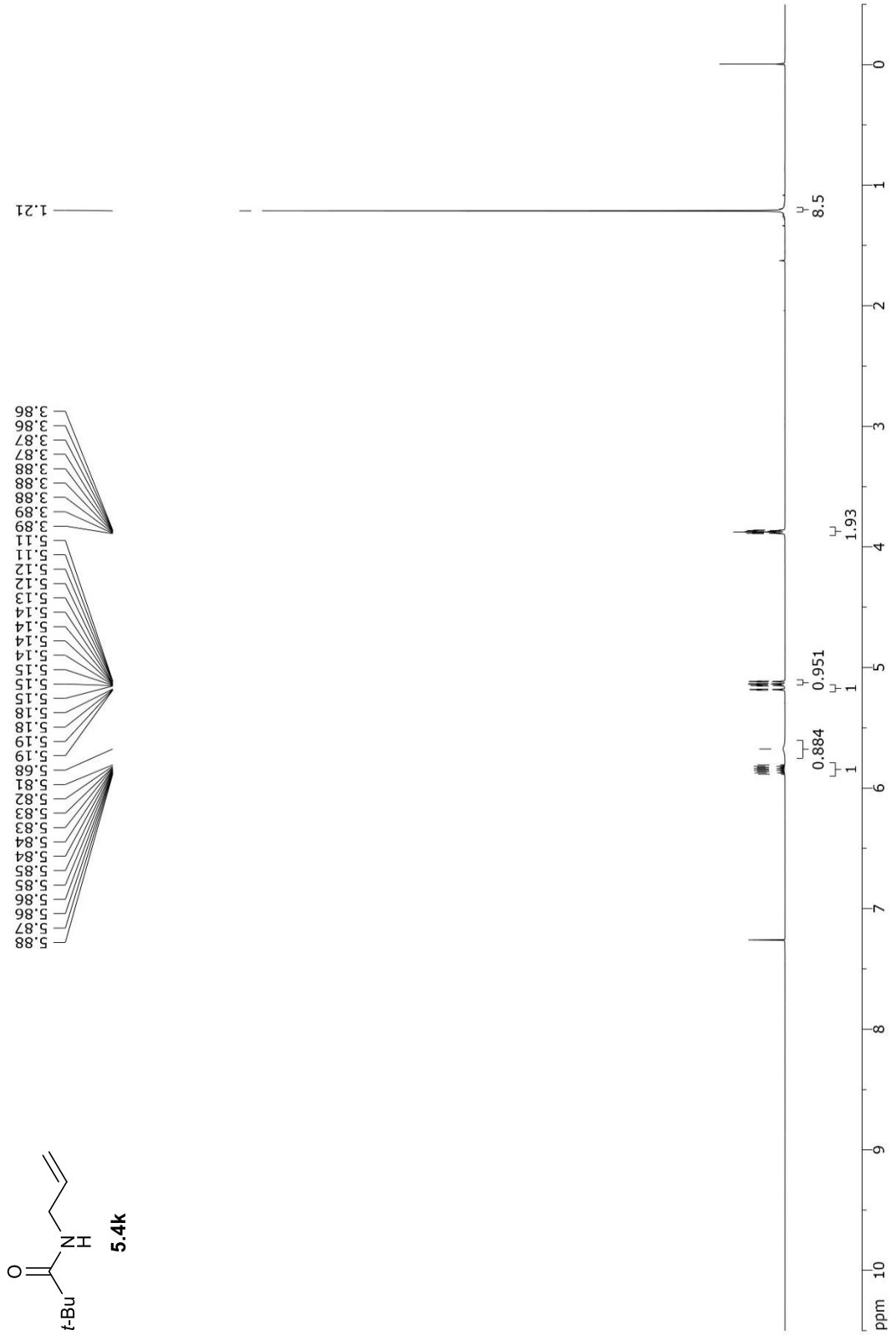
100
150
200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3.86
3.86
3.87
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3.88
3.88
3.88
3.89
3.89
5.11
5.11
5.12
5.12
5.13
5.14
5.14
5.14
5.15
5.15
5.15
5.18
5.18
5.19
5.19
5.68
5.81
5.82
5.83
5.83
5.84
5.84
5.85
5.85
5.86
5.86
5.87
5.88
8.5
1.93
0.951
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2
3
4
5
6
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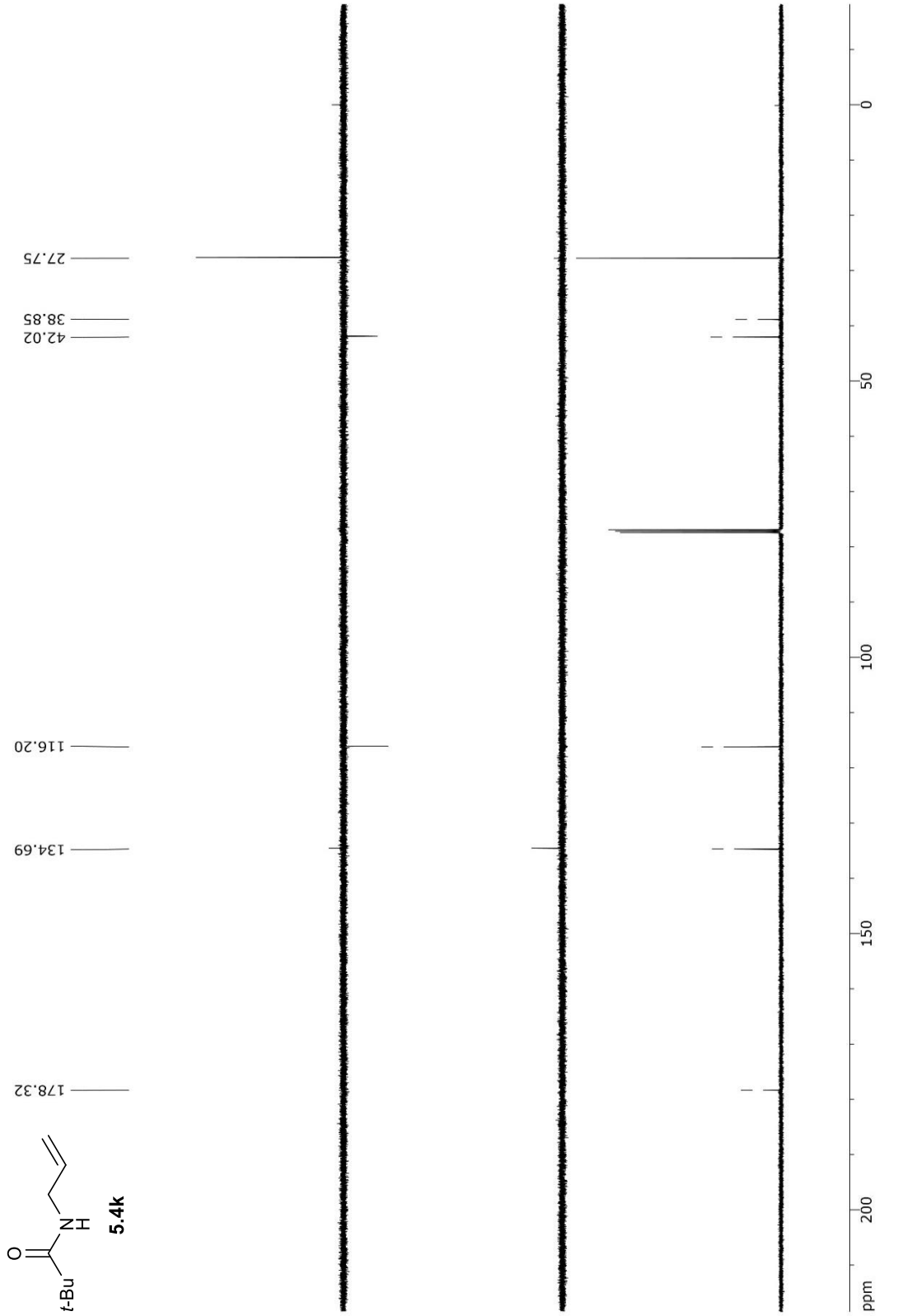
8
9
10
O
N
H
t-Bu
5.4k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38.85
27.75
t-Bu
O
N
H
5.4k
ppm
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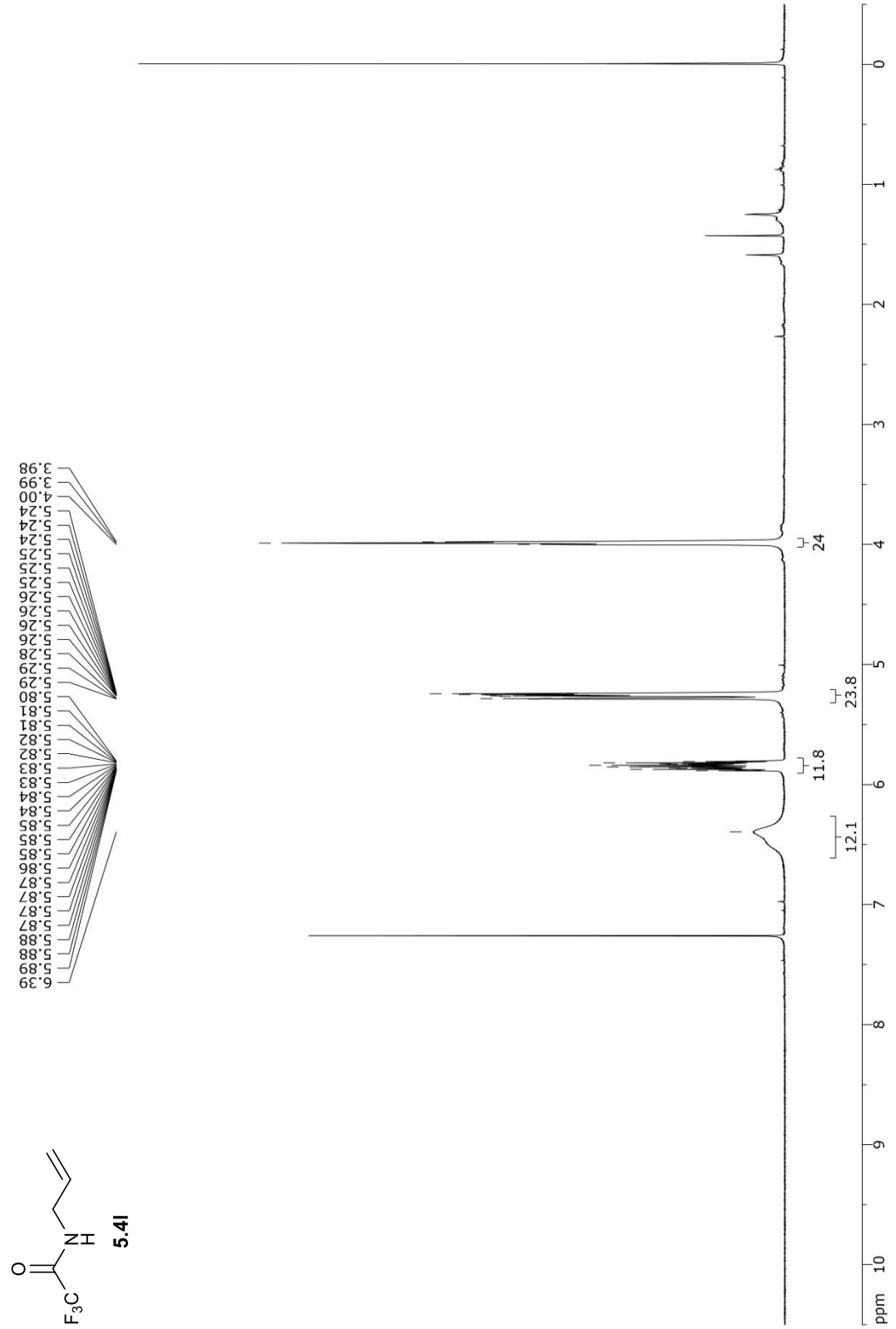
50
100
150
200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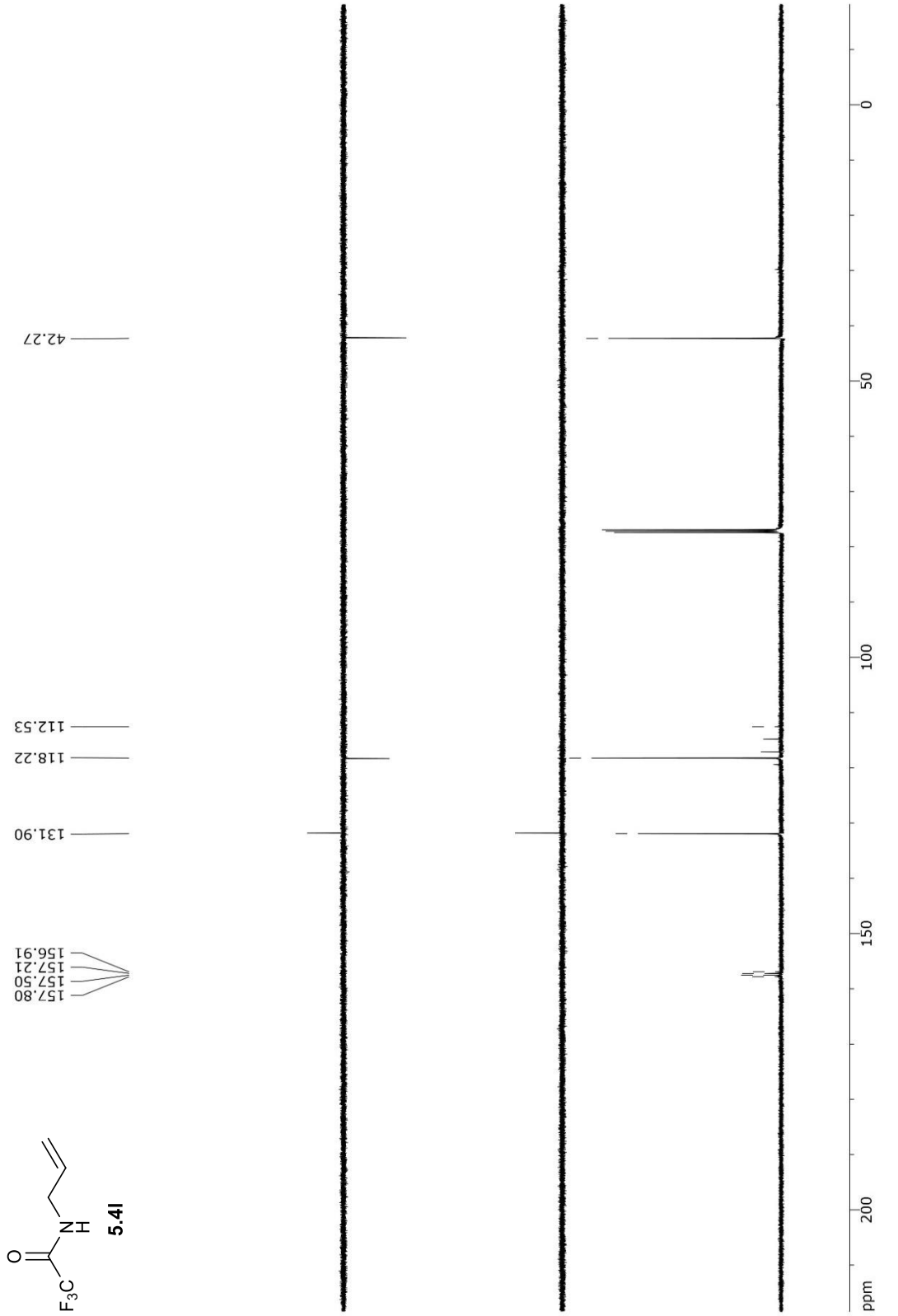
24
23.8
11.8
12.1
ppm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112.53
118.22
131.90
157.80
157.50
157.21
156.91
5.4l
O
N
H
F3C
ppm
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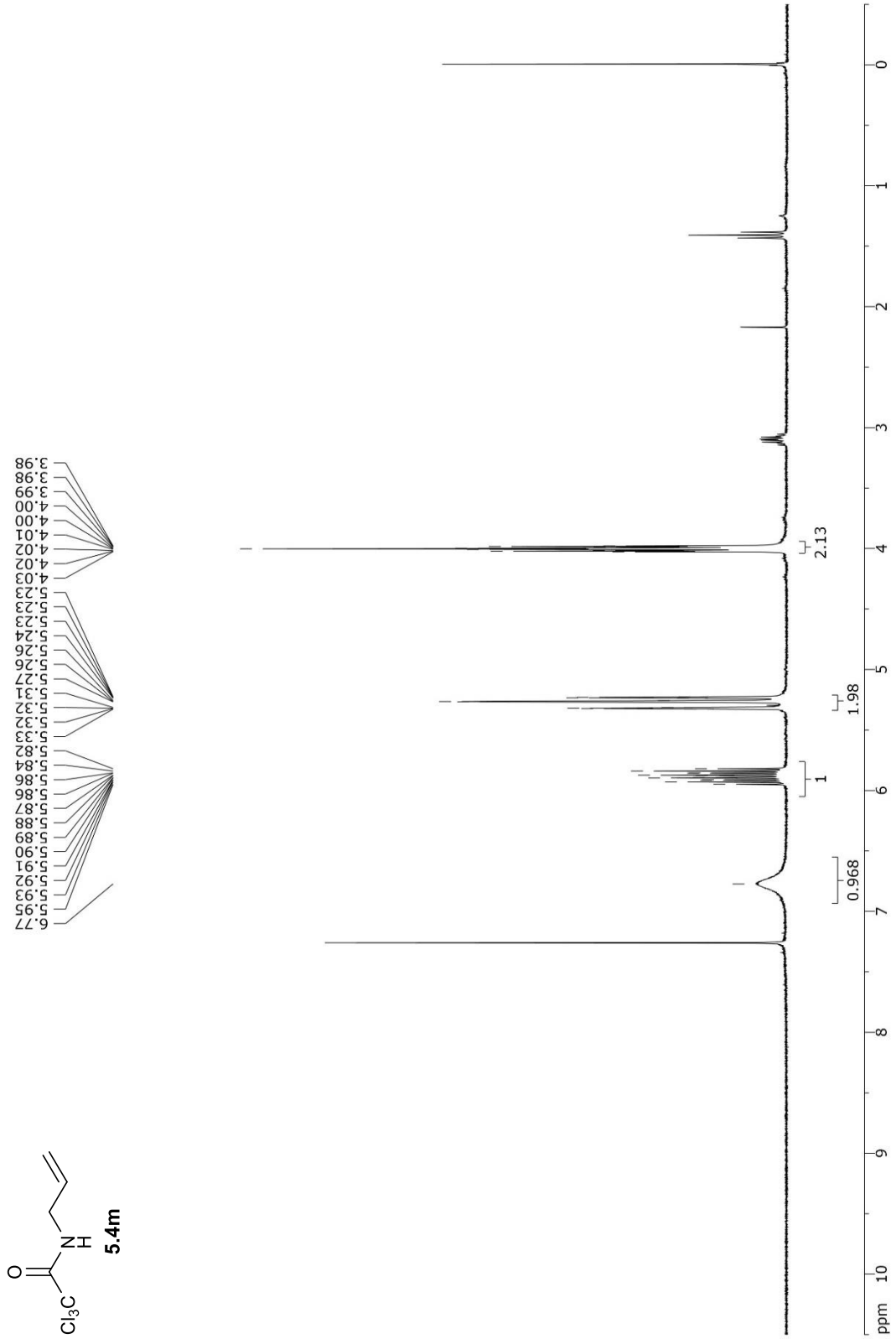
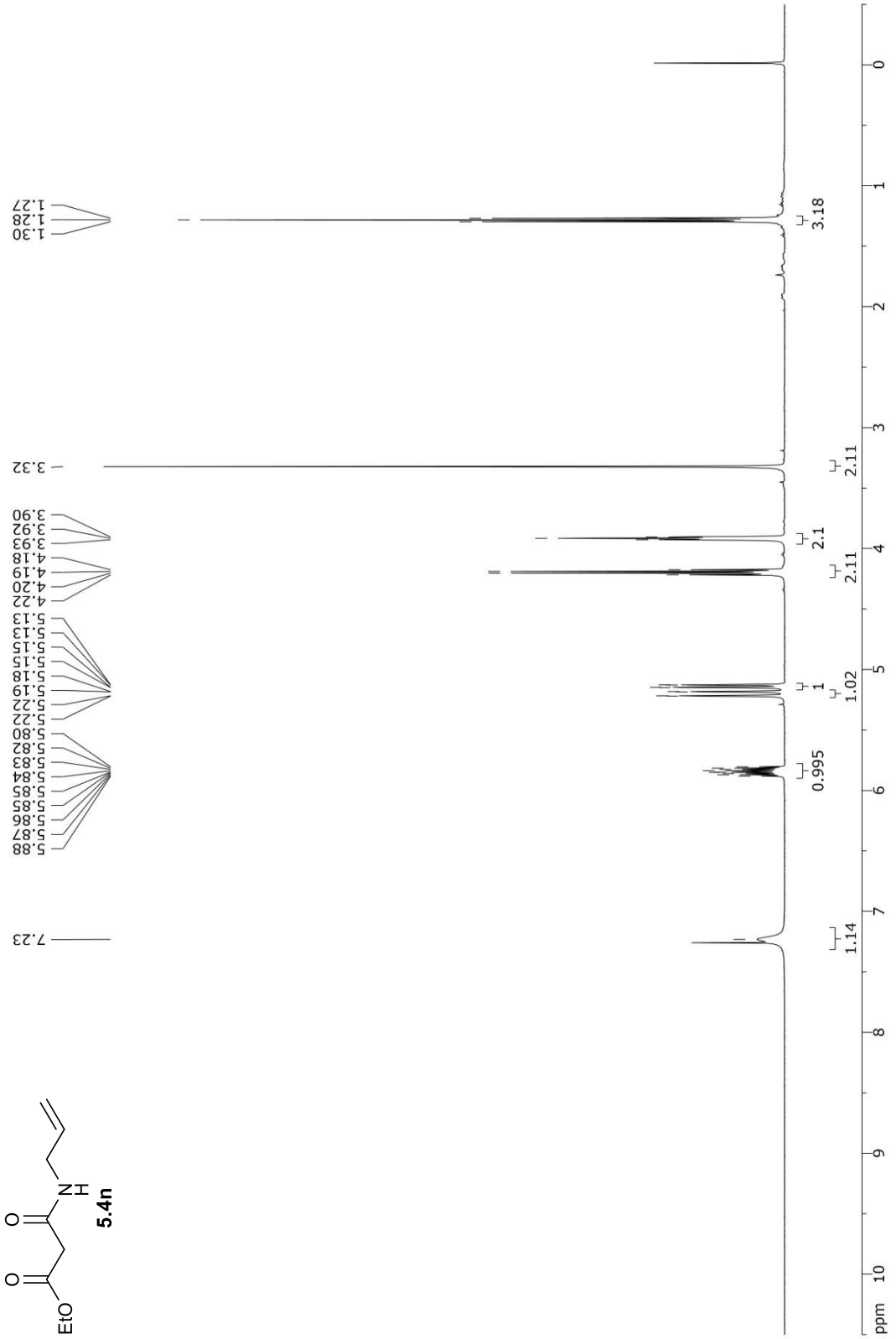
50
100
150
200


5.4m
Cl3C
O
N
H
6.77
5.95
5.93
5.92
5.91
5.90
5.89
5.88
5.87
5.86
5.86
5.84
5.82
5.33
5.32
5.32
5.31
5.27
5.26
5.26
5.24
5.23
5.23
5.23
4.03
4.02
4.02
4.01
4.00
4.00
3.99
3.98
3.98
2.13
1.98
1
0.968
ppm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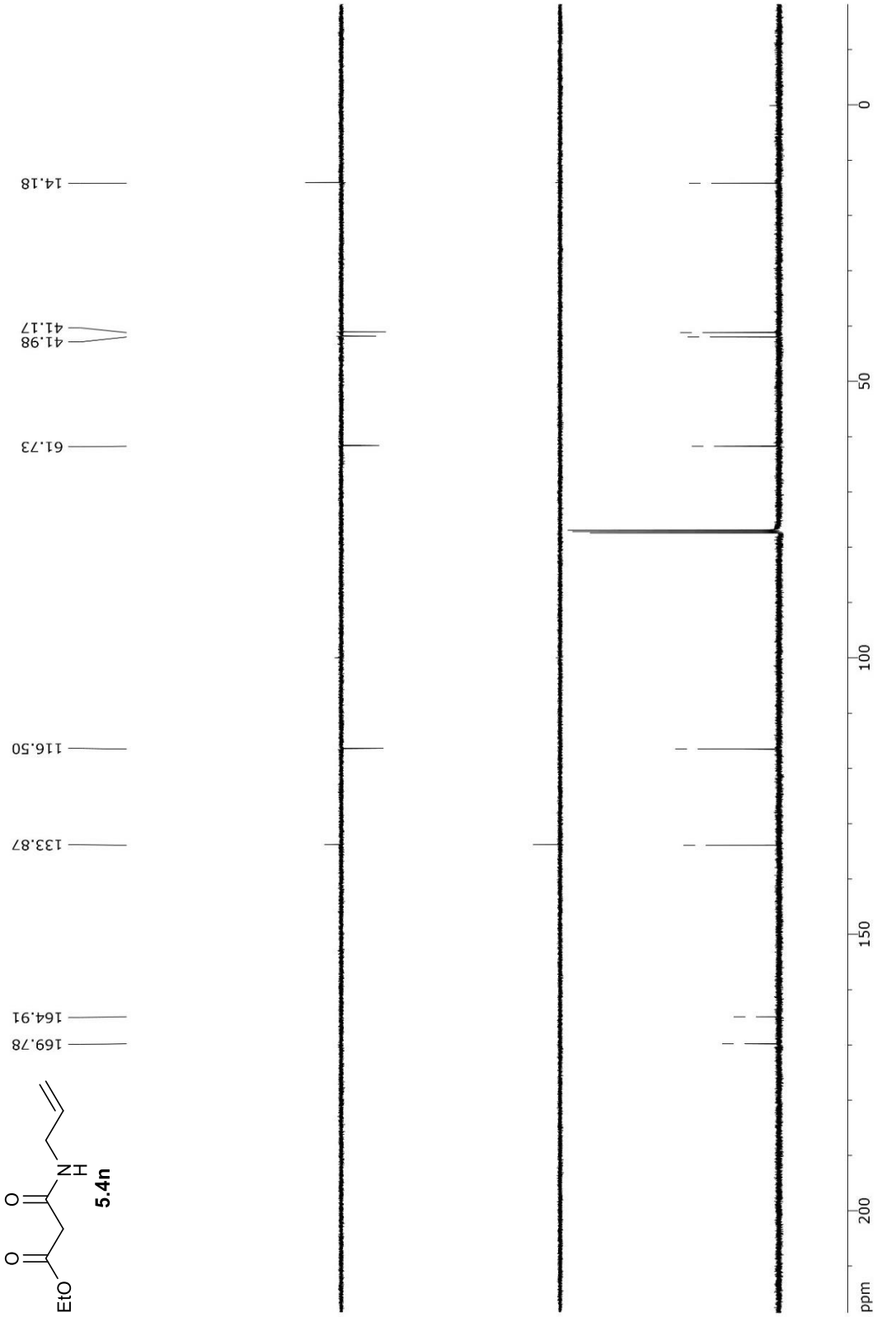
1.28
1.30
3.32
3.90
3.92
3.93
4.18
4.19
4.20
4.22
5.13
5.13
5.15
5.15
5.18
5.19
5.22
5.22
5.80
5.82
5.83
5.84
5.85
5.85
5.86
5.87
5.88
7.23
3.18
2.11
2.1
2.11
1
1.02
0.995
1.14
ppm
EtO
O
O
N
H
5.4n


14.18
41.17
41.98
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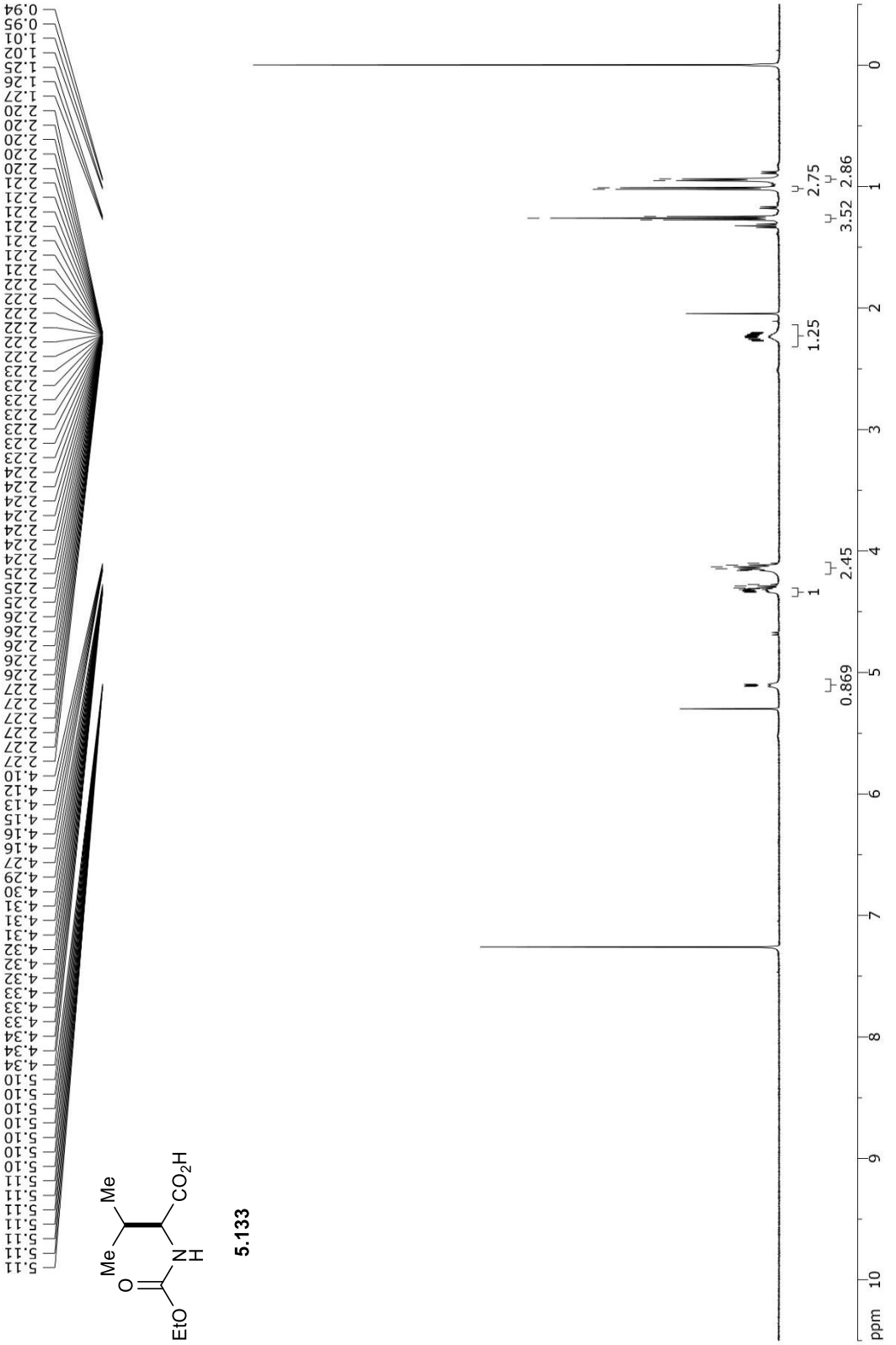
116.50
133.87
164.91
169.78
EtO
O
O
NH
5.4n
0
50
100
150
200
ppm


Me
Me
CO2H
O
N
H
EtO
5.133
ppm
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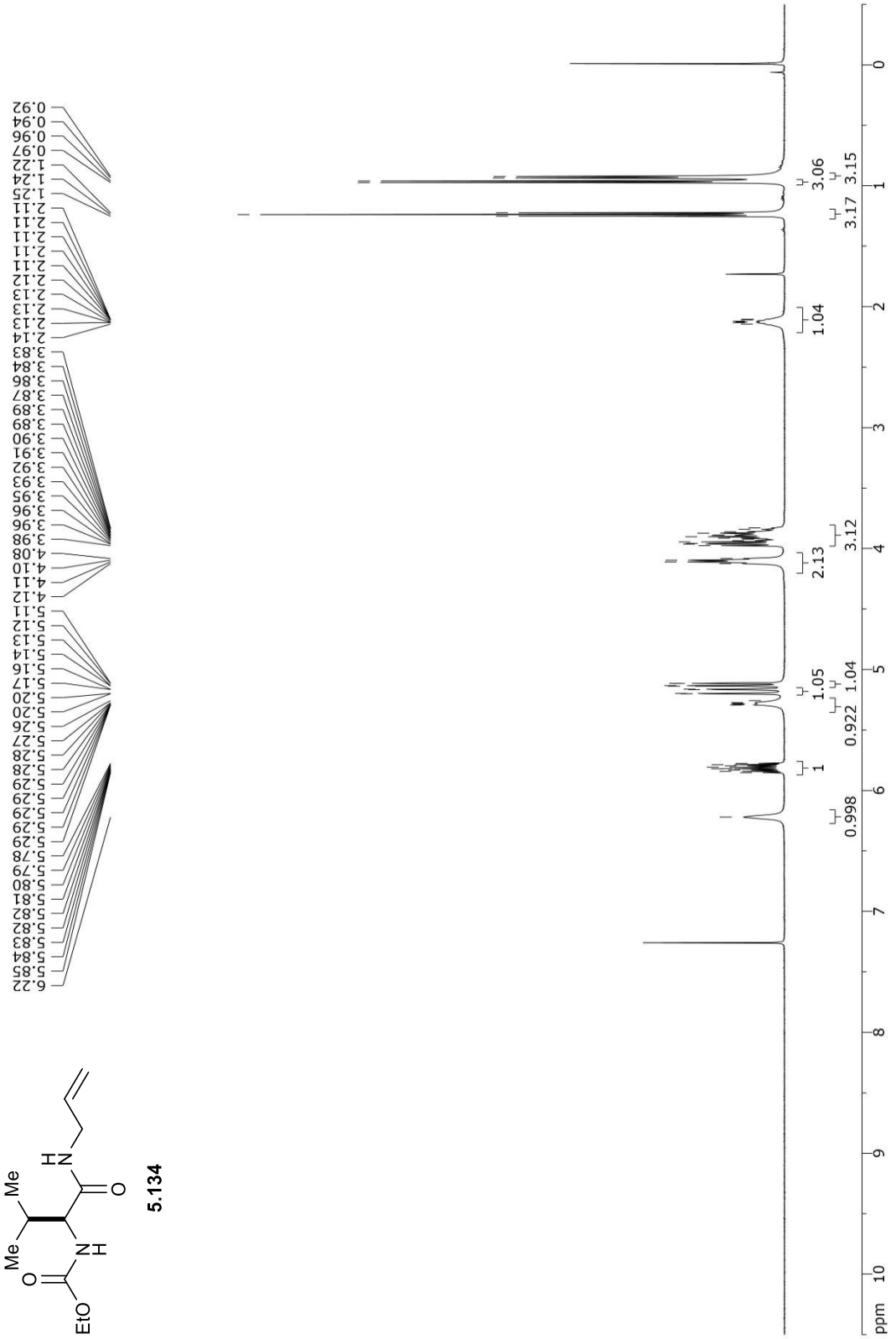
2.45
1.25
2.75
3.52
2.86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0.94
0.96
0.97
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1.24
1.25
2.11
2.11
2.11
2.11
2.11
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2.13
2.13
2.13
2.14
3.83
3.84
3.86
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3.89
3.89
3.90
3.91
3.92
3.93
3.95
3.96
3.96
3.98
4.08
4.10
4.11
4.12
5.11
5.12
5.13
5.14
5.16
5.17
5.20
5.20
5.26
5.27
5.28
5.28
5.29
5.29
5.29
5.29
5.29
5.78
5.79
5.80
5.81
5.82
5.82
5.83
5.84
5.85
6.22
0.998
1
1.05
0.922
1.04
2.13
3.12
1.04
3.17
3.15
3.06
ppm
10
9
8
7
6
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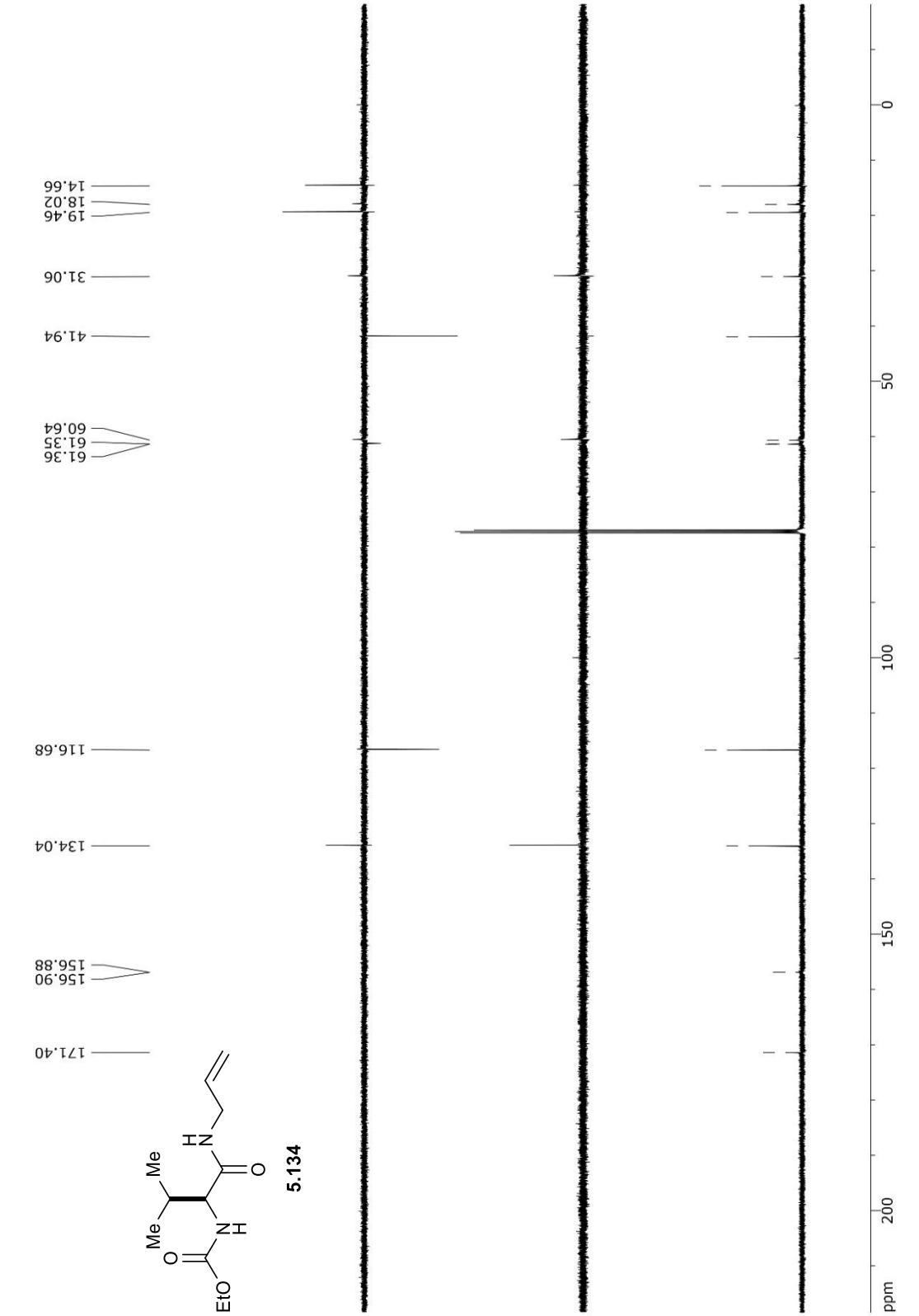
4
3
2
1
0
Me
Me
O
EtO
O
H
N
H
N
O

5.134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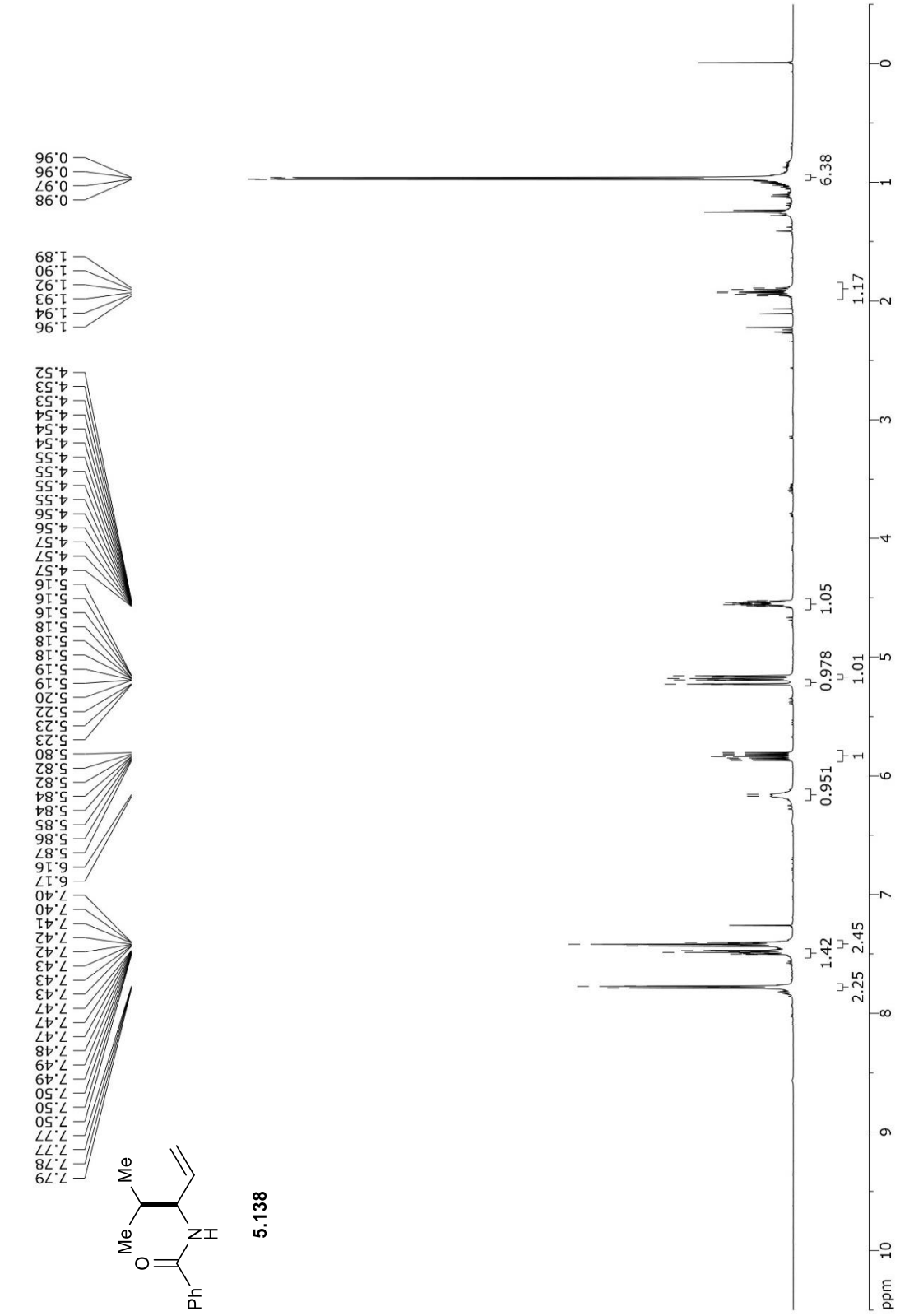
18.02
19.46
31.06
41.94
60.64
61.35
61.36
116.68
134.04
156.88
156.90
171.40
Me
Me
O
EtO
H
N
H
N
O
5.134
0
50
100
150
200
ppm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0.96
0.97
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1.92
1.93
1.94
1.96
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4.54
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4.54
4.55
4.55
4.55
4.55
4.56
4.56
4.57
4.57
4.57
5.16
5.16
5.16
5.18
5.18
5.18
5.19
5.19
5.20
5.22
5.23
5.23
5.80
5.82
5.82
5.84
5.84
5.85
5.86
5.87
6.16
6.17
7.40
7.40
7.41
7.42
7.42
7.43
7.43
7.43
7.47
7.47
7.47
7.48
7.49
7.49
7.50
7.50
7.50
7.77
7.77
7.78
7.79
Me
Me
O
N
H
Ph
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1.17
1.05
0.978
1.01
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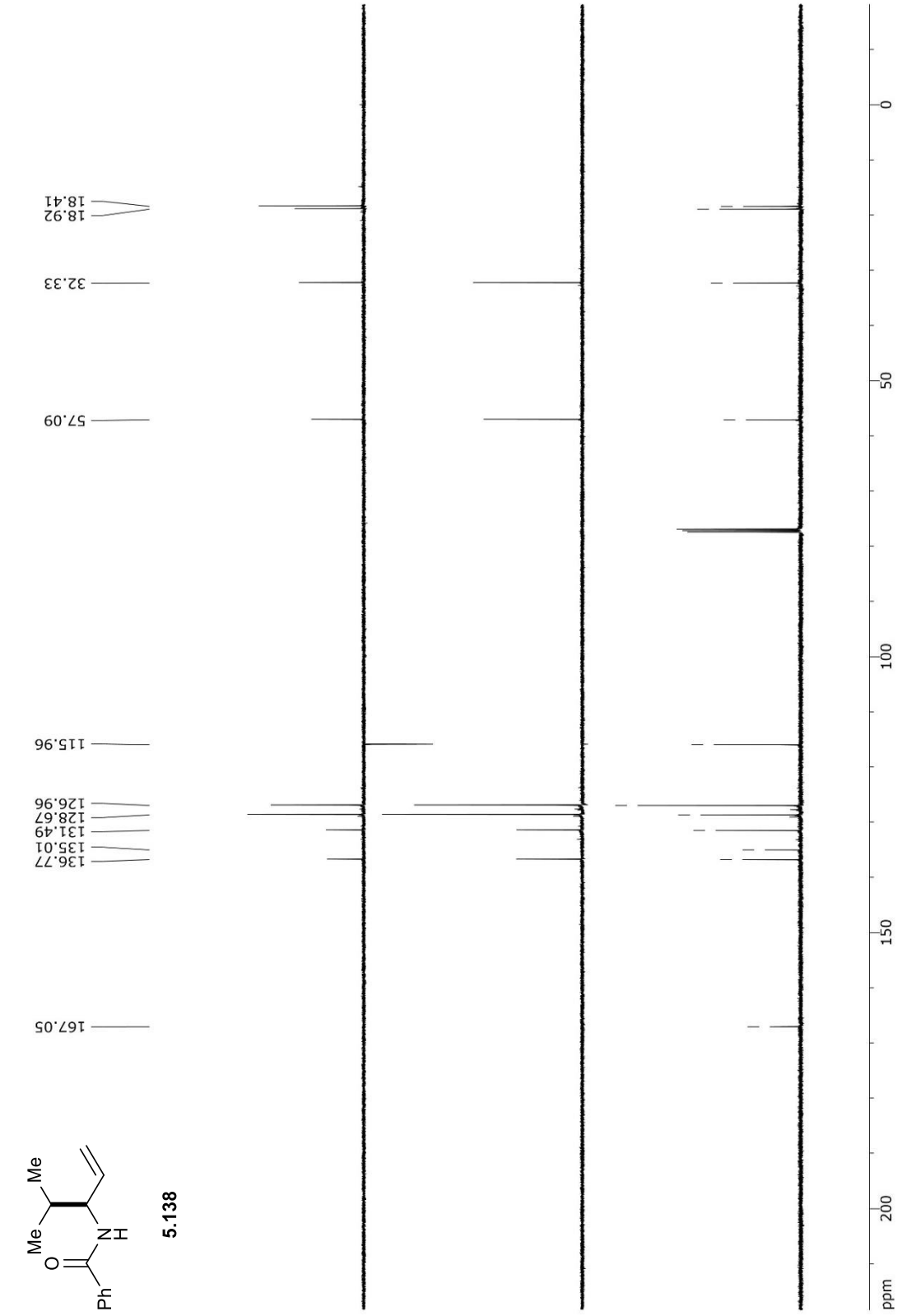
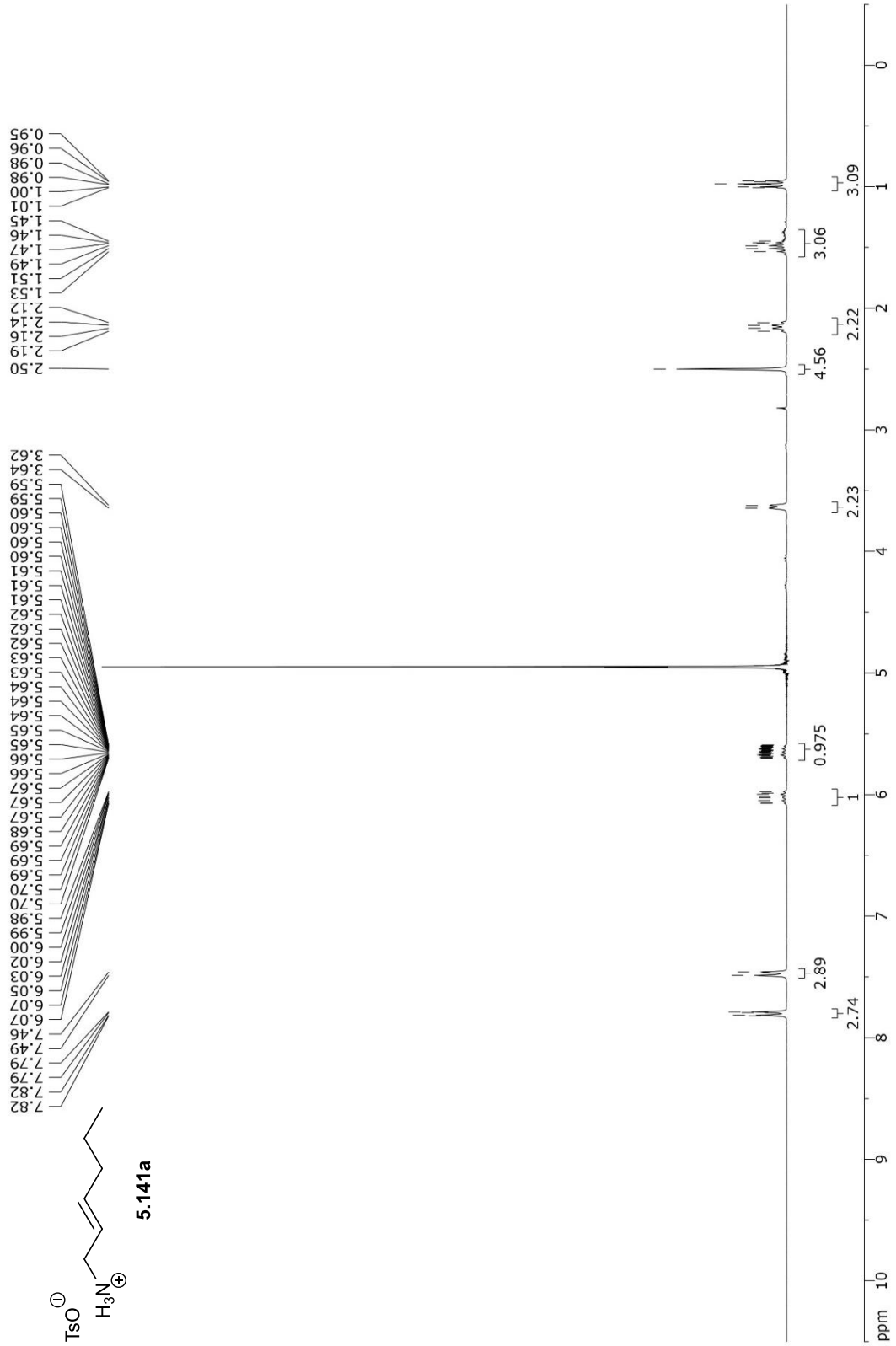
1
1.42
2.45
2.25
ppm


18.41
18.92
32.33
57.09
115.96
126.96
128.67
131.49
135.01
136.77
167.05
ppm
0
50
100
150
200
Me
Me
O
N
H
Ph
5.138


5.141a
TsO
H3N
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7.82
7.79
7.79
7.49
7.46
6.07
6.07
6.05
6.03
6.02
6.00
5.99
5.98
5.70
5.70
5.69
5.69
5.68
5.67
5.67
5.67
5.66
5.65
5.65
5.64
5.64
5.64
5.63
5.63
5.62
5.62
5.62
5.61
5.61
5.61
5.60
5.60
5.60
5.60
5.59
5.59
3.64
3.62
2.50
2.19
2.16
2.14
2.12
1.53
1.51
1.49
1.47
1.46
1.45
1.01
1.00
0.98
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2.89
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0.975
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4.56
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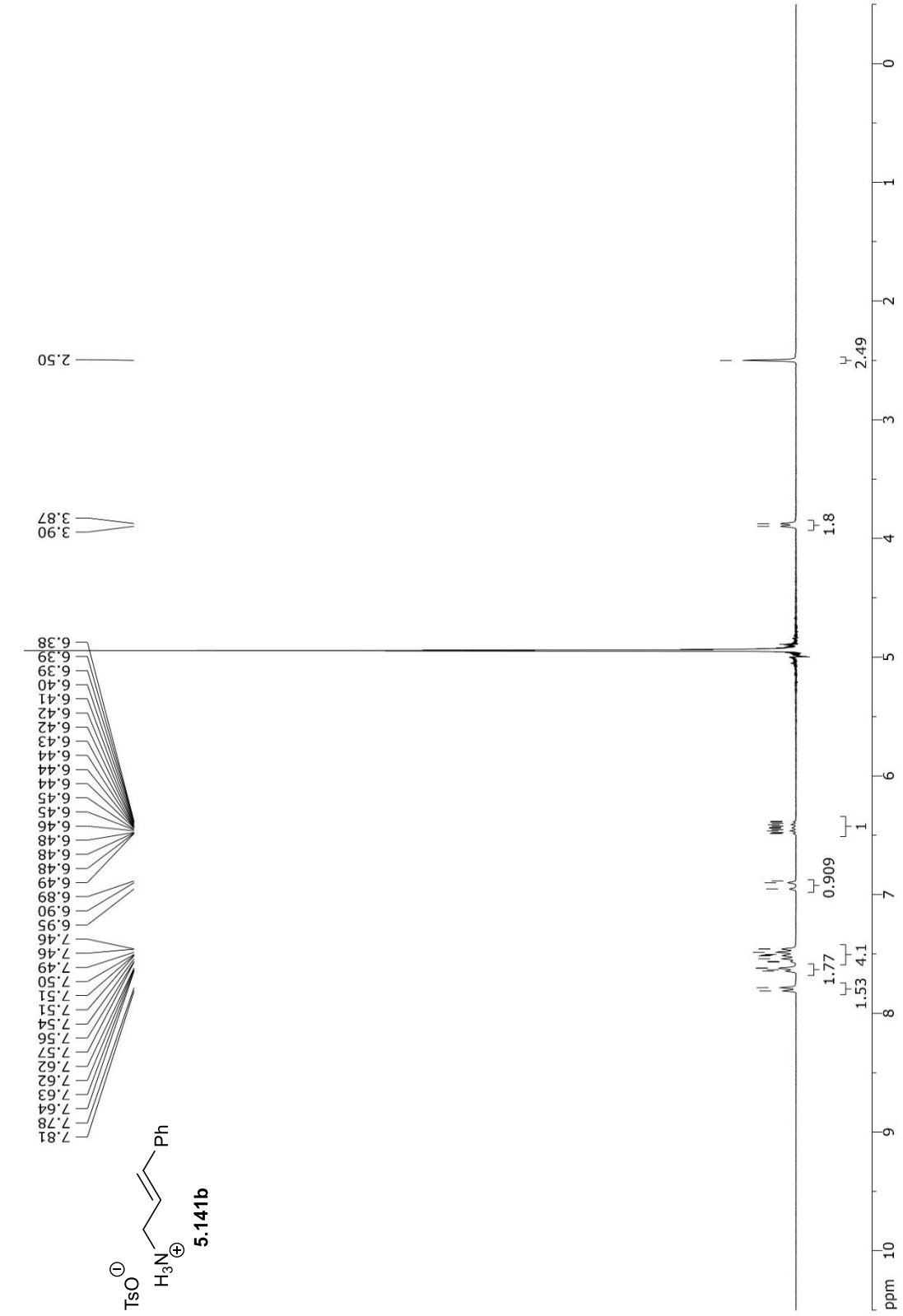
3.06
3.09
ppm


TsO
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Ph
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7.62
7.62
7.57
7.56
7.54
7.51
7.51
7.50
7.49
7.46
7.46
6.95
6.90
6.89
6.49
6.48
6.48
6.48
6.46
6.45
6.45
6.44
6.44
6.44
6.43
6.42
6.42
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6.39
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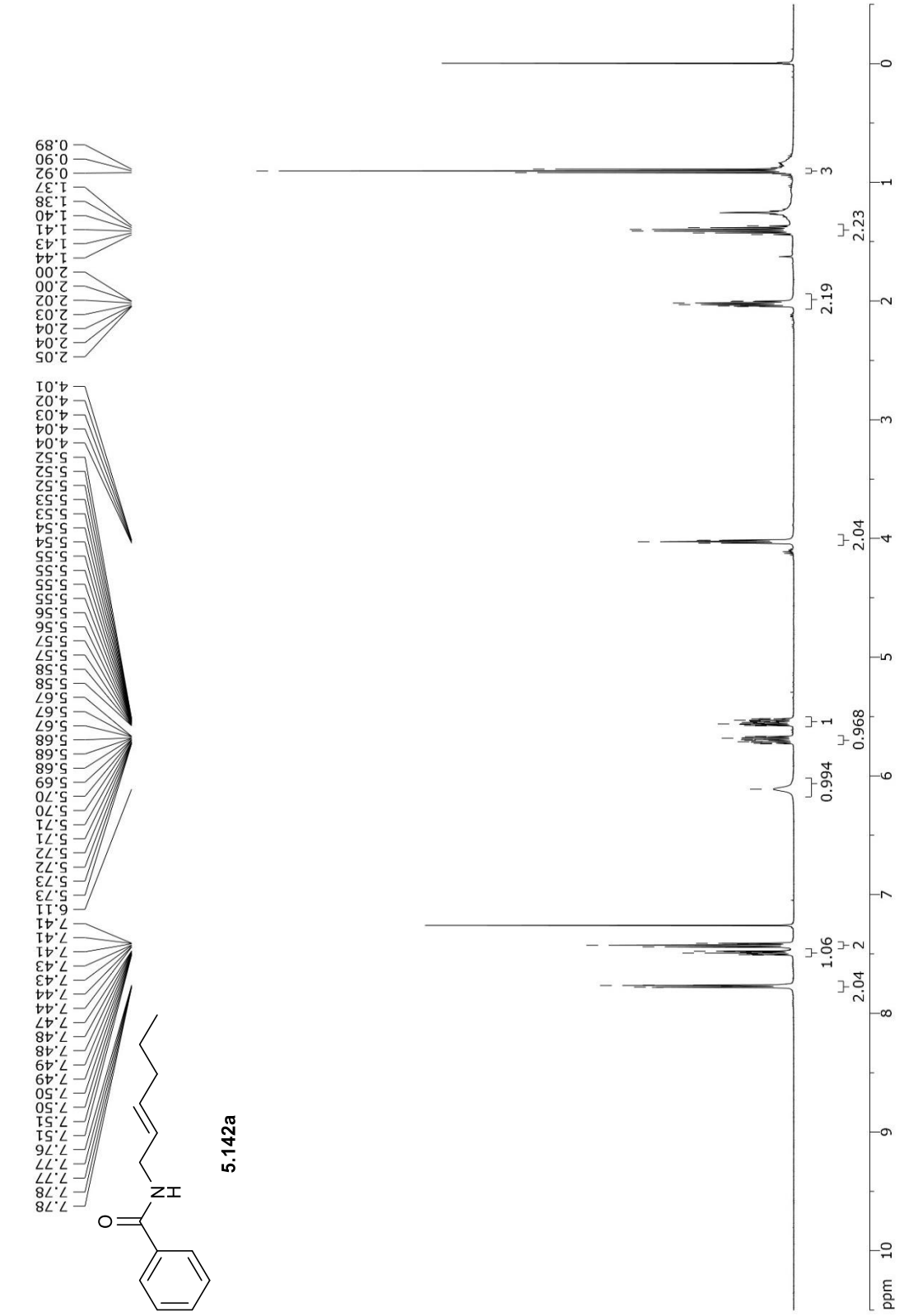
1.8
2.49
ppm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7.78
7.77
7.77
7.76
7.51
7.51
7.50
7.50
7.49
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7.48
7.47
7.44
7.44
7.43
7.43
7.41
7.41
7.41
7.41
6.11
5.73
5.72
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5.71
5.70
5.70
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5.58
5.57
5.57
5.56
5.56
5.55
5.55
5.55
5.55
5.54
5.54
5.53
5.53
5.52
5.52
5.52
4.04
4.04
4.03
4.02
4.01
2.05
2.04
2.04
2.03
2.02
2.00
2.00
1.44
1.43
1.41
1.40
1.38
1.37
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1.06
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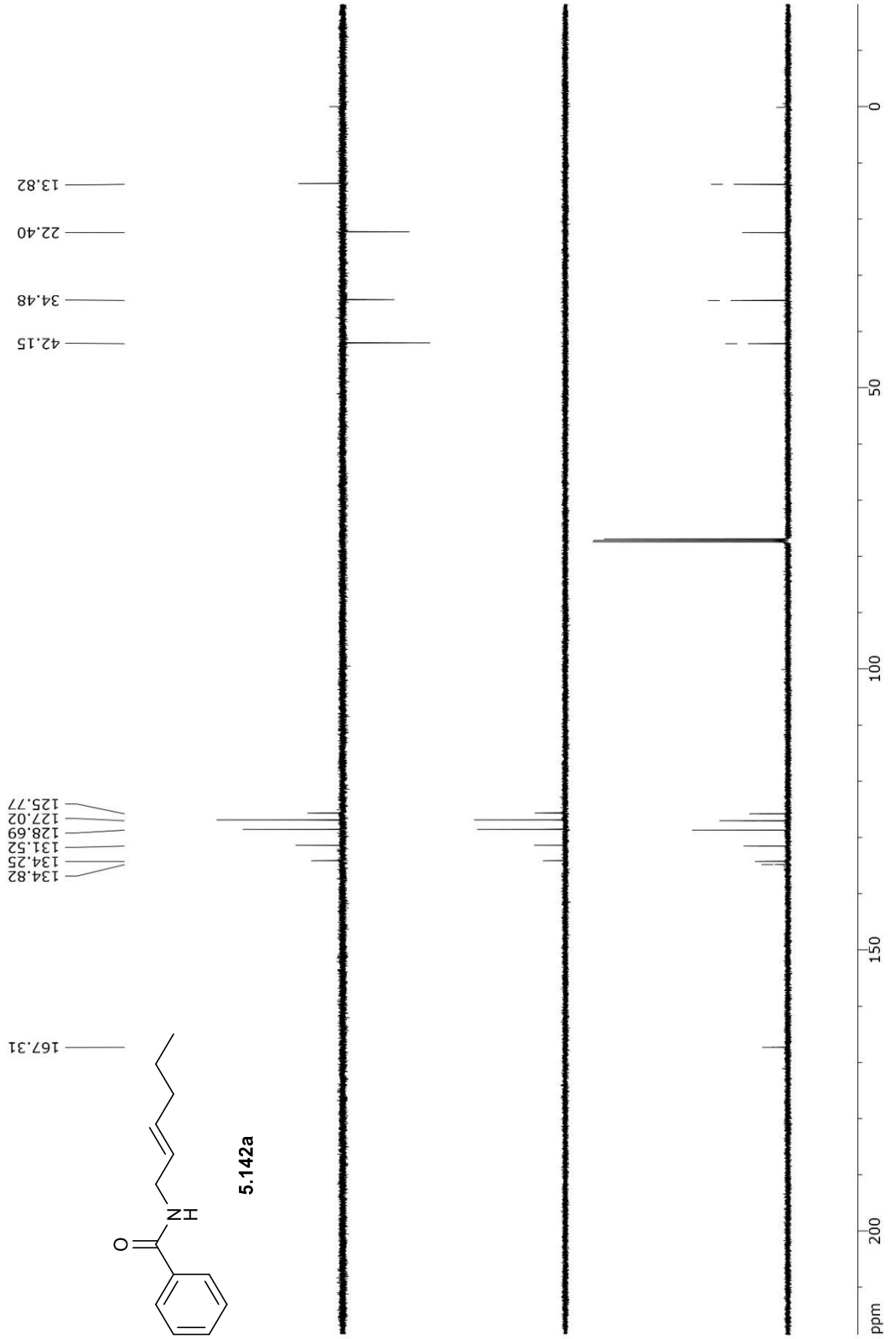
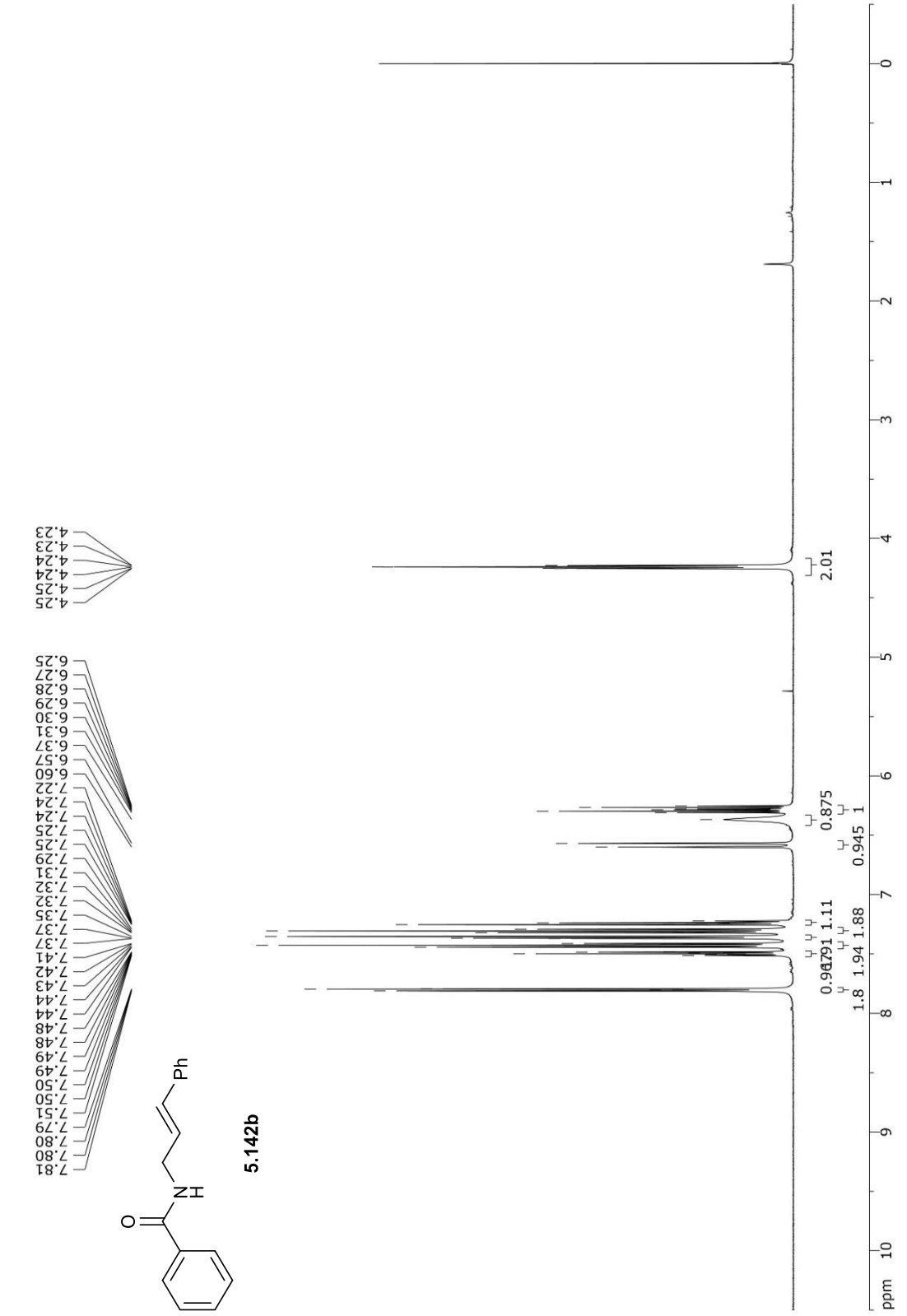
2.19
2.23
3
ppm


13.82
22.40
34.48
42.15
125.77
127.02
128.69
131.52
134.25
134.82
167.31
5.142a
O
NH
ppm
0
50
100
150
200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4.23
4.24
4.24
4.25
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6.25
6.27
6.28
6.29
6.30
6.31
6.37
6.57
6.60
7.22
7.24
7.24
7.25
7.25
7.29
7.31
7.32
7.32
7.35
7.37
7.37
7.41
7.42
7.43
7.44
7.44
7.48
7.48
7.49
7.49
7.50
7.50
7.51
7.79
7.80
7.80
7.81
Ph
N
H
O
5.142b
2.01
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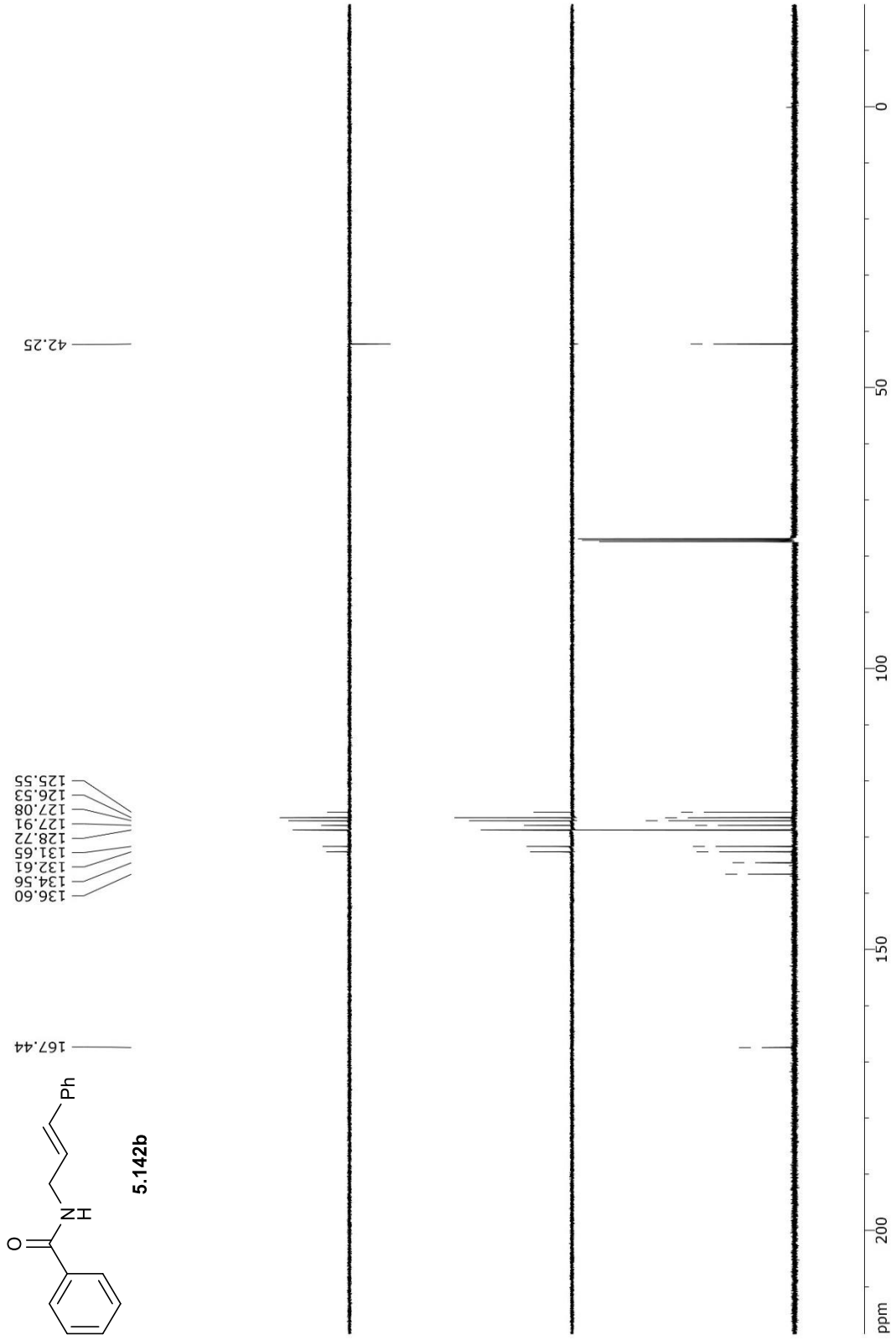
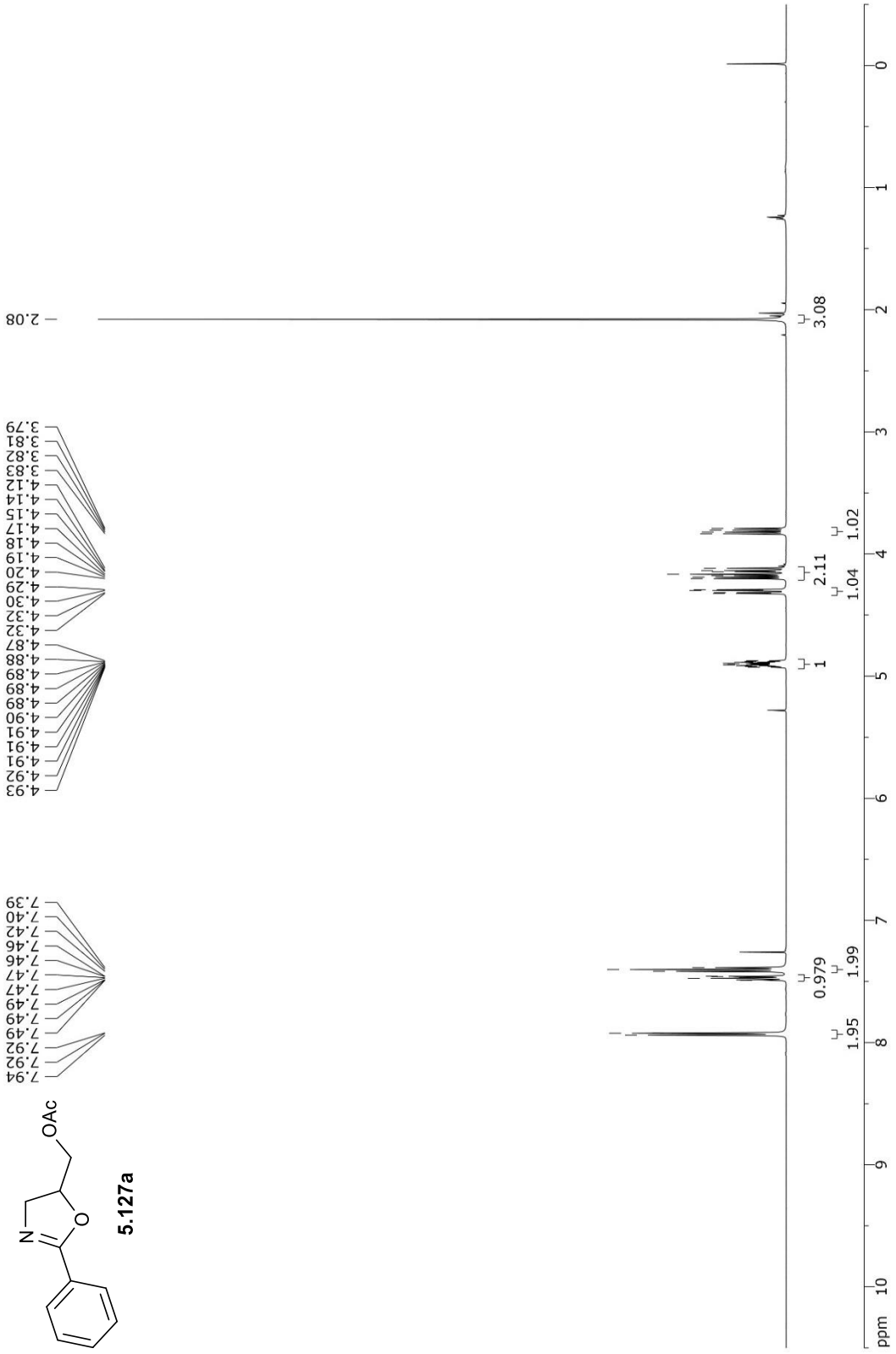
0.945 1
0.94 0.91 1.11
1.8 1.94 1.88
ppm


167.44
136.60
134.56
132.61
131.65
128.72
127.91
127.08
126.53
125.55
42.25
Ph
N
H
O
5.142b
0
50
100
150
200
ppm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OAc
N
O
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7.92
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7.49
7.49
7.47
7.47
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7.46
7.42
7.40
7.39
4.93
4.92
4.91
4.91
4.91
4.90
4.89
4.89
4.89
4.88
4.87
4.32
4.32
4.30
4.29
4.20
4.19
4.18
4.17
4.15
4.14
4.12
3.83
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2.08
3.08
2.11
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1.02
1
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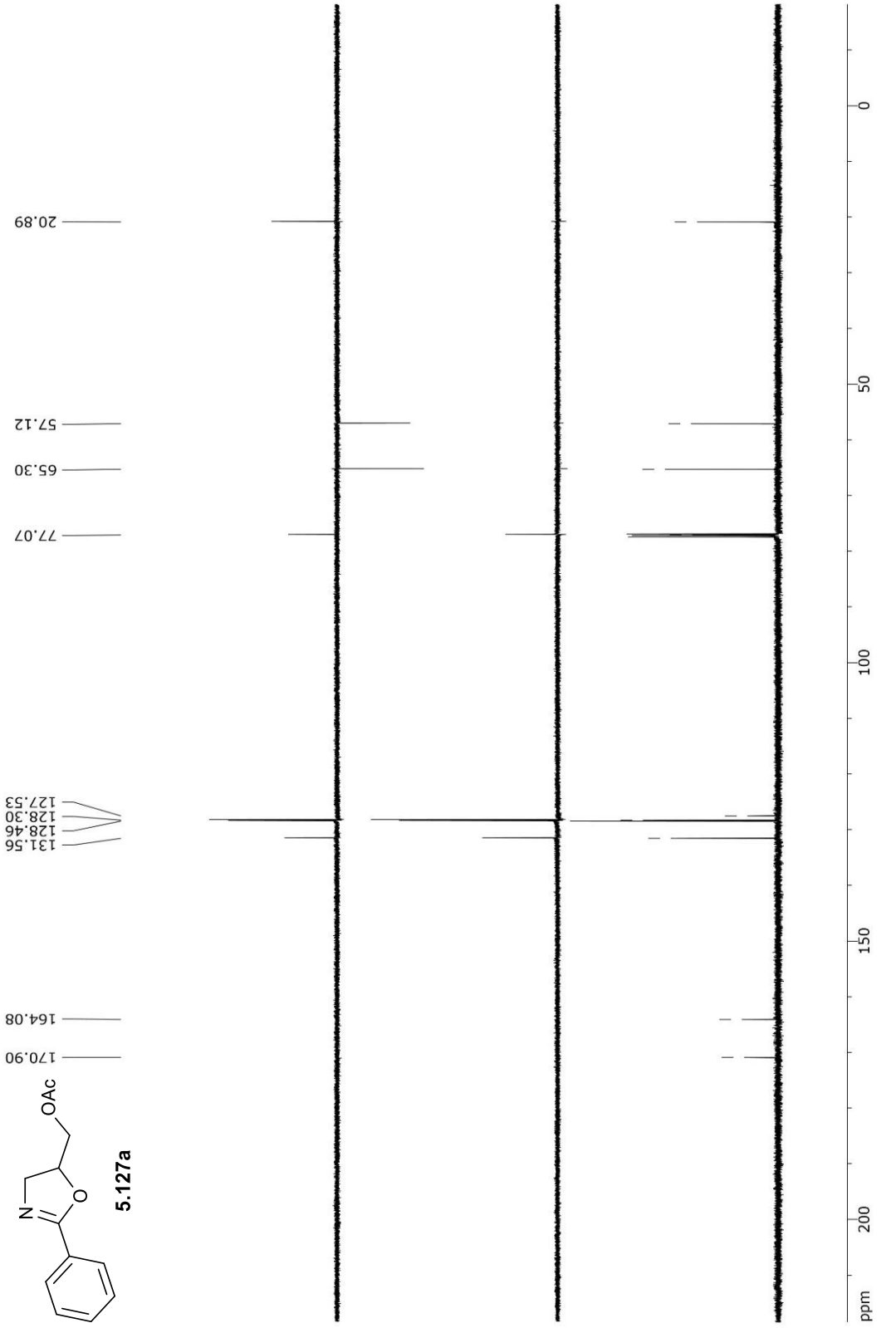
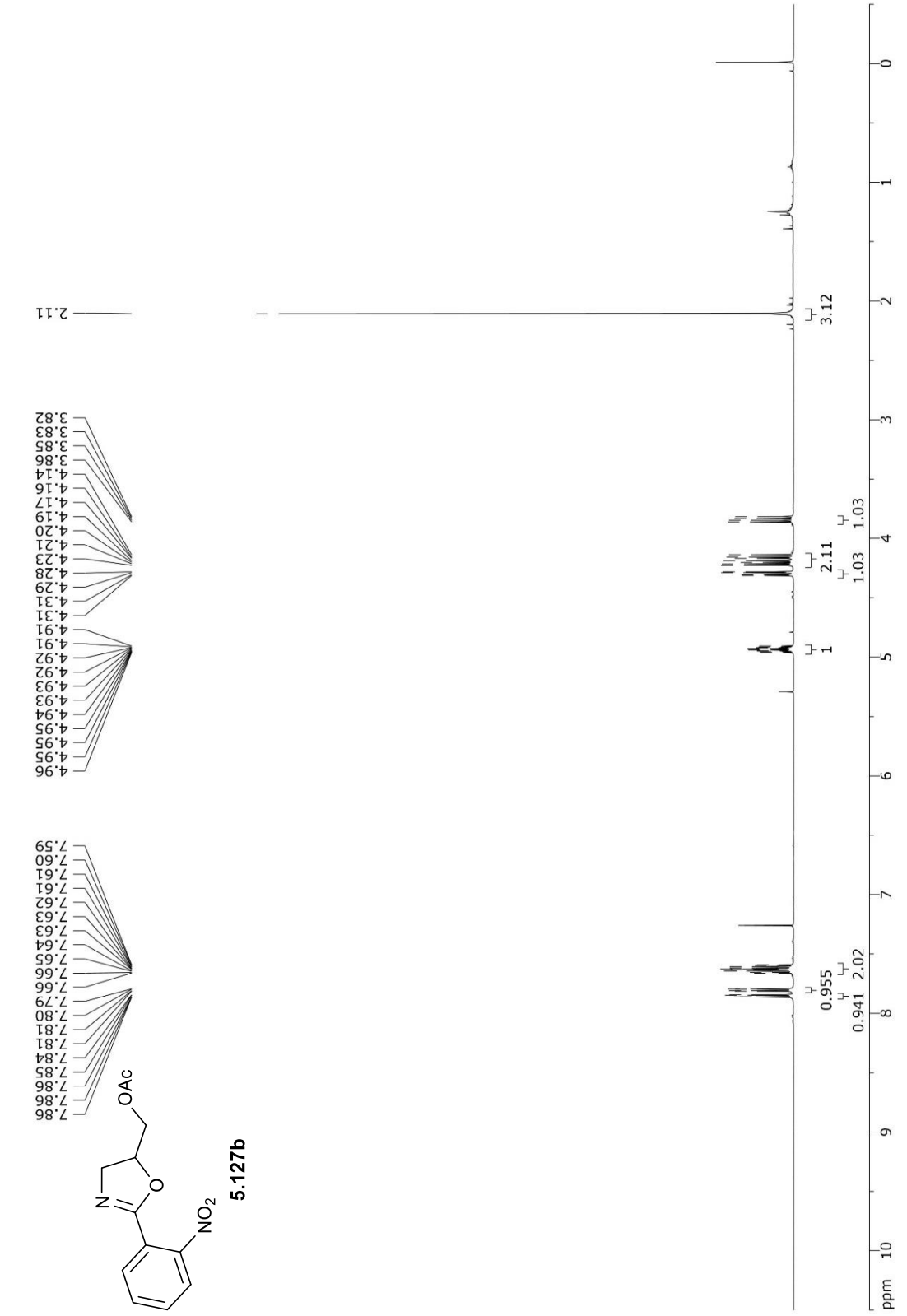
1.95
ppm


20.89
57.12
65.30
77.07
127.53
128.30
128.46
131.56
164.08
170.90
OAc
N
O
5.127a
ppm
0
50
100
150
200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3.85
3.86
4.14
4.16
4.17
4.19
4.20
4.21
4.23
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4.91
4.92
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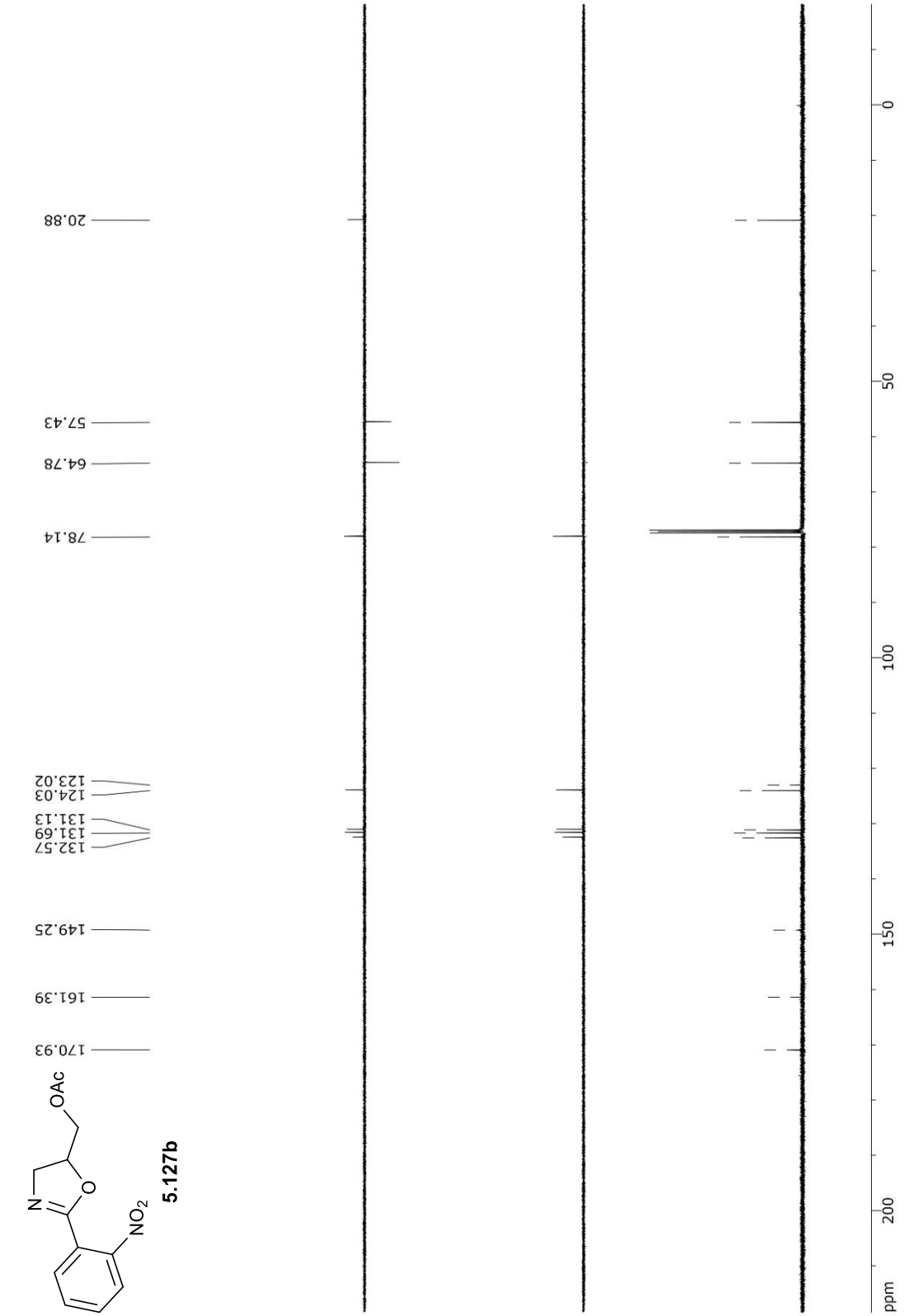
7.86
7.86
7.86
OAc
N
O
NO2
5.127b
3.12
1
2.11
1.03
1.03
0.955
0.941
2.02
ppm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57.43
64.78
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124.03
131.13
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161.39
170.93
OAc
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O
NO2
5.127b
ppm
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150
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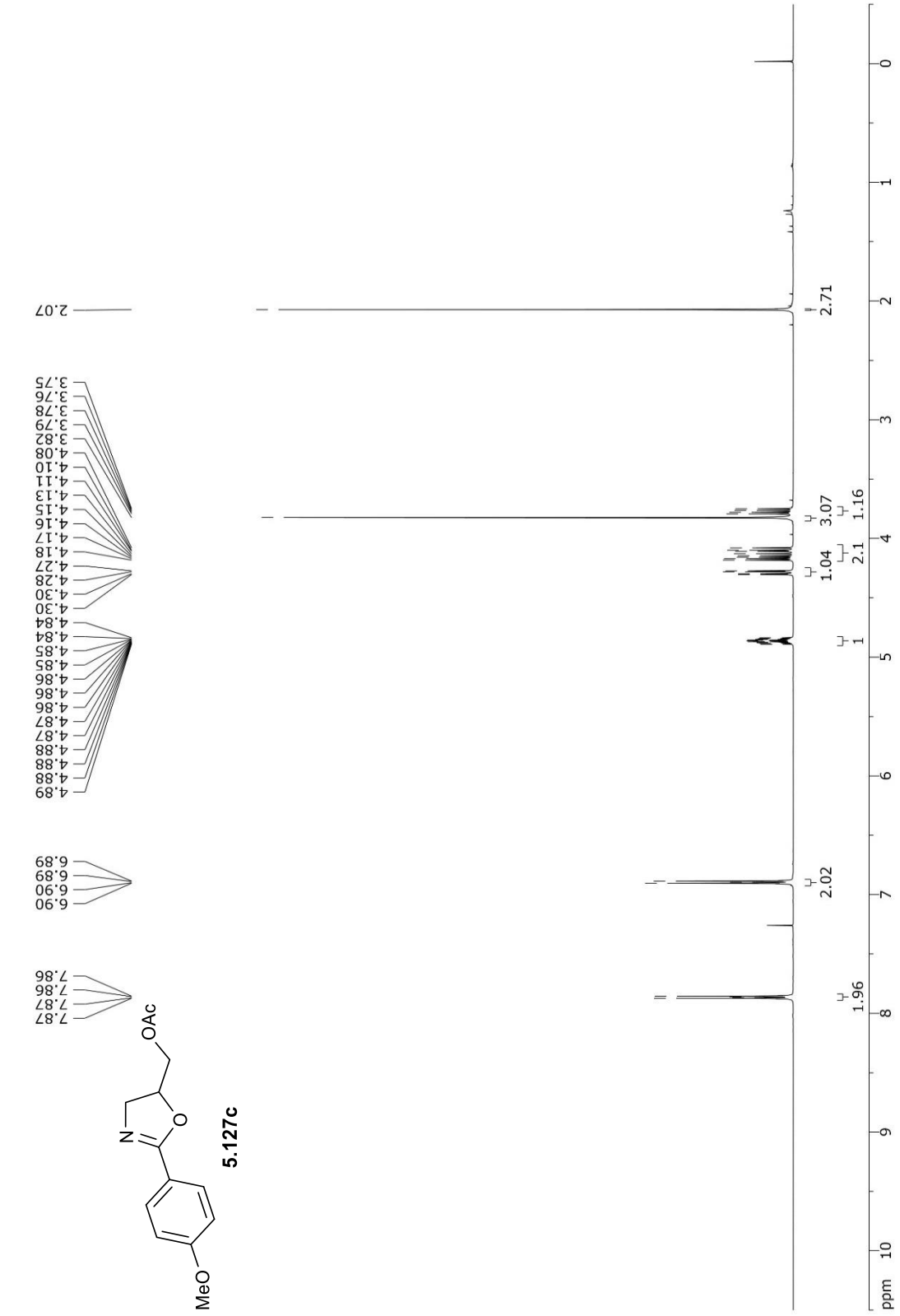
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3.75
3.76
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3.82
4.08
4.10
4.11
4.13
4.15
4.16
4.17
4.18
4.27
4.28
4.30
4.30
4.84
4.84
4.85
4.85
4.86
4.86
4.86
4.87
4.87
4.88
4.88
4.88
4.89
6.89
6.89
6.90
6.90
7.86
7.86
7.87
7.87
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5.127c
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3.07
1.16
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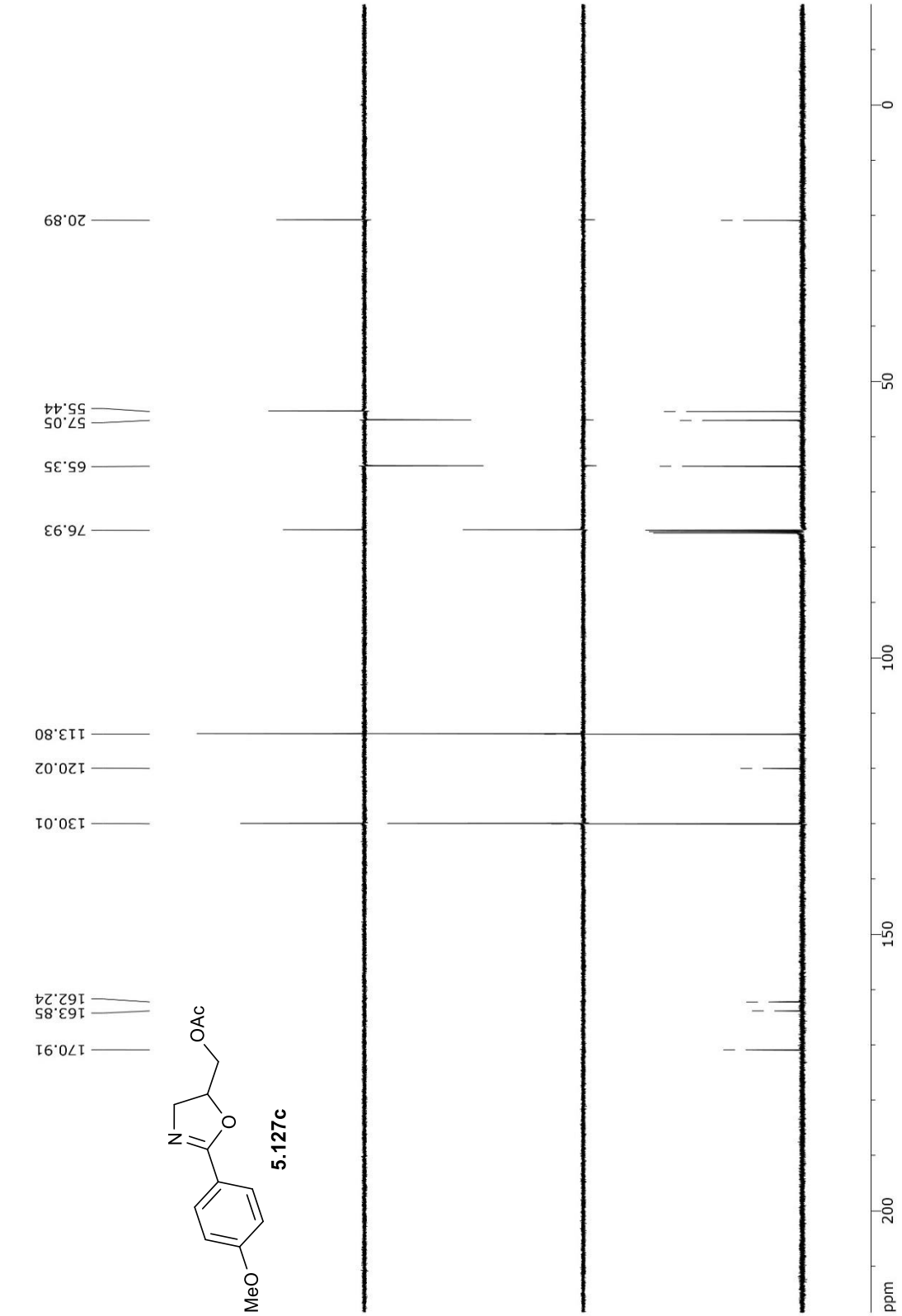
2.1
1
2.02
1.96
ppm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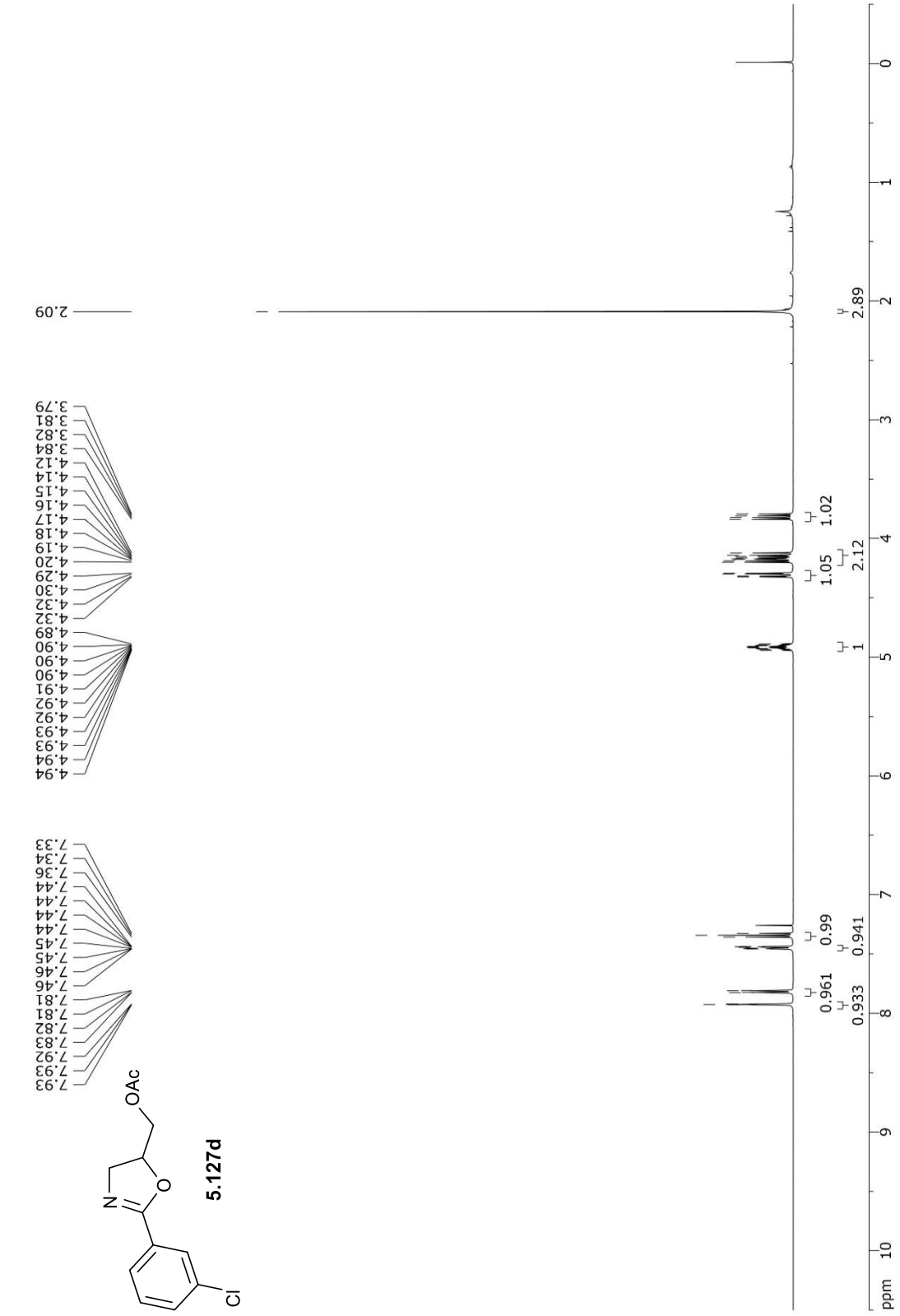
150
200
ppm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4.14
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4.16
4.17
4.18
4.19
4.20
4.29
4.30
4.32
4.32
4.89
4.90
4.90
4.90
4.91
4.92
4.92
4.93
4.93
4.94
4.94
7.33
7.34
7.36
7.44
7.44
7.44
7.44
7.45
7.45
7.46
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7.82
7.83
7.92
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2.89
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2.12
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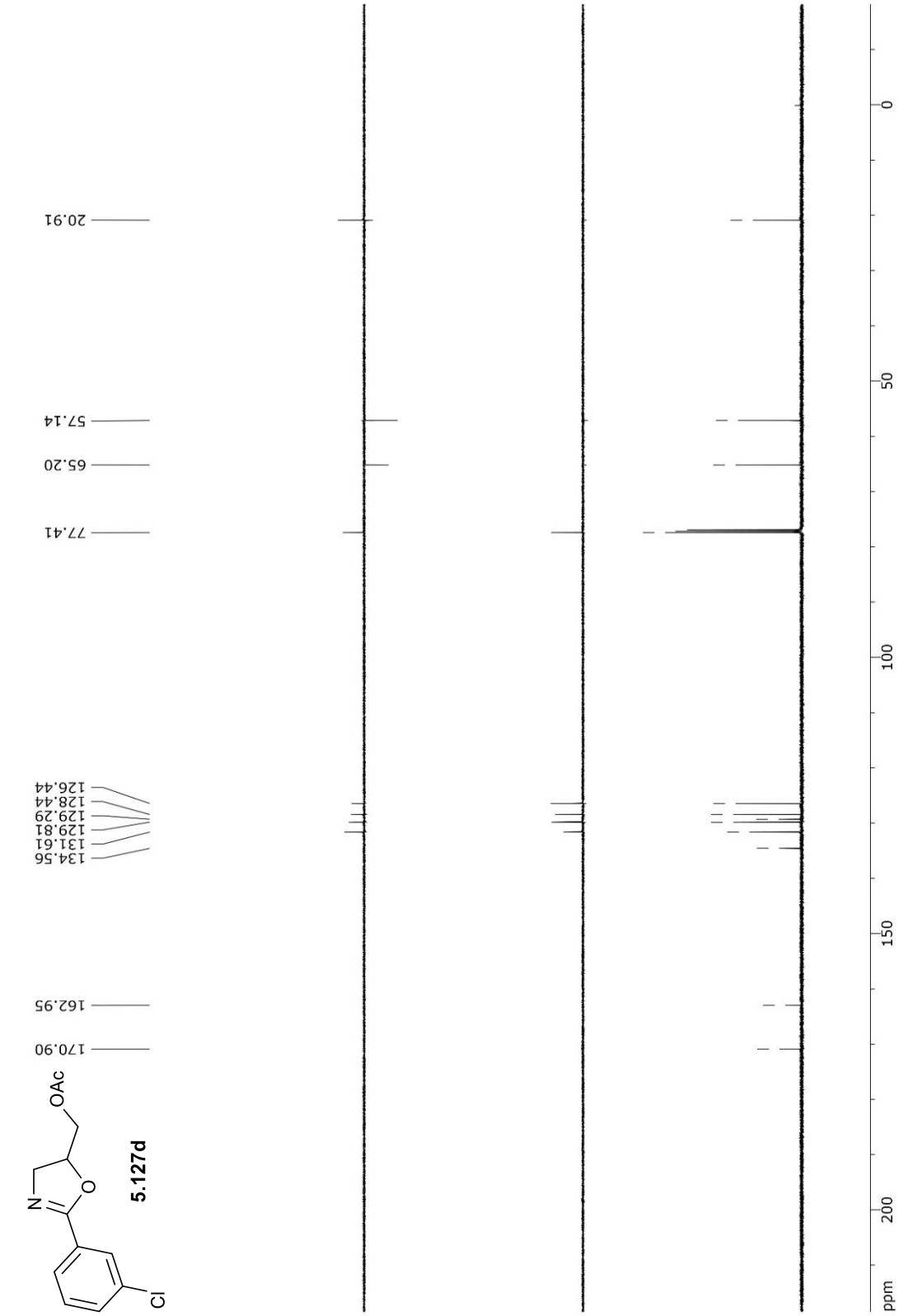
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126.44
128.44
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162.95
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O
Cl
5.127d
ppm
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150
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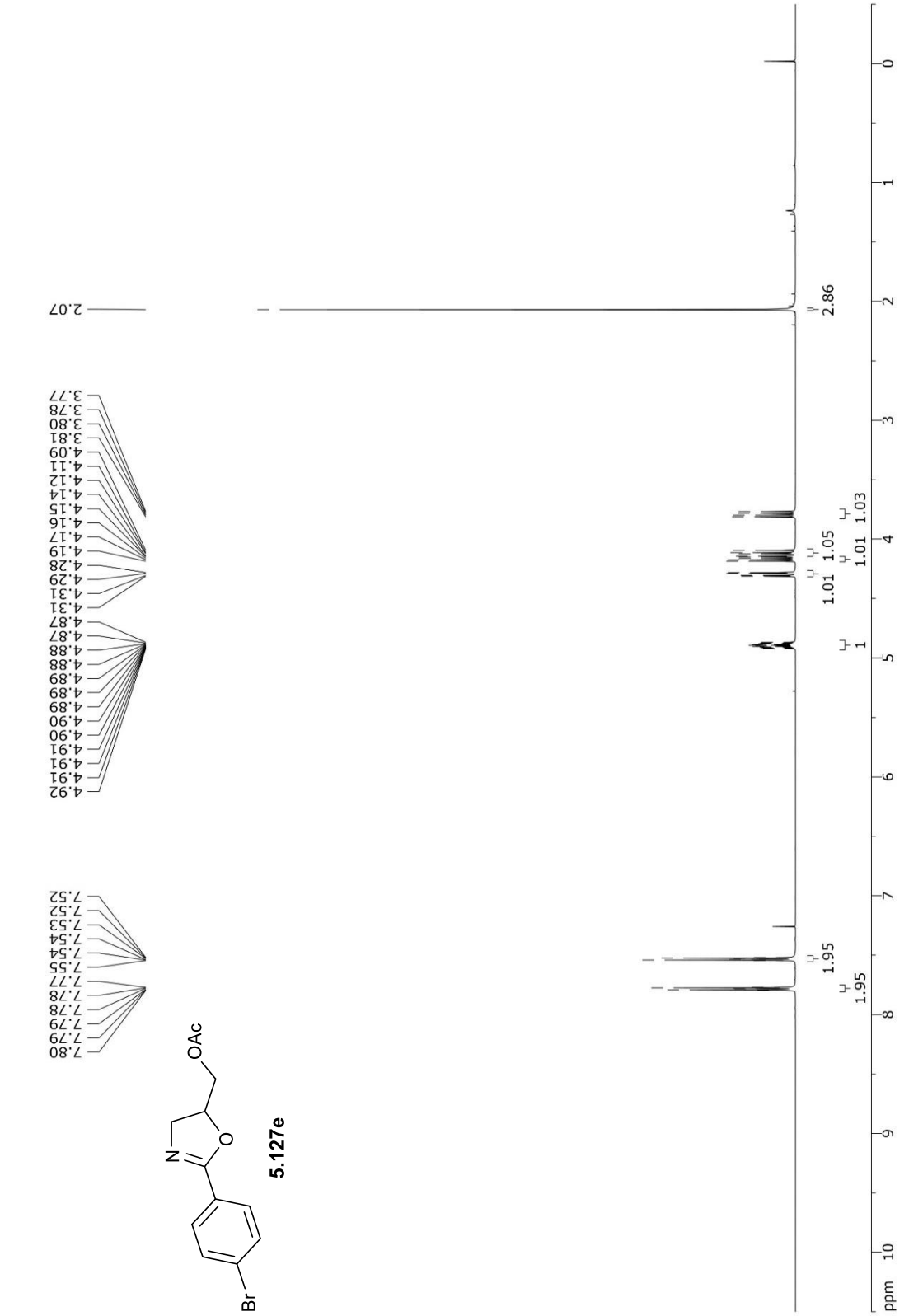
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3.77
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3.80
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4.11
4.12
4.14
4.15
4.16
4.17
4.19
4.28
4.29
4.31
4.31
4.87
4.88
4.88
4.89
4.89
4.89
4.90
4.90
4.91
4.91
4.91
4.92
7.52
7.52
7.53
7.54
7.54
7.55
7.77
7.78
7.78
7.79
7.79
7.80
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Br
5.127e
2.86
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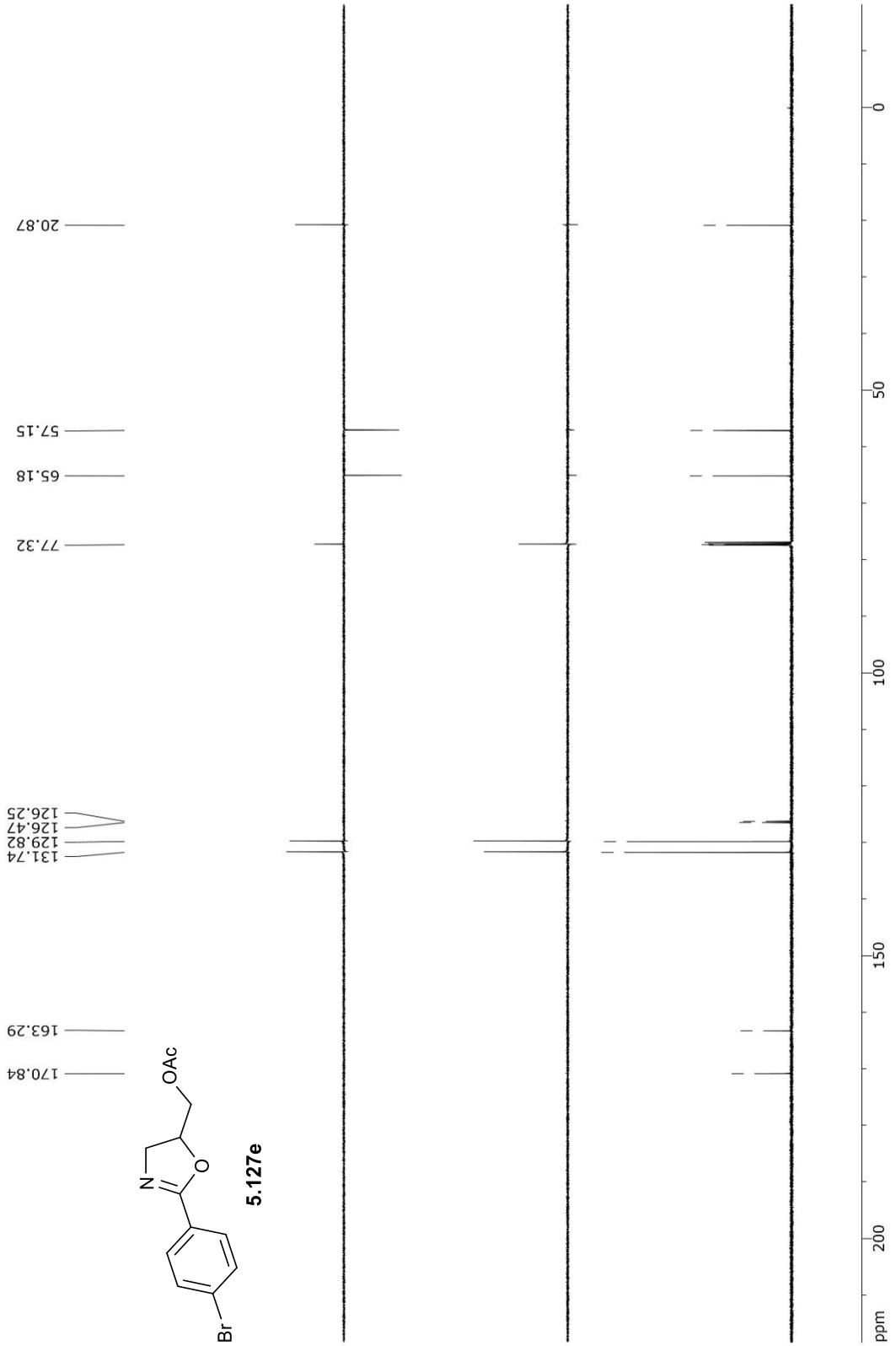
1.01
1.03
1.95
1.95
ppm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57.15
65.18
77.32
126.25
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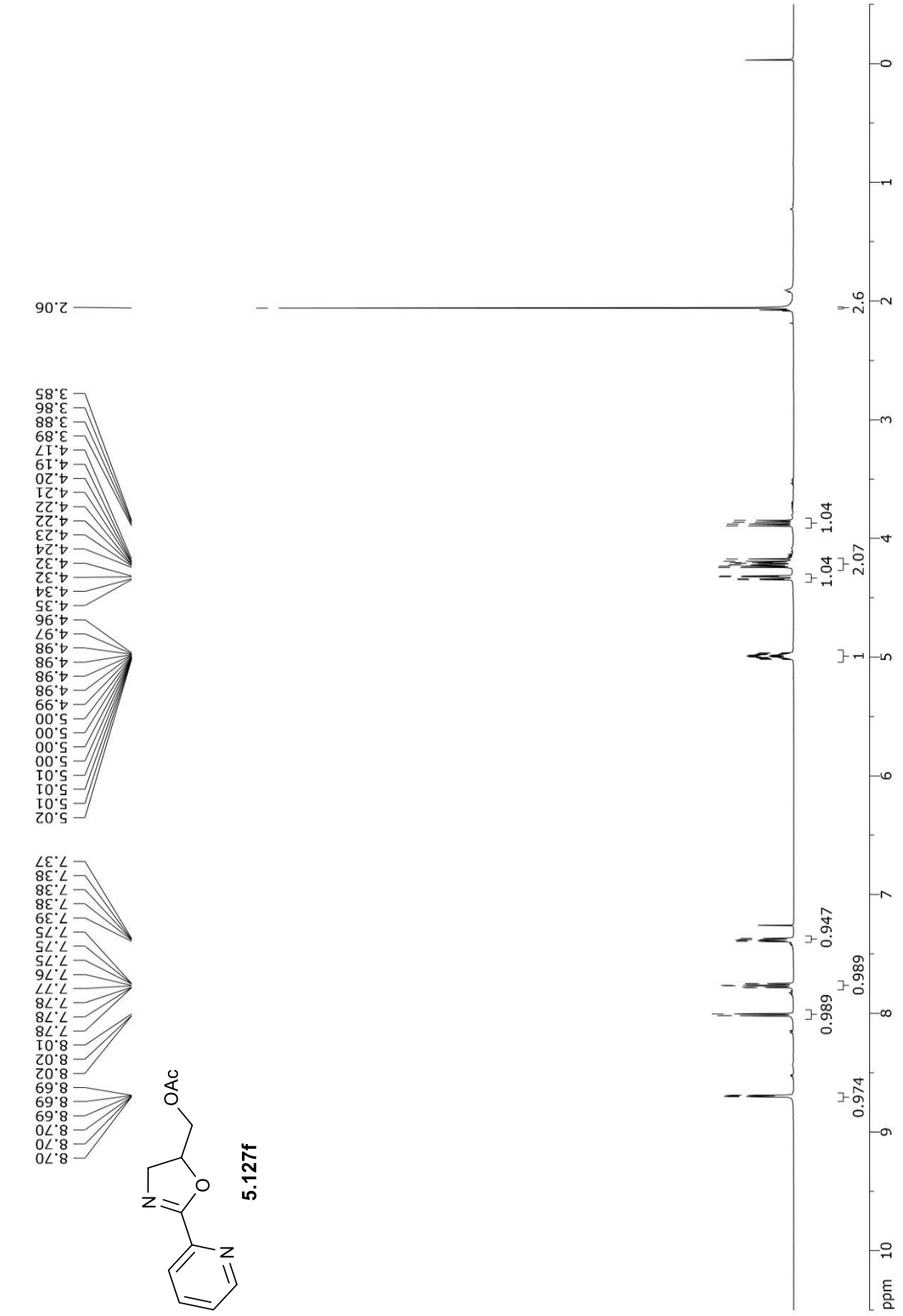
O
Br
5.127e
0
50
100
150
200
ppm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4.32
4.32
4.34
4.35
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4.97
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5.01
5.01
5.01
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7.38
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7.39
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7.75
7.75
7.76
7.77
7.78
7.78
7.78
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8.02
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8.69
8.69
8.70
8.70
8.70
OAc
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2.6
1.04
1.04
2.07
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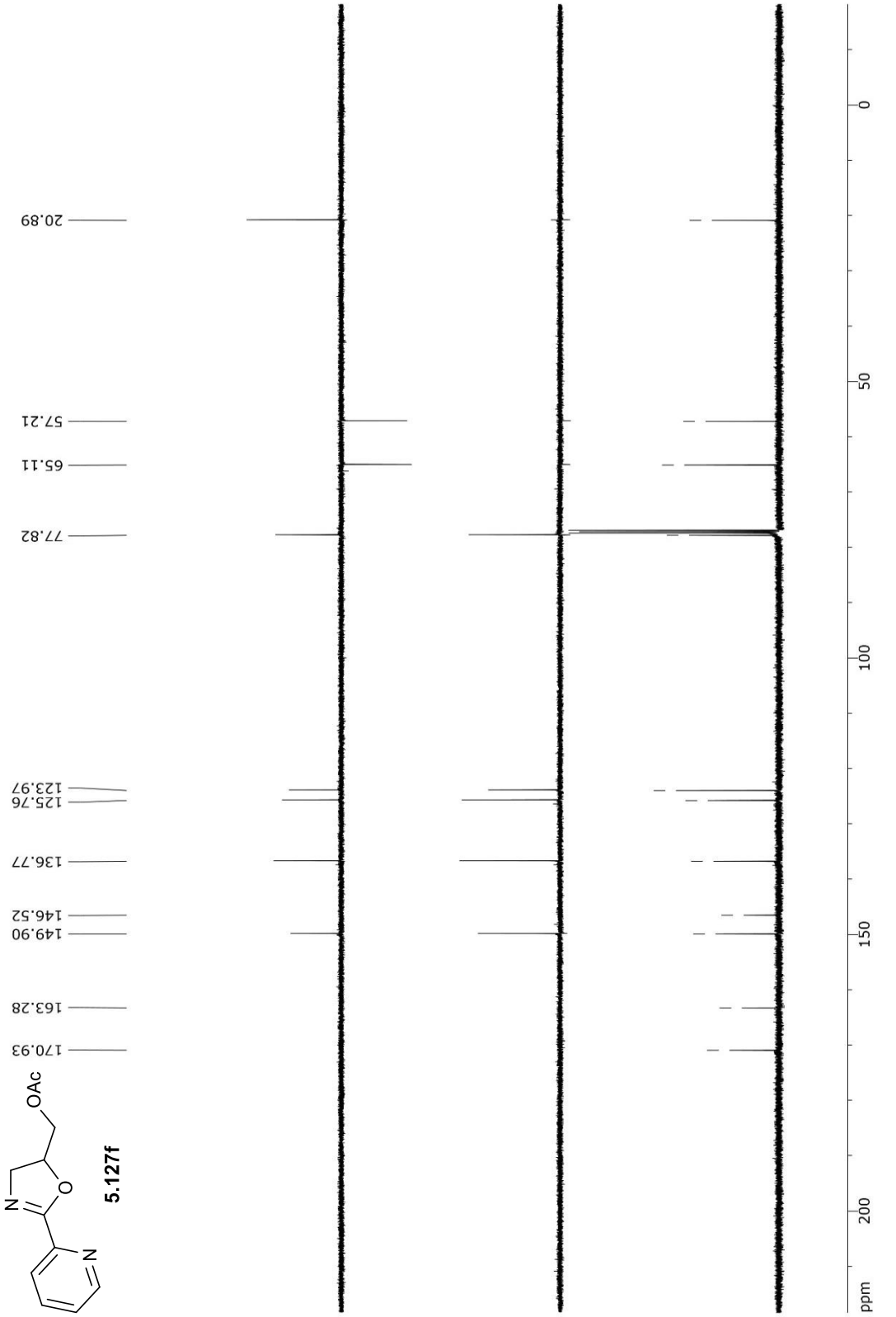
20.89
57.21
65.11
77.82
123.97
125.76
136.77
146.52
149.90
163.28
170.93
OAc
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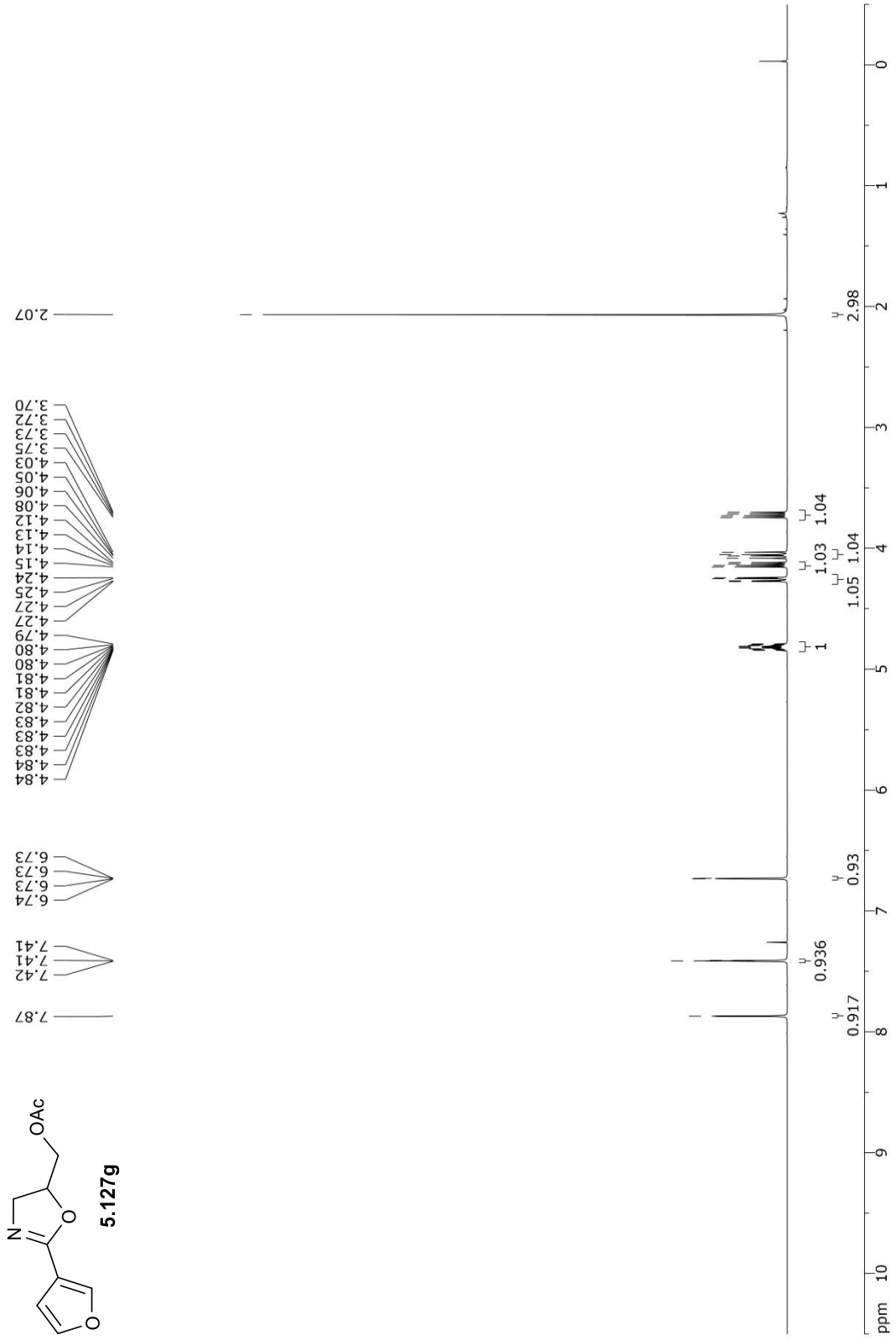
O
N
5.127f
0
50
100
150
200
ppm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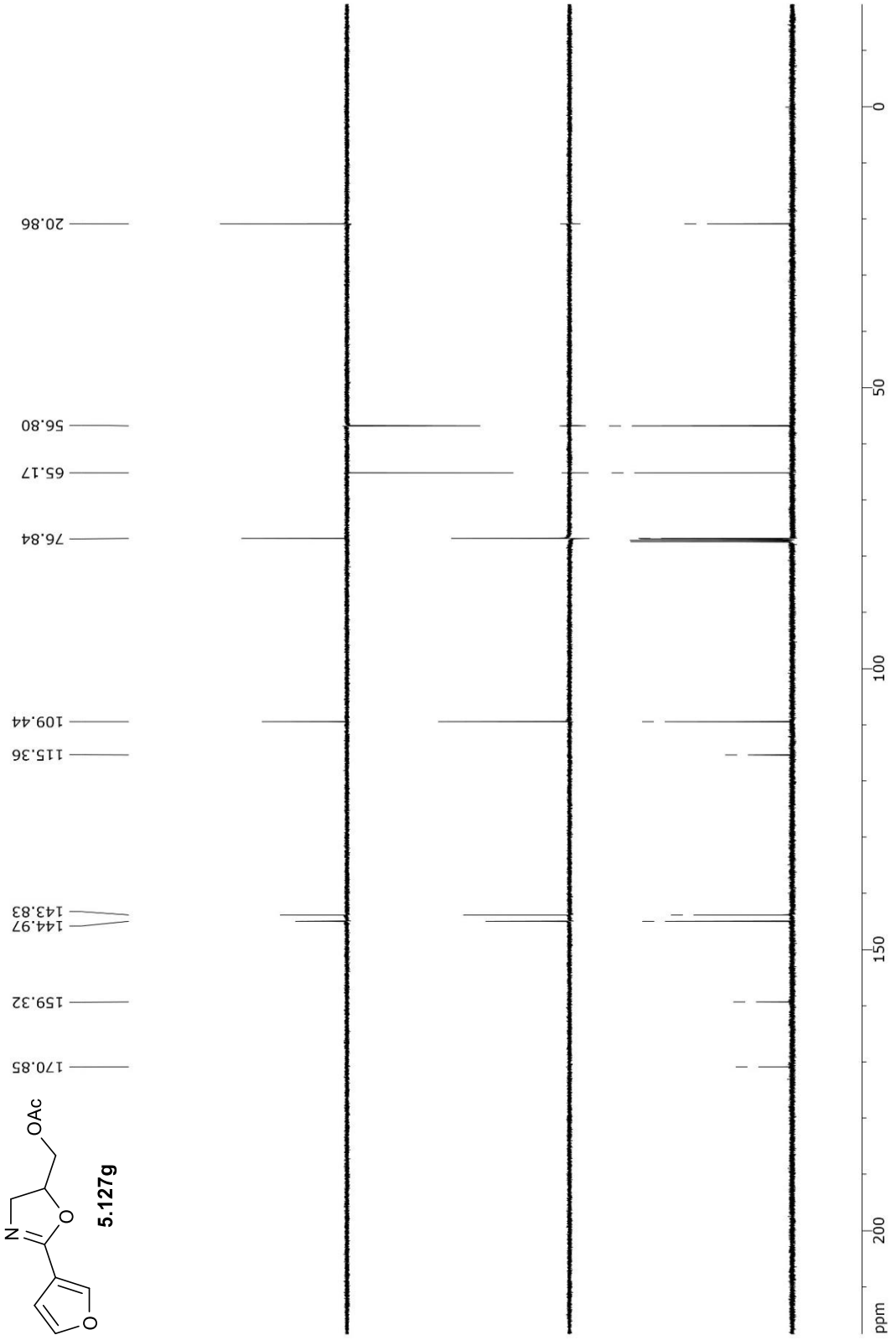
3.70
3.72
3.73
3.75
4.03
4.05
4.06
4.08
4.12
4.13
4.14
4.15
4.24
4.25
4.27
4.27
4.79
4.80
4.80
4.81
4.81
4.82
4.83
4.83
4.83
4.84
4.84
6.73
6.73
6.73
6.74
7.41
7.41
7.42
7.87
0.917
0.936
0.93
1
1.03
1.04
1.05
1.04
2.98
ppm
OAc
O
N
O
5.127g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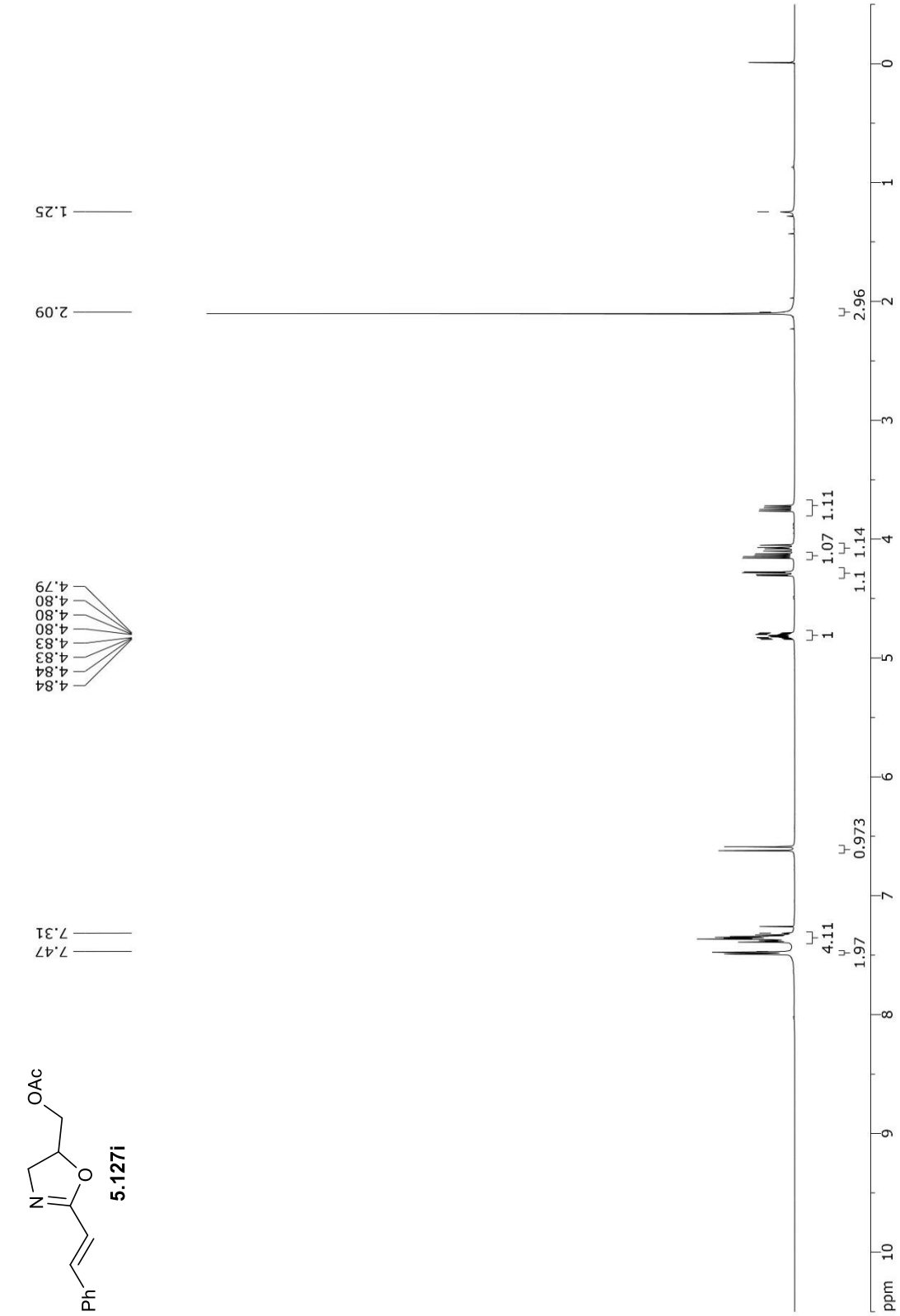
56.80
65.17
76.84
109.44
115.36
143.83
144.97
159.32
170.85
OAc
O
N
O
5.127g
0
50
100
150
200
ppm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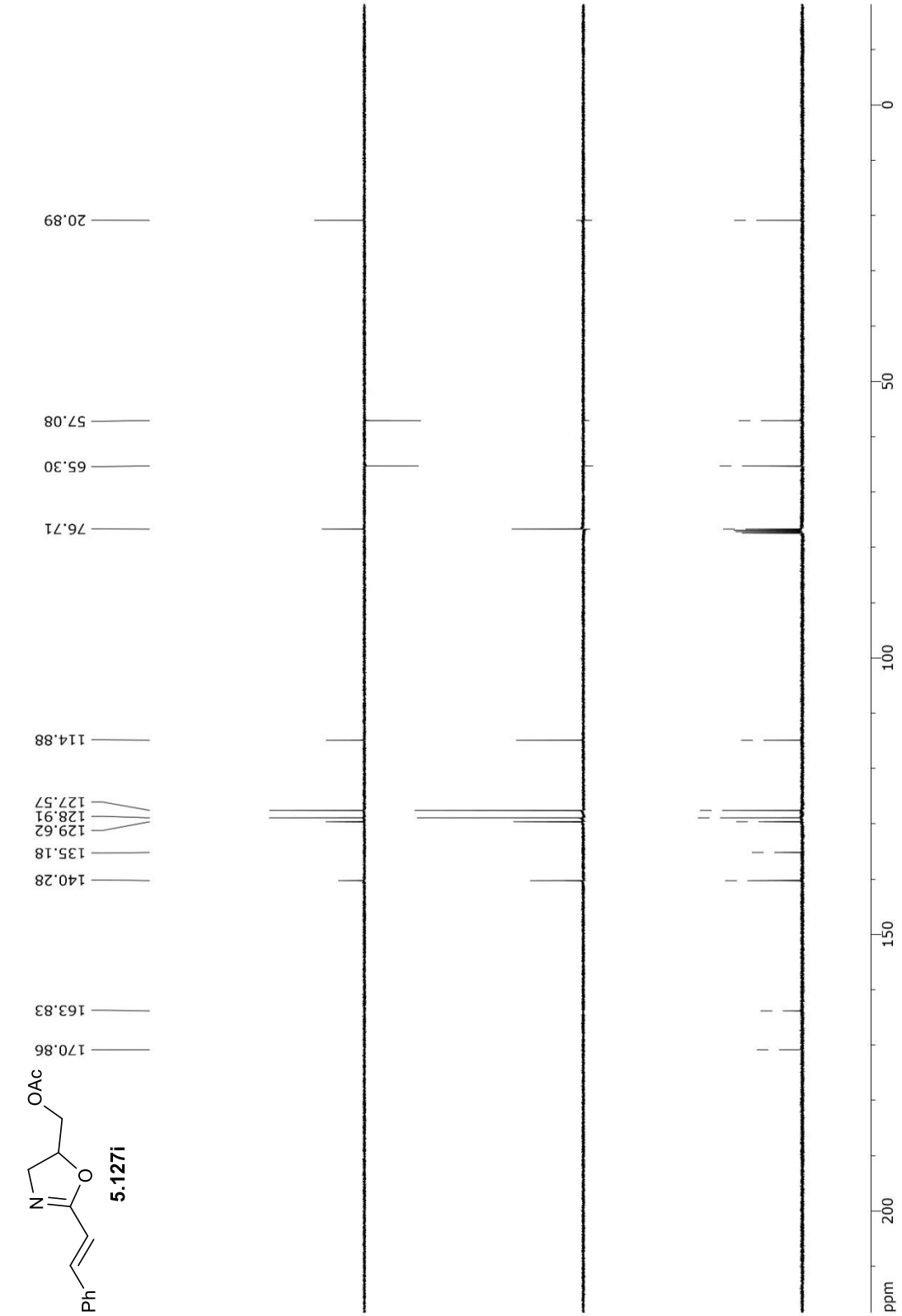
N
O
Ph
5.127i
7.47
7.31
4.84
4.84
4.83
4.83
4.80
4.80
4.80
4.79
2.09
1.25
4.11
1.97
0.973
1
1.1
1.07
1.14
1.11
2.96
ppm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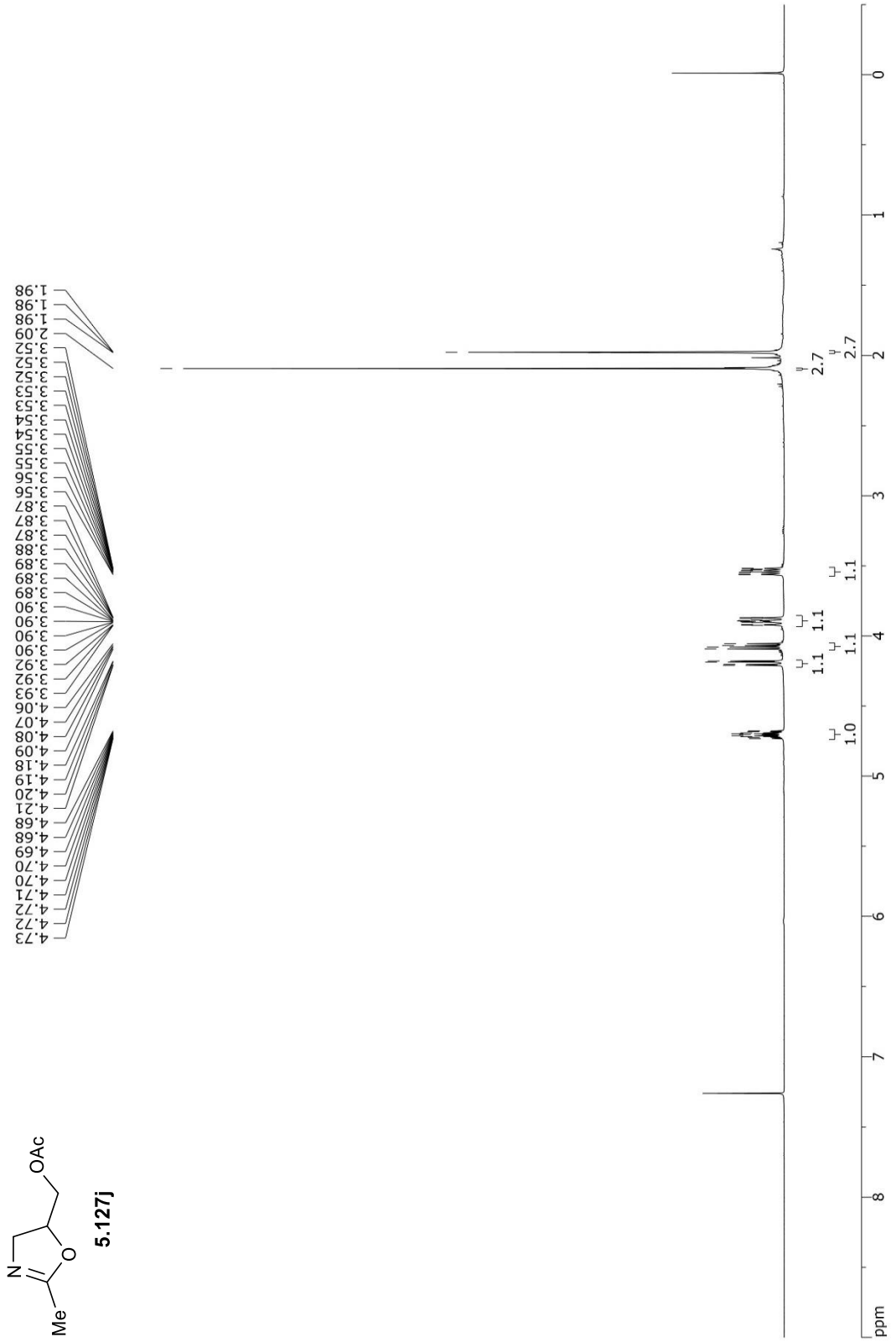
76.71
114.88
127.57
128.91
129.62
135.18
140.28
163.83
170.86
OAc
O
N
Ph
5.127i
0
50
100
150
200
ppm


OAc
N
O
Me
5.127j
1.98
1.98
1.98
2.09
3.52
3.52
3.52
3.53
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3.54
3.55
3.55
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3.88
3.89
3.89
3.90
3.90
3.90
3.90
3.92
3.92
3.93
4.06
4.07
4.08
4.09
4.18
4.19
4.20
4.21
4.68
4.68
4.69
4.70
4.70
4.71
4.72
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4.73
1.0
1.1
1.1
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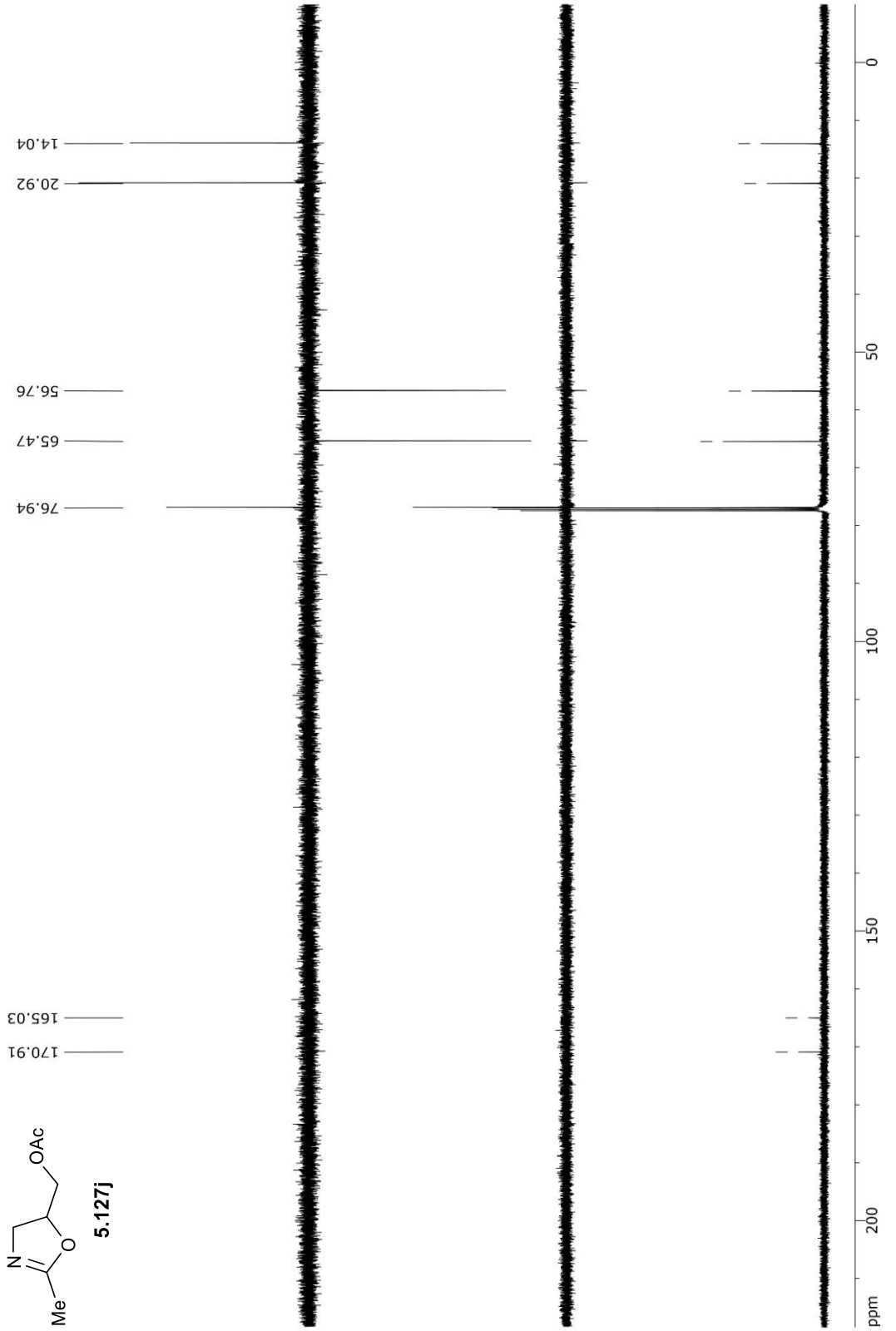
1.1
1.1
2.7
2.7
ppm


14.04
20.92
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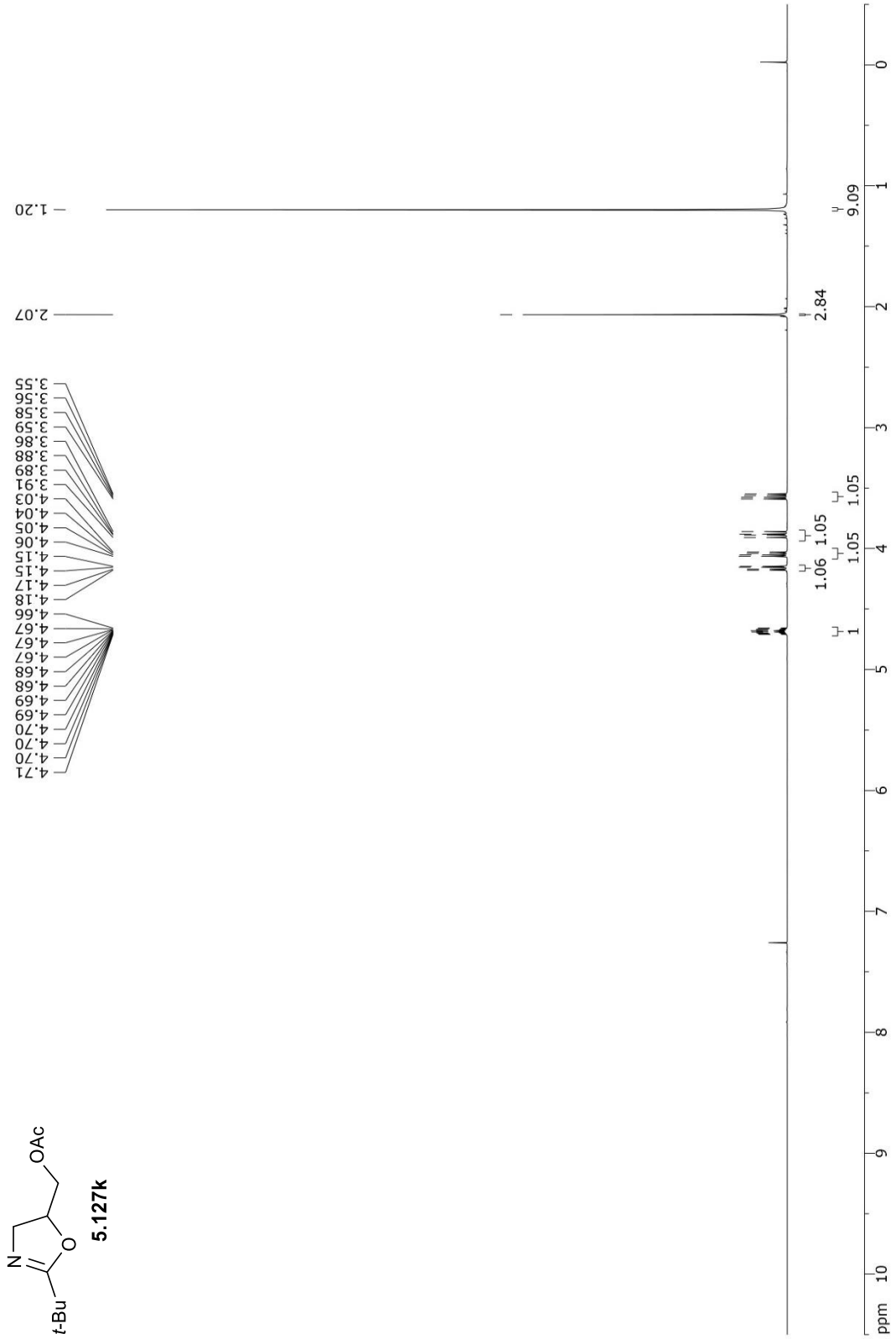
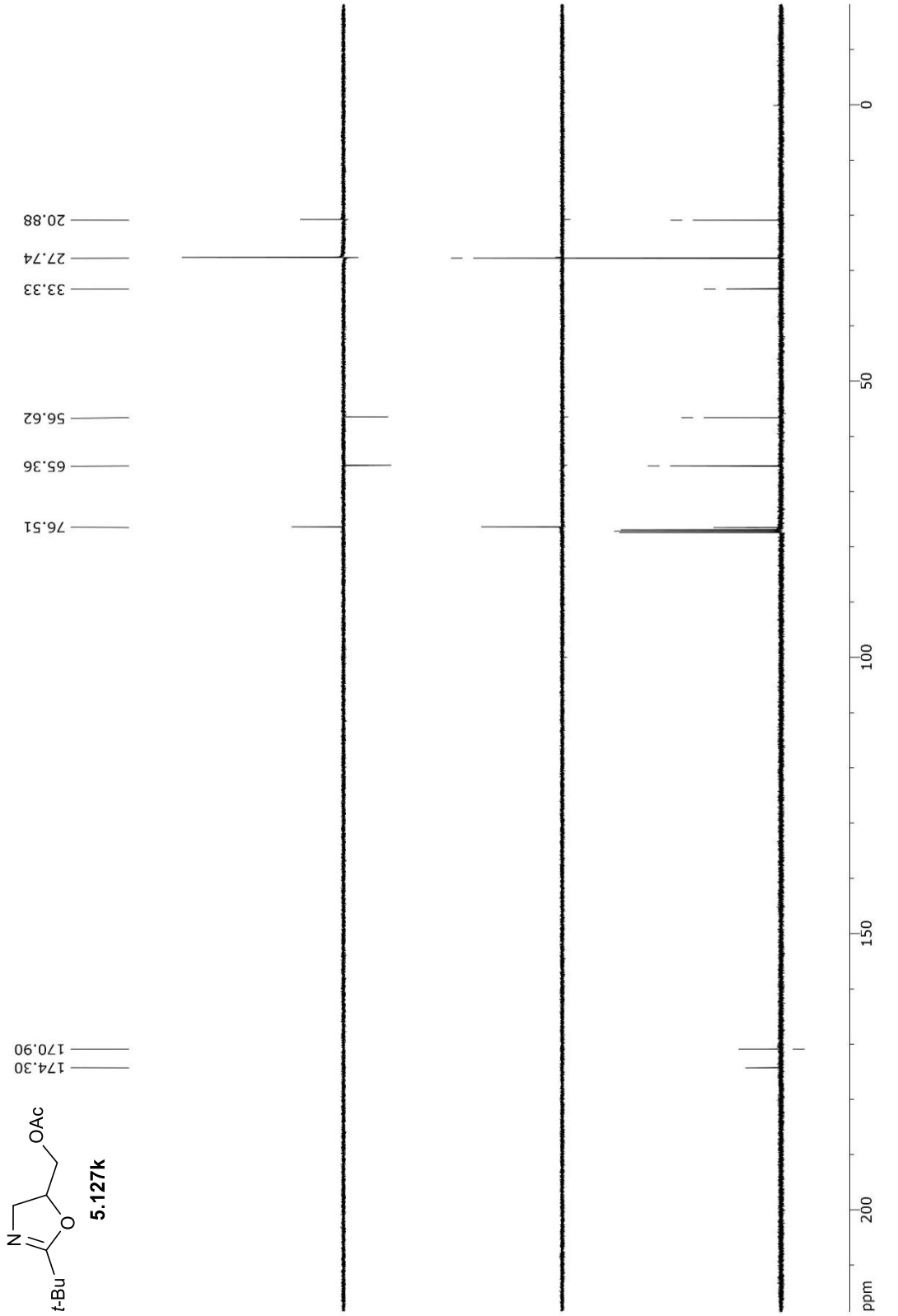
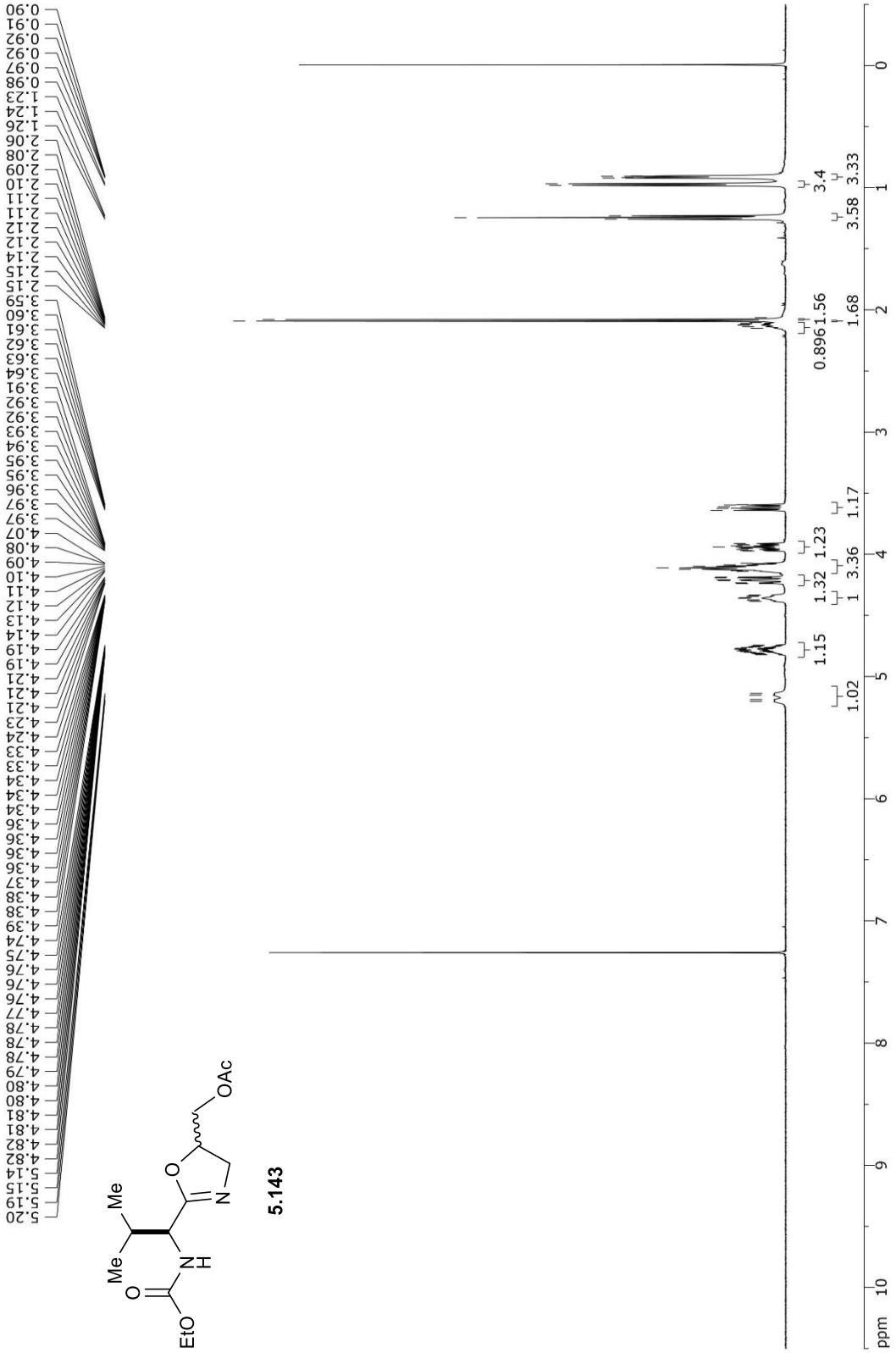
65.47
76.94
165.03
170.91
0
50
100
150
200
ppm
OAc
N
O
Me
5.127j


1.20
2.07
3.55
3.56
3.58
3.59
3.86
3.88
3.89
3.91
4.03
4.04
4.05
4.06
4.15
4.15
4.17
4.18
4.66
4.67
4.67
4.67
4.68
4.68
4.69
4.69
4.70
4.70
4.70
4.71
9.09
2.84
1.05
1.05
1.06
1.05
1
ppm
OAc
N
O
t-Bu
5.127k


20.88
27.74
33.33
56.62
65.36
76.51
170.90
174.30
OAc
N
O
t-Bu
5.127k
0
50
100
150
200
ppm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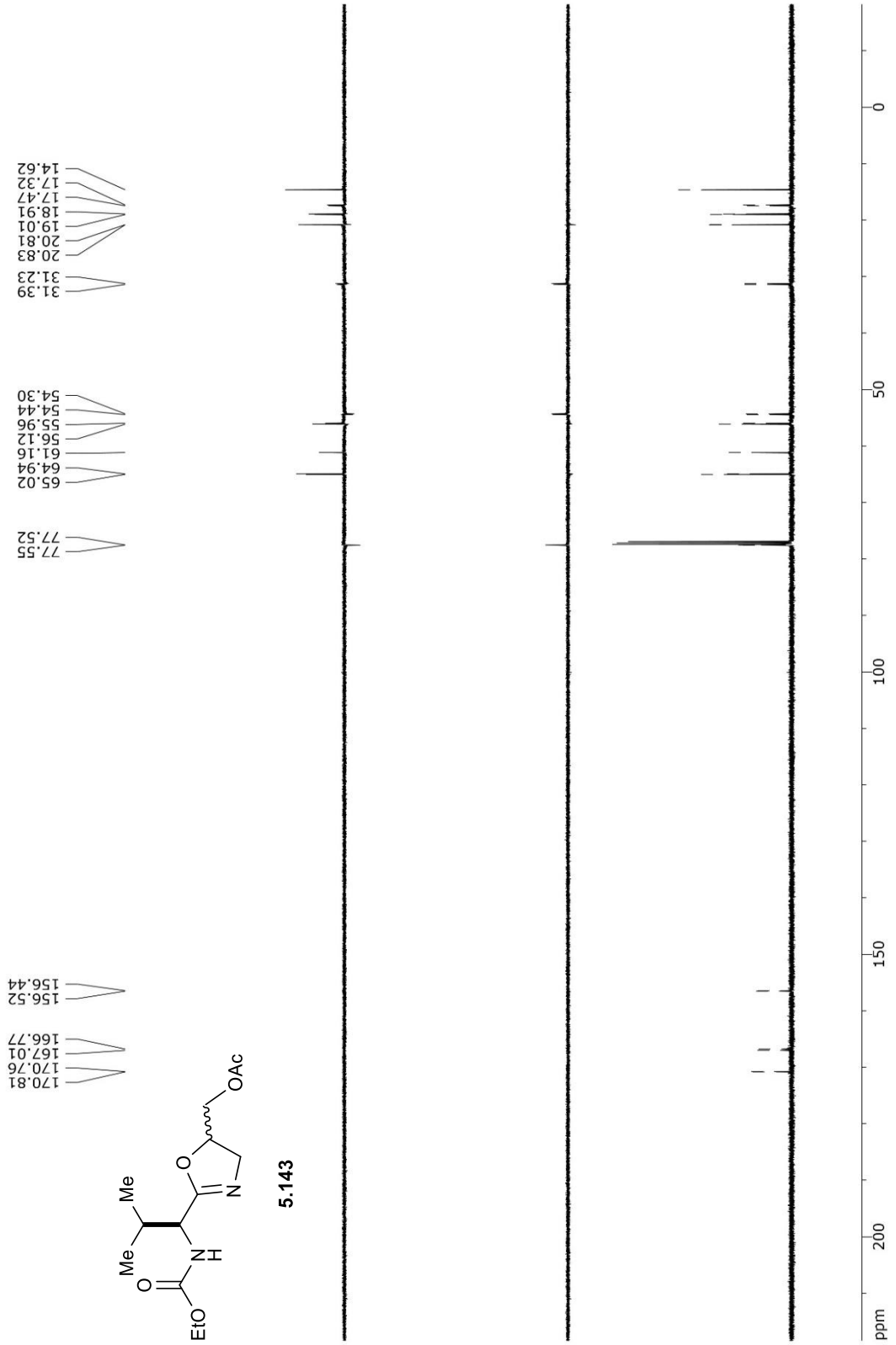
EtO
O
Me
Me
N
H
O
N
OAc
ppm
0 1 2 3 4 5 6 7 8 9 10
1.02
1.15
1
1.32
3.36
1.23
1.17
0.896
1.56
1.68
3.58
3.4
3.33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18.91
19.01
20.81
20.83
31.23
31.39
54.30
54.44
55.96
56.12
61.16
64.94
65.02
77.52
77.55
156.44
156.52
166.77
167.01
170.76
170.81
Me
Me
O
N
H
O
EtO
O
N
OAc
5.143
ppm
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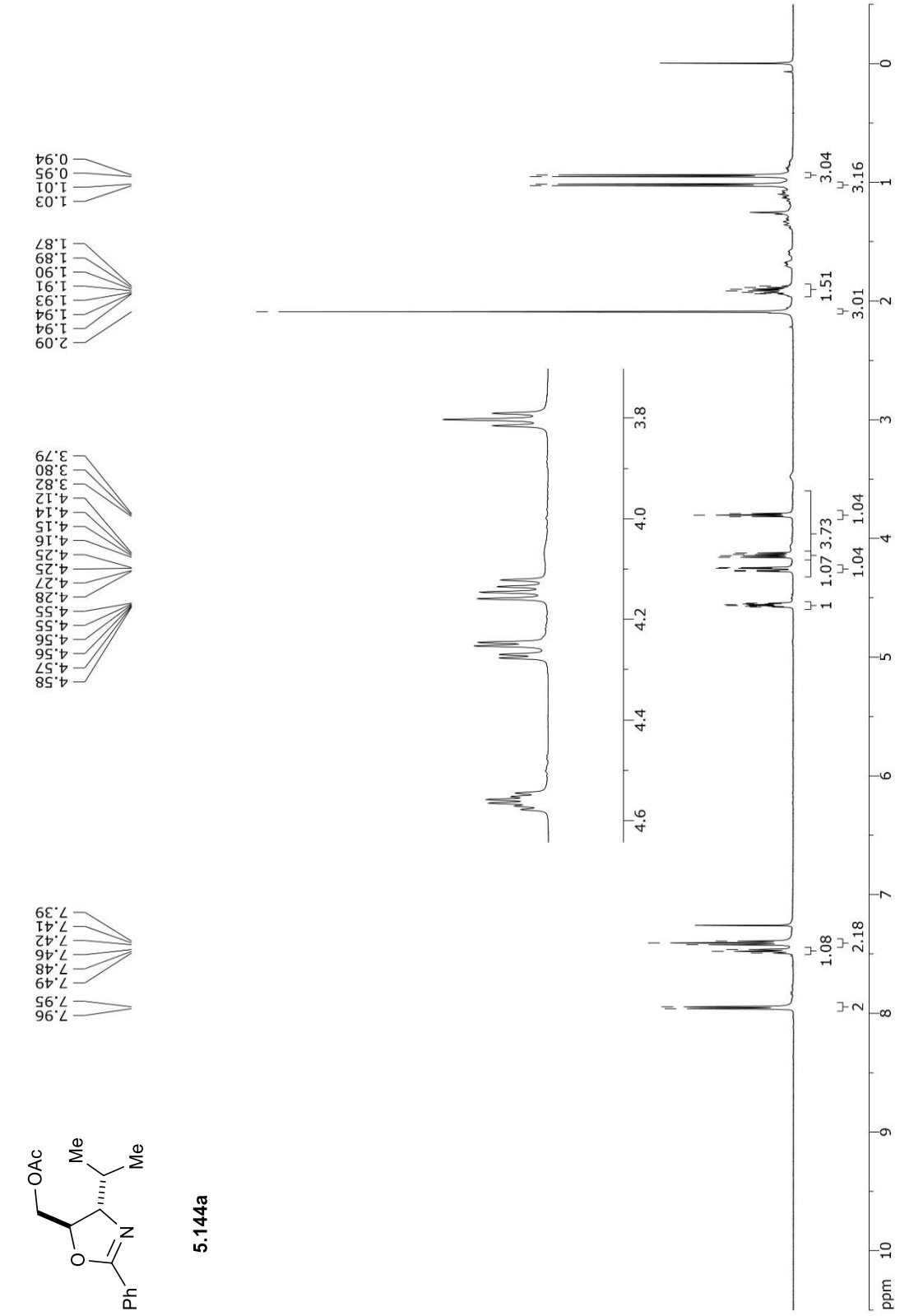
100
150
200


OAc
Me
Me
N
O
Ph
5.144a
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7.49
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7.46
7.42
7.41
7.39
4.58
4.57
4.56
4.56
4.55
4.55
4.28
4.27
4.25
4.25
4.16
4.15
4.14
4.12
3.82
3.80
3.79
2.09
1.94
1.94
1.93
1.91
1.90
1.89
1.87
1.03
1.01
0.95
0.94
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2.18
1.07
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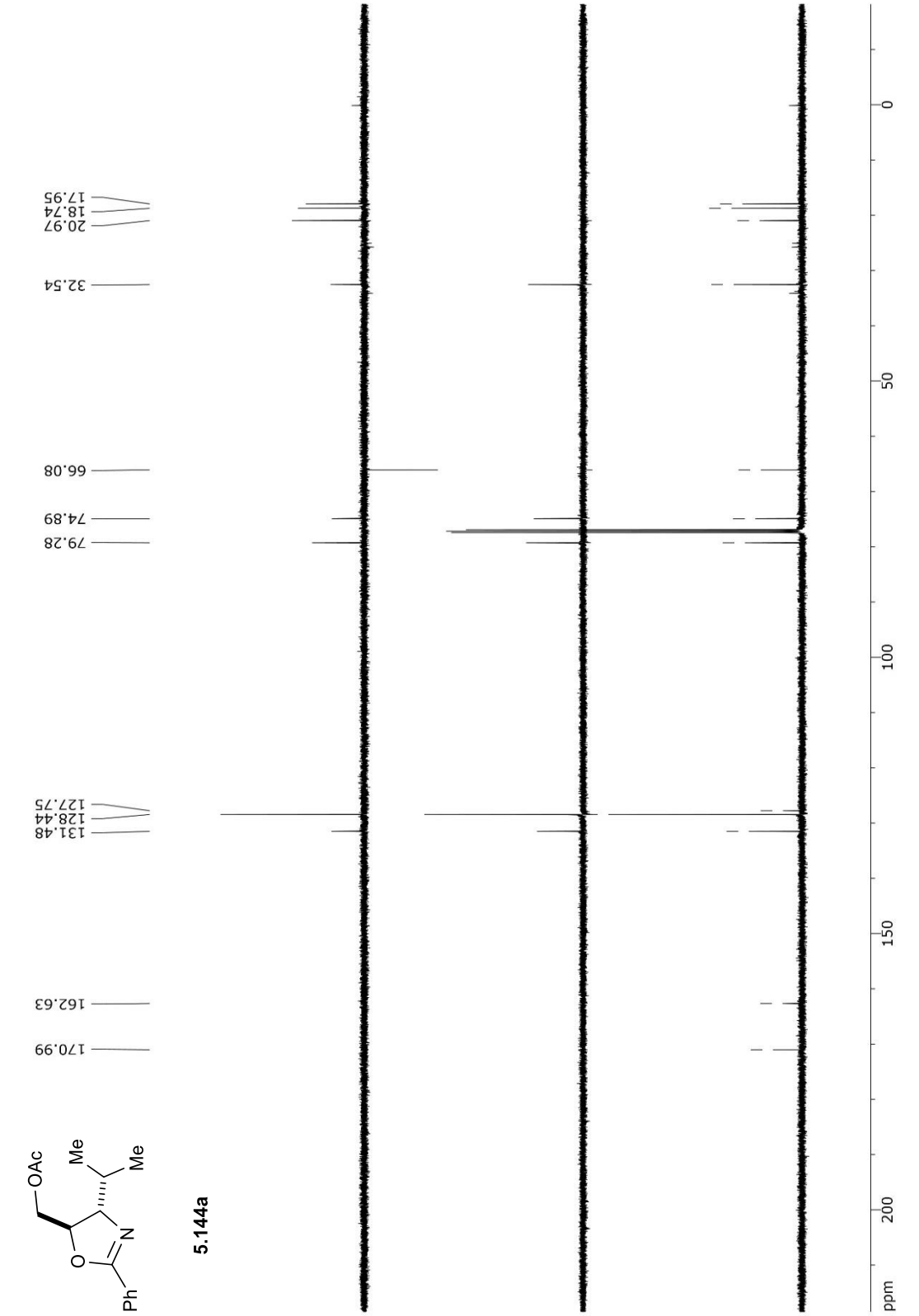
1.04
1.51
3.01
3.04
3.16
ppm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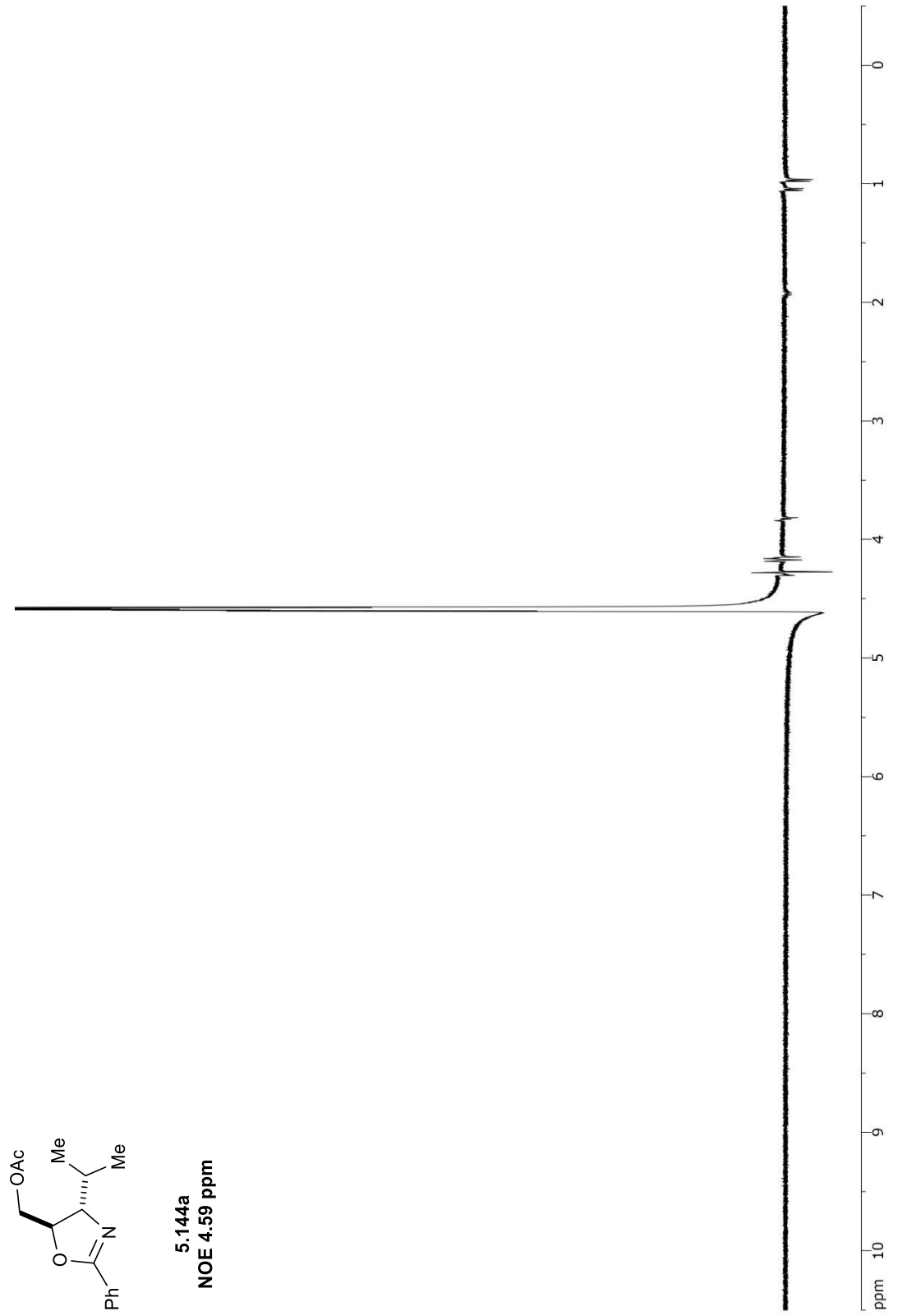
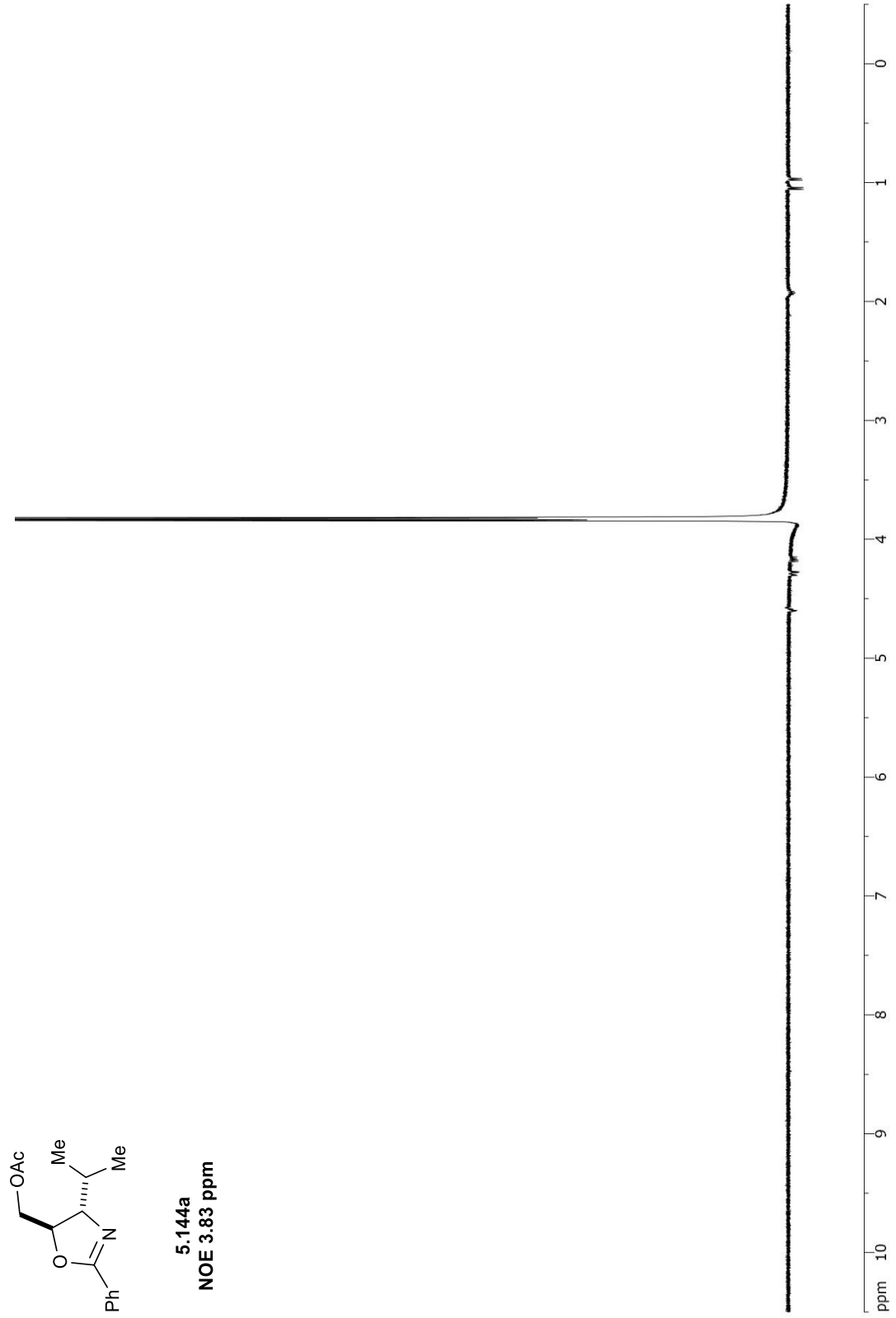
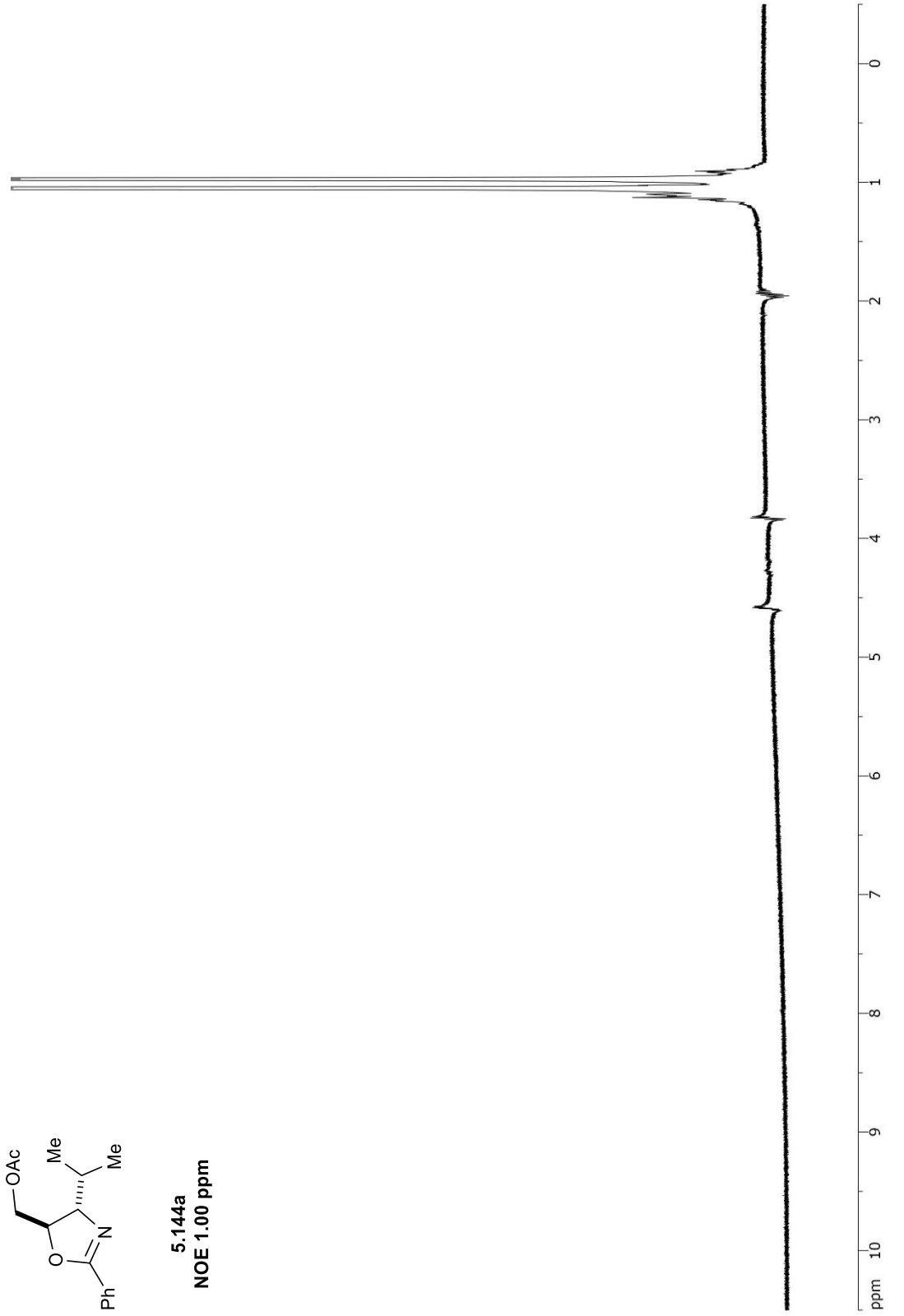
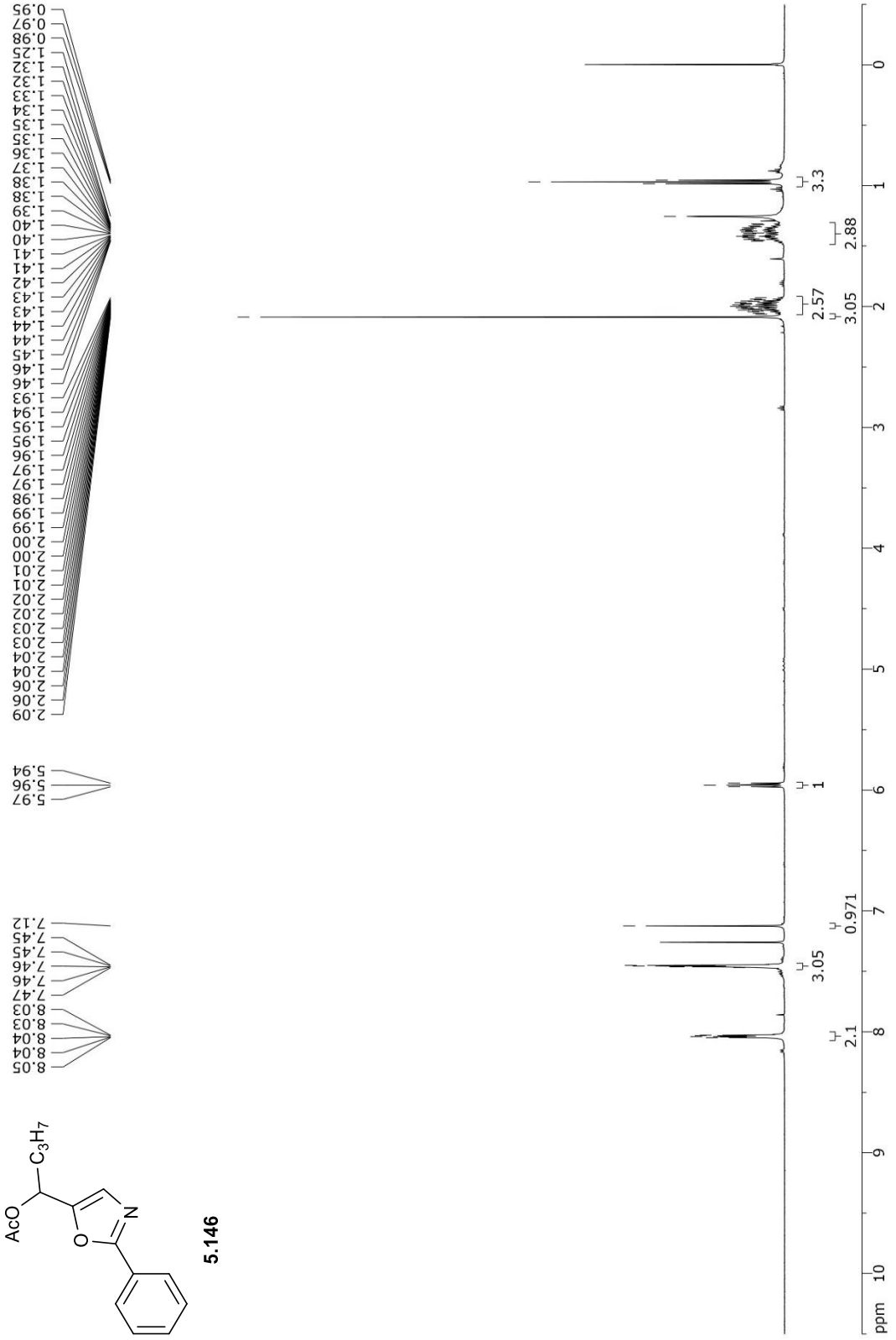
18.74
20.97
32.54
66.08
74.89
79.28
127.75
128.44
131.48
162.63
170.99
ppm
0
50
100
150
200
OAc
Me
Me
N
O
Ph
5.144a


OAc
Me
Me
N
O
Ph
5.144a
NOE 4.59 ppm
ppm
10
9
8
7
6
5
4
3
2
1
0


OAc
Me
Me
N
O
Ph
5.144a
NOE 3.83 ppm
ppm
10
9
8
7
6
5
4
3
2
1
0


OAc
Me
Me
N
O
Ph
5.144a
NOE 1.00 ppm
0
1
2
3
4
5
6
7
8
9
10
ppm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0.98
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1.32
1.33
1.34
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1.35
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1.38
1.39
1.40
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1.41
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1.42
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1.43
1.44
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1.45
1.46
1.46
1.93
1.94
1.95
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1.96
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2.00
2.01
2.01
2.02
2.02
2.03
2.03
2.04
2.04
2.06
2.06
2.09
5.94
5.96
5.97
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7.45
7.45
7.46
7.46
7.47
8.03
8.03
8.04
8.04
8.05
AcO
C3H7
O
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5.146
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1
3.05
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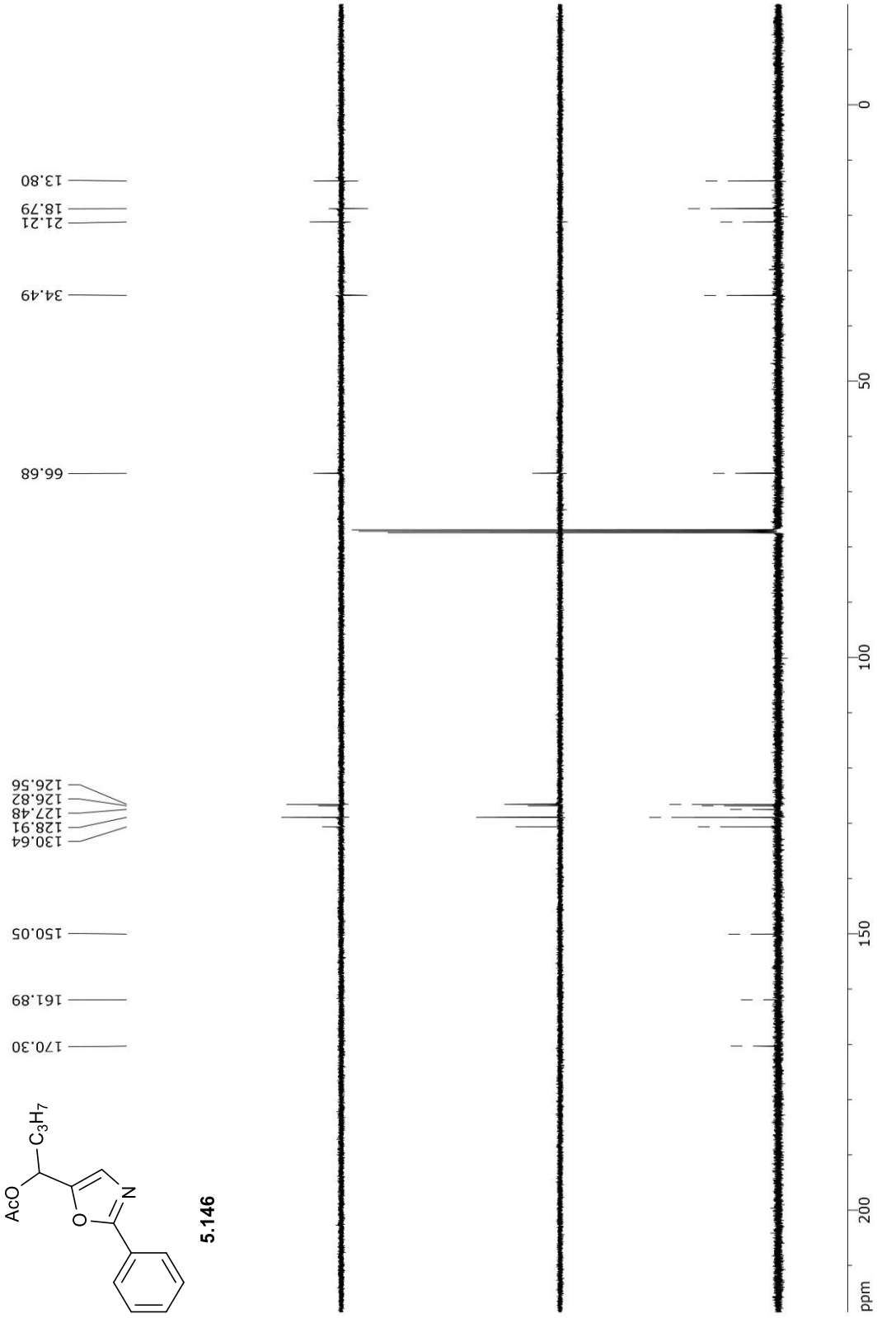
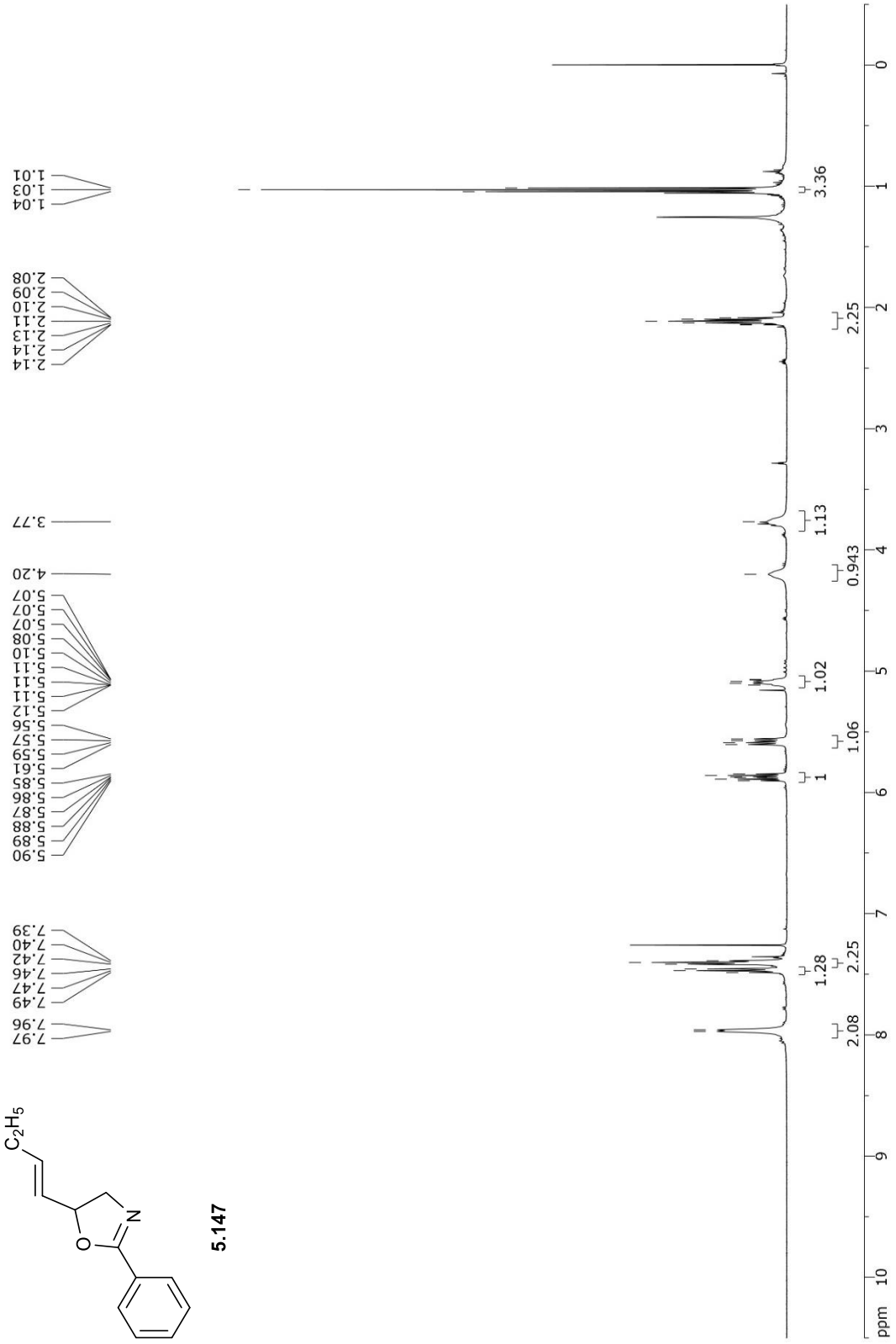
2.88
3.3
ppm


13.80
18.79
21.21
34.49
66.68
126.56
126.82
127.48
128.91
130.64
150.05
161.89
170.30
ppm
0
50
100
150
200
AcO
C_3H_7
O
N

5.146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1.01
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2.14
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2.10
2.09
2.08
3.77
4.20
5.07
5.07
5.07
5.08
5.10
5.11
5.11
5.11
5.12
5.56
5.57
5.59
5.61
5.85
5.86
5.87
5.88
5.89
5.90
7.39
7.40
7.42
7.46
7.47
7.49
7.96
7.97
2.08
1.28
2.25
1
1.06
1.02
0.943
1.13
2.25
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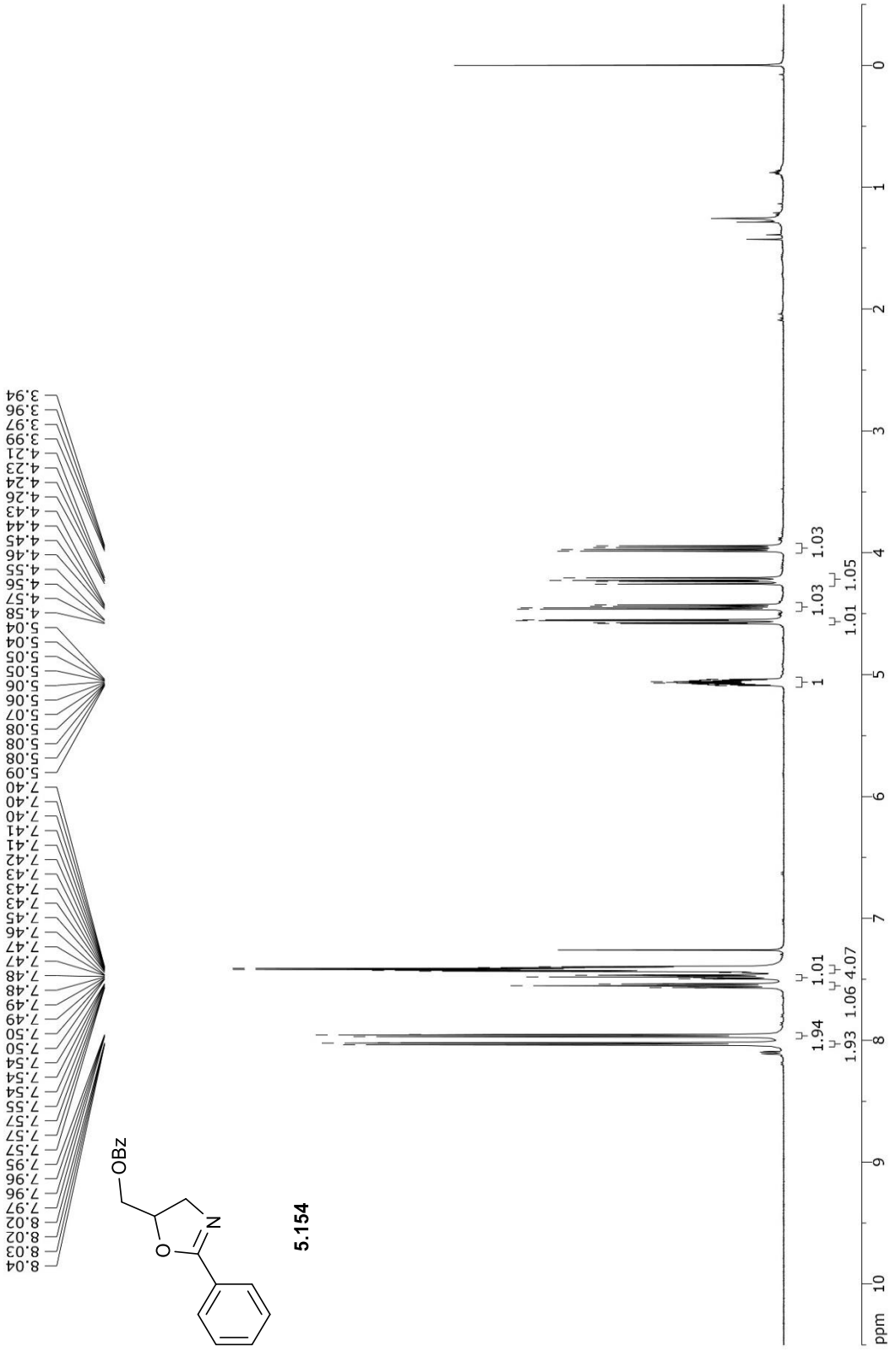
2
3
4
5
6
7
8
9
10
C2H5
O
N

5.147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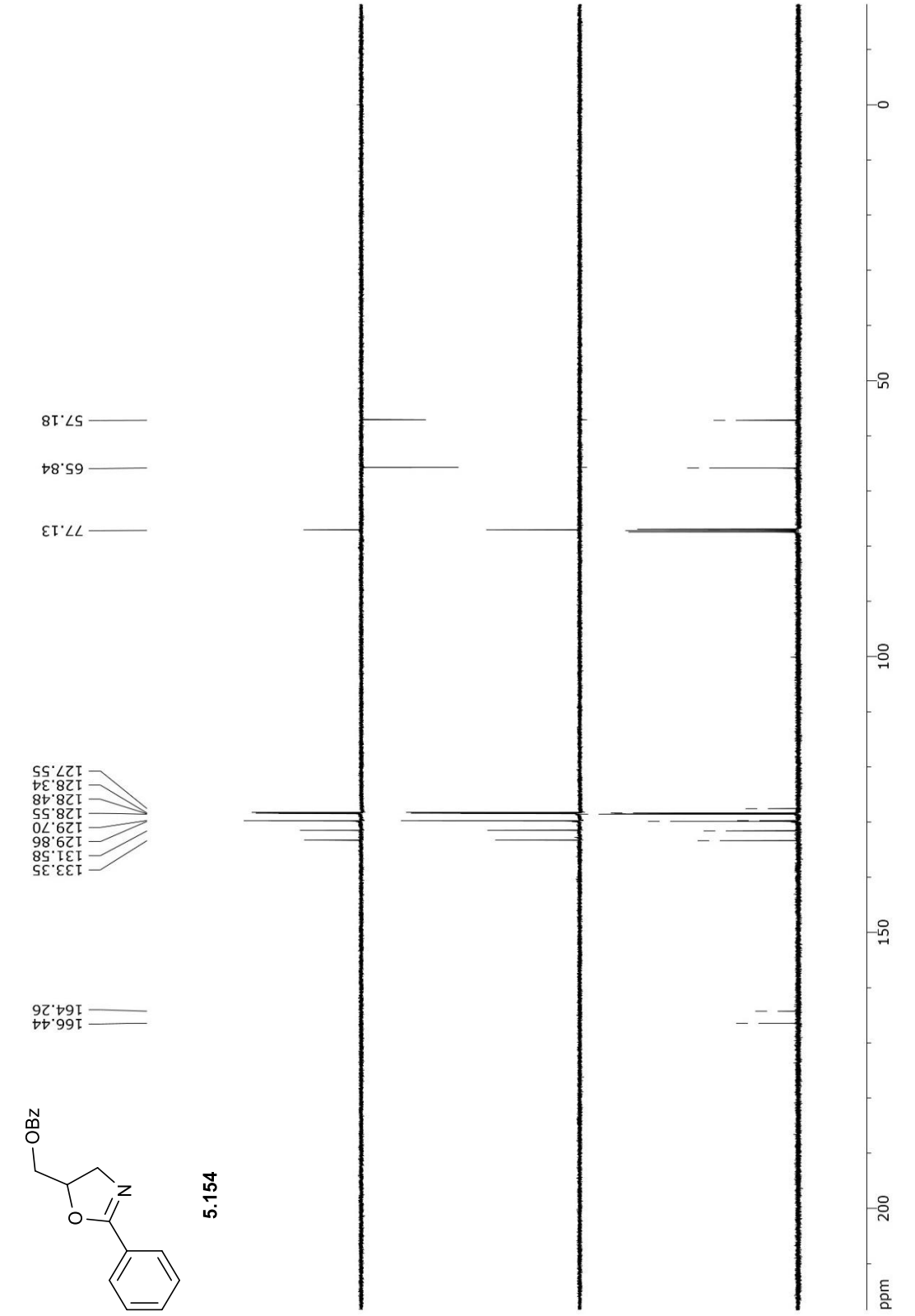
N
O
5.154
ppm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77.13
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128.34
128.48
128.55
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OBz
N
O
5.154
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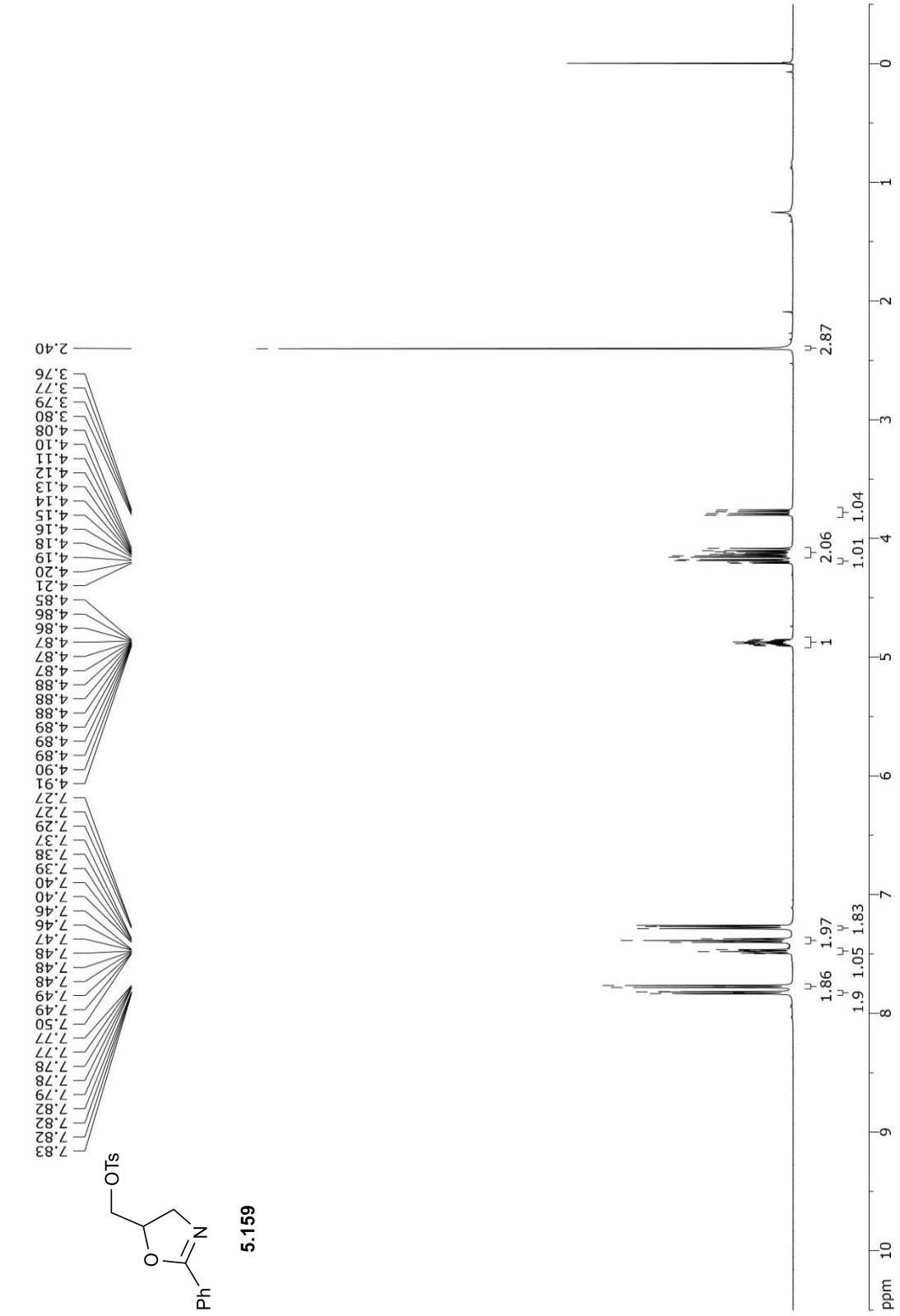
100
150
200
ppm


OTs
N
O
Ph
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3.77
3.79
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4.10
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4.12
4.13
4.14
4.15
4.16
4.18
4.19
4.20
4.21
4.85
4.86
4.86
4.87
4.87
4.87
4.88
4.88
4.88
4.89
4.89
4.90
4.91
7.27
7.27
7.29
7.37
7.38
7.39
7.40
7.40
7.46
7.46
7.47
7.48
7.48
7.48
7.49
7.49
7.50
7.77
7.77
7.78
7.78
7.79
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7.82
7.82
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1.01
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1.86
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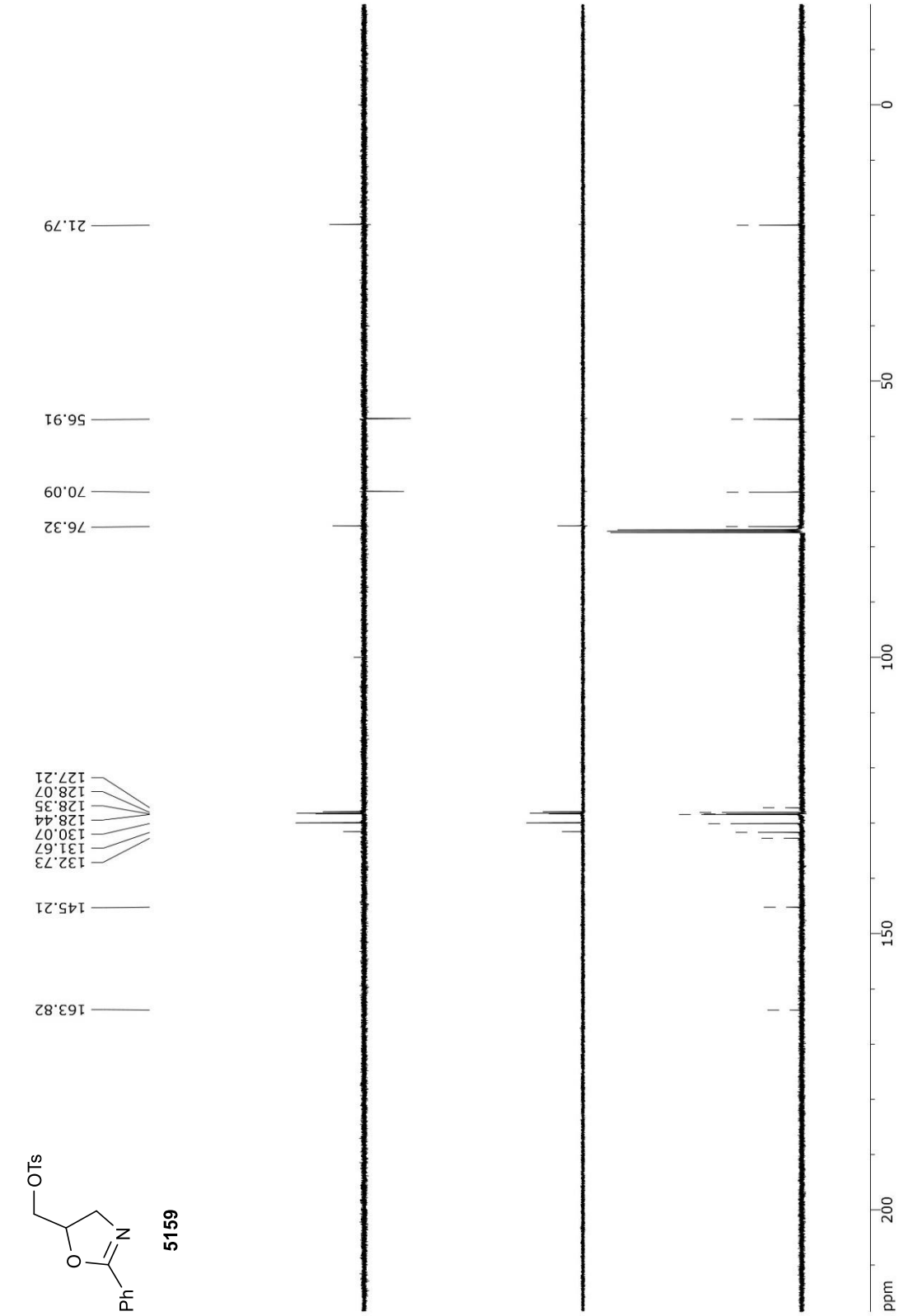
1.9
1.83
ppm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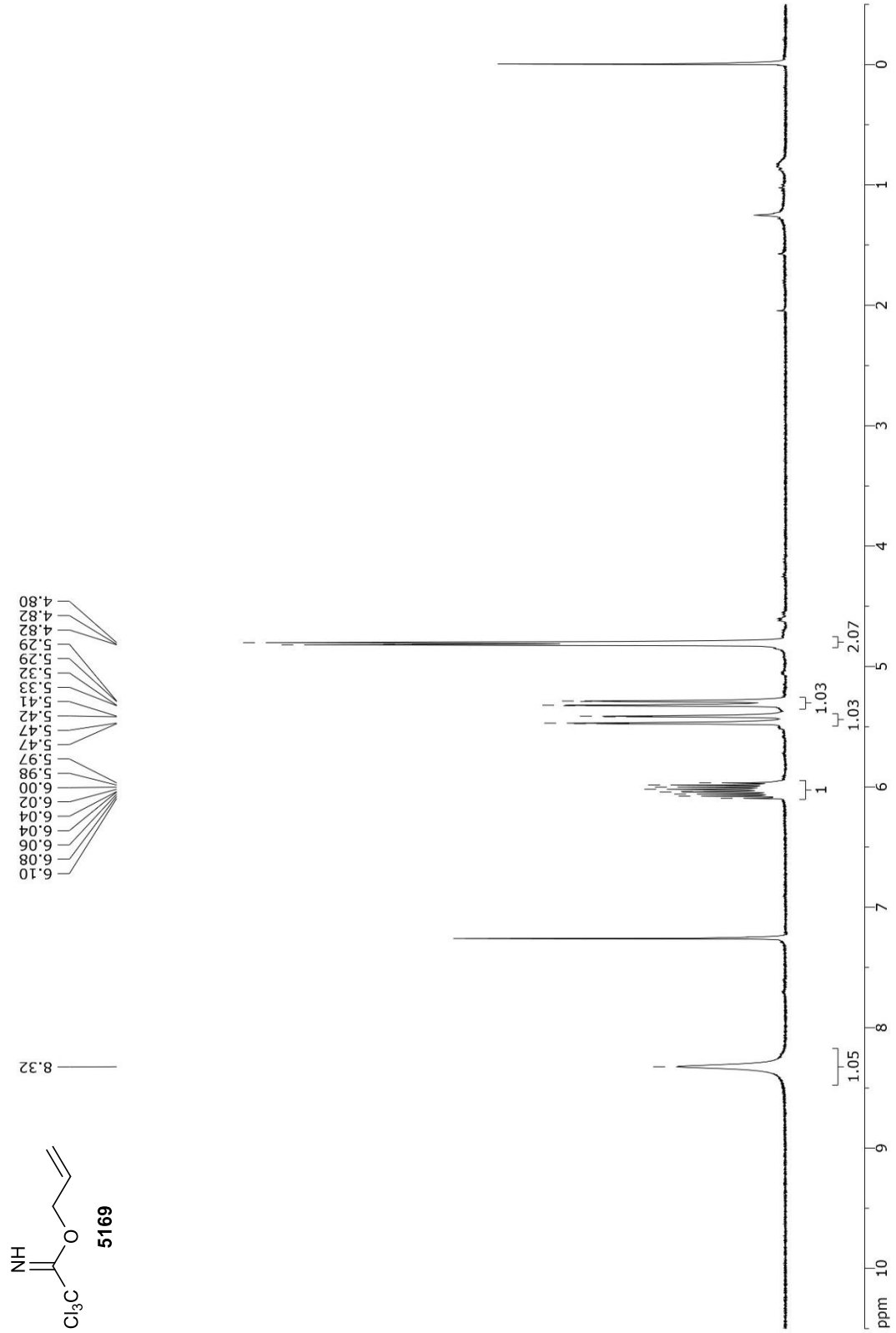
70.09
76.32
127.21
128.07
128.35
128.44
130.07
131.67
132.73
145.21
163.82
OTs
N
O
Ph
5159
0
50
100
150
200
ppm


5169
NH
O
Cl3C
8.32
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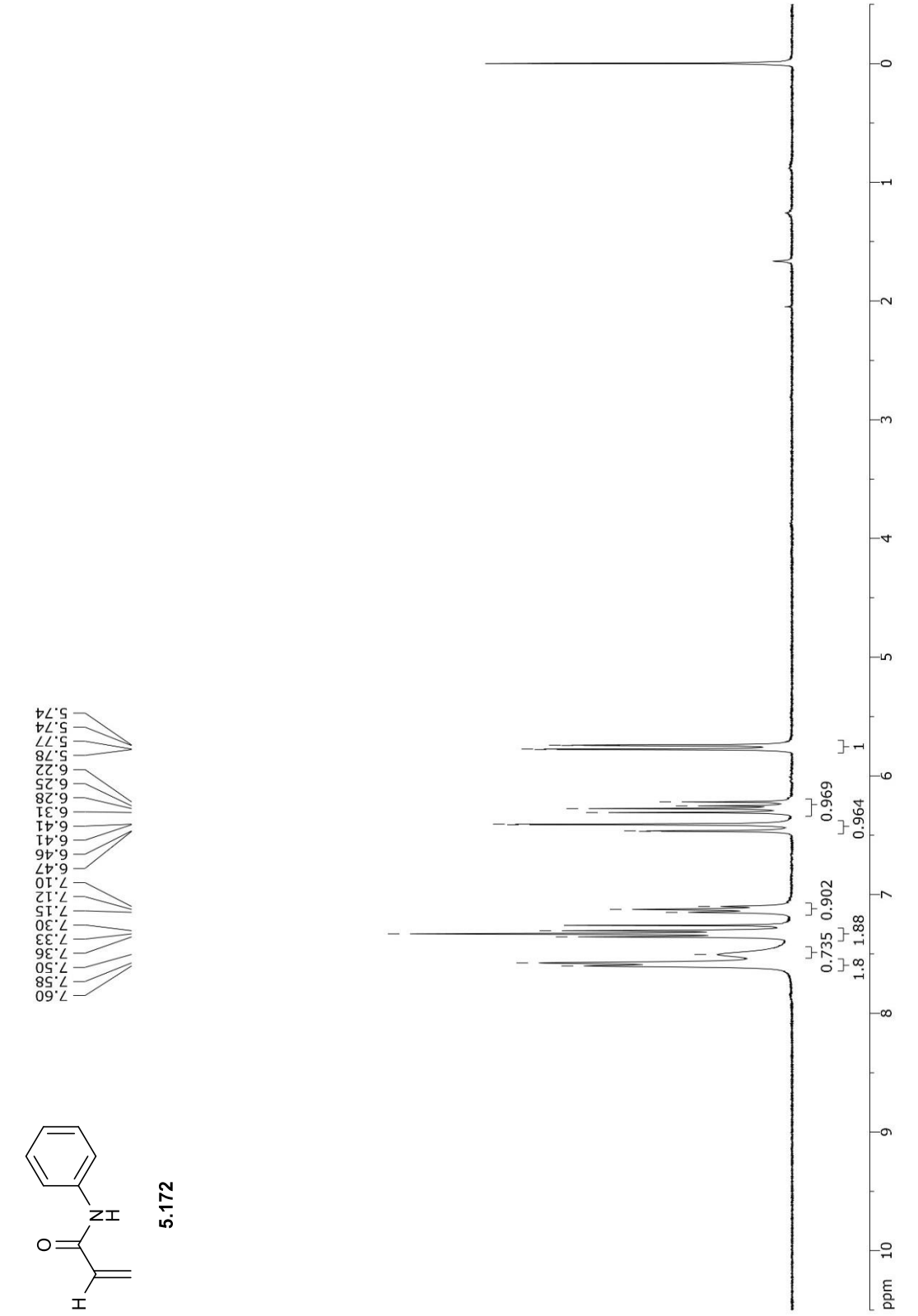
6.08
6.06
6.04
6.04
6.02
6.00
5.98
5.97
5.47
5.47
5.42
5.41
5.33
5.32
5.29
5.29
4.82
4.82
4.80
1.05
1
1.03
1.03
2.07
ppm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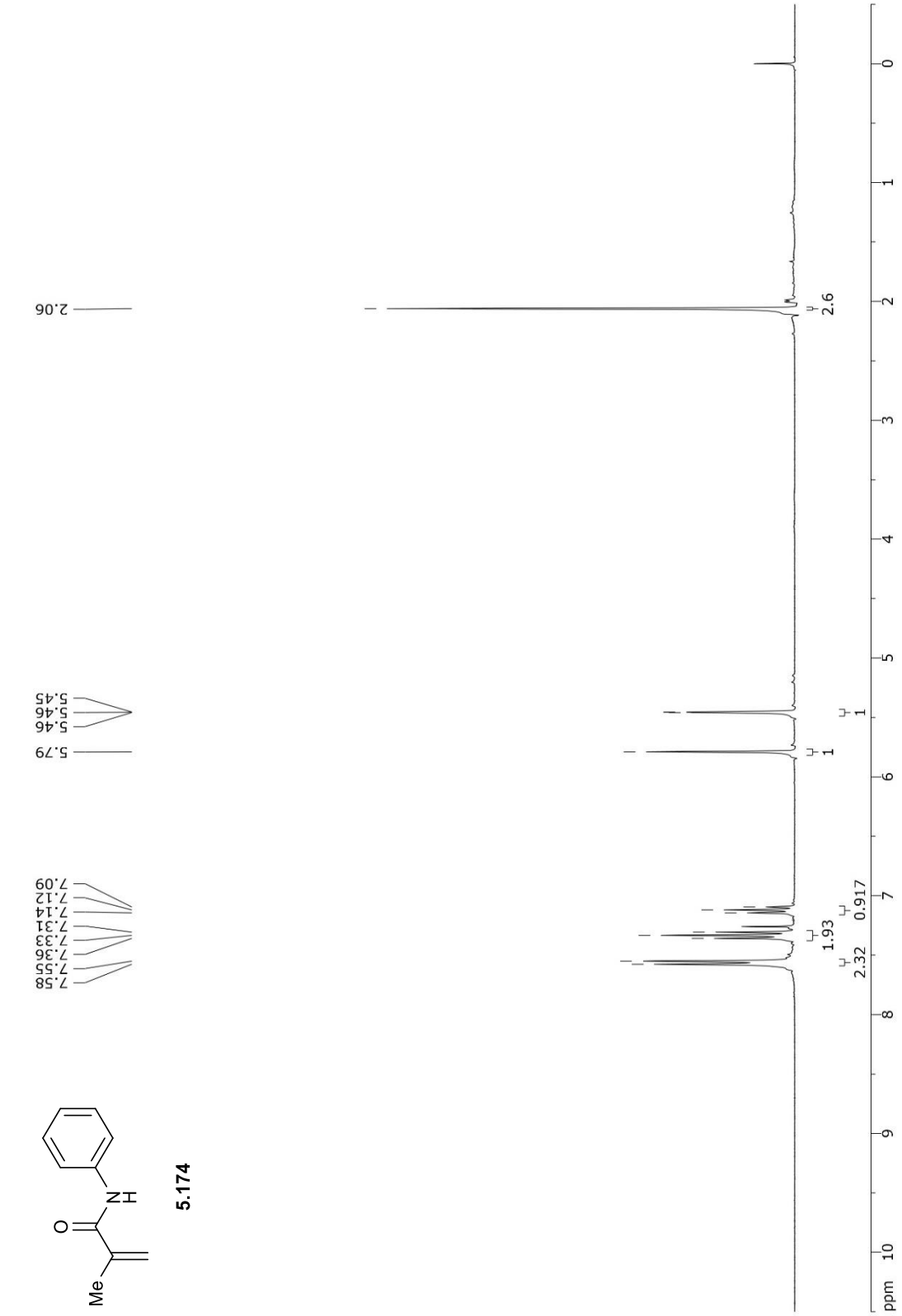
7.33
7.30
7.15
7.12
7.10
6.47
6.46
6.41
6.41
6.31
6.28
6.25
6.22
5.78
5.77
5.74
5.74
0.735
0.902
1.88
1.8
0.964
0.969
1
ppm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5.46
5.46
5.79
7.09
7.12
7.14
7.31
7.33
7.36
7.55
7.58
2.6
1
1
1.93
0.917
2.32
ppm
0
1
2
3
4
5
6
7
8
9
10
O
NH
Me

5.174